# Congress daily

PRECISION MEDICINE IN CANCER CARE

TUESDAY
SEPTEMBER 30 2014

DAILY EDITORIALS | SESSIONS NOT TO MISS | ORIGINAL ARTICLES | LBAs


ESMO MADRID 2014

**INSIDE...**

Congress Highlights
THE BEST OF THE ESMO 2014 CONGRESS
09.10 – 12.30 Madrid

**SESSION**

Challenge Your Expert
ADJUVANT TREATMENT OF BREAST CANCER
08.00 – 09.00 Alicante

PICKS OF THE DAY

# **Melanoma:** Latest trial results for targeted therapies

Announcements of late-breaking results yesterday brought delegates right up-to-date on the latest advances with targeted therapies in melanoma.

During the afternoon's Presidential Symposium, Professor Jeffrey Weber from the H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA, highlighted exciting phase III trial results demonstrating good tolerability and durable tumour regression with the checkpoint inhibitor nivolumab in metastatic melanoma patients who progressed on or after anti-CTLA-4 treatment. Results from 167 patients showed that the overall response rate (ORR) with nivolumab was nearly three times greater than that of the investigator's choice of standard chemotherapy (ICC; 32% versus 11%, respectively). The median duration of response had not yet been reached for nivolumab (versus 3.6 months for ICC).

*Nivolumab nearly tripled the response rate achieved with investigator's choice of chemotherapy for metastatic melanoma progressing on anti-CTLA-4 treatment*

**"The impressive data on duration of response suggest that there will be significant prolongation of progression-free and overall survival when the analysis of those data is mature,"** said Professor Weber. **"The differences in response rate and toxicity markedly favour the use of the PD-1 blocking antibody nivolumab compared to results seen with chemotherapy in patients that have failed ipilimumab."**

Data from phase III trials investigating the efficacy of adding a MEK inhibitor to first-line BRAF inhibition with vemurafenib, to prevent or delay resistance to BRAF inhibition in patients with BRAF V600E-mutated advanced melanoma, were discussed in 2 presentations.

Professor Grant McArthur from the Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia, presented results from 495 patients showing a significant increase in progression-free survival (PFS) with cobimetinib/vemurafenib compared with vemurafenib alone (9.9 months versus 6.2 months; hazard ratio [HR] 0.51; 95% confidence intervals [CI] 0.39–0.68; p<0.0001). There was a complete response rate of 10% with cobimetinib/vemurafenib compared with 4% for vemurafenib alone.

**"This study is very important as it shows that using drugs together to turn off two individual proteins (BRAF and MEK), that interact and bind to each other in the cell, gives much improved results for patients. This is fundamental concept that could have far reaching consequences for how we treat many cancers,"** said Professor McArthur.

A combination of dabrafenib and trametinib significantly improved overall survival (OS) compared with vemurafenib alone in a study of 704 patients reported by Dr Caroline Robert from the Institut Gustave Roussy, Villejuif, France. A pre-planned interim analysis demonstrated that the dabrafenib/trametinib combination was associated with a 31% improvement in OS and a 44% reduction in the risk of disease progression compared with vemurafenib alone. Median PFS was 11.4 months and 7.3 months for dabrafenib/trametinib and vemurafenib, respectively. The rates of adverse events were similar between treatment arms.

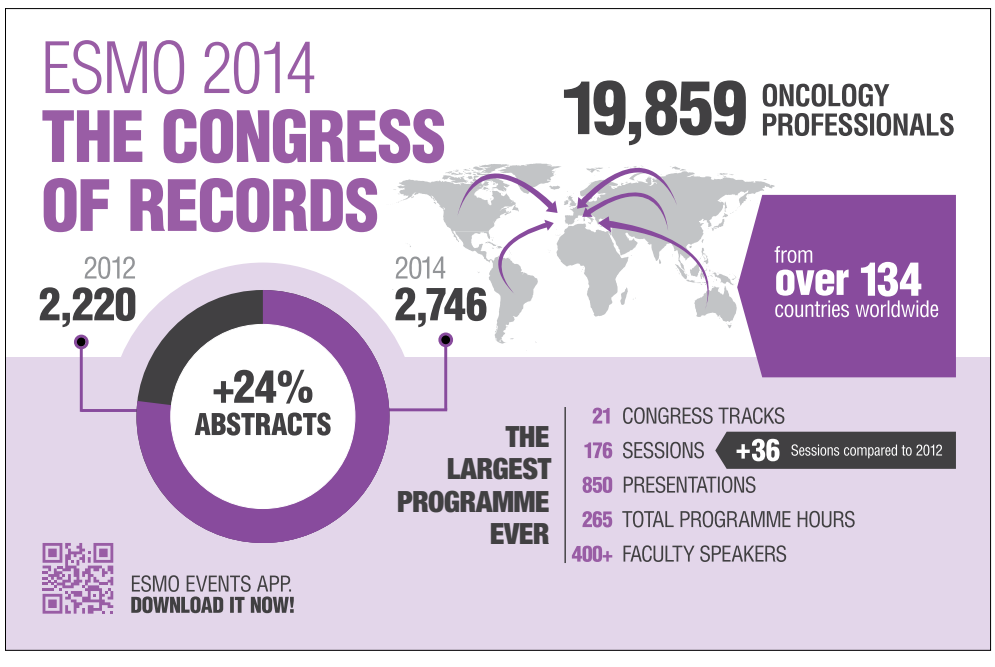
**"These results further corroborate the early preclinical data that more complete blockade of the MAP kinase pathway delays the emergence of resistance, translating into longer survival for the patients,"** observed Dr Robert.

*A dabrafenib/trametinib combination improved overall survival by 31% compared with vemurafenib*

Yesterday's Poster Discussion Session also contributed to the day's focus on melanoma.

Work on therapies targeting the NRAS driver gene is of great interest; NRAS is mutated in around one-fifth of melanoma patients and there are currently no approved treatments specifically for melanomas harbouring this mutation. Breaking results announced by Dr Carla Van Herpen from Radboud University Medical Centre, Nijmegen, The Netherlands, on 117 patients with NRAS-mutated melanoma confirmed earlier reports of activity with binimetinib, one of the first developmental therapies to target this pathway. In this single-arm trial, median PFS and median OS were 3.6 months (95% CI 2.6–3.8) and 12.2 months (lower 95% CI 7.9), respectively. A pivotal phase III study is on-going.


Another presentation from Dr Caroline Robert offered clinicians the first dosing recommendations for the PD-1-targeted checkpoint inhibitor pembrolizumab in melanoma patients. Randomised comparison of regimens of 10 mg/kg every 2 weeks or every 3 weeks showed no significant differences in ORR, PFS or safety; 2 mg/kg every 3 weeks was the recommended dose. ■



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30.09.2014



OVERALL **460** INVITED SPEAKERS

93 PHASE I; 22 PHASE I/II; 112 PHASE II; 2 PHASE II/III; AND 101 PHASE III TRIALS IN >125,000 PATIENTS

THIS IS **TRULY A GOLDEN AGE FOR CANCER MEDICINE** BUT WE STILL HAVE A LOT OF WORK TO DO. OUR PATIENTS ARE WAITING FOR THE FRUITS OF OUR LABOUR

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# Daily Editorial

**Evandro de Azambuja**
**Congress Daily Editor-in-Chief**

Institut Jules Bordet,
Brussels, Belgium

## ESMO 2014: What should be remembered?

Well, here we are at the end of another successful ESMO Congress and I think that this one really lived up to its promise.

Compared to 2012 we had a 24% increase in abstract submission and a 23% increase in registered attendees. We have heard an enormous amount of information from the cutting edge of clinical research over the last few days and the Editorial Team and I would like to take this opportunity to share our particular highlights from the scientific programme with you.

(L–R): Matthias Preusser, Giuseppe Curigliano, Erika Martinelli, Evandro de Azambuja, Floriana Morgillo and Markus Joerger

**Markus Joerger (Associate Editor):** Significant for me from this year's Congress are encouraging data from studies with checkpoint inhibitors indicating that immunotherapy can be extended to include tumours once considered to be poorly immunogenic. Presentations from early phase studies demonstrated good activity and tolerability with the anti-PD-1 antibody pembrolizumab as a single agent in head and neck and gastric cancers (Abstracts LBA31 and LBA15). Tumour PD-L1 expression appeared to be a useful predictive biomarker, highlighting the possibility of tailoring this treatment to patients most likely to benefit. Combinations of different types of checkpoint inhibitors (Abstract 1050O) and checkpoint inhibitors with standard therapy (Abstract 1053PD) also showed promising activity in renal and prostate cancers, respectively. The ability of the checkpoint inhibitors to prevent tumours from evading the immune system means that patients with many different tumour types may be able to benefit from this approach.

**Floriana Morgillo (Associate Editor):** Our increased understanding of the wide range of genomic variants within a tumour type has opened the door to the development of therapies specifically targeted to these variants. My choice of exciting findings from ESMO 2014 comes from two presentations that featured promising results with targeted agents in non-small-cell lung cancer (NSCLC) subtypes. One reported that the BRAF inhibitor, dabrafenib, which is used to treat BRAF V600E-mutated melanoma, produced responses in nearly one-third of patients with NSCLC harbouring the same mutation (LBA38_PR). The other study (LBA39_PR) indicated that a combination of the irreversible pan-HER tyrosine kinase inhibitor, neratinib, and the mTOR inhibitor, temsirolimus, may be a feasible approach to the treatment of patients with HER2-mutated tumours, which should be investigated further. These agents have the potential to successfully treat two more 'slices' of NSCLC and the results give us hope that different targeted treatments may provide efficacy in other subtypes.

**Giuseppe Curigliano (Guest Associate Editor):** It is of course always exciting to hear about new strategies being developed to combat cancer. However, my top pick of ESMO 2014 is the news that in the ghrelin receptor agonist anamorelin, we finally have an agent that can effectively and significantly reduce the effects of cancer cachexia. In our efforts to successfully treat the disease, it is easy to forget that this devastating condition will affect many of our cancer patients, irrespective of tumour type. It is associated with morbidity and death in a substantial number of patients and is a cause of extreme anxiety to them. The results from the phase III ROMANA 1 and 2 studies in NSCLC (1483O_PR) demonstrated significant benefits with anamorelin in body mass, body weight and patients' symptoms and concerns about anorexia-cachexia. These findings suggest that anamorelin has the potential to improve the lives of a significant number of cancer patients.

**Evandro de Azambuja (Editor-in-Chief):** For me, the results from the CLEOPATRA trial (Abstract 3500_PR), demonstrating that the addition of pertuzumab to first-line trastuzumab and docetaxel significantly prolonged overall survival in patients with HER2-positive metastatic disease, really stood out. This treatment combination has the potential to make a real difference to the lives of patients, increasing survival in HER2-positive metastatic breast cancer. Once considered a very aggressive disease, its prognosis has greatly improved with the use of anti-HER2 targeted agents. On a negative, but no less important note, the failure of lapatinib to improve on trastuzumab in early stage HER2-positive disease in one trial and the increased toxicity in another 1 (LBA7, Abstract 2530) will also help to define treatment strategies. These results highlight the urgent need for biomarkers to identify patients benefiting from a given treatment, taking into account treatment efficacy and toxicities. Finally, our increased understanding of the molecular complexities of breast cancer, as evidenced by the identification of significant genomic and immunologic differences between metastatic and primary tumour sites (Abstract 3510) and the identification of further predictive biomarkers (Abstract 2540) should help us to develop new strategies that will offer hope of a better outcome for our breast cancer patients.

I would like to thank the Editorial Team for their tremendous efforts in bringing you the Congress Daily newspapers. I would also like to remind delegates not to miss the very first ESMO ASIA Congress, which is being held in Singapore from 18–21 December 2015. The programme for the meeting, put together by an international committee, will allow delegates the rare opportunity to mix with regional and international experts in oncology. Finally, I hope you found the ESMO 2014 as stimulating and worthwhile as I did. I look forward to seeing you at the European Cancer Congress in Vienna, 25-29 September in 2015 and at the ESMO ASIA Congress. ■

# New data in malignant pleural mesothelioma

**Lung cancer and other thoracic malignancies**

The incidence of malignant pleural mesothelioma (MPM) is still increasing but its prognosis remains poor, with 5-year survival rates of only 5–10%[1] and most patients living for less than a year after diagnosis. Two presentations in yesterday's Proffered Paper Session on Small-cell Lung Cancer and Thoracic Malignancies, discussed treatment approaches and potential prognostic biomarkers in MPM.

In a late-breaking abstract, Professor Rolf A. Stahel from Universitatsspital, Zurich, Switzerland, reported the final results of the randomised phase II SAKK17/04 trial, demonstrating that the use of hemithoracic radiotherapy in the treatment of MPM after neoadjuvant chemotherapy and extrapleural pneumonectomy did not improve relapse-free survival (RFS). Among 54 R0 patients randomised, median RFS was 7.6 months without radiotherapy and 9.4 months with radiotherapy. The trial failed to meet its primary endpoint of a one-year increase in RFS, and so does not support the routine use of hemothoracic radiotherapy in this setting.

### *Radiotherapy did not improve RFS following R0 resection in MPM*

Dr Susana Cedres from Vall d'Hebron University Hospital, Barcelona, Spain, followed up this news with findings from a study characterising PD-L1 expression in MPM. Dr Cedres and her team analysed stained tissue samples from 77 patients with MPM. Of the 20.7% positive samples (defined as PD-L1 expression levels over 1%), 52.6% showed weak expression (intensity 1), 25% moderate (intensity 2) and 18.7% strong (intensity 3). PD-L1 staining was associated with histology: 60% of non-epithelial tumours expressed PD-L1 versus only 15% of epithelial tumours (p=0.033). The researchers also found an association between the staining results and survival. Median survival overall was 13.8 months: 4.79 months in PD-L1-positive patients compared with 16.3 months in PD-L1-negative patients (p=0.012). ■

1. American Cancer Society. http://www.cancer.org/cancer/malignantmesothelioma/detailedguide/malignant-mesothelioma-survival-statistics. Accessed 28 August 2014

**"PD-L1 immunohistochemical expression clearly appears to be an unfavourable prognostic marker in MPM," Dr Cedres concluded. "This study adds to the growing body of evidence that it warrants further investigation for selecting patients for immunotherapy."**

## Collating the data – clinical trials for rare cancers

Rare cancers account for a fifth of all neoplasms, but the group covers a wide variety of cancers, and all rare cancers together are not infrequent. Researchers sometimes struggle to recruit significant numbers of patients to trials and the lack of data hinders the diagnosis and treatment of patients. ESMO recognises the importance of these problems, and in 2009 it launched the 'Call to action against rare cancers,' which asks oncology professionals to prioritise quality treatment for these patients.

The issue was discussed in yesterday's Special Session on Rare Cancers Europe: How Clinical Trials Could Have Been Done, and Were Not, in Rare Cancers.

Dr Hans Gelderblom from Leiden University Medical Center, The Netherlands, spoke of the issues encountered in obtaining data to inform more effective treatments for soft tissue sarcomas. Controversy exists over the use of meta-analyses versus individual trials and the value of histotype-driven, smaller studies. Consensus on possible biomarkers, the use of centralised treatment (e.g. EORTC database) and negotiation with regulatory agencies to obtain flexibility in drug approvals, are all potential ways to improve treatment of rare cancers. Despite the problems, the quality of clinical research in rare cancers has dramatically improved, due to large cooperative efforts, said Professor Paolo Bruzzi, IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy, and is now close to that seen in trials in more frequent tumours.

This ESMO meeting brought together international stakeholders to consider when international trials might be appropriate for studying rare cancers, develop a systematic approach to prioritise such trials, and to work on practical issues that would enable such collaborations to be conducted in a speedy and cost-efficient manner.

Dr Roger Stupp from University Hospital Zurich, Switzerland, talked about a decade of negative trials in CNS. He mentioned the difficulty of measuring responses in assessing efficacy. He also cautioned about accelerated approval, citing the example of the approval of bevacizumab in glioblastoma, which did not improve survival and resulted in excess toxicity and treatment costs.

In closing the session, Dr Jan Bogaerts from the EORTC, Brussels, Belgium, summarised the methodological challenges of trials for rare cancers as being: few patients, low level of data/initial knowledge and a lack of clarity in the standard of care. The answers lie in more collaboration and randomised trials and, outside formal trials, the use of registries and the optimisation of referral practice.

**Information on rare cancers networking in Europe can be obtained from a number of sources, including the Rare Cancers Europe initiative developed by ESMO with partner organisations (http://www.rarecancerseurope.org/) and RARECARENet (http://www.rarecarenet.eu/rarecarenet/).**

## Targeted therapy fails to improve outcome in multiple myeloma

**Haematological malignancies**

Breaking results show that the selective proteasome inhibitor carfilzomib failed to significantly improve overall survival (OS) in heavily pretreated patients with relapsed and refractory multiple myeloma (RRMM).

The findings were presented by Professor Heinz Ludwig from the Wilhelminenspital, Vienna, Austria, in a late-breaking abstract during yesterday's Proffered Paper Session on Haematological Malignancies.

