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 alone³ 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/m², 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/m² plus Gem 1,000 mg/m² 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–I	12.2 ^c	NR
Cartwright, 2014 ¹¹	Retro	nab-P ^d /Gem	189	Gem-based regimens: 70	Gem-based regimens: KPS <70, 7%	10.2	NR
		Gem + other chemo	1,567			7.0	
		FOLFIRINOX	666			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–I	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/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: ^anab-P at 125 mg/m² the first 3 of 4 weeks (qw 3/4) unless otherwise indicated. ^bnab-P at 100, 125, or 150 mg/m² qw 3/4. ^cFor nab-P 125 mg/m² qw 3/4 (n=44). ^dDose and schedule of nab-P not reported. ^enab-P at 125 mg/m² and Gem at 1,000 mg/m² both given q2w. Supportive care also included dexamethasone 12 mg 30 min prior to chemotherapy administration. ^fnab-P at 100 or 125 mg/m² 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/m² plus Gem 1,000 mg/m² 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-O, 3-O desulfated heparin), chemotherapies (capecitabine ± cisplatin), hormone therapy (enzalutamide), and others (erlotinib and apatonsen). 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 <i>nab</i> -P ^a /Gem	N	MPC, %	Age, median, years	PS	Median OS (95% CI), months
Cohen, 2016 ⁵⁶	Ph Ib	Ist	Erlotinib ^b	19	63	63	ECOG 0–I	9.3 (3.3–15.4)
Ko, 2012 ⁵⁷	Ph I	Ist	Capecitabine ^c	15	100	62	ECOG 0–2	7.5 (NR)
De Jesus-Acosta, 2014 ⁵⁸	Ph II	Ist	Vismodegib added in cycle 2	59	100	60	ECOG 0–I	10 (7.3–11)
ALPINE	Ph Ib	Ist	Tarextumab	40	100	63	ECOG 0–I	11.6
O'Reilly, 2015 ⁵⁹	Ph Ib	Ist	Demcizumab	56	70	65	NR	10.1 (6.5–16.2)
Hidalgo, 2016 ⁶⁰	Ph Ib	Ist	Gem + demcizumab (no <i>nab</i> -P)					NR
Hingorani, 2016 ^{61–63}	Ph II	Ist	PEGPH20	74	100	NR	NR	12 (high-HA population)
			<i>nab</i> -P/Gem only	61				9 (high-HA population)
O'Reilly, 2016 ⁶⁴	Ph I	Ist	Necuparanib	27	100	63 (mean)	ECOG 0–I	13.1 (4.0–16.6) for patients who completed ≥1 dose
			Gem + necuparanib (no <i>nab</i> -P)	12				10.4 (6.1–21.8) for patients who completed ≥1 dose
Bhattacharyya, 2015 ⁶⁵	Inst.	Ist	VT-122CM	20	65	62	Mean ECOG 1.9	17.0
			<i>nab</i> -P/Gem only	17	76	60	Mean ECOG 2.1	9.3 (P<0.001)
Mahipal, 2015 ⁶⁶	Ph I	Ist	Enzalutamide	8	100	64	ECOG I	NR
Reni, 2014 ⁶⁷	Ph Ib	Ist	Capecitabine + cisplatin ^d	24	NR	63	KPS≤80, 13%	NR
Sigal, 2013 ⁶⁸	Ph II	Ist	2-O, 3-O desulfated heparin (ODSH)	10	NR	66	ECOG 0–I	NR
RAINIER	Ph II	Ist	Apatonsen	66	100	67	ECOG 0–I	5.3 (3.2–7.2)
Ko, 2016 ⁶⁹			<i>nab</i> -P/Gem only	66	100	66	ECOG 0–I	6.9 (P=NS)
El-Rayes, 2016 ⁷⁰	Ph Ib	≤2nd	BBI-608	37	100	63	ECOG 0–I	NR
Bahary, 2016 ⁷¹	Ph Ib	Ist	Indoximod	15	100	68	KPS≥70	NR
Borad, 2016 ⁷²	Ph I	Ist	Evofofamide	19	89	62	ECOG 0–I	14.2 (8.5–19.4)

Notes: ^a*nab*-P at 125 mg/m² the first 3 of 4 weeks (qw 3/4) unless otherwise indicated. ^b*nab*-P at 75, 100, or 125 mg/m² qw 3/4. ^cDose escalation of *nab*-P from 100 to 150 mg/m² on day 4 of a 14-day cycle. ^d*nab*-P at 100–150 mg/m² 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	RI
Sueyoshi, 2015 ⁵¹	Ph I	<i>nab</i> -P/Gem + radiation	15	Unresectable LAPC	63	PR=13% SD=67% PD=7%	NA	NA
Dean, 2016 ⁵²	Retro	<i>nab</i> -P/Gem → 5-FU CRT	42	Unresectable LAPC	66	pCR=33%	7%/38%	12%/63%
Idrees, 2016 ³³	Retro	<i>nab</i> -P/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%		
Peterson, 2016 ⁵³	Retro	<i>nab</i> -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	<i>nab</i> -P/Gem	23	Unresectable and borderline resectable	63	PR=35% pCR=0	30%/NR	26%/NR
