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Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

Update neue Therapien beim Mammakarzinom

GBG Jahrestreffen 24. – 26. Februar 2021

Prof. Dr. med. Frederik Marmé
Sektionsleiter Konservative Gynäkologische Onkologie
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Medizinische Fakultät Mannheim der Universität Heidelberg
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Potentielle Interessenskonflikte

Company/ name	Honoraria/ expenses	Consulting/advisory board	Funded research	Royalties/ patent	Stock options	Ownership/ equity position	Employee	Other (please specify)
AstraZeneca	X	X	X	-	-	-	-	-
GSK/Tesaro	X	X	X	-	-	-	-	-
Clovis	X	X	X	-	-	-	-	-
MSD	X	X	X	-	-	-	-	-
Novartis	X	X	X	-	-	-	-	-
Pfizer	X	X	X	-	-	-	-	-
Lilly	X	X	-	-	-	-	-	-
Roche	X	X	X	-	-	-	-	-
Gilead / Immunomedics	X	X	X	-	-	-	-	-
AMGEN	-	X	-	-	-	-	-	-
EISAI	X	X	-	-	-	-	-	-
Celgene	X	X	-	-	-	-	-	-
PharmaMar	-	X	X	-	-	-	-	-
Janssen-Cilag	-	X	-	-	-	-	-	-
GenomicHealth	X	X	-	-	-	-	-	-
Myriad Genetics	X	X	-	-	-	-	-	-
Seagen	-	X	-	-	-	-	-	-
GBG	-	-	X	-	-	-	-	-
AGO Studiengruppe	-	-	X	-	-	-	-	-

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	No, nothing to disclose
	Yes, please specify:

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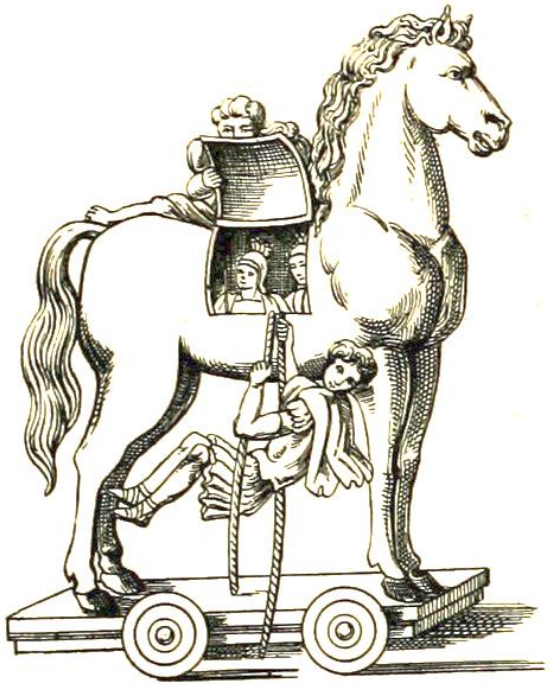
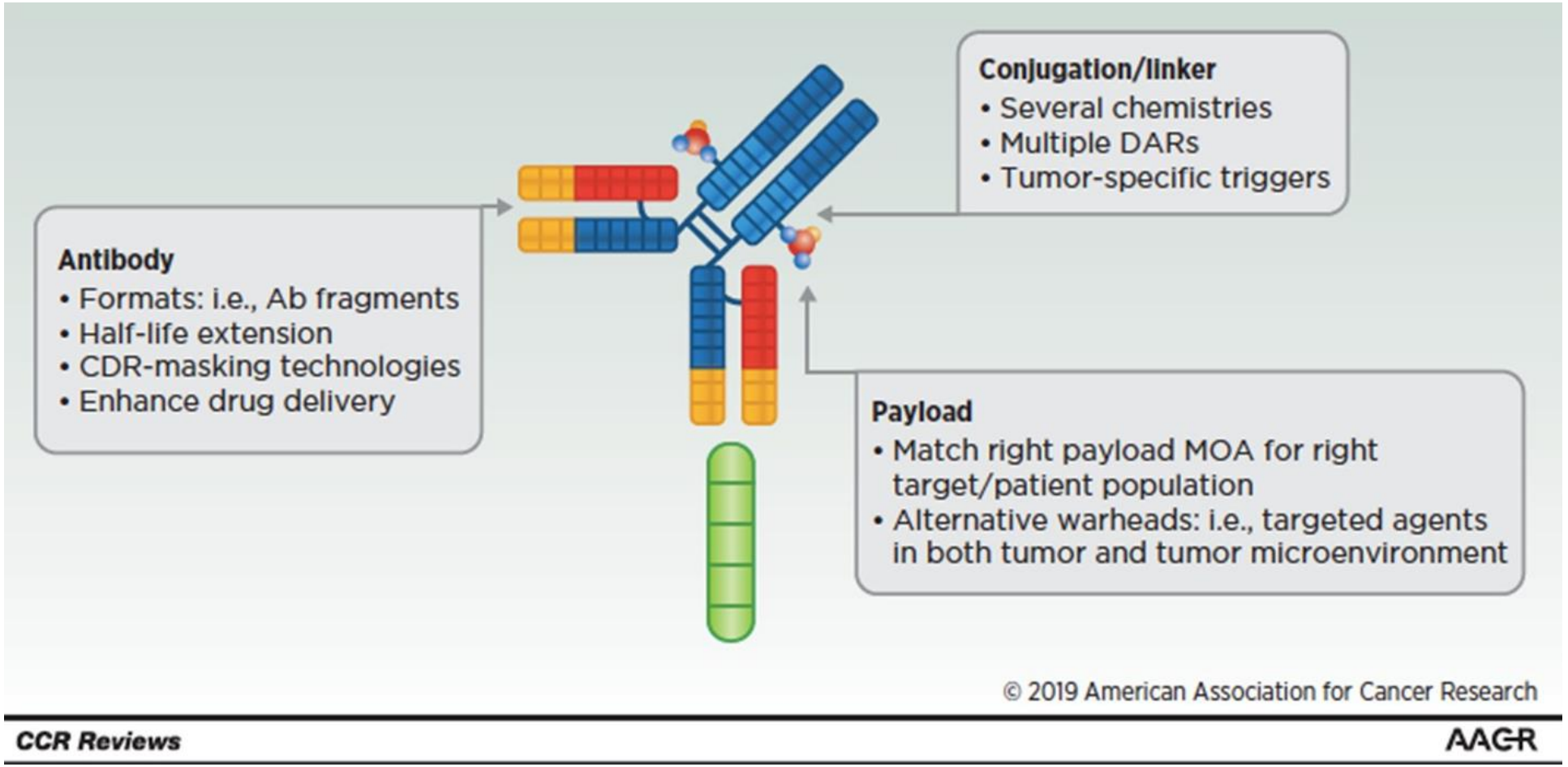
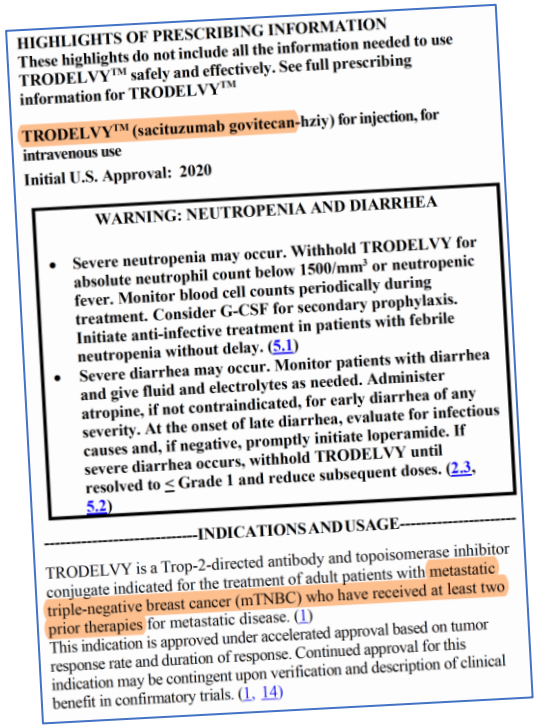
Antibody-Drug Konjugate

neue therapeutische Ansätze





Coats et al., Clin Cancer Res. 2019 Apr 12. pii: 1078-0432.CCR-19-0272. doi: 10.1158/1078-0432.CCR-19-0272



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRODELVY™ safely and effectively. See full prescribing information for TRODELVY™

TRODELVY™ (sacituzumab govitecan-hziy) for injection, for intravenous use

Initial U.S. Approval: 2020

WARNING: NEUTROPENIA AND DIARRHEA

- **Severe neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay. (5.1)**
- **Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤ Grade 1 and reduce subsequent doses. (2.3, 5.2)**

INDICATIONS AND USAGE

TRODELVY is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease. (1)

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1, 14)

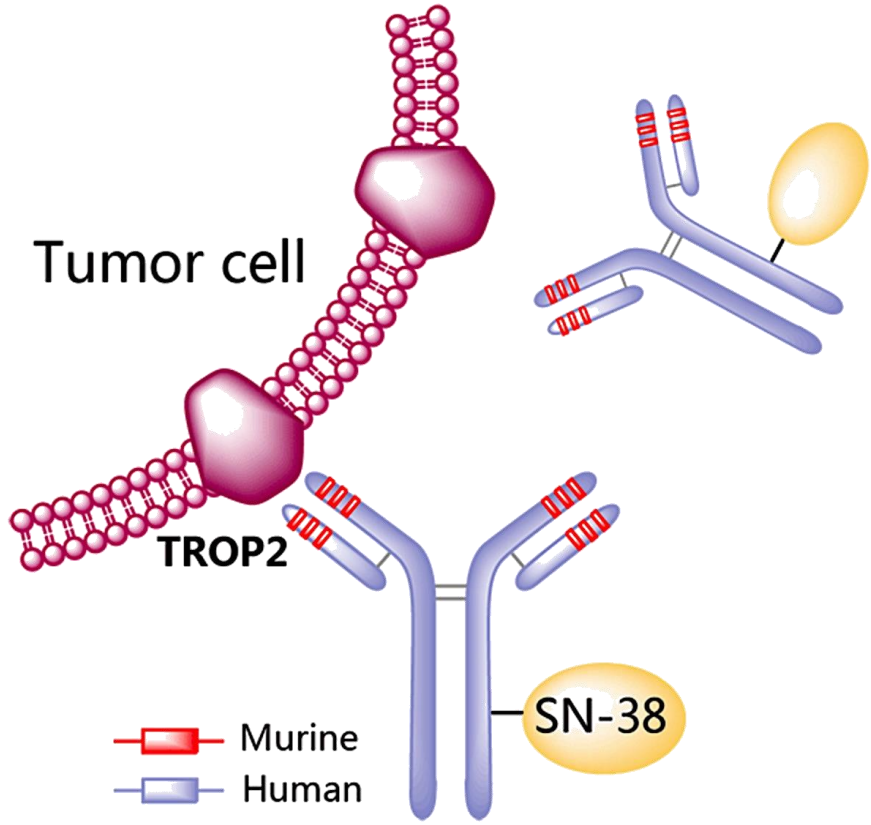
Sacituzumab Govitecan - Trodelvy

Anti-TROP2 ADC

Sacituzumab Govitecan (IMMU-132)

- Antibody-drug conjugate gerichtet gegen TROP-2 (Trophoplast antigen-2)
  - exprimiert in vielen soliden Tumoren inkl. MBC
- toxische „Fracht“:

  SN38 = aktiver Metabolit von Irinotecan
  - 100-1000-fach höhere Potenz > Irinotecan
  - verantwortlich für. NW-Potential von Irinotecan
    - ca. 1/3 Grad 3/4 Diarrhoe & Neutropenie
- Hohe „**drug-to-antibody“ Ratio**: 7.5 : 1
- Hydrolysierbarer Linker: „**Bystander**“ Effekt



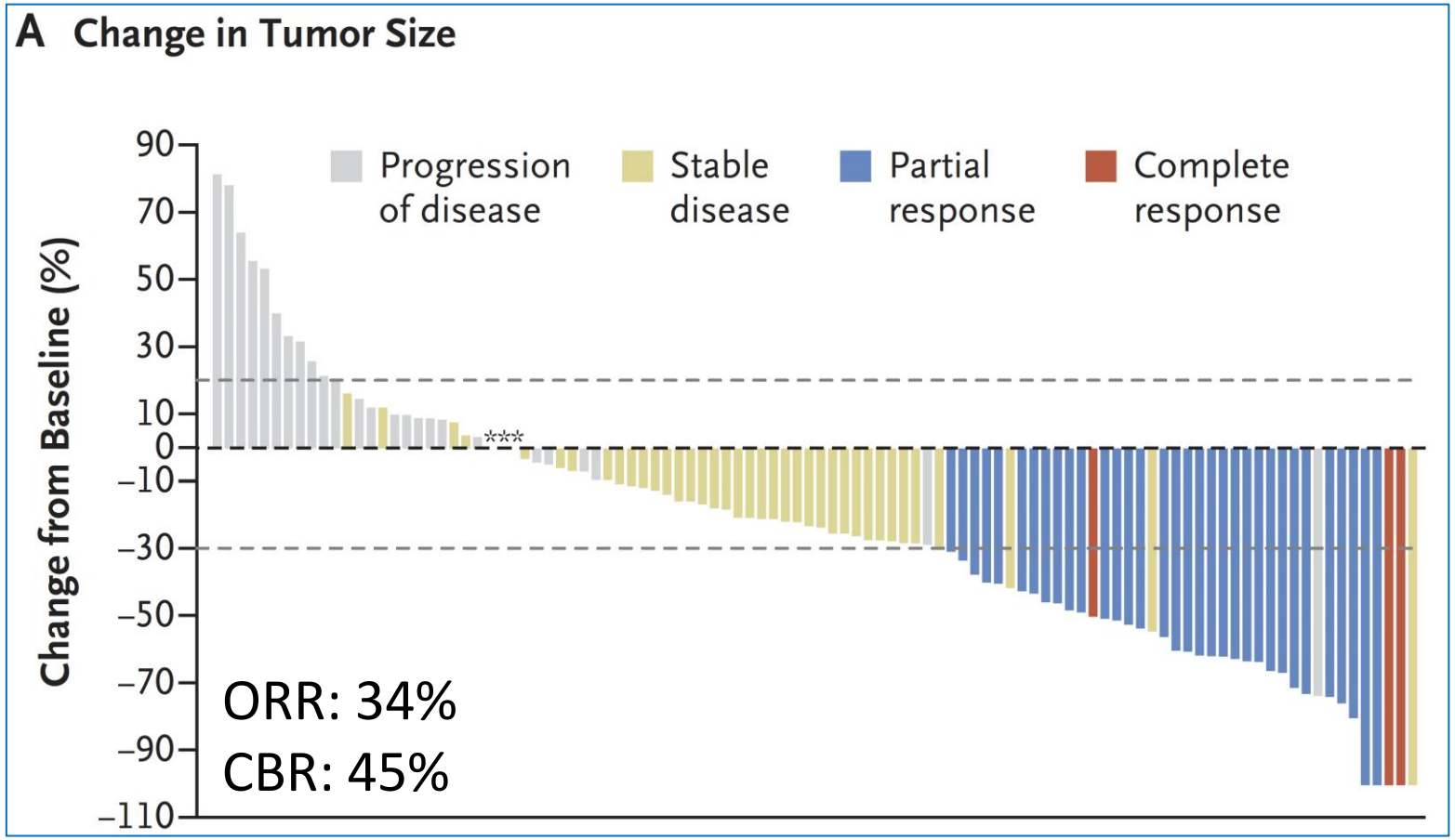
Bardia A et al., J Clin Oncol. 2017 Mar 14:JCO2016708297. doi: 10.1200/JCO.2016.70.8297.

Sacituzumab Govitecan bei stark vorbehandeltem mTNBC

n= 110
median 3 Vortherapien (2-10)
keine Präselektion nach TROP2
- 88% moderate bis starke Expression (IHC 2/3+)

ORR (confirmed): 34%
CBR (≥6 Monate): 45%
med. onset of response: 2.0 Monate
mDOR: 7.6 Monate
med. PFS: 5.5 Monate
med. OS: 12.7 Monate

Body system	Adverse event (AE)	All grades	Grade 3 or 4
Hematologic	Neutropenia	63%	41%
	Febrile neutropenia	8%	7%
	Anemia	52%	10%
	Leukopenia	24%	14%
Gastrointestinal	Nausea	63%	5%
	Diarrhea	56%	8%
	Vomiting	46%	5%
	Constipation	32%	1%



3rd Line: 41 %
≥ 4th Line: 59 %
Prior ICI: 17 %

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Bardia A et al., SABCS 2017
Bardia A et al., N Engl J Med. 2019 Feb 21;380(8):741-751.

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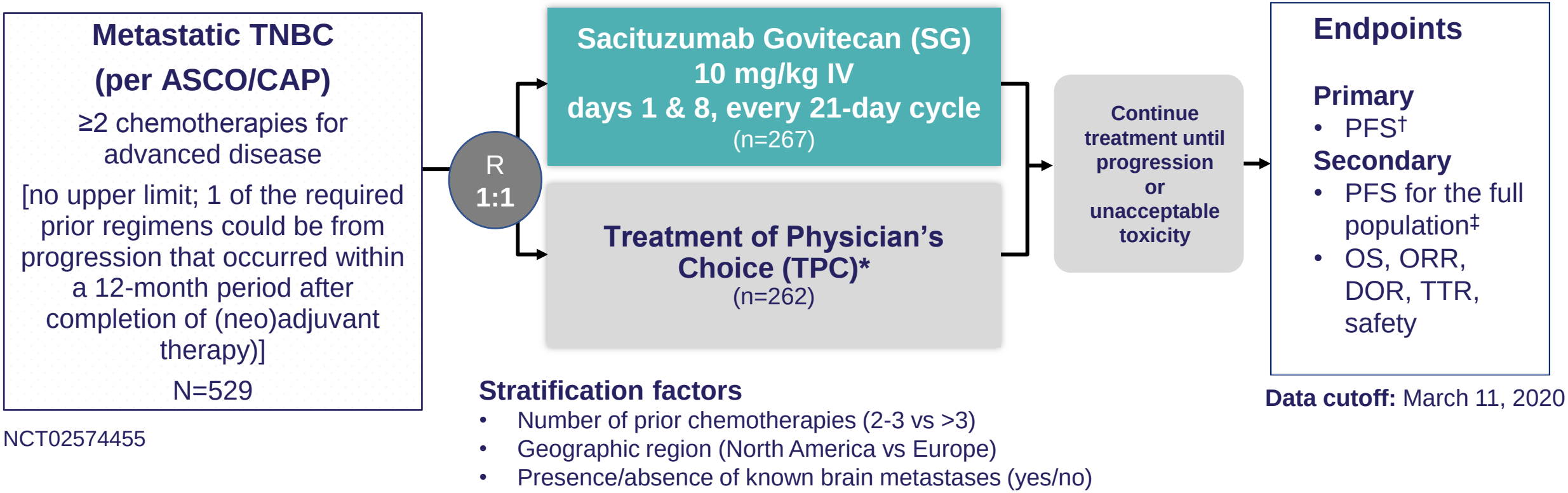
ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC



NCT02574455

Stratification factors

- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

Data cutoff: March 11, 2020

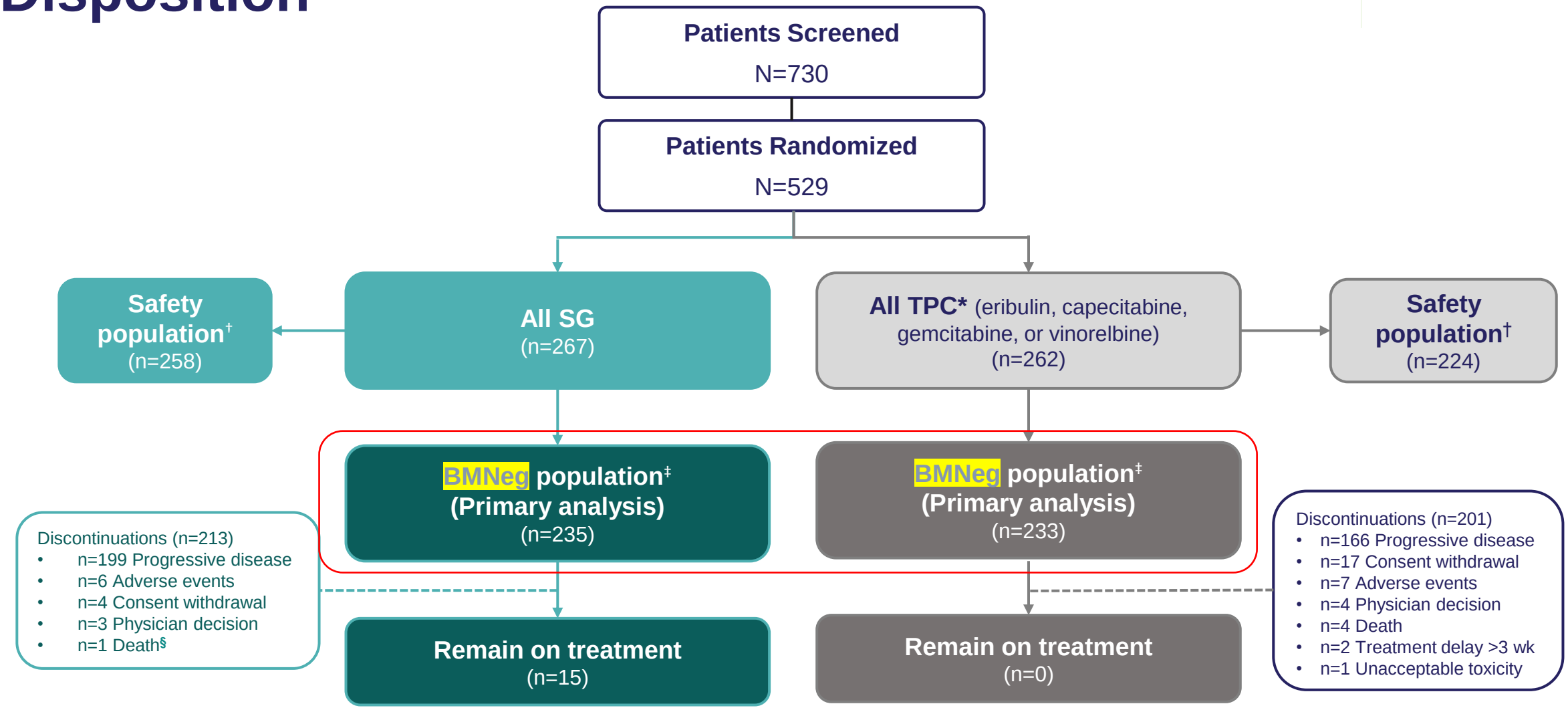
ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation. Here, we report the primary results from ASCENT, including PFS and OS.

