Advances in Breast Cancer

Mili Arora, MD

UC Davis Comprehensive Cancer Center

October 29, 2022

Outline

I. CDK 4/6 inhibitors

A. Survival update: PALOMA-2

B. Sequencing: MAINTAIN

II. Oral SERDs

A. EMERALD

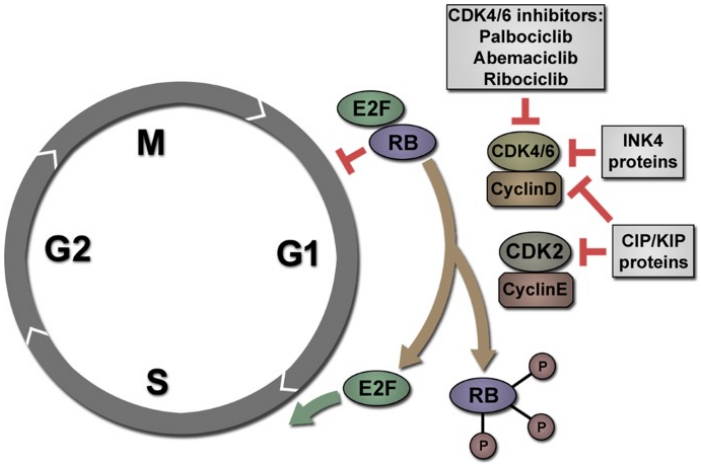
B. AMEERA-03

III. Antibody Drug Conjugates

A. TROPICS-02

B. DB-04

C. DAISY



CDK 4/6 inhibitors

Source: https://www.nature.com/articles/s41388-020-1354-9

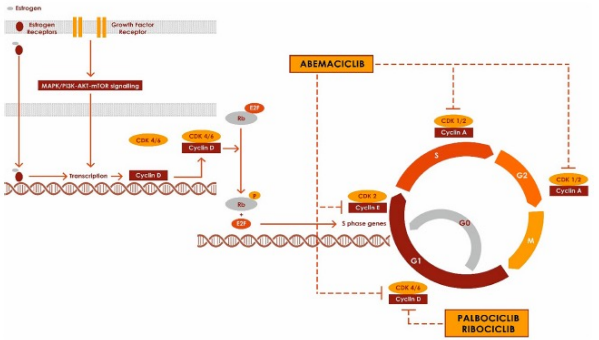
Differences in CDK 4/6 inhibitors

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

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/instance/8313476/bin/fonc-11-693104-g001.jpg

Clinical Activity of CDK 4/6 inhibitors

	Palbociclib	Ribociclib	Abemaciclib
Monotherapy	**Not approved**	**Not approved**	**FDA approved for monotherapy**
CNS activity	-	-	+
Adjuvant Setting	**No Benefit** 3-y IDFS 88.2% vs. 88.5% HR 0.93; 95% CI 0.76-1.15 **(PALLAS)** 3y-IDFS 82.1% vs. 77.7% HR 0.93; 95% CI 0.74 to 1.17 p=0.525 **(PENELOPE-B)**	**Study Ongoing** **(NATALEE)**	**Shown to have benefit** 2y-IDFS 92.2% vs. 88.7% HR 0.75; 95% CI, 0.60 to 0.93, P = .01. **(MonarchE)**



CDK4/6i Landscape

	PALOMA-1	PALOMA-2	PALOMA-3	MONALESSA-2	MONARCH-3	MONALEESA-3
Study Design	Phase II first line	Phase III first line	Phase III second line	Phase III first line	Phase III first line	Phase III first and second line
Endocrine Partner	Letrozole	Letrozole	Fulvestrant	Letrozole	Letrozole or anastrozole	Fulvestrant
CDK 4/5 Inhibitor	Palbociclib	Palbociclib	Palbociclib	Ribociclib	Abemaciclib	Ribociclib
Patients, N	165	666	521	668	493	367
HR	0.49	0.58	0.49	0.56	0.54	0.57
PFS, mos	20.2 vs. 10.2	24.8 vs. 14.5	NR vs 5.8	25.3 vs. 16	NR vs. 14.7	NR vs. 18.3
ORR, %	56 vs. 39	55.3 vs. 44.4	24.6 vs 10.9	52.7 vs. 37.1	59 vs. 44	40.9 vs. 28.7
OS, mos		53.9 vs 51.9	34.8 vs 28	63.9 vs 51.4	67.1 vs 54.5	53.7 vs 41.5,

Sequencing CDK 4/6 inhibitors

- Limited insight about the role of continuing CDK 4/6 inhibitors after receiving prior CDK 4/6 inhibitor
- Observational data exists for sequencing CDK 4/6 inhibitors
  - Abemacilclib
    - CBR/PFS/OS similar to MONARCH-1
    - DoR appx 6 months

MAINTAIN: Study Design

- Multicenter, randomized, placebo-controlled phase II trial

Adults with ER and/or PR ≥1%; HER2- MBC and progression on ET and CDK4/6i; ≤1 CT line for MBC; ECOG PS 0 or 1; postmenopausal (or premenopausal with GnRH agonist); stable brain metastases allowed
(N = 120)

Ribociclib 600 mg QD 3 wk on, 1 wk off
+ Switch ET*
(n = 60)

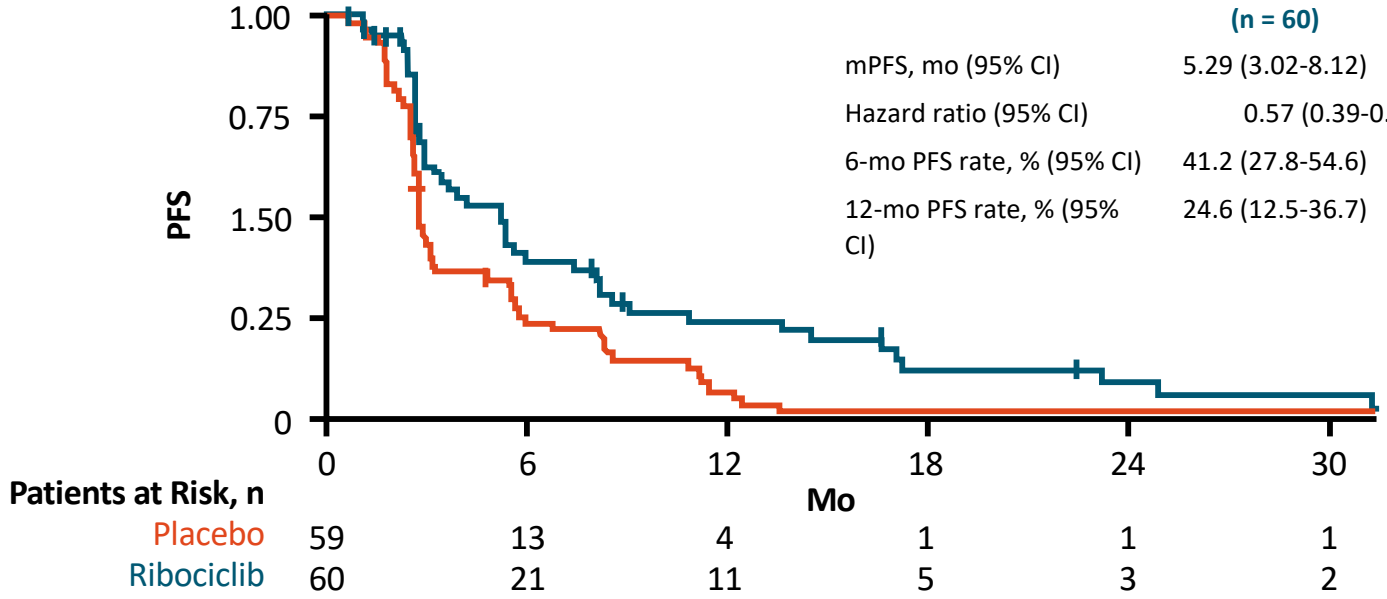
Placebo + Switch ET*
(n = 59)

*Patients with progression on AI for MBC and no prior fulvestrant received fulvestrant. After protocol amendment, patients who progressed on prior fulvestrant received exemestane.

- **Primary endpoint**: PFS (locally assessed per RECIST v1.1)
- **Key secondary endpoints**: ORR, CBR, safety, tumor response

Source: Kalinsky. ASCO 2022. Abstr LBA1004.
Slide credit: clinicaloptions.com

MAINTAIN: PFS

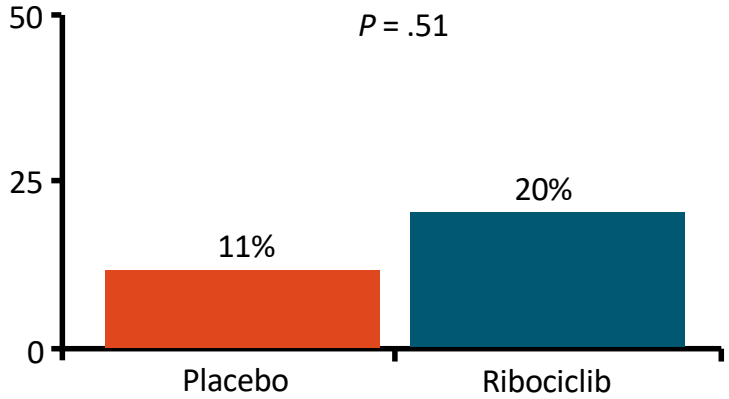


	Ribo + ET (n = 60)	Placebo + ET (n = 59)
mPFS, mo (95% CI)	5.29 (3.02-8.12)	2.76 (1.66-3.25)
Hazard ratio (95% CI)	0.57 (0.39-0.95); *P* = .006	
6-mo PFS rate, % (95% CI)	41.2 (27.8-54.6)	23.9 (12.8-35)
12-mo PFS rate, % (95% CI)	24.6 (12.5-36.7)	7.4 (0.4-14.3)

