THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

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Chemotherapy and Hormonal Therapy in the Metastatic Setting, ER+/HER-2- and TNBC

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Conflict of Interest

- Astra Zeneca and Merck: Consulting/Honorarium.

Outline

- Advanced stage: ER+
  - M-THOR inhibitors
  - CDK4/6 inhibitors
- Advanced stage: TNBC
  - Target therapy
  - PARP inhibitors
  - Immunotherapy

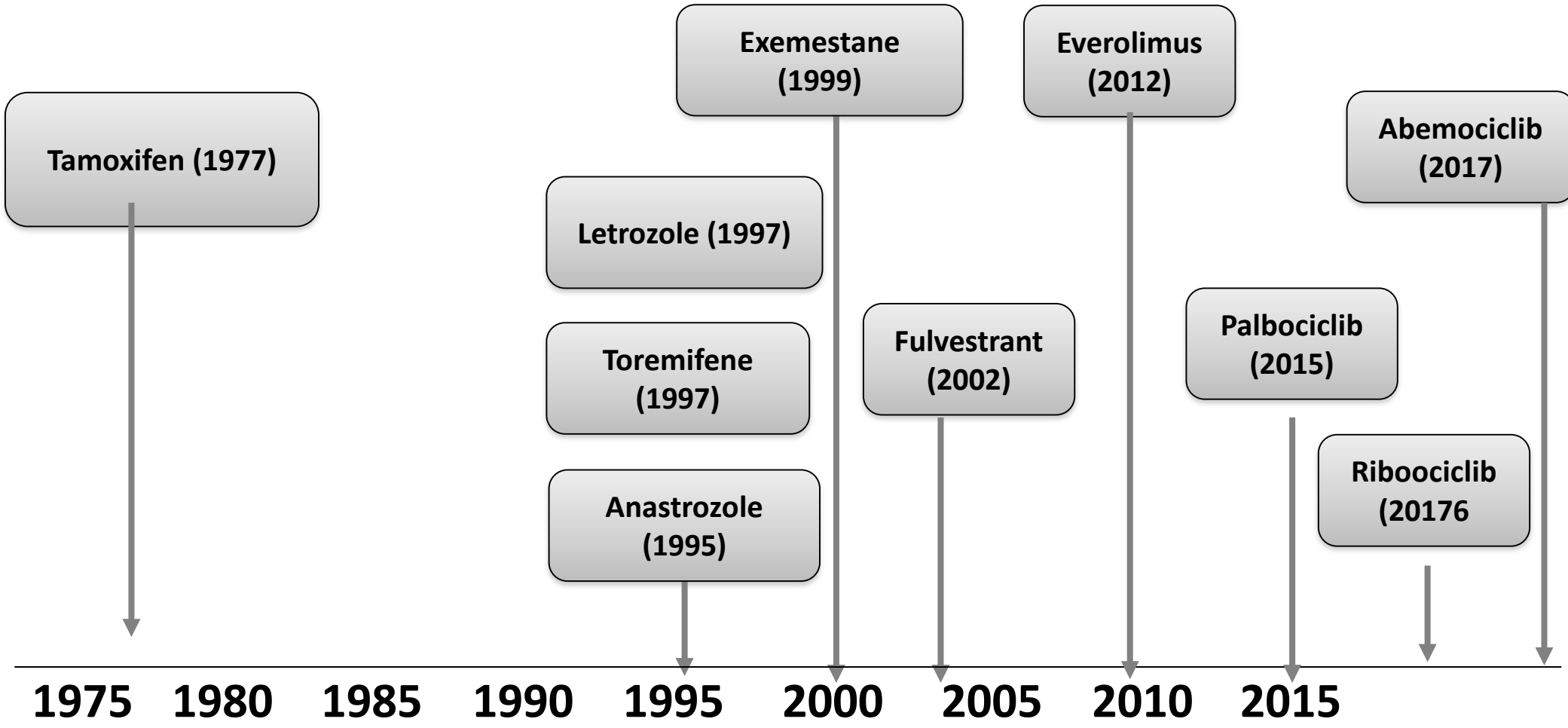
Current Treatment of Advanced Hormone Receptor Positive (HR+) HER2- Breast Cancer

- Nearly 75% of patients have invasive breast cancers are hormone receptor positive (HR^+)

- Endocrine therapy is the standard of care for patients with HR^+ breast cancer, recommended by national and international guidelines

- Several developments in the past years offer promising treatment options and better care for patients with HR^+, $HER2^-$ early and advanced breast cancer

Timeline of Approval of Agents for HR+ MBC



Trials of Hormone Therapy in First-Line Advanced Breast Cancer

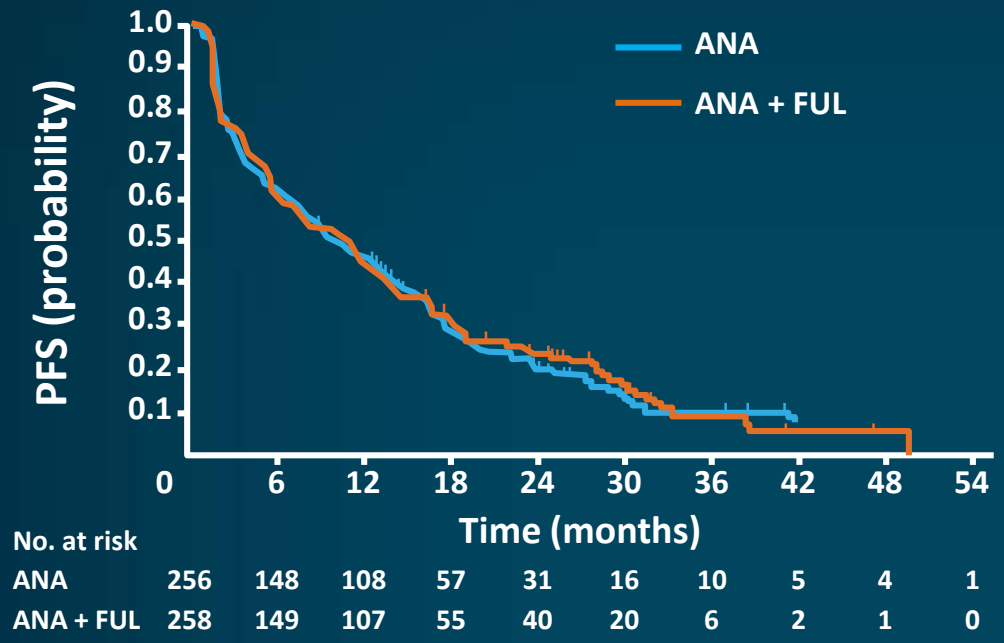
New approaches: 1st-line endocrine therapy for HR+ MBC:

Recent 1st Line Studies:

- Combination Endocrine Rx (Fulvestrant 250 + AI) (FACT; SWOG-0226)
- Fulvestrant 500 (FALCON)
- Addition of growth factor tyrosine kinase inhibitors (Bolero-II)
- Addition of CDK 4/6 inhibitors (PALOMA-1; PALOMA-2; MONALEESA-2), MONARCH-2

First-Line Anastrozole ± Fulvestrant ER+ MBC

FACT[1]: TTP

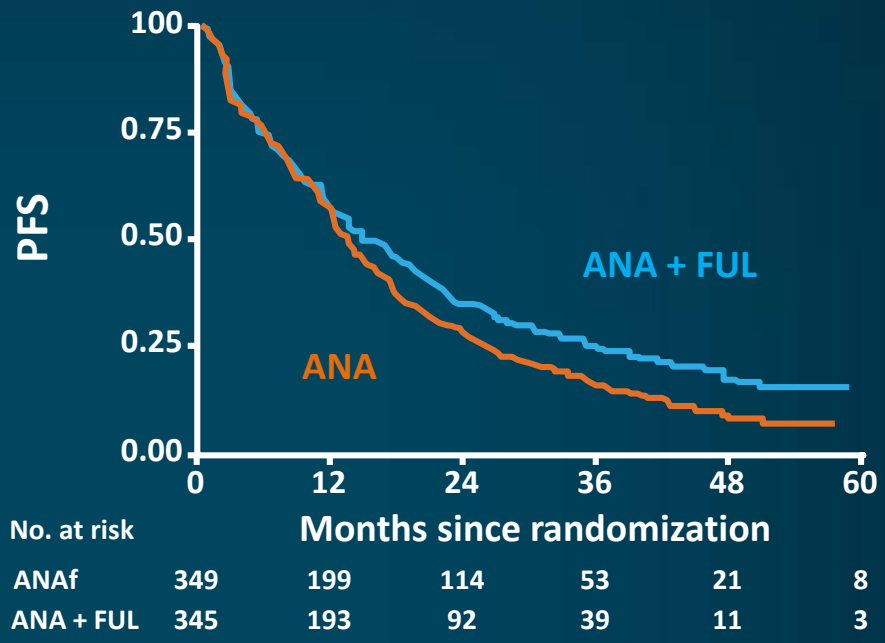


No. at risk										
ANA	256	148	108	57	31	16	10	5	4	1
ANA + FUL	258	149	107	55	40	20	6	2	1	0

	ANA + FUL (n = 258)	ANA (n = 256)
Patients with progression, no. (%)	200 (77.5)	200 (78.1)
Median TTP in months	10.8	10.2

Primary TTP analysis (log-rank test)
HR = 0.99 (95% CI, 0.81–1.20), *P*=0.91

SWOG 0226[2]: PFS



No. at risk						
ANAf	349	199	114	53	21	8
ANA + FUL	345	193	92	39	11	3

	Events	Median PFS (95% CI)
Combination	268	15.0 (13.2–18.4)
ANA	297	13.5 (12.1–15.1)

HR = 0.80 (95% CI, 0.68–0.94)
P=0.007 by stratified log-rank test

ER = estrogen receptor; MBC = metastatic breast cancer; ANA = anastrozole; FUL = fulvestrant; TTP = time to progression; SWOG = Southwest Oncology Group; PFS = progression-free survival; HR = hazard ratio (in reporting risk); CI = confidence interval.

1. Bergh J et al. *J Clin Oncol*. 2012;30:1919-1925. 2. Mehta RS et al. *N Engl J Med*. 2012;367:435-444.

Comparison of First-Line AI ± Fulvestrant Trials

	FACT[1]	SWOG 0226[2]
Patients (no.)	514	707
De novo metastatic disease	13%	39%
Prior adjuvant chemotherapy	45%	33%
Prior adjuvant ET (TAM)	68%	40%
Prior adjuvant AI	1.5%	Originally excluded
Median TTP/PFS range	10–11 mos	13–15 mos
PFS benefit	No	Yes
Median OS benefit	No (37.8 vs 38.2 mos)	Yes (41.3 vs 47.7 mos)

Fulvestrant 500 mg IM on Day 0 followed by
250 mg IM Day 14 and 28 then 250 mg every 28 days

TAM = tamoxifen; AI = aromatase inhibitor; OS = overall survival; IM = intramuscular; mos = months.

1. Bergh J et al. *J Clin Oncol*. 2012;30:1919-1925. 2. Mehta RS et al. *N Engl J Med*. 2012;367:435-444.

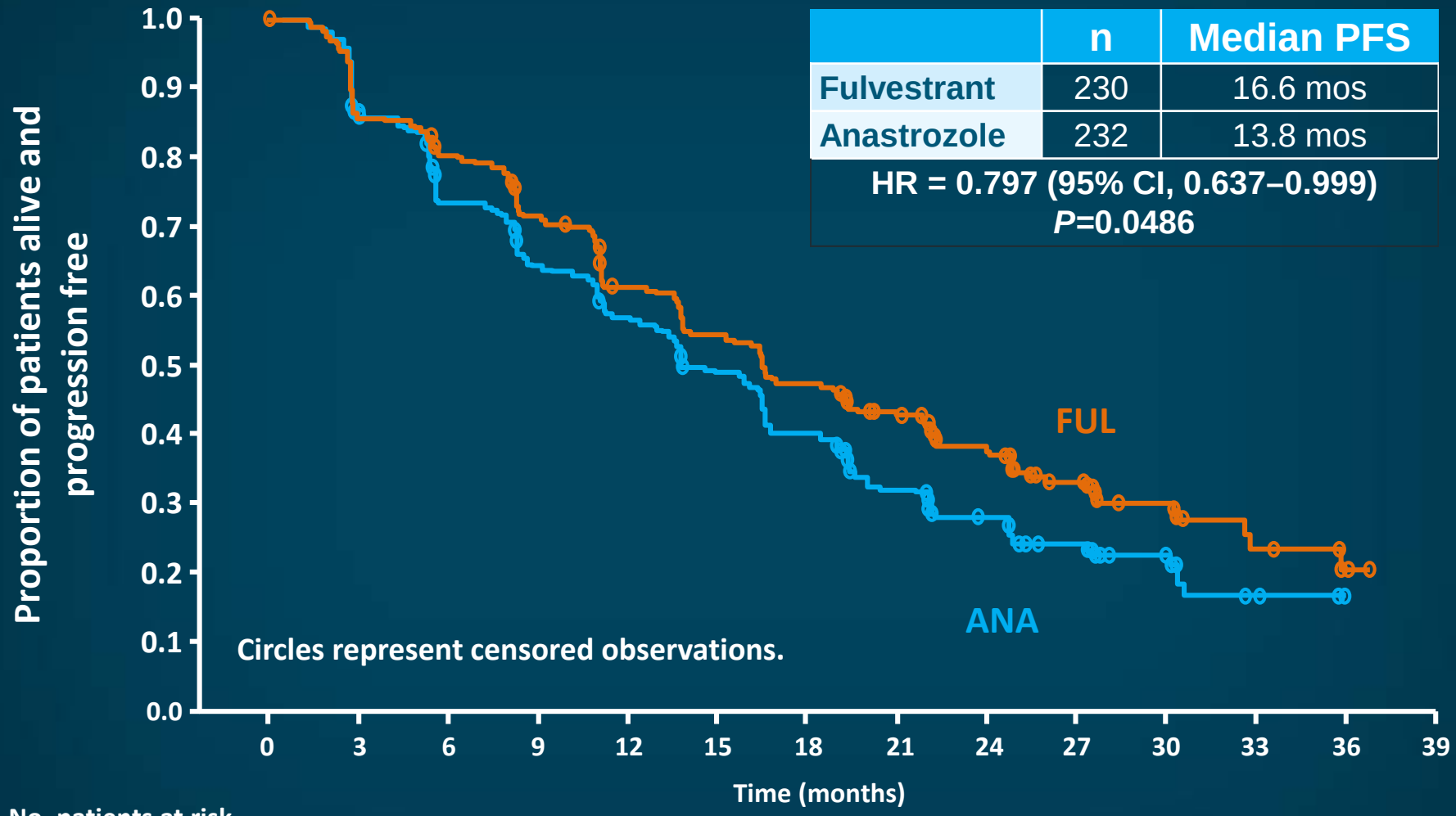
FALCON: (*F*ulvestrant and *A*nastrozo*L*e *CO*mpared in Hormonal Therapy-*N*aïve Advanced BC)

- Randomized, double-blind, parallel-group, international, multicenter study
- Randomization of 450 patients was planned to achieve 306 progression events; if true PFS HR was 0.69 this would provide 90% power for statistical significance at the 5% two-sided level (log-rank test).

BC = breast cancer; PgR = progesterone receptor; HER = human epidermal growth receptor; PO = by mouth; ORR = objective (or overall) response rate; CBR = clinical benefit rate; DoR = duration of response; EDoR = expected DoR; DoCB = duration of clinical benefit; EDoCB = expected DoCB; HRQoL = health-related quality of life; FACT-B = Functional Assessment of Cancer Therapy for BC; TOI = Trial Outcome Index.

Robertson JFR et al. *Lancet*. 2016;388:2997-3005.

FALCON: Primary Endpoint, PFS



	n	Median PFS
Fulvestrant	230	16.6 mos
Anastrozole	232	13.8 mos

HR = 0.797 (95% CI, 0.637–0.999)
P=0.0486

No. patients at risk

FUL	230	187	171	150	124	110	96	81	63	44	24	11	2	0
ANA	232	194	162	139	120	102	84	60	45	31	22	10	0	0

Robertson JFR et al. *Lancet*. 2016;388:2997-3005.

Major Challenge in Endocrine Resistance

- Approximately 30-50% of patients with HR^+ advanced breast cancer do not respond to initial endocrine therapy.
- The majority (if not all) of patients with HR^+ advanced breast cancer will ultimately progress despite endocrine therapy.

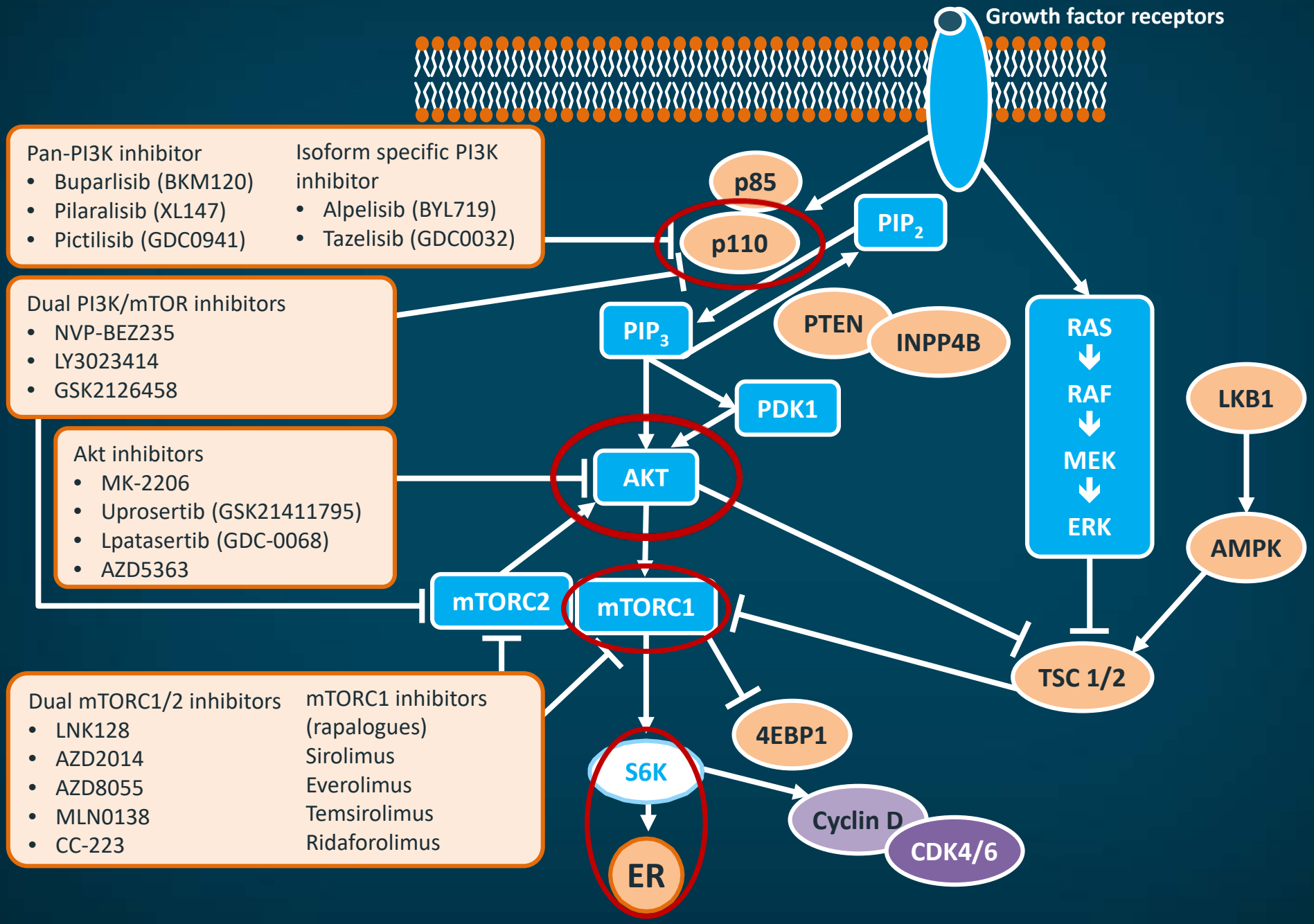
Bedard PL, et al. *Breast Cancer Res Treat*. 2008;108(3):307-317.

Approaches to Overcoming Resistance to Endocrine Therapy

Alterations of downstream signaling pathways such as PI3K, (mTOR and PI3K inhibitors)

Alterations of the cell cycle machinery (CDK inhibitors)

PI3 Kinase/mTOR Signaling



Randomized Phase III Placebo-Controlled Trial of Letrozole Plus Oral Temsirolimus As First-Line Endocrine Therapy in Postmenopausal Women With LABC/MBC

Phase 3 study;
N=1112
PMW with advanced HR+ HER2- BC
Previously un treated with non- and or steroidal AI therapy in adjuvant or metastatic setting

Letrozole 2.5 mg/day + Temsirolimus **30** mg/day x 5 every 2 weeks

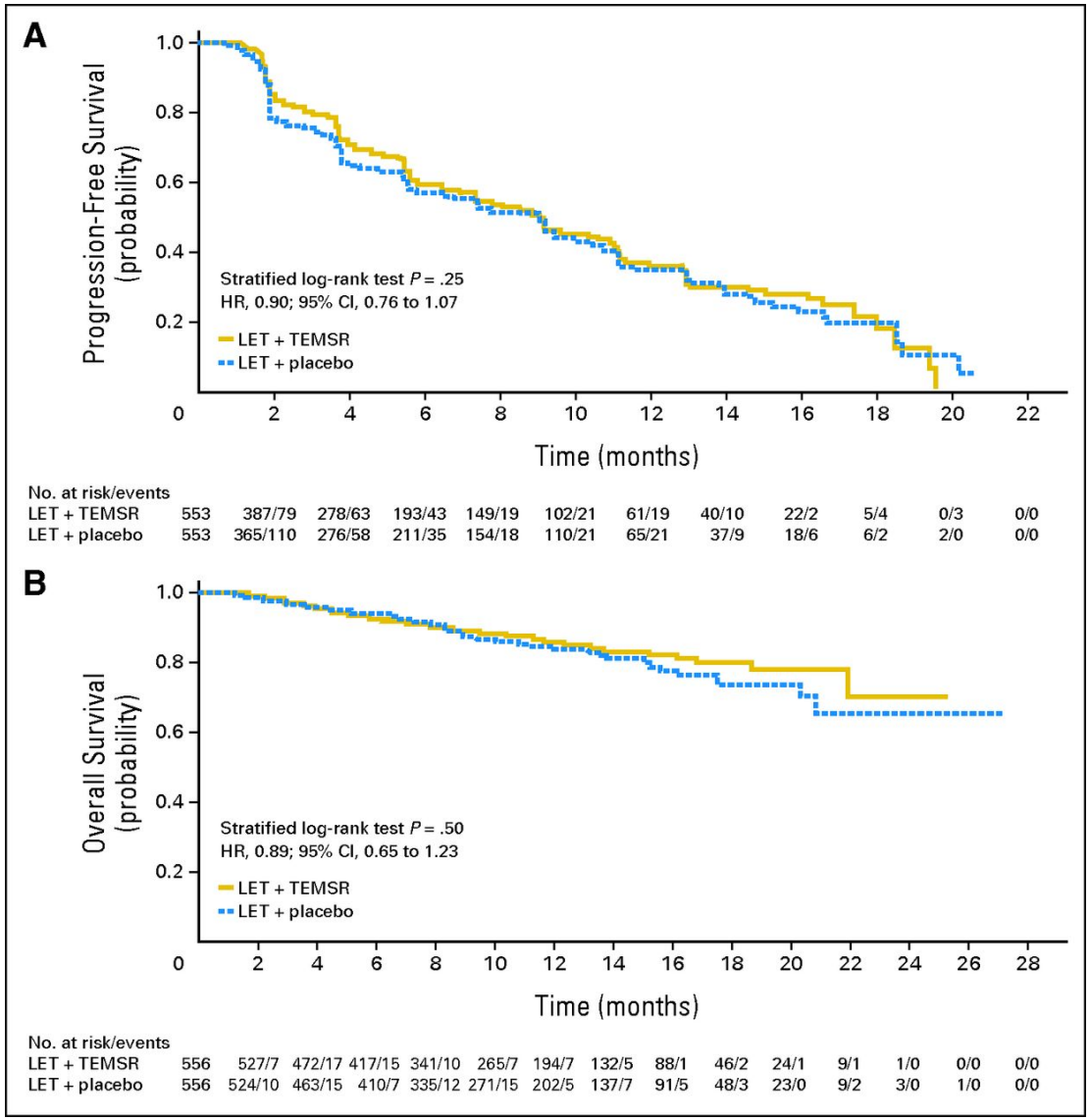
Letrozole 2.5 mg/d + **Placebo**

Primary
CBR at 6 months
Secondary
Safety, TTP, OS, ORR

	Let+Tem n =	**Let n =**	***P*-value**
RR (6 mo)	27%	27%	
TTP (mo)	8.9	9	0.25
Grade 3-4 toxicity	37%	24%	

Wolff A C et al. JCO 2013;31:195-202

Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival.

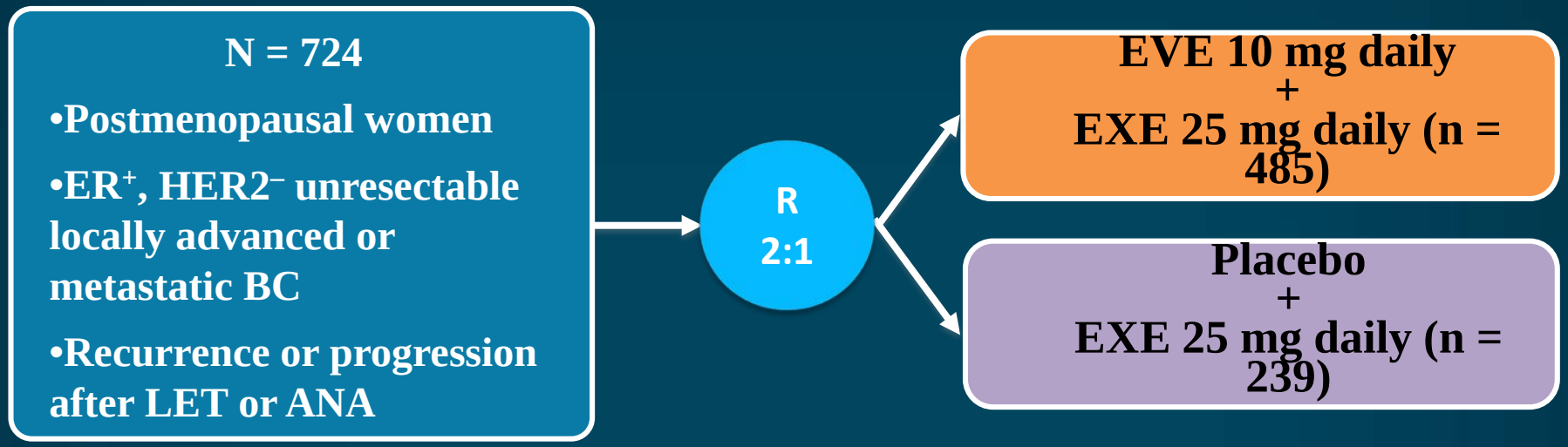


Wolff A C et al. JCO 2013;31:195-202

JOURNAL OF CLINICAL ONCOLOGY

Everolimus in Postmenopausal HR+ ABC

BOLERO-2: Study Design



Endpoints

- **Primary: PFS (local assessment)**
- Secondary: OS, ORR, CBR, QoL, safety, PK
- Exploratory: Biomarkers

Stratification:

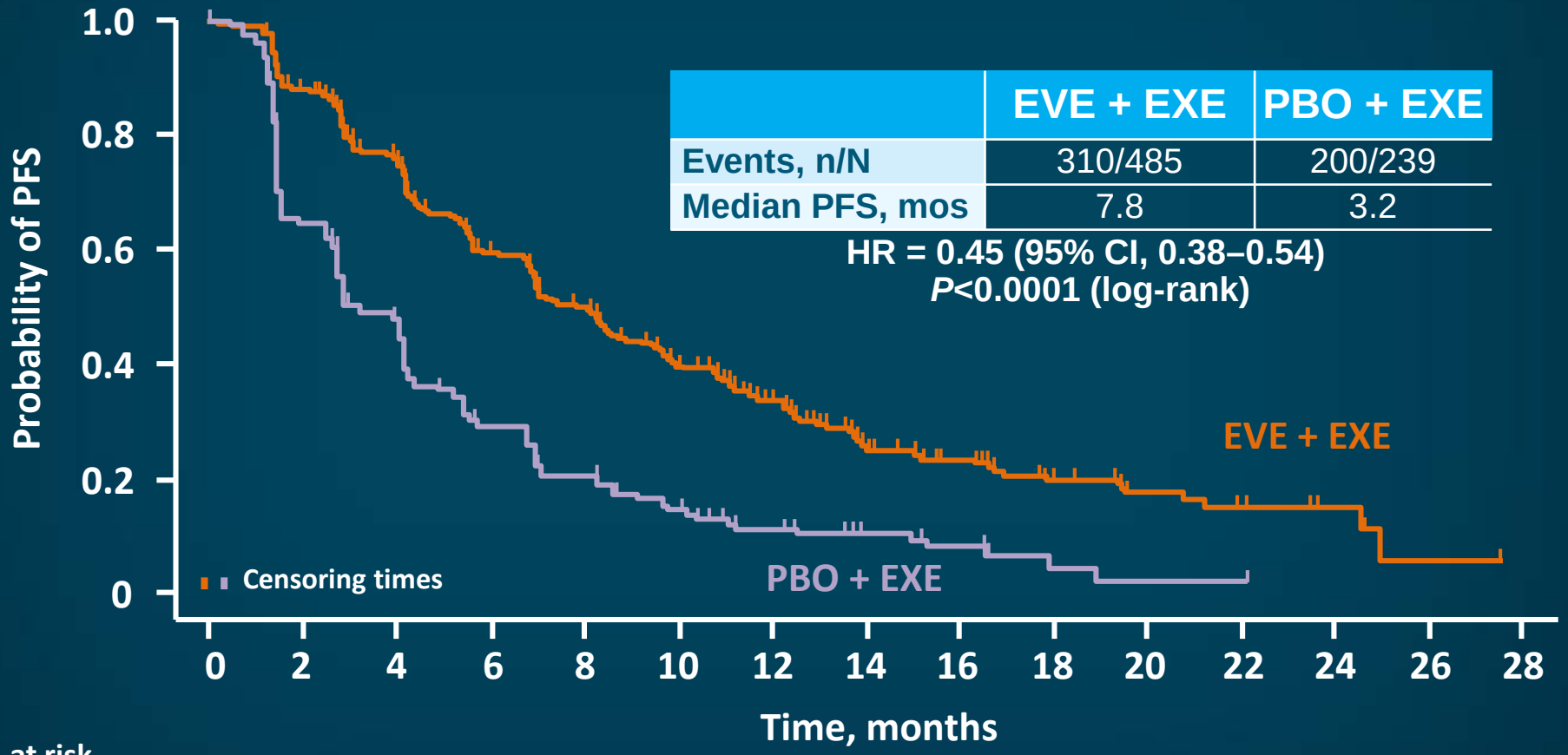
- Sensitivity to prior hormone therapy
- Presence of visceral metastases

EVE = everolimus; EXE = exemestane; PK = pharmacokinetics.

Baselga J et al. *N Engl J Med*. 2012;366:520-529.

BOLERO-2 (18-mos): Final PFS Analysis

Met primary endpoint (local assessment) (4.6-month prolongation of PFS)



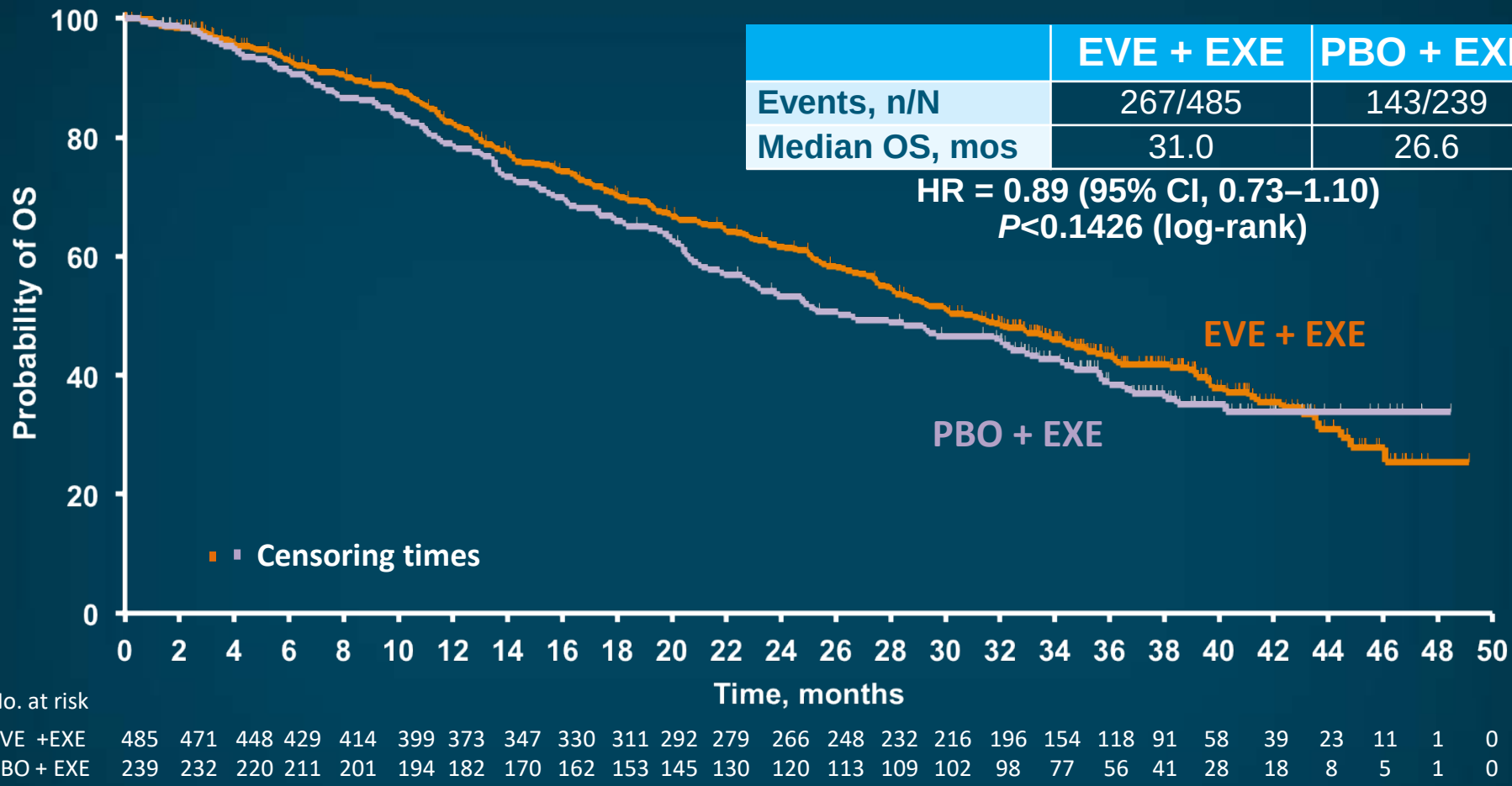
	EVE + EXE	PBO + EXE
Events, n/N	310/485	200/239
Median PFS, mos	7.8	3.2

HR = 0.45 (95% CI, 0.38–0.54)
P<0.0001 (log-rank)

No. at risk															
EVE + EXE	485	394	318	236	194	147	99	57	42	23	13	10	4	1	0
PBO + EXE	239	146	103	61	42	27	17	9	6	2	1	1	0	0	0

Yardley DA et al. *Adv Ther*. 2013;30:870-884., , Baselga J, et al. N Engl J Med 2012;366(6):520-9

BOLERO-2 (39 mos): Final OS Analysis



	EVE + EXE	PBO + EXE
Events, n/N	267/485	143/239
Median OS, mos	31.0	26.6

HR = 0.89 (95% CI, 0.73–1.10)
***P*<0.1426 (log-rank)**

No. at risk

EVE +EXE	485	471	448	429	414	399	373	347	330	311	292	279	266	248	232	216	196	154	118	91	58	39	23	11	1	0
PBO + EXE	239	232	220	211	201	194	182	170	162	153	145	130	120	113	109	102	98	77	56	41	28	18	8	5	1	0

- At 39-month median follow-up, 410 deaths had occurred (data cutoff date: 3 October 2013).
  - 267 deaths (55%) in the EVE + EXE arm vs 143 deaths (60%) in the PBO + EXE arm

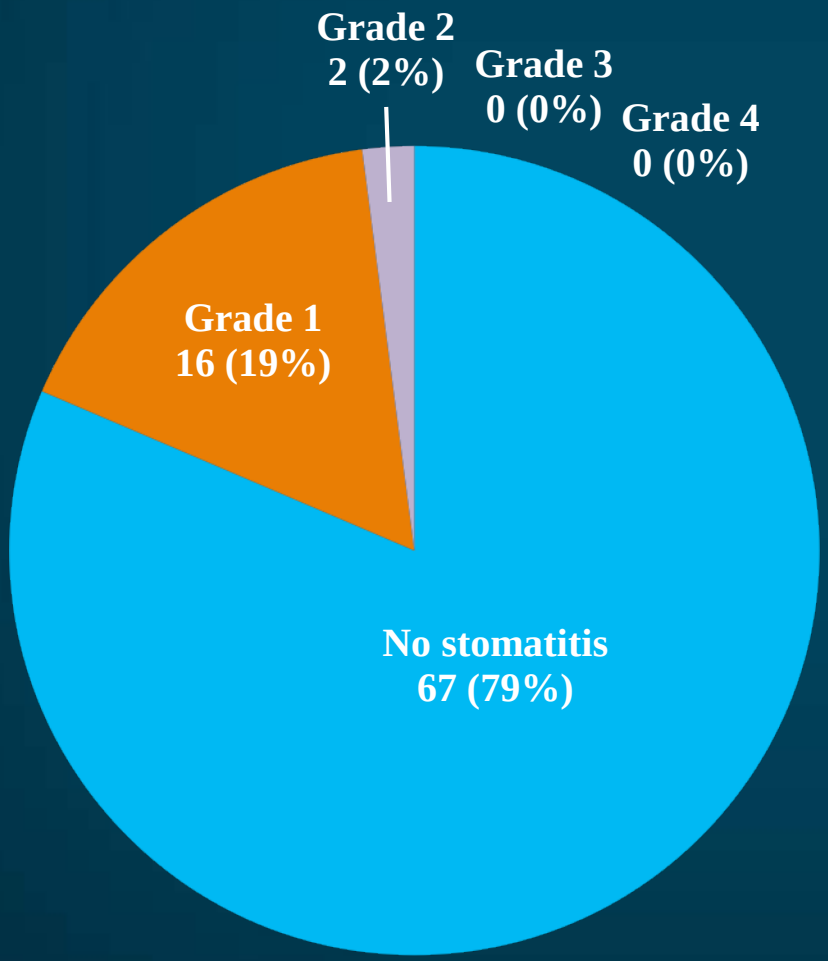
One-sided P value was obtained from log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS®.

Piccart M et al. *Ann Oncol.* 2014;25:2357-2362.

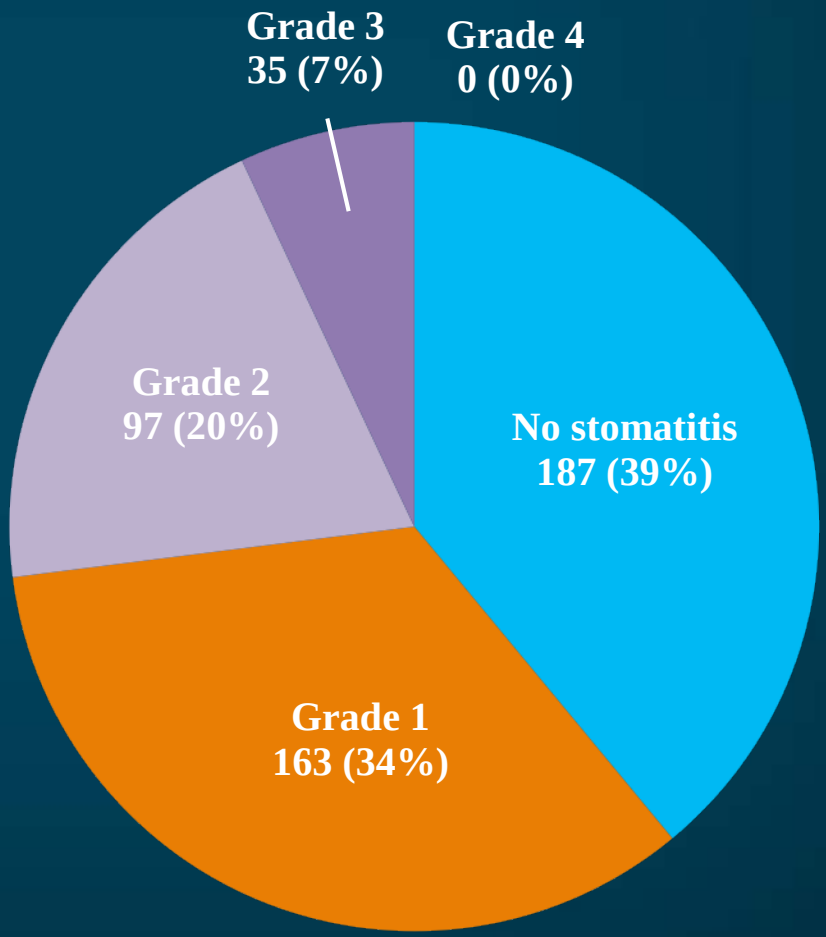
SWISH Study

Prevention of Everolimus-Related Stomatitis

SWISH (week 8)
Total patients = 85



BOLERO-2 (week 8)
Total patients = 482



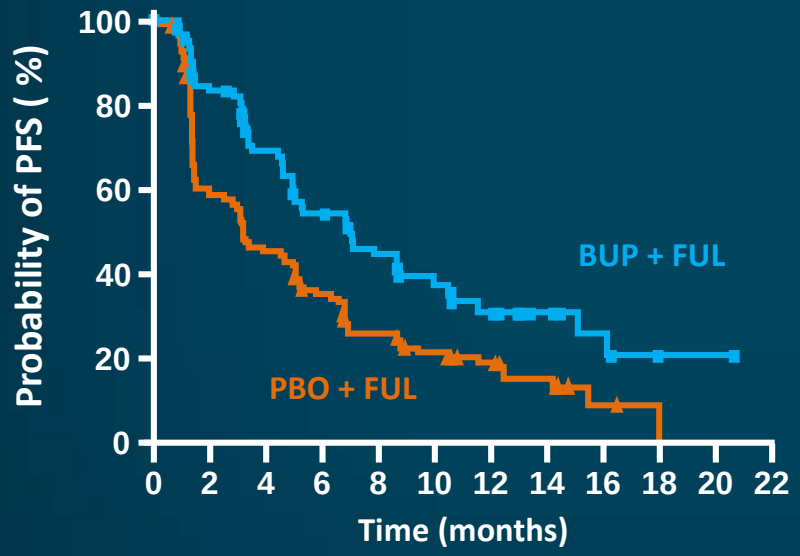
Rugo HS et al. *Lancet Oncol*. 2017;18:654-662.

