HR+/HER2- advanced breast cancer: How do the latest data on CDK4/6 inhibitors inform clinical decision making?

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How can biomarkers inform treatment selection in HR+/HER2- advanced breast cancer?

Dr Luca Malorni

Senior Medical Oncologist and Director of the Translational Research Unit,
Hospital of Prato,
Prato, Italy

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Why are biomarkers needed for CDK4/6 inhibitor therapy in HR+/HER2- advanced breast cancer?

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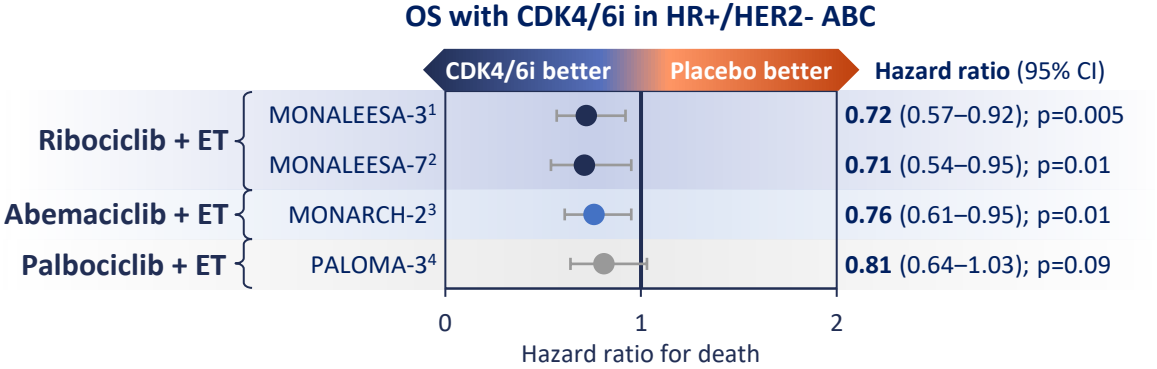
Need for biomarkers for CDK4/6i therapy in ABC

Addition of CDK4/6i to ET improved outcomes for patients with HR+/HER2- ABC[1–4]



Approximately 10% of patients have primary resistance to CDK4/6i and acquired resistance is nearly inevitable in most patients[5]

Biomarkers to identify resistance or predict response to CDK4/6i are an area of unmet clinical need[5]

ABC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival.

1. Slamon DJ, et al. *N Engl J Med*. 2020;382:514–24; 2. Im S-A, et al. *N Engl J Med*. 2019;381:307–16; 3. Sledge GW, et al. *JAMA Oncol*. 2020;6:116–24; 4. Turner NC, et al. *N Engl J Med*. 2018;379:1926–36; 5. McCartney A, et al. *Front Oncol*. 2019;9:666.

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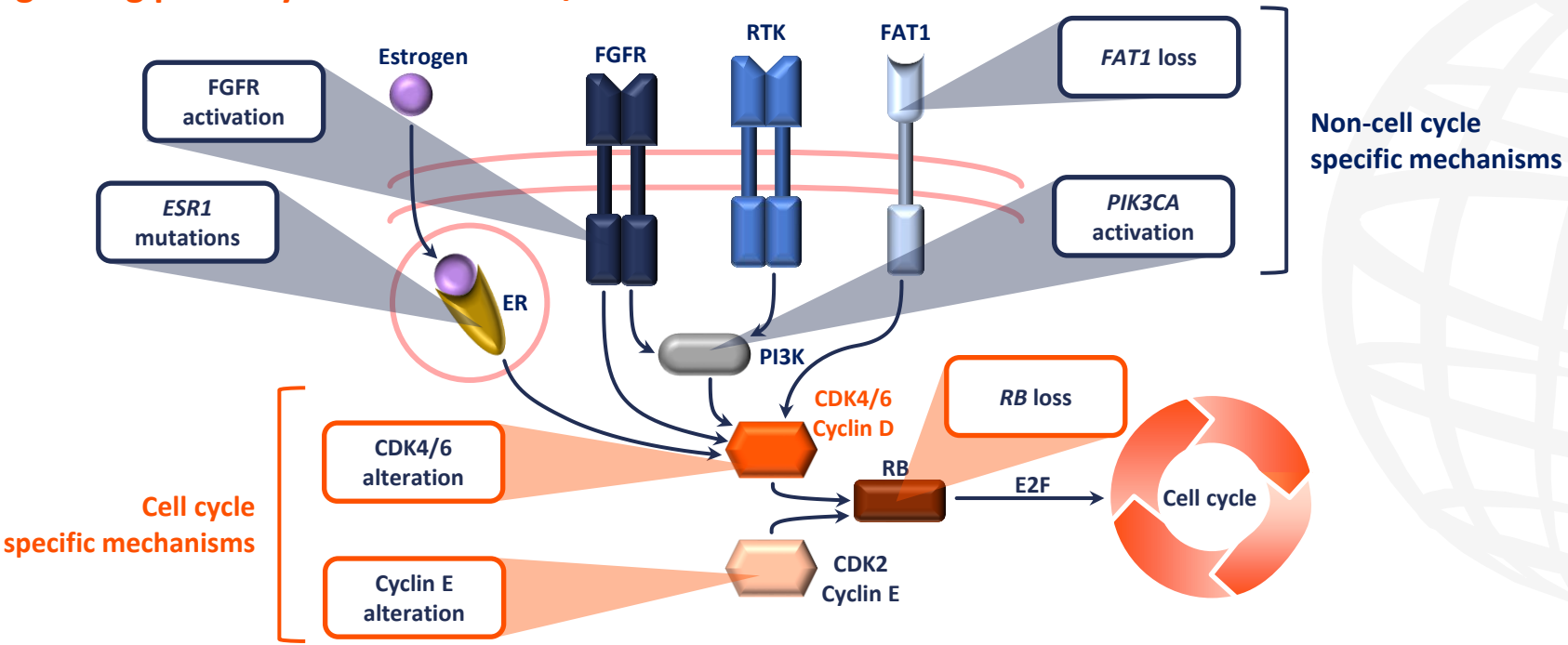
What mechanisms are believed to be implicated in resistance to CDK4/6 inhibitors?

Mechanisms of resistance to CDK4/6i

Signalling pathways linked to CDK4/6[1,2]



CDK, cyclin-dependent kinase; CDK4/6i, CDK 4 and 6 inhibitor; E2F, E2 transcription factor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; *FAT1*, FAT atypical cadherin 1; FGFR, fibroblast growth factor receptor; PI3K, phosphoinositide 3-kinases; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *RB*, retinoblastoma protein; RTK, receptor tyrosine kinase.

