National Community Oncology Dispensing Association, Inc.
PASSION FOR PATIENTS

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Updated 7/1/19

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, ribociclib, and abemaciclib) due to the progression free survival (PFS) advantages demonstrated in the PALOMA, MONALEESA, and MONARCH trials, summarized in *Table 2 of Supplemental Information within this PQI.* 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[5]. In addition, a recent 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 over time[11]. 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.[3]

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.

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- Assessment of drug interaction should be reviewed at baseline and throughout therapy as new medication are prescribed.
    - CDKi are cytochrome P450 3A4 substrates. Medication lists should be reviewed and alternatives discussed for strong inhibitors/inducers. The use of moderate CYP3A4 inducers/inhibitors should be reviewed and adjustments in dose and/or monitoring discussed with patients and providers.
- Due to the high rate of dose interruptions, care coordination is critical to ensure laboratory monitoring and assessments are occurring at appropriate times in order 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 one week assessment should be conducted for all CDKis, especially to support abemaciclib diarrhea management.
- Midcycle CBC is recommended for ribociclib and palbociclib
- EKG is recommended every 2 weeks for ribociclib for the first 2 cycles.

Patient Centered Activities:

- Provided Oncology Chemotherapy Education Sheet for their CDKi and hormonal therapy to patient.
- Ensure patients are aware their hormonal therapy does not stop when dose interruptions of CDKi therapy occur.
- Provide patient expectations of therapeutic assessment and laboratory monitoring when starting therapy, especially during first 8 weeks. Review 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 within this PQI* 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.
    - Provide antidiarrheal management guidance per Abemaciclib Diarrhea Management PQI.

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- 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:

- Copay cards: abemaciclib: https://www.verzenio.com/savings-support/savings-card
  palbociclib: https://www.ibrance.com/financial-support-resources
  ribociclib: https://www.copay.novartisoncology.com/?name=kisqali

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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 • Letrozole as initial endocrine-based therapy in postmenopausal women • Fulvestrant in women with disease progression following endocrine therapy	HR+/HER2- advanced or metastatic breast cancer in combination with • An AI as initial endocrine-based therapy for pre/peri or postmenopausal women • Fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy for postmenopausal women	HR+/HER2- advanced or metastatic breast cancer in combination with
Dosing	125 mg daily with food 3 wk on/1 wk off w/ continuous ET	600 mg daily qam without regards to meals 3 wk on/1 wk off w/ continuous ET	200mg daily monotherapy OR 150mg daily without regards to meals w/ continuous ET
Monitoring			
CBC w/diff:	D1&15 cycles 1&2,then Qcycle x 4, then Q3 mos* if no gr 3/4 neutropenia within first 6mos		D1&15 cycles 1&2,then Qcycle x 2
LFTs/Tbili:	NA	Q2wk x 4, then Qmos x 4, then Q3mos or as clinically indicated	Q2wk x 4, then Qmos x 2 (same as CBC), then Q3mos or as clinically indicted
Electrolytes (BMP)	NA	Qmos x 6	NA
EKG:	NA	Q2wk 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 w fever or <0.5: hold, initiate at reduced dose once returns to gr ≥2		Day 1 *of each cycle*: ANC ≥1.0 to start. Interrupt therapy until patient meets criteria at same dose if grade 3 ANC was experienced on Day 1 or at reduced dose if grade 4 or recurrent grade 3

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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; Gr 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	125mg→100mg→75mg daily 3 wk on/1 wk off 75mg 2 wk on/2 wk off has been reported	600mg→400mg→200mg daily 3 wk on/1 wk off	200mg→150mg→100mg→50mg twice daily continuously (200mg if monotherapy)
Adjustments at treatment initiation	Hepatic: Child Pugh Class C: reduce to 75mg daily 3 wk on/1 wk off	Hepatic: Child Pugh Class B or C: reduce to 400mg daily 3 wk on/1 wk 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 200mg; 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.
	DDIxn: 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

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Table 2: Clinical Trial Summary

	Patient Population	Description	Outcome
Paloma-1/ Trio-18[6,7]	Phase II 1st line Post-menopausal HR+/HER2-	Letrozole vs Letrozole + Palbociclib	ORR: 39% vs 55% PFS: 10.2 vs 20.2 months OS: 33.3 vs 37.5 months*
Paloma-2[10,11]	Phase III 1st line Post-menopausal HR+/HER2-	Letrozole + Placebo vs Letrozole + Palbociclib	ORR: 44% vs 55% PFS 14.5 vs 27.6 months
Paloma-3[16,17]	Phase III 2nd line or later Post-menopausal HR+/HER2-	Fulvestrant + placebo vs Fulvestrant + Palbociclib	PFS 4.6 vs 9.5 months OS: 28.0 vs 34.9 months OS: 29.7 vs 39.7 months (in those w/prior sensitivity to endocrine therapy)
Monaleesa-2[14]	Phase III 1st line Post-menopausal HR+/HER2-	Letrozole + Placebo vs Letrozole + Ribociclib	ORR: 39% vs 55% PFS: 16 vs 25.3 months
Monaleesa-7[22]	Phase III 1st line Pre- and peri-menopausal HR+/HER2-	OFS/AI or Tamoxifen + Ribociclib vs OFS/AI or Tamoxifen + Placebo	ORR: 36% vs 51% PFS 13.0 vs 23.8 months
Monalessa-3[19]	Phase III 1st line or 2nd line HR+/HER2-	Fulvestrant + Placebo vs Fulvestrant + Ribociclib	ORR: 36% vs 51% PFS: 18.3 vs NR*1st line ORR: 19 vs 41% PFS: 12.8 vs 20.5 months
MONARCH-1[20]	Phase II 3rd line or later HR+/HER2-	Abemaciclib monotherapy	ORR: 20% PFS: 6.0 months OS: 22 months
MONARCH-2[21]	Phase III 2nd line** Pre-/Peri-/Post-	Fulvestrant + Placebo vs Fulvestrant + abemaciclib	ORR: 21 vs 48% PFS: 9.3 vs 16.4months

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	menopausal HR+/HER2-		
MONARCH-3[18]	Phase III First Line Post-menopausal HR+/HER2-	NSAI + Placebo vs NSAI + Abemaciclib	ORR: 44 vs 59% PFS: 14.7 vs 28.18 months

*not statistically significant, potentially due to small population
**Progression during neo-adjuvant/adjuvant ET, <12months from end of adjuvant ET or during 1st line ET for advanced breast cancer treatment.

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