MUNICH 2018 ESMO

DAILY REPORTER

SECURING ACCESS TO OPTIMAL CANCER CARE

SUNDAY
21 OCTOBER 2018

Today's Top Picks

Novel combinations provide fresh hope in advanced breast cancer

Giuseppe Curigliano
European Institute of Oncology, Milan, Italy

In the Presidential Symposium yesterday, exciting new data were presented from a series of phase III trials of novel therapy combinations in advanced breast cancer. "These studies are providing us with the answers we need to more effectively treat the advanced stages of the disease across subtypes," remarked Professor Giuseppe Curigliano from the European Institute of Oncology, Milan, Italy.

SOLAR-1 is the first study of precision medicine in metastatic breast cancer. It demonstrated a significant progression-free survival (PFS) benefit with the phosphatidylinositol-3-kinase (PI3K) inhibitor alpelisib plus hormone therapy fulvestrant compared with placebo plus fulvestrant (Abstract LBA3_PR) in patients with *PI3K*-mutated cancer. Previously, the SANDPIPER study demonstrated a statistically significant but only modest (2-month) PFS benefit for the PI3K inhibitor taselisib plus fulvestrant combination, and was associated with substantial toxicity.[1] The SOLAR-1 study is the first to demonstrate a clinically meaningful benefit for an alpha selective PI3K inhibitor in the treatment of advanced breast cancer in post-menopausal patients. The PFS primary endpoint was assessed in a cohort of 341 patients with hormone receptor (HR)-positive, HER2-negative disease that was also positive for a *PIK3CA* mutation. At a median follow-up of 20 months, median PFS was 11.0 months with alpelisib–fulvestrant versus 5.7 months with placebo–fulvestrant (hazard ratio 0.65; p=0.00065). Importantly, the tolerability profile of alpelisib–fulvestrant was manageable: the most frequent adverse events (AEs) were hyperglycaemia (64% versus 10% with placebo–fulvestrant), diarrhoea (58% versus 16% with placebo–fulvestrant) and nausea (45% versus 22% with placebo–fulvestrant). There were few toxicity-related discontinuations (3% with alpelisib–fulvestrant versus 2% with placebo–fulvestrant).

In a second study of post-menopausal patients with HR-positive, HER2-negative advanced breast cancer who had progressed on tamoxifen and/or a non-steroidal aromatase inhibitor, a significant clinical benefit was reported for exemestane in combination with the first-in-class histone deacetylase (HDAC) inhibitor chidamide (Abstract 283O_PR). Median PFS was 7.4 months with chidamide plus exemestane versus 3.8 months with placebo plus exemestane (hazard ratio 0.755; 95% confidence interval 0.582–0.978; p=0.034). Serious AEs in the chidamide arm occurred in 51 (20.9%) patients and AEs were mainly haematological in nature. Professor Curigliano noted that this Chinese study is the first to report a PFS benefit with an oral HDAC inhibitor plus endocrine blockade compared with endocrine blockade alone in HR-positive advanced breast cancer. "As such, these findings are very significant and will undoubtedly prompt further research into new HDAC inhibitors in advanced breast cancer," he commented.

Practice-changing data were also presented from the first positive phase III study (IMpassion130) of immunotherapy as first-line treatment for metastatic triple-negative breast cancer (mTNBC; Abstract LBA1_PR). A total of 902 treatment-naïve patients were randomised to receive either atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel. The co-primary PFS endpoint was met, both in the intent-to-treat population (7.2 months versus 5.5 months; hazard ratio 0.80; p=0.0025) and in patients with PD-L1-positive disease (7.5 months versus 5.0 months; hazard ratio 0.62; p<0.0001). At interim analysis, a clinically meaningful median overall survival benefit was also demonstrated in the atezolizumab arm in the PD-L1-positive cohort (25.0 months versus 15.5 months; hazard ration 0.62). The atezolizumab combination was well tolerated. "These are unprecedented data in mTNBC," enthused Professor Curigliano, adding that, "IMpassion130 brings breast cancer into the immunotherapy arena."

Robust data from a large patient population indicate for the first time that immunotherapy is an effective first-line option for patients with mTNBC.

1. www.ascopost.com/News/58901

Anti-PD-1 provides hope for treating BCG-unresponsive bladder cancer

The anti-PD-1 checkpoint inhibitor, pembrolizumab, shows promising antitumour activity in patients with high-risk non-muscle invasive bladder cancer (NMIBC) that is unresponsive to the standard of care immunotherapy with Bacillus Calmette Guérin (BCG) vaccine, reported Professor Ronald de Wit from Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands, yesterday (Abstract 864O).

The preliminary data from the KEYNOTE-057 phase II study are in a cohort of patients with carcinoma *in situ* with or without papillary tumour, and show a 36.5% complete response (CR) rate at 3 months, with a median CR duration of 8.1 months. Encouragingly, around 85% of patients who responded achieved a response duration of ≥6 months.

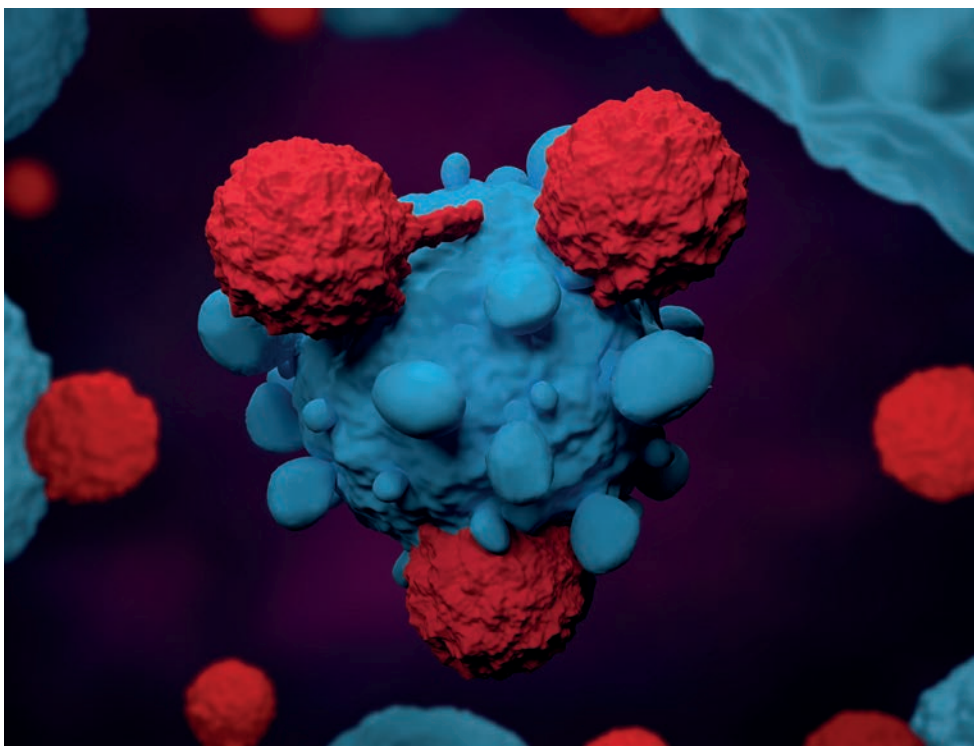
Pembrolizumab shows durable antitumour responses in patients with high-risk NMIBC.

This new era in immunotherapy offers new hope for patients with bladder cancer, including NMIBC, where previously there were few options that could provide durable responses.[1] Further data from the KEYNOTE-057 study are eagerly awaited.

1. Bellmunt J, et al. Cancer Treat Rev 2017;54:58–67

Renewed hope for immunotherapy combinations in metastatic urothelial carcinoma

Updated data from CheckMate-032, a multi-cohort study, presented yesterday (Abstract LBA32) provide additional insights into the efficacy of a nivolumab–ipilimumab immune checkpoint inhibitor combination in platinum pre-treated patients with metastatic urothelial carcinoma (mUC). Different doses of ipilimumab were explored as was the importance of the PD-L1 biomarker.



Extended follow-up from this open-label, phase I/II study revealed the most impressive efficacy with a combination of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3) in a cohort of 92 patients at a minimum follow-up of 7.9 months. The objective response rate was 38% with a median overall survival of 15.3 months. The response rate in the PD-L1 biomarker-positive population was 58%.

