

## Regimen Reference Order

### THOR – nivolumab + ipilimumab + PEMEtrexed + CARBOplatin

ARIA: LUNG – [nivo + ipi + PEME + CARBO]

LUNG – PEME Support (NSCLC)

**Planned Course:** Cycle 1: nivolumab + ipilimumab + PEMEtrexed + CARBOplatin, then  
 Cycle 2: nivolumab + PEMEtrexed + CARBOplatin, then  
 Cycle 3 and Onwards: nivolumab + ipilimumab alternating with nivolumab until  
 disease progression or unacceptable toxicity up to a maximum of 33 cycles  
 (1 cycle = 21 days)

**Indication for Use:** Lung Cancer Non-Small Cell Non-Squamous Metastatic

**Drug Alert:** Immune Checkpoint Inhibitor (nivolumab and ipilimumab)

**CVAD:** At Provider's Discretion

**Proceed with treatment if:**

**Cycles 1 and 2**

- ANC equal to or greater than  $1.5 \times 10^9/L$  AND Platelets equal to or greater than  $100 \times 10^9/L$
- AST/ALT equal to or less than 3 times the upper limit of normal
- Total bilirubin equal to or less than 1.5 times the upper limit of normal
- Creatinine clearance is equal to or greater than 45 mL/minute

**Cycle 3 and Onwards**

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

## SEQUENCE OF MEDICATION ADMINISTRATION

### Pre-treatment Requirements

Drug	Dose	CCMB Administration Guideline
folic acid	1 mg	Orally daily beginning 7 – 14 days prior to first dose of PEMEtrexed and continuing daily until 21 days after the last dose of PEMEtrexed (Self-administered at home)
vitamin B12	1000 mcg	Intramuscularly 7 – 14 days prior to first dose of PEMEtrexed (Note: vitamin B12 continues every 9 weeks until 6 weeks after last dose of PEMEtrexed [last dose Cycle 4, Day 1])
dexamethasone	8 mg	Orally once daily the day before, day of and the day after each dose of PEMEtrexed (Higher or additional doses are permitted) (Self-administered at home)

**Treatment Regimen – THOR – nivolumab + ipilimumab + PEMEtrexed + CARBOplatin**

Establish primary solution 500 mL of: normal saline

Drug	Dose	CCMB Administration Guideline
<b>Cycle 1 – nivolumab + ipilimumab + PEMEtrexed + CARBOplatin</b>		
nivolumab	4.5 mg/kg	IV in normal saline 100 mL over 30 minutes Use 0.2 or 0.22 micron filter <i>*Nursing Alert: After completion of nivolumab infusion, wait 30 minutes before administering ipilimumab</i> <i>*Nursing Alert: Start a new primary infusion line for ipilimumab</i>
ipilimumab	1 mg/kg	IV in normal saline 50 mL over 30 minutes Use 0.2 or 0.22 micron filter
aprepitant	125 mg	Orally 1 hour pre-chemotherapy
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
dexamethasone	4 mg	Orally 30 minutes pre-chemotherapy <i>*Nursing Alert: This dose is in addition to the 8 mg self-administered dose taken at home morning of Day 1</i>
PEMEtrexed	500 mg/m <sup>2</sup>	IV in normal saline 100 mL over 10 minutes <i>*Nursing Alert: CARBOplatin starts at least 30 minutes after completion of PEMEtrexed infusion</i>
CARBOplatin	AUC 5 mg/mL.min; maximum dose 750 mg (see table below)	IV in D5W 250 mL over 30 minutes
<b>Cycle 2 – nivolumab + PEMEtrexed + CARBOplatin</b>		
nivolumab	4.5 mg/kg	IV in normal saline 100 mL over 30 minutes Use 0.2 or 0.22 micron filter
aprepitant	125 mg	Orally 1 hour pre-chemotherapy
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
dexamethasone	4 mg	Orally 30 minutes pre-chemotherapy <i>*Nursing Alert: This dose is in addition to the 8 mg self-administered dose taken at home morning of Day 1</i>
PEMEtrexed	500 mg/m <sup>2</sup>	IV in normal saline 100 mL over 10 minutes <i>*Nursing Alert: CARBOplatin starts at least 30 minutes after completion of PEMEtrexed infusion</i>
CARBOplatin	AUC 5 mg/mL.min; maximum dose 750 mg (see table below)	IV in D5W 250 mL over 30 minutes

