Exploring Clinical Updates in HR+/HER2- Breast Cancer Treatment and the Impact on Patient Care

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Faculty and Staff Disclosures

Danielle Roman, PharmD, BCOP, has no relevant financial relationships with commercial interests to disclose.

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Patient Perspective

The *PT*CE planning staff would like to thank Lesley Kailani Glenn for sharing her story.

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Educational Objectives for Pharmacists

After completion of this activity, participants will be able to:

- Dissect emerging investigational approaches and long-term follow-up data for HR+ breast cancer treatment strategies
- Explore recent data supporting and investigating the use of CDK4/6 inhibitors for the treatment of HR+/HER2- breast cancer in the adjuvant setting
- Apply management and monitoring recommendations to therapeutic treatment strategies to support outcomes and quality of life in patients with HR+ breast cancer

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Educational Objectives for Pharmacy Technicians

After completion of this activity, participants will be able to:

- Recall emerging investigational approaches and long-term follow-up data for HR+ breast cancer treatment strategies
- Describe the rationale for use of CDK4/6 inhibitors for the treatment of HR+/HER2- breast cancer in the adjuvant setting
- Outline the pharmacy technician's role in supporting the pharmacist in the management and monitoring of therapeutic treatment strategies for patients with HR+ breast cancer

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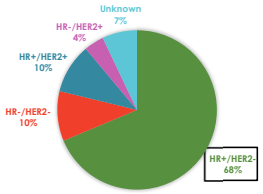
Breast Cancer: Epidemiology

- 287,850 new cases of female breast cancer in 2022
- HR+/HER2- is the most common subtype and has the best survival pattern
  - Highest rate of new cases in non-Hispanic White women

HR+/HER2- Breast Cancer

Stage at diagnosis	5-year relative survival (%)
All stages	94.4
Localized	100
Regional	90.1
Distant	31.9



HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

Cancer Statistics Explorer Network. National Cancer Institute (NCI). Accessed July 13, 2022. seer.cancer.gov/statistics-network; Cancer stat facts: female breast cancer subtypes. NCI. Accessed July 13, 2022. seer.cancer.gov/statfacts/html/breast-subtypes.html

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Introduction and Diagnosis

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Clinical Updates for HR+/HER2- Metastatic Breast Cancer

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Metastatic HR+/HER2- Breast Cancer: Treatment Overview

Treatment may include the following modalities:

Endocrine therapy (ET)

Chemotherapy

Targeted therapy

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, V.4.2022. © National Comprehensive Cancer Network, Inc., 2022.

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Options for Endocrine ± Targeted Therapy

1st Line (Preferred Options)	2nd and Subsequent Lines (Preferred Options)	Any Line of Therapy (Other Recommended)
• CDK4/6 inhibitor + AI • CDK4/6 inhibitor + SERD (fulvestrant) • Fulvestrant + nonsteroidal AI (anastrozole, letrozole)	• CDK4/6 inhibitor + fulvestrant • Alpelisib + fulvestrant (if PIK3CA mutation) • Everolimus + ET	• SERD • Nonsteroidal AI • Steroidal AI (exemestane) • SERM (tamoxifen)

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinases 4 and 6; ET, endocrine therapy; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, V.4.2022. © National Comprehensive Cancer Network, Inc., 2022.

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PALOMA Trials: Palbociclib

All patients were HR+/HER2- with advanced/metastatic breast cancer

	PALOMA-2	PALOMA-3
Arms	**Palbociclib + letrozole vs placebo + letrozole**	**Palbociclib + fulvestrant vs placebo + fulvestrant**
Patient population	Postmenopausal (n = 666)	Pre- and postmenopausal (n = 521)
Line of therapy	1st	2nd or subsequent (progression on ET)
Primary end point	PFS = 27.6 mo in palbociclib arm vs 14.5 mo in placebo arm (HR, 0.56; *P* <0.0001)	PFS = 9.5 mo in palbociclib arm vs 4.6 mo in placebo arm (HR, 0.46; *P* <0.0001)
Key secondary end point	OS = 53.9 mo in palbociclib arm vs 51.2 mo in placebo arm (HR, 0.956; 95% CI, 0.777-1.177)	Median OS = 34.9 mo in palbociclib arm vs 28 mo in placebo arm (*P* = 0.0221)

mo, months; OS, overall survival; PFS, progression-free survival.

