Optimizing Patient Outcomes in Pancreatic Cancer Treatment

Learning Objectives

Upon completion of this presentation, participants will be able to:

- Highlight the goals of treatment and current therapeutic options for the management of advanced pancreatic cancer in Canada
- Identify and discuss practical strategies for the optimal management of pancreatic cancer patients with *nab*-paclitaxel + gemcitabine, a new treatment for advanced pancreatic cancer
- Apply adverse event management strategies to select pancreatic cancer cases

Polling Question 1

- **How many patients with advanced or metastatic pancreatic cancer do you see per month?**
  - ❑ None
  - ❑ 1 to 5
  - ❑ 6 to 10
  - ❑ 11 to 15
  - ❑ >15

Pancreatic Cancer Is the 4th Leading Cause of Cancer Death in Canada (2015)

Males
41,000 Deaths

Site	Percent	Deaths
Lung	26.60%	10,900
Colorectal	12.4%	5,100
Prostate	10.1%	4,100
Pancreas	**5.6%**	**2,300**
Bladder	4.0%	1,600
Esophagus	3.9%	1,600
Leukemia	3.8%	1,550
Non-Hodgkin lymphoma	3.5%	1,450
Stomach	3.2%	1,300
Brain/CNS	3.0%	1,250

Females
37,000 Deaths

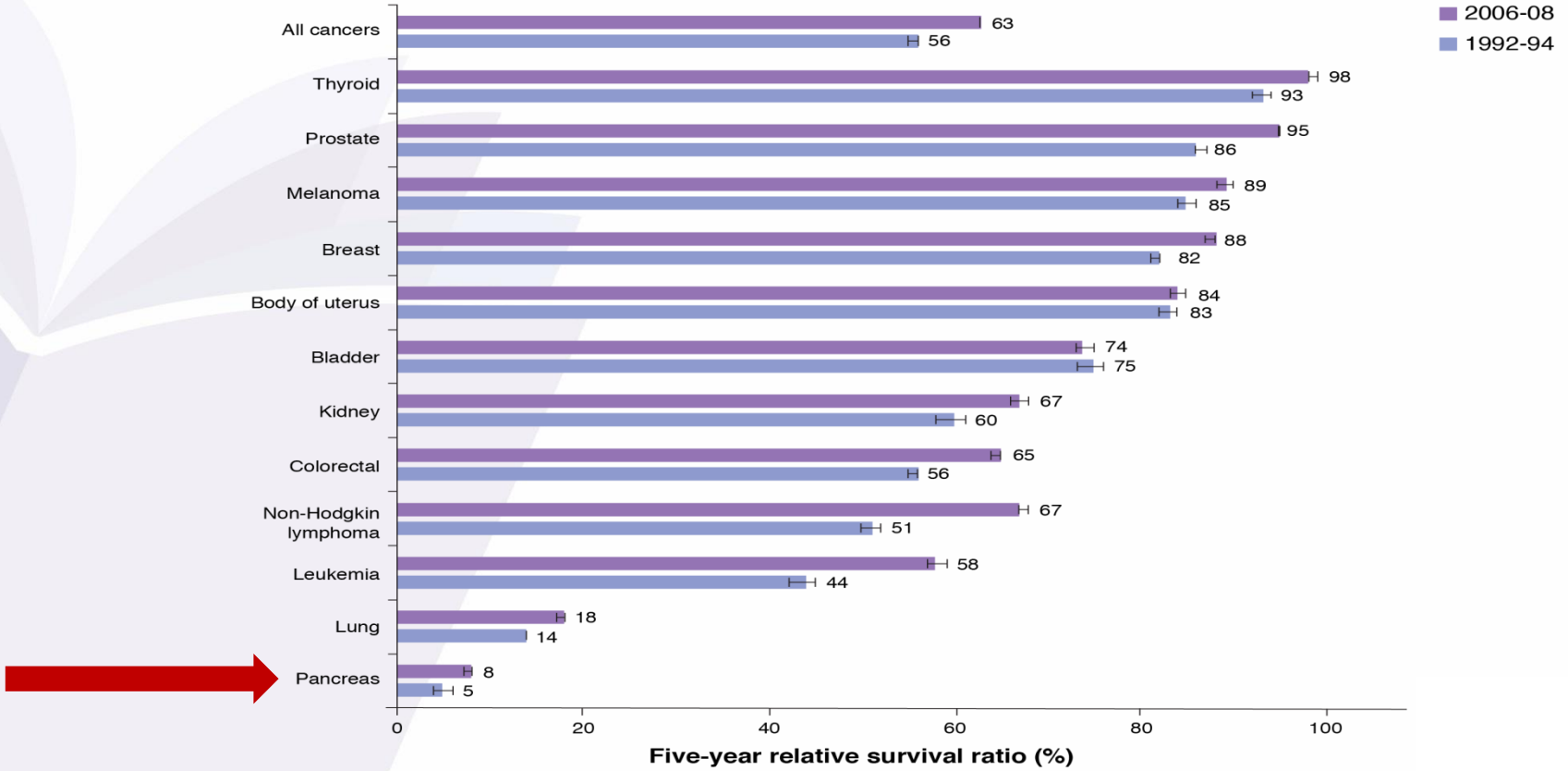
Site	Percent	Deaths
Lung	27.0%	10,000
Breast	13.6%	5,000
Colorectal	11.5%	4,200
Pancreas	**6.2%**	**2,300**
Ovary	4.7%	1,750
Non-Hodgkin lymphoma	3.3%	1,200
Leukemia	3.1%	1,150
Body of uterus	2.8%	1,050
Brain/CNS	2.3%	860
Stomach	2.1%	760

4,600 pancreatic deaths total

Pancreatic cancer has nearly equal incidence and mortality rates

Canadian Cancer Statistics 2015. Available at: www.cancer.ca/statistics.

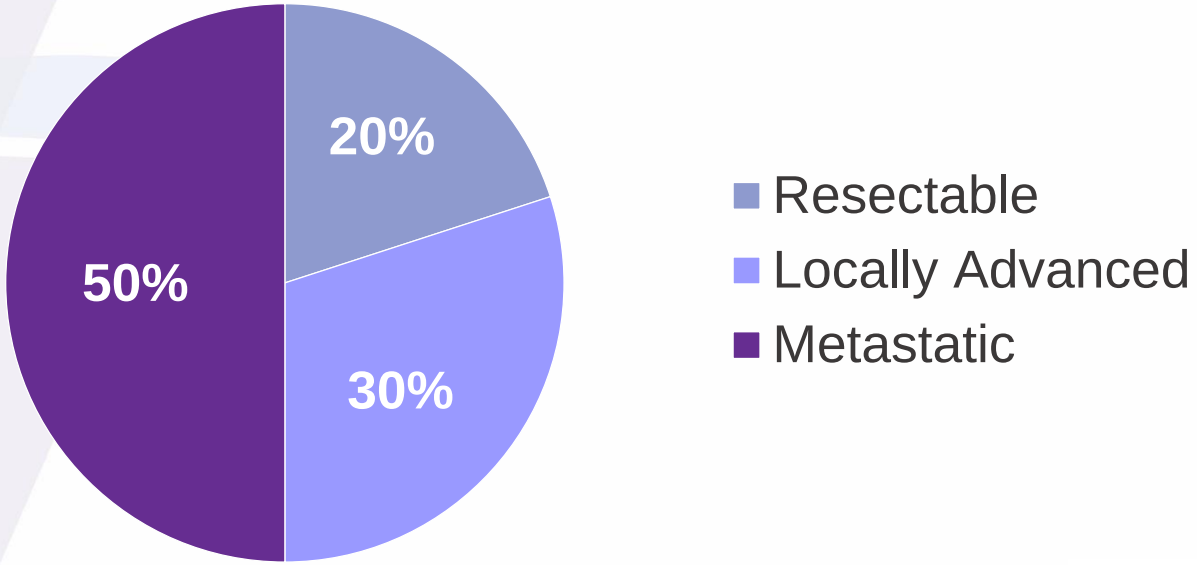
Overall 5-year Survival Rate for Pancreatic Cancer Remains Extremely Low



Canadian Cancer Statistics 2014. Available at: www.cancer.ca/statistics.

Most Pancreatic Cancers Are Diagnosed with Metastatic Disease

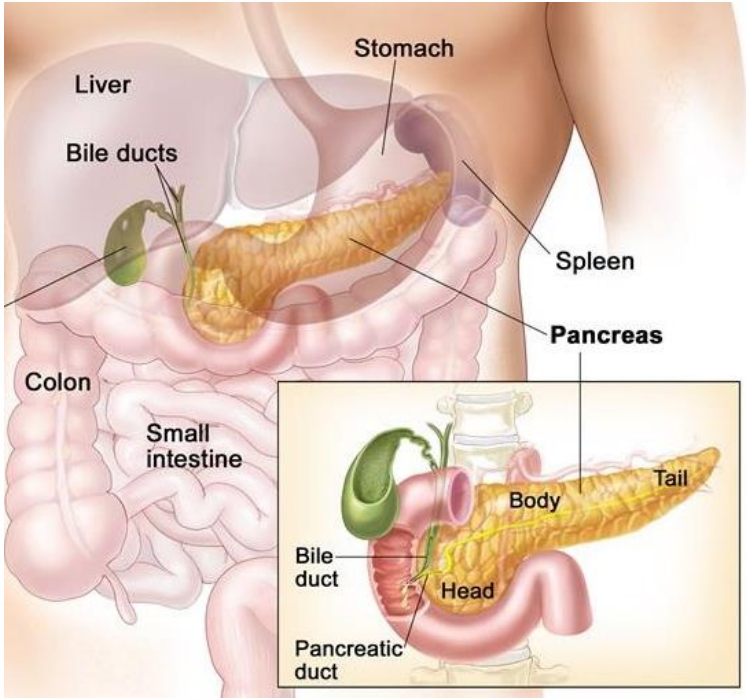
Estimated percentage of cases by stage at diagnosis



Adapted from: Kanji ZS, Gallinger S. *CMAJ.* 2013;185(14):1219–26.

