Collaboration: A Spanish perspective

Sitting in the heart of Spain, Madrid is Europe’s third largest city. It is a place to take in sculpture and art, sample the famous cocido madrileño and enjoy the cosmopolitan lifestyle.

Slightly away from the typical tourist routes around royal palaces and museums you find the Hospital Universitario de La Princesa, a state of the art hospital that is characterised by the wealth of medical science in its laboratories and clinics.

Dr Ramon Colomer, Head of the Medical Oncology Division, is proud of the role that Spanish research institutions play today in cancer research: “It is a privilege to work in a field where research makes such an impact for patients. Every day here in the hospital or when I speak to colleagues elsewhere in Spain I am reminded that our research is making a real difference to people’s lives on a global scale.”

It was Dr Colomer’s close links with ESMO, Madrid and the Spanish Society of Medical Oncology (SEOM) that made him the natural choice for the position of ESMO 2014 Local Chair and a key person for a successful congress in Madrid.

Now a senior figure in Spanish oncology, Dr Colomer found early inspiration in his successful career in the US. “As a breast cancer researcher in Bethesda and Georgetown, I witnessed the development of the monoclonal antibody trastuzumab,” he explains. “To see the antibody developed from the laboratory bench to the patient’s bedside was highly gratifying.”

Seeing how patients benefited from this therapeutic development helped to motivate Dr Colomer and oncology research became his passion. In 1991 he became the first Spanish recipient of a Young Investigator Award from the American Society of Clinical Oncology (ASCO).

As his career developed, Dr Colomer says he became increasingly aware that collaboration was vitally important for research to reach the clinic where it could make a real difference. In 2007 he became SEOM President, spending two years fostering networking among Spanish oncologists, raising the profile of Spain as a strong player in cancer research and authoring SEOM clinical guidelines. “Over the past decade we have seen tremendous progress in research across Spain,” he says. “We have shared research expertise, built up a global standing and, on the clinical side, worked tirelessly to ensure that Spain delivers the very best evidence-based cancer care to the patients.”

Dr Colomer’s group has recently published findings from a phase I clinical trial of the novel selective agent nintedanib plus paclitaxel in early HER2-negative breast cancer. “The exploration of new precision medicine drugs in cancer is my priority and this study is an example of the innovative approach to designing clinical trials,” he explained.

Tomorrow you can hear an analysis of expression patterns of PD-L1 in malignant pleurisythromas (Monday, 14.00 – 15.30, Seville, Abstract 15660). Dr Colomer today will discuss how this local study could support key advances in novel therapeutic development.

More Spanish insights. Do financial interests bias authors of treatment guidelines? Find out the results of a Spanish study at this afternoon’s Proffered Paper Session on Public Health and Health Economics (15.45 – 17.30, Pamplona, Abstract 13850).

The Proffered Paper Sessions at ESMO 2014 offer an excellent insight into Spain’s world-class collaborative research. Yesterday, for example, in a Proffered Paper Session on Gastrointestinal Tumors, Colorectal, clinicians from the Spanish Cooperative Group for the Treatment of Digestive Tumors presented the results of MACRO-2, a phase II trial of first-line treatment with mFOLFOX plus cetuximab to treat gastrointestinal tumours. During the afternoon Proffered Paper Session on CNS Tumours, Dr Carmen Balafó from the Hospital Germans Trias i Pujol, Barcelona, discussed data on MGMT methylation in tumour tissue and blood samples collected as part of a multicentre study across Spain comparing temozolomide (TMZ) versus TMZ plus bevacizumab, in glioblastoma.

Combined strength

SEOM has a strong partnership with ESMO, an in 2012, the two organisations signed a joint membership agreement to promote scientific activities and policy at a national and international level.

Discover the latest findings – over 60 posters from Spanish oncologists presented during our Poster Sessions today and tomorrow (12.45 – 13.45, poster area)

SEOM sees collaboration as a key to effective oncology research and its efficient translation to the clinic. SEOM President, Dr Pilar Garrido from Hospital Ramon y Cajal, Madrid, Spain, who will co-chair the ESMO-SEOM Joint Symposium (Monday, 14.15 – 15.45, Granada), explains: “In the era of precision medicine, the new exciting possibilities of translational research become more evident every day. At the same time, new challenges need to be faced, particularly regarding the implementation of these cutting edge advances in the clinic. I believe that the national medical societies and research cooperative groups have an important role in leading this.”

SEOM has 2000 members and combines the efforts of 17 multidisciplinary research cooperative groups.

“We are also fully committed to quality and to achieving targets,” says Dr Garrido. “The Society is involved in a variety of initiatives, including the common Biomarkers Platform in collaboration with the Spanish Society of Pathology, a common database to register the efficacy of treatment in collaboration with our Public Health authorities and a comparative analysis of different Medical Oncology Units across Spain. Through these initiatives we hope to achieve an accurate framework that will enable us to move forward to a real translational precision medicine approach for all our patients.”

How an understanding of melanoma development is changing the clinical landscape of its treatment. Malignant melanoma is among the most serious skin cancers and its incidence has risen steadily in the past few decades.

Although outcomes are good for patients diagnosed with early stage disease, more advanced stage melanoma, including metastatic melanoma has a particularly poor prognosis. Sadly, while significant advances have been made in the treatment of other cancers, the same cannot be said for metastatic melanoma, and survival among patients is largely unchanged over the past 25 years. However, in recent years, we have seen advances in our understanding of the mechanisms involved in the development of melanoma and the involvement of the immune system in this process. This greater understanding has led to the identification of specific therapeutic targets for melanoma.

Marked improvements in outcomes have been seen over the last few years with the introduction of new treatments: ipilimumab, a human anti-CTLA-4 monoclonal antibody; trametinib, an inhibitor of the mitogen-activated protein kinase enzymes MEK1 and MEK2; and BRAF inhibitors, such as vemurafenib. These treatments have given rise to enhanced outcomes, thereby expanding the options for patients. However, despite the clinical benefits of these newer agents, they may not be suitable for all patients. It is clear that further treatment options are needed.

