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Hopes rise for a liver cancer breakthrough in 2016

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2016 offers the hope of becoming a breakthrough year for advanced hepatocellular carcinoma, with no fewer than six phase III trials involving five novel targeted agents likely to render results, an unprecedented number.

However, all of these agents are going up against a condition that has been notoriously intractable to pharmaceutical development (see table below). Despite ranking among the most common forms of malignant disease, HCC has the fewest therapeutic options of any major cancer, with Bayer's Nexavar the sole approved drug in the indication.

EP Vantage's analysis of the field shows there are 11 agents currently in or entering phase III studies, and around a futher 15 in phase II. Among the more promising mid-stage candidates are Lilly's galunisertib, Merck KGaA's tepotinib and Astellas/Medivation's Xtandi.

Of the six agents expected to have 2016 phase III readouts, only two are risking going up against Nexavar, which itself has only shown a relatively modest 2.8-month increase in overall survival versus placebo. Those are Eisai's Lenvima, for which data are due in April, and Bristol-Myers Squibb's Opdivo. All the others are being tested in the second-line setting.

Common tactic

Seeking approval for second-line HCC has become a common tactic, owing to the lack of options after progression on or intolerance to Nexavar. This also gives the added benefit of allowing placebo to be used as control.

Taking this approach is the little-known US company Polaris, which should have first data readout this year with ADI-PEG20, a pegylated arginine deaminase. Polaris hopes that ADI-PEG20 will starve the tumour of arginine, an amino acid crucial to tumour cell metabolism and growth, by depleting it from the blood. The only data available are from a single-arm phase II study that showed a median OS in a mixed first/second-line population of 7.3 months. The company told *EP Vantage* that results of the phase III study of ADI-PEG 20 would be released at ASCO.

Results are also due imminently from Bayer's Resource study of Stivarga. Bayer's choice of the second-line setting is surprising because Stivarga is so closely related chemically to Nexavar, so it is not immediately clear why it should show an additional benefit in Nexavar failures.

Exelixis will be hoping to gain a second additional indication for its tyrosine kinase inhibitor Cometriq based on the Celestial study, after that drug's recent trial success in renal cell carcinoma.

ArQule and its partners Kyowa Hakko Kirin and Daiichi Sankyo are conducting two phase III studies of tivantinib, a Met inhibitor, both of which should render results this year. These enrol only patients with high Met status, who represent about 50% of all HCC patients. Overexpression of this receptor is related to higher recurrence rates after surgery, while high c-Met expression correlates with shorter survival.

The Metiv-HCC study will shortly undergo an interim analysis, with a possible early efficacy stop, and will reach the required number of events for its final analysis by the end of the year.

Lilly is the only other company to have pursued patient selection in HCC, testing Cyramza in patients with elevated alpha-fetoprotein in the Reach-2 study. This approach was developed after an analysis of its earlier Reach study, which showed a non-significant benefit in the overall population.

Phase III trials in advanced hepatocellular carcinoma							
Project	**Company**	**Study name**	**Patients**	**Comparator**	**Therapy line**	**Trial ID**	**Data**
ADI-PEG20	Polaris	-	636	Placebo	Second	NCT01287585	Due
Stivarga	Bayer	Resource	560	Placebo	Second	NCT01774344	Feb 2016
Lenvima	Eisai	-	954	Nexavar	First	NCT01761266	Apr 2016
Cometriq	Exelixis	Celestial	760	Placebo	Second	NCT01908426	Oct 2016
Tivantinib	Daiichi Sankyo/Arqule	Metiv-HCC	368	Placebo	Second	NCT01755767	Dec 2016
Tivantinib	Kyowa Hakko Kirin	Jet-HCC	160	Placebo	Second	NCT02029157	Dec 2016
Apatinib	Jiangsu HengRui	-	360	Placebo	Second	NCT02329860	Jan 2017
Opdivo	Bristol-Myers Squibb	CheckMate 459	726	Nexavar	First	NCT02576509	May 2017
Livatag	Onxeo	Relive	390	Best supportive care	Second	NCT01655693	Jul 2017
Cyramza	Lilly	Reach-2	399	Placebo	Second	NCT02435433	Oct 2017
Pexa-Vec	Sillagen	Phocus	600	+/- Nexavar	First	NCT02562755	Oct 2017
Donafenib	Suzhou Zelgen	-	600	Nexavar	First	NCT02645981	Dec 2018

Multiple failures

All of these companies should know that HCC will be a tough nut to crack. In the past decade the disease has seen multiple phase III trial failures, including many with agents that have approvals in other cancer indications. Pfizer's large phase III trial of Sutent, for example, failed even to demonstrate non-inferiority to Nexavar.

AbbVie's linifanib, which was also tested against Nexavar, and Roche's Tarceva, which was given in combination with the Bayer drug, also failed. Meanwhile, Bristol-Myers-Squibb's brivanib was examined unsuccessfully in first and second-line settings, and Novartis had no better luck with Afinitor in second-line HCC.

NCCN guidelines do recommend several chemotherapy regimens for post-Nexavar use, including gemcitabine/oxaliplatin, capecitabine alone or in combination with oxaliplatin, doxorubicin or gemcitabine/cisplatin. All of these have shown some marginal benefit based on small phase II trials.

Although HCC remains one of the most difficult cancers, it is surprising that Nexavar has been the standard of care for almost a decade. It would be a huge development if one or more of the 2016 readouts changed this.

This story has been amended to correct some timelines.

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