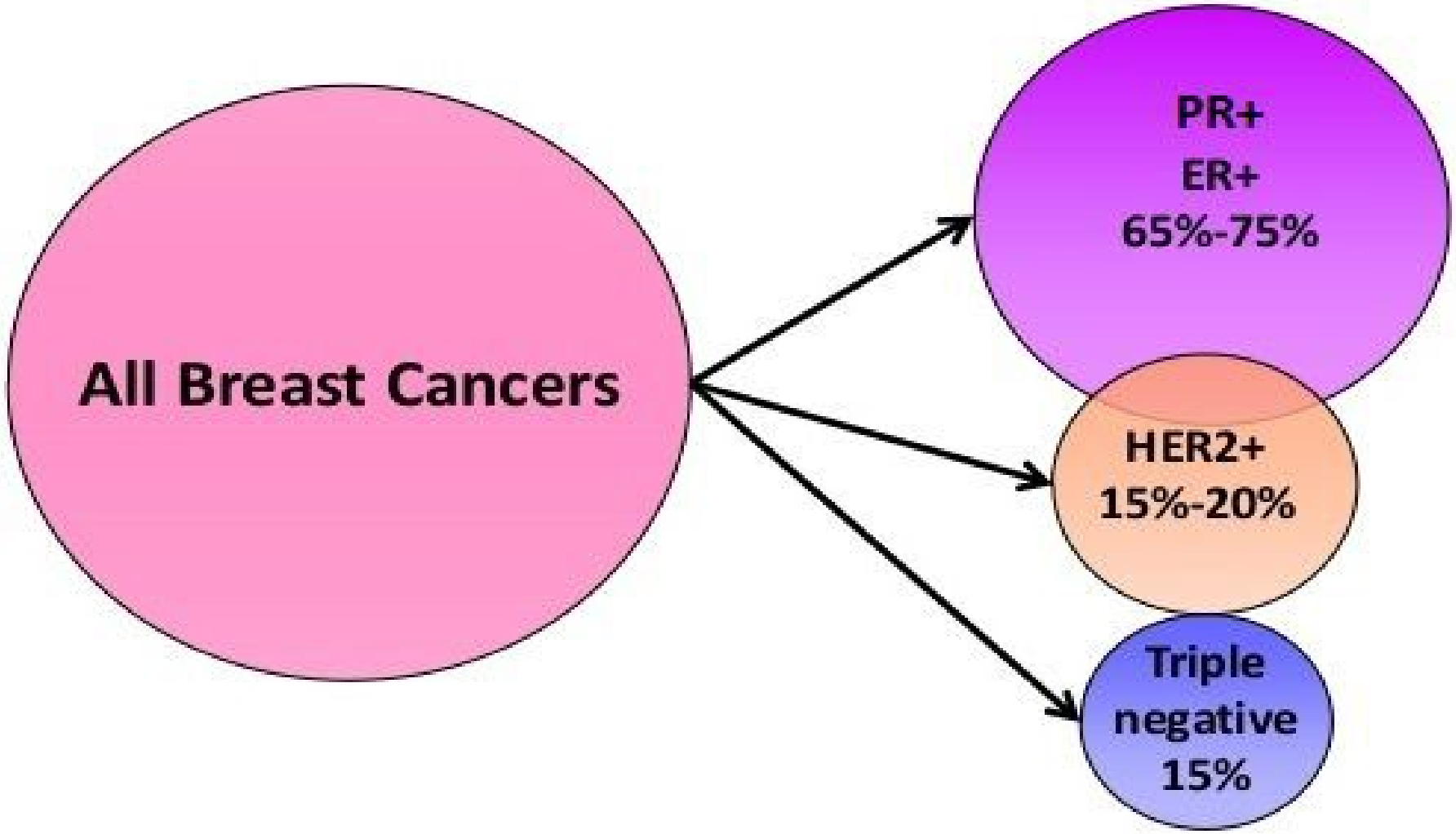
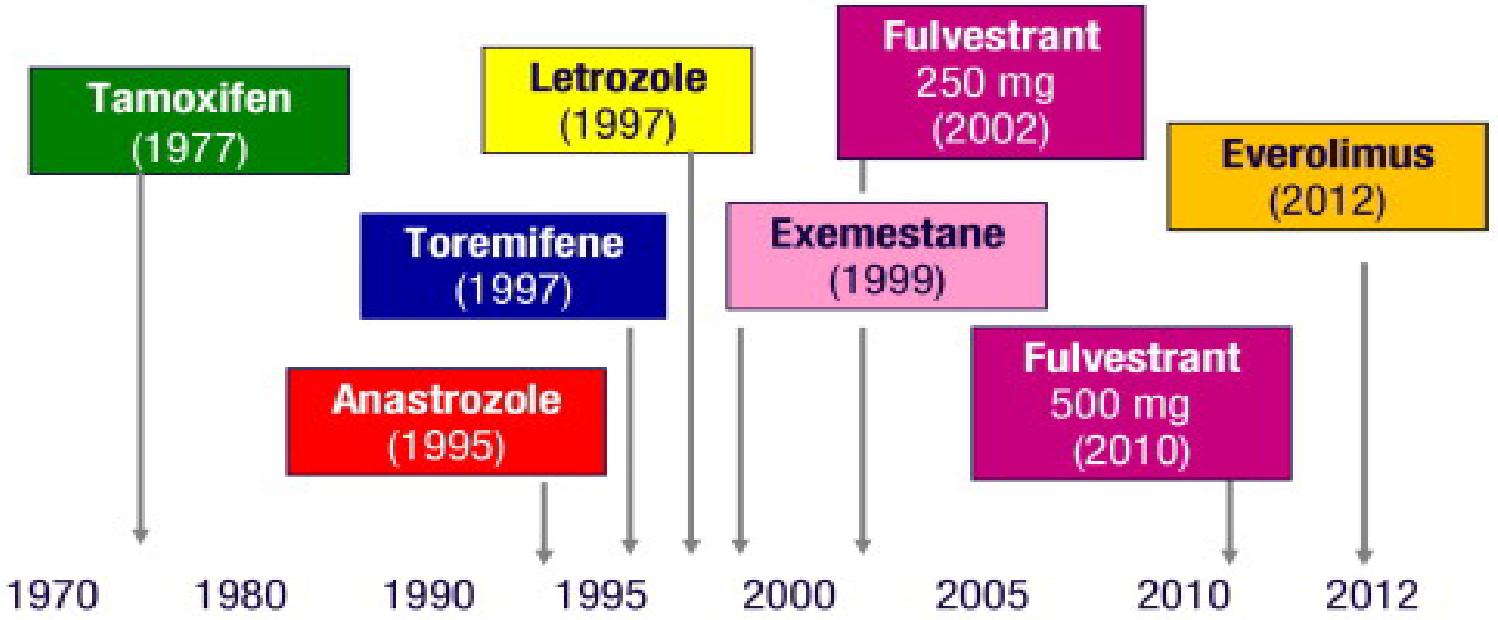
Systemic therapy for Breast Cancer: where are we?

Kamel Abou Hussein, MD

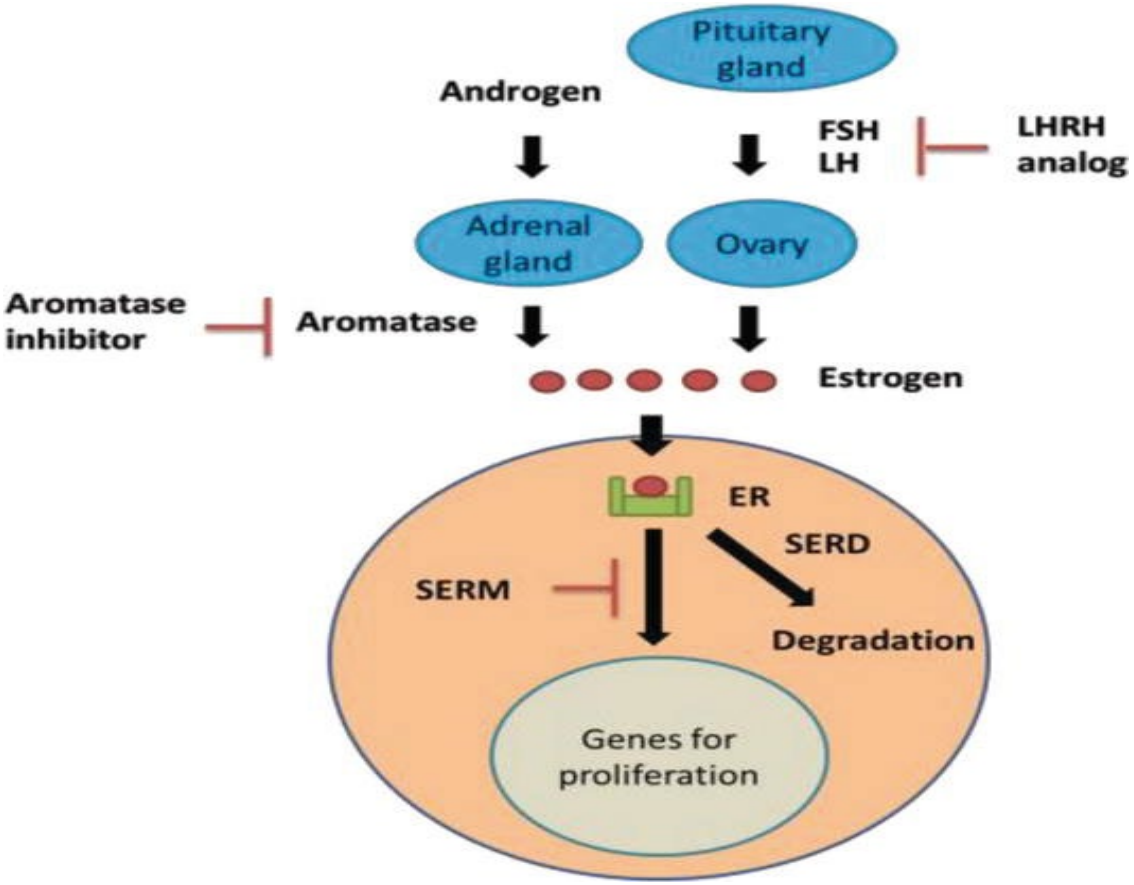
Subtypes



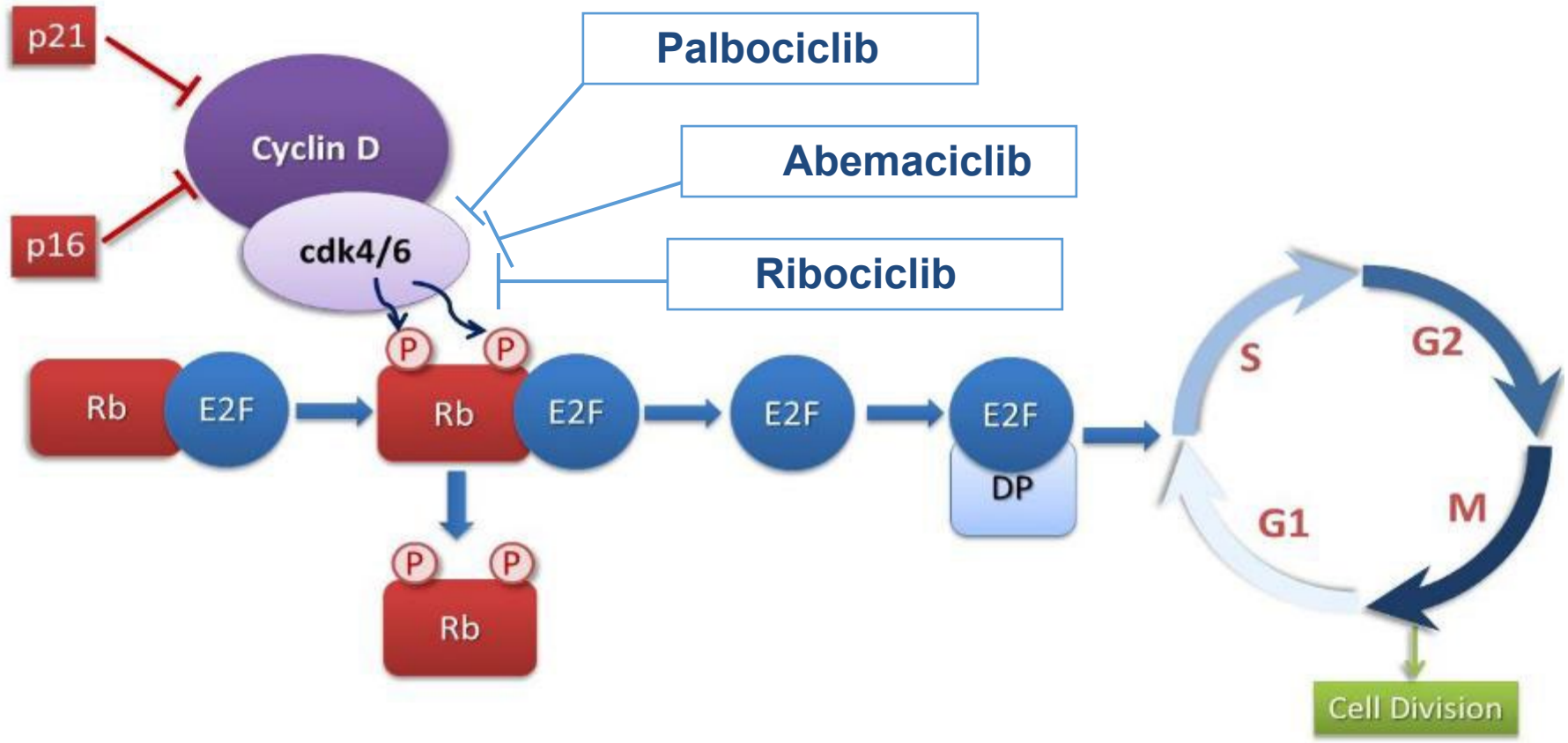


Targeted Therapies

Targeting the ER pathway



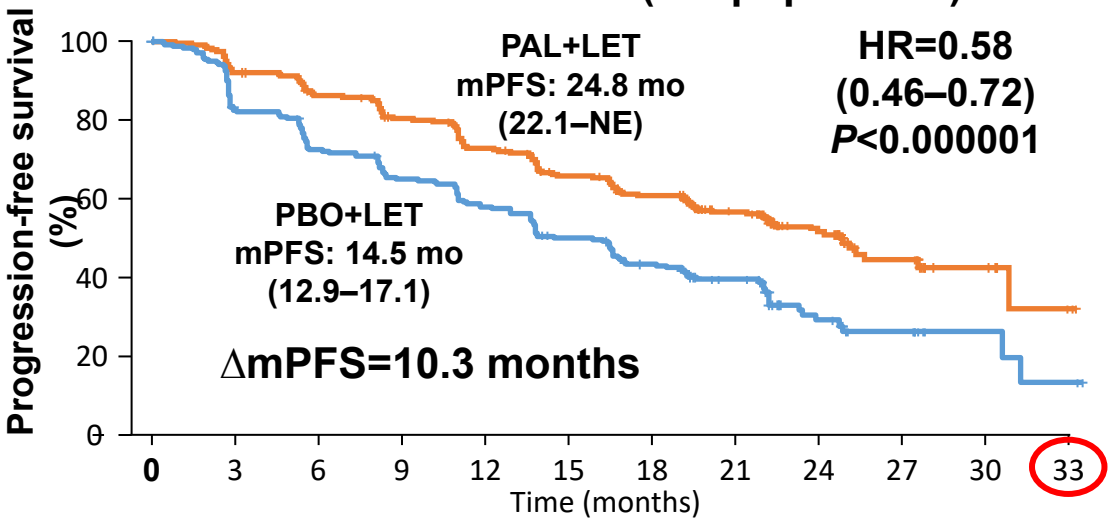
CDK4/6 Regulates Cell Cycle Progression



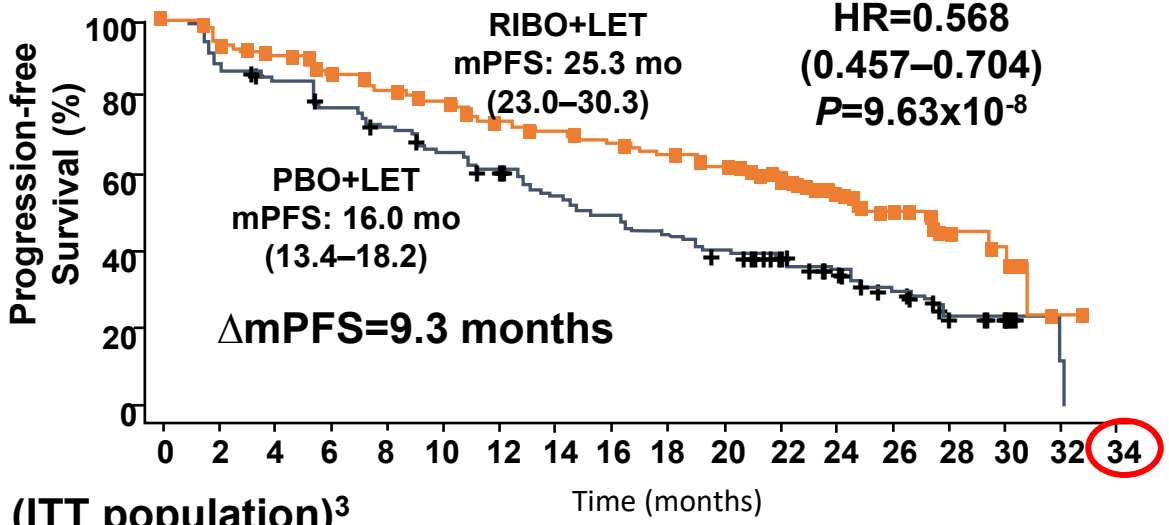
M, mitosis; Rb, retinoblastoma.
Adapted from Finn et al, 2016.

