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Positive Quality Intervention: Durvalumab (Imfinzi®) Therapy Overview

Description: The purpose of this PQI is to discuss the overall management of durvalumab and immune-mediated adverse events in the treatment of Stage III unresectable NSCLC and first-line extensive stage small cell lung cancer.

Background: Durvalumab is a PD-L1 blocking monoclonal antibody and immune checkpoint inhibitor indicated for: the treatment of adult patients with unresectable stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy and in combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). In a clinical study known as the PACIFIC trial, patients with stage III, unresectable NSCLC who completed at least 2 cycles of concurrent platinum based chemotherapy and definitive radiation within 42 days prior to initiation of durvalumab demonstrated a 2-year OS rate of 66% for durvalumab vs 55% with placebo (HR=0.68) and an updated 4-year OS rate of 50% for durvalumab and 36% with placebo (HR=0.71).[1,2,6] The median duration of PFS in the trial was 17.2 months for the durvalumab group versus 5.6 months in the placebo group (see **Stage III NSCLC Disease Overview** PQI).[1,2] Within ES-SCLC, the CASPIAN study reported patients receiving durvalumab with chemotherapy (etoposide and either carboplatin or cisplatin) had a median OS of 13.0 months versus 10.3 with chemotherapy alone (HR=0.73). Durvalumab belongs to the class of drugs that bind either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of a T-cell-mediated immune response. Durvalumab also has the potential to break peripheral tolerance and induce immune-mediated adverse events (imAEs or imARs). These reactions can occur during or after treatment with durvalumab has been completed or discontinued. In the PACIFIC study, imAEs of any grade irrespective of cause were reported in 24% of patients receiving durvalumab vs 8 % of placebo. Similarly, in the CASPIAN study, 20% of patients in the durvalumab + chemotherapy arm experienced imAEs versus 3% in the comparator arm. It is important to recognize key and potential imAEs early when managing patients.[2,3]

PQI Process: Upon order of durvalumab:

- Verify dosing of durvalumab as an intravenous infusion over 60 minutes
  - Stage III NSCLC
    - Weight 30 kg and more: 10 mg/kg every 2 weeks or 1500 mg every 4 weeks
    - Weight less than 30 kg: 10 mg/kg every 2 weeks
  - Extensive-Stage small cell lung cancer (ES-SCLC)[1]
    - Weight >30kg: 1500 mg every 3 weeks in combination with chemotherapy for 4 cycles, then 1500 mg every 4 weeks as a single agent
    - Weight <30kg: 20 mg/kg every 3 weeks in combination with chemotherapy for 4 cycles, then 10 mg/kg every 2 weeks as a single agent
- Durvalumab comes in both 500 mg/10mL and 120 mg/2.4 mL (both 50 mg/mL) single-dose vials
- Withdraw the required volume from the vial(s) and transfer into intravenous bag containing 0.9% Sodium Chloride or 5% Dextrose, mixing diluted solution by gentle inversion (do NOT shake). Final concentration should be between 1 mg/mL-15 mg/mL
- Administer intravenously over 60 minutes through line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter
- Follow the table below for guidelines regarding immune mediated adverse reaction/events, dosage reduction is not recommended[1]

imAE	Withhold Durvalumab	Discontinue Durvalumab	Steroids
Pneumonitis	Grade 2*	Grade 3 or 4	Grade 2: Initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper Grade 3,4: Initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper
Colitis	Grade 2 or 3*	Grade 4	Grade 2, 3, 4: Initial dose of 1-2mg/kg/day prednisone or equivalent followed by a taper
Hepatitis with no tumor involvement of the liver	ALT or AST > 3 and up to 8x ULN* Or total bilirubin 1.5 and up to 3x ULN*	ALT or AST >8x ULN Or Total Bilirubin >3x ULN	Grade 2, 3, 4: Initial dose of 1-2mg/kg/day prednisone or equivalent followed by a taper
Hepatitis with tumor involvement of the liver	ALT/AST at baseline >1 and up to 3x ULN and increase to >5 and up to 10x ULN* Or ALT/AST at baseline >3 and up to 5x ULN and increase to >8 and up to 10x ULN*	ALT or AST >10x ULN Or Total Bilirubin >3x ULN	
General Guidance	Grade 3 imAE	Grade 4 imAe or recurrent Grade 3 imAE: Discontinue if complete/partial resolution does not occur or unable to reduce steroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks	For other imAE: Grade 4: Initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper
Endocrinopathies	Grade 3 or 4 withhold until stable	Grade 3 or 4: permanently discontinue depending on severity	Adrenal insufficiency hypophysitis/hypopituitarism Grades 2,3,4: Initiate 1–2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as indicated
Nephritis with renal dysfunction	Grade 2 or 3 increased blood creatinine*	Grade 4 increased blood creatinine	Grade 2,3,4: Initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper
SJS, TEN, or DRESS	Suspected	Confirmed	Grade 2,3,4: Initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper
Myocarditis	N/A	Grade 2, 3, or 4	
Neurological Toxicities	Grade 2*	Grade 3 or 4	
Infusion Related Reaction	Grade 1, 2: Interrupt/slow rate of infusion and consider using pre-medications with subsequent doses	Grade 3 or 4	

* Resume durvalumab in patients with complete or partial resolution (Grade 0 or 1) after corticosteroid taper[4,5]

- Additional Adverse Event Management
    - Reactions occurring for All Grades include cough (40%), pneumonitis (34%), dyspnea (25%), fatigue (34%), upper respiratory infections (26%), and rash (23%) with 15% discontinuation rate due to adverse reactions
    - Consider use of imAE Assessment Tool

Patient Centered Activities:

- Counsel patient on imAE symptoms and when to report symptoms to oncologist
- Schedule regular visits for blood tests (CBC, renal, hepatic, pancreatic, thyroid) and monitoring
- Consider early initiation of steroids as necessary
- Imfinzi® Nurse Center available
    - Nurse Symptom Tracker, imAR Handbook, Wallet Card, Patient Brochures, Dosing Guide, App
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. Imfinzi (durvalumab) [prescribing information]. Wilmington, DE. AstraZeneca Pharmaceuticals LP.
2. Antonia SJ, Villegas A, Daniel D, et al; for the PACIFIC Investigators. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med*. 2018;379:2342-2350.
3. Davies, M., Duffield E., Durvalumab Immunotherapy: Nursing Management of Immune-Related Adverse Events During the Journey of Patients With Stage III Non-Small Cell Lung Cancer. Clin J Oncol Nurs. 2020 Jun 1;24(3):277-283.
4. Santini FC, Rizvi H, Plodkowski AJ, et al. Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC.
5. Sheth S, Gao C, Mueller N, *et al*. Durvalumab activity in previously treated patients who stopped durvalumab without disease progression. *Journal for ImmunoTherapy of Cancer* 2020;8:e000650.
6. Faivre-Finn C, Vicente D, Kurata T, et al. Durvalumab after chemoradiotherapy in stage III NSCLC: 4-year survival update from the phase 3 PACIFIC trial. Presented at: 2020 ESMO Virtual Congress; September 19-21, 2020.