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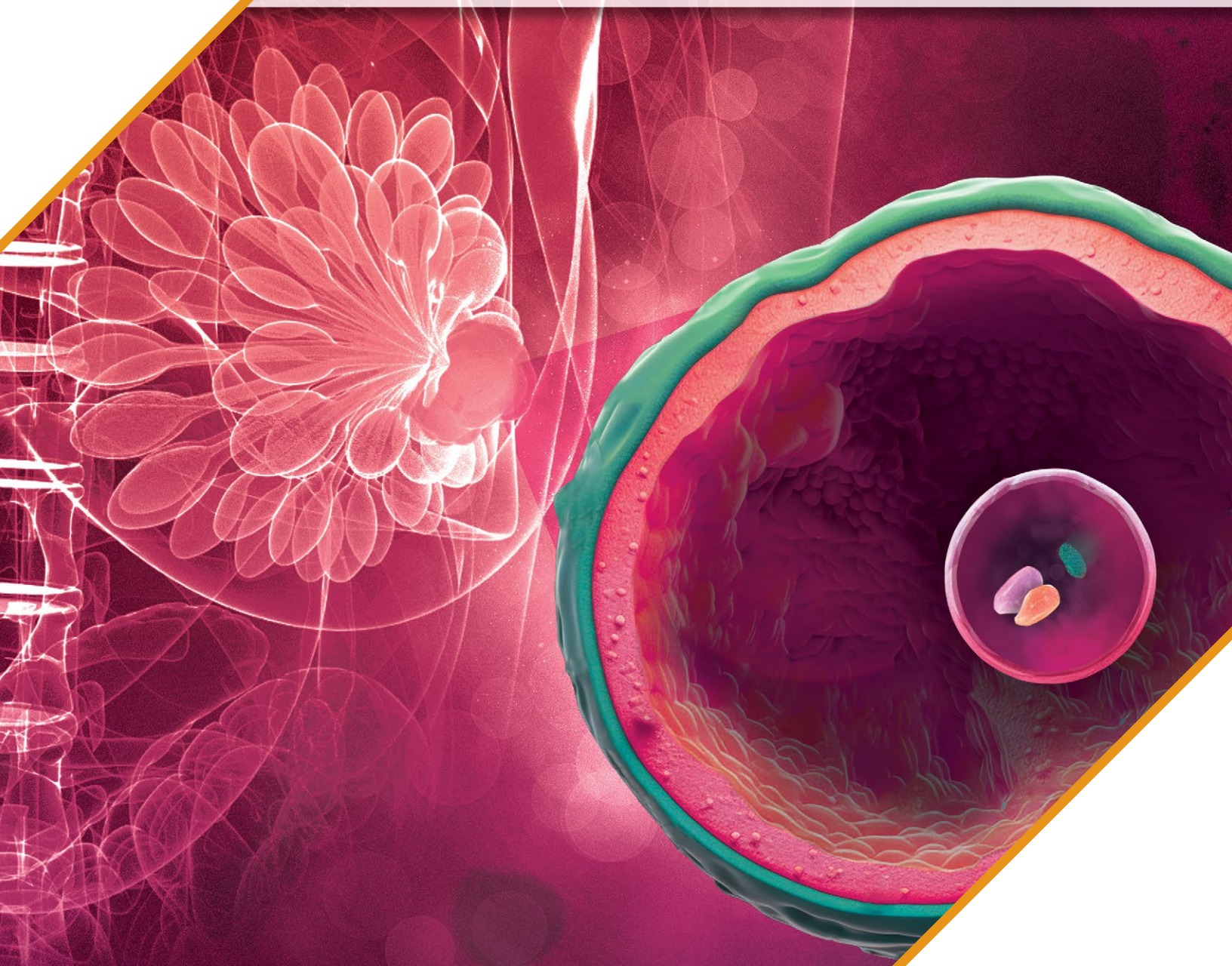
CDK 4/6 Inhibitors:
Practice-Changing Implications of Targeted Therapies in HR+/HER2- Breast Cancer

A Shared Decision-Making Guide



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Shared Decision-Making

WHAT IS SHARED DECISION-MAKING?

