Conference Insight
The European Cancer Congress 2013
Datamonitor Healthcare’s analysis of the key highlights

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Overview

Datamonitor Healthcare attended the 2013 European Cancer Congress (ECCO 17–ESMO 38–ESTRO 32) which took place between 27 September and 1 October in Amsterdam, Netherlands. Datamonitor Healthcare has identified the following key highlights from the meeting:

- The primary results of Phase III TH3RESA trial show that Kadcyla significantly improves progression-free survival in HER2-positive breast cancer patients who have received at least two prior treatments. The results of this trial are likely to drive uptake of Kadcyla in the third-line setting and strengthen the drug’s position in the HER2-positive breast cancer market. Kadcyla is also being investigated in the Phase III MARIANNE trial, which is directly comparing Kadcyla and Herceptin in the first-line treatment of metastatic HER2-positive breast cancer patients. The results of this trial are likely to have a significant impact on Kadcyla’s future commercial potential.

- The anti-programmed death 1 (PD-1) and PD-L1 agents continued to generate excitement at the 2013 congress. PD-1 and its ligands have emerged as a key target for developers looking for the next generation of immunotherapies. Bristol-Myers Squibb, Merck & Co, and Roche continue to compete to gain the coveted first-to-market status for this new wave of immunotherapies.

- Early data for BioMarin’s PARP inhibitor BMN-763 suggest that it may be an effective treatment for BRCA mutation-positive metastatic breast cancer patients. The development of PARP inhibitors for cancer has resurged recently, after a period in which disappointing clinical trial results cast a shadow over the drug class. However, with AstraZeneca’s olaparib in Phase III development for ovarian cancer and BMN-673 in Phase III for breast cancer, there is renewed hope that a PARP inhibitor will eventually reach the market.

- Phase III data from the TRINOVA-1 trial show that Amgen’s trebananib (AMG 386; Amgen/Dyax/Takeda) is associated with a high rate of edema. The higher rate of adverse event-related treatment discontinuations and edema events in the trebananib arm of the TRINOVA-1 trial must be concerning to Amgen. Datamonitor Healthcare believes that regulators will only approve the trebananib/paclitaxel regimen if results from the TRINOVA-1 trial prove that it provides patients with an overall survival benefit.

TH3RESA trial demonstrates superiority of Kadcyla

Primary results from TH3RESA show that Kadcyla significantly improves progression-free survival in the third-line treatment of HER2-positive breast cancer patients

The initial results from the Phase III TH3RESA trial are likely to drive uptake of Kadcyla (ado-trastuzumab emtansine; ImmunoGen/Roche/Chugai) in the third-line setting and strengthen the drug’s position in the HER2-positive breast cancer...
Kadcyla is also being investigated in the Phase III MARIANNE trial, which is directly comparing Kadcyla and Herceptin (trastuzumab; Roche/Chugai) in the first-line treatment of metastatic HER2-positive breast cancer patients. The results of this trial will be the most pivotal in terms of the impact they will have on Kadcyla’s future commercial potential.

Speaking on the second day of the 2013 European Cancer Congress (ECC 2013), Dr Hans Wildiers of University Hospital Leuven presented the initial results from the highly anticipated TH3RESA study. This was a Phase III trial of Kadcyla versus physician’s choice of treatment in advanced HER2-positive breast cancer patients who have received at least two prior treatments including Herceptin (trastuzumab, Roche/Chugai), Tykerb (lapatinib; GlaxoSmithKline), and a taxane. The 602 patients enrolled had received a median of four prior regimens (excluding hormonal therapy) in the recurrent/metastatic setting, and the majority (75.1%) had visceral disease. In patients receiving their physician’s choice of treatment, 83.2% received a HER2-directed regimen and 16.8% received single-agent chemotherapy.

The results of the trial showed that treatment with Kadcyla increased both progression-free survival (PFS) and objective response rate (ORR) in patients that were treated with the drug. HER2-positive breast cancer patients receiving Kadcyla demonstrated a median PFS of 6.2 months and ORR of 31.3%, significantly higher that the results observed from patients receiving their physician’s choice of treatment (PFS of 3.3 months and ORR 8.6%). Kadcyla was also found to demonstrate superior efficacy to the subset of regimens incorporating Herceptin, as the 80% of patients in the physician’s choice of treatment arm that received Herceptin demonstrated a median PFS of 3.2 months.

