Breast Cancer: Poster Review

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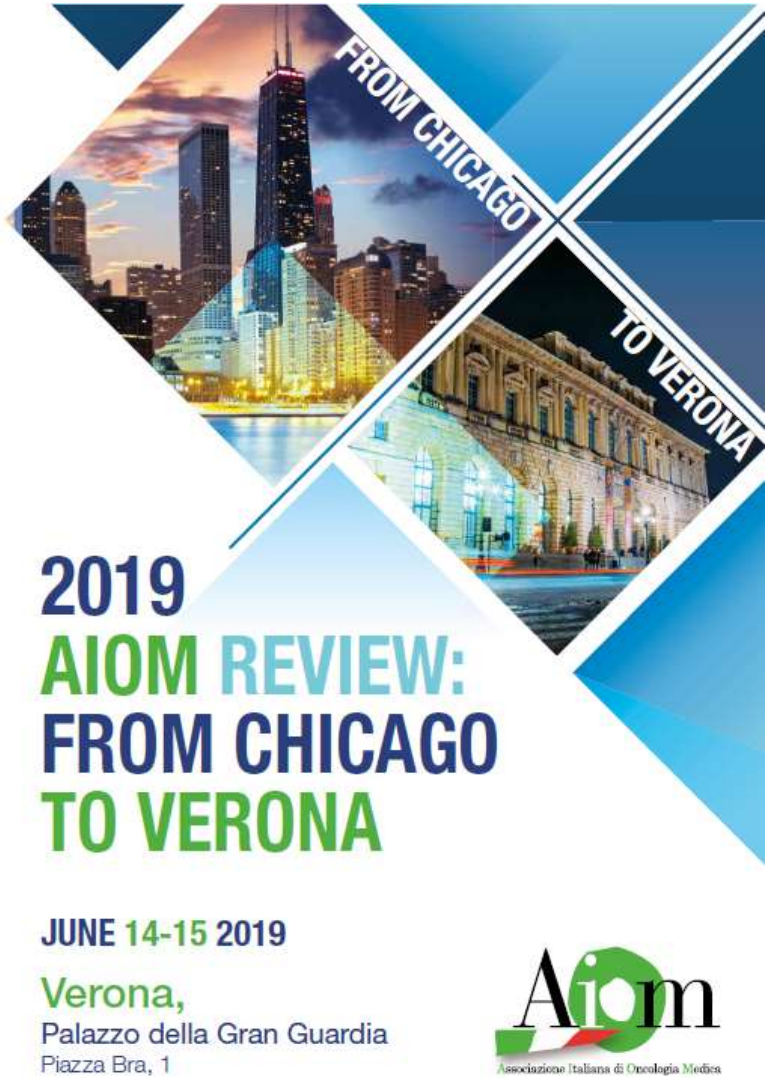
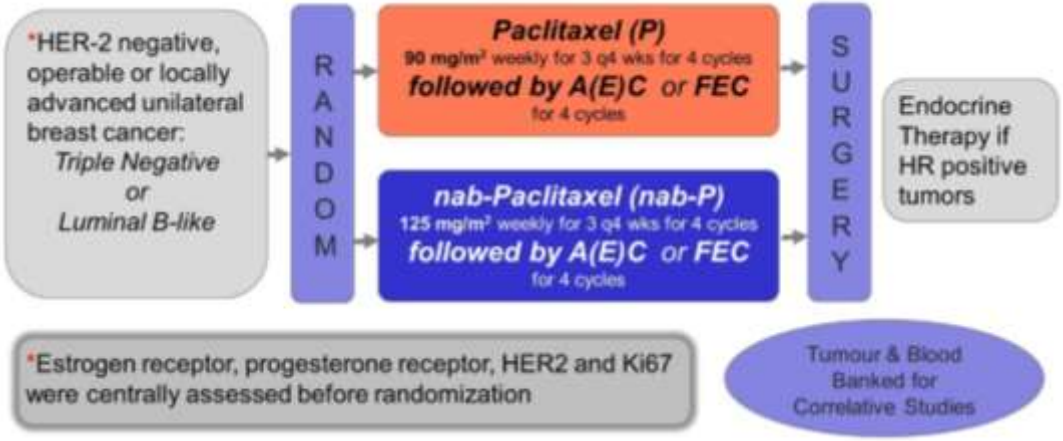


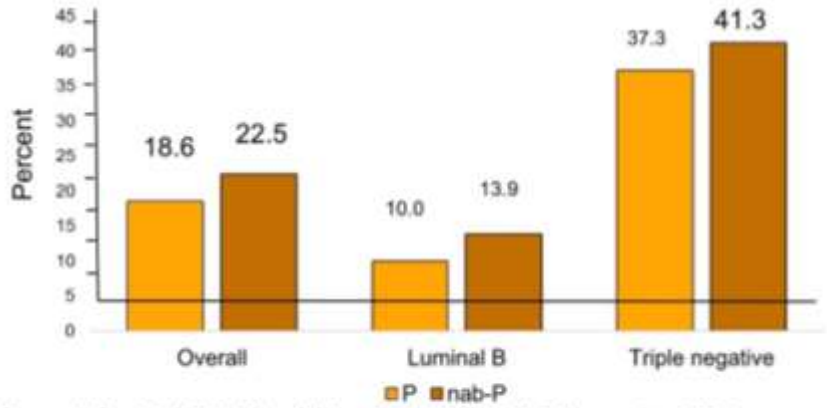
Chemotherapy optimization in the neoadjuvant setting

ETNA (Gianni et al, abstract 515)

Study design



Primary endpoint: pCR rate

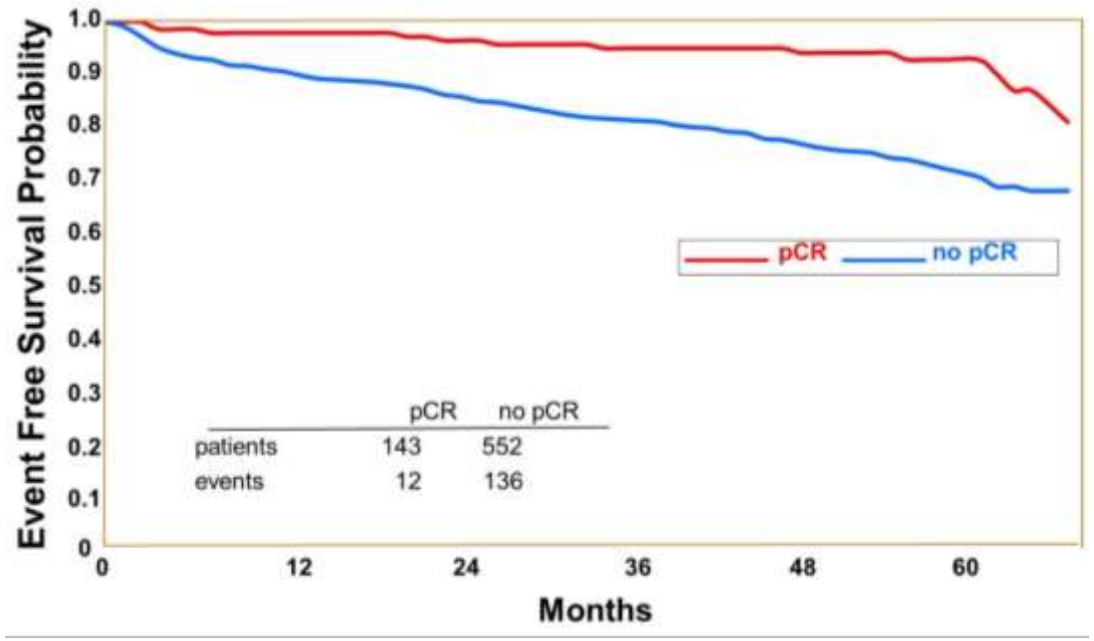


Overall: P vs *nab*-P -3.9 (-9.9-2.1); Odds ratio: 0.77 (0.52-1.13); p value 0.186
Cochran-Mantel-Haenszel test, controlling for tumor subtype and disease stage and quantified by OR and rate difference

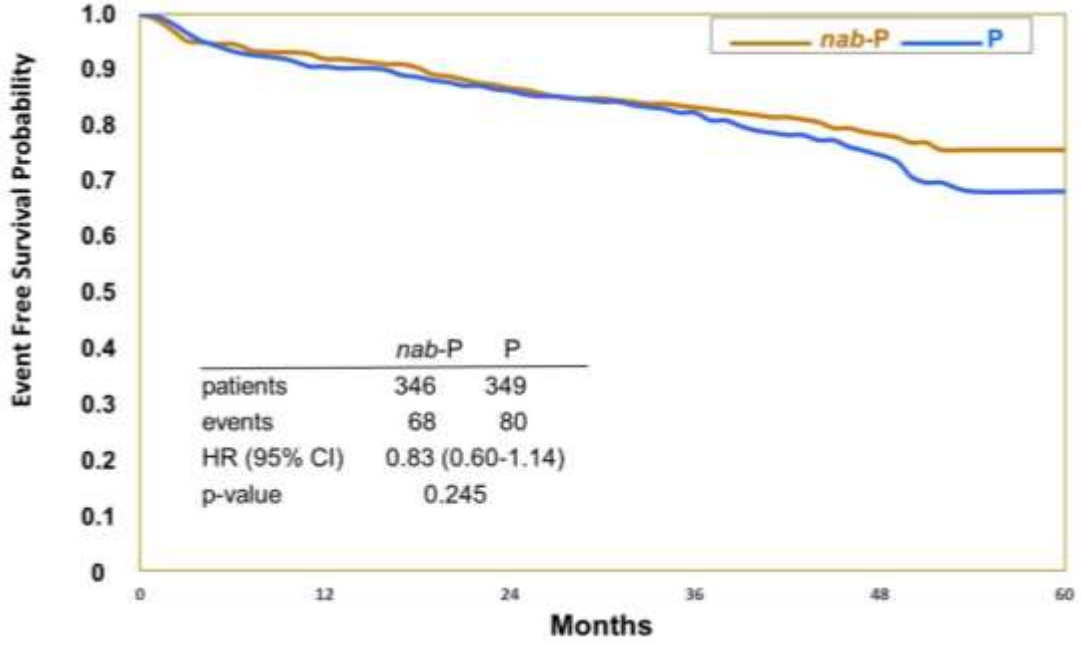
Gianni L et al, JAMA Oncol. 2018

ETNA (Gianni et al, abstract 515)

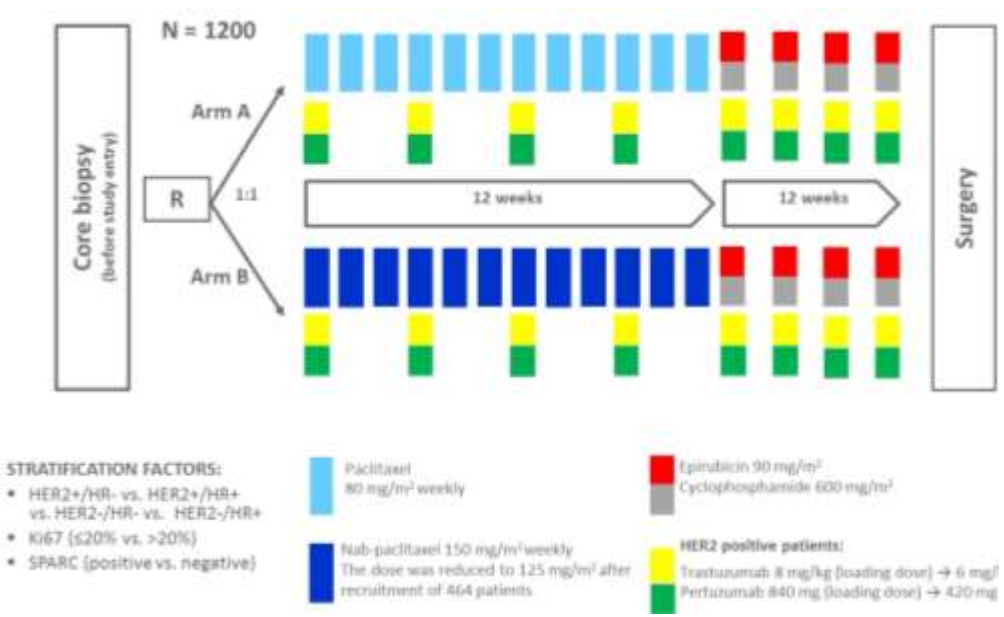
EFS by pCR (ITT)

