Today's Top Picks!

Congress Highlights
The best of the ESMO 2012 Congress
09:00 – 13:00 HALL A

Patient Cases
Hepatocellular carcinoma (HCC)
8:00 – 9:00 HALL H

Patient Cases
Prevention and treatment of skin toxicity
8:00 – 9:00 HALL G

ESMO VIENNA 2012

congressdaily

TUESDAY 2 OCTOBER 2012

Optimal treatment duration defined for trastuzumab

One year of adjuvant trastuzumab should remain the standard of care for HER2-postive early breast cancer patients, concluded both the 'Herceptin® Adjuvant Trial' (HERA) and 'Protocol for Herceptin® as Adjuvant therapy with Reduced Exposure' (PHARE) trials, presented in the Presidential Symposium Session yesterday.

"These long awaited results constitute a further milestone in the treatment of patients with early breast cancer over-expressing HER2-positive, corresponding to a population of about 12–15% of all cases of breast cancer," commented Professor Christoph Zielinski, from the Medical University Vienna, Austria. It was especially appropriate, he added, that the landmark data were presented on October 1 – International Breast Cancer Awareness Day.

Treatment with trastuzumab for 1 year has provided survival benefits to patients with HER2-positive early breast cancer for a number of years and is considered the standard of care. However, the optimal duration of trastuzumab had been much debated due to data from the Finland Herceptin® (FinHer) trial demonstrating improvements in disease-free survival (DFS) with 9 weeks of trastuzumab compared to no trastuzumab. The HER2 positive population in this trial was however, small.

In the PHARE trial, 3384 patients with HER2 positive early breast cancer who had received at least 4 cycles of (neo)-adjuvant chemotherapy and who were receiving adjuvant trastuzumab for a maximum of 6 months were randomized to either complete 12 months trastuzumab (n=1690) or to stop trastuzumab at 6 months (n=1690).

Results showed that DFS was 87.8% in the 12 month group versus 84.9% in the 6 month group (HR 1.28; 95% CI 1.05–1.56).

"The results were inconclusive for the non-inferiority hypothesis. Nevertheless, there was a trend favoring the standard 12 months' treatment. However there were significant differences in cardiac events favoring 6 months' treatment," said the trial presenter, Professor Xavier Pivot from University Hospital of Besançon, France.

Professor Pivot added that a multivariate analysis exploring subgroups would be presented at San Antonio Breast Cancer Symposium (SABCS) in December.

In the HERA trial, 5102 women with locally determined HER2-positive invasive early breast cancer were randomized after surgery to 1 year trastuzumab (n=1703); 2 years' trastuzumab (n=1701) or to observation (n=1698). The results showed that the DFS rate in the two arms was comparable (HR=0.99; 95% CI 0.85–1.14; p=0.86).

"The key message for 2012 is that 1 year of treatment with trastuzumab remains the standard of care for HER2 positive early breast cancer patients," said the HERA trial presenter Professor Richard Gelber, from the Dana Farber Cancer Institute, Boston, USA.

"There was no evidence of long term benefit of 2 years compared to 1 year trastuzumab when administered as sequential treatment following chemotherapy," said Professor Richard Gelber.

ESMO 2012 breaks all records

ESMO 2012 has proved our biggest and best congress yet with an astonishing 16,394 delegates. Wow! For late comers with so many attendees there was standing room only in many sessions like the Presidential Symposia, the ESMO-ASCO Joint Symposium on genomics in breast cancer, the Special Session on Melanoma, and all the Young Oncologist sessions to name a few.

"What's astonishing in the current financial climate is that attendance is even up on ESMO 2010 which had 15,949 attendees. This shows the importance that oncologists place on the value of our meeting," said Alan Howard, ESMO CEO.

In the current climate most other medical conferences, he added, are seeing a decrease in attendees.

Over 3000 delegates attended the Presidential Session on Sunday where Dr Alice Shaw from Massachusetts General Hospital Cancer Center, Boston, USA, presented her practice changing study on the use of crizotinib in ALK positive NSCLC patients.

Altogether over the last five days 140 sessions have been staged across 110 scientific and 30 educational sessions.

"What's been really striking to me has been the number of international delegates from outside Europe," said Dr Erika Martinelli from Seconda Università di Napoli, Italy.

The statistics show that 1116 delegates registered from the US, 539 from Japan, 479 from China, 292 from Argentina, and 258 from Brazil.

"What delegates seem to particularly enjoy about ESMO is the personal touch. People seem to find it a really easy Congress to navigate. It's the perfect size to get round and achieve an overview of what's really new in oncology while at the same time having the opportunity to network. You can make lots of new friends," said Dr Matthias Preusser, from the Comprehensive Cancer Center, Vienna, Austria. "It shows the human face of oncology."

One of the biggest hits of 2012 was the play '2084', written by Professor Michael Baum and starring our very own president Professor Martine Piccart.

ESMO also staged a strong exhibition with 68 companies having stands displaying the latest drugs and equipment. New for this year was the Society Village where for the first time 28 non profit associations and national and regional medical societies staged displays. Dr Ilya Tsimafeyeu, from the Russian Society of Clinical Oncology (RUSSCO), said that the Society Village had provided RUSSCO with the perfect opportunity to gain more members and meet with other national societies.

All this exciting activity has helped persuade 260 people to join ESMO during the meeting, bringing our membership up to 7,200 members. Thank you.

Is there an opportunity for personalized medicine in HCC?

Sorafenib became the standard treatment for advanced HCC five years ago after findings from the SHARP trial showed that treatment with this multi-targeted tyrosine kinase inhibitor (TKI) resulted in a 2.8 month improvement in overall survival (OS) compared with placebo. However, since then, results from Phase 3 trials evaluating targeted agents in this setting have been disappointing.

In April 2010, the SUN trial was discontinued after early data showed that sunitinib was inferior to sorafenib in terms of OS and was more toxic, despite the fact that this agent has a very similar molecular target profile to sorafenib. Then in December 2011, Bristol-Myers Squibb announced that the VEGFR- and FGFR-targeted agent, brivanib, did not improve OS as 2nd-line therapy compared with placebo in the BRISK-PS trial. This news was followed by a similar announcement in July 2012 for the BRISK-FL trial of brivanib as 1st-line therapy, which also failed to meet its primary OS endpoint. Continuing this pattern here at ESMO, findings from the SEARCH trial, reported during Sunday's Presidential Symposium, showed that the addition of erlotinib to sorafenib does not improve OS compared with sorafenib alone (median OS: 9.5 months [erlotinib + sorafenib] versus 8.5 months [sorafenib]; HR 0.929; CI: 0.781–1.106, p=0.204).

Commenting on this increasing tally of negative Phase 3 trials in advanced HCC, Professor Roberto Labianca, an expert in the treatment of gastrintestinal cancers from Riuniti Hospital, Bergamo, Italy, said "we've been conducting the same trials for 15 years – it's time we started selecting our patient populations based on the molecular target profile of the agents being studied, as has been done so successfully in other areas, for example, with trastuzumab in HER2-positive breast cancer".