Kadcyla also demonstrated a desirable safety profile, with 32.3% of Kadcyla patients experiencing grade 3 or higher adverse events compared to 43.5% of patients receiving their physician’s choice of treatment. More grade 3 or higher thrombocytopenia (4.7% vs 1.6%) was reported with treatment with Kadcyla, with more grade 3 or higher neutropenia (2.5% vs 15.8%), febrile neutropenia (0.2% vs 3.8%), and diarrhea (0.7% vs 4.3%) associated with physician’s choice of treatment. These safety results for Kadcyla are comparable with those observed in prior clinical trials.

Kadcyla is a HER2-targeted antibody-drug conjugate (ADC) which contains the humanized anti-HER2 immunoglobulin G1 (IgG1) Herceptin covalently linked to the microtubule inhibitory drug DM1 via a stable thioether linker. The Herceptin part of Kadcyla binds to HER2 on tumor cell surfaces and promotes internalization of the ADC. Inside the tumor cell, the DM1 moiety is released and binds to tubulin, disrupting microtubule assembly/disassembly dynamics and inhibiting cell division.

In February 2013, Kadcyla gained US approval for the treatment of HER2-positive metastatic breast cancer patients who have received prior treatment with Herceptin and a taxane chemotherapy. This approval was based on the results of the Phase III EMILIA trial, which investigated Kadcyla versus the combination of Tykerb and Xeloda (capecitabine; Roche/Genentech) as a second-line treatment for HER2-positive breast cancer patients. In this trial, patients in the Kadcyla arm demonstrated a median PFS benefit of 9.6 months, compared to 6.4 months for patients in the Tykerb and Xeloda arm. Additionally, patients receiving Kadcyla demonstrated a median overall survival (OS) benefit of 30.9 months compared to 25.1 months for patients receiving Tykerb and Xeloda.

The positive results of the EMILIA trial have driven rapid uptake of Kadcyla during the short time it has been on the market, generating sales of almost $90m in the US by the end of the first half of 2013. The initial results from the TH3RESA trial will further boost the drug’s position in this market and lead to a dramatic increase in uptake of Kadcyla in the third-line setting.

Kadcyla is also enrolled in another Phase III trial that is investigating the drug’s efficacy in the first-line setting. The MARIANNE trial is comparing three different treatment regimens (Kadcyla alone, Kadcyla in combination with Perjeta [pertuzumab; Genentech/Roche/Chugai], and Herceptin plus taxane chemotherapy) in treatment-naive patients with HER2-positive metastatic breast cancer. The first-line HER2-positive breast cancer treatment setting represents a large patient market.
population, and is currently dominated by treatment regimens that incorporate Herceptin. If Kadcyla can demonstrate a clinical benefit over Herceptin in this treatment setting, it is likely to generate significant commercial reward for Roche and help the company mitigate the decline in revenue expected when Herceptin biosimilars launch in this market in 2015.

**PD-1 and PD-L1 inhibitors continue to impress**

PD-1 and its ligands have emerged as a key target for developers looking for the next generation of immunotherapies

The anti-programmed death 1 (PD-1) and PD-L1 agents continued to generate excitement at ECC 2013. Bristol-Myers Squibb, Merck & Co, and Roche continue compete to gain the coveted first-to-market status for this new wave of immunotherapies.

PD-1 and its ligands, PD-L1 and PD-L2, are members of the CD28 and B7 family. The B7 family cell surface molecules and the CTLA-4 family both regulate complex signaling pathways that affect T-cell activation, tolerance, and immunopathology. The pathways have a similar effect on T-cell immune response, but they are distinct from each other.

Both Bristol-Myers Squibb and Merck are developing anti-PD-1 drugs (nivolumab and lambrolizumab, respectively). The US Food and Drug Administration (FDA) has granted fast track designation for nivolumab in three indications including melanoma, non-small cell lung cancer (NSCLC), and renal cell cancer (RCC), and designated lambrolizumab a breakthrough therapy for patients with advanced melanoma. However, Roche has approached the PD-1 pathway from a different angle, with its candidate MPDL3280A (RG-7446; Roche/Genentech) targeting the PD-1 ligands PD-L1 and B7-1.

