Evaluate Vantage

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Success still eludes pancreatic cancer pipeline

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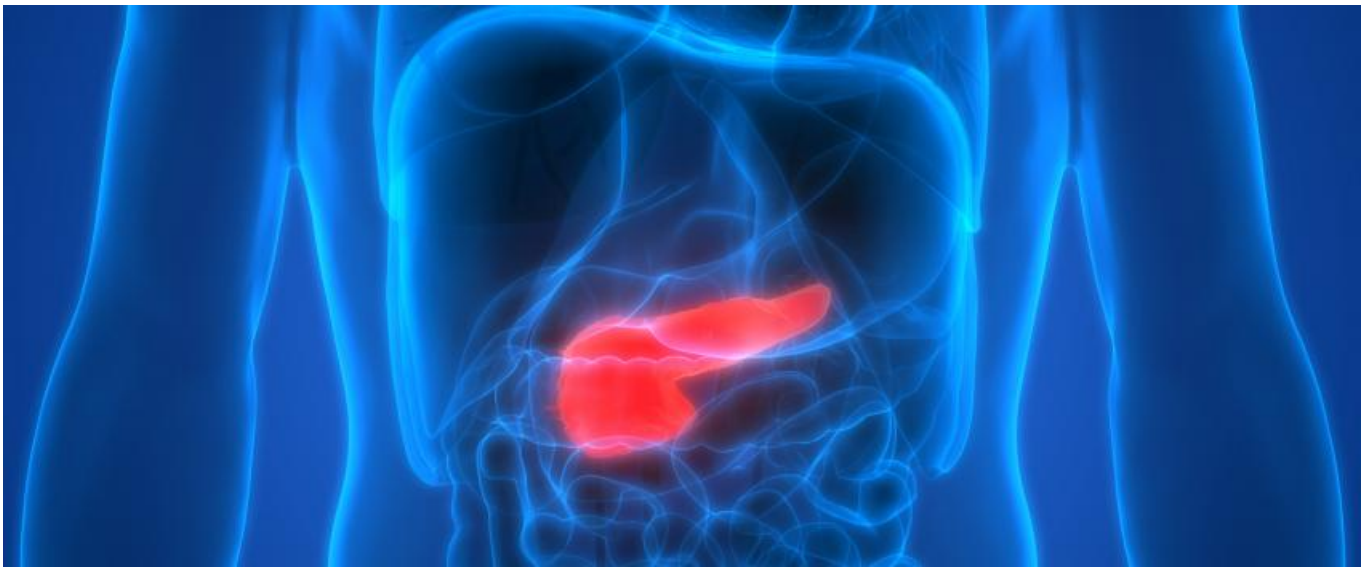

Nucana's recent setback with Acelarin adds to the long list of pancreatic cancer failures, and a look at the late-stage pipeline shows little concrete progress.

Pancreatic cancer has one of the worst survival rates in oncology, and attempts to develop therapies have so far largely disappointed. Just yesterday an investigator-sponsored trial using Nucana's Acelarin was stopped for lack of efficacy.

Since *Vantage* last looked at the later-stage pipeline in January there has been little good news, though promising early data with Astrazeneca's adavosertib grabbed headlines last week. There are big readouts coming soon from Lilly and Halozyme, while Erytech's Graspa could be one of the more promising approaches.

Erytech's study, Trybeca-1, is recruiting European patients, and the start of US patient enrolment is expected this quarter. The trial tests chemotherapy with or without eryaspase, and the primary endpoint is overall survival. A superiority analysis will happen when two thirds of subjects have died, with data likely in the first half of 2020.

Erytech will want a repeat of its phase II study, in which eryaspase plus chemotherapy showed a 43% reduction in risk of death (p=0.034; *Double pancreatic cancer surprise for Erytech's Graspa, March 27, 2017*) The project has had less success in leukaemia, so the focus is now on solid tumours.

Little confidence

Data are also expected with Halozyme's PEGPH20 and Lilly's pegilodecakin by the end of the year, but sentiment around both is low.

In December PEGPH20 is due to yield results from its phase III trial, which has a single primary endpoint, overall survival. The study previously had PFS as a co-primary but this was dropped, with Halozyme execs saying it was taking too long to accrue as more patients were being lost to follow-up than expected, but this tinkering with the trial design was taken as a bad omen (*Halozyme redesign dents confidence as rival readouts loom, November 27, 2018*).

Meanwhile, Lilly appears to be playing down the chances of pegilodecakin in pancreatic cancer. The company acquired the IL-10-targeted cytokine through its $1.6bn acquisition of Armo Biosciences.

On its second-quarter earnings call Lilly took the unusual step of claiming that that Armo had moved pegilodecakin into phase III on the back of limited phase I data, adding that lung and renal cancers were the more important indications.

