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REVIEW

nab-Paclitaxel for the treatment of pancreatic cancer

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Background: Nanoparticle albumin-bound paclitaxel (*nab*-P) plus gemcitabine (Gem) became a standard treatment option for metastatic pancreatic cancer (MPC) following positive results from a global phase III trial (MPACT). A large number of studies have now published results on the use of *nab*-P/Gem to treat advanced and early-stage disease, warranting a comprehensive review. The main goal of this systematic review is to summarize the efficacy and safety data of *nab*-P/Gem for the treatment of pancreatic cancer (PC).

Methods: This systematic review includes results from studies that either published results in a peer-reviewed journal or presented the results at a major oncology conference.

Results: Sixty-two studies were included (50 in the advanced/metastatic setting and 12 in the locally advanced setting). Most studies on the treatment of MPC were exclusively first line (33/50). Nevertheless, the studies in this review comprised a broad spectrum of patients, including those <65 and ≥65 years of age and those with a Karnofsky performance status of 70–100. Median overall survival (OS) in studies of *nab*-P/Gem in the advanced/metastatic setting ranged from 8.7 to 13.5 months. In addition, 15 studies of patients with advanced/metastatic PC examined *nab*-P/Gem as a backbone on which to add a variety of agents, including cancer stem cell inhibitors, stromal disrupting agents, and immune-modulating agents (median OS, 6.9–17 months). Ongoing trials are investigating *nab*-P/Gem with or without other agents across disease settings.

Discussion: Studies conducted after MPACT have demonstrated that *nab*-P/Gem is an effective regimen for the first-line treatment of MPC for a wide range of patients. Regimens using *nab*-P/Gem as a backbone on which to combine additional agents are being studied actively, particularly in the advanced disease setting. Ongoing studies will yield valuable insights on the utility of *nab*-P–containing regimens to improve patient outcomes in PC in both earlier-stage and advanced disease.

Keywords: pancreatic cancer, *nab*-paclitaxel, metastatic, neoadjuvant, systematic review

Introduction

More than 50,000 new pancreatic cancer (PC) cases and >40,000 cancer-related mortalities due to PC are expected in the USA in 2016.[1,2] The 5-year survival rate for all stages of PC combined is 8%. Although those with resectable disease have a more favorable prognosis (5-year survival ≈29%), ≈52% of patients are diagnosed with metastatic disease, which confers a less favorable outlook (5-year survival ≈3%).[2] Since the approval of gemcitabine (Gem) in 1997, no phase III trial in advanced/metastatic disease had demonstrated a clinically and statistically significant improvement in overall survival (OS) over Gem alone[3] until recently. The treatment landscape for metastatic

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disease has evolved to include 2 key regimens: folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) and nanoparticle albumin-bound paclitaxel (*nab*-P) plus Gem (*nab*-P/Gem). The FOLFIRINOX regimen was approved based on a French multicenter phase II/III trial that reported significant improvements in OS with FOLFIRINOX versus Gem (median, 11.1 vs 6.8 months; hazard ratio [HR], 0.57; $P<0.001$), but significant adverse events were also observed.[4] The *nab*-P/Gem regimen was approved in many countries after the phase III MPACT trial demonstrated that the addition of *nab*®-P (Abraxane®; Celgene Corporation, Summit, NJ, USA) to Gem improved OS versus Gem (median, 8.7 vs 6.6 months; HR, 0.72; $P<0.001$).[5] Currently, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) recommend treatment with FOLFIRINOX or *nab*-P/Gem as standards of care for patients with metastatic pancreatic cancer (MPC).[6,7] Age, performance status (PS), and other clinical factors are considered when deciding which regimen to use; Gem monotherapy is currently reserved for patients ineligible to receive combination chemotherapy.[6]

nab-P/Gem and FOLFIRINOX have not been approved for earlier-stage disease; however, numerous trials are exploring their utility. The NCCN recommends chemotherapy for unresectable locally advanced PC (LAPC) and chemoradiation for selected patients, preferably after induction chemotherapy for tumor control.[6] Currently, no clear evidence exists to support the use of *nab*-P/Gem over FOLFIRINOX or vice versa, and several trials are investigating their efficacy and safety.[8]

A population-based study of >3,000 patients showed that *nab*-P/Gem is the most commonly used chemotherapy regimen for the first-line treatment of MPC in the USA,[9] possibly due to the toxicity profile of FOLFIRINOX, which limits its use to younger/fitter patients. The extensive use of *nab*-P/Gem in both academic and community settings coupled with >100 current and active clinical trials in PC warrants a comprehensive review of clinical data to gain a better understanding of how this regimen is being used for the treatment of PC and associated outcomes. The overall goal of this review is to summarize recent data regarding the safety and efficacy of regimens that include *nab*-P/Gem for patients with PC.

