Regimen Reference Order – BRST – pembrolizumab + BrighTNess

ARIA: BRST - [pembro + BrighTNess Phase 1]
BRST - [pembro + BrighTNess Phase 2]
BRST - [pembro + BrighTNess Phase 3]

Planned Course: **Phase 1: pembrolizumab every 42 days + PACLitaxel (weekly) + CARBOplatin every 21 days 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 9) 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 x 10^9/L AND Platelets equal to or greater than 100 x 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 x 10^9/L AND Platelets equal to or greater than 100 x 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 x 10^9/L AND Platelets equal to or greater than 50 x 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**

***Note:** Hepatitis B serology results must be reviewed in accordance with CCMB Policy Hepatitis B Monitoring for Oncology and Hematology Patients*

SEQUENCE OF MEDICATION ADMINISTRATION

Pre-treatment Requirements

Drug	Dose	CCMB Administration Guideline
Phase 2 – AC (Dose Dense)		
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

Establish primary solution 500 mL of: normal saline

Drug	Dose	CCMB Administration Guideline
Phase 1 – pembrolizumab every 42 days + PACLitaxel (weekly) + CARBOplatin every 21 days (Cycles 1 to 4)		
Phase 1 - Cycles 1 and 3 ONLY		
Day 1		
pembrolizumab	4 mg/kg	IV in normal saline 100 mL over 30 minutes *Use 0.2 or 0.22 micron filter* **Alert: pembrolizumab only administered on Cycles 1 and 3 of Phase 1*
aprepitant	125 mg	Orally 1 hour pre-chemotherapy
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 **1 hour** prior to PACLitaxel **Nursing Alert: PACLitaxel starts **1 hour after completion** of dexamethasone infusion*
Wait 1 hour after completion of IV pre-medication(s) before starting PACLitaxel		
PACLitaxel	80 mg/m^2	IV in normal saline 250 mL over 1 hour, following the administration rates below: • Administer at 100 mL/hour for 15 minutes, then • Administer remaining volume over 45 minutes *Use non-DEHP bags and non-DEHP administration sets with 0.2 or 0.22 micron filter* **Alert: Gently invert bag 8 to 10 times immediately prior to administration of PACLitaxel to evenly distribute the drug*
CARBOplatin	AUC 5 mg/mL.min; maximum dose 750 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
dexamethasone	20 mg	IV in normal saline 50 mL over 15 minutes **1 hour** prior to PACLitaxel **Nursing Alert: PACLitaxel starts **1 hour after completion** of dexamethasone infusion*
Wait 1 hour after completion of IV pre-medication(s) before starting PACLitaxel		

PACLitaxel	80 mg/m^2	IV in normal saline 250 mL over 1 hour, following the administration rates below: • Administer at 100 mL/hour for 15 minutes, then • Administer remaining volume over 45 minutes *Use non-DEHP bags and non-DEHP administration sets with 0.2 or 0.22 micron filter* **Alert:* *Gently invert bag 8 to 10 times immediately prior to administration of PACLitaxel to evenly distribute the drug*
Phase 1 - Cycles 2 and 4 ONLY		
Day 1		
aprepitant	125 mg	Orally 1 hour pre-chemotherapy
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 **1 hour** prior to PACLitaxel **Nursing Alert:* *PACLitaxel starts **1 hour after completion** of dexamethasone infusion*
Wait 1 hour after completion of IV pre-medication(s) before starting PACLitaxel		
PACLitaxel	80 mg/m^2	IV in normal saline 250 mL over 1 hour, following the administration rates below: • Administer at 100 mL/hour for 15 minutes, then • Administer remaining volume over 45 minutes *Use non-DEHP bags and non-DEHP administration sets with 0.2 or 0.22 micron filter* **Alert:* *Gently invert bag 8 to 10 times immediately prior to administration of PACLitaxel to evenly distribute the drug*
CARBOplatin	AUC 5 mg/mL.min; maximum dose 750 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
dexamethasone	20 mg	IV in normal saline 50 mL over 15 minutes **1 hour** prior to PACLitaxel **Nursing Alert:* *PACLitaxel starts **1 hour after completion** of dexamethasone infusion*
Wait 1 hour after completion of IV pre-medication(s) before starting PACLitaxel		

