Investigating the "real-world" clinical impact of treatment sequencing in advanced pancreatic cancer outcomes: a PURPLE translational registry analysis

Jordan Santucci[1 3 14], Belinda Lee [1 2 3 4 5], Ben Thomson[2,3,4], Michael Michael[4], Julia Shapiro[6], Rachel Wong [7,8], Kate Clarke[9], Sharon Pattison[10], Matthew Burge[11], Rob Zielinski[12], Mehrdad Nikfarjam[13], Sumitra Ananda[1,4,8,14], Lara Lipton[1,2,6], Peter Gibbs[1,2,3,14]

[1]Walter & Eliza Hall Institute (WEHI), VIC, Australia, [2]The Royal Melbourne Hospital, VIC, Australia,[3]University of Melbourne, Australia, [4]Peter MacCallum Cancer Centre, VIC, Australia, [5]Northern Health, VIC Australia [6]Cabrini Health, VIC, Australian, [7]Eastern Health, VIC, Australia, [8]Epworth Health, VIC Australia, [9]Wellington Hospital, New Zealand, [10]Dunedin University Hospital, New Zealand, [11]Royal Brisbane and Women's Hospital, Australia, [12]Orange and Dubbo Base Hospitals, NSW, Australia, [13]Austin Health, Melbourne, Australia, [14]Western Health, Melbourne, Australia

Background

- Pancreatic ductal adenocarcinoma (PDAC) is the fourth most common cause of cancer-related deaths in Australia, with a dismal median overall survival (OS) of less than 12 months for advanced disease.(1)
- Gemcitabine monotherapy is an option for advanced PDAC in patients with poorer performance status or significant comorbidity profile but combination regimens with significant toxicities are now standard-of-care given superior survival outcomes (**Figure 1.**).(2)
- First-line chemotherapy combinations have not been compared in head-to-head trials in advanced PDAC.
- Data on optimum treatment sequencing is lacking.

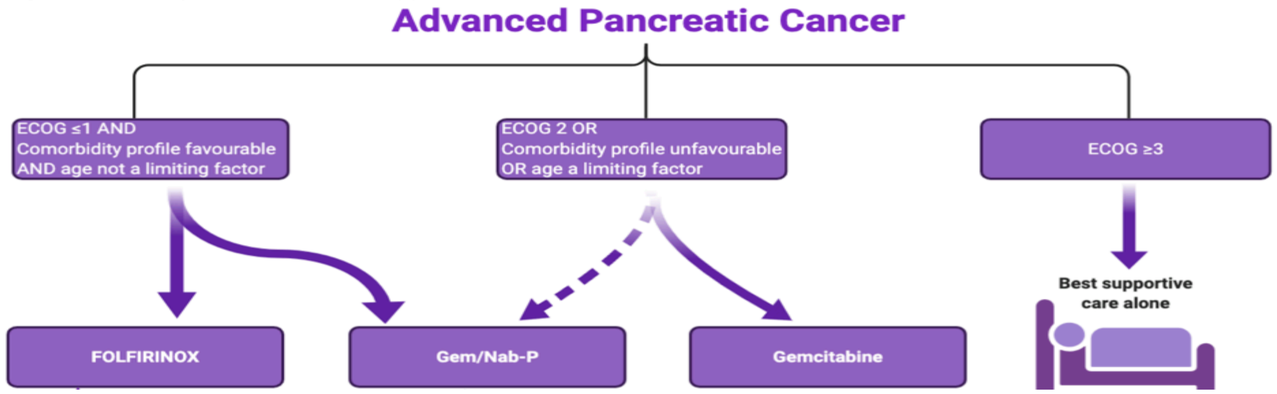
Aim

- To assess whether first-then-second-line treatment sequence wither either FOLFIRINOX or Gem/Nab-P as first-line palliative chemotherapy impacts survival outcomes.