Suggestions that this may indeed be the way forward in HCC were strengthened yesterday when Dr Bruno Daniele from Rummo Hospital, Benevento, Italy, presented final results from a randomized Phase 2 trial of the MET inhibitor, tivantinib (formerly known as ARQ 197), as 2nd-line therapy in unresectable HCC. In this trial, 107 patients with Child-Pugh (CP) A liver function and a Performance Status (PS) of <2 were randomized 2:1 to receive tivantinib or placebo. Although the primary endpoint of time to progression (TTP) showed a small benefit in favor of tivantinib in the overall intent-to-treat (ITT) population (median TTP: 6.9 versus 6.0 weeks; HR 0.64; 95% CI: 0.43–0.94, p=0.04), efficacy results among MET-positive patients treated with tivantinib were much more promising: median TTP was 11.7 weeks (versus 6.1 weeks for placebo; HR 0.43; 95% CI: 0.19–0.97, p=0.03), disease control rate (DCR) was 50% (versus 20% for placebo), and median OS was an impressive 7.2 months (versus 3.8 months for placebo; HR 0.38; 95% CI: 0.18–0.81, p=0.01). Dr Daniele commented that "the pronounced activity of tivantinib in MET-positive patients seen in this trial warrants further evaluation, and a Phase 3 trial in MET-positive HCC patients is being planned." Indeed, if these findings are confirmed in a Phase 3 trial, tivantinib would represent the first step towards personalized medicine in HCC.

Given this glimmer of hope, Professor Labianca suggested that it may be appropriate to "dig a little deeper" into the results obtained from recent negative Phase 3 trials. For example, as preclinical data suggest that the FGF pathway is implicated in the development of resistance to anti-VEGF therapy, could brivanib provide clinical benefit for relapsed patients with high FGF expression? Similarly, as the benefits of anti-EGFR therapy have been shown to be greater for patients with EGFR activating mutations in NSCLC, could erlotinib + sorafenib be an option for EGFR mutation-positive patients with advanced HCC? Or, put another way, would the BRISK-PS and SEARCH trials have been positive if patients had been selected based on expression of key molecular targets?

Negative data from the SEARCH trial reported here at ESMO also raise an important question regarding the viability of combination therapy in advanced HCC. "We mustn't forget that the vast majority of patients with HCC also have underlying liver disease, most commonly caused by alcohol abuse, hepatitis B or hepatitis C infections." Professor Labianca warned. "Many of these patients are very sick and it may be that combination therapy is just too toxic" he added.

Interestingly, the effect of liver disease etiology on sorafenib therapy was the subject of a presentation yesterday by Professor Jean-Pierre Bronowicki from the University Hospital of Nancy, Vandœuvre-lès-Nancy, France. Based on findings from the second interim analysis of GIDEON, a large observational study that is gathering information on the use of sorafenib in everyday clinical practice, Professor Bronowicki presented data to suggest that toxicity (drug-related adverse events and serious adverse events) was greater among patients with hepatitis C infection, whereas median OS appeared to be longer in this group compared with patients with hepatitis B infection or alcohol abuse as the underlying cause of liver disease. However, despite these apparent differences, Professor Bronowicki warned that these variations may reflect differences in prognosis associated with the natural history of the underlying liver disease rather than a difference in response to therapy. Nevertheless, data from studies such as GIDEON highlight the importance of considering both the cancer and the liver disease when treating patients with HCC, and serve as a strong reminder of the need for a multidisciplinary approach to patient care.

So, how can we move towards personalized medicine in HCC?

Answering this question, Professor Stefano Fagiuoli, from Riuniti Hospital, Bergamo, Italy, stresses that "We need to refine our selection criteria for patient eligibility for treatment. These criteria need to be based on a comprehensive evaluation of both the etiology of the underlying liver disease and a more reproducible assessment of portal hypertension, the key factor for the risk of decompensation." Adding to this, Professor Labianca comments that "We need to learn from our mistakes and ensure that future clinical trials of targeted therapies are conducted in selected patient populations based on the expression of key molecular targets".

Congress Highlights
The best of the ESMO 2012 Congress

The ESMO highlights session, traditionally held on the last day of the conference, provides delegates with arguably one of the best overviews of the latest developments in oncology.

In this not to be missed session, world leaders will provide 10 minute summaries of the main information that's emerged from ESMO 2012 in their fields. Sessions will cover everything from advances in the treatment of individual tumors to supportive and palliative care, public health, and basic and translational research.

International leaders presenting roundups at the session include Eric Van Cutsem who will summarise gastrointestinal and colorectal cancer, Jan Willem Coebergh oncology and public health, Matti Aapro supportive and palliative care, Sandrine Faivre head and neck cancer, Fatima Cardoso early breast cancer, and Tony Mok locally advanced and metastatic non-small cell lung cancer.

Professor Jean-Pierre Armand from the Gustave Roussy Institute, Villejuif, France commented "With the best will in the world the reality of attending an international meeting is that delegates just can't attend all the sessions they're interested in. The Highlights session allows you to fill in your gaps and get up to speed on everything you're interested in. With all the timings clearly labelled this allows you the opportunity to dip in and out," he says "Furthermore, in each field the new data has been placed in context by world authorities."

At the beginning of the session Francoise Meunier will deliver the ESMO Lifetime Achievement Award lecture on 'The EORTC mission and achievement: 50 years of progress against cancer."

"The EORTC exemplifies one of the very best scientific collaborations throughout Europe. In the field of sarcoma and glioblastoma in particular, it has made an extraordinary contribution to clinical progress and treatment harmonization across Europe," said Professor Armand.

09:00 ESMO Lifetime Achievement Award lecture - The EORTC mission and achievement : 50 years of progress against cancer
Françoise Meunier, Brussels, Belgium

09:15 Genitourinary tumors, non-prostate (other)
Thomas Powles, London, UK

09:25 Genitourinary tumors, non-prostate (RCC)
Manuela Schmidinger, Vienna, Austria

09:35 Genitourinary tumors, prostate
Ian Tannock, Toronto, ON, Canada

09:45 Gynecological cancers
Andres M. Poveda, Valencia, Spain

09:55 NETs
Kjell Öberg, Uppsala, Sweden

10:05 Hematological malignancies
Martin Dreyling, Munich, Germany

10:15 Gastrointestinal tumors, colorectal
Eric J.D. Van Cutsem, Leuven, Belgium

10:25 Gastrointestinal tumors, non-colorectal
Roberto Labianca, Bergamo, Italy

10:35 Supportive and palliative care
Matti S. Aapro, Genolier, Switzerland

10:45 Oncology and public health
Jan Willem Coebergh, Rotterdam, Netherlands

10:55 Coffee Break

11:15 Georges Mathé lecture
Jean-Pierre Armand, Villejuif, France

11:30 CNS tumors
Michael Weller, Zurich, Switzerland

11:40 Head and neck cancer
Sandrine Faivre, Clichy, France

11:50 Basic science and translational research (with focus on biomarkers)
Carlos Caldas, Cambridge, UK

12:00 Developmental therapeutics
Christian Dittrich, Vienna, Austria

12:10 Breast cancer, early
Fatima Cardoso, Lisbon, Portugal

12:20 Breast cancer, locally advanced and metastatic
Wolfgang Eiermann, Munich, Germany

12:30 NSCLC, locally advanced and metastatic (to include early stage)
Tony S. K. Mok, Hong Kong, China

12:40 Sarcoma
Alessandro Gronchi, Milan, Italy

12:50 Melanoma and other skin tumors
Ulrich Keilholz, Berlin, Germany

Treatment with bevacizumab beyond progression: A new standard in mCRC?

The addition of bevacizumab (BEV) to 5-FU-based chemotherapy has been a standard 1st-line treatment option for patients with metastatic colorectal cancer (mCRC) for many years, although the use of this agent beyond progression is an area of ongoing debate. However, emerging data suggest that this question may soon be answered.