PACLitaxel	80 mg/m^2	IV in normal saline 250 mL over 1 hour, following the administration rates below: • Administer at 100 mL/hour for 15 minutes, then • Administer remaining volume over 45 minutes *Use non-DEHP bags and non-DEHP administration sets with 0.2 or 0.22 micron filter* **Alert: Gently invert bag 8 to 10 times immediately prior to administration of PACLitaxel to evenly distribute the drug*
Phase 2 starts 1 week after Cycle 4, Day 15 of Phase 1 (pembrolizumab + PACLitaxel + CARBOplatin)		
Phase 2 – pembrolizumab every 42 days + AC (Dose Dense) every 14 days (Cycles 1 to 4)		
Establish primary solution 500 mL of: normal saline		
Phase 2 - Cycles 1 and 4 ONLY		
pembrolizumab	4 mg/kg	IV in normal saline 100 mL over 30 minutes *Use 0.2 or 0.22 micron filter* **Alert: 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^2	IV Push over 10 to 15 minutes
cyclophosphamide	600 mg/m^2	IV in normal saline 250 mL over 1 hour
Phase 2 - Cycles 2 and 3 ONLY		
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^2	IV Push over 10 to 15 minutes
cyclophosphamide	600 mg/m^2	IV in normal saline 250 mL over 1 hour
Phase 3 usually starts 30 to 60 days post-surgery		
Phase 3 – pembrolizumab every 42 days (Cycles 1 to 5)		
Establish primary solution 500 mL of: normal saline		
pembrolizumab	4 mg/kg	IV in normal saline 100 mL over 30 minutes *Use 0.2 or 0.22 micron filter*
Maximum pembrolizumab dose is 400 mg (every 42 days) 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

Hepatitis B serology

- Hepatitis B surface antigen and Hepatitis B core antibody (drawn within preceding 5 years)

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_2 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
- Full vital signs (temperature, heart rate, respiratory rate, blood pressure and O_2 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_2 saturation) at baseline and as clinically indicated
- No observation period required after pembrolizumab (Cycles 1 and 4) administration. 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_2 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
Phase 1 – pembrolizumab + PACLitaxel + CARBOplatin		
filgrastim (brand name specific) *(See Filgrastim Clinical Guide)*	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
aprepitant	80 mg	Orally once daily on Days 2 and 3
dexamethasone	8 mg	Orally once daily on Days 2 and 3
metoclopramide	10 – 20 mg	Orally every 4 hours as needed for nausea and vomiting
Phase 2 – pembrolizumab + AC (Dose Dense)		
pegfilgrastim (brand name specific) *(See Filgrastim Clinical Guide)*	6 mg	Subcutaneous once on Day 2 **Alert: pegfilgrastim to be given as a single dose once per chemotherapy cycle no sooner than 24 hours after chemotherapy*
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
Phase 3 – pembrolizumab		
None required		

DISCHARGE INSTRUCTIONS

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^2. If exceeding 360 mg/m^2, consideration to adding dexrazoxane should be given if patient is benefiting from DOXOrubicin therapy
- Due to the risk of reactivation of Hepatitis B virus (HBV) while on this treatment regimen, prescriber must adhere to CCMB Policy ***Hepatitis B Monitoring for Oncology and Hematology Patients*** for ordering and interpreting HBV serology and prescribing antiviral prophylaxis
- **ARIA ordering**:
    - **Note:** Upon completion of 4 cycles of **BRST - [pembro + BrighTNess Phase 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 - [pembro + BrighTNess Phase 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 750 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

Calculation of CARBOplatin dose: (maximum 750 mg)

Dose (mg) = target AUC (GFR + 25)

$$\text{GFR} = \frac{\text{N} \times (140 - \text{age in years}) \times \text{Actual Body Weight (kg)}}{\text{serum creatinine in micromol/L}} = \_\_\_ \text{ mL/min}$$

N = 1.23 in males

N = 1.04 in females

$$\frac{\text{AUC (mg/mL.min)}}{5} \times \frac{\text{GFR + 25 (mL/min)}}{\_\_\_\_ + 25} = \text{Total Dose (mg)}$$

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