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Big Readouts For AstraZeneca, Daiichi Sankyo And Gilead At Lung Cancer Congress

Data At WCLC From Tagrisso And A Host Of ADCs

by Andrew McConaghie

AstraZeneca's Tagrisso could consolidate its place in EGFR-positive lung cancer, while Daiichi looks to go it alone with its own antibody-drug conjugate.

The upcoming World Conference on Lung Cancer, being held in Singapore from 9-12 September, has a number of major readouts in targeted lung cancer therapy and antibody drug conjugates (ADCs) including presentations from *AstraZeneca*, *Daiichi Sankyo* and *Gilead*.

The meeting is particularly important for AstraZeneca, which is looking to extend its dominance in non-small cell lung cancer (NSCLC) with new data from its EGFR-targeting small-molecule blockbuster Tagrisso (osimertinib) and for its Daiichi Sankyo-partnered ADCs, Enhertu (trastuzumab deruxtecan) and late-stage candidate Dato-DXd (datopotamab deruxtecan).

Adding Chemo To Boost Tagrisso Response

In May, AstraZeneca reported positive high-level results from its FLAURA2 study evaluating Tagrisso in combination with chemotherapy for patients with locally advanced (Stage IIIB-IIIC) or metastatic (Stage IV) EGFR mutated NSCLC.

Tagrisso is the standard of care for newly diagnosed EGFR-mutated advanced NSCLC, but patients typically acquire resistance to the drug after one or two years. The hope is that by adding chemotherapy, treatment resistance and disease progression can be further delayed.

AstraZeneca announced in May that the FLAURA2 combination had produced a "statistically

significant and clinically meaningful improvement in PFS" compared with standard-of-care Tagrisso monotherapy. (Also see "*AstraZeneca Lifted By Tagrisso Combo Lung Cancer Data*" - Scrip, 17 May, 2023.)

A late-breaking plenary presidential symposium presentation will showcase the PFS data, and analysts will be watching to see if the results are impressive enough to make this the new standard of care. A key question will be around the level of added toxicity the chemo brings. AstraZeneca is expected to provide subgroup analyses, which could allow the selection of patients with higher-risk disease, who may benefit more from this escalation of treatment compared with Tagrisso monotherapy.

However, if a subsequent overall survival (OS) readout is particularly strong, the Tagrisso plus chemo combination may get taken up more widely. Analysts at J.P. Morgan have predicted the results could show a six-month benefit in PFS on top of the already strong Tagrisso monotherapy efficacy.

They added that FLAURA2 was likely to sustain Tagrisso peak sales of at least $7.3bn in 2028, broadly in line with consensus of $7.7bn. Last month, the Tagrisso-plus-chemotherapy combination was granted breakthrough therapy designation by the US Food and Drug Administration, setting it up for likely approval next year.

First Enhertu Survival Data In Lung Cancer

Last summer, Enhertu became the first HER2-directed therapy available for NSCLC after receiving accelerated approval from the US FDA.

This was based on an interim efficacy analysis of 52 patients from the DESTINY-Lung02 Phase II trial in patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations. This approval was based on objective response rate and duration of response, but investigators will present at WCLC the first OS and PFS results from the study in a mini-oral presentation.

The published abstract shows the median PFS on the lower 5.4mg/kg dose was 9.9 months and OS was 19.5 months (not evaluable on the higher 6.4 mg/kg dose). This was offset by Grade ⩾3 drug-related treatment-emergent adverse events (TEAEs) in 38.6% receiving the lower dose and 58% receiving the higher dose, with one death in each arm attributed to TEAEs.

HER2-positive lung cancer is an aggressive form of disease which commonly affects young patients, and the presentation will highlight the need for early use of HER2 diagnostics.

Daiichi Going It Alone With HER3 Targeting ADC

Daiichi Sankyo has enjoyed great success in its partnership with AstraZeneca on Enhertu, and

the two have high hopes for their late-stage Dato-DXd candidate, but the Japanese company is looking to step out of the shadow of its better-known partner with HER3-DXd (patritumab deruxtecan).

This is the first ADC candidate developed via its in-house platform that it intends to market without AZ's assistance. The company has developed it for patients with EGFR-mutated NSCLC, who have progressed after EGFR-targeting treatment, such as Tagrisso, and platinum-based chemotherapy.