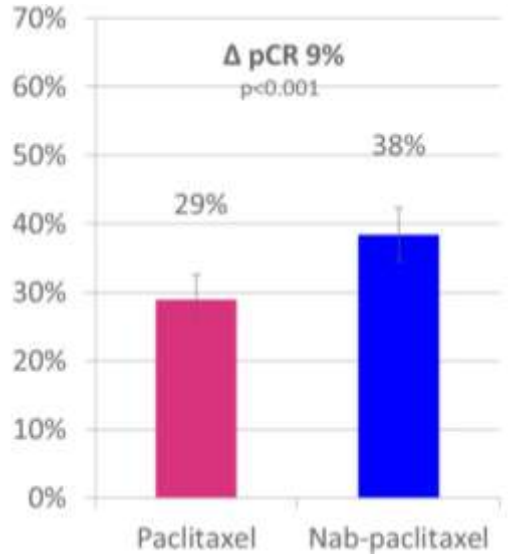


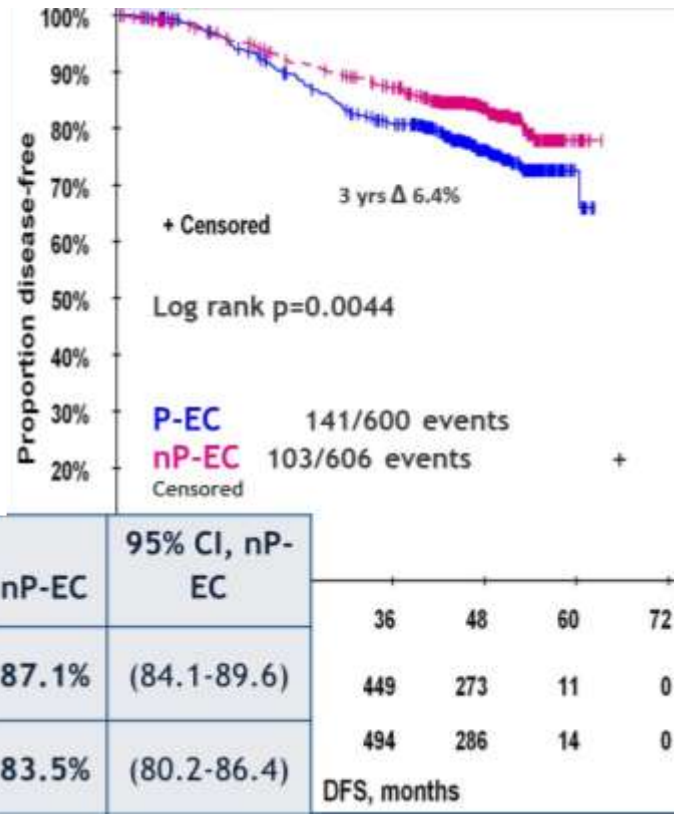
EFS by study arm (ITT)



GeparSepto study





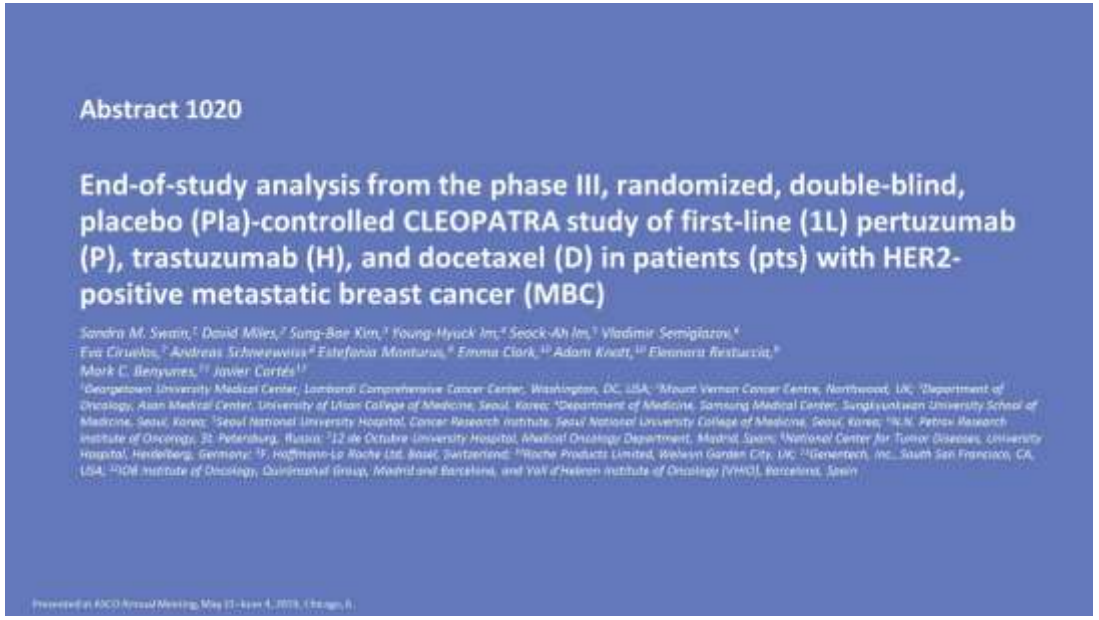


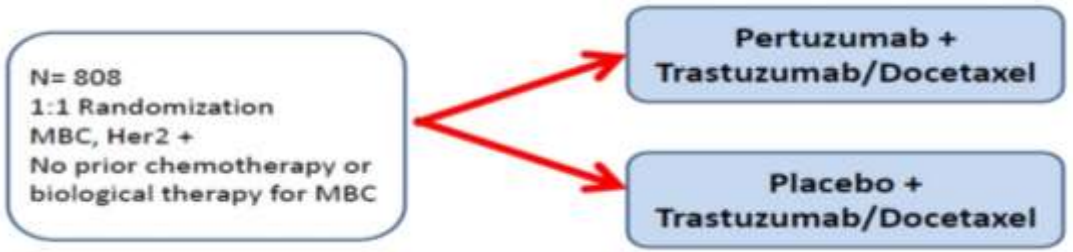
Time	P-EC	95% CI, P-EC	nP-EC	95% CI, nP-EC
3 yrs	80.7%	(77.2-83.7)	87.1%	(84.1-89.6)
4 yrs	76.2%	(72.3-79.5)	83.5%	(80.2-86.4)

Untch et al, Lancet Oncol 2016; Untch et al JCO 2019

Metastatic HER2+ Breast Cancer

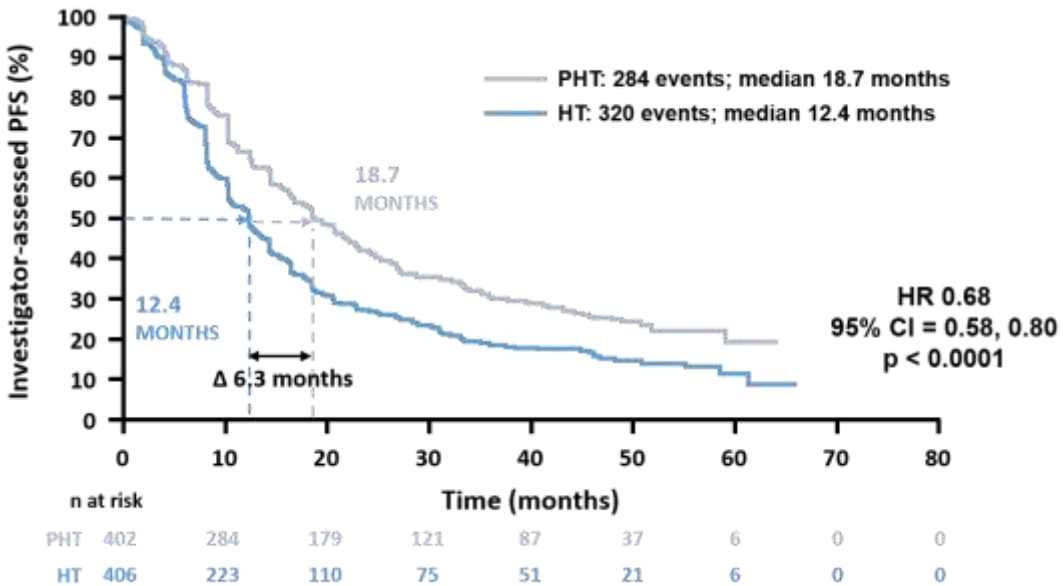
Cleopatra trial (Swain SM et al, abstract 1020)



