State of the Art
metastasierte Situation
HER2 negativ Hormonrezeptor positiv

Peter A. Fasching

FRIEDRICH-ALEXANDER
UNIVERSITÄT
ERLANGEN-NÜRNBERG
MEDIZINISCHE FAKULTÄT

Universitäts-
Brustzentrum
Franken

Universitätsklinikum
Erlangen
200 Jahre seit 1815

Interessenskonflikte (Conflict of interest)

- Dr. Fasching reports grants from Novartis, grants from Biontech, personal fees from Novartis, personal fees from Roche, personal fees from Pfizer, personal fees from Celgene, personal fees from Daiichi-Sankyo, personal fees from TEVA, personal fees from Astra Zeneca, personal fees from Merck Sharp & Dohme, personal fees from Myelo Therapeutics, personal fees from Macrogenics, personal fees from Eisai, personal fees from Puma, grants from Cepheid.

Patientinnen mit HER2 neg, HR pos Mammakarzinom,

Palliative Situation

Endokrine Therapie des metastasierten Mammakarzinoms

Guidelines Breast
Version 2019.1D

Indikation

Oxford LoE: 1a **GR: A** **AGO: ++**

Die endokrin-basierte Therapie ist die erste Therapie-option in der Behandlung des metastasierten hormonrezeptor-positiven (oder -unbekannten) Mammakarzinoms

- **Ausnahme: drohender Organausfall**
- **Cave: Der HR-Status kann sich im Laufe der Er-krankung verändern. Falls möglich, sollte eine Histo-logie der neuen Metastase gewonnen werden**

…. Aber machen wir das?

(Hartkopf et al. 2018)

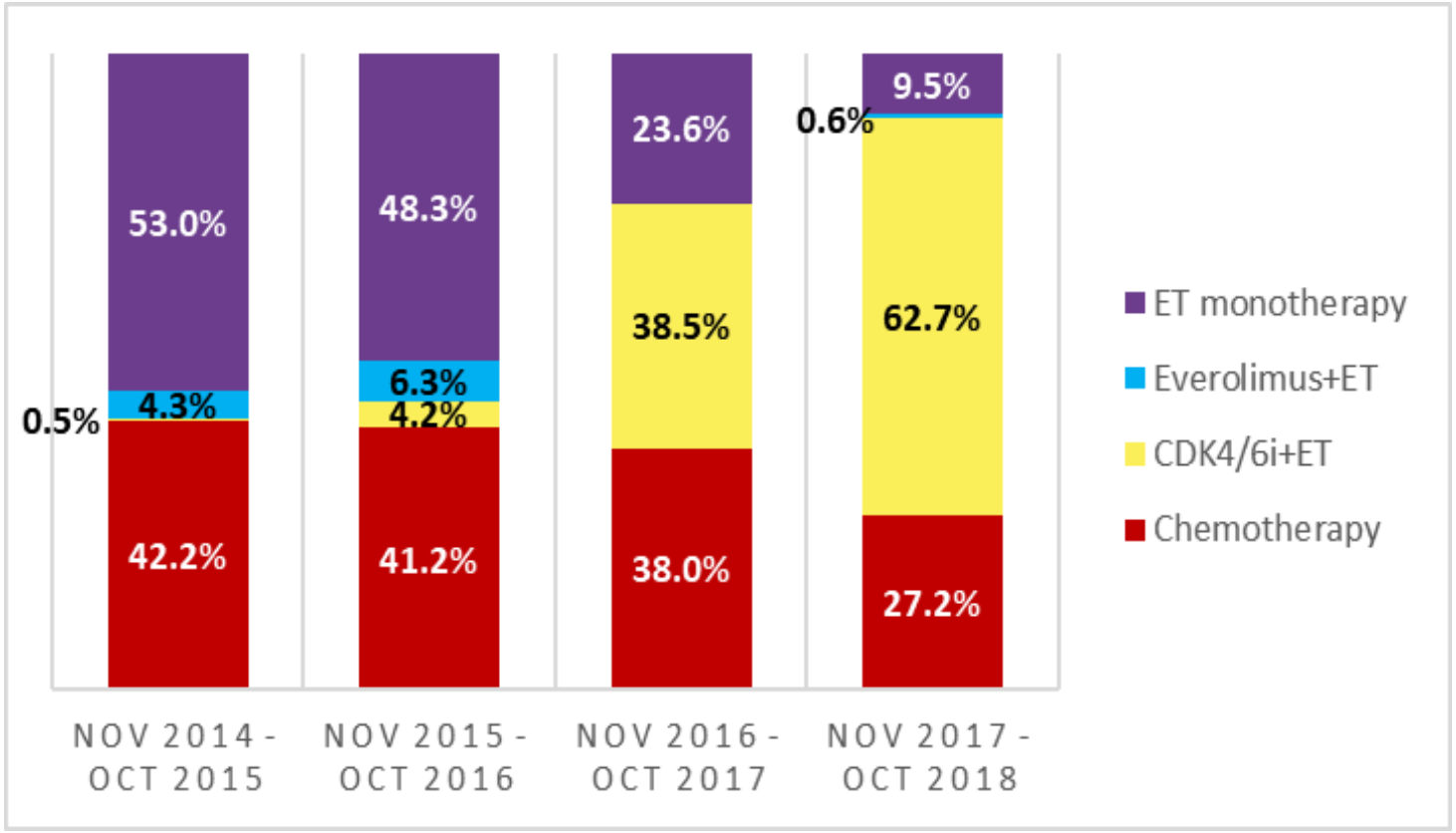
Table 7

Therapy sequences in the first three therapy lines. Listed are only combinations more frequent than 1% (AH: antihormone therapy, Chemo: chemotherapy; EVE: Everolimus + AH; Comparison of Chemo only patients across age groups by dashed arrows, comparison of AH only patient groups across age groups by bold arrows.).

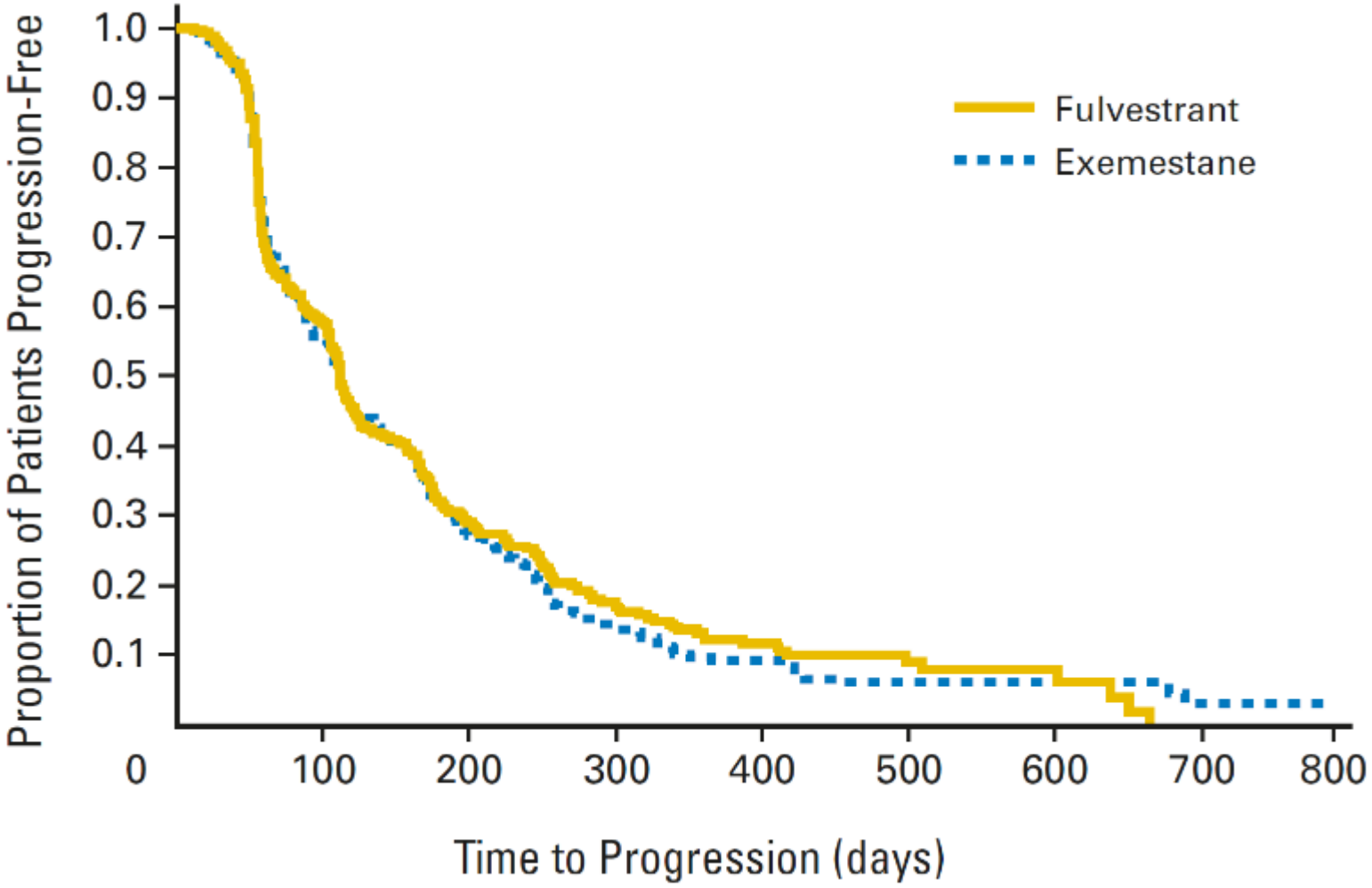
Therapy combination / N / % in patients < 50 years			Therapy combination / N / % in patients 50-65 years			Therapy combination / N / % in patients > 65 years		
1st: Chemo_2nd: Chemo_3rd: Chemo	30	24.19%	**1st: Chemo_2nd: Chemo_3rd: Chemo**	24	9.41%	*1st: AH_2nd: AH_3rd: AH*	24	10.26%
1st: Chemo_2nd: other_3rd: other	17	13.71%	1st: Chemo_2nd: AH_3rd: Chemo	23	9.02%	1st: AH_2nd: AH_3rd: Chemo	24	10.26%
1st: Chemo_2nd: AH_3rd: AH	11	8.87%	1st: Chemo_2nd: AH_3rd: AH	20	7.84%	**1st: Chemo_2nd: Chemo_3rd: Chemo**	22	9.40%
1st: Chemo_2nd: Chemo_3rd: other	9	7.26%	1st: Chemo_2nd: other_3rd: other	20	7.84%	1st: Chemo_2nd: AH_3rd: AH	19	8.12%
1st: Chemo_2nd: AH_3rd: Chemo	8	6.45%	1st: AH_2nd: Chemo_3rd: Chemo	17	6.67%	1st: AH_2nd: EVE_3rd: AH	12	5.13%
1st: AH_2nd: AH_3rd: Chemo	6	4.84%	1st: AH_2nd: AH_3rd: Chemo	16	6.27%	1st: AH_2nd: EVE_3rd: Chemo	12	5.13%
1st: Chemo_2nd: Chemo_3rd: AH	6	4.84%	1st: AH_2nd: EVE_3rd: Chemo	13	5.10%	1st: AH_2nd: AH_3rd: EVE	12	5.13%
1st: AH_2nd: Chemo_3rd: Chemo	5	4.03%	1st: AH_2nd: Chemo_3rd: AH	12	4.71%	1st: Chemo_2nd: other_3rd: other	11	4.70%
1st: other_2nd: Chemo_3rd: other	5	4.03%	1st: Chemo_2nd: Chemo_3rd: other	12	4.71%	1st: AH_2nd: Chemo_3rd: AH	9	3.85%
1st: AH_2nd: EVE_3rd: Chemo	4	3.23%	1st: Chemo_2nd: Chemo_3rd: AH	11	4.31%	1st: Chemo_2nd: AH_3rd: Chemo	9	3.85%
1st: AH_2nd: AH_3rd: EVE	3	2.42%	*1st: AH_2nd: AH_3rd: AH*	10	3.92%	1st: other_2nd: Chemo_3rd: other	7	2.99%
1st: AH_2nd: other_3rd: other	3	2.42%	1st: Chemo_2nd: AH_3rd: other	9	3.53%	1st: Chemo_2nd: AH_3rd: EVE	6	2.56%
1st: AH_2nd: EVE_3rd: AH	2	1.61%	1st: Chemo_2nd: AH_3rd: EVE	8	3.14%	1st: Chemo_2nd: Chemo_3rd: other	6	2.56%
1st: AH_2nd: EVE_3rd: other	2	1.61%	1st: AH_2nd: AH_3rd: EVE	7	2.75%	1st: Chemo_2nd: AH_3rd: other	5	2.14%
1st: AH_2nd: Chemo_3rd: AH	2	1.61%	1st: AH_2nd: EVE_3rd: AH	6	2.35%	1st: other_2nd: AH_3rd: other	5	2.14%
1st: Chemo_2nd: AH_3rd: EVE	2	1.61%	1st: Chemo_2nd: EVE_3rd: Chemo	6	2.35%	1st: other_2nd: other_3rd: other	5	2.14%
1st: Chemo_2nd: AH_3rd: other	2	1.61%	1st: other_2nd: Chemo_3rd: other	6	2.35%	1st: AH_2nd: Chemo_3rd: Chemo	4	1.71%
			1st: other_2nd: AH_3rd: other	5	1.96%	1st: AH_2nd: other_3rd: other	4	1.71%
			1st: EVE_2nd: Chemo_3rd: Chemo	4	1.57%	1st: Chemo_2nd: EVE_3rd: Chemo	4	1.71%
			1st: AH_2nd: other_3rd: other	4	1.57%	1st: other_2nd: EVE_3rd: other	4	1.71%
			1st: Chemo_2nd: Chemo_3rd: EVE	4	1.57%	1st: EVE_2nd: AH_3rd: Chemo	3	1.28%
			1st: other_2nd: other_3rd: other	4	1.57%	1st: EVE_2nd: Chemo_3rd: AH	3	1.28%
			1st: EVE_2nd: AH_3rd: Chemo	3	1.18%	1st: EVE_2nd: Chemo_3rd: Chemo	3	1.28%
			1st: AH_2nd: AH_3rd: other	3	1.18%	1st: AH_2nd: AH_3rd: other	3	1.28%
			1st: AH_2nd: Chemo_3rd: EVE	3	1.18%	1st: AH_2nd: Chemo_3rd: EVE	3	1.28%
						1st: Chemo_2nd: EVE_3rd: AH	3	1.28%
						1st: Chemo_2nd: Chemo_3rd: AH	3	1.28%

