Evaluate Vantage

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Treme climbs a new mountain

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Astrazeneca's Himalaya study is a surprising hit in first-line liver cancer, but competition is already present.

Astrazeneca's long-delayed Himalaya study in front-line liver cancer has apparently come up trumps. After Poseidon this is the second trial to suggest that tremelimumab might not, after all, be a write-off, and its success probably owes something to a novel dosing regimen that could avoid treme's toxicities.

Still, with Roche's Tecentriq plus Avastin already available, first-line liver cancer is no longer the immuno-oncology white space it once was. And several upcoming phase 3 readouts for Astra's rivals might make it harder still for the UK company to make a significant dent in this market.

The next relevant readout should come later this year from a Chinese study of Juangsu Hengrui's camrelizumab, though the big threats in terms of Western datasets are Beigene's Rationale-301 trial of tislelizumab, and Merck & Co/Eisai's Leap-002 study of Keytruda plus Lenvima. Both have primary completion dates next May.

Bristol Myers Squibb's Checkmate-9DW trial of Opdivo plus Yervoy is highly relevant, testing the same anti-PD-1/CTLA-4 mechanism as Himalaya, though it might not yield data until 2023. Notably, however, Opdivo has already failed in first-line liver cancer, as monotherapy in Checkmate-459 – a result that prompted this year's withdrawal of Opdivo's second-line label; a Yervoy combo remains available second line.

But Astra can celebrate the fact that, pending full data release from Himalaya, it looks like Imfinzi plus tremelimumab might be approvable in first-line liver cancer. Until the combo's unexpected success in the NSCLC study Poseidon, which also included chemo, tremelimumab had run up a dismal record of failures, and Astra seemed largely to have deprioritised it.

Selected pivotal studies containing tremelimumab				
Trial	**Cancer type**	**Treatment cohort(s)**	**Enrolment**	**Result/data due**
Arctic	3rd-line NSCLC	Imfinzi +/- tremelimumab	597	Fail
Eagle	2nd-line head & neck	Imfinzi +/- tremelimumab	736	Fail
Mystic	1st-line NSCLC	Imfinzi +/- tremelimumab	1,118	Fail
Poseidon	1st-line NSCLC	Imfinzi + chemo +/- tremelimumab	1,000	Tremelimumab combo arm positive for OS; Imfinzi arm negative for OS (both positive for PFS)
Neptune	TMB-high, 1st-line NSCLC	Imfinzi + tremelimumab	953	Fail
Danube	1st-line urothelial	Imfinzi +/- tremelimumab	1,126	Fail
Caspian	1st-line SCLC	Imfinzi + chemo +/- tremelimumab	988	Imfinzi arm positive for OS, tremelimumab combo arm negative for OS
Kestrel	1st-line head & neck	Imfinzi +/- tremelimumab	823	Fail
Himalaya	1st-line hepatocellular	Imfinzi +/- tremelimumab	1,504	Tremelimumab combo arm positive for OS; Imfinzi arm non-inferior for OS
Adriatic	SCLC maintenance	Imfinzi +/- tremelimumab	600	H2 2022
Strong	Various	Imfinzi +/- tremelimumab	1,200	2022 or beyond
Nile	1st-line urothelial	Imfinzi + chemo +/- tremelimumab	1,215	2022 or beyond
Source: clinicaltrials.gov & EvaluatePharma.				

Himalaya also included an Imfinzi-only cohort, but this did not appear to have performed as well, only meeting overall survival non-inferiority, as opposed to the combo's stated OS benefit, versus Nexavar. This is important, suggesting – as in Poseidon – that the anti-CTLA-4 MAb has an additive benefit, and that the success is not just down to Imfinzi.

Cracking the treme puzzle might be thanks to Himalaya's use of what Astra calls the Stride regimen, comprising just a single 300mg priming dose of treme together with Imfinzi, followed by Imfinzi alone. Still, this had not been employed in Poseidon.

But data at Asco in 2020 had already suggested the potential of Stride, in Study 22, comprising a mixture of first and second-line liver cancer subjects. This was said to read out positively, and though it had no control cohort it provided a way of handicapping the Himalaya result.

At present the front-line immuno-oncology space has only one US contender, Roche's Tecentriq plus Avastin having been approved last year on the basis of Imbrave-150; more recently a Tecentriq combo with Exelixis's Cabometyx failed the Cosmic-312 trial, however.

In China Innovent's Tyvyt is approved in combination with an Avastin biosimilar called Bevasda.

Keytruda plus Lenvima, meanwhile, got a US complete response letter because, after Tecentriq/Avastin's approval, the uncontrolled Keynote-524 trial no longer gave sufficient front-line backing. Keytruda retains a second-line label, having failed the potentially confirmatory Keynote-240 trial but succeeded in Keynote-394, a study in Asian patients.

For now Astra can celebrate tapping into treme's efficacy while avoiding its toxicity; this in itself is a big

surprise.

Selected phase 3 studies of anti-PD-(L)1 projects in first-line liver cancer				
Project	**Company**	**Design**	**Study**	**Result**
Opdivo	Bristol Myers Squibb	Vs Nexavar	Checkmate-459	Fail
Tecentriq	Roche	Avastin combo vs Nexavar	Imbrave-150	Success; US approval
Tecentriq	Roche/Exelixis	Cabometyx combo vs Nexavar	Cosmic-312	Fail
Tyvyt	Innovent	Bevasda (Avastin biosimilar) combo vs Nexavar	Orient-32	Success; China approval
Imfinzi	Astrazeneca	+/- tremelimumab vs Nexavar	Himalaya	Success
Camrelizumab	Jiangsu Hengrui	Apatinib combo vs Nexavar	NCT03764293	Ends Dec 2021
Tislelizumab	Beigene	Vs Nexavar	Rationale-301	Ends May 2022
Keytruda	Merck & Co/Eisai	Lenvima combo vs Lenvima	Leap-002	Ends May 2022
Toripalimab	Shanghai Junshi	Lenvima combo vs Lenvima	NCT04523493	Ends Aug 2023
Opdivo	Bristol Myers Squibb	Yervoy combo vs Nexavar or Lenvima	Checkmate-9DW	Ends Sep 2023
HLX10	Shanghai Henlius/Fosun	HLX04 (Avastin biosimilar) combo vs Nexavar	NCT04465734	Ends Oct 2023
Source: clinicaltrials.gov.				