COPENHAGEN 2016 ESMO

TUESDAY 11 OCTOBER, 2016

FROM DISEASE TREATMENT TO PATIENT CARE

DAILY REPORTER

Advancing the treatment of sarcoma

Neoadjuvant chemotherapy with three full-dose courses of the anthracycline epirubicin plus ifosfamide has a substantial clinical benefit over 'histology-adapted' chemotherapies in patients with localised high-risk soft tissue sarcomas (STS). These were the findings of a prospective randomised study (third futility analysis) reviewed in a Late-Breaking Abstract presentation yesterday by Dr Alessandro Gronchi from Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (Abstract LBA6_PR). In 286 adult STS patients at high risk of relapse, the probability of relapse-free survival (RFS; primary endpoint) at 46 months (median follow-up 12.34 months) was 62% with epirubicin plus ifosfamide versus 38% with histology-driven treatment (p=0.004). Dr Gronchi noted similar overall survival (OS) data (89% versus 64%; p=0.033), resulting in an increase of >20% in RFS and ≥10% in OS with the anthracycline-containing regimen compared with other chemotherapy regimens.

Subgroup analysis by histologically-tailored regimen suggested that patients with high-grade myxoid liposarcoma derived similar progression-free survival (PFS) and OS benefits from trabectedin compared with epirubicin plus ifosfamide. This patient subgroup will be expanded to further investigate this effect.

An increase in RFS >20% was reported with the anthracycline-containing regimen compared with histology-driven chemotherapy.

Further sarcoma data were reviewed during a Proffered Paper Session on Saturday in two presentations. In the first, trabectedin doubled median PFS (primary endpoint) compared with best supportive care (BSC) in a phase III study of 103 patients with pre-treated advanced STS (3.1 months versus 1.5 months, respectively; hazard ratio [HR] 0.39; 95% confidence interval [CI] 0.24–0.64; p<0.0001). Dr Axel Le Cesne from Institut de Cancérologie Gustave Roussy, Villejuif, France noted that trabectedin had greatest PFS benefit compared with BSC in patients with lipo-leiomyosarcoma (5.1 months versus 1.4 months, respectively; HR 0.29; 95% CI 0.15–0.55; p<0.0001; Abstract 13960). A similar degree of benefit has been reported with trabectedin in recent trials with similar patient populations.

In the second presentation, analyses of almost 27,000 sarcoma and connective tissue tumour patients from a French database (NETSARC) revealed a significantly lower rate of local relapse in patients who had been presented to a NETSARC multidisciplinary tumour board (NMTB) prior to initial treatment compared with those who had not (p<0.0001 at a median follow-up of 26 months; Abstract 13970). Reviewing the data, Professor Jean-Yves Blay from Université Claude Bernard, Lyon, France, noted that a lack of presentation to an NMTB was also an independent unfavourable prognostic factor for relapse on multivariate analysis (HR 1.8; p<0.0001), along with patient age and tumour grade, size and location. These observations provide a strong rationale for multidisciplinary discussion prior to initial treatment of patients with sarcoma. Professor Blay pointed out that a longer follow-up period is needed to evaluate the impact of NMTB presentation on metastasis-free and overall survival.

View the ESMO 2016 Broadcast on the YouTube playlist here.

ESMO 2016: *Daily Reporter* Editorial Team highlights

All good things must come to an end and so we reach the last day of ESMO 2016. In the opening edition of the *Daily Reporter*, we said our aim was to help you navigate the wealth of data in the packed Congress programme. We hope you feel that we have achieved this!

In this final edition, we wanted to share with you the Editorial Team's personal picks of the scientific programme. At a time when clinical investigation into targeted agents in oncology is highly active, it will come as no surprise that our selection centres around this type of therapy. Some studies stood out as providing valuable guidance for the clinical community.

Giuseppe Curigliano (Editor-in-Chief): For me, a real breakthrough came in the form of a new proposal for using targeted therapy in the adjuvant setting. That is, instead of adopting a one-size-fits-all approach, we should direct therapy to those patients with clinically and/or pathologically determined high-risk disease. Impressive survival results using this approach were achieved in two placebo-controlled, phase III trials—one investigating ipilimumab following complete resection of melanoma (EORTC 18071; overall survival [OS] hazard ratio [HR] 0.72; p=0.001; Abstract LBA2_PR) and the other looking at sunitinib following nephrectomy in renal cell carcinoma (disease-free survival [DFS] HR 0.761; p=0.03; S-TRAC; Abstract LBA11_PR). These results illustrate how targeted therapies can be most effectively extended into the adjuvant setting, at least at the current time.

Potentially practice-changing trial results in the first- and subsequent-line treatment of non-small-cell lung cancer (NSCLC) caught the attention of some of the team.

Floriana Morgillo (Associate Editor): I was particularly interested in the insight provided by several studies into treatment sequencing for *ALK*-rearranged or *EGFR* mutation-positive NSCLC. In *ALK*-rearranged disease for which crizotinib is currently the standard first-line treatment, the next-generation ALK inhibitor ceritinib prolonged progression-free survival (PFS) compared with chemotherapy (pemetrexed or docetaxel) following progression on crizotinib (HR 0.49; p<0.001) (ASCEND-5; Abstract LBA42_PR). Durable responses were seen in patients who had received multiple prior therapies, not including ALK inhibitors, with remarkable activity also in patients with brain metastases (ASCEND-3; Abstract 1208PD). In *EGFR* mutation-positive NSCLC, mature OS data from the LUX-Lung 7 study reported that first-line afatinib showed a non-significant trend towards a benefit over gefitinib (HR 0.86; p=0.258) (Abstract LBA43). Updated PFS and response rate (RR) analyses continued to show significant benefits for afatinib, confirming that it remains the preferred first-line choice over gefitinib.