The profile of melanoma research is such that tomorrow’s Presidential Symposium (Monday 16.00 – 17.20, Madrid) is dedicated to research in this tumour type. Three late-breaking abstracts of data from phase III trials, and with practice-changing potential, will be presented. Prof Jeffrey Weber from the H. Lee Moffitt Cancer Center Research Institute, Tampa, FL, USA will present results investigating the immune checkpoint inhibitor antibody, nivolumab, in patients with previously treated advanced melanoma, including those with ipilimumab-refractory disease (LB45_PR). Particularly exciting, I think, will be results from two studies comparing the use of first-line combined MEK and BRAF inhibition with BRAF inhibition alone in patients with tumours harbouring the BRAFV600E mutation. Results will be presented from two studies: one, from Dr Grant McArthur from the Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia investigating the addition of cobimetinib to vemurafenib (LB45_PR); and the other, reported by Dr Caroline Robert from the Institut Gustave Roussy, Villejuif, France comparing dabrafenib plus trametinib with vemurafenib (LB46_PR).

The focus in recent years on new molecular targets that modify the development of melanoma has given rise to new and exciting advances that may pave the way for much-needed novel therapies. Yesterday, the results from studies of novel agents and combinations were revealed in a Proffered Paper Session. Results of studies presented these therapies.”

Survival and quality of life outcomes will also be presented for nivolumab (1088PD) and a dabrafenib/trametinib combination (1091PD). Of particular interest will be results with the MEK inhibitor, binimetinib (LB3A5), in patients with NRAS-mutated melanoma, a poorly studied group of patients.

I believe that the treatment of melanoma, particularly advanced disease, has come a long way in recent years. Focused research has been invaluable for increasing our understanding of disease development, which in turn is reaping rewards in terms of expanding the novel, targeted therapies available to us. Combining agents with potentially synergistic qualities, either sequentially or concomitantly, offers even greater possibilities for enhancing the benefit of these therapies. Results of studies presented at ESMO 2014 will help us to assess the clinical value of these new approaches for melanoma and may even have implications for other tumour types. The future treatment of patients with melanoma is looking promising.

I would like to thank the Editorial Team of Associate Editors Markus Joerger, Fioriana Morgillo and Associate Guest Editor Giuseppe Curigliano for their assistance in producing the Congress Daily newspapers.
What's new in the management of CNS tumours?

Compliance with the NovoTTF-100A was high and was positively correlated with improved survival

Activity data of single-agent bevacizumab compared with fotemustine in recurrent glioblastoma were presented by Dr Alba Brandes from Azienda USL di Bologna Ospedale Bellaria, Bologna, Italy. Patients were randomised 2:1 to bevacizumab alone (3 mg/kg every 2 weeks, n=32) or fotemustine (75 mg/m² days 1, 8, 15, n=32), followed by fotemustine maintenance (100 mg/m² every 3 weeks) in patients with recurrent glioblastoma (AURAEG: ML2573B). There were fewer reports of grade 3–4 neutropenia/ trombocytopenia with bevacizumab than fotemustine, but a higher incidence of other complications, including intestinal perforation and cerebral ischaemia/hemorrhage. OS was similar with bevacizumab and fotemustine (median OS 7.3 and 8.7 months, respectively), and 6-month OS rates of 62.1% and 73.3%, respectively. A favourable OS effect of bevacizumab over fotemustine was seen in patients ≤55 years of age (hazard ratio [HR] 0.5; p<0.05). Bevacizumab did not improve outcome in relapsed glioblastoma compared with fotemustine.

The identification of predictive biomarkers is of particular interest in patients with glioblastoma. Tumour tissue MGMT methylation status is predictive of response to the alkylating agent TMZ. The potential utility of MGMT methylation in serum to predict response in unresectable disease was discussed by Dr Carmen Balana from Hospital Germans Trias i Pujol, Barcelona, Spain. In the multivariate, randomised GENOM 009 trial, the addition of bevacizumab to TMZ (n=45) significantly improved overall response rate (p=0.001) compared with TMZ alone (n=44), but improvement in progression-free survival (PFS) and OS did not reach statistical significance. MGMT methylation was found in 34 of 63 tissue samples (54%) and 11 of 74 serum samples (14.9%). Concordance of tumour tissue versus serum MGMT methylation status was low among 40 patients with samples available. While tissue methylation was associated with significantly prolonged PFS (p=0.01) and OS (p<0.001), serum methylation status was not. These results strongly suggest that the assessment of serum MGMT methylation status is impaired by contamination of DNA with circulating lymphocytes.

Serum MGMT methylation status does not predict outcome to temozolomide in glioblastoma

In gliomas, 1p19q co-deletion is associated with increased sensitivity to standard radiotherapy and/or chemotherapy, although its prognostic value is rather weak. Dr Mairead McNamara from Princess Margaret Hospital, Toronto, ON, Canada, presented results supporting 1p19q co-deletion as a predictive marker in lower-grade glioma patients receiving TMZ. In a retrospective review of data from 106 patients with anaplastic oligodendroglioma (AOD), anaplastic oligoastrocytoma (AOA), oligodenroglioma (OD) or oligoastrocytoma (OA), 1p19q status was codelleted/incompletely codelleted in 62%/25% of patients. Nearly half (49%) of patients received upfront TMZ alone. The median time to radiotherapy was 41.2 months in 9 patients with codelleted/incompletely deleted AOD receiving upfront TMZ alone, compared with 34.7 months for all 47 patients with AOD. The 5-year OS rate for 32 patients with AOD and 1p19q codelletion/incomplete deletion who received upfront TMZ alone was 95.5%. Performance status (0 versus 1) and 1p19q codelletion/ incomplete deletion (versus 1p or 19q loss alone) (HR, 0.36; p<0.005) were the only significant predictors for a favourable PFS within multivariate testing. These data support single-agent upfront TMZ in patients with 1p19q codelleted and partially deleted gliomas (non GBM).

