Dual therapy shows potential in melanoma

Two studies presented in the ESMO melanoma session yesterday point to the growing promise of dual blockade strategies in treatment of metastatic melanoma.

The BRAF inhibitor vemurafenib represents a new standard of care for metastatic melanoma patients with BRAF V600 mutations after showing improved progression-free survival compared to dacarbazine (DTIC). In many cases, however, benefits have proved short-lived as cancer cells develop resistance. Such observations have led to the initiation of new studies exploring treatment strategies targeting multiple signaling pathways at once.

In the first study, Dr Georgina Long and colleagues, from Westmead Hospital, University of Sydney, Australia, reported on a phase 2 study combining dabrafenib, an inhibitor of mutated BRAF 600, with trametinib, a selective MEK inhibitor. “The rationale behind adding the MEK inhibitor was that it blocks the same MAP kinase pathway as the BRAF inhibitor, but lower down. We hoped that by combining both drugs we would see significant delays in the emergence of resistance that would impact patients’ lives,” explained Dr Long.

In the study, 162 melanoma patients with BRAF V600 mutations were randomized 1:1:1 to receive either dabrafenib 150 mg twice daily; dabrafenib 150 mg twice daily plus trametinib 2 mg; or dabrafenib 150 mg twice daily plus trametinib 2 mg versus 5.8 months for patients receiving dabrafenib alone (HR 0.39, 95% CI 0.25 – 0.62; p<0.0001). Furthermore, the confirmed response rate was 76% for patients receiving dabrafenib plus trametinib 2 mg versus 54% for dabrafenib monotherapy (p=0.026).

Pyrexia (fever above 38.5°C) and chills were the most common adverse events reported, occurring in 71% and 58% of patients respectively receiving dual therapy. But the fever, she added, can easily be prevented with corticosteroids.

“Importantly, the combination also decreased the rate of the cutaneous toxicities compared with trametinib monotherapy, particularly the oncocogenic cutaneous toxicity of squamous cell carcinoma,” said Dr Long.

In the second study, Dr Rene Gonzalez and colleagues, from the University of Colorado at Denver, Aurora, USA, explored the strategy of combining vemurafenib with the MEK inhibitor, GDC-0973, in patients with unresectable or metastatic BRAF V600 melanoma mutations.

In the phase 1 dose escalation study, patients received vemurafenib 720 mg or 860 mg BID continuously, with GDC-0973 used at doses of 60 mg, 80 mg or 100 mg QD, with a varying regimen of 14 days on/14 days off, 21 days on and 7 days off and continuously. Results for individual patients showed decreases in tumor size from baseline ranging from 25% to 60%. The discussant Reinhard Dummer, from Zurich, Switzerland, commented that it was remarkable that every single patient showed a response. He added that he had never seen such striking response rates before in his career.

The most common adverse events were diarrhea (54.5%), rash (50%), nausea (38.6%), fatigue/asthenia (34.1%), liver function abnormality (25.0%) and photosensitivity/sunburn (25%). Only one patient developed cutaneous squamous cell carcinoma. “But this particular patient received low levels of the MEK inhibitor,” said Dr Gonzalez.

ESMO survey reveals ‘global pandemic’ of untreated cancer pain

Findings from an international survey presented in the Special Sessions yesterday morning concluded that hundreds of millions of cancer patients around the world are suffering needlessly due to government failures to ensure adequate access to pain-relieving drugs.

The International Collaborative Project to Evaluate the Availability and Accessibility of Opioids for the Management of Cancer Pain was conducted by ESMO and the Developing Countries Task Force (DCTF), together with the European Association for Palliative Care (EAPC), the Pain and Policies Study Group (PPSG) at the University of Wisconsin Carbone Cancer Centre, the Union for International Cancer Control (UICC) and the World Health Organization (WHO).

Lead author of the report, Professor Nathan Cherny, from Shaare Zedek Medical Center, Jerusalem, Israel, said, “Untreated cancer pain is a cause of major worldwide suffering, not because we don’t have the tools necessary to relieve pain, but because most patients don’t have access to the essential pain-relieving medications.”