Markus Joerger and **Stefan Zimmermann (Associate Editors)** both chose results from studies with checkpoint inhibitors in PD-L1-expressing NSCLC among their highlights. Arguably the most influential data here came from KEYNOTE-024, the first study of first-line pembrolizumab in patients with NSCLC and high PD-L1 expression (≥50% of tumour cells). The significant PFS (HR 0.50; p<0.001) and OS (HR 0.60; p=0.005) improvements seen with the PD-1 inhibitor over platinum-based chemotherapy (Abstract LBA8_PR) will change the future of treatment for such patients. The benefit of adding pembrolizumab to chemotherapy (carboplatin plus pemetrexed) in the first-line setting was suggested by the results of the phase I/II KEYNOTE-021 study (Abstract LBA46_PR) and this combination is likely to prove its worth in ongoing confirmatory phase III trials. Finally, the possibility of using PD-L1-directed treatment in previously treated NSCLC came closer to reality with results from the first phase III trial in this setting in which atezolizumab significantly improved OS compared with second- or third-line docetaxel (HR 0.73; p=0.0003) (OAK; Abstract LBA44_PR). We look forward to results from the ongoing CheckMate-227 (nivolumab and ipilimumab) and MYSTIC and NEPTUNE (durvalumab) studies, which are investigating potentially improved first-line immunotherapy options.

Left to right: **Stefan Zimmermann** (HFR Fribourg-Cantonal Hospital, Switzerland); **Markus Joerger** (St Gallen Cancer Centre, Switzerland); **Floriana Morgillo** (Second University of Naples, Italy); **Giuseppe Curigliano** (European Institute of Oncology, Milan, Italy); **Evandro de Azambuja** (Jules Bordet Institute, Brussels, Belgium).

Evandro de Azambuja (Associate Editor): Amid the excitement surrounding targeted agents, I was very interested to see data urging a note of caution. While the MONALEESA-2 study confirmed the superior efficacy of ribociclib plus hormonal therapy compared with hormonal therapy alone in post-menopausal women with hormone receptor-positive breast cancer (PFS, HR 0.556; p=0.00000329) (Abstract LBA1_PR), the FALCON study reminded us that a substantial proportion of these patients will experience a long median PFS (16.6 months) with hormone therapy alone (Abstract LBA14_PR). There is an urgent need to identify biomarkers predicting the lack of efficacy of these targeted agents, thus avoiding unnecessary costs and toxicities. No less important is the worrying underreporting of adverse events with targeted agents (Abstract 320P) and the poor access to them in some parts of Europe (Abstract 1389O_PR). Also, we cannot forget that some patients will do extremely well with standard treatments and it remains our duty to identify those.

Tailoring treatment, improved adverse event reporting and wider access to treatment are all considerations for targeted therapies.

So that's all from us for ESMO 2016! I would like to thank the *Daily Reporter* Editorial Team and all article contributors for their hard work in helping to put together what I think have been informative and stimulating newspaper editions. And I would like to thank you, the delegates, for taking the time to read the *Daily Reporter*.

We hope to see you all next year at ESMO 2017 in Madrid, Spain (8–12 September)!

ESMO and ASCO working together **to take better care of our patients**

Dr Daniel Hayes: *ASCO President, shares his thoughts on ESMO 2016*

"This has been an incredible meeting. As President of ASCO, I am actually envious of the amount of really terrific science. Several game changers were presented here—there were six *New England Journal of Medicine* papers over the five days, and that's unprecedented. The really great thing here is not that ESMO did a good job, or that ASCO does a good job, it's that we're doing a better job taking care of our patients and that's what we're seeing here this week. We're seeing a reduction in mortality in metastatic melanoma, metastatic recurrent ovarian cancer and non-small-cell lung cancer. Who thought we would ever see that? And it's not just the immunotherapy that's exciting—although I think it's the most exciting thing in oncology—it's also the PARP inhibitors, the CDK4/6 inhibitors and the mTOR inhibitors. There is so much going on, it's just unbelievable. I'm fond of saying I wish I was 30 years old again, for many reasons, not just for the science, but boy this is a great time to be an oncologist and it's a great time to be in the field. And the really great thing is the way that ESMO and ASCO are working together, not just to make these advances but also to apply them. Medicine doesn't work if it doesn't get to the patient and we have a number of challenges in this respect. We have to get the cost of these drugs down so that everyone can receive them. It's bad enough that any patient dies of metastatic cancer because we don't understand the cancer and we don't have the therapies, but it's even worse if a patient dies who could have been cured. And we have to fix that. ASCO's trying, ESMO's trying; we're working together. Let's face it, most of our fathers and grandfathers were fighting a war and trying to kill each other and now we're sitting around a table and trying to save lives. That's what we're supposed to do. And ESMO, this meeting, really shows that we can do that."

ESMO 2016: **Reflections and aspirations**

Professor Josep Tabernero: *Chair of the ESMO Cancer Medicines Working Group*

This ESMO Congress has been really spectacular. The scientific content has been focused on patient care, especially with a clinical and a translational approach. Importantly, we were able to secure an outstanding scientific programme. The programme included 47 Late-Breaking Abstracts, 11 of which were featured in the three Presidential Sessions. We have seen innovations in different diseases, among which are melanoma, non-small-cell lung cancer and ovarian cancer, giving very good news for patients. At the same time, several sessions discussed how we can make these drugs—these innovations—available to all patients. This is very important: ESMO is a worldwide society, in common with other societies, such as ASCO and the NCCN platform. As such, we think it's very important for us all to discuss with stakeholders how we can improve patient access to medicines, not only innovative agents but also all essential medicines. Even drugs that are relatively inexpensive are not available in many countries. So the discussion on accessibility relates to how we can formulate ESMO initiatives that policy makers can consider to help make these drugs available on a wider scale. For example, ESMO has established the Cancer Medicines Working Group that works very closely with the ESMO Magnitude of Clinical Benefit Scale Working Group in putting the efficacy and safety of drugs into perspective with the actual value they offer to the patient and, ultimately, value-based reimbursement. This is a crucial aspect because the only way to favour availability and dissemination is to address it in relation to different reimbursement policies. ESMO is working to secure the co-operation of all stakeholders, including reimbursing bodies, representatives of national health systems and national cancer plans, patients, specialists, health economists and the pharma companies. Our ultimate goal is to provide models that will enhance the availability of information worldwide.

