Evaluate Vantage

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AACR 2019 – Rubraca trial points to a place for Parps in pancreatic cancer

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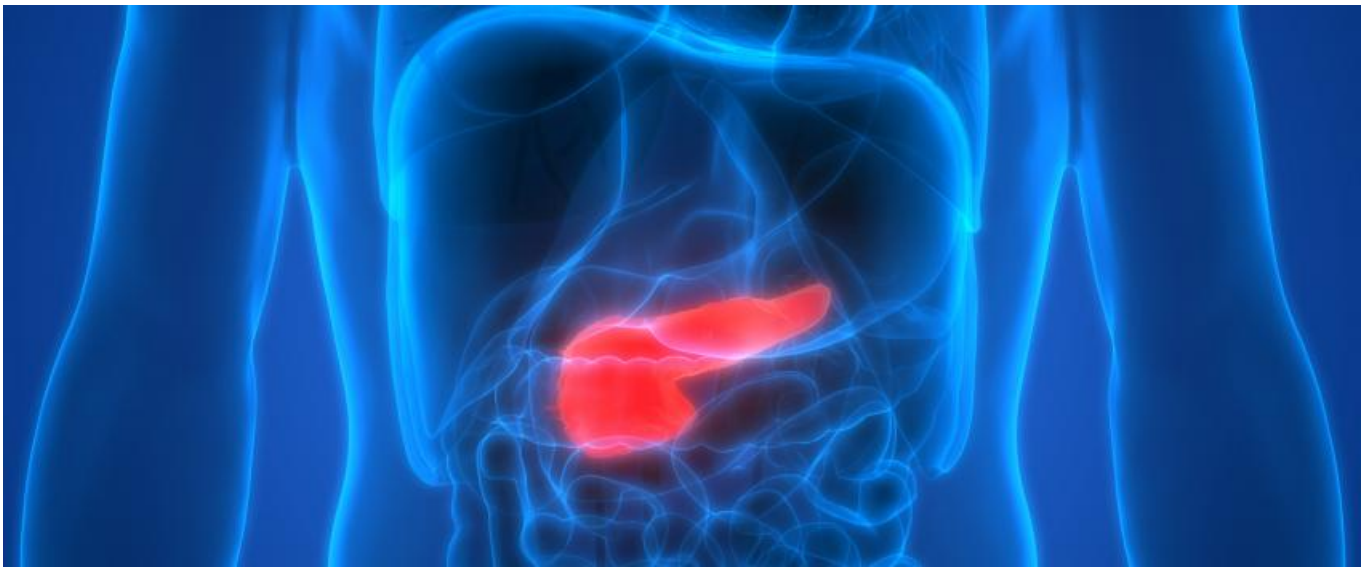

Encouraging early data from an academic trial of Clovis's Rubraca raise hopes that Parps could emerge as a more tolerable maintenance therapy for some pancreatic cancer patients.

Impressive results from a small trial of Clovis's Rubraca as a maintenance therapy in pancreatic cancer patients point to what Parp inhibitors might be capable of in this setting. Since this setting is currently the realm of highly toxic platinum-based chemotherapies, the prospect of a more tolerable treatment regimen, for certain patients at least, represents a notable advance in an area more commonly associated with setbacks.

At AACR today investigators from Penn University reported results from an uncontrolled trial recruiting patients positive for BRCA or PALB2 genetic mutations, who were in response to first-line chemotherapy. Six-month progression-free survival in such subjects approximates to 44%, the researchers said, and the trial aimed to push this above 60%.

The six-month PFS in the study currently stands at around 70%, the AACR data revealed. An overall remission rate of 38% has been achieved in the 19 patients evaluable so far, comprising one complete and six partial responses. Median PFS, from the start of Rubraca dosing, is 9.1 months, while median overall survival has yet to be reached.

Penn's Dr Kim Binder, presenting the data at an AACR press conference this morning, said the main goal of this trial was to maintain efficacy but cut chemo-associated toxicity, since demonstrating increased survival would necessitate a controlled study. "If we can improve on efficacy that would be great," she added.

She touted the results as highly encouraging, stressing no reported dose-limiting toxicities, but also cautioned that this was far from the final analysis of the trial, which seeks to recruit 42 subjects in total.

Polo success

These findings make for very interesting reading in the wake of Astrazeneca's success with the phase III Polo study of its Parp inhibitor Lynparza in a very similar setting; earlier this year the company said the trial had met its primary PFS endpoint, and a look at the data is keenly awaited. When this might be has yet to be disclosed, though Asco seems a likely venue.

The Penn study of Rubraca recruited similar patients to Polo, though it is not immediately clear whether Polo

also selected for the PALB2 genetic mutation, which occurs even less frequently than BRCA.

Around 6-8% of pancreatic cancer cases harbour either BRCA or PALB2 mutations, according to the Penn researchers. These tumours frequently respond very well to platinum-based chemotherapies, but long-term maintenance therapy is marked by substantial toxicities, hence the hope that the Parp class might offer a more tolerable option.

Selected trials of Parp inhibitors in pancreatic cancer					
Trial name/ID	**Setting/description**	**Product**	**Sponsors**	**Enrolment**	**Prima compl**
Phase III					
Polo (NCT02184195)	BRCA +ve, maintenance	Lynparza	Astrazeneca/Merck	154	Primar endpo met, awaiti data
Phase II					
NCT03140670	BRCA/PALB2 +ve, maintenance	Rubraca	U. Penn	42	Interi report primar compl 30/06/
NCT02890355	All comers, second-line, metastatic	Veliparib plus FOLFIRI or modified FOLFIRI.	NCI	143	May 2(
Parpvax (NCT03404960)	All-comers, maintenance	Zejula + Yervoy or Opdivo	U. Penn	84	Jan 20
NIRA-PANC (NCT03553004)	DNA repair mutation, second-line, metastatic	Zejula	U. Kansas	18	Feb 2(
NCT03682289	Basket trial incl pancreatic settings	AZD6738 +/- Lynparza	U. California	68	Mar 2(
NCT03601923	DNA repair mutation, second-line, metastatic	Zejula	Dana-Farber	32	Feb 2(
Dapper (NCT03851614)	Basket trial incl pancreatic setting	Imfinzi + Lynparza or Imfinzi plus cediranib	UHN, Toronto	90	Mar 2(
Source: EvaluatePharma, clinicaltrials.gov.					

Considering the strong scientific rationale for treating patients with a BRCA or related genetic mutation with a Parp inhibitor, it is notable that industry has invested little effort in testing these agents in pancreatic cancer. This is probably down to the historically intractable nature of this disease, and the relatively small commercial opportunity, but as the table above shows there has been a fair amount of academic interest.

Trials of note here include a study called Parpvax, which is also being run at the University of Pennsylvania. This is looking at whether checkpoint blockade can add anything to Parp inhibition in patients who respond to platinum chemotherapies; all patients regardless of genetic mutations are being recruited, presumably to see if the scope of the Parp inhibitors can be broadened to other types of homologous recombination deficiencies,

of which BRCA is one example.

In terms of commercial advantage, Astrazeneca and Merck & Co with Lynparza are obviously ahead here, but the trial reported today also stands Clovis in good stead. After Tesaro was bought by Glaxosmithkline Rubraca is the only Parp inhibitor in the hands of a small company, and Clovis needs all the help it can get.

This is an updated version of an earlier story.