The ADC targets receptor tyrosine-protein kinase ERBB3 (HER3), which has been found in 83% of primary NSCLC tumors and at high levels in EGFRm lung cancer.

The company will present results from the Phase II HERTHENA-Lung01 trial, which it hopes to subsequently submit as pivotal data to regulators.

The pre-published extract shows encouraging data, with the ADC given after either older EGFR-targeting drugs and platinum-based chemotherapy (PBC) or Tagrisso and PBC. In the first arm, confirmed overall response rate was 28.4%, median PFS was 5.5 months; and median OS (preliminary) was 11.9 months. Patients on the post-Tagrisso arm had similar outcomes.

An eventual FDA approval could make HER3-DXd the favored third-line option for EGFR-mutated advanced NSCLC, and the only approved targeted therapy for post-Tagrisso treatment.

Safety In Spotlight In Adding ADCs To Keytruda

Gilead's most important readout at the congress will be preliminary results from its Phase II EVOKE-2 trial, evaluating the TROP-2 directed ADC Trodelvy (sacituzumab govitecan) plus Merck & Co's Keytruda (pembrolizumab) with or without chemo in first-line NSCLC. The presentation will focus on data from the first two cohorts of the combination in PD-L1 high and PD-L1 low patients.

The company is hoping to eventually show that its ADC can add to the great progress made with Keytruda and chemo in frontline NSCLC. It would also like to capitalize on what appear to be disappointing results for AstraZeneca and Daiichi Sankyo's potential competitor.

AstraZeneca saw £10bn ($12.7bn) wiped off its market value in June after it posted early efficacy data from the TROPION-Lung01 trial of Dato-DXd, seen as a potential future market leader among TROP2-targeting antibody drug conjugates.

The company disclosed that its Phase III study had hit its PFS co-primary endpoint, but the measured language used in the communication suggested the results fell short of a clear 3-4 month PFS benefit over chemotherapy in second-line non-small cell lung cancer. (Also see "*Can*

Gilead And Merck Capitalize On AstraZeneca/Daiichi Sankyo's TROP2 Safety Concerns?" - Scrip, 4 Jul, 2023.)

However, the study's safety results were perhaps of greater concern, with AZ and Daiichi reporting at least "some" Grade 5 toxicities – ie patient deaths – linked to interstitial lung disease (ILD), an adverse event frequently seen with ADCs, but not usually proving fatal.

Dato-DXd had been seen as a potential best-in-class TROP targeting ADC, and Gilead's candidate now has a chance to demonstrate a superior profile. The EVOKE-2 study abstract published ahead of the presentation on 10 September focuses on an initial small subset of 44 patients. The presentation will include data taken at a later cut-off date including more patients.

The abstract shows that as of 13 January 2023, in the 26 of the 44 patients who were efficacy evaluable, ORR by investigator assessment was 75% (five confirmed partial responses and one pending confirmation) in cohort A and 44% (seven confirmed PRs and one pending confirmation) in cohort B.

Among safety-evaluable patients (n=44), the incidence of any-grade TEAEs was 96% (grade 3/4, 52%). TEAEs leading to discontinuation occurred in 7% of patients, and TEAEs leading to death were reported in three (7%) patients, though only one was considered related to study treatment. Nevertheless, the benefit/risk profile of both Trodelvy and Dato-DXd will be questioned in light of these results, and skepticism will persist in the absence of compelling efficacy data.

AstraZeneca is not presenting results of the TROPION Lung01 at WCLC, but will have results from another Dato-DXd study, TROPION Lung04. This is evaluating the ADC in combination with AstraZeneca's PD-L1 inhibitor, Imfinzi (durvalumab), with or without chemotherapy in patients with metastatic NSCLC, and will provide another chance for the ADC to show its potential in combination with a PD-L1 therapy.

AstraZeneca is expected to present TROPION Lung01 at the European Society of Medical Oncology, taking place in Madrid, Spain, next month. That will give analysts a chance to make a cross-trial comparison with Gilead's results, and weigh up either of the ADCs chances of playing a role in frontline lung cancer treatment.