EMJ EUROPEAN MEDICAL JOURNAL

ONCOLOGY

ISSN 2054-619X — Vol 3.2 • November 2015 • emjreviews.com

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ECC 2015
Vienna, Austria

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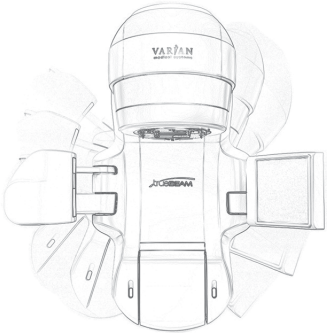

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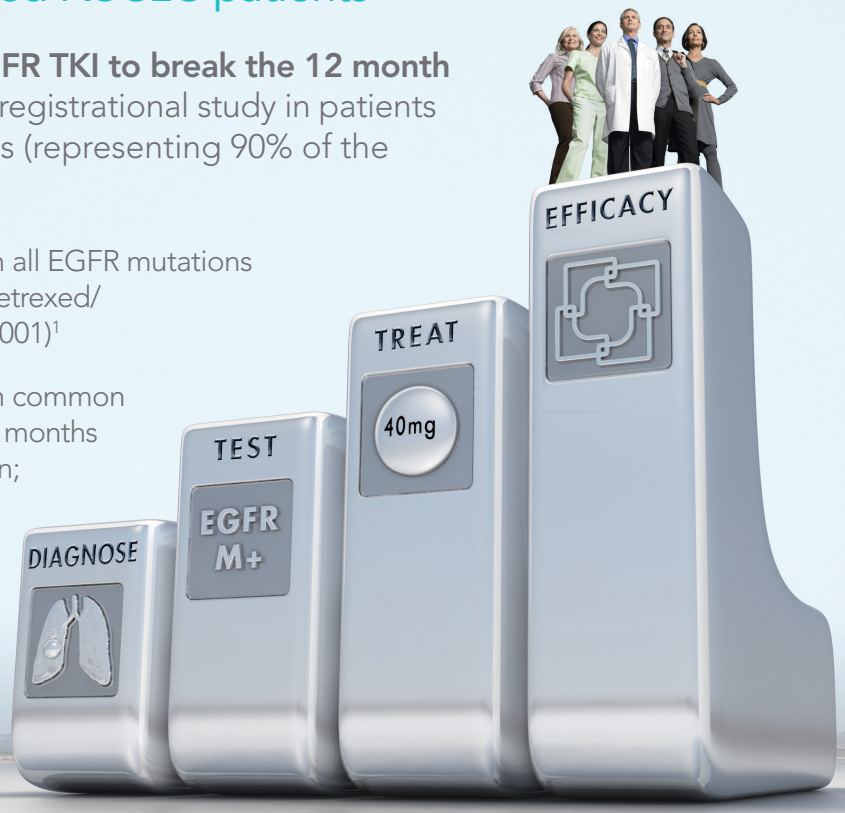

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EGFR, epidermal growth factor receptor; M+, mutation positive; HR, hazard ratio; NSCLC, non-small cell lung cancer

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Food should not be consumed for at least 3 hours before or at least 1 hour after taking Giotrif. **Contraindications:** Hypersensitivity to afatinib or to any of the excipients. **Warnings and Precautions:** Diarrhoea, including severe diarrhoea, has been reported most frequently within the first 6 weeks of treatment. Diarrhoea may result in dehydration, in rare cases with fatal outcome. Anti-diarrhoeal medicinal products should be readily available so that treatment can be initiated at first signs of diarrhoea. Severe diarrhoea may require interruption and dose reduction or discontinuation of therapy. Rash/acne has been reported which may occur or worsen in areas exposed to the sun. Severe skin reactions may require temporary interruption of therapy, dose reduction, additional therapeutic intervention and referral to a specialist. Treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions. Closer monitoring in female patients, patients with lower body weight and those with underlying renal impairment is recommended. There have been reports of ILD or ILD-like adverse reactions, including fatalities, in patients receiving GIOTRIF for treatment of NSCLC. Treatment should be interrupted if ILD is suspected. If ILD is diagnosed GIOTRIF should be permanently discontinued and appropriate treatment initiated. Pre-existing liver disease: periodic liver function testing is recommended. Worsening of liver function: dose interruption may become necessary. If severe hepatic impairment develops, treatment should be discontinued. Acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye: refer promptly to an ophthalmology specialist. If ulcerative keratitis is confirmed, treatment should be interrupted or discontinued. Use with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Left ventricular dysfunction has been associated with HER2 inhibition. Cardiac risk factors, conditions that can affect LVEF and those who develop cardiac signs/symptoms during treatment: cardiac monitoring including LVEF assessment should be considered. Ejection fraction below the institution's lower limit of normal: cardiac consultation and treatment interruption or discontinuation should be considered. Concomitant treatment with strong inducers of P-gp may decrease exposure to afatinib. Contains lactose. Patients with galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this product. **Interactions:** Administer strong P-gp inhibitors (e.g. ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) using staggered dosing, preferably 6 hours or 12 hours apart from GIOTRIF. Strong P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's wort *(Hypericum perforatum)*) may decrease exposure. Afatinib is a moderate inhibitor of P-gp. It is unlikely that treatment will result in changes of the plasma concentrations of other P-gp substrates. Afatinib may increase the bioavailability of orally administered BCRP substrates (e.g. rosuvastatin and sulfasalazine). **Fertility, pregnancy and lactation:** Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with GIOTRIF. There are no or limited amount of data from the use in pregnant women. Mothers should be advised against breast-feeding while receiving this product. An adverse effect on human fertility cannot be excluded. **Undesirable effects:** The most frequent adverse drug reactions were diarrhoea and skin related adverse events as well as stomatitis and paronychia. ILD-like adverse reactions were reported in 0.7% of afatinib treated patients. Bullous, blistering and exfoliative skin conditions have been reported including rare cases suggestive of Stevens-Johnson syndrome although in these cases there were potential alternative aetiologies. Very common (≥1/10): paronychia, decreased appetite, epistaxis, diarrhoea, stomatitis, rash, dermatitis acneiform, pruritus, dry skin. Common (≥1/100 to ≤1/10): cystitis, dehydration, hypokalaemia, dysgeusia, conjunctivitis, dry eye, rhinorrhoea, dyspepsia, cheilitis, alanine aminotransferase increased, aspartate aminotransferase increased, palmar-plantar erythrodysaesthesia syndrome, muscle spasms, renal impairment/renal failure, pyrexia, weight decreased. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** *20 mg* 28 tablets £2,023.28; *30 mg* 28 tablets £2,023.28; *40 mg* 28 tablets £2,023.28; *50 mg* 28 tablets £2,023.28. **Legal category:** POM **MA numbers:** *20 mg* EU/1/13/879/003 (28 x 1 film-coated tablets); *30 mg* EU/1/13/879/006 (28 x 1 film-coated tablets); *40 mg* EU/1/13/879/009 (28 x 1 film-coated tablets); *50 mg* EU/1/13/879/012 (28 x 1 film-coated tablets) **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, Binger Strasse 173, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in October 2013**

References 1. Sequist L, *et al. J Clin Oncol* 2013;31(27):3327–3334. **2.** Yang J C-H, *et al.* Presented at: 50th Ann Meeting of the American Society of Clinical Oncology (ASCO), Chicago, 30 May–3 June 2014. Oral presentation; Abstract 21366. **3.** Wu L, *et al. Lancet Oncol* 2014;15(2):213–222. **4.** Mok TS, *et al. N Engl J Med* 2009;361:947–957. **5.** Fukuoka M, *et al. J Clin Oncol* 2011;29:2866–2874. **6.** Rosell R, *et al. Lancet Oncol* 2012;13:239–246. **7.** Sebastian M, *et al. Eur Respir Rev* 2014;23:92–105.

Adverse events should be reported.
Reporting forms and information can be found at https://www.yellowcard.mhra.gov.uk/.
Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

UK/GIO-151009 February 2015

Welcome

Hello, and a very warm welcome to the *European Medical Journal Oncology,* your trusted source for the latest developments in the field of cancer research and treatment. Inside, you will find a wealth of breaking medical news and discoveries, most notably our extensive report on this year's annual meeting of the European Cancer Congress (ECC), which took place in the picturesque city of Vienna, Austria.

As a city that is frequently ranked as one of the best in the world for quality of life, and the world's number-one destination for international congresses and conventions, Vienna served as the perfect backdrop to this momentous occasion, and it truly was a time of groundbreaking medical discovery. Of course, the EMJ team was on-hand during every step of ECC to witness all of the most impactful scientific innovations, and our exhaustive congress review certainly reflects this.

Along with a hand-picked selection of some of the most fascinating breaking news stories, we have also included interviews with a number of experts in the field, as well as a carefully compiled assortment of abstract reviews from some of the brightest new scientific talent that was on display in Vienna. Of special note is a report on the discovery that social deprivation may have a positive impact on the incidence of a particular type of Hodgkin's lymphoma in children and young adults, as well as an abstract review concerning brain metastasis associated with non-small-cell lung cancer. These stories, along with a host of others, add up to make this edition of *EMJ Oncology* an utterly invaluable tool for practitioners and researchers, and we hope that the innovation we witnessed at ECC can be passed on to our readership.

We would like to thank all of our readers throughout the medical community for their continued and growing support this year. We are proud of our accomplishments in 2015, and are hopeful that 2016 will serve to build upon these successes. Our ultimate mandate is the exchange of scientific knowledge, for the betterment of medical practice and patient outcomes across Europe and the world at large. It is our hope that all of our publications will spark debate, challenge preconceptions, and incite progress in their respective fields. Of course, any feedback from our readers is valuable in this process and we welcome you to join the conversation.

On behalf of EMJ, I would like to wish you all the best for the remainder of the year; we look forward to seeing you in 2016!

Spencer Gore

Director, European Medical Journal

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Ovarian cancer: every three weeks as a 3-hour infusion at a dose of 1.1 mg/m^2, immediately after PLD 30 mg/m^2. All patients must receive corticosteroids 30 minutes prior to PLD (in combination therapy) or trabectedin (in monotherapy); Additional anti-emetics may be administered prn. The same dose should be given for all cycles provided that no grade 3-4 toxicities are seen and that the patient fulfils the re-treatment criteria. Dose reductions required if toxicities develop (see SmPC) and with hepatic impairment. Children & Adolescents; should not be used in children below 18 years with paediatric sarcomas because of efficacy concerns (see 5.1 for results of paediatric sarcoma study). **Contraindications:** Hypersensitivity to trabectedin or to any of the excipients, concurrent serious or uncontrolled infection, breast-feeding, combination with yellow fever vaccine. **Precautions and Warnings:** Must be administered under the supervision of a physician experienced in the use of chemotherapy. The following criteria are required to allow treatment: Absolute neutrophil count ≥1,500/mm^3, Platelet count ≥100,000/mm^3, Bilirubin ≤upper limit of normal (ULN), Alk phos ≤2.5 x ULN, Albumin ≥25 g/l, ALT and AST ≤2.5 x ULN, Creatinine clearance ≥30 ml/min (monotherapy), serum creatinine ≤ 1.5 mg/dl or creatinine clearance ≥60 ml/min (combination therapy), CPK ≤2.5 x ULN, Hb ≥9 g/dl. The same criteria must be met prior to re-treatment. Additional monitoring of haematological parameters, bilirubin, alkaline phosphatase, aminotransferases and CPK should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles. Creatinine clearance must be monitored prior to and during treatment. Special caution is advised for patients with hepatic impairment. Discontinue treatment until the patient fully recovers from rhabdomyolysis. **Interactions:** Substances that inhibit isoenzyme CYP3A4 may decrease metabolism and increase trabectedin concentrations. If such combinations are needed, close monitoring of toxicities is required. Potent inducers of CYP34A may decrease systemic exposure to trabectedin. Two in vivo drug-drug interaction phase 1 studies have confirmed trends toward increased and decreased trabectedin exposures when administered with ketoconazole and rifampicin, respectively. Avoid alcohol consumption. Caution should be taken with concomitant administration of inhibitors of P-gp. Combination of trabectedin with phenytoin or live attenuated vaccines not recommended. Caution with concomitant administration of medicinal products associated with rhabdomyolysis. **Pregnancy:** Should not be used during pregnancy unless clearly necessary. Men in fertile age and women of childbearing potential must use effective contraception during treatment and 3 months thereafter for women and 5 months for men. **Undesirable Effects:** Neutropenia, febrile neutropenia, leukopenia, anaemia, hypersensitivity, thrombocytopenia, fatigue, decreased albumin, headache, peripheral sensory neuropathy, dysgeusia, dizziness, paraesthesia, dyspnoea, cough, vomiting, nausea, constipation, diarrhoea, stomatitis, abdominal pain, dyspepsia, alopecia, myalgia, arthralgia, back pain, anorexia, dehydration, decreased appetite, weight decreased, hypokalaemia, infection, hypotension, flushing, fatigue, pyrexia, oedema, injection site reaction, increases in bilirubin, AST, ALT, Alk. Phos, GGT, CPK and creatinine, insomnia. Fatal adverse reactions have occurred, often due to a combination of events including pancytopenia, febrile neutropenia, some of them with sepsis, hepatic involvement, renal or multi-organ failure, rhabdomyolysis, hepatic failure and septic shock. Consult SmPC for further information about adverse events. **Legal Category:** POM. **Marketing Authorisation Nos.:** 0.25mg: EU/1/07/417/001 and 1mg: EU/1/07/417/002. **Basic NHS Price:** 0.25mg vial 1 = £363.00, 1mg vial 1 = £1366.00. **Marketing Authorisation Holder:** Pharma Mar, S.A. Avda. de los Reyes 1, Poligono Industrial La Mina, 28770 Colmenar Viejo (Madrid), Spain.Tel: +34 91 846 60 00. Additional information is available on request from the Marketing Authorisation Holder. **Date of Preparation:** September 2015. **Date of the Text:** 06/2015. ***Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard and www.hpra.ie; e-mail: medsafety@hpra.ie. Adverse events should also be reported to Pharma Mar, S.A. Pharmacovigilance Department email: phv@pharmamar.com; Tel: +34 91 823 47 49 (24hrs); Fax: +34 91 846 60 04.

1. Blay JY. Expert Rev Anticancer Ther. 2013;13(6 Supl 1):3-9.

2. The ESMO/European Sarcoma Network Working Group. Ann Oncol. 2014; 25 (Suppl 3):iii102-iii112.

**Local prescribing information should be considered for the exact approval in the country.

STS: Soft Tissue Sarcoma

Date of revision of the promotional material: October 2015

YON0215-788

Foreword

Dr Ahmad Awada

Head of the Medical Oncology Clinic, Jules Bordet Institute, Brussels, Belgium

Dear Colleagues,

I would like to present the latest edition of *EMJ Oncology* to our discerning readership. The edition includes the latest news and scientific developments from the 18th ECCO – 40th ESMO European Cancer Congress 2015 (ECC 2015). Held in the beautiful city of Vienna, Austria, from 25th–29th September under the congress theme of 'Reinforcing multidisciplinarity', this event once again attracted many prestigious international healthcare professionals from around the world.

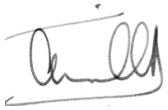
The scientific programme covered innovations, data, and novel approaches to treatment, including surgery and radiotherapy. A predominant focus was immunotherapy, from basic research to clinical practice. There has been a revolution in the management of haematological and solid tumours through the use of immunological approaches such as checkpoint inhibitors, alone or in combination. There was also much discussion regarding personalised medicine, with the debate focussing predominantly on clinical trial design for new molecular targeted therapies. Tumour heterogeneity at a biological level was also the focus of several presentations, and a number of new combination approaches were addressed to tackle this issue.

Another area which has taken a more prominent position within the scientific programme in recent years is that of cancer survivorship issues, which has seen physicians striving to address the complicated, often debilitating aftermath of cancer treatment. This year saw much discussion in this regard, and a number of new frontiers in care were uncovered.

> "There has been a revolution in the management of haematological and solid tumours through the use of immunological approaches such as checkpoint inhibitors, alone or in combination."

This review edition of *EMJ Oncology* will guide you through the meeting's most vital proceedings. Compiled within, you will find a full report of ECC 2015 and a review of some of the best abstracts and interviews from the brightest new minds in oncology. I would like to take this opportunity to thank all those who contributed to this edition; your work is lighting the way towards truly innovative medical science. On behalf of the editorial board, I would also like to thank you for reading and wish you all the best for the remainder of the year.

Yours sincerely,



Ahmad Awada

Head of the Medical Oncology Clinic, Jules Bordet Institute, Brussels, Belgium.

ECC ANNUAL CONGRESS 2015

MESSE WIEN,
VIENNA, AUSTRIA
25TH-29TH SEPTEMBER 2015

Welcome to the *European Medical Journal* review of the European Cancer Congress 2015

A very warm welcome to the *European Medical Journal* review of the European Cancer Congress 2015 (ECC 2015), recently held in Austria.

The country's capital, Vienna, on the beautiful blue Danube, was the backdrop to this year's annual congress. As well as being a historically artistic and intellectual location, the city was ranked as the world's number one destination for its culture of innovation in 2007 and 2008. The meeting attracted some of the world's most renowned researchers from the ever-evolving field of oncology.

The congress itself is a vital platform for integrating different areas of oncology in order to explore novel solutions, and ultimately help cancer patients. This is shown by the fact that the congress included nearly 18,000 participants and that over 2,023 abstracts were presented. All of this occurred for the benefit of the battle against a disease that is expected to be diagnosed in 21.7 million people by 2030. Despite this seemingly uphill struggle, Prof Martine Piccart, the Congress Chair and European CanCer Organisation (ECCO) President, summed up the significance of the congress during the opening ceremony: "All of us here are the voice of multidisciplinary cancer care in Europe and our teamwork is the most efficient weapon against cancer."

An inspiring element of the congress was the awards ceremony, which

honoured the progress that has already been made in the field. A few notable awards include the ECCO Lifetime Achievement Award 2015, presented to Prof Harry Bartelink (Netherlands) in recognition of his personal commitment to further progress against cancer. Since 2007, he has been researching predictive assays and image-guided intensity-modulated radiotherapy in lung, head and neck, and breast cancer. For contributions to the integration of translational research and clinical practice in the field of cancer, the ECCO Clinical Research Award 2015 was presented to Prof Martin van den Bent (Netherlands), who has been the principle investigator of a large number of international multicentre Phase II and III trials on both high and low-grade glial tumours. Another prestigious prize was the ESMO (European Society for Medical Oncology) Lifetime Achievement Award, which was awarded to Prof Nagahiro Saijo (Japan), a globally known leader in thoracic oncology who has dedicated his life to the diagnosis and innovation of treatment of thoracic malignancies. The ESMO Women for Oncology Award is a new accolade, launched at the 2015 congress to recognise an ESMO member who has significantly contributed to supporting the career development of women in oncology. It was presented to Dr Enriqueta Felip (Spain), an inspiring researcher who raised awareness of the dearth of women oncologists in leadership roles.

There was a plethora of revolutionary presentations over the 5 days of the congress, including an investigation into the influence of environmental factors on the risk of developing cancer, such as the unusual discovery that socioeconomic deprivation may have a positive impact on the incidence of the nodular sclerosis subtype of Hodgkin's lymphoma. An urgent call to action was also made to improve worldwide access to cancer surgery, train more cancer surgeons, and foster education regarding oncological care. Other studies reported on the success of new treatments; for example, two studies found that the targeted therapy, nivolumab, significantly increases survival in patients with advanced kidney cancer as well as non-squamous non-small-cell lung cancer.

"All of us here are the voice of multidisciplinary cancer care in Europe and our teamwork is the most efficient weapon against cancer."

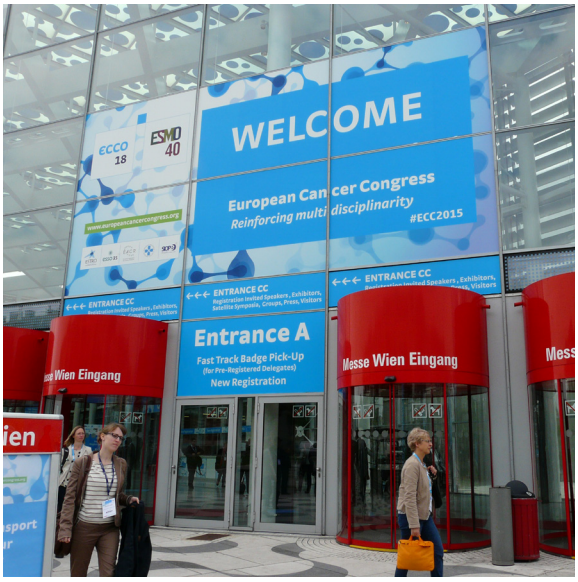
Given the huge exchange of data and ideas, it is easy to see that the congress is achieving its goal of combining the work of European oncology professionals with a further aim of improving the prevention, diagnosis, treatment, and care of cancer patients. The ECC congress will be held next year in Copenhagen, Denmark, and promises to deliver even more breakthroughs and further facilitate the ultimate goal of beating cancer.

HIGHLIGHTS

Safe Surgery Unavailable to Over 75% of Cancer Sufferers Worldwide

URGENT action is required to improve worldwide access to cancer surgery, train more cancer surgeons, and improve education about oncological care. In a presentation at ECC 2015, a major commission that addressed the state of global cancer surgery identified the astronomical effect that the current lack of safe cancer surgery could have on the world economy.

Whilst there will be almost 22 million new cancer patients by 2030, with over 17 million requiring surgery, there is little focus on improving access to safe surgery. In a press release dated 28th September, lead commissioner Prof Richard Sullivan, Institute of Cancer Policy, King's Health Partners Comprehensive Cancer Centre, King's College London, London, UK said: "With many competing health priorities and substantial financial constraints in many low and middle-income countries (LMICs), surgical services for cancer are given low priority within national cancer plans and are allocated few resources. As a result, access to safe, affordable cancer surgical services is dismal. Our new estimates suggest that fewer than 1 in 20 (5%) patients in low-income countries and only roughly 1 in 5 (22%) patients in middle-income countries can access even the most basic cancer surgery."



"...surgical services for cancer are given low priority within national cancer plans and are allocated few resources. As a result, access to safe, affordable cancer surgical services is dismal."

It is predicted that this will result in a global economic loss of $12 trillion by 2030, a figure equivalent to 1–1.5% of annual economic output in high-income countries, and 0.5–1% in LMICs. As well as this, more than $6 trillion could be lost between now and 2030 due to lack of effective action to train cancer surgeons and lack of improvements to cancer surgical systems.

19,127 oncology professionals

The authors emphasised that this dire situation can no longer be ignored. They call for a powerful political commitment from all countries to invest in actions such as surgical cancer training for general surgeons, an increase in gynaecological and surgical oncologists, and better regulation of public systems to improve access to cancer surgery and decrease its impact on the world economy.

Hormone Therapy May Stop Ovarian Failure and Preserve Fertility in Women with Breast Cancer

YOUNG women undergoing chemotherapy for breast cancer could be more likely to remain fertile if they also receive hormonal treatment, according to data from a study presented at ECC 2015.

Researchers suggested that addition of treatment with a so-called luteinising hormone-releasing hormone analogue, or LHRHa, during chemotherapy may protect a woman's ovaries; this may boost the probability of pregnancy following breast cancer treatment. Dr Matteo Lambertini, Medical Oncologist, IRCCS AOU San Martino-IST, Genoa, Italy said in an ECC press release on 28th September: "We found that temporary suppression of ovarian function with LHRHa significantly reduces the risk of premature ovarian failure (POF) caused by chemotherapy. It also seems to be associated with a higher pregnancy rate in young breast cancer patients."

The team conducted a meta-analysis including 12 randomised trials and a total of 1,231 breast cancer patients receiving chemotherapy, with or without LHRHa. Early calculations showed that rates of POF decreased by 64% in patients receiving LHRHa. However, the studies used different definitions of POF, with results varying widely. The analysis was then restricted to trials that used specific data on whether a woman's periods had restarted 1 year after chemotherapy. Rates were reduced by 45% with LHRHa in the eight relevant trials, while there was a strong association in results from all studies. These data highlight a striking overall reduction in POF through addition of LHRHa.

"We found that temporary suppression of ovarian function with LHRHa significantly reduces the risk of premature ovarian failure (POF) caused by chemotherapy. It also seems to be associated with a higher pregnancy rate in young breast cancer patients."

In the five studies that reported on pregnancies after breast cancer treatment, there was a total of 33 patients with pregnancies among those who received LHRHa alongside chemotherapy, and 19 among those who did not. This constituted an 83% increase in the chance of becoming pregnant. "In breast cancer patients, we believe there is now sufficient evidence to suggest that the administration of LHRHa could be considered a potential standard strategy to preserve ovarian function and might also play a role in increasing the likelihood of pregnancy after chemotherapy," added Dr Lambertini.

Variability in Treatment of Elderly European Breast Cancer Patients

EUROPEAN treatment of elderly breast cancer patients shows considerable variability with regard to each country's use of surgery, hormone therapy, and chemotherapy, according to new research presented at ECC 2015. Previous research on the variability of breast cancer treatment has tended to focus on younger patients, but these often cannot be compared with elderly patients who make up 40% of new diagnoses.

The European Registration of Cancer Care (EURECCA) study compared the treatment of 119,125 ageing breast cancer patients (≥70 years of age) diagnosed between 2000 and 2014 in six European countries (Belgium, Ireland, Netherlands, Poland, Portugal, and the UK). The study found that surgery was often omitted in older patients with Stage III tumours, with the rate of omission varying from 15% in Belgium to 37% in Ireland. The use of hormonal therapy for Stage I tumours varied even further: from 21% in the Netherlands to 82–88% observed in Ireland, Belgium, Portugal, and Poland. Additional variation was seen in the use of chemotherapy, with use being lowest in the Netherlands for all tumour stages (e.g. 9% for Stage III disease, compared with 26%, 30%, 58%, and 78% for Ireland, Belgium, Portugal, and Poland, respectively).

"Our research findings will contribute to improved treatment guidelines for elderly patients with breast cancer, which will lead to a more personalised treatment approach for this vulnerable patient group," said Dr Marloes Derks, Department of Surgery, Leiden University Medical Center, Leiden, Netherlands in a press release dated 27th September. Dr Derks further suggested: "In order to improve treatment approaches and outcomes in elderly patients with breast cancer, more observational studies based on data from large national population registries of older patients are needed. The quality of these national registries should be improved and a European collaboration to share this data should be encouraged. Furthermore, with regard to the increasing number of older patients with breast cancer, there is an urgent need to conduct age-specific clinical trials."

Treatment Delay or Termination Unnecessary in Pregnant Cancer Patients

REASSURING research has shown that a diagnosis of cancer in pregnant women should not mandate termination of pregnancy or a delay in treatment due to concerns over its effects on the developing child. The research, presented at ECC 2015, investigated children born following prenatal exposure to cancer treatment across a range of cancers and treatments.

The new study included 129 children who were age-matched to a control group born to cancer-free mothers, and examined the general health and mental development of all the children at 1.5 and 3 years. Of the children exposed to cancer therapy, 69% were exposed to chemotherapy, 3.1% to radiotherapy, 5.4% to both, 0.7% to trastuzumab, 0.7% to interferon β, 10.1% to surgery alone, and 10.9% of mothers received no treatment during pregnancy. The mental development of the children in the two groups was compared using the Bayley Scales of Infant Development.

The median average score for mental development in children exposed to chemotherapy was 100 versus 99.5 in the control group; was 102 in children exposed to radiotherapy versus 105 in the control group; was 111 in the surgery alone group versus 102 in the control group; and was 105 in the no treatment group versus 97.5 in the control group. After adjustment for a range of demographic factors, the researchers noted that mental development scores tended to increase by an average of 2.2 points with each week of gestation, which suggested that delayed development of mental processes was related to prematurity. This is relevant because in many cases the decision to induce preterm was taken in order to continue cancer treatment of the mother after delivery. No differences were found in the cardiac function of the 47 children in whom this variable was tested (29 exposed to chemotherapy versus 18 controls).

"Our results show that fear of cancer treatment is no reason to terminate a pregnancy, that maternal treatment should not be delayed, and that chemotherapy can be given," said Prof Frédéric Amant, gynaecological

oncologist, University Hospitals Leuven, Leuven, Belgium; Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, in an ECC press release dated 28th September 2015. Larger studies and a longer follow-up time are required to further document the long-term effects of each drug.

Nivolumab Improves Survival in Non-Squamous NSCLC Patients

PATIENTS with non-squamous non-small cell lung cancer (non-SQ NSCLC) display improved rates of survival when treated with nivolumab compared with docetaxel, according to data presented at ECC 2015.

"The results from the trial show that for patients with non-SQ NSCLC who have progressed on prior platinum-based chemotherapy, nivolumab is a good treatment option showing durable benefit with fewer side effects regardless of PD-L1 test results compared to treatment with docetaxel."

Non-SQ NSCLC patients have a dismal prognosis with limited treatment options once their disease has advanced and initial treatment with platinum-based chemotherapy has failed. Second-line treatment is typically with another chemotherapy drug, such as docetaxel. In the international CheckMate 057 clinical trial, 292 patients were randomised to receive intravenous nivolumab at a dose of 3 mg/kg every 2 weeks, and 290 were randomised to receive intravenous docetaxel at a dose of 75 mg/m^2 every 3 weeks.

The results demonstrated that significantly more of the patients who received nivolumab were alive at 12 months compared with those treated with docetaxel (51% versus 39%), and the difference remained at 18 months (39% versus 23%). While improvement in survival was observed in all participants, nivolumab was more effective in those patients whose tumours expressed the protein PD-L1 (programmed death ligand 1), which plays a role in the immune system's ability to recognise and attack tumours. An objective response rate of 31% was seen among patients with tumours expressing PD-L1 in at least 1% of cells, compared with a response rate of 9% observed in those with PD-L1 expressed in <1% of cells.

Fewer significant treatment-related adverse events (Grades 3–4) were observed in patients treated with nivolumab compared with those on docetaxel (10% versus 54%), which occurred regardless of PD-L1 expression. Furthermore, patient reported outcomes, as measured using the Lung Cancer Symptom Scale, showed that there was a superior quality of life and slower deterioration for patients treated with nivolumab versus docetaxel.

"The results from the trial show that for patients with non-SQ NSCLC who have progressed on prior platinum-based chemotherapy, nivolumab is a good treatment option showing durable benefit with fewer side effects regardless of PD-L1 test results compared to treatment with docetaxel," concluded Dr Leora Horn, Vanderbilt Ingram Cancer Center, Nashville, Tennessee, USA, in a press release dated 28th September 2015.

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Phase I Trial of New Third-line SCLC Treatment

THIRD-LINE treatment of small-cell lung cancer (SCLC) using rovalpituzumab tesirine (Rova-T) may represent a much needed new therapy option for patients with the condition; data from a Phase I trial of Rova-T were reported at ECC 2015.

SCLC makes up 14% of all lung cancers and does not have a good survival rate, often because the cancer has already metastasised by the time it is discovered. The current treatment is chemotherapy, with first-line therapy usually based on an etoposide/platinum combination and second-line being topotecan. Rova-T is an antibody–drug conjugate that recognises the cell surface receptor delta-like protein 3 (DLL3), which is expressed by ~70% of SCLCs.

The study recruited 79 patients with a median age of 62 years (range: 44–81) and who had progressed past first or second-line treatments. The participants received increasing doses of Rova-T until toxicity required them to stop further dose increases. Of the 48 tumour samples analysed, 33 were found to be DLL3+. A total of 29 DLL3+ patients received the maximum tolerated dose, with 10 (34%) having a partial response and 9 (31%) displaying stabilisation of disease.

Dr M. Catherine Pietanza, Assistant Attending Physician, Memorial Sloane Kettering Cancer Center, New York City, New York, USA, said in an ECC press release dated 28th September: "While other cancers have multiple treatment options, there is only one agent approved in SCLC, and none available in the third-line setting; the outlook for these patients is dismal." Dr Pietanza

added: "The high response rate is exciting in itself, and above that we have been able to identify a biomarker for SCLC in DLL3+, thus enabling us to 'target' treatment in SCLC. The activity of the drug that we have seen is remarkable, and importantly, the durable, long-term responses are notable in such an aggressive disease where progression is normally very rapid."

Primary Surgery Linked to Survival Benefit in Patients with Advanced Cancers of the Throat

PATIENTS with cancers of the mid and lower throat could have higher survival rates if their initial treatment includes surgery, according to study data presented at ECC 2015. Researchers revealed that in a nationwide study in Taiwan, 5 years following diagnosis, radical surgery was linked with significant overall survival benefits among patients whose cancers of the throat had begun to spread.

"We found that primary surgery was associated with better overall cancer survival in most subset analyses, which suggests that surgery may provide a survival benefit."

The study focussed on cancers of the oropharynx and hypopharynx, and involved 1,698 patients with oropharyngeal and 1,619 with hypopharyngeal cancer; all had Stage III or IVA disease. Data showed that radical surgery was performed on slightly over one-third of oropharyngeal and approximately half of hypopharyngeal cancer patients. The team then compared outcomes in those who did and did not undergo surgery, regardless of whether they received concurrent chemoradiotherapy (CCRT). Therefore, in both surgery and no-surgery groups, patients may or may not have received CCRT.

Rates of overall survival at 5 years in Stage III/IVA oropharyngeal cancer were higher for those who had surgery than for those who did not (Stage III: 59% versus 48%; Stage IVA: 51% versus 40%). They were also higher in the surgery group for Stage III/IVA hypopharyngeal cancer than the no-surgery group (Stage III: 54% versus 33%; Stage IV: 39% and 26%).

Dr Chih-Tao Cheng, Medical Researcher, Koo Foundation Sun Yat-Sen Cancer Center, Taipei City, Taiwan, said in an ECC press release dated 26th September: "Substantial improvements in the treatment of head and neck cancer have been made in the past two decades. However, overall survival rates for locoregionally advanced head and neck cancer remain unsatisfactory.

"We found that primary surgery was associated with better overall cancer survival in most subset analyses, which suggests that surgery may provide a survival benefit."

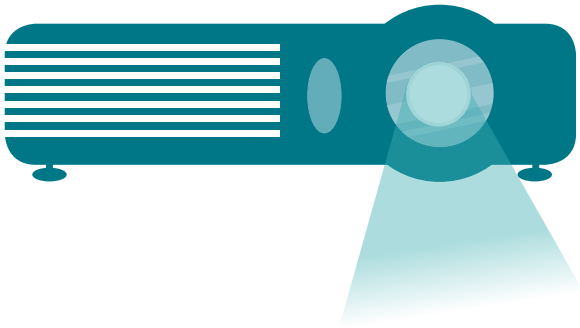
He also stressed the need for further research: "Recommending primary surgery or CCRT for advanced oropharyngeal and hypopharyngeal cancer patients remains controversial. These preliminary results were in line with our expectations, but further well-designed studies are required to confirm our findings."

Combined Therapy Improves Survival in Melanoma

APPROVAL of a combination of dabrafenib and trametinib by the European commission was granted following the results from the COMBI-v Phase III trial in melanoma, data from which were presented at ECC 2015.

The international COMBI-v study recruited a cohort of 704 melanoma patients who were not eligible for surgery or whose cancer had metastasised; the majority had either V600E or V600K mutations of the *BRAF* gene. The trial compared the combination therapy with the use of vemurafenib alone: patients were randomised to receive either 150 mg of dabrafenib twice per day plus 2 mg of trametinib once per day, or 960 mg of vemurafenib alone twice per day. Both vemurafenib and dabrafenib block the BRAF protein, while trametinib blocks another cell-signalling protein, MEK.

The combination therapy displayed a similar safety profile to vemurafenib, but greater efficacy. Survival was significantly longer in the combination therapy group, with a median overall survival of 25.6 months compared with 18 months in the vemurafenib group. Furthermore, the time without disease progression was significantly longer in the combination therapy group compared with monotherapy: 12.6 months compared with 7.3 months, the former period being the longest achieved in any randomised study of *BRAF* V600 patients. No unexpected side effects were observed in either group and rates of severe side effects were similar.



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"The increased survival among these patients is remarkable, and this median overall survival of more than 2 years is the longest in this category of patients in a Phase III randomised trial."

Prof Caroline Robert, Head of Dermatology, Institut Gustave Roussy, Paris, France, said in a press release dated 28th September: "This combination therapy is already available in the US and now also in Europe as a result of the European Commission's decision to approve its use. This long-term benefit in terms of overall survival confirms the major potential of this combination in patients with metastatic melanoma. A further question to investigate is the combination treatment versus new immunotherapies or combined with them."

"The increased survival among these patients is remarkable, and this median overall survival of more than 2 years is the longest in this category of patients in a Phase III randomised trial," commented Prof Robert. Follow-up of the surviving patients is ongoing.

Combination Therapy Improves Progression-Free Survival in Melanoma

TREATMENT with a combination of nivolumab and ipilimumab improves progression-free survival (PFS) in patients with advanced melanoma compared with treatment with either drug singly, according to new research presented at ECC 2015 in Vienna, Austria. Importantly, the data from the CheckMate 067 Phase III clinical trial demonstrate that the efficacy of the combination treatment remained high regardless of patient age, stage of disease, or presence of a cancer-driving mutation in the *BRAF* gene.

The study included 945 patients randomised to receive combination therapy or one of the two drugs alone. Average PFS was 11.5 months in patients receiving combination therapy, and 6.9 months and 2.9 months in patients receiving nivolumab or ipilimumab alone, respectively.

"These results provide evidence that the efficacy of the combination therapy is similar whether or not the tumours harbour *BRAF* mutations. This has important practical implications for clinicians treating patients with melanoma."

The researchers also investigated PFS in patients with and without the V600 *BRAF* mutation in all three treatment groups: average PFS was 11.7 and 11.2 months, respectively, in those receiving the combination treatment; was 5.6 months and 7.9 months, respectively, in those receiving nivolumab alone; and was 4 months and 2.8 months, respectively, in those receiving ipilimumab alone. This pattern of findings was also observed when patient groups were analysed according to the extent of the spread of their disease or according to their age (i.e. <65 years, 65–75 years, and >75 years).

"These results provide evidence that the efficacy of the combination therapy is similar whether or not the tumours harbour *BRAF* mutations. This has important practical implications for clinicians treating patients with melanoma," stated Dr James Larkin, Consultant Medical Oncologist, The Royal Marsden, London, UK. Dr Larkin also added: "The subgroups included in these analyses are those of particular interest to melanoma clinicians, such as patients aged 75 and over. We believe that the data will give confidence to patients and their healthcare providers that the combination of nivolumab and ipilimumab will be effective regardless of advanced age, the presence of a *BRAF* mutation, or poor prognostic factors."

Nivolumab Bolsters Overall Survival in Patients with Advanced Kidney Cancer

TARGETED therapy nivolumab significantly increases survival in patients with advanced kidney cancer whose disease has progressed after their first treatment, according to the results of a study presented at ECC 2015.

The CheckMate 025 Phase III clinical trial, which compared nivolumab with everolimus (the standard treatment), in patients with clear cell renal cell carcinoma is the first to demonstrate an improvement in overall survival in these patients for any immune checkpoint inhibitor drug. Nivolumab blocks the interaction between the programmed cell death protein 1 and another molecule called programmed cell death protein ligand 1 (PD-L1). However, the survival benefit was observed in patients regardless of the extent of tumoural PD-L1 expression.

"Although we cannot speculate at this time on when nivolumab might enter the clinic, we hope that this study will quickly lead to approval of nivolumab as a standard of care therapy for these patients."

The international CheckMate 025 Phase III clinical trial recruited 821 patients with advanced clear cell kidney cancer, who had received prior treatment, between October 2012 and March 2014. They were randomised to receive 3 mg/kg of nivolumab intravenously every 2 weeks or a 10 mg tablet of everolimus taken orally once per day.

According to Prof Padmanee Sharma, Departments of Genitourinary Medical Oncology and Immunology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, patients taking nivolumab had a median overall survival of 25 months as compared with 19.6 months for those taking everolimus. In addition, a greater proportion of patients had tumours that shrank in response to

nivolumab than to everolimus; the objective response rate was 25% for nivolumab versus 5.4% for everolimus.

"It is exciting to see the outcome of this study, as the results are significant and clinically meaningful to patients and healthcare professionals alike. They are likely to change the treatment of patients with advanced kidney cancer, whose disease has progressed on prior treatment," said Prof Sharma in an ECC press release dated 26th September. "Although we cannot speculate at this time on when nivolumab might enter the clinic, we hope that this study will quickly lead to approval of nivolumab as a standard of care therapy for these patients."

Cabozantinib Boosts Survival in Patients with Advanced Kidney Cancer

LIFE expectancy of patients with advanced kidney cancer is almost doubled through treatment with cabozantinib, a drug that inhibits the activity of tyrosine kinases, according to data presented at ECC 2015 by Prof Toni Choueiri, Associate Professor of Medicine, Harvard Medical School, Boston, Massachusetts, USA.

"The results of the METEOR trial indicate that cabozantinib is able to shrink tumours and slow down tumour growth much better than current standard treatment in patients who previously received VEGFR-targeted drugs."

Cabozantinib, which is predicted to change the way in which kidney cancer patients are treated, was compared with everolimus, the current standard treatment for the disease, in the Phase III clinical METEOR trial, from which the results of the first 375 patients from a total of 658 patients were revealed. The estimated median progression-free survival time for patients with advanced clear cell kidney cancer, randomised to receive cabozantinib, was 7.4 months, while this was 3.8 months for those taking everolimus. The objective response rate (the proportion of patients whose tumours shrank, assessed up to 17 months) was 21% for cabozantinib and 5% for everolimus. Overall survival of the 658 patients was also found to be one-third better for those taking cabozantinib.

Prof Choueiri discussed how cabozantinib targets cancer cells differently from standard therapy, which targets the vascular endothelial growth factor receptor (VEGFR), in an ECC press release dated 26th September: "Although treatment with VEGFR-targeted drugs has been very effective in the first line of therapy

for patients with advanced kidney cancer, in many cases tumour cells find ways to escape control by these drugs. Cabozantinib is a new drug that targets possible escape mechanisms of tumour cells, including the tyrosine kinases MET, VEGFR, and AXL. The results of the METEOR trial indicate that cabozantinib is able to shrink tumours and slow down tumour growth much better than current standard treatment in patients who previously received VEGFR-targeted drugs."

The researchers hope that cabozantinib will become available for patients in 2016. In the USA, the FDA has labelled cabozantinib as a breakthrough therapy, which may allow expedited development of the drug.

Hopes Raised in Battle Against Rare, Difficult-To-Treat Cancer

TUMOUR growth among both gastrointestinal and lung neuroendocrine tumours (NETs) may be delayed through the use of the mTOR inhibitor everolimus.

Reporting on the results of the international RADIANT-4 trial, a placebo-controlled, double-blind, Phase III study conducted in centres in 13 European countries, Korea, Japan, Canada, and the USA, Prof James Yao, Chair, Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, told ECC 2015 that the treatment had a significant effect in non-functional NETs. The trial included 302 patients with a median age of 63 years. Following randomisation, 205 patients received everolimus and 97 received placebo. The most common tumour sites were lung (30%) and ileum (24%).

Assessment of progression-free survival revealed a significant difference between the two groups. Prof Yao commented on the findings in an ECC press release dated 27th September: "We found a statistically significant 52% reduction in the risk of progression or death in favour of everolimus, and also a clinically meaningful 2.8-fold (7.1 months) improvement in median progression-free survival compared with those who had taken placebo. In addition, everolimus was well tolerated by the patients and its safety profile was good. We also saw a trend towards an improved overall survival, but the overall survival analysis is an interim one and it is too early to be able to be more definite about this at this time.

"Although we knew from previous studies that everolimus could delay the growth of pancreatic NETs, this is the first time we have been able to conclusively show that it is effective in other NET sites. We hope that our results will provide a new treatment

option for lung and gastrointestinal NETs, and we look forward to reporting further results from the trial, including those on final overall survival and quality of life, in the future."

Household Overcrowding Reduces Risk of Hodgkin's Lymphoma Subtype

SOCIAL deprivation may have a positive impact on the incidence of a particular subtype of Hodgkin's lymphoma (HL) in children and young adults. A study presented at ECC 2015 showed that development of the immune system in overcrowded households may provide protection against the nodular sclerosis (NS) subtype of HL.

"We knew already that recurrent infections may protect against childhood leukaemia, and now it looks as [though] we can add HL, and particularly its NS subtype, to the list."

In order to better understand the causes of HL, the researchers analysed each HL patient aged 0–24 years recorded in the Northern Region Young Persons' Malignant Disease Registry, a total of 621 cases. Age and sex were taken into account, alongside other factors including socio-economic deprivation.

The most significant finding was a decreased incidence of NS HL among those living in areas with more overcrowded households, with the number of cases of NS HL being halved by a 5% increase in the level of household overcrowding. This observation led the researchers to speculate that the recurrent infections to which children living in overcrowded conditions are more likely to be exposed may help to develop their immune systems and protect them against NS HL. However, the reverse trend of increased incidence with household overcrowding was seen in patients classified as having 'not otherwise specified' HL, and no measure of social deprivation was associated with the incidence of the 'mixed cellularity' and 'lymphocyte-rich' subtypes of HL.

Dr Richard McNally, Reader in Epidemiology, Institute of Health and Society, Newcastle University, Newcastle, UK, stated in an ECC press release dated 28th September that: "We knew already that recurrent infections may protect against childhood leukaemia, and now it looks as [though] we can add HL, and particularly its NS subtype, to the list. In order to further investigate the factors involved, prospective studies should investigate the hormonal changes and recurrent infections and their direct link to the risk of lymphoma, but such studies are difficult to do in rare diseases."

Dr McNally concluded that genetic studies, and case–control studies examining biological markers related to exposure to various infectious agents and hormonal status, could be carried out in order to add further knowledge to the causes of and protection against HL.

Wide Variations in Survival from Blood Cancers Between European Countries Revealed

SURVIVAL rates of cancer patients vary significantly across European countries, particularly in the case of blood cancers, according to the results of a EUROCARE comparative study presented at ECC 2015.

"Results from EUROCARE can help to identify regions of low survival where action is needed to improve patients' outcomes."

Dr Milena Sant, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, reported that results of the EUROCARE 5 study, which used information from patients diagnosed after 2000 in each European country, show that survival is generally low in Eastern Europe, but high in Northern and Central Europe. More specifically, cancers with a good prognosis had relatively large geographical variations. The most dramatic geographical variations were found in cancers of the blood, where there have been recent advances in treatment. Myeloid leukaemia, for example, showed the largest differences in survival rate. The European average was 53%, with variations of 33.4% in Eastern Europe and 51–58% in the rest of Europe (but this varied widely according to age). In comparison, cancers with a poor prognosis demonstrated smaller variations; the European average for first year relative survival for cancer of the oesophagus, for example, was 12%, with variations of 8% in Eastern Europe and 15% in central Europe.

In general, survival correlated positively with gross domestic project and total national expenditure on health (TNEH). Exceptions to this included countries such as Denmark and the UK, where survival was lower than their TNEH predicts. Other factors thought to create variations in survival are differences in the biology and behaviour of some cancers, screening and diagnosis, and the availability of new and better treatments, in addition to socioeconomic status, lifestyle, and general health differences between populations.

Dr Sant said in a press release dated 26th September: "Results from EUROCARE can help to identify regions of low survival where action is needed to improve patients' outcomes. Population-based survival information is essential for physicians, policy-makers, administrators, researchers, and patient organisations who deal with the needs of cancer patients, as well as with the issue of the growing expenditure on healthcare."

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Javier Cortés

Medical Oncologist and Head of the Breast Cancer Unit, Ramon y Cajal University Hospital, Madrid; Head of the Breast Cancer Clinical Research Program at Vall d'Hebron Institute of Oncology, Barcelona, Spain.

Dr Javier Cortés is extremely passionate about the field of oncology, and this was particularly striking during a recent interview the breast cancer specialist gave EMJ. It is clear that Dr Cortés has no shortage of ideas on how to drive forward the field of oncology – an area of medicine which has already seen many advancements in recent times. This theme formed the main focus of our discussion.

One thing is for certain: Dr Cortés is highly motivated by a desire to help those who are most in need. "When I was studying medicine I really wanted to do something with people who were really suffering," he explains when asked about his decision to first enter the field. After initially toying with the idea of going into AIDS research during his medical studies, a disease that was very prominent at the time, he decided to enter the world of oncology and join the fight against cancer. This decision ultimately led to a fascinating career, in which Dr Cortés has held a number of distinguished posts and experienced a great amount. Dr Cortés' success has led him to both the world-renowned Vall d'Hebron Institute of Oncology, Barcelona, and to his vital role leading the breast cancer and gynaecological programmes at the Ramon y Cajal University Hospital, Madrid.

His work in implementing change at Ramon y Cajal is something that Dr Cortés describes as being the most challenging aspect of his work. "Vall d'Hebron is considered one of the top hospitals for oncology in Europe, so it is clearly a challenge when you are coming from one of the best ones to a hospital which has great, great potential, and you always try to compare the good things in one hospital with the good things in the other," he says, "so the challenge is to really improve the number of clinical trials and the number of patients we can have here."

The improvement of clinical trials in general is something that came up time and again during the interview, underlining the importance they hold for Dr Cortés. "We have to start designing clinical trials in a more intelligent way," he explains, before describing some of the improvements he would like to see in terms of patient selection and the ways in which these studies are analysed. Whilst he acknowledges that improvements have been made in these respects, he argues that there is still some way to go to improve their design and implementation. "I think that all of these things have changed, and we will see a lot of changes in the upcoming years," he adds.

One particular change Dr Cortés would like to see is the way in which oncology units are managed and administered in Spain. He prefers the model that is used in the USA, and implemented these ideas during his previous role at Vall d'Hebron. This set-up allows responsibility and influence to be shared around a section, rather than centralised in the hands of the head of the unit. "I am proud because in the hospital I was in before, Vall d'Hebron, I had a really creative group of people. All of them are, and have been principle investigators of the same clinical trials, so all of them are already published. So people do not work for me. We all have to work together. This is something very well understood in the US," he says.

As is the case in all branches of medicine, money is a barrier to improving results and this is also true with regard to clinical trials. As such, Dr Cortés would like to see a greater level of funding for clinical trials from governments, and in particular from the European Union: "I think that the European Union is starting to give more and more money to healthcare, but a lot of that money is for basic or traditional research, which is great, but it will be important to invest some money into clinical trials, as the money we have for clinical trials is by far much lower than the money we have for basic or traditional research."

Dr Cortés also has a lot of ideas about how to improve clinical education in oncology in order to ensure that a stream of talented physicians continue to enter the field now and in the future. One factor that he believes could possibly dissuade junior medics from entering the field of oncology is the perception that a career in this area of medicine will mean experiencing a great deal of morbidity. This belief is not a true reflection of the reality in the modern age, however, according to Dr Cortés. "We need to translate to our students that, listen, this is not a specialty where you are only going to see patients dying and dying and dying. You have to understand that there are great treatment options with different therapies, chemotherapies, and targeted agents. It is such a great, great field and I think that people will really love it," he says with infectious zeal.

Dr Cortés also described further ways in which he believes more junior medics could be attracted to the field: "The most important thing is that oncology should be an obligatory subject here [in Spain] in the universities, and it is not, and I think that another important point, and this is something that we are working on, is for medical students to be integrated into the oncology department, in oncology units, in oncology meetings."

And what advice does he have for physicians about to begin a career in oncology? "The first thing I would recommend would be to criticise everything, to ask ourselves why the results are [as they are], how is the methodology, how are the statistics? When you are listening to a talk, we do not just have to listen: we have to criticise, to understand, to give different opinions. Sometimes we are right, sometimes we are not right; the beauty of our work is that we can change the future." He is also a strong proponent of oncologists being flexible. Dr Cortés believes that practitioners should try to work in a variety of different hospitals and institutions – something that he is very familiar with himself. "I think that [experiencing] two different ways of working is also going to help you to understand all of the opinions, all of the differences in work," he explains.

We thank Dr Cortés for his time in undertaking this interview with EMJ – we found his insight highly interesting and enjoyable.

Ross Abrams

Hendrickson Professor and Chair, Department of Radiation Oncology, Rush University Medical Center, Chicago, Illinois, USA.

Q: Was there anything in particular that influenced your decision to enter the field of oncology?

A: I began my medical career in the early 1970s, graduating from the University Of Pennsylvania School Of Medicine in 1973. During my first year as a medical student I was profoundly influenced by my encounters with Dr Arnold S. Relman who was, at the time, the Chairman of Internal Medicine at Penn. Dr Relman took it upon himself to teach history-taking and physical examination techniques to first-year students and I was among the four charges assigned to him. Ultimately, it was because of these encounters that I chose to undertake postgraduate training in internal medicine.

"Pancreatic cancer is like a huge iceberg..."

My decision to enter the subspecialty of medical oncology was subsequently driven by my early postgraduate training experiences as a house officer. At this formative time in my career, my mother was diagnosed with a regionally advanced breast cancer and was a participant in an early adjuvant trial. As a consequence, I looked more closely at oncology. I found that the opportunities to assist oncology patients with metastatic disease were enormous and I was very excited by recent developments in chemotherapy that, for the time, represented profound advances in lymphoma, breast cancer, and testicular cancer. I elected to continue training in medical oncology at the National Cancer Institute (NCI). The research opportunities available there convinced me that I had a passion for academia, just as my encounters

with Dr Eli Glatstein opened my eyes to the power and elegance of radiation oncology.

After much soul-searching, I decided to become a radiation oncologist and I was greatly aided in this endeavour by Drs James D. Cox and J. Frank Wilson. While there was much serendipity in my career choices, two constants are worth noting: the importance of family (both their own medical experiences and their support, especially from my wife) and the importance of my mentors (both those whom I chose, and those who chose me).

Q: How important has the work of the Radiation Therapy Oncology Group (RTOG), to which you have contributed, been in increasing knowledge in this field of medicine?

A: In my opinion, it is impossible to overestimate the extraordinary importance of the RTOG in advancing the field. This NCI-funded cooperative group has taught radiation oncologists of all stripes so much about statistics and clinical trial design. Not only that, but time and time again they have advanced disease management in every malignancy that we have been allowed to study by our sponsors and in which radiation has an important role to play.

In addition, this group, which is now the 'R' in the NRG Oncology Group, has taught radiation oncologists, surgical oncologists, and medical oncologists the power and beauty of what they can accomplish by working together with mutual respect. They have provided a research home for all physicians from these disciplines in which to accomplish much for their patients and their careers. The RTOG has stamped all of its work with the highest research quality and has provided important research tools, both for studying quality and improving quality in real time, thus improving care for individual patients and furthering ongoing technical improvement in radiotherapy treatment.

I am incredibly proud of the work I have done with this group, grateful for the opportunities I had with them, and honoured to say that its members are among my colleagues.

"My career in oncology spans 40 years..."

Q: In a recent article that you co-authored, you concluded that GSK3β expression is a strong prognosticator in pancreatic ductal adenocarcinoma, independent of other known factors such as tumour stage, nodal status, surgical margins, and CA 19-9. What impact are these findings likely to have in the near future?

A: This paper, authored by Prof Edgar Ben Joseph, shows the real power of working within the RTOG. This analysis was performed on a trial of adjuvant therapy for pancreatic cancer (RTOG 9704). Because tissue samples from these patients were collected as part of this research effort, there have been numerous opportunities for hypotheses, generating post-hoc translational analyses using these tissue samples, and associating observations with patient-specific outcomes. RTOG 9704 has provided many such opportunities and so will the current adjuvant trial, RTOG 0848, when it is completed. These studies have included correlations with HENT-1, which influences gemcitabine pharmacology, as well as correlations with CA 19-9 levels and radiation quality.

Q: To what extent has our knowledge of the field of oncology increased since you began your career?

A: My career in oncology spans 40 years and everything has changed: imaging (there were no computed tomography scans when I graduated from medical school!), pathology, molecular biology, computers, etc. These have been powerful changes for good, as they have increased understanding and emphasis on systems and quality.

Q: In your view, does the general public require better information regarding how to avoid risk factors for common types of cancer?

A: There are three realities regarding the human condition that need to be accepted with compassion and sensitivity: 1) we respond to immediate feedback much better than to delayed feedback; 2) human beings are absolutely capable of knowing something and then behaving completely inconsistently with that knowledge; and 3) avoidance of something scary or terrifying can be a lot easier than facing it if the 'something' does not bother you too much. I think that patients are often too embarrassed to say that they have lived

with something for a long time, and so they say they 'don't know'. By and large, people know about the risks of smoking, that exercise is good for you, that being obese is not as healthy as not being obese, and yet...

We should keep up our efforts in risk factor education; it is important and it does help. I think that where people need more knowledge is in understanding how different the various cancers are from each other in terms of management and prognosis, and how many malignancies there are.

Q: How far has our knowledge of pancreatic cancer increased over the course of your career? How has this translated into effective treatments?

A: Pancreatic cancer is like a huge iceberg bearing down on us and we are chipping off ice cubes! However, we are making incremental progress in understanding its biology and in developing drugs and insights.

Q: How would you describe the state of healthcare provision in the USA? How does this compare with the way healthcare is administered in Europe?

A: I am not an expert in these things. Nonetheless, my impression is that people get a healthcare system that reflects their cultural, political, and sociological values. Our system needs improvement: some things are too expensive and too many people are without coverage. We have overvalued procedures and undervalued primary care and prevention. We are now genuinely engaging these issues but it is painful. I cannot speak for the European models because I have not lived with them, but from a distance it seems to me that Europeans have a greater tolerance for queues and restricted choice than Americans have been willing to accept in the past.

Q: What are your professional goals over the next few years? Are there any new areas of research that you would like to move into?

A: I would like to finish RTOG 0848 because I believe it will resolve the issue of whether adjuvant chemoradiation therapy has a role to play after resection and chemotherapy for pancreatic cancer. I would also like to finish up some efforts in my department that, as Chairman, I feel I should not leave over to my successor.

Vincent Grégoire

Professor in Radiation Oncology, Department of Radiation Oncology, Centre for Molecular Imaging, Radiotherapy and Oncology, Université Catholique de Louvain, Saint-Luc University Hospital, Brussels, Belgium.

Q: Tell us a little about your medical career to date. How did you start out and what led you to your current position in radiation oncology at Saint-Luc University Hospital?

A: I guess it probably started when I was a medical student. I became interested in radiation biology while I was working in the laboratory as a research student, and then when I received my MD degree I decided to train as a radiation oncologist. Without doubt it was that initial period of research that inspired me to enter into a radiation oncology fellowship programme.

The second 'probably' is that, during this fellowship programme, I worked at the Netherlands Cancer Institute in Amsterdam for a year and a half, and after that I spent 2 years at the MD Anderson Cancer Center in Houston, Texas, USA. I guess that those were the second and third-most important movements in my professional life, not only because I learnt a few technical things in the field of research, but because I met people from outside Belgium and I accrued a 'network' of people with whom I am still interacting on an almost daily basis.

After the fellowship in Houston, I went back to my home city of Brussels where I obtained a position as a full staff radiation oncologist, and was asked to specifically take care of the head and neck cancer patients. This was another big step: developing the head and neck cancer programme both from

the research point of view and from the clinical point of view.

Q: You are known for publishing consensus guidelines for the selection and delineation of target volumes. Can you go into a little detail to explain your process in creating this work and what impact it has had on the field?

A: When I started my clinical duties as a staff member back in 1995/96, almost everyone in the field was still doing what we called 'two-dimensional radiation oncology' – nothing was volumetric. I found this frustrating and so on a regular basis I started to use computed tomography (CT) to create a 3D reconstruction of the target volumes I wanted to irradiate. Because we were not trained to work in 3D we had to totally change the way we were thinking, and so I went to the operating theatre and spoke with surgeons to try and learn what they do on a routine basis when they perform a surgical procedure for head and neck cancer. The objective was to try and transpose what they do, which is by definition a 3D process, into our own process now that we had routine access to 3D images.

This was the incentive for me to create the anatomical atlas in the late 1990s. The first iteration of the atlas was created at my institution following discussions with the radiologists, anatomists, and the head and neck surgeons. We then trialled the work with colleagues from outside of Belgium and then, after some years of use, I realised that it needed to be slightly updated and so we did an update 2 or 3 years ago. I believe, speaking modestly, that these are still the guidelines that are most widely used in the field of head and neck cancer, and have unified the practice between various centres and radiation oncologists around the world.

Q: Please give a brief outline of your current line(s) of research. What are your aims and what do you hope to achieve in the next year?

A: As well as my work on the atlas, I am also interested in improving the definition of tumours. Tumours are something you can palpate and can visualise when you do a head and neck examination; you can view them using CT but they are much more heterogeneous than they appear. Therefore, one of my research programmes uses molecular imaging to try and achieve a better view, with a more in-depth approach to understanding the heterogeneity of tumour volumes. For example, we can use different positron emission tomography tracers to determine if a tumour is hypoxic, highly glycolytic, or highly proliferative, and we can also use magnetic resonance imaging. The overall goal is better characterisation through the use of imaging tools, but characterisation from a biological point of view is certainly one field of research that we recently translated into some clinical programmes as well.

Another, more recent, research programme is concerned with trying to understand why a specific type of squamous cell carcinoma of the head and neck that is induced by human papilloma virus infection is much more radiation-sensitive than the typical squamous cell carcinoma induced by alcohol and tobacco abuse.

Q: How has the field of oncology evolved since your career began, and what impact has this had on your role within it?

A: I would say that there are three parallel aspects. Obviously, there has been a huge improvement in the technology we use in radiation oncology over the last 15–20 years. We are now using 3D imaging on a routine basis and we are also using multi-imaging modalities, as well as intensity-modulated radiation therapy that allows for far greater protection of the normal tissues around the target volume. So technological improvements have certainly been impactful.

Another major improvement has been in the routine practise of multidisciplinarity. In other words, today in 2015 there is not a single oncologist (radiation oncologist, medical oncologist, or surgical oncologist) who will solely decide on treatment; the approach is multidisciplinary. We meet on a weekly basis, if not more often, and we all decide together by reviewing all of the information required to determine the best approach for each patient. I understand that this approach is not always followed in all cancer practices, which is unfortunate because this clearly is a detrimental factor for patients. This is the second aspect that

has changed the way we are treating patients today, at least in my own practice.

The third aspect I should mention is that, during the last 20 years, we have learnt a lot about the disease itself and about what makes a cell cancerous. This has progressively translated, maybe slower than we would have expected, into improvements in therapeutic management, with new drugs, new radiation dosages, and a new level of interaction between the different disciplines.

Q: What is the most challenging aspect of your work?

A: As a radiation oncologist, the challenge is to adequately balance the technical, clinical, and biological aspects of what a cancer patient is. We could have a tendency to only focus on the technical aspects, which are very important, but that is only part of the story. The clinical aspect of performing a proper clinical examination and interacting properly with colleagues is, of course, extremely important too. We do not treat a bunch of cells, we treat a complex organism and having some comprehension or understanding of the biology behind it is obviously another important aspect. Combining these three aspects is probably the most challenging part of my work, and is also probably why I decided to embark on this specialisation and why I am still pleased to do it today.

Q: What are the greatest hurdles facing Europe in the fight against cancer, and what must be done to overcome them, not just by medical practitioners, but by governments, influencers, and the general populace?

A: Fragmentation is probably the greatest hurdle. Unfortunately, we still have people working in their own corner and pretending that they can do all of what should be done for their patients by themselves. This is absolutely wrong and not acceptable in 2015: we should work together and we should specialise or subspecialise.

In my opinion, we need to get people to organise themselves into cancer networks, cancer organisations, and cancer hospitals, although this is extremely difficult because medicine and oncology is a business. When someone says 'business' it means money, and people do not want to share their money and would rather keep it for themselves. In Belgium, for example, healthcare is a fee-for-service system. When I work I am paid and when I do not work then I am not paid, and so what is my incentive to refer patients to a bigger organisation that could take better care of them than I could myself?

Q: You have spent time working in the USA at the MD Cancer Center in Houston, Texas. Can you provide an overview of your experiences there? Were there any great cultural or attitudinal differences that influenced your practice?

A: I worked there for 2 years and it was a wonderful time for me, a hugely wonderful time. I was able to demystify what they do, or what they don't do, and so I no longer have a complex about only being a 'small Belgian' or a 'small European' when compared with Americans.

Another thing I learnt from my time in the USA is that if you define your goal and your objectives, and put together all the means necessary to reach your objective, then you will arrive there much faster than if you try to move forward in a disorganised way. I have to admit that when the Americans decide to run a programme, and it can be an industrial programme or a research programme, then they are extremely efficient. Not that they are more intellectually efficient, but rather they have a very pragmatic and efficient way of moving in the right direction. These are the two things that I learnt and that I am trying to implement here in Belgium, although it is not always easy to do so.

Q: What is the standard of oncological medicine in Belgium, and how does this compare with the rest of Europe and the world? Is there any disparity and, if so, what can be learnt from the Belgian experience?

A: In a nutshell, I would say that Belgian patients with cancer receive extremely good treatment, but I think that they could potentially receive even better treatment if oncology in Belgium was better organised. It is disorganised in the sense that there is no network and no referral centres –

everybody can do everything. I could provide lots of unfortunate clinical examples where patients may have lost the chance to be cured because they were not adequately treated, although, overall, the healthcare system and the oncology system in Belgium is pretty good. From my experience in Amsterdam, the healthcare system in the Netherlands is wonderful because only a few centres are allowed to do a few complex things. If the same model could be implemented in Belgium I would probably be the 'happiest man on earth', and I am working on it as the Ministry of Health and some governmental agencies invited me and other oncologists to work on proposals 2 years ago. The proposals were rapidly written and sent off but I guess they are still waiting somewhere on the desk of the minister; this subject is highly political, of course.

Q: Have you noticed any change or evolution in the teaching of oncology since you began your studies, and can any more be done to better educate medical students and encourage others to work in this field?

A: The answer is definitely 'yes'. I have already mentioned the importance of multidisciplinarity several times and that is what we teach students: not to work on their own and to work with the other disciplines, and we train them to refer patients to large centres where we believe (and there are data to show it) the oncological results are much better than when carried out remotely by non-experts. Another message is that we try to encourage students to enter into oncology programmes because we need manpower as the incidence of cancer is still rising, and so we need more and more experts and specialists, be it surgeons, radiation oncologists, or medical oncologists. It may not be seen as a 'fun' medical discipline (although it is interesting and, in my view, when something is interesting it is also fun) but we need to convince them to enter into these programmes and not just go into ophthalmology or dermatology because it is a '9 to 5' type of specialty that does not include weekend work.

Frank Meyskens, Jr

Professor of Medicine, Biological Chemistry, Public Health and Epidemiology, School of Medicine, and Director Emeritus, Chao Family Comprehensive Cancer Center, University of California Irvine (UCI), Irvine, California, USA.

Q: Who or what inspired you to specialise in oncology during your clinical and laboratory work?

A: My first experience with research in high school and college involved the study of cellular biochemistry. In medical school I was lucky enough to work with the pioneers of cell cycle research in the Laboratory of Radiobiology at UCSF, where I met James Cleaver, and I was there the evening that the data identifying the initial molecular defect of xeroderma pigmentosum came off the scintillation counter. I became involved with these patients and subsequently spent 6 months at the MRC building in Cambridge, UK, where I met Francis Crick among others. It was probably inevitable at this point that I would become an oncologist and 'physician scientist' (although that term is now regarded as somewhat old-fashioned), and this is the pathway I have followed. I became interested in prevention because I began my faculty career around the time that therapeutic nihilism was rampant: initial successes had been attained in the late 1950s and 1960s, and the explosion of scientific understanding regarding the basis of cancer pathogenesis was just beginning to be appreciated (in the late 1970s and early 1980s). The full story is actually much more complex than this though!

Q: You are actively involved in many clinical trials of investigational drugs for a range of cancer types – are there any Phase III trials close to being ready for reporting?

A: No. The great era of Phase III prevention trials is in a hiatus, with the emphasis now on establishing a firmer scientific base (beyond epidemiological observations) before proceeding to larger trials.

"Do not use tanning booths – they are probably more dangerous than the sunlight itself."

This includes Phase 0 pharmacodynamic studies, improved patient-derived mouse xenografts, and better biomarkers, although the latter two fields continue to struggle with the conundrum of how exactly to come up with a validated biomarker without doing definitive correlative trials! I have written extensively about these topics, as have others.

Q: Oncology is a field at the forefront of the introduction of personalised medicine and the use of companion diagnostics; how have these concepts altered the development landscape for new cancer drugs?

A: There is a clear focus on using mechanisms as the basis for drug development. The big hits that actually improve survival will remain few and far between (e.g. chronic myeloid leukaemia, anaplastic lymphoma kinase, and lung cancer). Regarding its use in patients with refractory disease, we are at the beginning of applying precision medicine and it remains to be seen whether it will be useful and affordable overall. Therefore, we should exercise cautious optimism.

Q: Much of your research focusses on melanoma. This disease does not seem to receive the same level of attention within the mainstream media that it used to, especially compared with cardiovascular disease, diabetes, etc. Have previous public awareness campaigns succeeded in making melanoma less common?

A: Melanoma has actually been in the news probably more than any other cancer in the past few years due to the success of targeted molecular therapy (although this has limited benefits) and the even greater effect and benefit of modern immunotherapy; but no, in fact the incidence of melanoma continues to increase. Early diagnosis has, however, had a big impact. The 5-year survival of cutaneous melanoma patients was about 40% when I started my faculty appointment in 1977, but for patients in the USA diagnosed today it is around 90%.

Q: Are there any preventative measures in addition to using sun block that individuals can take in order to minimise their risk of developing melanoma?

A: Do not use tanning booths – they are probably more dangerous than the sunlight itself. There are lots of claims for 'this' or 'that' magic potion or natural or nutraceutical product, but nothing has been proven.

Q: From the outside, it seems as if the American healthcare system may be changing significantly – could you speculate on how 'Obamacare' is likely to impact the treatment of cancer patients in the USA, if at all?

A: Indeed, Obamacare is the litmus test for the broader arena of inequality within a democracy! It provides financial coverage of basic screening studies. However, access to the management of detected problems has not yet been adequately addressed/worked out. In addition to prevention, screening programmes have been proposed as a way of improving cancer survival rates, although they rely on public compliance, as well as the diagnostic performance of the markers used to screen; there is also the risk of overtreatment.

Q: What are your views on the introduction of public screening programmes for different types of cancer?

A: In general, broad screening studies identify lesions, but personalised medicine (which is broader than precision medicine) will increasingly allow us to identify higher-risk individuals and therefore a better population for targeted screening and early detection; it is all about risk versus benefit.

Q: What are the most significant advances that you have witnessed in cancer prevention or treatment since your career began?

A: Reduction in tobacco usage. In California it was nearly 60% in men in the 1970s and now it is down to 15%. The situation in women is more complex, but, in general, smoking incidence is also low.

EDITORIAL BOARD INTERVIEWS

Q: Are there any areas of oncology research that you would like to move into in the near future?

A: We have been involved with redox regulation of transcriptional events for over 15 years, but funding has been difficult; many are now entering this arena. As I have become older, I have become intellectually engaged in end-of-life issues, especially vis-à-vis the medical–industrial complex, which is an unsolvable problem in the USA and one that is better addressed in many Asian and European countries. I have also published many poems and two books of poetry on the topic (*Aching for Tomorrow* [2007] and *Believing in Today* [2014]) as a prelude, if you will, to my recent academic involvement.

Q: How important are international congresses to oncologists?

A: That depends on the status of the oncologist. To a basic laboratory researcher they are not that important because individual fields move quickly. For a general practising oncologist, however, it is a good thing to do every few years.

Q: Are there any specific congresses that you look forward to each year?

A: The triennial Meeting of the International Federation of Pigment Cell Societies, as each of the regional societies tend to have emphasis areas.

Q: What advice would you give to young researchers or medical students thinking about specialising in oncology?

A: Become involved in research early – the field of oncology encompasses a broad range of activities, including basic laboratory work, population studies, public health, etc. Try to have clinical exposure early too – oncology encompasses nearly every specialty in one way or another, the big divide (or opportunity!) is surgical versus non-surgical. You must also be willing to work 80+ hours per week.

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INTELLIGENT APPLICATION OF BREAST CANCER TRIALS DATA IN THE CLINIC

Summary of presentations from the prIME Oncology satellite symposium held at the European Cancer Congress 2015 in Vienna, Austria, on 25th September 2015

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Speakers

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Disclosure: Pierfranco Conte has received consulting fees from Roche and Novartis. He has also received fees for non-CME services from Novartis, Roche, AstraZeneca, and Celgene. Joanne Franklin has no relevant financial relationships to disclose. Sibylle Loibl has received consulting fees (for her institution) from Celgene and Amgen. She has also received fees (for her institution) for performing contracted research for Amgen, AstraZeneca, Celgene, Roche, and Pfizer. Peter Schmid has received consulting fees from Genentech. Christos Sotiriou has received consulting fees from Cepheid, Astellas, and Vertex Pharmaceuticals. Sunil Verma has received consulting fees from Pfizer, Novartis, Roche, Amgen, AstraZeneca, Bristol-Myers Squibb, Merck, Eisai, and Eli Lilly.
Acknowledgements: Editorial assistance was provided by Ms Heather Tomlinson, prIME Oncology.
Support: This educational activity was supported by Roche and Genomic Health.
Citation: EMJ Oncol. 2015;3(2):40-48.

MEETING SUMMARY

This meeting commenced with a talk from Prof Loibl on neoadjuvant and adjuvant strategies for HER2-positive (human epidermal growth factor receptor 2-positive) early breast cancer (EBC), which featured a précis on the most pertinent, recent trial data and how these data may shape future treatment decisions in clinical practice. Prof Conte moved the discussion forward by addressing how recent studies may lead towards a new standard of care (SoC) and treatment paradigms in patients with metastatic breast cancer. Prof Schmid gave an overview of potential strategies that could be used to prevent or overcome endocrine therapy resistance in patients with hormone receptor-positive breast cancer. The session was concluded with a presentation on 'Precision Medicine for Metastatic Breast Cancer' by Prof Sotiriou, in which he highlighted the potential applications of precision medicine and some of the different approaches that have been used in metastatic breast cancer. Prof Verma, the meeting chair, opened the symposium and facilitated the discussion sessions. The contents of the presentations and discussions are summarised herein.

Neoadjuvant and Adjuvant Strategies for HER2-Positive Early Breast Cancer

Professor Sibylle Loibl

HER2-positive breast cancer is a particularly aggressive form of breast cancer that is found in approximately 20% of women diagnosed with breast cancer.[1] While patients with HER2-positive EBC have a good prognosis, challenges remain. There is a high recurrence rate despite treatment with trastuzumab, and neoadjuvant candidates have worse prognosis. Since the approval of trastuzumab, other HER2-targeted therapies have been designed and approved. Herein, the latest data on neoadjuvant and adjuvant strategies for treating patients with HER2-positive EBC will be discussed.

One evolving treatment strategy for HER2-positive EBC is dual HER2 blockade using two targeted agents. The NeoSphere trial was a four-arm study in the neoadjuvant setting evaluating whether the addition of pertuzumab, a humanised anti-HER2 monoclonal antibody, to docetaxel and trastuzumab could provide clinical benefit versus the other single-blockade cohorts. Patients receiving the double blockade plus docetaxel had a significantly higher pathological complete response (pCR) compared with trastuzumab plus docetaxel (45.8% versus 29.0%; p=0.0141); hormone receptor-positive patients derived the greatest benefit.[2] Five-year follow-up data demonstrated that patients with pCR displayed significantly better survival versus those without pCR (hazard ratio [HR]: 0.54, 95% confidence interval [CI]: 0.29–1.00). The data also suggest that there was an improvement in both progression-free survival (PFS) and disease-free survival (DFS) in the double-blockade cohort.[3] Confirmation of whether HER2 double blockade has a survival benefit is expected from the Phase III APHINITY trial,[4] which compares invasive DFS (iDFS) in patients receiving trastuzumab alone or trastuzumab plus pertuzumab for 1 year after anthracycline/taxane-based chemotherapy.

The Phase III ExteNET trial evaluated extended adjuvant treatment of EBC with neratinib, a dual HER2 and epidermal growth factor receptor inhibitor. High-risk patients were randomised to 12 months of neratinib or placebo following 12 months of trastuzumab. A statistically significant improvement in iDFS was seen with neratinib, compared with placebo (HR: 0.67, 95% CI: 0.50–0.91; p=0.0046); patients with hormone receptor-positive disease derived greater benefit than hormone receptor-negative patients.[5]

Chemotherapy-free treatment is also being explored in EBC. The Phase I/II ADAPT umbrella trial includes a sub-trial of hormone receptor-positive/HER2-positive patients randomised to trastuzumab emtansine (T-DM1), T-DM1 plus endocrine therapy, or trastuzumab and endocrine therapy. Interim results demonstrate a significantly higher pCR rate for the T-DM1 arms, with or without endocrine treatment (40.5% and 45.8%, respectively), versus the trastuzumab-treated group (6.7%).[6] The ATEMPT study is addressing a similar question in the adjuvant setting by comparing T-DM1 versus paclitaxel plus trastuzumab versus trastuzumab monotherapy, with results being expected soon.[7]

Trial data in the neoadjuvant setting show that chemotherapy-based treatment regimens consistently produce higher rates of pCR. However, the data indicate that longer chemotherapy-free treatment consisting of trastuzumab, lapatinib, or potentially T-DM1 (pending final data), and endocrine agents produces moderate rates of pCR (Figure 1)[2,6,8-11] and may be a valid treatment option. How patients who would benefit from chemotherapy-free treatment could be selected remains to be seen – determining whether a patient's tumour(s) harbours mutations in the gene encoding PI3 kinase (*PIK3CA*) may be one approach. A retrospective study combining data from the neoadjuvant GePAR studies, the Neo-ALTTO study, and the CHERLOB study, all of which evaluated *PIK3CA* mutations as predictors of pCR, revealed a significantly lower pCR rate in patients harbouring a mutation.[12] This effect was particularly pronounced in hormone receptor-positive patients.

It may be best to consider both the HER2 and the hormone receptor status of breast cancer patients when planning their treatment. Hormone receptor-negative/HER2-positive patients should receive anthracycline, a taxane, and anti-HER2 treatment. For patients achieving pCR, an option may be to reduce the duration of anti-HER2 treatment. For hormone receptor-positive/HER2-positive patients, it may be possible to downgrade chemotherapy and start with endocrine treatment plus double HER2 blockade with or without a PI3 kinase (PI3K) inhibitor. For non-pCR patients, chemotherapy or other investigational drugs may be required.

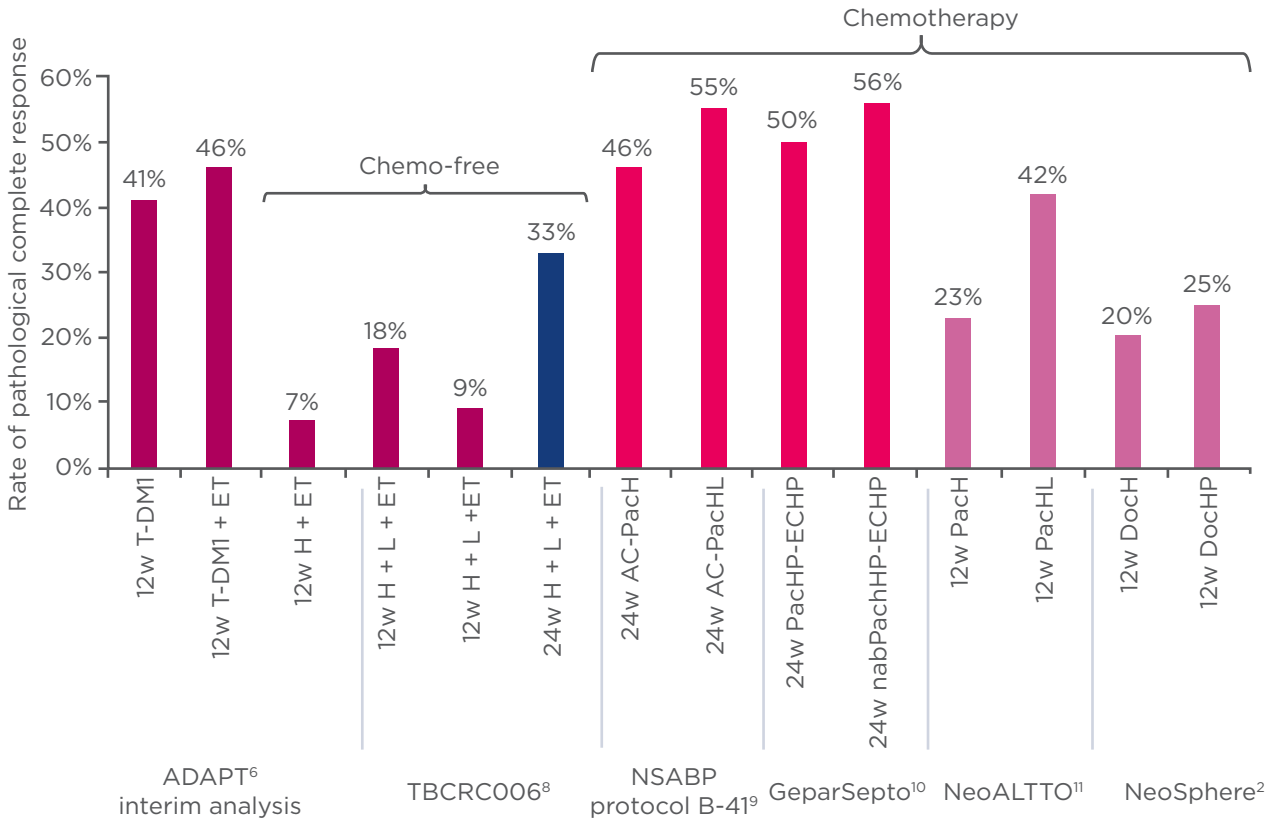

Figure 1: Rates of pathological complete response in HER2-positive early breast cancer.
A: doxorubicin; C: cyclophosphamide; Doc: docetaxel; E: epirubicin; ET: endocrine therapy; H: trastuzumab; L: lapatinib; nabPac: nab-paclitaxel; P: pertuzumab; Pac: paclitaxel; T-DM1: trastuzumab emtansine; w: weeks.