GAIN-1; Sliesoraitis, 2014 ⁵⁵	Ph II	<i>nab</i> -P/Gem	10	Resectable/borderline resectable	68		60%/75%	20%/25%
		Non-neoadjuvant historic controls	22		67		77%/NR	9%/NR
Alvarez, 2013 ⁴⁰	NR	<i>nab</i> -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	<i>nab</i> -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	<i>nab</i> -P/Gem	25	Resectable	65	RECIST PR=36% SD=18% PD=8%	80%/95%	4%/5%

Notes: ^a*nab*-P at 125 mg/m² the first 3 of 4 weeks (qw 3/4) unless otherwise indicated. ^b*nab*-P at 50–125 mg/m² qw 3/4. ^cDose and schedule of *nab*-P not reported. ^d*nab*-P at 100 mg/m² 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 $\geq$ 100) of *nab*-P/Gem $\pm$ other agents in pancreatic adenocarcinoma

Trial	Phase	Planned N	Patient population or stage of disease	Regimen	Planned primary endpoints
Metastatic or advanced stage					
<i>nab</i> -P/Gem only					
QOLINPAC, NCT02106884 ⁷³	II	110	Unresectable LAPC or metastatic	First-line <i>nab</i> -P/Gem vs Gem	Deterioration-free QOL using EORTC QLQ-C30
ALPACA, NCT02564146 ⁷⁴	II	325	Metastatic	First-line: induction with <i>nab</i> -P/Gem $\rightarrow$ <i>nab</i> -P/Gem vs induction with <i>nab</i> -P/Gem $\rightarrow$ <i>nab</i> -P/Gem or alternating Gem monotherapy and <i>nab</i> -P/Gem	OS
<i>nab</i> -P/Gem + other					
NCT02101021 ⁷⁵	III	430	Metastatic	First-line <i>nab</i> -P/Gem + momelotinib vs <i>nab</i> -P/Gem	DLT, OS
NCT02715804 ⁷⁶	III	420	Metastatic	First-line <i>nab</i> -P/Gem + PEGPH20 vs <i>nab</i> -P/Gem + placebo	PFS, OS
RESOLVE, NCT02436668 ⁴⁶	II/III	326	Metastatic	First-line <i>nab</i> -P/Gem + Ibrutinib vs <i>nab</i> -P/Gem + placebo	PFS
CARRIE, NCT02399137 ³⁶	II	260	Metastatic	First-line <i>nab</i> -P/Gem + MM-141 vs <i>nab</i> -P/Gem + placebo	PFS
YOSEMITE, NCT02289898 ³⁵	II	201	Metastatic	First-line <i>nab</i> -P/Gem + placebo vs <i>nab</i> -P/Gem + demcizumab + placebo (truncated course of demcizumab) vs <i>nab</i> -P/Gem + demcizumab	PFS
NCT02551991 ⁷⁷	II	168	Metastatic	First-line <i>nab</i> -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 <i>nab</i> -P/Gem alternating with FOLFIRI.3 vs <i>nab</i> -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 <i>nab</i> -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 <i>nab</i> -P RP2D + Gem 800 mg/m ² + cisplatin 30 mg/m ² + capec 1,250 mg/m ² q2w every 4 weeks vs <i>nab</i> -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 <i>nab</i> -P + FOLFIRI or <i>nab</i> -P + FOLFOX	MTD, DLTs, ORR
NCT02194829 ⁸²	I/II	133	Advanced	First-line <i>nab</i> -P/Gem ± MK-1775	Phase I: MTD Phase II: PFS
Resectable or locally advanced <i>nab</i> -P/Gem only					
LAPACT, NCT02301143 ^{44,83}	II	110	Untreated LAPC	<i>nab</i> -P/Gem	Time to treatment failure
APACT, NCT01964430 ⁴⁵	III	800	Resected	Adjuvant <i>nab</i> -P/Gem vs Gem	DFS
NEONAX, NCT02047513 ⁴⁷	II	166	Resectable	Neoadjuvant and adjuvant vs only adjuvant <i>nab</i> -P/Gem	Time to DFS
S1505, NCT02562716 ⁸⁴	II	112	Resectable	Neoadjuvant <i>nab</i> -P/Gem vs mFOLFIRINOX	OS
NCT02506842 ⁴⁸	III	300	Resected	Second-line adjuvant <i>nab</i> -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 <i>nab</i> -P/Gem	OS at 18 months
<i>nab</i> -P/Gem + other					
NEOLAP, NCT02125136 ⁴¹	II	168	Untreated unresectable or borderline resectable LAPC	Neoadjuvant <i>nab</i> -P/Gem vs <i>nab</i> -P/Gem followed by FOLFIRINOX	Conversion rate to resection
“Personalized Medicine,” NCT01726582 ⁸⁵	II	120	Resectable and borderline resectable	<i>nab</i> -P/Gem ± subsequent CRT with Gem or capec as neoadjuvant or adjuvant therapy vs other chemotherapies in similar settings vs CRT with Gem or capec in similar settings	Resectability rate
