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Congress Review

Review of the European Society for Medical Oncology (ESMO) Congress 2019

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Barcelona, a city with undisputed character, ambience, and beauty, played host this year to the prestigious annual European Society for Medical Oncology (ESMO) Congress 2019 for which we are happy to provide a comprehensive review, leaving nothing to be desired. The meeting welcomed 28,571 participants from 138 countries to join the discussion about the future of oncology with a focus on translating science into better patient care.

The congress was held in the hometown of ESMO president Dr Josep Tabernero, who in his second year of presidency opened the ceremony with a speech reflecting on the thriving community of ESMO. With 23,000 members and continuous expansion, the heavily influential meeting harnesses the power to change the way healthcare professionals apply their expertise in clinical practice. Dr Tabernero emphasised that the 360° approach exhibited by the society begins with "rigorous science"; this is a society which acts and helps to evolve the face of oncology. ESMO is a significant global platform at the forefront of oncology where ground-breaking discovery and science prevails. This year's meeting was not unlike previous years, and powerful conversations ensued.

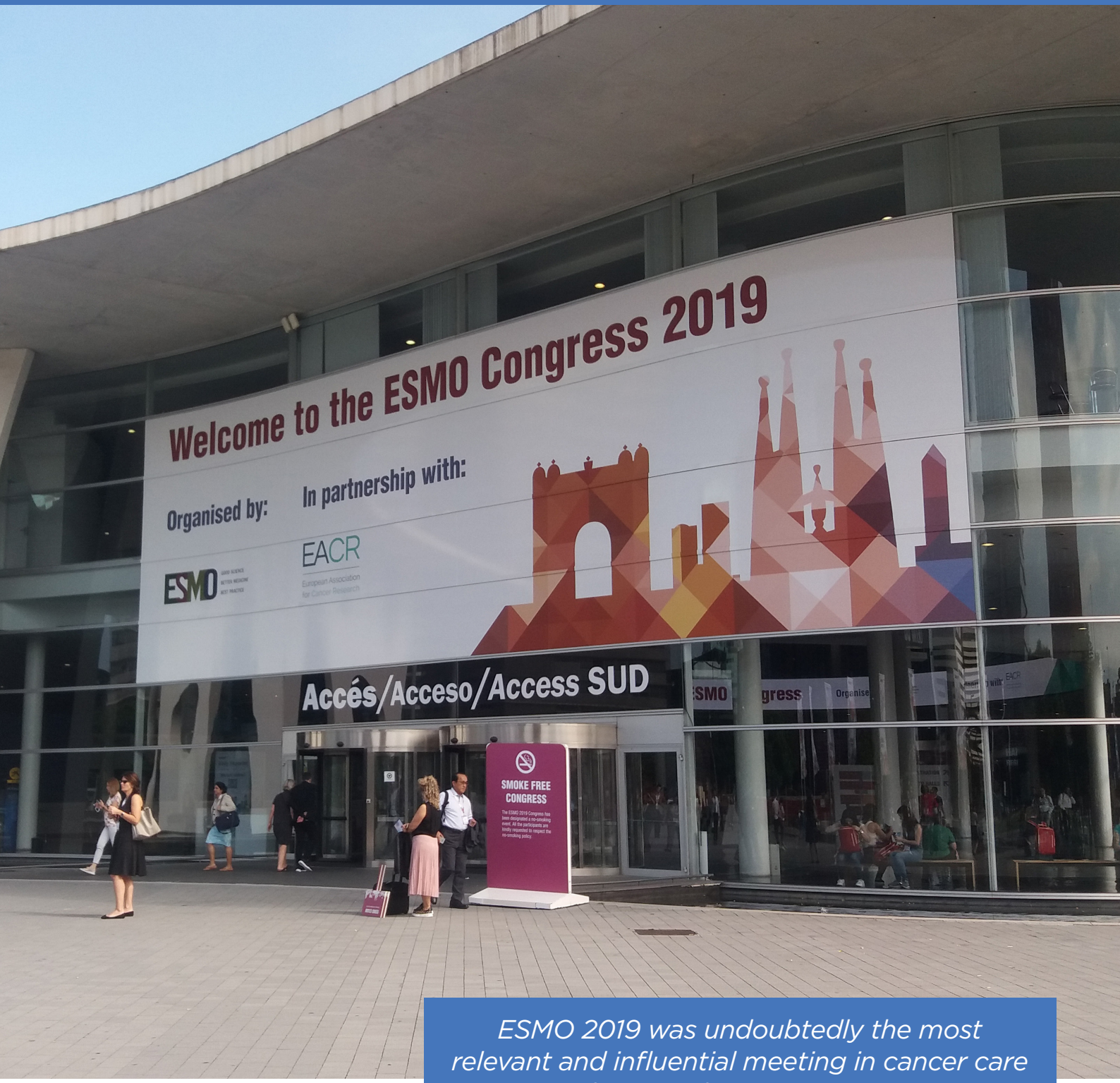
ESMO 2019 received a record-breaking 3,904 late-breaking abstracts, 1,736 of which were presented to delegates who attended the meeting. Herein, we have included a hand-picked selection of abstracts summarised by lead authors who presented their research at the congress. The abstracts summaries included in this review are explorations of some of the hottest topics in the field of oncology, including: treatment of non-resectable or metastatic soft tissue sarcomas by pazopanib in patients who are not eligible for chemotherapy; the burden of cancer in Europe; and results from a descriptive real-life study of collaborative management of immune-related adverse events induced by immune checkpoint inhibitors, amongst many more. The arsenal of outstanding abstracts presented at this year's ESMO Congress are respectfully represented in our collection of summaries.