It remains to be seen if there is a clinical advantage in targeting PD-1 or its ligands, but all three companies are competing to prove their drug is superior. With ongoing trials in multiple indications including melanoma, NSCLC, and RCC, it is a race to see who can gain the coveted first-to-market status and reap the anticipated significant commercial reward.

**Roche plays catch up with MPDL3280A in NSCLC**

Roche presented updated data from a Phase I study assessing the safety and efficacy of MPDL3280A monotherapy in NSCLC. The study showed that treatment with MPDL3280A was well tolerated, with rapid and durable responses. Mutational analysis showed that PD-L1 tumor status correlated with response to the drug. Preliminary data suggest that response rates were higher in former/current smokers compared to patients who had never smoked. This is the first study to suggest a potential relationship between smoking and response to inhibition of the PD-L1/PD-1 pathway.

The trial included 85 heavily pretreated NSCLC patients, with efficacy analysis including 53 patients who had received the first dose of MPDL3280A by 1 October 2012. Best objective response rate as measured by RECIST 1.1 criteria was achieved by 23% of the patients and the 24-week PFS rate was 44.7%. A higher ORR of 83% was observed in patients whose tumor expressed higher levels of PD-L1.

Roche has announced that it plans to initiate a Phase III trial (OAK) assessing the combination of MPDL3280A with docetaxel in second- and third-line NSCLC in Q1 2014. The trial will incorporate diagnostic testing using Roche’s Tissue Diagnostics immunohistochemistry (IHC) assay to identify patients with higher levels of PD-L1. The rapid progression to late-stage clinical trial is crucial for Roche to remain in the development fight with Bristol-Myers Squibb and Merck. Nivolumab and lambrolizumab are both already in ongoing Phase III trials for NSCLC. Roche’s positive Phase I data in smokers and ability to identify patients who respond could be an important advantage when recruiting patients for the OAK Phase III trial.
Bristol-Myers Squibb shows potential next generation of melanoma treatment

In a poster session on Friday 27 September, Bristol-Myers Squibb presented data for the combination of nivolumab and Yervoy (ipilimumab, Bristol-Myers Squibb) in advanced melanoma. These data were previously presented at the 2013 American Society of Clinical Oncology (ASCO) annual meeting earlier this year, but presentation of long-term survival results for monotherapy Yervoy has reignited excitement around the anti-PD-1 and anti-CTLA-4 combination. The success of Yervoy monotherapy in melanoma has been a catalyst for immunotherapy drug development in this indication in recent years. Nivolumab is the most advanced anti-PD-1 in development and has the most mature early-phase data. The company is attempting to leverage its strategic advantage in melanoma by trialing nivolumab in combination with Yervoy. Concurrent treatment with anti-PD-1 and anti-CTLA-4 agents resulted in synergistic antitumor activity in syngeneic murine tumor models. In this trial, advanced melanoma patients received nivolumab concurrently with Yervoy followed by nivolumab monotherapy. Data from this trial demonstrated that 53% of patients responded to concurrent nivolumab and Yervoy with an estimated one-year survival of 82%.

The long-term survival analysis for monotherapy Yervoy showed median overall survival (OS) benefit of 11.4 months across the total patient population. This included both previously treated (n=1,257) and previously untreated patients (n=604) who received Yervoy at different doses and regimens. These data have sparked speculation regarding the potential long-term clinical improvement for melanoma patients treated with the nivolumab and Yervoy combination. The combination could provide a significant breakthrough for this aggressive tumor type and the next seismic shift in melanoma therapy.

Early data for BioMarin’s BMN-673 resurrect hope for a PARP inhibitor in breast cancer

Phase III trial will determine the role of BMN-673 in the treatment of BRCA mutation-positive patients

BioMarin’s BMN-673 is a promising drug candidate that could become the first PARP inhibitor to gain approval for BRCA mutation-positive metastatic breast cancer. Early data from the Phase I/II trial suggest that BMN-673 may be effective in heavily pretreated patients and BioMarin is initiating a pivotal Phase III trial. The failure of Sanofi’s iniparib was a setback for PARP inhibitors but with AstraZeneca’s olaparib in Phase III development for ovarian cancer and BMN-673 in Phase III for breast cancer, there is renewed hope that a PARP inhibitor will eventually reach the market.