Finn RS, et al. *J Clin Oncol.* 2022;40(suppl 17):Abstr LBA1003; Cristofanilli M, et al. *Lancet Oncol.* 2016;17:425-439; Turner NC, et al. *N Engl J Med.* 2018;379:1926-1936; Cristofanilli M, et al. *J Clin Oncol.* 2021;39(15 suppl):Abstr 1000.

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MONALEESA Trials: Ribociclib

All patients were HR+/HER2- with advanced/metastatic breast cancer

	MONALEESA-2	MONALEESA-3	MONALEESA-7
Arms	**Ribociclib + letrozole vs placebo + letrozole**	**Ribociclib + fulvestrant vs placebo + fulvestrant**	**Ribociclib + ET (tamoxifen or AI) or placebo + ET**
Patient population	Postmenopausal (n = 668)	Postmenopausal (n = 726)	Premenopausal (n = 672)
Line of therapy	1st	1st or 2nd	1st line ET but may have received 1 previous line chemo for advanced
Primary end point	PFS = 25.3 mo ribociclib arm vs 16 mo placebo arm (HR, 0.568; $P = 9.63 \times 10^{-8}$)	PFS = 20.5 mo ribociclib arm vs 12.8 mo in placebo arm (HR, 0.593; *P* <0.001)	PFS = 23.8 mo ribociclib arm vs 13 mo placebo arm (HR, 0.55; *P* <0.0001)
Key secondary end point	Median OS = 63.9 mo ribociclib arm vs 51.4 mo placebo arm (HR, 0.76; *P* = 0.008)	Median OS = 53.7 mo ribociclib arm vs 41.5 mo placebo arm (HR, 0.73) **Statistically significant.*	OS at 42 mo = 70.2% in ribociclib arm vs 46% placebo arm (HR, 0.71; *P* = 0.00973)

Hortobagyi GN, et al. *Ann Oncol.* 2018;29:1541-1547; Hortobagyi GN, et al. *N Engl J Med.* 2022;386:942-950; Slamon DJ, et al. *N Engl J Med.* 2020;382:514-524; Im SA, et al. *N Engl J Med.* 2019;381:307-316; Tripathy D, et al. *Lancet Oncol.* 2018;19:904-915; Slamon DJ, et al. *J Clin Oncol.* 2021;39(15):1001.

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MONARCH Trials: Abemaciclib

All patients were HR+/HER2- with advanced/metastatic breast cancer

	MONARCH 1	MONARCH 2	MONARCH 3
Study design	• Open-label, phase 2, single arm • **Single agent abemaciclib**	• Phase 3 • Randomized to **fulvestrant + abemaciclib or fulvestrant + placebo**	• Phase 3 • Randomized to **nonsteroidal AI + abemaciclib or nonsteroidal AI + placebo**
Patient population	Pre- and postmenopausal (n = 132)	Pre- and postmenopausal (n = 669)	Postmenopausal (n = 493)
Line of therapy	At least 1 line of prior ET and 1 or 2 lines of chemotherapy in the metastatic setting	2nd or subsequent (progressed on prior ET)	1st
Primary end point	ORR = 19.7%	PFS = 16.4 mo abemaciclib arm vs 9.3 mo placebo arm (HR, 0.553; *P* <0.001)	PFS = 28.18 mo abemaciclib arm vs 14.76 mo placebo arm (HR, 0.54; *P* = 0.00002)
Key secondary end point	--	Median OS = 46.7 mo abemaciclib arm vs 37.3 mo placebo arm (HR, 0.76; *P* = 0.01)	--

Dickler MN, et al. *Clin Cancer Res.* 2017;23:5218-5224; Sledge GW, et al. *JAMA Oncol.* 2020;6:116-124; Johnston S, et al. *NPJ Breast Cancer.* 2019;5:5.