SCALOP-2, NCT02024009 ⁸⁶	I/II	289	LAPC	Induction <i>nab</i> -P/Gem → <i>nab</i> -P/Gem + RT → capec + RT ± nelfinavir vs 6 cycles of <i>nab</i> -P/Gem	OS, PFS

Abbreviations: 5-FU, 5-fluorouracil; capec, 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; na-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/m² plus Gem 1,000 mg/m² 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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References

1. American Cancer Society, editor. *Cancer Facts and Figures 2016*. Atlanta, GA: American Cancer Society; 2016.
2. Surveillance, Epidemiology, and End Results Program. SEER stat facts sheets: pancreas cancer; updated 2016. Available from: <http://seer.cancer.gov/statfacts/html/pancreas.html>. Accessed September 15, 2016.
3. Ciliberto D, Botta C, Correale P, et al. Role of gemcitabine-based combination therapy in the management of advanced pancreatic cancer: a meta-analysis of randomised trials. *Eur J Cancer*. 2013;49(3):593–603.
4. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817–1825.
5. Goldstein D, El-Maraghi RH, Hammel P, et al. *nab*-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. *J Natl Cancer Inst*. 2015;107(2):1–10.
6. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. V1. 2016. Available from: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed August 1, 2016.
7. Ducreux M, Cuhna AS, Caramella C, et al. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(Suppl 5):v56–v68.
8. Balaban EP, Mangu PB, Khorana AA, et al. Locally advanced, unresectable pancreatic cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016;34(22):2654–2668.
9. Abrams TA, Meyer G, Moloney J, et al. Patterns of chemotherapy (CT) use in a population-based US-wide cohort of patients (pts) with metastatic pancreatic cancer (MPC). Poster presented at: ASCO 2014 Annual Meeting [abstract 4131].
10. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol*. 2011;29(34):4548–4554.
11. Cartwright TH, Ginsburg A, Wilfong LS, Harrell RK, Hoverman JR. Use of first-line chemotherapy for advanced pancreatic cancer: FOLFIRINOX versus gemcitabine-based therapy. Poster presented at: ASCO 2014 Annual Meeting [abstract 4132].
12. Santoni M, Bittoni A, Andrikou K, et al. Does first-line therapy affect the outcome of patients with pancreatic cancer? Poster presented at: ESMO 2014 Annual Meeting [abstract 695P].
13. Krishna K, Blazer M, Wei L, et al. Modified gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer (MPC): a single institution experience. Poster presented at: ASCO 2015 Gastrointestinal Cancers Symposium [abstract 366].
14. Giordano G, Febraro A, Vaccaro V, et al. Nab-paclitaxel (nab-P) and gemcitabine (G) as first line chemotherapy (CT) in advanced pancreatic cancer (APDAC) patients (pts): an Italian “real life” study. Poster presented at: ESMO 2015 Annual Meeting [abstract 2334].
15. Hammel P, Bachet JB, Desrame J, et al. Nab-paclitaxel plus gemcitabine or plus simplified LV5FU2 as first-line therapy in patients with metastatic pancreatic adenocarcinoma: a GERCOR randomized phase II study. Poster presented at: ASCO 2016 Annual Meeting [abstract 4120].
16. Zhang DS, Wang DS, Wang ZQ, et al. Phase I/II study of albumin-bound nab-paclitaxel plus gemcitabine administered to Chinese patients with advanced pancreatic cancer. *Cancer Chemother Pharmacol*. 2013;71(4):1065–1072.

17. Shen L, Yu X, Hao J, et al. A phase II study of Chinese patients (pts) treated with *nab*-paclitaxel (*nab*-P) plus gemcitabine (gem) for metastatic pancreatic cancer (MPC). Poster presented at: ASCO 2016 Annual Meeting [abstract 327].