BELLE-2 Trial

Buparlisib—PI3K Inhibitor for PIK3CA Mutant MBC

	BUP + FUL	PBO + FUL
Median PFS, mos	7.0	3.2

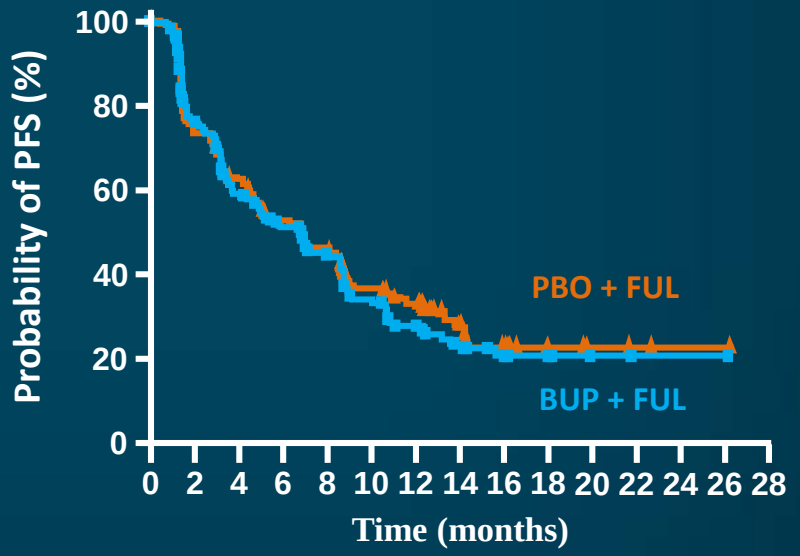
Stratified HR = 0.58 (95% CI 0.41–0.82)
One-sided nominal *P*<0.001



ctDNA mutant PIK3CA

	BUP + FUL	PBO + FUL
Median PFS, mos	6.8	6.8

Stratified HR = 1.02 (95% CI 0.82–1.34)
One-sided nominal *P*=0.557

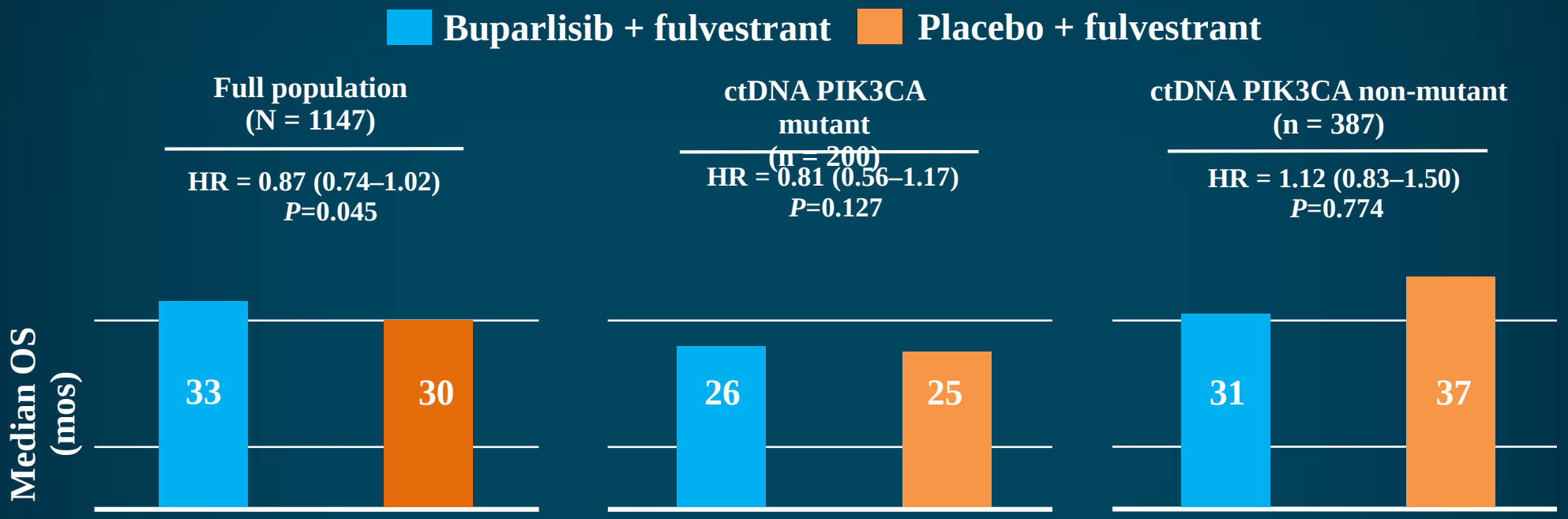


ctDNA non-mutant PIK3CA

BUP = buparlisib.

Baselga J et al. *Lancet Oncol.* 2017;18:904-916.

BELLE-2 Study: Overall Survival



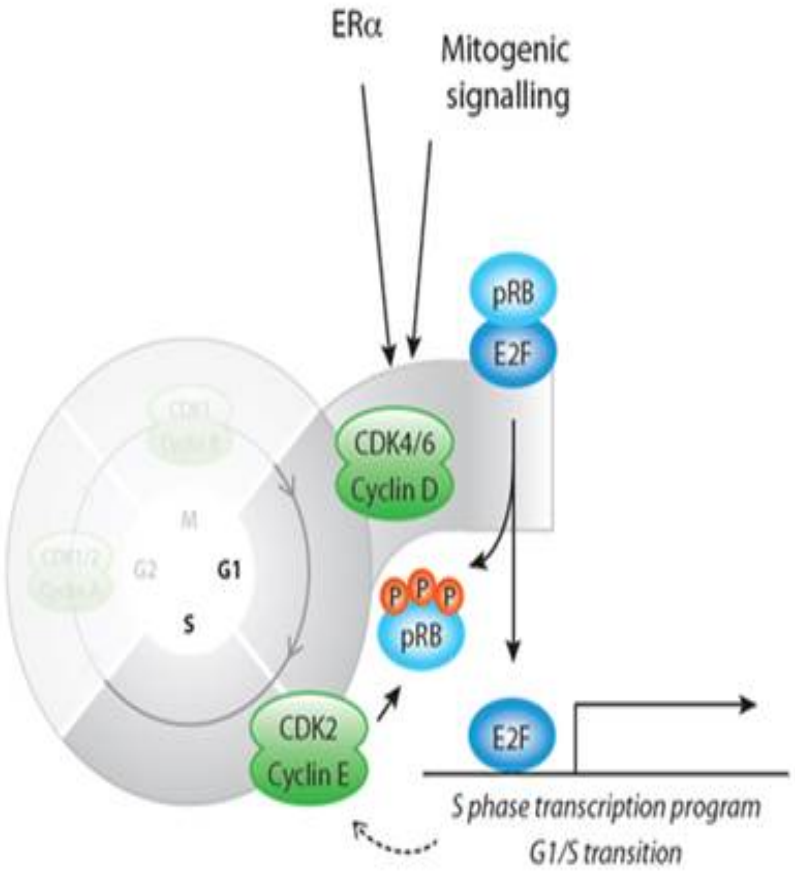
Is overall survival a sensitive endpoint in ER+ HER2– advanced breast cancer trials?

ctDNA= circulating tumor DNA

Campone M et al. SABCS 2017: abstract PD5-12.

CDK4/6 in Breast Cancer

- **Resistance to endocrine therapy presents a major clinical challenge.**
- **The growth of HR+ breast cancer is dependent on Cyclin D1, a direct transcriptional target of ER.**
- **Cyclin D1 activates CDK 4/6 resulting in G1–S phase transition and entry into the cell cycle.[1]**
- **Cell line models of endocrine resistance remain dependent on Cyclin D1 and CDK4/6.[2,3]**



CDK=cyclin-dependent kinase; ER=estrogen receptor; HR+=hormone receptor-positive.

1. Asghar U, et al. *Nat Rev Drug Discov*. 2015;14:130-46.
2. Miller T, et al. *Cancer Discov*. 2011; 1:338-51.
3. Thangavel C, et al. *Endocr Relat Cancer*. 2011;18:333-45.

Status of CDK4/6 Inhibitors in Development

	Palbociclib (Ibrance®, Pfizer)	Ribociclib (Kisqali®, Novartis)	Abemaciclib (Verzenio™, Eli Lilly)
Potency (IC_{50})	CDK4: 9–11 nM CDK6: 15 nM	CDK4: 10 nM CDK6: 39 nM	CDK4: 2 nM CDK6: 10 nM
Dose/schedule	125 mg daily, 3 weeks on/1 off	600 mg daily 3 weeks on/1 off	Combination:150 mg BID Monotherapy: 200 mg BID Continuous
Completed Phase III trials	1st line: **PALOMA-2** 2nd line: **PALOMA-3**	1st line: **MONALEESA-2** **MONALEESA-7** 2nd line: MONALEESA-3	1st line: **MONARCH-3** 1st or 2nd line: **MONARCH-2**
FDA approval status	2015: 1st line (with letrozole) 2016: 2nd line (with fulvestrant)	2017: 1st line (with letrozole)	2017: 2nd line (with fulvestrant) Single agent post-ET and chemo

BID = twice a day; Chemo = chemotherapy.

Palbociclib (Ibrance®) prescribing information (PI), 2017. Ribociclib (Kisqali®) PI, 2017. Abemaciclib (Verzenio™) PI, 2017.

CDKi Phase III Trials: First-Line Post-menopausal

	Palbociclib[1]	RIbociclib[2,3]	Abemaciclib[4]
	PALOMA-2	MONALEESA-2	MONARCH-3
Partner	Letrozole	Letrozole	Letrozole or anastrozole
Eligibility	No prior met ET	No prior met ET No adj AI <12 mos	No prior adv ET No adj AI <12 mos
Population	N = 666	N = 668	N = 493
De novo stage IV, %	31.1	34	39.8
Relapse ≤12 mos, %	22.1	1.2	0
Bone only, %	23.2	25	22.1
Response rate (%)			
ORR (%)	55.3 vs 34.7	47 vs 34	59 vs 44
CBR	84.9 vs 70.3	83 vs 77	79 vs 69

CBR = clinical benefit rate (CR + PR + SD ≥24 wks)

1. Finn RS et al. *N Engl J Med.* 2016;375:1925-1936. 2. Hortobagyi GN et al. *N Engl J Med*. 2016;375:1738-1748. 3. O'Shaughnessy J et al. *Breast Cancer Res Treat.* 2017;Nov 21: Epub ahead of print. 4. Di Leo A et al. ESMO 2017: abstract 236O_PR.

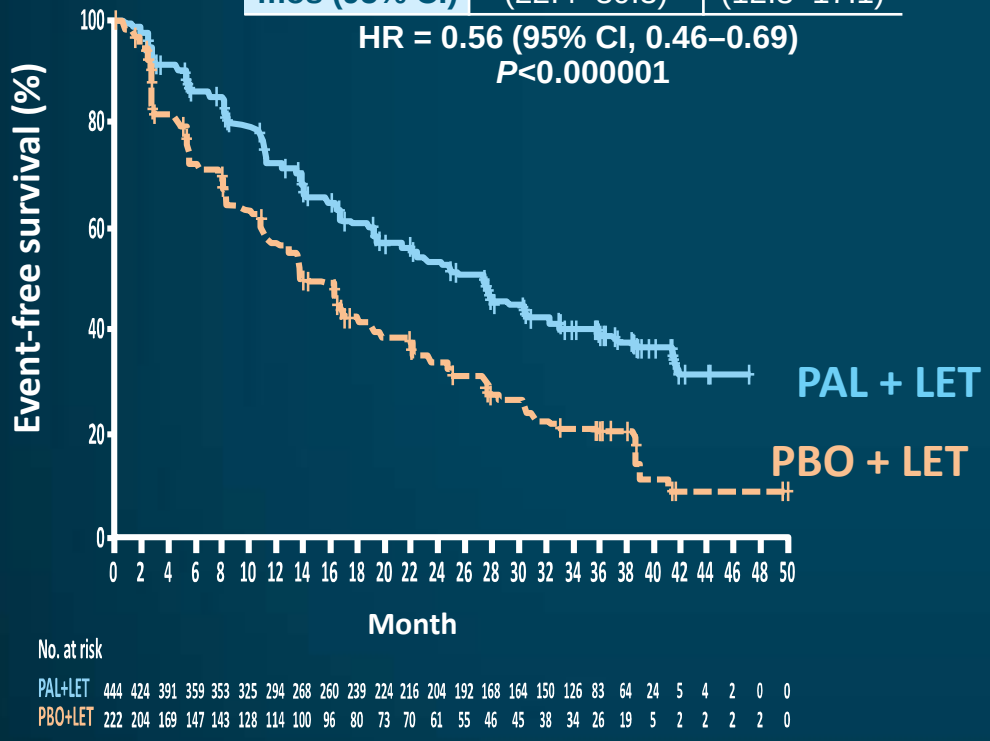
PALOMA-2 and MONALEESA-2: PFS

Investigator Assessment

PALOMA-2[1]

	PAL + LET	PBO + LET
Median PFS, mos (95% CI)	27.6 (22.4–30.3)	14.5 (12.3–17.1)

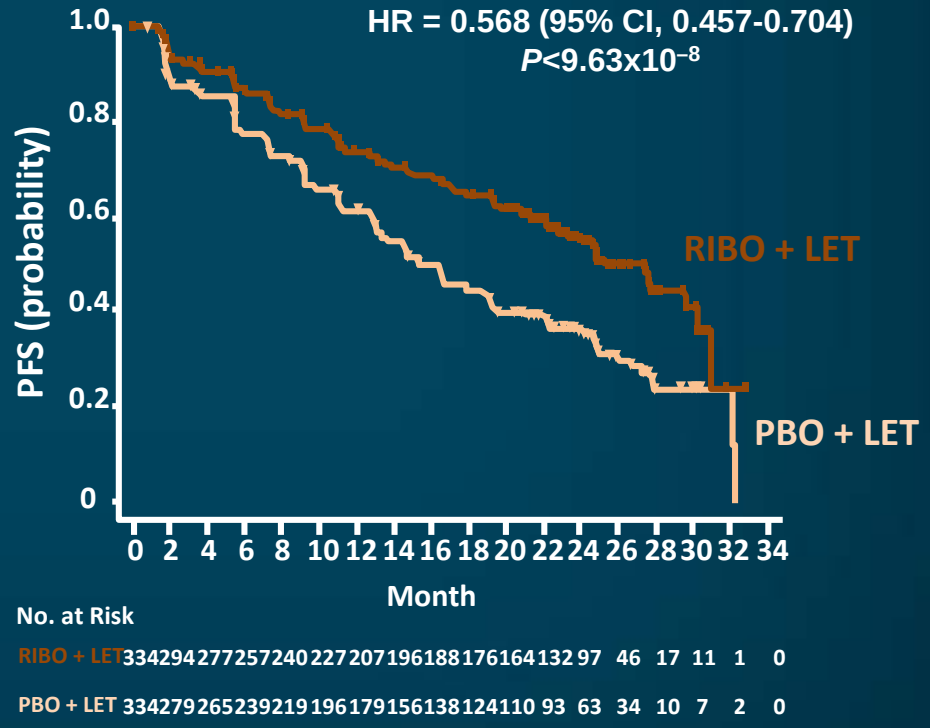
HR = 0.56 (95% CI, 0.46–0.69)
P<0.000001



MONALEESA-2[2]

	RIBO + LET	PBO + LET
Median PFS, mos (95% CI)	25.3 (23.0–30.3)	16.0 (13.4–18.2)

HR = 0.568 (95% CI, 0.457-0.704)
P<9.63x10^{-8}



PAL = palbociclib; LET = letrozole; PBO = placebo; RIBO = ribociclib; NR = not reached.

*These studies address different patient populations, thus yield different results.

1. Rugo H et al. SABCS 2017: abstract P5-21-03. 2. Hortobagyi GN et al. *J Clin Oncol*. 2017;35(suppl): abstract 1038.

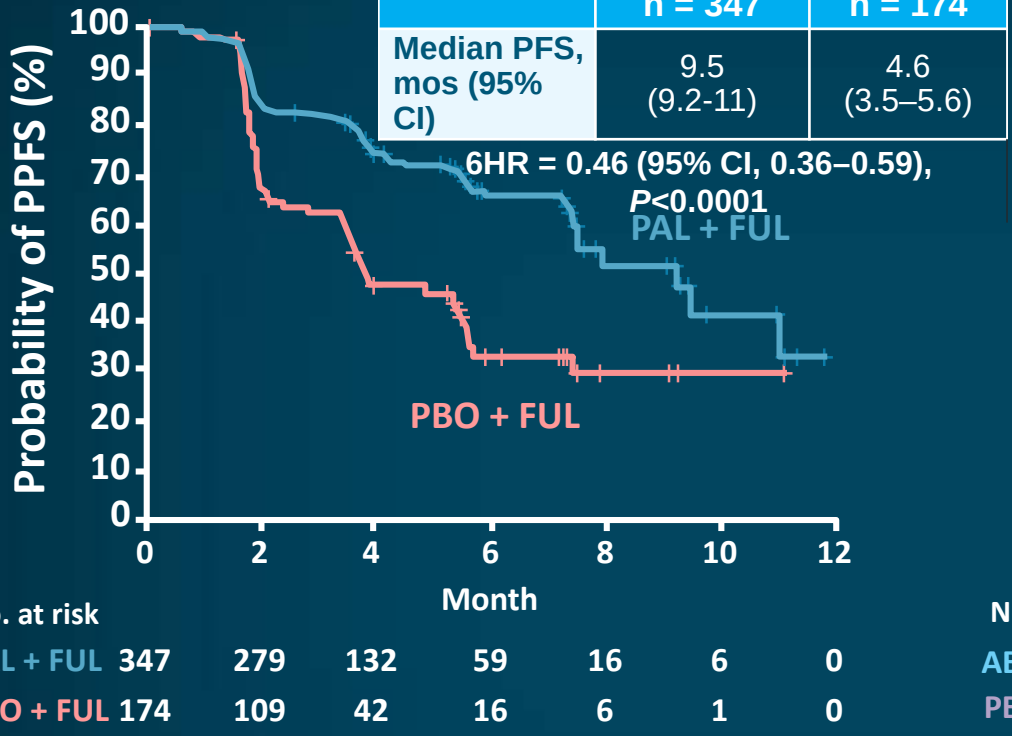
CDK Inhibitors Phase III Trials: 2nd Line

	Palbociclib[1]	RIbociclib[2]	Abemaciclib[3,4]
	PALOMA-3	MONALEESA-3	MONARCH-2
Partner	Fulvestrant	Fulvestrant	Fulvestrant
Eligibility	Relapse within 1 yr PD on 1st- line ET	Relapse within 1 yr PD on 1st-line ET	Relapse within 1 yr ET PD on 1st-line ET
Population (%)	N = 521, 2:1	Ongoing	N = 669; 2:1
Adjuvant	5%		60%
Premenopausal	21%		16%
Any met chemo	33%		Not allowed
Bone only	22%		28%
ORR (%)	19% vs 9%		48% vs 21%

1. Cristofanelli M et al. *Lancet Oncol*. 2016;17:425-439. 2. NCT02422615. 3. Sledge GW Jr et al. *J Clin Oncol*. 2017; 35:2875-2884. 4. Sledge GW Jr et al. *J Clin Oncol*. 2017;35(suppl): abstract 1000.