…. Ist es wirklich so schlimm?

(Huober et al. SABCS2017 und Schneeweiss et al. CONFIDENTIAL)



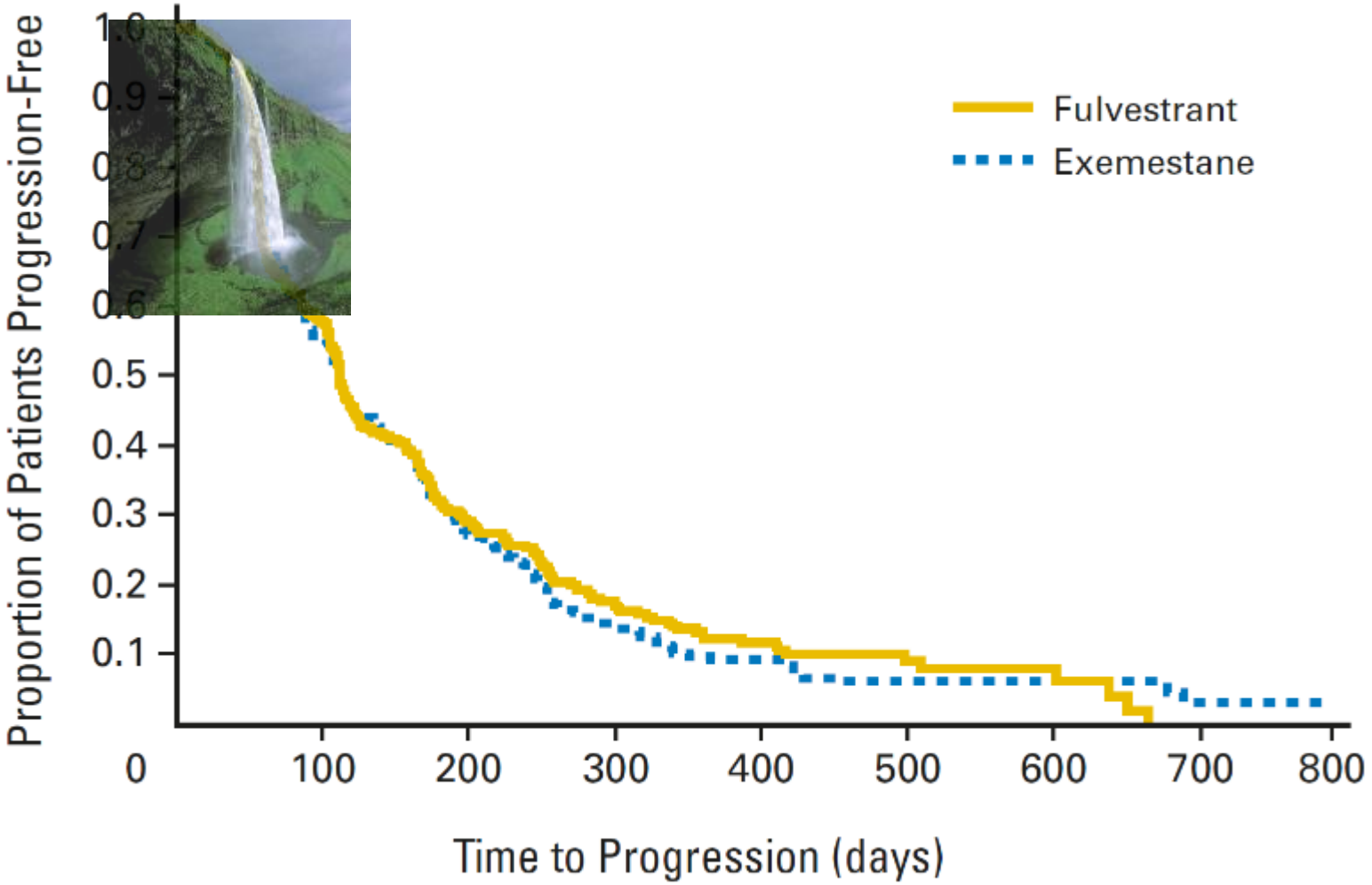
Schnelle Resistenz-Entwicklung nach antihormoneller Vortherapie (Chia et al. 2008)



FRIEDRICH-ALEXANDER
UNIVERSITÄT
ERLANGEN-NÜRNBERG
MEDIZINISCHE FAKULTÄT

Universitätsklinikum
Erlangen

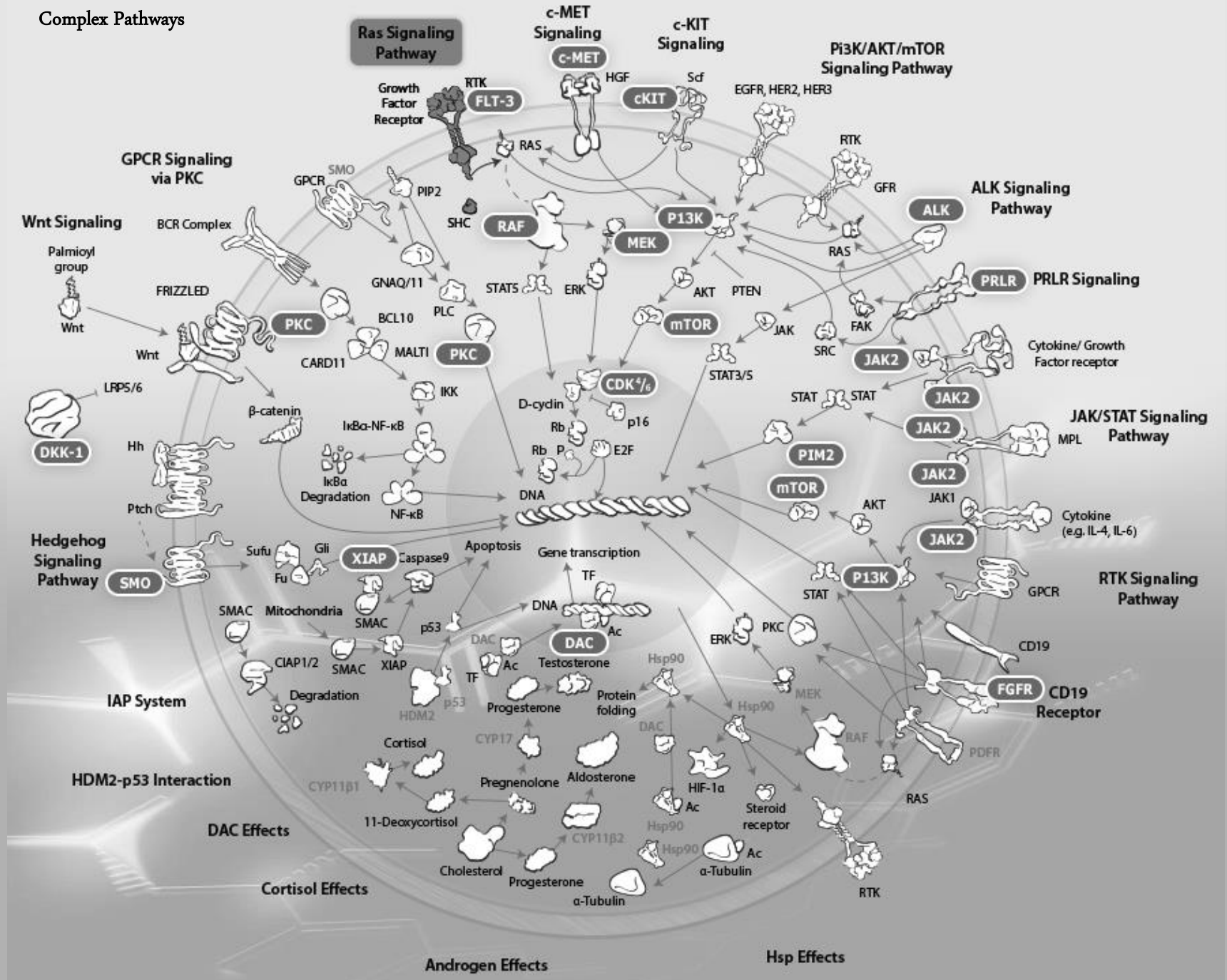
Schnelle Resistenz-Entwicklung nach antihormoneller Vortherapie (Chia et al. 2008)



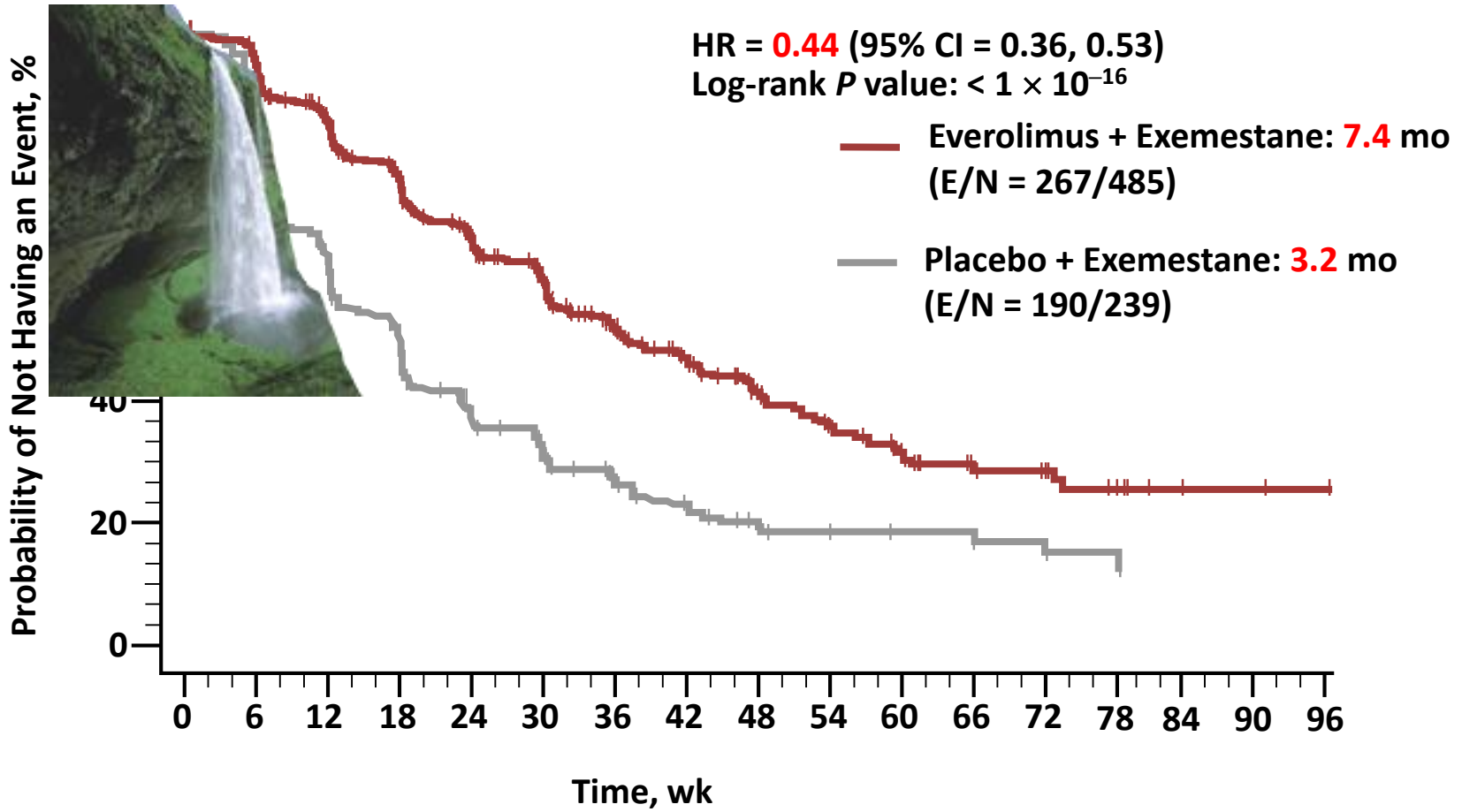
Fragen

- Was sind die Resistenzmechanismen?
- Wie können wir die Resistenz überwinden?

