Breast Cancer Update: HR+ and HER2+ disease

Evie Hobbs, MD
Assistant Professor
OHSU Breast Medical Oncology
Annual Hematology and Breast Cancer Update
April 16, 2022

Outline

HR+

Adjuvant abemaciclib (monarchE)

1L Ribociclib overall survival (Monaleesa-2)

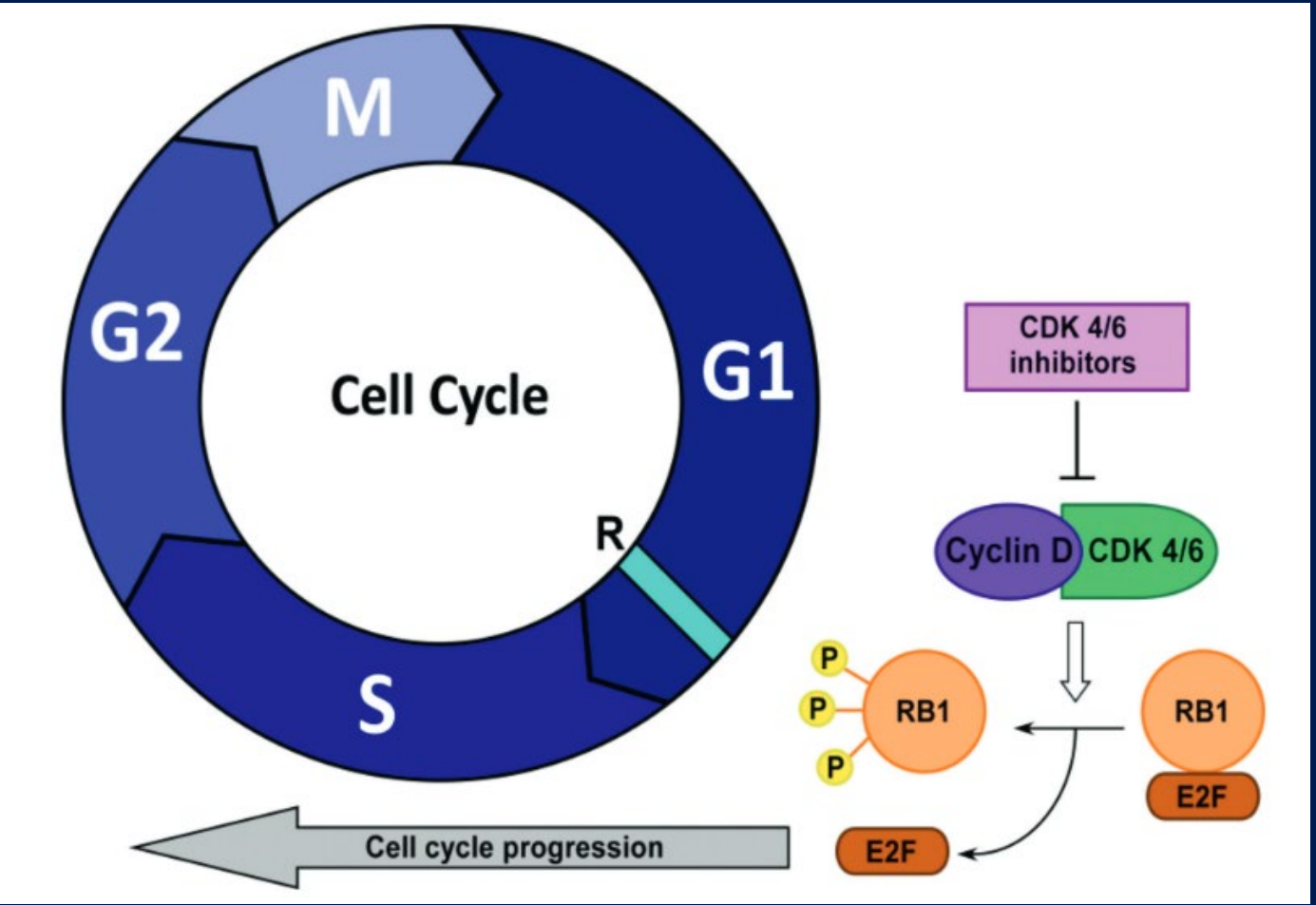
Elacestrant novel SERD (EMERALD)

HER2+

2L T-DXd vs TDM1 (DB-03)

Tucatinib Overall survival & brain metastases update (HER2CLIMB)

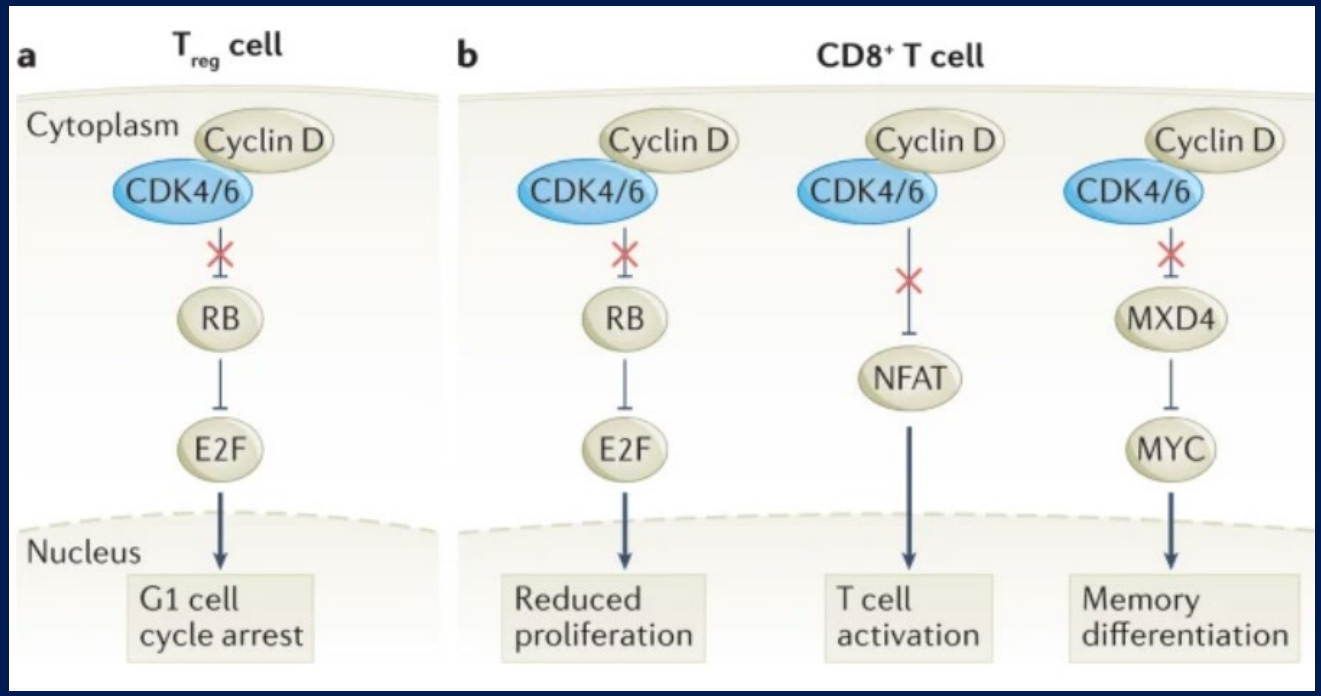
CDK4/6 inhibitors mechanism of action



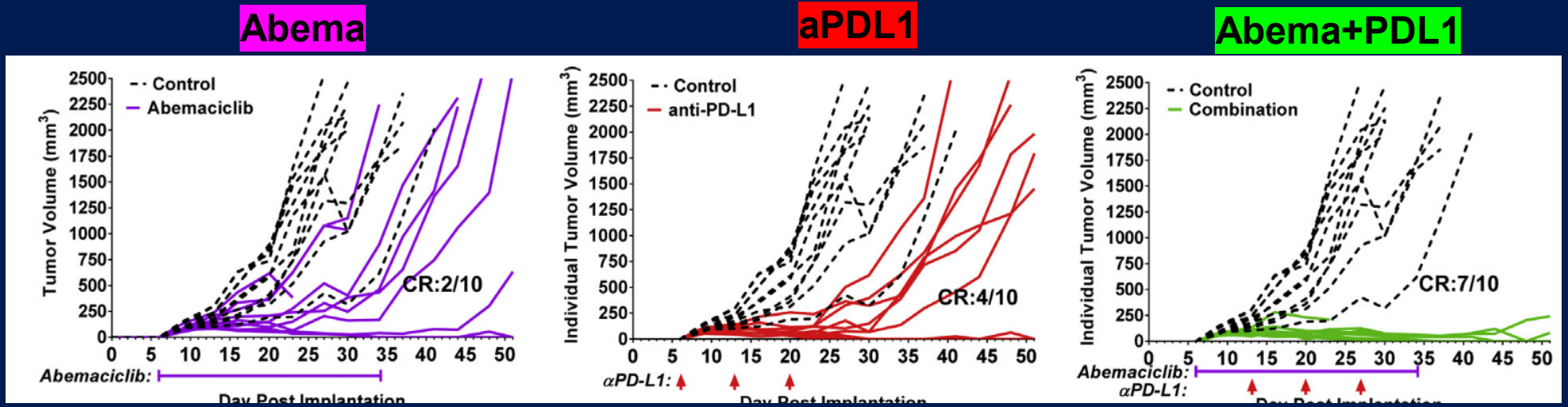
1. RB-dependent proliferation arrest
   - Cytostasis, apoptosis
2. RB non-canonical
   - Recruitment of histone modifiers
   - Activation of transcription factors
3. CDK4/6 non-RB substrates
   - Apoptosis, senescence
4. Differential effects on immune cell function

Goel Nat Rev Cacer 2022
Lallemand BJMO 2017

CDK4/6 inhibitors and immune modulation

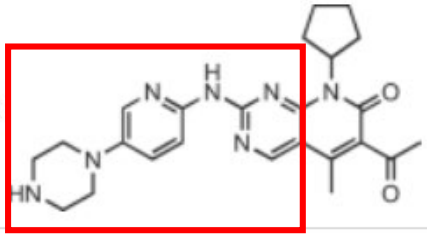
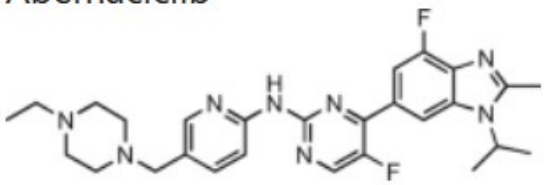
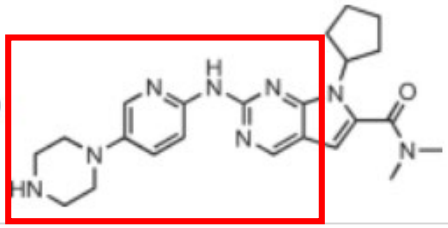
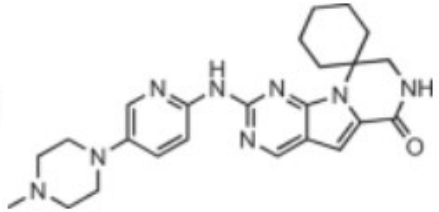


CDK4/6i synergy with aPDL1 (CRC xenograft)



Goel Nat Rev Cacer 2022; Schaer Cell Reports 2018

CDK4/6 inhibitors approved

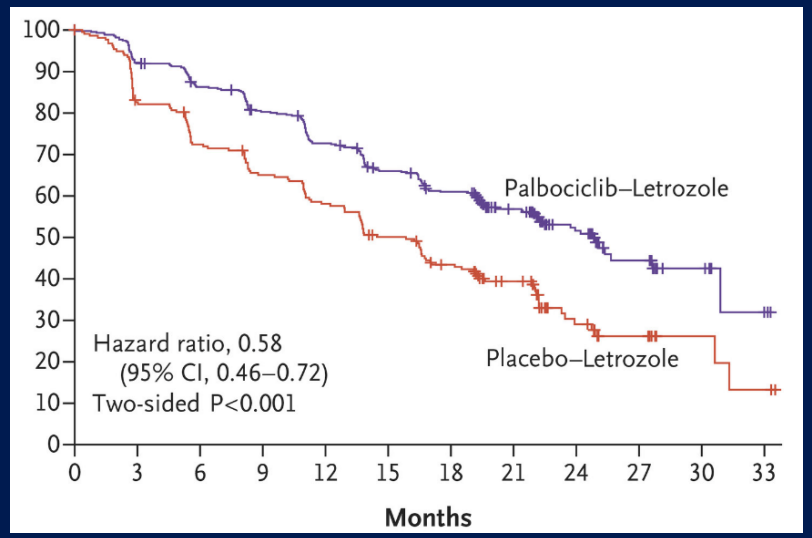
Agent	Selectivity (IC_{50})	Clinical development
Approved		
Palbociclib 	CDK4: 11 nM CDK6: 16 nM	Approved for HR^+, $HER2^-$ advanced breast cancer in combination with hormonal therapy
Abemaciclib 	CDK4: 2 nM CDK6: 10 nM	Approved for HR^+, $HER2^-$ advanced breast cancer in combination with hormonal therapy Approved as monotherapy for advanced HR^+, $HER2^-$ breast cancer Approved as adjuvant therapy for high-risk, early-stage HR^+, $HER2^-$ breast cancer in combination with hormonal therapy
Ribociclib 	CDK4: 10 nM CDK6: 39 nM	Approved for HR^+, $HER2^-$ advanced breast cancer in combination with hormonal therapy
Trilaciclib 	CDK4: 1 nM CDK6: 4 nM	Approved to reduce chemotherapy-induced bone marrow suppression in patients with extensive-stage SCLC

Goel Nat Rev Cancer 2022

CDK4/6 inhibitors in the 1L metastatic setting

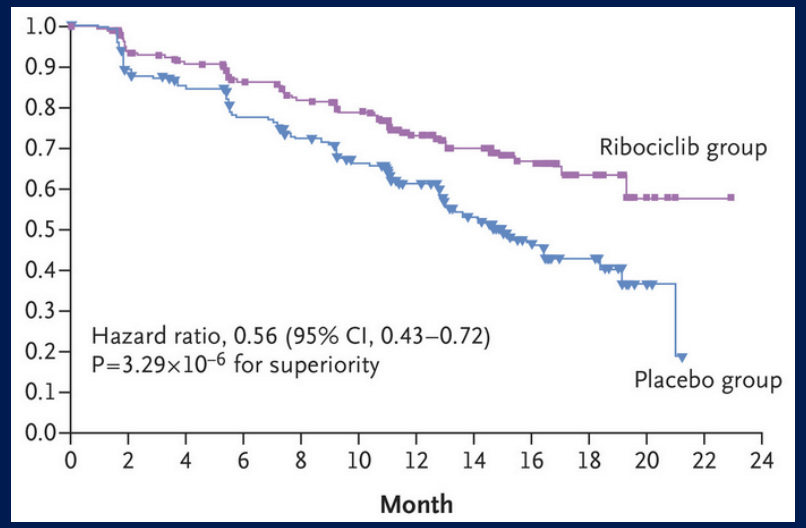
Progression free survival

Palbociclib
PALOMA-2



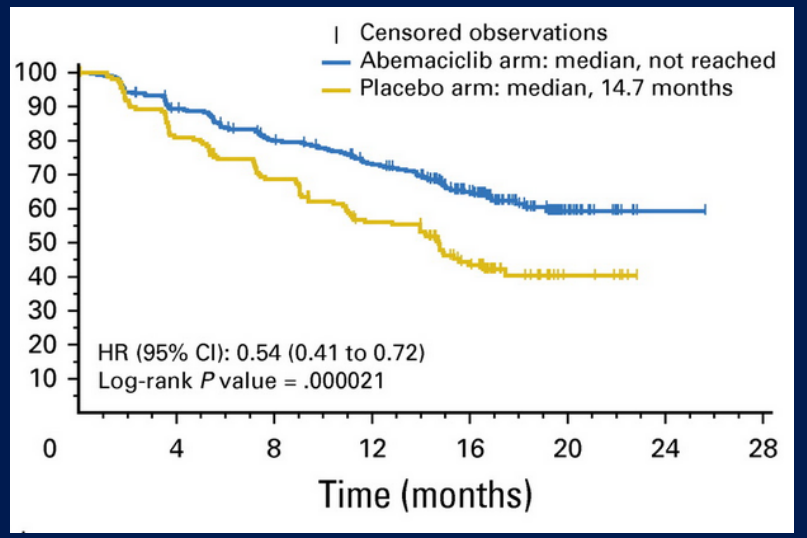
Finn NEJM 2016

Ribociclib
MONALEESA-2



Hortobagyi NEJM 2016

Abemaciclib
MONARCH-3



Goetz JCO 2017

Hazard Ratio = 0.54-0.58

CDK4/6 inhibitors in the adjuvant setting

Palbociclib
Penelope-B (x1y)
PALLAS (x2y)

Negative studies

Abemaciclib
monarchE (x2y)

FDA approval Oct 2021
LN+ Ki67 ≥ 20%

Ribociclib
EarLEE (x2y)
NATALEE (x3y)

Pending

MonarchE: Adjuvant abemaciclib in HR+ high clinical risk

Early stage HR+, HER2-, LN+
N = 5,637

Cohort 1 (Any Ki67)	Cohort 2 (Ki67 ≥ 20%)
≥ 4 axillary LN + OR ≥ 1 LN+ (1-3) AND Grade 3 or T ≥ 5cm	≥ axillary LN+ (1-3) AND Grade < 3 or T <5cm

→ **Abemaciclib + ET x2 years**

→ **ET alone x2 years**

ET: Tamoxifen, anastrozole, letrozole, exemestane

- Ki67 ≥ 20% on primary untreated specimen (MIB-1)
- LN on pathologic staging
- Cohort 2 started enrolling 1y after

Inclusion:
- LN+ microscopic or macroscopic
- Pre & postmenopausal
- Bilateral disease allowed

Exclusion:
- History of VTE (including line thrombosis)

