

Congress

daily

PRECISION MEDICINE IN CANCER CARE

MONDAY
SEPTEMBER 29 2014

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

ESMO

MADRID
2014

INSIDE...

Proffered Paper Session

SARCOMA

15.45 – 17.30 Sevilla



SESSION

PRESIDENTIAL
SYMPOSIUM 2

16.00 – 17.20 Madrid

PICKS
OF THE
DAY

Young Oncologists: How to achieve work-life balance

More than 70% of young oncologists (YOs) in Europe suffer symptoms of burnout, according to a recent ESMO survey. Burnt out clinicians suffer emotional exhaustion and lose compassion and meaning in their clinical work.



Dr Susana Banerjee

The ESMO Young Oncologists Committee surveyed 595 YOs in the largest survey of its kind. Results were presented yesterday by lead author Dr Susana Banerjee from The Royal Marsden NHS Trust, London, UK.

Dr Banerjee explained that burnout rates vary significantly across Europe ($p < 0.0001$). In central Europe, as many as 84.2% of respondents suffer, compared with 52.3% in the North.

But despite these variations, burnout truly is a Europe-wide problem. Dr Banerjee said that oncologists deliver bad news and witness suffering and death on a daily basis. She added, **“YOs are now facing increasing expectations and workloads with reducing resources.”**

Hospitals with small workforces ($p = 0.004$) and high patient numbers ($p = 0.007$) put oncologists at significant risk of burnout. A median of 50 patients per week were treated by survey respondents and such heavy workloads can spill over into personal and family time.

A lack of work-life balance also puts oncologists at significantly higher risk of burnout ($p < 0.001$). Oncologists who lack balance are 3.5 times more likely to suffer burnout than those who maintain a balanced lifestyle.

Fatigued oncologists offer uncompassionate patient care but ESMO also worries that they may

leave clinical practice entirely. Dr Banerjee pointed to a similar study run by ASCO this year and explained, **“What was worrying, was that 35% of US oncologists indicated that they would like to leave their current position within 2 years.”**¹

However, YOs in Europe can be reassured that the ESMO YO Committee takes burnout seriously. The important survey results have been brought to the attention of thousands of delegates here in Madrid and hit newspaper headlines across Europe.

Raising awareness is key to reducing stigma. If burnout is no longer stigmatised, struggling YOs may feel able to approach senior colleagues for support. Today, 73.4% of trainees and 82.6% of post-trainees never ask for support, while a shocking 74% report no access to support services.

Dr Laurence Albiges from Institut Gustave Roussy, Villejuif, France, dissected the survey results after they were presented yesterday afternoon. She too mentioned the ASCO survey and said that YOs should take comfort in the fact that – despite the threat of burnout – 82% of US oncologists are satisfied with their career choice and speciality.¹

“This specialty remains one of the most fascinating and rewarding,” said Chair of the ESMO Young YO Committee, Dr Raffaele Califano from The Christie NHS Foundation Trust and University of South Manchester Hospital, UK. Dr Raffaele urges YOs not to be discouraged.

Oncology does not have to be a stressful career. The YO Committee is taking action to support YOs and at yesterday's Breakfast Session delegates learned how to achieve that ever elusive work-life balance.

“Delegation and prioritisation are key to survive. I know my limits and how many patients I am able to take care of,” said Dr Pia Österlund from Helsinki University Central Hospital, Finland, who has recovered from an episode of burnout. She added, **“There are basic things in life that you need to take care of (for yourself) in order to take care of someone else.”**

Audience members were keen to agree. **“To provide the best support for your patients you need to devote time for yourself, family and friends,”** said YO Dr Giannis Mountzios from the University of Athens School of Medicine, Greece.

YOs at the Session learned that taking time to relax is not lazy but leads to success – for both themselves and their patients. ■

1. Shanafelt TD, et al. J Clin Oncol 2014;32:678–86



ESMO POCKET GUIDELINES
**UPPER
GASTROINTESTINAL
CANCERS**

CORRECTION: Please note that on pages 25 and 28 of this document under the Personalised Medicine sections the correct statement should read “Ramucirumab as single agent or in combination with paclitaxel has demonstrated an OS benefit and is approved in the US for advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma after disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy”.

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29.09.2014

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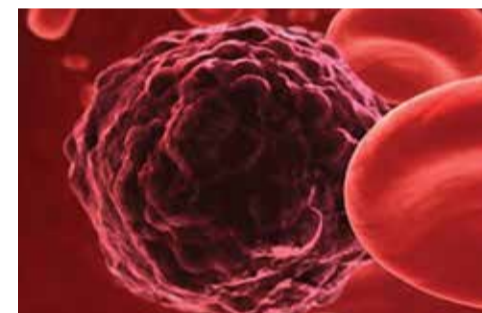
Daily Editorial



Giuseppe Curigliano
Congress Daily
Guest Associate Editor

European Institute of Oncology,
Milan, Italy

Liquid biopsies: Tumour diagnosis and treatment monitoring in a blood test. Liquid biopsies are non-invasive blood tests that detect circulating tumour cells (CTCs) and fragments of tumour DNA that are shed into the blood from the primary tumour and from metastatic sites.



This technology has enormous diagnostic and treatment implications for oncology and I believe it is poised to transform clinical practice. As an integral part of precision medicine, the importance of liquid biopsies was highlighted in a Special Session on Saturday, at which experts from around the world discussed its potential and limitations.

So, what's all the fuss about? Tumour genome sequencing to inform treatment decisions is already central to the management of many patients with cancer and I have witnessed this change the hallmark of cancer care. Tailored therapy relies on the identification of the correct molecular tumour target. Currently, tumour biopsy tissue, generally from the primary tumour, is used to determine molecular targets at a single time point, before treatment commences. These biopsies carry some risks for patients, they are painful, they are costly and, importantly, the process takes time. Also, given the complexities of tumour heterogeneity, both within a tumour and between a primary tumour and metastases, a tissue sample may not be a true representation of the molecular profile. A liquid biopsy, on the other hand, may capture the entire heterogeneity of the disease. What is more, tumour genotypes are notoriously unstable and prone to changes under selection pressure. In this regard, liquid biopsies offer what tissue biopsies cannot, due to risks to the patients and cost; the opportunity to take serial samples in order to monitor tumour genomic changes in real time. This will allow clinicians to ensure that the therapy they have selected, based

on a particular molecular target, remains relevant and observe the emergence of any resistance. Instead of waiting for information from scans, we may be able to identify at an earlier stage if a treatment is not working and to spare the patient the unnecessary toxicity of a drug that no longer provides any benefit. At the same time, we may be able to observe if any new molecular targets appear that could be suitable for treatment. All this could help to provide patients with the right treatment for the right target without delay.

Liquid biopsies also present us with a unique opportunity to move forward with our understanding of metastatic disease development and they may help to identify signalling pathways involved in cell invasiveness and metastatic competence. Ultimately, at some point in the not too distant future, these tests will be used in the diagnosis of cancer. This will revolutionise cancer care, providing clinicians with rapid access to information on a molecular level at diagnosis, thereby optimising treatment choices.

In terms of samples, CTCs have been the most studied. While these cells are relatively rare and require sensitive collection and enrichment technology, they provide information at both the genetic and cellular level. However, cell-free tumour DNA (cfDNA) is emerging as an effective alternative to CTCs, with the benefits of easier collection and analysis. Today, a Poster Discussion Session on Trials and Tribulations in Oncology: Future Approaches (13.00 – 14.00, Pamplona) will feature two abstracts on cfDNA liquid biopsies: one on the use of serial next generation sequencing of cfDNA to monitor response and progression during administration of drugs in the phase I setting (Abstract LBA6) and another on the *de*

novo detection of cfDNA in patients with refractory cancer (Abstract 1571PD). These studies should help us to build on our understanding of the type of information cfDNA-based liquid biopsies can give us. A report of the two abstracts will be featured in Tuesday's Congress Daily. We do know that standardisation will be a key factor in ensuring consistency between centres and in determining its clinical success. It is crucial that we standardise the assays used to evaluate cfDNA and also define the optimum sampling specimen (i.e. serum or plasma). In fact standardisation across the board would be ideal: blood collection, processing, storage, and DNA extraction, quantification, analysis and reporting of data. Future development of liquid biopsies will need to provide a cost-effective analysis, mainly identifying the genes known to be recurrently mutated in each tumour. Therefore, developing standardised methodologies for cfDNA analysis and validation in large prospective clinical studies is mandatory for the implementation of the liquid biopsy approach in the clinical management of cancer patients.

In the field of oncology, we see so many innovations come and go, without lasting impact. Will the promise of liquid biopsies be a clinical reality? It is hard for me to not to be excited about the benefits they can offer to patients and I believe that they will be invaluable to cancer research and treatment.

I would like to thank the Congress Daily Editorial Team of Evandro de Azambuja (Editor-in-Chief), Markus Joerger and Floriana Morgillo (Associate Editors) for giving me the opportunity to write this editorial. ■

Advances in the field of upper gastrointestinal cancers

Gastrointestinal tumours

Metastatic or locally advanced upper gastrointestinal (GI) cancers (tumours of the oesophagus, stomach, biliary tract, liver and pancreas) are characterised by a particularly poor prognosis and a high risk for mortality. This is due in part to their late diagnosis, making surgical resection technically unfeasible in many patients. Recently, efforts to improve outcomes of patients with upper GI cancers have focused on targeted therapies that disrupt pathways controlling cell growth, proliferation and/or metastases. Presentations at yesterday's Proffered Paper Session on Gastrointestinal Tumours, Non-colorectal, discussed the use of targeted therapies in this setting.