Methods

- Data from the PURPLE (Pancreatic cancer – Understanding Routine Practice and Lifting End results) registry for consecutive patients with locally-advanced, recurrent, or metastatic PDAC were extracted for all patients who received palliative chemotherapy between 2016 and May 2020.
- Clinicopathological characteristics for patients treated with first-line FOLFIRINOX and Gem/Nab-P were compared using the Chi-square or Mann-Whitney U tests.
- Survival estimates were calculated using the Kaplan-Meier method with Log rank tests for survival comparisons. The Breslow test was used when early treatment effect occurred.
- Cox proportional hazards regression was used to obtain hazard ratios (HR).

Figure 1. First-line standard-of-care palliative treatment options for advanced pancreatic cancer according to European, American, and National Comprehensive Cancer Network guidelines with adaptation from Lambert et al.(2)



ECOG = Eastern Cooperative Oncology Group performance status, which is a scale from 0 to 5 of increasing disability, 0 being no disability, 5 being dead. **FOLFIRINOX** = folinic acid, 5-fluorouracil, irinotecan, oxaliplatin. **Gem/Nab-P** = Gemcitabine plus Nab-Paclitaxel.

Results

Figure 2a. Impact of first-line palliative chemotherapy regimen on overall survival (OS) in advanced pancreatic cancer

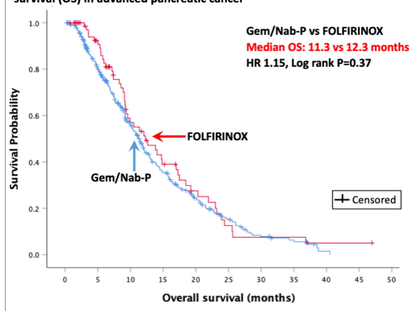


Figure 2b. Impact of first-line palliative chemotherapy regimen on progression-free survival (PFS) in advanced pancreatic cancer

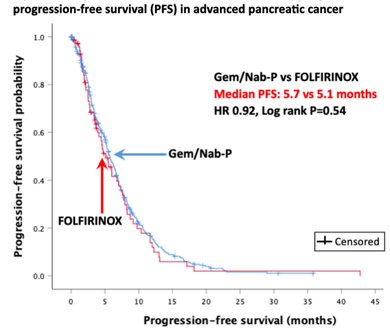


Figure 3a. Impact of treatment sequence on overall survival (OS) in advanced pancreatic cancer

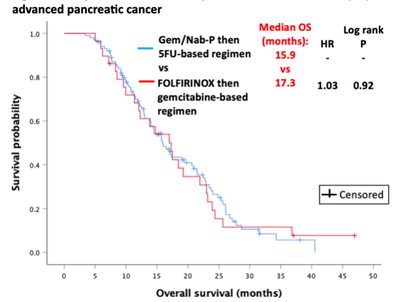


Figure 3b. Impact of treatment sequence on progression-free survival (PFS) in advanced pancreatic cancer

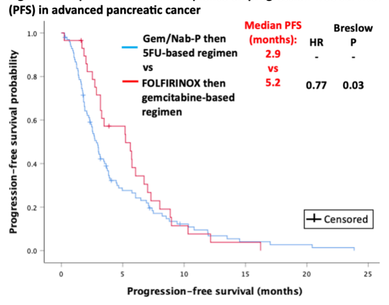


Table 1. Comparison of clinico-pathological characteristics of first-line palliative Gem/Nab-P- versus FOLFIRINOX-treated patients.

