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Asco-GI – Pancreatic cancer field awaits sparse data

Jacob Plieth

After a year in which the pancreatic cancer pipeline lost five phase III agents to clinical failure, investigators are anxiously looking for signs of progress in this notoriously difficult field.

Discussion at the Asco-GI symposium centred on why so many agents had failed recently, as well as which of the new strategies could be the most promising (see table below). At a keynote lecture on Friday Dr Volker Ellenreider, of the University of Goettingen, highlighted two relatively new phase III entrants: Halozyme's pegPH20 and the little-known napabucasin, being developed by Daiichi Sankyo's Boston Biomedical unit.

That said, a glance at the pipeline suggests that physicians are in for a relatively lean period, with only a handful of phase II and III pancreatic cancer trials set to read out this year. Dr Ellenreider's keynote shed little light on pancreatic cancer's numerous failures.

Agents that dropped out from the pipeline in 2016 have included vastly differing approaches, such as Newlink Genetics' vaccine algenpantucel-L, small molecules like Incyte's Jakafi, and radiolabelled antibodies such as Immunomedics' Y-90 clivutuzumab. As such there is no inference that can easily be drawn, other than that pancreatic cancer is incredibly hard to treat.

Halozyme, whose pegPH20 is only suitable for the roughly 30% of patients with high hyaluronan levels, recently published detailed phase II data in pancreatic cancer.

However, these have proven difficult to interpret and caused some concern among investors as Halozyme had already initiated the Halo-301 trial before they were available. The second stage of the two-part study did show solid improvements in progression-free and overall survival, but when combined with the first part – which might have been affected by a clinical hold – the OS benefit largely vanished.

Meanwhile, Daiichi's napabucasin, a Stat3 inhibitor that acts on cancer stemness pathways, has entered a very large phase III study on the basis of highly promising but early results. Daiichi reported at Asco last year that a phase I study with 29 evaluable patients showed disease control in 27, 10 of which amounted to partial responses.

Kyrie eleison – Lord have mercy

Pancreatic cancer specialists do have two phase III results to look forward to this year: Eleison's study of glufosfamide in the second-line setting and Astrazeneca's Lynparza in first-line maintenance of patients with gBRCA mutations, which are thought present in around 14% of pancreatic cancers.

Glufosfamide is a glucose conjugated prodrug of ifosfamide. An earlier phase III study, conducted by its originator, Threshold Pharmaceuticals, showed a 25% improvement in OS in the second-line setting but this failed to achieve statistical significance.

Meanwhile, Astra will soon see if Lynparza can extend its indicated range from BRCA-mutated ovarian cancer. The only prior data on Lynparza in pancreatic cancer come from a phase I study in which an overall response rate of 21.7% was reported in 23 heavily pretreated patients.

There are also a number of phase II trials that could render results in pancreatic cancer in the first half of this year, and could result in relatively quick moves into phase III.

Perhaps most important is Oncomed's Yosemite trial of demcizumab, an anti-DLL4 antibody. This is important as it is one of the two main datasets on which Celgene will base its decision on whether to opt into a licensing deal. Celgene, which owns Abraxane, is one of the two main players in pancreatic cancer.

Key programmes in pancreatic cancer				
Project	**Company**	**Design**	**Trial ID**	**Data**
Phase III				
Glufosfamide	Eleison	2nd-line, vs 5FU	NCT01954992	May 2017
Lynparza	Astrazeneca	1st-line maintenance, vs placebo	NCT02184195	Oct 2017
Nanoplatin	Orient/Nanocarrier	1st-line, gem +/- nanoplatin	NCT02043288	Mar 2018
GV1001	Samsung Pharma	1st-line, chemo +/- GV1001	NCT02854072	May 2018
pegPH20	Halozyme	1st-line, gem/Abraxane +/- pegPH20	NCT02715804	Oct 2018
AM0010	Armo Biosciences	2nd-line, Folfox +/- AM0010	NCT02923921	Jan 2019
Napabucasin	Sumitomo Dainippon	1st-line, gem/Abraxane +/- napabucasin	NCT02993731	Dec 2019
Masitinib	AB Science	1st-line, gem +/-masitinib	20013-002293-41	N/A
Imbruvica	Abbvie/J&J	1st-line, gem/Abraxane +/- Imbruvica	NCT02436668*	Mar 2018
Phase II				
Demcizumab	Oncomed	1st-line, gem/Abraxane +/- demcizumab	NCT02289898**	Q1 2017
ERY001	Erytech	2nd-line, Folfox4 +/- ERY001	NCT02195180	Q1 2017
MM-141	Merrimack	1st-line, gem/Abraxane +/- MM-141	NCT02399137***	Aug 2017
Pamrevlumab	Fibrogen	Neoadjuvant, gem/Abraxane +/- pamrevlumab	NCT02210559	Sep 2017
Acalabrutinib	Astrazeneca	2nd-line, +/- Keytruda	NCT02362048****	Dec 2017
Cyramza	Lilly	1st-line, Folfirinox +/- Cyramza	NCT02581215	Mar 2018
Abemaciclib	Lilly	2nd-line, +/- LY3023414 or galunisertib	NCT02981342	Dec 2018
Ubidecarenone	Berg	2nd/3rd-linbe, gem +/- ubidecarenone	NCT02650804	Jan 2019
siG12D Loder	Silenseed	1st-line, gem/Abraxane +/- siG12D Loder	NCT01676259	Feb 2019
*Note: *Resolve; **Yosemite; ***Carrie; ****Keynote-144.*				

Other companies reporting pancreatic data at Asco-GI included Armo Biosciences, which has a phase III trial with AM0010 (pegylated IL-10). Armo's 21-patient phase Ib study showed a 16% objective response rate, with two complete responses.

If anything, Asco-GI showed there remains a consensus among key opinion leaders that pancreatic cancer, which is usually diagnosed late and with a highly aggressive phenotype, has a number of features that make it uniquely difficult to treat among solid tumours.

It is the eleventh-most commonly diagnosed cancer, but ranks fourth by cancer-related death – and is expected to rise to second place soon, given the improving prognosis for other tumour types. If one thing remains clear it is that progress in treatment cannot come too soon.

To contact the writer of this story email Robin Davison, reporting from Asco-GI in San Francisco, at robind@epvantage.com or follow @RobinDavison2 on Twitter