Dr Yoon-Koo Kang from the University of Ulsan College of Medicine, Seoul, Korea, described the findings from a phase II study (STARGATE) of first-line capecitabine/cisplatin with or without sorafenib in 195 patients with metastatic adenocarcinomas of the stomach or gastroesophageal junction. Sorafenib is a multikinase inhibitor with activity against angiogenesis and the RAF-MEK-ERK pathway. The addition of sorafenib was well tolerated but did not improve the efficacy of the capecitabine/cisplatin combination. Overall response rates were comparable between capecitabine/cisplatin with and without sorafenib (54% versus 52%, respectively; $p=0.826$), as were progression-free survival (PFS, 5.6 months versus 5.3 months; hazard ratio [HR] 0.92; 95% confidence interval [CI] 0.67–1.27; $p=0.609$) and overall survival (OS) (median 11.7 months versus 10.8 months; HR 0.93; 95% CI 0.65–1.31; $p=0.661$). Dr Kang said that biomarker analysis may help to identify specific patients who could potentially benefit from the combination of capecitabine/cisplatin with sorafenib.

Dr Marianne Sinn from Charité-Universitätsmedizin Berlin, Germany, presented a late-breaking abstract (LBA) of results from the phase IIb, placebo-controlled study (CONKO-006), showing that adding sorafenib to 12 months of adjuvant gemcitabine did not improve survival in patients with R1-resected pancreatic cancer. Results for sorafenib plus gemcitabine ($n=57$) versus gemcitabine alone ($n=65$) were 9.6 months versus 10.7 months ($p=0.89$) for disease-free survival and 17.6 months versus 15.6 months ($p=0.90$) for OS. To date, this is the largest

randomised study designed exclusively for R1 resected disease.

CONKO-006: Adding sorafenib to adjuvant gemcitabine therapy in patients with R1-resected pancreatic cancer did not improve disease-free survival

Addition of the multikinase inhibitor, axitinib, to best supportive care (BSC) did not improve survival in patients with advanced hepatocellular carcinoma previously treated with antiangiogenic therapy, reported Dr Yoon-Koo Kang in an LBA. In this double-blind, randomised study of 202 patients, the median OS was 12.7 months with axitinib and 9.7 months with placebo (HR 0.168; $p=0.211$) and corresponding objective response rates (ORRs) were 9.7% and 2.9%. However, axitinib did significantly improve investigator-assessed PFS (3.6 months versus 1.9 months with placebo; $p=0.004$).

Further potential treatment options for patients with advanced hepatocellular carcinoma include monoclonal antibodies. Dr Andrew Zhu from Massachusetts General Hospital Cancer Center, Boston, MD, USA, presented data from the phase III REACH study of ramucirumab – an antivascular endothelial growth factor receptor two (VEGFR2) antibody – in patients previously treated with first-line sorafenib therapy. Ramucirumab failed to achieve a significant OS benefit (primary endpoint) in the whole population of 565 patients (9.2 months versus 7.6 months with placebo; HR 0.866; $p=0.1391$). However, among 250 patients with a prespecified elevated baseline alpha-fetoprotein (AFP) level (≥ 400 ng/mL), ramucirumab significantly improved OS (HR 0.67; $p=0.0059$), indicating the potential merit of investigating the relationship between AFP and ramucirumab.

In another LBA, Dr Kei Muro from Aichi Cancer Center Hospital, Nagoya, Japan, reported positive preliminary data for the novel anti-PD-1 antibody, pembrolizumab (10 mg/kg every 2 weeks), in a phase Ib study in 39 patients with PD-L1-positive advanced gastric cancer. Most patients had received ≥ 2 prior therapies. The ORR was a promising 30% in relapsed or metastatic gastric cancer and significant associations between PD-L1 expression and PFS ($p=0.032$) and ORR ($p=0.071$) were reported. ■

Findings from studies in patients with upper GI cancers point to the urgent need for biomarkers to identify which subpopulations will benefit from targeted therapy.

Anamorelin combats cancer cachexia

Supportive & palliative care

Cachexia, characterised by a substantial loss of skeletal muscle and fat, is common in cancer patients, particularly those with advanced disease, and is thought to be responsible for around 20% of deaths in cancer patients. To date, successful treatments have been elusive.

Anamorelin, a selective ghrelin receptor agonist with appetite-enhancing and anabolic activity, provided significant body mass and quality of life benefits in patients with cancer anorexia-cachexia, reported Dr Jennifer Temel from Massachusetts General Hospital, Boston, MA, USA, at Saturday's Proffered Paper Session on Supportive and Palliative Care. According to data from the randomised phase III ROMANA 1 and ROMANA 2 studies in nearly 1000 patients with non-small-cell lung cancer (NSCLC), anamorelin significantly increased lean body mass (>1.5 kg difference between the median change from baseline for anamorelin and placebo) and body weight ($p<0.0001$, each) compared with placebo over 12 weeks. Significant improvements in patient symptoms and concerns about anorexia-cachexia were also reported. There was, however, no improvement in the co-primary endpoint of handgrip strength in either study. Side effects related to anamorelin included hyperglycaemia and diabetes, but toxicity was usually mild. Anamorelin is the first compound showing significant and clinically relevant benefits in patients with cancer cachexia. ■

Anamorelin significantly improved lean body mass and weight compared with placebo in patients with anorexia-cachexia

SUPPORTING THE YOUNG BREAST CANCER PATIENT

Treating young patients with breast cancer brings with it a host of issues, including questions of genetic testing and fertility. Do not miss discussion of these and other topics in today's Patient Cases Session.

Session Info:
Patient Cases. Challenges
In Managing Breast Cancer
In Young Patients

DAY/DATE:
MONDAY 29 SEPTEMBER
16.00 – 17.00 ROOM: SALAMANCA

Helpful

Congress Information

Abstracts

Gain quick and easy access to ESMO 2014 abstracts from our scientific journal *Annals of Oncology*. Abstracts will also be on a USB key; the voucher is included in the delegate bag.



ePosters

A USB key voucher for the ePosters will be included in the delegate bag. Eight terminals with large plasma screens for poster viewing and communicating with presenters are available in Hall 8, ePoster area.

Madrid 3 for 2 Membership offer!

Stop by and see us at the Membership Services Desks in the registration area, at the Membership Services Centre or in the ESMO Members' Lounge to benefit from this special congress offer. Exhibition Hall - Booth S2

ESMO booth

For all educational products and services. Located in the Exhibition Hall - Booth S2



ESMO Membership Services Centre

The ESMO Team is available to answer all your membership needs. Located in the Exhibition Hall - Booth S2



For 2014 The ESMO Members' Lounge

Our exclusive 'members only' area, located in Hall 10, has been designed to provide ESMO members with an exclusive area to network with other members of the ESMO community, access your email, relax in between sessions and simply recharge your batteries.

Pathway of the day: CDK



Fabrice André

Institut Gustave Roussy,
Villejuif, France

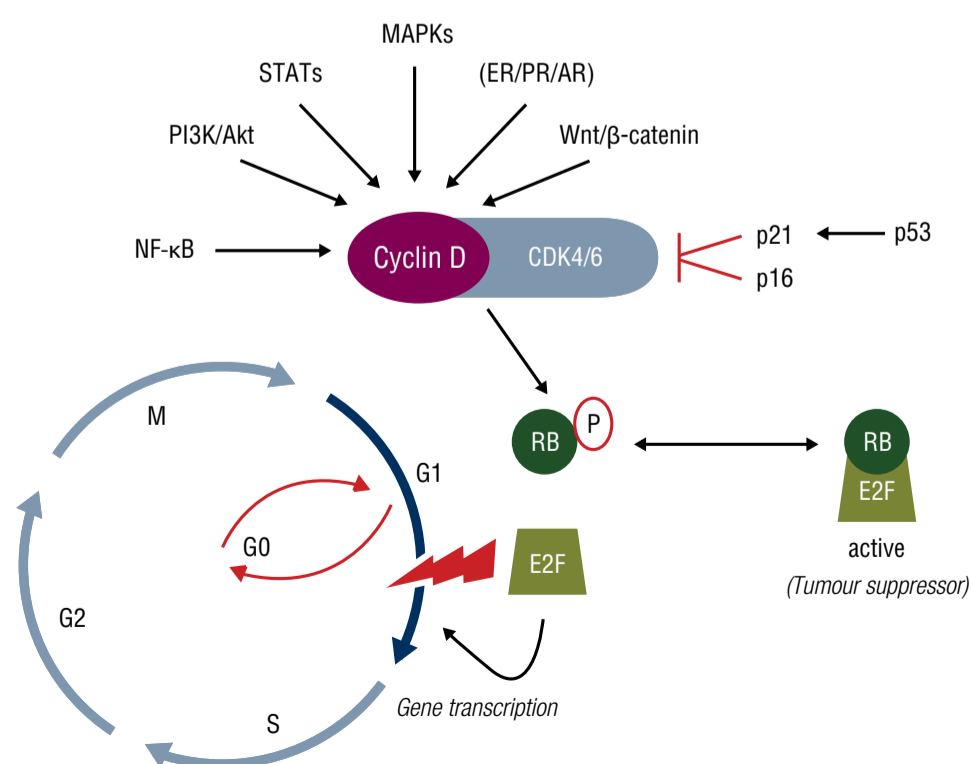
The cyclin-dependent kinase (CDK) pathway (see Figure) is a series of complexes formed between cyclins and their associated kinases. This pathway, along with its inhibitors (e.g. p16 family proteins) and regulators (e.g. pocket proteins, checkpoint kinases and regulatory phosphatases), controls the orderly progression through each stage of the cell cycle via phosphorylation of specific substrates. CDK inhibitors and regulators are important for controlling this process and are therefore responsible for regulating cell proliferation. Several CDKs (e.g. CDK 4) have been identified in mammalian cells and are associated with specific cyclin partners.

