Current and Emerging Biomarkers in Breast Cancer

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Biomarkers for Systemic Therapy in Metastatic Breast Cancer: ASCO Guideline Update

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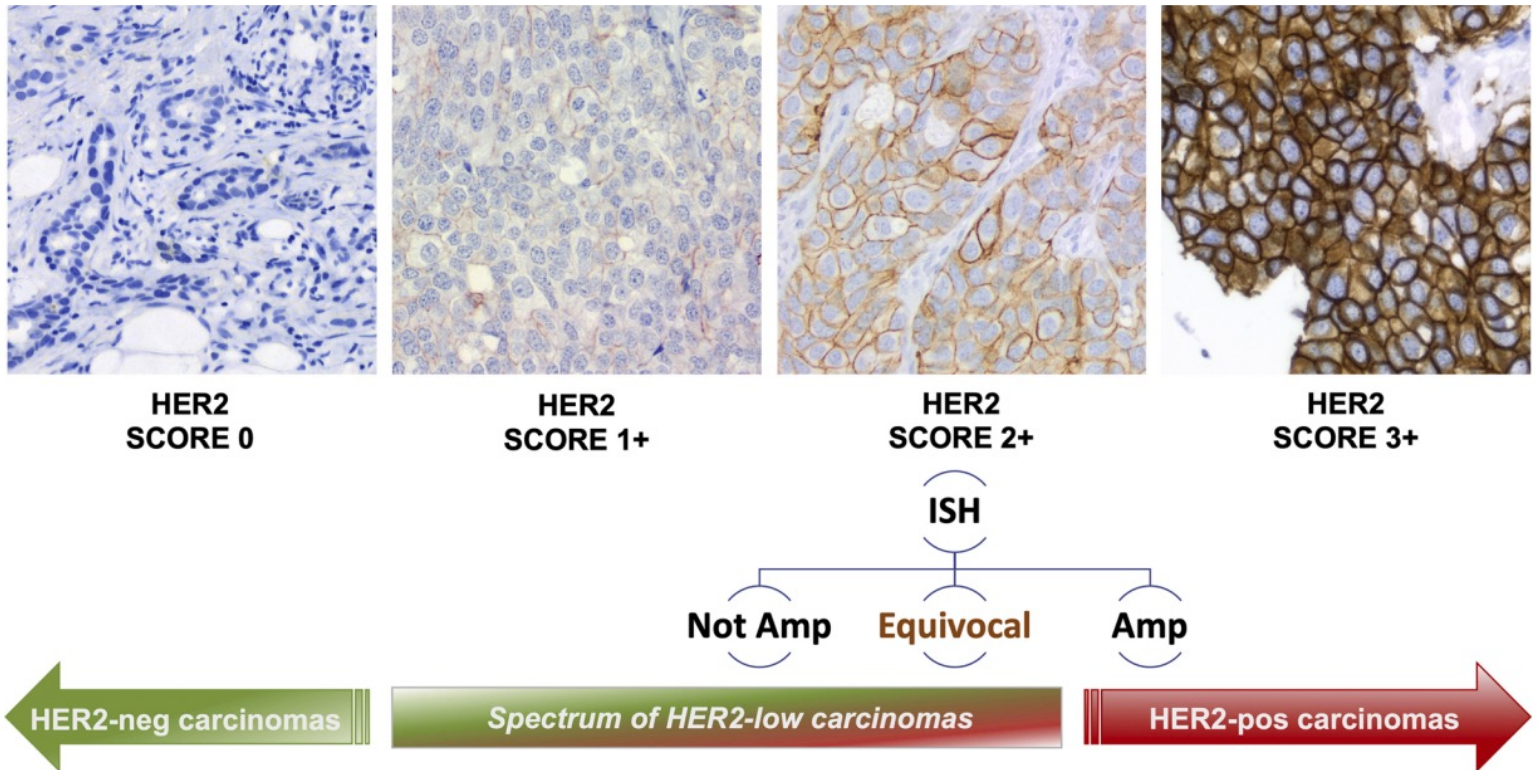
• J Clin Oncol 40:3205-3221; 2022

Topics

- 1) Her2 Low
- 2) PIK3CA, AKT Pathway Alterations
- 3) ESR1 Mutation
- 4) PD-L1
- 5) Mismatch Repair/Microsatellite Instability
- 6) Tumor Mutational Burden
- 7) Circulating Tumor DNA

