BC Cancer Protocol Summary for First Line Treatment of Locally Advanced and Metastatic Pancreatic Cancer with PACLitaxel NAB (ABRAXANE) and Gemcitabine

Protocol Code	*GIPGEMABR*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

ELIGIBILITY:

- Previously untreated locally advanced unresectable or metastatic pancreatic cancer (however could have received gemcitabine in the adjuvant setting)
- Performance Status 0 to 2
- Adequate hematologic, renal and hepatic function (including ANC greater than or equal to 1.5 x 10^9/L, Hgb greater than or equal to 90 g/L and bilirubin less than or equal to the upper limit of normal)

EXCLUSIONS:

- Ampullary cancer
- CNS metastatses unless previously treated
- Greater than or equal to grade 2 sensory or motor neuropathy
- Severe hepatic dysfunction contraindicating PACLitaxel NAB

CAUTION:

- Patients over 75 years of age

TESTS:

- Baseline: CBC and differential, platelets, bilirubin, ALT, alkaline phosphatase, creatinine, appropriate tumour markers and appropriate imaging study
- Before each treatment: CBC and differential, platelets
- Before each cycle: CBC and differential, platelets, bilirubin, ALT, alkaline phosphatase, creatinine
- If clinically indicated: CEA, CA 19-9
- Quantitative evaluation of disease response (appropriate tumours markers and imaging studies) every six to ten weeks: discontinue therapy if any progression of disease
- Assess for changes in neurologic function prior to each treatment cycle

PREMEDICATIONS:

- Antiemetic protocol for low-moderately emetogenic chemotherapy (see SCNAUSEA)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
PACLitaxel NAB (ABRAXANE)	125 mg/m^2 on days 1, 8, and 15	IV over 30 minutes*
gemcitabine	1000 mg/m^2 on days 1, 8, and 15	IV in 250 mL NS over 30 minutes

*in empty sterile bags and tubing with **15** micron filter; no specific material required for bag or tubing

Repeat every 28 days until disease progression.

DOSE MODIFICATIONS:

A. Dose Modifications for HEMATOLOGIC Toxicity
B. Dose Modification for NON-HEMATOLGIC Toxicity

Table 1- Dose Reductions for All Toxicities**

Agent	Starting Dose	Dose level - 1	Dose Level - 2
PACLitaxel NAB (ABRAXANE)	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 non-hematologic toxicities should not be re-escalated

A. Dose Modifications for Hematologic Toxicity:

1. Hematologic – Day 1

ANC (x10^9/L)		Platelets (x10^9/L)	Dose	
			PACLitaxel NAB (ABRAXANE)	**gemcitabine**
greater than or equal to 1.5	and	greater than or equal to 100	100%	
less than 1.5	or	less than 100	Delay by 1 week intervals until recovery	

2. Hematologic – Day 8

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose	
			PACLitaxel NAB (ABRAXANE)	gemcitabine
greater than or equal to 1.0	and	greater than or equal to 75	100%	
0.5 to less than 1.0	or	50 to less than 75	Reduce 1 dose level	
less than 0.5	or	less than 50	Omit doses	

3. Hematologic – Day 15

IF DAY 8 DOSES WERE REDUCED OR GIVEN WITHOUT MODIFICATION				
ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose	
			PACLitaxel NAB (ABRAXANE)	gemcitabine
greater than or equal to 1.0	and	greater than or equal to 75	Same as Day 8 doses	
0.5 to less than 1.0	or	50 to less than 75	Reduce 1 dose level from Day 8	
Less than 0.5	or	less than 50	Omit doses	
IF DAY 8 DOSES WERE OMITTED				
greater than or equal to 1.0	and	greater than or equal to 75	Reduce 1 dose level from Day 1	
0.5 to less than 1.0	or	50 to less than 75	Reduce 2 dose levels from Day 1	
less than 0.5	or	less than 50	Omit doses	

4. Febrile Neutropenia

- Delay until fever resolves and ANC greater than or equal to 1.5 x 10^9/L; resume at next lower dose level.

B. Dose Modifications for Non-Hematologic Toxicities:

1. Non – Hematologic Toxicities: PACLitaxel NAB (ABRAXANE®) and gemcitabine

Grade	Stomatitis	Diarrhea	Doses of PACLitaxel NAB (ABRAXANE) and gemcitabine
1	Painless ulcers, erythema or mild soreness	Increase of 2 to 3 stools/day or mild increase in loose watery colostomy output	Maintain dose
2	Painful erythema, edema, or ulcers but can eat	Increase of 4 to 6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Omit until toxicity resolved then resume at same dose level
3	Painful erythema, edema, or ulcers and cannot eat	Increase of 7 to 9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Omit until toxicity resolved then resume at next lower dose level
4	Mucosal necrosis, requires parenteral support	Increase of 10 or more stools/day or grossly bloody diarrhea, or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	Omit until toxicity resolved. At clinician's discretion, therapy could be resumed, but at a reduced dose

3. Sensory Neuropathy: PACLitaxel NAB (ABRAXANE)

Grade	Toxicity	Dose of PACLitaxel NAB (ABRAXANE)
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 less than or equal to Grade 1; resume at next lower dose level.
4	Disabling	Omit until improves to less than or equal to Grade 1; resume at next lower dose level.

4. Hepatic Dysfunctions

ALT or AST		Bilirubin	PACLitaxel NAB
Less than or equal to 10 x ULN	and	Greater than 1 to less than or equal to 1.5 x ULN	100%
Less than or equal to 10 x ULN	and/or	Greater than 1.5 to less than or equal to 5 x ULN	80%*
Greater than 10 x ULN	or	Greater than 5 x ULN	Hold

*may re-escalate dose if hepatic function normalizes and reduced dose is tolerated for at least 2 cycles

PRECAUTIONS:

1. An albumin form of PACLitaxel may substantially affect a drug's functional properties relative to those of drug in solution. **Do not** substitute with or for other PACLitaxel formulations.
2. **Extravasation**: PACLitaxel NAB causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
4. **Renal dysfunction**: Irreversible renal failure associated with hemolytic uremic syndrome may occur rarely with gemcitabine. Use caution with pre-existing renal dysfunction. No adjustment required of PACLitaxel NAB for mild to moderate renal impairment. It has not been studied in patients with creatinine clearance less than 30 mL/min.
5. **Pulmonary Toxicity**: Gemcitabine may cause acute shortness of breath. Discontinue treatment if drug-induced pneumonitis is suspected.
6. **Drug Interaction**: Possible interaction between gemcitabine and warfarin has been reported and may occur at any time. Close monitoring is recommended (monitor INR weekly during gemcitabine therapy and for 1 to 2 month after discontinuing gemcitabine treatment). PACLitaxel NAB is metabolized by CYP2C8 and CYP3A4; caution should be exercised when administering with drugs which are CYP2C8 or CYP3A4 inducers or inhibitors.
7. **Cardiac toxicity** has been reported rarely while patients receive PACLitaxel NAB. Severe cardiovascular events (3%), including chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension.
8. **Theoretical risk of viral disease transmission**, due to human albumin component, is extremely remote with the use of PACLitaxel NAB.

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Janine Davies at (604) 877-6000 or 1-800-670-3322 with any problems or questions regarding this treatment program.

References:

1. Von Hoff DD, Ervin T, Arena FP et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691-703.

2. Celgene Inc. ABRAXANE® product monograph. Mississauga, ON; 06 August 2020.