Altered expression of some of the cyclins in the CDK pathway results in cancer development. Mantle cell lymphoma is characterised by high expression of cyclin D1, a G1-phase cyclin, which promotes cell cycle progression. Increased expression is secondary to the translocation of the BCL1 locus on chromosome 11 onto chromosome 14 (t[11;14](q13;q32)) and is exacerbated by mutations in cyclin D1 regulatory elements.¹ When cyclin D1 is inhibited, cyclin D2 may come into play. Uveal melanoma is also a consequence of cyclin D1 overexpression. Furthermore, amplification of the cyclin D1 gene is observed in around 15–20% of breast cancers. A link has also been found between the presence of abnormally expressed

CDK pathway-associated cyclins (e.g. cyclin D) and regulator proteins (e.g. p16, p21 and p57), and aggressive pathological features and poor clinical outcomes in clear cell renal cell carcinoma.

A range of CDK inhibitors have entered clinical testing in cancer, including the broad range alvociclib and the highly specific CDK 4/6 inhibitor, palbociclib. Integral to the efficacy of CDK inhibitors will be the selection of the right inhibitor for the right target for any particular cancer and also the determination of whether optimal effects will be obtained with monotherapy or with a combination partner. Palbociclib is the selective CDK inhibitor at the most advanced stage of clinical investigation in cancer. It is currently in development as combination therapy with letrozole or exemestane for metastatic hormone receptor-positive breast cancer.^{2,3} Phase II trial results show that the palbociclib/letrozole combination improved progression-free and overall survival versus letrozole alone.² Activity of palbociclib in relapsed mantle cell lymphoma has also been reported.⁴ Other CDK 4/6 inhibitors, LY2835219 and LEE011, are being investigated in early phase trials in breast cancer and malignant rhabdoid tumours, neuroblastoma and cyclin D CDK4/6 pathway-activated tumours, respectively.^{5,6} ■

1. Weniger MA, et al. *Semin Hematol* 2012;48:214–26
2. Finn RS, et al. *AACR Annual Meeting*; San Diego, California, USA: 5–9 April 2014. Abstract CT101
3. Martin M, et al. *ESMO 2014:Abstract 409TIP*
4. Leonard JP, et al. *Blood* 2012;119:4597–607
5. Georger B, et al. *ESMO 2014:Abstract 455P*
6. Patnaik A, et al. *J Clin Oncol* 2014;32(Suppl 5s): Abstract 534



Regulation of cell cycle checkpoint control. Adapted from *Endocr Relat Cancer* 2011;18(4):C19–24

Young Oncologists networking in Madrid



On Saturday evening, over 150 Young Oncologists (YO) from all over Europe filled the stylish Ramses Restaurant in Madrid for some serious networking!

The enthusiastic crowd was addressed by ESMO Young Oncologist Committee (YOC) members Professor Fortunato Ciardiello from Seconda Università di Napoli, Naples, Italy, and Dr Raffaele Califano from The Christie NHS Foundation Trust and University of South Manchester Hospital, UK. Speaking on behalf of the Spanish Society of Medical Oncology (SEOM) was Dr Andrés Cervantes from the University of Valencia, Spain, who is Co-ordinator of SEOM's Young Oncologist and +MIR Groups.

Together, the speakers highlighted the importance of making connections and taking advantage of opportunities such as fellowships and abstract-related travel grants.

Dr Matthias Preusser from the Medical University of Vienna, Austria an ESMO YOC member who attended the evening, said mixing

and mingling is important for young oncologists. "It is a big thrust of what we do. Your early years of medical or laboratory practice can be intense, but networking helps you to look beyond your daily workload. It puts you in touch with like-minded people and experts who can help you to achieve your long-term ambitions and career goals. Hearing other people's stories and advice has certainly inspired me; contacts I've made at events like this have motivated me and introduced me to further important contacts to pursue my passions and interests."

Of course, networking is about so much more than getting ahead – it is about making friends too. Saturday saw YOs relax in the informal atmosphere as the room filled with lively chatter. Friendships forged during this congress may create an advice and support network for years – possibly decades – to come.

Anna Berghoff, a Young Oncologist from the Medical University of Vienna, Austria, commented, "It was a fantastic opportunity to both refresh friendships made at the 2012 Moonlight Networking event in Vienna and make new friends here in Madrid." ■

Screening reduces mortality risk for breast cancer

Breast cancer

A recent matched case-control study in the UK provides strong evidence to justify community breast cancer screening programmes, according to results of a major study presented by Dr Nathalie Massat from the Queen Mary University of London, UK, at yesterday's Proffered Paper Session on Public Health and Health Economics.

In this study, performed within the framework of the English National Breast Screening Programme, patients who had died due to invasive primary breast cancer during 2008 and 2009 were matched with a 'control': a patient diagnosed up to 6 months before the diagnosis of the test case, but still living at the time the test case died. Researchers compared the attendance at screening of each case and control and the treatment they received within 6 months of diagnosis.

Women who attended at least one routine screening session had an almost 60% reduction in the odds of breast cancer mortality, compared with those who never attended (odds ratio 0.41; 95% confidence intervals 0.30–0.55; $p < 0.001$). Odds ratios remained below 1 after adjustments for tumour pathology and treatments administered.

Breast cancer screening remains a significant protective factor against breast cancer mortality, irrespective of treatment

According to Dr Massat, the results are clear: screening remains a significant protective factor against mortality for women diagnosed with breast cancer. The results also suggest that the risk of mortality rises as the time since a patient's last routine screening increases. Differences in treatment after diagnosis had minimal impact on patient survival. ■

NSCLC: The struggle to improve outcomes

Lung cancer

One of the goals of every oncologist is to improve outcomes for their patients, primarily to extend survival with new treatments while maintaining quality of life. But for scientists working on non-small-cell lung cancer (NSCLC), progress has been particularly slow. At yesterday's Presidential Symposium, researchers reported results from two phase III studies; one in early stage and one in locally advanced/metastatic disease.

Dr Johan Vansteenkiste from University Hospital Leuven, Belgium, reported that adjuvant treatment with the cancer immunotherapeutic agent MAGE-A3 CI failed to improve disease-free survival (DFS) compared with placebo in patients with resected MAGE-A3-positive NSCLC, independent of whether patients received adjuvant chemotherapy. In the MAGRIT trial, 2272 patients were randomised to receive either MAGE-A3 CI or placebo (2:1 randomised selection) as 13 intramuscular injections over a period of 27 months; 52% of the patients also received adjuvant chemotherapy. The median DFS for all patients was 60.5 months for MAGE-A3 versus 57.9 months for placebo (hazard ratio [HR] 1.02; 95% confidence intervals [CI] 0.89–1.17; $p=0.7379$). There was also no DFS benefit for MAGE-A3 in the sub-group of patients not receiving adjuvant chemotherapy.

MAGE-A3 failed to improve clinical outcome in resected MAGE-A3-positive NSCLC

Following these disappointing results, the symposium heard from Dr Tony Mok from the Chinese University of Hong Kong, China, on the results of the IMPRESS study, investigating the continued use of gefitinib in patients with locally advanced/metastatic NSCLC with activating EGFR mutations, progressing on first-line gefitinib. The optimal second-line treatment approach for such patients has not previously been defined. Among 265 patients receiving cisplatin/pemetrexed, addition of gefitinib did not significantly improve the primary endpoint of progression-free survival compared with chemotherapy alone (median of 5.4 months for both, HR 0.86; 95% CI 0.65–1.13; $p=0.273$). Overall survival data are immature. This trial confirms that the standard of care for these patients should, at least for the time being, remain doublet chemotherapy alone.

“This study was designed to resolve a greatly debated issue – whether tyrosine kinase inhibitors should be continued beyond progression”

– COMMENTED DR MOK

“As the result demonstrated no difference in progression - free survival, the standard treatment is chemotherapy alone.” ■

RELAX!

In our exclusive ‘members only’ area, located in Hall 10

Breakthroughs in precision medicine recognised with Hamilton Fairley Award



Prof Rolf A. Stahel, Prof Heikki Joensuu and Dr Josep Tabernero

The targeted therapeutic imatinib is the poster story of precision medicine. For Professor Heikki Joensuu from University of Helsinki, Finland, it is also the success story of his career.

In 2000, Professor Joensuu and his colleagues identified imatinib as an effective treatment for advanced gastrointestinal stromal tumours (GISTs). Subsequent studies showed imatinib's potential as an adjuvant therapy for GISTs, with recurrence-free and possibly overall survival benefits. Research of such international significance does not go unnoticed.

On Friday, during the opening session of the ESMO 2014 Congress, Professor Joensuu was awarded ESMO's Hamilton Fairley Award. Established in memory of one of the founding fathers of European oncology, this distinguished award celebrates research of outstanding quality.

“I thoroughly welcome and embrace the nomination of Heikki Joensuu as recipient

of the 2014 Hamilton Fairley Award,” said Dr Josep Tabernero from Vall d'Hebron University Hospital, Barcelona, Spain, and Chair of the ESMO Fellowship and Award Committee.

“For more than 25 years, Heikki's tireless commitment to the field has significantly contributed to improved cancer diagnostics and cancer care”

– DR JOSEP TABERNEO

Spanning 3 decades, the breadth of Professor Joensuu's work expands far beyond GISTs. He has chaired important breast cancer trials such as FinHer and is a current member of the ESMO Faculty for Sarcoma.

“When I started my career as an oncologist there was no effective treatment for some of these cancers,” said Professor Joensuu. **“[Today] these seemingly miraculous results may be achieved by just taking a few tablets each day. This is an immense joy to the patients and their families.”**

Dr Tabernero described Professor Joensuu's work as **“truly ground-breaking cancer science”** that has benefited countless patients. According to Dr Tabernero, **“Heikki Joensuu is undoubtedly one of the world's leading trailblazers in drug discovery and precision oncology.”** ■

New data on first- and second-line ALK inhibition in NSCLC patients

Lung cancer

ALK gene rearrangements occur in 4–6% of patients with non-small-cell lung cancers (NSCLC) and these tumours show dramatic and sustained responses to treatment with ALK inhibitors, with crizotinib being the first-in-class ALK inhibitor. Unfortunately, resistance to crizotinib invariably develops. Presentations at yesterday's Proffered Papers Session on NSCLC, Metastatic 2, discussed the use of crizotinib in the first-line setting and second-generation ALK inhibitors in patients with crizotinib-resistant disease.