HER2-Positive Metastatic Breast Cancer: Standard of Care and What's Next

Professor Pierfranco Conte

Trastuzumab and other anti-HER2 agents have revolutionised the treatment of HER2-positive disease. However, questions remain about optimal treatment strategies in the metastatic setting. Is it feasible to target HER2 after progression on first-line treatment? What is the optimal sequence of anti-HER2 therapies? Is there a role for endocrine therapy in combination with anti-HER2 therapies?

Five trials have evaluated targeting HER2 after progression on trastuzumab.[13-17] Each trial demonstrated a significant prolongation of PFS irrespective of whether lapatinib, trastuzumab, or T-DM1 was used. Three of the trials, EMILIA,[16] EGF104900,[15] and Th3RESA,[17] also showed statistically and clinically significant improvements in overall survival (OS). Notably in both EGF104900 and Th3RESA, patients had received multiple lines of prior treatment. The survival gain observed over time is consistent with the efficacy of salvage anti-HER2 therapies.

There are several trials addressing the optimal sequencing of anti-HER2 agents in this setting. The CLEOPATRA study demonstrated that docetaxel/trastuzumab plus pertuzumab was more effective than docetaxel/trastuzumab alone (PFS: 18.7 versus 12.4 months, respectively; HR: 0.69, 95% CI: 0.58–0.80).[18,19] However, the applicability of the trial data may be limited as only 10% of the trial population had failed adjuvant trastuzumab, whereas in daily practice the majority of patients have received prior adjuvant trastuzumab. Two large trials examined potential treatment regimens for patients who progress during adjuvant trastuzumab or relapse very early (within 6 months). The EMILIA study compared T-DM1 with lapatinib plus capecitabine. T-DM1 treatment resulted in significant prolongation of PFS (9.6 versus 6.4 months; HR: 0.65, 95% CI: 0.55–0.77; p<0.0001) and a significant benefit in OS (30.9 versus 25.1 months; HR: 0.68, 95% CI: 0.55-0.85; p<0.001) versus lapatinib/capecitabine.[16]

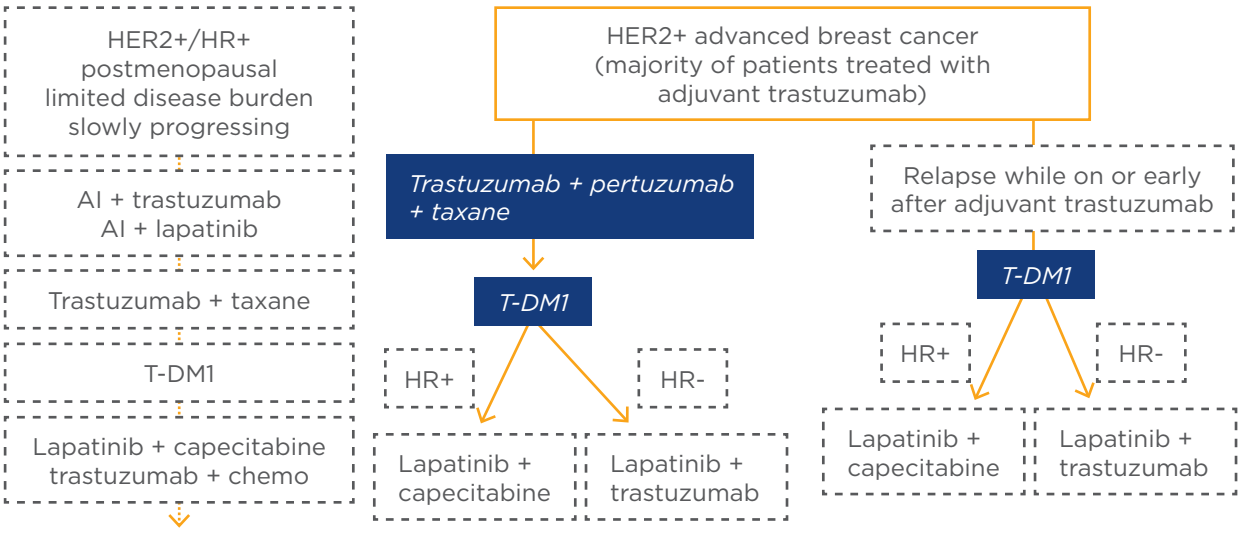

Figure 2: A new treatment algorithm for HER2-positive advanced breast cancer.
AI: aromatase inhibitor; HR: hormone receptor; T-DM1: trastuzumab emtansine.

The Th3ERSA study, which contained a more heavily pre-treated patient population, compared T-DM1 versus T-DM1 plus physician's choice treatment. T-DM1 was superior in terms of both PFS and OS.[17] It will be important to determine the efficacy of T-DM1 after the combination of trastuzumab, pertuzumab, and a taxane.

Also pertinent is whether there is any role for endocrine therapy in hormone receptor-positive/HER2-positive disease. Three relatively small randomised clinical trials, TAnDEM,[20] eLEcTRA,[21] and the trial by Johnston et al.,[22] have investigated this. Each study demonstrated that endocrine therapy alone is poorly effective, but if administered with lapatinib or trastuzumab it significantly increases response rate and PFS. Although the PFS rates are lower than those obtained using chemotherapy, adding anti-HER2 agents to endocrine therapy increases the efficacy of endocrine therapy. This is therefore an alternative option for selected patients, such as the frail and the elderly with limited tumour burden.

Newer therapeutic targets are also being looked at in the metastatic setting. Mutation of *PIK3CA*[23] is an emerging tumour marker and there are agents available for PI3K-mutated tumours. The mTOR inhibitor everolimus can be used to abrogate signalling through the PI3K–Akt–mTOR pathway. The BOLERO-1 and BOLERO-3 trials investigated the addition of everolimus to trastuzumab/paclitaxel in first-line therapy (BOLERO-1) and to trastuzumab/vinorelbine in second-line therapy (BOLERO-3). No statistically significant improvement was seen in BOLERO-1,[24] but the combination of everolimus with trastuzumab/vinorelbine in BOLERO-3 resulted in a significant improvement in median PFS (everolimus: 7 months, placebo: 5.78 months; HR: 0.78, 95% CI: 0.65–0.95; p=0.0067), although this gain was small.[25] The data are more powerful if patients are stratified according to PI3K pathway activation. Slamon et al.[26] performed a subanalysis of BOLERO-1 and BOLERO-3 in patients with an activated PI3K pathway (44% of the overall population). In this subpopulation, the addition of everolimus was quite effective, with a 33% reduction in the risk of progression (combined population: placebo versus everolimus, HR: 0.67, 95% CI: 0.48–0.93). While this does not constitute sufficient evidence to be practice-changing, the data suggest that combining mTOR/PI3K inhibitors with HER2-targeting agents may be a valid strategy in PI3K-mutated tumours.

A survey of trials in the metastatic setting would not be complete without mentioning the MARIANNE trial. This study compared T-DM1 ± pertuzumab versus trastuzumab plus docetaxel/paclitaxel with the SoC. The primary endpoint was non-inferiority and, assuming this was reached, the co-primary endpoint was superiority of the T-DM1 cohorts. While non-inferiority was demonstrated for T-DM1 ± pertuzumab versus SoC, neither arm proved to be superior to the SoC.[27]

In summary, the following treatment strategies may be recommended at the current time (Figure 2):

- For the majority of patients with HER2-positive metastatic breast cancer, standard first-line therapy should be a taxane plus trastuzumab plus pertuzumab
- For certain carefully selected patients with hormone receptor-positive/HER2-positive disease, specifically indolent with a limited tumour burden, the first-line treatment may be an aromatase inhibitor (AI) plus either lapatinib or trastuzumab
- T-DM1 may:
  - Provide an option for patients who progress while on, or very shortly after, adjuvant trastuzumab
  - Be considered the standard second-line treatment
  - Be an alternative option to taxane plus trastuzumab

Hormone Receptor-Positive Breast Cancer: Preventing and Overcoming Endocrine Therapy Resistance

Professor Peter Schmid

Endocrine resistance remains problematic in oestrogen receptor (OR)-positive, metastatic breast cancer. Resistance can be clinically categorised as either *de novo* resistance, which occurs early in the first 2 years of disease, or acquired resistance, which occurs at later disease stages. Strategies with the aim of reducing the risk of resistance are a current goal in the management of HER2-positive breast cancer. There are two main mechanisms of endocrine resistance: altered OR signalling and altered alterative signalling, e.g. through other growth factor receptors.[28] Agents that target either of these altered pathways may have utility in overcoming resistance. The OR ligand-binding domain, for example, is susceptible to mutations that lead to constitutive receptor activation and, consequently, resistance.[29] Using a selective OR degrader that downregulates the receptor, e.g. fulvestrant, may surmount this resistance.[30]

Historically, AIs have been used as first-line hormonal therapy in post-menopausal women with metastatic breast cancer, but poor PFS remains an issue. Fulvestrant may present a feasible alternative. The FIRST study compared high-dose fulvestrant (500 mg) with anastrozole in the first-line setting in a population in which 75% of patients were endocrine-therapy-naïve with *de novo* metastatic disease. The fulvestrant arm showed an advantage in terms of time to progression (HR: 0.66, 95% CI: 0.47–0.92; p=0.01) and a benefit in OS (HR: 0.70, 95% CI: 0.50–0.98; p=0.041).[31] The ongoing Phase III FALCON study should confirm these data.[32,33]

CDK4/6 inhibitors are another treatment option. CDK4/6 proteins are involved in regulating the cell cycle, and inhibiting their signalling should slow down the cell cycle and potentially overcome endocrine resistance. The Phase II PALOMA-1 trial compared letrozole ± the CDK4/6 inhibitor palbociclib in all-comers as well as a subpopulation of patients with cyclin D1 amplification or loss of p16. Overall results clearly demonstrated that the combination of letrozole and palbociclib was substantially better than letrozole alone; no added benefit was seen in the selected patients.[34] Data from the Phase III PALOMA-2 trial (comparing palbociclib and letrozole with letrozole alone) should confirm whether CDK4/6 inhibitors may be good candidates for first-line therapy.[35]

A third potential first-line therapy is the addition of bevacizumab to AIs. The current evidence base is conflicting. The CALBG 40503 trial, which investigated letrozole versus letrozole plus bevacizumab, reported a significant improvement in PFS,[36] while the LEA trial, comparing letrozole/fulvestrant versus letrozole/fulvestrant plus bevacizumab, showed a marginal albeit not statistically significant improvement.[37] Further investigation is required to clarify if there is a role for bevacizumab.

Adding molecularly targeted agents to endocrine therapy is also being investigated in the second line. Two trials have explored whether mTOR inhibitors can prevent/reverse endocrine resistance. BOLERO-2 compared exemestane alone with a combination of exemestane plus everolimus, with clear superiority achieved in the combination arm (HR: 0.38, 95% CI: 0.31–0.48).[38,39] In contrast, no change in PFS was observed in the HORIZION trial (letrozole ± temsirolimus).[40] Along with the differences in choice of AI and mTOR inhibitor, the conflicting data may also reflect the different study populations: 84% of patients in BOLERO-2 had prior endocrine response, whereas 57% of patients in HORIZION had received no prior endocrine therapy. These data may indicate that endocrine pathways must first be activated

(via prior endocrine therapy) in order for mTOR inhibitors to be effective.

This leads to the question of how to best select patients who will benefit from mTOR inhibitors. In BOLERO-2, the everolimus-related PFS benefit was maintained in patients regardless of *PIK3CA* gene alterations, although a subanalysis suggested that patients with ≤1 genetic alteration derive greater PFS benefit with everolimus.[41] Luminal B versus luminal A cancers also appear more sensitive to PI3K inhibitors.[42]

PI3K inhibitors and CDK4/6 inhibitors are also being investigated in the metastatic setting. The FERGI study looked at the addition of the pan-PI3K inhibitor pictilisib to fulvestrant; only a marginal improvement in PFS was observed.[43] The ongoing BELLE-2 trial,[44] which investigates the addition of the pan-PI3K inhibitor buparlisib to fulvestrant in patients who have received prior AI, may provide further clarity. As in the first line, CDK4/6 inhibitors also have activity in the metastatic setting. PALOMA-3 compared palbociclib plus fulvestrant versus placebo plus fulvestrant in patients with hormone receptor-positive/HER2-positive metastatic breast cancer and revealed a statistically significant improvement in PFS in the combination arm (9.2 versus 3.8 months; HR: 0.422, 95% CI: 0.32–0.56; p<0.001).[45]

In conclusion, when determining strategies for overcoming resistance it may be necessary to consider endocrine sensitivity (possibly by using biomarker testing), the time and type of resistance (primary versus secondary), and intrinsic subtype (luminal A or B) before the optimal treatment plan is developed.

Precision Medicine for Metastatic Breast Cancer

Professor Christos Sotiriou

The National Institutes of Health define precision medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."[46] This approach allows for the identification of 'driver' mutations specific to breast cancer, determination of genomic alterations that cause secondary resistance and DNA repair defects that may be therapeutic targets, and elucidation of immune escape mechanisms. Herein, several examples of how precision medicine has been used in breast cancer are discussed.

The first mutational landscape of metastatic breast cancer was recently published.[47] Retrospective analysis of biopsy sample data from the SAFIR01 and MOSCATO studies determined that, while metastatic tumours harboured mutations common to primary tumours (e.g. mutations in the genes encoding p53 and PI3K), they also displayed a high frequency of gene mutations that are rare in primary tumours (e.g. mutated *ESR1*, *TSC1*, and *TSC2*). In another recent study by Juric et al.,[48] the genomic evolution of a tumour in a patient with metastatic breast cancer with an activating *PIK3CA* mutation was studied. The patient had responded to the PI3Kα inhibitor BYL719, but eventually developed resistance. Post-mortem, metastatic lesions were analysed and compared with pre-treatment tumour tissue and it was determined that there was a convergent loss of *PTEN* in the tumour and this likely led to PI3Kα inhibitor resistance.

Precision medicine can also be used to identify DNA repair defects. This was highlighted in a recent publication by Alexandrov et al.[49] analysing 4,938,362 mutations from 7,042 tumours. More than 20 distinct mutational signatures were identified; 5 of these were found in breast cancer and 3 of them are involved in DNA repair, including 1 corresponding to *BRCA1/2* deficiency. Such information can be used to drive forward new targets for research and development. Sequencing technologies can be used to identify neoantigens (responsible for priming the immune response) or elucidate the presence of tumour-infiltrating lymphocytes (TILs); both are potential readouts for tumour growth/progression and TILs may have utility as surrogate markers for the efficacy of checkpoint inhibitors. These techniques may also be used to analyse genetic polymorphisms associated with immune effects, and this information could be exploited to produce immunotherapeutics.

There are clearly challenges with these technologies, one of which is how to define a driver mutation and determine if it has significant diagnostic, prognostic, or therapeutic implications in subsets of cancer patients for specific therapies. In breast cancer, the identification of these driver mutations has not met with total success. For example, the presence of *PIK3CA* mutations does not necessarily predict response to PI3K inhibitors or mTOR inhibitors. Similarly, it was anticipated

that cyclin D1 amplification or p16 loss may be good surrogate markers to predict response to palbociclib, but the trial data have disproven this. It seems that a single-gene alteration does not automatically mean a patient will respond to a drug.

A better approach may be to think beyond a single gene, and evaluate signal pathway activation and tumour dependency. Assessing multiple genomic alterations in conjunction with functional studies should also be considered. This was highlighted in the BOLERO-2 trial, which demonstrated that patients who have multiple alterations in their breast cancers do not benefit from the exemestane and everolimus combination, whereas if they have ≤1 mutation they derive great benefit.[41] Similar evidence in support of considering multiple genomic alterations comes from the *HER2* gene, which can harbour numerous mutations. One study demonstrated that there are mutations that activate the signalling pathways and other mutations that are non-pathway activating within *HER2*. There are also mutations that confer different drug responses; for example, the L755S mutation results in lapatinib resistance, while the D769H mutation does not. It would be ideal to determine which phenotype is associated with individual mutations in order to facilitate optimal treatment strategies.[50]

Tumour heterogeneity and evolution is another challenge to precision medicine. It has been demonstrated that geographical heterogeneity exists even within a tumour, with different areas containing different mutations.[51] For metastatic disease, the tumour evolves as a consequence of internal and external pressures, prior treatment, and different driver mutations which may be acquired and be sub-clonal. The result is a lesion very different from a primary tumour and consequently the metastatic tumour should be analysed when making treatment decisions.

In conclusion, when planning therapy it is important to remember that there is currently a lack of strong functional evidence to differentiate between driver and non-driver mutations. It may be necessary to look beyond one single gene and to also consider pathway activation, host interactions, the microenvironment, the immune system, and the significant problem of substantial intra-tumour and inter-lesion heterogeneity.

Please **click here** to see a webcast of the live meeting.

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INCORPORATING PARP INHIBITION IN CANCER THERAPY: KEY QUESTIONS, EXPERT ANSWERS

Summary of presentations from the prIME Oncology satellite symposium held at the European Cancer Congress 2015 in Vienna, Austria, on 27th September 2015

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Disclosure: Tristin Abair has no relevant financial relationships to disclose. Hilary Calvert has received consulting fees from AstraZeneca and holds intellectual property rights/is a patent holder for rucaparib (a Clovis Oncology product). Nicoletta Colombo has received consulting fees from AstraZeneca. Eric Pujade-Lauraine has received consulting fees from AstraZeneca, Pfizer, and Roche. Andrew Tutt has received grants/research support from AstraZeneca, Myriad Genetics, and Roche; received honoraria or consulting fees from EISAI, Merck Serono, and Vertex; received royalties from ICR Rewards to Inventors Scheme regarding olaparib in *BRCA1/2* malignancy; and has been named on a patent (KCL) for genome instability. Eric Van Cutsem has performed contracted research for Amgen, Bayer, Boehringer Ingelheim, Celgene, Lilly, Merck Serono, Novartis, Roche, and Sanofi.
Acknowledgements: Editorial assistance was provided by Ms Trudy Grenon Stoddert, prIME Oncology.
Support: AstraZeneca has provided a sponsorship grant toward this independent programme. In addition, this manuscript is supported by a grant from Clovis Oncology.
Citation: EMJ Oncol. 2015;3(2):49-58.

MEETING SUMMARY

This engaging symposium focussed on the rationale and current evidence supporting the role for poly(adenosine diphosphate-ribose) polymerase (PARP) inhibition in patients with cancer. The meeting opened with an overview of DNA repair and the biological basis for targeting this process in oncology, delivered by Prof Calvert. This was followed by a discussion from Prof Pujade-Lauraine that focussed on patient selection for PARP inhibition and the role for these agents in *BRCA*-mutated and *BRCA*-like cancers. Next, Prof Colombo presented a clinical scenario of *BRCA*-associated ovarian cancer and examined optimal treatment options in the first-line setting and for progressive disease. She also highlighted current clinical data and ongoing trials evaluating PARP inhibition in advanced ovarian cancer. Prof Tutt then discussed the potential role for PARP inhibitors in patients with breast cancer, focussing on a clinical scenario of triple-negative disease and emphasising current and investigational treatment options. Lastly, Prof Van Cutsem described emerging data and ongoing clinical studies evaluating PARP inhibition in the treatment of patients with pancreatic and gastric cancers, and how this could impact future clinical practice. The programme also included a PARP quiz, in which participants were polled at the beginning and conclusion of the symposium to examine their knowledge and practice patterns regarding the use of PARP inhibitors in oncology. The key highlights from these presentations and the PARP quiz are summarised herein.

Why Target DNA Repair Mechanisms in Cancer?

Professor Hilary Calvert

Prof Calvert began by discussing the importance of DNA repair in maintaining genomic integrity. Cells endure approximately 10,000–30,000 episodes of DNA damage on a daily basis as a result of replication errors, environmental factors, and other causes.[1] This threat is met with five distinct repair pathways: recombinational repair (homologous recombination and non-homologous end joining [NHEJ]), nucleotide excision repair, mismatch repair, base excision repair (BER), and direct reversal. There is considerable redundancy within the DNA repair system, such that a defect in one pathway can be overcome by the action of a different pathway, and loss or mutation of one repair protein allele can often be compensated for by normal expression of the other allele.

DNA damage repair has important implications in patients with cancer, including mutations in *BRCA1* and *BRCA2*.[2] *BRCA* mutation carriers with one dysfunctional gene can still perform homologous recombination due to the remaining normal gene. However, if DNA damage leads to loss of that remaining *BRCA* gene (a 'second hit'), cells cannot perform homologous recombination repair and are forced to undertake the more error-prone NHEJ instead. This results in accumulation of additional mutations and increased susceptibility to tumour formation.

Prof Calvert described how this deficiency in DNA repair also creates the possibility of synthetic lethal interactions with drugs that inhibit alternative DNA repair pathways.[2] Synthetic lethality results when inhibition of two pathways leads to cell death, while the loss of either pathway alone does not affect viability. Synthetic lethality has been elegantly illustrated by the inhibition of poly(adenosine diphosphate-ribose) polymerase (PARP) in cell lines and tumours with aberrant DNA repair mechanisms. Two articles published in *Nature* showed that cells deficient in *BRCA1/2* were highly sensitive to PARP inhibition and exhibited early cell death.[3,4] In normal cells, PARP activity repairs single-strand breaks via BER. If a PARP inhibitor (PARPi) is present, the break will not be repaired and will lead to double-strand breaks during DNA replication. In cells with one or two functional *BRCA* genes, these double-strand breaks will be repaired by homologous recombination. However, homologous recombination cannot occur in *BRCA*-deficient cells, leading to collapse of the replication fork and cell death. Therefore, the synthetic lethal interaction elicited by PARPi in *BRCA*-mutated cancers is targeted to the tumour cells specifically.

Prof Calvert emphasised that ongoing clinical trials are investigating PARPi alone and in combination regimens in cancers with *BRCA* mutations or deficiency in homologous recombination.[2] The complex role of DNA repair in oncogenesis suggests that additional synthetic lethal interactions may be found with continued investigation.

How to Identify Patients Who May Benefit From PARP Inhibitors

Professor Eric Pujade-Lauraine

Prof Pujade-Lauraine first asked participants to identify the greatest challenge they faced when ordering a *BRCA* test for a patient with advanced ovarian cancer. The responses were evenly divided between *BRCA* testing not being included in their country's national guidelines, *BRCA* testing being restricted to subsets of ovarian cancer according to family history and/or young age, mandatory pre-test genetic counselling delaying results, and non-reimbursement of *BRCA* testing. Prof Pujade-Lauraine agreed that there are substantial hurdles to *BRCA* testing, but emphasised that the time has come for incorporation of genetics into gynaecological oncology.

BRCA testing benefits both patients and their families by providing information on prognosis, treatment decisions, and follow-up. A pooled analysis of 26 observational studies of ovarian cancer showed that *BRCA1/2* carriers had significantly higher 5-year survival rates compared with non-carriers.[5] This improvement in survival may be linked to increased sensitivity to platinum agents and PARPi, informing treatment decisions.[1,6] For families, *BRCA* testing provides risk assessment and the opportunity for prophylactic surgery to reduce cancer risk.

Prof Pujade-Lauraine then discussed which patients with ovarian cancer should be considered for *BRCA* testing. Several population-based studies indicate that younger age and family history are not good predictors of *BRCA* mutation, with a similar median age at diagnosis for *BRCA1/2* mutation

carriers and non-carriers and approximately one-third of *BRCA1/2* mutation carriers having no family history of ovarian or breast cancer.[7-10] Population-based studies also demonstrated that histological type is not a foolproof predictor of *BRCA* status, with *BRCA* mutations detected in tumours of serous, endometrioid, and clear cell histology.[8,9,11]

Current guidelines recommend *BRCA* mutation testing in all patients with epithelial ovarian cancer, regardless of age or family history.[12,13] The current process for *BRCA* testing involves referral for genetic counselling and assessment of germline *BRCA* mutations. However, several studies suggest that an additional 5–7% of patients with ovarian cancer have somatic *BRCA* mutations within the tumour without germline mutations.[14-16] While these somatic mutations do not have implications for the patient's family, they can greatly impact treatment decisions, suggesting that tumour testing should also be considered.

Ongoing efforts are focussed on validating methods to achieve accurate *BRCA* testing results. The emergence of next-generation sequencing (NGS) also creates the opportunity to detect mutations in other genes beyond *BRCA1/2* that block homologous recombination function.[16] These types of mutations can confer sensitivity to PARPi and inform treatment decisions. The recently presented Phase II ARIEL2 trial investigated the ability of an NGS-based homologous recombination deficiency assay to predict benefit from the PARPi rucaparib in patients with platinum-sensitive, high-grade serous or endometrioid ovarian cancer.[17] Patients with *BRCA*-like tumours, defined by genome-wide loss of heterozygosity due to homologous recombination deficiency, achieved a median progression-free survival (PFS) benefit of 7.1 months, which was intermediate between the 9.4 months for *BRCA*-mutated tumours and 3.7 months for biomarker-negative tumours.

Prof Pujade-Lauraine concluded by emphasising that *BRCA* testing should be utilised in every patient with ovarian cancer. *BRCA* mutations are also found in several other types of cancer, such as breast cancer, pancreatic ductal adenocarcinoma, and prostate cancer.[1] *BRCA* mutation testing is currently recommended for patients with triple-negative breast cancer (TNBC) who are less than 50 years of age.[18] Testing in other tumour types such as pancreatic and prostate cancers is investigational, but could identify patients who may benefit from PARPi.

What Is the Optimal Treatment Approach for *BRCA*-Associated Advanced Ovarian Cancer?

Professor Nicoletta Colombo

Prof Colombo began by asking the audience what first-line treatment they would choose for a 51-year-old patient with Stage IIIC, high-grade serous, *BRCA*-associated ovarian cancer. The responses varied widely, with 43% selecting standard paclitaxel/carboplatin followed by maintenance PARPi and 27% choosing to add bevacizumab to standard chemotherapy with bevacizumab maintenance therapy. Fewer selected standard q3w paclitaxel/carboplatin alone (14%), dose-dense paclitaxel plus carboplatin (10%), or intraperitoneal (IP) chemotherapy (4%).

Prof Colombo commented that q3w paclitaxel plus carboplatin has been the standard first-line therapy for over a decade despite numerous clinical trials investigating substitution or addition of other chemotherapeutic agents.[19] Addition of the antiangiogenic therapy bevacizumab improves PFS and is currently used in Europe as front-line therapy with carboplatin/paclitaxel, followed by maintenance bevacizumab for a total of 15 months.[20-22] IP chemotherapy could also be considered, based on data from the Phase III Gynecologic Oncology Group (GOG) 172 trial showing that *BRCA1*-mutated ovarian cancer was highly sensitive to IP cisplatin/paclitaxel compared with intravenous chemotherapy (median overall survival [OS]: 84.1 versus 47.7 months; p=0.0002).[23] In fact, *BRCA1* mutation was an independent predictor of better survival in patients receiving IP therapy (hazard ratio [HR]: 0.67; p=0.032). Data regarding dose-dense administration of first-line paclitaxel have been conflicting, with one study showing significant benefit in PFS and OS and two similar trials showing no benefit.[24-26] Dose-dense first-line chemotherapy remains a reasonable option, but it is not clear whether this strategy offers a survival benefit.

