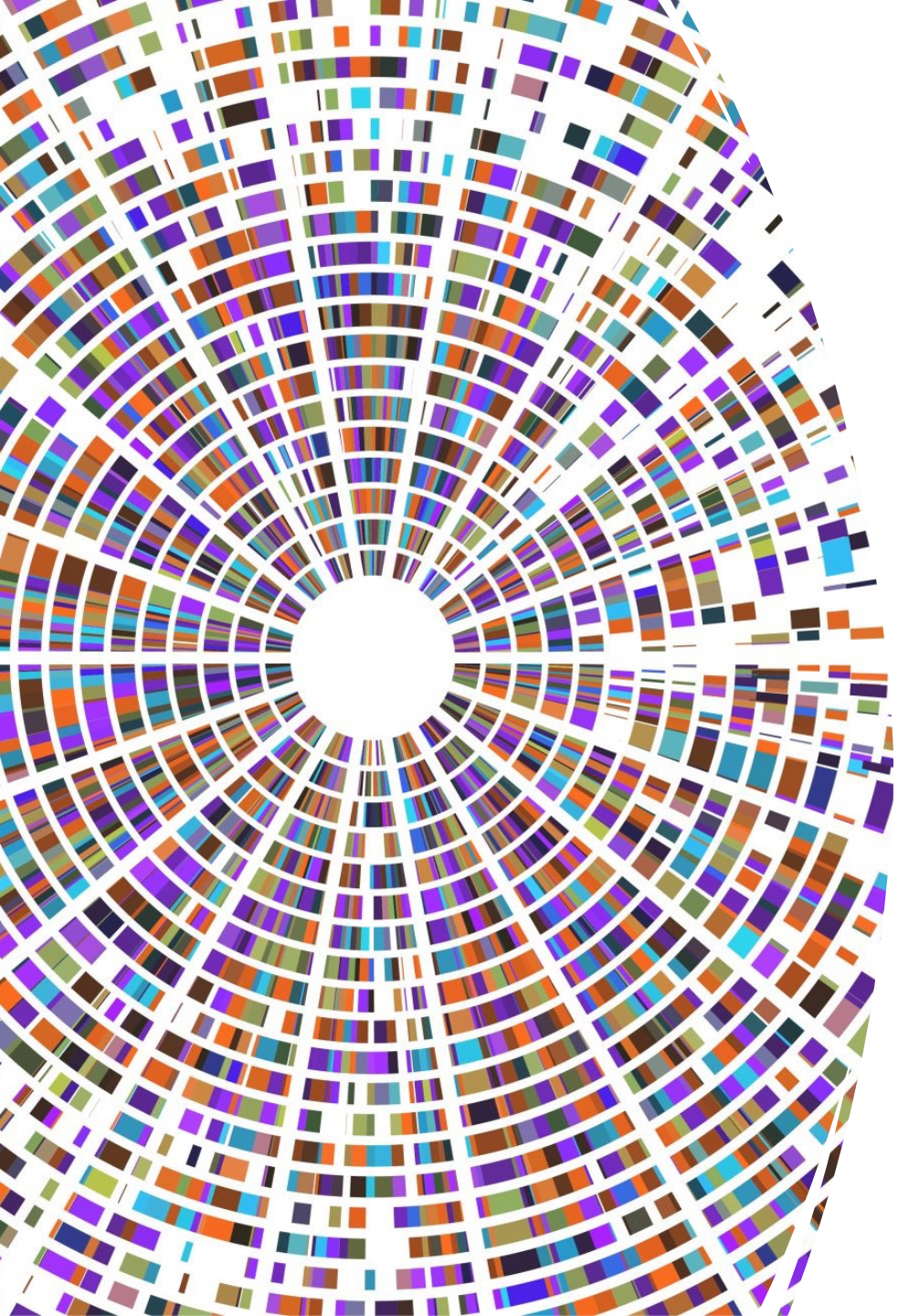

13th Annual WCS™

Sequencing Endocrine Therapy and Targeted Agents for the Treatment of Metastatic HR+/HER2- Breast Cancer

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March 2024

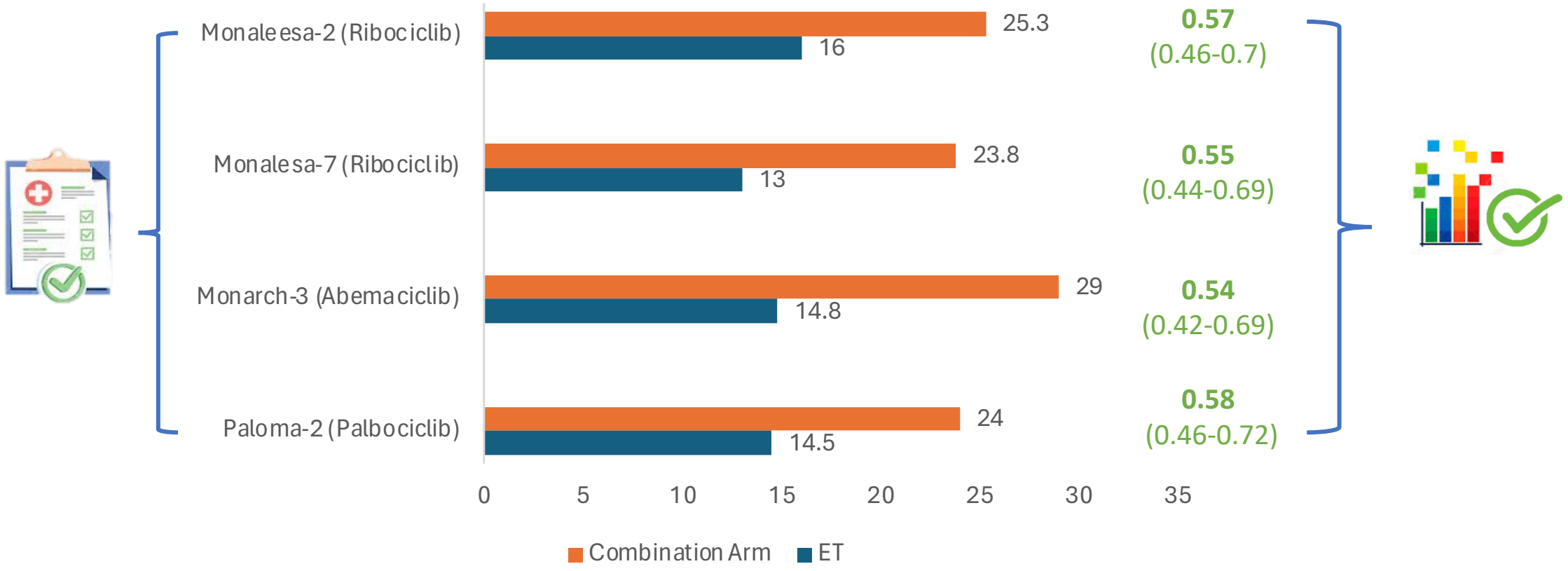
Introduction

- Endocrine therapy (ET) paired with cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is presently the accepted first-line therapy for most patients with hormone receptor (HR) positive, human epidermal growth factor receptor (HER2) negative advanced breast cancer.

- Nonetheless, resistance to ET and CDK4/6i is an inevitable outcome.

- The most effective treatment strategies following disease progression and their sequence are continually advancing in response to the rapidly shifting treatment landscape.

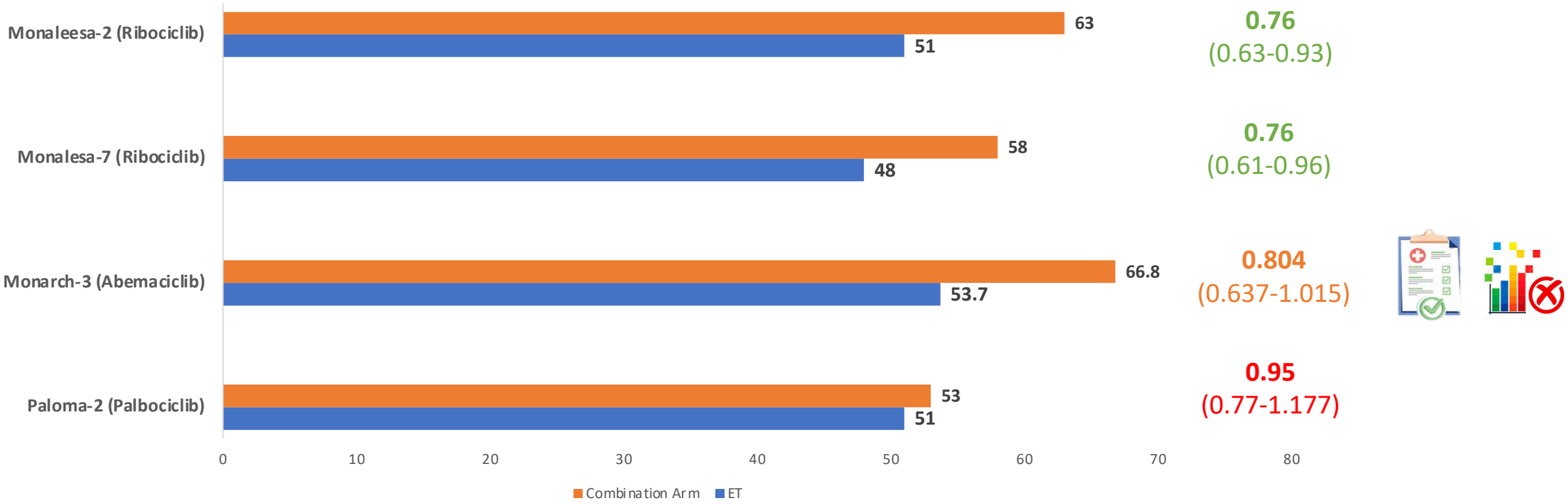
Progression Free Survival 1st Line CDK4/6i



Hortobagyi GN NEJM 2016
Hortobagyi GN NEJM 2022
Tripathy D Lancet Oncol 2018
Lu YS Clin Cancer Res 2022

Johnston *NPJ Breast Cancer*. 2019
Johnston S, SABCS 2023
Finn RS NEJM 2016
Finn RS JCO 2022

Overall Survival 1st Line CDK4/6i



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Lu YS Clin Cancer Res 2022

Johnston *NPJ Breast Cancer.* 2019
Johnston S, SABCS 2023
Finn RS NEJM 2016
Finn RS JCO 2022

Which CDK4/6i to chose?