1p19q codelletion/incomplete deletion is a strong predictor for upfront temozolomide in gliomas patients

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, Poster area.

Madrid 3 for 2 Members offer!

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

ESMO Members’ Services Centre

For all educational products and services. 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 inbetween sessions and simply recharge your batteries.
The hedgehog pathway consists of a number of critical traits evolution highly conserved components. Among those are the patched (PTCH) and smoothened (SMO) proteins, which are each encoded by multiple genes. PTCH is a membrane-associated receptor protein that actively suppresses the pathway by inhibiting SMO. It is the receptor for the hedgehog proteins. Mammalian hedgehog genes are split into three families: Sonic, Indian, and Desert, and Sonic is the most studied ligand for PTCH. Binding of a hedgehog ligand to PTCH results in the de-inhibition of SMO, leading to activation of the pathway. Abnormal activation of the hedgehog pathway is associated with the development of cancers, with the type of activation being linked to particular cancer types. For example, hedgehog-independent signaling driven via inactivating mutations, e.g., ligand receptor, PTCH, or activating mutations in SMO, is associated with basal cell carcinoma (BCC) and medulloblastomas.

The hedgehog pathway is a key regulator of differentiation and organ formation during embryonic development. Although it also has a role in the maintenance of some adult tissues (e.g., proliferating cell populations), deregulation of the hedgehog pathway in adults is associated with cancer development. Hedgehog pathway mutations are associated with basal cell carcinoma (BCC) and medulloblastomas.

Hedgehog (Hh); Sonic Hedgehog (Shh) signaling is activated in both autocrine and paracrine pathways. Activation of Hh signaling in a paracrine manner has been documented in various cancers, including breast, prostate, and ovarian cancers. In autocrine signaling, the hedgehog ligand binds to its receptor, PTCH, on the cell surface, leading to the activation of SMO. SMO then transduces the signal into the cell, leading to the activation of downstream targets, such as GLI transcription factors.

Shh and Sonic Hedgehog (Shh) are the major ligands of the hedgehog signaling pathway. In the absence of Shh, the patched (PTCH) receptor is phosphorylated and binds to Smoothened (SMO), resulting in the inhibition of downstream signaling pathways. When Shh is present, PTCH is no longer able to bind to SMO, allowing SMO to dimerize and translocate to the nucleus, where it acts as a transcription factor, promoting the expression of target genes.

In the context of cancer, the hedgehog pathway plays a crucial role in the proliferation, differentiation, and survival of cancer cells. In the early stages of malignant transformation, the hedgehog pathway is often activated, contributing to the development of cancer.

**Pathway of the day: Hedgehog**

**Translational research: The ESMO Award**

Professor Rolf A. Stahel, Professor Carsten Bokemeyer, and Dr Josep Tabernero.

"It is truly a great honour for me to receive the ESMO Award"

Said Professor Bokemeyer.

"I feel at home in this society, which has been for me the leader for many structural, educational and scientific developments in oncology throughout Europe for many years."

**Rolapitant and rivaroxaban: New data on supportive care**

The growing range of anticancer therapies has enhanced clinical outcomes and improved prognoses for many patients. However, therapy-induced toxicities and disorders linked to the cancer continue to have a detrimental impact. Notably, nausea and vomiting are distressing side effects of chemotherapy, with a particularly high incidence with platinum-based chemotherapy, while cancer increases the risk of venous thromboembolism (VTE). Yesterday’s Proffered Paper Session on Supportive and Palliative Care included two late-breaking studies. The recommended dose for expansion was sonidegib 400 mg/buparlisib 80 mg. Further investigation of this combination will follow.

**Supportive and palliative care**

Rolapitant significantly reduced cisplatin-induced nausea. Rolapitant had a higher complete response rate (defined as no emesis or rescue medication use) than placebo in the delayed phase, defined as >24–120 hours post-chemotherapy (72.5% vs 58.6%; p=0.001), the acute phase (83.7% vs 73.7%; p=0.005) and overall (70.1% vs 56.5%; p=0.001). Treatment-emergent toxicities were generally related to the underlying cancer or chemotherapy.

**Rolapitant significantly reduced cisplatin-induced nausea**

Rivaroxaban, an oral inhibitor of activated factor Xa, was no better than enoxaparin/vitamin K antagonist (VKA) in reducing recurrent VTE in patients with active cancer or a history of cancer, according to Dr Martin Prins from Maastricht University Medical Center, The Netherlands. However, the data from 8,282 cancer patients in two phase III studies did show that rivaroxaban significantly reduced the risk of major bleeding in patients with active cancer compared with VKA (hazard ratio [HR] 0.42; 95% confidence interval [CI] 0.18–0.99, although there was no difference in patients with a history of cancer (HR 0.23; 95% CI 0.03–2.06).
The promise of tumour-infiltrating lymphocytes for cancer treatment and as prognostic/predictive indicators

**Immunotherapy of cancer**

Solid tumours are made up of a variety of components, including malignant cells and endothelial, structural and immune cells. Cancer cells are able to shape the microenvironment to satisfy their own metabolic and immunological needs.

In opposition to this, tumour-infiltrating lymphocytes (TILs) are recruited into the tumour in an attempt to destroy cancer cells. Patients may obtain the most benefit from some given treatments according to the expression of TILs (e.g. chemotherapy and/or trastuzumab in breast cancer). Evidence is also accumulating to show that the quantity of TILs at diagnosis is associated with prognosis. TILs from a patient can be manipulated to be used as treatment for that patient's cancer.