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Disposition



*Patients in the TPC arm were randomized to: eribulin (n=139); vinorelbine (n=52); gemcitabine (n=38); capecitabine (n=33).

†All patients who received ≥1 dose of study treatment. ‡Seven pts in the SG arm and 32 pts in the TPC arm were randomized but not treated in the brain metastases-negative population.
§This was considered unlikely to be related to SG treatment.
BMNeg, brain metastases-negative; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

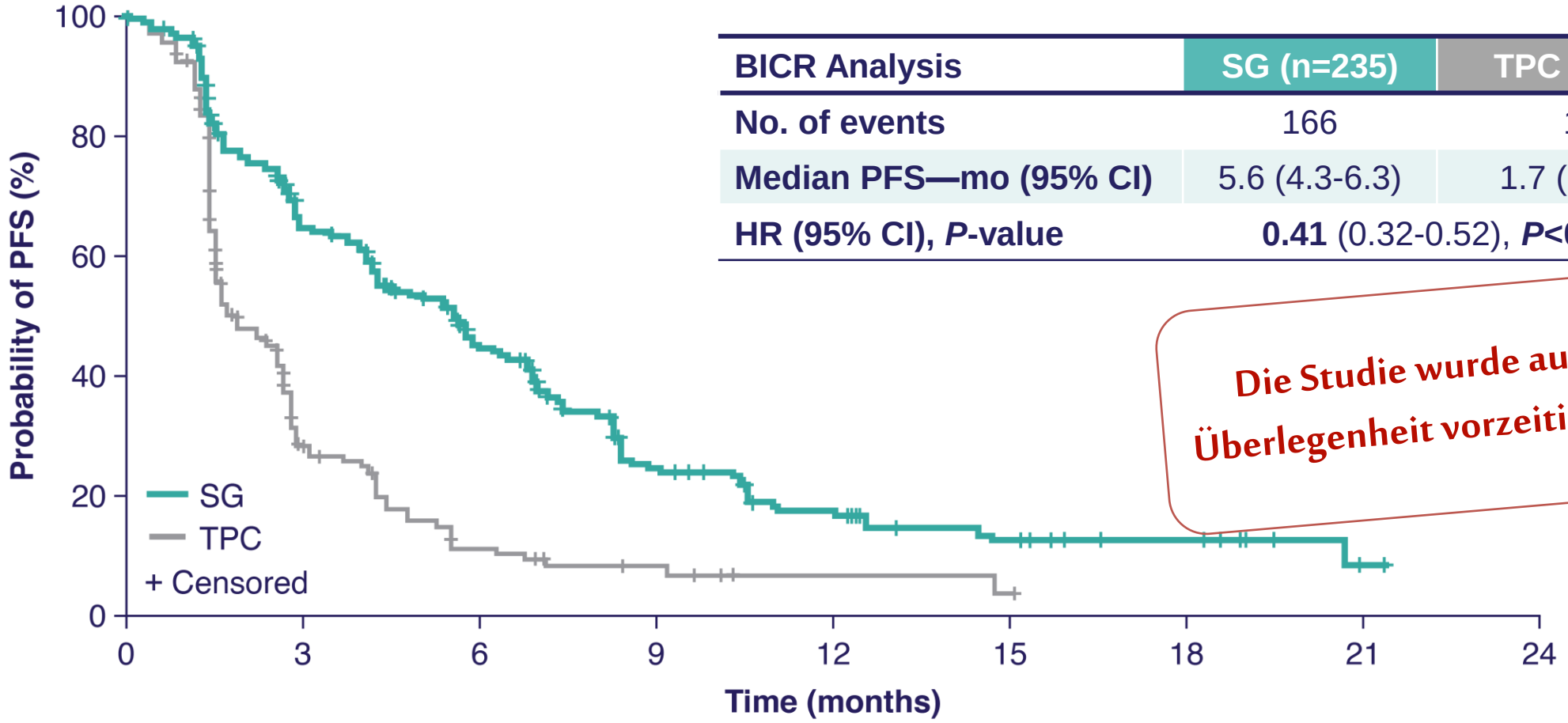
Demographics and Patient Characteristics

	SG (n=235)	TPC (n=233)
Female—no. (%)	233 (99)	233 (100)
Median age—yr (range)	54 (29-82)	53 (27-81)
Race or ethnic group—no. (%)		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other or not specified	10 (4)	15 (6)
ECOG PS—no. (%)		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
***BRCA 1/2* mutational status—no. (%)**		
Positive	16 (7)	18 (8)
Negative	133 (57)	125 (54)
Unknown	86 (37)	90 (39)
TNBC at initial diagnosis*		
Yes	165 (70)	157 (67)
No	70 (30)	76 (33)

	SG (n=235)	TPC (n=233)
Previous anticancer regimens† —median no. (range)	4 (2-17)	4 (2-14)
Most common previous chemotherapy—no. (%)		
Taxane‡	235 (100)	233 (100)
Anthracycline§	191 (81)	193 (83)
Cyclophosphamide	192 (82)	192 (82)
Carboplatin	147 (63)	160 (69)
Capecitabine	147 (63)	159 (68)
Previous PARP inhibitor—no. (%)	17 (7)	18 (8)
Previous use of checkpoint inhibitors—no. (%)	67 (29)	60 (26)
Most common sites of disease‖—no. (%)		
Lung only	108 (46)	97 (42)
Liver	98 (42)	101 (43)
Bone	48 (20)	55 (24)

Brain metastases-negative population.
*Patients on study either had TNBC at initial diagnosis or had hormone receptor-positive disease that converted to hormone-negative at time of study entry. †Anticancer regimens refer to any treatment regimen that was used to treat breast cancer in any setting ‡Includes: Paclitaxel, paclitaxel albumin, and docetaxel. §Includes: Doxorubicin, daunorubicin, epirubicin, and variations of those treatment names. ‖Based on independent central review of target and non-target lesions.
BRCA, breast cancer gene; ECOG PS, Eastern Cooperative Oncology Group performance status; PARP, poly-ADP ribose polymerase; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

Progression-Free Survival (BICR Analysis)



BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

Die Studie wurde aufgrund Überlegenheit vorzeitig beendet

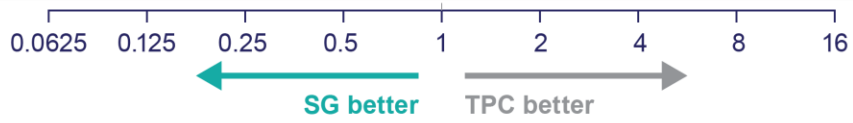
Number of patients at risk

SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
TPC	233	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

Primary endpoint (PFS) assessed by independent central review in the brain metastases-negative population, as pre-defined in the study protocol.
Secondary endpoint (PFS) assessed in the full population (brain metastases-positive and -negative) and PFS benefit was consistent (HR=0.43 [0.35-0.54], *P*<0.0001).
BICR, blind independent central review; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Progression-Free Survival by Subgroup

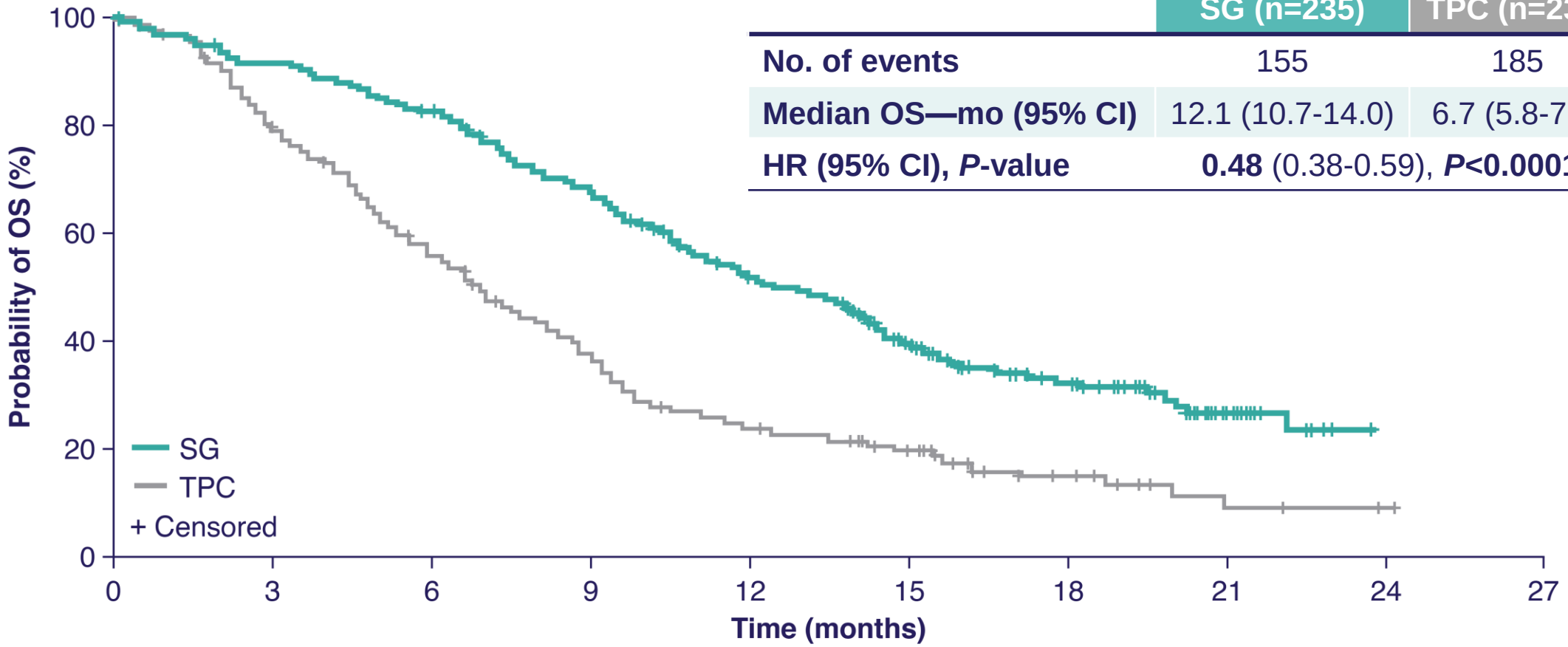
Subgroup	Median PFS, Months (95% CI) SG	TPC	HR (95% CI)	P value
Overall (n=468)	5.6 (4.3–6.3)	1.7 (1.5–2.6)	0.41 (0.33–0.52)	<0.0001
Age Group				
<65 (n=378)	4.6 (3.7–5.7)	1.7 (1.5–2.5)	0.46 (0.35–0.59)	<0.0001
≥65 (n=90)	7.1 (5.8–8.9)	2.4 (1.4–2.9)	0.22 (0.12–0.40)	<0.0001
Race				
White (n=369)	5.7 (4.3–6.8)	1.7 (1.5–2.6)	0.39 (0.30–0.51)	<0.0001
Black (n=56)	5.4 (2.8–7.4)	2.2 (1.5–2.9)	0.45 (0.24–0.86)	0.0152
Asian (n=18)	NE (1.3–NE)	1.5 (1.2–NE)	0.40 (0.08–2.08)	0.2781
Prior Therapies				
2-3 (n=330)	5.8 (4.2–7.1)	1.6 (1.5–2.5)	0.39 (0.29–0.52)	<0.0001
>3 (n=138)	5.6 (3.0–6.5)	2.5 (1.5–2.8)	0.48 (0.32–0.72)	0.0004
Region				
North America (n=298)	4.9 (4.0–6.3)	2.0 (1.5–2.6)	0.44 (0.33–0.60)	<0.0001
Rest of World (n=170)	5.9 (4.2–6.9)	1.6 (1.4–2.7)	0.36 (0.24–0.53)	<0.0001
Prior PD-L1/PD-1 use				
Yes (n=127)	4.2 (3.2–5.6)	1.6 (1.4–2.3)	0.37 (0.24–0.57)	<0.0001
No (n=341)	6.2 (4.9–7.1)	2.1 (1.5–2.7)	0.42 (0.32–0.56)	<0.0001
Liver Metastases				
Yes (n=199)	4.2 (2.8–5.8)	1.5 (1.4–2.4)	0.48 (0.34–0.67)	<0.0001
No (n=269)	6.8 (4.6–8.0)	2.3 (1.6–2.7)	0.36 (0.26–0.50)	<0.0001
Initial Diagnosis TNBC				
Yes (n=322)	5.7 (4.3–6.9)	1.6 (1.5–2.6)	0.38 (0.29–0.51)	<0.0001
No (n=146)	4.6 (3.7–6.9)	2.3 (1.5–2.8)	0.48 (0.32–0.72)	0.0004



Assessed by independent central review in brain metastases-negative population.
HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Overall Survival

	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

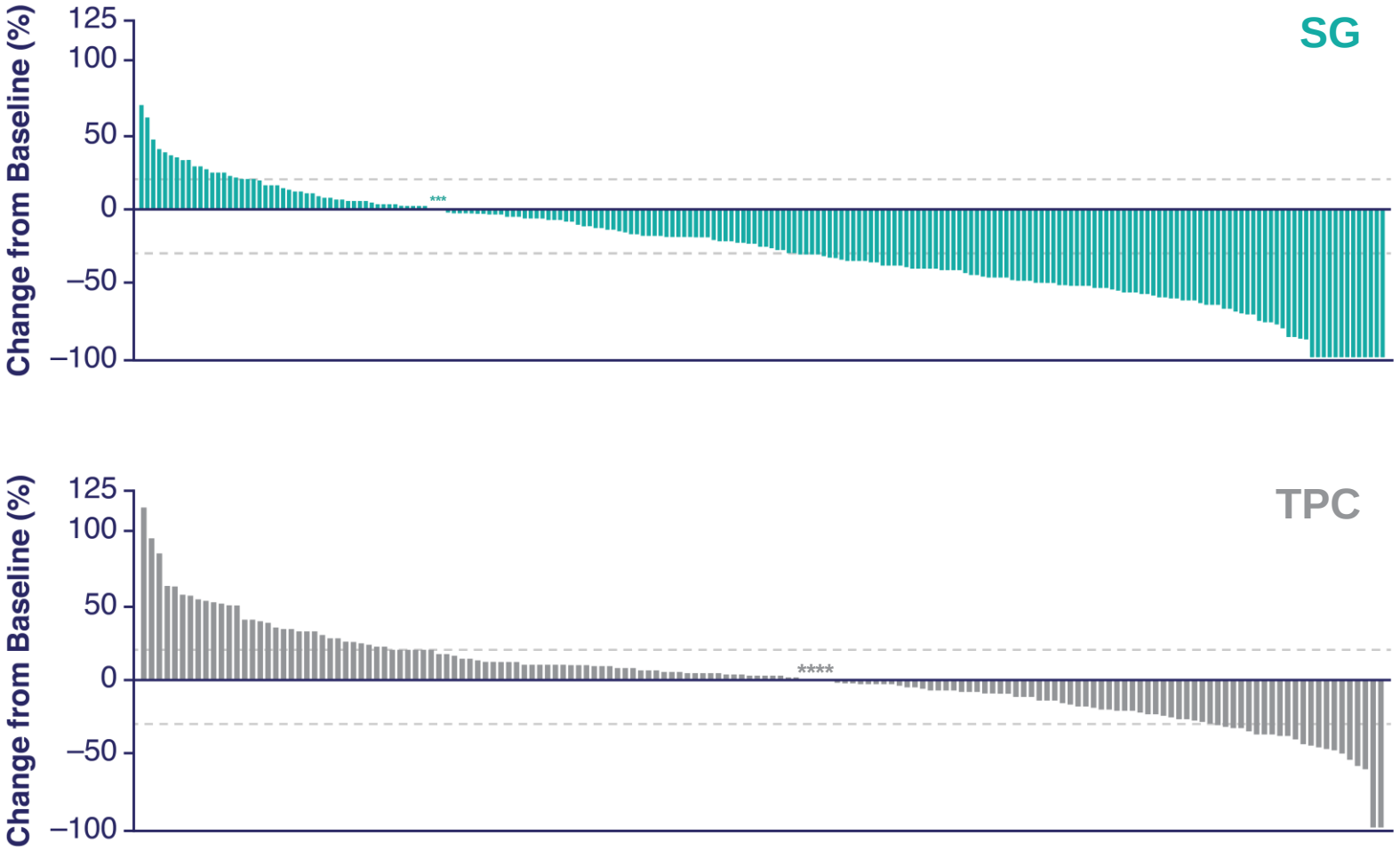


Number of patients at risk

SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

Assessed by independent central review in the brain metastases-negative population.
OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Overall Response and Best Percent Change From Baseline in Tumor Size



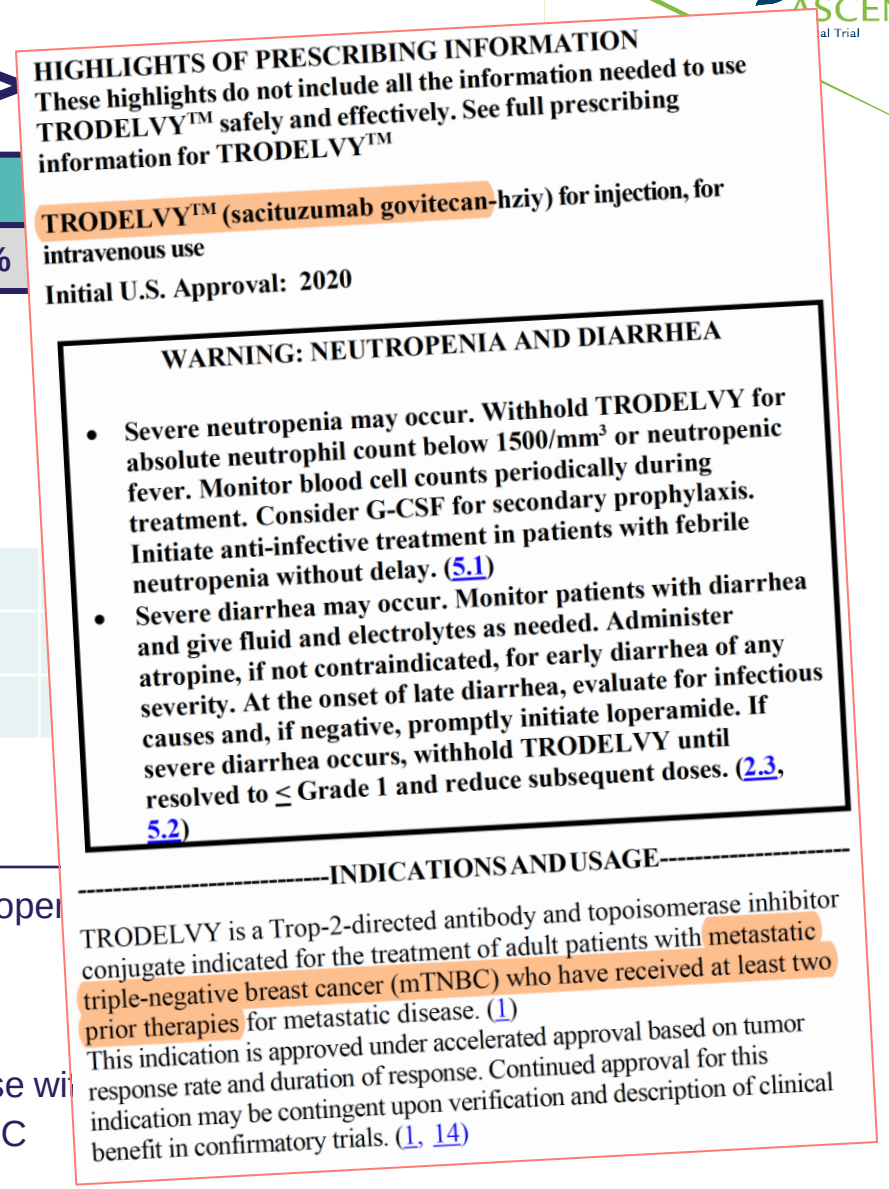
	SG (n=235)	TPC (n=233)
ORR—no. (%)	**82 (35)**	**11 (5)**
***P*-value**	**<0.0001**	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR—no. (%)	**105 (45)**	**20 (9)**
***P*-value**	**<0.0001**	
Median DOR —mo (95%CI)	**6.3 (5.5–9.0)**	**3.6 (2.8–NE)**
***P*-value**	**0.057**	

Assessed by independent central review in brain metastases-negative population.
*Denotes patients who had a 0% change from baseline in tumor size.
BICR, blind independent central review; CBR, clinical benefit rate (CR + PR + SD ≥6 mo); CR, complete response; DOR, duration of response; ORR, objective response rate; PR, partial response; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TTR, time to response.

TRAEs (All Grade, >20%; Grade 3/4, >

	TRAE*	SG (n=258) All grade %	SG (n=258) Grade 3, %	SG (n=258) Grade 4, %
Hematologic	Neutropenia†	63	46	17
	Anemia‡	34	8	0
	Leukopenia§	16	10	1
	Febrile neutropenia	6	5	1
Gastrointestinal	Diarrhea	59	10	0
	Nausea	57	2	<1
	Vomiting	29	1	<1
Other	Fatigue	45	3	0
	Alopecia	46	0	0

- Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukoper
  febrile neutropenia (6% vs 2%)
  - G-CSF usage was 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)
- No severe cardiovascular toxicity, no grade >2 neuropathy or grade >3 interstitial lung disease wi
- No treatment-related deaths with SG; 1 treatment-related death (neutropenic sepsis) with TPC
- AEs leading to treatment discontinuation were low for SG and TPC: 4.7% and 5.4%
- Patients received a median of 7 treatment cycles of SG, with a median treatment duration of 4.4 months (range, 0.03-22.9)



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This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1, 14)

*Patients may report more than 1 event per preferred term. AEs were classified according to the MedDRA systems of preferred terms and system organ class and according to severity by NCI CTCAE v4.03. †Combined preferred terms of 'neutropenia' and 'decreased neutrophil count'. ‡Combined preferred terms of 'anemia' and 'decreased hemoglobin'. §Combined preferred terms of 'leukopenia' and 'decreased white blood cell count'.
G-CSF, granulocyte-colony stimulating factor; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment-related AE.

