

## Regimen Reference Order

### BRST – pembrolizumab + BrighTNess (weekly CARBOplatin)

ARIA: BRST - [pemb + BrighTNess wkly Ph 1]

BRST - [pembro + BrighTNess Phase 2]

BRST - [pembro + BrighTNess Phase 3]

**Planned Course:** Phase 1: pembrolizumab every 42 days + PACLitaxel (weekly) + CARBOplatin (weekly) for 4 cycles (1 cycle = 21 days)

Phase 2: pembrolizumab every 42 days + AC Dose Dense every 14 days for 4 cycles (1 cycle = 14 days)

Phase 3: pembrolizumab every 42 days for 5 cycles (1 cycle = 42 days)

***See Appendix (page 8) for regimen Dosing Schema***

**Indication for Use:** Breast Cancer Neo-Adjuvant and Adjuvant; “Triple negative”

**CVAD:** Preferred (VESICANT INVOLVED)

#### ***Proceed with treatment if:***

##### ***Phase 1 (pembrolizumab + PACLitaxel + CARBOplatin)***

- ***ANC equal to or greater than  $1 \times 10^9/L$  AND Platelets equal to or greater than  $100 \times 10^9/L$***
- ***Total bilirubin less than 1.25 times upper limit of normal***
- ***AST/ALT less than 3 times upper limit of normal***
- ***Creatinine clearance greater than 30 mL/minute***

##### ***Phase 2 (pembrolizumab + AC (Dose Dense))***

- ***ANC equal to or greater than  $1 \times 10^9/L$  AND Platelets equal to or greater than  $100 \times 10^9/L$***
- ***Total bilirubin less than upper limit of normal***
- ***AST/ALT less than 2 times upper limit of normal***
- ***Creatinine clearance greater than 30 mL/minute***

##### ***Phase 3 (pembrolizumab)***

- ***ANC equal to or greater than  $1.5 \times 10^9/L$  AND Platelets equal to or greater than  $50 \times 10^9/L$***
  - ***Total bilirubin less than 1.5 times upper limit of normal***
  - ***AST/ALT less than 3 times upper limit of normal***
  - ***Creatinine clearance greater than 30 mL/minute***
- ❖ **Contact Physician if parameters not met**

## SEQUENCE OF MEDICATION ADMINISTRATION

### Pre-treatment Requirements

Drug	Dose	CCMB Administration Guideline
<b>Phase 2 – AC (Dose Dense)</b>		
Instruct patient to start vigorous oral pre-hydration (600-900 mL) the morning of cyclophosphamide treatment (Self-administered at home)		

### Treatment Regimen – BRST – pembrolizumab + BrighTNess (weekly CARBOplatin)

Establish primary solution 500 mL of: normal saline

Drug	Dose	CCMB Administration Guideline
<b>Phase 1 – pembrolizumab every 42 days + PACLitaxel (weekly) + CARBOplatin (weekly) (Cycles 1 to 4)</b>		
<b>Phase 1 - Cycles 1 and 3 ONLY</b>		
<b>Day 1</b>		
pembrolizumab	4 mg/kg	IV in normal saline 100 mL over 30 minutes Use 0.2 or 0.22 micron filter <i>*Alert: pembrolizumab only administered on Cycles 1 and 3 of Phase 1</i>
cetirizine	20 mg	Orally 1 hour prior to PACLitaxel
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
dexamethasone	20 mg	IV in normal saline 50 mL over 15 minutes <b>1 hour</b> prior to PACLitaxel <i>*Nursing Alert: PACLitaxel starts 1 hour after completion of dexamethasone infusion</i>

