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Oncology Drugs to Watch

Top takeaways from ESMO 2023

Introduction

By all accounts, this year's European Society of Medical Oncology Congress was buzzing with an energy not felt since the pre-pandemic days, as 33,000 attendees descended on Madrid to hobnob and apprise the most exciting new research into cancer treatments. As part of our Drugs to Watch coverage, Clarivate oncology experts pored over hundreds of abstracts to shortlist a few of particular interest. Among the key trends at ESMO 2023:

- **Cancers affecting women come into focus:** Breast cancer continues to be a major area of innovation in oncology, but this year's conference featured several promising avenues of research into gynecological cancers, including cervical, ovarian and endometrial cancers. Among the highlights were promising results for KEYTRUDA® plus concurrent chemoradiotherapy against high-risk locally advanced cervical cancer, as well as IMFINZI® and IMFINZI-plus-LYNPARZA® for newly diagnosed or recurrent endometrial cancer.

- **Checkpoint inhibitors show their staying power:** Treatments like KEYTRUDA®, IMFINZI® and OPDIVO® continue to dominate the oncology conference circuit as manufacturers explore new indications for these treatments.

- **ADCs and bispecific therapeutics make the scene:** As with ASCO, antibody drug conjugates and bispecific antibodies made a big splash at this year's conference, with a PADCEV®-plus-KEYTRUDA® combo drawing a standing ovation on strong bladder cancer mortality data. Another drug that caught our attention at this year's meeting was Amgen's bispecific T-cell engager tarlatamab for small-cell lung cancer.

"Innovation is at the heart of cancer research as exemplified at the ESMO 2023 meeting. Cutting-edge drugs with novel mechanisms of action like ADCs or BiTEs took center stage, and breakthrough data showing advances in patient populations where chemotherapy has long been the standard of care were in the limelight."

Leena Kathuria

Senior Manager, Healthcare Research & Data Analytics

Read on for the ten trial results that stood out to our oncology team – along with four of particular interest for the Mainland China market.

Methodology

Clarivate oncology experts sifted through more than 2,500 abstracts selected for presentation at the 2023 ESMO Congress, analyzing the published data and performing a qualitative assessment to shortlist those releases expected to have a significant impact on the cancer treatment landscape and/or the drug development

pipeline. In addition, Clarivate Asia-Pacific oncology experts identified key highlights for results presented from Mainland China. This report provides an in-depth analysis of groundbreaking clinical trial data releases across oncology indications. We shortlisted these abstracts based on, but not limited to, the following criteria:

- Unprecedented efficacy benefit over current therapies
- Clinical trials addressing unmet need in an underserved patient population
- Impact on competitive landscape and market dynamics
- Impact on the oncology drug pipeline
- Novel drug class or combinatorial approach

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Key global takeaways from ESMO 2023

1. Immunotherapy showed a significant pCR benefit in high-risk HR-positive, HER2-negative breast cancer. [1,2]

In the absence of EFS data, the future of perioperative immunotherapy in high-risk HR-positive, HER2-negative patients remains uncertain.

Context

Perioperative immunotherapy in combination with chemotherapy has become the standard of care in the treatment of early triple-negative breast cancer, supported by the significant benefit in pCR and EFS demonstrated by KEYTRUDA over chemotherapy in the Keynote-522 study[3]. However, the evidence of immunotherapy efficacy for the treatment of early HR-positive, HER2-negative disease has been lacking. At ESMO 2023, two Phase III studies (i.e., KEYNOTE-756 and CheckMate-7FL) reported for the first time the efficacy outcomes of neoadjuvant regimens containing immunotherapy agents; KEYTRUDA or OPDIVO in a high-risk HR-positive, HER2-negative population.

Key ESMO findings

Data from both trials showed a significant pCR rate benefit when adding KEYTRUDA (KEYNOTE-756) or OPDIVO (CheckMate-7FL) to neoadjuvant chemotherapy (KEYNOTE-756: 24.3% vs. 15.6%; P = 0.0005; CheckMate-7FL: 24.5% vs. 13.8%; P=0.0021) in high-risk HR-positive, HER2-negative patients, thereby meeting the primary endpoint in both studies. The benefit in pCR rates was higher in the PD-L1-positive subgroups (defined as CPS≥1 in KEYNOTE-756 and IC≥1% in CheckMate-

7FL), and this was particularly notable in the CheckMate-7FL study. Following neoadjuvant treatment and surgery, patients in both trials received adjuvant immunotherapy (or placebo) for one year, in combination with standard endocrine therapy. Results for the key endpoint of EFS—a coprimary endpoint in the KEYNOTE-756 trial and an exploratory endpoint in CheckMate-7FL—are still immature and were not reported.