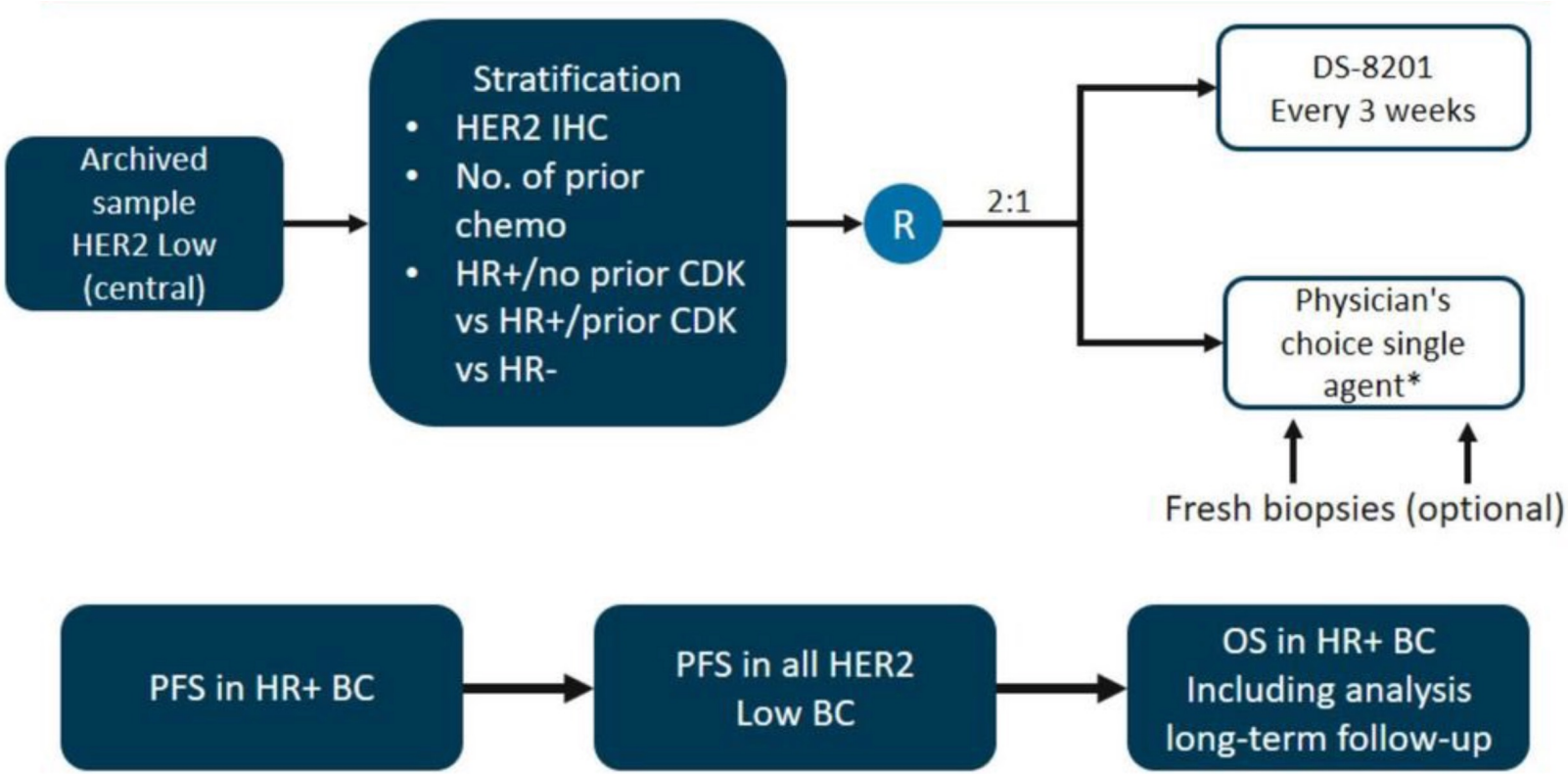
Definition of Her2 Low



- Occurs in 50-55% breast cancer

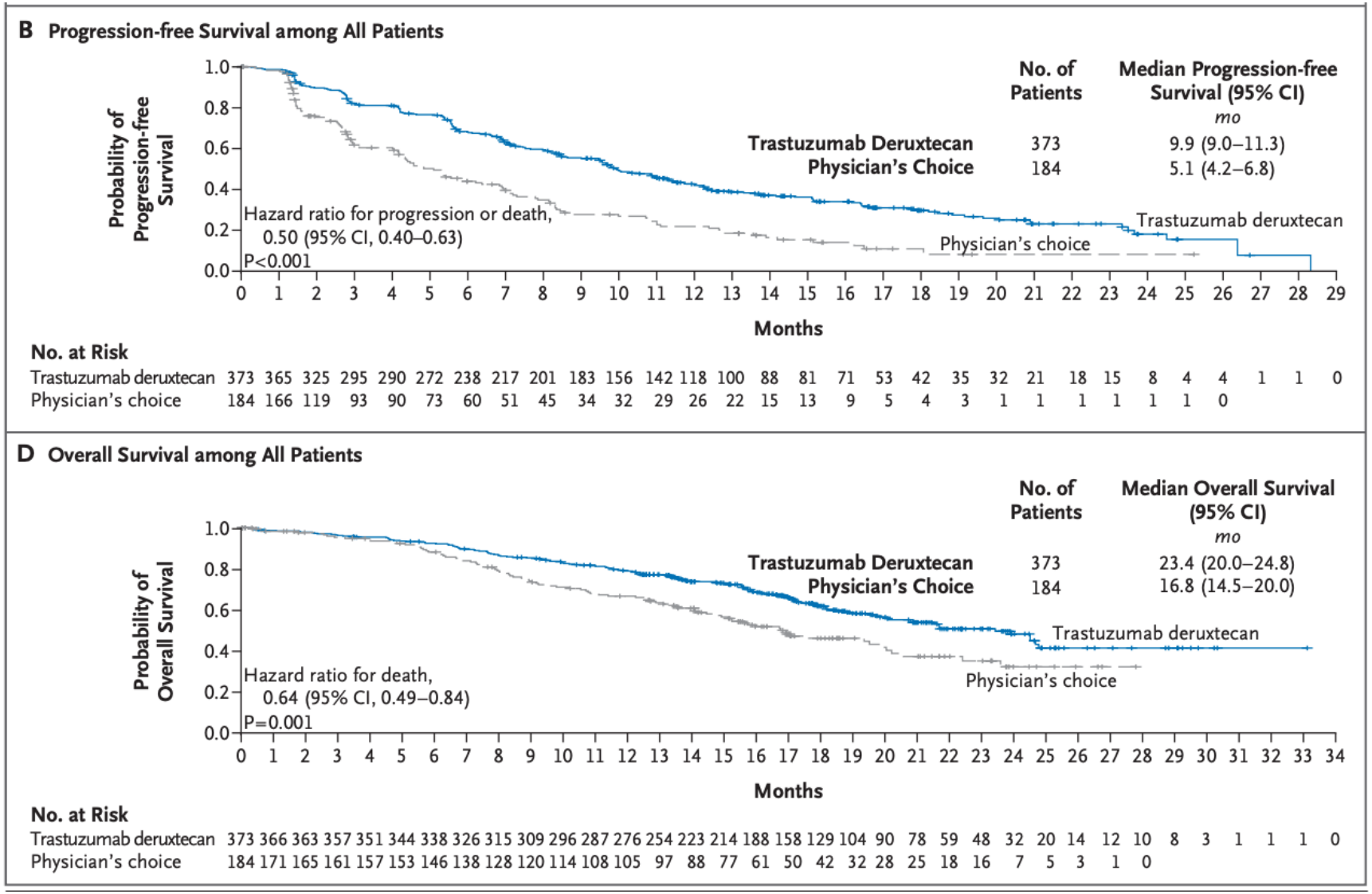
Marchiò. Semin Cancer Biol. 2021:72:123

DESTINY Breast 04: Trastuzumab Deruxtecan in Her2 Low BC



Modi. SABCS 2019. Abstract OT1-07-02.
Modi. ASCO 2022. LBA3. Modi. NEJM. 2022;387:9.

