From clinical trials to clinical practice: Applying CDK4/6 inhibitors in HR+/HER2– early breast cancer

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Where to go next for patients with HR+/HER2– early breast cancer

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What is the rationale for including targeted therapies in the treatment paradigm for HR+/HER2– early breast cancer?

Outcomes have improved but unmet needs remain for patients with HR+/HER2– EBC

Outcomes in HR+ EBC have improved in recent decades but recurrence risk persists[1,2]

Pooled EBCTCG analysis

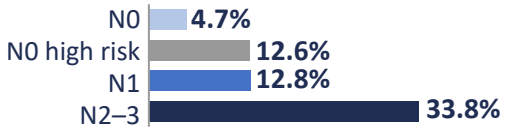
Women diagnosed with EBC between 1990 and 2009

151 trials
N=155,746
ER+ n=114,811

Women with ER+ EBC with 5 years of ET diagnosed between 2005 and 2009 had a **lower 10-year risk of distant recurrence** vs those diagnosed in the 1990s (HR 0.75, 95% CI 0.71–0.79)

ER+ disease is associated with a roughly **constant annual risk of recurrence that persisted** even in patients diagnosed between 2005 and 2009 (1.2%/year)

5-year risk of overall recurrence by nodal status[2]



Risk of recurrence in real-world monarchE- and NATALEE-eligible populations of patients[3]

US EHR analysis

monarchE or NATALEE eligible patients with HR+/HER2– EBC after SoC surgery + adjuvant ET (Jan 2011 to May 2024)

N=7,481

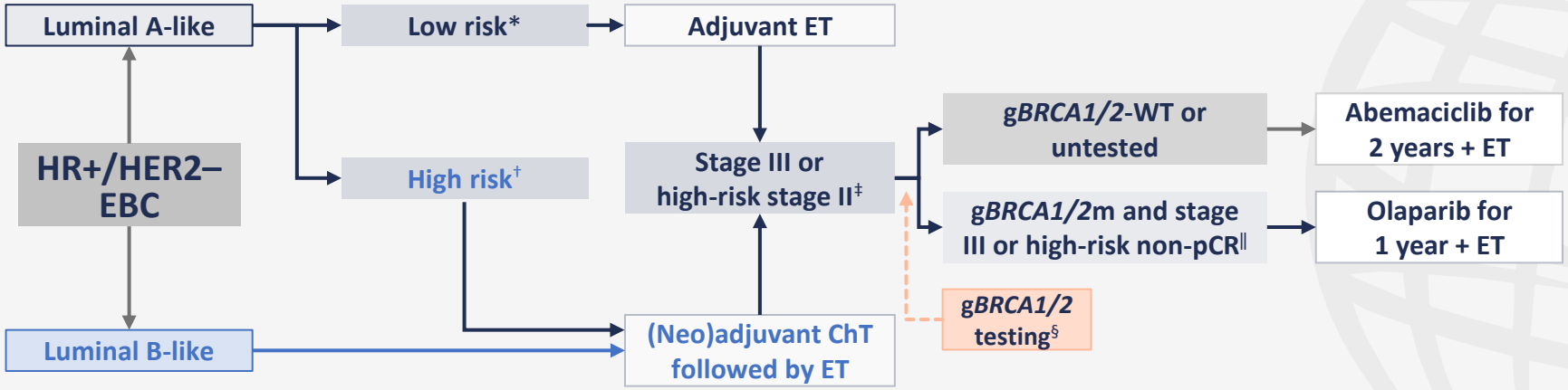
	monarchE eligible (n=2,534)	**NATALEE eligible** (n=1,157)
Median follow-up	53.4 months	55.1 months
5-year rate		
RFS	72%	81%
DRFS	75%	83%
OS	85%	90%

Considerable risk of early recurrence remains despite receiving SoC surgery and adjuvant ET

CI, confidence interval; DRFS, distant recurrence-free survival; EBC, early breast cancer; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; EHR, electronic health record; ET, endocrine therapy; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor positive; OS, overall survival; RFS, recurrence-free survival; SoC, standard of care. 1. Early Breast Cancer Trialists' Collaborative Group. *Lancet.* 2024;404:1407–18; 2. Jhaveri K, et al. *Ann Oncol.* 2024;35:S337–8; 3. Tarantino P, et al. Presented at SABCS, San Antonio, TX, USA. 10–13 December 2024. Abstr P2-12-02.