18. Ueno H, Ikeda M, Ueno M, et al. Phase I/II study of *nab*-paclitaxel plus gemcitabine for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. *Cancer Chemother Pharmacol*. 2016;77(3):595–603.
19. Kasuga A, Ueno H, Ikeda M, et al. Efficacy, safety and pharmacokinetics of weekly *nab*-paclitaxel plus gemcitabine in Japanese patients with metastatic pancreatic cancer (MPC): phase I/II trial. Presentation at the 2014 APA/JPS Meeting [abstract 14200].
20. Bachet J, Hammel P, Desrame J, et al. *Nab*-paclitaxel plus gemcitabine or plus simplified LV5FU2 as first-line therapy in patients with metastatic pancreatic adenocarcinoma. A GERCOR randomized phase II study (AFUGEM). Poster presented at: ESMO 2015 Annual Meeting [abstract P317].
21. Lo Re G, Santeufemia DA, Foltran L, Bidoli E, Basso SM, Lumachi F. Prognostic factors of survival in patients treated with *nab*-paclitaxel plus gemcitabine regimen for advanced or metastatic pancreatic cancer: a single institutional experience. *Oncotarget*. 2015;6(10):8255–8260.
22. Giordano G, De Vita F, Melisi D, et al. Analysis of activity, efficacy and safety of first line *nab*-paclitaxel (*nab*-P) and gemcitabine (G) in advanced pancreatic cancer (APDAC) frail and elderly patients (pts). Poster presented at: ESMO 2015 Annual Meeting [abstract P297].
23. Scheithauer W, Von Hoff DD, Ramanathan R, et al. Dose delivery in a phase III trial (MPACT) of weekly *nab*-paclitaxel (*nab*-P) plus gemcitabine (gem) vs gem alone for patients with metastatic adenocarcinoma of the pancreas. Poster presented at: ESMO 2013 Annual Meeting [abstract 2.586].
24. Guillen-Ponce C, Lopez R, Macarulla T, et al. A phase I/II trial to evaluate the efficacy and safety of *nab*-paclitaxel in combination with gemcitabine for the treatment of frail patients with advanced or metastatic pancreatic cancer: safety results of the phase I trial. Poster presented at: ESMO 2014 Annual Meeting [abstract 700].
25. Montes AF, Villarroel PG, Ayerbes MV, et al. Retrospective analysis of prognostic and predictive markers in patients with locally advanced unresectable or metastatic pancreatic adenocarcinoma treated with gemcitabine/*nab*paclitaxel: influence of the presence of stent. Poster presented at: ASCO 2015 Annual Meeting [abstract 483].
26. Park PYS, McAferty KV, Ahmadi M, et al. Radiological markers of treatment responsiveness in patients (pts) with metastatic pancreatic ductal adenocarcinomas (mPDAC) receiving systemic chemotherapy. Poster presented at: ASCO 2016 Annual Meeting [abstract 403].
27. Braithe FS, Patel M, Parisi M, Ni Q, Park SY, Faria C. Comparative effectiveness and resource utilization of *nab*-paclitaxel plus gemcitabine (*nab*-P+G) versus FOLFIRINOX (FFX) in first-line treatment of advanced pancreatic adenocarcinoma (PDAC) in a U.S. community oncology setting. Poster presented at: ASCO 2016 Annual Meeting [abstract 433].
28. Braithe FS, Patel M, Parisi M, Ni Q, Park SY, Faria C. Comparative effectiveness and resource utilization of *nab*-paclitaxel plus gemcitabine (*nab*-P+G) versus gemcitabine monotherapy (G) in first-line treatment of advanced pancreatic adenocarcinoma (PDAC) in a U.S. community oncology setting. Poster presented at: ASCO 2016 Annual Meeting [abstract 429].
29. Wang Y, Chen L, Camateros P, Gill S, Renouf DJ, Cheung WY. Comparative effectiveness of FOLFIRINOX or *nab*-paclitaxel plus gemcitabine in locally advanced or metastatic pancreatic cancer: a population-based analysis. Poster presented at: ASCO 2016 Annual Meeting [abstract 6561].
30. Chiorean EG, Von Hoff DD, Tabernero J, et al. Second-line therapy after *nab*-paclitaxel plus gemcitabine or after gemcitabine for patients with metastatic pancreatic cancer. *Br J Cancer*. 2016;115(2):188–194.
