2019
AIOM REVIEW:
FROM CHICAGO
TO VERONA

JUNE 14-15 2019

Verona,
Palazzo della Gran Guardia
Piazza Bra, 1

Aiom
Associazione Italiana di Oncologia Medica

BREAST CANCER
Highlights

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Outline

- Early breast cancer
  - HR+/HER2-
    - CT yes or no?
    - Extended adjuvant HT
  - HER2+
    - new hints for escalation and de-escalation
- Advanced breast cancer
  - HR+/HER2-
    - CDK4/6 inhibitors
    - Capivasertib
  - Immunotherapy
    - IMPASSION130
  - HER2+
- Survivorship

Recurrence Score: summary of TAILORx results

All patients

0-11	11-25	≥26
Good prognosis with ET: 94.0% iDFS 5 yrs	ET: 92.8% iDFS 5 yrs CT: 93.1% iDFS 5yrs	Assigned to CT + ET

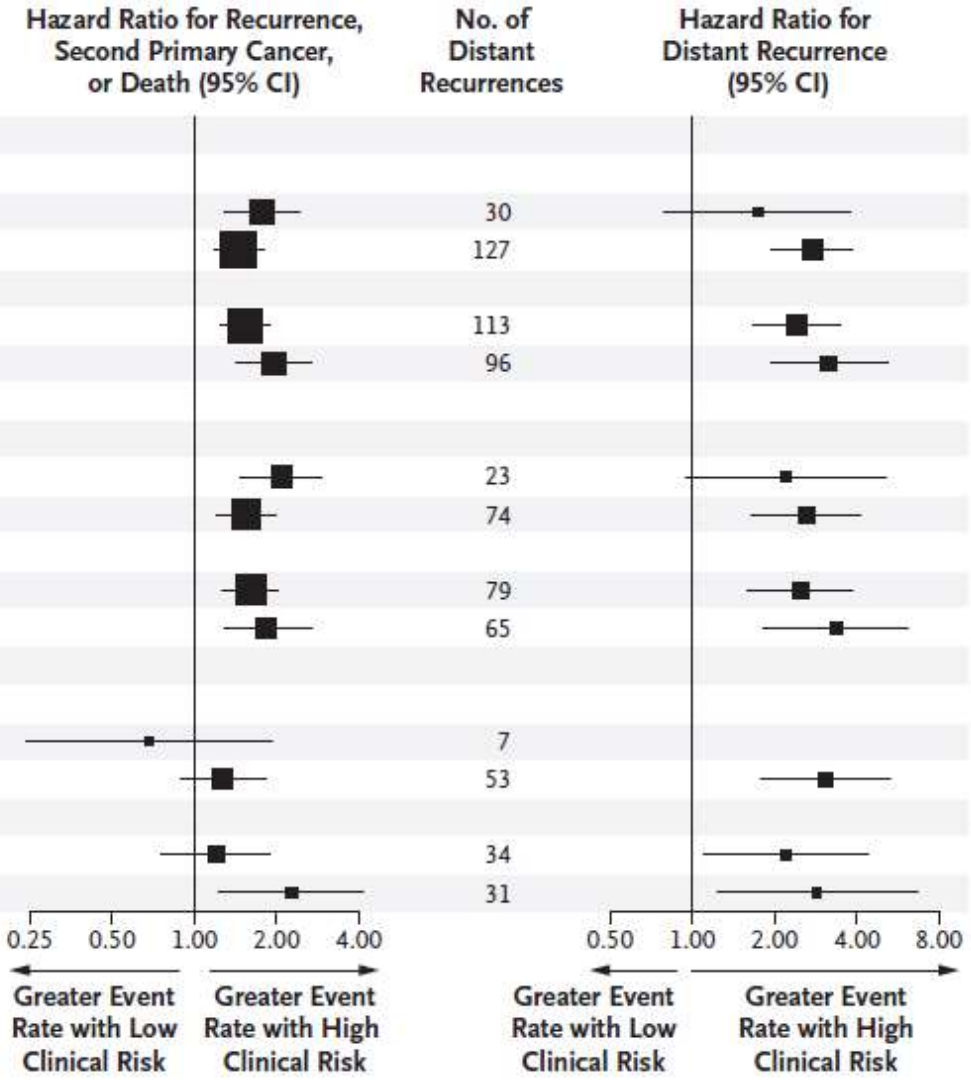
Young patients (≤50 yrs), n=2216

0-11	11-15	16-20	21-25	≥26
Good prognosis with ET: 95.1% iDFS 5 yrs	ET: 95.1% iDFS 5 yrs CT: 94.3% iDFS 5yrs	ET: 92.0% iDFS 5 yrs CT: 94.7% iDFS 5yrs 9% fewer iDFS events with CT (2% distant)	ET: 93.2% iDFS 5 yrs CT: 96.4% iDFS 5yrs 6% fewer iDFS events with CT (mainly distant)	Assigned to CT+ET

Sparano JA et al. *N Engl J Med* 2018

Effect of clinical risk on prognosis

Subgroup	No. of Patients	No. of Events	No. of Distant Recurrences
All patients	9427		
Endocrine therapy			
Low recurrence score (0–10)	1572	176	30
Intermediate recurrence score (11–25)	3282	422	127
Chemoendocrine therapy			
Intermediate recurrence score (11–25)	3214	389	113
High recurrence score (26–100)	1359	184	96
>50 Yr of age	6469		
Endocrine therapy			
Low recurrence score (0–10)	1160	135	23
Intermediate recurrence score (11–25)	2182	273	74
Chemoendocrine therapy			
Intermediate recurrence score (11–25)	2171	292	79
High recurrence score (26–100)	956	133	65
≤50 Yr of age	2958		
Endocrine therapy			
Low recurrence score (0–10)	412	41	7
Intermediate recurrence score (11–25)	1100	149	53
Chemoendocrine therapy			
Intermediate recurrence score (11–25)	1043	97	34
High recurrence score (26–100)	403	51	31



- **Low risk**
  - Tumor ≤ 1 cm & high grade
  - Tumor ≤ 2 cm & int. grade
  - Tumor ≤ 3 cm & low grade
- **High risk** – not meeting low risk criteria

Multivariate model for distant recurrence in RS 11-25 group:
(N=6496 cases and 240 distant recurrences):
- Clinical risk: HR for high vs. low risk 2.42, p<0.001
- Continuous RS: HR 1.08, p<0.001 (HR for a 1 point higher RS)

Sparano J, NEJM 2019

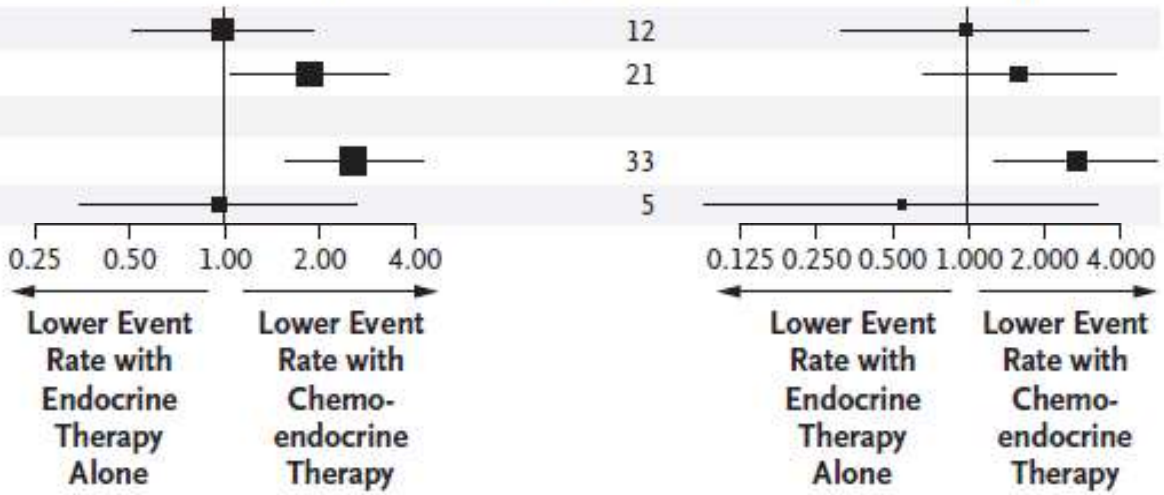
Effect of clinical risk on prediction of CT benefit: ≤50y, RS 16-25

	Estimated Absolute Chemo Benefit Not Stratified by Clinical Risk	Clinical Risk	No.	Estimated Absolute Chemo Benefit Stratified by Clinical Risk
RS 16-20 (N=886)	Δ +1.6% (±SE 1.9%)	Low	671 (76%)	Δ -0.2% (±SE 2.1%)
		High	215 (24%)	Δ +6.5% (±SE 4.9%)
RS 21-25 (N=476)	Δ +6.5% (±SE 3.7%)	Low	319 (67%)	Δ +6.4% (±SE 4.9%)
		High	157 (33%)	Δ +8.7% (±SE 6.2%)

Sparano J, ASCO 2019 & NEJM 2019

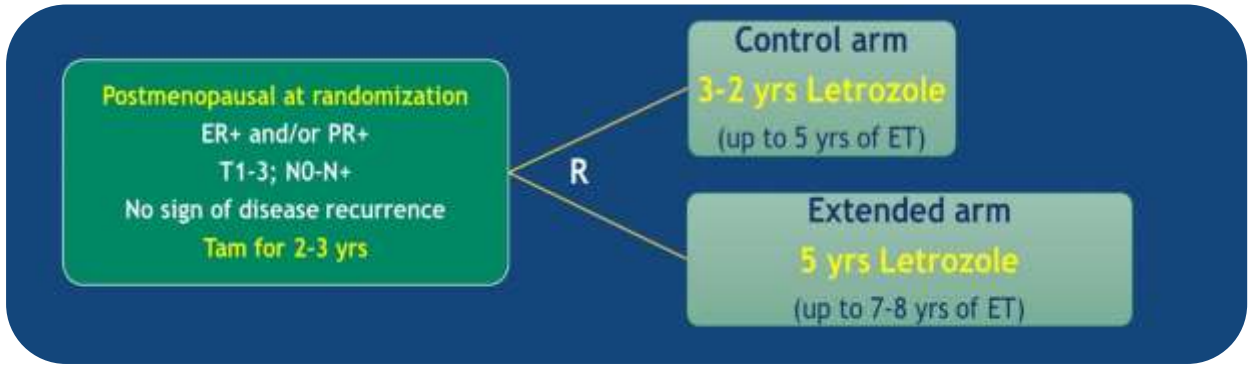
Effect of age and menopausal status on CT benefit (RS 16-25)

Subgroup	No. of Patients	No. of Events	No. of Distant Recurrences
≤40 Yr of age	203	35	12
41–45 Yr of age	441	51	21
46–50 Yr of age			
Before menopause	630	69	33
After menopause	141	15	5



Sparano J, ASCO 2019 & NEJM 2019

GIM4



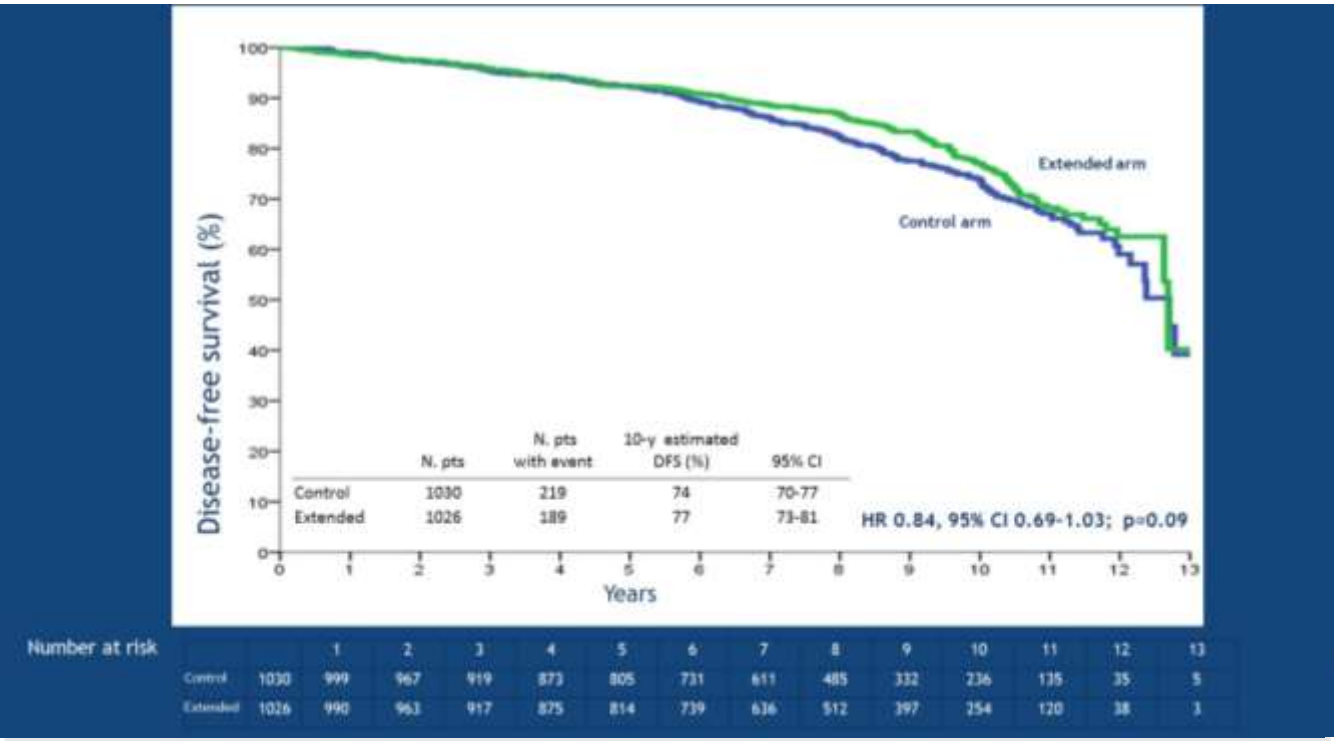
N=2056 in 64 Italian centers
Accrual time: 2005-2010
Median follow-up time: 10.4 years

		Control arm 2-3 year letrozole (n=1030)	Extended arm 5-year letrozole (n=1026)
Age, median (range)		60 (34-86)	61 (41-89)
Tumor size	pT1	704 (68%)	703 (68%)
	pT2	261 (25%)	252 (25%)
	pT3-4	34 (3%)	43 (4%)
	Unknown	31 (3%)	28 (3%)
Nodal status	pN0	581 (56%)	568 (55%)
	pN1-2-3	411 (40%)	428 (42%)
	Unknown	38 (4%)	30 (3%)
Histological grade	G1	156 (15%)	161 (16%)
	G2	564 (55%)	589 (57%)
	G3	221 (21%)	213 (21%)
	Unknown	89 (9%)	63 (6%)
HR status	ER+ and PR+	855 (83%)	866 (84%)
	ER+ or PR+	153 (15%)	146 (14%)
	Uknown	22 (2%)	14 (1%)
HER2 status	Positive	63 (6%)	60 (6%)
	Negative	851 (83%)	833 (81%)
	Unknown	116 (11%)	133 (13%)
Prior (neo)adjuvant CT	No	455 (44%)	450 (44%)
	Yes	557 (54%)	565 (55%)
	nknown	18 (2%)	11 (1%)
Prior duration of tamoxifen, years Median (IQR)		2.4 (1.9-3.3)	2.5 (1.9-3.3)

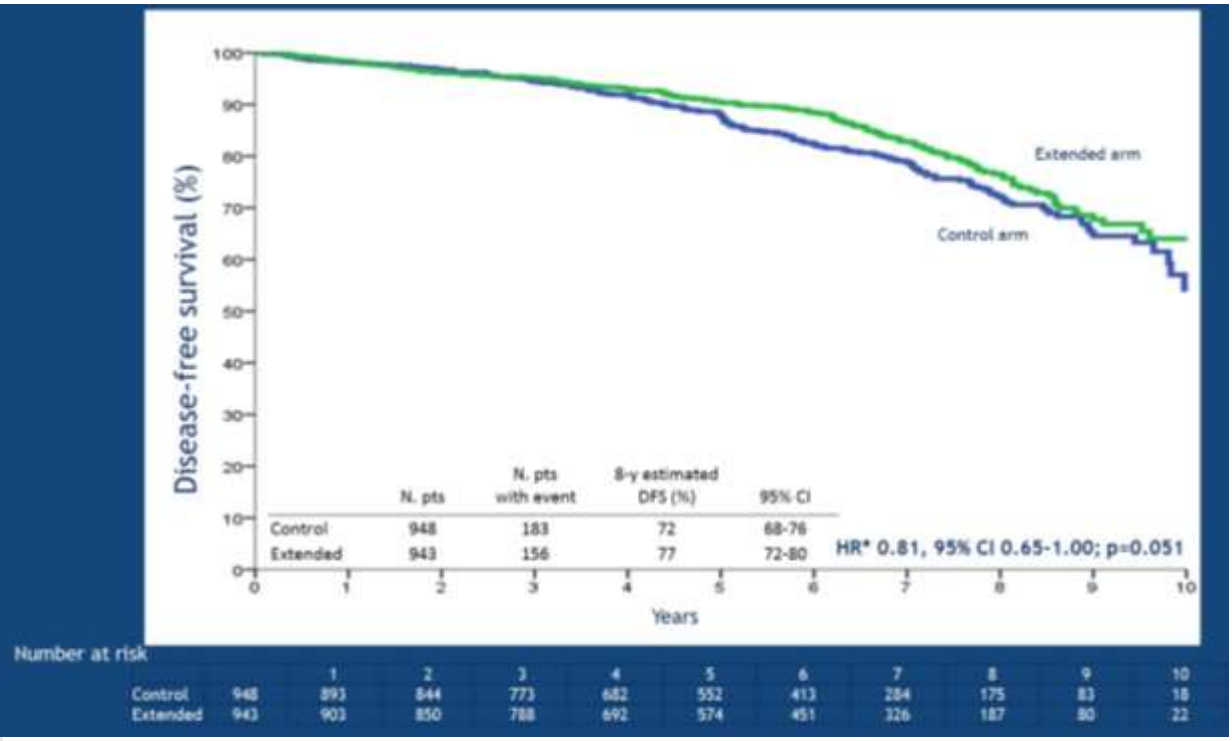
Del Mastro L, ASCO 2019

GIM4 – iDFS

ITT (n=2056)



Landmark (n=1891)



OS ITT: HR 0.82 (0.62-1.07)

OS Landmark: HR 0.86 (0.63-1.18)

Del Mastro L, ASCO 2019

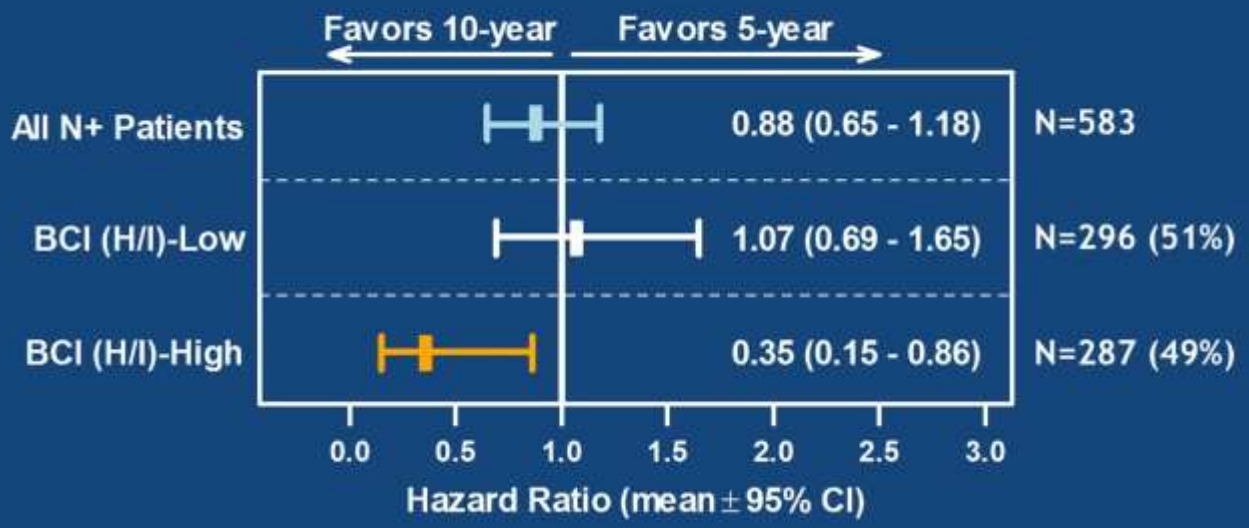
Studies of extended adjuvant AI

Trial	Initial treatment	Extended treatment	N	Median follow-up	HR (95% CI)	*p*
NSABP-B42 Mamounas 2006	AI(5y)/TAM+AI(5y)	Placebo vs AI(5y)	3996	6.9 y	0.85	0.48*
DATA Tjan-Heijnen 2017	Tam(2-3y)	AI (3y) vs AI(6y)	1912	4.2 y	0.79 (0.62-1.02)	0.07
IDEAL Block 2017	AI(5y)/TAM(5y)/TAM(2.5y) + AI(2.5y)	AI(2.5y) vs AI(5y)	1824	6.6 y	0.92 (0.74-1.16)	0.49
ABCSG-16 Gnant SABCS2017	OT(4-6y)	AI(2y) vs AI(5y)	3484	8.8 y	1.007 (0.87-1.16)	0.0925
GIM4 Del Mastro ASCO 2019	Tam(2-3y)	AI(3-2y) vs AI(6y)	2056	10.4 y	0.84 (0.69-1.03)	0.09

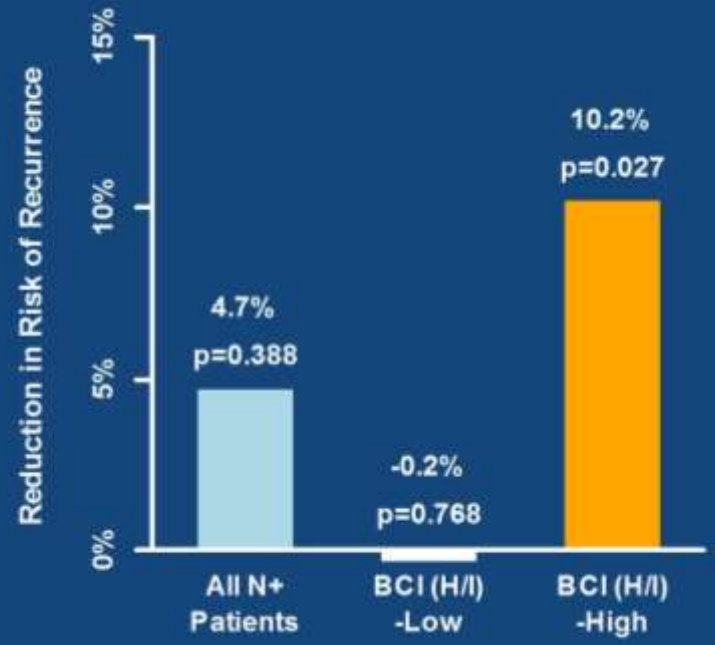
Trans-aTTom – primary endpoint

Relative benefit of extended tamoxifen by BCI status

Initial results for pts with node positive BC



Absolute benefit of extended tamoxifen by BCI status



Bartlett J, ASCO 2019

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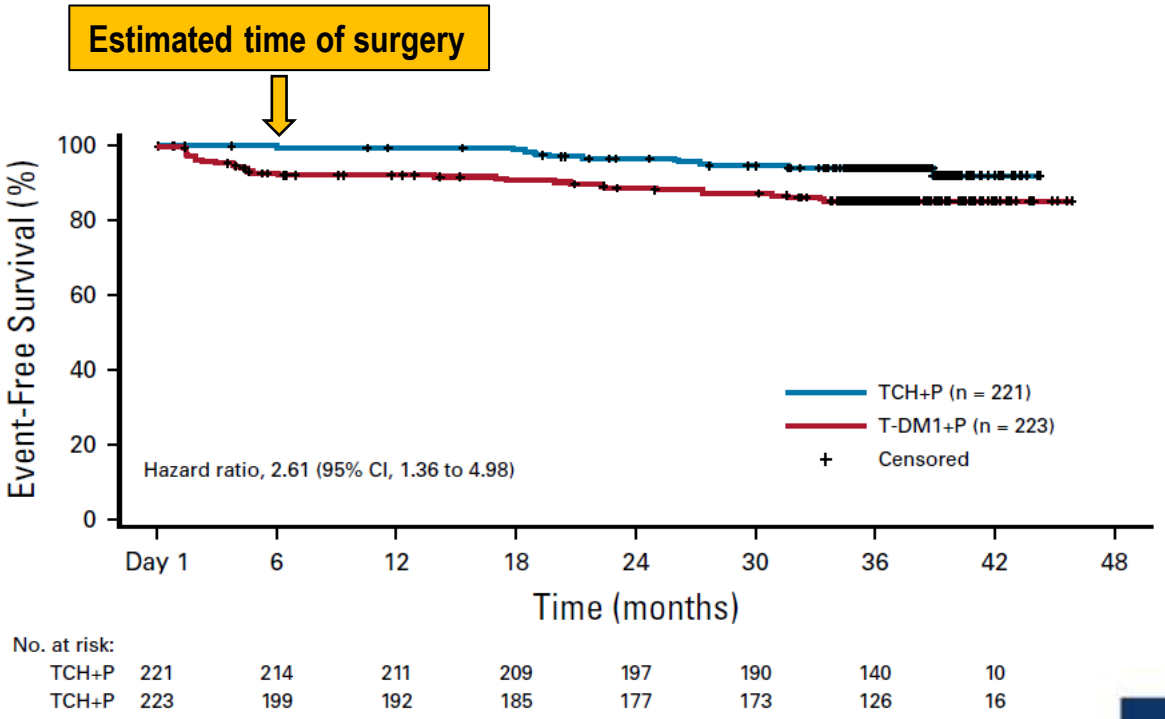
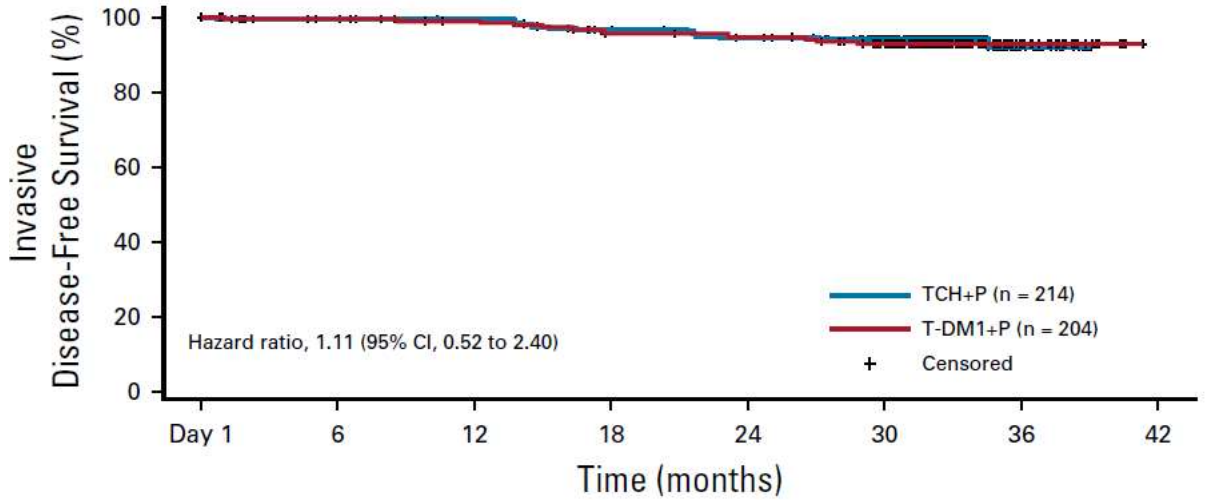
T-DM1 as neoadjuvant treatment for HER2+ BC

Trial	Population, study design	Arms	pCR %	p
KRISTINE *Hurvitz SA, Lancet Oncol 2018*	HER2+, ph III	TDM-1+P TCH+P	44% 56%	0.0155
WSG-ADAPT *Harbeck N, JCO 2017*	HER2+/HR+, ph II	Trastuzumab + ET T-DM1 T-DM1 + ET	15.1% 41% 41.5%	<0.001
PREDIX *Bergh J, ASCO 2019*	HER2+, ph II	T-DM1 TCH+P	45% 47%	0.359
DFHCC 14-409 *Metzger O, ASCO 2019*	HER2+, ph II	T-DM1+P	49.7%	-

KRISTINE





Locoregional progression before surgery:
6.7% in TDM1+P vs 0% in TCH+P

Event, n (%)	T-DM1+P with locoregional progression (n=15)	T-DM1+P without locoregional progression (n=208)
HER2 mRNA expression below the median,[a] n/N (%)	14/14 (100)	96/204 (47.1)
HER2 by IHC, n (%)		
IHC 2+	10 (66.7)	18 (8.7)
IHC 3+	5 (33.3)	190 (91.3)
HER2 2+/3+ heterogeneity, n (%)		
Focal (<30% staining of cells)	7 (46.7)	9 (4.3)
Heterogeneous (30% to 79% staining of cells)	5 (33.3)	22 (10.6)
Homogeneous (≥80% staining of cells)	3 (20.0)	177 (85.1)

[a]HER2 mRNA expression was not available for 1 patient in the locoregional progression group and for 4 patients in the no locoregional progression group.