In yesterday's proffered papers session, Dr Gianluca Masi from the University Hospital of Pisa, Italy, presented data from a randomized Phase 3 trial, conducted by the Gruppo Oncologico Nord Ovest (GONO), which evaluated the continuation of bevacizumab beyond progression in patients with mCRC who had received bevacizumab as part of their 1st-line therapy. In this trial, 184 patients who had progressed following 1st-line chemotherapy (FOLFOX, FOLFIRI or FOLFOXIRI) + bevacizumab were randomized to receive 2nd-line treatment with chemotherapy alone (either FOLFOX or mFOLFIRI) or in combination with bevacizumab 5 mg/kg every 2 weeks.

Despite accrual to this trial being stopped early, results showed that the addition of BEV was associated with a significant progression-free survival (PFS) benefit compared with chemotherapy alone (median PFS: 6.77 months versus 4.97 months; HR 0.65; 95% CI: 0.48–0.89, p=0.0062), and that this benefit was maintained across various patient subgroups. The safety profile of bevacizumab + chemotherapy was consistent with previously reported data. However, Dr Masi advised that overall survival (OS) data are still immature at this time, with only 46 and 52 events observed in the bevacizumab + chemotherapy and chemotherapy alone arms, respectively.

The decision to stop accrual to this trial was based on results from the similarly designed Treatment-across Multiple Lines (TML) trial reported in June 2012, which showed that bevacizumab continued with 2nd-line chemotherapy was associated with a significant improvement in OS in patients with mCRC.

"This is the second randomized trial investigating the impact of bevacizumab continuation beyond first progression", concluded Dr Masi. "The continuation of bevacizumab in combination with second-line chemotherapy represents a new treatment option", he added.

Treating HNSCC: It's not just about EGFR

The treatment of head and neck squamous cell carcinoma (HNSCC) continues to challenge the oncology community because suitable drug targets have been difficult to identify. Activating oncogene mutations are rare while mutations in tumor suppressor genes, for example P53 and NOTCH1, are relatively common (47% and 19% mutation rates, respectively).

In his presentation during the special session on biologically based treatment in HNSCC yesterday, Dr Antonio Jimeno from the University of Colorado School of Medicine, Aurora, Colorada, USA, reminded delegates that the epidermal growth factor receptor (EGFR) inhibitor, cetuximab, is currently the only targeted drug approved for use in HNSCC. However, it has relatively low clinical efficacy, which Dr Jimeno argued was probably due to the lack of any patient selection strategies used in previous clinical trials.

Recent research into the biology of HNSCC - for example the role of human papillomavirus (HPV) in a growing proportion of HNSCC patients, especially in Western countries – could inform patient selection for anti-EGFR therapy and also drive research into promising alternatives.

"There is growing evidence that HPV+ and HPV- HNSCC have a different biology, and we can expect it will require different therapy," said Dr Jimeno. Promising areas of research include PI3K and multi-kinase inhibition, antiangiogenesis and anti-lymphangiogenesis, for example through ALK1 modulation.

Daily Editorial

Step into the future

Erika Martinelli, Associate Editor
Seconda Università di Napoli, Italy

Congratulations on making it through the past five days of information overload! But what a spectacular, positive and encouraging time it has been. Events like these are vital for us as we balance the daily pressures of our clinical caseload with the necessary task of keeping abreast of the latest research findings and trial results. Now we begin the tough task of translating what we have learned into our everyday practice.

We have all heard important updates and seen trial results that could affect our standard treatments for some cancers. In my own field of gastrointestinal (GI) cancer, for example, data was presented from the CORRECT trial on the survival of patients treated with the oral multikinase inhibitor regorafenib (REG) in patients with metastatic colorectal cancer whose disease had progressed after all approved standard therapies. Median overall survival (OS) was 6.4 months (95% CI: 5.8–7.0) in the REG arm versus 5.0 months (95% CI: 4.4–5.9) in the placebo arm. OS rate at 6 and 12 months was 52.2% and 24.1% in the REG arm versus 43.1% and 17% in the placebo arm, respectively. It is important to stress the significance of this drug on a population with an unmet medical need before regorafenib. After standard chemotherapy you can usually only provide the best supportive care, but regorafenib actually gives patients hope for the future.

Regorafenib was approved by the FDA while we´ve all been here at the ESMO Congress. We now hope that the EMEA will be quick to approve as well.

Improvements in clinical outcomes are always encouraging, but I have also been struck by several 'null results'. For example, we heard in the first Presidential Symposium that the addition of cetuximab to capecitabine + cisplatin showed no benefit compared with capecitabine + cisplatin alone in the first-line treatment of advanced gastric cancer (LBA3). While results like these may seem disappointing, they also inform our work as much as positive trial results as we try to balance toxicity, efficacy, simplicity, quality of life and costs in patient treatment. Looking at the study from an academic point of view it could be useful to implement these negative results with a biomarker analysis, which could indicate the populations to target for future trials. In this sense we need to push research so that the effort that the patient made to take part in the study was not made in vain.

Similarly, in the first Presidential Symposium, we also learned about the disease-free survival (DFS) and OS results and subgroup analyses of the PETACC8 intergroup phase 3 trial. Adding cetuximab to FOLFOX4 offered no benefit to patients with resected, stage III, KRAS wild type colorectal cancer. However, subgroup analyses in this large trial suggest that patients with pT4N2 tumors may receive some benefit from cetuximab in this setting.

As young oncologists, our motto should be 'do research and understand biology'. Only with biological classification of each tumor will we gain a greater understanding on how to stratify adjuvant treatment, thus avoiding unsuccessful chemotherapy and negative trial results. I am excited to see what the future holds in terms of what will come out of research to allow us to choose the best treatment for cancer patients.

One of the overriding messages that we have heard in many of the sessions is the increasing importance of genetic and molecular profiling and the scope that the analysis of tumor biomarkers can have in optimizing and personalizing treatments to maximize efficacy. We may have heard it before but the significant number of oral and poster presentations including data on biomarkers has been overwhelming. Such a plethora of data emerging from ESMO gives me real hope that we may soon have more validated biomarkers that can be incorporated into the clinic to support our treatment decision-making.

The ESMO congress brings together such a large group of experts; there is no better way to facilitate the rapid dissemination of new information coming from laboratories and clinical trials. In this way, ESMO facilitates knowledge uptake and the standardization of the highest level of patient care across Europe.

This year we can boast the active participation of over 16,300 delegates, with the Congress Program comprising 140 different sessions delivered as part of 18 Proffered Paper sessions, 21 Poster Discussion sessions, 20 Special symposia, 18 Patient cases sessions, 15 Educational sessions, 9 Joint Symposia, 4 Keynote sessions, 3 Poster sessions covering 23 different categories, and for the first time ever at ESMO, 2 Presidential Symposia. There was also and an entire program dedicated to young oncologists.

I now encourage you to browse back through the abstracts to see what gems you have missed. Then continue your debates and discussions with your colleagues at work and online. Let us keep the discussion alive to fuel research and scrutinize results for clinical significance.

Finally, I encourage you to come to the Congress Highlights today (9:00–1:00 in Hall A), which will provide you with a round-up of the key messages in each oncology domain. Françoise Meunier, Director General of the European Organization for Research and Treatment of Cancer (EORTC), will also deliver the ESMO Lifetime Achievement Award lecture, a historical perspective on the past 50 years of progress in cancer treatment.

Who knows what two more years of progress will look like when we meet again at ESMO 2014 in Madrid. I am certain, however, that there will be much to celebrate.

