Advance reports

Included in this report are the highlights of the European Society of Medical Oncology congress, Vienna

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MET: a major target in oncology

A scientific overview of the MET pathway, and key data from tivantinib clinical trials to date, was highlighted at the European Society of Medical Oncology congress in Vienna recently.

Tivantinib, a selective, oral, non-ATP competitive inhibitor of the MET receptor tyrosine kinase, is the furthest advanced of the investigational agents in the Daiichi Sankyo oncology pipeline.

Christian Manegold, Head of Interdisciplinary Thoracic Oncology, Heidelberg University, Mannheim, looked at the clinical aspects of MET inhibition. He said that advances in understanding of the complexity of biologic pathways through which cancer grows and spreads have opened doors for promising new therapeutic approaches. One such pathway is MET. In healthy adults, MET in normal levels supports natural cellular functions. In many cancers, MET is inappropriately and continuously activated due to cellular mutations. When abnormally activated the MET pathway is frequently found to play a significant role in how certain cancers grow and spread, and is associated with poor outcomes in many cancers, including hepatocellular carcinoma (HCC) and Non-Small Cell Lung Cancer (NSCLC).

Tivantinib targets the MET pathway, binding to the MET receptor and disrupting the pathway, effectively locking MET in an inactive state. As a MET inhibitor, currently being evaluated as a single agent and in combination with other anti-cancer therapies in NSCLC, HCC and colorectal cancer, it has the potential to be the first approved medication in its class.

Bruno Daniele, Director of the Department of Oncology and Medical Oncology Unit, G. Rummo Hospital, Benevento spoke about MET in HCC. He said that HCC is often asymptomatic until it is in an advanced stage. It is usually diagnosed late with poor prognosis and no currently approved standard second-line treatment option. Tivantinib has demonstrated broad spectrum anti-tumour activity as a single agent and in combination with other therapies in preclinical studies, including MET high HCC cell lines. Tivantinib phase 2 clinical trial results in second-line HCC, showed a statistically significant improvement in time to progression (TTP) as compared to placebo in the intent to treat (ITT) population, the primary endpoint. Tivantinib also improved overall survival (OS) in the ITT population. Both TTP and OS were improved in patients whose tumours were MET positive.

Another presentation looked at tivantinib in NSCLC. Giorgio Scagliotti, Head of the Department of Clinical and Biological Sciences, University of Turin said that at diagnosis of lung cancer, the majority of all patients have already progressed to advanced stages, with limited available treatments and a five-year survival rate of only 1–2%. New treatment options that extend life without negatively impacting quality of life are therefore urgently needed.

Amplification of the MET pathway is associated with poor prognosis in NSCLC and resistance to EGFR kinase inhibitor treatments.

Phase 2 trial results show treatment with tivantinib, in combination with erlotinib (Tarceva®) significantly improved OS and progression free survival versus treatment with erlotinib alone in patients with non-squamous NSCLC. The MARQUEE phase 3 trial evaluated tivantinib in combination with erlotinib, in previously treated patients with locally advanced or metastatic, non-squamous, NSCLC.

Targeted therapy may benefit men whose prostate cancer has spread to their bones

A new-generation cancer drug could shrink prostate tumours that have spread to patients' bones and help to relieve bone pain, trial results suggest.

Results released at the ESMO congress found signs of patient benefit for Cabozantinib—one of a new breed of cancer therapies precisely targeted at tumours.

Cabozantinib was tested in a phase II trial of 51 men with metastatic castration-resistant prostate cancer whose disease was getting worse despite previous chemotherapy, and had spread to their bones.

After treatment with the drug, there was evidence that tumours had shrunk in 11 of 20 patients whose bone scans have been evaluated so far. Around half of the patients in the trial were suffering pain, and most of these men were using strong painkillers such as morphine for relief.

Following treatment, around 70% reported a substantial reduction in pain (10/14 patients) and more than half (7/12 patients) decreased their painkiller use. These patients also reported that the cancer was interfering less with their daily life, including their ability to sleep and carry out normal activities. The most common side-effects were high blood pressure, decreased appetite and back pain.

Professor de Bono, leader of the prostate cancer targeted therapy team at The Institute of Cancer Research, London, and honorary consultant at The Royal Marsden NHS Foundation Trust. said: "Although we have helped develop a number of new drugs for advanced prostate cancer over recent years, men's tumours ultimately develop resistance to treatment and so finding new options for men with late-stage disease is still crucially important. As prostate cancer progresses, it commonly spreads to men's bones, which can lead to bone fractures and severe pain. This drug has so far only been tested in a small number of patients and isn't curing them of their cancers, but it is showing promise at taking away the pain of prostate cancer and helping men live a normal life."

Professor Alan Ashworth, chief executive of The Institute of Cancer Research (ICR), said: "This is an exciting time for prostate cancer research, with four new drugs shown to extend life in advanced cancer in the last two years—three of which the ICR has helped develop. This latest treatment is another of the new generation of drugs precisely targeted at tumours, and it's promising that it is showing clear signs of activity and patient benefit."