Methods

The search terms "*nab*-paclitaxel and (pancreatic or pancreas)" were entered in PubMed to retrieve publications from January 1, 2011 to June 30, 2016. Abstracts from the annual meetings of the American Society of Clinical Oncology (ASCO) 2011–2016, the Gastrointestinal Cancers Symposium (ASCO GI) 2011–2016, the European Cancer Organisation/ESMO 2011–2015, the ESMO World Congress on Gastrointestinal Cancer 2015 and 2016, and the Italian Association of Medical Oncology (2014) were searched using the term "*nab*-paclitaxel." Clinical trials and institutional analyses of *nab*-P in all stages of PC were included. Duplicates, electronic abstracts, case studies, cost studies, meta-analyses, and studies of the effects of eligibility criteria were excluded. The website www.clinicaltrials.gov was searched using the terms "*nab*-paclitaxel" OR "Abraxane" AND "pancreatic" AND "adenocarcinoma" to identify ongoing trials without results; only open, active, phase II–III trials with a sample size ≥100 were included.

Results

Studies of *nab*-P in advanced/metastatic PC

Fifty studies evaluating *nab*-P in MPC were retrieved (Figure 1; Table 1). Approximately one-half were retrospective analyses. MPACT was the only phase III study, and all other prospective trials were phase I or II. Two-thirds of studies evaluated *nab*-P in the first-line setting, and approximately one-third of those studies assessed *nab*-P/Gem with an additional agent. *nab*-P was most often evaluated at a dose of

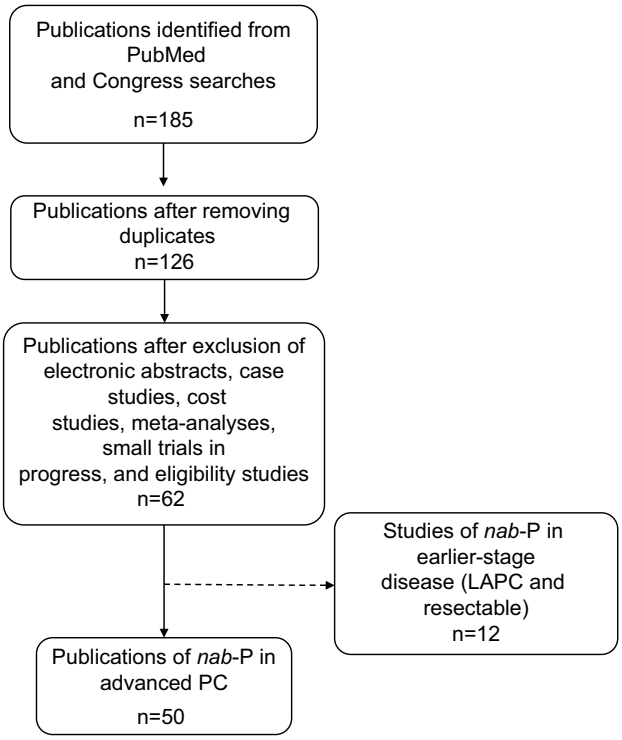

Figure 1 Schematic of method for systematically selecting studies for inclusion in the database.
Abbreviations: LAPC, locally advanced pancreatic cancer; *nab*-P, nanoparticle albumin-bound paclitaxel; PC, pancreatic cancer.

Table 1 Characteristics of advanced/MPC studies (n=50)

Characteristic	Number of studies (%)
Study design	1 (2)
Prospective	9 (18)
Pilot	6 (12)
Phase I	10 (20)
Phase I/II	1 (2)
Phase II	23 (46)
Phase III	
Retrospective/institutional experience	
First-line only *nab*-P	
Regimen	33 (66)
nab-P/Gem	29 (58)
nab-P/Gem + other agent	15 (30)
nab-P + other agent	3 (6)
nab-P monotherapy	3 (6)

Abbreviations: Gem, gemcitabine; MPC, metastatic pancreatic cancer; *nab*-P, nanoparticle albumin-bound paclitaxel.

125 mg/m^2, which was given the first 3 of 4 weeks (qw 3/4). The tables in this systematic review cover MPC (Tables 1–3), neoadjuvant treatment or locally advanced disease (Table 4), and ongoing trials in all settings (Table 5).

nab-P/Gem in MPC

Ten studies reported the median OS for first-line *nab*-P/Gem in patients with advanced PC;[5,10–18] Table 2 lists 8 of these studies with a population >45 patients. The most commonly used dose and schedule were those used in the MPACT trial: *nab*-P 125 mg/m^2 plus Gem 1,000 mg/m^2 administered on a qw 3/4 schedule.[5,14,19,20] Patients treated with this dose and schedule experienced a median OS ranging from 8.7 to 13.5 months[5,18] and 1-year survival ranging from 35% to 62%.[5,14,19,20] Most prospective studies evaluating this dose and schedule were single-arm trials.

nab-P/Gem in MPC – age

It may be expected that younger patients would experience longer survival and improved tolerability compared with older patients. However, most studies, including MPACT, suggest that older patients benefit from *nab*-P/Gem in terms of efficacy without increased risk of toxicity. Approximately 40% of patients enrolled in MPACT were >65 years.[5] Median OS was 9.6 and 7.7 months for patients <65 and ≥65 years, respectively, and the toxicity profiles were similar between age groups.[5] The combination in MPACT demonstrated significant OS benefit over Gem alone in both age groups: <65 years (HR, 0.65; P<0.001) and ≥65 years (HR, 0.80; P=0.048).