31. Giordano G, Febbraro A, Milella M, et al. Impact of second-line treatment (2L T) in advanced pancreatic cancer (APDAC) patients (pts) receiving first line *nab*-paclitaxel (*nab*-P) + gemcitabine (G): an Italian multicentre real life experience. Poster presented at: ASCO 2016 Annual Meeting [abstract 4124].
32. Schmidt SL, Durkal V, Jayavalan SP, et al. Outcomes in metastatic pancreatic adenocarcinoma (MPAC) patients treated with FOLFIRINOX (FFX)/FOLFOX(FX) and gemcitabine + *nab*-paclitaxel (NabG). Poster presented at: ASCO 2016 Annual Meeting [abstract 397].
33. Idrees K, Parikh A, Postlewait LM, et al. Treatment of borderline resectable (BR) and locally advanced (LA) pancreatic cancer in the era of FOLFIRINOX and gemcitabine plus *nab*-paclitaxel: a multi-institutional study. Poster presented at: ASCO 2016 Annual Meeting [abstract 451].
34. ClinicalTrials.gov. Study of ibrutinib vs placebo, in combination with *nab*-paclitaxel and gemcitabine, in the first line treatment of patients with metastatic pancreatic adenocarcinoma (RESOLVE). Available from: <https://clinicaltrials.gov/ct2/show/NCT02436668>. Accessed August 1, 2015.
35. ClinicalTrials.gov. Study of gemcitabine, ABRAXANE® plus placebo versus gemcitabine, ABRAXANE® plus 1 or 2 truncated courses of demcizumab in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma (YOSEMITE). Available from: <https://clinicaltrials.gov/ct2/show/NCT02289898>. Accessed August 1, 2016.
36. ClinicalTrials.gov. A phase 2 study of MM-141 plus *nab*-paclitaxel and gemcitabine in front-line metastatic pancreatic cancer (CARRIE). Available from: <https://clinicaltrials.gov/ct2/show/NCT02399137>. Accessed August 1, 2016.
37. Hochster HS, Wainberg ZA, Gutierrez M, et al. Phase 1 study of nivolumab + *nab*-paclitaxel +/- gemcitabine in pancreatic cancer: safety evaluation of patients treated with nivolumab + *nab*-paclitaxel in arm A. Poster presented at: AACR: Special Conference on Pancreatic Cancer 2016 [abstract A72].
38. MacKenzie S, Zeh H, McCahill L, et al. A pilot phase II multi center study of *nab*-paclitaxel and gemcitabine as preoperative therapy for potentially resectable pancreatic cancer (PC). Poster presented at: ASCO 2013 Annual Meeting [abstract 4038].
39. Barbour A, O'Rourke N, Chan H, et al. Initial survival outcomes for the AGITP GAP study – a phase II study of perioperative *nab*-paclitaxel and gemcitabine for resectable pancreatic ductal adenocarcinoma (PDAC). Poster presented at: ASCO 2016 Annual Meeting [abstract 4105].
40. Alvarez R, Musteanu M, Garcia-Garcia E, et al. Stromal disrupting effects of *nab*-paclitaxel in pancreatic cancer. *Br J Cancer*. 2013;109(4):926–933.
41. ClinicalTrials.gov. Trial to investigate intensified neoadjuvant chemotherapy in locally advanced pancreatic cancer (NEOLAP). Available from: <https://clinicaltrials.gov/ct2/show/NCT02125136?term=nab-paclitaxel+AND+pancreatic+AND+adenocarcinoma&rank=55>. Accessed August 1, 2016.
42. ClinicalTrials.gov. Phase II study of preoperative FOLFIRINOX versus gemcitabine/*nab*-paclitaxel in patients with resectable pancreatic cancer. Available from: <https://clinicaltrials.gov/ct2/show/NCT02243007?term=nab-paclitaxel+AND+pancreatic+AND+adenocarcinoma&rank=59>. Accessed August 1, 2016.
43. ClinicalTrials.gov. First line treatment of patients with metastatic pancreatic adenocarcinoma (GABRINOX). Available from: <https://clinicaltrials.gov/ct2/show/NCT01964287>. Accessed August 1, 2016.
44. Philip PA, Lacy J, Dowden SD, et al. LAPACT: an open-label, multicenter phase II trial of *nab*-paclitaxel (*nab*-P) plus gemcitabine (gem) in patients (pts) with locally advanced pancreatic cancer (LAPC). Poster presented at: ASCO 2016 Annual Meeting [abstract TPS477].
45. ClinicalTrials.gov. *Nab*-paclitaxel and gemcitabine vs gemcitabine alone as adjuvant therapy for patients with resected pancreatic cancer (the “apact” study) (apact). Available from: <https://clinicaltrials.gov/ct2/show/NCT01964430?term=nab-paclitaxel+AND+pancreatic+AND+adenocarcinoma&rank=24>. Accessed August 1, 2016.