Numerous sessions presented at the Congress provided exciting updates about cutting-edge research in the field. The studies presented gave plenty to consider, revolutionising conventional practices within the field. The RADICAL-RT trial addressed the side effects of postoperative radiotherapy in prostate cancer versus the benefits in an investigation into whether radiotherapy is required in these circumstances. Results from the ClarIDHy Phase III trial presented at Congress were the first to show the clinical benefit of targeted therapy for the treatment of cholangiocarcinoma and is an important study in support of tumour mutation profiling. Additionally, the combination of chemotherapy and immunotherapy is a prospect seen with utmost gravity for the treatment of bladder cancer, and is presented in the coming pages.

The session 'Level playing field: working for gender balance in oncology', which began with the striking statement that one out of six presidents in oncological societies are woman, is presented as a feature in this review. This was a stimulating discussion about the need for female representation in oncology at a global level, which tackled the balance of gender in medicine and argued that concerns are more far-reaching than a singular closure of the economic gap. The evolutionary advancements of the gender gap in oncology has a long way to go; further progression is mandatory at a faster pace, and necessary actions to take were also highlighted to build on plans for a gender-balanced future.

We had the pleasure of conducting a featured Congress interview with Guillem Argilés, Chair of the Young Oncologists Committee in ESMO.

"ESMO is a significant global platform at the forefront of oncology where ground-breaking discovery and science prevails."



ESMO 2019 was undoubtedly the most relevant and influential meeting in cancer care to happen this year in Europe

Dr Argilés reflects on his week at the congress, shares his thoughts about the benefits conferred by having a mentor, the effect this may have on young oncologists, and what young oncologists can teach the more experienced members of the ever-growing oncology committee.

ESMO 2019 was undoubtedly the most relevant and influential meeting in cancer care to happen this year in Europe, and provided an important platform for breakthrough science and discovery in the field. The initiatives taken at ESMO 2019 will continue to build throughout the next 12 months, and the discussion will inevitably recommence next year at the ESMO 2020 congress in Madrid. To devour more congress content, please enjoy the following review of ESMO's 2019 annual meeting.

Liquid Biopsy Successfully Used to Identify Complex Mutations in Lung Cancer Mutations

TARGETED medicine approaches may be advisable for non-small cell lung cancer (NSCLC) patients based on a simple blood test as opposed to more invasive tumour biopsies. This message was delivered as part of a press release on 30th September 2019 at the ESMO 2019 Congress in Barcelona, Spain. These liquid biopsies are able to detect circulating tumour DNA fragments harbouring NSCLC-specific genomic aberrations such as *ALK* gene rearrangements, and these results could hold wider implications for the ways in which clinicians employ these tests for a variety of other cancer screens.

The Phase III BFAST trial incorporated ≥2,000 untreated NSCLC patients into next-generation sequencing analysis involving blood tests for numerous driver genetic mutations. Of the cohort, 119 patients (5.4%) were seen to have ALK+ disease, and in a subsequent 12-month follow-up in which ALK-targeting alectinib was prescribed to 87 of these patients, 75.9% demonstrated a durative response over the 12 months. Although median progression-free survival was not reached, 12-month progression free survival reported by investigators was 78.4%.

The study represents a breakthrough in NSCLC diagnosis; despite our enhanced ability to identify targetable genetic mutations, challenges existed regarding the suitability of tumour samples for analysis. *ALK* gene rearrangements, although often actionable, are hard to detect, making the possibility of using blood screening for their identification all the more attractive.

"It is encouraging to see that increasing numbers of patients with lung cancer can benefit from liquid biopsy to identify their disease mutation instead of tissue samples," said Prof Alberto Bardelli, University of Turin, Turin, Italy, commenting on the study. "At present the technology is quite expensive but as it becomes more widely used, the cost is likely to come down so that testing becomes more affordable and available in daily practice."

"It is encouraging to see that increasing numbers of patients with lung cancer can benefit from liquid biopsy to identify their disease mutation instead of tissue samples,"

Combination Immunotherapy Significantly Improves 5-Year Metastatic Melanoma Survival

PREVIOUSLY regarded as untreatable due to factors such as chemotherapy ineffectiveness and the treatment difficulty following its spread, metastatic melanoma has been dealt a significant blow as seen from the CheckMate 067 trial results. In this study, one in two metastatic melanoma patients were seen to survive following 5 years of combination immunotherapy, a significant improvement from the standard-of-care. The results were presented as part of a press release on the 28th September 2019 at the ESMO Congress in Barcelona, Spain.

In the longest Phase III follow-up for a checkpoint inhibitor combination therapy, CheckMate 067 enrolled 945 patients with previously untreated Stage III or IV melanoma who were randomly allocated in a 1:1:1 ratio to nivolumab plus ipilimumab, nivolumab plus placebo, or ipilimumab plus placebo. Ipilimumab monotherapy was also compared to each of the nivolumab arms.