Phase III trials with CDK4/6 Inhibitors: 1st Line Endocrine Sensitive MBC

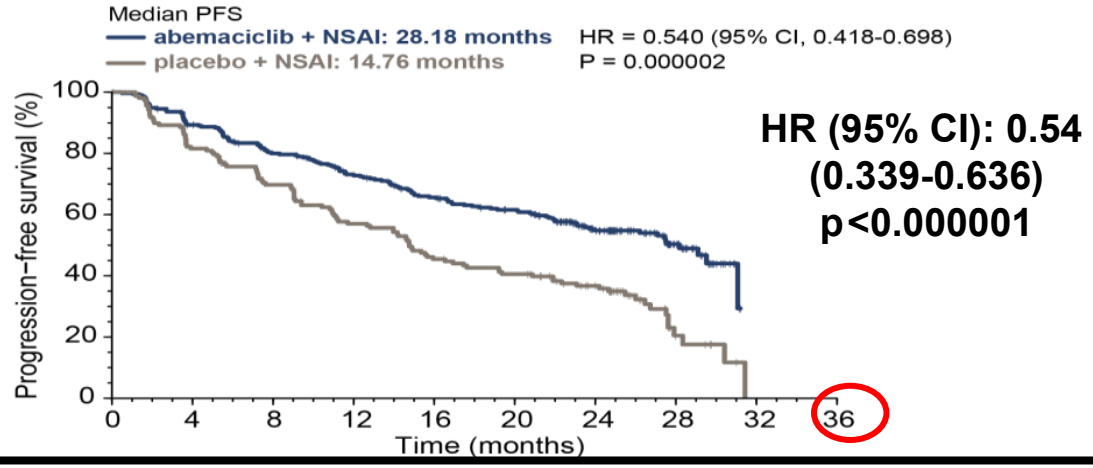
PALOMA-2: PFS (ITT population)[1]



MONALEESA-2: PFS (ITT population)[2]



MONARCH-3: PFS (ITT population)[3]



1. Finn RS, et al. N Engl J Med. 2016;375(20):1925-1936.
2. Hortobagyi G, et al. ASCO 2017. Poster 1038.
3. Goetz MP et al, proc AACR 2018

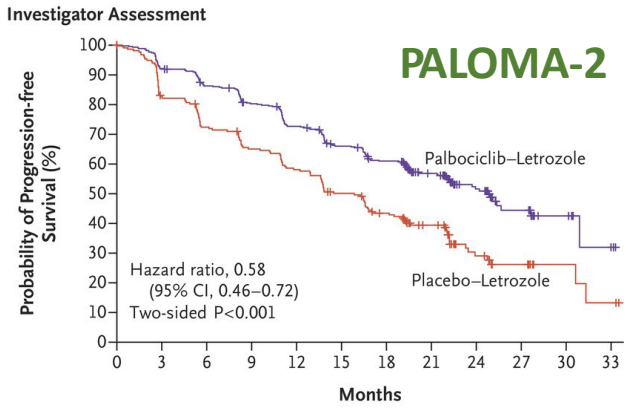
Palbociclib

Ribociclib

Abemaciclib

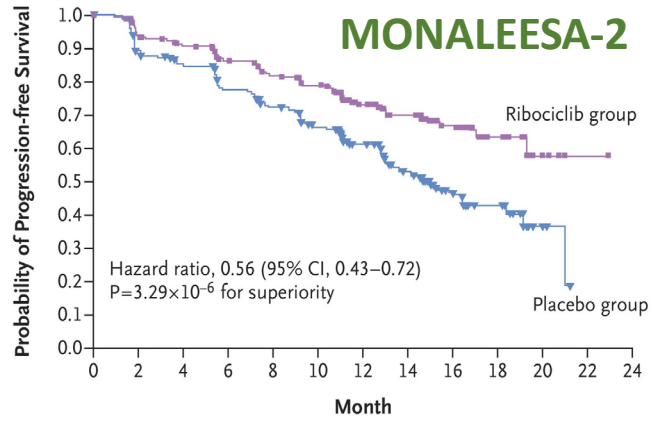
1st Line

PALOMA-2

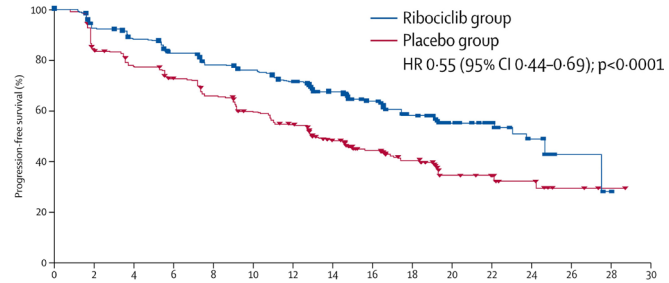


No. at Risk												
Palbociclib–Letrozole	444	395	360	328	295	263	238	154	69	29	10	2
Placebo–Letrozole	222	171	148	131	116	98	81	54	22	12	4	2

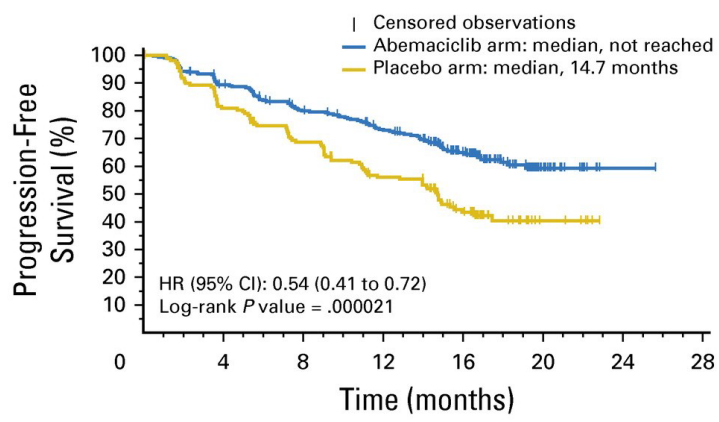
MONALEESA-2



No. at Risk													
Ribociclib	334	294	277	257	240	226	164	119	68	20	6	1	0
Placebo	334	279	264	237	217	192	143	88	44	23	5	0	0



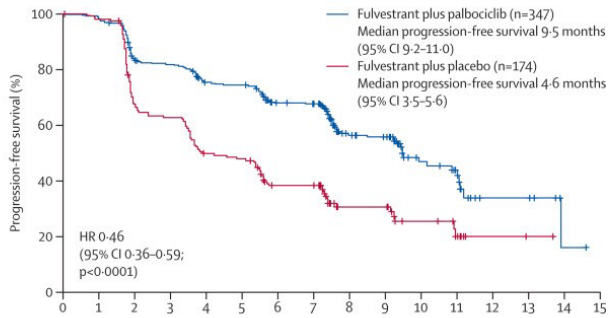
Abemaciclib



No. at risk:								
Abemaciclib arm	328	271	234	205	125	25	1	0
Placebo arm	165	127	105	82	45	7	0	0

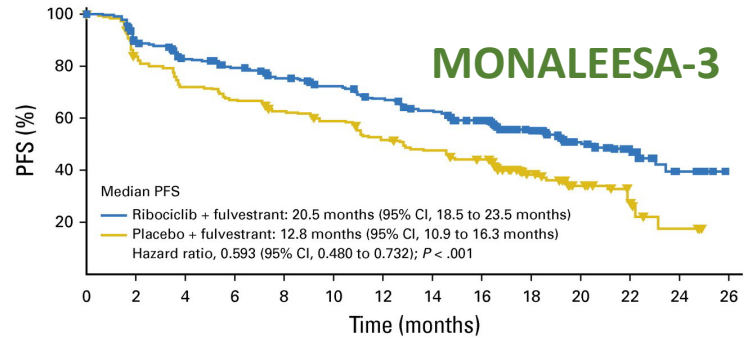
2nd Line

PALOMA-3



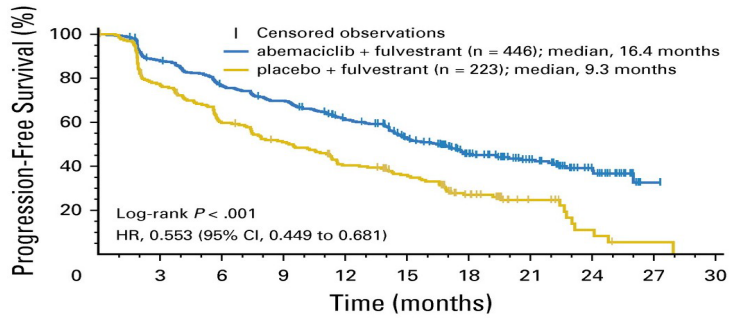
Number at risk															
Fulvestrant plus palbociclib	347	333	281	273	247	244	202	197	91	85	32	23	7	7	1	0
Fulvestrant plus placebo	174	165	112	105	83	80	59	58	22	22	13	7	2	1	0	0

MONALEESA-3



No. at risk:													
Ribociclib + fulvestrant	484	403	365	347	324	305	282	259	235	155	78	52	13	0
Placebo + fulvestrant	242	195	168	156	144	134	116	106	95	53	27	14	4	0

MONARCH 2



No. at risk											
abemaciclib + fulvestrant	446	367	314	281	234	171	101	65	32	2	0
placebo + fulvestrant	223	165	123	103	80	61	32	13	4	1	0

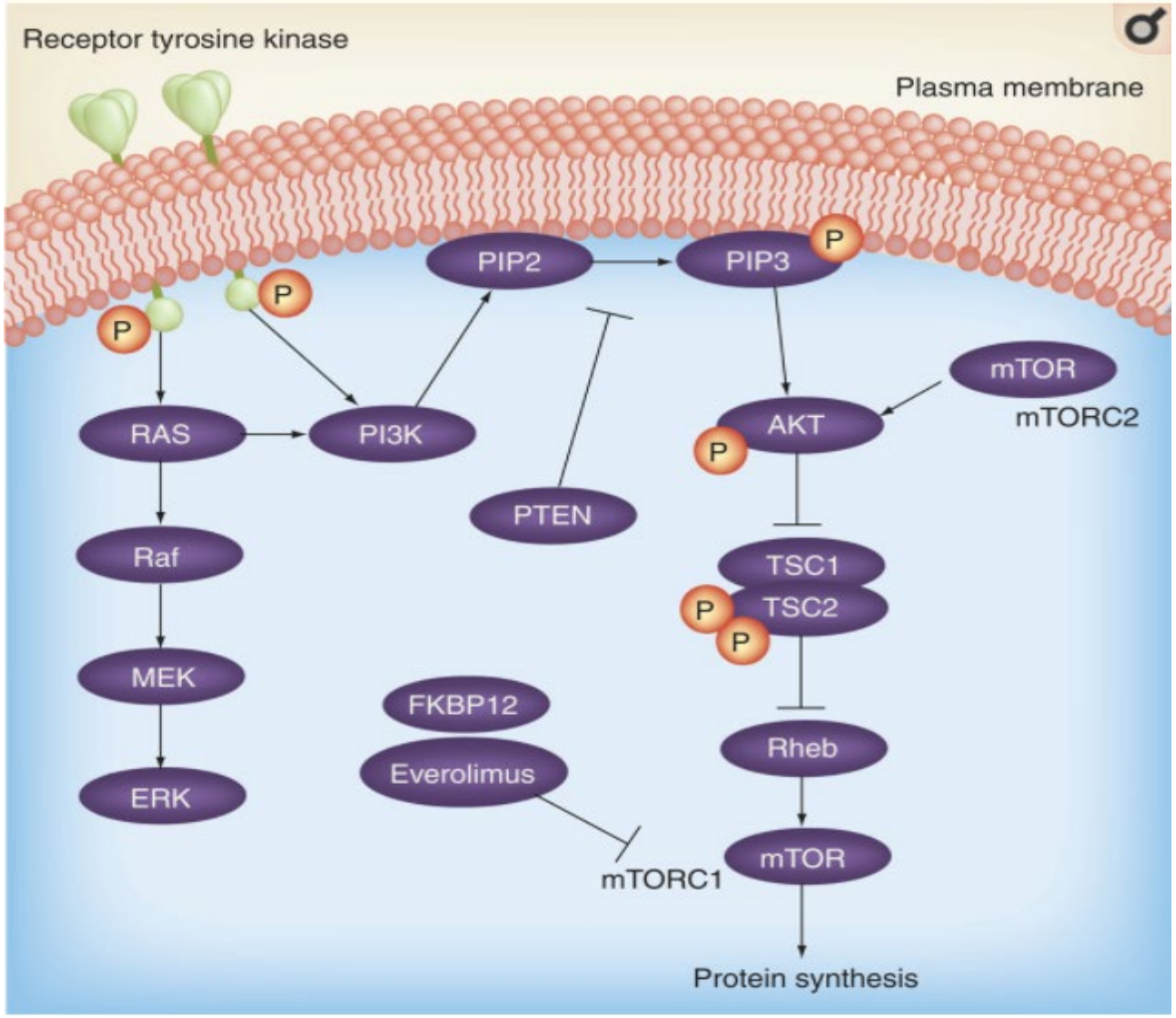
Line	Study Name	Endocrine Agent	CDK4/6i	PFS	HR
1st	PALOMA-1 Lancet 2015	Letrozole	Palbociclib	10.2m → 20.2m	0.49
	PALOMA-2 NEJM 2016	Letrozole	Palbociclib	14.5m → 24.8 m	0.58
	MONALEESA-2 NEJM 2016	Letrozole	Ribociclib	14.5m → ~26m	0.56
	MONALEESA-7* SABCS 2017	Letrozole + OFS	Ribociclib	13.0m → 23.8m	0.55
	MONARCH 3 JCO 2017	NSAI	Abemaciclib	14.7m → NR	0.54
2nd	PALOMA-3 NEJM 2015	Fulvestrant	Palbociclib	3.8m → 9.2m	0.42
	MONALEESA-3 ASCO 2018	Fulvestrant	Ribociclib	12.8m → 20.5m	0.59
	MONARCH 2 JCO 2017	Fulvestrant	Abemaciclib	9.3m → 16.4m	0.55
	MONARCH 2* ASCO 2018	Fulvestrant + OFS	Abemaciclib	10.5m → NR	0.45

**premenopausal women*

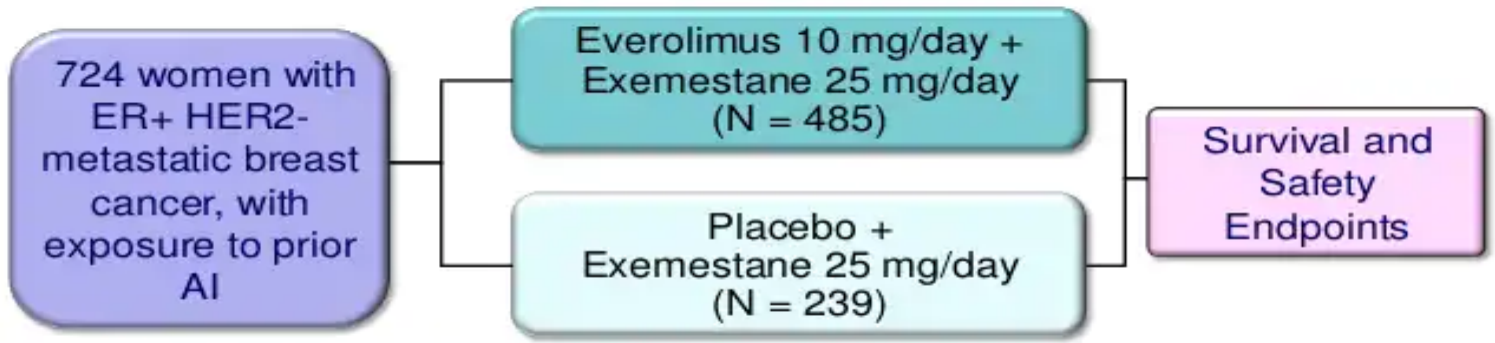
Overall Survival Benefit with CDK4/6 Inhibitors for ER-Positive, HER2-Negative Metastatic Breast Cancer

- MONALEESA-7: Ribociclib + endocrine therapy
  - HR (95% CI): 0.763 (0.608-0.956); Months: 58.7 vs 48.0
- MONALEESA-3: Ribociclib + fulvestrant
  - HR (95% CI): 0.726 (0.588-0.897); Months: 53.7 vs 41.5
- MONALEESA-2: Ribociclib + Letrozole
  - HR (95% CI): 0.76 (0.63-0.93); Months: 63.9 vs 51.4
- MONARCH 2: Abemaciclib + fulvestrant
  - HR (95% CI): 0.757 (0.606-0.945); Months: 46.7 vs 37.3
- PALOMA-3: Palbociclib + fulvestrant
  - HR (95% CI): 0.81 (0.65-0.99); Months: 34.8 vs 28.0