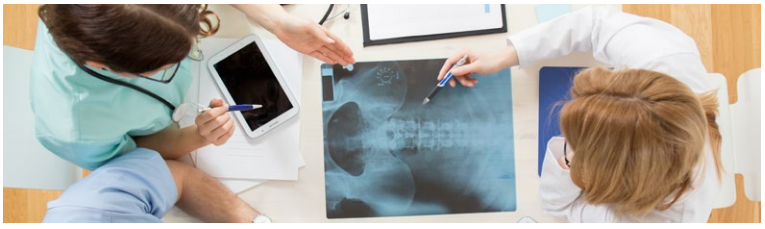
Shared decision-making (SDM) occurs when a healthcare provider and a patient work together to make a healthcare decision that is best for the patient. Optimal decision making takes into account evidence-based information about available options; the provider's knowledge and experience; and the patient's values, goals and preferences. Patients and their families/caregivers who are engaged in an SDM process are more likely to arrive at a treatment decision that works best for all those involved.

WHY IS SDM IMPORTANT IN BREAST CANCER?

Making informed decisions about treatment for breast cancer (BC) is challenging and can be daunting to the patient, who may be overwhelmed by therapeutic options and how they differ based on benefits, risks, and potential complications. Quite often, the choice of treatment may hinge on patient preferences. Patients and caregivers can play a collaborative and integral role with their healthcare team in determining a course of therapy that is in line with their lifestyles, goals, and desires for disease control.

Communication among patients/caregivers and providers can facilitate SDM, helping to improve patient adherence to therapy, enhance satisfaction with care delivery, and elevate quality of life. By successfully engaging with the healthcare team through SDM, patients may experience better therapeutic outcomes and higher-quality care.

Optimal care of BC involves the use of effective therapies that are supported by the latest evidence and guidelines, selected through a SDM process and individualized to each patient's needs.



The AXIS 6 Ease ("E's") to SDM

ENSURE

Ensure you see and treat the patient as an individual not a disease.

ELEVATE

Elevate the patient-centric experience and improve satisfaction with care.

ENABLE

Enable a long-term personal connection with your patients.

ESTABLISH

Establish co-created treatment plans that align medical evidence with patient preferences to foster adherence and optimize outcomes.

ELICIT

Elicit patient/caregiver preferences, values, and goals for therapy.

EVALUATE

Evaluate the risk/benefits and costs of treatment so they are aligned with patient expectations.

Identification of High-Risk HR+/HER2- Early Breast Cancer and Treatment Implications

Current NCCN Guidelines characterize HR+/HER2- breast cancer as high risk if it features ≥4 positive lymph nodes, or 1-3 positive nodes (with one or both of grade 3 disease or tumor size ≥5 cm).[1] International publications have also identified factors for high risk for disease relapse, including tumor grade 3, size (T3/4), nodal status (N2/3), expression of hormonal receptors (ER <10% and or PgR <20%), residual cancer burden (III), Ki-67 >30%, and genomic signature corresponding with a high-risk class.[2] Of note, the NCCN guidelines have recently removed Ki-67 as a consideration for adjuvant CDK4/6 inhibitor therapy for invasive breast cancer.[1] These factors may help to stratify risk and help clinicians tailor adjuvant treatment for their patients.

There are several studies that have evaluated the use of CDK4/6 inhibitors for patients with early HR+/HER2- breast cancer, many of which have used different criteria for risk stratification.

Agent	Study	Risk Criteria
Abemaciclib	monarchE[3]	High risk: ≥ 4 nodes, or if 1-3 nodes, then either grade 3 tumor, tumor size ≥ 5 cm, or Ki67 ≥20% - Study excluded patients with stage II and III N0 disease
Palbociclib*	PENELOPE-B[4]	High risk: Clinical Pathological Staging-Estrogen Receptor Grading Score ≥3 or 2 with yPN+
Ribociclib	NATALEE[5]	Patients with Stage III or IIB enrolled; Stage IIA N0 allowed if patients had other risk features such as grade 3, or grade 2 with Ki67 ≥ 20% or high genomic risk; Stage IIA N1 eligible

*Study did not report additional benefit in the adjuvant setting

Specific patient populations may respond poorly to CDK4/6 inhibitors due to intrinsic or acquired resistance; several markers associated with CDK4/6i resistance have been reported from studies of liquid biopsies and solid tumors in the setting of metastatic HR+/HER2- breast cancer.[6] These may be associated with lower progression-free survival and awareness of the potential implications of these markers may help to personalize treatment.[7]

Tactics for Weighing Risks/Benefits of CDK4/6 Inhibitors

For patients and clinicians alike, it is essential to weigh the risks and benefits of different treatment options and to be aware of the potential for not only acute side effects, but long-term side effects of different treatment options. Individual patient goals and preferences should be considered. The effects of treatment options on patient quality of life and independence are crucial. According to the American Society of Clinical Oncology, there are several tactics that may help to appropriately weigh the balance of risks and benefits of different treatment options, including:[8]

