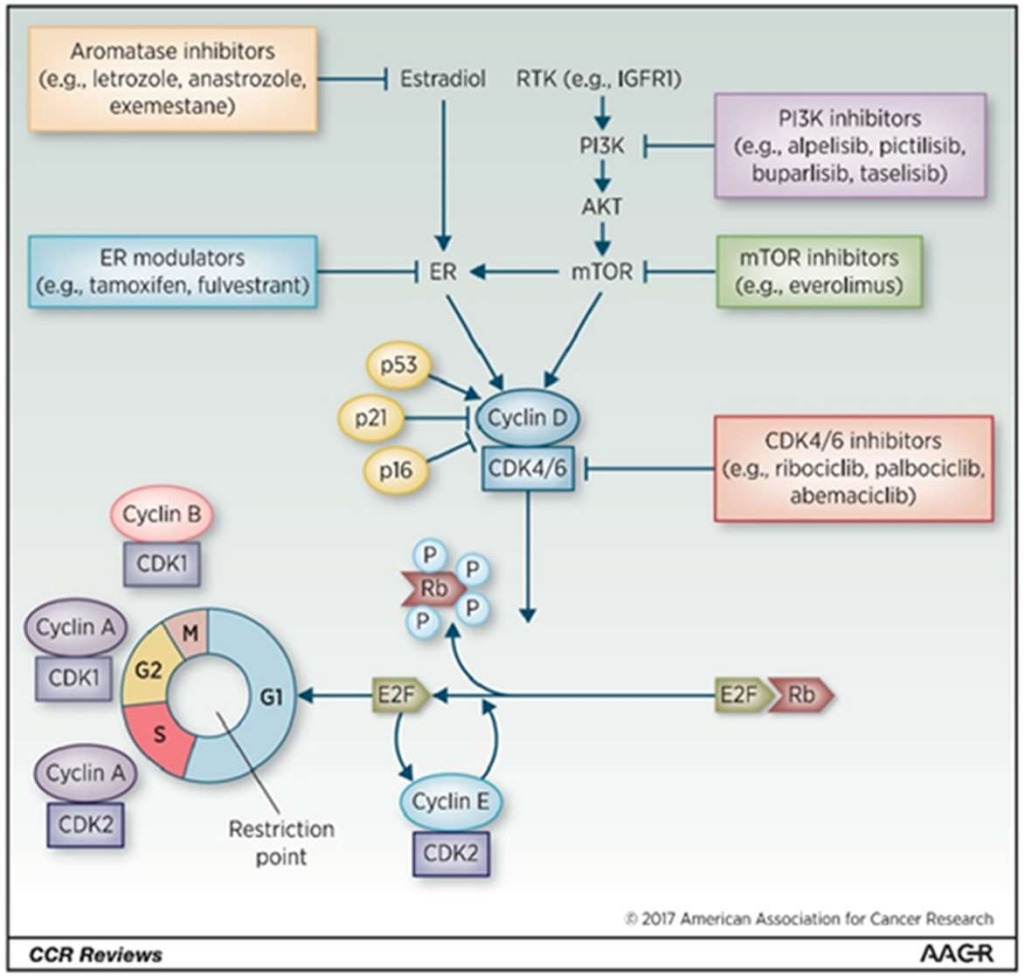
CDK4/6 inhibitors ： 愛乳適(IBRANCE)、擊癌利 (KISQALI)、捷癌寧 (VERZENIO)



和信治癌中心醫院
資深臨床藥師：方麗華

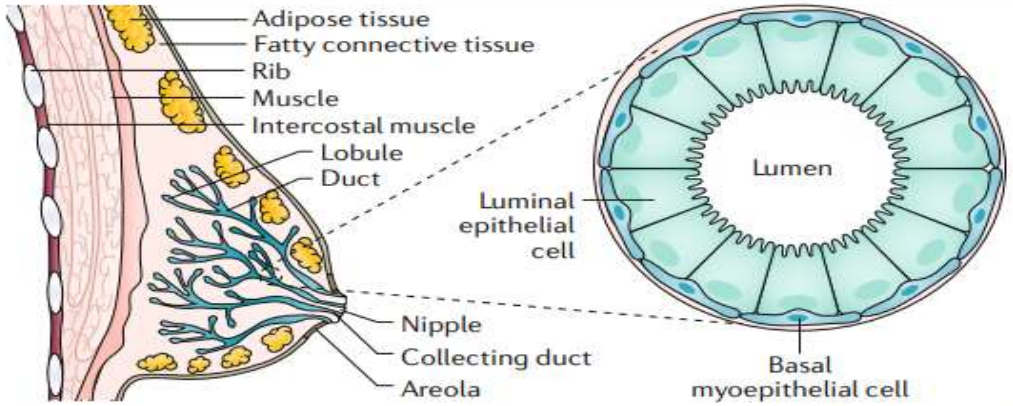
Outlines

- History of CDK4/6 Inhibitors (**cyclin-dependent kinases 4 and 6**)
- Role in Cancer treatment (Type of cancer, Driven gene, role of treatment)
- Drug mechanism
- Indications comparison
- Side effect management
- Education
- Conclusion

History of CKD4/6 inhibitors development

- 1990年代：細胞週期蛋白依賴性激酶（CDKs）被確定為細胞週期的重要調節因子。尤其是CDK4和CDK6，發現它們在細胞從G1期到S期的轉變是由其與Cyclin D的相互作用驅動的。
- 1995年：發現CDK4/6-Cyclin D 對細胞週期進展至關重要，激發了將這些激酶作為治療目標的興趣。
- 2000年代初：臨床前研究，抑制CDK4/6可以防止細胞週期進展，並在癌細胞中誘導細胞週期停滯。
- 2004年：輝瑞藥廠 Palbociclib（PD-0332991）作為CDK4/6的強效且選擇性的抑制劑。它在乳腺癌的臨床前模型中表現出顯著的抗腫瘤活性。
- 藥物

  1. Palbociclib (Ibrance) 2015 上市 .
  2. Ribociclib (Kisqali) 2017 上市
  3. Abemaciclib (Verzenio) 2017 上市



Histological subtypes

Preinvasive
Ductal carcinoma in situ (DCIS)
- Spreads through ducts and distorts ductal architecture; can progress to invasive cancer; unilateral

Lobular carcinoma in situ (LCIS)
- Does not distort ductal architecture; can be bilateral
- Risk factor rather than precursor

Invasive
Ductal carcinoma no special type (NST)
- Develops from DCIS; fibrous response to produce a mass; metastasizes via lymphatics and blood

Lobular carcinoma (ILC)
- Isolated tumor cells (*CDH1* mutations) minimal fibrous response; metastasizes preferentially via viscera

Intrinsic subtypes (PAM50)

Basal-like
TP53 mutations; genetic instability; *BRCA* mutations; medullary-like histology poorly differentiatied

Claudin-low
Largely triple-negative; metaplastic

HER2-enriched
HER2 amplification; *GRB7* amplification; *PIK3CA* mutations; *TOPO2* and/or *MYC* amplification; NST, pleiomorphic lobular and micropapillary histology

Normal-like[b]

Luminal B
PI3KCA mutations (40%); *ESR1* mutations (30–40%)[a]; *ERBB2* and *ERBB3* mutations; NST, micropapillary and atypical lobular histology

Luminal A
Activation of *ERS1*, *GATA3*, *FOXA1*, *XBP1*; NST, tubular cribriform and classic lobular histology

Breast cancer. *Nat Rev Dis Primers* **5,** 67 (2019).

Surrogate intrinsic subtypes

Triple-negative
ER–, PR–, HER2–; high grade; high Ki67 index; NST histology; special type histology (metaplastic, adenoid cystic, medullary-like and secretory); poor prognosis except for some special types

HER2-enriched (non-luminal)
ER–, PR–, HER2+; high grade; high Ki67 index; NST histology; aggressive disease but responds to targeted therapies; intermediate prognosis

Luminal B-like HER2+
ER+ but lower ER and PR expression than luminal A-like; HER2+; higher grade; high Ki67 index; NST and pleiomorphic; responds to targeted therapies; intermediate prognosis

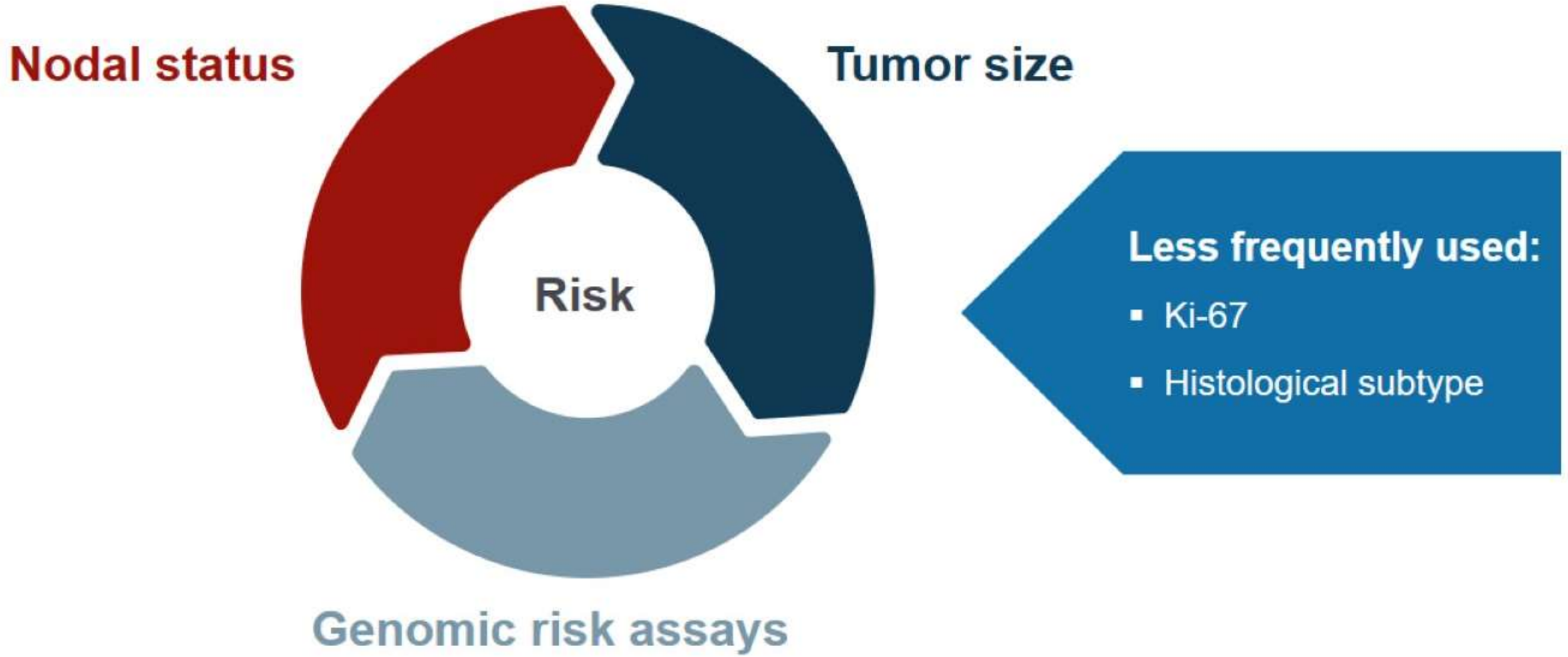
Luminal B-like HER2–
ER+ but ER and PR expression lower than in luminal A-like; HER2–; higher grade; high Ki67 index; high-risk GES; NST, micropapillary and lobular pleiomorphic histology; intermediate prognosis

Luminal A-like
Strongly ER+ and PR+; HER2–; low proliferation rates; typically low grade; low Ki67 index; low-risk GES; NST, tubular cribriform and classic lobular histology; good prognosis

10–15% **13–15%** **10–20%** **60–70%**

Proliferation
High grade
Basal-like genes — ER expression
HER2 expression — Low grade

Defining High Risk for Recurrence in Patients With EBC

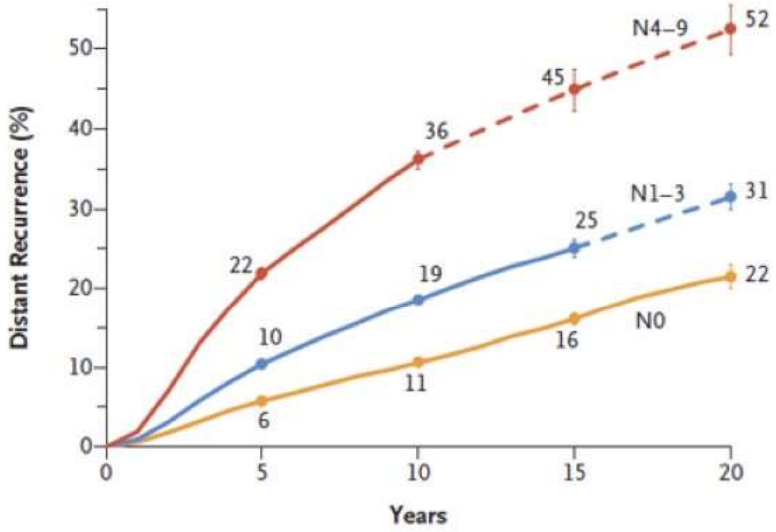


EBC, early breast cancer.
Cardoso F, et al. Ann Oncol. 2019;30:1194-1220. Erratum for: Ann Oncol. 2019;30:1194-1220. Erratum for: Ann Oncol. 2021;32:284.

Patient Empowerment

Patients Need to Know the Risk for Recurrence

20-y Risk for Distant Recurrence in Women With ER-Positive Breast Cancer



No. at Risk					
N4–9	12,333	8,116	2165	259	52
N1–3	31,936	23,576	7250	949	183
N0	29,925	24,081	8571	1982	414

No. of Events — annual rate (%)				
N4–9	2568 (4.8)	969 (4.0)	121 (3.1)	13 (2.2)
N1–3	3126 (2.2)	1421 (1.9)	241 (1.7)	39 (1.8)
N0	1646 (1.2)	835 (1.1)	272 (1.3)	68 (1.4)

EBC, early breast cancer; N, node; T, tumor.
Pan H, et al. N Engl J Med. 2017;377:1836-1846.

