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

Practice aid for HR+/HER2– early breast cancer

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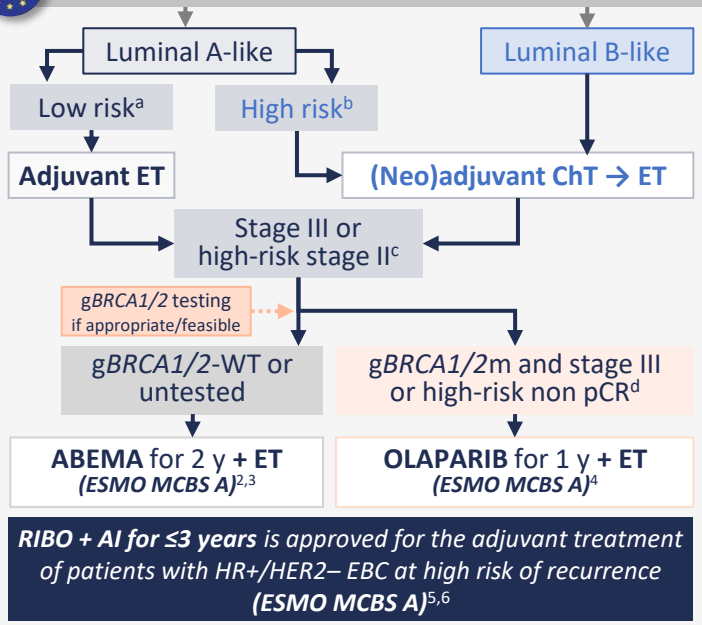
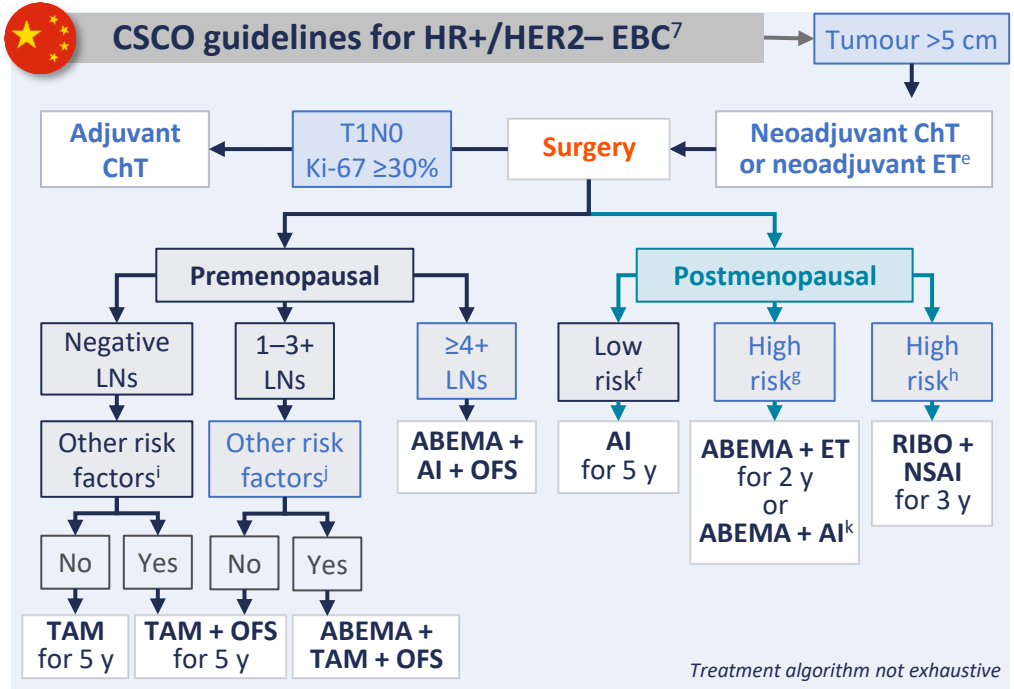
Targeted treatments are recommended by ESMO and the CSCO for patients with HR+/HER2– EBC

ESMO guidelines for HR+/HER2– EBC[1–4]



CSCO guidelines for HR+/HER2– EBC[7]



