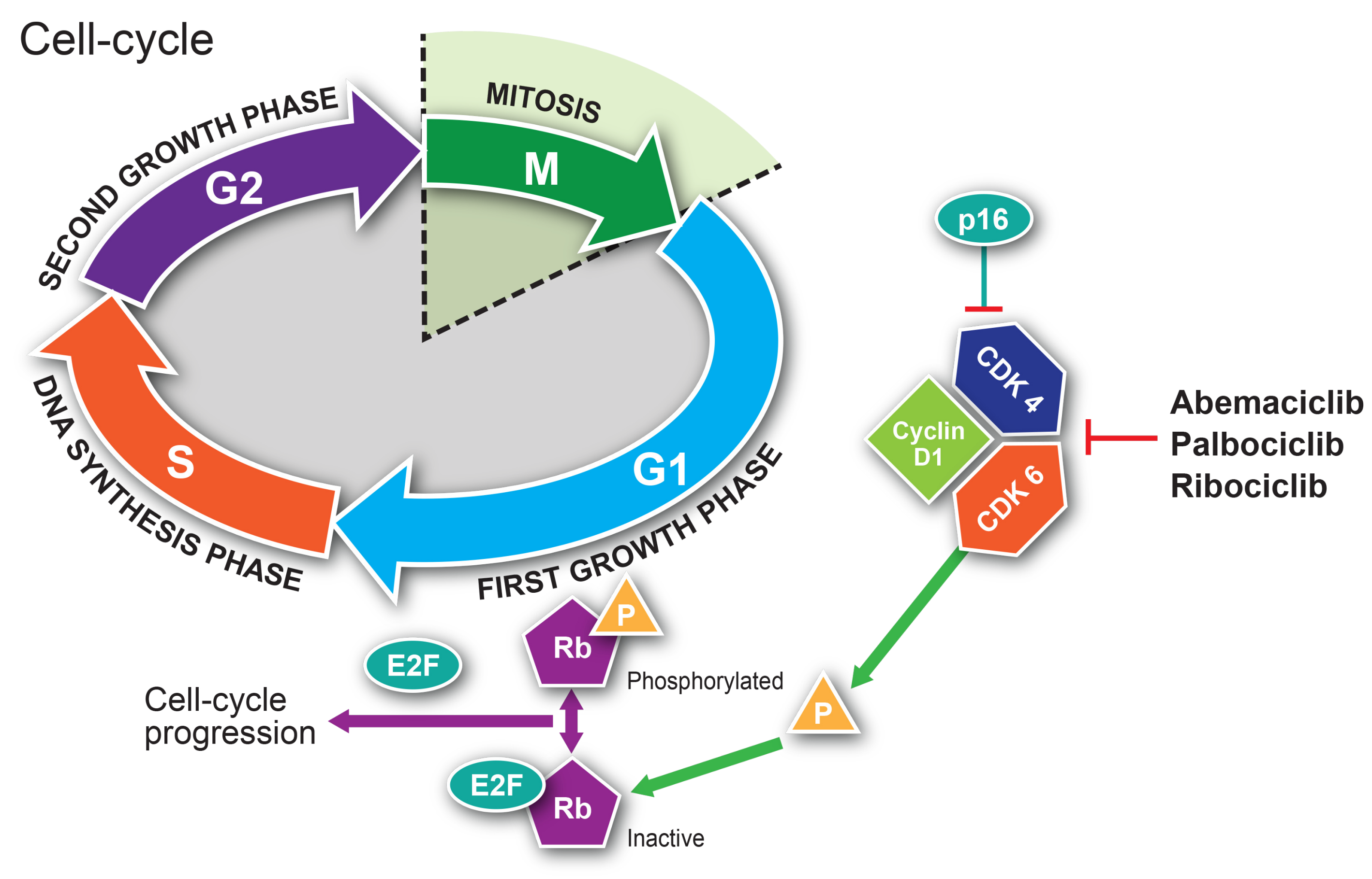
Understanding the Role of CDK4/6 Inhibitors in EBC

CDK4/6 inhibitors are a novel class of therapeutics that have demonstrated clinically meaningful improvements in PFS for patients with HR+/HER2- advanced or metastatic BC, and more recently, in high-risk EBC.