- Getting a second opinion
- Understanding the latest guideline recommendations
- Incorporating other decision-making tools
- Encouraging patient discussions with people they trust (clergy, family, social workers, etc.)
- Understanding statistical data for key outcomes and what these may mean (or not mean) for each individual patient

Additional considerations may be found at the Cancer.Net website:[8]
https://cancer.net/navigating-cancer-care/how-cancer-treated/making-decisions-about-cancer-treatment

Differentiating Factors Among CDK4/6 Inhibitors[9-13]

CDK4/6 Inhibitor	Abemaciclib	Palbociclib	Ribociclib
CDK4:CDK6 Inhibition Ratio	1:5	1:1.5	1:4
Half-Life	18.3 hours	29 ± 5 hours	32 hours
Starting Dose	150 mg orally twice daily with or w/o food	125 mg orally once daily with food for 21 days followed by 7 days off palbociclib	600 mg orally once daily with or w/o food for 21 days followed by 7 days off ribociclib
Monotherapy	FDA approved	Not approved	Not approved
CNS Activity	+	-	-
Key Side Effects (not a complete list)	GI toxicity (nausea, vomiting, diarrhea), fatigue	Neutropenia, leukopenia, fatigue	Neutropenia, hyponatremia, ↑ creatinine, QTc prolongation
Use in Adjuvant Setting for Early BC	Significant benefit in invasive disease-free survival reported in monarchE study	No benefit reported in PALLAS or Penelope-B	Significant benefit in invasive disease-free survival reported in NATALEE primary results[14]

Genetic Counseling and Education

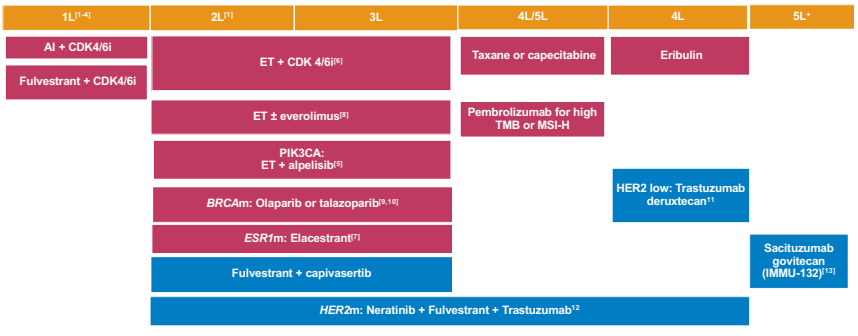
CDK4/6 inhibitors have been incorporated into treatment paradigms for advanced HR+ metastatic breast cancer, and recent studies such as monarchE and NATALEE have reported on the efficacy of agents such as abemaciclib and ribociclib in patients with early breast cancer.[3,14] However, these benefits have not been observed universally due to challenges with acquired or intrinsic treatment resistance. Recent investigations have addressed mechanisms for resistance to CDK4/6 inhibitors, including abnormal cyclin-E signaling and loss of retinoblastoma-1 function, and understanding the role of these and other mechanisms may help to guide personalized treatment. In a recent retrospective real-world analysis, patients with *PTEN* loss, *FGFR1* amplification, and DNA repair pathway gene mutations were associated with reduced progression-free survival in patients receiving CDK4/6 inhibitor therapy.[7]

Next generation sequencing is recommended as a means of detecting potentially actionable mutations for patients with metastatic breast cancer. With respect to unresectable or metastatic HR+/HER2- disease, current NCCN guidelines recommend testing for *PIK3CA* mutations with tumor or liquid biopsy to identify patients who may be a candidate for alpelisib plus fulvestrant (Category 1); they also recommend evaluation for *ESR1* mutation in patients with HR+/HER2- metastatic breast cancer to identify those who may be candidates for elacestrant (Category 2A) via next-generation sequencing or blood assessment.[1]

Current NCCN guidelines for breast cancer also recommend that patients with non-metastatic invasive breast cancer should receive genetic counseling and testing if the patient is at risk for hereditary breast cancer, has triple-negative breast cancer at any age, or is a candidate for treatment with olaparib.1 With respect to testing for high-penetrance breast cancer susceptibility genes (*BRCA1, BRCA2, CDH, PALB2, PTEN, STK11*, and *TP53*), guidelines suggest that this is clinically indicated for patients with breast cancer ≤50 years of age who have high risk HER2- cancer, to guide adjuvant decisions specific to olaparib.[15]