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Invasive Breast Cancer

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Preferred Regimens

First-Line Therapy

- Aromatase inhibitor + CDK4/6 inhibitor[b]
  - Aromatase inhibitor + ribociclib (category 1)[c]
  - Aromatase inhibitor + abemaciclib
  - Aromatase inhibitor + palbociclib
- Fulvestrant[d] + CDK4/6 inhibitor[b]
  - Fulvestrant + ribociclib (category 1)[e]
  - Fulvestrant + abemaciclib (category 1)[e]
  - Fulvestrant + palbociclib

Second- and Subsequent-Line Therapy

- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[f,g]
- For *PIK3CA* or *AKT1* activating mutations or PTEN alterations, see targeted therapy options, see BINV-Q (6)[h]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[i,j]

Other Recommended Regimens

First- and/or Subsequent-Line Therapy

- Selective ER down-regulator
  - Fulvestrant[k]
  - For *ESR1* mutated tumors, see BINV-Q (6)
- Selective ER down-regulator (fulvestrant) + non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[k]
- Non-steroidal aromatase inhibitor
  - Anastrozole
  - Letrozole
- Selective ER modulator
  - Tamoxifen
- Steroidal aromatase inactivator
  - Exemestane

Useful in Certain Circumstances

Subsequent-Line Therapy

- Megestrol acetate
- Estradiol
- Abemaciclib[l]
- Targeted therapy options, see BINV-Q (6)

Possible explanations for OS differences

- Crossover
- Missing data: more patients in placebo arm than in combination arm were lost to follow up in Paloma-2 (21% vs 13%)
- Population differences
- Continuation of Palbociclib beyond progression
- True efficacy differences between the drugs

Finn RS et al, JCO 2022 Mayer SABCS 2022

Clinical Implications… How to choose

Palbociclib

- Elderly with multiple comorbidities
- Compliance with intermittent dosing
- Need to change dose if side effects

Ribociclib

- Multiple caspsules, but easier titration if side effetcs
- Cardiac Dysfunction
  Electrolyte Imbalances
- Compliance with intermittent dosing

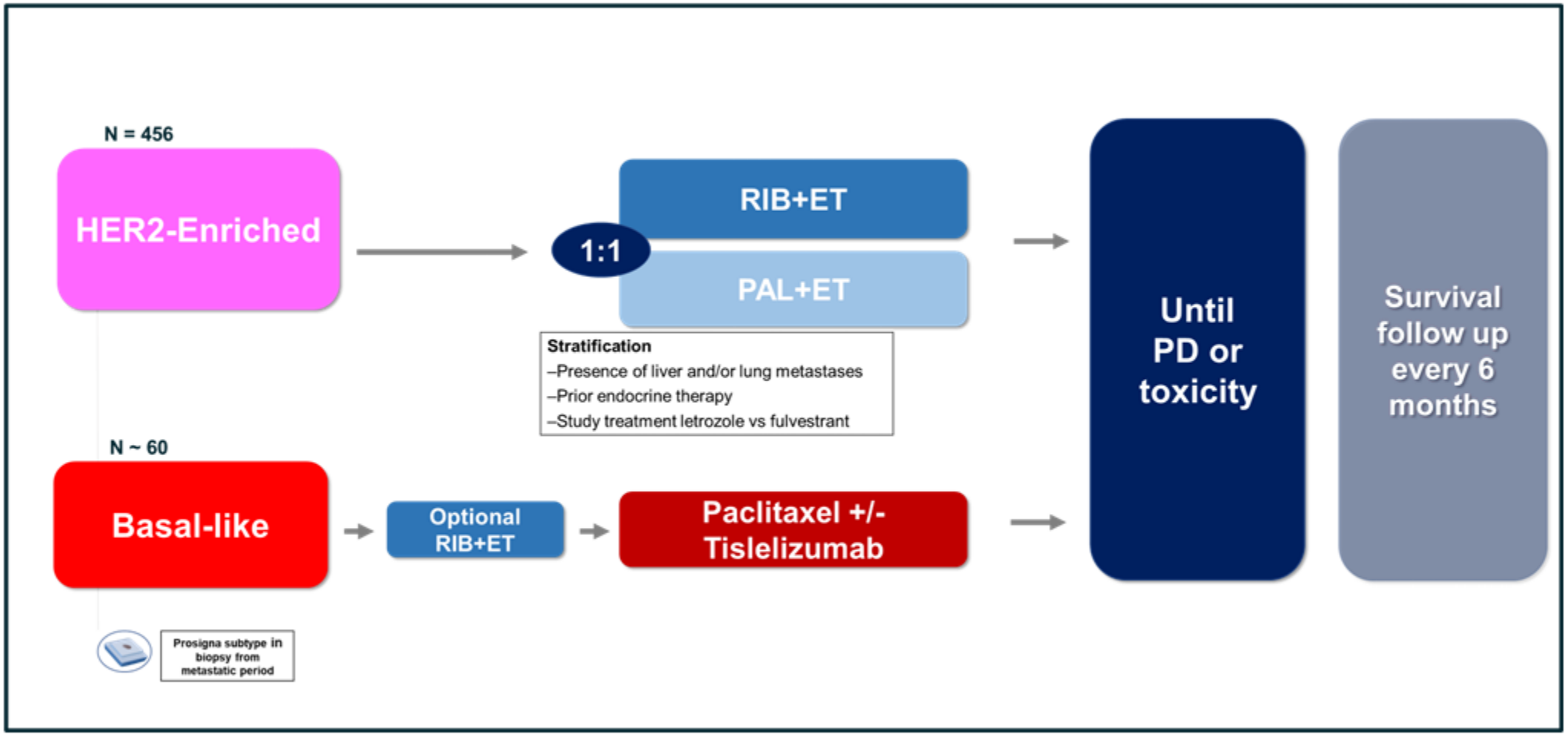
Abemaciclib

- Better compliance with Continuous Dosing
- History of Colitis
  IBS
- Twice a day

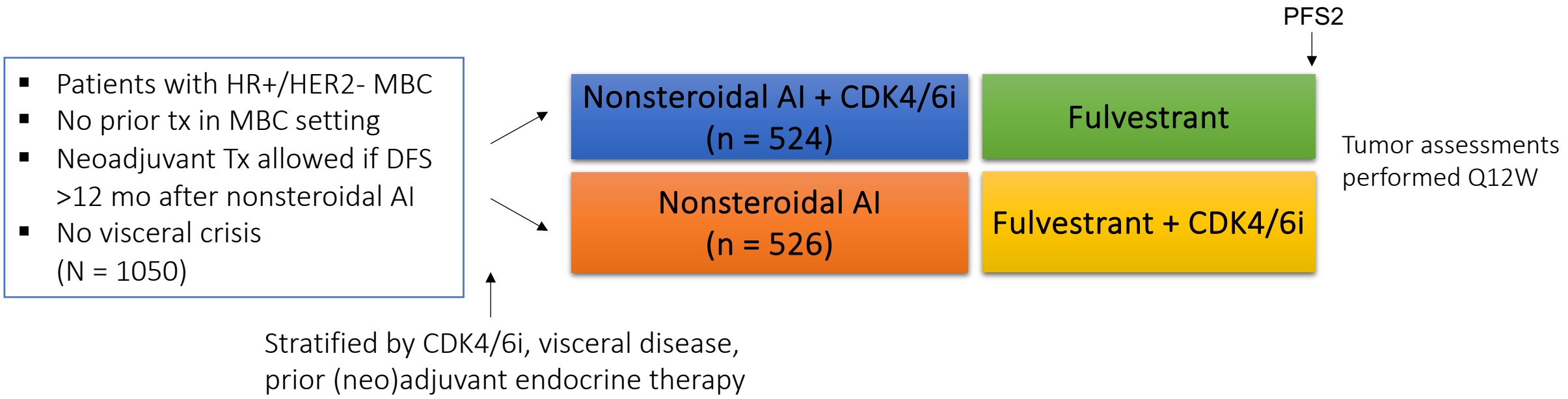
Head to Head Prospective Comparison: *Harmonia trial*

Key eligibility criteria

- Pre/Post menopausal or male patients
- Advanced/metastatic HR+/HER2-negative Breast Cancer
- ER IHC < 95%
- ≤ 1 prior endocrine therapy for metastatic breast cancer
- No prior CT for metastatic breast cancer



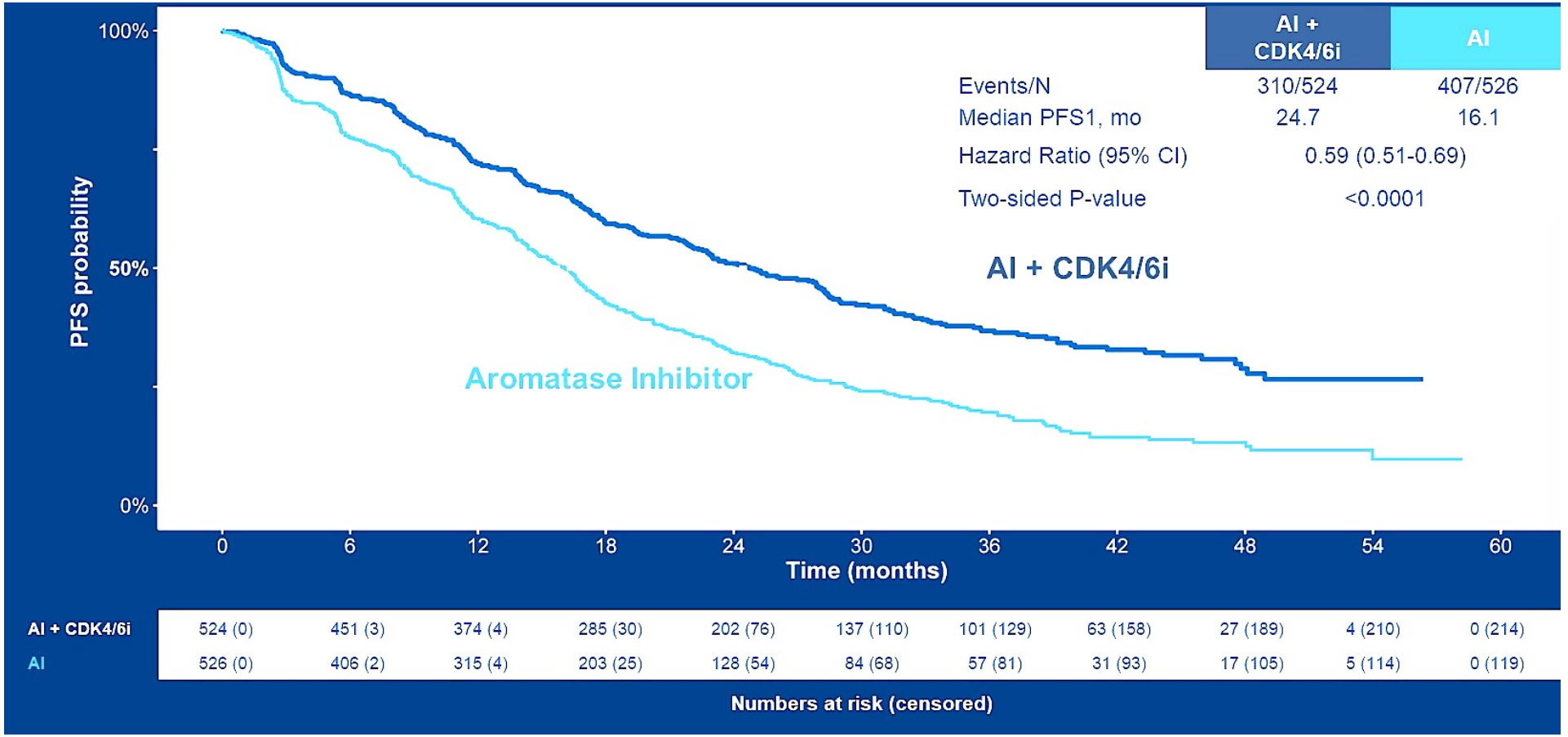
Should ALL patient be started on CDK4/6i?
SONIA Trial: Study Design



