MUNICH 2018 ESMO

DAILY REPORTER

SECURING ACCESS TO OPTIMAL CANCER CARE

TUESDAY
23 OCTOBER 2018

Today's Top Picks

Expanding immunotherapy for recurrent or metastatic head and neck squamous cell carcinoma

Pembrolizumab and nivolumab have demonstrated durable improvements in outcomes for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) following progression on or after platinum-containing chemotherapy. HNSCC represents a good target for immunotherapy as there is active immunosurveillance in the tumour microenvironment. Indeed, PD-L1 expression is often observed in HNSCC, which correlates with decreased overall survival (OS).[1] Several trials are investigating expanded use of checkpoint inhibitors as single agents and in combination with established treatments as well as with novel immune modulators.

In the Presidential Symposium yesterday, Professor Barbara Burtness (Yale University School of Medicine, New Haven, CT, USA) revealed promising new late-breaking data from the KEYNOTE-048 phase III trial of pembrolizumab in the first-line setting as monotherapy or in combination with a platinum chemotherapy plus 5-fluorouracil (5-FU) versus the standard EXTREME (cetuximab with platinum chemotherapy plus 5-FU) regimen (Abstract LBA8_PR). In the second interim analysis, pembrolizumab monotherapy significantly improved OS versus the EXTREME regimen in the subgroup of patients with PD-L1 combined positive score (CPS) ≥20 (hazard ratio [HR] 0.61; 95% confidence interval [CI] 0.45–0.83; p=0.0007) and ≥1 (HR 0.78; 95% CI 0.64–0.96; p=0.0086). The data in patients with CPS ≥20 were viewed as particularly exciting. The combination of pembrolizumab plus chemotherapy significantly improved OS versus EXTREME in the total unselected population (HR 0.77; 95% CI 0.63–0.93; p=0.0034). OS hypotheses to be tested at the final analysis include the superiority of pembrolizumab alone versus EXTREME in the total population and the superiority of pembrolizumab plus chemotherapy versus EXTREME in CPS ≥20 and ≥1 populations. Pembrolizumab alone and in combination had an at least comparable safety profile versus EXTREME. Professor Burtness concluded, "Pembrolizumab appears to prolong life even when the cancer continues to grow, suggesting it should be first-line therapy in recurrent or metastatic HNSCC. Whether pembrolizumab is given alone or with chemotherapy may depend on PD-L1 expression and we are conducting analyses to answer this question."

Promising data support the first-line use of checkpoint inhibitors in the treatment of recurrent or metastatic HNSCC.

In another approach, it has been hypothesised that the activity of the PD-L1 inhibitor, durvalumab, may be enhanced by overcoming intratumoural immune suppression using danvatirsen, an antisense oligonucleotide STAT3 inhibitor. Professor Ezra Cohen (Moores Cancer Center, University of California at San Diego, CA, USA) presented data from the SCORES phase Ib/II study that included patients with recurrent or metastatic HNSCC (Abstract 10440). Early results suggest encouraging antitumour activity with durvalumab plus danvatirsen in PD-L1-naïve patients. Further studies with combination immunotherapies in HNSCC are awaited.

1. Schneider S, et al. Histopathology 2018;73:573–84

The ESMO 2018 *Daily Reporter*: A round up of the Congress

Markus Joerger
Editor-in-Chief of the ESMO 2018 Daily Reporter, Cantonal Hospital, St. Gallen, Switzerland

All too soon, we find ourselves at the end of another extraordinary ESMO Congress! This is the ideal opportunity for the team at the *Daily Reporter* to look back over this year's newspaper editions and to ask ourselves if we did justice to the huge amount of data being presented at the meeting. I think we did.

It's quite a responsibility to be tasked with providing interesting and informative snapshots of each day's proceedings and also to make delegates aware of what we consider to be the most interesting sessions on offer. Conscious that Congress delegates come from all walks of oncology care, we tried to provide content combining articles with both specialist and broad appeal. Never an easy task, this year's editorial board, with its wide-ranging expertise, has risen to the occasion and has helped to produce a newspaper that has given delegates highlights from across the variety of tracks and sessions. The late-breaking abstracts, which are crucial to providing delegates with the latest information from trials, are always one of the main attractions at the Congress and the *Daily Reporter* has featured 28 of these over the course of the meeting, a number of which were simultaneously published in high-ranking peer-reviewed journals. While it is almost impossible to select the team's highlights from this year's newspapers, I think that the articles on SOLO1, JAVELIN Renal 101, IMpassion130, STAMPEDE, and KEYNOTE-048 merit particular mention because the data are practice changing. Finally, before I sign off, I would like to thank the editorial team—Carmen Criscitiello, Alessandra Curioni-Fontecedro, Rodrigo Dienstmann, Anna Maria Frezza, Matteo Lambertini and Jon Zugazagoitia—for all their hard work in bringing the *Daily Reporter* to you each day and to thank you for taking the time to read it.

From left to right: Matteo Lambertini; Carmen Criscitiello; Markus Joerger; Rodrigo Dienstmann and Alessandra Curioni-Fontecedro

ESMO 2018 all the facts & figures

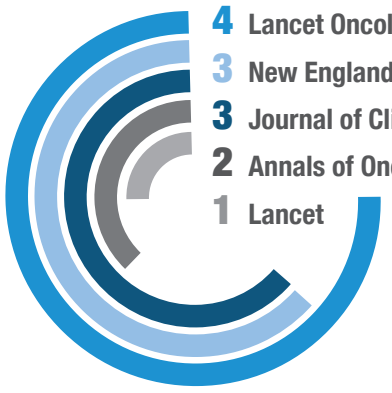
~28k Participants

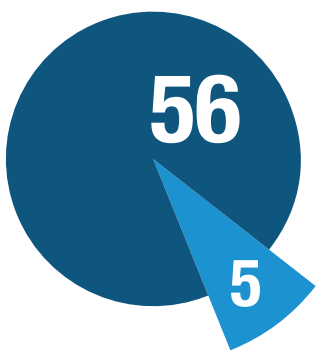
138 Countries

578 Invited speakers

20k ESMO Members

Simultaneous publications



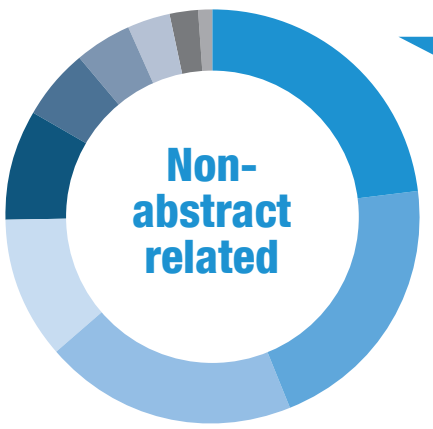


Satellite symposia

ESMO Colloquia

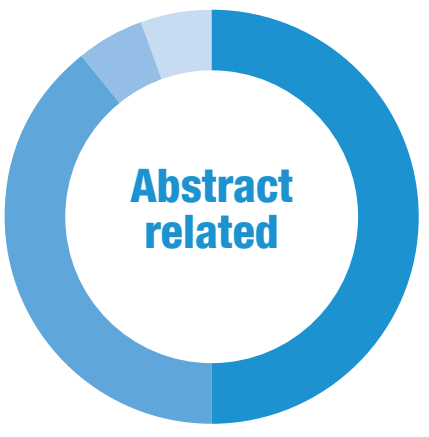
Accepted Abstracts

2052 **66** LBAs



- 21 Special symposia
- 19 Ad-hoc special sessions
- 18 Multidisciplinary sessions
- 10 Young Oncologists sessions
- 8 Patient Advocacy sessions
- 5 Controversy sessions
- 4 Joint symposia
- 3 Keynote sessions
- 2 Congress Highlights
- 1 Opening session

75% Scientific **195** SESSIONS **25%** Educational



- 28 Poster discussion sessions
- 22 Proffered paper sessions
- 3 Presidential Symposia
- 3 Poster sessions

- 25 Educational sessions
- 21 Challenge your expert
- 2 Clinical Practice Guidelines

ESMO would like to thank the *Daily Reporter* Editorial Team, Editor-in-Chief Markus Joerger and the Associate Editors Carmen Criscitiello, Alessandra Curioni-Fontecedro, Rodrigo Dienstmann, Anna Maria Frezza, Matteo Lambertini and Jon Zugazagoitia, together with TMC Strategic Communications, for their dedication in bringing you all the important news from ESMO 2018.

We think you will agree that the team did an amazing job of reflecting the Congress tagline in their articles and reports, and in representing the wide variety of sessions taking place at the meeting. Congratulations on another successful year!

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Further evidence of activity for atezolizumab plus chemotherapy in NSCLC: First-line data

Atezolizumab combinations have previously demonstrated clinical benefit in patients with advanced non-small-cell lung cancer (NSCLC).[1,2] These observations are supported by first data from the phase III IMpower130 trial, which were reported yesterday in a Late-Breaking Abstract presentation by Professor Federico Cappuzzo (Azienda Unità Sanitaria Locale della Romagna, Ravenna, Italy; Abstract LBA53). The study—in treatment-naïve patients with stage IV non-squamous NSCLC—met its co-primary endpoints of overall survival (OS) and progression-free survival (PFS).

At a median follow-up of ~19 months, atezolizumab combined with carboplatin and nab-paclitaxel (CnP; n=451) demonstrated statistically significant improvements in OS and PFS compared with CnP alone (n=228); median OS was 18.6 months versus 13.9 months, respectively (hazard ratio [HR] 0.79; p=0.033) and median PFS was 7.0 months versus 5.5 months (HR 0.64; p<0.0001). Benefits in outcomes were observed with the atezolizumab combination compared with the CnP arm regardless of PD-L1 expression (high, low and negative).

The addition of atezolizumab to first-line CnP chemotherapy resulted in significant survival benefits for patients with advanced NSCLC.

1. Socinski MA, et al. N Engl J Med 2018;378:2288–301
2. Giaccone G, et al. Eur J Cancer 2015;51:S107–8

Patients and priorities for future breast cancer research

Fatima Cardoso
Champalimaud Clinical Center, Lisbon, Portugal

Male breast cancer is a rare and therefore seldom studied malignancy, although there are reports of a rising incidence.[1] Clinical and pathological features may differ between male and female disease,[1] but the management of male breast cancer is primarily based on experience in women. Efforts are therefore being made to improve knowledge of the disease by scrutinising large retrospective databases and designing prospective, randomised studies for men with breast cancer. Findings from several such investigations were reviewed in a Poster Discussion Session yesterday.