Market impact

KEYTRUDA and OPDIVO (combined with chemotherapy) have demonstrated a higher pCR rate in high-risk HR-positive, HER2-negative patients, although a positive correlation with improved EFS remains to be demonstrated. The assessment of EFS as an exploratory endpoint in the CheckMate 7FL study cast doubts over the likelihood that data from this trial could be used to seek regulatory approval. In contrast, EFS is a dual primary endpoint in the KEYNOTE-756 study and, if positive, could lead to the label expansion of KEYTRUDA in this setting. Should KEYTRUDA be approved, we expect that the sustained long-term EFS benefit demonstrated by adjuvant treatment with CDK4/6 inhibitors (i.e., VERZENIO[4] and KISQALI[5]) in this population will greatly hamper the uptake of this regimen, especially in the absence of predictive biomarkers of response to neoadjuvant immunotherapy.

2. Overall survival in resectable early-stage NSCLC significantly improved by the addition of perioperative KEYTRUDA to neoadjuvant chemotherapy.[6-8]

KEYNOTE-671 data positions KEYTRUDA as the first perioperative regimen in resectable NSCLC, but competition from OPDIVO[9-11] and other drugs is imminent.

Context

In October 2023, the FDA approved KEYTRUDA as a perioperative addition to neoadjuvant chemotherapy for resectable NSCLC, based on the phase 3 KEYNOTE-671 trial in stage II, IIIA, or IIIB (T3-4N2) NSCLC.[12] Positive primary EFS endpoint data were reported at ASCO in June 2023,[13,14] and, just prior to the FDA approval, Merck & Co announced that the primary OS endpoint had also been met, although detailed data were not disclosed.[8] The early-stage resectable setting first saw the entry of immune checkpoint inhibitors, with TECENTRIQ adjuvant therapy in 2021, followed by neoadjuvant OPDIVO in 2022 and adjuvant KEYTRUDA in 2023. Trials of other ICIs are also underway in this setting, including the phase 3 CheckMate 77T trial which aims to support the approval of perioperative OPDIVO. Bristol-Myers Squibb reported in September 2023 that this trial met its EFS endpoint,[4] and the detailed data were reported at ESMO 2023.[10,15]

Key ESMO findings

KEYNOTE-671 data (median follow-up of 36.6 months) showed that median OS was significantly improved with neoadjuvant KEYTRUDA plus cisplatin-based chemotherapy followed by surgery and adjuvant KEYTRUDA, compared with neoadjuvant cisplatin-based chemotherapy and surgery, in resectable stage II, IIIA or IIIB NSCLC patients (not reached vs. 52.4 months; HR 0.72, P = 0.00517). OS rates at 36-months were 71.3% vs. 64.0%, and at 48 months were 67.1% vs. 51.5%. Median OS was similar across histological subtype, disease stage and nodal status, but differed across age (<65 years HR 0.57; ≥65 years HR 0.96), and PD-L1 expression level (PD-L1 TPS ≥50% HR 0.55; PD-L1 TPS 1-49% HR 0.69; PD-L1 TPS <1% HR 0.91). Updated EFS data were also reported (47.2 months vs. 18.3 months; HR 0.59).[1] Similarly designed CheckMate 77T trial data presented at ESMO showed that perioperative OPDIVO plus neoadjuvant platinum-based (cisplatin or carboplatin) chemotherapy significantly improved the primary endpoint of EFS compared with neoadjuvant platinum-based chemotherapy (not reached vs. 18.4 months; HR 0.58, P = 0.00025) to a similar extent to that reported for KEYTRUDA in KEYNOTE-671. EFS rates at 18 months were 70% vs. 50%. Median EFS differed across PD-L1 expression levels (PD-L1 TPS ≥50% HR 0.26; PD-L1 TPS 1-49% HR 0.76; PD-L1 TPS <1% HR 0.73), histology (nonsquamous HR 0.72; squamous HR 0.46), and also disease stage (stage II

HR 0.81; stage III HR 0.51), but not across age (<65 years HR 0.55; ≥65 years HR 0.61). OS data, a secondary endpoint, are not yet available.

Market impact

Competition in the early-stage resectable NSCLC market, with its recent range of new treatment options, is set to be fierce and complex. With the approval of perioperative KEYTRUDA based on the data from KEYNOTE-671, prescribers and patients now face a choice not only of whether to sequence immune checkpoint inhibitor therapy before or after surgery (neoadjuvant OPDIVO [EFS: HR 0.63][16], versus adjuvant TECENTRIQ [DFS: HR 0.66][17] or KEYTRUDA [DFS: HR 0.73][13]), but also of whether to use treatment both before and after (perioperative KEYTRUDA [OS: HR 0.72][6]). Several factors will influence these choices, including whether the stage of disease is such that the risk of delaying surgery to accommodate neoadjuvant treatment is acceptable (or even feasible), patient preference regarding the trade-off between treatment intensity and side-effect risk, and the differing burdens of care associated with the different treatment-sequencing options. As yet, there are insufficient data to make these decisions clear cut, although the report of OS data from KEYNOTE-671 is likely to give KEYTRUDA an advantage. With several further trials ongoing in this setting (not only CheckMate 77T of perioperative OPDIVO [EFS: HR 0.58][10], but also perioperative IMFINZI in AEGEAN [EFS: HR 0.68][19] and perioperative TECENTRIQ in IMpower030 [currently no EFS data]), the space is becoming highly dynamic.