Primary endpoint: PFS2 (time from randomization to second disease progression or death)

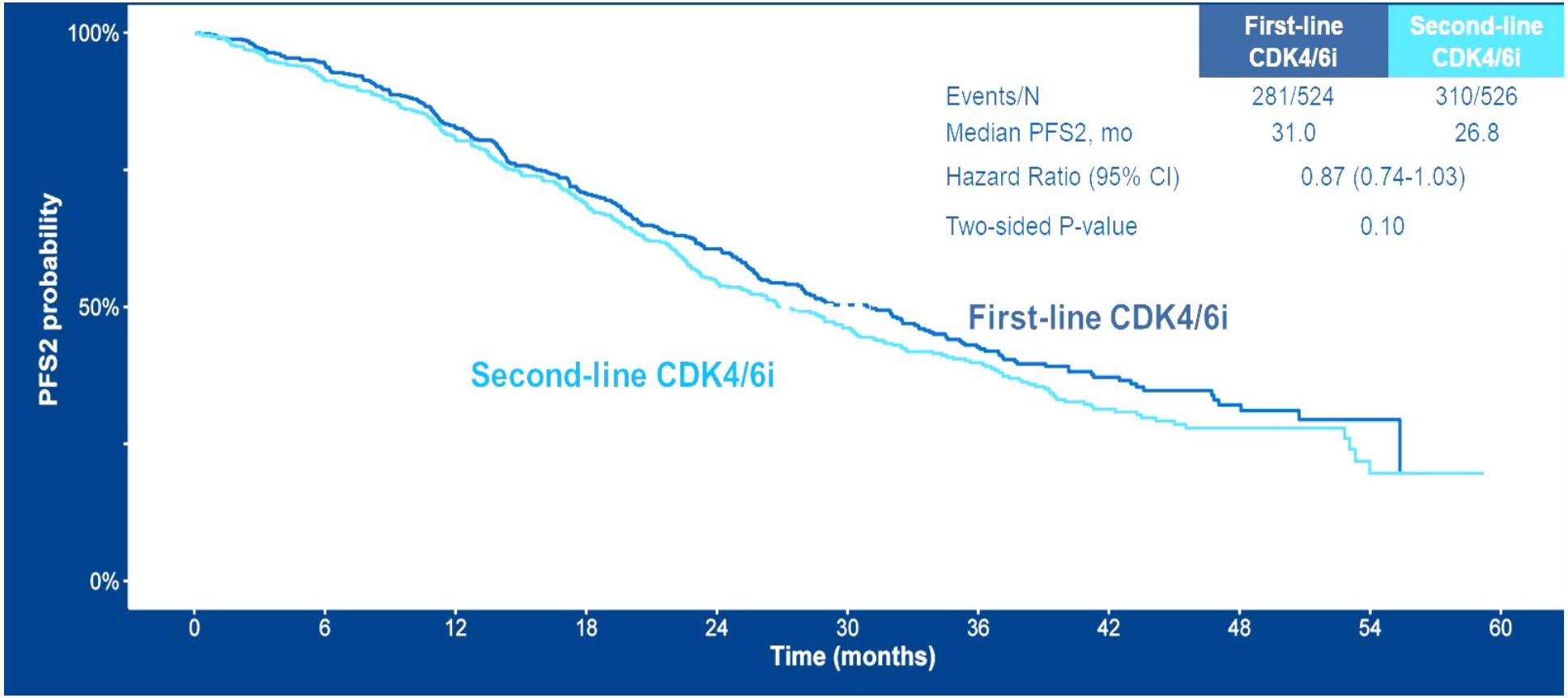
Sonke. ASCO 2023. Abstr LBA1000.