A large (N=16,701), comprehensive analysis of a multicentre database that compared one of the largest series of metastatic breast cancer in men (n=149) with a matched cohort of female cases, reported comparable outcomes and treatment effects (Abstract 294PD_PR). Similarly, safety data from a phase IIIb open-label study (CompLEEment-1) that included 39 male breast cancer patients found safety and tolerability of ribociclib (plus letrozole and goserelin) to be consistent with that previously reported in female postmenopausal patients (Abstract 293PD_PR). A prospective, randomised phase II multicentre study of 52 male breast cancer patients noted substantial reductions in oestradiol levels with gonadotropin-releasing hormone analogue combinations compared with increases following tamoxifen, the standard of care for hormone receptor (HR)-positive female breast cancer (Abstract 273PD_PR).

Male breast cancer and advanced HR+, HER2- premenopausal disease have been relatively neglected areas of breast cancer research.

Until recently, patients with premenopausal, HR-positive, HER2-negative advanced breast cancer have also been under-represented in clinical trials. The phase III MONALEESA-7 study in this setting demonstrated a doubling in progression-free survival in women who received ribociclib plus endocrine therapy compared with placebo plus endocrine therapy, a result very similar to the outcome obtained in post-menopausal women with the same treatment. Even though grade 3–4 adverse events were increased in the ribociclib arm,[2] according to patient-reported outcomes (PRO) data shared on Saturday (Abstract 291O), health-related quality of life (HRQoL) did not appear to be compromised. Clinically meaningful improvements in HRQoL were observed with ribociclib compared with worsening HRQoL in the placebo arm, underlining the importance of PRO in determining the overall impact of a treatment.

Patients can also help to inform future research priorities in metastatic breast cancer. A poster presented yesterday featured a top-10 list of research questions that matter most to patients and caregivers compiled from more than 1,000 survey responses (Abstract 354P). Research priorities were wide ranging and included biomarkers, the role of immunotherapy and management of treatment resistance.

1. Sanguinetti A, et al. Int J Surg Case Rep 2016;20S:8–11
2. Tripathy D, et al. Lancet Oncol 2018;19:904–15

A distinct tumour phenotype with high microsatellite instability and low tumour mutational burden

High tumour mutational burden (TMB-high) has been linked to high levels of neoantigens, cytotoxic immune infiltration and susceptibility to immune checkpoint inhibitors. High levels of genomic microsatellite instability loci (MSI-high), arising from defects in the DNA mismatch repair system, has been proposed as a surrogate for increased TMB and immunotherapy response.[1,2]

However, according to analysis of 1,057 MSI-high tumours of varying cancer types, around one-quarter had, in fact, low/intermediate TMB (TMB-LI) and not TMB-high (Abstract 1835PD). Among the cancer types with N>40 samples available, prevalence of MSI-high/TMB-LI tumours varied between cancer types, being highest in endometrial cancers and lowest in colorectal cancers (CRCs).

MSI-high/TMB-LI tumours may respond differently to immunotherapy.

MSI-high/TMB-LI tumours had lower mutational rates in homologous recombination and histone modifier genes as compared with MSI-high/TMB-high tumours. "These findings are interesting as they suggest that there may be other mechanisms for increased TMB and that MSI-high/TMB-LI tumours represent a distinct disease entity. If so, it will be important to evaluate how this tumour subtype responds to immunotherapy," comments Dr Ramon Salazar from Catalan Institute of Oncology, Barcelona, Spain.

Late-breaking first results from the CheckMate-142 trial raise hopes of a new first-line immunotherapy option for patients with MSI-high CRC (Abstract LBA18_PR). An objective response rate of 60%, including three complete responses and 24 partial responses, was seen in 45 patients receiving combined nivolumab and ipilimumab; the median duration of response has not yet been reached after a median follow-up of 13.8 months.

1. Fabrizio DA, et al. J Gastrointest Oncol 2018;9:610–7
2. Hellmann MD, et al. Cancer Cell 2018;33:843–52

Immune checkpoint inhibitors in first-line, advanced NSCLC: Expanding the evidence

Standard of care for first-line non-small-cell lung cancer (NSCLC) has long consisted of platinum-based doublet chemotherapy, although the PD-1 inhibitor pembrolizumab is now an alternative option as a single agent for patients with high PD-L1 expression (without *EGFR* or *ALK* tumour mutations) or combined with chemotherapy.

Several phase III trials are exploring other immunotherapy regimens as first-line treatment for advanced/metastatic NSCLC and new data from two trials were presented in Late-Breaking Abstract presentations at this Congress. The IMpower132 trial evaluated the addition of anti-PD-L1 atezolizumab to platinum-based chemotherapy plus pemetrexed in 578 patients with stage IV non-squamous NSCLC and met its co-primary endpoint of progression-free survival (PFS; hazard ratio [HR] 0.60; 95% confidence interval [CI] 0.49–0.72; p<0.0001; Abstract LBA54). Absolute PFS improvement in the overall population was 2.4 months and was confirmed across key clinical subgroups, including patients from Asia, never smokers, older patients and those without liver metastases at baseline. Preliminary overall survival (OS) data indicate improvements of around 4.5 months. More mature OS data are awaited.