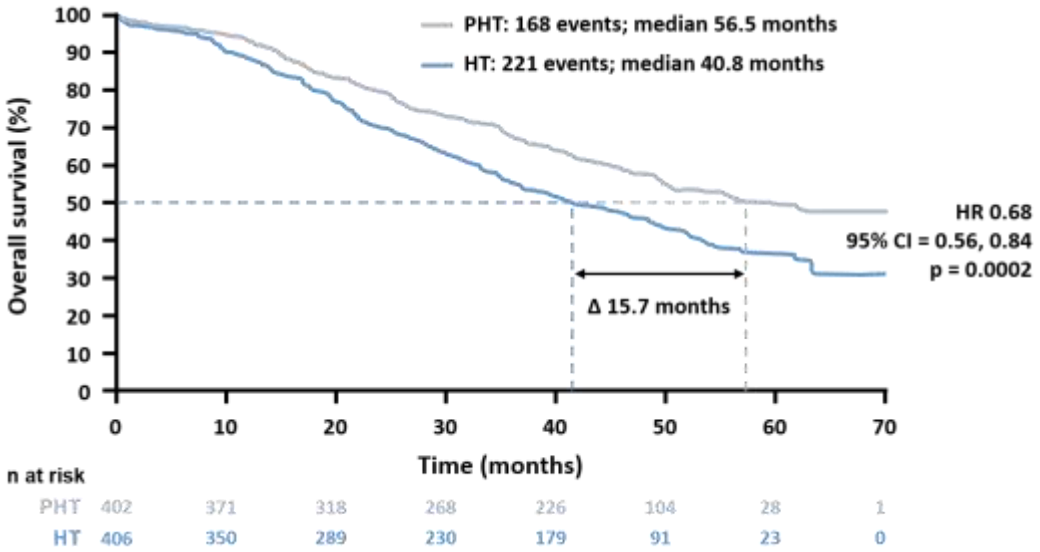


Cleopatra trial: Outcome results

PFS

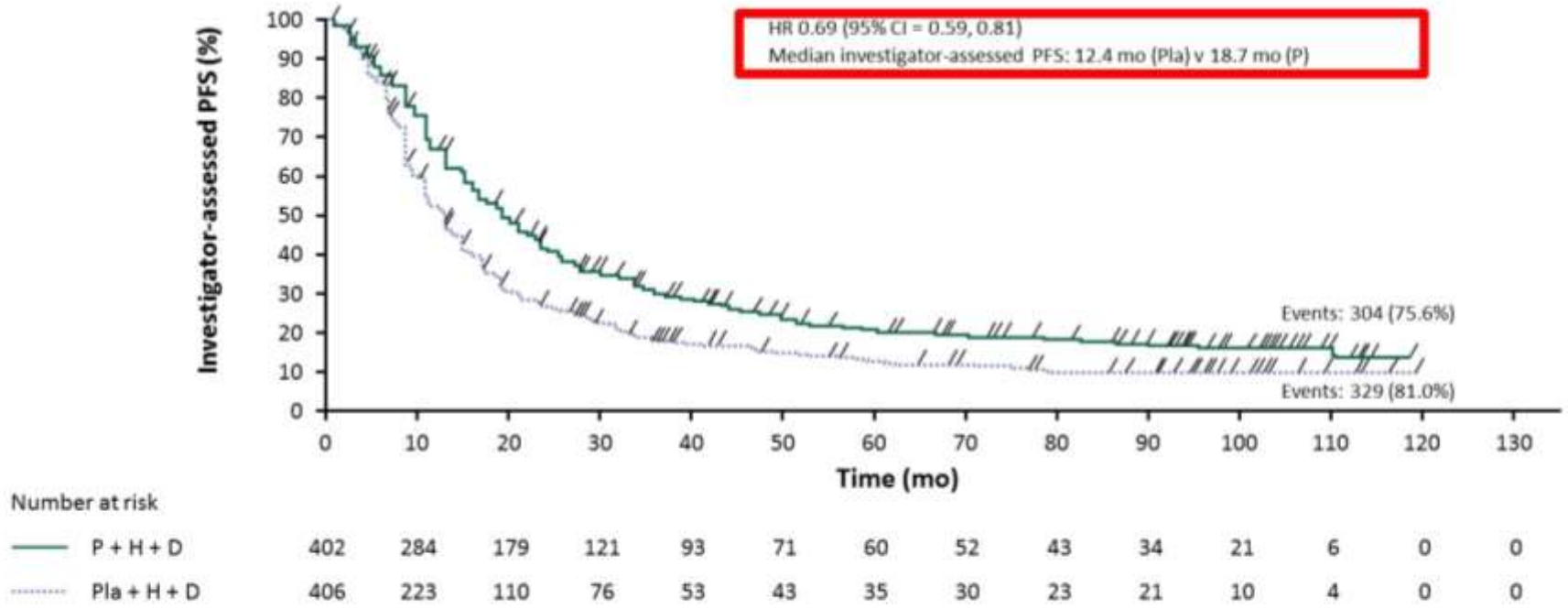


OS



Swain et al N Engl J Med. 2015

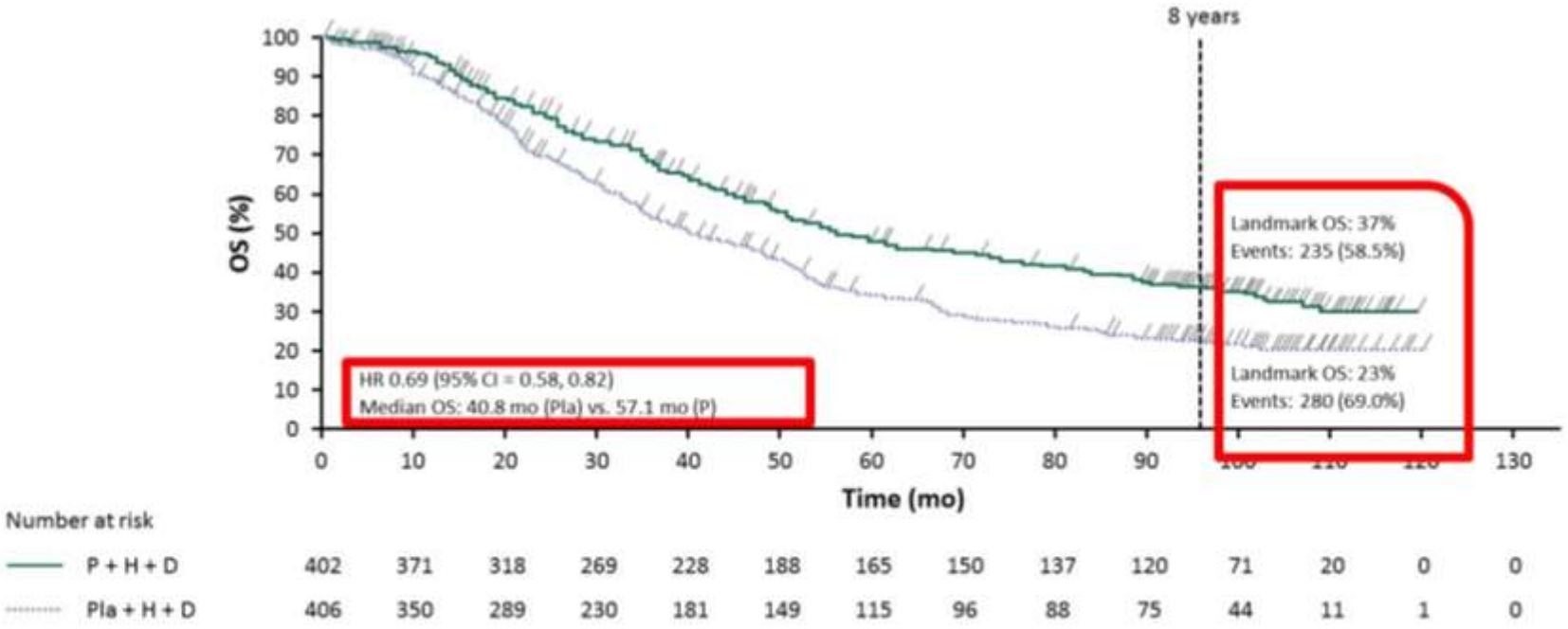
CLEOPATRA: End-of-study investigator-assessed PFS



* Crossover pts were analyzed in the Pla arm.
CI, confidence interval; D, docetaxel; H, trastuzumab; HR, hazard ratio; ITT, intention-to-treat; P, pertuzumab; PFS, progression-free survival; Pla, placebo; pts, patients.

Swain SM et al, abstract 1020 ASCO 2019

CLEOPATRA: End-of-study OS in the ITT population



* Crossover pts were analyzed in the Pla arm.
OS was compared between arms using the log-rank test, stratified by prior treatment status and geographic region. The Kaplan–Meier approach was used to estimate median OS, and a stratified Cox proportional hazards model was used to estimate the HR and 95% CIs.
CI, confidence interval; D, docetaxel; H, trastuzumab; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; P, pertuzumab; Pla, placebo.

Swain SM et al, abstract 1020 ASCO 2019

CLEOPATRA: Key safety

Pts, n (%)	Pre-crossover (safety population)		Crossover population
	P + H + D (n = 408)	Pla + H + D (n = 396)	P + H + D (n = 50)
Diarrhea	280 (68.6)	191 (48.2)	25 (50.0)
Grade ≥3	40 (9.8)	20 (5.1)	1 (2.0)
Rash	213 (52.2)	155 (39.1)	18 (36.0)
Grade ≥3	15 (3.7)	6 (1.5)	0
Symptomatic LVD as assessed by the investigator	6 (1.5)	7 (1.8)	1 (2.0)*
NYHA Functional Classification III/IV	4 (1.0)	4 (1.0)	1 (2.0)*
LVD (PT)	32 (7.8)	34 (8.6)	3 (6.0)
Grade ≥3	6 (1.5)	13 (3.3)	2 (4.0)*
SAE suggestive of CHF	8 (2.0)†	8 (2.0)	1 (2.0)*
Grade ≥3	7 (1.7)†	7 (1.8)	1 (2.0)*
LVEF decline ≥10% points from baseline to <50%, n/N (%)‡	28/394 (7.1)	28/378 (7.4)	3/49 (6.1)

* Onset ~46 mo after crossing to the P arm; resolution in 34 days; pt discontinued study medication.
† For the one pt with an event in this category since the previous analysis,[1] onset was ~77 mo on treatment in the P arm: resolution in 34 days; pt continued on study medication. ‡ N represents pts with both a baseline LVEF assessment and ≥1 post-baseline assessment.
CHF, congestive heart failure; D, docetaxel; H, trastuzumab; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; P, pertuzumab; Pla, placebo; pt, patient; PT, preferred term; SAE, serious adverse event.

Swain SM et al, abstract 1020 ASCO 2019

Metastatic Luminal Breast Cancer: CDK4/6 inhibitors and beyond

Combination of CDK4/6i + ET improves outcome

Study/Arms	[1]Paloma 1	[2]Paloma 2	[3]Monaleesa 2	[4]Monarch 3	[5]MONALEESA-7	[6]Paloma 3	[7]Monarch 2	[8]MONALEESA-3
Phase	2	3	3	3	3	3	3	3
CDK4/6i ET partner	Palbo AI	Palbo AI	Ribo AI	Abema AI	Ribo AI/Tam + OS	Palbo Fulvestrant	Abema Fulvestrant	Ribo Fulvestrant
N	165	666	668	493	642	521	669	726
Median PFS (months) Placebo	10.2	14.5	16	14.7	13.0	4.6	9.3	12.8
Median PFS (months) CDK 4/6i	20.2	27.6	25.3	28.1	23.8	11.2	16.4	20.5
HR 95% CI	0.48 0.31-0.74	0.56 0.46-0.69	0.54 0.41-0.69	0.55 0.44-0.69	0.55 0.44-0.69	0.50 0.40-0.62	0.553 0.45-0.68	0.593 0.480-0.732
P value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

[1]Finn R, et al. Lancet Oncol. 2015; 16:25-35; [2]Rugo H, et al, et al. SABCS. 2017; [3]Hortobagyi GN, et al. ASCO; [4]Goetz MP, et al. J Clin Oncol. 2017 Nov 10;35(32):3638-3646; [5]Tripathy D, et al. Lancet Oncol. 2018 Jul;19(7):904-915. [6]Turner NC, et al. N Engl J Med. 2015;373:209-219; [7]Sledge GW, et al. JCO. 2017;35:2875-2884; [8]Slamon DJ, et al. J Clin Oncol. 2018 Aug 20;36(24):2465-2472.

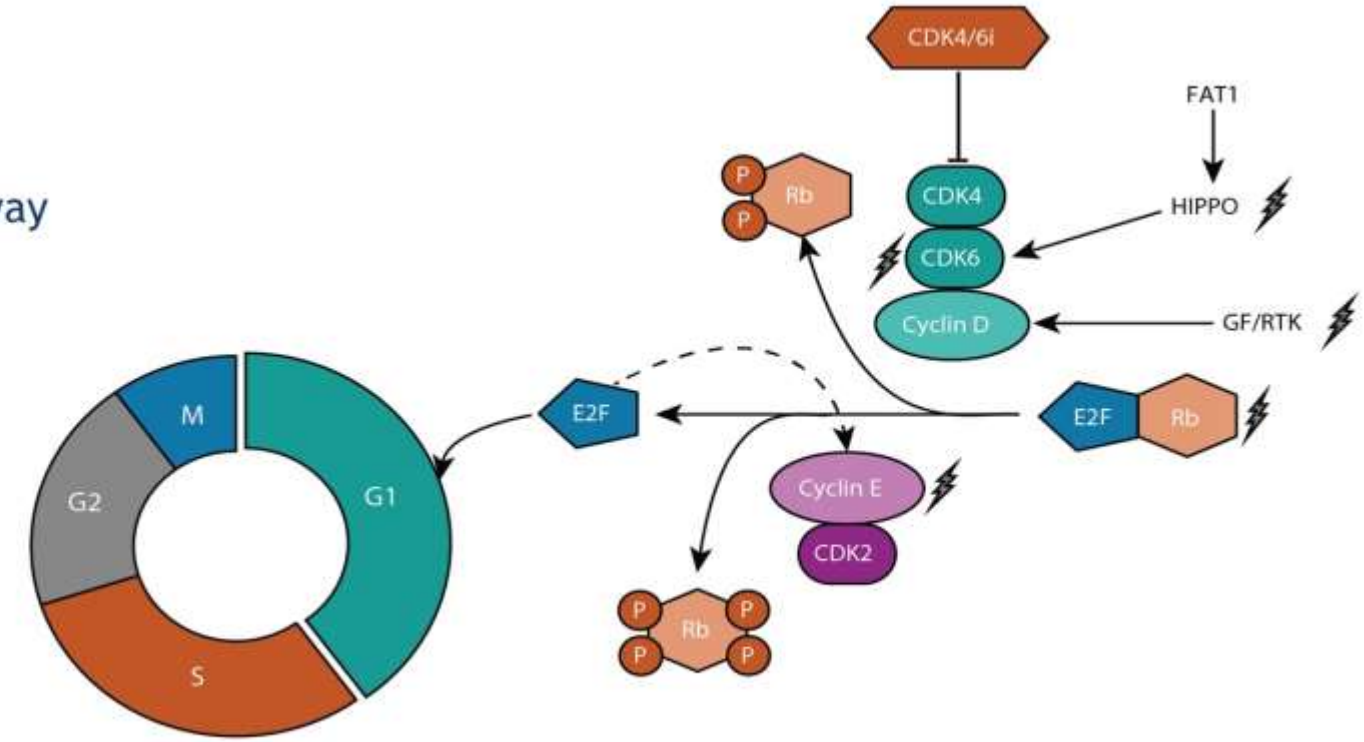
Multiple potential mechanisms of resistance to CDK4/6i

De Novo

- Rb1 Loss
- FAT1 loss via Hippo pathway
- High CCNE1 mRNA
- FGFR1 amplification

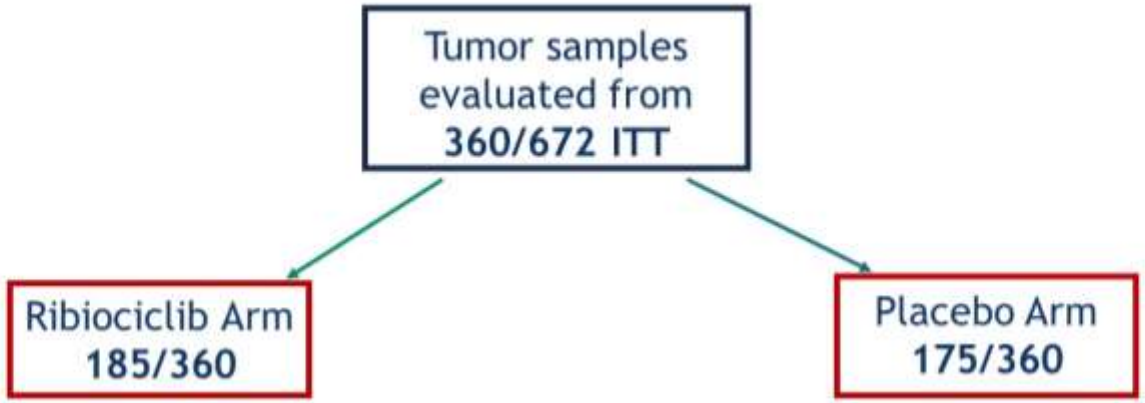
Acquired

- Rb1 loss
- Majority: unknown
- ERBB2 mutation
- PTEN loss of function mutations



Turner et al JCO 2019; Chandarlapaty and Razavi, JCO 2019; Razavi et al Cancer Cell 2018; O'Leary et al. Cancer Discovery 2018; Li et al., 2018, Cancer Cell 34, 893-905; Razavi et al ASCO 2019; [1]Finn et al., Lancet Oncol 2015; 16:25-35; [2]Cristofanilli et al., Lancet Oncol 2016; 17: 425 39; [3]Fribbens et al., JCO 2016; 34: 2961; [4]Finn et al., ESMO 2016; [5]Hortobagyi et al. Ann Onc 2018; Formisano et al Nat Commun 2019; Hortobagyi et al SABCS 2017

MONALEESA-7: Gene Expression Analysis using mRNA from Archival Tumor (Yen-Shen Lu et al. Abstract 1018)



- Customized NanoString nCounter® GX 800-gene panel containing genes related to breast cancer, profileration, cell cycle and RTK pathways
- **75% samples from primary tumor**
- Using Median expression as cut off: Patients classified as LOW vs HIGH
- **PFS benefit**: defined by Hazard ratio

MONALEESA-7: Gene Expression Analysis Results

PFS benefit with Ribociclib was similar in the low and high gene expression subgroups and ITT population

- Trend towards PFS benefit with Ribociclib with high CCND1, IGF1R and ERBB3
- Stronger trend towards PFS benefit with Ribociclib with low CCNE1 and MYC
- Trend towards similar PFS benefit with ribociclib regardless of low or high expression of ESR1, MKI67 and FGFR1

Phase II Abemaciclib in ER+ BC with Brain Mets (BM) (Anders et al, abstract 1017)