While many participants indicated that they would recommend PARPi therapy in the front-line setting, Prof Colombo emphasised that this option is not yet approved and would require enrolment in a clinical trial. Several studies evaluating PARPi are underway or planned, including in combination with front-line chemotherapy and/or as maintenance therapy (Table 1). The Phase III SOLO1 trial is comparing the PARPi olaparib versus

placebo as maintenance therapy in patients with *BRCA*-mutated advanced ovarian cancer following front-line chemotherapy;[27] patient accrual is complete and results are eagerly awaited. The ongoing Phase III PAOLA 1 trial randomised patients following first-line chemotherapy to maintenance bevacizumab with either olaparib or placebo.[28] If the SOLO1 and/or PAOLA 1 trials are positive, future selection of front-line therapy for *BRCA*-associated ovarian cancer may include the addition of olaparib as maintenance therapy.

Prof Colombo also asked the participants what second-line therapy they would recommend for platinum-sensitive, *BRCA*-mutated relapse following first-line paclitaxel/carboplatin. The majority selected carboplatin-based chemotherapy followed by olaparib maintenance (44%), although several also felt that a clinical trial of PARPi plus antiangiogenic therapy (22%) or carboplatin/gemcitabine with bevacizumab followed by bevacizumab maintenance therapy (27%) were also reasonable options.

Prof Colombo pointed out that two newly approved options, bevacizumab and olaparib, can now be added to standard second-line, platinum-based therapy. Bevacizumab is approved in combination with carboplatin/gemcitabine as second-line therapy for platinum-sensitive disease based on a significant median PFS benefit over chemotherapy alone in the Phase III OCEANS study (HR: 0.484; p<0.0001).[22,29] There are currently no predictive biomarkers for bevacizumab and it can only be utilised in first relapse. The second option, olaparib, was recently approved in Europe as maintenance therapy for platinum-sensitive, relapsed, *BRCA*-mutated, high-grade serous ovarian cancer based on the results of the Phase II Study 19.[15] Maintenance olaparib showed an impressive improvement in median PFS of 11.2 months compared with 4.3 months for placebo (HR: 0.18; p<0.0001). Olaparib can be given at first or subsequent relapse.

Table 1: Select Phase III clinical trials of PARP inhibitors in ovarian cancer.

PARP inhibitor	Study name	Population	Treatment	Status
Front-line ovarian cancer				
Olaparib	SOLO1	*BRCA1/2*-mutated (+ somatic)	Maintenance	Closed to accrual
Olaparib	PAOLA 1	High-grade serous or endometrioid	Maintenance combination with bevacizumab	Accruing
Veliparib	GOG-3005	High-grade serous carcinoma	Combined with front-line chemotherapy and ± maintenance	Accruing
Niraparib	ENGOT	Adaptive signature for homologous recombination-deficient, high-grade serous carcinoma	Maintenance	Proposed
Recurrent, platinum-sensitive ovarian cancer				
Olaparib	SOLO2	*BRCA1/2*-mutated (+ somatic)	Maintenance	Closed to accrual
Olaparib	SOLO3	*BRCA1/2*-mutated (+ somatic)	Monotherapy versus chemotherapy	Accruing
Niraparib	NOVA	High-grade serous carcinoma or *BRCA1/2*-mutated	Maintenance	Closed to accrual
Rucaparib	ARIEL3	High-grade serous or endometrioid	Maintenance	Accruing
Olaparib	OVM 1403	High-grade serous carcinoma	Olaparib versus olaparib/cediranib versus chemotherapy	Open, not yet accruing
Olaparib	ICON 9	High-grade serous carcinoma	Maintenance olaparib versus olaparib/cediranib	Not yet open

PARP: poly(adenosine diphosphate-ribose) polymerase.
Source: ClinicalTrials.gov

Exciting novel options are also emerging and may change future treatment of platinum-sensitive, relapsed ovarian cancer. For example, the randomised ICON6 trial[30] demonstrated a significant benefit in median OS of 6 months when the antiangiogenic agent cediranib was added to front-line platinum-based chemotherapy and continued as maintenance therapy. This is the first trial to show an OS benefit for antiangiogenic therapy in relapsed ovarian cancer. Another promising strategy is the chemotherapy-free combination of cediranib and olaparib, which recently showed a significant improvement in median PFS of 17.7 months compared with 9.0 months for olaparib alone in a randomised Phase II trial of patients with platinum-sensitive relapsed ovarian cancer (HR: 0.42; p=0.005).[31] Many clinical trials are examining PARPi in platinum-sensitive relapsed ovarian cancer, reflecting the increasing interest in this therapeutic strategy (Table 1).

Prof Colombo summarised by stating that patients with platinum-sensitive, relapsed, *BRCA*-mutated ovarian cancer have several options. Patients can be given gemcitabine/carboplatin with bevacizumab, reserving olaparib for subsequent platinum-sensitive relapse. Alternatively, patients can receive carboplatin-based chemotherapy followed by olaparib maintenance therapy in responders, reserving bevacizumab for subsequent platinum-resistant relapse. Ultimately, participation in clinical trials is always a good option in the front-line and relapsed setting, providing patients access to the best therapies available.

How Should PARP Inhibitors Be Incorporated in Breast Cancer Management?

Professor Andrew Tutt

Prof Tutt opened his presentation with a clinical scenario of a 37-year-old patient with *BRCA1*-mutated TNBC, presenting 8 months after completion of anthracycline and taxane-based adjuvant therapy with asymptomatic recurrence in the liver and supraclavicular lymph nodes. The majority of attendees recommended platinum-based chemotherapy (35%), while 27% chose chemotherapy followed by PARPi maintenance therapy, and 21% chose chemotherapy plus a PARPi. Only 11% and 6% recommended PARPi monotherapy or non-platinum chemotherapy, respectively.

Prof Tutt went on to emphasise the importance of homologous recombination deficiency in the risk of breast cancer. In addition to germline mutations in *BRCA1*, breast tumours themselves can have somatic mutations or promoter methylation of *BRCA1*, as well as mutation of *RAD51C* and other genes involved in regulation of homologous recombination.[32] This results in genomic instability and accumulation of gene rearrangements, insertions, and deletions across the genome, leaving a 'scar' of the homologous recombination defect. Studies are now investigating whether these scars of homologous recombination deficiency, and other biomarkers of homologous recombination defects, may predict potential benefit from platinums and PARPi.

Although platinum chemotherapy is not the current standard of care for breast cancer as a whole, ongoing trials are evaluating platinum-based chemotherapy in specific populations, including *BRCA*-mutated or *BRCA*-like tumours with homologous recombination deficiencies.[33] Prof Tutt described the recently reported results of the Phase III randomised TNT trial comparing carboplatin with docetaxel in patients with advanced TNBC or *BRCA1/2*-mutated breast cancer.[34] While there were no significant differences in the primary endpoint of objective response for carboplatin versus docetaxel in unselected patients with TNBC or in patients with wild-type *BRCA1/2*, those with *BRCA1/2* mutations achieved a doubled objective response rate (ORR) of 68.0% with carboplatin compared with 33.3% with docetaxel (p=0.03). When tumours were classified according to an NGS-based homologous recombination deficiency scar assay, high homologous recombination deficiency scores predicted increased responsiveness to both chemotherapies, not specifically carboplatin. In early-stage TNBC, the Phase II GeparSixto study[35] evaluated non-pegylated liposomal doxorubicin, paclitaxel, and bevacizumab with or without carboplatin. Tumours were tested for *BRCA* mutations and assessed for homologous recombination deficiency scar.[35,36] The addition of carboplatin significantly increased the rate of pathological complete response in patients with TNBC.[35] Similarly to the TNT trial, the presence of a homologous recombination deficiency scar was predictive for higher responsiveness to chemotherapy in both treatment arms and was not specifically predictive for platinum response.[36]

Table 2: Select Phase II/III clinical trials evaluating PARP inhibitors in breast cancer.

PARP inhibitor	Study name	Phase	Population	Treatment	Status
Early-stage breast cancer					
Olaparib	Olympia	III	*BRCA1/2*-mutated TNBC post neoadjuvant or adjuvant chemotherapy	Adjuvant therapy	Accruing
Rucaparib	RIO*	II	Newly diagnosed TNBC or germline *BRCA1/2*-mutated primary breast cancer	Short monotherapy course prior to surgery or neoadjuvant chemotherapy	Accruing
Veliparib	BRIGHTNESS	III	Early-stage TNBC	Neoadjuvant therapy	Accruing
Advanced breast cancer					
Olaparib	OlympiAD	III	*BRCA1/2*-mutated, anthracycline/taxane pretreated ABC	Monotherapy versus physician choice chemotherapy	Accruing
Niraparib	BRAVO	III	*BRCA1/2*-mutated, anthracycline/taxane pretreated ABC	Monotherapy versus physician choice chemotherapy	Accruing
Talazoparib	EMBRACA	III	*BRCA1/2*-mutated, anthracycline/taxane pretreated ABC	Monotherapy versus physician choice chemotherapy	Accruing
Veliparib	M12-895	II	*BRCA1/2*-mutated MBC	Veliparib + temozolomide versus veliparib + carbo/pac versus placebo + carbo/pac	Accruing
Veliparib	NCT02163694	III	*BRCA1/2*-mutated, HER2-negative ABC, first to third-line	Carbo/pac ± veliparib	Accruing

*Rucaparib Window of Opportunity Study. Details available at: http://www.isrctn.com/ISRCTN92154110.
ABC: advanced breast cancer; carbo: carboplatin; MBC: metastatic breast cancer; pac: paclitaxel; PARP: poly(adenosine diphosphate-ribose) polymerase; TNBC: triple-negative breast cancer.
Source: ClinicalTrials.gov

Prof Tutt then pointed out that studies have also demonstrated promising activity for PARPi in patients with *BRCA*-mutated advanced breast cancer, including olaparib, niraparib, and talazoparib.[37] A Phase II trial in *BRCA*-mutated advanced breast cancer demonstrated an ORR of 41% and 22% for two dose levels of olaparib.[38] Interestingly, this efficacy does not appear to extend to the general population of patients with sporadic TNBC, with a Phase II trial enrolling 26 patients with advanced TNBC showing no objective responses to olaparib.[39]

Prof Tutt concluded with a description of ongoing clinical trials evaluating PARPi therapy in breast cancer (Table 2). There is a suite of ongoing Phase III trials comparing the potent PARPi therapies olaparib (OlympiAD), niraparib (BRAVO), and talazoparib (EMBRACA) with standard chemotherapy in patients with *BRCA1/2*-mutated advanced breast cancer resistant to anthracyclines and taxanes.[40-42] PARPis are also being evaluated in combination with non-standard chemotherapeutic agents such as temozolomide or carboplatin/paclitaxel,[43,44] and as neoadjuvant or adjuvant therapy for *BRCA*-mutated early breast cancer.[45-47]

What Are the Implications of PARP Inhibition in Pancreatic and Gastric Cancers?

Professor Eric Van Cutsem

Prof Van Cutsem started his presentation with a clinical scenario, asking participants if they would consider *BRCA* testing for a 57-year-old patient with metastatic pancreatic cancer and a family history of ovarian and breast cancer. Sixty-one percent indicated that they would never or that

they would rarely consider *BRCA* testing for this type of patient, while 20% would test only if they knew there were carriers in the family. Only 20% said that they would always test for *BRCA* mutations.

Prof Van Cutsem then pointed out that pancreatic cancer is a very difficult disease to treat and, despite progress in recent years, there remains considerable room for improvement. DNA damage control is a key signalling pathway involved in pancreatic cancer and represents a novel therapeutic target.[1] Germline *BRCA1/2* mutations are found in approximately 5–7% of patients with unselected pancreatic cancer, with a higher frequency in patients with familial pancreatic cancer and/or an Ashkenazi Jewish heritage.[48] *BRCA2* mutation carriers have a 3.5-fold increased risk of developing pancreatic cancer.[1] Patients with *BRCA* mutations have a median age of diagnosis approximately 10 years younger than the general population, and data suggest a slightly more favourable outcome compared with non-*BRCA*-mutated pancreatic cancer.

Prof Van Cutsem added that while large, randomised data on *BRCA*-mutated pancreatic cancer are lacking, experience at Memorial Sloan-Kettering Cancer Center showed considerable sensitivity to platinum chemotherapy and PARPi in 15 patients with *BRCA1/2*-mutated pancreatic cancer.[49] One patient who received PARPi monotherapy and two of three patients who received PARPi plus chemotherapy achieved a partial response. In addition, five of six patients who received first-line platinum-based chemotherapy responded. A recent Phase II basket trial of olaparib in various advanced cancers also demonstrated promising activity in 23 pretreated patients with *BRCA*-mutated pancreatic cancer, including an ORR of 21.7%, median PFS of 4.6 months, and median OS of 9.8 months.[50] Several ongoing trials are evaluating the role for PARPi in pancreatic cancer, including olaparib, veliparib, and rucaparib in previously untreated or previously treated advanced pancreatic cancer (Table 3).[51-53]

Prof Van Cutsem then discussed the investigation of PARP inhibition in gastric cancer. While the prevalence of *BRCA* mutations in gastric cancer is relatively low, reduced expression of another gene involved in double-strand break repair, ataxia telangiectasia mutated (*ATM*), has been observed in gastric cell lines.[54] ATM expression is low or undetectable in 13–22% of gastric cancer patients, which is associated with shorter survival.[55,56] Interestingly, gastric cell lines with low ATM expression have demonstrated sensitivity to olaparib, creating a rationale for investigation of PARPi.[57]

Table 3: Selected clinical trials of PARP inhibitors in pancreatic cancer.

PARP inhibitor	Study name	Phase	Population	Treatment	Status
Olaparib	POLO	III	*BRCA1/2*-mutated metastatic pancreatic cancer without progression following first-line platinum chemotherapy	Monotherapy maintenance versus placebo	Accruing
Olaparib	NCT01296763	I/II	Advanced pancreatic cancer	Irinotecan, cisplatin, mitomycin C ± olaparib	Closed to accrual
Veliparib	NCT01489865	I/II	Metastatic pancreatic cancer, untreated and previously treated	In combination with modified FOLFOX6	Accruing
Veliparib	NCT01585805	I/II	*BRCA* or *PALB2*-mutated advanced pancreatic cancer, untreated or previously treated	Gemcitabine, cisplatin ± veliparib	Accruing
Rucaparib	RUCAPANC	II	*BRCA1/2*-mutated pancreatic cancer, relapsed disease after 1–2 prior lines of therapy	Monotherapy	Closed to accrual

PARP: poly(adenosine diphosphate-ribose) polymerase.
Source: ClinicalTrials.gov

Prof Van Cutsem described results from a recent Phase II randomised trial comparing paclitaxel/olaparib with paclitaxel/placebo, followed by maintenance olaparib or placebo, in patients with recurrent or metastatic gastric cancer.[54] Patients were tested for ATM expression and the study population was enriched for low or undetectable ATM levels. The addition of olaparib to paclitaxel did not significantly improve median PFS (the primary endpoint). However, olaparib/paclitaxel significantly prolonged median OS in the total patient population (13.1 versus 8.3 months, HR: 0.56; p=0.005) and in the cohort with low ATM expression (not reached versus 8.2 months, HR: 0.35; p=0.002). An ongoing Phase III trial in Asia is further exploring this combination in patients with advanced gastric cancer and disease progression following first-line therapy.[58]

Conclusions

Participants responded to polling questions on PARPi before and after the symposium in order to assess their learning. Attendees demonstrated increased knowledge regarding the role of *BRCA* mutations in prognosis and response to therapy in patients with ovarian cancer, with correct responses increasing from 54% to 80%. Clinicians also demonstrated increased understanding of which types of patients are most likely to have *BRCA* deficiency, including patients with TNBC, high-grade serous ovarian cancer, and pancreatic cancer with a family history. In addition, 90% of participants correctly answered that ATM is a potential predictive biomarker for PARPi sensitivity in gastric cancer, compared with 40% at the beginning of the symposium. Prof Calvert concluded by emphasising that PARPi represent an important innovation in the field of oncology and open the door for other novel therapies inhibiting DNA repair.

Please **click here** to see a webcast of the live meeting.

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CABOZANTINIB VERSUS EVEROLIMUS IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA: RESULTS OF A RANDOMISED PHASE III TRIAL (METEOR)

This late-breaking abstract was presented on 26th September 2015 in Presidential Session I, as part of the European Cancer Congress 2015 in Vienna, Austria

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Disclosure: Toni Choueiri has received advisory board and consultation fees from Pfizer, GSK, Novartis, Merck, Bayer, and Prometheus; and institutional research grants from Exelixis, Pfizer, GSK, Novartis, Merck, Roche, Tracon, and Peloton.
Acknowledgements: Writing assistance was provided by Dr Lucy Smithers, ApotheCom.
Support: The METEOR study was supported by Exelixis, Inc. The views and opinions expressed are those of the authors and not necessarily of Exelixis, Inc.
Citation: EMJ Oncol. 2015;3[2]:59-63.

MEETING SUMMARY

The METEOR trial of cabozantinib versus everolimus in advanced renal cell carcinoma (RCC) was reported by Prof Choueiri at the European Cancer Congress 2015. This presentation follows the publication in the *New England Journal of Medicine* of the METEOR trial back-to-back with the CheckMate 025 trial of nivolumab versus everolimus in the same patient setting. Excitingly, these trials demonstrated, for the first time, significant benefits over the standard of care for heavily pre-treated patients with advanced RCC. Cabozantinib, an oral multi-targeted tyrosine kinase inhibitor (TKI) aims to address the challenge of resistance to targeted therapy with TKIs. While the METEOR trial has not yet reached its final analysis of overall survival (OS), the clear progression-free survival (PFS) benefit, acceptable safety profile, and similar tolerability to other TKIs shown by cabozantinib indicate that this represents a promising new treatment option for second-line or subsequent therapy for patients with advanced RCC.

Cabozantinib Versus Everolimus in Patients with Advanced Renal Cell Carcinoma: Results of a Randomised Phase III Trial (METEOR)

Professor Toni Choueiri

While the 5-year survival rate for early stage RCC is high, it is <10% for patients with advanced or late-stage metastatic RCC, and has not improved significantly despite the availability of targeted agents.[1] Inactivation of the von Hippel–Lindau tumour suppressor protein in clear cell RCC, the predominant subtype in patients with RCC, upregulates vascular endothelial growth factor (VEGF), MET, and AXL tyrosine kinase signalling pathways, and drugs targeting the VEGF pathway are standard therapies in RCC.[2] However, resistance to targeted therapy occurs in most patients and has been associated with increased MET and AXL expression.[2] This represents a major challenge in improving medical outcomes for patients with RCC. While second-line treatment with the mammalian target of rapamycin (mTOR) inhibitor everolimus is associated with longer PFS, no significant OS benefit has been demonstrated.[3] Cabozantinib is an oral, small molecule inhibitor of multiple kinases, including MET, AXL, and VEGF receptors (VEGFR), and has demonstrated clinical activity in heavily pre-treated RCC patients.[4,5] The international, open-label Phase III METEOR trial was therefore designed to evaluate the efficacy and safety of cabozantinib compared with everolimus in patients with advanced RCC who had progressed after VEGF TKI therapy.[6]

Patients with advanced or metastatic clear cell RCC and measurable disease, who had received prior treatment with at least one VEGFR TKI and had progressed on therapy or within the last 6 months of the most recent dose of VEGFR TKI, were randomised 1:1 to receive 60 mg cabozantinib or 10 mg everolimus orally once daily. There was no limit to the number of prior therapies, which could include cytokines and anti-PD-1/PD-L1 monoclonal antibodies, but not an mTOR inhibitor, and patients with brain metastases were eligible if they were adequately treated and stable. Patients were stratified by Memorial Sloan-Kettering Cancer Center (MSKCC) risk group[7] and number of prior VEGFR TKI therapies. Treatment was continued until loss of clinical benefit or intolerable toxicity. Crossover between treatment groups was not allowed.

The METEOR 'trial within a trial' design allowed for appropriate statistical power for both the primary PFS endpoint and the secondary OS endpoint while avoiding over-representation of patients with rapidly progressing disease for the primary endpoint. The first 375 patients enrolled were evaluated for PFS, with 259 events estimated to be needed to provide 90% power to detect a hazard ratio (HR) of 0.667. For the OS endpoint, 408 events among 650 patients were estimated to be required to provide 80% power for detecting an HR of 0.75. An interim analysis of OS at the time of the primary endpoint analysis was planned. PFS and objective response rate (ORR) endpoints were assessed by the independent radiology review committee.

Of the 658 patients who were randomised, 330 received cabozantinib and 328 received everolimus, of whom the first 187 and 188, respectively, formed the PFS analysis population. By the primary endpoint analysis cut-off point, 40% of patients in the cabozantinib arm were still receiving treatment compared with 21% of patients in the everolimus arm. Patient characteristics were balanced between the treatment arms, with the majority of patients having a good performance status (68% of cabozantinib-treated patients and 66% of everolimus-treated patients had an Eastern Cooperative Oncology Group status score of 0) and being in a favourable or intermediate risk group according to MSKCC criteria. The majority of patients had received one prior VEGFR TKI (71% of cabozantinib-treated patients and 70% of everolimus-treated patients), with sunitinib the most common VEGFR TKI received (64% of cabozantinib-treated patients and 62% of everolimus-treated patients).

The primary endpoint of the trial was met, with a significant PFS benefit for cabozantinib compared with everolimus (Figure 1). The estimated median PFS was 7.4 months (95% confidence interval [CI]: 5.6–9.1) for cabozantinib-treated patients and 3.8 months (95% CI: 3.7–5.4) for everolimus-treated patients. The rate of disease progression or death was 42% lower with cabozantinib than with everolimus (HR for progression or death: 0.58, 95% CI: 0.45–0.75; p<0.001).

Analysis of the prespecified subgroups showed a PFS benefit regardless of the number of prior VEGF TKI treatments or MSKCC risk group. In a *post hoc* analysis of patients who had received sunitinib as their only prior VEGF TKI, the benefit of cabozantinib was even greater, with an estimated median PFS of 9.1 months (95% CI: 5.6–11.2) compared with 3.7 months (95% CI: 1.9–4.2) for everolimus (HR: 0.41, 95% CI: 0.28–0.61).

ORR, as assessed by the independent radiology review committee, was significantly higher with cabozantinib than with everolimus (21% versus 5%, respectively; p<0.001; Table 1). Although no complete responses were seen, more patients showed a partial response with cabozantinib than with everolimus, and fewer patients treated with cabozantinib had progressive disease as best response (14% versus 27% of those treated with everolimus). This highlights a low rate of patients with disease that is primarily refractory to this agent. The high level of disease control is also shown by the greater number of patients treated with cabozantinib who experienced tumour reduction as their best target lesion change from baseline (84% versus 59% of those treated with everolimus).

At the prespecified interim analysis, with a minimum follow-up of only 6 months after the last patient was enrolled, 49.5% of the events required for final analysis had occurred in the OS population. While a trend towards longer OS with cabozantinib was observed (HR: 0.67, 95% CI: 0.51–0.89; p=0.005), the interim boundary to reach significance (p≤0.0019) was not reached (Figure 2). Survival follow-up is continuing to the planned final analysis after 408 deaths occur.

Patients had a longer median exposure to cabozantinib (7.6 months, range: 0.3–20.5) than to everolimus (4.4 months, range: 0.21–18.9).

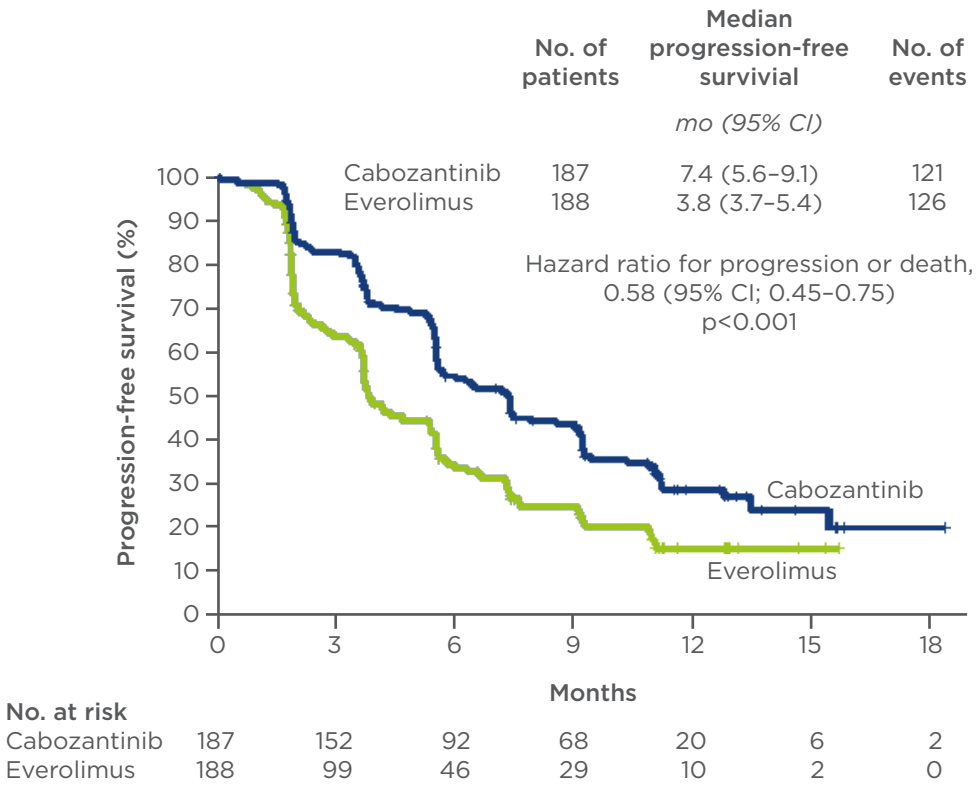

Figure 1: Kaplan–Meier estimate of progression-free survival.[6]
mo: months; CI: confidence interval.

Table 1: Tumour response in the progression-free survival population.[6]

	Cabozantinib (n=187)	Everolimus (n=188)
Objective response rate, %	21	5
95% confidence interval	16–28	2–9
p value	<0.001*	
Best overall response, %		
Complete response	0	0
Partial response	21	5
Stable disease	62	62
Progressive disease	14	27
Not evaluable/missing	3	6

*Cochran–Mantel–Haenszel test.
The objective response rate was consistent in patients who received sunitinib as their only prior vascular endothelial growth factor tyrosine kinase inhibitor.

Dose reductions to adjust to an individual patient's tolerance occurred more frequently with cabozantinib (60% of patients compared with 25% of everolimus-treated patients), similar to other VEGFR TKIs. The rates of discontinuation due to adverse events were similar for cabozantinib and everolimus (9% and 10%, respectively). The safety profile of cabozantinib in this trial was similar to that observed for other TKIs in this patient population, and distinct from that of everolimus (Table 2).[6] Diarrhoea, fatigue, palmar-plantar erythrodysesthesia, and hypertension were the most common Grade 3/4 adverse events with cabozantinib, compared with fatigue, anaemia, and hyperglycaemia with everolimus. The rate of serious adverse events was similar in both groups (40% for cabozantinib and 43% for everolimus).