46. Tempero MA, Coussens LM, Fong L, Manges R, Singh P, Li Y. A randomized, multicenter, double-blind, placebo-controlled study of the bruton tyrosine kinase inhibitor, ibrutinib, versus placebo in combination with *nab*-paclitaxel and gemcitabine in the first-line treatment of patients with metastatic pancreatic adenocarcinoma (RESOLVE). Poster presented at: ASCO 2016 Annual Meeting [abstract TPS483].

47. ClinicalTrials.gov. Neoadjuvant plus adjuvant or only adjuvant nab-paclitaxel plus gemcitabine for resectable pancreatic cancer (NEONAX). Available from: <https://clinicaltrials.gov/ct2/show/NCT02047513?term=nab-paclitaxel+AND+pancreatic+AND+adenocarcinoma&rank=34>. Accessed August 1, 2016.
48. ClinicalTrials.gov. Second-line adjuvant therapy with nab-paclitaxel plus gemcitabine versus oxaliplatin plus folinic acid and fluorouracil for gemcitabine-refractory pancreatic cancer after curative resection. Available from: <https://clinicaltrials.gov/ct2/show/NCT02506842?term=nab-paclitaxel+AND+pancreatic+AND+adenocarcinoma&rank=42>. Accessed August 1, 2016.
49. ClinicalTrials.gov. 2016. Available from: <https://clinicaltrials.gov>. Accessed August 1, 2016.
50. Giordano G, Febraro A, Vaccaro V, et al. Nab-paclitaxel (nab-P) and gemcitabine (G) as first line chemotherapy (CT) in advanced pancreatic cancer (APDAC) elderly patients (pts): an Italian "real life" study. Poster presented at: ESMO 2015 Annual Meeting [abstract P296].
51. Sueyoshi H, Ioka T, Tamura T, et al. Phase I study of chemoradiation therapy (nab-paclitaxel/gemcitabine) in 15 patients with unresectable locally advanced pancreatic cancer (UR-LAPC). Poster presented at: ASCO 2015 Annual Meeting [abstract 475].
52. Dean AP, Spry N, McGrath A. Nab-paclitaxel plus gemcitabine followed by radiotherapy with concurrent 5-fu in locally advanced unresectable pancreatic cancer: a Western Australian experience. Poster presented at: ASCO 2016 Annual Meeting [abstract 430].
53. Peterson S, Loaiza-Bonilla A, Ben-Josef E, et al. Neoadjuvant nab-paclitaxel and gemcitabine (AG) in borderline resectable (BR) or unresectable (UR) locally advanced pancreatic adenocarcinoma (LAPC) in patients ineligible for FOLFIRINOX. Poster presented at: ASCO 2016 Annual Meeting [abstract 328].
54. Van Laethem J, Bali MA, Borbath I, et al. Preoperative gemcitabine-nab-paclitaxel (G-NP) for (borderline) resectable (BLR) or locally advanced (LA) pancreatic ductal adenocarcinoma (PDAC): feasibility results and early response monitoring by diffusion-weighted (DW) MR. Poster presented at: ASCO 2016 Annual Meeting [abstract 4116].
55. Sliesoraitis S, Desai NV, Trevino JG, et al. Final results for gemcitabine with nab-paclitaxel in neoadjuvant treatment of resectable pancreatic adenocarcinoma: GAIN-1 study. Poster presented at: ASCO 2014 Annual Meeting [abstract e15201].
56. Cohen SJ, O'Neil BH, Berlin J, et al. A phase 1b study of erlotinib in combination with gemcitabine and nab-paclitaxel in patients with previously untreated advanced pancreatic cancer: an Academic Oncology GI Cancer Consortium study. *Cancer Chemother Pharmacol*. 2016;77(4):693–701.
57. Ko AH, Truong TG, Kantoff E, et al. A phase I trial of nab-paclitaxel, gemcitabine, and capecitabine for metastatic pancreatic cancer. *Cancer Chemother Pharmacol*. 2012;70(6):875–881.
58. De Jesus-Acosta A, O'Dwyer PJ, Ramanathan RK, et al. A phase II study of vismodegib, a hedgehog (hh) pathway inhibitor, combined with gemcitabine and nab-paclitaxel (nab-P) in patients (pts) with untreated metastatic pancreatic ductal adenocarcinoma (PDA). Poster presented at: ASCO 2014 Annual Meeting [abstract 257].