Clinico-pathological characteristic	Gem/Nab-P (n=376)	FOLFIRINOX (n=73)	P value
Age at diagnosis, median years (IQR)	67 (60-83)	59 (54-65)	**<0.001***
Male sex n (%)	198 (52.7)	44 (60.3)	0.47
ECOG performance status at first presentation n (%)			0.17
≤1	336 (89.4)	72 (98.6)	**(0.01)**
2	31 (8.2)	1 (1.4)	**(0.04)**
3	7 (1.9)	0	
4	1 (0.3)	0	
Obstructive jaundice at first presentation n (%)	96 (25.5)	17 (23.3)	0.69
Charlson Comorbidity Index score at first presentation n (%)			**0.002**
0	210 (55.9)	56 (76.7)	**(0.001)**
1	96 (25.5)	15 (20.5)	
≥2	69 (18.4)	2 (2.7)	**(0.001)**
Primary pancreatic tumour location n (%)			0.90
Unknown	14 (3.7)	3 (4.1)	
Body	80 (21.3)	14 (19.2)	
Head	209 (55.6)	40 (54.8)	
Tail	70 (18.6)	16 (21.9)	
Whole organ	3 (0.8)	0	
Stage at first presentation n (%)			0.77
Resectable	58 (15.4)	9 (12.3)	
Locally-advanced/borderline-resectable	109 (29.0)	23 (31.5)	
Metastatic	209 (55.6)	41 (56.2)	
Number of metastatic sites at onset of advanced disease n (%)			0.97
0	113 (30.1)	24 (32.9)	
1	154 (41.0)	29 (39.7)	
2	81 (21.5)	15 (20.5)	
≥3	28 (7.4)	5 (6.8)	
Metastatic site at onset of advanced disease n (%)			
Liver	188 (50.0)	33 (45.2)	0.45
Lung	59 (15.7)	11 (15.1)	0.89
Peritoneum or malignant ascites	39 (10.4)	7 (9.6)	0.84
Bone	7 (1.9)	2 (2.7)	0.62
Lymph nodes	70 (18.6)	11 (15.1)	0.47
Other	12 (3.2)	5 (6.8)	0.13
Prior treatment n (%)			
Neoadjuvant chemotherapy	17 (4.5)	2 (2.7)	0.49
Surgical resection of primary tumour	47 (12.5)	10 (13.7)	0.78
Adjuvant chemotherapy	45 (12.0)	9 (12.3)	0.93
Biliary stent	111 (29.5)	23 (31.5)	0.73
1st-line palliative treatment duration, median months (IQR)	4.0 (2.2-5.9)	3.2 (1.7-5.9)	0.30*
Received 2nd-line chemotherapy n (%)	140 (37.2)	32 (43.8)	0.29
Received 3rd-line chemotherapy n (%)	43 (11.4)	8 (11.0)	0.91

*P value for Mann-Whitney U test.

Patient and treatment details:

- 615 patients who received palliative chemotherapy and no radiotherapy included 197 (32%) with locally-advanced disease, 98 (16%) with post-resection recurrence, and 320 (52%) with de novo metastatic disease.
- Compared to 73 patients receiving first-line FOLFIRINOX, the 376 patients receiving Gem/Nab-P (**Table 1.**):
  - were older (median 67 vs 59 years, P<0.001),
  - had a higher Charlson Comorbidity Index (P=0.002),
  - had poorer performance status (ECOG≤1, P=0.01).
- Second-line therapy included:
  - Gem/Nab-P (n=19), Gem/Capecitabine (n=4), Gem/Cisplatin (n=1) and gemcitabine alone (n=5) in 29 patients receiving first-line FOLFIRINOX;
  - FOLFIRINOX (n=14), FOLFIRI (n=48), FOLFOX (n=34), experimental 5-fluorouracil (5FU) combination (n=2), and 5FU alone (n=3) in 101 patients receiving first-line Gem/Nab-P.

Efficacy of first-line treatment options:

- Median overall survival (OS) (12.3 vs 11.3 months P=0.37; **Figure 2a.**) and progression-free survival (PFS) (5.7 vs 5.1 months P=0.54; **Figure 2b.**) were not significantly different with FOLFIRINOX (n=73) vs Gem/Nab-P (n=376), respectively,
- Improved survival occurred with both combination regimens compared to first-line gemcitabine alone (n=75, median OS 7.3 months, P=0.03 for FOLFIRINOX and P=0.04 for Gem/Nab-P).

