SOTTOGRUPPI HER2+ E TN IN STADIO AVANZATO:
LO STANDARD

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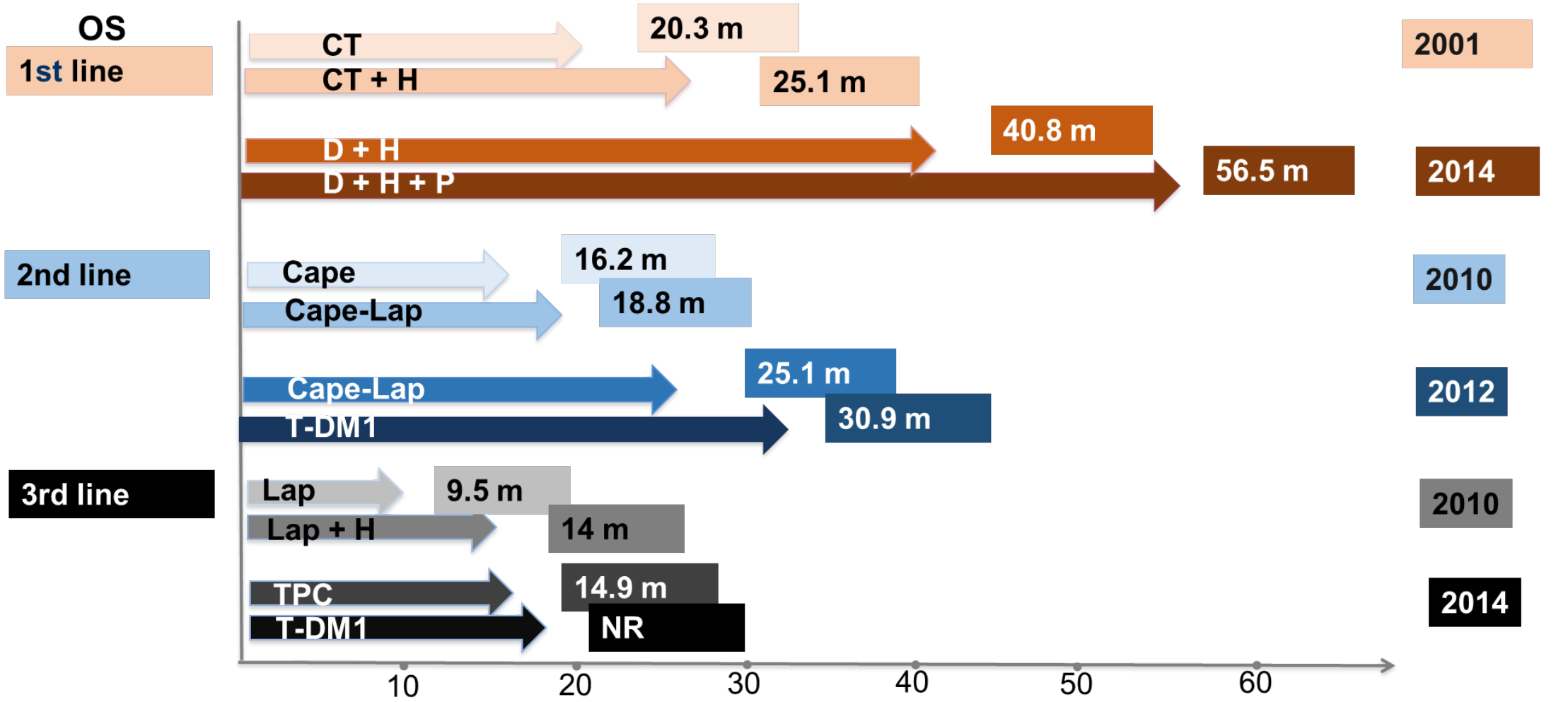
IOV - IRCCS

Treatment of HER2+ ABC: progress over time

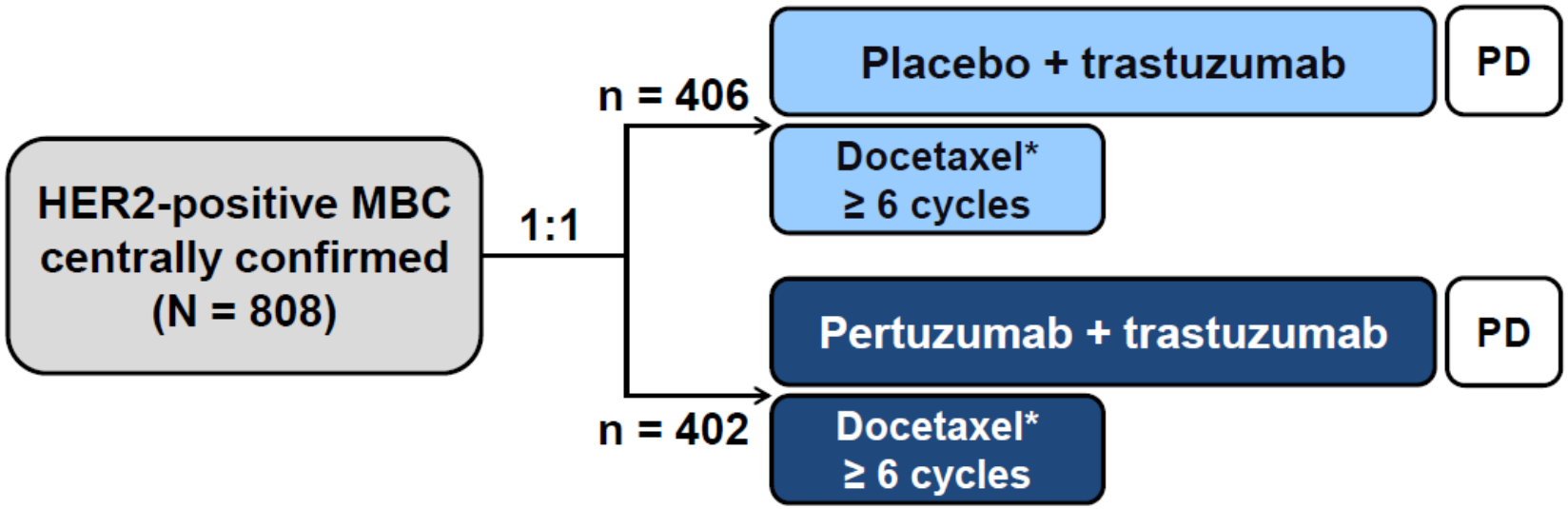


Slamon, NEJM 2001
Swain ESMO 2014

Cameron, Oncologist 2010
Verma, NEJM 2012

Blackwell, JCO 2010
Krop, Lancet Oncol 2014

Phase III CLEOPATRA study

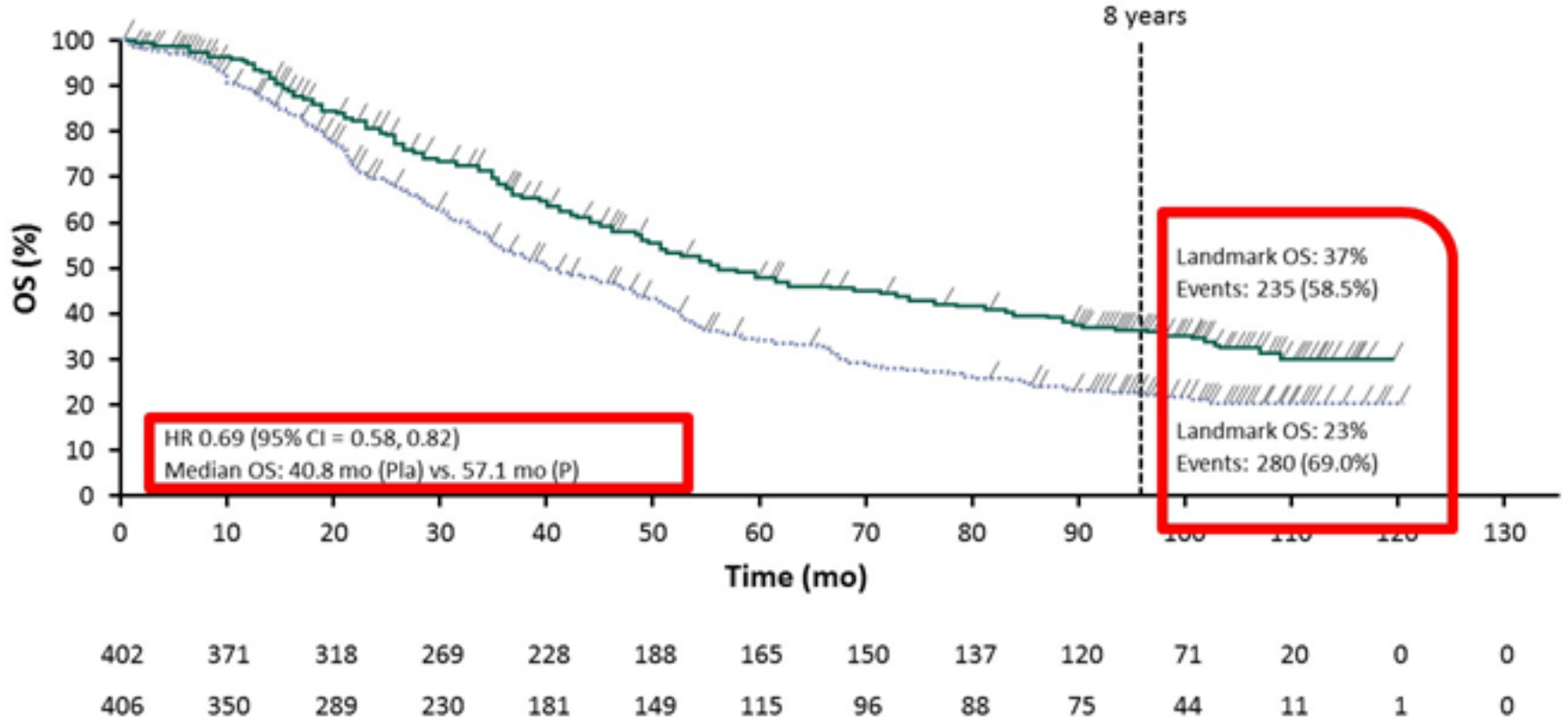


	Placebo +T+D (n = 406)	Pertuzumab +T+D (n = 402)
Prior (neo)adjuvant chemotherapy, n (%)		
Yes	192 (47.3)	184 (45.8)
No	214 (52.7)	218 (54.2)
Components of (neo)adjuvant therapy*, n (%)		
Anthracycline	164 (40.4)	150 (37.3)
Hormones	97 (23.9)	106 (26.4)
Taxane	94 (23.2)	91 (22.6)
Trastuzumab	41 (10.1)	47 (11.7)

Baselga J et al. N Engl J Med 2012; Swain S et al. Lancet Oncol 2013; Swain S et al. N Engl J Med 2015