Complex Pathways



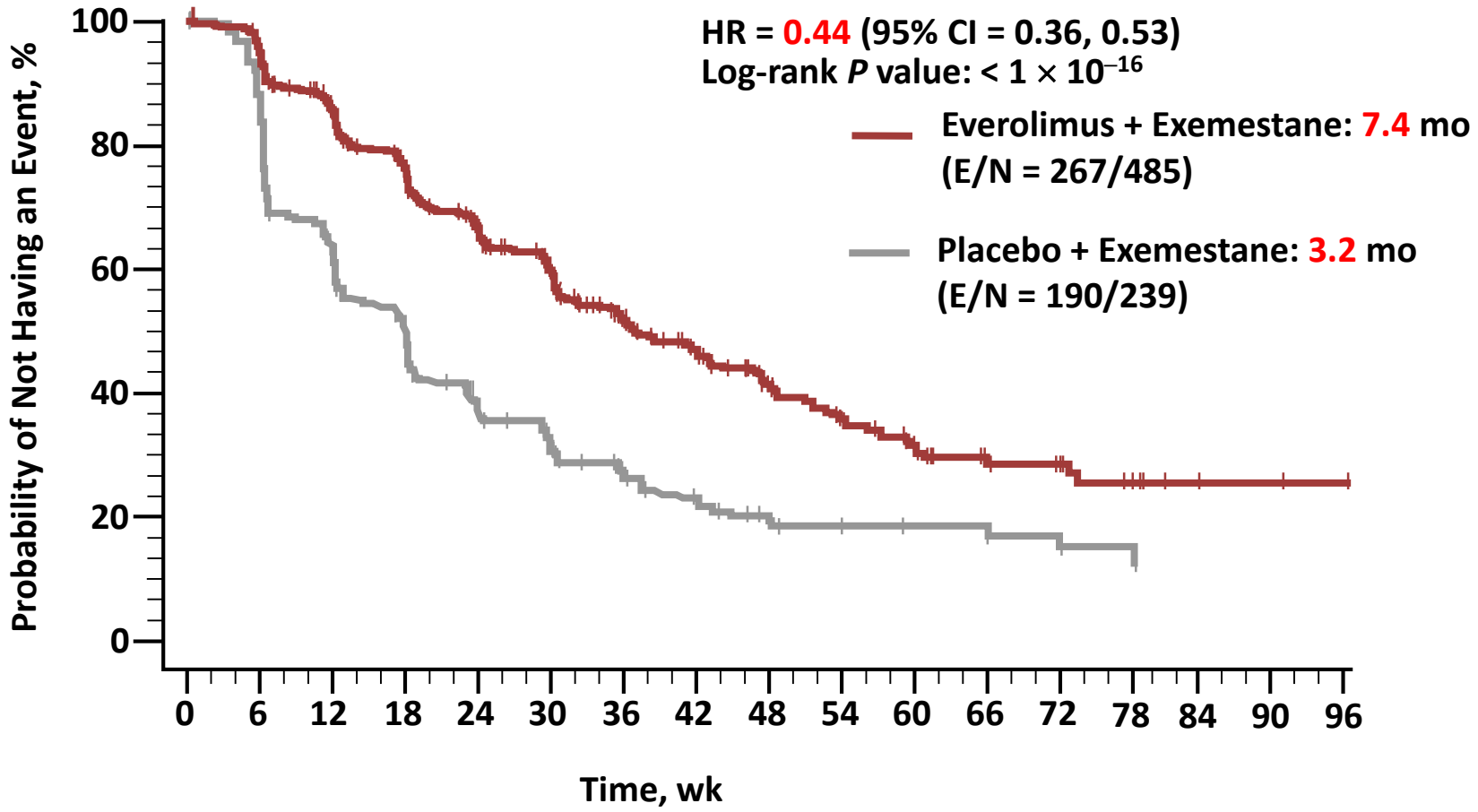
BOLERO-2: Primary Endpoint, PFS (Local Assessment)



Abbreviations: CI, confidence interval; E/N, patients with events/total patients; HR, hazard ratio; PFS, progression-free survival.

Hortobagyi G, et al. SABCS 2011; abstract S3-7 (oral).

BOLERO-2: Primary Endpoint, PFS (Local Assessment)

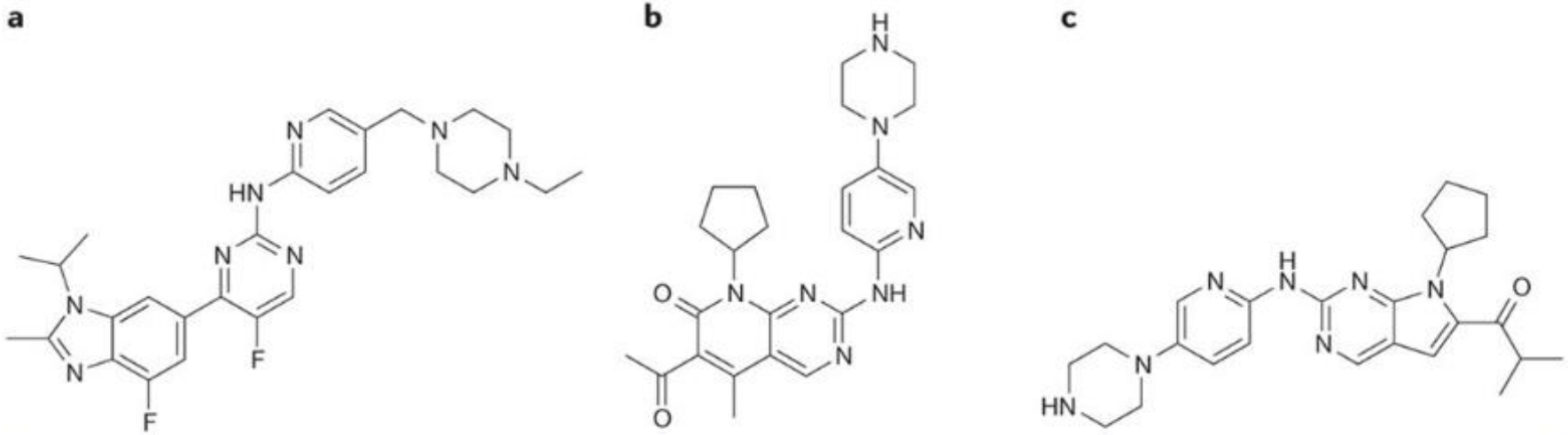


Abbreviations: CI, confidence interval; E/N, patients with events/total patients; HR, hazard ratio; PFS, progression-free survival.

Hortobagyi G, et al. SABCS 2011; abstract S3-7 (oral).

Selective CDK4/6 Inihibitors

Abemaciclib **Palbociclib** **Ribociclib**



	Abemaciclib (LY-2835219)	Palbociclib (PD-0332991)	Ribociclib (LEE011)
IC_{50}	CDK1: >1 μM	CDK1: >10 μM	CDK1: >100 μM
	CDK2: >500 nM	CDK2: >10 μM	CDK2: >50 μM
	CDK4: 2 nM	CDK4: 9–11 nM	CDK4: 10 nM
	CDK5: ND	CDK5: >10 μM	CDK5: ND
	CDK6: 5 nM	CDK6: 15 nM	CDK6: 39 nM
	CDK7: 300 nM	CDK7: ND	CDK7: ND
	CDK9: 57 nM	CDK9: ND	CDK9: ND

O'Leary *et al* Nat Rev Clin Oncol 2016

Nature Reviews | Clinical Oncology

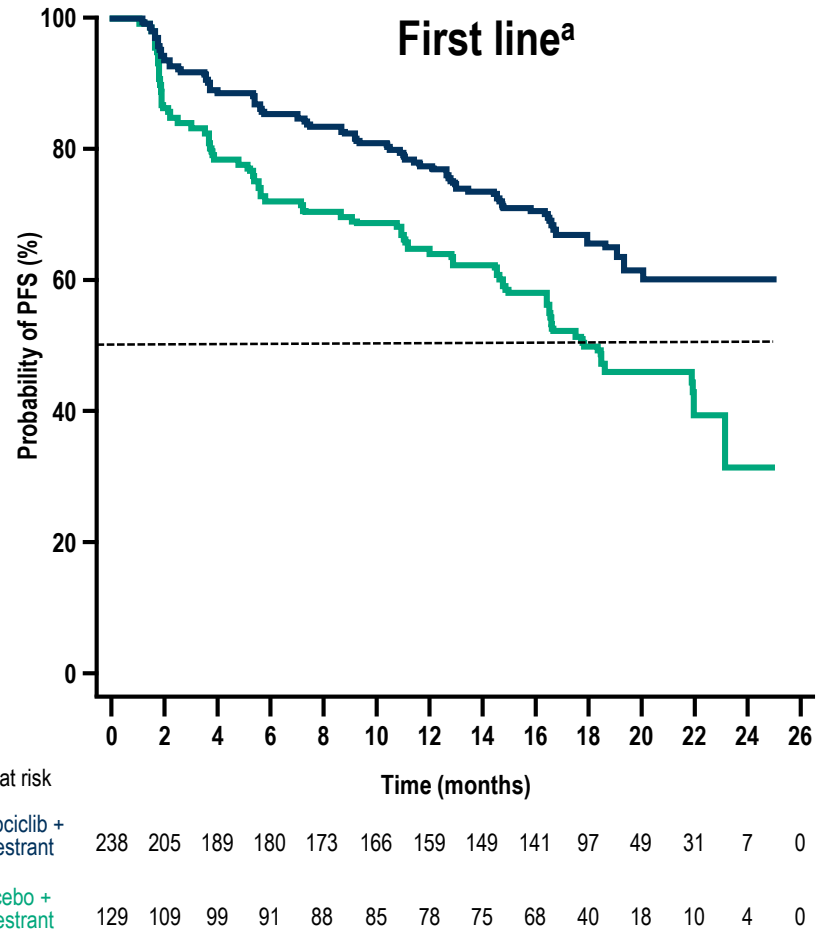
Studies with CDK 4/6 Inhibitors

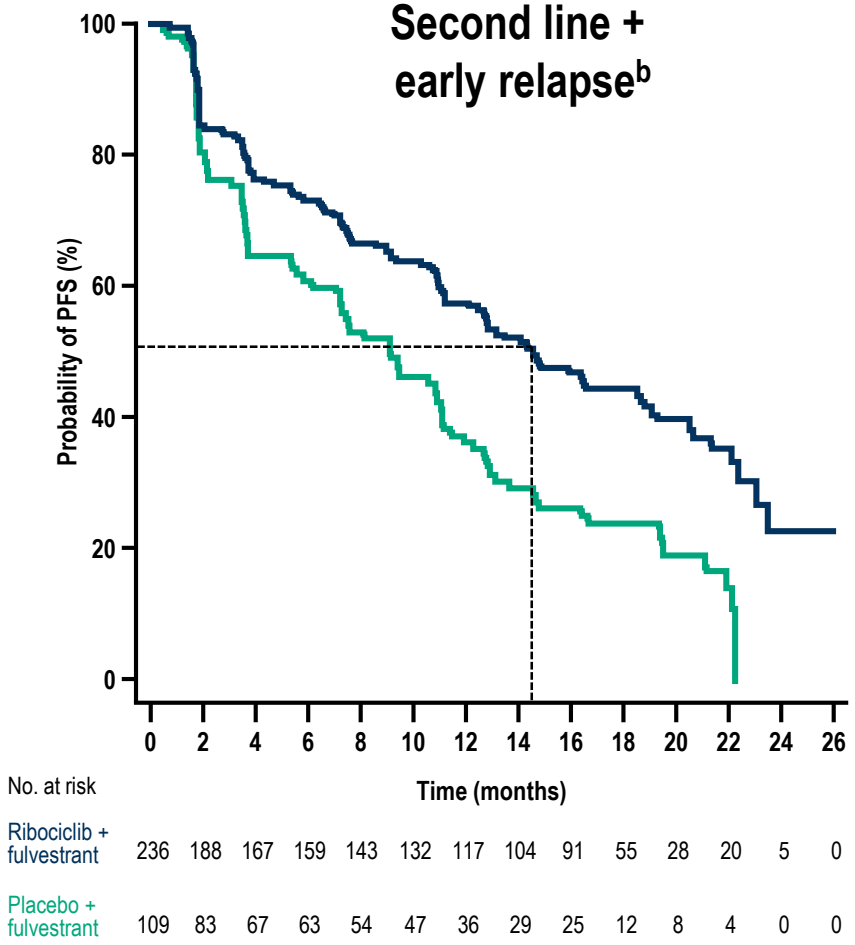
(nach Burstein ASCO 2018)