Gene therapy in metastatic melanoma: A promising concept?

Results of a first-in-man, proof of concept study of AMEP (a plasmid encoding the antiangiogenic metargidin peptide) in melanoma were presented yesterday by Dr Iben Spanggaard from the University Hospital Herlev, Denmark.

AMEP is a novel anti-cancer agent that has demonstrated antiangiogenic and anti-proliferative properties in in vitro and in vivo models by binding the cellular integrin receptors, α5β1 and αvβ3, bboth of which are highly expressed in activated endothelial and melanoma cells. In this study of 5 patients with disseminated melanoma, AMEP was injected into cutaneous melanoma lesions followed by electrotransfer (i.e. the use of electric pulses to transfer plasmid DNA into tissues) with needle electrodes. Treatment was associated with minimal toxicity, and 29 days post-treatment, all 5 'treated lesions' were stable in diameter whereas 4 out of 5 'control lesions' had increased by more than 20%. Response was not observed in any distant lesions.

These data suggest that electrotransfer of plasmid DNA may be an attractive alternative to viral gene therapy that warrants further evaluation and should be tested in clinical trials.

Molecular imaging in early drug development: Seeing the future

Yesterday's special symposium entitled 'A paradigm shift in early drug development: Individualizing to more patient benefit' comprised a series of informative and highly educational presentations from experts in the field. Among these was a presentation from Dr Kristoff Muylle, a Nuclear Medicine Physician at Jules Bordet Institute, Brussels, Belgium.

In his talk, Dr Muylle described the emerging role of imaging biomarkers in oncology and explained how they can be used to provide both prognostic and predictive information and to measure tumor response to a given therapy. He also described the benefits of imaging biomarkers over traditional sampling methods, not only because of the non-invasive nature of the assessment, but also because they provide a means of quantifying cellular targets for the entire disease burden, thereby avoiding sampling inaccuracy that can occur as a result of the inherent heterogeneity of cancer.

Finally, Dr Muylle described the great potential that molecular imaging holds for the future of drug development, both as a tool to assess drug targeting and enrich patient populations as well as for early response prediction, and provided excellent examples how molecular imaging has already been successfully implemented into clinical trials, with a specific focus on FDG-PET and immuno-PET.

Meeting the challenges of clinical trial design in cancer

Despite continuing advances in medicine and drug development technology, it remains very difficult for new cancer drugs to gain regulatory approval. This is partly due to the stringent standards set by the EMA and the FDA, but is also a direct result of the particular challenges that face clinical trialists working in cancer indications. Specifically, approvals of new agents are hindered by reliance of regulatory agencies on overall survival as a license-enabling endpoint, which often requires clinical trials with a large number of patients and an extensive follow-up. Surrogate endpoints, such as disease-free survival (DFS) and progression-free survival (PFS) are gaining traction, particularly in solid tumors. In hepatic cellular carcinoma and gastrointestinal stromal tumors, tumor response is under scrutiny as there is a realization that the traditional RECIST criteria, which require tumor shrinkage to classify a response, do not account for tumor stasis and/or necrosis, both of which are clinically meaningful and indicate drug activity. In other indications, biomarkers are a topic of intense study, with prostate-specific antigen losing relevance for some of the newer prostate cancer therapies, and hENT1 emerging as the first marker identified for pancreatic cancer (Abstract 709P, Poster session II, Sunday 30 September).

At this year's ESMO, presentations and posters throughout the program showcased the ingenuity and perseverance of the European clinical community in efforts to advance the study of anticancer agents.

Yesterday, Dr/Professor Arif Manji from The Hospital for Sick Children, Toronto, Canada, described the increased use of expanded cohort Phase 1 studies to gain additional clinical experience at recommended Phase 2 drug doses (abstract 455P). Dr Emilio Bria from Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy, presented results of a treatment interaction analysis based on data from randomized controlled trials in order to calculate the benefits (pathological complete response rates) versus potential harms (cardiotoxicity) associated with combining anthracyclines with anti-human epidermal growth factor receptor 2 (HER2) agents in women with breast cancer (abstract 322PD).

In other poster presentations, Dr Takanori Tanase from Taiho Pharmaceutical, Tokyo, Japan explored the relevance of PFS in colorectal cancer and commented on the importance of timing of imaging assessments (abstract 1378P); and Dr Chantal Dreyer from Hopital Beaujon, Clichy, France, evaluated the use of Choi criteria, already used for GIST, as an alternative to RECIST in patients with well differentiated pancreatic neuroendocrine tumors (PNET) treated with sunitinib or everolimus (abstract 1163P).

On Saturday, Professor Shukui Qin from the People's Liberation Army, Nanjing Bayi Hospital, China, and Professor Martine Piccart from Institut Jules Bordet and the Université Libre de Bruxelles, Brussels, Belgium, chaired the ESMO-CSCO Joint Symposium session session on the future of clinical trial design in cancer, where the faculty presented on a range of topics, including biopsy sample banks and biomarker-driven trials in breast cancer and non-small-cell lung cancer, with insights and experience provided by both Eastern and Western cancer centers involved in large clinical trials.

Professor Piccart described the long and expensive procedure associated with the development of new drugs, with only ~5% obtaining license approval, and the resulting delay in the availability of effective therapies to patients. "What is more frustrating is that after such a process we still have only a crude idea of the subsets of patients who will 'truly' benefit from a given agent", Professor Piccart said. Commenting on the future of clinical trial design, Professor Piccart underscored the need to adopt innovative strategies to accelerate drug development in a more efficient and targeted way. In breast cancer, Professor Piccart described data from the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALTTO), and the Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation (ALTTO) studies to illustrate how neoadjuvant trials could represent a smart, fast and cheap model for obtaining regulatory approval of effective agents.

Gastric cancer – a heterogeneous disease in need of a refined approach

In Sunday's Presidential Symposium, Professor Florian Lordick from the University Clinic Leipzig and the University Cancer Center (UCCL), Leipzig, Germany, presented data from the open-label randomized, controlled Phase 3 EXPAND trial of cetuximab in combination with capecitabine and cisplatin as first-line treatment for advanced gastric cancer (LBA3). The rationale for this trial came from previous Phase 2 trial data which suggested that cetuximab, an epidermal growth factor receptor (EGFR) antibody, in combination with first-line fluoropyrimidine with irinotecan or platinum compounds shows promising activity.

In the Phase 3 EXPAND trial, patients from 25 countries were randomized to receive 3-week cycles of capecitabine 1000 mg/m^2 twice daily (days 1–15) and cisplatin 80 mg/m^2 IV (day 1) plus weekly cetuximab (400 mg/m^2 loading dose on day 1 and 250 mg/m^2 thereafter) (n=455), or the capecitabine/cisplatin combination alone (n=449). Professor Lordick explained that baseline characteristics were balanced between treatment arms and that the median duration of cetuximab treatment was 14.9 weeks with a relative dose intensity of ≥80% received by 82% of patients. Unfortunately, progression-free survival (PFS), overall survival (OS) and best overall response rate (ORR) were similar between treatment arms (PFS HR1.091; 95% CI: 0.920–1.292, p=0.3158; OS HR 1.004; 95% CI: 0.866–1.165, p=0.9547; ORR 30% versus 29%). Median PFS and OS was also comparable across various subgroups.

Professor Lordick also explained that the addition of cetuximab was associated with more grade 3/4 adverse events, in particular, skin rash (13% versus 0%), diarrhea (8% versus 4%), hand-foot syndrome (7% versus 2%), hypomagnesemia (11% versus 1%) and hypokalemia (13% versus 9%).