1. Roberto M, et al. *Cancers*. 2021;13:332; 2. Pandey K, et al. *Int J Cancer*. 2019;145:1179–88.

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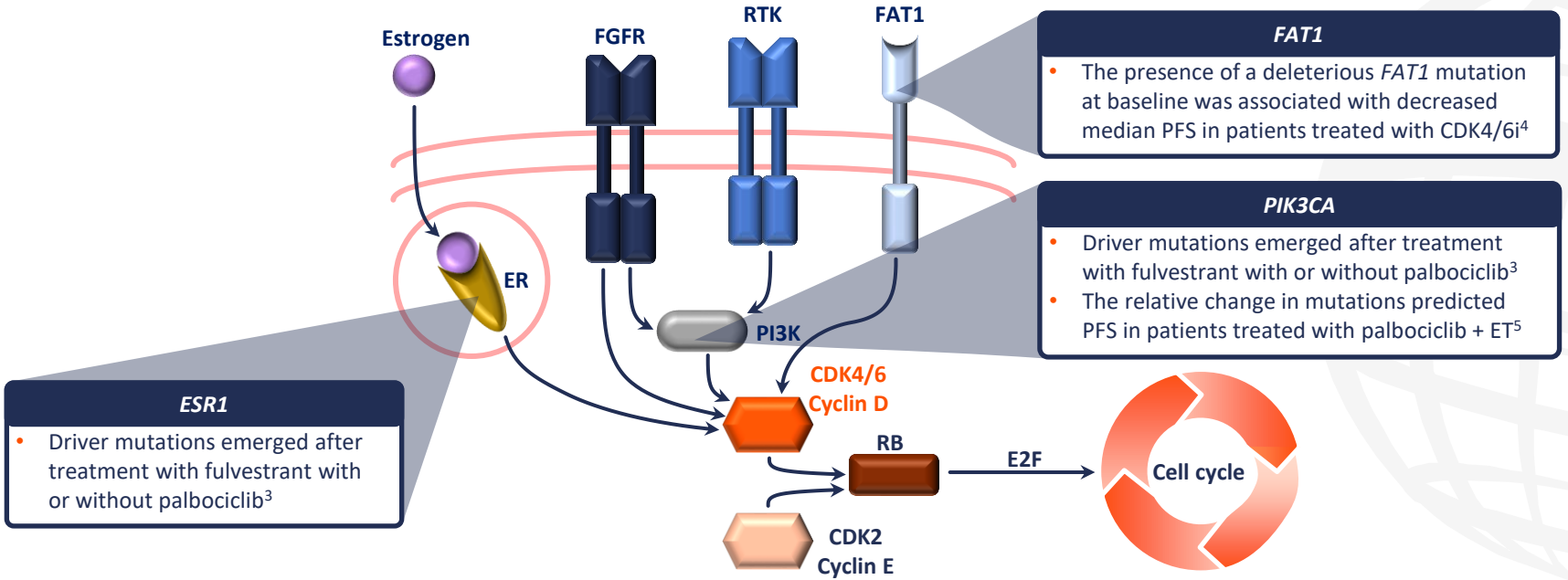
What is the evidence to date for possible biomarkers of response to CDK4/6 inhibitors?

Possible biomarkers for resistance to CDK4/6i

Signalling pathways linked to CDK4/6 and non-cell cycle-related biomarkers[1,2]



CDK, cyclin-dependent kinase; CDK4/6i, CDK 4 and 6 inhibitor; E2F, E2 transcription factor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; *FAT1*, FAT atypical cadherin 1; FGFR, fibroblast growth factor receptor; PI3K, phosphoinositide 3-kinases; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival; RB, retinoblastoma protein; RTK, receptor tyrosine kinase.

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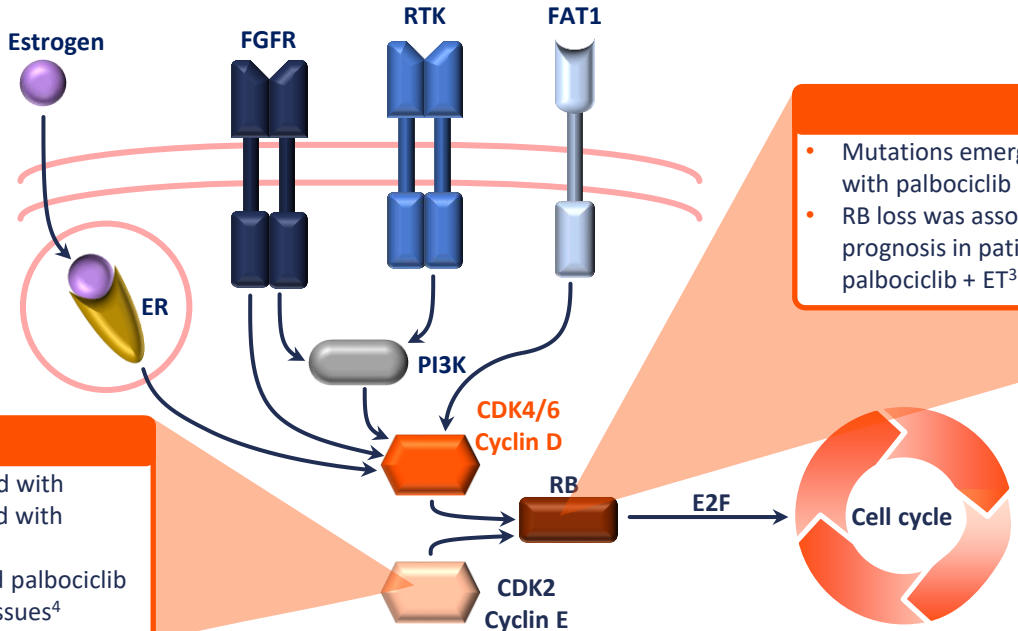
Possible biomarkers for resistance to CDK4/6i

Signalling pathways linked to CDK4/6 and cell cycle-related biomarkers[1,2]



Cyclin E

- Cytoplasmic cyclin E was associated with worse prognosis in patients treated with palbociclib + ET[3]
- *CCNE1* mRNA expression predicted palbociclib efficacy, especially in metastatic tissues[4]

RB

- Mutations emerged in patients treated with palbociclib plus fulvestrant[5]
- RB loss was associated with worse prognosis in patients treated with palbociclib + ET[3]

CCNE1, cyclin E1; CDK, cyclin-dependent kinase; CDK4/6i, CDK 4 and 6 inhibitor; E2F, E2 transcription factor; ER, estrogen receptor; ET, endocrine therapy; FAT1, FAT atypical cadherin 1; FGFR, fibroblast growth factor receptor; mRNA, messenger RNA; PI3K, phosphoinositide 3-kinases; RB, retinoblastoma protein; RTK, receptor tyrosine kinase.