The randomised phase III FOCUS trial in 315 patients compared single-agent carfilzomib with a combination treatment of low-dose corticosteroids and optional cyclophosphamide; patients were treated for 6 days on a 28-day cycle. Median OS in the treatment arm was 10.2 months versus 10.0 months in the active control arm (hazard ratio 0.97; 95% confidence intervals 0.76–1.24; p=0.4172). There was also no benefit of carfilzomib on progression-free survival (3.7 months versus 3.3 months). Grade ≥3 treatment-emergent adverse events (AEs) with carfilzomib and corticosteroids, respectively, included anemia (25.5% versus 30.7%), thrombocytopenia (24.2% versus 22.2%), neutropenia (7.6% versus 12.4%) and acute renal failure (7.6% versus 3.3%). 14.6% and 20.3% of patients, respectively, discontinued treatment due to an AE.

Several similar, on-going trials are currently exploring the potential of carfilzomib – in combination as well as a single agent – for second-line RRMM treatment. ■

**ESMO NOW HAS OVER 10,000 MEMBERS, THANK YOU!**

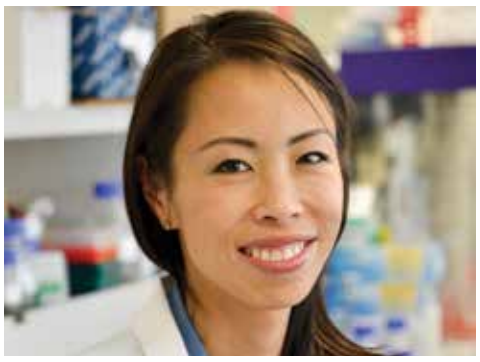
## Certificate of attendance

**Using your badge ID code you can print your certificate of attendance from Monday 29 September. Print from home up to one month after the congress from the ESMO website.**

Thank you for making ESMO 2014 a great success!



# Pathway of the day: PI3K/AKT/mTOR



**Sherene Loi**

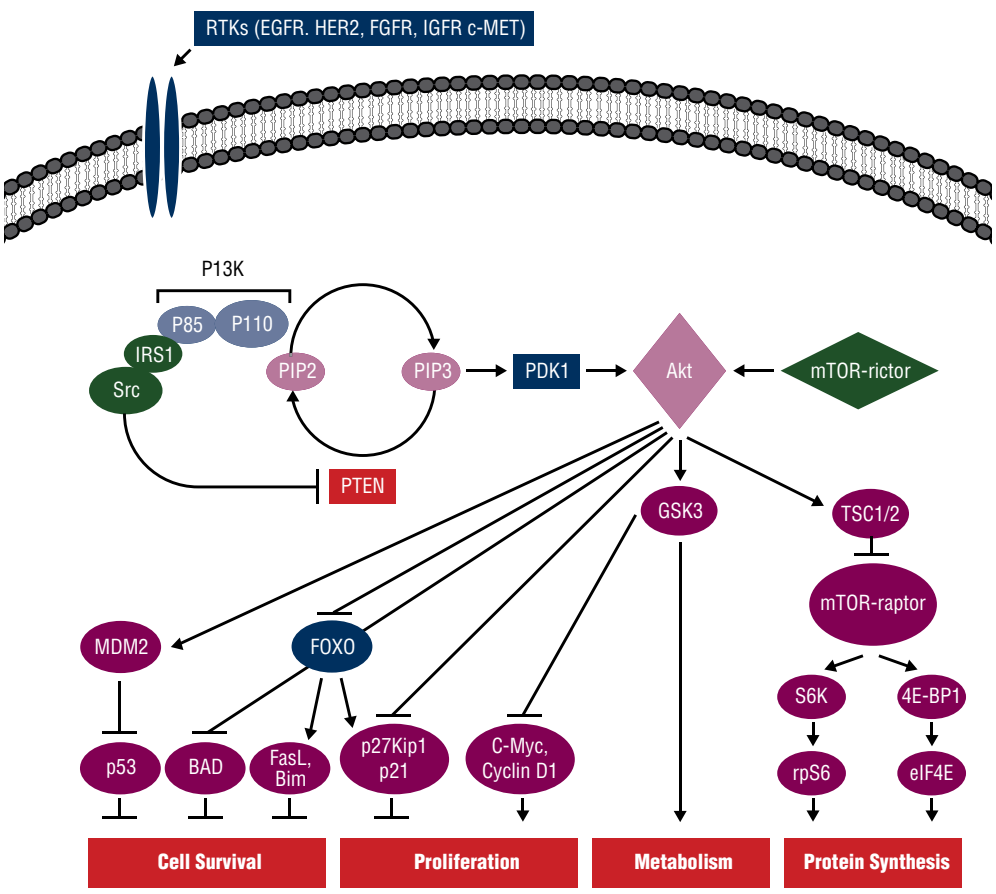
Peter MacCallum Cancer Centre,
East Melbourne,
VIC, Australia

The phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway (Figure) regulates essential cellular processes such as apoptosis, DNA repair, angiogenesis and metabolism. Despite its activity being tightly regulated in normal cells, deregulation of the PI3K/AKT/mTOR pathway is linked to the development of one-third of human cancers, including some breast, ovarian, prostate and non-small-cell lung cancers. In addition, deregulation of this pathway mediates resistance to conventional therapies including biological and hormonal therapies, tyrosine kinase inhibitors, radiation and cytotoxic agents.

The mechanisms driving the PI3K/AKT/mTOR pathway in cancer include amplification of PI3K genes, loss of the regulatory activity of phosphatase and tensin homologue (PTEN) and activating mutations or amplification of receptor tyrosine kinases, such as epidermal growth factor receptor family (EGFR) and HER2.

The important role of the PI3K/AKT/mTOR pathway in cancer development has made it a target for drug development efforts in recent years. Temsirolimus and everolimus are mTOR inhibitors that are in clinical use for various cancers, such as renal cell carcinoma and mantle cell lymphoma. Idelalisib, the first-in-class oral PI3K inhibitor, recently received regulatory approval for the treatment of leukaemias, including chronic lymphocytic leukaemia. Other inhibitors of AKT, PI3K and PI3K/mTOR are in clinical development. For example BYL-719, a selective PI3K inhibitor, has shown activity in patients with PI3K-mutated advanced solid tumours, including oestrogen receptor-positive metastatic breast cancer. Several dual PI3K/mTOR inhibitors (e.g. BGT-226, PF-04691502, GDC-0980 and GSK-2126458), either alone or in combination with other agents, have also demonstrated activity in early clinical studies of patients with advanced solid tumours. ■

1. Zardavas D, et al. Breast Cancer Res 2014;16:201
2. Saini KS, et al. Cancer Treat Rev 2013;39:935–46
3. Markman B, et al. Ann Oncol 2010;21:683–91
4. Markman B, et al. Curr Pharm Des 2013;19:895–906




Adapted from Breast Cancer Research 2014, 16:201

## Rethinking clinical trial design: a roadmap for the future?

**Public health**

Currently the gold standard endpoint used in clinical trials is overall survival (OS). However, in the current situation of targeted drugs and financial restrictions, a move away from the traditional trial design is required. The use of alternative endpoints to OS as a regulatory endpoint was discussed in a Controversy Session yesterday.

Dr Marc Buyse from the International Drug Development Institute (IDDI), Louvain-la-Neuve, Belgium, contended that OS should no longer be the primary endpoint for drug approval. OS is associated with longer follow-up times and more patients are required to show a treatment effect. In addition, OS is affected by competing risks for death, a problem likely to increase with the improved effectiveness of cancer drugs resulting in longer patient survival. The confounding effects on OS of post-progression treatment also has to be considered, he said.

In opposition, Professor Jonas Bergh from the Karolinska Institutet and University Hospital, Stockholm, Sweden, expressed concerns about the use of progression-free survival (PFS) as a surrogate for OS. He presented real clinical examples demonstrating the frequent discrepancies between PFS and OS and explained that in some cases PFS improvements may be associated with a worsening of patient quality of life.

Considering these issues, we should also take into account that comparative effectiveness research is designed to inform healthcare decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options. The evidence generated from research studies to compare drugs or ways to deliver healthcare is sourced in two ways: researchers look at all of the available evidence about the benefit and harm of each choice for different groups of people from existing clinical trials, studies and other research; and clinical scientists conduct studies that generate new evidence of effectiveness or comparative effectiveness of a test, treatment, procedure, or healthcare service. It is true that some treatments may not work for everyone, and that some treatments may work better for some people than others. This research can help identify to the treatments that may work best for an individual patient.

The time taken for new drug approvals was addressed earlier in the Congress in a presentation by Dr Nardin Samuel from University of Toronto, ON, Canada, in Sunday's Proffered Papers Session on Public Health and Health Economics. Comparing times to approval for 41 oncology treatments, the study found that the average time to approval for these drugs by the FDA was 6 months shorter than for the EMA and 7.6 months faster than Health Canada. ■

1. Berry DA. Nat Rev Clin Oncol 2011;9;199–207

#ESMO14

## Tumour molecular profiling: Are liquid biopsies reliable?

**General interest**

The ability of liquid biopsy to provide a non-invasive tool for the molecular profiling of tumours, while minimising risks to the patient and reducing the time required for sampling, makes this a desirable tool for physicians and patients alike. Two presentations at yesterday's Poster Discussion Session on Trials and Tribulations in Oncology: Future Approaches, discussed the reliability and applications of this technology.