**Low-dose interleukin-2 is feasible with TILs in the treatment of patients with metastatic melanoma**

Adaptive cell therapy (ACT) with TILs is an effective strategy for the treatment of metastatic melanoma. The technique involves the generation of TILs from a patient’s melanoma biopsy and the rapid expansion in an interleukin-2 (IL-2)-containing medium of lymphocytes displaying high anti-tumour activity. The TILs are subsequently reintroduced into the same patient following lymphodepletion and in the presence of high-dose IL-2. Despite having been described over a decade ago, ACT with TILs using lymphodepletion has not been as widely adopted as might be expected given its apparent efficacy. A contributing factor to this may be the toxicity associated with high-dose IL-2 which, although generally transient, can be severe. In yesterday’s Proffered Paper Session on Immunotherapy of Cancer, Dr Rike Andersen from Herlev Hospital, Denmark, reported the results from a phase II trial investigating the use of an attenuated regimen of low-dose IL-2 in patients receiving TILs for metastatic melanoma. Among the first 20 patients, toxicity was much lower than could be expected with high-dose IL-2 and there were 2 complete and 7 partial responses, 2 of which persisted beyond 2 years (overall response rate was 45%). Importantly, ACT with TILs was associated with the induction and persistence in peripheral blood of T cells with in vitro activity against melanoma cells. These results demonstrate that the use of a lower dose of IL-2 in the context of ACT with TILs is well tolerated and clinically effective.

**Low-dose IL-2-associated TILs infusion was associated with good clinical activity and tolerability**

The future of TILs therapy will be expanded by mapping the mutational sequencing of specific genes supposed to be oncogenes in human cancers to determine if the immune system can mount a T helper 1 (Th1) cell response against the mutation expressed by an epithelial cancer. Given that a major hurdle for the success of immunotherapies is the apparent low frequency of tumour-reactive T cells, the strategies reported here could be used to generate a T cell product that is highly enriched in mutation-reactive T cells for use in ACT. The ability to immunologically target unique mutations in cancers can potentially extend highly personalised immunotherapies to patients with solid tumours.

**The prognostic and predictive potential of TILs in breast cancer**

Data from large clinical studies in several types of cancer have demonstrated that marked infiltration of tumours by specific immune cell populations, including (but not limited to) CD8+ cytotoxic T lymphocytes, Th1 and Th17 CD4+ T cells, natural killer cells, dendritic cells and M1 macrophages, is an independent indicator of good prognosis. On the other hand, high levels of intra-tumoural CD4+CD25+Foxp3+ regulatory T cells, Th2 cells, CD4+ T cells, myeloid-derived suppressor cells, M2 macrophages and neutrophils have frequently been associated with a poor prognosis.

A wealth of data has been produced on the genes and proteins associated with the immune system (immunome) over the last few years. A number of issues remain to be addressed:

- Validation of whether TILs are prognostic or predictive in HER2-positive breast cancer, preferably in a large population set with an appropriate follow-up time
- Validation of immune genomic signatures that may be predictive and prognostic in patients with TNBC and HER2-positive disease
- Development and incorporation of an immunoscore into the traditional classification system

Enhancing antitumour immune response with checkpoint inhibitor therapy

**Immunotherapy of cancer**

Novel immunotherapy agents targeting specific regulatory checkpoints in the immune system offer potential benefits across a number of tumour types, such as breast cancer, melanoma, non-small-cell lung cancer, bladder cancer and renal cell carcinoma (RCC). Their efficacy comes from enhancing the endogenous antitumour immune response. Targets include the PD-1 receptor and its ligand, PD-L1, which help the tumour to evade the immune system.

Promising results from a phase |b study combining an anti-PD-1 monoclonal antibody (MPDL3280A) and the vascular endothelial growth factor inhibitor bevacizumab, with or without chemotherapy (FOLFOX), were reported yesterday by Dr Christopher Lieu from the University of Colorado Cancer Center, Aurora, CO, USA, in a Proffered Paper Session on the Immunotherapy of Cancer. Sixty-two patients with locally advanced or metastatic solid tumours were treated. Grade 3–4 adverse events included abdominal pain, hyperbilirubinaemia, pneumonia, tumour pain, neutropenia and diarrhoea. RESIST responses were reported in 3 patients (with colorectal cancer [CRC], melanoma and breast cancer) who received MPDL3280A plus bevacizumab and 1 patient (10 with CRC and 1 with breast cancer) who received MPDL3280A plus bevacizumab and FOLFOX. One patient with RCC in the FOLFOX group had a complete response. Dr Lieu made the point that the combination of MPDL3280A and bevacizumab, with or without chemotherapy, usually displayed good tolerability and that future studies should assess the clinical activity of such combinations against standard treatment.

Reference

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<td>Preplanned analysis of molecular subtypes</td>
<td>Prognostic impact of TNBC (n=134)HR: 0.77 (0.81–0.98) Predictive value for trastuzumab efficacy: p=0.02</td>
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Lymphocytic infiltration (assessed by haematoxylin and eosin and outcome in breast cancer)

- **Adapted for clinico-pathological factors. DFS, distant disease-free survival; OS, disease-free survival; HR, hazard ratio; pCR, pathological complete response.**
Prenatal exposure to medical radiotherapy and its impact on a child’s health

Although it is generally accepted that prenatal exposure to diagnostic-level radiation doses poses no risk to the foetus, less is known about the long-term implications of prenatal exposure to therapeutic doses. Yesterday, in a Patient Cases Session on Pregnancy, Fertility and Cancer, Dr Frédéric Amant from University Hospitals Leuven, Belgium, provided a greater insight into this subject.

Women receiving radiotherapy during pregnancy were retrospectively and prospectively included in an international registry. Children were assessed at 1.5, 3, 6 or 9 years of age using echocardiography and tests or questionnaires examining neurological, cognitive, general health and behavioural outcomes. Sixteen children and 10 adults were assessed. The median maternal and estimated foetal radiation doses were 48 Gy (range 12–70 Gy) and 91 mGy (range 0–1600 mGy), respectively. Cardiac function was normal in all subjects. Similarly, neuropsychological, behavioural and general health outcomes were within normal ranges. There was no linear relationship between foetal radiation dose and cognitive outcomes. One child exposed to a relatively low radiation dose (54 mGy), in the presence of other confounding pregnancy complications and preterm delivery, had severe cognitive delay.