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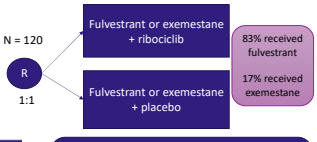
MAINTAIN: Continuing CDK4/6 Inhibitor After Progression

- Phase 2 randomized, double-blind, placebo-controlled trial evaluating continuation of CDK4/6 inhibitor + switching ET at progression
- Patients treated with prior fulvestrant received exemestane as ET in randomization and vice versa
- Prior CDK4/6 inhibitor: 84% palbociclib, 11% ribociclib, 2% abemaciclib, and 3% palbociclib + other CDK4/6 inhibitor



	Ribociclib arm	Placebo arm	
PFS (mo)	5.33	2.76	HR, 0.56; *P* = 0.02
PFS at 6 mo	42%	24%	--
PFS at 12 mo	25%	7%	--

Conclusions

- **Continuing CDK4/6 inhibitor at time of progression improved PFS** compared with switching ET alone
- Not incorporated into clinical guidelines yet

Kalinsky K, et al. *J Clin Oncol*. 2022;40(17 suppl). Published online June 8, 2022. doi: 10.1200/JCO.2022.40.17_suppl.LBA1004

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Summary: CDK4/6 Inhibitors in the Metastatic Setting

- All 3 **CDK4/6 inhibitors improved PFS** in metastatic HR+/HER2- breast cancer irrespective of biomarker selection
- Benefit in 1st line and subsequent lines of therapy
- Potential benefit of continuing CDK4/6 inhibitors beyond progression should be confirmed in additional trials

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Initiation of CDK4/6 Inhibitor

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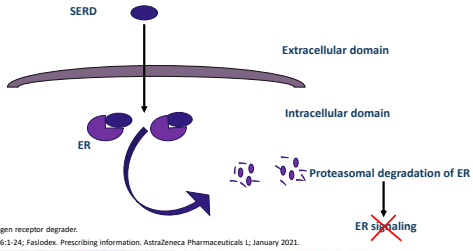
SERDs: Mechanism of Action

Fulvestrant	
Initial FDA approval: 2002	
Indications	HR+ advanced BC • Monotherapy with or without previous ET • Combined with abemaciclib, palbociclib, or ribociclib
Dosing	500 mg intramuscularly (IM) days 1, 15, 29, and once monthly thereafter



ER, estrogen receptor; SERD, selective estrogen receptor degrader.

Patel HK, Bihani T. *Pharmacol Ther*. 2018;186:1-24; Fasloдex. Prescribing information. AstraZeneca Pharmaceuticals L; January 2021.

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Oral SERDs

- MOA of oral SERD vs fulvestrant
  - Potentially greater antitumor activity with oral SERDs
  - Oral dosing may allow increased bioavailability
- *ESR1* gene mutations
  - Well-established mechanism of endocrine resistance
    - Leads to constitutive ER activation through estrogen-independent activation
    - Confers resistance to AIs
  - More frequent in advanced disease and after ET
  - Oral SERDs can potentially overcome this mechanism of endocrine resistance
- QOL benefit with an oral formulation

QOL, quality of life.