Dr Jean-Yves Pierga from Institut Curie, Paris, France, reported data from the phase II SHIVA trial, demonstrating that circulating tumour DNA expressed the same mutations as the tissue samples from metastases and was also able to detect mutations *de novo*. Mutations in all 16 solid tumour samples from patients with a variety of refractory tumours, including breast, lung and ovarian, were confirmed to be present in blood samples. The *de-novo* mutation was identified in a patient whose tumour biopsy was uninformative. Dr Pierga noted that analysis of samples at different time points could help to monitor disease progression and/or response to treatment.

In another presentation, Dr Jean-Sebastien Frenel from Institut de Cancerlogie de l'Ouest, St Herblain, France, reported results demonstrating the ability of serial next generation sequencing of cell-free tumour DNA (cfDNA) to monitor response and progression during targeted therapy. Among 135 plasma samples from 24 patients with a variety of gene mutations and tumour types, dynamic modifications in mutation allele frequency (AF) related to treatment were observed. Reductions in AF of cfDNA mutations, versus increases, during treatment were associated with a significantly longer time to progression (111 days for decrease versus 53 days for increase in AF; p=0.0169). ■

## Early breast cancer: Trastuzumab remains standard of care

**Breast cancer**

The latest analysis of the large phase III trial ALTTO in 8381 patients was presented at yesterday's Proffered Paper Session on Breast Cancer, Early Stage.

The results, presented by Dr Edith Perez from the Mayo Clinic, Jacksonville, FL, USA, followed the presentation of initial results at ASCO 2014, showing no statistically significant improvement in disease-free survival with the addition of lapatinib to trastuzumab for HER-2-positive early breast cancer.

Part of this latest analysis was conducted on the lapatinib alone arm of the study (n=2100), which was closed in 2011 due to futility (hazard ratio [HR] 1.34, not meeting the non-inferiority boundary of 1.11). Patients in the lapatinib arm who were disease-free at that time were offered additional trastuzumab as adjuvant treatment: 52% received at least one dose. Post-hoc analysis revealed a DFS benefit with trastuzumab in these patients (HR 0.67; 95% confidence intervals 0.49–0.91).

The inferiority of lapatinib as a single agent or in combination was reinforced by its poorer toxicity profile: adverse events and a failure to complete treatment were more common with lapatinib. It also failed to reduce first site metastases to the central nervous system, which occurred in around 2% of cases, regardless of treatment. ■

# Is precision medicine coming of age?

**General interest**

Rapid advances in high-throughput genomic technology are driving the evolution of precision medicine and genomic sequencing will eventually become a routine part of clinical practice. Precision medicine has the potential to improve health outcomes, reduce toxicity and increase cost efficiency. Importantly, it puts the patient at the centre and allows physicians to optimise disease management.

### *Precision medicine puts the patient at the centre of treatment*

Oncology will be one of the areas in which the impact of precision medicine will be greatest: it will transform cancer care in the coming decades. The power of precision medicine in oncology was first signalled by HER2[1], with its initial identification as a prognostic biomarker in breast cancer and the subsequent development of a HER2-targeted monoclonal antibody for treatment. This was followed by the emergence of a series of small molecule tyrosine kinase inhibitors, including imatinib, which transformed the survival prospects of patients with chronic myeloid leukaemia[1] and gefitinib and erlotinib, which improved survival for patients with non-small-cell lung cancer (NSCLC) and specific activating mutations of the epidermal growth factor receptor (EGFR). Today, genomic sequencing is identifying genes central to cancer biology; this is already being applied both in clinical trials and clinical practice, as illustrated by the identification of the EML4-ALK fusion gene in NSCLC and targeting with crizotinib, which is now available in many countries for the treatment of ALK-positive NSCLC.

While precision medicine has the potential to redefine every aspect of patient care, it does have limitations. Not all molecular alterations are predictive of response to a specific targeted treatment nor are they all druggable. Echoing this note of caution, Professor Charles Swanton from London Research Institute, UK, in a Special Session on Monday, Precision Medicine: Panacea or False Dawn, mentioned that genomics may not be quite so simple. Drivers of tumour growth may change during tumour evolution and treatment and the identification of sub-clonal driver events will limit the efficacy of single-agent targeted therapy. The need for repeat tumour samples to monitor these effects has opened up the field of liquid biopsies, said Professor Andrew Hughes from Macclesfield, UK. He also spoke of the emergence of new clinical trial designs, such as the so-called basket designs, to manage the investigations of targeted agents in smaller groups of patients.

Concluding the session, Dr Johann De Bono from the Royal Marsden Hospital NHS Foundation Trust, Sutton, UK, and Chair of the ESMO 2014 Scientific Steering Committee, said that, **"The presentations highlight how challenging [delivering precision medicine] is, but there is significant promise."**

Other issues which may delay the wider adoption of precision medicine may include: the cost of molecular sequencing; validation of specific biomarkers; the availability of molecularly targeted drugs; access to clinical trials; and managing patient expectations. Healthcare professionals will need to adapt to increasing challenges in the analysis of molecular data and the complexities involved in both informing patients about several clinical trials and then allocating them to the most promising trial protocol. Ethical issues, such as revealing increased risk and false-positive/false-negative results, are also a concern.

Precision medicine is based on the precept that detailed molecular characterisation of the patient's tumour and its microenvironment will enable tailored therapies to improve outcomes and decrease toxicity. However, there are numerous challenges we need to overcome before delivering on the promise of personalised cancer therapy. These include tumour heterogeneity and molecular evolution, the costs and potential morbidity of biopsies, lack of effective drugs against most genomic aberrations, technical limitations of molecular tests, and reimbursement and regulatory hurdles. Critically, successes and limitations surrounding personalised cancer therapy must be tempered with realistic expectations, which, today, encompass increased survival times for only a proportion of patients. ■

*ESMO has a significant number of educational materials on its OncologyPRO website (oncologypro.esmo.org)*

1. Ciardiello F, et al. Ann Oncol 2014;25:1673–8

# Refining the use of dual HER2 targeting in early breast cancer

**Breast cancer**

Dual HER2 blockade is suggested to be superior compared to single HER2 blockade in terms of pathological complete response (pCR) rates in the neoadjuvant treatment of patients with early breast cancer as well as in the metastatic setting. Three studies presented at yesterday's Proffered Paper Session on Breast Cancer, Early Stage, addressed ways to refine dual targeting with trastuzumab plus a HER2/EGFR2 inhibiting compound in combination with taxane-anthracyline-based chemotherapy in patients in this setting.

Lower than expected pCR rates were reported with a combination of afatinib and trastuzumab followed by epirubicin/cyclophosphamide/trastuzumab in a multicentre, open-label, phase II German study (the DAFNE study). Dr Claus Hanusch from the Rotkreuzklinikum München, Germany, explained that although the combination was fairly well tolerated, the pCR rate was below the targeted 55% (49.2% in the DAFNE study). In light of these results, a phase III trial of dual HER2 targeting using afatinib and trastuzumab as a part of neoadjuvant treatment is no longer supported, he said.

In another study, replacement of neoadjuvant paclitaxel by 3-weekly docetaxel following combined lapatinib/trastuzumab did not improve overall safety and tolerability of the treatment, reported Dr Hervé Bonnefoi from the Institute Bergonié, Bordeaux, France. In the randomised phase II EORTC 10054 study, patients received treatment with lapatinib or trastuzumab alone or in combination. The lapatinib alone arm of the study was closed early due to futility. The combination of lapatinib and trastuzumab resulted in a high pCR of 60.4%. However, the incidence of severe (grade 3–4) toxicity was also high and nearly half of patients (48%) receiving lapatinib and trastuzumab in combination with docetaxel required dose reduction of any of the agents. Interestingly, the pCR rate with trastuzumab single HER2 targeting was also high (51.9%) and tolerability was good. The EORTC 10054 study does not confirm the hypothesis that docetaxel given at a dose of 100 mg/m$^2$ every 3 weeks, instead of paclitaxel, has a better safety profile when combined with HER2-targeting agents.

### *Replacing neoadjuvant paclitaxel by docetaxel following lapatinib/trastuzumab did not improve treatment tolerability*

The identification of patients who may best respond to anti-HER2 targeting treatment in the neoadjuvant setting of breast cancer was addressed in a presentation by Dr Valentina Guarneri from Modena University Hospital, Italy. Given that PIK3CA mutations are common in breast cancer, the group performed retrospective and pooled analyses to evaluate the association between PIK3CA mutations and pCR rates. Results from a randomised study (the CherLOB study) demonstrated PIK3CA mutations in 20.8% of 106 patients. Mutation status was not associated with pCR rate across treatment arms (33.3% for wild-type [WT] versus 22.7% for mutated [MT]; p=0.34). However, among patients receiving dual treatment, the pCR rate was numerically higher in PIK3CA WT disease than in MT disease (48.5% versus 12.5%; p=0.06).