3. Perioperative IMFINZI plus chemotherapy improves pCR in resectable gastric or GEJ adenocarcinoma.[20]

Uncertainty looms around whether significant improvements in pCR in the MATTERHORN trial can translate to better survival outcomes in this setting.

Context

Perioperative chemotherapy is associated with better survival outcomes than adjuvant chemotherapy in resectable gastric or GEJ adenocarcinoma, but recurrence rates remain high despite multimodality treatment.[21] In June 2023, AstraZeneca announced that the Phase 3 MATTERHORN trial of perioperative IMFINZI plus FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) versus neoadjuvant FLOT met its key secondary endpoint of pathologic complete response (pCR).[22] In the same month, Merck & Co. revealed that the Phase 3 KEYNOTE-585 trial of perioperative KEYTRUDA plus chemotherapy had met pCR but not EFS (coprimary endpoints).[4]

Key ESMO findings

In MATTERHORN, IMFINZI plus FLOT demonstrated a 19% pCR rate by central review compared with 7% for placebo plus FLOT ($P < 0.00001$). The rate of patients with a pathological staging of T0 and/or N0 at the time of surgery, indicating tumor downstaging, was 23% versus 11%, respectively. The study is ongoing to assess the primary endpoint of EFS.[1] In KEYNOTE-585, the pCR rate was 13% with perioperative KEYTRUDA plus doublet chemotherapy vs 2% in the control group ($P < 0.0001$). While numerically large, the 20.1-month improvement in median EFS for KEYTRUDA plus chemotherapy was not statistically significant (HR 0.81, $P = 0.0198$) and there was no improvement in median OS at this interim analysis (HR 0.90). EFS and OS outcomes were similar irrespective of chemotherapy backbone (doublet chemotherapy or FLOT).[5] The incidence of treatment-related grade 3/4 adverse events compared with placebo plus chemotherapy was similar for both trials (58% versus 56%, and 64% versus 63%, respectively).[20,24]

Market impact

Improved survival is a major unmet need in resectable gastric or GEJ adenocarcinoma. While adding immunotherapy to chemotherapy showed large pCR improvements in both MATTERHORN and KEYNOTE-585, the latter trial did not lead

to statistically significantly better EFS, calling into question whether pCR is a reliable surrogate of longer-term outcomes after surgery and perioperative chemoimmunotherapy. In that context, the EFS readout for perioperative IMFINZI plus chemotherapy in MATTERHORN will be watched with great interest and will likely dictate whether IMFINZI can enter the yet-untapped resectable gastric or GEJ adenocarcinoma market segment.

4. KEYTRUDA plus CCRT significantly improves PFS in high-risk locally advanced cervical cancer.[25]

The first survival data from the Phase 3 KEYNOTE-A18 study positions KEYTRUDA® plus concurrent chemoradiotherapy as the new SOC for treatment-naive high-risk locally advanced cervical cancer.

Context

KEYTRUDA is already approved in combination with chemotherapy, with or without bevacizumab, for the treatment of PD-L1-positive persistent, recurrent, or metastatic cervical cancer, based on the KEYNOTE-826 trial.[26] However, the treatment landscape for locally advanced cervical cancer has remained static for the last two decades, since external beam radiotherapy (EBRT) plus chemotherapy followed by brachytherapy (concurrent chemoradiotherapy (CCRT)) became the standard of care.[27] These patients have a poor prognosis, and a high risk of recurrence.[28]

Key ESMO findings

KEYTRUDA plus CCRT demonstrated a statistically significant improvement in PFS compared with placebo plus CCRT; the 24-month PFS rate for the experimental arm was 67.8% vs. 57.3% (p=0.0020). Since this trial was testing in a potentially curative setting, this translates to a 10% increase in the number of patients cured. KEYTRUDA plus CCRT also reduced the risk of disease progression or death by 30% (HR=0.70 [95% CI: 0.55-0.89) and showed a particular benefit for FIGO 2014 stage III-IVA patients (HR = 0.58 [95% CI: 0.42-0.80]). A favorable trend towards extending OS was observed (HR=0.73 [95% CI: 0.49-1.07]), despite the OS data not yet being mature (103 events, 42.9% maturity). The safety profile of KEYTRUDA plus CCRT was manageable, with a very similar incidence of treatment-related adverse events between both treatment arms.[25]

Market impact

ENGOT-cx11/GOG-3047/KEYNOTE-A18 is the first Phase 3 study in which an immunotherapy has demonstrated a PFS improvement in locally advanced cervical cancer patients compared to the standard of care. As there have been no treatment advances for newly diagnosed patients with locally advanced cervical cancer in over 20 years and this setting accounts for approximately 35% of cervical cancer patients,[29] the label expansion of KEYTRUDA into the locally advanced setting would substantially augment the cervical cancer market. A similarly designed Phase 3 trial (CALLA) testing IMFINZI plus CCRT in locally advanced cervical cancer failed to demonstrate a PFS improvement last year,[30] which puts KEYTRUDA in an advantageous position. A sBLA seeking the approval of KEYTRUDA plus CCRT was accepted for FDA Priority Review in September 2023,[31] and, with a PDUFA date of January 20, 2024, the combination of KEYTRUDA with CCRT is likely to receive approval soon and experience fast uptake into the market.

5. IMFINZI and IMFINZI plus LYNPARZA improve PFS in newly diagnosed or recurrent endometrial cancer regardless of DNA-mismatch repair (MMR) status.[32]

The DUO-E trial results suggest adding a PARP inhibitor to an immune checkpoint inhibitor (ICI) provides the greatest benefit to MMR-proficient (pMMR) patients.

Context

ICIs have demonstrated impressive efficacy in first-line advanced or recurrent endometrial cancer, particularly in patients with MMR-deficient (dMMR tumors)[33-35]. In July 2023, JEMPERLI became the first approved ICI in the United States for first line use in dMMR patients, based on the Phase 3 RUBY trial. However, 75% of endometrial cancer patients are pMMR[36] and, unfortunately, these individuals do not experience the same level of benefit. Therefore, there is a pressing need for novel combinations that extend the effect of ICIs to the broader population. The Phase 3 DUO-E trial is investigating IMFINZI plus chemotherapy followed by IMFINZI alone or IMFINZI plus LYNPARZA maintenance in advanced or recurrent endometrial cancer. In May 2023, AstraZeneca announced that both IMFINZI alone and IMFINZI plus LYNPARZA significantly improved PFS over chemotherapy.

Key ESMO findings

When compared to chemotherapy, IMFINZI plus chemotherapy followed by IMFINZI alone or IMFINZI plus LYNPARZA maintenance improved PFS in the ITT population (9.6 months for the control arm vs. 10.2 months for IMFINZI alone (HR = 0.71, P = 0.003) vs. 15.1 months for IMFINZI plus LYNPARZA (HR = 0.55, P < 0.0001). In a pre-specified subgroup analysis, both experimental arms outperformed the chemotherapy arm in dMMR patients (PFS of 7.0 months vs. N.R. (HR = 0.42) vs. 31.8 months (HR = 0.41). However, pMMR patients saw a greater PFS benefit with IMFINZI plus LYNPARZA than with IMFINZI alone (9.7 months for the chemotherapy arm vs. 9.9 months for IMFINZI alone (HR = 0.77) vs. 15.0 months for IMFINZI plus LYNPARZA (HR = 0.57). Adding LYNPARZA led to an elevated incidence of Grade ≥3 adverse events (56.4% for the control, 54.9% for IMFINZI, and 67.2% for IMFINZI plus LYNPARZA), mainly attributed to a rise in anemias. At the time of the analysis, OS was still immature but showed a positive trend for both experimental arms.

Market impact

DUO-E is the first Phase 3 trial to show positive results of a PAPR inhibitor plus an ICI in endometrial cancer. Although the trial was not statistically powered to compare both experimental arms (IMFINZI alone versus IMFINZI plus LYNPARZA), pre-specified subgroup analysis suggests adding LYNPARZA to IMFINZI maintenance is especially beneficial for pMMR patients. If approved for a broad population, LYNPARZA plus IMFINZI could offer an effective alternative to patients with limited therapeutic options, potentially reaching a larger patient pool than JEMPERLI. Ongoing studies such as part 2 of the Phase 3 RUBY trial (evaluating JEMPERLI plus ZEJULA) or the Phase 3 LEAP-001 trial (investigating KEYTRUDA plus LENVIMA) will provide further insights into the most promising ICI combinations for endometrial cancer treatment.

6. PADCEV in combination with KEYTRUDA showed unprecedented OS benefit in previously untreated locally advanced or metastatic urothelial carcinoma.[37]

The combination challenges deep-seated first-line standard of care chemotherapies with practice changing survival gains in the treatment of metastatic urothelial carcinoma.

Context

Platinum-based chemotherapies have been the established standard of care for treatment-naïve locally advanced or metastatic urothelial carcinoma patients. Initial results from the Phase 1b/2 EV-103 / KEYNOTE-869 study, showed impressive response rates (ORR = 68%) with the combination of PADCEV plus KEYTRUDA in cisplatin-ineligible patients in this setting[38,39], supporting for the first time the

hypothesized synergy between an antibody drug conjugate and an immune checkpoint inhibitor, and winning accelerated approval by the FDA in April 2023. The Phase 3 EV-302 / KEYNOTE-A39 study was designed to build on the initial findings, with the inclusion of patients eligible for cisplatin- or carboplatin-containing chemotherapy, resulting in top-line survival data which were presented at ESMO 2023.[37]

Key ESMO findings

In this landmark Phase 3 trial, at a median follow-up of 17.2 months (n = 866), the combination of PADCEV plus KEYTRUDA met its defined dual endpoints of OS and PFS in patients eligible for platinum-based chemotherapies (i.e., gemcitabine plus cisplatin or carboplatin), with statistically significant survival improvements compared to chemotherapy regimens (OS was 31.5 months with the combination [n = 442] compared to 16.1 months in the chemotherapy arm [n = 444]; [HR] 0.47, P < 0.00001), demonstrating a clear reduced risk of survival by 53% compared to the standard of care chemotherapy regimens. The PFS benefit was also significant and sustained across cohorts, regardless of cisplatin eligibility or PD-L1 status (PFS was 12.5 months compared to 6.3 months in the chemotherapy arm; [HR] 0.45, P< 0.00001), reducing the risk of disease progression or death by 55%. Response rates in the combination arm were also superior to conventional chemotherapy regimens (68% in the combination arm, with a CR of 29% and PR of 39%, compared to 44% in the chemotherapy arm, with a CR of 13% and PR rate of 32%). The safety profile was manageable, consistent with previous findings and with no new safety signals.