A study (N=37) including patients treated with first-line or ≥ second-line *nab*-P/Gem for MPC showed that OS was not significantly different between patients ≥66 years and those <66 years of age (median, 10.5 vs 9 months; P=0.49).[21] Similarly, a large Italian database review of patients (N=208) with advanced PC treated with *nab*-P/Gem demonstrated that age (≥75 vs <75 years) was not significantly associated with efficacy or toxicity with respect to median OS

Table 2 Overall survival (OS) with first-line *nab*-P/Gem in studies of ≥45 patients with metastatic pancreatic cancer

First author, year	Type of study	Agent(s)[a]	n	Age, median, years	PS	Median OS (95% CI), months	*P* value
Von Hoff, 2011[10]	Ph I/II	*nab*-P[b]/Gem	67	61[c]	ECOG 0–1	12.2[c]	NR
Cartwright, 2014[11]	Retro	*nab*-P[d]/Gem	189	Gem-based	Gem-based regimens:	10.2	NR
		Gem + other chemo	1,567	regimens: 70	KPS <70, 7%	7.0	
		FOLFIRINOX	666	60	KPS <70, 1%	11.2	
Santoni, 2014[12]	Retro	*nab*-P[d]/Gem	41	66	NR	11.6	NR
		Gem	159			5.5	
		Gem + cisplatin/oxaliplatin	234			7.5	
		Gem + capecitabine	43			9.1	
		FOLFIRINOX	101			13.0	
Krishna, 2015[13]	Retro	*nab*-P/Gem[e]	49	65	ECOG 0–1	11.1 (5.3–not reached)	NA
MPACT	Ph III	*nab*-P/Gem	431	62	KPS <80, ≈7%	8.7 (7.9–9.7)	<0.001
Goldstein, 2015[5]		Gem	430	63	KPS <80, 8%	6.6 (6.0–7.2)	
Giordano, 2015[50]	Retro	*nab*-P[f]/Gem	208	67	ECOG PS 2, 17.8%	11 (8.8–13.2)	NA
Shen, 2016[17]	Ph II	*nab*-P/Gem	83	57	KPS 70–80, 30%	9.2 (5.29–7.16)	NA
Hammel, 2016[15]	Ph II	*nab*-P/Gem	39	65.3	ECOG 2, 15.4%	9.2 (6.0–13.6)	NR
		nab-P + sLV5FU2	75	66.2	ECOG 2, 16.0%	11.4 (8.8–16.6)	

Notes: [a]*nab*-P at 125 mg/m^2 the first 3 of 4 weeks (qw 3/4) unless otherwise indicated. [b]*nab*-P at 100, 125, or 150 mg/m^2 qw 3/4. [c]For *nab*-P 125 mg/m^2 qw 3/4 (n=44). [d]Dose and schedule of *nab*-P not reported. [e]*nab*-P at 125 mg/m^2 and Gem at 1,000 mg/m^2 both given q2w. Supportive care also included dexamethasone 12 mg 30 min prior to chemotherapy administration. [f]*nab*-P at 100 or 125 mg/m^2 qw 3/4.

Abbreviations: chemo, chemotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; Gem, gemcitabine; KPS, Karnofsky performance status; NA, not applicable; NR, not reported; *nab*-P, nanoparticle albumin-bound paclitaxel; Ph, phase; PS, performance status; Retro, retrospective; sLV5FU2, simplified leucovorin and 5-fluorouracil regimen.

(11.4 vs 11 months; *P*=0.86), disease control rate (69% vs 61%; *P*=0.64), grade 3/4 neutropenia (25% vs 28%), and neurotoxicity (9% vs 12%).[22] Additionally, an exploratory analysis from MPACT showed that the percentages of patients requiring *nab*-P dose reductions were similar between age groups (42% for patients ≥65 years vs 40% for patients <65 years).[23]

nab-P/Gem in MPC – PS

Data on whether patients with a better PS might receive greater benefit from *nab*-P/Gem than patients with a poorer PS are inconclusive; however, similar to the literature in older patients, several studies suggest that less fit patients receive meaningful benefit from the regimen. Stratification of the MPACT population by Karnofsky PS (KPS) demonstrated significantly better OS in the fitter (KPS 90–100) versus less fit (KPS 70–80) group in the combination arm (median, 9.7 vs 7.6 months; HR, 0.76; *P*=0.009) and the Gem arm (median, 7.9 vs 4.3 months; HR, 0.57; *P*<0.001).[5] In the KPS 70–80 subpopulation, *nab*-P/Gem extended median OS by >3 months compared with Gem alone (7.6 vs 4.3 months; HR, 0.59; *P*<0.001).