Bihani et al. *Clin Cancer Res*. 2017;23(16):4793-4804; Hernando C, et al. *Int J Mol Sci*. 2021;22:7812; Sanchez KG, et al. *J Clin Oncol*. Published online June 23, 2022. doi: 10.1200/JCO.22.00841

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AMEERA-3: Amcenestrant vs ET

Phase 2 open-label trial
- Pre- and postmenopausal women
- Advanced/metastatic ER+, HER2- BC
- Progressed on ≥6 months of continuous ET (0–2 lines in the metastatic setting)
- ≤1 line of chemotherapy or targeted therapy for metastatic disease
- ECOG PS 0–1

RANDOMIZED 1:1

- Amcenestrant 400 mg PO daily
- Physician choice (SOC):
  - Fulvestrant
  - AI
  - Tamoxifen

Until disease progression

Primary end point: PFS

- AMEERA-3 did not meet primary end point of improving PFS as assessed by an independent central review
- AMEERA-5, investigating palbociclib + amcenestrant, was stopped after not meeting the prespecified boundary for continuation
- Sanofi has discontinued its clinical development program for amcenestrant

Tolaney S, et al. *Cancer Res*. 2021;81(4_suppl):abstr OT-09-09; Press release. Sanofi. March 22, 2022. www.sanofi.com/en/media-room/press-releases/2022/2022-03-14-06-00-00-2402216; Press release. Sanofi. August 17, 2022. www.sanofi.com/en/media-room/press-releases/2022/2022-08-17-05-30-00-2499668

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EMERALD: Elacestrant vs Standard ET

Phase 3 open-label trial
- Men and postmenopausal women
- Advanced/metastatic ER+/HER2- BC
- Progressed or relapsed on or after 1-2 lines of ET for advanced disease
- Must have received prior CDK4/6 inhibitor
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0-1

RANDOMIZED 1:1

- Elacestrant 400 mg PO daily
- Physician choice (SOC):
  - Fulvestrant
  - AI

Given until disease progression

- Co-primary end points: PFS in all patients and PFS in m*ESR1*
- Stratification factors: *ESR1* mutation status, prior treatment with fulvestrant, presence of visceral metastases

Bidard F, et al. *J Clin Oncol*. Published online May 18, 2022. doi: 10.1200/JCO.22.00338

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EMERALD: Results

	All patients		Patients with m*ESR1*	
	Elacestrant (n=239)	SOC (n=238)	Elacestrant (n=115)	SOC (n=113)
6-month PFS (%)	34.3	20.4	40.8	19.1
12-month PFS (%)	22.3	9.4	26.8	8.2
Hazard ratio; *P* value	HR, 0.70; *P* = 0.002		HR, 0.55; *P* = 0.0005	
12-month OS (%)	79.3	73.3	82.6	73.6
Hazard ratio; *P* value	HR, 0.75; *P* = 0.821 (nonsignificant)		HR, 0.59; *P* = 0.0325 (nonsignificant)	

Conclusions
- Elacestrant improved PFS compared to SOC; median PFS numerically highest in the m*ESR1* patient population
  - Benefit for elacestrant in all subgroups
- **Elacestrant is currently considered investigational**; FDA currently reviewing application for approval

Bidard F, et al. *J Clin Oncol*. 2022; published online at ascopubs.org/journal/jco on May 18, 2022. Menarini Group and Radius Health submit new drug application to the U.S. FDA for elacestrant. News release. Menarini Group and Radius Health. June 22, 2022. Accessed June 24, 2022. https://bit.ly/3bfbVZ2

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Select Ongoing Oral SERD Trials

Advanced and metastatic			
Camizestrant			
SERENA-2	Phase 2	Camizestrant vs fulvestrant	After progression on prior line of treatment
SERENA-4	Phase 3	Camizestrant + palbociclib vs AI + palbociclib	1st line treatment
SERENA-6	Phase 3	Camizestrant + CDK4/6 vs continuing AI + CDK4/6 inhibitor	*ESR1* mutation without disease progression during 1st line treatment
Rintodestrant			
	Phase 1	Cohort A: Monotherapy Cohort B: In combination with palbociclib	Previously treated
Imlunestrant			
EMBER-3	Phase 3	Imlunestrant + abemaciclib vs physician's choice endocrine therapy vs imlunestrant	Previously treated with AI ± CDK4/6 inhibitor
Early stage			
Giredestrant			
lidERA	Phase 3	Giredestrant vs physician's choice ET	Adjuvant therapy
Imlunestrant			
EMBER-2	Phase 1	Imlunestrant	Neoadjuvant

Clinicaltrials.gov. Accessed October 18, 2022.