Market impact

The groundbreaking results of EV-302 / KEYNOTE-A39 presented at ESMO 2023, demonstrate discernible longer survival curves with the combination of PADCEV plus KEYTRUDA compared to conventional chemotherapy treatments. This regimen is certain to advance the SOC and lead to a paradigm shift in the treatment of locally advanced or metastatic urothelial carcinoma, independent of cisplatin-eligibility or biomarker status. We expect an approval, across the major markets in the first line setting for cisplatin-eligible patients starting in 2024. We also await results of the combination in the muscle-invasive setting, where it is being investigated as a novel neo(adjuvant) treatment option.

7. First ever Phase 3 data readouts of datopotamab deruxtecan yields mixed results in two of the most dynamic solid tumors, breast cancer and NSCLC.[40,41]

Interim results from the Phase 3 TROPION-Breast01 and TROPION-Lung01 trials demonstrate positive efficacy of datopotamab deruxtecan versus chemotherapy, however, safety remains a concern.

Context

Datopotamab deruxtecan (Dato-DXd), is a TROP2-targeting antibody-drug conjugate. TROP2 is a transmembrane protein that is highly expressed in several cancers, including breast cancer and NSCLC, which modulate carcinogenesis-promoting signaling pathways[42]. AstraZeneca and Daiichi Sankyo are evaluating Dato-DXd in various Phase 3 trials across different patient settings in breast cancer and NSCLC. These trials include TROPION-Breast01, evaluating Dato-DXd in patients with previously treated metastatic HR-positive / HER2-negative breast cancer, and TROPION-Lung01, evaluating Dato-DXd in patients with advanced or metastatic NSCLC (stage IIIB, IIIC, and IV) without actionable genomic alterations.

Key ESMO findings

Both the TROPION-Breast01 and TROPION-Lung01 Phase 3 trials met the co-primary endpoint of PFS. In the TROPION-Breast01 trial, patients treated with Dato-DXd experienced a statistically significant longer median PFS than standard

chemotherapy, 6.9 months vs. 5.9 months (HR 0.64, P < 0.0001). In the TROPION-Lung01 trial, patients treated with Dato-DXd also experienced a significantly longer median PFS in comparison with docetaxel, 4.4 months vs. 3.7 months (HR 0.75, P = 0.004). Improvements in both trials were supported by higher objective response rates in the Dato-DXd arm. Key subgroup analysis in the TROPION-Lung01 trial revealed that patients with non-squamous histology derived higher benefit with Dato-DXd treatment (median PFS: 5.6 months vs. 3.7 months, HR 0.63). At the time of this interim analysis, OS data numerically favored Dato-DXd in both trials, however, did not reach statistical significance. The overall safety profile of Dato-DXd was favorable and manageable with lower rates of grade ≥ 3 TRAEs than standard chemotherapy (21% vs. 45%) or docetaxel (25% vs. 41%) in the TROPION-Breast01 and TROPION-Lung01 trials, respectively. However, TROPION-Lung01 trial investigators highlighted grade ≥ 3 adverse events of special interest which occurred at a higher rate with Dato-DXd. These included stomatitis/oral mucositis (6% vs. 1%), ocular events (2% vs. 0%), infusion-related reactions (1% vs. 0%), and adjudicated drug-related interstitial lung disease (ILD) (3% vs. 1%). Grade 3 adjudicated drug-related ILD also occurred in the TROPION-Breast01 trial (1% vs. 0%).

Market impact

Interim data presented from both the TROPION-Breast01 and TROPION-Lung01 trials reported statistically significant PFS versus standard chemotherapy regimens, and an OS trend favoring Dato-DXd. Although this data is positive, the question of whether Dato-DXd will produce statistically significant longer OS remains. It will be important for Dato-DXd to do so to compete with the TROP2-targeting antibody-drug conjugate Trodelvy, which is approved for breast cancer and is in Phase 3 clinical trials for NSCLC. Moreover, safety concerns particularly in the TROPION-Lung01 trial may cast a shadow on the overall potential of this ADC. If approved, we anticipate a modest uptake of Dato-DXd in both HR-positive / HER2-negative breast cancer and non-squamous NSCLC. Although Phase 3 clinical trials are currently in progress in other breast cancer and NSCLC settings, HR-positive / HER2-negative breast cancer and non-squamous NSCLC are attractive commercially lucrative patient populations.