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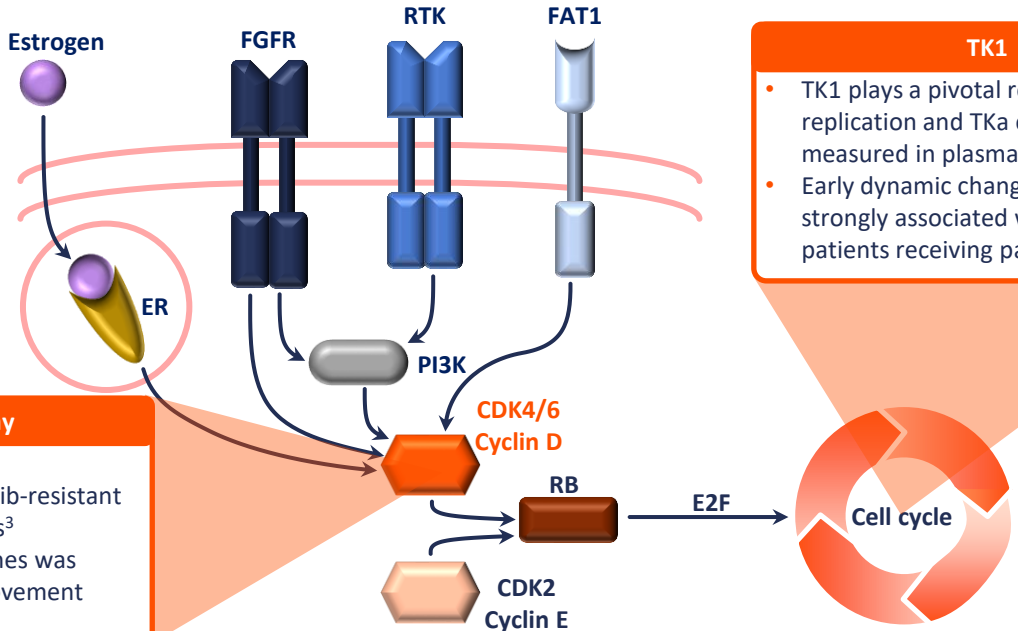
Possible biomarkers for resistance to CDK4/6i

Signalling pathways linked to CDK4/6 and cell cycle-related biomarkers[1,2]



CDK4/6–RB–E2F pathway

- A gene signature of E2F activity discriminated between palbociclib-resistant and palbociclib-sensitive cell lines[3]
- High expression of E2F target genes was associated with lack of PFS improvement from palbociclib[4]

TK1

- TK1 plays a pivotal role in DNA replication and TKa can be measured in plasma or serum[5]
- Early dynamic changes of TKa are strongly associated with outcome in patients receiving palbociclib[5,6]

CDK, cyclin-dependent kinase; CDK4/6i, CDK 4 and 6 inhibitor; E2F, E2 transcription factor; ER, estrogen receptor; FAT1, FAT atypical cadherin 1; FGFR, fibroblast growth factor receptor; PFS, progression-free survival; PI3K, phosphoinositide 3-kinases; RB, retinoblastoma protein; RTK, receptor tyrosine kinase; TK1, thymidine kinase 1; TKa, thymidine kinase activity.

1. Roberto M, et al. *Cancers*. 2021;13:332; 2. Pandey K, et al. *Int J Cancer*.2019;145:1179–88; 3. Malorni L, et al. *Oncotarget*. 2016;7:68012–22; 4. Turner NC, et al. *J Clin Oncol*. 2019;37:1169–78; 5. McCartney A, et al. *Clin Cancer Res*. 2020;26:2131–9; 6. Malorni L, et al. *Cancer Res*. 2021;81:PS5-05.

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How could new biomarker testing be implemented into clinical practice?

Present and future of biomarkers for CDK4/6i therapy in patients with HR+/HER2- ABC

Present

To date, none of the genomic drivers of CDK4/6i resistance are used as biomarkers in the clinic[1]

PIK3CA mutation testing is used to guide the use of PI3K inhibitors, not as a marker for CDK4/6i resistance[2]

Future

Clinically useful biomarkers [1]

Biomarker-guided therapeutic strategies[1]

Personalized treatment[1]

ABC, advanced breast cancer CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PI3K, phosphoinositide 3-kinases; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

1. Migliaccio I, et al. *Cancer Treat Rev*. 2021;93:102136; 2. Cardoso S, et al. *Ann Oncol*. 2020;31:1623–49.

What is the relevance of intrinsic HR+/HER2- breast cancer subtypes in clinical decision-making?

Prof. Aleix Prat

Head of the Medical Oncology Department, Hospital Clínic Barcelona, Barcelona, Spain

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What are the different intrinsic subtypes of breast cancer?

Phenotyping vs intrinsic subtyping

Biopsy

HR/HER2 phenotyping[1]

ER and PR

- **IHC**: HR protein expression on the tumour cell surface

HER2

- **IHC**: HER2 protein expression on the tumour cell surface
- **FISH**: HER2 gene amplification

Intrinsic molecular subtyping[2]

Multiple genes

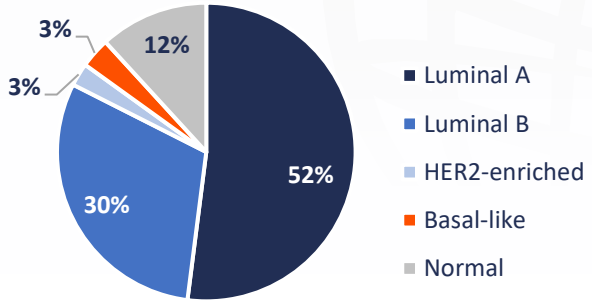
- **qRT-PCR or NGS**: mRNA levels in tumour cells
- **Includes ER, PR and HER2**

There are differences in tumour classification when comparing molecular assays and IHC[2]

Retrospective analysis of samples from the EGF30008 trial (NCT00073528)[3]

N=644

- Postmenopausal women with HR+/HER2- invasive breast cancer
- No prior therapy for advanced or metastatic disease
- PAM50 subtyping



ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; mRNA, messenger RNA; NGS, next-generation sequencing; PR, progesterone receptor; qRT-PCR, quantitative reverse transcription polymerase chain reaction.

1. Wu NC, et al. *Breast Cancer Res Treat*. 2018;172:327–38; 2. Kensler KH, et al. *Cancer Epidemiol Biomarkers Prev*. 2019;28:798–806; 3. Prat A, et al. *JAMA Oncol*. 2016;2:1287–94.