	N=58
Age (yrs), median (range)	55 (30, 79)
Female, n (%)	57 (98.3)
Race, n*a	43
Asian, n (%)	3 (5.2)
African American, n (%)	4 (6.9)
White, n (%)	35 (60.3)
Multiple, n (%)	1 (1.7)
Prior systemic therapy (N=52), median (range)	4.0 (1-11)
Prior systemic therapy in the metastatic setting, n (%)	51 (87.9)
Prior chemotherapy in the metastatic setting, n (%)	44 (75.9)
Median time from radiation to therapy, days	283.0
Prior radiotherapy to IC target lesion	
SRS, WBRT, or both	34 (58.6)
SRS-treated, n (%)	20 (34.5)
WBRT, n (%)	27 (46.6)
Surgical resection, n (%)	4 (6.9)
No prior SRS or WBRT, n (%)	24 (41.4)
Disease stage at initial diagnosis, n*a	52
0, 1, n (%)	7 (12.1)
II, III, n (%)	35 (60.3)
IV, n (%)	10 (17.2)

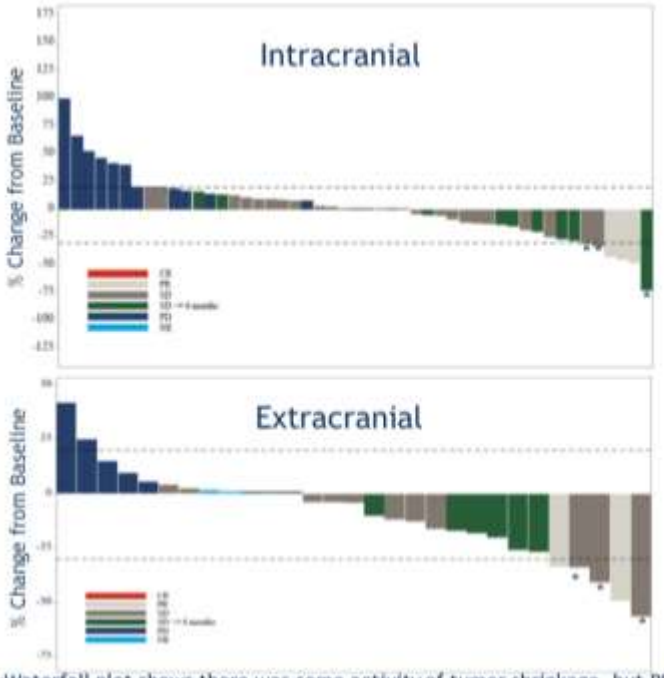
Key Eligibility

- CDK 4/6 naive patients
- ≥1 new/not previously irradiated measurable BM≥10mm or progressive previously irradiated BM

Primary Endpoint: OIRR

Abemaciclib in ER+ BC with BM: Results

Change in tumor size



Waterfall plot shows there was some activity of tumor shrinkage, but PR was not confirmed by subsequent tumor assessments.

Best overall response

	BOIRR[a]			BOERR[b]	
n, (%)	ALL N=58	EVAL N=52		ALL N=58	EVAL N=50
cOIRR[c]	3 (5)	3 (6)	cOERR[c]	2 (3)	2 (4)
IDCR	38 (66)	37 (71)	EDCR	30 (60)	30 (60)
ICBR	14 (24)	13 (25)	ECBR	12 (21)	12 (24)
CR	0 (0)	0 (0)	CR	0 (0)	0 (0)
PR	3 (5)	3 (6)	PR	2 (3)	2 (4)
SD	35 (60)	34 (65)	SD	28 (48)	28 (56)
SD ≥ 6 mo	11 (19)	10 (19)	SD ≥ 6 mo	10 (17)	10 (20)
PD	15 (26)	15 (29)	PD	9 (16)	9 (18)
OPD	13 (22)	13 (25)	OPD	9 (16)	9 (18)
CPD	2 (3)	2 (4)	CPD	0 (0)	0 (0)
NE	5 (9)	0 (0)	NE	19 (33)	11 (22)

Median treatment duration, 3.1 months (0.5, 35.4)

PFS

PFS (in months)	N=58
Bi-Compartmental PFS	
Number of events, n (%)	54 (93.1)
mPFS, median (95% CI)	4.4 (2.6, 5.5)
Intracranial PFS	
Number of events, n (%)	53 (91.4)
mPFS, median (95% CI)	4.9 (2.9, 5.6)
Extracranial PFS	
Number of events, n (%)	36 (62.1)
mPFS, median (95% CI)	6.6 (4.3, 12.4)

- ✓ Negative for primary endpoint: OIRR 6% (predicted > 11%)
- ✓ 38% had some tumor shrinkage and ICBR was 25%
- ✓ 41% had no prior SRS or WBRT. Of these 29% had SD>6 months

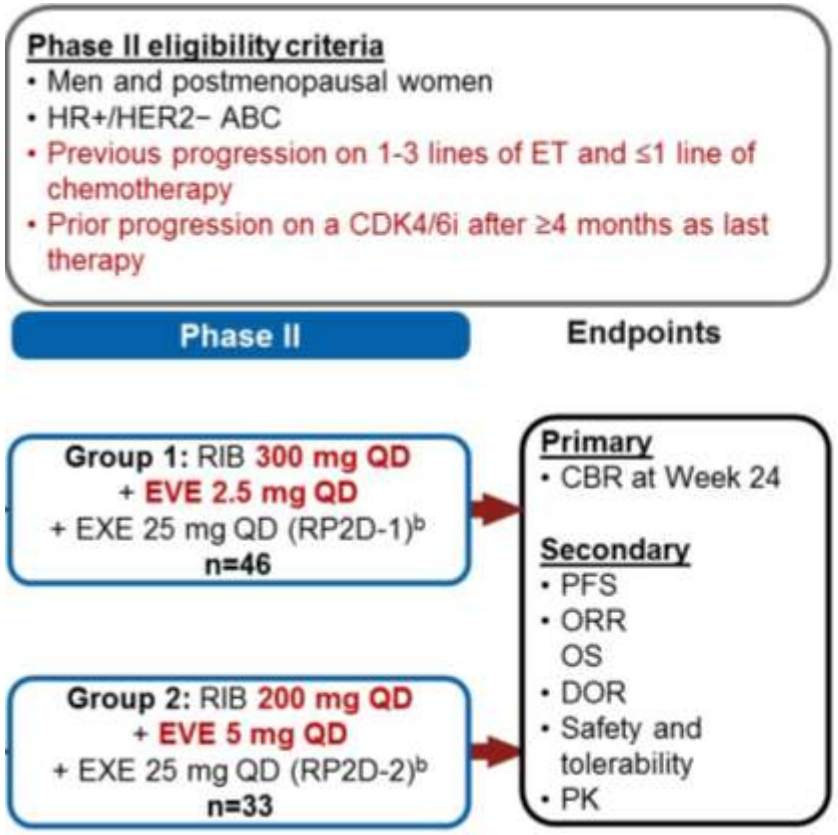
Treatment paradigm after progression on CDK4/6i

Current treatment options in second-line setting that «predate» CDK4/6i era:

- Fulvestrant (if not used in first-line)
- AI
- Everolimus+exemestane
- Chemotherapy
- Clinical trials
- Hopefully soon alpelisib for PIK3CA mut

Di Leo et al, JNCI 2014. Baselga et al, NEJM 2012. Yardley et al Adv Ther 2013. Bachelot et al JCO 2012. Kornblum et al JCO 2018. Bardia et al ASCO 2018. Dhakal et al ASCO 2018. Cook et al ASCO 2019. Andre et al NEJM 2019.

TRINITI-1 trial (Bardia et al, abstract 1016)



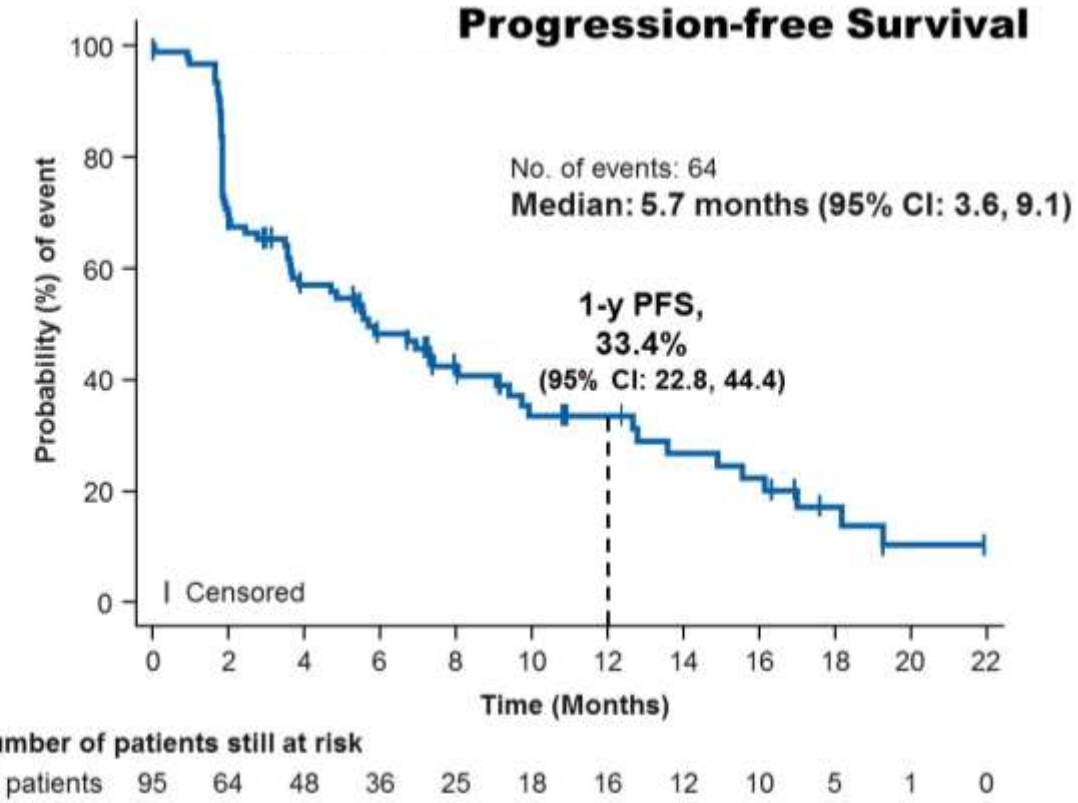
- **Primary endpoint**: CBR at Week 24 with predefined primary endpoint threshold of >10%
- **95/104** patients were post-CDK4/6i progression[c]
- Data cut-off: October 24, 2018
  - Average follow-up: 5.3 months, with a maximum of 22 months

TRINITI-1: Results

Best Overall Response[a]

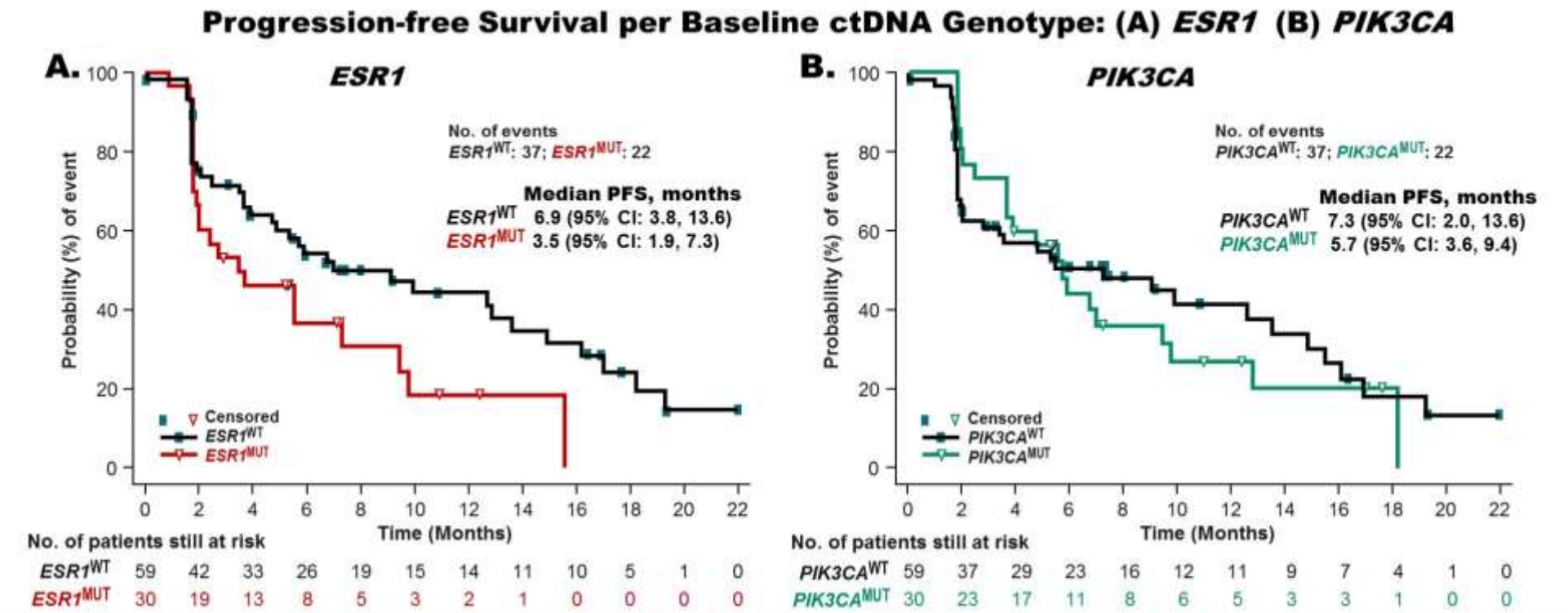
	Total Patients (N=95)
CBR at Week 24, n (%) (95% CI)[b]	**39 (41.1) (31.1, 51.6)**
DCR, n (%) (95% CI)[c]	58 (61.1) (50.5, 70.9)
ORR, n (%) (95% CI)[d]	**8 (8.4) (3.7, 15.9)**
DOR, median (95% CI), months[e]	5.6 (3.1, NE)
Best Overall Response, n (%)	
CR	1 (1.1)
PR	7 (7.4)
SD	47 (49.5)
PD	32 (33.7)
Non-CR/non-PD	3 (3.2)

[a] Local investigator assessment per RECIST 1.1. Patients with measurable disease at baseline: n=75; patients with only non-measurable disease at baseline: n=20. Five patients discontinued without post-baseline tumor evaluation. [b] CBR: patients with CR, PR, SD, or NCRNPD at Week 24. [c] DCR: patients with CR, PR, SD, or NCRNPD anytime during the study. [d] ORR: patients with CR or PR. [e] DOR: duration of ORR.