A small phase I/II trial examined the effect of *nab*-P/Gem in patients with an Eastern Cooperative Oncology Group (ECOG) PS of 2.[24] The results of the phase I portion suggest that these patients were able to receive the standard dose of *nab*-P/Gem; the relative dose intensity was 100% in 6 patients who received *nab*-P 125 mg/m^2 plus Gem 1,000 mg/m^2 qw 3/4.

In a retrospective analysis of 39 patients with unresectable LAPC or MPC treated with *nab*-P/Gem,[25] patients with an ECOG PS of 1 survived longer than patients with an ECOG PS of 2 (median OS, 15 vs 7 months; *P*=0.032).[25] Similarly, the previously mentioned Italian retrospective analysis of patients with advanced PC (N=208) treated with *nab*-P/Gem showed a numerically shorter OS in the ECOG PS 2 versus ECOG PS 0–1 group (median, 8.7 vs 11.2 months; *P*=0.07), but the difference was not significant.[22] In addition, toxicities did not appear to be influenced by PS, because similar percentages of patients with PS 0–1 and PS 2 developed neutropenia (31% and 34%, respectively) and neurotoxicity (17% in each group). Collectively, these studies suggest that, although PS may affect OS, *nab*-P/Gem seems to be effective regardless of PS.

nab-P/Gem in MPC – real-world comparative effectiveness studies

Although clinical trials comparing *nab*-P/Gem with FOLFIRINOX for the treatment of PC have not yet reported results, retrospective analyses have explored these standard-of-care regimens with one another and/or Gem for the treatment of MPC.[11,12,26–29] One study reported a median OS of 10.2 months with *nab*-P/Gem (n=189) versus 11.2 months with FOLFIRINOX (n=666) and 7 months for Gem combined with other chemotherapies (n=1,567).[11] Similar results were reported from another retrospective analysis: median OS of 11.6 months with *nab*-P/Gem (n=41) versus 13 months with FOLFIRINOX (n=101) and 7.5–9.1 months for Gem plus other chemotherapies (n=277).[12] A real-world analysis based on electronic medical records of patients (N=202) receiving first-line treatment for advanced PC demonstrated similar comparative effectiveness for *nab*-P/Gem versus FOLFIRINOX (database persistence [proxy for OS], median, 8.6 months in both groups), despite patients in the FOLFIRINOX group being significantly younger.[27] In addition, a retrospective analysis (N=150) of patients treated at 5 cancer centers in British Columbia, Canada, found that both *nab*-P/Gem and FOLFIRINOX produced similar outcomes and demonstrated longer OS versus Gem alone as treatment for unresectable PC (median, 11.6 and 11.2 vs 4.1 months, respectively; *P*<0.001 and *P*=0.039).[29] Patients who received FOLFIRINOX were younger (median age, 61 vs 70 years) and fitter (ECOG PS≤1, 91% vs 54%) than those who received *nab*-P/Gem.[29] Collectively, the OS with nab-P/Gem observed in MPACT was consistent with the OS observed in real-world observational data sets, and nab-P/Gem was comparable in effectiveness to FOLFIRINOX.

Subsequent therapies after first-line *nab*-P/Gem in MPC

Many recent analyses have examined the use of second-line therapies after *nab*-P/Gem.[27,30–33] Patients in MPACT who received second-line therapy (n=170) after *nab*-P/Gem experienced a numerically longer median OS than those who did not (n=250; median total OS, 12.8 and 6.3 months, respectively).[30] The longest total OS values were observed in patients who received first-line *nab*-P/Gem followed by fluoropyrimidine-containing second-line regimens (n=132; median, 13.5 months); a small number (n=18) received second-line FOLFIRINOX and experienced a median total OS of 15.7 months.[30] Another retrospective analysis from the previously described Italian registry (N=250) demonstrated similar findings, that is, a median OS of 13.5 months in patients who received second-line treatment after first-line *nab*-P/Gem (n=122).[31] More specifically, patients who received second-line FOLFOX/XELOX (n=56), FOLFIRI (n=24), and FOLFIRINOX (n=22) had median total OS values of 12.8, 13.2, and 13.8 months, respectively.[31] Consistent

findings have been observed in many other analyses, and the totality of data suggests that first-line *nab*-P/Gem followed by second-line therapy, particularly with regimens that contain a fluoropyrimidine, is feasible and beneficial to patients with advanced PC.[27,30–33]