Johnston JCO 2020

MonarchE: patient population

Postmenopausal 60%

Aromatase inhibitor 70%

- OFS 15%
- Tamoxifen 30%

Chemotherapy 95%

- Anthracycline + taxane 80%

Axillary LN ≥ 4 60%

Grade 3 40%

- G1 10%
- G2 50%

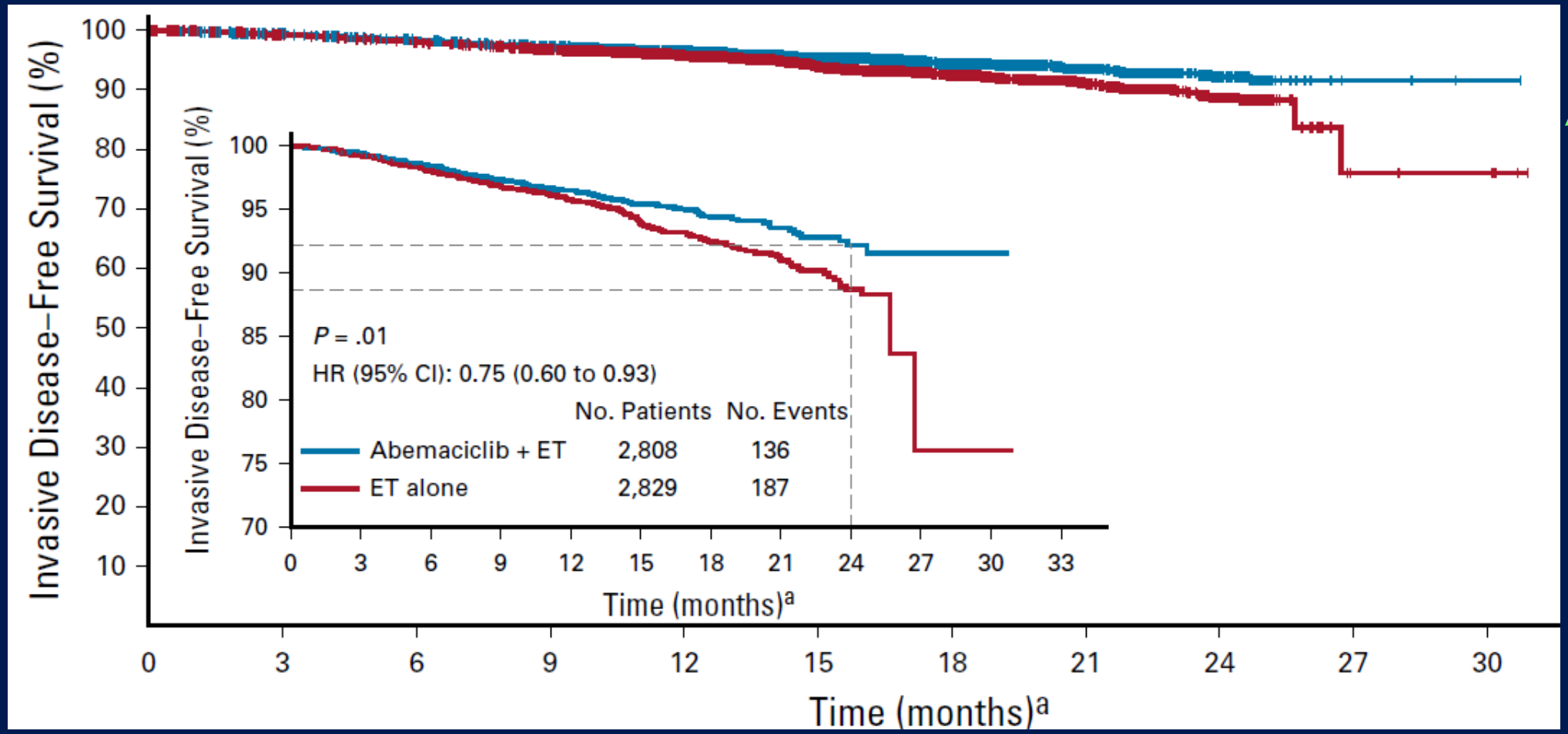
Tumor ≥ 5cm 20%

- T < 2cm 30%
- T 2-5cm 50%

Ki67 ≥ 20% 45%

Johnston JCO 2020

MonarchE: invasive disease free survival at 2 years



Δ +3.5%

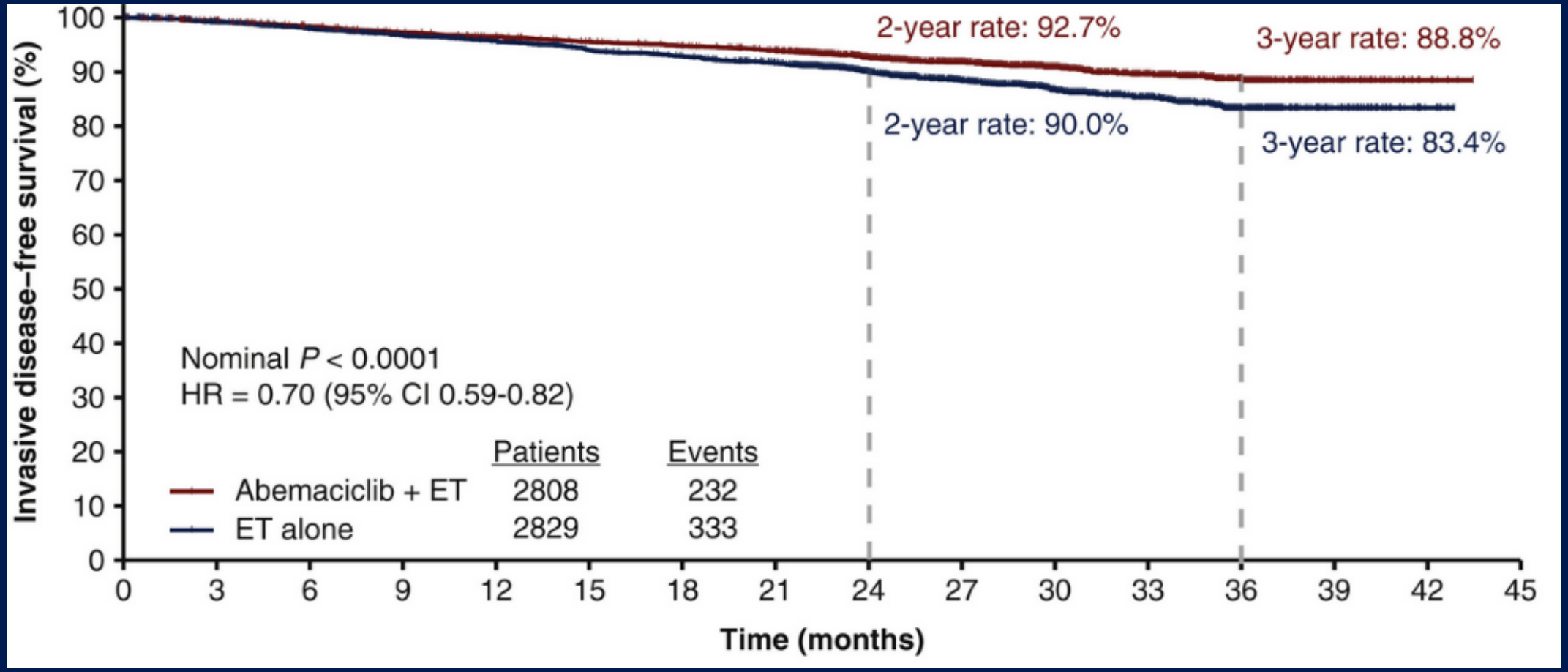
2y iDFS 92.2% versus 88.7%
HR 0.75, p = 0.01

Distant recurrence: 70%

Johnston JCO 2020

monarchE: iDFS ITT population at 3 years

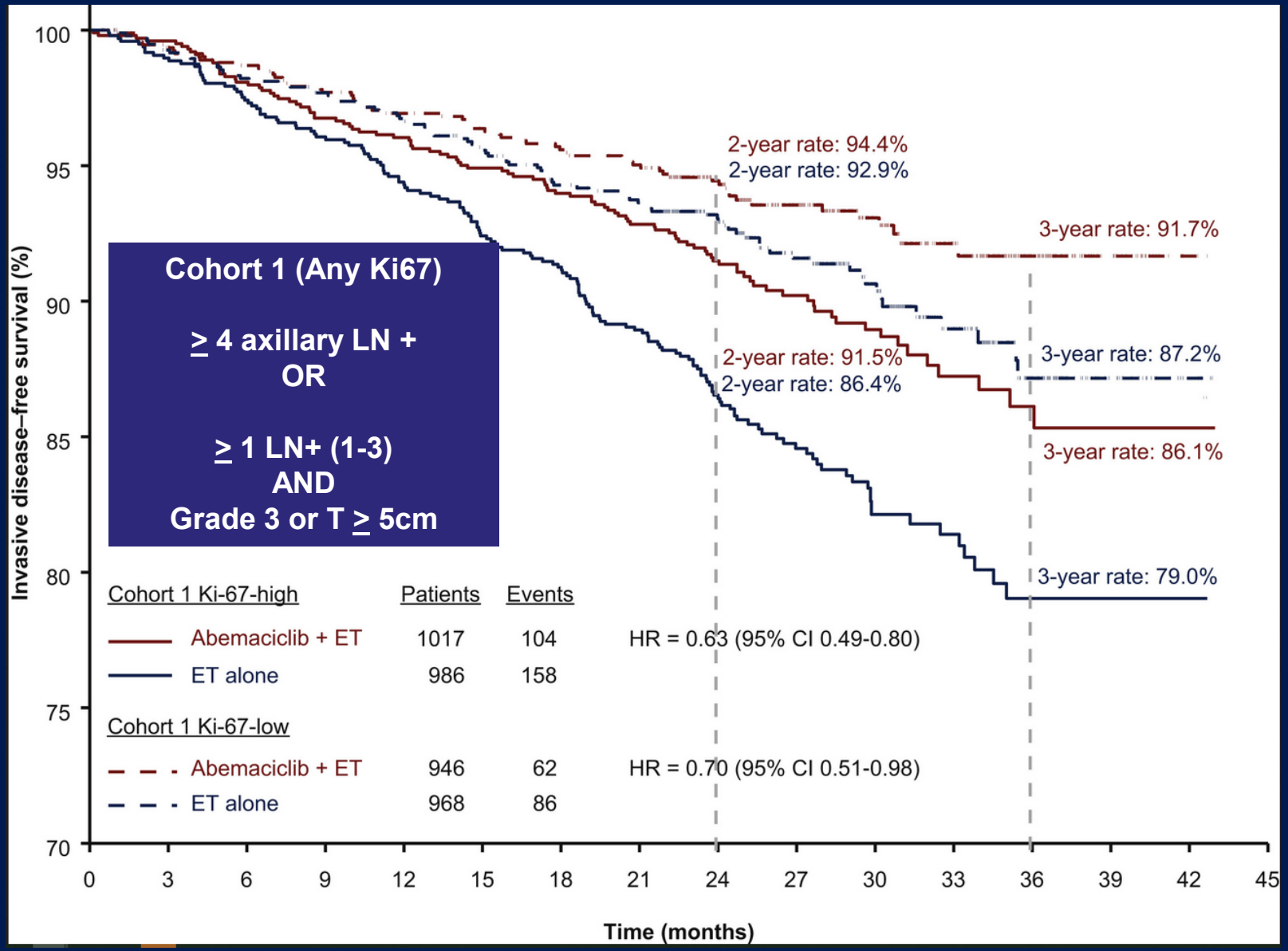
Cohort 1 & 2 (included low ki67)



Δ +5.3%

Harbeck Annals of Onc 2021

monarchE: iDFS cohort 1 by Ki67 (3 year follow-up)



Ki67 low: Δ +4.5%

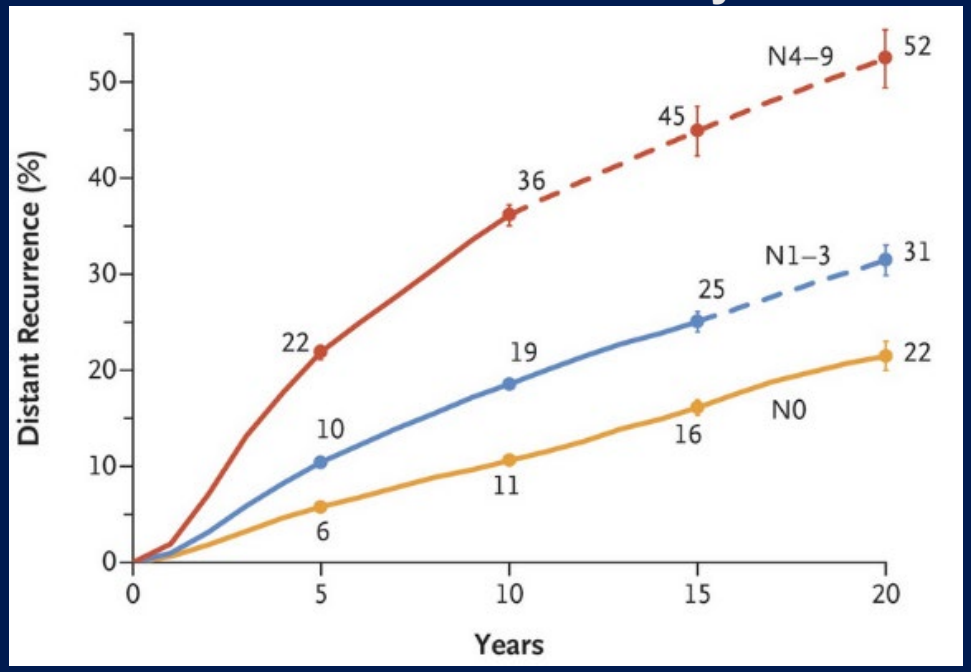
Ki67 high: Δ +7.1

Harbeck Annals of Onc 2021

20-year risks of breast cancer recurrence after stopping endocrine therapy at 5 years

N= 62,923 patients

Risk of distant recurrence by LN #



N 4-9 = 52%

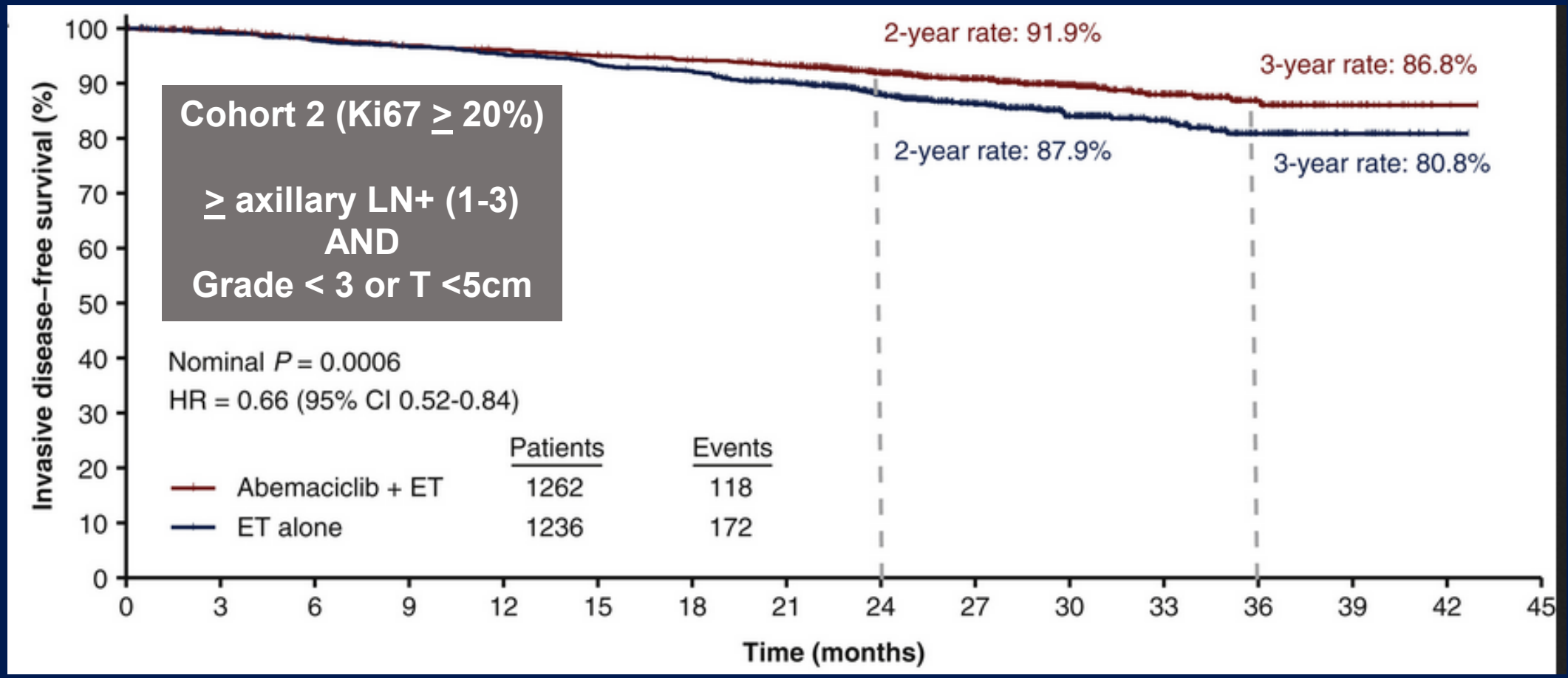
N 1-3 = 31%

N 0 = 22%

MonarchE Cohort 1: 50% will have late recurrences
***Ki-67 independent prognostic factor during the first 5 years but only moderate relevance thereafter.**

Pan, EBCTCG NEJM 2017

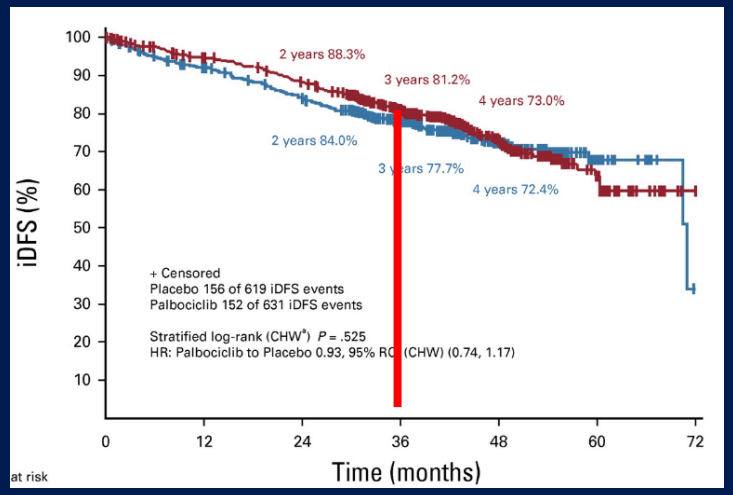
monarchE: iDFS cohort 2 (3 year follow-up)

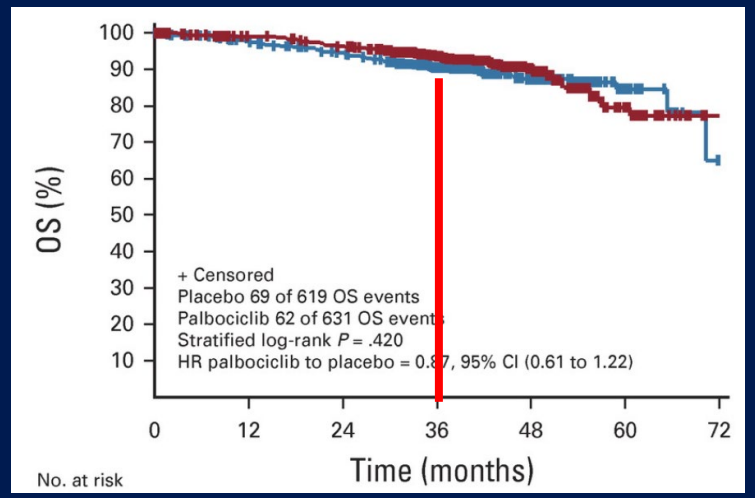


Δ +6%

Harbeck Annals of Onc 2021

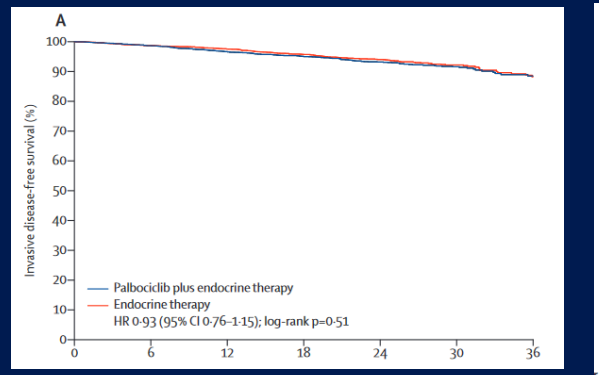
Penelope-B: adjuvant Palbociclib

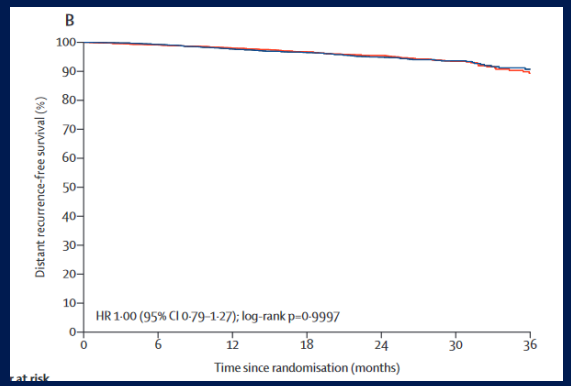




Palbociclib x1y
No pCR after NACT CPS-EG >3 or >2 ypN+
Discontinuation rate 20%
Median follow-up 42.8m
No difference Ki67 (post chemo <15 or >15%)
- Ki67 <15% roughly 75% both arms

PALLAS: adjuvant palbociclib





Palbociclib x2y
Stage II/III
Discontinuation rate 42%
Median follow-up 23.7m
No difference by grade
Ki67 not assessed

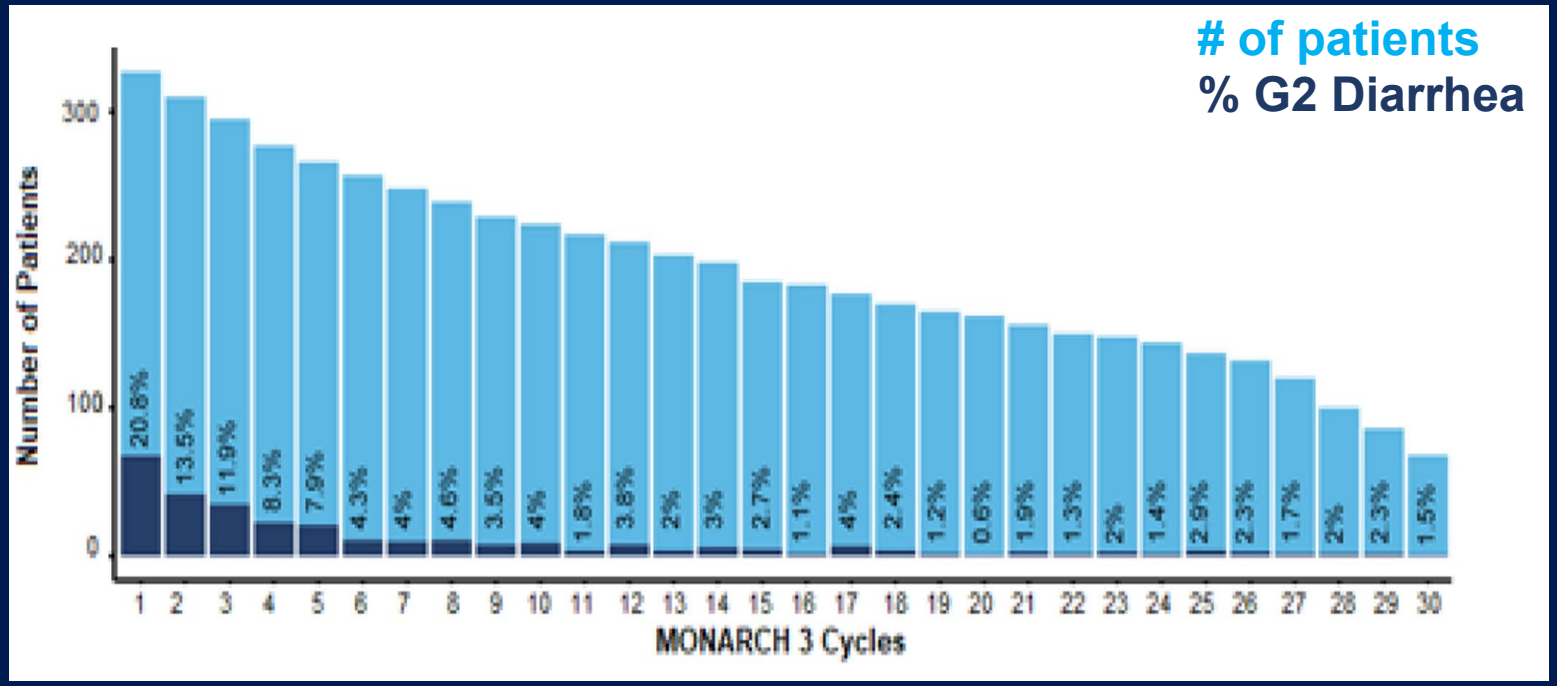
MonarchE
Slightly higher risk population
Lower discontinuation rate?
Continuous dosing, CDK4>CDK6

Mayer Lancet Onc 2021
Loibl JCO 2021

Adjuvant abemaciclib toxicity considerations

- 6.5% versus 1.1% of patients discontinued for AEs
- Patient time: lab monitoring, time, additional visits
- Rare serious side effects

Diarrhea – Monarch3: abemaciclib + AI



70-75% of patients required loperamide

Rugo The Oncologist 2020

MonarchE: Adverse events

Supplementary Table S4. Safety data in safety population at AFU1

≥10% in either arm	Abemaciclib+ ETN=2791, n (%)			ET alone N=2800, n (%)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Additional adverse events of interest						
Venous thromboembolic event[d]	71 (2.5%)	32 (1.1%)	6 (0.2%)	17 (0.6%)	7 (0.3%)	0[a]
PE	28 (1.0%)	24 (0.9%)	3 (0.1%)	4 (0.1%)	3 (0.1%)	0[a]
Interstitial lung disease[e]	89 (3.2%)	10 (0.4%)	0[b]	37 (1.3%)	1 (0.0%)	0
Serious adverse events						
Any SAEs	424 (15.2%)			247 (8.8%)		

European Journal of Haematology

ORIGINAL ARTICLE | Full Access

CDK 4/6 inhibitors are associated with a high incidence of thrombotic events in women with breast cancer in real-world practice

Malinda T. West, Claire E. Smith, Andy Kaempf, Tia C. L. Kohs, Ramin Amirsoltani, Jessica Ribkoff, Josh Lee Choung, Alison Palumbo, Zahi Mitri, Joseph J. Shatzel

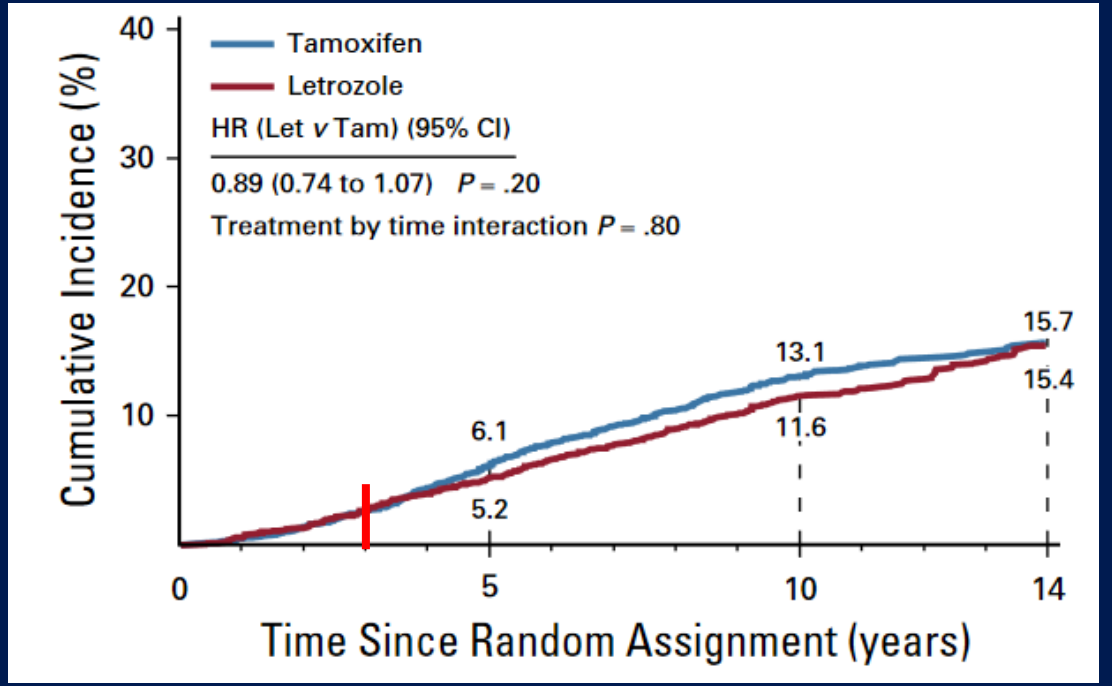
First published: 02 February 2021 | https://doi.org/10.1111/ejh.13590 | Citations: 6

Harbeck Annals of Onc 2021
West Eur J Haematology 2021

Adjuvant CDK4/6 inhibitor summary

- **Abemaciclib approved LN+ & Ki67 ≥ 20%, not anatomically high-risk**
  - Benefit not restricted to high Ki67 (similar hazard rates)
  - FDA weighed in immature OS data into decision (no difference in OS in the ITT)
  - Reliability of Ki67
- **Waiting for long term follow-up**
- **Will the benefit be sustained?**
- **Can cytostatic therapy can do any more than delay an inevitable relapse?**
- **Added toxicity**
- **Patient selection?**

Breast cancer mortality BIG-1-98



Ruhstaller JCO 2018

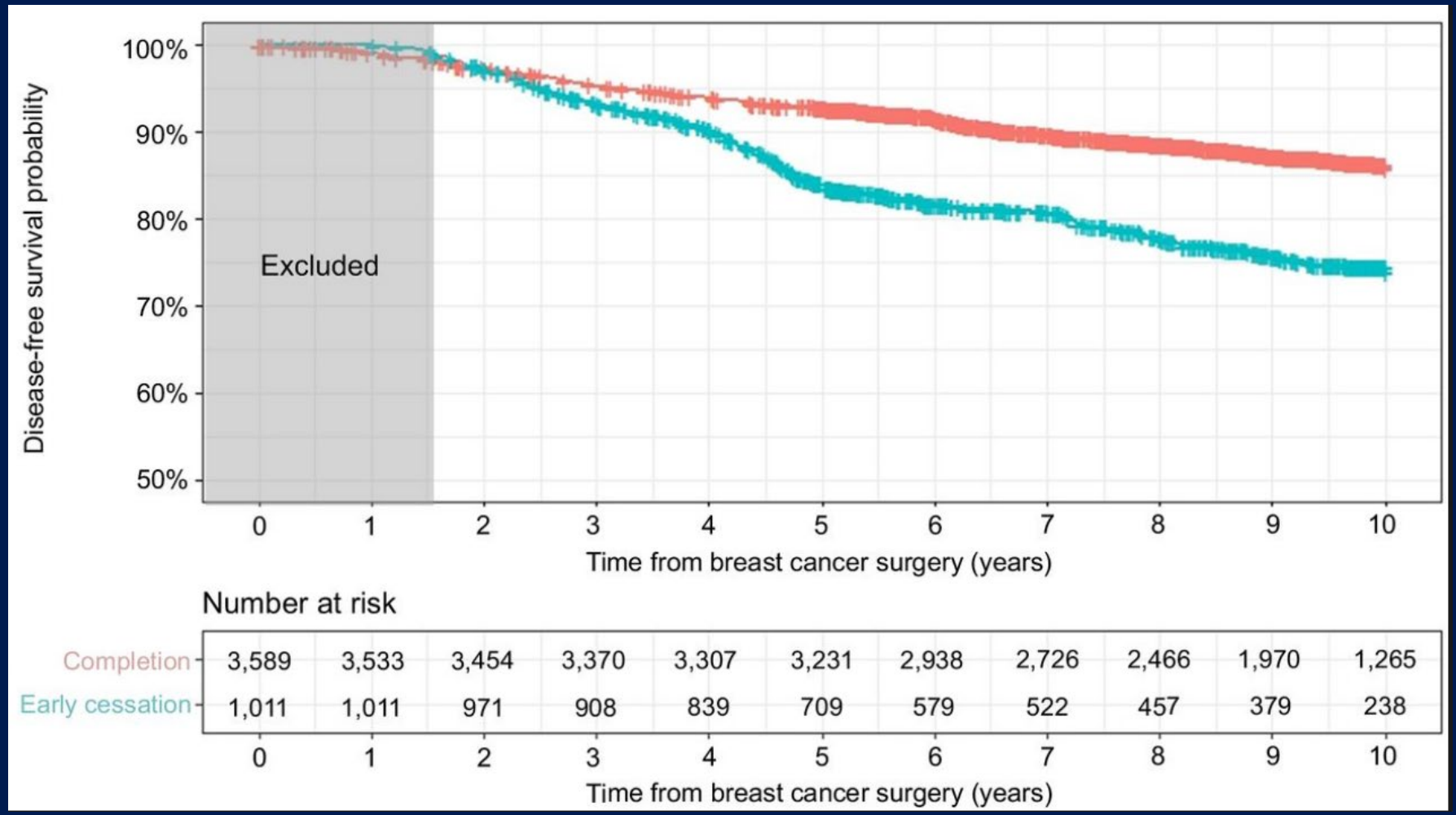
DARE Trial

Phase II trial of ctDNA guided adjuvant therapy for high risk stage II-III ER+, HER2- breast cancer

Intolerance to adjuvant endocrine therapy and outcomes

In real world 20% stop within 1 year and 30-60% stop before 5 years

Early cessation (within 6m) versus completion

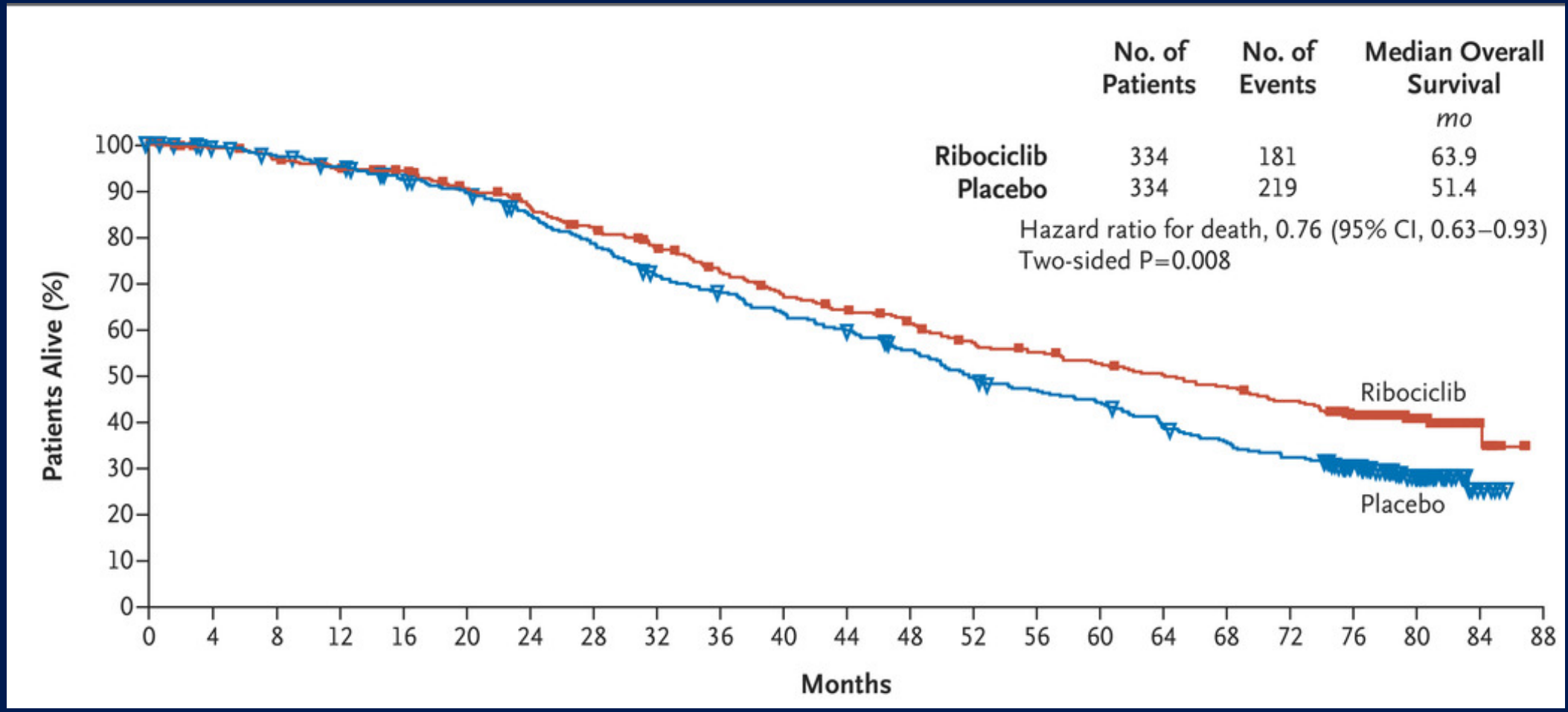


Collin CCR 2021

Ribociclib overall survival benefit

Monaleesa-2

Monaleesa-2: Postmenopausal
1L Ribociclib + letrozole



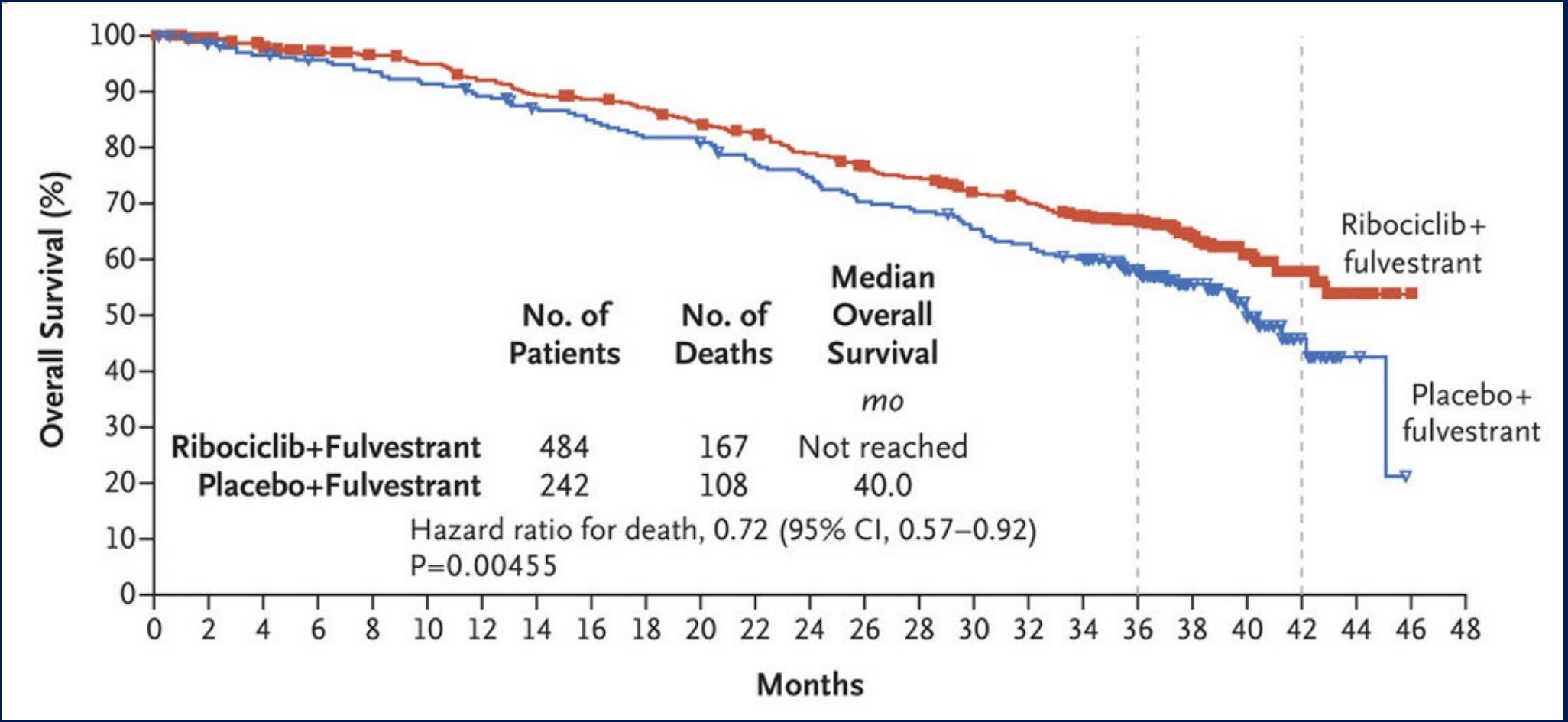
Δ +13m

Maintained across bone-only, visceral mets, number of metastatic sites, prior chemo, prior endocrine therapy