Further behind is Fibrogen, which has started screening patients for its phase III trial of pamrevlumab in locally advanced, unresectable pancreatic cancer. The study tests pamrevlumab plus chemotherapy versus placebo plus chemotherapy. The primary endpoints are overall survival and rate of resection.

Fibrogen has said that it will discuss accelerated approval with the FDA based on resection rate if improvements are shown after six months' treatment.

Setbacks aplenty

Plenty of others have found pancreatic cancer a tough nut to crack.

Yesterday Nucana reported that recruitment into a phase III trial of Acelarin, called Acelarate, had been suspended owing to lack of efficacy. The study, which had enrolled 200 patients, was testing Acelarin, a gemcitabine prodrug, versus gemcitabine alone; the prespecified futility analysis assessed whether Acelarin would demonstrate at least a 42% reduction in risk of death.

The investigators claimed that there were imbalances in the two study groups that might have contributed to the failure, and said they would carry out biomarker analyses before deciding on the next steps.

Acelarin is not the only recent disappointment. One of the most eagerly awaited readouts of this year involved the Polo trial of Lynparza in a maintenance setting. Progression-free survival did strongly favour the Astrazeneca/Merck & Co Parp, but was overshadowed by the absence of an overall survival benefit (*Asco 2019 – Polo reveals an overall survival hole, June 2, 2019*).

Two further projects, Celgene's Abraxane and Sumitomo Dainippon Pharma's Napabucasin, have also fallen short. The former is approved in first-line pancreatic cancer, but failed to improve disease-free survival in the Apact trial in an adjuvant setting; the latter failed a futility analysis in July.

Hope lies with novel projects just starting out in the clinic, although these are a long way from the market.

Last week saw promising early-stage data with Astrazeneca's adavosertib. This inhibits Wee1 kinase, an enzyme involved in DNA damage repair. In an investigator-sponsored phase I/II trial adavosertib plus radiation and gemcitabine in patients with locally advanced disease led to a median overall survival of 21.7 months, with no progression for a median of 9.4 months.

Astrazeneca has already started phase II trials in various solid tumours, but the programme does not appear to include pancreatic cancer so far. Meanwhile, an NCI-run phase II trial, Match, incorporating adavosertib and pancreatic tumours, is ongoing. The project looks to be one of just two Wee1 kinase inhibitors in clinical development, the other being Debiopharm's Debio 0123, which is in phase I in combination with carboplatin in advanced solid tumours.

A previous analysis run by *Vantage* showed 122 NMEs in the industry's pancreatic cancer pipeline. In reality a large proportion of these are likely to have been quietly abandoned, and success remains elusive.

Selected upcoming phase III pancreatic cancer trials

Project	Company	Description	Trial ID	Outcome
Imbruvica	Johnson & Johnson/Abbvie	BTK inhibitor	NCT02436668 (Resolve)	Failed
Abraxane	Celgene	Chemotherapy	NCT01964430 (Apact)	Failed (adjuvant setting)
Napabucasin	Sumitomo Dainippon	NANOG inhibitor; STAT3 inhibitor; Wnt/beta-catenin signalling pathway inhibitor	NCT02993731 (CanStem111P)	Failed
Lynparza	Astrazeneca/Merck & Co	Parp inhibitor	NCT02184195 (Polo)	Met PFS but missed OS
Acelarin	Nucana	Pyrimidine analogue	NCT03610100 (Acelarate)	Failed futility analysis
PEGPH20	Halozyme	Hyaluronan regulator	NCT02715804 (Halo-301)	OS data (single primary endpoint) due Dec 2019
AM0010 (pegilodecakin)	Lilly	IL-10 receptor agonist	NCT02923921 (Sequoia)	Results expected by end of 2019
Masican (masitinib)	AB Science	CD117 inhibitor; FGFR3 inhibitor; PDGFR antagonist	NCT03766295/ 2013-002293-41	Primary completion Jun 2020
Eryaspase (Graspa)	Erytech Pharma	Encapsulated L-asparaginase	NCT03665441 (Trybeca-1)	Interim analysis due H1 2020, primary completion Nov 2020
Gemzar	Unicancer consortium	Chemotherapy	NCT02539537 (Neopan)	Primary completion pushed out to Mar 2021
Glufosfamide	Eleison	Alkylating agent	NCT01954992	Primary completion Mar 2021
CPI-613 (devimistat)	Rafael Pharmaceuticals	Lipoate analog	NCT03504423	Primary completion Oct 2021
Pamrevlumab	Fibrogen	Anti-CTGF MAb	NCT03941093 (Lapis)	Primary completion Sep 2022

Sources: EvaluatePharma & clinicaltrials.gov.

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