Sacituzumab Govitecan bei Hirnmetastasen

Explorative Subgruppenanalyse der ASCENT-Studie

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der Universität Heidelberg

Universitätsklinikum Mannheim

San Antonio Breast Cancer Symposium®, December 8-11, 2020

Poster PD13-07

ASCENT Clinical Trial

Subgroup Analysis of Patients With Brain Metastases From the Phase 3 ASCENT Study of Sacituzumab Govitecan Versus Chemotherapy in Metastatic Triple-Negative Breast Cancer

Véronique Diéras,[1] Robert Weaver,[2] Sara M. Tolaney,[3] Aditya Bardia,[4] Kevin Punie,[5] Adam Brufsky,[6] Hope S. Rugo,[7] Kevin Kalinsky,[8] Tiffany Traina,[9] Leonard Klein,[10] Delphine Loirat,[11] Filipa Lynce,[3,12] Brooke Daniel,[13] Foluso Ademuyiwa,[14] Sara A. Hurvitz,[15] David M. Goldenberg,[16] Quan Hong,[16] Martin Olivo,[16] Loretta M. Itri,[16] and Lisa Carey[17]

Table 3: Responses (BICR Analysis)

	Brain Metastases-Positive (N=61)	
	SG (n=32)	TPC (n=29)
ORR—no. (%)	1 (3)	0
CBR—no. (%)*	3 (9)	1 (3)
Best overall response—no. (%)		
CR	0	0
PR	1 (3)	0
SD	15 (47)	9 (31)
SD >6 months	2 (6)	1 (3)
PD	11 (34)	11 (38)
Not evaluable	5 (16)	9 (31)

*CBR is defined as the percentage of patients with a confirmed best overall response of CR or PR and SD ≥6 months.
BICR, blind independent central review; CBR, clinical benefit rate; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Table 4: Progression-Free Survival

	Brain Metastases-Positive (N=61)	
BICR Analysis	SG (n=32)	TPC (n=29)
No. of events	24	21
Median PFS—mo (95% CI)	2.8 (1.5-3.9)	1.6 (1.3-2.9)
HR (95% CI)	0.65 (0.35-1.22)	
PFS rate—% (95% CI)		
At 3 months	41.4 (23.7-58.3)	27.7 (11.4-46.9)
At 6 months	9.0 (0.9-29.2)	6.9 (0.6-24.9)
At 9 months	9.0 (0.9-29.2)	0
At 12 months	9.0 (0.9-29.2)	0

BICR, blind independent central review; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Patients were eligible if they had stable CNS disease for ≥4 weeks by MRI

defined as ≥2 weeks from discontinuation of antiseizure medication and corticosteroid dose [≤20 mg prednisone equivalent] that was stable or decreasing for ≥2 weeks before randomization

Brain MRIs were required throughout the study

Table 5: Overall Survival

	Brain Metastases-Positive (N=61)	
	SG (n=32)	TPC (n=29)
No. of events	24	21
Median OS—mo (95% CI)	6.8 (4.7-14.1)	7.5 (4.7-11.1)
HR (95% CI)	0.87 (0.47-1.63)	

UMM UNIVERSITÄTSMEDIZIN MANNHEIM

Sacituzumab Govitecan
Dosismodulation und Effektivität & UGT1A1 Genotyp

San Antonio Breast Cancer Symposium®, December 8-11, 2020

Poster PS11-09

Impact of UGT1A1 Status on the Safety Profile of Sacituzumab Govitecan in the Phase 3 ASCENT Study in Patients With Metastatic Triple-Negative Breast Cancer

Hope S. Rugo,[1] Sara M. Tolaney,[2] Delphine Loirat,[3] Kevin Punie,[4] Aditya Bardia,[5] Sara A. Hurvitz,[6] Joyce O'Shaughnessy,[7] Javier Cortés,[8] Véronique Diéras,[9] Lisa Carey,[10] Luca Gianni,[11] Martine J. Piccart,[12] Sibylle Loibl,[13] David M. Goldenberg,[14] Quan Hong,[14] Martin Olivo,[14] Loretta M. Itri,[14] and Kevin Kalinsky[15]

OUTCOMES BY DOSE REDUCTION/INTERRUPTION

- In total, 26% and 22% of patients in the SG and TPC arm, respectively, had a dose reduction and 61% and 33% had a dose interruption
- Objective response rates and clinical benefit rates were improved with SG vs TPC for patients with dose reduction or interruption (**Table 4**)
- Efficacy outcomes for patients with dose reduction or interruption in the SG arm were similar to those for the overall population (**Table 4**)[8]

Table 4. Efficacy Outcomes for Patients With Dose Reductions or Interruptions (BMNeg Population)

	Overall BMNeg Population[9]		Dose Reductions		No Dose Reductions		Dose Interruptions		No Dose Interruptions	
	SG (n=235)	TPC (n=233)	SG (n=62)	TPC (n=52)	SG (n=173)	TPC (n=181)	SG (n=144)	TPC (n=78)	SG (n=91)	TPC (n=155)
ORR (BICR)—no. (%)	82 (35)	11 (5)	29 (47)	7 (13)	53 (31)	4 (2)	56 (39)	5 (6)	26 (29)	6 (4)
CBR (BICR)—no. (%)	105 (45)	20 (9)	37 (60)	11 (21)	68 (39)	9 (5)	71 (49)	12 (15)	34 (37)	8 (5)
Best Overall Response										
CR	10 (4)	2 (1)	5 (8)	1 (2)	5 (3)	1 (1)	7 (5)	0 (0)	3 (3)	2 (1)
PR	72 (31)	9 (4)	24 (39)	6 (12)	48 (28)	3 (2)	49 (34)	5 (6)	23 (25)	4 (3)
Median PFS (BICR) —mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)	8.3 (5.4-10.3)	2.9 (2.7-4.3)	4.6 (3.5-5.7)	1.5 (1.4-1.7)	5.7 (4.3-7.0)	2.7 (1.7-3.0)	4.2 (2.9-6.8)	1.6 (1.5-2.2)

Assessed in brain metastases-negative population (SG, n=235; TPC, n=233).
BICR, blind independent central review; BMNeg, brain metastases-negative; CBR, clinical benefit rate; CR, complete response; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

TRAEs BY *UGT1A1* GENOTYPE

- In total, 250 patients in the SG arm (97%) had *UGT1A1* genotype data at baseline
  - *1/*1 (wild-type; normal enzymatic activity): 45%
  - *1/*28 (heterozygous; reduced enzymatic activity): 38%
  - *28/*28 (homozygous; diminished enzymatic activity): 14%

Table 5. TRAEs by *UGT1A1* Genotype (All Grade, >20%; Grade 3/4, >5% of Patients)

		SG (n=250)†					
		*1/*1 Wild-Type (n=113)		*1/*28 Heterozygous (n=96)		*28/*28 Homozygous (n=34)	
	TRAE‡	All Grade, %	Grade ≥3, %	All Grade, %	Grade ≥3, %	All Grade, %	Grade ≥3, %
Hematologic	**Neutropenia**§	**76 (67)**	**60 (53)**	**55 (57)**	**45 (47)**	**24 (71)**	**20 (59)**
	Anemia‖	37 (33)	5 (4)	29 (30)	6 (6)	16 (47)	5 (15)
	Leukopenia**	18 (16)	10 (9)	13 (14)	9 (9)	8 (24)	5 (15)
	Lymphopenia¶	10 (9)	1 (1)	5 (5)	1 (1)	4 (12)	2 (6)
	Febrile neutropenia	**3 (3)**	**3 (3)**	**5 (5)**	**5 (5)**	**6 (18)**	**6 (18)**
	Thrombocytopenia#	3 (3)	0	6 (6)	0	4 (12)	4 (12)
Gastrointestinal	**Diarrhea**	**65 (58)**	**11 (10)**	**57 (59)**	**9 (9)**	**21 (62)**	**5 (15)**

Assessed in the safety population of patients with *UGT1A1* genotype. Shown are key TRAEs significantly impacted by the *UGT1A1* *28/*28 genotype. Other TRAEs like nausea, vomiting, constipation, fatigue, alopecia, and decrease appetite were not significantly impacted. †Seven patients had *UGT1A1* genotypes not listed in the table. ‡Patients may report more than 1 event per preferred term. Adverse events were classified according to the MedDRA systems of preferred terms and system organ class and according to severity by NCI CTCAE v4.03. §Combined preferred terms of 'neutropenia' and 'decreased neutrophil count'. ‖Combined preferred terms of 'anemia,' 'hemoglobin decreased,' and 'red blood cell count decreased.' **Combined preferred terms of 'leukopenia' and 'decreased white blood cell count.' ¶Combined preferred terms of 'lymphopenia' and 'decreased lymphocyte count.' #Combined preferred terms of 'thrombocytopenia' and 'decreased platelet count.'
MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE v4.03, National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03; SG, sacituzumab govitecan; TRAE, treatment-related adverse event; UGT, uridine diphosphate glucuronosyltransferase.

- Patients with *UGT1A1* *28/*28 had a higher incidence of grade ≥3 treatment-related AESIs vs *UGT1A1* *1/*1 and *1/*28, respectively (**Table 5**)
  - Neutropenia: 59% vs 53% and 47%
  - Febrile neutropenia: 18% vs 3% and 5%
  - Diarrhea: 15% vs 10% and 9%
- Treatment discontinuation due to TRAEs was higher for patients with *UGT1A1* *28/*28:
  - *1/*1: 2%
  - *1/*28: 1%
  - *28/*28: 6%

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Medizinische Fakultät Mannheim der Universität Heidelberg

Universitätsklinikum Mannheim

Sacituzumab Govitecan TROP2 Expression als prädiktiver Biomarker?

Explorative Subgruppenanalyse der ASCENT-Studie

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der Universität Heidelberg

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ASCENT Clinical Trial

Biomarker Evaluation in the Phase 3 ASCENT Study of Sacituzumab Govitecan Versus Chemotherapy in Patients With Metastatic Triple-Negative Breast Cancer

Sara A. Hurvitz,[1] Sara M. Tolaney,[2] Kevin Punie,[3] Delphine Loirat,[4] Mafalda Oliveira,[5] Kevin Kalinsky,[6] Amelia Zelnak,[7] Philippe Aftimos,[8] Florence Dalenc,[9] Sagar Sardesai,[10] Erika Hamilton,[11] Priyanka Sharma,[12] Sabela Recalde,[13] Eva Ciruelos Gil,[14] Tiffany Traina,[15] Joyce O'Shaughnessy,[16] Javier Cortes,[17] Michaela Tsai,[18] Linda Vahdat,[19] Véronique Diéras,[20] Lisa Carey,[21] Hope S. Rugo,[22] David M. Goldenberg,[23] Quan Hong,[23] Martin Olivo,[23] Loretta M. Itri,[23] and Aditya Bardia[24]

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To obtain presentation, https://bit.ly/2020hurvitzgs3-06

SAN ANTONIO BREAST CANCER SYMPOSIUM®

UT Health San Antonio | AACR American Association for Cancer Research | Baylor College of Medicine

ClinicalTrials.gov Number: NCT02574455

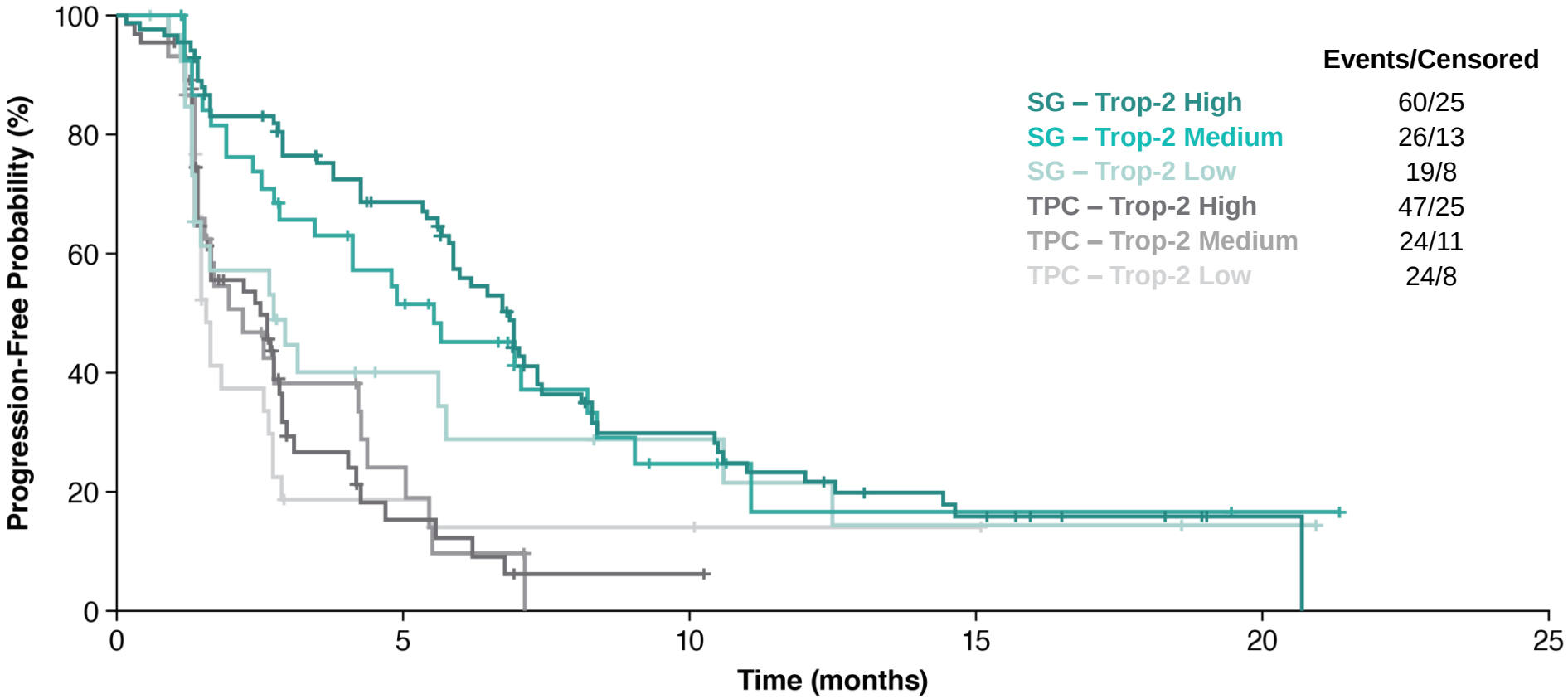
Demographics (Brain Mets-Negative)

	SG (n=235)	TPC (n=233)
Female—no. (%)	233 (99)	233 (100)
Median age—yr (range)	54 (29-82)	53 (27-81)
Race or ethnic group—no. (%)		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other or not specified	10 (4)	15 (6)
ECOG PS—no. (%)		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
***BRCA1/2* mutational status—no. (%)**	149 (63)	143 (61)
Positive	16 (7)	18 (8)
Negative	133 (57)	125 (54)
Trop-2 expression—no. (%)	151 (64)	139 (60)
(High) H-score 200-300	85 (56)	72 (52)
(Medium) H-score 100-200	39 (26)	35 (25)
(Low) H-score <100	27 (18)	32 (23)

	SG (n=235)	TPC (n=233)
Original diagnosis of TNBC*		
Yes	165 (70)	157 (67)
No	70 (30)	76 (33)
Previous anticancer regimens†—median (range)	4 (2-17)	4 (2-14)
Most common prior chemotherapy—no. (%)		
Taxane‡	235 (100)	233 (100)
Cyclophosphamide	192 (82)	192 (82)
Carboplatin	147 (63)	160 (69)
Capecitabine	147 (63)	159 (68)
Previous PARP inhibitor—no. (%)	17 (7)	18 (8)
Previous use of checkpoint inhibitors—no. (%)	67 (29)	60 (26)
Most common sites of disease§—no. (%)		
Lung only	108 (46)	97 (42)
Liver	98 (42)	101 (43)
Bone	48 (20)	55 (24)

Assessed in the brain metastases-negative population. *Patients in study either had TNBC at initial diagnosis or had hormone receptor-positive disease that converted to hormone-negative at time of study entry. †Anticancer regimens refer to any treatment regimen that was used to treat breast cancer in any setting. ‡Includes paclitaxel, paclitaxel albumin, and docetaxel. § Based on independent central review of target and nontarget lesions at baseline.
BRCA, breast cancer gene; ECOG PS, Eastern Cooperative Oncology Group performance status; H-score, histochemical score; PARP, poly-ADP ribose polymerase; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2.

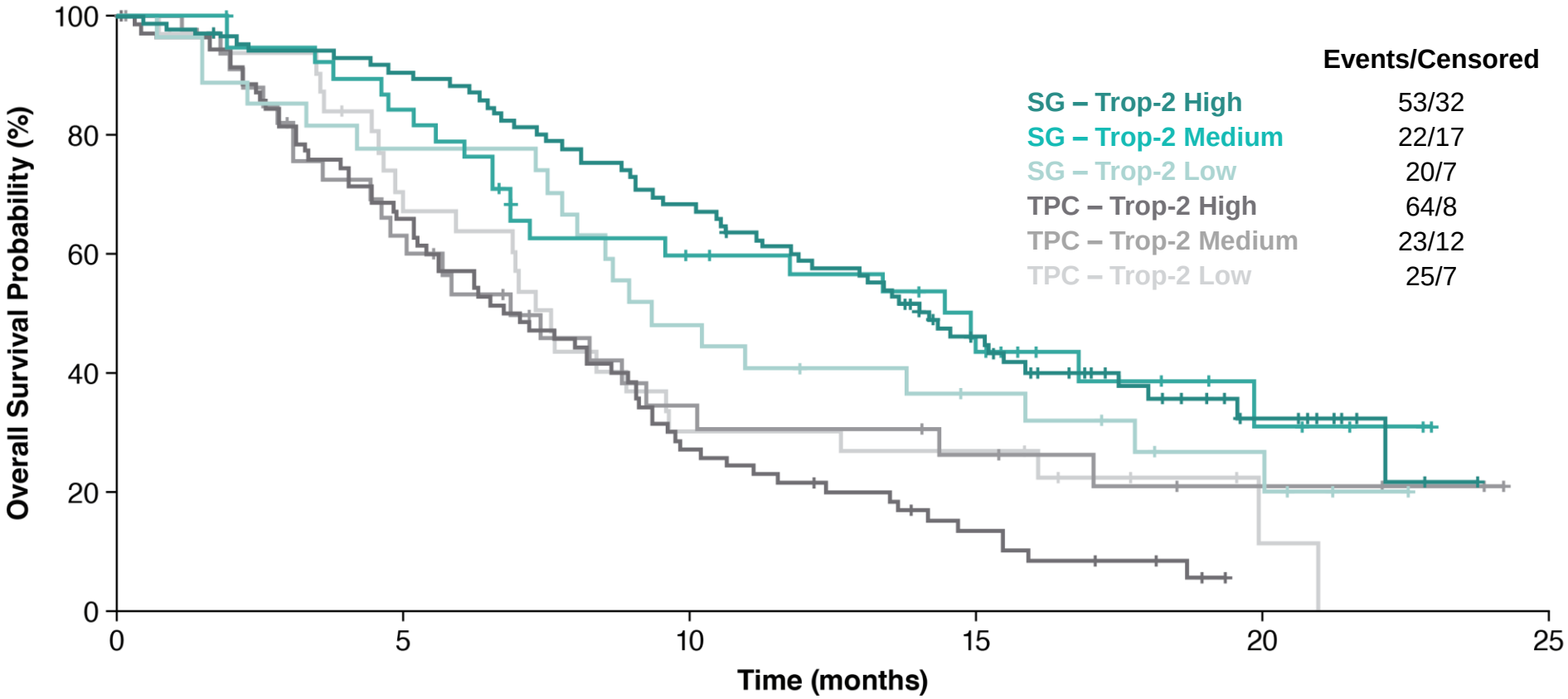
Progression-Free Survival by Trop-2 Expression



	Trop-2 High | H-score: 200-300		Trop-2 Medium | H-score: 100-200		Trop-2 Low | H-score: <100	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
Median PFS—mo (95% CI)	6.9 (5.8-7.4)	2.5 (1.5-2.9)	5.6 (2.9-8.2)	2.2 (1.4-4.3)	2.7 (1.4-5.8)	1.6 (1.4-2.7)

Assessed in brain metastases-negative population. Trop-2 expression determined in archival samples by validated immunohistochemistry assay and H-scoring.
H-score, histochemical score; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen-2.

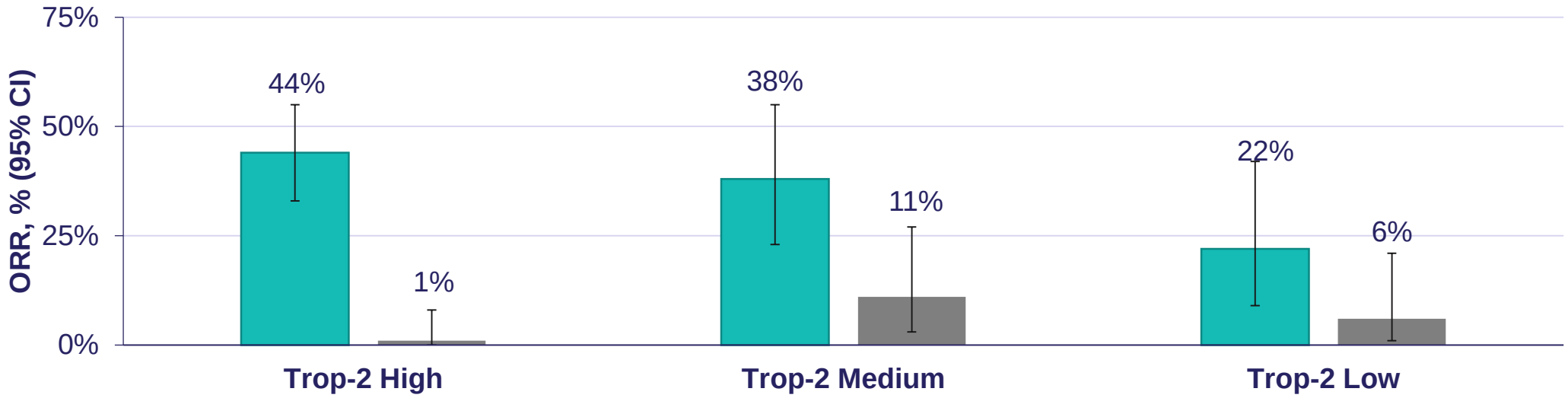
Overall Survival by Trop-2 Expression



	Trop-2 High | H-score: 200-300		Trop-2 Medium | H-score: 100-200		Trop-2 Low | H-score: <100	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
Median OS—mo (95% CI)	14.2 (11.3-17.5)	6.9 (5.3-8.9)	14.9 (6.9-NE)	6.9 (4.6-10.1)	9.3 (7.5-17.8)	7.6 (5.0-9.6)

Assessed in brain metastases-negative population. Trop-2 expression determined in archival samples by validated immunohistochemistry assay and H-scoring.
H-score, histochemical-score; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen-2.