Key Considerations for Optimal Sequencing of CDK4/6 Inhibitors

CDK4/6 inhibitors have been approved for multiple lines of treatment for patients with advanced HR+/HER2- breast cancer. While efficacy data have not conclusively supported the use of one agent over another, these agents have distinct safety profiles that may influence treatment selection.[16] Optimal sequencing following CDK4/6 inhibitor use for patients with metastatic HR+/HER2- breast cancer should account for individual patient functional status and tumor features; one suggested approach is outlined in the figure to the right.



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AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; TMB, tumor mutational burden.

Summary of Indications, Guidelines, and Topline Results of RWE and PROs to Help Facilitate Discussion and Collaborative Decision Making

CDK4/6 INHIBITOR INDICATIONS[11-13]

CDK4/6 Inhibitor	Indications
Abemaciclib	• In combination with tamoxifen or an aromatase inhibitor for adults with HR+/HER2-, node-positive early breast cancer at high risk of recurrence • In combination with an aromatase inhibitor as initial endocrine-based therapy for adults with HR+/HER2- advanced or metastatic breast cancer • In combination with fulvestrant for adult patients with HR+/HER2- advanced or metastatic breast cancer with disease progression following endocrine therapy • As monotherapy for adult patients with HR+/HER2- advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting
Palbociclib	• For adults with advanced or metastatic HR+/HER2- breast cancer in combination with: – An aromatase inhibitor as first hormonal-based therapy, or – Fulvestrant in patients with disease progression following hormonal therapy
Ribociclib	• For adult patients with HR+/HER2- advanced or metastatic breast cancer in combination with: – An aromatase inhibitor as initial endocrine-based therapy, or – Fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men

NCCN GUIDELINE RECOMMENDATIONS: HR+/HER2- MBC*

HR+/HER2– MBC and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Setting	Preferred regimens	Other recommended regimens (first and subsequent lines)
First Line	Aromatase inhibitor + CDK4/6 inhibitor • Aromatase inhibitor + ribociclib (category 1) • Aromatase inhibitor + abemaciclib • Aromatase inhibitor + palbociclib	Selective ER down-regulator • Fulvestrant • Elacestrant for ESR1-mutated tumors Selective ER down-regulator (fulvestrant, category 1) + non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1) Non-steroidal aromatase inhibitor • Anastrozole • Letrozole Selective ER modulator • Tamoxifen Steroidal aromatase inactivator • Exemestane
	Fulvestrant + CDK4/6 inhibitor • Fulvestrant + ribociclib (category 1) • Fulvestrant + abemaciclib (category 1) • Fulvestrant + palbociclib	
Second line	Fulvestrant + CDK4/6 inhibitor, if CDK4/6 inhibitor not previously used (category 1)	
	Alpelisib + fulvestrant, for *PIK3CA*-mutated tumors (category 1)	
	Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)	

HR+/HER2– MBC With Visceral Crisis or Endocrine Refractory

Setting	Subtype/Biomarker	Regimen
First Line	No germline BRCA1/2 mutation	Systemic chemotherapy
	Germline BRCA1/2 mutation	PARPi (olaparib, talazoparib) (Category 1, preferred)
Second line	HER2 IHC 1+ or 2+/ISH negative	T-DXd (Category 1, preferred)
	Not a candidate for T-DXd	Sacituzumab govitecan (Category 1, preferred)
		Systemic chemotherapy
Third line and beyond	Any	Systemic chemotherapy
	Biomarker positive (ie, MSI-H, NTRK, RET, RMB-H)	Targeted agents

*For additional treatment options particular to certain circumstances and information related to these options, please see NCCN guidelines. Gradishar WJ, et al. NCCN Guidelines for Breast Cancer. Version 4.2023.

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan.