How are targeted systemic therapies for HR+/HER2– early breast cancer currently integrated into clinical practice guidelines?

Targeted treatments are recommended by ESMO for patients with HR+/HER2– EBC[1]



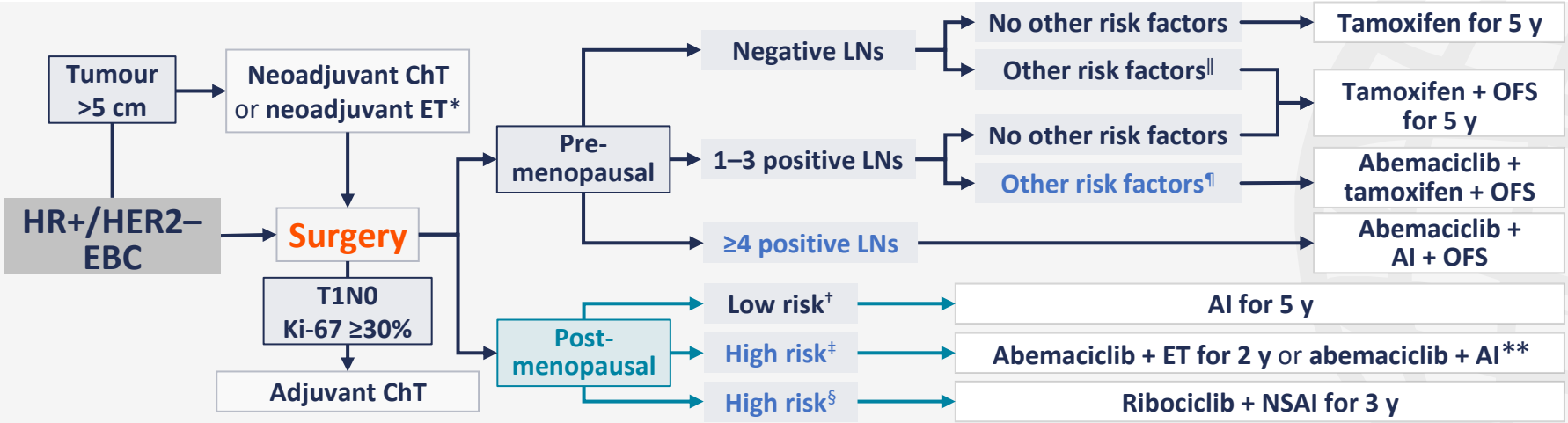
Ribociclib + AI approved in the EU for the adjuvant treatment of patients with HR+/HER2– EBC at high risk of recurrence[2] (MCBS: A[3]).

*'Low risk' implies low-risk genomic score and/or lower-risk features on traditional pathological analysis, including lower-grade histology, robust ER and PgR expression and lower measures of proliferation. †'High risk' implies high-risk genomic score and/or higher-risk features on traditional pathological analysis, including higher-grade histology, lower ER and PgR expression and higher measures of proliferation. ‡Stage N1 with primary tumour >5 cm, and/or grade 3 and/or Ki-67 ≥20%. §If appropriate and feasible. ‖Patients with HR+ tumours and non-pCR after neoadjuvant ChT require a pretreatment clinical stage and post-treatment pathological stage, estrogen receptor and tumour grade score ≥3 to receive olaparib.