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Ongoing Questions With Oral SERDs

- Oral SERDs purpose/place in therapy
  - Will oral SERDs replace the use of fulvestrant?
  - Potential role in early-stage breast cancer?
  - Potential role in combination with CDK4/6 inhibitors? PIK3CA inhibitors?
- Trial design questions
  - *ESR1* mutations only vs all patients – is *ESR1* mutation driving all of the benefit?

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IM and Oral SERDs

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TROPiCS-02: Sacituzumab govitecan

- Phase 3 randomized study in HR+/HER2- unresectable locally advanced or MBC
- Previously received 2-4 lines of chemotherapy for MBC (or 1 prior therapy for MBC if disease progression ≤12 mo after neoadjuvant chemotherapy)
  - Received prior taxane, CDK4/6 inhibitor, ET

R (1:1)

- N = 272: Sacituzumab govitecan 10 mg/kg IV Days 1 and 8 every 21 days
- N = 271: Physician's choice (TPC) (capecitabine, eribulin, vinorelbine, gemcitabine)

	Sacituzumab	TPC	
Median PFS (mo)	5.5	4	HR, 0.66; *P* = 0.0003
OS (mo)	14.4	11.2	HR, 0.79; *P* = 0.02
Grade ≥3 AE	74%	60%	--

AE, adverse effect; MBC, metastatic breast cancer.

Conclusions

- Sacituzumab govitecan is a treatment option for patients who have received multiple lines of prior chemotherapy
- Not incorporated into clinical guidelines yet

Rugo HS, et al. *J Clin Oncol*. Published online June 8, 2022. doi: 10.1200/JCO.2022.40.17_suppl.LBA1001; Rugo HS, et al. *Ann Oncol*. 2022;33(suppl_7):S808-S869.

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Clinical Updates for HR+/HER2- Early-Stage Breast Cancer

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Early-Stage HR+/HER2- Breast Cancer: Treatment Overview

Treatment may include the following modalities:

- Surgery
- ± Radiation
- ± Chemotherapy
- ET ± Targeted Agents
  - Olaparib
  - Abemaciclib

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, V.4.2022. © National Comprehensive Cancer Network, Inc., 2022.

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OlympiA: Adjuvant Olaparib for *BRCA1/2* Mutation

- Phase 3, double-blind trial
- **Olaparib vs placebo** for 1 year after local treatment and neoadjuvant or adjuvant chemo
- HER2- early BC, *BRCA1/2* germline
  - 17.8% HR+
- High-risk clinicopathological factors

	Olaparib	Placebo	
3-year iDFS	85.9%	77.1%	HR 0.58; *P* <0.001
3-year distant DFS	87.5%	80.4%	HR 0.57; *P* <0.001

Recommendations for olaparib in HR+/HER2- with *BRCA1/2* mutation

- If ≥4 positive lymph nodes after chemotherapy OR
- Residual disease following NACT and a CPS+EG score ≥3

CPS + EG, clinical stage, pathologic stage, estrogen receptor status, and tumor grade; NACT, neoadjuvant chemotherapy.

Tutt ANJ et al. *N Engl J Med*. 2021;384:2394-405; American Society of Clinical Oncology. *Management of Hereditary Breast Cancer Rapid Recommendation Update. J Clin Oncol*. 2021;39(26):2959-2961. Published June 15, 2021. Accessed July 13, 2022. www.asco.org/research-guidelines/quality-guidelines/guidelines/breast-cancer#/143725; NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, V.4.2022. © National Comprehensive Cancer Network, Inc., 2022.