Future directions

Future directions for *nab*-P/Gem include studies in which the regimen has been used as a backbone therapy (ie, with another agent) in MPC (Table 3) and as a doublet in locally advanced pancreatic cancer (Table 4). Table 5 displays a list of selected ongoing trials of *nab*-P/Gem with or without other agents as treatment for metastatic, locally advanced, and resectable disease.

nab-P/Gem as a backbone regimen in MPC (studies with results)

Because *nab*-P/Gem has demonstrated survival comparable to that with FOLFIRINOX and a more favorable toxicity profile, this regimen is commonly used as a chemotherapy backbone for other agents (Table 3). Agents combined with *nab*-P/Gem are diverse and include cancer stem cell inhibitors (demcizumab, vismodegib, tarextumab, and BBI-608), those with potential immune-modulating activities (indoximod), those directed against tumor stroma (PEGPH20 and 2-0, 3-0 desulfated heparin), chemotherapies (capecitabine ± cisplatin), hormone therapy (enzalutamide), and others (erlotinib and apatorsen). In 15 studies of patients with MPC treated with *nab*-P/Gem combined with other agents

Table 3 Studies of *nab*-P/Gem + another agent for advanced/metastatic pancreatic cancer (no cutoff based on N)

First author, year	Type of study	Line of Tx	Agent combined with *nab*-P[a]/Gem	N	MPC, %	Age, median, years	PS	Median OS (95% CI), months
Cohen, 2016[56]	Ph Ib	1st	Erlotinib[b]	19	63	63	ECOG 0–1	9.3 (3.3–15.4)
Ko, 2012[57]	Ph I	1st	Capecitabine[c]	15	100	62	ECOG 0–2	7.5 (NR)
De Jesus-Acosta, 2014[58]	Ph II	1st	Vismodegib added in cycle 2	59	100	60	ECOG 0–1	10 (7.3–11)
ALPINE O'Reilly, 2015[59]	Ph Ib	1st	Tarextumab	40	100	63	ECOG 0–1	11.6
Hidalgo, 2016[60]	Ph Ib	1st	Demcizumab	56	70	65	NR	10.1 (6.5–16.2)
			Gem + demcizumab (no *nab*-P)					NR
Hingorani, 2016[61–63]	Ph II	1st	PEGPH20	74	100	NR	NR	12 (high-HA population)
			nab-P/Gem only	61				9 (high-HA population)
O'Reilly, 2016[64]	Ph I	1st	Necuparanib	27	100	63 (mean)	ECOG 0–1	13.1 (4.0–16.6) for patients who completed ≥1 dose
			Gem + necuparanib (no *nab*-P)	12				10.4 (6.1–21.8) for patients who completed ≥1 dose
Bhattacharyya, 2015[65]	Inst.	1st	VT-122CM	20	65	62	Mean ECOG 1.9	17.0
			nab-P/Gem only	17	76	60	Mean ECOG 2.1	9.3 (P<0.001)
Mahipal, 2015[66]	Ph I	1st	Enzalutamide	8	100	64	ECOG 1	NR
Reni, 2014[67]	Ph Ib	1st	Capecitabine + cisplatin[d]	24	NR	63	KPS≤80, 13%	NR
Sigal, 2013[68]	Ph II	1st	2-O, 3-O desulfated heparin (ODSH)	10	NR	66	ECOG 0–1	NR
RAINIER Ko, 2016[69]	Ph II	1st	Apatorsen	66	100	67	ECOG 0–1	5.3 (3.2–7.2)
			nab-P/Gem only	66	100	66	ECOG 0–1	6.9 (P=NS)
El-Rayes, 2016[70]	Ph Ib	≤2nd	BBI-608	37	100	63	ECOG 0–1	NR
Bahary, 2016[71]	Ph Ib	1st	Indoximod	15	100	68	KPS≥70	NR
Borad, 2016[72]	Ph I	1st	Evofosfamide	19	89	62	ECOG 0–1	14.2 (8.5–19.4)

Notes: [a]*nab*-P at 125 mg/m^2 the first 3 of 4 weeks (qw 3/4) unless otherwise indicated. [b]*nab*-P at 75, 100, or 125 mg/m^2 qw 3/4. [c]Dose escalation of *nab*-P from 100 to 150 mg/m^2 on day 4 of a 14-day cycle. [d]*nab*-P at 100–150 mg/m^2 on days 1 and 14 every 4 weeks.

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Gem, gemcitabine; HA, hyaluronan; Inst, institutional analysis; KPS, Karnofsky performance status; MPC, metastatic pancreatic cancer; NR, not reported; *nab*-P, nanoparticle albumin-bound paclitaxel; NS, not statistically significant; OS, overall survival; Ph, phase; PS, performance status; Tx, treatment.

