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Using Cyclin-dependent Kinases 4/6 Inhibitors to Treat Hormone Receptor-positive Advanced Breast Cancer

Clinical management of adverse events and disease progression following treatment

Hormone receptor (HR)-positive HER2-negative breast cancer (BC)

- Most prevalent type of cancer (70%)[1]
- Risk of recurrence highest in 0–2 years[2]
- Adjuvant endocrine therapy (ET) reduces disease recurrence and mortality[1,3]

- Selective estrogen receptor (ER) modulators (SERMs)
  Example: Oral tamoxifen
- Aromatase inhibitors (Ais)
  Example: Oral anastrozole, letrozole, and exemestane
- Selective ER degraders/down-regulators (SERDs)
  Example: Intramuscular fulvestrant

Sensitivity to ET governs relapse and survival[2]

Classification	Time of relapse	Median overall survival
Primary endocrine-resistant	Within 0–2 years of ET	27.2 months
Secondary endocrine-resistant	After 2 years /within 1 year of completing ET	38.4 months
Endocrine sensitive	>1 year of adjuvant ET completion/ no prior ET exposure	43.2 months

- Primary endocrine-resistant group has the worst prognosis
- Patients are relatively younger with frequent visceral relapses, e.g. liver metastases

Approximately, 40% of patients experience relapse due to acquired resistance to ET[2,4]

Overcoming endocrine resistance with cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors (CDK4/6i)

CDK4/6, along with cyclin D1, control the G1–S phase transition of the cell cycle[5]

Acquired resistance to ET is associated with dependence on cyclin D1 and CDK4/6[6]

S1	S2
High expression of cyclin D1 in HR+ BC cells[7] • Direct transcriptional target of ER • Induced by RTK and oncogenic signalling	Hormone-independent activation of ER by cyclin D1[8]

- Small molecules that bind to the ATP-binding pocket of CDK4/6, inactivate the cyclin D-CDK4/6 complex, prevent phosphorylation of retinoblastoma protein, and induce cell cycle arrest[6]
- CDK4/6i, in combination with ET, are approved for clinical use in advanced-stage HR+ BC and as first-line therapy, in combination with aromatase inhibitors (AI), in high-risk early-stage BC[7]

Abemaciclib | Palbociclib | Ribociclib | Dalpiciclib (approved in China)

*Abbreviations: ATP: Adenosine triphosphate; EGFR: Epidermal growth factor receptor; ER: Estrogen receptor; HER2: Human epidermal growth factor 2; RTK: Receptor tyrosine kinase

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Benefits of CDK4/6i in metastatic BC[5]

Multiple randomised clinical trials show prolonged PFS (in months) with CDK4/6i treatment

AI naïve (ET sensitive)

PALOMA-2

- 24.8 — Palbociclib + letrozole
- 14.5 — Placebo + letrozole

MONARCH-3

- 28.2 — Abemaciclib + letrozole/anastrozole
- 14.8 — Placebo + letrozole/anastrozole

MONALEESA-2

- 25.3 — Ribociclib + letrozole
- 16.0 — Placebo + letrozole

DAWNA-2[9]

- 30.6 — Dalpiciclib + letrozole/anastrozole
- 18.2 — Placebo + letrozole/anastrozole

AI pretreated (ET resistant)

PALOMA-3

- 9.5 — Palbociclib + fulvestrant
- 4.6 — Placebo + fulvestrant

MONARCH-2

- 16.3 — Abemaciclib + fulvestrant
- 9.3 — Placebo + fulvestrant

DAWNA-1[10]

- 16.3 — Dalpiciclib + fulvestrant
- 7.2 — Placebo + fulvestrant

Both AI-naïve and AI-pretreated

MONALEESA-3

- 20.5 — Ribociclib + fulvestrant
- 12.8 — Placebo + fulvestrant

MONALEESA-7

- 23.8 — Ribociclib + ET
- 13.0 — Placebo + ET

Differences in the pharmacokinetics of CDK4/6i[11]

Palbociclib	Ribociclib	Abemaciclib
All three are orally bioavailable		
High selectivity for CDK4 and CDK6		
	Higher CDK4:CDK6 inhibition ratio (~4)	
		Highest CDK4:CDK6 inhibition ratio of 5
		Additional activity on multiple kinases

The CDK4/6i have similar efficacy but differ in their toxicity profiles

Adverse events (AEs) associated with the use of CDK4/6i[12,13]

Haematologic AEs

- Palbociclib and ribociclib – Asymptomatic neutropenia

Non-haematologic AEs

- Abemaciclib causes predominantly gastrointestinal toxicity, entailing grade 1–2 diarrhoea, fatigue, and abdominal pain
- In contrast to palbociclib, both abemaciclib and ribociclib cause hepatotoxicity
- Ribociclib prolongs QTc in <5% of patients necessitating ECG monitoring during the first two cycles
- Ribociclib confers a higher risk of respiratory injury

*Abbreviations: ECG: Electrocardiogram; PFS: Progression-free survival; QTc: QT interval

Guidelines for clinical management of CDK4/6i treatment-related AEs[12–14]

Neutropenia is the result of the cytostatic effect of CDK6 inhibition and is reversible