The efficacy of first-line crizotinib in improving progression-free survival compared with standard pemetrexed-platinum chemotherapy in patients with advanced ALK-positive NSCLC was established in the 343-patient phase III PROFILE 1014 study.¹ Dr Benjamin Solomon from the Peter MacCallum Cancer Centre, Melbourne,

VIC, Australia, reported additional data from this study showing that crizotinib numerically improved the time to intracranial progression compared with chemotherapy (hazard ratio [HR] 0.60) and in 79 patients with brain metastases at baseline (HR 0.45) ($p=NS$, each). In addition, the time to deterioration of symptoms was around four times longer in the crizotinib arm than in the chemotherapy arm (median 2.1 months versus 0.5 months; $p=0.0004$). These findings support the use of crizotinib as first-line therapy.

Don't miss the quality of life results from the PROFILE 1014 study in a presentation by Dr Fiona Blackhall at today's Poster Discussion Session on NSCLC, Metastatic **13.00 – 14.00, Granada: Abstract 1226PD**

The second-generation ALK inhibitor alectinib is a promising new treatment option for patients resistant to crizotinib, according to Dr Takashi Seto from the National Kyushu Cancer Center, Fukuoka, Japan. In a small pharmacological study in 24 patients with target lesions, alectinib led to a confirmed response rate of 58.3%. At a median follow-up of 141 days, 13/19 (68.4%) patients with brain metastases at baseline remained on study without disease progression. Gastrointestinal and visual side effects were reported with alectinib but were usually mild and manageable and no patient discontinued treatment due to safety concerns. ■

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

#ESM014



YO Breakfast

HELPING YOUNG ONCOLOGISTS TO MANAGE THE DOCTOR / CANCER PATIENT RELATIONSHIP

In this morning's YO Breakfast, young oncologists will be able to get expert advice on how to build a safe and supportive relationship with patients. Professor Lesley Fallowfield from the University of Sussex, Brighton, UK, will discuss ways that you can best communicate with your patients and where the risks and boundaries lie.

Session Info:
Young Oncologist Breakfast. Risks and boundaries: The doctor / cancer patient relationship

DAY/DATE:
MONDAY 29 SEPTEMBER
08.00 – 08.45 ROOM: PALMA

Immunotherapy – revolution for renal cell carcinoma?

Immunotherapy of cancer

Treatment of advanced renal cell carcinoma (RCC) is particularly challenging for clinicians, even after the introduction of vascular endothelial growth factor- and mTOR-targeting drugs, as resistance evolves rapidly.

However, immunotherapeutic strategies are potentially redefining treatment pathways, effectively boosting the patient's own 'natural' capacity to destroy cancerous cells.

Some of the fundamental principles of immune response against cancer were described yesterday by Dr Suzy Scholl from Institut Curie, Paris, France, in an Educational Session.

Major players involved in immune therapy include tumour-associated macrophages, memory tumour macrophages and immune checkpoint pathways, with the latter leading to the development of anti-PD-1 monoclonal antibodies. Looking at the mutational status of the tumour can offer potential targets for immunotherapy.

In metastatic RCC (mRCC), monoclonal antibodies are being developed to inhibit the T cell protein PD-1 that binds the immunosuppressive ligand PD-L1. The binding of PD-L1 to PD-1 blocks T cell differentiation, thereby mediating immunological tolerance and allowing tumours to grow unchecked.

Early studies with anti-PD-1 and anti-PD-L1 antibodies have shown significant promise in cancer treatment in different tumour types.¹ However, while the antibodies may increase survival, randomised controlled trial data on drug combinations are sparse.

A recent phase I trial explored the combination of nivolumab, an anti-PD-1 monoclonal antibody, and ipilimumab, a monoclonal antibody targeting the T cell receptor cytoxic T-lymphocyte antigen 4 (CTLA-4). The trial tested the safety of the new drug combination in 44 patients with mRCC, explained Dr Hans Hammers from Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA, in Saturday's Proffered Paper Session on Immunotherapy of Cancer. Patients, approximately 80% of whom had received prior systemic therapy, were randomised to receive 3 mg/kg of nivolumab and 1 mg/kg of ipilimumab or 1 mg/kg of nivolumab and 3 mg/kg of ipilimumab every 3 weeks for 4 doses.

Overall, patients receiving a lower dose of nivolumab and a higher dose of ipilimumab had a better response to treatment. Objective response rates were 43% and 48%, respectively, with disease stabilisation in 24% and 35% of patients, respectively.

Treatment-related adverse events were experienced by the majority of patients. The most common grade 3–4 adverse events were gastrointestinal disorders and hepatic events.

“It is encouraging to see evidence of durable antitumour activity and acceptable safety from the combination therapy”

– COMMENTED DR HAMMERS WHO LED THE TRIAL

“A multicentre phase III trial in first-line mRCC is planned.”

Other research seeks to optimise combination therapies and the sequence in which they are administered. These studies are looking at patient selection by the identification of valid biomarkers, such as tumour cell PD-L1 expression, as a predictive marker of response to treatment combinations. ■

1. McDermott D, et al. *Cancer Med* 2013;2:662–73

Personalised medicine: New targets for metastatic breast cancer immunotherapy

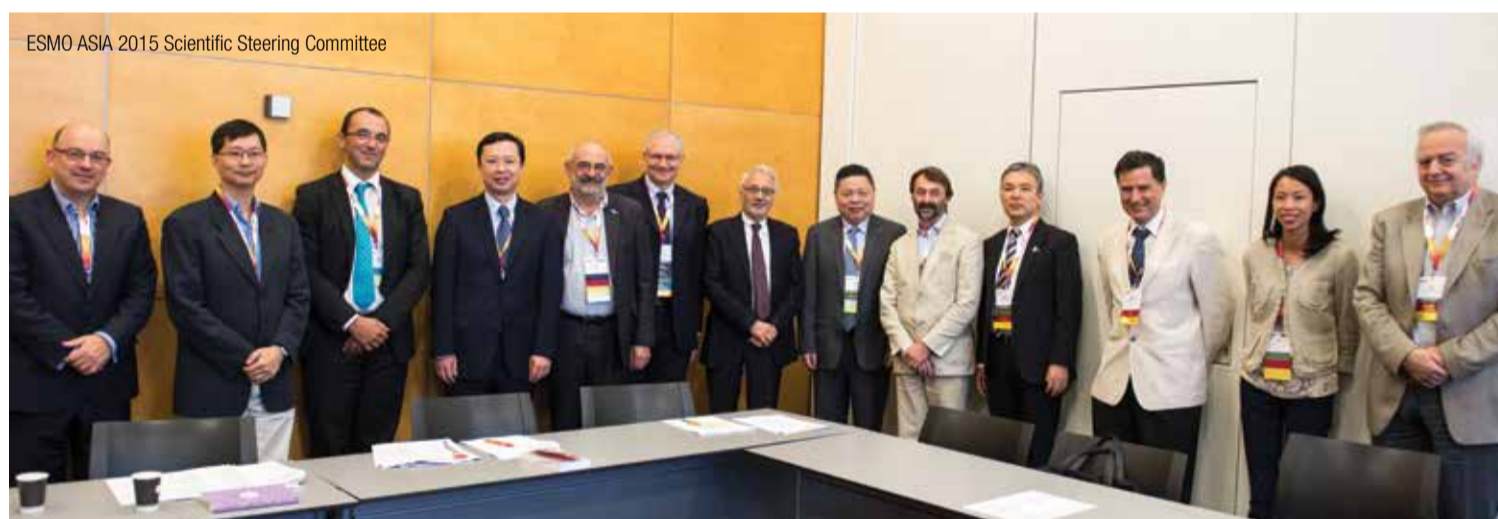
Breast cancer

Breast cancer is often cited with reverence whenever people talk about personalised medicine. While the concept remains more of a dream than a reality for most cancers, the use of endocrine treatment in oestrogen receptor-positive and trastuzumab in HER2-positive breast cancer has become standard.

A team in France is now investigating the genomic and immune landscape of metastatic breast cancer. At yesterday's Proffered Paper Session on Breast Cancer, Metastatic, Dr Fabrice André from Institut Gustave Roussy, Villejuif, France, described how his team analysed samples of metastatic lesion biopsies from two previous trials, SAFIRO1 and MOSCATO. Whole exome sequencing of 93 samples and immunostaining of 280 samples revealed that metastatic breast cancer differs dramatically from primary tumours. Metastases showed enrichment of mutations in genes involved in resistance or migration mechanisms compared with primary tumours. The numbers of metastases demonstrating tumour-infiltrating lymphocytes (TILs) and PD-1- or PD-L1-positivity was low ($\leq 5\%$), although the rates were higher among HER2-positive tumours (16% for TILs and 8.3% for PD-L1).

What are the clinical implications of 'immunome' data from SAFIRO1? This study supports the concept of developing and potentially incorporating an 'immunoscore' into the traditional classification of breast cancer, thus providing an essential prognostic and potentially predictive tool in the pathology report. These data may be incorporated into clinical trials for subtypes of breast cancer in the metastatic setting with drugs that target immune-cell-intrinsic checkpoints. Blockade of one of these checkpoints, CTLA-4 or the PD-1 receptor, may provide proof of concept for the activity of an immune modulation approach in the treatment of a breast cancer patient.