CLEOPATRA: end-of-study results

mPFS 18.5m

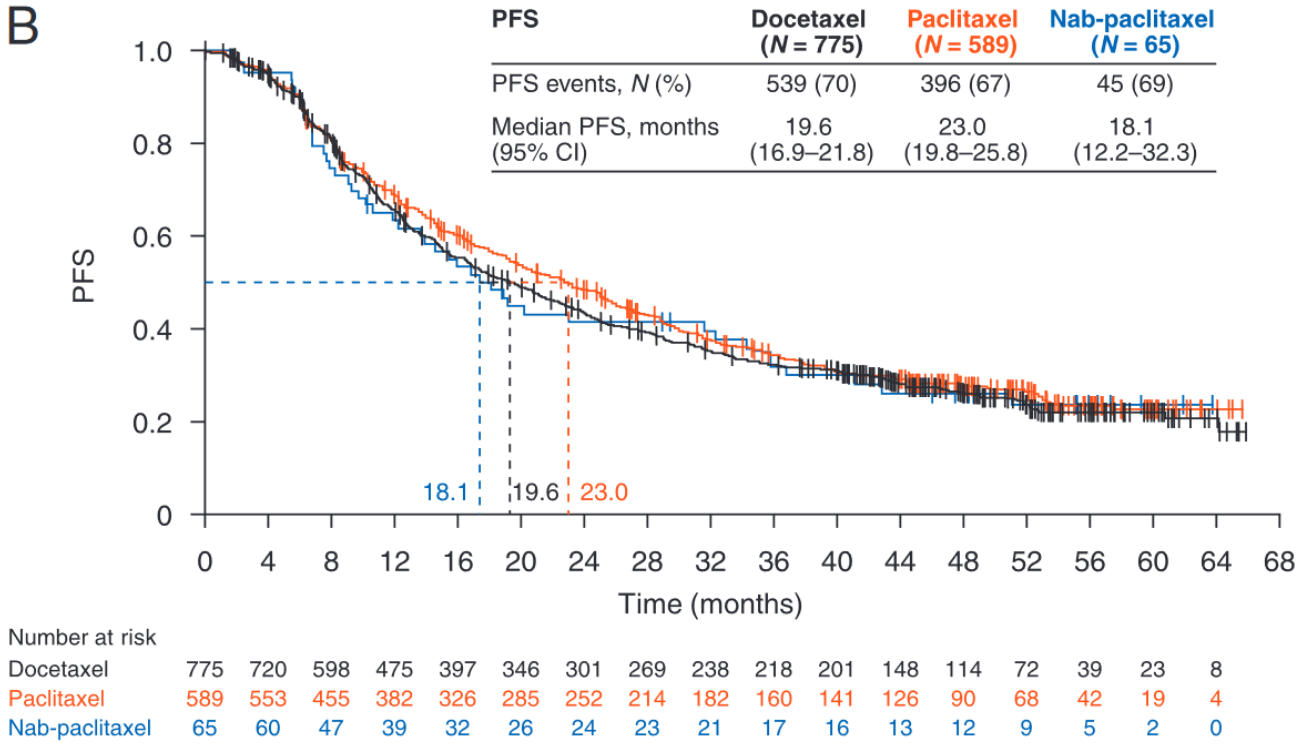


* Crossover pts were analyzed in the Pla arm.
OS was compared between arms using the log-rank test, stratified by prior treatment status and geographic region. The Kaplan–Meier approach was used to estimate median OS, and a stratified Cox proportional hazards model was used to estimate the HR and 95%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

Swain et al, Abstr. 1020, ASCO 2019

PERUSE: single-arm phase IIIb study

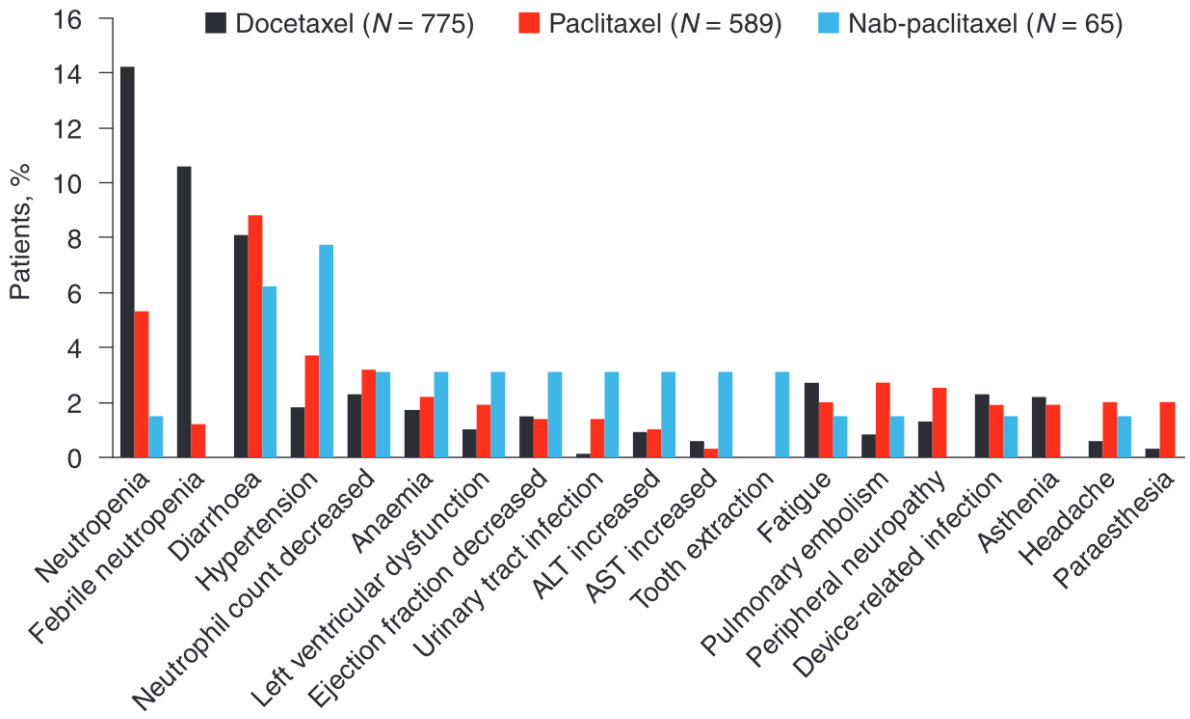
B



PFS	Docetaxel (*N* = 775)	Paclitaxel (*N* = 589)	Nab-paclitaxel (*N* = 65)
PFS events, *N* (%)	539 (70)	396 (67)	45 (69)
Median PFS, months (95% CI)	19.6 (16.9–21.8)	23.0 (19.8–25.8)	18.1 (12.2–32.3)

Number at risk

Docetaxel	775	720	598	475	397	346	301	269	238	218	201	148	114	72	39	23	8
Paclitaxel	589	553	455	382	326	285	252	214	182	160	141	126	90	68	42	19	4
Nab-paclitaxel	65	60	47	39	32	26	24	23	21	17	16	13	12	9	5	2	0



Bachelot T, Ann Oncol 2019

Enthuse for PERUSE: when clinical judgment overcomes regulatory boundaries

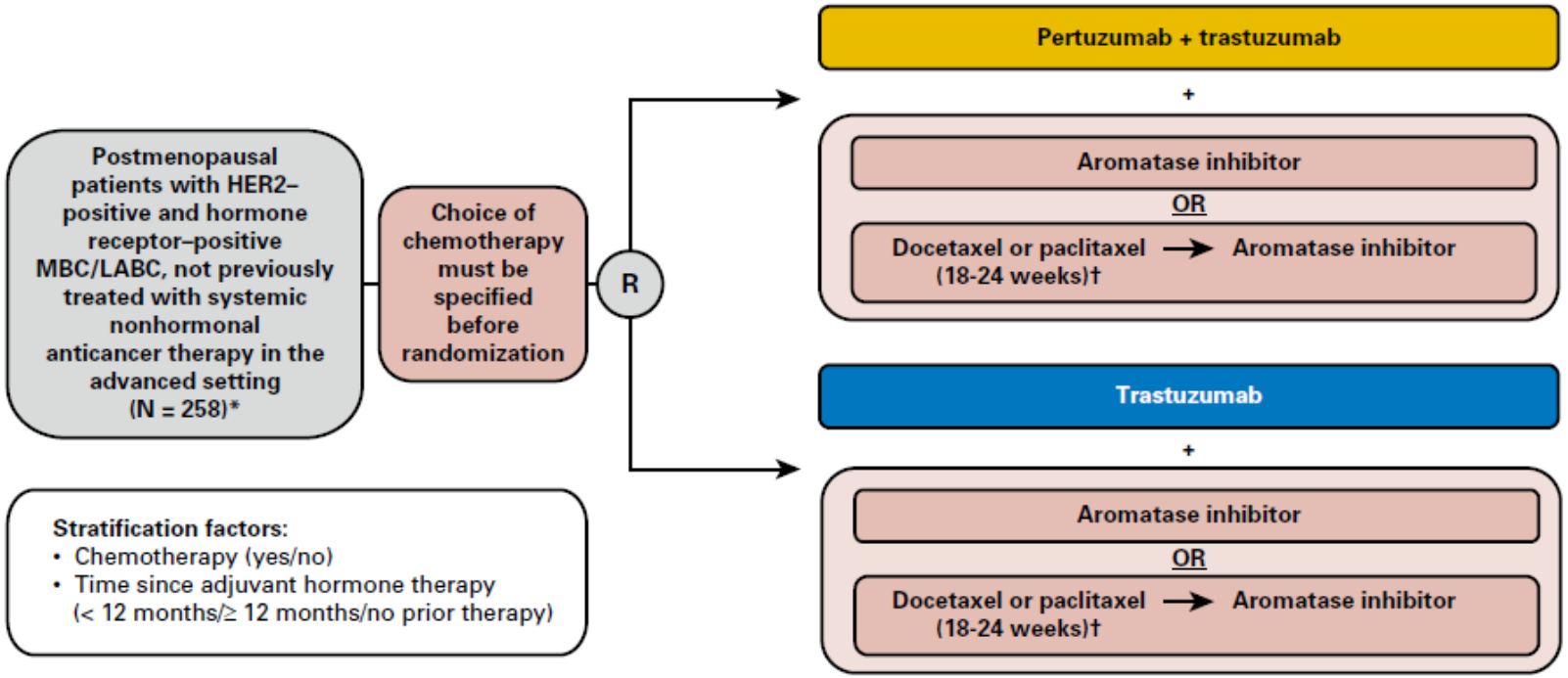
- 35% de novo; 30% pre-treated with trastuzumab (46% of non-de novo stage IV): median PFS favorably compares with CLEOPATRA.

- Paclitaxel schedule was not collected (an estimation that two-thirds of patients received weekly schedule is simply presumed).

- Similar results in HR+ and HR-, however use of HT was not known.

Guarneri V, Ann Oncol 2019

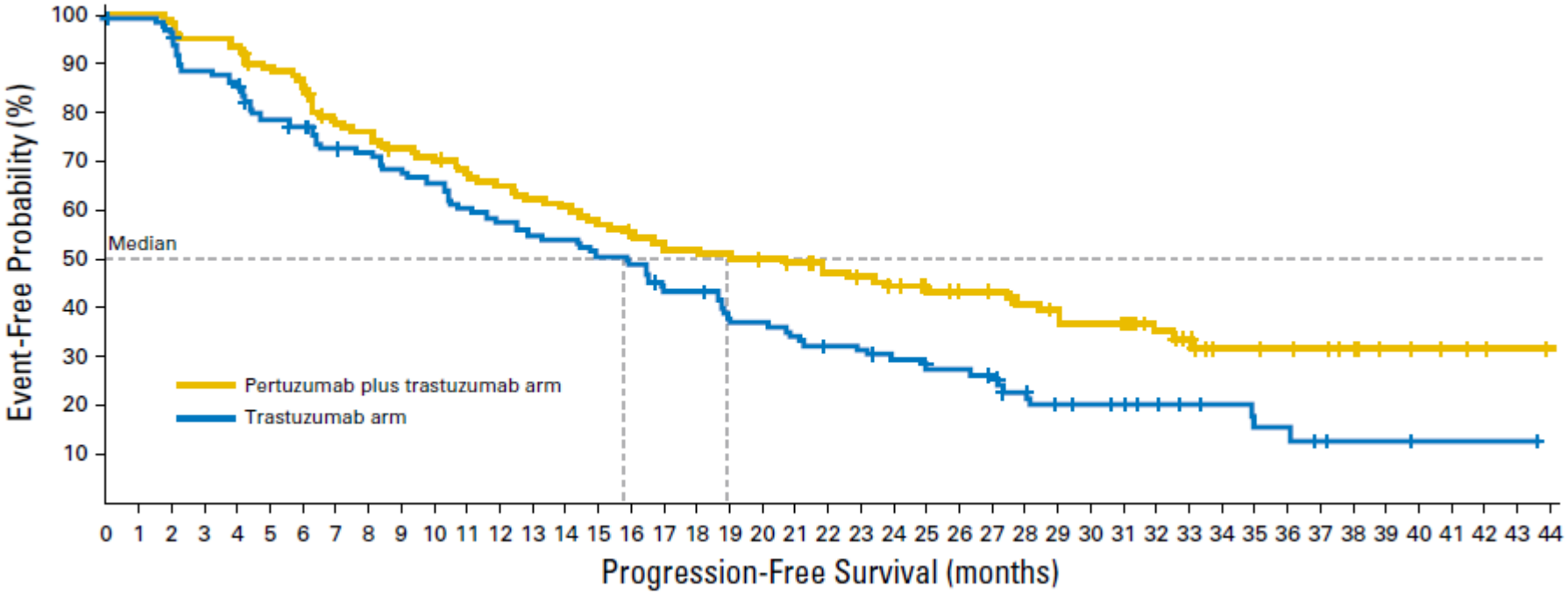
PERTAIN Randomized Phase II study



	Induction CT YES N=148	induction CT NO N=111
Visceral disease	75.3%	64.3%
≥3 organ involved	38.4%	26.4%
<3 organ involved	61.6%	73.2%
Previous systemic therapy	46.6%	58.9%
Adjuvant/neoadjuvant CT	52.0%	48.2%
Adjuvant/neoadjuvant trast	31.5%	23.3%
Adjuvant/neoaduvant HT	36.3%	48.2%