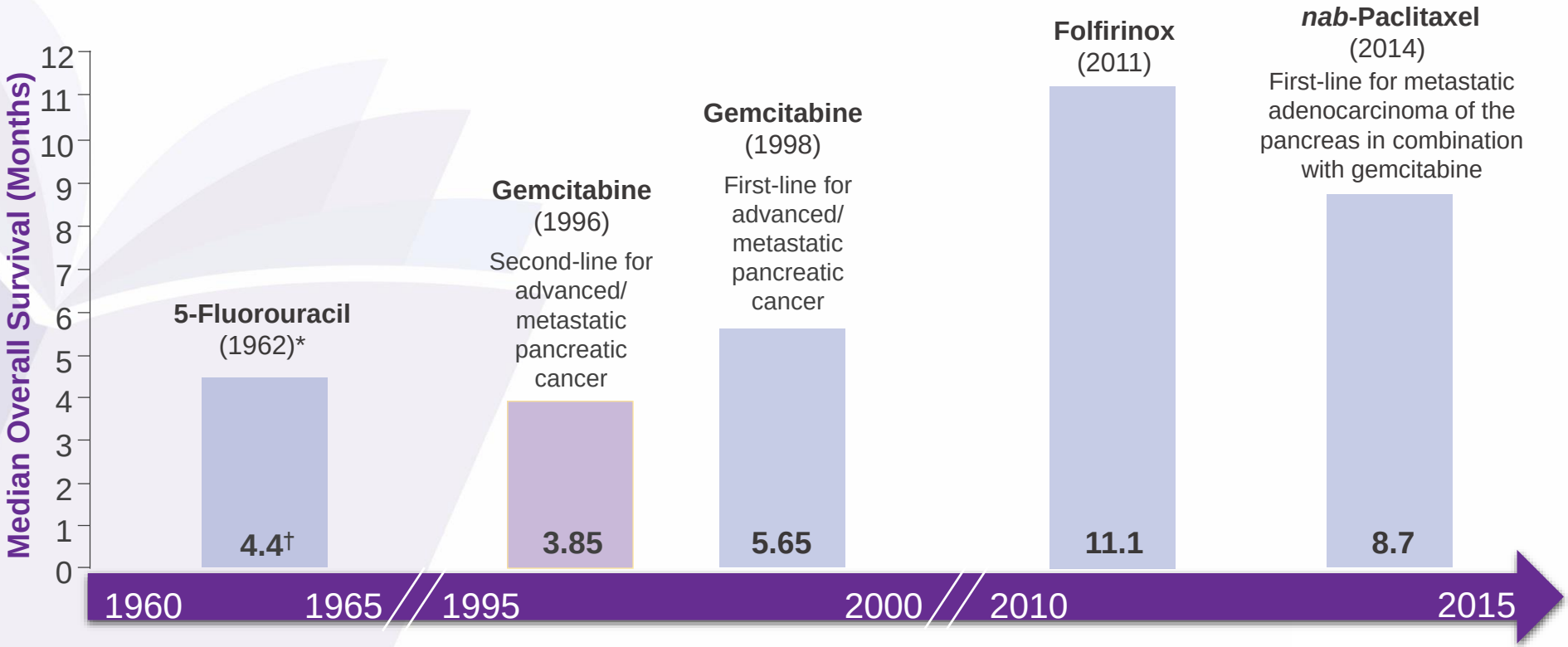
Challenges of Diagnosing and Treating Pancreatic Cancer in Canada

- Most patients present with vague and nonspecific symptoms
- Few patients diagnosed with pancreatic cancer have identifiable risk factors
- There are no detection tools to diagnose this disease in its early stages
- Many patients suffer from rapidly declining performance scores
- Pancreatic stroma is resistant to therapies; impedes drug delivery



Canadian Cancer Statistics 2013. Available at: www.cancer.ca/statistics; American Cancer Society: Cancer Statistics 2016. Available at: www.pancreatic.org; Kanji ZS, et al. *CMAJ*. 2013;185(14):1219–26. Image from Terese Winslow.

Key Milestones in the Treatment of Metastatic Pancreatic Cancer



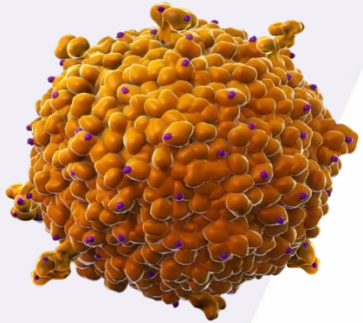
*US FDA approval date; †versus gemcitabine monotherapy (Burris H, et al., 1997)

Burris H, et al. *European Journal of Cancer*. 1997;33:S18–22; Rothenberg ML, et al. *Annals of Oncology*. 1996;7:347–53; Conroy T, et al. *NEJM*. 2011;264:1817–25; Goldstein D, et al. *JNCI J Natl Cancer Inst*. 2015;107(2):1–10.

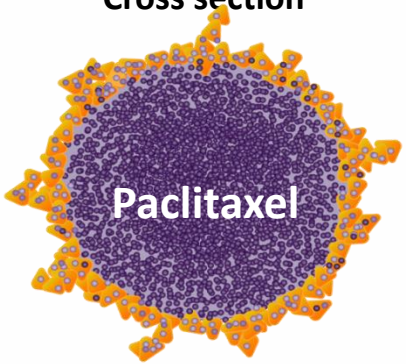
What Is *nab*-Paclitaxel (Abraxane)?

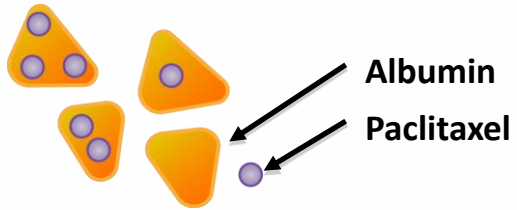
- Paclitaxel formulated as albumin-bound nanoparticles
  - Mean size of 130 nm
  - Paclitaxel causes stabilization of the microtubules, leading to inhibition of mitosis and tumour proliferation, and ultimately results in cell death
  - *nab*-Paclitaxel is a nanotechnology-derived agent that improves the ability of the therapy to reach the tumour site

***nab*-Paclitaxel nanoparticle**



Cross section

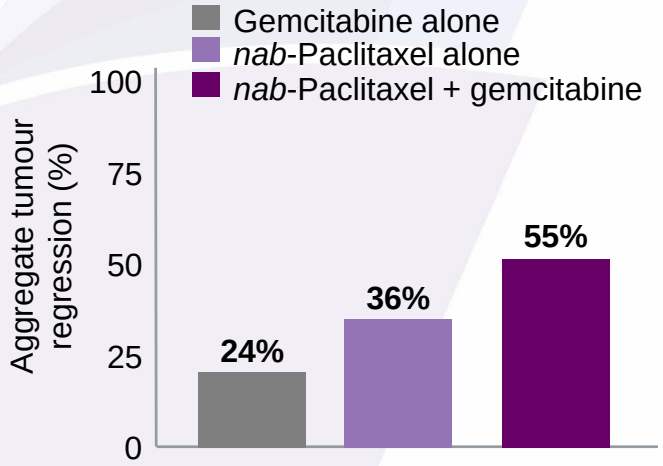




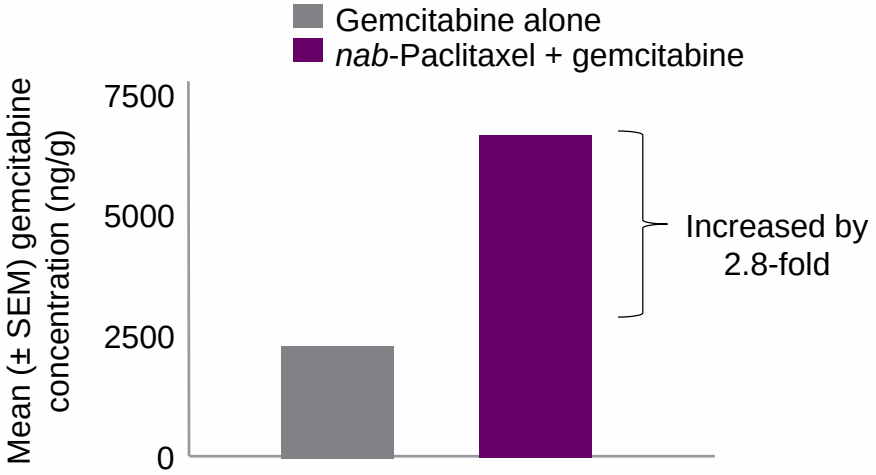
Kratz, et al. *J Control Release.* 2008;132(3):171–83; Lohmann AE, et al. *Curr Oncol.* 2013;20(2):97–103; Ibrahim, et al. *Clin Cancer Res*. 2002;8(5):1038–44.

Preclinical Studies: *nab*-Paclitaxel Enhances Gemcitabine Delivery and Efficacy

- Synergistic antitumour activity when *nab*-paclitaxel is combined with gemcitabine



- *nab*-Paclitaxel led to higher intratumour gemcitabine levels



SEM, standard error of the mean.

Von Hoff DD, et al. *J Clin Oncol*. 2011;29:4548–54.

MPACT vs. ACCORD/PRODIGE: Trial Design

	nab-Paclitaxel + Gemcitabine (MPACT)	FOLFIRINOX (ACCORD/PRODIGE)
Study design	Phase III	Phase II/III
Patients enrolled	861 (431 *nab*-P + Gem)	342 (171 FOLFIRINOX)
No. of participating countries	11	1
Canadian participation	Yes	No
Study sites **Academic site participation** **Community site participation**	151 Yes Yes	48 Yes No
Location of primary tumour – Head	44%	38%
Age limit	No upper limit	≤75 years
Age ≥65 **Age ≥75**	42% 10%	29% 0%
Performance status	KPS 70 – 100 (ECOG 0–2)	ECOG 0–1
ECOG 0 **ECOG 1** **ECOG 2**	16% 77% 7%	37% 62% <1%

ECOG, Eastern Cooperative Oncology Group. KPS, Karnofsky Performance Status.

Data from separate clinical trials. Comparative clinical significance has not been proven. Von Hoff DD, et al. *N Engl J Med*. 2013:369(18):1691–703; Reni M, et al. *J Med Econ.* 2014;17(5):338–46; Conroy T, et al. *N Eng J Med.* 2011;364:1817–25; Gourgou-Bourgarde S, et al. *J Clin Oncol*. 2013;31(1):23–9.

MPACT vs. ACCORD/PRODIGE: Efficacy

	nab-Paclitaxel + Gem (MPACT)	FOLFIRINOX (ACCORD/PRODIGE)
Overall Survival		
Control arm (gemcitabine)	Median OS: 6.6 months	Median OS: 6.8 months
Experimental arm	Median OS: 8.7 months	Median OS: 11.1 months
Hazard ratio, *p*-value	HR 0.72, $p<0.001$	HR 0.57, $p<0.001$
Progression Free Survival		
Control arm (gemcitabine)	Median PFS: 3.7 months	Median PFS: 3.3 months
Experimental arm	Median PFS: 5.5 months	Median PFS: 6.4 months
Hazard ratio, *p*-value	HR 0.69, $p<0.001$	HR 0.47, $p<0.001$
Overall Response Rate		
Control arm (gemcitabine)	7%	9%
Experimental arm	23%	31%
***p*-value**	p <0.001	p <0.001

Data from separate clinical trials. Comparative clinical significance has not been proven.