[a]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. [b]Implies high-risk genomic score and/or higher-risk features. [c]Stage N1 with primary tumour >5 cm, and/or grade 3 and/or Ki-67 ≥20%. [d]HR+ tumours and non-pCR after neoadjuvant ChT require a pretreatment clinical stage and post-treatment pathological stage, ER and tumour grade score ≥3 to receive olaparib. [e]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 recommended (or fulvestrant if AI 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 [f]Implies (1) negative LNs; (2) 1–3+ LNs with grade 1–2, tumour <5 cm and Ki-67 <20%. [g]Implies (1) ≥4+ LNs; (2) 1–3+ LNs with other risk factors, such as grade 3, tumour ≥5 cm, or Ki-67 ≥20%. [h]Implies stage II or III disease, encompassing node negative with grade 3/2 and Ki-67 ≥20% or high-risk genetic profiles. [i]Grade 2–3, tumour >2 cm, or high Ki-67. [j]Such as grade 3, tumour ≥5 cm, or Ki-67 ≥20%. [k]If abemaciclib is not tolerated, switching to another CDK4/6 inhibitor, e.g. ribociclib, may be appropriate.

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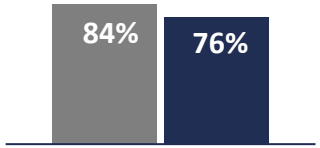
Two CDK4/6 inhibitors are approved for HR+/HER2– EBC and maintain long-term efficacy profiles[a]

monarchE: ABEMA + ET vs ET alone[8]

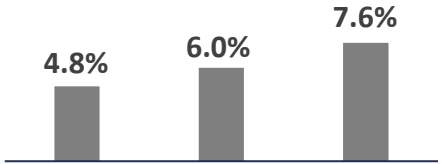
N=5,637[b] | Median follow-up: **54 months**



IDFS 5-year rate

HR 0.68
95% CI 0.60–0.77
p<0.001

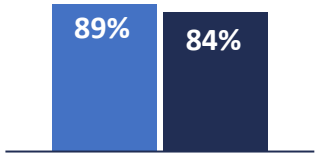
DRFS
HR 0.68
95% CI 0.59–0.77
p<0.001



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

NATALEE: RIBO + NSAI vs NSAI alone[9,10]

N=5,101[c] | Median follow-up: **44 months**

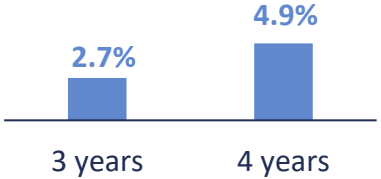


IDFS 4-year rate

HR 0.72
95% CI 0.61–0.84
p<0.0001

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

[a]**Direct comparisons between trials should not be made due to differences in trial design.**
[b]Abemaciclib + ET, n=2,808; ET alone, n=2,829 (data cut-off 3 July 2023). [c]Ribociclib + NSAI, n=2,549; NSAI alone, n=2,552 (data cut-off 29 April 2024).

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Abemaciclib and ribociclib have well established safety profiles[a]

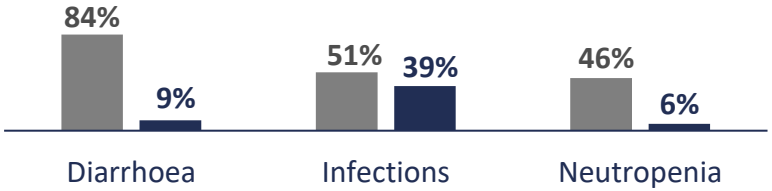
monarchE: ABEMA + ET vs ET alone[8,11]

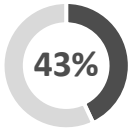
N=5,591 (ITT)[11] Median follow-up: **27 months**[11]

Any grade AEs[11b]	Grade ≥3 AEs[11b]	SAEs[11b]
98% vs 89%	50% vs 16%	15% vs 9%

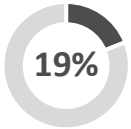
5-year follow-up (N=5,637): SAEs **6.5%** vs **7.3%**[8]

Most common AEs (≥10% in ABEMA + ET arm)[11b]





Experienced AE-related ABEMA dose reductions[11b]



Discontinued ABEMA or all treatment in the ABEMA arm due to AEs[11b]

Mostly due to: Diarrhoea, neutropenia and **fatigue**[11]