Palbociclib and Abemaciclib: PFS 2nd-Line

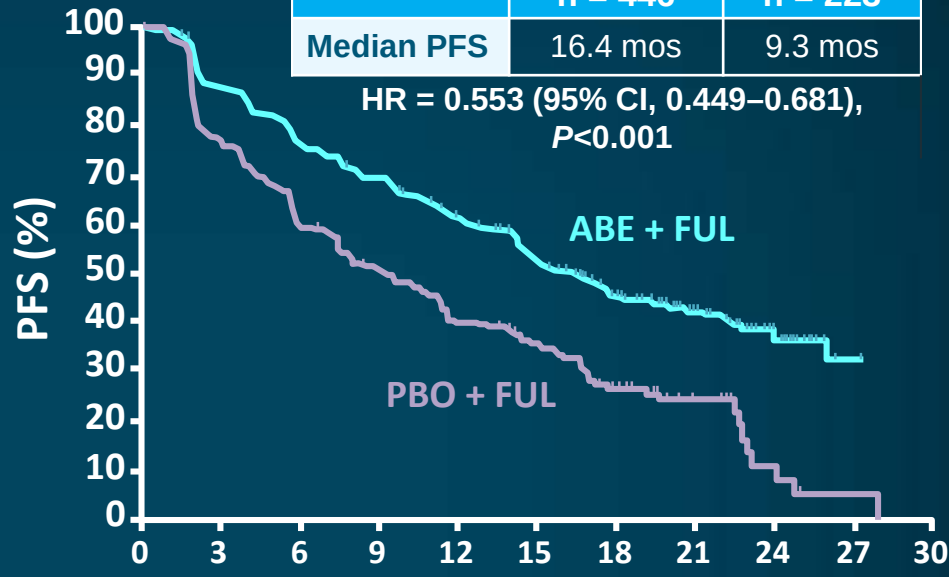
	PAL + FUL n = 347	PBO + FUL n = 174
Median PFS, mos (95% CI)	9.5 (9.2-11)	4.6 (3.5–5.6)



No. at risk							
PAL + FUL	347	279	132	59	16	6	0
PBO + FUL	174	109	42	16	6	1	0

PALOMA-3[1]
9.5 mos vs 4.6 mos, HR = 0.46 (*P*<0.0001)

	ABE + FUL n = 446	PBO + FUL n = 223
Median PFS	16.4 mos	9.3 mos



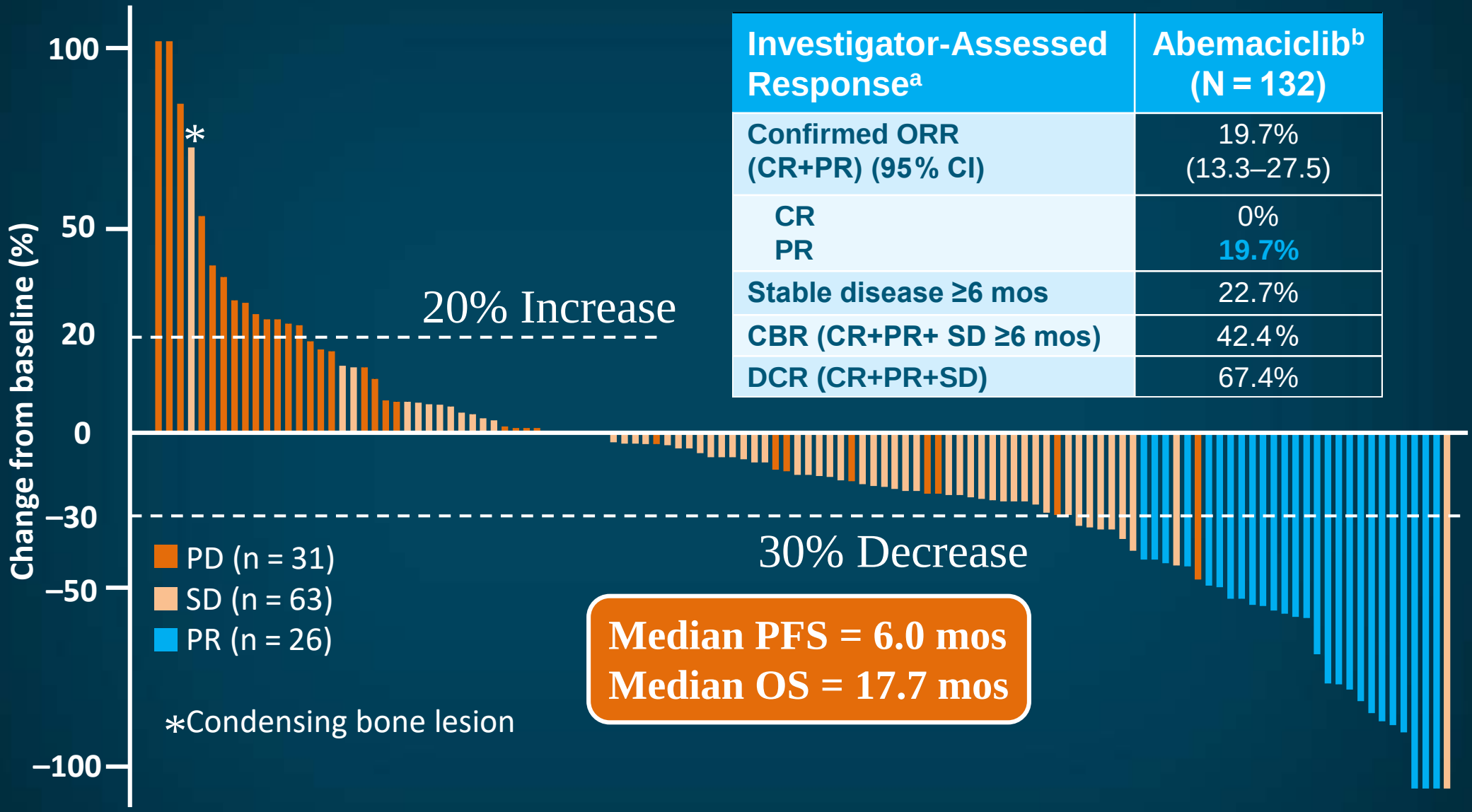
No. at risk											
ABE + FUL	446	367	314	281	234	171	101	65	32	2	0
PBO + RUL	223	165	123	103	80	61	32	13	4	1	0

MONARCH-2[2,3]
16.4 mos vs 9.3 mos, HR = 0.55 (*P*<0.001)

108 premenopausal patients had the same benefit as in PALOMA 3 but with added goserelin.[4]

1. Cristofanilli M et al. *Lancet Oncol*. 2016;17:425-439. 2. Sledge GW Jr et al. *J Clin Oncol*. 2017;35:2875-2884. 3. Sledge GW Jr et al. *J Clin Oncol*. 2017;35(suppl): abstract 1000. 4. Loibl S et al. *Oncologist*. 2017;22:1028-1038.

MONARCH 1: Late-Line Abemaciclib ER+ MBC



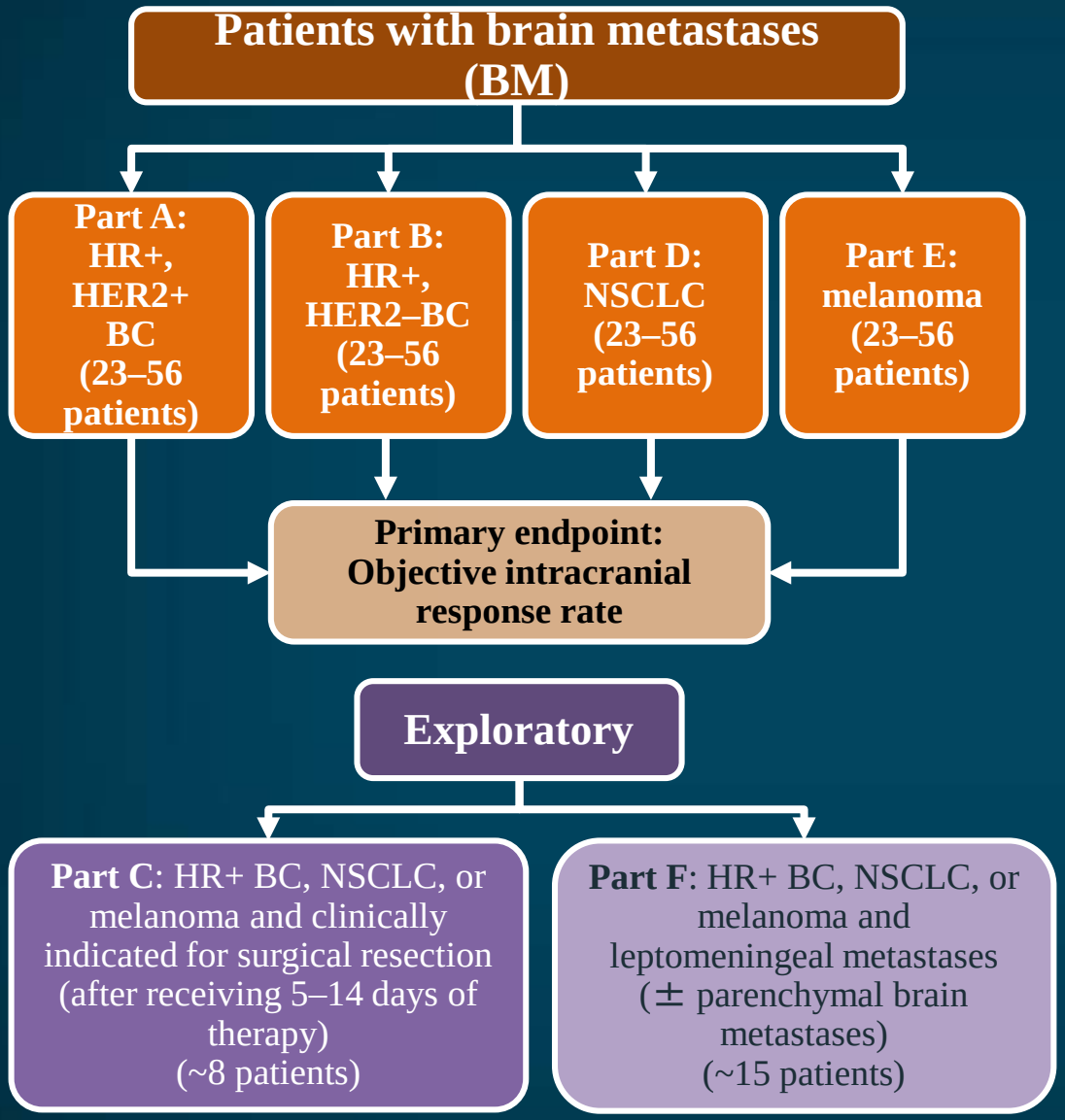
Investigator-Assessed Response[a]	Abemaciclib[b] (N = 132)
Confirmed ORR (CR+PR) (95% CI)	19.7% (13.3–27.5)
CR	0%
PR	19.7%
Stable disease ≥6 mos	22.7%
CBR (CR+PR+ SD ≥6 mos)	42.4%
DCR (CR+PR+SD)	67.4%

[a]Assessments based on independent review were comparable. [b]200 mg monotherapy dose.

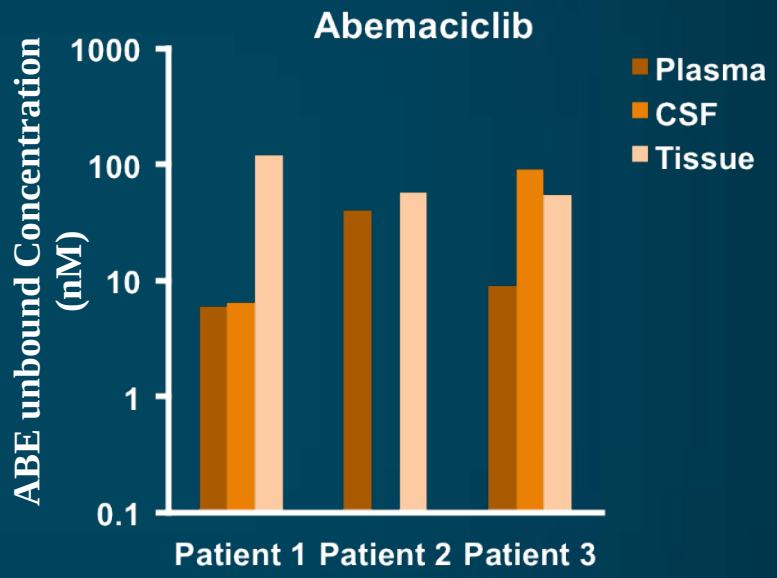
CR = complete response; PR = partial response; DCR = disease control rate; SD = stable disease.

Dickler MN et al. *Clin Cancer Res.* 2017;23:5218-5224.

Abemaciclib for Brain Metastases*



Plasma, CSF, and resected tumor tissue unbound concentrations of ABE

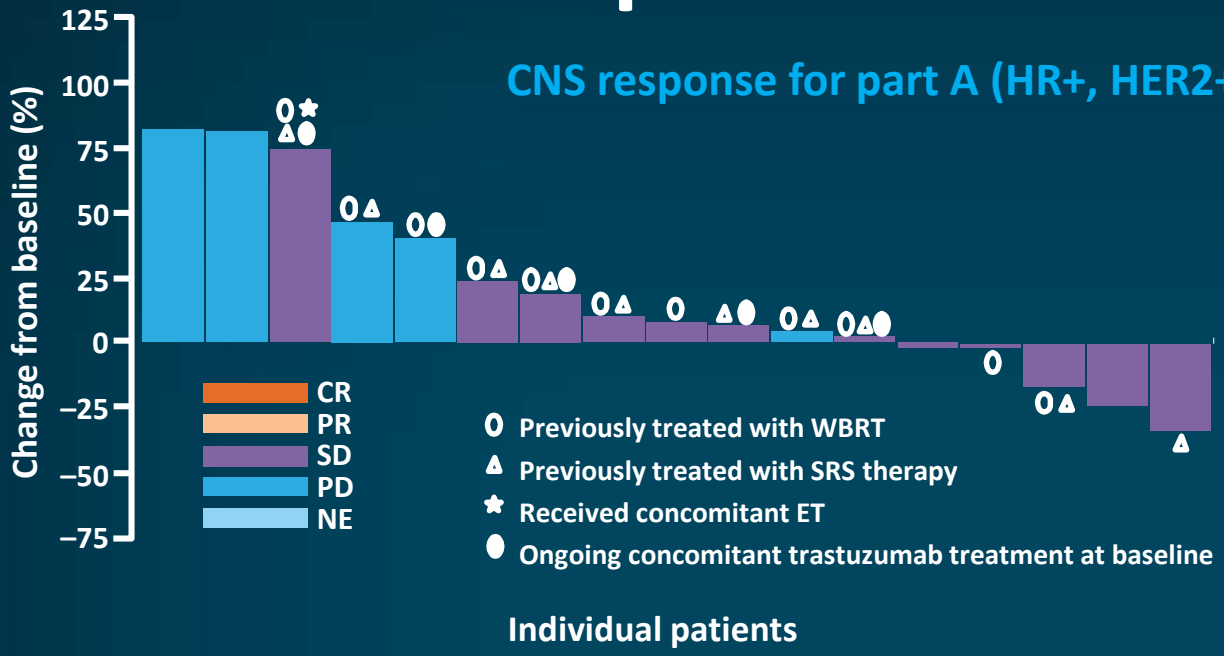


8.7% ORR; 17% CBR
Heavily-pretreated BM metastatic BC

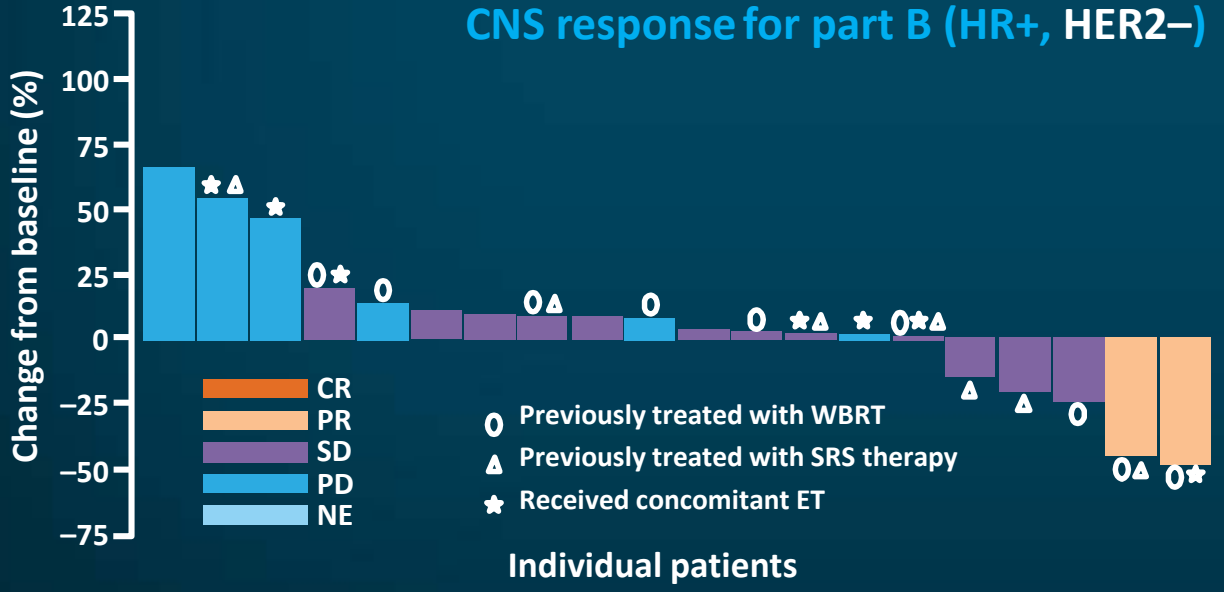
NSCLC = non-small-cell lung cancer; CSF = cerebrospinal fluid. * Abemaciclib is not FDA-approved for this indication.

NCI02308020. Sahebjam S et al. *J Clin Oncol*. 2016;34(suppl): abstract 526. Tolaney SM et al. *J Clin Oncol.* 2017;35(suppl): abstract 1019.

CNS Responses with Abemaciclib



Responders	N = 23
OIRR, n (%) (95% CI)	**0 (0.0)** (NA)
CR, n (%)	0 (0.0)
PR, n (%)	0 (0.0)
SD, n (%)	12 (52.2)
SD ≥6 mos, n (%)	1 (4.3)
PD, n (%)	11 (47.8)
CBR, n (%) (95% CI)	**1 (4.3)** (0.0–12.7))



Responders	N = 23
OIRR, n (%) (95% CI)	**2 (8.7)** (0.0–20.2)
CR, n (%)	0 (0.0)
PR, n (%)	2 (8.7)
SD, n (%)	13 (56.5)
SD ≥6 mos, n (%)	2 (8.7)
PD, n (%)	8 (34.8)
CBR, n (%) (95% CI)	**4 (17.4)** (1.9–32.9)

Bachelot T et al. SABCS 2017: abstract P1-17-03.

Summary of 1st and 2nd line CDK4/6i Trials

Table 1. Select Randomized Clinical Studies of Endocrine Therapy Plus CDK4/6-Directed Therapy in Estrogen Receptor–Positive Metastatic Breast Cancer

Study	Regimen	Phase	No.	PFS, Endocrine Alone (months)	PFS, + CDK 4/6 Inhibitor (months)	Hazard Ratio (95% CI)
First line						
PALOMA-1	Letrozole with or without palbociclib	II	165	10.2	20.2	0.488 (0.319 to 0.748)
PALOMA-2	Letrozole with or without palbociclib	III	666	14.5	24.8	0.58 (0.46 to 0.72)
MONALEESA-2	Letrozole with or without ribociclib	III	668	14.7	25.3	0.56 (0.43 to 0.72)
MONARCH-3	NSAI with or without abemaciclib	III	493		NCT 21*	
Second line						
PALOMA-3	Fulvestrant with or without palbociclib	III	521	4.6	9.5	0.46 (0.36 to 0.59)
MONARCH-2	Fulvestrant with or without abemaciclib	III	669	9.3	16.4	0.553 (0.449 to 0.681)
MONALEESA-3	Fulvestrant with or without ribociclib	III	725		NCT02422615	

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; PFS, progression-free survival; NSAI, nonsteroidal aromatase inhibitor.
*Interim analysis reportedly met primary end point of improved PFS in the combination arm.[8]

Wander S, Mayer EL, Burstein HJ. J Clin Oncol 2017

Side effects of CDK4/6 inhibitors

Table 2. Dosing and Toxicity for Cyclin-Dependent Kinase 4/6 Inhibitors

	Palbociclib (125 mg per day [3 weeks on, 1 week off])		Ribociclib (600 mg per day [3 weeks on, 1 week off])		Abemaciclib (200 mg twice per day [continuous])	
Common Adverse Event*	All Grades	Grade 3 and 4	All Grades	Grade 3 and 4	All Grades	Grade 3 and 4
Neutropenia	74-81	54-67	74	59	46	27
Thrombocytopenia	16-22	2-3	NR	NR	16	3
Fatigue	37-40	2-4	37	2	40	3
Diarrhea	21-26	1-4	35	1	86	13
Nausea	25-35	0-2	52	2	45	3
QTc prolongation	NR	NR	3	NR	NR	NR

NOTE. Data are given as percent.
Abbreviation: NR, not reported; QTc, corrected QT interval.
*Common adverse events in phase III trials in the metastatic setting.

Wander S, Mayer EL, Burstein HJ. J Clin Oncol 2017

Progression on CDK4/6 Inhibitors

- Per NCCN 2017 guidelines: If disease progression on CDK4/6 inhibitor + letrozole, there are no data to support an additional line of therapy with another CDK4/6 inhibitor regimen.
- Resistance mechanisms for CDK4/6
  - Rb mutation
  - Collateral pathways, eg, PI3K
  - Switch to cyclin E
  - Resistance to the endocrine therapy, eg, ESR1 or HER2 mutation
- Clinical trial approaches to overcoming resistance
  - CDKi-free period then rechallenge
  - Add additional agents (PI3K, mTOR inhibitors)
  - Switch endocrine therapies

ESR = erythrocyte sedimentation

NCCN Clinical Practice Guidelines in Oncology. Breast Cancer V3. 2017. December 15, 2017.
Turner NC,et al. *Lancet.* 2017;389:2403–2414.

Summary: CDK4/6 Inhibitors in ER+ MBC

- The 3 CDK4/6 inhibitors seem to be consistent and comparable in prolonging PFS in combination with endocrine therapy in the metastatic setting with acceptable toxicity.
- We have no overall survival data yet in phase III trials.
- Selection of agent, sequence, and number of drugs should be patient-specific; most patients are receiving CDK4/6i + AI in US.
- Given activity in advanced setting, now moving to adjuvant setting
- Resistance is universal
    - Next generation of trials is looking at switching ET or CDKI with addition of other drugs to inhibit resistance pathways.