Hurvitz SA, ASCO 2019 & JCO 2019

DFHCC 14-409 – study design and results

- Centrally-confirmed HER2+ BC
- Stage II and III (N = 164)

Single Arm

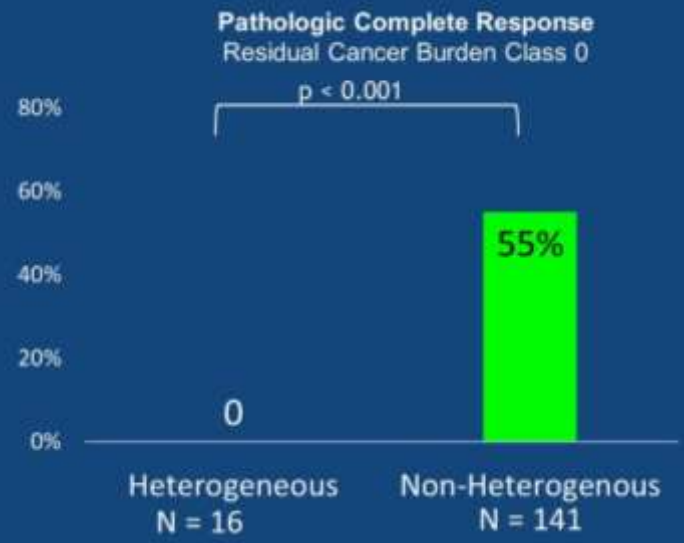
T-DM1 + Pertuzumab q3w x 6

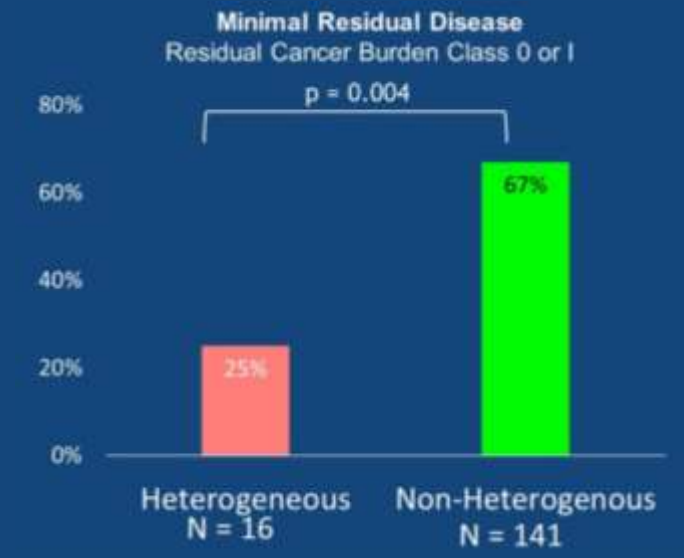
SURGERY

HER2 heterogeneity defined as either:

1) HER2 positivity by FISH in > 5% and < 50% of tumor cells (CAP guideline)
2) An area of tumor that tested HER2 negatve

Primary endpoint: Relationship between pCR (RCB 0) and intratumor heterogeneity of HER2 amplification





Metzger O, ASCO 2019

APHINITY: summary of biomarkers data

Biomarkers	Outcome	Pertuzumab benefit
PI3K/PTEN/AKT pathway alteration	worse	no interaction
MYC and ZNF703 ampl	better	no interaction
TOP2A ampl	worse	no interaction
LumA	better	no interaction
Basal	worse	no interaction
T-cell signature +	better	no interaction
CD274 high	better	increased
CXCL9 high	better	increased
IFNy high	better	increased
High TILs	better	increased
High HER2 CN	better	increased

Need for integrated biomarkers including other known prognostic factors in order to estimate individual absolute risk and absolute benefit of escalated/de-escalated treatment options.

Krop I, ASCO 2019

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MONALEESA-7 Study Design

First Phase III trial with a CDK4/6 inhibitor exclusively in premenopausal patients

Pre/perimenopausal women[a] with HR+/HER2− ABC

No prior ET for ABC[b]
≤ 1 prior CT for ABC

N = 672

Randomized 1:1

Ribociclib
600 mg/day;
3 weeks on/1 week off
+
NSAI/TAM[c] + GOS[d]
n = 335

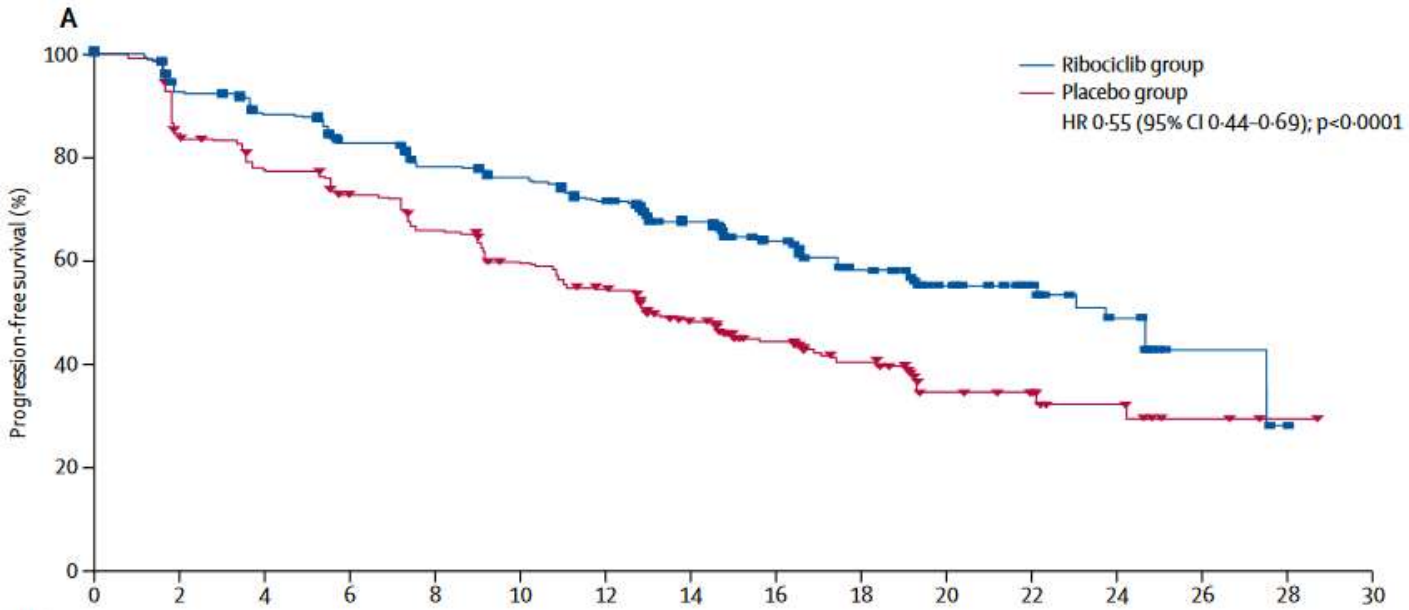
Placebo
3 weeks on/1 week off
+
NSAI/TAM[c] + GOS[d]
n = 337

Primary endpoint
- PFS (local)

Key secondary endpoint
- OS

Select secondary endpoints
- HRQOL
- ORR
- TTDD of ECOG PS
- Safety

Stratification Factors
- Liver/lung metastasis (yes/no)
- Prior chemotherapy (yes/no)
- Combination partner (NSAI/TAM)



Number at risk (number censored)

Ribociclib group	335 (0)	301 (9)	264 (12)	264 (15)	245 (20)	235 (23)	219 (25)	178 (55)	136 (88)	90 (124)	54 (156)	40 (170)	20 (187)	3 (202)	1 (203)	0 (204)
Placebo group	337 (0)	273 (12)	248 (15)	230 (19)	207 (21)	183 (25)	165 (27)	124 (50)	94 (72)	62 (97)	31 (121)	24 (128)	13 (138)	3 (147)	1 (149)	0 (150)

- 41% de novo ABC

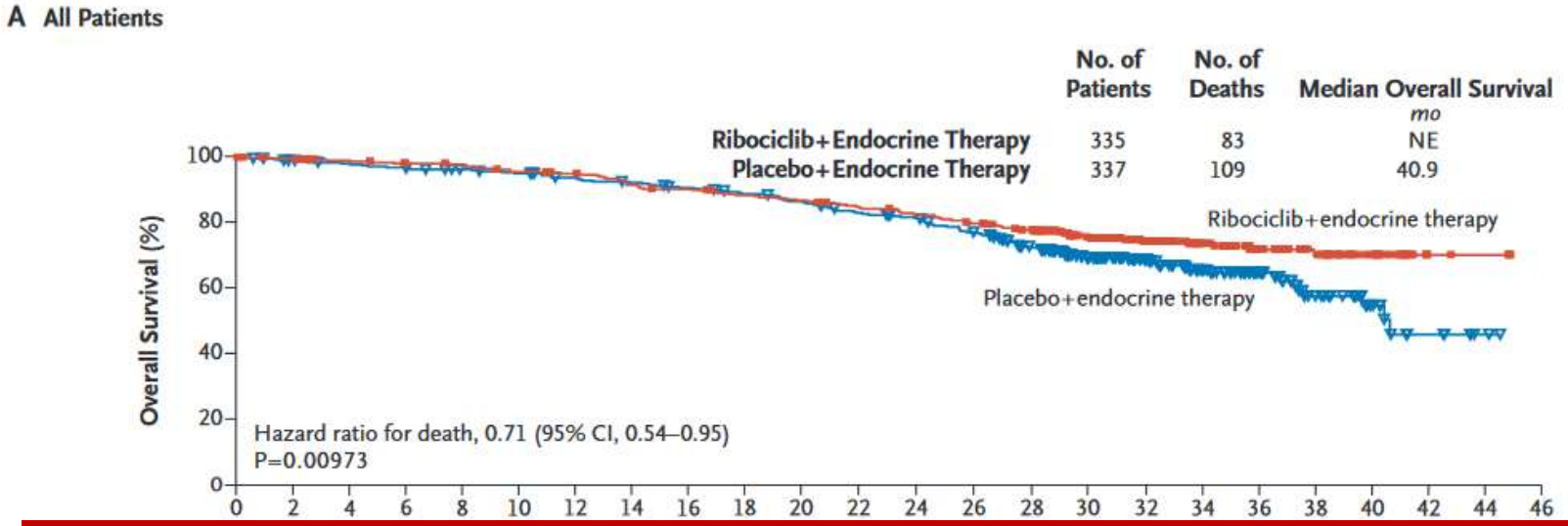
- 60% ET naive
- 40% Adj/neo ET
  - 30% PD<12 months after ET
  - 10% PD>12 months after ET

- 45% CT naive
- 55% previous CT
  - 14% CT for ABC
  - 41% CT for EBC only

Tripathy D, Lancet Oncol 2018

MONALEESA-7: OVERALL SURVIVAL

Second interim OS analysis (75% events), median FU 35 months, 60% power, crossing the O'Brien-Fleming boundary (p 0.01018)



- ≈ 29% relative reduction in risk of death
- The *P* value of .00973 crossed the prespecified boundary to claim superior efficacy

Landmark Analysis

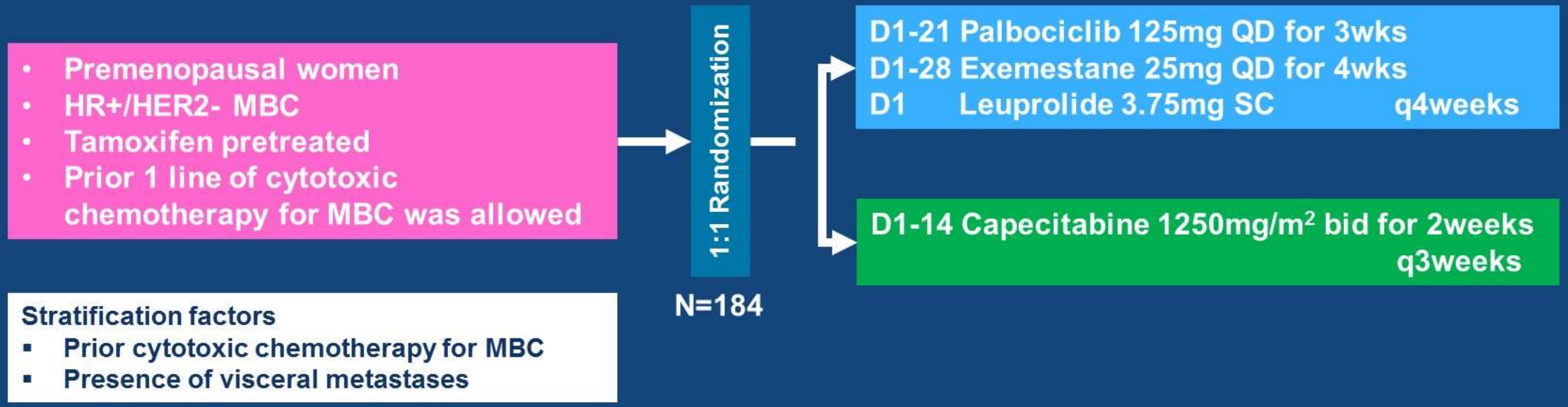
Kaplan-Meier	Ribociclib + ET	Placebo + ET

"Because the efficacy stopping boundary was crossed, the results reported here showed the superiority of ribociclib to placebo with respect to the key secondary end point of overall survival, and, according to the protocol, are considered final."

Hurvitz S, ASCO 2019, Im SA, NEJM 2019

Young-PEARL (KCSG BR 15-10) Study Design

- **Prospective, multi-center, open-label, randomized phase II study**



- **Primary endpoint: Investigator-assessed progression-free survival**
- Secondary endpoints: Disease control rate (DCR), Overall survival (OS), Toxicity, QoL, Biomarkers

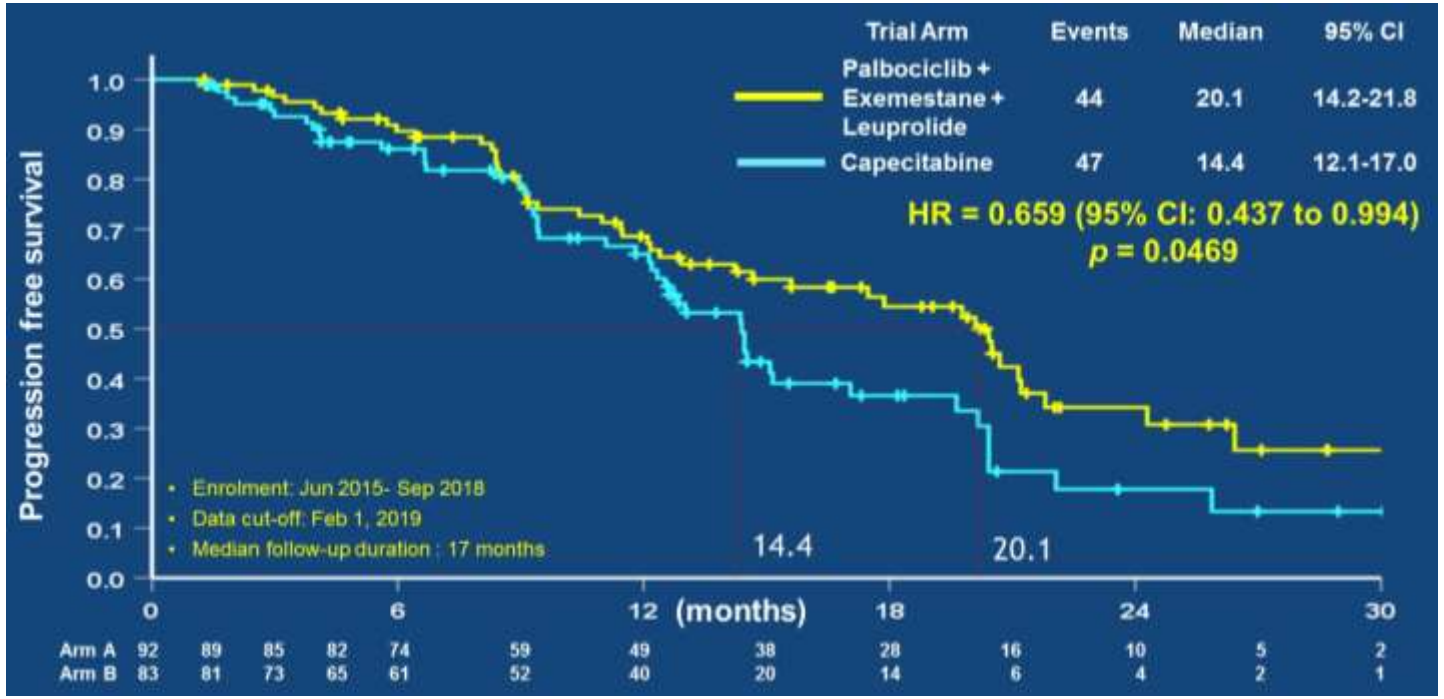
HR, hormone receptor; HER2, human epidermal receptor-2; MBC, metastatic breast cancer QoL, quality of life; GnRH, gonadotropin releasing hormone