ESMO 2016: Facts & Figures

20,522 ATTENDEES

FROM OVER **124** COUNTRIES

515 SPEAKERS

74% MALE

26% FEMALE

194 SESSIONS

55 SATELLITE SYMPOSIA

22 CONGRESS TRACKS

PARALLEL TOP-TIER PUBLICATIONS WITH ESMO 2016 PRESENTATIONS

6 IN *THE NEW ENGLAND JOURNAL OF MEDICINE*

2 IN *LANCET ONCOLOGY*

PROGRAMME OVERVIEW

75% SCIENTIFIC

25% EDUCATIONAL

1,639 ACCEPTED

2,884 ABSTRACTS SUBMITTED

Immune checkpoint inhibitors for urothelial cancer: **New hope with new options**

Platinum-based chemotherapy has been the mainstay of treatment for urothelial cancer; however, targeted biologics are now gaining prominence in this setting. Programmed death-1 (PD-1/PD-L1) checkpoint inhibitors facilitate tumour infiltration by T cells, resulting in targeted destruction by the immune system.

Earlier this year, the PD-L1 inhibitor atezolizumab was approved by the US FDA for the treatment of locally advanced/metastatic urothelial cancer. Late-breaking results for other PD-1/PD-L1 inhibitors in urothelial cancer offer hope for the future treatment of metastatic urothelial cancer in the post-chemotherapy setting.

Pembrolizumab has been investigated as a first-line treatment for metastatic urothelial cancer in 374 patients enrolled in the open-label phase II KEYNOTE-052 study as reported on Saturday by Dr Arjun Balar of the NYU Langone Medical Center, New York, USA (Abstract LBA32_PR). Preliminary results were very promising, with objective and complete response rates of 24% and 6%, respectively, in the overall population. Notably, in a subpopulation of 30 patients with combined tumour and immune cell PD-L1 expression of ≥10%—the cut-off point determined to identify those patients most likely to respond to pembrolizumab—11 patients (objective response rate 37%) responded to treatment. At a median 8-month follow-up, the median duration of response is yet to be reached in any patient subgroup in this study and toxicity was manageable.

The PD-1 inhibitor nivolumab is approved for the treatment of a number of advanced cancers. Results from CheckMate 275—to date, the largest phase II trial of nivolumab in locally advanced urothelial cancer—were presented on Saturday by Professor Matthew Galsky from Mount Sinai School of Medicine, New York, USA (Abstract LBA31_PR). While objective and complete responses were seen in 19.6% and 2.3%, respectively, of the 265 patients evaluated for efficacy, higher respective objective and complete response rates of 28.4% and 4.9% were reported in 81 patients with tumour cell PD-L1 expression of ≥5%. At a median follow-up of 7 months, the median duration of response had not been reached. Professor Galsky added that these data will now be used to support the US registration of nivolumab for the treatment of metastatic urothelial cancer after failure of platinum-based chemotherapy, an indication for which the US FDA has granted Breakthrough Therapy Designation.

Commenting on his results, Dr Balar said, "These findings, together with results from a previous study with atezolizumab, suggest that in the very near future immunotherapy will become a potential standard of care in the first-line setting for these patients."

Optimal duration of adjuvant capecitabine **for stage III colon cancer still equivocal**

Final results from a phase III study of adjuvant capecitabine therapy in stage III colon cancer indicate a lack of superiority in disease-free survival (DFS) with treatment extension to 48 weeks compared with the standard of 24 weeks. These findings were revealed yesterday in a poster by Dr Shigeki Yamaguchi from Saitama Medical University International Medical Center, Hidaka, Japan (Abstract 469PD).

At a median follow-up of 60 months, 3-year DFS was 75.3% versus 70.0% and 5-year DFS 68.7% versus 65.3%, in the 48-week and 24-week treatment arms, respectively (hazard ratio 0.866; 95% confidence interval 0.717–1.046; p=0.068).

Prolonging adjuvant capecitabine treatment does not significantly improve disease-free survival.

The trial was conducted to investigate the optimal duration of adjuvant capecitabine treatment following observations of a peak in risk of recurrence of curatively resected colon cancer at 12–18 months post-surgery in patients who received the conventional 24 weeks, but not in those who received 48 weeks, of capecitabine therapy.[1]

Despite the lack of superiority in DFS (the primary endpoint), differences in favour of longer-term treatment were observed in 5-year overall survival (87.6% versus 83.2%; p=0.0159) and 5-year relapse-free survival (74.1% versus 69.3%; p=0.0207), suggesting that further investigation of optimal treatment duration may be warranted.

Discussing the results, Dr Richard Adams from Cardiff University, UK, noted that caution would need to be used in the application of the results from this non-US-, non-European-based population.