On Sunday 29 September, Dr Ramesh Ramanathan presented interim data from a Phase I/II trial of BMN-673 in advanced ovarian and breast cancer patients with deleterious mutations in BRCA1 or BRCA2 genes (BRCAm). Among the 14 breast cancer patients with germline BRCA-associated tumors (gBRCA) that were treated at the dose of 1mg/day selected for the Phase III study, the confirmed RECIST response rate was 50% (seven confirmed objective responses: one complete and six partial). The median PFS had not been reached for these patients but it was expected to exceed six months.

Preliminary data from the Phase I/II trial had been presented at the American Society of Clinical Oncology annual meeting in June. The updated data presented at ECC 2013 showed that in the 18 gBRCA patients in the breast cancer cohort the response rate was 44% and the clinical benefit rate was 72%, with five patients having stable disease for more than 24 weeks.

The Phase I/II study assessed BMN-673 in multiple advanced tumor types with DNA-repair pathway deficiencies, including BRCAm breast and ovarian cancers. BRCAm breast and ovarian cancer patients enrolled in the study were required to have received no more than four prior treatment regimens for metastatic disease. Dosing of BMN-673 varied depending on whether patients were assigned to dose escalation or dose expansion cohorts.
PARP inhibitors block the activity of PARP, an enzyme that plays an essential role in DNA repair mechanisms. PARP inhibitors act by directly blocking enzymatic activity, or by causing PARP to accumulate on DNA (PARP trapping), which results in DNA replication inhibition and cell death. Tumor cells with BRCA1/2 gene mutations are dependent on PARP for DNA damage repair, and PARP inhibition selectively kills BRCA1- or BRCA2-deficient cells. As DNA repair is inhibited by PARP inhibitors, they are often sequenced after a cytotoxic chemotherapy which works by damaging DNA.

BRCA1/2 encode proteins that are required for DNA damage repair. Inherited mutations in these genes have been linked to a predisposition for development of breast and ovarian cancers. In the US, it has been estimated that inherited BRCA1 and BRCA2 mutations account for 5–10% of breast cancers and 10–15% of ovarian cancers among white women.

BioMarin has initiated a Phase III pivotal study of BMN-673 in BRCAm advanced or metastatic breast cancer. The study will enroll approximately 429 subjects and it will be an open-label 2:1 randomized, parallel, two-arm study of BMN-673 monotherapy (1mg, once daily in cycles of 21 continuous days) compared to physicians’ choice (capecitabine, eribulin, gemcitabine or vinorelbine). The patients will have received no more than two prior chemotherapy regimens and the primary outcome of the study will be PFS.

BMN-673’s advancement into a Phase III pivotal study reflects the growing momentum of PARP inhibitor development for cancer therapy, and suggests that this drug class could provide promising future therapies for BRCAm-associated cancers. The development of PARP inhibitors for cancer has resurfaced recently, after a period in which disappointing clinical trial results cast a shadow over the drug class. Initial results for AstraZeneca’s olaparib were disappointing and Sanofi’s leading PARP inhibitor candidate, iniparib, failed in a Phase III clinical trial for triple-negative breast cancer. Subsequent research has shown that iniparib may not actually be a potent PARP inhibitor but these high profile failures were enough to lead to a degree of suspicion about the potential of PARP inhibition. Datamonitor Healthcare has maintained that PARP inhibitors could be successful if the clinical trials are adequately designed with appropriately selected patients.

The initiation of BMN-673’s Phase III trial follows AstraZeneca’s announcement in May 2013 that it was initiating a Phase III study of its PARP inhibitor olaparib in BRCAm advanced platinum-sensitive ovarian cancer. The data from these Phase III trials will show whether or not PARP inhibitors have a role to play in the treatment of BRCAm patients. Other notable drugs in the PARP inhibitor pipeline include Tesaro’s niraparib (Phase III trials in BRCAm breast cancer and BRCAm ovarian cancer), Clovis Oncology’s rucaparib (Phase II trial for ovarian cancer), and AbbVie’s veliparib (multiple Phase II studies for oncology indications).

