Evaluate Vantage

May 10, 2021

Esmo Breast Cancer – Astra and Daiichi square up to Gilead

Jacob Plieth

Datopotamab, a project with a very similar mechanism to Trodelvy, shows impressive early data in triple-negative breast cancer.

Early reports on the efficacy of Daiichi Sankyo's datopotamab deruxtecan suggest that Astrazeneca might not have been foolish to part with $1bn for rights to it a year ago. The data, in 21 late-line triple-negative breast cancer subjects, show an impressive 43% overall response rate.

But the presentation, given at Saturday's Esmo Breast Cancer congress, also highlighted what will no doubt be a closely watched adverse event: a 63% rate of stomatitis, including 13% at grade 3 or above. With Gilead recently launching Trodelvy, a very similar drug, the battle lines have been drawn.

Cross-trial comparisons are unavoidable. Trodelvy's label in third-line or later TNBC cites a 33% ORR in the single-cohort Imu-132-01 study, while the controlled Ascent trial yielded 11.8 months of median overall survival, a 4.9-month benefit over chemo alone ($p<0.0001$). The drug has a boxed warning of neutropenia and diarrhoea, while Ascent showed a 17% rate of stomatitis.

The two assets are mechanistically similar, both targeting the Trop2 antigen. Both are antibody-drug conjugates, with Trodelvy using an SN38 payload and datopotamab DXd, a topoisomerase I inhibitor; DXd is same toxic payload employed in Enhertu, the anti-Her2 drug at the heart of Astra and Daiichi's 2019 tie-up.

Enhertu is now one of Astra's most important growth drivers, and its success prompted the group to double down on Daiichi, handing across another $1bn last year for datopotamab (*Another Astra-Daiichi tie-up puts Trop2 in focus, July 27, 2020*).

Trodelvy is also approved for urothelial bladder cancer, on an accelerated basis, while datopotamab is being studied in lung cancer in addition to TNBC. Relatively high rates of stomatitis were also seen in datopotamab's NSCLC trial.

Tropion-Pantumor01

The Esmo data over the weekend came from a January 8 cut of 21 evaluable subjects in a TNBC cohort of the Tropion-Pantumor01 trial; patients had failed a median four prior treatments, eight had failed immunotherapy and two were post Trodelvy.

Stomatitis and mucosal inflammation caused dose reductions in 25% of patients. Another reason for caution is

that four of the nine partial remissions seen have yet to be confirmed centrally.

Be that as it may, Trop2 is clearly emerging as an exciting anticancer target, something backed up by sellside consensus for 2026 revenue forecasts for Trodelvy and datopotamab – $2.7bn and $1.2bn respectively, according to *Evaluate Pharma*.

As such, it might be surprising that there are apparently just two other Trop2-targeting industry assets in clinical trials, both in development by Chinese groups: Kelun's ADC SKB264 and Shanghai Junshi's naked antibody JS108.

Another Chinese company, Bio-Thera, had an ADC coded BAT8003 in phase 2, but ran into problems with its batansine-derived payload, and reportedly canned development of all conjugates using this technology. Pfizer dropped its anti-Trop2 ACD PF-06664178 back in 2016.

Clinical-stage assets against Trop2

			Sales forecasts ($m)			
Project	**Company**	**Modality**	**2020**	**2022e**	**2024e**	**2026e**
Trodelvy	Gilead (ex Immunomedics)	MAb-SN38 conjugate	118	751	1,652	2,687
Datopotamab deruxtecan (DS-1062)	Astrazeneca/Daiichi Sankyo	MAb-topoisomerase I inhibitor conjugate	-	11	312	1,218
SKB264	Klus Pharma (Kelun)	MAb-belotecan-derived payload conjugate	No consensus available; ph1/2 in solid tumours incl TNBC			
JS108	Shanghai Junshi	Humanised MAb	No consensus available; ph1 solid tumour trial started recently			

Source: Evaluate Pharma sellside consensus & clinicaltrials.gov.

Investors are also focused on Trodelvy's phase 3 Tropics-02 study, testing the drug in third-line Her2-negative but HR-positive breast cancer patients, an important label expansion play.

Importantly, Tropics-02 specifies that patients must have failed at least one CDK4/6 inhibitor, meaning Ibrance, Kisqali or Verzenio. Earlier phase 1 data suggest that Trodelvy gives overall survival of only around 11 months in post-CDK4/6 patients, versus 22 months in those with no prior CDK4/6 therapy.

All will be revealed in the second half, when Tropics-02 is due to yield results.