1. Takahashi T, et al. J Clin Oncol 2011;29(Suppl 4):Abstract 517

Custirsen: Disappointment so far despite a strong biological rationale

There is an unmet need for novel molecular targets and therapies to improve survival in patients with metastatic castrate-resistant prostate cancer (mCRPC). Clusterin overexpression in many cancer types results in resistance to a number of chemotherapeutic agents through cytoprotective and anti-apoptotic means. Depletion of clusterin could therefore potentially increase the efficacy of existing treatments. Custirsen is an antisense oligonucleotide targeting secretory clusterin expression that was linked to survival improvements in phase II trials of mCRPC[1,2] and untreated lung cancer.[3]

The eagerly awaited results of the phase III AFFINITY trial of custirsen plus cabazitaxel/prednisone in mCRPC were reported yesterday by Professor Karim Fizazi of the Institut Gustave Roussy, Villejuif, France (Abstract LBA9_PR). Addition of custirsen did not significantly improve overall survival compared with cabazitaxel/prednisone in the total population (n=635; 14.2 months versus 13.4 months, respectively; p=0.529) or in a poor prognosis subgroup (n=392; 11.1 months versus 10.9 months, respectively; p=0.470). Similar results were reported previously in SYNERGY (custirsen plus docetaxel/prednisone in mCRPC).

It now seems unlikely that custirsen will be developed further in mCRPC.

The question of whether custirsen plus docetaxel is effective in patients with lung cancer will be answered by the ENSPIRIT trial, due to report in 2017.

1. Chi KN, et al. J Clin Oncol 2010;28:4247–54
2. Saad F, et al. Clin Cancer Res 2011; 17:5765–73
3. Laskin JJ, et al. J Thorac Oncol 2012; 7:579–86

Financial toxicity worsens clinical outcomes and quality of life

There is growing awareness of the financial burden that cancer has on patients and their families, where the diagnosis and/or treatment often affect a person's ability (as well as that of their carers) to continue working. There is also a growing recognition of the concept of 'financial toxicity'—a term coined to depict the distress from economic hardship equivalent to that of the physical and psychological toxicities of cancer. A recent literature review determined that financial toxicity has a huge impact on clinical outcomes and quality of life (QoL).[1]

Yesterday, Dr Francesco Perrone from the National Cancer Institute, Naples, Italy, presented the results of a pooled analysis examining the impact of financial difficulties on Italian cancer patients enrolled in 16 multicentre, prospective clinical trials in lung, breast or ovarian cancer (Abstract 10200_PR) between 1999 and 2015.

Using a question on financial aspects in the EORTC QoL C30 questionnaire, patients were asked to score financial difficulties associated with disease or its treatment. At baseline, 26% of 3,670 patients experienced financial difficulties and this was significantly correlated with worse baseline QoL but not increased risk of death. During treatment, 2,735 patients (around 75%) completed questionnaires, with 616 (22.5%) developing financial toxicity, which was significantly associated with an increased risk of death (hazard ratio 1.20; 95% confidence interval 1.05–1.37; p=0.007).

Professor Richard Sullivan of the Institute of Cancer Policy, King's College London, UK, who has published widely on cancer policy and economics, says that the situation is worrying. "Beyond the obvious detrimental impact that cancer has on a patient's health and wellbeing, the financial burden faced by patients, even in high income countries with good public health systems, is substantial. The combination of money problems and diminished clinical outcomes is a wake-up call for governments to properly address this under-recognised problem," he added.

1. O'Connor JM, et al. J Community Support Oncol 2016;14:101–6

SPECTAcolor: The first prospective genetic screening platform for patients with advanced colorectal cancer

As discussed in the *Daily Reporter* yesterday, oncology trials are focusing increasingly on precision medicine, by assessing treatments that target pathways specifically activated in an individual patient in order to give the best chance of positive outcomes. The Screening Platform for Efficient Clinical Trial Access in advanced colorectal cancer (SPECTAcolor) is an EORTC initiative that co-ordinates gene-panel sequencing of patient tissue samples from 32 centres in 11 countries to identify causative genetic alterations and, if feasible, match patients with recruiting trials of targeted therapies.

The results of the first SPECTAcolor cohort of approximately 400 patients were presented yesterday by the project's co-ordinating oncologist, Dr Gunnar Folprecht of the University Hospital Carl Gustav Carus, Dresden, Germany (Abstract 4580). Among the patients screened to date, approximately 10% had potentially actionable mutations making them possible candidates for enrollment into studies with mutated gene-specific inclusion criteria.

In addition to SPECTAcolor, SPECTAmel, SPECTAlung, SPECTAbrain and SPECTAprostate are related ongoing screening platforms for patients with melanoma, and thoracic, neurological and prostate cancers. These initiatives promise to increase the efficiency of patient recruitment in precision-medicine trials and, it is hoped, improve the likelihood of better treatment responses as a result.

Commenting on the SPECTA initiative, Dr Fabrice André from Institut Gustave Roussy, France, said that, "When discussing molecular screening programmes, it's important to define how they will be evaluated. The number of patients presenting with potentially actionable alterations can no longer be regarded as evaluation criteria." He added that four criteria define successful programmes: 1. the number of patients who receive a matched therapy; 2. the number of new targets/drugs identified from the programme; 3. improvement in progression-free and overall survival, and; 4. the quality of translational research performed in the context of the programme.

Many molecular screening programmes are now in their mature phases and some scepticism has arisen about their utility. Dr André believes it is important for leaders in the field to ensure programmes are robust and will have real-world value.

By screening patients for biomarkers relevant to targeted clinical studies, SPECTAcolor increases opportunities for patients with colorectal cancer to access studies with new, molecularly defined approaches.

New data on anti-PD-1 therapy in patients with brain metastases

Brain metastases are a common complication of melanoma and are associated with poor prognosis. The pressing need for effective management is in part due to the extended survival times afforded by improved primary tumour treatments, particularly targeted therapies. While survival is prolonged, unfortunately there is a greater frequency of brain metastases. Reduced blood–brain barrier penetration and resistance development may limit the brain activity of some targeted agents that show excellent extracranial activity, such as the ALK inhibitor crizotinib in lung cancer. The activity of other agents, such as immunotherapies, remains unclear because patients with brain metastases are often excluded from clinical trials. Data from a retrospective analysis provide important new information on this issue.