Professor Thomas Powles from Barts Cancer Institute, London, UK, notes that the data are intriguing and, "They begin to suggest that the dosing of ipilimumab may be relevant for clinical activity in mUC and that the PD-L1 biomarker is important in selecting patients. This N1I3 combination looks competitive in any setting in urothelial cancer, including against front-line cisplatin-based therapy, which has not always been the case with immunotherapy combinations in this cancer." Grade 3–4 adverse events were slightly higher with N1I3 than nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1) and nivolumab alone but, importantly, the safety profile appears manageable. "Patient selection will be important. Ongoing randomised phase III studies with N1I3 in the front-line metastatic setting will test this hypothesis robustly," concludes Professor Powles.

Nivolumab plus ipilimumab combination appears efficacious in heavily pre-treated mUC.

New annual ESMO Breast Cancer Congress starts in 2019

The first congress will be held in May in Berlin, Germany and will take place annually. This congress aims to deliver a comprehensive overview of the latest practice-changing data and provide guidance on how to take this information from bench to bedside to improve outcomes for your patients.

Developed by a committee of world-leading breast cancer experts, co-chaired by Professor Giuseppe Curigliano (European Institute of Oncology, Milan, Italy) and Professor Sibylle Loibl (German Breast Group, Neu-Isenburg, Germany), this is a highly recommended event for all oncology professionals managing patients with breast cancer.

ESMO 2018 Wi-Fi access

Wi-Fi access is free to the ESMO Congress delegates

Connection information:
Network name (SSID): ESMO2018
No authentication is needed once selected

Unravelling the potential of immunoradiotherapy

Suresh Senan
Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Netherlands

It has long been recognised that the effectiveness of radiation therapy in animal models is influenced by the host's immune system.[1,2] Recent work indicates that radiation can induce immunogenic cell death, modulate the tumour microenvironment, lead to adaptive upregulation of PD-L1, upregulate major histocompatibility complex (MHC) expression, increase neoantigen and infiltrating T-cell repertoire, and work synergistically with immune checkpoint inhibitors to stimulate the immune system.[3] With immune checkpoint inhibitors now shown to be effective in several metastatic tumour types, there is growing interest in clinical trials evaluating the integration of radiotherapy with these agents.

Impressive clinical results were observed in the PACIFIC study, where unselected patients with stage III non-small-cell lung cancer, on completing standard concurrent chemoradiotherapy, were randomised to either an anti-PD-L1 antibody (durvalumab) for 12 months or to placebo.[4] Progression-free survival with durvalumab was more than 11 months longer compared with placebo, and an advantage in overall survival has been reported. The observed efficacy has stimulated research into more optimal interactions between radiation and checkpoint inhibitors, for example, with the concurrent administration of these agents during chemoradiotherapy, and also in combination with stereotactic radiotherapy in metastatic disease.

Much hope has been pinned on exploiting the so-called abscopal effect, which occurs when the immune priming signal of local radiation combined with systemic checkpoint inhibitors leads to improved distant tumour control. However, areas of discordance between preclinical and clinical data with regard to optimal radiation doses, the timing and sequencing of different modalities, and varying immune responses based on sites of radiation, all indicate that more research is needed in order to optimise clinical trial design.

1. Jurin M, Suit HD. Cancer Res 1972;32:2201–11
2. Stone HB, et al. J Natl Cancer Inst 1979;63:1229–35
3. Kordbacheh T, et al. Ann Oncol 2018;29:301–10
4. Antonia S, et al. N Engl J Med 2017;377:1919–29

Don't miss the Special Session
'Integrating radiation in immunotherapy schemes'

Today, 11.00 – 12.30 in Hall A1 – Room 16.

Hyperprogression in focus: A new biomarker and definition

A small subset of patients with intrinsic resistance to anti-PD-1/PD-L1 therapy experience extremely rapid tumour progression following immunotherapy.[1] It is critical that this phenomenon—described as hyperprogression—is clearly defined and identified as early as possible to avoid potentially detrimental effects of immune checkpoint blockade and to manage patient expectations. However, predictive biomarkers of hyperprogression are largely unknown.

A small study reviewed in a Poster Discussion Session yesterday found that levels of pre-treatment CD4+ highly differentiated (i.e. loss of CD27 and CD28) T-cells (THD) accurately predicted response to PD-1/PD-L1 blockade (Abstract 54PD). Specifically, a THD baseline value <40% was associated with hyperprogressive disease. Reflecting on the data, session co-moderator and ESMO 2018 *Daily Reporter* Associate Editor Dr Rodrigo Dienstmann (Vall d'Hebron Institute of Oncology [VHIO], Barcelona, Spain) noted that, "While this was a small study, the ability of THD to unequivocally identify hyperprogressors prior to initiating immunotherapy is a very significant finding that could influence future treatment with immune checkpoint inhibitors."

Baseline CD4+ THD profile strongly correlated with response to anti-PD-1/PD-L1 immunotherapy and progression-free survival.

Today, for the clinician selecting patients for immune checkpoint inhibitor therapy, the situation is further complicated by the lack of one standard definition of hyperprogressive disease. A set of specific radiological criteria were recently defined by VHIO investigators,[2] and a poster presented yesterday (Abstract 1841P) confirmed that their definition was strongly prognostic following exposure to PD-1/PD-L1 blockade. Moreover, it appears to be biologically robust and easy to use when compared with Institut Gustave Roussy's original definition of hyperprogression. Dr Stefan Zimmermann (Lausanne University Hospital, Switzerland) said that, "Beyond an optimised definition of the phenomenon, today's clinicians lack clear predictors of hyperprogression to guide therapy. Moving forward, validation of early signals in larger datasets from prospective trials is now needed."

1. Ferrara R, et al. JAMA Oncol 2018. Sep 6. Epub ahead of print
2. Matos I, et al. J Clin Oncol 2018:36(Suppl):3032

ESMO YOUNG ONCOLOGISTS

ESMO Young Oncologists – meet your mentors!

One of the highlights of this year's Young Oncologist (YO) Track is the ever-popular Mentorship Session, which is taking place tomorrow (Monday, 22 October 09.30 – 10.30, ICM – Room 14c).

If you're a young oncologist, this session represents an excellent opportunity to discuss your educational and career development choices with leading oncology experts in clinical oncology, basic science, translational research and from industry. During the session, key opinion leaders will share their professional and personal experiences in an informal setting to encourage open discussion with mentors and peers. The session is free to attend; however, pre-registration is required as seats are limited.

Whole-genome sequencing: Good news for breast cancer patients?

Carlos Caldas
Cancer Research UK Cambridge Institute and Cancer Centre, University of Cambridge, UK

Genetic factors play an important role in breast cancer aetiology and pathogenesis. It is natural to assume—particularly from the patients' perspective—that profiling a breast cancer patient's genome and comparing it with normal DNA from the same patient (usually extracted from white blood cells), could help in the quest to provide personalised medicine and maximally effective treatment. A discussion at this morning's Challenge Your Expert Session, 'Personalised breast cancer medicine: Should all patients have whole genome sequencing?' will highlight the advantages and disadvantages of conducting whole genome sequencing (WGS) on all patients.

WGS, alongside the development of bioinformatic tools, continues to provide us with valuable information that expands our knowledge of breast cancer driver mutational events, pathway activation and dependency, total tumour mutation burden and mutation signatures. However, there are important scientific, logistical and operational challenges that remain.

Notably, pinpointing genomic driver events as actionable, validated targets for therapy has so far largely eluded us and we still lack clear evidence for the benefit of targeted systemic treatment for many putative genetic driver mutations. As a consequence, these issues hinder the broad implementation of WGS in the clinic.

Future research efforts, including the implementation of ultra-deep sequencing and monitoring of circulating tumour (ct) DNA will undoubtedly help to better elucidate the genetic events underlying sensitivity and resistance to anticancer treatments. This may help to improve patient outcomes in the future by providing guidance on the most appropriate treatment—including combinations—to use.[1] WGS has the enormous potential to help across all of these areas: mutation signatures could be used to select targeted treatments (for example with PARP inhibitors); total mutation burden could help decide on immunotherapy; and structural variants are ideal barcodes for tumour monitoring using ctDNA. All of these aspects will be covered during this session.