Rimawi, J Clin Oncol 2018

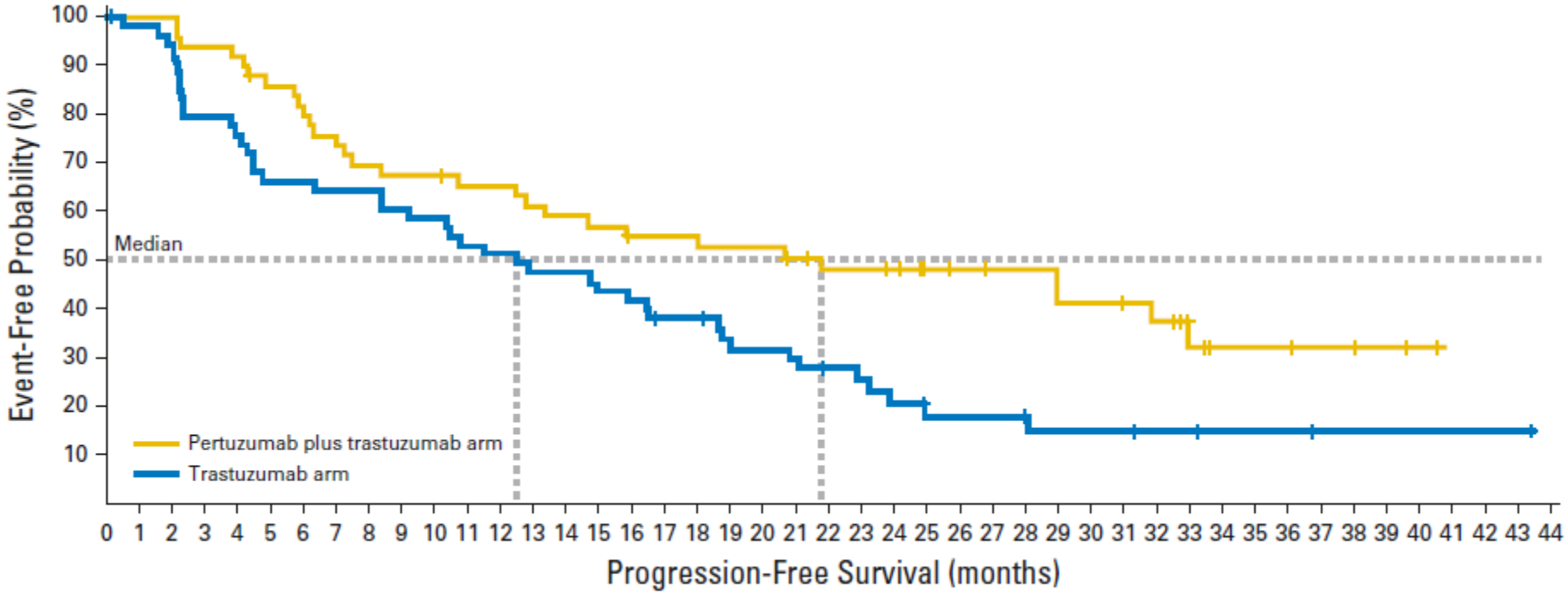
PERTAIN: progression-free survival



	Trastuzumab	Trastuzumab+ pertuzumab	HR (95% CI)	*p*
ITT population	15.80	18.89	0.65 (0.48-0.89)	.007

Rimawi, J Clin Oncol 2018

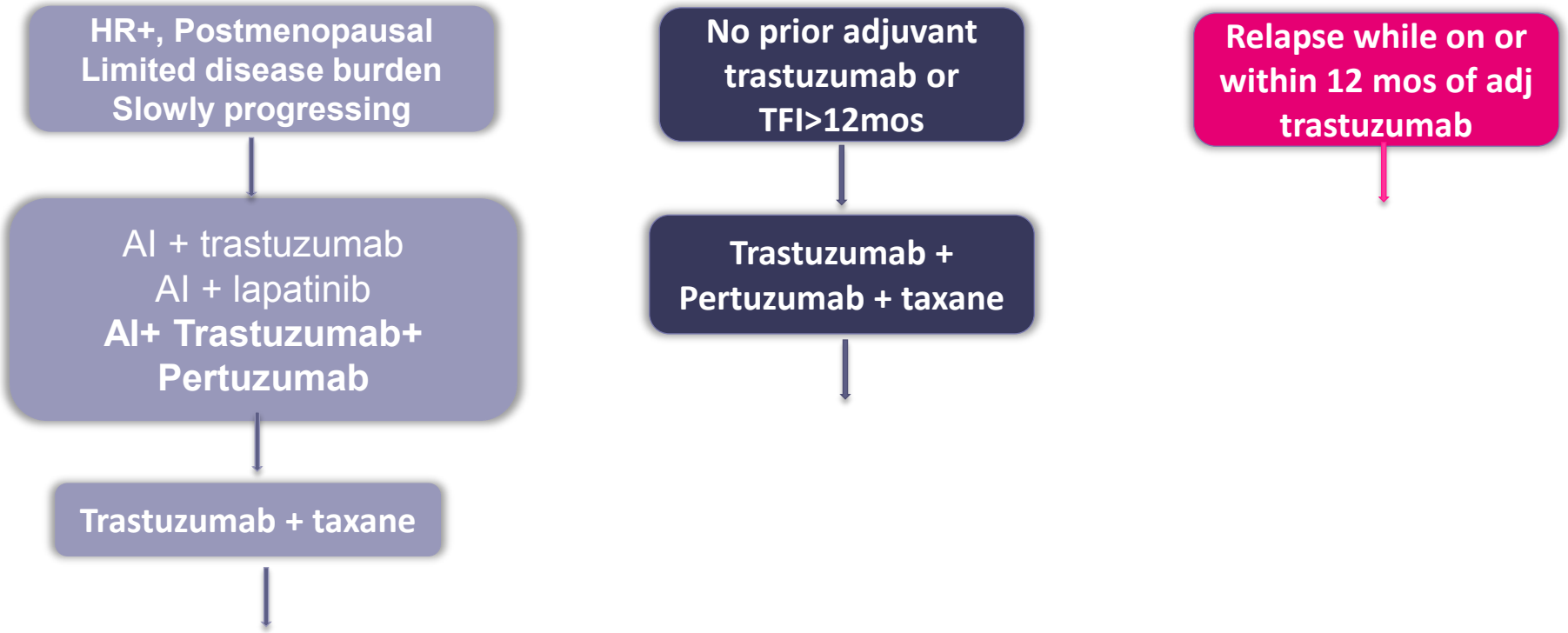
PERTAIN: progression-free survival according to induction CT



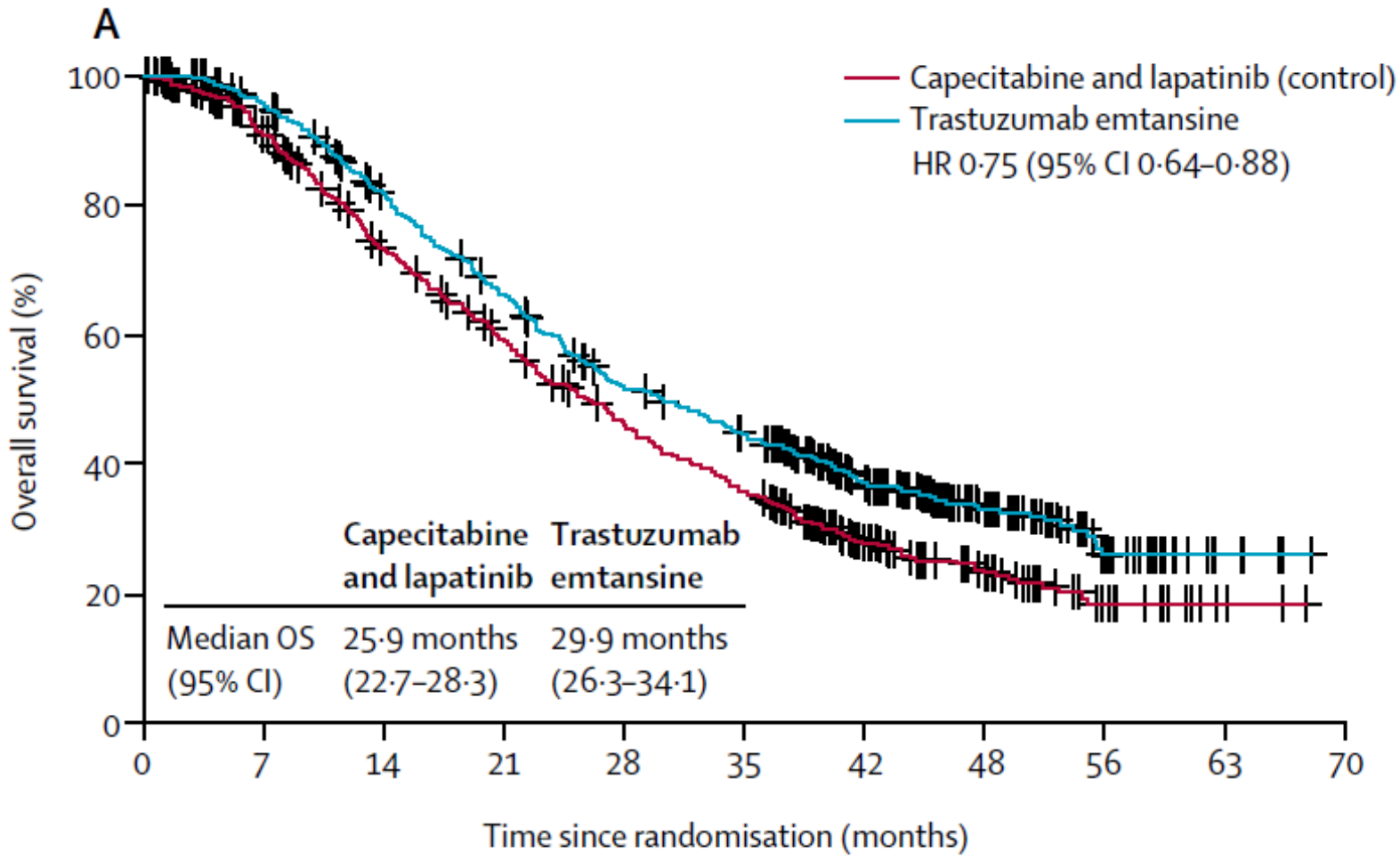
	Trastuzumab	Trastuzumab+ pertuzumab	HR (95% CI)	*p*
ITT population	15.80	18.89	0.65 (0.48-0.89)	.007
Induction chemotherapy NO	**12.45**	**21.72**	**0.55 (0.34-0.88)**	**.0111**