Hortobagyi NEJM 2022

Ribociclib overall survival benefit
Monaleesa-3

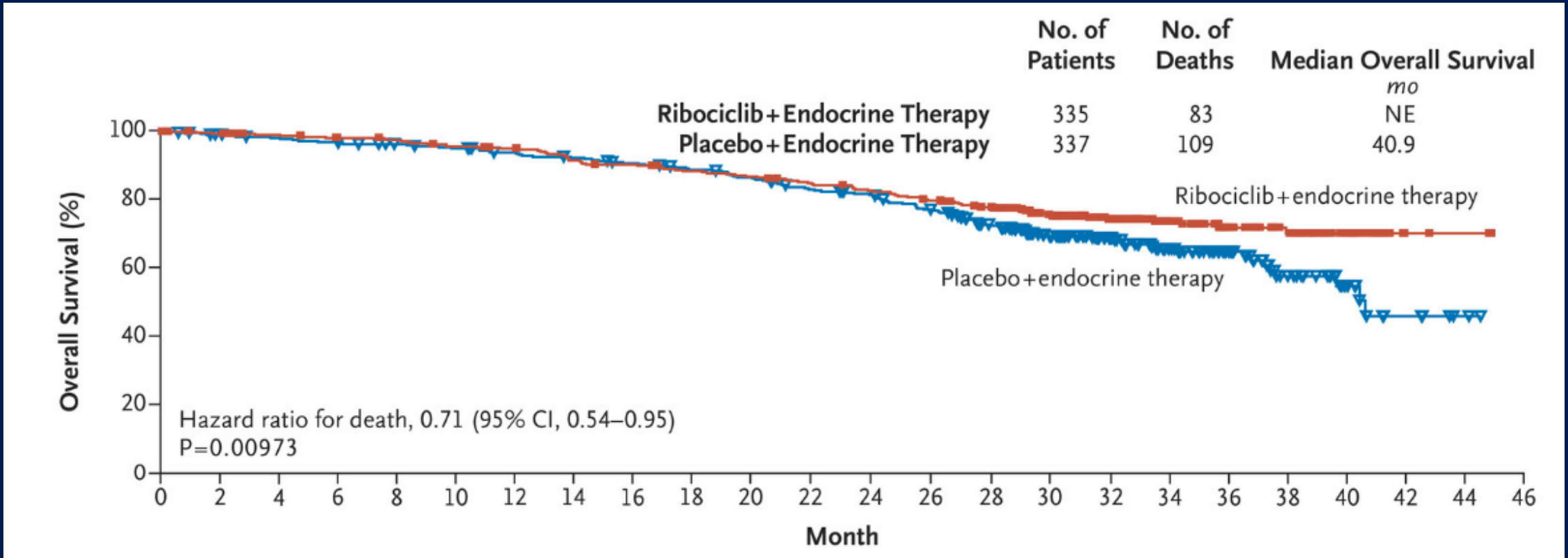
Monaleesa-3: Postmenopausal
Ribociclib + fulvestrant



Slamon NEJM 2020

Ribociclib Overall Survival Benefit
Monaleesa-7

Monaleesa-7: Premenopausal
Ribociclib + TAM or AI/OFS



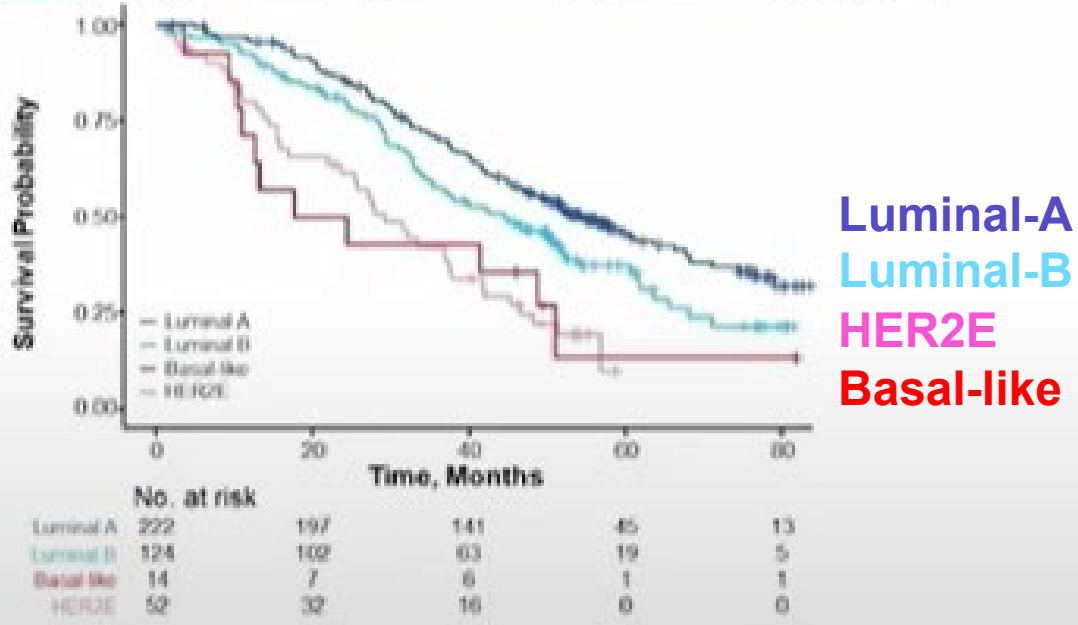
Im NEJM 2019

Ribociclib OS benefit by intrinsic subtype

Pooled analysis Monaleesa -2, -3, 7

Placebo + ET

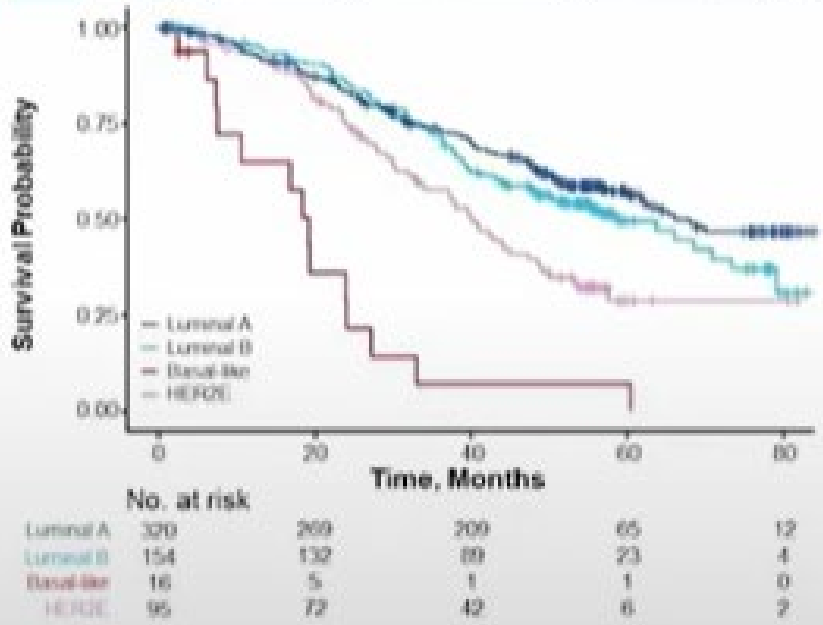
	n (%)	Events, n	OS, median, mo	95% CI
Luminal A	222 (54)	122	54.6	48.3-66.2
Luminal B	124 (30)	79	44.9	35.5-52.6
HER2E	52 (13)	39	29.4	23.9-42.0
Basal-like	14 (3)	11	21.2	12.8-NR



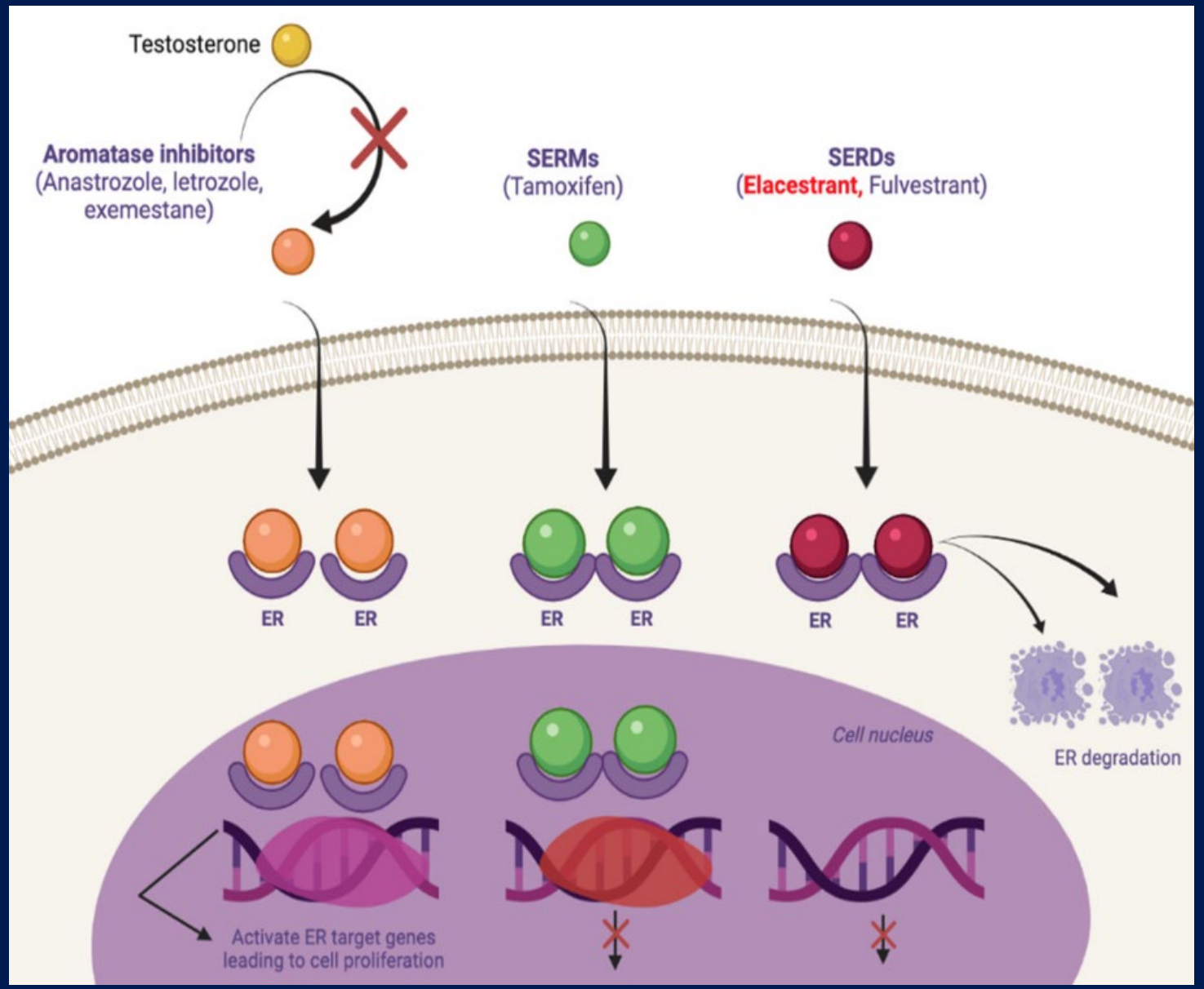
Luminal-A
Luminal-B
HER2E
Basal-like

Ribociclib + ET

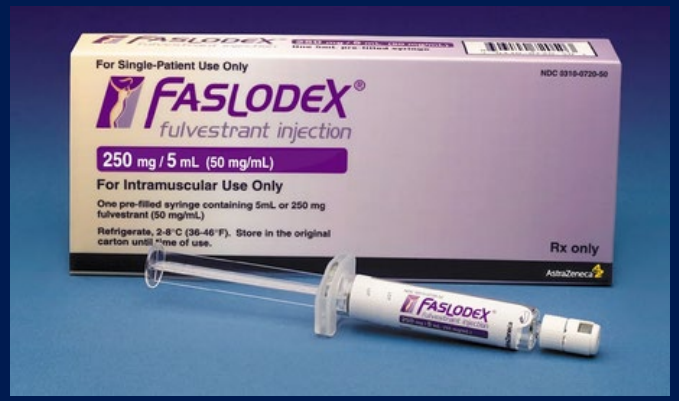
	n (%)	Events, n	OS, median, mo	95% CI
Luminal A	320 (55)	135	68.0	61.5-NR
Luminal B	154 (26)	75	58.8	48.3-79.2
HER2E	95 (16)	59	40.3	33.4-49.0
Basal-like	16 (3)	14	19.4	10.7-33.2