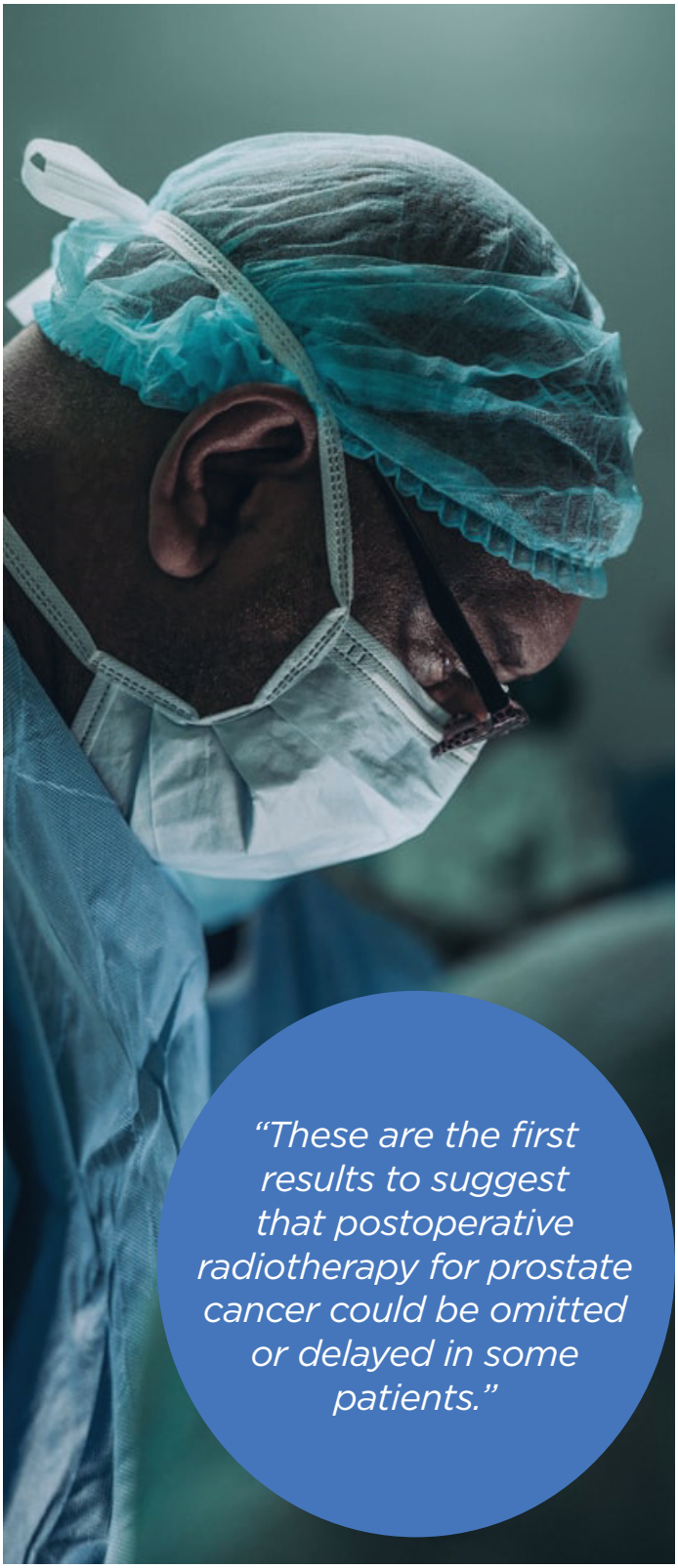
Representing a major improvement on what had be seen historically, 5-year overall survival rates for the nivolumab plus ipilimumab, nivolumab only, and ipilimumab only arms were 52%, 44%, and 26%, respectively. The proportion of patients currently alive and free from subsequent therapy was 45% and 58% for ipilimumab and nivolumab respectively; however, combination therapy increased this to 74%.

Prof James Larkin, study author from Royal Marsden NHS Foundation Trust, London, UK, commented that "this treatment transforms the disease to one with an approximately 50% cure rate. The priority now is to find ways to cure the remaining 50%" Despite this success, the researchers state that there is still work needing to be done in determining which patients are most likely to benefit from combination immunotherapy. "The decision on which treatments to give is a matter for doctors to discuss with individual patients and their families." Additional research is also required for identifying patients resistant to immunotherapy, a vulnerable demographic requiring a different therapeutic approach.

"this treatment transforms the disease to one with an approximately 50% cure rate. The priority now is to find ways to cure the remaining 50%"

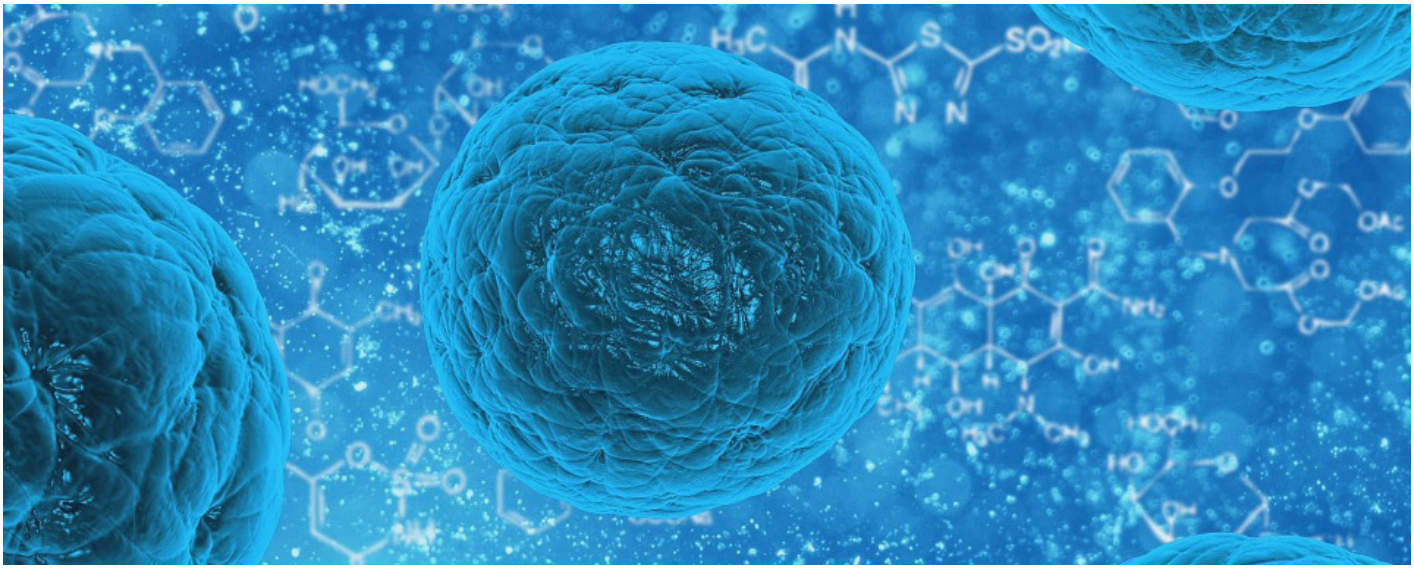
Postoperative Radiotherapy No Longer Necessary in Prostate Cancer Surgery

MEN with prostate cancer may not be required to undergo postoperative radiotherapy for prostate cancer according to the results of a recent study presented at this year's ESMO Congress in Barcelona, Spain, and reported in a press release dated 27th September 2019. Speculation surrounding the detrimental side effects versus the benefits of radiotherapy following prostate cancer surgery was addressed in the RADICALS-RT trial, the largest trial of its kind.