Study looked at 88 trials involving 62,923 patients with ER-positive EBC who were disease-free after 5 years

Risks for distant recurrence for patients with T2 disease were 19% (T2N0), 26% (T2N1-3), and 41% (T2N4-9)

Risk strongly correlated with original TN status

Treatment of HR+/HER2- EBC

Endocrine Therapy

- Tamoxifen
- Aromatase inhibitors
- Ovarian suppression (LHRH analogues) in high-risk premenopausal women
- Extended adjuvant therapy (10 yr vs 5 yr)

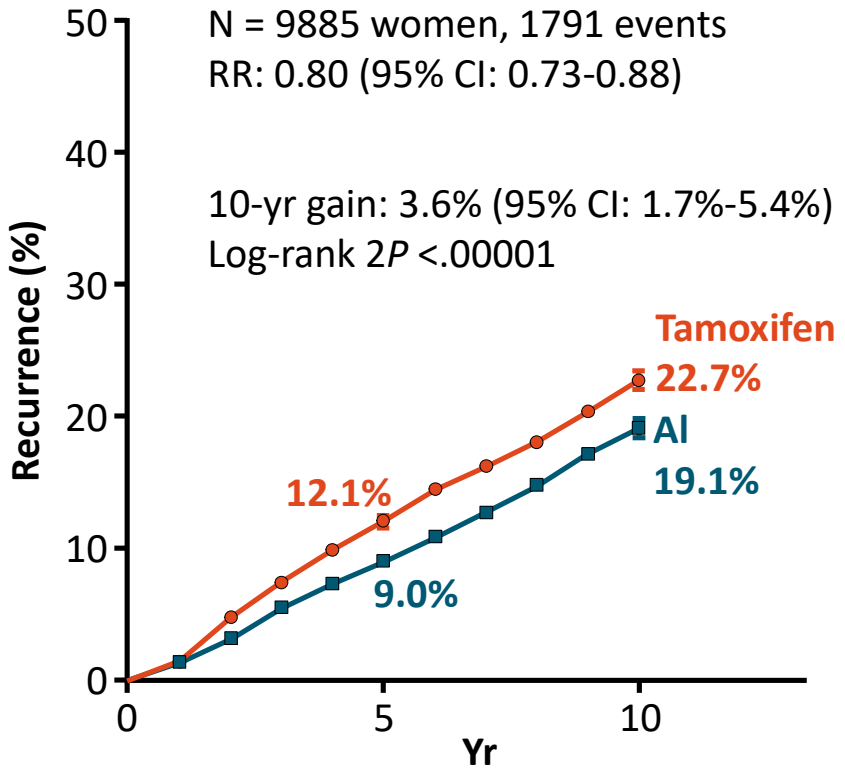
Chemotherapy

- Benefit depends on risk for recurrence and biology of the disease

Unmet Need

- Identifying patients with HR+ breast cancer who have primary endocrine resistance and preventing or delaying recurrence with additional therapy

Meta-analysis of 5 Yr of AI vs 5 Yr of Tamoxifen



Early Breast Cancer Trialists Collaborative Group. Lancet. 2015;386:1341. Cardoso. Ann Oncol. 2019;30:1194.

Slide credit: clinicaloptions.com

Patient Empowerment
Biomarker Testing to Stratify Patient Risk for Recurrence

Clinical Variables Predictive of Distant Recurrence[1]

- Nodal status
- Tumor size
- Grade
- ER
- PR
- Ki-67
- HER2 status

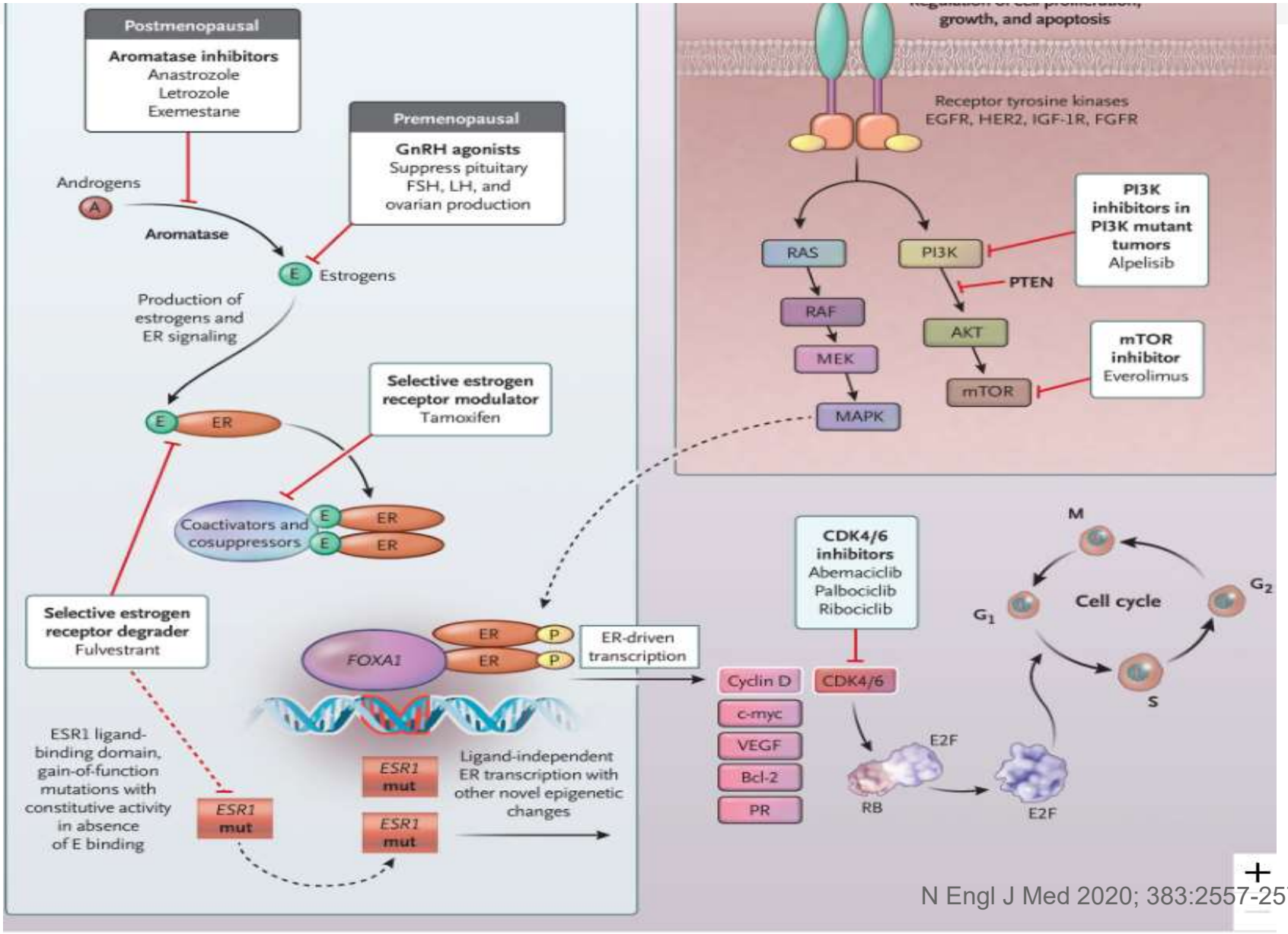
Multigene/Molecular Scores for Prediction of Recurrence[2]

Score	Details
Breast Cancer Index®	Multigene assay using qRT-PCR; combination of 2 biomarkers: H/I and MGI; FFPE used to extract RNA to perform analysis
Genomic Grade Index	97 gene-based assay using DNA micro array; fresh frozen material used to perform analysis
Immunohistochemical Score 4	Includes information on ER, PR, Ki67, and HER2; FFPE blocks used to extract RNA to perform IHC for ER, PR, Ki67, and HER2
MammaPrint®	70 gene-based expression profile using DNA microarray; fresh frozen material used to perform analysis
Oncotype DX Breast Recurrence Score®	21 gene-based expression profile score using qRT-PCR (16 cancer genes, 5 housekeeping genes); FFPE blocks used to extract RNA
Prosigna® Risk of Recurrence Score	50 gene-based expression profile score using qRT-PCR; FFPE blocks used to extract RNA to perform analysis

It is the policy of Medscape Education to avoid the mention of brand names or specific manufacturers in accredited educational activities. However, manufacturer names related to large panel tests are provided in this activity in an effort to promote clarity for the learner.

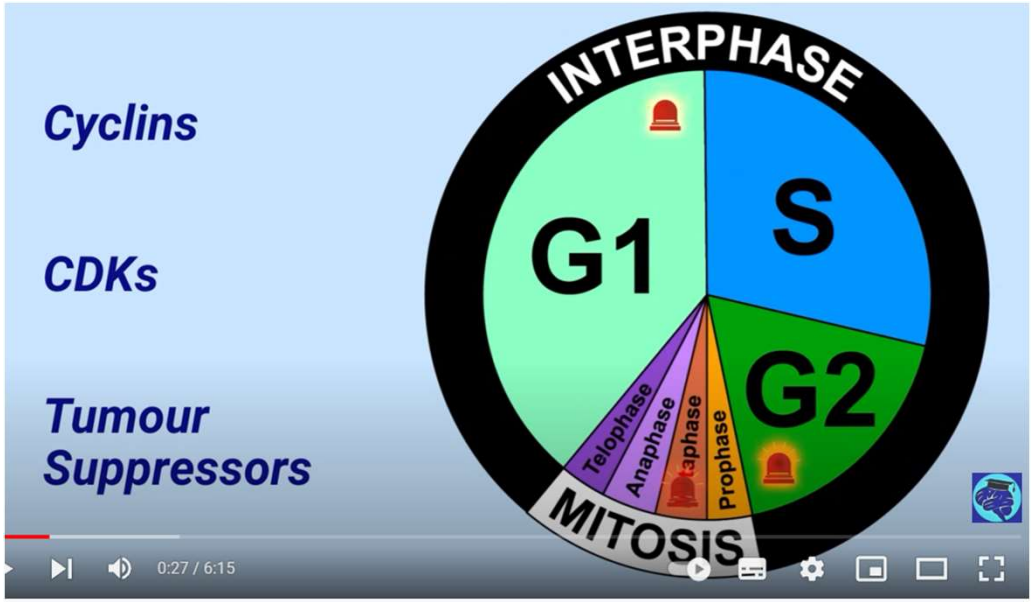
FFPE, formalin-fixed paraffin-embedded blocks; H/I, HOXB13/IL17BR; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MGI, molecular grade index; PR, progesterone receptor; qRT-PCR, quantitative real-time polymerase chain reaction.

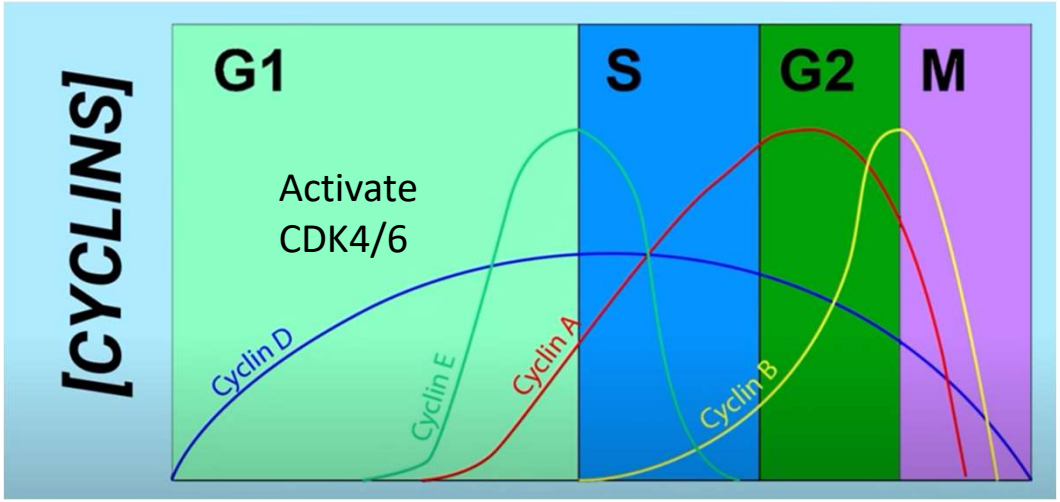
1. Sestak I, et al. J Natl Cancer Inst. 2013;105:1504-1511; 2. Sestak I, et al. Breast Cancer Res. 2015;17:10.