Von Hoff DD, et al. *N Engl J Med*. 2013:369(18):1691–703; Reni M, et al. *J Med Econ.* 2014;17(5):338–46; Conroy T, et al. *N Eng J Med.* 2011;364:1817–25; Gourgou-Bourgarde S, et al. *J Clin Oncol*. 2013;31(1):23–9.

MPACT vs. ACCORD/PRODIGE: Safety

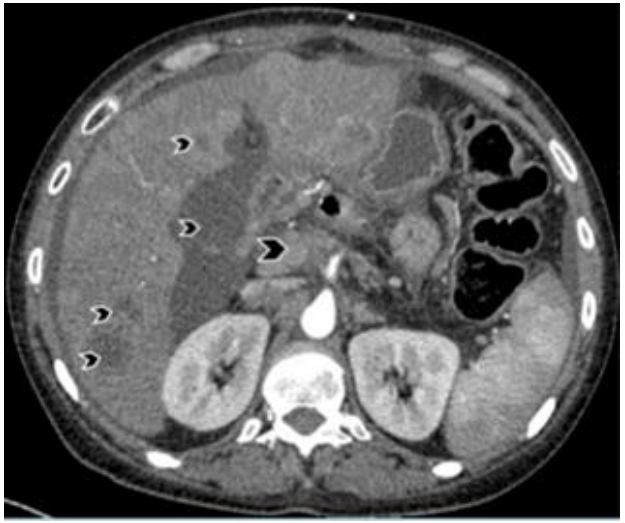
	MPACT		ACCORD/PRODIGE	
Grade ≥3	***nab*-P + Gem (n = 431)**	**Gemcitabine (n = 430)**	**FOLFIRINOX (n = 171)**	**Gemcitabine (n = 171)**
Neutropenia, %	33	21	45.7	21.0
Use of growth factors, %	26	15	42.5	5.3
Febrile neutropenia, %	3	1	5.4	1.2
Fatigue, %	18	9	23.6	17.8
Neuropathy, %	17	1	9	0
Diarrhea, %	6	1	12.7	1.8

Data from separate clinical trials. Comparative clinical significance has not been proven.

Conroy T, et al. *N Engl J Med.* 2011;364:1817–25; Von Hoff DD, et al. *N Engl J Med*. 2013:369(18):1691–703; ABRAXANE® product monograph. Mississauga, ON: Celgene Inc; 2016.

Case 1: Patient Profile

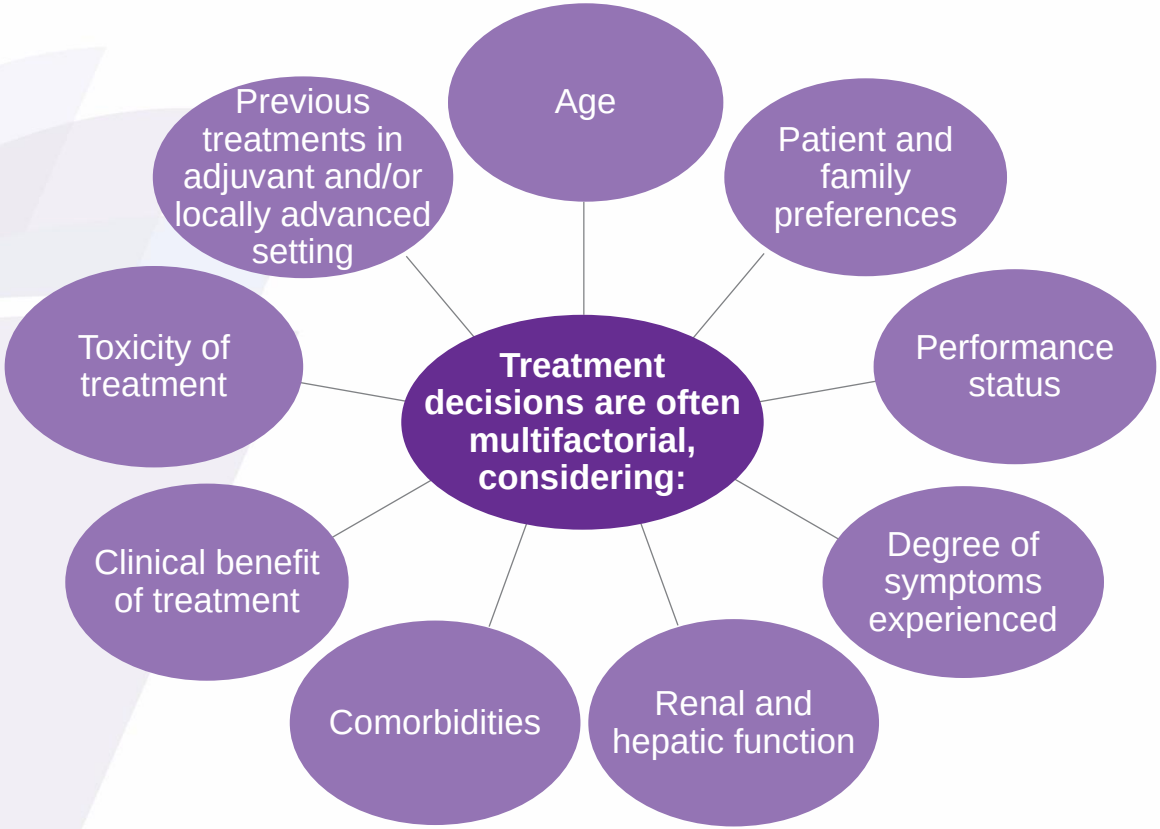
- 67-year-old female with a history of hypertension and type 2 diabetes
- Presented with the following symptoms
  - Weight loss (8 kg), abdominal and back pain, fatigue
- ECOG performance status: 1 (KPS 90)
- Liver function tests 2x ULN
  - Elevated ALP and GGT, but bilirubin within normal range
- Abdominal CT revealed pancreatic head mass, numerous liver metastases, and ascites
  - Biopsy confirmed adenocarcinoma



What patient goals and characteristics are considered when evaluating treatment options?

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status.

Treatment Considerations for Patients with Advanced Pancreatic Cancer



Current Chemotherapy Options in Canada

Chemotherapy	Guidelines
FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin)	• NCCN recommends as **first-line** treatment for patients with metastatic or locally advanced unresectable disease with good performance status **(limited to ECOG 0–1)** • ASCO also recommends as first-line treatment for patients meeting: – ECOG 0–1, favourable comorbidity profile, patient preference and support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services
Gemcitabine + *nab*-paclitaxel	• NCCN recommends as **first-line** treatment for patients with metastatic or locally advanced unresectable disease with good performance status **(reasonable for patients with KPS ≥70)** • ASCO also recommends as first-line treatment for patients meeting: – ECOG 0–1, relatively favorable comorbidity profile, and patient preference and support system for relatively aggressive medical therapy
Gemcitabine monotherapy	• NCCN & ASCO recommend for patients with poor performance status

NCCN Clinical Practice Guidelines in Oncology, Pancreatic Adenocarcinoma, v1, 2016.
Sohal DP, et al. *J Clin Oncol.* 2016. [Epub ahead of print] www.asco.org/guidelines/MetPC.

Polling Question 2

- **Should *nab*-paclitaxel/gemcitabine be considered in a patient >65 years old?**
  - ❑ **Yes**
  - ❑ **No**

MPACT Study Design

Patients with metastatic pancreatic adenocarcinoma who received no prior cytotoxic chemotherapy

Eligibility criteria included age ≥18 years, KPS ≥70, normal bilirubin, ANC ≥1.5 × 10^9/L, Hb ≥9g/dL

N=861

RANDOMIZED 1:1
Stratified by KPS, region, liver metastasis

***nab*-Paclitaxel 125 mg/m² IV over 30–40 minutes followed by gemcitabine 1,000 mg/m² on days 1, 8, and 15 of each 28-day cycle**
N=431

Gemcitabine 1,000 mg/m² given weekly for 7 weeks followed by a 1-week rest period in cycle 1 and in cycle 2 and onwards was administered on days 1, 8, and 15 of each 28-day cycle
N=430

PRIMARY ENDPOINT:
Overall survival

SECONDARY ENDPOINTS:
Progression-free survival and Overall response rate

Treatment was administered until disease progression or development of unacceptable toxicity.

ANC, absolute neutrophil count; Hb, hemoglobin; IV, intravenous; KPS, Karnofsky Performance Status; MPACT, Metastatic Pancreatic Adenocarcinoma Clinical Trial.

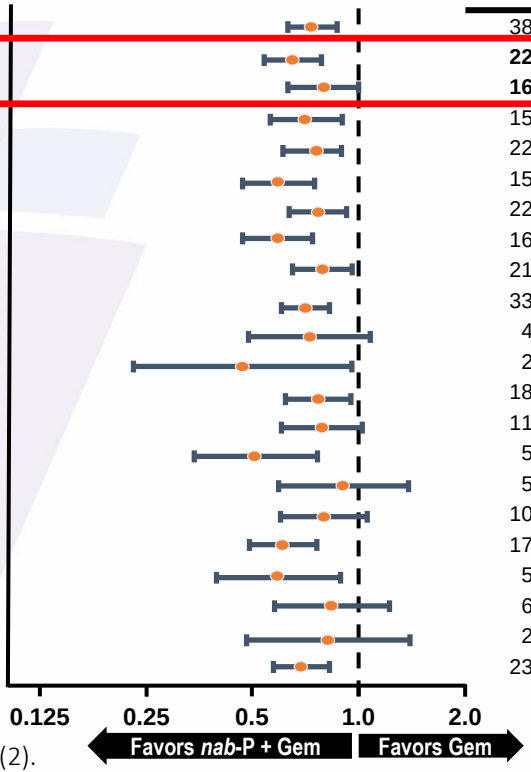
Von Hoff DD, et al. *N Engl J Med*. 2013:369(18):1691–703.