TRINITI-1: Biomarker Analysis

Patients with *ESR1* or *PIK3CA* mutation had numerically shorter median PFS vs those with WT



TRINITI-1 study

- Encouraging results
- Next step: RCTs CDK4/6i + ET + everolimus vs ET + everolimus
- Biomarker analyses are hypothesis generating and need validation
  - Shorter PFS in pts with cfDNA mutations could be a reflection of aggressive tumor/high tumor burden?
  - ESR1 mutants: choice of SERD as ET partner?
- Currently, CDK4/6i should not be used beyong progression outside of clinical trials

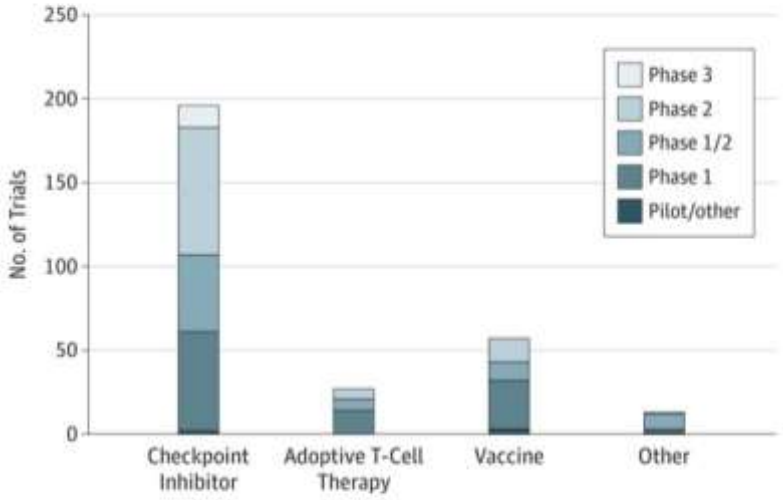
Immunotherapy in Breast Cancer

The immunotherapy landscape in breast cancer

- April 2018: review of ClinicalTrials.gov identified 293 actively accruing trials evaluating immunotherapeutic agents in breast cancer

- There is an urgent need to identify reliable biomarkers of response (and resistance) to immunotherapy in order to:
  - Select patients who will benefit from immunotherapy
  - Avoid unnecessary side effects
  - Avoid «financial toxicity»

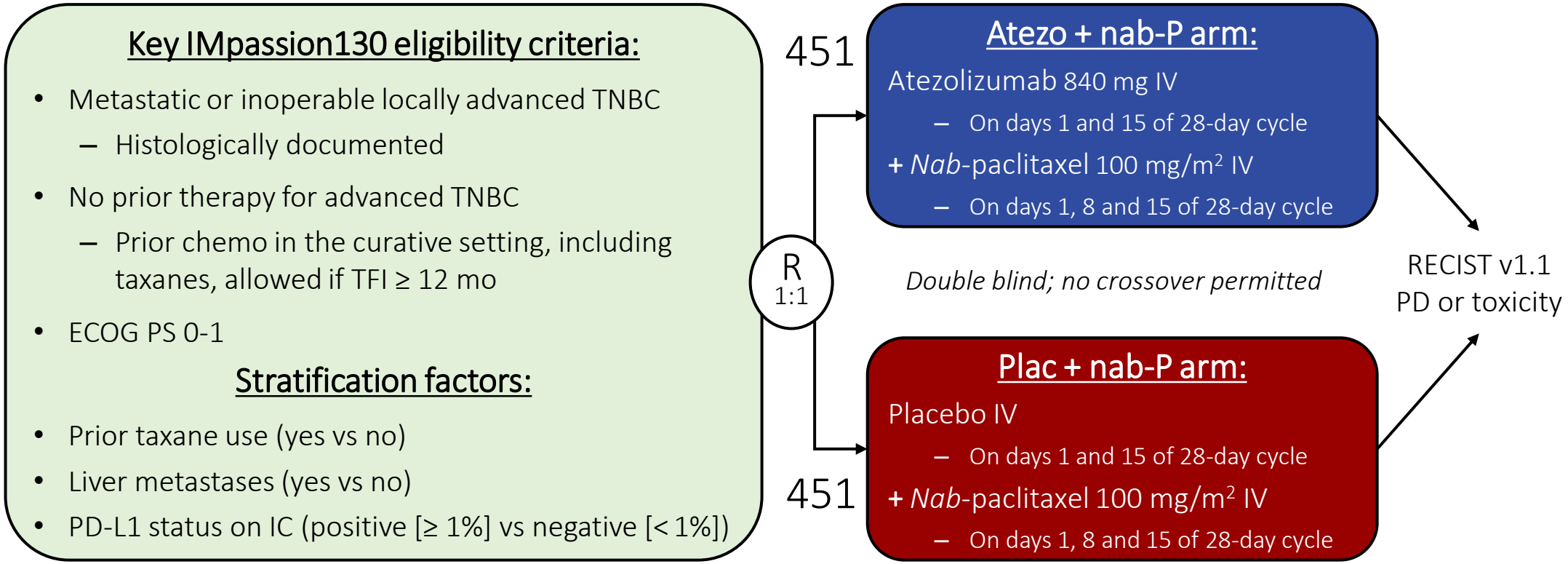
Figure 1. Breast Cancer Immunotherapy Trials by Type of Immunotherapeutic Agent or Strategy Being Investigated and by Study Phase



No. of trials	Checkpoint Inhibitor	Adoptive T-Cell Therapy	Vaccine	Other
Phase 3	13	0	0	0
Phase 2	76	6	14	1
Phase 1/2	46	7	11	9
Phase 1	59	14	29	2
Pilot/other	2	0	3	1

Adams S et al JAMA Oncol 2019

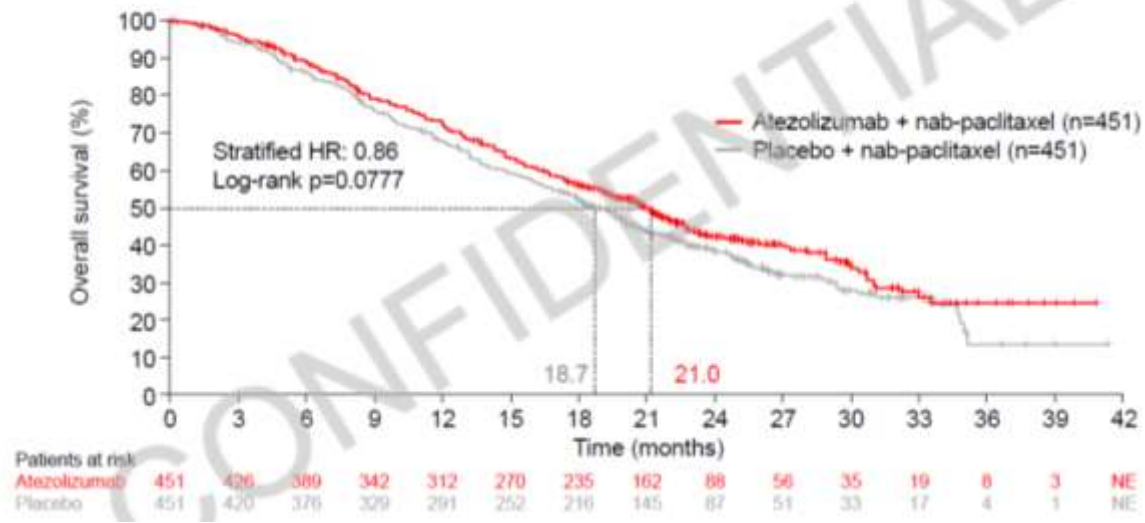
IMpassion130: study design



Schmid P NEJM 2018

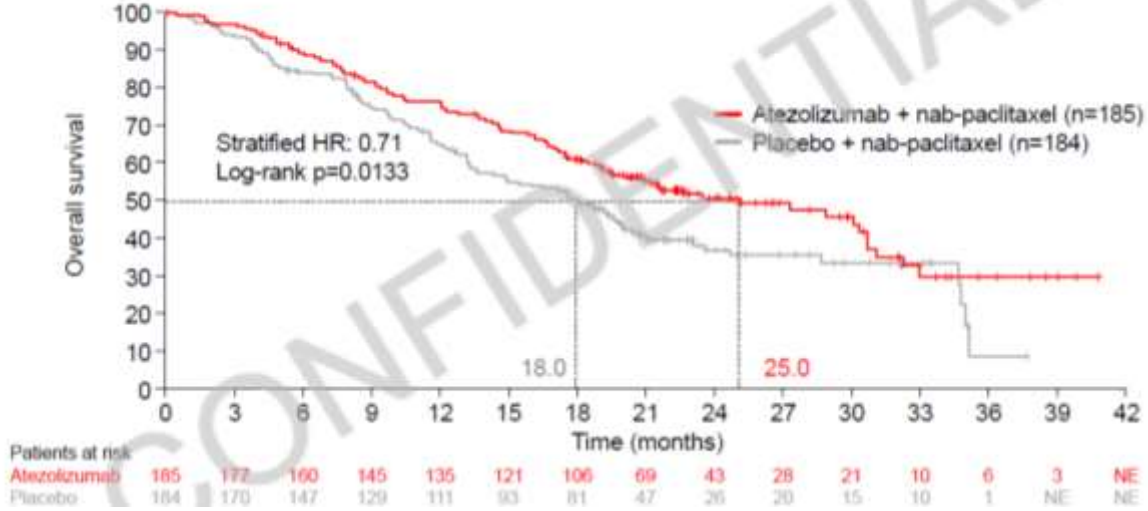
IMpassion130: Outcome results

OS in the ITT population (second interim)



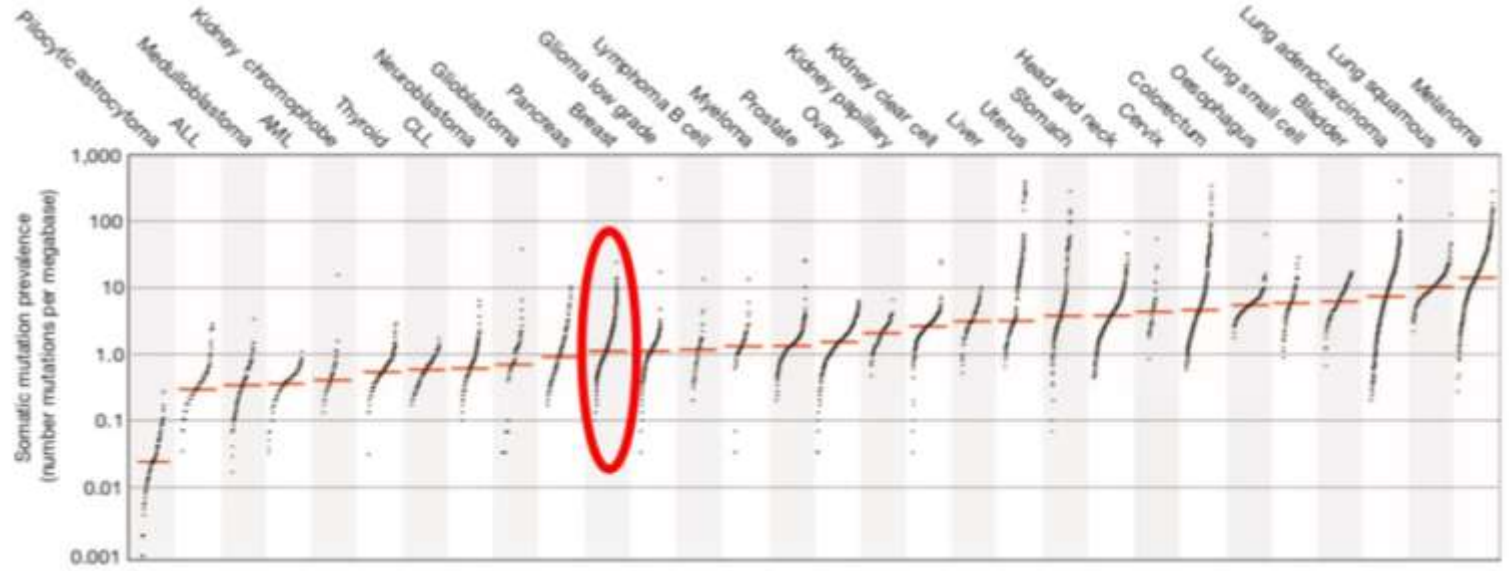
OS in the PD-L1+ population (second interim)