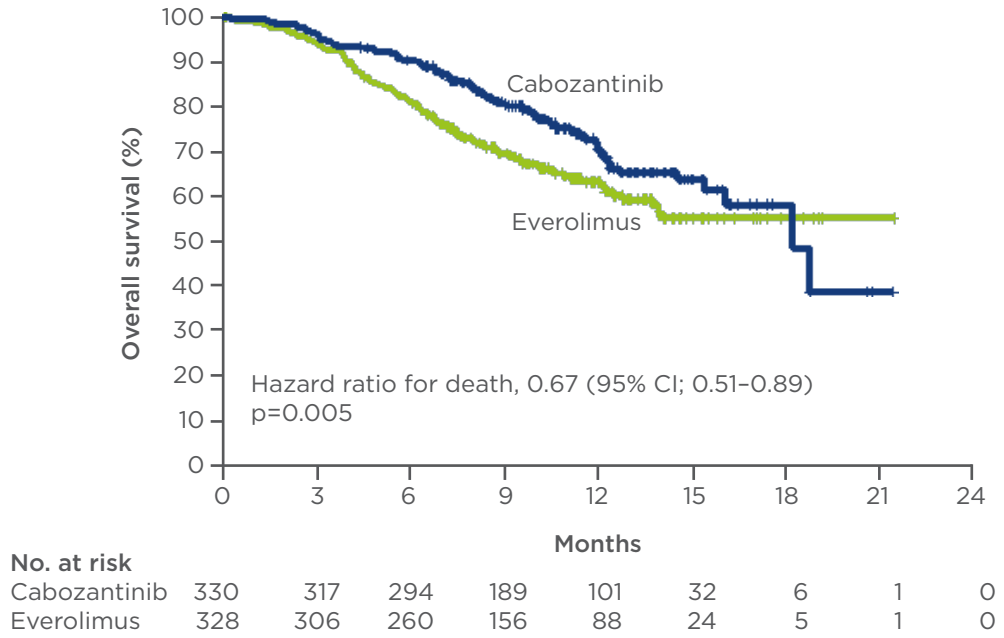

Figure 2: Kaplan-Meier estimate of overall survival at interim analysis.[6]
CI: confidence interval.

Table 2: All-cause adverse events.[6]

Preferred term, %	Cabozantinib (n=331)		Everolimus (n=322)	
	All grades	Grade 3/4	All grades	Grade 3/4
Any adverse event*	100	68	>99	58
Diarrhoea	74	11	27	2
Fatigue	56	9	46	7
Nausea	50	4	28	<1
Decreased appetite	46	2	34	<1
PPE syndrome	42	8	6	<1
Hypertension	37	15	7	3
Vomiting	32	2	14	<1
Weight decreased	31	2	12	0
Constipation	25	<1	19	<1
Anaemia	17	5	38	16
Cough	18	<1	33	<1
Dyspnoea	19	3	28	4
Rash	15	<1	28	<1
Events of interest				
Hyperglycaemia	5	<1	19	5
Pneumonitis	0	0	10	2
Gastrointestinal perforation	<1	<1	<1	<1
Fistula	<1	<1	0	0

*Events reported in at least 25% of patients in either study group.
PPE: palmar-plantar erythrodysesthesia.

In conclusion, METEOR met its primary endpoint, with cabozantinib nearly doubling median PFS compared with everolimus in patients with advanced RCC previously treated with VEGFR TKI therapy, which is a significant improvement over the current standard of care. Cabozantinib improved ORR, and the interim analysis showed a strong trend for OS favouring cabozantinib. The safety profile of cabozantinib is similar to previous experience in this patient population,[4] and tolerability is similar to that of other TKIs in this patient population. Cabozantinib represents a potential new treatment option for second-line or subsequent therapy for advanced RCC.

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PERSPECTIVES IN MANAGEMENT OF EGFR-TKI RESISTANCE

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Patients with epidermal growth factor receptor (EGFR)-mutated (*EGFR*$^{mut+}$) non-small-cell lung cancer (NSCLC) benefit more from first-line treatment with EGFR tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib, erlotinib, and afatinib, than from standard chemotherapy.[1-4] Despite an initial dramatic response, however, virtually all *EGFR*$^{mut+}$ NSCLCs progress due to acquired resistance. Among the various mechanisms responsible for acquired resistance, the onset of a secondary T790M mutation represents the most frequent event and occurs in approximately 60% of cases.[5,6] For these reasons, investigations have focussed on the potential efficacy of a new class of drugs able to irreversibly inhibit mutant EGFRs, in particular those with the T790M mutation, with minimal or no activity against the wild-type EGFR.

Rociletinib is an oral, irreversible, potent inhibitor of activating EGFR mutations, as well as the T790M mutation, with no activity against the wild-type EGFR. A large Phase I/II study evaluated the efficacy of rociletinib in *EGFR*$^{mut+}$ NSCLC patients who failed treatment with EGFR-TKIs.[7] Among the 46 patients with confirmed T790M-positive tumours, the response rate (RR) was 59% and median progression-free survival (PFS) was 13.1 months. Interestingly, among the 17 T790M-negative patients, the RR was 29% and median PFS was 5.6 months. Of these 17 patients, 12 had been receiving an EGFR inhibitor immediately before rociletinib, which suggests that the tumour response was related to drug efficacy and not simply to tumour re-population with clones sensitive to EGFR-TKIs. In a further analysis of this trial, RR was identical between patients in whom the presence of the T790M mutation was detected in tumour tissue or in circulating DNA, suggesting the possibility of using a simple blood test instead of a tumour re-biopsy for assessing T790M status.[8]

AZD9291 is the other mutant-specific EGFR-TKI currently under investigation. The RR was 51% in a Phase I study conducted in 253 patients with advanced NSCLC refractory to first or second-generation EGFR-TKIs. Importantly, RRs were 61% and 21% in T790M-positive and T790M-negative cases, respectively. Furthermore, in the few T790M-negative patients responding to the drug, chemotherapy was the last treatment before starting AZD9291. Overall, these data indicate that the drug has specific activity in the T790M-positive population.[9]

Unfortunately, acquired resistance to rociletinib and AZD9291 therapy also occurs and available data suggest that the mechanisms of resistance to the two agents are not identical.[10-12] Three major drug resistance mutations were detected in the *EGFR* gene of patients progressing to rociletinib or AZD9291: L718Q, L844V, and C797S. Importantly, the C797S mutation only occurs in AZD9291-resistant tumours, whereas the other two mutations are observed in rociletinib-resistant tumours. Remarkably, preclinical models harbouring an EGFR-activating mutation alone (exon 19 deletions or L858R point mutation) and developing resistance through C797S remain sensitive to gefitinib and afatinib. The immediate clinical consequence is that the latter EGFR-TKI could be offered to patients developing resistance after initial therapy with AZD9291. In contrast, models harbouring three *EGFR* mutations (exon 19 deletions or L858R plus T790M plus C797S) were resistant to all currently available EGFR-TKIs. Therefore, identification of mechanisms of resistance to EGFR-TKIs is of crucial relevance for defining which agent should be used first and for determining the optimal sequencing of treatment.

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NOVEL SYSTEMIC THERAPY APPROACHES TO BRAIN METASTASES: LUNG

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Brain metastases are common in non-small-cell lung cancer (NSCLC), especially in adenocarcinomas. Historical series have demonstrated rates of brain metastases of around 40%,[1] and unbiased estimates from the control arms of the prophylactic cranial irradiation trials have demonstrated rates of 13–27% in patients with radically treatable NSCLC.[2] However, patients with brain metastases from NSCLC do not all behave similarly. Several classification systems have been proposed for patients with NSCLC brain metastases, including the recursive partitioning analysis classification and, more recently, the lung cancer-specific graded prognostic assessment scoring criteria.[3] Brain metastases arise through the mobilisation of NSCLC cells through the capillaries, lodging there due to size restriction, and then extravasating into the brain parenchyma, which requires the activation of a number of oncogenes and non-oncogenic molecular pathways. Metastases then grow along vasculature either through vessel co-option or through neo-angiogenesis.[4]

Challenges to drug therapy for NSCLC brain metastases exist primarily due to the existence of the blood–brain and the blood–tumour barriers,[4] which involve a number of cellular and molecular factors that prevent or minimise drug transfer, such as tight junctions and drug efflux pumps. This is problematic because the traditional therapy for NSCLC brain metastases, whole-brain radiotherapy, has recently been proven ineffectual in the randomised QUARTZ trial.[5]

Therapeutic strategies for management of brain metastases can be contingent on a molecular agnostic approach. Studies have demonstrated that VEGF-A is critical for the establishment of brain metastases and, in preclinical models, bevacizumab results in long-term dormancy of micrometastases.[6] The efficacy of bevacizumab in NSCLC has not been unequivocally proven. The PASSPORT trial has established that it is safe to administer bevacizumab to NSCLC patients with brain metastases,[7] and the BRAIN trial has demonstrated an intracranial objective response rate (ORR) of 61.2% for the combination bevacizumab–carboplatin–paclitaxel, which is higher than would be expected from chemotherapy alone.[8]

In patients with oncogene-addicted NSCLC, targeting the activated oncogene can result in excellent intracranial responses. For example, erlotinib displays little activity in EGFR wild-type NSCLC,[9] but intracranial responses are often reported and a median intracranial survival without progression of 12.3 months can be observed in EGFR-mutant NSCLC.[10] Robust data from the LUX3 trial have demonstrated a similar hazard ratio for progression-free survival of 0.52 for afatinib (versus chemotherapy) in patients with brain metastases compared with those without. Case reports and one large series have demonstrated the intracranial activity of pulsed-dose erlotinib in

patients with brain/leptomeningeal disease.[11] Brain metastases are particularly problematic in patients with anaplastic lymphoma kinase fusions. Pooled analysis of the PROFILE 1005 and 1007 trials has demonstrated intracranial responses, more so after whole-brain radiotherapy.[12] Whilst data are limited to small numbers, ceritinib has demonstrated an intracranial disease response rate of up to 79% in the ASCEND-1 study, alectinib has demonstrated a CNS ORR of up to 57% in Phase II data, and brigantinib has demonstrated 53% in a Phase I study.

Immune checkpoint inhibition may play a role in NSCLC patients with brain metastases, given lymphocyte trafficking within the brain. In a trial of ipilimumab for the treatment of melanoma with small metastases not irradiated, with or without steroid use, responses were predominantly observed in the steroid-untreated cohort,[13] which warns of the potential negative regulatory role of steroid use. In NSCLC, atezolizumab has been shown to be safe in NSCLC patients with treated, stable brain metastases,[14] and a Phase II trial of pembrolizumab in patients with small NSCLC brain metastases not on steroids has reported a preliminary ORR of 33%.[15]

In conclusion, systemic therapy can be active for selected NSCLC patients with brain metastases. Bevacizumab is safe and may have activity. Kinase inhibitors against active oncogenes are highly active, and immune checkpoint inhibitors seem safe and active in small-volume metastases without steroid dependency.

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A NOVEL LOOK AT CHRONIC LYMPHOCYTIC LEUKAEMIA – FIRST-LINE TREATMENT

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Chronic lymphocytic leukaemia (CLL) is the most common haematologic malignancy in the Western Hemisphere. The management of CLL is determined by activity of the disease, staging, age, and comorbidities. CLL is typically sensitive to a variety of cytotoxic drugs, but the disease itself is considered incurable. Patients with advanced disease are treated at diagnosis, whereas others, regardless of their prognostic indicators, are offered treatment only at disease progression. Given the heterogeneity of the clinical manifestations and

prognosis of CLL, patients are likely to benefit from a personalised therapeutic approach.

Although patients with symptomatic and/or progressive disease should be treated, randomised studies and a meta-analysis indicate that early initiation of chemotherapy based on alkylating agents does not show benefit in CLL, and may in fact increase mortality. Over the past few years, more effective therapies have emerged in the treatment of CLL, especially combinations of anti-CD20 monoclonal antibodies (mAbs) with purine analogs, bendamustine, or chlorambucil.[1] These more intensive treatments induce higher response rates, longer response duration, and longer survival in younger, fitter patients. The approval of rituximab-based immunochemotherapy can be viewed as a substantial therapeutic advance in CLL. A large Phase III randomised trial demonstrated that rituximab combined with fludarabine and cyclophosphamide (RFC) increased overall response and complete response rates, and prolonged progression-free survival (PFS) and overall survival (OS) compared with fludarabine and cyclophosphamide (FC) in previously untreated patients who were younger and fitter.[2] On the basis of these results, RFC has become the first-line treatment of choice in younger CLL patients. However, chlorambucil with anti-CD20 mAbs is currently the first-line treatment for progressive CLL in frail, elderly, and unfit patients.

The results of a large randomised Phase III trial on patients with comorbidities have recently been reported. Three first-line chemoimmunotherapy regimes were tested in this trial: combined obinutuzumab and chlorambucil; combined rituximab and chlorambucil; and chlorambucil monotherapy (CLL11).[3] Patients with previously untreated CLL and a score higher than 6 on the Cumulative Illness Rating Scale or an estimated creatinine clearance of 30–69 mL per minute were included (n=781). Treatment with obinutuzumab plus chlorambucil or rituximab plus chlorambucil increased response rates and prolonged PFS compared with chlorambucil monotherapy. Median PFS was 26.7 months with obinutuzumab–chlorambucil, 15.2 months for rituximab–chlorambucil, and 11.1 months for chlorambucil alone (p<0.001). In addition, patients treated with obinutuzumab–chlorambucil demonstrated longer OS than chlorambucil alone (p=0.002). The U.S. FDA and EMA have approved obinutuzumab for use with chlorambucil in patients with previously untreated CLL. In a recent randomised trial (COMPLEMENT 1),[4] ofatumumab plus chlorambucil therapy was also compared with chlorambucil alone in patients with CLL who required therapy and were considered inappropriate for fludarabine-based therapy, due to advanced age and/or comorbidities. The results of this study indicate that ofatumumab plus chlorambucil is superior to chlorambucil alone in this patient population.[4]

Patients with 17p/*TP53* deletions have a poor prognosis in first-line chemotherapy regimens, typically demonstrating a median OS of <36 months. These patients are usually refractory to conventional chemotherapy with fludarabine, FC, and even RFC immunotherapy. However, the use of B cell receptor (BCR) signal transduction inhibitors ibrutinib and idelalisib represents a promising new strategy for targeted CLL treatment, including patients with 17p/*TP53* deletions.[5-7] These drugs are more promising for this patient population and should be used up front. Ibrutinib and idelalisib are available in oral preparations and are administered as continuous treatment. Recent clinical studies have demonstrated that ibrutinib and idelalisib are well tolerated and have an excellent safety profile, both in patients with refractory CLL and in previously-untreated patients. Despite the significant progress made in recent years, the therapies available currently are only partially effective in CLL patients, exposing an obvious need to develop better strategies and new, more specific, and more active drugs.

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IMMUNOTHERAPY IN NSCLC 2015 – ANY PLACE FOR VACCINATION STRATEGIES?

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Cancer immunotherapy, in a broad sense, is any interaction with the immune system to treat cancer.

One approach is antigen-specific immunotherapy, which aims to specifically prime the immune system to recognise a tumour as foreign, and thereby generate specific antibodies and/or cytotoxic T cells. This is 'therapeutic cancer vaccination'. Examples include: the MAGE-A3 vaccine, which has been studied in resected early stage, non-small-cell lung cancer (NSCLC); the BLP-25 vaccine in locally advanced NSCLC after chemoradiotherapy, e.g. belagenpumatucel-L; and the TG4010 vaccine in advanced-stage NSCLC (Table 1).

Table 1: Results of randomised controlled trials (RCTs) on vaccines in NSCLC.

Compound	Trial design	N	Study population	Treatment arms	Primary endpoint	Other endpoints
Tecemotide	Phase III RCT (START)	1,513	Stage III NSCLC after chemoradiation therapy	LBLP-25 vaccine versus placebo	OS: HR 0.88; 95% CI: 0.75–1.03; p=0.123	Subgroup analysis: concurrent chemoradiation: HR 0.78; 95% CI: 0.64–0.95; p=0.016
TG4010	Phase II B RCT (TIME)	221	Untreated patients with Stage IV MUC1-positive NSCLC	Chemotherapy with TG4010 vaccine versus chemotherapy with placebo	TrPAL biomarker: probability of HR<1 in patients with normal TrPAL levels treated with TG4010 >95%: achieved	PFS: HR 0.78; 95% CI: 0.55–1.10. PFS in non-squamous NSCLC: HR 0.71 [0.51-0.97]
	Phase III RCT (TIME)	800	Untreated patients with Stage IV non-squamous MUC1-positive NSCLC		OS (Phase III part ongoing)	Safety, response rate, duration of response
MAGE-A3	Phase III RCT (MAGRIT)	2,270	Completely resected MAGE-A3 positive Stage IB-IIIA NSCLC	MAGE-A3 vaccine versus placebo	DFS: HR 1.02; 95% CI: 0.89–1.18; p=0.738	Prospective validation of predictive gene signature not feasible

START: stimulating targeted antigenic responses to NSCLC trial; NSCLC: non-small-cell lung cancer; OS: overall survival; HR: hazard ratio; CI: confidence interval; TrPAL: triple positive activated lymphocytes; PFS: progression-free survival; DFS: disease-free survival; MAGRIT: MAGE-A3 as Adjuvant Non-Small Cell LunG CanceR ImmunoTherapy.

Mucin MUC1 expression is altered, mainly by aberrant glycosylation, in many cancer types including NSCLC. The tecemotide (L-BLP25) vaccine comprises of tandemly repeated MUC1-peptides in a liposomal formulation. The Stimulating Targeted Antigenic Responses to NSCLC Trial (START) was a Phase III, double-blind, randomised controlled trial (RCT) that compared maintenance therapy with tecemotide (n=829) or placebo (n=410) in patients with unresectable Stage III NSCLC, who did not show disease progression after sequential or concurrent chemoradiotherapy.[1] The primary endpoint – overall survival (OS) – was not significantly different between the vaccine and placebo group (25.6 versus 22.3 months). However, pre-planned subgroup analysis showed that the patients treated with concurrent chemoradiotherapy (n=829) had a 10.2-month improvement in OS (30.8 versus 20.6 months, adjusted hazard ratio [HR] 0.78, p=0.016). The consequent trial was START 2, a similar large RCT in patients who completed concurrent chemoradiotherapy for unresectable Stage III NSCLC (NCT02049151). However, this RCT and further development of tecemotide was abandoned after disappointing results were achieved in a smaller trial in Japanese patients with Stage III NSCLC and concurrent chemoradiotherapy.

TG4010 is a vaccine based on a recombinant viral vector (attenuated strain of vaccinia virus), expressing both the tumour-associated antigen MUC1 and interleukin-2. This vaccine was evaluated in the Phase IIB/III RCT TIME trial (NCT01383148). This double-blind, placebo-controlled trial evaluated standard first-line chemotherapy with or without TG4010 in MUC1-positive Stage IV NSCLC patients. In the Phase IIB part, the predictive value of activated NKs (TrPAL: triple positive activated lymphocytes) was evaluated based on a progression-free survival (PFS) endpoint, and reported in an interim report at the 2014 ESMO meeting.[2] PFS was in favour of the vaccine arm. In subgroup analyses, the effect was more pronounced in patients with non-squamous NSCLC (HR 0.71, 95% confidence interval [CI] 0.51-0.97) than with squamous histology. Therefore, a decision was made to continue the Phase III part of the trial in non-squamous NSCLC only, with OS as the primary endpoint.

The MAGE-A3 protein is totally tumour-specific and present in about 35% of early stage NSCLC. In the hypothesis-generating double-blind, randomised, placebo-controlled Phase II study, 182 patients with completely resected MAGE-A3-positive Stage IB-II NSCLC received recombinant MAGE-A3 protein combined with an immunostimulant (13 doses over 27 months) or placebo.[3] No significant toxicity was observed. There was a 24% (non-significant) improvement in disease-free survival (DFS, HR: 0.76; 95% CI: 0.48–1.21). The ensuing large Phase III study, MAGE-A3 as Adjuvant Non-Small Cell LunG CanceR ImmunoTherapy (MAGRIT), was reported at the ESMO 2014 meeting.[4] MAGE-A3 positive patients with completely resected Stage IB–II–IIIA NSCLC and adjuvant chemotherapy as clinically indicated were randomly assigned to receive MAGE-A3 vaccine or placebo (ratio 2:1). Almost 14,000 surgical patients were screened: 4,210 patients were MAGE-A3 positive (33%) and 2,312 patients were randomised. The median DFS (primary endpoint) was slightly better with MAGE-A3 (60.5 versus 57.9 months), but the difference was unfortunately not significant (HR: 1.02, 95% CI: 0.89–1.18, p=0.74). No subgroups with potential benefit could be identified. Based on this disappointing result, further development of the MAGE-A3 vaccine in NSCLC has been abandoned.

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THE SENTINEL LYMPH NODE IN BREAST CANCER: A STATE-OF-THE-ART CONSOLIDATED TECHNIQUE

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Breast cancer is the second most commonly diagnosed cancer worldwide and a major public health concern, with current issues mainly related to preserving quality of life with the most appropriate treatment. The sentinel lymph node biopsy (SLNB) is part of this approach and a safe and effective alternative to the gold standard axillary lymph node dissection (ALND)[1-3] in early stage breast cancer (ESBC). The SLNB has been shown to reduce side effects in arm morbidity and deliver a better quality of life, especially in the surgical management.[4]

The indications of SLNB have slightly changed since the 2005 recommendations of the American Society of Clinical Oncology (ASCO),[2] with current uses of SLNB according to the revised guidelines in 2014[5] for patients with ESBC, multicentric tumours, and ductal carcinoma *in situ* with mastectomy.

There are currently no recommendations for the use of a specific colloid between the ^{99m}Tc-sulphur colloid and ^{99m}Tc-nanocolloid, which are passively drained through the lymphatic system similar to the metastatic process. Some new alternative techniques such as ^{99m}Tc-tilmanocept, which may reduce the number of nodes necessary for accurate axillary staging,[6] and superparamagnetic iron oxide, which is one of the promising non-irradiating alternative techniques, are now available.[7] The use of blue dye injection during surgery appears to be strongly recommended in order to decrease the false negative rate (FNR) and increase sensitivity.[8]

All injection approaches (peritumoural, subdermal, periareolar, intradermal, subareolar) either have satisfactory SLNB detection rates or can be used complementarily, even if the peritumoural injection seems to be the most effective technique according to the last European Association of Nuclear Medicine guidelines,[9] but nevertheless remain difficult to perform for non-palpable tumours. The uncommon drainage to the internal mammary chain reinforces the interest of using pre-operative lymphoscintigraphy (Figure 1) and SPECT/CT imaging (Figure 2).

Figure 1: Anterior and lateral view of a breast lymphoscintigraphy. Axillary drainage with sentinel lymph node and second echelon nodes.

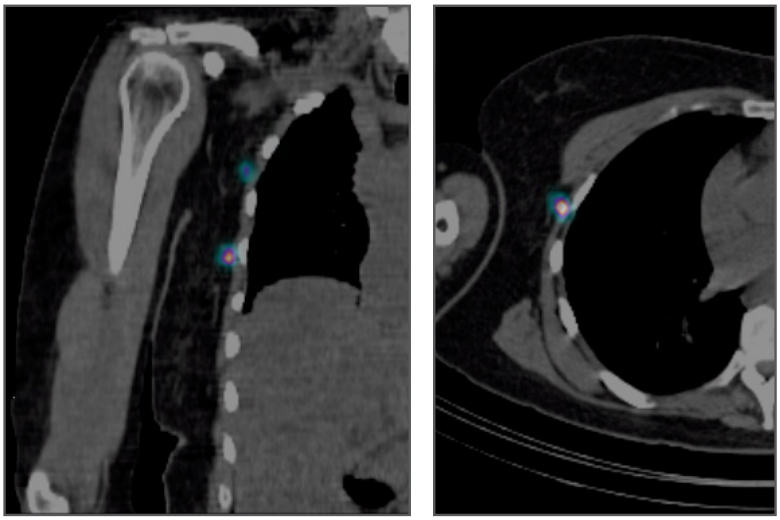

Figure 2: Localisation of axillary draining nodes with SPECT-CT.

Even if SLNB is a well-known technique, many controversies concerning SLNB and ALND are currently being debated. Randomised control trials show that performing a systematic ALND for patients with positive sentinel lymph nodes could be overridden in women with ESBC with only one or two positive sentinel nodes.[4,10] ALND could also be omitted for patients with a positive sentinel lymph node if they underwent systemic therapy and radiation therapy.[11] Conversely, individual studies still show that women with SLNB micrometastasis who did not perform ALND have an increased risk of a 5-year recurrence rate, even if the impact of micrometastasis in sentinel nodes on survival rates remains unclear.[12]

The other controversial aspects are the accuracy of SLNB after neoadjuvant chemotherapy, which can lead to an increased risk of FNRs, the utility to perform internal mammary node dissection,[12] and the different ways to perform SLNB, with or without preoperative lymphoscintigraphy and dual mapping (radioisotope and blue dye).[1,8]

Compared with the historical FNR of 5% in SLNBs, the observed increase of up to 16.7%[2] reminds us how important it is to continue to enhance and standardise this technique.

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ADJUVANT RADIOTHERAPY IN RECTAL CANCER

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According to current guidelines, the standard treatment for locally advanced rectal cancer patients is preoperative (chemo)radiotherapy followed by total mesorectal excision (TME).[1-6] Several trials have compared preoperative with postoperative chemoradiotherapy. In the CAO/ARO/AIO-94 trial,[5] patients with locally advanced rectal cancer were randomly assigned to receive either preoperative chemoradiotherapy (50.4 Gy in fractions of 1.8 Gy with a continuous infusion of 5-fluorouracil [5-FU] during the first and fifth week of radiotherapy) or postoperative chemoradiotherapy (50.4 Gy in fractions of 1.8 Gy with a 5.4 Gy boost and a continuous infusion of 5-FU during the first and fifth week of radiotherapy). Although 5-year overall survival rates were not different (76% versus 74% for preoperative and postoperative chemoradiotherapy, respectively; p=0.80), preoperative chemoradiotherapy was beneficial in terms of 5-year local relapse rate (6% versus 13%; p=0.006), Grade 3–4 acute toxicity (27% versus 40%; p=0.001), and long-term toxicity (14% versus 24%; p=0.01). Long-term follow-up results demonstrated a persisting significant improvement of pre versus postoperative chemoradiotherapy in terms of local control (10-year local relapse rate: 7.1% versus 10.1%; p=0.048). There were no significant differences in terms of overall survival (59.6% versus 59.9%; p=0.85) or incidence of distant metastases (29.8% versus 29.6%; p=0.90). The NSABP R-03 trial[6] found that preoperative chemoradiotherapy significantly improved the rate of 5-year disease-free survival compared with postoperative chemoradiotherapy (67.4% versus 53.4%; p=0.011) and showed a trend towards an improved overall survival (74.5% versus 65.6%; p=0.065).[6] These trials demonstrate that preoperative chemoradiotherapy reduces local recurrence rates, has less acute and long-term toxicity, and enables a higher rate of sphincter-saving surgery by downsizing, while distant relapse and overall survival rates are similar.