The first author of the study Prof Chris Parker, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK, commented: "The results suggest that radiotherapy is equally effective whether it is given to all men shortly after surgery or given later to those men with recurrent disease. There is a strong case now that observation should be the standard approach after surgery and radiotherapy should only be used if the cancer comes back." This suggests that side-effects, which include urethral stricture and urinary incontinence and that are experienced by many men following radiotherapy, could be avoided. The authors note that whilst complications after surgery alone are still a risk, surgery plus radiotherapy confers an even greater risk.

The study was presented as part of a meta-analysis with results from the RAVES and GETUG-AFU17 trials, a collection of data derived from a total of 2,151 men. The results of the meta-analysis were said to have provided further evidence towards the observational and salvage radiotherapy approach to treatment. Dr Xavier Maldonado, Hospital Universitari Vall d'Hebron, Barcelona, Spain, confirmed, "These are the first results to suggest that postoperative radiotherapy for prostate cancer could be omitted or delayed in some patients." He went on to say that monitoring would be paramount if patients required salvage radiotherapy and longer follow-up to reach the primary endpoint of the trial: to ensure full toxicity report and freedom from distant metastases at 10 years.



Promising Response for First-Line Immunotherapy in Advanced Hepatocellular Carcinoma

DATA on first-line immunotherapy for the treatment of advanced hepatocellular carcinoma (HCC) may indicate preferable clinical outcomes compared to current standard of care for this type of cancer. These results were from a recent study presented at this year's ESMO Congress in Barcelona, Spain, and reported in a press release dated 27th September 2019.

According to the study, first-line nivolumab showed improvements in overall survival, response rate, and safety profile compared to sorafenib which is used as the current treatment for advanced HCC. HCC is typically diagnosed in later stages of the disease, by which point therapeutic options are not readily available. The study author Dr Thomas Yau, University of Hong Kong, Shatin, China, commented on the importance of the results: "The encouraging efficacy and favourable safety profile seen with nivolumab demonstrates the potential benefit of immunotherapy as a first-line treatment for patients with this aggressive cancer."

"...it is becoming apparent that immunotherapy could have a role for the first-line treatment of advanced HCC and the differences in response rates are clinically meaningful."

The trial included 743 participants with advanced HCC who were randomised to receive either nivolumab or sorafenib. Participants who took nivolumab showed a greater median overall survival of 16.4 months compared to those who took sorafenib, who had a median overall survival of 14.7 months. The data from the study did not achieve its statistically significant prespecified primary endpoint for overall survival, therefore the data must be considered accordingly; however, the study did show increased overall survival, higher complete response rate, and participant-reported improved quality of life with nivolumab, suggesting that clinical benefit was observed. Although the study data did not meet its predefined threshold, it offers important insights into HCC therapy, as highlighted by Dr Angela Lamarca, Christie NHS Foundation, Manchester, UK: "...it is becoming apparent that immunotherapy could have a role for the first-line treatment of advanced HCC and the differences in response rates are clinically meaningful."

Increased Anticancer Drug Costs: Are They Worth it?

THE COST of treatment is a major reason for patients to be denied access to newer anticancer treatment drugs. According to two studies presented at a press conference on 27th September 2019 at the annual ESMO congress, Barcelona, Spain, many novel anticancer medicines provide little value for patients compared to standard treatment.

The two studies investigated the connection between clinical benefit and pricing in Europe and the USA in regard to novel cancer medicine. Medicines introduced in the last 15–20 years for solid tumours were investigated to determine whether their monthly treatment costs were associated with clinical benefits. The focus was to determine improved outcomes for factors such survival, quality of life, and treatment complications compared to the standard treatment options.

The first study's results revealed that almost half of the new drugs for treatment of solid tumours approved in Europe between 2004 and 2017 had low added value scores on the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS). Furthermore, more than two-thirds had low value on the Added Therapeutic Benefit Ranking (ASMR) scale used by French drug regulators. Dr Marc Rodwin, Law School, Suffolk University, Boston, USA, stated that "most of the new drugs had low added value, so doctors and patients shouldn't assume that just because a drug is new, it's going to be better." Data revealed that on average new drug costs were €2,525 more per month than active control comparator drugs for the same cancer type.

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Drugs approved for adult solid tumours in four European countries and in the USA from 2009–2017, displayed no link between drug cost and clinical benefit measures by ESMO-MCBS and the American Society of Clinical Oncology Value Framework (ASCO-VF) in the second study. However, median drug prices in Europe were less than half of the USA prices, and the average monthly drug cost for drugs with low benefit scores on ESMO-MCBS ranged from €3,944–4,770 ($4,361–5,273) in the European countries compared to €11,249 ($12,436) in the USA.

These studies delineated that drug costs were not associated with clinical benefit score in the countries investigated. Co-author Prof Kerstin Vokinger, University of Zurich, Switzerland, stated that "some of the more expensive drugs for prostate and lung cancer in Switzerland had lower ESMO-MCBS scores, while cheaper drugs had higher scores. Therefore, it is important that drug pricing is aligned with clinical value and that resources are spent on innovative medicines that offer improved outcomes."