### *The activity of dual therapy with lapatinib/trastuzumab was higher in tumours without PIK3CA mutations than in those with mutations*

These findings were confirmed in a pooled analysis on data from two other randomised trials[1,2] (n=702 patients), which also showed that mutation status did not influence response to single-agent therapy, although PIK3CA WT breast carcinomas are suggested to be more sensitive to dual HER2-targeting compared with PIK3CA MT tumours. Prospective testing may help to further define the role of PIK3CA mutation status as a potential predictor for the selection of women for neoadjuvant dual HER2-targeting treatment. ■

1. Loibl S, et al. San Antonio Breast Cancer Symposium 2013:Abstract S4-06
2. Baselga J, et al. Eur J Cancer 2013;49(Suppl 2):Abstract 1859


Professor Miklos Pless

# Does neoadjuvant radiotherapy improve NSCLC treatment outcomes?

**Lung cancer and other thoracic malignancies**

"Encouraging," is how Professor Miklos Pless from Kantonsspital, Winterthur, Switzerland, yesterday described the final results of the SAKK 16/00 trial in a Proffered Paper Session on NSCLC, Locally Advanced and Metastatic.

The use of neoadjuvant chemotherapy prior to surgery is a standard treatment option for patients with locally advanced non-small-cell lung cancer (NSCLC). This phase III randomised trial investigated the benefits of adding radiotherapy to neoadjuvant chemotherapy (chemoradiotherapy, CRT) for these patients.

A total of 232 patients with resectable stage IIIA/N2 NSCLC received either neoadjuvant chemotherapy (cisplatin and docetaxel) alone or followed by an accelerated concomitant boost of radiotherapy; both arms received subsequent surgery. The median follow-up was 53 months. SAKK 16/00 is the first completed trial to compare neoadjuvant CRT with chemotherapy in this setting.

Professor Pless reported that the response rate was higher with CRT than with chemotherapy alone (61% compared with 44%, respectively). "Resection rates after surgery were 91% with CRT and 81% with chemotherapy. Pathological complete remission rates were 16% and 12%, respectively," Professor Pless remarked. Despite these improvements, CRT failed to significantly improve the primary endpoint of event-free survival (EFS, p=0.665), nor did it prolong median overall survival (OS, p=0.938), although increases of 1.3 months and 11 months were reported for EFS and OS, respectively. Professor Pless noted that surgery after induction treatment was safe. ■

*Adding radiotherapy to neoadjuvant chemotherapy did not significantly improve event-free or overall survival in patients with resectable NSCLC*

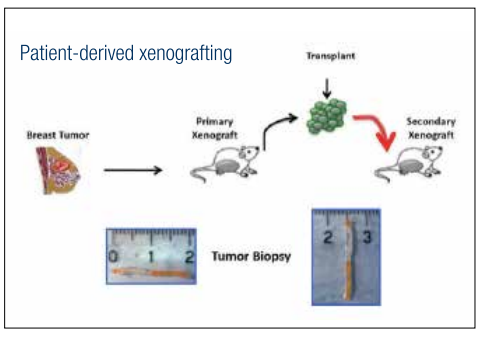
# Patient-derived xenografts: Helping to tailor cancer treatments in 'avatars'

**General interest**

Frequently, anticancer drugs that showed activity in preclinical tests fail to live up to their promise in the clinical setting and stop development in phase I trials. This may be an indication that the preclinical models used are not representative of the clinical situation.

Traditionally, tissue xenografts derived from cell lines have been used as a preclinical test for new chemotherapeutic agents. These cell lines may differ in their growth patterns from the original cells as a result of a change in the host microenvironment. As a consequence, the cells may respond differently to anticancer treatments to the tumour from which they were derived.

Patient-derived xenografts (PDX) involve the grafting of recently acquired tumour tissue from patients into immunodeficient mice. The xenografts can then be successively harvested and implanted into additional mice to create a supply of xenograft models. A particular advantage of PDX is that the original tumour characteristics, including histology, phenotype and genotype, are maintained. Metastatic patterns also appear to be similar to those of the original tumour. Because of this, PDX offers an important model for the study of human tumour biology and the effects of novel anticancer drugs in the preclinical setting.




Perhaps the most critical issue not addressed fully to date is whether the response of PDX models to a particular treatment is the same as the response of the original tumour. This is important both to establish the suitability of PDX as experimental models and to help in the identification of markers predictive of response, which could be of use in the clinical setting. Furthermore, information on resistance of PDX to different agents can be exploited to improve cancer treatments.

The ability of PDX to reflect clinical responses to treatment was reported by Professor Justin Stebbing from Imperial College London, UK, in Monday's Poster Discussion Session on Trials and Tribulations in Oncology: Future Approaches. Positive and negative outcomes to treatment of patients with a variety of solid tumours were accurately replicated by PDX, regardless of the tumour type or treatment. Based on 96 correlations in 65 patients, sensitivity was calculated to be 99%, specificity 70% and predictive values up to 94%. Models generated from first resection were still able to reproduce outcomes to treatments used for recurrent disease.

### *PDX accurately replicated patient outcomes to treatment, regardless of tumour type or treatment*

The latest resurgence of interest in PDX is due in part to the unique contribution this type of xenografting can make to precision medicine. However, the technique is not without its drawbacks, which include and are not limited to: the relatively high cost of the process; the delay in the tumour take rate or time to engraftment (i.e. the time between transplant and tumour growth); the variation in the success of engraftment; and the uncertainty as to whether tumour heterogeneity is conserved in successive generations. Time to, and success of, engraftment is faster (less than 3 months) and higher (50–70%) in triple-negative and HER2-positive breast cancer; for oestrogen receptor-positive disease, time to engraftment can be around 5 months, with an engraftment rate of 20–30%.

The use of PDX should improve the translation of antitumour activity from the preclinical to the clinical setting and should help in the tailoring of treatment to individual patients. The wider availability of models with tumours derived from metastatic sites and treatment-resistant disease should further increase the scope of this technique. ■

# Challenges persist for young adults with cancer

**General interest**

During yesterday's Educational Session, Professor Sophie Fosså from Oslo University Hospital, Radium Hospital, Oslo, Norway gave an overview of cancer in adolescents and young adults.

She said that unfavourable risk factors found in adult cancer patients are observed more often in young patients, while no age-specific clinical or molecular/biological risk factors have been identified. Professor Fosså added that large gaps remain in the understanding of cancer in young adults, particularly in relation to epidemiology, clinical and translational data.

A key point made by Professor Fosså was that no universally-accepted age definition exists for 'young' cancer patients and this was echoed by Dr Valérie Laurence from the Institut Curie, Paris, France, who provided an insight into the management of common cancers in this population. Although progress has been made in the survival of cancer patients in general, she stressed that this could not be said for those in the 15–24 years age range. Dr Laurence said that these younger cancer patients have been largely ignored by clinical trials, which has often led to their omission from adult and paediatric treatment guidelines. She said there was a clear need to address this by encouraging the accrual of young adults into clinical trials and providing expert care for them in a specialised setting.

In an effort to understand the longer-term impact of childhood cancer, Dr Daniel Stark from the University of Leeds, UK, said that evidence pointed to persistent health problems among adult survivors. Problems include second cancers, cardiovascular events, renal impairment and reduced fertility. ■

# Can we predict patient response to prostate cancer therapies?

**Genitourinary tumours**

Initial results from 2 studies have identified a number of candidate biomarkers associated with clinical outcomes in patients with metastatic castration-resistant prostate cancer (mCRPC), delegates heard in late-breaking abstracts during Monday's Proffered Paper Session on Genitourinary Tumours, Prostate.

Prostate cancer is still the second most frequent cause of cancer death in men. Clinicians can already select from a wide range of treatment options, including endocrine treatment, chemotherapy, bone-targeted treatments and immunotherapy. Therefore, the identification of predictive biomarkers to guide clinicians on the most appropriate systemic treatment approaches is needed urgently.

Dr Joaquin Mateo of The Royal Marsden NHS Trust, Surrey, UK, yesterday announced preliminary results for the first 30 patients enrolled in a two-part adaptive phase II trial. Patients with mCRPC were treated with the PARP repair inhibitor, olaparib, and clinical and molecular responses to treatment were monitored to identify possible predictive markers. Ten patients (33%) responded to olaparib and in these patients, researchers found loss of function in genes involved in DNA repair, including BRCA2 and ATM. Olaparib was well tolerated by the study patients.