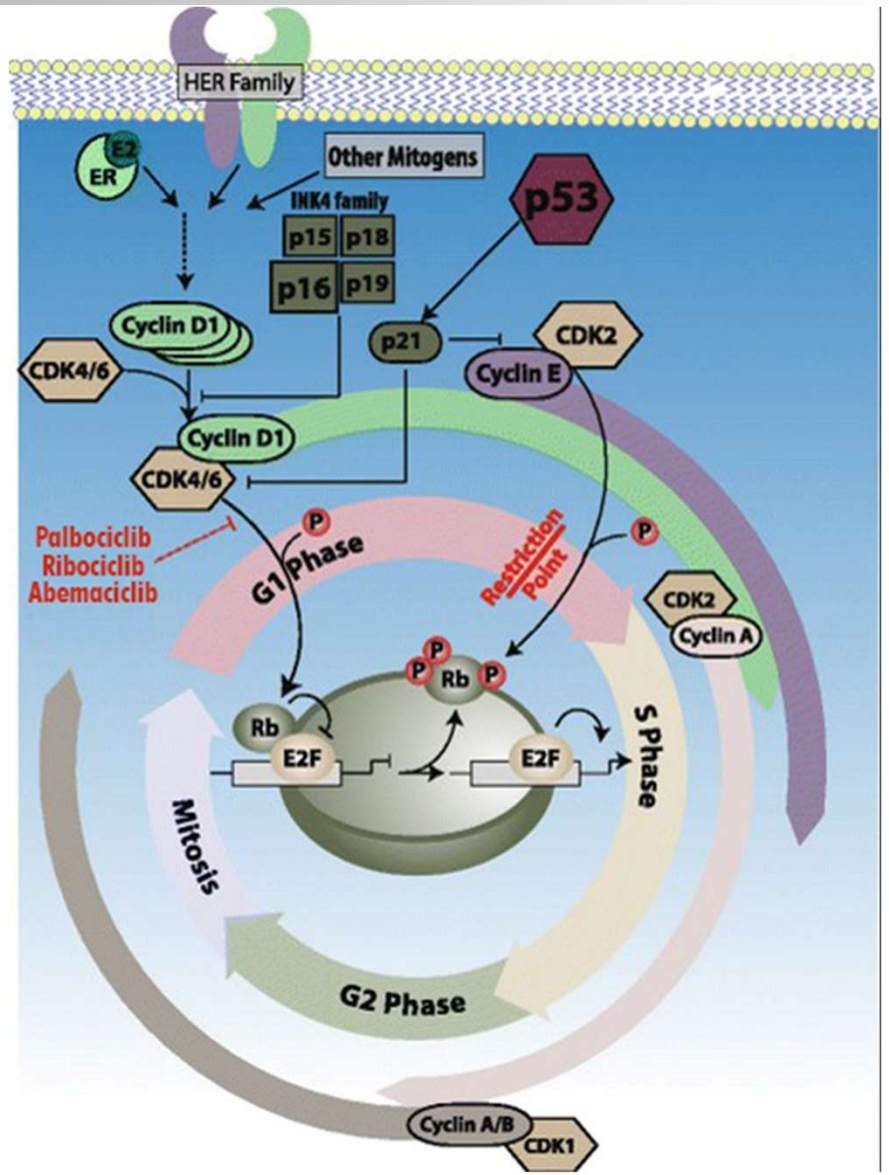


N Engl J Med 2020; 383:2557-2570

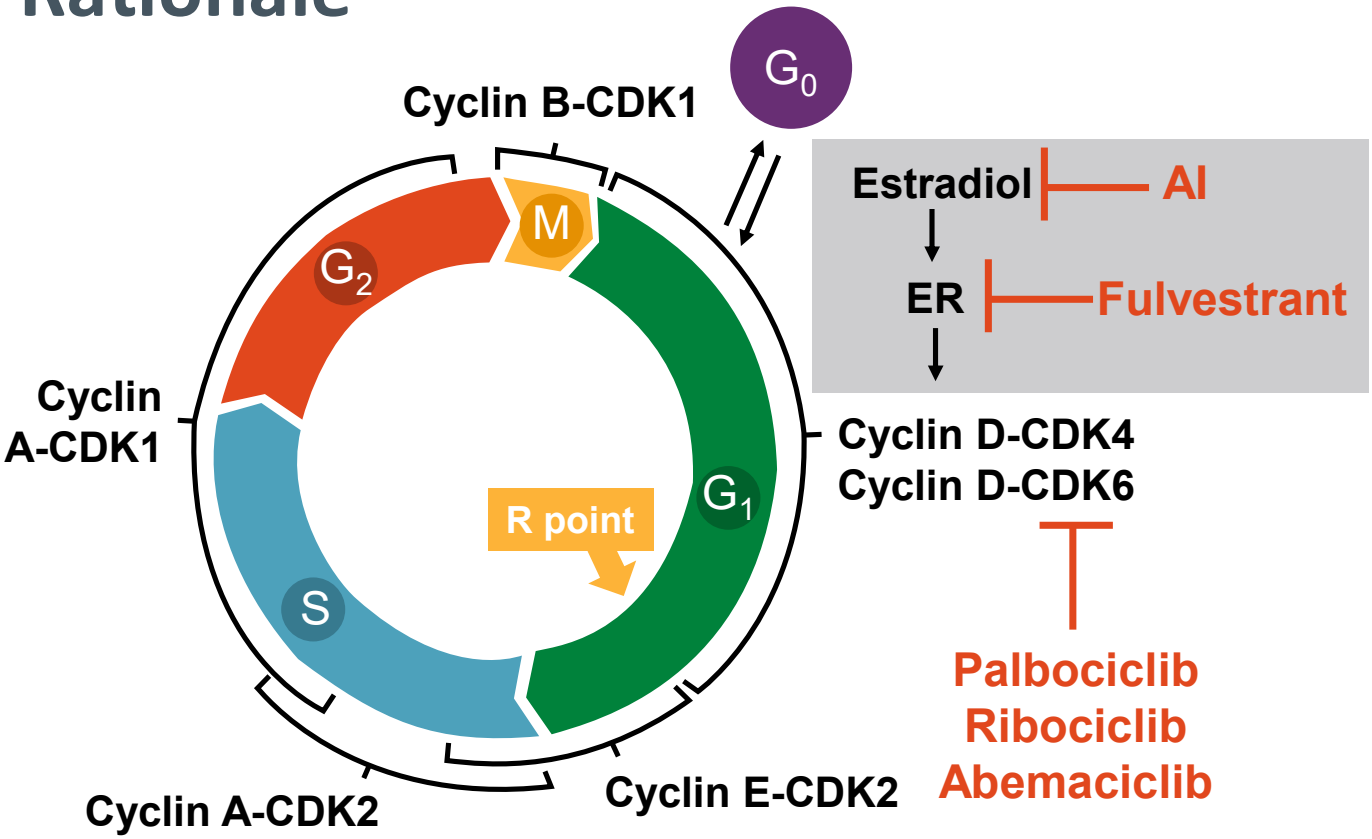
1. CDK4/6 Inhibitors always go with hormone
2. Drug Difference by side effects


Cyclins
CDKs
Tumour Suppressors
INTERPHASE
G1
S
G2
MITOSIS
Telophase
Anaphase
Prophase
0:27 / 6:15


[CYCLINS]
G1
S
G2
M
Activate
CDK4/6
Cyclin D
Cyclin E
Cyclin A
Cyclin B


HER Family
ER
E2
Other Mitogens
INK4 family
p15
p18
p16
p19
p53
p21
Cyclin D1
CDK4/6
CDK2
Cyclin E
Cyclin D1
CDK4/6
Palbociclib
Ribociclib
Abemaciclib
G1 Phase
Restriction Point
CDK2
Cyclin A
Rb
E2F
S Phase
Mitosis
G2 Phase
Cyclin A/B
CDK1

Targeting CDK4/6 in HR+, HER2- Metastatic BC: Rationale



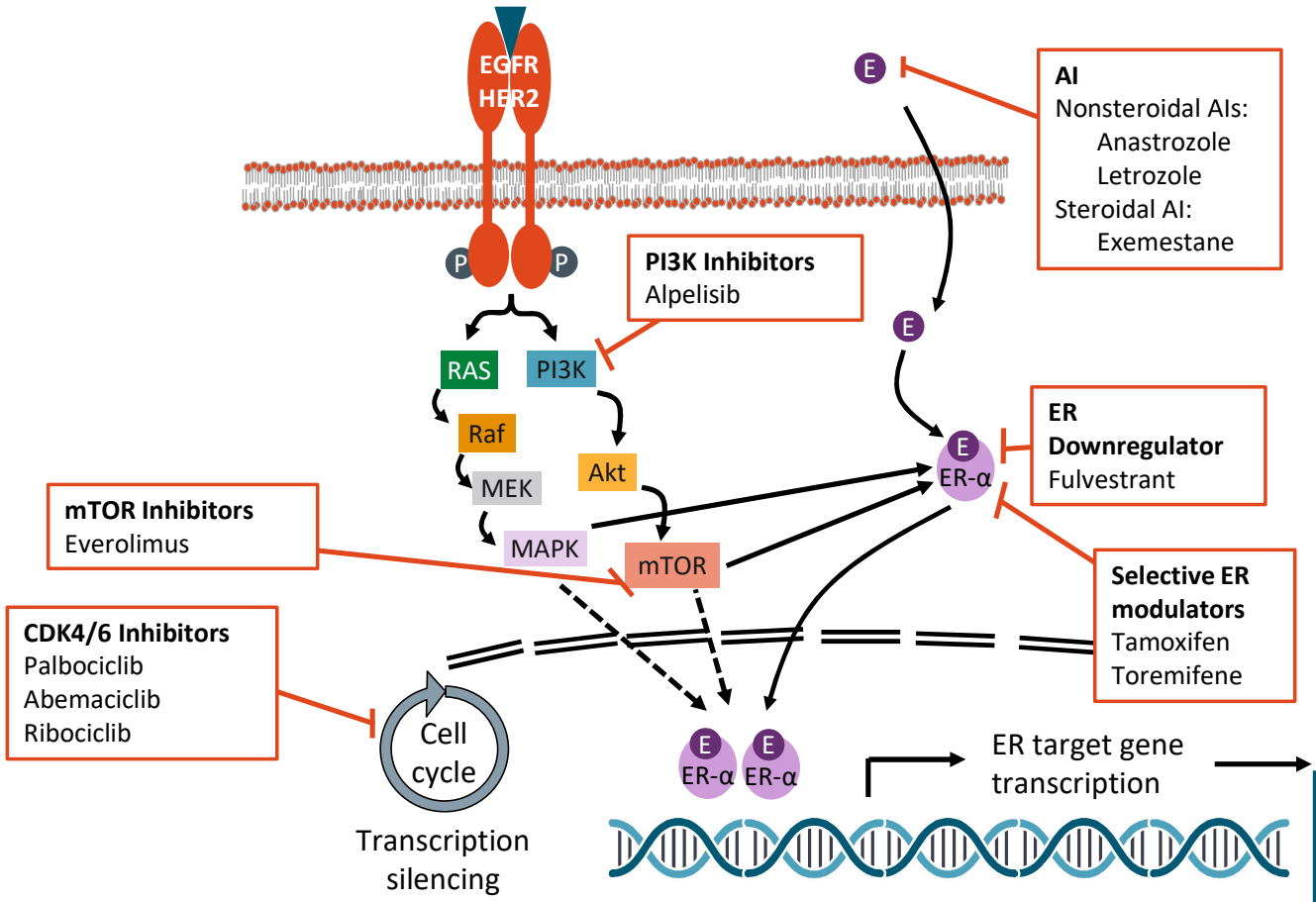
1. Mitogenic pathways, including estrogen signaling, stimulate cyclin D production
2. Binding of cyclin D activates CDK4/6, an important player in driving cell cycle progression in ER+ BC
3. Selectively inhibiting CDK4/6 causes cell cycle arrest in G1 phase, resulting in reduced cell viability and tumor shrinking

Because cyclin D–CDK4/6 activation occurs downstream of estrogen signaling, ET + CDK4/6 inhibitor combination therapy has synergistic antitumor activity against HR+ BC

References in slidenotes.

Slide credit: clinicaloptions.com

Combining Targeted and Antiestrogen Therapies to Overcome Resistance in HR+ Advanced BC

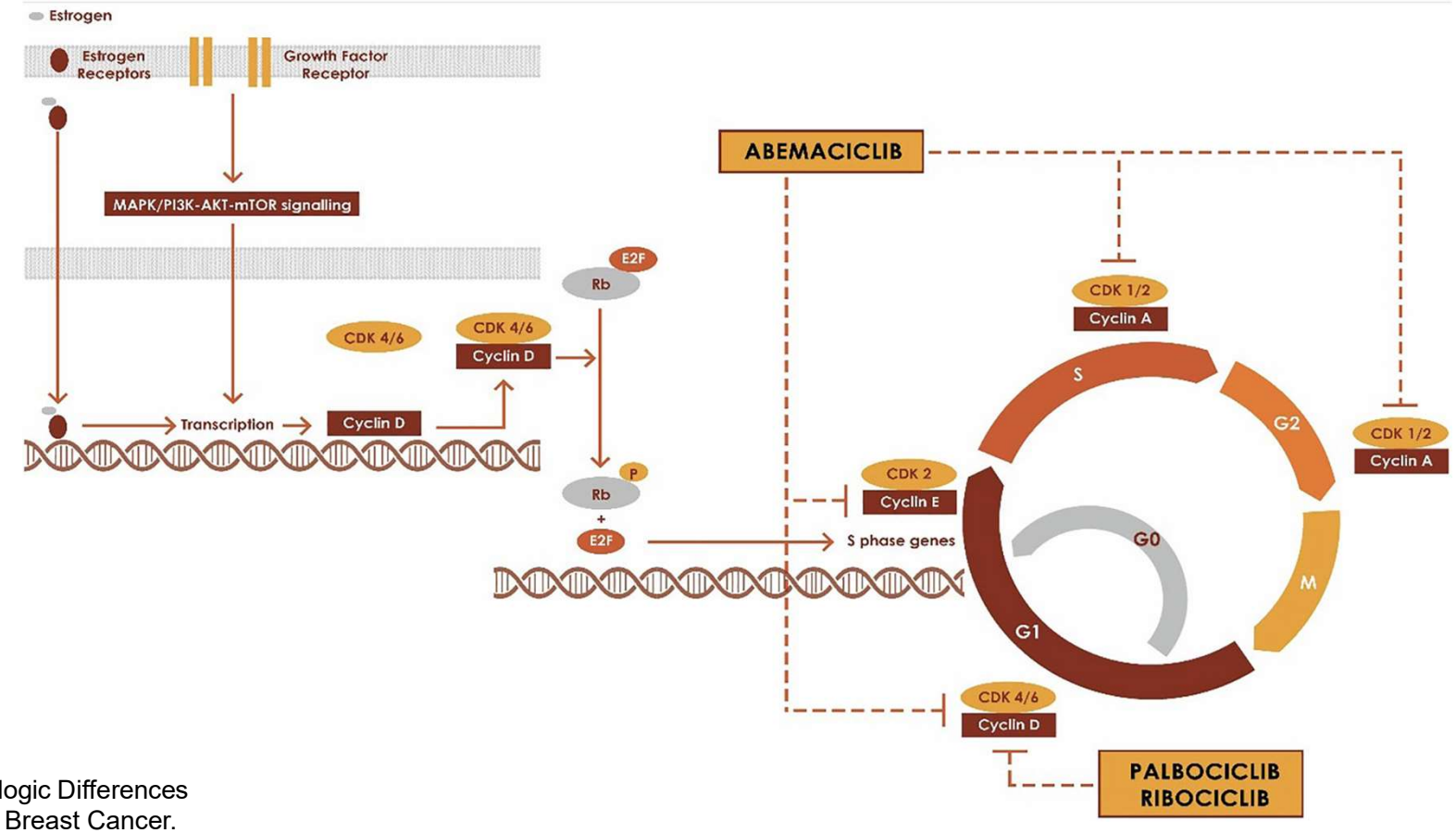


- ~ 30% of HR+ MBCs are de novo resistant to ET(Endocrine therapy), with most developing acquired resistance
- Mechanisms of resistance may include loss/alteration of ER expression; overexpression/activation of GF receptors; or activation of downstream signal transduction pathways

Brufsky. Oncologist. 2018;23:528. AlFakeeh. Curr Oncol. 2018;25:S18.