How Do CDK4/6 Inhibitors Work?



CDK4/6 inhibitors work by blocking CDK4/6-mediated repression of *Rb*, a tumor suppressor gene that regulates the cell cycle. In the presence of CDK4/6 inhibitors, *Rb* remains bound to E2F transcription factors, and genes required for DNA replication are not transcribed.

Figure adapted from Battisti N, et al. 2018.

FDA-Approved[a] CDK4/6 Inhibitors for BC

As of November 2022, there are 3 FDA-approved CDK4/6 inhibitors for BC treatment:

AGENT	FDA-APPROVED INDICATION(S)
Abemaciclib	• **In combination with ET (tamoxifen or AI) for the adjuvant treatment of HR+/HER2-, node-positive EBC at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA-approved test** • In combination with AI as initial ET for the treatment of HR+/HER2- advanced or metastatic BC • In combination with fulvestrant for the treatment of HR+/HER2- advanced or metastatic BC with disease progression following ET • As monotherapy for the treatment of HR+/HER2- advanced or metastatic BC with disease progression following ET and prior chemotherapy in the metastatic setting
Palbociclib	• Treatment of HR+/HER2- advanced or metastatic BC in combination with: – AI as initial ET in postmenopausal women or in men – Fulvestrant in patients with disease progression following ET
Ribociclib	• Treatment of HR+/HER2- advanced or metastatic BC in combination with: – AI as initial ET – Fulvestrant as initial ET or following disease progression on ET in postmenopausal women or in men

Abemaciclib is the only CDK4/6 inhibitor approved by the FDA and recommended by the NCCN for adjuvant treatment of high-risk EBC.

[a]As of November 2022.

monarchE: Adjuvant Abemaciclib + ET in Node-Positive, HR+/HER2- EBC

Global, randomized, open-label phase 3 study

- HR+/HER2- resected EBC without evidence of distant metastases
- Pathologic lymph node involvement and ≥1 of the following indicating a higher risk of recurrence:
  — ≥4 positive axillary lymph nodes
  — Tumor size of ≥5 cm
  — Grade 3 (≥8 points on the Bloom Richardson grading system)
  — Ki-67 index ≥20% on untreated breast tissue
- ECOG PS ≤1 and adequate organ function