1. Arnedos M, et al. Nat Rev Clin Oncol 2015;12:693–704

Don't miss the Challenge Your Expert Session
'Personalised breast cancer medicine: Should all patients have whole genome sequencing?'

Today, 08.00 – 09.00 in Hall B3 – Room 20.

Hopes raised for preventing breast cancer treatment-associated cardiotoxicity

Cardiotoxicity is a serious complication of some breast cancer treatments, particularly anthracyclines and trastuzumab.[1,2] Tomorrow, Professor Jihyoun Lee from Soon Chun Hyang University Hospital, Seoul, Republic of Korea, will report that myocardial infarction (MI) and congestive heart failure (CHF) occur significantly more frequently in breast cancer survivors than in age- and sex-matched non-cancer controls (Poster Display Session, 12.45 – 13.45, Hall A3; Abstract 249P). The data are from a retrospective cohort study of over 112,000 patients and over 560,000 controls.

In particular, Professor Lee will report that the risk of MI and CHF is especially high in younger patients aged ≤50 years (hazard ratios of 1.73 and 3.56, respectively), and that the cumulative incidence of these cardiotoxicity events is particularly high within a year of breast cancer diagnosis and treatment.

There is an increased risk of MI and CHF in the early phase of breast cancer survivorship, especially in younger patients.

"Although younger women are generally considered to be at low risk of cardiovascular disease, these age-matched data indicate that treatment-associated cardiotoxicity is a particular concern in younger patients," commented Dr Evandro de Azambuja from Institut Jules Bordet, Brussels, Belgium. "Based on this, it would seem wise to monitor younger patients particularly closely and not exclude the possibility of cardiac events in this population, as previously thought." Curiously, the authors found that patients treated with a taxane-based chemotherapy had an increased risk of MI and CHF. However, it should also be reported whether or not these patients received anthracycline-based chemotherapy (and the cumulative dose) prior to taxane.

"In addition, we need to do more to prevent cardiotoxicity in the first place," continued Dr de Azambuja. "I was therefore very excited to see the data presented yesterday showing that lisinopril and carvedilol may be cardioprotective in patients receiving trastuzumab. Previous trials also demonstrated a cardioprotective effect, but they had small sample sizes."

Presented by Professor Pamela Munster (Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA), the large, prospective, randomised controlled trial showed that prophylactic treatment with the angiotensin converting enzyme inhibitor, lisinopril, or the beta-blocker, carvedilol, significantly reduced cardiac event rates in patients with breast cancer receiving trastuzumab therapy (37% and 31%, respectively, versus 47% with placebo; Abstract 192PD). In addition, simultaneous treatment with trastuzumab and either lisinopril or carvedilol was associated with less requirement for trastuzumab interruption, compared with placebo (p=0.007). This kind of approach should be considered in patients treated with adjuvant trastuzumab to avoid interrupting a treatment that demonstrates a survival benefit. Those benefits were restricted to the anthracycline-treated cohort only. Also, it should be further tested in patients with metastatic disease in whom the duration of anti-HER2 drug treatment is generally longer than 1 year.

"The cardioprotective benefits of prophylactic lisinopril or carvedilol are potentially practice-changing in patients treated with adjuvant anthracycline and trastuzumab," said Dr de Azambuja.

1. Upshaw JN. Gland Surg 2018;7:350–65
2. Martel S, et al. Expert Opin Drug Saf 2017;16:1021–38

Does adding bevacizumab to erlotinib improve survival for *EGFR*-mutant advanced NSCLC?

First-line treatment with combined bevacizumab and erlotinib may improve overall survival (OS) in patients with *EGFR*-mutant metastatic non-small-cell lung cancer (NSCLC), according to a recent meta-analysis of 10 studies.[1] However, these exploratory subgroup analysis results require further validation in prospective randomised controlled trials (RCTs).

Unfortunately, the situation is still unclear following the presentation yesterday afternoon of conflicting results from 2 RCTs. In a phase II RCT, adding bevacizumab to erlotinib failed to improve progression-free survival (PFS) over erlotinib alone in patients with advanced NSCLC with *EGFR* mutations in exons 19 or 21 (hazard ratio [HR] 0.81; p=0.39), reported Dr Thomas Stinchcombe (Duke Cancer Center, Durham, NC, USA; Abstract 1444P). OS data for the study are still immature but currently do not indicate any benefit with the combination treatment.

In the same session, however, Dr Yosuke Kawashima (Sendai Kousei Hospital, Japan) presented interim findings of a phase III RCT, suggesting that combined bevacizumab and erlotinib improves PFS in chemotherapy-naïve patients with advanced NSCLC harbouring *EGFR* mutations, compared with erlotinib alone (HR 0.605, p=0.0157; Abstract 1441P). OS follow-up is ongoing.

Commenting on the conflicting results, Dr Stefan Zimmermann (Lausanne University Hospital, Switzerland) said that, "Most adequately powered studies to date show a PFS improvement with the combination, so the potential for VEGF-targeting approaches to forestall the emergence of resistance seems real. The information that we are missing is mature OS results from randomised trials and results using third-generation TKIs, such as osimertinib."

1. Zhao B, et al. Lung Cancer 2018;122:10–21

Treating melanoma – what don't we know?

Paolo A. Ascierto
Melanoma, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy

The incidence of malignant melanoma has continued to rise over the past 40 years and historically the prognosis for patients with advanced disease has been poor. However, owing to huge advances in our understanding of the disease, immunotherapies and molecular-targeted therapies are revolutionising the standard of care for patients with advanced melanoma. While we can now cure about half of these patients, for the remainder, who will die within around 3 years of diagnosis, we have to find ways to overcome primary and acquired resistance to treatments.

Further efforts are also needed to identify biomarkers that are predictive of response and survival after treatment with new immunotherapies, particularly given the highly heterogeneous nature of the disease. Recognising these biomarkers is especially important with more aggressive combinations, when the proportion of patients who develop severe toxicities is almost as high as the proportion who achieve a response.[1]

While immunotherapies that block T-cell checkpoint receptors induce a durable response in some patients, targeted therapies, such as MAPK pathway inhibitors, induce high response rates but with common relapses.[2] Combining targeted agents with immunotherapy has been proposed to improve long-term outcomes and targeted therapies may have an immunomodulatory effect that can synergise with immunotherapy-induced activation.

Currently, only clinical factors usefully drive our treatment decisions. Better responses to all treatments, including immunotherapies and targeted therapies, are found in patients with good risk factors, such as normal lactate dehydrogenase levels, low tumour burden and absence of brain metastases. Patients with poor risk factors have a lot of unmet needs, including a high probability of primary and/or acquired resistance, and we need to increase our efforts to improve long-term outcomes for these patients.

1. Rozeman EA, et al. Am J Clin Dermatol 2018;19:303–17
2. Deken MA, et al. Oncoimmunology 2016;5:e1238557

Don't miss the Educational Session
'Unresolved questions in melanoma'

Today, 16.30 – 18.00 in ICM – Room 1.

Managing patients with breast cancer diagnosed during pregnancy

Fedro Alessandro Peccatori
European Institute of Oncology (IEO), Milan, Italy

The management of any cancer during pregnancy represents a complex medical situation requiring a multidisciplinary team to adequately evaluate potential maternal benefits and possible risks to the foetus.[1] Although breast cancer is the most frequently diagnosed malignancy in pregnant women, it is a rare condition. However, there should be an increased awareness of cancer in pregnancy, particularly considering the current trend for postponing pregnancy to later in life.

Breast cancer arising in young women appears to have unique biological features, and pregnancy can add further complexity to its biology. This, together with the tendency for a more advanced cancer stage at presentation owing to delayed diagnosis, may explain the poorer outcomes observed in these women.[2] Therefore, correct management of this challenging medical situation in centres with adequate expertise following the available guidelines is strongly recommended.[1–3] Breast cancer surgery can be performed safely at any time during gestation, provided there is a careful risk/benefit assessment of anaesthesia.[2] In contrast, it is preferable to postpone radiotherapy until after delivery due to the risk of adverse effects to the foetus.[2] Although anti-HER2 agents and endocrine therapy should be avoided during the whole course of pregnancy, chemotherapy can be used to treat breast cancer in the second and third trimesters and should follow the standard recommendations as for the non-pregnancy setting based on tumour biology and staging.[2] Chemotherapy is contraindicated in the first trimester owing to its association with obstetric and foetal complications.[3] Importantly, in children with prior *in utero* exposure to anticancer treatments, a continued follow-up of their health is recommended to monitor the potential risk of long-term complications.