8. Primary analysis of the phase II DeLLphi-301 study evaluating tarlatamab in heavily pre-treated SCLC patients.[46]

Early benchmark-beating results from the DeLLphi-301 trial could help tarlatamab position as the standard of care in this setting.

Context

More than 80% of SCLC patients express DLL3 on the surface of cancer cells, making it a lucrative target.[44] Tarlatamab is a first-in-class bispecific T-cell engager (BiTE) that binds to DLL3 on target cancer cells and CD3 on T cells, resulting in T cell-dependent lysis of tumor cells. At WCLC 2022, Amgen reported initial positive results from a Phase 1 (DeLLphi-300) study of tarlatamab including an ORR of 23.4%, median DOR of 12.3 months, DCR of 51.4% and the median OS of 13.2 months in relapsed/refractory SCLC patients.[45] The results from a potentially registrational phase 2, DeLLphi-301, trial of tarlatamab in relapsed/refractory SCLC patients with two or more prior lines of treatment were presented at ESMO 2023.

Key ESMO findings

The Phase 2 DeLLphi-301 study demonstrated an ORR of 40.0%, median PFS of 4.9 months, median OS of 14.3 months, and median DCR of 70% at median follow-up of 10.6 months, at the 10 mg of tarlatamab. The median DOR was not reached. Overall, tarlatamab showed favorable safety with cytokine release syndrome (51.1%) being the most common treatment-emergent adverse event, and only 3% patients discontinued treatment at both doses. Also, ORR at 100 mg dose was lower than that at 10 mg dose depicting a potential lack of dose response.[46] Moreover, the absence of a control arm

in DeLLphi-301 trial could be considered a limitation as it presents a challenge in making meaningful comparisons.

Market impact

Currently, there are no approved therapies in the third-line treatment of SCLC and a high unmet need exists for these patients due to the extremely aggressive nature of the disease. With these remarkable ORR and survival data from the DeLLphi-301 trial, tarlatamab is likely to become the SOC in heavily pretreated SCLC patients who had failed at least two prior lines of treatment. Based on these exceptional and potentially registration enabling results in SCLC, we expect tarlatamab to gain approval as third-line therapy for SCLC.

9. WELIREG delays disease progression and improves responses in pretreated advanced renal cell carcinoma (RCC).[47]

LITESPARK-005 data could position WELIREG as a staple in later-line advanced RCC, but the absence so far of an OS benefit may hinder adoption.

Context

WELIREG is a first-in-class hypoxia-inducible growth factor-2α (HIF-2α) inhibitor approved for the treatment of Von Hippel-Lindau (VHL) disease-associated RCC (3-5% of RCCs). The agent is undergoing a comprehensive development program to expand its label across multiple sporadic RCC settings, including in late-line advanced or metastatic settings and in combination with other targeted therapies in the adjuvant and first-line settings. In August 2023, Merck & Co. announced that the phase 3 LITESPARK-005 trial, evaluating WELIREG in advanced RCC patients with 1 to 3 prior lines of therapy (including, at least, an anti-angiogenic agent and a PD-1 / PD-L1 inhibitor), met its co-primary endpoint of PFS[48]. First data were presented at ESMO 2023.[47]

Key ESMO findings

At the first pre-planned interim analysis, single agent WELIREG decreased the risk of progression or death by 25% compared with AFINITOR (co-primary endpoint; HR 0.75, P < 0.001). The PFS benefit remained consistent with extended follow-up at the second interim analysis (HR 0.74), and PFS rates at 12 and 18 months were 33.7% vs. 17.6% and 22.5% vs.9%, respectively. Key secondary endpoints were also met, including a substantial increase in ORR (21.9% vs. 3.5%, P< 0.0001; CR rate was 3.5% vs. 0%) and duration of response (19.5 months vs. 13.7 months), and an improvement in quality of life (increase in time to symptomatic deterioration per FKSI-DRS scale; HR 0.53, P < 0.001). OS, the trial's other co-primary endpoint, was still immature and only showed a trend favoring WELIREG (median OS of 21 months vs. 17.2 months; HR 0.87, P = 0.095); the investigators intend to conduct further tests on OS in subsequent analysis. The agent was safe and well tolerated, with 5.9% vs. 14.7% of patients discontinuing therapy due to any AEs and grade 3-5 TRAEs occurring in 38.7% vs. 39.4% of patients.

Market impact

LITESPARK-005 is the first phase 3 study to demonstrate positive outcomes in advanced RCC following PD-(L)1 and angiogenesis inhibition, a population with strong unmet needs and a lack of effective treatment options, particularly in the third and later lines. In September 2023, Merck & Co filed an sNDA for WELIREG in this setting based on then-undisclosed data from the trial; the FDA subsequently accepted the filing, granting priority review and setting a PDUFA date of January 17, 2024[49]. Based on WELIREG's strong PFS and ORR data, we anticipate that this label expansion will be successful, positioning the agent as an effective and tolerable option in the later lines of therapy. However, the absence of an OS benefit so far and the weakness of AFINITOR as a comparator raise some doubts, which may limit the

wide adoption of WELIREG in this setting. Nevertheless, this study establishes HIF-2α inhibition as a promising new mechanism of action in sporadic RCC, paving the way for further approvals of WELIREG across the treatment algorithm.