Source: Kalinsky. ASCO 2022. Abstr LBA1004.
Slide credit: clinicaloptions.com

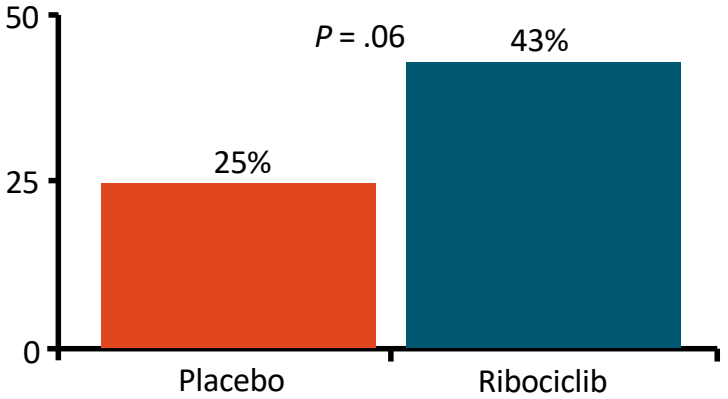
MAINTAIN: Responses

Overall Response Rate (n = 70)



Characteristic	Placebo (n = 35)	Ribociclib (n = 35)
CR, n (%)	0 (0)	2 (6)
PR, n (%)	4 (11)	5 (14)
Median DoR, mo (IQR)	14.8 (6.7-21.3)	18.8 (11.4-50.2)

Clinical Benefit Rate (n = 105)

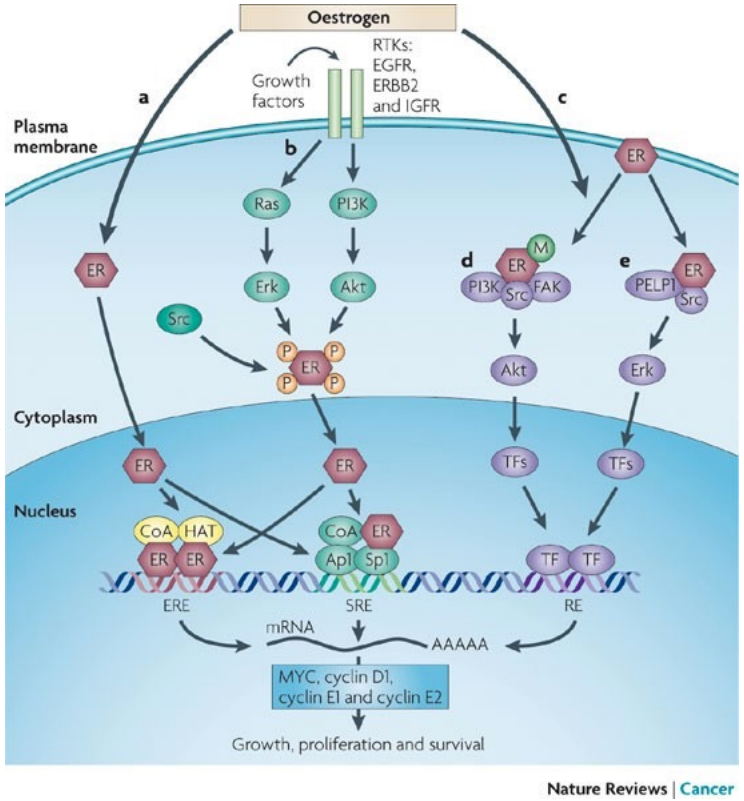


Characteristic	Placebo (n = 57)	Ribociclib (n = 49)
CR/PR/SD ≥24 wk, n (%)	14 (25)	21 (43)

Source: Kalinsky. ASCO 2022. Abstr LBA1004.
Slide credit: clinicaloptions.com

MAINTAIN: Conclusion

- Ribociclib and switching endo rx vs placebo and switching endo rx in patients who rec'd prior CDK 4/6 inhibitors improved PFS
  - Median PFS 5.29 vs 2.76 mos (p = .006)
- Safety profile is manageable
- Ongoing prospective trials
  - Ph II PALMIRA (ongoing palbo w/endo rx switch)
  - Ph II PACE (fulvestrant vs palbo w/fulvestrant vs palbo w/fulvestrant and avelumab after progression on AI/CDK 4/6i)
- Genomic data to predict who might benefit from sequencing



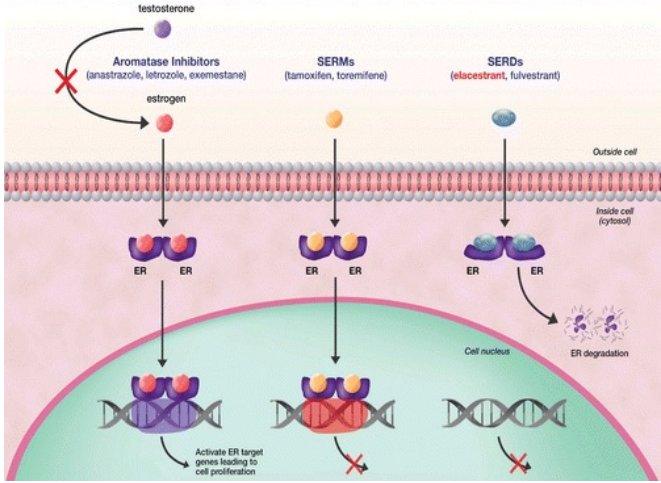
Endocrine resistance

Source: https://www.nature.com/articles/nrc2713

Oral SERD: selective estrogen receptor degrader / downregulator

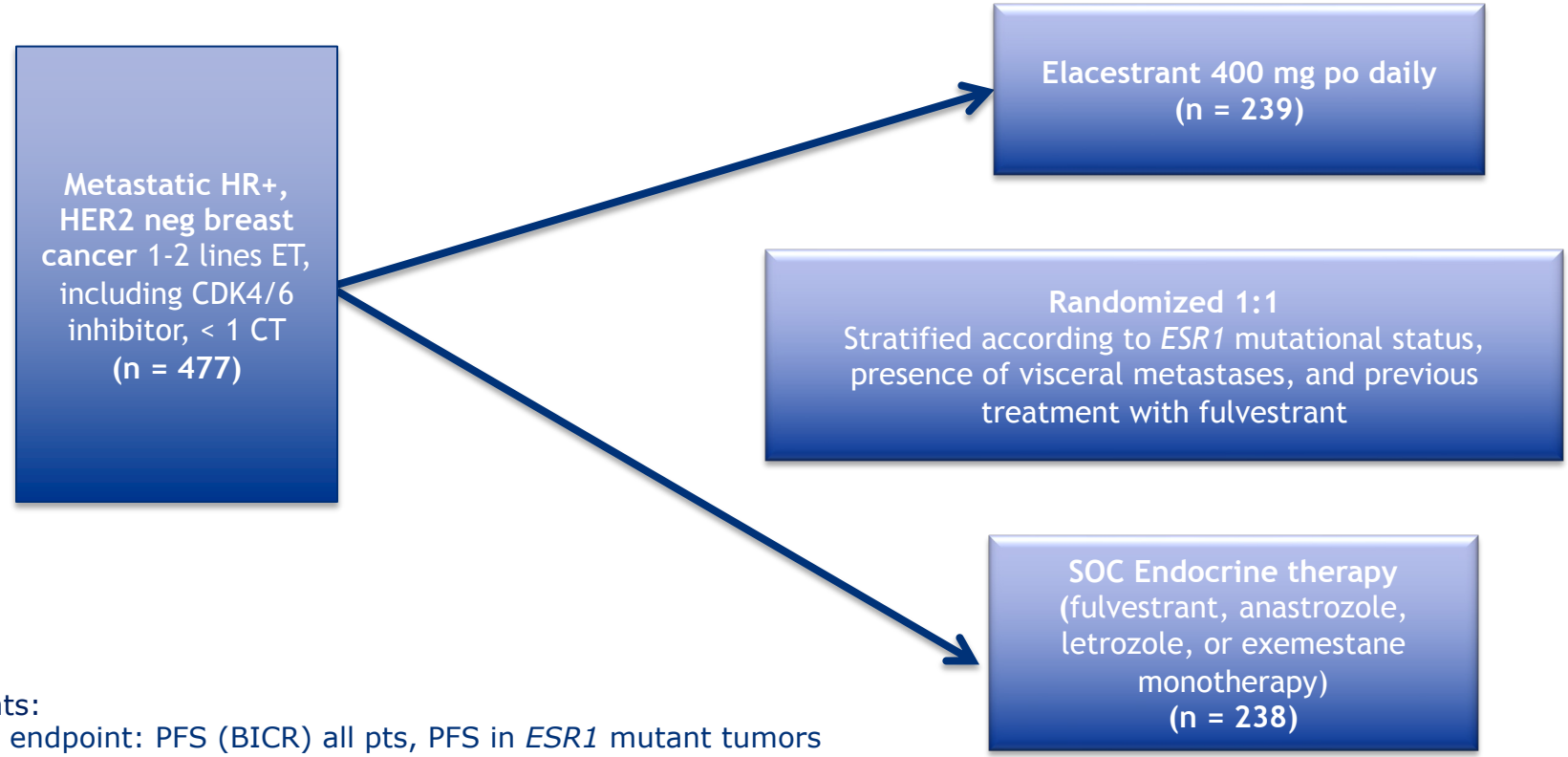
- Resistance mechanism: *ESR1*
  - Estrogen receptor–dependent transcription and proliferation in the absence of estrogen
  - Predict resistance to AIs
- SERD: binds to estrogen receptor

  causing ER to be degraded/downregulated
- Fulvestrant only FDA approved SERD
  - Intramuscular, twice monthly
- Multiple oral SERDs in pipeline



Source: https://www.futuremedicine.com/doi/10.2217/fon-2019-0370

EMERALD– Trial Design

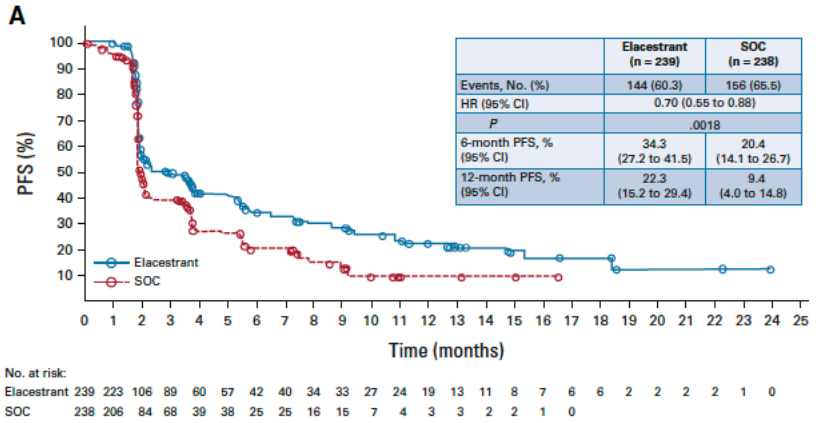


Endpoints:
Primary endpoint: PFS (BICR) all pts, PFS in *ESR1* mutant tumors
Secondary endpoints: OS all pts, OS *ESR1* mutations, DoR, ORR, CBR, safety