PI3K/AKT/mTOR pathway



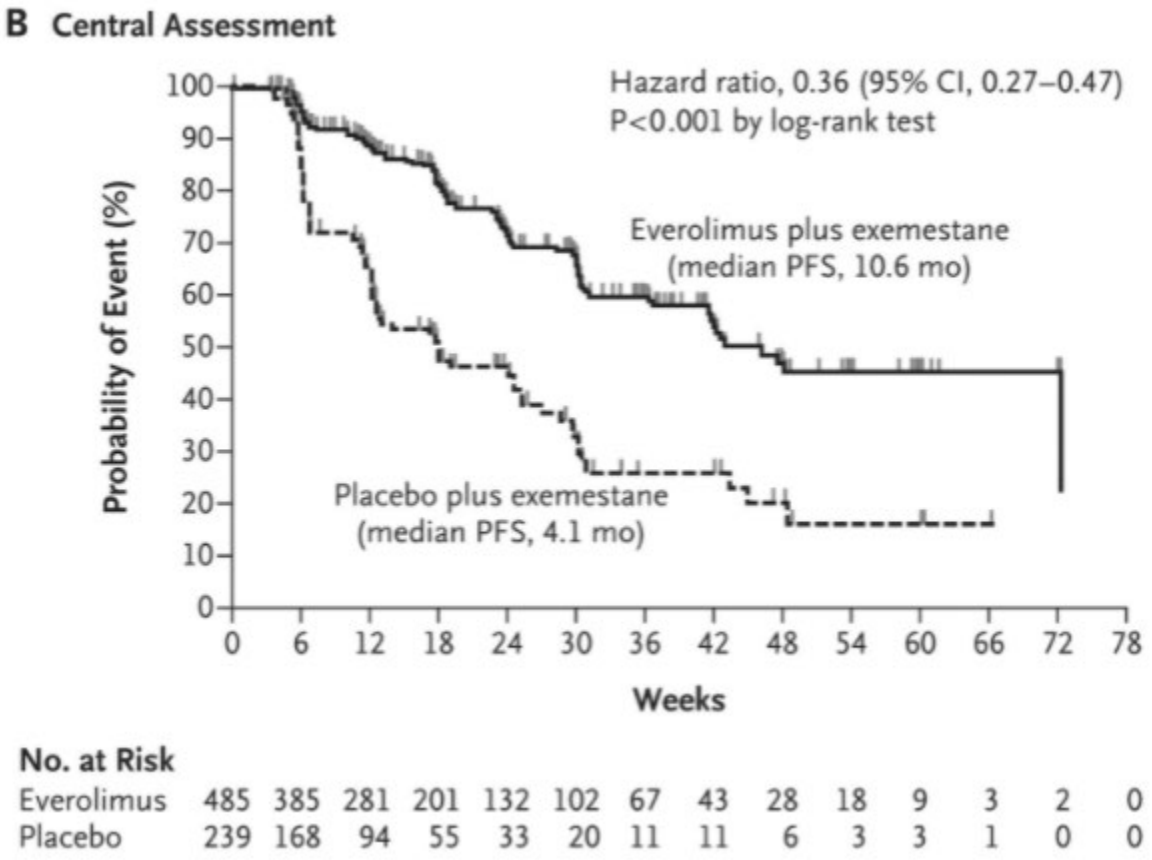
BOLERO-2: A Trial of Everolimus in HR+ Breast Cancer



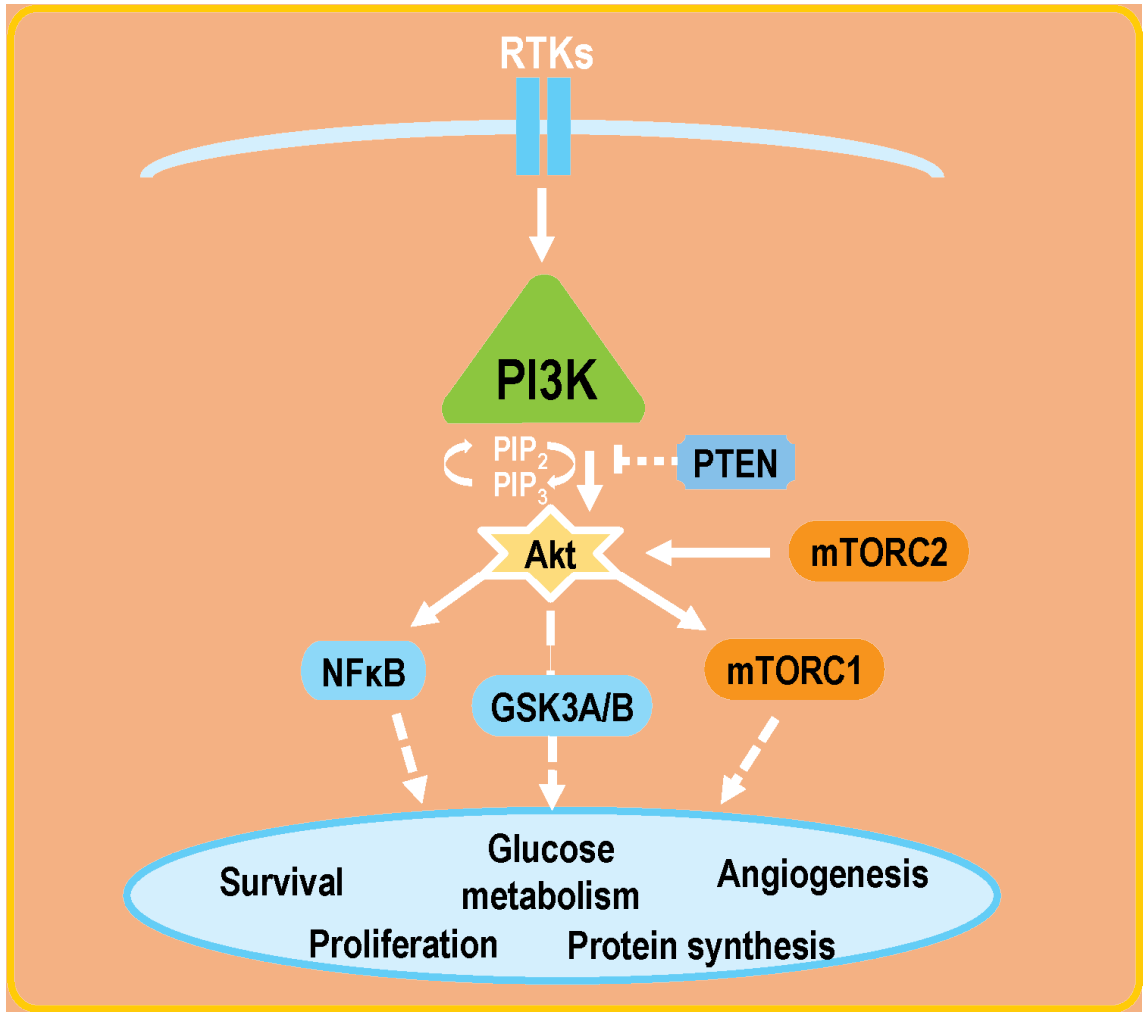
Everolimus: Mammalian target of rapamycin (mTOR) inhibitor

Baselga et al, NEJM 2012

BOLERO-2 primary endpoint PFS



PI3K Inhibitors: Mechanism of Action



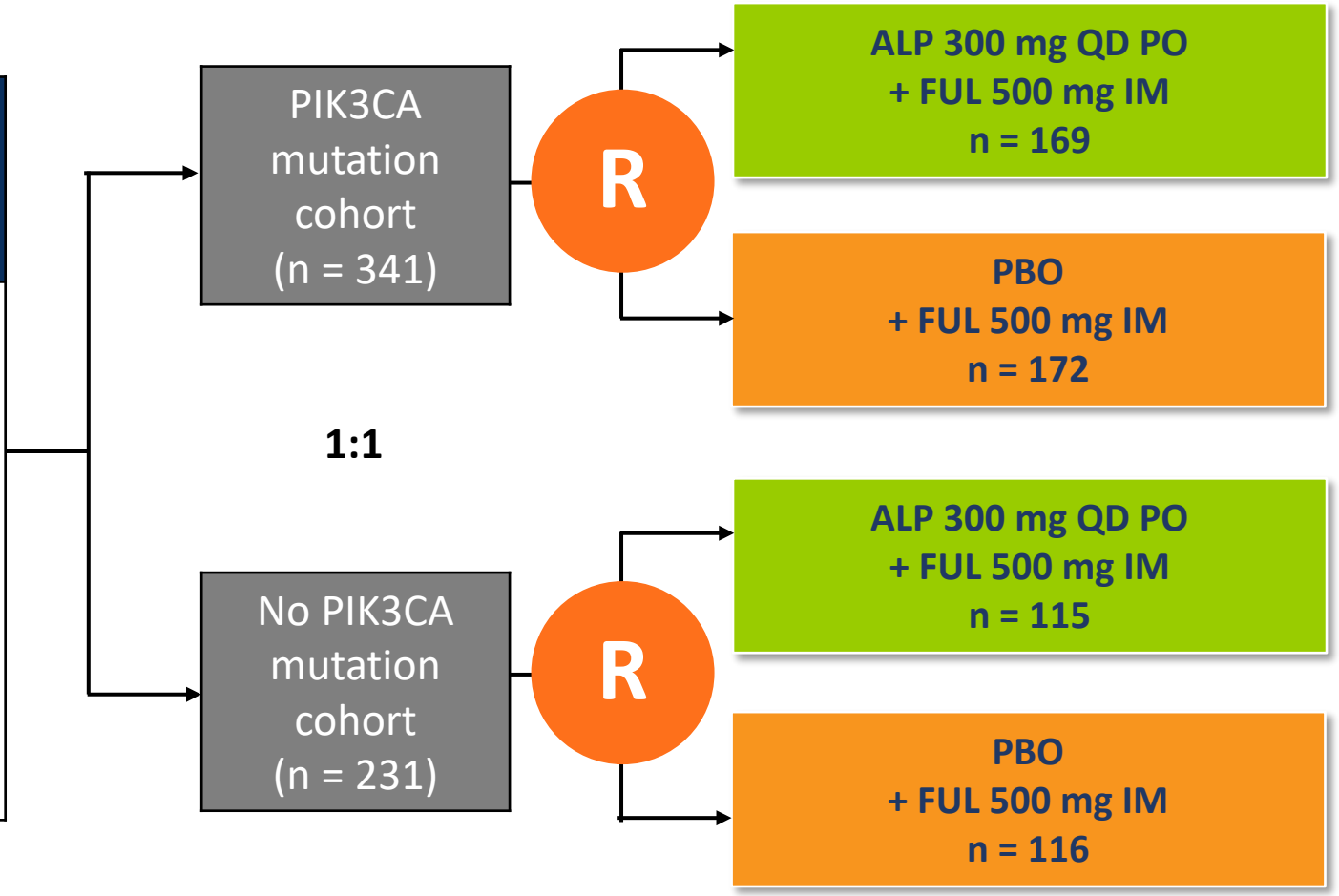
- PI3K is involved in the activation of Akt.
- Hyperactivation of the PI3K pathway is implicated in malignant transformation, cancer progression and endocrine therapy resistance.
- PIK3CA encodes the alpha isoform of the PI3K catalytic subunit.
- Around 40% of patients with HR+, HER- BC present with an activating PIK3CA tumor mutation.
- Alpelisib is a specific inhibitor of the PI3K alpha isoform.

André F et al. ESMO 2018;Abstract LBA3_PR.

SOLAR-1 Phase III Study Design

Men or postmenopausal women, with HR+, HER2- advanced breast cancer

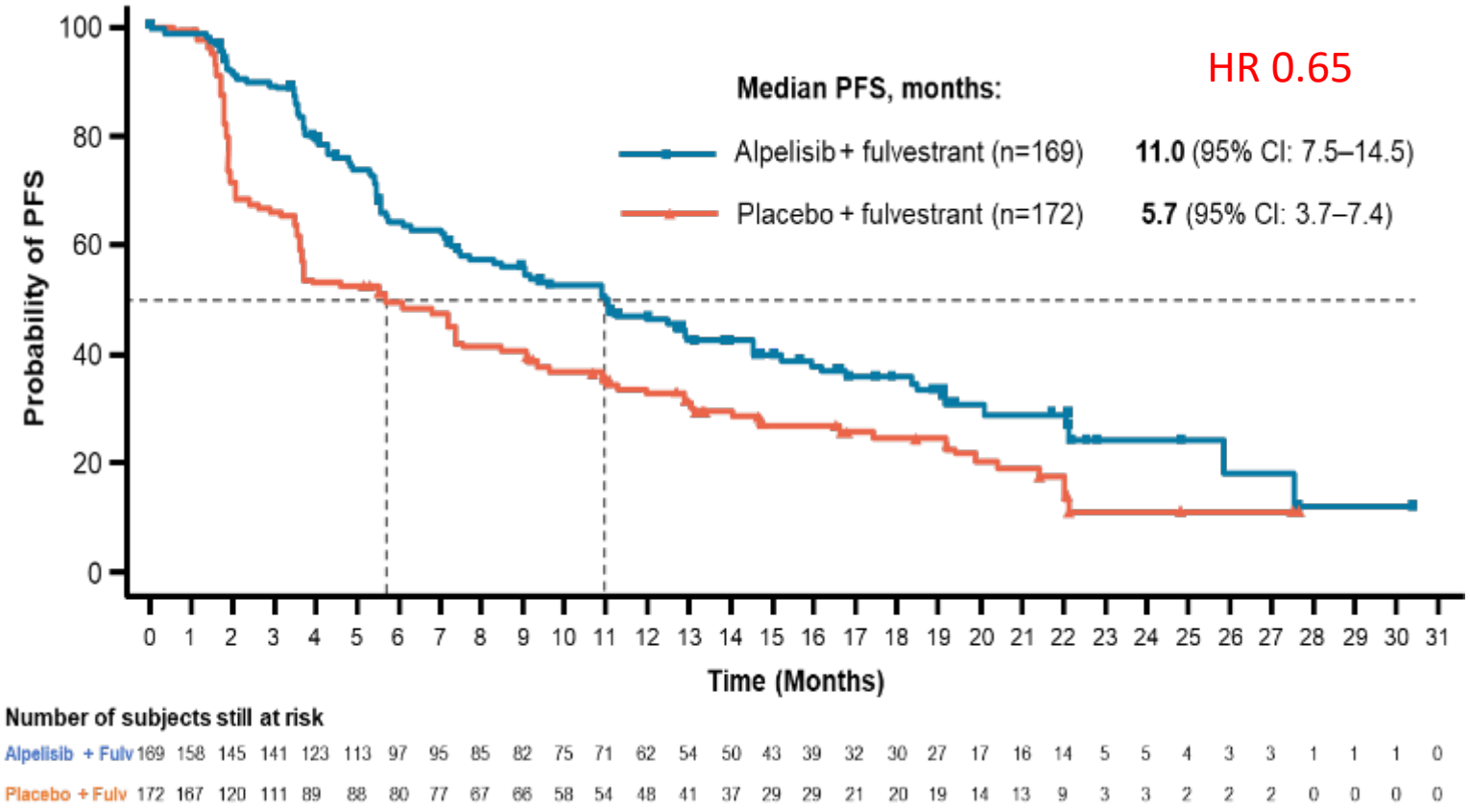
- Recurrence/progression on/after prior AI
- Identified PIK3CA status (in archival or fresh tumor tissue)
- ECOG performance status ≤1 (N = 572)



Primary endpoint: PFS in PIK3CA mutation cohort

André F et al. ESMO 2018;Abstract LBA3_PR.

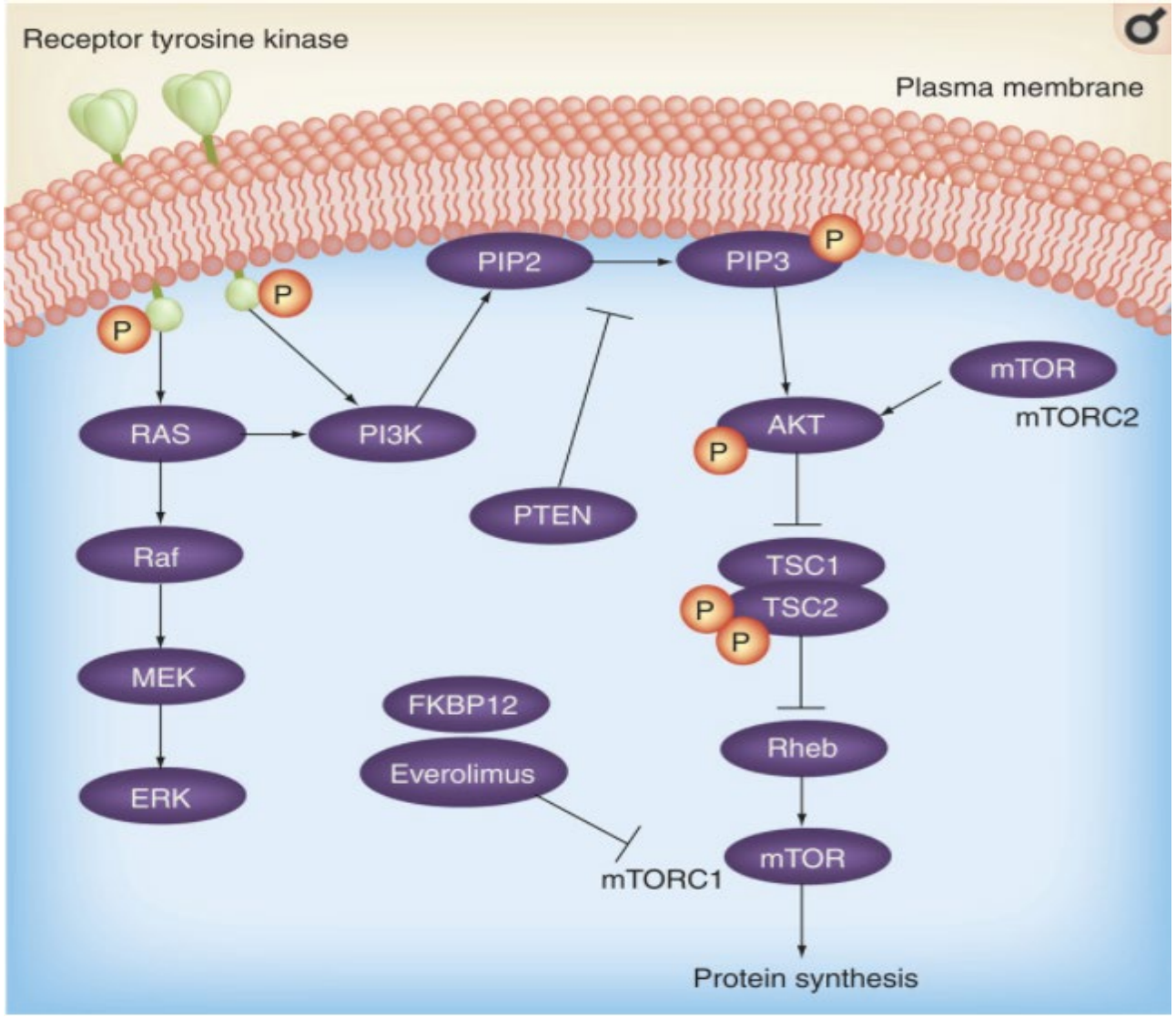
SOLAR-1: Alpelisib Improved PFS in the *PIK3CA*-mutant cancers