Rimawi, J Clin Oncol 2018

HER2+ MBC: treatment algorithm

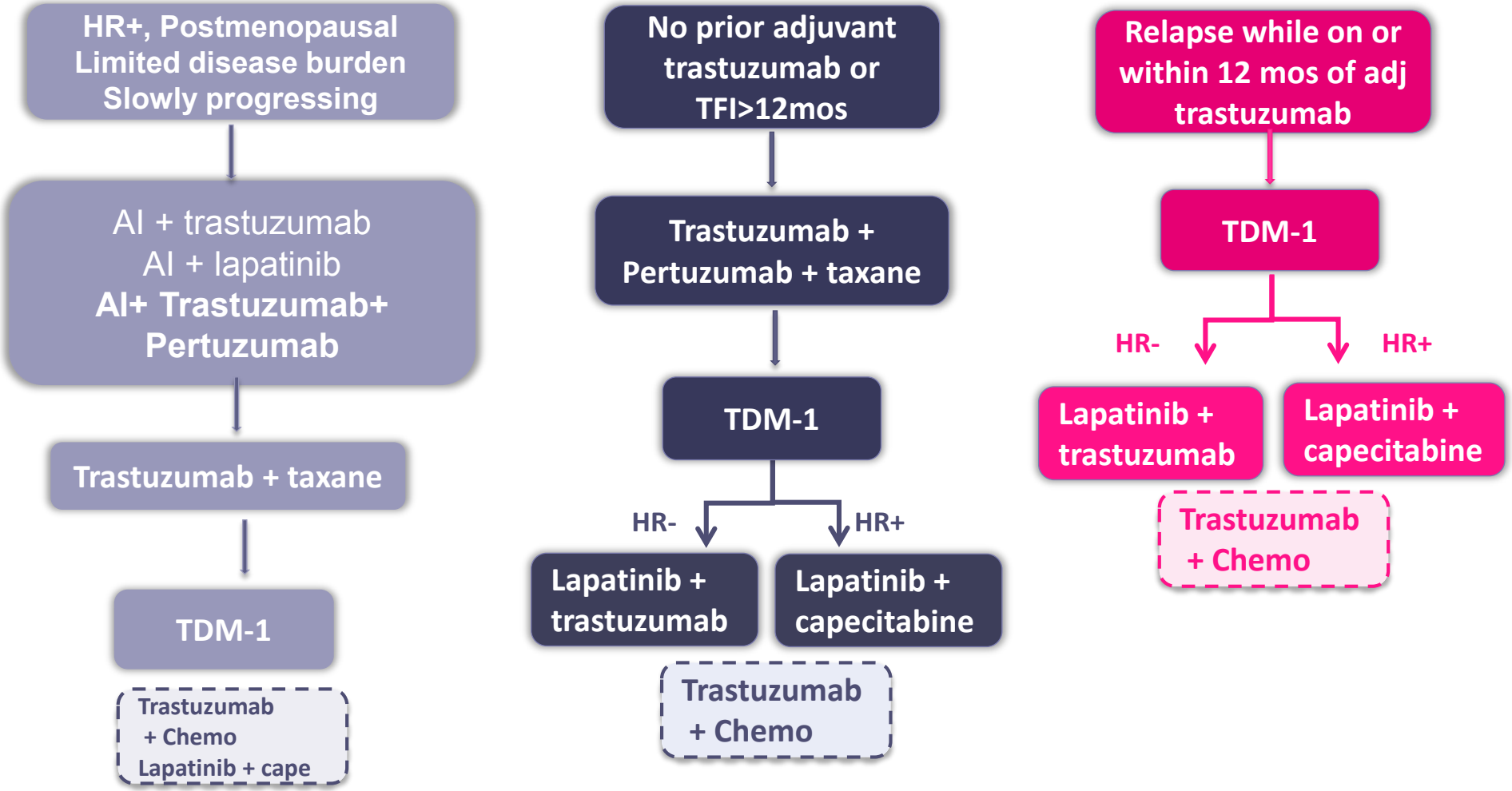


EMILIA trial: Final OS Analysis



Dieras V, et al. Lancet Oncology 2017

HER2+ MBC: treatment algorithm



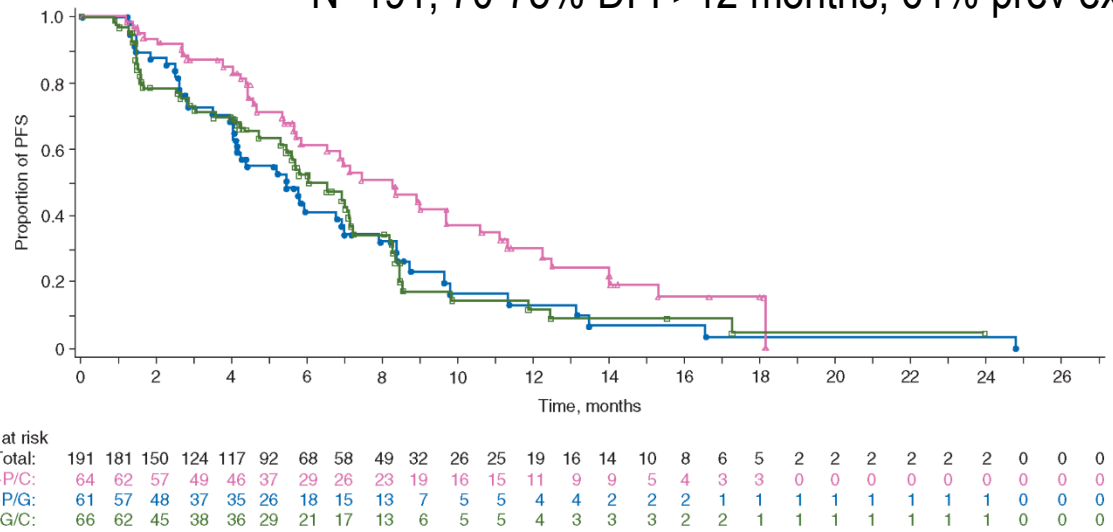
Metastatic TNBC

- Chemotherapy has been the standard for decades
- Most pts received A-T as adjuvant/neoadjuvant treatment
- Frequent visceral metastases, poor survival from the onset of MBC
- High attrition rate: a long-term treatment sequence is not possible
- Clinical trials
- Best option first

tnAcity Phase II

A

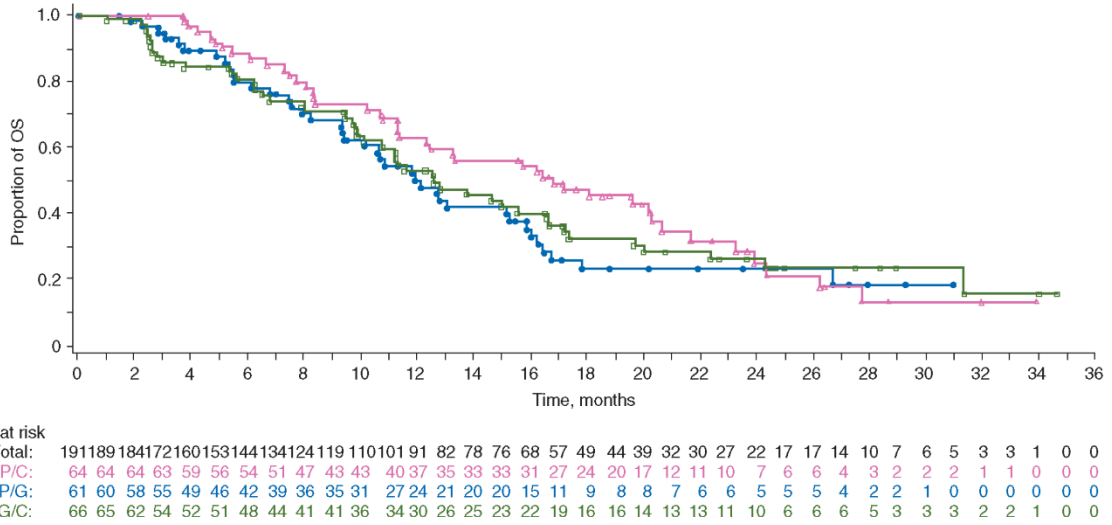
N=191; 70-75% DFI >12 months, 64% prev exposed to taxane



	nab-P/C	*nab*-P/G	G/C
Median PFS, months	8.3	5.5	6.0
HR (95% CI) *P* value	– –	0.59 (0.38 - 0.92) 0.02[a]	0.58 (0.37 - 0.90) 0.02[a]
12-month PFS rate, %	30	13	11

[a] Compared with *nab*-P/C.

B



	***nab*-P/C**	***nab*-P/G**	**G/C**
Median OS, months	**16.8**	**12.1**	**12.6**
HR (95% CI) ***P* value**	**–** **–**	**0.73 (0.47 - 1.13)** **0.16[a]**	**0.80 (0.52 - 1.22)** **0.29[a]**

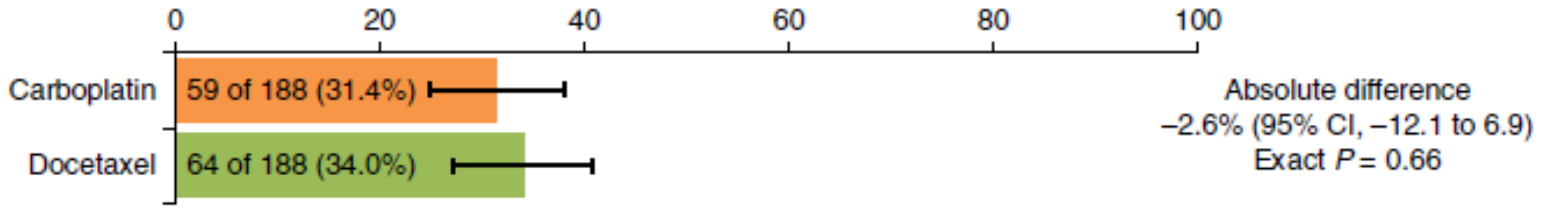
[a] Compared with *nab*-P/C.