1. Peccatori FA, et al. Ann Oncol 2013;24(Suppl 6):vi160–70
2. Peccatori FA, et al. Cancer Biol Med 2018;15:6–13
3. Loibl S, et al. JAMA Oncol 2015;1:1145–53

Don't miss Monday's Multidisciplinary Interactive Session
'Managing early breast cancer during pregnancy'

Monday, 22 October 09.30 – 10.30, Hall B3 – Room 23.

Molecular tumour boards: Striving for precision medicine

Rodrigo Dienstmann
Associate Editor of the ESMO 2018 Daily Reporter, Vall d'Hebron Institute of Oncology, Barcelona, Spain

The advent of newer technologies in recent times has given us a greater insight into the genetic basis of cancer and there has been a paradigm shift from a simplified model of 'one gene, one therapy' to a model in which the choice of therapy reflects all the genetic alterations identified in an individual patient's tumour. Molecular tumour boards—a relatively recent development in oncology—are intended to integrate a range of specialists who can interpret this information into practical management strategies.

The addition of a molecular perspective to the traditional multidisciplinary management of patients promises improved outcomes via precision cancer therapy. Case discussion in a molecular tumour board is believed to offer an optimal approach to matching the unique genetic profile of a patient's cancer with a drug (or combination of drugs) with the highest evidence of targetability. Prioritising driver over passenger genomic alterations and the right drugs when multiple targetable alterations are found represents a challenging task. Patients can be matched to standard-of-care approved therapies or be referred to clinical trials with novel agents. However, cancers are complicated by intra-tumour heterogeneity and clonal evolution due to prior therapies, which helps explain drug treatment failures observed in phase I trials with promising drugs.[1] Liquid biopsies may play a role in this context. Moreover, potential and confirmed germline genetic events identified during tumour and/or normal DNA sequencing may pose significant challenges for oncologists who are ill-prepared to handle incidental findings that have both a therapeutic impact for the individual cancer patient and clinical implications for at-risk family members. Molecular tumour boards may help to address these issues by providing an improved pathway to match patients to the most appropriate care.

1. Tannock IF, Hickman JA. N Engl J Med 2018;375:1289–94

Don't miss the Multidisciplinary Interactive Session
'Molecular tumour boards in the practice of precision oncology'

Today, 16.30 – 17.30 in Hall A1 – Room 16.

The right time to discontinue immunotherapy

Some patients are known to experience long-term benefit after immunotherapy, as demonstrated with the anti-PD-1 antibody nivolumab in previously treated non-small-cell (NSCLC) cancer patients enrolled in the CheckMate 003 trial.[1] Median progression-free survival (PFS) was 10.3 months in patients who received nivolumab for 1 year and had not been reached in those who received continuous nivolumab.[1] Also, in CheckMate 141, immunotherapy with nivolumab has shown persistent overall survival (OS) benefit over a minimum 2-year follow-up period in patients with metastatic or recurrent head and neck squamous cell carcinoma (HNSCC), irrespective of PD-L1 status.[2] Similarly, for patients with advanced melanoma in the CheckMate 069 and CheckMate 067 studies, those who discontinued combination therapy with nivolumab plus the CTLA-4 inhibitor, ipilimumab, because of immune-mediated adverse events (AEs) during the induction phase, continued to benefit from treatment. The median PFS was 8.4 months compared with 10.8 months in patients who did not discontinue therapy at this time.[3] One hypothesis for the continued benefit of immunotherapy in patients who prematurely stop treatment because of AEs is that toxicity is a pharmacodynamic marker of immune activation.[3] However, a retrospective analysis of patients with advanced melanoma who received either mono- or combination immunotherapy and who were followed for a median 28 months revealed that even when complete response was not achieved before treatment discontinuation, patients still benefited from favourable long-term survival endpoints.[4]

These studies raise the question of the optimal timing for discontinuing immunotherapy.

1. Spigel DR, et al. Ann Oncol 2017;28(Suppl 5):461
2. Ferris RL, et al. AACR Annual Meeting 2018: Abstract CT116
3. Schadendorf D, et al. J Clin Oncol 2017;35:3807–14
4. Rosner S, et al. J Clin Oncol 2017;35(Suppl):9548

Don't miss the Challenge Your Expert Session
'The right time for discontinuing immunotherapy'

Today, 08.00 – 09.00, Hall A1 – Room 16.

Does neoadjuvant chemotherapy have a role in the treatment of localised soft-tissue sarcoma?

Alessandro Gronchi
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Several randomised trials have investigated (neo)adjuvant chemotherapy in the treatment of localised soft-tissue sarcoma (STS) over the past 40 years; however, evidence has not been conclusive, mostly due to the disease's heterogeneity and patient selection variability.[1] The recent ISG-STS1001 trial compared standard full-dose anthracycline plus ifosfamide versus histotype-tailored chemotherapy in patients with resectable high-risk STS of the extremities or trunk wall.[1] The study was stopped slightly ahead of schedule (median follow-up of 12.3 months) following an interim analysis showing a statistically significant benefit in terms of both relapse-free and overall survival in favour of neoadjuvant therapy with epirubicin and ifosfamide. If results are confirmed in the final analysis, the ISG-STS1001 trial will provide randomised evidence of the efficacy of neoadjuvant therapy with full-dose anthracycline plus ifosfamide in patients with high-risk extremity and superficial trunk STS. While we await the final analysis, the interim results of the study have been taken into account in the recent ESMO–EURACAN Clinical Practice Guidelines on sarcoma,[2] which now state that neoadjuvant chemotherapy can be considered an option in individual patients with high-risk STS, for shared decision making.

If the final results of the ISG-STS1001 trial confirm the superiority of the standard arm, a change to treatment recommendations and neoadjuvant chemotherapy may become the standard in high-risk STS. If this is the case, the multidisciplinary management of patients with STS in high-volume centres with expertise in the field will become all the more crucial.

1. Gronchi A, et al. Lancet Oncol 2017;18:812–22
2. Casali PG, et al. Ann Oncol 2018;29(Suppl. 4):iv51–67

Don't miss the Multidisciplinary Interactive Session
'Pre-op/neoadjuvant treatments in sarcomas: "Think twice before you open it"'

Today, 11.10 – 12.15 in Hall B3 – Room 20.

New hope in the treatment of brain tumours

The prognosis for patients with glioblastoma—the most common malignant brain tumour in adults—is particularly grim, with few new treatment options in the past decade.[1] Even with standard-of-care neurosurgery followed by concomitant chemoradiotherapy and systemic temozolomide then adjuvant systemic temozolomide, overall survival for patients with newly diagnosed glioblastoma is only around 14 months.[2]

Immune-based targeted therapies have emerged as potential novel treatments, paralleling our greater understanding of the genetic and epigenetic basis of the development and progression of glioblastoma.

Immune-based treatment will be the focus of a Special Symposium today: 'Novel therapies for brain tumours', 11.00 – 12.30, ICM – Room 13.

However, trials of immune-based therapies have, as yet, not shown the success observed in other tumour types. Glioblastoma vaccines aimed at triggering a tumour-specific immune response are known to induce such a response in clinical trials, but no clinical benefit has been reported. Immune checkpoint inhibitors, such as the anti-PD-1 antibody nivolumab, showed great promise in preclinical studies, but unfortunately, these results have not yet been replicated in patients.[3] It is likely that any benefit of immune-based therapies for patients with glioblastoma may come from combining different immune checkpoint inhibitors, and results from several large clinical trials are expected to provide further insights soon.