MPACT: Baseline Characteristics

Variable		*nab*-Paclitaxel + Gem (n=431)	Gemcitabine (n=430)
Age	Median years (min, max)	62 (27, 86)	63 (32, 88)
	≥65 years old, %	41	44
Sex	Male, %	57	60
KPS	90–100, %	58	62
	70–80, %	42	38
Pancreatic primary location	Head, %	44	42
	Body, %	31	32
	Tail, %	24	26
Current site(s) of metastasis	Lung, %	35	43
	Liver, %	85	84
Number of metastatic sites	1, %	8	5
	2, %	47	48
	≥3, %	45	47
Level of carbohydrate antigen 19-9	Normal, %	16	15
	Elevated, <59 x ULN, %	32	32
	Elevated, ≥59 x ULN, %	52	53
Previous Whipple	Yes, %	7	7
Biliary stent	Yes, %	19	16

Von Hoff DD, et al. *N Engl J Med*. 2013:369(18):1691–703.

MPACT Trial: Treatment Effect on Survival Favoured the *nab*-Paclitaxel/Gemcitabine Arm for Patients < or > 65 Years



Group	*nab*-P + Gem Events/n	*nab*-P + Gem Median OS, mo	Gem Events/n	Gem Median OS, mo	HR	*P*-value
All patients	380/431	8.7	394/430	6.6	0.72	<0.0001
Age <65 years	**220/254**	**9.6**	**222/242**	**6.8**	**0.65**	**<0.0001**
Age ≥65 years	**160/177**	**7.7**	**172/188**	**6.5**	**0.80**	**0.0484**
Female	157/186	9.7	156/173	7.1	0.71	0.0039
Male	223/245	8.1	238/257	6.2	0.74	0.0016
KPS 70–80	156/179	7.6	153/161	4.3	0.59	<0.0001
KPS 90–100	220/248	9.7	240/268	7.9	0.77	0.0053
Primary tumour location: head	167/191	9.5	170/180	6.4	0.59	<0.0001
Primary tumour location: other	210/237	8.1	221/246	6.9	0.79	0.0171
Liver metastases	331/365	8.3	331/360	5.9	0.71	<0.0001
No liver metastases	49/66	11.1	63/70	10.2	0.73	0.1109
1 metastatic site	25/33	12.9	20/21	9.0	0.47	0.0384
2 metastatic sites	184/202	8.6	185/206	6.9	0.77	0.0164
3 metastatic sites	117/136	7.9	129/140	5.9	0.79	0.0688
>3 metastatic sites	54/60	8.7	60/63	5.0	0.51	0.0012
Normal CA 19-9	50/60	9.3	49/56	7.0	0.90	0.6401
CA 19-9 ULN to <59 × ULN	108/122	8.8	109/120	7.3	0.80	0.1114
CA 19-9 ≥59 × ULN	177/197	8.4	184/195	5.7	0.61	<0.0001
Australia	52/61	9.4	57/59	6.7	0.59	0.0104
Eastern Europe	63/64	7.7	60/62	5.9	0.84	0.3715
Western Europe	28/38	10.7	27/38	6.9	0.82	0.4705
North America	237/268	8.8	250/271	6.6	0.69	<0.0001

Updated database cutoff was May 9, 2013.

Goldstein D, et al. *J Natl Cancer Inst.* 2015;107(2).

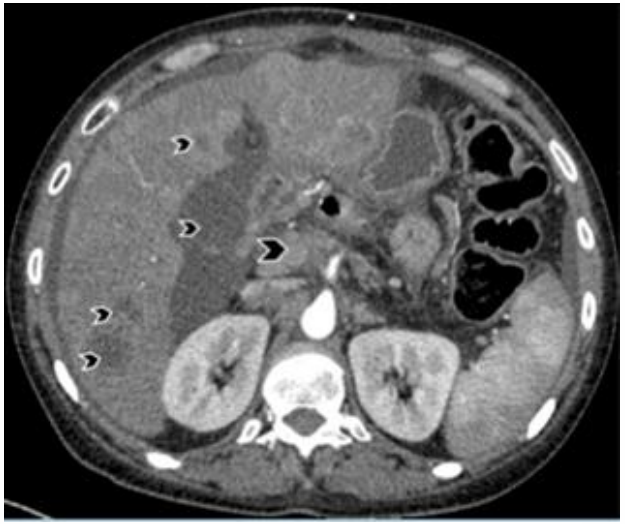
Expert Recommendation: Patients >65 years old

- Yes, it is appropriate to use *nab*-paclitaxel/gemcitabine in a patient >65 years old, based on the MPACT protocol and trial results

Expert opinion of steering committee.

Case 1 (cont'd)

- What if she was 78 years old?
- History of hypertension and type 2 diabetes
- Presented with the following symptoms
  - Weight loss (8 kg), abdominal and back pain, fatigue
- ECOG performance status: 1 (KPS 90)
- Liver function tests 2x ULN
  - Elevated ALP and GGT, but bilirubin normal
- Abdominal CT revealed pancreatic head mass, numerous liver metastases, and ascites
  - Biopsy confirmed adenocarcinoma



CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status.

Polling Question 3

- **Should *nab*-paclitaxel/gemcitabine be considered in a patient >75 years old?**
  - ❑ **Yes**
  - ❑ **No**

MPACT: Eligibility Criteria and Enrolment by Age

- Eligible adults were ≥18 years of age; no upper age limit for inclusion
- Of the 431 patients enrolled in MPACT who received *nab*-P/gem:
  - 41% were ≥65 years
  - 10% were ≥75 years

Studies did not include a sufficient number of patients in this age group to determine whether they responded differently than younger patients

***nab*-Paclitaxel product monograph states:**

- Patients ≥75 years with metastatic pancreatic cancer who received *nab*-paclitaxel/gemcitabine had a higher risk of serious AEs and AEs that led to treatment discontinuation
- Age ≥75 was not significantly associated with OS, but the study was not powered to show difference

AE, adverse event. Gem, gemcitabine. *nab*-P, *nab*-paclitaxel.

ABRAXANE® product monograph. Mississauga, ON: Celgene Inc.; 2016.
Giordano G, et al. *ESMO* 2014. Abstract 713P.; Von Hoff DD, et al. *N Engl J Med*. 2013:369(18):1691–1703.

Expert Recommendation: Patients >75 years old

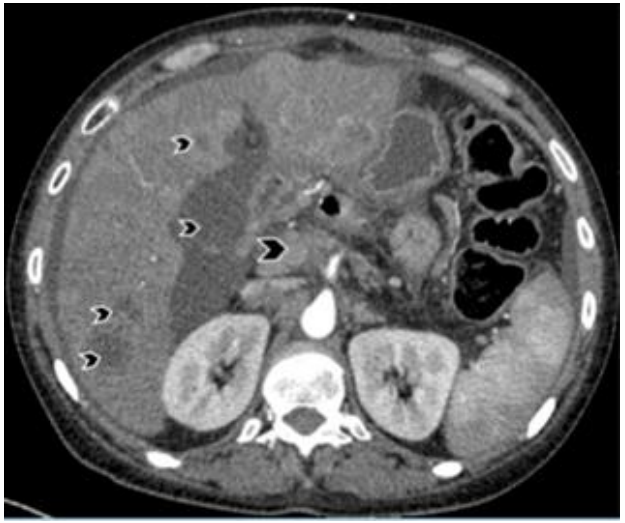
It may be reasonable to use *nab*-paclitaxel/gemcitabine in well-selected patients ≥75 years old based on MPACT trial inclusion criteria while considering the following:

- Carefully assess patients ≥75 years for their ability to tolerate *nab*-paclitaxel in combination with gemcitabine
- Suggest restricting use to patients with better performance status
- Could consider initial dose modifications at discretion of physician
- If available, geriatric assessment may be helpful for patients in whom ability to tolerate treatment unclear

Expert opinion of steering committee.

Case 1 (cont'd)

- 67-year-old female, history of hypertension and type 2 diabetes
- Presented with the following symptoms
  - Weight loss (8 kg), abdominal and back pain, fatigue
- What if she had an ECOG performance status of 2? (previously ECOG 1)
- Liver function tests 2x ULN
  - Elevated ALP and GGT, but bilirubin within normal range
- Abdominal CT revealed pancreatic head mass, numerous liver metastases, and ascites
  - Biopsy confirmed adenocarcinoma



CT, computed tomography; ECOG, Eastern Cooperative Oncology Group.

Polling Question 4

- **Should *nab*-paclitaxel/gemcitabine be considered in a patient with an ECOG of 2?**
  - ❑ **Yes**
  - ❑ **No**

Estimated Conversion Between KPS and ECOG

KPS	MPACT Study (*nab*-P + Gem Arm)	ECOG Performance Status
100 – Normal; no evidence of disease	69/429 (16%)	**0** – Fully active, no restriction in predisease performance
90 – Minor signs or symptoms	179/429 (42%)	**1** – Restricted in physically strenuous activity but ambulatory and able to carry out light work
80 – Normal activity with effort; some signs or symptoms	149/429 (35%)	
70 – Cares for self; unable to carry on normal activity	30/429 (7%)	**2** – Ambulatory; capable of all self-care but unable to work; up more than 50% of waking hours
60 – Occasional assistance required; capable of most self-care	2/429 (<1%)	

ECOG, Eastern Cooperative Group Performance Status . KPS, Karnofsky Performance Status.

Ma C, et al. *Eur J Cancer*. 2010;46(18):3175–83.
Von Hoff DD, et al. *N Engl J Med*. 2013:369(18):1691–1703.

MPACT: Baseline Characteristics

Eligible adults for the MPACT trial had a KPS score of 70 or more

Variable		*nab*-P + Gem n=431	Gem n=430	All Patients n=861
Age	Median years (range)	62 (27–86)	63 (32–88)	63 (27–88)
	≥65 years old, %	41	44	42
Sex, %	Male	57	60	58
KPS, %	100	16	16	16
	90	42	46	44
	80	35	30	32
	70	7	8	7
	60	<1	0	<1
Pancreatic primary tumour location, %	Head	44	42	43
	Body	31	32	31
	Tail	24	26	25
	Unknown	1	1	1
Current site(s) of metastasis, %	Liver	85	84	84
Number of metastatic sites, %	1	8	5	6
	2	47	48	47
	3	32	33	32
	>3	14	15	14

Von Hoff DD, et al. *N Engl J Med*. 2013:369(18):1691–1703.