“Our results suggest various gene and immunotherapy targets for treatment; we are exploring whether these are suitable as general targets for metastatic breast cancers or as specific targets for more personalised treatment of certain sub-types,” said Dr André. ■



ESMO takes the congress to Asia

ESMO has partnerships with many international societies and attracts members from all corners of the globe. With almost 20% of our current members from the Asia Pacific region, it is now time to take our congress to Asia. “This region has an impressive research output, but ESMO members here find it challenging to travel to events in Europe,” explains Dr Patrick Tan from Duke-NUS Graduate Medical School, Singapore, and ESMO's Local Congress Officer for Asia Pacific. “Many local members have asked us to hold a congress in Asia – and now their requests are answered.”

ESMO now proudly announces its first ever ESMO Asia Congress. The 4-day event will be held in December 2015 in Singapore, an accessible location for all Asia-based delegates.

“ESMO Asia 2015 will report the latest advances in research and clinical care – not only from Asia but the global oncology community,” says ESMO and Congress President Prof Rolf A. Stahel. “Expert speakers will discuss issues of international importance and delegates will have the opportunity to interact with speakers and network with peers in the Asian oncology community.”

An international scientific committee will prepare a programme packed with the latest research findings and updated guidelines on the latest standards of care across all major tumour types.

“This will be ESMO's first, large-scale event to be held in Asia, which builds upon the success of smaller and more focused educational programmes we have organised in the past,” says Dr Tan.

Over 3000 regional oncologists have participated in activities organised by ESMO in Asia Pacific, including summits, preceptorship meetings and courses, and institutional programmes.

ESMO's expansion of events and oncology networks across the globe is a key part of its vision to improve the standard of care for all cancer patients through research and education. ■

SAVE THE DATE

ESMO ASIA 2015
18 - 21 December 2015
Singapore

Find out more details online
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Have your photo taken at the 40th anniversary photo area
ESMO Main Booth S1

Mixed news from immunotherapy trials in NSCLC

Lung cancer

The search for immunotherapeutics to improve outcome for patients with non-small-cell lung cancer (NSCLC) continues, and results from 2 trials with novel agents were reported in late-breaking abstracts on Sunday.

Dr Walburga Engel-Riedel from the Hospital of Cologne, Germany, presented results from a randomised phase II trial of the immune modulator imprime PGG (PGG) during the Poster Discussion Session on Immunotherapy of Cancer yesterday afternoon. In an earlier trial, PGG significantly increased objective response rates (ORR) in stage IV NSCLC patients receiving carboplatin-paclitaxel chemotherapy and the epidermal growth factor receptor-targeting antibody cetuximab.¹

In this latest trial, cetuximab was replaced with the vascular endothelial growth factor-targeting antibody bevacizumab, but the combination failed to significantly improve clinical outcome. Dr Engel-Riedel remarked on non-significant but still remarkable numerical increases in ORR (60.4% versus 43.5%) and overall survival (16.1 months versus 11.6 months) in patients receiving PGG.

More promising results were presented earlier in the day during the Proffered Paper Session on NSCLC, Metastatic 2. Dr Edward Garon from the David Geffen School of Medicine at UCLA, Santa Monica, CA, USA, discussed his research on the targeted monoclonal antibody pembrolizumab, which prevents PD-1 ligand (PD-L1) binding to T cells, allowing them to differentiate and destroy cancer cells.

Data from 282 patients in the randomised and non-randomised cohorts of the phase I KEYNOTE-001 study were analysed. Patients with treatment-naïve or previously treated advanced NSCLC received pembrolizumab 2 mg/kg (every 3 weeks) or 10 mg/kg (every 2 or 3 weeks). Dr Garon reported an ORR for all patients of 21% (assessed by RECIST v1.1) or 23% (assessed by immune-related response criteria [irRC]). The ORR was highest in patients with strong PD-L1 expression ($\geq 50\%$ staining): 39% (RECIST) and 47% (irRC), compared with 16% and 9% in patients with weak or negative PD-L1 expression. Grade ≥ 3 treatment-related adverse events occurred in 24 patients (9%), with pneumonitis being the most common ($n=5$). ■

“PD-L1 may be an important biomarker for the clinical activity of pembrolizumab; patients with high expression appear to derive particular benefit from this immunotherapeutic. This observation will be validated in additional patients.”

– SAID DR GARON

Advanced breast cancer: New data from the clinical trial and real-world settings

Breast cancer is the most common cancer in women worldwide. But, despite major advances in cancer care, locally advanced and metastatic breast cancer remain a challenge for oncologists. Results from 3 studies presented yesterday shed light on some recently investigated treatment approaches.

During the Presidential Symposium, Dr Sandra Swain from the Washington Hospital Center, Washington DC, USA, reported the final overall survival (OS) analysis of the CLEOPATRA study showing an unprecedented OS increase for HER2-positive metastatic breast cancer patients receiving a combination treatment first line. A total of 808 patients received trastuzumab and docetaxel, with either placebo or pertuzumab. After a median follow-up of 50 months, the combination with pertuzumab increased median OS to 56.5 months – a statistically significant increase of 15.7 months compared with the placebo arm ($p=0.0002$).

Addition of pertuzumab to trastuzumab and docetaxel resulted in a 15.7-month survival benefit in HER2-positive metastatic breast cancer patients

Dr Swain highlighted how findings from the study, published last year, were quickly integrated into clinical guidelines, so that the dual anti-

“This is the kind of survival improvement for which we have worked, and this data will be incredibly meaningful to patients and their families”

– DR SANDRA SWAIN

HER2 blockade (trastuzumab plus pertuzumab) in combination with docetaxel chemotherapy is now the standard of care for first-line HER2-positive metastatic breast cancer patients.

Earlier yesterday afternoon, during the Proffered Paper Session on Breast Cancer, Metastatic, Dr José Baselga from Memorial Sloan-Kettering Cancer Center, New York, NY, USA, reported the results in a late-breaking abstract (LBA) of a phase III trial investigating the addition of sorafenib to capecitabine for 537 patients with locally advanced or metastatic HER2-negative breast cancer. Adding sorafenib did not improve median progression-free survival (PFS) compared with placebo (5.5 months versus 5.4 months, respectively). Moreover, there was a trend towards a worse OS with sorafenib (18.9 months versus 20.3 months for placebo) that Dr Baselga said was not explained by treatment-related toxicity.

In another LBA, the PFS analysis of the non-interventional German trial, BRAWO, captured plenty of attention at a Poster Discussion Session yesterday when presented by Dr Peter Fasching from the University Hospital Erlangen and German Breast Group, Germany. Among 500 patients with oestrogen receptor-positive breast cancer treated in routine clinical practice with everolimus and exemestane, the median PFS was 8 months. Among patients with advanced disease receiving these drugs as first-line therapy, the median PFS was 10.1 months. These real-world PFS results and the toxicity profile, Dr Fasching explained, are in line with the results of the phase III BOLERO-2 trial in this setting. ■

The BRAWO trial: real-world results of exemestane in breast cancer patients match those of a pivotal phase III study

Double chemotherapy for pancreatic cancer

Gastrointestinal tumours

Disappointing results on the use of a virus to treat pancreatic cancer have revealed a new, combination taxane treatment for pancreatic cancer. The surprising finding was announced by Dr Tanios Bekaii-Saab from Ohio State University, Columbus, OH, US, who presented the results of a phase II trial at yesterday's Poster Discussion Session on Gastrointestinal Tumours, Non-colorectal.

The trial was designed to assess the oncolytic activity of the naturally occurring virus, reovirus, which was suggested to work in synergy with taxanes to lyse cells with an abnormally activated RAS signalling pathway, as frequently found in metastatic adenocarcinoma of the pancreas (MAP). Seventy-three MAP patients received paclitaxel and carboplatin; half of the patients also received reovirus treatment for 5 days.

While the combination proved to be safe and both treatment arms performed better than historical controls, there was no statistically significant difference in objective response rates or in levels of stable disease between the treatment arms. Median progression-free survival was 4.6 months for patients receiving reovirus plus chemotherapy versus 5.1 months for those receiving chemotherapy only ($HR=1.07$; $p=0.81$). Despite the lack of evidence for any reovirus activity, Dr Bekaii-Saab stressed how the paclitaxel-carboplatin combination was more efficacious than expected. It may have comparable activity to the nab-paclitaxel/gemcitabine doublet in first-line MAP treatment. “This is the first report of paclitaxel-carboplatin in MAP, which proved to have higher activity than anticipated, suggesting that similar to other disease settings, such as lung and breast cancer, this combination is an acceptable choice in patients with MAP,” remarked Dr Bekaii-Saab. ■

SOCIETY VILLAGE

Do not miss the opportunity to discover oncology societies from around the world.

Among exhibitors in the Society Village you can meet representatives from 17 affiliated national and international societies based in Europe and beyond. Find out how they support research and improve clinical practice among their members.

ESMO is privileged to collaborate on joint initiatives with many of these organisations, including several Joint Symposia at this Congress.



Meet with international oncology societies in the Society Village, located near the main entrance to the Exhibition

Important aspects in neuro-oncology

CNS tumours

An Educational Session yesterday discussed issues in the care of patients with primary and metastatic brain tumours.

Professor Roger Stupp from Zurich University Hospital, Switzerland, explained that brain metastases are a manifestation of a primary tumour, rather than a diagnosis. Histology, molecular characteristics and primary tumour origin dictate treatment choice, although he cautioned against overestimating the benefit of therapy. He also outlined the difficulty in providing an accurate prognosis, but that this should be taken into account when considering treatment goals, prioritising quality of life (QoL).

Dr Alba Brandes from Bellaria-Maggiore Hospital Azienda USL of Bologna, Italy, discussed recurrent

glioblastoma. She stressed that each treatment should aim to improve QoL and disease burden. Also, clinical trials may not demonstrate results that are acceptable to drug authorities, despite clear treatment benefits in certain sub-populations. A particular example described was bevacizumab, which is available for recurrent glioblastoma in the USA, but not in all European regions.