COMMENTING ON THE RESULTS, DR AMANT SAID

“It’s a good feeling to know that research data can be implemented immediately into the clinic. Our data will inform physicians and patients and help them to take decisions in a difficult situation.”

Metastatic CRC: Today’s clinical trials lead to tomorrow’s clinical practice

Numerous advances have been made in the treatment of metastatic colorectal cancer (mCRC) patients, providing an ever-expanding choice of agents, including targeted therapies. However, there is still much to be learned about these therapies. How will they be combined with each other and/or with cytotoxic chemotherapy? What is the optimum sequence for available therapies?

Yesterday, three presentations in the Proffered Paper Session on GI, Colorectal, further expanded our knowledge of maintenance treatments for patients with mCRC; for whom there is no clear recommendation following first-line systemic therapy. Two phase III studies of bevacizumab-based maintenance therapy revealed favourable efficacy in this setting. Dr Benoist Chibaudel from Hôpital Saint Antoine, Paris, France, described the final results of the GERCOR DREAM study in 452 patients receiving investigational bevacizumab-based maintenance therapy (alone or with erlotinib) following any bevacizumab-based induction therapy. After a median 50-month follow-up, bevacizumab/erlotinib was superior to bevacizumab monotherapy in terms of progression-free survival (PFS) (hazard ratio [HR] 0.77; p=0.017) and overall survival (OS; HR 0.80; p=0.034). Dr Chibaudel said that the OS benefit was evident among all subgroups, including those with RAS mutations.

Maintenance bevacizumab/erlotinib significantly increased survival compared with bevacizumab after first-line chemotherapy-bevacizumab induction in mCRC

In contrast, Dr Susanna Hegewisch-Becker from Hôpital, Hamburg, Germany, reported that bevacizumab monotherapy was non-inferior to the standard care, fluoropyrimidine/bevacizumab maintenance, after first-line induction with fluoropyrimidine/oxaliplatin/bevacizumab in time to failure of strategy (TFS, primary endpoint) and also PFS, in 473 patients with mCRC. In this study (AO KRK 0207), fluoropyrimidine/bevacizumab maintenance was superior to no treatment in all patients, and across all subgroups analysed, whereas there was no significant difference between all treatment arms for OS. Bevacizumab monotherapy was superior to no treatment and as effective as fluoropyrimidine/bevacizumab among patients with RAS and BRAF wild-type status, while there was no difference between the monotherapy and no treatment patients with poorer prognosis and tumours bearing any mutation (RAS or BRAF). It is worth mentioning here that stapping targeted chemotherapy, such as oxaliplatin, before the initially planned 24 weeks of induction, did not have an impact on patients’ prognosis or on differences between the maintenance arms, reinforcing the concept of terminating oxaliplatin before cumulative neuropathy occurs.

A phase II study (MORD-2) examining maintenance therapy with mFOLFOX/ cetuximab or cetuximab monotherapy following induction with mFOLFOX/cetuximab found that cetuximab monotherapy was non-inferior to the combination regimen as first-line therapy. Dr Pilar García-Afonso from Gregorio Marañon Hospital, Madrid, Spain, reported there were no significant differences between the maintenance therapy regimens in relation to PFS, OS, objective response rate and 9-month PFS rate. A phase II trial is required to confirm these findings.

Gastrointestinal tumours

**Today, a Special Symposium on Advances in Precision Medicine of Metastatic Colorectal Cancer** (14.15 – 15.45, Barcelona) will provide insights into the molecular understanding of mCRC, potentially leading to a new classification and the identification of novel therapy targets.

**KEY EDUCATIONAL SESSIONS SUNDAY 28 SEPTEMBER**

**Systemic treatment of metastatic NSCLC**

(Repeated session)

09.00 – 10.30 Pamplona

**Actual issues in neurooncology**

09.15 – 10.45 Alicante

**Update in genitourinary oncology**

(Repeated session)

11.00 – 12.30 Valencia

**Ovarian cancer**

(Repeated session)

14.00 – 15.30 Cordoba

**Update in the management of metastatic breast cancers**

(Repeated session)

14.00 – 15.30 Pamplona

**Fundamental principles of cancer immunotherapy: What the clinician needs to know**

16.00 – 17.30 Granada

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16.00 – 17.30 Granada
Dovitinib: DOVIGIST meets its primary endpoint

Metastatic NSCLC: New findings, new avenues to explore}

lung cancer continues to be the most common cancer, and the biggest cancer killer, worldwide.

Gastrointestinal stromal tumours (GISTs) are rare sarcomas comprising diverse molecular subsets with differing prognoses in the advanced and localised settings. Imatinib has improved the prognosis of patients with advanced GISTs, although disease progression inevitably occurs within 2–3 years. Other therapies are needed and yesterday’s Poster Discussion Session on Sarcoma, offered some hope with the presentation of findings from a phase II study of dovitinib, a small-molecule multitargeted receptor tyrosine kinase inhibitor.

Professor Heikki Joensuu from Helsinki University Central Hospital, Finland, presented findings from this single-arm study. DOVIGIST, in 39 patients with advanced/metastatic GIST refractory/intolerant to imatinib, or recurrent GIST after adjuvant imatinib. DOVIGIST met its primary endpoint of a clinically meaningful disease control rate (DCR, as per RECIST 1.1 criterion) of ≥45% at 12 weeks, with a DCR of 52.6% (90% confidence intervals [CI] 38.2–66.6). The median progression-free survival was 20.1 weeks (90% CI 13.2–32.1). The most common grade 3–4 treatment-related toxicities were fatigue (12.8%), diarrhoea, vomiting and hypertyrosinaemia (7.7% each). There was one death from suspected dovitinib-related heart attack. Professor Joensuu commented that the promising efficacy and manageable safety profile of dovitinib warranted further investigation of this agent in GIST.

