Written By: Ann Schwemm, PharmD, MPH, BCOP
University of Minnesota Health

Positive Quality Intervention: CDK4/6 Inhibitors in HR+/HER2- Advanced Breast Cancer

Description: Cyclin-dependent kinase (CDK) 4/6 inhibitors have demonstrated significant advances in the treatment of hormone receptor (HR) positive and human epidermal growth factor receptor (HER2) negative advanced breast cancer. While current available data do not support the preferential use of one agent over the other, the dosing and safety monitoring differ and may help in treatment decision making with patients. Multi-disciplinary care teams have key roles in education and supportive care management to optimize the use of these agents and disease response.[1,2]

Background: Patients with HR+/HER2- advanced breast cancer should be considered candidates for CDK inhibitors (CDKi) therapy (palbociclib,[3] ribociclib,[4] and abemaciclib[5]) due to the progression free survival (PFS) advantages demonstrated in the PALOMA,[6,7] MONALEESA,[8,9] and MONARCH[10,11,12] trials. A recent meta-analysis of the trials evaluating CDKi in HR+/HER2- advanced breast cancer demonstrated a 50% reduction in the rate of disease progression when CDKis were used in the first or second line setting irrespective of age, site of metastasis, and disease free interval.[13] In addition, a publication of long term follow up of PALOMA-2 reported the safety profile remained favorable and with no differences in patient reported quality of life with the addition of palbociclib to endocrine therapy (ET) over time.[14] CDKis work at CDK 4/6 resulting in the blockade of phosphorylation of the retinoblastoma (Rb) protein which hinders the activation of transcription factors involved in S-phase entry, arresting the cell cycle progression at G1-phase.[15]

PQI Process: Upon receipt of an order for a CDK inhibitor:

- Ensure the patient has HR+/HER2- advanced breast cancer
- If patient had recently been on endocrine only therapy and experienced disease recurrence or progression, ensure endocrine therapy was changed along with prescribing of CDKi; new hormonal therapy can be started while access to new CDKi is in process
- There is no data to support continued CDKi use following disease progression; although switching from one to another due to tolerability is appropriate
- Assessment of drug interaction should be reviewed at baseline and throughout therapy
    - CDKi are cytochrome P450 3A4 substrates; medication lists should be reviewed and alternatives discussed for strong inhibitors/inducers and the use of moderate CYP3A4 inducers/inhibitors should be reviewed and adjustments in dose and/or monitoring discussed
- Due to the high rate of dose interruptions, care coordination is critical to ensure laboratory monitoring and assessments are occurring at appropriate times to avoid unnecessary holds while ensuring the safe monitoring; if a cycle is delayed, future labs should be adjusted from the true start of the current cycle
- A 7 day follow up should be conducted for all CDKis, especially abemaciclib for diarrhea management
- Midcycle CBC is recommended for ribociclib and palbociclib
- EKG is recommended every 2 weeks for ribociclib for the first 2 cycles
- Refer to Abemaciclip (Verzenio®) Diarrhea Management PQI for side effect management

Patient Centered Activities:

- Provided Oral Chemotherapy Education (OCE) Sheet for CDK 4/6 inhibitor and hormonal therapy to patient, as well as Oral Chemotherapy Education Supplemental Sheet
- Ensure patients are aware their hormonal therapy does not stop when holding CDKi therapy

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- Provide patient expectations of therapeutic assessment and laboratory monitoring when starting therapy, especially during first 8 weeks
- Educate that more than half of patients will require dose interruption or reduction, although ADRs generally resolve rapidly
- Review with patients as they require dose reductions there is no dose response established with CDKi; regardless of dose, patients can continue to experience efficacy
- Refer to *Table 1 of Supplemental Information* for drug-specific dosing, monitoring, and counseling
- Provided instructions for use of loperamide and potentially provide a prescription for diphenoxylate/atropine for patients prescribed abemaciclib
- All medications should be stored in a cool dry place at room temperature; if dispensed in blister packaging, CDKis should stay in original packaging
- Take medication at approximately the same time each day, do not double doses if one is forgotten
- Patient Assistance: NCODA Financial Assistance Tool

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Supplemental Information:

Table 1: Dosing and Monitoring Guideline Summary

	Palbociclib	**Ribociclib**	**Abemaciclib**
FDA Indication	HR+/HER2- advanced or metastatic breast cancer in combination with • An AI as initial ET therapy in postmenopausal women/men • Fulvestrant in adults with disease progression following ET	HR+/HER2- advanced or metastatic breast cancer in combination with • An AI as initial ET for pre/peri or postmenopausal women • Fulvestrant as initial ET or following disease progression on ET for postmenopausal women	HR+/HER2- advanced or metastatic breast cancer in combination with • An AI as initial ET in postmenopausal women/men • Fulvestrant in adults with disease progression following ET • Monotherapy after progression on ET and chemo in metastatic setting
Dosing	125 mg daily with food 21 days on/7 days off + continuous ET	600 mg daily qam without regards to meals 21 days on/7 days off + continuous ET	200 mg twice daily monotherapy OR 150 mg twice daily without regards to meals + continuous ET
Monitoring			
CBC w/diff:	D 1&15 cycles 1&2,then prior to each cycle x 4, then Q3 months* if no grade 3/4 neutropenia within first 6 months		D 1&15 cycles 1&2,then prior to each cycle x 2
LFTs/Tbili:	NA	Every 2 weeks x 4, then monthly x 4, then every 3months or as clinically indicated	Every 2 weeks x 4, then monthly x 2 (same as CBC), then every 3months or as clinically indicted
Electrolytes (BMP)	NA	Monthly x 6	NA
EKG:	NA	Every 2 weeks x 3; <450msec to initiate, refer to PI for management after initiation	NA
Neutropenia Management	*Day 1 of each cycle* must have ANC ≥1.0 to start *D15 first 2 cycles*: ANC 0.5-1.0 continue and recheck day 22; if <0.5 at day 22: start next cycle at reduced dose once improves to grade 2. At any time: ANC<1.0 with fever or <0.5: hold, resume at reduced dose once returns to grade ≥2		Day 1 *of each cycle*: must have ANC ≥1.0 to start. Interrupt therapy until recovered, then resume at same dose if grade 3 ANC was experienced on Day 1 or at reduced dose if grade 4 or recurrent grade 3

	Palbociclib	**Ribociclib**	**Abemaciclib**
Hepatobiliary Management (onset: 2-6 months)	N/A	LFTs>3-5xULN AND Tbili<2xULN: interrupt until returns to baseline, restart at same dose; If recurrence: resume at dose reduction** LFTs>5-20xULN AND Tbili<2xULN: interrupt therapy until return to baseline, restart at dose reduction; Grade 3 recurrence, discontinue. LFTs>20xULN: Discontinue	LFTs >3-5xULN AND Tbili<2xULN: no interruption; if recurrence: consider interruption and dose reduction** LFTs>5-20xULN AND Tbili<2xULN: interrupt therapy until resolution to baseline or grade 1, restart at dose reduction LFTs>20xULN: Discontinue
Dose Reductions	125 mg→100 mg→75 mg daily 21 days on/7 days off 75 mg 14 days on/14 days off has been reported	600 mg→400 mg→200 mg daily 21 days on/7 days off	200 mg→150 mg→100 mg→50 mg twice daily continuously (200 mg if monotherapy)
Adjustments at treatment initiation	Hepatic: Child Pugh Class C: reduce to 75 mg daily 21 days on/7 days off	Hepatic: Child Pugh Class B or C: reduce to 400 mg daily 21 days on/7 days off	Hepatic: Child Pugh Class C: reduce to once daily dosing
	Renal: Not studied <15ml/min, not anticipated to impact metabolism	Renal: eGFR 15-30ml/min reduce to 200 mg; not studied <15ml/min	Renal: Not studied <30ml/min, not anticipated to impact metabolism. SCr increases anticipated after initiation, not anticipated to reflect change in renal function.[1] Assess along with severity of diarrhea
Drug-Drug Interaction: Strong CYP3A4 inhibitors and inducers should be avoided, including grapefruit. Moderate CYP3A4 inhibitors and inducers should be discussed with prescribers			
Assessment to review:	Fevers, chills, dizziness; SOB, weakness; unusual bruising or bleeding; chest pain, tachypnea, tachycardia; adherence; laboratory values		
	At week 1: adherence and ensuring day 15 labs to be complete		At week 1: N/V, diarrhea, utilization of antidiarrheals

*Grade 3 anemia can occur late, therefore continued periodic monitoring is recommended.

**Dose reductions are not warranted if baseline liver function tests are grade 2 at baseline; grade 2 AST/ALT with Tbili elevation (in absence of cholestasis) therapy should be discontinued.