Evaluate Vantage

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Esmo 2022 – the new liver cancer entrants line up

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Late-breakers give tislelizumab, camrelizumab and Keytruda outside chances to add to the first-line armamentarium.

Front-line liver cancer, a setting into which immunotherapy has only made recent inroads, will soon see more competition. Whether that competition will include Beigene/Novartis, Jiangsu Hengrui or even Merck & Co/Eisai will be down to those companies and the FDA.

This is because pivotal data from their three anti-PD-1 approaches, just revealed in three Esmo late-breaking abstracts, show each to have some merit, but the studies in question also come with important caveats. The datasets will be picked apart at the meeting's Saturday morning session, and will be closely watched by the next expected entrant, Astrazeneca.

Astra's Imfinzi, with or without the anti-CTLA-4 MAb tremelimumab, is awaiting US approval based on a roughly three-month overall survival benefit over Nexavar in the Himalaya trial. The company's US filing was accepted with priority review in April, and the Pdufa date is expected to fall in the fourth quarter.

Nexavar as well as Lenvima are front-line standards of care in liver cancer. They were joined in 2020 by Roche's Tecentriq plus Avastin combo, which beat Nexavar in the Imbrave-150 trial and marked immunotherapy's first success in this tricky field, which had seen Bristol Myers Squibb trip up in Opdivo's Checkmate-459 trial.

Up next

Now the stage is set for the next act. Pivotal studies of Jiangsu Hengrui's camrelizumab plus the tyrosine kinase inhibitor rivoceranib, and of Beigene/Novartis's tislelizumab monotherapy, were earlier toplined positive versus Nexavar, and Esmo has shown the actual numbers for the first time.

The camrelizumab combo stands out in having yielded a 22.1-month median OS benefit – the highest ever on a cross-trial basis. However, the study was conducted largely in China, though it did include some US and European hospitals. Jiangsu is not known to have a US presence, and camrelizumab has never been filed in the US; it is approved in China, including for second-line liver cancer.

Meanwhile, Beigene plans a 2023 US filing for tislelizumab based on Rationale-301, a global study that also appears heavily weighted towards Chinese hospitals. A big caveat here, however, is that this has only shown

non-inferiority to Nexavar, and the Esmo abstract reveals a 15% reduction in risk of death, with the confidence interval's upper bound over 1.0.

The authors call tislelizumab's OS benefit "clinically meaningful", and Beigene might also point to Eisai's Lenvima, which secured its first-line label based on non-inferiority to Nexavar.

A separate problem for the FDA is the acceptability or otherwise of datasets that were generated largely outside the US. Moreover, Beigene and its partner Novartis have yet to get tislelizumab across the US regulatory line, with Covid delaying an FDA decision in oesophageal cancer, and a second-line lung cancer filing recently being abandoned.

Cross-trial comparisons in 1st-line liver cancer					
			mOS		
Drug(s)	**Company**	**Trial**	**Active**	**Control**	**Stats**
US approved					
Nexavar	Bayer	Sharp	10.7mth	7.9mth*	HR=0.69, p=0.00058
Lenvima	Eisai	Reflect	13.6mth	12.3mth	HR=0.92^
Tecentriq + Avastin	Roche	Imbrave-150	NE	13.2mth	HR=0.58, p=0.0006
Awaiting US approval					
Imfinzi	Astrazeneca	Himalaya	16.6mth	13.8mth	HR=0.86^
Imfinzi + tremelimumab			16.4mth		HR=0.78, p=0.0035
Not US approved					
Camrelizumab + rivoceranib	Jiangsu Hengrui	SHR-1210-III-310	22.1mth	15.2mth	HR=0.62, p<0.0001
Tislelizumab	Beigene/ Novartis	Rationale-301	15.9mth	14.1mth	HR=0.85^
Failed studies					
Opdivo	Bristol Myers Squibb	Checkmate-459	16.4mth	14.7mth	HR=0.85, p=0.075
Keytruda + Lenvima	Merck & Co/Eisai	Leap-002	21.2mth	19.0mth**	HR=0.84, p=0.0227
*Note: ^successful only on a non-inferiority basis; *placebo; **Lenvima (all others used Nexavar as control). NE=not estimable; Source: product labels, The Lancet, Esmo & company statements.*					

Where does this leave Merck & Co? The Leap-002 study of Keytruda combined with Lenvima that features in its Esmo late-breaker was already known to have been a failure.

However, the trial's authors call the combo's median OS benefit, revealed as 21.2 months, "the longest ... ever reported in first-line hepatocellular carcinoma phase 3 studies" (a claim clearly made before they had a chance to see Jiangsu Hengrui's camrelizumab plus rivoceranib data).

Merck/Eisai's problem is that Leap-002 logically used as a control not Nexavar but the numerically more efficacious Lenvima. Keytruda already carries a second-line liver cancer label, as does Opdivo, and Merck is not thought to be pursuing approval based on Leap-002.

"The median OS of 19.0 months with Lenvima monotherapy supports its role as a standard of care," the late-breaker's authors conclude.

The Esmo conference takes place in Paris on September 9-13. A recording of a discussion between Jacob Plieth and the biotech investor Brad Loncar about the meeting's themes is available below:

https://t.co/uLD0ngDfUd

— Brad Loncar (@bradloncar) September 6, 2022