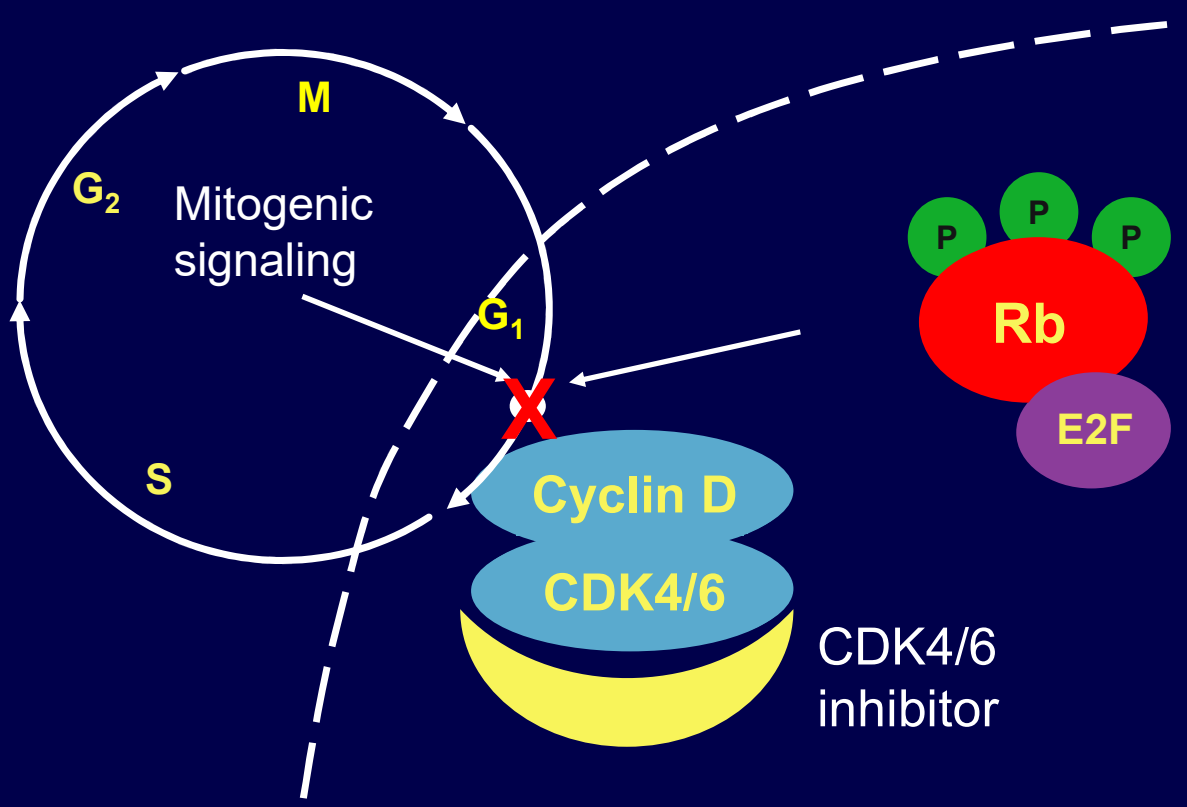
Slide credit: clinicaloptions.com

Mechanism of action of CDK 4/6 inhibitors

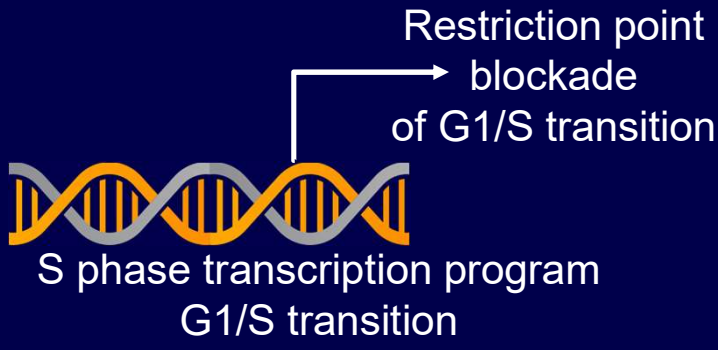


Clinical and Pharmacologic Differences
of CDK4/6 Inhibitors in Breast Cancer.
doi: 10.3389/fonc.2021.693104 Front. Oncol. 11:693104.

Mechanism of Action of CDK4/6 Inhibitors



- RB (retinoblastoma (Rb) protein) not phosphorylated
- E2F transcription inhibited
- Arrest of cell cycle at G1/S transition restriction point

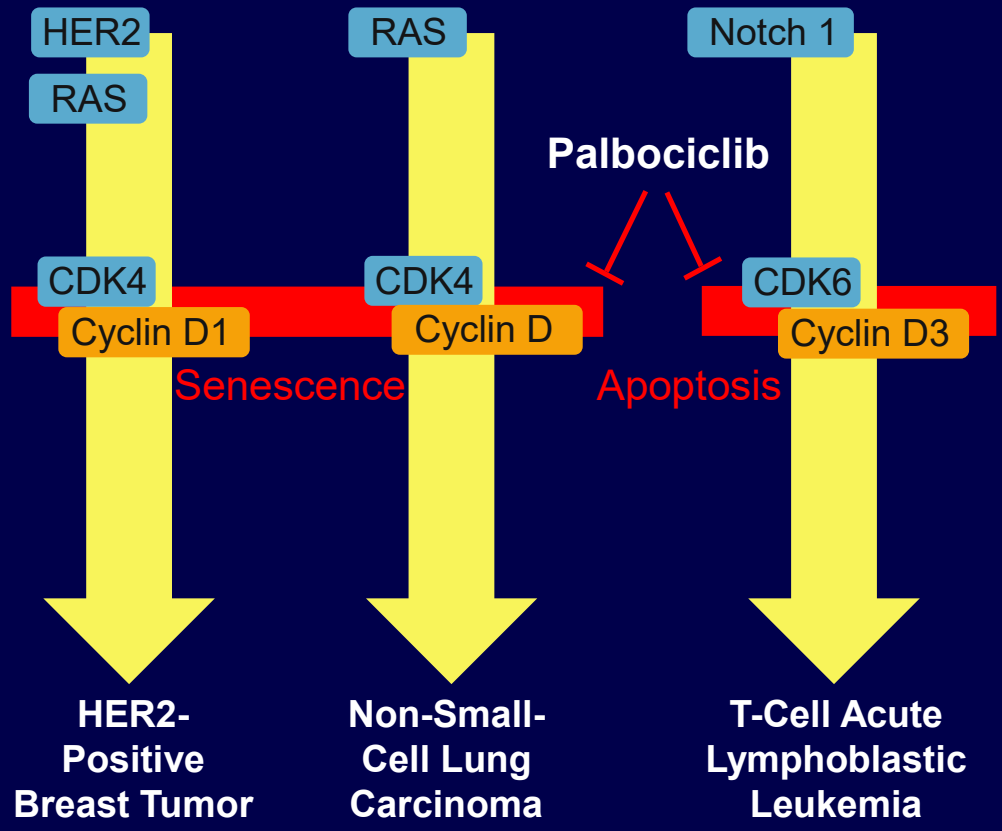


Otto T, et al. Nat Rev Cancer. 2017;17:93-115.

Slide credit: clinicaloptions.com

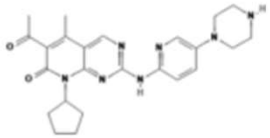
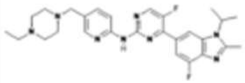
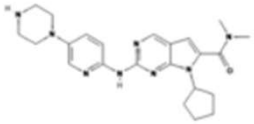
Senescence or Apoptosis With CDK4/6 Inhibition

- Preclinical mouse models suggest that CDK4/6 inhibitors may lead to alternative mechanisms of tumor cell disruption
  - Dependent on reliance on different cyclin D-CDK4/6 combinations
- CDK4/6 inhibition is associated with quiescence that is reversible or senescence that is irreversible in different tumor cell types
- In liposarcoma cells, senescence is correlated with MDM2 degradation



Malumbres M. Cancer Cell. 2012;22:419-420. Finn RS, et al. Breast Cancer Res. 2009;11:R77. Anders L, et al. Cancer Cell. 2011;20:620-634. Kovatcheva M, et al. Oncotarget. 2015;6:8226-8243.

Slide credit: clinicaloptions.com

	Palbociclib (pd-0332991; ibrance, pfizer)	Abemaciclib (ly2835219; verzenio, lilly)	Ribociclib (lee011; kisquali, novartis)
Chemical structure			
Ic50 (nm)			
Cdk4-cyclin d1	11	2	10
Cdk6-cyclin d1-2-3	15	10	39
Absorption	Increased with high-fat, high-calorie food	NR	NR
Distribution	2583 L	690.3 L	1090 L
Metabolism	Liver (cyp3a and sult2a1)	Liver (cyp3a4)	Liver (cyp3a4)
Excretion	Feces (~74%)	Feces (~81%)	Feces (~69%)
	Urine (~18%)	Urine (~3%)	Urine (~23%)
Bioavailability	46%	45%	NR
Time to peak (hours)	6–12	8	1–4
Half-life elimination (hours)	29 ± 5	18.3	30–55
Protein binding	~85%	93–98%	~70%
Mtd/rp2d	125/125 mg/day on a 21-of-28-day schedule	200 mg twice daily	900/600 mg/day on a 21-of-28-day schedule
Dlts	Neutropenia	Fatigue	Neutropenia, asymptomatic thrombocytopenia, mucositis, pulmonary embolism, hyponatremia, QTcF, prolongation (> 500 ms), increased

Pharmacology of the three approved CDK4/6 inhibitors.

	Palbociclib	Ribociclib	Abemaciclib
Half-life	29 (+/-5) hours	32 hours	18.3 hours
Primary site of metabolism	Hepatic	Hepatic	Hepatic
Cell Cycle Arrest	G1 phase	G1 Phase	G1, G2 phase
Targets	CDK4 and CDK6	CDK4 and CDK6	CDK1, CDK2, CDK4, CDK5 CDK6, CDK 9, CDK14, CDKs16-18
Dosing	125mg once daily for 21 days followed by 7 days off	600mg one daily for 21 days	150mg twice day continuously
Myelosuppression	++	++	+
GI toxicity	+	+	++
LFT abnormalities	–	+	+
Pneumonitis	+ (rare)	+ (rare)	+ (rare)

Front. Oncol., 12 July 2021 Sec. Breast Cancer
https://doi.org/10.3389/fonc.2021.693104

	Palbociclib (pd-0332991; ibrance, pfizer)	Abemaciclib (ly2835219; verzenio, lilly)	Ribociclib (lee011; kisquali, novartis)
Dlts	Neutropenia	Fatigue	Neutropenia, asymptomatic thrombocytopenia, mucositis, pulmonary embolism, hyponatremia, QTcF, prolongation (> 500 ms), increased creatinine
Route of administration	Oral	Oral	Oral
Recommended dose	125 mg once daily for 21 days, followed by 7 days off, repeat every 28 days	150 mg twice daily Dose modifications	600 mg once daily for 21 days, followed by 7 days off, repeat every 28 days
Renal impairment			
Crcl > 15 ml/min	No dosage adjustament	No dosage adjustament	No dosage adjustament
Crcl ≤ 15 ml/min	NR	NR	NR
Esrd	NR	NR	NR
Hepatic impairment*			
Mild/moderate	No dosage adjustament	No dosage adjustament	No dosage adjustament
Severe	Reduce dose to 75 mg	Reduce dose to once daily	Reduce dose to 400 mg

DLT dose-limiting toxicity, ESRD end-stage renal disease, IC50 half maximal inhibitory concentration, MTD maximum tolerated dose, NR not reported, RP2D recommended phase II dose

npj Breast Cancer 5, 27 (2019). https://doi.org/10.1038/s41523-019-0121-y

Impact of CDK4/6 Inhibition on PFS: First-line Setting

Phase III Study	PALOMA-2[1,2]	MONALEESA-2[3,4]	MONARCH-3[5,6]	MONALEESA-3[7,8]	MONALEESA-7[9]
Setting	1st line	1st line	1st line	1st and 2nd line	1st line*
Endocrine partner	Letrozole	Letrozole	Letrozole or anastrozole	Fulvestrant	Tamoxifen, letrozole, or anastrozole
CDK4/6 inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Ribociclib
No. patients	666	668	493	365	672
HR	0.563	0.56	0.54	0.55	0.55
PFS, mos	27.6 vs 14.5	25.3 vs 16	28.18 vs 14.76	33.6 vs 19.2	23.8 vs 13.0
ORR, %	55.3 vs 44.4	52.7 vs 37.1	59 vs 44	40.9 vs 28.7†	41 vs 30

*1st line ET; up to 1 prior line of CT permitted in advanced setting (14% of patients had received CT in advanced setting). †Includes 1st and 2nd line.

1. Finn. NEJM. 2016;375:1925. 2. Rugo. Breast Cancer Res Treat. 2019;174:719. 3. Hortobagyi. NEJM. 2016;375:1738. 4. Hortobagyi. Ann Oncol. 2018;29:1541. 5. Goetz. JCO. 2017;35:3638. 6. Johnston. NPJ Breast Cancer. 2019;5:5. 7. Slamon. JCO. 2018;36:2465. 8. Slamon. NEJM. 2020;382:514. 9. Tripathy. Lancet Oncol. 2018;19:904.

Key phase II/III trials of CDK4/6 inhibitors for HR+, HER2− ABC

CDK4/6 inhibitor	# line of treatment	Trial name	Phase	Arms	mPFS (hazard ratio, 95% CI, *p* value)	ORR*	mOS (hazard ratio, 95% CI, *p* value)
Palbociclib	1st line	PALOMA-1/TRIO-18 [5, 24•]	II	Palbo + letrozole vs. letrozole	20.2 vs. 10.2 months (0.49, 0.32–0.75, $p = 0.0004$)	55.0% vs. 39.0% ($p = 0.047$)	37.5 vs. 33.3 months (0.897, 0.49–1.35, $p = 0.42$)
		PALOMA-2 [8•, 11•]	III	Palbo + letrozole vs. placebo + letrozole	27.6 vs. 14.5 months (0.56, 0.46–0.69, $p < 0.001$) [11•]	55.3% vs. 44.4% ($p = 0.03$) [8•]	Pending
	Later line	PALOMA-3 [13, 16•, 25•]	III	Palbo + fulvestrant vs. placebo + fulvestrant	9.5 vs. 4.6 months (0.46, 0.36–0.59, $p < 0.0001$)	25% vs. 11% (*p* value N/A)	34.9 vs. 28.0 months (0.81, 0.64–1.03, $p = 0.09$)
Ribociclib	1st line	MONALEESA-2 [6•, 7•]	III	Ribo + letrozole vs. placebo + letrozole	25.3 vs. 16.0 months (0.57, 0.46–0.70, $p < 0.0001$)	42.5% vs. 28.7% ($p < 0.0001$)	Pending
		MONALEESA-7 [12•, 21•]**	III	Ribo + goserelin + AI*** or tamoxifen vs. placebo + goserelin + AI or tamoxifen	23.8 vs. 13.0 months (0.55, 0.44–0.69, $p < 0.0001$)	51% vs. 36% ($p = 0.00032$)	70.2% vs. 46.0% at 42 months (0.71, 0.54–0.95, $p < 0.01$)
	2nd line	MONALEESA-3 [15•, 22•]	III	Ribo + fulvestrant vs. placebo + fulvestrant	20.5 vs. 12.8 months (0.59, 0.48–0.73, $p < 0.0001$)	40.9% vs. 28.7% ($p = 0.003$)	NR vs 40.0 months (0.724, 0.568–0.924, $p = 0.00455$)
Abemaciclib	1st line	MONARCH-3 [9•, 10•]	III	Abema + AI vs. placebo + AI	28.2 vs. 14.8 months (0.54, 0.42–0.70, $p = 0.000002$)	61.0% vs. 45.5% ($p = 0.003$)	Pending
	2nd line	MONARCH-2 [14•, 23•]	III	Abema + fulvestrant vs. placebo + fulvestrant	16.4 vs. 9.3 months (0.55, 0.45–0.68, $p < 0.001$)	48.1% vs. 21.3% ($p < 0.001$)	46.7 vs 37.3 months (0.757, 0.606–0.945, $p = 0.01$)
	Later line	MONARCH-1 [17•]	II	Abema	6 months	19.7%	17.7 months

AI, aromatase inhibitor; *CDK4/6*, cyclin-dependent kinase 4 and 6; *HER2*, human epidermal growth factor 2; *HR*, hormone receptor; *ORR*, objective response rate; *mOS*, median overall survival; *mPFS*, median progression-free survival; *Palbo*, palbociclib; *Ribo*, ribociclib; *Abema*, abemaciclib

*ORR: in patients with measurable disease at baseline

**MONALEESA-7 was the only trial enrolled only premenopausal women with HR+, HER2− ABC

***AI: all AI in this table indicates non-steroidal AI (i.e., letrozole or anastrozole)

Curr Oncol Rep . 2020 May 16;22(6):57.