No benefit noted in the non mutant cohort

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
At final PFS analysis, superiority was declared if one-sided, stratified log-rank test *P* value was ≤ 0.0199 (Haybittle–Peto boundary).
[a] Mutation status determined from tissue biopsy.
1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

PI3K/AKT/mTOR pathway



FAKTION: Capivasertib + Fulvestrant for AI-Resistant ER-Positive, HER2-Negative mBC

- Phase II study of capivasertib + fulvestrant vs placebo + fulvestrant (N = 140)
  - Relapse or progression on an AI
  - Capivasertib (AZD5363): selective, oral AKT inhibitor
- Capivasertib + fulvestrant improved PFS in endocrine-resistant mBC vs placebo + fulvestrant
  - Primary endpoint met
  - Trend toward improvement in OS
- Ongoing Phase III CAPitello291 Trial
- IPATunit150: ipatasertib +/- palbociclib and fulvestrant

Outcome	CAP + FULV (n = 69)	PBO + FULV (n = 71)
Median PFS, mos	10.3	4.8
	HR: 0.57 *P* = .0035	
Median OS, mos	26.0	20.0
	HR: 0.59 *P* = .071	

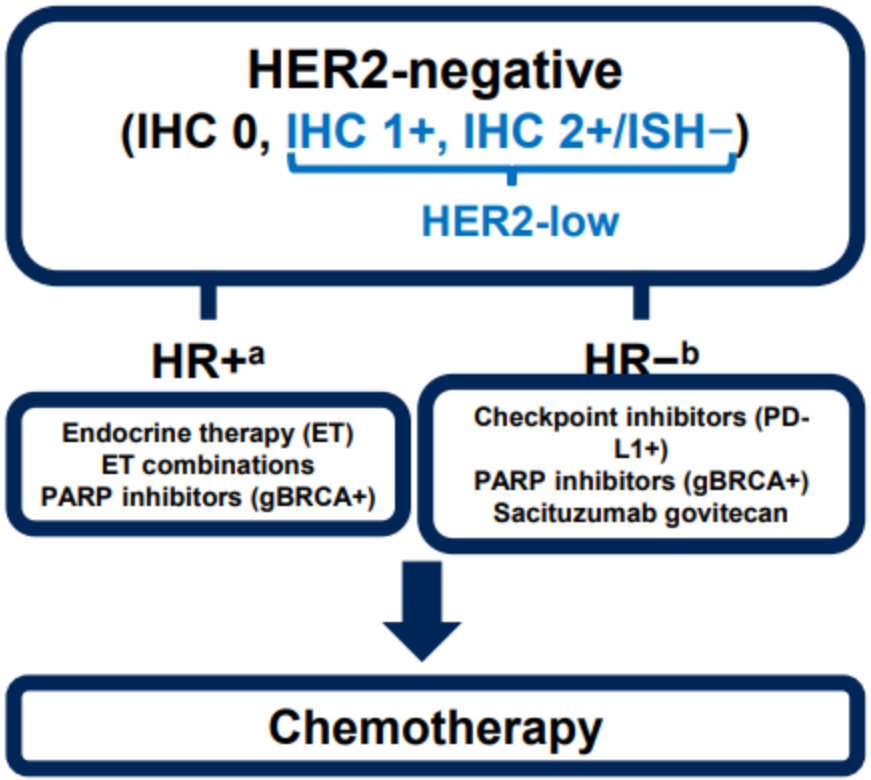
- Similar benefit was observed in patients with PI3K/AKT/PTEN-activated and nonactivated tumors
- 39% of patients in the capivasertib + fulvestrant arm required dose reductions, primarily due to diarrhea and rash, and 12% discontinued due to toxicity

Jones RH, et al. Lancet Oncol 2020.

Her-2 low

HER2-low mBC: Unmet Clinical Need

Current Standard of Care



- **HER2-low mBC is defined by IHC scores of 1+ or 2+/ISH−**
  - This is a heterogenous population with a high prevalence of HR coexpression and without a distinct biology
- **HER2-low mBC is treated as HER2− mBC, with limited options for later lines of therapy[1-4]**
  - Current HER2-targeted therapies are not effective for patients with tumors that express lower levels of HER2
- **Therapeutic options for patients with HR+/HER2− mBC after CDK4/6i progression have limited efficacy**
  - Real-world studies suggest a PFS of <4 months after progressive disease with CDK4/6i[5]
- **Limited benefit exists for patients who progress after multiple lines of chemotherapy**
  - In a pooled analysis of patients with HER2− mBC, eribulin and capecitabine provide minimal benefit, with a mPFS of ~4 months and mOS of ~15 months[6]

CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; gBRCA+, germline breast cancer gene positive; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; mOS, median overall survival; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death ligand 1; mPFS, median progression-free survival; T-DXd, trastuzumab deruxtecan.
[a]Immunoreactive for estrogen or progesterone receptor in ≥1% tumor cell nuclei. [b]Immunoreactive for estrogen or progesterone receptor in <1% tumor cell nuclei.

1. Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-1962. 2. Aogi K, et al. *Ann Oncol*. 2012;23:1441-1448. 3. Eiger D, et al. *Cancers (Basel)*. 2021;13(5):1015. 4. Fehrenbacher L, et al. *J Clin Oncol*. 2019;38(5):444-453. 5. Mo H, et al. *Clin Breast Cancer*. 2022;22:143-148. 6. Kaufman PA, et al. *J Clin Oncol*. 2015;33:594-601.

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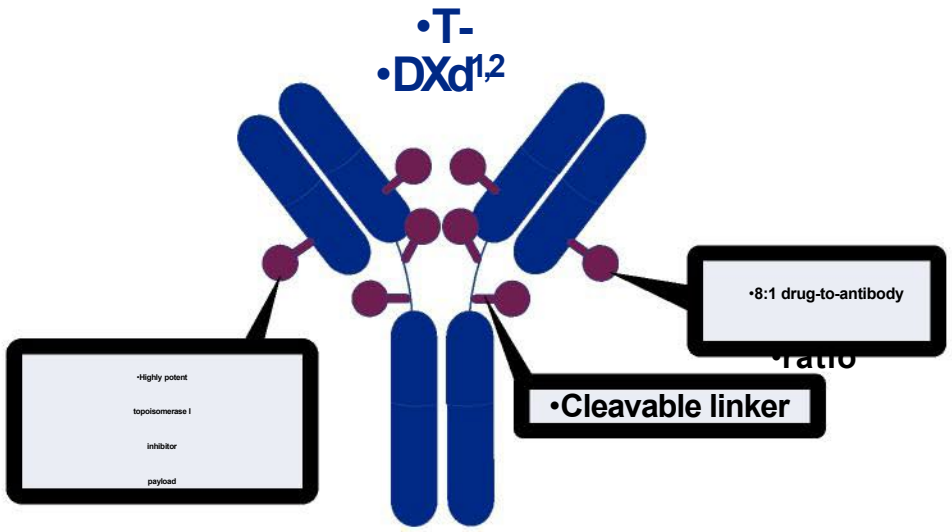
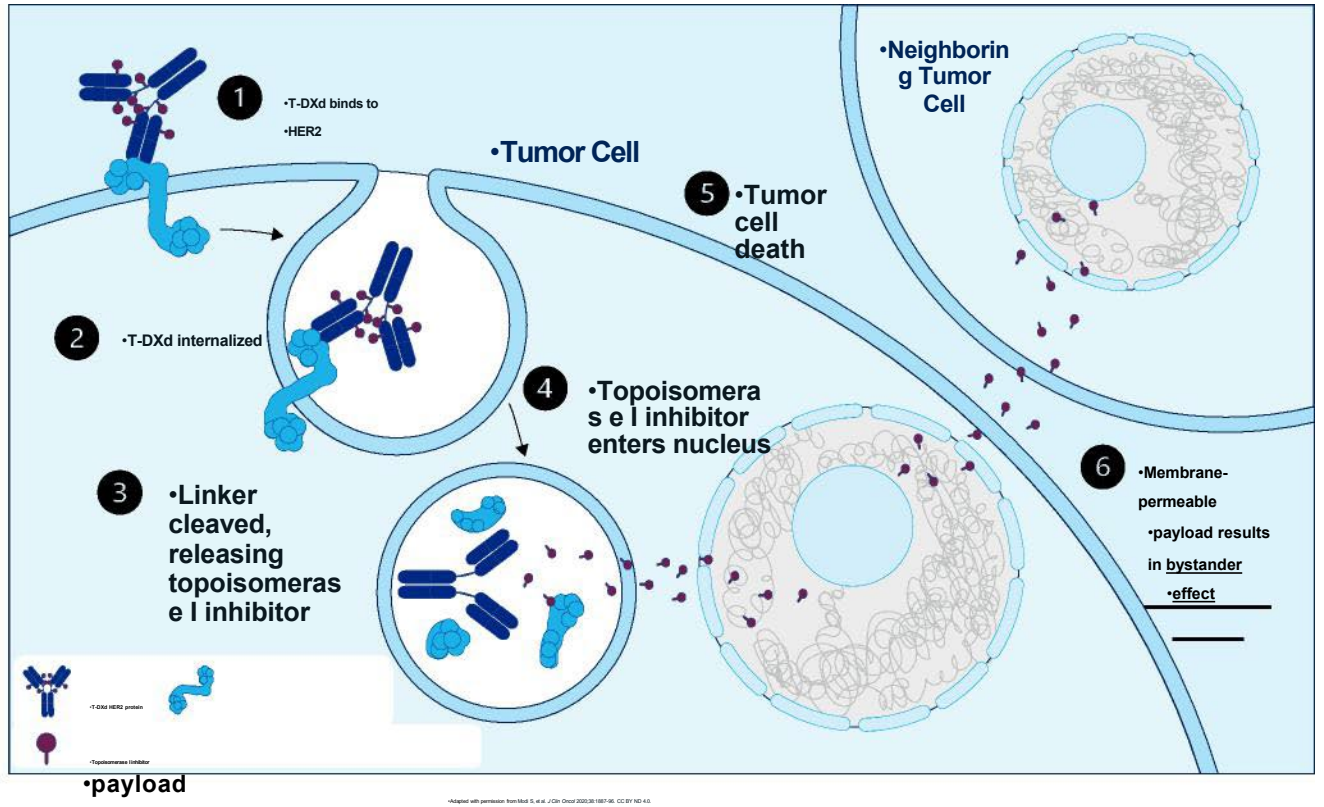
•T-DXd MOA, Bystander Effect, and Rationale for Targeting HER2-low mBC





•Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]

- **Results from a phase 1b study have reported efficacy of T-DXd in heavily pretreated patients (N = 54) with HER2-low mBC, with a mPFS of 11.1 months and an ORR of 37.0%[3]**

•HER2, human epidermal growth factor receptor 2; MOA, mechanism of action; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan. 1. Nakada T, et al. *Chem Pharm Bull*. 2019;67:173-185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22:5097-5108. 3. Modi S, et al. *J Clin Oncol.* 2020;38:1887-1896.

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DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

Stratification factors
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

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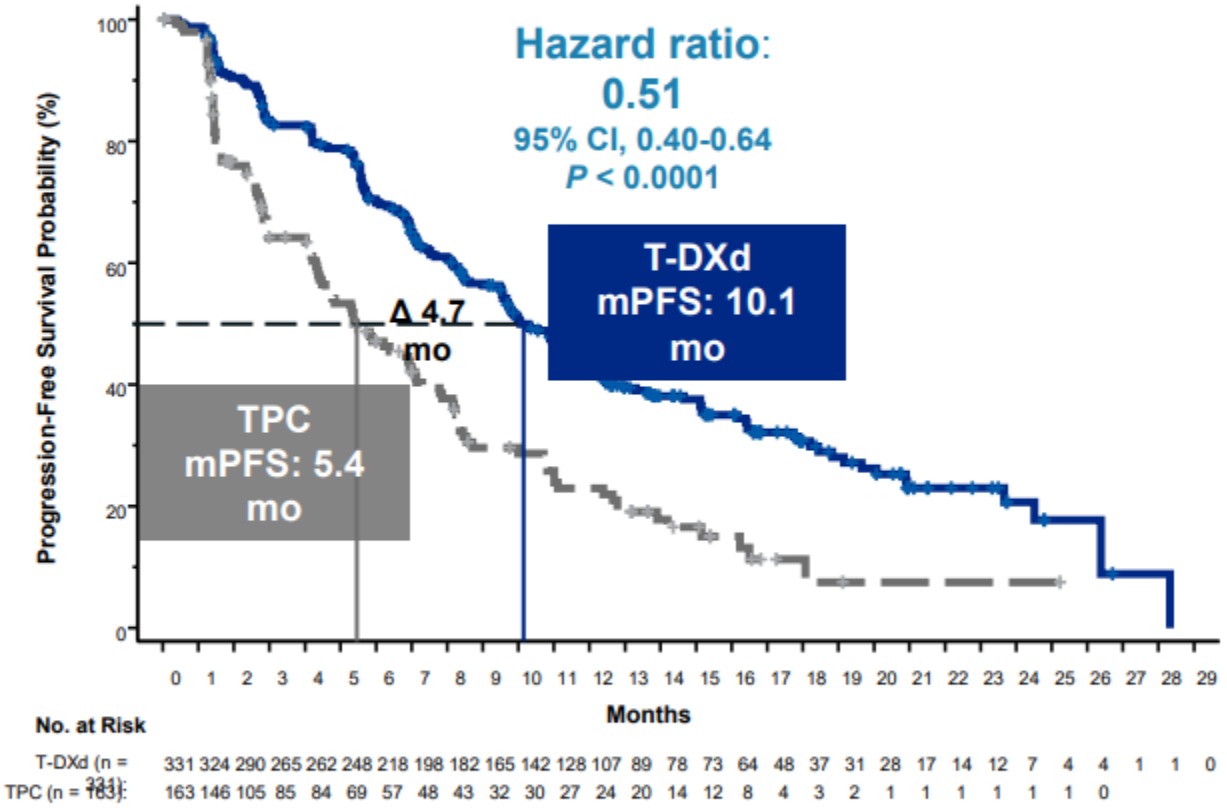
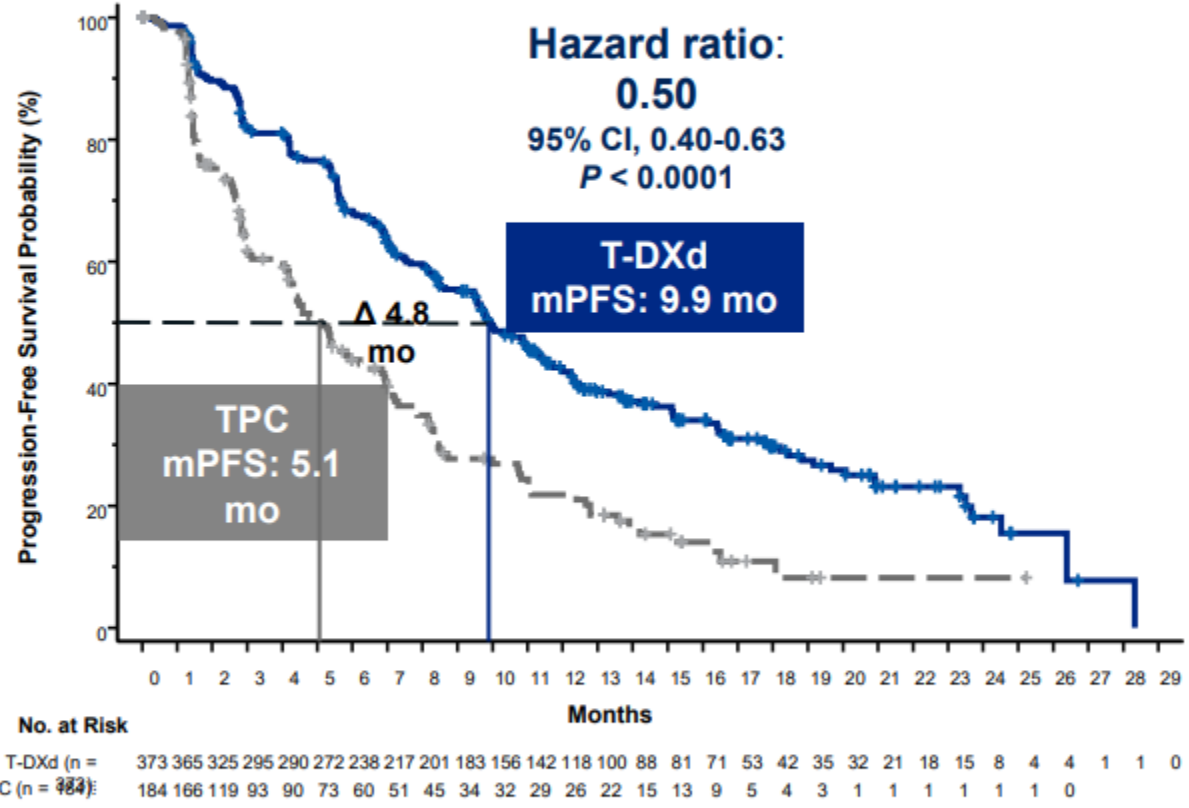
PFS in HR+ and All Patients

Hormone receptor–positive



All patients



PFS by blinded independent central review.

HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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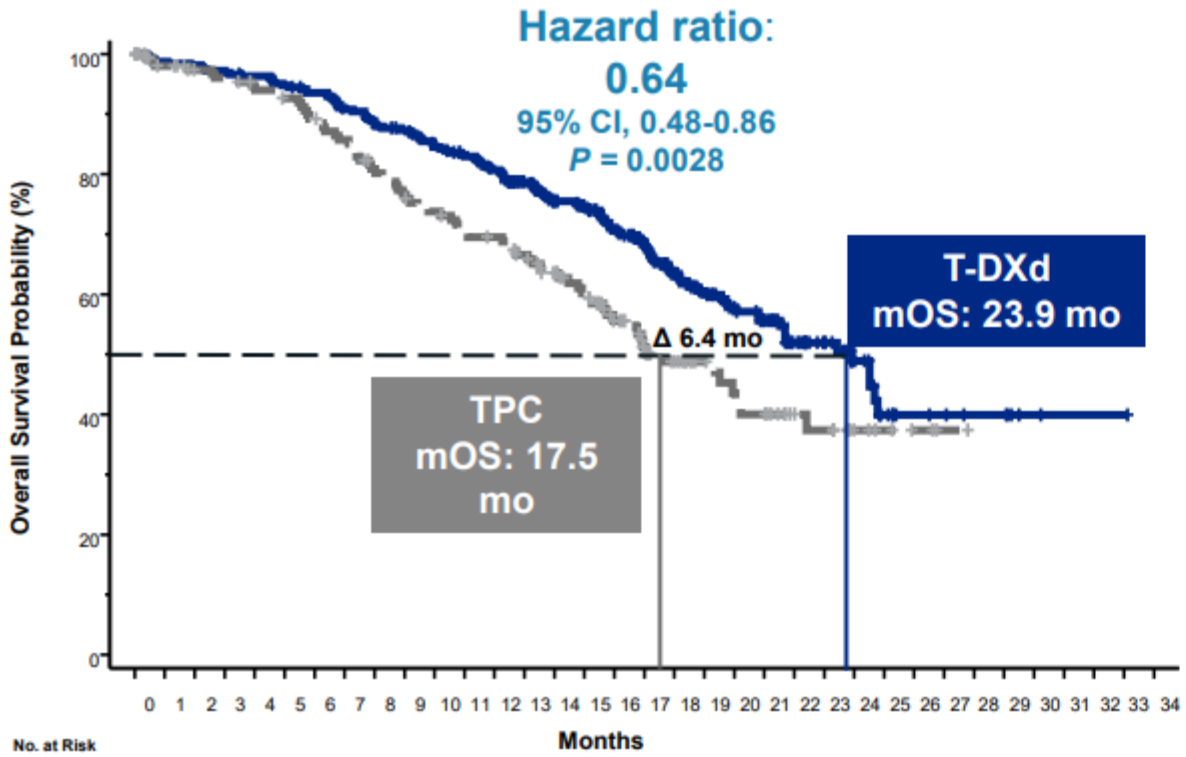
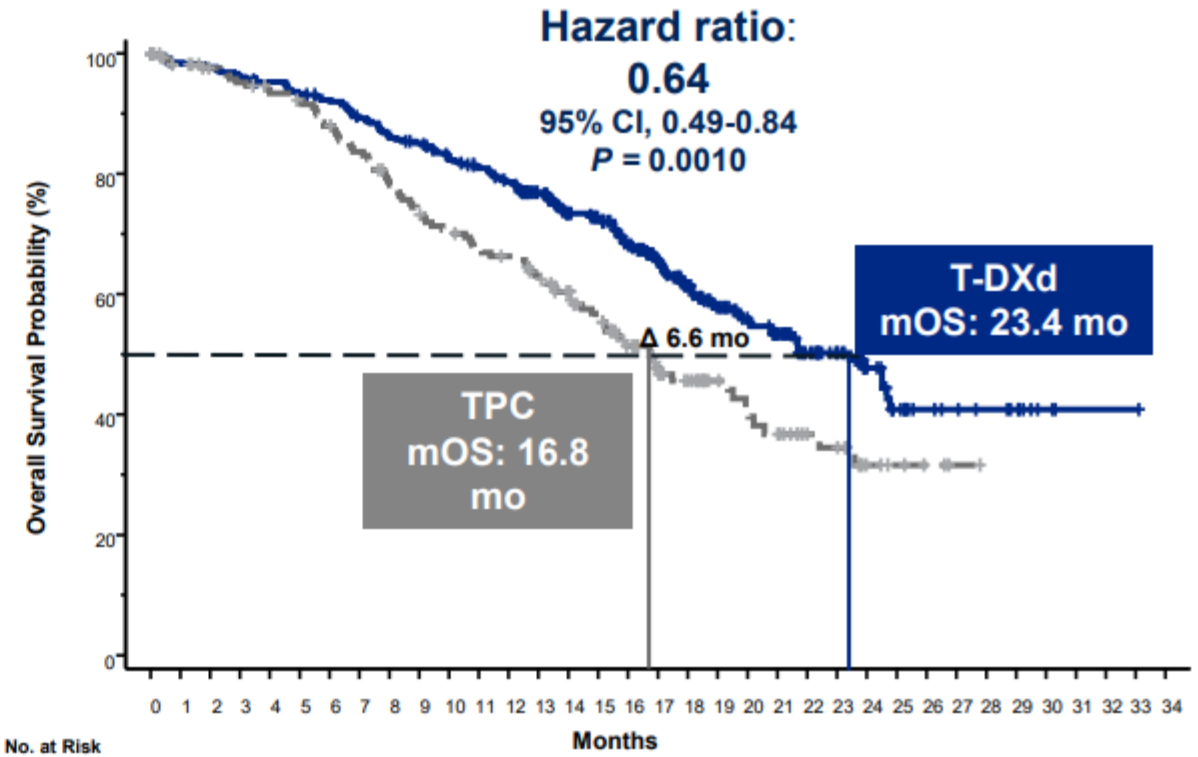
OS in HR+ and All Patients

Hormone receptor–positive



All patients



HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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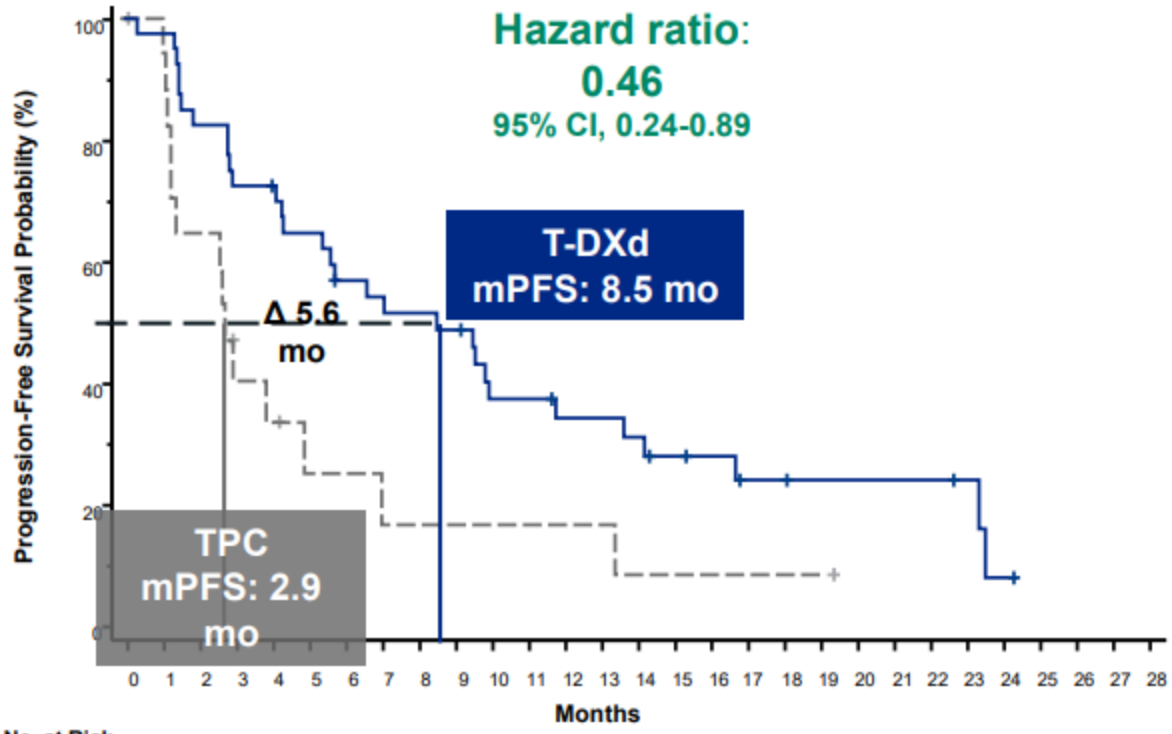
PFS and OS in HR− (Exploratory Endpoints)

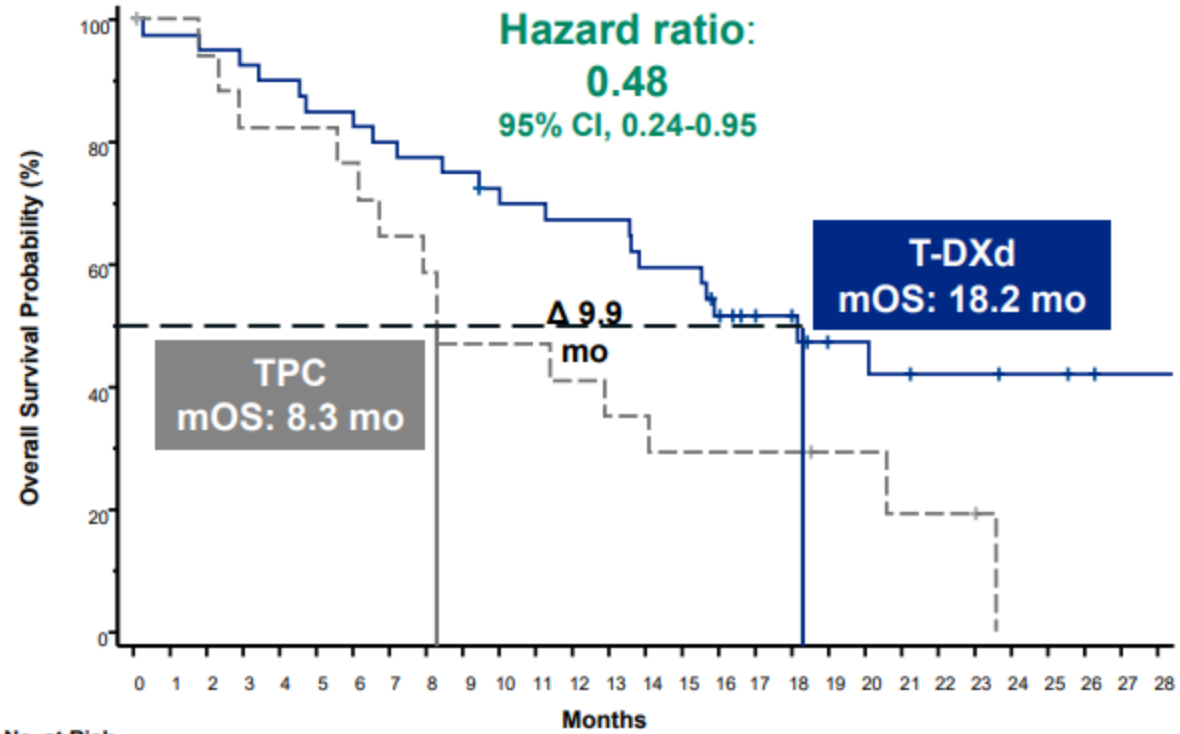
PFS



No. at Risk

T-DXd (n = 40):	40	39	33	29	28	25	21	20	19	18	13	13	11	11	10	8	7	5	5	4	4	4	4	3	1	0
TPC (n = 18):	18	17	11	7	6	4	3	3	2	2	2	2	2	2	1	1	1	1	1	1	0					

OS



No. at Risk

T-DXd (n = 40):	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
TPC (n = 18):	18	17	16	14	14	14	3	11	10	8	8	8	7	6	6	5	5	5	5	3	3	2	2	2	0				

HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based on data from the electronic data capture corrected for misstratification.

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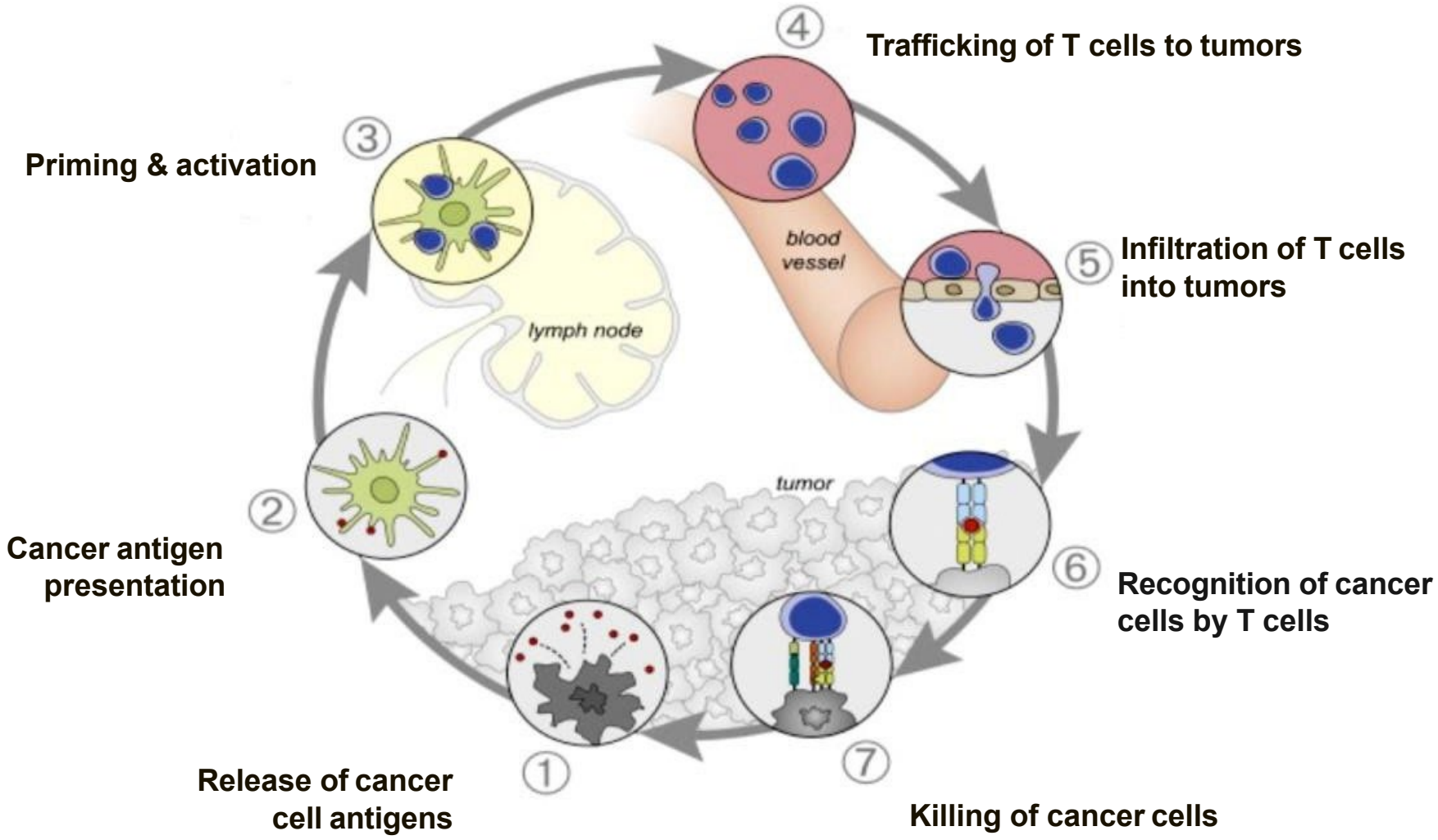
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Triple Negative Breast Cancer

Antitumor Immunity Is a Dynamic Process



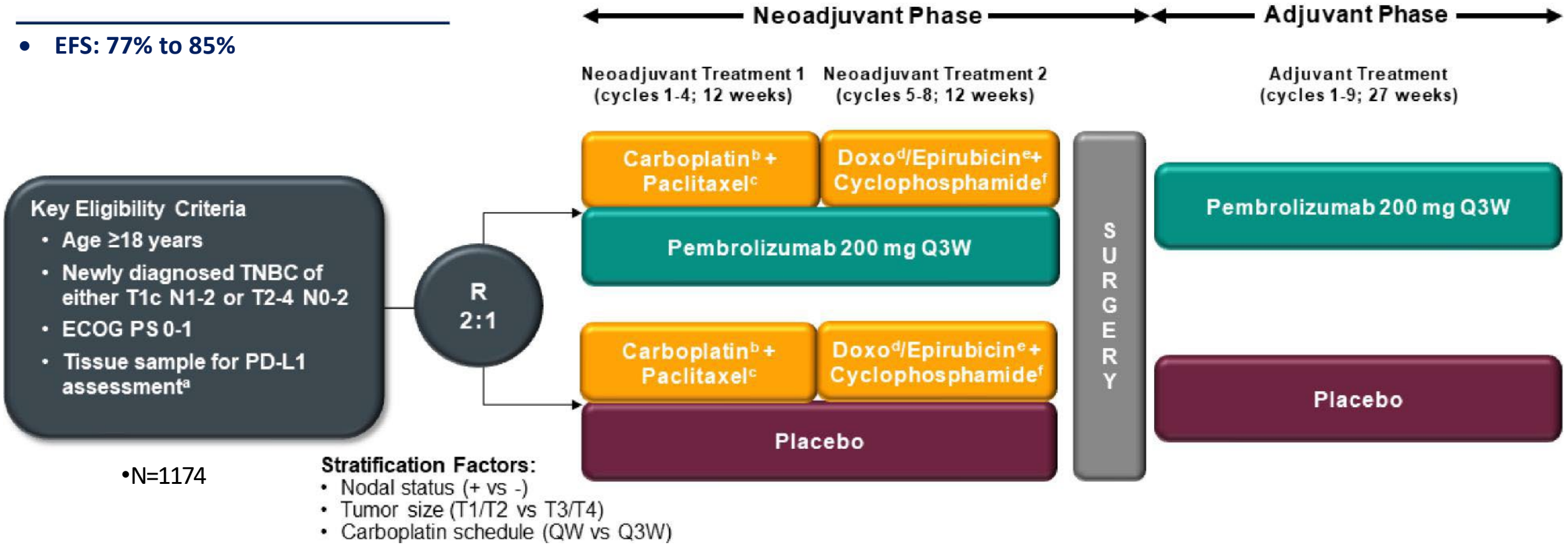
Chen and Mellman 2013; Liakou et al. 2008; Herr and Morales 2008; Bajorin et al. 2014