R

1:1

- 150-mg abemaciclib BID up to 2 years
- Physician's choice ET

n=2,808

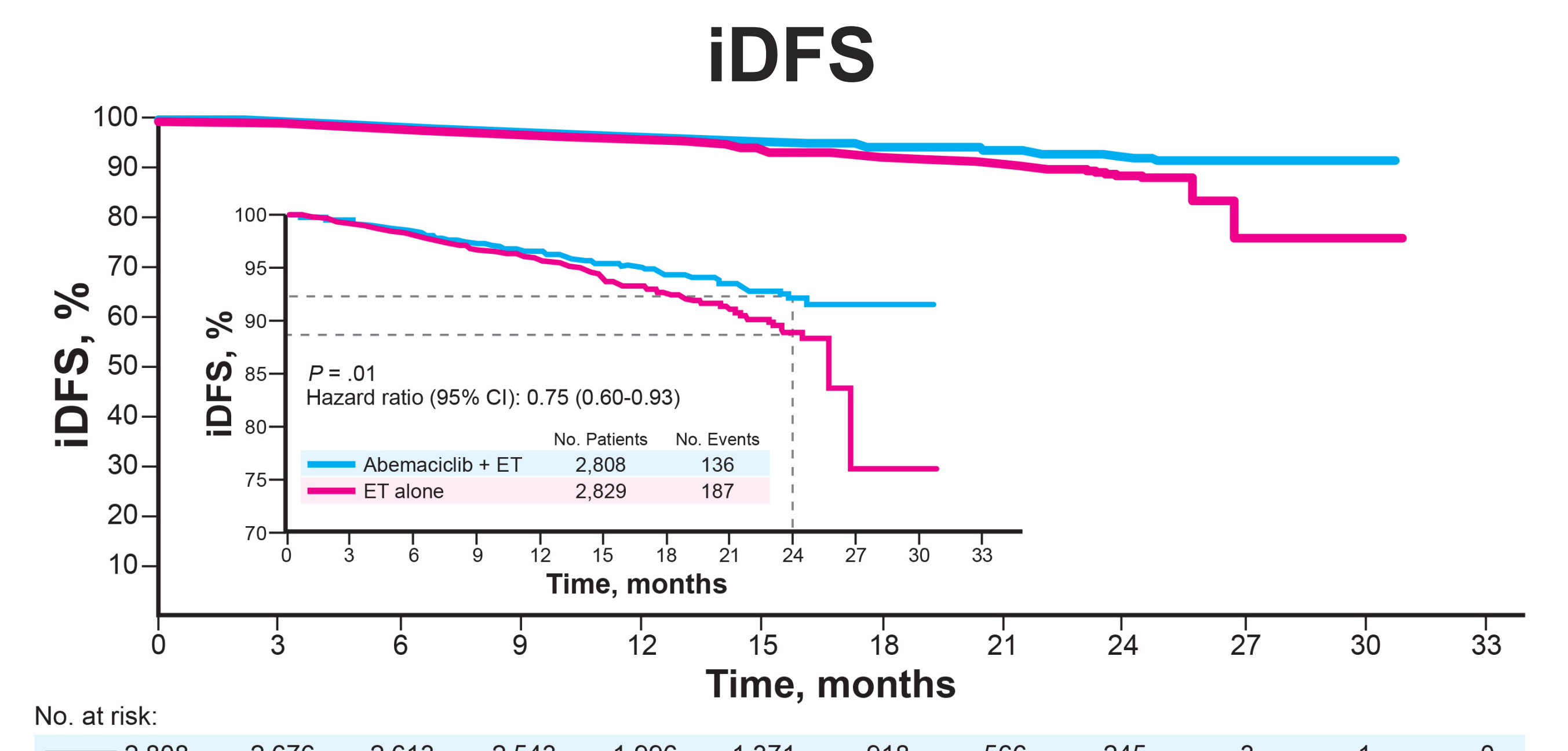
- Physician's choice ET

n=2,829

PRIMARY ENDPOINT	SECONDARY ENDPOINTS
• iDFS	• iDFS for participants with Ki-67 index ≥20% • DRFS • Overall survival • Change from baseline on FACT-B and FACT-ES

In the RCT monarchE, abemaciclib added to standard adjuvant ET significantly improved iDFS (top graph) and DRFS (bottom graph) among patients with HR+/HER2-, node-positive, high-risk EBC with manageable safety.