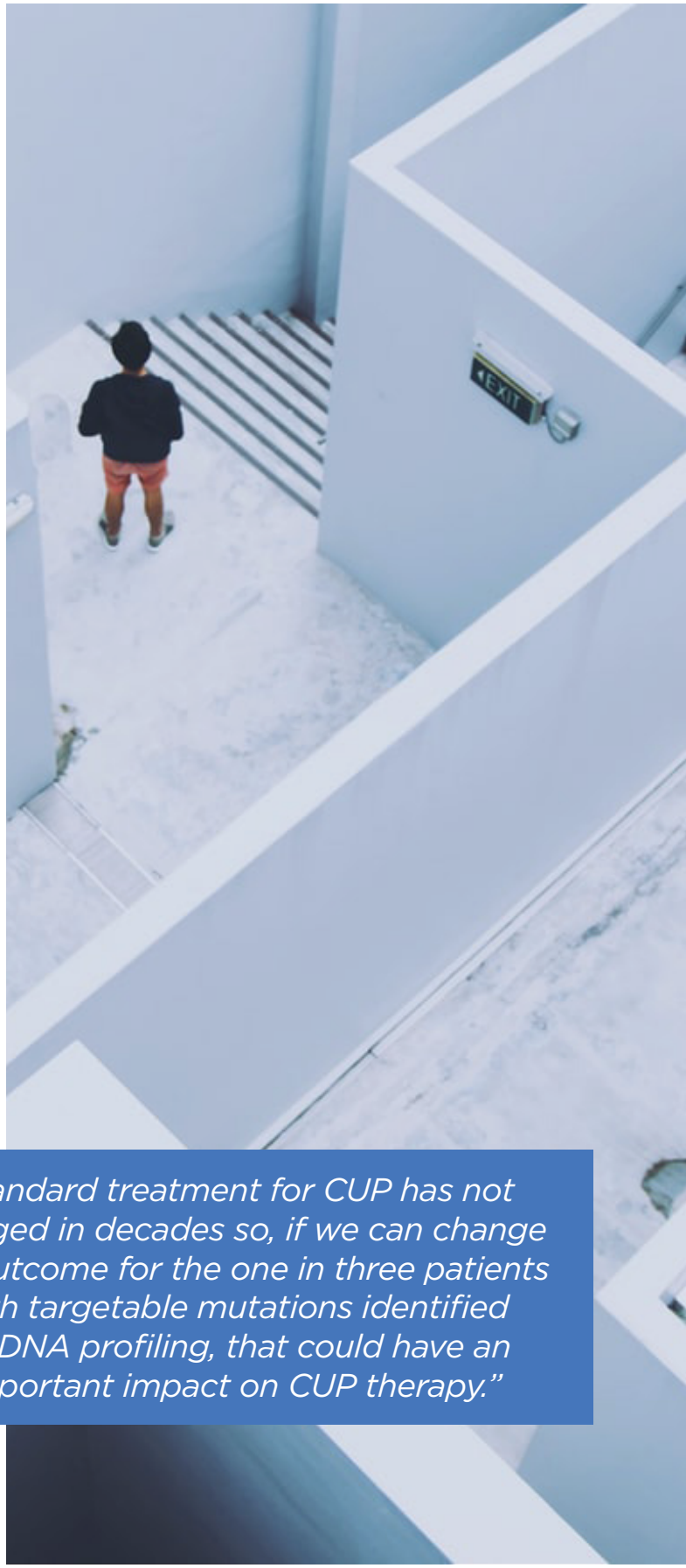
Drugs Targeted to DNA Alterations may Improve Patient Outcomes for Cancers of Unknown Primary

METASTASISED tumours are difficult to treat for many reasons, one of which being that no primary tumour site can be identified by the time of diagnosis. This results in approximately one in three patients not being adequately treated with standard chemotherapy. Novel treatments for these cancers, commonly known as carcinoma of unknown primary (CUP), are now being revealed by DNA profiling, as revealed in a study at ESMO 2019 and stated in a press release dated the 28th September.

Following an unsuccessful identification of the cancer site of origin from which the cancer has spread, the patient receives standard anticancer treatment, with little chance of a cure or palliative care to relieve symptoms. Surprisingly, CUP affects 1 in 15 cancer patients, and of these, only 1 in 10 survive for 1 year. Results from a study presented at ESMO 2019, that analysed 303 CUP tissue samples in search of DNA changes that could be targeted, revealed that 32% of the cancers could have been targeted with recent, mutation-specific drugs.

The first author of the study, Prof Jeffrey Ross, Upstate Medical University, Syracuse, New York, USA, commented that: "standard treatment for CUP has not changed in decades so, if we can change the outcome for the one in three patients with targetable mutations identified by DNA profiling, that could have an important impact on CUP therapy."

The techniques that were used in this study are now being applied in the ongoing prospective CUPISCO trial, which is randomising CUP patients to either standard platinum-based chemotherapy or individualised targeted treatment or immunotherapy based on their tumour's genetic mutations. Prof Ross urged that: "CUP is a bit of a pariah because people don't understand it and assume that nothing can be done. We need to change that attitude and encourage clinicians to look for and treat the drivers of each patient's disease as shown by DNA profiling."