Between December 2010 and July 2012, the survey gathered information submitted by experts from 76 countries and 19 Indian states. The results, which collectively represent 56% of all countries, revealed that:

• Very few countries provide all 7 of the opioid medications considered essential for pain relief by the International Association for Hospice and Palliative care
• In many countries, fewer than 3 of the 7 medications are available
• In many countries, the medications that are available are either unsubsidized or weakly subsidized by government, with availability often limited
• Many countries have highly restrictive regulations limiting the entitlement of cancer patients to receive prescriptions, including restrictive limits on the duration of prescriptions, restrictions on dispensing, and bureaucratic barriers in the prescribing and dispensing processes
• The issues were found to be particularly severe in Africa, Asia, the Middle East and Latin and Central America

Findings from this survey highlight the urgent need to review drug control policies and repeal the excessive restrictions which are impeding a fundamental aspect of cancer care. “The study has provided an unprecedented wealth of knowledge that will be an essential tool in lobbying to reformulate national plans for the treatment of cancer pain,” said Professor Cherny.
Novel hypoxia drug shows promise in pancreatic cancer

Combination therapy with the investigational agent TH-302 (in combination with DOX), and gemcitabine improved overall survival (OS) in patients with locally advanced pancreatic cancer, according to results from a phase II study presented at the ESMO Congress 2012, in Madrid, Spain. Treatment with TH-302 340 mg/m² plus gemcitabine, 0.75 mg/m² with TH-302 340 mg/m² plus gemcitabine, and TH-302 340 mg/m² plus gemcitabine 25% with TH-302 340 mg/m² plus gemcitabine 34% and TH-302 340 mg/m² plus gemcitabine alone, resulted in a 15% increase in OS that was statistically significant compared with gemcitabine alone. TH-302 340 mg/m² plus gemcitabine 25% with TH-302 340 mg/m² plus gemcitabine 34% and TH-302 340 mg/m² plus gemcitabine alone, resulted in a 15% increase in OS that was statistically significant compared with gemcitabine alone.

Diving right into research

In the Breakfast Session yesterday young oncologists were given a ‘blue print’ for making an impact on clinical research.

Professor Marko Frascovi from the Comprehensive Cancer Center in Vienna, Austria, said, “Think like a person, live like a doctor and work like a realist, he said.”

Explaining his audience to be daring or “think out of the box”, he recalled that his own early career had not been easy too. After having published a case report in the New England Journal of Medicine about treating a young patient with lipid tumors with corticosteroids.

He, therefore, mentioned that although improvements in overall survival did not reach statistical significance, the improvements in median progression free survival reported in February this year, he added, “I am very happy to be treated with a drug that is not only effective but also well tolerated.”

He added, “Only few have been designed to target a significantly improvement in overall survival and failure caused by a cross over component, whereas existing gemcitabine would only be cross over to receive gemcitabine plus TH-302 open disease progression.

Laura Landers, a breast cancer and patient- rights advocate from Harvard Medical School, said that the phase III study had been as far as we have to date, and that the phase III trial is to be initiated in the next two years.

It was also of great importance, he added, that patients had to be involved. “You would like much collaboration as prior.Without this you will not reach the level,” he added. He, therefore, emphasized that only few have been designed to target a significantly improvement in overall survival and failure caused by a cross over component, whereas existing gemcitabine would only be cross over to receive gemcitabine plus TH-302 open disease progression.

Twitter hashtag: #ESMO12

Today’s Special Sessions for Young Oncologists

Designed for younger researchers and practitioners, the Young Oncologists Breakfast Sessions will answer questions specific to the current stage of your career.

YO BREAKFAST

Today’s breakfast session on how to plan and conduct a successfully research independently "will be held while the highly experienced Professor Wilhelmina Kikstra, President of the Austrian Society of Oncology, Medical University of Vienna, Austria.

YO BREAKFAST

Sunday 30 September 08:00 – 08:50 HALL X

Poster Presentation II

During the afternoon poster session, our newly appointed YOC Chair from the Netherlands, Dr Boudewijn van Doorn, will present findings from the open-label, randomized, Phase III EURACT trial of capecitabine in combination with cetuximab and docetaxel as the third-line treatment for advanced gastric carcinoma. The primary endpoint of PFS was to be presented, together with data for key secondary endpoints, including OS, PFS, and overall response and toxicity.

Patient rights and obligations

Yesterday’s Patient Symposium reviewing Patient rights and obligations, entitled ‘The health care system and patients’ rights’, was attended by several European cancer patients and highlighted the role patients play in building good relationships with their doctors.