Leptomeningeal metastasis (LM), a lethal yet common complication of cancer, also requires alternative treatment options. The potential role of intra-cerebrospinal fluid (CSF) chemotherapy as an adjunct to systemic therapy has been explored in a randomised study of 73 patients with LM from breast cancer (Abstract 3710). Intra-CSF liposomal cytarabine plus systemic therapy improved LM-related progression-free survival—the primary endpoint—compared with systemic therapy alone and quality of life was preserved. There was a trend towards improvement in the secondary endpoint of overall survival.

1. Weller M, et al. Nat Rev Dis Prim 2015;1:15017
2. Weller M, et al. Lancet Oncol 2017;18:e315–29
3. Lim M, et al. Nat Rev Clin Oncol 2018;15:422–42

Reducing treatment burden—is de-escalation feasible in early breast cancer?

The last few decades have seen a dramatic improvement in the survival of breast cancer patients, due largely to treatment escalation, especially with the addition of new drugs such as targeted agents. Whilst a greater number of patients now survive breast cancer, attention must switch to improving patients' quality of life (QoL), limiting morbidity without compromising patient survival, and avoiding unnecessary overtreatment. Trials focusing on treatment de-escalation are therefore of growing importance.[1]

As an example, the current standard of care in early HER2-positive breast cancer is adjuvant chemotherapy plus 1 year of trastuzumab. In the recently presented PERSEPHONE trial, 6 months of trastuzumab was non-inferior to 12 months of anti-HER2 therapy in the adjuvant setting and was associated with reduced cardiotoxicity and associated cost.[2] "The results of PERSEPHONE should be considered in the context of other trials that could not demonstrate the non-inferiority of 6 months of trastuzumab versus the standard 12-month duration and also recognise that some 'high-risk' patients still derive most benefit from the 1-year duration," said Dr Evandro de Azambuja, Institut Jules Bordet, Brussels, Belgium. "We need to identify those patients who really do not need 1 year of trastuzumab," he added. More importantly, future research efforts in this field should be focused mainly on de-escalating chemotherapy, as successfully demonstrated in a study of adjuvant paclitaxel and trastuzumab,[3] considering the higher burden on patients' QoL and risk of long-term side effects associated with the use of cytotoxic therapy (anthracyclines).

"De-escalation was also investigated in the Short-HER study, which failed to demonstrate the non-inferiority of 9 weeks versus 1 year of adjuvant trastuzumab combined with chemotherapy[4]," said Dr Giuseppe Curigliano of the European Institute of Oncology, Milan, Italy, adding, "1-year trastuzumab remains the standard." However, a short trastuzumab administration period decreases the risk of severe cardiac toxicity and can be an option for patients with cardiac events during treatment and for those with a low risk of relapse. The PHERGAIN trial, investigating PET scanning to identify patients who may not need chemotherapy and who could benefit from anti-HER2 drugs in the neoadjuvant setting, is another example of a de-escalation strategy.

Adjuvant radiotherapy (RT) following breast-conserving surgery is an important component of treatment for early breast cancer but in some patients with a very low likelihood of relapse, the risks may be greater than the benefits.[5] In low-risk patients with early breast cancer who do not undergo RT, overall survival is not decreased and local recurrences are treatable. Long-term efficacy and safety evidence support hypo-fractionated treatment as a standard for most patients, particularly those over 50 years. Other examples of RT de-escalation include partial breast irradiation as an option for low-risk disease and omission of the RT 'boost' in patients aged ≥60 years with low-grade tumours and/or favourable tumour biology receiving adjuvant endocrine therapy. "To date, however, clinical practice has not changed, possibly because of the challenges associated with patient selection," suggested Dr Curigliano. "If patients can be accurately stratified according to risk to avoid unnecessary toxicity, and we can assess the need for adjuvant breast RT on an individual patient basis, it would surely represent a significant step forward in reducing the burden of treatment—a goal that is becoming increasingly important in breast cancer treatment today."

1. Smith I. The Breast 2017;32(Suppl 1):S3
2. Hiller L, et al. BMC Cancer 2018;18:391
3. Tolaney SM, et al. N Engl J Med 2015;372:134–41
4. Conte PF, et al. J Clin Oncol 2017;35, no.15(Suppl):Abstract 501
5. Battacharya IS, et al. Clin Oncol 2018;30:158–65

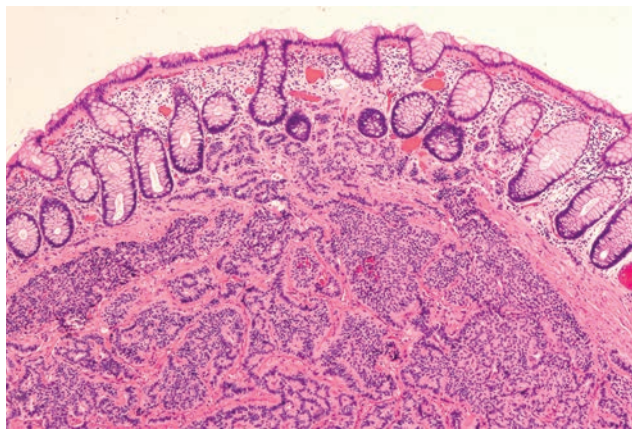
Don't miss today's Special Symposium
'Safe de-escalation of therapy in the management of early breast cancer'

11.00 – 12.30, Hall A2 – Room 18.

Join the conversation

@myESMO
#ESMO18

New treatments for neuroendocrine tumours



Alessandra Curioni Fontecedro

Associate Editor of the ESMO 2018 Daily Reporter, University Hospital of Zurich, Switzerland

The incidence and prevalence of neuroendocrine tumours (NETs) have dramatically increased over the past four decades, possibly due to earlier diagnosis.[1] Furthermore, survival has also improved over time, especially for late-stage gastrointestinal and pancreatic NETs.[1] Therapeutic options have also greatly improved for NETs over the last 10 years. Targeted drugs such as the mTOR inhibitor everolimus and the multiple tyrosine kinase inhibitor sunitinib were approved, respectively, for the treatment of a broad spectrum of NETs and pancreatic NETs. More recently, the peptide receptor radionuclide therapy, 177Lu-dotatate has been approved for the treatment of adults with somatostatin receptor-positive gastroenteropancreatic NETs.

Responses to immune checkpoint blockade are also encouraging; at ESMO 2017, the phase Ib KEYNOTE-028 study demonstrated objective responses and stable disease with the anti-PD-1 pembrolizumab in heavily pretreated patients with high-grade pancreatic NETs or carcinoid tumours expressing PD-L1.[2] In a Proffered Paper Session tomorrow ('NETs and endocrine tumours,' 14.45 – 16.15, Hall A1 – Room 16; Abstract 1308O), clinical activity is reported from a phase II study with the anti-PD-1 spartalizumab (PDR001) in patients with well-differentiated, non-functional NETs. Interestingly, the highest responses were found in those with tumours of thoracic origin (73% disease control rate).

Despite these advances, there are many unmet needs in the management of NETs. In a Poster Display Session today (12.45 – 13.45, Hall A3 – Poster Area in the Networking Hub; Abstract 1328P), key areas for improvement identified by patients, patient advocates and healthcare professionals include access to gold standard care, provision of information and patient involvement in research.

Professor Eric Raymond from Saint-Joseph Hospital, Paris, France, noted that treatment sequencing also remains a matter of debate and a major effort must be pursued to understand the molecular features of these tumours, identify predictive biomarkers of response to novel treatments and improve patient outcomes.

1. Dasari A, et al. JAMA Oncol 2017;3:1335–42
2. Mehnert JM, et al. Ann Oncol 2017;28(Suppl 5):Abstract 4270

Don't miss the Special Symposium
'Emerging therapies in neuroendocrine and endocrine malignancies'

Today, 14.45 – 16.15 in Hall B3 – Room 22.

ESMO updates its patient guides for women with cancer

From left to right: Nicoletta Colombo, Elzbieta Senkus-Konefka, Lise Bjerrum Thisted, Kathi Apostolidis.

As part of ESMO's commitment to supporting patients with cancer, yesterday saw the launch of an updated series of women-specific patient guides, which includes ovarian, breast and cervical cancers.