Results were also presented from the second interim analysis of the IMpower131 trial of atezolizumab in combination with chemotherapy in 1,021 patients with stage IV squamous-cell NSCLC (Abstract LBA65). Median PFS was 6.5 months in patients who received atezolizumab, carboplatin and nab-paclitaxel versus 5.6 months without the addition of atezolizumab (HR 0.74; 95% CI 0.62–0.87; p=0.0004) with median OS of 14.6 months versus 14.3 months, respectively (HR 0.92; 95% CI 0.76–1.12; p=0.41). Final results are awaited.

Combining atezolizumab with chemotherapy improved PFS with numerical improvements in OS in first-line advanced NSCLC.

Ovarian cancer has a lasting impact on life and wellbeing

The diagnosis and treatment of ovarian cancer has a particularly detrimental impact on patients' quality of life (QoL).[1] In a survey of patients who were long-term survivors of ovarian cancer (diagnosed >8 years previously), the results of which were presented on Saturday (Abstract 939PD), more than half (52%) of the 239 patients recruited developed recurrent disease and 40% were still undergoing treatment. Symptoms such as fatigue, bone pain and polyneuropathy continued to affect at least 25% of those surveyed. Most patients believed that healthy nutrition (67%) and physical activity (55%) positively impacted the course of their disease and so after being diagnosed, 53% had taken steps to change their eating habits, while 66% exercised regularly.

Describing fear of progression as the 'new kid on the block', Dr Sarah Blagden from the University of Oxford, UK, highlighted it as an important concern for patients with ovarian cancer. In a presentation on Friday, she reported results of the first randomised, controlled study of psychological intervention for ovarian cancer patients, which revealed that both three 90-minute psychological support sessions given 6–12 weeks after chemotherapy and standard of care led to an equivalent improvement in health status and QoL (Abstract 940O). There was an improvement in the symptoms of depression for all patients following completion of chemotherapy. However, only psychological support led to a significant improvement in fear of progression scores.

"Our results show for the first time in a randomised oncology setting that fear of progression is responsive to therapy," said Dr Blagden.

1. Wilson MK, et al. J Gynecol Oncol 2018;29:e81

Combined PD-1 and CTLA-4 inhibition signals a new approach for neoadjuvant treatment in dMMR early colon cancer

Combining nivolumab and ipilimumab has been shown to give durable clinical benefit in advanced mismatch repair-deficient (dMMR) metastatic colorectal cancer (CRC).[1] Yesterday, in a Late-Breaking Abstract presentation, Dr Myriam Chalabi from the Netherlands Cancer Institute, Amsterdam, reported results from the first study to investigate this combination in the neoadjuvant treatment of early-stage colon cancers (Abstract LBA37_PR). Major pathological responses—including 4 complete responses—were observed in all 7 patients with dMMR cancers but not in patients with MMR-proficient (pMMR) tumours. However, significant post-treatment increases in T-cell infiltration were seen in both dMMR and pMMR tumours. Pre-treatment measures of tumour inflammation, including T-cell receptor clonality and IFNγ gene signatures, appeared to have limited value for predicting response.

Neoadjuvant combined immunotherapy could be a potential future standard of care for early-stage dMMR colon cancer.

Professor George Coukos, Ludwig Institute for Cancer Research, Lausanne, Switzerland, commented, "The high immune reactivity of early MSI-positive CRC supports the use of immunotherapy early in the disease. The major pathological response rate reported in this study is astonishing and is one of the most remarkable findings at this meeting." He concluded, "The impressive activity of this nivolumab–ipilimumab combination in the neoadjuvant setting is potentially paradigm shifting in dMMR CRC."

1. Overman MJ, et al. J Clin Oncol 2018;36:773–9

TRIBE-2: First- and second-line FOLFOXIRI/bevacizumab is the most effective treatment option for mCRC

Late-breaking interim results at a median 22.8 months' follow-up from the phase III, randomised TRIBE-2 trial suggest that giving patients with metastatic colorectal cancer (mCRC) FOLFOXIRI/bevacizumab as both first- and second-line therapy is more efficacious than administering first-line FOLFOX/bevacizumab followed by second-line FOLFIRI/bevacizumab (Abstract LBA20). Compared with receiving sequential oxaliplatin- then irinotecan-based therapy (FOLFIRI/bevacizumab), patients receiving FOLFOXIRI/bevacizumab have significantly longer median progression-free survival in both the first-line setting (12.0 months versus 9.9 months; hazard ratio [HR] 0.73; p<0.001) and the second-line setting (18.9 months versus 16.2 months; HR 0.69; p<0.001). The trial, which enrolled 679 patients, is ongoing at multiple sites in Italy.

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Is it time to re-assess trial inclusion criteria?

It is clear that there are barriers to the inclusion of 12–25-year-olds in both adult and paediatric early-phase clinical trials due to arbitrary age limits. This premise follows a review of phase I/II solid tumour and lymphoma trials initiated over a 6-year period at the Gustave Roussy Cancer Campus, Villejuif, France, presented yesterday by Dr Aurore Vozy (Abstract 424P_PR). Of 465 open trials, only 65 (14%) included teenagers aged 12–17 years. Dr Vozy argued that the current age limit for adult trials should be reviewed in Europe; it has already been successfully lowered to 12 years in the USA and presents no additional risk to patients. Access to paediatric clinical trials by young adults (19–25 years) is also obstructed by current upper age limits; over half of the 62 paediatric trials reviewed excluded this age group.

