EMJ EUROPEAN MEDICAL JOURNAL

ONCOLOGY

ISSN 2054-619X Vol 6.1 • December 2018 • europeanmedical-journal.com

INSIDE

Review of

ESMO 2018

Munich, Germany

Contents

"A very warm welcome to EMJ Oncology 6.1, which is filled to the brim with exciting content, including our independent review of the European Society for Medical Oncology (ESMO) Congress 2018..."

Spencer Gore, CEO

Editorial Board

VIEW IN FULL ←

Aims and Scope

The European Medical Journal (EMJ) is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

EMJ also publishes 16 therapeutic area journals, which provide concise coverage of salient developments at the leading European congresses. These are published annually, approximately 6 weeks after the relevant congress. Further details can be found on our website: www.europeanmedical-journal.com

Editorial Expertise

EMJ is supported by various levels of expertise:

- Guidance from an Editorial Board consisting of leading authorities from a wide variety of disciplines.
- Invited contributors are recognised authorities from their respective fields.
- Peer review, which is conducted by EMJ's Peer Review Panel as well as other experts appointed due to their knowledge of a specific topic.
- An experienced team of editors and technical editors.

Peer Review

On submission, all articles are assessed by the editorial team to determine their suitability for the journal and appropriateness for peer review.

Editorial staff, following consultation with either a member of the Editorial Board or the author(s) if necessary, identify three appropriate reviewers, who are selected based on their specialist knowledge in the relevant area.

All peer review is double blind.

Following review, papers are either accepted without modification, returned to the author(s) to incorporate required changes, or rejected.

Editorial staff have final discretion over any proposed amendments.

Submissions

We welcome contributions from professionals, consultants, academics, and industry leaders on relevant and topical subjects.

We seek papers with the most current, interesting, and relevant information in each therapeutic area and accept original research, review articles, case reports, and features.

We are always keen to hear from healthcare professionals wishing to discuss potential submissions, please email: editorial.assistant@emjreviews.com

To submit a paper, use our online submission site: www.editorialmanager.com/e-m-j

Submission details can be found through our website: www.europeanmedical-journal.com/contributors/authors

Reprints

All articles included in EMJ are available as reprints (minimum order 1,000). Please contact hello@europeanmedical-journal.com if you would like to order reprints.

Distribution and Readership

EMJ is distributed through controlled circulation to healthcare professionals in the relevant fields across Europe.

Indexing and Availability

EMJ is indexed on DOAJ, the Royal Society of Medicine, and Google Scholar®; selected articles are indexed in PubMed Central®.

EMJ is available through the websites of our leading partners and collaborating societies.

EMJ journals are all available via our website: www.europeanmedical-journal.com

Open Access

Congress Notice

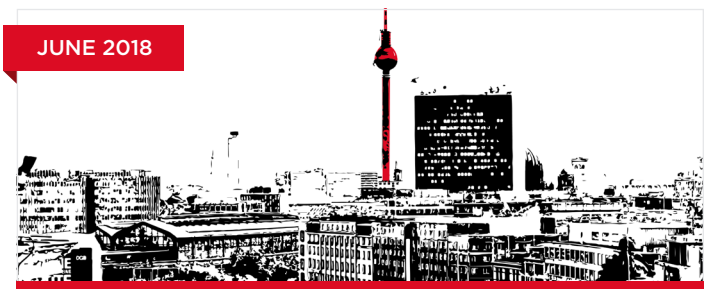
Staff members attend medical congresses as reporters when required.

This Publication

European Medical Journal Oncology is published once a year. For subscription details please visit: www.europeanmedical-journal.com

Front cover and contents photograph: Munich, Germany, home of the ESMO 2018. © Calin-Andrei Stan / 123rf.com

EMJ Oncol.



European Medical Journal 3.2

EMJ 3.2 has entered the building! This truly multidisciplinary eJournal returns for its 10th issue and its second of 2018. *EMJ 3.2* includes a plethora of high-quality peer-reviewed...

VIEW ALL JOURNALS ←

Welcome

A very warm welcome to *EMJ Oncology 6.1*, which is filled to the brim with exciting content, including our independent review of the European Society for Medical Oncology (ESMO) Congress 2018 alongside cutting-edge peer-reviewed articles tackling some of the most challenging and relevant topics in the fields of oncology and haematology today.

In such a fast-paced field, staying up-to-date with the newest research and data is paramount for healthcare professionals from every discipline of medicine. This is why we are so proud to present our Congress Review of ESMO 2018, in which you will find our coverage of the top news stories announced at the meeting. Alongside this, you will find fascinating summaries of the three presidential symposia held at ESMO, which feature updates from the IMpassion130, PALOMA-3, and SOLAR-1 studies, to name just a few. This year's congress was bigger and better than ever and it was a pleasure for EMJ to be able to attend. We look forward to hearing your thoughts on the progress that has been made over the past year.

Alongside our Congress Review, you will find a selection of peer-reviewed articles covering a plenitude of topics. This year's Editor's Pick is by Kesavan and Collins: a review that discusses the very latest in T cell lymphoma research, presenting novel therapies that could help address the limited prognosis faced by many patients. In addition, the authors discuss the future of more individualised treatment in order to maximise the benefit seen by each patient. Furthermore, you can refresh your knowledge of prostate-specific antigen and the clinical issues arising from increased levels of the protein, as well as epidemiological, clinical, and pathological aspects of prostate cancer in the narrative review by Randazzo et al. Sharma and Sweetenham provide an update on brand new chemotherapy-free therapies for mantle cell lymphoma, an exciting prospect that could lessen the burden of treatment for many patients. In addition, Davis and Keedy present a review of novel treatments for soft tissue sarcomas, including histology-directed therapy.

This year has certainly been an exciting one in the field of oncology. As always, it is our pleasure to report on the progress being made by researchers, scientists, and clinicians across Europe and the world in this exciting field. I hope you enjoy reading the eJournal, and I look forward to hearing your feedback and hopefully to seeing you at next year's ESMO Congress for even more lively debate and exciting presentations.

Kind regards,

Spencer Gore

Chief Executive Officer, European Medical Group

ion torrent

Oncomine IVD solutions—it's about time

Test faster to enable faster treatment

When your patients' samples are analyzed with the NGS-based Ion Torrent™ **Oncomine™ Dx Target Test** in your own hospital laboratory, you can get answers within a week, even from small biopsies, allowing you to make faster therapeutic decisions for more patients. Ask your pathologist about Ion Torrent™ Oncomine™ IVD solutions.

Find out more at **www.oncomine.com**

ThermoFisher SCIENTIFIC

Foreword

In this edition of *EMJ Oncology*, four papers will be published that review three different topics. The first topic is in relation to two types of lymphoma: T cell lymphoma and mantle cell lymphoma. What is common to these papers is the improved understanding of the biology of these malignancies, which ultimately will lead to more targeted therapies in addition to the currently available treatments.

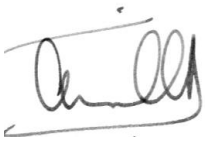
The second topic is in relation to a completely different tumour type: prostate cancer. Two papers review the commonly known biomarker prostate-specific antigen (PSA) and its screening value, emphasising the importance of informed consent before ordering a PSA blood test. Other potential biomarkers at the genomic and epigenetic levels are reviewed in the second paper.

"Selective therapeutic approaches will significantly improve the outcomes of our patients for both haematological and solid tumours."

The high-quality papers in this edition effectively summarise the current situation in basic, translational, and clinical research. This encompasses our understanding of the biology of cancer cells and their environment, which dedicated chemists have helped to develop. Selective therapeutic approaches will significantly improve the outcomes of our patients for both haematological and solid tumours.

Finally, it is of utmost importance to develop validated biomarkers as prognostic tools and, in particular, predictive tools of tumour response or, preferably, tumour resistance. The latter will help to avoid prescribing patients inefficacious, toxic, and costly anticancer agents. Thank you to all who have contributed to this new edition of *EMJ Oncology*, I hope you find it an insightful and informative read.

Kind regards,



Dr Ahmad Awada

Université Libre de Bruxelles, Belgium

Available now.

Included inside:

Congress Review

+ Review of EHA Stockholm, Sweden, 14th–17th June 2018

Interviews

Symposium Review

+ Planning Your Next Move in Philadelphia Chromosome Positive Leukaemias

Abstract Reviews

Articles

+ Editor's Pick: Allogeneic Haematopoietic Stem Cell Transplantation for Chronic Myeloid Leukaemia in the Era of Tyrosine Kinase Inhibitors Ahmet Emre Eskazan, Mario Tiribelli
+ Therapeutic Options in Myelodysplastic Syndromes: Established and Emerging Therapies Nina Kim, Shyamala Navada
+ Making Rituximab Directly Cytotoxic for Substantial Improvement in Therapeutic Efficacy Xinjian Chen

And even more...

EMJ Hematology 6.1 provides influential articles, presentations of scientific research and clinical practice, and an in-depth review of EHA 2018.

Subscribe for free.

EUROPEANMEDICAL-JOURNAL.COM /SUBSCRIBE

Congress Review

Review of the European Society for Medical Oncology (ESMO) Congress 2018

Location: Munich, Germany – Internationales Congress Center München (ICM)

Date: 19.10.18–23.10.18

Citation: EMJ Oncol. 2018;6[1]:12-35. Congress Review.

Representing an essential platform for collective discussions on this year's theme of 'securing access to optimal cancer care', the European Society for Medical Oncology (ESMO) Congress 2018 welcomed >26,000 oncology professionals through the doors of the Internationales Congress Center München (ICM) in the heart of Munich, Germany. Spanning 5 days, ESMO 2018 took place in the Bavarian capital from 19th–23rd October and involved a balanced programme of sessions, discussions, presentations, and debates. Herein, the EMJ provides their signature independent review of the congress for your enjoyment; whether you missed the event or would like to reflect on those amazing memories, the Congress Review section of *EMJ Oncology 6.1* is not to be missed.

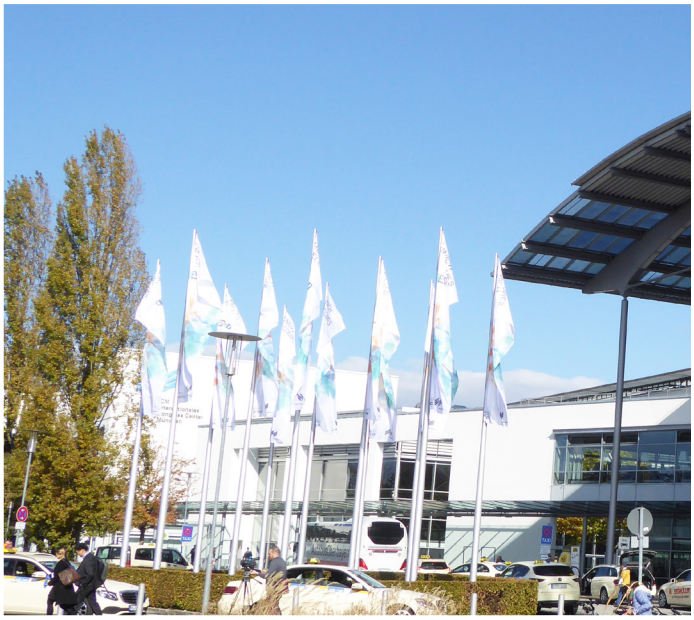
Welcoming attendees from across the globe at the inspiring Opening Session, ESMO President Prof Josep Tabernero highlighted the focus of ESMO 2018 as innovation, integration, and sustainability: all essential factors to ensure that cancer patients receive the best care. For the first time, the European Oncology Nursing Society (EONS) Congress took place this year alongside the ESMO Congress, and Dr Lena Sharp, EONS President, took to the stage to comment on this prime example of integration among oncology societies. Four outstanding professionals were then recognised for their contributions to the field of oncology, beginning with Prof Jean-Charles Soria who received the ESMO Award for his vital role in making precision medicine available to patients. The ESMO Award for Translational Research was presented to Prof Pasi A. Jänne for his discovery of *EGFR* mutations in lung cancer, followed by the ESMO Women for Oncology Award, which was bestowed to Dr Margaret Foti for her outstanding contributions to the development of women in oncology. Lastly, the ESMO Lifetime Achievement Award was received by Prof Tony Mok, who is well recognised for his practice-changing influences on the oncology community. With great applause and a huge sense of anticipation throughout the main auditorium, the ESMO 2018 Congress was officially underway.

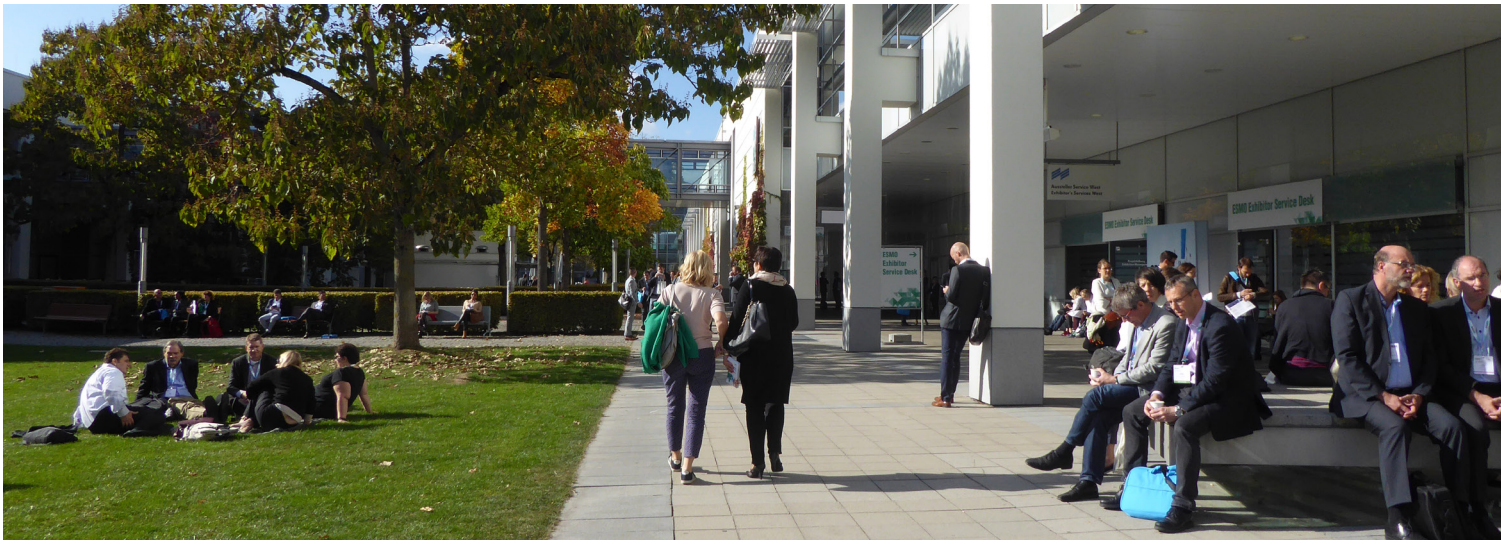
During the next 4 days, a myriad of scientific sessions and lectures were available for attendees, covering hot topics such as Big Data, genomics, and immunotherapy. Other key parts of the programme were also well-attended, including the Young Oncologists track, which focussed on burnout among young professionals, and the Patient Advocacy track, emphasising the key parts patients play in the battle against cancer. As discussed, collaboration with the EONS was new to this year's ESMO programme and offered oncology nurses a dedicated 3-day track to highlight the importance of their role in the multidisciplinary management of oncology patients. The vast congress programme developed by the ESMO 2018 Congress Officers will lead to transformations of oncology research into everyday practice.

"Summarising the new data available from key cancer trials, these sessions provided delegates with a one-of-a-kind opportunity to learn from the very best researchers in the field..."

This year's ESMO Congress also featured three much-anticipated Presidential Symposia. Summarising the new data available from key cancer trials, these sessions provided delegates with a one-of-a-kind opportunity to learn from the very best researchers in the field; a summary of these fascinating session can be found within. By covering breast, prostate, and head and neck cancers, to name but a few, the presenters described their new results with the hope of providing answers to some of the questions surrounding effectively treating advanced stages of various cancer subtypes. To complement the array of scientific sessions on offer, attendees were also invited to the exhibition halls and the ESMO Society Village to browse the broad range of specialised companies and societies working to enhance clinical practice and patient care, providing delegates with a well-rounded insight into the world of oncology, from small-scale research to industry developments.

Other field-changing revelations from ESMO 2018 comprised the influence of exercise for lung cancer patients, post-chemotherapy effects on fertility outcomes, and the financial burden of disease for cancer patients, showing the true variation in education available to attendees at this inspiring event. Supplemented by summaries of a selection of ESMO abstract presentations, this Congress Review section provides a comprehensive summary of the 5 days in Munich and will inspire further debate and discussion throughout the coming year. Ready for even more ground-breaking developments from the oncology sphere, the EMJ team look forward to seeing you all at the ESMO Congress 2019 in Barcelona, Spain.





Short-Course Trastuzumab Proposals for Treatment of HER2+ Early Breast Cancer

A 9-WEEK COURSE of trastuzumab treatment for HER2+ breast cancer has been shown to be a viable alternative to the standard 12-month treatment and a treatment course reduction by even 6 months is cost effective, saving thousands of pounds per patient, according to the results of two studies presented in an ESMO press release dated 19th October 2018.

Non-inferiority of 6-month trastuzumab treatment compared to standard 12-month treatment was assessed by the Short-HER trial studying 1,254 HER2+ early breast cancer patients. Patients were randomised to receive either a 9-week or 1-year course of trastuzumab alongside chemotherapy. Patients were followed-up for a median of 6 years. Results showed that the shorter course did not achieve non-inferiority, but it was associated with a reduction in the rate of severe cardiac toxicity.

Subgroup analysis was then carried out to assess whether specific groups of patients would achieve non-inferiority when treated with the short course of trastuzumab. Pathogenic tumour (pT) size and nodal status (N) were found to be independent prognostic factors for disease-free survival. Patients with low and intermediate risk (pT <2 cm and No, and pT <2 cm and any N category, respectively) had similar 5-year disease-free survival with a 9-week course of trastuzumab (88%) compared to 1 year (89%; hazard ratio: 1.02; 95% confidence interval: 078–1.33). Risk of cardiac events was nearly 3-times lower for the 9-week compared to the 1-year groups (4.5% versus 12.8%).

The study was underpowered and therefore was unable to prove non-inferiority; 1-year trastuzumab remains the standard of care for HER2+ early breast cancer. However, Prof Pierfranco Conte, University of Padua, Padua, Italy, and lead author of the study highlighted that these results support the choice to stop trastuzumab treatment before 1 year in patients who develop a cardiac event without fear of compromising treatment efficacy.

"The results, alongside the clinical effectiveness results demonstrating non-inferiority, are the first steps in the safe reduction of treatment for many women with HER2+ breast cancer."

A second study presented showed that a 6-month course of adjuvant trastuzumab was cost-effective compared to a 12-month treatment course. The landmark PERSEPHONE trial results analysing 3,759 patients showed an average cost saving of nearly £10,000 per patient. Further studies are needed to carry out further sensitivity analysis; however, Prof Claire Hulme, University of Leeds, Leeds, UK commented that: "The results, alongside

the clinical effectiveness results demonstrating non-inferiority, are the first steps in the safe reduction of treatment for many women with HER2+ breast cancer. They present an opportunity for significant cost savings for health service providers."

Use of Non-Conventional Therapies: Patient Perspectives

WHY do some patients with cancer make use of non-conventional therapies? And does this present oncologists with new challenges? These crucial questions were answered in studies presented at the ESMO Congress 2018, reported in a ESMO press release dated 10th October 2018.

Researchers from the University Hospital Mannheim, Mannheim, Germany used a structured survey to question 152 outpatients receiving care at a sarcoma centre on their use of non-conventional therapies. The patients had been treated for sarcoma, desmoid tumours, or gastrointestinal stromal tumour. The survey revealed the reasons why patients chose to make use of complementary and alternative medicines:

- To strengthen their immune system: 78%.
- To strengthen their body's powers: 76%.
- To reduce tension and stress: 54%.
- To leave nothing unattempted: 53%.
- To do something for themselves: 49%.
- To fight the tumour: 45%.
- To reduce side effects: 37%.
- To detoxify: 34%.

The results also showed that just over half (51%) of the individuals had used alternative treatment methods previously and 15% had used alternative methods only during the disease. Furthermore, 44% of individuals reported that receiving a cancer diagnosis had galvanised their interest in alternative treatments.

Currently, ESMO has acknowledged the benefits of several non-conventional therapies: physical exercise, hypnosis, yoga, acupuncture, and mindfulness-based stress reduction programmes. However, there are several non-conventional therapies that ESMO does not recommend as they have been associated with no positive outcomes or with negative outcomes. These therapies include ozone therapy, herbs, minerals, antioxidant supplements, and high-dose vitamins.

It was found that although nearly half of patients asked their oncologist for information about the side effects of cancer therapies, oncologists did not represent the primary source of information about non-conventional therapies. In fact, only 7% of patients asked their oncologist about non-conventional therapies, suggesting a potential barrier to information. Instead, patients accessed information on the Internet and other media resources (43%), from their friends (15%), and from healing professionals (14%).

Speaking about these study findings on behalf of ESMO, Dr Markus Joerger, Cantonal Hospital, St Gallen, Switzerland noted that the fact patients did not perceive non-conventional therapies to be high risk was a significant problem for oncologists. He noted: "Patients tend to believe that supplements or herbs are generally safe, but they are not without risk. In daily practice, if you don't know what your patient is taking as alternative medicine, the risk of drug–drug interactions can significantly increase and can have an impact on clinical outcomes."

"Patients tend to believe that supplements or herbs are generally safe, but they are not without risk."

Financial Issues Impact Psychological Cancer Burden

INCOME LOSS, a significant financial concern for cancer patients, is associated with adverse psychological effects in addition to material hardship, according to the results of a German study. Supplementing American studies that have shown economic burden is associated with high cancer morbidity and mortality, these novel findings, detailed in a ESMO press release dated 16th October 2018, highlight the specific psychological impact of monetary losses for cancer patients and the absence of clear procedures to tackle this issue.

After conducting a systematic literature review of the tools used to measure financial cancer burden, Prof Eva Winkler, National Centre for Tumor Diseases, Heidelberg, Germany, and her team discovered a lack of European investigations into this topic. In line with ESMO's key commitment to alleviate the financial burden of cancer, a questionnaire was created to assess this component of the disease based on material aspects, psychological effects, and behavioural changes, and a total of 247 patients (neuroendocrine tumours: n=122; colorectal cancer: n=125) provided responses. Between November 2016 and March 2017, 80.6% of patients stated that they had high cancer-related out-of-pocket costs, which could include co-payments for prescription drugs, travel expenses to care centres, and childcare costs. In addition, cancer-related income loss, mostly due to being unable to work or working reduced hours, was noted by 37.2% of participants and resulted in losses of >€800 per month for half of these patients.

While these results clearly showed the financial impact of cancer, particularly in German patients, further analysis indicated that the bigger the loss of income, the more negatively the patients perceived their quality of life, leading to higher levels of distress. "More research is needed to determine what actions are necessary at the system level, for example, an extension of the period of eligibility for sickness benefits, or at the individual level, like targeted consulting and support services," commented Prof Winkler. Further assessments in other European countries are now warranted and development of a valid instrument to measure subjective financial burden in European patients is necessary to support their psychological wellbeing.

Adherence to Cancer Screening: EDIFICE Results

"IT IS CLEAR that oncology has shifted from being merely reactive to being proactive and cancer screening is fully in line with this idea," said Prof Martin-Moreno, Medical School and Clinical Hospital, University of Valencia, Valencia, Spain, when commenting on behalf of ESMO on the results of a study into patient adherence to cancer screening. This study was reported in a ESMO press release dated 20th October 2018. Prof Martin-Moreno went on to state: "It [cancer screening] has the potential to make a major contribution to effective early diagnosis, if wide coverage, informed choice, and equitable distribution of screening services are ensured."

Researchers in France have been investigating adherence to cancer screening for a number of years to better understand this issue. The EDIFICE programme has been running since 2005 and has been conducted every 3 years. The 2017 results were presented at ESMO. In the 2017 study, 12,046 individuals filled out an online questionnaire. Previous rounds of the programme had been implemented using a telephone questionnaire.

The 2017 results showed that participation rates for breast cancer screening were very high, with 94% of respondents stating that they had had a mammogram. Breast cancer screening is freely accessible to all women in France aged from 50–74 years old. However, despite these high uptake rates, it was noticed that those who were socially vulnerable were more likely to be reluctant to take part in screening programmes, leading the authors to speculate that breast cancer prevention was not a priority for this demographic. Social vulnerability was also a relevant factor regarding screening adherence in other types of cancer. For instance, socio-economic deprivation and living alone were associated with a reluctance to undergo cervical cancer screening. It was noted that those who were socially marginalised were also at greater risk of developing cervical cancer.

"It is clear that oncology has shifted from being merely reactive to being proactive and cancer screening is fully in line with this idea."

Another barrier identified to cancer screening uptake was that of medical scepticism. The researchers found that adherence to breast cancer and colorectal cancer screening programmes was negatively influenced by medical scepticism. Reasons mentioned were a lack of trust in the effectiveness of the protection offered by screening programmes and doubts about the progress of clinical research.

It is hoped that a greater understanding of patient adherence to screening programmes will enable improved uptake in the future.

Exercise Shown to Benefit Patients with Advanced Lung Cancer

FATIGUE and wellbeing were both improved when patients with advanced lung cancer undertook regular exercise, according to a ESMO press release dated 20th October 2018. Two studies highlighted the value of exercise for patients with advanced lung cancer, despite it previously being believed that only those with early-stage cancer would benefit from exercise.

An exercise survey was completed by patients at a cancer centre in Queensland, Australia; nearly 90% of those who completed the survey had advanced lung cancer. Results showed that 54% were unaware of the benefits of exercise and only 22% reached the healthy activity levels recommended by the World Health Organization (WHO). Over 60% of responders said they did not exercise because of fatigue or shortness of breath.

"Physical fitness is a key factor in determining whether patients can start treatment and maintain dosing."

Data showed that patients who were less active had significantly less support than those who were more active. Researchers asked what type of exercise plan patients would find most helpful and most suggested more education, group exercise classes, and other support at the same location that they were receiving their treatment.

A second study (N=227) of patients with advanced or metastatic lung cancer randomised patients to receive either combined resistance and aerobic training for up to 45 minutes three times a week along with care management phone calls (CMPC) or CMPC alone for 24 weeks. Patients who completed at least 70% of the exercise sessions achieved significant benefits. Fatigue scores improved by 10% in the combined group, compared with 2% improvement for the CMPC only group (p=0.01). Functional wellbeing improved by 11% compared to 3% in the CMPC only group (p=0.03), and overall physical and functional wellbeing improved by 8% compared to 4% (p=0.04), respectively.

Dr Martijn Stuiver, Amsterdam University of Applied Medicine, Amsterdam, Netherlands highlighted that healthcare providers need to find out which type of exercise is most suitable to each patient and encourage them to conduct the exercise, highlighting the potential benefits. Dr Stuiver further emphasised the impact exercise can have on the treatment regime of cancer patients: "Physical fitness is a key factor in determining whether patients can start treatment and maintain dosing. Exercise may therefore become a primary adjuvant therapy to improve fitness so that patients are in the best possible shape to start or continue treatment and tolerate toxicities of other therapies."

Single-Centre Experience of Post-Chemotherapy Fertility Outcomes

CHEMOTHERAPY'S impact on post-therapy fertility in breast cancer patients was examined by a study presented at the ESMO Congress and reported in a ESMO press release dated 20th October 2018. Today, individuals being treated for breast cancer aged under 40 are typically offered fertility preservation, as those who survive have a significantly reduced chance of pregnancy compared with the general population, being 70% less likely to become pregnant.

One of the main motivations behind the study was outlined by one of the study's authors, Dr Jérôme Martin-Babau, Centre Armoricain de Radiothérapie, Plérin, France. He explained: "We wanted to find out whether the need and demand for it [fertility preservation] among breast cancer survivors was on a par with the level of investment and organisation called for by the policymakers." The population studied were 60 patients who had been treated by chemotherapy for non-metastatic breast cancer. The median age of these women was 36 years at the time of diagnosis. All participants who undertook the survey were in complete remission. As the researchers expected, most individuals (83%) experienced a total absence of menstruation during the course of their chemotherapy regimen. However, a finding that was not expected was that 86% of those individuals declared that their menstrual cycles returned to normal within a year after the cessation of chemotherapy. Dr Marin-Babau commented this was "an indication that the treatment had not completely damaged their ovaries."

The researchers found that the desire of individuals to bear children changed during the course of treatment. After treatment, 1 in 10 women stated they had plans to become pregnant, which contrasted with one-third of women prior to the commencement of chemotherapy. It was also found that of the six women who still desired children, four of them became pregnant, although two of these women miscarried. The researchers sounded several notes of caution about their findings, explaining that one-third of potential participants had not responded to the survey and that their findings reflected a single-centre experience.

Olaparib Extends Progression-Free Survival for Patients with Ovarian Cancer

OLAPARIB, a poly ADP ribose polymerase (PARP) inhibitor, has been shown to improve progression-free survival (PFS) substantially in patients newly diagnosed with ovarian cancer with *BRCA1* or *2* mutations, according to the SOLO-1 Phase III trial data reported in a ESMO press release dated 21st October 2018.

A total of 391 patients with high-grade, serious or endometrioid ovarian cancer who were in clinically complete or partial response after chemotherapy were randomised 2:1 to receive either olaparib 300 mg twice daily tablets (n=260) or placebo (n=131) for 2 years. The study aimed to evaluate frontline olaparib maintenance therapy after platinum-based chemotherapy in patients with a *BRCA* mutation.

"These are outstanding results in a worsening disease setting. Not only was olaparib efficacious but it was also shown to be well tolerated."

Median follow-up was 41 months. Primary PFS analysis showed a significant 70% reduction in the risk of progression or death for those treated with olaparib compared to placebo. Olaparib adverse events were low grade, with the most common Grade ≥3 toxicities being anaemia (22%) and neutropenia (8%). There was no clinically relevant change in quality of life between groups and only 12% of olaparib patients discontinued treatment, all of these patients did so because of associated toxicities rather than disease progression.

Dr Kathleen Moore, Stephenson Cancer Center, University of Oklahoma, Oklahoma City, Oklahoma, USA, further explained the results: "The median PFS for patients who received placebo was only 13.8 months, while the median PFS for those who received olaparib was not reached but looks to be approximately 3 years longer than the placebo group [hazard ratio: 0.30; 95% confidence interval: 0.23–0.41; p<0.0001]." Dr Moore went on to emphasise that current data suggest that >50% of olaparib-treated women were still progression-free at 4 years, compared to 11% of the placebo group.

"These are outstanding results in a worsening disease setting. Not only was olaparib efficacious but it was also shown to be well tolerated," summarised Prof Isabelle Ray-Coquard, Université Claude Bernard Lyon Est, Lyon, France. These results are truly unprecedented and mark a dramatic change in the potential treatment for this subgroup of BRCA-mutated ovarian cancer patients; however, how these data could help in the treatment of other carcinomas still needs further investigation.

Immune Checkpoint Inhibitors Effective in Mismatch Repair-Deficient Colorectal Cancer

CHECKPOINT inhibition with nivolumab and ipilimumab has been shown to be highly effective in early-stage mismatch repair-deficient (dMMR) colon cancer patients. This first-of-its-kind Phase II trial was presented at ESMO 2018 and the results, described in a ESMO press release dated 22nd October 2018, were far more significant than those from studies of metastatic colorectal cancer.

As immunotherapy is already an established treatment strategy for many tumour types, showing durable responses in metastatic colorectal cancers, researchers from the Netherlands Cancer Institute, Amsterdam, Netherlands, set out to investigate its use in dMMR early-stage colorectal cancer, which has a high mutational load and immune checkpoint upregulation. The exploratory trial recruited 14 patients with early-stage colorectal cancer, 7 of whom had dMMR tumours. The patients were treated with nivolumab (two 3 mg/kg doses on Day 1 and Day 15) and ipilimumab (one 1 mg/kg dose on Day 1) to enhance the immune response by blocking programmed cell death protein-1 and cytotoxic T lymphocyte-associated protein-4, respectively.

Defined as <5% of viable tumour cells remaining, major pathological responses were noted in 100% of the patients with dMMR colon cancer following treatment, with 57% of these patients experiencing complete responses. In contrast, those patients with mismatch repair-proficient cancer did not show any major pathological responses. Commenting on the significance of this first study of immune checkpoint inhibitors in early-stage colon cancer, lead author Dr Myriam Chalabi, Netherlands Cancer Institute, explained: "For dMMR tumours, the results were amazing, with 100% of patients so far having either complete or near complete responses within the short timeframe, which is usually 4 weeks."

While the small sample size and lack of control arm are two limitations of this study, the authors hope that the results will have implications for clinical practice in the future. "Our data suggest that neoadjuvant immunotherapy in dMMR colon cancer warrants further research and has the potential to change the standard of care," commented Dr Chalabi. Further larger studies of immunotherapy in the neoadjuvant setting and for earlier-stage tumours are therefore necessary to replicate these findings.

Immunotherapy's Impact on Triple Negative Breast Cancer

TRIPLE NEGATIVE breast (TNB) cancer is the most aggressive form of breast cancer. Relatively rare, TNB primarily affects younger women, and, once metastatic, the median TNB survival time is 12–15 months. However, a new therapeutic hope has emerged in the results of a recent Phase III trial, which were reported in a ESMO press release dated 20th October 2018, that investigated the effects of an atezolizumab–nab-paclitaxel therapeutic combination.

TNB cancers do not express oestrogen or HER2 receptors, thus the resistance of the tumours to hormone therapy or HER2-based therapeutics leaves chemotherapy as the sole treatment option; however, most patients develop resistance to chemotherapy within a few months. The new combination therapy has shown great potential in TNB care. "Atezolizumab in combination with nab-paclitaxel is the first targeted treatment to improve survival in metastatic triple negative breast cancer," explained Prof Peter Schmid, St. Bartholomew's Breast Cancer Centre, Barts Health NHS Trust; Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, UK.

"Atezolizumab in combination with nab-paclitaxel is the first targeted treatment to improve survival in metastatic triple negative breast cancer."

In total, 902 metastatic TNB patients who had not previously received treatment for metastatic disease were enrolled into the trial and randomised to receive either the standard chemotherapeutic, nab-paclitaxel, with the PD-L1 targeting antibody, atezolizumab, (combination) or nab-paclitaxel with a placebo (control). Across the entire study population, median progression-free survival and overall survival were both higher in individuals receiving the combination therapy compared with the control group: 7.2 months versus 5.5 months and 21.3 months versus 17.6 months, respectively. Focussing more specifically on patients with PD-L1 positive cancers, median progression-free survival and overall survival were 7.5 months versus 5.0 months and 25.0 months versus 15.5 months, respectively.

With limited side effects, most of which were attributed to the chemotherapy rather than the PD-L1 antibody, atezolizumab combination therapy appears to be a promising option for future TNB treatment, especially for those with PD-L1 positive cancers. Prof Schmid concluded: "Immune therapy on top of standard chemotherapy prolonged survival by ten months in patients with tumours expressing PD-L1. This combination should become a new treatment option for patients with metastatic triple negative breast cancer."

Age: A Barrier to Clinical Trial Participation?

AGE LIMITS for participation in clinical trials were the focus of a study that was presented at the ESMO Congress and reported in a ESMO press release dated 21st October 2018. The study authors set out to examine whether young individuals (aged from 12–25 years old) had access to clinical trials.

On one hand, those under the age of 18 years are barred from taking part in adult clinical trials in Europe, as the legal minimum age is 18 years nearly everywhere. One of the study authors, Dr Aurore Vozy, Gustave Roussy Institut de Cancérologie, Villejuif, France, gave an example of how this could be problematic: "We know, however, that certain girls will develop genetically-driven breast cancers very early in

life; there are no paediatric trials for this disease, yet these patients are systematically barred from participating in the relevant adult trials." The alternative situation is that young adults in their early twenties can develop tumours that more typically occur in children; however, paediatric clinical trials will tend to have an upper age limit of either 18 or 12 years.

"...these patients are systematically barred from participating in the relevant adult trials."

In order to examine the extent of this potential issue, the researchers reviewed all of the Phase I and Phase II trials that were initiated for solid tumours or lymphomas at the Gustave Roussy Institut de Cancérologie from 2012–2017; this encompassed 465 trials, of which 65 allowed the enrolment of individuals aged 12–17 years. Examination of the 389 trials that were not available to adolescents determined that 55% of them had the potential to be relevant for that demographic; furthermore, 28 of the trials were investigating tumour types that are especially common among adolescents. Examination of the 62 paediatric trials revealed that >50% did not recruit patients who were aged from 19–25 years. However, 10 of these trials were investigating tumour types that occurred in the 19–25-year-old age bracket.

Dr Vozy suggested several potential solutions:

- Increasing the age limit in paediatric trials to 25 years in certain cases.
- Lowering the minimum age to participate in clinical trials to 12 years, which has already been adopted in the USA.
- Including dedicated adolescent cohorts within adult clinical trials.

ESMO have already begun working towards the removal of these barriers. In conjunction with the European Society for Paediatric Oncology (SIOPE), they created the Cancer in Adolescents and Young Adults Working Group in 2016. The aim of this group is to both raise awareness of such barriers and work to influence authorities and stakeholders to facilitate the amelioration of the barriers.

Checkmate, Cancer! Positive Results for Immunotherapy to Treat Colorectal Cancer

LATE-BREAKING results from the CheckMate-142 trial suggest that immunotherapy with nivolumab and a low-dose ipilimumab could represent a promising first-line treatment for some forms of metastatic colorectal cancer. These findings, reported in a ESMO press release dated 22nd October 2018, build on previous results from the same trial that led to the treatment combination's authorisation by the U.S. Food and Drug Administration (FDA).

Unlike previous reports, the latest CheckMate-142 results from the study focussed on patients who had received no initial treatment for microsatellite instability (MSI)-high colorectal cancer. In total, 45 patients (median age: 66 years, 51% male) were treated with the nivolumab–ipilimumab combination; they were followed-up for endpoint response for a median of 13.8 months.

The results of this treatment were hugely positive, with 60% of patients achieving the objective response rate, 7% having a complete response, and 84% of patients demonstrating tumour shrinkage. The 12-month progression-free survival and overall survival were similarly encouraging at 77% and 83%, respectively. The low dosage of ipilimumab resulted in decreased toxicity, with 16% of patients reported to have experienced treatment-related Grade 3 and 4 toxicities and 7% discontinuing treatment as a result.

"The combination of low-dose ipilimumab and nivolumab has a durable clinical response and is well tolerated as a first line treatment in patients with MSI-high metastatic colorectal cancer."

This effective treatment could have a huge impact on the lives of MSI-high metastatic colorectal cancer patients, offering clinicians a first-line option with proven efficacy. "The combination of low-dose ipilimumab and nivolumab has a durable clinical response and is well tolerated as a first line treatment in patients with MSI-high metastatic colorectal cancer," explained study author Prof Heinz-Josef Lenz, University of Southern California Norris Comprehensive Cancer Centre, Los Angeles, California, USA.

Further study, particularly a Phase III trial, is required before these results can be verified but, nonetheless, these results represent an important development for the treatment of this at-risk population.

First Overall Survival Results for Palbociclib

THE FIRST overall survival results from a Phase III study for a cyclin-dependent kinase (CDK) 4/6 inhibitor were reported at the ESMO Congress and described in a ESMO press release dated 20th October 2018. Speaking on behalf of ESMO, Dr Carmen Criscitiello, European Institute of Oncology, Milan, Italy, declared: "These data were much awaited, as the clinical benefit obtained with CDK 4/6 inhibitors was incontestable, but there was the hot question whether the progression-free survival benefit translates into overall survival benefit."

CDK4/6 inhibition treatment has been proposed as a possible solution for preventing or overcoming the development of resistance to hormonal therapy in advanced hormone receptor positive (HR+), HER2- breast cancer. The development of such a treatment is important as the majority of patients with HR+ breast cancer develop resistance to hormonal therapies over the passage of time. Previous results from the PALOMA-3 trial had revealed that palbociclib, a CDK 4/6 inhibitor, when used in combination with fulvestrant, resulted in an increase in progression-free survival in a group of 521 women with HR+, HER2- breast cancer who had progressed on hormonal therapy.

In a new analysis of PALOMA-3 data after a median follow-up of 44.8 months, the researchers carried out an overall survival analysis after around 60% of the patients in the trial had died. The results of the analysis demonstrated

an increase in overall survival of 6.9 months (median overall survival: 34.9 months; 95% confidence interval: 28.8–40.0) in the palbociclib and fulvestrant cohort compared with the placebo and fulvestrant cohort (median overall survival: 28.0 months; 95% confidence interval: 23.6–34.6; p=0.043).

"These data were much awaited, as the clinical benefit obtained with CDK 4/6 inhibitors was incontestable."

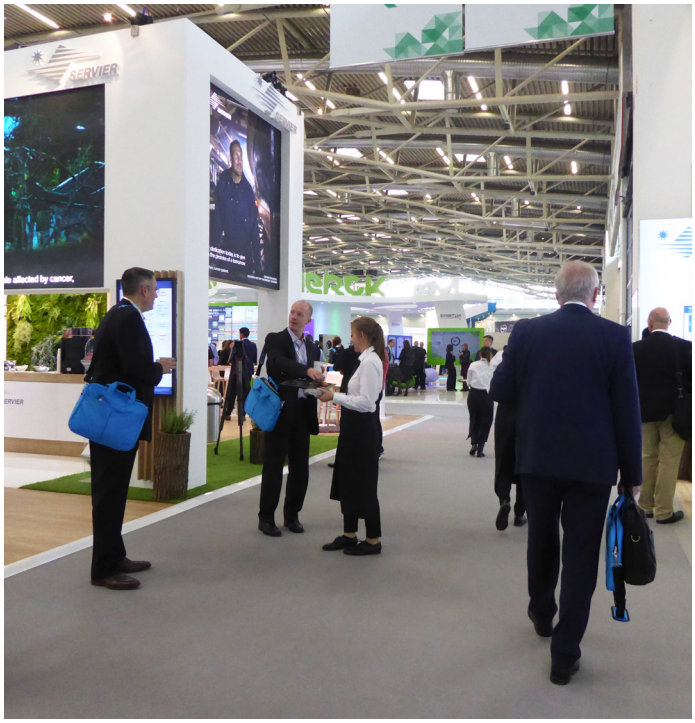
Dr Criscitiello concluded: "This randomised Phase III trial shows for the first time an improvement in overall survival with a CDK4/6 inhibitor in the metastatic setting for HR+, HER2- breast cancer." She also noted: "This study was underpowered for overall survival, so the data should be cautiously interpreted. Although the results strongly suggest that the progression-free survival benefit may translate into overall survival benefit, the other trials conducted with CDK4/6 inhibitors will contribute to confirm the estimate of the overall survival benefit observed in this study."

High Non-Adherence to Hormone Therapy in Premenopausal Breast Cancer Patients

TREATMENT with tamoxifen, a form of hormone therapy, is common for breast cancer patients, but new research presented in an ESMO press release dated 19th October 2018 indicates that adherence to the drug is concerningly low. While previous studies have shown many breast cancer patients discontinue long-term therapy, this study by the Institut Gustave Roussy, Villejuif, France, is the first to reveal the extent of treatment non-adherence within this population via serum level measurement after 1 year, as opposed to self-reported adherence.

Using data from the CANTO trial, a prospective study examining the long-term impact of breast cancer treatment side-effects in around 12,000 patients, the researchers analysed 1,799 premenopausal women who had been prescribed tamoxifen to treat their early-stage (I–III) breast cancer. The patients' tamoxifen level within their serum was measured at 1, 3, and 5 years and their self-reported adherence rates were recorded.

"We need to understand the patients most at risk of being nonadherent early in their treatment and provide targeted interventions aiming to improve their self-efficacy and self-management of side-effects"



After the first year, results showed that 16.0% (n=188) of these patients were not adequately adherent to the treatment, with serum tamoxifen levels of <60 ng/mL. Of these, 10.7% had an undetectable level of the medication, with the remaining 5.3% of patients shown to be poorly adherent, with serum tamoxifen levels below the expected steady-state concentration expected after 3 months. In addition, <50% of these 188 patients self-reported not taking their tamoxifen as prescribed.

These results are considerably higher than expected and pose a challenge to clinicians, who need to develop a personal relationship with patients to encourage them to openly discuss side effects and adherence with their physician. "We need to understand the patients most at risk of being nonadherent early in their treatment and provide targeted interventions aiming to improve their self-efficacy and self-management of side-effects," explained Dr Barbara Pistilli, Institut Gustave Roussy, Villejuif, France.

While the wider application of these results was limited by the French-only cohort and the fact that data was only recorded at one timepoint per year, they still represent an important step in encouraging further doctor–patient discussion in the management of breast cancer. The study remains ongoing, awaiting data from its 3 and 5-year endpoints, which will be better able to quantify the impact of non-adherence on mortality and recurrence.

Renal Cancer Revolution: Avelumab plus axitinib combination proving effective

PREVIOUSLY untreated renal cell carcinoma (RCC) patients could benefit from a combination therapy comprising the immune checkpoint blocker avelumab and the tyrosine kinase inhibitor (TKI) axitinib, suggest data from the JAVELIN Renal 101 trial presented in a ESMO press release dated 21st October 2018. "JAVELIN Renal 101 is the first positive Phase III study combining an immune checkpoint blocker with a TKI alone in the first line treatment of advanced RCC," commented Dr Robert Motzer, Memorial Sloan Kettering Cancer Center, New York City, New York, USA.

In total, 886 kidney cancer patients (Memorial Sloan Kettering Cancer Center) were examined; 442 were administered the oral avelumab–axitinib combination (avelumab 10 mg/kg intravenously every 2 weeks, axitinib 5 mg twice daily), while the remaining 444 were given 50 mg oral sunitinib once per day on a 4/2 schedule (4 weeks on-drug, 2 weeks off-drug). The study's primary endpoints were PFS in PL-L1+ patients up to 30 months, and overall survival in these patients up to 5 years.

Results of this new treatment combination were encouraging, with a median PFS of 13.8 months in the combination arm versus 7.2 months in the sunitinib arm (hazard ratio [HR]: 0.61; p<0.0001) in patients with PD-L1+ tumours; when assessed irrespective of PD-L1+ expression,

PFS was 13.8 and 8.4 months, respectively (HR: 0.69, p=0.0001). Additionally, the confirmed objective response rate was shown to be more than doubled in the combination arm (55.2%) versus the sunitinib arm (25.5%) (95% confidence interval: 49.9–61.2 and 20.6–30.9, respectively). "The combination benefit was shown in all subgroups of patients by independent review as well as by investigators, and whether tumour cells stained positive for PD-L1 or not," explained Dr Motzer.

These results represent response rates that are twice those of the current standard of care and, whilst further study is warranted, this combination could be a powerful option for this vulnerable patient cohort. "TKI, and checkpoint blockers like avelumab, both may have potential immune-modulating functions that, when combined, may provide clinical benefit in patients with advanced RCC that exceeds the effects of the respective drugs alone, without compromising toxicity," concluded Dr Motzer.