(including 10 phase I trials), the median OS ranged from 6.9 to 17 months.

nab-P/Gem as a backbone regimen in MPC (studies without results)

Thirty ongoing phase II and III trials of *nab*-P in PC with a sample size of ≥100 were identified, including 16 MPC trials (all first line); most included an additional agent (Table 5). For example, the phase II/III RESOLVE trial (N=326) is evaluating *nab*-P/Gem, with or without the Bruton tyrosine kinase inhibitor ibrutinib, as first-line treatment of MPC.[34] Based on promising results from phase I/II trials (Table 3), a phase III trial (N=420) is investigating PEGPH20 in combination with *nab*-P/Gem in patients with high levels of hyaluronan, and demcizumab with *nab*-P/Gem is being evaluated in the phase II YOSEMITE trial (N=201).[35] Another noteworthy ongoing trial is a phase II study (N=260) of *nab*-P/Gem plus istiratumab (MM-141; a bispecific antibody

Table 4 Locally advanced and/or earlier-stage pancreatic cancer studies of ≥15 patients that include treatment with nab-P/Gem

First author, year	Type of study	Regimen[a]	N	Stage	Age, median, years	Response data	Resection rate in all patients/in patients who underwent resection	
							R0	R1
Sueyoshi, 2015[51]	Ph I	*nab*-P[b]/Gem + radiation	15	Unresectable LAPC	63	PR=13% SD=67% PD=7%	NA	NA
Dean, 2016[52]	Retro	*nab*-P/Gem → 5-FU CRT	42	Unresectable LAPC	66	pCR=33%	7%/38%	12%/63%
Idrees, 2016[33]	Retro	*nab*-P[c]/Gem	26	BL resectable (77%) and LAPC (23%)	NR	pCR=15%	NR/86% (not given for each group)	NR
		FOLFIRINOX	59	BL resectable (63%) and LAPC (37%)	NR	pCR=5%		NR
Peterson, 2016[53]	Retro	*nab*-P/Gem	20	BL resectable (70%) and unresectable (30%); patients ineligible for FOLFIRINOX	69	PR=20%	20%/67%	NA
NEOPAX, Van Laethem, 2016[54]	Ph 0	*nab*-P/Gem	23	Unresectable and borderline resectable	63	PR=35% pCR=0	30%/NR	26%/NR
GAIN-1; Sliesoraitis, 2014[55]	Ph II	*nab*-P[d]/Gem	10	Resectable/borderline resectable	68		60%/75%	20%/25%
		Non-neoadjuvant historic controls	22		67		77%/NR	9%/NR
Alvarez, 2013[40]	NR	*nab*-P/Gem	16	Resectable, 44%; borderline resectable, 56%	58	PR by PET, 50%; no objective responses; 1 complete pathological response, 6 GRT-1, 1 GRT-2, 2 GRT-3	69%/92%	6%/8%
GAP; Barbour, 2015[39]	Ph II	*nab*-P/Gem	41	Resectable	65	Pancreatic resection rate, 73%	1-mm margin: 37%/52% 0-mm margin: 61%/86%	1-mm margin: 34%/48% 0-mm margin: 10%/14%
MacKenzie, 2013[38]	Ph II	*nab*-P/Gem	25	Resectable	65	RECIST PR=36% SD=18% PD=8%	80%/95%	4%/5%

Notes: [a]*nab*-P at 125 mg/m^2 the first 3 of 4 weeks (qw 3/4) unless otherwise indicated. [b]*nab*-P at 50–125 mg/m^2 qw 3/4. [c]Dose and schedule of *nab*-P not reported. [d]*nab*-P at 100 mg/m^2 qw 3/4.

Abbreviations: 5-FU, 5-fluorouracil; BL, baseline; CRT, chemoradiation therapy; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; Gem, gemcitabine; GRT, grade of residual tumor; LAPC, locally advanced pancreatic cancer; NA, not applicable; NR, not reported; *nab*-P, nanoparticle albumin-bound paclitaxel; pCR, pathological complete response; PET, positron emission tomography; Ph, phase; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; Retro, retrospective; SD, stable disease.

against ErbB3 and insulin-like growth factor-1 [IGF-1] receptor) for the first-line treatment of patients with MPC and high serum levels of free IGF-1.[36] Finally, whether the combination of *nab*-P/Gem with checkpoint inhibitors will be an effective strategy for PC is an important question, because checkpoint inhibitors have recently provided breakthrough treatment options for several tumor types and are currently being explored in a number of PC trials. Data on such combinations (eg, *nab*-P/Gem and nivolumab)[37] are preliminary at this point.