Thymidylate synthase-negativity was associated with higher response rates and improved progression-free survival with pemetrexed/cisplatin compared with gemcitabine/cisplatin

Another biomarker, folate receptor (FR) overexpression, may be useful for therapy selection for certain groups of patients with NSCLC. From a phase II trial in 199 patients with FR-expressing NSCLC, Dr Nasser Hanna from Indiana University, Indianapolis, IN, USA, presented results showing that adding the FR-targeted drug vintafolide to docetaxel/second-line significantly improved OS compared with docetaxel alone in a subgroup of patients with adenocarcinoma (HR: 0.51; p=0.017). However, no benefit of vintafolide was seen in the overall patient group.

Pemetrexed/cisplatin will remain the standard first-line treatment over large parts of Europe, given the superiority against cisplatin/gemcitabine seen in the large Scagliotti trial and the favourable safety profile of pemetrexed.

The small benefit of afatinib compared with erlotinib in relapsed/refractory squamous cell NSCLC is not clinically relevant

What are the conclusions from these presentations? Immunohistochemical expression of TS (pemetrexed) and folate receptor (vintafolide) are promising new biomarkers to individualise second-line treatment of metastatic NSCLC. Pemetrexed/cisplatin will remain the standard first-line treatment over large parts of Europe.

We can also say that to all intents and purposes, afatinib and erlotinib are equally efficacious in the treatment of EGFR-mutated NSCLC. From a phase II trial in 199 patients with FR-expressing NSCLC, Dr Nasser Hanna from Indiana University, Indianapolis, IN, USA, presented results showing that adding the FR-targeted drug vintafolide to docetaxel/second-line significantly improved OS compared with docetaxel alone in a subgroup of patients with adenocarcinoma (HR: 0.51; p=0.017). However, no benefit of vintafolide was seen in the overall patient group.

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Prostate cancer: Defining the role of immunotherapy

Vaccines
For decades, research into cancer vaccines yielded disappointing results. However, advances in vaccine technology and molecular biology helped researchers to turn a corner. In 2010, the vaccine sipuleucel-T won FDA approval, becoming the first therapeutic cancer vaccine. It is currently approved for asymptomatic or minimally symptomatic metastatic CRPC.

Sipuleucel-T contains activated antigen-presenting cells loaded with the antigen prostasin acid phosphatase, a molecule present on most prostate cancer tumour cells. The vaccine primes the immune system to battle tumours and stimulates a strong immune response against cancer cells, leading to improved survival. In the IMPACT III trial sipuleucel-T increased median survival in metastatic prostate cancer patients by 4.1 months compared with placebo (25.8 months versus 21.7 months, respectively). Another vaccine, Prostvac-VF is now in phase III development following promising phase II clinical results last year, which reported increased survival by over 8 months compared with controls in metastatic CRPC.

Checkpoint inhibitors
The immune system offers oncologists many possible targets for therapeutic interventions. The checkpoint inhibitor ipilimumab is at the forefront of cancer immunotherapy. It blocks CTLA-4, a receptor that down-regulates T cells. By blocking CTLA-4, ipilimumab inhibits the T cell immunesuppressive pathway, leading to cell activation, proliferation and tumour infiltration. It may even lead to tumour cell death.

In September last year, it was reported that ipilimumab failed to significantly improve survival compared with placebo in a phase II trial in previously-treated CRPC. The drug is still under investigation in patients with less-advanced prostate cancer. It is also being trialed in combination with chemotherapy and radiotherapy.

Sonidegib shows durable efficacy in basal cell carcinoma
The hedgehog signalling pathway (see the ‘Pathway of the Day’ article in today’s Congress Daily newspaper) plays a key role in processes such as cell differentiation and embryonic organ formation. In adults, inappropriate mutation or deregulation of this pathway is linked to cancer development, including basal cell carcinoma (BCC).

In yesterday’s Proffered Paper Session on Melanoma and Other Skin Tumours, Dr Reinhard Dummer from Universitätsklinik Zürich, Switzerland, described the results in a late-breaking abstract from BOLT, a randomised, phase II study of the hedgehog inhibitor sonidegib in 230 patients with locally advanced (a; n=194) or metastatic (m; n=36) BCC. Dr Dummer explained that 200 mg/day sonidegib was associated with a 12-month event-free survival rate of 62.3% among 38 responding patients with LaBCC. Investigation of all patients with disease control revealed a clear reduction from baseline to week 9 and week 17 in GLI1 levels (a marker of hedgehog pathway activation) (p<0.001 for both). The 200 mg/day dose had a better benefit-risk profile than an 800 mg/day dose.

Melanoma and other skin tumours
Hear the latest results of a trial of androgen deprivation therapy plus ipilimumab in men with hormone-naïve metastatic prostate cancer being presented today Poster Discussion Session on Immunotherapy of Cancer: 13.00 – 14.00, Valencia: Abstract 1063P0D
Early clinical studies have shown that the activity of anti-CTLA-4 agents can be enhanced when administered with vaccines. To maximise combination therapies, it will be crucial to establish the optimal combinations and sequences of systemic therapy.

References
4. http://www.nature.com/geneTherapyProducts/ApprovedProducts/ucm210215.htm
Tailoring therapy according to CRC subtype

There is growing evidence that some therapies may be more effective or better tolerated in patients with certain colorectal cancer (CRC) tumour types, which could pave the way for tailoring therapy according to tumour biomarkers.