MPACT: Overall Survival by KPS Score

KPS Subgroup	*nab*-Paclitaxel/Gemcitabine		Gemcitabine		Hazard Ratio $HR_{A+G/G}$ 95% CI	*P*-value
	Death/n (%)	Median OS 95% CI (months)	Death/n (%)	Median OS 95% CI (months)		
90–100	187/248 (75)	9.7 (8.7, 10.9)	212/268 (79)	7.9 (7.0, 9.0)	0.75 (0.62, 0.92)	0.006
70–80	142/179 (79)	7.6 (6.4, 8.4)	146/161 (91)	4.3 (3.8, 5.7)	0.61 (0.48, 0.78)	<0.001
100	49/69 (71)	12.6 (9.6, 14.9)	43/69 (62)	10.9 (7.5, 13.5)	0.92 (0.60, 1.41)	0.697
90	138/179 (77)	8.9 (7.9, 10.1)	169/199 (85)	7.1 (6.5, 8.7)	0.72 (0.57, 0.91)	0.006
80	114/149 (77)	8.1 (7.4, 9.6)	115/128 (90)	5.6 (4.2, 6.6)	0.55 (0.41, 0.72)	<0.001
70	28/30 (93)	3.9 (2.3, 5.5)	31/33 (94)	2.8 (1.8, 4.0)	0.99 (0.57, 1.72)	0.963

Note: The hazard ratio, two-sided 95% confidence interval, and *P*-value were estimated using stratified Cox proportional hazard model.
Note: Subgroup analyses include only patients with corresponding baseline data.

Tabernero J, et al. *Oncologist.* 2015;20(2):143–150.

Expert Recommendation: Patients with ECOG 2

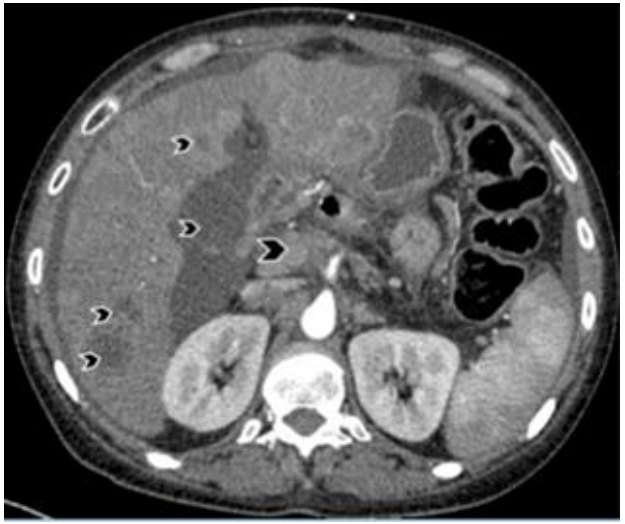
- Importance of clinical judgment, appropriate patient selection, and discussion with patients for patients with KPS of 70, given lower median OS in MPACT trial subgroup analysis
- Yes, it may be appropriate to offer *nab*-paclitaxel/gemcitabine in a patient with performance status KPS ≥70 based on MPACT trial inclusion criteria
- Could consider dose modifications at discretion of physician

KPS	ECOG Performance Status
100 – Normal; no evidence of disease	0 – Fully active, no restriction in predisease performance
90 – Minor signs or symptoms	1 – Restricted in physically strenuous activity but ambulatory and able to carry out light work
80 – Normal activity with effort; some signs or symptoms	
70 – Cares for self; unable to carry on normal activity	2 – Ambulatory; capable of all self-care but unable to work; up more than 50% of waking hours
60 – Occasional assistance required; capable of most self-care	

Expert opinion of steering committee.

Case 1 (cont'd)

- 67-year-old female with a history of hypertension and type 2 diabetes
- Presented with the following symptoms
  - Weight loss (8 kg), abdominal and back pain, fatigue
- ECOG performance status: 1 (KPS 90)
- What if bilirubin 1.5 x ULN?
- Abdominal CT revealed pancreatic head mass, numerous liver metastases, and ascites
  - Biopsy confirmed adenocarcinoma



CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status.

Polling Question 5

- **Should *nab*-paclitaxel/gemcitabine be considered in a patient with elevated bilirubin?**
  - ❑ **Yes**
  - ❑ **No**

Use of *nab*-Paclitaxel Has Not Been Adequately Studied in Patients with Hepatic Dysfunction

- Patients with bilirubin levels above the ULN were excluded from the MPACT trial for pancreatic cancer
- Exposure and toxicity of paclitaxel can increase with hepatic impairment

Von Hoff DD, et al. *N Engl J Med*. 2013:369(18):1691–1703.
ABRAXANE® product monograph. Mississauga, ON: Celgene Inc.; 2016.

Recommendations for Starting Dose in Metastatic Pancreatic Cancer Patients with Hepatic Impairment

	SGOT (AST) Levels		Bilirubin Levels	*nab*-Paclitaxel Dose
Mild	<10 x ULN	AND	>ULN to ≤1.5 x ULN	125 mg/m^2
Moderate	<10 x ULN	AND	>1.5 to ≤3 x ULN	Not recommended
Severe	<10 x ULN	AND	>3 to ≤5 x ULN	Not recommended
	>10 x ULN	OR	>5 x ULN	Not recommended

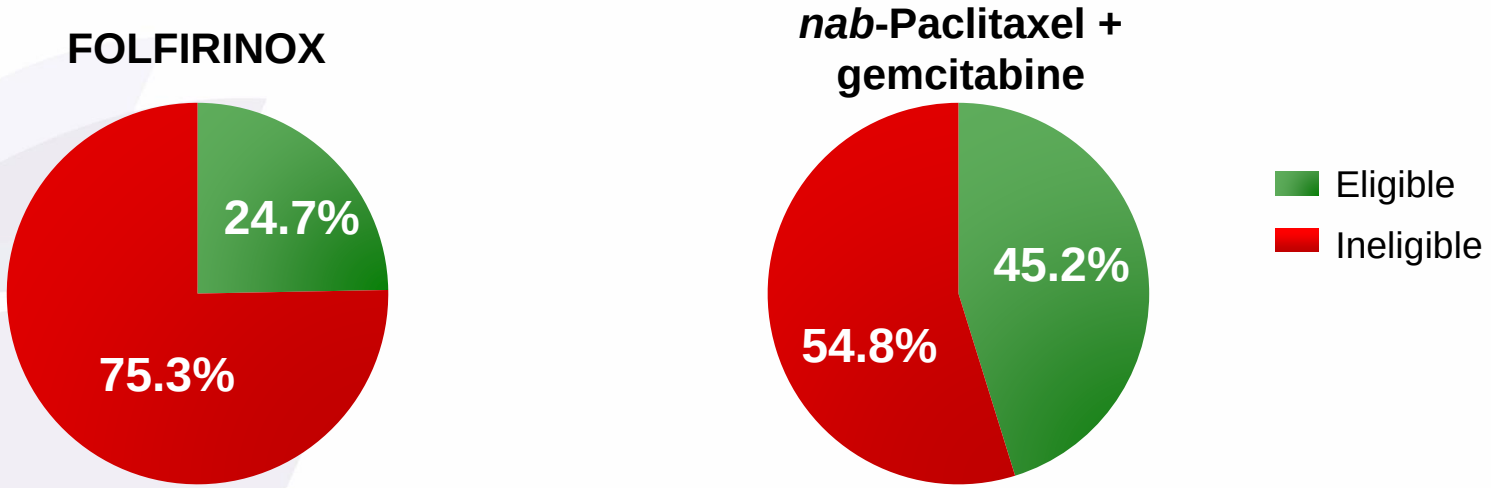
AST, aspartate aminotransferase. SGOT, serum glutamic-oxaloacetic transaminase.
ABRAXANE® package insert. Summit, NJ: Celgene Corporation; 2015.

Expert Recommendation: Patients with Elevated Bilirubin

- The use of *nab*-paclitaxel has not been adequately studied in patients with hepatic dysfunction; with limited data, use with caution and make attempts to lower/normalize bilirubin
- Because the exposure and toxicity of paclitaxel can increase with hepatic impairment, *nab*-paclitaxel is not recommended for pancreatic cancer patients with moderate or severe hepatic impairment (bilirubin >1.5 x ULN)
- Consider use in patients with stable, modest elevation of bilirubin (≤1.5 x ULN) as per U.S. package insert
- There is some clinical experience using *nab*-paclitaxel/gemcitabine in patients with a bilirubin up to 2 x ULN – it may be best to start with a modest dose reduction and then adjust based on toxicity
- Patients should be monitored closely

Expert opinion of steering committee.

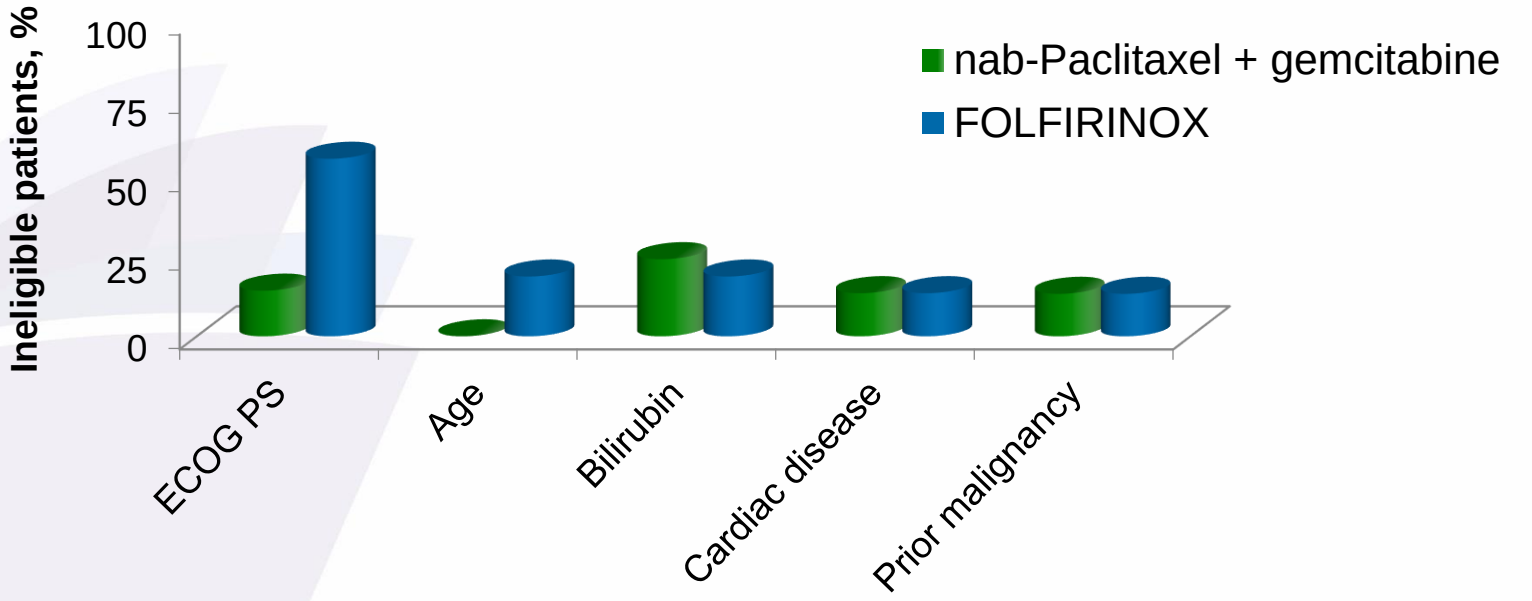
Eligibility of Patients for First-line *nab*-Paclitaxel/Gemcitabine vs. FOLFIRINOX