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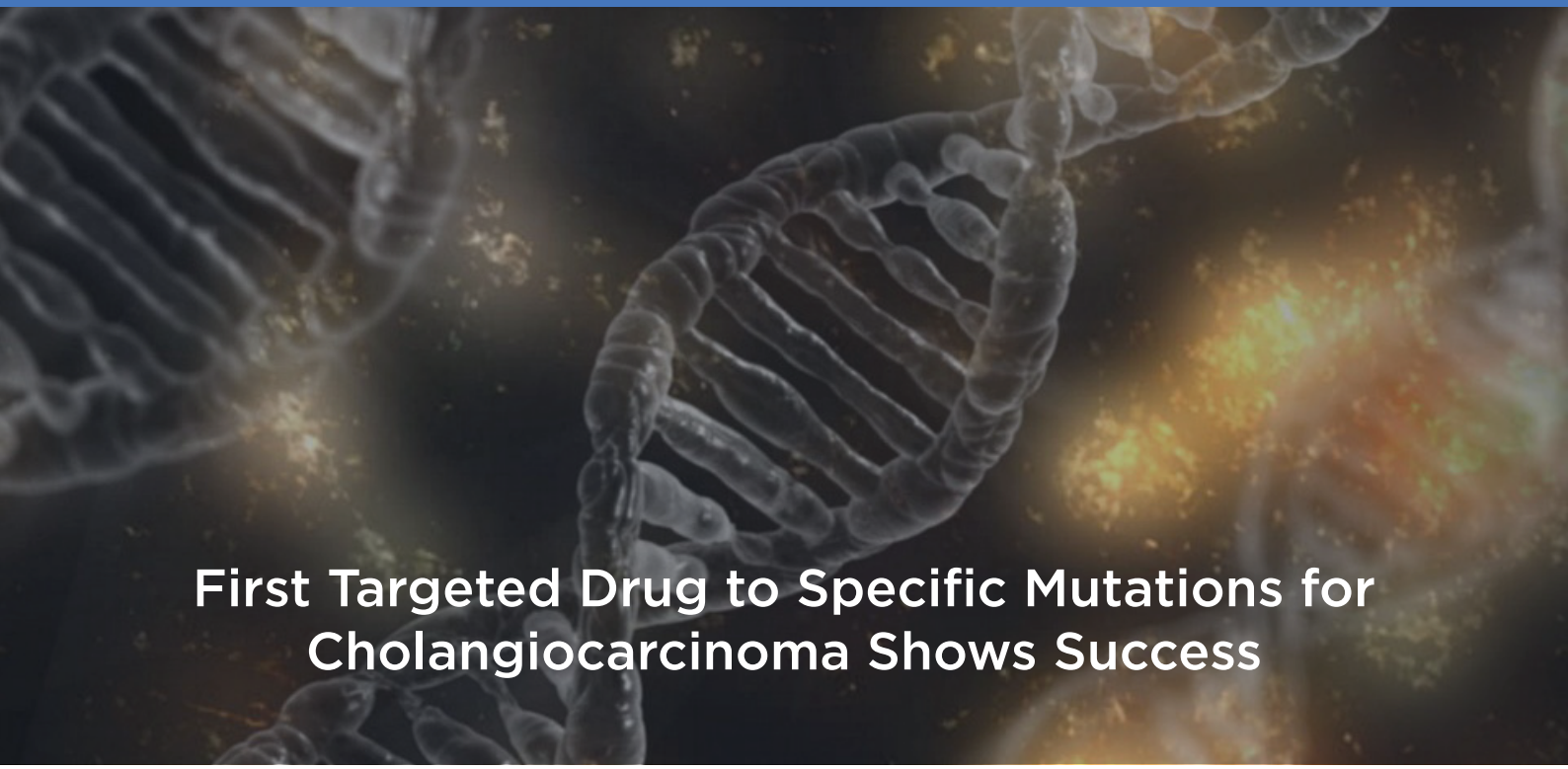


First Targeted Drug to Specific Mutations for Cholangiocarcinoma Shows Success

CHOLANGIOCARCINOMA is an aggressive subtype of bile duct cancer and has a poor prognosis. Most patients die from the disease; therefore, new treatments that are more directed to the specific disease need to be developed. The results of the ClarIDHy Phase III trial, that were presented at the ESMO 2019 Congress in a press release dated 30th September, are the first to show the clinical benefit of targeted therapy for the treatment of cholangiocarcinoma.

Dr Chris Verslype, University Hospital Leuven, Leuven, Belgium, noted: "It is the first time in cholangiocarcinoma that a Phase III study tests a drug targeted to a specific anomaly, and it seems to work. Importantly, you identify suitable patients by selecting them for *IDH1* mutation. It is precision medicine brought to the clinic. And it is very likely to change clinical practice. It will, for sure, drive the further development of targeted therapy for this disease."

The study investigated whether the drug ivosidenib, that targets the isocitrate dehydrogenase 1 (I*DH1*) mutation that is seen in 15% of patients, improves the progression-free survival (PFS) in cholangiocarcinoma patients. Patients with advanced cholangiocarcinoma and *IDH1* mutations (N=185) were randomised to ivosidenib or matched placebo. When the patient's disease progressed, they could crossover from placebo to ivosidenib.

"It is the first time in cholangiocarcinoma that a Phase III study tests a drug targeted to a specific anomaly, and it seems to work."

Median PFS was significantly longer in the ivosidenib group compared to placebo (2.7 months versus 1.4 months, respectively; hazard ratio: 0.37; 95% confidence interval: 0.25–0.54; p<0.001). Furthermore, the median PFS rate at 6 months for the ivosidenib group was 32% compared to no patients being progression free at this timepoint.

"The findings mean all patients with cholangiocarcinoma should be tested for *IDH1* mutation. Tumour mutation profiling should be a new standard for the care for patients with this heterogeneous tumour type," commented the study author Dr Ghassan Abou-Alfa, Memorial Sloan-Kettering Cancer Center, New York City, New York, USA.

Novel Front-Line Treatment Changes Treatment Outlook for Non-Small Cell Lung Cancer

OSIMERTINIB significantly lengthens overall survival in patients with the *EGFR* exon 19 L858R mutation implicated in advanced non-small cell lung cancer (NSCLC), compared to older generation EGFR-tyrosine kinase inhibitors (*EGFR*-TKI). These results from the FLAURA trial were presented at a press release on 28th September 2019 at the ESMO congress in Barcelona, Spain.

