Experimental therapeutics from Bridgebio, Incyte and Johnson & Johnson, all targeting FGFR, show promise in patients whose tumours are driven by this genetic mutation.

It has taken a while for FGFR inhibitors to make their mark in oncology, but today’s era of targeted therapy has identified the rare disease cholangiocarcinoma, also known as bile duct cancer, as one area in which they could be active.

If this proves to be the case then Novartis might be rueing the day it let its FGFR-selective asset infigratinib go for just $65m. This is the amount that the private start-up Bridgebio had paid the Swiss group in January for rights to infigratinib, which on Friday at Esmo put up very early data suggesting that it might have promise.

Dr Ian Chau, of the Royal Marsden NHS Foundation Trust, said FGFR gene fusions were common in some types of cholangiocarcinoma, and compared the emerging field to that of Alk and EGFR mutations in certain types of lung cancer that can now be targeted by Alk and EGFR inhibitors.

Infigratinb, a selective FGFR1-3 kinase inhibitor, is in a phase II cholangiocarcinoma trial; its previous update at Asco reported the overall remission rate as 15%. This cohort comprised 61 subjects, 78% of whom had an FGFR fusion.

The updated Esmo cohort centred on 71 patients, however, all of whom were FGFR-positive, and here the overall remission rate rose to 25%. Crucially, across the two cohorts responses were observed only in patients with FGFR fusions, Dr Chau said when discussing the abstract.

Incyte’s fighting chance

Another FGFR1-3 kinase inhibitor that investors have had on their radar is Incyte’s pemigatinib. The company’s phase II Fight-202 trial has enrolled three cholangiocarcinoma patient cohorts: FGFR2 translocations, other FGF/FGFR alterations, and no FGF/FGFR genetic alterations.

In the first cohort, amounting to 47 subjects, 19 partial remissions have been reported, Esmo heard today. Echoing the infigratinib experience the other two cohorts have produced no remissions. Incyte says it wants to start Fight-302, a phase III study in first-line cholangiocarcinoma patients with activating FGFR2 translocations,
Meanwhile, Johnson & Johnson’s erdafitinib is described as a pan-FGFR (FGFR1-4) inhibitor, and was recently granted US breakthrough therapy designation in bladder cancer. A cholangiocarcinoma study in Asian subjects has shown six partial remissions among 11 evaluable subjects, all of whom had had an FGFR alteration, Esmo heard.

With all three of these experimental agents the most common treatment-related adverse event was hyperphosphatemia.

<table>
<thead>
<tr>
<th>Project</th>
<th>Company</th>
<th>Trial ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infigratinib</td>
<td>Bridgebio (ex Novartis)</td>
<td>NCT02150967</td>
</tr>
<tr>
<td>Pemigatinib</td>
<td>Incyte</td>
<td>NCT02924376</td>
</tr>
<tr>
<td>Erdafitinib</td>
<td>Johnson &amp; Johnson</td>
<td>NCT02699606</td>
</tr>
</tbody>
</table>

The work suggests that a greater understanding of the drivers of some cancers has led to progress in FGFR inhibition being made at last; some earlier molecules were perhaps simply being tested in groups of patients that were genetically too broad (Therapy focus – Another try for FGFR inhibitors, July 14, 2016).

There are also other FGFR inhibitors in development, including Hutchison China Meditech’s sulfatinib, which hits FGFR1 as well as VEGFR, and is in a phase III neuroendocrine tumour study. Clovis is testing lucitinib, an FGFR1-selective molecule, in the phase II Finesse trial in HR-positive, Her2-negative breast cancer.

As ever with targeted therapy, however, there is a downside, and Dr Chau reported resistance to FGFR-targeted therapy among some treated patients, whose tumours had developed alternative growth pathways. As in Alk and EGFR-positive NSCLC, future-generation inhibitors should now be sought that might be able to tackle these relapsing patients, he stated.