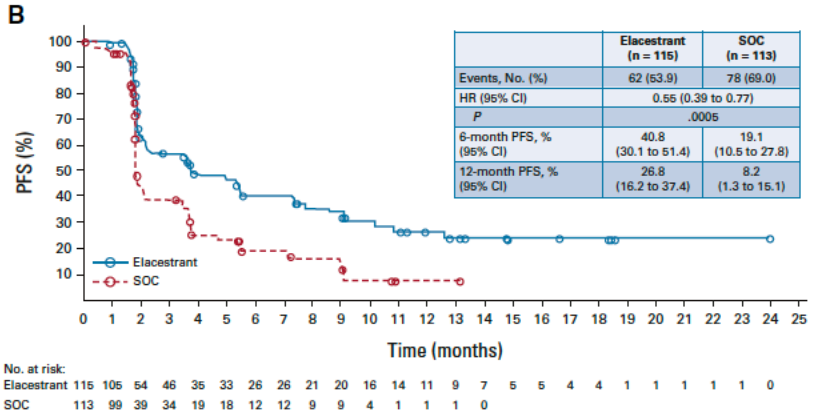
EMERALD Baseline Characteristics

Parameter	Elacestrant		SOC					
			Total		Fulvestrant		AI	
	All (n = 239)	*ESR1* Mutation (n = 115)	All (n = 238)	*ESR1* Mutation (n = 113)	All (n = 165)	*ESR1* Mutation (n = 83)	All (n = 73)	*ESR1* Mutation (n = 30)
No. of prior lines of endocrine therapy in the advanced or metastatic setting, n (%)								
1	129 (54.0)	73 (63.5)	141 (59.2)	69 (61.1)	120 (72.7)	64 (77.1)	21 (28.8)	5 (16.7)
2	110 (46.0)	42 (36.5)	97 (40.8)	44 (38.9)	45 (27.3)	19 (22.9)	52 (71.2)	25 (83.3)
No. of prior lines of chemotherapy in the advanced or metastatic setting, n (%)								
0	191 (79.9)	89 (77.4)	180 (75.6)	81 (71.7)	132 (80.0)	64 (77.1)	48 (65.8)	17 (56.7)
1	48 (20.1)	26 (22.6)	58 (24.4)	32 (28.3)	33 (20.0)	19 (22.9)	25 (34.2)	13 (43.3)
Prior therapies for advanced or metastatic disease, n (%)								
Any prior endocrine therapy[b]	232 (97.1)	112 (97.4)	233 (97.9)	109 (96.5)	161 (97.6)	79 (95.2)	72 (98.6)	30 (100.0)
Fulvestrant	70 (29.3)	27 (23.5)	75 (31.5)	28 (24.8)	6 (3.6)	1 (1.2)	69 (94.5)	27 (90.0)
AI	193 (80.8)	101 (87.8)	193 (81.1)	96 (85.0)	159 (96.4)	78 (94.0)	34 (46.6)	18 (60.0)
Tamoxifen	19 (7.9)	9 (7.8)	15 (6.3)	9 (8.0)	10 (6.1)	6 (7.2)	5 (6.8)	3 (10.0)
mTOR inhibitor	10 (4.2)	6 (5.2)	6 (2.5)	3 (2.7)	5 (3.0)	2 (2.4)	1 (1.4)	1 (3.3)
PI3K inhibitor	3 (1.3)	1 (0.9)	1 (0.4)	0	1 (0.6)	0	0	0

EMERALD: PFS



	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)

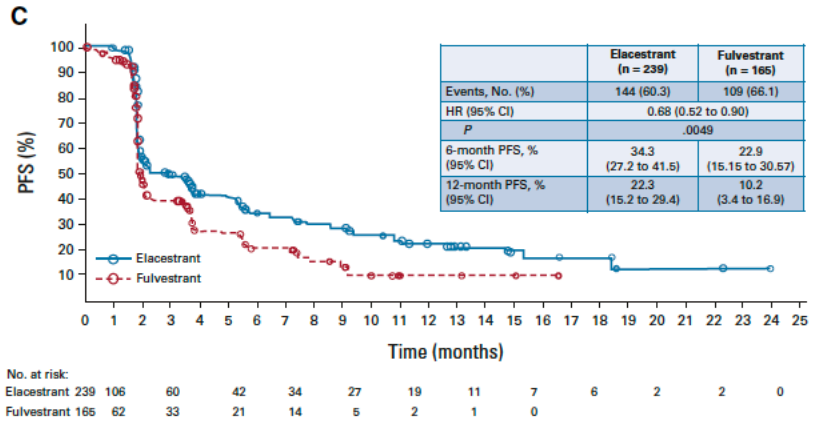


	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

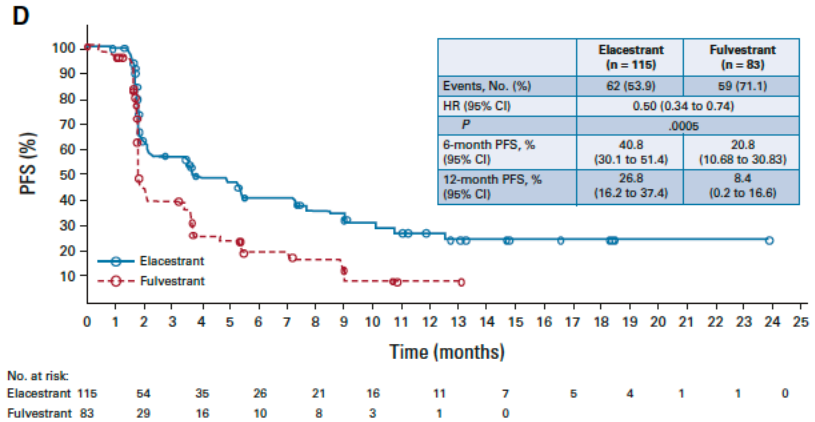
Elacestrant vs SOC in all pts

Elacestrant vs SOC in pts w/*ESR1* mutations

EMERALD: PFS



	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)	22.9 (15.15 to 30.57)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	10.2 (3.4 to 16.9)



	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)	20.8 (10.68 to 30.83)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.4 (0.2 to 16.6)