Linie	Studie	Therapie	CDK 4/6	PFS (Monate)	HR
1	PALOMA1	Letrozol	Palbociclib	10,2→20,2	0,49
1	PALOMA2	Letrozol	Palbociclib	14,5→24,8	0,58
1	MONALEESA2	Letrozol	Ribociclib	14,5→ca 26	0,56
1	MONALEESA7	Letrozol/ Ov Suppress	Ribociclib	13,0→23,8	0,55
1	MONARCH3	NSAI	Abemaciclib	14,7→???	0,54
1	MONALEESA3	Fulvestrant	Ribociclib	18,3→???	0,57
2	PALOMA3	Fulvestrant	Palbociclib	3,8→9,2	0,42
2	MONALEESA3	Fulvestrant	Ribociclib	9,1→14,6	0,57
2	MONARCH2	Fulvestrant	Abemaciclib	9,3→16,4	0,55
2	MONRACH2	Fulvestrant/ Ov Suppres	Abemaciclib	10,5→???	0,45

PFS BENEFIT CONSISTENT ACROSS TREATMENT SETTINGS

MONALEESA-3
Mammary Oncology Assessment of LEE011's Efficacy and Safety





MUNICH 2018 ESMO congress

[a]No prior endocrine therapy for ABC;
[b]Up to one line of prior endocrine therapy for ABC or relapse on/within 12 months of (neo)adjuvant endocrine therapy; [c]Investigator assessed.

1. Slamon DJ et al. ASCO 2018;abst 1000 (oral); 2. Slamon DJ et al. *J Clin Oncol* 2018;36:2465–2472.

Endokrine Therapie der prämenopausalen Patientin mit HER2-negativem metastasiertem Mammakarzinom

Guidelines Breast
Version 2019.1D

	Oxford		
	LoE	GR	AGO
▪ GnRH-A + Fulvestrant + Palbociclib	2b	B	++
▪ GnRH-A + AI + Palbociclib*	5	D	++
▪ GnRH-A + AI + Ribociclib	1b[a]	B	++
▪ GnRH-A + Fulvestrant + Abemaciclib	2b	B	++
▪ GnRH-A + Tamoxifen (vs. OFS od. Tam)	1a	A	++
▪ Unterdrückung der Ovarialfunktion (OFS)	2b	B	+
▪ Tamoxifen	2b	B	+
▪ GnRH-A + AI (first + second line)	2b	B	+
▪ GnRH-A + Fulvestrant	1b	B	+
▪ Aromataseinhibitoren ohne OFS	3	D	- -

* Extrapoliert aus Daten postmenopausaler Patientinnen (mit AI)

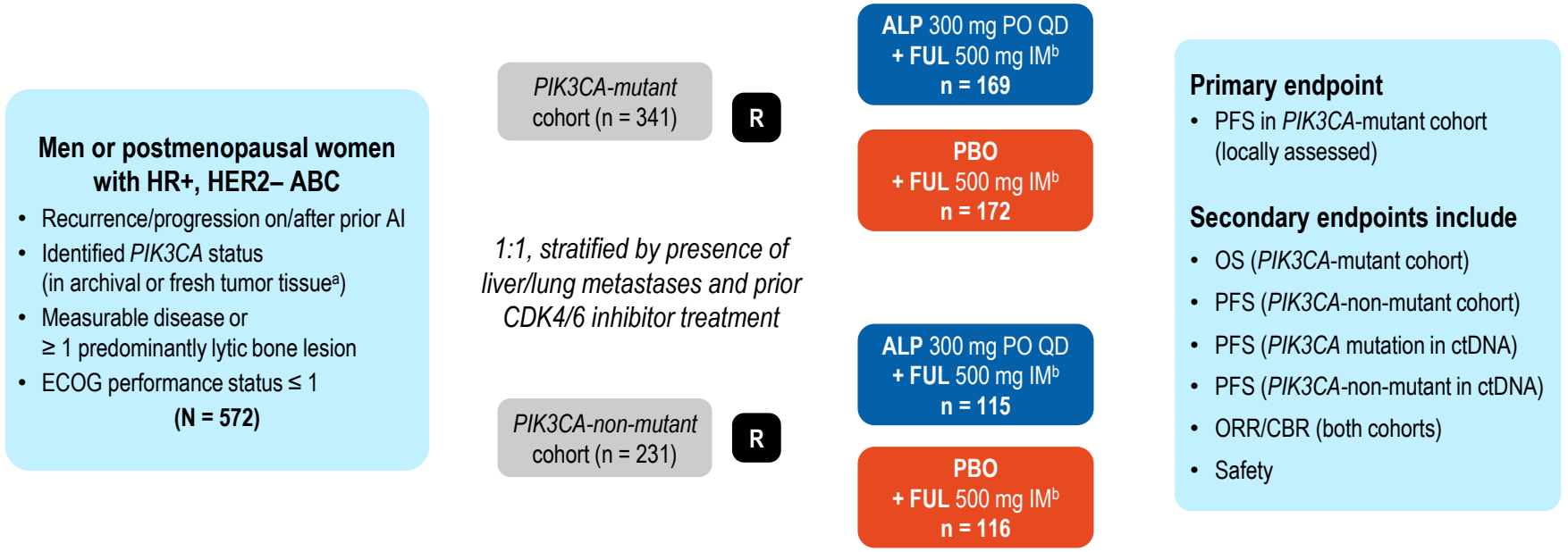
Endokrin-basierte Therapie der postmenopausalen Patientin mit HER2-negativem metastasiertem Mammakarzinom

Guidelines Breast
Version 2019.1D

	Oxford		
	LoE	GR	AGO
▪ CDK4/6-Inhibitor (Abemaciclib, Palbociclib, Ribociclib)			
▪ + nicht-steroidaler AI	1b	B	++
▪ + Fulvestrant	1b	B	++
▪ Abemaciclib Monotherapie	3	C	+/-
▪ Everolimus			
▪ + Exemestan	1b	A	+
▪ + Tamoxifen	2b	B	+
▪ + Letrozol	2b	B	+/-
▪ + Fulvestrant	2b[a]	B	+
▪ CDK4/6i beyond progression	5	D	-

Ausblick HER2 neg HR pos

SOLAR-1: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial (NCT02437318)[1]



- The primary endpoint included all randomized patients in the *PIK3CA*-mutant cohort; PFS was analyzed in the *PIK3CA*-non-mutant cohort as a proof of concept
- Safety was analyzed for all patients who received ≥ 1 dose of study treatment, in both cohorts

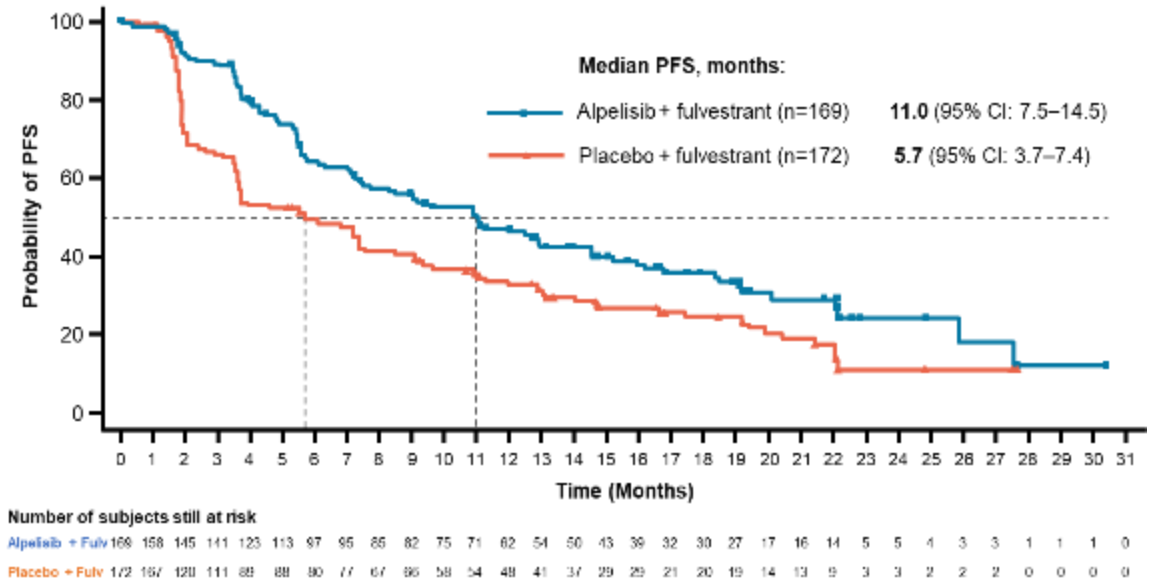
ABC, advanced breast cancer; AI, aromatase inhibitor; ALP, alpelisib; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant; HER2–, human epidermal growth factor receptor-2–negative; IM, intramuscular; ORR, overall response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, oral; QD, once daily; R, randomization.

[a] More than 90% of patients had mutational status identified from archival tissue.

[b] Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.

1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

Primary endpoint:
Locally assessed PFS in the *PIK3CA*-mutant cohort

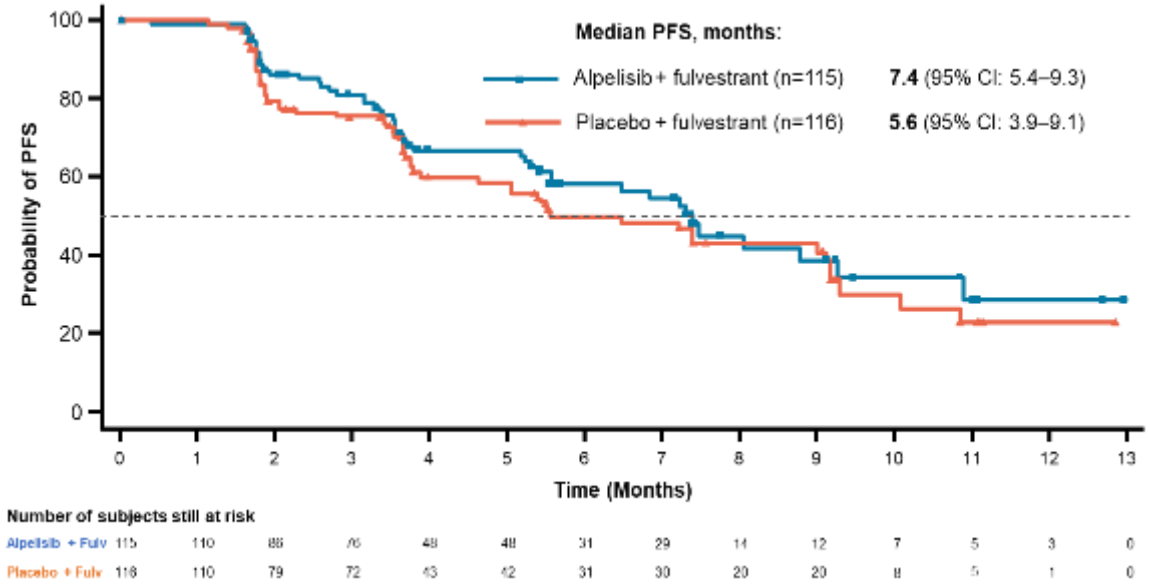


Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5–14.5)	5.7 (3.7–7.4)
HR (95% CI)	0.65 (0.50–0.85)	
p-value	0.00065	