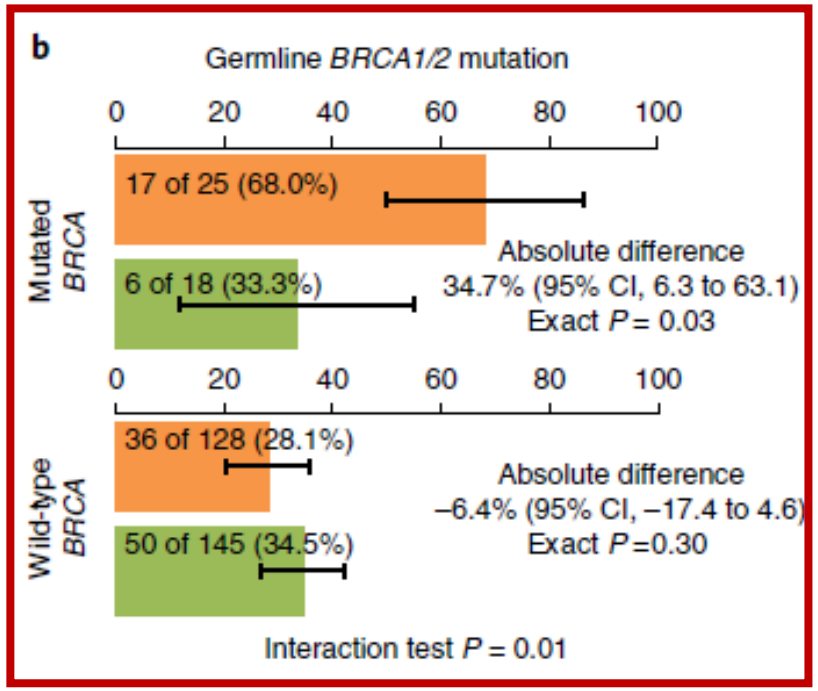
Yardley D et al, Ann Oncol 2018

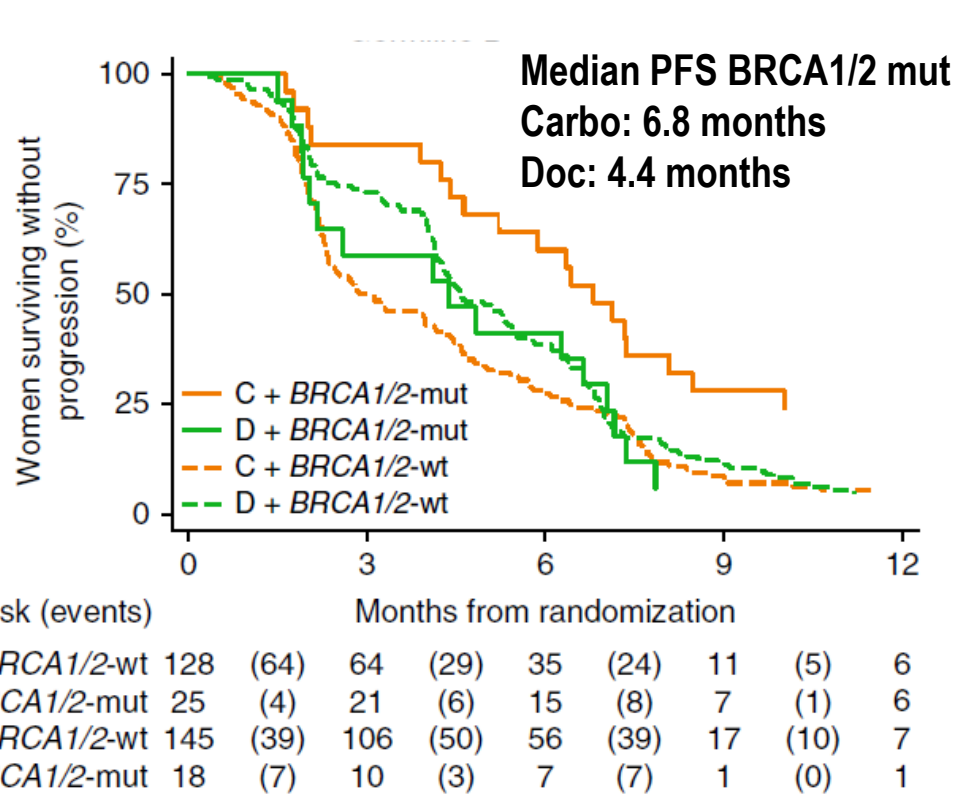
TNT: 1st line phase III trial for TN metastatic BC

N=376

66% of pts: previously unexposed to taxane





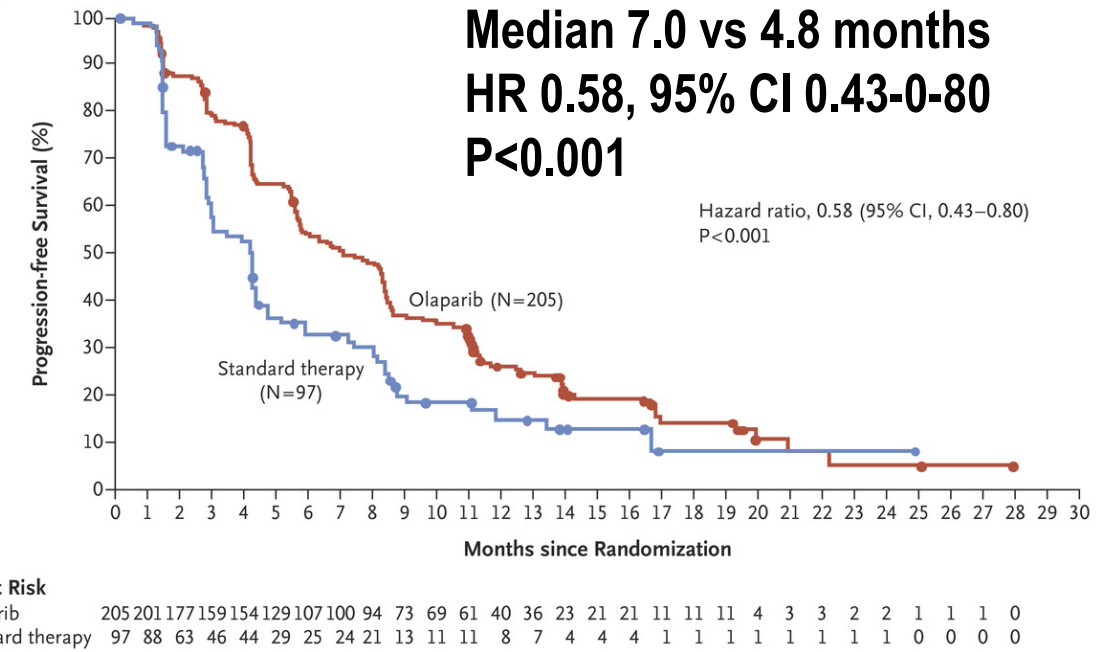


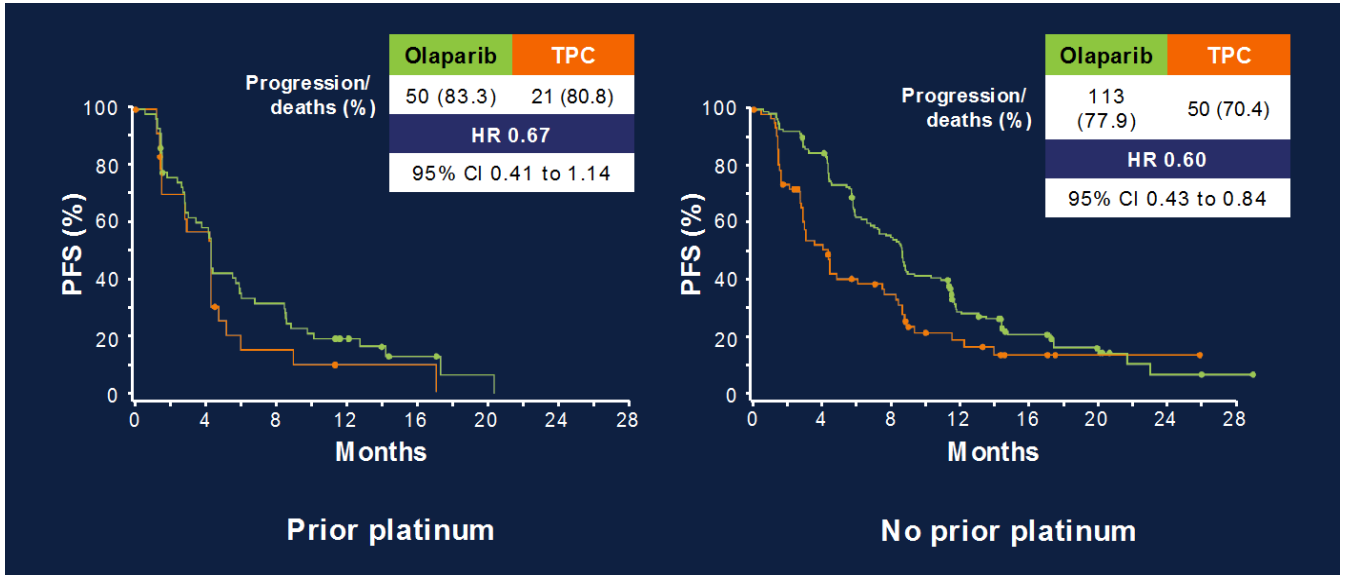
Key
Carboplatin
Docetaxel
95% CI

Tutt A et al, Nat Med 2018

OlympiAD: PFS results

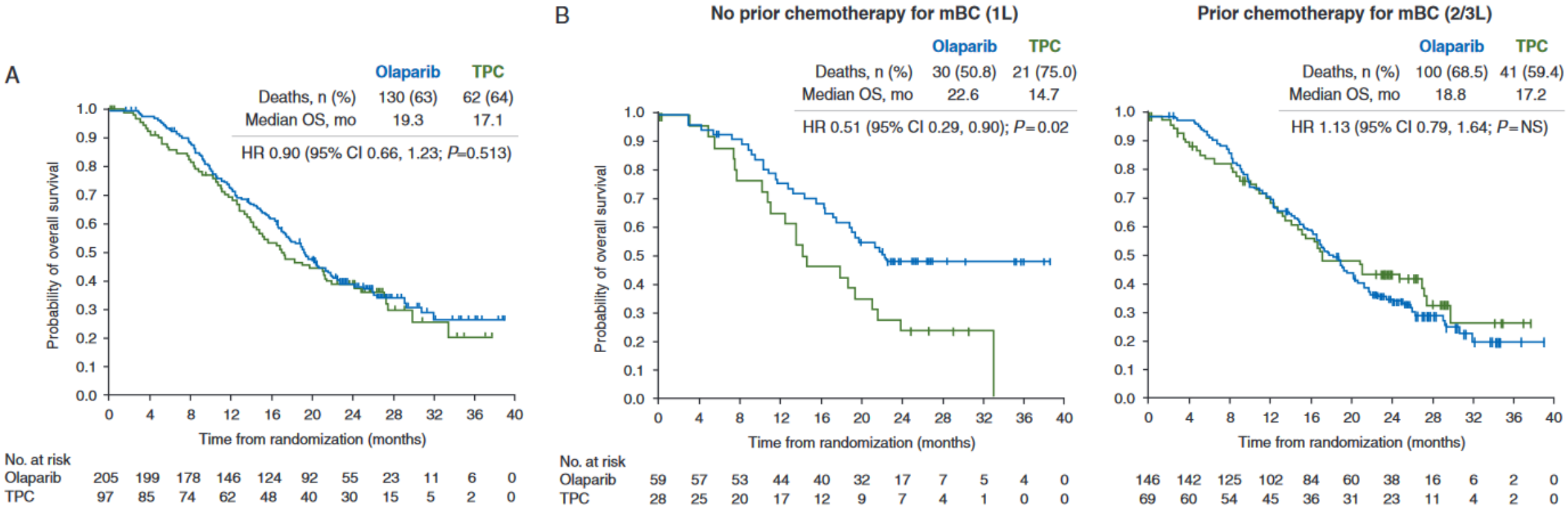
50% TN; A/T PRETREATED; MOST pts RECEIVED CT FOR MBC; TN: NON-PLATINUM RESISTANT





Robson M, NEJM 2017

OlympiAD: OS results



Robson M, Ann Oncol 2019

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

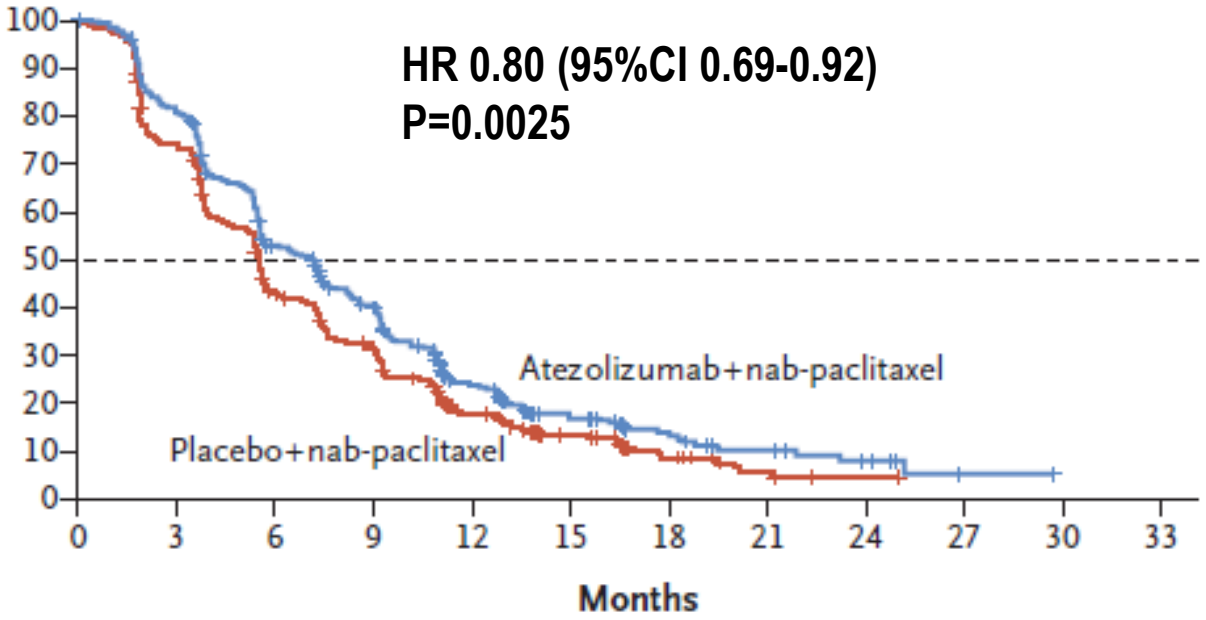
IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were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