ORR by Trop-2 Expression

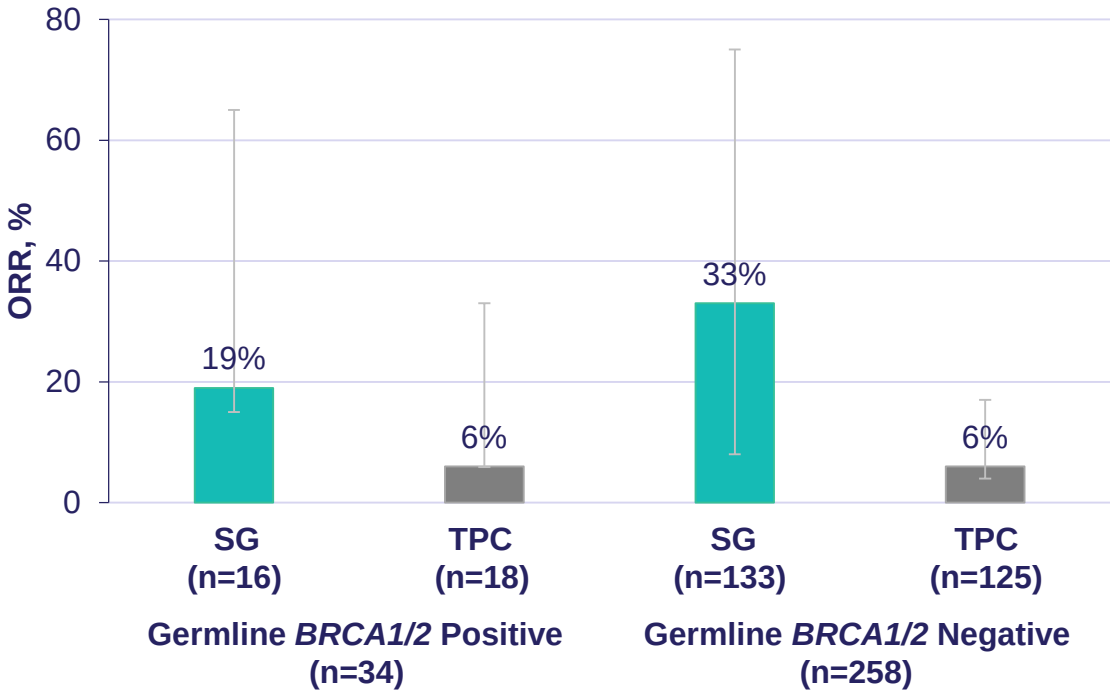


	Trop-2 High H-score: 200-300 (n=157)		Trop-2 Medium H-score: 100-200 (n=74)		Trop-2 Low H-score: <100 (n=59)	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
ORR—% (no.)	44% (37)	1% (1)	38% (15)	11% (4)	22% (6)	6% (2)
95% CI	33-55	0-8	23-55	3-27	9-42	1-21

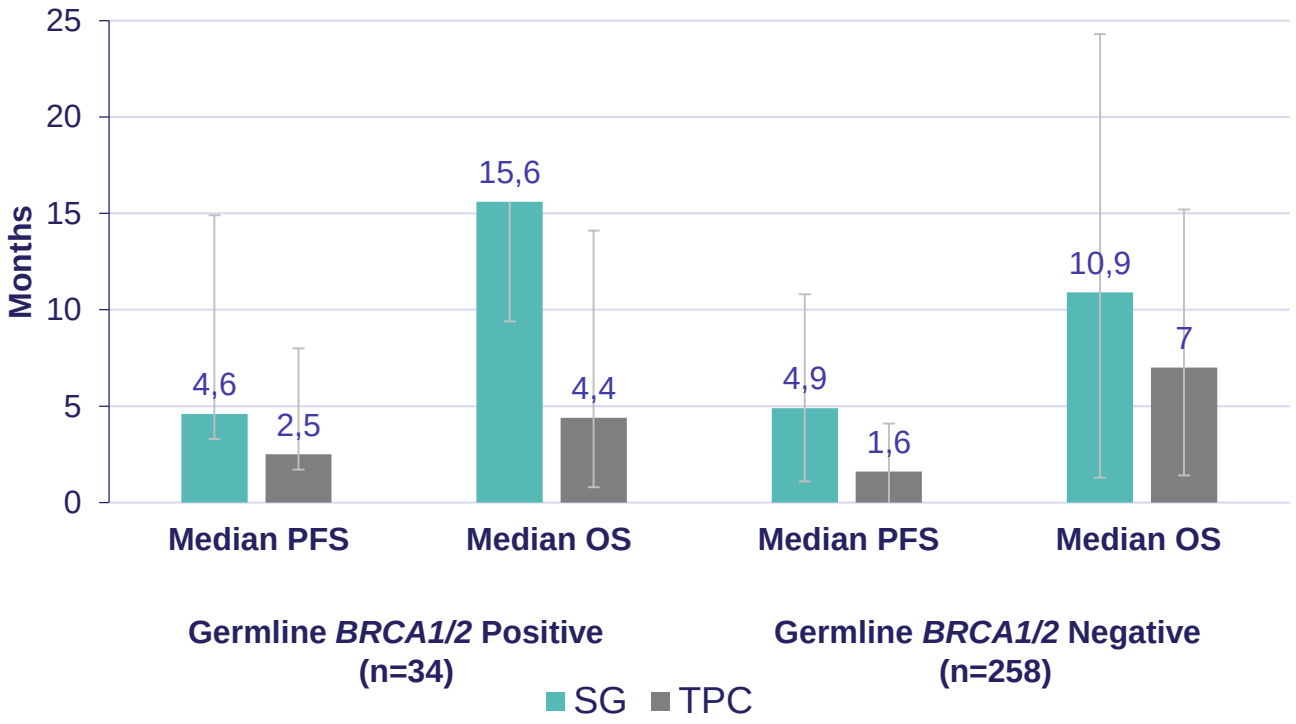
Assessed in the brain metastases-negative population. ORR and PFS are assessed by BICR. Trop-2 expression determined in archival samples by validated immunohistochemistry assay and H-scoring.
BICR, blind independent central review; H-score, histochemical-score; ORR, objective response rate; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen-2.

Efficacy Summary by Germline *BRCA1/2* Status

ORR by *BRCA1/2* Status



PFS and OS by *BRCA1/2* Status



Assessed in the brain metastases-negative population. ORR and PFS are assessed by BICR.
BICR, blind independent central review; *BRCA*, breast cancer gene; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen-2.

Conclusions

- Outcomes in these subgroups confirm that clinical benefit with SG versus TPC in previously treated mTNBC is irrespective of level of Trop-2 expression
  - Higher efficacy outcomes were observed in patients treated with SG who had a medium/high Trop-2 H-score (vs low Trop-2 H-score) versus those treated with TPC
- SG outperformed TPC regardless of germline *BRCA1/2* mutation status at study entry
- Caution should be exercised in data interpretation given the small sample sizes in the Trop-2 low subgroup and germline *BRCA1/2*-positive subgroup
- Trop-2 expression did not affect toxicity, and SG demonstrates a manageable safety profile consistent with that of the ASCENT overall study population and shown in previous reports[1]

BRCA, breast cancer gene; H-score, histochemical score; mTNBC, metastatic triple-negative breast cancer; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen-2.

1. Bardia A, et al. ESMO 2020. Abstract LBA17.

Sacituzumab Govitecan

Hormonrezeptor-positives stark vorbehandeltes Mammakarzinom

Sacituzumab Govitecan bei stark vorbehandeltem HR+/HER2- MBC

Phase I/II BASKET trial

HR+/HER2- Cohort

Keine Selektion für TROP-2 Expression

Vortherapien :

- **5 Linien für MBC**
- **2 Linen CHT für MBC**
- **69% prior CDK4/6i**
- **54% prior mTORi**

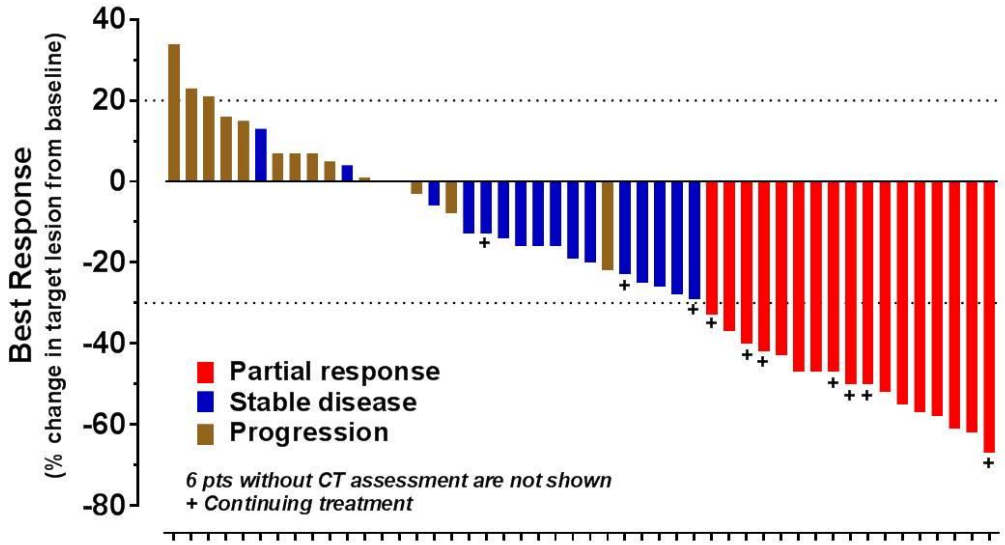
Hauptsächliche Tox:

Neutropenie (42% ¾°)

Diarrhoe

Nausea & Vomiting

Tumor Response to Sacituzumab Govitecan



Median number of metastatic chemo lines: 2
Median number of prior metastatic lines: 5

Local Response Evaluation by RECIST1.1	
Objective response rate	31% (17/54)
CR	0
PR	17
Clinical benefit rate (CR+PR+SD ≥6 months)	48% (26/54)

- 63% (34/54) of patients with at least one CT response assessment had reduction of target lesions (sum of diameters)

med. PFS 6.8 months

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PRESENTED BY: Aditya Bardia
Contact: Bardia.Aditya@mgh.harvard.edu

Immunomedics

11

Bardia A et al., ASCO 2018 oral session MBC

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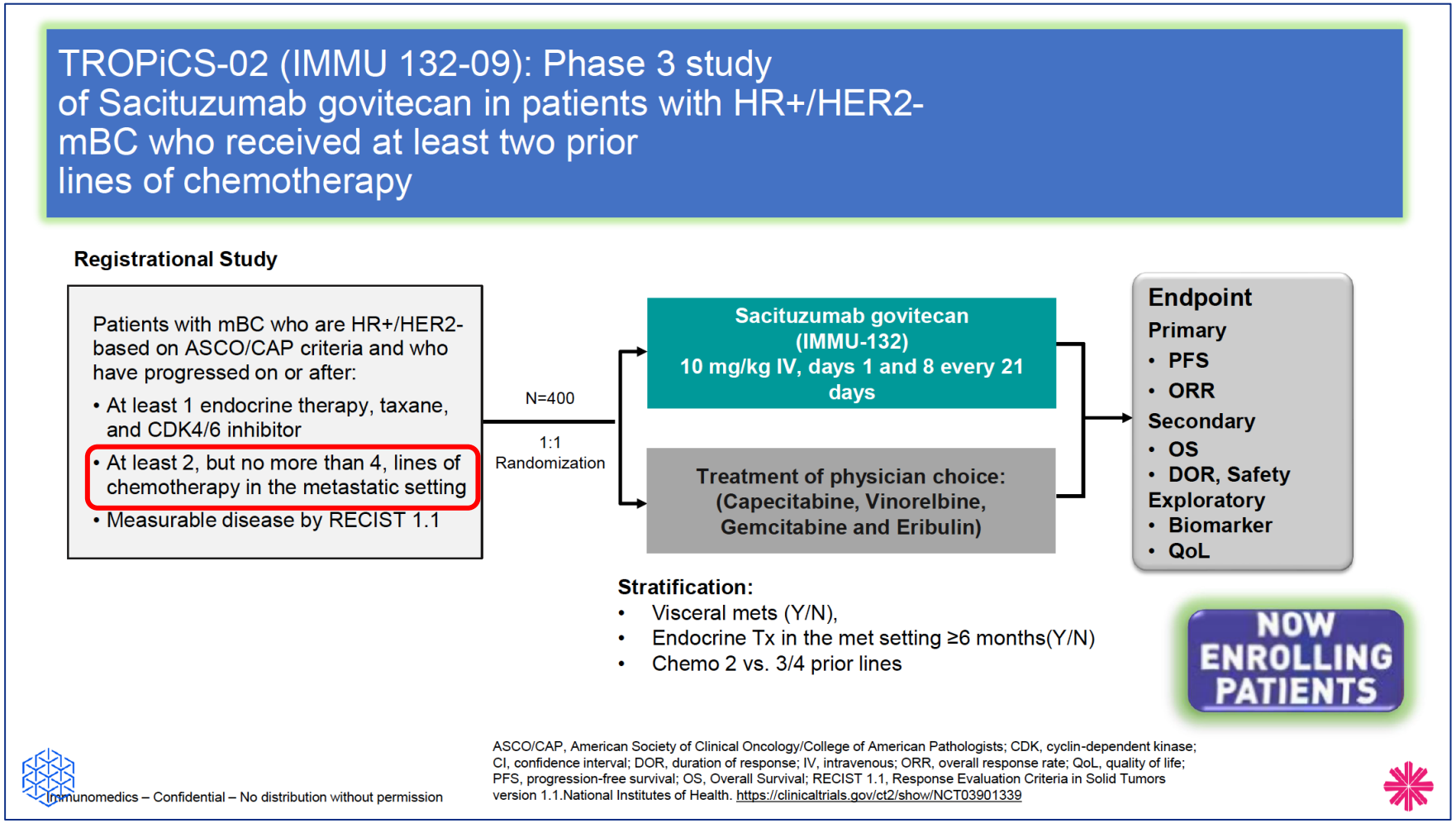
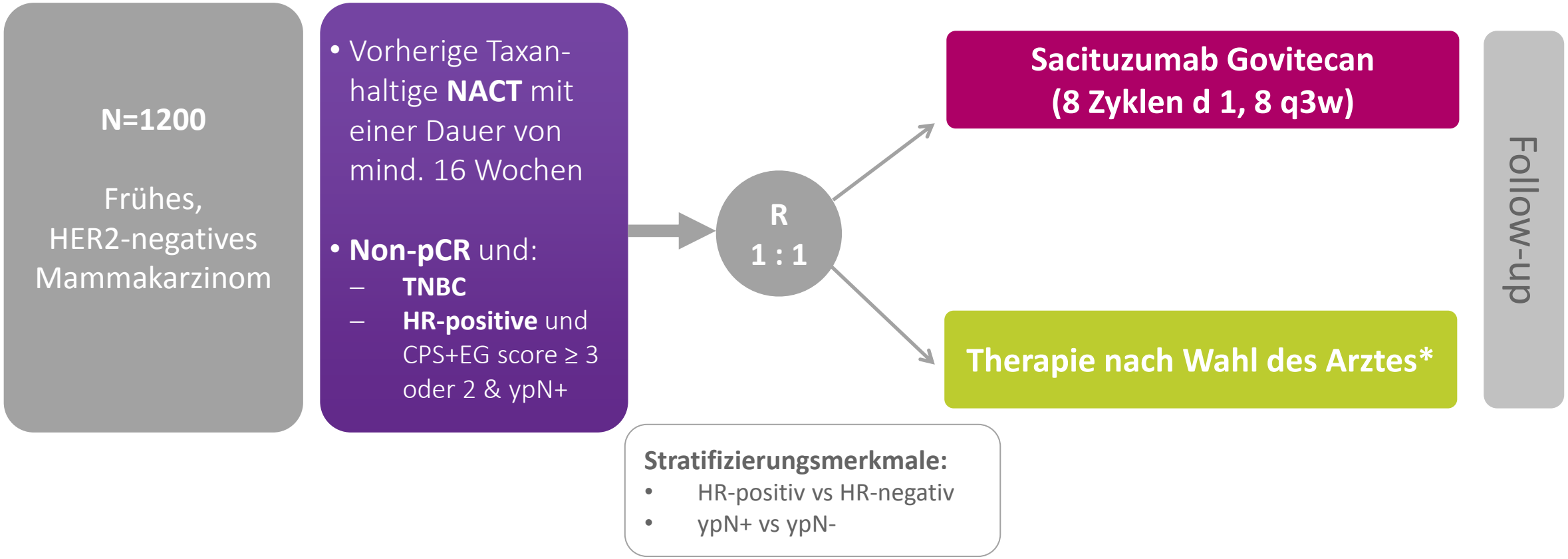
Medizinische Fakultät Mannheim der Universität Heidelberg

Universitätsklinikum Mannheim

Phase III Studien: TNBC & HR+/HER2- MBC



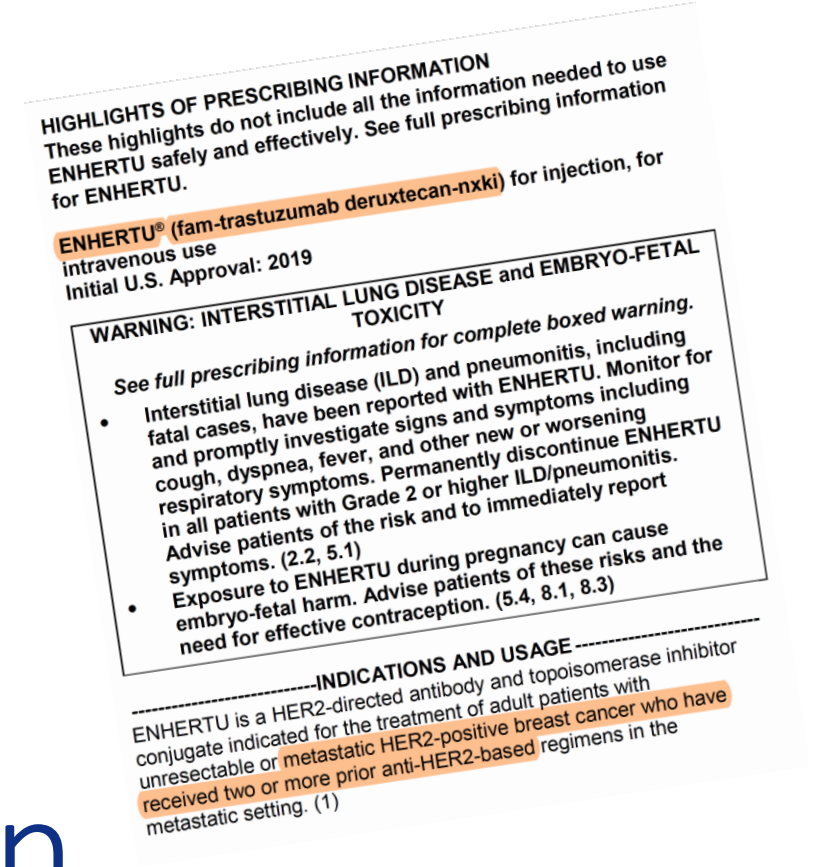
SASCIA: Studiendesign



*__Capecitabine__ (8 Zyklen) oder __platinhaltige Chemotherapie__ (8 Zyklen) oder Beobachtung
Hintergrundtherapie: bei HR-positiven Patientinnen wir die endokrine Therapie nach lokalen Leitlinien durchgeführt
The start of endocrine therapy will be at the discretion of the investigator

Fazit – Sacituzumab Govitecan

- Signifikant besseres OS, PFS & ORR in stark vorbehandelten TNBCs (Phase 3)
- Zulassung durch FDA für 3rd Line mTNBC
- Deutliches Wirksamkeitssignal für stark vorbehandeltes HR+/HER2- MBC, Phase 3 läuft
- Toxizität:
  - Neutropenie, febrile Neutropenie, Anämie (ggfs. G-CFS)
  - Diarrhoe (ggfs. prophylakt Loperamid)
  - Bauchkrämpfe mit Diarrhoe als cholinerge Reaktion (Atropin)
  - Allergische Reaktionen
- AE-bedingt Therapieabbrüche selten (4,7%)
- Dosisreduktion aufgrund von AE führt nicht zu verminderten Effektivität
- Exploratorisch:
  - UGT1A1 *28 homozygot häufigere Therapieabbrüche?
  - Wirkung bei Hirnmetastasen
  - Effektivität unabhängig vom BRCA Status
  - Unabhängig von Trop-2 Expression – möglich Trop-2 low geringerer Nutzen
  - Zurückhaltende Interpreation aufgrund kleiner Gruppengröße (Trop-2 low, UGT1A1 *28, BRCA)
- Laufende Studien in D: SASCIA & TROPICs02



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ENHERTU safely and effectively. See full prescribing information for ENHERTU.

ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use
Initial U.S. Approval: 2019

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms. (2.2, 5.1)
- Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception. (5.4, 8.1, 8.3)

----------INDICATIONS AND USAGE----------

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. (1)

Trastuzumab-Deruxtecan

Anti-HER2 ADC

DESTINY-Breast01: Trastuzumab Deruxtecan (DS-8201)

Einarmige Phase 2, n=184

HER2+ MBC

Anti-HER2 ADC (1:8)

- prior T-DM1 must!
  - *T-DM1 (100%)*
  - *Trastuzumab (100%)*
  - *Pertuzumab (65%)*
  - *Other HER2 (54%)*
- Keine ILD in Anamnese
- Nur stabile, behandelte BM

1° Endpunkt:

- *ORR (BICR)*

2° Endpunkte:

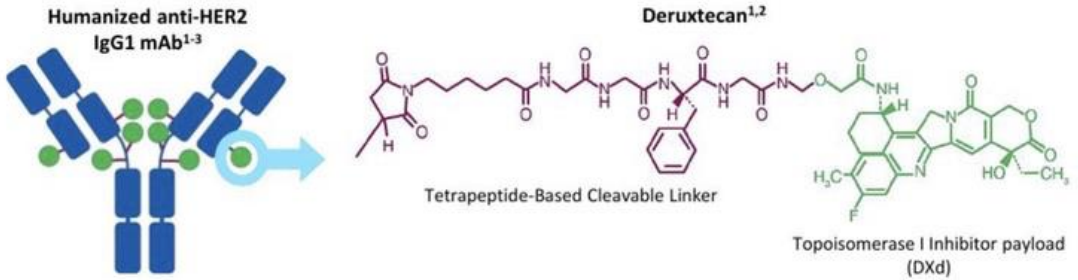
- *OS, PFS(local)*
- *ORR, CBR*
- *etc*

San Antonio Breast Cancer Symposium®, December 10-14, 2019

Trastuzumab Deruxtecan (DS-8201) is a Novel ADC Designed to Deliver an Optimal Antitumor Effect

Trastuzumab deruxtecan is an ADC composed of 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



- Payload MOA: topoisomerase I inhibitor
- High potency of payload
- High drug to antibody ratio ≈ 8
- Payload with short systemic half-life
- Stable linker-payload
- Tumor-selective cleavable linker
- Membrane-permeable payload

Bystander-Effekt

The clinical relevance of these features is under investigation.

ADC, antibody-drug conjugate; MOA, mechanism of action.

1. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. Clin Cancer Res. 2016;22(20):5097-5108. 3. Trail PA, et al. Pharmacol Ther. 2018;181:126-142. 4. Ogitani Y, et al. Cancer Sci. 2016;107(7):1039-1046.

DESTINY-Breast01: Trastuzumab Deruxtecan (DS-8201)

Einarmige Phase 2, n=184

HER2+ MBC

Anti-HER2 ADC (1:8)

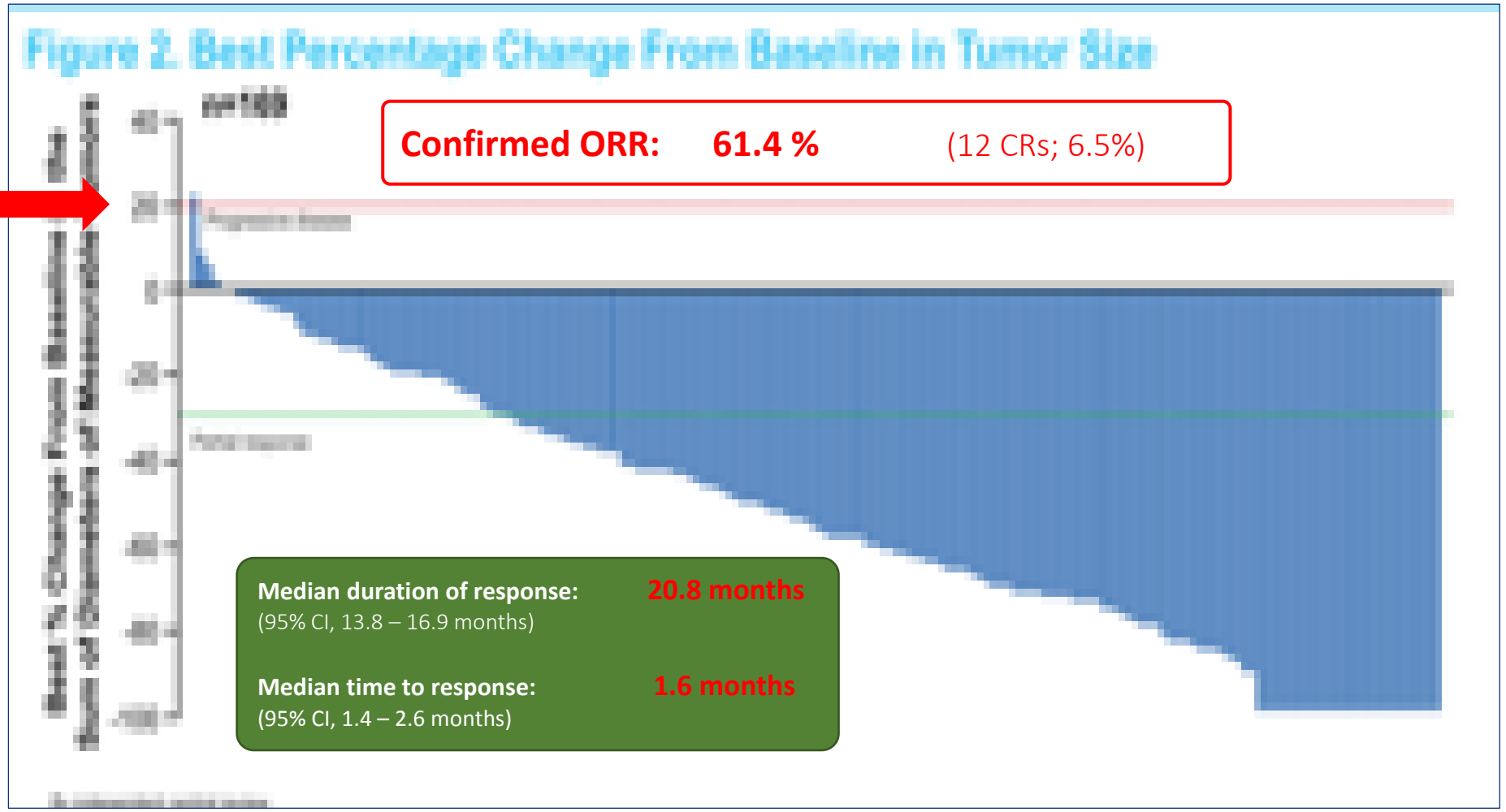
- prior T-DM1 must!
  - *T-DM1 (100%)*
  - *Trastuzumab (100%)*
  - *Pertuzumab (65%)*
  - *Other HER2 (54%)*
- Keine ILD in Anamnese
- Nur stabile, behandelte BM

1° Endpunkt:

- *ORR (BICR)*

2° Endpunkte:

- *OS, PFS(local)*
- *ORR, CBR*
- *etc*



DESTINY-Breast01: Trastuzumab Deruxtecan (DS-8201)

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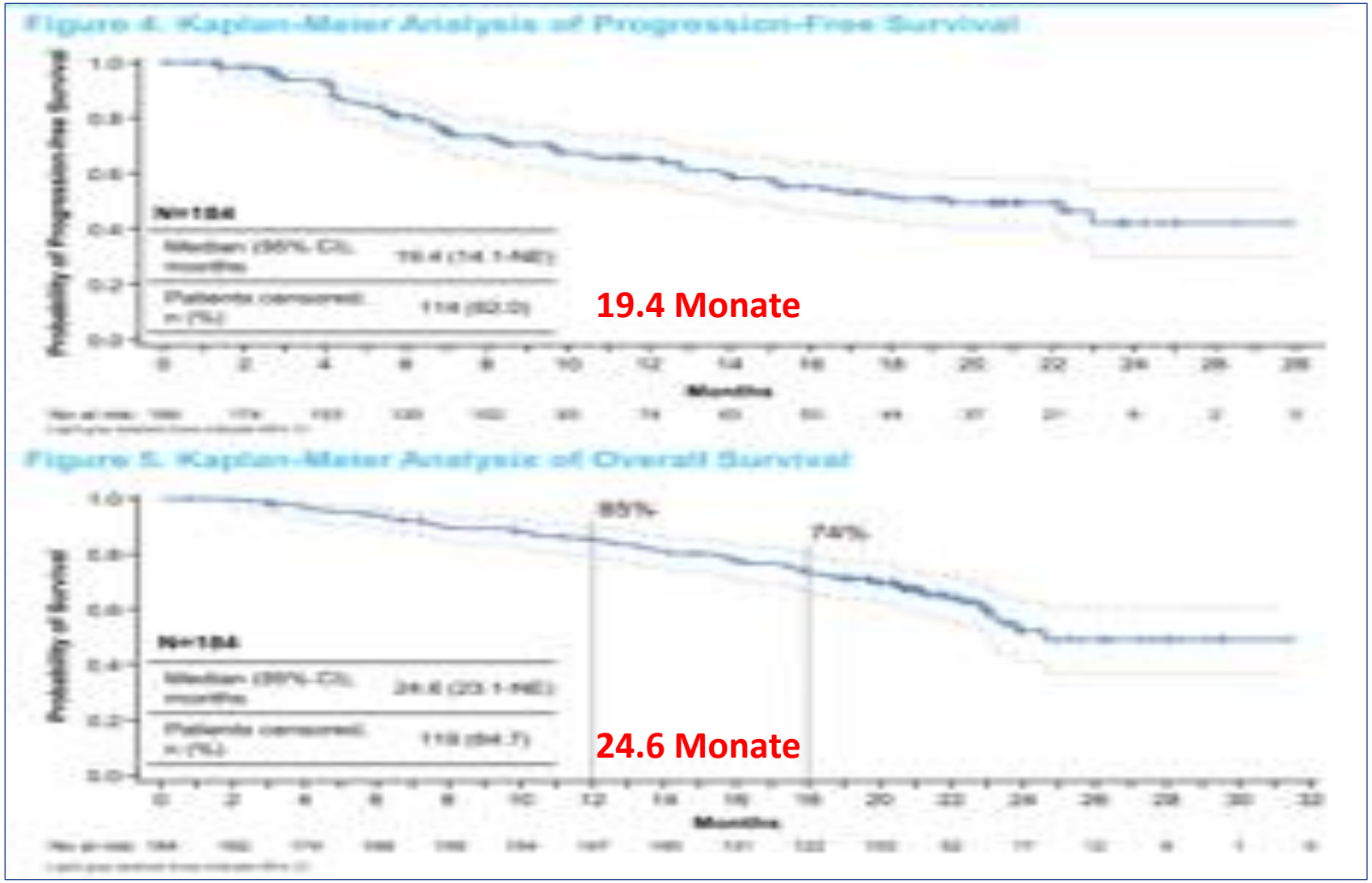

Modi S et al., SABCS 2020 PD3-06

DESTINY-Breast01: Trastuzumab Deruxtecan (DS-8201)

Einarmige Phase 2, n=184

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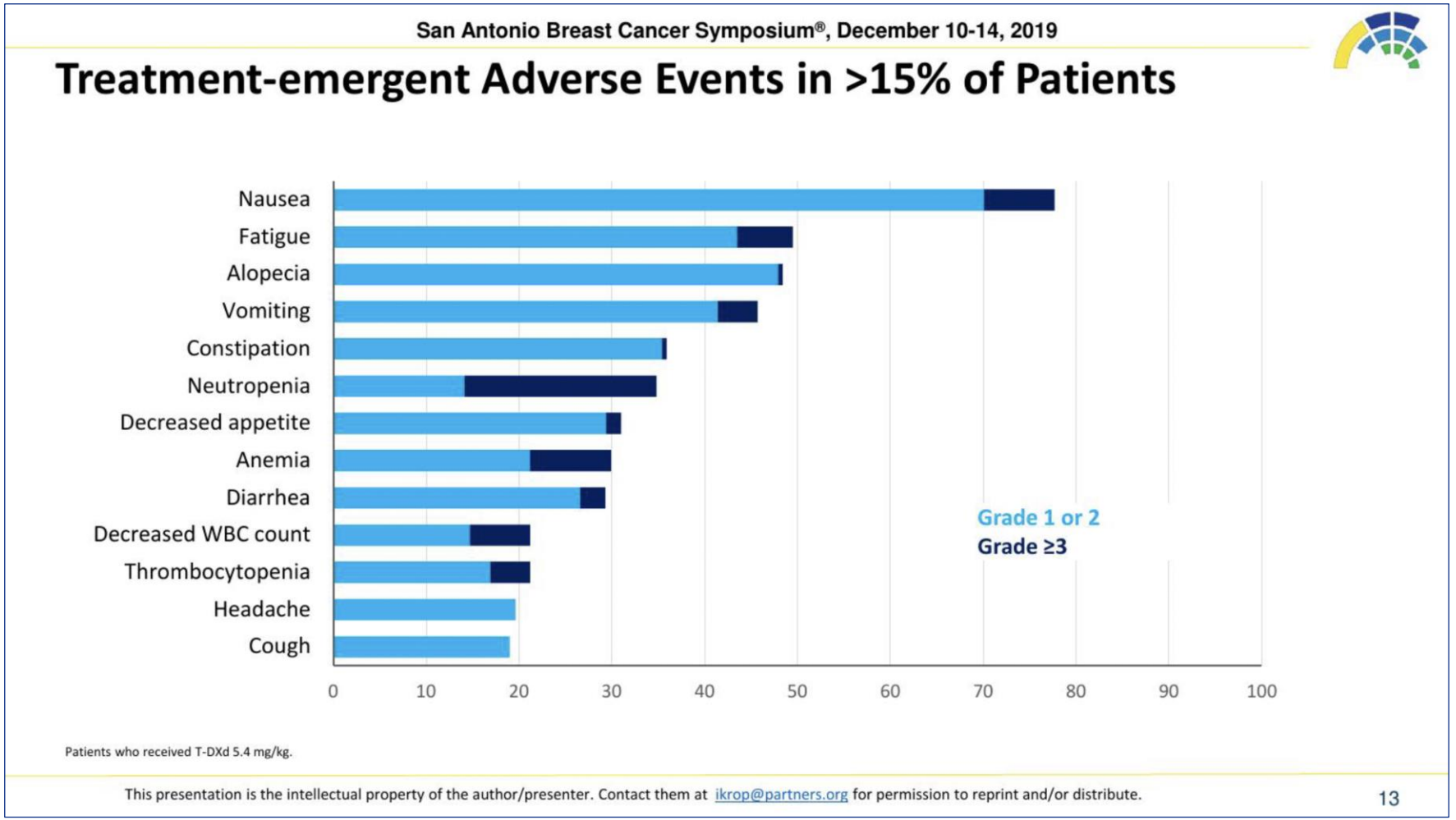

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Einarmige Phase 2, n=184

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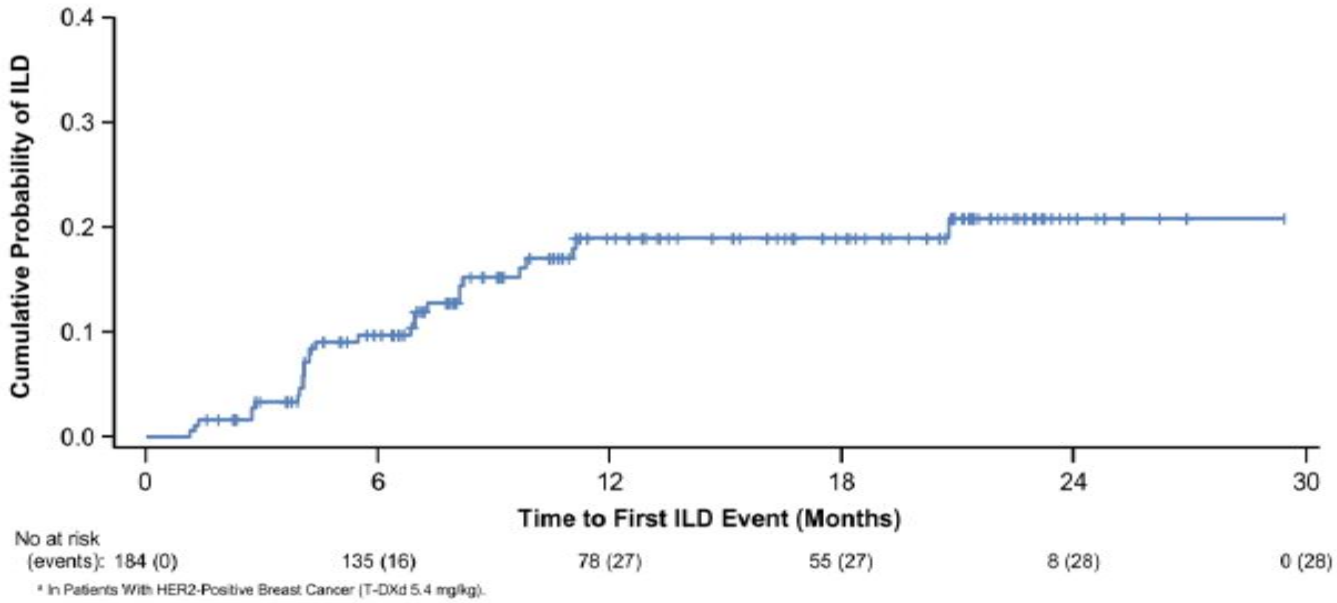
- *ORR, CBR*
- *etc*

Table 4. Drug-related ILD/Pneumonitis[a]

Interstitial lung disease, n (%)	T-DXd 5.4 mg/kg (N=184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade/ Total
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	**28 (15.2)**

[a]As determined by an independent interstitial lung disease adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.

Figure 6. Cumulative Probability of Adjudicated Drug-related Any-grade ILD[a]



[a] In Patients With HER2-Positive Breast Cancer (T-DXd 5.4 mg/kg).

Modi S et al., SABCS 2020 PD3-06

DESTINY-Breast01: Trastuzumab Deruxtecan (DS-8201)

Einarmige Phase 2, n=184

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Figure 6. Cumulative Probability of Adjudicated Drug-related Any-grade ILD[a]

Promptly Investigate Evidence of ILD

- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

For Asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (eg, ≥0.5 mg/kg prednisone or equivalent)
- Withhold trastuzumab deruxtecan until recovery to Grade 0
  - If resolved in ≤28 days from date of onset, maintain dose
  - If resolved in >28 days from date of onset, reduce dose one level

For Symptomatic ILD (Grade ≥2)

- Promptly initiate corticosteroid treatment (eg, ≥1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan

[a] In Patients With HER2-Positive Breast Cancer (T-DXd 5.4 mg/kg).

Modi S et al., SABCS 2020 PD3-06

Enhertu

trastuzumab deruxtecan

AUTHORISED
This medicine is authorised for use in the European Union.

Table of contents

Overview

Enhertu is a medicine used to treat breast cancer that is metastatic (has spread to other parts of the body) or cannot be removed by surgery.

It can only be used when the cancer has been shown to 'overexpress HER2': this means that the cancer produces a protein called HER2 in large quantities on the surface of the tumour cells, which makes the tumour cells grow more quickly.

Enhertu is used on its own in patients who have received two or more HER2-targeted treatments.

It contains the active substance trastuzumab deruxtecan.

Trastuzumab Deruxtecan

HER2+, BRAIN Mets

Trastuzumab Deruxtecan & Hirnmetastasen

DESTINY-Breast01 Study Design:
An Open-Label, Multicenter, Phase 2 Study

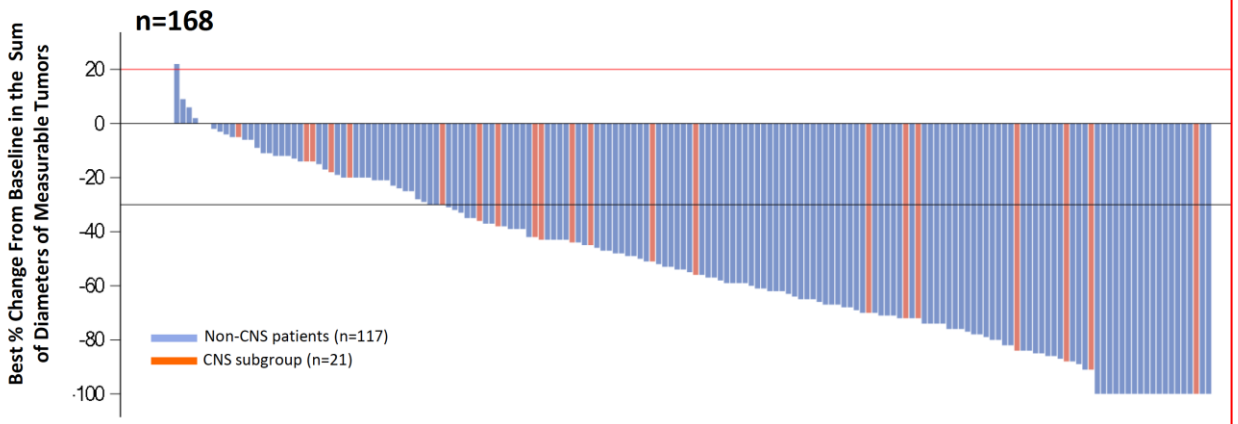
Population

- ≥18 years of age
- Unresectable and/or metastatic BC
- HER2 positive (centrally confirmed on archival tissue)
- Prior T-DM1
- Excluded patients with history of significant ILD
- Stable, treated brain metastases were allowed

Patients were included if:

- **They had brain metastases that were treated, asymptomatic, or did not require therapy to control symptoms**
- **They had radiation, surgery, or other therapy (including steroids or anticonvulsants) to control symptoms more than 60 days before randomization**
- **Brain imaging was performed every 6 weeks for patients with a history of brain metastases**

DESTINY-Breast01
Best Change in Tumor Size



Data Cutoff: August 1, 2019

- **24 patients (13.0%) had CNS metastases at baseline**
  - 11 (45.8%) ongoing
  - 13 (54.2%) discontinued, primarily for progressive disease (6/24, 25.0%)

Primary Endpoint: Objective Response Rate

Intent-to-Treat Analysis	CNS Subgroup (n=24)	All Patients (N=184)
Confirmed ORR by ICR	**58.3% (n=14)** (95% CI, 36.6%-77.9%)	**60.9% (n=112)** (95% CI, 53.4%-68.0%)

Trastuzumab Deruxtecan & Hirnmetastasen

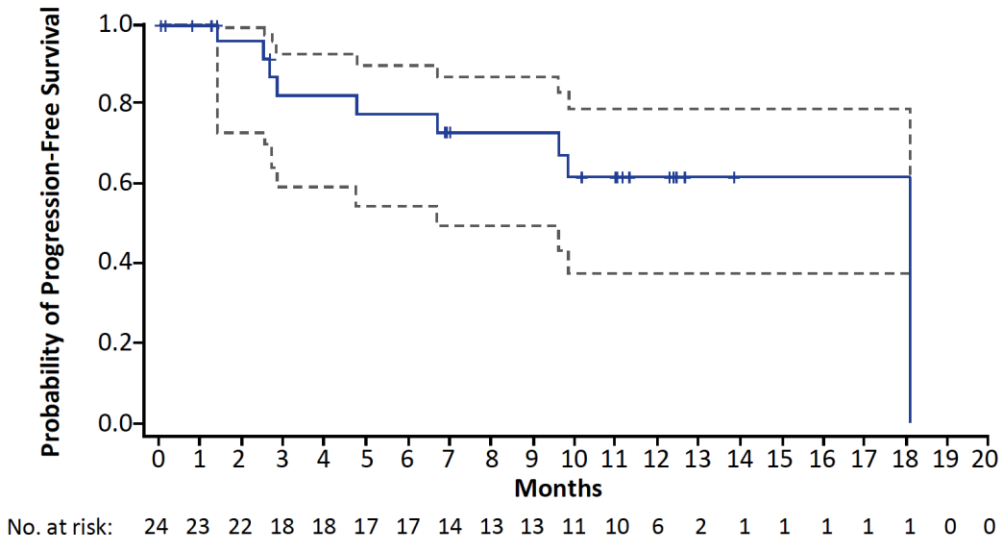
European Society for Medical Oncology (ESMO) Breast Cancer Virtual Meeting, 23-24 May 2020

DESTINY-Breast01

Progression-Free Survival

CNS Subgroup (n=24)

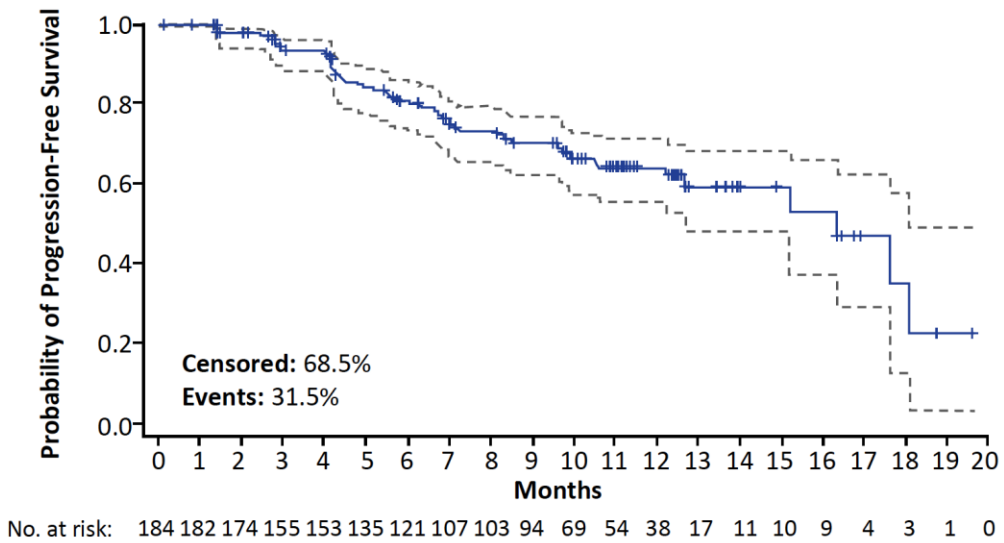
Median: 18.1 months (95% CI, 6.7-18.1)



Median follow-up, 11.0 months (range, 0.7-19.6 months)

All Patients (N=184)

Median: 16.4 months (95% CI, 12.7-NE)



Median follow-up, 11.1 months (range, 0.7-19.9 months)

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Jerusalem G et al., ESMO Breast 2020

Medizinische Fakultät Mannheim der Universität Heidelberg

Universitätsklinikum Mannheim

Trastuzumab Deruxtecan & Hirnmetastasen

European Society for Medical Oncology (ESMO) Breast Cancer Virtual Meeting, 23-24 May 2020

DESTINY-Breast01

Sites of Progression

Site of PD	CNS Subgroup (n=24)	Non-CNS Patients (n=160)	All Patients (N=184)
Patients with progression on study, n (%)	**8 (33.3)**	**40 (25.0)**	**48 (26.1)**
Lung	3 (12.5)	17 (10.6)	20 (10.9)
Liver	2 (8.3)	12 (7.5)	14 (7.6)
Brain	2 (8.3)	2 (1.3)	4 (2.2)
Bone	1 (4.2)	2 (1.3)	3 (1.6)
Lymph node	1 (4.2)	11 (6.9)	12 (6.5)
Pleura	1 (4.2)	1 (0.6)	2 (1.1)
Soft tissue	1 (4.2)	0	1 (0.5)
Chest wall	0	4 (2.5)	4 (2.2)
Muscle	0	1 (0.6)	1 (0.5)
Peritoneum	0	1 (0.6)	1 (0.5)

For patients in the CNS subgroup, a CT or MRI of the brain was mandatory every 6 wks (±7 days).