Almost twice as many patients were eligible for *nab*-Paclitaxel + gemcitabine therapy vs. FOLFIRINOX therapy

Peixoto RD, et al. *Am J Clin Oncol.* 2015. [Epub ahead of print]

Top Reasons for Ineligibility



- 267/473 (56.4%) patients had ECOG ≥2 and, therefore, were ineligible for FOLFIRINOX
- The greater OS in FOLFIRINOX-eligible vs. *nab*-paclitaxel/gemcitabine-eligible patients likely reflects the exclusion of ECOG PS 2 patients in the former trial

Peixoto RD, et al. *Am J Clin Oncol.* 2015. [Epub ahead of print]

Real World Clinical Effectiveness: Canadian Data (BCCA)

- To examine and compare the real world effectiveness of FOLFIRINOX, *nab*-paclitaxel + gemcitabine, and gemcitabine in patients with unresectable pancreatic cancer
- Retrospective analysis of patients (n=150) from 5 cancer centres in BC

Wang Y, et al. *ASCO* 2016 [Abstract 6561].

FOLFIRINOX and *nab*-Paclitaxel/Gemcitabine Demonstrate Significantly Longer OS vs. Gem

Treatment	n	Median Age	ECOG 0–1	ECOG 2+	Metastatic disease	OS, months
Gemcitabine	32	74	43%	57%	78%	4.1
nab-Paclitaxel + gemcitabine	59	70	54%	46%	80%	11.6
FOLFIRINOX	59	61	91%	9%	59%	11.2

- Note: Patients who received FOLFIRINOX were younger, in better performance status, and had less disease burden at presentation

Wang Y, et al. *ASCO* 2016 [Abstract 6561].

Reasons for Treatment Discontinuation

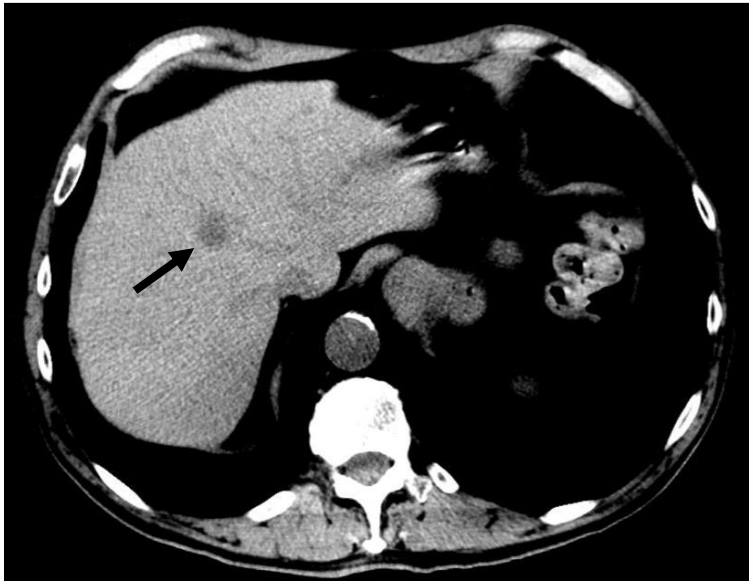
	FOLFIRINOX	*nab*-P/Gem	Gem	*p*-value
Day requiring dose modification	Day 14	Day 44	Day 21	0.0407
Treatment discontinuations, n (%)	50 (85%)	41 (78%)	30 (94%)	
Reason for discontinuation, n (%)				
Toxicity	16 (36%)	7 (17%)	7 (23%)	0.119
Progression	12 (27%)	17 (41%)	7 (23%)	0.203
Death	4 (9%)	3 (7%)	7 (23%)	0.091
Other	11 (25%)	13 (32%)	10 (33%)	0.691

- Patients on FOLFIRINOX and gemcitabine required earlier dose modification than *nab*-paclitaxel + gemcitabine

Wang Y, et al. *ASCO* 2016 [Abstract 6561].

Case 2: Patient Profile

- 62-year-old male
- Patient had pain, fatigue, weight loss, jaundice, biliary obstruction
- CT scan showed pancreatic head mass, dilated common bile duct, presence of liver metastases
- Biliary stent was placed; bilirubin dropped
- ECOG performance status: 1 (KPS 90)
- Patient received *nab*-paclitaxel plus gemcitabine treatment (125/1000 mg/m^2)



nab-Paclitaxel + Gemcitabine Treatment Administration

Evidence-based dosing per the MPACT trial

Start with *nab*-paclitaxel

Administer 125 mg/m² as an IV infusion over 30 – 40 minutes

Follow immediately with gemcitabine

Administer gemcitabine 1000 mg/m² as an IV infusion over 30 – 40 minutes

Administer *nab*-paclitaxel + gemcitabine on days 1, 8, and 15 of each 28-day cycle

ABRAXANE® product monograph. Mississauga, ON: Celgene Inc.; 2015.

Summary of Safety Profile from MPACT

	nab-Paclitaxel + Gemcitabine (n = 421)		Gemcitabine (n = 402)	
AEs leading to death within 30 days last dose	4%		4%	
	All Grades	**Grade ≥3 AEs**	**All Grades**	**Grade ≥3 AEs**
Hematologic AEs, %				
Neutropenia	42	33	30	21
Anemia	42	12	33	8
Thrombocytopenia	30	13	29	8
Leukopenia	14	9	10	4
Use of growth factors, %	26		15	
Febrile neutropenia, %	3		1	
Nonhematologic AEs, %				
Fatigue	59	18	46	9
Peripheral neuropathy	54	17	13	1
Nausea	54	6	48	3
Alopecia	50	1	5	0
Peripheral edema	46	3	30	3
Diarrhea	44	6	24	1
Pyrexia	41	3	28	1

ABRAXANE® product monograph. Mississauga, ON: Celgene Inc; 2016; Von Hoff DD, et al. *N Engl J Med*. 2013:369(18):1691–1703.

Summary of Adverse Events Resulting in *nab*-Paclitaxel Dose Adjustments

Dose Reduction	Withholding or Delay	Discontinuation
Most common AEs (≥5%) resulting in dose reduction of *nab*-paclitaxel	Most common AEs (≥5%) leading to withholding or delay of *nab*-paclitaxel	Most common AEs (≥2%) resulting in permanent discontinuation of *nab*-paclitaxel
▪ Neutropenia (10%) ▪ Peripheral neuropathy (6%)	▪ Neutropenia (16%) ▪ Peripheral neuropathy (15%) ▪ Thrombocytopenia (12%) ▪ Fatigue (8%) ▪ Anemia (5%) ▪ Diarrhea (5%)	▪ Peripheral neuropathy (8%) ▪ Fatigue (4%) ▪ Thrombocytopenia (2%)

ABRAXANE® package insert. Summit, NJ: Celgene Corporation; 2015.

Managing Toxicities in MPACT

Objective

- This exploratory analysis characterized the use of dose reduction or delay to manage toxicities and the effect of that dose modification on efficacy in the MPACT trial

Scheithauer W, et al. *J Gastrointest Oncol.* 2016;7(3):469–478.

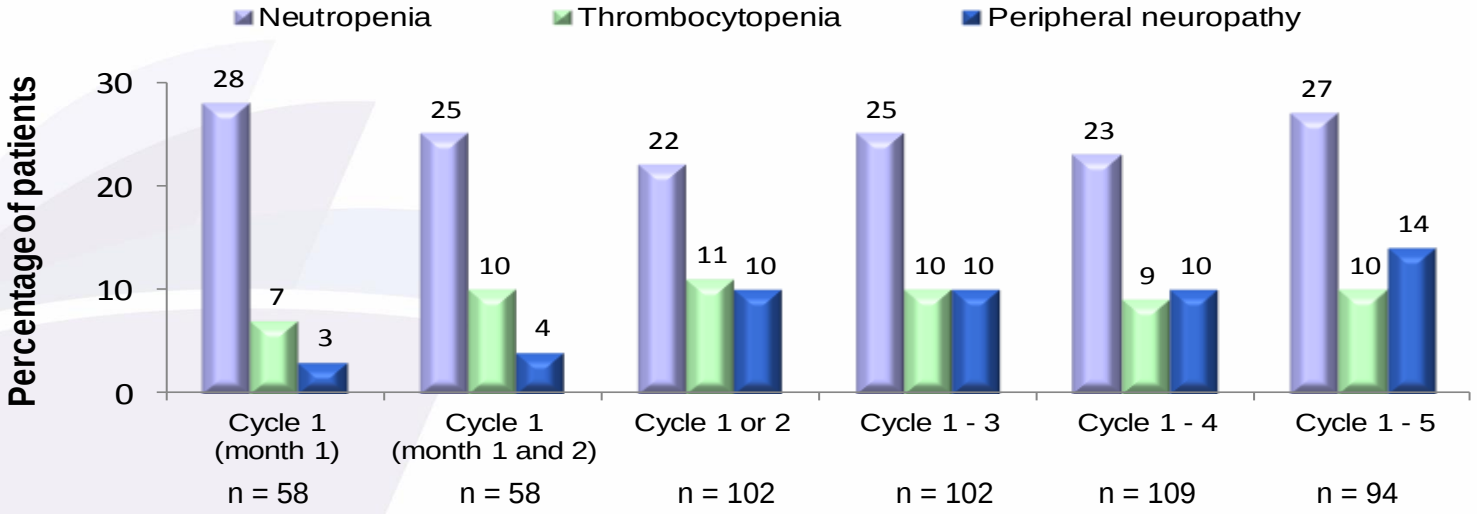
Treatment Exposure

	nab-P + Gem n = 421	
	nab-P	Gem
Per-protocol/total doses, n/n (%)	4116/5770 (71%)	3731/5888 (63%)
Patients with ≥1 dose delay, n (%)	300 (71%)	295 (70%)
Patients with ≥1 dose reduction, n (%)	172 (41%)	198 (47%)

- Most dose modifications occurred after the first 3 months (2 cycles) of treatment
- Patients who underwent dose modifications of *nab*-P had greater treatment exposure than those who did not in terms of treatment duration, number of cycles administered, and cumulative dose of *nab*-P delivered

Scheithauer W, et al. *J Gastrointest Oncol.* 2016;7(3):469–478.