- The primary endpoint crossed the prespecified Haybittle–Peto boundary (one-sided p≤0.0199)

Proof of Concept: PFS in the *PIK3CA*-non-mutant cohort

Proof of concept criteria were not met in the PIK3CA-non-mutant cohort



Data cut-off: Dec 23, 2016	Alpelisib + fulvestrant (N=115)	Placebo + fulvestrant (N=116)
Number of PFS events, n (%)	49 (42.6)	57 (49.1)
Progression	47 (40.9)	57 (49.1)
Death	2 (1.7)	0
Censored	66 (57.4)	59 (50.9)
Median PFS (95% CI)	7.4 (5.4–9.3)	5.6 (3.9–9.1)
HR (95% CI)	0.85 (0.58–1.25)	
Posterior probability HR<1, %	79.4	

- Proof of concept criteria: estimated hazard ratio ≤0.60 and posterior probability ≥90% that the hazard ratio was <1
- Patients with *PIK3CA*-non-mutant disease were followed up for safety alongside the *PIK3CA*-mutant cohort

Patientinnen mit triple negativem Mammakarzinom,

Palliative Situation

Tripel negatives mBC unabhängig von Keimbahnmutation für BRCA 1/2

Guidelines Breast
Version 2019.1D

	Oxford		
	LoE	GR	AGO
▪ Chemotherapie wie bei Patientinnen mit HR-pos / HER2-neg mBC			+/-
▪ Carboplatin (vs. Docetaxel)	1b[a]	B	+/-
▪ Gemcitabin/Cisplatin (vs. Gem/Pac)	1b	A	+
▪ Nab-Paclitaxel/Carboplatin (vs. Carbo/Gem)	2b[a]	B	+
▪ Bevacizumab zusätzlich zur first-line Zytostatikatherapie	1b	B	+
▪ Atezolizumab plus Nab-Paclitaxel first-line, bei PD-L1 IC Positivität[#]	1b	B	+

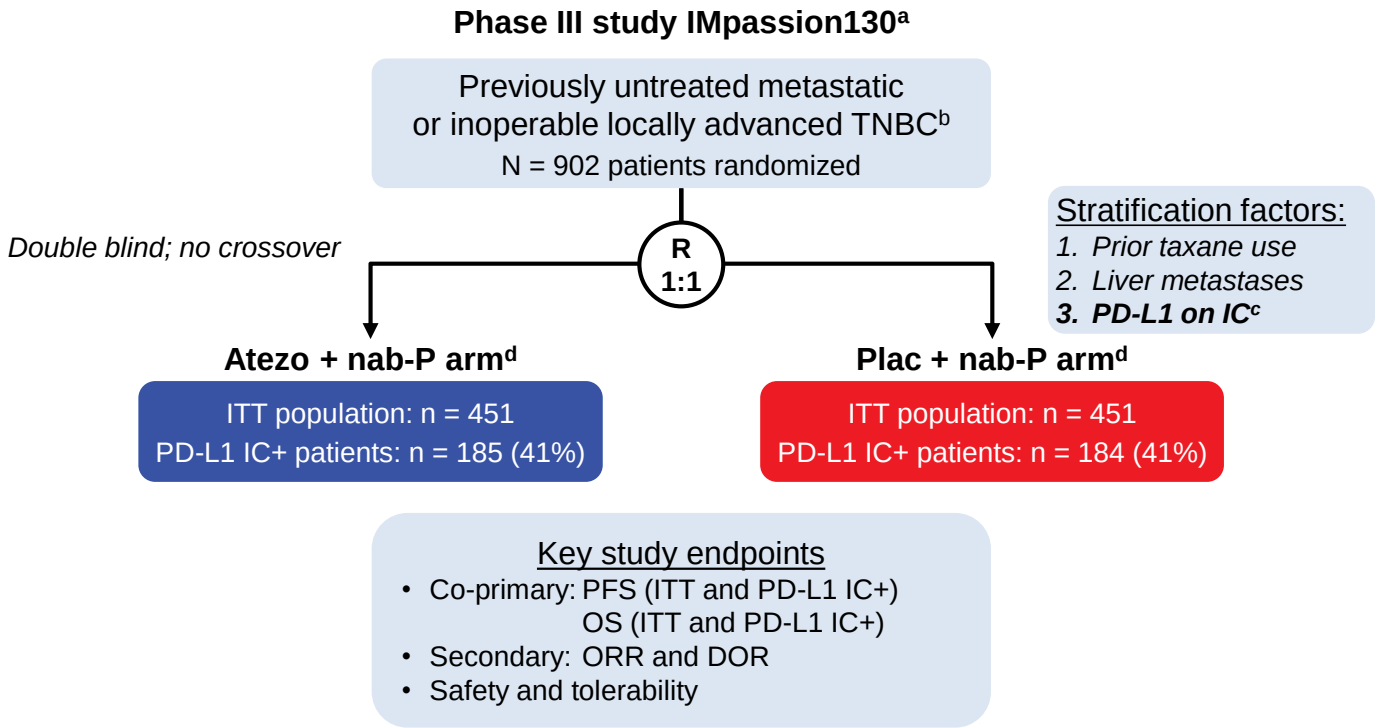
≥ 1% bestimmt auf Immunzellen (IC) (siehe Kapitel „Pathologie“)

mBC mit Keimbahnmutation für BRCA 1/2

	Oxford		
	LoE	GR	AGO
▪ Standardtherapie entsprechend gBRCA1/2 negativ			++
▪ Carboplatin (vs. Docetaxel) (wenn Platin-naiv)	1b	B	+
▪ PARP-Inhibitoren			
▪ HER2-negativ:			
▪ Olaparib	1b	B	+
▪ Talazoparib	1b	B	+/-
▪ HER2-positiv:			
▪ Olaparib	5	D	+/-
▪ Talazoparib	5	D	+/-

PD1 als Prädiktor für Atezolizumab

IMpassion130 study design: Prespecified analyses in the ITT and PD-L1 IC+ population

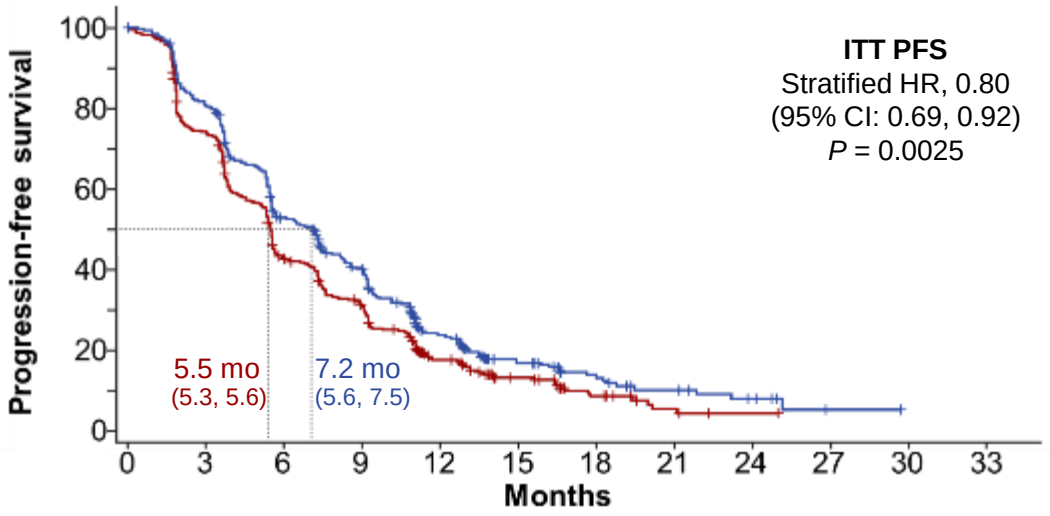


[a] NCT02425891. [b] Locally evaluated per ASCO-CAP guidelines. Prior chemotherapy in the curative setting, including taxanes, allowed if treatment-free interval ≥ 12 mo.
[c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status, PD-L1+: PD-L1 on ≥ 1% of IC). [d] Atezolizumab or placebo 840 mg IV on days 1 and 15 + *nab*-paclitaxel 100 mg/m^2 IV on days 1, 8 and 15 of 28-day cycle until RECIST v1.1 PD. 1. Schmid *N Engl J Med* 2018.

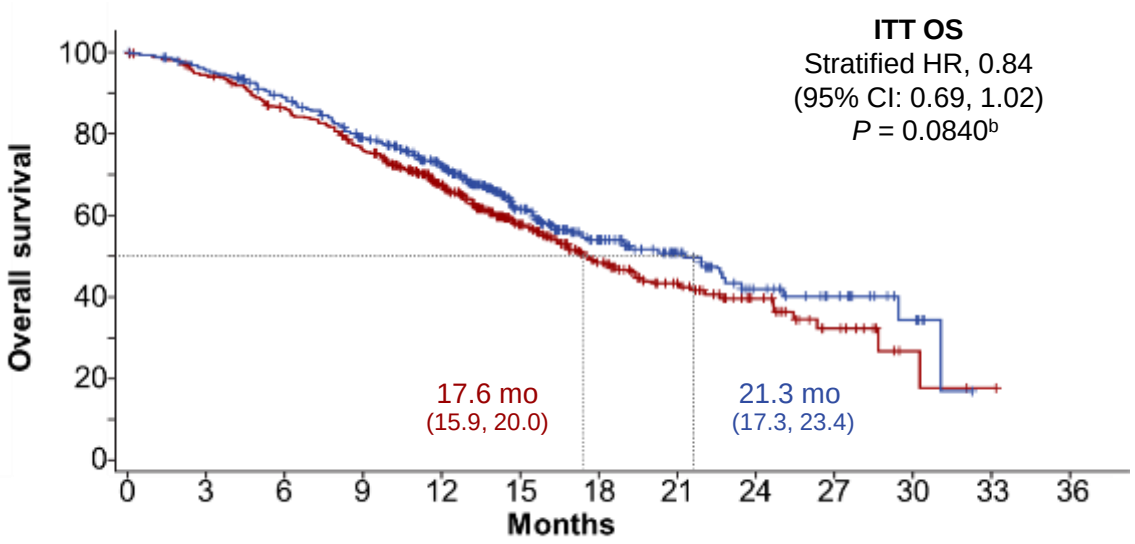
Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

IMpassion130 primary analysis[1,2]: Clinically meaningful PFS and OS benefit in the PD-L1+ population

ITT population



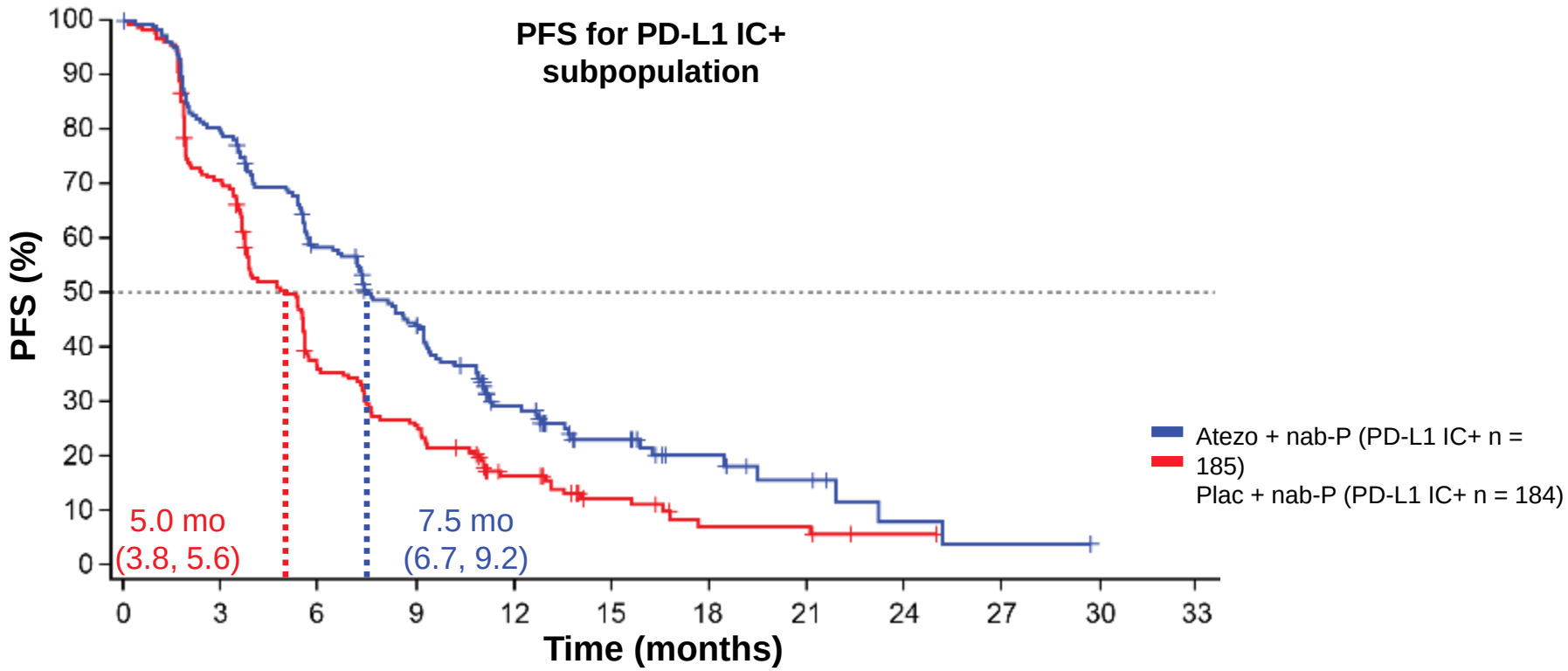
ITT PFS
Stratified HR, 0.80
(95% CI: 0.69, 0.92)
P = 0.0025



ITT OS
Stratified HR, 0.84
(95% CI: 0.69, 1.02)
P = 0.0840[b]

NE, not estimable.
Median follow-up (ITT): 12.9 months.
[a] PD-L1+: PD-L1 in ≥ 1% of IC. [b] Not significant. [c] Not formally tested per hierarchical study design.
1. Schmid *N Engl J Med* 2018. 2. Schmid ESMO 2018 [LBA1_PR].