Cabozantinib is an oral targeted drug known as a kinase inhibitor that is being developed by Exelixis. It blocks two molecules involved in cancer growth and spread: VEGFR2, which cancers use to form new blood vessels so they can tap into the supply of nutrients in the blood system, and MET, which is known to be abnormally activated in prostate cancer.

Regorafenib: new drug for colorectal cancer

Stivarga (regorafenib) has recently been approved by the US Food and Drug Administration (FDA) and provides a new treatment for patients with metastatic colorectal cancer (mCRC) who have exhausted all other options.

Stivarga is the second drug approved by the FDA for the treatment of mCRC in the past two months, following the approval of Zaltrap (aflibercept) as a second-line therapy in August.

According to the World Health Organization, colorectal cancer is the fourth most common cause of cancer mortality in the world. The disease afflicts over 140,000 people annually and causes more than 51,000 deaths each year in the US alone, according to the National Institutes of Health.

Stivarga was developed by Bayer for the treatment of mCRC in patients who have stopped responding to multiple targeted therapies and chemotherapies. These include fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapeutic regimens, as well as anti-VEGF and anti-EGFR targeted therapies. The drug is administered orally and is a multi-kinase inhibitor, blocking enzymes that up-regulate tumour growth.

The treatment of mCRC involves standard chemotherapy regimens such as FOLFOX (oxaliplatin, leucovorin, and fluorouracil), FOLFIRI (irinotecan, leucovorin, and fluorouracil), and CapeOX (oxaliplatin and capecitabine), often in combination with targeted therapies, including the biologics Avastin, Erbitux (cetuximab), Zaltrap, and Vectibix (panitumumab). Since Stivarga has been approved to treat patients who have failed both chemotherapy and targeted therapies, it will initially be used only after all other options have been exhausted.

The efficacy of Stivarga was demonstrated in a single Phase III clinical trial known as CORRECT (COlorectal cancer treated with REgorafenib or plaCebo after failure of standard Therapy). This was an international, multicenter, randomised, double-blind trial conducted in 760 patients whose disease had progressed after treatment with currently available therapies. Patients were assigned to treatment with either Stivarga or placebo, accompanied by best supportive care (BSC). The drug increased median overall survival (OS) to 6.4 months versus 5.0 months with placebo (p=0.0102). Progression-free survival (PFS) also increased by two months with Stivarga, compared to 1.7 months with placebo (p<0.0001).

However, the drug comes with a boxed warning stating patients are at risk of developing fatal liver toxicity, which was observed in 0.3% of the 1100 Stivarga-treated patients across all clinical trials. Additionally, the prescribing information warns of the risk of severe or life-threatening haemorrhage, and gastrointestinal perforation. Other side effects include weakness or fatigue, high blood pressure, loss of appetite, weight loss, and dysphonia.

New tailored treatment in HER2-positive breast cancer improves survival and reduces side effects

Data from the Phase III EMILIA study, presented at the ESMO congress, shows that T-DM1 (trastuzumab emtansine) prolongs the lives of patients with advanced HER2-positive breast cancer when compared with the only approved licensed treatment combination, lapatinib and capecitabine, (30.9 months versus 25.1 months, HR=0.682; P=0.0006), while significantly reducing the side effects of chemotherapy.

T-DM1 is known as an "antibody-drug conjugate" (ADC), and is the first medicine of its kind for breast cancer; it incorporates the HER2-targeted antibody, Herceptin, with the chemotherapy agent, DM1 (emtansine) as a single therapy. T-DM1 has been designed to seek out and destroy only the cancerous cells in a two-stage attack. First, it attaches to the HER2 growth receptor (found on the surface of the cell) and blocks signals that encourage the cancer to grow and spread; next, it penetrates the cell's outer defences and releases a payload of chemotherapy to destroy it from within. This targeted approach means that healthy cells are preserved, and the unpleasant side effects commonly associated with chemotherapy are substantially reduced.

Professor Paul Ellis, Professor of Cancer Medicine at King's College London, said: "These results are truly outstanding and will positively alter the outlook and outcomes for patients with HER2-positive breast cancer. For T-DM1 to offer such a significant survival benefit, while also improving the quality of patients' lives by reducing the side effects of chemotherapy, is a remarkable achievement—particularly as HER2-positive breast cancer is so difficult to treat in its advanced stages."

Patients who received T-DM1 experienced fewer, less severe side effects than those who received lapatinib plus capecitabine. In addition, fewer patients who received T-DM1 experienced Grade 3 (categorised as "severe") or higher side effects than those who received lapatinib plus capecitabine (40.8% versus 57%).

The most common Grade 3 or higher side effects associated with T-DM1 in the EMILIA study were low platelet count (12.9% versus 0.2%), increased levels of enzymes released by the liver and other organs (aspartate aminotransferase: 4.3% versus 0.8%; alanine aminotransferase: 2.9% versus 1.4% and anaemia 2.7% versus 1.6%). In most patients these levels had returned to normal by the time of the next dose of T-DM1.