Phenotyping vs intrinsic subtyping

Biopsy

HR/HER2 phenotyping[1]

ER and PR
- **IHC**: HR protein ex
  the tumour cell su

HER2
- **IHC**: HER2 protein expression on the tumour cell surface
- **FISH**: HER2 gene amplification

Intrinsic molecular subtyping[2]

HR+/HER2- HER2-enriched tumours

- Do not overexpress *HER2* gene, protein or phospho-protein[2,4]
- Have a profile that is undistinguishable from HER2+ tumours[4]

There are differences in tumour classification when comparing molecular assays and IHC[2]

Retrospective analysis of samples from the EGF30008 trial (NCT00073528)[3]

- Postmenopausal women with
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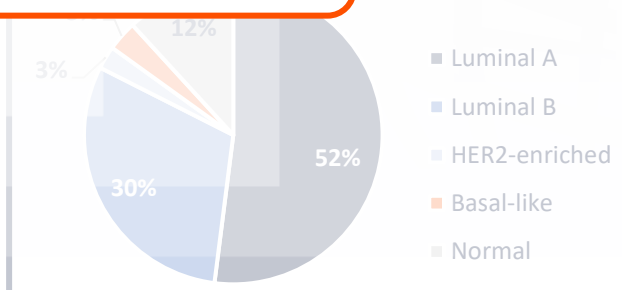

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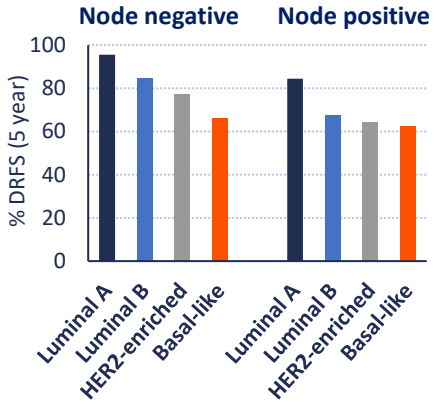
What is the prognostic value of intrinsic subtypes in HR+/HER2- breast cancer?

Prognostic value of intrinsic subtypes

Early diseases

PAM50 dataset[1]

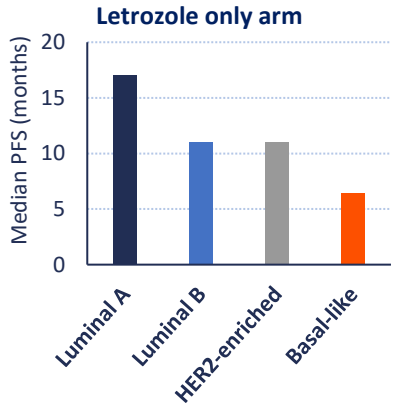
- 1,380 patients with HR+ breast cancer
- Adjuvant tamoxifen



Advanced or metastatic diseases

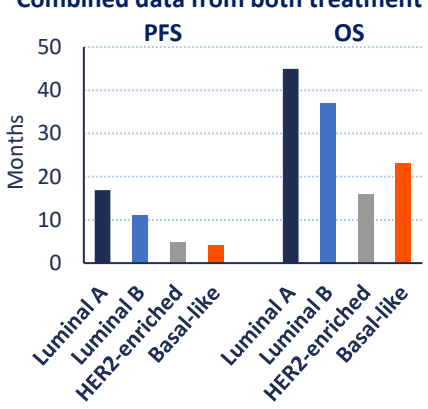
PALOMA-2[2]

- 666 postmenopausal women with HR+/HER2- ABC
- Letrozole + palbociclib or placebo



Retrospective analysis of EGF30008[3]

- 644 postmenopausal women with HR+/HER2- invasive breast cancer with no prior therapy for advanced or metastatic disease
- Lapatinib plus letrozole or placebo plus letrozole



Only patients with HER2-enriched disease benefited from lapatinib

- PFS:
  - Lapatinib: 6.5 months
  - Placebo: 2.6 months
- Hazard ratio = 0.24
- p=0.02

ABC, advanced breast cancer; DFRS, distant relapse-free survival; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival; PFS, progression-free survival.

1. Prat A, et al. *Ann Oncol*. 2012;23:2866–73; 2. Cejalvo JM, et al. *Cancer Treat Rev*. 2018;67:63–70; 3. Prat A, et al. *JAMA Oncol*. 2016;2:1287–94.

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What is the evidence for efficacy of CDK4/6 inhibitors in different intrinsic subtypes in HR+/HER2- breast cancer?

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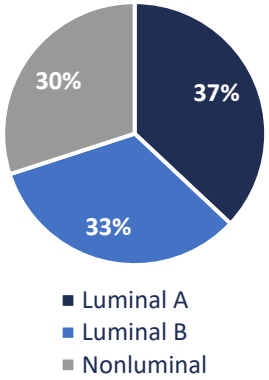
Palbociclib efficacy in different intrinsic subtypes

Analysis of data from PALOMA-3

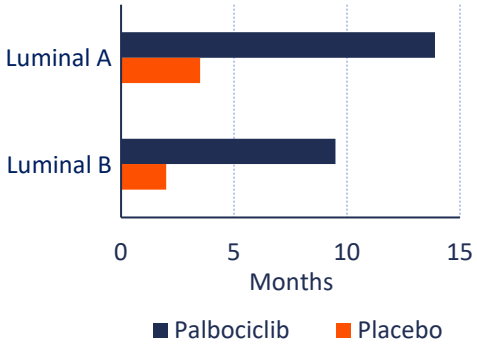
- HR+/HER2- patients with ABC receiving fulvestrant plus palbociclib or placebo
- 142 metastatic biopsy samples from 521 total patients

To investigate whether intrinsic subtypes affect PFS in patients receiving palbociclib

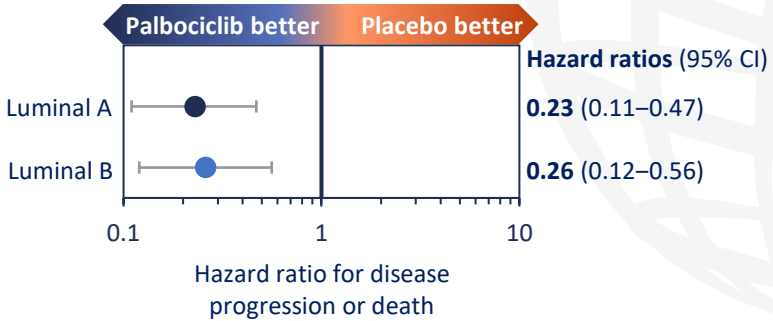
Intrinsic subtypes



Median PFS



Impact of intrinsic subtype on PFS



ABC, advanced breast cancer; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PFS, progression-free survival.

Finn RS, et al. *Breast Cancer Res Treat*. 2020;184:23–35.