"The combination benefit was shown in all subgroups of patients by independent review as well as by investigators, and whether tumour cells stained positive for PD-L1 or not."

Cancer Drug Reimbursement Approval Time Varies Across Europe

DISPARITY in the time taken for health technology assessment (HTA) decisions regarding the reimbursement of new anticancer drugs following European Medicines Agency (EMA) approval has been highlighted between various European nations in the results of a new study, which was presented at the ESMO Congress and reported in a ESMO press release dated 19th October 2018. Some countries were shown to take >3-times as long to approve reimbursement.

A HTA process has been adopted by many European countries. The process involves undertaking a systematic cost-benefit analysis of a treatment once it has been approved by the EMA. This process is conducted prior to determining whether or not to reimburse the use of the treatment for routine patient care.

"It is a country's responsibility to ensure sufficient administrative capacity so that processes like HTA that were put in place for the benefit of society do not start harming citizens."

The researchers focussed their attention on four countries: England, Scotland, France, and Germany. They tracked the time between EMA approval for the 47 drugs approved for use in 77 solid tumour indications from January 2007–December 2016 and HTA decisions being made by the health authorities in the four countries. The findings revealed a significant discrepancy in median time from EMA approval to HTA decision:

- England: 405 days.
- Scotland: 384 days.
- Germany: 209 days.
- France: 118 days.

It was also found that the drugs ranked as being of the highest benefit on the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) had a decision made on them more swiftly. These were typically approved for reimbursement, with Germany approving all such drugs, Scotland 95%, England 92%, and France 90%.

The overall findings represented sobering news, Dr Bettina Ryll, Chair of the ESMO Patient Advocacy Working Group, declared: "We in melanoma still mourn the lives we lost due to the tardy and inconsistent introduction of approved innovative therapies." Dr Ryll went on to issue a call: "It is a country's responsibility to ensure sufficient administrative capacity so that processes like HTA that were put in place for the benefit of society do not start harming citizens. And we need more pragmatic approaches to reducing uncertainty; simply letting patients die while waiting for data to mature is not a civilised option."

In addition to ensuring sufficient administrative capacity, it was also suggested that HTA agencies could use the ESMO-MCBS as a decision-making tool. As only four countries were investigated in this study, insights into HTA procedures in other European countries may prove equally enlightening.

New ESMO Designated Centres of Integrated Oncology and Palliative Care

"ESMO is committed to increasing awareness and education to bring patient-centred care closer to all professionals, to improving collaboration between healthcare providers for the good of patients and to promoting research, so that patient-centred interventions are not only integrated, but also based on the best evidence." These words are taken from a ESMO position paper published in 2017, in which ESMO declared that supportive and palliative care should be a core component of therapy for cancer. It was in this spirit that the ESMO Congress saw the recognition of 20 recently accredited Designated Centres of Integrated Oncology and Palliative Care, as reported in a ESMO press release dated 16th October 2018.

"...while survival and disease-free survival are both fundamental factors, overall quality of life is also crucial for patients."

The objective of the ESMO Designated Centre of Integrated Oncology and Palliative Care programme is threefold: firstly, to encourage national health bodies to integrate palliative care services into their cancer care guidelines; secondly, to promote the training and education of medical oncologists and other healthcare professionals in palliative care; and thirdly, to facilitate and expand ESMO's work with other medical organisations and associations in the support of palliative care development. Designation as a Centre of Integrated Oncology and Palliative Care is valid for a 3-year period, after which reapplication is necessary.

Speaking about the importance of palliative care, one of the authors of the ESMO 2017 position paper, Dr Karin Jordan, University of Heidelberg, Heidelberg, Germany, stated: "Over the last decade, we have recognised that while survival and disease-free survival are both fundamental factors, overall quality of life is also crucial for patients. At any stage of the cancer pathway, physical, psychological, social, existential, and spiritual support and rehabilitation are often needed."

Of the 20 centres to achieve ESMO Designated Centre of Integrated Oncology and Palliative Care status, 11 were from Europe, including the first centres from Denmark and Estonia. Other countries that saw their first Designated Centre were Japan and Qatar. Additionally, 54 centres achieved reaccreditation, which took the total of Designated Centres worldwide to 216, highlighting the increased reach of this ESMO programme.

Cancer Patients Share Experiences via Social Media

TWITTER can be used as a forum for sharing experiences of disease, and cancer is currently the most commonly discussed disease on the site. Presented at ESMO 2018 and reported in a ESMO press release dated 12th October 2018, a recent exploratory study analysed >6,000 tweets and retweets posted with the hashtag #BreastCancer, since this is the top cause of cancer-related deaths in women, showing that diagnosis, treatment, and prevention were among the most discussed topics.

"Many of the patients we see in daily practice use social media to search for information about their disease, so, as care providers, we wanted to know what kind of content they find there," explained study author Dr Rodrigo Sánchez-Bayona, Clinica Universidad de Navarra, Pamplona, Spain. As part of a larger study that analysed the presence of different diseases on social media, breast cancer was chosen for this subanalysis due to its high prevalence worldwide. Tweets (n=3,703) and retweets (n=2,638) posted during a 7-day time period were categorised according to twitter user, content, user aim, and stigmatising attitude.

The results showed that while 1 in 3 tweets contained medical content, 40% of the tweets came from institutions or public accounts, resulting in 90% of the information being informative. In addition, 44.5% of the tweets were focussed on prevention and the most common aim of patients using Twitter was to share their cancer experiences. With regard to stigmatisation, Dr Sánchez-Bayona explained that the finding that <15% of tweets contained stigmatising statements could be attributed

to the numerous successful breast cancer awareness campaigns and highlighted the importance of comparisons with the presence of other tumour types on social media.

The user information collected from this study will enable advocacy organisations to create relevant medical content specific to particular patients, as well as using social media to disseminate information to a broad audience. With such a rich pool of patient data available on Twitter, it was concluded that it may be effective at assessing attitudes to many types of diseases. "This analysis also illustrates the presence of patients in large numbers on Twitter. We should take that as corroboration of a new reality: patients now use the web to find information, and social media must be an integral part of our communication with them," commented ESMO spokesperson Dr Marina Garassino, Istituto Nazionale dei Tumori, Milan, Italy. With the potential for fast and wide publication of medical content, it is expected that the use of Twitter for sharing both disease information and patient experiences will increase.

Precision Medicine Moves into the Oncology Community

TARGETED drugs for advanced cancers are being used in healthcare facilities other than highly specialised centres, according to results reported in a ESMO press release dated 9th October 2018. With more community patients being able to benefit from precision medicine in their treatment centres, targeted treatment is changing the way oncology patients are cared for, potentially enhancing survival and quality of life.

"It is so encouraging to see how precision medicine is changing the way we treat our patients in the community and our next step is to analyse the effects of targeted treatment on survival and quality of life."

From 2013–2017, large-scale tumour profiling was performed on 6,177 patients with advanced cancer at 5 hospitals of Cancer Treatment Centers of America. Using the data to match patients to targeted treatment, 47% of the DNA mutations identified were clinically relevant and included alterations, most commonly gene amplifications (32%) and alterations in *KRAS* (23%) and *PIK3CA* (15%). A total of 57% of patients with DNA alterations matched to targeted therapies were receiving treatments approved by the U.S. Food and Drug Administration (FDA) for other tumour types, while 15% of the patients received treatments in clinical trials. The team noted that they hope the latter figure will increase to as high as 50% of patients receiving treatment through clinical trials or off-label with approved medicines in the next few years.

"It is so encouraging to see how precision medicine is changing the way we treat our patients in the community and our next step is to analyse the effects of targeted treatment on survival and quality of life," elucidated Dr Ricardo H. Alvarez, Cancer Treatment Centers of America, Atlanta, Newnan, Georgia, USA. These results were welcomed by the authors' European colleagues also, with Dr Joaquin Mateo, involved in the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT), commenting: "This is an important study because of the large number of patients and what it tells us about the impact of genomic research on patient care and clinical decisions in the community where the majority of patients are treated." In order to implement precision medicine within the oncology community and allowing it to reach a wider selection of patients, more detailed information on the use of tumour profiling to inform treatment decisions and the cost of analysing DNA samples is now required.

Treatment with Probiotics Reduces Chemotherapy-induced Diarrhoea

CHEMOTHERAPY-induced diarrhoea is a serious, but often under-reported, side effect as a result of current standard anticancer treatment. Chemotherapies can have a significant impact on the gut microbiome; however, the results of an Indian study, reported in a ESMO press release dated 21st October 2018, highlight the beneficial effects of probiotics on preventing diarrhoea.

"Chemotherapy-induced diarrhoea is an under-reported, unpleasant, and sometimes a serious side-effect of chemotherapy," explained study lead Prof Atul Sharma, All India Institute of Medical Sciences, New Dehli, India when outlining the reasoning for the investigation. A total of 291 participants (80% of which were male and aged around 46 years) were randomised into two groups. One hundred and forty-five of the patients received two probiotic sachets a day containing 900 billion colony forming units of four different bacterial strains: 4 strains of *Lactobacilli*, 3 strains of *Bifidobacteria*, and 1 strain of *Streptococcus thermophiles*. The control group (consisting of 146 patients) received 2 sachets of placebo a day. Treatment regimens commenced 14 days before the initiation of fluoropyrimidine and/or irinotecan-based chemotherapy and continued until 2 weeks after the third chemotherapy cycle.

The study did not meet the primary endpoint of reducing Grade 3 and 4 diarrhoea incidences, with 8.0% and 2.0% of participants receiving probiotics reporting Grade 3 and 4 diarrhoea compared with 4.1% and 0.0% in the control group, respectively. However, overall administration of probiotics was shown to decrease the incidence of diarrhoea with 199 incidences reported in the probiotic group compared with 220 in the placebo group. The use of probiotics was also shown to reduce the levels of inflammatory markers, such as vascular endothelial growth factor, clusterin, and faecal calprotectin, the clinical significance of which requires further investigation.

Prof Atul Sharma concluded: "Though it did not meet its primary endpoint in reducing incidence of Grade 3 and 4 diarrhoea, it helped to reduce the incidence of all grade of diarrhoea." The study again highlights the importance of a healthy gut microbiome and offers a potential solution to one of the most common adverse events as a result of chemotherapy.

"Though it did not meet its primary endpoint in reducing incidence of grade 3 and 4 diarrhoea, it helped to reduce the incidence of all grade of diarrhoea."

Congress Feature

Summary of the ESMO 2018 Presidential Symposia

During this year's ESMO Congress, the EMJ team attended the three hotly-anticipated Presidential Symposia chaired by ESMO President Prof Josep Tabernero. Here, we bring you our own summary of the groundbreaking findings presented during these sessions, encompassing late-breaking data from studies of advanced cancer subtypes, such as breast, prostate, ovarian, and oropharyngeal cancer.

Presidential Symposium 1

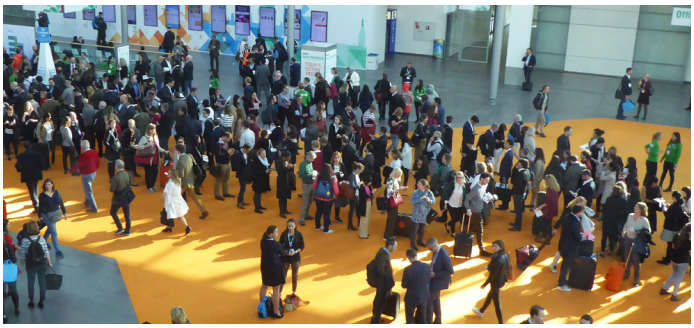
Saturday 20th October 2018

Assisted by co-chair Prof Andrés Cervantes, Prof Tabernero announced the opening of ESMO 2018's first Presidential Symposium, which began with a discussion of the practice-changing data from the IMpassion130 trial,[1] the first positive Phase III study of first-line immunotherapy treatment for metastatic triple-negative breast cancer (TNBC). This randomised, double-blind trial investigated atezolizumab in combination with nab-paclitaxel versus placebo with nab-paclitaxel in 902 treatment-naïve TNBC patients, a patient subset that commonly experiences poor outcomes compared to patients with other breast cancer subtypes. With known efficacy in multiple cancers, the anti-programmed death ligand-1 (PD-L1) antibody atezolizumab with the addition of chemotherapy to enhance anti-tumour activity showed a statistically significant progression-free survival (PFS) benefit and improved overall survival (OS) in a PD-L1+ TNBC population. No negative effects were observed in the PD-L1- population and the combination treatment was well tolerated, establishing atezolizumab with nab-paclitaxel as a new standard of care for this difficult-to-treat patient population. "Impassion130 brings breast cancer into the immunotherapy arena," concluded discussant Prof Giuseppe Curigliano, European Institute of Oncology, Milan, Italy. Turn to the Congress Review section for a more detailed discussion of these results.

With breast cancer being the leading cause of cancer-related death in women,[2] the three remaining studies of this session focussed on advanced breast cancer patients, who represent a population in need of new, more effective treatments. The first of the studies presented during this session, and also summarised in the Congress Review section, was the first mature OS analysis from the PALOMA-3 Phase II study,[3] which investigated cyclin dependent kinases (CDK)4/6 inhibitor palbociclib in combination with fulvestrant for women with *HR+ HER2-* advanced breast cancer. By performing an OS

analysis in 521 randomised patients with a median follow-up of 44.8 months, a clinically meaningful improvement in OS was shown with the combination treatment, while the difference in PFS gain was also maintained. With such positive results for this patient population, a discussion around the guidelines for the treatment of advanced breast cancer patients was noted as necessary, and discussants suggested that a meta-analysis of all CDK4/6 inhibitor trials is warranted to investigate their efficacy in this cancer subtype.

Supplementing these results was the presentation of the SOLAR-1 study,[4] which is the first study of precision medicine in metastatic breast cancer. After positive preliminary evidence of clinical activity of PI3K inhibitor alpelisib in combination with fulvestrant, this Phase III, randomised, controlled trial demonstrated a significant PFS benefit with alpelisib compared to placebo in 341 *HR+ HER2- PIK3CA+* advanced breast cancer patients. Additionally, the tolerability profile of the alpelisib-fulvestrant combination was good and the majority of adverse events were of severity Grade 1/2, including hyperglycaemia, diarrhoea, and rash. The final investigation presented during the Saturday session involved post-menopausal *HR+ HER2-* advanced breast cancer patients who were treated with a histone deacetylase inhibitor in combination with an endocrine blockade.[5] Patients who received chidamide, currently approved for peripheral T cell lymphoma, with exemestane had a significant improvement in PFS versus the placebo group (7.4 months versus 3.8 months; hazard ratio: 0.755). With manageable adverse effects, most commonly haematological, chidamide is the first oral histone deacetylase to show such positive effects when combined with an aromatase inhibitor in *HR+* breast cancer, and these findings will prompt further research into this method of targeting malignant breast tissue.



Commenting on the implications of the novel data revealed during the first Presidential Symposium, Prof Curigliano stated: "These studies are providing us with the answers we need to more effectively treat the advanced stages of the disease across subtypes."

Presidential Symposium 2

Sunday 21st October 2018

During his second Presidential Symposia of ESMO 2018, Prof Tabernero, joined by co-chair Prof Fortunato Ciardiello, welcomed attendees to the reveal yet more promising data from recent oncology trials, including new insights into the management of prostate cancer. Presented by Mr Alex Hoyle, the first trial of this session explored the hypothesis that low-risk metastatic hormone-sensitive prostate cancer patients benefit from combined treatment of abiraterone acetate, prednisolone, and androgen deprivation therapy (ADT). Retrospective stratification of patients from the ongoing multi-arm randomised controlled STAMPEDE trial,[6] which assessed novel approaches for the treatment of men with prostate cancer who are starting long-term ADT for the first time, was performed, classifying patients into high or low-risk or volume metastatic disease. The results showed that the combination therapy improved all survival endpoints, highlighting the applicability of this treatment strategy for all metastatic hormone-sensitive prostate cancer patients regardless of their risk and/or volume classification. Supplementing these findings were more data from the STAMPEDE trial, this time focussing on the role of radiotherapy for patients with newly diagnosed metastatic disease.[7] Compared to standard care alone (lifelong ADT) and with no association with the extent of metastases, radiotherapy plus standard care improved failure-free survival (Hazard ratio: 0.68; 95% confidence interval [CI]: 068–0.84) in a comparison involving 2,061 patients. The researchers also noted an improvement in OS of patients with oligometastatic disease, supporting the role for localised radiotherapy in newly diagnosed metastatic prostate cancer patients with a low metastatic burden.

Reflecting on the ever-increasing role of immunotherapy in shifting the focus of cancer treatments, the next late-breaking trial revealed to the audience was the Phase III JAVELIN Renal 101 trial,[8] a randomised trial of combined axitinib and avelumab for advanced renal cell carcinoma. Out of a total of 886 kidney cancer patients, 442 were administered the immune checkpoint blocker avelumab in combination with axitinib, while 444 patients received sunitinib. Results of the trial showed significant improvements in PFS in the combination arm compared to the sunitinib arm (13.8 months versus 8.4 months), irrespective of the patient PD-L1 expression, as well as higher overall response rates (55.2 versus 25.5). As the first results to show positive outcomes from combining an immune checkpoint blocker with a tyrosine kinase inhibitor for the treatment of advanced renal cell carcinoma, this combination therapy may have potential to improve the poor outlook for these patients.

The Sunday session drew to a close with the final presentation, evaluating the use of a PARP inhibitor as maintenance therapy after first-line chemotherapy in ovarian cancer patients. The SOLO1 trial[9] is a Phase II trial investigating olaparib treatment in 391 newly diagnosed *BRCA*-mutated patients with advanced ovarian cancer. After follow-up of 41 months, a statistically significant and clinically meaningful improvement in PFS was shown compared to placebo, meeting the study's primary endpoint: olaparib reduced the risk of progression or death by 70% compared to placebo. Currently approved as a maintenance therapy for platinum-sensitive relapsed ovarian cancer patients and for *BRCA*-mutated patients after ≥3 prior lines of chemotherapy, these unprecedented results suggest earlier use of olaparib may be beneficial in select ovarian cancer patients, with few concerns of adverse effects or changes in health-related quality of life. More details of the JAVELIN Renal 101 trial and the SOLO1 trial are available within the Congress Review section.

Presidential Symposium 3

Monday 22nd October 2018

During his final Presidential Symposia of ESMO 2018, Prof Tabernero was joined by Prof Solange Peters, ESMO Scientific Committee Chair, to chair discussions around the remaining three late-breaking trials to be revealed at the event. Continuing the theme of improving the management of advanced-stage cancers, results from the KEYNOTE-048 study[10] were described. The open-label, randomised Phase III study investigated first-line pembrolizumab for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). After randomisation of 882 patients to 200 mg pembrolizumab, pembrolizumab plus chemotherapy, or the standard EXTREME regimen, OS was significantly improved for certain patients. Specifically, OS increased in the PD-L1 combined positive score ≥20 and ≥1 populations after treatment with pembrolizumab compared to EXTREME regimen, while when chemotherapy was added, OS improved in the total population. These novel results support the use of the immune checkpoint inhibitor pembrolizumab and pembrolizumab plus chemotherapy as first-line standards of care for recurrent or metastatic HNSCC patients who are not curable by local therapy.

Next were new insights into the treatment of patients with human papilloma virus (HPV)-positive throat cancer, who are now believed to benefit more from chemoradiotherapy than cetuximab with radiotherapy. Results from this late-breaking trial, which compared side effects and survival outcomes of these two treatments in 334 HPV-positive throat cancer patients, showed that cisplatin was associated with significantly higher 2-year OS rates (97.5%) compared with cetuximab (89.4%).[11] Cancer recurrence rates were also lower in patients treated with cisplatin (16.1% versus 6.0%) and there were no differences in the total number of side effects or toxic events. The researchers concluded that the combination of cisplatin and radiotherapy gives a great benefit in terms of survival in these select patients and, therefore, should be the first treatment option considered. The next steps will involve genotyping patients to determine who will benefit most from this treatment.

Drawing the 2018 Presidential Symposia to a close was the ALESIA trial,[12] a randomised, multicentre, Phase III open-label study of alectinib versus crizotinib in Asian patients with treatment-naïve anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (NSCLC). The investigation recruited 187 participants from 21 sites and randomised them to receive 250 mg crizotinib twice daily or 600 mg alectinib twice daily. After approximately 15 months follow-up, investigator-assessed median PFS was 11.1 months in the crizotinib group but unreached in the alectinib group, remaining consistent when adjusted for age, sex, and smoking status. Additionally, with a more promising safety profile compared to crizotinib (adverse events occurring in 28.8% and 48.8%, respectively), the researchers concluded that ALESIA confirmed the systemic and intracranial efficacy of alectinib over crizotinib for the treatment of anaplastic lymphoma kinase-positive advanced NSCLC Asian patients, consistent with results of the global ALEX study.[13]

From attending these sessions and learning more about the very latest and ongoing research of advanced cancer therapeutics, it is clear that oncology remains as fast-paced as ever. With new insights revealed every day, patient care will continue to be enhanced, leading to better outcomes and prognosis for many. We are sure you will join us in eagerly awaiting the presentation of exciting new results from the coming year at the ESMO 2019 Congress in Barcelona, Spain, moving us one step closer to achieving guaranteed remission of cancer.

References

1. Schmid et al. Atezolizumab and neb-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018. [Epub ahead of print].
2. Bray F et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018. [Epub ahead of print].
3. Turner NC et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med. 2018. [Epub ahead of print].
4. Novartis Pharmaceuticals. Study assessing the efficacy and safety of alpelisib plus fulvestrant in men and postmenopausal women with advanced breast cancer which progressed on or after aromatase inhibitor treatment. (SOLAR-1). NCT02437318. https://clinicaltrials.gov/ct2/show/NCT02437318.
5. Chipscreen Biosciences Ltd. Trial of chidamide in combination with exemestane in patients with advanced breast cancer. NCT02482753. https://clinicaltrials.gov/ct2/show/NCT02482753.
6. Medical Research Council. Systemic therapy in advancing or metastatic prostate cancer: evaluation of drug efficacy (STAMPEDE). NCT00268476. https://clinicaltrials.gov/ct2/show/NCT00268476.
7. Parker CC et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): A randomised controlled Phase 3 trial. Lancet. 2018. [Epub ahead of print].
8. Choueiri TK et al. Avelumab plus axitinib vs sunitinib as first-line treatment of advanced renal cell carcinoma: Phase 3 study (JAVELIN Renal 101). J Clin Oncol. 2017;35(Suppl 15).
9. AstraZeneca. Olaparib maintenance monotherapy in patients with BRCA mutated ovarian cancer following first line platinum-based chemotherapy. (SOLO-1). NCT01844986. https://clinicaltrials.gov/ct2/show/NCT01844986.
10. Merck Sharp & Dohme Corp. A study of pembrolizumab (MK-3475) for first line treatment of recurrent or metastatic squamous cell cancer of the head and neck (MK-3475-048/KEYNOTE-048). NCT02358031. https://clinicaltrials.gov/ct2/show/NCT02358031.
11. Mehanna K et al. Cetuximab versus cisplatin in patients with HPV-positive, low risk oropharyngeal cancer, receiving radical radiotherapy. Ann Oncol. 2018; 29(Suppl 8).
12. Hoffmann-La Roche. A study to evaluate and compare the efficacy and safety of alectinib versus crizotinib and to evaluate the pharmacokinetics of alectinib in asian participants with treatment-naive anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). NCT02838420. https://clinicaltrials.gov/ct2/show/NCT02838420.
13. Hoffman-La Roche. A study comparing alectinib with crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non-small cell lung cancer participants (ALEX). NCT02075840. https://clinicaltrials.gov/ct2/show/NCT02075840.

Buyer's Guide

- 10X GENOMICS
- ABBVIE, INC.
- ACCELL CLINICAL RESEARCH LLC
- ACCORD HEALTHCARE, LTD.
- ADVANCED ACCELERATOR APPLICATIONS, A NOVARTIS COMPANY
- ALMAC DIAGNOSTICS
- AMGEN
- AMOY DIAGNOSTICS CO., LTD.
- APTITUDE HEALTH
- APTUS HEALTH, INC.
- ARCHERDX
- AROG PHARMACEUTICALS, INC.
- ASTELLAS PHARMA EUROPE EMEA, LTD.
- ASTRAZENECA
- BAXTER INTERNATIONAL, INC.
- BAYER AG
- BBMRI-ERIC
- BEACON MEDICARE, LTD.
- BEIGENE, LTD.
- BIOCARTIS
- BIOCLINICA
- BIOCYTOGEN BOSTON CORPORATION
- BIOMAPAS
- BIOPTICON CORPORATION
- BIO-RAD LABORATORIES GMBH
- BIOTYPE DIAGNOSTIC GMBH
- BOEHRINGER INGELHEIM INTERNATIONAL GMBH
- BRISTOL-MYERS SQUIBB
- CALITHERA BIOSCIENCES
- CARIS LIFE SCIENCES
- CATALYSIS SL
- CELGENE
- CELLDEX THERAPEUTICS
- CELLTRION HEALTHCARE CO., LTD.
- CENTRE LEON BERARD
- CEPHEID, INC.
- CLINICAL RESEARCH MALAYSIA (CRM)
- CLOVIS ONCOLOGY
- CMED
- COVANCE/CHILTERN
- DAIICHI SANKYO ONCOLOGY EUROPE GMBH
- DAVA ONCOLOGY
- DEFINIENS AG
- DELCATH SYSTEMS, INC.
- DIGNITANA
- DR. REDDY'S LABORATORIES, LTD.
- ECS SCREENING
- ELI LILLY AND COMPANY
- ERYTECH PHARMA
- EUROFINS BIOMNIS
- EUROPITAL BVBA
- EUSA PHARMA
- EXELIXIS
- F. HOFFMANN-LA ROCHE AG
- FRESENIUS KABI
- GEDEON RICHTER, PLC.
- GENEXPLAIN GMBH
- GENMAB
- GENOMIC HEALTH, INC.
- GILEAD SCIENCES, INC.
- GLAXOSMITHKLINE
- HALIODX SAS
- HALOZYME, INC.
- HEALTHCARE X.0 GMBH
- HELSINN HEALTHCARE SA
- HTG MOLECULAR DIAGNOSTICS, INC.
- IBM WATSON HEALTH
- ICE COLD MOUTHPIECE
- IMAGINAB, INC.
- IMMUNOMEDICS, INC.
- INCYTE BIOSCIENCES INTERNATIONAL SARL
- INVIVOSCRIBE TECHNOLOGIES, INC.
- IOVANCE BIOTHERAPEUTICS
- IPSEN
- IQVIA
- ITM ISOTOPEN TECHNOLOGIEN MÜNCHEN AG

- JANSSEN PHARMACEUTICAL, INC.
- LOXO ONCOLOGY, INC.
- M3 GLOBAL RESEARCH
- MACROGENICS, INC.
- MEDAC PHARMA
- MEDIAN TECHNOLOGIES
- MEDIFOOD
- MEDSCAPE ONCOLOGY
- MERCK AND CO.
- MGZ - MEDICAL GENETICS CENTER
- MOLECULAR HEALTH GMBH
- MYLAN
- MYRIAD GENETICS
- NANOSTRING TECHNOLOGIES
- NEOGENOMICS, INC.
- NOONA HEALTHCARE OY
- NOVARTIS ONCOLOGY
- NOVELLA CLINICAL LLC
- NOVOSANIS NV
- NUTRICIA ADVANCED MEDICAL NUTRITION
- OMNICARE HOLDING GMBH & CO. KG
- ONCARE GMBH
- ONCLIVE®
- ONCODNA
- ONCOMPASS MEDICINE HUNGARY KFT
- PAXMAN
- PAXXO AB
- PFIZER ONCOLOGY
- PHARMADAB DOO
- PHARMAMAR SA
- PHILIPS MOLECULAR
- PIERRE FABRE
- PIVOTAL SOFTWARE
- PRECISION FOR MEDICINE, ONCOLOGY AND RARE DISEASE
- PRIME ONCOLOGY
- PUMA BIOTECHNOLOGY
- RAKUTEN ASPYRIAN, INC.
- SANDOZ
- SANOFI GENZYME
- SEATTLE GENETICS
- SERACARE LIFE SCIENCES, INC.
- SERVIER
- SIVAN INNOVATION, LTD.
- SOPHIA GENETICS
- SOTIO AS
- STEMLINE THERAPEUTICS, INC.
- STILLA TECHNOLOGIES
- SYNEOS HEALTH
- SYSMEX INOSTICS/SYSMEX EUROPE GMBH
- TAKEDA ONCOLOGY
- TESARO, INC.
- TEVARIS GMBH
- THERMO FISHER SCIENTIFIC
- TRIO-TRANSLATIONAL RESEARCH IN ONCOLOGY
- ULTIVUE, INC.
- VARIAN MEDICAL SYSTEMS

VIEW CONGRESS REVIEW ←

Interview

In this edition's Editorial Board interviews, Dr Fausto Roila discusses his career, research, and advice for young oncologists

Dr Fausto Roila

S. M. della Misericordia Hospital, Italy

Firstly, what inspired you to become a doctor and, more specifically, to specialise in oncology and cancer therapeutics?

In 1979, I graduated in medicine and surgery at the University of Perugia, Perugia, Italy. At the time, I was a volunteer in the internal medicine department of the Perugia hospital where, day-by-day, I tried to acquire skills with the hope of being able to work as a general practitioner in the future. In the meantime, I was given the possibility to spend 6 months of training in medical oncology. I was persuaded by my tutor to take on this experience with the possibility of going back if I was not comfortable. I found the impact of working with cancer patients really traumatic and the thing that shocked me the most was that the patients underwent chemotherapy treatments that induced a lot of nausea and vomiting not controlled by any drug (barbiturates were administered to make the patient sleep) and this was considered inevitable. Therefore, I began to take care of supportive therapy and the prevention of chemotherapy-induced nausea and vomiting.

"I spend my working days in the front-line, helping my collaborators to make difficult decisions, doing the inpatient visit at least three times a week....and participating in two multidisciplinary groups."

You are the director of medical oncology at S. M. della Misericordia Hospital, Perugia, Italy, and specialise in supportive care. What does your day-to-day routine consist of?

In addition to co-ordinating the work of 15 medical oncologists and endeavouring to better organise the assistance and treatment of

cancer patients, I spend my working days at the front-line, helping my collaborators to make difficult decisions, doing the inpatient visit at least three times a week (we have 22 dedicated beds), and participating in two multidisciplinary groups (one on urological cancer and one on lung cancer). Research remains an important part of my work. We have numerous clinical trials that sometimes offer one more treatment possibility to our patients and I am trying, with increasing difficulty (scarcity of funds and the difficulties associated with a large bureaucracy), to plan independent research on supportive therapies.

Supportive care for cancer patients must cover a broad spectrum of adverse effects as a result of the malignancy and the therapeutics used to treat the patients. Regarding supportive care, please could you describe your role within patient treatment and recovery?

Oncologists involved in supportive care have the task of improving the quality of life of cancer patients by reducing and sometimes controlling the symptoms of the tumour and the side effects of anticancer therapies. This is only possible if the oncologist considers it essential that the prolongation of survival should be associated with a good quality of life; i.e., with or without minimal nausea and vomiting, fatigue, infections, and other adverse effects.

What is your opinion on the use of cannabinoids in supportive care? Do you think there should be legislative changes regarding the use of this category of drug?

Absolutely not, at least not for cancer patients. In fact, there are literature reviews showing that cannabinoids did not add anything to the drugs already available to control pain (cannabinoids have a similar efficacy to codeine, which is clearly inferior to morphine for pain control) or in regard to nausea and vomiting (cannabinoids have similar efficacy to the high doses of metoclopramide that were used in the '80s) and are not at all effective in controlling anorexia. The cannabinoids require more and more research to demonstrate if they have an added value compared to what we already have. Therefore, lacking these data, cannabinoids are an incorrect way to control symptoms.

"The cannabinoids require more and more research to demonstrate if they have an added value compared to what we already have. Therefore, lacking these data, cannabinoids are an incorrect way to control symptoms."

Hair loss as a result of chemotherapy is a common adverse effect, what are your strategies to prevent this therapy-related alopecia?

Unfortunately, regardless of U.S. Food and Drug Administration (FDA) approvals, there is no truly effective treatment in the prevention of chemotherapy-induced alopecia. Also, scalp refrigeration started before chemotherapy administration and continued for about 90 minutes after the end of treatment has obtained poor results. In fact, the treatment response criteria used in these studies are unfortunately misleading: a fall of <50% of the hair present on the scalp (grade 1 toxicity) is considered a positive response. Obviously, if a patient loses 20–30% of their hair the result is not so aesthetically satisfying for the patient. In the case of the prevention of anthracyclines-induced alopecia, the drugs used as adjuvant treatment in breast cancer, the response rate considering the above criteria is only 16%.

You have recently published the paper titled: "Conflict of interest among Italian medical oncologists: A national survey." What were the main findings from this study, and how do these affect medical oncologists in the future?

The Italian College of Medical Oncology Chiefs (CIPOMO) promoted the survey on the conflict of interest among Italian oncologists because unfortunately in our country (as well as in other countries) we do not talk so much about

this problem. Therefore, CIPOMO is considered important to establish what is the perception of oncologists on the conflict of interest. This increasingly affects every field of medicine, from care of patients to physician's training, from clinical research to the formulation of guidelines, from regulatory agencies which approve drugs to the associations of doctors and patients and to the scientific journals. The survey shows that 62% of the 321 oncologists who replied to the questionnaire said they had received payment from the pharmaceutical industry in the last 3 years. Two of the most worrying aspects related to conflicts of interest are that the training of doctors is almost completely delegated to the pharmaceutical industry and the problem of the authorship of clinical research published in an international journal. The ghost writer, paid by the industry to write scientific work, does not sign the paper, while the guest authors sign the paper as real authors even if they did not write the research protocol and did not participate in the data collection, elaboration, and interpretation. The result is that the doctors chosen by the industry increase their reputation; the industry will therefore decide the future top figures in the medical field.

"Two of the most worrying aspects related to conflicts of interest are that the training of doctors is almost completely delegated to the pharmaceutical industry and the problem of the authorship of clinical research published in an international journal."

In September 2018 the BBC journalist, Rachael Bland, died as a result of her cancer. Rachael had become a potent voice discussing her cancer in her podcast titled "You, Me and the Big C". How important do you feel more open and frank discussions about cancer, diagnostics, therapeutics, and death are to the field of oncology?

I consider Rachael's contributions very important in understanding the different problems related to cancer diagnosis and treatment, and I hope that more and more people can help us with the diffusion of the important messages concerning risk factors of cancer and its prevention, diagnosis, and therapeutic approach, including not only the advances in curative therapies but also supportive and palliative therapies.

"The participation of doctors at conferences is very important not only for the scientific aspects but also because an interaction with various experts is possible."

How important do you feel attending congresses, both large and small, is to personal development and the progression of the field?

The participation of doctors at conferences is very important not only for the scientific aspects but also because an interaction with various experts is possible. However, there are some limitations: regarding the conferences of the international associations such as the American Society of Clinical Oncology (ASCO), the contemporaneity of many sessions allows participants to be present at only a few. Furthermore, the pharmaceutical industry's stands often appear to be designed more to market their products than provide correct information on new drugs, which is frustrating. Regarding small conventions, the advantage is that all the sessions are consecutive and therefore all can be attended. However, often the topics chosen by the organisers are strongly conditioned by the pharmaceutical industry that supports them. It is time for public institutions to organise conferences in which independent speakers take stock of the role and value of new drugs.

If you were in charge of organising the European Society for Medical Oncology 2019 Congress, what would you place at the heart of the event? How would you ensure that all attendees, both young and old, could get the most out of the meeting?

The answer to this question is not simple. In any case, I think that the most important problem in medical oncology is the control of the excessive costs of new cancer drugs. These costs are exaggerated because about 70% of new drugs are approved based on surrogate endpoints, which are often not real endpoints. Therefore, their added value compared to the alternatives available has not been defined. Furthermore, the confirmatory studies that the regulatory agencies require to be quickly carried out have not been reported even after several years. Another big issue is the affordability; this could be solved only if all national health systems collaborated to face this problem.

Finally, if you could give one piece of advice to upcoming oncologists, what would it be?

The simplest advice I can give to young oncologists is to learn how to read the results of clinical studies, including the impact on quality of life for those taking the new treatments and the pharmacoeconomic analyses published in the literature; only an intellectual independence can allow us to effectively understand the real value of the new drugs in terms of clinical and economical benefit (increase in survival, quality of life, and cost effectiveness) so that the national health services can afford it.

"The simplest advice I can give to young oncologists is to learn how to read the results of clinical studies, including the impact on quality of life for those taking the new treatments and the pharmacoeconomic analyses published in the literature..."

VIEW MORE INTERVIEWS ONLINE ←

The Right Therapy Starts with the Right Test: Novel Therapeutic Approaches in Oncology Foster the Need for an Appropriate Molecular Profiling Strategy

An Update from the European Society for Medical Oncology (ESMO) Congress 2018

Speakers: Luca Quagliata

Clinical Sequencing and Oncology Division, Thermo Fisher Scientific, Waltham, Massachusetts, USA

Disclosure: Luca Quagliata is an employee of Thermo Fisher Scientific. He has declared no further conflicts of interest.

Acknowledgements: Dr Quagliata collected this information at the ESMO Congress 2018 and acknowledges the support of Thermo Fisher Scientific Clinical Sequencing Division Team during the event.

Support: The writing and publication of this article were supported by Thermo Fisher Scientific.

Citation: EMJ Oncol. 2018;6[1]:42-48.

Meeting Summary

Adding a molecular perspective to the traditional multidisciplinary management of cancer patients is substantially hampering the adoption of precision therapy. Indeed, at this year's European Society for Medical Oncology (ESMO) Congress in Munich, Germany, gathering >28,000 healthcare professionals spanning a range of disciplines, fields, and stakeholder groups, and >500 invited speakers, much attention focussed on discussing how to facilitate the integration of molecular data in the clinical management of cancer patients.

INTRODUCTION

A number of novel treatment options, either in the form of new agents or updated therapeutic strategies, with sequential drug exposure and dosage adjustments, were presented and debated during the event. Furthermore, along with the novelties in the drug space, the scene was equally occupied by the companion diagnostic compartment, with a substantial number of dedicated workshops, satellite events, and new product launches. Three critical factors have emerged as necessary for any meaningful molecular diagnostic approach to impact patient outcomes through clinical actionability.

Tumour Tissue Requirements

The need for minimal tissue sample starting material should be a basic requirement for any test to be broadly introduced into routine clinical practice. Low input means, for example, being able to assess genomic variants from small needle biopsy and cytological specimens. This is commonly used for non-small cell lung carcinoma (NSCLC) diagnosis and will eventually lead to more patients with actionable results.

Testing Turnaround Times

Complete biomarker results should be available within days rather than weeks. Indeed, many European institutions have started to build in-house sequencing facilities to reduce the time to obtain final results; this allows clinicians to start treating patients more quickly, aiming to achieve diagnosis and treatment initiation within days (Figure 1). Conversely, also hampered by logistical issues, the institutions that outsource tests can take weeks to deliver data,[1,2] a timeframe that is no longer acceptable, especially in cases such as late-stage NSCLC. In addition, when the number of samples to be tested reaches substantial proportions, the outsourcing testing strategy can result in increased pressure on the healthcare system due to third-party margins along with shipment fees, leading to higher overall costs regardless of the payer.[3]

Adequate Biomarker Coverage

Testing should include updated relevant biomarkers based on current knowledge and ongoing late-phase clinical trials. In fact, while offering a single, very large panel testing for hundreds of genes, of which many currently hold limited or no clinical actionability, biomarkers covering a plethora of genomic variants for many cancer types might be a very attractive research-oriented solution; a dedicated test covering clinically relevant genes is a more pragmatic and cost-effective approach.

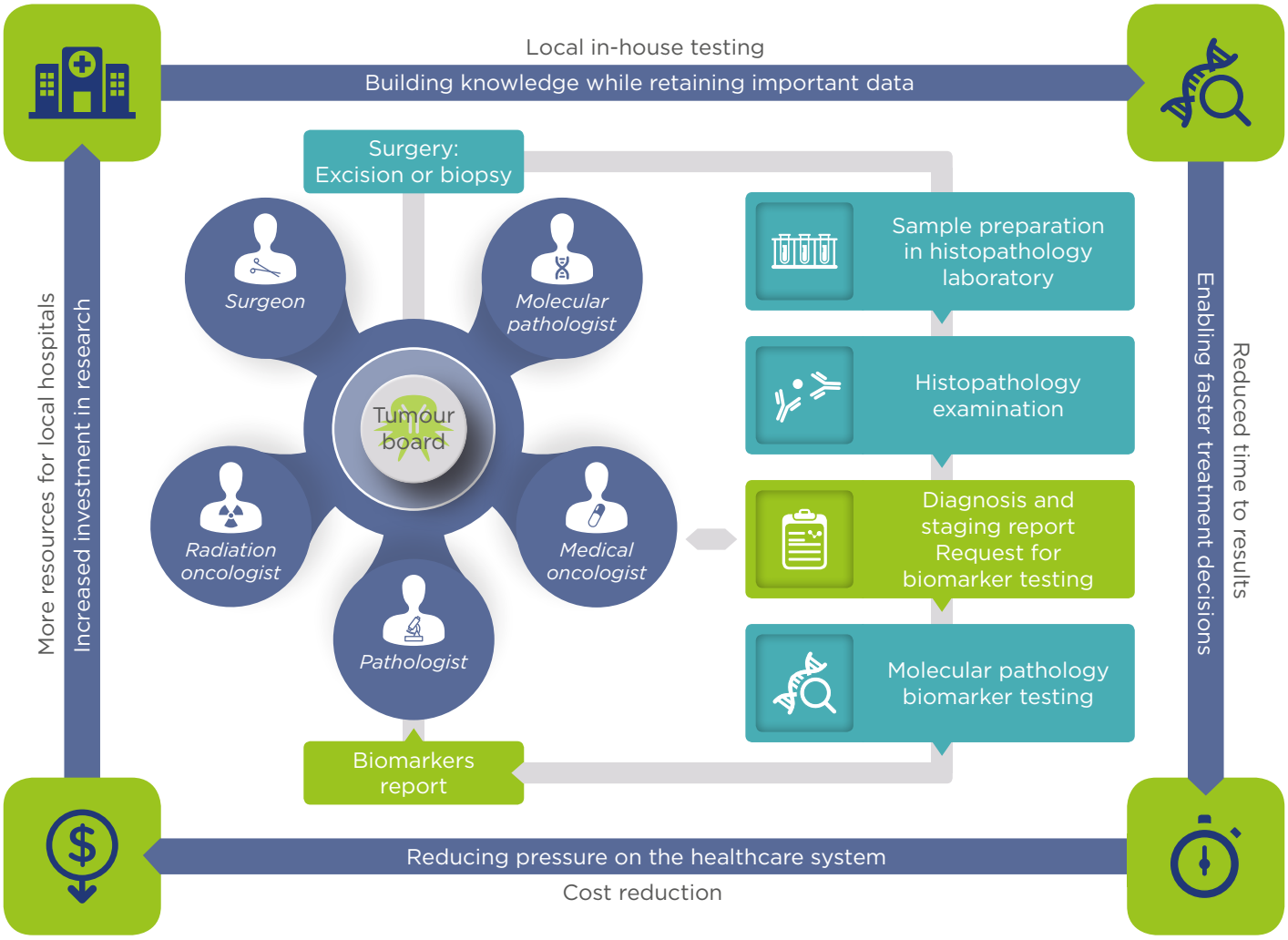


Figure 1: In-house testing and its associated benefits.

A model to fit molecular tumour boards and foster local interactions among healthcare professionals, generating and retaining both knowledge and precious data.

Furthermore, in 46–80% of patient cases, the starting material is too minimal for large panel analysis.[2,4] In some cases, this testing approach may require a rebiopsy, which comes with associated risks, elevated costs, and treatment delays or, when not applicable, can lead to suboptimal therapy selection.

While in the early years of biomarker testing outsourcing was a logical choice due to technical and investment constraints, nowadays outsourcing is largely reduced due to the fast development of sequencing technologies and the dramatic reduction in the cost of in-house biomarker testing. Therefore, sending to third-party labs is now a non-sustainable long-term approach.

Finally, given that precision oncology is a medical practice deployed at the local level, at the patient's bedside, and mostly via interactions between local healthcare professionals, in-house molecular profiling is the best fit to this model. In many of the ESMO-hosted discussions, it was clear that the flexibility to triage patient samples and to discuss in depth the findings at local tumour boards is key to providing optimal, truly personalised care.

NOVEL OPPORTUNITIES FOR LUNG TUMOUR TREATMENT AND TESTING

Targeted agents, such as the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors gefitinib, erlotinib, afatinib, and osimertinib, have considerably transformed the management of patients with EGFR-mutated NSCLC, representing one of the most significant advances in lung tumour treatment for decades. The introduction of these agents into clinical practice has been developed along with the advances made in the molecular pathology field and the broad adoption of next-generation sequencing (NGS), allowing a robust and sensitive evaluation of EGFR status.

Furthermore, the recent success of immunotherapy in the metastatic NSCLC setting (independent from the EGFR status) has revolutionised the entire treatment scenario. Nonetheless, >50% of treated patients show no clear evidence of responding to immune checkpoint-blocking (ICB) therapies, underlining the need to develop new, robust predictive biomarkers that should appropriately guide the selection of ICB agents.[5] Programmed death-ligand 1 (PD-L1) expression, assessed by immunohistochemistry (IHC), has emerged as a predictive marker for the use of ICB agents in NSCLC.[6] However, despite currently being the most commonly used biomarker in the immune oncology space, the analysis of PD-L1 by IHC comes with several significant challenges, including variability in preanalytical conditions, the use of different antibodies along with different staining platforms, the lack of an unequivocal type of scoring system, the typical IHC interobserver variability, and the issue of intrinsic tumour heterogeneity.[5,6] Additionally, it is currently acknowledged that some patients with low or no PD-L1 expression may still benefit from checkpoint inhibition. Recently, the tumour cell mutational burden (TMB) status has been correlated with distinct degrees of clinical benefits in ICB-treated patients with various tumour types, including NSCLC.[6] High mutational load/burden is commonly defined as ≥100 non-synonymous single nucleotide variants per genome as identified via whole-exome sequencing;[7] however, this threshold can greatly vary between tumour types.[7] Thus, major challenges remain to improve the robustness of TMB and eventually introduce it into routine diagnostics. Among these challenges, the definition of the optimal tumour purity, the minimal sequencing depth, and the need to identify an appropriate threshold for defining high and low mutational burden for different tumour types are key.[5,7] In summary, while PD-L1 expression and TMB value may aid the identification of ICB responders, they identify distinct subclasses of patients and are not a clear dichotomous set of biomarkers.[8-10] Outcomes from ESMO 2018 highlighted the need to further expand our understanding behind response to ICB, for example, focussing on the activity of tumour-infiltrating T cells through T cell receptor characterisation via sequencing.