HRQOL OUTCOMES IN SELECT CDK4/6 INHIBITOR STUDIES (TABLE ADAPTED FROM DI LAURO ET AL.)[23]

Study	CDK4/6i	Population	Better outcomes in CDK4/6i cohort	Comparable outcomes in CDK4/6i cohort and control group	Better outcomes in control group
MONARCH-3	Abemaciclib	Total population		GHS	Diarrhea scores, nausea/vomiting, appetite loss
	Abemaciclib	Japanese patients	Financial difficulties	GHS	Diarrhea
MONARCH-2	Abemaciclib	Total population	TTD of pain scores	GHS	Diarrhea scores, nausea/vomiting, appetite loss
	Abemaciclib	Japanese patients	Role functioning	GHS	Diarrhea
monarchE	Abemaciclib	Total population		GHS/QoL	
PALOMA-2	Palbociclib	Total population	Pain scores; TTD of GHS	GHS/QoL	
	Palbociclib	Asian patients		FACT-B/FACT-G total scores	
PALOMA-3	Palbociclib	Total population	Pain scores, GHS/QoL, TTD	GHS	Hair loss
	Palbociclib	Asian patients	Dyspnea	GHS/QoL	
PENELOPE-B	Palbociclib	Total population		Physical, cognitive, and emotional fatigue, GHS/QoL	
MONALEESA-2	Ribociclib	Total population	Pain scores	EORTC QLQ-C30 GHS/QoL TTD by ≥10% in overall HR-QoL	
	Ribociclib	US patients	Pain scores	EORTC QLQ-C30 GHS/QoL TTD by ≥10% in overall HR-QoL	
	Ribociclib	Patients ≥65	Pain scores	EORTC QLQ-C30 GHS/QoL TTD by ≥10% in overall HR-QoL	
MONALEESA-3	Ribociclib	Total population	TTD ≥10% in overall HR-QoL TTD ≥10% in EORTC QLQ-C30 functioning scores	EORTC QLQ-C30 GHS/QoL	
PALOMA-3	Ribociclib	Total population		GHS; consistent HRQoL between arms	

EORTC, European Organization for Research and Treatment of Cancer; EQ-5D, EuroQoL five dimensional; GHS, global health status; HRQoL, health-related quality of life; TTD, time to deterioration.

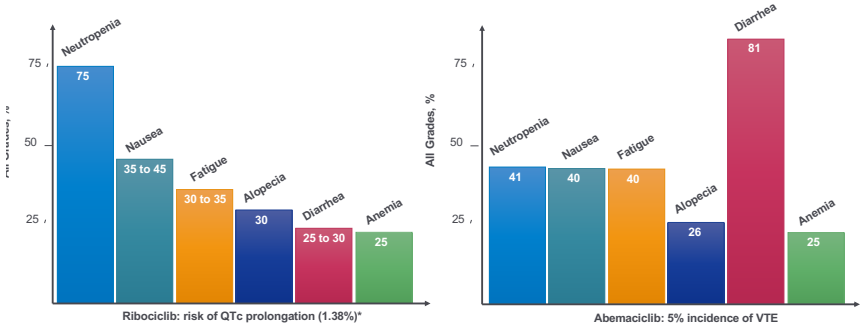
SELECT REAL-WORLD STUDIES OF CDK4/6 INHIBITORS

CDK4/6 Inhibitor	Key Outcomes from Real-World Study
Abemaciclib	**Cuyun Carter et al.**[17] 118 female patients with HR+/HER2- MBC • Abemaciclib used as 1L in 28.8% of patients, 2L in 21.2%, 3L in 20.3%, later in 29.7% • Monotherapy in 12.7% of patients, combination w/fulvestrant in 59.3%, aromatase inhibitor in 22.9%, AI and fulvestrant in 5.1% • 41.2% of patients assessed for real world response had a complete or partial response • Median real world time to first response: 3.6 months • 12 month real world PFS probability: 61.7%
	Dannehl et al.[18] 1474 patients with early breast cancer • 1121 were HR+/HER2-, and 217 fulfilled monarchE inclusion criteria • Of the 217, 48.9% received no adjuvant or neoadjuvant chemotherapy
Palbociclib	**Patt et al.**[19] 813 patients with HR+/HER2- metastatic/advanced BC • 11% of patients discontinued AI + palbociclib due to toxicity • Median real-world PFS: 20.0 months • Best real world best tumor response: 51.9% • Patients starting at 125 mg per day had a median RWPFS of 27.8 months, RWBTR of 54.0%
	Rugo et al.[20] 2888 patients with HR+/HER2- metastatic breast cancer • Median OS approximately 5.9 months greater in patients receiving palbociclib • PFS was 5.4 months greater in patients receiving palbociclib
Ribociclib	**Fernandez-Cuerva et al.**[21] 53 female patients with HR+/HER2- MBC • Neutropenia reported in 69.8% of patients • Overall median PFS w/ribociclib: 27.3 months • 94.4% started ribociclib at 600 mg dose • 58% required dose reductions (not associated with loss of efficacy)
	Jackisch et al.[22] 2581 patients with HR+/HER2- advanced BC • 1L AI/FUL + ribociclib had median PFS durations in real world database consistent with those in the MONALEESA 2,3, and 7 trials • 1L AI/FUL + ribociclib had superior PFS in real world compared with 1L ET or CT

RWBTR, real-world best tumor response; RWPFS, real-world progression-free survival.