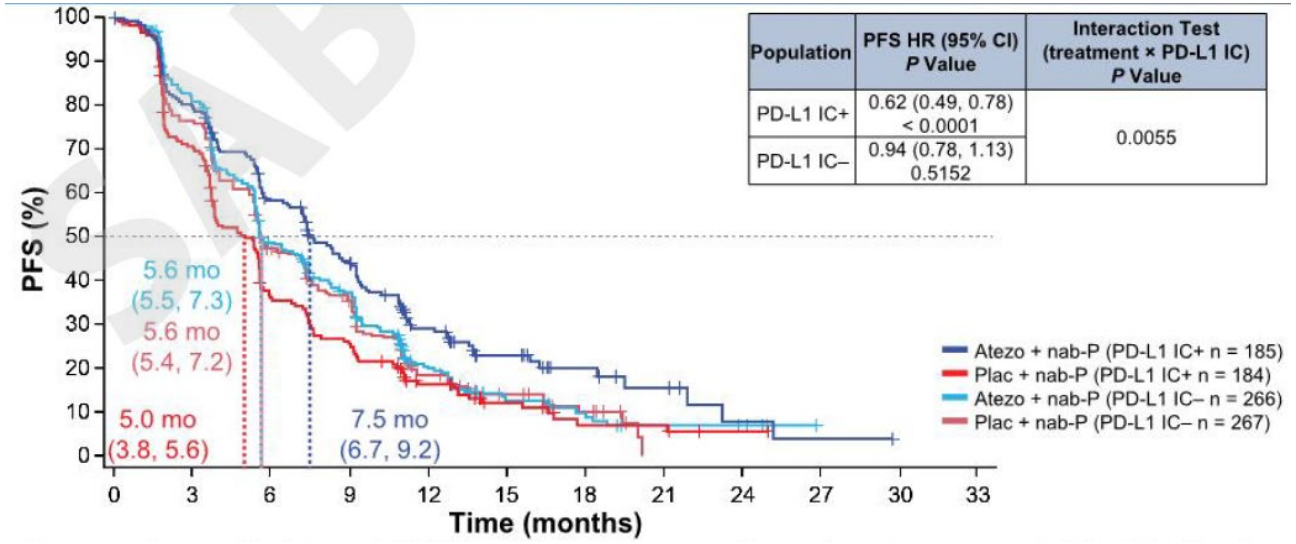
PFS ITT



HR 0.80 (95%CI 0.69-0.92)
P=0.0025

	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



Population	PFS HR (95% CI) *P* Value	Interaction Test (treatment × PD-L1 IC) *P* Value
PD-L1 IC+	0.62 (0.49, 0.78) < 0.0001	0.0055
PD-L1 IC–	0.94 (0.78, 1.13) 0.5152	

PD-L1+	mPFS, months (95%CI)	1yr PFS% (95%CI)
Atezo+Nab	7.5 (6.7-9.2)	29.1 (22.2-36.1)
Plac+Nab	5.0 (3.8-5.6)	16.4 (10.8-22.0)

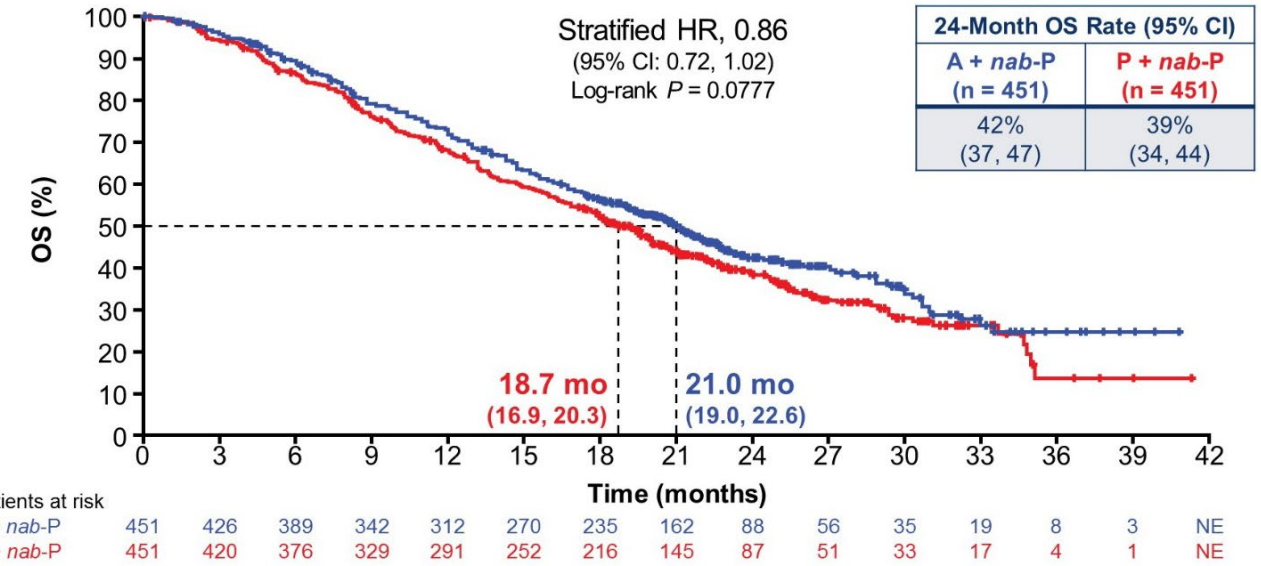
41% PD-L1+
SP142, 1% of positively stained IC over the total tumor area

Schmid P, NEJM 2018

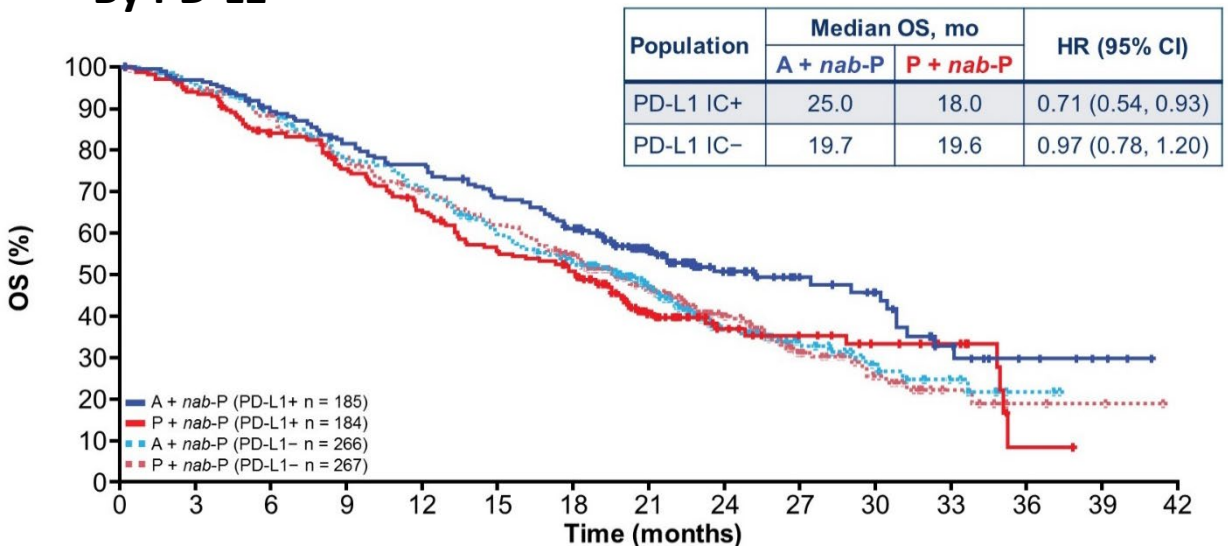
IMpassion130: OS

2° interim (59% deaths in ITT population)

ITT



By PD-L1



Population	Median OS, mo		HR (95% CI)
	A + *nab*-P	P + *nab*-P	
PD-L1 IC+	25.0	18.0	0.71 (0.54, 0.93)
PD-L1 IC−	19.7	19.6	0.97 (0.78, 1.20)

Schmid P, ASCO 2019

1st line treatment of metastatic TNBC, BRCAwt

BRCAwt: DFI>12months

PD-L1+

Atezo + nab-paclitaxel
Carbo + taxane (nab)
Taxane+/- Bev

PD-L1-

Carbo + taxane (nab)
Taxane +/- Bev

BRCAwt: DFI<12months

Carbo +/- Gem
Capecitabine +/- VNB

In yellow: not yet approved/off-label

1st line treatment of metastatic TNBC, BRCAmut

BRCAmut: DFI>12months

PD-L1+ ↙ ↘ PD-L1-

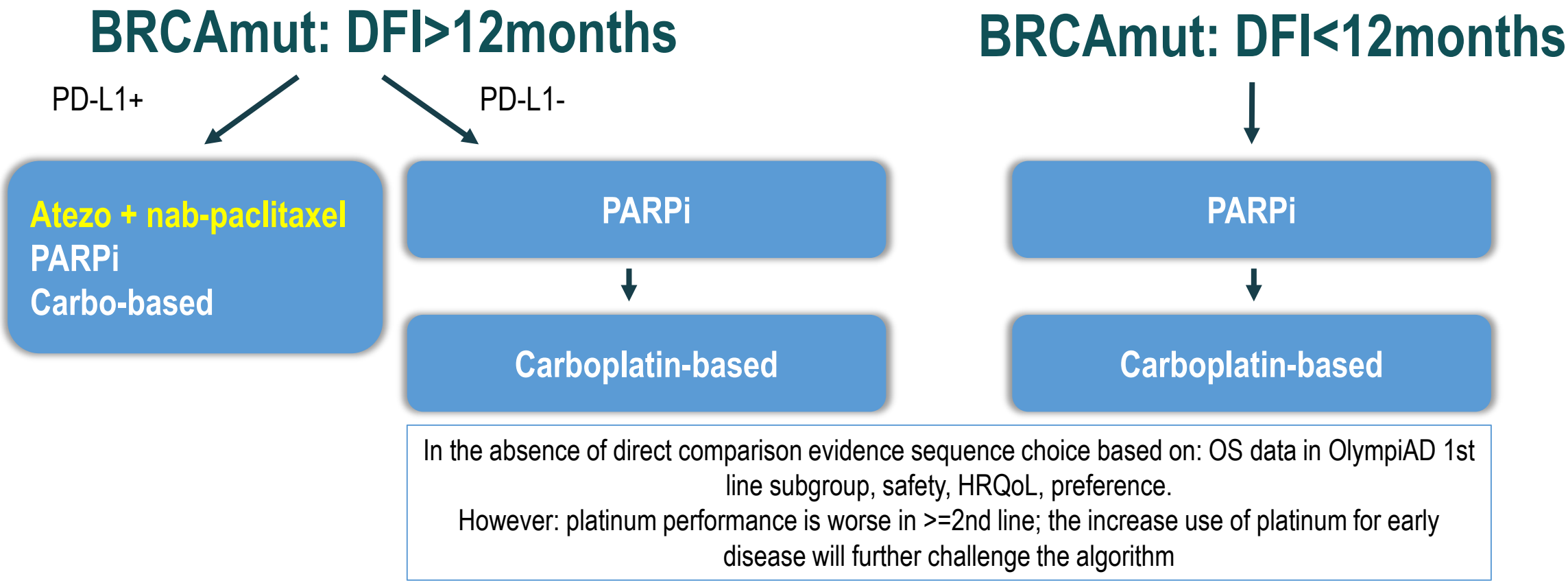
Atezo + nab-paclitaxel
PARPi
Carbo-based

