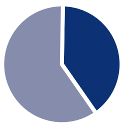
HR+, HER2- Early Breast Cancer:
CDK4/6 Inhibitors and Trial Endpoints

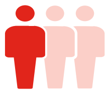
Identifying Patients With HR+, HER2- EBC at High Risk for Disease Recurrence

Endocrine therapy (ET) is the backbone of adjuvant treatment in patients with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative early breast cancer (EBC) and has transformed outcomes for patients[1]

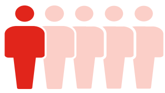


Despite adjuvant ET, **up to 41% of patients remain at risk of disease recurrence over the next 20 years**[1,2]

In patients with node-positive, high-risk disease[3,4]:



~1 in 3 is at risk of recurrence within 5 years



~1 in 5 is at risk of mortality within 5 years

Recurrence risks may be **comparable to early TNBC**, which is considered the most aggressive breast cancer subtype[4]

CDK4/6 Inhibitors for Select Patients With High-Risk Disease

CDK4/6i

Two CDK4/6i are currently approved by regulatory authorities (e.g. FDA and European Commission) for treating select patients with HR+, HER2- EBC who are at high risk of disease recurrence.[5-9]

The trials that led to the approval of adjuvant CDK4/6i had specific features related to[7-9]:

- Patient population
- Risk factors
- ET partner
- Dosing schedule/ treatment duration
- Data maturity
- Endpoints

Patients with high-risk disease may benefit from adjuvant CDK4/6i in combination therapy to reduce their risk of recurrence.[7-9] Understanding these clinical trials is essential for interpreting the results and selecting adjuvant therapy.

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Efficacy Endpoints in Adjuvant CDK4/6i Trials

Overall survival (OS) is a clinically meaningful measure of **efficacy** and is considered the **gold standard endpoint** in oncology clinical trials[10,11]

However, **OS is historically a challenging primary endpoint** in HR+ EBC,[10,11] often requiring meta-analyses with large patient numbers to demonstrate improvement in breast cancer mortality[12-15]

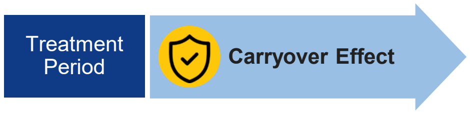
The trials leading to adjuvant CDK4/6i approval have used **invasive disease-free survival (IDFS) as the primary efficacy endpoint**[7-9]

- Distant relapse-free survival (DRFS) and distant disease-free survival (DDFS) were additional surrogate endpoints for OS[7-9]

Surrogate Endpoints for OS

Improvement in these surrogate endpoints means fewer recurrences and fewer instances of metastatic disease[16]

		IDFS	DRFS	DDFS
Local	Local invasive recurrence	✓		
	Invasive ipsilateral breast tumor recurrence	✓		
Regional	Regional invasive recurrence	✓		
	Invasive contralateral breast cancer	✓		
Distant	Distant recurrence	✓	✓	✓
	Second primary non-breast invasive cancer	✓		✓
Death of Any Cause		✓	✓	✓



In addition to study endpoints, the **carryover effect** of adjuvant therapy has been used to evaluate the efficacy of ET[12,13]

The term **carryover effect** has been used to describe the long-lasting benefit of ET in reducing the risk of recurrence **after stopping the initial treatment**[12,13,17]

Evaluating the **long-term efficacy of CDK4/6i** on recurrence risk is ongoing[7,8]

Two CDK4/6i are currently approved by regulatory authorities (e.g. FDA and European Commission) for treating select patients with HR+, HER2- EBC who are at high risk of disease recurrence.[5,6] Understanding the adjuvant CDK4/6i trial results is important for guiding treatment decisions.

References: **1.** Hussain M, et al. *Ther Adv Med Oncol.* 2025;17:17588359251326710. **2.** Pan H, et al. *N Engl J Med.* 2017;377(19):1836-1846. **3.** Sheffield KM, et al. *Future Oncol.* 2022;18(21):2667-2682. **4.** Rugo HS, et al. Presented at: *ESMO Breast 2025*. Poster 215P. **5.** Abemaciclib [EU SmPC]. Amsterdam, The Netherlands:European Medicines Agency; Eli Lilly Nederland B.V., 2026. **6.** Ribociclib [EU SmPC]. Amsterdam, The Netherlands: European Medicines Agency; Novartis Europharm Limited, 2026. **7.** Rastogi P, et al. *J Clin Oncol.* 2024;42(9):987-993. **8.** Slamon D, et al. *N Engl J Med*. 2024;390(12):1080-1091. **9.** Johnston SRD, et al. *J Clin Oncol*. 2020;38(34):3987-3998. **10.** Delgado A, Guddati AK. *Am J Cancer Res.* 2021;11(4):1121-1131. **11.** Untch M, et al. *Eur J Cancer.* 2024;202:113977. **12.** EBCTCG. *Lancet*. 2015;365(9472):1687-1717. **13.** EBCTCG. *Lancet.* 2011;378(9793):771-784. **14.** EBCTCG. *Lancet.* 2025;406(10503):603-614. **15.** Francis PA. *J Clin Oncol.* 2023;41(7):1370-1375.
16. Hudis CA, et al. *J Clin Oncol.* 2007;25(15):2127-2132. **17.** Chumsri S, Thompson EA. *Lancet.* 2020;395(10218):91-92.

Abbreviations: CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; DDFS=distant disease-free survival; DRFS=distant relapse-free survival; EBC=early breast cancer; ET=endocrine therapy; EU= European Union; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IDFS=invasive disease-free survival; OS=overall survival; SmPC= Summary of Product Characteristics; TNBC=triple-negative breast cancer.