The ESMO guidelines[7] advocate postoperative chemoradiation and adjuvant chemotherapy in patients who received no preoperative chemoradiotherapy in cases of: involved circumferential resection margins, perforation of the tumour area, and in other cases with a high risk of local recurrence (≥pT3b and/or N+). Postoperative chemoradiation is also indicated in the case of refusal or no susceptibility for required radical surgery after endorectal local excision (pT1 tumours with adverse factors such as involved margins, poor differentiation, sm3 and lymphovascular invasion; or pT2 tumours). Although postoperative (chemo)radiotherapy has the advantage of a better patient selection on the basis of pathological staging, the increased toxicity (small bowel, perineal scar), poor compliance, and higher local recurrence rates make preoperative chemoradiotherapy the preferred treatment.

Conclusions

- Preoperative (chemo)radiotherapy followed by TME is the standard treatment for locally advanced rectal cancer
- The choice of radiotherapy or chemoradiotherapy depends on the tumour and patient characteristics
- Postoperative chemoradiotherapy is indicated for patients who did not receive preoperative chemoradiotherapy and with adverse features on pathology, such as perforation or involvement of the circumferential resection margin
- Postoperative chemoradiotherapy is associated with higher local recurrence rates and an increased toxicity compared with preoperative chemoradiotherapy

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GENETIC TRAITS FOR MYELOID MALIGNANCIES: CURRENT CONCEPTS FOR FAMILIAL AML

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Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) are related heterogeneous haematopoietic stem cell clonal disorders characterised by defective haematopoiesis and premature mortality in many patients. The majority of MDS and AML cases are sporadic, but there are also rare cases in which two or more affected individuals are found within the same family: familial myelodysplasia and leukaemia. These disorders arise as isolated malignancies, or as part of a wider syndrome.[1] With recent advances in sequencing technologies, mutations in >10 genes, corresponding to between 50–70% of familial cases have now been uncovered. Collectively, familial cases represent a high-risk group of patients who require unique follow-up and treatment strategies to achieve cancer risk reduction, prevention, and best management.

Our interest in this field began over 10 years ago when two siblings presented with AML at St Bartholomew's Hospital, London, UK.[2] Inherited N-terminal mutations were detected in the transcription factor CCAAT/enhancer binding protein-alpha (*CEBPA*) in three affected members of the family, with the onset of overt disease accompanied by the acquisition of an additional mutation within the C-terminal part of the protein. Analysis from a recent international collaboration of 24 affected individuals from 10 families[3] revealed that AML with germline *CEBPA* mutation is associated with a favourable 10-year overall survival rate, approaching 67%. The median age of onset is 24.5 years (range: 2–46 years), with clinical outcomes resembling sporadic AML harbouring double *CEBPA* mutations. The cumulative incidence of relapse in our familial series was 56% at 10 years, but patients responded well to secondary therapies with a long median survival post-relapse. While such favourable outcomes may reflect an earlier age of onset, the observation that somatic C-terminal mutations are unstable throughout the disease course, with the occurrence of novel mutations at relapse, suggests that patients are cured of their initial disease but predisposed to new episodes of leukaemia. In light of these findings, we advocate the introduction of germline testing in *CEBPA*-mutated AML in patients <50 years of age to identify novel familial cases, where genetic counselling of patients and screening of all potential sibling donors is essential to prepare for treatment escalation and identify asymptomatic mutation carriers at risk of disease.

CEBPA represents one of the best characterised genetic loci predisposing to familial leukaemia. The motivation of the entire research community working on inherited leukaemia is to improve patient care by establishing a pipeline that incorporates input from clinicians, diagnostic services, genetic counsellors, and researchers

across all patients. There are challenges ahead as the identification of patients in this particular group is hindered by the lack of available family history, wide variation in the age of onset, disease phenotype, and penetrance of mutations. This is compounded by a paucity of clinical guidelines and the absence of customised diagnostics to meet the clinical need of these patients and their families.

Going forward, sequencing advances are accelerating efforts to elucidate the genetic landscape of familial leukaemia, offering an opportunity to identify novel germline mutations and decipher the intra and inter-familial disease heterogeneity and evolution. Overall the success of developing an effective familial leukaemia roadmap will be dependent on engaging with the entire haematology community, and creating a global network to combine efforts and share individual experiences and data.

Acknowledgments

Cancer Research UK (CRUK) and Bloodwise Programme award 14032.

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TARGETING OSTEOSARCOMA: WHAT IS THE DIFFERENCE BETWEEN ADULT AND PAEDIATRIC PATIENTS?

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Osteosarcoma is the most frequent primary malignant bone tumour. Its peak incidence is in adolescence, and the teenage and young adult (TYA) age group is therefore usually the focus of attention. However, taken together at least half of all osteosarcomas arise in patients older than 18 years.[1] While adolescents are usually affected by tumours which arise in an extremity and are a first cancer, both the proportion of osteosarcomas involving axial sites[1] and the proportion of those presenting as secondary malignancies[2] increase in adults, particularly above the age of 40 years. The proportion of patients presenting with metastases at diagnosis increases above the age of 60 years.[3]

For more than three decades, the most successful multidisciplinary treatment protocols have included several months of preoperative (neoadjuvant) chemotherapy, followed by surgery of the primary tumour and then several more months of postoperative (adjuvant) chemotherapy. Primary metastases, usually to the lung, must also be removed surgically if treatment is to be curative. As for systemic treatment, a combination of high-dose methotrexate, doxorubicin (Adriamycin), and cisplatin (MAP) is often considered standard. It has not been proven that adding additional agents to MAP will lead to improved outcomes.

It is often assumed that adult patients will not tolerate the intensive treatment regimens, which were developed for children and adolescents. The available evidence, however, suggests that standard treatment is usually feasible in younger adults aged 18–40 years and that adults aged 41–65 years can be treated, albeit at the price of considerable toxicity, with dose-adjusted regimens that try to avoid high-dose methotrexate. There are almost no data concerning osteosarcoma chemotherapy above the age of 65 years, but it may be assumed that it would be even more toxic and probably often not feasible. A recent meta-analysis of 4,403 osteosarcoma patients below the age of 50 years, treated through a variety of multidrug protocols, suggested that adolescents and adults experienced less toxicity than children.[4] In this analysis, children also achieved a slightly higher 5-year overall survival rate (66%) than adolescents (62%) or adults (63%).[4] Older adults above the age of 60 years have been reported as having far inferior outcomes.[2] Differences of tumour presentation (more axial primaries, more primary metastases,

more secondary osteosarcomas) and less intensive treatment may contribute to the inferior prognosis of older adults with osteosarcoma.

Prospective osteosarcoma studies often target patients up to the age of 40 years. The European and American Osteosarcoma Study EURAMOS-1, which accrued 2,260 patients from 326 institutions in 17 countries, is the largest example.[5] While successful in answering its primary objectives,[6,7] the goal of accruing young adults as well as paediatric and adolescent patients was not achieved as intended: only 252 of the 2,260 registered patients (11%) were above the age of 19 years.[5] The reasons why so few adults were recruited are probably numerous, but their lack of centralisation into institutions that treat larger patient numbers may be paramount. In contrast to the somewhat more centralised and 'trial addicted' paediatric and TYA infrastructures in which children and adolescents are usually treated, adults with osteosarcoma too often find themselves in institutions that see very few bone sarcoma patients and therefore shy away from the considerable burdens associated with trial activation.

Molecular heterogeneity and instability are hallmarks of osteosarcoma, with most tumours carrying hundreds and thousands of genetic alterations. It is therefore not surprising that targeted therapies have not yet made a significant impact on this disease. It is currently completely uncertain whether any suitable targets, if discovered, might differ between paediatric and adult patients. Investigations into the biology of osteosarcoma are ongoing and in close cooperation with clinical studies, aiming to integrate both areas of research.[8] Targeting treatment infrastructures will need to accompany such endeavours if children, adolescents, and adults are to benefit from future progress at the same pace.

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SAFE HANDLING CONSIDERATIONS IN HIPEC

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Hyperthermic intraperitoneal chemotherapy (HIPEC) is a cancer treatment that involves perfusion of the abdominal cavity with a cytostatic drug heated to 42°C for approximately 90 minutes after cytoreductive surgery. HIPEC is a single chemotherapy treatment performed in the operating room, and it is utilised when standard systemic chemotherapy has limited efficacy due to

a low concentration of intravenously administered cytostatics within the tumour. The heat makes the drug more effective in killing cancer cells, while also increasing blood flow throughout the entire area. HIPEC is usually used to treat pseudomyxomas, mesotheliomas, colorectal carcinomas, ovarian cancers at the stage of peritoneal carcinomatosis, and other cancers in the abdominal cavity.

All cytostatics are prepared under aseptic conditions in a pharmacy (usually in a central cytostatics compounding unit). Frequently used cytostatics include cisplatin, carboplatin, oxaliplatin, doxorubicin, mitomycin C, paclitaxel, and docetaxel. During and after a 90-minute perfusion, the heated cytostatic penetrates into the bloodstream. Detected plasma concentrations are usually around the lower limit of a therapeutic range. This is the reason for chemotherapy-induced serious side effects, such as haematological toxicity, chemotherapy-induced nausea and vomiting, and renal failure.

Safe chemotherapy administration by HIPEC has to be based on drug stability at higher temperatures. For this reason, it is very important to use a suitable solvent solution. A 0.9% saline solution is used in our hospital, and HIPEC is performed with cisplatin. We have proven by high-performance liquid chromatography with UV detection that cisplatin, carboplatin, and doxorubicin have very good stability in 0.9% saline solution after 90 minutes at 42°C. In contrast, oxaliplatin in saline solution underwent degradation to only 15% of parent drug after 90 minutes of incubation at 42°C. It is possible to use other solutions in HIPEC treatment, such as solutions for peritoneal dialysis or dextrose solutions. For the reason of chemical stability, it is better to only administer oxaliplatin in a 5% dextrose solution. However, chemoperfusion with 5% dextrose causes perioperative glucose and electrolyte shifts, and can result in temporarily significant hyperglycaemia, hyponatraemia, and metabolic acidosis.

Handling of cytostatic solutions in an operating room should follow standard oncology pharmacy procedures with all protective aids. Proper cytotoxic waste disposal and standard cleaning are important, as is decontamination after inadvertant release of cytostatic drugs using ESOP spill kit and guidelines.

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CHIMERIC ANTIGEN RECEPTOR T CELL TARGETING OF CHILDHOOD CANCERS

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More than 20 years after Zelig Eshhar first discovered that chimeric antigen receptors (CARs) can redirect T cell activation to surface antigens, the strategy has shown its potential for cancer therapy. In pilot and early clinical trials performed at several independent sites in North America, adoptive transfer of CAR T cells recognising CD19 demonstrated impressive clinical activity in patients with B cell malignancies.[1-4] Today, a large number of clinical CAR T cell trials are registered, mostly against CD19 or other B cell targets. The published clinical trials vary substantially with regard to CAR composition, viral gene transfer, and targeted epitope. Complete responses were shown to require some level of persistence of CAR T cells in the patient´s peripheral blood, which in turn relies on *in vitro* culture methods that maintain the

proliferative potential of T cells, stable CAR gene transfer, and the presence of a costimulatory signal. The major toxicity was a cytokine release syndrome characterised by high temperatures and arterial hypotension, which has become manageable with the use of an interleukin 6 receptor antagonist.[1] Potential advantages of CAR T cells over bispecific antibodies are their persistence *in vivo* and homing to the central nervous system. The need for individualised manufacturing of CAR T cells still impedes their broad implementation for the treatment of B cell cancers.

A further challenge is to extend the promise of the CAR T cell strategy to solid cancers. One obstacle is that potential CAR target antigens in solid tumours are heterogeneously expressed. This will very likely result in antigen-negative relapses, as observed even with the reliably expressed B cell antigen CD19. Thus, CAR T cell products in solid tumours will likely have to target more than a single antigen to eliminate the disease. In our group, we are developing CAR T cells against the ganglioside antigen GD2 in childhood cancers. A first-in-man clinical trial performed at Baylor College of Medicine has shown antitumour activity of first-generation GD2-specific CAR T cells against neuroblastoma.[5] Based on our finding that GD2 is also expressed in many Ewing sarcomas,[6] we are now exploring the use of GD2-specific CAR T cells in this cancer.

Inhibitory features of the tumour microenvironment will likely impair T cell function in solid tumours and induce tolerance and exhaustion. Innovative approaches and combination strategies are needed to recruit adoptively transferred CAR T cells into the stroma of solid tumours and enhance their local antitumour activity. Immune checkpoint inhibitors are attractive combination partners for novel immunotherapies.

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CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY: A HIGHLY PENETRANT CHILDHOOD CANCER SUSCEPTIBILITY SYNDROME WITH A BROAD TUMOUR SPECTRUM

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The key objectives of this presentation given in the scientific symposium "Childhood Cancer - Bad Luck or Bad Genes?" at the ECC 2015 were (i) the delineation of the current knowledge on the phenotype associated with constitutive mismatch repair deficiency (CMMRD) resulting from biallelic germline mutations in one of the four mismatch repair (MMR) genes, and to provide information (ii) on clinical diagnostic criteria that should raise the suspicion of CMMRD syndrome in a paediatric/young adult cancer patient, as well as (iii) on the diagnostic steps to confirm or refute the suspected diagnosis of CMMRD syndrome.

CMMRD due to homozygous or compound heterozygous mutations in one of the MMR genes, *MLH1*, *MSH2*, *MSH6*, or *PMS2*, is now recognised as a distinct childhood cancer susceptibility syndrome with its own OMIM number (#276300). The tumour spectrum of CMMRD syndrome overlaps with

that of Turcot syndrome and, retrospectively, it is almost certain – albeit not genetically proven – that the first patients with this cancer syndrome were described by Jacques Turcot in 1959.[1] However, we now know from the analysis of over 150 CMMRD patients that the tumour spectrum is much broader and includes not only brain tumours as well as colorectal adenomas and carcinomas, but also other carcinomas of the Lynch syndrome spectrum and haematological malignancies.[2] In fact, any malignancy in a paediatric or young adult patient could be a CMMRD-associated one. Most CMMRD patients show (non-neoplastic) features that may serve as diagnostic signposts for CMMRD syndrome when present in a cancer patient. Among these features, 'café au lait' spots reminiscent of neurofibromatosis type 1 and other pigmentary alterations are the most frequently found.[3]

Still today, the diagnosis of CMMRD is delayed or even prevented in many patients. This is not only due to a lack of awareness for this rare cancer predisposition syndrome, but also due to the diagnostic difficulties that result from the broad tumour spectrum in combination with the lack of unique disease-specific clinical features. To improve this situation, a European consortium named Care for CMMRD (C4CMMRD) developed a three-point scoring system for the suspected diagnosis of CMMRD in a paediatric/young adult cancer patient.[3] According to this scoring system, tumours highly specific for CMMRD are assigned three points, malignancies overrepresented in CMMRD two points, and all other malignancies one point. To reach the diagnostic three points, paediatric or young adult patients who have only one or two points attributable to their tumour also need to show one or more additional (non-neoplastic) features, which are weighted with one or two points according to their specificity for CMMRD. Furthermore, several strategies to definitely confirm or refute the suspected clinical diagnosis were developed and evaluated in different laboratories of the European consortium. These include: refined mutation analysis protocols for the notoriously difficult *PMS2* gene, which is affected by biallelic mutations in >50% of CMMRD patients;[4,5] a simple germline microsatellite instability (MSI) assay, which can be used as a pre-test to substantiate the suspected clinical diagnosis or as a screening tool in large cohorts of patients;[6] and *ex vivo* MSI and methylation tolerance assays that also allow for a reliable diagnosis in patients with equivocal mutation analysis results.[7]

With the broader application of the diagnostic criteria and subsequent assays to confirm/refute the diagnosis, it will be possible to unequivocally identify most CMMRD patients at the time they develop their first tumour. This will allow for adequate counselling of the family. Of note, a second presentation given by Franck Bourdeaut in the same scientific symposium at ECC 2015 discussed counselling strategies for parents of paediatric cancer patients.

Even though ascertainment bias has to be taken into account, it is fair to say say that, based on current knowledge, the tumour risk associated with CMMRD is extremely high. Therefore, the European consortium proposed possible surveillance protocols for second malignancies in patients and equally affected siblings.[8] These protocols largely overlap with those proposed by an international consortium headed by a Canadian group.[9] However, it is currently too early to say whether they can improve the prognosis. Equally, optimal treatment modalities for CMMRD are currently unknown. However, there is evidence that thiopurines and methylating agents may be less efficient due to the underlying defect.[10] Furthermore, recent characterisation of CMMRD-associated brain tumours revealed an intriguing molecular signature resulting from a complete ablation of replication repair in these tumours, which may open up new avenues of therapeutic intervention.[11] Although many of the current CMMRD patients will die from cancer, it is the hope that a systematic collection and evaluation of all clinical data will help to improve management of CMMRD. Therefore, the presentation was finished by a call to include all patients and their siblings and parents in a registry that was established by the European consortium C4CMMRD.

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ARE PD-1 AND PD-L1 RELEVANT TARGETS IN PAEDIATRIC MALIGNANCIES?

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In the last 5 years, immune checkpoint inhibitors have shown remarkable success in adult malignancies. In particular, monoclonal antibodies that block the interaction between programmed death ligand 1 (PD-L1), present on the surface of tumour or antigen-presenting cells, and programmed death 1 (PD-1), present on the surface of chronically activated lymphocytes, have shown impressive tumour responses in a wide range of cancers, including those that are not traditionally considered to be immunogenic. Such agents potentially provide an 'off the shelf' immunotherapy, unleashing endogenous anti-tumour immune responses to generate durable tumour control in a significant number of patients. A number of these agents have now been licensed as first or second-line therapeutics. Some of the most impressive results to date have been seen when antibodies targeting PD-1 are combined with those targeting the immune checkpoint molecule CTLA-4, with objective response rates seen in 57% of patients with metastatic melanoma.[1] Across all tumour types, the most consistent response biomarker appears to be the expression of PD-L1 on tumour cells. However, although higher responses are reported in patients with tumours carrying immunohistochemically detectable PD-L1, patients whose tumours do not express PD-L1 can still have impressive responses to PD-1 blockade. Recent reports have suggested that response is also likely to be predicted by the 'mutational burden' of the tumour, which is consistent with the significant response rates seen in highly mutated tumours such as melanoma and non-small-cell lung cancer.[2]

Although there are now in excess of 100 trials of this class of agents in progress in adults, the first paediatric studies have only opened recently, and there are no paediatric clinical data reported as of yet. The relatively low mutational burden in most paediatric cancers has generated some caution as to whether they will prove as effective as in adult cancers. Nevertheless, although most paediatric cancers lack true neoantigens, numerous tumour antigens have been identified, and in some instances weak endogenous immune responses to these have been identified.[3] Our aim has been to obtain preclinical data to support the paediatric development of these agents. We have explored the efficacy of anti-PD-1 and anti-CTLA-4 agents in syngeneic neuroblastoma models and demonstrated potent responses, with regression of established tumours and durable disease control, particularly when the two agents are used in combination or when checkpoint blockade is combined with tumour peptide vaccine. In a spontaneous neuroblastoma model, control of advanced tumours could be achieved by combination of immunomodulatory antibody with low-dose cyclophosphamide. Although

encouraging, the efficacy of immunotherapy agents in preclinical models has in general correlated poorly with clinical responses. More compelling evidence to further the translation of these agents into the paediatric population is therefore provided by the expression of PD-L1 in a range of paediatric cancers. We have demonstrated high levels of membranous expression of PD-L1 in a high proportion of primary human neuroblastoma (72%), alveolar rhabdomyosarcoma (86%), embryonal rhabdomyosarcoma (50%), Ewing's sarcoma (57%), and osteosarcoma (47%). The levels of expression compare favourably with those seen in adult malignancies with proven response to this class of agents. Furthermore, in the 115 tumours examined, increased proportion of $CD8^+$ tumour-infiltrating lymphocytes (TILs) correlated with expression of PD-1 expression by the $CD8^+$ cells. Patients with PD-L1-positive tumours with a high frequency of TILs had a significantly better survival than patients with PD-L1-negative tumours. This strongly suggests that the PD-1/PD-L1 pathway is active in these tumours, and supports the therapeutic potential of targeting these molecules in childhood cancer.

Although it is hoped that the initial paediatric Phase I studies of these agents will provide some signal of response, it may be that this is not seen in this very heavily pretreated population. Although many of the adult studies have reported responses in patients who have recently received chemotherapy, the degree of immunosuppression may be less than that seen in many of the very intensive paediatric treatment protocols. Furthermore, both paediatric preclinical studies and adult clinical data suggest that there is significant advantage to be obtained by combinational therapies, and such approaches should be explored in paediatric patients if single-agent studies are unsuccessful.

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MRI-LINAC IS A WAY TO IMPROVE TREATMENT DELIVERY

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Radiotherapy is fundamentally changing. In the previous century, radiotherapy was predominantly used to treat microscopic tumour remnants after surgery. To reach this goal, relatively low doses of radiation were used, delivered in multiple fractions, on a relatively large area of the body. The treatment itself was planned based on an X-ray image alone, where the tumour and normal tissue were generally not visible. Furthermore, daily movement of tumours and normal tissue could not be visualised and therefore could not be compensated for during treatment.

Sophisticated techniques are currently being introduced to deliver radiotherapy more accurately. In the last decade, treatment planning has changed from being based on X-ray scans to being based on computed tomography (CT) and magnetic resonance imaging (MRI) scans. MRI has the highest soft tissue contrast and is therefore the optimum type of planning for visualisation of tumours and normal tissue. Furthermore, several techniques have become available to help the radiation account for the movements of the patient.

A breakthrough in 2003 was the introduction of the CT-linear accelerator (linAc): a linAc combined with CT. The CT-linAc is now considered the current clinical standard in radiotherapy equipment. The possibility of performing a full CT scan of each fraction of the treatment area has changed the way radiotherapy is performed. For lung and brain cancers, the amount of treatment fractions changed from 35 to approximately 1–3. All kinds of basic rules, such as whether to deliver a homogeneous dose or not, are still being questioned.

'Look while you treat' as a new concept seems able to bring more advantages to radiotherapy with regard to safety and likely local control. Radiotherapy departments are therefore increasingly being equipped with all kinds of imaging machines. There are eight CT-linAcs and one CT simulator at the radiotherapy department in Utrecht, Netherlands. The department also currently has two MRI simulators, one MRI-guided brachytherapy bunker, one MRI-guided high intensity focussed ultrasound machine, and two MRI-linAcs. It can be expected that all radiotherapy departments will be increasingly equipped with their own MRIs.

An MRI-linAc has been in development at the University Medical Center Utrecht in collaboration with industry, since 1998. This resulted in a prototype in 2006 and a clinical machine that is currently being prepared for clinical studies. The integrated 1.5 Tesla MRI has full diagnostic MRI quality and is able to produce images during the delivery of radiotherapy. The theoretical gain is to decrease morbidity, as imaging with optimal soft tissue contrast will be able to account for changes such as movement, shrinking, and deformation during treatment. Furthermore, it can be expected that a higher dose will be able to be safely administered to the tumour. However, many technical and difficult procedures still need to be developed and approved before the machine is released into clinics. In research, tumour biology may become more apparent during treatment. It is also likely that current fractionation will be extremely reduced for several tumour sites, and new treatment sites, such as radiotherapy for renal cell cancer, might become available.

A consortium of leading international cancer centres has been developed to propose the value of the MRI-linAc. Close collaboration will facilitate a controlled clinical introduction, including faster accrual in joint trials, set standards on quality, rapid inclusion of large patient numbers, and the use of large data and data sharing. The 'Elekta ATLANTIC Consortium' defined 25 tumour sites likely to have clinical benefit from the MRI-linAc, and 77 study proposals have been drafted. Industry will financially support clinical studies for the nine tumour sites that have been prioritised.

The optimal organisation of the consortium has been outlined in order to reach the goals set, together with IDEAL as a method for the clinical introduction of complex interventions. Predicate studies are currently being performed, such as MRI sequence optimisation, MRI contouring, and planning. The first-in-man study will be performed shortly in Utrecht. Consortium-wide studies on clinical introduction and value proposition will follow.

Regarding the current paradigm change in radiotherapy, it is important not to consider the MRI-linAc as simply a linAc with an MRI, but to allow a more surgical treatment approach through optimal use of the MRI-linAc. This will change our way of using radiotherapy in clinical practice.

TARGETING THE TUMOUR MICROENVIRONMENT

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Myeloid cells infiltrating the tumour microenvironment, especially tumour-associated macrophages (TAMs), are essential contributors to cancer-related inflammation, a state known to accelerate tumour progression and promote carcinogenesis. TAMs are conditioned by the tumour microenvironment to acquire pro-tumour functions, such as promoting angiogenesis and supporting tumour cell proliferation and migration. In recent years, effective strategies targeting TAMs have been successfully developed and the initial indication is that they can be clinically beneficial.

One approach to targeting TAMs is to inhibit the colony stimulating factor 1 (CSF-1)/CSF-1 receptor (CSF1R) signalling pathway, which promotes the differentiation of myeloid progenitors into the heterogeneous population of mononuclear phagocytes (monocytes and macrophages). Several inhibitors of CSF1R have been developed, including

a humanised monoclonal antibody, RG7155, that blocks receptor dimerisation and activation, and which was demonstrated to effectively reduce the number of TAMs and to increase the CD8/CD4 T cell ratio in tumour biopsies from patients with various types of malignancy. Clinical objective responses were observed following the treatment of patients with diffuse-type giant cell tumours, which is a disease characterised by the overexpression of CSF-1.[1]

The kinase antagonist BZL-945 has an affinity for CSF1R more than 3,200-fold higher than other ligands, and its antagonistic action blocks glioma progression and improves survival in preclinical models. Interestingly, CSF1R blockade in this context did not result in TAM depletion, but instead contributed, together with glioma-supplied factors (i.e. granulocyte macrophage colony-stimulating factor and interferon gamma), to 're-education' of macrophages from a pro-tumour phenotype to an anti-tumour effector cell.[2]

An alternative approach is to use anti-tumour compounds shown to have specific effects on the tumour microenvironment. For example, the compound trabectedin, approved in Europe and recently in the USA, causes cell cycle arrest in tumour cells by binding to and damaging DNA, although this 'conventional' effect is only part of this molecule's complex mechanism of action. It has been demonstrated that trabectedin has marked effects on the tumour microenvironment. For example, the compound interferes with the transcription of specific genes and is able to reduce the expression of several inflammatory cytokines and chemokines, such as interleukin 6, CCL2, and CXCL8, as well as angiogenic factors such as vascular endothelial growth factor and angiopoietin 2. Perhaps the most interesting effect of trabectedin is its selective activation of caspase 8, the key effector molecule of the extrinsic apoptotic pathway, in mononuclear phagocytes. Treatment with trabectedin causes a selective depletion of TAMs in the tumours of different mouse models, and this effect is an important component of its anti-tumour efficacy.[3] A reduction in blood monocytes and TAMs was also observed in human patients treated with trabectedin.

Overall, we now have a number of successful strategies to target the tumour microenvironment, especially the associated macrophages, and the initial results are highly encouraging. However, to go a step further, it is now clear that combination therapies must be pursued: the combination of anti-macrophage strategies with conventional chemotherapy or other state-of-the-art therapies (e.g. anti-angiogenesis, immunotherapy) will likely provide a better chance of achieving more effective anti-tumour responses.