BRCAmut: DFI<12months

↓

In yellow: not yet approved/off-label

1st line Treatment of metastatic TNBC, BRCA mut



In yellow: not yet approved/off-label

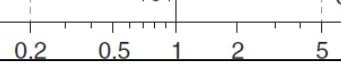
Pooled analyses of eribulin in metastatic breast cancer patients with at least one prior chemotherapy

X. Pivot[1*], F. Marmé[2], R. Koenigsberg[3,4], M. Guo[5], E. Berrak[6] & A. Wolfer[7]

[1]Department of Oncology, Centre Hospitalier Universitaire de Besançon, Service d'Oncologie Médicale, Besançon cedex, France; [2]National Centre for Tumour Diseases, Heidelberg, Department of Gynecologic Oncology, University Hospital, Heidelberg, Germany; [3]3rd Medical Department—Centre for Oncology and Haematology, Ludwig Boltzmann Institute for Applied Cancer Research (LBI-ACR VIEnna)—LB Cluster Translational Oncology, Kaiser Franz Josef-Spital, Vienna; [4]3. Med. Abt.—Zentrum für Onkologie und Hämatologie, Ludwig Boltzmann Institut für angewandte Krebsforschung (LBI-ACR VIEnna), Kaiser Franz Josef-Spital, Wien, Austria; [5]Departments of Biostatistics, Oncology PCU; [6]Oncology, Eisai Inc., Woodcliff Lake, USA; [7]Department of Medical Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

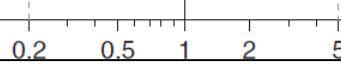
OS

Subgroup	Events/*n* – Eribulin	Events/*n* – Comparator	Median (months) – HR (95% CI)	Eribulin/Comp	*P* value
Overall	844/946	621/698	0.85 (0.76, 0.94)	15.0/12.6	0.002
HER2 status					
Positive	136/150	97/104	0.75 (0.57, 1.00)	13.5/11.7	0.051
Negative	590/663	442/497	0.84 (0.74, 0.96)	15.1/12.0	0.008
Unknown	118/133	82/97	0.98 (0.73, 1.32)	16.5/16.9	0.894
ER status					
Positive	484/544	348/401	0.87 (0.75, 1.00)	15.7/13.5	0.058
Negative	285/319	225/237	0.72 (0.59, 0.86)	12.9/9.4	<0.001
Unknown	75/83	48/60	1.05 (0.70, 1.57)	17.1/20.4	0.816
Triple negative					
Yes	179/199	144/153	0.72 (0.57, 0.90)	12.4/8.1	0.005
No	665/747	477/545	0.86 (0.76, 0.97)	15.7/14.0	0.017
Site of disease					
Visceral disease	713/782	540/608	0.87 (0.78, 0.98)	14.3/12.0	0.025
Nonvisceral disease[b]	122/153	75/84	0.78 (0.57, 1.07)	18.6/16.2	0.128
Number of organs involved					
≤2	406/471	276/324	0.89 (0.76, 1.05)	16.2/15.5	0.168
>2	438/475	345/374	0.79 (0.68, 0.91)	13.1/10.4	0.002
HER2 negative and ER positive					
Yes	384/433	270/314	0.89 (0.75, 1.04)	15.7/14.3	0.152
No	460/513	351/384	0.80 (0.69, 0.92)	14.3/11.2	0.002



PFS

Subgroup	Events/*n* – Eribulin	Events/*n* – Comparator	Median (months) – HR (95% CI)	Eribulin/Comp	*P* value
Overall	826/946	592/698	0.87 (0.78, 0.97)	3.9/3.2	0.017
HER2 status					
Positive	131/150	86/104	1.00 (0.75, 1.35)	3.7/4.2	0.970
Negative	579/663	425/497	0.83 (0.73, 0.95)	3.7/2.9	0.007
ER status					
Positive[b]	467/544	322/401	0.84 (0.72, 0.98)	4.1/3.4	0.031
Negative	285/319	218/237	0.83 (0.68, 1.00)	3.2/2.8	0.061
Triple negative					
Yes	177/199	141/153	0.77 (0.60, 0.97)	2.8/2.5	0.028
No	649/747	451/545	0.90 (0.79, 1.02)	4.1/3.7	0.100
Site of disease					
Visceral disease	697/782	519/608	0.92 (0.81, 1.04)	3.7/3.1	0.176
Nonvisceral disease	121/153	68/84	0.68 (0.48, 0.95)	4.4/3.4	0.022
Number of organs involved					
≤2	400/471	273/324	0.87 (0.74, 1.03)	4.2/4.0	0.116
>2	426/475	319/374	0.86 (0.74, 1.01)	3.6/2.8	0.072
HER2 negative and ER positive					
Yes	375/433	258/314	0.87 (0.73, 1.03)	4.1/3.4	0.106
No	451/513	334/384	0.86 (0.74, 1.00)	3.7/3.0	0.045

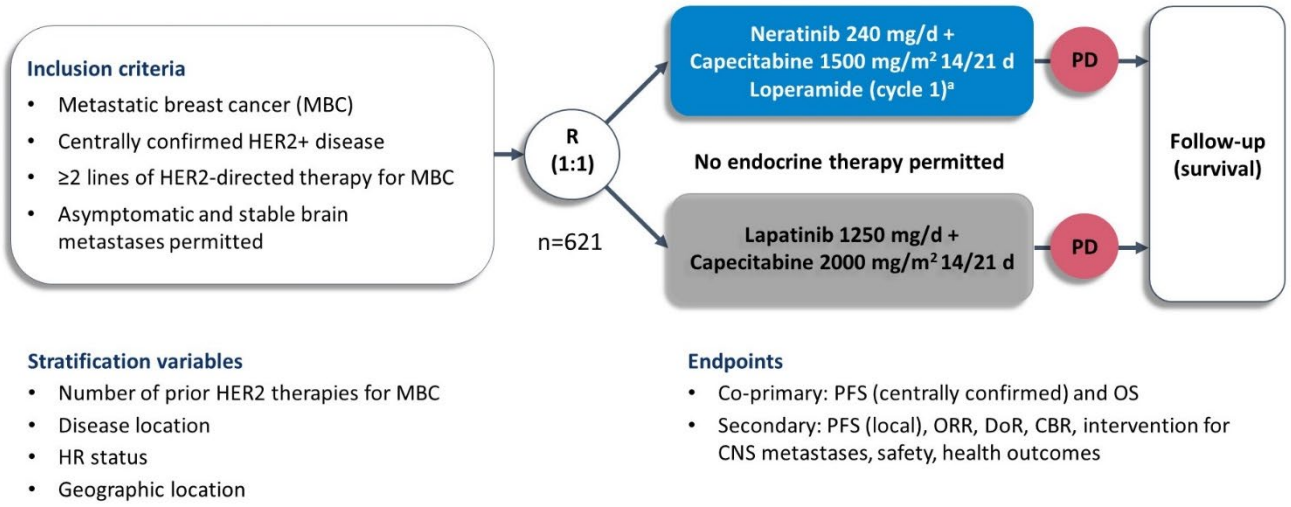


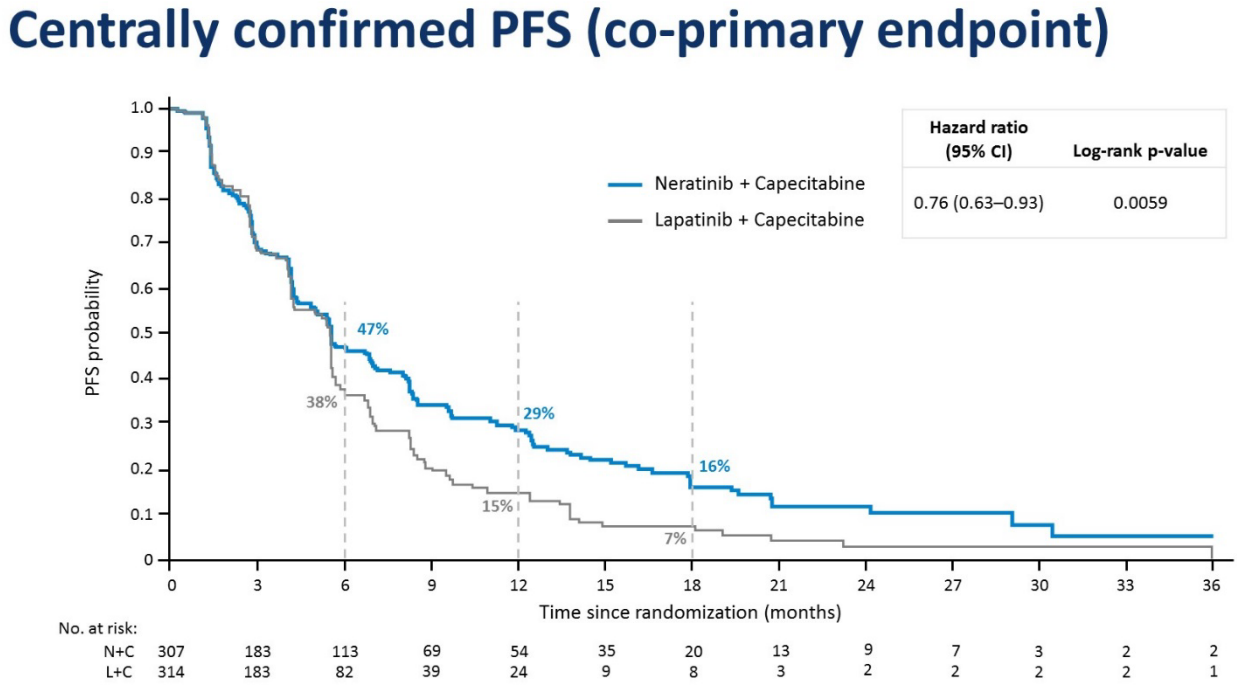
HER2+ MBC: keep an eye on…

- Novel TKIs
  - Irreversible pan-HERi
    - Neratinib + Capecitabine > Lapatinib + Capecitabine in 3+ line (PFS, NALA phIII; 60% prev exposed to trast+pert, TDM1 or both)
    - Pyrotinib + Capecitabine > Lapatinib + Capecitabine in 1-3 line (PFS, phII, 46% trastuzumab-naive)
  - Tucatinib (reversible, HER2 selective): HER2climb phIII ongoing (trast + cape + tuc vs trast + cape + tuc)
- Antibody-drug conjugates
  - Trastuzumab-deruxtecan (DS-8201a): 60% ORR, n=114 pts pre-treated with T-DM1 (ph1)
  - Trastuzumab-duocarmazine (SYD985): 33% ORR, n=48 pts pre-treated with T-DM1 (ph1)
- Immunotherapy
  - Margetuximab + CT > Trastuzumab + CT in late line (SOPHIA)
  - Immune checkpoint inhibitors
    - Encouraging results from pembrolizumab + trastuzumab (PANACEA) and atezolizumab + T-DM1 (KATE2)

Saura C, ASCO 2019; Ma F, J Clin Oncol 2019; Tamura K, Lancet Oncol 2019; Banerji U, Lancet Oncol 2019; Rugo H, ASCO 2019; Loi S, Lancet Oncol 2019; Emens LA, SABCS 2018