Designed to burst the bubble of scientific jargon surrounding the complex area of cancer, each guide is carefully created to provide the very latest information on diagnosis and management, covering key areas relevant to patients and carers. At yesterday's launch event, a distinguished panel of experts—including physicians, a cancer nurse and a patient advocate—who contributed to the women-specific ESMO patient guides discussed the care taken in the development of the guides. Key to the process was putting the patient at the centre and focussing on their needs. Also, with so much information available online, it is paramount that the material patients access is from a reliable source. "The ESMO Patient Guides provide easy-to-read, accessible, reliable information," said Professor Nicoletta Colombo (University of Milan-Bicocca, Italy).

Attendees of the event were encouraged to make use of the patient guides within their care teams and to tell their patients about them. The guides could facilitate conversations between members of the healthcare team and their patients. Lise Bjerrum Thisted, a cancer nurse who, on behalf of EONS, helped create the cervical cancer patient guide, commented on how the user-friendly guides inform patients on treatment choices, which can help them in the important process of shared decision-making. She also said that the guides can facilitate patients in making informed, positive lifestyle changes. Kathi Apostolidis, from the European Cancer Patient Coalition (ECPC) and a breast cancer patient advocate, explained how the ESMO patient guide on survivorship has specific advice and recommendations for patients both during and after treatment. The session concluded with a call to action for all oncologists to use these guides with their patients.

Visit the ESMO booth to pick up a copy of the English-language version of the patient guides for free.

The guides are regularly updated to keep patients and carers abreast of key developments in the diagnosis and management of each disease. All patient guides are available in numerous languages and can be accessed via the ESMO website: www.esmo.org/Patients/Patient-Guides.

How can we further improve the treatment of young women with early breast cancer?

A substantial proportion of premenopausal patients with hormone receptor (HR)-positive early breast cancer are not adherent to their adjuvant endocrine therapy, despite its proven benefits in reducing the risk of disease recurrence. Findings from the prospective, multicentre, longitudinal CANTO cohort study were presented on Friday (Abstract 1850_PR). Serum levels of endocrine therapy 1 year after starting treatment indicated that 13% of patients were non-adherent and another 5% were poorly adherent.

Almost 1 in 5 young women with early breast cancer are inadequately adherent with endocrine therapy.

"It is vital that younger women understand the importance of continuing their medication for the full prescribed period, and the potential implications of non-adherence," stated Professor Olivia Pagani from Oncology Institute of Southern Switzerland, Bellinzona. "Possible reasons for poor or non-adherence include side effects, such as hot flushes, psychological distress associated with a breast cancer diagnosis at a young age and/or fertility-related concerns and the wish for future motherhood."

"The physician–patient relationship is key to identifying and improving patient adherence, through open communication, management of side effects and reassurance that the long-term treatment benefits will outweigh the undesirable aspects they are experiencing," she continued.

Which adjuvant endocrine therapy provides the best outcomes in premenopausal women with HR-positive early breast cancer? This question has been investigated in the phase III, randomised HOBOE-2 trial, providing the first data on the efficacy of 5 years of letrozole, letrozole–zoledronic acid (ZA) or tamoxifen in patients receiving triptorelin. Late-breaking data for 1,065 patients, after a median follow-up of 65 months, were presented yesterday (Abstract LBA14_PR). Letrozole–ZA significantly improved 5-year disease-free survival (DFS) compared with tamoxifen (hazard ratio 0.52; p=0.003); differences between letrozole–ZA and letrozole and between tamoxifen and letrozole were not significant. However, the toxicity of letrozole–ZA and letrozole alone was worse compared with tamoxifen. The authors concluded that letrozole–ZA might be considered for clinical practice following a discussion with patients regarding its cost-effectiveness. "These data suggest that escalating adjuvant therapy by adding ZA to aromatase inhibitors (AIs) and ovarian function suppression (OFS) may improve outcomes as compared with tamoxifen plus OFS. In the absence of benefit with ZA in women receiving AIs plus OFS and without a clear definition of the population of patients most likely to profit from this strategy, its routine administration should be discouraged," concluded Professor Pagani.

In the HOBOE-2 trial, adjuvant letrozole plus ZA provided improved DFS compared with tamoxifen in premenopausal early breast cancer patients receiving medical ovarian function suppression. The increased toxicity and the absence of benefit in women receiving letrozole and OFS prevent its routine administration in clinical practice.

Fighting against immune checkpoint inhibitor resistance

Sanjay Popat
The Royal Marsden NHS Trust and the National Heart & Lung Institute, Imperial College, London, UK

Many patients treated with anti-PD-1/PD-L1 therapy develop resistance that is either innate with no clinical benefit or is acquired, such that initial clinical benefit is followed by treatment resistance.[1] Intrinsic factors that lead to innate resistance include lack of antigenic mutations, loss of tumour antigen expression, loss of HLA expression, alterations in antigen processing machinery, alterations of several signalling pathways (MAPK, PI3K, WNT, IFN) and constitutive PD-L1 expression.[1] The tumour microenvironment, characterised by infiltration of CD8+ T-cells, chemokines and other innate immune factors, also appears to play a key role in determining initial response to immunotherapy. However, there is currently no single biomarker that predicts treatment efficacy, likely due to the complexity of the relationship between the immune system, the tumour milieu and other host factors.

Potential mechanisms of acquired resistance include loss of T-cell function, lack of T-cell recognition by downregulation of tumour antigen presentation and development of escape mutation variants in the cancer.[1] Longitudinal gene expression profiling during various stages of treatment (pre-treatment, on-treatment and at progression) may allow for a deeper analysis of potential mechanisms of resistance and the identification of molecular and clinical predictors. These evaluations may also lead to different strategies to combat resistance. Current approaches include combination therapy, for example dual checkpoint blockade or administering targeted therapy with immunotherapy.

Tomorrow morning, data from a phase II study combining nivolumab with sitravatinib, a spectrum-selective TKI that targets TAM receptors (including Axl and Mer) and vascular endothelial growth factor family receptors will be presented in a Proffered Paper Session (Monday, 22 October 11.15 – 12.45 in Hall A2 – Room 18; Abstract 1129O). The rationale is that sitravatinib may enhance antitumour activity through depletion of immunosuppressive type 2 tumor-associated macrophages, regulatory T-cells and myeloid-derived suppressor cells, and so improve or restore the clinical activity of checkpoint inhibitor therapy. The combination of sitravatinib with nivolumab appeared to have some clinical benefit in patients with non-small-cell lung cancer who progressed on or after checkpoint inhibitor therapy and further results are awaited.

Tomorrow afternoon, the mechanisms and management of immunotherapy resistance will be discussed further in the Educational Session, 'The force awakens: Immunotherapy in thoracic malignancies' (Monday, 22 October 14.45 – 16.15 in Hall A2 – Room 18).

Immune checkpoint inhibitor therapy resistance is a clinical problem we face daily. I look forward to hearing colleagues discuss resistance mechanisms and also new trial data on how such mechanisms are being exploited.

1. Sharma P, et al. Cell 2018;168:707–23

ctDNA: A screening tool for early-stage cancer and cancer relapse

The huge potential of circulating tumour DNA (ctDNA) detection as a non-invasive approach for the early detection of cancers at treatable stages, and thus reduce cancer-related mortality, is becoming increasingly apparent.[1]

In a Proffered Paper Session yesterday, Dr Minetta Liu (Mayo Clinic Cancer Center, Rochester, MN, USA) reviewed the latest data from the large Circulating Cell-free Genome Atlas observational study[2,3] (Abstract 500) in which three plasma cell-free DNA (cfDNA) multicancer detection assays consistently detected multiple stage I–IV malignancies. "This approach could help us with the early detection of cancers currently associated with significant mortality when diagnosed at a late stage," she noted. A further cfDNA screening project in 1,006 elderly individuals without a history of cancer identified chromosomal aberrations in 30 participants, with three haematological malignancies and two cases of monoclonal B-cell lymphocytosis subsequently confirmed (Abstract 13360).

ctDNA methods have also been evaluated as a means of identifying patients at highest risk of relapse even before they receive adjuvant therapy, and for detecting relapse at an early stage. An analysis of patients with stage II–III melanoma found a significant correlation between detection of ctDNA at baseline with subsequent relapse and inferior distant metastasis-free survival (Abstract 520). Similar findings are reported in a Poster Discussion Session today ('Gastrointestinal tumours, colorectal 2', 16.45 – 17.45, ICM – Room 14b); ctDNA detection was able to stratify patients with stage I–IV colorectal cancer according to risk of disease recurrence before adjuvant chemotherapy (Abstract 456PD). Additionally, ctDNA enabled detection of recurrence over 9 months earlier than standard-of-care CT-imaging.