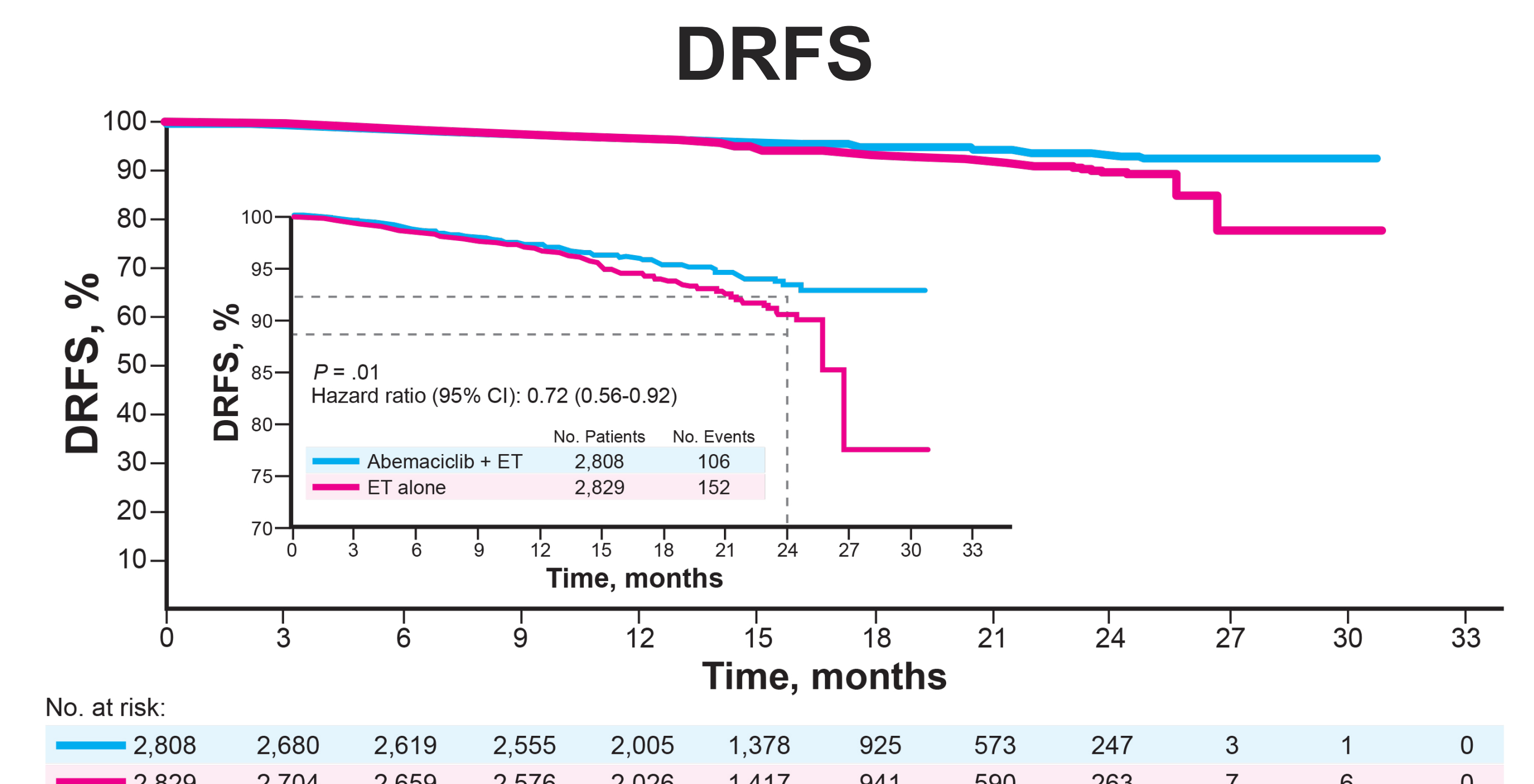
iDFS



No. at risk:

2,808	2,676	2,613	2,543	1,996	1,371	918	566	245	3	1	0
2,829	2,699	2,649	2,562	2,013	1,405	932	586	262	7	6	0

DRFS



No. at risk:

2,808	2,680	2,619	2,555	2,005	1,378	925	573	247	3	1	0
2,829	2,704	2,659	2,576	2,026	1,417	941	590	263	7	6	0

The most frequent AEs in the abemaciclib arm were:

82.2% DIARRHEA

44.6% NEUTROPENIA

38.4% FATIGUE

- Majority were grade 1-2
- Diarrhea occurred early (median time to onset for any grade: 8 days), was short-lived (median duration for grades 2-3: 5-6 days), and was managed with antidiarrheal medication
- VTE and ILD were reported more often in the abemaciclib arm, although serious AEs were uncommon

Key Take-Aways

CDK4/6 inhibition in combination with ET has demonstrated benefit in both advanced/metastatic BC and high-risk EBC

Abemaciclib is the only CDK4/6 inhibitor approved by the FDA and recommended by the NCCN for adjuvant treatment of high-risk EBC

Abemaciclib combined with adjuvant ET is associated with a high rate of gastrointestinal toxicities, primarily diarrhea, of grade 1-2 in most cases

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Abbreviations:

AE: adverse event
AI: aromatase inhibitor
BID: 2 times daily
DRFS: distant relapse-free survival
(E)BC: (early) breast cancer
ECOG PS: Eastern Cooperative Oncology Group performance status
ET: endocrine therapy
FACT-B/ES: Functional Assessment of Cancer Therapy – Breast/Endocrine Subscale
FDA: US Food and Drug Administration
HER2: human epidermal growth factor receptor 2
HR: hormone receptor
iDFS: invasive disease-free survival
ILD: interstitial lung disease
NCCN: National Comprehensive Cancer Network
PFS: progression-free survival
Rb: retinoblastoma protein
RCT: randomized controlled trial
VTE: venous thromboembolism