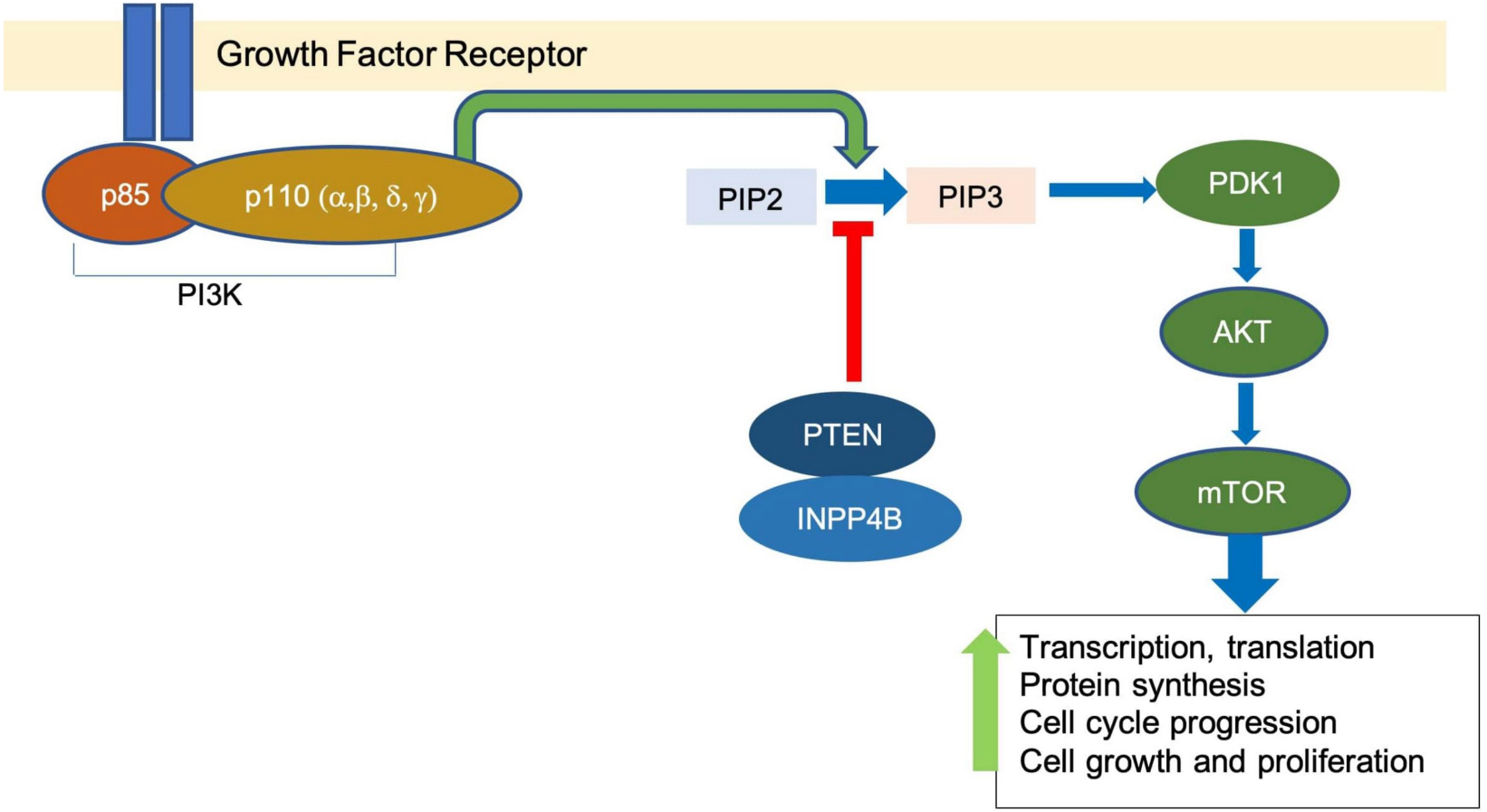
Destiny-Breast 04: Trastuzumab Deruxtecan improves PFS and OS in Her2 Low Disease



Modi. ASCO 2022. LBA3. Modi. NEJM. 2022;387:9.

PIK3CA/AKT/ mTOR Pathway

- *PI3K/AKT* pathway hyperactivation occurs in up to 50% of HR+ breast cancer
  - Mostly *PIK3CA* point mutation
  - 2-4% AKT substitutions



PIK3CA Mutation

- Patients with PIK3CA mutation are eligible for inhibitor alpelisib
- Testing done with next generation sequencing of tumor tissue or circulating tumor DNA (ctDNA) in plasma
  - If no mutation identified in ctDNA, then recommend tissue testing most recent sample available
  - PIK3CA mutations can be acquired during treatment
- SOLAR-1
  - Randomized alpelisib-fulvestrant vs. placebo-fulvestrant
  - In patients with *PIK3CA*-mutation, mPFS was 11.0 months (95% CI 7.5-14.5) with alpelisib-fulvestrant as compared to 5.7 months (95% CI 3.7-7.4) with fulvestrant alone
  - No statistically significant difference in OS

AKT Targeted Inhibition

- Capivasertib taken 400 mg BID 4 days on/3 days off
- NCI MATCH EA131-Y Trial: Capivasertib in AKT1 E17K-Mutated Tumors
  - 35 patients with E17K mutated metastatic disease (51% with breast cancer)
  - ORR 28.6% (95% CI: 15-46%)
  - Median DoR: 4.4 months (3.1 to >31.7 months)

Capivasertib (AZD5363) plus fulvestrant versus placebo plus fulvestrant after relapse or progression on an aromatase inhibitor in metastatic ER positive breast cancer (FAKTION): A phase II trial

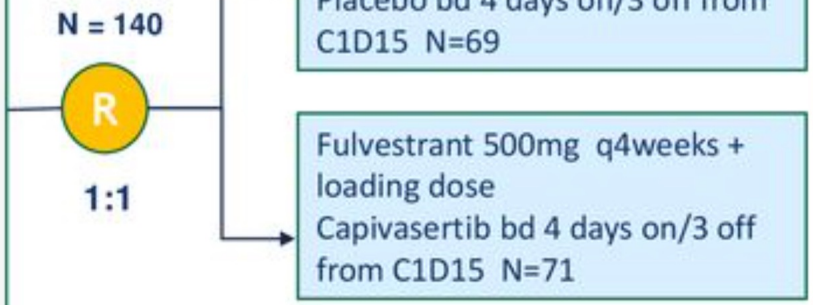
Phase 1b

3+3 design N=9 participants - Capivasertib Starting dose with fulvestrant 500mg: 400mg bd 4 days on / 3 days off

No DLT but 2 withdrawals in 9 participants - Dose not increased to the established single agent dose 480mg bd 4/7

Eligibility

- Post-menopausal women
- ER+/Her2- Metastatic or unresectable LABC
- Prior AI therapy for MBC/LABC with PD **or** relapse on adjuvant AI
- Maximum 1 line chemotherapy for MBC
- Maximum 3 lines ET for MBC
- Measurable or non-measurable disease
- Controlled type II diabetes allowed



Primary endpoint:

PFS in overall population

Secondary endpoints:

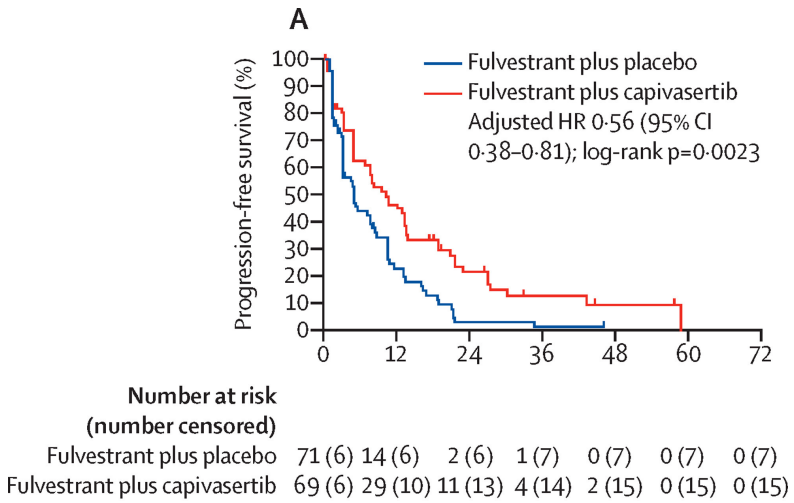
Safety and toxicity

Objective Response rates, CBR and OS: in overall population and pathway activated