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Ribociclib efficacy in different intrinsic subtypes

Analysis of data from MONALEESA-2, -3, and -7

1,160 tumour samples from HR+/HER2- ABC

MONALEESA-2	MONALEESA-3	MONALEESA-7
Postmenopausal women (N=668)	Postmenopausal women and men (N=726)	Pre- and perimenopausal women, all receiving goserelin (N=672)
1:1	2:1	1:1
Ribociclib + letrozole vs Placebo + letrozole	Ribociclib + fulvestrant vs Placebo + fulvestrant	Ribociclib + tamoxifen or NSAI vs Placebo + tamoxifen or NSAI

To evaluate the association of intrinsic subtypes with PFS in the MONALEESA trials

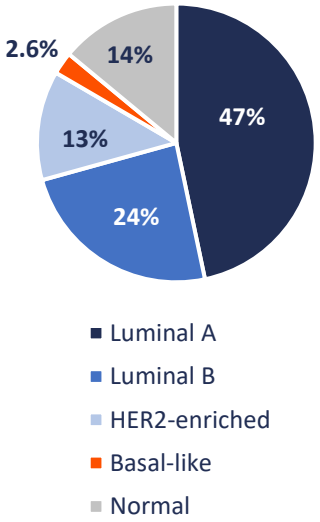
ABC, advanced breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NSAI, nonsteroidal aromatase inhibitor, PFS, progression-free survival.

Prat A, et al. *J Clin Oncol.* 2021; Online ahead of print doi: 10.1200/JCO.20.02977.

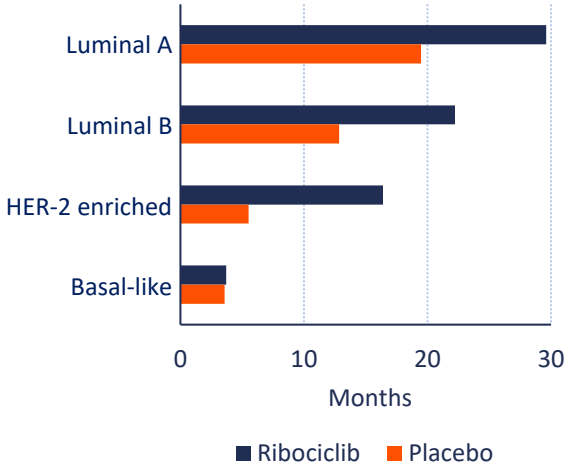
Ribociclib efficacy in different intrinsic subtypes

Analysis of data from MONALEESA-2, -3, and -7

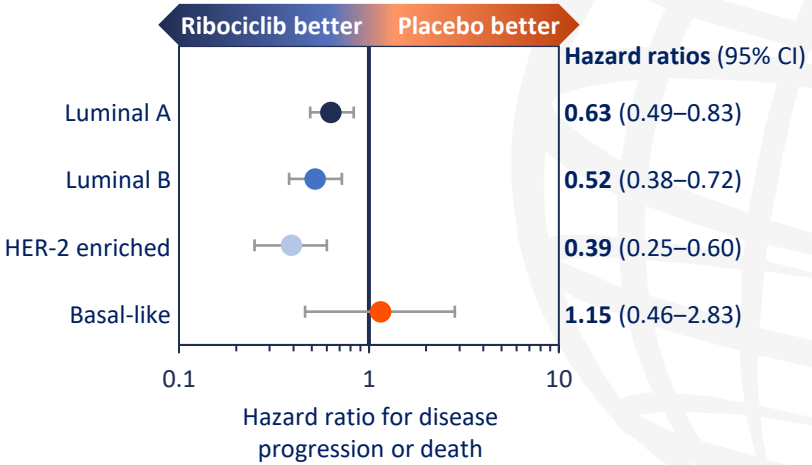
Intrinsic subtypes



Median PFS



Impact of intrinsic subtype on PFS



CI, confidence interval; HER2, human epidermal growth factor receptor 2; PFS, progression-free survival.

Prat A, et al. *J Clin Oncol.* 2021; Online ahead of print doi: 10.1200/JCO.20.02977.

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How can intrinsic subtypes help inform treatment selection in HR+/HER2- breast cancer?

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Intrinsic subtyping may inform treatment choice

Current guidelines (ESMO)[1]

HR+ breast cancer

- ET is the preferred option for HR+ disease
- A CDK4/6i plus ET is the standard of care for patients with HR+/HER2- ABC
- The CDK4/6i can be combined with an AI or with fulvestrant in *de novo* or recurrent ABC
- The addition of everolimus to an AI is a valid option for some patients
- Tamoxifen or fulvestrant can also be combined with everolimus

Potential impact of intrinsic subtyping[1–7]

HR+/HER2- ABC

Luminal

- ET + CDK4/6i
- mTOR inhibitor (everolimus) + AI
- CT

HER2-enriched

- ET + ribociclib
- ET + lapatinib
- mTOR inhibitor (everolimus) + AI
- CT + ICI?

Basal-like

- CT+ ICI?

Potential treatment options according to intrinsic subtype based on retrospective and exploratory analyses; confirmatory clinical trials are ongoing

ABC, advanced breast cancer; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CT, chemotherapy; ESMO, European Society for Medical Oncology; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICI, immune checkpoint inhibitors; mTOR, mechanistic target of rapamycin.

1. Cardoso S, et al. *Ann Oncol*. 2020;31:1623–49; 2. Finn RS, et al. *Breast Cancer Res Treat*. 2020;184:23–35; 3. Prat A, et al. *J Clin Oncol.* 2021; Online ahead of print doi: 10.1200/JCO.20.02977; 4. Cejalvo JM, et al. *Cancer Treat Rev*. 2018;67:63–70; 5. Prat A, et al. *JAMA Oncol*. 2016;2:1287–94; 6. Prat A, et al. *Oncologist*. 2019;24:893–900; 7. ClinicalTrials.gov. NCT04251169. Available at: www.clinicaltrials.gov/ct2/show/NCT04251169 (accessed 28 May 2021).

How do patient and disease characteristics impact treatment choice and response to CDK4/6 inhibitor therapy?

Dr Barbara Pistilli

Medical Oncologist
and Head of the Breast Cancer Unit,
Gustave Roussy,
Villejuif, France

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Does patient age make a difference to the clinical benefit and tolerability experienced with CDK4/6 inhibitor therapy?