A lower age limit of 12 years for adult trials and an upper limit of 25 years for paediatric trials would make sense in certain cases, suggested Dr Vozy.

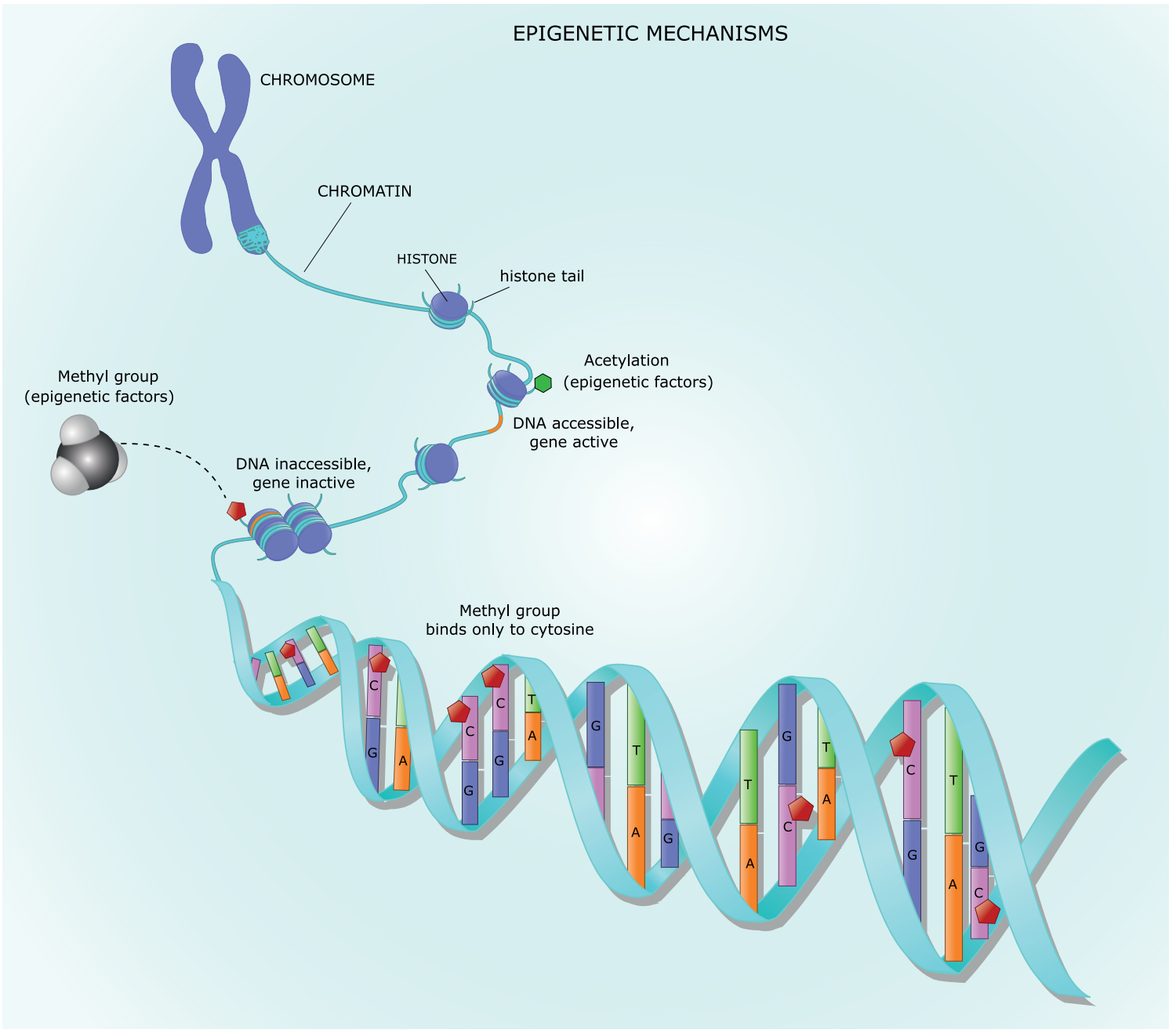
Dr Annalisa Trama from Fondazione Istituto Nazionale dei Tumori, Milan, Italy, said, "Age eligibility criteria are still applied to many trials despite international recommendations to the contrary. This is disappointing, particularly as UK monitoring studies show that adjusting the age criteria substantially increases the numbers of adolescents/young adults (AYAs) enrolling into trials."

Dr Trama continued, "But age is just one factor that restricts access to cancer trials for AYAs. Other factors influencing the availability of trials for AYAs include the lack of preclinical research, tissue availability (already reduced by lesser involvement in trials) and pharmaceutical company incentives to conduct high-cost trials for this patient group. Collaboration among AYA representatives and the paediatric and adult communities is also needed to improve recruitment."

The study findings are pertinent given that the incidences of some cancers are increasing in younger populations. Yesterday, Dr Aimilia Exarchakou (London School of Hygiene and Tropical Medicine, UK) reported an almost 3-fold increase in the incidence of colorectal cancer (CRC) among 20–29-year-olds in England between 1993 and 2014 (Abstract 1559O).

"These data call for biological and translational research studies to understand the biological characteristics of CRC in AYAs, and elucidate whether these differ from adult CRC. A major challenge here is the availability of AYA tumour tissue owing to the relatively rare occurrence of CRC in this age group. Establishing a centralised repository of tissue from AYAs with CRC is urgently needed," said Dr Trama.