Clinical management
Monitor blood counts prior to initiation therapy
Consider dose reduction in cases of:
- Recurrent uncomplicated Grade 3 neutropenia
- Prolonged (>1 week) recovery from Grade 3 neutropenia
- Febrile neutropenia recovered to Grade 2

Interstitial lung disease (ILD)
Severe lung inflammation reported in treatment with all three CDK4/6i

Clinical management
- Regular monitoring for symptoms of ILD or pneumonitis (hypoxia, cough, dyspnea)
- Suspend or discontinue treatment if Grade >2 symptoms appear and/or worsen

Venus thromboembolism
Abemaciclib + hormone therapy: 2%
Hormone therapy alone: 0.5%
Risk ratio: 2.62

Clinical management
Primarily treated with anti-coagulants

QTcF prolongation
Prolongation of the QT interval associated with palbociclib and ribociclib treatment is dose-dependent and clinically uncomplicated

Clinical management
Review concomitant medications that further increase the risk of QTcF prolongation

Diarrhoea
Gastrointestinal toxicity with abemaciclib does not impact the magnitude of the benefit (PFS in months)
- Diarrhoea within 7 days: 28.2
- No diarrhoea in first 7 days: 29.1
- Placebo: 14.8

Clinical management
- Treat with antidiarrheal agents like loperamide
- Recommend increasing fluid intake and avoiding lactose and alcohol consumption
- Consider suspending the dose for Grade 2 or higher symptoms
- Grade 3 or 4 may require hospitalisation

AEs are effectively managed by supportive medications and/or dose adjustments, with no detriment to PFS

Impact of CDK4/6i treatment on quality of life (QoL)[15,16]

Overall, the addition of CDK4/6i to ET does not worsen patient HR-QoL
- Positive trend towards pain improvement

Exception: Gastrointestinal toxicities influence HR-QoL of patients treated with abemaciclib

Impact of age on CDK4/6i efficacy[17,18]

- Given higher comorbidities, older patients may consider QoL as important or even more important than survival
- CDK4/6i + ET is equally effective in older patients
- Older patients experience similar to slightly increased toxicity than younger patients

Patients with metastatic BC will eventually progress on the combination therapy due to genetically acquired resistance to ET, CDK4/6i, or both

MONALEESSA –2, –3, –7

Ribociclib vs placebo
- Frequency of mutations in genes *ESR1*, *RB1*, *FAT3*, and *TET2* higher at end-of-treatment
- Percentage of patients with high total mutational burden[19] (>10 mutation/MB) increased at end-of-treatment in ribociclib arm vs placebo

Mechanisms of resistance to combination CDK4/6i and ET[20]

- Upregulation of CDK6/cyclin D1
- *RB1* loss or mutation
- Upregulation of CDK2/ cyclin E1 (CCNE1)
- PI3K/AKT pathway alteration
- Alterations in RAS/MAPK pathway

*Abbreviations: HR-QoL: Health-related quality of life; QTcF: QT interval corrected for heart rate using the Fridericia formula

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Therapeutic strategies following progression on CDK4/6i therapy[20]

MAINTAIN (PFS in months)

- 5.29 — Ribociclib + switch ET
- 2.76 — Placebo + switch ET
  - Continuing with CDK4/6i beyond progression; switching CDK4/6i has added advantage

PACE (palbociclib + fulvestrant (SERD) + avelumab)

- 4.8 — Fulvestrant
- 4.6 — F+palbociclib
- 8.1 — F+P+avelumab
  - Addition of immunotherapy benefits PFS

DESTINY-Breast04 (antibody-drug conjugate anti-HER2)

- 10.1 — Trastuzumab deruxtecan
- 5.4 — TPC

TROPiCS-02 (antibody-drug conjugate anti-Trop2)

- 5.5 — Sacituzumab govitecan
- 4.0 — TPC

PADA-1 (ET)[21]

- 11.9 — Fulvestrant (ET) + palbociclib
- 5.7 — AI + palbociclib

SERENA-2 (oral SERDs in patients with *ESR1* mutations)[21]

- 7.2 — Camizestrant
- 3.7 — Fulvestrant

EMERALD (ET in patients with *ESR1* mutation)[22] (PFS rate)

- 34.3% — Elacestrant
- 20.4% — ET (SERD of choice)

CAPItello-291: Capivasertib in patients with AKT pathway alterations[21]

- 10.3 — Capivasertib + fulvestrant
- 4.8 — Placebo + fulvestrant

SOLAR-1: Alpelisib in patients with *PIK3CA*-mutation[21]

- 11.0 — Alpelisib + fulvestrant
- 5.7 — Placebo + fulvestrant

INAVO120: Inavolisib in patients with *PIK3CA*-mutation[21]

- 15 — Inavolisib + palbociclib + fulvestrant
- 7.3 — Placebo + palbociclib + fulvestrant
  - Early reduction in *PIK3CA* circulating tumour DNA (ctDNA) in plasma samples from patients treated with palbociclib and fulvestrant, strongly predicts improved PFS[23]

Key messages

- Combination of CDK4/6i and ET prolongs PFS in patients with advanced HR+ HER2-BC
- Dose reductions allow control of CDK4/6i treatment-related adverse events without compromising efficacy and preserve the patient's QoL
- Monitoring the presence of acquired genetic mutations within the circulating tumour DNA pool guides targeted therapeutic approaches following disease progression on CDK4/6i

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