AI, aromatase inhibitor; ChT, chemotherapy; EBC, early breast cancer; ESMO, European Society for Medical Oncology; ET endocrine therapy; g*BRCA1/2*m, germline *BRCA1/2* mutation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MCBS, magnitude of clinical benefit scale; pCR, pathological complete response; PgR, progesterone receptor; WT, wild-type.

1. Loibl S, et al. *Ann Oncol.* 2024;35:159–82; 2. EMA. Ribociclib SmPC. Available at: https://bit.ly/3ZjJ8b7 (accessed 17 February 2025); 3. ESMO. MCBS: ribociclib. Available at: https://bit.ly/4g35CU2 (accessed 17 February 2025).

Targeted treatments are recommended by the CSCO for patients with HR+/HER2– EBC



Treatment algorithm not exhaustive.

*Neoadjuvant ChT preferred; neoadjuvant ET considered if (1) ChT is contraindicated; (2) patient is temporarily unsuitable for surgery or does not require immediate surgery; (3) patient is insensitive to or has inadequate response to neoadjuvant ChT. For postmenopausal patients, AIs are recommended (or fulvestrant if AI is not appropriate); for premenopausal patients, neoadjuvant AI + OFS may be used. The response to neoadjuvant ET should be evaluated every 2 months; if effective and well tolerated, treatment may continue for up to 6 months. †'Low risk' implies (1) negative LNs; (2) 1–3 positive LNs with grade 1–2, tumour <5 cm and Ki-67 <20%. ‡'High risk' implies (1) ≥4 positive LNs; (2) 1–3 positive LNs with other risk factors, such as grade 3, tumour ≥5 cm, or Ki-67 ≥20%. §'High risk' implies stage II or III disease, encompassing node-negative with grade 3/2 and Ki-67 ≥20% or high-risk genetic profiles. ‖Grade 2–3, tumour >2 cm, or high Ki-67. ¶Such as grade 3, tumour ≥5 cm, or Ki-67 ≥20%. **If abemaciclib is not tolerated, a switch to another CDK4/6 inhibitor, e.g. ribociclib, may be deemed appropriate.

AI, aromatase inhibitor; ChT, chemotherapy; CSCO, Chinese Society of Clinical Oncology; EBC, early breast cancer; ET endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LN, lymph node; OFS, ovarian function suppression; NSAI, nonsteroidal aromatase inhibitor; y, years.

Li J, et al. *Transl Breast Cancer Res.* 2024;5:18.

In light of the approved targeted systemic therapies for HR+/HER2– early breast cancer, what unmet needs remain?

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Integrating CDK4/6 inhibitors into the treatment pathway for HR+/HER2– early breast cancer

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What is the current status of CDK4/6 inhibitors for patients with HR+/HER2– early breast cancer?

CDK4/6 inhibitors in HR+/HER2– EBC: Where are we now?

Abemaciclib[1]

- In **combination with ET** for the **adjuvant treatment** of adult patients with **HR+/HER2– node-positive EBC at high risk of recurrence**[1]
- In pre- or perimenopausal women, AI ET should be combined with an LHRH agonist[1]

ESMO MCBS:[2] A

Ribociclib[3]

- In **combination with AI** for the **adjuvant treatment** of patients with **HR+/HER2– EBC at high risk of recurrence**[4]
- In pre- or perimenopausal women, or in men, the AI should be combined with an LHRH agonist[4]

ESMO MCBS:[4] A

Palbociclib[5,6]

Phase III trials in EBC showed no improvement in IDFS:*

- PALLAS[5]
- PENELOPE-B[6]

Dalpiciclib[7,8]

In phase II clinical trials in China:*

- DARLING-02[7]
- NCT06341894[8]

European Society of Medical Oncology (ESMO): Clinical Practice Guidelines[9]
After completion of locoregional therapy, consider **abemaciclib + ET** for 2 years in patients with stage III or high-risk stage II EBC [I, A]

Chinese Society of Clinical Oncology (CSCO): Breast Cancer Guidelines[10]
Key recommendations: For HR+ BC, **CDK4/6 inhibitors** are preferred. Some patients with locally advanced BC in need of neoadjuvant ET may be treated with **ET + CDK4/6 inhibitor** or may participate in a clinical trial. If **abemaciclib** is not tolerated due to adverse effects during treatment, it may be appropriate to switch to another CDK4/6 inhibitor, e.g. **ribociclib**

*NB: Snapshot of trials in phase II or III development as stated; not an exhaustive list of all trials investigating these agents. AI, aromatase inhibitor; BC beast cancer; EBC, early BC; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; LHRH, luteinising hormone-releasing hormone; MCBS, magnitude of clinical benefit score.

