Positive Quality Intervention: Darolutamide (Nubeqa) in combination with Docetaxel (Taxotere) for Metastatic Hormone Sensitive Prostate Cancer

Description: This PQI aims to provide information on the administration and management of adverse events, patient follow-up, and recommended dose reductions for darolutamide in combination with docetaxel for metastatic hormone sensitive prostate cancer (mHSPC).

Background: Darolutamide is an androgen receptor inhibitor. In preclinical studies, darolutamide does not appear to cross the blood-brain barrier, resulting in decreased neurological side effects, including seizures, which can be seen with other medications in this class. Docetaxel is a microtubule inhibitor. Darolutamide is indicated in combination with docetaxel for men with metastatic hormone-sensitive prostate cancer. The patient received 6 cycles of docetaxel, starting within 6 weeks of initiating darolutamide. Androgen deprivation therapy (ADT) should also be initiated within 12 weeks of starting therapy unless the individual has undergone bilateral orchiectomy. Median overall survival in the darolutamide plus docetaxel plus ADT arm has not yet been reached, but showed a 32% reduced risk of death, while docetaxel-plus-placebo arm was 48.9 month median overall survival (HR=0.68, 95% confidence interval [CI], 0.57-0.80). Time to disease progression 64% risk reduction compared to the control arm. Treatment with darolutamide and docetaxel resulted in a statistically significant delay in time to pain progression with time not yet being reached vs. 27.5 months respectively (HR = 0.79, 95% CI = 0.66–0.95). It was also noted that the addition of darolutamide does not significantly increase toxicity when added to ADT and docetaxel. Darolutamide is a generally well-tolerated drug. Serious Grade 3/4 adverse effects have an incidence of less than 1% in patients treated with darolutamide plus ADT alone but this doubles with the addition of docetaxel. It is important to distinguish chemotherapy side effects from darolutamide side effects and make appropriate dose modifications. NCCN has designated darolutamide plus docetaxel plus ADT as category 1 preferred regimen in mHSPC.

PQI Process:

- Start ADT within 12 weeks before administering darolutamide and docetaxel
- Initiate darolutamide at 600 mg twice daily with food
  - For patients with severe renal impairment (eGFR 15-29 mL/min) the recommended dose is 300 mg BID
  - For patients with moderate hepatic impairment (Child-Pugh class B) recommended dose is 300 mg BID
- Start docetaxel IV 75mg/m² every 3 weeks for 6 cycles within 6 weeks of initiating darolutamide

Darolutamide dose management:

- Treatment with darolutamide can be continued until disease progression/or unacceptable toxicity even if a dose of docetaxel is delayed, interrupted, or discontinued
- For severe renal impairment not receiving hemodialysis (GFR 15-29 mL/min/1.73 m²) reduce dose to 300 mg BID
- Hold darolutamide or dose reduce to 300 mg BID for grade 3 adverse reaction; may be resumed at 600 mg twice per day once the adverse reaction returns to baseline
- Doses under 300 mg twice a day are not recommended

Permanently discontinue darolutamide in the event of:

- Grade 3-4 ischemic heart disease
- Development of seizures during darolutamide therapy
Clinical pearls

- Optimize cardiovascular risk factor management - hypertension, diabetes, dyslipidemia
- Use effective contraception during treatment and for 1 week post last dose of darolutamide
- Avoid using darolutamide with a combined P-gp and strong or moderate CYP3A4 inhibitor/inducer
  - If combination is necessary, monitor patient more frequently
- Review prescribing information of the BCRP, OATP1B3, OATP 1B1 substrates when used concomitantly with darolutamide

Docetaxel dose management

- Administer drug when ANC is at least 1500 cells/mm³ or higher
- Dose reduce to 60 mg/m² if the patient experiences febrile neutropenia, ANC of <500 cells/mm³ for more than 1 week, severe or cumulative skin toxicities, or moderate neurotoxicity
- If the patient continues to experience the above side effects at 60 mg/m² the treatment should be discontinued
- Grade 3 liver dysfunction - reduce docetaxel by 20%
- Permanently discontinue docetaxel in the event of:
  - Grade 4 liver dysfunction
  - Severe hypersensitivity reaction to docetaxel

Clinical pearls

- Monitor for fluid retention, and manage per institution guidelines
- Be aware of the irritant/vesicant potential of docetaxel and consider central line in patients with poor IV access
- Pre-medicate with oral dexamethasone 8 mg twice daily x 3 days, starting the day before docetaxel administration
- Consider prophylactic pegfilgrastim 24 hours post docetaxel due to risk for febrile neutropenia

Patient-Centered Activities:

- Provide darolutamide Oral Chemotherapy Education Sheet and docetaxel Intravenous Cancer Treatment Education Sheet
- Side effects of combination therapy with darolutamide and docetaxel include neutropenia, neutropenic fevers, musculoskeletal pain, constipation, decreased appetite, rash, bleeding, weight gain, and hypertension
- Discuss risk for serious side effects including severe infusion reaction, development of seizures, and ischemic heart disease
- Ensure proper contraception and pregnancy protection is used and ensure the patient is aware that fertility may be impaired
- Provide education on temperature monitoring, whom to call if fever develops, and neutropenic precautions
- Recommend that patient immediately report any new or worsening symptoms
- Discuss the possible need for dose modifications of darolutamide, docetaxel, or both due to side effects
- Ensure the patient is aware of the use of steroids to prevent anaphylaxis and fluid retention associated with docetaxel

Reference: