Regimen Reference Order

THOR – nivolumab + ipilimumab + PEMEtrexed + CISplatin

ARIA: LUNG – [nivo + ipi + PEME + CIS]
LUNG – PEMEtrexed support (NSCLC)

Planned Course: **Cycle 1: nivolumab + ipilimumab + PEMEtrexed + CISplatin, then**
Cycle 2: nivolumab + PEMEtrexed and CISplatin, 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 x 10^9/L AND Platelets equal to or greater than 100 x 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 greater than 45 mL/minute***

Cycle 3 and Onwards

- ***ANC equal to or greater than 1.5 x 10^9/L AND Platelets equal to or greater than 50 x 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 + CISplatin

Establish primary solution 500 mL of: normal saline

Drug	Dose	CCMB Administration Guideline
Cycle 1 – nivolumab + ipilimumab + PEMEtrexed + CISplatin		
nivolumab	4.5 mg/kg	IV in normal saline 100 mL over 30 minutes *Use 0.2 or 0.22 micron filter* **Nursing Alert: After completion of nivolumab infusion, wait 30 minutes before administering ipilimumab* **Nursing Alert: Start a new primary infusion line for ipilimumab*
ipilimumab	1 mg/kg	IV in normal saline 50 mL over 30 minutes *Use 0.2 or 0.22 micron filter* **Nursing Alert: magnesium sulfate starts at least **30 minutes after completion** of ipilimumab infusion*
magnesium sulfate	2 g	IV in normal saline 1000 mL over 2 hours (Pre hydration)
aprepitant	125 mg	Orally 1 hour pre-chemotherapy
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
dexamethasone	4 mg	Orally 30 minutes pre-chemotherapy **Nursing Alert: This dose is in addition to the 8 mg self-administered dose taken at home morning of Day 1*
OLANZapine	2.5 mg	Orally 30 minutes pre-chemotherapy
PEMEtrexed	500 mg/m^2	IV in normal saline 100 mL over 10 minutes **Nursing Alert: CISplatin starts at least **30 minutes after completion** of PEMEtrexed infusion*
CISplatin	75 mg/m^2	IV in normal saline 500 mL over 1 hour **Alert: CISplatin infusion must be complete prior to mannitol administration*
mannitol	12.5 g	IV in normal saline 1000 mL over 2 hours (Post hydration)
Cycle 2 – nivolumab + PEMEtrexed + CISplatin		
nivolumab	4.5 mg/kg	IV in normal saline 100 mL over 30 minutes *Use 0.2 or 0.22 micron filter* **Nursing Alert: magnesium sulfate starts at least **30 minutes after completion** of nivolumab infusion*
magnesium sulfate	2 g	IV in normal saline 1000 mL over 2 hours (Pre hydration)
aprepitant	125 mg	Orally 1 hour pre-chemotherapy
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
dexamethasone	4 mg	Orally 30 minutes pre-chemotherapy **Nursing Alert: This dose is in addition to the 8 mg self-administered dose taken at home morning of Day 1*

OLANZapine	2.5 mg	Orally 30 minutes pre-chemotherapy
PEMEtrexed	500 mg/m^2	IV in normal saline 100 mL over 10 minutes **Nursing Alert: CISplatin starts at least **30 minutes after completion** of PEMEtrexed infusion*
CISplatin	75 mg/m^2	IV in normal saline 500 mL over 1 hour **Alert: CISplatin infusion must be complete prior to mannitol administration*
mannitol	12.5 g	IV in normal saline 1000 mL over 2 hours (Post hydration)
Cycles 3 to 35 (Note: Cycles alternate between nivolumab + ipilimumab [odd Cycles] and nivolumab [even Cycles])		
Cycles 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33 and 35 – nivolumab + ipilimumab		
nivolumab	4.5 mg/kg	IV in normal saline 100 mL over 30 minutes *Use 0.2 or 0.22 micron filter* **Nursing Alert: After completion of nivolumab infusion, wait 30 minutes before administering ipilimumab* **Nursing Alert: Start a new primary infusion line for ipilimumab*
ipilimumab	1 mg/kg	IV in normal saline 50 mL over 30 minutes *Use 0.2 or 0.22 micron filter*
Cycles 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 and 34 – nivolumab		
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 **Alert: This is the last dose of vitamin B12 that will be given as part of this regimen*
Maximum nivolumab dose is 360 mg 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_2 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

Cycles 1 and 2

- Baseline blood pressure immediately prior to magnesium infusion and repeat 15 minutes after start of magnesium infusion

Recommended Support Medications

Drug	Dose	CCMB Administration Guideline
Cycles 1 and 2		
aprepitant	80 mg	Orally once daily on Days 2 and 3
dexamethasone	8 mg	Orally once daily on Days 3 and 4 Note additional Pre-treatment Requirements for PEMEtrexed
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
Cycles 3 to 35		
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
- CISplatin is ototoxic and nephrotoxic
- CISplatin can cause hypomagnesemia
- 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 **PEME 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
- Due to long duration of administration, Cycles 1 and 2 can only be administered at CCMB MacCharles in Winnipeg