**Negative side effects take shine off positive PFS data for trebananib**

**Phase III data show that Amgen’s trebananib is associated with a high rate of edema**

On Tuesday 1 October, Amgen presented interim data from the TRINOVA-1 Phase III pivotal study of trebananib in advanced ovarian cancer. In June 2013, the company released top-line data from TRINOVA-1 indicating that patients treated with trebananib benefitted from a median PFS benefit. The data presented at ECC 2013 confirmed this PFS advantage but also revealed more detail on the adverse events associated with trebananib treatment. The higher rate of adverse event-related treatment discontinuations and edema events in the trebananib arm of the TRINOVA-1 trial must be concerning to Amgen. In order to gain approval, trebananib will have to demonstrate a significant OS benefit.

Trebananib is an intravenously administered peptide-Fc fusion protein that inhibits tumor angiogenesis by blocking the interaction of angiopoietins with Tie2 receptor at sites of neovascularization.
Ovarian cancer is the fourth most common cancer among women, and has the highest mortality rate of all gynecological cancers. Incident cases of ovarian cancer in the US, Japan, France, Germany, Italy, Spain, and the UK are expected to increase from 66,400 in 2013 to 73,700 in 2021.

There is high unmet need in the treatment of advanced ovarian cancer. Treatment options for patients with disease that does not respond to platinum-based chemotherapy (platinum-resistant patients) are limited, and consequently the prognosis for this patient group is poor. Currently, platinum-resistant ovarian cancer patients commonly receive single-agent non-platinum based chemotherapy, and treatment response rates are typically below 20%.

TRINOVA-1 is a randomized, double-blind, placebo-controlled Phase III pivotal trial assessing the efficacy and safety of trebananib in partially platinum-sensitive or platinum-resistant advanced ovarian cancer patients. Patients in the study were required to have already been treated with one platinum-based chemotherapy regimen within the 12 months prior to their enrollment into the study. Patients were randomized to receive once-weekly treatment with intravenous trebananib 15mg/kg plus intravenous paclitaxel 80mg/m² (cycle of three weeks on followed by one week off), or once-weekly intravenous placebo plus paclitaxel. The primary endpoint was PFS and OS was a key secondary endpoint.

Patients in the trebananib arm of the trial had a significantly improved PFS of 7.2 months compared to the patients in the placebo arm (5.2 months). At a planned interim analysis of OS (313 deaths), there was a trend in improvement (median OS of 19.0 months in the trebananib arm vs 17.3 months in the placebo arm). The incidence of grade ≥3 adverse events was similar in both arms (54% in the placebo arm vs 56% in the trebananib arm), but trebananib was associated with more adverse event-related treatment discontinuations (6% in the placebo arm vs 17% in the trebananib arm) and edema events (28% in the placebo arm vs 64% in the trebananib arm).

Although the primary endpoint of TRINOVA-1 is PFS, it is very important that TRINOVA-1 produces favorable OS data, as this will be the key to a successful trebananib marketing application. In the platinum-resistant setting, there are no subsequent therapy options for further disease control and extension of life. Drugs seeking approval for the treatment of platinum-resistant patients should therefore be able to demonstrate that they can extend life (increase OS) rather than just prolong the period of time over which a patient’s disease remains stable (PFS). Consequently, Datamonitor Healthcare believes that regulators will only approve the trebananib/paclitaxel regimen if results from the TRINOVA-1 trial prove that it provides patients with an OS benefit. The data on OS in the TRINOVA-1 study are not expected to mature until sometime in 2014.

Amgen is trialing trebananib in two further pivotal studies that will affect its future uptake if it gains approval for the treatment of ovarian cancer. TRINOVA-2 is investigating trebananib in combination with PEGylated liposomal doxorubicin for treatment of partially platinum-sensitive or platinum-resistant advanced ovarian cancer, while TRINOVA-3 is evaluating trebananib in combination with paclitaxel and carboplatin for first-line advanced ovarian cancer therapy. If both TRINOVA-1 and 2 are successful, trebananib could be indicated in two separate chemotherapy regimens for platinum-resistant disease.