Progression Free Survival First Line



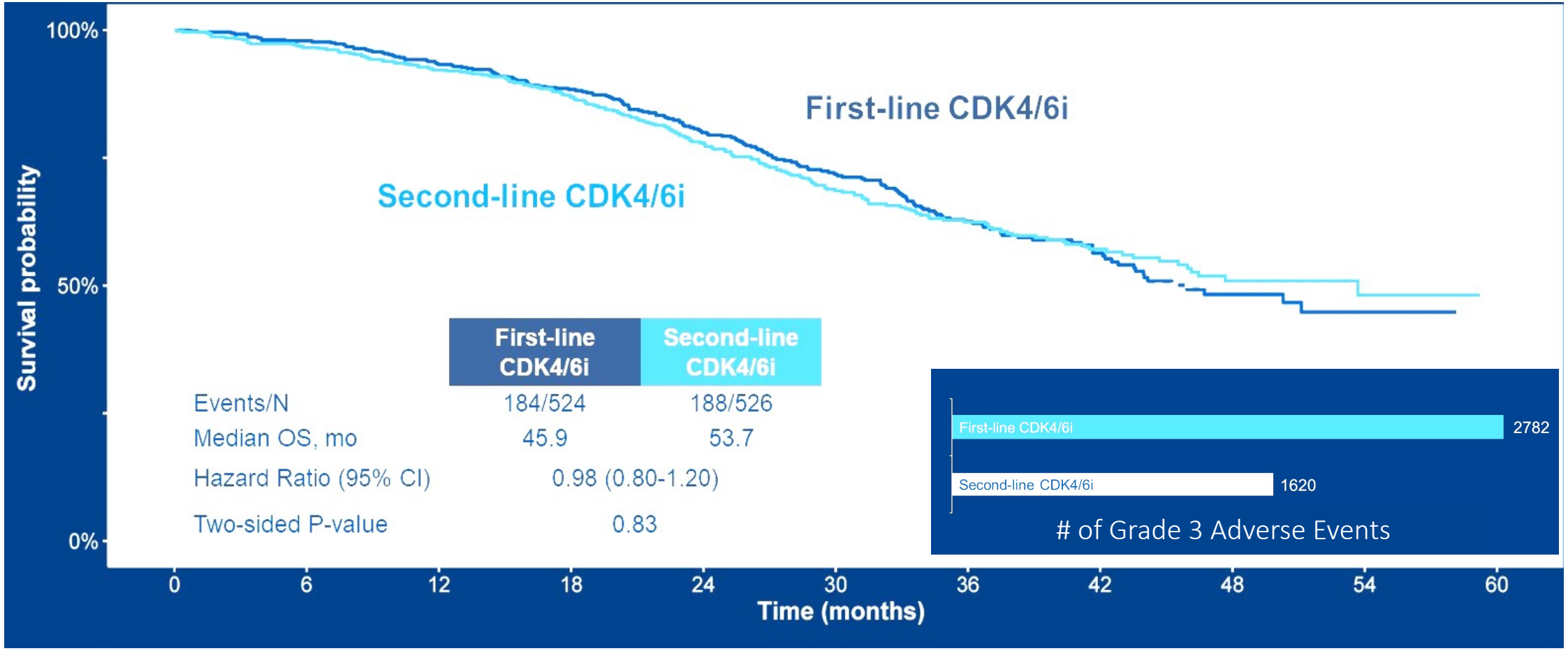
Sonke. ASCO 2023 LBA1000

Primary Endpoint: PFS2



Sonke. ASCO 2023 LBA1000

Overall Survival

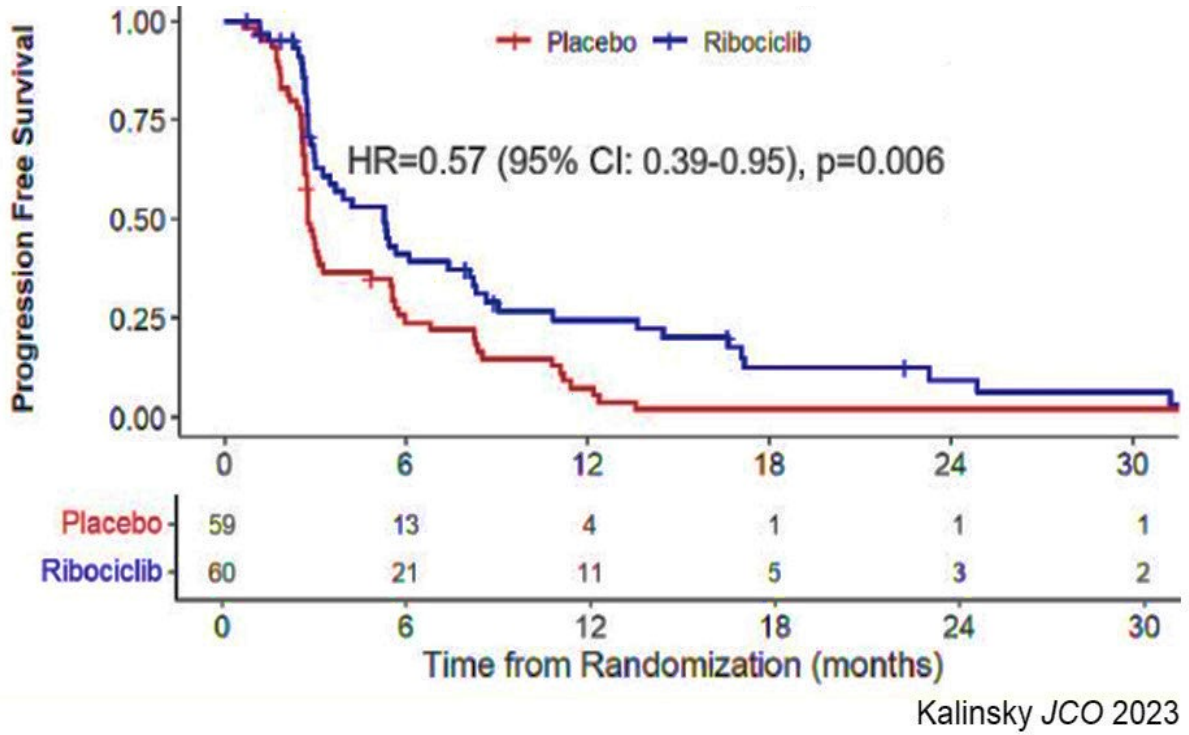


Sonke. ASCO 2023 LBA1000

The Switch Game Upon Progression…

MAINTAIN TRIAL PFS

ET +/- Ribociclib after Palbociclib



Kalinsky *JCO* 2023

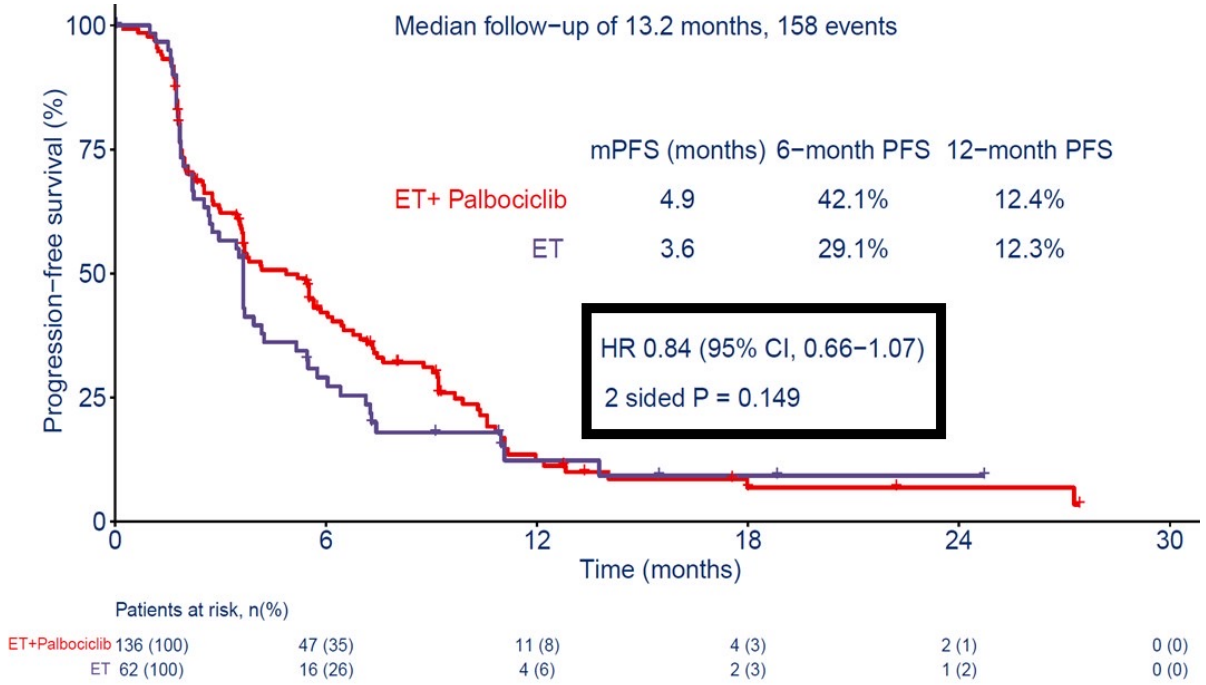
Significant benefit of CDK4/6i switch

Palbo→Ribo

The Switch Game Upon Progression

PALMIRA TRIAL PFS

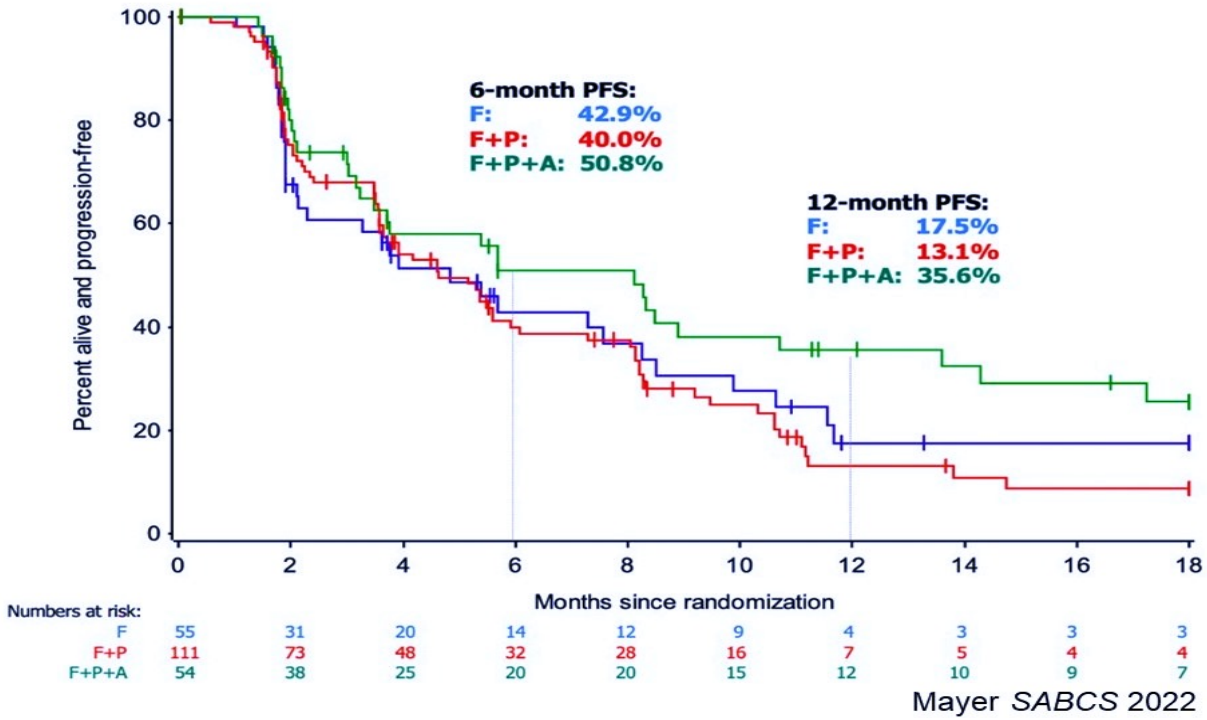
ET +/- Palbociclib after Palbociclib



Llombart-Cussac ASCO 2023

PACE TRIAL PFS

Fulvestrant +/- Palbociclib after Palbociclib

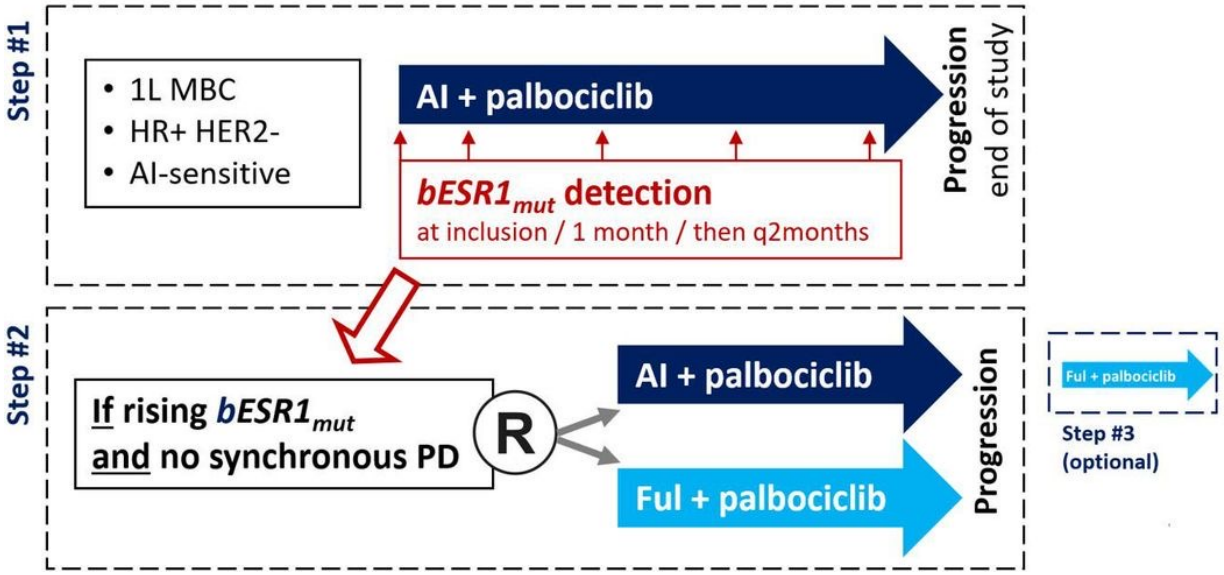


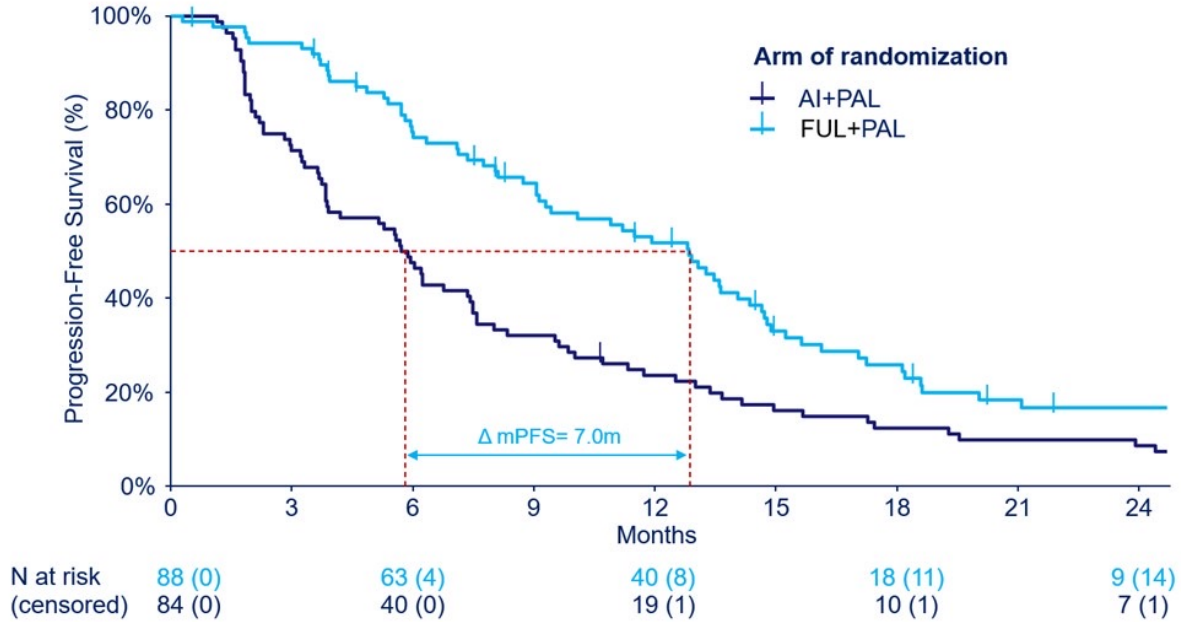
Mayer *SABCS* 2022

No PFS benefit in ET switch and keeping same CDK4/6i

Palbo→Palbo

Early Switch→ Biomarker Driven: PADA Trial





Updated Results: PFS1

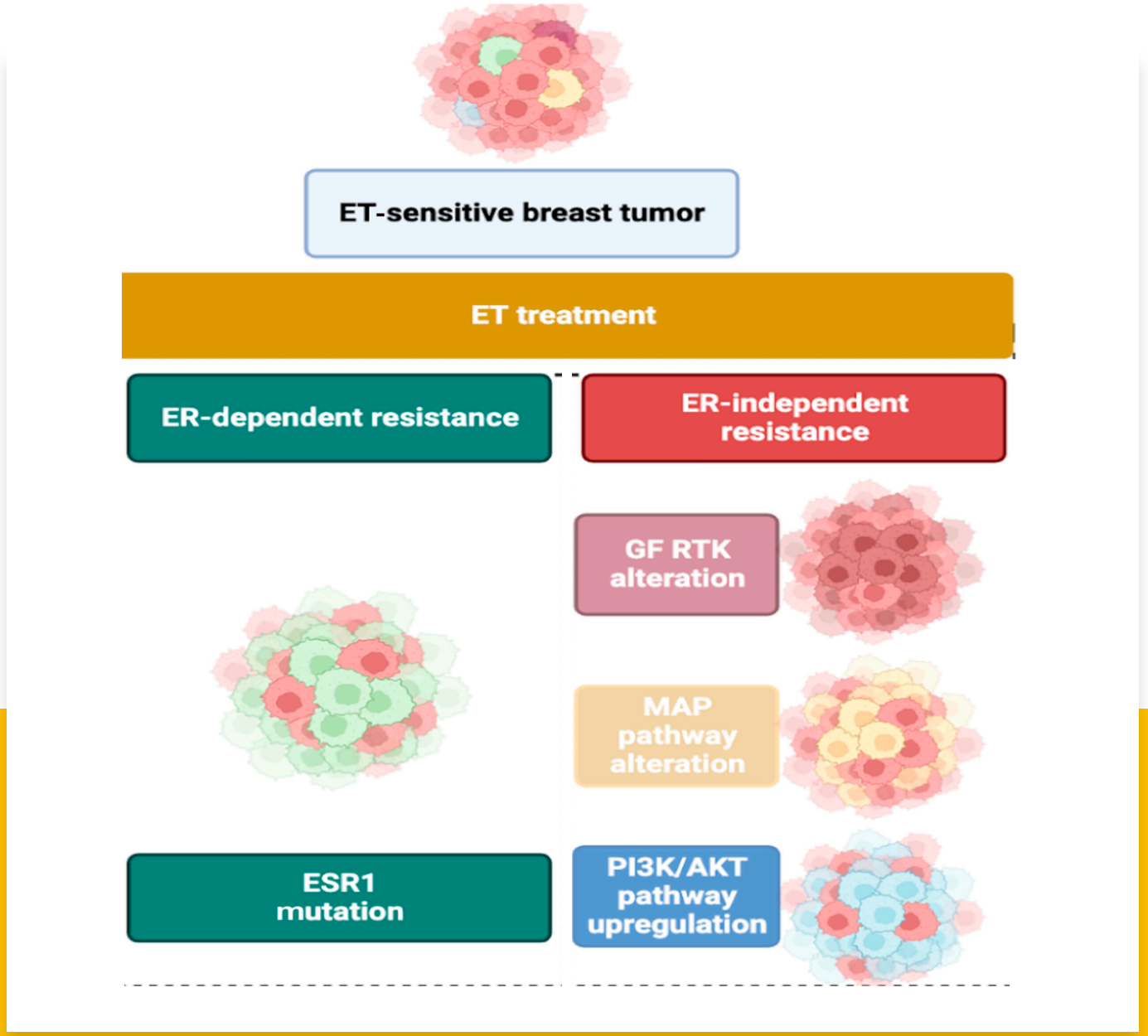
FUL+PAL mPFS: 12.8 months, 95%CI [9.3;14.7]

AI+PAL mPFS: 5.8 months, 95%CI [3.9;7.5]

PFS HR= 0.54 [0.38;0.75]