Hampered by compelling evidence in the metastatic setting, accumulating data from preclinical investigations and retrospective studies of human lung cancer samples have been discussed, suggesting the presence of an immunosuppressive microenvironment in the early stage of the disease. This serves as another

indicator of the importance of investigating the role of T cells via repertoire analysis and an important reason to thoroughly investigate the role of T cells and T cell receptors. In fact, immunotherapy is now also studied in non-metastatic NSCLC.[11] Trials of checkpoint inhibitors have recently been completed (or are currently ongoing) in early-stage resectable NSCLC in different settings (neoadjuvant, combined neoadjuvant, and adjuvant therapy) and in various combinations with standard of care modalities. For example, very encouraging results have been reported in the PACIFIC trial,[12] wherein progression-free survival (PFS) was significantly longer with durvalumab versus placebo after chemoradiotherapy in Stage III NSCLC. This is an important development for immunotherapy, given that 30–60% of patients with Stage I–III NSCLC will ultimately develop post-resection metastases.[11]

Another important option for lung cancer treatment, largely discussed at this year's ESMO Congress, relies on agents targeting genomic fusion products. For instance, ALK and ROS1 rearrangements define an important molecular subgroup (3–5% of cases) in advanced NSCLC, with major clinical implications. Now that alectinib has replaced the first-in-class ALK/ROS1/MET inhibitor (crizotinib) as the standard first-line therapy for ALK-positive advanced NSCLC,[13] it is becoming clear that, after initial response to treatment, resistance develops and patients invariably progress. While other potent ALK inhibitors and brain-penetrable compounds have been approved, including brigatinib, ceritinib, and lorlatinib, questions remain concerning the optimisation of treatment sequencing strategies to prevent or reduce resistance. To this end, performing highly sensitive molecular profiling, allowing the detection of new rising genomic alterations and eventually impairing clinical response, will support the development of these novel treatment schemes.

Furthermore, tyrosine receptor kinase (TRK) fusion agents took to the stage at this year's ESMO Congress. A genomic rearrangement known as TRK fusion occurs when a member of the neurotrophic tyrosine receptor kinase (*NTRK*) gene family fuses with another unrelated gene, producing an altered tropomyosin receptor kinase (Trk) protein.[14] This novel protein product is permanently activated (i.e., uncontrolled kinase function), triggering a constant oncogenic signal cascade, which becomes the primary driver of tumour cell growth in patients with TRK fusion-positive cancer. *NTRK1/2/3* gene fusions occur in various adult and paediatric solid tumours with varying prevalence, including appendiceal cancer, cholangiocarcinoma, colorectal cancer, gastrointestinal stromal tumours, infantile fibrosarcoma, lung cancer, mammary analogue secretory carcinoma of the salivary gland, melanoma, pancreatic cancer, thyroid cancer, and various sarcomas.[15] Only sensitive and specific tests can reliably detect TRK fusion-positive events. The ESMO Precision Medicine Working Group has released specific suggestions[16] that recommend RNA-based NGS testing as the preferred method to investigate genomic alterations such as gene fusions. Fluorescence *in situ* hybridisation can also be used to test for TRK fusion cancer, while IHC can detect the presence of the Trk protein. However, both approaches substantially lack sensitivity and specificity, thus leading to suboptimal patient selection.

Among the presented new agents, entrectinib is a central nervous system-active potent inhibitor of all Trk proteins, as well as ROS1 and ALK.[17] Prof Demetri, Boston, Massachusetts, USA, presented an integrated efficacy and safety analysis from three Phase I/II clinical trials using entrectinib: ALKA,[18] STARTRK-1,[19] and STARTRK-2.[20] Data show that treatment with entrectinib induced responses that were durable in >50% of treated patients. Notably, entrectinib is well tolerated with limited side effects and induces clinically meaningful systemic responses across tumours with a variety of histologies and in patients with and without central nervous system disease. This represents an advance in precision medicine, with entrectinib offering benefits for *NTRK*-fusion-positive patients as a tumour agnostic targeted therapy. Based on these results, screening patients for *NTRK* gene fusions in solid tumours should be actively considered.

NEW OPPORTUNITIES IN OVARIAN AND BREAST CANCERS: THE NEED FOR *BRCA* TESTING

During the ESMO Congress, the first Phase III study of a poly (ADP-ribose) polymerase inhibitor as maintenance therapy after first-line chemotherapy for ovarian cancer positive findings were reported. In the SOLO1 trial[21] of olaparib in patients with *BRCA*-mutated advanced ovarian cancer, the primary endpoint (investigator-assessed PFS) was successfully met, with a statistically significant and clinically meaningful improvement compared to placebo. At a median follow-up of 41 months, maintenance olaparib reduced the risk of disease progression or death by 70% compared to placebo. These unmatched findings were reinforced by a significant improvement in median time to first subsequent therapy or death (51.8 months for olaparib versus 15.1 months for placebo). Notably, adverse events were mostly low grade, while health-related quality of life scores did not change from baseline following olaparib exposure. These data suggest that poly (ADP-ribose) polymerase inhibitors may have an earlier entry point in the treatment of ovarian cancer and underline the importance of determining *BRCA* status at diagnosis by sequencing. Dr Curigliano, Milan, Italy, commented on SOLAR-1 trial data. SOLAR-1[22] demonstrated a significant PFS benefit with the phosphatidylinositol-3-kinase (PI3K) inhibitor, alpelisib, plus hormone therapy, fulvestrant, compared with placebo plus fulvestrant in patients with PI3K-mutated cancer. This study also highlighted the value of determining yet another genomic biomarker status (i.e., PI3K mutations) at diagnosis by sequencing to accurately select the treating agent. Finally, robust data from a large patient population study indicate for the first time that immunotherapy could be an effective first-line option for patients with metastatic triple-negative breast cancer. Additional studies will now be conducted to reinforce these preliminary findings.

LIQUID BIOPSY FOR ROUTINE TESTING: HYPES AND HOPES

Supported by the aforementioned examples and with the advent of targeted therapies, molecular profiling is often needed to guide therapeutic decisions, both at diagnosis and following the development of resistance, resulting in multiple tissue biopsies during the disease course. However, intratumour heterogeneity and clonal evolution due to prior lines of therapies further foster the complexity of the treatment decision, representing a truly challenging task for current therapeutic approaches.[23] Dr Besse, Villejuif, France, in multiple appearances during the ESMO Congress, emphasised that while the gold standard method for molecular profiling involves the examination of DNA/RNA extracted from a tissue biopsy, some clear drawbacks are associated with this approach. For instance, the lack of feasibility in some cases due to the anatomical position of the tumour mass, the invasiveness of the procedure, and the possible acquisition of insufficient tissue all lead to suboptimal overall testing quality of gene sequencing.[24] In the oncology community, interest is growing in the use of less invasive and costly approaches, such as liquid biopsy, analysing circulating tumour DNA (ctDNA) released into plasma from cancer cells during apoptosis or necrosis.[25]

Nowadays, ctDNA tests are used primarily for patients when tissue samples are not available, or to guide targeted therapy in specific clinical situations (e.g., resistance after tyrosine kinase inhibitor treatment). Dr Dienstmann, Barcelona, Spain, commented that during a study of patients receiving osimertinib, MET amplification (15%) and EGFR Cys797Ser mutation (7%) were the most common resistance mechanisms, with no evidence of an acquired EGFR Thr790Met mutation. Conversely, the incidence of Thr790Met mutation in the standard-of-care arm was found in about 47% of cases. These findings underline the need to sequence ctDNA with a multiplex gene panel-based approach rather than with a single gene testing approach (i.e., only looking for Thr790Met).[26]

In addition, much hope is pinned on the further development of liquid biopsy applications, for example, detecting minimal residual disease or risk of relapse in early stages, a path that is actively explored in several ongoing studies.[27] For example, Dr Bonanno, Padova, Italy, presented interim findings from the MAGIC-1

trial[28] suggesting that changes in plasma levels of a *KRAS* mutation significantly correlated with the radiological assessment of disease progression in patients with advanced NSCLC receiving either chemotherapy or immunotherapy. Moreover, the data also suggest that, in patients receiving immunotherapy, early reduction of the mutated allele abundancy in plasma may predict favourable outcomes.

CALLING ON MOLECULAR DIAGNOSTICS

Given the rapidly increasing amount of genomic information available, thanks to the reduction in sequencing cost and the democratisation of molecular profiling, clinicians are now confronted with the need to prioritise driver over passenger genomic alterations and choose the most appropriate treatment when multiple targetable alterations are found.

During the ESMO Congress 2018, key opinion leaders from across the globe highlighted that molecular tumour boards, a new form of interaction for medical professionals, are rapidly diffusing into major cancer reference centres.[23] The main goal for a molecular tumour board is to match the unique genetic profile of a patient's cancer with a drug (or combination therapy) having the highest evidence of clinical actionability, or to explore the possibility of enrolling patients into a recruiting clinical trial. Dr Curioni, Zurich, Switzerland, part of the ESMO press committee, highlighted that lung cancer is an extraordinary example that demonstrates the value of multidisciplinary discussion of molecular tumour profiling data, which has resulted in a dramatic improvement in the prognosis of cancer patients harbouring driver genetic alterations in genes like *ALK*, *ROS1*, *EGFR*, *cMET*, *BRAF*, and *NTRK*.[29] Prof André, Villejuif, France, highlighted the first ESMO scale to rank and prioritise genomic alterations: ESMO scale for clinical actionability of molecular targets (ESCAT). ESCAT aims to improve the interpretation of sequencing results and link them to appropriate clinical trials. Furthermore, the ESMO Precision Medicine Working Group released updated recommendations concerning sequencing practice, including detection of TRK fusions, microsatellite instability, and a general guide on how to handle genetic variants detected by NGS. Also highlighted was the unmet need to integrate multiple layers of data from curated available sources (National Cancer Institute [NCI], The Cancer Genome Atlas [TCGA], ESMO-OncologyPro, and ESCAT) and present them in an intuitive and accessible manner while still accurately offering a complete picture of an individual's medical profile in the form of a clinical decision support tool. This represents the next challenge for companies serving cancer-treating clinicians. The key to success for such a tool is a simple and direct workflow of guided steps for clinicians to navigate the magnitude of molecular information, enabling decisions to be made as quickly and reliably as possible. Moving in this direction, the ESMO Magnitude of Clinical Benefits scale (ESMO-MCBS) is a tool designed to assess the clinical benefit of different cancer medications, allowing stakeholders to discriminate between high-value treatments (i.e., improving survival and/or quality of life of cancer patients, from modest to marginal approaches). At this year's ESMO Congress, a set of workshops aimed to address how to prepare the next generation of the ESMO-MCBS for the integration of molecular diagnostics-related benefits in the cost calculation process.[30] Given that diagnostics-related reimbursement policies across the European Union (EU), the USA, and the Asia-Pacific region will likely evolve in the near future, much attention will be paid to this topic at next year's Congress.

Overall, the ESMO Congress highlighted that in order to make precision medicine the global standard of care, including the wide application of genome-analysis in the form of a feasible diagnostic solution, and not only as a privileged option for a few national healthcare systems, a variety of socioeconomic factors will need to be considered.[31] Health policy makers, medical institutions, manufacturers, clinicians, and biomedical researchers, along with patient associations, will have to engage in this process through global initiatives, while being able to deploy them at the local level.[32]

CONCLUSION

To conclude, the list of new therapies associated with specific biomarkers is growing steadily.

What was once a vision for improved cancer care is now a reality, with molecular insights resulting in better patient management, reduced treatment side effects, and enhanced quality of life. At this year's ESMO Congress, most key opinion leaders clearly pointed out that investments in high-quality molecular profiling for tumour patients will undoubtedly have an impact on appropriate treatment decisions and, thus, eventually impact clinical outcomes.

References

1. Yu TM et al. Multiple biomarker testing tissue consumption and completion rates with single-gene tests and investigational use of oncomine dx target test for advanced non-small-cell lung cancer: A single-center analysis. Clin Lung Cancer. 2018;pii: S1525-7304(18)30204-3.
2. Miller TE et al. Clinical utility of reflex testing using focused next generation sequencing for management of patients with advanced lung adenocarcinoma. J Clin Pathol. 2018. [Epub ahead of print].
3. Hamblin A et al. Clinical applicability and cost of a 46-gene panel for genomic analysis of solid tumours: Retrospective validation and prospective audit in the UK National Health Service. PLoS Medicine. 2017;14(2):e1002230.
4. Prager GW et al. Global cancer control: Responding to the growing burden, rising costs and inequalities in access. ESMO Open. 2018;3(2):e000285.
5. Topalian SL et al. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat Rev Cancer. 2016;16(5):275-87.
6. Frampton GM et al. Assessment and comparison of tumor mutational burden and microsatellite instability status in >40,000 cancer genomes. Anns Oncol. 2016;27(6 suppl 1):520.
7. Rizvi NA et al. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015;348(6230): 124-8.
8. Ma W et al. Current status and perspectives in translational biomarker research for PD-1/PD-L1 immune checkpoint blockade therapy. J Hematol Oncol. 2016;9(1):47.
9. Topalian SL et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. New Eng J Med. 2012;366:2443-54.
10. Garon EB et al. Pembrolizumab for the treatment of non-small-cell lung cancer. New Eng J Med. 2015; 372(21):2018-28.
11. Forde PM et al. Neoadjuvant PD-1 blockade in resectable lung cancer. New Eng J Med. 2018;378(21):1976-86.
12. AstraZeneca. A global study to assess the effects of MEDI4736 following concurrent chemoradiation in patients with Stage III unresectable non-small cell lung cancer (PACIFIC). NCT02125461. https://clinicaltrials.gov/ct2/show/NCT02125461.
13. Peters S et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. New Eng J Med. 2017;377(9):829-38.
14. Kumar-Sinha C et al. Landscape of gene fusions in epithelial cancers: Seq and ye shall find. Genome Med. 2015;7:129.
15. Amatu A et al. NTRK gene fusions as novel targets of cancer therapy across multiple tumour types. ESMO Open. 2016;1(2):e000023
16. Reis-Filho J. Detecting MSI and TRK fusion using NGS: ESMO recommendations. ESMO 2018 Congress, 19th-23rd October, 2018.
17. Drilon A et al. Safety and Antitumor Activity of the Multitargeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib: Combined Results from Two Phase I Trials (ALKA-372-001 and STARTRK-1). Cancer Discov. 2017;7(4):400-9.
18. Demetri G. Efficacy and Safety of Entrectinib in Patients with NTRK Fusion-Positive (NTRK-fp) Tumors: Pooled Analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. ESMO 2018 Congress, 19th – 23rd October, 2018.
19. Hoffmann-La Roche. study of oral RXDX-101 in adult patients with locally advanced or metastatic cancer targeting NTRK1, NTRK2, NTRK3, ROS1, or ALK molecular alterations. (STARTRK-1). NCT02097810. https://clinicaltrials.gov/ct2/show/NCT02097810.
20. Hoffmann-La Roche. Basket study of entrectinib (RXDX-101) for the treatment of patients with solid tumors harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK gene rearrangements (Fusions) (STARTRK-2). NCT02568267. https://clinicaltrials.gov/ct2/show/NCT02568267.
21. AstraZeneca. Olaparib maintenance monotherapy in patients with BRCA mutated ovarian cancer following first line platinum based chemotherapy. (SOLO-1). NCT01844986. https://clinicaltrials.gov/ct2/show/NCT01844986.
22. Novartis Pharmaceuticals. Study assessing the efficacy and safety of alpelisib plus fulvestrant in men and postmenopausal women with advanced breast cancer which progressed on or after aromatase inhibitor treatment. (SOLAR-1). NCT02437318. https://clinicaltrials.gov/ct2/show/NCT02437318.
23. Tannock IF, Hickman JA. Limits to personalized cancer medicine. New Eng J Med. 2016;375(13):1289-94.
24. Karachaliou N et al. Real-time liquid biopsies become a reality in cancer treatment. Ann Transl Med. 2015;3(3):36.
25. Bernabé R et al. What do we need to make circulating tumour DNA (ctDNA) a routine diagnostic test in lung cancer? Eur J Cancer. 2017;81: 66-73.
26. Tang ZH, Lu JJ. Osimertinib resistance in non-small cell lung cancer: Mechanisms and therapeutic strategies. Cancer Lett. 2018;420: 242-6.
27. Cheung AH et al. Latest development of liquid biopsy. J Thorac Dis. 2018;10(Suppl 14):S1645-51.
28. Bonanno L et al. Liquid biopsy as tool to monitor and predict clinical benefit from chemotherapy (CT) and immunotherapy (IT) in advanced non-small cell lung cancer (aNSCLC): A prospective study. Ann Oncol. 2018;29(Suppl 8).
29. Curioni Fontecedro A. Harnessing the power of big data to optimise cancer management. ESMO Daily Reporter, Saturday 20th October, P.10. Available at: https://www.esmo.org/content/download/158452/2894554/file/ESMO-2018-Congress-Daily-Reporter-Saturday.pdf. Last accessed: 22 November 2018.
30. Saluja R et al. Examining trends in cost and clinical benefit of novel anticancer drugs over time. J Oncol Pract. 2018;14(5):e280-94.
31. Remon J, Dienstmann R. Precision oncology: Separating the wheat from the chaff. ESMO Open. 2018;3(6).
32. Siew-Kee Low et al. Breast cancer: The translation of big genomic data to cancer precision medicine. Cancer Sci. 2018;109(3):497-506.

Prediction with Precision: Does TAILORx Make Chemotherapy a Personalised Treatment?

This symposium took place on 20th October 2018, as part of the European Society for Medical Oncology (ESMO) Congress in Munich, Germany

Chairperson: Joseph Sparano[1]

Speakers: Joseph Sparano,[1] Frédérique Penault-Llorca,[2] Ulrike Nitz[3]

1. Department of Medical Oncology, Montefiore Medical Center, New York City, New York, USA
2. Department of Biopathology, Centre Jean Perrin, Clermont-Ferrand, France
3. Department of Gyneco-oncology, Evangelisches Krankenhaus Bethesda, Mönchengladbach, Germany

Disclosure: Prof Sparano has no relevant financial interests or relationships to disclose. Prof Penault-Llorca has personal financial interests in AbbVie, Agendia, AstraZeneca, BMS, Genomic Health, Eli Lilly, Merck, MSD, Myriad, NanoString, Novartis, Pfizer, and Roche; and institutional financial interests in Agendia, AstraZeneca, BMS, Genomic Health, MSD, Myriad, NanoString, and Roche; as well as non-financial interests in AbbVie, AstraZeneca, BMS, MSD, and Roche (congress invitations). Prof Nitz has personal financial interests in Agendia, Amgen, AstraZeneca, Celgene, Genomic Health, Pfizer, Novartis, Roche, and Teva; and institutional financial interests in Agendia, Amgen, AstraZeneca, Celgene, Deutsche Krebshilfe, Genomic Health, Pfizer, Novartis, Roche, and Teva.

Acknowledgements: Medical writing assistance was provided by Lorena Tonarelli.

Support: The symposium and the publication of this article were funded by Genomic Health. The views presented are those of the speakers and are not necessarily those of Genomic Health.

Citation: EMJ Oncol. 2018;6[1]:50-57.

Meeting Summary

Adjuvant chemotherapy (CT) is commonly recommended to breast cancer patients following surgery. However, not all patients benefit from it, and the intervention is associated with a substantial clinical burden, which also negatively affects quality of life. The aim of this symposium was to provide insights into the use of the 21-gene Oncotype DX® Breast Recurrence Score (RS) assay (Genomic Health Inc., Redwood City, California, USA) to optimise treatment decisions. The symposium started with an overview of the role of biomarkers in precision medicine in early breast cancer, provided by Prof Sparano, with a focus on recent developments in predicting CT benefit and assisting with the treatment decision-making based on the Oncotype DX® assay. CT is becoming a personalised medicine, comparable with oestrogen receptor (ER) expression testing and hormonal therapy, or human epidermal growth factor receptor (HER)2 testing and trastuzumab. Prof Sparano, the principal investigator of the TAILORx study, presented clinical trial and real-world evidence demonstrating a lack of CT benefit in approximately 80% of patients (those with RS results 0–25) and a substantial benefit in about 20% of patients (mainly those with RS results 26–100). This was

brought into the perspective of clinical practice by Prof Penault-Llorca, who discussed the value of genomic assays versus classical pathological parameters and predictors of prognosis (e.g., age, ER and HER2 status, histological subtypes, Ki67 +/- mitotic index) and their associated risk of CT overtreatment and undertreatment. Prof Penault-Llorca also provided an insight into the lack of interchangeability of currently available genomic breast cancer tests. The symposium concluded with a presentation by Prof Nitz on CT decisions, specifically in node-positive breast cancer patients. Clinical and real-world data from large registries support CT decisions based on RS, independent of nodal status, to prevent overtreatment in daily routine.

Practice Changing Events: What Did We Learn?

Professor Joseph Sparano

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes that may provide prognostic and/or predictive information that cannot be derived otherwise.[1] They must demonstrate accuracy and reliability (analytical validity) and be statistically associated with the clinical outcome of interest (clinical validity).[2] Additionally, their use in medical decision-making should lead to a change in treatment paradigms, which improves long-term patient outcomes (clinical utility).[2] However, the latter is rarely demonstrated.

Biomarkers are increasingly used in breast cancer to guide therapy management and enable tailored treatment.[3] Several developments have led to changes from a one-size-fits-all treatment approach, with surgery and radiotherapy for all patients, to precision medicine. In the late 1970s, the introduction of ER expression testing guided endocrine therapy selection. The late 1990s saw a breakthrough in treatment personalisation, with HER2 testing being used to guide the use of anti-HER2 therapy in metastatic breast cancer and subsequently in early-stage breast cancer. Likewise, the Oncotype DX® assay can be used to guide CT use in ER-positive HER2-negative early breast cancer.

Gene expression studies have demonstrated that breast cancer is highly heterogeneous, comprising biologically distinct tumour subtypes,[4] and that prognosis and prediction of the benefit of CT are mostly driven by proliferation, ER, and ER-dependent genes.[5] Several genomic assays have been developed on this basis. However, analyses have shown a 40–60% discordance in risk classification when other assays were compared with the Oncotype DX® assay, and fewer patients were classified as high-risk (and thus requiring CT) by the Oncotype DX® assay (Table 1).[6-15]

The Oncotype DX® test estimates distant recurrence risk (DR) at 10 years and can predict CT benefit in women with hormone receptor (HR)-positive HER2-negative breast cancer, thereby assisting with systemic adjuvant treatment decisions.[16,17] Specifically, this assay generates binary results in terms of prediction of CT benefit for node-negative patients, with those with RS 0–25 showing no benefit from chemoendocrine therapy over endocrine therapy alone, and those with RS 26–100 showing substantial CT benefit (Box 1).[16,18-20]

The clinical validity of the Oncotype DX® assay has been reported in several trials. Prognostic information was demonstrated (level 1B evidence) in the prospective validation study NSABP-B14 using archived tumour samples from ER-positive node-negative breast cancer patients who had been followed-up for 10 years. Patients (n=668) had been treated with tamoxifen without CT and their RS results significantly correlated with DR rates.[17]

The predictive value for CT benefit was initially demonstrated with the two-arm validation study NSABP-B20 (level 1B evidence), in which ER-positive node-negative breast cancer patients (n=651) were randomised to receive either tamoxifen plus CT or tamoxifen alone. The study showed low DR rates at 10-year follow-up with endocrine therapy alone for RS 0–17 versus substantial CT benefit for RS 31–100 (relative risk [RR]: 0.26; 95% confidence interval [CI]: 0.13–0.53; decrease in absolute risk: 27.6%).[16]

Table 1: Discordance between the Oncotype DX® Breast Recurrence Score and other assays.

Study†	Overall discordance*			
	BCI	ROR	EP/EP Clin	MMP
	Overall	Overall	Overall	Overall
TransATAC Sestak et al.,[7] 2016	42%			
OPTIMA‡ Bartlett et al.,[8] 2016		50%		
Marin General Hopsital Alvarado et al.,[9] 2015		46%		
TransATAC Dowsett et al.,[10] 2013		43%		
Swiss Study Varga et al.,[11] 2013			47% or 50%	
French Study Clough et al.,[12] 2013				57%
US Oncology/UCSF Study Denduluri et al.,[13] 2011				58%
McGill U Study Maroun et al.,[14] 2015				53%
Florida Study Shivers et al.,[15] 2013				44%

*Overall discordance=any difference in risk classification between the RS assay and other; †Four studies did not include risk classification information appropriate for inclusion in this table; ‡Study used non-standard RS cut-off for the RS versus MMP comparison.

BCI: Breast Cancer Index; EP: EndoPredict®; EP Clin: EndoPredict® plus clinical features; MMP: MammaPrint®; ROR: Prosigna®; RS: Recurrence Score.

Adapted from Varga et al.[6]

Box 1: The Oncotype DX® Breast Recurrence Score (RS) assay provides clarity for adjuvant treatment decisions.

Guiding Treatment

TAILORx results eliminate uncertainty around intermediate scores and show that most patients do not benefit from chemotherapy.[16,18]

Reducing Over and Undertreatment

TAILORx shows that clinical risk features alone are not sufficient to determine chemotherapy benefit.[16,18]

73% of patients with high-clinical risk* had Recurrence Score results 0–25 and may have been **overtreated** without the Recurrence Score result.

*High clinical risk: Grade 1, >3 cm; Grade 2, >2 cm; Grade 3, >1 cm.

43% of patients with Recurrence Score results 26–100 had low-clinical risk** and may have been **undertreated** without the Recurrence Score result.

**Low clinical risk: Grade 1, ≤3 cm; Grade 2, ≤2 cm; Grade 3, ≤1 cm.

Similar prediction of CT benefit was demonstrated for patients with RS 26–100 in the overall patient population of the NSABP-B20 trial (12% of whom were HER2-positive by reverse transcription-PCR)[19] and in the subpopulation that included only HER2-negative disease.[18,20] For patients with an intermediate RS result, CT did not seem to confer a benefit. Indeed,

the wide CI for patients with RS 10–25 could not exclude a clinically important advantage.[16] The TAILORx study was designed to address this question and has generated level 1A evidence that the Oncotype DX® assay can identify a large proportion of patients with HR-positive, HER2-negative, axillary node-negative disease who do not benefit from adjuvant CT.[18,21] Thus, the trial provided an unprecedented level of evidence supporting the use of the Oncotype DX® test RS to guide CT use.[18]

Another prospective validation study, SWOG-8814, has provided level 1B evidence demonstrating the value of the Oncotype DX® assay to predict CT benefit also in node-positive patients.[22] Data from the prospective WSG Plan B trial also provide evidence that the Oncotype DX® assay may be used to spare CT in patients with up to three positive axillary nodes.[22,23]

The clinical use of the Oncotype DX® test irrespective of nodal status has been confirmed in prospective registries and population-based analyses, including the Clalit registry study and the SEER database study, respectively.[24–26] These consolidate data from patients tested with the Oncotype DX® test in Israel and the USA. In patients with limited nodal involvement, data confirm that those with low RS results who are treated with endocrine therapy alone have excellent clinical outcomes with low DR rates.[24,25]

The available evidence for the Oncotype DX® test has led to updated recommendations by the National Comprehensive Cancer Network (NCCN) and the German Institute for Quality and Efficiency in Health Care (IQWiG); both of these organisations support the use of the Oncotype DX® assay for guiding adjuvant CT treatment decisions in breast cancer.[28,29]

TAILORx Results: The Right Treatment for the Right Patient

Professor Joseph Sparano

Results of the aforementioned randomised adjuvant breast cancer treatment trial, TAILORx, were presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.[18] The trial was designed to address the challenge of integrating molecular diagnostic testing into clinical practice. The primary objective was to more precisely determine the effect of CT, if any, in patients at intermediate risk of DR (RS 11–25). Investigators used the Oncotype DX® test on every patient to quantify individual risk and assign treatment accordingly.[18]

The TAILORx trial used different RS groups (RS 0–10, 11–25, 26–100) from those used previously (RS 0–18, 18–30, 31–100).[16-18] The RS result groups were selected based on the CI in the NSABP B-20 study to minimise the potential for overtreatment and undertreatment, while preserving prediction of CT benefit in patients with RS 26–100. When the NSABP B-20 data were reanalysed using the TAILORx RS ranges, the treatment effect of CT was similar to that of the original analysis.[19] Consequently, TAILORx participants with RS 0–10 were treated with endocrine therapy alone; those with RS 26–100 received CT and endocrine therapy, as it had been previously demonstrated that these patients derive substantial benefit from CT and it would have been unethical to randomise these patients.[17-19] To more precisely define the effect of CT with RS 11–25, 6,711 women (the primary study group) were randomised to receive endocrine therapy either with or without CT.[18]

Among patients with RS 0–10 who were uniformly treated with endocrine therapy, the DR-free interval (coprimary endpoint) at 5 and 9 years was 99.3% and 96.8%, respectively, indicating that these patients can be spared CT.[18] In patients with RS 11–25, the invasive disease-free survival (coprimary endpoint) as well as the distant relapse-free interval, relapse-free interval, and overall survival (secondary endpoints) were similar between those treated with endocrine therapy alone and those treated with CT plus endocrine therapy, indicating little or no benefit of CT over endocrine therapy at 9 years.[18] Patients with RS 26–100 presented a DR of 13% at 9 years with CT plus endocrine therapy, which is consistent with previous studies demonstrating similar outcomes in these patients: 12% DR at 10 years for patients treated with CT plus endocrine therapy versus 27% for patients with endocrine therapy alone in NSABP-B20 study.[19]

Altogether, the TAILORx primary analysis confirms that while patients with RS 0–25 do not benefit from receiving CT in addition to endocrine therapy, those with RS 26–100 derive substantial benefit from it.[18,19] Additional exploratory subgroup analyses showed no significant interactions between CT treatment and the majority of the prognostic covariates examined, including tumour size (≤2 cm versus >2 cm), histological grade, and clinical risk category. This suggests that clinical pathological parameters do not predict CT benefit in the RS 11–25 arms.[18] In these exploratory analyses, only age showed a significant correlation (p=0.004), since young patients (≤50 years) with RS 16–25 appeared to derive some benefit (1.6% and 6.5% absolute CT benefit in RS groups 16–20 and 21–25, respectively) from adding CT to adjuvant hormonal treatment.

Of note, patient characteristics in the TAILORx study were comparable to those in average clinical practice, as demonstrated by a comparison of the TAILORx study population with the SEER database.[30] Similarly, the proportion of patients identified as deriving substantial benefit from CT (RS 26–100) was consistently in the range of 15–20% in clinical studies and registries.[18,26,30-32]

Overall, the TAILORx study adds to the body of evidence demonstrating that the Oncotype DX® assay can predict the magnitude of CT benefit in HR-positive, HER2-negative, node-negative breast cancer patients. The data show that the vast majority of patients with RS 0–25 do not derive a benefit from CT (study TAILORx, level 1A evidence),[18] whereas patients with RS 26–100 (study NSABP-B20, level 1B evidence) derive a substantial clinical benefit from CT.[16]

Managing Decisions with Traditional Pathological Parameters and Other Tools: What is the Evidence?

Professor Frédérique Penault-Llorca

Classical prognostic factors and predictors of treatment response in breast cancer include age, histological subtypes, ER and HER2 status, Ki67 +/- mitotic index, vascular invasion, and tumour margins. Although useful, their clinical validity has not been systematically demonstrated. Furthermore, no factor has shown the ability to predict CT benefit; as a consequence, their use can result in CT overtreatment or undertreatment in >40% of patients.[33] For example, the proliferation index Ki67 has demonstrated significant limitations due to a consistent lack of reproducibility. This has led the ASCO Tumor Marker Guidelines Committee to conclude that the evidence supporting the clinical use of Ki67 was insufficient to recommend its routine use.[34]

Considering the limitations of classical pathological parameters and strong clinical trial evidence on genomic assays, expert panels, such as the St Gallen International Expert Consensus, have endorsed the use of genomic assays in women with HR-positive breast cancer to avoid unnecessary CT.[35]

In the TAILORx study, unlike RS results, clinicopathological parameters (tumour size and grade) were found to have no predictive value for CT benefit in randomised arms.[18] From a practical viewpoint, RS results thus contribute to reducing the risk of CT overtreatment or undertreatment. In the TAILORx trial, among the 2,812 patients with high clinical risk (Grade 1 and tumour size >3 cm, Grade 2 and tumour size >2 cm, or Grade 3 and tumour size >1 cm), 73% had RS 0–25 and would have been overtreated if a treatment decision would have been driven by classical pathological parameters alone. By contrast, among the patients with RS 26–100, 43% had low clinical risk (all other cases with known values for grade and tumour size) and would potentially have been undertreated without the RS result, effectively depriving them of the substantial CT benefit that patients in this RS range can experience.[18]

Genomic breast cancer assays other than the Oncotype DX® assay (e.g., MammaPrint® [Agendia, Amsterdam, Netherlands], Prosigna® [NanoString, Seattle, Washington, USA], and EndoPredict® [Myriad Genetics, Salt Lake City, Utah, USA]) have also been validated. However, the available tests are not interchangeable because of substantial differences in terms of genes selected, analytic and clinical evaluation, and risk assessment.

Additionally, as discussed, the tests have been shown to be highly discordant.[36] The Oncotype DX® assay is the only test that has been used in HR-positive patients in randomised clinical trials with or without CT to assess the interaction between RS and CT benefit. The Oncotype DX® assay was proven to identify the small proportion of patients (with RS 26–100) who will overall benefit from CT, thereby minimising the unnecessary use of CT in the majority of patients (with RS 0–25).[18] This is supported by high-level evidence,[16,18,22,26,31] which contrasts with the paucity of clinical trial data on some of the other tests, particularly the lack of level 1A evidence for EndoPredict and Prosigna.[21] Limited evidence supports the use of the Oncotype DX® assay and MammaPrint for predicting late recurrence, although this may not be a crucial issue given that high-risk patients usually receive CT.

On the basis of the available evidence, the Oncotype DX® assay has been incorporated into staging guidelines of the American Joint Committee on Cancer (AJCC), according to which patients with RS 0–10 are reclassified as Stage IA regardless of tumour size and grade parameters. NCCN guidelines also recognise the Oncotype DX® test as a predictor of adjuvant CT benefit in node-negative patients.[28]

Guiding Chemotherapy Decisions in Node-Positive Breast Cancer

Professor Ulrike Nitz

It has long been assumed that lymph node status was driving prognosis, based on evidence suggesting that overall survival decreases with greater nodal involvement.[37] The TransATAC study also showed that nodal status is an independent predictor of DR. In the different RS risk groups, recurrence rates were very similar in node-negative and 1–3 node-positive disease but increase substantially with larger tumour burden (pN2).[38] The study enrolled 2,929 HR-positive breast cancer women treated with anastrozole monotherapy. Of these, 1,231 were analysed for the Oncotype DX® assay to assess and validate prognosis value specifically in node-positive patients. It was validated that RS results from the Oncotype DX® assay strongly correlate with DR.[38]

Level 1B evidence supporting the predictive value of CT benefit in node-positive patients was brought by the SWOG-8814 study.[22] This showed that in 413 node-positive patients randomised to endocrine treatment or CT plus endocrine therapy, RS result was a strong predictor of CT benefit for disease-free survival in patients with RS 31–100, and of no CT benefit in patients with RS of 0–17.[22] Taken together, these data confirm that the Oncotype DX® assay is both prognostic and predictive for CT benefit, regardless of nodal status.

Prof Nitz, investigator of the WSG Plan B study, pointed to consistent results from this prospective randomised Phase III trial, which included 2,642 HER2-negative primary breast cancer patients who were node-negative (N0) at high risk or node-positive with 1–3 nodes (N1).[23] The 5-year distant disease-free survival of patients with RS 0–10 treated with endocrine therapy alone (n=348) was similar in high-risk N0 and N1 subjects (97.7% and 97.9%, respectively).

Notably, this was comparable with the 5-year DR-free interval rate (99.3%) of N0 patients with RS 0–10 receiving endocrine treatment alone in TAILORx (n=1,626),[30] confirming that these patients have good outcomes without CT, regardless of nodal status.

The prospective evidence from registries on the use of RS results to guide treatment choice in breast cancer is concordant with clinical trial findings and validates the clinical use of the Oncotype DX® assay in patients with micrometastases or positive lymph nodes.[24,26] This indicates that patients with RS 0–17 have favourable clinical outcomes with endocrine therapy alone and can avoid unnecessary CT.

It is worth considering that a major clinically relevant discordance exists between the classical prognostic marker Ki67 and the RS result reflected in the Plan B study, with a significant proportion of patients having low Ki67 but high RS results, and vice versa. Therefore, a treatment decision based solely on Ki67 can potentially lead to an increased risk of CT overtreatment or undertreatment.[27]

The main implication for clinical practice, based on the available evidence, is that CT benefit is absent in early-stage breast cancer patients presenting with RS 0–17, low in those with

RS 18–30, and substantial with RS 31–100. Further prospective data are expected from the ongoing RxPONDER study of women with node-positive, HR-positive, HER2-negative breast cancer (n=10,000).[39] Those with RS 0–25 will be randomised to CT plus endocrine therapy or endocrine therapy alone and will be followed-up for up to 10 years. The primary endpoint is to assess RS predictive value of RS results for CT benefit. RxPONDER aims to consolidate the body of evidence supporting the use of the Oncotype DX RS assay in breast cancer patients and to define more precisely the magnitude of CT benefit in node-positive patients with RS 0–25.

Conclusion

The lack of accurate predictors of CT benefit has long been a limitation in HR-positive, HER2-negative, early-stage breast cancer, resulting in the inadequate use of CT in a significant number of patients and leading to an increased risk of overtreatment and undertreatment. Evidence indicates that the 21-gene Oncotype DX® Breast Recurrence Score (RS) test can identify with precision patients who can benefit from CT in addition to endocrine therapy and, in parallel, those who can avoid unnecessary CT and the associated burden. In women with HR-positive, HER2-negative, node-negative breast cancer, CT benefit varies with the combination of RS and age, and some benefit has been observed in patients ≤50 years with RS 16–25. In women with limited nodal involvement, CT can be avoided if RS is 0–17 because this patient group is better managed with endocrine therapy alone. Notably, in the TAILORx study, 73% of the patients in the RS 0–25 group had a high clinical risk, as assessed by classical pathological parameters, and 43% of the patients with RS 26-100 had low clinical risk. This suggests that CT is used unnecessarily in 73% of node-negative patients with high clinical risk, and that 43% of node-negative patients with a high RS result might be undertreated if decisions are based solely on a clinical risk assessment.

References

1. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69(3):89-95.
2. Hayes DF. Biomarker validation and testing. Mol Oncol. 2015;9(5):960-6.
3. Ades F et al. Understanding breast cancer – The long and winding road. BBA Clin. 2017;7:64-77.
4. Sorlie T et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA. 2003;100(14):8418-23.
5. Wirapati P et al. Meta-analysis of gene expression profiles in breast cancer: Toward a unified understanding of breast cancer subtyping and prognosis signatures. Breast Cancer Res. 2008;10(4):R65.
6. Varga Z et al. A summary of head-to-head comparisons of patient risk classifications by the 21-gene Recurrence Score assay and other genomic assays for early breast cancer. Poster. ESMO 2017, 8-12 September, 2017.
7. Sestak I et al. Cross-stratification and differential risk by breast cancer index and recurrence score in women with hormone receptor-positive lymph node-negative early-stage breast cancer. Clin Cancer Res. 2016;22(20):5043-8.
8. Bartlett JM et al. Comparing breast cancer multiparameter tests in the OPTIMA prelim trial: No test is more equal than the others. J Natl Cancer Inst. 2016;108(9).
9. Alvarado MD et al. A prospective comparison of the 21-gene recurrence score and the PAM50-based prosigna in estrogen receptor-positive early-stage breast cancer. Adv Ther. 2015;32(12):1237-47.
10. Dowsett M et al. Comparison of PAM50 risk of recurrence score with Oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. J Clin Oncol. 2013;31(22):2783-90.
11. Varga Z et al. Comparison of EndoPredict and Oncotype DX test results in hormone receptor positive invasive breast cancer. PLoS One. 2013;8(3):e58483. Erratum in: PLoS One. 2013;8(10).
12. Clough KB et al. A comparison of risk classification as assessed by the Mammaprint® and oncotype DX® assays. Breast. 2013; 22(1 suppl):S20-S70.
13. Denduluri N et al. Concordance between the 21-gene recurrence score (RS) and the 70-gene profile (MP) in breast cancer (BC) patients (pts). J Clin Oncol. 2011; 29(27 suppl):13.
14. Maroun R et al. A head-to-head comparison of Mammaprint and Oncotype Dx: A McGill University Health Center Experience. J Clin Oncol. 2015;33(suppl):11017.
15. Shivers SC et al. Direct comparison of risk classification between MammaPrint(R), Oncotype DX(R) and MammoStrat(R) assays in patients with early stage breast cancer. Cancer Res. 2014;73(24 suppl):P6-06-02.
16. Paik S et al. Gene expression and benefit of CT in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006;24(23):3726-34.
17. Paik S et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004;351(27):2817-26.
18. Sparano JA et al. Adjuvant CT guided by a 21-gene expression assay in breast cancer. N Engl J Med. 2018;379(2):111-21.

19. Sparano JA, Paik S. Development of the 21-gene assay and its application in clinical practice and clinical trials. J Clin Oncol. 2008;26(5):721-8.

20. Geyer CE et al. 21-gene assay as predictor of chemotherapy benefit in HER2-negative breast cancer. NPJ Breast Cancer. 2018;4:37.

21. Simon RM et al. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. 2009;101(21):1446-52.

22. Albain KS et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on CT: A retrospective analysis of a randomised trial. Lancet Oncol. 2010;11(1):55-65.

23. Gluz O et al. Prognostic impact of recurrence score (RS), grade/Ki67 central pathological review and anthracycline (A)-free vs. A-containing chemotherapy (CT) on distant and locoregional disease-free survival (DDFS/LRFS) in high clinical risk HER2-early breast cancer (EBC): WSG Plan B trial results. Poster LBA11. ESMO 2017, 8-12 September, 2017.

24. Stemmer MS et al. Clinical outcomes in ER+ HER2-node-positive breast cancer patients who were treated according to the recurrence score results: Evidence from a large prospectively designed registry. NPJ Breast Cancer. 2017;3:32.

25. National Cancer Institute (NHI). Surveillance, Epidemiology, and End Results program. Available at: https:// seer.cancer.gov/. Last accessed: 28 November 2018.

26. Petkov VI al. Breast-cancer-specific mortality in patients treated based on the 21-gene assay: A SEER population-based study. NPJ Breast Cancer. 2016;2:16017.

27. Gluz O et al. West German Study Group Phase III Plan B Trial: First prospective outcome data for the 21-gene recurrence score assay and concordance of prognostic markers by central and local pathology assessment. J Clin Oncol. 2016;34(20):2341-9.

28. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology – Breast Cancer. 2018. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx. Last accessed: 28 November 2018.

29. Institute for Quality and Efficiency in Health Care. Biomarker tests in breast cancer: New study data indicate advantage for certain patients. 2018. Available at: https://www.iqwig.de/en/press/ press-releases/biomarker-tests-in-breast-cancer-new-study-data-indicate-advantage-forcertain-patients.10059.html. Last accessed: 30 November 2018.

30. Sparano JA et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med. 2015;373(21):2005-14.

31. Stemmer MS et al. Clinical outcomes in patients with node-negative breast cancer treated based on the recurrence score results: Evidence from a large prospectively designed registry. NPJ Breast Cancer. 2017;3:33.

32. Blohmer J-U et al. Population sizes of patients with node negative, HR+, HER2- primary breast cancer, using standard and TAILORx 21-gene recurrence score cut-off values. Poster 192P. ESMO 2017, 8-12 September, 2017.

33. Cardoso F et al. (eds.) Breast Cancer: Essentials for Clinicians, 2017, ESMO.

34. Harris L et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007;25(33):5287-312.

35. Curigliano G et al. De-escalating and escalating treatments for early-stage breast cancer: The St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. Ann Oncol. 2017;28(8):1700-12.

36. Bartlett JMS et al. Comparison of multiparameter tests in the UK OPTIMA-Preliminary trial. San Antonio Breast Cancer Symposium (SABCS), 9-13 December, 2014.

37. Brouchkaert O et al. Breast cancer phenotype, nodal status and palpability may be useful in the detection of overdiagnosed screening-detected breast cancers. Ann Oncol. 2013;24(7):1847-52.

38. Dowsett M et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: A TransATAC study. J Clin Oncol. 2010;28(11):1829-34.

39. National Cancer Institute (NCI). Tamoxifen citrate, letrozole, anastrozole, or exemestane with or without chemotherapy in treating patients with invasive RxPONDER breast cancer. NCT01272037. https://clinicaltrials.gov/ct2/show/NCT01272037.

Genomic Profiling Clinical Trials in Cancer of Unknown Primary

This summary is based on oral and poster presentations that took place at the European Society for Medical Oncology (ESMO) Congress in Munich, Germany on 19th–23rd October 2018. It also includes an abstract from the American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, Illinois, USA on 1st–5th June 2018

Speakers: George Pentheroudakis,[1] Alwin Krämer[2]

1. Ioannina Medical School, University of Ioannina, Ioannina, Greece
2. Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center and University of Heidelberg, Heidelberg, Germany

Disclosure: Prof Pentheroudakis has received honoraria for speaking and an advisory role, as well as research funding, from Amgen, Merck & Co. Inc., AstraZeneca, Roche, BMS, Novartis, MSD, Lilly, and Boehringer. Prof Krämer has received grants and research support from Merck & Co. Inc., and Bayer AG, along with other fees from F. Hoffmann-La Roche and Daiichi Sankyo Company Ltd.

Acknowledgements: Prof Pentheroudakis gave an oral presentation at ESMO 2018. Prof Krämer presented a poster at ASCO 2018[1] and, at ESMO 2018, spoke at a sponsored symposium and presented a poster.[2] Medical writing assistance was provided by Helen Saul.

Support: This article was commissioned and supported by Roche Ltd., which also sponsored some of the presentations covered. Roche Ltd. has reviewed this article for medical accuracy.

Citation: EMJ Oncol. 2018;6[1]:58-66.

Meeting Summary

Cancer of unknown primary (CUP) accounts for 3–5% of all cancers,[3,4] and prognosis is poor for most patients, with a median survival of 6–9 months.[5] Clinical and pathological diagnostic work-up is required to determine whether patients belong to the favourable or unfavourable subset of CUP. Only 15–20% of patients belong to favourable subsets and have responses to therapy and outcomes similar to those of patients with the equivalent known metastatic primary tumour.[4]

For the patients in the unfavourable subsets (around 80–85% of CUP patients) treatment to date has been with chemotherapy. Median survival is <1 year[5] and clinicopathological management of these patients is not expected to improve outcomes further. However, two different approaches involving genetic testing to guide patient management have the potential to offer progress.

The first approach is to use gene or methylation profiling tests to identify the tissue of origin. A number of tests are available that can be used to examine the gene expression or methylation signature of the CUP sample and assign a tissue of origin biologically. This approach is being used in clinical trials,[6] but there is not yet solid clinical evidence that offering primary-specific therapy to these patients improves outcomes.

The second approach is to identify genomic aberrations that can be targeted therapeutically. Comprehensive genomic profiling (CGP) can identify aberrations that can be targeted with available agents in some patients,[1] but there is no high-level evidence concluding that this approach improves outcomes. A novel molecularly guided trial, CUPISCO,[7] was recently initiated and will address this issue in a Phase II, randomised, active-controlled, multicentre setting in patients with newly diagnosed, poor-prognosis CUP. The study aims to show the benefit associated with the use of genomic profiling to allocate molecularly targeted therapies or immunotherapies compared with the standard treatment of platinum-based chemotherapy in patients with CUP.