•KEYNOTE 522: New standard of care for high-risk TNBC

•**Primary Endpoints Results**:

- **pCR: 51% vs 65%**

- **EFS: 77% to 85%**

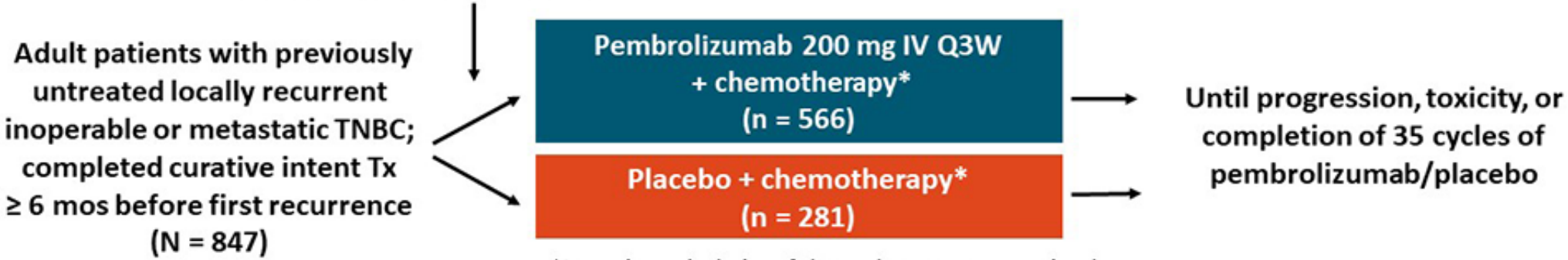


•N=1174

KEYNOTE-355: Study Design

- Randomized, double-blind, multicenter phase III trial

Stratified by chemotherapy (taxane vs gem/carbo); PD-L1 tumor expression (CPS > 1 vs < 1); previous Tx with same class of chemotherapy for EBC (Y vs N)



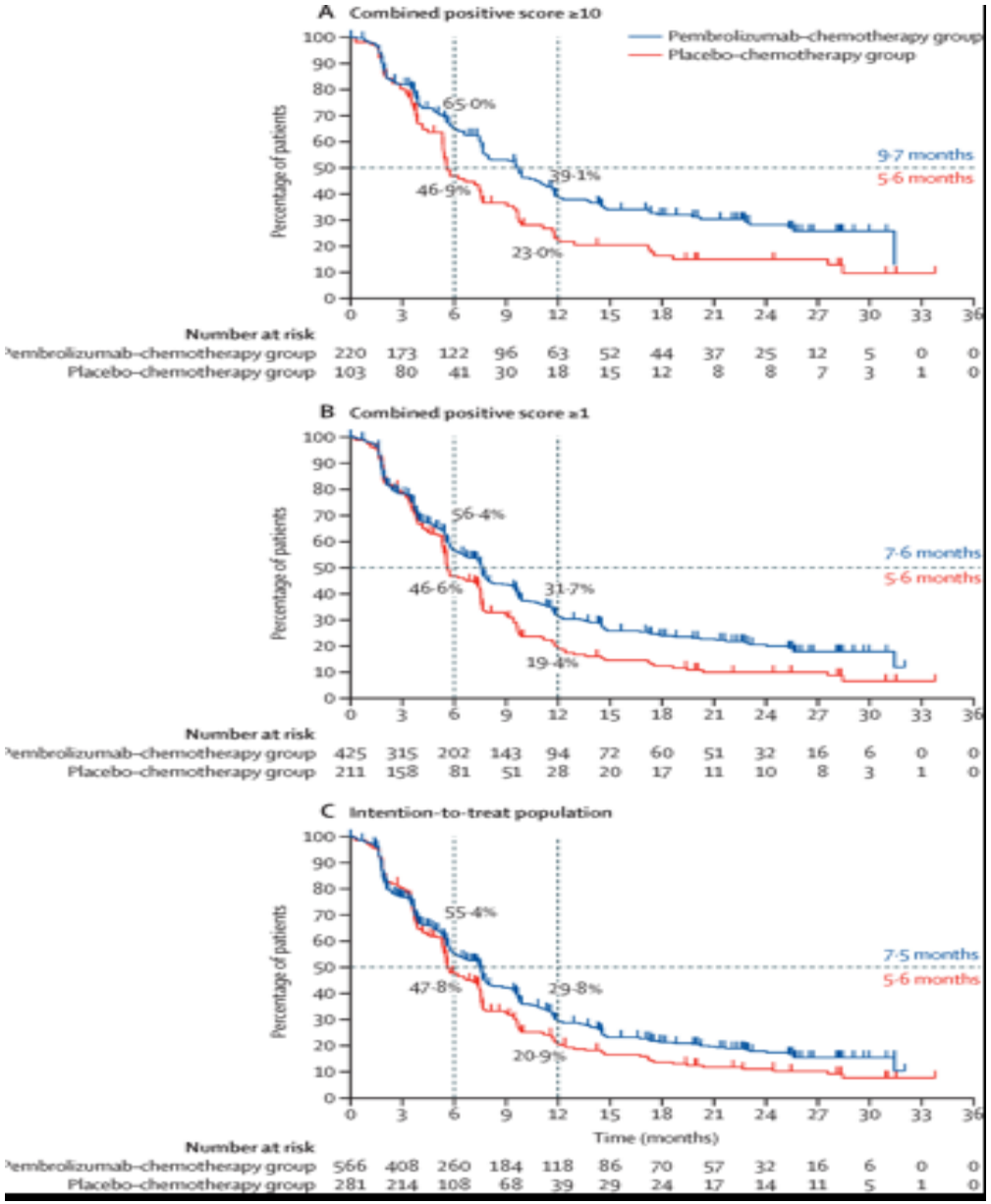
*Investigator's choice of chemotherapy was permitted:

- Nab-paclitaxel 100 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- Paclitaxel 90 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- Gem 1000 mg/m^2 + carbo AUC 2 on Days 1, 8 of 21-day cycle

- Primary endpoints: PFS and OS (PD-L1 CPS ≥ 10, PD-L1 CPS ≥ 1, and ITT)
- Secondary endpoints: ORR, DoR, DCR, safety

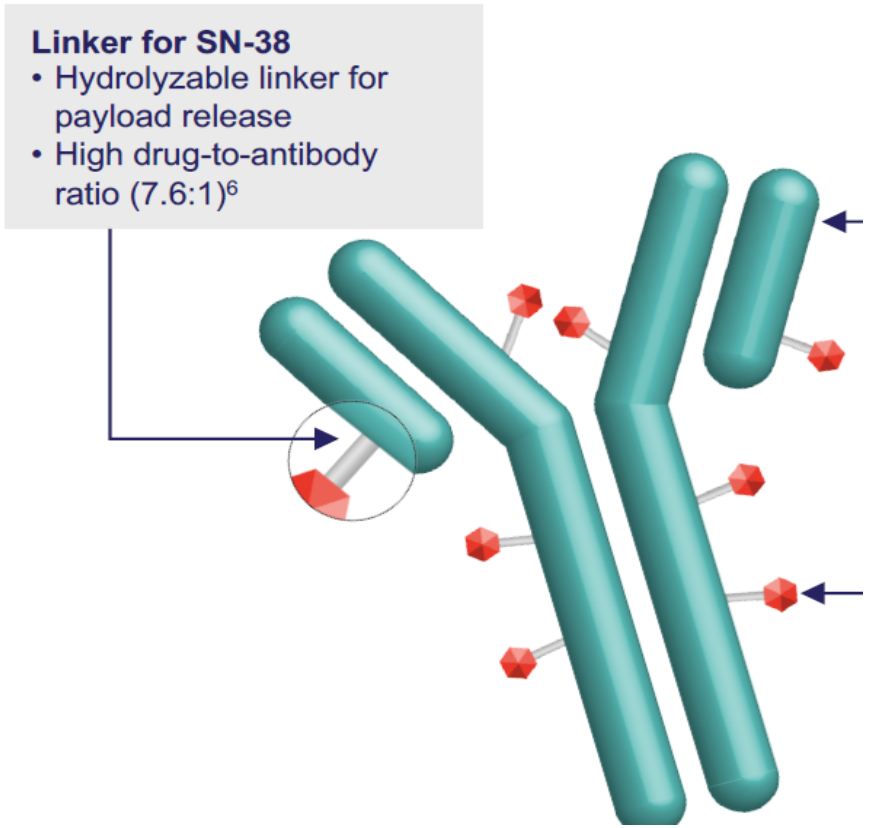
Cortes. ASCO 2020. Abstr 1000.

Slide credit: clinicaloptions.com

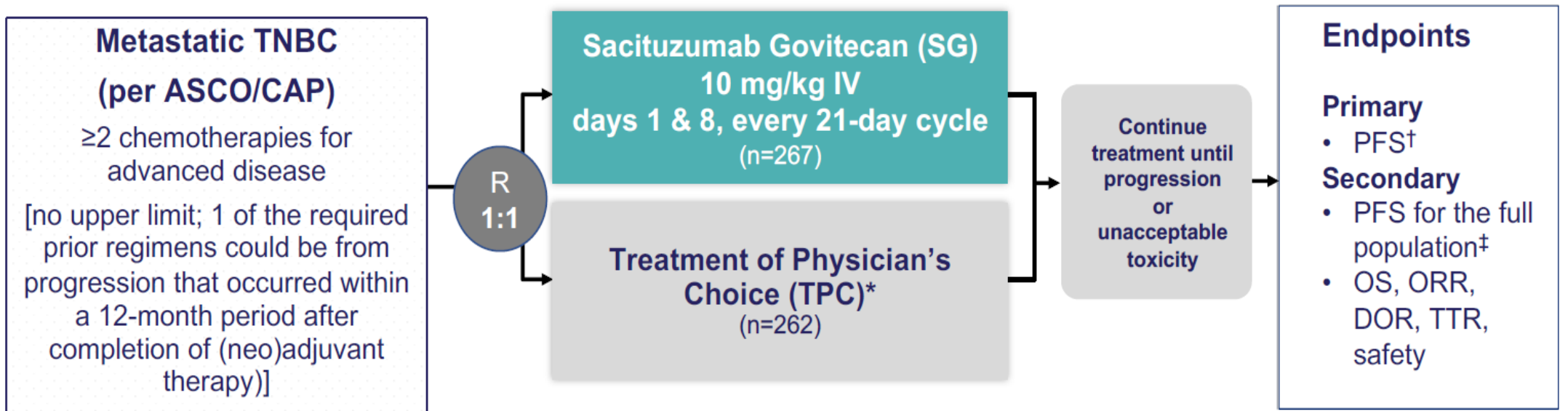

A Combined positive score ≥10
Pembrolizumab–chemotherapy group
Placebo–chemotherapy group
Percentage of patients
65·0%
46·9%
39·1%
23·0%
9·7 months
5·6 months
Number at risk
Pembrolizumab–chemotherapy group 220 173 122 96 63 52 44 37 25 12 5 0 0
Placebo–chemotherapy group 103 80 41 30 18 15 12 8 8 7 3 1 0
B Combined positive score ≥1
Percentage of patients
56·4%
46·6%
31·7%
19·4%
7·6 months
5·6 months
Number at risk
Pembrolizumab–chemotherapy group 425 315 202 143 94 72 60 51 32 16 6 0 0
Placebo–chemotherapy group 211 158 81 51 28 20 17 11 10 8 3 1 0
C Intention-to-treat population
Percentage of patients
55·4%
47·8%
29·8%
20·9%
7·5 months
5·6 months
Time (months)
Number at risk
Pembrolizumab–chemotherapy group 566 408 260 184 118 86 70 57 32 16 6 0 0
Placebo–chemotherapy group 281 214 108 68 39 29 24 17 14 11 5 1 0

Sacituzumab Govitecan (SG) Is a First-in-Class Trop-2–Directed ADC

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- SG is distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Granted accelerated approval by the FDA for metastatic TNBC and fast-track designation in metastatic urothelial cancer[7]



ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC



NCT02574455

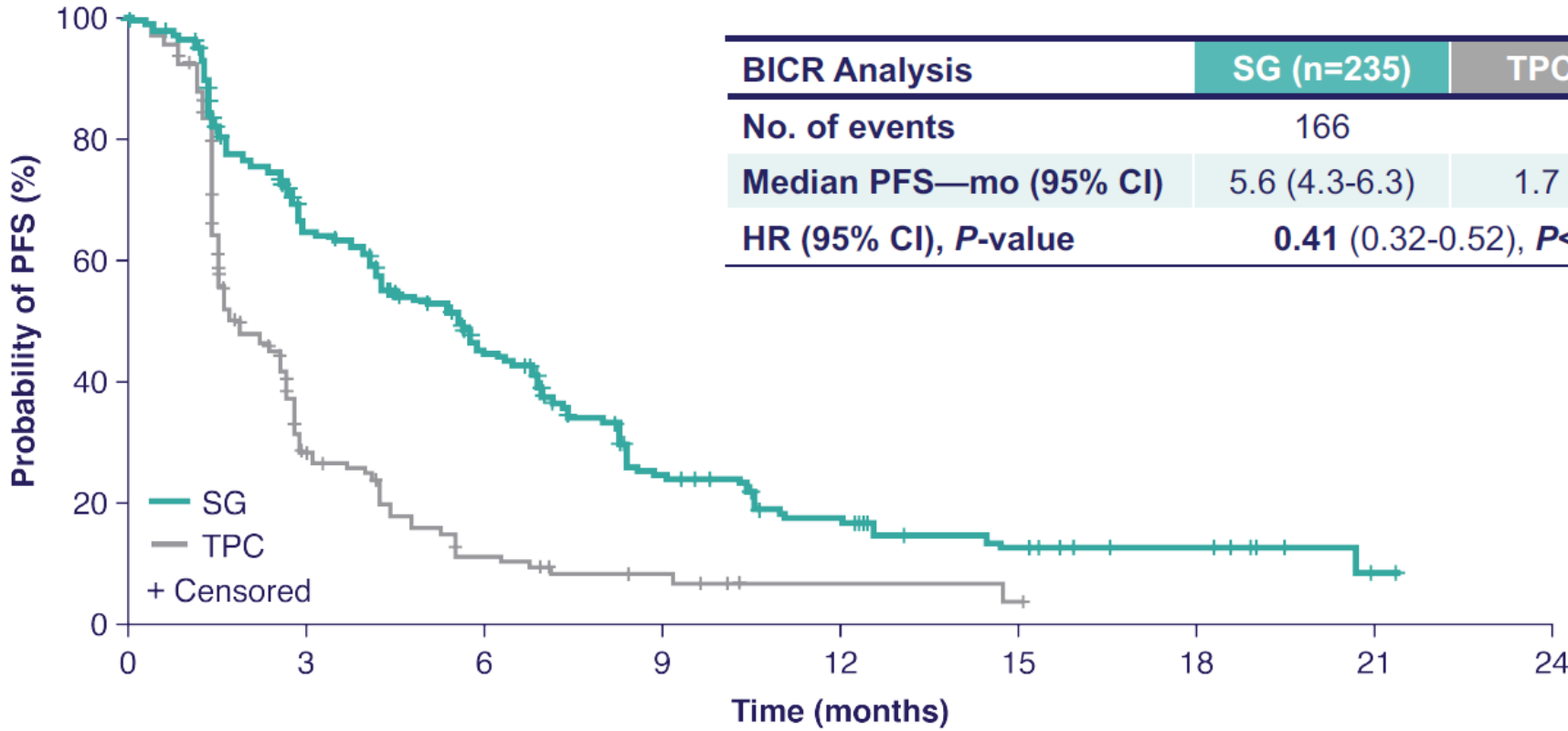
Stratification factors

- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

Data cutoff: March 11, 2020

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation. Here, we report the primary results from ASCENT, including PFS and OS.