FC Bidard, ASCO 2023

ET Resistance Mechanisms



Gnant M, et al Am Soc Clin Oncol Educ Book 2023

EMERALD Trial

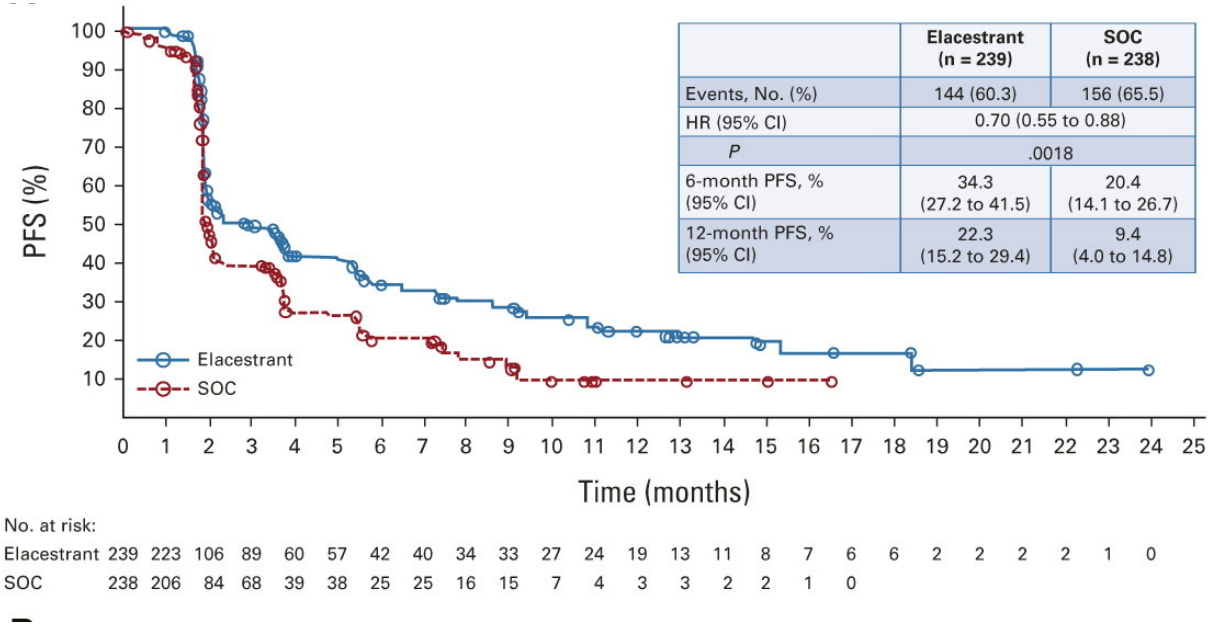
MBC with 1-2L ET, prior CDK4/6 ≤ 1 Ctx

- Elacestrant
- Investigator's choice : -AI, Fulvestrant

Endpoint	Elacestrant	Standard of Care	HR (95% CI)	*p* value
All patients	(*n* = 239)	(*n* = 238)		
Median PFS	2.79 months	1.91 months	0.697 (0.552-0.880)	.0018
Patients with *mESR1*-positive	(*n* = 115)	(*n* = 113)		
Median PFS	3.78 months	1.87 months	0.546 (0.387-0.768)	.0005

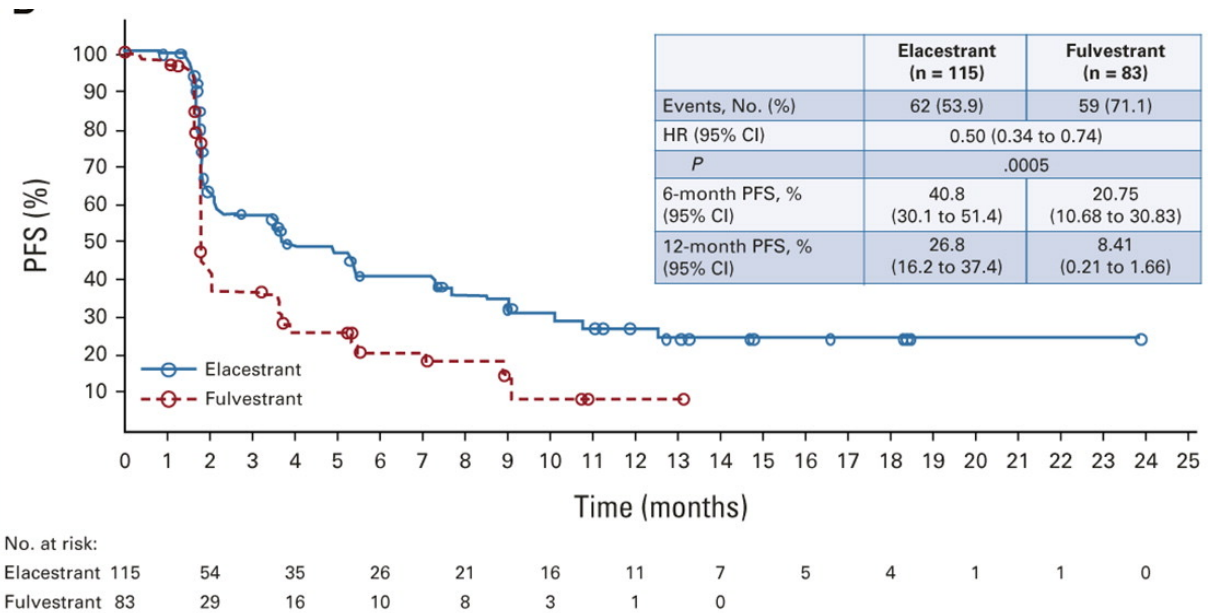
Significant PFS improvement versus SOC both in the overall population and in patients with *ESR1*

PFS in all patients vs SOC



	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

PFS in ESR1 + vs Fulvestrant



	Elacestrant (n = 115)	Fulvestrant (n = 83)
Events, No. (%)	62 (53.9)	59 (71.1)
HR (95% CI)	0.50 (0.34 to 0.74)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	20.75 (10.68 to 30.83)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.41 (0.21 to 1.66)