<b>Cycles 3 to 35</b> (Note: Cycles alternate between nivolumab + ipilimumab [odd Cycles] and nivolumab [even Cycles])		
<b>Cycles 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33 and 35 – nivolumab + ipilimumab</b>		
nivolumab	4.5 mg/kg	IV in normal saline 100 mL over 30 minutes Use 0.2 or 0.22 micron filter <i>*Nursing Alert: After completion of nivolumab infusion, wait 30 minutes before administering ipilimumab</i> <i>*Nursing Alert: Start a new primary infusion line for ipilimumab</i>
ipilimumab	1 mg/kg	IV in normal saline 50 mL over 30 minutes Use 0.2 or 0.22 micron filter
<b>Cycles 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 and 34 – nivolumab</b>		
nivolumab	4.5 mg/kg	IV in normal saline 100 mL over 30 minutes Use 0.2 or 0.22 micron filter
vitamin B12	1000 mcg	Cycle 4 Only: Intramuscular once <i>*Alert: This is the last dose of vitamin B12 that will be given as part of this regimen</i>
<b>Maximum nivolumab dose is 360 mg</b> All doses will be automatically rounded that fall within the DSG Approved Dose Bands. See THOR DSG – Dose Banding document for more information		

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

## REQUIRED MONITORING

### All Cycles

- CBC, serum creatinine, urea, electrolytes, liver enzymes, total bilirubin, albumin, glucose and TSH as per Physician Orders
- Cortisol levels should be checked prior to each ipilimumab dose (every second cycle) and at physician's discretion
- Medical oncologist or designate (i.e. family practitioner in oncology) must assess patient for immune-mediated adverse reactions prior to each cycle
- 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 is required after nivolumab or ipilimumab. 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>Cycles 1 and 2</b>		
aprepitant	80 mg	Orally once daily on Days 2 and 3
dexamethasone	8 mg	Orally once daily on Day 3 Note additional Pre-treatment Requirements for PEMEtrexed
metoclopramide	10 – 20 mg	Orally every 4 hours as needed for nausea and vomiting
<b>Cycles 3 to 35</b>		
None required		

## DISCHARGE INSTRUCTIONS

### All Cycles

- 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 on call should be contacted

### Cycles 1 and 2

- Instruct patient to continue taking folic acid, dexamethasone and anti-emetic(s) at home
- vitamin B12 is part of this treatment regimen. Patient should notify clinic if they are receiving vitamin B12 for other indications
- Reinforce applicable safe handling precautions of medications, blood and body fluids for 48 hours after completion of chemotherapy

**ADDITIONAL INFORMATION**

- Grade 3/4 toxicities are very common with this regimen
- folic acid, vitamin B12 and dexamethasone are prescribed to decrease PEMEtrexed toxicity
- During Cycles 1 and 2, dexamethasone is also prescribed post treatment for delayed nausea
- Non-Steroidal Anti-Inflammatory drugs (NSAIDs) may increase the toxicity of PEMEtrexed. Hold NSAIDs for 2 days before, the day of and for 2 days after PEMEtrexed
- Support protocol under **PEM Support (NSCLC)** in the “Lung Cancer” folder is to be used to order folic acid and the first dose of vitamin B12
- nivolumab and ipilimumab are Immune Checkpoint Inhibitors. Consult with oncologist for immune-mediated adverse reactions; corticosteroids are often indicated
- Administration site restrictions are in place for ipilimumab. ipilimumab should only be administered at a facility where pharmacy compounding occurs on site
- CARBOplatin dose considerations:
  - CCMB Thoracic DSG uses **actual body weight** to calculate GFR
  - CCMB Thoracic 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 Thoracic DSG**

*Calculation of CARBOplatin dose: (maximum 750 mg)*

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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;"/> 5	x	GFR + 25 (mL/min) <hr style="width: 50%; margin: 0 auto;"/> ___ + 25	=	Total Dose (mg) <hr style="width: 50%; margin: 0 auto;"/>
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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)*