Given these results from a large and well conducted trial, Professor Lordick concluded that the addition of cetuximab showed no benefit compared with chemotherapy alone (capecitabine + cisplatin) for the first-line treatment of advanced gastric cancer, and suggested that further classification of this heterogeneous disease may be required before advances in patient care can be made.

These data raise the question of whether trials in such unselected patient populations should still be conducted. The majority of patients with gastric cancer still present at an advanced stage, and despite advances in diagnostic and treatment strategies and a decline in incidence rates, outcomes remain poor. Whilst the use of classical chemotherapy agents has been explored thoroughly, and continues to be investigated, either alone or in various combinations, advances have been slow and the efficacy of these agents has reached a plateau. As such, the focus of research has shifted toward developing a greater understanding of the molecular biology of carcinogenesis and the cancer cell phenotype. This, in turn, will hopefully enable the development of rationally-designed drugs that target molecular aberrancies in signal transduction pathways specific to gastric cancer. For example, overexpression of members of the human epidermal growth factor receptor family has been reported in gastric cancer, with emerging data showing that EGFR and human epidermal growth factor receptor 2 (HER2) overexpression correlate with poor prognosis. As a result, several monoclonal antibodies and kinase inhibitors are undergoing clinical evaluation in this area, and findings from the Phase 3 ToGA trial recently showed that trastuzumab (in combination with chemotherapy) was associated with a survival benefit in HER2-positive patients with advanced gastric cancer.

As the efficacy of trastuzumab has been demonstrated in a patient population overexpressing the HER2 receptor, it seems logical that any benefits of an EGFR-targeted therapy may also be confined to a subset of patients overexpressing EGFR. This theory was explored yesterday when Dr Tom Samuel Waddell from the Royal Marsden Hospital, Sutton, UK, presented updated data and translational results from the REAL-3 trial, which evaluated the addition of the anti-EGFR antibody, panitumumab (P), to epirubicin (E), oxaliplatin (O) and capecitabine (C) in patients with advanced esophago-gastric cancer. In this trial, patients with untreated, metastatic or locally advanced esophago-gastric cancer were randomized to EOC or modified-dose EOC + P. Dr Waddell explained that although the addition of panitumumab did not provide an improvement in OS or PSF in the overall study population, OS was significantly improved in patients who experienced grade 1–3 rash (77%, n=209), a known surrogate marker of response to EGFR inhibitors, compared with those without rash (23%, n=63): median OS was 10.2 months versus 4.3 months (p<0.001), and similar improvements were also seen in terms of ORR and PFS. In contrast, the presence of KRAS or PIK3CA mutation had negative prognostic value by multivariate analysis.

Just before you go....

Before dashing off remember to collect your CME certificate of attendance and CME credits.

A certificate of attendance is available to all delegates and can be printed at the internet kiosks in the main entrance. Just log in with your last name and badge ID number, and you'll be asked to complete the Congress evaluation questionnaire before receiving your certificate.

As an ESMO member you can avoid the queues by printing your certificate from the comfort of the Membership Lounge.

The ESMO 2012 Program has been designated for a maximum of 24 European CME credits (ECMECs), participants can earn a maximum of 6 credits per day, 3 for a half day, along with 25 ESMO-MORA category 1 points. For US delegates – the American Medical Association (AMA) has awarded the program Physician's Recognition Award category 1 credits.

All isn't lost if you don't have time to complete the questionnaire onsite – you'll have until 2 November to print out your certificate online from the ESMO website.

Fellowship Awards

The characterization of lung cancer: Choose your targets!

Although lung cancer has long remained the leading cause of cancer-related deaths worldwide, there may be a glimmer of hope for the future treatment of this deadly disease.

Professor Jean-Charles Soria from the Institut Gustave Roussy gave a compelling keynote lecture at yesterday's lung cancer session, where he explained how the approach to treating non-small-cell lung cancer (NSCLC) is currently being revisited based on the emergence of molecular portraits that have allowed for the identification of new molecular subtypes.

In his talk, Professor Soria explained that, beyond the now classical oncogene drivers represented by EGFR mutations and ALK translocations, many other molecular abnormalities have been reported in various genes, including PI3K, PTEN, AKT1, MDM2, APC, HER2, KDR, MET, CTNNB1, ATM, BRAF, RET and ROS. Although the full implications of each of these molecular abnormalities are not yet understood, for many of these, corresponding molecular targeted therapies are being developed.

Professor Soria went on to provide a review of key genetic alterations identified in NSCLC as well as an update on the clinical development of agents designed to target these abnormalities. For example, the latest evidence suggests that FGFR1 amplification is present in 5% of adenocarcinomas and in 20% of squamous-cell carcinomas. Currently, there are several FGFR-targeted agents (BJG398, AZD4547, JNJ-42756493, TKI258 and EOS3810), some of which may serve as potential drugs for patients with NSCLC and FGFR1 amplification in the future.

Molecular alteration	Frequency in Adenocarcinoma	Frequency in Squamous cell carcinoma	Potential Drugs
EGFR mutation	10 40%	2 5%	Gefitinib, erlotinib, afatinib, PF-00299804
EML4-ALK translocation	5 7%	Rare	Crizotinib, ASP3026, AP26113, CH5424802 LDK-378, HSP90 inhibitors
ROS translocation	2%	Rare	Crizotinib, ASP3026, AP26113, CH5424802 LDK-378, HSP90 inhibitors
RET translocation	2%	Rare	Vandetanib
HER2 mutation or amplification	2%, 6%	Rare, 2%	Trastuzumab, PF-00299804, Afatinib
PI3K mutation or amplification	5%, <10%	5%, <10%	GDC-0941, GDC 0980, XL-147, XL-765, BEZ-235, BKM120, BYL 719, PF-05212384
MET amplification	<10%	<10%	XL184, ARQ917, MetMab
RAS mutation RAF mutation	10 30%, 3%	5%, 2%	Sorafenib, AZD6244; GSK1120212; AS703026, RO4987655, MEK162
FGFR1 amplification	5%	20%	BJG398, AZD4547, TKI258, EOS 3810

Despite the promising data collected so far, Professor Soria emphasized the need to move towards an integrated approach to characterizing lung cancer, incorporating clonal architecture, new targets and resistance mechanisms, DNA repair complexity and related biomarkers, and biomarkers of activity for immunotherapies, in order to further stratify patients where no key driver has been identified. "Characterization of the genomic changes that drive an individual patient's disease is now critical to inform rationally targeted therapies and treatment planning for patients with NSCLC", he concluded.

Data fails to support routine use of doxorubicin and ifosfamide combination for soft tissue sarcoma

In the oncology community, it is common knowledge that sarcomas are rare tumours. Indeed, their overall incidence is approximately five per 100,000 people every year, making the feasibility of conducting statistically powered clinical trials a significant challenge. Adding to this is the fact that sarcomas are made up of several different histological types, so conducting a clinical trial in one specific histological type of sarcoma is virtually impossible!

Professor Winette van der Graaf

Considering our current knowledge, survival data from the EORTC Soft Tissue and Bone Sarcoma Group presented at yesterday's second Presidential Symposium was received with great interest. This was a randomized phase 3 trial (EORTC 62012), designed to evaluate single agent doxorubicin versus doxorubicin plus ifosfamide as first-line chemotherapy in patients with advanced or metastatic soft tissue sarcoma. Professor Winette van der Graaf from Nijmegen, The Netherlands, explained that "the study was initiated to address concerns that previous studies comparing these agents in soft tissue sarcomas had used suboptimal doses of ifosfamide", adding that "non-randomized data had suggested that a higher dose of this drug could increase response rate and progression-free survival".