FC Bidard, JCO 2022

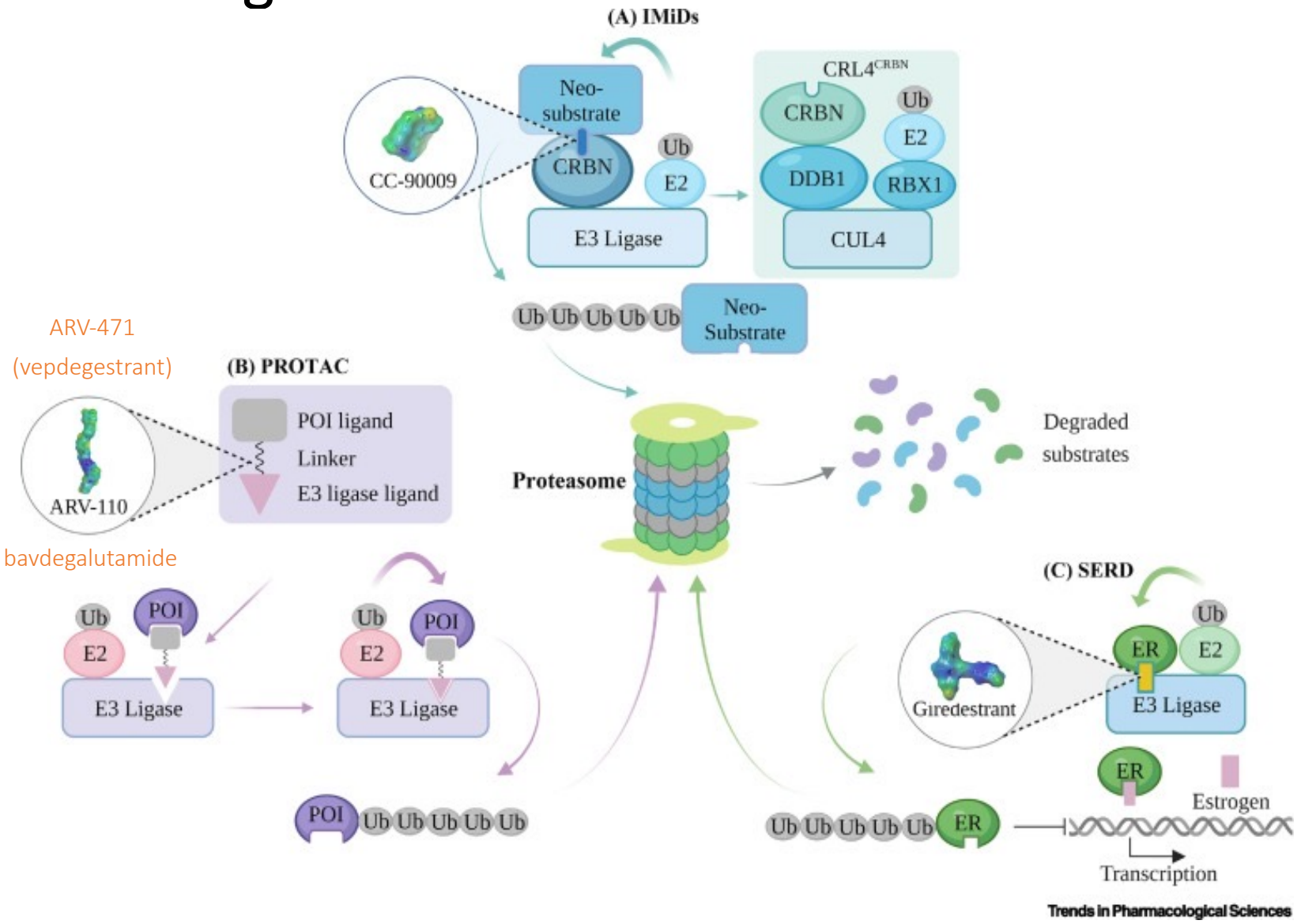
Ongoing Trials Oral SERDS

Trial	Oral SERD	Phase	N	ET line	Investigational Arm	Comparator Arm	Primary Endpoint	ClinicalTrials.gov
AMEERA-3	Amcenestrant	II	367[b]	1–2	Amcenestrant 400mg	Physician's choice ET (Fulvestrant, AI, Tamoxifen)	PFS	NCT04059484
AMEERA-5	Amcenestrant	III	1068[b]	1	Amcenestrant 200mg + Palbociclib[a]	Letrozole + Palbociclib[a]	PFS	NCT04478266
persevERA	Giredestrant	III	978	1	Giredestrant 30mg + Palbociclib[a]	Letrozole + Palbociclib[a]	PFS	NCT04546009
SERENA-4	Camizestrant	III	1342	1	Camizestrant 75mg + Palbociclib[a]	Anastrozole + Palbociclib[a]	PFS	NCT04711252
SERENA-6	Camizestrant	III	302	1 (*ESR1*[mut] ctDNA)	Camizestrant 75mg + Palbociclib/Abemaciclib[a]	AI (letrozole/ anastrozole) + Palbociclib/Abemaciclib[a]	PFS	NCT04964934
EMBER-3	Imlunestrant	III	800	2 (prior AI alone or with CDK4/6i)	Imlunestrant 400mg vs Imlunestrant + Abemaciclib[a]	Physician's choice ET (fulvestrant/ exemestane)[a]	PFS	NCT04975308
SERENA-2	Camizestrant	II	240[b]	2	Camizestrant 75/150/300mg	Fulvestrant	PFS	NCT04214288
EMERALD	Elacestrant	III	477[b]	2–3, post CDK4/6i	Elacestrant 400mg	Physician's choice ET (Fulvestrant/AI)	PFS in all patients and in *ESR1*[mut]	NCT03778931
acelERA	Giredestrant	II	303 [b]	2-3	Giredestrant 30mg	Physician's choice ET (Fulvestrant/AI)	PFS	NCT04576455

Notes: [a]Also with luteinizing hormone releasing hormone agonist if premenopausal (or male in EMBER-3). [b]Recruitment completed.
Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy; N, target enrolment; PFS, progression free survival; SERD, selective estroger

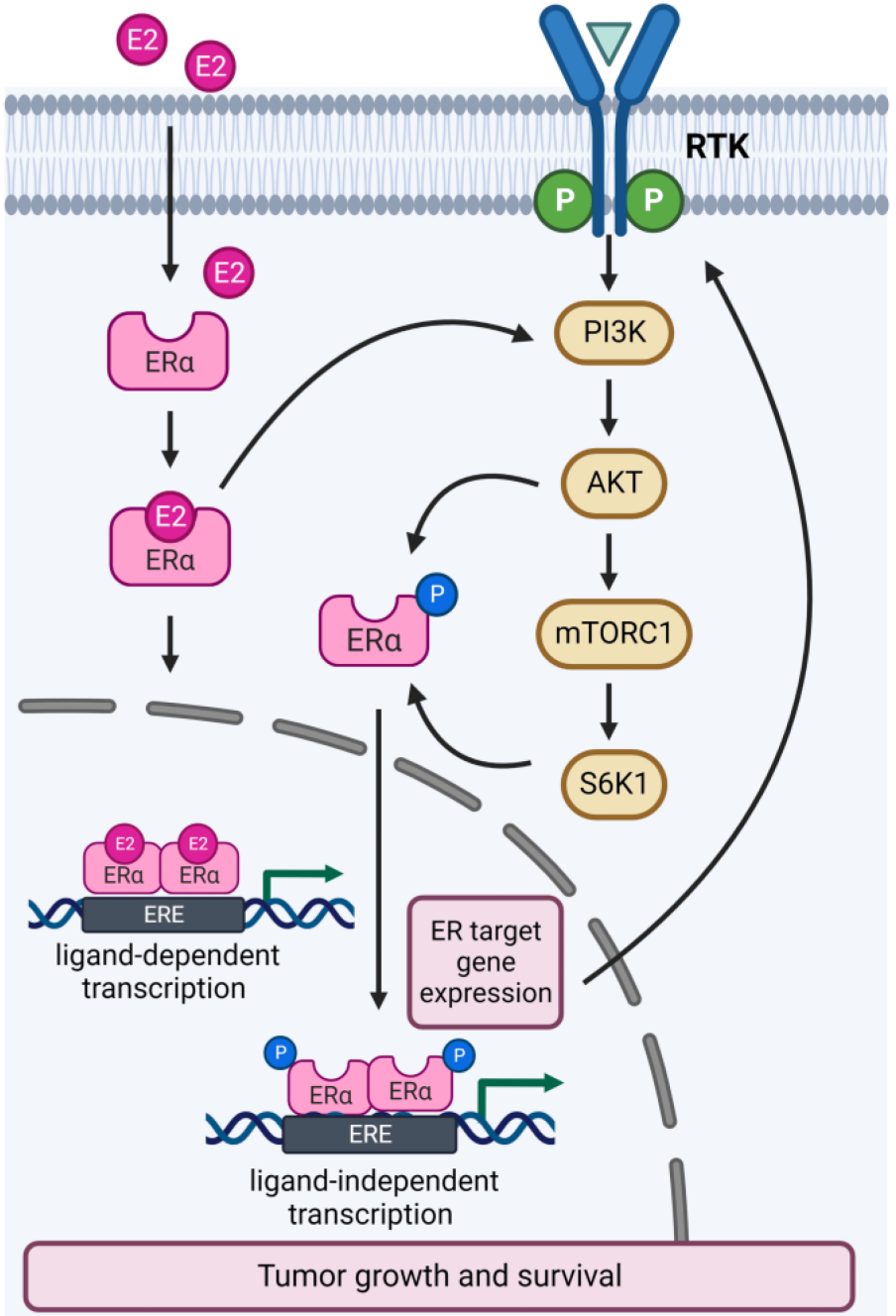
Downton T *Drug Des Devel Ther*. 2022

Targeted Protein Degradation



Fang Y, et al. Trends Pharm Scien 2023

PI3K/AKT/mTOR pathway



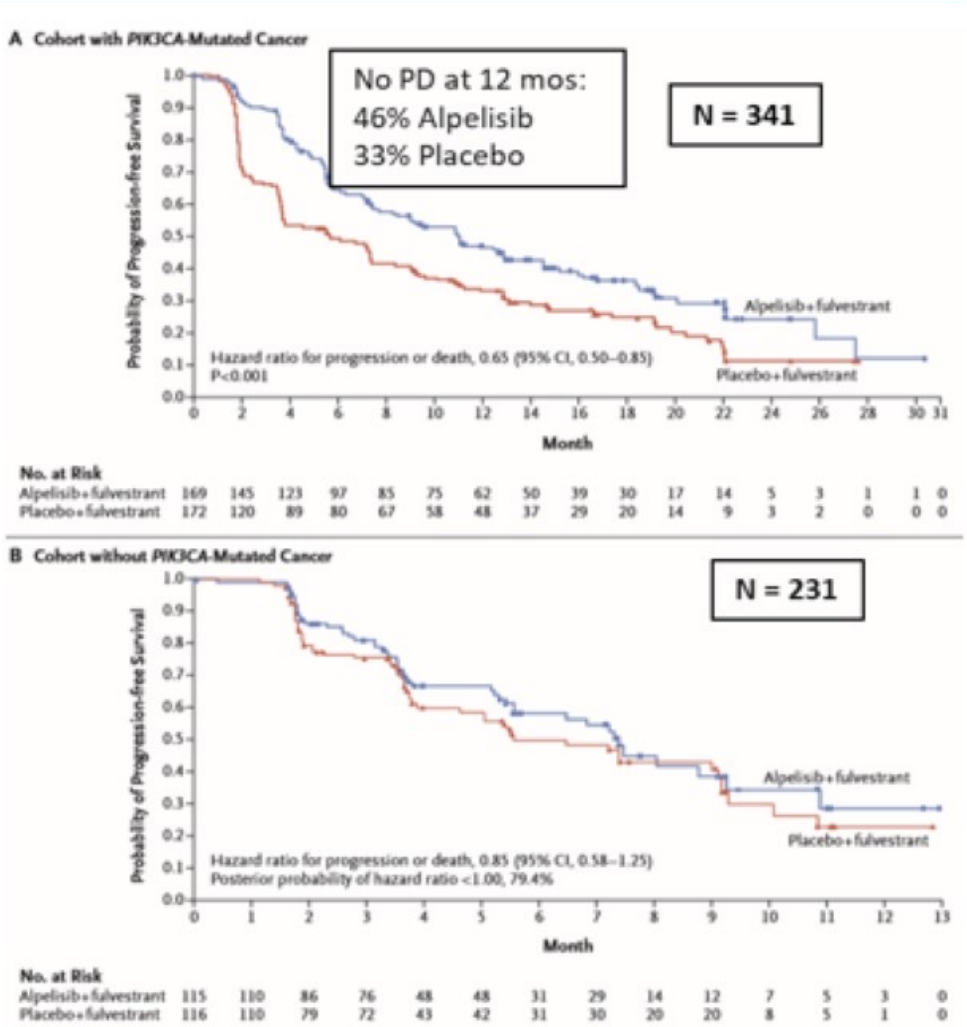
Alves, C.L.; Ditzel, H.J. *Int. J. Mol. Sci.* **2023**,