**"These findings are encouraging on two levels"**

– DR MATEO COMMENTED

**"Not only did olaparib show clinical activity, but we have also identified potential markers that clinicians may be able to use to select patients most likely to respond to this treatment. Our trial has now completed recruitment for the test set and we are ready to open the biomarker-driven validation set soon."**

A second study presented by Dr Eleni Efstathiou from the University of Texas MD Anderson Cancer Center, Houston, TX, USA, evaluated whether androgen signalling biomarkers could predict response to dasatinib or sunitinib when added to abiraterone in patients with mCRPC. Dr Efstathiou's analysis was based on the first 41 patients to complete the study. The previously identified molecular signature – androgen receptor (AR)-N terminal overexpression; the ratio of AR-C terminal expression / AR-N terminal expression ≥ 0.8; and CYP17 expression – was highly predictive for clinical outcome ($p<0.0001$). Research continues and will focus on biomarker-based treatment allocation. ■

# Precision medicine and the changing clinical trials landscape in cancer

**General interest**

Advances in molecular and genomic analysis are stimulating substantial changes in the design of human cancer trials, delegates were told at yesterday's ESMO-ASCO Joint Symposium on The Evolution of the Clinical Trials Landscape, chaired by ESMO 2014 Congress President, Professor Rolf A. Stahel from University Hospital Zurich, Switzerland.

While randomised trials still represent the gold-standard trial design, a variety of limitations, including cost, duration and a focus often on efficacy rather than toxicity, indicate the need for improvements, said Dr Gary Lyman from the Fred Hutchinson Cancer Research Center, Seattle, WA, USA. He spoke of the need to supplement data from randomised trials with that from other approaches, but to understand any shortcomings and their impact on the conclusions drawn.

Predictive biomarkers should be identified alongside any new therapies being developed, Dr Roy Herbst from Yale Cancer Center, New Haven, CT, USA, told delegates. The BATTLE-2 trial in lung cancer is modelled on this approach and its adaptive randomisation design will be a model for future studies. Professor Herbst also described the Lung-Map trial, a collaboration between governments, academia and industry, which will genomically screen lung cancer patients and assign treatment in a Master Protocol based on the biomarkers identified. Dr Denis Lacombe from the EORTC, Brussels, Belgium, supported this need for collaborative molecular screening platforms and presented information on EORTC SPECTA (Screening Patients for Efficient Clinical Trial Access), a pan-European programme that utilises expertise across countries to increase patient access to clinical trials, avoid duplication of effort and cost, and optimise regulatory approval.

PROFESSOR STAHEL ECHOED THESE SENTIMENTS BY ADDING,

**"In Europe, we have to cross the borders to be efficient."**

The Breast International Group (BIG), co-founded and chaired by Professor Martine Piccart from the Jules Bordet Institute, Brussels, Belgium, is another example of an initiative developed to speed up trial enrolment. It brings together international academic research units and runs more than 30 clinical trials. Earlier this year, BIG announced the launch of the AURORA programme, involving large scale molecular analysis of tissue and fluid samples from patients with metastatic disease. The results should provide a better understanding of genetic changes and help to identify mechanisms of response or resistance to treatment. It is hoped that the results may enable the targeting of therapy to individual patients according to the genetic profile of their tumour. ■

# What are the best treatment options for metastatic colorectal cancers?

**Gastrointestinal tumours**

Late-breaking data presented yesterday in a Proffered Paper Session highlighted strong clinical evidence supporting the epidermal growth factor receptor inhibitor cetuximab as a targeted therapy in the first-line treatment of patients with metastatic colorectal cancer (CRC).

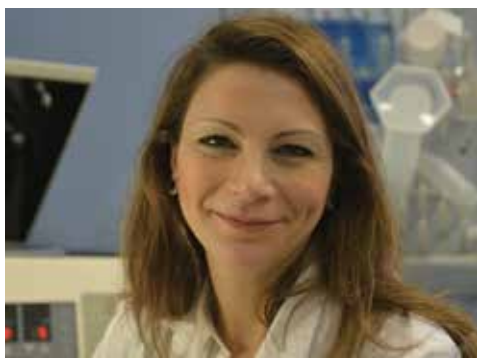
Two analyses of phase III trials in patients with KRAS wild-type CRC looked more closely at the effects of first-line chemotherapy (FOLFIRI or mFOLFOX6) plus either cetuximab or the vascular endothelial growth factor inhibitor bevacizumab on outcome.

Professor Alan Venook from the University of California, San Francisco, CA, USA, announced findings from analyses on a subset of patients in the CALGB/SWOG 80405 trial who went on to receive surgery. After being randomised to one of the two therapeutic regimens (cetuximab or bevacizumab), a total of 180 patients were able to have surgery after treatment; 58% of these had been in the cetuximab arm.

In all, 132 patients showed no evidence of residual disease immediately after their surgery, with a median overall survival (OS) of 64.7 months. Professor Venook said that the study results raised a number of questions specifically relating to the subset of patients rendered disease free. For instance, molecular characterisation of primary and metastatic tumours could help to determine whether certain RAS mutations are prognostic in this highly select group of patients.

Results from an independent radiological review of the FIRE-3 study were presented by Dr Sebastian Stintzing from the University of Munich, Germany. The addition of cetuximab to FOLFIRI resulted in significantly higher overall response rates (72.0% versus 56.1%; p=0.003), rates of early tumour shrinkage (ETS, 68.2% versus 49.1%; p=0.0005) and depth of response (DpR, maximum tumour shrinkage; -48.9% versus -32.3%; p<0.0001) compared with the addition of bevacizumab. ETS was significantly associated with OS independently of treatment arm and DpR was significantly associated with post-progression survival in the cetuximab arm. "These response-related outcomes may go some way towards explaining the significant survival advantage of the cetuximab arm in FIRE-3," concluded Dr Stintzing. ■





**Floriana Morgillo**
**Congress Daily Associate Editor**

Second University of Naples, Italy,

# **ESMO Fellowships:** Expanding educational opportunities for young oncologists.

Advances in the understanding of cancer biology and the search for new ways to tackle the disease require continued research. Time and resources are major limitations for young oncologists who want to further develop their research experience.

ESMO recognises the need to provide support for young oncologists and offers a range of Fellowships to help with education in clinical and translational research, which will in due course lead to professional development.

In 2008, I was delighted to be awarded a Translational Research Fellowship by ESMO for my research into acquired resistance of tumour cells to agents targeting epidermal growth factor receptor (EGFR) in non-small-cell lung cancer (NSCLC). The activity of the EGFR tyrosine kinase inhibitors (TKIs) in NSCLC is limited by the emergence of drug resistance, which develops ultimately in all patients. At the time of the award, I had just finished a PhD in medical oncology and had come to the end of a fellowship programme at the MD Anderson Cancer Center in Houston, TX, USA. The ESMO grant allowed me to come back to Europe to work under the mentorship of Professor Fortunato Ciardiello.

We used human TKI-resistant lung adenocarcinoma cells to investigate resistance to the EGFR TKIs erlotinib and gefinitib, the dual EGFR/vascular endothelial growth factor (VEGF) TKI vandetanib and the multikinase inhibitor sorafenib. Results suggested the involvement of AKT- and MAPK-driven intracellular signals in enabling cancer cell growth in the presence of either the selective or the broad-spectrum TKIs. Gene expression profiling revealed a pattern consistent with the epithelial-mesenchymal transition (EMT) phenotype of TKI-resistant cell lines, which showed increased tumour invasion, metastatic dissemination and acquisition of resistance compared with the parent cell line. This activity was inhibited by selective MEK inhibitors, which were able to revert the EMT phenotype. Subsequent studies demonstrated how combinations of EGFR TKIs and other inhibitors, such as sorafenib or metformin, act synergistically in NSCLC cells, highlighting the importance of combining inhibition of cell surface receptors and downstream signalling.

The findings from our preclinical studies provided some important rationale for the future treatment of NSCLC cancer patients and led directly to clinical studies investigating combined treatment strategies.

Throughout the duration of the Fellowship, I was able to develop my skills as an independent researcher, present my data at international congresses and gain from the experience of meeting and discussing my research with scientists from around the world. The research resulted in publication of a number of papers in high profile medical journals.

This year, I was one of 2 past Fellowship award recipients selected to present our research findings at the ESMO 2014 Congress. The number of young oncologists attending yesterday's YO Special Session is an indication of the high degree of interest in these awards.

Receiving the ESMO Fellowship represented a step forward for me in my career as a researcher in the field of oncology. It also gave me a real understanding of the importance of such Fellowships in enabling the new generation of oncologists to contribute fully to the research effort to develop new and better ways to treat cancer. ■

**The ESMO Fellowship represented a step forward for me in my career as a researcher in oncology**

# ESMO Women for Oncology

**General interest**

Despite the ever-increasing number of women who opt for medicine as a profession and subsequently specialise in oncology, leadership roles continue to be dominated by men.