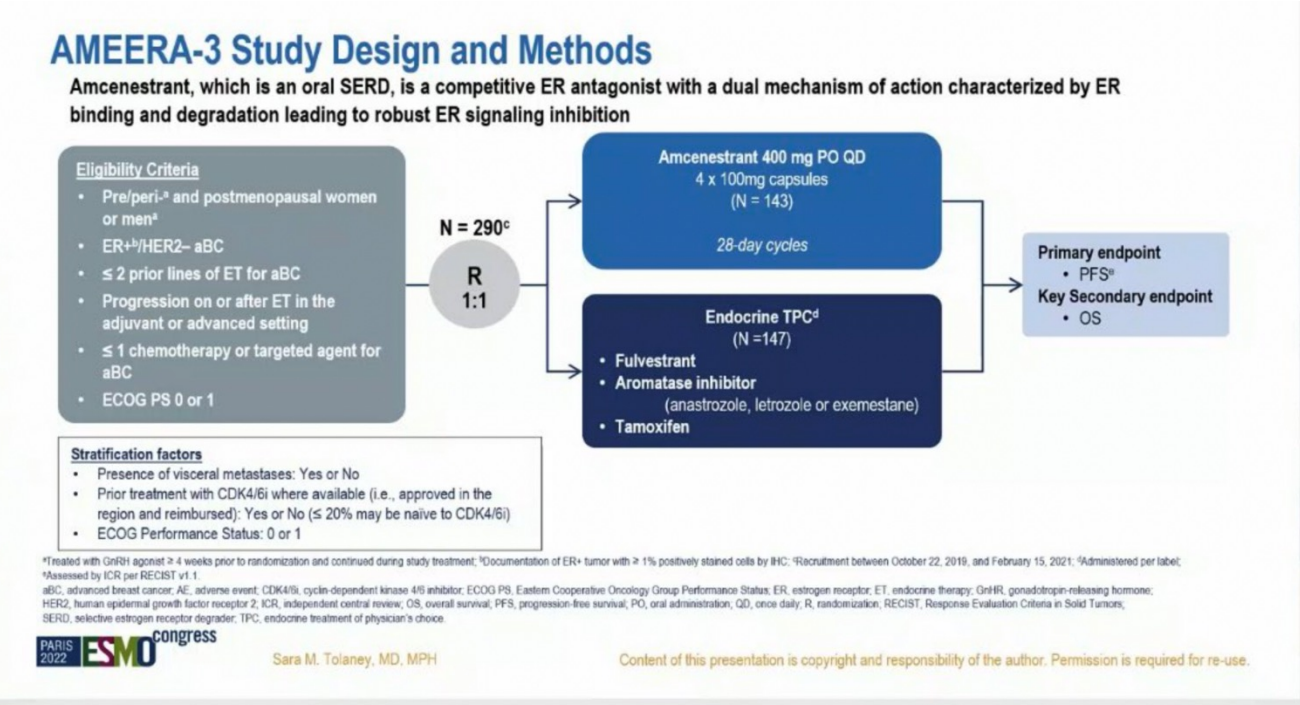
Elacestrant vs fulvestrant in all pts

Elacestrant vs fulvestrant in pts w/*ESR1* mutations

EMERALD: Conclusion

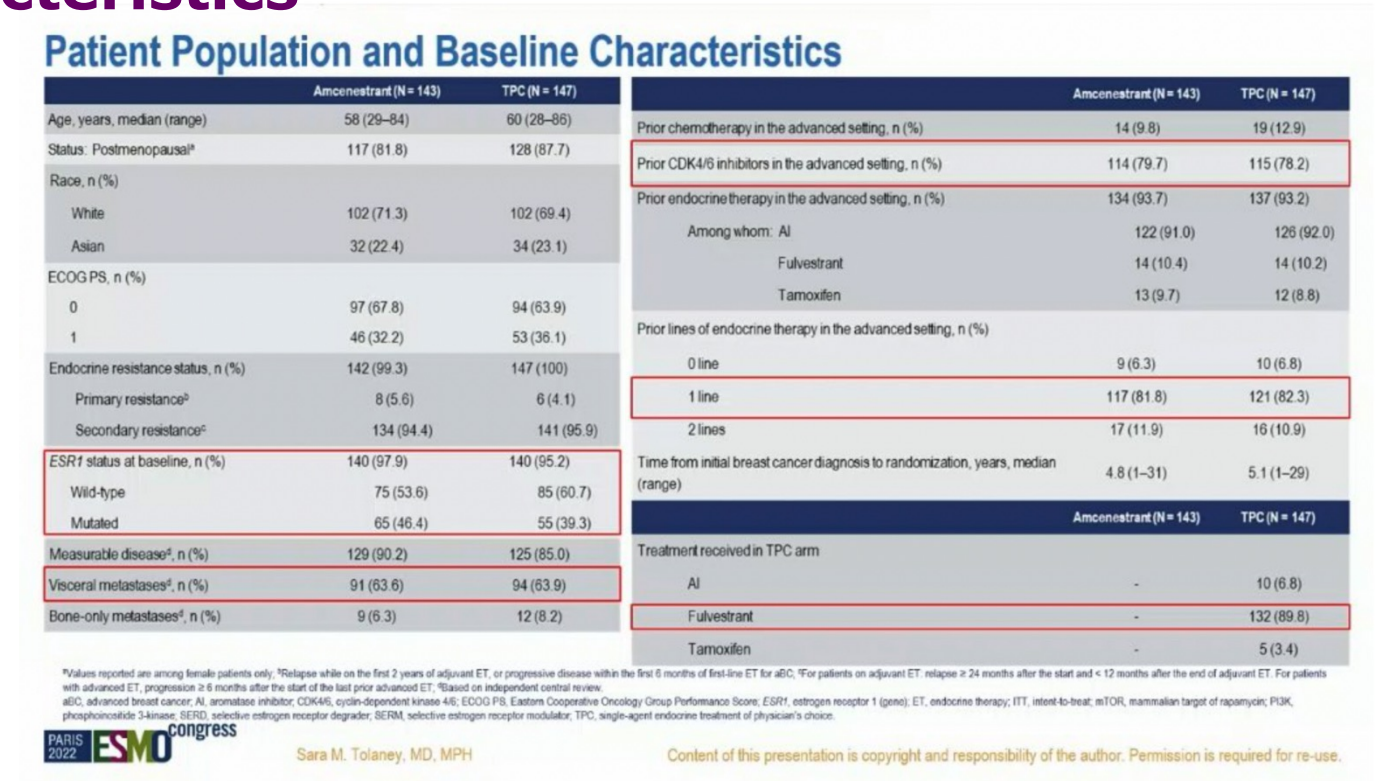
- Elacestrant first oral SERD to show benefit in randomized ph III trial
  - Statistically significant prolonged PFS
  - Magnitude of PFS benefit lower in *ESR1* WT tumors
  - Reasonable safety profile
    - Nausea, vomiting, fatigue
- Elacestrant under review by the FDA
- Combination therapies
  - CDK 4/6i, mTORi, *PIK3CA*i

AMEERA-3 Study Design and Methods



Source: ESMO 2022.

AMEERA-3 Patient Population and Baseline Characteristics



Patient Population and Baseline Characteristics

	Amcenestrant (N = 143)	TPC (N = 147)
Age, years, median (range)	58 (29–84)	60 (28–86)
Status: Postmenopausal[a]	117 (81.8)	128 (87.7)
Race, n (%)		
White	102 (71.3)	102 (69.4)
Asian	32 (22.4)	34 (23.1)
ECOG PS, n (%)		
0	97 (67.8)	94 (63.9)
1	46 (32.2)	53 (36.1)
Endocrine resistance status, n (%)	142 (99.3)	147 (100)
Primary resistance[b]	8 (5.6)	6 (4.1)
Secondary resistance[c]	134 (94.4)	141 (95.9)
ESR1 status at baseline, n (%)	140 (97.9)	140 (95.2)
Wild-type	75 (53.6)	85 (60.7)
Mutated	65 (46.4)	55 (39.3)
Measurable disease[d], n (%)	129 (90.2)	125 (85.0)
Visceral metastases[d], n (%)	91 (63.6)	94 (63.9)
Bone-only metastases[d], n (%)	9 (6.3)	12 (8.2)

	Amcenestrant (N = 143)	TPC (N = 147)
Prior chemotherapy in the advanced setting, n (%)	14 (9.8)	19 (12.9)
Prior CDK4/6 inhibitors in the advanced setting, n (%)	114 (79.7)	115 (78.2)
Prior endocrine therapy in the advanced setting, n (%)	134 (93.7)	137 (93.2)
Among whom: AI	122 (91.0)	126 (92.0)
Fulvestrant	14 (10.4)	14 (10.2)
Tamoxifen	13 (9.7)	12 (8.8)
Prior lines of endocrine therapy in the advanced setting, n (%)		
0 line	9 (6.3)	10 (6.8)
1 line	117 (81.8)	121 (82.3)
2 lines	17 (11.9)	16 (10.9)
Time from initial breast cancer diagnosis to randomization, years, median (range)	4.8 (1–31)	5.1 (1–29)

	Amcenestrant (N = 143)	TPC (N = 147)
Treatment received in TPC arm		
AI	-	10 (6.8)
Fulvestrant	-	132 (89.8)
Tamoxifen	-	5 (3.4)

[a]Values reported are among female patients only. [b]Relapse while on the first 2 years of adjuvant ET, or progressive disease within the first 6 months of first-line ET for aBC. [c]For patients on adjuvant ET: relapse ≥ 24 months after the start and < 12 months after the end of adjuvant ET. For patients with advanced ET, progression ≥ 6 months after the start of the last prior advanced ET. [d]Based on independent central review.

aBC, advanced breast cancer; AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group Performance Score; *ESR1*, estrogen receptor 1 (gene); ET, endocrine therapy; ITT, intent-to-treat; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; TPC, single-agent endocrine treatment of physician's choice.

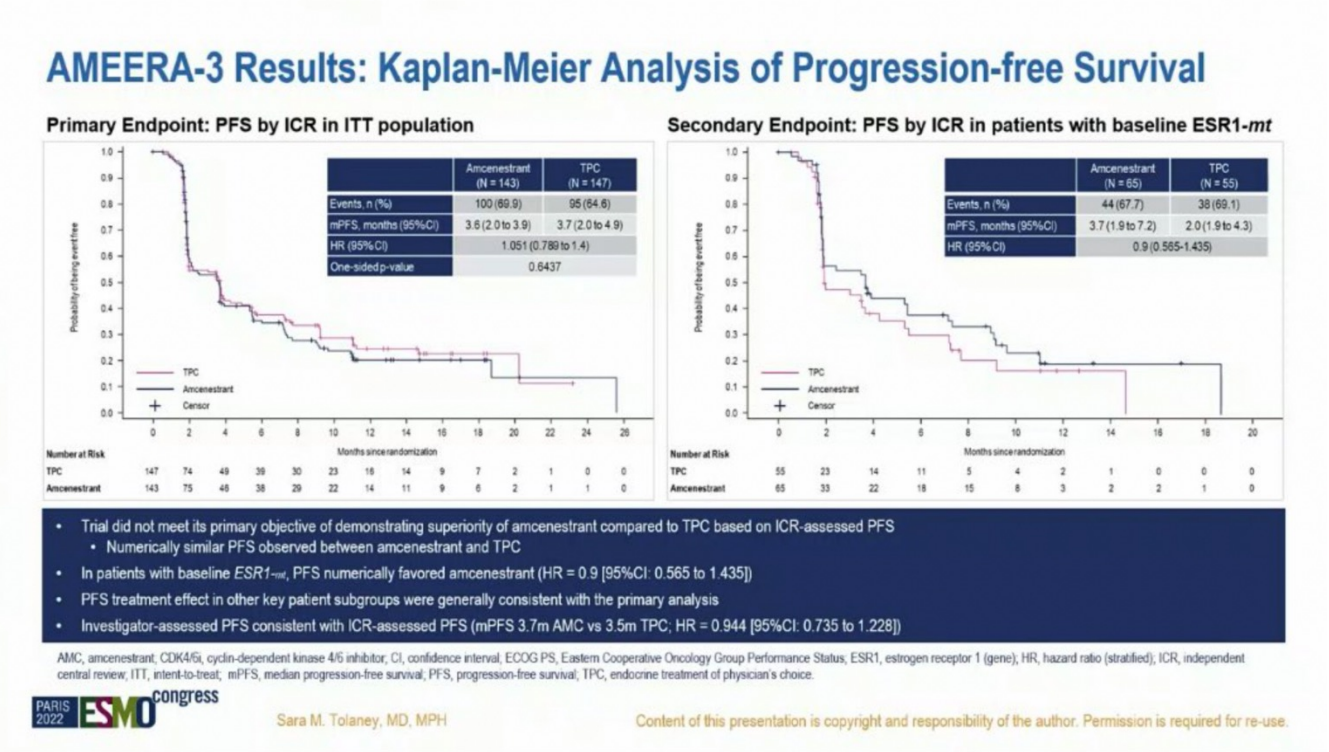
PARIS 2022 ESMO congress

Sara M. Tolaney, MD, MPH

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Source: ESMO 2022.

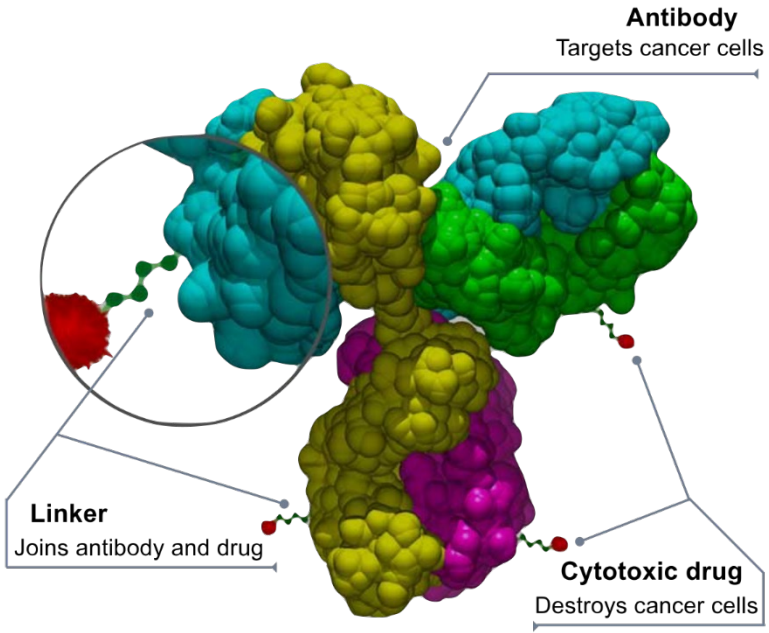
AMEERA-3 Results



Source: ESMO 2022.