~ 40%



Schmid P ASCO 2019

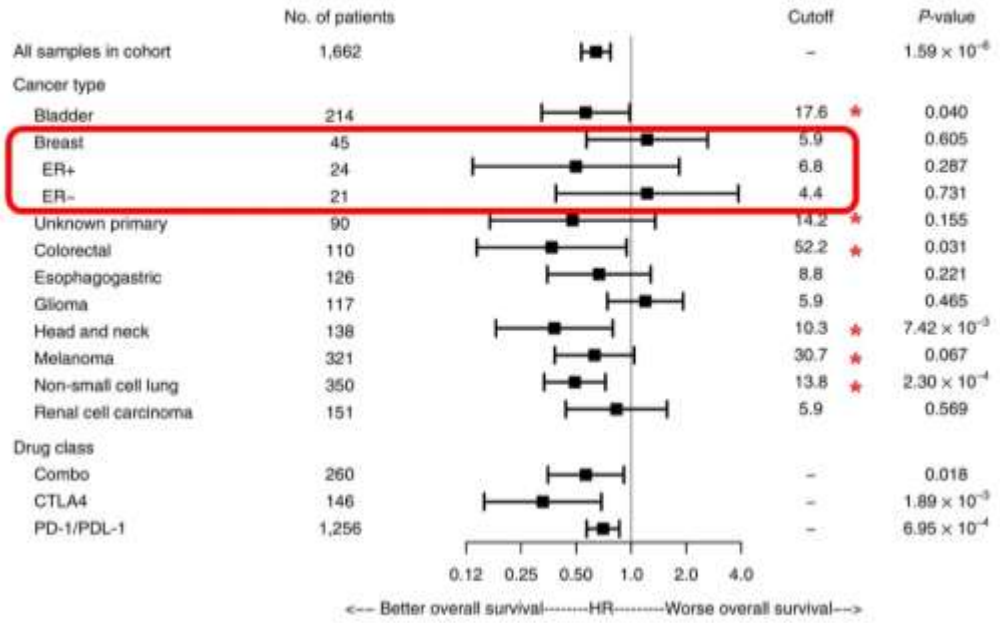
TMB across tumor types



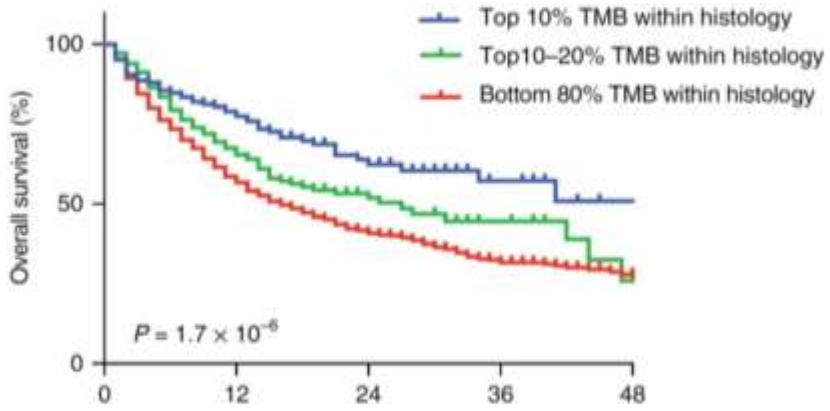
Alexandrov et al Nature 2013; Narang et al BMC Cancer 2019; Barroso-Sousa et al Proc ASCO 2018

TMB as an immunotherapy biomarker

There may not be *one universal definition* of high TMB



Effect of mutational load on overall survival after treatment with immune checkpoint inhibitors (ICI)



Tumors sequenced with targeted NGS (MSK-IMPACT)

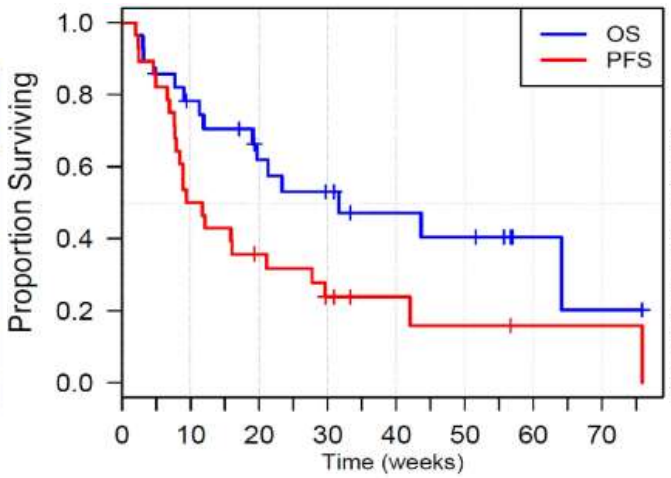
Samstein RM et al, Nat Genet 2018

Pembrolizumab in pts with MBC with reported high (>9 mut/mb) TMB: TAPUR study (Alva et al, abstract 1014)

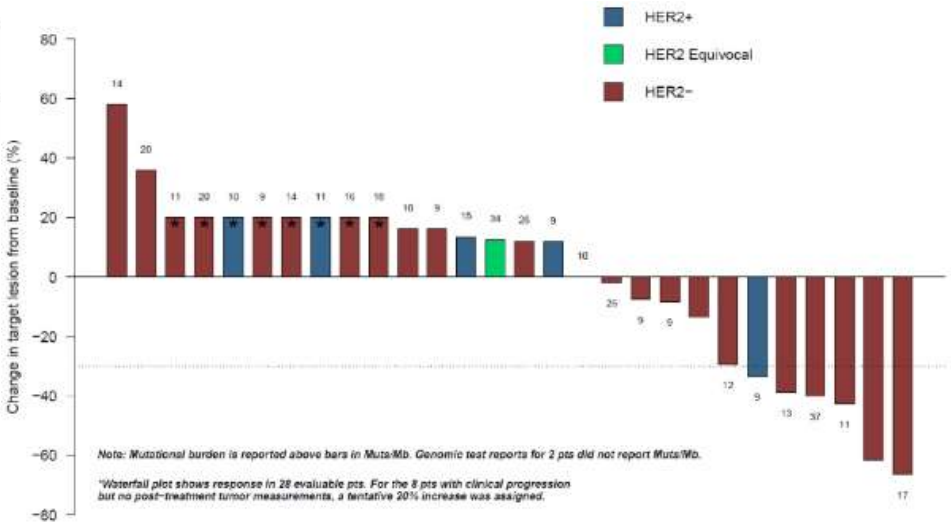
Clinical outcomes

Clinical Outcomes	
DC (OR or SD 16+wks) N (%), [90% CI]	10 (37%), [24%, 46%]
OR (CR or PR) N (%), [95% CI]	6 (21%), [8%, 41%]
mPFS, wks, (95% CI)	10.6 (7.7, 21.1)
mOS, wks, (95% CI)	31.6 (11.9, inf)

OS and PFS



Change in tumor size by HER2 status



Pembrolizumab in 28 pts with MBC with reported high (>9 mut/mb) TMB: TAPUR study (Alva et al, abstract 1014)

Clinical outcomes

Clinical Outcomes	
DC (OR or SD 16+wks) N (%), [90% CI]	10 (37%), [24%, 46%]
OR (CR or PR) N (%), [95% CI]	6 (21%), [8%, 41%]
mPFS, wks, (95% CI)	10.6 (7.7, 21.1)
mOS, wks, (95% CI)	31.6 (11.9, inf)

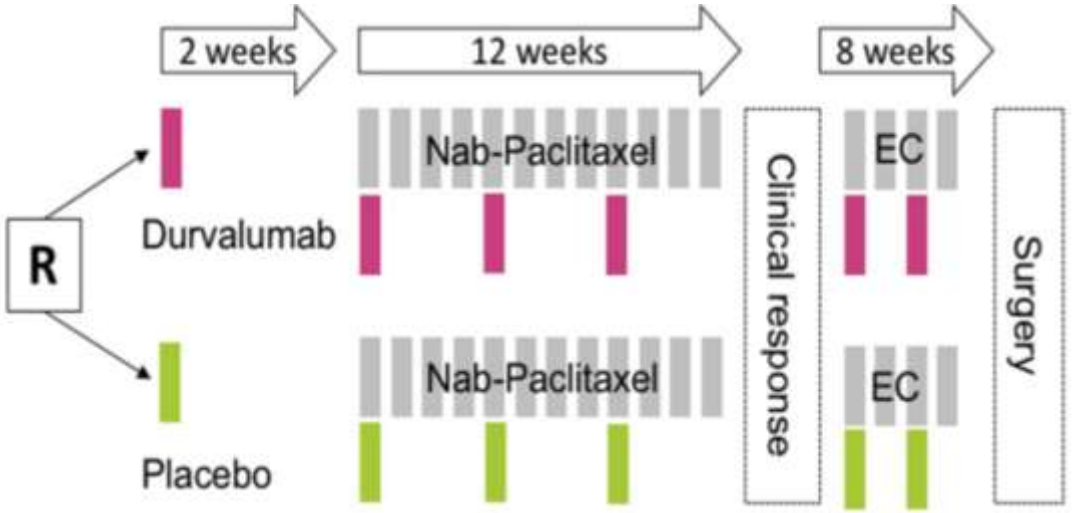
2 prior Tx 7%
≥ 3 prior Tx 93%

Historical Clinical outcomes

	Ref.	Drug	ORR
TNBC 2L+	Adams S et al, Ann Oncol 2019	Pembrolizumab	5.3%
	Emens L et al, JAMA Oncol 2018	Atezolizumab	7.0%