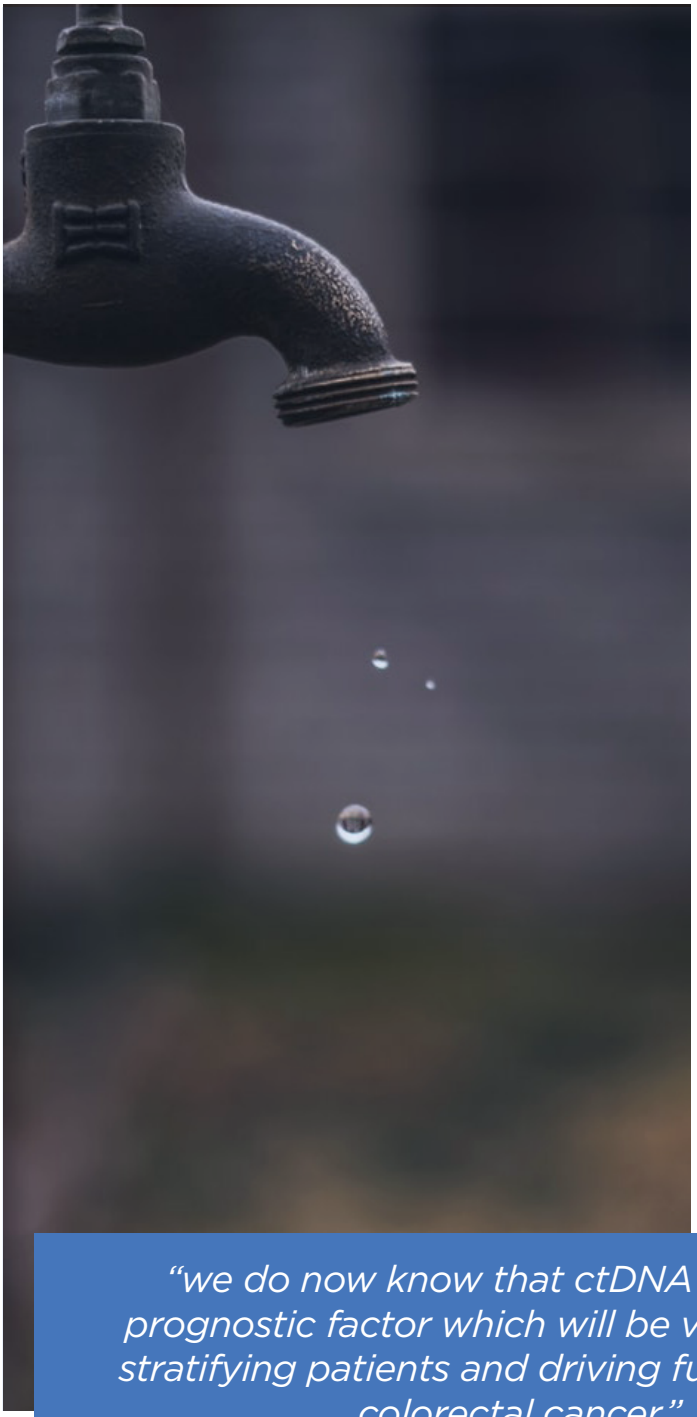
Results from the trial show that median survival with osimertinib was 38.6 months compared to 31.8 months with first generation *EGFR*-TKI, with a hazard ratio of 0.799 (p=0.0462). Furthermore, results revealed that 54% of patients in the osimertinib group were alive at 3 years compared to 44% in the standard care group. Prof Suresh Ramalingam, Winship Cancer Institute of Emory University, Atlanta, USA, stated that "the survival results are both statistically significant and clinically meaningful with first-line osimertinib for *EGFR* mutated patients. This is the first time a TKI has proven to extend survival relative to another TKI in lung cancer therapy."

Prof Ramalingam also stated that 31% of the patients in the control group crossed over to the osimertinib arm after disease progression; as such, a total of 47% of patients in the control group received post-study therapy. Prof Ramalingam validated the findings and stated that this was "consistent with what we would expect in the real-world setting, since only about 50% of patients develop the *T790M* mutation and will be candidates for osimertinib."

According to Prof Ramalingam "FLAURA met both its primary and key secondary endpoints and showed a favourable safety profile for osimertinib. The results further reinforce the clinical utility and superiority of osimertinib in the front-line setting. Based on these data, osimertinib should be the preferred front-line therapy for *EGFR*-mutated lung cancer patients. "Dr Pilar Garrido, Ramón y Cajal University Hospital, Madrid, Spain added that the results are positive for patients and also important for the debate about the best treatment sequence considering that osimertinib is the only TKI approved for second-line treatment in patients who develop resistance to *T790M*. She additionally added that it is important that patients are informed about the survival advantage, yet should the treatment fail the only option is chemotherapy.

"This is the first time a TKI has proven to extend survival relative to another TKI in lung cancer therapy"

Liquid Biopsy Could Play Important Role in Colorectal Cancer Diagnosis



LIQUID biopsy may be of increasing importance in the identification of colorectal cancer (CRC) in patients who are likely to experience a relapse following surgery, and may also allow the opportunity to optimise treatment for patients on an individual basis, according to research presented at ESMO Congress 2019, Barcelona, Spain, and in a press release dated 28th September 2019.