Dr. Katharina Stolz, a breast cancer and patient- rights advocate from Harvard Medical School, said that the phase III study had been as far as we have to date, and that the phase III trial is to be initiated in the next two years.

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Treatment advances in head and neck cancer

Winning combination for gastric cancer

Prof. Dr. Kiran Vaddi, from Vardhman College of Medical Sciences, New Delhi, India, opened the symposium on molecular neuro-oncology about glioblastoma patients. Another potential 'druggable' molecular alteration is a specific type of epidermal growth factor receptor (EGFR) that is being explored in randomized clinical trials investigating vaccination strategies. The number of validated biomarkers for virtually every cancer will be explored and those are important advances that are not to be missed.

Treatment choices based on risk factors are locally advanced head and neck cancers were considered in an educational session yesterday afternoon.

The value, said Professor Groot, is reductions in

The value, said Professor Groot, is reductions in activity, recovery of quality of life, and improved treatment outcomes. Studies have shown that testing for isocitrate dehydrogenase (IDH) mutations is not just helpful for the diagnosis of grade II and grade III anaplastic glioma, but also has significant prognostic implications. For glioblastoma, MGMT has been identified as an important prognostic, and for some patient populations, a predictive marker. But in the big question is molecular-targeted therapy with decision making in the clinical setting? Of course, we know that genetic testing for some cancers such as HER2 testing for breast cancer or RAS mutations testing for colorectal cancer. What we need is to identify that ErbB2-defined breast cancer or RAS-defined colorectal cancer is not clinically validated, although there is plenty of encouraging data emerging, including presentations here of ESMO and ASCO this year. Deregulation of the BRAF pathway in melanoma has led to the development of BRAF inhibitors, with vemurafenib. In the future, biomarkers will need to be found that identify patients who have the potential to respond, he concluded.

Future therapies are expected to be based on the development of targeted agents for pediatric brain cancer subtypes, for example sonic hedgehog inhibitors in medulloblastoma patients. But even as the proof of biomarkers expands, said the session, it is essential that development of new targeted therapies in head and neck cancer patients is evaluated on a case-by-case basis, with validated clinical performance being an important piece. This pattern is now making headway.

As a young oncologist I am thrilled about the speed at which oncology is moving forward at the moment and that becomes clear once again here at the ESMO 2012 meeting. Attending this meeting incredibly motivates me to continue being part of research and oncology help to develop new therapies that are now being developed for brain tumor patients. The moment and that becomes clear once again here at the ESMO 2012 meeting. Attending this meeting incredibly motivates me to continue being part of research and oncology help to develop new therapies that are now being developed for brain tumor patients.

Treatment makes headway

In my opinion, one major obstacle is bringing new biomarkers into everyday clinical work and for the benefit of patients who have the most limitations for biomarker testing. It is important to understand that assays that can separate 2 subpopulations with different outcomes are especially helpful in advanced disease. This is being explored in randomized clinical trials investigating vaccination strategies. The number of validated biomarkers for virtually every cancer will be explored and those are important advances that are not to be missed.

Melanomas are a genetically and phenotypically diverse group of neoplasms that are important advances not only in adult, but also in pediatric neuro-oncology. Today’s symposium focused on the molecular heterogeneity of metastasized, brain tumor patients. Here at the ESMO 2012 meeting, I am thrilled about the speed at which oncology is moving forward at the moment and that becomes clear once again here at the ESMO 2012 meeting. Attending this meeting incredibly motivates me to continue being part of research and oncology help to develop new therapies that are now being developed for brain tumor patients.
The presence of brain metastases should not preclude patients from being entered into clinical trials, regardless of the type of disease. This issue has been the subject of many previous trials treating patients with solitary brain metastases with chemotherapy, suggesting that brain disease is not the primary determinant of the survival when patients have disseminated disease.

Professor Brada concluded that for future studies there is a need for subgroup analyses where patients have disseminated disease. The presence of brain metastases should not preclude patients with asymptomatic brain metastases from being treated with systemic therapy, and Professor Michael Brada’s advice was to treat patients with a wide range of tumors.