Introduction

CUP is a heterogeneous disease with diverse origins, meaning the primary tumour has not been identified. CUP is essentially a disease of metastases that disseminate early and aggressively, and for which standard clinical and pathological diagnostic work-up does not identify the primary tumour. Multiple metastases develop in an unpredictable pattern.[5]

The disease is not as rare as is sometimes assumed; it accounts for 3–5% of all cancers[3,4] and is the fourth most common cause of cancer-related deaths.[8] Prognosis is poor in the vast majority of patients. The median survival is 6–9 months[5] and only 15–20% of patients belong to a favourable subset with a median overall survival of 12–36 months.[9] There is a high unmet need for new treatments for CUP, and its management remains a major challenge.

Cancers of Unknown Primary: Do Clinical and Standard Pathological Decision Parameters Dominate the Treatment Algorithms or Can Treatment be Improved Using Genetic Profiling?

Professor George Pentheroudakis

An Overview of Clinical and Pathological Management of Cancer of Unknown Primary Patients

The standardised diagnostic work-up is defined in the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines.[9] The first step involves thorough pathological and clinical diagnostic work-up. The pathological diagnosis involves immunohistochemistry of tissue samples to rule out treatable tumours, such as germ cell cancers, lymphomas, melanomas, and sarcomas. Once the tumour is known to be epithelial, cytokeratin (CK) cocktails, such as CK7/CK20, allow the pathologist to assign a tissue of suggestive origin to the CUP tumour. Although in most cases the pathologist can determine whether the CUP is of epithelial origin, frequently it is not possible to suggest the specific epithelial tissue of origin of the tumour with a high level of confidence.

The clinical work-up comprises a thorough medical history, physical examination, and CT scans of the head, thorax, abdomen, and pelvis. Female patients should have a mammography. In most CUP cases, several tumour markers are elevated in the blood, but this often does not help determine the primary tissue of origin. The ESMO Guidelines[9] suggest testing for serum α-fetoprotein and human chorionic gonadotropin in patients with midline metastatic nodal disease and in patients with liver metastases in order to not miss hepatoma and germ cell tumours. A serum prostate-specific antigen test is recommended for males with adenocarcinomatous bony metastases. Signs, symptoms, and laboratory abnormalities direct the physician towards additional relevant procedures. Head and neck PET and CT scans are only useful if locoregional therapy is being considered for the CUP patient, for example, in patients with squamous cell carcinoma affecting the cervical lymph nodes.

A key decision-making point in the management of CUP is to decide whether the CUP patient belongs to favourable or unfavourable subsets; only 15–20% of CUP patients belong to favourable subsets.[9]

Favourable subsets include men with poorly differentiated carcinoma with midline nodal distribution (extragonadal germ cell syndrome); women with papillary serous adenocarcinoma of the peritoneal cavity; women with adenocarcinoma involving only axillary lymph nodes, squamous cell carcinoma involving cervical lymph nodes, or poorly differentiated neuroendocrine carcinomas; men with blastic bone metastases and/or elevated prostate-specific antigen; patients with metastases with a colon cancer immunohistochemical profile (CK7-, CK20+, CDX2+); and patients with single-site metastases.[4]

Cancers in these subsets are very likely to respond to primary-specific treatment, which translates into a better prognosis compared to patients belonging to the large group with unfavourable prognosis CUP. Prof Pentheroudakis argued that, from a biological standpoint, these tumours are not CUP in a strict sense. Several retrospective series examining the natural behaviour and biology of CUP tumours in favourable subset patients have suggested patients in this group have responses to therapy and outcomes that are similar to those with the equivalent known metastatic primary tumour.[4] For example, women with axillary lymph node adenocarcinoma can be managed as if they have breast cancer, and patients with squamous cell carcinoma in the cervical lymph nodes can be treated as if they have head and neck cancer.

The unfavourable subsets encompass 80% of patients with CUP. These patients typically have several metastases in the viscera (liver, bones, veins, lungs) and no identifiable primary tumour. To date, treatment has been platinum-based chemotherapy and median survival is <1 year. Prof Pentheroudakis commented that the clinicopathological approach to treatment of CUP will not improve outcomes further.

Patient Management Relies on Two Distinct Approaches

Genetic testing has the potential to offer new lines of progress. There are two main approaches: the first is to use molecular tests to identify the tissue of origin, while the second is to use tests to find genomic aberrations that can be targeted therapeutically.

The first approach, identifying the tissue of origin, rests on the premise that each tumour type has a distinct molecular profile, identified by examination of RNA expression or gene methylation analysis of the CUP sample. The expression signature is compared to known expression signatures from several solid tumours and a CUP sample is assigned a tissue of origin biologically; this was not possible by clinicopathological means. These tests have been validated in typical metastatic solid tumours and were shown to have an accuracy of 85–90%.[10] A number of tests are available, which analyse between 10 and 2,000 genes simultaneously and distinguish between 6 and 50 different cancer types. They variously use messenger RNA, microRNA, or DNA methylation.

To date, there is no evidence of improved outcomes using molecular testing that enables the patient with CUP to receive primary-specific therapy. The best evidence comes from a cohort study led by investigators at the Sarah Cannon Cancer Institute in Dallas, Texas, USA.[11] Of 289 treatment-naïve CUP patients enrolled, assays were taken successfully in 252 patients and 247 (98%) had a tissue of origin predicted. Primary-specific therapy was received by 194 patients and in this group, median survival was 12.5 months (95% confidence interval: 9.1–15.4 months). Prof Pentheroudakis said this is slightly longer than the overall survival rates historically seen with chemotherapy, but the difference is small. He also noted that the trial was not randomised.

An ongoing randomised French trial, GEFCAPI 04,[6] including 223 treatment-naïve patients with CUP, may provide clearer answers. Molecular profiling of tissue samples from all patients has been carried out with the aim of assigning biologically a tissue of origin. Patients have been randomised into blinded or unblinded groups; in the unblinded arm of the trial, the results of profiling were known to the investigator and the patient received primary-specific therapy. In the blinded arm, results were not disclosed and patients were treated with standard chemotherapy with cisplatin and gemcitabine. The primary endpoint is progression-free survival and the results are expected in 2019.

The second approach uses genomic profiling to find genomic aberrations that can be targeted therapeutically. The two most commonly cited tests are the Foundation One[12] and Caris Life Sciences[13] assays. In 2015, the Foundation One platform was used to perform a mutation analysis of 236 genes along with next-generation sequencing of rearrangements in 19 genes. One study found that the test identified mutations that could be targeted with currently available drugs in 20% of cases (n=200).[14] In 2014, the Caris Life Sciences platform was used to perform a mutation analysis of 47 genes, immunohistochemistry for 23 markers, and fluorescence/chromogenic *in situ* hybridisation of 7 genes. It was used to profile 1,806 CUP cases and biologically relevant mutations were found in almost all cases (96%).[15] However, 3 years later, investigators used an updated version of the Caris platform, a 592 gene NextSeq panel, to profile 389 CUP cases and identified therapeutically targetable mutations in 22% of patients.[16] The latter result is more realistic, Prof Pentheroudakis concluded.

If genomic profiling identifies a targetable mutation in a tissue sample of CUP, and the patient receives targeted treatment, is the outcome improved as compared to standard chemotherapy? This approach has been trialled in metastatic solid tumours,[17] but not in CUP, Prof Pentheroudakis said. The question of whether this approach is effective in CUP will not be answered before results are available from trials such as CUPISCO (Figure 1).[7] This randomised Phase II trial will compare platinum-based chemotherapy with molecularly-targeted therapies relevant for the aberrations found by genomic profiling. This study includes only patients with histologically confirmed CUP and Prof Pentheroudakis commented it is expected to provide hints as to whether the approach is effective.

Overall, Prof Pentheroudakis stated that there is not yet high-level evidence to suggest that treating CUP patients with primary tumour-specific therapy, or targeting relevant genomic aberrations, does indeed improve outcomes for these patients. Trials such as GEFCAPI 04[6] and CUPISCO[7] will provide long-awaited answers.

A Proposal for Patient Management in Cancers of Unknown Primary

Prof Pentheroudakis outlined a scheme for the management of CUP patients. When a patient presents with possible CUP, the first stage of management is clinical evaluation and biopsy. Anamnesis, physical examination, imaging, and standard pathology investigations using immunohistochemistry can identify the primary site, in which case the patient does not have CUP.

If the primary site is not identified by imaging or pathological diagnosis, the next step uses clinicopathological information to determine whether the patient belongs to one of the favourable subsets of CUP. Patients belonging to these subsets are treated with primary-specific therapy. However, 80–85% of CUP patients have non-favourable CUP. In theory, gene expression and/or gene methylation profiling could assign the tissue of origin in 80–85% of these cases,[10] and the choice then is either to offer primary-specific therapy or enter the patient into a clinical trial.

In the remaining 15–20% of cases, the tissue of origin is not identified, despite profiling analyses,[10] because of a failure of the test or an inadequate sample. The option for these patients is either a clinical trial or next-generation sequencing profiling of the tumour to find a targetable mutation. If a genomic aberration is found, treatment still depends on access to targeted drugs. Prof Pentheroudakis said that in countries such as Greece, access to targeted drugs is difficult because their use in CUP is not included in the approved indications. Furthermore, he stated that there is no high-level evidence to guarantee that this targeted approach will be effective. For example, a *BRAF* mutation may, in theory, be effectively treated if the CUP has metastasised from melanoma, but not if it has metastasised from colon cancer. Data from clinical trials are necessary to resolve this question.

In conclusion, it is first important to decide whether patients have favourable versus unfavourable CUP. Molecular testing may be able to assign the tissue of origin and to identify targetable genomic aberrations. However, high-level evidence to prove that

targeting specific mutations will improve patient outcomes is still missing; ongoing clinical trials will address this question.

Addressing Unmet Needs in Cancers of Unknown Primary with a Novel Molecularly-Guided Trial

Professor Alwin Krämer

At ESMO 2018, Prof Krämer also highlighted the importance of genomic profiling in this setting. At a sponsored symposium entitled 'Comprehensive genomic profiling: Taking precision medicine from vision to reality', he reviewed the evidence supporting the use of genomic profiling in patients with CUP.

In 2015, a study also highlighted by Prof Pentheroudakis profiled CUP samples using Foundation One CGP; 125 patients had adenocarcinoma of unknown primary and 75 had non-adeno-CUP syndrome. Of a total of 200 CUP cases profiled, 96% harboured at least one genomic alteration and ≥1 clinically relevant genomic alteration was identified in 85% of cases (169 out of 200).[14]

The types of genomic alterations identified showed a pattern similar to those seen in many other cancer types: few genes had frequent aberrations and vast numbers of other genes had rare aberrations, including some that would be amenable to targeted treatment.

Furthermore, a retrospective analysis of 6,116 CUP samples from the Foundation Core database identified complex immune genomic signatures using CGP. This study found that approximately 10% of patients with CUP harboured a high tumour mutational burden (TMB) status.[19] Another analysis of 4,210 samples found that 1.6% showed a high microsatellite instability (MSI) status.[19] These genomic signatures broaden treatment options to include immune-oncology therapies.

Earlier this year, Prof Krämer presented research at the American Society of Clinical Oncology (ASCO) Annual Meeting 2018, examining the overlap between different pathways in a population of CUP patients[1] in collaboration with Foundation Medicine.

The objective of the study was to analyse genomic profiles of CUP samples and characterise the association between clinical phenotype, affected signalling pathways, and candidacy for molecularly targeted therapies or immune checkpoint inhibitor (ICPI) treatment. Biopsies from 4,650 patients with CUP were sequenced with FoundationOne CGP and actionable alterations were identified for the majority of patients. A median of three genomic aberrations per sample was identified. Most samples (3,675 out of 4,650; 79.0%) harboured ≥1 genomic aberration or biomarker relevant for targeted therapy or ICPI; an additional 485 (10%) had genomic aberrations associated only with an investigational targeted therapy. More than one-third of the group (1,767 out of 4,650; 38%) harboured a genomic aberration specific for one of eight common targeted therapy/ICPI strategies, with 275 (5.9%) having a profile relevant to >1 of those eight strategies.

Profiling also offered insights into CUP subtypes that may be associated with reduced efficacy for some therapies: of 554 (12.1%) samples with high TMB or MSI, 145 (26.7%) harboured a genomic aberration known or suspected to reduce ICPI sensitivity (Table 1).

The study concluded that this knowledge-based approach in CUP patients describes informative genomic features. Coupled with the availability of a growing collection of targeted agents and immunotherapies, a new and rationally designed treatment paradigm, independent of tissue of origin, may now be possible in CUP. This approach can be assessed in prospective randomised trials investigating targeted therapies and ICPI; however, clinical studies evaluating this potentially promising approach are currently lacking.

At the ESMO Congress, Prof Krämer said these data were confirmed by another study on genomic aberrations in CUP, which was performed at the Memorial Sloan Kettering Cancer Center (MSKCC), New York City, New York, USA.[20] Investigators used MSK-IMPACT technology, a deep coverage hybridisation capture-based assay encompassing 341 cancer-associated genes (later expanded to 410 cancer-

associated genes). In this study, 333 CUP patients were evaluated and profiling was performed on samples from 150 patients. The results showed that 30% of cases (n=45 out of 150) harboured ≥1 lesion that was amenable to targeted therapy by licensed drugs. Of this group, 10% (15 out of 150) received matched therapy. Time to treatment failure ranged from <1–14 months, with several patients remaining on targeted therapy at the time of data cut-off. An additional 14% of patients had dominant mutation signatures, including high TMB and high MSI,[20] that, again, suggest that immune-oncology therapies would be appropriate.

Together, these results suggest that genomic profiling can identify clinically relevant genomic alterations and direct new treatment options in patients with CUP. However, there remains a lack of high-level evidence to demonstrate the efficacy and safety of this approach. Clinical trials are needed to compare molecularly guided therapy versus standard chemotherapy across a large cohort of patients with CUP.

CUPISCO: Comprehensive Genomic Profiling and Molecularly-Guided Therapy in Cancer of Unknown Primary

The aforementioned data form the rationale for the CUPISCO trial, recently initiated by Roche and presented at the ESMO Congress 2018.[2] CUPISCO is a Phase II, randomised, active-controlled, multicentre study of patients with newly diagnosed, unfavourable CUP.[7] The study will compare the efficacy and safety of targeted therapy or immunotherapy guided by genomic profiling with platinum-based standard chemotherapy.

The trial will be launched in 101 institutions in 23 countries and will include 790 patients with CUP; it has been activated in 15 of the 23 countries already. Adults with newly diagnosed, poor prognosis CUP, as described in the ESMO Guidelines,[9] are eligible to enter the trial. Exclusion criteria include non-epithelial cancer, squamous-cell CUP, and patients belonging to favourable subsets of CUP.

As outlined in Figure 1, all enrolled patients receive genomic profiling with Foundation Medicine Tumor Profiling of tissue and blood; all also receive three induction cycles of platinum-based chemotherapy. Those who respond to these three initial cycles of chemotherapy are randomised in a 3:1 ratio either to experimental treatment (n=354) or to the standard treatment arm (n=118) of continued chemotherapy for an additional three cycles. The experimental treatment arm is composed of nine strata depending on the alteration identified: seven of the strata are molecularly-targeted therapies to an identified genomic aberration, while an additional two arms cover immunotherapy. Patients with TMB-high or MSI-high tumours receive atezolizumab alone, while those with TMB-low or unknown receive atezolizumab in combination with platinum-based chemotherapy.

Table 1: Genomic profiling of carcinomas of unknown primary to support clinical decisions.

Therapy class	Samples relevant to therapy	Samples relevant for other therapy (n)							
		ALKi	EGFRi	HER2i	SMOi	BRAFi	AKTi	PARPi	anti-PD-L1
ALKi	30	-	0	0	1	0	3	1	2
EGFRi	98		-	10	0	0	7	4	14
HER2i	329			-	3	1	40	19	35
SMOi	48				-	2	8	7	21
BRAFi	102					-	15	6	9
AKTi	608						-	42	91
PARPi	259							-	53
anti-PD-L1	438								-

anti-PD-L1: anti-programmed death-ligand 1; i: inhibitor.

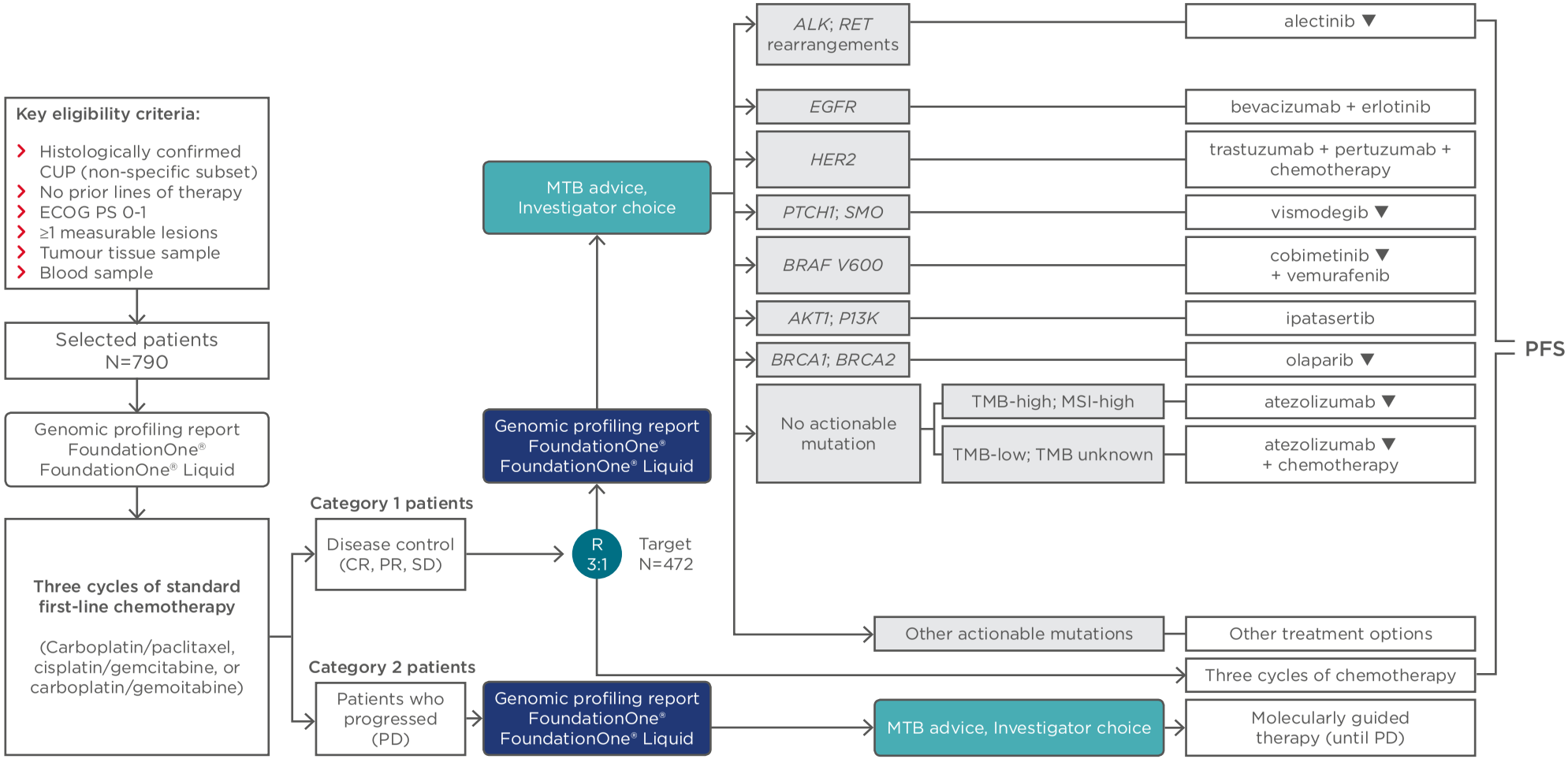


Figure 1: CUPISCO study design.

Randomisation is stratified by sex and response during the induction period (CR and PR versus SD). Genes listed comprise the confirmed selection of variants. Experimental genes may also be used for therapy selection. Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important and adverse events should be reported to your respective local office.

CR: complete response; CUP: cancer of unknown primary; ECOG PS: Eastern Cooperative Oncology Group performance status; MSI: microsatellite instability; MTB: Molecular Tumour Board; PD: progressive disease; PFS: progression-free survival; PR: partial response; R: randomisation; SD: stable disease; TMB: tumour mutational burden.

Adapted from Krämer et al.[18]

Patients whose tumours harbour a mutation that could be targeted by a specific drug not provided in the experimental study arm can receive this treatment in a tenth stratum of the study. Those whose disease progresses after the first three induction cycles of chemotherapy will have access to the targeted treatments shown in the experimental arm of the trial but in a non-randomised fashion.

A key element of the study design is a molecular tumour board, comprising the investigator, reference pathologist, reference oncologist, and, when appropriate, a cancer genomics consultant. The board will advise on experimental therapy choice for patients randomised to molecularly-guided therapy and for those who did not respond to the induction chemotherapy. As highlighted in the aforementioned ASCO abstract,[1] given the overlap of some alterations, the choice of targeted therapy may be ambiguous in some cases (approximately 6%), but the molecular tumour board will follow a charter of guidance for therapy selection in hese cases.

In patients who responded to induction chemotherapy, the primary endpoint in CUPISCO is progression-free survival, defined as the time from randomisation to the first occurrence of disease progression or death from any cause. Secondary endpoints are overall survival, objective response rate, and duration of clinical benefit.

Response will be assessed by the investigator via a physical examination, CT scans, and MRI, using Response Evaluation Criteria In Solid Tumors (RECIST version 1.1) at the end of the induction period, every 3 treatment cycles and every 3 months during follow-up. Adverse events (AE) will be monitored and documented continuously during the study, and serious AE will also be documented and reported, as will AE of special interest.

The prospective randomised CUPISCO study has been set up against a background of a lack of high-level evidence to support potentially promising new approaches in the treatment of CUP. With the advent of large-scale DNA sequencing technologies, and the availability of a growing collection of targeted agents and immunotherapies, a new and rationally designed treatment paradigm may now be possible for CUP that is independent of the tumour of origin and customised to the patient.

Conclusion

CUP is associated with a poor prognosis and represents a high unmet medical need. For patients presenting with CUP, thorough clinical and pathological diagnostic work-up is necessary to establish whether the disease belongs to the favourable or unfavourable subsets. For patients whose disease falls into the unfavourable subsets, new molecular tests offer the possibility of assigning biologically a tissue of origin. When this is not possible, genomic profiling may identify genomic aberrations that can be targeted with available drugs; it has been established that most CUP carry at least one such aberration. Furthermore, CUP represents an ideal model to test the clinical utility of genomic profiling in a histology-independent setting. It allows for a pan-cancer analysis of the function and effect of targeted therapies and immunotherapy in an, until recently, almost neglected disease.

However, to date there is a lack of high-level evidence to suggest that genetic approaches improve the outcomes of CUP patients. CUPISCO is a novel clinical trial that aims to show benefit associated with genomic profiling used to define molecularly-targeted treatments. The Phase II trial of patients with newly diagnosed unfavourable CUP will compare the safety and efficacy of these targeted therapies with standard platinum-based chemotherapy. Clinical trials such as CUPISCO are necessary before a new and rationally designed treatment paradigm will become standard management for patients with CUP.

References

1. Krämer A, Losa F. Genomic profiling of carcinomas of unknown primary (CUP) to support clinical decisions. J Clin Oncol. 2018;36(15suppl):e24162.
2. Krämer A et al. Comprehensive profiling and molecularly guided therapy (MGT) for carcinomas of unknown primary (CUP): CUPISCO: A Phase II, randomised, multicentre study comparing targeted therapy or immunotherapy with standard platinum-based chemotherapy. Ann Oncol. 2018;29(suppl8).
3. Stella GM et al. Cancers of unknown primary origin: Current perspectives and future therapeutic strategies. J Transl Med. 2012;10(1):12.
4. Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet. 2012;379(9824):1428-35.
5. Ettinger DS et al. NCCN clinical practice guidelines in Oncology for occult primary. J Natl Compr Cancer Netw. 2011;9(12):1358-95.
6. Gustave Roussy, Cancer Campus, Grand Paris. Trial comparing a strategy based on molecular analysis to the empiric strategy in patients with cup (GEFCAPI04). NCT01540058. https://clinicaltrials.gov/ct2/show/NCT01540058.
7. Hoffmann-La Roche. A Phase II randomized study comparing the efficacy and safety of targeted therapy or cancer immunotherapy versus platinum-based chemotherapy in patients with cancer of unknown primary site (CUPISCO). NCT03498521. https://clinicaltrials.gov/ct2/show/NCT03498521.
8. Pavlidis N, Fizazi K. Cancer of unknown primary (CUP). Crit Rev Oncol Hematol. 2005;54(3):243-50.
9. Fizazi K et al. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v133-8.
10. Dolled-Filhart MP, Rimm DL. Gene expression array analysis to determine tissue of origin of carcinoma of unknown primary. Cancer Cytopathol. 2013;121(3):129-35.
11. Hainsworth JD et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: A prospective trial of the Sarah Cannon research institute. J Clin Oncol. 2013;31(2):217-23.
12. Foundation Medicine. Foundation Medicine home page. Available at: https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx. Last accessed: 16 November 2018.
13. Caris Life Sciences. CMI overview. Available at: https://www.carislifesciences.com/cmi-overview/. Last accessed: 16 November 2018.
14. Ross JS et al. Comprehensive genomic profiling of carcinoma of unknown primary site: New routes to targeted therapies. JAMA Oncol. 2015;1(1):40-9.
15. Gatalica Z et al. Comprehensive tumor profiling identifies numerous biomarkers of drug response in cancers of unknown primary site: Analysis of 1806 cases. Oncotarget. 2014;5(23):12440-7.
16. Gatalica Z et al. Comprehensive analysis of cancers of unknown primary for the biomarkers of response to immune checkpoint blockade therapy. Eur J Cancer. 2018;94:179-86.
17. Le Tourneau C et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): A multicentre, open-label, proof-of-concept, randomised, controlled Phase 2 trial. Lancet Oncol. 2015;16(13):1324-34.
18. Krämer A et al. Comprehensive profiling and molecularly guided therapy (MGT) for carcinomas of unknown primary (CUP): CUPISCO – A Phase II, randomised, multicentre study comparing targeted therapy or immunotherapy with standard platinum-based chemotherapy. European Society for Medical Oncology (ESMO) 2018 Congress, 19–23 October 2018, Munich, Germany. Available at https://cupfoundjo.org/wp-content/uploads/2018/10/ESMO-2018_CUPISCO-poster.pdf. Last accessed: 22 November 2018.
19. Gay LM et al. Mutational burden of tumors with primary site unknown. J Clin Oncol. 2017;35(15Suppl):3039.
20. Varghese A et al. Clinical and molecular characterization of patients with cancer of unknown primary in the modern era. Ann Oncol. 2017;28(12):3015-21.

Coming soon.

EMJ provides influential articles, presentations of scientific research and clinical practice, and in-depth reviews of international medical congresses.

Subscribe to *EMJ Gastroenterology* for free.

EUROPEANMEDICAL-JOURNAL.COM /SUBSCRIBE

Abstract Reviews

Discover the latest research and results as *EMJ Oncology* brings to you abstract reviews of presentations made at ESMO 2018

First In-Human Study with GSK3359609, an Inducible T cell Costimulator Receptor Agonist in Patients with Advanced, Solid Tumours: Preliminary Results from INDUCE-1

Authors: *Aaron R. Hansen,[1] Todd M. Bauer,[2] Victor Moreno,[3] Michele Maio,[4] Stefanie Groenland,[5] Juan Martin-Liberal,[6] Hui Gan,[7] Danny Rischin,[8] Michael Millward,[9] Anthony J. Olszanski,[10] Daniel C. Cho,[11] Elaine Paul,[12] Marc Ballas,[13] Catherine Ellis,[13] Helen Zhou,[14] Sapna Yadavilli,[13] Jafar Sadik Shaik,[15] Emmett V. Schmidt,[16] Axel Hoos,[13] Eric Angevin[17]

1. Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, Canada
2. Sarah Cannon Research Institute/Tennessee Oncology, Nashville, Tennessee, USA
3. Medical Oncology-Start Madrid-FJD, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain
4. Division of Medical Oncology and Immunotherapy, University Hospital of Siena, Siena, Italy
5. Medical Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, Netherlands
6. Vall d`Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain
7. Cancer Clinical Trial Centre, Austin Hospital, Melbourne, Australia
8. Peter MacCallum Cancer Centre and the University of Melbourne, Melbourne, Australia
9. Sir Charles Gairdner Hospital, Nedlands, Australia
10. Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA
11. Department of Medicine, New York University Langone Medical Center, New York City, New York, USA
12. Oncology, R&D, GlaxoSmithKline, Research Triangle Park, North Carolina, USA
13. Oncology, R&D, GlaxoSmithKline, Collegeville, Pennsylvania, USA
14. QSci, Clinical Statistics, GlaxoSmithKline, Collegeville, Pennsylvania, USA
15. Clinical Pharmacology, GlaxoSmithKline, Collegeville, Pennsylvania, USA
16. Early Oncology, Clinical Development, Merck & Co Inc, North Wales, Pennsylvania, USA
17. Drug Development Department, Département d'Innovation Thérapeutique et des Essais Précoces, Gustave Roussy Institut de Cancérologie, Villejuif, France

*Correspondence to Aaron.Hansen@UHN.ca

Disclosure: Dr Hansen has received fees for providing advisory and consulting services and

research support for Genentech/Roche, Merck, GSK, Bristol-Myers Squibb, Novartis, Boston Biomedical, and Boehringer-Ingelheim. Dr Bauer has received fees for consulting or acting in an advisory role for Ignyta, Guardant Health, Loxo, Pfizer, and Moderna Therapeutics; and has received research funding from Daiichi Sankyo, Medpacto, Inc., Incyte, Mirati Therapeutics, Medimmune, AbbVie, AstraZeneca, Leap Therapeutics, MabVax, Stemline Therapeutics, Merck, Lilly, GlaxoSmithKline, Pfizer, Novartis, Genentech/Roche, Deciphera, Merrimack, Immunogene, Millennium, Ignyta, Calithera Biosciences, Kolltan Pharm., Principa Biopharma, Peleton, Immunocore, Aileron Therapeutics, Roche, BMS, Amgen, Moderna Therapeutics, Sanofi, Boehringer Ingelheim, Astellas Pharma, Five Prime Therapeutics, Jacobio, Top Alliance BioScience, Loxo, Janssen, Clovis Oncology, Takeda, Karyopharm Therapeutics, Onyx, Phosplatin Therapeutics, and Foundation Medicine. Dr Maio has received fees related to advisory boards and travel from GSK, Bristol-Myers Squibb, AstraZeneca, Roche, Merck Sharp & Dohme, and Incyte. Dr Gan has received fees for consulting or acting in an advisory role from Abbvie and Merck Serono; has received fees for being on a speaker's bureau for Abbvie, Bristol Myers Squibb, Ignyta, Merck, Serono, and Eisai; has received research funding from Abbvie; and has received money for travel, accommodation, and expenses from Abbvie, Ignyta, and Merck Sharp & Dohme. Dr Rischin has sat on advisory boards/steering committees (uncompensated) for Merck, Amgen, Regeneron, and Bristol-Myers Squibb. Dr Millward has received fees for sitting on advisory boards for Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, and AstraZeneca. Dr Olszanski has received fees for consulting or acting in an advisory role for Bristol-Myers Squibb, G1 Therapeutics, Kyowa Hakko Kirin, Merck, Takeda, Array, Pfizer, EMD Serono, and Iovance. Dr Cho has received honoraria from Bristol-Myers Squibb, Exelixis, and Genentech; and has received fees for consulting or acting in an advisory role from Pfizer and Prometheus. Dr Angevin has received fees for consulting or acting in an advisory role from Merck Sharp & Dohme, GlaxoSmithKline, Celgene Research; has received money for travel, accommodations, and expenses from AbbVie, Roche, Sanofi, and Pfizer; and has been a principal or sub-investigator for Abbvie, Aduro, Agios, Amgen, Argen-x, Astex, AstraZeneca, Aveo pharmaceuticals, Bayer, Beigene, Blueprint, BMS, Boeringer Ingelheim, Celgene, Chugai, Clovis, Daiichi Sankyo, Debiopharm, Eisai, Eos, Exelixis, Forma, Gamamabs, Genentech, Gortec, GSK, H3 biomedecine, Incyte, Innate Pharma, Janssen, Kura Oncology, Kyowa, Lilly, Loxo, Lysarc, Lytix Biopharma, Medimmune, Menarini, Merus, Merck Sharp & Dohme, Nanobiotix, Nektar Therapeutics, Novartis, Octimet, Oncoethix, Oncopeptides AB, Orion, Pfizer, Pharmamar, Pierre Fabre, Roche, Sanofi, Servier, Sierra Oncology, Taiho, Takeda, Tesaro, and Xencor. Dr Paul, Dr Ballas, Dr Ellis, Dr Zhou, Dr Yadavilli, and Dr Shaik are employees of and hold stocks/shares in GlaxoSmithKline. Dr Hoos is employee of and holds stocks/shares in GlaxoSmithKline; and is a Non-executive Director: Shareholder of Imugene. Dr Schmidt is an employee of and holds stocks/shares in Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. The remaining authors have declared no conflicts of interest.

Acknowledgements: The authors thank the patients and families, as well as site staff and the GlaxoSmithKline 204691 study team.

Support: Funding for this study (NCT02723955) was provided by GlaxoSmithKline in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, USA.

Keywords: Dose escalation, GSK3359609, inducible T cell costimulator (ICOS), ICOS agonist, IgG1, IgG4, inducible T cell costimulator receptor, pembrolizumab, pharmacodynamics, pharmacokinetics.

Citation: EMJ Oncol. 2018;6[1]:68-71. Abstract Review No. AR1.

BACKGROUND

Inducible T cell costimulator (ICOS), a member of the CD28/B7 receptor superfamily, is expressed on T cells after T cell receptor engagement with cognate antigen.[1] ICOS provides a costimulatory signal augmenting T cell expansion, function, and survival, and is involved in B cell function.[2-4] GSK335609 is a humanised IgG4 antibody engineered to reduce Fc-mediated depleting effects yet retain cross-linking for potent agonist activity.[5] Engagement of ICOS to stimulate agonist function is hypothesised to translate into an optimal therapeutic effect.[4,6] GSK3359609's unique mechanism offers an opportunity to investigate the antitumour potential of targeting a T cell costimulator alone and in combination.

METHODS

INDUCE-1 is a dose escalation (DE) and ongoing expansion phase study of GSK3359609 alone (Part 1) and in combination with pembrolizumab (Part 2).[7] The modified toxicity probability interval informed DE decisions with three or more patients enrolled per dose level (DL). GSK3359609 was administered as an intravenous infusion every 3 weeks (Q3W) with or without 200 mg pembrolizumab Q3W; treatment continued up to 2 years or until progression or

unacceptable toxicity. To be included in the study, patients needed to have metastatic or relapsed invasive malignancy, measurable disease, received five or fewer lines of prior therapy in the advanced setting, adequate organ function, and no active autoimmune disease requiring treatment; the PK/PD cohorts required pre-treatment and Day 43 on-treatment tumour biopsies. The primary objective was to determine safety, tolerability, and maximum tolerated (MTD) GSK3359609 dose.

RESULTS

In the DE phase and the PK/PD cohort, 98 patients enrolled. In Part 1, 22 patients enrolled in the DE cohort and 40 patients enrolled in the PK/PD cohort. In Part 2, 36 patients enrolled in the DE cohort. Most patients had microsatellite stable colorectal carcinoma (26%) and ≥2 baseline target lesions (57%); 37% had received ≥3 prior lines of therapy in the advanced setting and 31% prior anti-programmed cell death protein 1/ligand-1 therapy. In Part 1 (n=62), 22 patients (35%) had at least one treatment-related adverse event (TR-AE). The most frequent TR-AE (≥3 patients) were fatigue (15%), aspartate transaminase (AST) elevations (5%), and diarrhoea (3%); AST elevations were the most frequent Grade 3 or 4 TR-AE (n=2 [3%]). In Part 2, 15 patients (42%) had at least one TR-AE; the most frequent TR-AE were AST elevations (8%) and pyrexia (8%); no Grade 3 or 4 TR-AE occurred in >1 patient. One DLT occurred in DE: Grade 3 pneumonitis in a Part 2 patient treated at the top GSK3359609 DL of 3 mg/kg, which led to discontinuation of both drugs. In the PK/PD cohort, liver enzyme increases in one patient (GSK3359609 3 mg/kg) were DLT and the only TR-AE leading to treatment discontinuation. Disease progression was the primary reason for treatment discontinuation (92%). Approximate dose proportional increases in systemic GSK3359609 concentrations over 0.01–3.00 mg/kg DL were observed. At DL ≥0.3 mg/kg, ICOS receptor occupancy was ≥75% across the dosing interval. On-target PD effects in tumour infiltrating lymphocytes and clinical activity were observed in Part 1 and 2, including in anti-programmed cell death protein 1/ligand-1 therapy experienced patients (Figure 1).

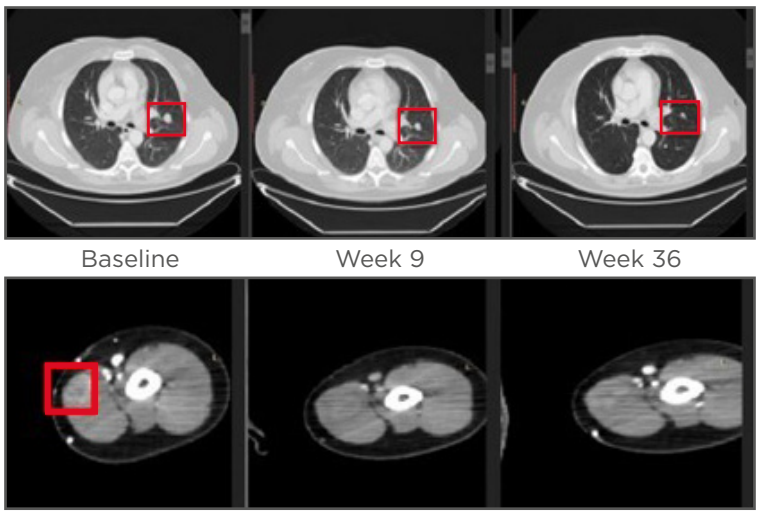


Figure 1: Axial CT images of left upper lobe lung lesion and subcutaneous left bicep lesion.

Fifty-three-year-old male diagnosed with Stage IIIc, BRAF/cKIT mutation-negative nodular melanoma; previous regimens included treatment with the combination of ipilimumab and nivolumab for approximately 2 months (BoR was SD); nivolumab alone for approximately 1 year (BoR was SD). At baseline, total disease burden was five target lesions (sum of diameters was 225 mm) and multiple non-target lesions. In this study, the patient received GSK3359609 monotherapy in three 0.1 mg/kg doses until Week 48. After Week 48, the dose was 1 mg/kg; the BoR was PR.

BoR: best overall response; PR: partial response; SD: stable disease.

CONCLUSION

GSK3359609 alone and in combination with pembrolizumab was well-tolerated across the 0.001–3.000 mg/kg dose range. MTD was not reached; the maximum administered dose was 3 mg/kg. A range of doses (≥0.1–1.0 mg/kg) showed biological and clinical activity. These doses are under investigation in expansion cohorts to establish the GSK3359609 dose and assess clinical activity across different patient groups. Preliminary biological and clinical data support the mechanism of action of a non-depleting ICOS agonist as a clinical target.

References

1. Hutloff A et al. ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. Nature. 1999;397(6716):263-6.
2. Simpson TR et al. Regulation of CD4 T cell activation and effector function by inducible costimulator (ICOS). Curr Opin Immunol. 2010;22(3):326-32.
3. Mak TW et al. Costimulation through the inducible costimulator ligand is essential for both T helper and B cell functions in T cell-dependent B cell responses. Nat Immunol. 2003;4(8):765-72.
4. Fan X et al. Engagement of the ICOS pathway markedly enhances efficacy of CTLA-4 blockade in cancer immunotherapy. J Exp Med. 2014;211(4):715-25.
5. Mayes P et al. The promise and challenges of immune agonist antibody development in cancer. Nat Rev Drug Disc. 2018;17(7):509-27.
6. Brett S et al. Nonclinical evaluation of a non-depleting, first-in-class humanized IgG4 agonist anti-ICOS antibody. Abstract 1840P. ESMO Congress, 19-23 October, 2018.
7. GlaxoSmithKline. Dose Escalation and Expansion Study of GSK3359609 in Subjects With Selected Advanced Solid Tumors (INDUCE-1). NCT02723955. https://clinicaltrials.gov/ct2/show/NCT02723955.

Preliminary Safety, Efficacy, and Pharmacokinetic and Pharmacodynamic Characterisation from GARNET, a Phase I Clinical Trial of the Anti-PD-1 Monoclonal Antibody TSR-042 in Patients with Recurrent or Advanced Microsatellite Instability-High Endometrial Cancer

Authors: *Ana Oaknin,[1] Susan L. Ellard,[2] Charles Leath, III,[3] Victor Moreno,[4] Rebecca Kristeleit,[5] Wei Guo,[6] Sharon Lu,[6] David Jenkins,[6] Kristen McEachern,[6] Kai Yu Jen,[6] Steven Dunlap,[6] Ellie Im,[6] Lucy Gilbert[7]

1. Vall d´Hebrón Institute of Oncology (VHIO), Vall d´Hebrón University Hospital, Barcelona, Spain
2. British Columbia Cancer Agency and University of British Columbia, Vancouver, Canada
3. University of Alabama at Birmingham, Birmingham, Alabama, USA
4. START MADRID-FJD, Hospital Fundación Jiménez Díaz, Medical Oncology Department, Madrid, Spain
5. Department of Oncology, UCL Cancer Institute, University College London, London, UK
6. TESARO, Inc., Waltham, Massachusetts, USA
7. Research Institute-McGill University Health Centre, Montreal, Canada

*Correspondence to aoaknin@vhio.net

Disclosure: Dr Oaknin has served on advisory boards for Roche, AstraZeneca, PharmaMar, Clovis Oncology, Immunogen, and TESARO, Inc., and has received support for travel and accommodation from Roche, AstraZeneca, and PharmaMar. Dr Ellard has served on advisory boards for AstraZeneca and Astellas, and has received speaker honoraria from AstraZeneca. Dr Leath has served on advisory boards for Mateon and Celsion. Dr Kristeleit has served on advisory boards for InCyte, Roche, Clovis Oncology, Merck, TESARO, Inc; and has a consultancy with Basilea.

Dr Gilbert has served on advisory boards for AstraZeneca and Roche. The remaining authors have stock and other ownership interests in, and are employed by, TESARO, Inc.

Acknowledgements: Medical writing assistance was funded by TESARO, Inc. (Waltham, Massachusetts, USA), co-ordinated by Dr Teodor G. Paunescu, and provided by Dr Nicole Renner and Dena McWain, Ashfield Healthcare Communications, Middletown, Connecticut, USA.

Keywords: Anti-programmed death (PD)-1, endometrial cancer (EC), immunotherapy, microsatellite instability (MSI), microsatellite instability-high (MSI-H), TSR-042.

Citation: EMJ Oncol. 2018;6[1]:71-73. Abstract Review No. AR2.

At the European Society for Medical Oncology (ESMO) 2018 Congress, data from the ongoing Phase I clinical trial of the anti-programmed death (PD)-1 monoclonal antibody TSR-042 were presented. Blocking PD-1 has been shown to increase antitumour immune responses and overall survival of patients with multiple tumour types.[1] TSR-042 is an investigational humanised monoclonal antibody that targets PD-1, effectively blocking interaction with its ligands PD-L1 and PD-L2. TSR-042 is being evaluated in patients with advanced solid tumours in the ongoing Phase I GARNET trial.[2] Safety and efficacy data from the microsatellite instability-high (MSI-H) endometrial cancer (EC) cohort, as well as pharmacokinetics (PK) and receptor occupancy (RO) at the recommended Phase II dose (RP2D), were presented.

Patients with previously treated MSI-H EC were evaluated and received TSR-042 500 mg every 3 weeks for the first four cycles and 1,000 mg every 6 weeks thereafter. Antitumour activity was assessed by immune-related Response Evaluation Criteria in Solid Tumors (irRECIST). Serum and peripheral blood mononuclear cells were collected for PK and RO measurements, respectively.

At the time of the analysis, 35 patients with MSI-H EC were treated with TSR-042; the median age was 63 years, 37% of patients had International Federation of Gynecology and Obstetrics (FIGO) Stage I cancer at diagnosis, and 34% had FIGO Stage III. The median number of prior regimens was two (range: 1–4).

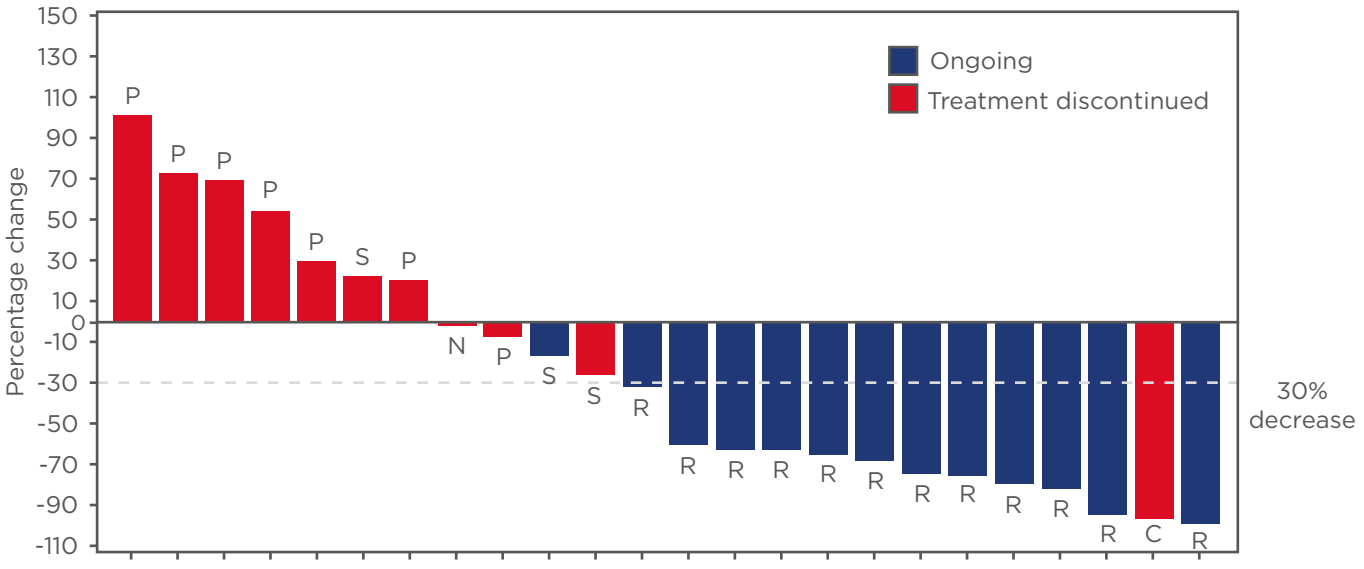


Figure 1: Best percentage change in total tumour burden from baseline based on immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) in patients with recurrent or advanced microsatellite instability-high endometrial cancer.*

*One patient out of the 25 evaluable patients did not have a post-baseline tumour assessment and was not included in this waterfall plot.