In a move to try and understand the reasons for this and address the imbalance, ESMO launched the 'Women for Oncology' forum in 2013 under the leadership of past President Professor Martine Piccart, now followed through by Professor Solange Peters, member of the ESMOs Executive Board. **"As the number of females entering into the medical profession increases, we need to work to gain more representatives in important positions. ESMO started the dialogue with women in oncology with the goal of providing strategic solutions to common challenges in our profession."**

New for 2014, ESMO has announced the Women for Oncology Award. The award will recognise individuals who contribute significantly to support the career development of women in oncology and who actively work to make organisations aware that female oncologists are valuable resources.

Dr Pilar Garrido, Spanish Society of Medical Oncology (SEOM) President, involved in the initiative commented, **"Ideally, there would be equal opportunities and career advancement would be based on merit. Female professionals need networking forums such as Women for Oncology to share best practices. We can help each other when we work as a team."** ■

# New targeted treatment, new challenges to health services

The radical transformation of cancer diagnosis and treatment by personalised medicine poses challenges to healthcare services. A Special Symposium yesterday, The Impact on Health Services from Personalised Targeted Therapies, addressed the clinical and economic challenges that healthcare systems will face as they attempt to adapt.

Novel treatments are not the only concern, said Dr Valery Lemmens from the Eindhoven Cancer Registry, The Netherlands, healthcare systems must adjust to cope with the comorbidity of the ageing population too. By 2040, people over 75 years will represent around 14% of the population in an average European country and the number of new cancer patients/year will increase by a staggering 40%. Balancing the cost of new diagnostic procedures and treatments will be key, continued Professor Yolande Lievens from Ghent University Hospital, Belgium. In order to effectively assess the role of a new treatment within a healthcare system, it will be crucial to provide information on its impact on increasingly stretched healthcare budgets. She said, **"Cost effectiveness analysis is not enough and budget impact is equally relevant."**

It's never too late to start, was the message from Professor José Martín-Moreno from the University of Valencia, Spain, who recognised the need for the National Cancer Control Programmes of European countries to start preparing now for the future. He said that strategies in areas such as professional training, biobanks, clinical trials and patient education should start being developed now to ensure the effective introduction of personalised medicine.

Earlier in the Congress, Dr Nereo Segnan from S. Giovanni University Hospital, Torino, Italy, discussed the contribution of specific screening strategies to precision medicine. He warned of the delicate balance between over diagnosis, over treatment and life saved because of cancer screening. Efforts to mitigate this include personalising screening on the basis of risk stratification. However, he advised that this also has its drawbacks, particularly when patients at low risk for a cancer are not screened despite there being an established screening programme in their region.

It should be borne in mind that the almost limitless volume of data generated from biobanks and whole genome sequencing is a significant obstacle to their implementation. This will be the case at least until more information is known on how to accurately interpret the data from a clinical perspective. Alongside this will be the need to formulate protocols encapsulating consent, analysis and result reporting. ■

# Best posters of the day

| Monday, 28 September | |
|---|---|
| Breast cancer, early stage | 322 |
| Gastrointestinal tumours, non-colorectal | 640 |
| Head & neck cancer | 1000 |
| Immunotherapy of cancer | 1063 |
| NSCLC, early stage, SCLC & thoracic malignancies, other | 1186 |
| Sarcoma | 1438 |



# NSCLC: Two promising targeted therapies

**Lung cancer and other thoracic malignancies**

Results from recent phase II studies have added two more treatments to the growing list of promising targeted therapies currently under development for patients with specific molecular subtypes of advanced non-small-cell lung cancer (NSCLC) patients.

Data from late-breaking abstracts presented at yesterday's Proffered Paper Session on Locally Advanced and Metastatic NSCLC showed clinical activity with dabrafenib and neratinib, both of which will be taken forward further development.

Dr David Planchard from Institut Gustave Roussy, Villejuif, France, described how 84 patients with stage IV NSCLC carrying the BRAF V600E mutation (which occurs in approximately 1.5% of all tumours) received treatment with dabrafenib.

Dabrafenib showed significant clinical activity, with durable responses and an acceptable safety profile. Among the 78 patients who had failed at least one previous treatment, the overall response rate was 32% (all partial responses [PRs]), with a median duration of response of almost 1 year (11.8 months). Three of 6 patients receiving treatment first-line had PRs. In summary, Dr Planchard said, **"these findings establish dabrafenib as an effective treatment option for patients with previously treated advanced BRAF V600E non-small cell lung cancer."**

Continuing the session, Dr Benjamin Besse, also from Institut Gustave Roussy, presented positive news about the clinical progress of neratinib, a tyrosine kinase inhibitor which targets tumours carrying HER2 mutations. These somatic mutations are found in approximately 2–4% of patients with NSCLC. Laboratory studies suggest that the combined inhibition of HER2 and the mammalian target of rapamycin (mTOR) signalling pathway has synergistic effects in HER2-driven lung tumours.[1]

A two-stage phase II trial is comparing the efficacy of neratinib as a single agent and in combination with the mTOR inhibitor temsirolimus in patients with stage IIIB/IV NSCLC.

Late-breaking results from the first stage of the trial show that the combination arm met the criteria for continuation of the study into stage 2, with a preliminary objective tumour response rate in the combination arm (3/14 patients). Additional patient recruitment has already begun, Dr Besse announced. Toxicity was manageable, with prophylactic loperamide for diarrhoea. ■

Dr Besse commented, **"HER2 mutated non-small cell lung cancer represents a very small number of patients, but it reflects the new face of NSCLC - it is not a single homogeneous disease, but a lot of different molecularly defined subsets of patients with potential 'drugable targets', for which specific strategies should be addressed."**

1. Perera SA, et al. Proc Natl Acad Sci USA 2009;106:474–9

# Can PORT improve outcomes in resected stage III ypN2 NSCLC?

**Lung cancer and other thoracic malignancies**

Patients with non-small-cell lung cancer (NSCLC) stage IIIA and persistent N2 disease following induction chemotherapy have a markedly worse prognosis than those achieved nodal downstaging.

The use of post-operative radiotherapy (PORT) to improve outcome in these patients was discussed by Dr Charlotte Billiet from University Hospitals Leuven, Belgium, in yesterday's Proffered Papers Session in NSCLC, Locally Advanced and Metastatic. A total of 103 patients with stage III pN2 NSCLC who received induction chemotherapy and surgery were selected from a prospective database. Patients with incomplete tumour resection or persistent ypN2 status (n=53) received 3D PORT (total dose 50–66 Gy). Among all 103 patients, 5-year overall survival (OS) was 31.3% and relapse-free survival was 29.8%. PORT was associated with significantly improved 5-year OS (relative risk 0.441, p=0.017) in multivariate analysis, along with post-chemotherapy downstaging (p=0.030) and completeness of resection (p<0.001). These findings highlight the potential of PORT to improve outcome in stage IIIA-pN2 NSCLC with poor prognostic factors. Results will need to be confirmed in a prospective trials and the community eagerly awaits the first results from the prospective EORTC LungART trial addressing the question of whether PORT is beneficial in stage IIIA-pN2 NSCLC.

Commenting on the trial, Professor Solange Peters from Lausanne University, Switzerland, highlighted several limitations, including the lack of a comparative arm. Patients receiving PORT represented a limited subgroup analysed as part of a distinct patient population characterised by the absence of the two important risk factors. Nevertheless, authors reported a better outcome for this subgroup, suggesting a role for PORT in compensating for the risks factors as well as maybe playing a role in limiting disease progression. Importantly, the authors confirmed that more than a third of stage IIIA N2 NSCLC will have a prolonged OS using a well conducted multimodality treatment. However, the trial did not contribute towards answering the question of the role of PORT in stage III NSCLC.

Only the prospective phase III EORTC/IFCT LungART trial, randomising PORT in surgical stage IIIA NSCLC, will provide us with a definitive answer, said Professor Peters. Of note, the SAKK 16/00 prospective radiation trial negative results might suggest the adoption of more caution in the routine use of PORT in the multimodality management of stage IIIA NSCLC. Guidance for the use of PORT in this setting has been outlined in the latest version of the ESMO Guidelines. ■



# Crizotinib: Improved QoL in ALK-positive NSCLC

**Lung cancer and other thoracic malignancies**

The phase III PROFILE 1014 study confirmed the progression-free survival superiority of crizotinib over platinum-based chemotherapy as first-line treatment for ALK-positive advanced non-small-cell lung cancer (NSCLC) (n=343).[1]

In a presentation at yesterday's Poster Discussion Session on NSCLC, Metastatic, Dr Fiona Blackhall from The Christie NHS Foundation Trust, Manchester, UK, reported that crizotinib also significantly improved global quality of life (QoL) in this study: 36% of patients reported a QoL improvement with crizotinib versus 19.6% of those treated with chemotherapy (p<0.05). A significant improvement was defined as a ≥10-point reduction for a specific item on the QLQ-LC13 symptom scale. More patients on crizotinib also showed significant improvements in physical functioning and symptoms of fatigue, cough and dyspnoea. QoL rates were significantly better for crizotinib versus chemotherapy for alopecia and sore mouth, but worse for crizotinib versus chemotherapy for diarrhoea. ■

1. Mok T, et al. J Clin Oncol 2014;32:5s:Abstract 8002.

#ESMO14

# Is enough progress being made in the treatment of sarcomas?

**Sarcoma**

The relative rarity of sarcomas means that investigation of new treatment options for patients with these forms of cancer is limited. At Monday's Proffered Paper Session on Sarcoma, the results of potential treatment options, including targeted therapeutics, combination therapies and chemotherapy, were discussed.