Selective CDK4/6 Inhibitors: Comparison of Key Clinical Characteristics

	Palbociclib	Ribociclib	Abemaciclib
Route	PO	PO	PO
Dose, mg	125 QD	600 QD	200 BID
Schedule	3 wks on/1 wk off	3 wks on/1 wk off	Continuous
Half-life, hr	27	32.6	17-38
ORR (monotherapy), %	6	2.3	19.7
Key grade 3/4 toxicities, %	Neutropenia, 51 Thrombocytopenia, 22	Neutropenia, 28 Thrombocytopenia, 9	Neutropenia, 27 Diarrhea, 20 Fatigue, 13
CNS penetration	Uncertain	No	Yes

DeMichele A, et al. Clin Cancer Res. 2015;21:995-1001. Hamilton E, et al. Cancer Treatment Rev. 2016;45:129-138. Infante JR, et al. Clin Cancer Res. 2016;22:5696-5705. Dickler MN, et al. ASCO 2016. Abstract 510. Barroso-Sousa R, et al. Breast Care. 2016;11:167-173.

Abemaciclib monotherapy

Trial	Population : endocrine-refractory HR + , HER2– MBC previously treated with chemotherapy.	No. of patients	ORR	Median PFS
nextMONARCH **open-label, controlled, randomized, Phase 2 study**	abemaciclib 150 mg and tamoxifen 20 mg (A + T),	n = 78),	34.6%	9.1 months vs 7.4 months (abemaciclib 150mg) (HR 0.815, P = 0.293).
	abemaciclib 150 mg (A-150),	(n = 79)	24.1%	6.5 months vs 7.4 months (A-200), HR 1.045, P = 0.811).
	abemaciclib 200 mg and prophylactic loperamide (A-200)	(n = 77)	32.5%	

Breast Cancer Res Treat. 2022; 195(1): 55–64.

Adjuvant therapy

Dosing Considerations for Adjuvant CDK4/6 Inhibitors

Dosing Consideration	Ribociclib (NATALEE)[1,2]	Abemaciclib (monarchE)[3,4]
CDK4/6i schedule	▪ 400 mg PO QD (3 wk on/1 wk off)	▪ 150 mg PO BID continuously
Timing for starting CDK4/6i	▪ Randomized ≤12 mo of starting (neo)adjuvant ET ▪ Before randomization: – Diagnosis ≤18 mo – Completed any prior (neo)adjuvant CT and adjuvant RT >14 days	▪ Randomized ≤16 mo from surgery ▪ Before randomization: – Completed any prior adjuvant CT ≥21 days – Completed any prior adjuvant RT ≥14 days
CDK4/6i duration	3 yr	2 yr
Permitted ET	▪ NSAI* – Letrozole 2.5 mg/day – Anastrozole 1 mg/day	▪ Standard ET per physician's choice (eg, letrozole, anastrozole, exemestane, tamoxifen, GnRH agonist) ▪ NO fulvestrant
Adjuvant ET duration	≥5 yr	5-10 yr
Notable DDIs	▪ Avoid grapefruit products, St John's wort, strong CYP3A4 inhibitors and inducers	▪ Avoid grapefruit products, ketoconazole, strong CYP3A4 inducers ▪ Dose reduce when coadministering strong CYP3A4 inhibitors other than ketoconazole

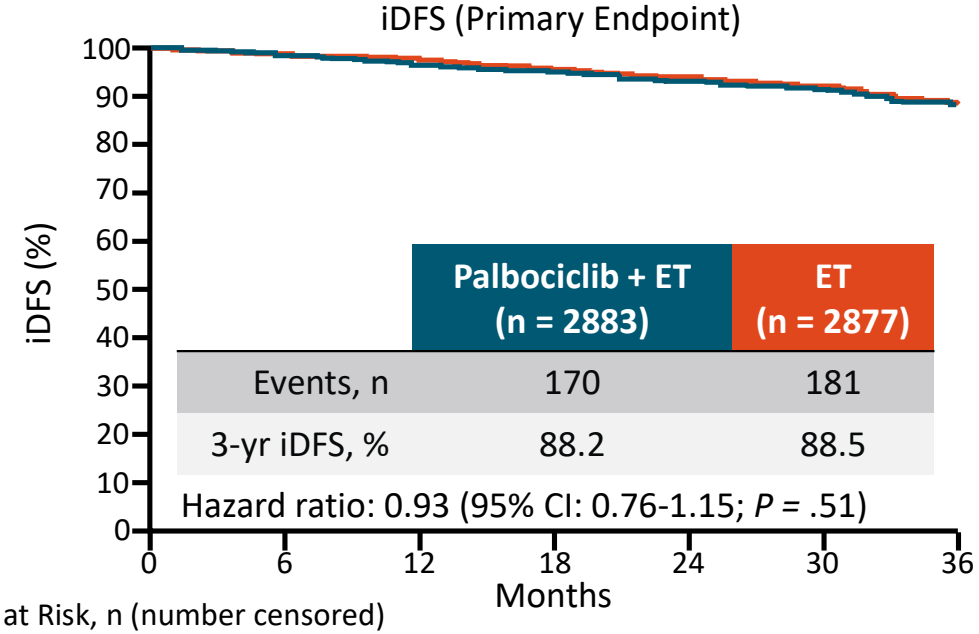
*Premenopausal women and men also received goserelin 3.6 mg Q28D.

- For ages ≥75 yr, consider starting abemaciclib at 100 mg BID; escalate to 150 mg BID as tolerated

1. Slamon. Ther Adv Med Oncol. 2023;15:17588359231178125. 2. Ribociclib PI. 3. Johnston. JCO. 2020;38:3987. 4. Abemaciclib PI.

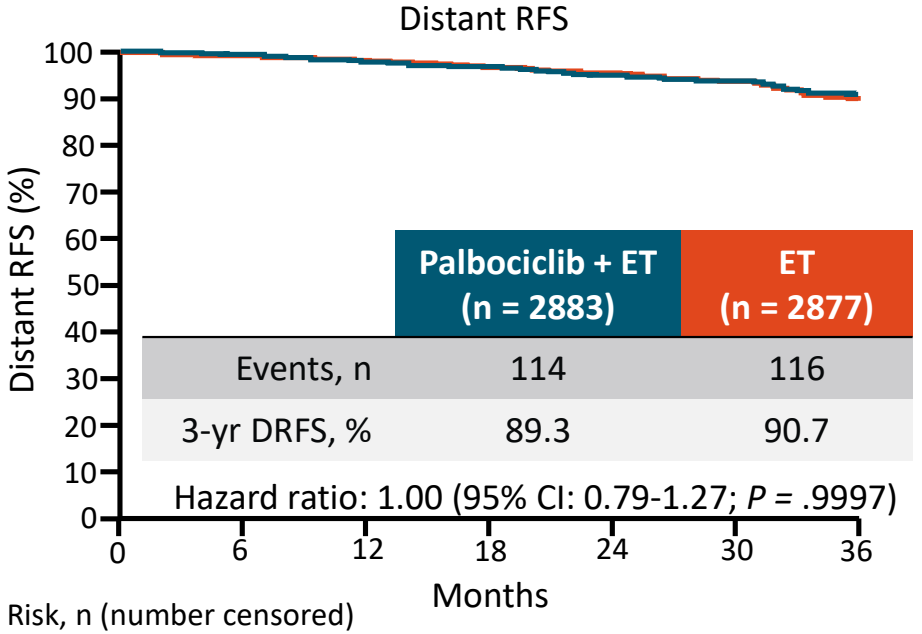
PALLAS: Adjuvant Palbociclib (2 yrs) + ET in Stage II-III HR+/HER2- EBC (early breast cancer)

- Multicenter, randomized, open-label phase III trial in patients with stage II-III HR+/HER2- EBC within 12 mos from diagnosis; after completion of definite breast surgery and any indicated (neo)adj CT or RT



Pts at Risk, n (number censored)

Palbo + ET	2883(0)	2684(163)	2563(253)	1946(827)	1257(1488)	583(2145)	163(2554)
ET	2877(0)	1649(193)	2535(250)	1953(796)	1275(1444)	574(2131)	172(2524)



Pts at Risk, n (number censored)

Palbo + ET	2883(0)	2692(165)	2573(256)	1956(843)	1270(1508)	588(2172)	163(2586)
ET	2877(0)	1662(195)	2554(261)	1976(811)	1288(1473)	579(2171)	175(2567)

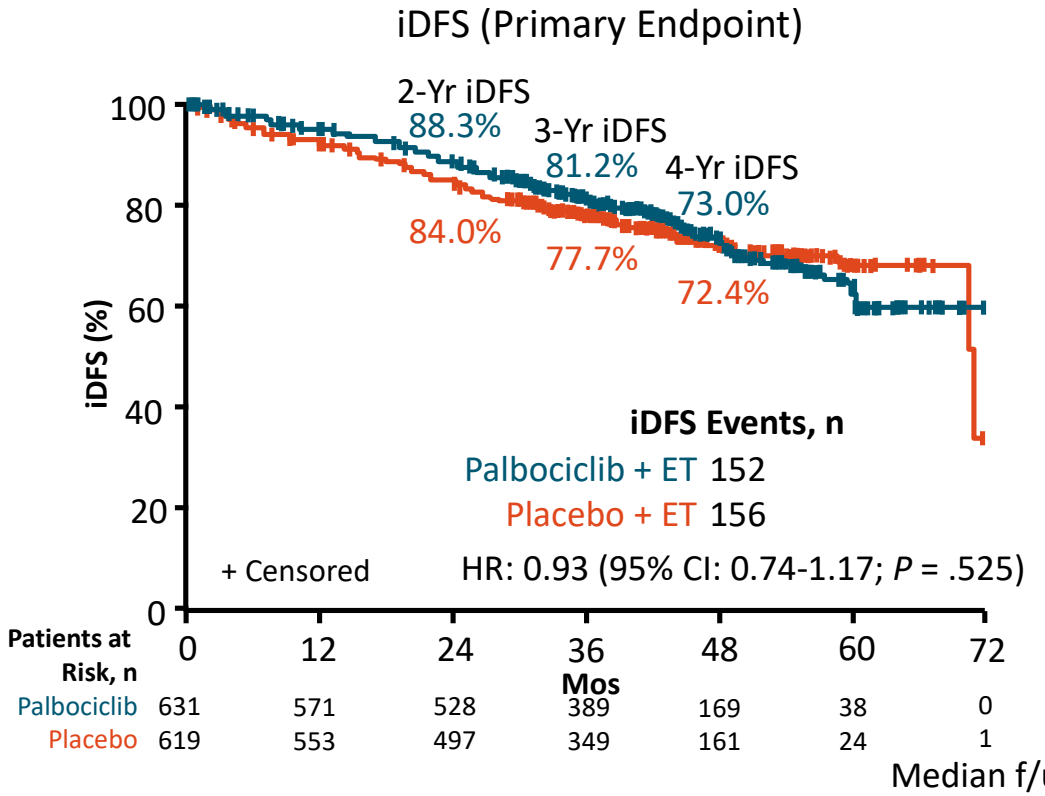
Median f/u: 23.7 mos

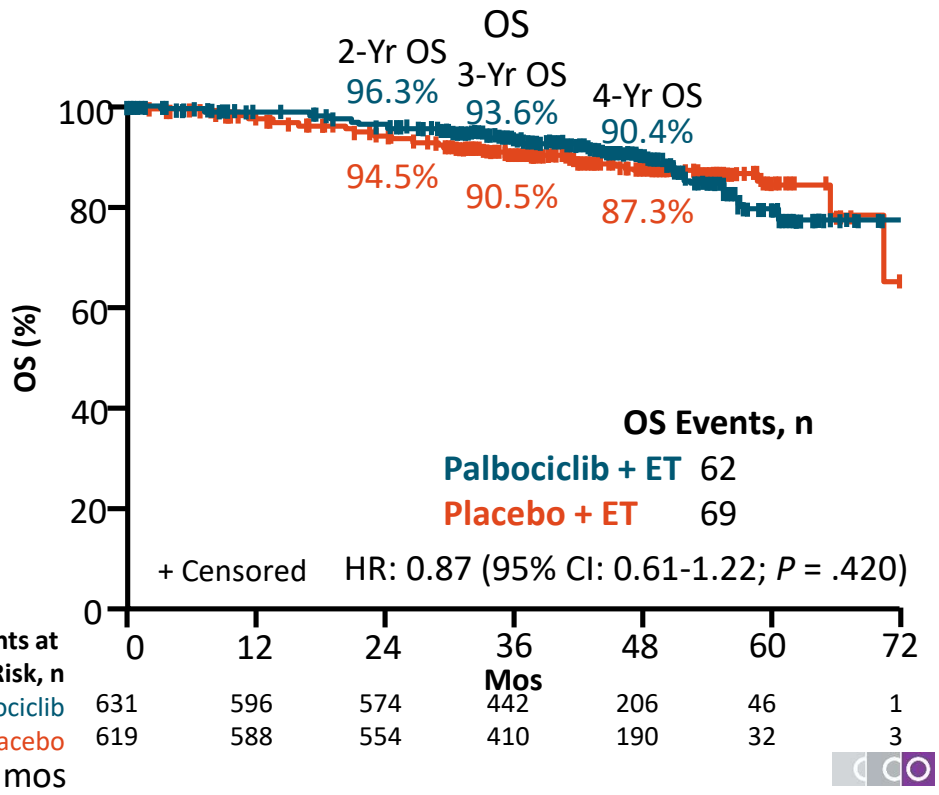
Mayer. Lancet Oncol. 2021;22:212.