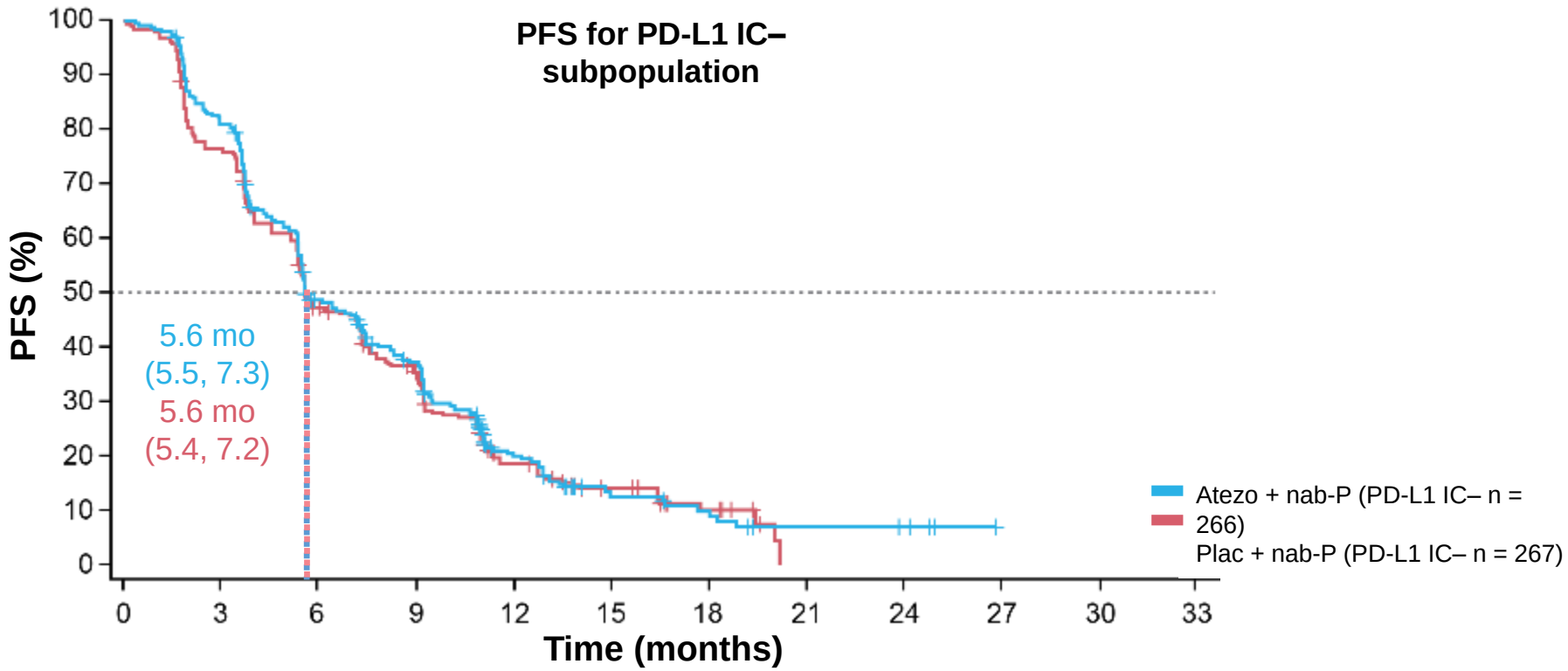
PD-L1 IC status (positive vs negative) predicts PFS benefit with atezolizumab + *nab*-paclitaxel



Median PFS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values except for PD-L1 IC+ PFS are nominal *P* values. Data cutoff: April 17, 2018.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

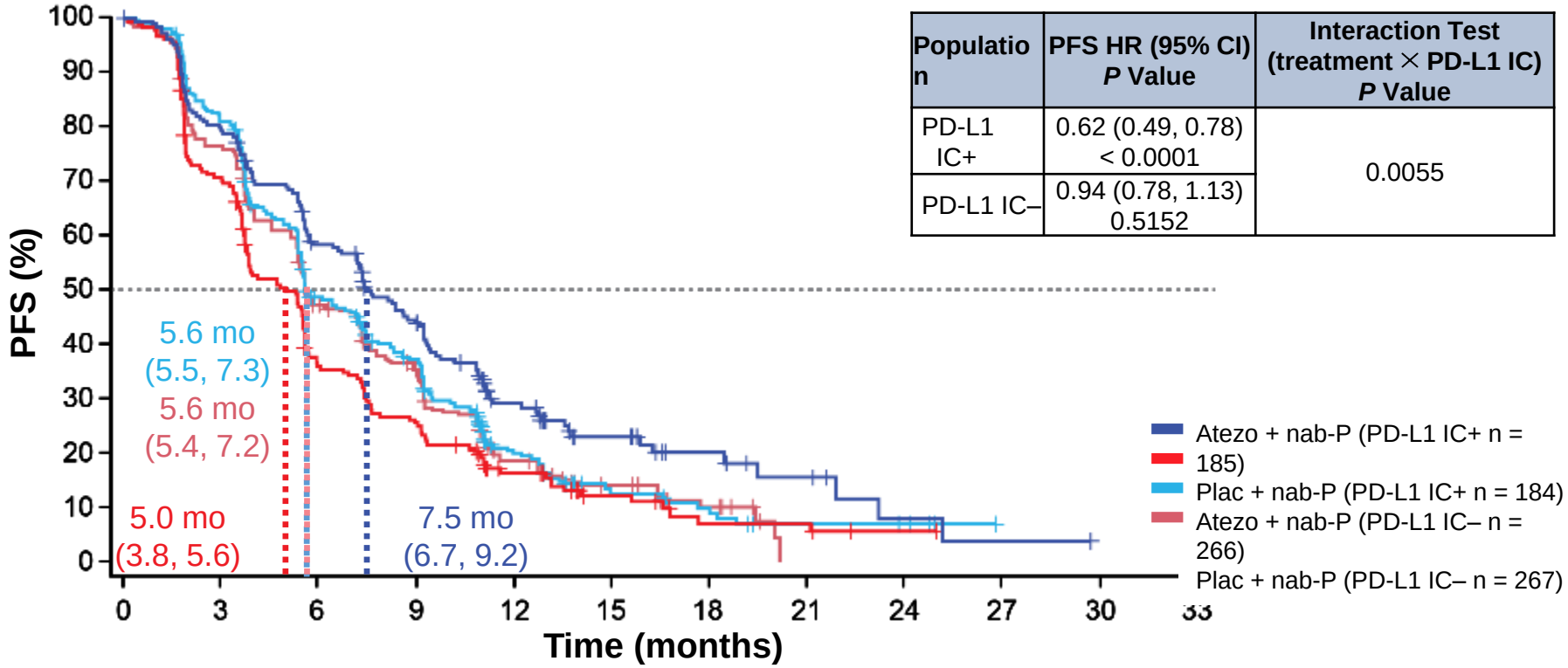
PD-L1 IC status (positive vs negative) predicts PFS benefit with atezolizumab + *nab*-paclitaxel



Median PFS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values except for PD-L1 IC+ PFS are nominal *P* values. Data cutoff: April 17, 2018.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

PD-L1 IC status (positive vs negative) predicts PFS benefit with atezolizumab + *nab*-paclitaxel



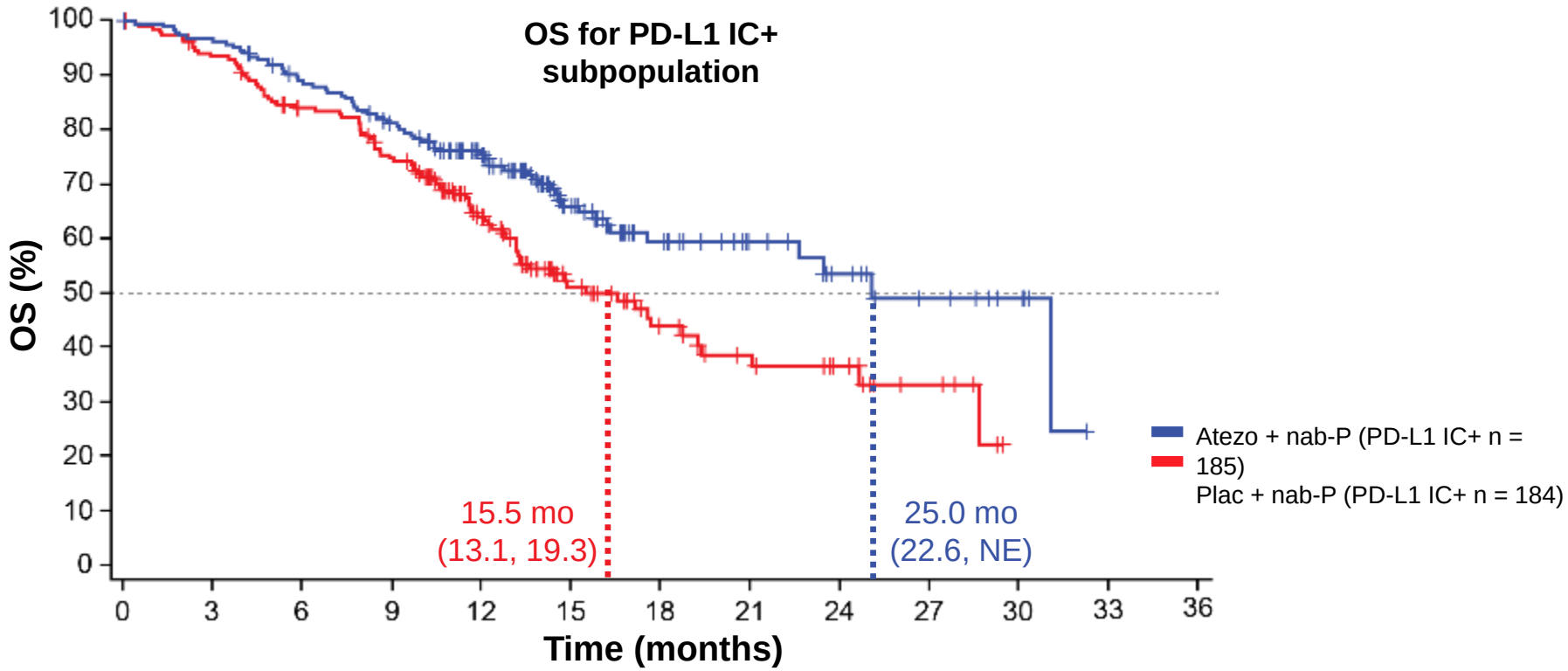
Population	PFS HR (95% CI) *P* Value	Interaction Test (treatment × PD-L1 IC) *P* Value
PD-L1 IC+	0.62 (0.49, 0.78) < 0.0001	0.0055
PD-L1 IC–	0.94 (0.78, 1.13) 0.5152	

- A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant
- PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + *nab*-paclitaxel

Median PFS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values except for PD-L1 IC+ PFS are nominal *P* values. Data cutoff: April 17, 2018.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

PD-L1 IC status (positive vs negative) predicts OS benefit with atezolizumab + *nab*-paclitaxel

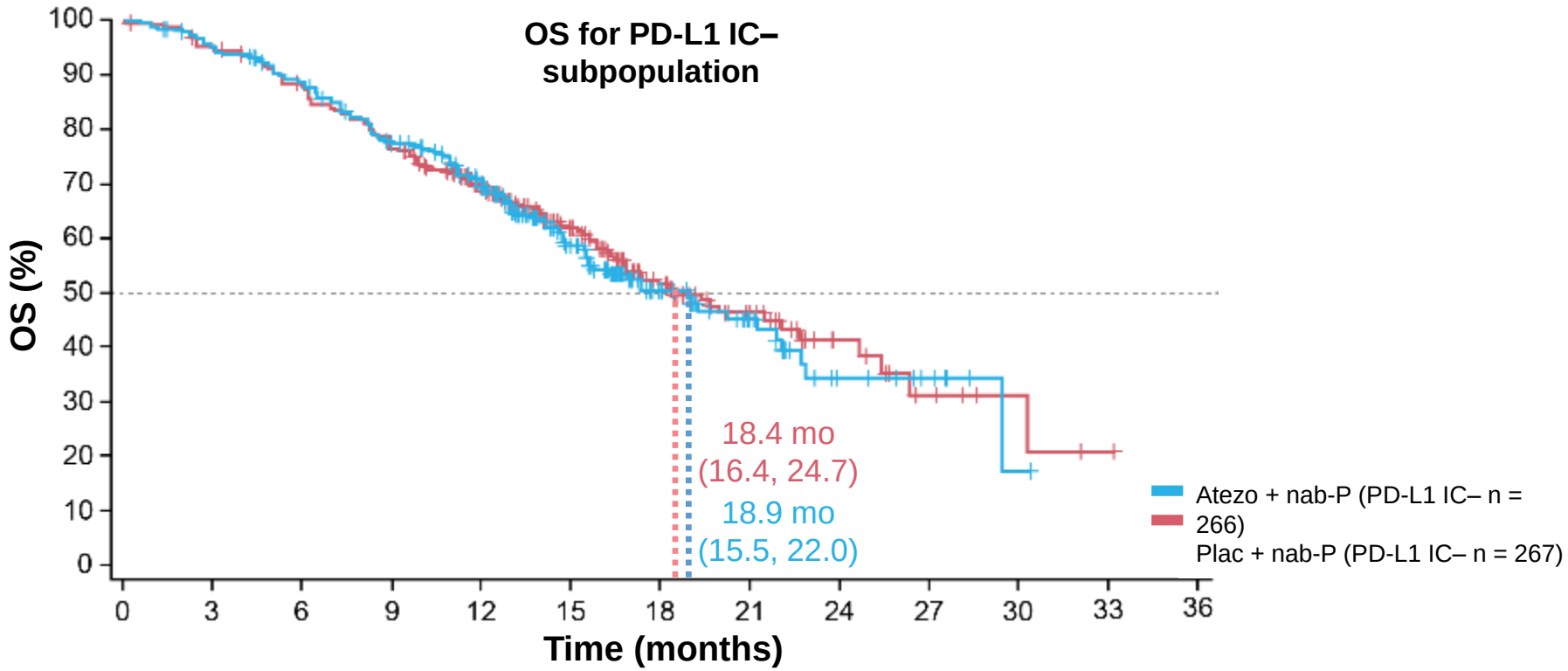


- A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant
- PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + *nab*-paclitaxel

Median OS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values are nominal. Data cutoff: April 17, 2018.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

PD-L1 IC status (positive vs negative) predicts OS benefit with atezolizumab + *nab*-paclitaxel

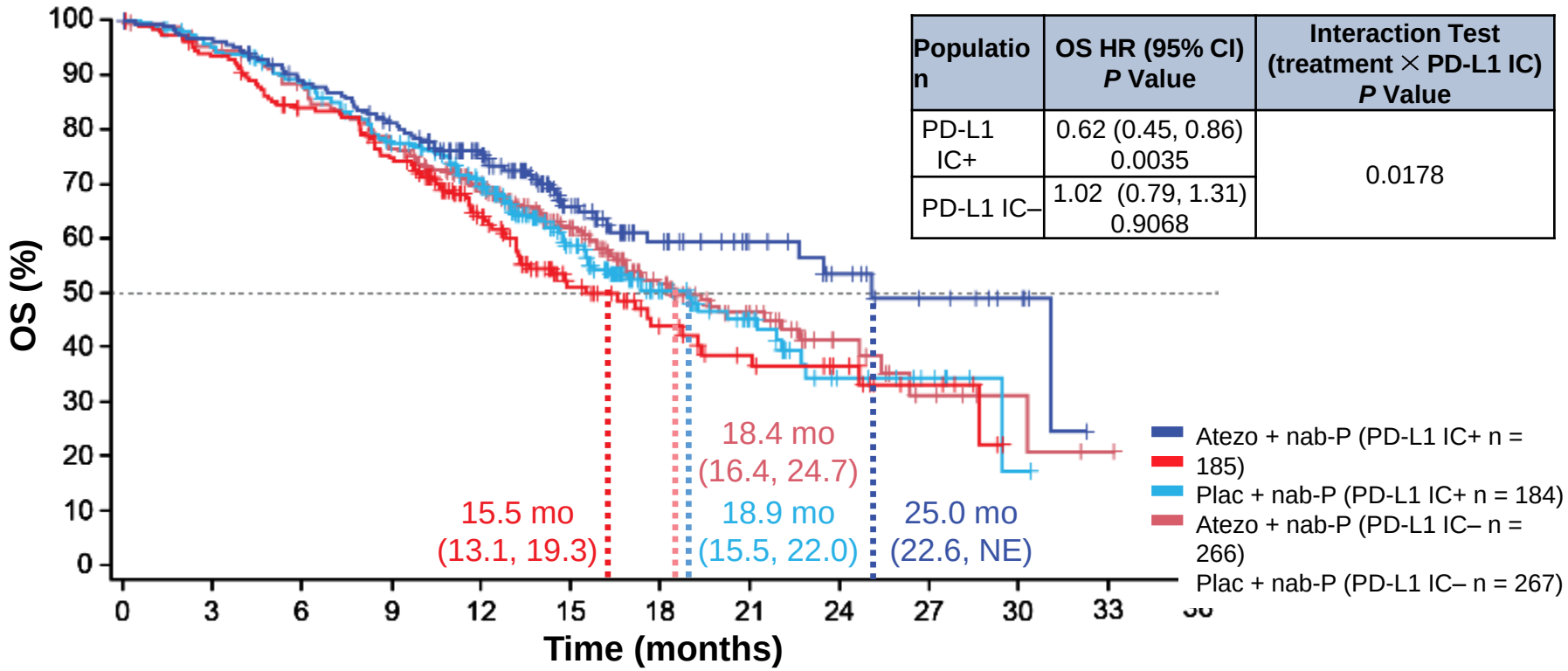


- A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant
- PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + *nab*-paclitaxel

Median OS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values are nominal. Data cutoff: April 17, 2018.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

PD-L1 IC status (positive vs negative) predicts OS benefit with atezolizumab + *nab*-paclitaxel



Population	OS HR (95% CI) *P* Value	Interaction Test (treatment × PD-L1 IC) *P* Value
PD-L1 IC+	0.62 (0.45, 0.86) 0.0035	0.0178
PD-L1 IC–	1.02 (0.79, 1.31) 0.9068	

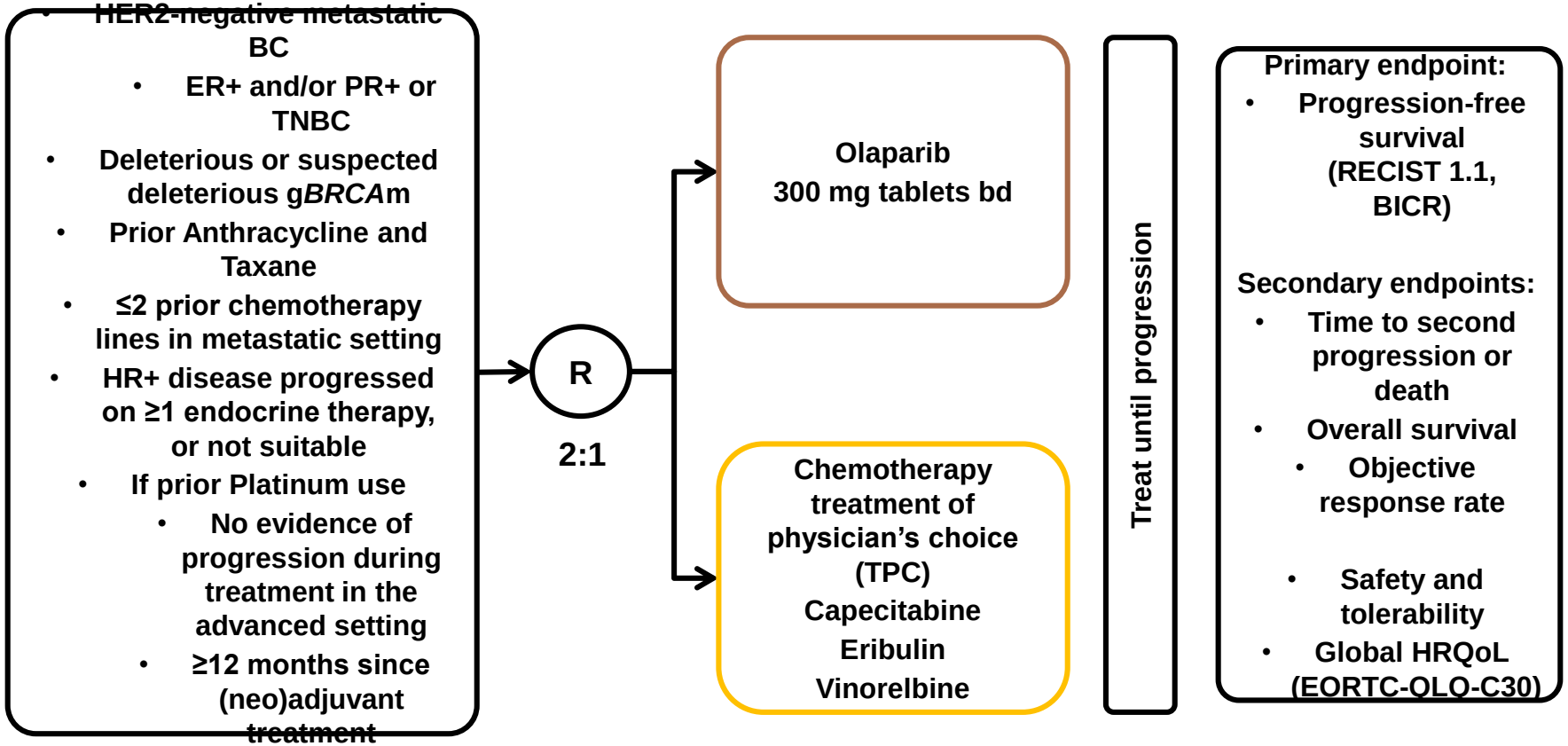
- A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant
- PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + *nab*-paclitaxel

Median OS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values are nominal. Data cutoff: April 17, 2018.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

PARP Inhibitoren beim Mammakarzinom

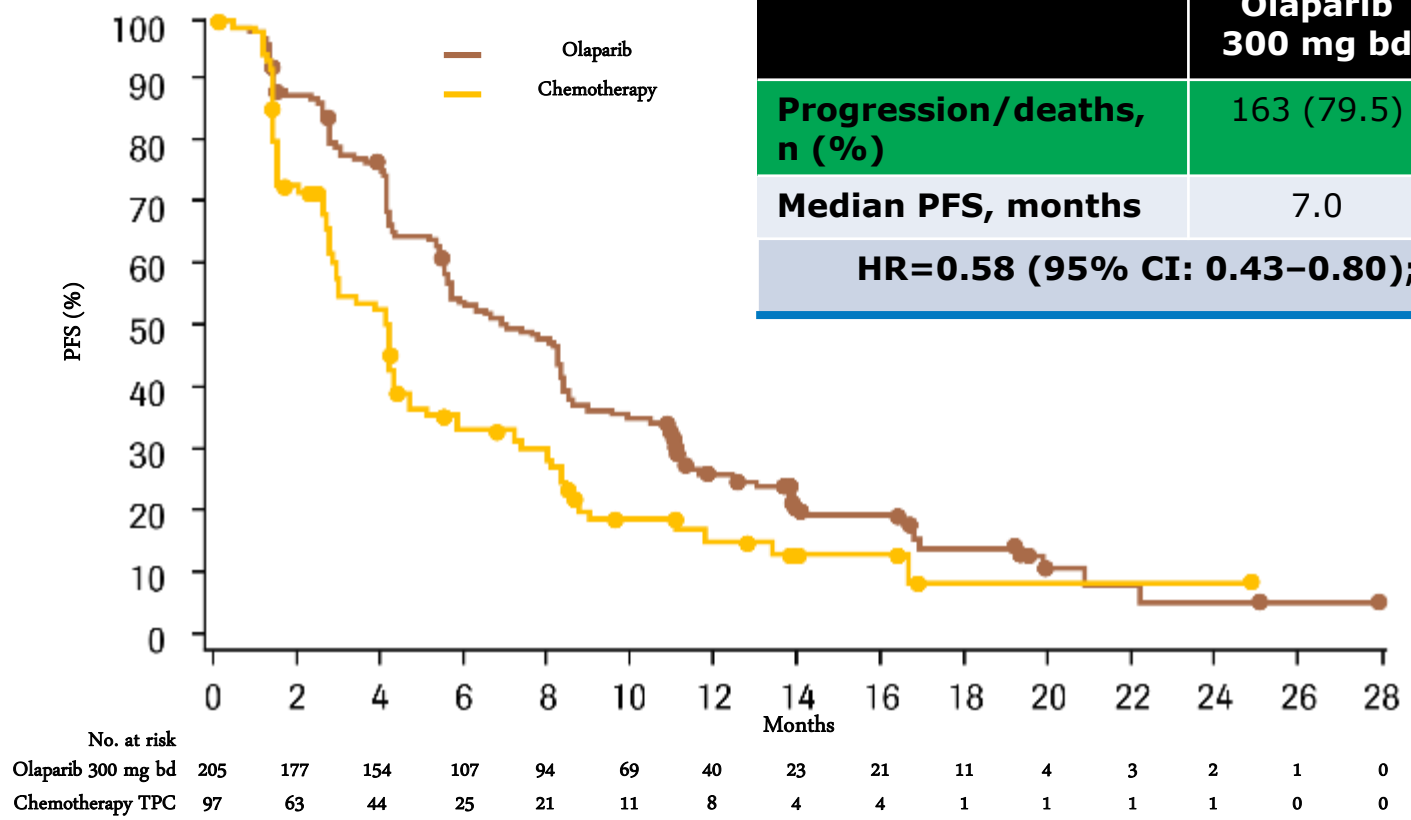
OlympiAD - Study Design



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

Mod. Robson ME et al. ASCO 2017, Plenary Session – Breast Cancer – Metastatic, Abstract No. LBA4

OlympiAD – Primary Endpoint: Progression-Free Survival by BICR

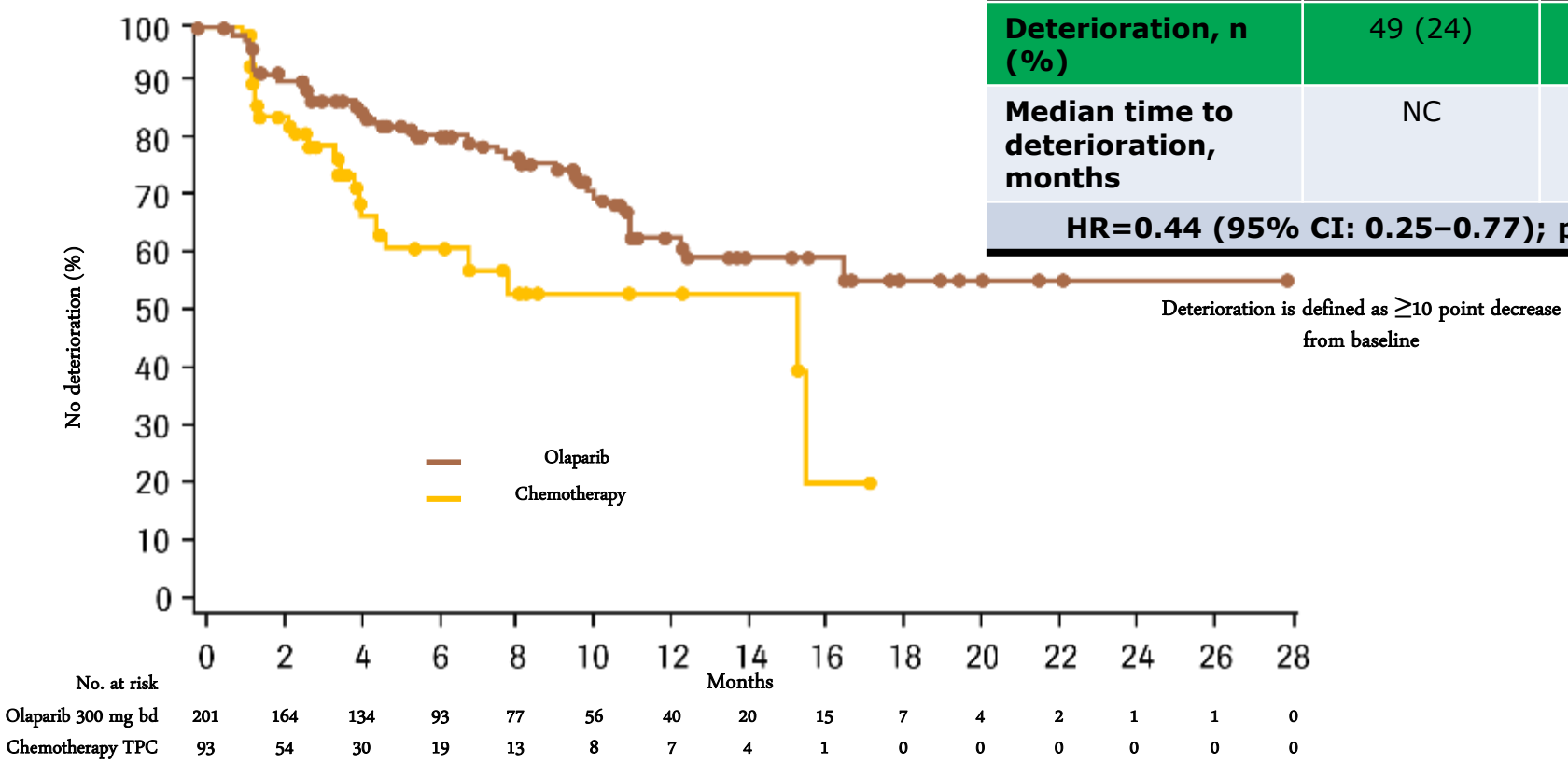


	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR=0.58 (95% CI: 0.43–0.80); p=0.0009		

Mod. Robson ME et al. ASCO 2017, Plenary Session – Breast Cancer – Metastatic, Abstract No. LBA4

OlympiAD – Time to Deterioration of Global HRQoL

	Olaparib 300 mg bd	Chemotherapy TPC
Deterioration, n (%)	49 (24)	25 (27)
Median time to deterioration, months	NC	15.3
HR=0.44 (95% CI: 0.25–0.77); p=0.0043		

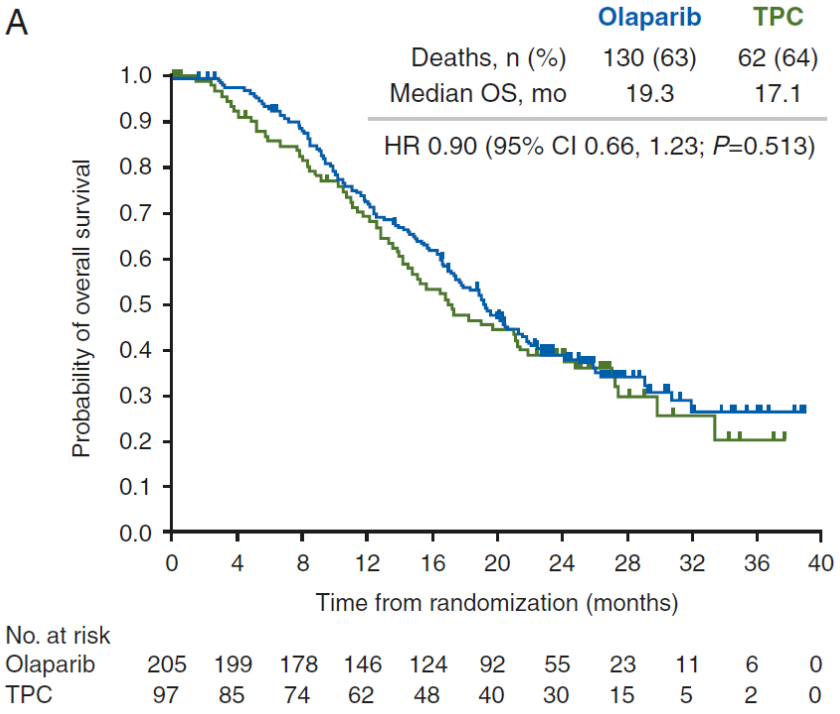


Mod. Robson ME et al. ASCO 2017, Plenary Session – Breast Cancer – Metastatic, Abstract No. LBA4

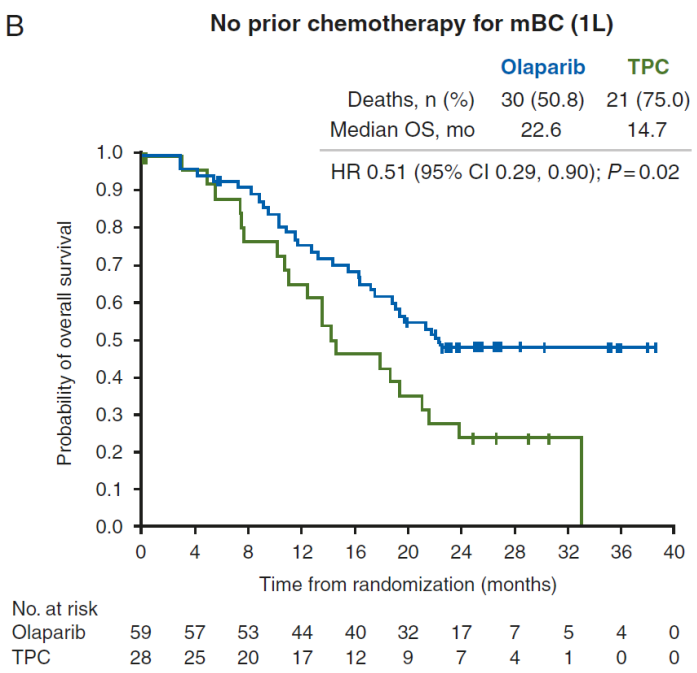
OlympiaD – Finale Overall Survival Analyse

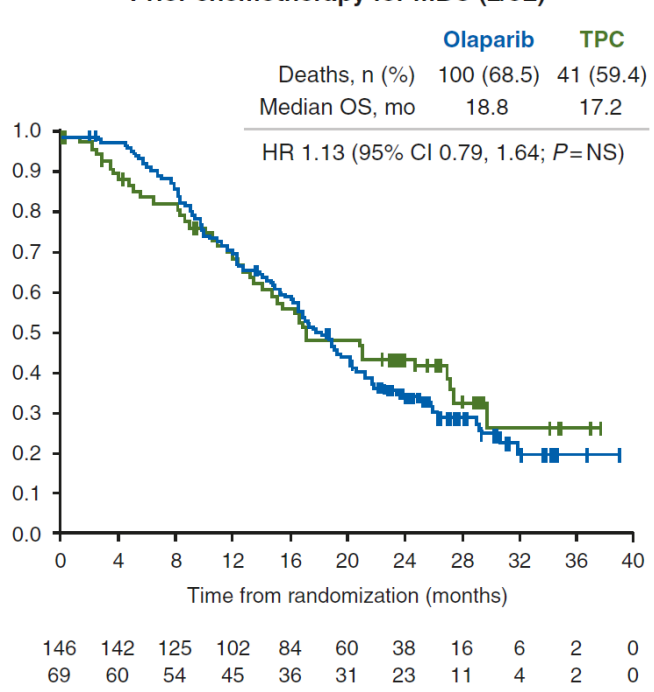
(Robson et al. Ann Oncol 2019)

A



B





Zusammenfassung

- Standard bei HR pos HER2 neg ist die endokrine Therapie
- CDK4/6 Inhibitoren haben sich etabliert
- Endokrine Resistenz zu überwinden scheint ein Erolgskonzept zu sein (ähnlich wie bei den HER2 pos Tumoren)
- Nach langer Zeit mehrere Durchbrüche beim TNBC
- Immuntherapie wird neuer Standard 1st line
- BRCA Mutierte profitieren von PARP Inhibtion