Evaluate Vantage

July 03, 2017

Therapy focus – Opdivo and Livatag could add to liver cancer options

Jacob Plieth

Investors interested in hepatocellular carcinoma are in for a busy month, with two phase III studies expected to render results. These are the closely watched Checkmate-459 trial of Bristol-Myers Squibb's Opdivo used first-line and the Relive study testing Onxeo's Livatag, a nanoparticle formulation of doxorubicin, in second or later-line settings.

Appetites have been whetted by early data at last week's Esmo World Congress on Gastrointestinal Cancer, and expectations are high for positive results with Opdivo, as the drug has shown activity in first and second-line hepatocellular carcinoma (HCC) in the earlier Checkmate-040 trial. On the basis of this, Bristol has already filed the anti-PD-1 MAb in the US for second-line use, seeking accelerated approval (see tables below).

That filing has an FDA action date of September 24, so Bristol will be hoping for an unambiguous PFS result in Checkmate-459. And, if it does subsequently obtain regulatory clearance, it could use the data both for a fast move to first-line status and as the confirmatory phase III study required with accelerated approval.

Head to head or sequenced?

Checkmate-459 is testing Opdivo head to head against Bayer's Nexavar, though the crossover design means the overall survival comparison is likely to be more of a sequenced combination versus the kinase inhibitor alone. The trial has response rate and OS as co-primary endpoints, although survival data are not expected to become available until October 2018.

In the case of the Onxeo's Relive, which tests two doses of Livatag, external expectations are more modest, despite the lower efficacy bar set by virtue of the study having best standard of care – effectively palliative care – as control.

However, after the recent approval of Stivarga for second-line HCC, Relive's results will be have to match or beat those of the newer Bayer agent for Livatag to gain traction in the second-line setting. The Resorce phase III of Stivarga showed a 2.8-month survival advantage (*Bayer quietly claims its liver cancer prize, June 29, 2016*).

While Bayer's commercial franchise in HCC has been strengthened by the approval of Stivarga, it is likely to come under pressure on both first and second fronts from new agents over the next year.

In the first-line setting this pressure will initially come from Eisai's Lenvima, which may compete with Nexavar. Lenvima has just been filed for HCC in Japan, and Eisai expects to make EU and US filings by the end of September.

Results from the Japanese company's Reflect phase III study, which were presented at Asco last month, met the statistical criteria for non-inferiority, the primary endpoint, but also showed significant benefits over Nexavar in terms of PFS, time to progression and response rate.

Reflect study results			
Endpoint	**Lenvima (n=478)**	**Nexavar (n=476)**	**Statistics**
Median OS	13.6 mth	12.3 mth	HR = 0.92, non-inferior
Median PFS	7.4 mth	3.7 mth	HR = 0.66, p<0.00001
Median time to progression	8.9 mth	3.7 mth	HR = 0.63, p<0.00001
Overall remission rate	24.1%	9.2%	p<0.00001

Over the next nine months the HCC field will see three other phase III readouts, one of which is first line: the

Phocus study of Sillagen/Transgene's oncolytic virus Pexa-Vec will report in October. Phocus tests Pexa-Vec in combination with Nexavar and should provide an interesting comparison with Lenvima and Opdivo.

However, a separate trial seems to be anticipating the direction in which HCC is heading: Sillagen and Transgene recently announced plans for a phase I/II study to test Pexa-Vec in combination with Opdivo.

The other two near-term readouts are second line: Lilly's Reach-2 study of Cyramza, recruiting patients with elevated alpha fetoprotein, and Exelixis's Celestial trial of Cabometyx. Hopes are high for Cabometyx, and Exelixis and Bristol are testing the combination of this project with Opdivo with or without Yervoy in RCC and potentially HCC once the outcome of Celestial is known.

Opdivo backbone

With Opdivo likely to become the backbone of HCC therapy, one question will be Merck & Co's strategy in this indication, given that it is running two similar phase III studies, one in Asian patients, with second-line Keytruda.

These do not read out until 2019, and seem unlikely to offer much commercial traction if Opdivo first becomes established as a front-line treatment. Merck is also running a single-arm phase II study, Keynote-224, due to report data later this year.

There are of course numerous other studies of anti-PD-(L)1 agents testing the water in early trials for HCC. Astrazeneca is trialing Imflinzi and tremelimumab alone and in combination, while Novartis is testing PRD-001 alone and with the c-Met inhibitor capmatinib and with the anti-FGFR4 FGF401.

Beigene, which reported early data at the Esmo World Congress on Gastrointestinal Cancer, and Jiangsu HengRui are both conducting monotherapy studies in HCC with their respective anti-PD-1 MAbs BGB-A317 and SHR-1210.

Unless there is a major upset with Checkmate-459, HCC looks set to become an indication where the market, at least in terms of checkpoint inhibitors, is dominated by Opdivo. The question then will be with what agents this will be combined.

Phase III trials in advanced hepatocellular carcinoma

Project	Company	Study	Setting	Trial ID	Data
Opdivo	Bristol-Myers Squibb	Checkmate-459	1L	NCT02576509	Jun 2017
Livatag	Onxeo	Relive	2L	NCT01655693	Jul 2017
Cyramza	Lilly	Reach-2	2L	NCT02435433	Oct 2017
Pexa-Vec	Sillagen/Transgene	Phocus	1L	NCT02562755	Oct 2017
Cometriq	Exelixis	Celestial	2L	NCT01908426	Early 2018
Keytruda	Merck	Keynote-240	2L	NCT02702401	Feb 2019
Donafenib	Suzhou Zelgen	–	1L	NCT02645981	Feb 2019
Therasphere	BTG	Yes-P	1L	NCT01887717	Jun 2019
Therasphere	BTG	Stop-HCC	1L	NCT01556490	Jul 2019
Thermodox	Celsion	Optima	2L	NCT02112656	Nov 2019
Keytruda	Merck	Keynote-394	2L	NCT03062358	Dec 2019

To contact the writer of this story email Robin Davison at robind@epvantage.com or follow @RobinDavison2 on Twitter