Molecular markers are becoming increasingly useful for decision-making in patients with gliomas, according to Professor Michael Weller from Zurich University Hospital, Switzerland. Chromosome 1p/19q codeletion status is prognostic and predictive in anaplastic glioma, MGMT methylation status is increasingly used as a predictive marker for temozolomide use and IDH mutations confer favourable prognosis across all glioma entities. ■

1. Schneller F, et al. J Thorac Oncol 2014;9:40.

Familial cancers: Clinical and ethical issues for oncologists

A family history is an important risk factor for developing cancer. Genetic testing to help in identifying and quantifying individual cancer risks has increased in speed and sensitivity. Such advances, unimaginable before the Human Genome Project, will hit mainstream medicine in 10 to 15 years. However, while commonplace genetic testing will assist in early detection and prevention – key for families with heritable malignancies – oncologists must be aware of the ethical, psychological and cost issues surrounding these tests.

At Saturday's Special Symposium on Germline Genetics, Important Issues for Oncologists, Professor Rosalinda Eeles from Royal Marsden Hospital, Sutton, UK, explained the spectrum of risk associated with germline genetic variation, from common risk variants conferring a slightly increased risk through to higher risk variants, which may predispose to cancer. This variation is being used to develop targeted screening programmes; intensive programmes for some cancers with high-risk variants, such as breast and colon, and standard screening programmes for other tumour types at an earlier stage of research.

Germline mutations have important implications for treatment, said Dr Gillian Mitchell from the Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, in terms of both efficacy and toxicity. The presence of the same mutation in every tumour cell, unlike most somatically mutated tumours, should increase the chance of a response to treatment targeting the mutation. Germline genetic information also helps oncologists to avoid cancer treatments that could exacerbate a patient's chance of developing additional tumours.

"Genetics can be ethically complex as it involves families and not just individuals," said Professor Shirley Hodgson from the University of London, UK, at Sunday's Patient Cases Session on Clinical and Ethical Issues in Cancer Genetics. Professor Hodgson explained how the decisions made by an individual can affect the wider family and how this opens up a whole range of issues, including confidentiality and the conflicts between an individual's wishes and the rights of family members. ■

Clinical practice is set to change with the broader use of genetic testing in healthy individuals with a positive family history of cancer.

Highlights of head and neck cancers at ESMO 2014

Head and neck cancer

Promising progress in the development of treatments and discovery of predictive biomarkers for head and neck cancers (HNCs) has been presented in late-breaking abstracts at Proffered Paper and Poster sessions over the last 2 days.

At Saturday's Proffered Paper Session, Dr Jean-Pascal Machiels from Cliniques Universitaires Saint Luc, Brussels, Belgium, presented results from 483 patients with recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck with progression on/after platinum-based chemotherapy in the phase III LUX-H&N 1 trial, showing that second-line afatinib significantly improved progression-free survival (PFS) compared with standard methotrexate treatment (median 2.6 months versus 1.7 months; hazard ratio 0.80; 95% confidence intervals 0.65–0.98; $p=0.03$). Afatinib did not significantly improve overall response rates (ORRs) or overall survival (OS).

"Many potential reasons could explain why we were not able to demonstrate a survival benefit," Dr Machiels said. "It could be simply because afatinib does not improve survival. However, 50% of the patients in both arms received subsequent therapies that could have influenced the survival benefit, for example a significant number of patients received subsequent anti-EGFR therapies in the methotrexate arm."

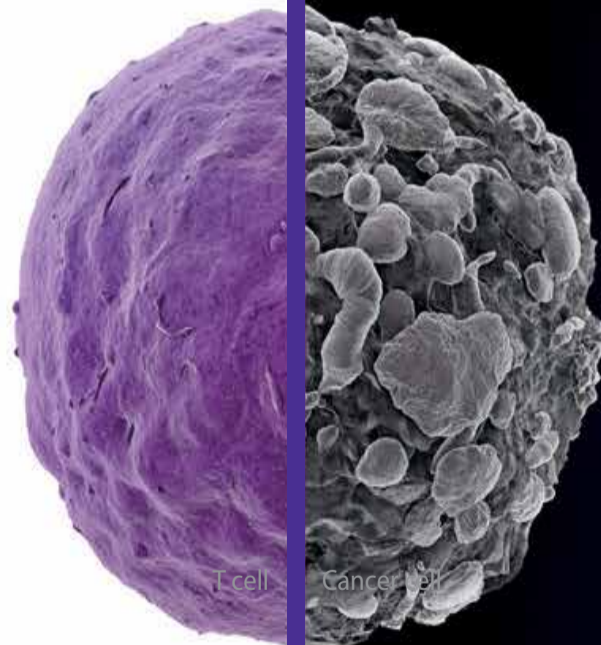
In another presentation, Dr Makoto Tahara from the National Cancer Center Hospital East, Kashiwa, Japan, highlighted new data on predictive biomarkers for lenvatinib efficacy in refractory differentiated thyroid cancer, using blood ($n=387$) and tissue ($n=183$) samples from 392 patients in the phase III SELECT trial. In lenvatinib-treated patients, low levels of baseline angiopoietin-2 were significantly associated with tumour shrinkage ($p=0.017$) and prolonged PFS ($p=0.018$). Activity of lenvatinib was, however, independent of BRAF/KRAS mutation status.

Interesting results from a phase Ib study showing that the anti-PD-1 antibody, pembrolizumab, is safe and effective in human papillomavirus (HPV)-positive and -negative R/M HNC, were presented by Dr Laura Chow from the University of Washington, Seattle, WA, USA, in yesterday's Poster Discussion Session on HNC. Among 60 patients with tumour expression of PD-L1, 23 were HPV-positive. While pembrolizumab showed similar response rates in both HPV-positive and -negative disease (20% versus 19%), both PFS (17.2 versus 8.1 months) and OS (not reached versus 9.5 months) were prolonged in HPV-positive patients. Expression of PD-L1 correlated positively with ORR ($p=0.018$) and PFS ($p=0.024$); ORR was highest (50%) among the 12 patients with high PD-L1 expression.

Dr Chow said that these findings support the development of pembrolizumab as a treatment for HNC. ■

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Reference: 1. Melcher A, Parato K, Rooney CM, Bell JC. Thunder and lightning: immunotherapy and oncolytic viruses collide. *Mol Ther* 2011;19:1008-1016.

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Phase III trial data suggest potential new treatment strategies for prostate cancer

Genitourinary tumours

In the last few years we witnessed the approval of several new agents for metastatic prostate cancer that have resulted in improved overall survival (OS). Currently, androgen deprivation therapy (ADT) remains a central part of treatment for patients with high-risk non-metastatic and also metastatic prostate cancer. Despite the generally good response of metastatic disease to this approach, many men will eventually develop castration-resistant prostate cancer (CRPC), for which prognosis is still poor. Data from randomised phase III trials presented at yesterday's Proffered Paper Session on GU, Prostate, have shown a significant OS benefit in patients with 'high-volume' metastatic prostate cancer receiving combined antiandrogen and docetaxel as first-line treatment and have suggested a benefit of adding local radiotherapy to androgen deprivation in newly diagnosed high-risk non-metastatic (MO) prostate cancer.

High-volume prostate cancer is a poor prognostic factor in patients with hormone-naïve metastatic prostate cancer. A retrospective subanalysis from the randomised CHAARTED study in 790 men with first-line metastatic prostate cancer was reported by Dr Christopher Sweeney from the Dana Farber Cancer Institute, Boston, MA, USA. The addition of docetaxel to ADT in patients with high-volume disease improved OS from 32.2 to 49.2 months ($p=0.0013$). Additionally, combined chemo-hormonal treatment among 518 men resulted in an improvement of: prostate-specific antigen (PSA) <0.2 at 12 months ($p=0.0011$), time to PSA or clinical progression ($p<0.0001$) and time to clinical progression ($p<0.0001$). These results are of substantial clinical relevance and will change practice in patients with high-volume untreated metastatic prostate cancer.

Professor Giuseppe Curigliano from the European Institute of Oncology, Milan, Italy, commented, "The investigators demonstrated that patients with 'high-volume', castration-sensitive metastatic disease benefit from upfront docetaxel and it appears to confer a survival benefit that is superior to docetaxel given for metastatic castration-resistant disease. However, there is a need to develop better models to determine who 'high-' and 'low-' volume disease groups should include to avoid, for example, discrimination between a patient with several small lesions and one with a single large lesion."

Adding docetaxel to ADT in untreated newly diagnosed, high-volume metastatic prostate cancer improved survival by 17 months

Dr Charles Ryan from the University of California, San Francisco, USA, reported the final OS results of the randomised COU-AA-302 study in 1088 patients comparing the selective CYP17 inhibitor, abiraterone acetate, plus prednisone over prednisone alone in chemotherapy-naïve metastatic CRPC. Disease progression and survival benefits had previously been reported in a planned interim analysis.¹ With a median follow-

up of 49.4 months, abiraterone acetate plus prednisone significantly prolonged OS compared with prednisone alone (median OS 34.7 months versus 30.3 months; hazard ratio [HR] 0.80; 95% confidence intervals [CI] 0.69–0.93; $p=0.0027$).

"In future trials it will be important to select patients responsive versus resistant to abiraterone or other anti-androgen agents"

– SAID PROFESSOR GIUSEPPE CURIGLIANO, COMMENTING ON THE RESULTS.

It has recently been shown that the detection of androgen-receptor splice variant 7 messenger RNA (AR-V7) in circulating tumour cells from men with advanced prostate cancer was associated with resistance to enzalutamide and abiraterone.² Among men receiving enzalutamide, AR-V7-positive patients had lower PSA response rates than AR-V7-negative patients (0% versus 53%) and shorter PSA progression-free survival (PFS; median 1.4 months versus 6.0 months; $p<0.001$) and OS (median, 5.5 months versus not reached; $p=0.002$). Similar findings were made among men receiving abiraterone. These findings require large-scale prospective validation.