YOUNG PEARL: patients' characteristics

	Palbo+Exe+GnRH, N=92	Cape, N=86
Age, median (range)	44 (31-58)	44 (28-53)
PR+ PR-	76.1% 23.9%	74.4% 25.6%
Bone only Visceral	23.9% 48.9%	20.9% 50.0%
Stage IV de novo DFI<24m DFI>24m	30.4% 13.0% 56.5%	30.2% 17.4% 52.3%
TAM resistance*	82.6%	89.5%
Prior CT for MBC	23.9%	20.9%
No tx for MBC 1 line for MBC 2 lines for MBC	50.0% 32.6% 17.4%	51.2% 34.9% 12.8%
Prior ET for EBC	65.2%	64.0%

*including pts relapsing <12months after adj TAM

Park YH, ASCO 2019



	Palbociclib + Exemestane + Leuprolide N=92 (%)	Capecitabine N=86 (%)	P-value
ORR (N=178)	34 (37.0%)	29 (34.9%)	0.781
ORR (measurable N= 119)	31 (50.8%)	26 (44.8%)	0.387
DCR (N=178)	89 (96.7%)	78 (94.0%)	0.480
DCR (measurable N=119)	58 (95.1%)	51 (87.9%)	0.262
CBR (N=178) (CR + PR + SD ≥ 24 weeks)	74 (80.4%)	58 (69.9%)	0.105
CBR (measurable N= 119) (CR + PR + SD ≥ 24 weeks)	48 (78.7%)	38 (65.5%)	0.134

Park YH, ASCO 2019

CDK4/6i: Biomarkers

- Prognostic markers of early progression (no interaction with palbociclib) in PALOMA-3: circulating tumor fraction >10%, FGFR1 gain, TP53 mut in ctDNA.[1]
- High CCNE1 expression associated with reduced palbociclib efficacy.[2]
- Intrinsic resistance to CDK4/6i: RB1 loss-of-function, FAT1 loss-of-function (CDK6 upregulation).[3]
- Acquired resistance: post-CDK4/6i samples enriched for RB1 loss, PTEN loss, FAT loss.[4]

1. O'Leary B, ASCO 2019; 2. Turner N, J Clin Oncol 2019; 3. Li, Cancer Cell 2018; 4. Razavi P, ASCO 2019

FAKTION Trial design

Phase 1b

3+3 design - fulvestrant 500mg q 4weeks + loading dose (LD) C1D15: Starting dose capivasertib 400mg bd 4 days on / 3 days off
N=9 SRC recommended not to dose escalate to established single agent dose 480mg bd 4 days on / 3 days off

Phase 2

Eligibility

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

Exclusion

- Prior fulvestrant or PI3K/AKT/mTOR inhibitor therapy

N = 140

R

1:1

Fulvestrant 500mg q4weeks + LD
Capivasertib 400mg bd 4 days on / 3 days off from C1D15
N=69

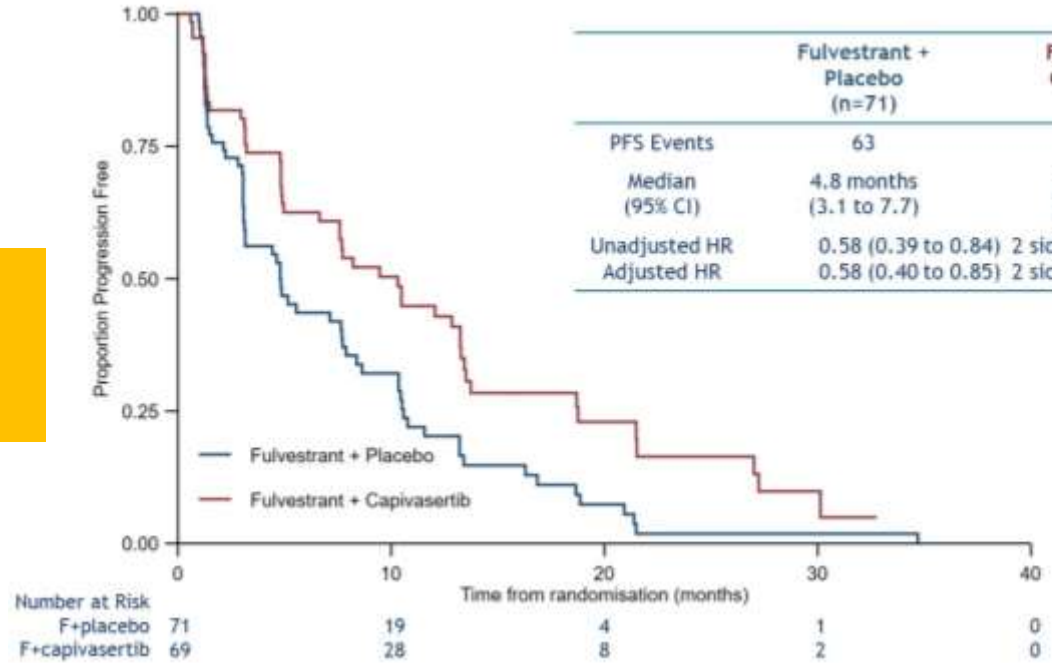
Fulvestrant 500mg q4weeks + LD
Placebo bd 4 days on / 3 days off from C1D15
N=71

Primary endpoint:
Investigator assessed PFS in the intent to treat (ITT) population

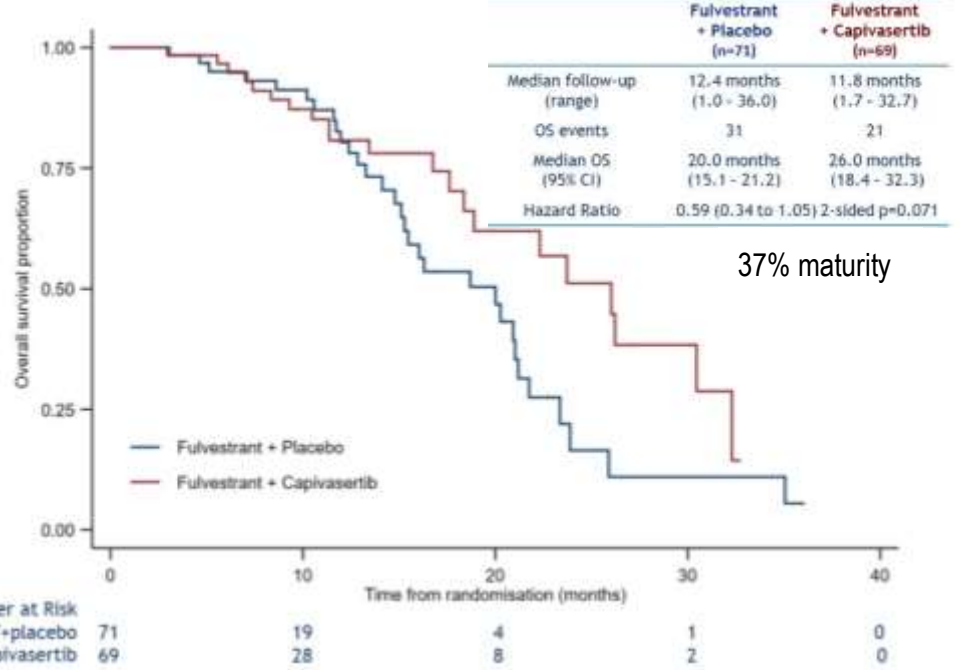
Secondary endpoints:

- Safety and toxicity
- Objective Response rate (ORR), Clinical Benefit Rate (CBR) and Overall Survival (OS) in ITT population
- PFS/ORR/CBR in PI3K/AKT/PTEN pathway activated vs non-activated tumours

PFS and OS in the ITT population



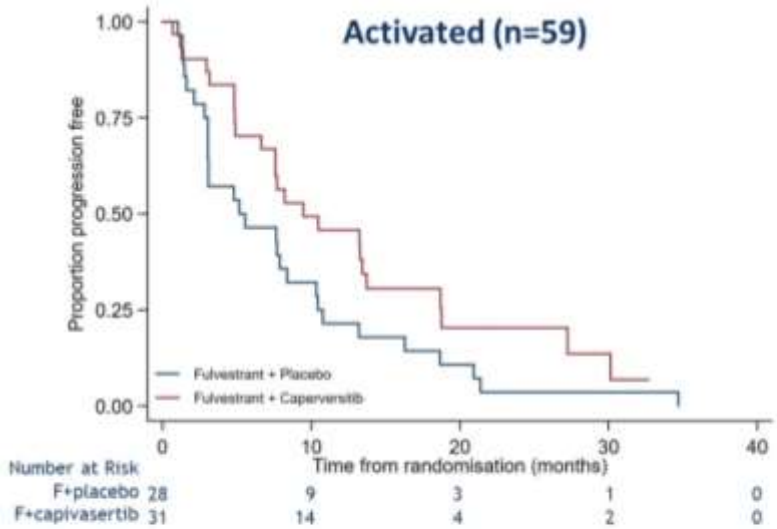
	Fulvestrant + Placebo (n=71)	Fulvestrant + Capivasertib (n=69)
PFS Events	63	49
Median (95% CI)	4.8 months (3.1 to 7.7)	10.3 months (5.0 to 13.2)
Unadjusted HR	0.58 (0.39 to 0.84) 2 sided p = 0.004	
Adjusted HR	0.58 (0.40 to 0.85) 2 sided p = 0.005	



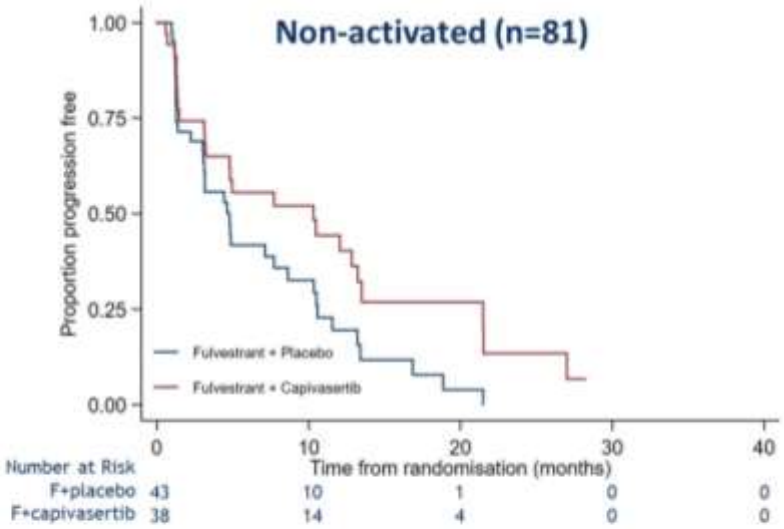
	Fulvestrant + Placebo (n=71)	Fulvestrant + Capivasertib (n=69)
Median follow-up (range)	12.4 months (1.0 - 36.0)	11.8 months (1.7 - 32.7)
OS events	31	21
Median OS (95% CI)	20.0 months (15.1 - 21.2)	26.0 months (18.4 - 32.3)
Hazard Ratio	0.59 (0.34 to 1.05) 2-sided p=0.071	

37% maturity

PFS according to PI3k/AKT/PTEN pathway activation (hotspot PIK3CA mutations and PTEN by IHC)



	Fulvestrant + Placebo (n=28)	Fulvestrant + Capivasertib (n=31)
Median (95% CI)	5.2 months (3.1 to 8.4)	9.5 months (6.6 to 13.7)
Hazard Ratio	0.59 (0.34 to 1.03) 2-sided p=0.064	



	Fulvestrant + Placebo (n=43)	Fulvestrant + Capivasertib (n=38)
Median (95% CI)	4.8 months (3.0 to 8.6)	10.3 months (3.2 to 13.2)
Hazard Ratio	0.56 (0.33 to 0.96) 2-sided p=0.035	

Jones RH, ASCO 2019

Safety of PI3K/AKT/mTOR inhibitors + ET in HR+/HER2- BC

	Capivasertib + Fulvestrant		Everolimus + exemestane		Alpelisib + Fulvestrant	
	Any G	G3-4	Any G	G3-4	Any G	G3-4
Diarrhoea	35%	4%	17%	1%	58%	7%
Rash	18%	0	17%	1%	36%	10%
Hyperglycaemia	16%	0	12%	3%	64%	37%
Vomiting	21%	0	-	-	27%	1%
Nausea	51%	0	12%	1%	45%	3%
Infections	18%	3%	-	-	-	-
Stomatitis	7%	0	53%	9%	25%	3%

Jones RH, ASCO 2019; Jerusalem G, Ann Oncol 2016; André F, NEJM 2019

Outline

- Early breast cancer
  - HR+/HER2-
    - CT yes or no?
    - Extended adjuvant HT
  - HER2+
    - new hints for escalation and de-escalation
- Advanced breast cancer
  - HR+/HER2-
    - CDK4/6 inhibitors
    - Capivasertib
  - Immunotherapy
    - IMPASSION130
  - HER2+
- Survivorship

IMpassion130 study design

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

Atezo + nab-P arm:

Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

Plac + nab-P arm:

Placebo IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

RECIST v1.1
PD or toxicity

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

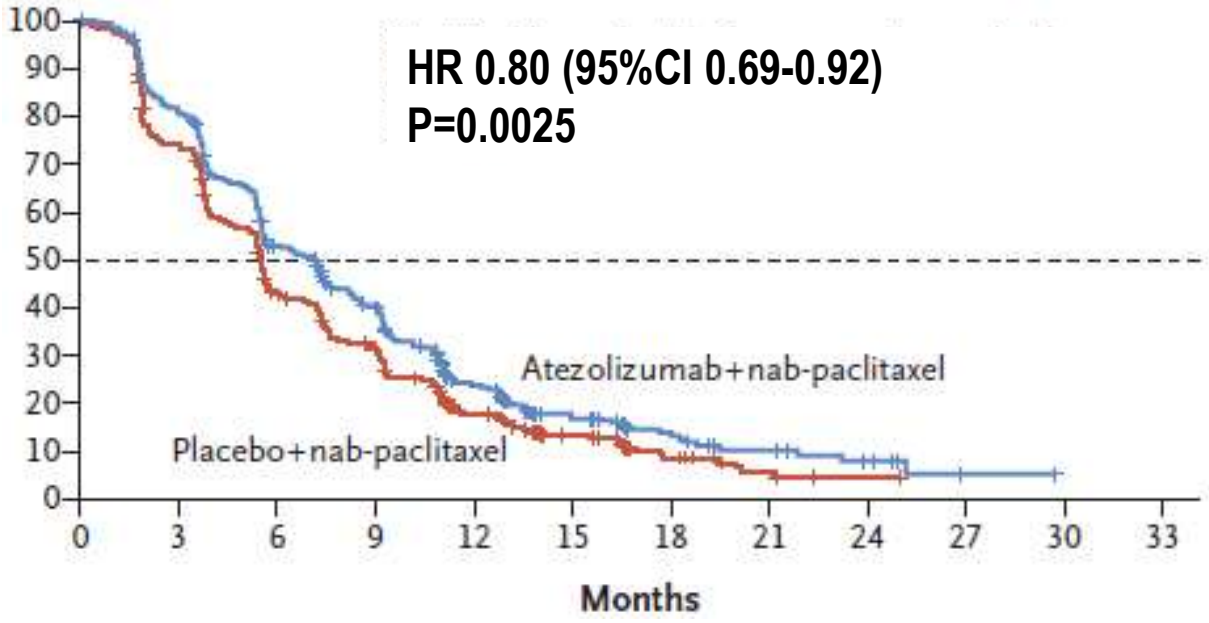
IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR) http://bit.ly/2DMhayg