Votrient® (pazopanib) versus sunitinib in advanced renal cell carcinoma meets primary endpoint

The Phase III study COMPARZ (COMParing the efficacy, sAfety and toleRability of paZopanib vs. sunitinib) has met its primary endpoint in a study presented at the ESMO congress.

In the open-label, head-to-head study, pazopanib demonstrated non-inferiority to sunitinib in terms of progression free survival. Patients in the study were treated for advanced renal cell carcinoma (aRCC) with a component of clear cell histology and had received no prior systemic therapy for advanced or metastatic renal cell carcinoma.

In the study, 1110 patients were randomised to receive treatment with either pazopanib or sunitinib at their respective, approved treatment doses (pazopanib 800mg/daily; sunitinib—50mg/daily for four weeks followed by two weeks off treatment). Treatment was continued in both arms until

patients showed signs of disease progression, unacceptable toxicity, voluntarily withdrew from the study or died due to any cause. The primary endpoint was non-inferiority in progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response, health-related quality of life (QoL), safety and medical resource utilisation.

According to results based on independent review, COMPARZ showed that pazopanib was non-inferior to sunitinib with a hazard ratio for PFS of 1.047 (95% CI 0.898, 1.220); predefined criterion for non-inferiority was the upper bound of a two-sided 95% CI of 1.25. Median PFS was 8.4 months (95% CI 8.3, 10.9) for pazopanib compared to sunitinib at 9.5 months (95% CI 8.3, 11.1). The secondary endpoint of ORR (by independent review) showed an ORR of 31% in the pazopanib arm compared to 25% in the sunitinib arm, (p = 0.032).

Interim analysis of OS data showed that the pazopanib versus sunitinib hazard ratio for OS was 0.908 (95% CI 0.762, 1.082; p-value = 0.275) [median OS of 28.4 months (95% CI 26.2, 35.6) compared to sunitinib at 29.3 months (95% CI 25.3, 32.5)].

Study findings also showed there was a statistically significant outcome in favour of pazopanib for 11 of the 14 domains from four quality of life (QOL) instruments which included measures of fatigue, mouth and throat soreness, as well as hand and foot soreness among other measures.

The most common adverse events in this study for pazopanib compared to sunitinib, respectively, included: diarrhoea (63% versus 57%); fatigue (55% versus 63%); hypertension (46% versus 41%); nausea (45% versus 46%); decreased appetite (37% versus 37%); ALT increase (31% versus 18%); hair colour changes (30% versus 10%); hand-foot syndrome (29% versus 50%); taste alteration (26% versus 36%); and, thrombocytopenia (10% versus 34%).

In addition, 42% of patients in the pazopanib arm and 41% in the sunitinib arm had serious adverse events. Serious adverse events (AE) occurring in 3% or more of patients in the pazopanib arm were ALT increase and AST increase. Serious AEs occurring in 3% or more of patients in the sunitinib arm were pyrexia and thrombocytopenia.

Thirteen subjects (2%) had fatal AEs in the pazopanib arm and 19 subjects (3%) in the sunitinib arm had fatal AEs. There was no predominant fatal event. Eleven subjects had fatal AEs that were considered drug-related by investigator assessment: 3 (<1%) in the pazopanib arm and 8 (1%) in the sunitinib arm.

Personalised medicine: new survey

One third of cancer patients are unaware of the fact that it is now possible to determine who is most likely to benefit from particular treatments, according to new survey data presented at the ESMO congress.

Personalised medicine is about matching patients to the treatments that work best for them, with the ultimate goal of everyone being treated as an individual. In oncology, personalised medicine is becoming a clinical reality, with targeted treatments already in use.

Professor Tejpar, University Hospital of Leuven, Belgium and colleagues surveyed 811 patients diagnosed with cancer in the last five years using telephone-based questionnaires. The patients included 164 with late-stage breast cancer, 157 with stage III/IV non-small cell lung cancer and 490 with metastatic colorectal cancer from Argentina, China, France, Germany, Italy, Spain and the UK.

Results showed that 32% (260) of those interviewed thought no tests were available to determine which cancer treatments might work in certain individuals, while 53% thought that testing might be possible.

The survey revealed breast cancer patients were the best-informed about testing, with 62% thinking testing might be possible, compared with 52% with colorectal cancer and 48% with non-small cell lung cancer.

The survey also revealed that 66% (532) of respondents would be willing to delay treatment if this helped to select the most effective drug, and that 54% of these would be willing to delay treatment for more than two weeks. Furthermore, most patients (69%) would be willing to undergo additional tumour biopsies as part of the treatment selection process, and 91% would allow hospitals to retain their tumour samples for future research.

Professor Tejpar said: "It was really striking participants were willing to allow hospitals to retain their tumour samples even if this didn't directly relate to their own treatment. It shows they want to advance research and help others with the disease."