Yesterday, Dr Christian Blank presented a poster by Dr John Park (Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, Australia; Abstract 1114PD) on the efficacy of anti-programmed death-1 (PD-1) therapies in treating brain metastases from melanoma. In a retrospective analysis of 66 patients with intracranial metastases (38% had ≥5) and relatively poor prognostic features (elevated lactate dehydrogenase [50%] and/or performance status ≥2 [32%]), an intracranial response rate (ICRR) of 20% was reported with anti-PD-1 therapy (nivolumab or pembrolizumab); ICRR was lower for patients with symptomatic lesions (11%) and those receiving steroids for brain metastases (14%). With a median follow-up of 7 months, median intracranial progression-free survival (PFS) and overall survival were 5.3 months and 9.9 months, respectively. Symptoms and steroid treatment for brain metastases were associated with significantly shorter PFS.

Is an intracranial response rate of 20% good enough for patients with brain metastases from melanoma?

Concluding, Dr Christian Blank said that on the basis of these results, anti-PD-1 therapy may not be the best option for the treatment of brain metastases; combinations of checkpoint inhibitors or checkpoint inhibitors with the appropriate targeted therapy may be required in addition to radiotherapy. He added that treatment should be given upfront in this population with such a high unmet medical need.

Positive new phase III data for sunitinib as adjuvant therapy in high-risk RCC

The first trial of a tyrosine kinase inhibitor to show prolonged disease-free survival (DFS) following adjuvant treatment for renal cell carcinoma (RCC) was reviewed yesterday by Dr Alain Ravaud from CHU Bordeaux Hôpital St André, Bordeaux, France, in a Late-Breaking Abstract presentation (Abstract LBA11_PR).

Results of the S-TRAC trial suggest that sunitinib may be of benefit to a broader range of patients in the future.

The double-blind, phase III S-TRAC trial randomised 615 treatment-naïve patients at high risk of recurrent RCC post-nephrectomy to sunitinib (50 mg/day) or placebo for 1 year. DFS by blinded independent central review (primary endpoint) was significantly longer with sunitinib compared with placebo (median DFS 6.8 months versus 5.6 months; hazard ratio [HR] 0.761; p=0.030). These potentially practice-changing data were confirmed in secondary DFS analyses that included a higher risk patient subgroup (HR 0.737; p=0.044).

The safety profile of sunitinib was manageable; a similar incidence of serious adverse events (AEs) was reported in the sunitinib and placebo arms, although an increased incidence of grade ≥3 AEs was observed with sunitinib (62.1%) compared with placebo (21.1%).

Sunitinib has been considered a standard of care in the treatment of advanced RCC since its initial approval in 2006. Results of the S-TRAC trial suggest that sunitinib may be of benefit to a broader range of patients in the future. However, the small DFS benefit should be carefully analysed due to the associated side effects and cost of the therapy.

Cabozantinib superior to sunitinib in phase II study of metastatic RCC

Compared with sunitinib, first-line cabozantinib significantly improved progression-free survival (PFS) and objective response rate (ORR) in patients with metastatic renal cell carcinoma (mRCC). These were the conclusions of a randomised, multicentre phase II trial reported in a Late-Breaking Abstract presentation yesterday by Dr Toni Choueiri from the Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, Massachusetts, USA (Abstract LBA30_PR).

Cabozantinib has recently shown superior PFS, overall survival and ORR compared with everolimus in previously treated patients with mRCC,[1] while sunitinib is considered the reference standard of care for the first-line treatment of mRCC.[2]

In the phase II ALLIANCE study, 157 intermediate- or poor-risk patients who had not received prior systemic therapy were randomised to cabozantinib (60 mg once daily [qd]) or sunitinib (50 mg qd, 4 weeks on/2 weeks off). Median PFS (primary endpoint) was considerably prolonged with cabozantinib compared with sunitinib (8.2 months versus 5.6 months, respectively), equivalent to a 31% reduction in median rate of progression or death with cabozantinib (hazard ratio 0.69; 95% confidence interval 0.48–0.98; p=0.012) at a median follow-up of 20.8 months. ORR was also markedly and significantly higher with cabozantinib (46%) versus sunitinib (18%). Adverse events (AEs) were reported at a similar incidence in the cabozantinib and sunitinib treatment arms (70.5% and 72.2% of patients, respectively, experienced grade ≥3 AEs).

"These data show that cabozantinib has the potential to become a first-line standard treatment for mRCC," concluded Dr Choueiri.

This randomised, phase II trial has demonstrated for the first time superior activity of a new therapy compared with sunitinib in previously untreated patients with RCC.

1. Choueiri T, et al. N Engl J Med 2015;373:1814–23
2. Oudard S, et al. Cancer Treat Rev 2011;37:178–84

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A novel prognostic biomarker of poor overall survival in advanced CRC

Colorectal cancer (CRC) can have highly variable prognoses and treatment outcomes and, as a result, assessment of molecular markers has become a major factor in therapeutic decision-making for this disease.

Yesterday, Professor Frédérique Penault-Llorca of the Centre Jean Perrin, Clermont-Ferrand, France, presented on the discovery of a novel genetic prognostic factor in stage III CRC (Abstract 4590), identified using prospectively collected tissue samples from an interventional study. PETACC8, a phase III, open-label, randomised study of FOLFOX-4 plus cetuximab versus FOLFOX-4 alone for patients with resected stage III colon cancer,[1] was used to assess the prognostic effects of a number of gene mutations.