Schmid P, ESMO 2018, NEJM 2018

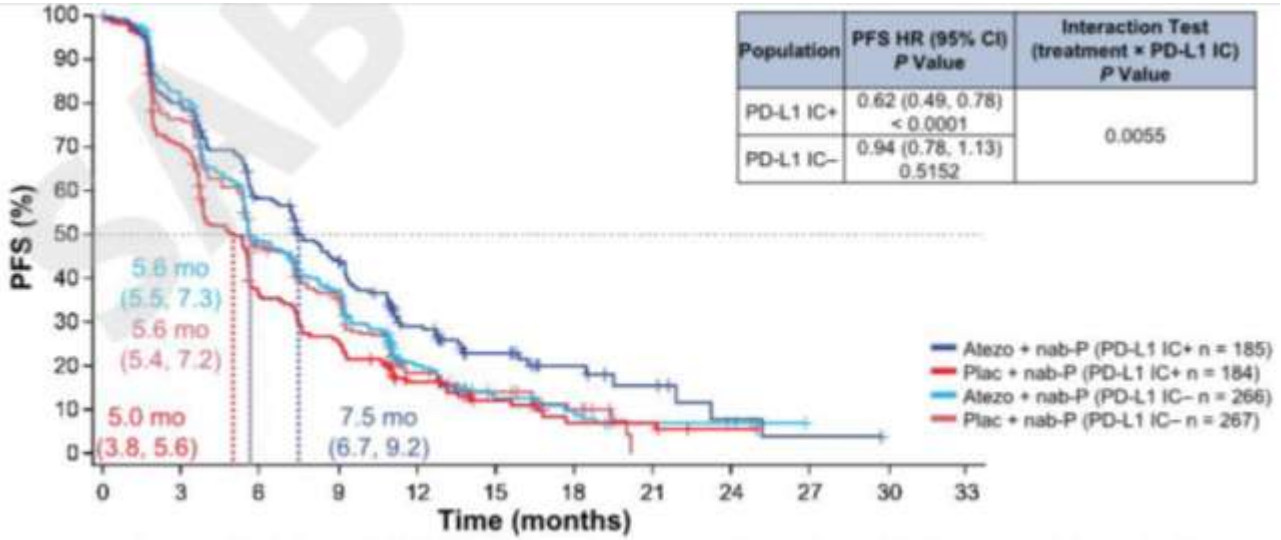
Primary analysis: PFS

PFS ITT



	Events/pts	mPFS, months (95%CI)	1yr PFS% (95%CI)
Atezo+Nab	358/451	7.2 (5.6-7.5)	23.7 (19.6-27.9)
Plac+Nab	378/451	5.5 (5.3-5.6)	17.7 (14.0-21.4)

PFS by PD-L1



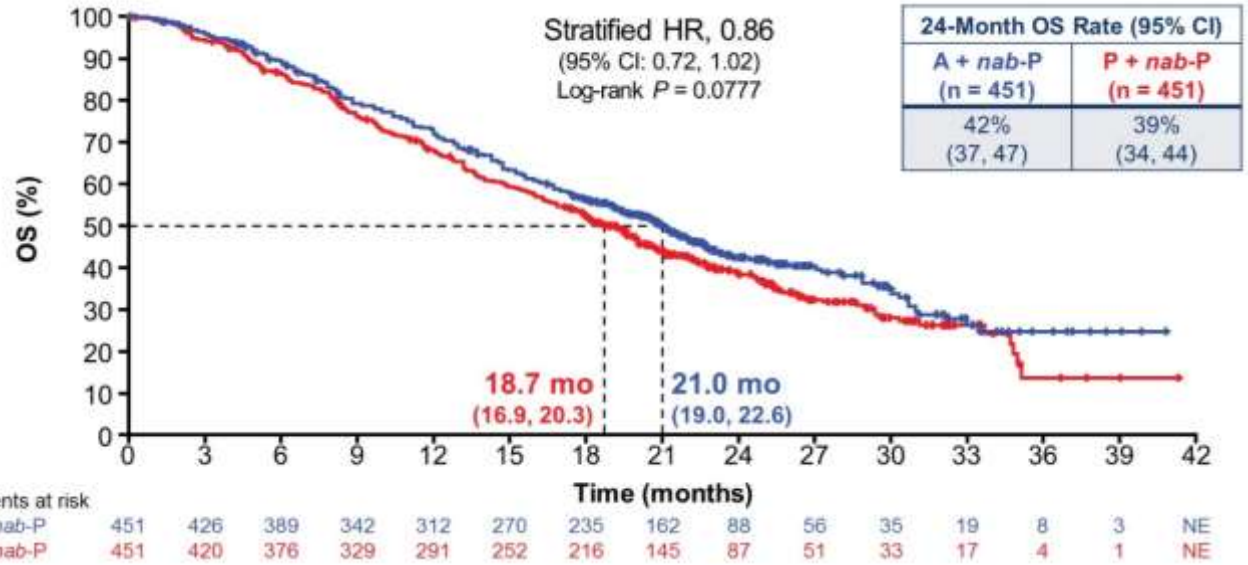
PD-L1+	mPFS, months (95%CI)	1yr PFS% (95%CI)
Atezo+Nab	7.5 (6.7-9.2)	29.1%
Plac+Nab	5.0 (3.8-5.6)	16.4%

Schmid P, NEJM 2018

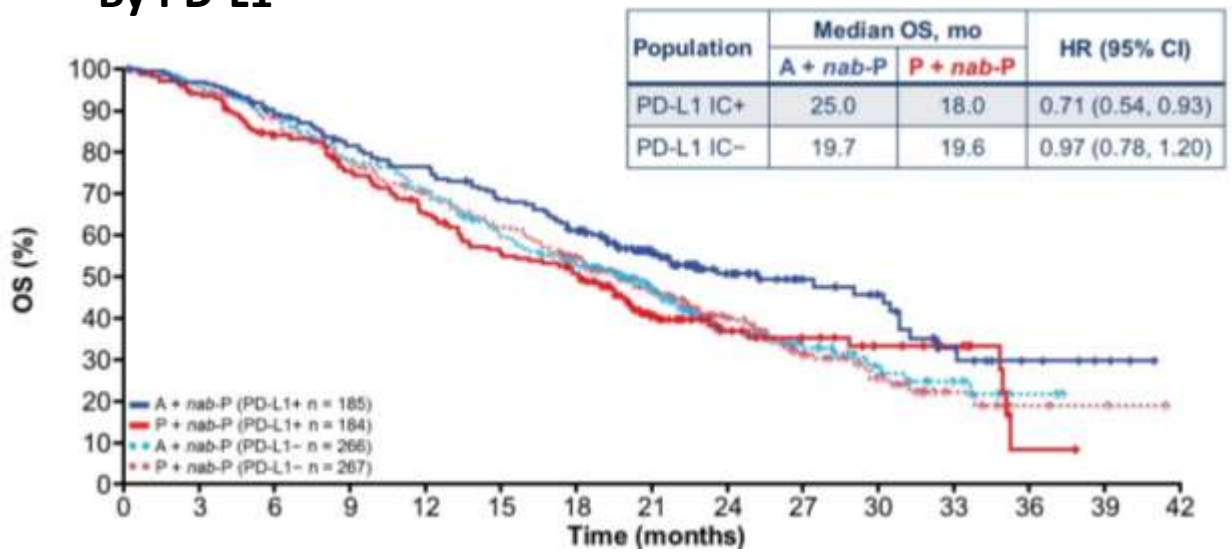
IMpassion130: OS

2° interim (59% deaths in ITT population)

ITT



By PD-L1



Schmid P, NEJM 2018; Schmid P, ASCO 2019

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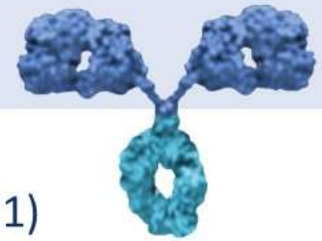
Margetuximab: Fc-engineered to Activate Immune Responses

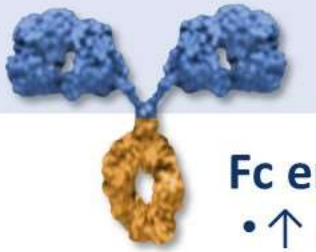
Trastuzumab

Fab:
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival



Fc:
- Wild-type immunoglobulin G1 (IgG1) immune effector domains
- Binds and activates immune cells

Margetuximab[1,2]



Fab:
- Same specificity and affinity
- Similarly disrupts signaling

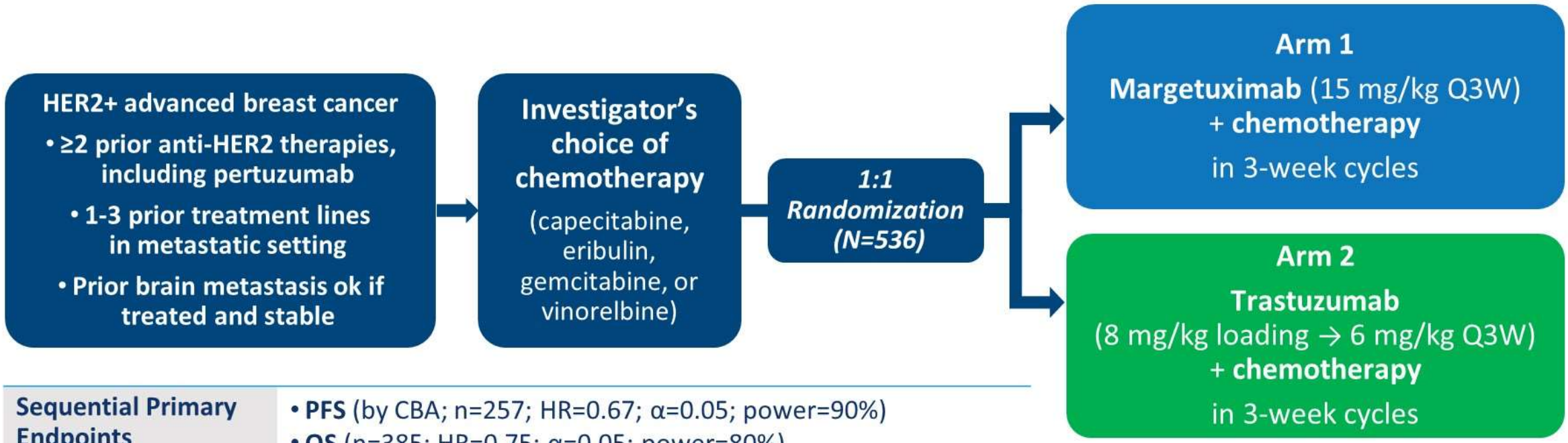
Fc engineering:
- ↑ Affinity for activating FcγRIIIA (**CD16A**)
- ↓ Affinity for inhibitory FcγRIIB (**CD32B**)

Margetuximab Binding to FcγR Variants:

Receptor Type	Receptor	Allelic Variant	Relative Fc Binding	Affinity Fold-Change
Activating	**CD16A**	158F	Lower	6.6x ↑
		158V	Higher	4.7x ↑
	CD32A	131R	Lower	6.1x ↓
		131H	Higher	↔
Inhibitory	**CD32B**	232I/T	Equivalent	8.4x ↓

1. Nordstrom JL, et al. *Breast Cancer Res*. 2011;13(6):R123. 2. Stavenhagen JB, et al. *Cancer Res*. 2007;67(18):8882-8890.

Study CP-MGAH22-04 (SOPHIA) Design[1,2]



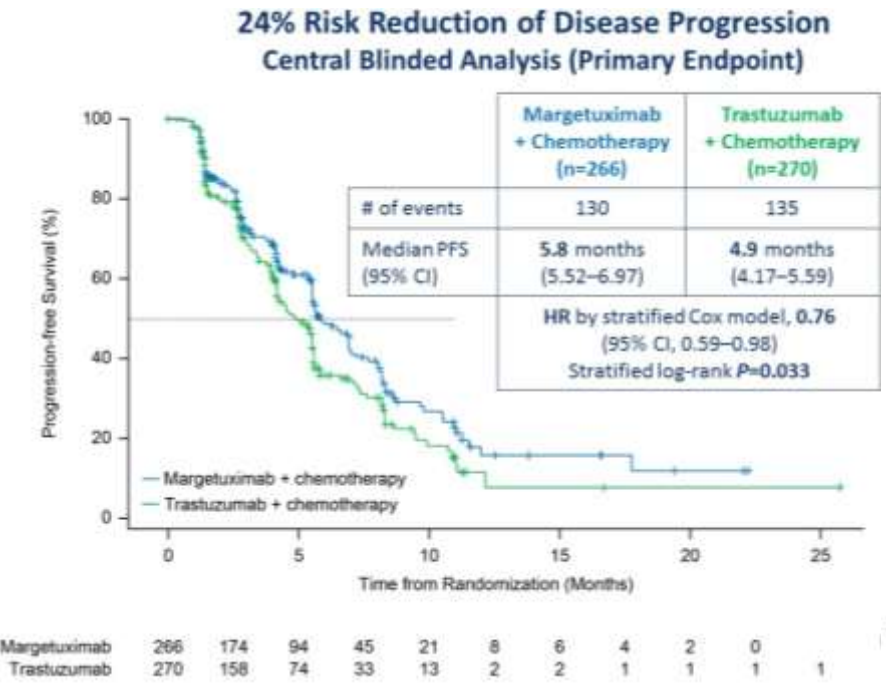
Sequential Primary Endpoints	• **PFS** (by CBA; n=257; HR=0.67; α=0.05; power=90%) • **OS** (n=385; HR=0.75; α=0.05; power=80%)
Secondary Endpoints	• PFS (Investigator assessed) • Objective response rate (by CBA)
Tertiary/Exploratory Endpoints	• Clinical benefit rate (CBR), duration of response (DoR) • Safety profile, antidrug antibody • Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

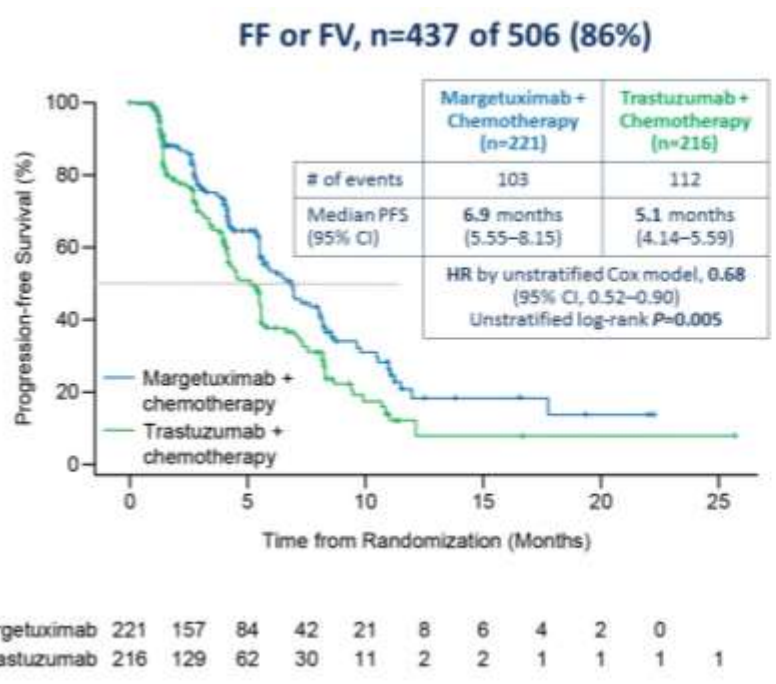
Stratification:
- Chemotherapy choice
- Prior therapies (≤2 *vs* >2)
- Metastatic sites (≤2 *vs* >2)