Slide credit: clinicaloptions.com

PENELOPE-B: Palbociclib + ET in HR+/HER2- BC at High Risk of Relapse After Neoadjuvant Chemotherapy

- Randomized, double-blind, placebo-controlled phase III trial in patients with confirmed HR+/HER2- BC with residual disease after ≥ 16 wks of neoadjuvant CT with CPS-EG score ≥ 3 or 2 with ypN+





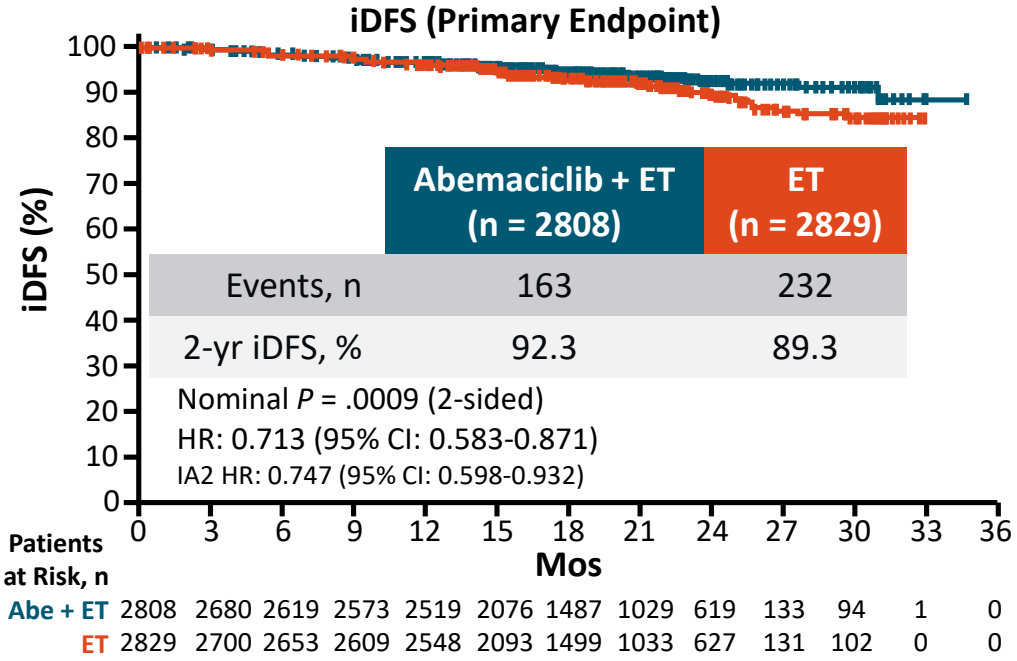
Median f/u: 42.8 mos

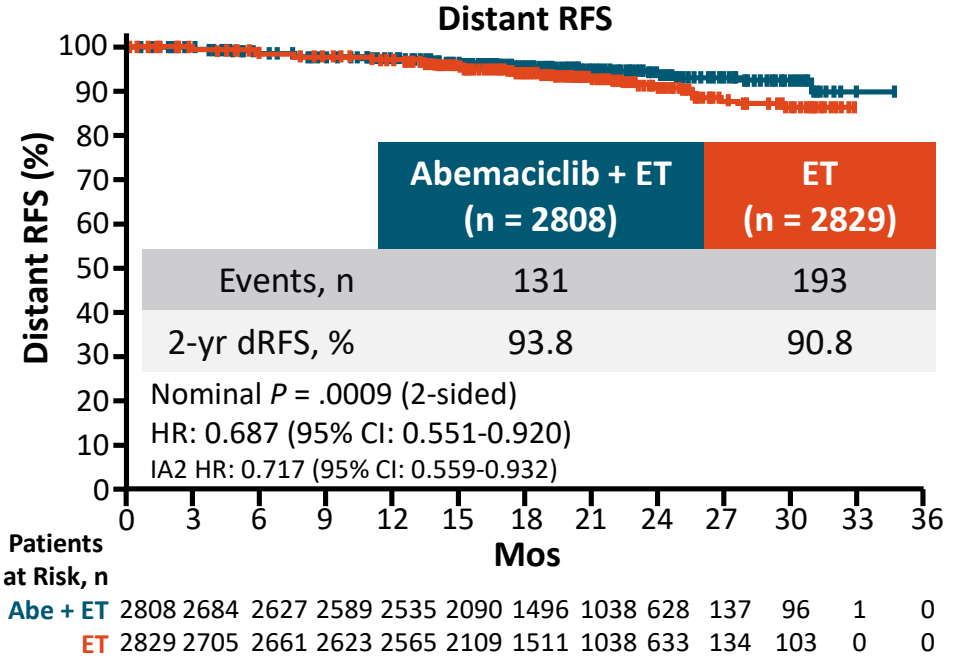
Loibl. SABCS 2020. Abstr GS1-02. Reproduced with permission.

Slide credit: clinicaloptions.com

monarchE: Adjuvant Abemaciclib (2 yrs) + ET in High-Risk, Node-Positive, HR+/HER2- EBC

- International, randomized, open-label phase III trial in patients with high-risk, N+, HR+/HER2- EBC; prior (neo)adjuvant CT permitted with no distant metastasis and ≤ 16 mos from surgery





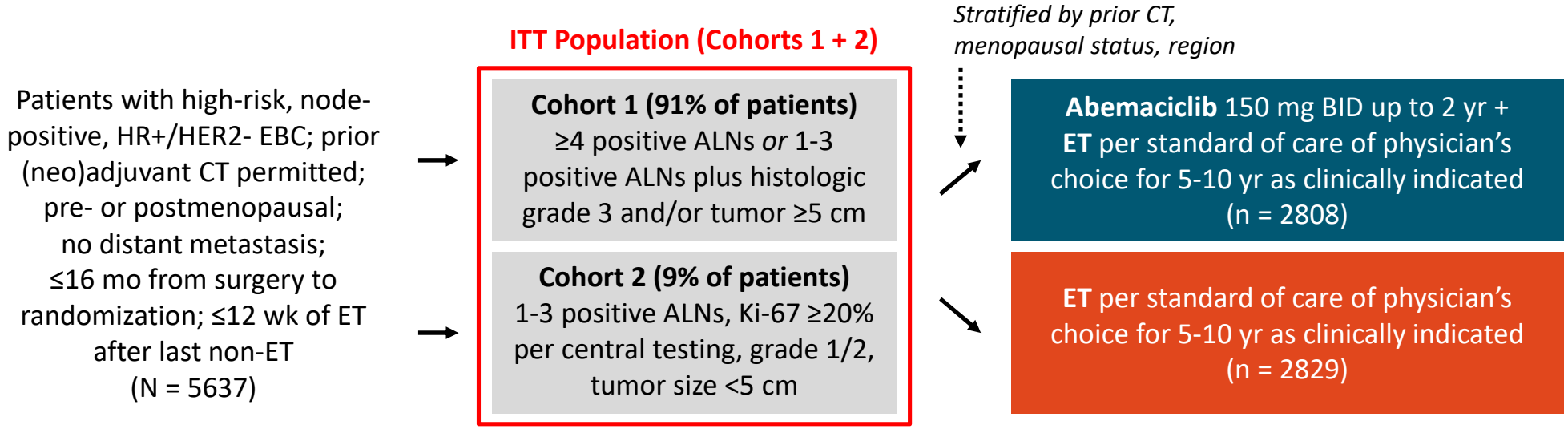
Clinically meaningful reduction in risk of developing distant metastasis with greater treatment benefit at PO analysis

Rastogi. SABCS 2020. Abstr GS1-01.

Slide credit: clinicaloptions.com

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

- International, randomized, open-label phase III trial

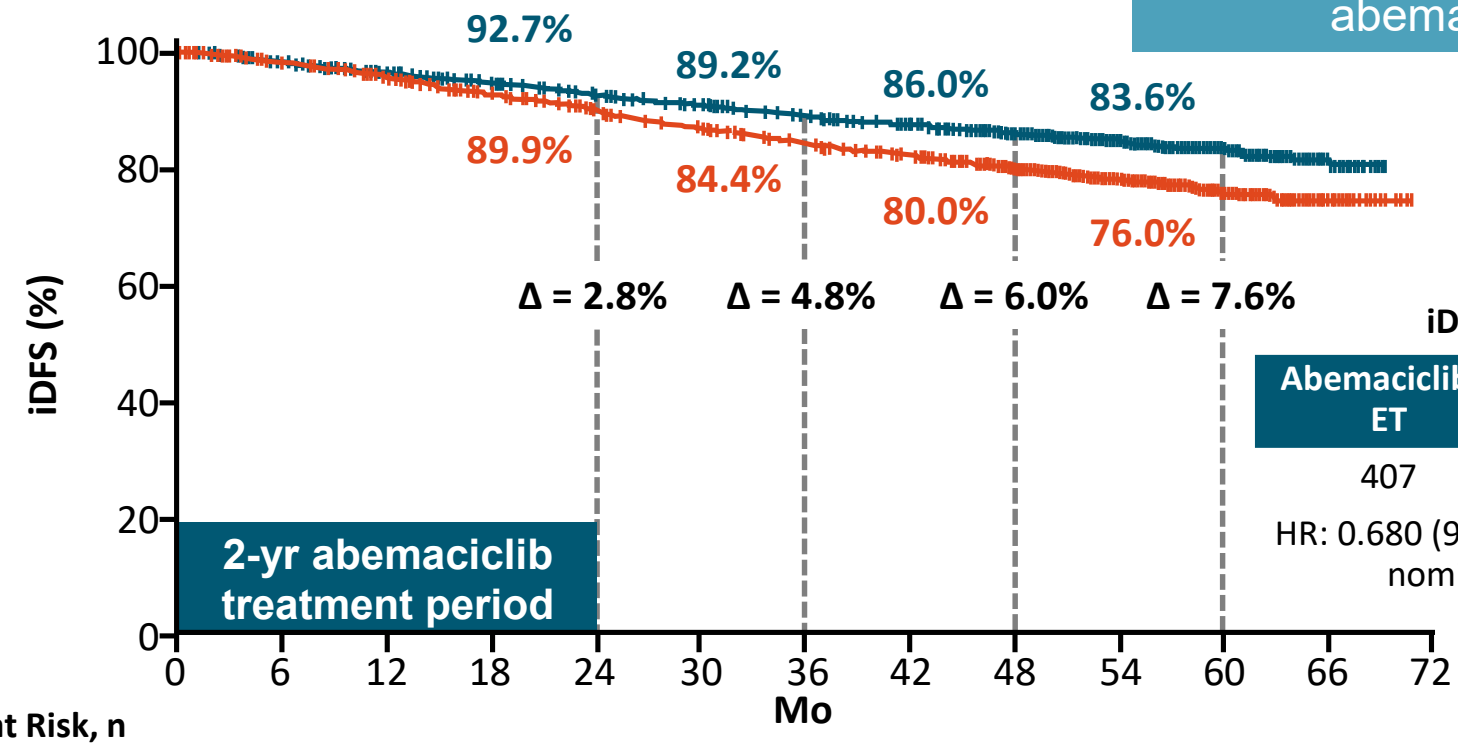


- **Primary endpoint:** iDFS
- **Key secondary endpoints:** iDFS in Ki-67 high (≥20%) population, DRFS, OS, safety, PROs

Rastogi. JCO. 2024;[Epub]. Johnston. JCO. 2020;38:3987.

monarchE: iDFS in ITT Population at Median Follow-up of 4.5 Yr (OS IA3)

At OS IA3:
All patients off abemaciclib; >80% followed for ≥2 yr since completing abemaciclib



iDFS Events

Abemaciclib + ET	ET Alone
407	585

HR: 0.680 (95% CI: 0.599-0.772; nominal *P* <.001)

Patients at Risk, n

Abemaciclib + ET	2808	2621	2549	2479	2408	2347	2284	2220	2095	1175	490	74	0
ET alone	2829	2653	2573	2474	2374	2281	2195	2125	1974	1124	473	67	0

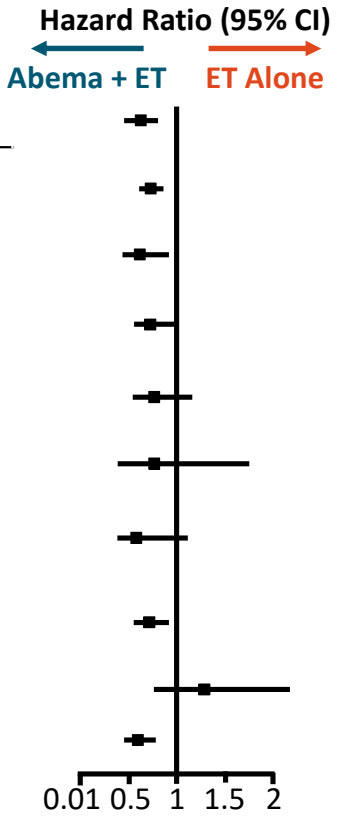
Consistent benefit across all patient and disease subgroups, independent of Ki-67 index

Rastogi. JCO. 2024;[Epub].

monarchE Exploratory Analyses of Predictive Biomarkers: Who Is More (or Less) Likely to Benefit?

Molecular Profiling* of Baseline Tumors[1]

4-Yr iDFS Rate, %	Abema + ET	ET Alone	Hazard Ratio (95% CI)
ITT	86.0	80.0	0.68 (0.60-0.77)
Biomarker subset	77.4	69.8	0.70 (0.56-0.88)
▪ Luminal A	87.5	81.4	0.59 (0.37-0.95)
▪ Luminal B	76.3	66.6	0.70 (0.51-0.97)
▪ HER2 enriched	52.6	42.5	0.74 (0.46-1.2)
▪ Basal	57.1	46.7	0.75 (0.29-1.9)
▪ Inferred Oncotype-RNA score ≤25	90.2	84.2	0.59 (0.33-1.10)
▪ Inferred Oncotype-RNA score >25	72.3	64.1	0.73 (0.57-0.92)
▪ *MYC* amp	--	--	1.30 (0.77-2.2)
▪ *MYC* wt	--	--	0.62 (0.47-0.8)



*Using RNA sequencing and whole exome sequencing.

