From publication to practice: How trial data translate to clinical use of CDK4/6 inhibitors in patients with HR+/HER2- advanced breast cancer

CDK, cyclin-dependent kinase; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

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What factors can help determine which CDK4/6 inhibitor to prescribe?

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CDK, cyclin-dependent kinase.

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Overall survival in HR+/HER2- ABC across Phase III RCTs

Trial	MONALEESA-7[1]	MONALEESA-3[2]	MONARCH-2[3]	PALOMA-3[4]
Treatment	Ribociclib	Ribociclib	Abemaciclib	Palbociclib
Endocrine therapy	NSAI/tamoxifen (+ goserelin)	Fulvestrant	Fulvestrant	Fulvestrant
Participants (N)	672	726	669	521
OS (hazard ratio, 95% CI)	0.71 (0.54, 0.95)	0.72 (0.57, 0.92)	0.757 (0.606, 0.945)	0.81 (0.64, 1.03)
p value	0.00973	0.00455	0.01	0.09

ABC, advanced breast cancer; CI, confidence interval; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; RCT, randomized controlled trial.

1. Im SA, et al. *N Engl J Med*. 2019;381:307–16. 2. Slamon D, et al. *N Engl J Med*. 2020;382:514–24. 3. Sledge GW, et al. *JAMA Oncol*. 2019;e194782. doi:10.1001/jamaoncol.2019.4782 [Epub ahead of print]. 4. Turner NC, et al. *N Engl J Med*. 2018;379:1926–36.

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Menopause status	Pre or peri	Post	Any	Any
Eligibility based on prior ET	No prior ET for advanced disease	Treatment naïve or ≤1 ET for advanced disease, or relapse ≤12 mo from end of neoadj/adj ET	PD on neoadj/adj ET, ≤12 mo from end of adj ET or on first-line ET for advanced disease	PD on prior ET for metastatic disease

ABC, advanced breast cancer; adj, adjuvant ; CI, confidence interval; ET, endocrine therapy; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; mo, months; neoadj, neoadjuvant; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; PD, progressive disease; RCT, randomized controlled trial.

1. Im SA, et al. *N Engl J Med*. 2019;381:307–16. 2. Slamon D, et al. *N Engl J Med*. 2020;382:514–24. 3. Sledge GW, et al. *JAMA Oncol*. 2019;e194782. doi:10.1001/jamaoncol.2019.4782 [Epub ahead of print]. 4. Turner NC, et al. *N Engl J Med*. 2018;379:1926–36.

Impact of sensitivity to previous hormonal therapy on overall survival: An example from PALOMA-3[1]

Sensitivity to previous hormonal therapy*	No. of patients (%)	Hazard ratio (95% CI)	Median OS, months (95% CI)	
			Palbociclib + fulvestrant	Placebo + fulvestrant
Yes	410 (79)	0.72 (0.55, 0.94)	39.7 (34.8, 45.7)	29.7 (23.8, 37.9)
No	111 (21)	1.14 (0.71, 1.84)	20.2 (17.2, 26.4)	26.2 (17.5, 31.8)
p value for interaction		0.12		

OS based on prior response to ET was also assessed in MONALEESA-3:[2†]

- Endocrine naïve (n=213), HR=0.64 (95% CI 0.38, 1.05)
- Endocrine sensitive (n=429), HR=0.74 (95% CI 0.55, 1.01)
- Endocrine resistant (n=78), HR=0.70 (95% CI 0.37, 1.33)

In MONARCH-2, OS was compared in patients with primary and secondary resistance to ET:[3‡]

- Primary resistance (n=172), HR=0.686 (95% CI 0.451, 1.043)
- Secondary resistance (n=488), HR=0.787 (95% CI 0.606, 1.021)

*Patients were defined as sensitive to prior endocrine therapy if they had a relapse after 24 months of adjuvant ET or had a clinical benefit (objective response [complete or partial] or stable disease lasting ≥24 weeks) from prior ET in the context of advanced disease.
†Naïve - patients who didn't receive ET in any setting; Resistant - patients with progressive disease within the first 6 months of first-line ET for advanced breast cancer while on ET or patients with relapse within the first 2 year of (neo)adjuvant therapy; Sensitive – all remaining patients.
‡Primary - patients whose disease relapsed during the first 2 years of neoadjuvant or adjuvant ET or progressed within the first 6 months of first-line ET; Secondary: patients who did not meet the criteria for primary ET.
CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; OS, overall survival.
1. Turner NC, et al. *N Engl J Med*. 2018;379:1926–36. 2. Supplement to: Slamon DJ, et al. *N Engl J Med*. 2020;382;514-24. 3. Sledge GW, et al. *JAMA Oncol*. 2019;e194782. doi:10.1001/jamaoncol.2019.4782 [Epub ahead of print]

Safety considerations for CDK4/6 inhibitors

	Abemaciclib[1]	Palbociclib[2]	Ribociclib[3,4]
Neutropenia (grade 3/4), %	25.4	68.4	58.6
Diarrhoea (grade 3/4), %	11.7	1.0	2.4
Cardiac considerations	Grade 3/4 VTE in 2% of patients		QTcF interval increase >60 msec from baseline in 7.3% of patients receiving ribociclib plus NSAI
Drug–drug interactions	Avoid strong CYP3A4 inhibitors and CYP3A4 inducers		• Avoid strong CYP3A4 inhibitors and strong CYP3A4 inducers • Avoid drugs with known potential to prolong QT interval • Can inhibit activities of drug transporters P-gp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1 and BSEP
Special warnings	Permanently discontinue CDK4/6 inhibitors in patients with severe ILD/pneumonitis		

BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CDK, cyclin-dependent kinase; CYP3A4, cytochrome P450 3A4; GI, gastrointestinal; ILD, interstitial lung disease; MATE1, multidrug and toxin extrusion protein 1; NSAI, non-steroidal aromatase inhibitor; OATP1B1/1B3, organic anion-transporting polypeptide 1B1 and 1B3; OCT, organic cation transporters; P-gp, P-glycoprotein; QTcF, corrected QT interval by Fridericia; VTE, venous thromboembolism.

1. Abemaciclib Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/9532 (Accessed February 2020). 2. Palbociclib Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/7946 (Accessed February 2020). 3. Ribociclib Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/8110 (Accessed February 2020). 4. Hortobagyi GN, et al. *Ann Oncol.* 2018;29:1541–7.

Dosing schedules for CDK4/6 inhibitors

CDK4/6 inhibitor	Dose
Abemaciclib[1]	150 mg BID*
Palbociclib[2]	125 mg QD for 21 consecutive days followed by 7 days off treatment
Ribociclib[3]	600 mg (three 200 mg film-coated tablets) QD for 21 consecutive days followed by 7 days off treatment

Dose reductions with ribociclib can be done immediately without waiting for a new prescription[4]

*When used in combination with endocrine therapy.
BID, twice daily; CDK, cyclin-dependent kinase; QD, once daily.
1. Abemaciclib Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/9532 (Accessed February 2020). 2. Palbociclib Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/7946 (Accessed February 2020). 3. Ribociclib Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/8110 (Accessed February 2020). 4. Spring LM, et al. *Curr Oncol Rep*. 2019;21:25.