Solar Trial: PIK3CA Mutaded HR positive Alpelisib + Fulvestrant

- Key points:
  - ~60% were PIK3CA mutant

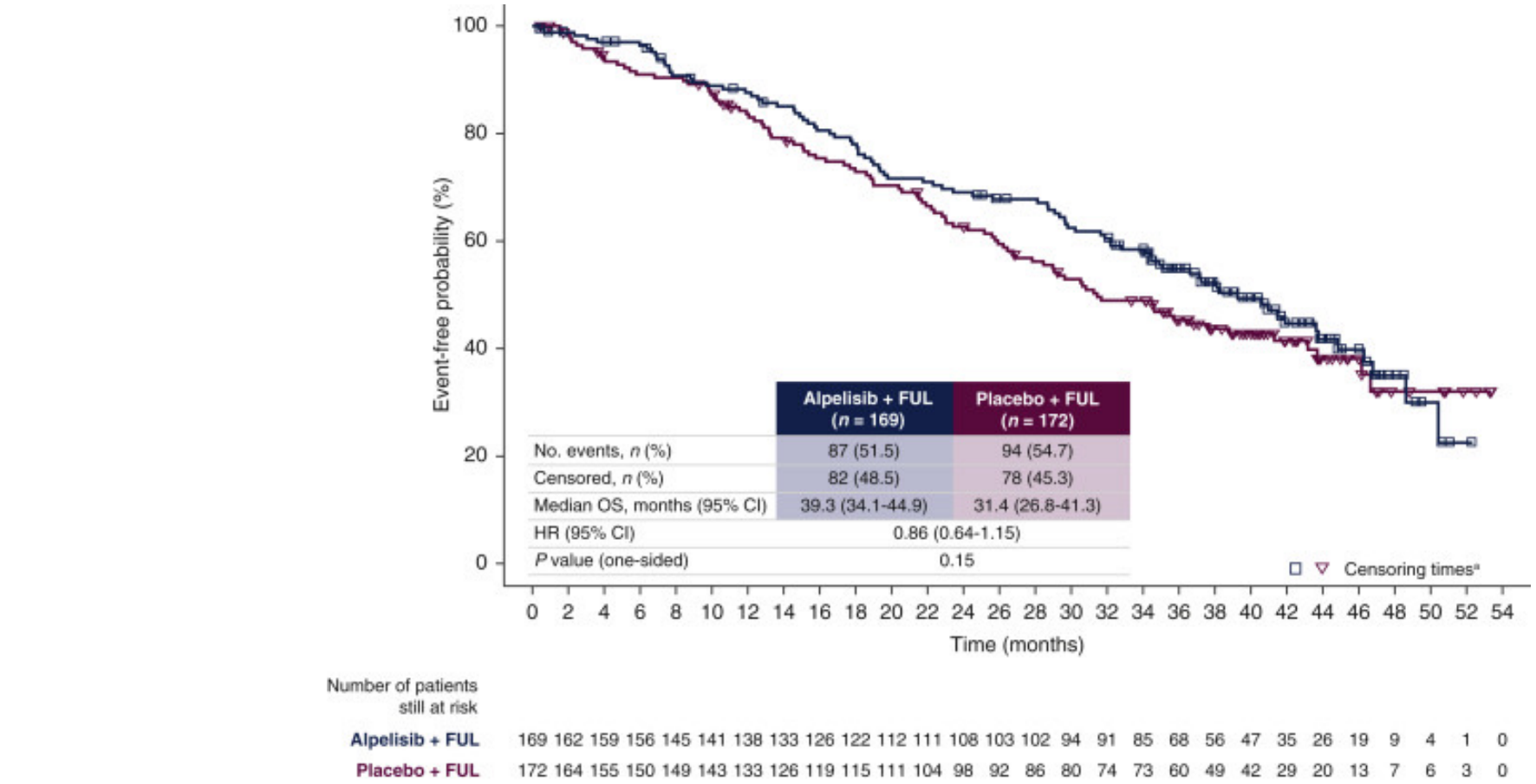
- **mPFS (median follow-up: 20 mo)**
  - 11.0 mo (95% CI: 7.5, 14.5) in the alpelisib–fulvestrant arm
  - 5.7 mo (95% CI: 3.7, 7.4) in the placebo–fulvestrant group
  - HR for progression or death, 0.65; 95% CI: 0.50, 0.85; $P < 0.001$
  - Blinded independent review: 11.1 vs 3.7 mo

- **mPFS: Non mutant**
  - 7.4 mo in the alpelisib–fulvestrant group
  - 5.6 mo in the placebo–fulvestrant group
  - HR for progression or death, 0.85; 95% CI: 0.58, 1.25



Andre F, et al. *N Engl J Med*.2019;380:1929-1940.

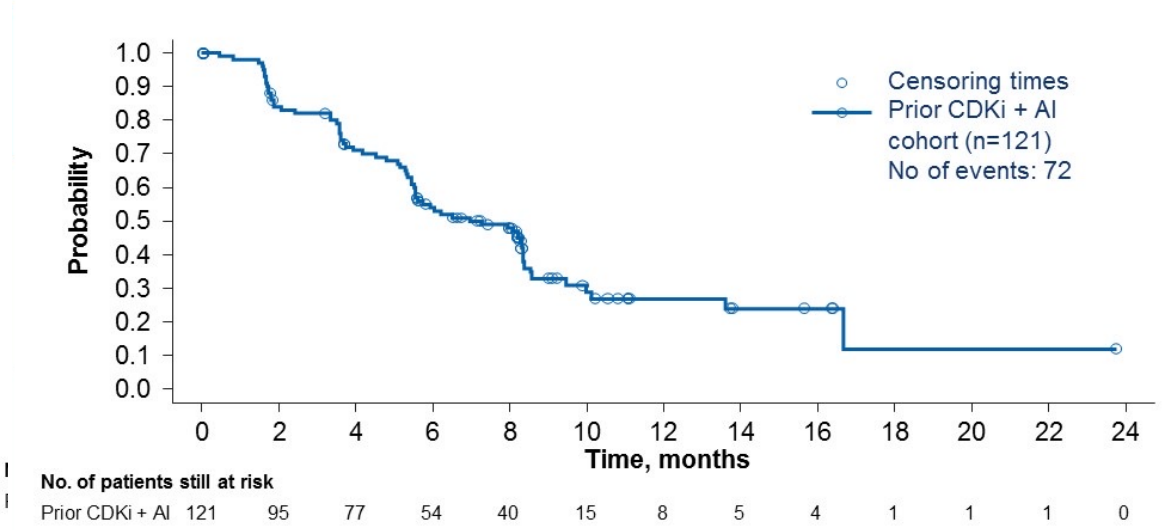
Final OS in Solar Trial



Andre F. et al Annals of Oncology 2021

Bylive Trial: Alpelisib+ Fulvestrant After Prior CDK4/6i

Endpoint	Prior CDKi + AI (Cohort A) (n=121)
Primary endpoint: Patients who were alive without disease progression at 6 mo	**50.4%** (n=61; 95% CI, 41.2-59.6)
Secondary endpoint: Median PFS	**7.3 mo** [n=72 (59.5%) with event]; 95% CI, 5.6-8.3)