Commenting on the data, ESMO 2018 *Daily Reporter* Associate Editor Dr Carmen Criscitiello (European Institute of Oncology, Milan, Italy) said, "These are important findings as they confirm the potential of ctDNA as an approach to detect malignancies at an early stage and to prospectively identify patients at greatest risk of relapse following therapy. The sensitivity for cancer detection is quite variable by tumour type and there is still broad scope for improvement. In the post-operative setting, ctDNA could not only identify patients with 'minimal residual disease', who are at extremely high risk of recurrence, but could also allow assessment of the efficacy of adjuvant treatments."

The public health implications of early cancer detection are wide reaching.

1. Han X, et al. Genomics Proteomics Bioinformatics 2017;15:59–72
2. Liu MC, et al. J Clin Oncol 2018:36(Suppl):536
3. Oxnard GR, et al. J Clin Oncol 2018:36(Suppl):LBA8501

Immune-related adverse events: Friend or foe?

Immunotherapy to boost the body's natural defences against cancer has improved the outcomes of many patients over recent years, but treatments that stimulate the immune system are also associated with immune-related adverse events (irAEs). These include skin toxicities, colitis, hepatitis, pneumonitis and hypothyroidism, and have been widely documented in clinical trials.[1,2] The tolerability of immune checkpoint inhibitors is nevertheless reported to be superior to that of chemotherapy, although less is known about the relative toxicities of these treatments in the real-world setting. This was the focus of a poster presentation yesterday that retrospectively reviewed real-world data for 205 patients with metastatic non-small-cell lung cancer (NSCLC; Abstract 1229P). Fewer patients receiving second-line immunotherapy than chemotherapy experienced grade 3–4 or any grade adverse events resulting in treatment change or discontinuation (13% versus 34%, respectively; p=0.002). A significantly lower proportion of patients receiving immunotherapy than chemotherapy also had adverse events at 1, 2, 3 and 4 months of treatment.

Intriguingly, as experience with immunotherapy accumulates, evidence suggests the existence of a relationship between irAEs and improved clinical responses to anti-PD-(L)1 agents. In 64 patients with advanced cancer treated with the anti-PD-1 agent nivolumab, an objective response was observed in most (77.7%) patients with irAEs compared with 18.9% in those without irAEs (odds ratio 15.0; p<0.0001; Abstract 1227P). However, a large analysis of over 600 patients with solid tumours (mostly melanoma and NSCLC)—to be presented in a Poster Discussion Session tomorrow ('Immunotherapy of cancer 2,' 09.30 – 10.40, Hall B3 – Room 21)—failed to show a positive relationship between irAEs and survival (Abstract 1141PD). Eight-, 12- and 16-week multivariable landmark analyses found no significant association between irAEs and either progression-free or overall survival.

Irrespective of their relationship with efficacy, careful and timely management of irAEs is essential in order to achieve optimal patient outcomes. The management of immunotherapy-related toxicity will be discussed in a Multidisciplinary Interactive Session this afternoon, with focus on gastrointestinal toxicity, neurotoxicity and options for treating beyond acute toxicity.

Don't miss the Multidisciplinary Interactive Session, 'Management of toxicities of immunotherapy' today, 15.00 – 16.00 in Hall A1 – Room 16.

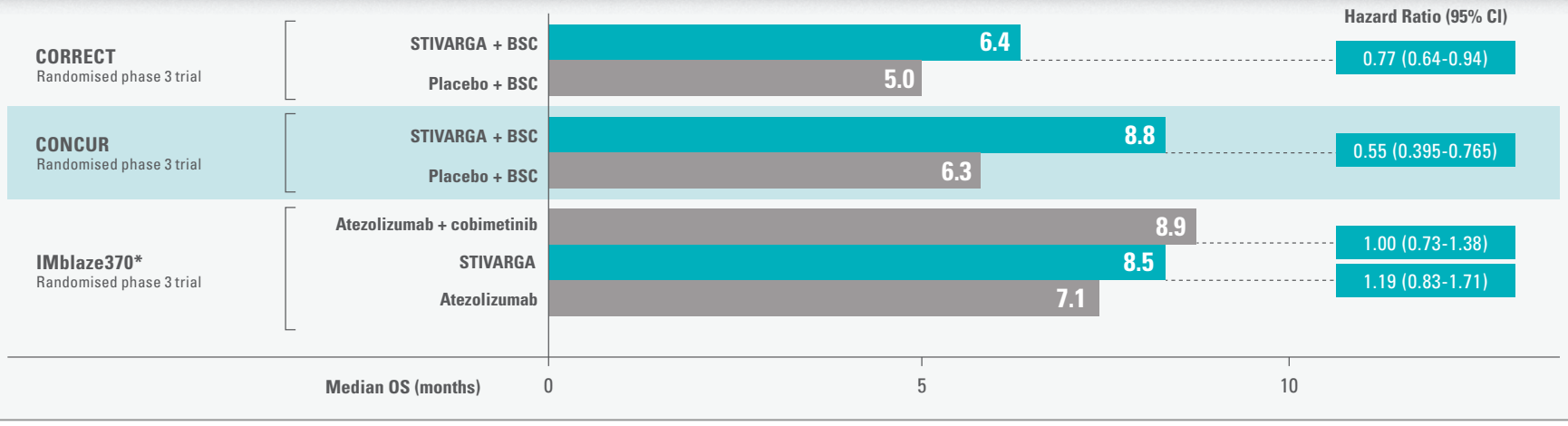
Commenting on these presentations, Professor John Haanen from Netherlands Cancer Institute, Amsterdam, said, "The data suggest a possible relationship between immune-related toxicity and objective response, but not survival, to anti-PD-(L)1 drugs. This actually becomes a double-edged sword. In other words, do we need toxicity for response? Unfortunately, the development of toxicity is a rather poor biomarker because we currently have no way of predicting who will and who will not develop irAEs; this is an area where more research is needed. In addition, if we could more fully understand the underlying biology of immune-related events, we would possibly be able to develop ways to separate toxicity from efficacy."

1. Postow MA, et al. N Engl J Med 2018;378:158–68
2. Baxi S, et al. BMJ 2018;360:k793

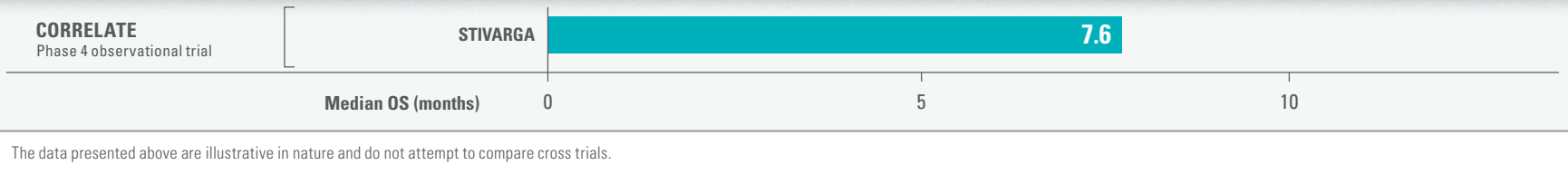
Consider STIVARGA® (regorafenib) to extend overall survival (OS) for your 3L patients with mCRC

Robust median OS improvements with STIVARGA demonstrated across a range of studies

Median OS results across phase 3 clinical trials[1-3]



Median OS results from phase 4 CORRELATE study[4]



The data presented above are illustrative in nature and do not attempt to compare cross trials.

