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The first big test for the son of Enhertu

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Readout of Tropion-Lung01, testing the most advanced indication for datopotamab, could lead to a first-half US filing.

The next big test of Daiichi Sankyo's antibody-drug conjugation prowess, which spawned Enhertu and a multi-billion dollar alliance with Astrazeneca, is approaching. Datopotamab deruxtecan, an ADC against Trop2, will shortly yield data from its first phase 3 study, Tropion-Lung01, and if favourable this will lead to a first-half regulatory filing.

This will also be a test for Trop2 inhibition, a strategy that so far has yielded the marketed but rather underwhelming Gilead drug Trodelvy. While Trodelvy is approved for breast and bladder cancers, datopotamab's first indication is lung cancer, though the Gilead project is in pivotal development in other settings too, including NSCLC.

Tropion-Lung01 enrolled a broad treatment-refractory NSCLC population, and tests datopotamab versus docetaxel. Patients without actionable genomic alterations including EGFR and Alk must have failed chemo and an anti-PD-(L)1 drug, but those with a mutation must only have failed targeted therapy or chemo or anti-PD-(L)1.

The trial's co-primary endpoints are overall and progression-free survival. Trop2 is said to be overexpressed in several cancers, but the study does not limit patients to those expressing it. However, it would be logical to expect Trop2-positive patients to do best, and unspecified biomarkers will be evaluated in Tropion-Lung01 for potential associations with efficacy.

Since anti-PD-(L)1 therapy became a NSCLC standard of care relatively recently it is difficult to gauge second-line expectations, but median overall survival after failure of a platinum-based chemotherapy and immunotherapy is less than a year, according to Tropion-Lung01's trials-in-progress abstract presented at Asco 2021.

For the trial to be considered at success, datopotamab needs to show at least a two-month mPFS advantage over docetaxel, Jefferies analysts believe; they expect around four months' mPFS from the control arm. A "dream scenario" would see the ADC double mPFS, and raise the prospect of datopotamab replacing chemo in early NSCLC settings, they write.

Blockbuster sales

It is difficult to handicap the result of Tropion-Lung01, though there have been positive hints, most recently

from a TNBC cohort of the Tropion-Pantumor01 study presented at last month's San Antonio Breast Cancer Symposium, showing a 32% ORR and 16.8-month median response duration.

In NSCLC specifically last year's World Lung conference included data from the uncontrolled Tropion-Lung02 trial, in which a datopotamab combo with Keytruda yielded ORR of 62% front line and 24% in the second-line or later settings. Cross-trial comparisons show Keytruda alone yielding ORRs in NSCLC of 27-45% first line.

As such datopotamab seems to add at least some efficacy, so all it has to do now is demonstrate this as a monotherapy and beat docetaxel. Another key point is safety. Enhertu carries a boxed warning about interstitial lung disease (ILD), and caution about this applies to all Daiichi ADCs; three potential ILD events are "pending adjudication" in Tropion-Lung02.

$2.35bn up front

Astra paid Daiichi $1.35bn in 2019 for rights to what became Enhertu, and its faith was rewarded when the drug scored a massive victory in breast cancer at last year's Asco. In 2020 Astra gave Daiichi a further $1bn up front for datopotamab, hoping that the Japanese group's conjugation technology, validated by Enhertu, could score with a second mechanism.

That mechanism, Trop2 antagonism, is best known for being used by Gilead's Trodelvy. This is also an ADC but which has a different design, and whose arguable success in its main approved use, triple-negative breast cancer, has been largely overshadowed by Enhertu.

The mechanism has limited biopharma involvement, though in 2021 Merck & Co paid Kelun $47m for rights to two ADCs, including MK-2870/SKB-264, which hits Trop2.

Should Tropion-Lung01 succeed perhaps interest will pick up. Current sellside consensus has datopotamab sales topping $2bn by 2028, according to *Evaluate Pharma,* though that number is heavily risk adjusted. Peak estimates sit considerably higher, particularly when the project's potential in other tumour types is considered.

Additional uses for datopotamab include first-line NSCLC (Tropion-Lung08 study), ER-positive Her2-negative breast cancer (Tropion-Breast01) and front-line triple-negative breast cancer (Tropion-Breast02).

Trop2-targeting ADCs in clinical development

Project	Company	Type of payload	Status
Trodelvy	Gilead (ex Immunomedics)	SN38	Marketed for breast cancer; ph3 includes Evoke-01 trial in post-IO NSCLC
Datopotamab deruxtecan	Daiichi Sankyo/Astrazeneca	Topoisomerase I inhibitor exatecan	Ph3 includes Tropion-Lung01 in previously treated NSCLC
MK-2870/ SKB-264	Kelun/Merck & Co	Belotecan derivative KL610023	Ph3 TNBC study (S Korea) not yet recruiting
ESG-401	Escugen/Sorrento	SN38	Ph1/2 solid tumour trial
BIO 106	Bionecure	Unknown	Ph1/2 trial +/- Keytruda
DB-1305	Dualitybio	Topoisomerase I inhibitor P1021	Ph1/2 solid tumour trial
JS108	Shanghai Junshi	Tub196	Ph1 solid tumour trial
BL-M02D1	Systimmune	Unknown	Ph1 in solid tumours including gastrointestinal & TNBC
FZ-AD004	Shanghai Fudan-Zhangjiang	Topoisomerase I inhibitor BB05	Ph1 IND accepted Jan 2023

Notes: ADC=antibody-drug conjugate; this table has been updated to include additional projects. Source: Evaluate Pharma & clinicaltrials.gov.

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