GeparNuevo study

Study design

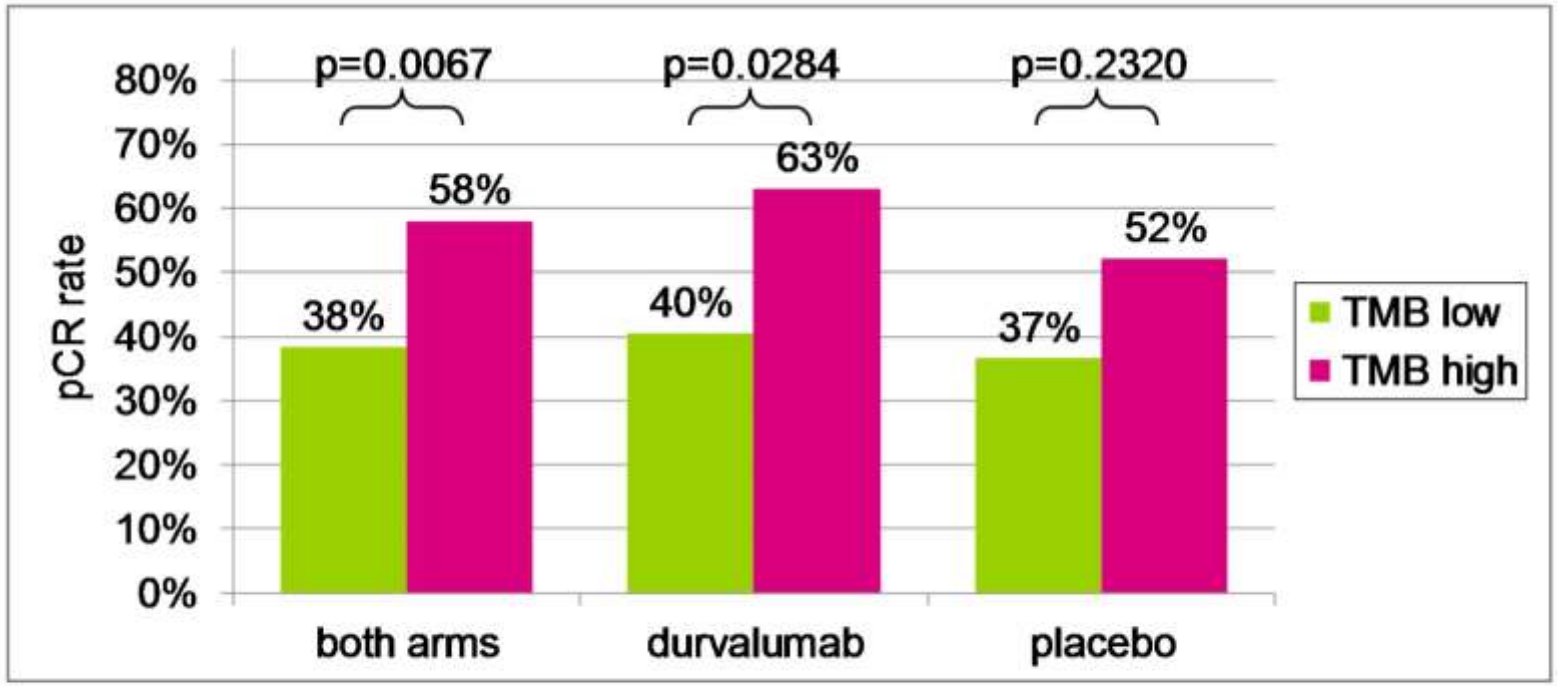


pCR rate

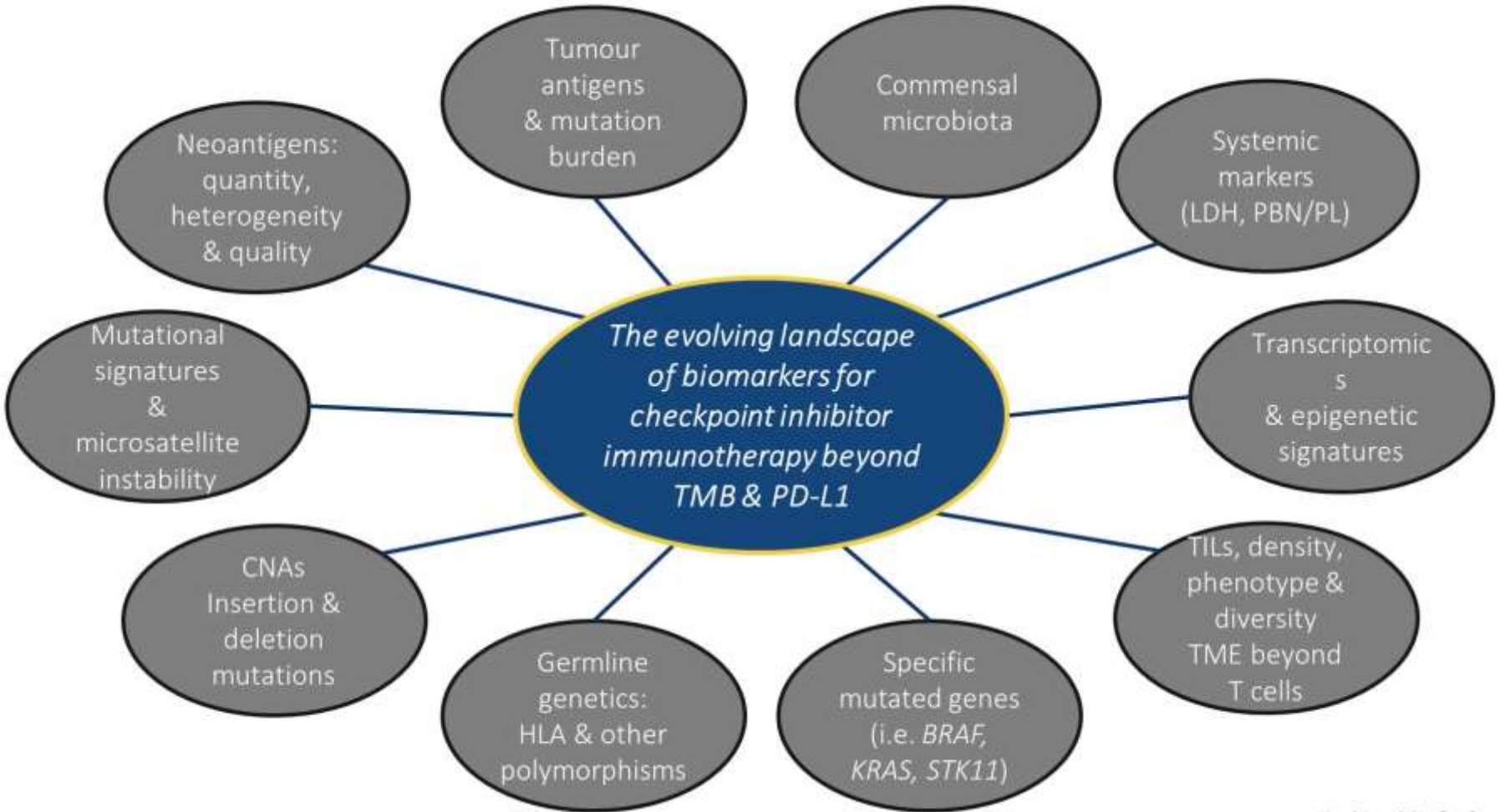
	Durvalumab	Placebo	P-value
All patients (n=174)	53%	44%	0.287
Window patients (n=117)	61%	41%	0.048

Loibl S et al, Ann Oncol 2019

GeparNuevo: Response based on TMB (Seliger et al, abstract 588)

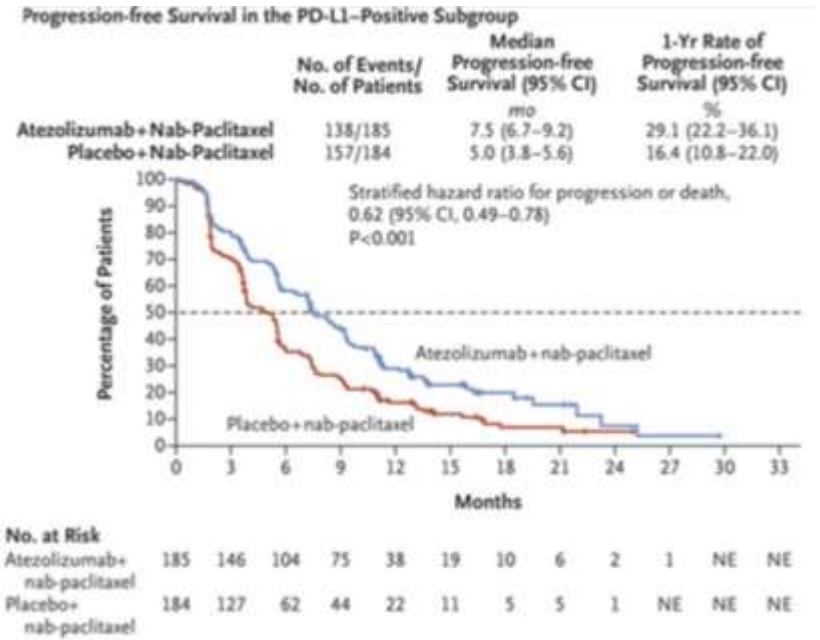


Median TMB: 1.52 mutations/MB
TMB low: below 66.7% percentile; TMB high: above 66.7% percentile
Top TMB tertile PCR 58% versus low TMB tertile 38%

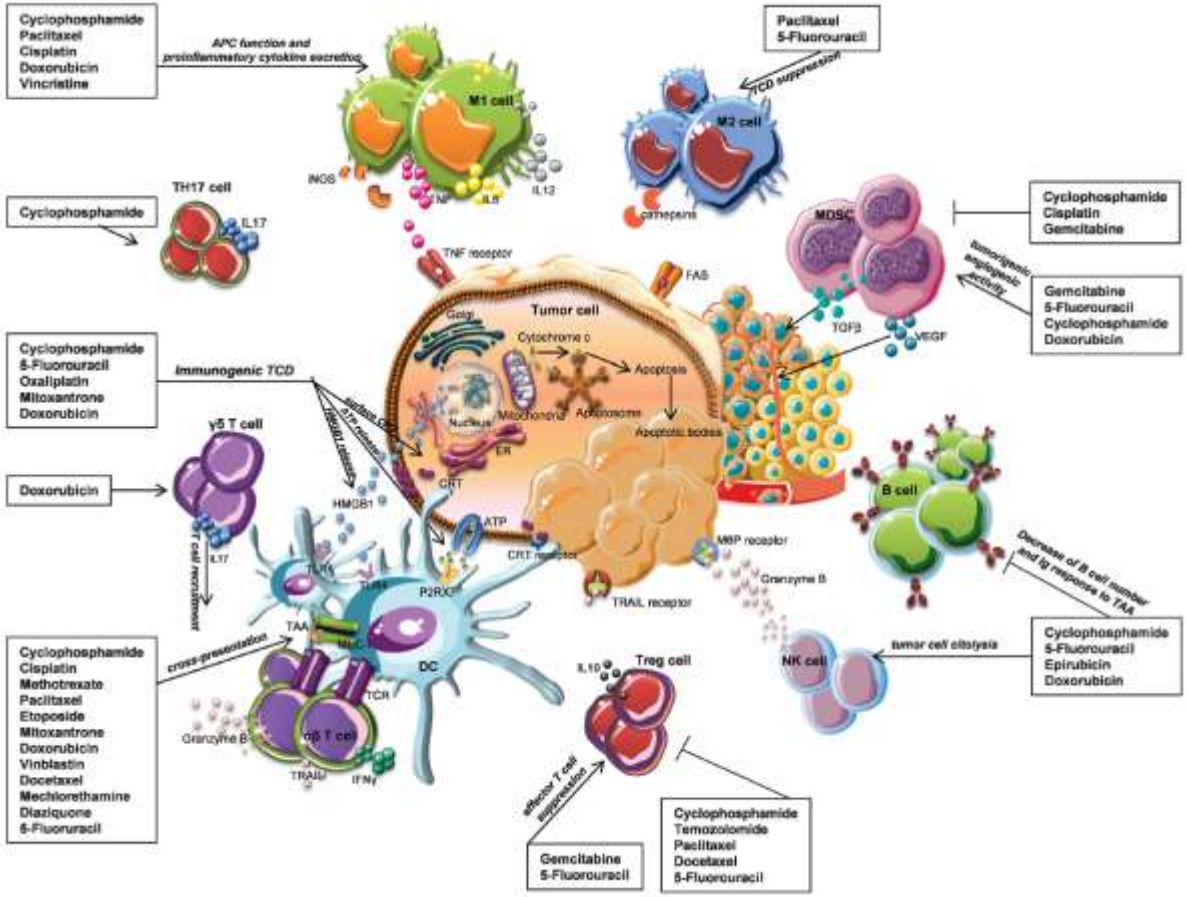


Havel J et al, Nat Rev Cancer 2019

Refining immunotherapy strategies: Which is the best chemotherapeutic partner?

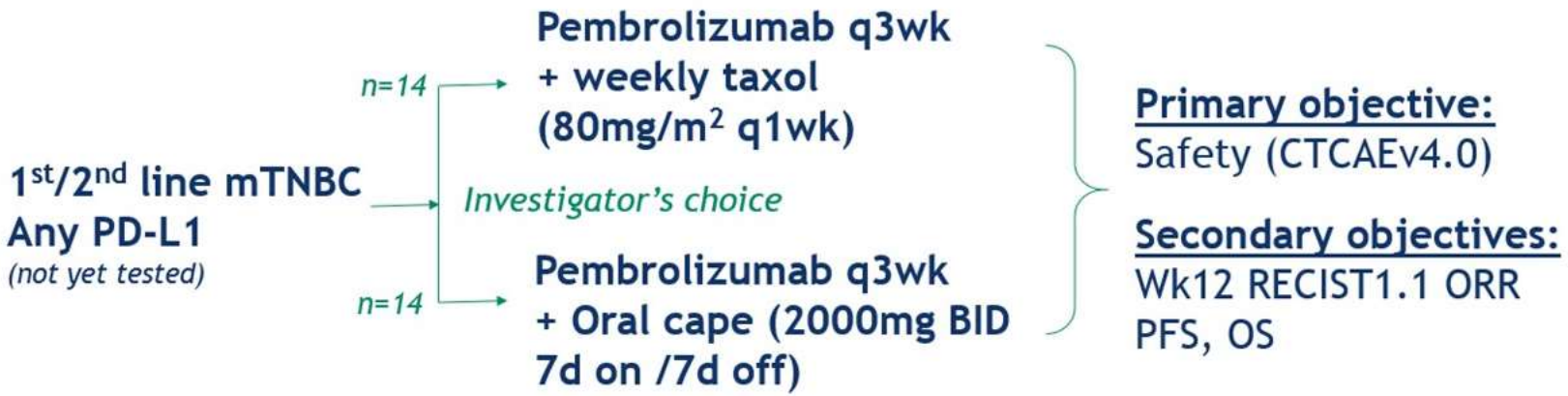


Schmid P et al, N Engl J Med 2018



Bracci L Cell Death and Differentiation 2014

First or second-line pembrolizumab with weekly taxol or capecitabine for mTNBC (Page et al, abstract 1015)



Exploratory objectives presented today:

- Peripheral blood immune effects of taxol v. cape
- Efficacy in Impassion130-eligible (*de novo* or curative chemo>12mo) & Impassion130-ineligible (2nd-line or chemo<12mo) populations

Pembrolizumab with weekly taxol or capecitabine for mTNBC: Results

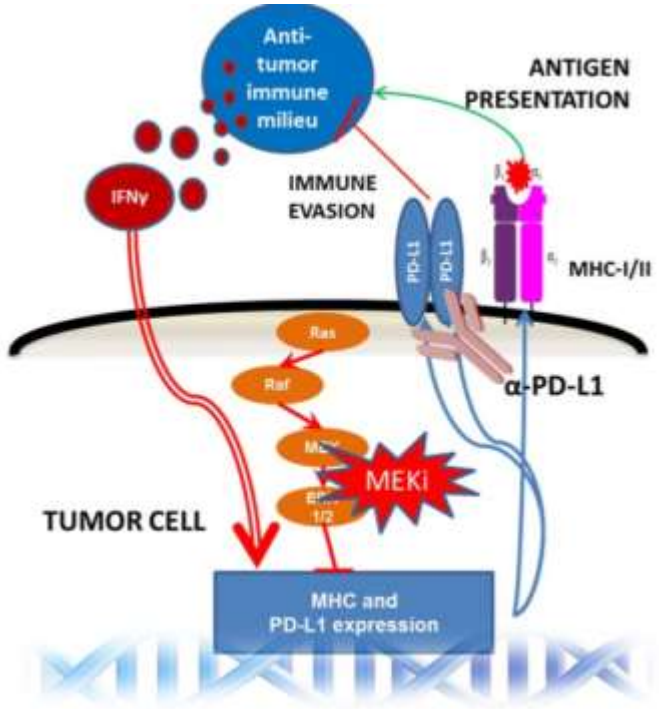
	<12 mo from last chemo	>12 mo from last chemo	All
Taxol	0% ORR (0/5)+ 0% CBR (0/5)	38% ORR (3/8)++ 50% CBR (4/8)	23% ORR (3/13) 31% CBR (4/13)
Cape	38% ORR (3/8) 50% CBR (4/8)	50% ORR (3/6) 67% CBR (4/6)	43% ORR (6/14) 57% CBR (8/14)
All	23% ORR (3/13) 31% CBR (4/13)	43% ORR (6/14) 57% CBR (8/14)	33% ORR (9/27) 44% CBR (12/27)