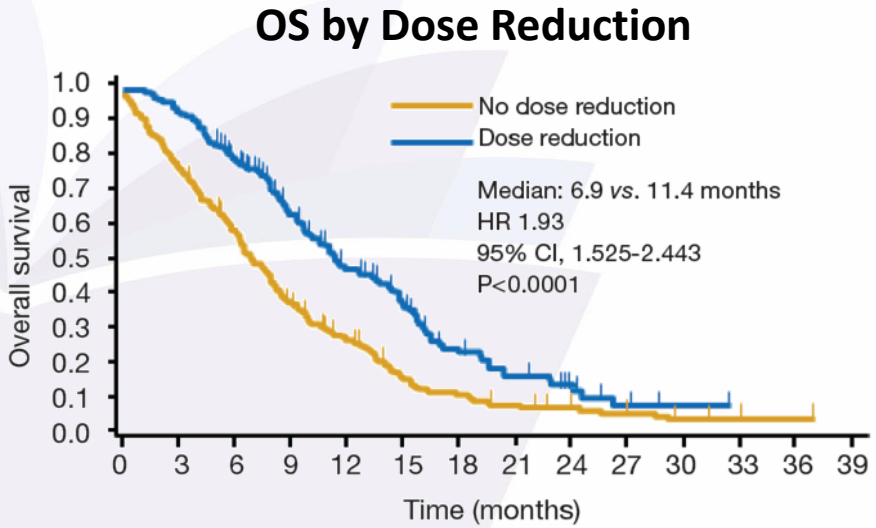
AEs Leading to *nab-P*aclitaxel Dose Reduction by Cycle

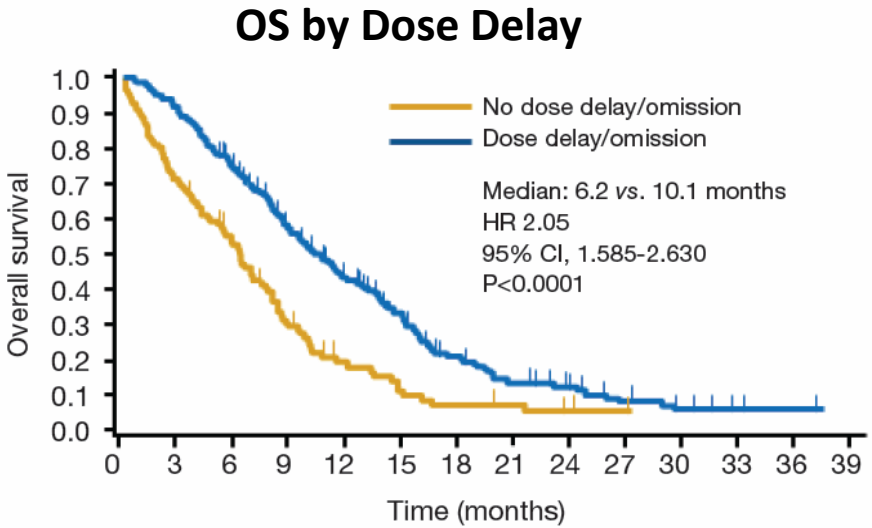


- Neutropenia caused highest rate of dose reductions over the first 5 cycles
- Rates of dose reductions due to peripheral neuropathy increased with increasing numbers of treatment cycles

Scheithauer W, et al. *J Gastrointest Oncol.* 2016;7(3):469–478.

Overall Survival Was Longer for Patients Who Underwent a Dose Reduction or Dose Delay





- Protocol-specified dose modifications to alleviate toxicities can be carried out without reducing the efficacy of the established *nab*-paclitaxel dose

Scheithauer W, et al. *J Gastrointest Oncol.* 2016;7(3):469–478.

Treating to Progressive Disease in MPACT

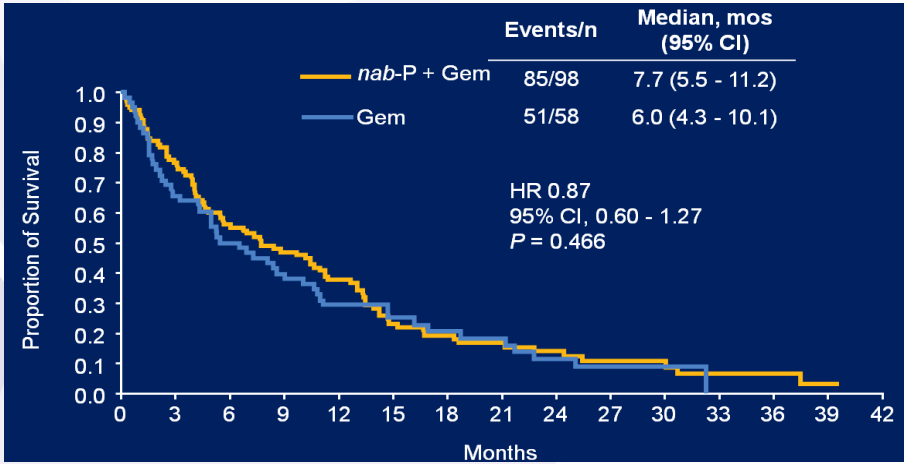
Objective

- To evaluate the efficacy and safety of *nab*-paclitaxel + gemcitabine vs. gemcitabine alone in patients with metastatic pancreatic cancer treated to progressive disease or until unacceptable toxicity

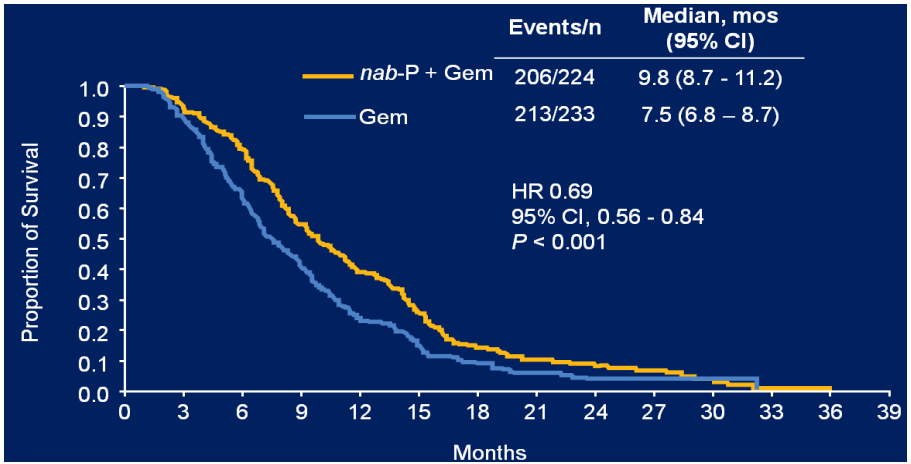
Vogel A, et al. Poster at ESMO 2015 [Abstract 2358].

Overall Survival Was Longer for Patients Who Were Treated to Progressive Disease

OS in Patients treated to AEs



OS in Patients Treated to PD



- Patients treated to PD had greater treatment exposure and dose intensity than those treated to AEs, which may explain differences in OS
  - Indicates that *nab*-P + Gem treatment can be optimized for maximum benefit
- Results of this analysis support treating patients until PD when possible

Vogel A, et al. Poster at ESMO 2015 [Abstract 2358].

Case 2 (cont'd)

- On day 8 of the treatment cycle, the patient develops high grade cytopenias (neutropenia and thrombocytopenia)
- Labs reveal:
  - ANC = 0.75 $x10^9$/L
  - Platelets = 60 $x10^9$/L

Polling Question 6

- **What steps would you take to manage this treatment-related toxicity?**
  - ❑ Keep regimen at same dose and carefully monitor patient
  - ❑ Delay doses until neutrophil and platelet counts recover
  - ❑ Reduce both *nab*-P and gem doses by 1 level
  - ❑ Reduce only *nab*-P 1 dose level
  - ❑ Omit *nab*-P dose
  - ❑ Other

Dose Reductions for All Toxicities*

Agent	Starting Dose	Dose Level 1	Dose Level 2
***nab*-Paclitaxel**	125 mg/m^2	100 mg/m^2	75 mg/m^2
Gemcitabine	1000 mg/m^2	800 mg/m^2	600 mg/m^2

*Doses reduced for hematologic or nonhematologic toxicities should not be re-escalated

If additional dose reduction required – discontinue treatment

ABRAXANE® product monograph. Mississauga, ON: Celgene Inc; 2016.
BCCA Protocol Summary for First Line Treatment of Locally Advanced and Metastatic Pancreatic Cancer with *nab*-Paclitaxel and Gemcitabine. 2015.

Dose Recommendation and Modifications for Neutropenia/Thrombocytopenia: Including Use of Growth Factors

Cycle Day	ANC Count (x10^9/L)		Platelet Count (x10^9/L)	*nab*-P Dose	Gem Dose
Day 1	≥1.5	AND	≥100	Treat on time at current dose levels	
	<1.5	OR	<100	Delay doses until recovery	
Day 8	≥1.0	AND	≥75	Treat on time at current dose levels	
	≥0.5 but <1.0	OR	≥50 but <75	Reduce doses 1 dose level	
	<0.5	OR	<50	Withhold doses	
Day 15: IF day 8 doses were given without modification					
Day 15	≥1.0	AND	≥75	Treat on time at current dose levels	
	≥0.5 but <1.0	OR	≥50 but <75	Treat at current dose level and follow with **WBC growth factors**	
	<0.5	OR	<50	Withhold doses	
Day 15: IF day 8 doses were reduced					
Day 15	≥1.0	AND	≥75	Return to day 1 dose level and follow with **WBC growth factors**	
	≥0.5 but <1.0	OR	≥50 but <75	Treat with Day 8 dose level and follow with **WBC growth factors**	
	<0.5	OR	<50	Withhold doses	
Day 15: IF day 8 doses were withheld					
Day 15	≥1.0	AND	≥75	Return to Day 1 dose level and follow with **WBC growth factors**	
	≥0.5 but <1.0	OR	≥50 but <75	Reduce 1 dose level and follow with **WBC growth factors**	
	<0.5	OR	<50	Withhold doses	

ANC, absolute neutrophil count. WBC, white blood cell.

ABRAXANE® product monograph. Mississauga, ON: Celgene Inc.; 2016.

