Designing Clinical Trials in 3rd Line or Greater Pancreatic Cancer

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Background

Pancreatic cancer (PC) continues to increase in incidence without significant improvement in overall survival

~20% of PC patients, or ~10,000 patients annually, seek 3rd line or greater (≥ 3L) PC treatments (Abrams, et al 2017; Bachet, et al 2009)

No standard of care exists beyond the 2nd line (2L) as described by ASCO guidelines

Despite substantial patient interest and clear unmet medical need, few large-scale trials are conducted in ≥ 3L PC due to:

- Short expected survival times
- High levels of existing comorbidities
- Adherence to trial protocol while managing social and economic considerations, such as hospice, in late-stage cancer
- Sponsor and investigator pessimism around expected positive outcomes

The following analysis was developed to assist trial sponsors in designing more effective trials in the ≥ 3L population and managing the unique challenges associated with late-stage pancreatic cancer

Methods

Analysis of deidentified data from the Pancreatic Cancer Action Network (PanCAN) Constituent & Trial Management System, Clinical Trial Finder, and Patient Central call center

Retrospective literature search of prospective Phase II or III clinical trials conducted between 2000 and 2018 with >20 subjects in ≥ 2L therapy

Retrospective analysis of summary deidentified trial data conducted by Novella Clinical in PC

Preliminary data from Tyme-88-Panc, a prospective study in ≥ 2L metastatic PC

Additional References:

Noel et al. Feasibility of SM-88 in PC after multiple prior lines and ECOG < 2 J Clin Oncol 37, 2019 (suppl 4; abstr 310)

Noel et al. Phase II trial of SM-88 in patients with metastatic pancreatic cancer: Preliminary results of the first stage. J Clin Oncol 37, 2019 (suppl 4; abstr 200)

Wang-Gillam et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet, 2016 (Vol 387; p545-557)

Growing Demand for ≥ 3L Trials

In 2018, 31% of clinical trial searches with PanCAN were looking for ≥ 3L trials

- ≥ 3L clinical trial searches increased by 51% since 2015

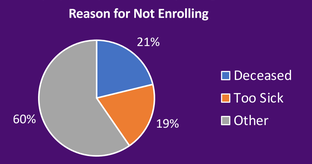
133 clinical trials were potentially open to ≥ 3L patients in 2018, but a majority focused on existing drugs and phase I trials

Trials Accepting ≥ 3L PC Patients in 2018	# of Trials
All trials	133 (100%)
Including development-stage therapies	49 (37%)
Phase II or III, development-stage therapies	11 (8%)
Phase III, any therapy	1 (0.7%)
Phase I, Phase I/II or Pilot	90 (68%)
Single site	73 (55%)

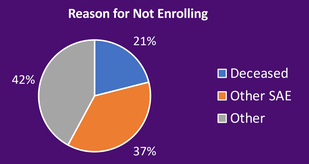
Enrollment is Possible in the ≥ 3L Setting

Comorbidities may compromise ultimate patient enrollment rate

40% of patients seeking ≥ 3L trials through PanCAN died or became too sick (entered hospice or reported having significant side effects/symptoms) before completing enrollment



At completion of Tyme-88-Panc enrollment (n=36), 58% (11/19) of patients that consented, but were not enrolled, died or experienced other SAEs during screening (mean 2.5 week period)



Even with significant screening SAEs, Tyme-88-Panc still enrolled >1 patient /site /month (p/s/m) in the month before completing enrollment

- Historical industry average of 0.26 p/s/m for 1st line trials and 0.35 p/s/m for refractory PC trials (Novella Clinical internal analysis), demonstrating increasing level of interest for novel therapies in later stage trials
- Randomization may complicate enrollment since many subjects specifically choose experimental therapies based on poor outcomes for existing therapies

Varied Reasons for Discontinuations to be Expected

Recent 1st and 2nd line PC trials have reported ~40-50% of treatment discontinuations were not related to radiographic progression. This would be expected to increase in the ≥ 3L setting

- 50% (10/20) of subjects have reported discontinuing the Tyme-88-Panc trial due to reasons other than disease progression

26% (10/38) of patients enrolled in Tyme-88-Panc discontinued prior to completing four weeks of therapy for reasons other than radiographic progression or drug-related adverse events

- Many ≥ 3L patients suffer unrelated SAEs due to disease or previous therapy
- Economically, advanced cancer patients often also have to decide between clinical trials and important home health services provided by hospice, especially if they are functionally compromised

Determining Primary Endpoints

Overall survival (OS) is the most accepted primary endpoint in pancreatic cancer and has been the basis for all recent product approvals

- Mean and median survival after progressing on 2L therapy was only 3.0 months based on 19 2L Phase II or III trials since 2000
- Time between progression on 2L and initiation of 3L (estimated average one month) should be minimized to increase time for benefit from 3L therapy

	Arm	N	ORR	Median Months		
				2L PFS	2L OS	OS post 2L PFS
Napoli-1	Lipo irinotecan +5FU/LV	117	7.7%	3.1	6.1	**3.0**
	5FU/LV	119	0.8%	1.5	4.2	**2.7**
Median of 19 other 2L PC trials		1,452 (30-196)	8.1% (0-24%)	2.4 (1.4-5.5)	5.9 (3.0-9.9)	**3.0 (0.5-7.0)**

Overall Response Rates (ORR) may not adequately reflect anti tumor activity in pancreatic cancer for a number of reasons such as:

- High stromal content
- Imaging inaccuracy
- Built up chemo resistance

Line of Therapy	Investigator Reported Mean ORR	
	5FU-based	Gem-based
1st *	31%	29%
	▼	▼
2nd **	11%	9%
	▼	▼
3rd ***	0%	0%

* Conroy et al 2011 (FOLFIRINOX); Von Hoff et al 2013 (GA)
** Mean of three recent prospective trials containing 5FU and four containing gemcitabine
*** None found throughout literature search

Proper assessment of tumor response may depend on biological as well as anatomic assessment of response

- Alternative imaging modalities or criteria should also be considered

Conclusions

Clinical trial enrollment should be a consideration for all patients

Patient demand along with a lack of standard of care make third line pancreatic cancer treatments a critical area for further study

Therapeutic effect must be evaluated in terms of both quality and quantity of life

Safety may be evaluated in this patient population, however a high level of comorbidities must be accounted for

Novel mechanisms should also be pursued both based on limitations of the two current backbone therapies (5FU and gemcitabine) as well as patient interest in less toxic therapeutic alternatives

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