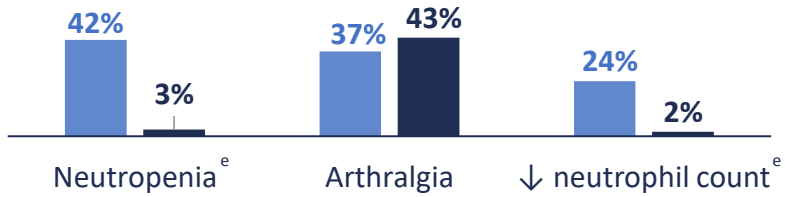
NATALEE: RIBO + NSAI vs NSAI alone[12,13]

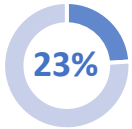
N=5,101 (ITT)[12] Median follow-up: **34 months**[12]

Any grade AEs[12c]	Grade ≥3 AEs[12c]	SAEs[12c]
98% vs 87%	63% vs 18%	13% vs 10%

4-year follow-up: AE incidence remained stable[9]

Most common AEs (≥10% in either arm)[13d]





Experienced AE-related RIBO dose reductions[13d]

Mostly due to neutropenia and **↓ neutrophil count**[13]

Discontinued RIBO due to AEs[13d]

Mostly due to ↑ ALT and **↑ AST**[13]

[a]**Direct comparisons between trials should not be made due to differences in trial design.** [b]Abemaciclib + ET, n=2,791; ET alone, n=2,800 (data cut-off 1 April 2021).[11] [c]Ribociclib + NSAI, n=2,524; NSAI alone, n=2,444 (data cut-off 11 January 2023).[12] [d]Ribociclib + NSAI, n=2,525; NSAI alone, n=2,442 (data cut-off 21 July 2023).[13] [e]Included in the AESI grouping 'neutropenia'.[13]

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Key strategies for maximizing the potential of CDK4/6 inhibitors in patients with HR+/HER2– EBC

Risk stratification of HR+/HER2– EBC informs treatment decision-making[14]

Rik stratification assessment features	Risk assessment-guided treatment decision making
Clinicopathological	
• Age	**Low risk**
• Menopausal status	**ET only**
• Tumour size	
• Nodal status	**Low-to-intermediate risk**
• Histologic type	**(± ChT) + ET ± CDK4/6i**
• Tumour grading	
• HR expression level	**Intermediate-to-high risk**
• Proliferation markers	**ChT + ET ± CDK4/6i**
Genomic profile	
• Subtype signatures	
• Commercial assays	

- **Ensure treatment adherence** through appropriate patient selection, considering patient preferences and effectively managing side effects[1,15,16]
- **Be aware of when side effects may occur**, e.g. risk of liver toxicity early in CDK4/6 inhibitor treatment[11,13]
- **Be alert to potential cumulative side effects with combination therapy**, e.g. cardiotoxicity (RIBO + TAM), or VTEs/ATEs (ABEMA + TAM)[3,5,17,18]
- **Review concomitant medications** for potential drug–drug interactions[3,5,19]
- **Managing low grade toxicity** to maximize QoL[20]
- **Engage support of the nursing team** to assist with patient education, side-effect management and side-effect reporting[21]
- **Patient education** on potential side effects and action if a side effect occurs[15,17,18,21]

The safety profiles of CDK4/6 inhibitors are generally manageable, yet important to monitor[2,5]

Management of some AEs may require dose interruption and/or reduction[2,5]

Special warnings & precautions

Abemaciclib[2]

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

Ribociclib[5]

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

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Abbreviations and references

Abbreviations

ABEMA, abemaciclib; AE, adverse event; AESI, AE of special interest; AI, aromatase inhibitor; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATE, arterial thromboembolic events; CDK4/6i, CDK4/6 inhibitor; ChT, chemotherapy; CI, confidence interval; CSCO, Chinese Society of Clinical Oncology; DDFS, distant disease-free survival; DRFS, distant relapse-free survival; EBC, early breast cancer; ER, oestrogen receptor; ESMO, European Society of Medical Oncology; ET, endocrine therapy; gBRCA1/2, germline BRCA1/2; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor positive; IDFS, invasive disease-free survival; ILD, interstitial lung disease; LN, lymph node; MCBS, magnitude of clinical benefit score; NSAI, nonsteroidal aromatase inhibitor; OFS, ovarian function suppression; pCR, pathological complete response; PgR, progesterone receptor; QoL, quality of life; RIBO, ribociclib; SAE, serious AE; TAM, tamoxifen; VTE, venous thromboembolism; WT, wild-type; y, years.

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