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Asco-GI – immuno-oncology makes progress in liver cancer

Jacob Plieth

Astrazeneca looks to enter a field in which Merck & Co recently tripped up, and in which Roche is the only IO player.

The tectonic plates in liver cancer could be about to shift again, with Astrazeneca claiming that the results of its Himalaya trial of Imfinzi plus tremelimumab showed an “unprecedented” level of overall survival in the front-line setting.

The findings, presented at Asco-GI this week, are intended to challenge Roche’s Tecentriq, which as part of an Avastin combo is the only other IO drug to carry a first-line label, but which on a cross-trial basis still has the upper hand. Keytruda has been hit with a complete response letter in this setting, leaving Merck & Co fighting it out for second-line use.

Himalaya and Merck’s Keynote-394 trials had both been toplined as positive last year, but Asco-GI saw full data presented for the first time. Himalaya had been noted as a rare success for tremelimumab, and one that Astra attributes to use of the novel Stride regimen, comprising a single 300mg priming dose of treme together with Imfinzi, followed by Imfinzi alone.

“We are looking at whether this single [treme] priming dose could have application on other tumour types,” Dave Fredrickson, Astrazeneca’s head of oncology, told *Evaluate Vantage*.

Unprecedented?

Full data make Astra’s claim of unprecedented survival hard to square, however. Tecentriq plus Avastin had been approved on the back of a 42% reduction in risk of death in the Imbrave-150 study, whereas the Astra combo managed only 22% in Himalaya, Asco-GI has heard.

Mr Fredrickson said what was truly unprecedented in Himalaya was three-year survival, which amounted to 31% for the combo versus 20% for Nexavar. Imbrave-150 has so far only shown data out to 18 months, so it has yet to be seen how Roche squares up against this claim.

The questions for Astra now are when it expects to file, and whether the company will submit Imfinzi monotherapy as well as the treme combo. Liver cancer would be only Imfinzi’s third approved US use, after the withdrawal of its urothelial carcinoma label a year ago.

The group will not reveal whether it has filed, but said regulatory discussion began as soon as Himalaya was

toplined last October. “The question with the FDA will indeed be whether [Imfinzi monotherapy] gets into the label,” said Mr Fredrickson. “But our focus is going to be on the combination.”

It was already known that the Imfinzi monotherapy cohort in Himalaya had performed worse than the combo, showing only non-inferiority versus Nexavar, and not superiority.

But Asco-GI revealed that at 16 or so months’ follow-up median survival benefit was actually pretty close for the combo and monotherapy arms. But across the whole study risk of death was a less impressive 14% for Imfinzi alone.

Immuno-oncology in hepatocellular carcinoma				
		ORR	**mPFS**	**mOS**
First line				
Imbrave-150 (Roche)*	Tecentriq + Avastin (vs Nexavar)	28% vs 12%	6.8mth vs 4.3mth (HR=0.59)	NE vs 13.2mth (HR=0.58)
Himalaya (Astrazeneca)**	Imfinzi + tremelimumab (vs Nexavar)	20% vs 5%	3.8mth vs 4.1mth (HR=?)	16.4mth vs 13.8mth (HR=0.78)
	Imfinzi (vs Nexavar)	17% vs 5%	3.7mth vs 4.1mth (HR=?)	16.6mth vs 13.8mth (HR=0.86)
Second line				
Checkmate-040 (Bristol Myers Squibb)^	Opdivo + Yervoy	33%	NA	NA
Keynote-224 (Merck & Co)^	Keytruda	17%	NA	NA
Keynote-394 (Merck & Co)^^	Keytruda vs placebo	14% vs 1%	2.6mth vs 2.3mth (HR=0.74)	14.6mth vs 13.0mth (HR=0.79)
*Notes: *available under full approval; **possible registrational study; ^available under accelerated approval; ^^possible confirmatory study. Source: product labels & Asco-GI.*				

Other IO players have not fared well in first-line liver cancer: Bristol’s Checkmate-459 trial of Opdivo monotherapy was a bust, while Merck/Eisai’s Keytruda plus Lenvima combo got a US complete response letter because the uncontrolled Keynote-524 trial gave it insufficient backing.

Merck’s next hope is Leap-002, a study of the same combo versus Lenvima alone that ends in July. In the meantime at Asco-GI the company is presenting data from Keynote-394, a controlled study that might serve to formalise the second-line label that Keytruda was granted on an accelerated basis back in 2018.

Merck’s big problem here is that Keynote-394 was conducted in Asia, and whether the US regulator will accept it is unclear. Asked about this the group told *Vantage* that the trial was only one of seven in Merck’s global development programme in liver cancer, and would “add to the body of evidence”, but confirmed that the data were being discussed with regulators as a potential confirmatory study in the US.

Moreover, the Keynote-394 data do not seem overwhelmingly strong. There was a 21% reduction in risk of death versus best supportive care, but the median survival advantage was only 1.6 months, and the response rate is below that of Opdivo plus Yervoy on a cross-trial basis. There were three Keytruda-related deaths, from gastrointestinal haemorrhage, autoimmune hepatitis and soft tissue infection, Merck said.

Front-line liver is one cancer type where Keytruda has failed to make its mark. Perhaps this is one reason why Astra expects it to serve as a springboard for the Imfinzi/treme combo into gastrointestinal cancers.

This story was amended after Astra clarified that it was not looking to test the Stride regimen in its other IO approaches.

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Evaluate HQ
44-(0)20-7377-0800

Evaluate Americas
+1-617-573-9450

Evaluate APAC
+81-(0)80-1164-4754