**Wait 1 hour after completion of IV pre-medication(s) before starting PACLitaxel**

PACLitaxel	80 mg/m <sup>2</sup>	IV in normal saline 250 mL over 1 hour, following the administration rates below: <ul style="list-style-type: none"> <li>Administer at 100 mL/hour for 15 minutes, then</li> <li>Administer remaining volume over 45 minutes</li> </ul> Use non-DEHP bags and non-DEHP administration sets with 0.2 or 0.22 micron filter <i>*Alert: Gently invert bag 8 to 10 times immediately prior to administration of PACLitaxel to evenly distribute the drug</i>
CARBOplatin	AUC 1.5 mg/mL.min; maximum dose 225 mg (see table below)	IV in D5W 250 mL over 30 minutes

**Days 8 and 15**

cetirizine	20 mg	Orally 1 hour prior to PACLitaxel
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
dexamethasone	20 mg	IV in normal saline 50 mL over 15 minutes <b>1 hour</b> prior to PACLitaxel <i>*Nursing Alert: PACLitaxel starts 1 hour after completion of dexamethasone infusion</i>

**Wait 1 hour after completion of IV pre-medication(s) before starting PACLitaxel**

PACLitaxel	80 mg/m <sup>2</sup>	IV in normal saline 250 mL over 1 hour, following the administration rates below:
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		<ul style="list-style-type: none"> <li>Administer at 100 mL/hour for 15 minutes, then</li> <li>Administer remaining volume over 45 minutes</li> </ul> <p>Use non-DEHP bags and non-DEHP administration sets with 0.2 or 0.22 micron filter</p> <p><b>*Alert:</b> Gently invert bag 8 to 10 times immediately prior to administration of PACLitaxel to evenly distribute the drug</p>
CARBOplatin	AUC 1.5 mg/mL.min; maximum dose 225 mg (see table below)	IV in D5W 250 mL over 30 minutes
<b>Phase 1 - Cycles 2 and 4 ONLY</b>		
<b>Day 1, 8, 15</b>		
cetirizine	20 mg	Orally 1 hour prior to PACLitaxel
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
dexamethasone	20 mg	IV in normal saline 50 mL over 15 minutes <b>1 hour</b> prior to PACLitaxel <b>*Nursing Alert:</b> PACLitaxel starts <b>1 hour after completion</b> of dexamethasone infusion
<b>Wait 1 hour after completion of IV pre-medication(s) before starting PACLitaxel</b>		
PACLitaxel	80 mg/m <sup>2</sup>	IV in normal saline 250 mL over 1 hour, following the administration rates below: <ul style="list-style-type: none"> <li>Administer at 100 mL/hour for 15 minutes, then</li> <li>Administer remaining volume over 45 minutes</li> </ul> <p>Use non-DEHP bags and non-DEHP administration sets with 0.2 or 0.22 micron filter</p> <p><b>*Alert:</b> Gently invert bag 8 to 10 times immediately prior to administration of PACLitaxel to evenly distribute the drug</p>
CARBOplatin	AUC 1.5 mg/mL.min; maximum dose 225 mg (see table below)	IV in D5W 250 mL over 30 minutes
<b>Phase 2 starts 1 week after Cycle 4, Day 15 of Phase 1 (pembrolizumab + PACLitaxel + CARBOplatin)</b>		
<b>Phase 2 – pembrolizumab every 42 days + AC (Dose Dense) every 14 days (Cycles 1 to 4)</b>		
Establish primary solution 500 mL of: normal saline		
<b>Phase 2 - Cycles 1 and 4 ONLY</b>		
pembrolizumab	4 mg/kg	IV in normal saline 100 mL over 30 minutes Use 0.2 or 0.22 micron filter <b>*Alert:</b> pembrolizumab only administered on Cycles 1 and 4 of Phase 2
aprepitant	125 mg	Orally 1 hour pre-chemotherapy

ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
dexamethasone	12 mg	Orally 30 minutes pre-chemotherapy
OLANzapine	2.5 mg	Orally 30 minutes pre-chemotherapy
DOXOrubicin	60 mg/m <sup>2</sup>	IV Push over 10 to 15 minutes
cyclophosphamide	600 mg/m <sup>2</sup>	IV in normal saline 250 mL over 1 hour
<b>Phase 2 - Cycles 2 and 3 ONLY</b>		
aprepitant	125 mg	Orally 1 hour pre-chemotherapy
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
dexamethasone	12 mg	Orally 30 minutes pre-chemotherapy
OLANzapine	2.5 mg	Orally 30 minutes pre-chemotherapy
DOXOrubicin	60 mg/m <sup>2</sup>	IV Push over 10 to 15 minutes
cyclophosphamide	600 mg/m <sup>2</sup>	IV in normal saline 250 mL over 1 hour
<b>Phase 3 usually starts 30 to 60 days post-surgery</b>		
<b>Phase 3 – pembrolizumab every 42 days (Cycles 1 to 5)</b>		
<b>Establish primary solution 500 mL of: normal saline</b>		
pembrolizumab	4 mg/kg	IV in normal saline 100 mL over 30 minutes <i>Use 0.2 or 0.22 micron filter</i>
<b>Maximum pembrolizumab dose is 400 mg (every 42 days)</b>		
All doses will be automatically rounded that fall within CCMB Approved Dose Bands. See Dose Banding document for more information		

In the event of an infusion-related hypersensitivity reaction, refer to the 'Hypersensitivity Reaction Standing Order'

## REQUIRED MONITORING

### Phase 1 (pembrolizumab + PACLitaxel + CARBOplatin)

Cycles 1 to 4

Day 1

- CBC, serum creatinine, urea, electrolytes, liver enzymes, total bilirubin, albumin, glucose and TSH as per Physician Orders
- Cortisol at physician's discretion
- Full vital signs (temperature, heart rate, respiratory rate, blood pressure and O<sub>2</sub> saturation) at baseline and as clinically indicated
- No observation period required after pembrolizumab (Cycles 1 and 3) and PACLitaxel administration. Patient can be discharged from treatment room if stable whether they had a reaction or not

Days 8 and 15

- CBC, serum creatinine, urea, electrolytes, liver enzymes, total bilirubin, albumin, glucose and TSH as per Physician Orders
- Full vital signs (temperature, heart rate, respiratory rate, blood pressure and O<sub>2</sub> saturation) at baseline and as clinically indicated
- No observation period required after PACLitaxel administration. Patient can be discharged from treatment room if stable whether they had a reaction or not

**Phase 2 (pembrolizumab + AC Dose Dense)**

## Cycles 1 to 4

- CBC, serum creatinine, urea, electrolytes, liver enzymes, total bilirubin, albumin, glucose and TSH as per Physician Orders
- Morning cortisol required prior to Cycle 4. Cortisol at physician's discretion for Cycles 1 to 3
- Left Ventricular Ejection Fraction (LVEF) monitoring is recommended at baseline and as clinically indicated
- Full vital signs (temperature, heart rate, respiratory rate, blood pressure and O<sub>2</sub> saturation) at baseline and as clinically indicated
- No observation period required after pembrolizumab administration (Cycles 1 and 4). Patient can be discharged from treatment room if stable whether they had a reaction or not

**Phase 3 (pembrolizumab)**

## All Cycles

- CBC, serum creatinine, urea, electrolytes, liver enzymes, total bilirubin, albumin, glucose and TSH as per Physician Orders
- Cortisol at physician's discretion
- Full vital signs (temperature, heart rate, respiratory rate, blood pressure and O<sub>2</sub> saturation) at baseline and as clinically indicated
- No observation period required after pembrolizumab administration. Patient can be discharged from treatment room if stable whether they had a reaction or not