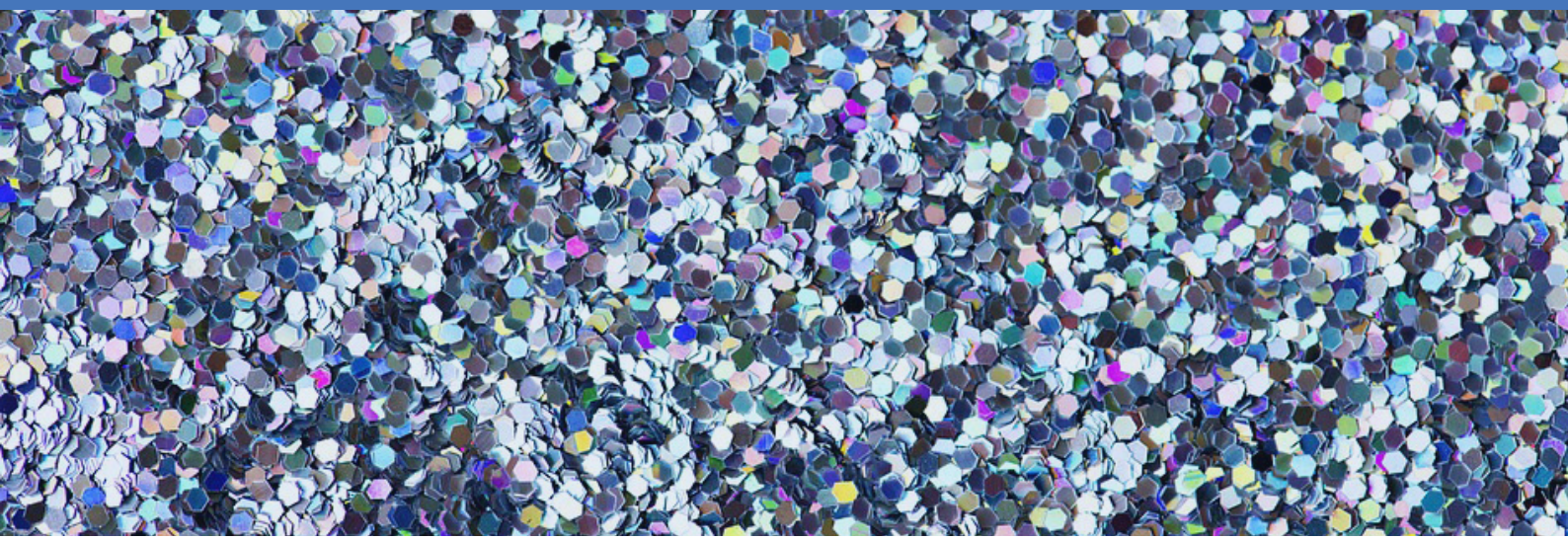
The Phase III IDEA-FRANCE trial studied 805 patients who underwent liquid biopsy before having chemotherapy to treat Stage III CRC. Of the cohort, 109 patients had circulating tumour DNA (ctDNA) found in their blood. Within this group, 2-year disease free survival (DFS) was found to be 64%, compared with 82% of the ctDNA negative group.

Study author Prof Julien Taieb, Prof Hôpital European Georges Pompidou, Paris, France, discussed the study: "In this large prospective trial, we confirmed that ctDNA is an independent prognostic factor in colorectal cancer and that approximately six out of ten patients who are ctDNA positive will remain disease-free 2 years after standard adjuvant chemotherapy, compared to eight out of ten of those who are ctDNA negative."

Results from the study also showed that adjuvant treatment over 6 months was superior to 3 months of treatment, in both ctDNA positive and ctDNA negative patients. Treatment for 6 months in ctDNA positive patients was also found to result in a similar prognosis to ctDNA negative patients who underwent 3 months of treatment. In 90% of cases, adjuvant therapy was folinic acid, fluorouracil, and oxaliplatin.

"we do now know that ctDNA is a major prognostic factor which will be very useful in stratifying patients and driving future trials of colorectal cancer,"

"ctDNA testing did not predict which patients should have 3 or 6 months of adjuvant chemotherapy and there is continuing debate over the optimal type and duration of treatment for patients who are ctDNA positive, but we do now know that ctDNA is a major prognostic factor which will be very useful in stratifying patients and driving future trials of colorectal cancer," continued Prof Taieb, adding: "In all subgroups, ctDNA positive patients who only had 3 months of adjuvant therapy had the worst prognosis."



Exciting New Prospect for Bladder Cancer Patients

> *"This is remarkable. We are now eager to see if patients receiving the two therapies together live longer, and with a similar quality of life, than those receiving chemotherapy and immunotherapy alone or sequentially."*

COMBINATION therapy with chemotherapy and immunotherapy could offer improved outcomes for some bladder cancer patients according to the results of a recent study presented as part of an ESMO press release dated 30th September. The study compared the combination therapy to chemotherapy or immunotherapy alone of sequentially to assess whether progression-free survival could be improved.

Currently, cisplatin-based chemotherapy is the first-line treatment for patients with metastatic urothelial cancer, and immunotherapies such as the PD-L1 inhibitors atezolizumab and pembrolizumab are approved for patients ineligible or unresponsive to chemotherapy. The current study, named IMvigor130, is the first to assess the outcomes for patients administered a combination of both treatments, whether they are eligible or ineligible for chemotherapy. The study enrolled 1,213 patients with metastatic urothelial cancer from 35 countries and randomised them 1:1:1 to receive A) atezolizumab plus platinum-based chemotherapy, B) atezolizumab alone, or C) placebo plus platinum-based chemotherapy. Chemotherapy plus atezolizumab improved the median time to progression of metastatic tumours by 2 months in comparison to chemotherapy alone. Furthermore, the patients in Arm A had an 18% reduced likelihood of progression. An additional trend was noted for improved survival in patients with overexpression of PD-L1 who were treated with atezolizumab alone compared to chemotherapy.

Dr Enrique Grande, MD Anderson Cancer Centre, Madrid, Spain, was lead author of the study and commented: "This is a new option for the upfront treatment of patients with metastatic urothelial cancer. Longer follow-up is needed on overall survival and we will continue to search for biomarkers to identify which patients respond best to this therapy." Dr Ignacio Durán, Hospital Universitario Marques de Valdecilla-IDIVAL, Santander, Spain, added: "This is remarkable. We are now eager to see if patients receiving the two therapies together live longer, and with a similar quality of life, than those receiving chemotherapy and immunotherapy alone or sequentially. The interim analysis of overall survival seems to be promising, but data are immature: overall survival data are needed to consider the combination of chemotherapy and immunotherapy as a new standard of care."