In this trial, 455 patients aged 18–60 years with locally advanced or metastatic, grade 2 or 3 soft tissue sarcoma, were randomized to receive either doxorubicin (75 mg/m^2, bolus or 72h IC) alone or in combination with ifosfamide (10 g/m^2 over 4 days with mesna and pegfilgrastim) as first-line treatment. Randomization was stratified by performance status, age, presence or absence of liver metastases and histological grade. Patients were treated every 3 weeks until either disease progression or a maximum of 6 cycles had been administered. Professor van der Graaf advised that after a median follow-up of 56 months, no significant difference in overall survival (OS) was seen between the treatment arms. Median OS was 14.3 months with doxorubicin/ifosfamide and 12.8 months with doxorubicin (HR 0.83; 95% CI: 0.67–1.03, p=0.076), and OS at 1 year was 60% with doxorubicin/ifosfamide and 51% with doxorubicin. However, doxorubicin/ifosfamide was associated with a longer progression-free survival (median: 7.4 months versus 4.6 months; HR 0.74; 95% CI: 0.60–0.90, p=0.003) and higher overall response rate (26.5% versus 13.6%) compared with doxorubicin alone, but this was at the cost of increased toxicity.

Professor van der Graaf concluded that the lack of a significant improvement in OS means that the routine use of this intensive combination of doxorubicin and ifosfamide is not supported for soft tissue sarcoma in the palliative setting – the standard treatment remains single-agent doxorubicin. However, she added that that combination therapy could be an option for selected patients aged <60 years if tumor shrinkage was critical, although the toxicity profile of this treatment combination should also be considered. "As always, the pros and cons of combination therapy should be discussed with the patient", she added.

The Challenge of Overcoming Resistances in Targeted Therapies for Melanoma

Phase 3 single-agent clinical trials have established BRAF inhibitors as a new standard of care for patients with BRAF-mutated melanoma. Therefore, attention has now turned to understanding mechanisms of resistance and exploring the scope for combination treatments.

During yesterday's Special Symposium on 'Melanoma therapy: From frustration to enthusiasm,' Dr Keith Flaherty of Massachusetts General Hospital, Boston, USA, observed that the wide variety of resistance mechanisms identified so far do not yet point to an obvious approach for developing specific targeted therapies.

Currently, various studies exploring a broad spectrum of agents in combination with BRAF inhibitors are ongoing. Combinations of BRAF inhibitors with anti-apoptotic drugs and agents targeting developmental pathways in melanoma seem to show promise, although no associated predictive biomarker has yet been validated, making it difficult to target these therapies to patients who are most likely to respond.

However, Dr Flaherty noted that in BRAF-mutant melanoma, MAPK reactivation is common, and emerging data suggest that dual inhibition of BRAF and MEK may suppress or delay resistance compared with BRAF inhibition alone. Data supporting this has been presented at ESMO 2012 by Dr Georgina Long from Westmead Hospital, Sydney, Australia.

Antivirals and chemotherapy: Managing cancer patients with hepatitis

Active hepatitis B virus (HBV) and hepatitis C virus (HCV) are highly prevalent around the world. Approximately one third of the world's population (over 2 billion people) has been infected with HBV and 350 million have chronic HBV infection. Around 150 million people have chronic HCV infection and 350,000 people die annually from HCV-related liver diseases.

According to the World Health Organization (WHO), 1 million people a year die from HBV- and HCV-related liver disease.

In the special symposium yesterday on 'Key topics in supportive care', Dr John Lubel of Eastern Health, Melbourne, Australia, presented strategies and approaches to dealing with patients infected by HBV and HCV who are undergoing chemotherapy. Different strategies are necessary for their effective treatment, he said, because the two viruses differ significantly in virology, natural history and therefore management approaches.

In chronic viral hepatitis there is equilibrium between the host's immunity and viral replication, resulting in immunosuppression that doesn't inhibit viral replication. In non-cirrhotic HCV patients, this rarely results in significant complications; HCV patients undergoing immunosuppressive therapy, such as chemotherapy, generally just require monitoring.

In contrast, patients with HBV may have significant hepatitis 'flares' following periods of immunosuppression which may lead to hepatic failure, the need for liver transplant or death in the most extreme cases. Although HBV does not kill cells, inflammation results from immune-mediated injury and therefore generally occurs following periods of maximal immunosuppression. To prevent such reactivation, Dr Lubel recommended that patients with chronic HBV take antiviral prophylaxis prior to immunosuppressive chemotherapy and remain on antivirals for a year after chemotherapy is finished.

Patients with high viral loads should take antiviral agents such as entecavir and tenofovir; these drugs have a high genetic barrier to viral resistance. Lamivudine is acceptable for patients with low or undetectable viral loads.

Dr Lubel warned that in patients who seem to have cleared their hepatitis B infection, reactivation of the virus can occur with the subsequent reappearance of surface antigen (seroreversion) followed by clinically significant HBV flares. He also noted that the risk of this seems to be particularly high for chemotherapy regimens containing the anti CD20 antibody, Rituximab. Thus, patients who cannot be closely monitored for virus reactivation through monthly HBV DNA quantification and liver function tests should also receive antiviral prophylaxis.

Dr Lubel advised that the management of HBV and HCV should be in the domain of the hepatologist. "The essential role of the oncologist is to be aware of the problem and screen appropriately", said Dr Lubel.

PARP inhibition: Promise for ovarian and endometrial cancer

Homologous recombination deficiency (HRD) is a defining characteristic of cancers in patients with germline BRCA mutations. This deficiency is exploited by poly ADP ribose polymerase (PARP) inhibitors. Offering tumor-specific synthetic lethality, PARPs provide clear clinical efficacy as single agents.

Professor Stan Kaye from the Royal Marsden Hospital, London, UK, explained to delegates yesterday that PARP inhibitors have an excellent toxicity profile. Indeed, their application has now been extended to patients not known to have germline BRCA mutations, but who suffer from platinum-sensitive, serous ovarian cancer.

Speaking in the morning symposium on emerging diagnostic and therapeutic targets in gynecological cancers, Professor Kaye noted that the PARP inhibitor, olaparib, improved progression-free survival (PFS; HR 0.35; 95% CI: 0.25–0.49, p<0.0001), but not overall survival (HR 0.94; 95% CI: 0.63–1.39, p=0.748) in a recent randomized maintenance therapy trial. It also demonstrated a PFS benefit as maintenance therapy following chemotherapy with carboplatin/paclitaxel (median PFS: 12.2 months versus 9.6 months; HR 0.51; 95% CI: 0.34–0.77, p=0.0012), but OS data are not yet mature.

Several PARP inhibitors are now in clinical development and the focus is increasingly moving to their application in germline BRCA associated disease, where their benefit is likely to be greatest. Among these, BMN-673 is a new compound and is the most potent and selective PARP inhibitor reported to date (up to 700-fold more active *in vitro* in BRCA-defective cell lines versus olaparib, with substantial increase in efficacy *in vivo* in the MX xenograft). A Phase I trial of BMN-673 is in progress and preliminary data are promising.

HRD has also been observed in endometrial cancer, Professor Kay noted, although he suggested that the phenomenon is most likely to relate to genetic instability caused by the characteristic PTEN loss seen in this disease (particularly type I) rather than BRCA dysfunction. Results from *in vitro* studies suggest that PARP inhibitors could also be beneficial for endometrial cancer therapy.