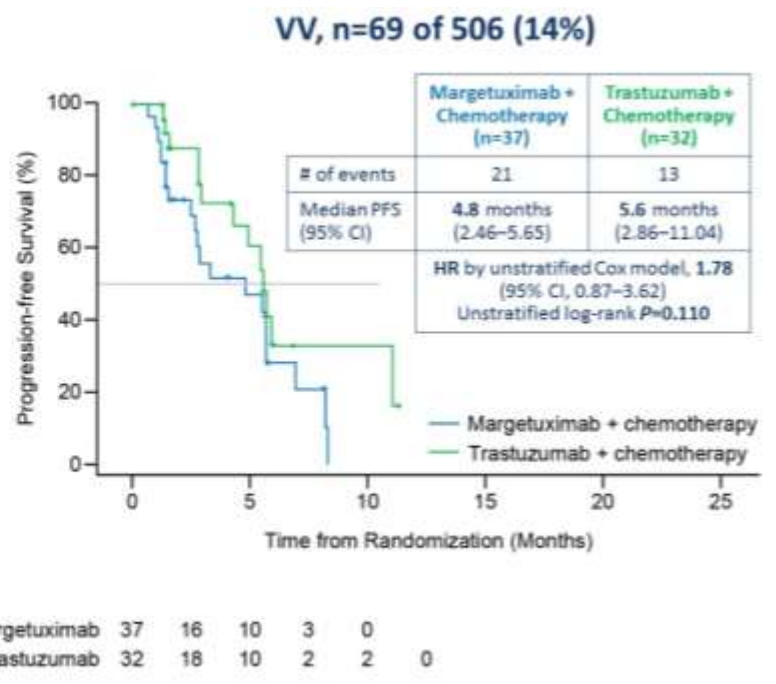
HR=hazard ratio; CBA=central blinded analysis.

1. Rugo HS, et al. *J Clin Oncol*. 2016;34(suppl 15):TPS630. 2. Clinicaltrials.gov. NCT02492711. www.clinicaltrials.gov/ct2/show/NCT02492711. Accessed April 8, 2019.

SOPHIA TRIAL: PFS results







Safety: infusion related-reactions any grade 13% (Margetuximab) vs 4% (Trastuzumab); grade 3/4 4% (Margetuximab) vs 0% (Trastuzumab)

Rugo H, ASCO 2019

Outline

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    - Capivasertib
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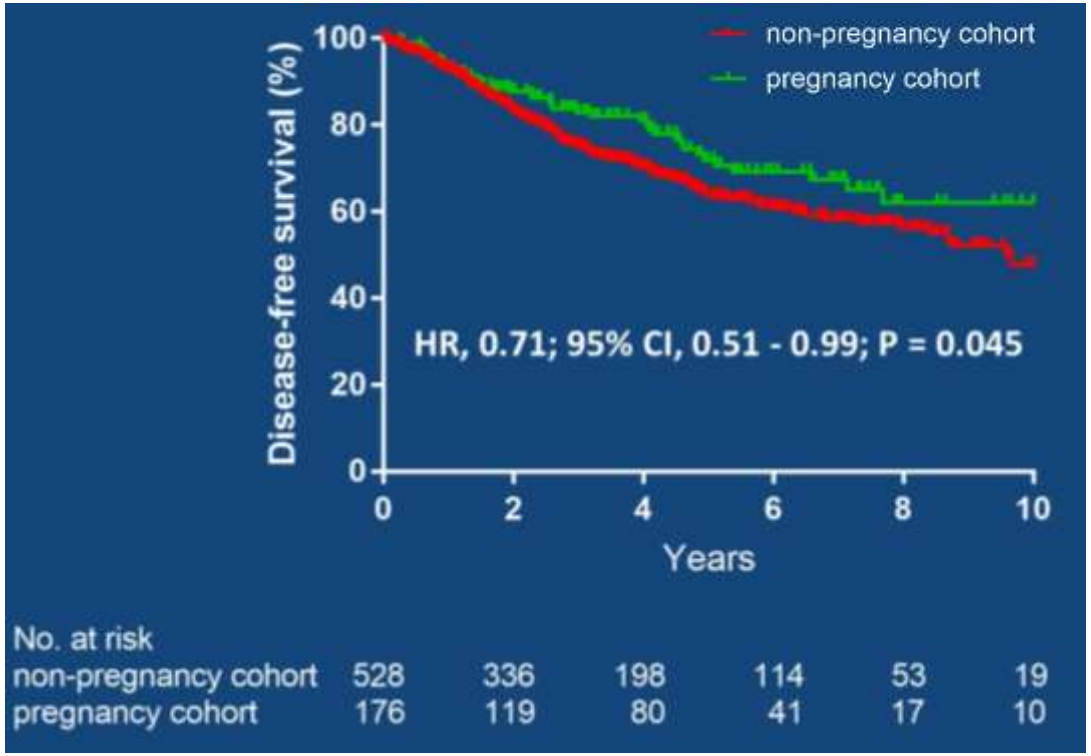
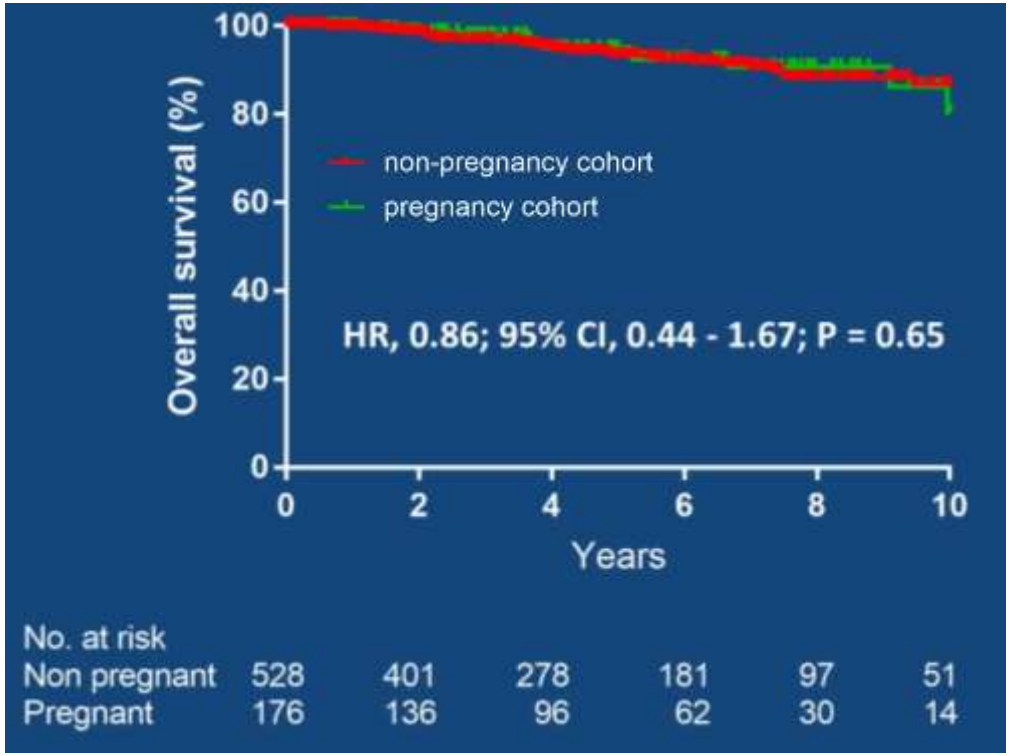
    - IMPASSION130
  - HER2+
- Survivorship

Safety of pregnancy after BC in BRCA mut carriers



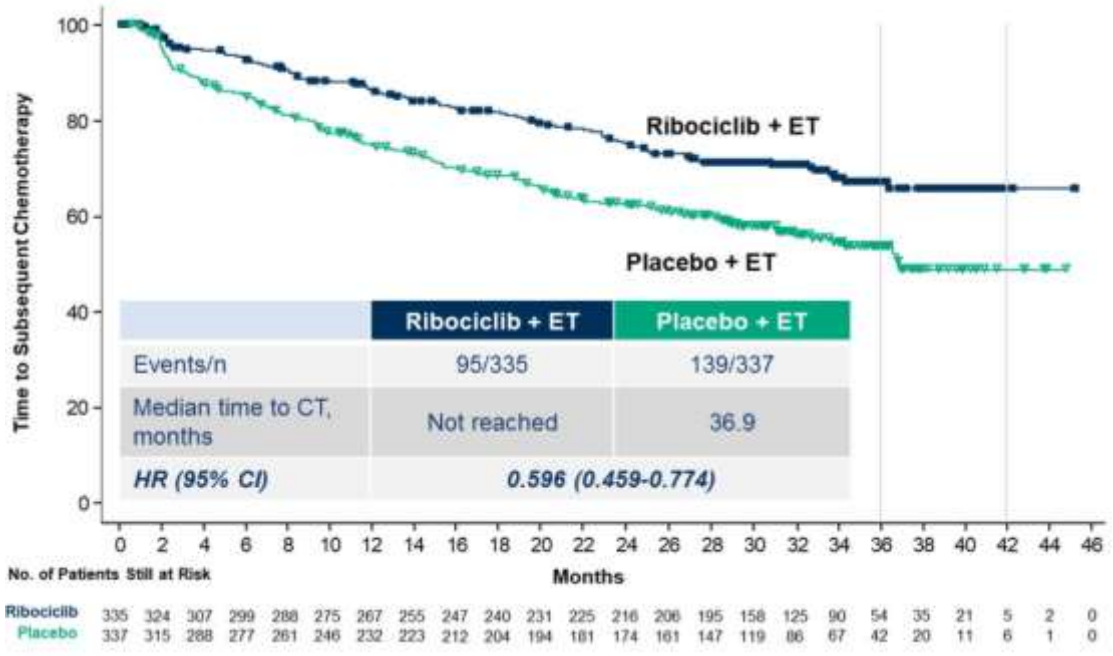
Cox model adjusted HR: 0.87 (95%CI 0.61-1.23), p=0.41

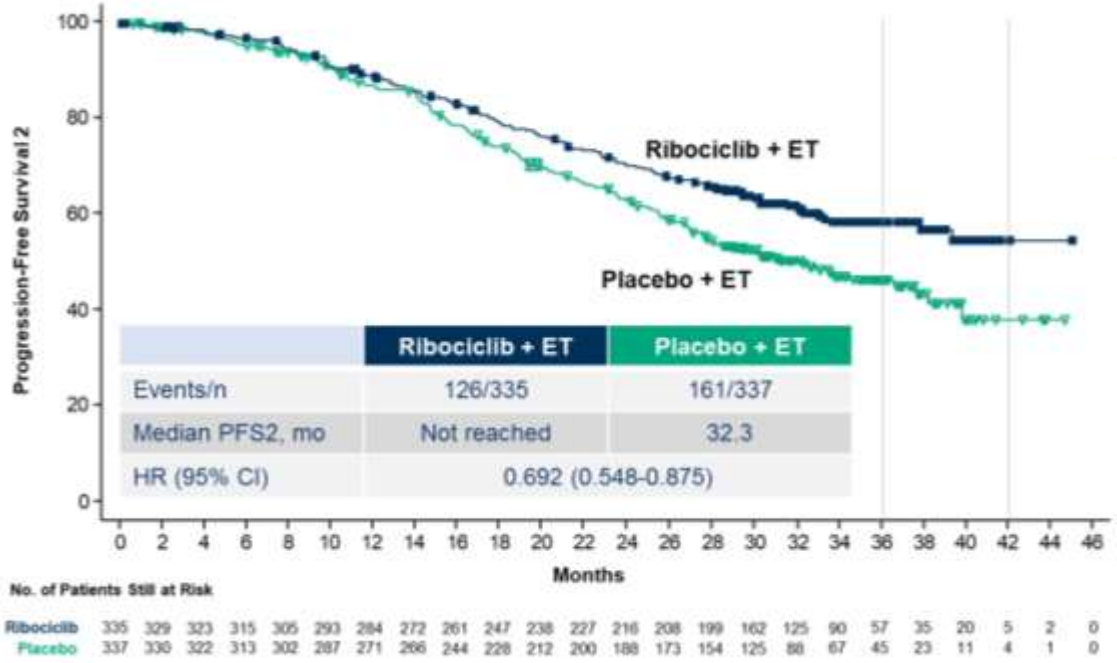


Cox model adjusted HR: 0.88 (95%CI 0.50-1.56), p=0.66

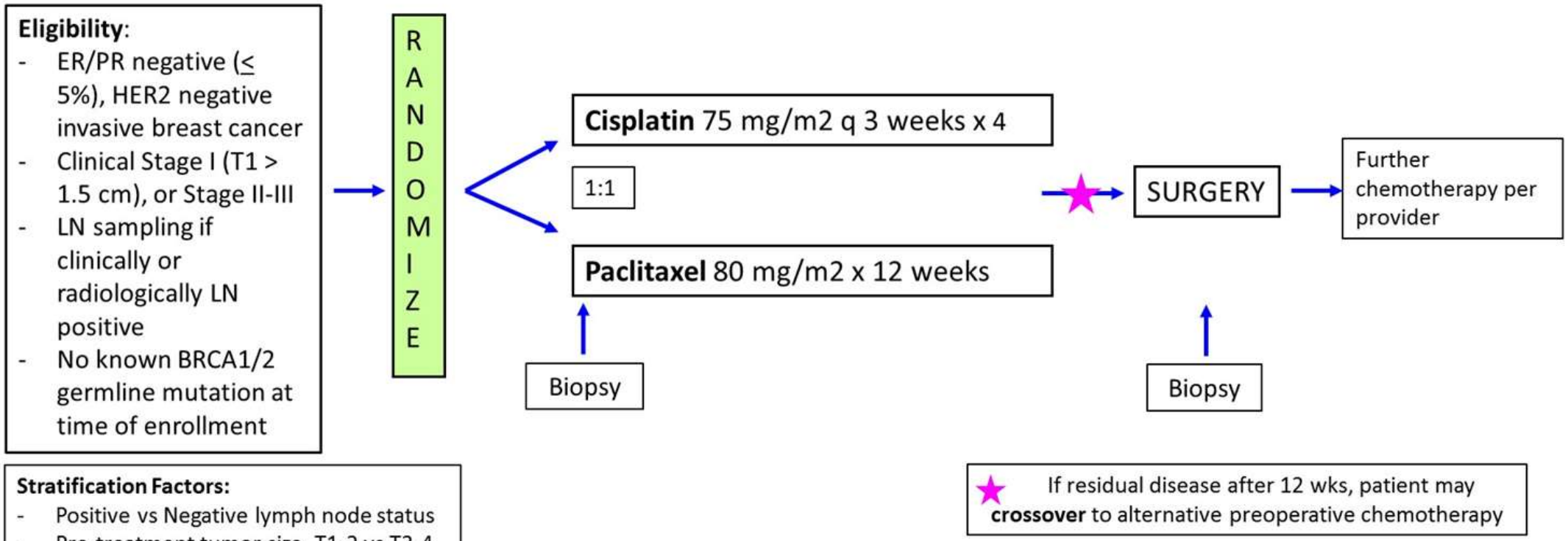
Presented By Matteo Lambertini at 2019 ASCO Annual Meeting

