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, 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), unresectable hepatocellular carcinoma in combination with tremelimumab, and in combination with gemcitabine and cisplatin for adult patients with locally advanced or metastatic biliary tract cancer. 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). 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). 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-related adverse events (irAEs). These reactions can occur during or after treatment with durvalumab has been completed or discontinued. In the PACIFIC study, irAEs 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 irAEs versus 3% in the comparator arm. It is important to recognize key and potential irAEs early when managing patients.

**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 < 30 kg: 10 mg/kg every 2 weeks
  - Extensive-Stage small cell lung cancer (ES-SCLC)
    - 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

**IMPORTANT NOTICE:** NCODA has developed this Positive Quality Intervention platform. This platform is intended as an educational aid, does not replace the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication. The materials contained in this platform do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA. NCODA does not ensure the accuracy of the information presented and assumes no liability relating to its accuracy. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. It is the individual’s sole responsibility to seek guidance from a qualified healthcare professional. Updated 3.3.23
- Follow the table below for guidelines regarding immune related adverse reaction/events, dosage reduction is not recommended

<table>
<thead>
<tr>
<th>irAE</th>
<th>Withhold Durvalumab</th>
<th>Discontinue Durvalumab</th>
<th>Steroids</th>
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| 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 1-2 mg/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 1-2 mg/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 | For other irAE: Grade 4: Initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper |
| General Guidance                          | Grade 3 irAE         | Grade 4 irAE or recurrent Grade 3 irAE: 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 |
| 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

- 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 irAE Assessment Tool

Patient-Centered Activities:

- Provide Intravenous Cancer Treatment Education (IVE) Sheet
- Counsel patient on irAE 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
- Patient Assistance: NCODA Financial Assistance Tool

References:
1. Imfinzi (durvalumab) [prescribing information]. Wilmington, DE. AstraZeneca Pharmaceuticals LP.
5. 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.