1. EMA. Abemaciclib SmPC. Available at: https://bit.ly/4g304cq (accessed 17 February 2025); 2. ESMO. MCBS: abemaciclib. Available at: https://bit.ly/3DS7UrO (accessed 17 February 2025); 3. EMA. Ribociclib SmPC. Available at: https://bit.ly/4hkelTc (accessed 17 February 2025); 4. ESMO. MCBS: ribociclib. Available at: https://bit.ly/4g35CU2 (accessed 17 February 2025); 5. Gnant M, et al. *J Clin Oncol.* 2022;40:282–93; 6. Marmé F, et al. *ESMO Open.* 2024;9:103466; 7. Zhang L, et al. *J Clin Oncol.* 2024;42(Suppl. 16):TPS626; 8. ClinicalTrials.gov. NCT06341894. Available at https://clinicaltrials.gov/ (accessed 17 February 2025); 9. Loibl S, et al. *Ann Oncol.* 2024;35:159–82; 10. Li J, et al. *Transl Breast Cancer Res.* 2024;5:18.

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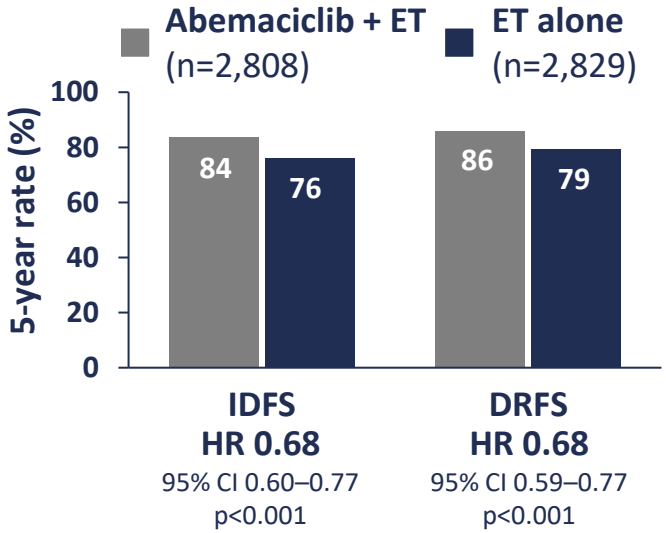
What do the latest pivotal trial data tell us about the efficacy of CDK4/6 inhibitors in patients with HR+/HER2– early breast cancer?

Efficacy of abemaciclib is maintained long-term

monarchE trial 5-year ITT data

N=5,637

- Data cut-off: 3 July 2023
- Median follow-up: 54 months (IQR 49–59)



OS
immature

HR 0.90
95% CI 0.75–1.09
p=0.284

Absolute improvement in IDFS and DRFS deepened at 5 years vs previous years

Rate at	IDFS (%)	DRFS (%)
2 years	**2.8**	**2.5**
3 years	**4.8**	**4.1**
4 years	**6.0**	**5.3**
5 years	**7.6**	**6.7**

IDFS and DRFS benefit was consistent across all subgroups evaluated

CI, confidence interval; DRFS, distant relapse-free survival; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; IQR, interquartile range; ITT, intention-to-treat; OS, overall survival.

Rastogi P, et al. *J Clin Oncol.* 2024;42:987–93.