C: immune-related complete response; N: not evaluable; P: immune-related progressive disease; R: immune-related partial response; S: immune-related stable disease.

Of the 25 evaluable patients (≥12 weeks of follow-up in the study), a response was seen in 13 patients and the overall response rate was 52% (95% confidence interval: 31.3–72.2). One patient had a complete response and partial responses (PR) occurred in 12 patients (48%), including 1 patient with unconfirmed PR who is ongoing in the study. In addition, 3 patients (12%) had stable disease, 7 patients (28%) had progressive disease, and 2 patients did not have an evaluable tumour assessment (Figure 1). The median duration of response was not reached and 12 of the 13 responders (92%) are ongoing in the study. Three patients with a PR have been receiving TSR-042 for >60 weeks.

Of the 35 patients, 23 (66%) had ≥1 treatment-related treatment-emergent adverse event. Grade ≥3 treatment-related treatment-emergent adverse events were reported in 4 patients (11%) and were noted as leukopenia, neutropenia, anaemia, alanine aminotransferase increased, and aspartate aminotransferase increased. No treatment-related death or treatment discontinuation was reported. TSR-042 exhibited linear and dose-proportional PK, and maintained serum concentrations at least 8-fold higher than required for full RO throughout the course of treatment.

These preliminary efficacy data indicate robust clinical activity of TSR-042 in patients with previously treated recurrent or advanced MSI-H EC and a safety profile consistent with approved PD-1 inhibitors. Safety and efficacy data for TSR-042 at the RP2D support the unique and convenient dosing schedule of 500 mg every 3 weeks for the first four cycles and 1,000 mg every 6 weeks thereafter. PK was consistent across patients and full RO was achieved at RP2D.

References

1. Gong J et al. Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: A comprehensive review of registration trials and future considerations. J Immunother Cancer. 2018;6(1):8.
2. Sachdev JC et al. Safety, pharmacodynamic, and pharmacokinetic profile of TSR-042, an anti–PD–1 monoclonal antibody, in patients (pts) with advanced solid tumors. Ann Oncol. 2017(Suppl 5):28:420;1185P.

Patient Reports of Mouth Symptoms after Radiotherapy Treatment for Head and Neck Cancer: An International Survey

Authors: Chris Curtis,[1] Alessia Nicotera,[2] Carlotta Griseri,[2] *Hazel Roddam[2]

1. The Swallows Head & Neck Cancer Charity, Blackpool, UK
2. University of Central Lancashire, Preston, UK

*Correspondence to HRoddam@uclan.ac.uk

Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: This research was co-designed, conducted, and reported by patient advocates and a patient-led charity. Chris Curtis is a patient advocate. The authors thank all the patients who responded to this survey.

Keywords: Co-design, head and neck cancer, international, mouth symptoms, patient experience, radiotherapy, survey, xerostomia.

Citation: EMJ Oncol. 2018;6[1]:73-74. Abstract Review No. AR3.

BACKGROUND

People with head and neck cancer frequently have symptoms that are caused by their disease or by their treatments, which may significantly impact on their quality of life living with and beyond cancer.[1-5] This international research survey captured a self-rating report by people who have had radiotherapy (RT) treatment for head and neck cancer regarding their experience of oral symptoms, including dry mouth (xerostomia).

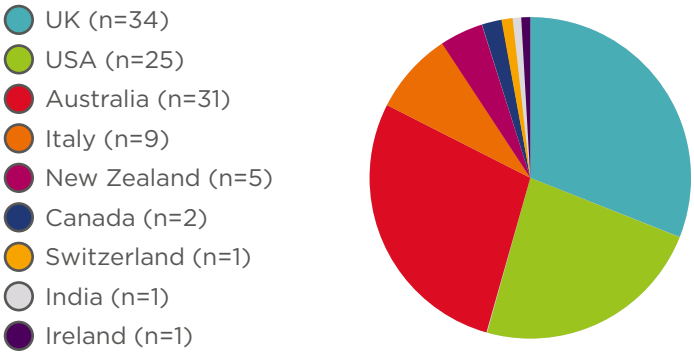


Figure 1: The proportion of total survey responders by country.

METHOD

This survey was designed by patients, and then submitted for ethical approval in collaboration with a healthcare researcher. The international survey was open to anyone >18 years old who had had treatment for head and neck cancer, whether or not they currently had symptoms of dry mouth. The electronic survey was in English and the ethical permissions granted that patients who wished to take part could request assistance, if needed, due to illness, fatigue, confidence in accessing the internet, or English literacy. Participant recruitment was supported through a wide range of networks including healthcare practitioners, charities, and patient support groups. The average time to complete the 18-item survey was <10 minutes, including both multiple choice and open questions. Statistical analysis reflected correlations between the participant demographics and self-reporting of symptoms. An interpretive analysis of free text responses highlighted patient values and priorities.

RESULTS

Over 100 individuals responded to the survey from across the UK, USA, Canada, Australia, India, and mainland Europe. Almost 75% of respondents (74.54%) stated that they had experienced dryness in the mouth or throat at least 50% of the time over the past 7 days. Furthermore, the results demonstrated that few respondents had received much information about dry mouth; >78% stated they had either received very little information or no information about the possible symptoms of dry mouth. Additionally, 88% of respondents stated that their oncologist had given them no advice about protecting their salivary glands via protective treatments. The analysis demonstrates patterns between the patient demographics, types of radiotherapy treatments, time since treatment, and current symptoms. This is the first time that this original dataset was presented. The findings also generated insights into the self-reported impact of these symptoms on patients' quality of life.

CONCLUSION

This study comprises important evidence of patients' experiences and symptoms post-treatment. The cross-sectional dataset also indicates the global view of recent and current RT treatment approaches. Future collaborative studies between researchers, patient groups, and pharmaceutical companies are imperative.

This research was presented by a patient advocate. The poster was awarded first prize for Best Poster at the ESMO 2018 conference.

References

1. Kamal et al; MD Anderson Head and Neck Cancer Symptom Working Group. Patient reported dry mouth: Instrument comparison and model performance for correlation with quality of life in head and neck cancer survivors. Radiother Oncol. 2018;126(1):75-80.
2. Kakoei S et al. Xerostomia after radiotherapy and its effect on quality of life in head and neck cancer patients. Arch Iran Med. 2012;15(4):214-8.
3. Ganzer H et al. The eating experience in long-term survivors of head and neck cancer: A mixed-methods study. Support Care Cancer. 2015;23(11):3257-68.
4. Dirix P et al. The influence of xerostomia after radiotherapy on quality of life: Results of a questionnaire in head and neck cancer. Support Care Cancer. 2008;16(2):171-9.
5. Lin A et al. Quality of life after parotid-sparing IMRT for head-and-neck cancer: A prospective longitudinal study. Int J Radiat Oncol Biol Phys. 2003;57(1):61-70.

New Immunotherapy Approaches for The Treatment of Cancer: Reported at the European Society for Medical Oncology Congress 2018

Authors: Philippe Aftimos, Christiane Jungels, Nuria Kotecki, Leila Shaza, *Ahmad Awada

Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
*Correspondence to ahmad.awada@bordet.be

Disclosure: Dr Jungels declares travel expenses from Pharmamar and Bayer. Dr Awada declares advisory board honorarium from Cantargia. Dr Aftimos declares travel expenses from Roche and MSD; speaker's fees from Amgen and Novartis; and advisory board and consultant fees from Boehringer Ingleheim, Macrogenics, and Synthon. The remaining authors declare no conflicts of interest.

Keywords: Immunotherapy, European Society for Medical Oncology (ESMO), new drug, solid tumours.

Citation: EMJ Oncol. 2018:6[1]:75-76.
Abstract Review No. AR4.

Immunotherapy is currently a pillar in the treatment of cancer, in addition to surgery, radiotherapy, chemotherapy, and molecular-targeted therapies.

Our team, in collaboration with other investigators, reported the results of four important early clinical trials involving innovative immunotherapeutic approaches at the European Society for Medical Oncology (ESMO) Congress 2018 in Munich, Germany.

Flament et al.[1] reported Phase I studies assessing the safety and clinical activity of multiple doses of a NKG2D-based chimeric antigen receptor T cell therapy, CYAD-01, in metastatic solid tumours, in particular colorectal cancer and haematological malignancies. The THINK study, which is investigating chimeric antigen receptor T cell therapy without preconditioning, demonstrated the feasibility of multiple doses;[2] however, it is too early to conclude on the anti-tumour activity of this approach. Two other studies are ongoing, one of them in combination with neoadjuvant FOLFOX in colorectal cancer (SHRINK study).[3]

Awada et al.[4] reported a first-in-class, first-in-human Phase I/IIa trial of CAN04, a monoclonal antibody targeting IL-1 receptor accessory protein (IL1RAP), in patients with solid tumours. IL1RAP is a coreceptor for the IL-1 receptor, which is expressed on human cancer cells. CAN04 showed mainly infusion-related adverse events mitigated with a reduced priming dose of CAN04 and premedication. An expansion cohort is expected with a single agent and in combination with chemotherapy in non-small cell lung cancer and advanced pancreatic cancer.

Cho et al.[5] presented data on M7824, a bifunctional fusion protein targeting programmed death ligand 1 and TGF-β in patients with advanced squamous cell carcinoma of the head and neck. In summary, M7824 showed promising early clinical activity and a manageable safety profile. In this trial, an objective response rate of 22% was observed with a possible trend toward higher activity in human papilloma virus-positive tumours and evidence of clinical activity irrespective of programmed death ligand 1 status.

Finally, Awada et al.[6] reported the results of the translational part of a Phase I trial with copanlisib, a phosphoinositide 3-kinase (PI3K) inhibitor, and how this inhibition modulates the immune and tumour microenvironment in patients with non-Hodgkin lymphoma (NHL) or advanced solid tumours. The conclusion was that high prevalence of the PI3K isoforms, especially α in both NHL and solid tumours, and δ in NHL, is consistent with a role for PI3K signalling in immune suppression. The immune modulation profile of copanlisib supports combination studies with immunotherapy.

References

1. Flament A et al. Phase 1 studies assessing the safety and clinical activity of multiple doses of a NKG2D-based CAR-T therapy, CYAD-01, in metastatic colorectal cancer. Ann Oncol. 2018;29(suppl_8):viii150-204.
2. Celyad. A dose escalation Phase I study to assess the

safety and clinical activity of multiple cancer indications (THINK). NCT03018405. https://clinicaltrials.gov/ct2/show/NCT03018405.

3. Celyad. Dose Escalation and Dose Expansion Phase I Study to Assess the Safety and Clinical Activity of Multiple Doses of NKR-2 Administered Concurrently With FOLFOX in Colorectal Cancer With Potentially Resectable Liver Metastases (SHRINK). NCT03310008. https://clinicaltrials.gov/ct2/show/NCT03310008.
4. Awada A et al. A first-in-class, first-in-human Phase I/IIa trial of CAN04, targeting interleukin-1 receptor accessory protein (IL1RAP), in patients with solid tumors. Ann Oncol. 2018;29(suppl 8):viii400-41.
5. Cho BC et al. M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-β , in patients (pts) with advanced SCCHN: Results from a Phase 1 cohort. Ann Oncol. 2018;29(suppl 8): viii372-99.
6. Awada A et al. PI3K inhibition and modulation of immune and tumor microenvironment markers by copanlisib in patients with non-Hodgkin's lymphoma or advanced solid tumors. Ann Oncol. 2018;29(suppl_8):viii14-57.

Major Determinants of Delayed Access to Innovative Medicines for Metastatic Melanoma: The Results of the Melanoma World Society (MWS) and European Association of Dermato-Oncology (EADO) Survey

Authors: *Lidija Kandolf Sekulovic,[1] Sanjiv Agarwala,[2] Gabriela Cinat,[3] Axel Hauschild,[4] Claus Garbe[5]

1. Department of Dermatology, Faculty of Medicine, Military Medical Academy, Belgrade, Serbia
2. Department of Medical Oncology, St. Luke's Hospital & Health Network, Bethlehem, Pennsylvania, USA
3. Médica Oncóloga Instituto de Oncología Angel Roffo, Universidad de Buenos Aires Fundación CIDEA, Buenos Aires, Argentina
4. Department of Dermatology, University Clinic Schleswig-Holstein, Kiel, Germany
5. Centre for Dermatooncology, Department of Dermatology, Eberhard Karls University, Tuebingen, Germany

*Correspondence to lkandolfsekulovic@gmail.com

Disclosure: Dr Kandolf Sekulovic has no conflict of interest to declare regarding this article but has received relevant financial funding for activities outside the submitted work, which are speaker's fees from Roche, Novartis, Bristol-Myers Squibb, and MSD. Dr Agarwala has received travel and accommodations expenses from MSD and Bristol-Myers Squibb. Dr Hauschild has received clinical trial support, speaker´s honoraria, or consultancy fees from Amgen, Bristol-Myers Squibb, Merck Serono, MSD, Novartis, Oncosec, Philogen, Pierre Fabre, Provectus, Regeneron, and Roche. Dr Cinat has received speaker's honoraria or consultancy fees from Novartis, MSD, Bristol-Myers Squibb, Merck Serono, and Roche. Dr Garbe has declared no conflicts of interest.

Acknowledgements: The authors would like to acknowledge the support of their coauthors involved in the survey. Dr Kandolf Sekulovic was responsible for preparation of this ESMO abstract summary.

Keywords: Access, immuno-oncology, innovative medicines, metastatic melanoma, targeted therapy, treatment.

Citation: EMJ Oncol. 2018;6[1]:76-78. Abstract Review No. AR5.

At the 2018 European Society for Medical Oncology (ESMO) Congress in Munich, Germany, the Melanoma World Society (MWS) and European Association of Dermato-Oncology (EADO) presented the results of a survey assessing worldwide access to first-line recommended treatments for metastatic melanoma and the major determinants of access.

Metastatic melanoma is a chemotherapy-resistant cancer with a median survival of 6–9 months prior to 2010.[1] In recent years, a major breakthrough was achieved with targeted therapy and immunotherapy, leading, for the first time, to significantly prolonged survival for this group of patients, with nearly 50% of

patients in good prognostic groups surviving up to 5 years based on recent trials.[2-5] However, despite the high efficacy of targeted therapy and immunotherapy, they have high costs, which has led to restricted access to these treatments in parts of Europe; in 2016, >5,000 patients did not have access to these treatments.[6] Significant delays in reimbursement and different insurance coverage are some of the challenges healthcare systems face when trying to adapt to the rising costs of cancer care.[6] In this setting, there is a clear need for an objective measurement of clinical benefit of every treatment and development of value-based pricing.

Table 1: Estimated number of patients without access to innovative medicines in surveyed countries.

	Estimated number of metastatic melanoma patients	Patients treated with innovative medicines (%)	Patients without the access to innovative medicines (%)	Estimated number of patients without access
USA	9,000	60	40	3,600
China	4,200	10–30	70	2,940
Australia	3,000	>90	<10	0
Latin America				
Argentina	600	70	30	200
Mexico	NA	NA	NA	NA
Chile	350	<10	90	315
Brazil	2,000	10–30	70	1,400
Europe				
Austria	200	>90	<10	0
Belgium	350	>90	<10	0
Denmark	350	>90	<10	0
France	2,000	>90	<10	0
Germany	3,000	>90	<10	0
Greece	NA	>90	<10	0
Ireland	140	>90	<10	0
Italy	2,000	>90	<10	0
Netherlands	800	>90	<10	0
Portugal	200	30–50	50	100
Spain	400	>90	<10	0
Switzerland	350	>90	<10	0
UK	2,000	70–90	<10	200
Albania	30	10–30	70	21
Belarus	250	<10	90	225
Bosnia and Herzegovina	60	>90	10	50
Bulgaria	150	50–70	30	105
Croatia	100	>90	<10	0
Czech Republic	400	70–90	10	360
Estonia	50	>90	<10	0
Lithuania	50	30-50	50	25
FYR Macedonia	80	30-50	50	40
Poland	1,000	>90	<10	0
Romania	NA	50-70	30	NA
Serbia	200	30-50	50	100
Slovenia	150	>90	<10%	0
Ukraine	500	<10%	90	450
Total	33,960			10,131

NA: data not available.

The American Society of Clinical Oncology (ASCO) framework net clinical benefit 16 score and the ESMO magnitude of clinical benefit score have both been developed with the intention of being used for developing pricing and prioritisation of medicines for reimbursement and/or insurance coverage.[7,8]

The degree of inequality and major determinants of access to innovative treatments for metastatic melanoma have been largely unexplored. The MWS and EADO conducted a web-based survey on access to first-line recommended treatments for metastatic melanoma by current guidelines (National Comprehensive Cancer Network [NCCN], ESMO, and European Organisation for Research and Treatment of Cancer [EORTC]/EADO/European Dermatology Forum [EDF]) among melanoma experts from 1st September 2017–1st December 2018 from 34 countries: the USA, China, Australia, Argentina, Brazil, Chile, Mexico, and 27 European countries. Data on licensing and reimbursement of medicines and the number of patients treated were correlated with the data on health expenditure per capita, Mackenbach score of health policy performance, health technology assessment, and the ASCO and ESMO magnitude of clinical benefit scores of clinical benefit and market price of medicines.[7-10] Regression analysis for evaluation of correlation between the parameters was carried out using SPSS software.

In this study, the estimated number of patients without access in surveyed countries worldwide was 10,131 (Table 1). The recommended BRAFi+MEKi combination and anti-PD1 immunotherapy were registered and fully reimbursed in 17 (50.0%) of the countries, and anti-CTLA4+anti-PD1 combination in 9 (26.4%) countries. In 14 (41.1%) countries, the majority of patients were treated according to the recommended guidelines. Median delay in reimbursement was 871 days (range: 0–1,274 days). These results were in correlation with ASCO (rho=0.819; p=0.004), and ESMO scores of clinical benefit (rho=0.933, p<0.01) and median market price (rho=0.694, p=0.026), as well as with health expenditure per capita, health policy performance scores, and health technology assessment implementation (p<0.05). The medicines with the highest scores of clinical benefits were the ones with the longest delay in access. In the majority of countries (64.2%) price negotiations or managed entry agreements with national authorities were necessary for reimbursement.[10]

In conclusion, great discrepancy exists in metastatic melanoma treatment globally. Access to innovative medicines correlated with economic parameters as well as with healthcare system performance parameters. Patient-orientated drug development, market access, and reimbursement pathways must be urgently found.

References

1. Eigentler TK et al. Palliative therapy of disseminated malignant melanoma: A systematic review of 41 randomised clinical trials. Lancet Oncol. 2003;4(12):748-59.
2. Ugurel S et al. Survival of patients with advanced metastatic melanoma: The impact of novel therapies-update 2017. Eur J Cancer. 2017;83:247-57.
3. Long GV et al. Long-term outcomes in patients with BRAF V600-mutant metastatic melanoma who received dabrafenib combined with trametinib. J Clin Oncol. 2018;36(7):667-73.
4. Callahan MK et al. Nivolumab plus ipilimumab in patients with advanced melanoma: Updated survival, response, and safety data in a Phase I dose-escalation study. J Clin Oncol. 2018;36(4):391-5.
5. Hodi SF et al. Durable, long-term survival in previously treated patients with advanced melanoma (MEL) who received nivolumab (NIVO) monotherapy in a Phase I trial. Abstract CT001. AACR Annual Meeting, 16-20 April, 2016.
6. Kandolf Sekulovic L et al. More than 5000 patients with metastatic melanoma in Europe per year do not have access to recommended first-line innovative treatments. Eur J Cancer. 2017;75:313-22.
7. Schnipper LE et al. Updating the American Society of Clinical Oncology Value Framework: Revisions and reflections in response to comments received. J Clin Oncol. 2016;34(24):2925-34.
8. Cherny NI et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol. 2017;28(10):2340-66.
9. Mackenbach JP, McKee M. A comparative analysis of health policy performance in 43 European countries. Eur J Publ Health. 2013;23(2):195-201.
10. Kandolf Sekulovic L et al. Access to innovative medicines for metastatic melanoma worldwide: Melanoma World Society and European Association of Dermato-oncology survey in 34 countries. Eur J Cancer. 2018;104:201-9.

VIEW MORE ABSTRACTS ONLINE ←

Novel Targets and Therapies in T Cell Lymphoma

EDITOR'S PICK

This issue's Editor's Pick is from Kesavan and Collins, presenting the recent advances in our understanding of the cellular pathogenesis of T cell non-Hodgkin lymphoma (NHL) and the potential of clinically targeted therapies. There is an urgent and unmet clinical need to improve the limited prognosis faced by patients with T cell NHL, but, excitingly, with our rapidly evolving understanding of tumour biology, we are unravelling the biology of the various T cell NHL subtypes and exploiting it to our advantage. We are now approaching an era in which we will not only be able to target the cells of origin but also be able to customise therapy.

Samantha Warne

Editor

Authors: *Murali Kesavan, Graham P. Collins

Department of Clinical Haematology, Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford University Hospitals; Department of Oncology, University of Oxford, Oxford, UK
*Correspondence to murali.kesavan@oncology.ox.ac.uk

Disclosure: Dr Collins has received honoraria from Takeda, Roche, BMS, MSD, Gilead, and Celleron, and has received research support from Celgene, Amgen, Pfizer, MSD, and Celleron. Dr Kesavan has declared no conflicts of interest.

Acknowledgements: Dr Collins acknowledges support from the Haematology and Stem Cells theme of the National Institute for Health Research Oxford Biomedical Research Centre. Dr Kesavan acknowledges support from the Haematology Society of Australia and New Zealand (HSANZ). Both authors acknowledge support from the Oxford Cancer Research UK Experimental Cancer Research Centre. Dr Kesavan performed the literature review and wrote the first draft of the manuscript. Dr Collins designed the paper and reviewed and co-wrote the manuscript.

Received: 17.04.18

Accepted: 09.10.18

Keywords: Biology, cell of origin, immunotherapies, JAK/STAT, NFκB, novel pathways, novel therapies, PI3k/Akt/mTOR, targeted therapy, T cell lymphoma.

Citation: EMJ Oncol. 2018;6[1]:79-90.

Abstract

This review presents the recent advances in our understanding of the cellular pathogenesis of T cell non-Hodgkin lymphoma (NHL) and the potential of clinically targeted therapies. Patients with T cell NHL continue to face a limited prognosis, with the large majority experiencing a relapsed/refractory disease course and succumbing to their disease. Recent significant advances in our understanding of lymphomagenesis have not only revealed the complexity of T cell NHL but also helped to identify the cellular structures and pathways required for tumour proliferation, immune evasion, and therapy resistance. The NFκB pathway plays a critical role in T cell lymphoma through complex interactions with cell surface receptors and ligands, the proteasome, and crosstalk with ancillary pathways,

such as the PI3K/Akt/mTOR cascade, which are also involved in chemokine and cytokine-mediated cellular signalling and growth. There is now also growing evidence for recurrent mutations involving the JAK/STAT pathway in a number of T cell lymphoma subtypes. Preclinical studies have highlighted the importance of novel cell surface proteins, downstream pathways, proteasome activation of NFκB, nuclear transport proteins, folate metabolism, epigenetic regulators, and cell of origin derivation. These advances represent a new era in T cell NHL therapy development. Although the optimal chemoimmunotherapy combination for first-line and salvage therapy is yet to be defined, the future paradigm is clearly shifting towards a biology-driven approach, which will hopefully yield improved outcomes for all patients with T cell lymphoma.

INTRODUCTION

The rapid evolution of laboratory technologies over the last decade has enhanced our ability to understand the intricate pathways involved in lymphoma biology and therapy resistance, heralding an era of novel, targeted, non-chemotherapy-based approaches to treatment.[1] However, the outcome of most peripheral T cell lymphoma (PTCL) subtypes remains poor, highlighting the limitations of traditional chemotherapy and the importance of a biology-driven paradigm.[2] This article presents an update on recent advances in T cell lymphoma biology by examining the current evidence for pathways implicated in disease and commenting on their therapeutic potential (Figure 1).

THE NFκB PATHWAY

A common characteristic of various lymphoma and leukaemia subtypes is constitutive expression of NFκB, a master regulator of the inflammatory response.[3,4] In the canonical (classical) signalling pathway, NFκB release is mediated by the activation of proinflammatory cell surface receptors (TNF receptor, IL receptor, Toll-like receptor, T cell receptor [TCR], epidermal growth factor receptor), activating the IκB kinase complex.[4] In the non-canonical (alternative) signalling pathway, NFκB activation is triggered by signalling from CD40L, lymphotoxin receptor, and B cell activating factor receptor.[5] Once activated, NFκB directly binds to DNA, propagating a number of pro-oncogenic changes. Its role in lymphomagenesis can be broadly separated into three categories: proinflammatory (upregulation of cytokines, such as IL-6, IL-8, and TNF-α, and chemokines, such as CXCL2), antiapoptotic, and induction of mitogenic proteins (e.g., c-Myc).[4,6,7]

As demonstrated by Wang et al.,[8] tyrosine kinase interaction with the TCR signalosome (TCR proteins acting as a network hub, orchestrating interactions to control signalling)[9] leads to activation of the NFκB pathway and production of specific transcription factors required for T cell lymphoma proliferation, immune evasion, and therapy resistance. Furthermore, NFκB activation has been shown to induce programmed cell death protein-1 (PD-1) expression and histone modification in T cells, macrophages, and B cells, leading to T cell exhaustion.[8] With recent advances in small molecule therapy, it is now possible to target components and ancillary pathways involved in NFκB activation.[10]

CELL SURFACE TARGETS

CD30

The discovery of immunohistochemistry and the understanding that a proportion of T cell lymphomas express CD30 have led to the successful development of anti-CD30 as a therapeutic strategy, especially for anaplastic large cell lymphoma (ALCL), in which CD30 stimulation is known to upregulate NFκB activity.[11] Brentuximab vedotin (BV) is an antibody–drug conjugate that targets CD30 in which the conjugated agent, monomethyl auristatin E, is a potent anti-tubulin toxin. BV has shown profound anti-tumour activity as a single agent in relapsed ALCL. Among 58 patients with relapsed/refractory ALCL treated with single agent BV, an overall response rate (ORR) of 86% and complete response (CR) rate of 57% was observed,[12] which translated to a 5-year overall survival of 60%, an unprecedented survival rate in this patient group.[13] Efforts are now being made to use BV in the upfront setting. Twenty-six patients with CD30-expressing

T cell lymphoma (16 of whom had ALCL) were treated with cyclophosphamide, doxorubicin, and prednisolone in combination with BV. The ORR was 100%, with a 92% CR rate. The estimated 5-year progression-free survival (PFS) and overall survival were 52% and 80%, respectively, which compares favourably with historical data.[14] The results of a subsequent Phase III, randomised, double-blind, placebo-controlled trial, ECHELON-2,[15] comparing cyclophosphamide, doxorubicin, and prednisolone in combination with BV with standard cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, are eagerly awaited.

TCRB1 and *TCRB2*

More recently, the ability to discriminate between normal and abnormal T cells through analysis of the TCR β-chain has been explored. There are two genes involved in the TCR β-chain constant region (*TCRB1* and *TCRB2*), which are expressed in a mutually exclusive manner. Hence, a normal population of T cells will comprise a mixture of *TCRB1*+ and *TCRB2*+ cells.[16,17] In their landmark paper, Maciocia et al.[18] demonstrated tumour cell clonality, based on *TCRB1*+/- status, in peripheral blood, marrow, and tissue samples from patients with a range of T cell non-Hodgkin lymphoma (NHL) subtypes. Using a mouse model of T cell NHL, the researchers demonstrated the efficacy of targeting *TCRB1*-expressing malignant T cell clones with anti-TCRB1 chimeric antigen receptor-expressing T cells.[18] These findings carry significant implications not only for therapy but also for diagnosis and disease monitoring.

Cell Surface Receptors

Cell surface receptors also provide a means for malignant T cell survival through interaction with external stimuli within the pathological niche. The transmembrane receptor integrin αvβ3, expressed on malignant cells, plays a pivotal role in this interaction. Thyroid hormones are known to exert their action through simultaneous binding of nuclear receptors and integrin αvβ3.[19,20] Cayrol et al.[21] demonstrated that thyroid hormones at physiologic levels can stimulate murine T cell lymphoma via intracellular pathways, ultimately leading to activation of NFκB and angiogenesis promotion. Furthermore, using a PTCL not otherwise specified (PTCL-NOS) xenograft model, Cayrol et al.[21] demonstrated the therapeutic efficacy of cilengitide (a clinically available integrin αvβ3 inhibitor). Mice treated with cilengitide had a statistically significant reduction in tumour size, associated with decreased NFκB pathway activation and increased apoptosis.[21]

IL receptors also play an important role in the activation of the NFκB pathway. Recent evidence has identified a pathogenic role for IL-7 and IL-7R in T cell lymphomas.[22-25] Using mouse models, Yasunaga et al.[26] demonstrated that increased IL-7R signalling promoted tumour growth and steroid resistance in lymphoid malignancies. Conversely, inhibition of IL-7R signalling using an antibody–drug conjugate could effectively reduce tumour size, limit secondary lymph node infiltration, and potentially overcome steroid resistance.[26]

Programmed Cell Death Protein-1/ Programmed Death-Ligand 1

As previously noted, NFκB pathway activation induces PD-1/programmed death ligand-1 (PD-L1) expression in a number of different cell types, including T cells and macrophages. Histopathological studies have confirmed increased PD-1/PD-L1 expression in a number of T cell NHL, especially in nodal and extranodal aggressive phenotypes.[27-29] Thus, PD-1/PD-L1 blockade has been the focus of a number of early-phase studies in lymphoma.

Nivolumab, a fully human IgG4 monoclonal antibody (mAb) against PD-1, was noted to induce an ORR of 15% and 40% in mycosis fungoides (MF) and PTCL NOS, respectively, at a median follow-up of 67 weeks.[30] However, it must be noted that the number of participants in this early-phase study was limited and no cases of CR were observed in the T cell NHL cohorts.[30] Nevertheless, given the signal of favourable activity combined with an acceptable safety profile, further studies are underway exploring the potential for combining PD-1 inhibition with other agents.

Ansell et al.[31] recently reported preliminary findings of a Phase I study of nivolumab and ipilimumab combination therapy, a human mAb targeting CTLA-4 (involved in the non-canonical NFκB pathway), in heavily pretreated NHL. Of the 11 T cell NHL subjects (7 cutaneous T cell lymphomas [CTCL] and 4 PTCL-NOS), only 1 (9%)

achieved a partial response, 4 (36%) had stable disease, and no cases of CR were observed. The median overall survival in the T cell NHL cohort was 13.2 months, with a median progression-free survival of 2 months. Despite the limited number of participants, these results were favourable when compared to the B cell NHL cohort and similar to those noted in prior studies of nivolumab monotherapy.[31]

Chronic Epstein–Barr virus infection is known to induce PD-1/PD-L1 expression. Given its association with extranodal natural killer/T cell lymphoma (ENKTL), there has been increasing interest in its role in this subtype of T cell NHL. Retrospective studies have identified PD-L1 expression as a potential marker of favourable disease control, with improved OS and PFS noted in both advanced and nasal-type lymphomas.[32,33] Although combination chemotherapy is still the preferred first-line treatment,[34-37] novel therapies are being studied in the relapsed/refractory setting. In a recently published study, Kwong et al.[38] treated seven ENKTL patients with relapsed/refractory disease following exposure to L-asparaginase-containing regimens. Patients received single agent pembrolizumab (anti-PD-1 mAb) at a fixed dose of 2 mg/kg at 3-weekly intervals (with the exception of one patient who was dosed at 2-weekly intervals). After a median of seven cycles of therapy and a median follow-up of 6 months, all patients demonstrated a response, with five (71%) meeting the criteria for CR and strength of PD-1 expression correlating with disease response.[38]

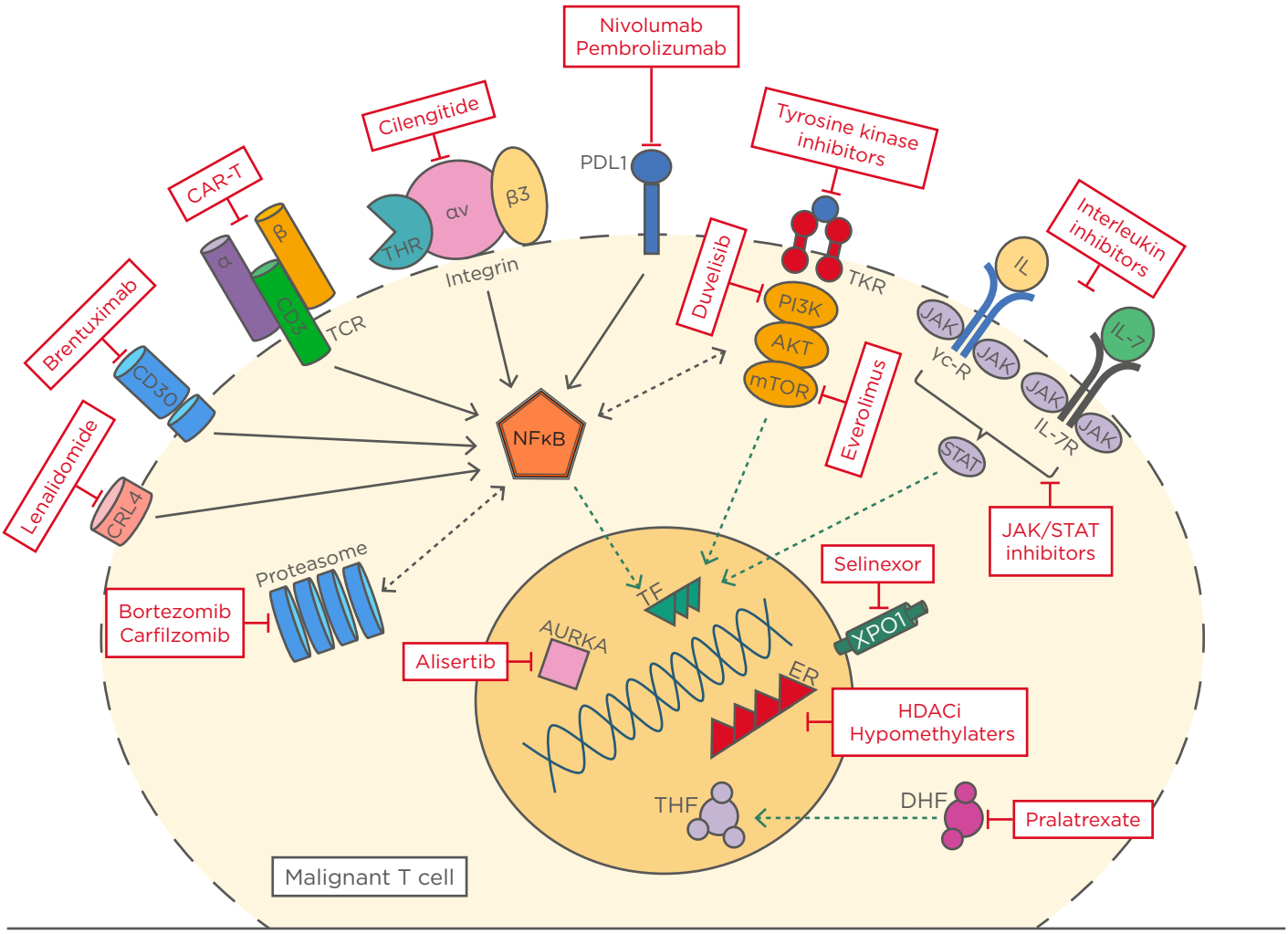


Figure 1: An overview of novel targets in T cell lymphoma.

AURKA: Aurora A kinase; CAR-T: chimeric antigen receptor T cell; DHF: dihydrofolate; ER: enhancer; HDACi: histone deacetylase inhibitor; TCR: T cell receptor; TKR: tyrosine kinase receptor; THF: tetrahydrofolate; TF: transcription factor.

PI3K/AKT/mTOR PATHWAY INHIBITION

Although not directly linked to NFκB regulation, there is considerable cross-talk between the PI3K pathway and canonical activation of NFκB via AKT.[39] Direct suppression of either pathway results in a reciprocal reduction in activity of the other.[40] Various B cell lymphoma models have also demonstrated simultaneous activation of both pathways contributing to lymphomagenesis.[41,42] In this regard, a number of recent studies have identified the sensitivity of B and T cell lineage leukaemia and lymphoma cells to autoimmunity checkpoint activation (to avoid clonal deletion by autoreactive B and T cell receptors), via upregulation of numerous pathways, including PI3K activation.[43-45]

Given that *in vitro* PI3K-δ/γ subunit inhibition can directly supress T cell lymphoma growth and proliferation, Horwitz et al.[46] studied the activity of duvelisib (a novel PI3K-δ/γ) in a Phase I open-label trial in patients with relapsed/refractory PTCL-NOS (n=16) and CTCL (n=19), the majority of the latter group being histone deacetylase inhibitor-resistant. The researchers observed an ORR of 50% and 31.6% for PTCL-NOS and CTCL, respectively, with three patients achieving a CR. Changes in cytokine profile correlated with disease response, with an increase in soluble CD40L and IL-17α conferring a favourable outcome.[46] Once again, despite limited participant numbers, preliminary data for PI3K inhibitors in T cell lymphoma is promising and the outcomes of a number of forthcoming clinical trials investigating novel combinations that include PI3K pathway inhibition are eagerly awaited.

The mTOR pathway is defined by the complex and inter-related activation of two distinct protein complexes, mTORC1 and mTORC2, which interact closely with the PI3K pathway and act upstream from and influence NFκB. Together, the interaction and activation of this protein complex leads to eIF4E and Akt activation, which promotes cell growth, survival, and proliferation in a number of malignancies, including T cell NHL.[47-49]

Preliminary studies, however, show that inhibition of mTORC1 alone leads to upregulation of Akt through disruption of its inhibitory influence on mTORC2.[49] *In vitro* studies with everolimus (a first-in-class mTOR inhibitor) confirmed its inhibitory effect on mTORC1 and showed potential for efficacy in PTCL-NOS.[50] This was confirmed in the clinical setting by Witzig et al.,[51] following their study of 16 patients with relapsed T cell NHL (CTCL [n=7], PTCL-NOS [n=4], ALCL [n=2], ENKTL [n=1], angioimmunoblastic T cell lymphoma [AITL, n=1], and T cell acute lymphoblastic leukaemia/lymphoma [n=1]). The group observed a 44% (7/16) ORR and a median PFS of 4.1 months in response to a once daily oral everolimus dose of 10 mg. With a median duration of response of 8.5 months in responders, proof of concept was established.[51] There are currently a number of early-phase trials underway testing the efficacy of second-generation mTOR inhibitors (which target both mTOR complexes) alone and in combination for relapsed/refractory T cell NHL. Furthermore, small molecules have been developed that can target both the mTOR and PI3K enzymes.[52]

PROTEASOME INHIBITION AND IMMUNOMODULATION

Despite the wide availability of a number of pharmacologic agents targeting the proteasome and considering its integral role in regulating the NFκB pathway (phosphorylation and ubiquitination of IκB), only a limited number of studies have assessed their role in T cell NHL. Zinzani et al.[53] first reported on the efficacy of bortezomib (a first-generation proteasome inhibitor) in their 2007 Phase II study. They demonstrated a signal, predominantly in CTCL, with a 67% ORR that was sustained over 7–14 months.[53] Subsequently, Ishida et al.[54] demonstrated encouraging activity of lenalidomide monotherapy in adult T cell leukaemia/lymphoma (ATLL), which is prevalent in Japan, accounting for 25% of PTCL cases. In a Phase II study of 26 patients with relapsed ATLL, Ishida et al.[54] observed an ORR of 42%, which met the study's primary endpoint. This response was noted across all presentations of ATLL but the most encouraging response was noted in lymphomatous and unfavourable chronic presentations.[54] More recently, through global transcriptome analysis, proteasome inhibition with ixazomib (a proteasome subunit beta type-5 inhibitor) significantly improved tumour response and overall survival in T cell

NHL xenograft models via downregulation of Myc and checkpoint kinase-1.[55]

NUCLEAR TRANSPORTATION

The nuclear export receptor exportin 1 (XPO1) is a mediator of nuclear protein migration, including NFκB, and overexpressed in a number of haematological malignancies.[56,57] Preclinical data demonstrated that inhibiting XPO1 led not only to an overall increase in cellular tumour suppressor proteins within malignant cells but isolated these proteins to the nucleus, promoting apoptosis and significantly prohibiting tumour cell growth and proliferation.[56-58]

Selinexor is a first-in-class oral selective inhibitor of nuclear export. In their study of 79 patients with relapsed/refractory NHL, Kuruvilla et al.[59] observed an ORR of 31% (n=22), which included 4 cases of CR. The most prevalent safety concerns were Grade 3–4 thrombocytopenia and neutropenia, which occurred in 32% and 47% of patients, respectively. Tumour biopsies confirmed decreases in cell signalling pathways, reduced proliferation, and, most importantly, nuclear localisation of XPO1 cargos.[59] Although T cell NHL patients were not included in this study, the pharmacodynamic results reported were very encouraging.[59] However, the subsequent Australian Phase II study of single agent selinexor in relapsed/refractory T cell NHL[60] was terminated early due to enrolment challenges (n=16 at time of study closure), with the results yet to be published. Despite this, the Singaporean National Cancer Centre has recently launched a Phase I trial of selinexor in combination with standard dose ifosfamide, carboplatin, and etoposide for relapsed/refractory PTCL.[61] Furthermore, *in vivo* studies using eltanexor, a second-generation selective inhibitor of nuclear export, have shown early promise, with clinical trials forthcoming.[62]

THE COMMON GAMMA: JAK/STAT

The common gamma (γc) receptor-dependent cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21) and their receptor targets play a critical role in T cell immunity. The receptors for these respective cytokines lack intrinsic kinase activity and, as such, their functionality is dependent on their association with JAK cytoplasmic tyrosine kinases. Cytokine binding to receptors leads to cross-JAK phosphorylation, phosphorylation of the intracellular cytokine receptor tail, and creates a docking site for STAT. Once activated, phosphorylated STAT translocates to the nucleus and acts as a transcription factor.[63] Almost all forms of T cell lymphoma have now been associated with disorders involving activation of the γc/JAK/STAT system.[64-71] It is now understood that activation of the γc/JAK/STAT system alone is not sufficient to cause abnormal T cell proliferation. For this to occur, the entire pathway, from cytokine receptor augmentation to STAT phosphorylation and nuclear transportation, must be activated.[63] There is growing preclinical evidence for the efficacy of JAK/STAT inhibitors in T cell NHL[72] and this will undoubtedly transfer into the early-phase clinical setting.

AURORA A KINASE INHIBITION

Aurora A kinase is a serine/threonine kinase that plays an integral role in cellular mitosis by localising to the centrosome and regulating chromatid segregation from prophase to metaphase. While expression is limited in normal tissue, overexpression has been identified in a number of malignancies, including subsets of T cell NHL.[73,74] Subsequently, upon development of the selective oral aurora A kinase inhibitor, alisertib, a number of early-phase studies were performed.[75-77]

Initial results from two pivotal Phase II studies of relapsed/refractory lymphoma revealed an ORR of approximately 30%, with a promising signal in PTCL-NOS and transformed mycosis fungoides;[75,76] however, these results have not translated into improved patient outcomes. As presented by O'Connor et al.,[77] the interim analysis of the multicentre, randomised Phase II study of alisertib versus investigator choice for relapsed/refractory PTCL failed to meet significance and resulted in the study being prematurely terminated. Of the 238 patients randomised, the ORR of alisertib and investigator choice were 33% versus 43%, including a superior CR rate in favour of the latter.[77] Despite these findings, the combination potential of alisertib remains to be explored. This result, however, underscores the importance of subjecting novel

agents to randomised trials against standard of care before their adoption into routine practice.

EPIGENETIC DYSREGULATION

Gene transcription is not only dependent on a number of intracellular pathways but also relies on DNA interaction with the histone protein octamer, commonly known as the nucleosome. This interaction is largely controlled by post-translational modification of the histone protein, including acetylation and methylation.[78] Direct methylation of cytosine bases within DNA is an additional mechanism of transcriptional control that is often linked to histone modification patterns and these processes together are termed epigenetic regulation. Mutations of enzymes involved in post-translational modifications lead to aberrant DNA methylation and promote oncogenesis. With respect to T cell NHL, studies have demonstrated recurring mutations in TET2, isocitrate dehydrogenase (IDH), and DNA methyltransferase 3 (DNMT3). Both TET2 and IDH mutations result in increased DNA methylation, thus establishing a role for demethylating agents and histone deacetylase inhibition in T cell NHL.[2]

Delarue et al.[79] studied 19 patients mainly with relapsed/refractory PTCL (as first-line therapy for 2 patients) who were treated with the hypomethylating single agent 5-azacyctidine. Ten patients had a previous or concomitant diagnosis of myelodysplastic syndrome, mainly chronic myelomonocytic leukaemia. A 53% ORR was observed but 9 out of 12 patients (75%) with AITL responded.[79] Of interest, eight patients with AITL who had *Tet2* mutation status available had a mutation. A number of trials are ongoing using demethylating agents in combination.[80]

Promising early-phase data using first-generation histone deacetylase inhibitors (HDACi) led to the rapid approval of a number of agents for a variety of T cell NHL subtypes.[81-86] However, single-agent activity is modest and has meant that while approved in the USA, European approval has not been forthcoming. In addition, randomised trials of single agent HDACi with standard of care have not been conducted, undermining confidence in their use. When faced with a modest activity signal as a single agent, focus has rightly shifted to combination therapies.

In their Phase Ib/II study of first-line romidepsin plus standard CHOP, Dupuis et al.[87] demonstrated significant responses, albeit with associated myelotoxicity and potential cardiac toxicity. The ORR of 68% (51% CR, 17% partial response), PFS of 57%, overall survival of 76.5%, at a median follow-up of 17.5 months, came at a cost, with two-thirds of patients experiencing at least one serious adverse event.[87] However, given the promising response and survival outcomes, the planned Phase III trial of romidepsin plus standard CHOP study[88] was initiated.

The novel combination of HDACi and proteasome inhibitors also shows considerable promise. In their Phase II study of panabinostat plus bortezomib for relapse/refractory PTCL or NK/T cell NHL, Tan et al.[89] reported an ORR of 43% (10 out of 23), with 22% (5 out of 23) of patients attaining a CR. The median time to response was 6 weeks. Myelotoxicity was once again identified as the major concern, with approximately two-thirds of patients experiencing Grade 3/4 haematotoxicity.[89] The encouraging results of this study have led to second-generation combination therapies, with a study of romidepsin plus carfilzomib for relapsed/refractory PTCL currently recruiting in the UK.[90] This study is also investigating the potential utility of HR23B protein expression as a predictive biomarker of response. HR23B was identified in a genome-wide loss-of-function screen to identify genes involved in the sensitivity of tumour cells to HDACi.[91] The protein has an important role in shuttling ubiquitinated proteins to the proteasome.[92] Retrospective studies have identified an association between HR23B expression and response of cutaneous T cell lymphoma.[93] Prospective confirmation is required before its use as a predictive biomarker is established.