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STEREOTACTIC BODY RADIATION THERAPY FOR OLIGO-METASTASES

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Lung, liver, and bone are common sites of metastases and sometimes only 1–5 metastases occur in a single organ, often referred to as oligo-metastases. In general, systemic therapy is the preferred option for metastatic cancer, but the oligo-metastatic state is believed to represent an intermediate stage between primary cancer without metastases and widespread disease. Patients may benefit in terms of improved survival if they are offered surgery or ablative therapy during the oligo-metastatic stage of the disease.[1]

A number of retrospective analyses demonstrate that 30–40% of patients with metastatic colorectal cancer with limited involvement of the liver may survive 5 years after treatment with surgical resection. In a large cohort study from the Memorial

Sloan Kettering Cancer Center (New York City, NY, USA), 37% of patients were alive 5 years after surgical resection of colorectal carcinoma liver metastases. The study identified five prognostic variables related to survival: node-positive primary, long disease-free interval before diagnosis of metastases, number and size of metastases, and level of carcinoembryonic antigen.[2]

Most studies on stereotactic body radiation therapy (SBRT) of metastases are retrospective and relatively small. In general, they demonstrate favourable 1 and 2-year local control rates of 70–100%. Survival rates vary due to variation in the selection of patients.[3] Recently, a study describing a cohort of 321 patients treated with SBRT for 1–6 metastases, primarily in the lung and liver, was published.[4] All patients were deemed unsuitable for surgery and radiofrequency ablation (RFA), 42% had been treated with surgical resection or RFA, and 60% had been treated with chemotherapy before they were referred for SBRT. The patients were followed for a median of 5 years and the analysis demonstrated a median survival of 2.4 years and survival rate of 23% at 5 years after SBRT. None of the histological types had more favourable survival than others. A World Health Organization performance status of 0–1, small size and number of metastases, long disease-free interval, and both pre and post-SBRT chemotherapy were all independent prognostic factors related to survival. Patients with 0, 1, 2, 3, and 4–5 unfavourable pre-treatment risk factors had a median survival of 7.5, 2.8, 2.5, 1.7, and 0.8 years, respectively.

These data do not prove that SBRT cures patients with metastases and it is still strongly recommended to include patients in randomised clinical trials. However, the results are encouraging and show that selected patients may become long-term survivors after SBRT for limited involvement of the lung and the liver. In addition, the results of the cohort study are in favour of combined systemic therapy and SBRT.

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MOLECULAR BASIS FOR RADIOTHERAPY IN SYNERGY WITH IMMUNOTHERAPY

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The peculiar observation that local radiation therapy (RT) occasionally induces systemic control of metastases is over 60 years old,[1] but these 'away from the target' or 'abscopal' effects were only recently demonstrated in preclinical models to depend on activation of anti-tumour immune responses.[2]

A decade ago, we hypothesised that local RT could mimic the effects of vaccination through modified autologous irradiated tumour cells, and induce responses in tumours otherwise resistant to immune checkpoint blockade. Initial experiments using the poorly immunogenic 4T1 mouse carcinoma demonstrated that RT led to the activation of tumour-specific T cells in the presence of CTLA-4 blockade, resulting in systemic responses.[3] Multiple mechanisms underlying the pro-immunogenic effects of RT have since been described.[4] RT induces immunogenic cell death, mediated by the convergent release of tumour antigens from dying cells together with danger signals, known as damage-associated molecular patterns. The latter activate dendritic cells (DCs) to uptake antigens, migrate to draining lymph nodes, and cross-present them to tumour-specific T cells.[5] RT also facilitates tumour rejection by inducing the production of chemokines that enhance recruitment of cytotoxic T cells (CTLs) to the tumour.[6] In addition, through enhancing the

expression of major histocompatibility complex class I molecules, NKG2D ligands, and death receptors, it facilitates the recognition and killing of tumour cells by CTLs.[7-9] These data support a working model, whereby RT converts the tumour into an antigen source. The process mimics that of a live attenuated vaccine against infectious pathogens. The irradiated tumour is permeated by CTLs that induce waves of cell killing, leading to more antigen release and more priming of anti-tumour T cells to multiple tumour antigens, culminating in a sustained immune response effective at eliminating non-irradiated metastases.[10] Analysis of the T cell receptor repertoire in 4T1 tumours shows the expansion of multiple T cell clones in mice treated with RT and CTLA-4 blockade, supporting this hypothesis.[11]

The optimal RT dose and fractionation regimen to best shift the microenvironment of established tumours from immunosuppression towards immune activation remains undefined. To address this issue we compared different RT regimens for their ability to induce abscopal responses, by irradiating one of two synchronous tumours in murine models. Regardless of the regimen used, RT alone was unable to induce abscopal responses in two carcinoma models: TSA and MCA38. Conversely, in the presence of an anti-CTLA-4 antibody, RT induced responses in both the irradiated and the non-irradiated tumour. Noticeably, abscopal responses were seen mainly with fractionated RT (8 Gy × 3 or 6 Gy × 5), but not when a single 20 Gy dose regimen was tested.[12] We have recently found that effectiveness of fractionated RT may be at least partially explained by its ability to increase recruitment of DCs to the irradiated tumour. We have consistently shown that the number of DCs available to cross-present the tumour antigens released by RT is a critical determinant of the magnitude of the anti-tumour response elicited by RT and anti-CTLA-4 treatment.[13] We are working to fully elucidate the molecular mechanisms responsible for the superior efficacy of fractionated RT to synergise with anti-CTLA-4 and other immunotherapies. While the optimal clinical RT regimen with immune checkpoint inhibitors remains undefined, it is notable that the best abscopal responses reported in patients treated with RT and anti-CTLA-4 were achieved with regimens comparable to the ones effective preclinically.[14,15] In addition, we have seen abscopal responses in an ongoing prospective clinical trial of patients with metastatic non-small cell lung cancer testing the combination of RT given as 6 Gy × 5 or 9.5 Gy × 3 with ipilimumab (NCT02221739).[16] Thus, emerging evidence that RT can induce responses to anti-CTLA-4 antibody in cancers, such as lung cancer (shown to be unresponsive to anti-CTLA-4 alone),[17] supports the concept we introduced a decade ago that RT has the potential to be an optimal partner to immunotherapy.[18]

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THE IMPORTANCE OF IMAGE-GUIDED ONCOLOGICAL INTERVENTION STANDARDISATION AND DATABASE COLLECTION

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Biobanks are repositories for the storage and retrieval of biological samples from a large number of subjects. A major goal of biobanks is the organised collection of biological material and associated information in order to spread access among scientists requiring this information.[1]

Until recently, imaging data coming from sources such as magnetic resonance imaging or computed tomography were not included in biobanks; imaging biobanks are currently at an early stage of development. In 2014, the European Society of Radiology established a dedicated working group (ESR WG on Imaging Biobanks) aimed at monitoring the existing imaging biobanks in Europe, promoting the federation of imaging biobanks, and communication of their findings in a white paper.[2]

The challenges associated with reliably connecting or integrating imaging into a biobank are to provide a structured, unified approach for storage of, and access to, these data from distributed databases, and imaging data having to be processed in order to extract quantitative information relating to an 'imaging biomarker'. Only a small number of quantitative imaging biomarkers exist today, but some of the major European biobanks have launched new projects aimed at branching into medical imaging.

Several fundamental issues are still restraining the establishment of imaging biomarkers that would otherwise be recognised as standard. Too many sources of uncertainty still exist with imaging biomarkers, including biological variability, measurement variability, inter-vendor variability, and even inter-equipment variability. The latter is illustrated by the fact that the coefficient of variations using diffusion-weighted imaging varied significantly between scanners, presumably due to image noise.[3] To reduce this variation, consistent setup of scanner parameters may improve reproducibility of biomarkers.

In conclusion, there is a need to improve the standardisation, harmonisation, reproducibility, validation, comparison, and integration of existing and emerging imaging biomarkers.[2]

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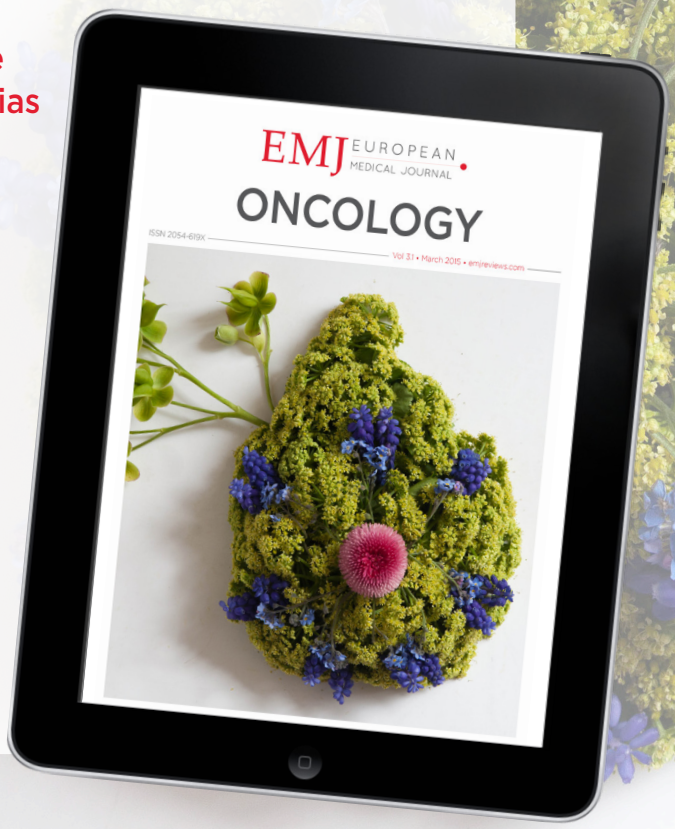

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CURRENT AND FUTURE DEVELOPMENTS IN THE TREATMENT OF CD30+ LYMPHOMAS

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Disclosure: Lena Specht is a member of the advisory board for Takeda Pharmaceuticals.
Support: The publication of this article was funded by Takeda. The views and opinions expressed are those of the authors and not necessarily of Takeda.
Received: 17.08.15 **Accepted:** 22.10.15
Citation: EMJ Oncol. 2015;3[2]:87-93.

ABSTRACT

CD30 is a cell membrane protein expressed on the surface of a range of lymphomas, which has important diagnostic, pathogenic, and prognostic roles. The most common CD30+ lymphomas are Hodgkin's lymphoma (HL) and anaplastic large cell lymphoma (ALCL), but other types of lymphoma also express CD30, although less frequently. Attempts to develop a monoclonal antibody therapy that targets CD30 were initially unsuccessful, but recent Phase I and II trials have shown promising results from the use of the immune conjugate brentuximab vedotin in HL and ALCL. Phase III trials are ongoing to evaluate clearly the benefit–risk ratio when compared with standard treatment. The first of these to report preliminary findings, the AETHERA trial, showed improved progression-free survival times in relapsing/refractory HL patients treated with brentuximab vedotin as a consolidation therapy after autologous stem cell transplantation compared with those receiving placebo. Patients with rarer CD30+ lymphomas may also benefit from brentuximab vedotin therapy in the future. Moreover, combination treatment with immunomodulatory and cell cycle checkpoint modulators that are currently under development, as well as conventional chemotherapeutic agents, may yield further benefits. To this end, improved methods of CD30 detection and quantitation will improve the delineation of non-HL subtypes in which CD30-targeted therapy may be clinically indicated.

Keywords: CD30+ lymphoma, Hodgkin's lymphoma (HL), immune conjugate, monoclonal antibody (mAb), clinical trial.

BACKGROUND: DISCOVERY, STRUCTURE, FUNCTION, AND DETECTION OF CD30

Until 1982, the neoplastic cells of Hodgkin's lymphoma (HL) were largely uncharacterised in terms of their surface markers. The establishment of a stable HL cell line led to the discovery of a surface marker that was almost ubiquitous on Reed–Sternberg (RS) cells as well as Hodgkin's cells, the pathological hallmark of HL.[1] CD30 (also referred to as tumour necrosis factor [TNF] receptor superfamily member 8, Ki-1 antigen, CD30 ligand receptor, and lymphocyte activation antigen CD30) is a member of the TNF receptor superfamily. The protein contains extracellular, transmembrane, and intracellular domains (overall molecular weight: 120 kDa) and there are two isoforms generated by alternative splicing of the gene, which is located at Chr 1p36.22. CD30 is only expressed by activated lymphocytes, both T and B lineages. The extracellular domain can also be cleaved to produce a soluble, cytoplasmic form (85 kDa), which has an undetermined function. Soluble CD30 can be used as a biomarker of disease stage in HL. Indeed, the specificity of CD30 expression to disease states gives it powerful diagnostic[2-4] and predictive functions,[5] although this is not current practice in most hospitals at present.

Table 1: Summary of CD30⁺ diseases.

Tissue type	Disease	CD30 positivity
Non-neoplastic T and B cells	Reactive conditions, e.g. infectious mononucleosis, HIV, and other viral diseases	Highly variable
Lymphomas with near-ubiquitous CD30 expression	Hodgkin's lymphoma Anaplastic large cell lymphoma Enteropathy-associated T-cell lymphoma	96% 100% 100%
T-cell lymphomas	Multiple subtypes of peripheral T-cell lymphoma Cutaneous T-cell lymphoma (mycosis fungoides/ Sézary syndrome) Angioimmunoblastic T-cell lymphoma	≈20–50% 5–33% 0–64%
B-cell lymphomas	Primary mediastinal large B-cell lymphoma Primary effusion lymphoma Burkitt's lymphoma Diffuse large B-cell lymphoma	85% 70% 30% ≈10%
Other	Nasopharyngeal carcinoma Embryonal carcinoma (a form of germ cell tumour)	≈10% 70%

After its initial characterisation in RS cells, CD30 has been shown to be expressed by most human lymphomas, including B and T-cell lymphomas, to variable extents. In addition to its expression by 98% of HL cells, CD30 is ubiquitously expressed by anaplastic large cell lymphoma (ALCL, both kinase-positive and kinase-negative subtypes) and primary cutaneous ALCL.[6] Other CD30⁺ diseases comprise a variety of less common types of B and T-cell lymphomas, as well as reactive conditions (Table 1). Peripheral T-cell lymphomas (PTCLs) and some B-cell lymphomas, such as diffuse large B-cell lymphoma (DLBCL), can now be subcategorised based upon gene expression profiles that correlate with CD30 expression.[7]

The function of CD30 is 2-fold and depends on which intracellular signal transduction pathways are activated. After binding to its ligand (CD30L, CD153), the protein–ligand complex can activate the TNF receptor-associated factor (TRAF) 2 or TRAF5 pathways. The former leads to activated cell proliferation via interactions with MAPK8/JNK and NF-κB,[8-10] as seen in aggressive ALCL, while the interaction between CD30 and TRAF5 leads to apoptosis.[11] In HL, TRAF2 and TRAF5 signalling is CD30L-independent, and both protein complexes aggregate in the cytoplasm close to the cell membrane.[12] CD30 has been shown to upregulate the expression of intercellular adhesion molecule-1, most likely via the upregulation of NF-κB.[13] The induction of apoptosis is observed in lymphomatoid papulosis, which is a relatively indolent T-cell cutaneous lymphoma.[14] Driving the choice of signalling pathway towards the TRAF5 pathway is an interesting and unexplored therapeutic option.

METHODS OF CD30 DETECTION AND THEIR LIMITATIONS

The expression of CD30 is determined using three techniques: immunohistochemistry (IHC), mostly using antibodies against the extracellular domain; flow cytometry; and enzyme-linked immunosorbent assays for the soluble form.[15]

There are broad-ranging technical considerations inherent in making a histological diagnosis of lymphoma, including small numbers of available cells, poor fixation, failure to recognise staining patterns, and inappropriate controls. Indeed, an observational study of laboratories conducting CD30 testing (n=172) found that 77% of sites produced inadequate staining, mostly because of the high rate of false-negative findings.[16] The choice of technique is also dependent on tissue type. For example, flow cytometry is only appropriate for fresh samples, including those from blood or bone marrow aspirates, and solid-tissue biopsies are generally not appropriate. Furthermore, fixation of cells prior to IHC analyses can introduce inaccuracies if delayed or not conducted appropriately. However, a recent study indicated that there is a high degree of correlation between IHC findings and mRNA expression levels providing that adequate controls are used for the IHC (usually tonsil) and that appropriate monoclonal antibodies (mAbs) are used.[17]

NOVEL THERAPEUTIC OPTIONS THAT TARGET CD30

One of the most successful recent advances in cancer therapeutics has been the development of targeted strategies against tumour cell-specific surface antigens by mAbs. Prior to the development of mAbs, HL and ALCL were treated with traditional chemotherapeutic agents (e.g. ABVD, BEACOPP, CHOP, CHOEP) and autologous stem cell transplantation (ASCT) for relapses, but, despite leading to a cure in 70–80% of patients with advanced HL, these treatments have previously caused irreversible side effects in some patients and remain far from optimal even now. The cure rates are substantially lower for patients with ALCL, meaning that there is a clear clinical need for new therapies in this area. Furthermore, relapse rates for some CD30^{+} diseases were high and patients often developed refractory disease for which novel therapeutic options were required. For HL and ALCL, the discovery of CD30 yielded an obvious target as it is overexpressed on the surface of tumour cells in virtually all cases (Table 1).

The cloning and characterisation of CD30 in HL led to the development of the first CD30-targeted mAb in 1992.[18,19] However, although this monovalent mAb showed reasonable levels of tolerability, the results of Phase I and II trials showed disappointing levels of efficacy. Since 1992, a range of monovalent (CD30-specific), bispecific (CD30 and another target antigen), and radiolabelled (^{131}I-anti-CD30) mAbs have been developed for HL and ALCL. Almost without exception, each strategy failed in Phase I or II trials: antibodies were neutralised by soluble CD30,[20] failed to bind appropriately to CD30 in humans despite being efficacious in animal studies,[18] or failed to blockade CD30 signalling.[21] One initially promising candidate molecule that was shown to be safe and modestly effective in HL and ALCL,[22-24] SGN-30, subsequently showed unacceptable toxicity when combined with chemotherapy in terms of episodes of pneumonitis,[25] and clinical trials were discontinued. Unacceptable toxicity in terms of haematological effects also ended the development of the ^{131}I-anti-CD30 radiolabelled mAb.[26]

There was one exception to these disappointing initial studies and that came with the development of brentuximab vedotin. Brentuximab vedotin is a conjugate of a mAb against CD30 (cAC10) and an antimitotic cytotoxic compound, monomethyl auristatin E (MMAE).[27] The anti-CD30 antibody and MMAE are linked to form a compound that is stable in the plasma and then dissociates once internalised by a tumour cell. Brentuximab vedotin is internalised after binding to CD30, after which MMAE is released into the tumour cell to mediate its anti-tubulin action, leading to G2/M cell cycle arrest and apoptosis. As a result of the disease cell-targeting nature of the CD30 mAb conjugate, the side effect profile of brentuximab vedotin is relatively low, although not negligible in either HL or ALCL, with approximately 20% of patients suffering Grade 1 or 2 side effects.[28-30] The most common adverse effects in the Phase II trials were fatigue, nausea and vomiting, sensory neuropathy (most of which resolved completely after the cessation of treatment), upper respiratory infection, diarrhoea, anaemia, and thrombocytopaenia. Potentially serious but rare adverse events associated with brentuximab vedotin include pancreatitis and progressive multifocal leukoencephalopathy.[31-33]

As a result of the encouraging early trial data, the United States Food and Drug Administration (FDA) granted accelerated approval to brentuximab vedotin in 2011 for the treatment of patients with relapsed HL post-ASCT, patients with HL who have failed two standard chemotherapy regimens, patients with ALCL who have failed one multiple agent chemotherapeutic regimen, and those for whom transplantation is not an option. In a subsequent attempt to improve the cure rate in patients with newly diagnosed HL, brentuximab vedotin has been combined with standard chemotherapy in a single Phase I study.[34] The study findings showed that >90% of patients (46/51) achieved a complete response. When bleomycin was removed from the regimen, the risk of pulmonary toxicity was removed with no effect on clinical response rates. The same research group is now conducting a Phase II trial of brentuximab vedotin + AVD in previously untreated unfavourable disease, and have shown no additional toxicity when combined with radiotherapy.[35]

Two Phase III trials are now ongoing to assess brentuximab vedotin + AVD versus the standard ABVD regimen in untreated, advanced HL. The ECHELON-1 study in advanced HL has just finished recruiting patients, but increased levels of neutropenia were found in the experimental arm, which led to the routine prophylactic use of growth factor in all patients who received combined brentuximab vedotin + AVD. Data from this trial are expected in 2018. Furthermore, the

LYSA/FIL/EORTC trial in patients with early unfavourable HL is still recruiting.[36] In this trial, all patients will receive four cycles of either experimental or standard treatment followed by involved site radiotherapy.

For patients with relapsed/refractory HL, Phase II trials have shown an overall response rate (ORR) ranging from 47–75% when brentuximab vedotin is used as a single drug.[28,37,38] One study indicated that patients who achieved a complete response displayed an overall survival rate of 73% (95% confidence interval [CI]: 57–88%) and a progression-free survival (PFS) rate of 58% (95% CI: 41–76%).[39] A systematic review of the literature has suggested that brentuximab vedotin can prolong long-term survival in such patients post-ASCT when compared with conventional treatment approaches.[40] Phase I trials are also showing encouraging results for transplant-naïve patients with refractory HL, suggesting that brentuximab vedotin could represent a useful bridge to transplantation.[30,41] Further studies will be needed to confirm this role, as a study from Turkey has suggested that early transplantation after treatment with brentuximab vedotin is indicated during the early optimal window of opportunity because of declining response rates after six cycles.[42] Encouragingly for patients with either anaplastic lymphoma kinase (ALK)-positive or ALK-negative ALCL, ORRs of 50% and 76% have been observed in two Phase II studies with prolonged durations of response.[28,29]

The AETHERA trial assessed the use of brentuximab vedotin (1.8 mg/kg every 3 weeks versus best supporting care) as consolidation therapy after ASCT for up to 16 cycles in a randomised, double-blind, multicentre trial. The results of the trial have demonstrated improved 2-year PFS in patients that received brentuximab vedotin versus placebo (63% versus 51%; p<0.001).[43] Brentuximab vedotin post-transplant was approved by the FDA on the basis of this study, with the European Medicines Agency (EMA) currently reviewing a similar application. The ECHELON-2 Phase III trial is designed to test brentuximab vedotin + CHP versus the standard CHOP regimen in patients with newly diagnosed ALCL and CD30$^+$ T-cell lymphomas; its recruitment period is still open.

Beyond HL, the majority of patients with relapsed PTCL have few treatment options. PTCLs comprise a heterogeneous range of aggressive natural killer (NK) and T-cell lymphomas, including ALCL, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), NK/T-cell lymphomas, angioimmunoblastic T-cell lymphoma (AITL), and cutaneous T cell lymphomas, including mycosis fungoides/Sézary syndrome, amongst others. Many of the lymphoma subtypes that fall under the diagnosis of PTCL have some degree of CD30 positivity, and affected patients have poor outcomes.[17] Between 40–65% of patients with PTCL will relapse after initial multiple agent chemotherapy[44] and no standardised treatment protocols are accepted for these patients, creating a clear unmet clinical need. To date, brentuximab vedotin is only licensed for use in patients with relapsing/refractory HL and systemic ALCL. It is yet to be clarified whether and how patients with other forms of CD30$^+$ lymphoma will benefit from brentuximab vedotin therapy.

A Phase II study regarding the use of brentuximab vedotin in patients with a range of relapsed PTCL diseases, including mature NK/T-cell lymphomas (n=34), AITL (n=13), and PTCL-NOS (n=21), has been reported.[45] Combined complete and partial response rates ranged from 33–54% across these disease subtypes, but it is not clear whether IHC estimates of CD30 positivity correlate with disease response to brentuximab vedotin. A separate Phase II study assessed the use of brentuximab vedotin in patients with two forms of cutaneous T-cell lymphoma, mycosis fungoides/Sézary syndrome.[46] Patients had CD30 expression levels that ranged from 0–100%. Patients with CD30$^+$ levels <5% were less likely to achieve a complete response than those with levels >5%. Brentuximab vedotin is now being tested against standard treatment (methotrexate or bexarotene) in the ALCANZA randomised trial in CD30$^+$ cutaneous T-cell lymphomas.[47] This level of efficacy in the forms of lymphoma with relatively low CD30 expression levels mentioned above gives rise to the hope that brentuximab vedotin could be an effective treatment for patients with a broad range of lymphomas.

With regards to B-cell lymphomas, a Canadian study demonstrated that CD30 is expressed by 25% of DLBCLs and is a favourable prognostic factor.[48,49] Correspondingly, clinical responses were observed in 44% of relapsed/refractory patients with CD30$^+$ DLBCL (n=49), and also in some patients with other types of B-cell lymphoma.[50] Preclinical studies have indicated that brentuximab vedotin is effective against cell lines and *in vivo* mouse models of CD30$^+$ primary effusion

lymphoma, a B-cell form of non-HL.[51] Taken together, these data support further clinical studies of brentuximab vedotin in DLBCL and other rarer forms of B-cell lymphoma. Future work that separates out patients with higher levels of CD30 expression will be required to optimise the subgroups of individuals that will benefit most from brentuximab vedotin therapy.

AREAS OF ONGOING RESEARCH

Brentuximab vedotin is one of a series of mAb conjugates to be approved. Preclinical studies are ongoing to develop inotuzumab ozogamicin and polatuzumab vedotin for clinical trials, as well as a raft of others that adopt tumour cell targeting to deliver cytotoxic agents intracellularly. Further data regarding the use of these agents from preclinical studies are eagerly awaited.

Several other therapeutic strategies are coming to the bedside for the treatment of CD30$^+$ neoplasms, including immunotherapy via cell checkpoint inhibition, principally by programmed cell death protein-1 (PD-1) blockade, and immunomodulation, via the engagement of cytotoxic immune effector cells against tumour cells. RS cells in classical HL evade immune detection by expressing proteins of the PD-1 pathway. The surface expression of PD-1 proteins enables tumour cells to evade cell killing by CD8$^+$ T cells;[52] accordingly, programmed death ligand-1 (PD-L1) and PD-L2 are overexpressed by RS cells, particularly in the nodular sclerosis form of HL as a consequence of the amplification of Chr 9p24.1.[53] Inhibition of PD-1 expression is therefore being investigated as a potential therapeutic strategy. Nivolumab is a mAb targeted to block PD-1, and has been shown to have an acceptable safety profile (22% Grade 3 toxicities) when used in patients with relapsed/refractory HL, including patients that had relapsed after treatment with brentuximab vedotin.[54] In terms of response rates, of the 23 patients participating in a Phase II study published this year: 3 showed stable disease, 16 had a partial response, and 4 had a complete response; the PFS rate at 24 weeks was 86%.

SUMMARY AND CONCLUSIONS

Recent advances in the clinical management and molecular understanding of classical HL and other more common subtypes have yielded novel management options that may be applicable across a wide range of CD30$^+$ conditions. The less common subtypes of CD30$^+$ lymphomas have been neglected in terms of funding and research interest in the past. Of particular interest is brentuximab vedotin, an antibody conjugate drug against CD30 that targets an antimitotic compound specifically to disease cells. Future studies will be required to assess the use of combination therapies of any of these strategies with brentuximab vedotin, with or without standard chemotherapeutic regimens and before or after ASCT. It will be with advances in the molecular biological understanding of each lymphoma subtype that a truly personalised approach will be developed that is maximally effective with minimal side effects for each patient.

Acknowledgements

Medical writing assistance was provided by Dr Natalie Morris (Oxford Science Editing Ltd., Oxford, UK).

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