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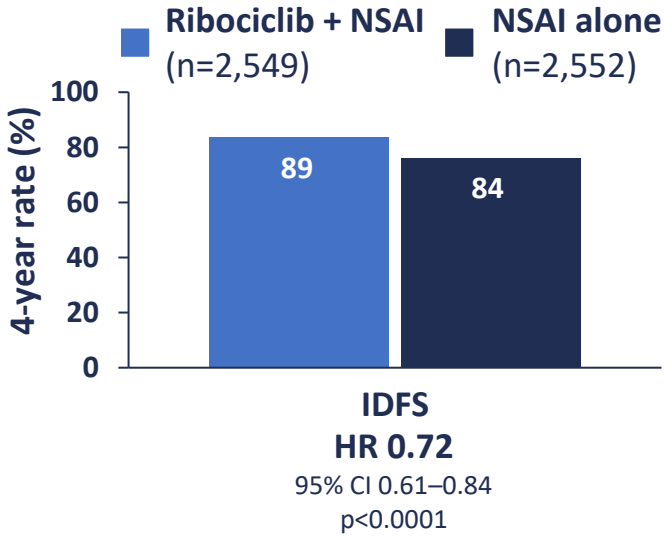
Efficacy of ribociclib is maintained long-term

NATALEE trial 4-year ITT data[1,2]

N=5,101

- Data cut-off: 29 April 2024
- Median follow-up: 44.2 months



OS
HR 0.83
95% CI 0.64–1.07
p=0.077

DDFS
HR 0.72
95% CI 0.60–0.85
p<0.0001

DRFS
HR 0.71
95% CI 0.59–0.84
p<0.0001

Absolute benefit in IDFS continued to increase at 4 years vs previous years

Rate at	IDFS (%)
3 years	**2.7**
4 years	**4.9**

Consistent IDFS benefit observed across subgroups evaluated

CI, confidence interval; DDFS, distant disease-free survival; DRFS, distant relapse-free survival; EBC, early breast cancer; HR, hazard ratio; IDFS, invasive disease-free survival; ITT, intention-to-treat; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; SABCS, San Antonio Breast Cancer Symposium.

1. Fasching PA, et al. Presented at: ESMO 2024, Barcelona, Spain. 13–17 September 2024. Abstr LBA13;
2. Hurvitz SA, et al. Presented at: SABCS, San Antonio, TX, USA. 10–13 December 2024. Abstr P4-09-22.

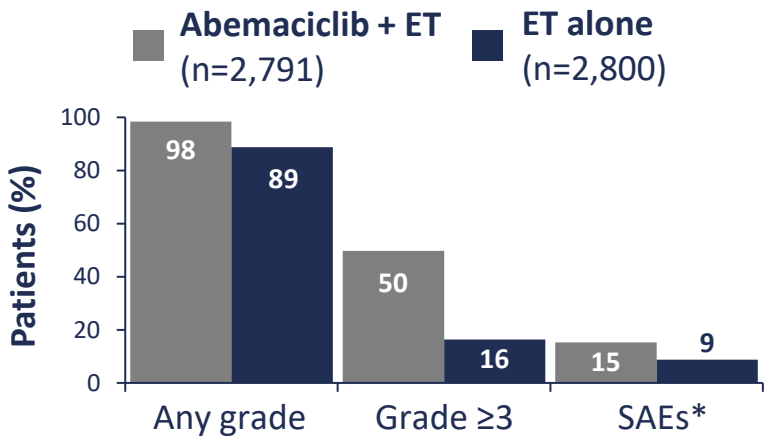
What key safety considerations should be taken into account in light of the pivotal trials for CDK4/6 inhibitors in patients with HR+/HER2– early breast cancer?

Abemaciclib has a well-established safety profile

monarchE trial safety data[1,2]

N=5,591

- Data cut-off: 1 April 2021
- Median follow-up: 27 months



Five-year follow-up (N=5,637): Higher rates of SAEs in ET-alone arm vs abemaciclib + ET (7.3% vs 6.5%)[2]

Most common AEs (≥10% in the abemaciclib + ET arm)

Abemaciclib + ET		ET alone
84%	Diarrhoea	9%
51%	Infections	39%
46%	Neutropenia	6%
41%	Fatigue	18%
30%	Nausea	9%

AE-related abemaciclib dose reductions

43% due to AEs — Most commonly: **Diarrhoea** (17%), **Neutropenia** (8%), **Fatigue** (5%)

Discontinuation of abemaciclib or all treatment in the abemaciclib arm

19% due to AEs — Most commonly: **Diarrhoea** (5%), **Fatigue** (2%), **Neutropenia** (1%)

*SAEs included deaths, initial/prolonged hospitalization, or life-threatening events.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ET, endocrine therapy; NSAI, nonsteroidal aromatase inhibitor.
1. Rugo HS, et al. *Ann Oncol.* 2022;33:616–27; 2. Rastogi P, et al. *J Clin Oncol.* 2024;42:987–93.

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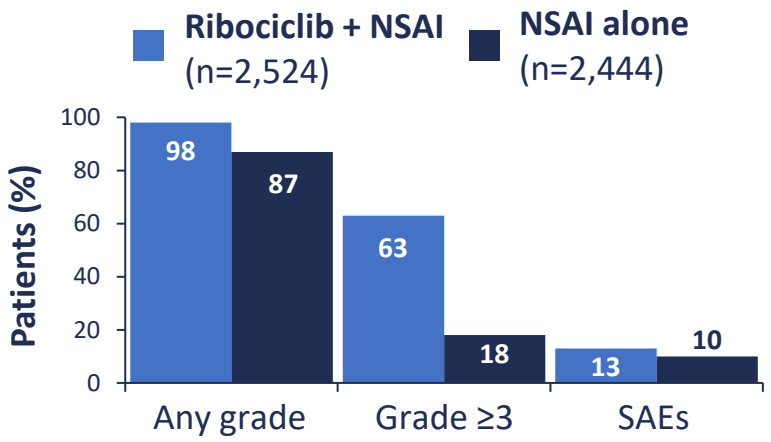
Ribociclib has a well-established safety profile

NATALEE trial safety data[1–3]

N=5,101

- Data cut-off: 11 January 2023[1]
- Median follow-up: 34 months[1]



4-year follow-up (N=5,101): Incidence of AEs remained stable from prior analyses[2]

Most common AEs (≥10% in the ribociclib + NSAI arm)*[3]

Ribociclib + NSAI		NSAI alone
42%	Neutropenia†	3%
37%	Arthralgia	43%
24%	Neutrophil count ↓†	2%
23%	Nausea	8%
23%	Headache	17%

AE-related ribociclib dose reductions*[3]

23% due to AEs — Most commonly: **Neutropenia** (9%); **Neutrophil count ↓** (6%)

Discontinuation of ribociclib*[3]

20% due to AEs — Most commonly: **↑ ALT** (7%); **↑ AST** (3%)

*Ribociclib + NSAI, n=2,525; NSAI alone, n=2,442 (data cut-off 21 July 2023). †Included in the AESI grouping 'neutropenia'.
AE, adverse event; AESI, AE of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSAI, nonsteroidal aromatase inhibitor; SAE, serious AE.
1. Slamon D, et al. *N Engl J Med.* 2024;390:1080–91; 2. Fasching PA, et al. Presented at ESMO 2024, Barcelona, Spain. 13–17 September 2024. Abstr LBA13;
3. Barrios C, et al. Presented at ESMO 2024, Barcelona, Spain. 13–17 September 2024. Abstr 113MO.

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How can CDK4/6 inhibitors address the unmet needs of patients with HR+/HER2– early breast cancer?

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Achieving state-of-the-art care with CDK4/6 inhibitors in patients with HR+/HER2– early breast cancer

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What role does risk stratification play when considering treatment with CDK4/6 inhibitors for patients with HR+/HER2– early breast cancer?