FOLATE METABOLISM

Neoplastic T cell proliferation depends on DNA and RNA synthesis, which require folate metabolism.[94] Pralatrexate is an antineoplastic folate analogue that directly targets both cellular folate transport and metabolism through enzyme inhibition, disrupting DNA and RNA synthesis.[95] Early *in vitro* studies demonstrated the cytotoxic activity of pralatrexate in a number of lymphoproliferative disorder cell lines and xenograft models.[96-98]

The pivotal PROPEL study,[99] a Phase II single-arm, open-label study, enrolled 115 patients with relapsed or refractory PTCL. Of the 109 evaluable patients, the ORR was 29% (n=32), which included 11% CR (n=12) and 18% partial response (n=20). The median duration of response was 10 months, with a median PFS and OS of 3.5 and 14.5 months, respectively.[99] The early durable responses observed led to the rapid approval of this agent in the USA for relapsed/refractory PTCL. Similar to with HDACi, no randomised trial was performed and a European license has not yet been granted.

The recent Phase I/II study of pralatrexate in Japanese patients supported the PROPEL data. Following an identical dosing regimen, the authors reported an ORR of 45% among the 20 evaluable Japanese patients.[99,100] Although both studies demonstrated high rates of mucositis, this may be mitigated by concomitant leucovorin administration, thus enhancing the safety of this combination.[101]

The efficacy of pralatrexate in relapsed/refractory disease has led investigators to explore its combination potential. Shustov et al.[102] recently presented preliminary data from their Phase I dose-escalation study of upfront pralatrexate 30 mg/m^2 per day for 1–8 days, plus standard dose CHOP. Of the 27 evaluable patients, the researchers observed an investigator-assessed ORR and CR of 89% and 67%, respectively. The only treatment-related Grade >3 adverse events noted were neutropenia (n=4). The maximum tolerated dose of pralatrexate was not reached.[102] Although preliminary, the relative safety of pralatrexate plus CHOP is reassuring and no doubt the efficacy of this and other similar novel combinations will be explored further with planned Phase II and III studies.

FOLLICULAR HELPER T CELL DERIVATION

A subset of CD4+ T cells, follicular helper T (Tfh) cells, play a critical role in physiologic immunity.[103] Localised in lymphoid organs, Tfh cells have features of both central and effector memory T cells[104] and, in comparison to normal B and T cells, Tfh express high levels of inducible costimulator (ICOS) and chemokine receptor 5. Through the influence of ICOS activity, Tfh cells undergo differentiation, with a high affinity for expression of BCL6, IL-24, IL-4, CXCL13, and PD1, in addition to ICOS and chemokine receptor 5.[103,105-108] ICOS ligand activation is also closely linked with NFκB regulation.[109] Thus, Tfh cells are a key effector cell at the interface between innate immunity and normal B and T cell maturation, with dysregulation leading to both autoimmune dysfunction and lymphomagenesis.

Gene expression studies of malignant T cells in AITL have established a striking similarity to Tfh cells, sufficiently supporting their role as the cell of origin in AITL. This is further supported by the biochemical and clinical features of AITL, including autoimmune dysregulation and enhanced B cell activation. Subsequent targeted sequencing studies have demonstrated recurrent mutations of *TET2*, *DNMT3A*, and *IDH2*, and loss of *RHOA* (coding for GTPase Rhoa) in AITL of Tfh cell origin.[110-112] With this knowledge, Tfh cells have also now been defined as the cell of originin subsets of other T cell NHL, including PTCL-NOS and CTCL.

With respect to therapeutic implications, establishing Tfh cell derivation by pathologic and genetic analysis may select for tumour types that are sensitive to direct antibodies that target highly expressed antigens (e.g., ICOS, PD1, CXCR13). These tumours may also be susceptible to NFκB pathway (also regulated by ICOS ligand activation) targets, demethylating agents, and histone deacetylase inhibition. Further studies are required to establish the true impact of Tfh cell derivation in T cell NHL.

CONCLUSION

As it stands, the majority of patients presenting with T cell NHL will not successfully achieve a complete remission with current first-line standard of care chemotherapy, subsequently experiencing a relapsing/remitting course and eventually succumbing to their disease.[113-116] Of the small proportion of patients who do achieve a favourable response, there is no consensus on consolidation approaches and those unsuitable for transplantation are likely to experience disease relapse.[117-119] There is an urgent and unmet clinical need to improve the limited prognosis faced by these patients.

With a rapidly evolving understanding of tumour biology, we are gradually able to unravel the underlying biology of the various T cell NHL subtypes and exploit it to our advantage. One of the major hurdles to managing the disease is our inability to specifically target neoplastic T cells without diminishing the innate immunogenicity of normal T cells. As outlined, the medical community is now approaching an era in which we will not only be able to target the cells of origin, but we will be able to customise therapy based on identifying a patient's unique immunophenotypic, histopathologic, and genetic features (Figure 1). Just as combination immunochemotherapy has dramatically changed the outcomes for B cell lymphoma, we now have the knowledge and the tools required to reshape the future of T cell NHL. Of those targets discussed, targeting cell surface molecules, such as CD30, with antibody–drug conjugates has changed standard of care for relapsed ALCL and may impact front-line treatment of CD30-positive tumours. To further impact survival, it is unlikely that a single target will suffice; rational combinations of targeted agents (with or without more conventional chemotherapy) in biomarker-defined populations represent the way forward in this heterogeneous disease.

References

1. Dunleavy K et al. New strategies in peripheral T-cell lymphoma: Understanding tumor biology and developing novel therapies. Clin Cancer Res. 2010;16(23):5608-17.
2. O'Connor OA et al. Changing the paradigms of treatment in peripheral T-cell lymphoma: From biology to clinical practice. Clin Cancer Res. 2014;20(20):5240-54.
3. Guzman ML et al. Nuclear factor-κB is constitutively activated in primitive human acute myelogenous leukemia cells. Blood. 2001;98(8):2301-7.
4. Pires BRB et al. NF-kappaB: Two sides of the same coin. Genes (Basel). 2018;9(1).
5. Sun SC. Non-canonical NF-κB signaling pathway. Cell Res. 2011;21(1):71-85.
6. Hayden MS et al. Shared principles in NF-kappaB signaling. Cell. 2008;132(3):344-62.
7. Vandenabeele P et al. Molecular mechanisms of necroptosis: An ordered cellular explosion. Nat Rev Mol Cell Biol. 2010;11(10):700-14.
8. Wang T et al. T-cell receptor signaling activates an ITK/NF-κB/GATA-3 axis in T-cell lymphomas facilitating resistance to chemotherapy. Clin Cancer Res. 2017;23(10):2506-15.
9. Smith SE et al. Multiplex matrix network analysis of protein complexes in the human TCR signalosome. Sci Signal. 2016;9(439):rs7.
10. Gupta SC et al. Inhibiting NF-kappaB activation by small molecules as a therapeutic strategy. Biochim Biophys Acta. 2010;1799(10-12):775-87.
11. Wright CW et al. CD30 activates both the canonical and alternative NF-κB pathways in anaplastic large cell lymphoma cells. J Biol Chem. 2007;282(14):10252-62.
12. Pro B et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: Results of a Phase II study. J Clin Oncol. 2012;30(18): 2190-6.
13. Pro B et al. Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood. 2017;130(25):2709-17.
14. Fanale MA et al. Five-year outcomes for frontline brentuximab vedotin with CHP for CD30 expressing peripheral T-cell lymphomas. Blood. 2018;131(19):2120-4.
15. Seattle Genetics, Inc. ECHELON-2: A Comparison of Brentuximab Vedotin and CHP With Standard-of-care CHOP in the Treatment of Patients With CD30-positive Mature T-cell Lymphomas (ECHELON-2). NCT01777152. https://clinicaltrials.gov/ct2/show/NCT01777152.
16. Sims JE et al. Complexity of human T-cell antigen receptor beta-chain constant- and variable-region genes. Nature. 1984;312(5994):541-5.
17. Tunnacliffe A et al. Sequence and evolution of the human T-cell antigen receptor beta-chain genes. Proc Natl Acad Sci U S A. 1985;82(15):5068-72.
18. Maciocia PM et al. Targeting the T cell receptor beta-chain constant region for immunotherapy of T cell malignancies. Nat Med. 2017;23(12):1416-23.
19. Barreiro Arcos ML et al. Thyroid hormones increase inducible nitric oxide synthase gene expression downstream from PKC-ζ in murine tumor T lymphocytes. Am J Physiol Cell Physiol. 2006;291(2):C327-36.
20. Barreiro Arcos ML et al. Cooperative nongenomic and genomic actions on thyroid hormone mediated-modulation of T cell proliferation involve up-regulation of thyroid hormone receptor and inducible nitric oxide synthase expression. J Cell Physiol. 2011;226(12):3208-18.
21. Cayrol F et al. Integrin αβ3 acting as membrane receptor for thyroid hormones mediates angiogenesis in malignant T cells. Blood. 2015;125(5):841-51.
22. Zenatti PP et al. Oncogenic IL7R gain-of-function mutations in childhood T-cell acute lymphoblastic leukemia. Nat Genet. 2011;43(10):932-9.
23. Adachi T et al. Hair follicle-derived IL-7 and IL-15 mediate skin-resident memory T cell homeostasis and lymphoma. Nat Med. 2015;21(11): 1272-9.
24. Mazzucchelli RI et al. The human IL-7 receptor gene: Deletions, polymorphisms and mutations. Semin Immunol. 2012;24(3):225-30.
25. Tal N et al. Interleukin 7 and thymic stromal lymphopoietin: From immunity to leukemia. Cell Mol Life Sci. 2014;71(3):365-78.
26. Yasunaga M et al. Immunoregulation by IL-7R-targeting antibody-drug conjugates: Overcoming steroid-resistance in cancer and autoimmune disease. Sci Rep. 2017;7(1):10735.
27. Zaja F et al. CD38, BCL-2, PD-1, and PD-1L expression in nodal peripheral T-cell lymphoma: Possible biomarkers for novel targeted therapies? Am J Hematol. 2017;92(1):E1-2.
28. Krishnan C et al. PD-1 expression in T-cell lymphomas and reactive lymphoid entities: Potential overlap in staining patterns between lymphoma and viral lymphadenitis. Am J Surg

Pathol. 2010;34(2):178-89.

29. Gatalica Z et al. Programmed cell death 1 (PD-1) and its ligand (PD-L1) in common cancers and their correlation with molecular cancer type. Cancer Epidemiol Biomarkers Prev. 2014;23(12):2965-70.
30. Lesokhin AM et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: Preliminary results of a Phase Ib study. J Clin Oncol. 2016;34(23):2698-704.
31. Ansell S et al. A Phase 1 study of nivolumab in combination with ipilimumab for relapsed or refractory hematologic malignancies (CheckMate 039). Blood. 2016;128:183.
32. Jo JC et al. Expression of programmed cell death 1 and programmed cell death ligand 1 in extranodal NK/T-cell lymphoma, nasal type. Ann Hematol. 2017;96(1):25-31.
33. Kim WY et al. Expression of programmed cell death ligand 1 (PD-L1) in advanced stage EBV-associated extranodal NK/T cell lymphoma is associated with better prognosis. Virchows Arch. 2016;469(5):581-90.
34. Wang H et al. Comparison of gemcitabine, oxaliplatin and L-asparaginase and etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone as first-line chemotherapy in patients with stage IE to IIE extranodal natural killer/T-cell lymphoma: A multicenter retrospective study. Leuk Lymphoma. 2015;56(4):971-7.
35. Wang L et al. First-line combination of gemcitabine, oxaliplatin, and L-asparaginase (GELOX) followed by involved-field radiation therapy for patients with stage IE/IIE extranodal natural killer/T-cell lymphoma. Cancer. 2013;119(2):348-55.
36. Zhang L et al. Five-year analysis from phase 2 trial of "sandwich" chemoradiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma. Cancer Med. 2016;5(1):33-40.
37. Li X et al. DDGP versus SMILE in newly diagnosed advanced natural killer/T-cell lymphoma: A randomized controlled, multicenter, open-label study in China. Clin Cancer Res. 2016;22(21):5223-8.
38. Kwong YL et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. Blood. 2017;129(17):2437-42.
39. Hussain AR et al. Cross-talk between NFkB and the PI3-kinase/AKT pathway can be targeted in primary effusion lymphoma (PEL) cell lines for efficient apoptosis. PLoS One. 2012;7(6):e39945.
40. Kloo B et al. Critical role of PI3K signaling for NF-kappaB-dependent survival in a subset of activated B-cell-like diffuse large B-cell lymphoma cells. Proc Natl Acad Sci U S A. 2011;108(1):272-7.
41. Liu P et al. Targeting the phosphoinositide 3-kinase pathway in cancer. Nat Rev Drug Discov. 2009;8(8):627-44.
42. Fruman DA et al. The PI3K pathway in human disease. Cell. 2017;170(4):605-35.
43. Chen Z et al. Signalling thresholds and negative B-cell selection in acute lymphoblastic leukaemia. Nature. 2015;521(7552):357-61.
44. Shojaee S et al. Erk negative feedback control enables pre-B cell transformation and represents a therapeutic target in acute lymphoblastic leukemia. Cancer Cell. 2015;28(1):114-28.
45. Shojaee S et al. PTEN opposes negative selection and enables oncogenic transformation of pre-B cells. Nat Med. 2016;22(4):379-87.
46. Horwitz SM et al. Activity of the PI3K-δ,γ inhibitor duvelisib in a Phase 1 trial and preclinical models of T-cell lymphoma. Blood. 2018;131(8):888-98.
47. Sabatini DM. mTOR and cancer: Insights into a complex relationship. Nat Rev Cancer. 2006;6(9):729-34.
48. Hsieh AC et al. Targeting eukaryotic translation initiation factor 4E (eIF4E) in cancer. Clin Cancer Res. 2010;16(20):4914-20.
49. Moskowitz AJ, Horwitz SM. mTOR inhibition in T-cell lymphoma: A path(way) forward. Blood. 2015;126(3):284-6.
50. Darwiche N et al. Inhibition of mammalian target of rapamycin signaling by everolimus induces senescence in adult T-cell leukemia/lymphoma and apoptosis in peripheral T-cell lymphomas. Int J Cancer. 2011;129(4):993-1004.
51. Witzig TE et al. The mTORC1 inhibitor everolimus has antitumor activity in vitro and produces tumor responses in patients with relapsed T-cell lymphoma. Blood. 2015;126(3):328-35.
52. Tarantelli C et al. PQR309 is a novel dual PI3K/mTOR inhibitor with preclinical antitumor activity in lymphomas as a single agent and in combination therapy. Clin Cancer Res. 2018;24(1):120-9.
53. Zinzani PL et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol. 2007;25(27):4293-7.
54. Ishida T et al. Multicenter Phase II study of lenalidomide in relapsed or recurrent adult T-cell leukemia/lymphoma: ATLL-002. J Clin Oncol. 2016;34(34):4086-93.
55. Ravi D et al. Proteasomal inhibition by ixazomib induces chk1 and myc-dependent cell death in t-cell and hodgkin lymphoma. Cancer Res. 2016;76(11):3319-31.
56. Gravina GL et al. Nucleo-cytoplasmic transport as a therapeutic target of cancer. J Hematol Oncol. 2014;7:85.
57. Tan DSP et al. Promising SINEs for embargoing nuclear-cytoplasmic export as an anticancer strategy. Cancer Discov. 2014;4(5):527-37.
58. Lapalombella R et al. Selective inhibitors of nuclear export show that CRM1/XPO1 is a target in chronic lymphocytic leukemia. Blood. 2012;120(23):4621-34.
59. Kuruvilla J et al. Selective inhibition of nuclear export with selinexor in patients with non-Hodgkin lymphoma. Blood. 2017;129(24):3175-83.
60. Karyopharm Therapeutics, Inc. Efficacy and safety study of selinexor in relapsed or refractory peripheral T-cell lymphoma or cutaneous T-cell lymphoma. NCT02314247. https://clinicaltrials.gov/ct2/show/NCT02314247.
61. National Cancer Centre, Singapore. Phase I trial of selinexor (KPT-330) and ifosfamide, carboplatin, etoposide (ICE) in peripheral T-cell lymphoma. NCT03212937. https://clinicaltrials.gov/ct2/show/NCT03212937.
62. Hing ZA et al. Next-generation XPO1 inhibitor shows improved efficacy and in vivo tolerability in hematological malignancies. Leukemia. 2016;30(12):2364-72.
63. Waldmann TA, Chen J. Disorders of the JAK/STAT pathway in T cell lymphoma pathogenesis: Implications for immunotherapy. Annu Rev Immunol. 2017;35:533-50.
64. Odejide O et al. A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. Blood. 2014;123(9):1293-6.
65. Choi J et al. Genomic landscape of cutaneous T cell lymphoma. Nat Genet. 2015;47(9):1011-9.
66. Zhang J et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature. 2012;481(7380):157-63.
67. Koo GC et al. Janus kinase 3-activating mutations identified in natural killer/T-cell lymphoma. Cancer Discov. 2012;2(7):591-7.
68. Crescenzo R et al. Convergent mutations and kinase fusions lead to oncogenic STAT3 activation in anaplastic large cell lymphoma. Cancer Cell. 2015;27(4):516-32.
69. Ohgami RS et al. STAT3 mutations are frequent in CD30+ T-cell lymphomas and T-cell large granular lymphocytic leukemia. Leukemia. 2013;27(11):2244-7.
70. Jerez A et al. STAT3 mutations unify the pathogenesis of chronic

lymphoproliferative disorders of NK cells and T-cell large granular lymphocyte leukemia. Blood. 2012;120(15):3048-57.

71. Kataoka K et al. Integrated molecular analysis of adult T cell leukemia/lymphoma. Nat Genet. 2015;47(11):1304-15.
72. Nairismagi M et al. Oncogenic activation of JAK3-STAT signaling confers clinical sensitivity to PRN371, a novel selective and potent JAK3 inhibitor, in natural killer/T-cell lymphoma. Leukemia. 2018;32(5):1147-56.
73. Yakushijin Y et al. The expression of the aurora-A gene and its significance with tumorgenesis in non-Hodgkin's lymphoma. Leuk Lymphoma. 2004;45(9):1741-6.
74. Manfredi MG et al. Characterization of alisertib (MLN8237), an investigational small-molecule inhibitor of aurora a kinase using novel in vivo pharmacodynamic assays. Clin Cancer Res. 2011;17(24):7614-24.
75. Friedberg JW et al. Phase II study of alisertib, a selective Aurora A kinase inhibitor, in relapsed and refractory aggressive B- and T-cell non-Hodgkin lymphomas. J Clin Oncol. 2014;32(1):44-50.
76. Barr PM et al. Phase II intergroup trial of alisertib in relapsed and refractory peripheral T-cell lymphoma and transformed mycosis fungoides: SWOG 1108. J Clin Oncol. 2015;33(21):2399-404.
77. O'Connor OA et al. first multicenter, randomized Phase 3 study in patients (Pts) with relapsed/refractory (R/R) peripheral T-cell lymphoma (PTCL): Alisertib (MLN8237) versus investigator's choice (Lumiere trial; NCT01482962). Blood. 2015;126:341.
78. Plass C et al. Mutations in regulators of the epigenome and their connections to global chromatin patterns in cancer. Nat Rev Genet. 2013;14(11):765-80.
79. Delarue R et al. Treatment with hypomethylating agent 5-azacytidine induces sustained response in angioimmunoblastic T cell lymphomas. Blood. 2016;128:4164.
80. Owen A. O'Connor. Romidepsin plus oral 5-azacitidine in relapsed/refractory lymphoid malignancies. NCT01998035. https://clinicaltrials.gov/ct2/show/NCT01998035.
81. O'Connor OA et al. Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: Results of the pivotal Phase II BELIEF (CLN-19) study. J Clin Oncol. 2015;33(23):2492-9.
82. Coiffier B et al. Results from a pivotal, open-label, Phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol. 2012;30(6):631-6.
83. Piekarz RL et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood. 2011;117(22):5827-34.
84. Piekarz RL et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin Oncol. 2009;27(32):5410-7.
85. Olsen EA et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol. 2007;25(21):3109-15.
86. Duvic M et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood. 2007;109(1):31-9.
87. Dupuis J et al. Combination of romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated patients with peripheral T-cell lymphoma: A non-randomised, Phase 1b/2 study. Lancet Haematol. 2015;2(4):e160-5.
88. The Lymphoma Academic Research Organisation. Efficacy and safety of romidepsin CHOP vs CHOP in patients with untreated peripheral t-cell lymphoma. NCT01796002. https://clinicaltrials.gov/ct2/show/NCT01796002.
89. Tan D et al. Panobinostat in combination with bortezomib in patients with relapsed or refractory peripheral T-cell lymphoma: An open-label, multicentre Phase 2 trial. Lancet Haematol. 2015;2(8):e326-33.
90. University of Birmingham. Evaluation of the Combination of Romidepsin and Carfilzomib in Relapsed/Refractory Peripheral T Cell Lymphoma Patients (RomiCar). NCT03141203. https://clinicaltrials.gov/ct2/show/NCT03141203.
91. Fotheringham S et al. Genome-wide loss-of-function screen reveals an important role for the proteasome in HDAC inhibitor-induced apoptosis. Cancer Cell. 2009;15(1):57-66.
92. Chen L et al. Ubiquitin-associated (UBA) domains in Rad23 bind ubiquitin and promote inhibition of multi-ubiquitin chain assembly. EMBO Reports. 2001;2(10):933-8.
93. Khan O et al. HR23B is a biomarker for tumor sensitivity to HDAC inhibitor-based therapy. Proc Natl Acad Sci U S A. 2010;107(14):6532.
94. Zinzani PL et al. Panoptic clinical review of the current and future treatment of relapsed/refractory T-cell lymphomas: Peripheral T-cell lymphomas. Crit Rev Oncol Hematol. 2016;99:214-27.
95. Marchi E et al. Pralatrexate pharmacology and clinical development. Clin Cancer Res. 2013;19(24):6657-61.
96. Izbicka E et al. Distinct mechanistic activity profile of pralatrexate in comparison to other antifolates in in vitro and in vivo models of human cancers. Cancer Chemother Pharmacol. 2009;64(5):993-9.
97. Toner LE et al. The schedule-dependent effects of the novel antifolate pralatrexate and gemcitabine are superior to methotrexate and cytarabine in models of human non-Hodgkin's lymphoma. Clin Cancer Res. 2006;12(3 Pt 1):924-32.
98. Wang ES et al. Activity of a novel anti-folate (PDX, 10-propargyl 10-deazaaminopterin) against human lymphoma is superior to methotrexate and correlates with tumor RFC-1 gene expression. Leuk Lymphoma. 2003;44(6):1027-35.
99. O'Connor OA et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: Results from the pivotal PROPEL study. J Clin Oncol. 2011;29(9):1182-9.
100. Maruyama D et al. Phase I/II study of pralatrexate in Japanese patients with relapsed or refractory peripheral T-cell lymphoma. Cancer Sci. 2017;108(10):2061-8.
101. O'Connor OA et al. Pralatrexate: A comprehensive update on pharmacology, clinical activity and strategies to optimize use. Leuk Lymphoma. 2017;58(11):2548-57.
102. Shustov A et al. Pralatrexate in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in previously untreated patients with peripheral T-cell lymphoma (PTCL): A Phase 1 dose-escalation study. Blood. 2017;130:818.
103. Ahearne MJ et al. Follicular helper T-cells: Expanding roles in T-cell lymphoma and targets for treatment. Br J Haematol. 2014;166(3):326-35.
104. Breitfeld D et al. Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production. J Exp Med. 2000;192(11):1545-52.
105. Kim CH et al. Unique gene expression program of human germinal center T helper cells. Blood. 2004;104(7):1952-60.
106. Yu D et al. The transcriptional repressor Bcl-6 directs T follicular helper cell lineage commitment. Immunity. 2009;31(3):457-68.
107. Chtanova T et al. T follicular helper cells express a distinctive transcriptional profile, reflecting their role as non-Th1/Th2 effector cells that provide help for B cells. J Immunol. 2004;173(1):68-78.
108. Nurieva RI et al. Bcl6 mediates the

development of T follicular helper cells. Science. 2009;325(5943): 1001-5.

109. Oh H et al. NF-κB: Roles and regulation in different CD4(+) T-cell subsets. Immunol Rev. 2013;252(1): 41-51.

110. Iqbal J et al. Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. Blood. 2010;115(5):1026-36.

111. de Leval L et al. Advances in the understanding and management of angioimmunoblastic T-cell lymphoma. Br J Haematol. 2010;148(5):673-89.

112. Piccaluga PP et al. Gene expression analysis of peripheral T cell lymphoma, unspecified, reveals distinct profiles and new potential therapeutic targets. J Clin Invest. 2007;117(3):823-34.

113. Vose J et al.; International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: Pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124-30.

114. Foss FM et al. Peripheral T-cell lymphoma. Blood. 2011;117(25): 6756-67.

115. Abouyabis AN et al. A systematic review and meta-analysis of front-line anthracycline-based chemotherapy regimens for peripheral T-cell lymphoma. ISRN Hematol. 2011;2011:623924.

116. Abramson JS et al. Peripheral T-cell lymphomas in a large US multicenter cohort: Prognostication in the modern era including impact of frontline therapy. Ann Oncol. 2014;25(11):2211-7.

117. Mak V et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: Spectrum of disease and rare long-term survivors. J Clin Oncol. 2013;31(16):1970-6.

118. d'Amore F et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol. 2012;30(25):3093-9.

119. Kewalramani T et al. Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. Br J Haematol. 2006;134(2):202-7.

Recent Advances in the Treatment of Metastatic Soft Tissue Sarcoma

Authors: *Elizabeth J. Davis, Vicki L. Keedy

Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA
*Correspondence to Elizabeth.j.davis@vumc.org

Disclosure: The authors have declared no conflicts of interest.

Received: 28.08.18

Accepted: 02.10.18

Keywords: Eribulin, ipilimumab, nivolumab, olaratumab, pembrolizumab, soft tissue sarcoma (STS), trabectedin.

Citation: EMJ Oncol. 2018;6[1]:91-101.

Abstract

Soft tissue sarcomas (STS) are a rare group of heterogeneous malignancies with >50 histologic subtypes that have varying biological behaviour and responsiveness to systemic therapy. The mainstay of therapy for metastatic STS in recent decades has been doxorubicin. To improve survival outcomes, numerous agents have been combined with doxorubicin; however, no combination has led to a survival benefit over doxorubicin alone until the recent use of olaratumab, a monoclonal antibody targeting platelet-derived growth factor-α. In addition to olaratumab, several other new drugs have surfaced as promising treatment options. Marine-derived chemotherapy agents, eribulin and trabectedin, are active in selecting STS subtypes. Both agents are effective in liposarcoma, while trabectedin also has activity in leiomyosarcoma. Further understanding of the importance of STS subtype-directed therapy, as well as the genomic complexities of STS, has led to development of several small molecule inhibitors for specific STS histologies. Agents targeting vascular endothelial growth factors, platelet-derived growth factors, and cyclin-dependent kinases 4 and 6 have all shown some efficacy in various STS subtypes. Similar to the selective activity of cytotoxic agents and small molecule inhibitors, immunotherapy, which has revolutionised management of numerous cancers, has also demonstrated activity in select STS subtypes. Collectively, these novel therapies highlight the importance of histology-directed approaches and of a greater understanding of the genomic landscape of STS. This review describes advances in chemotherapy, molecularly targeted, and immunotherapy agents for STS.

INTRODUCTION

Soft tissue sarcomas (STS) are a rare group of heterogeneous malignancies with >50 histologic subtypes that have varying biological behaviour and responsiveness to systemic therapy. Doxorubicin has been the mainstay of treatment in numerous subtypes of metastatic STS for decades, achieving response rates (RR) of 12–29% and average life expectancies of 12–18 months (Table 1).[1-7] Until recently, numerous agents have been combined with doxorubicin with limited benefit. Olaratumab, a fully human IgG1 monoclonal antibody that targets platelet-derived growth factor receptor (PDGFR)-α, combined with doxorubicin resulted in a near doubling of overall survival (OS) compared with doxorubicin alone.[4] Aside

from doxorubicin-based regimens, novel chemotherapy agents, eribulin and trabectedin, have demonstrated efficacy in the L-sarcomas, liposarcoma (LPS), and leiomyosarcoma (LMS), highlighting the role of histology-directed therapy for these malignancies.

Further understanding of the importance of subtype-directed therapy and the genomic complexities of STS has led to the development of small molecule inhibitors for certain STS histologies (Table 2).[8-13] Tyrosine kinase inhibitors (TKI) (imatinib, sunitinib, and regorafenib) have dramatically changed the treatment landscape and outcomes for gastrointestinal stromal tumour (GIST), one of the most common STS subtypes.[14-16] Imatinib, cediranib, and pexidartinib have also demonstrated activity in some of the rarest, chemo-refractory STS subtypes, including dermatofibrosarcoma protuberans,[17,18] alveolar soft part sarcoma (ASPS),[19] and tenosynovial giant cell tumour.[20,21] The increased efficacy of these agents is due to the complex STS genomic landscape, including alterations to KIT, PDGFR-β, vascular endothelial growth factor receptors (VEGFR), and colony stimulating factor-1. Other more common STS also demonstrate potentially targetable aberrations in VEGFR, PDGFR-α and β, and cyclin-dependent kinases (CDK), suggesting a need for study of additional targeted therapies.

Similar to the selective activity of cytotoxic agents and small molecule inhibitors, immunotherapy, which has revolutionised the management of numerous cancers, has also demonstrated activity in select STS subtypes. Immunotherapy trials have shown activity in undifferentiated pleomorphic sarcoma (UPS) and LPS (Table 3).[22-25] Factors such as tumour microenvironment, tumour mutational burden, and the transcriptome have been associated with response to immunotherapy; however, the data for these factors in STS are limited.[26,27] Correlative work to understand the relevant factors for predicting response in STS is ongoing. Numerous studies, including combinations of immunotherapy agents or immunotherapy combined with radiotherapy and/or chemotherapy, are also in progress.

As in other cancers, the understanding of the genomic complexity of STS has expanded over the past decade and spurred development of novel agents. The treatment paradigm for STS has shifted from treating all subtypes similarly towards a more histology-directed approach. In this review, the authors summarise recent developments in the treatment of non-GIST STS, as well as ongoing studies within the realms of chemotherapy, targeted therapies, and immunotherapy.

Table 1: Chemotherapy studies in advanced soft tissue sarcoma.

Study	Number of participants	Histology	Regimen	RR (%)	Median PFS (months)	Median OS (months)
Judson et al.,[1] 2014	228 227	STS	Doxorubicin 75.0 mg/m^2 Doxorubicin 75.0 mg/m^2, ifosfamide 10.0 g/m^2	*14.0 *26.0	*4.6 *7.4	12.8 14.3
Tap et al.,[2] 2017	323 317	STS	Doxorubicin 75.0 mg/m^2 Doxorubicin/evofosfamide 75.0/300.0 mg/m^2	*18.0 28.0	6.0 6.3	19.0 18.4
Ryan et al.,[3] 2016	221 226	STS	Doxorubicin 75.0 mg/m^2 Doxorubicin/palifosfamide 75.0/450.0 mg/m^2	*19.0 *27.0	5.2 6.0	16.9 15.9
Tap et al.,[4] 2016	67 66	STS	Doxorubicin 75.0 mg/m^2 Doxorubicin 75.0 mg/m^2, olaratumab 15.0 mg/kg	11.9 18.2	4.1 6.6	*14.7 *26.5
Demetri et al.,[5] 2016	345 173	LPS/LMS	Trabectedin 1.5 mg/m^2 Dacarbazine 1,000.0 mg/m^2	9.9 6.9	*4.2 *1.5	12.4 12.9
Schöffski et al.,[6] 2016	228 224	LPS/LMS	Eribulin 1.4 mg/m^2 Dacarbazine 850.0–1,200.0 mg/m^2	4.0 5.0	2.6 2.6	*13.5 *11.5
Demetri et al.,[7] 2017	71 72	LPS	Eribulin 1.4 mg/m^2 Dacarbazine 850.0–1,200.0 mg/m^2	1.0 0.0	*2.9 *1.7	*15.6 *8.4

*Statistically significant.

LMS: leiomyosarcoma; LPS: liposarcoma; OS: overall survival; PFS: progression-free survival; RR: response rate; STS: soft tissue sarcoma.

Table 2: Targeted agents in soft tissue sarcoma.

Study	Number of participants	Histology	Regimen	RR (%)	Median PFS (months)	Median OS (months)
van der Graaf et al.,[8] 2012	246 123	STS (non-LPS)	Pazopanib 800 mg daily Placebo	6.0 0.0	*4.6 *1.6	12.5 10.7
Chi et al.,[9] 2018	166	STS	Anlotinib 12 mg daily on Day 1–14 of a 21-day cycle	13.0	5.6	12.0
Mir et al.,[10] 2016	28 28 20 23 13 14 27 27	LPS LMS SS Other	Regorafenib 160 mg Placebo Regorafenib 160 mg Placebo Regorafenib 160 mg Placebo Regorafenib 160 mg Placebo	0.0 0.0 0.0 4.0 8.0 0.0 11.0 0.0	1.1 1.7 *3.7 *1.8 *5.6 *1.0 *2.9 *1.0	4.7 8.8 21.0 9.1 13.4 6.7 12.1 9.5
Dickson et al.,[11] 2013	30	DDLPS/WDLPS	Palbociclib 200 mg daily on Day 1–14 of a 21-day cycle	3.0	4.5	NR
Dickson et al.,[12] 2016	60	DDLPS/WDLPS	Palbociclib 125 mg daily on Day 1–21 of a 28-day cycle	1.7	4.5	NR
Gounder et al.,[13] 2018	26 30	DDLPS	Selinexor 60 mg twice a week Placebo	0.0 0.0	5.5 2.7	NR NR

*Statistically significant.

DDLPS: dedifferentiated liposarcoma; LMS: leiomyosarcoma; LPS: liposarcoma; NR: not reported; OS: overall survival; PFS: progression-free survival; RR: response rate; SS: synovial sarcoma; STS: soft tissue sarcoma; WDLPS: well-differentiated liposarcoma.

NOVEL CHEMOTHERAPY AGENTS AND COMBINATIONS

Doxorubicin has been the backbone of treatment for advanced STS for >40 years. The addition of ifosfamide (and its analogues evofosfamide and palifosfamide) and dacarbazine has resulted in improved RR but lacked a significant survival benefit and with increased toxicities.[1,3,28-30] Olaratumab, a monoclonal antibody that targets PDGFR-α, was the first agent to be combined with doxorubicin and demonstrated an OS benefit in patients with metastatic STS. Olaratumab targets PDGFR-α by blocking the binding of PDGF ligands and preventing receptor activation. PDGFR-α is overexpressed in some STS subtypes[31,32] and preclinical work in LMS cell lines has demonstrated antitumour efficacy,[33] providing rationale for investigation in STS patients. A Phase I/II study[4] enrolled varied STS subtype patients and randomised them 1:1 to doxorubicin with olaratumab versus doxorubicin alone. The progression-free survival (PFS) was 4.1 months and 6.6 months in the monotherapy and combination arms, respectively (p=0.0615), and the OS nearly doubled following combination therapy (26.5 months compared with 14.7 months with doxorubicin alone [p=0.0003]). The reason for the survival improvement with olaratumab remains unclear and preliminary analysis of the PDGFR-α expression status suggested no association with outcomes. Further investigation of the mechanism of action of olaratumab is needed to understand how the drug alters the tumour microenvironment and potentially improves the efficacy of doxorubicin. Olaratumab–doxorubicin combination therapy increased rates of neutropenia (58% versus 35%), mucositis (53% versus 35%), nausea (73% versus 52%), vomiting (45% versus 18%), and diarrhoea (34% versus 23%) compared with doxorubicin alone. However, despite increased neutropenia, there was no difference in the rates of febrile neutropenia or infection between the study arms. Infusion reactions, including two Grade 4 events, occurred in 13% of patients treated with combination therapy, but no cases were reported in those treated with doxorubicin alone.[4] This study led to conditional approval of olaratumab in 2016 by the European Medicines Agency (EMA) and accelerated approval by the U.S. Food and Drug Administration (FDA) for the

treatment of patients with STS not amenable to curative treatment with radiotherapy or surgery and with a histologic subtype for which an anthracycline-containing regimen is appropriate.

Data from the ANNOUNCE study,[34] a Phase III trial comparing outcomes of STS patients treated with doxorubicin and olaratumab or doxorubicin alone, are expected in late 2019, and the results will determine whether the survival benefit withstands in a larger population. The results may also identify subtypes that have the greatest benefit and the mechanism of this survival benefit. Other ongoing studies are investigating neoadjuvant olaratumab as well as combinations with other sarcoma chemotherapy (gemcitabine–docetaxel,[35] doxorubicin–ifosfamide,[36] and doxorubicin–trabectedin[37]) and immunotherapy (pembrolizumab)[38] agents, which may identify additional roles for olaratumab in STS. Trabectedin is a synthetically derived tetrahydroisoquinoline alkaloid originally isolated from the marine ascidian *Ecteinascidia turbinata*. Trabectedin binds to the minor groove of DNA, resulting in a conformational change of the DNA, bending towards the major groove and altering transcription regulation.[39] The first Phase II studies of trabectedin in patients with advanced STS demonstrated a RR of 4–17%, median PFS of 1.9 months, and median OS of 9.2–12.8 months.[40-43] Given the paucity of treatment options for STS and the clinical activity and tolerability, the drug received approval by the EMA in 2007 for the treatment of patients with advanced STS after failure of anthracyclines and ifosfamide or for those who were unfit to receive these agents.

In these initial Phase II studies, patients with L-sarcomas, particularly LMS and myxoid round cell LPS, showed the greatest benefit.[40-44] Therefore, a multicentre Phase III trial[45] compared trabectedin 1.5 mg/m^2 every 3 weeks to dacarbazine 1,000 mg/m^2 every 3 weeks in L-sarcoma patients after prior anthracycline treatment and at least one additional regimen. The median PFS was improved, measuring 4.2 months versus 1.5 months ($p<0.001$) with trabectedin and dacarbazine, respectively. In addition, the median PFS improvement was greatest in the myxoid round cell LPS group, totalling 5.6 months versus 1.5 months with trabectedin and dacarbazine, respectively.

Table 3: Immunotherapy studies in sarcoma.

Study	Number of participants	Histology	Regimen	RR (%)	Median PFS (months)	Median OS (months)
Tawbi et al.,[22] 2017	80	STS/bone	Pembrolizumab (200 mg q3wk)	18 (UPS, LPS) 5 (CS, OST)	4.1 1.9	11.4 12.0
Ben-Ami et al.,[23] 2017	12	LMS/uterine	Nivolumab (3 mg/kg q2wk)	0	1.8	NR
D'Angelo et al.,[24] 2018	85	STS/bone	Nivolumab (3 mg/kg q2wk) Ipilimumab/nivolumab (1 mg/kg/3 mg/kg q3wk for 4 cycles, nivolumab q2wk for 2 years)	5 (ASPS, LMS) 16 (LMS, MFS, UPS, AS)	1.7 4.1	10.7 14.3
Toulmonde et al.,[25] 2018	57	LMS UPS Other GIST	Cyclophosphamide (50 mg bid qow) and pembrolizumab (200 mg q3wk)	0 0 7 (SFT) 0	1.4 1.4 1.4 1.4	9.2 5.6 7.1 NYR

AS: angiosarcoma; ASPS: alveolar soft part sarcoma; bid: twice daily; CS: chondrosarcoma; GIST: gastrointestinal stromal tumour; LMS: leiomyosarcoma; LPS: liposarcoma; MFS: myxofibrosarcoma; NR: not reported; NYR: not yet reached; OS: overall survival; OST: osteosarcoma; PFS: progression-free survival; q: every; qow: every other week; RR: response rate; SFT: solitary fibrous tumour; STS: soft tissue sarcoma; UPS: undifferentiated pleomorphic sarcoma; wk: week.

There was no difference in RR or OS. Trabectedin was also well tolerated, with the most common serious adverse events (AE) being myelosuppression and transient liver function test elevation.[5] This study led to FDA approval for trabectedin in 2015 for the treatment of patients with unresectable or metastatic LPS or LMS who had received a prior anthracycline-containing regimen. Trabectedin became the third FDA-approved drug for STS treatment after doxorubicin (1974) and pazopanib (2012).[45] The approval of trabectedin, based on improvement in PFS, demonstrates the acceptance of disease stability as a meaningful endpoint in metastatic STS and highlights that disease response by Response Evaluation Criteria in Solid Tumors (RECIST) is uncommon in STS, underscoring the need for novel systemic therapies.

Eribulin mesylate is a synthetically derived analogue of halichondrin B, which was originally derived from a marine sponge. It is a non-taxane microtubule inhibitor that prevents mitotic spindle formation, inducing cell cycle arrest.[46] Eribulin was initially FDA-approved to treat advanced or metastatic breast cancer. Similar to trabectedin, a Phase II study[47] of eribulin in multiple STS subtypes demonstrated activity solely in the L-sarcomas. The proportion of LMS and LPS patients who were progression-free at 12 weeks was 31.6% and 46.9%, respectively, which compared favourably to historical controls.[47] Due to the activity in L-sarcomas, a Phase III study[6] compared the efficacy of eribulin 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle with dacarbazine 850–1,200 mg/m^2 every 3 weeks only in these patients. The OS was improved, totalling 13.5 months versus 11.5 months with eribulin and dacarbazine, respectively (p=0.0169), and there was no difference in PFS or RR.[6] In a preplanned subgroup analysis, the primary benefit of eribulin was in LPS, with improved OS (15.6 months versus 8.4 months, respectively [p<0.001]) and PFS (2.7 months versus 1.9 months, respectively [p=0.0015]) in the eribulin group compared to the dacarbazine group. Notably, there was no difference in RR.[7] In both cohorts, eribulin was associated with a greater incidence of AE Grade ≥3 (67%) than dacarbazine (56%). Most severe AE were haematologic; however, the incidence of neutropenic fever was low.[6] Collectively, these data led to the approval of eribulin by the EMA and FDA in 2016 for patients with unresectable or metastatic LPS after a prior anthracycline-based regimen, but not for patients with LMS. This agent provides a reasonable second-line option for treating advanced LPS because it demonstrated a 2-month survival benefit and was reasonably well tolerated.

TARGETED AGENTS

Over the past two decades, molecularly targeted agents have emerged as effective anti-cancer therapies. The success of imatinib and trastuzumab in revolutionising the treatment of chronic myelogenous leukaemia and HER-2-positive breast cancer, respectively, sparked greater analysis of cancer genomics and evaluations of how genetic abnormalities could be used in developing novel anticancer strategies. STS demonstrate overexpression and/or mutations of numerous potential therapeutic targets. For example, overexpression of VEGF has been associated with higher-grade tumours and worse outcomes in sarcoma patients, and targeting VEGF has been explored as a potential therapeutic strategy with reasonable efficacy.[48-50] Increased expression of CDK4, CDK6, and PDGF, as well as mutations in PDGFR-α and β, have also been described in STS. These molecular abnormalities have provided justification for several studies, which are described in greater detail later in this review.[4,8,32,51]

Pazopanib is an oral, synthetically derived indazole pyrimidine that inhibits VEGFR 1–3, PDGFR-α and β, and c-kit.[52] VEGF and PDGF are factors in STS angiogenesis, providing a rationale to study pazopanib as a treatment option. An initial Phase II study evaluated daily 800 mg pazopanib in 142 advanced STS patients in a Simon two-stage design.[53] Patients were stratified into four cohorts: adipocytic sarcoma, LMS, synovial sarcoma (SS), and other sarcomas. The adipocytic cohort closed after the first stage, but the other three cohorts completely accrued. The PFR at 12 weeks for the LMS, SS, and other sarcomas was 44%, 49%, and 39%, respectively. PFS and OS compared favourably to historical controls; in the LMS, SS, and other sarcomas, the median PFS and OS were 91 and 354, 161 and 310, and 91 and 299 days, respectively.[53] These data provided the basis for the

Phase III study of pazopanib in patients with advanced STS except the adipocytic subtypes.[8] Patients were randomised 2:1 to receive either daily 800 mg pazopanib or a placebo. The median PFS was improved with pazopanib, recorded as 4.6 months versus 1.6 months with placebo (p<0.0001). However, the OS was not significantly different with pazopanib and placebo (12.5 months versus 10.7 months, respectively [p=0.25]) and the RR were 6% with pazopanib and 0% in the placebo group. The most common severe AE were fatigue (13%), hypertension (7%), anorexia (6%), and diarrhoea (5%).[54] Overall quality of life was not significantly worsened by pazopanib.[54] This study led to the approval of pazopanib in 2012 by the EMA and the FDA for patients with advanced STS, except adipocytic sarcomas, who have received previous chemotherapy. This approval again demonstrates the value of stable disease in the treatment of metastatic STS.

Anlotinib is an oral multikinase inhibitor that targets VEGFR 2 and 3, fibroblastic growth factor receptor 1–4, PDGFR-α and β, c-kit, Ret, Aurora-B, c-FMS, and discoidin domain receptor 1.[55] An initial Phase II study of this agent included 166 sarcoma patients who received a daily 12 mg anlotinib dose in a 2-week-on and 1-week-off regimen.[5] The ORR was 13%. Responses were seen in 8% (2/26) of LMS, 11% (2/18) of fibrosarcoma (FS), 17% (8/47) of SS, 46% (6/13) of ASPS, and 14% (1/7) of clear cell sarcoma patients. The overall median PFS and OS were 5.6 months and 12.0 months, respectively.[9] A Phase III study of this agent randomised 233 patients with SS, LMS, and ASPS to either anlotinib (n=158) or placebo (n=75). The median PFS was 6.3 months for anlotinib versus 1.5 months for placebo (hazard ratio: 0.33; p<0.0001). The PFS improvement was greatest in the ASPS cohort, recorded as 18.2 months versus 3.0 months (hazard ratio: 0.14; p<0.0001) with anlotinib and placebo, respectively. The ORR was 10.1% for anlotinib versus 1.3% for placebo (p=0.0145). The most common Grade ≥3 AE were hypertension (19%), gamma glutamyl transferase elevation (4.4%), triglyceride elevation (4.4%), low-density lipoprotein elevation (3.2%), hyponatraemia (3.2%), and neutrophil count reduction (3.2%).[56] Overall, anlotinib is well tolerated and its use is promising in multiple STS subtypes. It is currently being evaluated in a Phase III study versus dacarbazine in LMS, SS, and ASPS patients.[57]

Regorafenib is an oral TKI that targets VEGFR 1–3, PDGFR, KIT, RET, and Raf, and is EMA and FDA-approved to treat GIST, colorectal cancer, and hepatocellular cancer. REGOSARC[10] was a double-blind, placebo-controlled Phase II study of four cohorts of STS: LPS, LMS, SS, and other sarcomas. Patients were randomly assigned to receive 160 mg daily regorafenib on Days 1–21 of a 28-day cycle or placebo. There were no significant differences in RR or OS; however, the median PFS was significantly improved in all cohorts except for LPS. The most common Grade 3/4 AE included asthenia (13%), hand and foot skin reaction (15%), hypertension (19%), and hypophosphataemia (13%). There was one Grade 5 hepatitis-induced liver failure that was related to regorafenib.[10] This study demonstrates the activity of regorafenib in non-adipocytic STS, and further investigation in a Phase III study against an active agent is warranted.