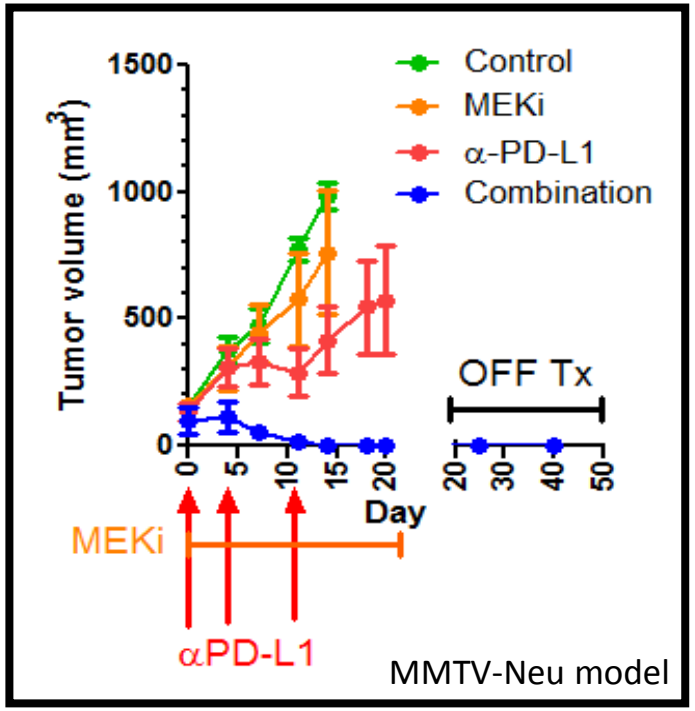
Signal in quickly progressing TNBC?

Improved ICD signal in capecitabine treated tumors or chemoresistance to taxanes

Refining immunotherapy strategies: Can targeted agents improve response?

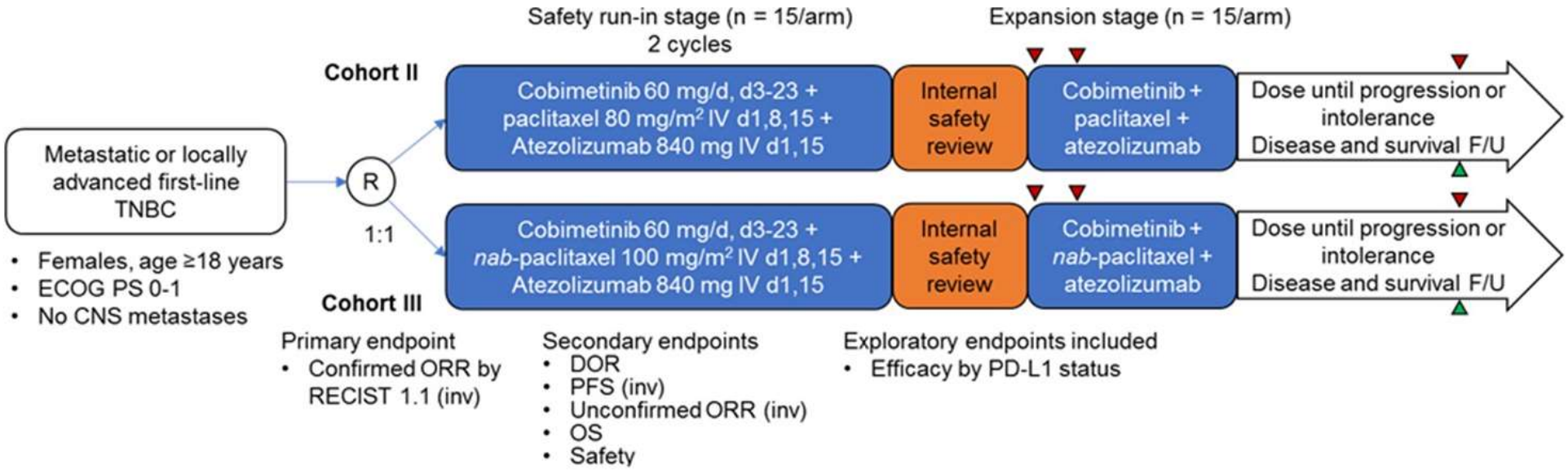
- The MEK pathway is active in TNBC
- Activation suppresses inflammatory resposes to T-cells, leading to reduced antigen presentation and PD-L1 expression
- Combining MEKi with anti-PD-L1i may improve antigen presentation while blocking PD-L1 mediated suppression
- Sinergistic activity of MEKi and anti-PD-L1i





Loi S et al, Clin Cancer Res 2016

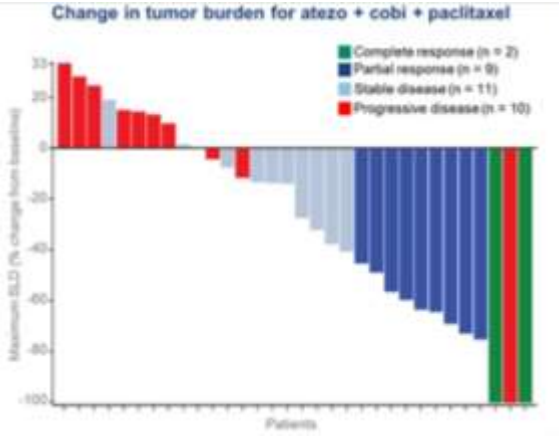
Phase II COLET study: Atezolizumab + Cobimetinib + Paclitaxel/nab-paclitaxel as first-line treatment for mTNBC (Brufsky et al, abstract 1013)



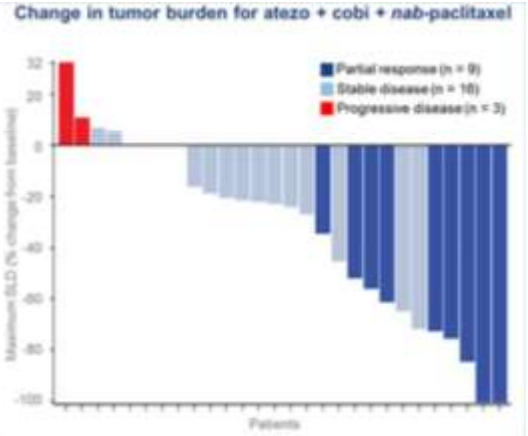
Phase II COLET study: Outcome results

ORR

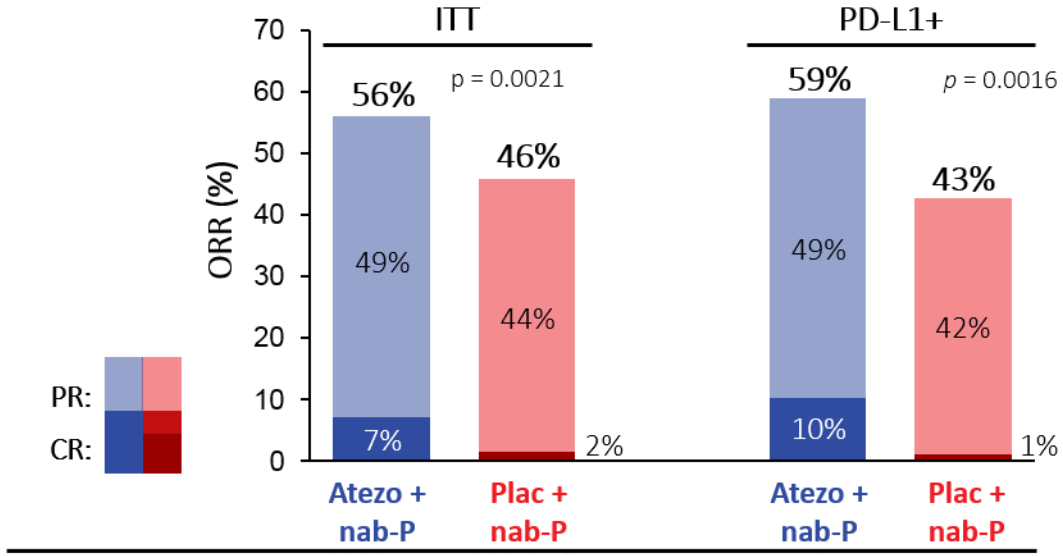
11/32 (34%)



9/28 (32%)



ORR in the IMpassion130



Schmid P NEJM 2018

Phase II COLET study: Outcome results

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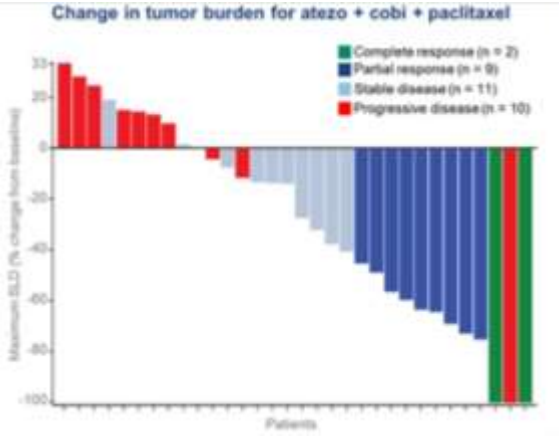

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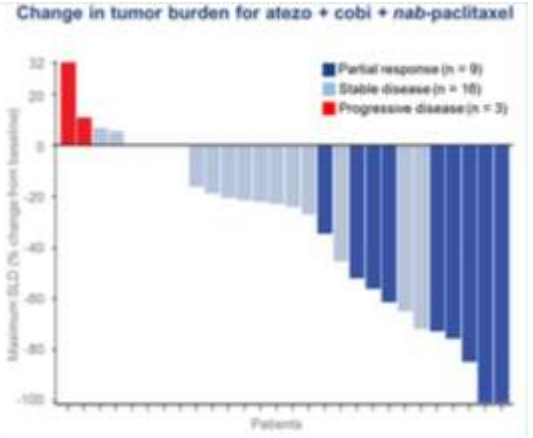
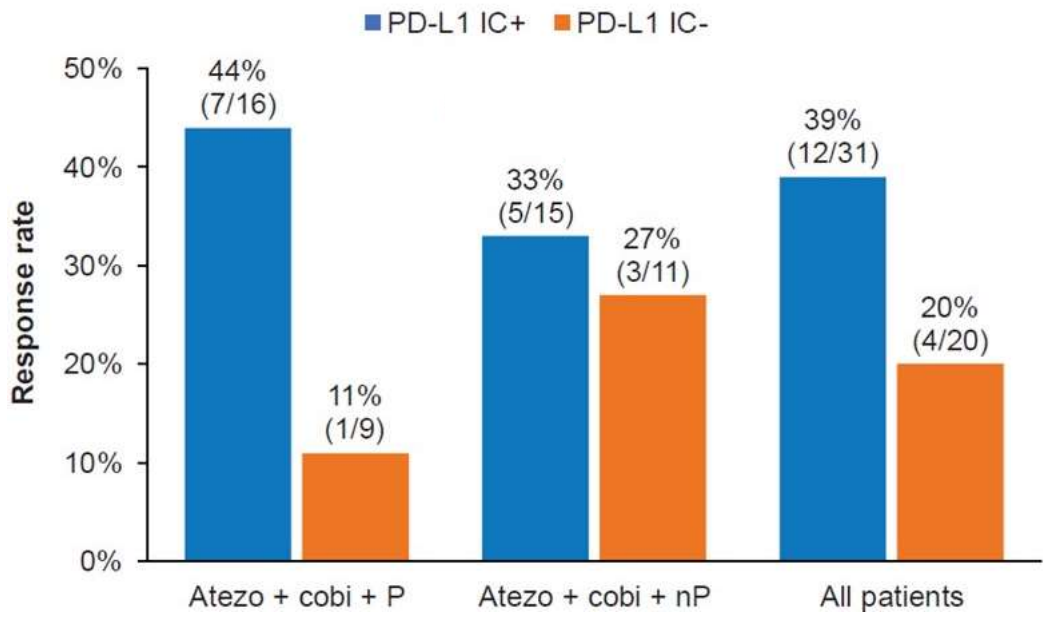


ORR by PD-L1 status



Immunotherapy in Breast Cancer

- Need for better biomarkers and for an understanding of their relationship to one another
- Is there a role for improving response to immune checkpoint inhibitors by selecting the best chemotherapeutic partner?
- Re-thinking targeted therapies in combination with immune checkpoint inhibitors

Grazie