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Impact of patient age on CDK4/6i therapy

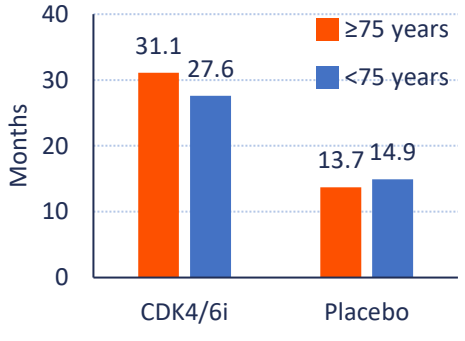
Combined data from PALOMA-2, MONALEESA-2 and MONARCH-3

- 1,827 patients with HR+/HER2- breast cancer
- 1,105 received one of three CDK4/6i plus AI
- 722 received placebo plus AI
- 10.8% of patients were aged ≥75 years

To examine the efficacy and safety of CDK4/6i plus AI combinations in older women

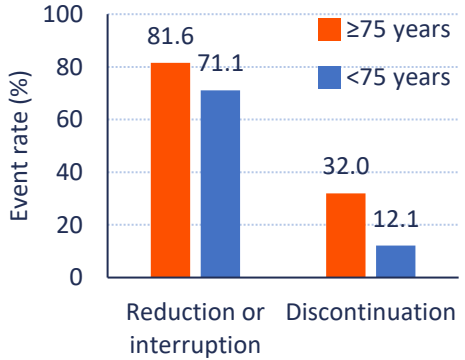
Efficacy

Median PFS



Safety

AE leading to dose modification



- **The benefit of CDK4/6i was comparable between older and younger patients**
- **Rates of toxicity and dose modification were higher in older compared with younger patients**
- **Diarrhoea and fatigue were more common in older patients**

AE, adverse events; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PFS, progression-free survival.

Howie LJ, et al. *J Clin Oncol*. 2019;37:3475–83.

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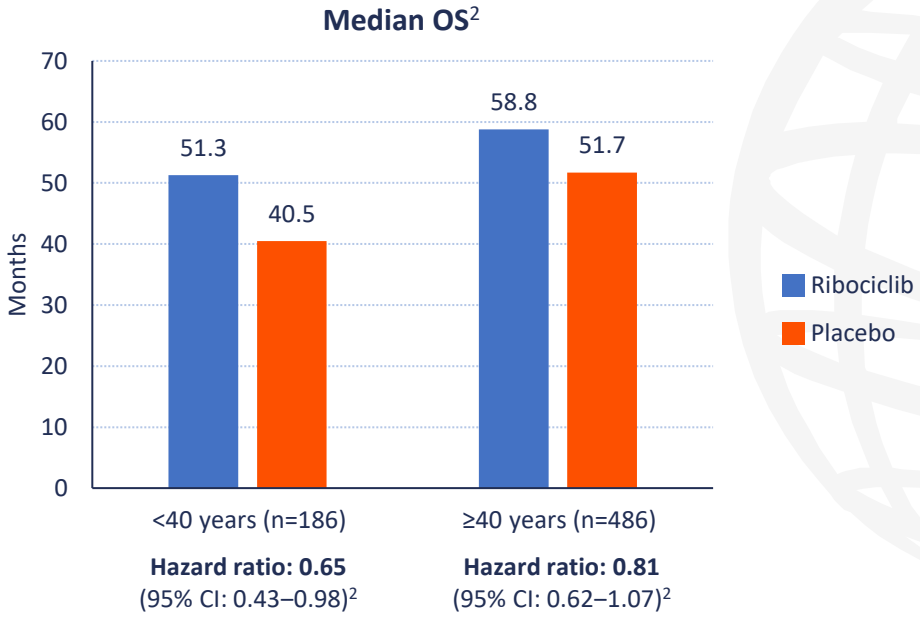
Impact of patient age on CDK4/6i efficacy

Sub-analysis of MONALEESA-7 at 53.5 months' median follow-up

N=672

- Pre- and peri-menopausal women[1]
- 18–59 years of age[1]
- HR+/HER2- advanced breast cancer[1]
- 27.7% of patients were aged <40 years[1]

Breast cancer is more aggressive and associated with poorer prognosis in younger versus older women[1]



CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival.

1. Im S-A, et al. *N Engl J Med*. 2019;381:307–16; 2. Lu Y-S, et al. *Ann Oncol*. 2021;32:S62.

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What do clinical trial data tell us about the influence of menopausal status on the efficacy of different CDK4/6 inhibitors?

Menopausal status and CDK4/6i efficacy

OS Data from MONALEESA-7 and MONALEESA-3

MONALEESA-7[1]

- 672 pre- and peri-menopausal
- HR+/HER2- ABC

1:1

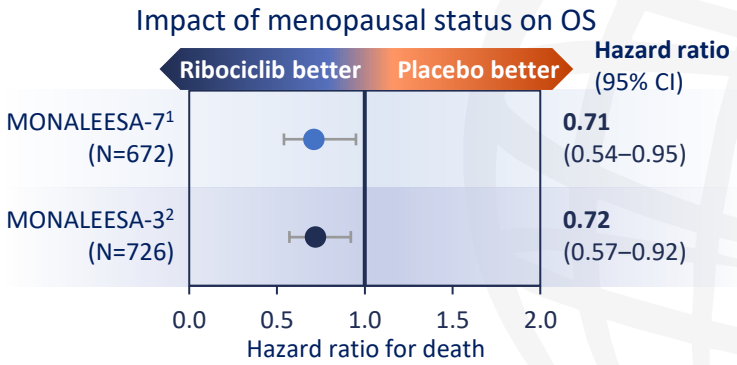
- Ribociclib
- Placebo (plus goserelin and NSAI or tamoxifen)

MONALEESA-3[2]

- 726 men and post-menopausal women
- HR+/HER2- ABC

2:1

- Ribociclib
- Placebo (plus fulvestrant)



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1. Im S-A, et al. *N Engl J Med*. 2019;381:307–16; 2. Slamon DJ, et al. *N Engl J Med*. 2020;382:514–24.