While surgery is the standard approach for a patient with progressive desmoid tumours, it is not always a viable option. Dr Bernd Kasper from the University of Heidelberg, Mannheim, Germany, presented promising findings from a phase II trial showing that the anti-bcr-abl tyrosine kinase inhibitor imatinib has potential in patients with advanced disease for whom surgery is not suitable. In the trial, 37 patients were treated with imatinib 800 mg daily for 2 years. After 6 months of treatment, 24 patients (65%) were free of tumour progression. One patient had a partial response and 23 had stable disease. One patient finished treatment due to toxicity. Follow-up is continuing.

Dr Axel Le Cesne from Institut Gustave Roussy, Villejuif, France, reported that maintenance treatment with trabectedin beyond 6 cycles significantly prolonged median progression-free survival (PFS) in patients with advanced soft tissue sarcoma. In this phase II trial, 178 patients with at least stable disease after the first 6 cycles of trabectedin were randomised to continuous treatment with trabectedin or treatment interruption: the median PFS after randomisation was 7.2 months versus 4.0 months (p=0.031) for continuous and interrupted therapy, respectively. Twelve-month overall survival (OS) rates were 84.6% and 69.2%, respectively. This approach should be investigated further.

There is little information on the survival of elderly patients being treated with standard first-line chemotherapy for metastatic soft tissue sarcoma. Professor Winette Van der Graaf from Radboud University Medical Centre, Nijmegen, The Netherlands, presented the results of a pooled analysis of data from 11 EORTC trials involving 274 elderly patients (>65 years) treated with standard chemotherapy drugs. On average, elderly patients had worse outcomes than their younger counterparts, with median OS times of 9.7–12.0 months versus 11.1–13.2 months (depending on the type of chemotherapy), respectively, and PFS times of 2.2–5.2 months versus 2.8–6.2 months, respectively. Professor Van der Graaf highlighted the need for new treatments for elderly sarcoma patients.

### *Older GIST patients have worse outcomes to standard chemotherapy than younger patients*

In a late-breaking abstract, Dr Jean-Yves Blay from Université Claude Bernard Lyon I, France, reported that adding pazopanib to best supportive care significantly prolonged PFS in patients with gastrointestinal stromal tumours (GISTs) resistant to the tyrosine kinase inhibitors (TKIs), imatinib and sunitinib, a group with poor prognosis. Among 81 patients randomised, the 4-month PFS rates were 47.7% and 19.5% for best supportive care (BSC) with and without pazopanib, respectively (hazard ratio [HR] 0.56; 95% confidence intervals [CI] 0.34–0.93; p=0.02). This is the first randomised trial of pazopanib in this setting.

### *Adding pazopanib to BSC more than doubled the 4-month PFS rate in TKI-resistant GISTs*

The potential of zoledronate to improve the efficacy of chemotherapy plus surgery in the treatment of patients with osteosarcoma was discussed by Dr Sophie Piperno-Neumann from Institut Curie, Paris, France. The second interim results of a randomised, open-label trial involving 318 patients revealed no benefit of adding zoledronate to standard treatment, either on event-free (HR 1.31; 95% CI 0.79–2.18; p=0.17) or overall (HR 1.42; 95% CI 0.70–2.88; p=0.21) survival. As a consequence of these results, accrual to the trial was stopped. ■

### *Adding zoledronate to surgery and chemotherapy did not improve event-free or overall survival in osteosarcoma patients*

# Congress Daily Editorial Team: Thank you!

ESMO would like to thank the Congress Daily Editorial Team, along with Matthias Preusser and Erika Martinelli who reported on the Young Oncologist sessions and TMC Strategic Communications, for all their hard work in bringing you the news from ESMO 2014 over the past four days. Covering an important Congress with such a dense programme was a challenge and the team spent many hours debating over 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 Congress and in highlighting the many important sessions that took place. Well done!

tmc STRATEGIC COMMUNICATIONS



# Doctor to patient boundaries – where to draw the line

**Young oncologist sessions**

Do you struggle to remain detached from patients? If so, you are not alone. A recent survey has revealed that many young oncologists (YOs) struggle to draw the line between professional empathy and emotional attachment.

Of the 338 YOs surveyed, 95.5% reported that they try not to display emotion towards patients. However, almost 60% of respondents noted that they find it difficult to provide truthful prognoses to patients that they have developed a 'relationship' with, explained Professor Lesley Fallowfield from the Brighton and Sussex Medical School, Brighton, UK, as she presented the results at yesterday's YO Breakfast Session.

**"It is important to display empathy but if this is not done in a professional manner it can be mistaken for friendship,"** said Professor Fallowfield. She explained that misconstrued friendship can increase an oncologist's workload and potentially affect their ability to maintain a work-life balance.

Social media can also intrude into an oncologist's personal life. Professor Fallowfield said that many YOs are unsure how to handle Facebook 'friend' requests and Twitter 'follows' from patients. The survey also revealed that over half of oncologists provide patients with their personal contact details and are on first name terms.

**"I was surprised to see how many oncologists allow patients to use their first names,"** said YO Dr Erika Martinelli from Second University of Naples, Italy.

Professor Fallowfield provided helpful guidance on how to maintain boundaries and highlighted the need for further YO training and educational materials. ■

# Excel with ESMO Young Oncologists

A record-breaking 3,622 young oncologists (YOs) are now ESMO members. Here in Madrid the YO Track Sessions have proved more popular than ever.

Early each morning enthusiastic YOs gathered at the Breakfast Sessions to hear speakers offer practical advice on how to survive the rigours of oncology.

Although it may be a demanding career, senior mentors are on hand to help YOs to excel. At the Vesalius talk, senior peers shared advice on career development while speakers at the YO Forum gave hints and tips on how to find the perfect mentor, along with writing tricks relevant to early career researchers.

Young researchers picked up even more advice at the YO Masterclass, where they learned all about the best ways to integrate basic science into clinical research.

Two YOs who have received recognition for their outstanding research are Dr Floriana Morgillo from the Second University of Naples, Italy, and Dr Hatem Azim from the Institut Jules Bordet, Brussels, Belgium. Both researchers have been completing projects funded by the ESMO Fellowship Programme, which supports YOs through educational opportunities.

Dr Manish Singhal from the International Oncology Cancer Centre, Noida, India, also received recognition for achieving the highest mark in the 2013 ESMO Examination.

All of the Track sessions were designed to meet the specific needs of YOs today. Members of ESMO's Young Oncologists Committee – who are all YOs themselves – planned the session agendas and interacted with other YOs throughout the Congress.

The networking event gave all YOs the opportunity to expand their network, share experiences and make new friends from all across Europe.

Stay connected with access to online resources: log into YO Corner to read reviews of the latest research and test your diagnostic skills. ■

# Different approaches to treating solid tumours

**Genitourinary tumours**

Late-breaking abstracts revealed new data on targeted therapies in sessions on non-prostate genitourinary tumours yesterday.

Hot on the heels of the FDA's approval of the immunomodulator pembrolizumab for malignant melanoma, new results suggest this monoclonal antibody may also be effective against urothelial cancer. In a morning session focusing on immunotherapy in these tumours, Dr Elizabeth Plimack of the Fox Chase Cancer Center, Philadelphia, PA, USA, described the results from the KEYNOTE-012 study in which single-agent pembrolizumab was given to 29 patients with tumours expressing PD-L1. The overall response rate (ORR) was 24% (7/29), with 6 of the patients still responding up to 40+ weeks since receiving the initial dose. Three patients have had a complete response. Tolerability to treatment was acceptable.

**The results justify further development of pembrolizumab for patients with urothelial cancers,** Dr Plimack said.

Disappointing results in the afternoon's Poster Discussion Session reported that adding the src inhibitor, saracatinib, to the vascular endothelial growth factor inhibitor cediranib, did not improve outcome for patients with metastatic clear cell renal cell carcinoma (mRCC). According to Dr Thomas Powles from St Bartholomew's Hospital NHS Foundation Trust, London, UK, in this randomised phase II trial in 138 patients, cediranib showed only modest activity, with an ORR of 13% and median progression-free survival of 5.4 months. Addition of saracatinib did not significantly improve these results. ■