Take home points in HT in ER+ HER-2- MBC

- Endocrine therapy is the cornesrtone of the first-line therapy of HR+ HER-2- MBC. The median itme to progresión is 12 to 24 months

- Fulvestrant is superior than anastrozole in first line therapy and an option in first-line therapy

- CDK inhibitors -based therapy wirh AI or fulvestrant is a new option the in first line therapy of patients with ER+ MBC including those progressing on adjuvant hormonal therapy

- The best sequency is unknown. However, consider tumour biology, clinical features including prior adjuvant therapy and patient factors including PS and organ function when sele
most appropriate therapy

Target Therapy in ER-, PR-, and HER-2 normal (TNBC) Metastatic Breast Cancer

TNBC

Frequency: 10-20% of patients with breast cancer

Definition: It is clinically defined as ER-negative <1%), PR-negative(,1%) and HER2- non-overexpressing (IHC 0-1 or IHC 2+ FISH-)

Heterogeneous disease with generally virulent natural history

Rapid rise in risk of recurrence following diagnosis

Increase risk of brain mets

Rapid progression from distant recurrence to death

Currently, there are no molecular targets for this subtype of breast cancer

TNBC

- Existing Therapies
  - Chemotherapy including platinum salts
- Future Directions:
  - PARP inhibitors
  - Immunotherapies
  - Androgen receptor inhibitors

TNBC is not one disease

Basal-like 1: cell cycle, DNA repair and proliferation genes

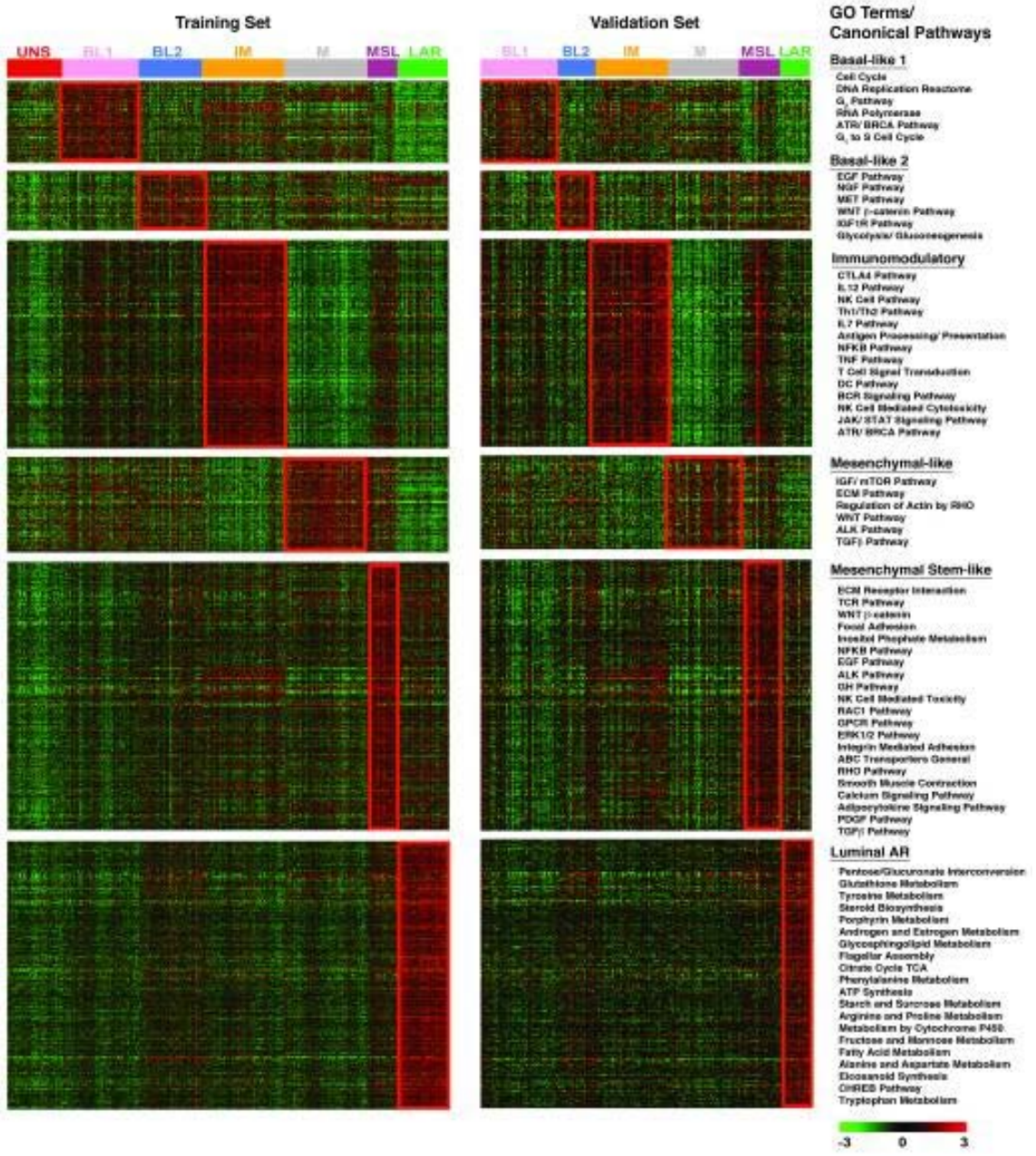
Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)

IM: immune cell processes (medullary breast cancer)

M: Cell motility and differentiation, EMT processes

MSL: similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

LAR: Androgen receptor and downstream genes, luminal features



Lehmann et al. J Clin Invest 2011

Current Treatment Options for Metastatic TNBC

- Sequential single-agent chemotherapy is the preferred approach for most pts with metastatic TNBC
  - Combination chemotherapy can be used for pts requiring more rapid response but does not improve OS

Taxanes	Anthracyclines	Antimetabolites	Other Microtubule Inhibitors	Platinum Agents
▪ Paclitaxel ▪ Nab-paclitaxel ▪ Docetaxel	▪ Doxorubicin ▪ Pegylated liposomal doxorubicin ▪ Epirubicin	▪ Capecitabine ▪ Gemcitabine	▪ Vinorelbine ▪ Eribulin ▪ Ixabepilone	▪ Carboplatin ▪ Cisplatin

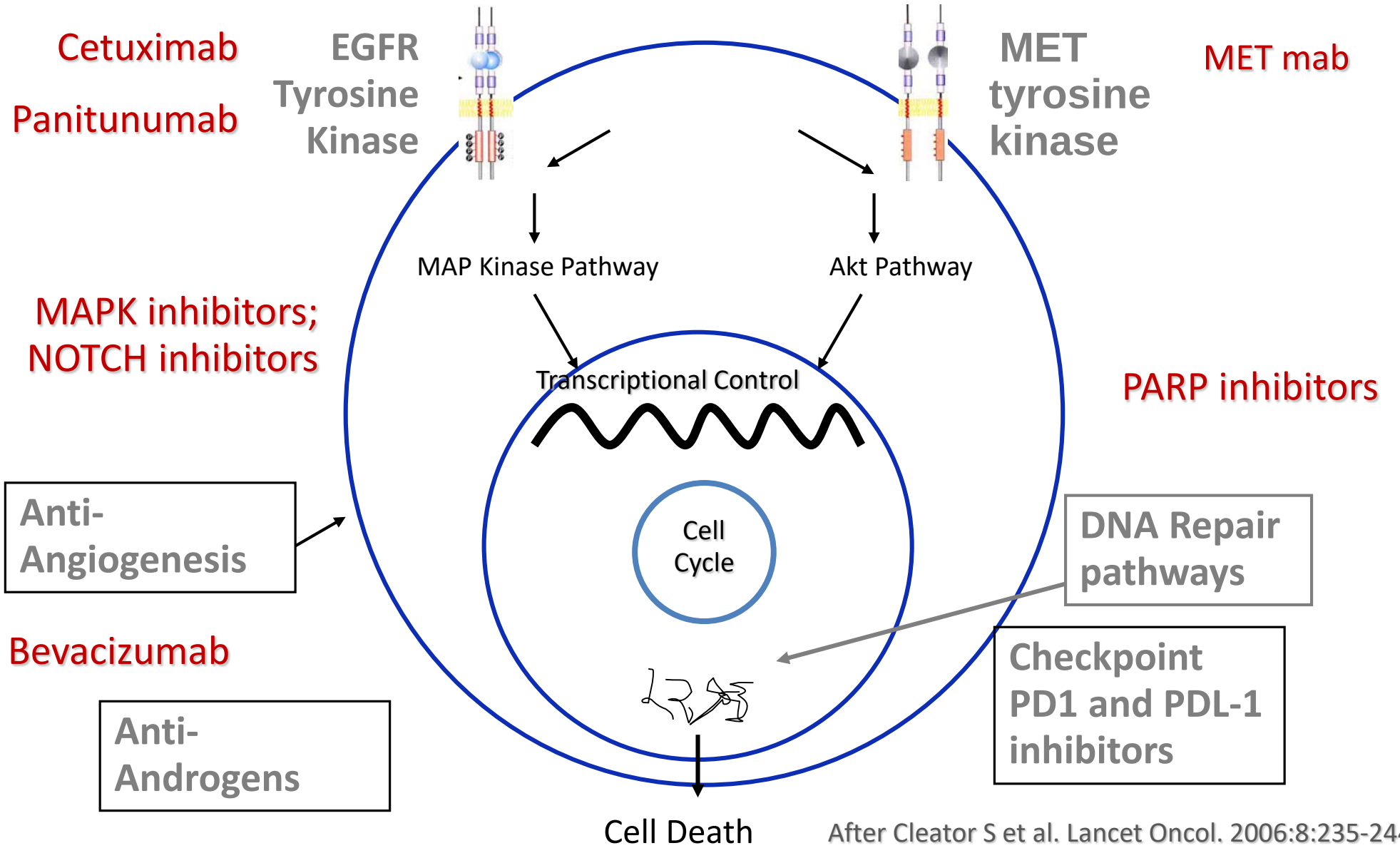
- Pts should generally remain on a regimen until best response, disease progression, or significant toxicity

Zeichner SB, et al. Breast Cancer (Auckl). 2016;10:25-36.
Wahba HA, et al. Cancer Biol Med. 2015;12:106-116.

Low Response Rates in Pretreated mTNBC

Drug	Phase	N	Population	ORR, %	PFS, months	OS, months	Source
1st-line treatment							
Carboplatin	III	188	1st line	31	3.1	12.4	Tutt A, SABCS 2014
Docetaxel	III	188	1st line	36	4.5	12.3	Tutt A, SABCS 2014
Cisplatin/ Carboplatin	II	86	1st line (80.2%)	26	2.9	11.0	Isakoff SJ, J Clin Oncol, 2015
≥1st-line treatment							
Ixabepilone	II (pooled analysis)	60	Resist to AC-T or just to T	6-17	1.6-2.7	--	Perez EA, Breast Cancer Res Treat 2010
Capecitabine	III (pooled analysis)	208	Prior A, T or resist to A, T	15	1.7	--	Perez EA, Breast Cancer Res Treat 2010
Eribulin	III (pooled analysis)	199	≥1 prior chemo	11	2.8	12.4	Pivot X, Ann Oncol 2016

Triple-Negative Breast Cancers: Some Potential Therapeutic Targets



After Cleator S et al. Lancet Oncol. 2006:8:235-244

PARP inhibitors

OlympiAD study design

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious g*BRCA*m
- Prior anthracycline and taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

Olaparib
300 mg tablets bd

2:1 randomization

Chemotherapy treatment of physician's choice (TPC)

- Capecitabine
- Eribulin
- Vinorelbine

Treat until progression

Primary endpoint:

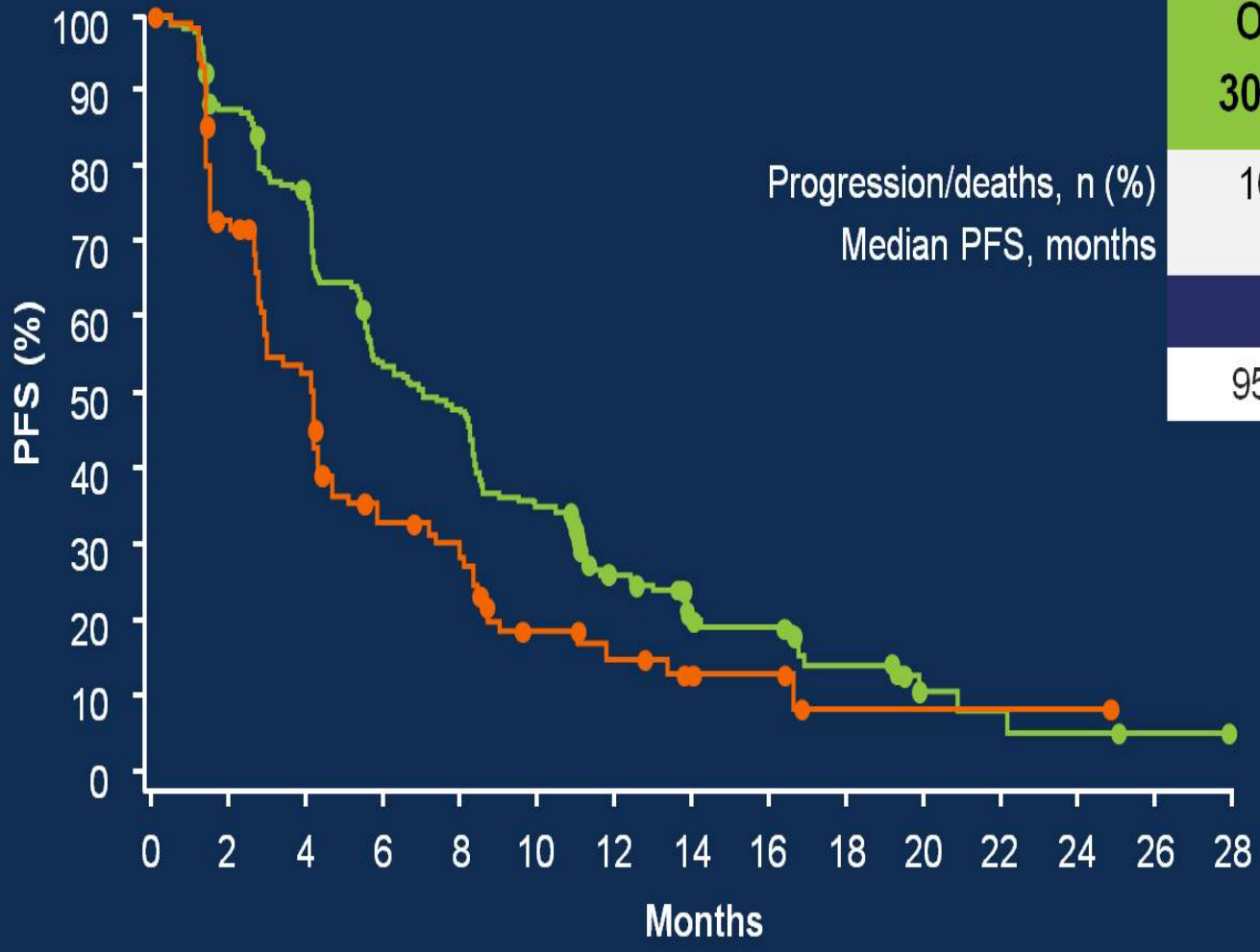
- Progression-free survival (RECIST 1.1, BICR)

Secondary endpoints:

- Time to second progression or death
- Overall survival
- Objective response rate
- Safety and tolerability
- Global HRQoL (EORTC-QLQ-C30)

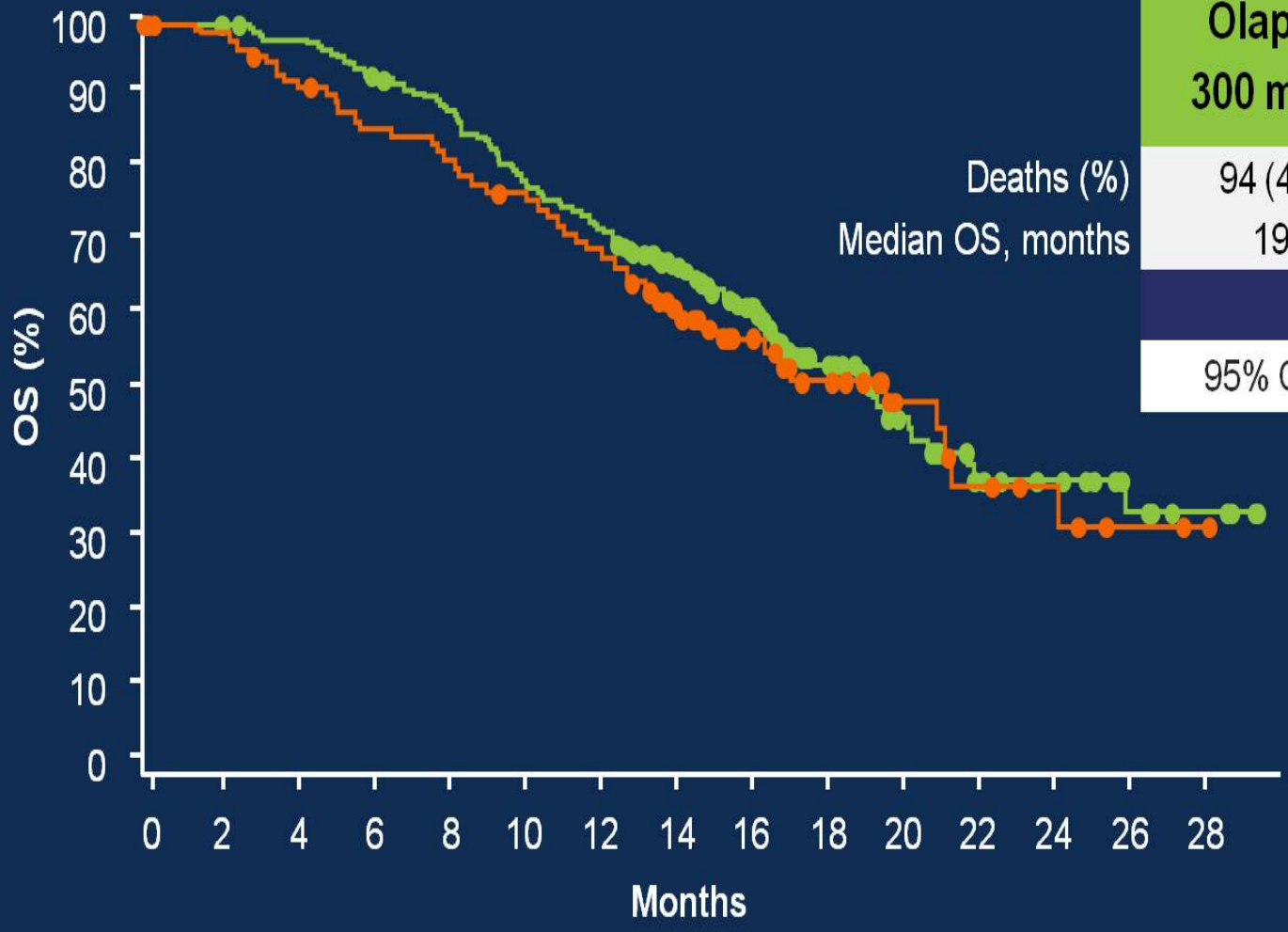
BICR, blinded independent central review; ER, estrogen receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple negative breast cancer

Primary endpoint: progression-free survival by BICR



	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58		
95% CI 0.43 to 0.80; *P*=0.0009		

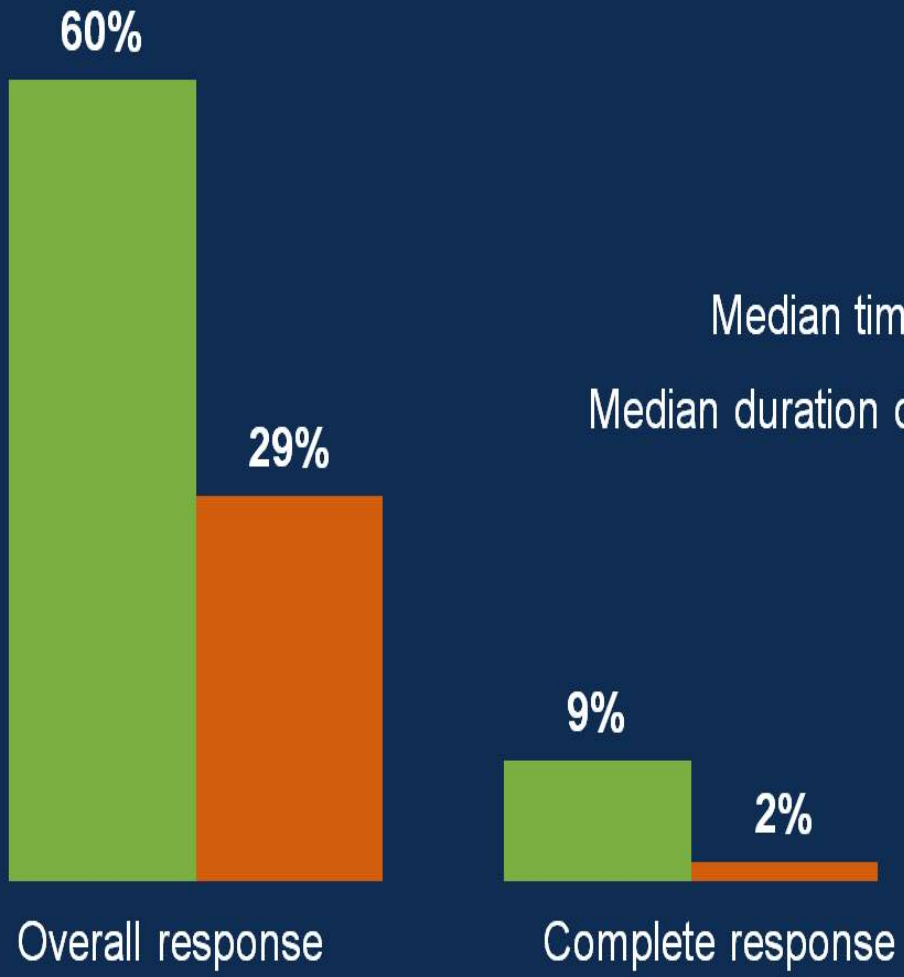
Overall survival (interim analysis; 46% data maturity)