59. O'Reilly EM, Smith LS, Bendell JC, et al. Final results of phase Ib of anticancer stem cell antibody tarextumab (OMP-59R5, TRXT, anti-notch 2/3) in combination with nab-paclitaxel and gemcitabine (nab-P+Gem) in patients (pts) with untreated metastatic pancreatic cancer (mPC). Poster presented at: ASCO 2015 Annual Meeting [abstract 278].
60. Hidalgo M, Cooray P, Carrato A, et al. A phase 1b study of the anticancer stem cell agent demcizumab (DEM) and gemcitabine (GEM) +/- nab-paclitaxel in patients with pancreatic cancer. Poster presented at: ASCO 2016 Annual Meeting [abstract 341].
61. Hingorani S, Bullock A, Harris W, et al. Final analysis of stage 1 data from a randomized phase 2 study of PEGPH20 plus nab-paclitaxel/gemcitabine in stage IV previously untreated pancreatic cancer patients, utilizing VENTANA companion diagnostic assay. Poster presented at: ESMO World Congress on Gastrointestinal Cancers 2016 [abstract PD-006].
62. Hingorani SR, Harris WP, Seery TE, et al. Interim results of a randomized phase II study of PEGPH20 added to nab-paclitaxel/gemcitabine in patients with stage IV previously untreated pancreatic cancer. Poster presented at: ASCO 2016 Annual Meeting [abstract 439].
63. Bullock AJ, Hingorani SR, Wu XW, et al. Final analysis of stage 1 data from a randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine in stage IV previously untreated pancreatic cancer (pts), utilizing VENTANA companion diagnostic assay. Poster presented at: ASCO 2016 Annual Meeting [abstract 4104].
64. O'Reilly EM, Mahalingam D, Roach JM, et al. Safety, pharmacokinetics, pharmacodynamics, and antitumor activity of necuparanib combined with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer: updated phase 1 results. Poster presented at: ASCO 2016 Annual Meeting [abstract 4117].
65. Bhattacharyya GS, Babu KG, Bondarde SA, et al. Effect of coadministered beta blocker and cox-2 inhibitors to patients with pancreatic cancer prior to receiving albumin-bound paclitaxel. Poster presented at: ASCO 2015 Annual Meeting [abstract 302].
66. Mahipal A, Springett GM, Burke N, et al. Phase I trial of enzalutamide in combination with gemcitabine and nab-paclitaxel for the treatment of advanced pancreatic cancer. Poster presented at: ASCO 2015 Annual Meeting [abstract 467].
67. Reni M, Belli C, Balzano G, et al. Phase IB trial of nab-paclitaxel plus gemcitabine, capecitabine, and cisplatin (PAXG regimen) in patients with stage III pancreatic adenocarcinoma. Poster presented at: ESMO World Congress on Gastrointestinal Cancer 2014 [abstract 711P].
68. Sigal D, Marcus SG, Rosen PJ, et al. Association of 2-O, 3-O desulfated heparin (ODSH) plus combination gemcitabine (G)/nab-paclitaxel (A) with preliminary benefit in untreated metastatic pancreatic cancer plus combination gemcitabine (G)/nab-paclitaxel (A) with preliminary benefit in untreated metastatic pancreatic cancer. Poster presented at: ASCO 2013 Annual Meeting [abstract 284].
69. Ko AH, Murphy PB, Peyton JD, et al. A randomized, double-blinded, placebo-controlled phase II trial of gemcitabine (gem) plus nab-paclitaxel (nab-P) plus apatersen (A) or placebo (pl) in patients (pts) with metastatic pancreatic cancer (mPC): the RAINIER trial. Poster presented at: ASCO 2016 Annual Meeting [abstract 4119].
70. El-Rayes BF, Shahda S, Starodub A, O'Neil BH, Hanna WT, Oh C. A phase Ib extension study of cancer stemness inhibitor BB608 (napabucasin) in combination with gemcitabine and nab-paclitaxel (nab-PTX) in patients (pts) with metastatic pancreatic cancer. Poster presented at: ASCO 2016 Annual Meeting [abstract 4128].
71. Bahary N, Garrido-Laguna I, Wang-Gillam A, et al. Results of the phase Ib portion of a phase I/II trial of the indoleamine 2,3-dioxygenase pathway (IDO) inhibitor indoximod plus gemcitabine/nab-paclitaxel for the treatment of metastatic pancreatic cancer. Poster presented at: ASCO 2016 Annual Meeting [abstract 452].
72. Borad MJ, Kwak EL, Wang-Gillam A, Ibrahim A, Aldridge J, Olszanski AJ. Evofosfamide combined with gemcitabine/nab-paclitaxel in patients with previously untreated locally advanced or metastatic pancreatic adenocarcinoma (PAC): results of a phase I trial. Poster presented at: ASCO 2016 Annual Meeting [abstract 4114].