TAS-102 is a combination of trifluridine (a novel oral nucleoside) and tipiracil hydrochloride (a thymidine phosphorylase inhibitor). In yesterday’s Poster Paper Session on Gastrointestinal Tumours, Colorectal, Professor Eric van Cutsem from University Hospital Leuven, Belgium, presented a late-breaking abstract (LBA) based on findings from the phase III RECURSE study in 800 patients with metastatic CRC refractory to standard therapies receiving TAS-102 or placebo. Results were prospectively analysed in relation to subgroups, such as KRAS mutation, prior regorafenib, race and region. A similar benefit in terms of overall (OS) and progression-free survival (PFS) was observed across different subgroups, with all subgroups showing a benefit. The hazard ratios (HRs) for OS and PFS were 0.68 (95% confidence intervals [CI] 0.58–0.81; p<0.0001) and 0.48 (95% CI 0.41–0.57; p<0.0001), respectively, both favouring TAS-102.

TAS-102 had an overall and progression-free survival benefit across all subgroups of patients with mCRC, including those with KRAS-mutated tumours.

In another LBA presented during the same session, Dr Rachel Midgley from the University of Oxford, UK, revealed that results from the randomised phase III QUASAR2 study corroborated findings from other studies, showing no role for adjuvant bevacizumab in stage II-III CRC. Of interest, patients harbouring microsatellite stable tumours and receiving bevacizumab/capecitabine had significantly worse disease-free survival than those who received capecitabine alone (HR 1.43; p=0.005). Dr Midgley added that this association was not observed for patients harbouring microsatellite instability tumours.

An association between tumour subtype and toxicity from standard palliative care was discussed in an LBA presented by Dr Frank Sinicrope from the Mayo Clinic, Rochester, NY, USA, during yesterday’s Poster Discussion Session on Gastrointestinal, Colorectal. In 2381 patients with advanced CRC randomised to FOLFOX with/without cetuximab, among a number of interactions identified between toxicity and tumour location and subtype, an association between distal tumour location and high adverse event rates for patients with sporadic DNA mismatch repair remained significant in multivariate analysis (p=0.011).

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* LUR-Lung 3 (N=345), 519 del19 patients, as gemcitabine/cisplatin, median OS 39.2 vs 21.1 months, p=0.0005, 95% CI 0.36-0.79, P<0.0001; LUR-Lung 6 (N=364), 186 del19 patients, as gemcitabine/cisplatin, median OS 31.4 vs 14.8 months, p=0.044; 95% CI 0.43-0.94, P<0.0229

* as measured by European Organisation for Research and Treatment of Cancer (EORTC) questionnaire.

HR = hazard ratio; O/E = overall survival; PFS = progression-free survival; QoL = quality of life


NEWS

Sunday 28 September: ESMO’s Joint Symposia

Room: Valencia
Session Info: ESMO-JSMO: How to integrate genome sequencing data in oncology
Session Time: 09.15 – 10.45

Room: Bilbao
Session Info: ESMO-EONS: Oral tumour therapy: Collaboration and coordination of healthcare professional activities to enhance patient adherence
Session Time: 14.15 – 15.45

For the second Presidential Symposium tomorrow, ESMO has selected what it considers to be 3 of the most important late-breaking abstracts on melanoma submitted to this year’s congress.

Do not miss this opportunity to hear more about these studies, which are predicted to have a significant clinical impact.
Haematological malignancies – heralding a new era?

CANCER DRUGS: EVALUATING THE APPROVAL PROCESS

Novel cancer treatments are needed urgently and potential drugs must be translated from bench to bedside as rapidly as is possible to do safely. But do European drugs spend too long in the approval pipeline?

In today’s unmissable Proffered Paper Session, Dr Nardin Samuel from the University of Toronto, ON, Canada, will present the findings of research investigating the speed of approval of cancer drugs (Abstract 10360_PR).

Dr Samuel will discuss the significant differences in the rates of drug approval between the European Medicines Agency, Health Canada and the Food and Drug Administration of the USA. The findings will be pertinent to all European oncologists who strive to treat patients as effectively as possible.

Session Info:
Proffered Paper Session, Public health and health economics

DAY/DATE:  SUNDAY 28 SEPTEMBER 15.45 – 17.30 ROOM: PAMPLONA

Haematological malignancies

Chemotherapy has traditionally been the backbone treatment for haematological malignancies but there is a need for novel approaches to improve outcomes. The targeting of signalling pathways as a therapeutic approach to haematological malignancies was addressed in a Special Symposium yesterday.

Small molecule B cell receptor kinase inhibitors are associated with impressive activity in pretreated patients with B cell lymphomas (BCL), said Dr Ingo Ringhausen from “Klinikum rechts der Isar,” Munich, Germany. However, most patients will relapse within a year. Benefit may be greater in the first-line setting, although monotherapy is still unlikely to be curative in low-grade lymphomas. The molecular processes underlying drug resistance to these agents and the identification of the combination of drugs that will be most active are the next steps to further improve patient outcome.

Dynamic BH3 profiling may provide a personalised, functional test for predicting a patient’s response to conventional chemotherapy or BCL-2 inhibition, said Dr Anthony Letai from the Dana-Farber Cancer Institute, Boston, MA, USA. BH3 profiling, which measures how much a cell is primed for apoptosis, can be used to test whether a patient’s cancer cells will respond to a specific agent.

Ex-vivo testing of the sensitivities of molecular subgroups to different drugs may provide a way of translating our new found wealth of molecular knowledge of the genetic changes involved in lymphoma to the clinic, commented Dr Thorsten Zenz from National Center for Tumor Diseases and German Cancer Research Center, Heidelberg, Germany. Existing cell line sensitivity data (such as that from the Cancer Cell Line Encyclopedia) can be explored to investigate molecularly determined action.

The potential of the CDK inhibitors for the treatment of chronic lymphocytic leukaemia is attracting renewed interest, Dr Paolo Ghià from Universita Vita-Salute San Raffaele and Istituto Scientifico San Raffaele, Milan, Italy, told delegates. Selective CDK inhibition may lead to apoptosis independently of TP53, the main cause of disease refractoriness. A number of novel CDK agents, which may offer hope particularly in the case of relapsed disease, have already entered clinical trials.