PROFFERED PAPERS, BREAST CANCER, METASTATIC MONDAY OCTOBER 1 **13:55 – 15:55 HALL A**

First results of TURANDOT Trial

Don't miss tomorrow's presentation on the 'capeciTabine and bevacizUmab Randomised Against avastiN anD taxOl Trial' (TURANDOT) trial, Professor Christoph Zielinski from the Comprehensive Cancer Centre, Vienna, Austria, will present the first efficacy results from the phase 3 study run by the Central European Cooperative Oncology Group (CECOG). The trial compared two bevacizumab containing regimens as first-line therapy for HER2 negative metastatic breast cancer.

Professor Zielinski, commented "While seeing a significantly better progression free survival and overall response rate with paclitaxel + bevacizumab regimens in this randomized controlled trial, the interim analysis shows that overall survival was most probably not compromised by the use of capecitabine + bevacizumab as compared to the other regimen. This is particularly remarkable, as overall survival and its comparison between the two study arms was the primary end point of the study."

Before you go...

pick up your copy of the ESMO Pocket Guidelines

Breast Cancer Celgene, Hall X, Booth 131
Supportive Care Grünenthal, ESMO Booth 29, Society Village
Urogenital Cancer Janssen, Hall Z, Booth 109,110
Lung Cancer Lilly Oncology, Hall Y, Booth 125
NETs & GIST Novartis Oncology, Hall X, Booth 125
Sarcoma PharmaMar, Hall X, Booth 128

Managing the costs of emerging oncology therapies

ESMO as an organization is not shying away from the current global economic crisis and is conscious of the growing need to address issues of health economics in the field of oncology. The Young Oncologist's breakfast session yesterday was a forum exploring the management and the costs of emerging therapies.

Professor Jose Martin-Moreno from the University of Valencia, Spain, told the delegates that the annual EU cost of cancer care was a staggering €124 billion each year. In addition to health care costs, he added, this figure took into account additional factors such as the loss of productivity and mortality. Research suggests that European countries are spending between 4.1% and 10.6% of health care resources on cancer care.

Across Europe, cancer spending is being limited, said Professor Martin-Moreno. The Greece-bail-out package limits health system spending to 6% of GDP, he said, and furthermore patient co-payments are being introduced on hospital care and drugs in Portugal. "The financial crisis has exacerbated social inequality, including health. Co-payments represent a 'de facto' tax on the sick. Inequity in drugs and treatment stems from differences in income, social strata and geography. These are very important challenges that need to be addressed," said Professor Martin-Moreno.

In the long run, he said, personalized medicine, offers the potential for cost savings. "But it comes with implications for large short-term investments," he cautioned.

Changes needed to be introduced in the way randomized trials are conducted.

Ms Elena Nicod, from the London School of Economics (LSE), UK, provided an overview of how Health Technology Assessments (HTAs) actually work across Europe. Differences and similarities, she said, exist in the way HTAs assessed the same drugs.

"The aim of HTA is to provide efficiency in health care resource allocation and value for money," said Ms Nicod. But while therapy X may be deemed cost-effective in country A, it may not be considered cost effective in country B because of differences in the level of evidence presented.

"We need to identify the reasons for these differences and differentiate whether they are a consequence of national-specific considerations or HTA processes. We believe that it is also important to differentiate HTA processes per therapy area."

The LSE, she said, has recently undertaken a study comparing HTA recommendations across England, Scotland, Sweden, Canada, and Australia.

"Our study showed that some therapies are more likely to be covered in some countries than others. For example, in Canada CNS drugs are more likely to be rejected than orphan drugs and cancer drugs, while in Scotland orphan drugs were more likely to be rejected than cancer and CNS drugs."

The differences, she said, are a consequence of context specific considerations, such as national preferences, HTA processes and the way evidence is collected, and interpreted.

In the question and answer session, it was suggested that in future, there might be a possibility for European countries to join forces for joint HTA.

In the final session, Professor Andy Grieve from the SVP Clinical Trials Methodology Innovation Center, Cologne, Germany, described the innovative new process of adaptive design.

"An adaptive design is one that uses accumulating data from the ongoing trial to modify aspects of the study without undermining the validity and integrity of the trial," said Professor Grieve.

Aspects of studies that could be modified, he explained, included the number of subjects, study duration, endpoint selection, treatment duration, patient population, number of treatments, number of interim analyses and hypotheses.

An adaptive design requires the trial to be conducted in several stages with access to the accumulated data. "At any stage, the data may be analyzed and next stages redesigned taking into account all available data," explained Professor Grieve.

But the long lag times of months and years that it takes to observe survival endpoints can make it difficult to introduce adaptive design. In leukemia, for example, the most commonly used response criteria in phase 2 trials of complete remission, could be used instead. "It's relatively easy to implement adaptive randomization if endpoints are available soon after treatment," explained Professor Grieve.

A good example of adaptive design, he said, was the phase 2 I-SPY-2 neoadjuvant breast cancer study in moderate to high-risk primary breast cancer.

"Here a single control arm was compared with multiple drugs, with the idea of identifying biomarker signatures that predict outcomes to drugs. When you see that one agent is doing better than the others you can bias randomization towards that drug," said Grieve.

"What's particularly interesting is the I-SPY-2 is being run by a consortium out of MD Anderson, but the drugs have been provided by 5 different Pharma companies. It shows that the way forward in future, in order to reduce the cost of trials, we should organize more such collaborations," said Professor Greive.

At the end of the session audience questions included whether a special QALY system should be introduced for cancer drugs.

Furthermore, in addition to the cost of the drugs, people felt there was also a need to assess the cost of the condition to society. "With the new targeted agents we also need to be able to take into consideration factors such as whether patients can stay in employment. There is a real need to develop novel HTA methodologies because at present they're very clunky," said Professor Gore.

Commenting on the Forum, Professor Jean-Pierre Armand, from the Institute Gustave Roussy, Villejuif, France, said, "This session really introduced young doctors to the reality of practicing oncology in Europe. They will see clearly that across different countries they don't have access to the same drugs at the same time for their patients,"

In countries like Lithuania, he said, just €35 per head of the population per year is provided for cancer, whereas in countries like Germany and France provide €150 per head of the population per year.

One of the reasons for the high cost of drugs, added Professor Armand, has been the failure of drugs to get through phase 3 trials. "We need to be intelligent and make sure that we're not running huge phase 3 trials when we have early indications that drugs may not be effective, and also not running long-lasting trials when we know that the drug works. This was particularly the case with the crizotinib data presented for ALK-positive lung cancers at ESMO 2012," he said.

Is there a role for bevacizumab in GBM?

Bevacizumab is used to treat several types of cancer, and most recently has been approved for the treatment of recurrent glioblastoma (GBM) in the United States, Switzerland and a few other countries. However, support for this agent in GBM is not unanimous since the same data that led to its accelerated approval in the United States was rejected by the European Medicines Agency (EMA). Further research to elucidate the true benefits of bevacizumab in GBM is therefore needed and several clinical trials are in progress.