10. PSMA-targeted radioligand PLUVICTO extends rPFS in post-AR inhibitor, taxane-naive mCRPC.[50]

rPFS results from the Phase 3 PSMAfore trial position PLUVICTO as a promising frontline treatment option for mCRPC, despite unclear OS benefit.

Context

The PSMA-targeted radioligand PLUVICTO is approved in the United States and Europe for the treatment of mCRPC patients following progression on both AR inhibitors and taxane-based chemotherapy. Novartis is further evaluating PLUVICTO for earlier lines of treatment in two Phase 3 trials, the PSMAfore trial in taxane-naive (but post-AR inhibitor) metastatic castrate-resistant prostate cancer (mCRPC), and the PSMAddition trial in combination with AR inhibitors in metastatic hormone-sensitive prostate cancer (mHSPC). In December 2022, Novartis announced that the Phase 3 PSMAfore trial met the primary endpoint of radiographic progression-free survival (rPFS).[51] The primary efficacy and safety results were presented at ESMO 2023.

Key ESMO findings

The primary analysis from PSMAfore demonstrated that PLUVICTO more than doubled rPFS over control in taxane-naive mCRPC (12.0 vs. 5.6 months; HR 0.43, $P < 0.0001$). The second interim OS analysis (at 45% of events) showed a higher risk of death for PLUVICTO (HR 1.16) in the intent-to-treat population. When adjusted for the high rate of crossover (84%) from the control arm to PLUVICTO upon disease progression, PLUVICTO showed a 20% reduction in the risk of death (HR 0.80). ORR and median duration of response were meaningfully improved by PLUVICTO over control (51% vs. 15% and 13.6 months vs. 10.1 months). PLUVICTO had a better safety profile than control, with a lower incidence of grade ≥3 AEs and serious AEs.

Market impact

PLUVICTO has rapidly secured a substantial market share in later-line mCRPC in its first year on the market. The large rPFS benefit and favorable safety outcomes from the PSMAfore trial support use of PLUVICTO in taxane-naive mCRPC, although these outcomes are somewhat marred by the lack of a clear and unequivocal OS benefit. FDA regulatory submission is now pushed to 2024 instead of this year, as OS data collection continues.[52] These mixed results may cast a shadow over two other PSMA-targeted radioligands, POINT Biopharma's ^{177}Lu-PNT-2002 and Curium's ^{177}Lu-PSMA-I&T, which are under evaluation in the same treatment setting as PSMAfore and in similarly designed Phase 3 trials (SPLASH and ECLIPSE, respectively). The choice of AR inhibitors as the comparator arm in PSMAfore is debatable because physicians are unlikely to prescribe two AR inhibitors consecutively in clinical practice, and docetaxel is the standard of care for taxane-naive mCRPC patients progressing on AR inhibitors. If granted, a label expansion of PLUVICTO based on PSMAfore may be restricted to patients ineligible for, or who refuse, taxane-based chemotherapy.

Key ESMO 2023 takeaways from Mainland China

1. Senaparib proves effective as a maintenance treatment in newly diagnosed FIGO stage III-IV ovarian cancer patients.[53]

Can senaparib outcompete its existing rivals in the first-line treatment setting in Mainland China?

Context

While maintenance treatment with LYNPARZA and ZEJULA has greatly improved outcomes in the first-line metastatic ovarian cancer patients, treatment discontinuation due to safety issues associated with prolonged use of these drugs is a potential concern in this setting.

Key ESMO findings

Impact therapeutics / Junshi Biosciences presented encouraging findings from phase 3 FLAMES trial in 404 newly diagnosed FIGO stage III/IV ovarian cancer patients who had achieved complete or partial response after first-line platinum-based chemotherapy. Patients receiving 100 mg senaparib QD demonstrated a significant improvement in PFS over placebo (HR 0.43, 95% CI 0.32-0.58, P < 0.0001), regardless of their BRCA mutation status. While 66.3% patients receiving the drug experienced grade ≥3 adverse events (versus 20.3% in the placebo arm) less than 5% patients discontinued treatment due to adverse events and no fatalities were reported.

Market impact

In August 2023, Junshi Biosciences announced the acceptance of the NDA for senaparib as a maintenance treatment following first-line therapy in patients with advanced ovarian cancer. If approved, senaparib will be the first domestic PARP inhibitor to enter this first-line treatment setting. While senaparib has a promising clinical profile with fewer treatment discontinuations it may face strong competition from existing PARP inhibitors in the first-line maintenance setting, particularly ZEJULA, which is dosed once-daily and is not biomarker restricted.

2. **The addition of perioperative BAIZEAN to neoadjuvant chemotherapy improves pathological response in resectable early-stage NSCLC patients.[54]**

Label expansion in the early-stage setting will further strengthen the *BAIZEAN foothold in the NSCLC market in Mainland China*.

Context

BeiGene's *BAIZEAN* is already a mainstay of the NSCLC market in Mainland China, with approvals in the first-line metastatic setting as monotherapy and in combination with chemotherapy. Like many established NSCLC drugs, BAIZEAN is moving into earlier treatment settings and new label expansions here will boost its outreach in Mainland China.