A previous post-hoc analysis of this dataset revealed that the presence of *BRAF* and *KRAS* mutations predicted shorter durations of disease-free and overall survival.[2] The present analysis showed that alterations (mutations or amplifications) of *ERBB2*, a key tumourigenesis driver, were detected in 3.9% of 1,795 patients in PETACC8 and predicted a significantly shortened duration of recurrence-free and overall survival. Professor Penault-Llorca concluded by advocating the use of next-generation sequencing and fluorescence *in situ* hybridisation (FISH) to analyse this rare but potentially useful prognostic biomarker and facilitate the use of targeted CRC therapies in the adjuvant setting.

1. Taieb J, et al. Lancet Oncol 2014;15:862–73
2. Taieb J, et al. JAMA Oncol 2016;14:1–11

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Delegate **voices**

"Great variety—how do you choose what to go to?! And it's a good social networking space for meeting colleagues and opinion leaders."

Sarah Payne, Honorary Consultant at Guy's and St Thomas', London, UK

"I've heard a lot of interesting data – significant advances are clearly being made across many tumour types, although we still have much work to do."

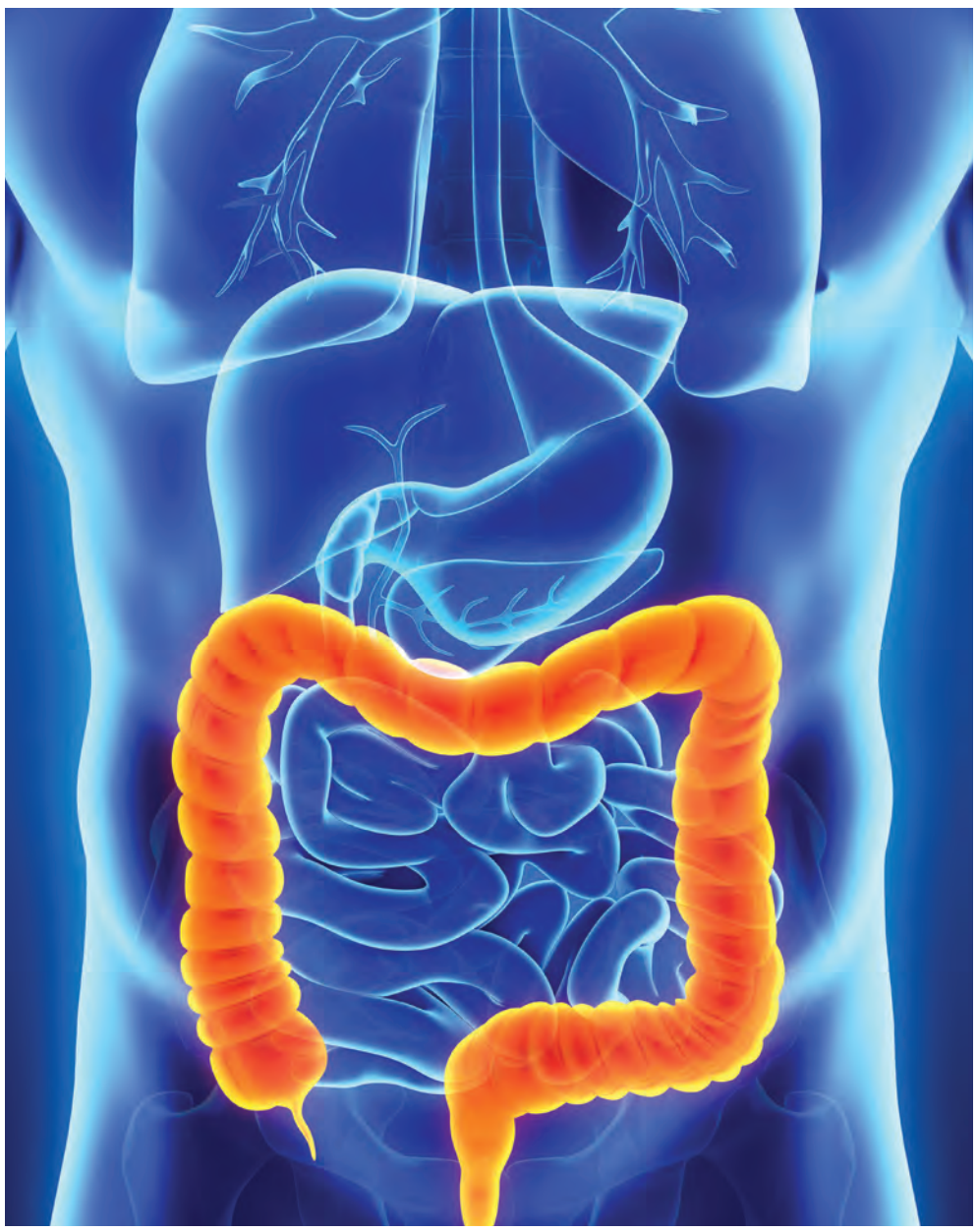
Theo Smalberger, Medical Oncologist, South Africa

"I've really enjoyed the congress this year – it has been well organised and the scientific content has been great, particularly the breast and lung cancer data. I'm looking to join the Young Oncologist initiative and will be back next year!"

Thais Abreu de Almeida, Oncologist, Brazil

"I've been most interested in the breast cancer track – the MONALEESA 2 data might mean a change in the standard of care and makes treatment sequencing less certain especially in light of the FALCON study results. It will be interesting to see how this story evolves at future congresses."