Abiraterone acetate plus prednisone prolonged survival compared with prednisone alone in chemotherapy-naïve metastatic CRPC

This OS benefit was maintained despite the fact that 44% of patients in the control arm subsequently received abiraterone acetate plus prednisone. Tolerability was acceptable, although grade 3–4 adverse events of special interest were more common in the combination arm. These results confirm that the survival benefit of abiraterone acetate seen in patients who previously received chemotherapy is also apparent in chemotherapy-naïve metastatic CRPC.

Dr Kim Chi from the University of British Columbia, Vancouver, Canada, reported that the addition of the targeted agent, custirsen, to docetaxel plus prednisone did not improve survival over docetaxel/prednisone alone. Custirsen is a second generation antisense oligonucleotide that targets clusterin, a pro-survival cellular protein overexpressed in response to cellular stress, such as chemotherapy. Among 1022 randomised patients, there was no OS difference between the treatment arms (median 23.4 months with custirsen versus 22.2 months without; HR 0.93; $p=0.21$). Furthermore, there were more grade ≥ 3 toxicities in the custirsen arm and more patients discontinuing due to toxicity (41% compared with 29% in the control arm). The lack of a significant efficacy benefit of custirsen over standard therapy, coupled with the markedly higher incidence of severe adverse events, indicates that custirsen did not add any therapeutic benefit in patients with metastatic CRPC.

The use of radiotherapy in addition to ADT in patients with newly diagnosed non-metastatic (MO) prostate cancer was supported by an analysis of prospectively collected data from the large randomised STAMPEDE trial (ADT versus various treatment combinations), which was presented by Dr Nicholas James from the University of Warwick, Coventry, UK. All 694 patients included in the analysis had been enrolled into the control arm, both before and after the introduction of mandatory radiotherapy in addition to ADT for NOMO disease. The 2-year OS and failure-free survival (FFS) rates were 95% and 79%, respectively. Although patients with N+ disease had a higher risk of failure than those with NO disease (HR 1.87), planned radiotherapy improved 2-year FFS for both NOMO disease (HR 0.33; 95% CI 0.18–0.62) and N+MO disease (HR 0.45; 95% CI 0.25–0.80) compared with no planned radiotherapy. The results support the findings of previous randomised trials for NOMO disease^{3,4} and suggest that patients with N+ non-metastatic disease may also benefit from the addition of planned radiotherapy to ADT. Commenting on the results, Dr Eleni Efstathiou from the MD Anderson Cancer Center, Houston, TX, USA, remarked, "This confirms previously reported trials on locally advanced disease. Importantly, data suggest that lymph node-positive, non-metastatic disease may warrant more aggressive combinatorial strategies incorporating radiotherapy and systemic treatment. Data will need to mature and a confirmatory trial is likely warranted for current practice to be altered. Importantly, safety of such an approach is of the essence, given the involved field and diversity in radiation treatment rendered based on availability. Undoubtedly, the data presented is in line with the biology of the disease."

Radiotherapy added to ADT improved failure-free survival in patients with newly diagnosed NOMO and N+MO prostate cancer

Results from a late-breaking abstract presented by Dr Jennifer Cullen from Center for Prostate Disease Research, Rockville, MD, USA, in yesterday's Poster Discussion Session on Genitourinary Tumours, Prostate, demonstrated the utility of the 17-gene Genomic Prostate Score (GPS) in predicting recurrence following radical prostatectomy for localised prostate cancer. Using 402 biopsy specimens from 431 patients, GPS was a significant and independent predictor of the time to biochemical ($p<0.001$) and metastatic recurrence ($p=0.032$) and was strongly associated with adverse pathology ($p<0.001$) and high-grade disease ($p<0.001$).

In addition to the findings from these trials, the need for a new taxonomy for metastatic prostate cancer to cover the range of molecular subtypes revealed by biopsies was discussed by Dr Mark Rubin from Weill Cornell Medical College, New York, NY, USA, as part of Saturday's Special Symposium on Precision Medicine in Prostate Cancer. The involvement of different signalling pathways and tumours with alterations in DNA damage repair are among the differences that may help to tailor treatment. Reproducible post-treatment histologic definitions and molecular testing should be included in any future taxonomy. ■

1. Ryan CJ, et al. N Engl J Med 2013;368:138–48
2. Antonarakis ES, et al. N Engl J Med 2014;371:1028–38
3. Warde P, et al. Lancet 2011;378:2104–11
4. Widmark A, et al. Lancet 2009;373:301–8

Best posters of the day



Saturday, 27 September

Breast cancer, locally advanced and metastatic	344
Developmental therapeutics	457
Genitourinary tumours, non-prostate	(2 winners) 862 and 823
Genitourinary tumours, prostate	793
Gynaecological cancers	890
Neuroendocrine & endocrine tumours and CUP	1155

Sunday, 28 September

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Targeted therapies improve the outlook for gynaecological cancers

Excitement about promising targeted therapies for gynaecological cancers was fuelled by important trial results from three late-breaking abstracts (LBAs) announced during the afternoon's Proffered Paper Session.

In the first of two LBAs on cervical cancer, Professor Paul Symonds from the University of Leicester, UK, presented results from CIRCCA, a randomised, double-blind phase II trial of the vascular endothelial growth factor receptor inhibitor cediranib in 69 patients with metastatic/recurrent disease. Adding cediranib to carboplatin-paclitaxel significantly increased median progression-free survival (PFS) (36 weeks versus 31 weeks; hazard ratio [HR] 0.59; 80% confidence intervals [CI] 0.40–0.87; $p=0.040$) and led to a trend in increased overall response rates (66% versus 45%; $p=0.054$). There was no significant increase in median overall survival (OS).

"Recurrent or metastatic cervix cancer is really difficult to treat with a low response rate and poor survival. This study has opened up a new avenue of investigation for a difficult-to-treat cancer," said Professor Symonds.

In the second cervical cancer LBA, Dr Krishnansu Tewari from Irvine Medical Center, Orange County,

CA, USA, presented the final OS analysis of the GOG 240 trial, which led to the FDA approval last month of bevacizumab as the first targeted therapy for advanced cervical cancer in combination with chemotherapy. Patients receiving bevacizumab survived for 3.5 months longer than those in the placebo arm (HR 0.76; 95% CI 0.62–0.95; $p=0.0068$) and the survival benefit of bevacizumab was sustained beyond 50 months.

Addition of bevacizumab to first-line chemotherapy prolonged median survival by 3.5 months in advanced cervical cancer

Important advances are also being made in single-agent treatment regimens. Fibroblast growth factor receptor 2 (FGFR2) mutations occur in around 10% of endometrial cancers and are associated with poor prognosis. Dr Gottfried Konecny from the University of California, Los Angeles, CA, USA, presented the results of a phase II trial of the oral multikinase and FGFR inhibitor dovitinib in patients with metastatic endometrial cancer progressing on chemotherapy. Although there was no difference in the primary endpoint (18-week PFS rates) in patients with and without the FGFR2 mutation ($n=22$), median PFS and OS were 1.4 months and 10.9 months greater, respectively. ■



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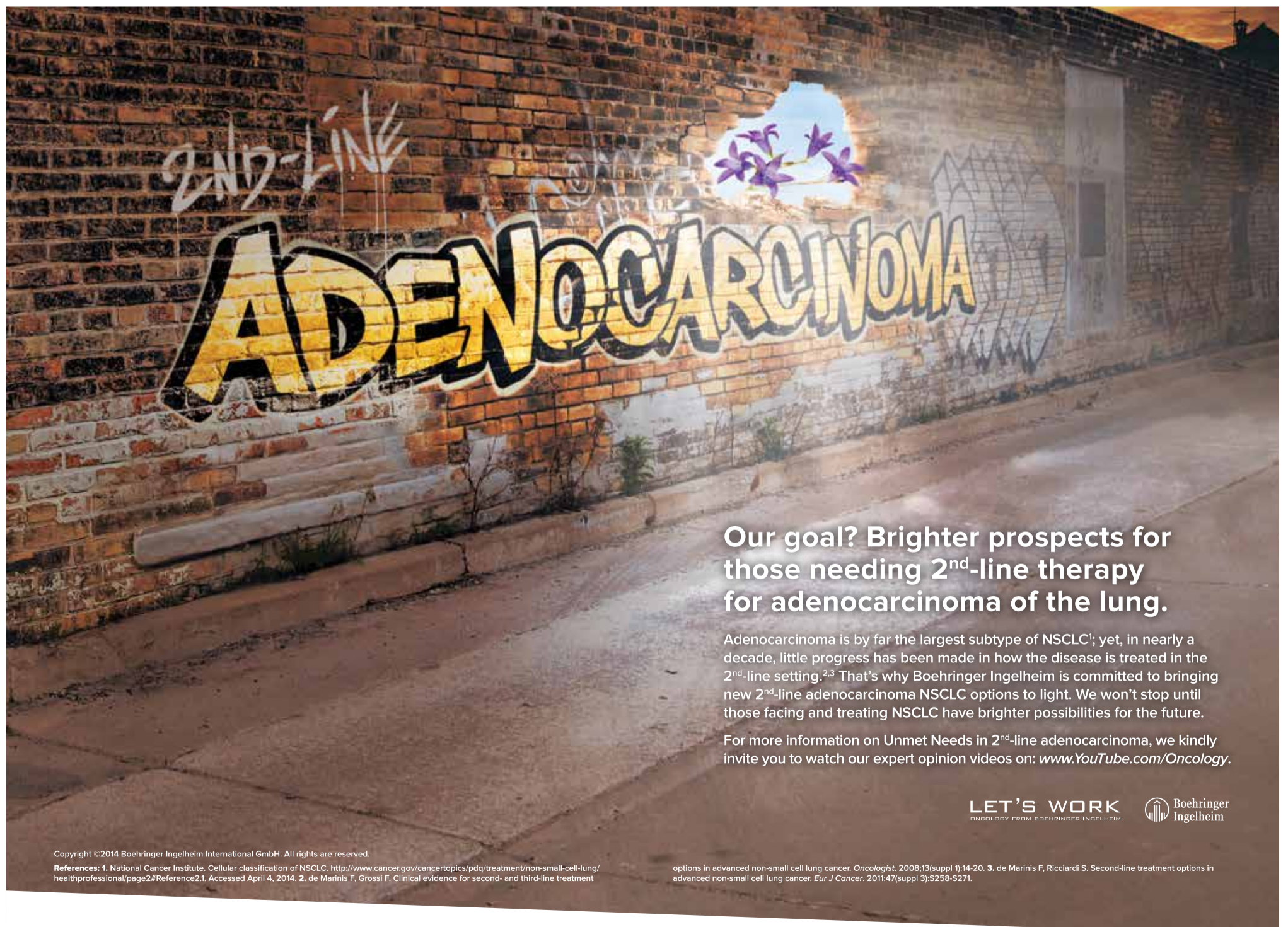
Room: Alicante
Session Info: ESMO-SIOPE Session: Long-term side effects in adolescent and young adults
Session Time: 09.15 – 10.45