73. ClinicalTrials.gov. Quality of life study in patients with locally advanced or metastatic pancreatic cancer treated with gemcitabine in combination with nab-paclitaxel (QOLINPAC). Available from: <https://clinicaltrials.gov/ct2/show/NCT02106884?term=nab-paclitaxel+AND+pancreatic+AND+adenocarcinoma&rank=54>. Accessed August 1, 2016.
74. ClinicalTrials.gov. First-line treatment of metastatic pancreatic cancer with nab-paclitaxel and gemcitabine (ALPACA). Available from: <https://clinicaltrials.gov/ct2/show/NCT02564146?term=NCT02564146&rank=1>. Accessed August 1, 2016.
75. ClinicalTrials.gov. Gemcitabine and nab-paclitaxel combined with momelotinib in participants with previously untreated metastatic pancreatic ductal adenocarcinoma. Available from: <https://clinicaltrials.gov/ct2/show/NCT02101021>. Accessed August 1, 2016.

76. ClinicalTrials.gov. A study of PEGylated recombinant human hyaluronidase in combination with *nab*-paclitaxel plus gemcitabine compared with placebo plus *nab*-paclitaxel and gemcitabine in participants with hyaluronan-high stage IV previously untreated pancreatic ductal adenocarcinoma. Available from: <https://clinicaltrials.gov/ct2/show/NCT02715804>. Accessed August 1, 2016.
77. ClinicalTrials.gov. Study of nanoliposomal irinotecan (nal-IRI)-containing regimens in patients with previously untreated, metastatic pancreatic adenocarcinoma. Available from: <https://clinicaltrials.gov/ct2/show/NCT02551991>. Accessed August 1, 2016.
78. ClinicalTrials.gov. Sequential treatment of nab-paclitaxel + gemcitabine / FOLFIRI.3 vs nab-paclitaxel + gemcitabine in 1st line treatment of metastatic pancreatic cancer (FIRGEMAX). Available from: <https://clinicaltrials.gov/ct2/show/NCT02827201>. Accessed August 1, 2016.
79. ClinicalTrials.gov. Phase I/II study of nab-paclitaxel and gemcitabine followed by AG-mFOLFOX in patients with metastatic pancreatic adenocarcinoma (SEQUENCE). Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02504333>. Accessed August 1, 2016.
80. ClinicalTrials.gov. A phase I-II study of PAXG in stage III-IV pancreatic adenocarcinoma (PACT-19). Available from: <https://clinicaltrials.gov/ct2/show/NCT01730222?term=nab-paclitaxel+AND+pancreatic+AND+adenocarcinoma&rank=12>. Accessed August 1, 2016.
81. ClinicalTrials.gov. Phase I/II study to evaluate nab-paclitaxel in substitution of CPT11 or oxaliplatin in FOLFIRINOX schedule as first line treatment in metastatic pancreatic cancer (NabucCO). Available from: <https://clinicaltrials.gov/ct2/show/NCT02109341>. Accessed August 1, 2016.
82. ClinicalTrials.gov. Paclitaxel albumin-stabilized nanoparticle formulation and gemcitabine hydrochloride with or without WEE1 inhibitor MK-1775 in treating patients with previously untreated pancreatic cancer that is metastatic or cannot be removed by surgery. Available from: <https://clinicaltrials.gov/ct2/show/NCT02194829>. Accessed August 1, 2016.
83. ClinicalTrials.gov. Phase 2 nab[™]-paclitaxel (Aabraxane[®]) plus gemcitabine in subjects with locally advanced pancreatic cancer (LAPC) (LAPACT). Available from: <http://www.clinicaltrials.gov/ct2/show/NCT02301143>. Accessed August 1, 2016.
84. ClinicalTrials.gov. S1505: combination chemotherapy or gemcitabine hydrochloride and paclitaxel albumin-stabilized nanoparticle formulation before surgery in treating patients with pancreatic cancer that can be removed by surgery. 2016. Available from: <https://clinicaltrials.gov/ct2/show/NCT02562716>. Accessed September 15, 2016.
85. ClinicalTrials.gov. Pancreas cancer: molecular profiling as a guide to therapy before and after surgery ("personalized medicine"). Available from: <https://clinicaltrials.gov/ct2/show/NCT02562716>. Accessed August 1, 2016.
86. ClinicalTrials.gov. Systemic therapy and chemoradiation in advanced localised pancreatic cancer-2 (SCALOP-2). Available from: <https://clinicaltrials.gov/ct2/show/NCT02024009>. Accessed August 1, 2016.

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