STIVARGA's tailored approach to dosing helps extend potential benefits for patients with mCRC

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend the following dose escalation schedule[5,6]

STIVARGA dose escalation approach based on ReDOS[5-7†]

	Cycle 1				Cycle 2
Week	1	2	3	4	1
Once-daily dose	80 mg	120 mg	160 mg	Dosing-free interval	Last dose from Cycle 1

Regorafenib dose optimization study[7]

- ReDOS is a randomized phase 2 study of a planned dose escalation with STIVARGA (starting from a lower dose) compared to the standard dose in patients with refractory mCRC[‡§]
- Median OS was 9.0 months with the STIVARGA escalating dose vs 5.9 months with the STIVARGA standard dose (*P*=0.0943)

- The recommended dosage of regorafenib is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks, followed by 1 week off therapy. This 4-week period is considered a treatment cycle. Dosage interruptions and/or dose reductions may be required based on individual safety and tolerability. Dosage modifications are to be applied in 40-mg (1 tablet) steps. The lowest recommended daily dose is 80 mg. The maximum daily dose is 160 mg

3L, third-line; BSC, best supportive care; CORRECT, COloRectal cancer treated with REgorafenib or plaCebo after failure of standard Therapy; CORRELATE, Safety and Effectiveness of Regorafenib in Routine Clinical Practice Settings; ReDOS, REgorafenib Dose Optimization Study.

*This study was designed to evaluate the primary endpoint of OS in 3 study arms: atezolizumab + cobimetinib, atezolizumab monotherapy, and regorafenib. The combination regimen of atezolizumab + cobimetinib failed to meet its primary endpoint of superior OS relative to regorafenib. The OS difference between the combination arm and the regorafenib arm was not statistically significant (*P*=0.9871).

†The study supporting the dose escalation schedule has not been reviewed by the FDA. The study was a randomised, phase 2, US-based trial, through the ACCRU (Academic and Community Cancer Research United) research network, that looked at the proportion of patients who completed 2 cycles of STIVARGA and initiated a third cycle (N=116).[3] The efficacy of the alternative dosing schedule cannot be compared to the efficacy of other trials.[7]

‡Escalating dose regimen was 80 mg orally, once daily on days 1 through 7; 120 mg orally, once daily on days 8 through 14; 160 mg orally, once daily on days 15 through 21; followed by 7 days off therapy. Cycle 2 started at the last level dosed during Cycle 1.

§Standard dosing regimen was regorafenib 160 mg orally, once daily for 21 days, followed by 7 days off therapy.

Stivarga 40 mg film-coated tablets (Refer to full SmPC before prescribing.)
Composition: *Active ingredient*: 40 mg regorafenib. *Excipients:* Cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone (K-25), silica (colloidal anhydrous), iron oxide red (E172), iron oxide yellow (E172), lecithin (derived from soya), macrogol 3350, polyvinyl alcohol (partly hydrolysed), talc, titanium dioxide (E171). **Indication:** As monotherapy for the treatment of adult patients with: 1. metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy; 2. unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib; 3. hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Warnings and Precautions:** It is recommended to perform liver function tests before initiation of treatment and monitor closely (at least every 2 weeks) during the first 2 months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment. Stivarga is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). In cases of worsening infection events, interruption of Stivarga treatment should be considered. Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding. Patients with oesophageal varices should be evaluated and treated as per SOC/guidelines before starting treatment with Stivarga. Permanent discontinuation should be considered in the event of severe bleeding. Discontinuation of Stivarga is recommended in patients developing gastrointestinal perforation or fistulae. Patients with a history of ischaemic heart disease should be monitored for clinical signs and symptoms of myocardial ischaemia. In patients who develop cardiac ischaemia and/or infarction, interruption of Stivarga is recommended until resolution. The decision to restart Stivarga therapy should be based on careful consideration of the potential benefits/risks of the individual patient. Stivarga should be permanently discontinued if there is no resolution. In patients developing posterior reversible encephalopathy syndrome (PRES), discontinuation of Stivarga, along with control of hypertension and supportive medical management of other symptoms is recommended. Blood pressure should be controlled prior to initiation and during treatment and it is recommended to treat hypertension. In cases of severe or persistent hypertension despite adequate medical management, treatment should be temporarily interrupted and/or the dose reduced. In case of hypertensive crisis, Stivarga should be discontinued. For patients undergoing major surgical procedures it is recommended to interrupt treatment temporary for precautionary reasons, and to resume treatment based on clinical judgment of adequate wound healing. Management of hand-foot skin reaction (HFSR) may include the use of keratolytic creams and moisturizing creams for symptomatic relief. Dose reduction and/or temporary interruption, or, in severe or persistent cases, permanent discontinuation of Stivarga should be considered. It is recommended to monitor biochemical and metabolic parameters during treatment and to institute replacement therapy if required. Dose interruptions or reduction, or permanent discontinuation should be considered in case of persistent or recurrent significant abnormalities. In clinical trials, a higher incidence of HFSR, severe liver function test abnormalities and hepatic dysfunction was observed in Asian (in particular Japanese) patients treated with Stivarga compared with Caucasians. This medicinal product contains 55.8 mg sodium per daily dose of 160 mg, equivalent to 3% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Each daily dose of 160 mg contains 1.68 mg of lecithin (derived from soya). There is insufficient data on patients who discontinued sorafenib therapy due to sorafenib-related toxicity or only tolerated a low dose (< 400 mg daily) of sorafenib. **Undesirable effects:** *Very common:* infection,‖ thrombocytopenia, anaemia, decreased appetite and food intake, haemorrhage,‖ hypertension, dysphonia, diarrhoea, stomatitis, vomiting, nausea, hyperbilirubinaemia, increase in transaminases, HFSR, rash, asthenia/fatigue, pain, fever, mucosal inflammation, weight loss. *Common:* leucopenia, hypothyroidism, hypokalaemia, hypophosphataemia, hypocalcaemia, hyponatraemia, hypomagnesaemia, hyperuricaemia, dehydration, headache, tremor, peripheral neuropathy, taste disorders, dry mouth, gastro-oesophageal reflux, gastroenteritis, alopecia, dry skin, exfoliative rash, muscle spasms, proteinuria, increase in amylase, increase in lipase, abnormal International normalized ratio. *Uncommon:* hypersensitivity reaction, myocardial infarction, myocardial ischaemia, hypertensive crisis, gastrointestinal perforation,‖ gastrointestinal fistula, pancreatitis, severe liver injury,‖ nail disorder, erythema multiforme. *Rare:* keratoacanthoma/squamous cell carcinoma of the skin, PRES, Stevens-Johnson syndrome, toxic epidermal necrolysis.
‖Fatal cases have been reported.
Classification for supply: Medicinal product subject to restricted medical prescription.
Marketing Authorisation Holder: Bayer AG, D-51368 Leverkusen, Germany
Date of the underlying Prescribing Information: June 2018

REFERENCES: 1. Grothey A, Van Cutsem E, Sobrero A, et al; for the CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863):303-312. **2.** Li J, Qin S, Xu R, et al; on behalf of the CONCUR Investigators. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2015;16(6):619-629. **3.** Bendell J, Ciardiello F, Tabernero J, et al. Efficacy and safety results from IMblaze370, a randomised phase III study comparing atezolizumab+cobimetinib and atezolizumab monotherapy vs regorafenib in chemotherapy-refractory metastatic colorectal cancer. *Ann Oncol.* 2018;29(suppl 5). doi:10.1093/annonc/mdy208.003. Abstract LBA-004. **4.** Ducreux M, Petersen LN, Öhler L, et al; CORRELATE Investigators. Safety and effectiveness of regorafenib in patients with metastatic colorectal cancer in routine clinical practice: final analysis from the prospective, observational CORRELATE study. Poster presented at: European Society for Medical Oncology (ESMO) 20th World Congress on Gastrointestinal Cancer; June 20-23, 2018; Barcelona, Spain. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer V.2.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed July 13, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer. V.2.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed July 13, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. **7.** Bekaii-Saab TS, Ou F-S, Anderson DM, et al. Regorafenib dose optimization study (ReDOS): a randomized phase II trial to evaluate dosing strategies for regorafenib in refractory metastatic colorectal cancer (mCRC)—an ACCRU Network study. Poster presented at: American Society of Clinical Oncology (ASCO) 2018 Gastrointestinal Cancers Symposium; January 18-20, 2018; San Francisco, CA.

G.MKT.SM.ON.08.2018.2596
PP-TKI-DE-0001-1

Stivarga® (regorafenib) tablets