Efficacy of first-then-second line treatment sequences:

- Median OS did not differ significantly between Gem/Nab-P then 5FU-based (n=101) and FOLFIRINOX then gemcitabine-based (n=29) treatment sequences (15.9 vs 17.3 months P=0.91, respectively; **Figure 3a.**);
- Median PFS was significantly shorter with Gem/Nab-P then 5FU-based treatment compared to the alternate sequence (2.9 vs 5.2 months P=0.03, respectively; **Figure 3b.**)
- Locally-advanced PDAC patients treated with Gem/Nab-P then 5FU-based sequences had significantly longer median OS than those receiving FOLFIRINOX then gemcitabine-based sequences (22.5 vs 13.8 months P=0.01, respectively).
- Conversely, in mPDAC, FOLFIRINOX then gemcitabine-based sequences were superior to Gem/Nab-P then 5FU-based sequences (median PFS 5.6 vs 2.3 months, P=0.03).

Discussion & Conclusion

Significance:

- Consistent with prior studies, first-line palliative Gem/Nab-P and FOLFIRINOX had comparable survival outcomes and were associated with longer survival than gemcitabine alone.(3)
- Limited observational data in PDAC suggest equivalent efficacy of alternative first-then-second-line treatment sequences.(4) Likewise, we observed similar OS between treatment with FOLFIRINOX then gemcitabine-based regimens as compared with Gem/Nab-P then 5FU-based regimens, but PFS was longer with the former sequence.
- Different treatment sequencing approaches may be required for de novo metastatic as compared with locally-advanced PDAC.

Limitations:

- This is a retrospective observational cohort study and thus subject to selection bias, most evident in expected differences in age and fitness by indication between the FOLFIRINOX and Gem/Nab-P groups.
- Dose modifications, number of treatment cycles and toxicities were not compared. This is particularly pertinent to FOLFIRINOX treatment, which frequently requires dose modification potentially altering its efficacy in the "real-world". However, we did not observe significantly earlier treatment cessation with first-line FOLFIRINOX compared to Gem/Nab-P (median treatment duration 3.2 vs 4.0 months, P=0.30).
- The smaller number of patients receiving first-line FOLFIRINOX compared to Gem/Nab-P limited the power of analyses. This reflects current Australian Medicare reimbursement guidelines.

Conclusion:

- There was no significant difference in OS between first-then-second-line treatment sequences with either FOLFIRINOX or Gem/Nab-P as the first-line regimen, despite patients receiving FOLFIRINOX being younger, and having better performance status and less comorbidity.
- Differences observed between locally-advanced disease and metastatic PDAC require further exploration.
- Head-to-head randomised clinical trials are needed to make firm conclusions regarding the optimal initial treatment and sequence of regimens for each patient subset.

References:

1. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet. 2016;388(10039):73-85.
2. Lambert A, Schwarz L, Borbath I, Henry A, Van Laethem JL, Malka D, et al. An update on treatment options for pancreatic adenocarcinoma. Ther Adv Med Oncol. 2019;11:1758835919875568.
3. Chiorean EG, Cheung WY, Giordano G, Kim G, Al-Batran SE. Real-world comparative effectiveness of nab-paclitaxel plus gemcitabine versus FOLFIRINOX in advanced pancreatic cancer: a systematic review. Ther Adv in Med Oncol. 2019;11:1758835919850367.
4. Kieler M, Unseld M, Bianconi D, Schindl M, Kornek GV, Scheithauer W, et al. Impact of New Chemotherapy Regimens on the Treatment Landscape and Survival of Locally Advanced and Metastatic Pancreatic Cancer Patients. J Clin Med. 2020;9(3).

Acknowledgements: Dr Belinda Lee provided supervision and guidance to ensure completion of this project. Division of Systems Biology and Personalised Oncology at Walter and Eliza Hall Institute hosted and supported this study. Access to PURPLE was granted by BioGrid Australia. This research was funded by the Philip Hemstritch Foundation and the Pancare Foundation.