Simon Oliver, Researcher, UK



Nintedanib shows clinical activity in a phase III study of refractory CRC

The oral multiple angiokinase inhibitor nintedanib appears to have activity in refractory metastatic colorectal cancer (CRC) according to the findings of the phase III LUME-Colon 1 study. Reviewing the data in a Late-Breaking Abstract presentation on Sunday (Abstract LBA20_PR), Professor Eric Van Cutsem from University Hospitals Leuven, Belgium, noted the statistically significant improvement in progression-free survival (PFS) observed with nintedanib (hazard ratio 0.58; 95% confidence interval 0.49–0.69; p<0.0001) versus best supportive care (BSC), but cautioned that this did not translate into an overall survival (OS) advantage (co-primary endpoint).

Nintedanib is a new compound that appears to have activity in a patient population with limited treatment options.

In this trial, 768 patients with refractory metastatic CRC were randomised to nintedanib plus BSC versus placebo plus BSC. The study was conducted after an earlier phase I/II study suggested the agent had similar efficacy to bevacizumab when given as first-line treatment in combination with mFOLFOX6.[1] Consistent with the phase I/II findings, nintedanib appeared to be well tolerated; grade ≥3 adverse events occurring more frequently in the nintedanib than placebo arm were liver-related investigations (16% versus 8%) and fatigue (9% versus 6%).

Nintedanib is a new compound that appears to have activity in a CRC patient population with limited treatment options, and further analyses of the phase III data are ongoing. The agent is currently approved in the EU for the treatment of idiopathic pulmonary fibrosis and for non-small-cell lung cancer after first-line chemotherapy, based on the LUME-Lung 1 trial, which demonstrated significantly extended median OS (approximately 25% of patients survived for ≥2 years) with nintedanib plus docetaxel versus docetaxel alone.[2]

1. Van Cutsem E, et al. Ann Oncol 2015;26:2085–91
2. Reck M, et al. Lancet Oncol 2014;15:143–55

Controversy of the Day: Tailoring treatment in **elderly cancer patients**

Professor Hans Wildiers:
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The treatment of elderly patients with cancer is complicated by pre-existing co-morbidities, cognitive problems and, sometimes, reduced physical fitness. We need tools to identify which patients will best benefit from a particular treatment approach and geriatric assessments (GAs) can provide valuable information to guide management decisions.[1,2] A number of poster presentations at ESMO 2016 shed further light on this area.

An abbreviated comprehensive GA (CGA), used to designate patients as 'fit', 'medium fit' or 'unfit', effectively predicted survival and competing risk of death in 195 patients ≥75 years old with high-risk resected colorectal cancer (CRC) receiving adjuvant therapy (Abstract 545P). 'Unfit' patients were more likely to die of non-cancer-related causes than 'fit' patients (subdistribution hazard ratio [HR] 22.29; 95% confidence interval [CI] 5.24–94.78).

Two posters reported the designs of ongoing trials using GAs to tailor treatment strategies to older patients. The GrantPax multicentre, interventional trial in patients ≥75 years with pancreatic cancer is basing treatment—nab-paclitaxel/gemcitabine, gemcitabine alone or best supportive care—on baseline CGA scores (Abstract 714TiP). In the NORDIC9 trial (Abstract 601TiP), associations between outcome and GAs, biomarkers and pre-treatment characteristics in elderly patients with metastatic CRC are being investigated.

Several studies reported relationships between outcome and a variety of measures. Our study in metastatic CRC (Abstract 546P) and another in metastatic gastric cancer (Abstract 650P) confirm Eastern Cooperative Oncology Group (ECOG) performance score as a prognostic tool for patients ≥70 years old, but specific parameters such as nutritional status, measured by Mini Nutritional Assessment (MNA®), provide additional information. In metastatic breast cancer, the Charlson Comorbidity Index score was a significant prognostic indicator for survival in patients >65 years who received either primary tumour removal or no surgery (Abstract 252P). A phase II trial in 102 patients receiving chemotherapy ± bevacizumab for metastatic CRC reported that baseline scores for the Spitzer quality of life index and Köhne prognostic group criteria were prognostic for overall and progression-free survival (Abstract 583P).

The GrantPax trial is one of the first to assign anticancer treatment to elderly patients strictly according to baseline CGA scores.

The importance of cognitive function for compliance with oral anticancer treatment was also stressed (Abstract 1497P). Among 126 patients receiving oral anticancer therapy, working memory disorders were significantly associated with treatment non-adherence (HR 1.38; p=0.0326) and were significantly worse with increasing age. Depression was also significantly associated with treatment non-adherence (HR 4.67; p=0.0352).

These studies are heartening, in that they indicate the importance with which the oncology community views tailoring treatment to the elderly and that geriatric assessment provides additional information and benefit to patients. However, the variety of measures used highlights the continued and urgent need for standardised, validated, predictive tools.

1. Decoster L, et al. Clin Colorectal Cancer 2016. Aug 8. E-pub ahead of print
2. Wildiers H, et al. J Clin Oncol 2014;32: 2595–603

Selumetinib plus docetaxel fails to show significant benefits **over docetaxel alone in *KRAS*-mutant NSCLC**

The eagerly awaited first prospective phase III trial in *KRAS*-mutant non-small-cell lung cancer (NSCLC; N=510), evaluating selumetinib plus docetaxel versus docetaxel alone as second-line treatment ('SELECT-1'), has failed to meet its primary endpoint of improvement in progression-free survival (PFS).

Dr Pasi Jänne from Dana-Farber Cancer Institute, Boston, Massachusetts, USA, presented the findings in a Late-Breaking Abstract presentation yesterday (Abstract LBA47_PR). He noted that despite observing a significant improvement in PFS and response with the MEK1/2 inhibitor combination in an earlier phase II study,[1] the phase III data were disappointing in this *KRAS*-mutant population that is associated with a particularly poor prognosis and is notoriously difficult to treat. Median PFS was 3.9 months with selumetinib plus docetaxel and 2.8 months with placebo plus docetaxel (hazard ratio 0.93; 95% confidence interval 0.77–1.12; p=0.44). Similarly, the combination did not show a significant effect on overall survival, while a trend towards a higher objective response rate was observed with selumetinib compared with placebo (20.1% versus 13.7%; odds ratio 1.61; p=0.051). The selumetinib plus docetaxel combination was associated with a higher incidence of grade ≥3 adverse events (AEs), serious AEs, and AEs leading to hospitalisation compared with the docetaxel arm.