**Recommended Support Medications**

Drug	Dose	CCMB Administration Guideline
<b>Phase 1 – pembrolizumab + PACLitaxel + CARBOplatin</b>		
filgrastim (brand name specific) <i>(See Filgrastim Clinical Guide)</i>	5 mcg/kg (rounded to nearest 300 mcg or 480 mcg)	Subcutaneous once daily on Days 3 to 5, Days 10 to 12 and Days 17 to 19
dexamethasone	8 mg	Orally once daily on Days 2 and 3, 9 and 10, and 16 and 17
metoclopramide	10 – 20 mg	Orally every 4 hours as needed for nausea and vomiting
<b>Phase 2 – pembrolizumab + AC (Dose Dense)</b>		
pegfilgrastim (brand name specific) <i>(See Filgrastim Clinical Guide)</i>	6 mg	Subcutaneous once on Day 2 <i>*Alert: pegfilgrastim to be given as a single dose once per chemotherapy cycle no sooner than 24 hours after chemotherapy</i>
aprepitant	80 mg	Orally once daily on Days 2 and 3
dexamethasone	8 mg	Orally once daily on Days 2, 3 and 4
OLANzapine	2.5 mg	Orally the evening of Day 1 then twice daily on Days 2, 3 and 4. Also use OLANzapine 2.5 to 5 mg AS NEEDED for breakthrough nausea and vomiting (including Days 1 to 4) up to a maximum of 10 mg per day. Contact clinic if nausea/vomiting is not adequately controlled
<b>Phase 3 – pembrolizumab</b>		
None required		

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## DISCHARGE INSTRUCTIONS

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### Phase 1 (pembrolizumab + PACLitaxel + CARBOplatin)

- Patients should be instructed to contact their cancer team immediately if symptoms of hypersensitivity reactions occur after discharge
- Ensure patient receives filgrastim supply if patient is self-administering at home
- Instruct patient to continue taking anti-emetic(s) at home
- Confirm that patient has received the CCMB Immune Checkpoint Inhibitor Medical Alert wallet card
- Reinforce to patient the immune-mediated adverse reactions and importance of reporting immediately
  - For severe symptoms, the patient should be instructed to go to the nearest emergency room. Oncologist should be contacted
- Reinforce applicable safe handling precautions of medications, blood and body fluids for 48 hours after completion of chemotherapy

### Phase 2 (pembrolizumab + AC Dose Dense)

- Patients should be instructed to contact their cancer team immediately if symptoms of hypersensitivity reactions occur after discharge
- Ensure patient receives pegfilgrastim supply if patient is self-administering at home
- Instruct patient to:
  - Continue taking anti-emetic(s) at home. Patients should be instructed not to use OLANzapine and metoclopramide concurrently due to drug interactions
  - Maintain oral intake of 2000 mL (8 glasses) of fluid daily at home
  - Empty bladder every 2 hours while awake and at bedtime for 24 hours after each dose of cyclophosphamide
  - Obtain immediate assistance as per your clinic's contact instructions if:
    - Symptoms of hemorrhagic cystitis (e.g. dysuria, hematuria)
    - Unable to drink recommended amount of fluid
- Confirm that patient has received the CCMB Immune Checkpoint Inhibitor Medical Alert wallet card
- Reinforce to patient the immune-mediated adverse reactions and importance of reporting immediately
  - For severe symptoms, the patient should be instructed to go to the nearest emergency room. Oncologist should be contacted
- Reinforce applicable safe handling precautions of medications, blood and body fluids for 48 hours after completion of chemotherapy

### Phase 3 (pembrolizumab)

- Patients should be instructed to contact their cancer team immediately if symptoms of hypersensitivity reactions occur after discharge
- Confirm that patient has received the CCMB Immune Checkpoint Inhibitor Medical Alert wallet card
- Reinforce to patient the immune-mediated adverse reactions and importance of reporting immediately
  - For severe symptoms, the patient should be instructed to go to the nearest emergency room. Oncologist should be contacted