Key ESMO findings

The phase 3 RATIONALE-315 trial showed that BAIZEAN plus chemotherapy followed by surgery and adjuvant BAIZEAN significantly improves major pathological response (MPR) rate compared with neoadjuvant chemotherapy and surgery (56.2% months vs. 15%; P< 0.0001) in resectable stage II-IIIA NSCLC patients. Patients in the BAIZEAN versus control arm demonstrated statistically significant and clinically meaningful improvement in event free survival (EFS). The study also met its key secondary endpoint of pathological complete response (pCR) rates (40.7% vs. 5.7%; P< 0.0001). No new safety signals emerged.

Market impact

The late-stage pipeline in the perioperative space in Mainland China is very active. If approved, we anticipate BAIZEAN will garner significant uptake in the perioperative (neoadjuvant and adjuvant) treatment setting, considering its long-term physician familiarity, affordability, and eligibility for reimbursement. However, it may face strong competition from other emerging immune checkpoint inhibitors in the perioperative

space including Innovent's TYVYT, another established domestic player, KEYTRUDA, IMFINZI, TUOYI and adebrelimab.

3. **CEJEMLY could serve as a new treatment option for first line HER2-negative locally advanced or metastatic gastric / GEJ adenocarcinoma patients.[55]**

On its way to becoming the first PD-L1 inhibitor to gain approval for the first-line treatment setting.

Context

The first-line metastatic HER2-negative gastric / GEJ adenocarcinoma patient population is the largest gastroesophageal cancer population in terms of drug-treatable patients in Mainland China. Chemotherapy has been the mainstay treatment option in this patient setting. Market growth in this area is almost exclusively a result of the launch and continued uptake of immune checkpoint inhibitors.

Key ESMO findings

CStone presented positive findings from phase 3 GEMSTONE-303 study. CEJEMLY plus chemotherapy showed a statistically significant improvement in OS (15.64 months vs. 12.65 months; HR 0.75; P<0.0060) and PFS (7.62 months vs. 6.08 months; HR 0.66; P < 0.0001) compared with chemotherapy, in HER2-negative first-line gastric / GEJ adenocarcinoma patients with PD-L1 expression ≥5%. ORR also improved with the addition of CEJEMLY to chemotherapy. No new safety concerns were identified in the study.

Market impact

Based on the positive trial data CStone has filed an sBLA to NMPA in February 2023 seeking label expansion for CEJEMLY as a first-line treatment for locally advanced or metastatic gastric / GEJ adenocarcinoma patients. In addition to an array of multiple immune checkpoint inhibitors available for the first line treatment, this setting is likely to witness the launch of novel targeted therapies over the next five years. Given the large volume of eligible patient pool and the continued need for effective treatment alternatives in this setting, CEJEMLY has the potential to garner substantial sales despite stiff competition and modest uptake.

4. **Erdafitinib, a selective pan-FGFR inhibitor, showed encouraging efficacy outcomes in high-risk NMIBC patients.[56,57]**

What is the way forward in NMIBC patients: oral or intravesical erdafitinib?

Context

As of today, TURBT is the main treatment option for NMIBC patients in Mainland China. Following TURBT, patients at intermediate or high risk of recurrence generally receive intravesical chemotherapy or intravesical BCG (induction and maintenance). For patients with T1 high-grade tumors or who are BCG-refractory, radical cystectomy may be considered but not all patients are eligible or are willing to undergo the procedure. As a result, there is long-standing need for more effective targeted treatment alternatives in this setting.

Key ESMO findings

Janssen presented promising findings from a Phase 2 study (THOR-2) demonstrating that oral erdafitinib (6 mg) elicited a prolonged recurrence free survival (RFS) compared with intravesical chemotherapy (HR: 0.28 [0.13-0.62], p=0.0008). Median RFS was not achieved in patients receiving erdafitinib (vs. 11.6 months for chemotherapy) at a median follow-up of 13.8 months. A higher rate of grade ≥3

treatment related adverse events were noted in patients receiving erdafitinib (31% vs 4% [chemotherapy]) leading to treatment discontinuation (28.6% vs. 0%).

Additionally, Janssen presented initial data for TAR-210, an erdafitinib intravesical delivery system, in intermediate-risk patients with history of low-grade papillary disease and BCG-refractory high-risk NMIBC patients. TAR-210 showed a high CR rate in intermediate-risk patients (87%) and 82% recurrence-free rate in high risk NMIBC patients. Notably, no dose-limiting toxicities or fatalities were observed in this study.

Market Impact

NMIBC patients have high expression levels of FGFR3 mutations compared with the muscle-invasive patients. While more data is warranted, encouraging findings from these studies show an important clinical advancement for the management of high-risk NMIBC patients with select FGFR alterations. If approved, erdafitinib may fulfil an unmet need for BCG-refractory patients for whom no other targeted agents are currently approved and thus is poised to garner significant uptake in a highly underserved patient segment in Mainland China.

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