	Olaparib 300 mg bd	Chemotherapy TPC
Deaths (%)	94 (45.9)	46 (47.4)
Median OS, months	19.3	19.6
HR 0.90		
95% CI 0.63 to 1.29; *P*=0.5665		

At risk, n																
Olaparib 300 mg bd	205	205	199	189	178	159	146	109	78	46	30	18	14	8	4	0
Chemotherapy TPC	97	92	85	78	74	69	62	50	34	24	13	9	7	4	2	0

Objective response by BICR



	Olaparib 300 mg bd	Chemotherapy TPC
n	167	66
Median time to response, days	47	45
Median duration of response, months	6.2 (4.6–7.2)	7.1 (2.8–12.2)

Study Design: EMBRACA

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation*†

Stratification factors:

- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

R 2:1

Talazoparib
1 mg PO daily

Treatment (21-day cycles) continues until progression or unacceptable toxicity

Physician's choice of therapy (PCT)‡: capecitabine, eribulin, gemcitabine, or vinorelbine

Phase 3, international, open-label study
randomized
431 patients in 16 countries and 145 sites

Primary endpoint

- **Progression-free survival by RECIST by blinded central review**

Key secondary efficacy endpoints

- **Overall survival (OS)**
- **ORR by investigator**
- **Safety**

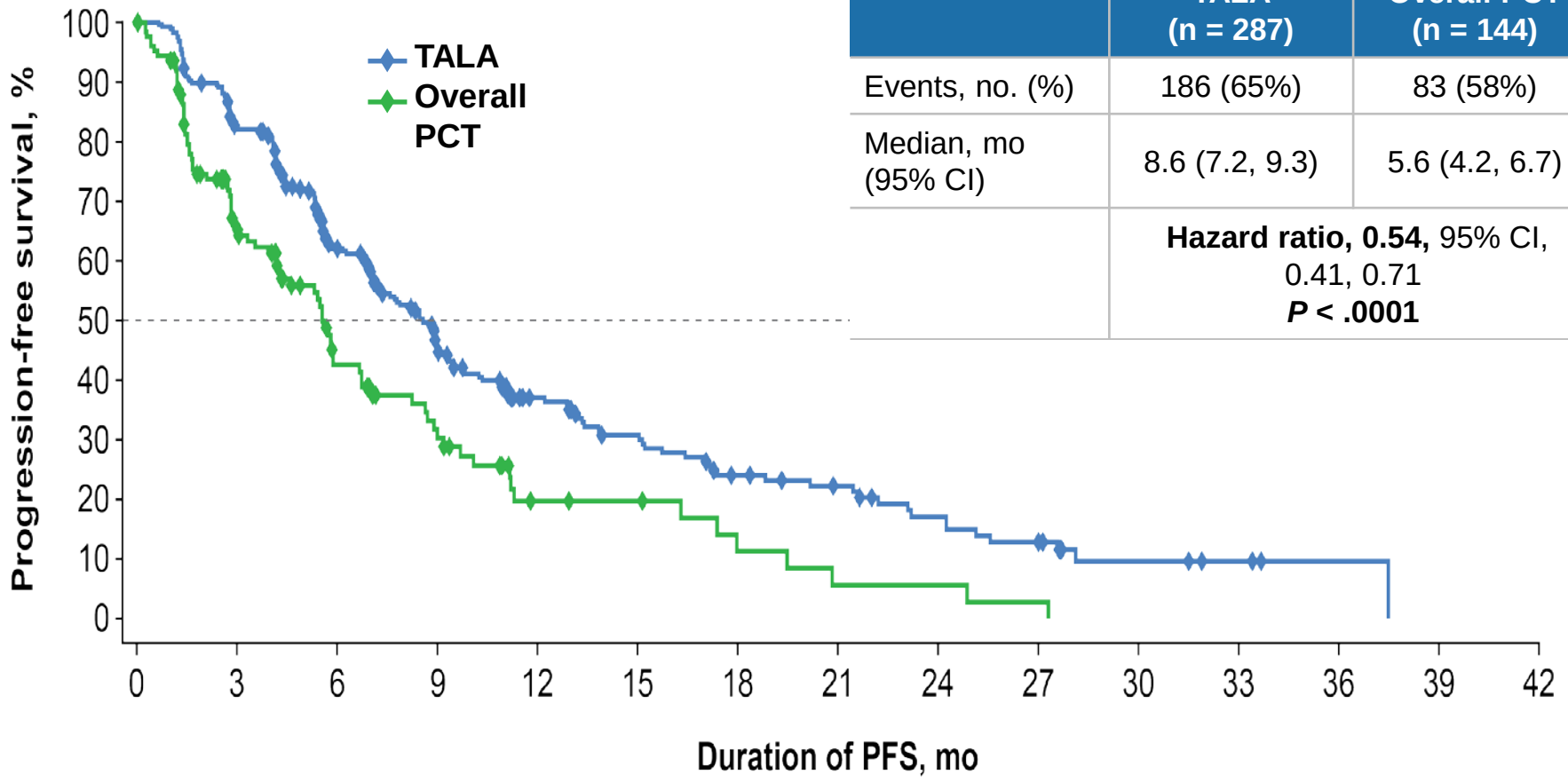
Exploratory endpoints

- **Duration of response (DOR) for objective responders**
- **Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)**

Abbreviations: CNS, central nervous system; EORTC, European Organisation for Research and Treatment of Cancer; HER2, human epidermal growth factor receptor 2; mets, metastases; PO, orally (per os);
QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire Core 30; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1;
TNBC, triple-negative breast cancer.
*Additional inclusion criteria included: no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or anthracycline unless medically contraindicated. †HER2-positive disease is excluded. ‡Physician's choice of therapy must be determined prior to randomization.
www.clinicaltrials.gov (NCT01945775)

Primary Endpoint: PFS by Blinded Central Review

	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	



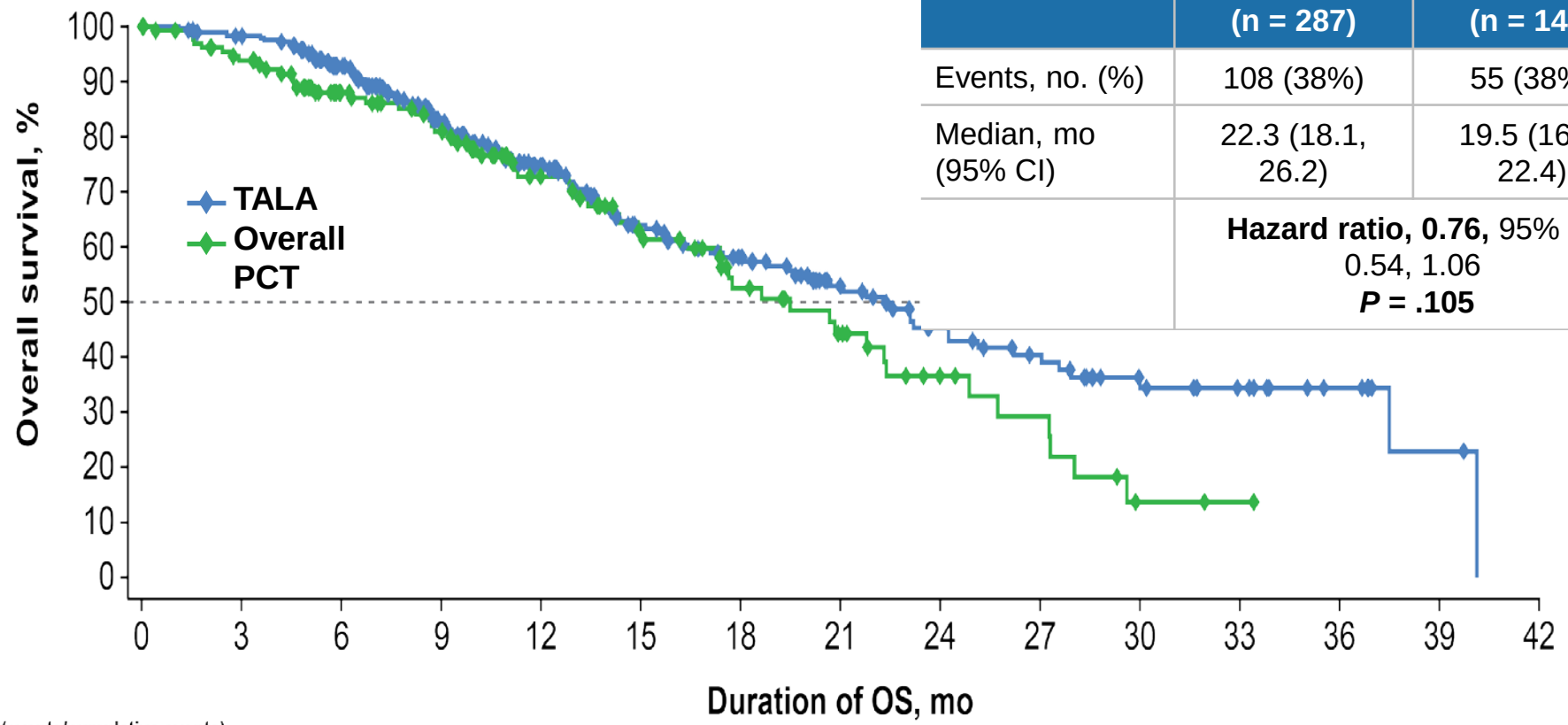
No. at risk (events/cumulative events)

TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

1-Year PFS 37% vs 20% Median follow-up time: 11.2 months

Interim OS Analysis: Secondary Endpoint

	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	108 (38%)	55 (38%)
Median, mo (95% CI)	22.3 (18.1, 26.2)	19.5 (16.3, 22.4)
	Hazard ratio, 0.76, 95% CI, 0.54, 1.06 ***P* = .105**	



No. at risk (events/cumulative events)

TALA	287 (0/0)	278 (5/5)	236 (15/20)	179 (24/44)	132 (16/60)	91 (17/77)	74 (8/85)	52 (6/91)	38 (7/98)	30 (4/102)	18 (4/106)	14 (0/106)	8 (0/106)	2 (1/107)	0 (1/108)
PCT	144 (0/0)	119 (8/8)	92 (7/15)	78 (7/22)	55 (7/29)	41 (7/36)	28 (6/42)	20 (4/46)	11 (3/49)	8 (2/51)	2 (4/55)	1 (0/55)	0 (0/55)	0 (0/55)	0 (0/55)

Survival Probability at:	TALA (n = 287)	Overall PCT (n = 144)
Month 24, % (95% CI)	45% (36.7-53.5)	37% (24.1-49.1)
Month 36, % (95% CI)	34% (25.3-43.7)	0%

Secondary/Exploratory Endpoints

	TALA	Overall PCT
Best overall response [measurable disease]*	**n = 219**	**n = 114**
Complete response, no. (%)	12 (5.5%)	0
Partial response, no. (%)	125 (57.1%)	31 (27.2%)
Stable disease, no. (%)	46 (21.0%)	36 (31.6%)
Non-evaluable, no. (%)	4 (1.8%)	19 (16.7%)
Objective response by investigator [measurable disease]*	**n = 219**	**n = 114**
ORR, % (95% CI)	62.6 (55.8-69.0)	27.2 (19.3-36.3)
Odds ratio (95% CI); 2-sided *P* value**	**4.99 (2.9-8.8); *P* < .0001**	
Clinical benefit rate at 24 weeks [ITT]	**n = 287**	**n = 144**
CBR24, % (95% CI)	68.6 (62.9-74.0)	36.1 (28.3-44.5)
Odds ratio (95% CI); 2-sided *P* value**	**4.28 (2.70-6.83); *P* < .0001**	
DOR by investigator [subgroup with objective response]	**n = 137**	**n = 31**
Median (IQR), mo	5.4 (2.8-11.2)	3.1 (2.4-6.7)

Abbreviation: IQR, interquartile range.
*Per RECIST version 1.1, confirmation of complete response or partial response was not required. **CMH=Cochran-Mantel-Haenszel.

Mesenchymal, Mesenchymal Stem Cell-like

M: Cell motility and differentiation, EMT processes

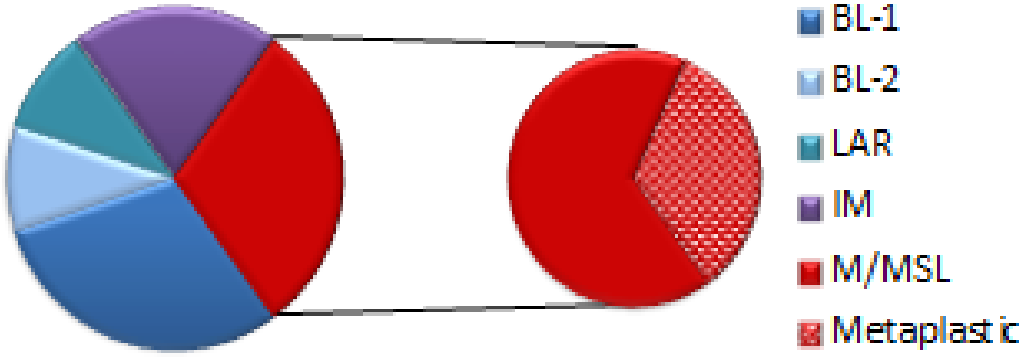
MSL: similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

- 20-30% of TNBCs
- cell motility
- EMT
- Angiogenesis
- p53 mutant
- PIK3CA mutations
- MSL- low expression of proliferation genes

Lehmann et al. J Clin Invest 2011

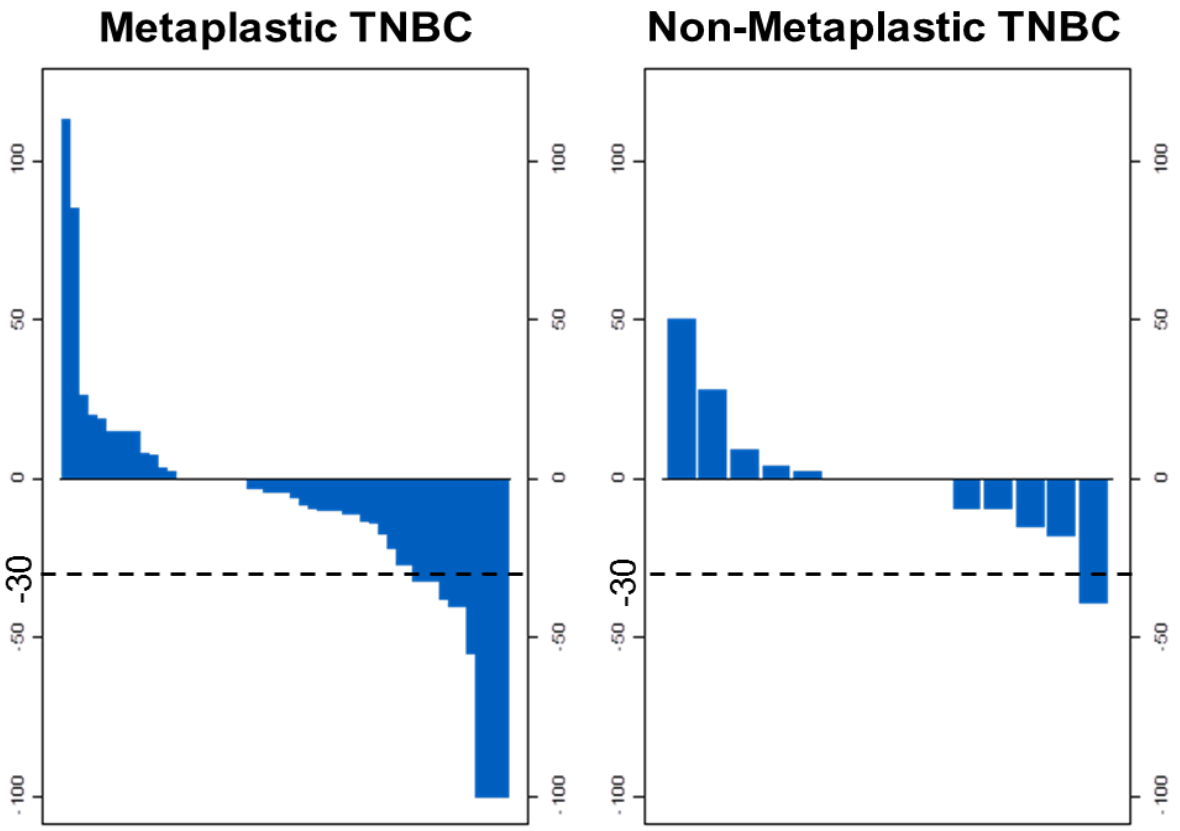
Metaplastic Breast Cancer

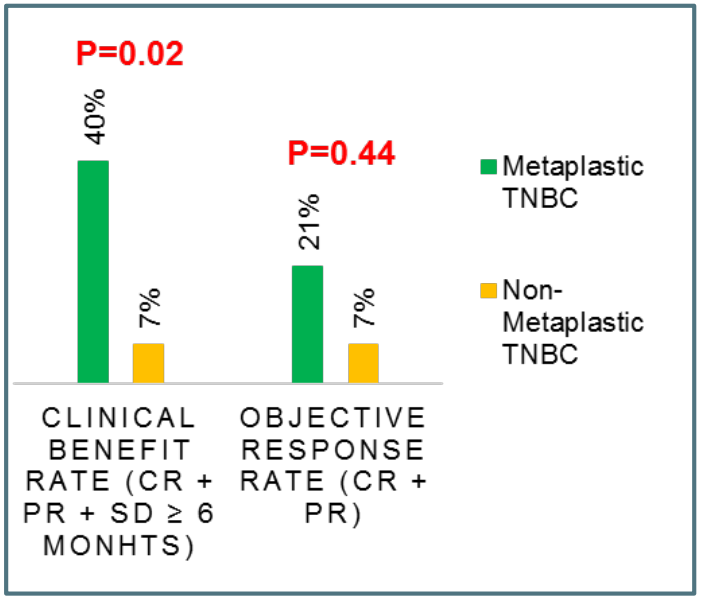
- Metaplastic breast cancers make up ~30% of TNBCs classified as mesenchymal
- Identified by light microscopy
  - Epithelial and non-epithelial components (mesenchymal)
- High incidence of PI3K pathway activating aberrations
- VEGF/HIF1-a production



Prat, *Breast Cancer Res;* 2010
Lehmann, *The Journal of Pathology;* 2014

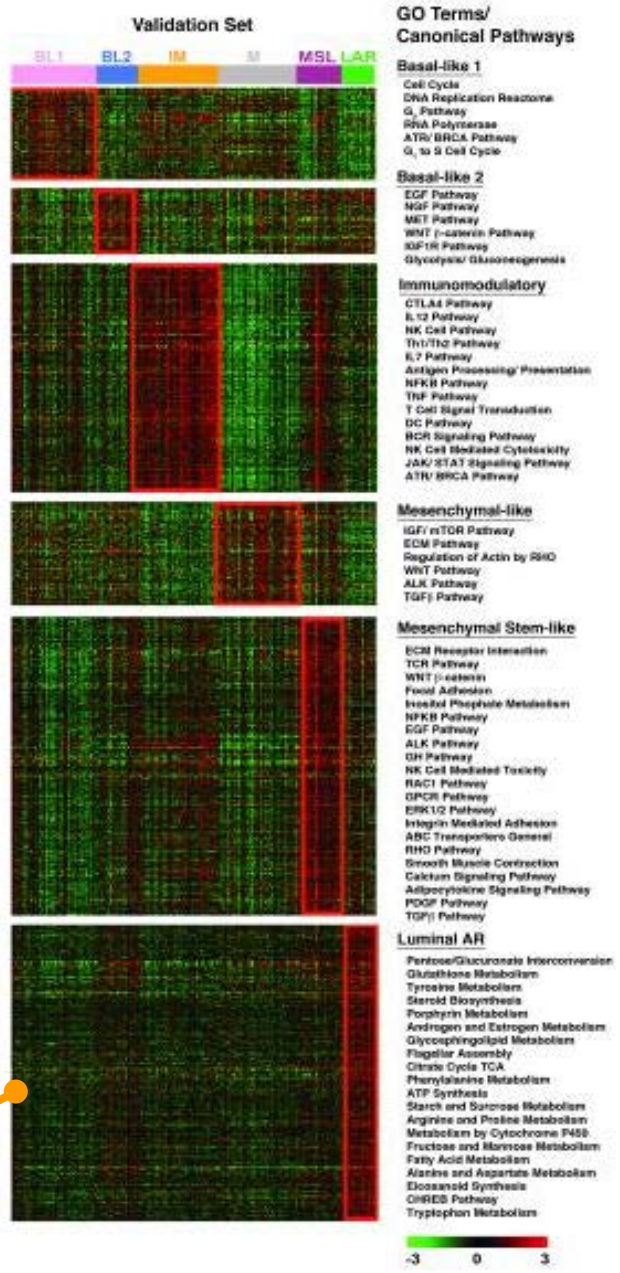
Better Response to M-Thor inhibitor and Bevacizumab in Metaplastic TNBC





Basho…Moulder, AACR 2016

LAR: Androgen Receptor+ TNBC



LAR: Androgen receptor and downstream genes, luminal features

- **10-20% of TNBCs**
- **heavily enriched in hormonally regulated pathways**
- **strong correlation with apocrine signatures**
- **high expression of luminal cytokeratins**
- **PIK3CA mutations**
- **improved RFS**

Lehmann et al. J Clin Invest 2011

Androgen Receptor inhibitors

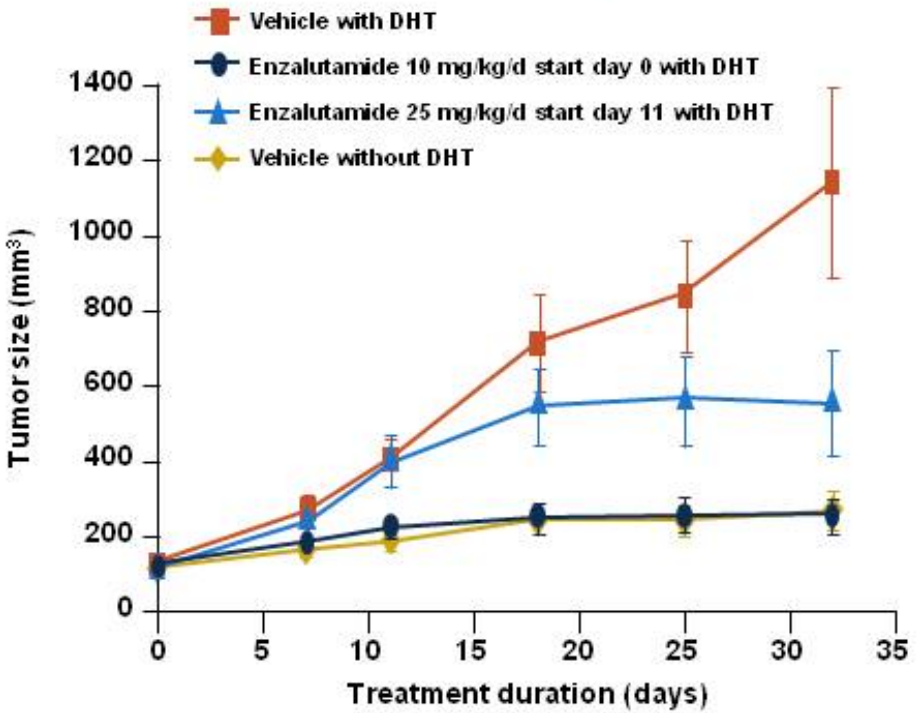
AR Signaling and Triple-Negative Breast Cancer

Advanced TNBC

- AR expression and signaling are present in TNBC[1-3]
- Phase 2 trial of bicalutamide in 26 patients with metastatic AR+ (IHC ≥ 10%) TNBC (TBCRC011):
  - Clinical benefit rate at 24 weeks 19% (95% CI: 7, 39)[4]
  - Median PFS 12 weeks (95% CI: 11, 23)[4]

Hypothesis: Enzalutamide will have activity in advanced AR+ (by IHC) TNBC

Preclinical Activity of Enzalutamide in an AR+ TNBC Cell Line (MDA-MB-453)



CI = confidence interval; DHT = dihydrotestosterone; IHC = immunohistochemistry; TNBC = triple-negative breast cancer.