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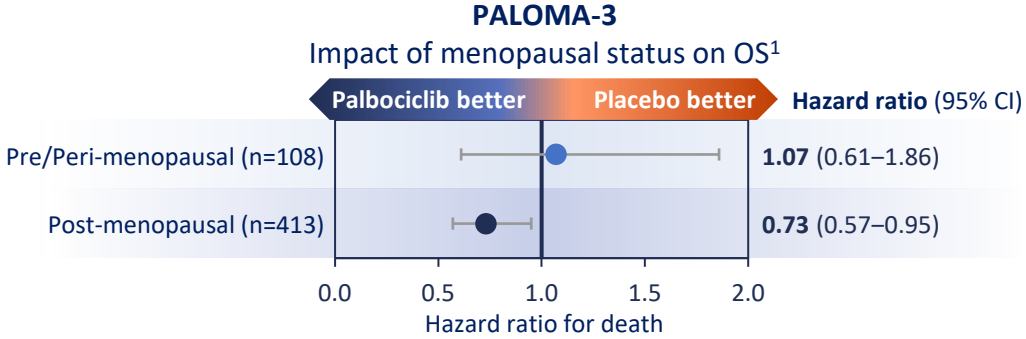
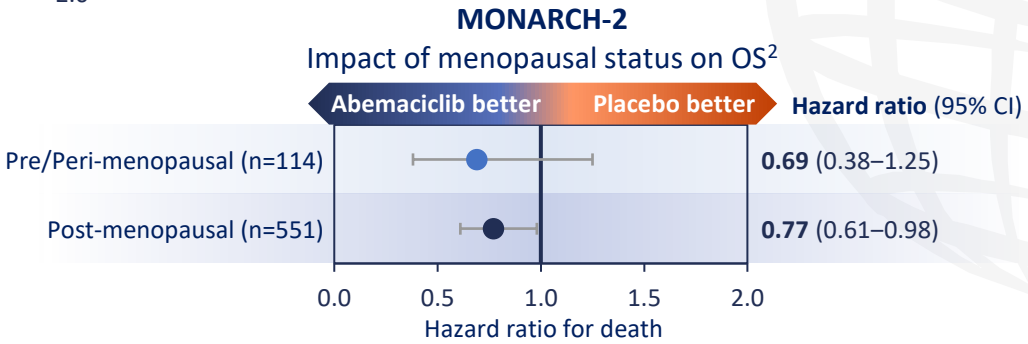
Menopausal status and CDK4/6i efficacy

Sub-analyses of OS data from PALOMA-3 and MONARCH-2





CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; OS, overall survival.

1. Turner NC, et al. *N Engl J Med*. 2018;379:1926–36; 2. Sledge GW, et al. *JAMA Oncol*. 2020;6:116–24.

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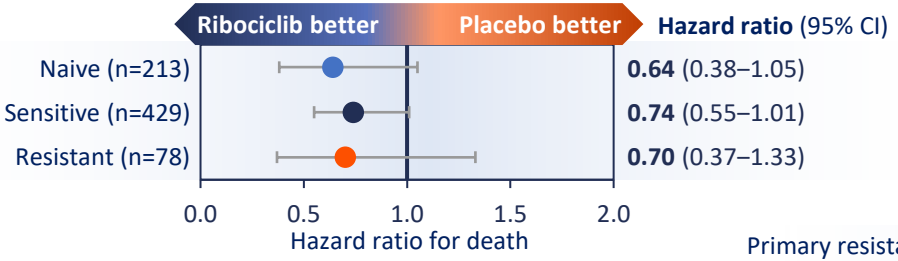
How does previous sensitivity to endocrine therapy impact the efficacy of CDK4/6 inhibitors?

Impact of previous ET on CDK4/6i therapy

Sub-analyses of OS data from MONALEESA-3, MONARCH-2 and PALOMA-3

MONALEESA-3

Impact of sensitivity to prior ET on OS[1]

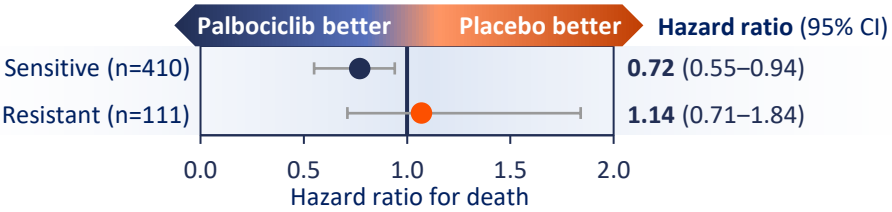


MONARCH-2

Impact of ET resistance on OS[2]

PALOMA-3

Impact of sensitivity to prior ET on OS[3]



CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; ET, endocrine therapy; OS, overall survival.

1. Slamon DJ, et al. *N Engl J Med*. 2020;382:514–24; 2. Sledge GW, et al. *JAMA Oncol*. 2020;6:116–24; 3. Turner NC, et al. *N Engl J Med*. 2018;379:1926–36.

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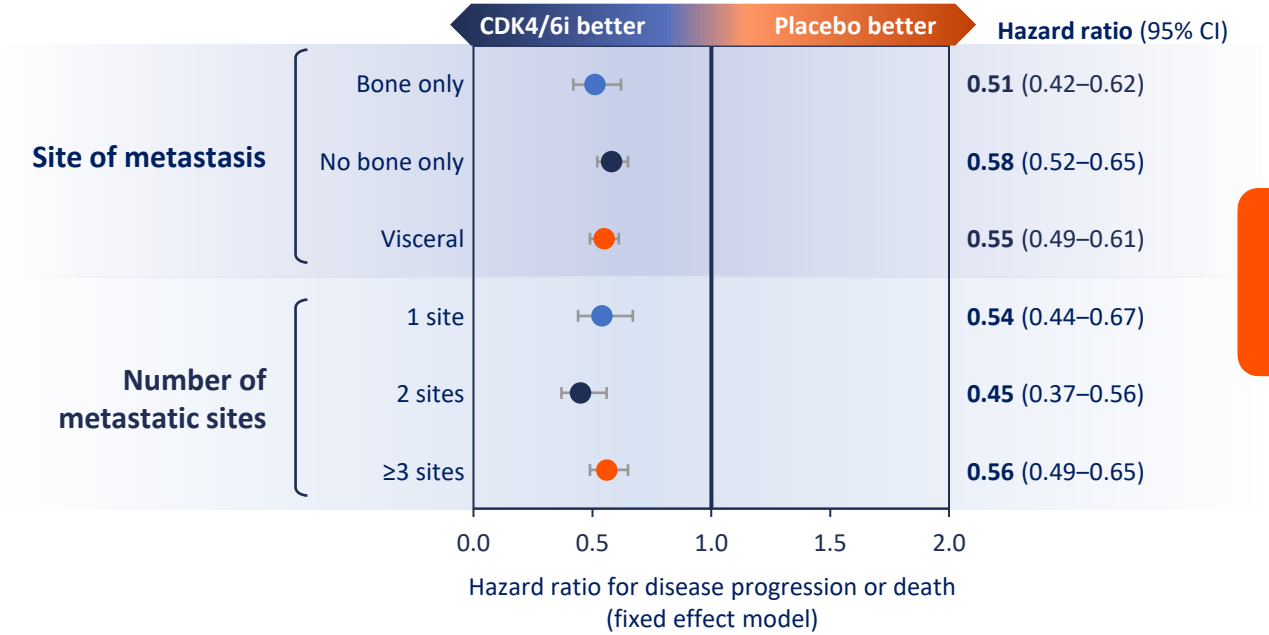
What is the impact of bone and visceral metastasis on the efficacy of CDK4/6 inhibitors?

Impact of metastases on CDK4/6i therapy

Meta-analysis of PFS data from the MONARCH, PALOMA and MONALEESA trials



CDK4/6i improved PFS independent of the sites and number of metastases

CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; PFS, progression-free survival.