- Sites of progression were similar among all patients and the CNS subgroup
- Overall, only 4 of 48 patients had progression in the CNS
- CNS progression events:
  - At 78 and 85 days in the CNS subgroup
  - At 323 and 498 days in patients without a history of CNS metastases

Jerusalem G et al., ESMO Breast 2020

Trastuzumab Deruxtecan

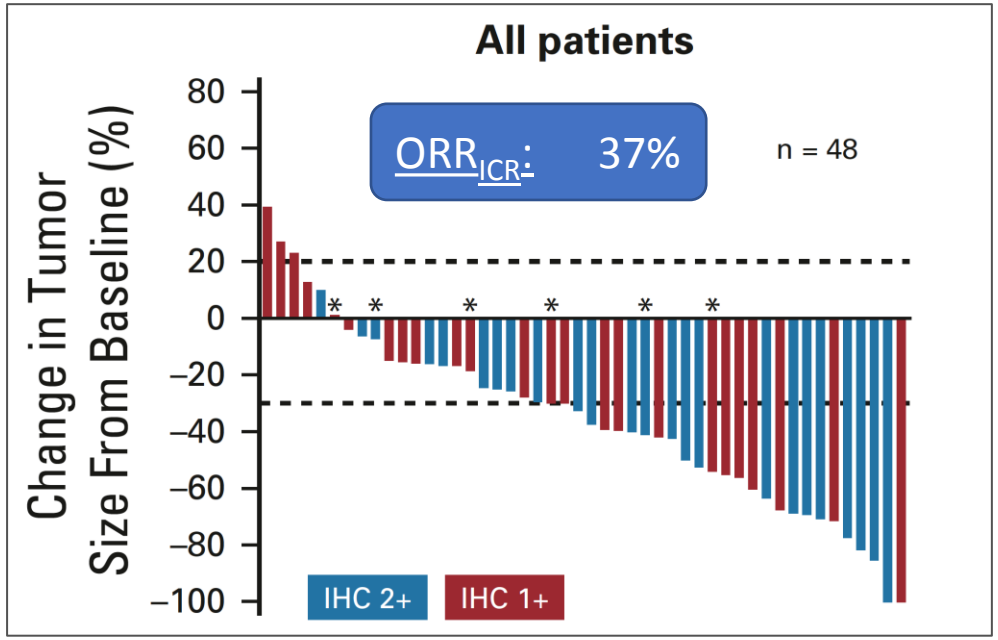
In HER2 low MBC

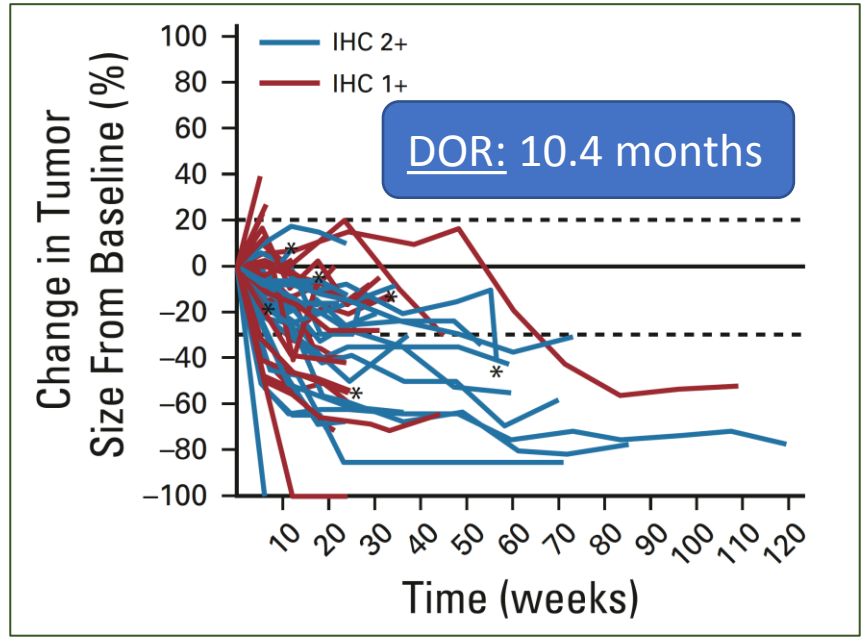
original reports

Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low–Expressing Advanced Breast Cancer: Results From a Phase Ib Study

Shanu Modi, MD[1]; Haeseong Park, MD, MPH[2]; Rashmi K. Murthy, MD, MBE[3]; Hiroji Iwata, PhD, MD[4]; Kenji Tamura, MD, PhD[5]; Junji Tsurutani, MD, PhD[6]; Alvaro Moreno-Aspitia, PhD[7]; Toshihiko Doi, MD, PhD[8]; Yasuaki Sagara, MD[9]; Charles Redfern, MD[10]; Ian E. Krop, MD, PhD[11]; Caleb Lee, MD, PhD[12]; Yoshihiko Fujisaki, MS[13]; Masahiro Sugihara, PhD[13]; Lin Zhang, MD, PhD[12]; Javad Shahidi, MD[12]; and Shunji Takahashi, MD[14]

- N=54
- HER2-low:
  IHC 1+ or 2+/FISH-
- Prior lines: 7.5
- ≥ 5 prior lines: 83.3%
- HR+ 87%
- HR- 13%





ORR$_{inv}$: 44%

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Modi S et al., *Journal of Clinical Oncology* 38, no. 17 (June 10, 2020) 1887-1896.

Medizinische Fakultät Mannheim der Universität Heidelberg

Universitätsklinikum Mannheim

Laufende Studien mit Trastuzumab Deruxtecan

Studien-Name	Setting	Design	Status
DESTINY-Breast02 N=600 NCT03523585	**HER2+** LABC/MBC Progressed on/after T-DM1	DS 8201a *versus* Physician´s choice	recruiting
DESTINY-Breast03 N=500 NCT03529110	**HER2+** LABC/MBC Previously treated with trastuzumab and taxane	DS 8201a *versus* T-DM1	recruiting
DESTINY-Breast04 N=540 NCT03734029	**HER2 low** LABC/MBC HR pos: progressed on ET HR neg.: 1 or 2 CTX	DS 8201a *versus* Physician´s choice	recruiting
GBG 103 DESTINY-Breast05 N=1600 NCT04622319	**HER2+** Post-neoadjuvant Non-pCR, high-risk	DS 8201a *versus* T-DM1	recruiting
DESTINY-Breast06 N=850 NCT04494425	**HR+/HER2 low** LABC/MBC progressed on ≥2 lines ET	DS 8201a *versus* Physician´s choice CTX	recruiting

DESTINY-Breast05 (DS8201-A-U305) Study Design

T-DXd vs. T-DM1 in high-risk HER2-positive early breast cancer patients with residual invasive disease following neoadjuvant therapy

Key Eligibility:

- eBC with residual disease following neoadjuvant therapy
- Completion of **neoadjuvant therapy*** including trastuzumab followed by surgery
- **High-risk**** of recurrence (**inoperable** at presentation or **node-positive**)
- Centrally confirmed HER2+ status
- ECOG PS: 0-1

Stratification:

- Operative status at presentation (operable vs inoperable)
- Post-neoadjuvant pathologic nodal status (positive vs negative)
- Tumor hormone receptor (HR) status (positive vs negative)
- HER2-targeted neoadjuvant therapy (single vs dual)

R
1:1

N = 1,600

Investigational Arm:
Trastuzumab deruxtecan (T-DXd; DS-8201)
Day 1 every 3 weeks for 14 cycles (N=800)

Control Arm:
Trastuzumab emtansine (T-DM1)
Day 1 every 3 weeks for 14 cycles (N=800)

***Neoadjuvant therapy** to include at least 16 weeks of total systemic treatment in the preoperative setting, including:

- At least 9 weeks of HER2-targeted therapy including **trastuzumab** (with or without pertuzumab) and,
- At least 9 weeks of **taxane** therapy

****High-risk definitions:**

- **Inoperable:** Inoperable breast cancer at presentation (Stage T4NxM0 or TxN2-3M0)
- **Node-positive:** positive regional lymph nodes following neoadjuvant therapy irrespective of presence or absence of residual invasive cancer in the breast.

Additional Notes: Randomization within 12 weeks of surgery; adjuvant radiotherapy and/or endocrine therapy per protocol and local guidelines.

Endpoints:

- **Primary:**
  - **IDFS** (Invasive disease-free survival)
- **Secondary:**
  - **DFS** (Disease-free survival)
  - **DRFI** (Distant recurrence-free interval)
  - **BMFI** (Brain metastases-free interval)
  - **OS** (Overall survival)
  - **Adverse events**
- **Exploratory:**
  - **PROs** (Patient reported outcomes; QoL)
  - **Biomarkers** associated with efficacy/safety
  - **PK** associated with efficacy/safety

eBC=early breast cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; HER2=Human epidermal growth factor receptor 2; PK=pharmacokinetics; QoL=quality of life R=randomization

San Antonio Breast Cancer Symposium® - December 8-11, 2020

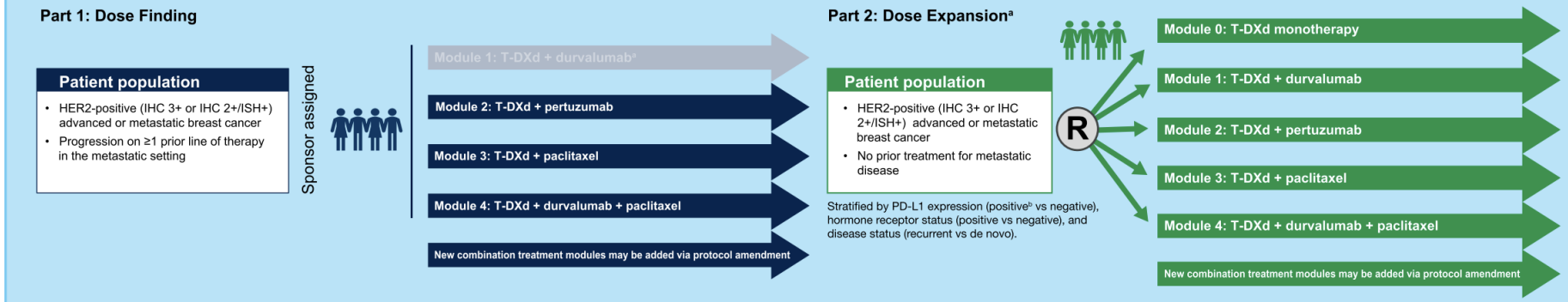
OT-03-04

Trastuzumab deruxtecan (T-DXd; DS-8201) combinations in patients with HER2-positive advanced or metastatic breast cancer: a phase 1b/2, open-label, multicenter, dose-finding and dose-expansion study (DESTINY-Breast07)

Fabrice André,[1] Erika Hamilton,[2] Sherene Loi,[3] Peter Schmid,[4] Tinghui Yu,[5] Helen Broadhurst,[6] Sarice Boston,[5] Celina D'Cruz,[5] Pia Herbolsheimer,[5] Komal Jhaveri[7]

METHODS

DESTINY-Breast07: A Phase 1b/2, Open-Label, Multicenter, Dose-Finding and Dose-Expansion Trial of T-DXd Combinations in Patients With HER2+ Advanced or Metastatic Breast Cancer (N≈350)



HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan.
[a] Dose finding for module 1 may not be necessary due to potential recommended phase 2 dose (RP2D) determination in a separate study (BEGONIA; NCT03742102).

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PD-L1, programmed cell death 1 ligand 1; R, randomly assigned to open modules; T-DXd, trastuzumab deruxtecan.
[a] The part 2 dose-expansion phase will use the RP2D determined in part 1.
[b] PD-L1 positive is defined as IHC ≥1%.

San Antonio Breast Cancer Symposium® - December 8-11, 2020

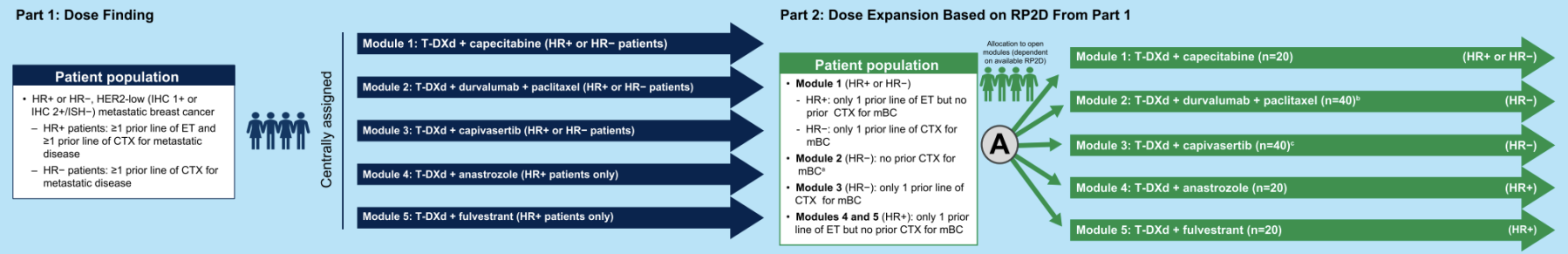
OT-03-05

Trastuzumab deruxtecan (T-DXd; DS-8201) in combination with other anticancer agents in patients with HER2-low metastatic breast cancer: a phase 1b, open-label, multicenter, dose-finding and dose-expansion study (DESTINY-Breast08)

Komal Jhaveri,[1] Erika Hamilton,[2] Sherene Loi,[3] Peter Schmid,[4] Annie Darilay,[5] Chen Gao,[5] Gargi Patel,[6] Magdalena Wrona,[7] Fabrice André[8]

METHODS

DESTINY-Breast08: A Phase 1b, Open-Label, Modular, Dose-Finding and Dose-Expansion Trial of T-DXd Combinations in Patients With HER2-Low Metastatic Breast Cancer



CTX, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan.

A, allocation; CTX, chemotherapy; ET, endocrine therapy; HR, hormone receptor; mBC, metastatic breast cancer; RP2D, recommended phase 2 dose; T-DXd, trastuzumab deruxtecan.
[a] Patients who have received CTX in the neoadjuvant or adjuvant setting are eligible, as long as they have had a disease-free interval of >12 months. [b] Molecularly defined subgroup of special interest, PD-L1(+). [c] Molecularly defined subgroup of special interest, AKT/PTEN/PIK3CA altered.

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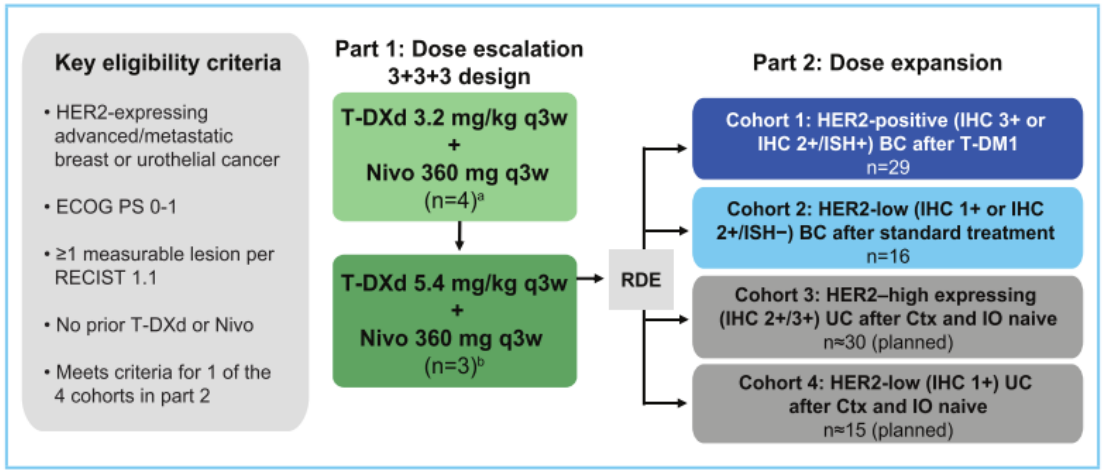
San Antonio Breast Cancer Symposium® - December 8-11, 2020

PD3-07

Trastuzumab deruxtecan (T-DXd; DS-8201) with nivolumab in patients with HER2-expressing advanced breast cancer: a 2-part, phase 1b, multicenter, open-label study

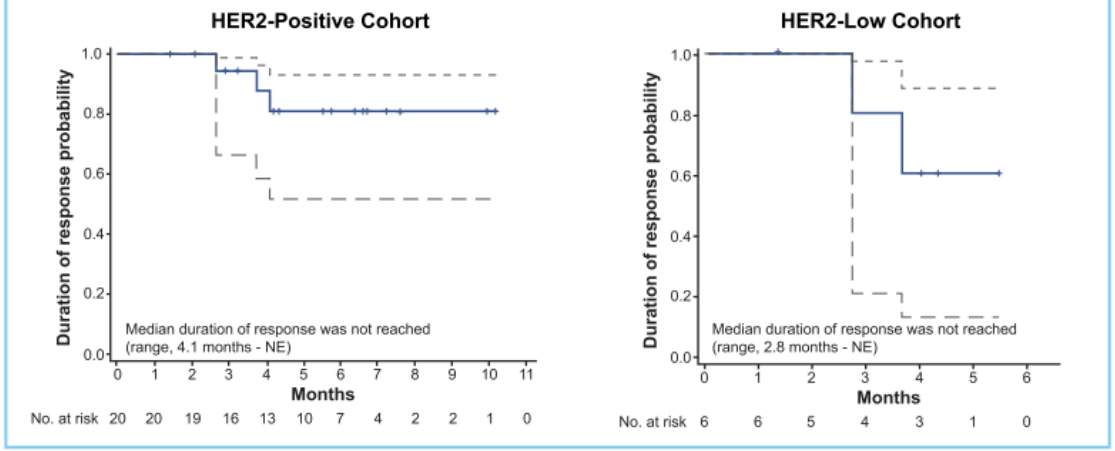
Erika Hamilton,[1] Charles L. Shapiro,[2] Daniel Petrylak,[3] Valentina Boni,[4] Miguel Martin,[5] Gianluca Del Conte,[6] Javier Cortes,[7] Laila Agrawal,[8] Hendrik-Tobias Arkenau,[9] Antoinette R. Tan,[10] Philip Debruyne,[11] Anna Minchom,[12] Annemie Rutten,[13] Frances Valdes-Albini,[14] Evan Y. Yu,[15] Bincy Augustine,[16] Anthony D'Amelio Jr,[16] Daniel Barrios,[16] Sara A. Hurvitz[17]

Figure 2. Study Design



BC, breast cancer; Ctx, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IO, immuno-oncologic; ISH, in situ hybridization; Nivo, nivolumab; q3w, every 3 weeks; RDE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors;

Figure 3. Kaplan-Meier Analysis of Duration of Response by ICR

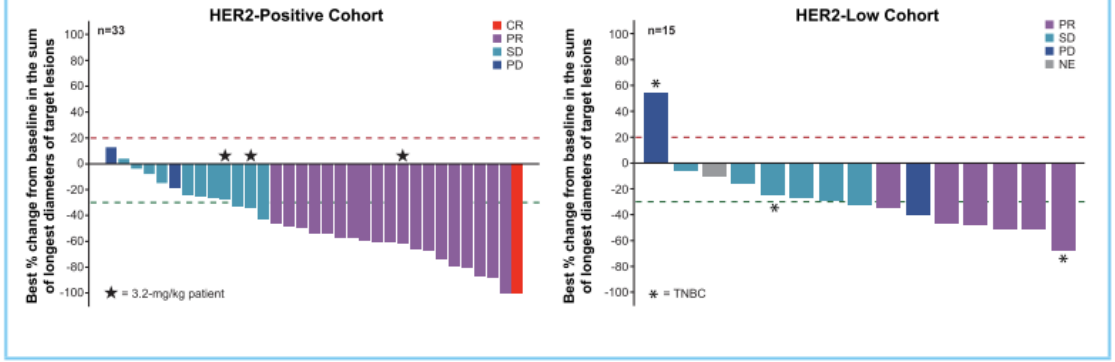


HER2, human epidermal growth factor receptor 2; ICR, independent central review; NE, not estimable.