Risk stratification of HR+/HER2– early breast cancer informs management of systemic therapy

Tools used and features assessed in risk stratification

Clinicopathological features

- Age
- Menopausal status
- Tumour size
- Nodal status
- Histologic type
- Tumour grading
- HR expression level
- Proliferation markers

Risk assessment-guided treatment decision making

Low risk	Low-to-intermediate risk	Intermediate-to-high risk
• Tumour diameter <2 cm • Nodal status N0 • HR level high • Grade 1 • Proliferation index low • Genomic risk low	• Tumour diameter 2–5 cm • Nodal status N1 • Grade 2 • Proliferation index intermediate • Genomic risk intermediate	• Tumour diameter >5 cm • Nodal status ≥N2 • Grade 3 • Proliferation index high • Genomic risk high/intermediate
ET only	**(± ChT) + ET ± CDK4/6i**	**ChT + ET ± CDK4/6i**

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ChT, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.
Morganti S, et al. *Breast Cancer Res Treat.* 2022;192:465–84.

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How would you advise selecting the optimal CDK4/6 inhibitor for eligible patients with HR+/HER2– early breast cancer?

In your opinion, what are some key considerations for maximizing the potential of CDK4/6 inhibitors in patients with HR+/HER2– early breast cancer?

The safety profile of CDK4/6 inhibitors: Generally manageable, yet important to monitor

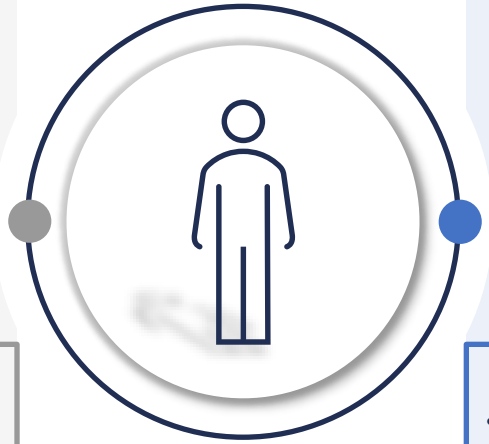
Abemaciclib[1]

Very common* AEs

- Infections
- Neutropenia, leukopenia, anaemia, thrombocytopenia, lymphopenia
- Decreased appetite, diarrhoea, vomiting, nausea, stomatitis
- Headache, dysgeusia, dizziness
- Fatigue

Special warnings/precautions†

- Neutropenia
- Infections/infestations
- Diarrhoea
- ↑ ALT/AST
- ILD/pneumonitis
- VTEs/ATEs



Ribociclib[2]

Very common‡ AEs

- Infections
- Neutropenia, leukopenia
- Cough
- Nausea, diarrhoea, constipation, abdominal pain
- Alopecia
- Headache
- Fatigue, asthenia, pyrexia
- Abnormal liver function tests

Special warnings/precautions†

- Neutropenia
- Hepatobiliary toxicity
- QT interval prolongation
- Severe cutaneous AEs
- ILD/pneumonitis
- ↑ Blood creatinine

*Possibly affecting ≥1/10 people, as listed in the SmPC, based on data reported in the phase III trials of abemaciclib + ET (N=3,559) and during post-marketing experience.[1]
†Not necessarily very common. ‡Possibly affecting ≥1/10 people, as listed in the SmPC, based on data reported in the phase III NATALEE trial of ribociclib + AI (N=2,525) and during post-marketing experience.[2]
↑, increased; AE, adverse event; AI, aromatase inhibitor; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATE, arterial thromboembolic event; ET, endocrine therapy; ILD, interstitial lung disease; SmPC, summary of product characteristics; VTE, venous thromboembolic event.
1. EMA. Abemaciclib SmPC. Available at: https://bit.ly/4g1Z7BE (accessed 17 February 2025); 2. EMA. Ribociclib SmPC. Available at: https://bit.ly/3ZjJ8b7 (accessed 17 February 2025).

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