The TKI described thus far have limited or no activity in adipocytic sarcomas, suggesting that alternative targets are needed. Palbociclib is an oral inhibitor of CDK4 and CDK6 that prevents phosphorylation of the retinoblastoma protein and can result in tumour stasis or regression.[58] CDK4 is overexpressed in two subtypes of adipocytic sarcoma, well-differentiated LPS (WDLPS) and dedifferentiated LPS (DDLPS), as compared to normal fat cells.[59] Preclinical work demonstrated the antitumour activity of palbociclib in WDLPS/DDLPS cell lines and in xenografts.[60] Two Phase II studies[11,12] confirmed antitumour activity of palbociclib in 90 patients with WDLPS/DDLPS. The studies evaluated different dosing regimens, either 200 mg daily on Days 1–14 of a 21-day cycle (high dose) or 125 mg daily on Days 1–21 of a 28-day cycle (low dose). The primary endpoint was met in both studies, achieving a PFS at 12 weeks of 66% in the high-dose and 57% in the low-dose group. The median PFS was 18 weeks in both studies and the low dose was slightly better tolerated. Grade 3/4 AE were primarily haematologic: anaemia (17% versus 22%), thrombocytopenia (30% versus 7%), neutropenia (50% versus 36%), and febrile neutropenia (3% versus 0%) with the high and low doses, respectively.[11,12] Correlative work from paired tumour biopsies demonstrated that benefit from palbociclib treatment was

associated with downregulation of MDM2,[61] suggesting a potential biomarker that could be used to predict response to CDK4 inhibition.

Another potential novel treatment approach for DDLPS is selinexor, an oral selective inhibitor of nuclear export that binds to the nuclear export protein XPO1. This causes tumour suppressor proteins to accumulate in the nucleus, resulting in selective destruction of cancer cells while sparing the healthy cells. A Phase II study evaluated selinexor 60 mg twice a week in 56 patients with advanced DDLPS. The primary endpoint was PFS and selinexor demonstrated a trend towards improved PFS over placebo (5.5 months versus 2.7 months; p=0.26). Treatment was well tolerated, with the most common Grade 3/4 AE being hyponatraemia (19.2%), anaemia (19.2%), thrombocytopenia (11.5%), neutropenia (7.7%), and hyperglycaemia (7.7%).[13] The Phase III portion of the study is still ongoing and is comparing selinexor to placebo in patients with advanced DDLPS.[62]

IMMUNOTHERAPY

Immunotherapy was first described as a potential anticancer strategy in the 19th century in sarcoma patients. Streptococcal antigens (Coley's toxins) were injected into sarcomas and resulted in tumour shrinkage.[63] However, there was doubt about these findings, and investigation of chemotherapy and radiation took precedence over further investigation of immunotherapeutic options. More recently, immunotherapy agents targeting T cell checkpoint molecules, such as cytotoxic T lymphocyte-associated protein 4 and programmed death receptor (PD-1) and its ligand (PD-L1), have revolutionised the treatment of numerous malignancies.[64-68] However, the success of immunotherapy agents in sarcoma in the modern era has been limited (Table 3).

One of the initial investigations of immunotherapy in sarcoma was SARC028,[22] a two-cohort, single-arm, open-label Phase II study of pembrolizumab, an anti-PD-1 monoclonal antibody, administered intravenously (IV) every 3 weeks at a dose of 200 mg. Forty patients were enrolled into each of the bone and soft tissue cohorts. The STS cohort was split into 10 patients with each of the following histologies: UPS, LPS, LMS, or SS. RR were highest in the UPS and LPS cohorts, measuring 40% and 20%, respectively. No responses were seen in LMS patients. In the bone cohort, the RR were 5% (1 out of 22) in osteosarcoma, 20% (1 out of 5) in chondrosarcoma, and 0% (0 out of 13) in Ewing's sarcoma. The median PFS and OS were 18 and 49 weeks in the STS cohort, and 8 and 52 weeks in the bone cohort, respectively. Treatment was well tolerated, with treatment-related serious AE occurring in 11% of patients. AE included pneumonitis (4%), adrenal insufficiency (4%), pulmonary embolism (2%), interstitial nephritis (2%), infectious pneumonia (2%), bone pain (2%), hypoxia (2%), and pleural effusion (2%). There were no Grade 5 AE. The study concluded that pembrolizumab was promising in UPS and LPS and recently completed enrolment of additional patients into these cohorts. Select results from correlative work were included in the initial analysis. PD-L1 expression was identified in 5% (2 out of 40) of the STS samples, both cases were from UPS patients who had responded to therapy. However, responses were also noted in non-PD-L1-expressing LPS patients, suggesting that predicting response to anti-PD-1 therapy is based on more than PD-L1 expression.[22] Additional correlative work from this study is pending and will offer further insight into the role of immunotherapy in sarcoma.

A smaller study[23] evaluated nivolumab, an anti-PD-1 monoclonal antibody, 3 mg/kg IV every 2 weeks in patients with metastatic uterine LMS. Twelve patients were enrolled and no responses were seen, suggesting a lack of benefit and precluding further enrolment. The median PFS was 1.8 months and a median OS was not reached. Treatment-related serious AE occurred in 25% of patients, with solitary cases of abdominal pain, elevated amylase and lipase, and fatigue. Correlative work demonstrated PD-1 and PD-L1 expression in 20% of samples, but no correlation with outcomes was observed.[23] In combination with the findings from SARC028, this study further demonstrates the lack of efficacy of anti-PD-1 monotherapy in LMS. LMS resistance may be due to the density of tumour-associated macrophages, PTEN mutations, and reduced expression of genes encoding neoantigens.[69,70] However, recent translational work suggests that LMS is an inflamed tumour type with high levels of T cell-related gene expression

and occasional strong expression of PD-L1, indicating that immunotherapy may be effective but that a combination strategy may be a better approach.[71]

Combining immunotherapy agents, such as ipilimumab, an anti-cytotoxic T lymphocyte-associated protein 4 monoclonal antibody, and nivolumab, is an effective strategy in melanoma and renal cell carcinoma.[72,73] As a result of the potential synergy of these agents, a Phase II study evaluated two treatment strategies: nivolumab with or without ipilimumab in sarcoma. Treatment included 3 mg/kg IV nivolumab every 2 weeks or 1 mg/kg IV ipilimumab with 3 mg/kg nivolumab every 3 weeks for four doses, followed by 3 mg/kg nivolumab every 2 weeks for up to 2 years. The study was not designed to compare results between treatment arms. The RR was 5% with nivolumab and 16% with combination therapy. In the monotherapy arm, responses were seen in ASPS and non-uterine LMS, while, in the combination treatment arm, responses were seen in LMS (n=2), UPS (n=2), myxofibrosarcoma, and angiosarcoma. The median PFS and OS were 1.7 and 10.7 months and 4.1 and 14.3 months with monotherapy and combination therapy, respectively. Given that the monotherapy did not reach its target RR, nivolumab alone is considered inactive; however, the combination has activity similar to other approved sarcoma therapies and is being further investigated in UPS and LPS. Treatment-related serious AE occurred more frequently with combination therapy (26% versus 19%) than in the monotherapy arm. AE included adrenal insufficiency, elevated alanine and aspartate aminotransferase, hyponatraemia, anaemia, fatigue, pain, and pruritus with dual agent therapy, and anaemia, thrombocytopenia, anorexia, dehydration, diarrhoea, fever, elevated creatinine, and pleural effusion in the monotherapy cohort. Correlative work, including PD-L1 expression, tumour-infiltrating lymphocytes, mutational burden, neoantigen analysis, and T cell receptor clonality, is in progress.[24] Results of these studies will help determine factors that predict response or suggest a role for further study of combination immunotherapy in sarcoma.

Adding chemotherapy, targeted therapy, or radiation therapy to immunotherapy to augment efficacy is an area of active investigation. Combining axitinib, a pan-VEGFR inhibitor, with pembrolizumab has showed promise in treating ASPS. The 3-month PFS rate was 90.9% (95% confidence interval: 50.8–98.7) and ORR was 45.5% (95% confidence interval: 18.1–75.4). Correlative studies found high plasma angiogenic activity, a circulating neutrophil:lymphocyte ratio <4.1, low naïve fraction CD4+ tumour-infiltrating lymphocytes, and low PD1+CD8+ peripheral blood mononuclear cell were associated with lack of progression. Overall, this combination was well tolerated and demonstrated activity in ASPS, warranting further study.[74]

Given the potential immunomodulatory effects of metronomic cyclophosphamide and its activity in STS treatment, the French Sarcoma Group combined oral cyclophosphamide 50 mg twice daily every other week with 200 mg pembrolizumab IV every 3 weeks in four cohorts: LMS (n=15), UPS (n=16), GIST (n=10), and other sarcomas (n=16).[25] There was one partial response in a patient with solitary fibrous tumour and the median PFS was equal across cohorts at 1.4 months. The OS varied and was 9.2 months, 5.6 months, 7.1 months, and not yet reached in the LMS, UPS, other, and GIST cohorts, respectively. Correlative work demonstrated PD-L1 expression in immune cells was 23%, 64%, 29%, and 43% in the LMS, UPS, other, and GIST cases, respectively.[25] The only patient with immune cell PD-L1 expression >10% was also the only patient who responded to therapy. Additional translational studies evaluated expression of CD8, CD68, CD163, and IDO1. However, given the lack of reference values for these markers in sarcoma, the findings were difficult to interpret. Results were compared to a dataset derived from non-small cell lung cancer patients and revealed that CD8 densities were significantly lower in sarcoma patients compared to non-small cell lung cancer patients. Also, high infiltration by CD163+ macrophages and by macrophages that expressed IDO1 was seen in sarcomas, which potentially provides a mechanism for the PD-1 resistance seen in these tumours. An increased plasma kynurenine:tryptophan ratio correlated with increased IDO1 expression, adding further support to the IDO1 pathways as a mechanism of resistance to anti-PD-1 therapy.[25]

CONCLUSION

STS are a highly heterogeneous group of tumours with varying responses to treatment. Given their variable genomic makeup, histology-directed therapy should be regarded as the future of treatment. Currently, combined doxorubicin and olaratumab is the first-line treatment regimen for numerous STS subtypes; however, results of the Phase III study may discern subtypes that derive the greatest benefit. Trabectedin and eribulin have demonstrated efficacy in the L-sarcomas, but further investigation is needed to understand why these subtypes have the greatest success. Targeted therapies, such as pazopanib, have an established role in treating non-adipocytic STS. Novel agents, anlotinib, palbociclib, and selinexor, have shown promise in Phase II studies; however, larger, confirmatory Phase III studies are awaited to determine whether new options for LMS, SS, ASPS, and DDLPS will become available. The role of immunotherapy in STS remains uncertain and is currently only recommended within the context of a clinical trial. Responses in UPS and LPS are encouraging; however, additional studies evaluating more patients, combination strategies, and correlative work are needed. Collectively, the results of recent studies demonstrate the ability of the sarcoma community to enrol histology-tailored trials, which will allow for the development of more subtype-specific therapies.

References

1. Judson I et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: A randomised controlled Phase 3 trial. Lancet Oncol. 2014;15(4):415-23.
2. Tap WD et al. Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): An international, multicentre, open-label, randomised Phase 3 trial. Lancet Oncol. 2017;18(8):1089-103.
3. Ryan CW et al. PICASSO III: A Phase III, placebo-controlled study of doxorubicin with or without palifosfamide in patients with metastatic soft tissue sarcoma. J Clin Oncol. 2016;34(32):3898-905.
4. Tap WD et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: An open-label Phase 1b and randomised Phase 2 trial. Lancet. 2016;388(10043):488-97.
5. Demetri GD et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: Results of a Phase III randomized multicenter clinical trial. J Clin Oncol. 2016;34(8):786-93.
6. Schöffski P et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: A randomised, open-label, multicentre, Phase 3 trial. Lancet. 2016;387(10028):1629-37.
7. Demetri GD et al. Activity of eribulin in patients with advanced liposarcoma demonstrated in a subgroup analysis from a randomized Phase III study of eribulin versus dacarbazine. J Clin Oncol. 2017;35(30):3433-9.
8. van der Graaf WT et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): A randomised, double-blind, placebo-controlled Phase 3 trial. Lancet. 2012;379(9829):1879-86.
9. Chi Y et al. Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, in patients with refractory metastatic soft tissue sarcoma. Clin Cancer Res. 2018. [Epub ahead of print].
10. Mir O et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): A randomised, double-blind, placebo-controlled, Phase 2 trial. Lancet Oncol. 2016;17(12):1732-42.
11. Dickson MA et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. J Clin Oncol. 2013;31(16):2024-8.
12. Dickson MA et al. Progression-free survival among patients with well-differentiated or dedifferentiated liposarcoma treated with CDK4 inhibitor palbociclib: A Phase 2 clinical trial. JAMA Oncol. 2016;2(7):937-40.
13. Gounder MM et al. Phase 2 results of selinexor in advanced de-differentiated (DDLS) liposarcoma (SEAL) study: A Phase 2/3, randomized, double blind, placebo controlled cross-over study. J Clin Oncol. 2018;36(Suppl 15):11512.
14. Dagher R et al. Approval summary: Imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin Cancer Res. 2002;8(10):3034-8.
15. Demetri GD et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: A randomised controlled trial. Lancet. 2006;368(9544):1329-38.
16. Demetri GD et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): An international, multicentre, randomised, placebo-controlled, Phase 3 trial. Lancet. 2013;381(9863):295-302.
17. Stacchiotti S et al. Efficacy and biological activity of imatinib in metastatic dermatofibrosarcoma protuberans (DFSP). Clin Cancer Res. 2016;22(4):837-46.
18. Gooskens SL et al. Imatinib mesylate for children with dermatofibrosarcoma protuberans (DFSP). Pediatr Blood Cancer. 2010;55(2):369-73.
19. Kummar S et al. Cediranib for metastatic alveolar soft part sarcoma. J Clin Oncol. 2013;31(18):2296-302.
20. Cassier PA et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. Cancer. 2012;118(6):1649-55.
21. Tap WD et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. N Engl

J Med. 2015;373(5):428-37.

22. Tawbi HA et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): A multicentre, two-cohort, single-arm, open-label, Phase 2 trial. Lancet Oncol. 2017;18(11):1493-501.
23. Ben-Ami E et al. Immunotherapy with single agent nivolumab for advanced leiomyosarcoma of the uterus: Results of a Phase 2 study. Cancer. 2017;123(17):3285-90.
24. D'Angelo SP et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): Two open-label, non-comparative, randomised, Phase 2 trials. Lancet Oncol. 2018;19(3): 416-26.
25. Toulmonde M et al. Use of PD-1 targeting, macrophage infiltration, and IDO pathway activation in sarcomas: A Phase 2 clinical trial. JAMA Oncol. 2018;4(1):93-7.
26. Johnson DB et al. Targeted next generation sequencing identifies markers of response to PD-1 blockade. Cancer Immunol Res. 2016;4(11):959-67.
27. Hugo W et al. Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. Cell. 2016;165(1):35-44.
28. Weh HJ et al. Treatment results obtained in metastatic soft-tissue sarcoma with a combination of doxorubicin and dacarbazine or doxorubicin and ifosfamide. Cancer Chemother Pharmacol. 1993; 31(Suppl 2):S189-93.
29. Santoro A et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: A randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 1995;13(7):1537-45.
30. Antman K et al. An intergroup Phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol. 1993;11(7):1276-85.
31. Shah GD et al. Rationale for the development of IMC-3G3, a fully human immunoglobulin G subclass 1 monoclonal antibody targeting the platelet-derived growth factor receptor alpha. Cancer 2010; 116(4 Suppl): 1018-26.
32. Movva S et al. Multi-platform profiling of over 2000 sarcomas: Identification of biomarkers and novel therapeutic targets. Oncotarget. 2015;6(14): 12234-47.
33. Loizos N et al. Targeting the platelet-derived growth factor receptor alpha with a neutralizing human monoclonal antibody inhibits the growth of tumor xenografts: Implications as a potential therapeutic target. Mol Cancer Ther. 2005;4(3):369-79.
34. Eli Lilly and Company. A study of doxorubicin plus olaratumab (LY3012207) in participants with advanced or metastatic soft tissue sarcoma (ANNOUNCE). NCT02451943. https://clinicaltrials.gov/ct2/show/NCT02451943.
35. Eli Lilly and Company. A study of olaratumab (LY3012207) in participants with advanced soft tissue sarcoma (ANNOUNCE 2). NCT02659020. https://clinicaltrials.gov/ct2/show/NCT02659020.
36. Eli Lilly and Company. A study of olaratumab (LY3012207), doxorubicin, and ifosfamide in participants with advanced or metastatic soft tissue sarcoma. NCT03283696. https://clinicaltrials.gov/ct2/show/NCT03283696.
37. University of Miami. Trabectedin, doxorubicin and olaratumab in patients with metastatic or recurrent leiomyosarcoma. NCT03437070. https://clinicaltrials.gov/ct2/show/NCT03437070.
38. Eli Lilly and Company. A study of olaratumab (LY3012207) plus pembrolizumab in participants with advanced or metastatic soft tissue sarcoma. NCT03126591. https://clinicaltrials.gov/ct2/show/NCT03126591.
39. D'Incalci M, Jimeno J. Preclinical and clinical results with the natural marine product ET-743. Expert Opin Investig Drugs. 2003;12(11):1843-53.
40. Yovine A et al. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. J Clin Oncol. 2004;22(5):890-9.
41. Garcia-Carbonero R et al. Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. J Clin Oncol. 2004;22(8):1480-90.
42. Garcia-Carbonero R et al. Ecteinascidin-743 (ET-743) for chemotherapy-naive patients with advanced soft tissue sarcomas: Multicenter phase II and pharmacokinetic study. J Clin Oncol. 2005;23(24):5484-92.
43. Le Cesne A et al. Phase II study of ET-743 in advanced soft tissue sarcomas: A European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. J Clin Oncol. 2005;23(3):576-84.
44. Takahashi M et al. Efficacy of trabectedin in patients with advanced translocation-related sarcomas: Pooled analysis of two Phase II studies. Oncologist. 2017;22(8): 979-88.
45. Barone A et al. FDA approval summary: Trabectedin for unresectable or metastatic liposarcoma or leiomyosarcoma following an anthracycline-containing regimen. Clin Cancer Res. 2017;23(24):7448-53.
46. Dybdal-Hargreaves NF et al. Eribulin mesylate: Mechanism of action of a unique microtubule-targeting agent. Clin Cancer Res. 2015;21(11):2445-52.
47. Schöffski P et al. Activity of eribulin mesylate in patients with soft-tissue sarcoma: A Phase 2 study in four independent histological subtypes. Lancet Oncol. 2011;12(11):1045-52.
48. Yudoh K et al. Concentration of vascular endothelial growth factor in the tumour tissue as a prognostic factor of soft tissue sarcomas. Br J Cancer. 2001;84(12):1610-5.
49. Chao C et al. Vascular endothelial growth factor and soft tissue sarcomas: Tumor expression correlates with grade. Ann Surg Oncol. 2001;8(3):260-7.
50. Potti A et al. Determination of vascular endothelial growth factor (VEGF) overexpression in soft tissue sarcomas and the role of overexpression in leiomyosarcoma. J Cancer Res Clin Oncol. 2004;130(1):52-6.
51. Heinrich MC et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science. 2003;299(5607):708-10.
52. Kumar R et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. Mol Cancer Ther. 2007;6(7):2012-21.
53. Sleijfer S et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: A Phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol. 2009;27(19):3126-32.
54. Coens C et al. Health-related quality-of-life results from PALETTE: A randomized, double-blind, Phase 3 trial of pazopanib versus placebo in patients with soft tissue sarcoma whose disease has progressed during or after prior chemotherapy-a European Organization for research and treatment of cancer soft tissue and bone sarcoma group global network study (EORTC 62072). Cancer. 2015;121(17):2933-41.
55. Sun Y et al. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. J Hematol Oncol. 2016;9(1):105.
56. Yihebali Chi YY et al. Anlotinib for metastasic soft tissue sarcoma: A

randomized, double-blind, placebo-controlled and multi-centered clinical trial. J Clin Oncol. 2018; 36(15 Suppl):11503.

57. Advenchen Laboratories, LLC. A Phase III trial of anlotinib in metastatic or advanced alveolar soft part sarcoma, leiomyosarcoma and synovial sarcoma (APROMISS). NCT03016819. https://clinicaltrials.gov/ct2/show/NCT03016819.
58. Fry DW et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Mol Cancer Ther. 2004;3(11):1427-38.
59. Singer S et al. Gene expression profiling of liposarcoma identifies distinct biological types/subtypes and potential therapeutic targets in well-differentiated and dedifferentiated liposarcoma. Cancer Res. 2007;67(14):6626-36.
60. Barretina J et al. Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. Nat Genet. 2010;42(8):715-21.
61. Kovatcheva M et al. MDM2 turnover and expression of ATRX determine the choice between quiescence and senescence in response to CDK4 inhibition. Oncotarget. 2015;6(10):8226-43.
62. Karyopharm Therapeutics Inc. Selinexor in advanced liposarcoma (SEAL). NCT02606461. https://clinicaltrials.gov/ct2/show/NCT02606461.
63. Coley WB. II. Contribution to the knowledge of sarcoma. Ann Surg. 1891;14(3):199-220.
64. Wolchok JD et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013;369(2):122-33.
65. Pembrolizumab superior to ipilimumab in melanoma. Cancer Discov. 2015;5(6):568.
66. pembrolizumab has antitumor activity in advanced head and neck cancer. Cancer Discov. 2016;6(7):693.
67. De Marinis F, Passaro A. [Nivolumab in second-line treatment of squamous non-small cell lung cancer.]. Recenti Prog Med. 2016;107(12):634-40. (In Italian).
68. First-line atezolizumab effective in bladder cancer. Cancer Discov. 2016;6(8):OF7.
69. Ganjoo KN et al. The prognostic value of tumor-associated macrophages in leiomyosarcoma: A single institution study. Am J Clin Oncol. 2011;34(1): 82-6.
70. George S et al. Loss of PTEN Is associated with resistance to anti-PD-1 checkpoint blockade therapy in metastatic uterine leiomyosarcoma. Immunity. 2017;46(2):197-204.
71. Pollack SM et al. T-cell infiltration and clonality correlate with programmed cell death protein 1 and programmed death-ligand 1 expression in patients with soft tissue sarcomas. Cancer. 2017;123(17):3291-304.
72. Nivolumab (Opdivo) plus ipilimumab (Yervoy) for metastatic melanoma. Med Lett Drugs Ther. 2015;57(1483):168.
73. Motzer RJ et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378(14):1277-90.
74. Wilky BA et al. A Phase II trial of axitinib plus pembrolizumab for patients with advanced alveolar soft part sarcoma (ASPS) and other soft tissue sarcomas (STS). J Clin Oncol. 2018;36(Suppl 15):11547.

Clinical Issues for Prostate-Specific Antigen Screening: A Narrative Review

Authors: *Marco Randazzo, Anna Höhener, Hubert John, Yves Wyss

Department of Urology, Kantonsspital Winterthur, Winterthur, Switzerland
*Correspondence to marco_randazzo1@hotmail.com

Disclosure: The authors have declared no conflicts of interest.

Received: 20.07.18

Accepted: 20.09.18

Keywords: Prostate cancer mortality, prostate cancer prevalence, prostate cancer screening, prostate-specific antigen (PSA).

Citation: EMJ Oncol. 2018;6[1]:102-108.

Abstract

Prostate cancer, with its remarkably high prevalence, frequently creates clinical problems in terms of screening and diagnosis, as well as identifying the optimal window for treatment. Moreover, the prostate-specific antigen (PSA) blood test, despite being easy to perform, is routinely carried out without the patient's informed consent. Although PSA-based screening for prostate cancer can reduce cancer-specific mortality, informed decision-making is mandatory; however, the clinician's daily routine often neglects this critical discussion before performing a PSA blood test. This narrative review discusses the main questions regarding PSA screening and provides information on the epidemiological, clinical, and pathological aspects of prostate cancer.

INTRODUCTION

"Despite numerous clinical advances and innovations with hormonal palliation, age-adjusted death rates for prostatic cancer have not significantly changed in the past 40 years."[1] This is how Dr Gerald P. Murphy, leading cancer researcher and professor of urology, described the clinical situation of prostate cancer (PCa) in 1974.[1] In 1987, the prostate-specific antigen (PSA) blood test was first described as a potential screening tool for PCa detection by Stamey et al.[2] in a study that compared PSA to prostatic acid phosphatase. The results showed that PSA concentration was proportional to tumour volume and was a much better tumour marker than prostatic acid phosphatase.[2] Stamey et al.[2] also noted that less differentiated PCa with Gleason patterns 4 and 5 showed less positivity for PSA. A few years later, Catalona et al.[3] published a landmark study showing that PSA was a useful adjunct to rectal examination for detecting PCa. Thus, a novel blood test able to detect PCa was introduced to clinical practice in the early 1990s. One must be aware that the prostate is embedded deep within the pelvis and apart from a digital rectal examination (DRE), which provides limited information on the consistence of the dorsal prostate part, no other clinical test was able to enhance diagnostics in PCa until MRI was developed for PCa screening.

Nowadays, screening for PCa is a controversial issue for several reasons.[4] For example, there is ongoing scientific discussion regarding a lack of effect of PSA screening on PCa mortality reduction;[5] however, many believe that PSA is a 'simple' blood test and very easy to perform. This belief has led to widespread use of this

screening test, especially by general practitioners and urologists in the USA, and has resulted in a pronounced increase in PCa incidence.[6] The high prevalence of PCa makes the discrimination between indolent and clinically relevant, potentially life-threatening PCa very difficult. Therefore, PCa is called a 'two-faced disease' by some.[7] In addition, the results of the Prostate Cancer Prevention Trial (PCPT),[8] which showed nearly 15% of men who were screened and had a normal PSA level had PCa, added additional uncertainty of the quality of this blood test in daily practice. Of note, the remarkable prevalence of PCa has been a well-known phenomenon for >50 years.[9] This narrative review discusses the clinical and pathological aspects of PCa screening.

CURRENT EVIDENCE: HOW DOES PROSTATE-SPECIFIC ANTIGEN SCREENING AFFECT PROSTATE CANCER INCIDENCE AND MORTALITY?

A discussion on screening for a disease cannot take place without considering the prevalence and natural history of the condition. The prevalence of PCa is high and several autopsy studies have determined the relative frequency to be from 30–50%, depending on the age and the ethnicity of the patient group.[10] Some of these studies were published as early as 1954.[9] Table 1 summarises the prevalence of PCa according to age and ethnicity.[10]

Natural History of Prostate Cancer

PCa is known to have a long natural history. For instance, the SPCG-4 trial[11] reported that approximately 30% of men not treated with curative intent died 18 years after randomisation (mean age: 65 years). Roughly 40% of patients developed distant metastases during this follow-up period and the use of androgen-deprivation therapy at 18 years was approximately 70%. Another study has shown that after a mean follow-up of 21 years, 16% of men died due to PCa[12] (initial tumour stage: T2M0) and distant metastases occurred in 18% of patients at Year 32.[13]

In the pre-PSA era, Barnes[14] investigated the natural history of patients with localised PCa who were treated conservatively. Half of the study participants survived for 10 years and 30% survived for 15 years. The most important prognostic factor affecting survival during this time was the grade of differentiation.[15] Patients with poorly differentiated PCa were shown to have a shorter duration of natural history, with a 5-year cause-specific survival of 87% (well-to-moderately differentiated PCa), compared to 34% with poorly differentiated PCa.[16] Importantly, one of the most relevant factors predicting overall survival is the competing medical hazard, as shown by Albertsen et al.[17] Depending on the mode of detection, either clinically or screen-detected, PCa has a long natural history, which needs to be considered when counselling older patients for a PSA blood test.

Men undergoing PSA screening need to be aware of both the epidemiological and clinical background of PCa. Furthermore, men facing the decision of whether to undergo PSA screening need to understand the value of PSA-based screening in terms of the number of patients needed to be diagnosed to prevent one PCa death.[18] Importantly, there is significant variation in the extent of shared decision-making in current PCa screening and treatment literature.[19]

Table 1: Prevalence of prostate cancer according to age and ethnicity.[10]

	Prostate cancer prevalence (%)		
Age (years)	Caucasian	African-American	Asian
40–49	23.2	35.4	2.8
50–59	22.1	45.9	7.9
60–69	29.0	46.9	14.5
>70	<47.4	<50.5	<28.9

Table 2: Characteristics of three major prostate cancer screening studies.[20-22]

	ERSPC[20]	PLCO[21]	CAP[22]
Number and allocation of study participants	182,160 (S: 82,816; C: 99,184)	76,693 (S: 38,343; C: 38,350)	419,582 (S: 189,386; C: 219,439)
Randomisation interval (years)	1993–2003	1993–2001	2001–2009
Control group characteristics	No screening	Usual care	No screening
Screening interval (years)	Between 2 and 7	1	No interval, one single PSA test
Age of participants (years)	50–74	55–74	50–69
Compliance to biopsy (%)	85.6	30.0–40.0	NA
PSA threshold	3 ng/mL (most centres)	4 ng/mL	3 ng/mL
Screening stop	Ongoing	After six rounds	Single PSA test
Estimated mean lead-time in control arm (years)	0.7–1.7	3.1–3.4	NA
Rate ratio for death from PCa (95% CI)	0.80 (0.65–0.98); p=0.04 at 9 years 0.73 (0.61–0.88); p<0.0007 at 13 years	1.13 (0.75–1.70); NS at 7 years 1.11 (0.83–1.50); NS at 10 years	0.96 (0.85–1.08)

C: control group; CI: confidence interval; NA: data not available; NS: nonsignificant; PCa: prostate cancer; PSA: prostate-specific antigen; S: screening group.

ERSPC AND PLCO: THE TWO MOST IMPORTANT RANDOMISED CONTROLLED SCREENING STUDIES TO DATE

There are two major randomised controlled trials investigating the benefit of repeated PSA-screening on PCa mortality: the ERSPC[20] and the PLCO[21] studies. Table 2 summarises the characteristics of these two studies and compares them to the CAP study.[20-22] In the screening groups of PLCO and ERSPC, the adherence to prostate biopsy was reported as 41–64% and 85%, respectively.[23,24] It is important to note that study participants in the PLCO control arm received usual care; thus, >30% of study participants were pre-screened using a PSA test. Furthermore, in the PLCO control group, >80% of study participants reported PSA testing during study follow-up;[25] however, the extent of further diagnostic work-up among screened participants from the control group (e.g., prostate biopsy and subsequent treatment) is not provided in the original study.[26] When the estimated mean lead time as a proxy for PSA tests and further investigation among participants of the control group of both studies is compared, these values indicate a higher diagnostic work-up in PLCO than in ERSPC (estimated mean lead time: 3.1–3.4 years versus 0.7–1.7 years, respectively).[27] Taken together, the results of the ERSPC study showed a reduction of PCa mortality, while those of the PLCO study did not, which is attributable to the high frequency of opportunistic screening in the usual care control group.

Other screening studies for PCa have also been included in review articles or in the calculations for meta-analyses.[28] For instance, a Swedish study[29] randomised 1,494 participants to screening; overall, four rounds were performed, of which two were carried out by DRE only. However, DRE-only screening is insufficient to detect PCa at an early stage because only locally advanced PCa will be detected. This reduced the treatment efficacy in terms of mortality reduction. Moreover, in men with PSA levels below commonly used biopsy thresholds (e.g., 0–3 ng/mL, the PSA stratum in which most men will have a PSA value[30]), the positive

predictive value of DRE for PCa detection has been shown to be very low at 5–30%.[31] Despite its low number of participants and the insufficient screening method, data from this study are still used for meta-analysis calculations, remarkably altering the significance of high-level evidence.[28]

BIOPSY TECHNIQUE: INFLUENCE ON CANCER DETECTION AND OVERDIAGNOSIS

Many recent screening studies have used transrectal ultrasound (TRUS)-guided biopsy. With the results of two important studies,[32,33] the evidence is clear that TRUS-guided biopsy is inferior to MRI-guided biopsy in terms of diagnosis and detection of clinically relevant disease.

The PROMIS study[32] investigated whether multiparametric MRI (MP-MRI) could discriminate between participants with and without clinically significant PCa based on template prostate mapping (TPM) biopsy as a reference test. TPM biopsy was performed by sampling the entire prostate every 5 mm to accurately characterise disease status and reduce verification bias. A comparison of MP-MRI and TRUS biopsy in terms of sensitivity, specificity, positive predictive value, and negative predictive value on PCa findings was also performed.

On TPM biopsy, 40% (230 out of 576) of cancers were clinically significant, defined as having a Gleason score of ≥4+3 or a maximum cancer core length of ≥6 mm.[32] For clinically significant cancer, MP-MRI was more sensitive (93%; 95% confidence interval [CI]: 88–96%) than TRUS biopsy (48%; 95% CI: 42–55%; p<0.0001) but less specific (41%; 95% CI: 36–46% for MP-MRI versus 96%; 95% CI: 94–98% for TRUS biopsy; p<0.0001).[32] The authors concluded that if triaged men were screened using MP-MRI, 27% of primary biopsies could be avoided and 5% fewer diagnoses of clinically insignificant PCa would be made.[32] If subsequent TRUS biopsies were directed by MP-MRI findings, up to 18% more cases of clinically significant cancer might have been detected as compared to the standard pathway of TRUS biopsy. MP-MRI could also reduce overdiagnosis of clinically insignificant PCa and improve detection of clinically significant PCa according to the study authors. MP-MRI could be recommended as a triage test before prostate biopsy in men who present with an elevated serum PSA.

The PRECISION study[34] evaluated whether MP-MRI with targeted biopsy in the presence of an abnormal lesion was noninferior to standard TRUS biopsy in the detection of clinically significant PCa, defined as any Gleason score ≥7. A maximum of 3 areas that were suggestive for PCa were permitted to be chosen for targeted biopsy, with a maximum of 4 biopsy cores obtained per area, resulting in a maximum of 12 biopsy cores per participant. Standard biopsy was a 10–12-core TRUS-guided biopsy. Clinically significant PCa was detected in 95 men (38%) in the MRI-targeted biopsy group compared to 64 (26%) by standard biopsy. This study showed that MRI improved the diagnosis of PCa by enhancing the detection of clinically significant cancer, while also ruling out insignificant cancers following investigation of an abnormal PSA.

The results of these two studies, therefore, confirmed the value of MRI for patients with elevated PSA. However, neither the ERSPC nor the PLCO studies used imaging-enhanced biopsy techniques. The role of TRUS as an imaging tool has also been discussed in the literature. 'Hypoechogenic lesions' were considered pathologic by some authors but were found to be unspecific in clinical use. This makes it difficult for TRUS to be used to differentiate aggressive PCa and other inflammatory or benign tissues;[35] nevertheless, recent research has indicated its potential role in the detection of aggressive PCa.[36]

THE EPIDEMIOLOGICAL ISSUE OF PROSTATE-SPECIFIC ANTIGEN SCREENING

Based on two large screening studies providing conflicting results in terms of disease-specific survival,[24,26,37] several medical associations have changed their guidelines for practical management, including the United States Preventive Services Task Force (USPSTF).[38] The change in USPSTF guidelines influenced PCa screening because there was a decrease in PSA testing in some countries, which led

to more aggressive disease being missed at diagnosis.[39] However, in comparison, testing in other countries may have increased. The crux is that the underlying prevalence of PCa[10] frequently leads to well-differentiated, small PCa foci that have a low potential to harm the patient, leading to increased numbers needing to be detected (27 cases) to prevent one PCa death during 13 years of study follow-up.[24] Due to the high PCa prevalence and untargeted use of PSA in primary care, in terms of opportunistic screening and subsequent prostate biopsy, the face of PCa has changed remarkably in recent decades, resulting in a considerable increase in PCa incidence.[40] In most cases, PCa is not diagnosed clinically and is instead detected by needle biopsy at an early stage. In addition, since the introduction of MRI to clinical practice, these PCa foci can be detected visually.[32,33] Emerging molecular imaging techniques will enrich the future of diagnosis and therapy.[41]

PROSTATE-SPECIFIC ANTIGEN SCREENING IN DAILY PRACTICE

Before the guidelines were changed, there was an increase in PSA screening during recent decades and the changing attitude to screening has led to a migration towards more cases of low-risk PCa.[42] Frequently, patients ask healthcare providers for PSA testing. Although plenty of guidelines and recommendations on PCa screening exist, they seem not to be in accordance with screening policies of the past.[43-45] It must be acknowledged that information about optimal retesting schedules is often sparse; in particular, retesting men most often does not rely on baseline serum PSA,[43] although baseline values offer a powerful risk stratification.[46] Importantly, the evidence for predictive properties for future PCa risk of a single PSA measurement has increased over the years.[47-49] Moreover, the vast majority of a screened population will feature low PSA values at first screening. Therefore, in terms of PCa screening, healthcare providers carry a far-reaching responsibility in several ways. First, the patient is seeking advice as to whether to perform screening by a blood test. The patient generally has little knowledge about the screening performance of a test or about the exact prevalence of the disease. Second, PSA screening is being performed as a 'single doctor screening modality'. For instance, screening for malignancies, such as colonic, lung, or breast, requires the collaboration with other disciplines, e.g., the gastroenterologist to perform a coloscopy or the radiologist to perform the CT scan, whereas PSA screening can be done by almost every doctor independently. Since most patients rely entirely on the doctor's evaluation, a discussion prior to blood withdrawal regarding the diagnostic consequences, harms, and benefits of PSA screening is warranted. With regard to the normal PSA value, approximately 50% of men aged 50–70 years will have a PSA <1 ng/mL.[46] These men will have a very low probability of developing harmful PCa during the next couple of years. If PSA is >3 ng/mL, risk calculators can help stratify patients.[50]

Box 1: Possible algorithm for a screening visit for prostate cancer.

1. Take the patient's history of:
   - Lower urinary tract symptoms.
   - Sexual intercourse (including masturbation) within the last 9 days.
   - First-degree relatives with prostate cancer.
2. Inform the patient about the prevalence and the clinical relevance of prostate cancer.
3. Inform the patient about the harms (roughly 40% overdiagnosis in population-based studies when TRUS-Bx, depending on a clear PSA cut-off, is applied; e.g., 3 ng/mL) and benefits (roughly 30% reduction in mortality after 13 years when corrected for non-participation).
4. Send patient to blood withdrawal after informed consent is given.
5. If PSA is found to be elevated (>3 ng/mL), use risk calculators.

PSA: prostate-specific antigen; TRUS-Bx: transrectal ultrasound biopsy.

THE VALUE OF FAMILY HISTORY IN PROSTATE CANCER

A family history (FH) of PCa is a known risk factor for future PCa development. Meta-analysis results have supported the hypothesis that having a first-degree relative diagnosed with PCa is a significant risk factor for future PCa development in the index patient.[51,52] This effect was particularly true for clinically diagnosed disease before the PSA screening era. Reported risk ratios vary from 2.5–3.4-fold higher than those of men with a negative FH, with a greater number of family members affected or younger age at diagnosis increasing this risk even further.[53] A positive FH is, therefore, a key factor for identifying individuals who have an inherited predisposition to PCa. The goal of a FH inventory is to provide enough information for a risk assessment with respect to further investigations. However, the predominant part of the underlying data of those studies was gathered before or at the beginning of the PSA era. On the other hand, some noteworthy contemporary studies have failed to reproduce a correlation between a positive FH and PCa aggressiveness;[54] for instance, the PCPT found PSA levels, DRE, and previous biopsy, but not positive FH, to be significant predictors for high-grade disease, despite a very high rate of positive FH of 17%.[55] A limitation of this study was the high rate of positive FH and the randomisation of men with exclusively low baseline PSA. Moreover, a PCa diagnosis raises awareness of the disease for the patient's family members as well as for their healthcare providers and, thereby, exposes male relatives to increased PSA testing and subsequent prostate biopsy. Additionally, a higher socioeconomic status was shown to be associated with detection of more localised but not metastatic PCa.[56] Thus, a percentage of men with a positive FH diagnosed with PCa could be explained by increased screening behaviour. Box 1 gives a possible algorithm of how a screening visit might be carried out.

CONCLUSION

Screening for PCa by a PSA blood test has been shown to reduce disease-specific mortality. However, because of the high prevalence of PCa, many clinically irrelevant tumours will be detected if a static cut-off value (e.g., 3 ng/mL) is applied. Therefore, 27 detections are needed to prevent 1 PCa death. Before the PSA blood test is performed, informed consent is necessary and the decision to screen should be well considered. Most men aged 50–70 years will have a low PSA value of <1 ng/mL.[30,46] These men will also have a low risk of developing harmful PCa within the next couple of years. If a PSA value is found to be constantly elevated (i.e., ≥3 ng/mL), risk calculators should be applied. If the calculated risk is found to be increased, MRI fusion biopsy is the best biopsy method for these patients.

References

1. Murphy GP. Prostate cancer. CA Cancer J Clin. 1974;24(5):282-8.
2. Stamey TA et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med. 1987;317(15):909-16.
3. Catalona WJ et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med. 1991;324(17): 1156-61. Erratum in: N Engl J Med. 1991;325(18):1324.
4. Tabayoyong W, Abouassaly R. Prostate cancer screening and the associated controversy. Surg Clin North Am. 2015;95(5):1023-39.
5. Lin KW, Ebell MH. How to counsel men about PSA screening. Am Fam Physician. 2016;94(10):782-4.
6. Siegel RL et al. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7-30.
7. Kwiatkowski M et al. Prostate cancer screening: And yet it moves! Asian J Androl. 2015;17(3):437-8.
8. Thompson IM et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med. 2004;350(22):2239-46.
9. Franks LM. Latent carcinoma of the prostate. J Pathol Bacteriol. 1954;68(2):603-16.
10. Jahn JL et al. The high prevalence of undiagnosed prostate cancer at autopsy: Implications for epidemiology and treatment of prostate cancer in the prostate-specific antigen-era. Int J Cancer. 2015;137(12):2795-802.
11. Bill-Axelson A et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med. 2014;370(10):932-42.
12. Johansson JE et al. Natural history of early, localized prostate cancer. JAMA. 2004;291(22):2713-9.
13. Popiolek M et al. Natural history of early, localized prostate cancer: A final report from three decades of follow-up. Eur Urol. 2013;63(3): 428-35.
14. Barnes RW. Survival with conservative therapy. JAMA. 1969;210(2):331-2.

15. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol. 1974;111(1):58-64.
16. Chodak GW et al. Results of conservative management of clinically localized prostate cancer. N Engl J Med. 1994;330(4):242-8.
17. Albertsen PC et al. Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol. 2011;29(10):1335-41.
18. Heidenreich A et al.; European Association of Urology. EAU guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol. 2014;65(1):124-37.
19. Martínez-González NA et al. Shared decision-making for prostate cancer screening and treatment: A systematic review of randomised controlled trials. Swiss Med Wkly. 2018;148:w14584.
20. Schröder FH et al.; ERSPC Investigators. Prostate cancer mortality at 11 years follow-up. N Engl J Med. 2012;366(11):981-90.
21. Andriole GL et al.; PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009;360(13):1310-9.
22. Martin RM et al.; CAP Trial Group. Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: The CAP randomized clinical trial. JAMA. 2018;319(9):883-95.
23. Grubb RL 3rd et al. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian cancer screening trial: Update on findings from the initial four rounds of screening in a randomized trial. BJU Int. 2008;102(11):1524-30.
24. Schröder FH et al.; ERSPC Investigators. Screening and prostate cancer mortality: Results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet. 2014;384(9959):2027-35.
25. Shoag JE et al. Reevaluating PSA testing rates in the PLCO Trial. N Engl J Med. 2016;374(18):1795-6.
26. Andriole GL et al.; PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009;360(13):1310-9.
27. Tsodikov A et al. Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO Trials. Ann Intern Med. 2018;168(8):608-9.
28. Ilic D et al. Screening for prostate cancer: An updated Cochrane systematic review. BJU Int. 2011;107(6):882-91.
29. Sandblom G et al. Randomised prostate cancer screening trial: 20 year follow-up. BMJ. 2011;342:d1539.
30. Randazzo M et al. A "PSA Pyramid" for men with initial prostate-specific antigen ≤3 ng/ml: A plea for individualized prostate cancer screening. Eur Urol. 2015;68(4):591-7.
31. Carvalhal GF et al. Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng./ml. or less. J Urol. 1999;161(3):835-9.
32. Ahmed HU et al.; PROMIS study group. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): A paired validating confirmatory study. Lancet. 2017;389(10071):815-22.
33. Kasivisvanathan V et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med. 2018;378(19):1767-77.
34. Kasivisvanathan V et al.; PRECISION Study Group Collaborators. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med. 2018;378(19):1767-77.
35. Pallwein L et al. Ultrasound of prostate cancer: Recent advances. Eur Radiol. 2008;18(4):707-15.
36. Yang T et al. The predictive efficacy of hypoechoic lesion in ultrasound for prostate cancer in Chinese people: Five-year experience in a moderated 10-core transperineal prostate biopsy procedure. Oncotarget. 2017;8(45):79433-40.
37. Schroder FH et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med. 2012;366(11):981-90.
38. Grossman DC et al.; US Preventive Services Task Force., Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2018;319(18):1901-13.
39. Gejerman G et al. US Preventive Services Task Force prostate-specific antigen screening guidelines result in higher Gleason score diagnoses. Investig Clin Urol. 2017;58(6):423-8. Erratum in: Investig Clin Urol. 2018;59(4):283.
40. Center MM et al. International variation in prostate cancer incidence and mortality rates. Eur Urol. 2012;61(6):1079-92.
41. Hofman MS et al. [^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): A single-centre, single-arm, Phase 2 study. Lancet Oncol. 2018;19(6):825-33.
42. Cooperberg MR et al. Contemporary trends in low risk prostate cancer: Risk assessment and treatment. J Urol. 2007;178(3 Pt 2):S14-9.
43. Nordström T et al. Prostate-specific antigen (PSA) testing is prevalent and increasing in Stockholm County, Sweden, despite no recommendations for PSA screening: Results from a population-based study, 2003-2011. Eur Urol. 2013;63(3):419-25.
44. Tuppin P et al. Prostate-specific antigen use among men without prostate cancer in France (2008-2010). Bull Cancer. 2012;99(5):521-7.
45. Van der Meer S et al. Prostate specific antigen testing policy worldwide varies greatly and seems not to be in accordance with guidelines: A systematic review. BMC Fam Pract. 2012;13:100.
46. Randazzo M et al. Is further screening of men with baseline PSA < 1 ng ml^{-1} worthwhile? The discussion continues-Results of the Swiss ERSPC (Aarau). Int J Cancer. 2015;137(3):553-9.
47. Fang J et al. Low levels of prostate-specific antigen predict long-term risk of prostate cancer: Results from the Baltimore Longitudinal Study of Aging. Urology. 2001;58(3):411-6.
48. Loeb S et al. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. Urology. 2006;67(2):316-20.
49. Vickers AJ et al. Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: Case-control study. BMJ. 2010;341:c4521.
50. Pereira-Azevedo N et al. Head-to-head comparison of prostate cancer risk calculators predicting biopsy outcome. Transl Androl Urol. 2018;7(1):18-26.
51. Bruner DW et al. Relative risk of prostate cancer for men with affected relatives: Systematic review and meta-analysis. Int J Cancer. 2003;107(5):797-803.
52. Johns LE, Houlston RS, A systematic review and meta-analysis of familial prostate cancer risk. BJU Int. 2003;91(9):789-94.
53. Brandt A et al. Age-specific risk of incident prostate cancer and risk of death from prostate cancer defined by the number of affected family members. Eur Urol. 2010;58(2):275-80.
54. Thomas JA 2nd et al. Prostate cancer risk in men with prostate and breast cancer family history: Results from the REDUCE study (R1). J Intern Med. 2012;272(1):85-92.
55. Thompson IM et al. Assessing prostate cancer risk: Results from the Prostate Cancer Prevention Trial. J Natl Cancer Inst. 2006;98(8):529-34.
56. Bratt O et al. Effects of prostate-specific antigen testing on familial prostate cancer risk estimates. J Natl Cancer Inst. 2010;102(17):1336-43.

Mantle Cell Lymphoma: Are New Therapies Changing the Standard of Care?

Authors: *Susmita Sharma,[1] John W. Sweetenham[2]

1. Department of Hematology/Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA
2. Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA

*Correspondence to oncodocsus@gmail.com

Disclosure: The authors have declared no conflicts of interest.

Received: 23.05.18

Accepted: 28.09.18

Keywords: Autologous stem cell transplant (ASCT), clinical trials, mantle cell lymphoma (MCL), novel therapy.

Citation: EMJ Oncol. 2018;6[1]:109-119.

Abstract

The prognosis of mantle cell lymphoma (MCL) has improved rapidly over recent years with the evolution of new management strategies. The disease, once considered fatal, has now become more of a chronic illness, with recurrent relapses that can be managed with a variety of treatment modalities, such as chemoimmunotherapy, stem cell transplantation, and novel targeted therapies. Several treatment options are already available for young, fit patients with newly diagnosed MCL, while many newer agents are being tested in relapsed/refractory MCL. The need for more effective treatment strategies in the elderly population is being addressed by numerous ongoing studies. With the advent of newer treatment modalities with more efficacy and less toxicity, it is now necessary to re-evaluate the way MCL is managed. This paper provides a comprehensive review of emerging, novel agents for the treatment of MCL.

INTRODUCTION

Mantle cell lymphoma (MCL), a distinct and aggressive form of B cell lymphoma, represents about 7% of all lymphomas in Europe and the USA. The median age at diagnosis is 60 years, with a male predominance (2:1). Patients generally present with advanced-stage (Stage III–IV) disease, extensive lymphadenopathy, blood and bone marrow involvement, and splenomegaly. Some present with pancytopenia or extensive leukocytosis (leukaemic presentation). Extranodal sites, such as the gastrointestinal tract, are also frequently involved.[1] The pathological hallmark of MCL is the expression of the cyclin D1 protein, which occurs as a result of aberrant expression of the B Cell Lymphoma 1 gene (*BCL1*). A small number of MCL cases express cyclin D2 or D3 instead of cyclin D1. Additionally, some MCL cases have other acquired alterations, such as abnormalities in *TP53* or the deletion of the INK4a/ARF locus on chromosome 9p21. Cyclin D1-negative cases are very rare and may express SOX11 (SRY-Box 11), which is highly specific for MCL.[2]

The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms subdivided MCL into indolent variants (leukaemic, non-nodal, and *in situ* MCL)

and classical MCL.[3] The two subtypes have variable clinical courses. A minority of patients with indolent disease may survive many years without treatment, whereas, in most patients, it behaves more aggressively. There is no clear demarcation between indolent and aggressive variants and treatment depends on the patient's prediagnosis health status, performance status, disease burden, and age, as well as other prognostic factors. The current standard treatment is chemoimmunotherapy with or without autologous stem cell transplantation (ASCT). Although initial therapy can achieve high overall response rates (ORR), most patients eventually succumb to their disease. Novel therapeutic agents targeting specific abnormalities have shown efficacy in relapsed/refractory disease and are now being tested as frontline treatment. In this review, the authors explore the role of current treatment modalities in the context of developing new targeted therapies for MCL.

RISK ASSESSMENT

Risk stratification in MCL combines clinical, laboratory, radiological, and molecular findings. The recently formulated MCL Prognostic Index (MIPI) and its simplified version, which take into account independent prognostic factors, such as age, performance status, leukocyte count, and lactate dehydrogenase (LDH), have made it easier to stratify MCL patients into low, intermediate, or high-risk groups for treatment purposes. The prognostic factors for shorter overall survival (OS) according to the MIPI are higher age, worse Eastern Cooperative Oncology Group (ECOG) performance status, higher LDH level, and higher white blood cell count at diagnosis. The Ki-67 protein is an independent predictor of outcome and its measurement provides additional discriminatory power to the MIPI.[4,5] Some proliferation-associated genes, such as *RAN*, *MYC*, *SLC29A2*, and *TNFRSF10B*, were identified as prognostic factors in a small study but are yet to be validated by additional studies.[6,7] A complex karyotype is associated with decreased progression-free survival (PFS) and aggressive disease in newly diagnosed MCL, and is considered a strong predictor of OS independent of MIPI.[8,9]

WAIT AND WATCH

Over the past few years, researchers have tried to identify a subgroup of patients who have indolent disease with extended survival. Although specific diagnostic criteria are not available for the recognition of these patients, some clinicopathological studies have identified the non-nodal leukaemic variant with splenomegaly, low Ki-67 proliferation index, lack of SOX11 expression, and hypermutated immunoglobulin heavy chain: a complex karyotype with normal LDH, and β2-microglobulin levels as potential predictors of indolent behaviour.[6] These patients usually have a low MIPI score and are asymptomatic. Two separate studies reported by Martin et al.[10] and Eve et al.[11] in 2009 indicated that these patients could be kept on 'wait and watch' for a long period of time without any detrimental effect on outcome. Occasionally, secondary abnormalities, often involving *TP53*, may occur and lead to very aggressive disease, emphasising the importance of close surveillance in these cases.[12]

INITIAL MANAGEMENT

Elderly or Low-Risk Mantle Cell Lymphoma Patients

Considering the incurable nature of MCL and the high rate of toxicity associated with currently available dose-intensified regimens, most elderly patients or those with low MIPI scores and/or asymptomatic disease can be managed safely with observation until they become symptomatic. For symptomatic, elderly patients, for whom the intensive treatment strategies are not viable, the choice of therapy includes various nonintensive chemoimmunotherapy regimens, each with different survival benefits and toxicity profiles (Table 1).[13-20] Bendamustine plus rituximab (RTX) (BR); RTX, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); R-CHOP followed by RTX maintenance; and consideration for clinical trials are standard options for these patients

Young, Fit Symptomatic Patients

Intensive chemoimmunotherapy with or without ASCT remains a cornerstone of MCL treatment in young, fit patients. The MCL Network

Phase III trial[16] established the superiority of ASCT over INF-α treatment following CHOP in the frontline setting. Molecular remission is considered one of the important predictors of favourable treatment outcome.[21,22] Several studies[17-20] have evaluated different induction regimens, which can yield complete remission (CR) or negative minimal residual disease before ASCT consolidation. Currently, the standard induction regimens for young, fit patients include intensive chemoimmunotherapy regimens, such as RTX-hyper-cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride, and dexamethasone (CVAD); methotrexate (MTX); or cytarabine (Ara-C), or a modified Nordic regimen (maxi-CHOP) (alternating with RTX plus high-dose cytarabine), or less intensive regimens (such as R-CHOP) alternating R-CHOP and RTX plus dexamethasone, high-dose cytarabine, and cis-platin (R-DHAP); or BR. In transplant-eligible patients, these regimens are followed by ASCT consolidation in first CR. Results of some studies comparing different treatment strategies in newly diagnosed MCL cases are depicted in Table 1.[13-20]

AUTOLOGOUS STEM CELL TRANSPLANTATION

ASCT has been tested in various clinical MCL settings and superior outcomes have been reported. In a report by the European MCL Network, 122 patients who responded to initial CHOP-like therapy were randomly assigned to ASCT or two additional cycles of consolidation followed by IFN-α maintenance; the patients receiving ASCT had superior PFS and OS. Similar encouraging results were obtained in other studies,[23,24] leading to the establishment of ASCT as a component of frontline therapy for MCL in young, fit patients. Although the treatment-related toxicity and mortality associated with ASCT have always been a cause of concern and hesitation for its use in the elderly population, some recent studies have suggested that ASCT consolidation might be safe, feasible, and worth consideration in selected patients >65 years old.[25,26] Yet, poor quality of life, long-term side effects, and late relapses seen in patients who survive long after high-dose therapy and ASCT have compelled scientists to investigate other potentially curative and less toxic regimens. The role of consolidation with ASCT after intensive chemoimmunotherapy is being considered. Various combinations of chemoimmunotherapies and novel agents are being studied, with the aim of replacing ASCT as a frontline therapy in MCL.[17,18] The long-term outcome report of a Phase II study investigating RTX-hyper-CVAD alternating with a MTX-Ara-C combination without ASCT in newly diagnosed young MCL patients reported an ORR of 97%, CR of 87%, and median OS and failure-free survival of 13.4 years and 6.5 years, respectively.[18] These results, therefore, demonstrated the feasibility of ASCT-free treatment in MCL.

MAINTENANCE THERAPY

Studies have indicated that incorporating a maintenance therapy into the treatment strategy of MCL prolongs remission duration and ultimately survival. The Phase III LyMA trial[27] compared maintenance RTX therapy versus observation following treatment with R-DHAP±R-CHOP, high-dose therapy, and ASCT in MCL patients <66 years old and observed superior 4-year OS (89% [RTX] versus 80% [observation]) and PFS (83% [ASCT] versus 64% [observation]; p<0.001) in the RTX maintenance arm. Additionally, long-term follow-up of the randomised European MCL elderly trial,[28] which evaluated RTX versus IFN maintenance following initial response to R-CHOP, revealed a 5-year PFS and an OS of 51% versus 22% (p<0.0001) and 79% versus 59% (p=0.002), respectively. Similarly a study comparing RTX-fludarabine and cyclophosphamide (R-FC) with R-CHOP followed by maintenance with either RTX or IFN-α in patients ≥60 years old (median age: 70 years) reported that although CR rates were similar with R-FC and R-CHOP (40% and 34%, respectively), progressive disease was more frequent with R-FC and OS was significantly shorter with R-FC than with R-CHOP (4-year survival rate: 47% versus 62%, respectively). Among patients who responded to R-CHOP, maintenance therapy with RTX significantly improved OS compared with those who received maintenance with INF (4-year survival rate: 87% versus 63%).[29] Results of these trials encouraged investigators to explore options for durable maintenance therapy. Nevertheless, not all patients benefit from maintenance therapy, as seen from the results of a subgroup study of the StiL NHL trial.[13]

Table 1: Comparison of some of the first-line treatment regimens for mantle cell lymphoma.

Study	Regimens studied or compared	Total number of patients (number per treatment)	Median age, years (age range)	Response rate* (%)	PFS	OS	Comments
Rummel et al.,[13] 2013	R-CHOP versus BR	94 (48 versus 46)	70.0	ORR: 91% versus 93% CR: 30% versus 40%	Median: 22.1 months versus 35.4 months	Median: NR	10-year follow-up results of this trial presented at the 2017 ASCO Annual Meeting confirm superiority of BR to R-CHOP.
Robak et al.,[14] 2015	R-CHOP versus VR-CAP	487 (244 versus 243)	66.0 (26–88)	ORR: 89% versus 92%	14.4 months versus 24.7 months	4-year OS: 54% versus 64%	Adverse effects were more common in the VR-CAP group but without significant increase in TRM.
Branca et al.,[15] 2015	R-BAC± ASCT±RM	22	67.0 (57–83)	CR: 76% at 33 months	80% (median follow-up: 33 months)	80% (at 33 months)	OS: 100% and 71% in ASCT and RM arms after 23 months and 41 months median follow-up, respectively.
Dreyling et al.,[16] 2008	ASCT versus IFN-α consolidation	122 (62 versus 60)	55.6	CR/Cru: 81% versus 28% PR: 17% versus 72%	39 months versus 17 months	NR versus 56 months	No significant difference in OS and PFS.
Chihara et al.,[17] 2016	R-hyperCVAD /MTX (alternating)	97	61.0 (41–80)	ORR: 97% CR: 87%	Median: 4.8 year	Median: 10.7 years	In patients aged ≤65 and >65 years, median FFS and OS were 6.5 versus 3.0 years and 13.4 versus 4.9 years, respectively.
Eskelund et al.,[18] 2016	Alternating maxi-CHOP/ high-dose cytarabin with R +HDT (BEAM or BEAC) and ASCT	160	56.0	CR: 89.7%	Median: 11 year	Median: NR Median follow-up: 11.4 years	Continuous late relapses and increased mortality compared to general population.
Widmer et al.,[19] 2018	R-CHOP or R-DHAP or R-Maxi-CHOP + HD-ASCT versus R-hyperCVAD/ MTX-Ara-C (without HD-ASCT)	35 (24 versus 11)	54.4	CR/Cru: 95.8% versus 100.0%	5-year PFS: 56.9 years versus 33.1 years	5-year OS: 88.7% versus 76.9%	No significant difference in OS and PFS. Higher toxicities and hospitalisations in R-hyper CVAD/ MTX-Ara-C group.
Hermine et al.,[20] 2016	R-CHOP + ASCT versus R-CHOP/ R-DHAP+ high-dose cytarabin myeloablation + ASCT	466 (234 versus 232)	56.0	ORR: 97% versus 98% CR: 76% versus 83%	5-year PFS: 45% versus 73%	5-year OS: 69% versus 76%	Higher rate of observed toxicities in cytarabin group. Median TTF: 3.9 years versus 9.1 years.

*Response rate reflects response after ASCT, as applicable.

Ara C: cytarabin; ASCO: American Society of Clinical Oncology; ASCT: autologous stem cell transplant; BEAM: carmustine (BCNU), etoposide, cytarabine, melphalan; BEAC: BCNU, etoposide, cytarabine, cyclophosphamide; BR: bendamustine, rituximab; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CR: complete response; Cru: complete response unconfirmed; DHAP: dexamethasone, high-dose cytarabine, cisplatin; FFS: failure-free survival; HDT: high-dose therapy; hyperCVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; MTX: methotrexate; NR: not reached; OS: overall survival; PFS: progression-free survival; PR: partial response; R: rituximab; R-BAC: rituximab, bendamustine, cytarabin; RM: rituximab maintenance; TBI: total body irradiation; TTF: time to failure; TRM: transplant related mortality; VR-CAP: bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone.

Table 2: Novel agents used in the treatment of mantle cell lymphoma.

Study	Regimen/drug	Study population; median age, years (age range)	Disease status	Response	Survival	Toxicity/comments
Rule et al.,[30] 2017	Ibrutinib versus temsirolimus	139 versus 141; 68	R/R received at least one rituximab-containing regimen	ORR: 72% versus 40% CR: 23% versus 3%	Median OS: 30.3 versus 23.5 months Median PFS: 25.4 versus 6.2 months	Treatment discontinuation due to adverse events: 6% versus 26%
Wang et al.,[31] 2016	Bortezomib	155; 65 (42–89)	R/R	RR: 32% CR: 8%	Median OS: 23.5 months Median DOR: 9.2 months TTP: 6.7 months	Most common Grade ≥3 toxicity was peripheral neuropathy.
Desai et al.,[32] 2014	Lenalidomide	134; 67 63% of participants ≥65 years old	R/R	RR: 28% CR: 7.5% DOR: 16.6 months	Median OS: 19 months Median PFS: 4 months	Haematological toxicity was most common.
Wang et al.,[33] 2017	Lenalidomide + rituximab	38; 65 (42–86)	Newly diagnosed	ORR: 92% CR: 64% (at 30 months)	2-year OS: 85% 2-year PFS: 97%	Responses were independent of MIPI score/LDH level.
Tobinai et al.,[34] 2017	Obinutuzumab	15; 71 (22–85)	Heavily pretreated R/R	ORR: 27% CR: 14%	Median response duration: 9.8 months	Median response duration in rituximab-refractory patients: >6 months.

CR: complete response; DOR: duration of response; LDH: lactate dehydrogenase; MIPI: Mantle Cell Lymphoma Prognostic Index; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; R/R: relapsed/refractory; RR: response rate; TTP: time to progression.

The trial compared the effect of RTX maintenance with observation after first-line treatment with BR in patients with previously untreated MCL and found no survival benefit in patients receiving RTX compared to those on observation after 4.5 years follow-up.

MANAGEMENT OF RELAPSED/ REFRACTORY MANTLE CELL LYMPHOMA

A watch and wait strategy can be feasible in some relapsed asymptomatic patients who have an indolent course. Once symptoms arise, various treatment options can be considered, including radiotherapy for local relapse, radioimmunotherapy, targeted agents, chemotherapy, and immunomodulatory agents, such as the BR regimen, bortezomib, lenalidomide, or ibrutinib (Table 2).[30-34] Though the use of high-dose chemotherapy and ASCT has not demonstrated promising results in the relapsed/refractory setting, results of some studies indicate that in certain patients with long initial responses to salvage therapy, ASCT after second CR can be of benefit.[35]

NOVEL THERAPIES

Burton's Tyrosine Kinase Inhibitors

The B cell receptor is a surface receptor complex on B cells and signals through the spleen tyrosine kinase, phosphoinositide-3-kinase (PI3K), Burton's tyrosine kinase (BTK), and protein kinase C beta. These signals lead to NFκB and AKT activation, which promotes survival and proliferation of normal and malignant B cells. Persistent activation of the B cell receptor pathway has been found to be a major contributor to the pathogenesis of MCL and targeting this pathway has been shown to be effective in MCL.[36]

Ibrutinib is an oral irreversible BTK inhibitor that binds to cysteine 481 in the phosphorylation site of BTK. The results of a Phase II trial demonstrating a 68% ORR, 21% CR, and median PFS of 13.9 months in a study cohort that included heavily pretreated patients and those with high MIPI scores led to the approval of ibrutinib for previously treated MCL patients.[37]

Real-world data on the efficacy and outcome of ibrutinib are sparse. Results of a study using data from the global Named Patient Program (NPP),[38] including 715 patients from 26 countries with a median age of 70 years who received ibrutinib for relapsed/refractory MCL, were presented at the 21st Congress of the European Hematology Association (EHA). These results were similar to those of the Phase III RAY (MCL3001) trial,[29] which showed that 52.3% (95% confidence interval: 43.5–60.4) of global patients remain on treatment after 12 years. Another study that analysed pooled data from 370 patients, with a median age of 67 years, who were receiving ibrutinib for their relapsed/refractory MCL, and enrolled across three different studies (PCYC-1104 [n=111], SPARK [n=120], and RAY [n=139]), demonstrated an excellent outcome, with a median duration of follow-up of 41.1 months, CR rate of 26.5%, median PFS of 13.0 months, and median OS of 26.7 months.[39] Despite these encouraging results, it has been observed that 30–40% of patients with MCL do not respond to ibrutinib and even among those who respond initially, the majority of patients ultimately develop resistance.[40] Other studies have revealed that patients who fail ibrutinib therapy are not likely to respond to salvage chemotherapy and have a poor outcome, with an OS of 2.9 months.[41] A Phase I study by Martin et al.[42] reported that palbociclib, a selective CDK4/CDK6 inhibitor, can overcome ibrutinib resistance and sensitise MCL cells to ibrutinib in certain patient groups, achieving a better response rate in patients receiving a combination of these drugs compared to ibrutinib alone.

Acalabrutinib, a novel irreversible second-generation BTK inhibitor with a high rate of durable response and favourable safety profile, has recently been approved for use in relapsed/refractory MCL by the U.S. Food and Drug Administration (FDA) following the results of a Phase II, single-arm, multicentre trial.[43] The study included 124 patients with relapsed/refractory MCL who had received a median of two previous therapies. All patients received acalabrutinib 100 mg twice a day until disease progression or an unacceptable toxicity level were reached. This resulted in an ORR of 81%, CR of 40%, and a 12-month OS and PFS of 72% and 87%, respectively. In addition, tirabrutinib (ONO/GS-4059), another oral BTK inhibitor, demonstrated a relative response rate of 92% (11 of 12 participants) in patients with a median treatment duration of 40 weeks.[44] Other BTK inhibitors thought to be more selective and potent are also being developed and have shown promising results.[45]

Phosphoinositide-3-Kinase Inhibitors

Idelalisib, an oral potent inhibitor of the d-isoform of PI3K, has been implicated in the regulation of the activation, proliferation, migration, and survival of B lymphocytes. In a Phase I dose-escalation study[46] of idelalisib, which enrolled 40 previously treated (a median of four prior therapies) MCL patients, an ORR of 40% was observed. However, the duration of response and PFS were very short (2.7 months and 3.7 months, respectively).[46] In a Phase II safety and efficacy study of copanlisib, a pan-class I PI3K inhibitor, in patients with relapsed/refractory indolent and aggressive lymphomas, including 11 MCL patients, a response was seen in 7 out of the 11 recruited MCL patients (2 CR and 5 partial responses, with an ORR of 63.6%).[47] Duvelisib (IPI-145), an oral PI3K inhibitor, has also shown efficacy in mouse models of MCL.[31]

Bortezomib

Bortezomib is a proteasome inhibitor that induces cell cycle arrest and apoptosis in MCL cells. In addition, it sensitises malignant lymphoid cells to the cytotoxic effects of chemotherapy and glucocorticoids. The PINNACLE trial[48] and LYM-3002[14] study led to the FDA approval of bortezomib for the treatment of relapsed/refractory MCL and as a frontline therapy for MCL, respectively. The combination of bortezomib with various chemotherapeutic agents has been tested previously and in the ongoing trials. The bendamustine, bortezomib, and RTX regimen (BVR) remains the therapeutic pathway of choice. The BVR regimen resulted

in an ORR of 71% in relapsed/refractory MCL patients with manageable toxicities in one study,[49] and is also being studied in an intergroup randomised Phase III trial as a frontline therapy for older, treatment-naïve MCL patients, with the results awaited.[50]

Lenalidomide

Lenalidomide is a structural analogue of thalidomide with enhanced immunological and anticancer properties and less severe toxicity. It is an immunomodulator that works through multiple mechanisms, including, but not limited to, direct tumour cytotoxicity; inhibition of angiogenesis; interaction with the tumour microenvironment; modulation of vascular endothelial growth factors; and inhibition of metastasis and cellular proliferation.[32] Extensive preclinical and clinical studies (EMERGE)[51] led to the FDA approval of lenalidomide for the treatment of MCL patients whose disease progressed or relapsed after two prior therapies (one of them including bortezomib).

Lenalidomide as a single agent is effective in the management of MCL in patients who have progressed, relapsed, or are intolerant or refractory to novel agents, such as ibrutinib.[33] The combination of lenalidomide with various agents, such as dexamethasone, bendamustine, temsirolimus, and RTX, has been tested in numerous Phase II and III trials,[52] out of which the combination of lenalidomide with RTX has been deemed more effective and less toxic than other drug combinations (Table 2).[30-34] In one study, this combination was found to be useful as an initial therapy for MCL, with 80% of patients achieving minimal residual disease-negative CR after 3 years of treatment. This response was associated with improved quality of life and manageable toxicity. The promising results from these studies warrant a head-to-head comparison with standard regimens, particularly in patients who are not eligible for intensive chemotherapy and ASCT. However, lenalidomide-based regimens may impair haematopoietic stem cell collection after prolonged therapy and compromise outcomes of subsequent ASCT in eligible patients. Patients receiving lenalidomide for MCL can experience a tumour flare reaction, a syndrome that presents with painful lymph nodes and/or spleen enlargement and can be accompanied by fever, rash, and clear lymphocytosis.

Temsirolimus and Everolimus

The identification of the involvement of the PI3-kinase/Akt/mTOR pathway in the pathogenesis of MCL led to the investigation of temsirolimus as a possible therapy for MCL. Two separate Phase II trials tested two different doses of temsirolimus: a 250 mg weekly intravenous dose[53] and a 25 mg weekly intravenous dose.[54] The two trials resulted in an ORR of 38% and 41%, respectively, with dose-dependent haematological toxicities. A subsequent randomised Phase III trial[55] comparing temsirolimus in two dosing levels with a regimen of choice, selected by the investigators, showed that 175 mg weekly temsirolimus for 3 weeks followed by 75 mg weekly had an ORR of 22% and a median PFS and OS of 4.8 months and 12.8 months, respectively. These data led to the approval of temsirolimus for use in relapsed MCL in the European Union (EU). A study combining temsirolimus with RTX[56] observed an ORR of 59% and a CR of 18.5%, with a median OS of 29.5 months and time to progression of 9.7 months. These results are comparable to the lenalidomide-RTX combination, but the temsirolimus–RTX combination was associated with a higher incidence of severe toxicities. Another mTOR inhibitor, everolimus, has also demonstrated activity in MCL in a Phase IItrial,[57] and it is being explored as part of combination regimens alongside other investigational MCL therapies.

Venetoclax

Venetoclax is an oral selective inhibitor of the prosurvival protein BCL2 and restores the apoptotic ability of malignant cells. This is a promising agent showing activity in relapsed/refractory MCL. In an initial Phase I study of relapsed/refractory non-Hodgkin's lymphoma, the cohort of relapsed/refractory MCL patients (n=28) who had received a median of three previous therapies attained an ORR and a CR of 75% and 21%, respectively, and 1-year OS was 82%, with a median PFS of 14 months. The most common Grade 3–4 toxicity was haematological.[58] The combination of venetoclax and ibrutinib was investigated in a Phase II study that included 23 patients with relapsed/refractory MCL,

30% of whom had failed ASCT, while one was a treatment-naïve MCL patient (5%). OR and CR were achieved in 71% and 63% of all patients, respectively, and the estimated PFS and OS was 74% and 81%, respectively, at 8 months.[59] A Phase III trial[60] comparing a combination of venetoclax and ibrutinib versus ibrutinib and placebo in MCL patients aged ≥18 years is ongoing, with the aim of evaluating dose-limiting toxicities, occurrence of tumour lysis syndrome, and PFS among two study groups.

MISCELLANEOUS AGENTS

Monoclonal Antibodies

RTX is a type I chimeric anti-CD20 antibody that induces cell death primarily through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. RTX, as a single agent or in combination with various chemotherapy regimens, has been extensively tested and used as frontline therapy and maintenance therapy in MCL.[15-17,55] However, suboptimal responses and resistance to RTX have remained a challenge. Ofatumumab is a fully human type I anti-CD20 monoclonal antibody that binds to a different epitope of CD20 than RTX, resulting in higher binding affinity and enhanced complement-dependent cytotoxicity.[34] Obinutuzumab is a humanised, type II, anti-CD20 monoclonal antibody. In culture and xenograft models, obinutuzumab has demonstrated an improved ability to induce direct cell death, as well as antibody-dependent cellular cytotoxicity, compared with RTX.[61] Ofatumumab and obinutuzumab have been approved for use in certain patients with follicular lymphoma and chronic lymphocytic leukaemia, and are being studied in MCL.

Chimeric Antigen Receptor T Cells

In chimeric antigen receptor (CAR) T cell therapy, immune cells are taken from a patient's bloodstream and are reprogrammed to recognise and attack a specific protein found in cancer cells. The cells are then reintroduced into the patient, allowing the cells to detect and destroy targeted tumour cells. The anti-CD19 CAR T cell product, axicabtagene ciloleucel, has been approved in patients with relapsed/refractory diffuse large B cell lymphoma based on the results of the ZUMA-1 trial.[62] Axicabtagene ciloleucel is now being investigated in relapsed/refractory MCL in the ZUMA-2 trial (Table 3).[50,63-67] Case reports of anti-CD19 CAR T cells improving the response to chemotherapy in chemoresistant MCL have been reported;[68] however, further studies are needed to estimate the potential of anti-CD19 CAR T cell therapy in MCL.

Allogeneic Stem Cell Transplant

The potential benefit of allogeneic stem transplantation (alloSCT) is related to the graft-versus-lymphoma effect and the low risk of therapy-related myelodysplastic syndrome/acute myeloid leukaemia. Myeloablative alloSCT is not an option for the majority of MCL patients because of their older age at diagnosis and presence of comorbidities. Multiple study groups have investigated the role of reduced-intensity conditioning alloSCT (RIST) in MCL in a small series and have reported conflicting outcomes.[69-72] A retrospective registry analysis of a large cohort of patients (N=324), which included patients who had undergone RIST for MCL from January 2000 to December 2008, was published recently. The study reported a higher toxicity rate and relapse rate of 25% and 40%, respectively, at 1 and 5 years associated with chemo-refractory disease post transplantation (hazard ratio: 0.49; p=0.01) and concluded that RIST cannot be recommended as a routine part of first-line therapy, for which ASCT remains the consolidation procedure of choice.[73] Durable remissions have been reported with alloSCT but at the expense of higher treatment-related mortality; hence, this potentially curative procedure should be reserved for highly selected patients, such as those with multiply relapsed or refractory disease.

ONGOING CLINICAL TRIALS AND RESEARCH

There are numerous ongoing studies of patients with MCL. Some studies are evaluating different chemoimmunotherapy novel agent combinations, whereas others are investigating entirely chemotherapy-free regimens in the relapsed/refractory as well as frontline settings (as standalone regimens or as induction regimens before ASCT). Studies of particular significance are listed in Table 3.[50,63-67]

Table 3: Ongoing clinical trials in mantle cell lymphoma.

Study	Study type	Drugs/regimens	Patient status	Study purpose	Primary endpoints
NCT01415752[50]	Phase II, intergroup	BR f/b rituximab consolidation versus RBV f/b rituximab versus BR f/b LR versus RBV f/b LR	≥60 years of age with untreated MCL	To determine if addition of bortezomib to an induction regimen of BR and lenalidomide to consolidation regimen of rituximab improves PFS	PFS/objective response rate
NCT01776840[63]	Randomised, double-blind, comparative	BR + ibrutinib versus BR alone	Newly diagnosed MCL patients aged ≥65 years.	To compare the safety and efficacy of the two regimens	PFS
NCT02858258[64]	Randomised, Phase III, open-label, multicentre	R-CHOP/R-DHAP followed by ASCT versus R-CHOP + ibrutinib /R-DHAP followed by ASCT and ibrutinib versus R-CHOP + ibrutinib /R-DHAP followed by ibrutinib maintenance	Previously untreated adult patients <65 years of age at an advanced stage (II–IV)	Establish one of three study arms as a future standard	FFS
NCT02601313[65]	Phase II, multicentre	Anti-CD19 CAR T cell product axicabtagene ciloleucel	R/R MCL patients with up to five prior regimens that must have included anthracycline or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, or anibrutinib/acalabrutinib	To evaluate the safety and efficacy of axicabtagene ciloleucel	ORR
NCT01865110[66]	Phase III, interventional	8 cycles of R-CHOP versus 3 cycles of R-CHOP/3 cycles of R-HAD induction followed by combined RL versus rituximab alone as maintenance in patients responding to induction	≥60 years of age with untreated MCL ineligible for autologous transplant, but fit enough to tolerate the R-HAD therapy	To evaluate whether the addition of lenalidomide to standard rituximab maintenance improves outcome	PFS
NCT01662050[67]	Phase II	6 cycles of age-adjusted rituximab, bendamustine, and cytarabin as induction therapy	≥65 years of age, newly diagnosed, and fit according to geriatric or 60–65 years of age, fit or unfit, assessment newly diagnosed, and not eligible for high-dose chemotherapy and transplant	To determine the safety and efficacy of the regimen	CR at the end of treatment or toxicity requiring treatment termination

ASCT: autologous stem cell transplantation; BR: bendamustine, rituximab; CAR: chimeric antigen receptor; CR: complete response; f/b: followed by; FFS: failure-free survival; MCL: mantle cell lymphoma; ORR: overall response rate; PFS: progression-free survival; R/R: relapsed/refractory; R-CHOP: rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone; R-DHAP: rituximab-dexamethasone, high-dose cytarabine, cisplatin; R-HAD: rituximab, high-dose cytarabine, dexamethasone.

CONCLUSION

MCL is predominantly a disease of older patients, for whom intensive chemotherapy regimens are often poorly tolerated. Even in younger patients, the long-term side effects of intensive chemotherapy regimens are significant. Chemotherapy-free combination regimens represent a potential novel approach. The recent observation that the negative prognostic impact of TP53 mutations is not observed in patients treated with ibrutinib, lenalidomide, and RTX combination therapy supports the continued investigation of this regimen and similar regimens to formulate a chemotherapy-free and less toxic treatment regimen for MCL patients. Until then, intensive chemoimmunotherapy followed by ASCT, when feasible, remains the best standard of care.

References

1. Dreyling M et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(Suppl 4):62-71.
2. Mozos A et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. Haematologica. 2009;94(11):1555-62.
3. Swerdlow SH et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-91.
4. Hoster E et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Cell. 2008;111(2):558-65.
5. Hoster E et al. Prognostic value of Ki-67 index, cytology, and growth pattern in mantle-cell lymphoma: Results from randomized trials of the European Mantle Cell Lymphoma Network. J Clin Oncol. 2016;34(12):1386-94.
6. Hartmann E et al. Five gene model to predict survival in mantle-cell lymphoma using frozen or formalin-fixed, paraffin-embedded tissue. J Clin Oncol. 2008;26(30):4966-72.
7. Fernàndez V et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. Cancer Res. 2010;70(4):1408-18.
8. Cohen JB et al. Complex karyotype is associated with aggressive disease and shortened progression-free survival in patients with newly diagnosed mantle cell lymphoma. Clin Lymphoma Myeloma Leuk. 2015;15(5):278-85.
9. Sarkozy C et al. Complex karyotype in mantle cell lymphoma is a strong prognostic factor for the time to treatment and overall survival, independent of the MCL international prognostic index. Genes Chromosomes Cancer. 2014;53(1):106-16.
10. Martin P et al. Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Oncol. 2009;27(8):1209-13.
11. Eve HE et al. Time to treatment does not influence overall survival in newly diagnosed mantle-cell lymphoma. J Clin Oncol. 2009;27(32):e189-90.
12. Sietse M et al. Expression of TP53 is associated with outcome of MCL independent of MIPI and Ki-67 in trials of the European-MCL Network. Blood. 2017:131(4):417-20.
13. Rummel MJ et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: An open-label, multicentre, randomised, Phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203-10.
14. Robak T et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. N Engl J Med. 2015;372(10):944-53.
15. Branca A et al. Rituximab-bendamustine cytarabine (R-BAC) as frontline therapy in mantle cell lymphoma: A single centre experience. Blood. 2015;126(23):2710.
16. Dreyling M et al. Early consolidation with myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle cell lymphoma: Long term follow up of a prospective randomized trial. Blood. 2008;112(11):769.
17. Chihara D et al. Rituximab plus hyper-CVAD alternating with MTX/Ara-C in patients with newly diagnosed mantle cell lymphoma: 15-year follow-up of a Phase II study from the MD Anderson Cancer Center. Br J Haematol. 2016;172(1):80-8.
18. Eskelund CW et al. 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): Prolonged remissions without survival plateau. Br J Haematol. 2016;175(3):410-8.
19. Widmer F et al. R-hyper-CVAD versus R-CHOP/cytarabine with high-dose therapy and autologous haematopoietic stem cell support in fit patients with mantle cell lymphoma: 20 years of single-center experience. Ann Hematol. 2018;97(2):277-87.
20. Hermine O et al. Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): A randomised, open-label, Phase 3 trial of the European Mantle Cell Lymphoma. Lancet. 2016;388(10044):565-75.
21. Hoster E, Pott C. Minimal residual disease in mantle cell lymphoma: Insights into biology and impact on treatment. Hematology Am Soc Hematol Educ Program. 2016;2016(1):437-45.
22. Liu H et al. Detection of minimal residual disease following induction immunochemotherapy predicts progression free survival in mantle cell lymphoma: Final results of CALGB 59909. Haematologica. 2012;97(4):579-85.
23. Damon LE et al. Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. J Clin Oncol. 2009;27(36):6101-8.
24. Geisler CH et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: A nonrandomized Phase 2 multicenter study by the Nordic Lymphoma Group. Blood. 2008;112(7):2687-93.
25. Dahi PB et al. Favorable outcomes in elderly patients undergoing high-dose therapy and autologous stem cell transplantation for non-Hodgkin lymphoma. Biol Blood Marrow Transplant. 2014;20(12):2004-9.
26. Jantunen E et al. Autologous stem-cell transplantation in patients with mantle cell lymphoma beyond 65 years of age: A study from the European Group for Blood and Marrow Transplantation (EBMT). Ann Oncol. 2012;23(1):166-71.
27. Le Gouill S et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. N Engl J Med. 2017;377(13):1250-60.
28. Hoster E et al. Rituximab maintenance after first-line immunochemotherapy in mantle cell lymphoma: Long-term follow-up of the randomized European MCL Elderly Trial. Blood. 2017;130(Suppl 1):153.
29. Kluin-Nelemans HC et al. Treatment of older patients with mantle-cell lymphoma. N Engl J Med. 2012;367(6):520-31.
30. Rule S et al. Ibrutinib vs temsirolimus: Three-year follow-up of patients with previously treated mantle cell lymphoma from the Phase 3, international, randomized, open-label RAY study. Hematol Oncol. 2017;35(Suppl 2).
31. Wang J et al. The effects of PI3K-δ/γ inhibitor, duvelisib, in mantle cell lymphoma in vitro and in patient-derived xenograft studies. Blood. 2016;128(22):3016.
32. Desai M et al. Lenalidomide in relapsed or refractory mantle cell lymphoma: Overview and perspective. Ther Adv Hematol. 2014;5(3):91-101.
33. Wang M et al. Observational study of lenalidomide in patients with mantle cell lymphoma who relapsed/progressed after or were refractory/intolerant to ibrutinib (MCL-004). J Hematol Oncol. 2017;10(1):171.
34. Tobinai K et al. A review of obinutuzumab (GA101), a novel type II anti-CD20 monoclonal antibody, for the treatment of patients with B-cell malignancies. Adv Ther. 2017;34(2):324-56.
35. Fenske TS et al. Autologous or reduced-intensity conditioning allogeneic hematopoietic cell transplantation for chemotherapy-sensitive mantle-cell lymphoma: Analysis of transplantation timing and modality. J Clin Oncol. 2014;32(4):273-81.
36. Fichtner M et al. The role of B

cell antigen receptors in mantle cell lymphoma. J Hematol Oncol. 2017;10:164.

37. Wang ML et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507-16.

38. Rule S. Real-world experience of ibrutinib in >700 patients with mantle-cell lymphoma: Data from a global named patient program. Abstract P699. EHA Congress, 9-12 June, 2016.

39. Rule S et al. Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: A pooled analysis from three open-label studies. Br J Haematol. 2017;179(3):430-8.

40. Hershkovitz-Rokah O et al. Ibrutinib resistance in mantle cell lymphoma: Clinical, molecular and treatment aspects. Br J Haematol. 2018;181(3):306-19.

41. Martin P et al. Postibrutinib outcomes in patients with mantle cell lymphoma. Blood. 2016;127(12): 1559-63.

42. Martin P et al. A Phase I trial of ibrutinib plus palbociclib in patients with previously treated mantle cell lymphoma. Blood. 2016;128(22):150.

43. Wang M et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): A single-arm, multicentre, Phase 2 trial. Lancet. 2018;391(10121):659-67.

44. Walter HS et al. A Phase 1 clinical trial of the selective BTK inhibitor ONO/GS-4059 in relapsed and refractory mature B-cell malignancies. Blood. 2016;127(4):411-9.

45. Seiler T, Dreyling M. Bruton's tyrosine kinase inhibitors in B-cell Lymphoma. Current experience and future perspectives. Expert Opin Investig Drugs. 2017;26(8):909-15.

46. Kahl BS et al. A Phase 1 study of the PI3Kd inhibitor idelalisib in patients with relapsed/refractory mantle cell lymphoma (MCL). Blood. 2014;123(22):3398-406.

47. Dreyling M et al. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. Ann Oncol. 2017;28(9):2169-78.

48. Goy A et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: Updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann Oncol. 2009; 20(3):520-5.

49. Friedberg JW et al. The combination of bendamustine, bortezomib and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. Blood. 2011;117(10):2807-12.

50. Eastern Cooperative Oncology Group. Rituximab, bendamustine hydrochloride, and bortezomib followed by rituximab and lenalidomide in treating older patients with previously untreated mantle cell lymphoma. NCT01415752. https://clinicaltrials.gov/ct2/show/NCT01415752.

51. Goy A et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: Phase II MCL-001 (EMERGE) study. J Clin Oncol. 2013;31(29):3688-95.

52. Ruan J et al. Lenalidomide plus rituximab as initial treatment for mantle-cell lymphoma. N Engl J Med. 2015;373(19):1835-44.

53. Witzig TE et al. Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma. J Clin Oncol. 2005;23(23):5347-56.

54. Ansell SM et al. Low-dose, single-agent temsirolimus for relapsed mantle cell lymphoma: A Phase 2 trial in the North Central Cancer Treatment Group. Cancer. 2008;113(3):508-14.

55. Hess G et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. J Clin Oncol. 2009;27(23):3822-9.

56. Ansell SM et al. Temsirolimus and rituximab in patients with relapsed or refractory mantle cell lymphoma: A Phase 2 study. Lancet Oncol. 2011;12(4):361-8.

57. Witzig TE et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed aggressive lymphoma. Leukemia. 2011;25(2):341-7.

58. Gerecitano JF et al. A Phase 1 study of venetoclax (ABT-199 / GDC-0199) monotherapy in patients with relapsed/refractory non-hodgkin lymphoma. Abstract 254. ASH Annual Meeting, 5-8 December, 2015.

59. Tam CS et al. Ibrutinib plus venetoclax for the treatment of mantle-cell lymphoma. N Engl J Med. 2018;378(13):1211-23.

60. Pharmacyclics LLC. Study of ibrutinib combined with venetoclax in subjects with mantle cell lymphoma (SYMPATICO). NCT03112174. https://clinicaltrials.gov/ct2/show/NCT03112174.

61. Morschhauser FA et al. Obinutuzumab (GA101) monotherapy in relapsed/refractory diffuse large b-cell lymphoma or mantle-cell lymphoma: Results from the Phase II GAUGUIN study. J Clin Oncol. 2013;31(23):2912-9.

62. Kite, A Gilead Company. A Phase 1-2 multi-center study evaluating axicabtagene ciloleucel in subjects with refractory aggressive non-hodgkin lymphoma (ZUMA-1) (ZUMA-1). NCT02348216. https://clinicaltrials.gov/ct2/show/NCT02348216.

63. Janssen Research & Development, LLC. A study of the Bruton's tyrosine kinase inhibitor ibrutinib given in combination with bendamustine and rituximab in patients with newly diagnosed mantle cell lymphoma. NCT01776840. https://clinicaltrials.gov/ct2/show/NCT01776840.

64. Dreyling M. ASCT after a rituximab/ibrutinib/ara-c containing induction in generalized mantle cell lymphoma. NCT02858258. https://clinicaltrials.gov/ct2/show/NCT02858258.

65. Kite, A Gilead Company. A Phase 2 multicenter study evaluating subjects with relapsed/refractory mantle cell lymphoma (ZUMA-2). NCT02601313. https://clinicaltrials.gov/ct2/show/NCT02601313.

66. The Lymphoma Academic Research Organisation. R-CHOP + R-HAD vs R-CHOP followed by maintenance lenalidomide + rituximab vs rituximab for older patients with MCL. NCT01865110. https://clinicaltrials.gov/ct2/show/NCT01865110.

67. Fondazione Italiana Linfomi ONLUS. Phase II study of age-adjusted rituximab, bendamustine, cytarabine as induction therapy in older patients with MCL (FIL-RBAC500). NCT01662050. https://clinicaltrials.gov/ct2/show/NCT01662050.

68. Chen W et al. Anti-CD19 chimeric antigen receptor T cells improve responses to chemotherapy-refractory mantle cell lymphoma: A case report. Blood. 2016;128(22):5393.

69. Tam CS et al. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood. 2009;113(18):4144-52.

70. Maris MB et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. Blood. 2004;104(12):3535-42.

71. Le Gouill S et al. Reduced-intensity conditioning allogeneic stem cell transplantation for relapsed/refractory mantle cell lymphoma: A multicenter experience. Ann Oncol. 2012;23(10):2695-703.

72. Cook G et al. Outcome following reduced-intensity allogeneic stem cell transplantation (RIC AlloSCT) for relapsed and refractory mantle cell lymphoma (MCL): A study of the British Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2010;16(10):1419-27.

73. Robinson SP et al. Long-term outcome analysis of reduced-intensity allogeneic stem cell transplantation in patients with mantle cell lymphoma: A retrospective study from the EBMT Lymphoma Working Party. Bone Marrow Transplantation. 2018;53(5):617-24.

Events

16TH JANUARY 2019

Clinical Advances in Myeloma 2019

London, UK

The America Square Conference Centre in London, UK, plays host to this CPD-certified event as it returns for its third meeting. Speakers from prestigious institutions from across the UK... Read More

23RD–25TH JANUARY 2019

13th Dutch Hematology Congress (DHC) 2019

Arnhem, Netherlands

Onco-haematology is a core element of the DHC, an event designed to keep attendees up-to-date with the latest innovations and developments in the field... Read More

5TH FEBRUARY 2019

The Royal Marsden Nutrition and Cancer Study Day

London, UK

How important is nutrition to cancer care? The Royal Marsden Nutrition and Cancer Study Day aims to inform and educate on this very point... Read More

25TH–27TH FEBRUARY 2019

17th International Congress on Targeted Anticancer Therapies 2019 (TAT 2019)

Paris, France

Targeted therapies for the treatment of cancers are being achieved in an increasing number of cases. The TAT congress has been at the forefront of this innovation and discovery... Read More

7TH–9TH MARCH 2019

ESSO Advanced Course on the Management of HIPEC after CRS 2019

Hamburg, Germany

Offering opportunities to 'learn by doing', this fantastic education course gives attendees the chance to discover more about hyperthermic intraperitoneal chemotherapy (HIPEC) after cytoreductive surgery (CRS)... Read More

14TH–16TH MARCH 2019

7th Edition of the International Congress on Innovative Approaches in Head and Neck Oncology 2019 (ICHNO 2019)

Barcelona, Spain

Before Barcelona opens its doors to ESMO 2019, the 7th edition of the ICHNO meeting moves to the Catalan capital. Focussing purely on head and neck cancers... Read More

6TH–9TH APRIL 2019

American Radium Society 101st Annual Meeting 2019 (ARS 2019)

Dana Point, California, USA

Head to the west coast of the USA and Dana Point, California to make the most of the 101st ARS meeting. The historic event boasts a packed schedule... Read More

27TH–1ST OCTOBER 2019

European Society for Medical Oncology (ESMO) 2019

Barcelona, Spain

After the tremendous success of this year's meeting, promising to be bigger and better than ever before, the ESMO Congress returns in late September 2019... Read More