Room: Granada
Session Info: ESMO-ASCO: The evolution of the clinical trial landscape
Session Time: 11.00 – 12.30

Room: Valencia
Session Info: ESMO-EANM: Impact of molecular imaging on management of lymphoma
Session Time: 11.00 – 12.30

Room: Granada
Session Info: ESMO-SEOM Joint Symposium: Investigation driven precision oncology
Session Time: 14.15 – 15.45

Room: Pamplona
Session Info: ESMO-ESTRO-ESSO: Integration of local therapy with targeted agents in oligometastatic breast cancer
Session Time: 14.15 – 15.45



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For more information on Unmet Needs in 2nd-line adenocarcinoma, we kindly invite you to watch our expert opinion videos on: www.YouTube.com/Oncology.

LET'S WORK
ONCOLOGY FROM BOEHRINGER INGELHEIM

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References: 1. National Cancer Institute. Cellular classification of NSCLC. <http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional/page2#Reference2.1>. Accessed April 4, 2014. 2. de Marinis F, Grossi F. Clinical evidence for second- and third-line treatment options in advanced non-small cell lung cancer. *Oncologist*. 2008;13(suppl 1):14-20. 3. de Marinis F, Ricciardi S. Second-line treatment options in advanced non-small cell lung cancer. *Eur J Cancer*. 2011;47(suppl 3):S258-S271.

Advances in molecular profiling are set to refine the treatment of metastatic CRC

Gastrointestinal tumours



Prof. Thomas Seufferlein

The need to revise treatment strategies as understanding of the molecular profile of metastatic colorectal cancer (mCRC) increases was discussed in a Special Symposium yesterday on Advances in Precision Medicine of Metastatic Colorectal Cancer.

CRC can now effectively be subdivided into 6 clinically relevant subtypes, based mainly on gene expression profiling, Dr Krisztian Homicsko from UNIL-CHUV, Lausanne, Switzerland, told delegates. These subtypes have different prognoses and different responses to treatment and so will be invaluable for tailoring therapy to patients. Validation studies are, however, still required.

Dr Federica Di Nicolantonio from the University of Torino Medical School, Candiolo, Italy, described findings from the CRC Tumor Cancer Genome

Atlas (TCGA), which reveal a wide range of genetic alterations that lead to deregulation of five main signalling pathways: WNT, TGF- β , p53, PI3K and receptor tyrosine kinase-RAS signalling. She cautioned that due to the complexity of the signalling pathways, targeting more than one pathway will be necessary for prolonged responses. Clonal selection and evolution of CRC tumours also pose problems for therapy, explained Professor Josep Tabernero from Vall d'Hebron University Hospital, Barcelona, Spain. An example of this has been observed during treatment with EGFR inhibitors, when RAS wild-type tumours began to show an increase in RAS mutant cells. So tumour profiling should ideally be conducted throughout treatment to ensure that it remains appropriate.

Advances in immunotherapy mean that there has also been renewed interest in this type of treatment for CRC. Trials investigating a number of approaches, including anti-checkpoint inhibitor monoclonal antibodies, immunomodulating cytotoxic drugs and immunoadjuvant cytokines, have been designed, said Dr Pierpaolo Corrales from Siena University Hospital, Italy, and their results may change the landscape of CRC.

Session Chair, Professor William Steward from the University of Leicester, UK, concluded that these techniques will be of huge clinical utility in the future. ■

NSCLC: Significant intratumour heterogeneity confirmed

Lung cancer

A genomic sequencing study by researchers from the UK has found significant spatial and temporal intratumour heterogeneity in non-small-cell lung cancer (NSCLC). This heterogeneity means that a single tumour is made up of cells with quite different genetic profiles and characteristics able to drive cancer progression, evasion of a patient's immune responses and the development of drug resistance.

At yesterday's Proffered Paper Session on NSCLC, Early Stage, Dr Mariam Jamal-Hanjani from UCL Cancer Institute, London, UK, presented findings in a late-breaking abstract from one of the first studies to explore the genetic evolution of NSCLC tumours over time.

Researchers performed multi-region whole exome sequencing on 37 samples from 11 primary NSCLC tumours. They observed intratumour heterogeneity in every tumour. The research team used the sequencing data to construct a phylogenetic tree for each tumour. Tree analysis showed that mutations in potential driver genes occurred both early and late in the course of the disease; 35% of these mutations were heterogeneous.

"Understanding the pathways of tumour evolution may help us to identify molecules that can act as therapeutic targets, but also assess key points in cancer progression when they are most effective," said Dr Jamal-Hanjani. "These pathways look increasingly promising as targets for precision medicine." ■

Oncologists are eager to understand how intratumour heterogeneity affects biomarker validation, therapeutic responses and, ultimately, patient survival

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EU indication

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* LUX-Lung 3 (N=345): 169 del19 patients, vs pemetrexed/cisplatin, median OS 33.3 vs 21.1 months (HR 0.54; 95% CI, 0.36-0.79; P=0.0015). LUX-Lung 6 (N=364): 186 del19 patients, vs gemcitabine/cisplatin, median OS 31.4 vs 18.4 months (HR 0.64; 95% CI, 0.44-0.94; P=0.0229).

[#] as measured by European Organisation for Research and Treatment of Cancer (EORTC) questionnaires.

HR = hazard ratio; OS = overall survival; PFS = progression-free survival; QoL = quality of life.

Yang JC, et al. ASCO presentation and abstract J Clin Oncol 32:5s, 2014 (suppl; abstr 8004^A).

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Neoadjuvant, Triple Negative Breast Cancer

A Phase 3 Study Evaluating the Safety and Efficacy of the Addition of Veliparib Plus Carboplatin Versus the Addition of Carboplatin to Standard Neoadjuvant Chemotherapy Versus Standard Neoadjuvant Chemotherapy in Subjects With Early Stage Triple Negative Breast Cancer (Brightness)

ClinicalTrials.gov Identifier: NCT02032277

Patient Population

- Women \geq 18 years of age
- Histologically confirmed invasive breast cancer
- Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor (HER)2-negative (triple negative) cancer of the breast

Endpoints

Primary Endpoints

Pathological Complete Response (pCR)

Secondary Endpoints

Rate of eligibility for breast conservation after therapy

Tertiary Endpoints

Event Free Survival
Overall Survival
Clinical Response Rate
pCR plus minimal residual disease (defined as residual cancer burden class I)
Eastern Cooperative Oncology Group performance status
Breast cancer related quality of life

Advanced Squamous NSCLC

A Phase 3 Study Evaluating the Safety and Efficacy of the Addition of Veliparib Plus Carboplatin and Paclitaxel Versus Placebo Plus Carboplatin and Paclitaxel in Previously Untreated Subjects With Advanced or Metastatic Squamous Non-Small Cell Lung Cancer (NSCLC)

ClinicalTrials.gov Identifier: NCT02106546

Patient Population

- Men and women \geq 18 years of age with life expectancy $>$ 12 weeks
- Cytologically or histologically confirmed squamous NSCLC
- Advanced or metastatic squamous NSCLC, not amenable to surgical resection or radiation with curative intent
- Has not received prior cytotoxic chemotherapy

Endpoints

Primary Endpoints

Overall Survival

Secondary Endpoints

Progression-free Survival
Objective Response Rate

Tertiary Endpoints

Duration of Overall Response
Eastern Cooperative Oncology Group performance status
Quality of Life



Advanced BRCA-Associated Breast Cancer

A Phase 3 Study Evaluating the Safety and Efficacy of Carboplatin and Paclitaxel With or Without Veliparib in HER2-Negative Metastatic or Locally Advanced Unresectable Breast Cancer Gene (BRCA)-Associated Breast Cancer (brocade3)

ClinicalTrials.gov Identifier: NCT02163694

Patient Population

- Men and women \geq 18 years of age
- Locally advanced (unresectable) or metastatic HER2-breast cancer
- Suspected deleterious or deleterious BRCA1 and/or BRCA2 germline mutation
- No more than 2 prior lines of DNA-damaging therapy for metastatic breast cancer
- No prior PARP inhibitors
- Stable CNS metastases

Endpoints

Primary Endpoints

Progression-free Survival

Secondary Endpoints

Overall survival
Clinical benefit rate
Objective Response Rate
Progression-free survival 2
Duration of overall response

Tertiary Endpoints

Change in Eastern Cooperative Oncology Group performance status
Change in Quality of Life

If you're interested in learning more about these trials, visit [ClinicalTrials.gov](https://www.clinicaltrials.gov). Veliparib is an investigational drug which has not been approved by regulatory agencies. Efficacy and safety have not been established.

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