Piezzo M, et al. *Int J Mol Sci*. 2020;21:6400.

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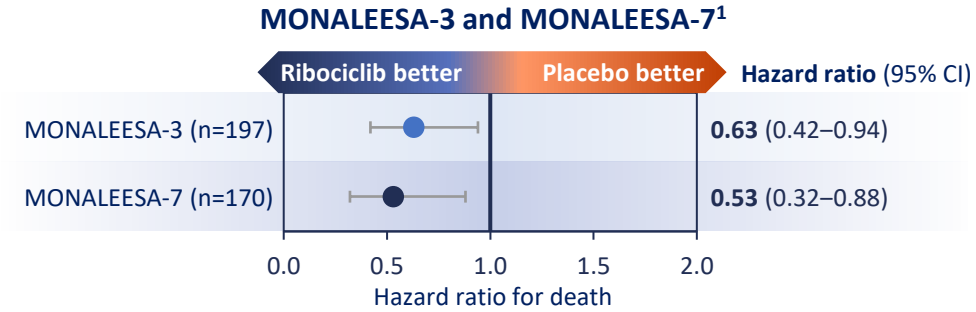
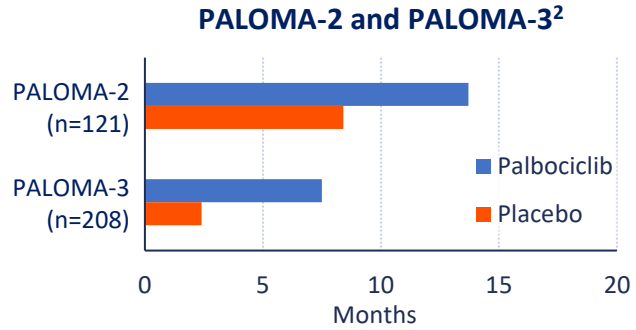
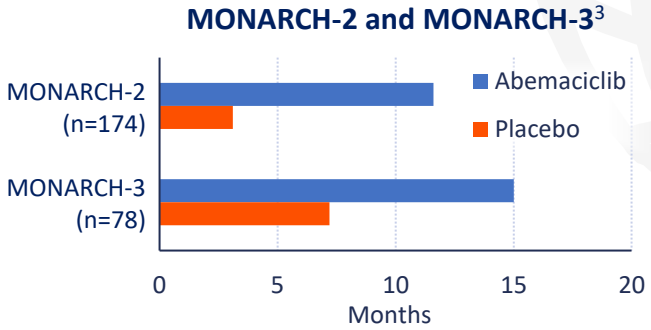
Impact of liver metastases on CDK4/6i therapy

OS in patients with liver metastases



PFS in patients with liver metastases





CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; OS, overall survival; PFS, progression-free survival.

1. Yardley DA, et al. *J Clin Oncol*. 2020;38(15_Suppl):1054; 2. Serra F, et al. *Drugs Context*. 2019;8:212579; 3. DiLeo A, et al. *Cancer Res*. 2018;78:P5-21-02.

What is the evidence for CDK4/6 inhibitors in patients with HR+/HER2- breast cancer with CNS metastases?

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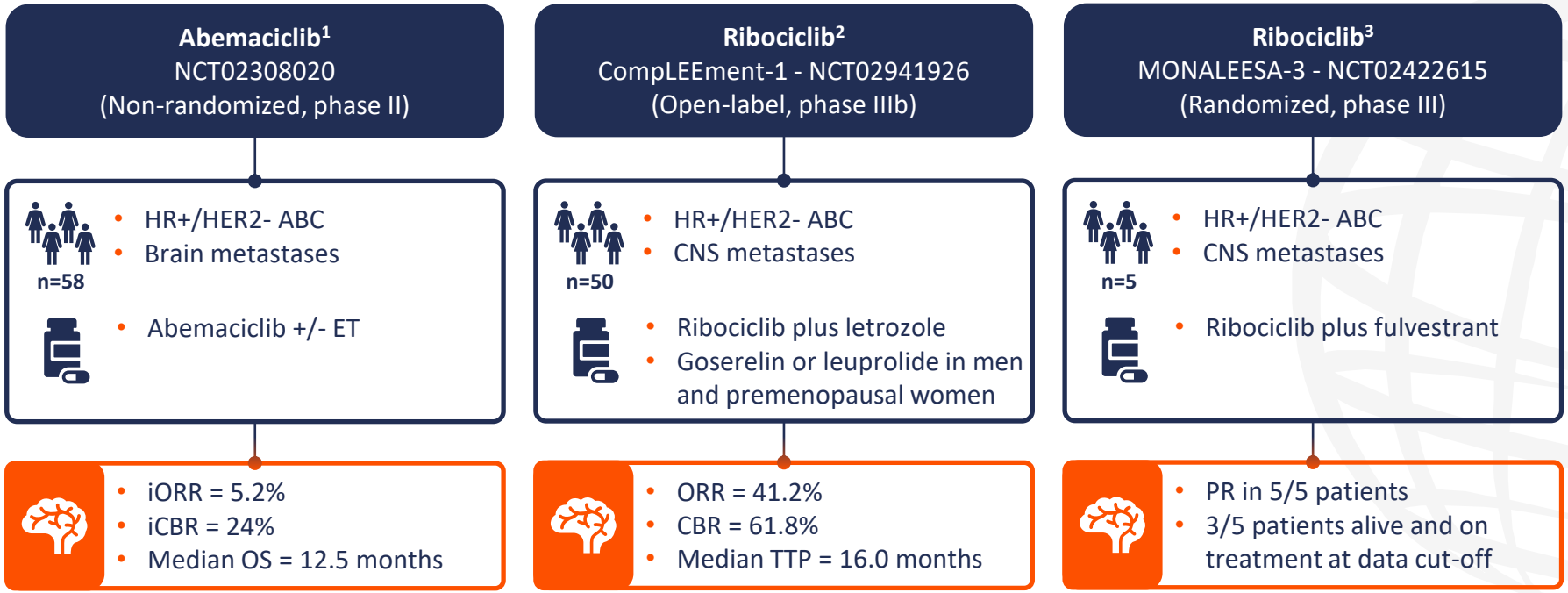
CDK4/6i in patients with CNS metastases



ABC, advanced breast cancer; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CNS, central nervous system; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iCBR, intracranial CBR; iORR, intracranial ORR; ORR, overall response rate; OS, overall survival; PR, partial response; TTP, time to progression.

1. Tolaney AM, et al. *Clin Cancer Res.* 2021;26:5310–9; 2. Cottu PH, et al. *Ann Oncol.* 2019;30(Supp_5):V118;
3. Yardley DA, et al. American Society of Clinical Oncology Annual Meeting 2020;Poster 139.

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