Oral selective estrogen receptor degraders



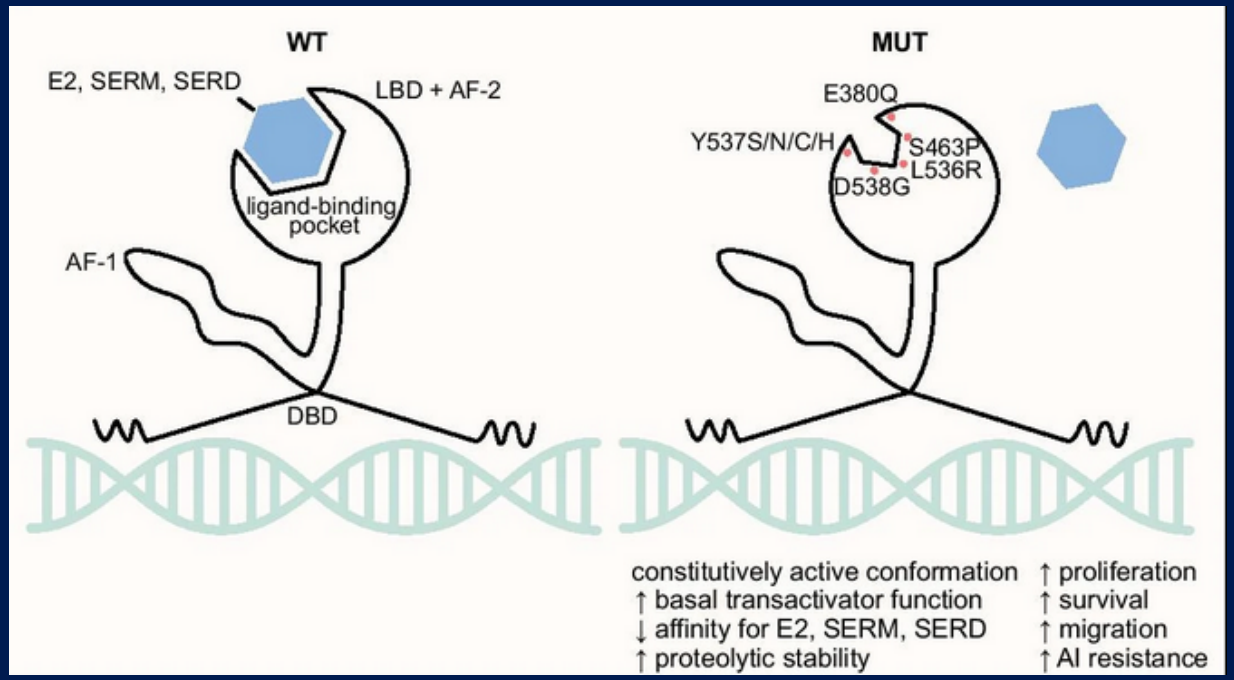
Fulvestrant



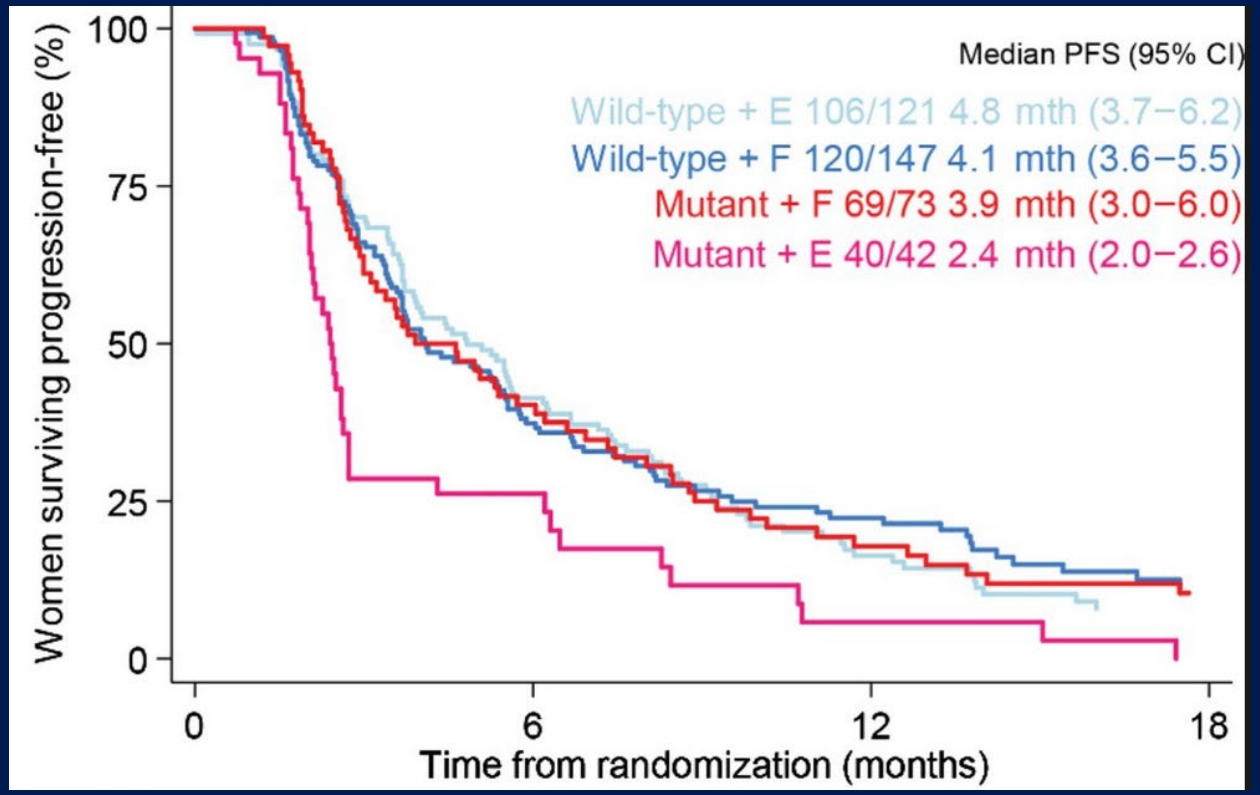
Hernando In J Mol Sci 2021

ESR1-mutations: resistance to aromatase inhibitors

ESR1-mt, incidence 20-40% advanced disease



Combined analysis SoFEA/EFECT by ESR1
Exemestane vs fulvestrant

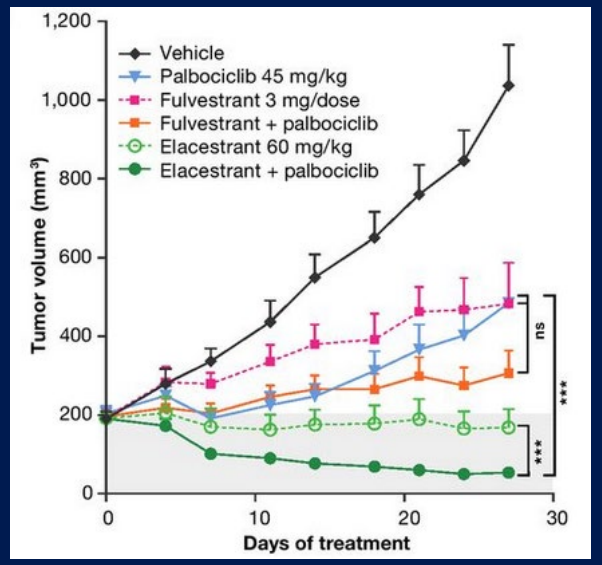


Brett Br Ca Res 2021
Turner CCR 2020

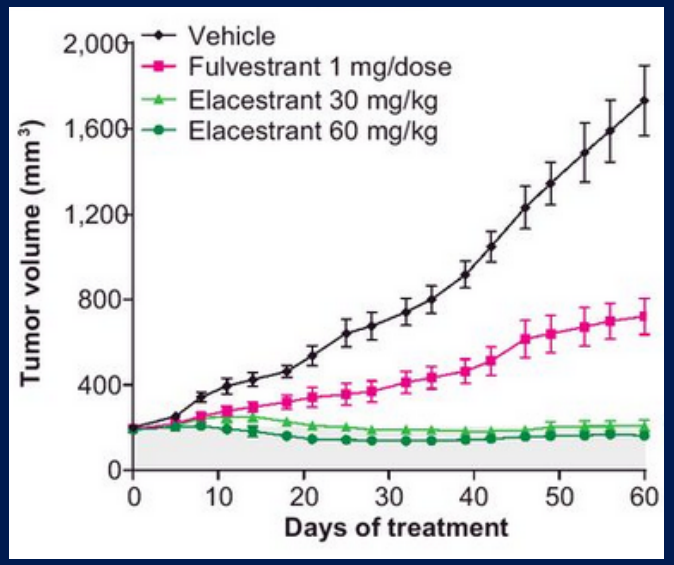
Elacestrant: oral selective estrogen receptor degrader

In vivo efficacy

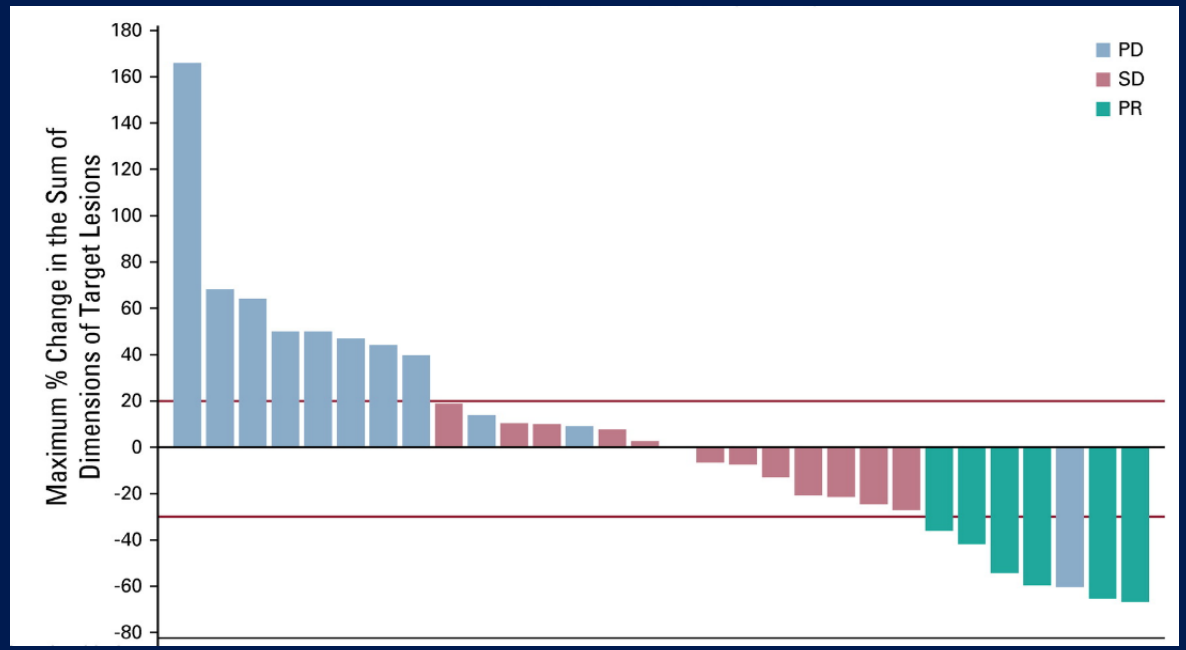
ESR1-wt



ESR1-mt



Phase 1



Bihani CCR 2017
Bardia JCO 2021

EMERALD: P3 Elacestrant vs SOC for ER+/HER2- advanced breast cancer

N = 477

HR+ metastatic postmenopausal

Elacestrant
400mg PO daily

SOC: fulvestrant or AI

(70% received fulvestrant)

Inclusion
1-2 L of endocrine therapy
Prior tx with CDK4/6i
≤ 1L of chemo

Co-Primary: PFS ESR1-mt
PFS in all patients
(ESR1-mt by ctDNA Guardant360)

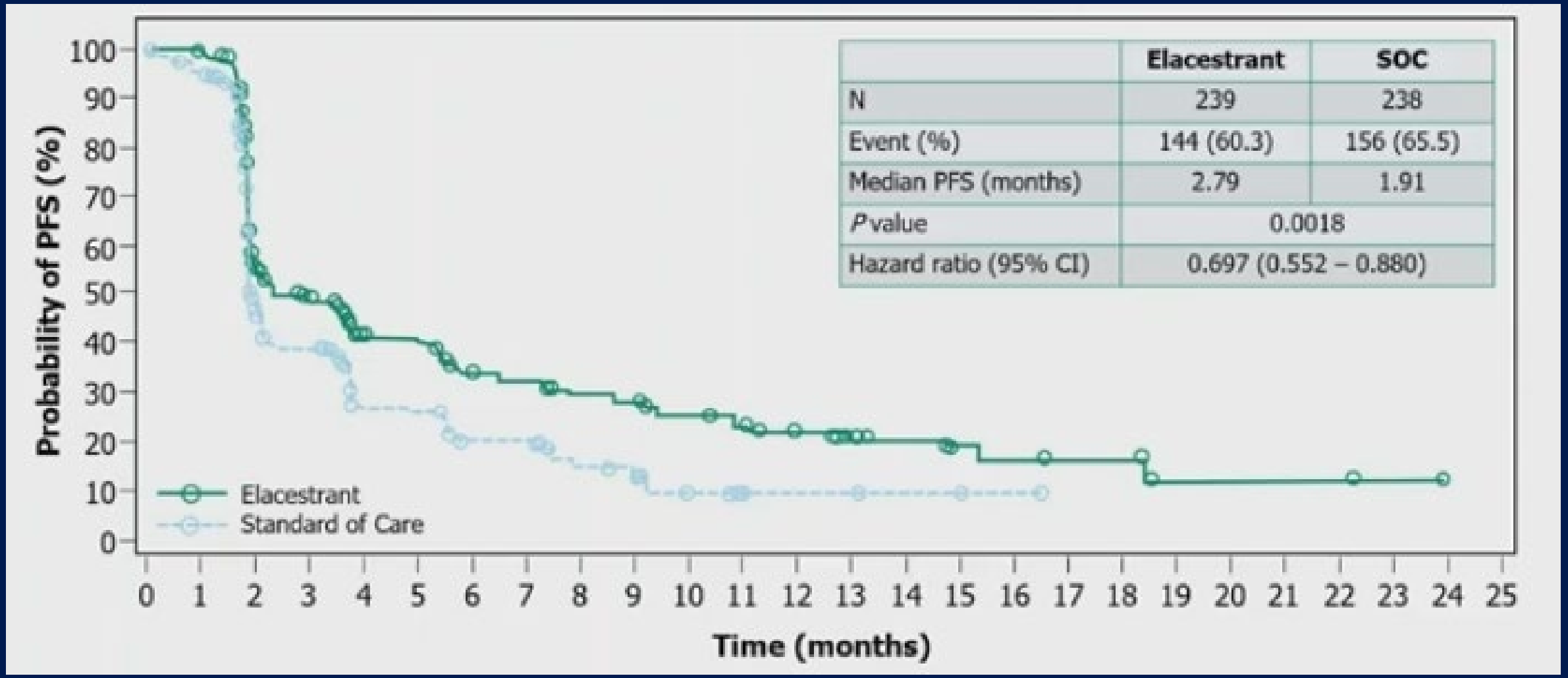
EMERALD: Demographics and characteristics

Parameter	Elacestrant		SOC	
	All (N=239)	*mESR1* (N=115)	All (N=238)	*mESR1* (N=113)
Visceral metastasis*, n (%)	163 (68.2)	81 (70.4)	168 (70.6)	83 (73.5)
Bone-only disease, n (%)	38 (15.9)	14 (12.2)	29 (12.2)	14 (12.4)
Prior adjuvant therapy, n (%)	158 (66.1)	62 (53.9)	141 (59.2)	65 (57.5)
Number of prior lines of endocrine therapy,** n (%)				
1	129 (54.0)	73 (63.5)	141 (59.2)	69 (61.1)
2	110 (46.0)	42 (36.5)	97 (40.8)	44 (38.9)
Number of prior lines of chemotherapy,** n (%)				
0	191 (79.9)	89 (77.4)	180 (75.6)	81 (71.7)
1	48 (20.1)	26 (22.6)	58 (24.4)	32 (28.3)

Majority of patients had visceral disease
50% received 1L ET
20% received 1L chemotherapy

Bardia SABCS 2021 abs GS2-02

EMERALD: PFS ITT population (ESR-wt + ESR-mt)

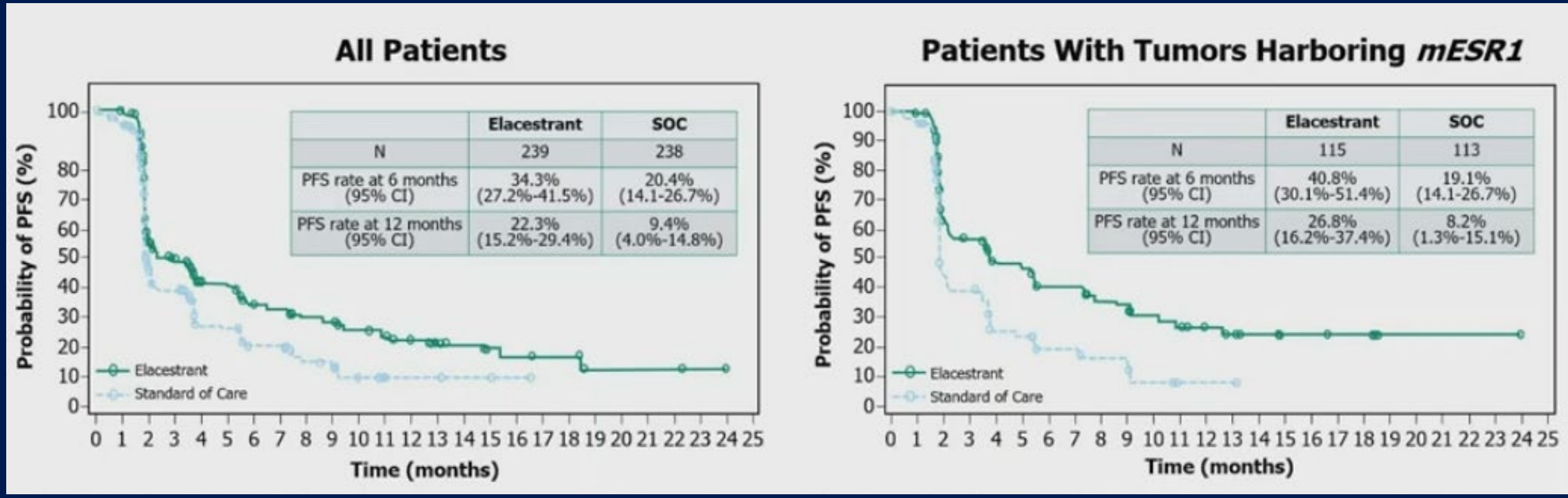


	Elacestrant	SOC
N	239	238
Event (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.79	1.91
P value	0.0018	
Hazard ratio (95% CI)	0.697 (0.552 – 0.880)	

mPFS 2.8 versus 1.9 months

Bardia SABCS 2021 abs GS2-02

EMERALD: PFS all patients and mESR1 by PFS 6/12m

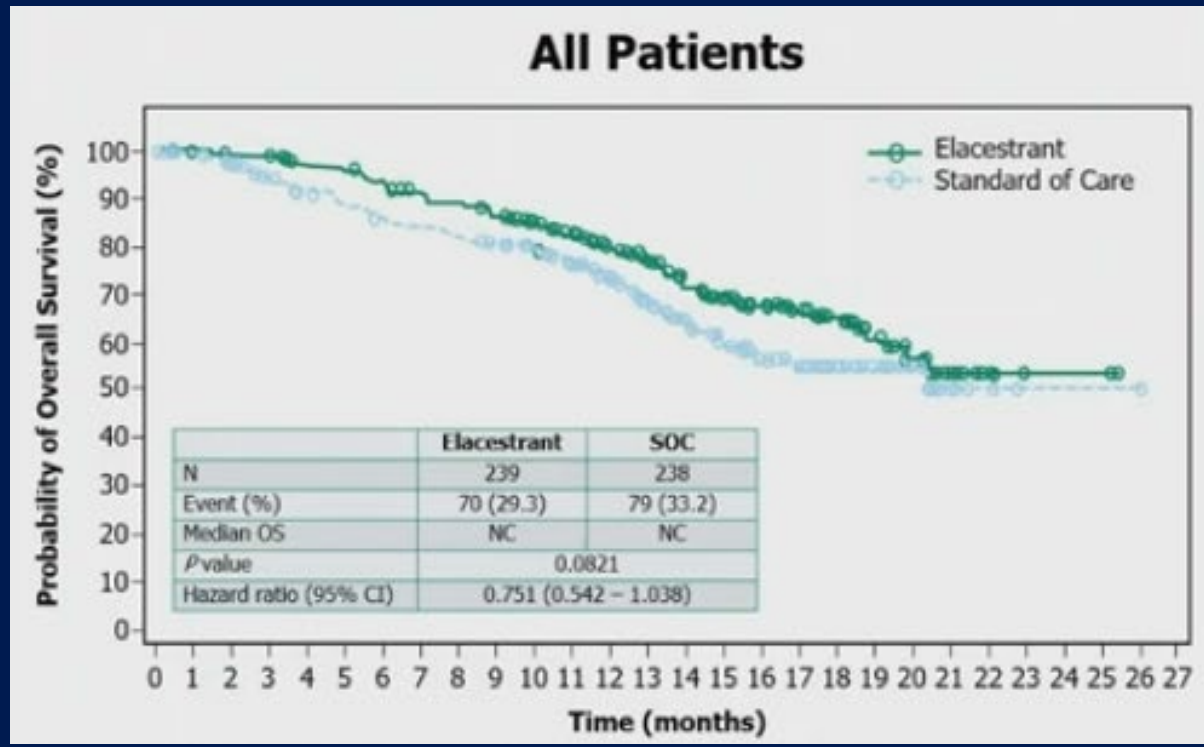


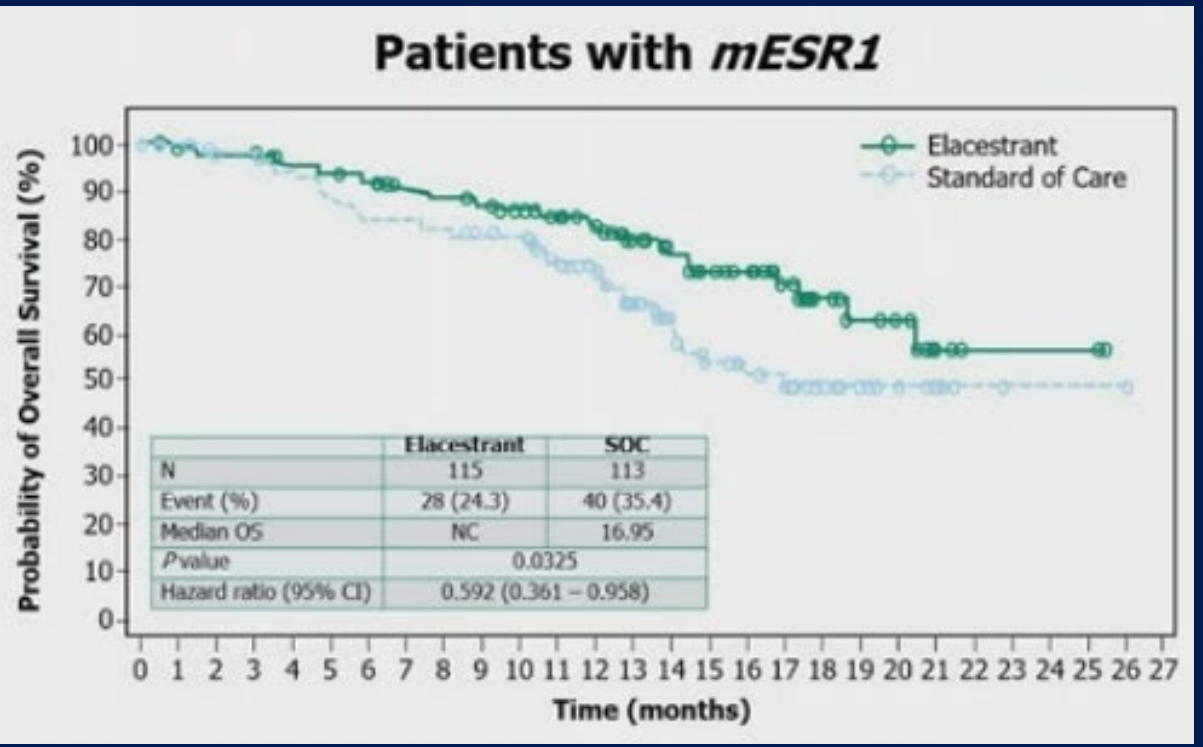
6m: 34% vs 20% Δ +14%
12m: 22% vs 9% Δ +13%

6m: 41% vs 19% Δ +22%
12m: 27% vs 8% Δ +19%

Bardia SABCS 2021 abs GS2-02

EMERALD: Overall survival interim analysis (mature late 2022/early 2023)





Trend towards OS benefit

Bardia SABCS 2021 abs GS2-02

EMERALD: Adverse events

	Elacestrant		Fulvestrant/AI	
	All Grades	G3/4	All Grades	G3/4
Nausea	35%	2.5%	19%	1%
Vomiting	19%	1%	8.8%	-
Dyspepsia	10%	-	2.6%	-
Dec appetite	15%	<1%	9%	<1%
Constipation	12%	-	7%	-
Back pain	14%	2.5%	9.6%	1%

Roughly same:
Fatigue, arthralgias, diarrhea, AST/ALT elevations, hot flushes, headache

EMERALD: Conclusions

- 40-50% of patients will progress within 2 months
- Activity in ESR1-mutants
- Oral SERD >> versus fulvestrant
- Will elacestrant replace AI in early stage or 1L setting?

Novel estrogen degraders, modulators in development

Open at OHSU:

Neoadjuvant (ISPY2)
- Amcenestrant

Metastatic
- Camizestrant (SERENA4)
- OP-1250 (Olema)

Drug; Class	ESR1-MUT cells/PDX	Completed trials	Current trials
lasofoxifene; SERM	Drug effective; no resistance	PEARL Phase 3 trial for osteoporosis showed ↓ breast cancer incidence *Toxicities* arthralgia (25%), hot flashes (13%), VTE (1.5% over 5Y)	*Phase 2* NCT04432454 (ELAINE-2): lasofoxifene + abemaciclib for ESR1-MUT and progressed on ET NCT03781063 (ELAINE): lasofoxifene versus fulvestrant for ESR1-MUT and progressed on AI + CDK4/6i
bazedoxifene; SERM/SERD	Drug effective; relative resistance	FDA-approved, EMA-approved for postmenopausal osteoporosis/hot flashes *Toxicities* hot flashes (13%), arthralgia (11%), VTE (0.5% over 3Y)	*Phase 2* NCT02448771: bazedoxifene + palbociclib for progressed on ET
H3B-6545; SERCA	Drug effective; relative resistance	*Phase 1* NCT03250676: H3B-6545 progressed on ET + CDK4/6i: 47% stable disease, 9% partial response *Toxicities* Sinus bradycardia, diarrhea, nausea, fatigue, hot flashes, anemia	*Phase 1* NCT04288089: H3B-6545 + palbociclib for progressed on ET *Phase 2* NCT03250676: H3B-6545 for progressed on ET + CDK4/6i
Elacestrant; SERD			
Amcenestrant (SAR439859); SERD	relative resistance	NCT03284957 (AMEERA-1): amcenestrant + palbociclib or alpelisib progressed on ET, ESR1-WT: 24-wk CBR 37% progressed on ET, ESR1-MUT: 24-wk CBR 32% *Toxicities* Nausea (18% G1-2), fatigue (18% G1-2), hot flashes (10% G1-2)	NCT04059484 (AMEERA-3): amcenestrant versus AI/fulvestrant/tamoxifen for progressed on ET *Phase 3* NCT04478266 (AMEERA-5): amcenestrant + palbociclib versus letrozole + palbociclib for treatment-naïve
camizestrant (AZD9833); SERD	Drug effective; no resistance	*Phase 1* NCT03616587 (SERENA-1): camizestrant progressed on ET (82% fulvestrant, 68% CDK4/6i): ORR 14%, 24-wk CBR 67% *Toxicities* Visual disturbances (51% G1-2, 2% G3), sinus bradycardia (45% G1-2), nausea (18% G1-2), fatigue (13% G1-2), dizziness (8% G1-2, 2% G3)	*Phase 2* NCT04214288 (SERENA-2): camizestrant versus fulvestrant for progressed on ET NCT04588298 (SERENA-3): camizestrant versus fulvestrant for treatment-naïve *Phase 3* NCT04711252 (SERENA-4): camizestrant + palbociclib versus anastrozole + palbociclib for treatment-naïve
giredestrant (GDC-9545); SERD	Drug effective	*Phase 1* NCT03332797: giredestrant progressed on ET: ORR 11%, 24-wk CBR 44% *Toxicities* Fatigue (21% G1-2), nausea (21% G1-2), hot flashes (17% G1-2), arthralgia (17% G1-2), diarrhea (17% G1-2)	*Phase 2* NCT04576455 (acelERA): giredestrant versus fulvestrant/AI for progressed on ET *Phase 3* NCT04546009: giredestrant + palbociclib versus letrozole + palbociclib for treatment-naïve
rintodestrant (G1T48); SERD	Drug effective; no resistance	-	*Phase 1* NCT03455270: rintodestrant + palbociclib for progressed on ET
Zn-c5; SERD	Drug effective	-	*Phase 1* NCT04176747: ZN-c5 NCT04514159: ZN-c5 + abemaciclib NCT03560531: ZN-c5 + palbociclib
LSZ102; SERD	Not reported	-	*Phase 1* NCT02734615: LSZ102 + ribociclib or alpelisib for ET-resistant
ARV-471; SERD (PROTAC)	Drug effective	-	*Phase 2* NCT04072952: ARV-471 + palbociclib for progressed on ET
LY3484356; SERD	Not reported	-	*Phase 1* NCT04188548 (EMBER): LY3484356 + abemaciclib, everolimus, alpelisib, trastuzumab, AI in various combinations
D-0502; SERD	Drug effective	-	*Phase 1* NCT03471663: D-0502 + palbociclib for progressed on ET

13+ in development

Brett Br Ca Res 2021

Landscape of treatment for advanced HER2+ disease

First line

Docetaxel + HP
Paclitaxel + HP
Doce + Carbo+ HP

Second line

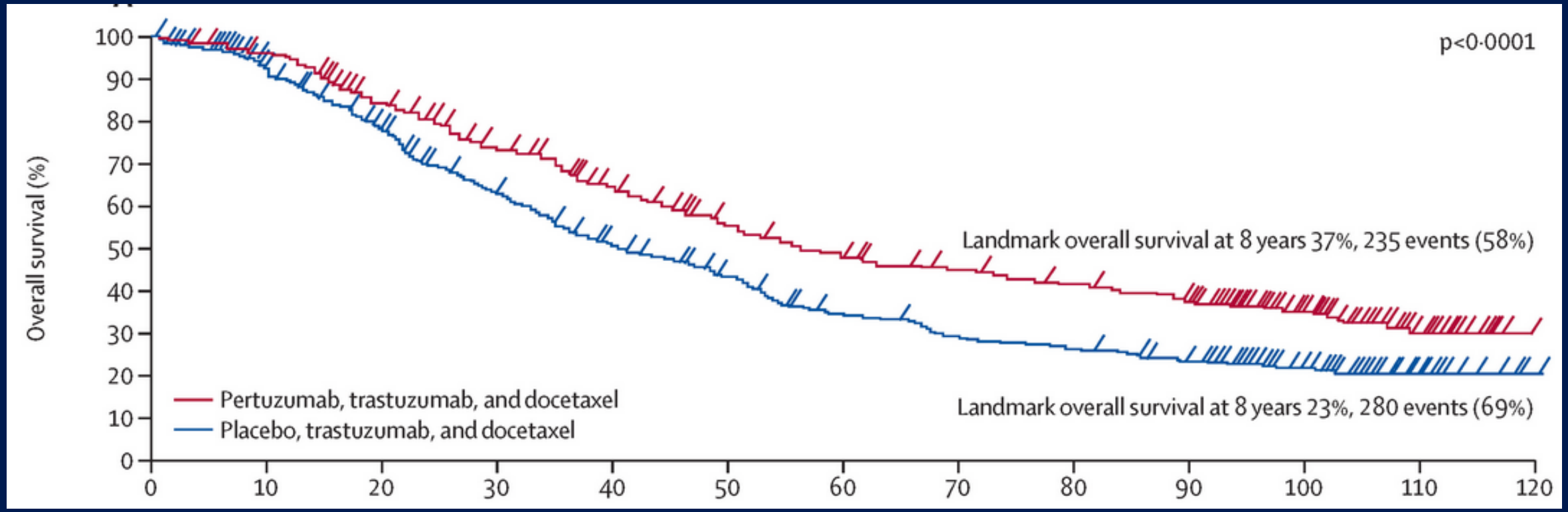
T-DM1
Trastuzumab deruxtecan
Tucatinib + trastuzumab + capecitabine

Third line

Trastuzumab deruxtecan
Tucatinib + trastuzumab + capecitabine
Neratinib + capecitabine
Lapatinib + trastuzumab +/- capecitabine
Margetuximab + chemo
Trastuzumab + chemo

Trastuzumab/Margetuximab chemo partners
- Capecitabine
- Docetaxel
- Paclitaxel +/- carboplatin
- Eribulin
- Gemcitabine
- Vinorelbine

1L THP CLEOPATRA 8yr follow-up

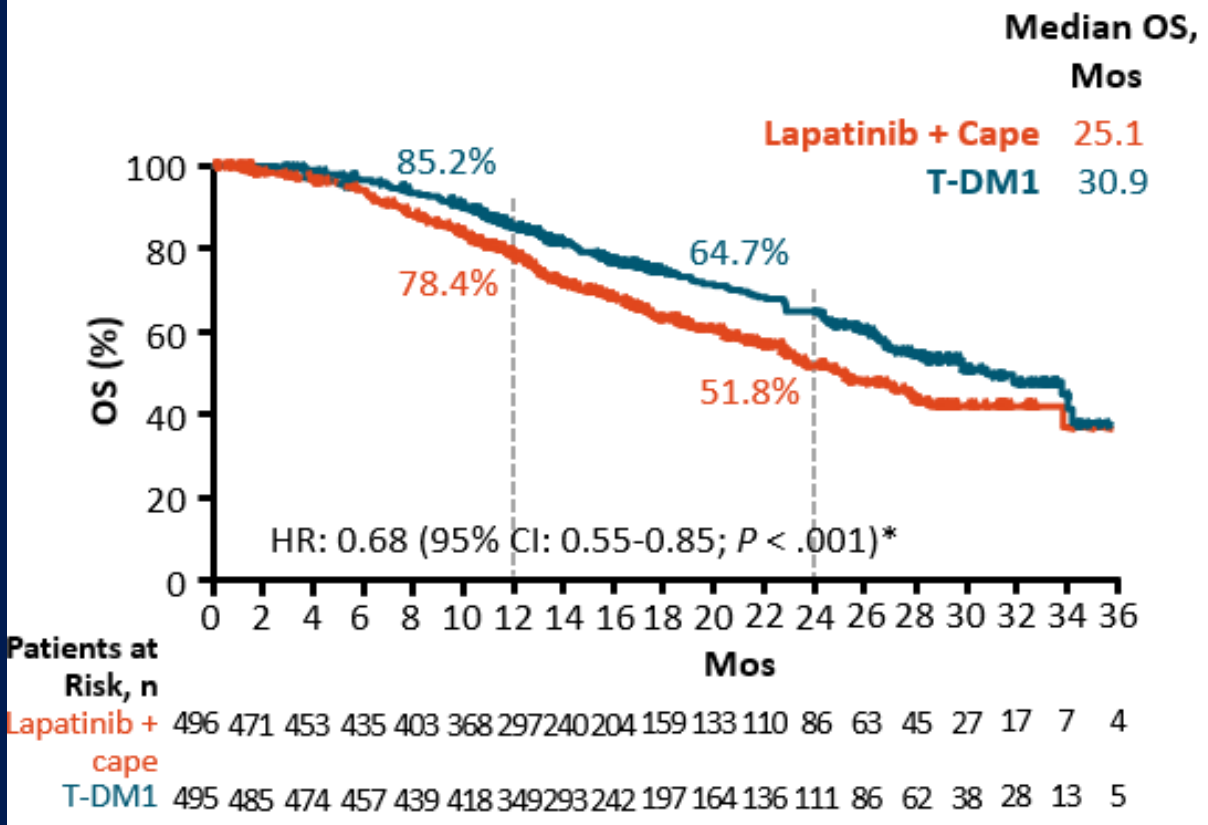


Dual blockade improved mOS by 16 months
Median OS = 4.7 years
Alive at 8y 37%

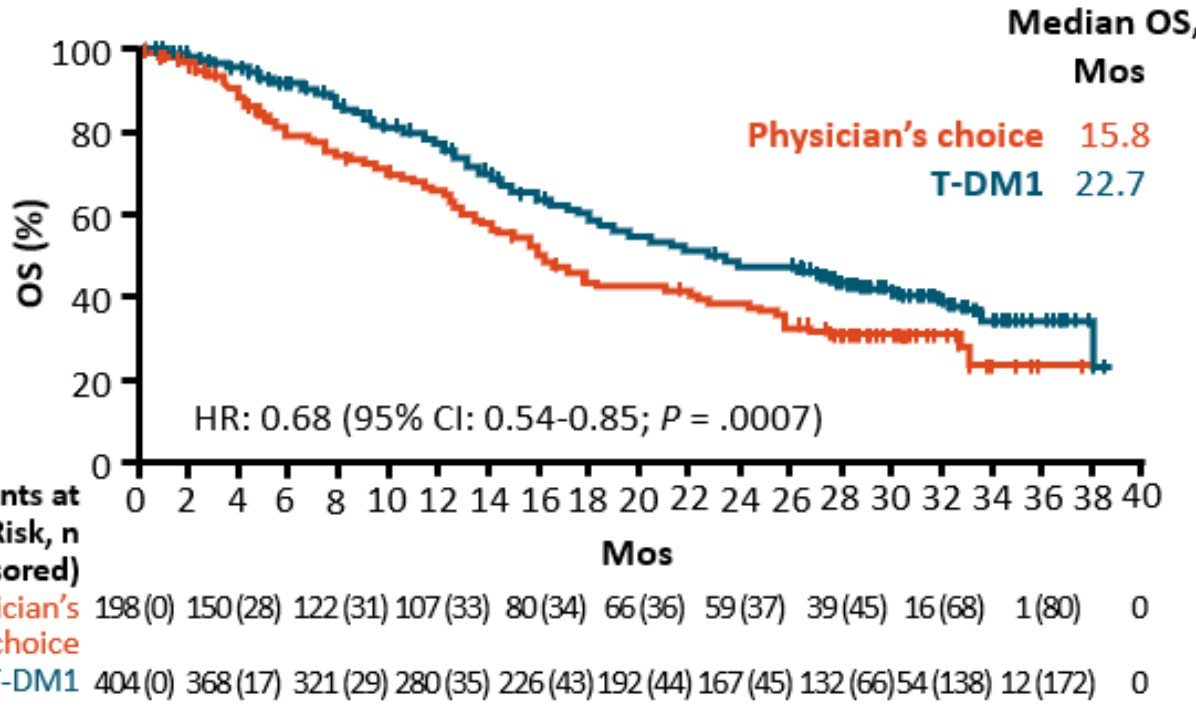
Swain Lancet Onc 2020

2L T-DM1

- **EMILIA[1]:** Randomized phase III study of lapatinib + capecitabine vs T-DM1 for HER2+ MBC with progression on trastuzumab + taxane (N = 991)

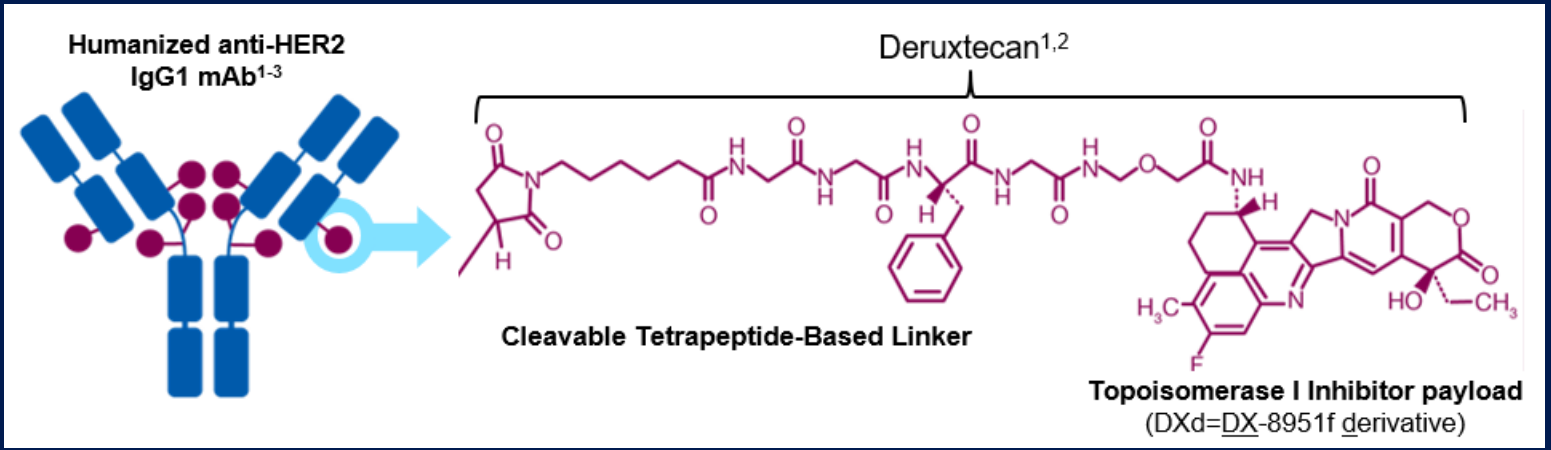


- **TH3RESA[2]:** Randomized phase III study of physician's choice vs T-DM1 for HER2+ MBC with progression on a taxane, lapatinib, and ≥ 2 HER2-targeted regimens including trastuzumab (N = 602)



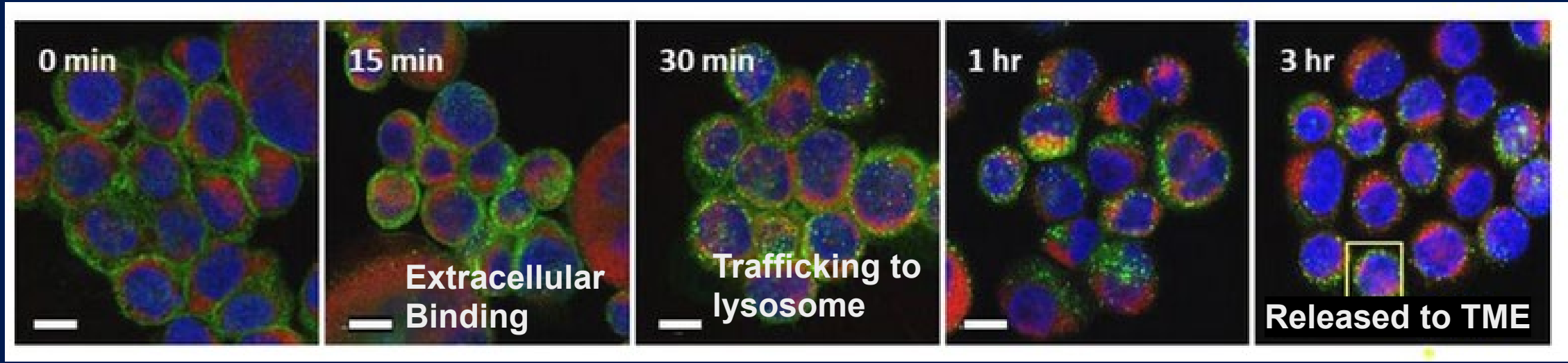
Verma NEJM 2012, Krop Lancet Oncol 2017

Trastuzumab deruxtecan (T-Dxd)



Stable linker in circulation (released in plasma 2% vs 18% TDM1)
Wider therapeutic index with lower toxicity

Fluorescence labeled- Datopotomab-DXd

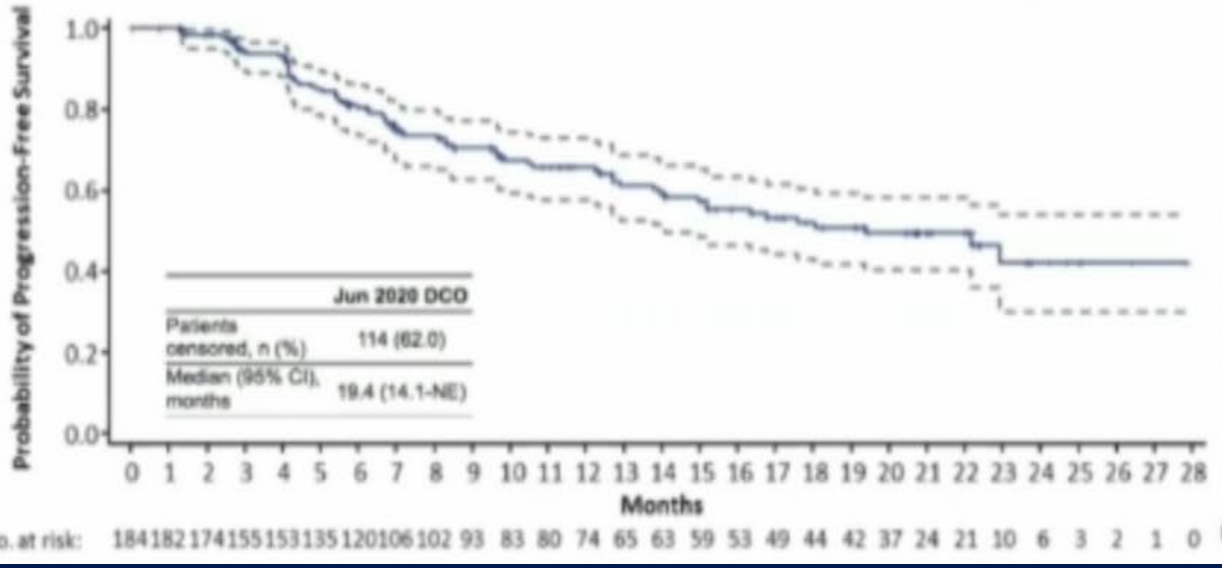


Okajima Mol Ca Ther 2021

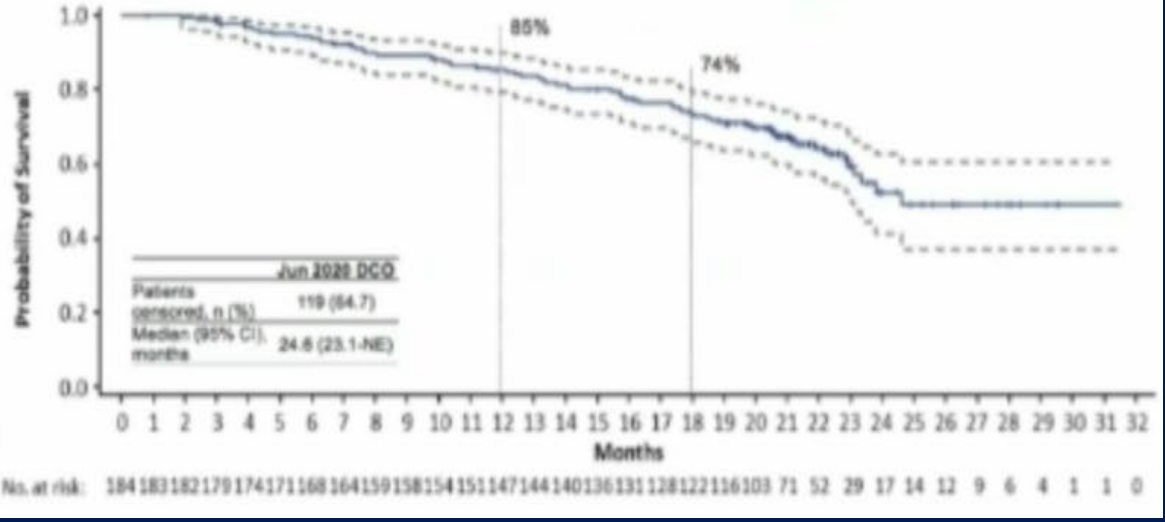
3L Trastuzumab deruxtecan (T-Dxd): DESTINY-Breast01 P2 single arm

Median follow-up 20.5 months
ORR 61.4%

Median PFS 19.4 mo (14.1 – NE)



Median OS 24.6 mo (23.1 - NE)
Only 35% of events

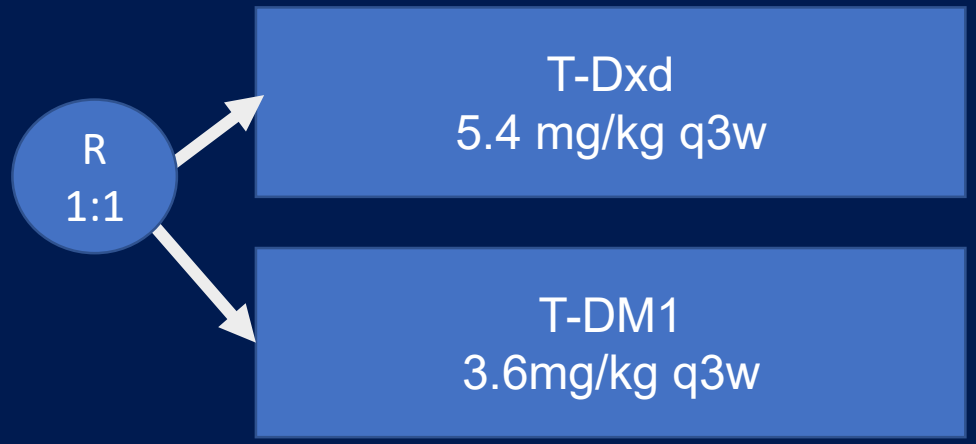


Modi NEJM 2020

2L DESTINY-Breast03: Trastuzumab deruxtecan vs TDM1

N = 524

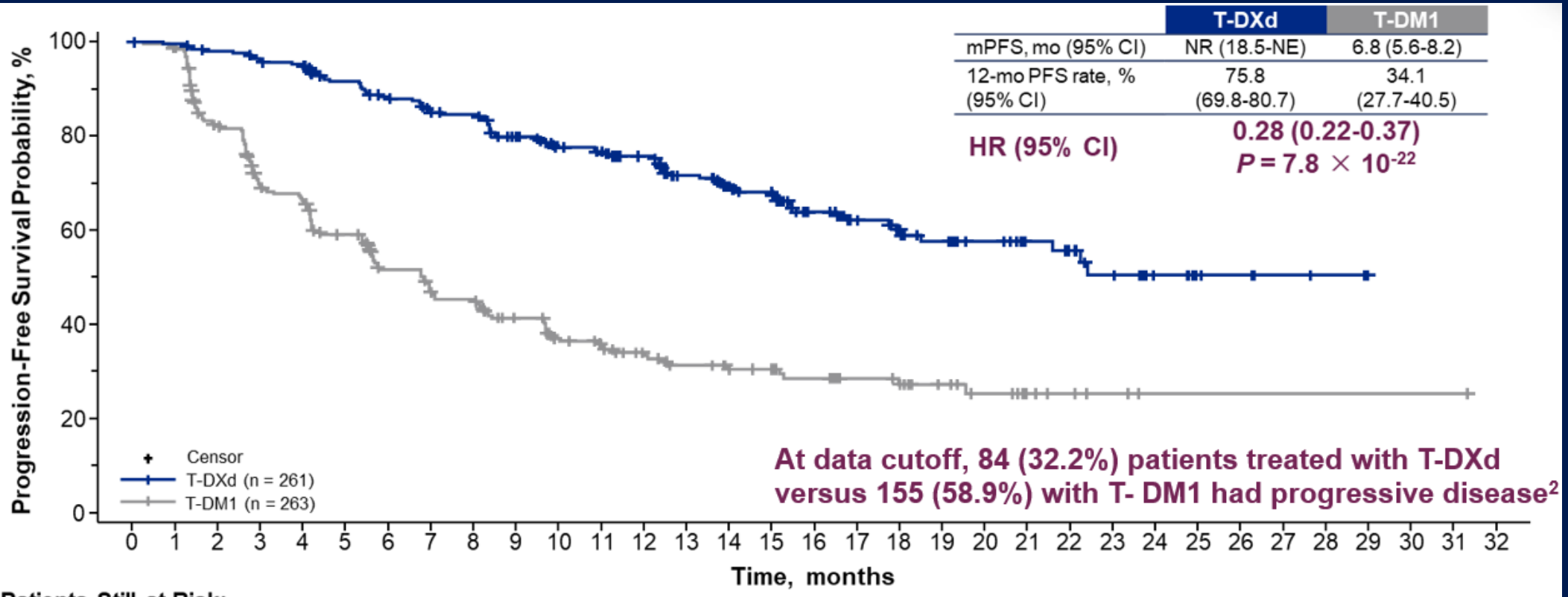
Advanced HER2+
Prior taxane + trastuzumab
Stable brain mets
No HER2 ADC <12m (TDM1)



Primary: PFS
Secondary: OS

Prior trastuzumab = 100%
Prior pertuzumab = 62%
Prior lines of therapy for metastatic dz
1 = 50%, >1 = 50%
History of brain mets 23%
Baseline brain mets: 16%

DESTINY-Breast03: Progression free survival (blinded review)



Patients Still at Risk:

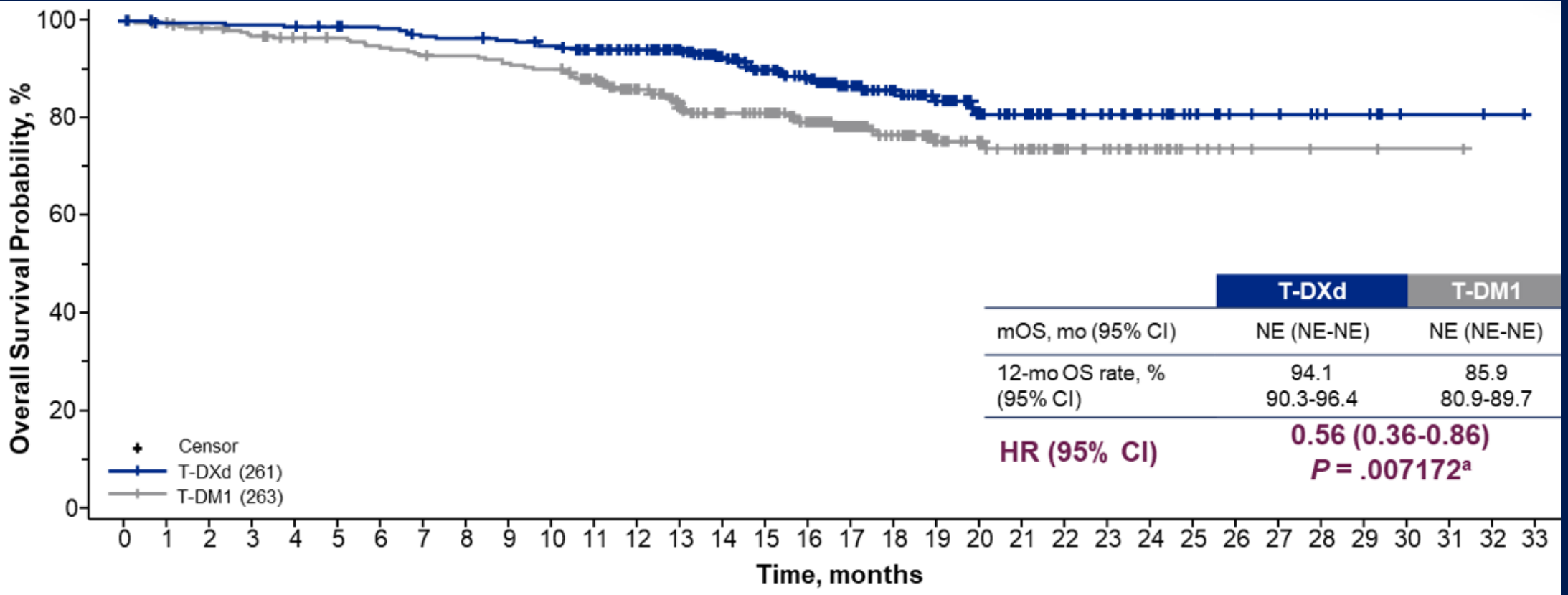
T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0			
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

BICR, blinded independent central review; CI, confidence interval; DCO, data cutoff; HR, hazard ratio; mPFS, median progression-free survival; NE, not evaluable; NR, not reached; PFS, progression-free survival; T-DM1, ado-trastuzumab emtansine; T-DXd, fam-trastuzumab deruxtecan-nxki.
Median PFS follow-up for T-DXd was 15.5 months (95% CI, 15.1-16.6) and for T-DM1 was 13.9 months (95% CI, 11.8-15.1).
1. Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 16-21, 2021. Presentation 2525. 2. Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021. Presentation GS3-01.

Daiichi-Sankyo | AstraZeneca

12m PFS
Δ +41.7m

DESTINY-Breast03: Overall survival



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 90.3-96.4	85.9 80.9-89.7
HR (95% CI)	0.56 (0.36-0.86) *P* = .007172[a]	

12m OS
Δ +8m

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

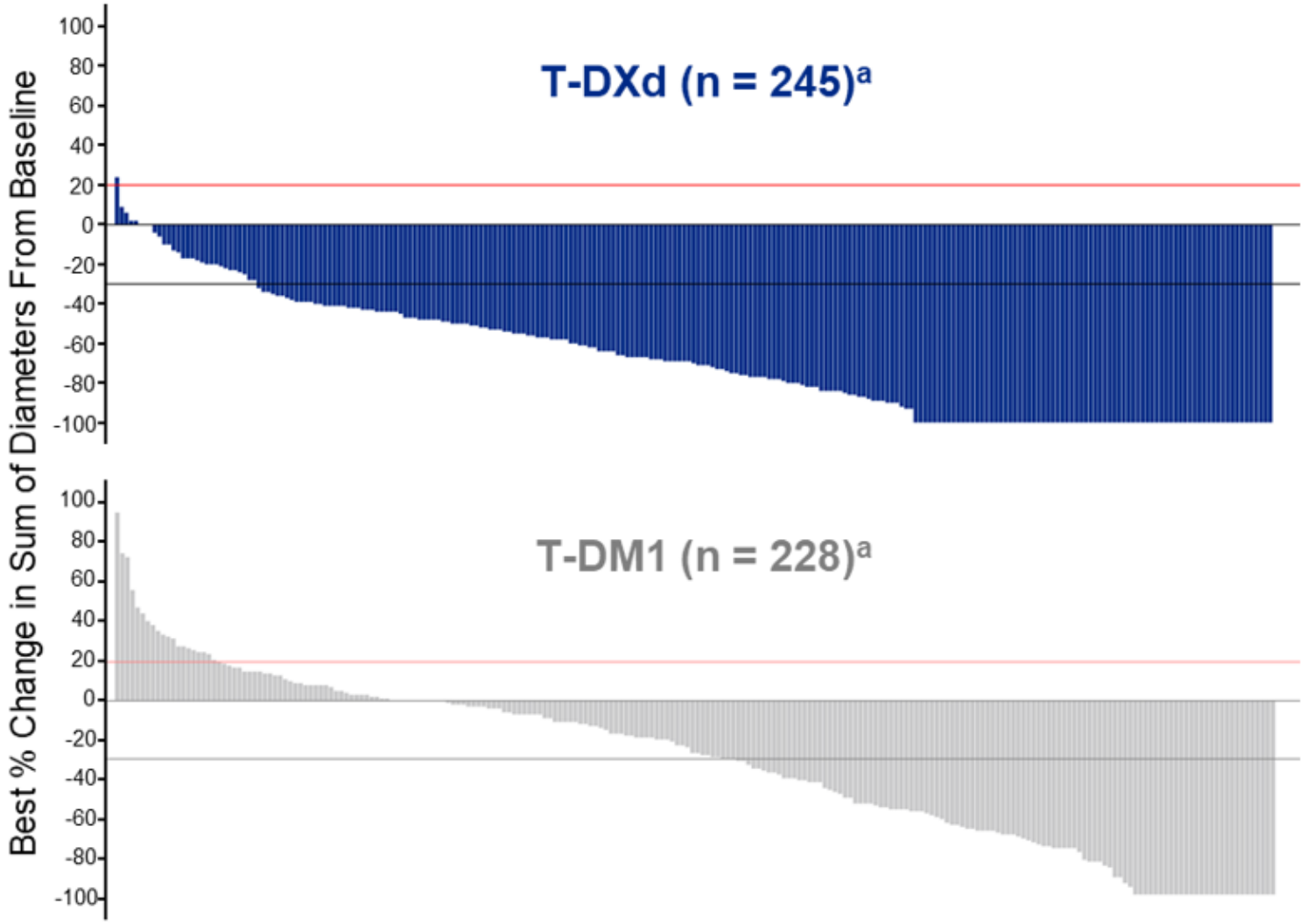
[a] *P* = .007172, but does not cross pre-specified boundary of *P* < .000265

DCO, data cutoff; HR, hazard ratio; mOS, median overall survival; NE, not evaluable; OS, overall survival; T-DM1, ado-trastuzumab emtansine; T-DXd, fam-trastuzumab deruxtecan-nxki.

Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 17-21, 2021. Presentation 2525.

Daiichi-Sankyo | AstraZeneca

DESTINY-Breast03: Confirmed best ORR



	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b]	208 **(79.7)**	90 **(34.2)**
[95% CI]	[74.3-84.4]	[28.5-40.3]
	P < .0001	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

CR, complete response; DCO, data cutoff; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, ado-trastuzumab emtansine; T-DXd, fam-trastuzumab deruxtecan-nxki.

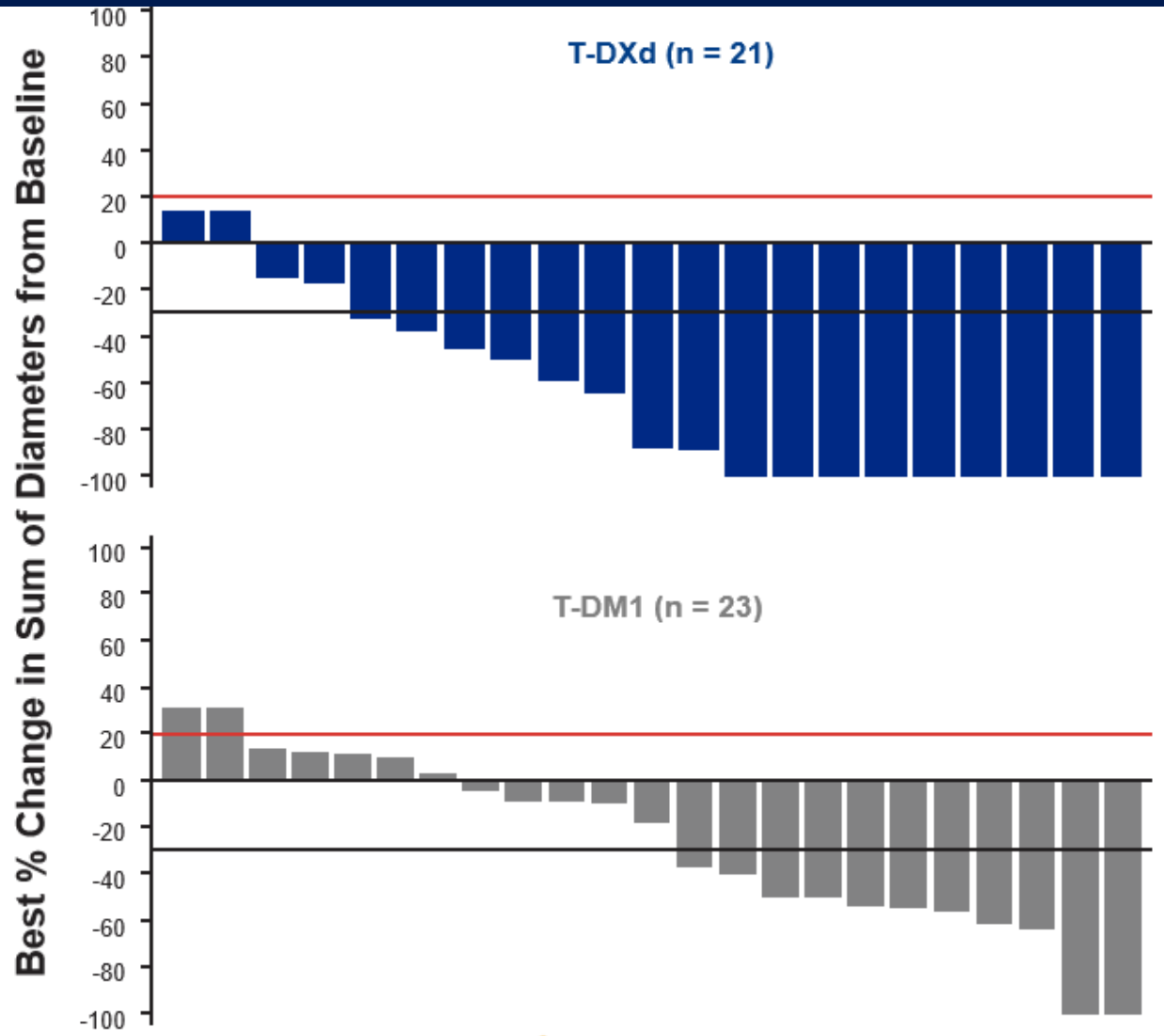
[a] Only subjects with measurable disease at baseline and at least one postbaseline target lesion assessment are included. [b] Based on BICR.

Red line at 20% indicates progressive disease; black line at -30% indicates partial response.

Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 17-21, 2021. Presentation 2525.

Daiichi-Sankyo | AstraZeneca

DESTINY-Breast03: Intracranial brain mets ORR



	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/Non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not Evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)
Patients with Objective Response of CR or PR, n	23	12

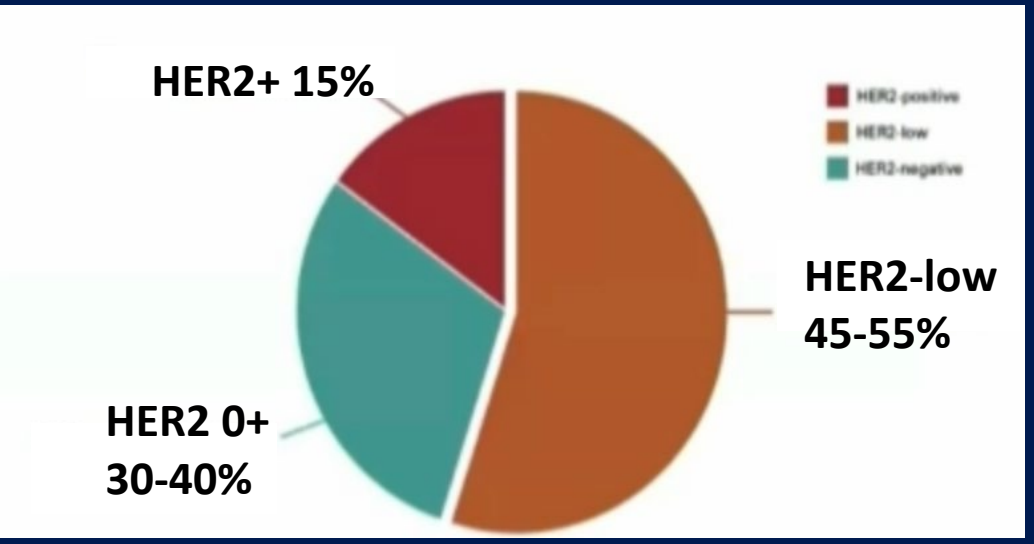
See full list of abbreviations in the speaker notes.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment.

Daiichi-Sankyo | AstraZeneca

Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021. Presentation GS3-01.

DESTINY Breast 04: T-DXd in HER2-low

Press Release February 21 2021



HER2-low
(IHC 1-2+, FISH-neg)
HR+ or HR-
1-2L prior chemo
No hx of HER2+

R
1:1

T-DXd
5.4 mg/kg q3w

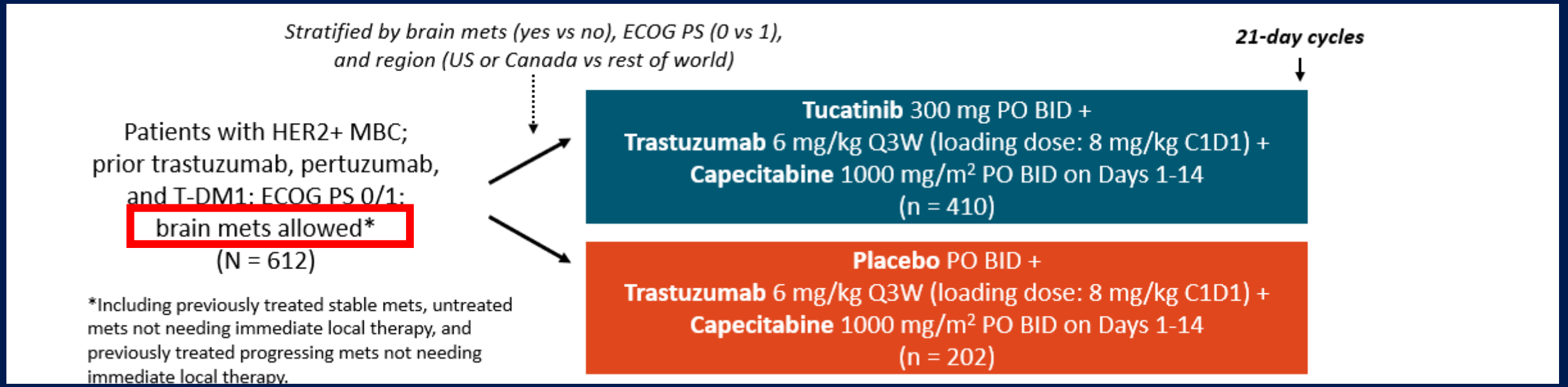
Capecitabine
Eribulin
Gemcitabine
Taxane

Endpoints met: PFS and OS (regardless of HR-status)

Schettini NPJ Breast Ca 2021

HER2CLIMB: Tucatinib + capecitabine + trastuzumab

Prior TH, T-DM1 (2-3L)



50% presence or history of brain metastases

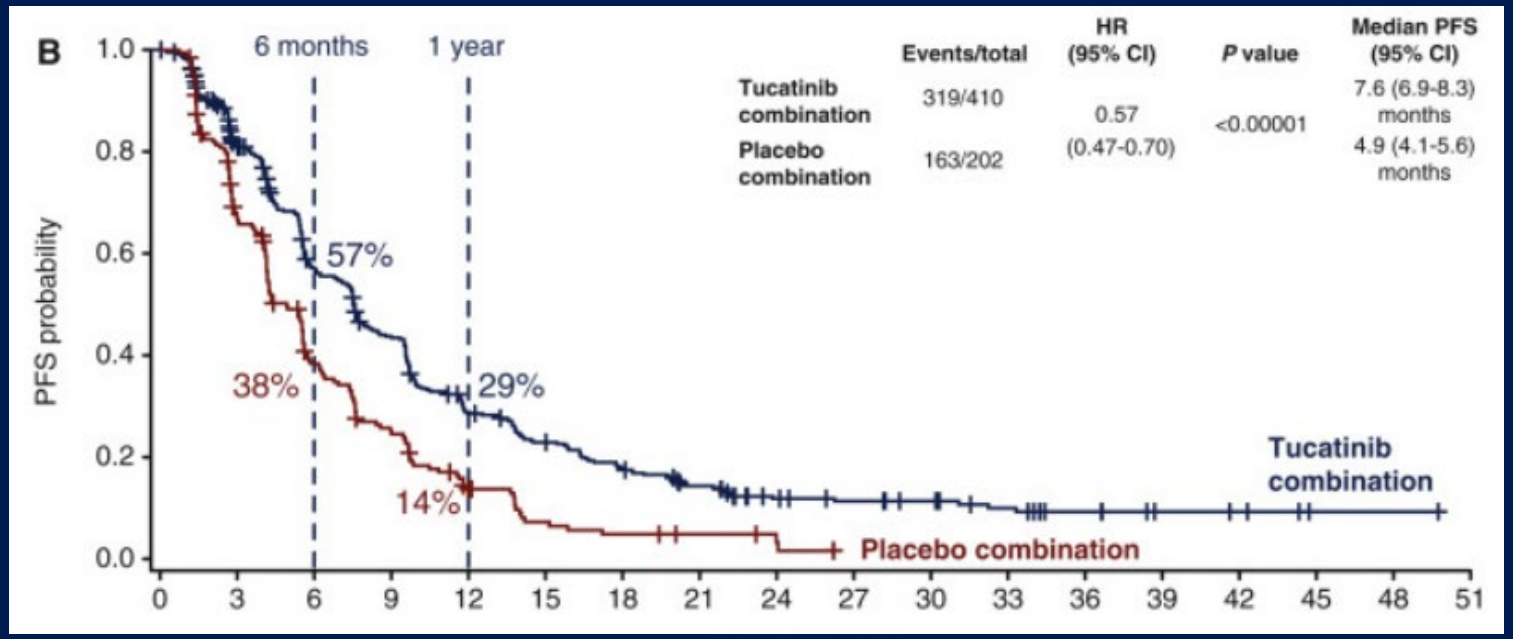
- **Treated/stable: 60%**
- **Untreated 22%**
- **Treated progressing 18%**

Murphy NEJM 2019

HER2CLIMB: tucatinib + capecitabine + trastuzumab: final analysis

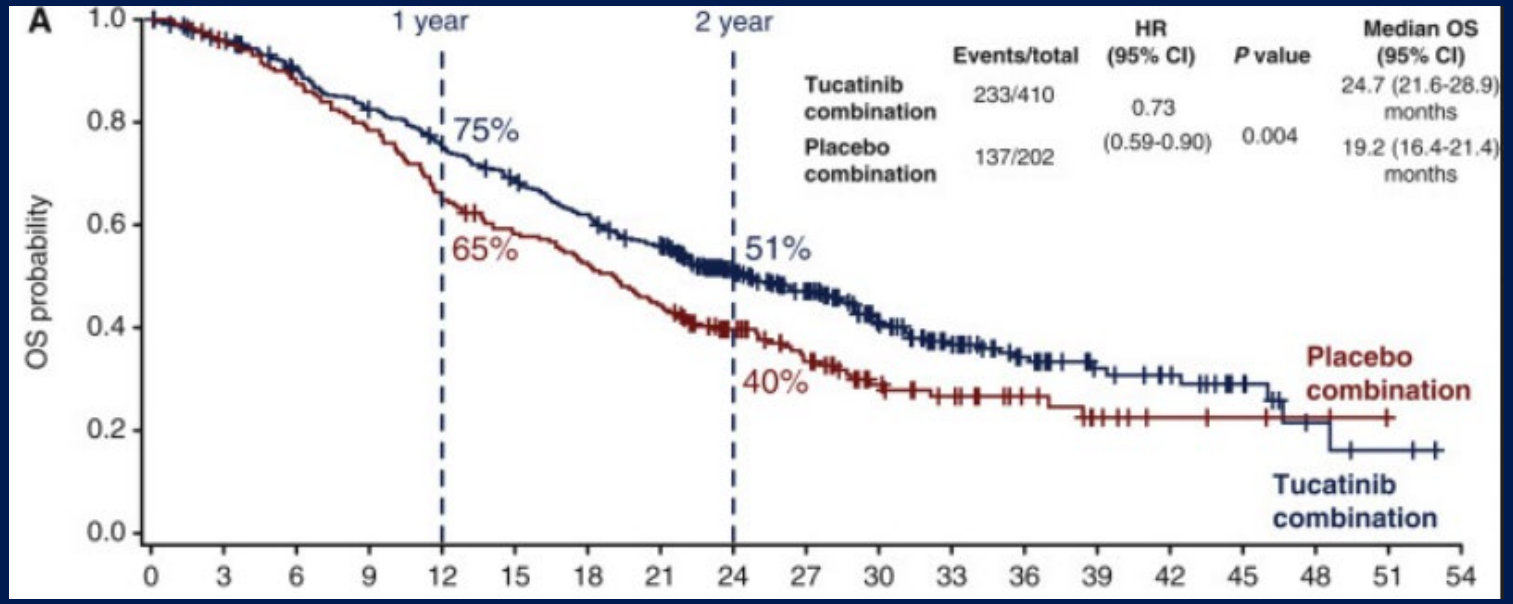
Prior TH, T-DM1 (2-3L)

PFS



PFS
Δ +3m

OS



OS
Δ +5.5m

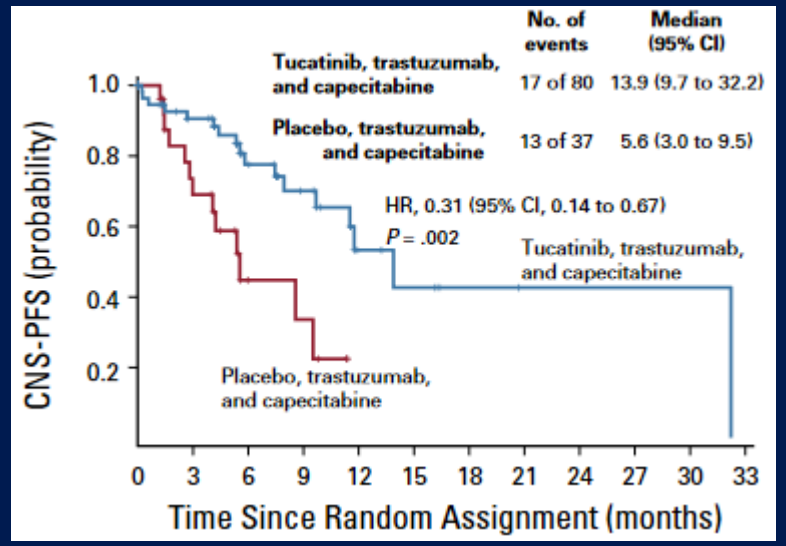
Curigliano Annals of Oncol 2022

HER2CLIMB: tucatinib + capecitabine + trastuzumab: intracranial efficacy

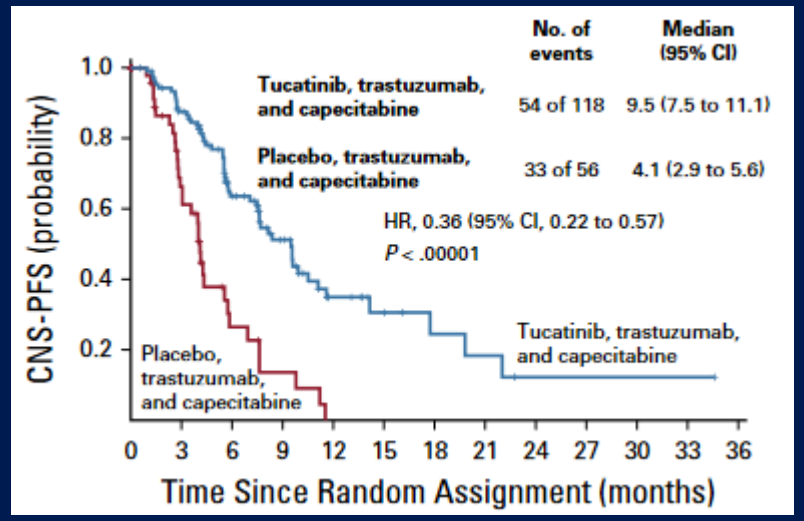
Prior TH, T-DM1 (2-3L)

Characteristic	No. (%) Tucatinib, Trastuzumab, and Capecitabine (n = 198)	Placebo, Trastuzumab, and Capecitabine (n = 93)	Total (N = 291)
BM treatment status at baseline			
Treated and stable[b]	80 (40.4)	37 (39.8)	117 (40.2)
Treated and progressing[c]	74 (37.4)	34 (36.6)	108 (37.1)
Untreated[d]	44 (22.2)	22 (23.7)	66 (22.7)
Prior therapy for BMs			
Radiation therapy	140 (70.7)	64 (68.8)	204 (70.1)
WBRT	77 (38.9)	45 (48.4)	122 (41.9)
Targeted radiation therapy	92 (46.5)	32 (34.4)	124 (42.6)
Surgery	33 (16.7)	13 (14.0)	46 (15.8)

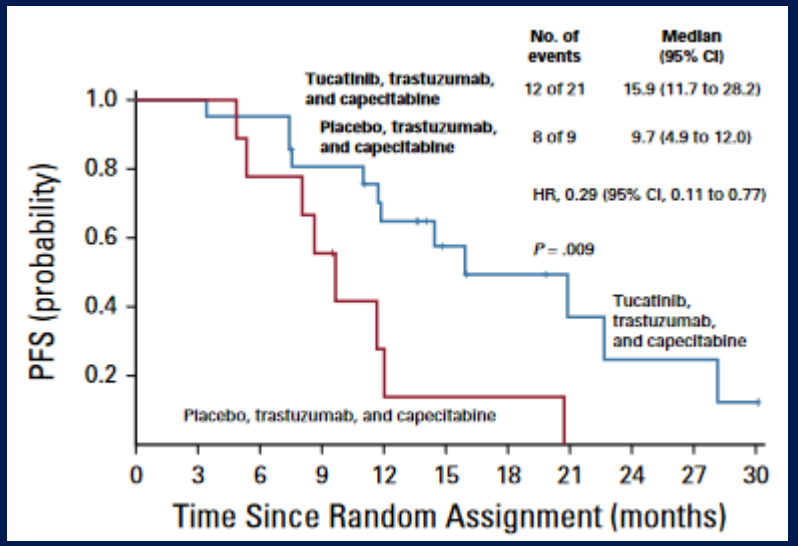
Stable brain mets



Active brain mets



Isolated CNS progression (continued on therapy)



Lin JCO 2020

Outline

HR+

Adjuvant abemaciclib (monarchE)

1L Ribociclib overall survival (Monaleesa-2)

Elacestrant novel SERD (EMERALD)

HER2+

2L T-DXd vs TDM1 (DB-03)

Tucatinib Overall survival & brain metastases update (HER2CLIMB)

Questions?

hobbev@ohsu.edu