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Palbociclib for Adjuvant Treatment

	PALLAS	PENELOPE-B
Trial design	Phase 3, randomized	Phase 3, randomized, double-blind, placebo-controlled
Arms	ET + palbociclib x 2 years vs ET	ET + palbociclib x 13 months vs ET + placebo
Patient population	Pre- and postmenopausal (N = 5796)	Pre- and postmenopausal; no pCR after taxane-containing NACT and at high risk of relapse (N = 1250)
Primary end point	iDFS at 4 years = 84.2% with palbociclib + ET vs 84.5% with ET (HR, 0.96; *P* = 0.65)	iDFS at 3 years = 81.2% with palbociclib + ET vs 77.7% with placebo + ET (HR, 0.93; *P* = 0.525)
Key secondary end point	--	3-year OS = 93.6% with palbociclib and 90.5% with placebo (HR, 0.87; *P* = 0.420)

Summary:
No benefit with the use of adjuvant palbociclib added to standard ET for all patients or patients at high risk for relapse.

iDFS, invasive disease-free survival; pCR, pathologic complete response.

Gnant M, et al. *J Clin Oncol*. 2022;40:282-293; Loibl S, et al. *J Clin Oncol*. 2021;39:1518-1530.

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MONARCH-E: Adjuvant Abemaciclib + ET for High-Risk, Early-Stage BC

Phase 3, open-label trial

N = 5637
- HR+/HER2-, high-risk* early-stage BC
- Previously received surgery ± radiation ± neoadjuvant/adjuvant chemotherapy

***High-risk defined**

Cohort 1:
- ≥4 positive LN
- 1-3 positive LN and a high-feature (tumor ≥5 cm or histologic grade 3)

Cohort 2: 1-3 positive LN and Ki-67 ≥20%

RANDOMIZED 1:1

- ET 5-10 years + abemaciclib 150 mg PO BID x 2 years
- ET 5-10 years

- Primary end point: iDFS in ITT (cohorts 1 and 2)

LN, lymph node.

Johnston SR, et al. *J Clin Oncol*. 2020;38:3987-3998; Harbeck N, et al. *Ann Oncol*. 2021;32:P1571-P1581.

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MonarchE: Results

27-month follow-up:

	Abemaciclib + ET	ET alone	
3-year iDFS	88.8%	83.4%	HR, 0.70; *P* <0.0001

- FDA approved for adjuvant treatment of HR+/HER2-, LN+ early BC at high risk of recurrence and a Ki-67 score ≥20%
- NCCN Guidelines recommend to offer to patients with ≥4 + LN or 1-3 + LN + ≥1 additional high-risk feature (grade 3, T ≥5 cm, or Ki-67 score ≥20%)
- ASCO guidelines recommend to use according to FDA indication or as outlined by NCCN

Harbeck N, et al. *Ann Oncol*. 2021;32(P1571-P1581); Giordano SH, et al. *J Clin Oncol*. 2022;40(3):307-309; NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, V.4.2022. © National Comprehensive Cancer Network, Inc., 2022; Kisqali. Prescribing information. Novartis Pharmaceuticals Corp; January 2022.

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Summary: CDK4/6 Inhibitors in the Adjuvant Setting

- Consider adjuvant abemaciclib x 2 years + ET for LN+ disease and high-risk feature(s)
- Adjuvant palbociclib + ET did not improve outcomes over standard ET
- AE profile is manageable and consistent with use in the metastatic setting

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CDK4/6 Inhibitor Therapy Management

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CDK4/6 Inhibitors: Quality of Life (QOL)