Progression-Free Survival (BICR Analysis)



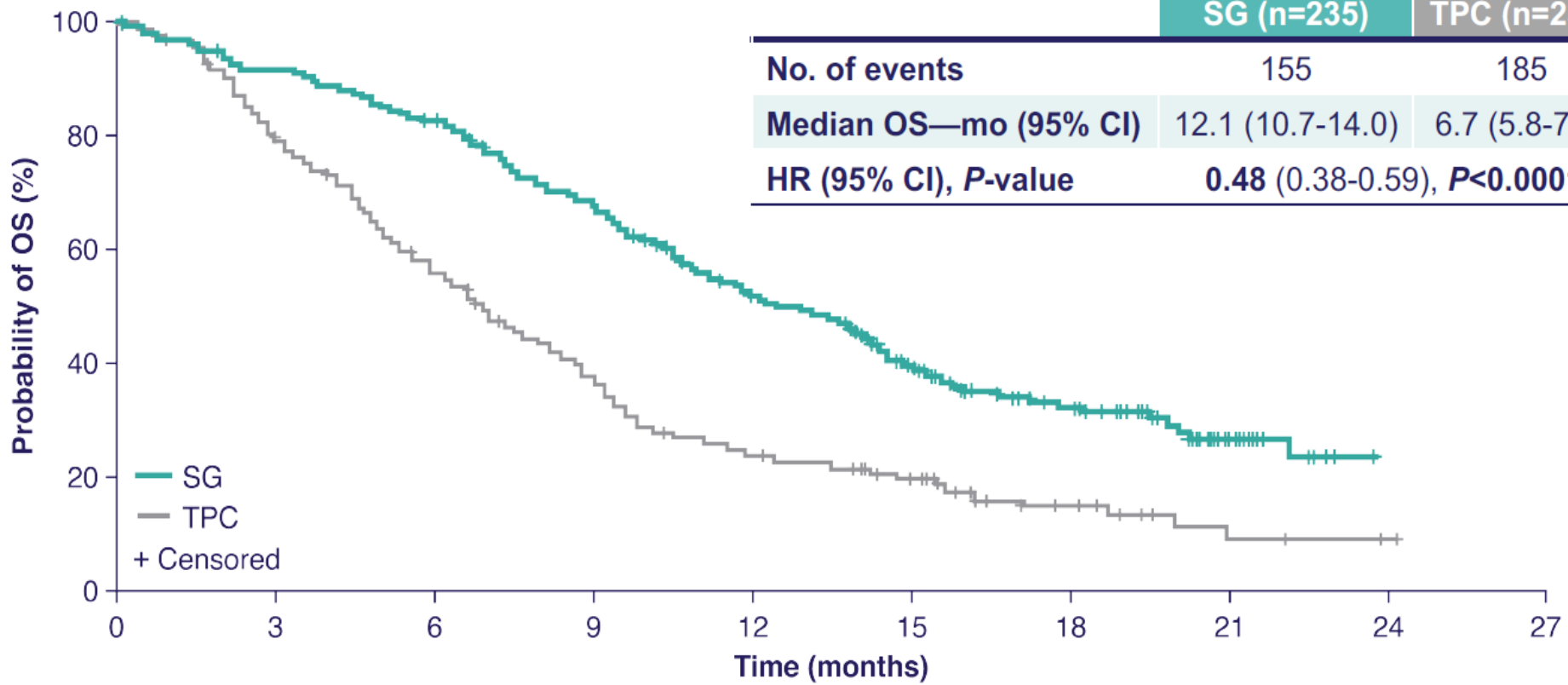
BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

Number of patients at risk

SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
TPC	233	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

Overall Survival

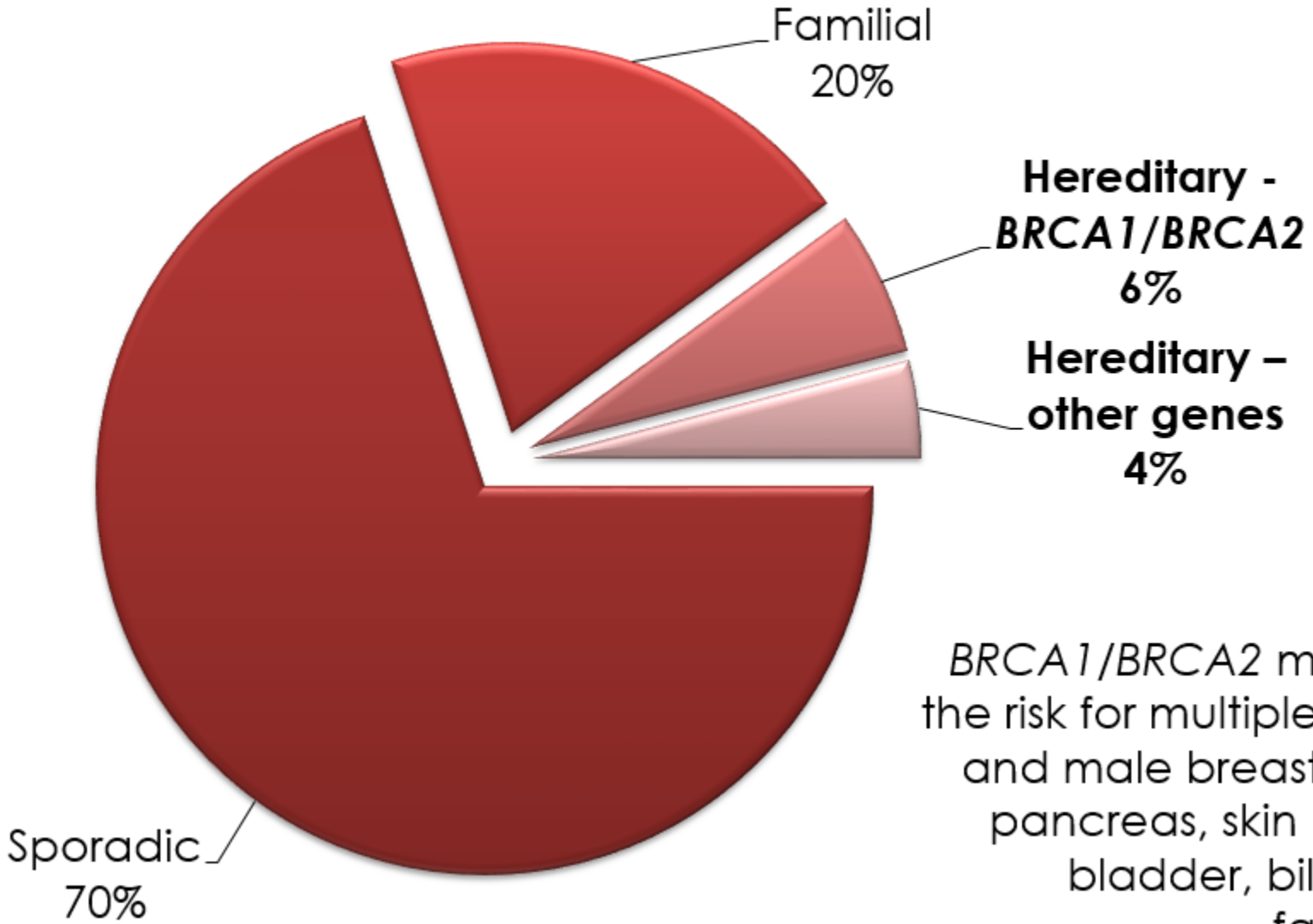
	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	



Number of patients at risk

SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

Breast cancer – why does it happen?



BRCA1/BRCA2 mutations increase the risk for multiple cancers: female and male breast, ovary, prostate, pancreas, skin (melanoma), gall bladder, bile duct, stomach, fallopian tube, etc.

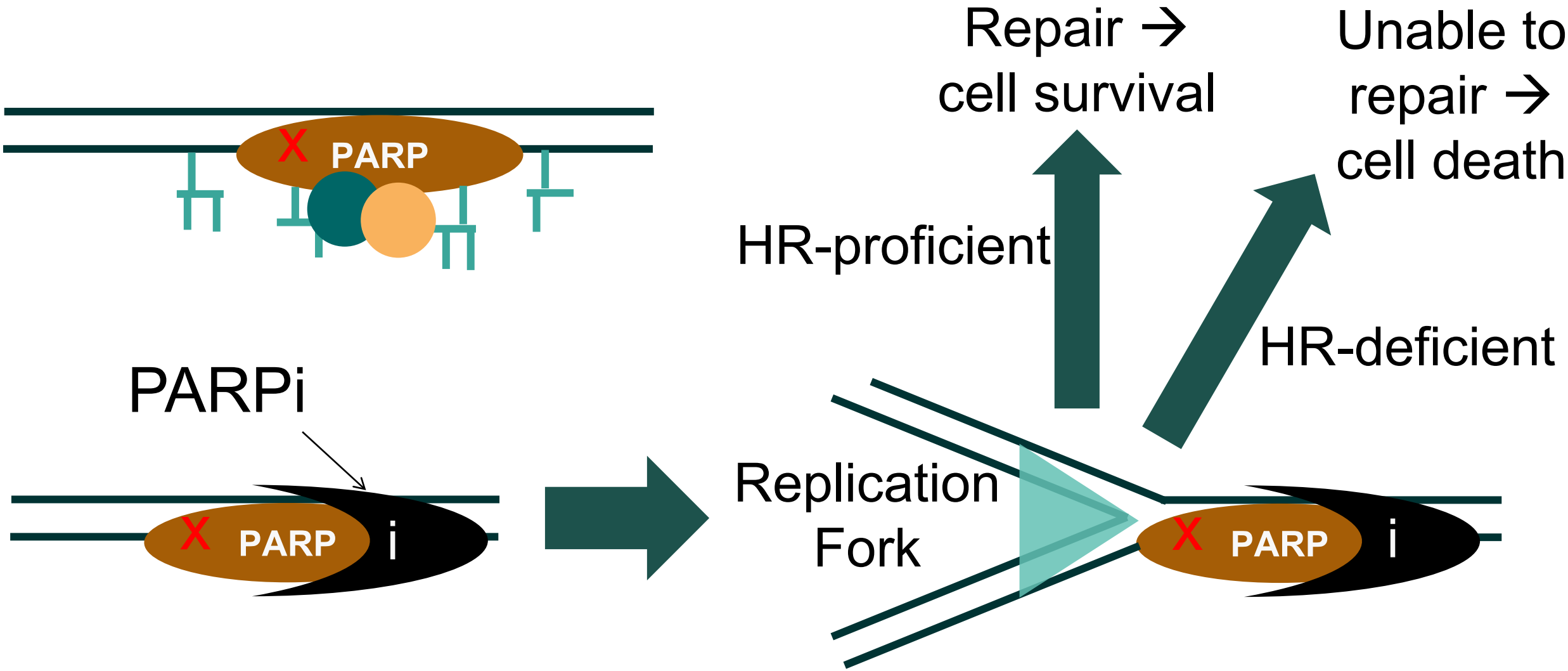
PARP inhibitors

- Poly[ADP]ribose polymerase (PARP): key component of the base-excision DNA repair pathway
- Especially effective in patients with BRCA mutations

- Germline deleterious BRCA mutations
  - General population 1 in 500
  - 5% of breast cancers, 10% of ovarian, also prostate, pancreas, melanoma

DeVita V, et al. Cancer. 9th ed, 2011. Chapter 42, Poly(ADP-ribose) polymerase inhibitors.
National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian, version 1.2018.

PARPi Mechanism



HR = Homologous recombination

Adapted from Livraghi L, et al. *BMC Medicine*. 2015;13:188.

FDA Indications

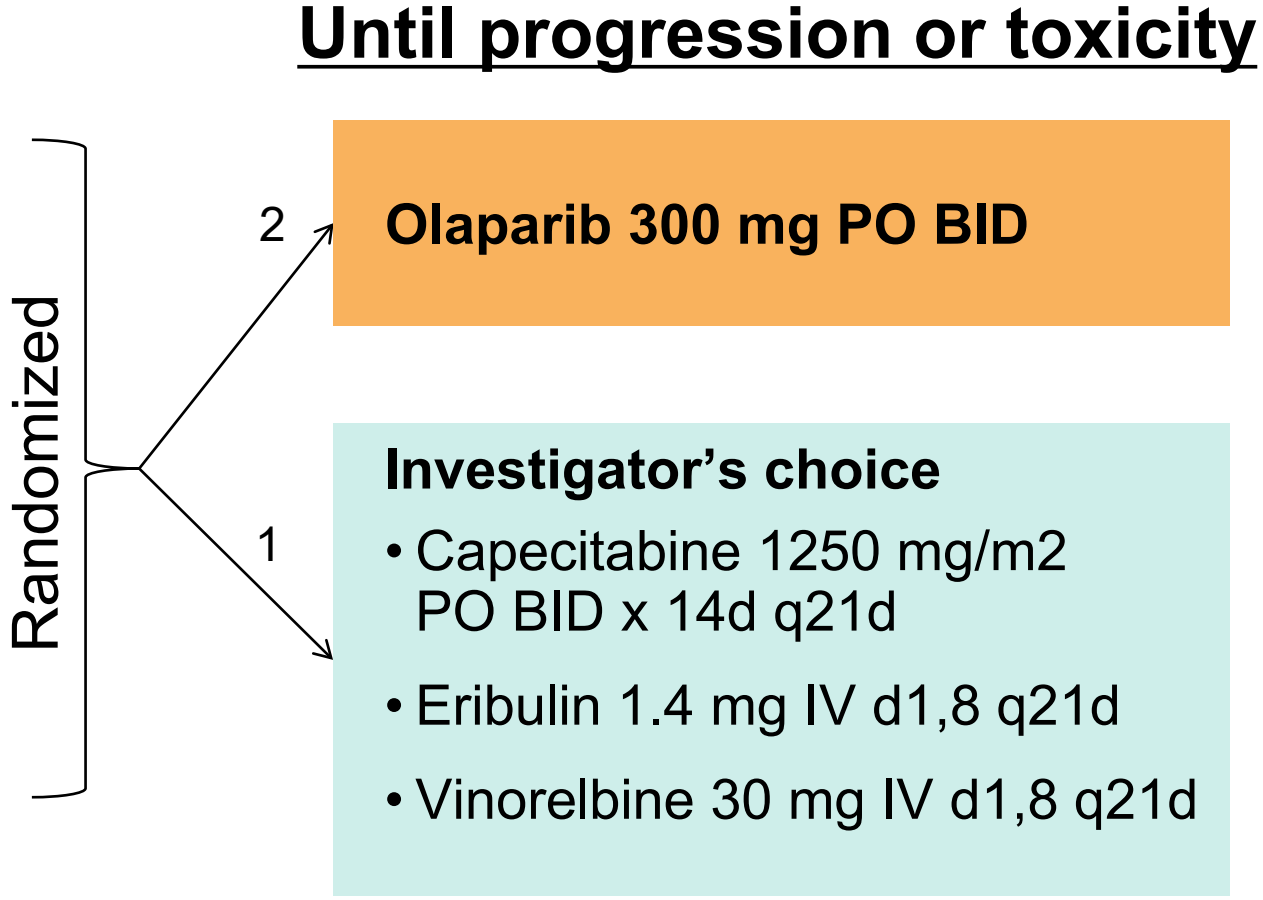
	Olaparib (Lynparza®)	Rucaparib (Rubraca®)	Niraparib (Zejula®)	Talazoparib (Talzenna®)
Ovarian (monotherapy)	g*BRCA*m, 3th line	*BRCA*m, 3rd line	4th line	-
Ovarian (maint for platinum-sensitive recurrent)	Approved	Approved	Approved	-
Ovarian (maint after first line platinum)	*BRCA*m (+/- bev) or HRD (+ bev)	-	Approved	-
Breast (mono for *gBRCAm*, HER2-)	Metastatic, after chemo	-	-	Metastatic or advanced
Pancreas (maint after first line platinum for g*BRCA*m)	Approved	-	-	-
Prostate (metastatic castrate-resistant)	After enza or abi	After enza or abi AND docetaxel	-	-

Redelico T. *J Adv Pract Oncol*. 2019;10(4):402-8.

Abi = abiraterone, Enza = enzalutamide Bev = bevacizumab; HRD = homologous recombination deficient

OlympiAD

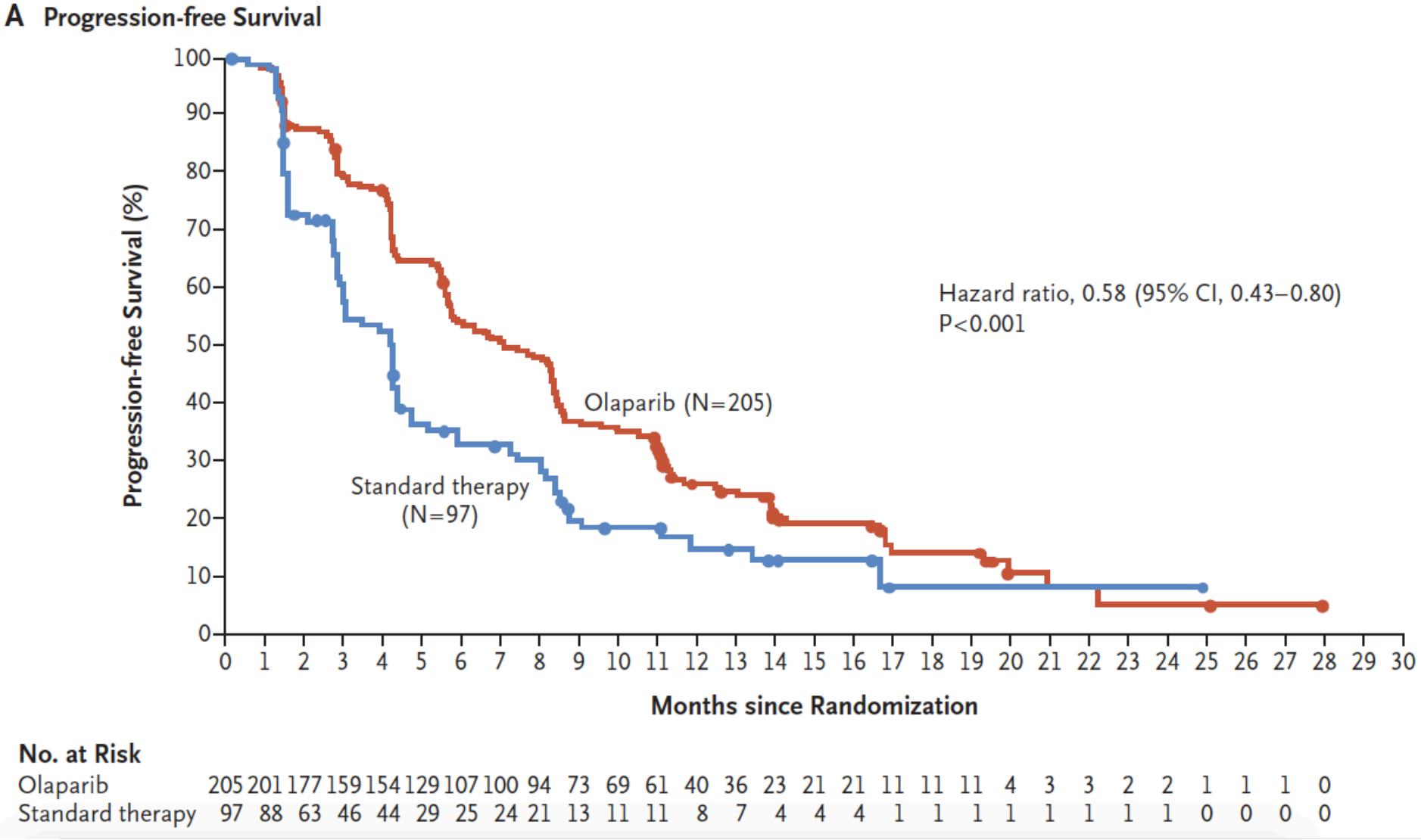
- Metastatic breast cancer
- HER2–
- Germline *BRCA* mutation
- Prior treatment with an anthracycline and a taxane in either adjuvant or metastatic setting
- If ER/PR+, must have progressed on at least one endocrine therapy
- ≤2 prior lines of chemotherapy



No crossover between treatment arms

Robson M, et al. *N Engl J Med*. 2017; 377:523-533.