**The working group believes that more work needs to be done on the same quality of delivered in an academic institution as by an ESMO member practice.** To ensure consistency of treatment, the group therefore works with ESMO to support practice oncologists in delivering the best possible care to their patients, explained Dr Robert Eckert, Chair of the ESMO Community Oncology Working Group.

Dr Eckert from Weindlingen, Germany, explained that yesterday’s special session ‘Excellence in Oncology’ was a great success and that European Cancer Care Unit (ECCO) is an important initiative, including the need to ensure uniform data collection in a way that does not enhance bureaucracy and that can be translated into quality improvements in everyday practice.

Professor Carsten Bokeymer from University Cancer Center, Hamburg, Germany, outlined the challenge of quality assurance in oncology treatment delivery, with 46 quality measures for oncology practices having been defined from 67 measures selected from the literature concerning medical oncology treatment in general and treatment of breast and colorectal cancer in particular, with 6 measures used to pilot data collection. Dr Brummer advised that the first experience in Germany showed that many oncologists were willing to participate. However, there are still a number of challenges, including the need to assess where data collection is best fit that does not enhance bureaucracy and that can be translated into quality improvements in everyday practice.

Professor David Kerr, from the Universities of Oxford and Cornell, addressed the serious issue of drug-drug interactions. His talk was highlighted by clear interaction and safety data for dose modifications are limited, careful action is always required. Although safety data for dose modifications are limited, careful action is always required.

To conclude, Professor David Kerr highlighted the importance of drug-drug interactions with chemotherapy and other medications, and the need for accurate monitoring of these interactions and their management in clinical practice.
Joint ESMO-ESTRO symposium tackles brain metastases

The joint ESMO-ESTRO symposium yesterday explored innovative approaches to the treatment of brain metastases, including prevention in patients with primary cancers, treating patients with human epidermal growth factor 2 (HER2)-positive metastatic breast cancer (MBC) and brain metastases with the combination of lapatinib and cetuximab, and the potential for radiation dose escalation.

The Symposium began with an overview of how cerebrospinal fluid (CSF) and brain metastases are related and how brain metastases occur. Dr. Gril, the moderator of the session, said that the blood-brain barrier remains an obstacle for drug delivery. He also mentioned that brain metastases occur in 3-40% of patients with solid tumors and are associated with a poor prognosis. Traditional drug delivery approaches to the treatment of brain metastases are often ineffective due to the blood-brain barrier, which restricts the delivery of drugs to the brain. However, recent advances in targeted therapies and immunotherapies have opened new avenues for molecular neuro-oncology diagnosis and treatment.

The next day, Dr. Gril introduced the concept of brain metastases and provided an overview of the current challenges in the treatment of brain metastases. He highlighted the importance of understanding the biology of brain metastases and the need for innovative approaches to overcome the limitations of traditional treatments. Dr. Gril also discussed the potential for radiation dose escalation, which could improve the outcome of patients with brain metastases. He concluded by emphasizing the importance of continued research and collaboration in the field of neuro-oncology.

Key points:
- Brain metastases are a major cause of morbidity and mortality in patients with solid tumors.
- Traditional drug delivery approaches to the treatment of brain metastases are often ineffective due to the blood-brain barrier, which restricts the delivery of drugs to the brain.
- Recent advances in targeted therapies and immunotherapies have opened new avenues for molecular neuro-oncology diagnosis and treatment.
- Radiation dose escalation could improve the outcome of patients with brain metastases.

The next step, said Dr. Gil, should be to launch Phase 2-3 clinical trials to improve and result in better systemic disease control, the number of patients with brain metastases likely to increase.

Preventing the development of brain metastases in patients with primary cancers is a feasible goal, argued Dr. Giri, from the National Institute of Health, Bethesda, MD, USA. Brain metastases in patients with primary breast tumors have 10-15% 5-year survival (5-10%) and GI tract (4-6%). Traditional drug delivery approaches to the treatment of brain metastases are often ineffective due to the blood-brain barrier, which restricts the delivery of drugs to the brain. However, recent advances in targeted therapies and immunotherapies have opened new avenues for molecular neuro-oncology diagnosis and treatment.

Brain metastases occur in 3-40% of patients with MBCs that overexpress HER2, explained Dr. Gil. The next step, said Dr. Gil, should be to launch Phase 2-3 clinical trials to improve and result in better systemic disease control, the number of patients with brain metastases likely to increase.