Summary of Adverse Events, Management Strategies and Therapy Adherence Strategies

SIDE EFFECT PROFILE OF CDK 4/6i + ET



Hematologic and non-hematologic adverse events should be monitored for and managed according to the prescribing information for the CDK4/6 inhibitor used for treatment.[11-13]

Figure courtesy of Joyce A. O'Shaughnessy, MD: compiled from the reported toxicity of the randomized trials.
Thein KZ, et al. *JNCCN*, 2019;17(3.5):CLO19-052.
CDK, cyclin-dependent kinase; VTE, venous thromboembolism.

Discussion of Progressive/Resistant Disease: Monitoring and Reacting

NCCN guidelines recommend several monitoring measures during treatment of patients with metastatic breast cancer to assess treatment efficacy and limit potential treatment toxicity.[1] These include assessment of symptoms, physical examination, laboratory evaluation, imaging, and possibly biomarker tests. The NCCN guidelines advocate for shared decision-making and accounting for patient preferences when treatment plans are being put together. Some of the key parameters for disease progression may include:[1]

- New or worsening disease on physical examination, radiographic evaluation, or functional imaging
- Worsening symptoms, unexplained weight loss, or reductions in performance status
- Laboratory abnormalities such as hypercalcemia, elevation in liver function tests, or tumor markers

Sample Questions for Clinicians to Pose to Patients to Facilitate Shared Decision-Making

- What do you already know and understand about breast cancer?
- Are there any aspects of treatment that you are worried about?
- What would you like most from your treatment?
- What is your #1 priority that we accomplish during our visit today?
- What has happened with you since our last visit?
- Are you able to tolerate the treatment we've chosen? If not, why not? How can we provide improved support to enhance your treatment?
- Do you understand the different treatment choices? What else would you like to know about them?
- Do you understand why we've chosen this treatment? What else would you like to know about it?
- Do you have any questions about the benefits or risks of the different treatments we are considering for your disease?
- Are you able to make a decision now, or do you need more time to think about it?
- Would you like to be involved with a patient/caregiver support group?
- How do feel? Are you experiencing any symptoms?
- Are you experiencing any side effects related to your treatment? How has this impacted your lifestyle and quality of life?
- Is your condition interfering with your work, social events, or everyday activities at home?

- What goals do you have regarding your cancer treatment? Have these goals changed since our last visit? It might be:
  - Keeping the symptoms of disease under control
  - Minimizing risks and side effects from treatment
  - Finding a treatment with a dosing/administration option that's easy and convenient
  - Selecting a treatment that is cost effective
- What is most important to you/your family as we discuss current or new treatment options? It might be:
  - Keeping out-of-pocket costs low
  - Resolving disease symptoms
  - Avoiding treatment-related adverse events
  - Maintaining a specific level of functionality
  - Improving quality of life

Sample Questions for Patients to Pose to Clinicians to Facilitate Shared Decision-Making[25,26]

- Will you tell me about the risks and benefits of the different treatments that we are talking about?
- How do these treatments work?
- What can I expect from the treatments that we are discussing?
- Are the treatment options that you are presenting covered in guidelines, and if so, can you tell me where I might be able to find more details?
- Is there a treatment option that you prefer, and if so, why?
- Are there any ongoing clinical trials that I might benefit from? If there are, where can I learn more about them?
- How will my other health problems be influenced by the treatment that we select?
- If I want to consult another physician or other providers before making a treatment decision, do you have any recommendations?
- What are the timelines and duration of the treatment options that we are discussing?
- What are the financial costs of the treatments, and what financial burden will these present to me?

Additional questions to pose to your clinician regarding testing, diagnosis, care team experience, treatment options, surgery, radiation, and clinical trilas are available form the NCCN Guidelines for Patients (Invasive Breast Cancer), pages 83-90. This document is available at: https://www.nccn.org/patients/guidelines/content/PDF/breast-invasive-patient.pdf.

Potential questions to pose to the healthcare team are also available at the Cancer.Net website, https://www.cancer.net/cancer-types/breast-cancer/questions-ask-health-care-team.

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