- Consistent benefit observed across[1,2]:
  - Molecular subtypes
  - Inferred 21-gene Oncotype score
  - Most common oncogenic alterations
  - Ki-67 index
  - ER/PgR expression and status
- Potentially less benefit if *MYC* amp[1]
- ctDNA+ status at Mo 24 predictive for recurrence (PPV = 100%)[3]
  - But 21% with persistent ctDNA-negative status experienced recurrence (NPV = 79%)

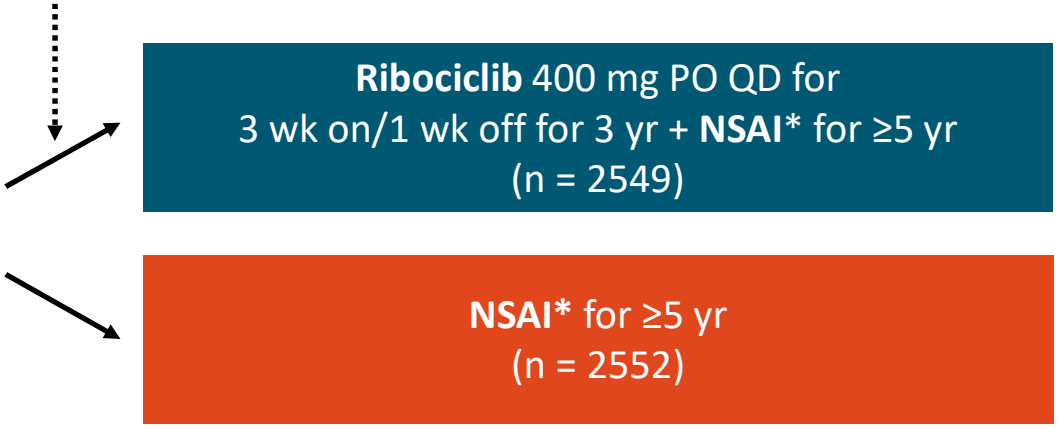
1. Turner. SABCS 2023. Abstr GS03-06. 2. Goetz. ESMO 2023. Abstr 240MO. 3. Loi. SABCS 2023. Abstr PS06-01.

NATALEE: Adjuvant Ribociclib + ET in Intermediate- to High-Risk HR+/HER2- EBC

- International, randomized, open-label phase III trial

Stratified by stage (II vs III), menopausal status (men and premenopausal vs postmenopausal women), prior (neo)adjuvant CT (yes vs no), geography (N America/W Europe/Oceania vs rest of world)

Pre/postmenopausal women and men with HR+/HER2- EBC; stage IIA (either N0 with grade 2 and Ki-67 ≥20%, Oncotype DX RS ≥26, or high risk via genomic risk profiling, N0 with grade 3, or N1, stage IIB (N0 or N1), or stage III disease; prior ET up to 12 mo permitted; prior (neo)adjuvant CT permitted (N = 5101)



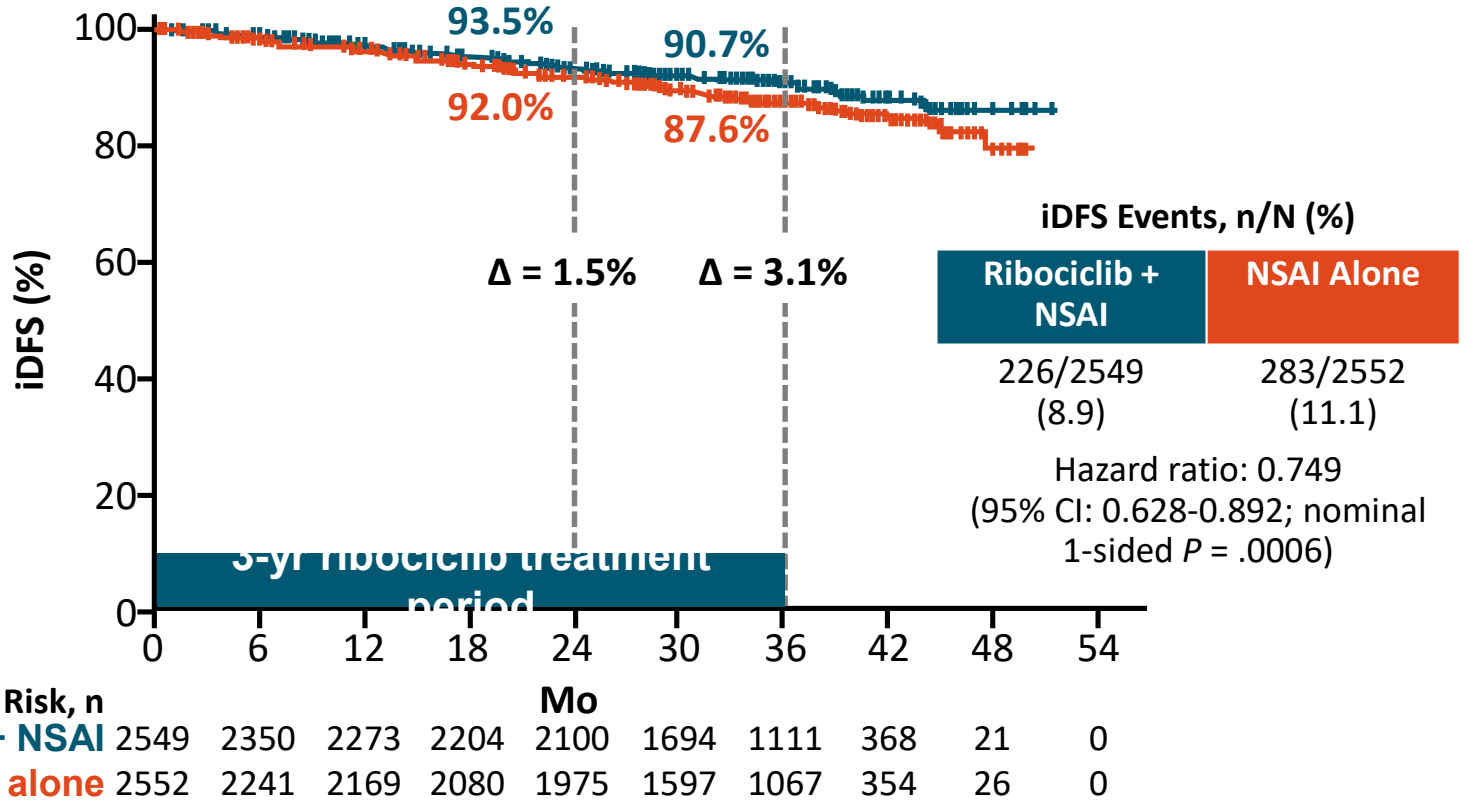
*Letrozole or anastrozole. Men and premenopausal women also received goserelin 3.6 mg/28 d.

- **Primary endpoint:** iDFS (STEEP criteria)
- **Key secondary endpoints:** recurrence-free survival, DDFS, OS, PROs, PK, safety

Hortobagyi. SABCS 2023. Abstr GS03-03. Slamon. ASCO 2023. Abstr LBA500. NCT03701334.

NATALEE: Final iDFS Analysis at Median Follow-up of 33.3 Mo

At Final iDFS Analysis:
Ribociclib ongoing for 20.7%; d/c for AEs in 19.5%

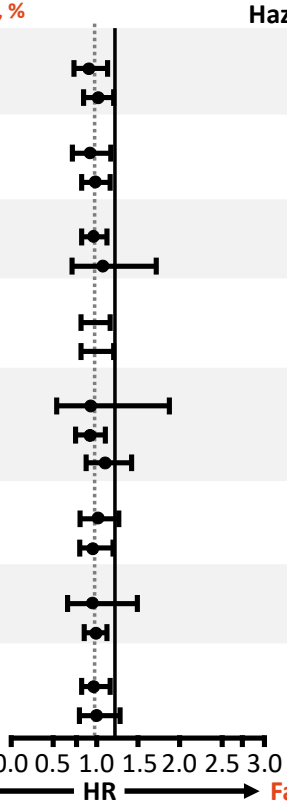


Ribociclib + NSAI significantly reduced risk of invasive disease by 25.1% vs NSAI alone (*P* = .0006)

Hortobagyi. SABCS 2023. Abstr GS03-03.

NATALEE: iDFS in Prespecified Subgroups at Median Follow-up of 33.3 Mo

Subgroup	Ribociclib + NSAI No. Events	Ribociclib + NSAI 3-Yr iDFS, %	NSAI Alone No. Events	NSAI Alone 3-Yr iDFS, %	Hazard Ratio	95% CI
Menopause status						
Men and premenopausal women	83/1125	91.8	114/1132	88.2	0.688	0.519-0.913
Postmenopausal women	143/1424	89.7	169/1420	87.1	0.806	0.645-1.007
AJCC stage						
Stage II	55/1101	94.2	80/1034	92.6	0.700	0.496-0.986
Stage III	170/1528	88.1	203/1512	83.8	0.755	0.616-0.926
Prior CT						
Yes	203/2249	90.5	255/2245	87.1	0.746	0.620-0.897
No	23/300	92.0	28/307	91.2	0.852	0.491-1.479
Region						
North American Western Europe/Oceania	131/1563	91.1	166/1565	87.5	0.748	0.595-0.941
Rest of world	95/986	90.1	117/987	87.6	0.774	0.591-1.015
Histologic grade at time of surgery						
Grade 1	9/213	95.1	13/217	93.1	0.708	0.303-1.657
Grade 2	118/1460	91.5	155/1432	88.0	0.696	0.548-0.885
Grade 3	80/684	87.5	89/702	85.9	0.890	0.658-1.204
Ki-67 status						
Ki-67 ≤20%	93/1199	91.8	117/1236	89.8	0.794	0.605-1.042
Ki-67 >20%	98/920	89.0	125/937	84.9	0.743	0.570-0.988
Nodal status						
N0	20/285	93.2	31/328	90.6	0.723	0.412-1.288
N1-N3	206/2261	90.3	251/2219	87.1	0.759	0.631-0.912
Prior ET						
Yes	150/1826	91.4	186/1805	88.4	0.755	0.609-0.936
No	76/723	88.9	97/747	85.8	0.771	0.571-1.040



Consistent benefit across subgroups, including stage II, III, N0, and N+ disease

Hortobagyi. SABCS 2023. Abstr GS03-03.

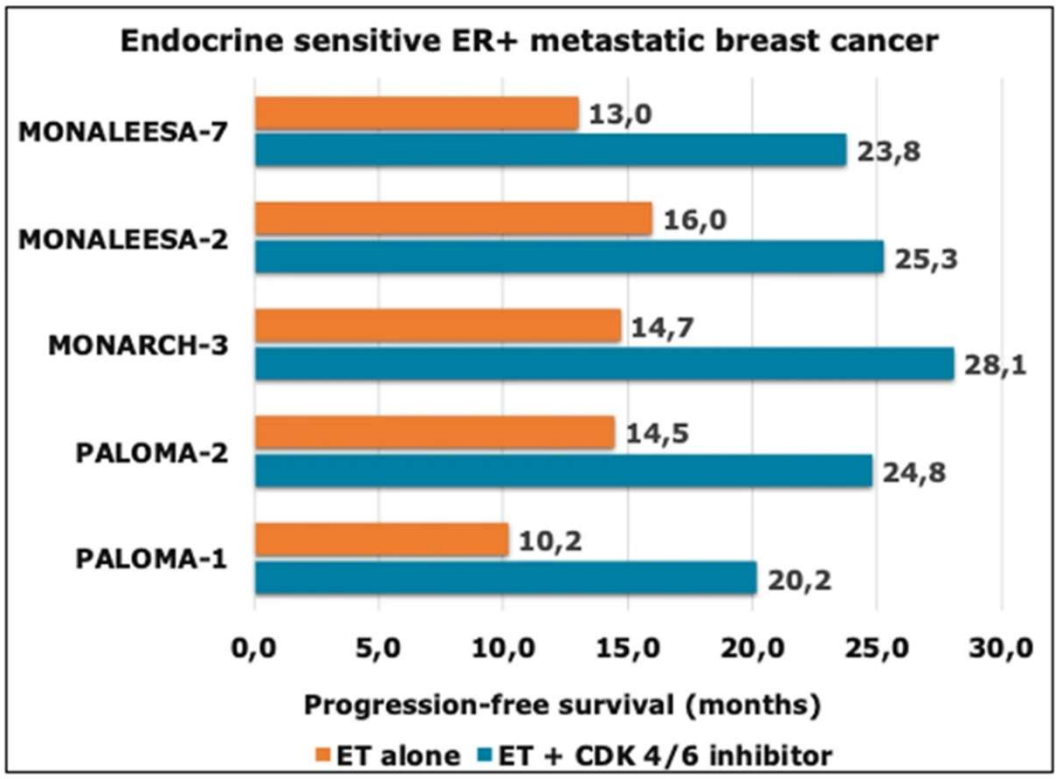
Trial	Population (adjuvant therapy)	No. of patients	Median follow-up	Investigational regimen	IDFS	Approval status
PALLAS J Clin Oncol . 2022 Jan 20;40(3):282-293.	Patients with stage II/III, HR+/HER2-breast cancer	5761	31.0 months	ET plus palbociclib for 2 years	4-year IDFS: 84.2% vs 84.5% (HR 0.96; P = .65)	Not approved
Penelope-B J Clin Oncol . 2021 May 10;39(14):1518-1530	Patients with stage II/III, HR+/HER2-breast cancer with residual disease after neoadjuvant chemotherapy and with high-risk features (CPS+EG score ≧3 or ≧2 with ypN+)	1250	42.8 months	ET plus palbociclib for 1 year	4-year IDFS: 73.0% vs 72.4% (HR 0.93; P = .525)	Not approved
monarchE Lancet Oncol . 2023 Jan;24(1):77-90	Patients with HR+/HER2(-) node(+) breast cancer with≧4 positive nodes or 1-3 nodes and at least one of the following: tumor size ≧5 cm, grade 3, or Ki-67 ≧20%	5637	54.0 months	ET plus abemaciclib for 2 years	5-year IDFS: 83.6% vs 76.0% (HR 0.680; P < .001)	Approved by the FDA
NATALEE N Engl J Med 2024;390:1080-1091	Patients with stage II/III, HR+/HER2(-)breast cancer. Stage IIA requires additional high-risk features (grade 3 or grade 2 with Ki-67 ≧20%, Oncotype DX ≧26, or high risk per genomic risk profiling)	5101	33.0 months	ET plus ribociclib for 3 years	3-year IDFS: 90.7% vs 87.6% (HR 0.748; P = .0014)	Not approved yet