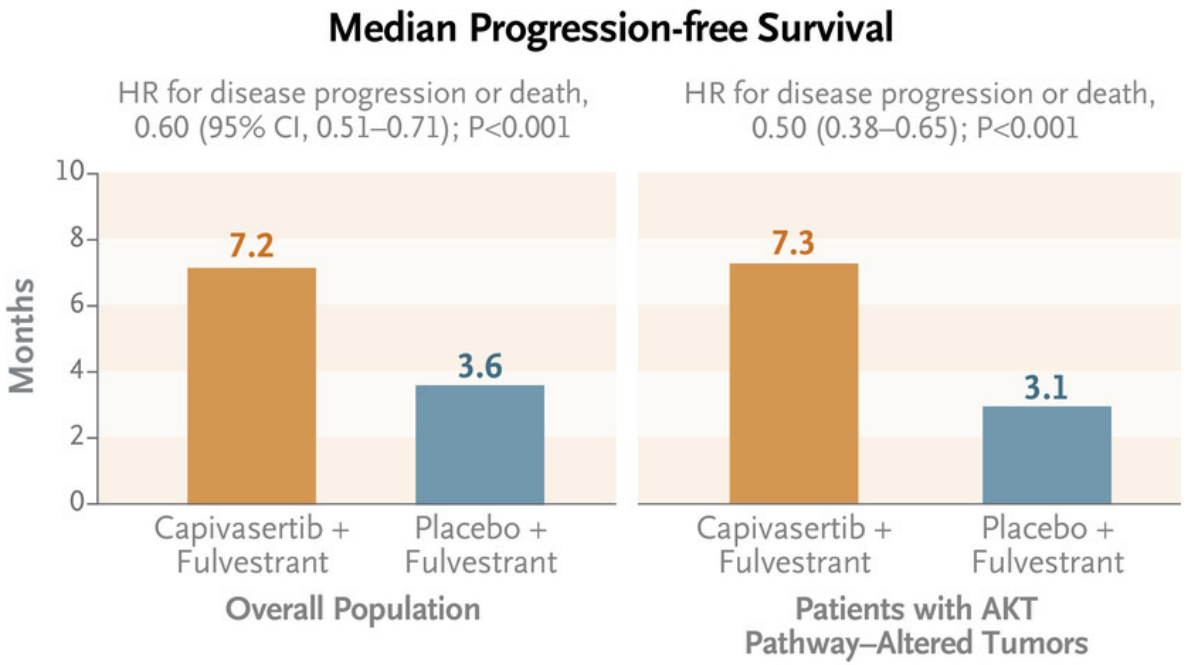


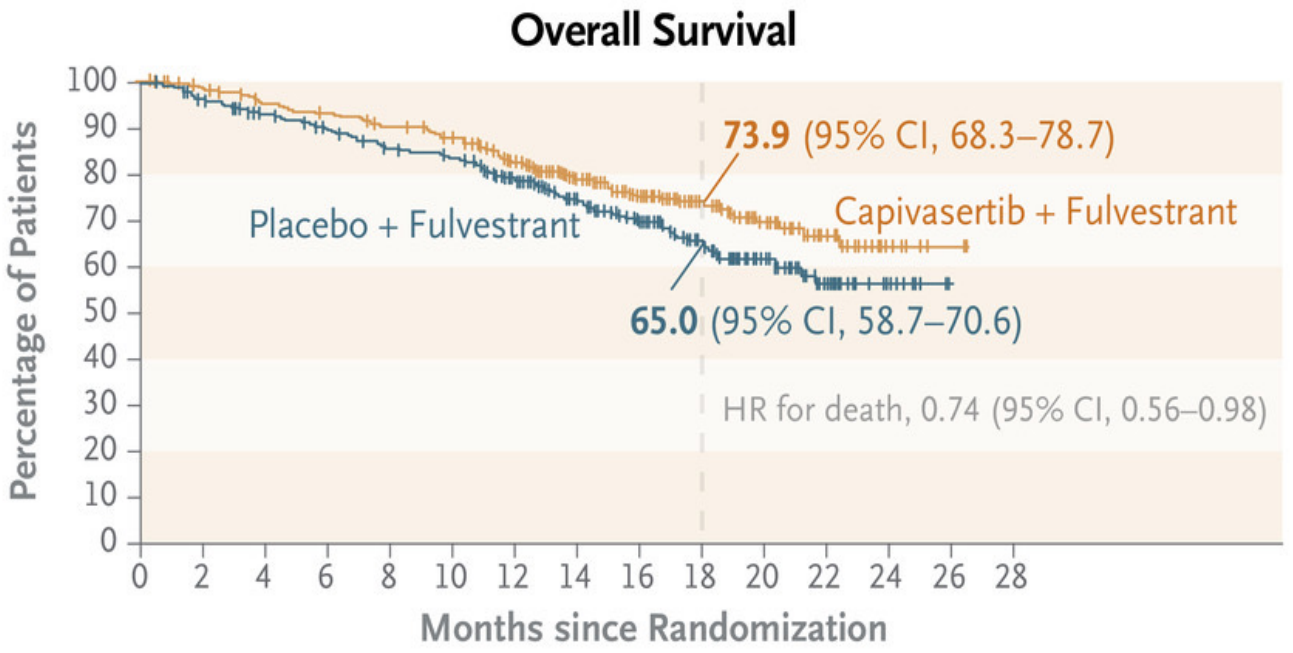
In SOLAR-1, 44.4% of patients in the *PIK3CA*-mutant cohort with prior CDKi treated with alpelisib plus fulvestrant were alive without disease progression at 6 months

Rugo, H ASCO 2020

AKT Pathway: CAPItello-291-Cavasertib

Phase 3, randomized, double-blind trial, pre-, peri-, and postmenopausal women and men with HR+ HER-2neg, ABC who have relapse or disease progression during or after tx with an AI, with or without previous (CDK4/6) inhibitor





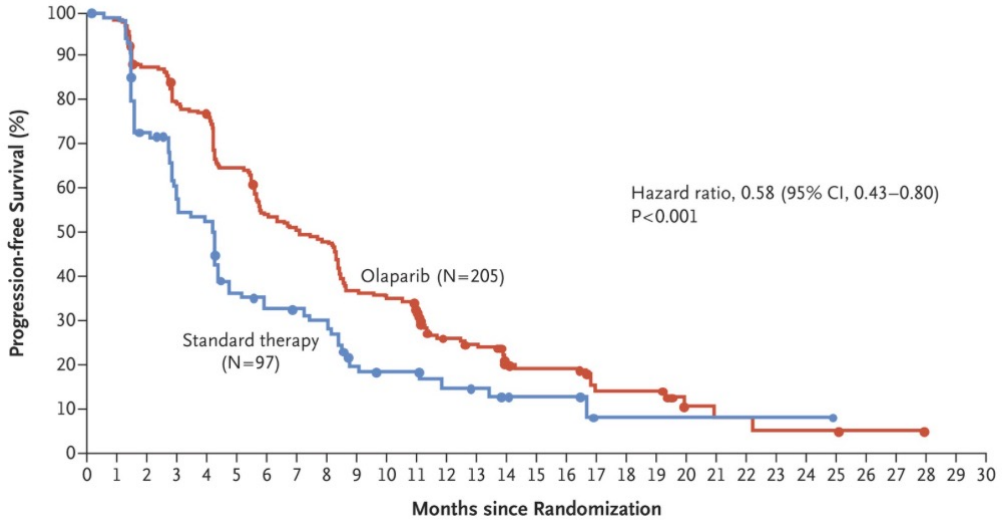
Turner NC, et al. NEJM 2023

BRCA1/2

- Olaparib or Talazoparib (PARP inhibitor)
  - Approved for germline BRCA mutant HR+/HER2- MBC
- **OlympiAD1**: mPFS 7.0 mo with Olaparib vs 4.2 mo with TPC (HR 0.58, P <0.0009)
- **EMBRACA2**: mPFS 8.6 mo with Talazoparib vs 5.6 mo with TPC (HR 0.54, P <0.001)

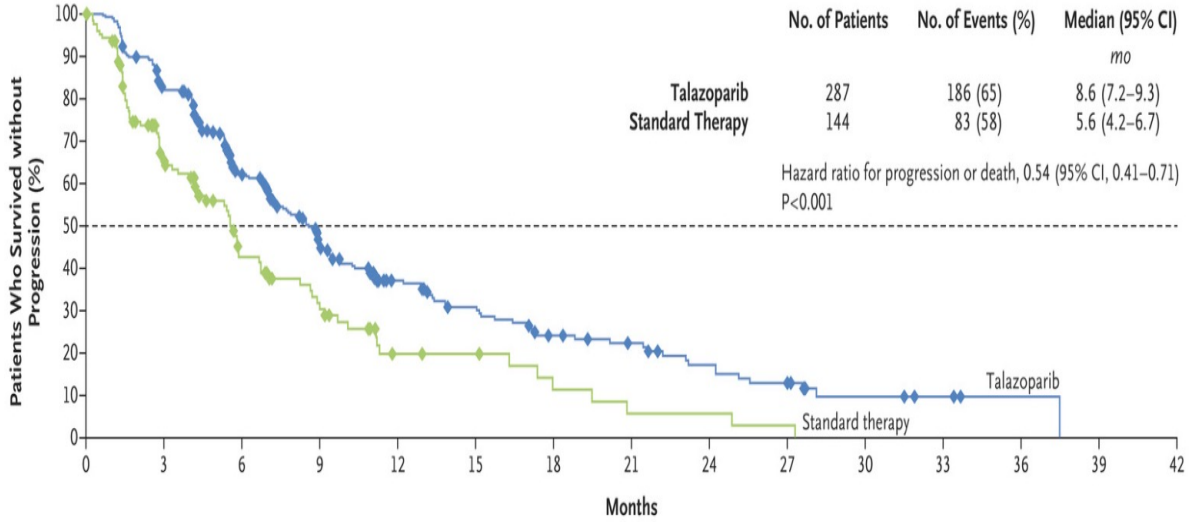
Germline testing should be done in all patients with MBC to determine eligibility to PARPi therapy

OlympiAD1 PFS



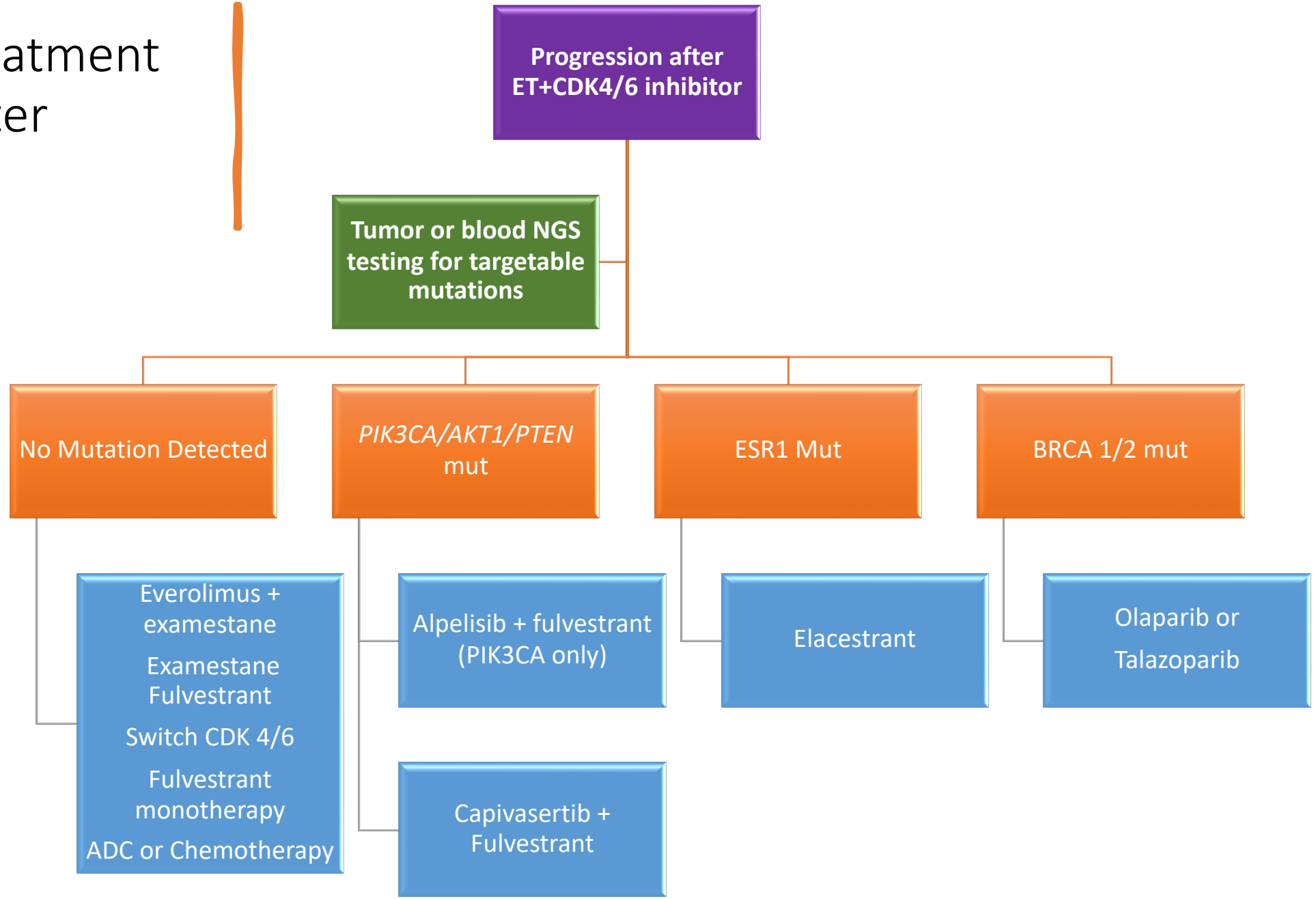
Robson M et al N Engl J Med 2017

EMBRACA PFS



Litton JK et al N Engl J Med 2018

Proposed treatment strategies after CDK4/6i



Summary

First-Line Preference:

CDK4/6i +ET is the preferred 1st line treatment approach.

Patient comorbidities, can guide the selection of the CDK4/6 agent.

However, strategic consideration should be given to certain patients who may potentially defer initiation of this combination.

Switching Strategies:

The efficacy of switching strategies may not universally benefit all patients, with limited observed improvement. In cases where switching is warranted, adjustment of both ET and CDKi is advisable for better outcomes.

Molecular Testing Guidance:

Molecular testing conducted upon disease progression holds promise in providing tailored guidance for the sequential administration of therapies, thereby optimizing treatment strategies.

Enhancements to Endocrine Therapy Backbone:

Advancements in the ET backbone, such as the integration of oral SERDs, PROTACs, and other innovative modalities, present opportunities for improving therapeutic efficacy and patient outcomes.