OlympiAD – Progression-Free Survival



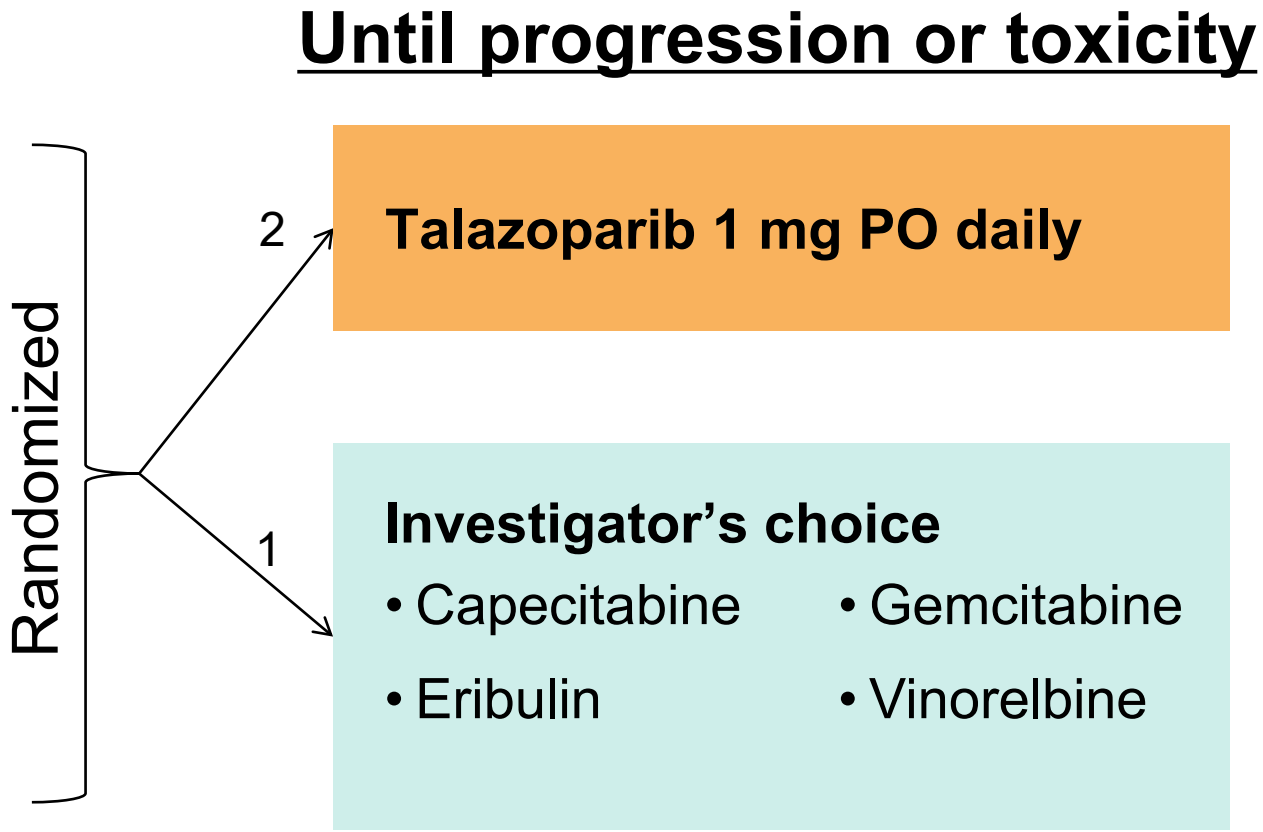
Median PFS 7.0 vs. 4.2 months

HR 0.58
95% CI 0.43-0.80
P<0.001

Robson M, et al. *N Engl J Med*. 2017; 377:523-533.

EMBRACA

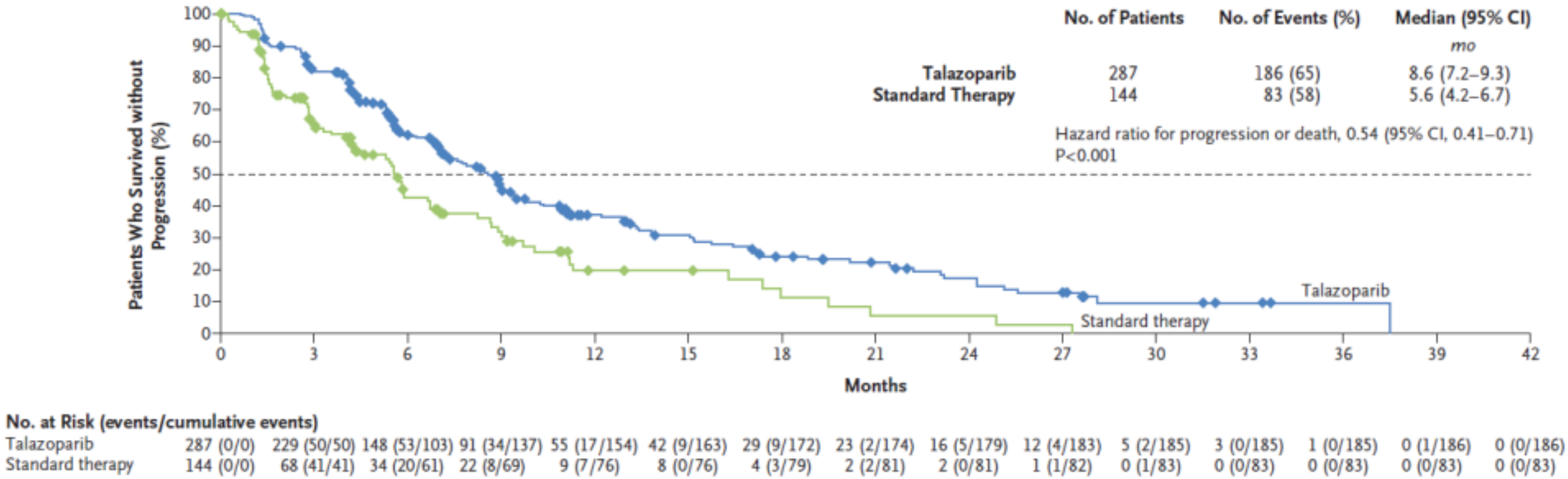
- Locally advanced (uncurable) or metastatic
- HER2 –
- Germline *BRCA* mutation
- Prior treatment with taxane OR anthracycline
- ≤3 prior lines of chemotherapy



No crossover between treatment arms

Litton JK, et al. *N Engl J Med*. 2018; DOI: 10.1056/NEJMoa1802905.

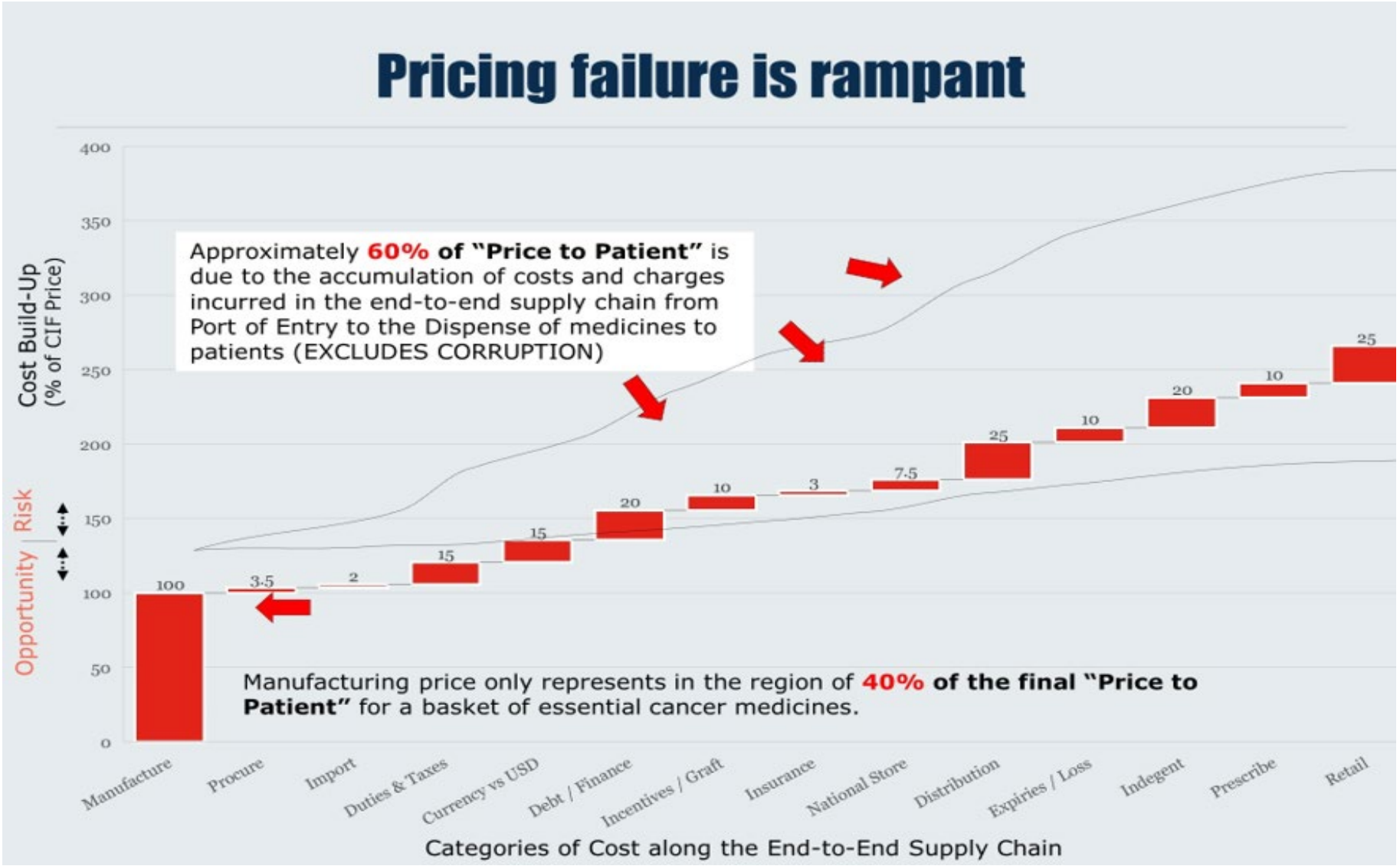
EMBRACA – Progression Free Survival



Median PFS 8.6 vs. 5.6 months **HR 0.54; 95% CI 0.41-0.71; P<0.001**

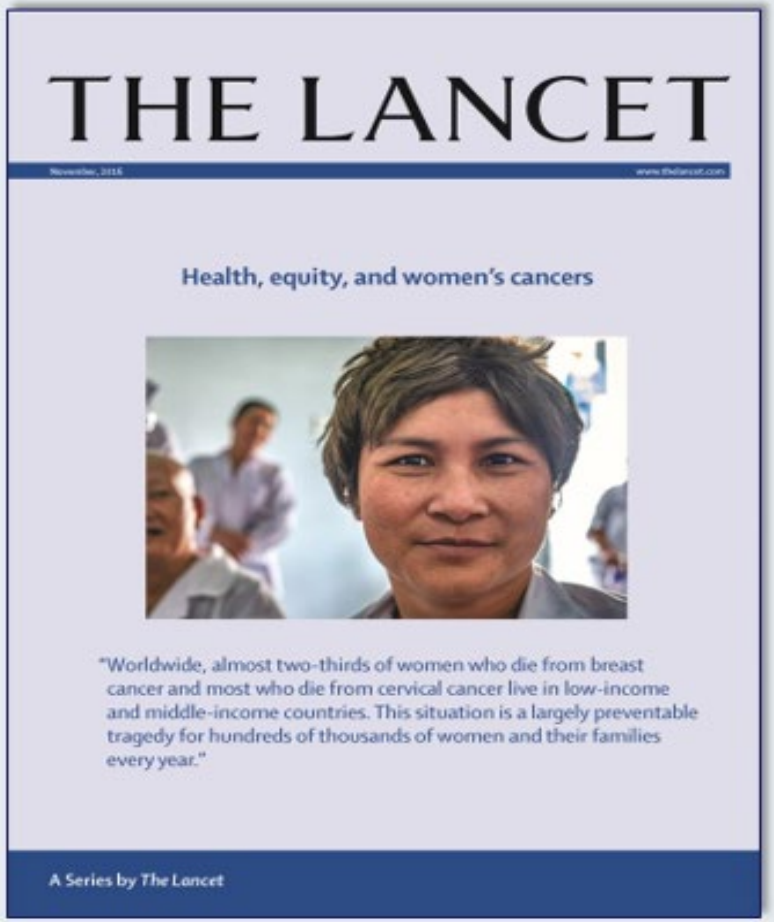
Litton JK, et al. *N Engl J Med*. 2018; DOI: 10.1056/NEJMoa1802905.

Value and cost of incorporating New Targeted therapeutics in the Management of breast cancer!


Pricing failure is rampant
Approximately 60% of "Price to Patient" is due to the accumulation of costs and charges incurred in the end-to-end supply chain from Port of Entry to the Dispense of medicines to patients (EXCLUDES CORRUPTION)
Manufacturing price only represents in the region of 40% of the final "Price to Patient" for a basket of essential cancer medicines.
Cost Build-Up (% of CIF Price)
Opportunity | Risk
400
350
300
250
200
150
100
50
0
100
3.5
2
15
15
20
10
3
7.5
25
10
20
10
25
Manufacture
Procure
Import
Duties & Taxes
Currency vs USD
Debt / Finance
Incentives / Graft
Insurance
National Store
Distribution
Expiries / Loss
Indegent
Prescribe
Retail
Categories of Cost along the End-to-End Supply Chain

Vote No! Why? Women die of cancer because

- Poverty
- Ethnicity
- Society and Culture
- Politics



Delays kill

Mortality increases as delay increases

Breast cancer surgery delay for 1000 women (baseline 12% mortality)

Projected additional deaths due to delay:

4 weeks +10

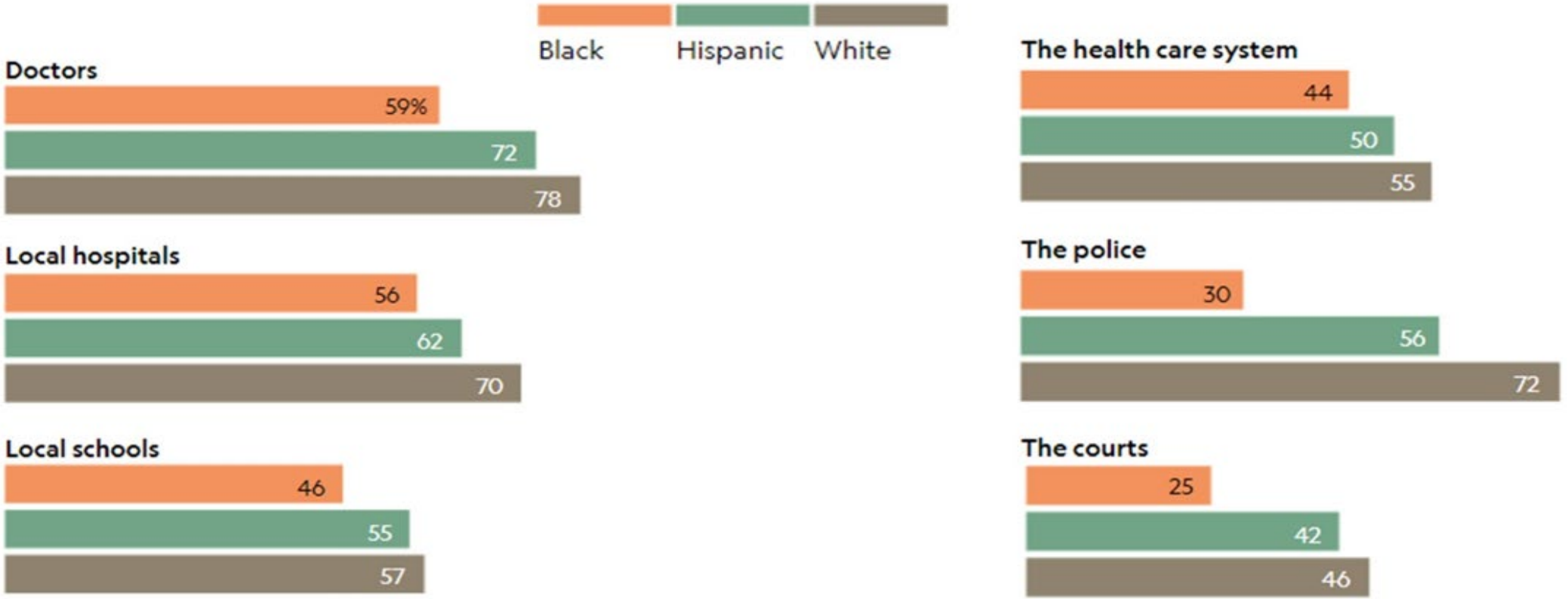
8 weeks +20

12 weeks +31

Clinician Barriers to Ensuring Racial and Ethnic Diversity in Clinical Trials

- Limited physician communication with patients re: patient enrollment
- Physician bias
- Limited time and resources
- Lack of knowledge regarding trial availability
- Lack of workforce diversity

Can you trust these institutions to do what is right for you or your community all or almost all of the time?



The Undefeated and the Kaiser Family Foundation
M. Fletcher, Nat'l Geographic 2020

Thank you