Yesterday, findings from 2 clinical trials evaluating bevacizumab in GBM were presented as part of the proffered papers session in CNS tumors. In the first, Professor Bruno Chauffert from Oncolopole, Centre Hospitalier Universitarie, Amiens, France, described findings from a randomized Phase 2 trial of bevacizumab + irinotecan as neoadjuvant and adjuvant therapy added to temozolomide-based chemoradiation versus temozolomide-based chemoradiation alone in 120 patients with unresectable de novo GBM. Despite a trend towards improved progression-free survival (PFS) with the addition of bevacizumab + irinotecan (PFS at 6 months: 65% versus 41%; PFS at 12 months: PFS 31% versus 18%), there was no difference in overall survival (OS) between the treatment groups (OS at 6 months: 75% versus 72%; OS at 12 months: 48% versus 50%).

Given these data, it is worth noting that Roche recently announced that a Phase 3 trial of bevacizumab as adjuvant therapy to temozolomide-based chemoradiation in patients with GBM met its co-primary endpoint of improving PFS. However, it is not yet known whether this PFS benefit will translate into a survival advantage since OS data from this trial will not be available until 2013.

Following Professor Chauffert's presentation, Dr Emeline Tabouret from AP-HM, Timone Hospital, Marseille, France, presented data from her institute which suggest that matrix metalloproteinase 2 (MMP2) may be a predictive marker of response to bevacizumab in patients with high grade glioma. In a cohort of 26 patients treated with bevacizumab, high baseline MMP2 was associated with an 83.3% probability of response compared with only 15.4% in patients with low baseline MMP2 (p=0.001). MMP2 also correlated with both PFS (p=0.007) and OS (p=0.005) according to multivariate analysis. Thus, despite the small sample size, MMP2 level appeared to be a promising candidate for predicting bevacizumab activity.

T-DM1 delivers survival benefits in metastatic breast cancer

Trastuzumab Emtansine (T-DM1) produced significant benefits in overall survival (OS) and progression-free survival (PFS) compared to capecitabine and lapatinib (Cap + Lap) in HER2-positive locally advanced metastatic breast cancer patients, reported the phase 3 EMILIA study yesterday afternoon. The study also demonstrated significant improvements in the side effect profile for T-DM1.

"T-DM1 should offer an important therapeutic option in the treatment of HER2-positive metastatic breast cancer," said study presenter Dr Sunil Verma, from Sunnybrook Odette Center, Toronto, Canada.

T-DM1 is an antibody-drug conjugate incorporating the HER2-targeted anti-tumor properties of trastuzumab together with the cytotoxic activity of the microtubule inhibitor DM1, conjugated by a stable linker.

In the study patients with confirmed HER2-positive metastatic breast cancer and prior treatment with trastuzumab and a taxane were randomized to receive T-DM1 at a dose of 3.6 mg/kg IV every 3 weeks (n=495) or a combination of cap 1000 mg/m^2 bid on days 1–14 every 3 weeks and lap 1250 mg orally once daily on days 1–21 (n=496). Both treatment arms, added Professor Verma, were well balanced.

Results showed the median OS was 30.9 months for T-DM1 versus 25.1 months for Cap + Lap (HR=0.682, 95% CI, 0.55–0.85; p=0.0006). PFS by independent review was 9.6 months for T-DM1 versus 6.4 months for Cap + Lap (HR=0.60, 95% CI, 0.55–0.77, p<0.0001).

Adverse events leading to treatment discontinuation occurred in 10.7% of patients receiving Cap + Lap compared to 5.9% receiving T-DM1. Adverse events greater that grade 3 included diarrhea that occurred in 20.7% of patients receiving Cap + Lap compared to 1.6% receiving T-DM1; hand-foot syndrome that occurred in 16.4% receiving Cap + Lap compared to 0% in patients receiving T-DM1; and vomiting occurred in 4.5% receiving Cap + Lap compared to 0.8% receiving Cap + Lap.

24% of the audience had consulted ESMO Cinical Practice Guidelines more than 10 times in the past year, and 29% less than 10 times

YO activities a fantastic success

The Young Oncologists track at ESMO 2012 proved an outstanding success with standing room only in many of the seven dynamic sessions. The sessions were so packed that in many cases delegates were forced to sit on the floor.

"What was particularly noteworthy this year was how many of the young oncologists came from out of Europe," said Dr Erika Martinelli from Seconda Università di Napoli, Italy.

First up on Friday afternoon was the 'Master class' on clinical trial design, with presenters reviewing issues around trial design in the era of targeted agents and biomarkers.

The Vesalius talk, held later on Friday, explored challenges in career development.

"What was really striking from the comments was that young oncologists throughout the world face the same challenges in combining their clinical and research work," said Dr Martinelli.

At the end of the session Professor Martin Gore from the Royal Marsden Hospital, London, UK, told them, that the most important thing they could do for their patients was to establish an emotional relationship. "If you care enough you'll go one step further and check the literature and ask your boss," he said.

Breakfast sessions included how to make an impact on clinical research in the early stages of your career, how to plan and conduct a successful research fellowship, and how to write a good review article. "The breakfast sessions provided important lessons that delegates could take on board to develop their academic careers," said Dr Matthias Preusser, from the Comprehensive Cancer Center, Vienna, Austria. "They proved to be a really friendly environment with everyone feeling relaxed enough to ask lots of questions."

The Health Economics Forum yesterday proved particularly thought provoking, showing young oncologists the evolving economic landscape that they will have to work with.

But it wasn't all hard work. New for ESMO 2012 was the Moonlight Network, giving young oncologists the opportunity to mingle in a relaxed environment.

Finally, congratulations to our newly appointed YOC chair as of January 2013, Dr Rafaelle Califarno from The Christie NHS Foundation Trust, Manchester.

TODAY'S EDUCATIONAL SESSIONS

Decision making & management of glioma: Practical considerations (Repetition)
09:15 – 10:45 Hall H

Diagnosis and management issues in lymphoma (Repetition)
11:00 – 12:30 Hall K

Towards integrated management of patients with carcinoma of an unknown primary site (CUP) (Repetition)
09:15 – 10:45 Hall G

Updates in supportive and palliative care (Repetition)
11:00 – 12:30 Hall G

ESMO would like to thank our Congress Daily Editorial Team:
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tmc STRATEGIC COMMUNICATIONS

Clinically Actionable Biomarkers in Pancreatic Cancer Therapy

Drug therapy for pancreatic ductal adenocarcinoma remains minimally effective with significant barriers to developing treatments.

In the Special Symposium 'From biology to treatment in advanced pancreatic cancer', Professor Margaret Tempero from the University of California, San Francisco (UCSF), California, USA, said that clinical trials are limited due to the unusual aggressiveness of the malignancy. Tissue samples are also rare because so few patients receive surgical interventions.

Professor Tempero highlighted studies demonstrating the importance of clinically actionable biomarkers. The role of biomarkers is to predict prognosis, response to treatments and provide a surrogate of therapeutic benefit, she said.

So far, researchers have identified distinct metastatic patterns, which may be governed by early genetic aberrations. There also appear to be specific genetic subclasses of this adenocarcinoma that, when evaluated in human cell lines, track to chemotherapy opening the way for more targeted, optimized treatment regimens.

The biomarker hENT1 has already been confirmed as a predictive biomarker for treatment outcome with gemcitabine (RTOG 9704 trial). Approximately 40% of pancreatic cancer patients test positive for hENT1; with ongoing studies now looking to validate this biomarker to pre-select patients suitable for gemcitabine therapy.

Among other research, she considered, whether candidate biomarker expression of S100A2 calcium binding protein might predict responses to pancreatectomy.

Given the growing importance of genetic profiling, Professor Tempero, called for a collaborative effort to building biorepositories from primary and secondary tumor sites, with associated germline DNA.

Before dashing off remember to collect your CME certificates of attendance and CME credits


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