Table 2. Summary of Efficacy by ICR

	HER2 positive (n=32)	HER2 low (n=16)
Confirmed ORR by ICR [95% CI][a]	59% [41-76] (n=19)	38% [15-65] (n=6)
CR	3% (n=1)	0
PR	56% (n=18)	38% (n=6)
SD	31% (n=10)	38% (n=6)
PD	6% (n=2)	13% (n=2)
NE	3% (n=1)	13% (n=2)
DCR, median [95% CI][b]	91% [75-98] (n=29)	75% [48-93] (n=12)
DOR, median [95% CI], months[c]	NE [4.1-NE]	NE [2.8-NE]

Figure 4. Best Percent Change From Baseline in Tumor Size for Individual Patients



While the confirmed ORR for the T-DXd and Nivo combination was similar to that of T-DXd when administered as monotherapy, longer follow-up and additional studies are needed to determine whether addition of immunotherapy to T-DXd provides further clinical benefit than T-DXd treatment alone

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Fazit – Trastuzumab Deruxtecan

- unglaubliche Wirksamkeit bei stärkst vorbehandelten HER2+ MBC
  - ORR 61.4%, DOR 20.8 Mo.
- Zulassung durch EMA erfolgt – Markteinführung in D noch ausstehend
- Toxizitäten (Auswahl):
  - N&V, Appetitlosigkeit
  - GI (Obstipation/Diarrhoe)
  - Myelotoxizität
  - PNEUMONITIS/ILD im Fokus – frühzeitige Diagnostik & Intervention!
- Explorativ: Krankheitskontrolle bei stabilen CNS-Mets
- Wirksamkeitssignal auch bei HER2 low MBC (Phase III Studien laufen)
- Viele Studien bei MBC, EBC und in Kombinationen (Destiny Breast05 über die GBG)

Weitere ADCs

Trastuzumab Duocarmazine – SYD985

Next Generation HER2-ADCs: SYD985

SYD985: [vic-]

- HER2-targeting antibody-dr conjugate (ADC) based on trastuzumab
- Protease cleavable linker w DNA alkylating toxin duocar
- Toxin incorporated into the drug as an inactive prodrug
- Proteolytic cleavage results release of the membrane permeable active toxin

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

Tulip trial: SYD985.002

R 2:1

- SYD985
- Treatment physician's choice (TPC)*

Primary endpoint:
PFS (centrally assessed)

Secondary endpoints:
OS, ORR, investigator assessed PFS, QoL, and safety

*TPC:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + vinorelbine
- Trastuzumab + eribulin

HR- HER2 low
N=17

Saura C et al, ASCO 2018

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY:

UMM UNIVERSITÄTSMEDIZIN MANNHEIM

Saura C et al., ASCO 2018 PD session MBC, abstract #

Weitere ADCs

U3-1402

PD1-09

San Antonio Breast Cancer Symposium® - December 8-11, 2020

Safety and Efficacy Results From the Phase 1/2 Study of U3-1402, a Human Epidermal Growth Factor Receptor 3 (HER3)-Directed Antibody Drug Conjugate (ADC), in Patients With HER3-Expressing Metastatic Breast Cancer (MBC)

Ian Krop,[1] Kan Yonemori,[2] Shunji Takahashi,[3] Kenichi Inoue,[4] Takahiro Nakayama,[5] Hiroji Iwata,[6] Tatsuya Toyama,[7] Yutaka Yamamoto,[8] Masato Takahashi,[9] Akihiko Osaki,[10] Shigehira Saji,[11] Yasuaki Sagara,[12] Joyce O'Shaughnessy,[13] Tiffany Traina,[14] Shoichi Ohwada,[15] Zhenhao Qi,[16] Yang Qiu,[16] Hiroshi Onuma,[15] Om Sharma,[16] Sabeen F. Mekan,[16] Norikazu Masuda[17]

Figure 1. Structure of HER3-DXd (Antibody-Drug Conjugate)

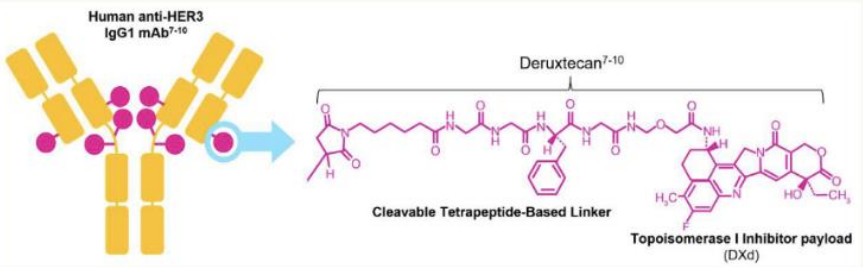
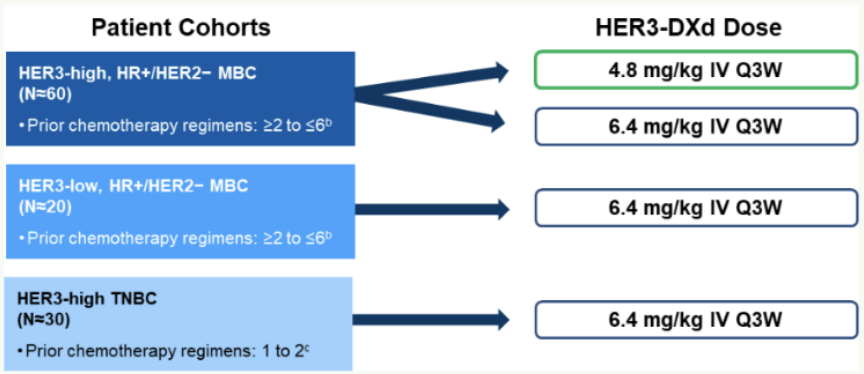
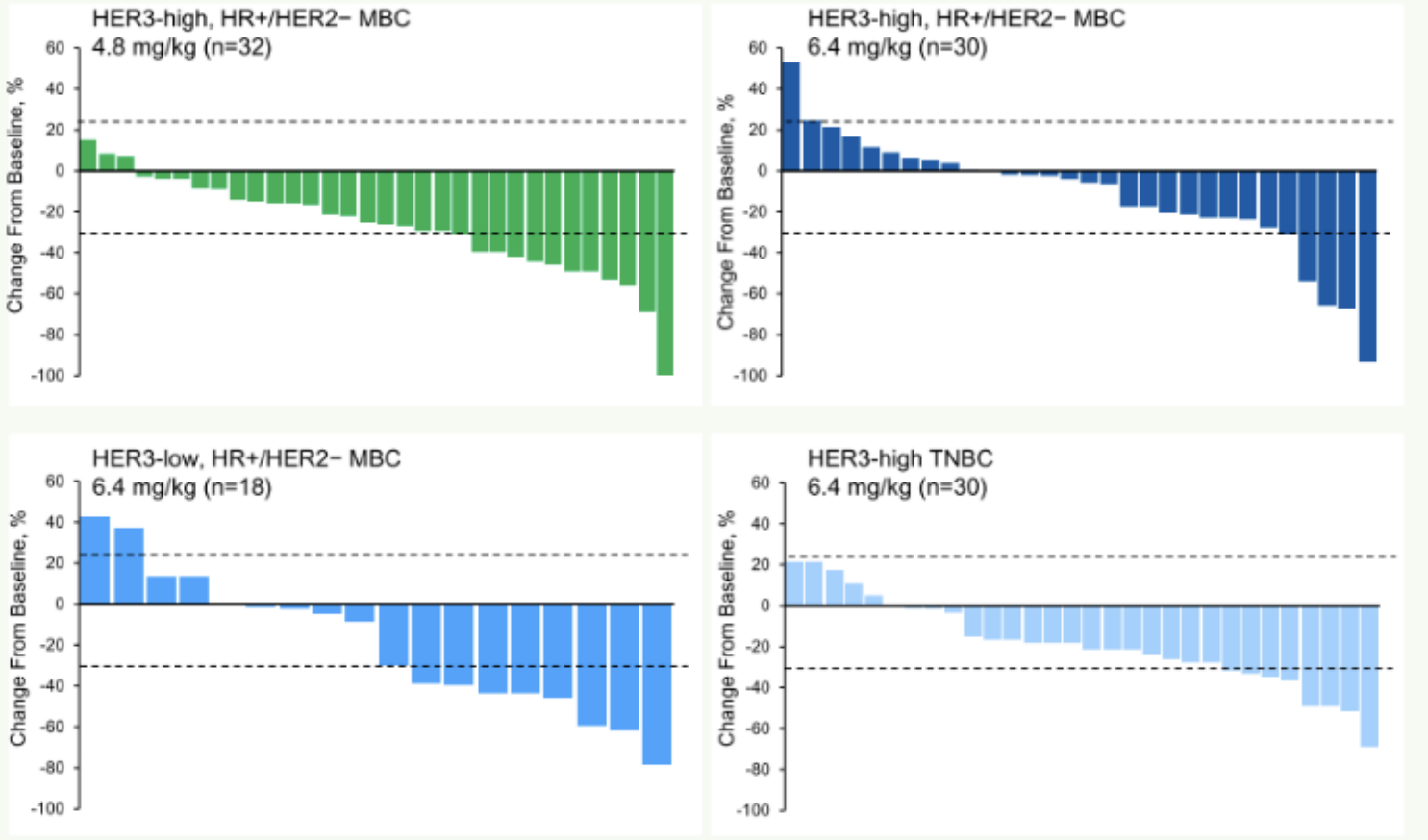


Figure 2. Study Design for the Dose Expansion Part of U31402-A-J101[a]



IV, intravenously. [a]HER3-DXd at doses of 1.6, 3.2, 4.8, 6.4, and 8.0 mg/kg Q3W was evaluated in the dose escalation and dose finding parts of the study. [b]≥2 lines in the locally advanced/metastatic setting. [c] In the locally advanced/metastatic setting.

Figure 3. Best Change in Tumor Size by BICR



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Medizinische Fakultät Mannheim der Universität Heidelberg

Universitätsklinikum Mannheim

Weitere ADCs in Entwicklung beim mTNBC

HER2		
Agent	**Payload**	**Status**
T-DM1	maytansine	Approved for ABC
XMT – 1522	dolaflexin	Phase I
SYD985	duocarmycin	Phase III ongoing
DS8201a	deruxtecan	Phase II
MM – 302	liposomal doxorubicin	Terminated
MEDI 4276	tubulysin	unknown
RC48-ADC	auristatin	In Phase II

Other Targets I		
Agent	**Payload**	**Status**
Ladiratuzumab Vedotin (A)	vedotin	In Phase II
PF-06647263 (B)	calicheamicin	Terminated
PF-06647020 (C)	auristatin	In Phase I

Other Targets II		
Agent	**Payload**	**Status**
Sacituzumab Govitecan (D)	govitecan	Phase III
Glembatumumab vedotin (E)	vedotin	Phase II
SAR566658 (F)	DM4	Phase I

Ponde et al., Curr Treat Options Oncol. 2019 Apr 1;20(5):37

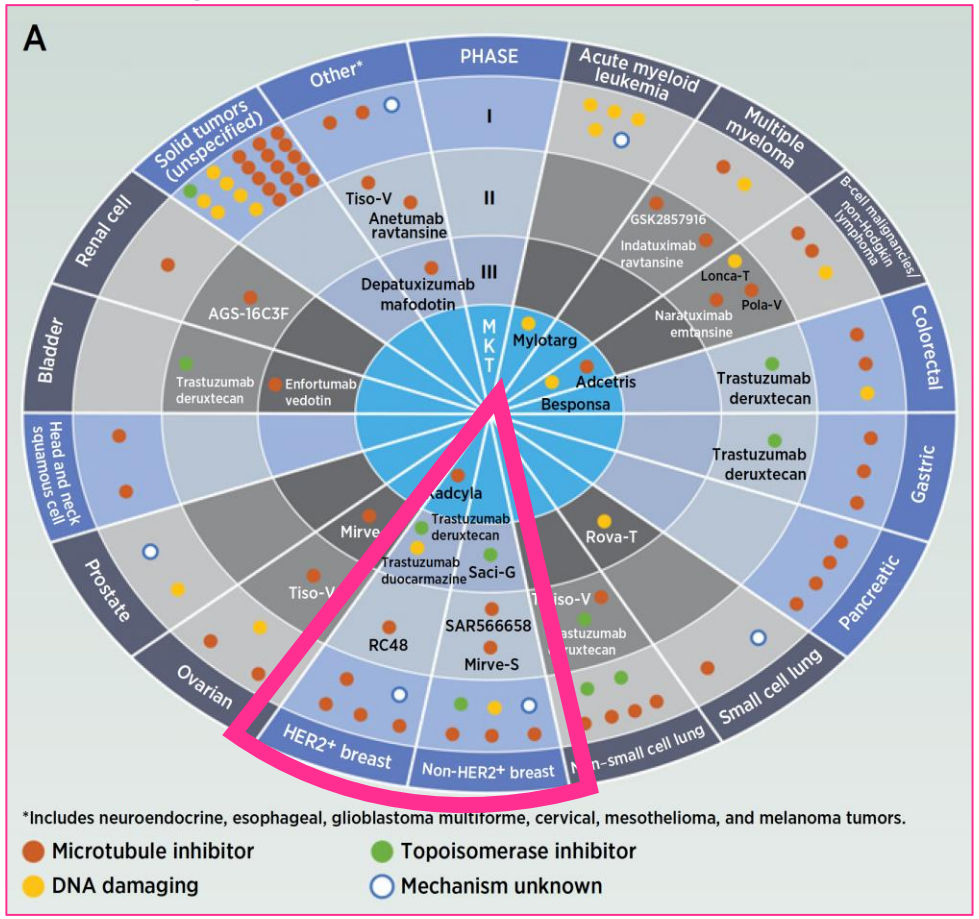
Weitere ADCs in Entwicklung beim (m)TNBC

	Target	Cytotoxic payload	Main indication	Phase	ClinicalTrials.gov identifier
Sacituzumab govitecan (IMMU-132)[47]	TROP2	SN-38	Triple-negative breast cancer	3	NCT02574455; NCT02161679
Inotuzumab ozogamicin (CMC-544)[48]	CD22	Calicheamicin	Acute lymphoblastic leukaemia	3	NCT01564784
Anetumab ravtansine (BAY 94-9343)[49]	Mesothelin	DM4	Mesothelioma	2	NCT02610140
Gemtuzumab ozogamicin[50]	CD33	Calicheamicin	Acute myeloid leukaemia, acute promyelocytic leukaemia	2	NCT01409161; NCT01869803
Depatuxizumab mafodotin (ABT-414)[51]	EGFR	MMAF	Glioblastoma	2	NCT02573324; NCT02343406
Glembatumumab vedotin (CDX-011)[52]	GPNMB	MMAE	Osteosarcoma, melanoma, triple-negative breast cancer	2	NCT02487979; NCT02302339
Denintuzumab mafodotin (SGN-CD19A)	CD19	MMAF	Diffuse large B-cell lymphoma	2	NCT02592876
Mirvetuximab soravtansine (IMGN-853)[53]	Folate receptor α	DM4	Folate receptor α-positive epithelial ovarian cancer	2	NCT02631876
			TNBC	1 2	NCT03045393 NCT03106077
Ladiratuzumab vedotin	SGN-LIV1A	MMAE	TNBC	2	NCT01969643 ...

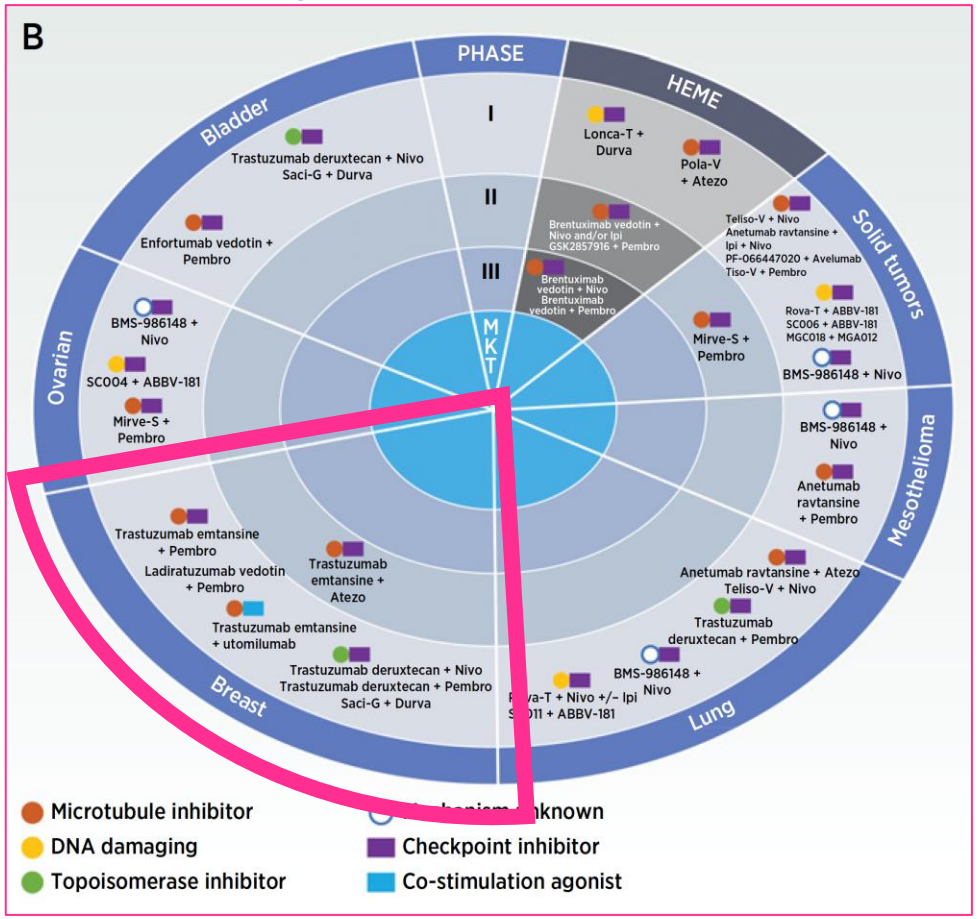
Modifiziert und erweitert nach: Thomas A et al, Lancet Oncol. 2016 Jun;17(6):e254-62.

ADCs in klinischer Entwicklung

ADCs in clinical development as of March 2019



ADCs in combination with checkpoint inhibitors

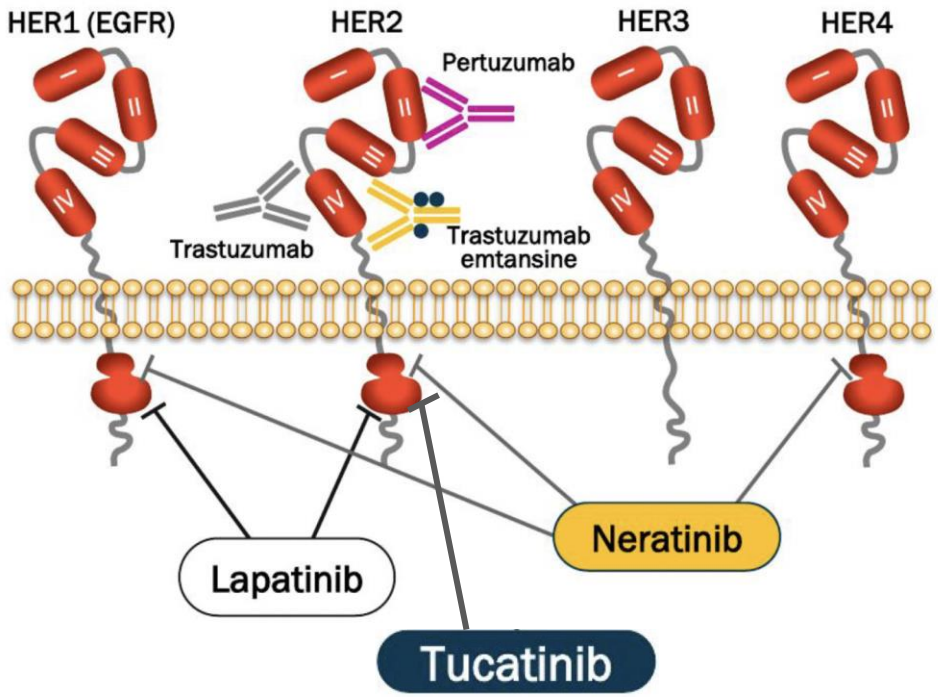


Coats et al., Clin Cancer Res. 2019 Apr 12. pii: 1078-0432.CCR-19-0272. doi: 10.1158/1078-0432.CCR-19-0272

FAZIT – ADCs

- ADCs erweitern das Spektrum der therapeutischen Möglichkeiten über die Grenzen von Tumorentitäten und Subtypen
- Rasante klinische Entwicklung
- Inzwischen 3 zugelassene ADCs für MBC, viele in klinischer Entwicklung
- Potential mit T-DM1 in der (post-neo)Adjuvanz bereits belegt
  - Weitere Entwicklung bei EBC im Gange
  - Potential für Deeskalationsstrategien?
- Interessante Kombinationsmöglichkeiten (IO, PARPi, Tkis)

Tyrosine Kinase Inhibitors for HER2+ BC



	Binding	Targets
Lapatinib	Reversible	HER1, HER2
Neratinib	Irreversible	Pan-HER
Pyrotinib	Irreversible	Pan-HER
Poziotinib	Irreversible	Pan-HER
Tucatinib	Reversible	HER2 specific

Modi S; SABCS 2019 CSF#1

HER2CLIMB: Tucatinib vs Placebo (+Tras/Cap)