1. Farmer P et al. *Oncogene*. 2005;24:4660-4671; 2. Doane AS et al. *Oncogene*. 2006;25:3994-4008; 3. Lehmann BD et al. *J Clin Invest*. 2011;121:2750-2767; 4. Gucalp A et al. *Clin Cancer Res*. 2013;19:5505-5512.

PRESENTED AT: ASCO Annual '15 Meeting

Study Schema (MDV3100-11)

Eligibility

- "AR positive" advanced TNBC*
- ECOG-PS ≤ 1
- Any number of prior therapies permissible
- Evaluable bone-only disease allowed
- No CNS metastases
- Sufficient tissue to enable biomarker discovery

Endpoints

Primary
- CBR16

Other Key Endpoints
- CBR24
- Response rate
- PFS
- OS
- Safety
- AR biomarker discovery

Treatment

Enzalutamide 160 mg/day orally

Stage 1
≥ 3 of 26 Evaluable have CBR16
"Go" to Stage 2

Stage 2
≥ 9 of 62 Evaluable have CBR16
Rejection of H_0

Statistical considerations
- 85% power to detect true CBR16 = 8% tested against 1-sided alternative (CBR16 ≥ 20%); alpha = 5%

*A separate consent allowed tissue submission for central AR IHC testing at anytime. "AR positive" was defined as IHC staining in >0% of tumor nuclei. Physicians and patients were blinded to actual % AR staining. CBR = clinical benefit rate; CBR16 = 16-week CBR; CBR24 = 24-week CBR; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; H_0 = null hypothesis; IHC = immunohistochemistry; ITT = intent-to-treat. www.clinicaltrials.gov, NCT01889238.

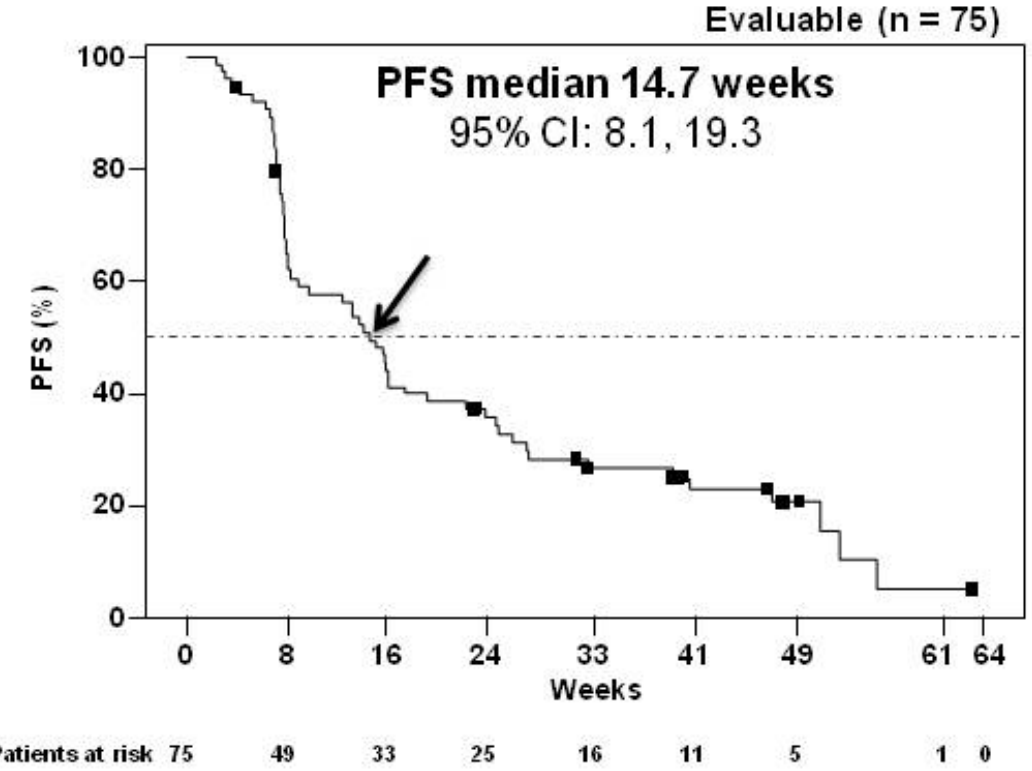
Clinical Benefit in Evaluable and ITT Populations

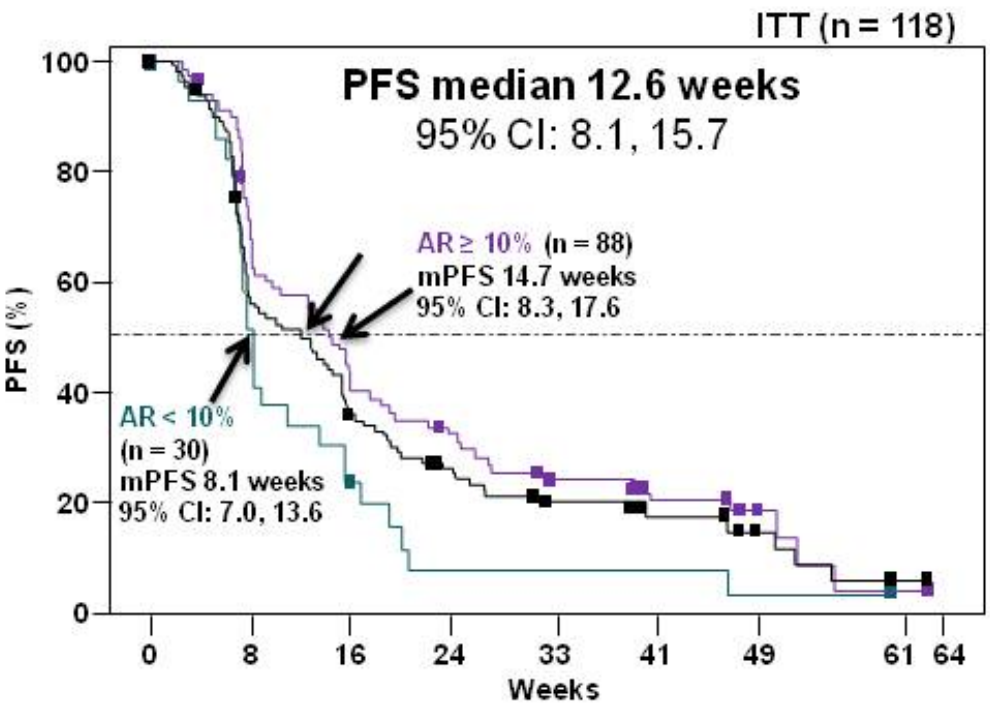
	Evaluable Patients (n = 75)	ITT Patients (n = 118)
Primary Endpoint		
CBR16, % (95% CI) n	**35%** (24, 46) n = 26	**25%** (17, 33) n = 29
Secondary Endpoints		
CBR24, % (95% CI) n	**29%** (20, 41) n = 22	**20%** (14, 29) n = 24
CR or PR, % n	**8%** n = 6	**6%** n = 7

Evaluable = AR IHC ≥ 10% and ≥ 1 post-baseline tumor assessment;
ITT = AR IHC > 0% by central assessment and received ≥ 1 dose of enzalutamide.

Data cutoff 24 March 2015.

PFS in Evaluable and ITT Populations



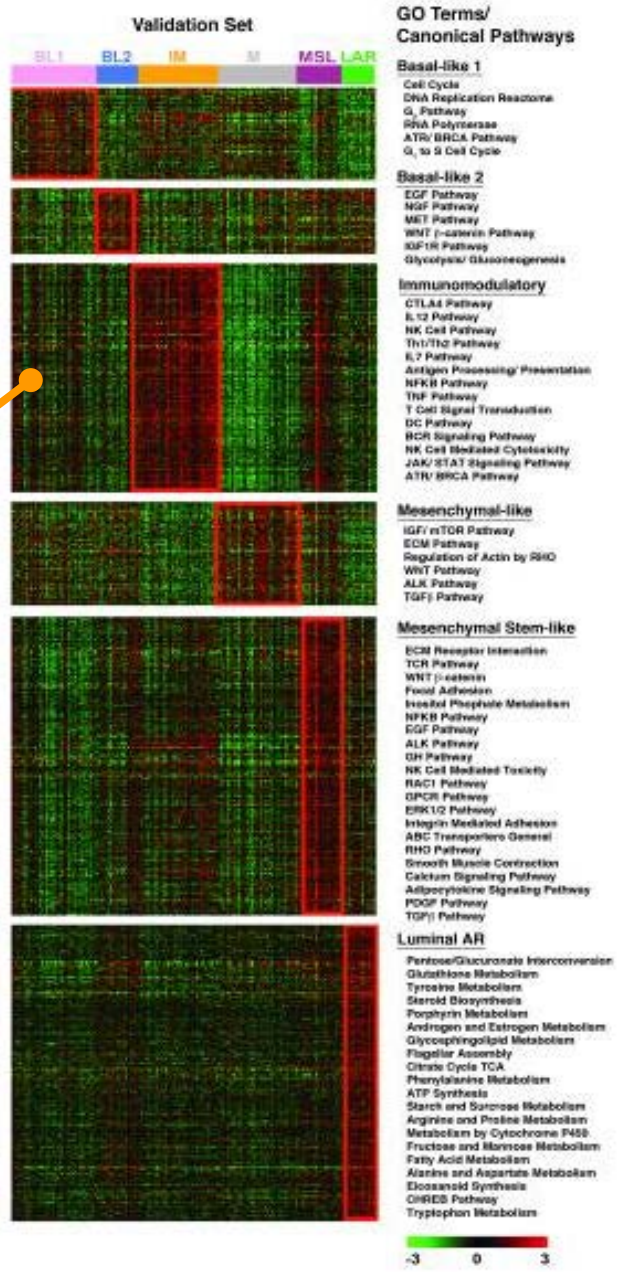


Evaluable = AR IHC ≥ 10% and ≥ 1 post-baseline tumor assessment;
ITT = AR IHC > 0% by central assessment and received ≥ 1 dose of enzalutamide.

Data cutoff 24 March 2015.

Immunomodulatory TNBC

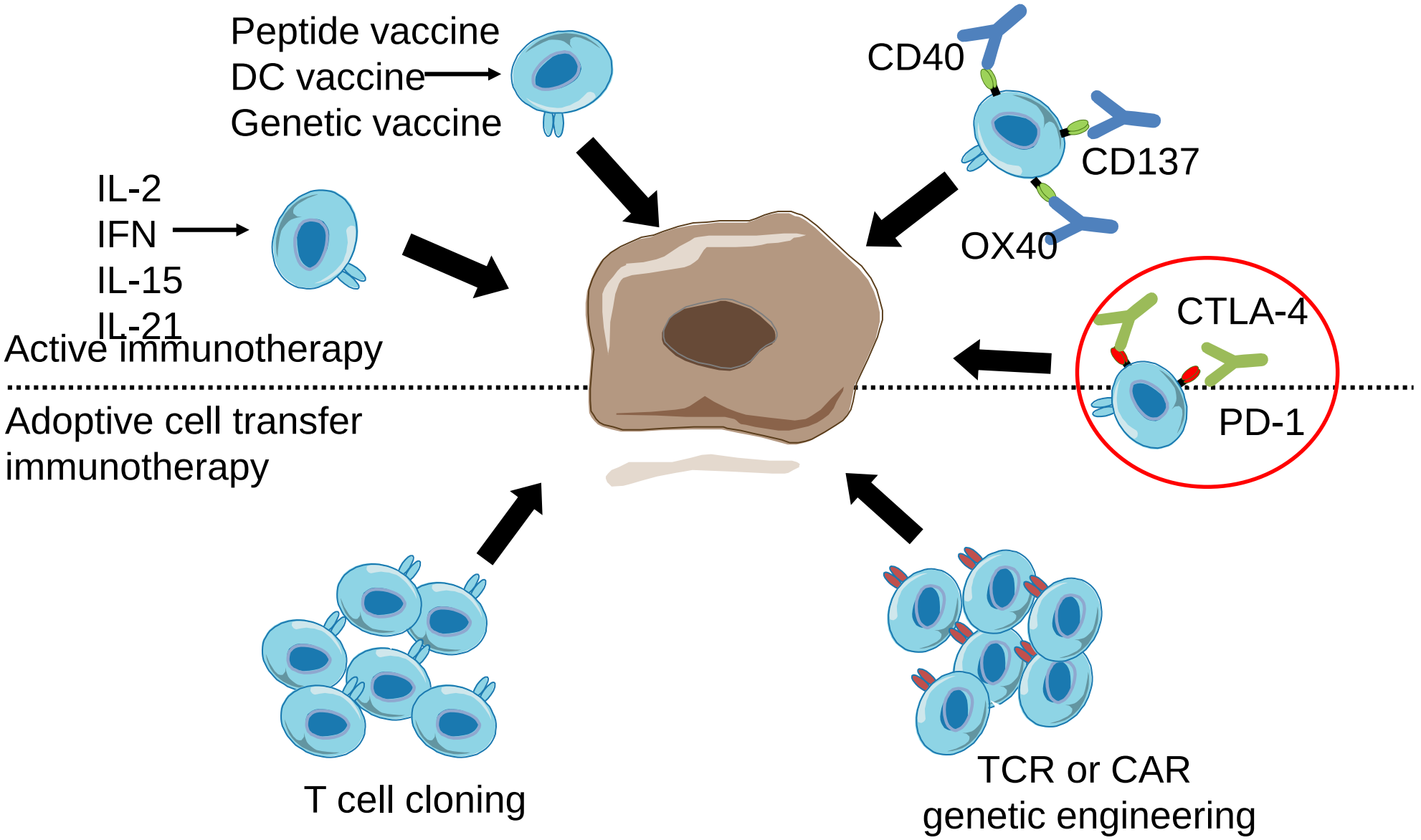
IM: immune cell processes (medullary breast cancer)



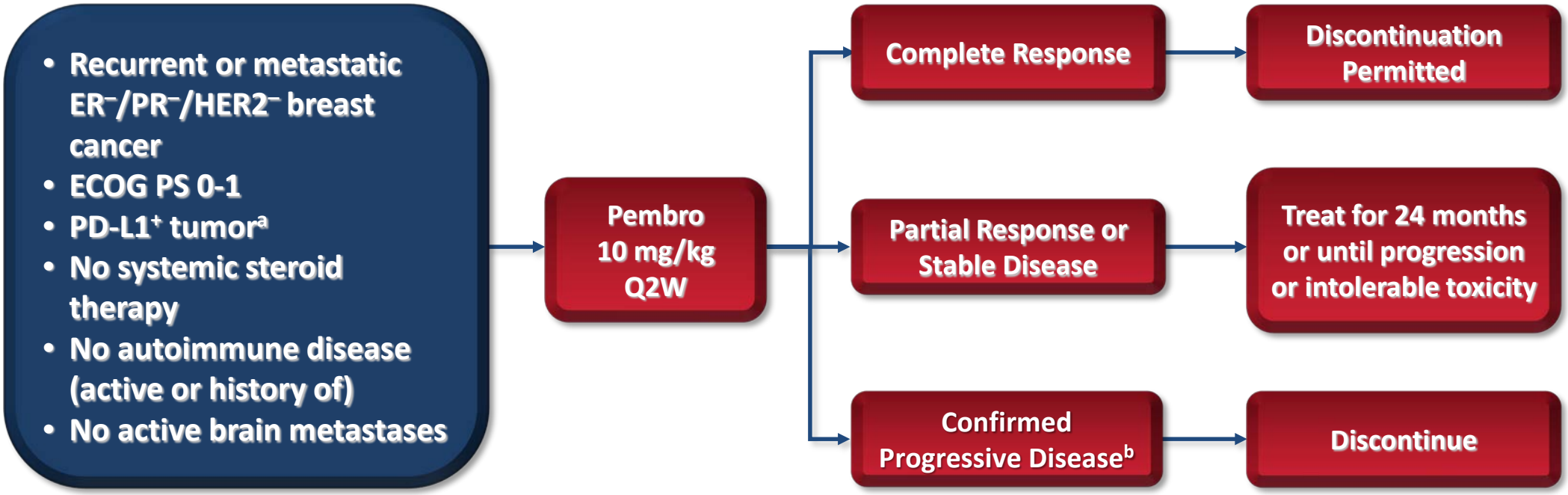
- 10-15% of TNBCs
- enriched in immune cell processes
- Medullary subtype
- -p53 mutant

Lehmann et al. J Clin Invest 2011

General Approaches for Cancer Immunotherapy



KEYNOTE-012:
Triple-Negative Breast Cancer Cohort



- **PD-L1 positivity:** 58% of all patients screened had PD-L1-positive tumors
- **Treatment:** 10 mg/kg IV Q2W
- **Response assessment:** Performed every 8 weeks per RECIST v1.1

Nanda R, et al. *JCO* 2016

Table 3. Best Overall Response Based on Response Evaluation Criteria in Solid Tumors v1.1 as Assessed by Central Review

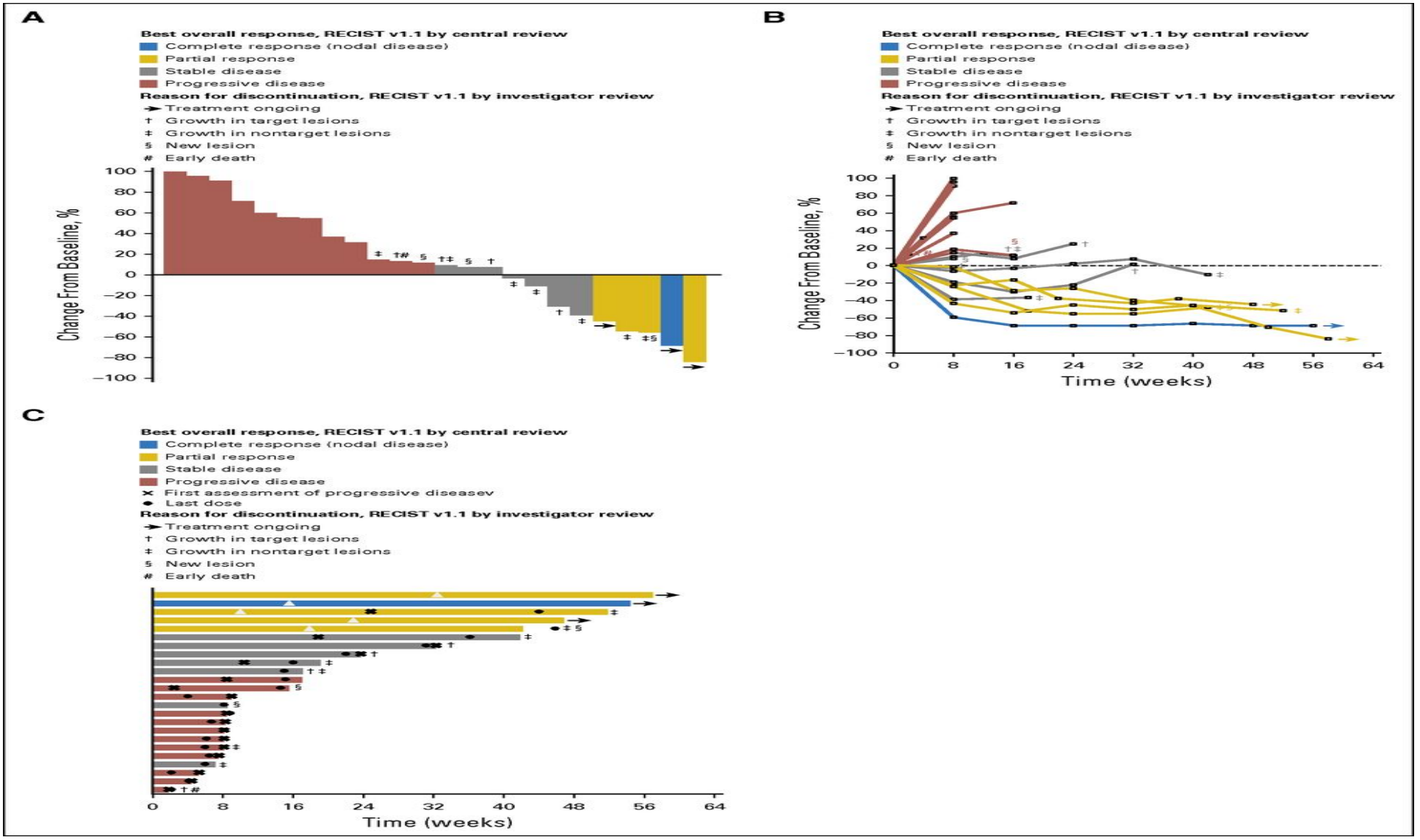
Response Type	Patients Evaluable for Response, N = 27*
Overall response rate, % (95% CI)	18.5 (6.3 to 38.1)
Best overall response, No. (%)	
Complete response†	1 (3.7)
Partial response†	4 (14.8)
Stable disease	7 (25.9)
Progressive disease	13 (48.1)
No assessment‡	2 (7.4)

*Includes patients with measurable disease at baseline, based on Response Evaluation Criteria in Solid Tumors v1.1 as assessed by central review, who received at least one pembrolizumab dose. Five patients were excluded because they did not have centrally confirmed measurable disease at baseline.