Precision medicine—what's on the horizon?



Improved understanding of cancer cell molecular drivers is increasingly allowing therapy to be tailored to the individual, and targeted therapy and immunotherapy herald new hopes for patients. Currently, one of the hottest areas of research is epigenetics—enzymes and protein domains that regulate gene expression and that may be involved in cancer pathogenesis.[1]

Epigenetic changes, such as the silencing of a tumour suppressor gene, can lead to uncontrolled cell growth. However, these changes are reversible, and targeting epigenetic regulators may be a promising approach to managing cancer.

Latest data on epigenetic-targeted drugs presented at this year's ESMO Congress.

In a phase I/IIa study of one of a new class of drugs targeting the epigenetic readers, bromodomain and extra-terminal (BET) proteins, BMS 986158 showed dose-dependent and reversible pharmacodynamic effects on BET gene expression and was well tolerated in 68 safety-evaluable heavily pretreated patients with advanced cancer (Abstract 4110). Preclinical data with NE02734—a novel, potent dual inhibitor of BET and two other bromodomain-containing proteins—revealed significant antiproliferative activity across a spectrum of solid cancers, with an effect greater than BET inhibition alone (Abstract 429P). Clinical studies of NE02734 are planned.

The first-in-class small molecule, tazemetostat, an oral inhibitor of enhancer of zeste homologue 2 (EZH2), is an epigenetic silencer and cell cycle regulator. In a two-stage, phase II study in 32 patients, tazemetostat was generally well tolerated but failed to pass stage-two futility criteria. However, long-term clinical activity was seen in 3 patients with INI1-negative sinonasal or spindle-cell sarcomas, which have oncogenic dependence on EZH2 (Abstract 1611PD).

Tipifarnib is an inhibitor of farnesyltransferase, a key enzyme in the function of *HRAS*, a proto-oncogene overexpressed and mutated in several cancers. Preliminary phase II data demonstrated that 6 of 11 evaluable patients with *HRAS* mutated head and neck squamous cell carcinomas not responding to previous therapy achieved a confirmed partial response with tipifarnib (Abstract 10460).

"Targeted therapies, particularly epigenetics, are very hot at the moment and we hope that encouraging preliminary data from some studies will translate into exciting new future treatment options," commented Professor Fabrice André (Institut Gustave Roussy, Villejuif, France). "However," he advised, "to optimise time and resource use, precision medicine research must focus on the clinically actionable targets most likely to impact patient management.[2]"

1. Biswas S, Rao CM. Eur J Pharmacol 2018;837:8–24
2. Mateo J, et al. Ann Oncol 2018;29:1895–902

Do MAGE-A SPEAR T-cells have potential as cancer immunotherapy?

The highly targeted investigational therapy consisting of melanoma-associated antigen (MAGE) specific peptide enhanced affinity receptor (SPEAR) T-cells utilises a patient's T-cells to produce a genetically engineered T-cell receptor (TCR) protein directed against family A (MAGE-A). MAGE-A cancer antigens are expressed at relatively high levels in several solid tumours, including non-small-cell lung cancer (NSCLC), melanoma, urothelial and head and neck cancers. First-in-human phase I dose-escalation trials are ongoing and preliminary findings from three studies were presented on Saturday.

In a Late-Breaking Abstract presentation (Abstract LBA38), data from two studies investigating MAGE-A10c796T in 11 patients with the above tumour types reported serious adverse events (SAEs) in 7 patients, including two cases of cytokine release syndrome (CRS) and one case of haemoptysis related to T-cell therapy. The investigators noted that there was no evidence of off-target binding or alloreactivity. As efficacy was limited at the dose levels studied and most adverse events were consistent with other immunotherapies, both trials are ongoing with dose escalation.

A third study (Abstract 1156P) is exploring the safety of MAGE-A4c1032T in a range of advanced solid tumours. Initial data were presented from 6 patients treated at two different doses (0.1×10^9 [n=3] and 1.0×10^9 [n=3]), all of whom had stage III–IV ovarian cancer. Investigator-assessed best responses were stable disease in 4 patients and disease progression in two. T-cell infusion-related SAEs comprised CRS, encephalopathy and muscular weakness, and treatment-related SAEs were seen in 2 patients. Transduced T-cells were detectable in the peripheral blood and showed greater persistence over time at the higher dose.

SPEAR T-cells were detectable in the peripheral blood of patients with ovarian cancer.

Dr Alessandra Curioni-Fontecedro, Associate Editor of the ESMO 2018 *Daily Reporter* (University Hospital of Zurich, Switzerland), commented, "Despite severe side effects occurring in all three trials, targeted T-cell treatments represent a new, interesting way to treat solid tumours."

Immunotherapy plus BRAF/MEK inhibitor combination increases duration of response in *BRAF*-mutated advanced melanoma

Combination therapy with BRAF and MEK inhibitors is associated with response rates of up to 70% in patients with *BRAF*-mutated melanoma; however, response duration remains limited.[1] Immunotherapy is revolutionising the treatment of many advanced-stage cancers. This could also include patients with advanced melanoma, according to phase II data from part 3 of the 5-part KEYNOTE-022 trial, presented yesterday (Abstract 1244O).