NALA, phase III trial

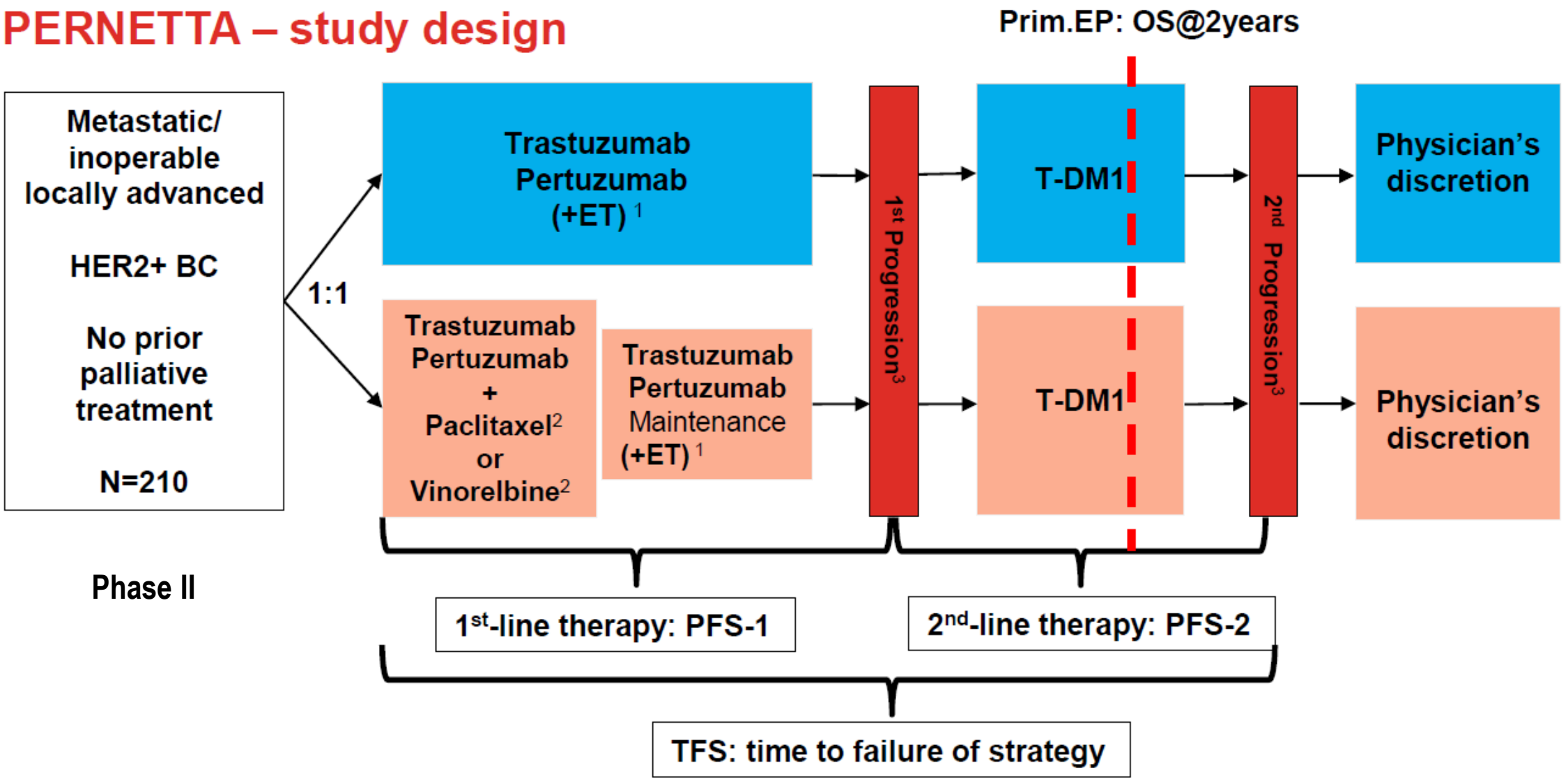




- Time to intervention for CNS metastasis with N+C (cumulative incidence 22.8% vs 29.0% p=0.043
- 24% G3 diarrhea

Saura C, ASCO 2019

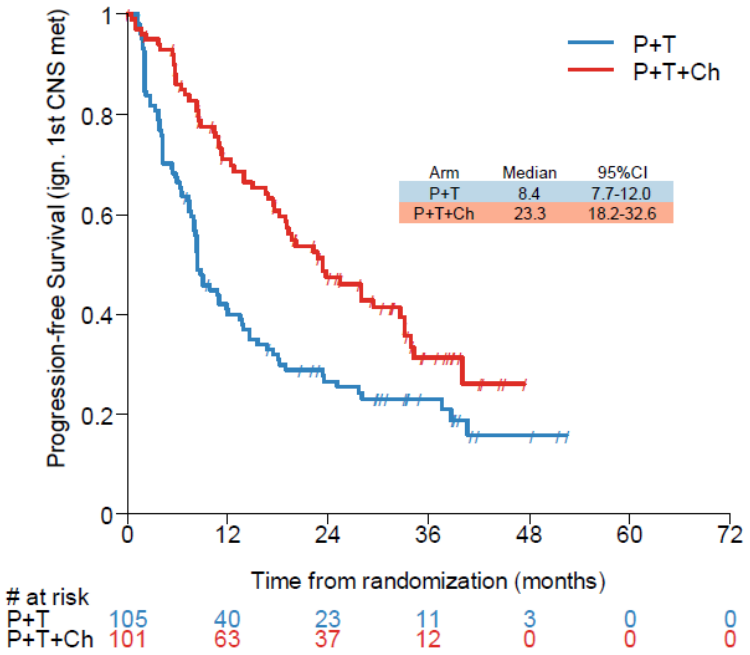
PERNETTA – study design



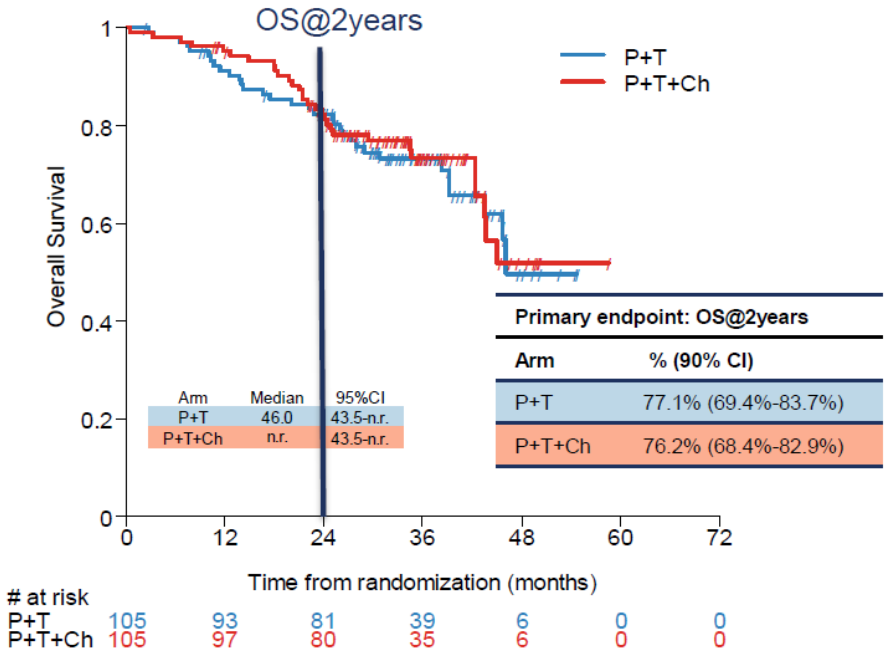
[1] Patients with hormone receptor positive disease should receive endocrine treatment (ET) when treated without chemotherapy
[2] At least 4 months, unless unacceptable toxicity or progressive disease is observed
[3] New parenchymal CNS metastases only do not count as progression requiring the initiation of second- or third-line treatment

Trastuzumab: 8mg/kg / 6mg/kg q3w **Pertuzumab:** 840mg / 420mg q3w **Paclitaxel:** 90mg/m^2 d1/8/15 q4w **Vinorelbine:** 25mg/m^2 resp. 30mg/m^2 d1/8 q3w **T-DM1:** 3.6mg/kg q3w

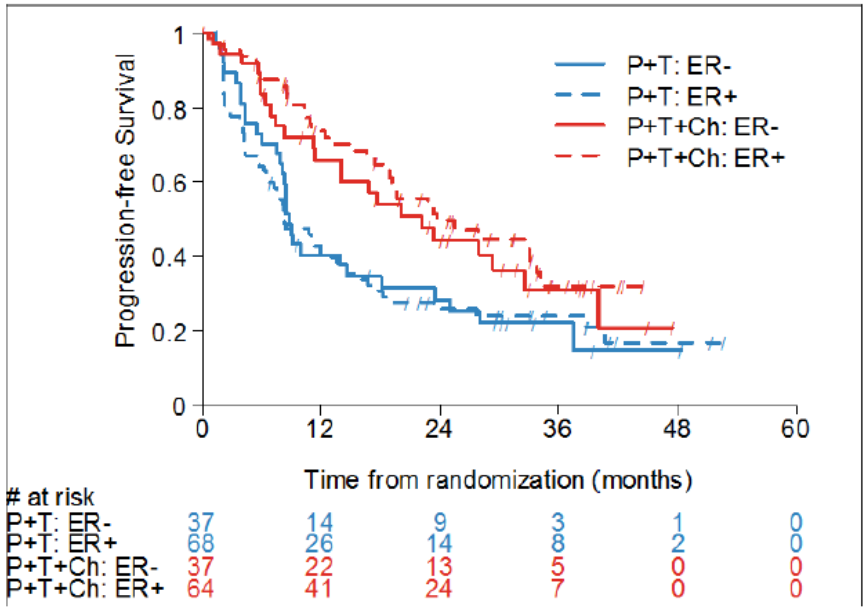
PFS of first-line therapy (PFS-1)

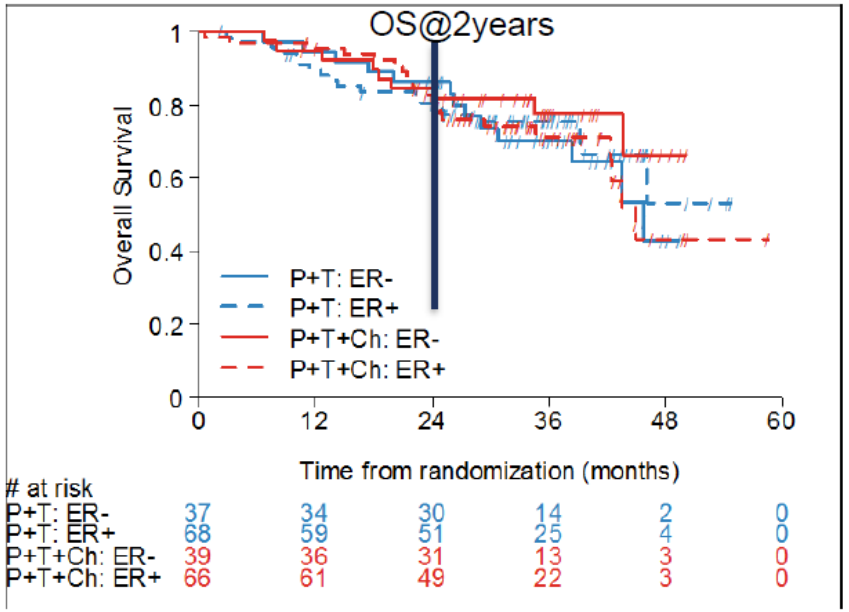


Overall survival



Median FU: 36 months





Small proportion of patients who received ET therapy despite ER +ve status (<20%)

Huober J, ESMO 2018 & ESMO Breast 2019

New drugs/combinations

- Other immunotherapy combinations (i.e. PARPi, activity in early trials MEDIOLA and TOPACIO) or immunotherapy + CT for DFI<12 months (IMpassion132)
- AKT inhibitors + taxane in 1st line in PIK3CA/AKT/PTEN-altered tumors (LOTUS and PAKT, ongoing phase III trials)
- Antibody-drug conjugates in later lines
- Antiandrogens