Drug	Study	QOL assessment	Outcome
Palbociclib	PALOMA-2	• FACT-Breast • EuroQOL 5 dimensions	• No significant change in QOL from baseline • Improved pain scores in palbociclib arm
	PALOMA-3	• EORTC QLQ-C30 • QLQ-BR23 (BC module)	• Palbociclib improved global QOL scores and pain scores • Palbociclib delayed deterioration in global QOL and pain
Ribociclib	Pooled analysis MONALEESA -2, -3, -7	• EORTC QLQ-C30	• Ribociclib delayed deterioration in QOL • Time to definitive deterioration in global health status, pain, and emotional functioning scores was longer with ribociclib vs placebo
Abemaciclib	MONARCH-2	• mBPI-sf • EORTC QOL-C30 • QLQ-BR23	• QOL scores similar between arms • Abemaciclib delayed pain deterioration • Favored abemaciclib arm for all symptoms except diarrhea
	MONARCH-3	• EORTC QOL-C30 • QLQ-BR23	• No meaningful differences in global QOL, functioning, and most symptoms for abemaciclib arm vs control arm except diarrhea

Conclusions:
- CDK4/6 inhibitors improve or maintain QOL scores
- Often improve pain scores

Rugo HS, et al. *Ann Oncol.* 2018;29:888-894; Harbeck N, et al. *Ann Oncol.* 2016;27:1047-1054; Fasching PA, et al. *Ann Oncol.* 2020;31(suppl 4):S350-S351; Kaufman PA, et al. *Oncologist.* 2020;25:e243-51; Goetz MP, et al. *Oncologist.* 2020;25:e1346-1354.

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Quality of Life

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CDK4/6 Inhibitor: Toxicity Overview

	Abemaciclib	Palbociclib	Ribociclib
Most common AE	Diarrhea	Neutropenia	Neutropenia
Common grade 3-4 AEs	• Neutropenia • Leukopenia • Diarrhea	• Neutropenia • Leukopenia	• Neutropenia • Leukopenia
FDA label warning and precautions	• Neutropenia • Diarrhea • Hepatotoxicity • VTE	• Neutropenia	• Neutropenia • QT prolongation • Hepatobiliary toxicity
Other AEs with CDK4/6 inhibitor class	• Anemia • Thrombocytopenia • Infections	• Nausea/vomiting • Weakness • Fatigue	• Alopecia • ILD

ILD, interstitial lung disease; VTE, venous thromboembolism.

McAndrew NP, et al. *JCO Oncol Pract.* 2021;18(5):319-27; Hecht KA, Selby C. *Ann Pharmacother*. 2019;53(2):195-203; FDA Drug Safety Communication. Published September 13, 2019. Accessed July 13, 2022. www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-severe-lung-inflammation-ibrance-kisqali-and-verzenio-breast-cancer

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Monitoring Parameters

CDK4/6 inhibitor	CBC with differential	Liver function tests	Serum electrolytes (K, ca, mg, phos)	ECG	Signs of VTE
Abemaciclib	Baseline, q2w x 2 mo, monthly x 2 mo, then as needed	Baseline, q2w x 2 mo, monthly x 2 mo	NA	NA	Throughout treatment
Palbociclib	Baseline, day 15 x 2 cycles, prior to each cycle	NA	NA	NA	NA
Ribociclib	Baseline, q2w x 2 cycles, prior to each cycle x 4, then as needed	Baseline, q2w x 2 cycles, prior to each cycle x 4, then as needed	Baseline, monthly x 6 mo	Baseline, day 14 of cycle 1, day 1 of cycle 2	NA

Ibrance. Prescribing information. Pfizer Inc; September 2019; Kisqali. Prescribing information. Novartis Pharmaceuticals Corp; January 2022; Verzenio. Prescribing information. Eli Lilly and Company; October 2021.