Neoadjuvant trials for patients with resectable, borderline resectable, or LAPC (studies with results)

Several recent studies (n=12) examined neoadjuvant *nab*-P/Gem as a strategy for improving R0 resection rates in resectable tumors or converting borderline resectable tumors to resectable tumors. One of the main pathologic predictors of survival after surgery is resection margin status; a negative resection margin (R0) is associated with better prognosis compared with a positive margin. Eight of the 12 studies had a total enrollment of ≥15 patients (Table 4). Noteworthy among these is a pilot phase II study in which patients with resectable PC (N=25) were treated with neoadjuvant *nab*-P/Gem for 3 cycles.[38] Surgical resection was possible in 84% of patients and resulted in R0 resection in 95% of resected cases, or 80% of the intention-to-treat population.[38] The phase II GAP study also evaluated neoadjuvant *nab*-P/Gem for 2 cycles in patients with resectable PC (N=41).[39] After neoadjuvant treatment, 73% of the patients underwent pancreatic resection.[39] Similar results were reported from another trial of neoadjuvant *nab*-P/Gem (administered for 2 cycles) in patients with resectable or borderline resectable tumors (N=16).[40] Seventy-five percent of patients underwent surgery, and R0 resection was achieved in 69% of the intention-to-treat population – 92% of those who underwent surgery.

Table 5 Selected ongoing phase II/III trials (N≥100) of *nab*-P/Gem ± other agents in pancreatic adenocarcinoma

Trial	Phase	Planned N	Patient population or stage of disease	Regimen	Planned primary endpoints
Metastatic or advanced stage *nab*-P/Gem only					
QOLINPAC, NCT02106884[73]	II	110	Unresectable LAPC or metastatic	First-line *nab*-P/Gem vs Gem	Deterioration-free QOL using EORTC QLQ-C30
ALPACA, NCT02564146[74]	II	325	Metastatic	First-line: induction with *nab*-P/Gem → *nab*-P/Gem vs induction with *nab*-P/Gem → *nab*-P/Gem or alternating Gem monotherapy and *nab*-P/Gem	OS
nab-P/Gem + other					
NCT02101021[75]	III	430	Metastatic	First-line *nab*-P/Gem + momelotinib vs *nab*-P/Gem	DLT, OS
NCT02715804[76]	III	420	Metastatic	First-line *nab*-P/Gem + PEGPH20 vs *nab*-P/Gem + placebo	PFS, OS
RESOLVE, NCT02436668[46]	II/III	326	Metastatic	First-line *nab*-P/Gem + Ibrutinib vs *nab*-P/Gem + placebo	PFS
CARRIE, NCT02399137[36]	II	260	Metastatic	First-line *nab*-P/Gem + MM-141 vs *nab*-P/Gem + placebo	PFS
YOSEMITE, NCT02289898[35]	II	201	Metastatic	First-line *nab*-P/Gem + placebo vs *nab*-P/Gem + demcizumab + placebo (truncated course of demcizumab) vs *nab*-P/Gem + demcizumab	PFS
NCT02551991[77]	II	168	Metastatic	First-line *nab*-P/Gem vs nal-IRI + 5-FU + folinic acid vs nal-IRI + 5-FU + folinic acid + oxaliplatin	PFS
FIRGEMAX, NCT02827201[78]	II	124	Metastatic	First-line *nab*-P/Gem alternating with FOLFIRI.3 vs *nab*-P/Gem	PFS at 6 months

(*Continued*)

Table 5 (*Continued*)

Trial	Phase	Planned N	Patient population or stage of disease	Regimen	Planned primary endpoints
SEQUENCE, NCT02504333[79]	I/II	180	Metastatic	First-line *nab*-P/Gem → recommended dose of modified FOLFOX from phase I	Phase I: safety, DLT Phase II: OS at 12 months
PACT-19, NCT01730222[80]	I/II	134	Advanced	Phase II: first-line *nab*-P RP2D + Gem 800 mg/m^2 + cisplatin 30 mg/m^2 + cape 1,250 mg/m^2 q2w every 4 weeks vs *nab*-P 125 mg/m^2 + Gem 1,000 mg/m^2 qw 3/4	Phase I: DLT Phase II: PFS for stage IV, resectability rate for stage III
NabucCO, NCT02109341[81]	I/II	114	Metastatic	First-line *nab*-P + FOLFIRI or *nab*-P + FOLFOX	MTD, DLTs, ORR
NCT02194829[82]	I/II	133	Advanced	First-line *nab*-P/Gem ± MK-1775	Phase I: MTD Phase II: PFS
Resectable or locally advanced *nab*-P/Gem only					
LAPACT, NCT02301143[44,83]	II	110	Untreated LAPC	*nab*-P/Gem	Time to treatment failure
APACT, NCT01964430[45]	III	800	Resected	Adjuvant *nab*-P/Gem vs Gem	DFS
NEONAX, NCT02047513[47]	II	166	Resectable	Neoadjuvant and adjuvant vs only adjuvant *nab*-P/Gem	Time to DFS
S1505, NCT02562716[84]	II	112	Resectable	Neoadjuvant *nab*-P/Gem vs mFOLFIRINOX	OS
NCT02506842[48]	III	300	Resected	Second-line adjuvant *nab*-P 100 mg/m^2 + Gem 1,000 mg/m^2 vs oxaliplatin + folinic acid + 5-FU	OS
NCT02243007[42]	II	112	Resectable	Neoadjuvant FOLFIRINOX vs *nab*-P/Gem	OS at 18 months
nab-P/Gem + other					
NEOLAP, NCT02125136[41]	II	168	Untreated unresectable or borderline resectable LAPC	Neoadjuvant *nab*-P/Gem vs *nab*-P/Gem followed by FOLFIRINOX	Conversion rate to resection
"Personalized Medicine," NCT01726582[85]	II	120	Resectable and borderline resectable	*nab*-P/Gem ± subsequent CRT with Gem or cape as neoadjuvant or adjuvant therapy vs other chemotherapies in similar settings vs CRT with Gem or cape in similar settings	Resectability rate
SCALOP-2, NCT02024009[86]	I/II	289	LAPC	Induction *nab*-P/Gem → *nab*-P/Gem + RT → cape + RT ± nelfinavir vs 6 cycles of *nab*-P/Gem	OS, PFS