No improved clinical outcome with the addition of selumetinib to docetaxel in *KRAS*-mutant NSCLC patients.

Selumetinib was granted Orphan Drug Designation by the US FDA in May 2016 for the adjuvant treatment of thyroid cancer and is being further investigated as an adjuvant treatment option for high-risk thyroid cancer (for its capacity to re-sensitise tumour cells to radioactive iodine) and other tumour types.

1. Jänne PA, et al. Lancet Oncol 2013; 14:38–47

ESMO would like to thank the *Daily Reporter* Editorial Team, Editor-in-Chief Giuseppe Curigliano and the Associate Editors Evandro de Azambuja, Markus Joerger, Floriana Morgillo and Stefan Zimmermann, and TMC Strategic Communications, for all their hard work in bringing you the news from ESMO 2016 over the past five days. Covering an important Congress with such a dense programme was a challenge and the team spent many hours debating what would be of most interest to you. We hope you agree that the team did a fantastic job in capturing the essence of the ESMO 2016 Congress and in highlighting the many important sessions that took place. Well done!

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GIOTRIF® Abbreviated European Prescribing Information. Please refer to local prescribing information as it may vary between countries. Different brand names are used in some countries. Presentations: Film-coated tablets each containing 20 mg, 30 mg, 40 mg or 50 mg afatinib (as dimaleate). Indication: GIOTRIF® as monotherapy is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s); locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy. Posology and method of administration: EGFR mutation status should be established prior to initiation of GIOTRIF®. Recommended dose is 40 mg oral once daily to be taken without food. Dose escalation to a maximum of 50 mg/day may be considered in patients who tolerate 40 mg/ day. Symptomatic adverse reactions may be successfully managed by treatment interruption and dose reductions or treatment discontinuation. No starting dose adjustment necessary in patients with mild or moderate renal or hepatic impairment. Not recommended in patients with severely impaired renal function (< 30 mL/min creatinine clearance), severe hepatic impairment, children or adolescents. Contraindications: Hypersensitivity to afatinib or to any of its excipients. Special warnings and precautions for use: Diarrhoea, including severe diarrhoea, and rash/acne may require interruption and dose reduction or discontinuation of therapy. Higher exposure to afatinib has been observed in female patients, patients with lower body weight and those with underlying renal impairment. Interstitial Lung Disease (ILD) or ILD-like adverse reactions, including fatalities, have been reported in patients receiving GIOTRIF®. If ILD is diagnosed, permanently discontinue GIOTRIF®. Discontinue GIOTRIF® in patients who develop severe hepatic impairment. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Cardiac monitoring, including an LVEF assessment, should be considered in patients with cardiac risk factors and patients who develop relevant cardiac signs/symptoms during treatment. GIOTRIF® contains lactose. Interactions: P-gp inhibitors should be administered using staggered dosing, preferably 6 hours or 12 hours apart from GIOTRIF®. Strong inducers of P-gp may decrease exposure to afatinib. It is unlikely that GIOTRIF® changes the plasma concentrations of other P-gp substrates. GIOTRIF® may increase the bioavailability of orally administered breast cancer resistance protein (BCRP) substrates. Fertility, pregnancy and lactation: Women of childbearing potential should be advised to avoid becoming pregnant. No or limited amount of data are available from use in pregnant women. The risk for humans is thus unknown. Advise against breast-feeding while receiving GIOTRIF®. An adverse effect on fertility cannot be excluded. Effects on ability to drive and use machines: Minor influence. Undesirable effects: Very common: diarrhoea, rash, dermatitis acneiform, pruritus, dry skin, epistaxis, decreased appetite, paronychia. Common: cystitis, dehydration, hypokalaemia, dysgeusia, conjunctivitis, dry eye, rhinorrhoea, dyspepsia, cheilitis, alanine aminotransferase increased, aspartate aminotransferase increased, palmarplantar erythrodysaesthesia syndrome, muscle spasms, renal impairment/renal failure, pyrexia, weight decreased. Uncommon: keratitis, interstitial lung disease. Liver function test abnormalities including elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed. Overdose: dermatological (rash/ acne) and gastrointestinal events (especially diarrhoea). Marketing Authorisation Number(s): EU/1/13/879/001 to EU/1/13/879/012. Marketing Authorisation Holder: Boehringer Ingelheim International GmbH, Binger Strasse 173, D-55216 Ingelheim am Rhein, Germany. Date of last revision of prescribing information: 24/05/2016.

Afatinib is approved in a number of markets, including the EU, Japan, Taiwan and Canada under the brand name GIOTRIF® and in the US under the brand name GIOTRIF®. In Europe it is approved for: 1) the treatment of epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s); 2) locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy. Registration conditions differ internationally, please refer to locally approved prescribing information. Afatinib is under regulatory review by health authorities in other countries worldwide. Afatinib is not approved in other indications. The compulsory product information is freely available at the booth.

EGFR M+=epidermal growth factor receptor mutation positive; NSCLC=non-small cell lung cancer; PFS=progression-free survival; OS=overall survival; TTF=time to treatment failure.

1. Yang JC et al. Lancet Oncol. 2015;16(2):141-51.
2. Sequist LV et al. J Clin Oncol. 2013;31(27):3327-3334.
3. Wu YL et al. Lancet Oncol. 2014;15(2):213-22.
4. Park K et al. Lancet Oncol. 2016;17(5):577-89.

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