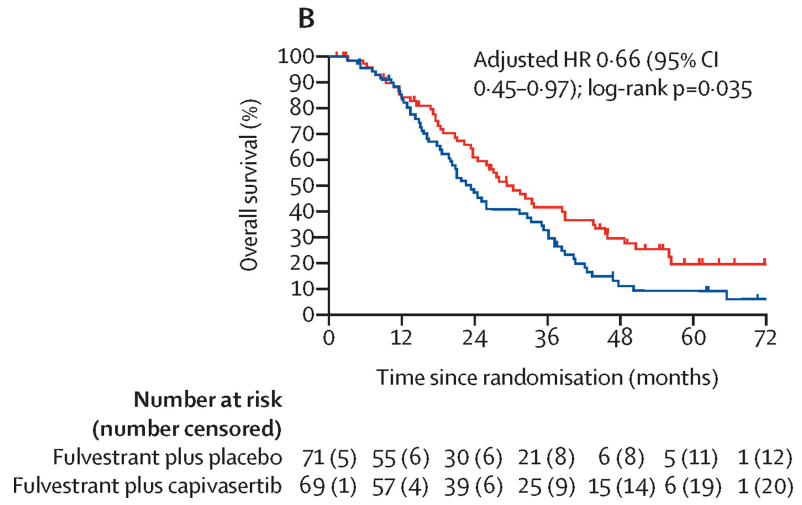
Effects of Capivasertib on the PK of fulvestrant

FAKTION: Capivasertib increased PFS and OS in ITT Population

PFS	Fulvestrant + Capivasertib	Fulvestrant + Placebo
Median PFS, months (95% CI)	10.3 (5.0-13.4)	4.8 (3.1-7.9)
Adjusted Hazard Ratio (95% CI)	0.56 (0.38-0.81)	
P	0.0023	



OS	Fulvestrant + Capivasertib	Fulvestrant + Placebo
Median OS, months (95% CI)	29.3 (23.7-39.0)	23.4 (18.7-32.7)
Adjusted Hazard Ratio (95% CI)	0.66 (0.45-0.97)	
P	0.035	



Howell. Lancet Oncol. 2022;23:851.

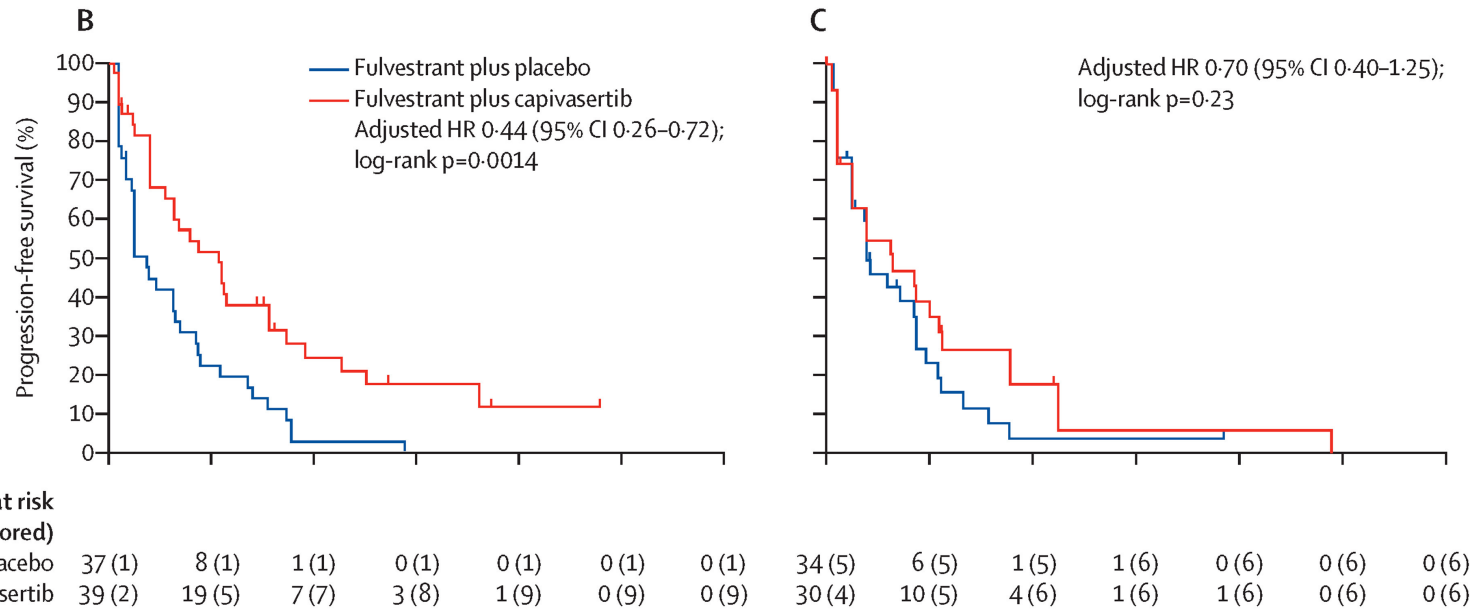
FAKTION: PFS in *PIK3CA/AKT/PTEN* Pathway Altered vs. Nonaltered

Pathway Altered

	Fulvestrant + Capivasertib	Fulvestrant + Placebo
Median PFS, months (95% CI)	12.8 (6.6-18.8)	4.6 (2.8-7.9)
Adjusted Hazard Ratio (95% CI)	0.44 (0.26-0.72)	
P	0.0014	

Pathway Non-Altered

	Fulvestrant + Capivasertib	Fulvestrant + Placebo
Median PFS, months (95% CI)	7.7 (3.1-13.2)	4.9 (3.2-10.5)
Adjusted Hazard Ratio (95% CI)	0.70 (0.40-1.25)	
P	0.23	



Howell. Lancet Oncol. 2022;23:851.

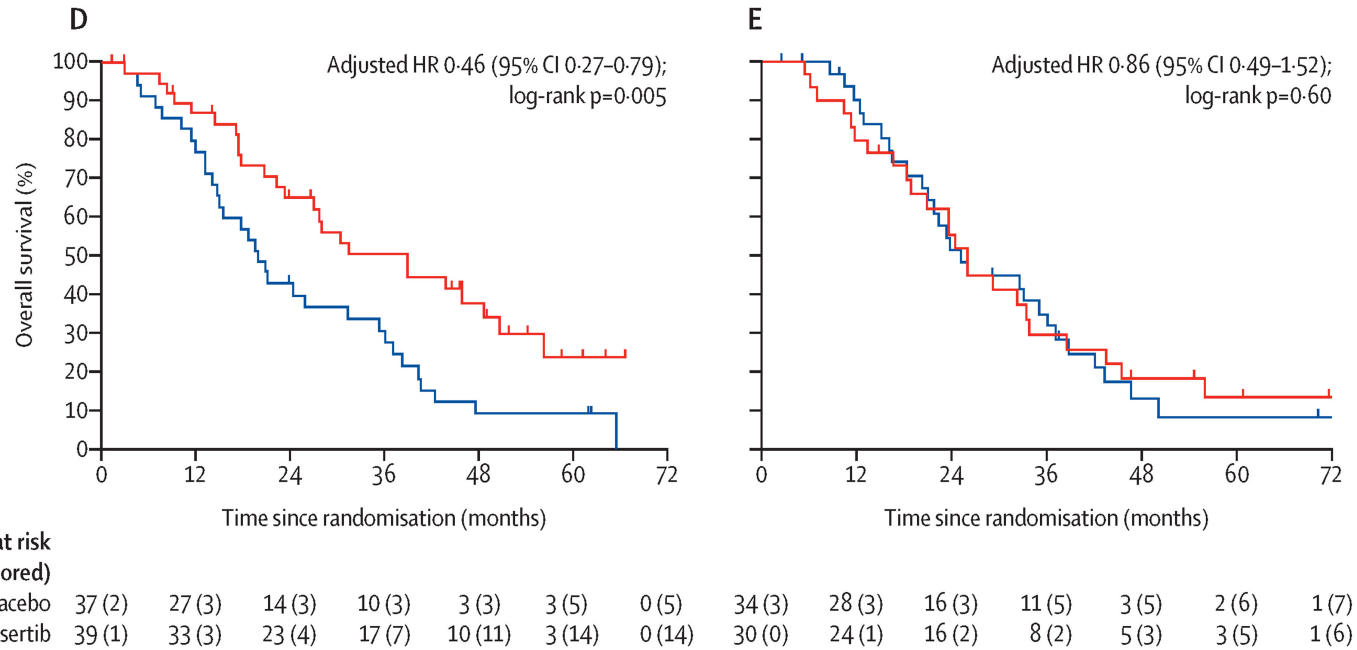
FAKTION: OS in *PIK3CA/AKT/PTEN* Pathway Altered vs. Nonaltered

Pathway Altered

	Fulvestrant + Capivasertib	Fulvestrant + Placebo
Median OS, months (95% CI)	38.9 (23.3-50.7)	20.0 (14.8-31.4)
Adjusted Hazard Ratio (95% CI)	0.46 (0.27-0.79)	
P	.0047	

Pathway Non-Altered

	Fulvestrant + Capivasertib	Fulvestrant + Placebo
Median OS, months (95% CI)	26.0 (18.4-33.8)	25.2 (20.3-36.2)
Adjusted Hazard Ratio (95% CI)	0.86 (0.49-1.52)	
P	.60	



Number at risk (number censored)														
Fulvestrant plus placebo	37 (2)	27 (3)	14 (3)	10 (3)	3 (3)	3 (5)	0 (5)	34 (3)	28 (3)	16 (3)	11 (5)	3 (5)	2 (6)	1 (7)
Fulvestrant plus capivasertib	39 (1)	33 (3)	23 (4)	17 (7)	10 (11)	3 (14)	0 (14)	30 (0)	24 (1)	16 (2)	8 (2)	5 (3)	3 (5)	1 (6)

Howell. Lancet Oncol. 2022;23:851.

CAPItello 291

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

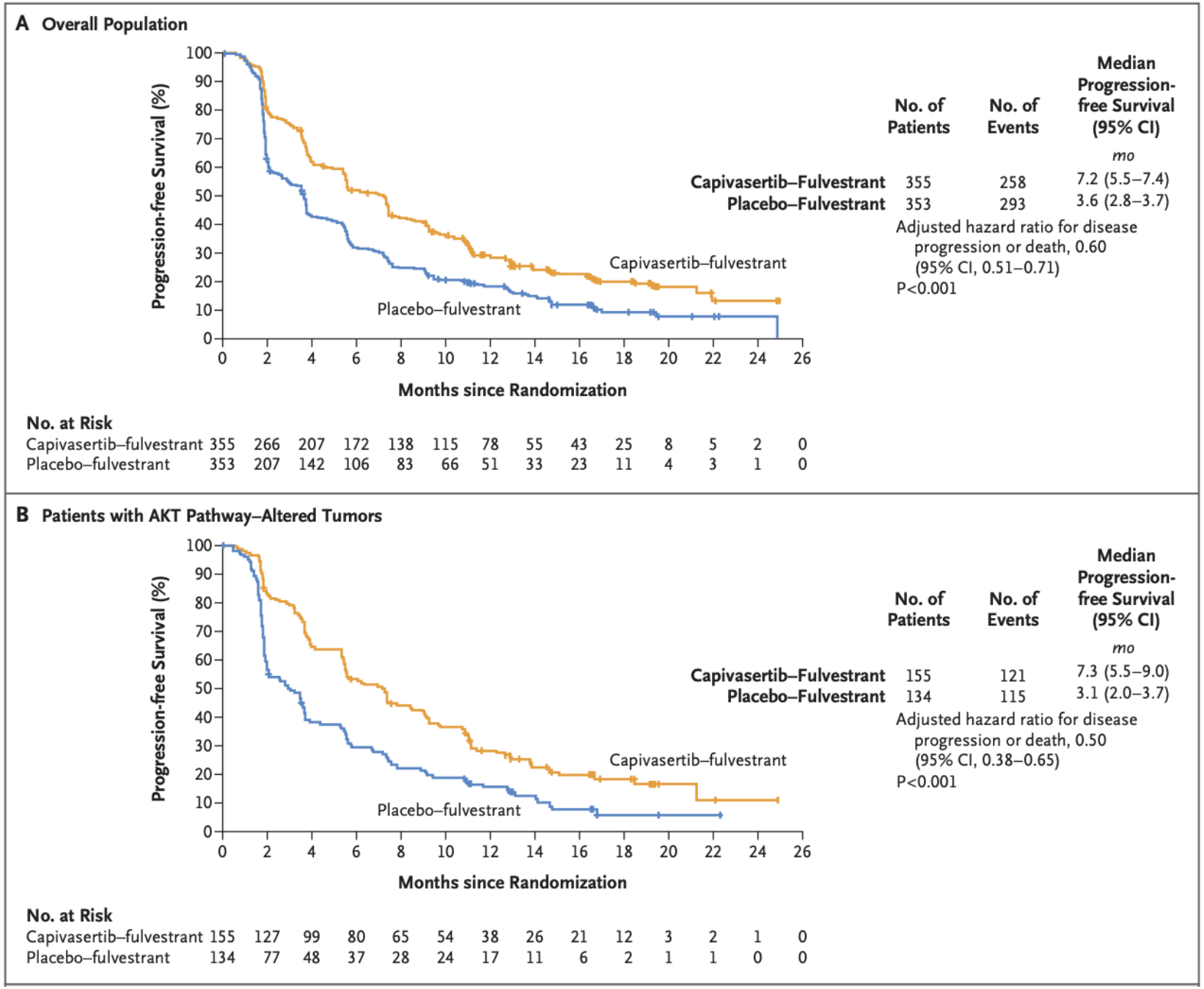
Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

Turner et al. NEJM. 2023; 388:2058-2070.

CAPItello 291: Improved PFS with Capivasertib

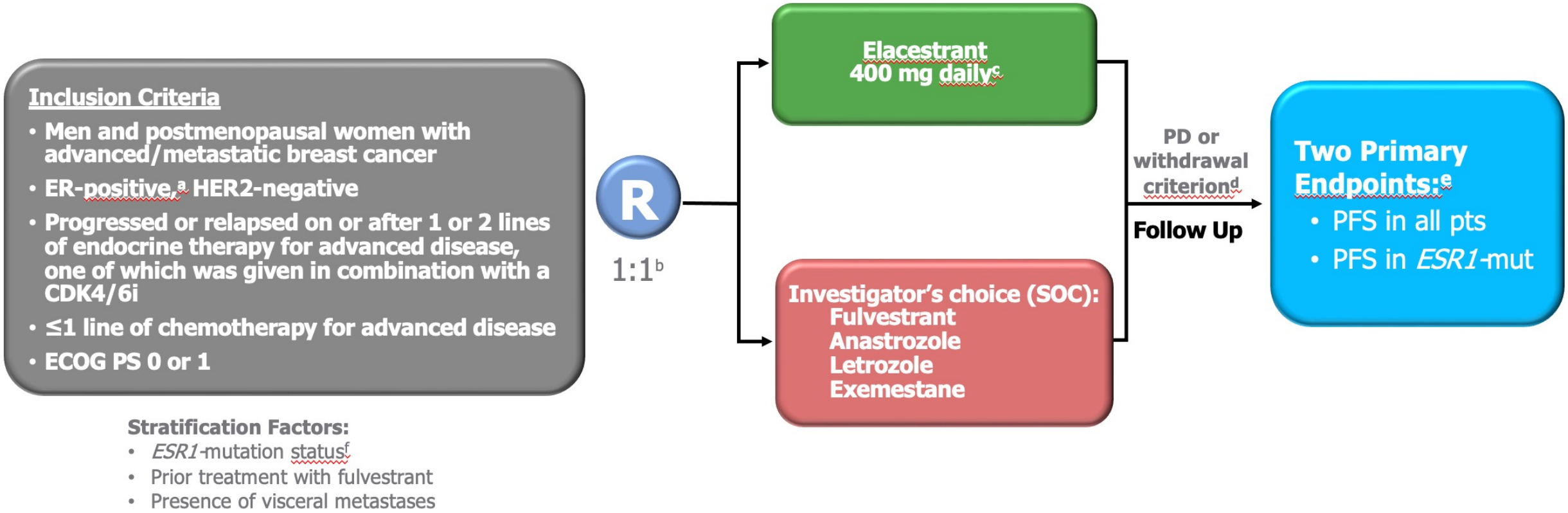


Turner. NEJM. 2023;388:2058.

ESR1 Mutation

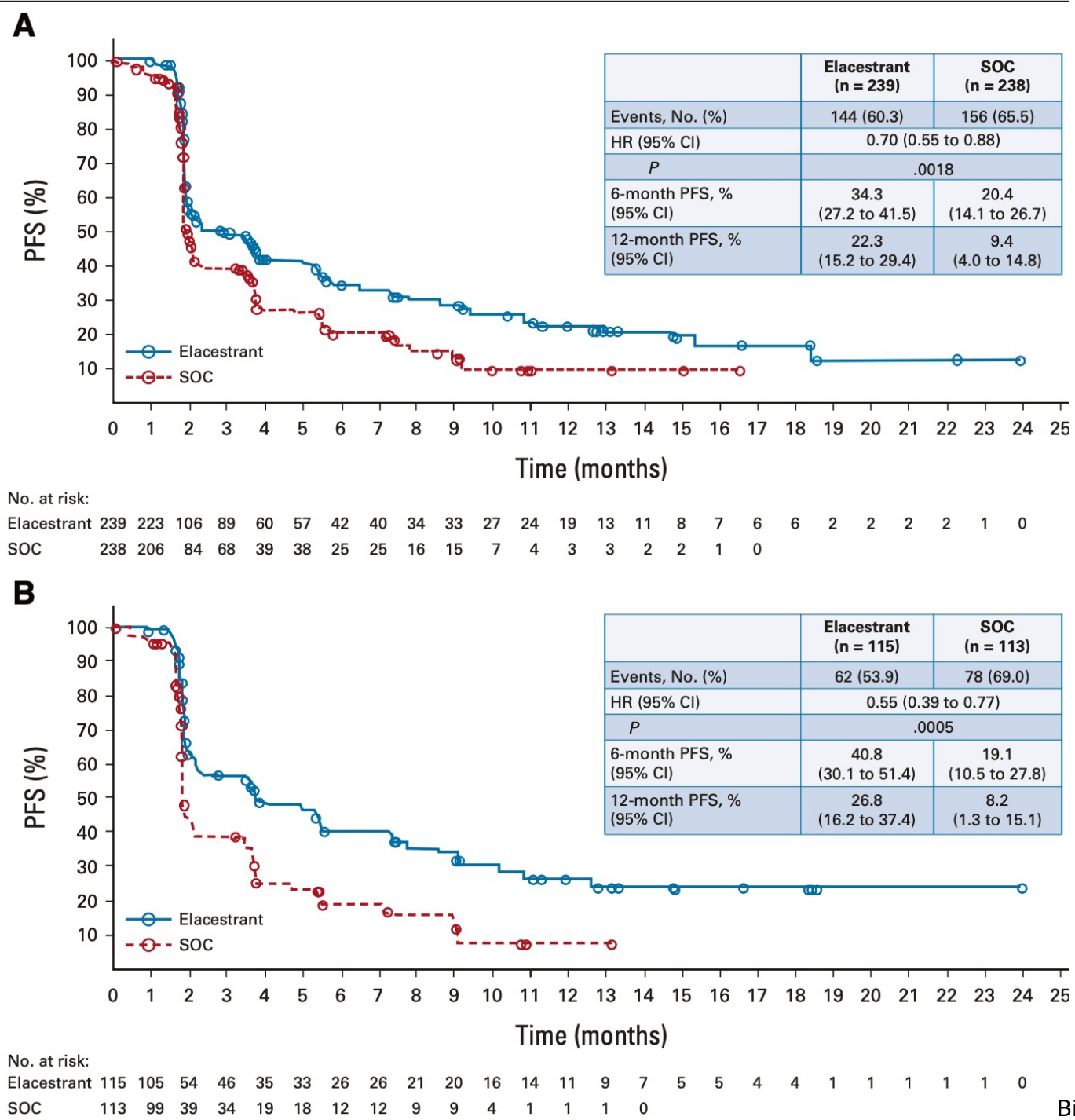
- *ESR1* mutations confer resistance to AI, partial resistance to SERMs/SERDs
- Mostly acquired mutations due to selection pressure
- Testing should be routine at recurrence or at the time of progression
- Detectable by ctDNA analysis in blood
  - ctDNA testing has greater sensitivity than tissue testing
- Elacestrant (oral SERD) is newly approved for *ESR1*-mutated advanced HR+/Her2- breast cancer that has progressed on at least one line of prior endocrine therapy

EMERALD



Bidard et al. JCO; 2022; 28: 3246-3256

EMERALD: Elacestrant improves PFS in ITT and in patients with *ESR1* mutation as compared to 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)

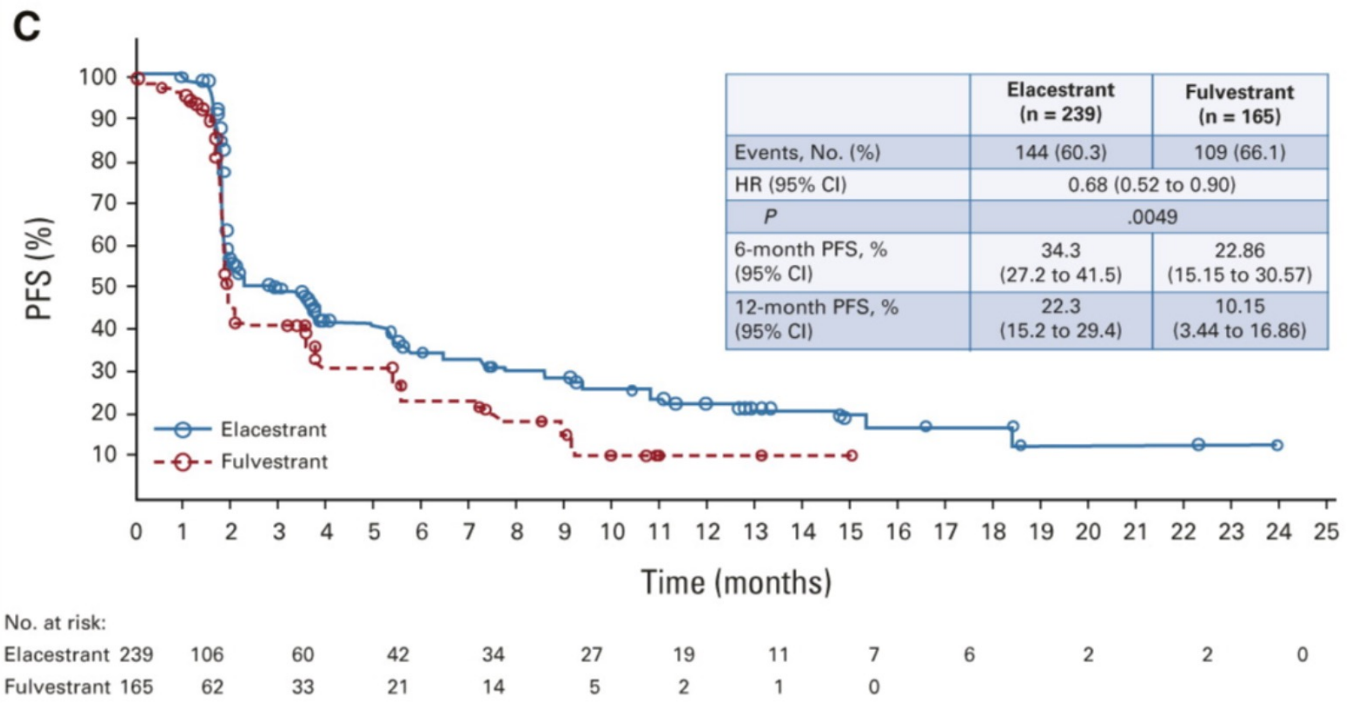
All patients

	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

ESR1 mutation

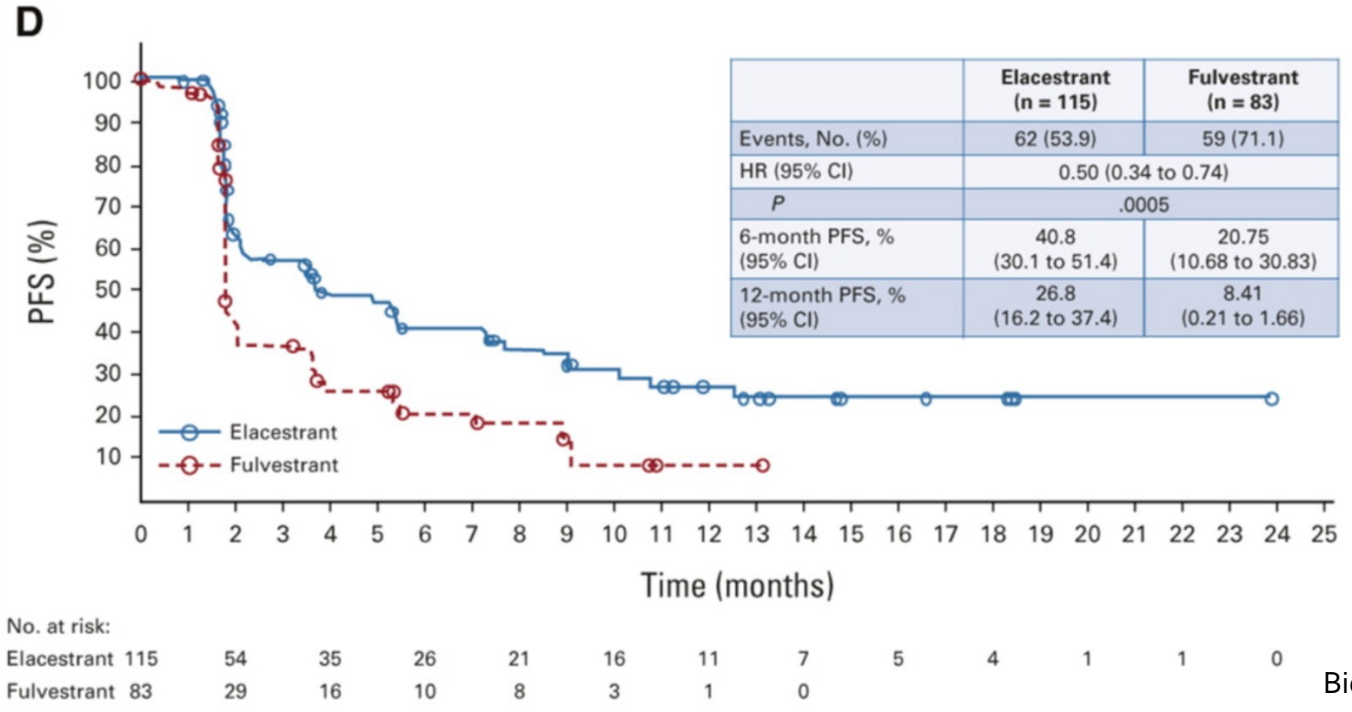
Bidard et al. JCO; 2022; 28: 3246-3256

EMERALD: Elacestrant improves PFS in ITT and *ESR1* mutation as compared to Fulvestrant



	Elacestrant (n = 239)	Fulvestrant (n = 165)
Events, No. (%)	144 (60.3)	109 (66.1)
HR (95% CI)	0.68 (0.52 to 0.90)	
P	.0049	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	22.86 (15.15 to 30.57)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	10.15 (3.44 to 16.86)

All patients



	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)

ESR1 mutation

Bidard et al. JCO; 2022; 28: 3246-3256

Germline *BRCA 1/ BRCA 2*

- Germline mutation establishes eligibility for treatment with poly ADP-ribose polymperase (PARP) inhibitors olaparib or talazoparib for patients with pathogenic or likely pathogenic mutation
- OlympiAD
  - mPFS 7.0 months with Olaparib vs. 4.2 months with standard chemotherapy (HR 0.58, 95% CI 0.43-0.80)
  - No statistically significant improvement in OS with Olaparib
- EMBRACA
  - mPFS 8.6 months with Talazoparib vs. 5.6 months with standard chemotherapy (HR 0.54, 95% CI 0.41-0.71)
  - No statistically significant improvement in OS with Talazoparib

PD-L1

- Keynote 355
  - Pembrolizumab + chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine-carboplatin) vs. chemotherapy in frontline mTNBC
  - PD-L1 ≥ 10: mPFS 9.7 months with pembrolizumab-chemotherapy vs. 5.6 months with placebo-chemotherapy (HR 0.65; 95% CI 0.49-0.86)
- FDA approval using 22C3 assay, which evaluated PD-L1 staining the tumor and surrounding stroma to calculate CPS (number of PD-L1 staining tumor cells, lymphocytes, and macrophages divided by total number of viable tumor cells)

Mismatch repair/ Microsatellite Instability

- Determine eligibility for dostarlimab-gxly or pembrolizumab
- Keynote 158 (phase II)
  - Pembrolizumab in advanced MSI-H/dMMR solid malignancies
  - ORR 34.3% (95% CI, 28.3-40.8)
  - mPFS 4.1 months (95% CI 2.4-4.9)

Tumor Mutational Burden

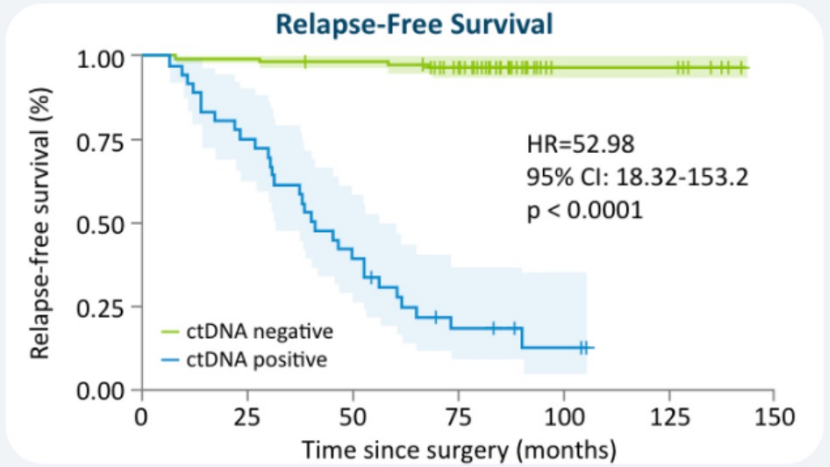
- Eligibility for pembrolizumab monotherapy
- Keynote 158
  - High TMB defined as at least 10 mutations per megabase
  - 29% of patients (95% CI, 21-39) with objective response
- TAPUR Study (phase II)
  - Patients with high TMB (range 9-37 mutations/Mb) and MBC
  - Objective response 21% (95% CI, 8-41)
  - Disease control rate (objective response or stable disease for at least 16 weeks) 37% (95% CI 21-50)

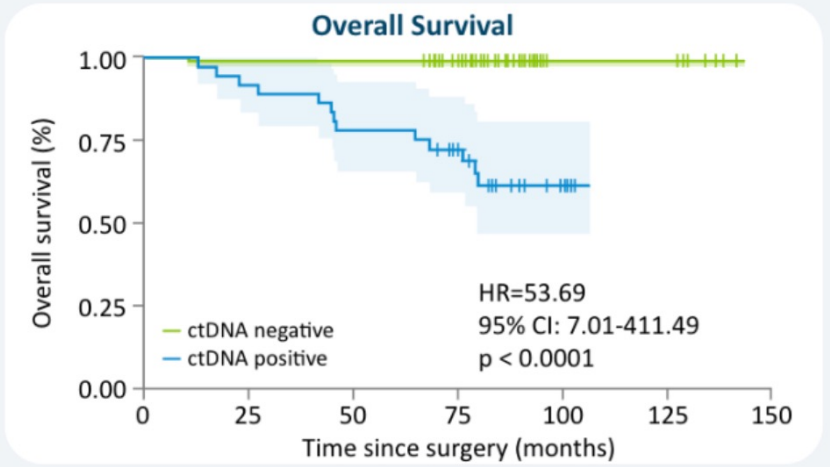
ctDNA Positivity Associated with Relapse

- The Exploratory Breast Lead Interval Study (EBLIS) is the largest breast cancer cohort with the longest ctDNA follow-up
  - ctDNA detected ahead of clinical or radiographic relapse in 30/34 relapsed patients (sensitivity 88%)
  - All ctDNA positive patients relapsed
  - Of 122 non-relapsed patients, 116 patients were ctDNA negative consistently
  - Metastatic relapse predicted with median lead time of 10.5 months (range 0-38 months)

Cailleux et al. JCO Precision Oncology; 2022
Shaw et al. ASCO 2022

ctDNA positivity Associated with Relapse and Lower Overall Survival





Shaw et al. ASCO 2022

ctDNA Testing in Current Practice

- ASCO Update 2022: Insufficient data to recommend routine use of ctDNA to monitor response to therapy among patients with metastatic breast cancer

Thank you!