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CDK4/6 Inhibitor: Dose Modifications

Dose reductions often required for neutropenia

CDK4/6 inhibitor	Starting dose	1st dose reduction	2nd dose reduction	3rd dose reduction
Abemaciclib (in combination)	150 mg BID	100 mg BID	50 mg BID	NA
Abemaciclib (single agent)	200 mg BID	150 mg BID	100 mg BID	50 mg BID
Palbociclib	125 mg	100 mg	75 mg	NA
Ribociclib	600 mg	400 mg	200 mg	NA

Ibrance. Prescribing information. Pfizer Inc; September 2019; Kisqali. Prescribing information. Novartis Pharmaceuticals Corp; January 2022; Verzenio. Prescribing information. Eli Lilly and Company; October 2021.

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Administration

Agent	Frequency of administration	Schedule	Timing in relation to food
Abemaciclib	Twice daily	Continuous	With or without food
Palbociclib	Once daily	Days 1-21 every 28 days	Capsules: With food Tablets: With or without food
Ribociclib	Once daily	Days 1-21 every 28 days	With or without food

Ibrance [capsules]. Prescribing information. Pfizer Inc; September 2019; Ibrance [tablets]. Prescribing information. Pfizer Inc; November 2019; Kisqali. Prescribing information. Novartis Pharmaceuticals Corp; January 2022; Verzenio. Prescribing information. Eli Lilly and Company; October 2021.

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CDK4/6 Inhibitors: Drug Interactions

- All 3 agents are primarily metabolized by CYP3A and SULT2A1 enzymes
- Avoid strong CYP3A inhibitors
  - If combination cannot be avoided, reduce as follows:
    - Abemaciclib 100 mg PO BID
    - Palbociclib 75 mg daily
    - Ribociclib 400 mg daily
- Avoid strong and moderate CYP3A inducers
- Avoid grapefruit and grapefruit juice
- Avoid QTc-prolonging medications with ribociclib
  - Tamoxifen may prolong QTc

CYP3A, cytochrome P450 family 3 subfamily A; SULT2A1, sulfotransferase family 2A member 1.

Ibrance. Prescribing information. Pfizer Inc; September 2019; Kisqali. Prescribing information. Novartis Pharmaceuticals Corp; January 2022; Verzenio. Prescribing information. Eli Lilly and Company; October 2021.

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SERDs: Adverse Effects

Toxicity	Elacestrant		Fulvestrant	
	All grade	Grade 3/4	All grade	Grade 3/4
Any AE	92%	27%	86%	20.5%
Nausea	35%	2.5%	18.8%	0.9%
Fatigue	19%	0.8%	18.8%	0.9%
Vomiting	19%	0.8%	8.3%	0
Decreased appetite	14.8%	0.8%	9.2%	0.4%
Arthralgia	14.3%	0.8%	16.2%	0
Diarrhea	13.9%	0	10%	0.9%
Constipation	12.2%	0	6.6%	0
Hot flush	11.4%	0	8.3%	0

- Manageable safety profile
- Nausea was the most common AE
- <10% of patients discontinued study drug due to AE

Bidard F, et al. *J Clin Oncol*. Published online May 18, 2022. doi: 10.1200/JCO.22.00338

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Conclusion

- CDK4/6 inhibitors have significantly prolonged PFS and, in some trials, OS in the 1st line and subsequent lines for patients with HR+/HER2- metastatic breast cancer
- Oral SERDs are promising investigational agents, especially in patients with an *ESR1* mutation
- Adjuvant abemaciclib may be offered to patients with HR+/HER2- early-stage breast cancer and high-risk features
- Pharmacists play an important role in identifying and managing CDK4/6 toxicities and potential drug interactions

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Additional Resources

Article	
McAndrew NP, Finn RS. Clinical review on the management of hormone receptor-positive metastatic breast cancer. *JCO Oncol Pract*. 2021;18(5):319-327.	
Guidelines	
NCCN Guidelines for Patients	www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf www.nccn.org/patients/guidelines/content/PDF/breast-invasive-patient.pdf
NCCN Clinical Practice Guidelines	www.nccn.org/professionals/physician_gls/pdf/breast.pdf

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Thank you!

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