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Therapeutic Focus – Liver cancer focus switches to second-line as Nexavar proves a tough nut to crack

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Clinical readouts next year could pave the way for a change in the treatment of liver cancer, an area in which Bayer and Onyx's blockbuster Nexavar at present dominates as the only approved targeted therapy for advanced disease.

Although Nexavar continues to beat others in head-to-head studies, failure on the multi-kinase inhibitor is a real problem and other therapeutic approaches that target alternative pathways are desperately needed (see table). However, given the litany of failures against Nexavar, competitor focus – at least for now – seems to be on offering improved second-line options.

The competition

Phase III results in the second-line setting are expected next year from Novartis's Afinitor and Eli Lilly's antibody ramucirumab, which recently showed efficacy in gastric cancer. ArQule, meanwhile, is soldiering on with its cMET inhibitor tivantinib, using a personalised approach by testing the drug in MET-high patients.

"This is nothing like hepatitis where you have two or three agents that really look fantastic," says Markus Peck-Radosavljevic, associate professor of medicine and vice-chairman at the department of gastroenterology and hepatology at Medizinische Universität Wien, Austria."

We thought all of them [in the head-to-head trials] would be promising but they failed, so we are becoming very cautious at this point. It's all incremental improvements if at all, and I think everybody is looking into biomarkers like crazy," he adds.

Behind the disease

Hepatocellular carcinoma (HCC) is a primary cancer of the liver affecting the hepatocytes and is responsible for some 90% of primary liver cancers in adults. Among major risk factors, the World Health Organisation says hepatitis B and C together are responsible for 50% and 85% of primary liver cancers in high and low income countries respectively.

Liver transplantation and surgical resection can treat small or slow-growing tumours; however, because HCC is mostly asymptomatic in early-stage disease, few patients are diagnosed early enough to be eligible. The median survival time for patients with advanced disease is less than a year.

"In the earlier treatment phases you have curative treatment options," says Professor Peck-Radosavljevic. "The biggest impact on patient survival would be the screening of the risk groups, so screening of all cirrhotics in Europe and all chronic hepatitis B patients in Asia is recommended, but it's not done sufficiently and of course it's a major undertaking."

"The other issue is among patients with chronic infection," says Mark Thursz, professor of hepatology at Imperial College and consultant at St Mary's Hospital, London. "They need to be in the surveillance programme to pick up early tumours, which are curable. Once a patient presents with the symptomatic tumours it's invariably too late."

Limited options

Nexavar (sorafenib) was approved five years ago as the only targeted therapy in the disease. It inhibits multiple intracellular and cell surface kinases, including the vascular endothelial growth factor receptor, which are thought to be involved in tumor cell signalling, apoptosis and angiogenesis. According to *EvaluatePharma* sales are forecast to reach $848m by 2018 for this indication alone.

As effective as it has proven, eventually Nexavar loses its efficacy. "Then you usually see progression and it's actually quite difficult to say what to do. It's not even clear at the moment if you should stop the drug or

continue. There is simply no data available" says Professor Peck-Radosavljevic.

"If you treat patients in advanced-stage disease that means this is not optimal. We need better options, definitely, and that is what everybody is looking for."

Head-to-head setbacks

Despite the need for improved options, Nexavar continues to dominate the liver cancer space and contenders have made little progress.

Brivanib, Bristol-Myers Squibb's dual inhibitor of fibroblast growth factor receptors and VEGF signalling, failed to show non-inferiority over Nexavar in the first-line setting in the BRISK-FL phase III trial. This disappointment came after the drug failed to show overall survival at the end of last year in the second-line BRISK-PS phase III trial.

Meanwhile, ABT-869 (linifanib), a multikinase inhibitor from Abbott, also failed to show an advantage over Nexavar. Its phase III study was terminated on the advice of an independent data-monitoring committee. In July, the 731-patient Search study failed to show that the addition of Roche's EGFr tyrosine kinase inhibitor Tarceva (erlotinib) on top of Nexavar provided an additional benefit.

Development of another multi-kinase inhibitor, Pfizer's Sutent (sunitinib), in liver cancer was terminated in phase III back in 2010 when a higher incidence of adverse events occurred compared with the Nexavar arm. Sutent also failed to show any advantage over the Bayer/Onyx drug (*Therapeutic focus – Sutent liver cancer failure leaves thin late-stage pipeline, April 26, 2010*).

Competition on the horizon?

However, with the increased medical need for new treatments with proven efficacy, Novartis and Lilly look to be leading the race to offer compounds with alternative mechanisms of actions that might finally topple, or at least challenge, Nexavar's dominance. Data read outs from both groups are expected next year.

Novartis's Afinitor (everolimus) is an mTOR inhibitor in a phase III study called Evolve-1. mTOR is a serine/threonine protein kinase that indirectly modulates angiogenesis. The study is comparing Afinitor with placebo in patients whose disease progressed with Nexavar or who were intolerant to the Bayer/Onyx product.

Another second-line treatment is ramucirumab (IMC-1121B) from Lilly, a monoclonal antibody inhibitor of VEGFR-2. This is in a phase III trial, Reach, comparing the drug and against placebo after failure on Nexavar, and is due to report late next year. In phase II trials testing the antibody as first-line monotherapy in patients with advanced HCC, median progression-free survival was 4 months while overall survival was 12 months, with a time to progression of 4.2 months.

Ramucirumab targets the receptor rather than the VEGF ligand and is also in trials for a number of other tumour types, including breast, colorectal cancer and NSCLC, with recent phase III success in gastric cancer (*Lilly's ramucirumab comes off the bench with a clutch single, October 16, 2012*).

Selected phase III liver cancer pipeline				
Product	**Generic name**	**Company**	**Pharmacology class**	**Trial ID**
Afinitor	everolimus	Novartis	Rapamycin analogue (mTOR inhibitor)	NCT01035229
IMC-1121B	ramucirumab	Lilly	Anti-VEGFr MAb	NCT01140347
ThermoDox	doxorubicin hydrochloride	Celsion	Anthracycline	NCT00617981
Brivanib	brivanib	Bristol-Myers Squibb	FGFR & VEGFr kinase inhibitor	NCT00825955 NCT00858871
TSU-68	orantinib	Otsuka Holdings/Pfizer	Tyrosine kinase inhibitor	NCT01465464
PI-88	muparfostat	Progen Pharmaceuticals/Medigen Biotechnology	Heparan sulphate mimetics & heparanase inhibitor	NCT01402908
NIK-333	peretinoin	Kowa	Apoptosis inducer	NCT01640808
Aptocine	talaporfin sodium	Light Sciences Oncology	Porphyrin	NCT00355355
ADI-PEG 20	arginine deiminase (pegylated)	Polaris Group	Arginine inhibitor	NCT01287585
Immuncell-LC	activated T-lymphocyte	Innocell/Lymphotec	Immunostimulant	NCT00699816

Other late-stage products

It is not only the big players that are developing alternatives; smaller companies are also getting in on the act, and two are investigating the use of heat and light-activated drugs.

Celsion’s ThermoDox is in a phase III trial called Heat in combination with radiofrequency ablations (RFA) compared wit RFA alone. ThermoDox is an encapsulation of the established chemotherapy drug doxorubicin in a liposome, using heat activation to release the drug. The primary endpoint is progression-free survival, with 380 events required for final analysis, this is projected to occur towards the end of the year.

Aptocine (talaporfin sodium) from Light Sciences Onology is a light-activated drug that results in the production of singlet oxygen, which attacks target tissues. The Washington-based company says its Phase III trial in HCC has been completed; however, no results have been published.

In other late-stage approaches Otsuka Holdings is recruiting into its phase III trial of TSU-68 (orantinib) in combination with transcatheter arterial chemoembolisation. The drug is an oral tyrosine kinase inhibitor of VEGFR-2, PDGFR and FGFR.

Meanwhile, the California-based Polaris Group is looking to recruit 633 patients who have failed prior systemic treatment into its phase III trial. In the study patients will receive weekly intramuscular injections of ADI-PEG 20, which is an arginine-degrading enzyme. The company states that hepatocellular carcinomas have been found to require arginine, with the hypothesis that if arginine is restricted the carcinoma cells will be unable to survive.

Making things personal

The race is also under way to find biomarkers that show which patients would respond to a specific treatment. Despite its recent setbacks in NSCLC, ArQule's c-Met inhibitor ARQ 197 (tivantinib) has shown promise as a second-line liver cancer treatment in specific patient populations.

Met is a receptor tyrosine kinase, and in phase II results at this year’s Asco in the MET-high cohort there were statistically significant improvements in overall and progession-free survival. Median overall survival was 7.2 months versus 3.8 months in the placebo arm, while median progression-free survival was 2.4 months with treament and 1.5 months for placebo. ArQule estimates that MET could be over-expressed in 40-50% of patients.

“Tivantinib looked good in this subgroup of patients that were high expressors of this cMet receptor. It was not effective in patients that did not express it, so biologically it made sense. This is something that looks

promising and as a rationale it is a little bit more intelligent than giving everybody the same drug," says Professor Peck-Radosavljevic.

Analysts at RBC note that the phase III trial in MET-high patients will start early next year under a special protocol assesment agreement with the FDA. The study is looking to recruit 300 previously treated patients with MET diagnostic-high inoperable HCC.

With biomarker discovery a key development that has yet to be fully understood Professor Peck is optimistic about the future of liver cancer treatments.

"I am sure there will be progress in the next three years. But it's absolutely hard to predict at the moment because – in trying approaches and classes of molecules that haven't been tried before – until you see any data it is just a guessing game," he says.

"But I am positive there will be progress because I can't really imagine that all of this will not lead to meaningful results."

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