Future of Oral SERDs?

- Amcenestrant was pulled from further development
  - AMEERA-5 did not meet prespecified criteria for continuation
- Difference between elacestrant vs amcenestrant
  - AMEERA3 not powered to look at *ESR1* mutations
  - AMEERA3 with more pts w/fulvestrant in control arm
- Elacestrant under FDA review
- Other oral SERDs ongoing development

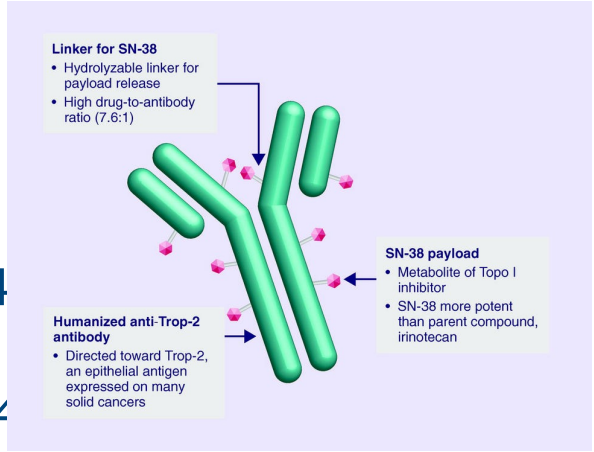


ADC: Antibody Drug Conjugates

Source: https://www.google.com/url?sa=i&url=https%3A%2F%2Fen.wikipedia.org%2Fwiki%2FAntibody-drug_conjugate&psig=AOvVaw1fCImfp7VBJAC1OQn8-9gp&ust=1666503235124000&source=images&cd=vfe&ved=0CAwQjRxqFwoTCOCrx7yO8_oCFQAAAAAdAAAAABAE

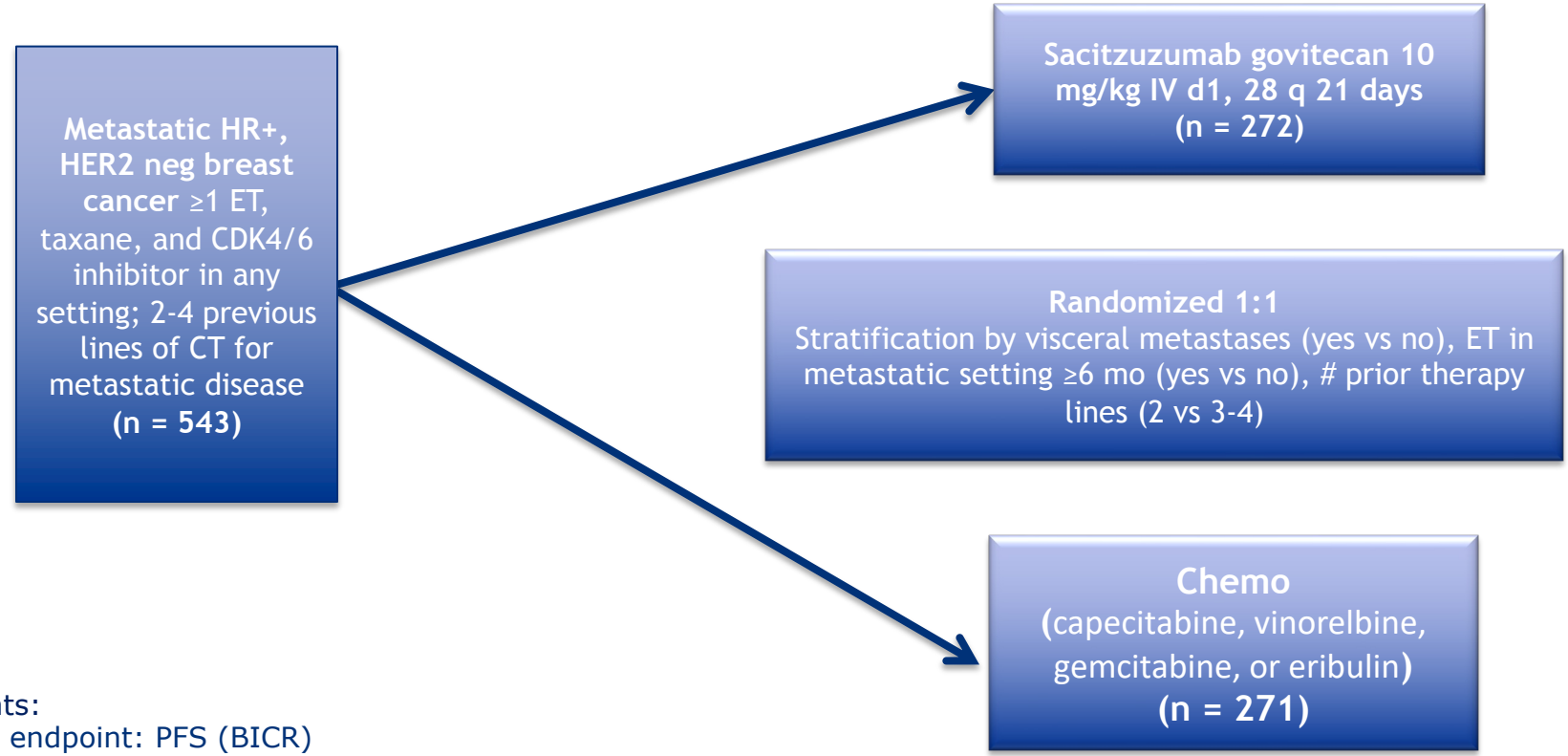
Sacituzumab govitecan-hziy

- FDA approved in April 2020 for previously treated mTNBC
- Confirmatory phase III trial: ASCENT
- SG vs chemo
  - Second line or greater mTNBC
  - Manageable safety profile
  - Median PFS 5.6 vs 1.7 months (HR 0.4 p<0.001)
  - Median OS 12.1 vs 6.7 months (HR 0.4 p<0.001)



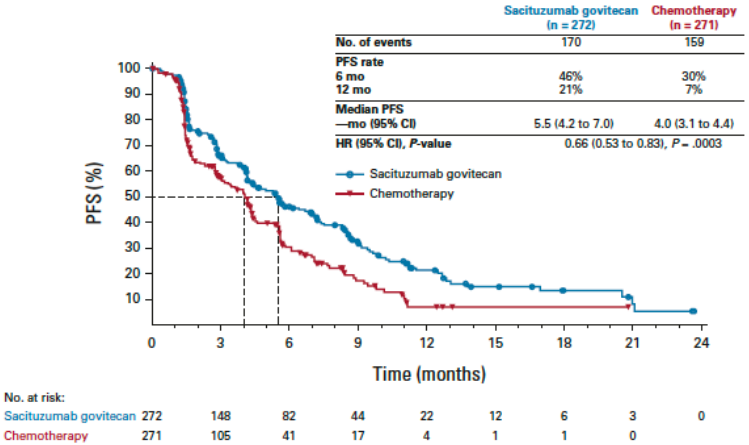
Source: https://www.cancer.gov/news-events/cancer-currents-blog/2020/fda-sacituzumab-govitecan-triple-negative-breast-cancer

TROPICS-02– Trial Design



Endpoints:
Primary endpoint: PFS (BICR)
Secondary endpoints: OS, ORR, DoR, CBR (LIR and BICR), PRO, safety

TROPICS-02 PFS



Efficacy Outcome	SG (n = 272)	Chemotherapy (n = 271)
Median PFS, months (95% CI),	5.5 (4.2 to 7.0)	4.0 (3.1 to 4.4)
HR; *P* (95% CI)	0.66 (0.53 to 0.83); *P* = .0003	
PFS rate, %, months (95% CI)		
6	46 (39 to 53)	30 (24 to 37)
12	21 (15 to 28)	7 (3 to 14)
Median OS, months (95% CI)	13.9 (12.7 to 15.4)	12.3 (10.8 to 14.2)
HR; *P* (95% CI)	0.84 (0.67 to 1.06); *P* = .14	
Objective response rate, No. (%)	57 (21)	38 (14)
Best overall response, No. (%)		
Complete response	2 (1)	0
Partial response	55 (20)	38 (14)
Stable disease	142 (52)	106 (39)
Stable disease ≥ 6 months	35 (13)	21 (8)
Progressive disease	58 (21)	76 (28)
Not evaluable	15 (6)	51 (19)
CBR,[a] No. (%)	92 (34)	59 (22)
Median DOR, months (95% CI)	7.4 (6.5 to 8.6)	5.6 (3.8 to 7.9)

TROPICS-02: OS in ITT Population

OS in ITT Population (First Planned Interim Analysis)	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
Median OS, mo (95% CI)*	14.4 (13.0-15.7)	11.2 (10.1-12.7)
▪ Stratified hazard ratio (95% CI) ▪ Stratified log-rank *P* value	0.79 (0.65-0.96) .020	
12-mo OS, % (95% CI)	61 (55-66)	47 (41-53)
Events, n	191	199

*Median follow-up 12.5 mo.