## ADDITIONAL INFORMATION

- pembrolizumab is an Immune Checkpoint Inhibitor. Consult with oncologist for immune-mediated adverse reactions; corticosteroids are often indicated
- PAclitaxel may cause progressive, irreversible neuropathy
- Cumulative DOXOrubicin dose should be calculated and should not exceed 360 mg/m<sup>2</sup>. If exceeding 360 mg/m<sup>2</sup>, consideration to adding dexrazoxane should be given if patient is benefiting from DOXOrubicin therapy
- **Note:** Upon completion of 4 cycles of BRST - [pemb + BrighTNess wkly Ph 1], patients should be started on BRST - [pembro + BrighTNess Phase 2] to complete 8 cycles of neoadjuvant therapy
  - BRST - [pembro + BrighTNess Phase 2] should begin 7 days after Cycle 4, Day 15 of BRST - [pemb + BrighTNess wkly Ph 1]
- **Note:** At Cycle 4 of Phase 1 and Phase 2 regimens, an entry called “*Physician Reminder-PembBRIGHTNESS protocol timing 1 Units Insert Miscellaneous once*” will appear in the electronic drug order. No action is required. **This prompt is to remind the prescriber to order the next regimen as part of the pembrolizumab + BrighTNess protocol**
- **Note:** At Cycle 3 of BRST - [pembro + BrighTNess Phase 2], an entry called “*Physician Reminder -Order morning cortisol and TSH 1 Units Insert Miscellaneous once*” will appear in the electronic drug order. No action is required. **This prompt is to remind the prescriber to order morning cortisol and TSH with Cycle 4 bloodwork as required by surgical oncologist prior to definitive surgery**
- **Note:** Upon completion of neoadjuvant chemotherapy and definitive surgery, patient should be placed on BRST - [pembro + BrighTNess Phase 3]. Adjuvant treatment usually starts between 30 to 60 days after surgery
- CARBOplatin dose considerations:
  - CCMB Breast DSG uses **actual body weight** to calculate GFR
  - CCMB Breast DSG uses a maximum CARBOplatin dose of 225 mg for this regimen
  - If calculated CARBOplatin dose differs **more than 10%** from prescribed CARBOplatin dose, contact the prescriber

CARBOplatin Dosing Calculations per CCMB Breast DSG		
<b>Calculation of CARBOplatin dose: (maximum 225 mg)</b>		
Dose (mg) = target AUC (GFR + 25)		
$\text{GFR} = \frac{N \times (140 - \text{age in years}) \times \text{Actual Body Weight (kg)}}{\text{serum creatinine in micromol/L}} = \text{___ mL/min}$		
N = 1.23 in males		
N = 1.04 in females		
AUC (mg/mL.min) <hr style="width: 50%; margin: 0 auto;"/> 1.5	X	GFR + 25 (mL/min) <hr style="width: 50%; margin: 0 auto;"/> ___ + 25
		=
		Total Dose (mg) <hr style="width: 50%; margin: 0 auto;"/>

AUC = Area Under Curve

*The estimated creatinine clearance is based on limited evidence. Sound clinical judgment and interpretation of the estimation are required, because the equation above may not be appropriate for some patient populations (for example, acute renal failure).*

### Appendix Dosing Schema

	Phase 1 – Cycle 1 (21-day cycle)				Phase 1 – Cycle 2 (21-day cycle)				Phase 1 – Cycle 3 (21-day cycle)				Phase 1 – Cycle 4 (21-day cycle)			
	Day	1	8	15	Day	1	8	15	Day	1	8	15	Day	1	8	15
pembrolizumab																
PACLitaxel																
CARBOplatin																

	Phase 2 – Cycle 1 (14-day cycle)			Phase 2 – Cycle 2 (14-day cycle)			Phase 2 – Cycle 3 (14-day cycle)			Phase 2 – Cycle 4 (14-day cycle)			Phase 3 – Cycles 1 to 5 (42-day cycle)						
	Day	1	8	Day	1	8	Day	1	8	Day	1	8	Day	1	8	15	22	29	36
pembrolizumab																			
DOXOrubicin																			
cyclophosphamide																			

**Key:**



Indicates that *pembrolizumab* will be administered on this day



Indicates that *chemotherapy* will be administered on this day