Part 3 of KEYNOTE-022 is a randomised, placebo-controlled trial of pembrolizumab in combination with the BRAF inhibitor, dabrafenib, and MEK inhibitor, trametinib, in patients with treatment-naïve, *BRAF V600E/K*-mutated, advanced melanoma.

The objective response rate with pembrolizumab plus dabrafenib–trametinib was 63% versus 72% with dabrafenib–trametinib alone, with a higher proportion in the pembrolizumab arm achieving a complete response (18% versus 13%). Notably, median duration of response was 18.7 months with the pembrolizumab combination versus 12.5 months with BRAF/MEK inhibition alone.

Response durations of ≥18 months were more frequent with pembrolizumab–dabrafenib–trametinib versus dabrafenib–trametinib alone (60% versus 28%).

The trial also showed significantly longer progression-free survival with the pembrolizumab combination (16.0 months versus 10.3 months; hazard ratio [HR] 0.66; p=0.04287), although this did not reach the study's pre-specified significance threshold (HR ≤0.62 and p≤0.025). These efficacy findings were not without an increase in side effects: patients in the pembrolizumab combination arm experienced more grade 3–5 adverse events (58% versus 27%).

1. Eroglu Z, Ribas A. Ther Adv Med Oncol 2016;8:48–56

Vaccination approach offers hope for patients with HER2 low-expressing TNBC

Patients with HER2 low-expressing triple-negative breast cancer (TNBC) derive significant clinical benefit from a nelipeptimut-S (NeuVax) vaccine in combination with trastuzumab. These are the key findings of a prespecified interim analysis of a randomised phase IIb study presented in a Proffered Paper Session yesterday (Abstract 1128O). The activity of the NeuVax vaccine/trastuzumab combination in reducing recurrence of HER2 low-expressing, node positive and/or TNBC was compared with trastuzumab plus granulocyte-macrophage colony-stimulating factor in 275 patients. The primary endpoint was disease-free survival (DFS) at 24 months.

In patients with HER2 low-expressing TNBC, estimated 24-month DFS was 91.1% in the vaccine arm and 69.9% in the control arm (hazard ratio 0.26; p=0.02). This level of significance was not replicated in the overall study population or in node-positive patients.

Both regimens appeared to be well tolerated; there were no grade 4–5 adverse events and no between-treatment differences in cardiac, local or systemic toxicities.

Professor Giuseppe Curigliano from the University of Milan, Italy, noted, "Patients with TNBC are in desperate need of more effective treatment options and a vaccination approach that is able to reduce disease recurrence could potentially be practice changing. As the authors suggest, this finding should be further explored in a phase III setting. Other potential applications for vaccines like NeuVax can be for the prevention of HER2-positive ductal carcinoma *in situ*."

The clinical benefits of the vaccine–trastuzumab combination were not compromised by increased cardiac or other toxicities compared with trastuzumab alone.

The predictive power of blood-based measurement of tumour mutational burden in NSCLC

Measurement of tumour mutational burden in blood (bTMB) is being evaluated as a potential method to select patients who will benefit from immunotherapy. In retrospective analyses of two phase II trials (POPLAR and OAK), bTMB was found to be a predictive biomarker for progression-free survival (PFS) in patients receiving the anti-PD-L1 antibody, atezolizumab, as monotherapy (second-line and beyond) for non-small-cell lung cancer (NSCLC).[1]

In a Late-Breaking Abstract presentation yesterday, Dr Edward Kim (Levine Cancer Institute, Charlotte, NC, USA) shared new findings from the first prospective study of bTMB, the phase II B-F1RST trial, which evaluated bTMB as a predictive biomarker for atezolizumab in first-line NSCLC (Abstract LBA55). The trial is now fully enrolled (n=153) and data are available from 119 patients in the biomarker-evaluable population.

Over a minimum of 6 months' follow-up, 28 patients with bTMB ≥16 mut/Mb, a cut-off validated in analyses of POPLAR and OAK, had numerically higher median PFS compared with 91 patients with bTMB <16 mut/Mb (4.6 months versus 3.7 months; hazard ratio 0.66; 90% confidence interval 0.42–1.02; p=0.12). Confirmed objective response rates of 28.6% and 4.4% (p=0.0002) were observed in the bTMB high and low subgroups, respectively. Overall survival data are not mature and will continue to be followed.

These primary data suggest that a bTMB cut-off score of ≥16 showed a numerical improvement in clinical outcomes in patients with NSCLC treated with atezolizumab monotherapy.

Further evidence for the utility of bTMB are awaited from the ongoing randomised phase III B-FAST study in first-line NSCLC.

1. Gandara DR, et al. Nat Med 2018;24:1441–8

ESMO Young Oncologist Fellowship Awards

The 2018 Young Oncologist (YO) research fellowship awardees were announced in a ceremony held during the session 'Fellowships in Europe: Educational opportunities for young oncologists' yesterday. Dr Evandro De Azambuja, Chair of the ESMO Fellowship and Award Committee, presented the research awards to the five chosen recipients.

Guiding treatment for breast cancer: What's new?

There is now an unprecedented number of agents for the treatment of patients with early breast cancer and, while the search for new and improved agents must continue, there needs to be a concerted effort to more effectively tailor current therapies to patients.