Note: WBC GFs not funded for metastatic pancreatic cancer in many provinces.

Dose Modifications for Hematologic Toxicity (Without Growth Factors)

Cycle Day	ANC (x10^9/L)		Platelets (x10^9/L)	*nab*-Paclitaxel Dose	Gemcitabine Dose
Day 1					
	≥1.5	and	≥100	100%	
	<1.5	or	<100	Delay by 1 week intervals until recovery	
Day 8					
	≥1.0	and	≥75	100%	
	0.5 to <1.0	or	50 to <75	Reduce 1 dose level	
	<0.5	or	<50	Omit doses	
Day 15: If day 8 doses were reduced or given without modification					
	≥1.0	and	≥75	Same as Day 8 doses	
	0.5 to <1.0	or	50 to <75	Reduce 1 dose level from Day 8	
	<0.5	or	<50	Omit doses	
Day 15: If day 8 doses were omitted					
	≥1.0	and	≥75	Reduce 1 dose level from Day 1	
	0.5 to <1.0	or	50 to <75	Reduce 2 dose levels from Day 1	
	<0.5	or	<50	Omit doses	

ABRAXANE® package insert. Summit, NJ: Celgene Corporation; 2015.
BCCA Protocol Summary for First Line Treatment of Locally Advanced and Metastatic Pancreatic Cancer with *nab*-Paclitaxel and Gemcitabine. 2015.

Expert Faculty Approach

- **What steps would you take to manage this treatment-related toxicity?**
  - ❑ Keep regimen at same dose and carefully monitor patient
  - ❑ Delay doses until neutrophil and platelet counts recover
  - ❑ Reduce both *nab*-P and gem doses by 1 level
  - ❑ Reduce only *nab*-P 1 dose level
  - ❑ Omit *nab*-P dose
  - ❑ Other

Case 2 (cont'd)

- Patient continues treatment on day 8 at a reduced dose of *nab*-paclitaxel (100 mg/m^2) and gemcitabine (800 mg/m^2)
- Day 15 labs reveal:
  - ANC = 1.2 x10^9/L
  - Platelets = 76 x10^9/L

Polling Question 7

- **What steps would you take to manage this patient?**
  - ❑ Increase doses back to starting dose
  - ❑ Only increase gem dose; continue *nab*-P dose the same as day 8
  - ❑ Continue both doses the same as day 8
  - ❑ Reduce both does 1 level from day 8
  - ❑ Omit both doses
  - ❑ Other

Expert Faculty Approach

- **What steps would you take to manage this patient?**
  - ❑ Increase doses back to starting dose
  - ❑ Only increase gem dose; continue *nab*-P dose the same as day 8
  - ❑ Continue both doses the same as day 8
  - ❑ Reduce both does 1 level from day 8
  - ❑ Omit both doses
  - ❑ Other

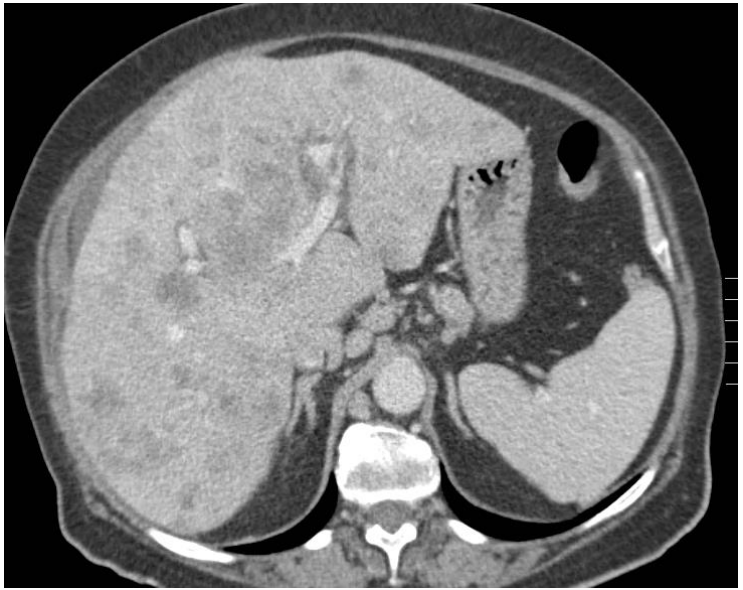
Expert Recommendation: Dose Delays or Modifications for Neutropenia

- WBC growth factors not funded for metastatic pancreatic cancer in many provinces
- Use U.S. package insert guidelines (or BCCA protocol)
  - Canadian product monograph differs (WBC growth factors vs. dose reduction)
- Treat day 1 with ANC >1500
- If day 8 or 15 omitted, don’t make it up
- If day 15 omitted, then reassess to start next cycle at day 22

Expert opinion of steering committee.

Case 3: Patient Profile

- 74-year-old female
- Patient has weight loss, epigastric pain, bloating, and jaundice
- CT scan showed large mass on head of pancreas with diffuse liver metastases
  - Biopsy performed and confirmed adenocarcinoma
- ECOG performance status: 2 (KPS 70)



Case 3: Management

- Due to the patient's age and performance status, the physician and patient decided to initiate *nab*-paclitaxel + gemcitabine therapy
- Patient initiated on full dose *nab*-paclitaxel + gemcitabine
  - *nab*-Paclitaxel: 125 mg/m^2, gemcitabine 1000 mg/m^2
  - Days 1, 8, and 15; every 28 days
- During cycle 5, day 1, the patient develops Grade 3 neuropathy
- The patient reports:
  - 'Pins and needles' sensation in her hands
  - Tendency to drop things
  - Difficulty walking

Polling Question 8

- **What is your next step in managing this treatment-related toxicity?**
  - ❑ Keep regimen at same dose and carefully monitor patient
  - ❑ Keep regimen at same dose and treat with pregabalin or gabapentin
  - ❑ Reduce both *nab*-P and gem doses by 1 level
  - ❑ Reduce only *nab*-P 1 dose level
  - ❑ Omit *nab*-P dose
  - ❑ Omit both *nab*-P + gem doses
  - ❑ Other

Dose Modifications for Sensory Neuropathy

Grade	Toxicity	Dose of *nab*-Paclitaxel
1	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Maintain dose
2	Sensory alteration or paresthesia (including tingling) but not interfering with function, but not interfering with ADL	Maintain dose
3	Sensory alteration or paresthesia interfering with ADL	Omit until improves to ≤ Grade 1; resume at next lower dose level
4	Disabling	Omit until improves to ≤ Grade 1; resume at next lower dose level

BCCA Protocol Summary for First Line Treatment of Locally Advanced and Metastatic Pancreatic Cancer with *nab*-Paclitaxel and Gemcitabine. 2015.

Grade 3 Neuropathy Diminishes When Patients Take a Break from *nab*-Paclitaxel Treatment (MPACT)

- *nab*-Paclitaxel-related Grade 3 peripheral neuropathy developed in a median of 140 days (20 weeks)
- Median time to improvement by 1 Grade
  - About 20 days
- Median time to improvement to Grade ≤1
  - About 30 days

ABRAXANE® product monograph. Mississauga, ON: Celgene Inc.; 2015.
Von Hoff DD, et al. *N Engl J Med*. 2013:369(18):1691–1703.

Expert Faculty Approach

- **What is your next step in managing this treatment-related toxicity?**
  - ❑ Keep regimen at same dose and carefully monitor patient
  - ❑ Keep regimen at same dose and treat with pregabalin or gabapentin
  - ❑ Reduce both *nab*-P and gem doses by 1 level
  - ❑ Reduce only *nab*-P 1 dose level
  - ❑ Omit *nab*-P dose
  - ❑ Omit both *nab*-P + gem doses
  - ❑ Other

Expert Recommendation: Dose Delays or Modifications for Neuropathy

- Grade 2 neuropathy
  - Could consider either reducing 1 dose level or hold until recovered to Grade ≤1 (depending on patient, activity level)
  - Can continue gemcitabine without dose modification

Per product monograph and MPACT protocol:

- Grade 3 neuropathy
  - Hold until recovered to Grade ≤1
  - Continue gemcitabine
  - Resume at reduced dose level
- Grade 1 neuropathy
  - Continue gemcitabine + *nab*-paclitaxel without dose modifications
  - Monitor closely

Expert opinion of steering committee.

Expert Recommendations Resource

Canadian Expert Recommendations for the Utilization of Abraxane (nab-Paclitaxel) Plus Gemcitabine in Pancreatic Cancer

Available at OncologyEducation.com

http://www.oncologyeducation.com/information/gi-updates/slideshows/canadian-gi-experts-2016/

Symptoms Management Resource

- Prompt management of the many symptoms and problems associated with pancreatic cancer is essential to minimize distress and optimize quality of life for patients with this devastating disease:
  - Fatigue
  - Pain
  - Depression
  - Bile duct obstruction
  - Gastrin outlet / duodenal obstruction
  - Hyperglycemia
  - Pancreatic insufficiency
  - Weight loss / anorexia / cachexia
  - Nausea and vomiting
  - Gastroparesis
  - Thromboembolic events

Family Practice Oncology Network Guidelines & Protocols

http://www.bccancer.bc.ca/health-professionals/networks/family-practice-oncology-network/guidelines-protocols

Key Learnings

- With the lowest 5-year survival rate of any cancer, the management of pancreatic cancer patients is challenging and frustrating
- There are three chemotherapy options for pancreatic cancer in Canada – FOLFIRINOX, *nab*-paclitaxel + gemcitabine, and gemcitabine monotherapy
- FOLFIRINOX and *nab*-paclitaxel + gemcitabine are preferred and effective treatment options in patients with metastatic pancreatic cancer who have good performance status
- *nab*-Paclitaxel + gemcitabine is an important new first-line treatment that is also an option for patients with a less robust performance status (i.e., ECOG 2)
- A Canadian population-based study revealed that modified FOLFIRINOX and *nab*-paclitaxel + gemcitabine confers real world effectiveness for advanced pancreatic cancer patients

Key Learnings

- Patients receiving *nab*-paclitaxel + gemcitabine should be monitored for neutropenia, thrombocytopenia, peripheral neuropathy, and fatigue
- Adverse events associated with *nab*-paclitaxel/gemcitabine treatment are acceptable and manageable
  - AEs are generally Grade 3 or lower and resolve without specific treatment
  - Grade 3 neuropathy often diminishes when patients have a break from *nab*-paclitaxel
- The regimen, with a starting dose of *nab*-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2, is feasible
  - Dose modifications to alleviate toxicities were not detrimental and should be used in clinical practice