MONALEESA-7: other endpoints





TBCRC 030 – study design



Primary Objective: To determine the association of HRD score with pathologic response to neoadjuvant platinum or taxane-based chemotherapy in TNBC
Primary Endpoint: response determined by Residual Cancer Burden : RCB 0/1 = response, RCB 2/3 or crossover = non-response
Secondary Endpoint: pathologic complete response (pCR)

Response	Cisplatin (N=72)		Paclitaxel (N=68*)		Total (N=140*)	
	N	%	N	%	N	%
Responder (RCB 0/1)	19	26.4%	15	22.1%	34	24.3%
Non-responder (RCB 2/3 or crossover)	53	73.6%	52	76.5%	105	75.0%
pCR	11	15.3%	8	11.8%	19	13.6%
non-pCR	61	84.7%	60	88.2%	121	86.4%

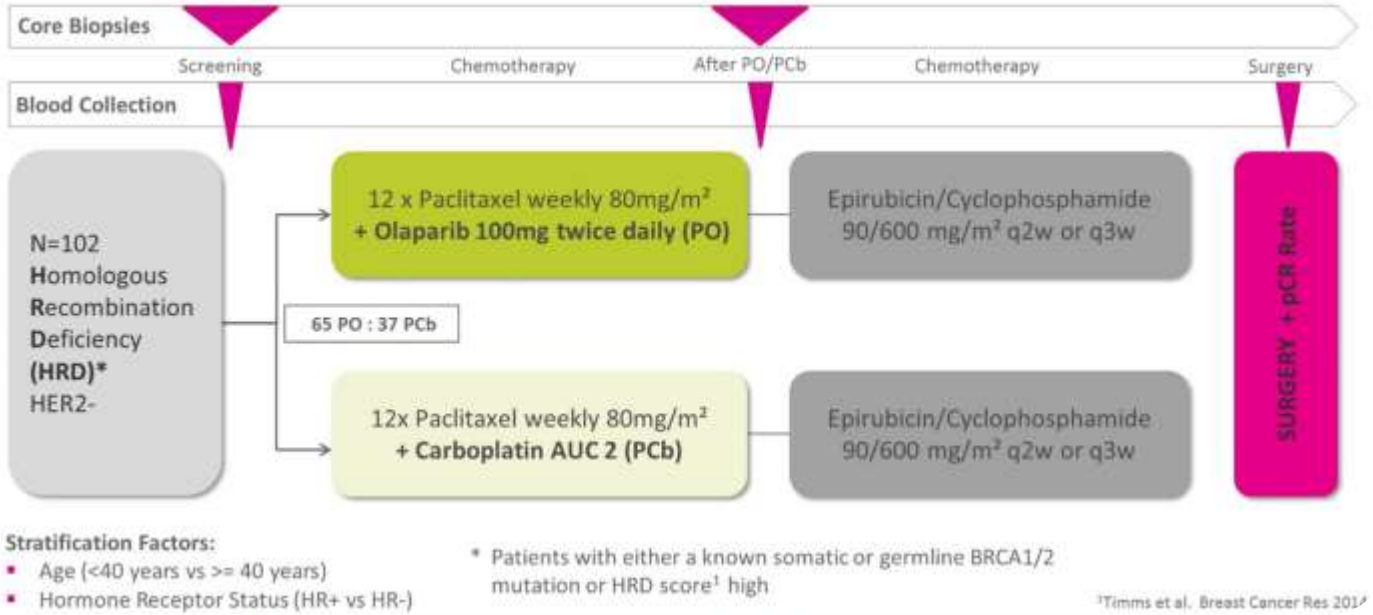
- One patient completed paclitaxel treatment but was lost to f/u before surgery and does not have an RCB score.

- No association was seen between HRD score and RCB response to either neoadjuvant cisplatin or paclitaxel.

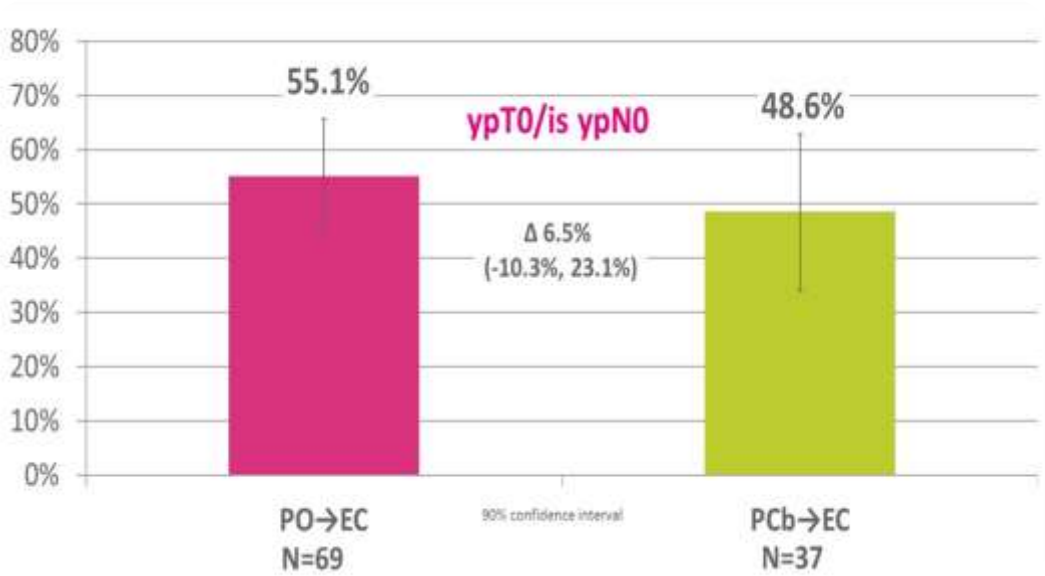
Cisplatin, n=56	RCB 0/1	RCB 2/3 crossover	OR (95% CI)
HRD+	9 (23%)	30 (77%)	2.22 (0.39, 23.68)
HRD-	2 (12%)	15 (88%)	

Paclitaxel, n=49	RCB 0/1	RCB 2/3 crossover	OR (95% CI)
HRD+	10 (29%)	25 (71%)	0.90 (0.19, 4.95)
HRD-	4 (31%)	9 (69%)	

GeparOLA



Primary endpoint - pCR

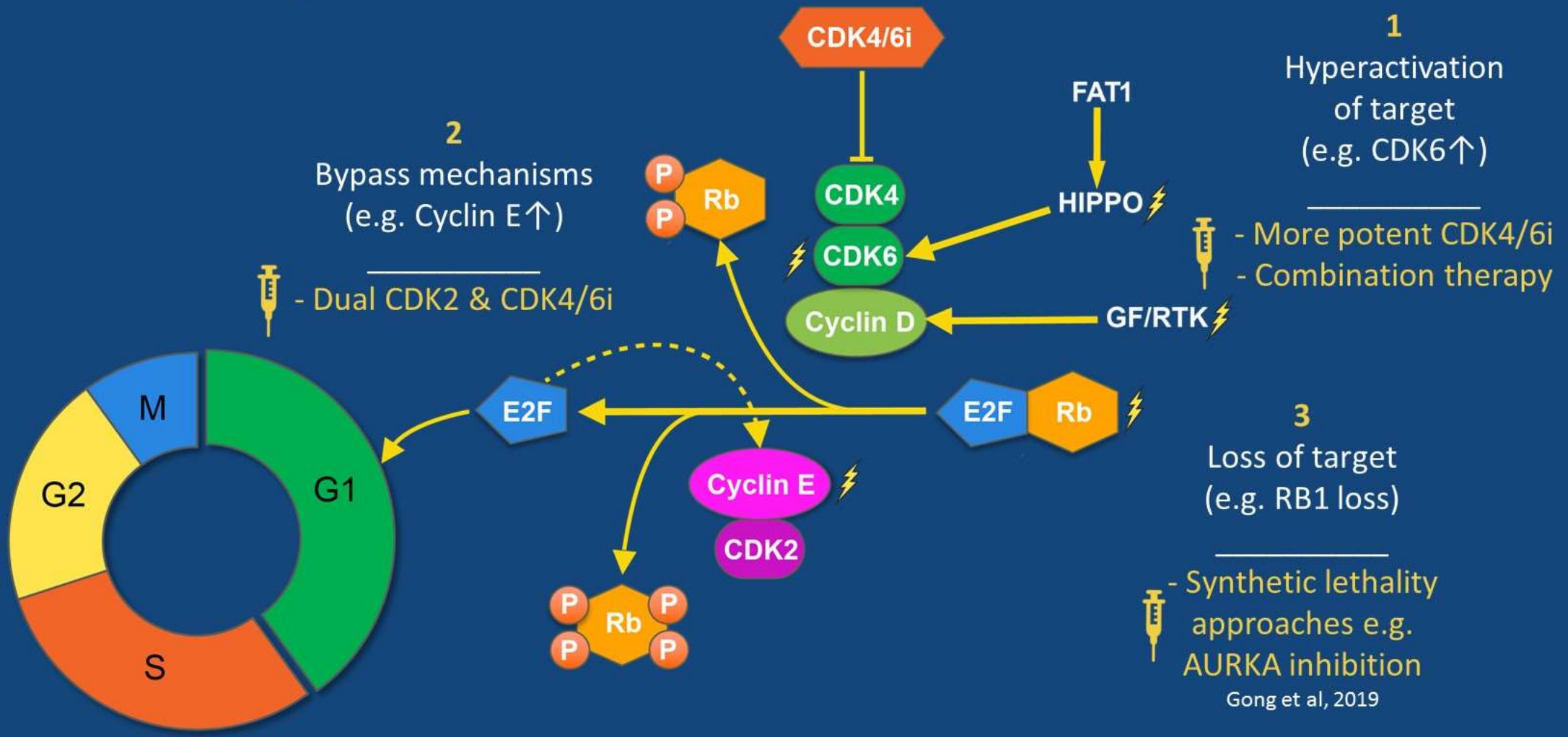


N+ population: 24.5% in PO vs 45.7% in PCb

PRIMARY ENDPOINT

- Assess pCR rate of neoadjuvant paclitaxel-olaparib (PO) → EC in HRD pts
- A rate in the PO arm of 55% or lower should be excluded with α=0.1 to support a subsequent phase III trial
- No formal comparison between arms

Three main mechanisms of resistance to CDK4/6i with distinct potential therapeutic implications



Chandarlapaty and Razavi, *JCO* 2019

Study Design

Key eligibility criteria

- Metastatic breast cancer
- HR + (ER and/or PR >1%, HER2-negative)
- Measurable or evaluable disease
- At least 2 prior lines of hormonal therapy (adjuvant plus metastatic setting) or appropriate candidates for chemotherapy
- 0-2 prior lines of chemotherapy for advanced disease
- No prior eribulin or PD-1/PD-L1 inhibitor therapy
- Archival tumor tissue required (or biopsy)*
- ECOG PS 0-2

N=88

R
1:1

Eribulin + Pembrolizumab

Pembrolizumab 200 mg IV
- On day 1 of 21-day cycle

+ Eribulin 1.4 mg/m^2 IV
- On days 1, 8 of 21-day cycle

Restaging scans obtained every 9 weeks

Eribulin:

Eribulin 1.4 mg/m^2 IV
- On days 1, 8 of 21-day cycle

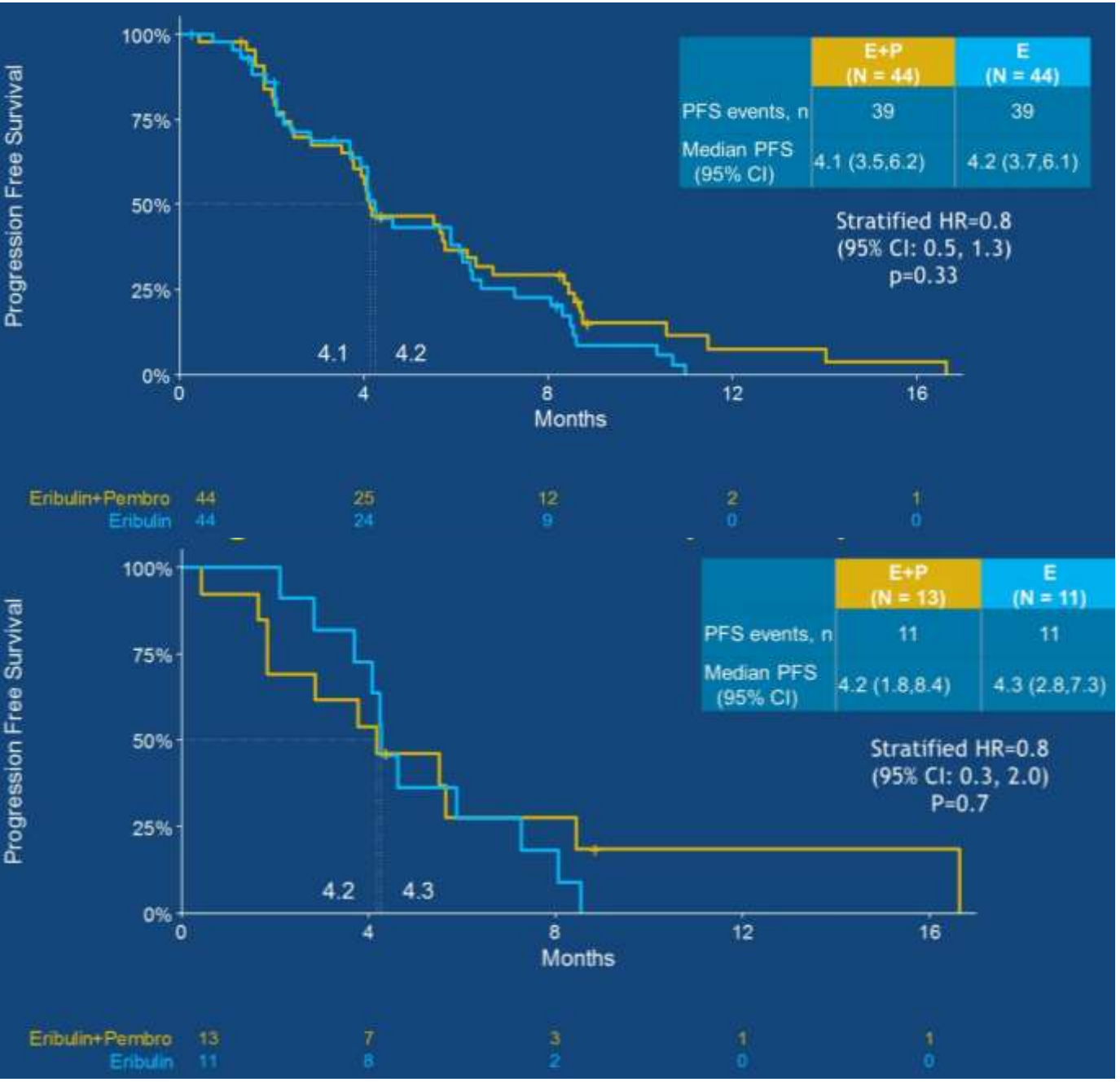
Pembrolizumab:

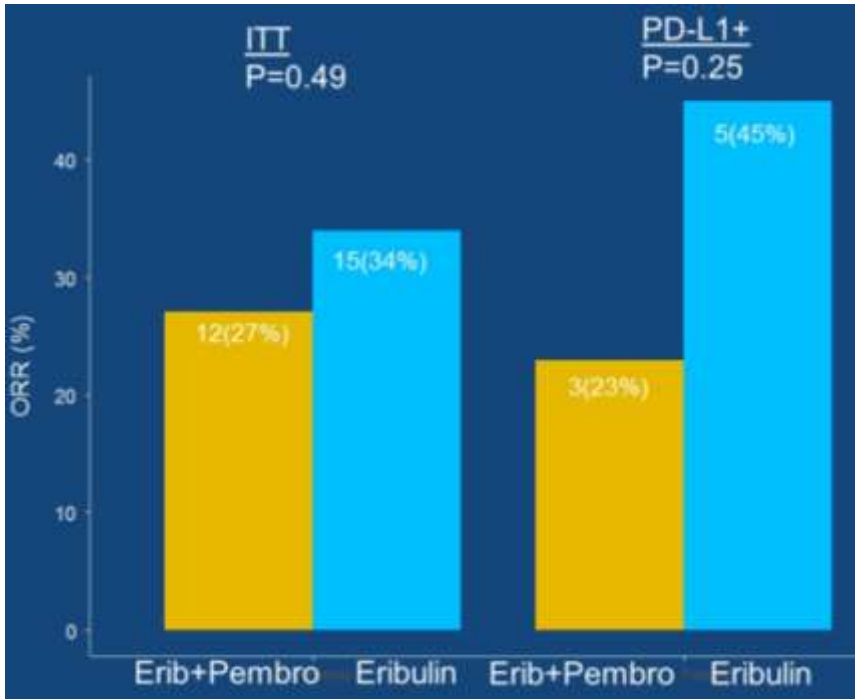
Pembrolizumab 200 mg IV
- On day 1 of 21-day cycle

Biopsy at time of progression

*Serial blood collected for ctDNA and PBMCs and stool collected for microbiome analyses

NCT03051659





Response (RECIST 1.1)	Eribulin + Pembrolizumab	Eribulin
ITT population		
PR	27%	34%
SD	43%	36%
SD>24 wks	20%	16%
CBR (PR +SD>24wks)	48%	50%
DOR, median (range)	1.5 (0-13.6)	2.1 (0.2-4.6)
PD-L1+ patients		
PR	23%	45%
SD	46%	45%
SD>24 wks	15%	18%
CBR (PR +SD>24wks)	39%	63%
DOR, median (range)	0.6 (0-1)	2.1 (1-4.6)

ITT Population: Prior Cancer Therapy

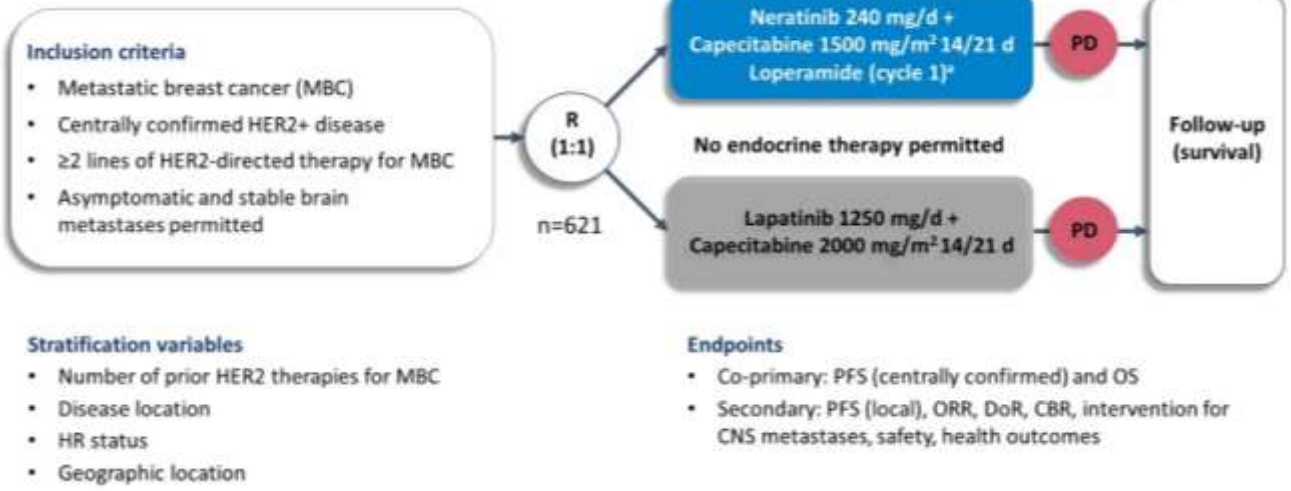
	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
Settings of prior therapy		
Adjuvant and/or neoadjuvant	**158 (59%)**	**145 (54%)**
Metastatic only	108 (41%)	125 (46%)
Prior metastatic lines of therapy		
≤2	175 (66%)	180 (67%)
>2	91 (34%)	90 (33%)
Prior anti-HER2 therapy		
Trastuzumab	**266 (100%)**	**270 (100%)**
Pertuzumab	**266 (100%)**	**269 (100%)**
T-DM1	**242 (91%)**	**247 (92%)**
Lapatinib	41 (15%)	39 (14%)
Other HER2	6 (2%)	6 (2%)
Prior chemotherapy		
Taxane	252 (95%)	249 (92%)
Anthracycline	118 (44%)	110 (41%)
Platinum	34 (13%)	40 (15%)
Prior endocrine therapy	126 (47%)	133 (49%)

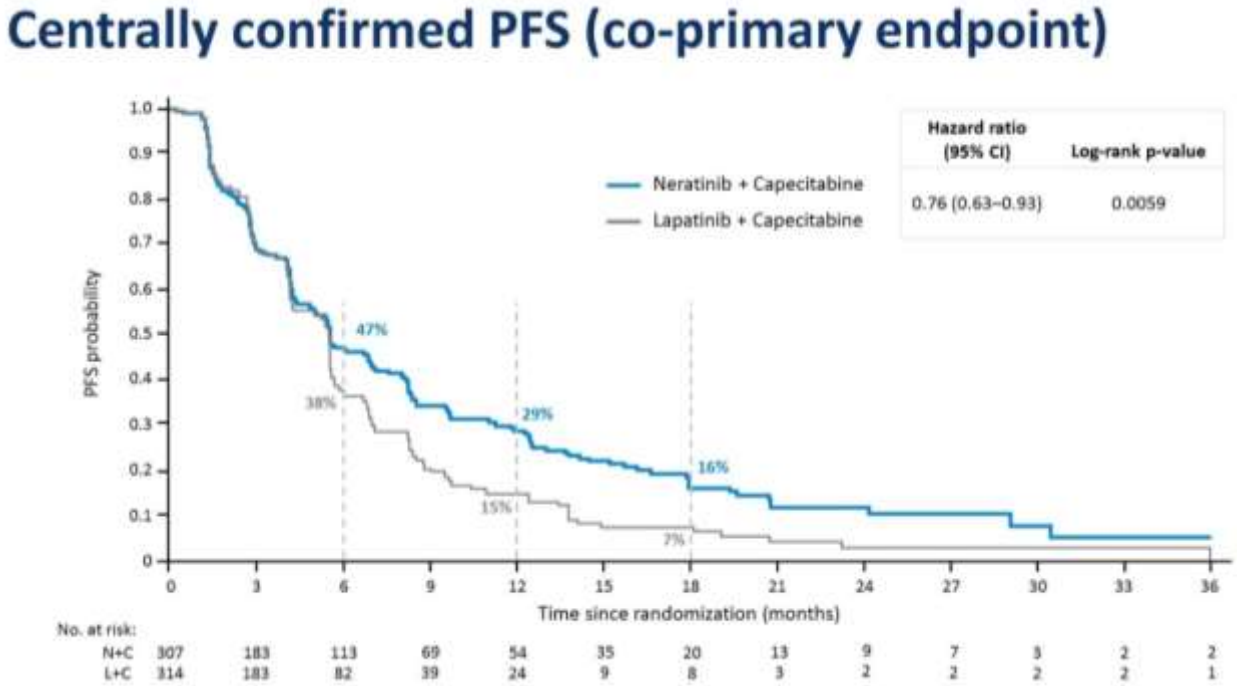
Treatment arms overall balanced

ITT population: N=536.

Presented By Hope Rugo at 2019 ASCO Annual Meeting

NALA, phase III trial



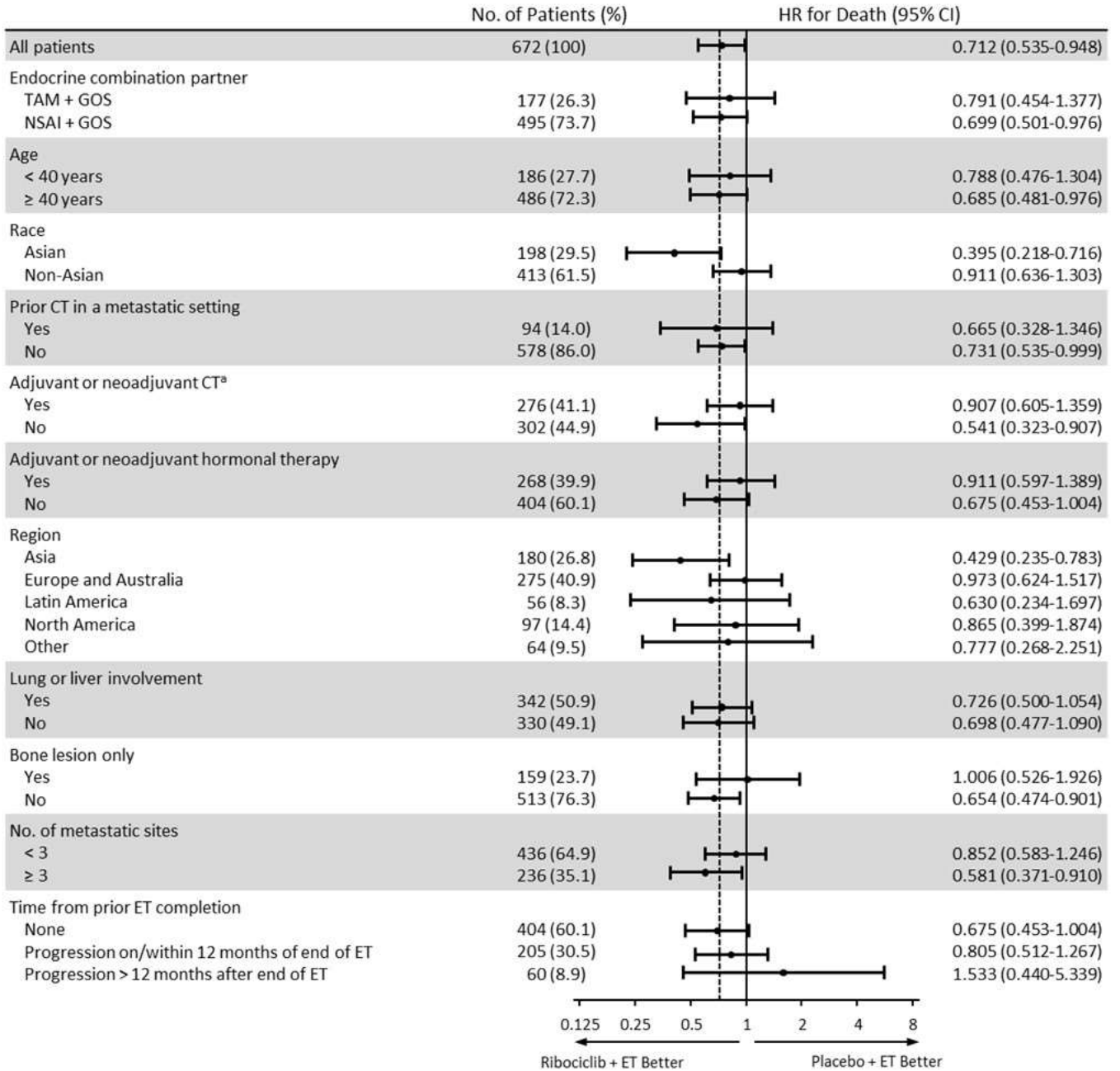


- Time to intervention for CNS metastasis with N+C (cumulative incidence 22.8% vs 29.0% p=0.043
- 24% G3 diarrhea

Saura C, ASCO 2019

Overall Survival Subgroup Analysis

- Consistent OS benefit seen within subgroups



[a] In patients with no prior chemotherapy in the metastatic setting.

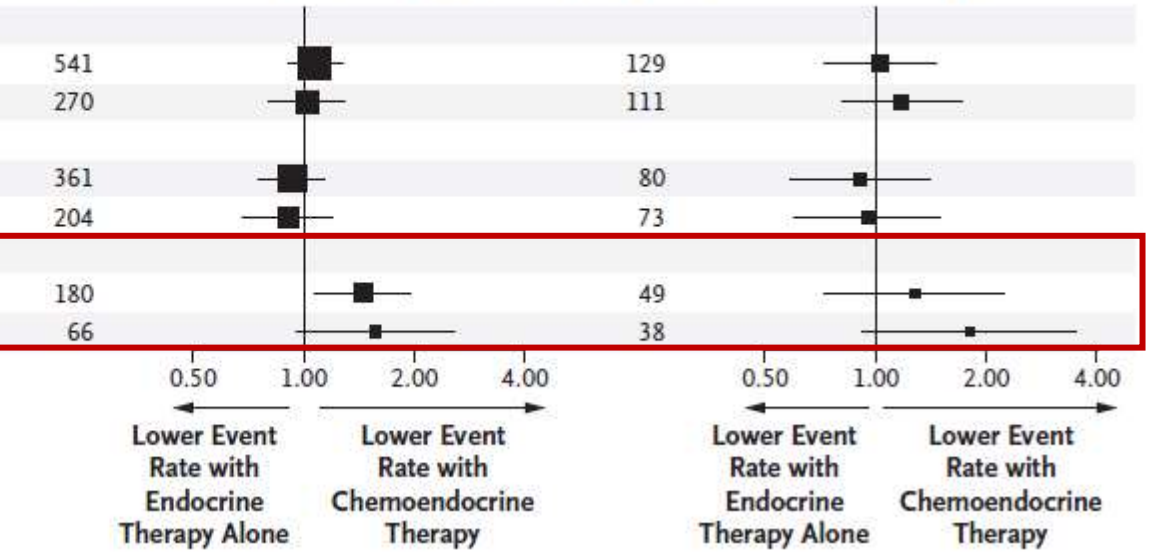
Hurvitz S, ASCO 2019, Im SA, NEJM 2019

Effect of clinical risk on prediction of CT benefit

RS 11-25

A

Subgroup	No. of Patients	No. of Events	Hazard Ratio for Recurrence, Second Primary Cancer, or Death (95% CI)	No. of Distant Recurrences	Hazard Ratio for Distant Recurrence (95% CI)
All patients					
Low clinical risk	4799	541		129	
High clinical risk	1697	270		111	
>50 Yr of age					
Low clinical risk	3173	361		80	
High clinical risk	1180	204		73	
≤50 Yr of age					
Low clinical risk	1626	180		49	
High clinical risk	517	66		38	



Sparano J, ASCO 2019 & NEJM 2019