In the Short-HER trial, 9 weeks of adjuvant trastuzumab plus chemotherapy did not demonstrate non-inferiority to 1 year of treatment; grade ≥2 cardiac events were more frequent with longer treatment.[1] A sub-group analysis revealed that patients with low- and intermediate-risk disease, based on nodal status and tumour size, may benefit from the shorter treatment duration (Abstract 191PD_PR). Five-year disease-free survival (DFS) in the low- and intermediate-risk groups (85% of the total population) was similar in the long- and short-duration arms (hazard ratios [HRs] 0.96 and 0.89, respectively); grade ≥2 cardiac events were greater in the long-duration arm (HRs 2.85 and 2.79, respectively). In a Late-Breaking Abstract presentation, shorter duration of adjuvant trastuzumab (6 months versus 1 year) was found to be cost-effective based on data from the PERSEPHONE trial, with cost savings but no adverse effect on quality of life (Abstract LBA12_PR). Nevertheless, in clinical practice, adjuvant trastuzumab should be administered for up to 1 year.

The Short-HER trial also looked at the prognostic use of tumour infiltrating lymphocytes (TILs), which are associated with improved outcomes in triple-negative breast cancer (TNBC).[2] Over a median follow-up of 6.1 years, an increase in TILs led to better metastasis-free survival (HR 0.76 for each 10% TILs increment; p=0.006; Abstract 1860). Results from the MATADOR trial, comparing adjuvant docetaxel–doxorubin–cyclophosphamide (TAC) with dose-dense doxorubicin–cyclophosphamide (ddAC), suggested that TILs may also help to select the appropriate type of chemotherapy (Abstract 189PD). In patients with high TIL scores (≥20%), relapse-free survival was numerically longer with TAC compared with ddAC; the reverse was true for patients with low TIL scores (<20%).

TILs may be used to direct the duration and type of chemotherapy.

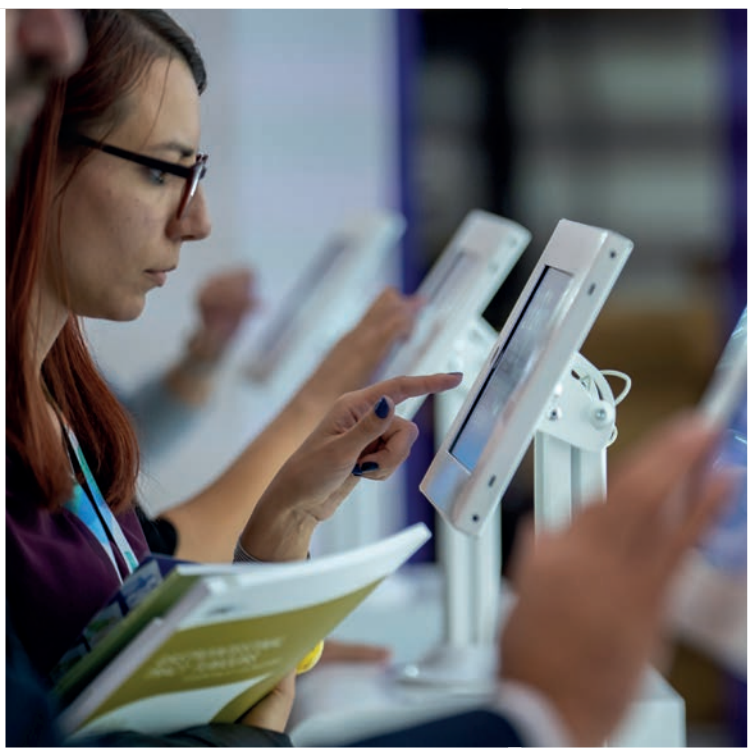
Response as a guide to optimal treatment was also discussed. In a Late-Breaking Abstract presentation of ADAPT TN data, the previously reported pathological complete response (pCR) rate benefit with nab-paclitaxel–carboplatin versus nab-paclitaxel–gemicitabine in TNBC,[3] failed to translate into improvements in 3-year event-free survival and overall survival (Abstract LBA13). In a longer (6-year) follow-up of the phase III NEOS trial in patients receiving letrozole with or without chemotherapy, distant disease-free survival (DDFS) was significantly worse in patients with progressive disease (PD) during neoadjuvant endocrine therapy than in those with responses or stable disease (HR 4.83; p<0.001; Abstract 1840). Predictive PD markers were progesterone receptor status and Ki67.

In the NeoSphere study, PAM50-derived scores for surgical samples from patients with ER-positive tumours and residual disease receiving anti-HER2 therapy were shown to be helpful in identifying those who would benefit from post-neoadjuvant treatment escalation (Abstract 190PD). Finally, in a poster presentation yesterday, circulating tumour cells (CTCs) were identified in 23 of 65 patients with TNBC after neoadjuvant chemotherapy and were independently predictive of decreased relapse-free survival (Abstract 225P).

"These studies highlight just a few of the wide variety of biomarkers that may have the potential to improve treatment personalisation for early breast cancer," said Dr Javier Cortés from the Breast Cancer Research Program at Vall d'Hebron Institute of Oncology, Barcelona, Spain. "Further confirmative studies are required to determine those that can be used confidently in daily clinical practice."

1. Conte P, et al. Ann Oncol 2018. Sep 13. Epub ahead of print
2. Adams S, et al. J Clin Oncol 2014;32:2956–66
3. Gluz O, et al. J Natl Cancer Inst 2018;110:628–37

ESMO 2018: In pictures



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