In concluding the session, Dr Fathi Davies from the Royal Marsden Hospital, Sutton, UK, reminded delegates that although a target may be present, it doesn’t guarantee that the patient will respond to therapy. This highlights the need for better biomarkers to more effectively direct treatment for patient care. With the greater number of drugs available, it is important to think about tackling this now.

Locoregionally advanced rectal cancer: A multidisciplinary approach

In an Educational Session today, the importance of a multidisciplinary approach for the treatment of locoregionally advanced rectal cancer (LARC) was discussed.

Radiotherapy has a role both for improving resectability in unresectable disease, and for reducing the risk for recurrence in patients with high- and moderate-risk, resectable LARC, according to Dr Fab Girone-Jones from Mount Vernon Cancer Centre, Northwood, UK. In resectable LARC, both short-course radiotherapy and chemoradiotherapy can be considered. A multidisciplinary tumour board decision and involvement of patients in decision-making processes is key to achieving individualised treatment.

Professor Andrés Cervantes, University of Valencia, Spain, added that although neoadjuvant chemotherapy demonstrates high response rates in phase II studies of LARC, it should still be seen as experimental. Phase III studies of risk-adapted neoadjuvant treatment of LARC as well as the value of the addition of chemotherapy in high-risk LARC are required.

Adding to the discussion, Professor Cornelis van de Velde from Leiden University Medical Center, The Netherlands, stated that there is still room to improve surgery of higher-risk LARC — e.g. using robotic techniques to ultimately reduce the risk of local relapse and enhance functional outcomes. Collection of outcome data of patients with LARC was also identified as being important.

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Palbociclib plus letrozole prolongs PFS in metastatic breast cancer regardless of biomarker positivity

Earlier in 2014, positive results from the PALOMA-1/TRIO study of palbociclib, a highly selective reversible inhibitor of cyclin-dependent kinase (CDK) 4/6, were reported at the American Association for Cancer Research annual meeting. In this phase II study, first-line palbociclib/letrozole significantly improved progression-free survival (PFS) compared with letrozole alone in postmenopausal women with oestrogen receptor (ER)-positive HER2-negative metastatic breast cancer.

In a bid to further understand the possible therapeutic role of palbociclib in metastatic breast cancer, potential biomarkers were analysed in relation to PFS. In yesterday’s Proffered Paper Session on Developmental Therapeutics, Dr Yueji Jiang from Pfizer Inc, San Diego, CA, USA, described the findings from this analysis. Specific biomarkers included alterations of the cell-cycle regulatory genes, CCND1 and CDKN2A. Regardless of positivity for CCND1 and CDKN2A, the palbociclib/letrozole combination was associated with longer PFS than letrozole alone. Biomarker-positive patients had a median PFS of 26.1 months with palbociclib/letrozole and 7.5 months with letrozole alone (hazard ratio [HR] 0.2; 95% confidence interval [CI] 0.07–0.71). Corresponding results for the biomarker-negative group were 35.3 months and 5.7 months (HR 0.2; 95% CI 0.07–0.71). The significant PFS superiority of the combination was also maintained in patients for whom biomarker positivity was prospectively selected. The expression level of the proliferation biomarker, Ki67 (cut-off >20%), which is both prognostic and in some cases predictive of therapy in breast cancer, did not influence the efficacy of treatment in relation to PFS.  


Targeted therapy – a new spectrum of toxicities

It was hoped that targeted therapies would treat tumours with minimal toxicity. However, agents such as monoclonal antibodies, tyrosine kinase inhibitors (TKIs) and mTOR inhibitors, induce adverse events that are usually very different from those of traditional chemotherapy, but which, in most cases, occur as frequently.

Generally targeting a tumour pathway will cross-target the same pathway in normal tissues. With immunotherapies, normal tissues will be affected as ‘innocent bystanders’ by the hyperactivation of the immune system. The challenge oncologists face in recognizing and managing these toxicities was discussed yesterday in a Special Symposium on Targeting Precision Medicine Toxicity.

Cardiac toxicity caused by targeted agents is commonly due to myocyte dysfunction, without cell death, explained Dr Lillian Su, from Princess Margaret Hospital, Toronto, ON, Canada. These effects are not cumulative and are generally reversible. Common cardiac toxicities include: ventricular dysfunction; immune-mediated and autoimmune myocarditis; and prolongation of the QTc interval.

Dr Guy Meyer from Université Paris Descartes, France, and Dr Fausto Rolli, from Santa Maria Hospital, Terri, Italy, spoke about the difficulties in distinguishing between drug-related toxicities and the effects of cancer with regard to pulmonary and endocrine toxicities (including hypothyroidism and hypogonadism), respectively. Increased awareness among oncologists about the complications of cancer treatments may improve their detection and management.

The skin is a key site of toxicity related to many targeted therapies and adverse events range from the mild and manageable through to effects of major concern, such as BRAF inhibitor-associated skin tumours, said Dr Caroline Robert from Institut Gustave Roussy, Villejuif, France. Information and education of doctors and patients alike should help to reduce the severity of these effects and limit their impact.

Women treated with aromatase inhibitors for breast cancer are at an increased risk of skeletal complications, including bone loss and arthralgias, said Dr Ignacio Tusquets from Hospital del Mar, Barcelona, Spain. Biomarkers, such as mutations in genes encoding factors for oestrogen and vitamin D metabolism, may be useful in identifying risk and appropriate management strategies.

Gastrointestinal toxicities, which are a major cause of morbidity and, in some cases, mortality in clinical trials, are becoming more common with new classes of anticancer drugs, warned Dr Jervoise Andreyev from The Royal Marsden Hospital, London, UK. He suggested that multidisciplinary assessment, rational use of supportive drugs and targeted nutritional therapy can transform outcomes for patients and represent an effective use of healthcare resources.

With education, keen surveillance and early intervention, severe toxicities can be managed.
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