†Confirmed responses only.

‡Signifies patients who discontinued therapy before the first postbaseline scan because of progressive disease or a treatment-related adverse event.

Antitumor activity of pembrolizumab based on RECIST v1.1 assessed by central review.



Rita Nanda et al. JCO 2016;34:2460-2467

Study Design – KEYNOTE-086 Cohort A

Patients

- Age ≥18 y
- Centrally confirmed TNBC[a]
- ≥1 prior systemic treatment for mTNBC with documented PD
- ECOG PS 0-1
- LDH <2.5 x ULN
- Tumor biopsy sample for PD-L1 evaluation
- No radiographic evidence of CNS metastases
- Measurable disease per RECIST v1.1 by central review

N = 170

Pembrolizumab 200 mg IV Q3W

for 2 years or until PD, intolerable toxicity, patient withdrawal, or investigator decision

Protocol-specified follow-up

- Primary end points: ORR[b] and safety
- Secondary end points[b]: DOR, DCR,[c] PFS, OS

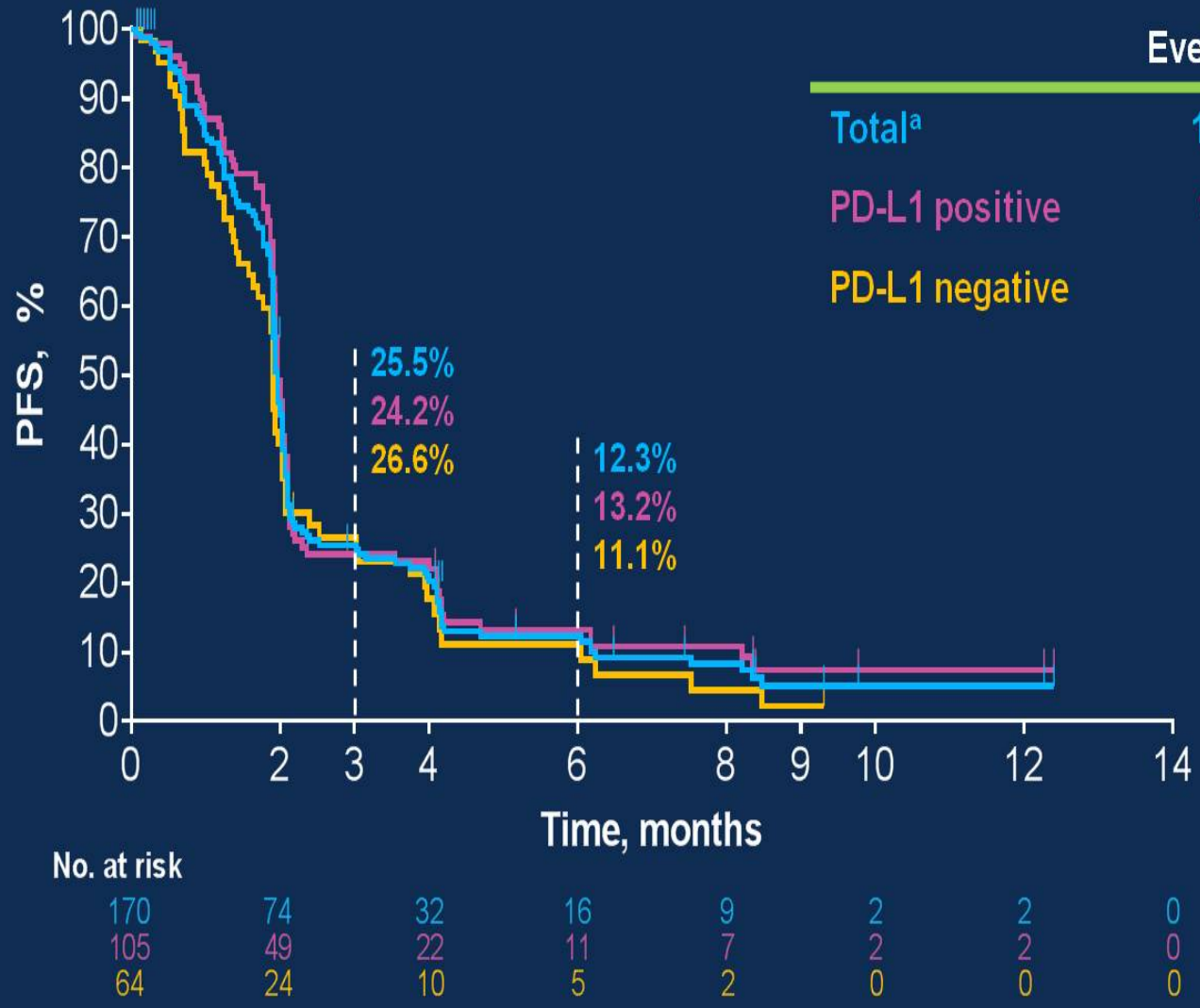
[a]<1% tumor cells positive for ER and PR by IHC, irrespective of intensity, and HER2 IHC 0 or 1+ or FISH negative. [b]Assessed in the total population and in the PD-L1–positive population. [c]DCR = disease control rate = SD ≥24 wk + CR + PR.

Best Overall Response
(RECIST v1.1, Central Review)

	Total Population[a] N = 170	PD-L1 Positive n = 105	PD-L1 Negative n = 64
ORR, n (%) [95% CI]	8 (4.7) [2.3-9.2]	5 (4.8) [1.8-10.9]	3 (4.7) [1.1-13.4]
DCR,[b] n (%) [95% CI]	13 (7.6) [4.4-12.7]	10 (9.5) [5.1-16.8]	3 (4.7) [1.1-13.4]
Best Overall Response, n (%)			
Complete response	1 (0.6)	1 (1.0)	0
Partial response	7 (4.1)	4 (3.8)	3 (4.7)
Stable disease	35 (20.6)	22 (21.0)	12 (18.8)
Progressive disease	103 (60.6)	66 (62.9)	37 (57.8)
Not evaluable[c]	5 (2.9)	2 (1.9)	3 (4.7)
Not able to be assessed[d]	19 (11.2)	10 (9.5)	9 (14.1)

[a]Includes the patient with unknown PD-L1 status. [b]DCR = disease control rate = SD ≥24 wk + CR + PR. [c]Patients who had ≥1 postbaseline tumor assessment, none of which were evaluable. [d]Patients who had no postbaseline tumor assessment because of death, withdrawal of consent, loss to follow-up, or start of new anticancer therapy. Data cutoff date: Nov 10, 2016.

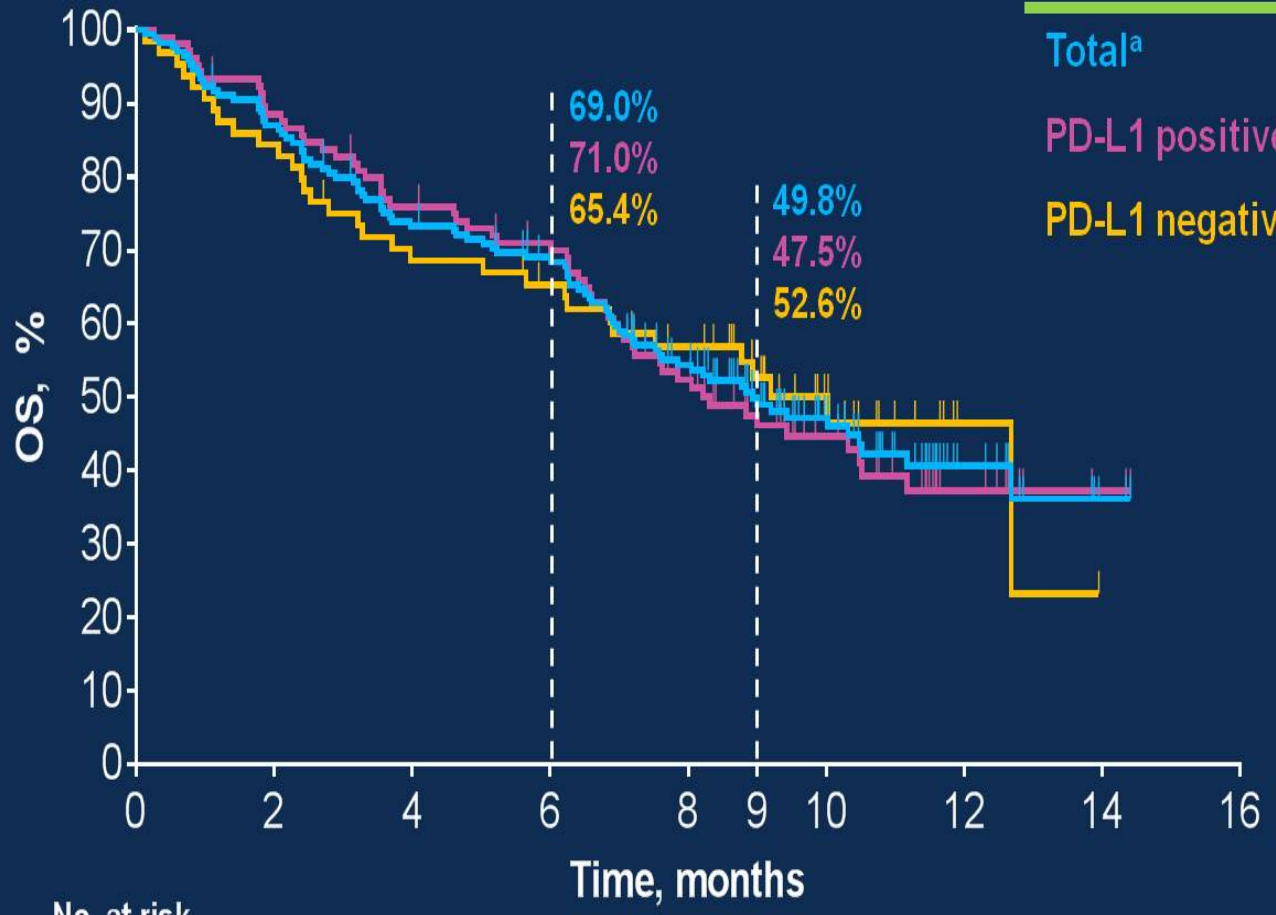
Kaplan-Meier Estimate of PFS
(RECIST v1.1, Central Review)



	Events/Pts, n	Median (95% CI)
Total[a]	148/170	2.0 mo (1.9-2.0)
PD-L1 positive	90/105	2.0 mo (1.9-2.1)
PD-L1 negative	57/64	1.9 mo (1.6-2.0)

[a]Includes 1 patient with unknown PD-L1 status who experienced PD.
Data cutoff date: Nov 10, 2016.

Kaplan-Meier Estimate of OS



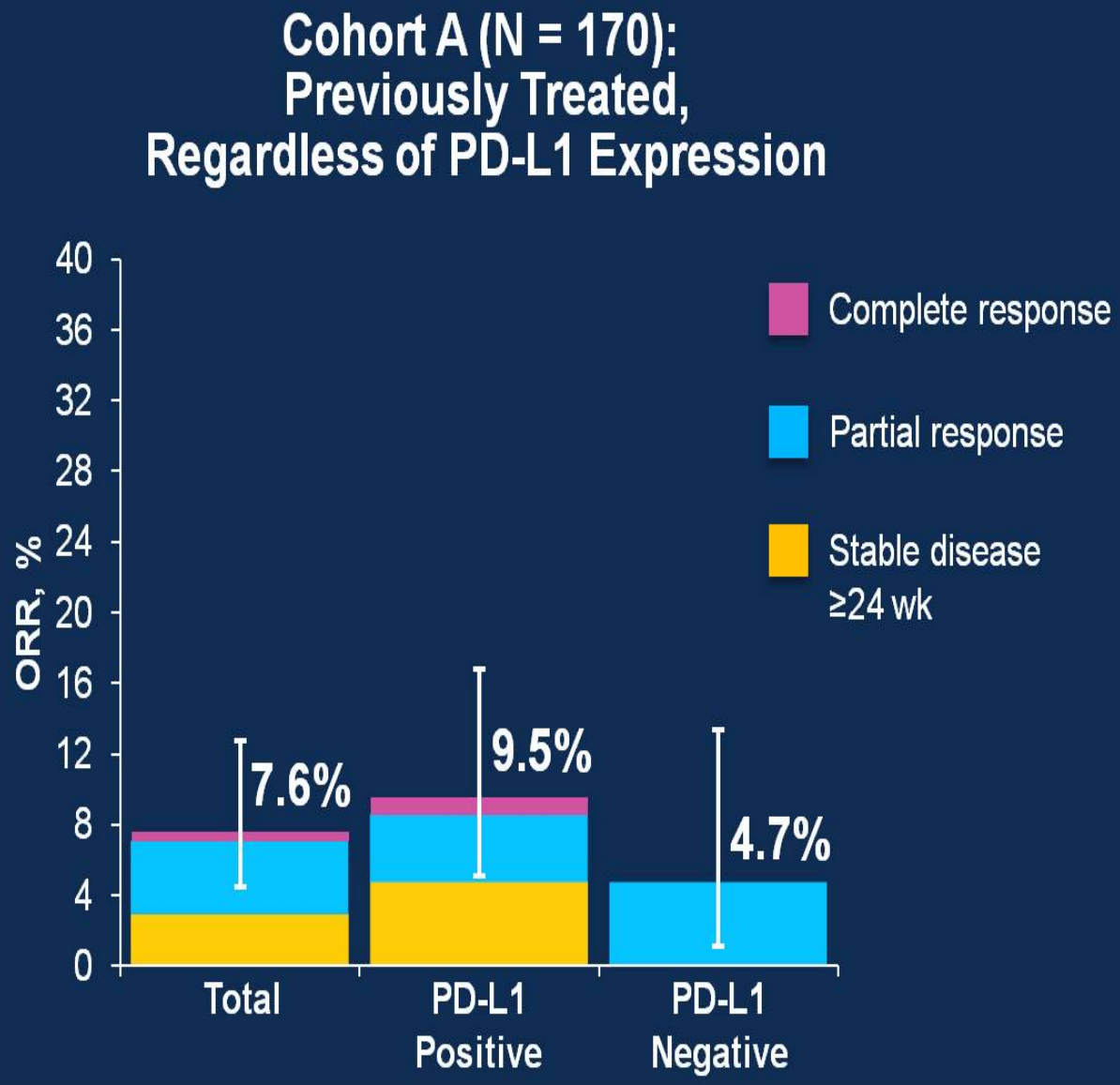
No. at risk

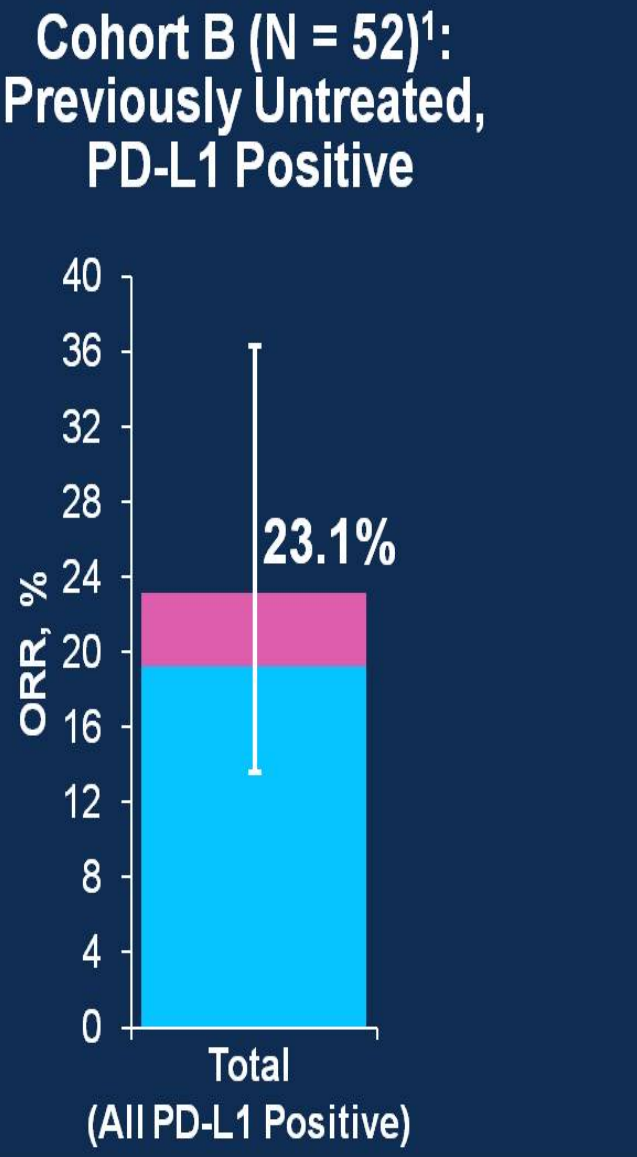
170	147	122	110	79	41	13	2	0
105	92	78	70	46	26	10	2	0
64	54	43	39	32	14	2	0	0

	Events/Pts, n	Median (95% CI)
Total[a]	90/170	8.9 mo (7.2-11.2)
PD-L1 positive	58/105	8.3 mo (6.9-10.5)
PD-L1 negative	32/64	10.0 mo (6.2-NR)

NR, not reportable.
[a]Includes 1 patient with unknown PD-L1 status who was alive at data cutoff.
Data cutoff date: Nov 10, 2016.

Pembrolizumab Antitumor Activity in Previously Treated and Previously Untreated mTNBC





1. Adams S et al. ASCO Annual Meeting; Jun 2-6, 2017; Chicago, IL; abstr 1088; presented Sunday, Jun 4, from 8:00-11:30 am on poster board #80.

Exposure and AE Summary

	N = 170
Exposure, median (range)	
Time on therapy	56.5 d (1-378)
No. of doses	3 (1-19)
Treatment related, n (%)	
Any Grade	102 (60.0)
Grade 3-4	21 (12.4)
Led to death	0
Led to discontinuation	7 (4.1)
Immune mediated[a]	
Any Grade	32 (18.8)
Grade 3-4	2 (1.2)
Led to death	0
Led to discontinuation	2 (1.2)

Most Common AEs

	Any Grade N = 170	Grade 3-4 N = 170
Treatment related, incidence ≥5%, n (%)		
Fatigue	35 (20.6)	1 (0.6)
Nausea	18 (10.6)	1 (0.6)
Decreased appetite	13 (7.6)	0
Hypothyroidism	13 (7.6)	0
Diarrhea	12 (7.1)	3 (1.8)
Asthenia	11 (6.5)	0
Arthralgia	10 (5.9)	0
Pruritus	10 (5.9)	0
Immune mediated,[a] incidence ≥3 patients, n (%)		
Hypothyroidism	19 (11.2)	0
Hyperthyroidism	8 (4.7)	0
Pneumonitis	6 (3.5)	1 (0.6)

[a]Based on a list of terms specified by the sponsor and included regardless of attribution to study treatment or immune relatedness by the investigator; related terms included.
Data cutoff date: Nov 10, 2016.

Conclusions

- TNBC is a very heterogeneous disease
- Chemotherapy including platinum salts is modestly effective in metastatic BRCA normal TNBC. TTP and overall survival are short
- New agents including PARP, AKT, PDL-1, PD-1 and androgen receptor inhibitors are promising.
- Molecular driven trial are needed to rapidly evaluate novel therapeutics in metastatic TNBC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