- Statistically significant improvement in OS with sacituzumab govitecan vs physician's choice
  - 21% reduction in risk of death
  - 3.2 mo longer OS for patients who received sacituzumab govitecan vs physician's choice

Source: Rugo. ESMO 2022. Abstr LBA76.
Slide credit: clinicaloptions.com

TROPICS-02: Conclusion

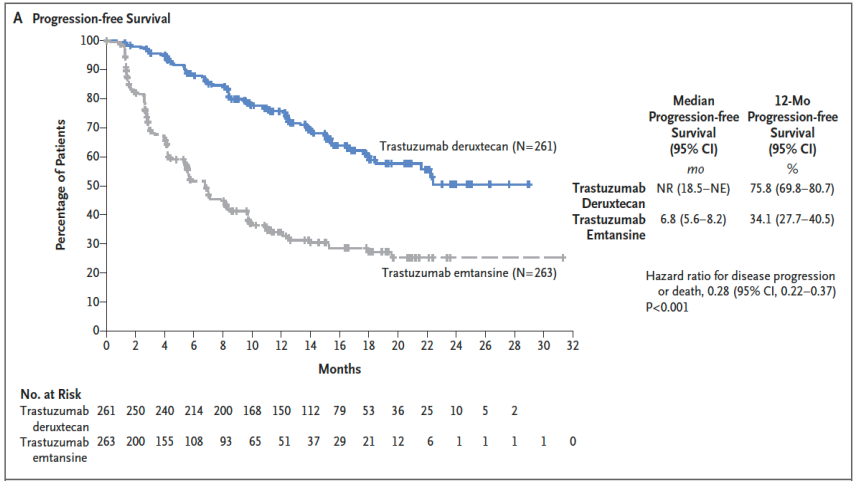
- SG improved PFS, OS, ORR
  - Median PFS
  - Median 3.2 mos OS benefit
- Safety c/w prior studies
  - Neutropenia, diarrhea, fatigue, and alopecia

Trastuzumab deruxtecan (T-Dxd)

- Trastuzumab deruxtecan (T-Dxd)
  - Potent ADC: trastuzumab bound to topoisomerase I inhibitor
    - Drug to antibody ratio 8:1
  - DB-01: phase II single arm trial, showed durable anti-tumor activity in heavily pretreated population (n=184) metastatic HER2 3+ or positive by ISH disease
  - FDA approved in Dec 2019 after progression on 2 or more lines of rx

Trastuzumab deruxtecan (T-Dxd): DB-03

- Phase III randomized trial of T-Dxd vs T-DM1
- n=524
- mPFS NR vs 6.8 months, HR 0.28
- FDA revised indication after progression on 1 line or w/i 6 mos of rec'g therapy

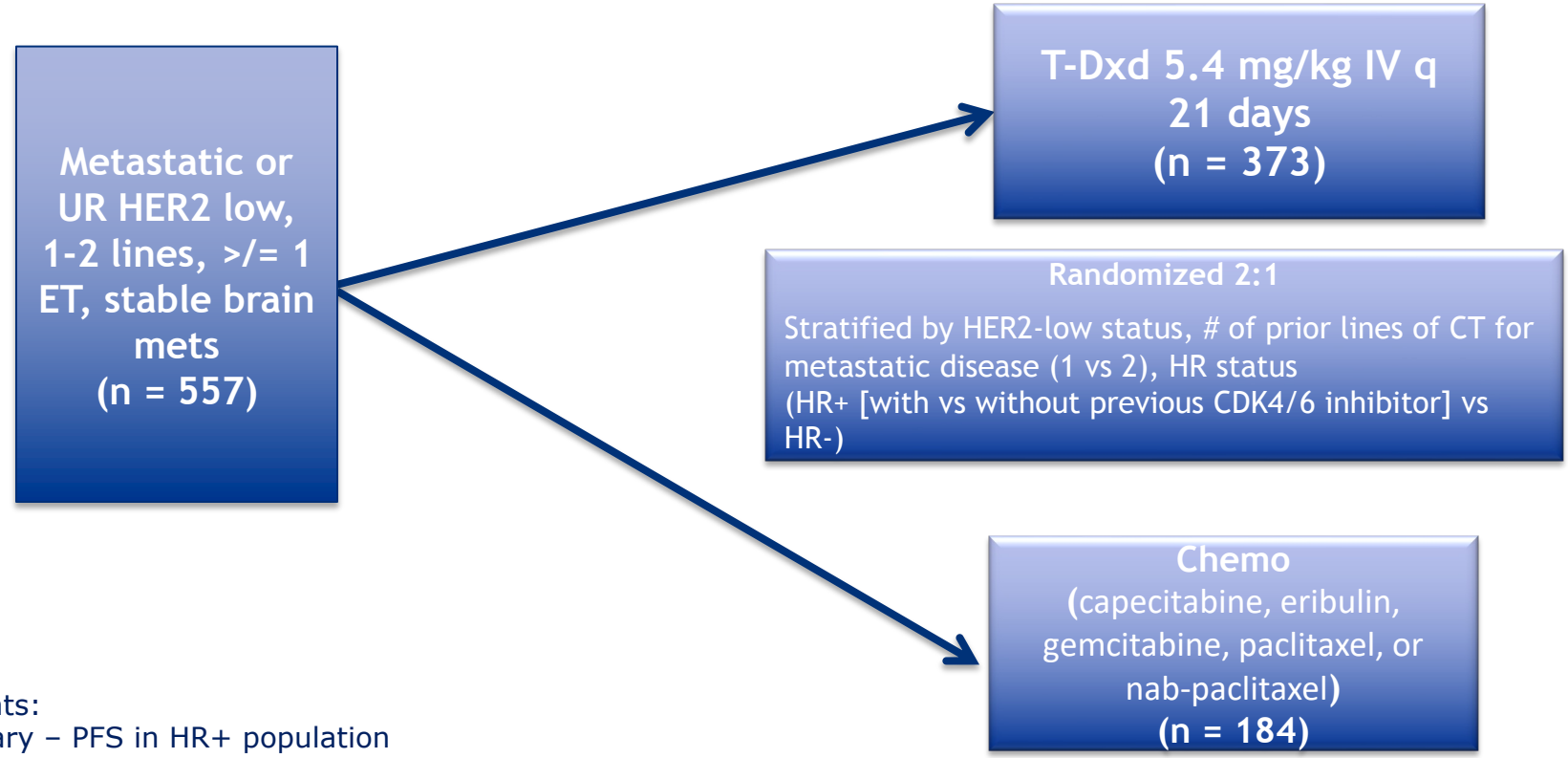


Source: NEJM DBO03

Background: DB-04

- Approximately 60% of breast cancers express low HER2
  - HER2 low: HER2 1+, 2+, negative ISH
- Prior trials using HER2 directed therapy failed to show response in HER2 low tumors
- DB-04 evaluates efficacy, safety of T-Dxd in pretreated patients with HER2 low tumors vs physician choice chemo

DB-04– Trial Design



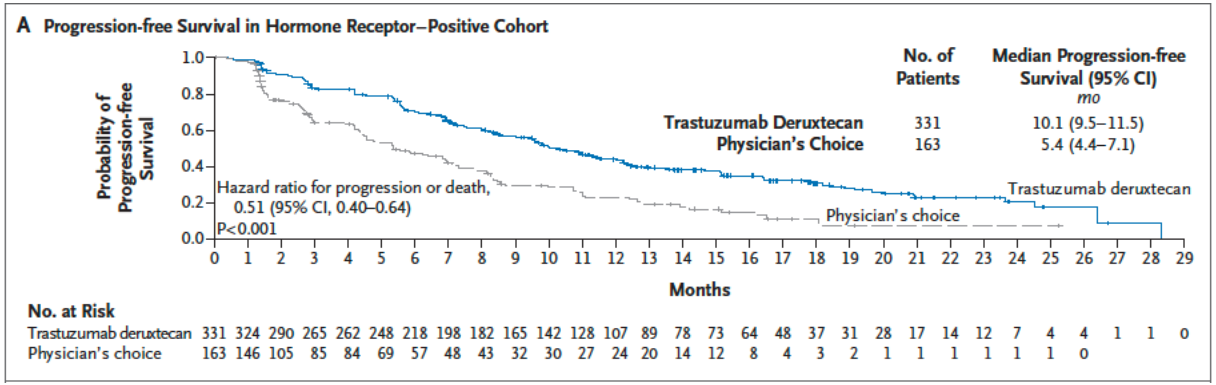
Endpoints:

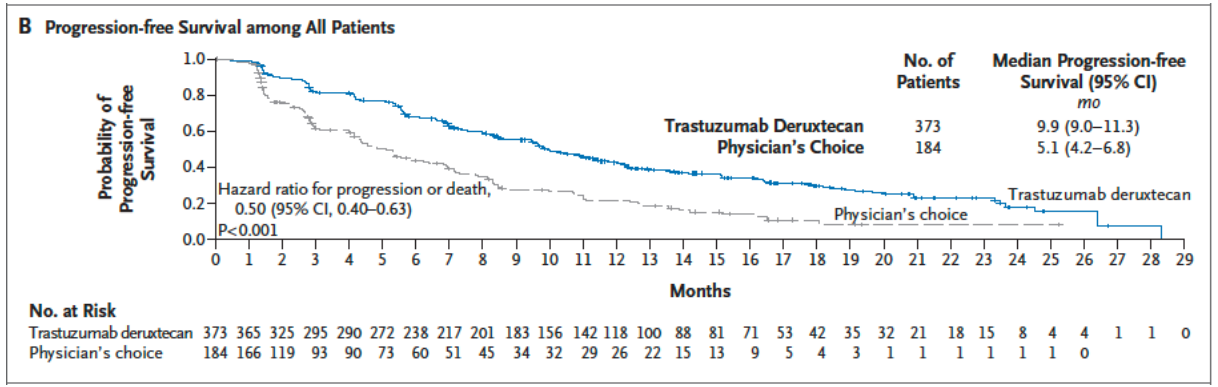
- Primary – PFS in HR+ population
- Secondary – PFS (all patients), OS in HR+ and in all patients, PFS by investigator, ORR, DoR, efficacy in HR- patient population

