Evaluate Vantage

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Therapy focus – Another try for FGFR inhibitors

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In the shadow of immuno-oncology big pharma and biotechs alike continue to develop targeted projects attacking various aspects of tumour metabolism. One such approach, fibroblast growth factor receptor (FGFR) inhibition, has a growing pipeline that could start generating pivotal data in the next year or two.

Since *EP Vantage* last wrote about this class the leading candidate, Bristol-Myers Squibb's brivanib, has been abandoned. However, a new generation of late-stage agents has emerged, and biomarker tests to detect tumours expressing FGFR genetic alterations have helped to identify a subset of patients that could show a greater benefit (see table below).

FGFR inhibitors are often combined with angiogenesis inhibition mechanisms like vascular endothelial growth factor (VEGF) blockers, and are intended to block tumour cell proliferation that is caused by disrupted gene signalling. Brivanib was a dual inhibitor of VEGF and FGFR thought to add additional angiogenesis-blocking qualities, although it was shelved after it failed to show non-inferiority to Nexavar in hepatocellular carcinoma in the Brisk-FL study (*Therapeutic focus – Expectations rising for FGF inhibitors, March 18, 2011*).

Now licensed to ZAI Lab in China, Brivanib was tested in all comers. The next round of data should tell the sector whether a biomarker-driven treatment protocol can allow FGFR inhibition agents to outperform existing drugs.

But first, this

This might not, however, be revealed by trials of the leading candidate, Hutchison China Meditech's sulfatinib, a dual FGFR and VEGFR inhibitor undergoing phase III trials in China in pancreatic and non-pancreatic neuroendocrine tumours.

These studies should read out in 2018 and 2019, but do not appear to select patients based on biomarkers; they are similar in size to pivotal trials of Afinitor in neuroendocrine tumours, so they should deliver robust data in an all-comers population.

Selected late-stage FGFR projects				
Project	**Generic mame**	**Company**	**Pharmacology class**	**Trial ID**
Phase III				
sulfatinib	sulfatinib	Hutchison China Meditech	FGFR & VEGFR inhibitor	NCT02588170, NCT02589821
Phase II				
ARQ 087	–	ArQule	FGFR antagonist	NCT01752920
erdafitinib	erdafitinib	Johnson & Johnson	Pan-FGFR inhibitor	NCT0236559, NCT02699606
BGJ398	infigratinib	Novartis	Pan-FGFR kinase inhibitor	NCT02160041, NCT02150967
INCB54828	–	Incyte	FGF inhibitor	NCT02393248
AZD4547	–	AstraZeneca	FGFR tyrosine kinase inhibitor	NCT02154490, NCT02117167, NCT02299999
lucitanib	lucitanib	Clovis Oncology/Servier	FGFR 1-3, VEGFR 1-3 & PDGFR α/β kinase inhibitor	NCT02053636, NCT02109016, NCT02202746, NCT02747797
B-701	–	BioClin Therapeutics	FGFR3 kinase inhibitor	NCT02401542
FGF401	–	Novartis	FGFR4 inhibitor	NCT02325739

But before those broad pivotal trials read out, the sector should have some hint at how much promise there is in a biomarker driven approach, as phase II trials of ArQule's ARQ 087, Johnson & Johnson's erdafitinib, Novartis's BGJ398 and Clovis Oncology's lucitanib all hit their expected completion dates this year and in 2017.

Lucitanib is now Clovis's number two asset, after the PARP inhibitor rucaparib, and could be first up in returning biomarker-driven data. This project, which blocks FGFR 1-3, VEGFR 1-3 and platelet-derived growth factor receptors (PDGFR) alpha and beta, has enrolled patients with FGFR 1-amplified squamous non-small cell lung cancer, and had a primary completion date of June 1, 2016; another trial in FGF-aberrant advanced breast cancer is expected towards the end of the year.

Similarly, ArQule's ARQ 087, which has pan-FGFR activity, could deliver data by the year end from a phase I/II trial in intrahepatic cholangiocarcinoma with FGFR2 gene fusion. Preliminary data published at the ESMO world gastrointestinal congress showed a 25% response rate consisting of three partial responses in 12 evaluable FGFR-positive patients.

The first entrants from big pharma should yield data next year. J&J's erdafitinib is due to report urothelial cancer data in early 2017, while Novartis's BGJ398 should provide an update in glioblastoma towards the end of 2017.

Astra substudies

Other big names that have made it as far as phase II include Incyte, with INCB54828, which is not due to report data until 2018, and AstraZeneca, which has got AZD4547 into three major personalised medicine trials: Safir02_Breast, Safir02_Lung, and the 10,000-patient Lung-Map study.

Lung-Map, run by the US National Cancer Institute, is in squamous cell carcinoma, Safir02_Breast in Her2-negative disease, and Safir02_Lung in EGFR and ALK-negative disease. All three sort patients based on genomic testing, and as Astra is a collaborator on both of the Safir trials its candidates, including '4547, figure prominently.

Phase I marks Bayer's presence in this space, with three projects active in the clinic – one of which is an antibody-drug conjugate collaboration with Seattle Genetics. Daiichi Sankyo has two shots on goal with DS-1123 and U3-1784 – both of these should have results next year.

Eisai, Lilly, Astellas, Otsuka and Roche subsidiary Chugai have also put down markers in phase I.

Precision medicine is a focus in oncology with the US government's cancer "moonshot", and it seems that

biomarker-led research into FGFR inhibition is maturing at a very fortunate time (*JP Morgan – Jumping in front of the cancer immunotherapy parade, January 12, 2016*). Selecting patients based on genomic profile gives these agents a better chance of success, and if this does not work then perhaps nothing will.

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