Abbreviations: 5-FU, 5-fluorouracil; cape, capecitabine; CRT, chemoradiation therapy; DFS, disease-free survival; DLT, dose-limiting toxicity; EORTC, European Organisation for Research and Treatment of Cancer; FOLFIRI, folinic acid, 5-fluorouracil, and irinotecan; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; Gem, gemcitabine; LAPC, locally advanced pancreatic cancer; MTD, maximum tolerated dose; nal-IRI, nanoliposomal irinotecan; *nab*-P, nanoparticle albumin-bound paclitaxel; OS, overall survival; PFS, progression-free survival; QOL, quality of life; qw 3/4, first 3 of 4 weeks; RP2D, recommended phase II dose; RT, radiotherapy.

Neoadjuvant trials for patients with resectable, borderline resectable, or LAPC (studies without results)

The phase II NEOLAP trial (N=168) will examine the ability of neoadjuvant *nab*-P/Gem versus FOLFIRINOX to convert unresectable LAPC or borderline resectable tumors to resectable tumors (Table 5).[41] Another phase II study (N=112) is comparing neoadjuvant *nab*-P/Gem versus FOLFIRINOX followed by resection in patients with potentially resectable tumors.[42] The randomized phase II LAPACT study (N=110) is investigating time to treatment failure in patients with unresectable LAPC treated with *nab*-P/Gem.[43,44]

Ongoing adjuvant trials for patients with resectable PC

The ongoing phase III APACT study is evaluating *nab*-P/Gem versus Gem monotherapy as adjuvant treatment in patients who have undergone macroscopic complete resection for non-MPC (Table 5).[45,46] Two other studies are also examining *nab*-P/Gem as adjuvant therapy: the phase II NEONAX study (N=166; *nab*-P/Gem as adjuvant only vs as neoadjuvant plus adjuvant)[47] and a second-line adjuvant phase III trial in patients who experienced disease relapse during Gem-based adjuvant therapy (N=300).[48]

Discussion

Multiple studies have demonstrated that first-line treatment with *nab*-P/Gem improves survival in patients with MPC, with OS similar to or better than that observed in MPACT. These studies have helped to confirm the dose and schedule of *nab*-P 125 mg/m^2 plus Gem 1,000 mg/m^2 qw 3/4 as an effective and tolerable option for patients with MPC. Retrospective analyses of comparisons between *nab*-P/Gem and FOLFIRINOX suggested similar efficacy outcomes between the regimens, despite differences in patient populations; *nab*-P/Gem was used in a broader spectrum of patients.

Most studies demonstrated an OS benefit with *nab*-P/Gem regardless of age group; similarly, patients seem to derive substantial clinical benefit from *nab*-P/Gem regardless of PS. The demonstrated efficacy of first-line *nab*-P/Gem has led to a number of studies examining regimens afterward as second-line therapy.[27,30–33] These studies showed that second-line treatment after *nab*-P/Gem is feasible and that fluoropyrimidine-containing regimens, and not exclusively FOLFIRINOX, are appropriate options in this setting.

There are currently >100 ongoing trials (combined target enrollment >9,500 patients) assessing different *nab*-P regimens for the treatment of PC, and these studies will provide critical information regarding optimal combinations for specific patient populations.[49]

Conclusion

In summary, *nab*-P/Gem is an effective and well-tolerated regimen for patients with PC. Ongoing trials will evaluate *nab*-P in all stages of PC. The combination of *nab*-P/Gem has become a standard of care for MPC and a backbone onto which novel therapies are added in ongoing trials. Future directions in this field will revolve around improving our understanding of PC, including its molecular biology, and identifying subsets of patients that may benefit from specific treatments.

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