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

These risks are **like early TNBC**, which is considered the most aggressive breast cancer subtype[4]

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

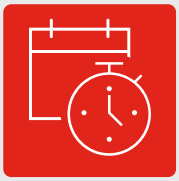
Two cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) **reduce recurrence risk** in combination with ET and are **FDA approved** for select patients with high-risk, HR+, HER2- EBC[a,5-9]

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

[a]Approval varies by country. Review your national guidelines for approval information.

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]

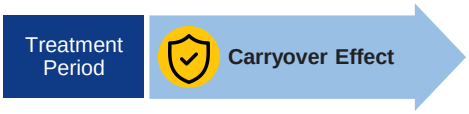
The trials leading to adjuvant CDK4/6i approval have used **invasive disease-free survival (IDFS) as the primary efficacy endpoint**[7-9]

- 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]

There are 2 FDA-approved CDK4/6i for use in combination with ET for treating patients with high-risk, HR+, HER2- EBC.[5,6] Understanding the adjuvant CDK4/6i trial results is important for guiding treatment decisions

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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; FDA=US Food and Drug Administration; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IDFS=invasive disease-free survival; OS=overall survival; TNBC=triple-negative breast cancer.

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