DB-04 Baseline Characteristics

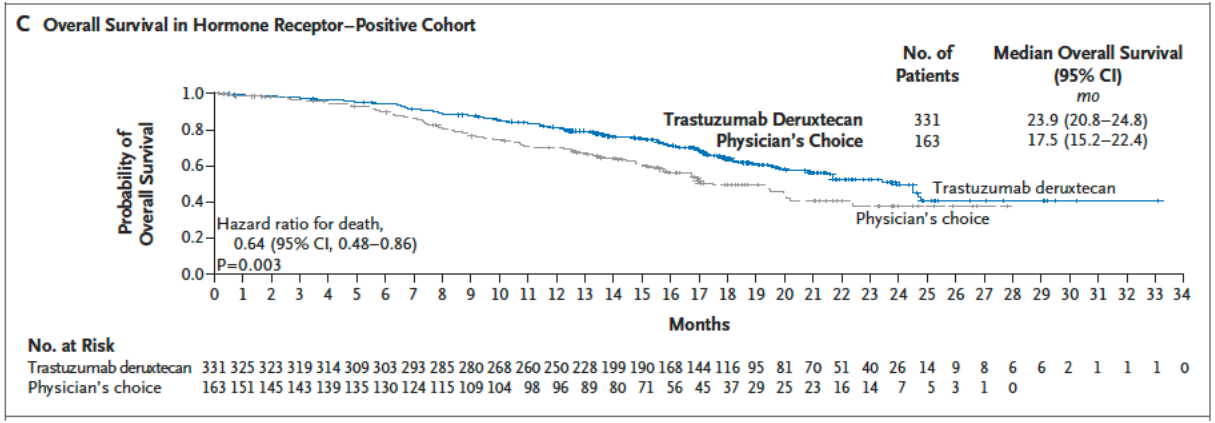
Characteristic	Hormone Receptor–Positive Cohort		All Patients	
	Trastuzumab Deruxtecan (N=331)	Physician's Choice of Chemotherapy (N=163)	Trastuzumab Deruxtecan (N=373)	Physician's Choice of Chemotherapy (N=184)
HER2-low status — no. (%)‡				
IHC 1+	193 (58.3)	95 (58.3)	215 (57.6)	106 (57.6)
IHC 2+ and ISH-negative	138 (41.7)	68 (41.7)	158 (42.4)	78 (42.4)
ECOG performance-status score — no. (%)§				
0	187 (56.5)	95 (58.3)	200 (53.6)	105 (57.1)
1	144 (43.5)	68 (41.7)	173 (46.4)	79 (42.9)
Hormone receptor–positive — no. (%)¶	328 (99.1)	162 (99.4)	333 (89.3)	166 (90.2)
Metastasis — no. (%)				
Brain	18 (5.4)	7 (4.3)	24 (6.4)	8 (4.3)
Liver	247 (74.6)	116 (71.2)	266 (71.3)	123 (66.8)
Lung	98 (29.6)	58 (35.6)	120 (32.2)	63 (34.2)
Previous cancer therapy — no. (%)				
Targeted therapy	259 (78.2)	132 (81.0)	279 (74.8)	140 (76.1)
CDK4/6 inhibitor	233 (70.4)	115 (70.6)	239 (64.1)	119 (64.7)
Immunotherapy	10 (3.0)	8 (4.9)	20 (5.4)	12 (6.5)
Other	128 (38.7)	70 (42.9)	140 (37.5)	76 (41.3)
Endocrine therapy	330 (99.7)	160 (98.2)	347 (93.0)	165 (89.7)
Chemotherapy	331 (100)	162 (99.4)	373 (100)	183 (99.5)
Lines of therapy for metastatic disease				
Median no. of lines (range)	3 (1–9)	3 (1–8)	3 (1–9)	3 (1–8)
No. of lines — no. of patients (%)				
1	23 (6.9)	14 (8.6)	39 (10.5)	19 (10.3)
2	85 (25.7)	41 (25.2)	100 (26.8)	53 (28.8)
≥3	223 (67.4)	108 (66.3)	234 (62.7)	112 (60.9)

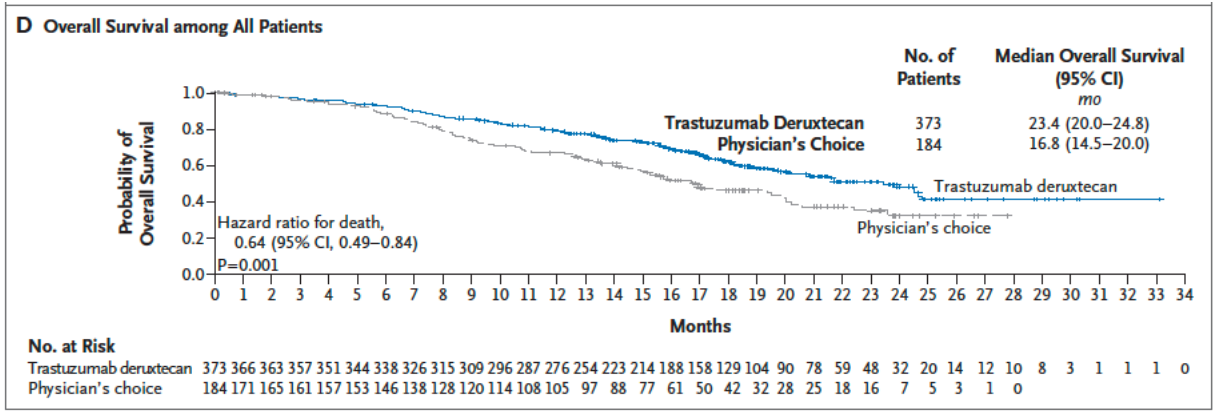
DB-04: PFS


A Progression-free Survival in Hormone Receptor–Positive Cohort
Probability of Progression-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
No. of Patients
Median Progression-free Survival (95% CI)
mo
Trastuzumab Deruxtecan 331 10.1 (9.5–11.5)
Physician's Choice 163 5.4 (4.4–7.1)
Hazard ratio for progression or death, 0.51 (95% CI, 0.40–0.64)
P<0.001
Trastuzumab deruxtecan
Physician's choice
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Months
No. at Risk
Trastuzumab deruxtecan 331 324 290 265 262 248 218 198 182 165 142 128 107 89 78 73 64 48 37 31 28 17 14 12 7 4 4 1 1 0
Physician's choice 163 146 105 85 84 69 57 48 43 32 30 27 24 20 14 12 8 4 3 2 1 1 1 1 1 1 0


B Progression-free Survival among All Patients
Probability of Progression-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
No. of Patients
Median Progression-free Survival (95% CI)
mo
Trastuzumab Deruxtecan 373 9.9 (9.0–11.3)
Physician's Choice 184 5.1 (4.2–6.8)
Hazard ratio for progression or death, 0.50 (95% CI, 0.40–0.63)
P<0.001
Trastuzumab deruxtecan
Physician's choice
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Months
No. at Risk
Trastuzumab deruxtecan 373 365 325 295 290 272 238 217 201 183 156 142 118 100 88 81 71 53 42 35 32 21 18 15 8 4 4 1 1 0
Physician's choice 184 166 119 93 90 73 60 51 45 34 32 29 26 22 15 13 9 5 4 3 1 1 1 1 1 1 0

DB-04: OS


C Overall Survival in Hormone Receptor–Positive Cohort
No. of Patients
Median Overall Survival (95% CI)
mo
Trastuzumab Deruxtecan 331 23.9 (20.8–24.8)
Physician's Choice 163 17.5 (15.2–22.4)
Probability of Overall Survival
Trastuzumab deruxtecan
Physician's choice
Hazard ratio for death, 0.64 (95% CI, 0.48–0.86)
P=0.003
Months
No. at Risk
Trastuzumab deruxtecan 331 325 323 319 314 309 303 293 285 280 268 260 250 228 199 190 168 144 116 95 81 70 51 40 26 14 9 8 6 6 2 1 1 1 0
Physician's choice 163 151 145 143 139 135 130 124 115 109 104 98 96 89 80 71 56 45 37 29 25 23 16 14 7 5 3 1 0


D Overall Survival among All Patients
No. of Patients
Median Overall Survival (95% CI)
mo
Trastuzumab Deruxtecan 373 23.4 (20.0–24.8)
Physician's Choice 184 16.8 (14.5–20.0)
Probability of Overall Survival
Trastuzumab deruxtecan
Physician's choice
Hazard ratio for death, 0.64 (95% CI, 0.49–0.84)
P=0.001
Months
No. at Risk
Trastuzumab deruxtecan 373 366 363 357 351 344 338 326 315 309 296 287 276 254 223 214 188 158 129 104 90 78 59 48 32 20 14 12 10 8 3 1 1 1 0
Physician's choice 184 171 165 161 157 153 146 138 128 120 114 108 105 97 88 77 61 50 42 32 28 25 18 16 7 5 3 1 0

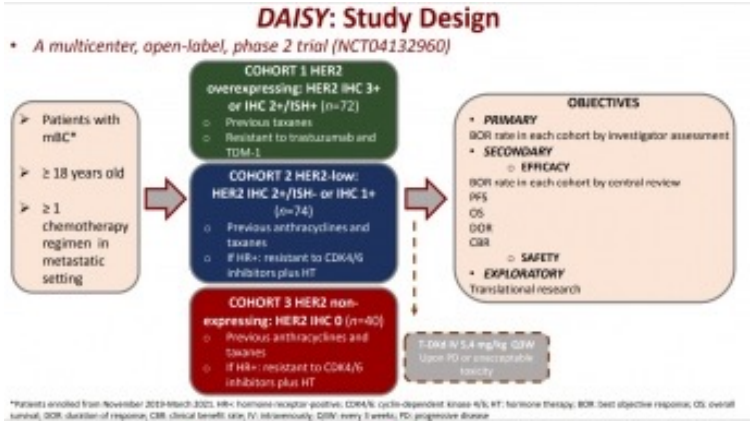
DB-04: Adverse events of special interest

- LV dysfunction in 17 (4.6%) with T-DXd
- Incidence of ILD/pneumonitis with T-DXd: 45 patients (12.1%)
  - 13 (3.5%) grade 1
  - 24 (6.5%) grade 2
  - 5 (1.3%) grade 3
  - 3 (0.8%) grade 5 events

DB-04 Conclusion

- Significant improvement in PFS and OS of T-Dxd
  - Median PFS 9.9 vs 5.1 mo: HR: 0.50; *P* <.001
  - Median OS 23.4 vs 16.8 mo: HR: 0.64; *P* = .001
- Safety consistent with prior studies
- FDA revised indications for T-Dxd to include HER2 low patients in August 2022

DAISY Trial



- 186 patients
  - 71% HR+ tumors
  - 82% > 3 lines therapy
  - Cohort 1: 68 (IHC 3+),
    Cohort 2: 73 (IHC 1+/2+)
    Cohort 3: 38 (IHC 0)

DAISY: Results and Safety

- Cohort 1: ORR 70.6%, PFS 11.1 mos
- Cohort 2: ORR 38%, PFS 6.7 mos
- Cohort 3: ORR 30%, PFS 4.2 mos