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Imaging biomarkers in the era of targeted therapies

A variety of imaging techniques and technologies are helping clinicians to evaluate treatment outcomes as well as to determine the stage and spread of disease in patients. Various imaging modalities, including conventional imaging, PET/CT, and MRI, are used to evaluate treatment success, to determine the stage and spread of disease; and 18F-DOPA and 68Ga-DOTA-NOC, that are successfully employed for CNS neoplastic diseases; and 11C-methionine, markers of protein metabolism are employed for the early detection of multiple myeloma.

Some malignancies do not show an increase in glucose consumption with conventional PET imaging. In this situation, PET imaging with alternative tracers to FDG for PET scans. “Some malignancies that are not FDG avid can be imaged using alternative PET tracers,” said Fanti also introduced a wide range of alternative PET tracers to PET imaging. He highlighted how molecular imaging can be used to improve clinical decision-making and predict treatment response. He showed that the time to perform an adequate analysis of PET images is an essential step in the process of molecular imaging. He presented results to show that high-risk tumors can be classified as low-risk tumors using molecular imaging. He concluded that molecular imaging can be used as an important tool in the management of patients with malignancy.

The growth of tailored therapy, which requires accurate and reliable treatment response assessment, is essential to achieve the goals of personalized medicine. The growth of tailored therapy, which requires accurate and reliable treatment response assessment, is essential to achieve the goals of personalized medicine. The growth of tailored therapy, which requires accurate and reliable treatment response assessment, is essential to achieve the goals of personalized medicine.
First line oral therapy for advanced renal cell carcinoma

Offers a significant improvement in progression-free survival versus placebo in:

- Treatment-naïve patients: 11.1 months vs. 2.8 months¹
- Cytokine-pretreated patients: 7.4 months vs. 4.2 months¹
- Combined population: 9.2 months vs. 4.2 months¹

Has a low incidence of grade 3 or 4 adverse events including fatigue, hand-foot syndrome and mucositis/stomatitis¹

Maintains patients’ health-related quality of life¹

Prescribing Information
(Please refer to full summary of product characteristics)

Votrient® (pazopanib) 200mg and 400mg film-coated tablets. Each tablet contains pazopanib hydrochloride, equivalent to 200mg and 400mg of pazopanib, respectively. Indications: In adults for the treatment of advanced renal cell carcinoma (RCC) and for use with prior cytokine therapy.

Dose and administration: Osimertinib can be administered with or without food. Pazopanib should be administered with food.

Off-label use:
- Cardiac and persists despite anti-hypertensive therapy and dose reduction.
- Is persistently elevated (140/90 mmHg) or if arterial hypertension is severe

Dose modification:
- Decrease pazopanib dose if systolic blood pressure (BP) increases ≥15 mmHg. Discontinue pazopanib if BP increases ≥30 mmHg. Monitor for hypertension early (≤1 week after starting treatment)
- Episodes of hypertension, including hypertensive crisis, have occurred in pazopanib studies. Control BP prior to initiating pazopanib treatment. Monitor patients for signs and symptoms of cardiac dysfunction. Cardiac dysfunction may include heart failure. Consider taking medications in patients with cardiac dysfunction.
- Avoid concomitant use with strong inhibitors of CYP3A4 and CYP2C8.

Interactions:
-Avoid concomitant use with strong inhibitors of CYP3A4 and CYP2C8.
-Use with caution in patients with significant risk of haemorrhage.
- Avoid concomitant use with strong inhibitors of CYP3A4 and CYP2C8.

Undesirable effects:
- VTEs including venous thrombosis and fatal PE have occurred in pazopanib users. Be aware of these events.
- Events of cardiac dysfunction (e.g. CHF and LVEF decline) have not been studied in patients with moderate to severe heart failure or those with New York Heart Association classes III or IV.

Special warnings and precautions:
- Elderly: Limited data in patients ≥65 years.
- Not to be used in children.

Contra-indications:
- Hypersensitivity to active substance or excipients.
- Calcium channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II antagonists, diuretics.

Efficacy and safety data:
- In a Phase III trial comparing pazopanib to placebo, the median progression-free survival for patients treated with pazopanib was 10.8 months, compared to 3.8 months for those treated with placebo.

References: