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The quest for efficacy in pancreatic cancer

Joanne Fagg

Late-stage therapies from Fibrogen, Tyme and Novartis need to avoid the same pitfalls as Erytech and Rafael.

Pancreatic cancer has produced a fair number of blow-ups, with Erytech's Graspa and Rafael's devimistat recently joining a long list of clinical failures. But several new therapies have entered late-stage trials since *Evaluate Vantage* last looked at the pipeline. Novartis is making a big push here, recently starting a phase 3 trial of its anti-TGF-β MAb NIS793; the Swiss group yesterday also said that a new arm, testing its PD-1 MAb spartalizumab and anti-IL-1 beta antibody canakinumab, would soon be added to the non-industry-sponsored multi-arm phase 3 Precision Promise study.

Many of the late-stage candidates, due to start yielding data in 2022, are aimed at adenocarcinoma, the most common type of pancreatic cancer. First up should be results from Fibrogen's pamrevlumab and Tyme's SM-88. Meanwhile, combinations of various projects with checkpoint inhibitors are in earlier stages.

Next year's data

An interim analysis of the pivotal Lapis study of Fibrogen's pamrevlumab, featuring event-free survival data, is expected in the second half of 2022. The project is a first-in-class inhibitor of connective tissue growth factor, which is said to promote tumour growth. Lapis tests pamrevlumab plus chemotherapy as a neoadjuvant therapy in locally advanced disease.

Fibrogen believes that the EFS endpoint is registrational in this setting, and plans to discuss the interim results of the trial with the FDA, with the goal of supporting an accelerated approval filing.

Pamrevlumab is also being tested in metastatic disease, in the phase 2/3 Precision Promise adaptive clinical run by the US patient group the Pancreatic Cancer Action Network (Pancan). Pancreatic cancer cases are often diagnosed at late, difficult-to-treat stages, and fewer than 20% of patients are candidates for surgery as their disease has already spread.

In Precision Promise pamrevlumab is given plus chemotherapy versus standard of care in first/second-line metastatic patients. The primary measure is overall survival.

However, pamrevlumab is not the only project that Pancan is investigating. Precision Promise also includes SM-88 from Tyme Technologies as a second-line therapy versus standard of care. SM-88 (racemetyrosine) is said to work by interrupting protein synthesis, leading to oxidative stress-related apoptosis.

Tyme expects an efficacy and tolerability review of the first 100 patients to occur in the second half of 2022.

But SM-88 has already disappointed, with data released in early 2019 showing a low response rate in a single-arm trial in patients receiving the therapy in second, third or fourth-line settings. The second part of the same study in third-line patients was wound down in June to focus on the Precision Promise trial.

New to phase 3

Meanwhile, Novartis's spartalizumab and canakinumab, plus chemo, will be added to Precision Promise in early 2022, the company disclosed during a media event yesterday.

A few months ago Novartis also began a phase 3 trial of its anti-TGF-β MAb NIS793, combining it with chemotherapy in first-line metastatic disease. Primary completion is not until 2026, although interim readouts will likely come before then.

TGF-β is said to play a key role in regulating the tumour microenvironment, and targeting TGF-β in oncology is a crowded field. However, the failure this year of Merck KGaA/Glaxosmithkline's bintrafusp alfa, an anti-PD-L1/TGF-β fusion protein, effectively killed off this asset and has dented some hopes for TGF-β inhibition.

Novartis is also combining NIS793 with its own anti-PD1 project, spartalizumab, and chemotherapy, in a phase 2 trial. The company must hope that, by giving anti-PD-L1 and TGF-β as separate components, with the promise of flexible dosing, this might help its project avoid the same fate as bintrafusp. The phase 2 study has a primary completion date in 2023.

Meanwhile, there are numerous pancreatic cancer studies testing checkpoint inhibitors: clinicaltrials.gov lists 48 active trials involving Keytruda. The Merck anti-PD-1 MAb can theoretically be used for specific pancreatic tumour types – those with high microsatellite instability or defective DNA mismatch repair, or high tumour mutational burden – although these are rare in pancreatic cases.

A few interesting phase 2 studies include joining Keytruda with Eisai's VEGFR antagonist Lenvima, and Verastem's focal adhesion kinase inhibitor defactinib. Other checkpoint inhibitors such as Libtayo, Tecentriq and Opdivo also appear to be in active development.

Selected phase 3 projects in pancreatic cancer				
Product	**Mechanism**	**Company**	**Setting**	**Note**
Pamrevlumab	Anti-connective tissue growth factor MAb	Fibrogen/Bristol Myers Squibb	Neoadjuvant, locally advanced, also 1L/2L metastatic	Ph3 Lapis, EFS data H2 2022, neoadjuvant treatment + chemo Also part of Precision Promise study* as 1L/2L
Fuzuloparib (SHR3162)	Parp 1 & 2 inhibitor	Jiangsu Hengrui Pharmaceuticals	gBRCA/PALB2+, maintenance (responders to 1st-line platinum chemo)	Ph3 recruiting, monotherapy, primary completion Jul 2022
SM-88 (racemetyrosine)	Mucin cell surface associated 1 inhibitor	Tyme Technologies/Eagle Pharmaceuticals	2L metastatic	Ph2/3 monotherapy vs chemo, Precision Promise*, review of 100 patients due H2 2022
NIS793	TGF beta 1 antibody	Novartis/Xoma	1L metastatic	Ph3 + chemo, started Sep 2021 Ph2 +/- spartalizumab + chemo, primary completion 2023
Immuncell-LC	Cytokine induced killer cell therapy	Green Cross Cell	Adjuvant post surgery	Ph3 +/- gemcitabine, started Sept 2021
Spartalizumab (PDR001) + canakinumab (Ilaris)	Anti PD-1 MAb + anti-IL-1 beta MAb	Novartis	TBC	Combination + chemo will be added to Precision Promise* study early 2022

**Run by Pancreatic Cancer Action Network (Pancan). Source: clinicaltrials.gov, company releases & Evaluate Pharma*