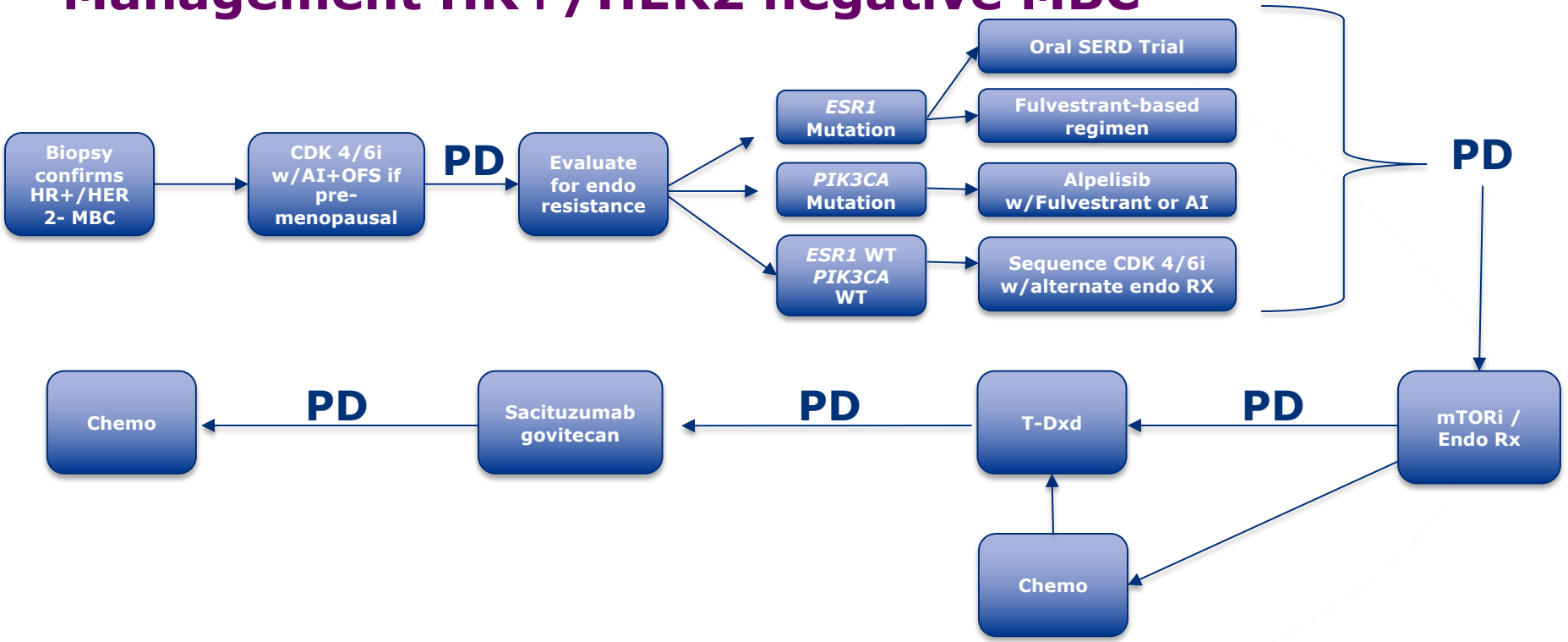
- Rate of ILD: 2.8%, all grade 1 & 2

T-Dxd in HER2 low tumors

- T-Dxd effective for HER2 low disease
- Response appears to be associated with HER2 expression
- 30% response in HER2 0 by IHC tumors
  - Translational and exploratory analyses from DAISY at ESMO 2022
    - Low uptake of T-Dxd in HER2 0 cells- bystander effect (payload diffuses across cell membrane to neighboring cells)
    - Spatial distribution of HER2 matters
    - Much more to come regarding MOA

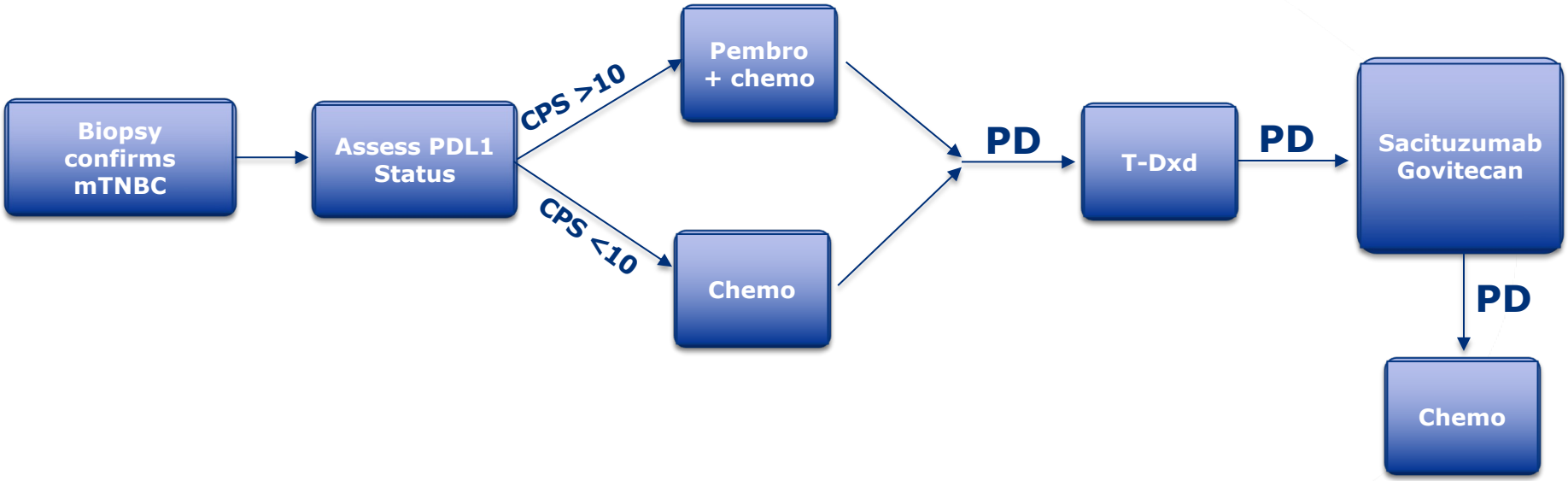
How I treat Advanced Breast Cancer

Management HR+/HER2 negative MBC



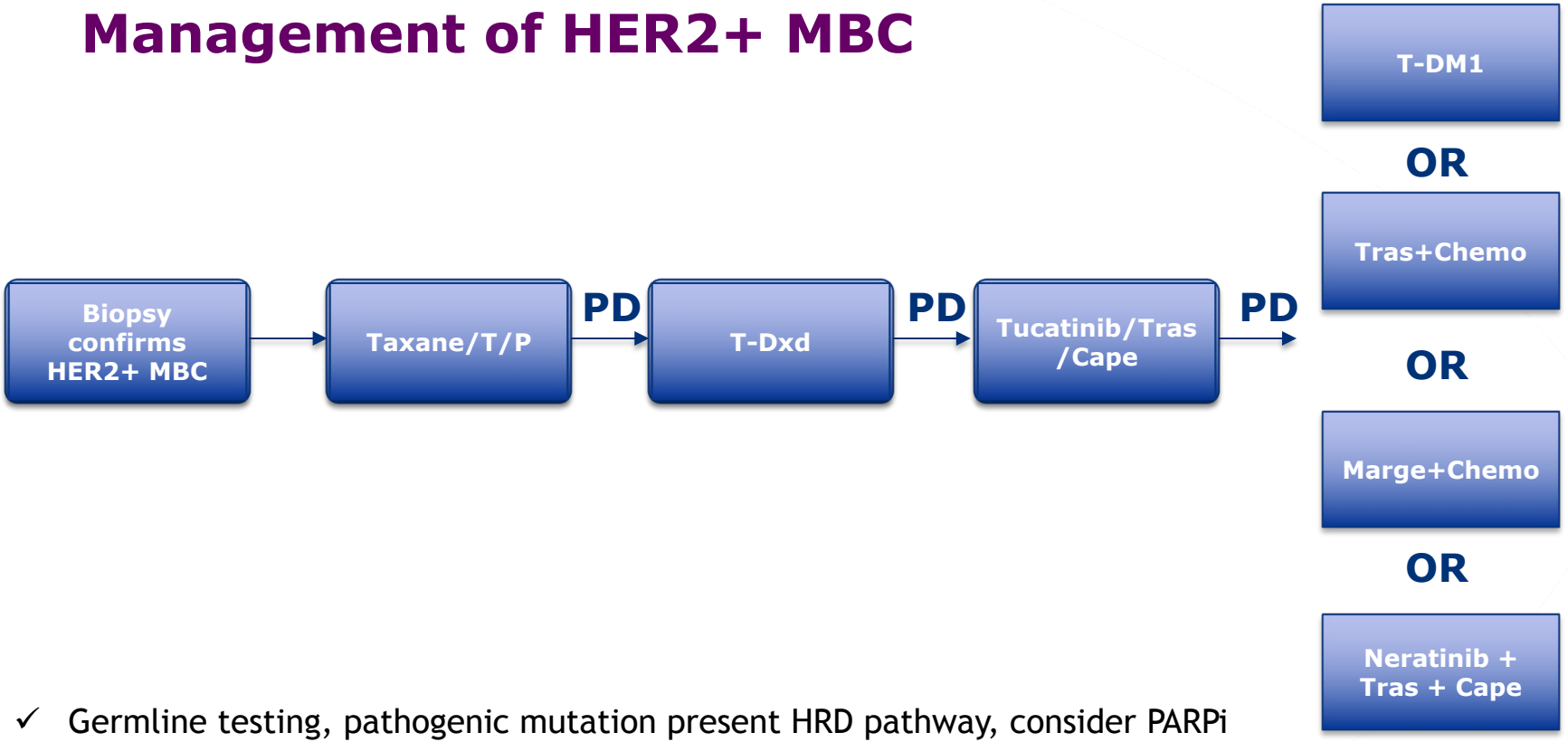
- ✓ Germline testing, pathogenic mutation present HRD pathway, consider PARPi
- ✓ Continuously assess for clinical trial eligibility
- ✓ Rebiopsy if possible, or send ctDNA assay for molecular analysis at disease progression

Management of TNBC



- ✓ Germline testing, pathogenic mutation present HRD pathway, consider PARPi
- ✓ Continuously assess for clinical trial eligibility
- ✓ Consider rebiopsy and send for molecular analysis at disease progression

Management of HER2+ MBC



- ✓ Germline testing, pathogenic mutation present HRD pathway, consider PARPi
- ✓ Continuously assess for clinical trial eligibility
- ✓ Consider rebiopsy and send for molecular analysis at disease progression