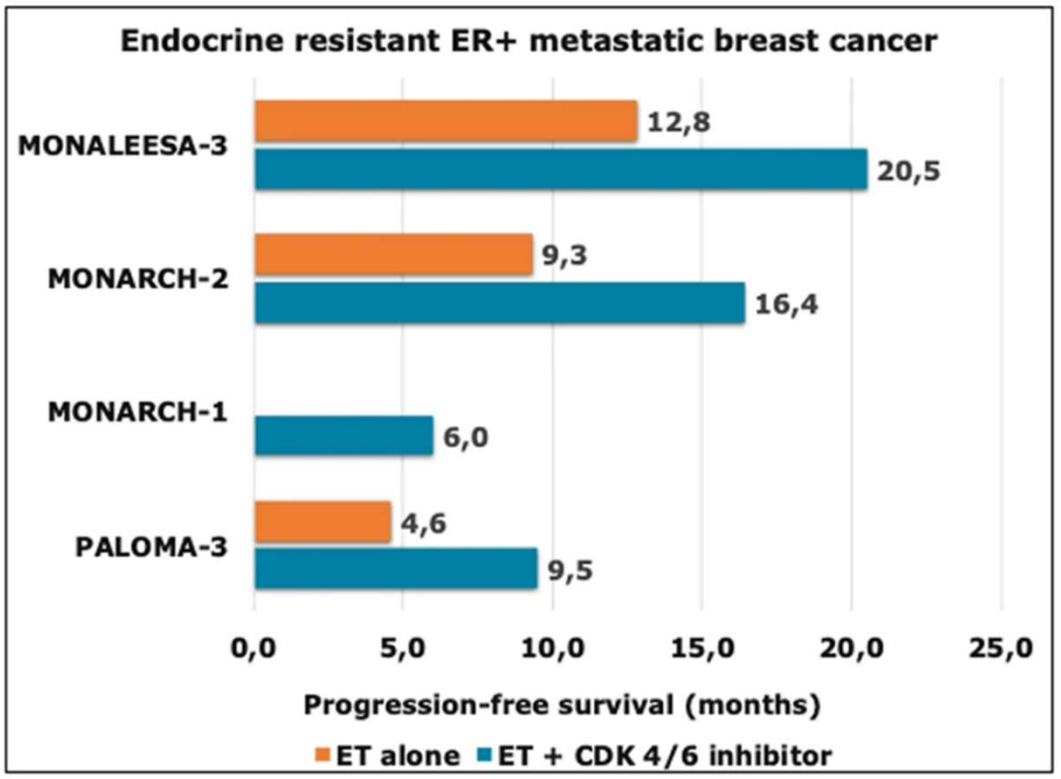
Conclusion：(CDK4/6 inhibitors)：advanced breast cancer with ER +，Her2（-）, Ribociclib and Abemaciclib can be used adjuvant breast cancer

Cyclin-Dependent kinase inhibitor : in advanced breast cancer ER+, Her2(-)
ORR 50%, pregression free survival 24 months
CDk4： proliferation, CDK6： stem cell
ORR : 50%)，PFS : 24 months

藥名	作用地點	• 適應症與給藥方法與劑量
Palbociclib (Ibrance)	CDK4, CDK6	• Advanced Breast cancer (HR+, HER2-) (3weeks, off one week) 給3週，停一週 (125mg qd) 或palbociclib 125mg qd for 5 days with 2 days of rest (給5天休2天)
Ribociclib (Kisqali)	CDK4, CDK6	• Advanced Breast cancer (HR+, HER2-) (early, advanced) • (3weeks, off one week) 給3週，停一週 (600mg qd), • Adjuvant : 400mg QD
Abemaciclib (Verzenio)	CDK4/less CDK6	• Breast cancer (HR+, HER2-) (none-stop) 不停藥 (150 or 200mg bid, 兩者抑制作用相等) • Monotherapy 可單獨治療 • Adjuvant therapy (早期輔助化療) • ADR : diarrhea, got/gpt elevated, Cr elevated (decrease tubular secretion)

Paloma:Palbociclib , Monaleesa :Ribociclib, Monarch:Abemaciclib



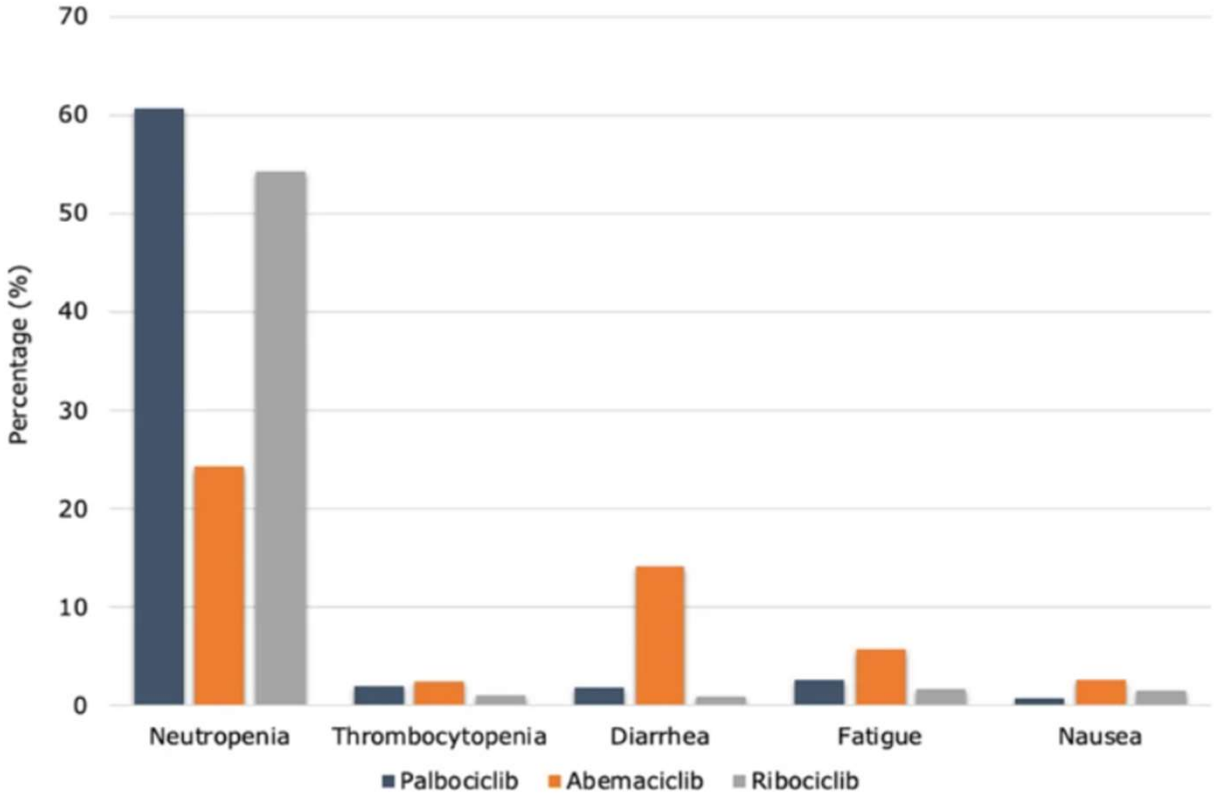


Progression-free survival (PFS) of CDK4/6 inhibitors in clinical trials. Upper and lower panels are referred to endocrine-sensitive and endocrine-resistant settings, respectively

npj Breast Cancer 5, 27 (2019). https://doi.org/10.1038/s41523-019-0121-y

Common toxicities of CDK 4/6 inhibitors reported in pivotal trials

Fig. 2



Common grade 3–4 adverse events reported in pivotal trials of CDK4/6 inhibitors

Key AEs With CDK4/6 Inhibitors: Monitoring and Prevention

Diarrhea	Hepatobiliary Toxicity	QT Prolongation	Neutropenia	VTE	ILD/ Pneumonitis
Abemaciclib **Palbociclib** **Ribociclib**	**Abemaciclib** **Ribociclib**	**Ribociclib**	**Abemaciclib** **Palbociclib** **Ribociclib**	**Abemaciclib**	**Abemaciclib** **Palbociclib** **Ribociclib**
Antidiarrheal therapy Increase oral hydration Notify healthcare provider	LFTs before starting tx, Q2W x 2 mos, then: ▪ *Abemaciclib,* as indicated ▪ *Ribociclib,* at start of cycle x 4 cycles	ECG before cycle 1, Day 14 of cycle 1, start of cycle 2, then as indicated Electrolytes at start of cycle x 6 cycles, then as indicated	CBC before starting treatment, then: ▪ *Abemaciclib,* Q2W x 2 mos, QM x 2 mos, then as indicated ▪ *Palbociclib,* D1 and D15 of C1-2, then as indicated ▪ *Ribociclib,* Q2W x 2 cycles, start of next 4 cycles, then as indicated	Monitor for signs and symptoms of thrombosis or pulmonary embolism	Monitor for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea)

Abemaciclib PI. Palbociclib PI. Ribociclib PI.

Slide credit: clinicaloptions.com

Effect of toxicity in selecting CDK4/6 inhibitors

	 Elderly patients	 Patients with cardiovascular disease	 Patients with hepatic impairment	 Patients with comorbidities
Neutropenia	✓			✓
Diarrhoea	✓			✓
Thromboembolic events	✓	✓		✓
Reversible transaminitis	✓		✓	✓
QTc prolongation	✓	✓		✓

npj Breast Cancer 5, 27 (2019). https://doi.org/10.1038/s41523-019-0121-y

Who May Benefit From Adjuvant Treatment With CDK4/6 Inhibitors for HR+/HER2- EBC?

Eligible | Eligible if meet additional criteria | Ineligible

AJCC Anatomical Staging	TN (M0)	NATALEE: Ribociclib	monarchE: Abemaciclib
IA	T1N0		
IB	T0N1mi		
	T1N1mi		G3 or Ki67 ≥20%
IIA	T0N1		
	T1N1		G3 or Ki67 ≥20%
	T2N0	G3, or G2 with Ki-67 ≥20% or high genomic risk*	
IIB	T2N1		G3 or Ki67 ≥20%
	T3N0		
IIIA	T0N2		
	T1N2		
	T2N2		
	T3N1		
	T3N2		
IIIB	T4N0		
	T4N1		
	T4N2		
IIIC	Any TN3		

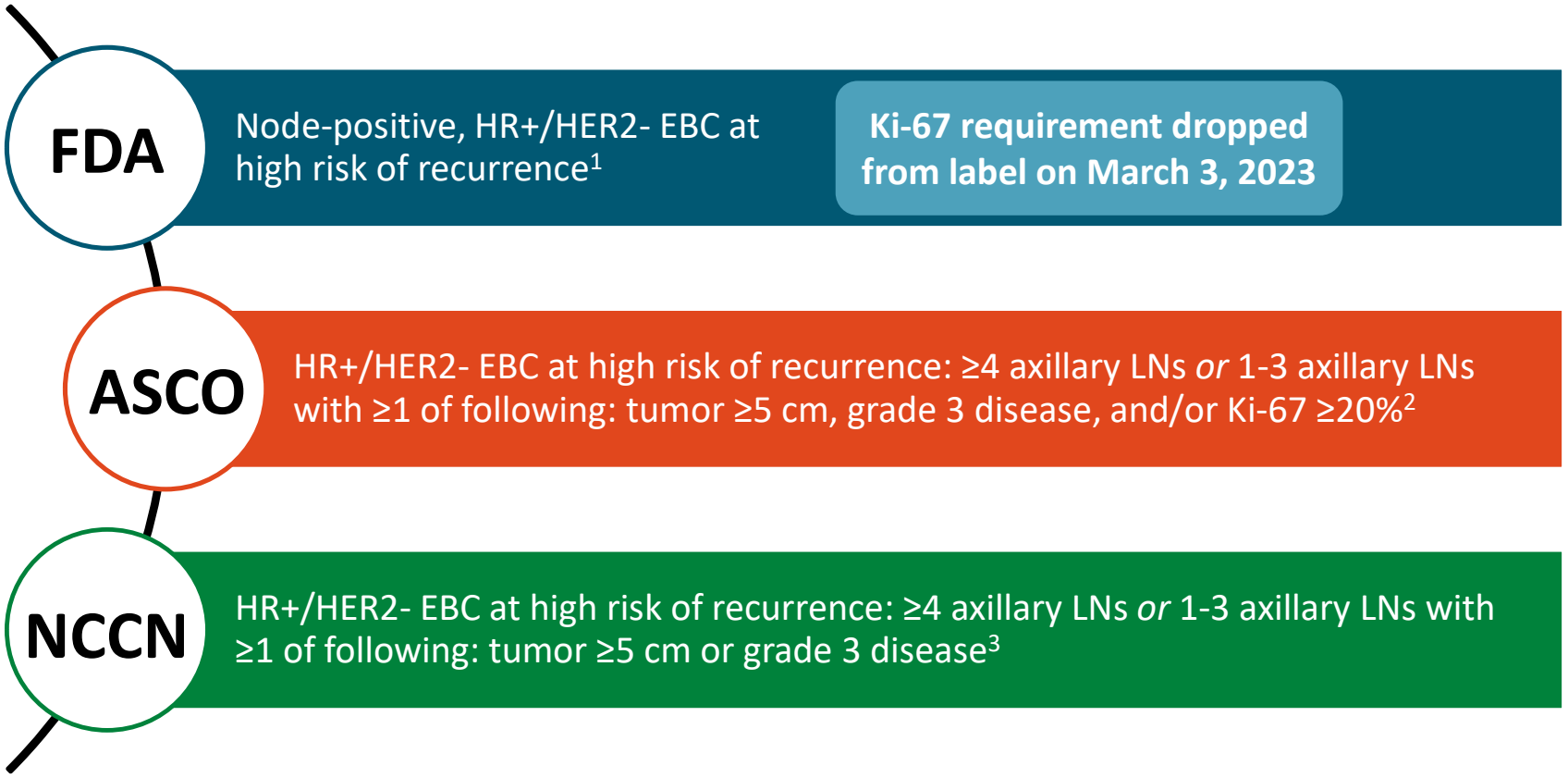
*According to Oncotype DX, Prosigna PAM50, or EndoPredict EPclin Risk Score.

- Pre/postmenopausal women
- Men
- **Tx choice depends on:**
  - Approval (abemaciclib approved, ribociclib investigational)
  - Access
  - Risk
  - Long-term efficacy
  - Safety profile
  - Patient preference
- **Do not forget to test for g*BRCA*m** – determines eligibility for adjuvant olaparib (OlympiA)

Harbeck. ASCO 2023. Breast Cancer—Local/Regional/Adjuvant: Abstracts Discussion 1.

Slide credit: clinicaloptions.com

Approvals and Recommendations: Adjuvant Abemaciclib + ET



1. Abemaciclib PI. 2. Giordano. JCO. 2022;40:307. 3. NCCN. Breast cancer. v.1.2024.

Slide credit: clinicaloptions.com

Thank you for listening

癌information症資訊store雜貨店

癌症藥物(專業版) 癌症藥物(民眾版) 癌症另類輔助治療 各類癌症治療 兒童幹細胞移植

癌症臨床藥物資料庫

本資料庫由癌症臨床藥師方麗華所建立，關注癌症藥物、補充治療資訊、兒童幹細胞移植等領域。
搜尋結果均以本站制定的格式編寫，提供專業人士及一般民眾更易閱讀的藥物資訊！

快速搜尋癌症藥物、用藥相關知識