Phase III, n=612

HER2+ MBC

Tucatinib = hoch HER2 selektiver TKI

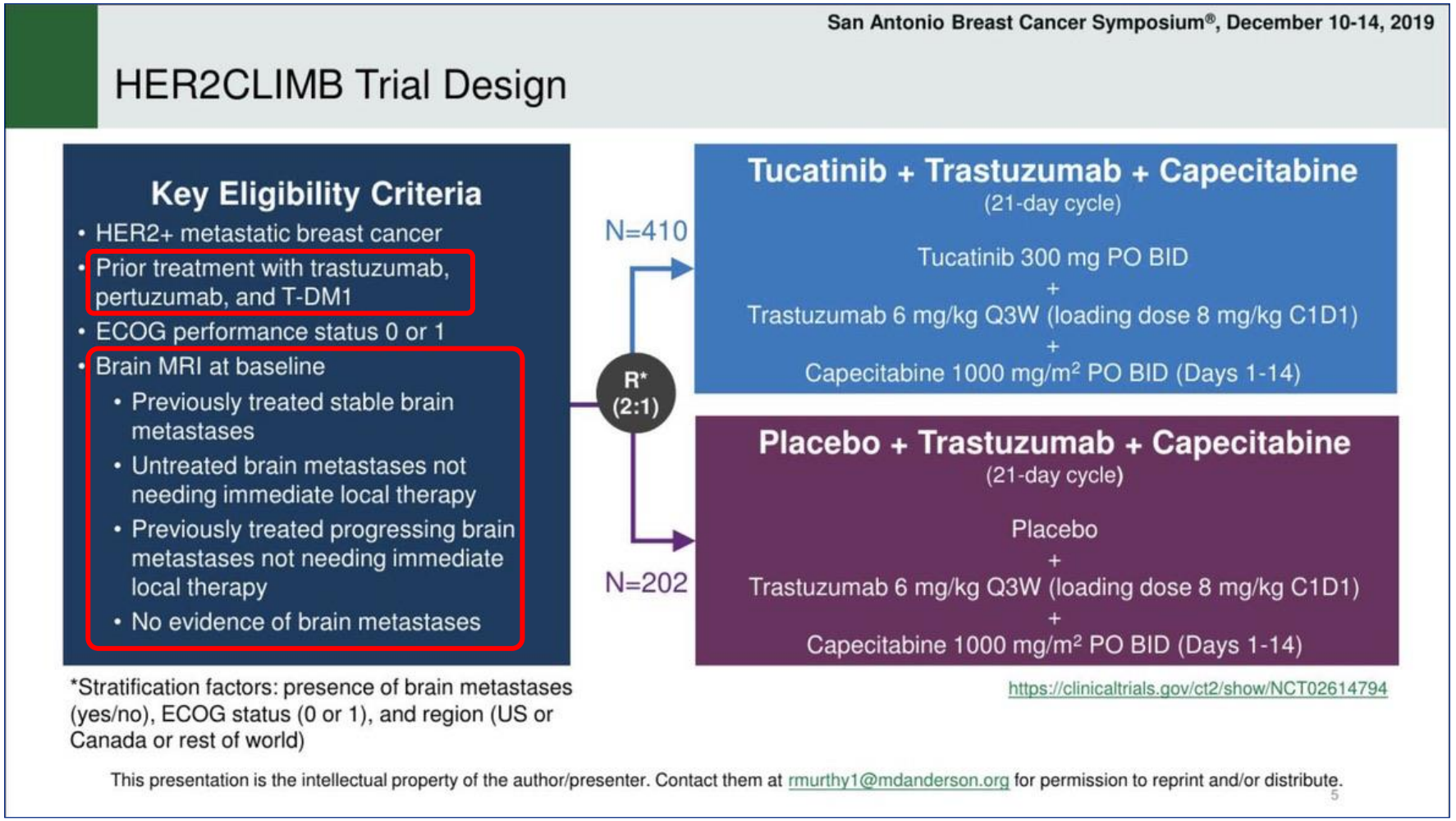
- MUST: prior
  - *Trastuzumab*
  - *Pertuzumab*
  - *T-DM1*
- Med. 3 prior Lines MBC
- Hirnmetastasen erlaubt
  - N=391
  - *Stabile o. unbehandelte bzw. progrediente ohne direkten Bedarf an lokaler Therapie*

1° Endpunkt:

- *PFS (BICR)*

2° Endpunkte:

- *OS, PFS(BrainMets)*
- *Confirmed ORR*



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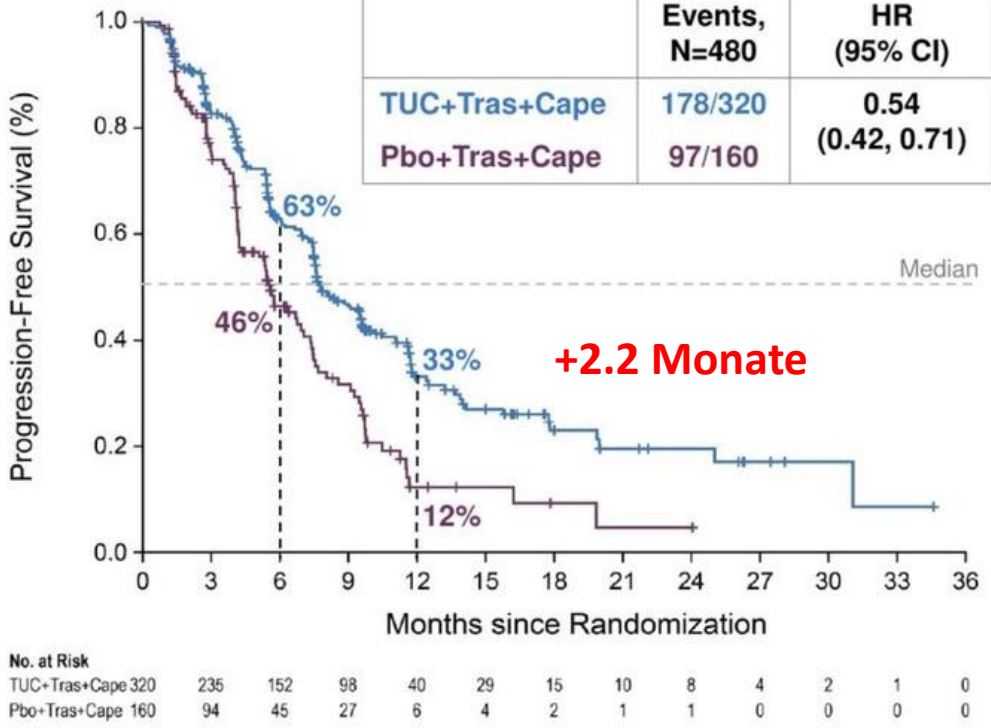
Progression-Free Survival in the Primary Endpoint Population

	Events, N=480	HR (95% CI)	P Value
TUC+Tras+Cape	178/320	0.54 (0.42, 0.71)	<0.00001
Pbo+Tras+Cape	97/160		



Risk of progression or death was reduced by 46% in the primary endpoint population

One-year PFS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
33% (27, 40)	12% (6, 21)
Median PFS (95% CI):	
7.8 months (7.5, 9.6)	5.6 months (4.2, 7.1)

Prespecified efficacy boundary for PFS: P=0.05
Data cut off: Sep 4, 2019

In allen Subgruppen gleiche Effekte!

HER2CLIMB: Tucatinib vs Placebo (+Tras/Cap)

Phase III, n=612

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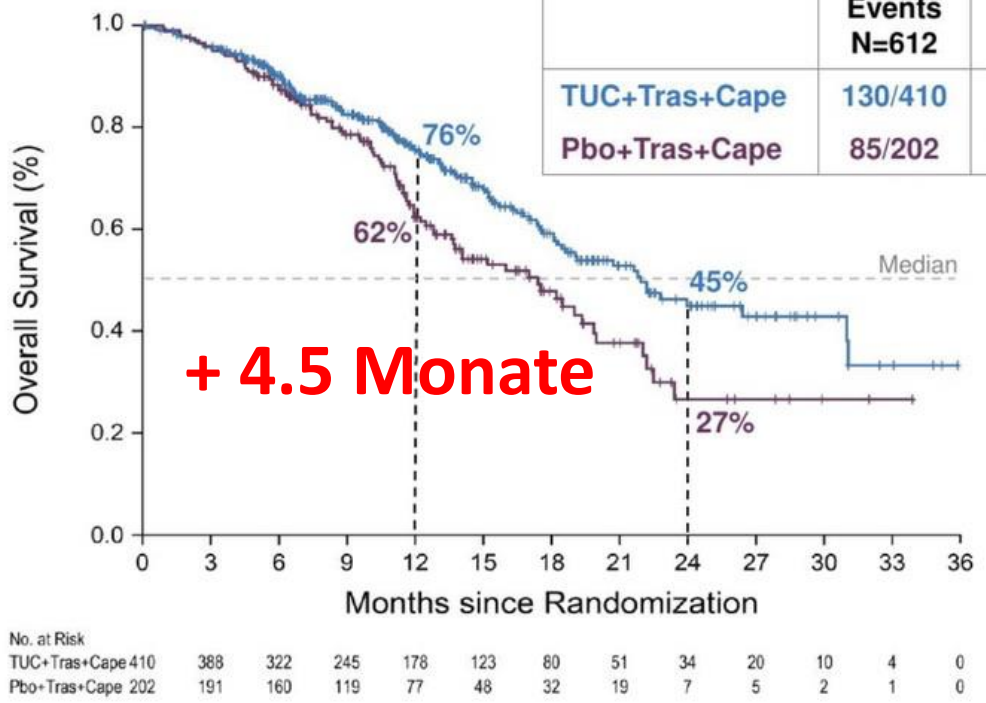
Overall Survival in the Total Study Population

	Events N=612	HR (95% CI)	P Value
TUC+Tras+Cape	130/410	0.66 (0.50, 0.88)	0.00480
Pbo+Tras+Cape	85/202		



Risk of death was reduced by 34% in the total population

Two-year OS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
45% (37, 53)	27% (16, 39)
Median OS (95% CI):	
21.9 months (18.3, 31.0)	17.4 months (13.6, 19.9)

Prespecified efficacy boundary for OS (P=0.0074) was met at the first interim analysis.
Data cut off: Sep 4, 2019

In allen Subgruppen gleiche Effekte!

HER2CLIMB: Tucatinib vs Placebo (+Tras/Cap)

Phase III, n=612

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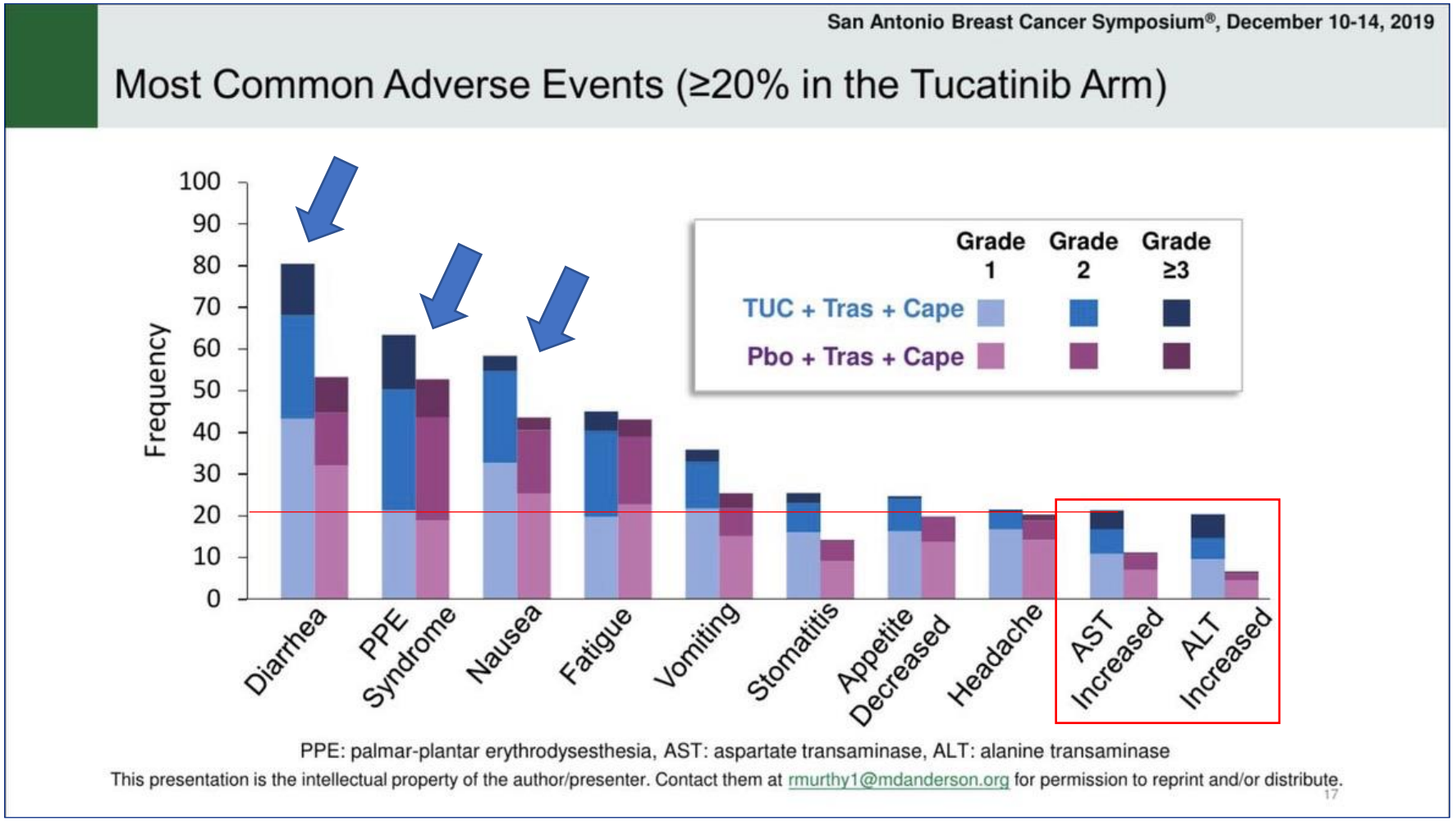

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Phase III, n=612

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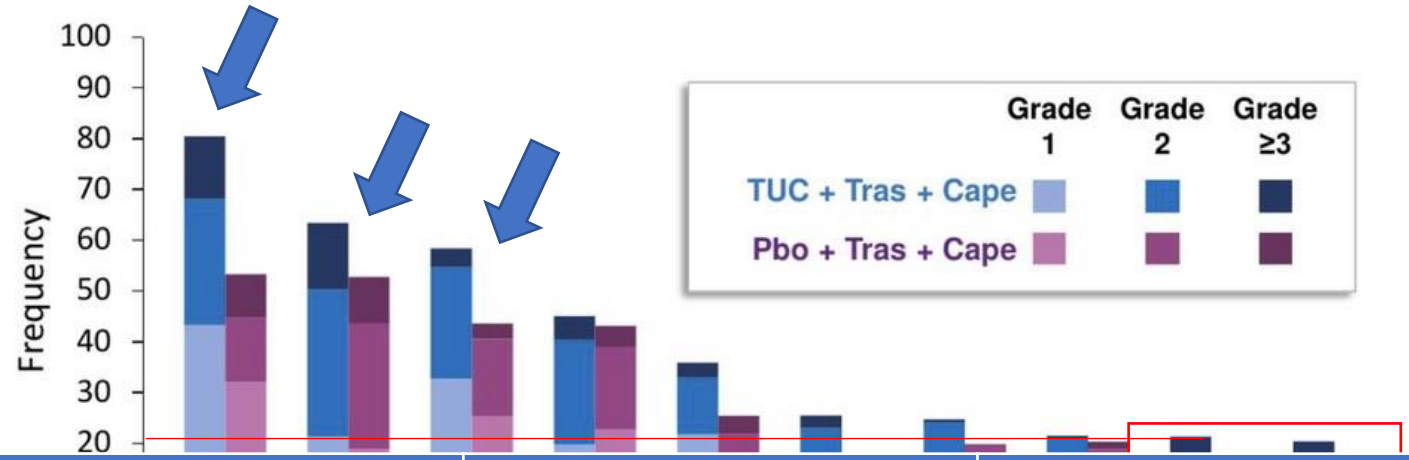
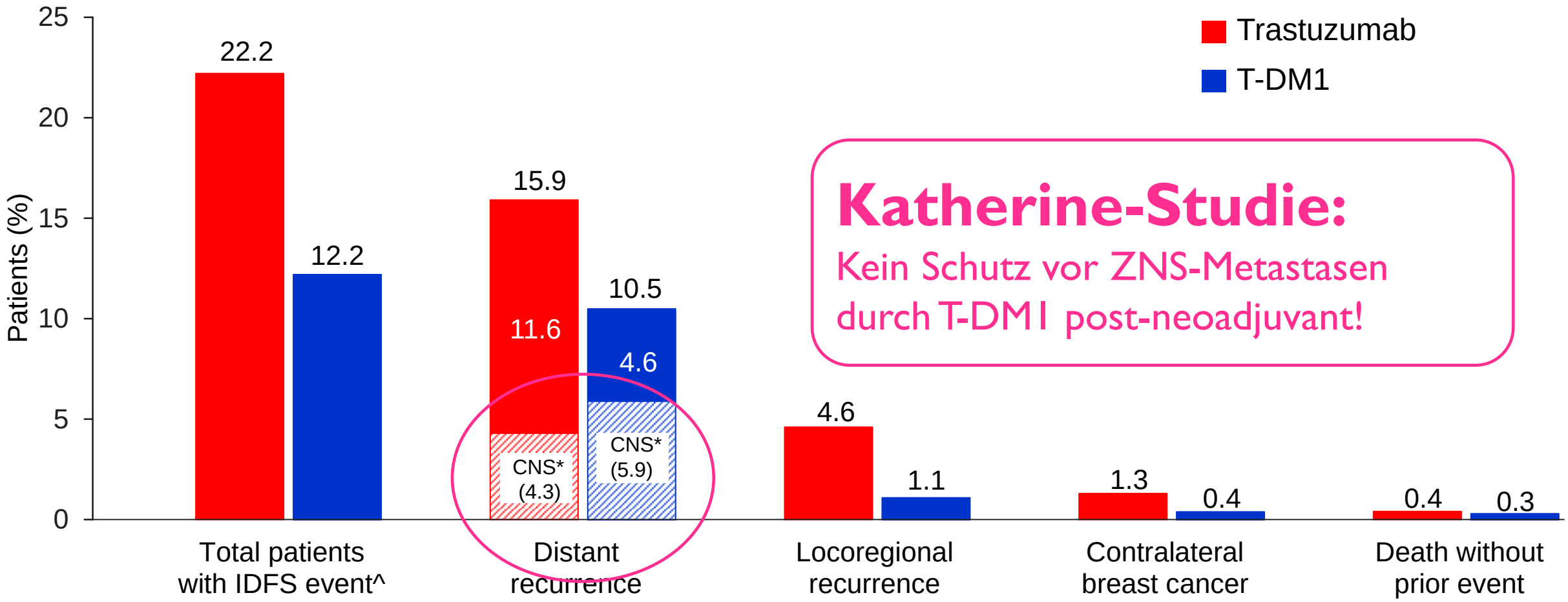
Most Common Adverse Events (≥20% in the Tucatinib Arm)



	Tuc+Trast+Cap	Tras+Cap
Grade 3 events	55%	49%
Abbruch wg Tuc /Plac	6%	3%
Deaths to AE	2%	3%

Tucatinib & ZNS Mets.

First IDFS Events



Katherine-Studie:

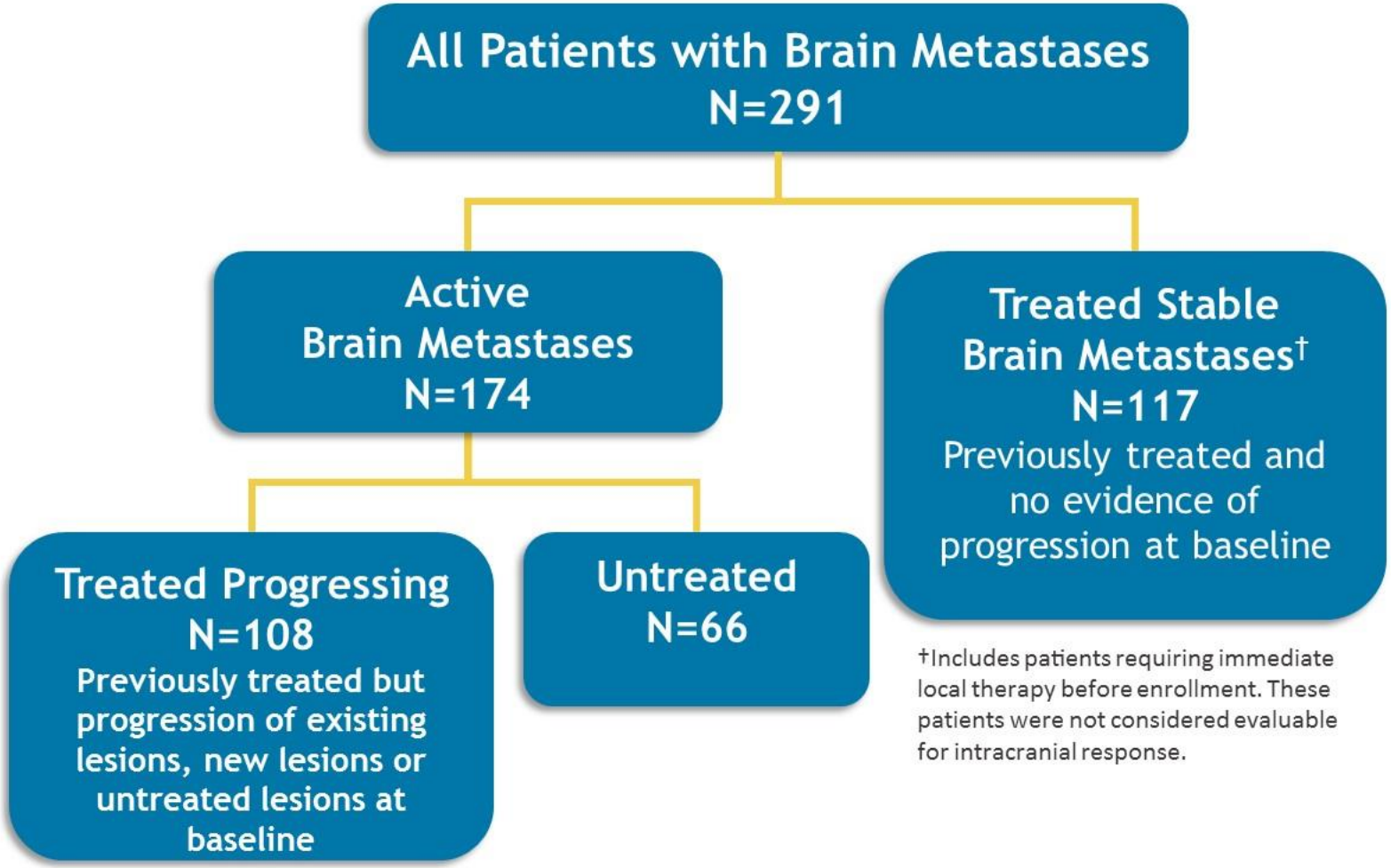
Kein Schutz vor ZNS-Metastasen durch T-DM1 post-neoadjuvant!

^Patients who experience additional IDFS event(s) within 61 days of their first IDFS event are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Locoregional recurrence; [3] Contralateral breast cancer; [4] Death without prior event.

***CNS metastases as component of distant recurrence (isolated or with other sites).** **Trastuzumab** **T-DM1**

HER2CLIMB Analysis of Patients with Brain Metastases

- Brain MRI at baseline for all patients
- Brain MRI for brain metastases patients every 6 weeks in first 24 weeks, every 9 weeks thereafter
- Eligible brain metastases patients:
  - Not requiring immediate local therapy
  - Requiring local therapy during screening could be eligible after washout*



†Includes patients requiring immediate local therapy before enrollment. These patients were not considered evaluable for intracranial response.

*These patients were included in the Treated Stable group for analysis.

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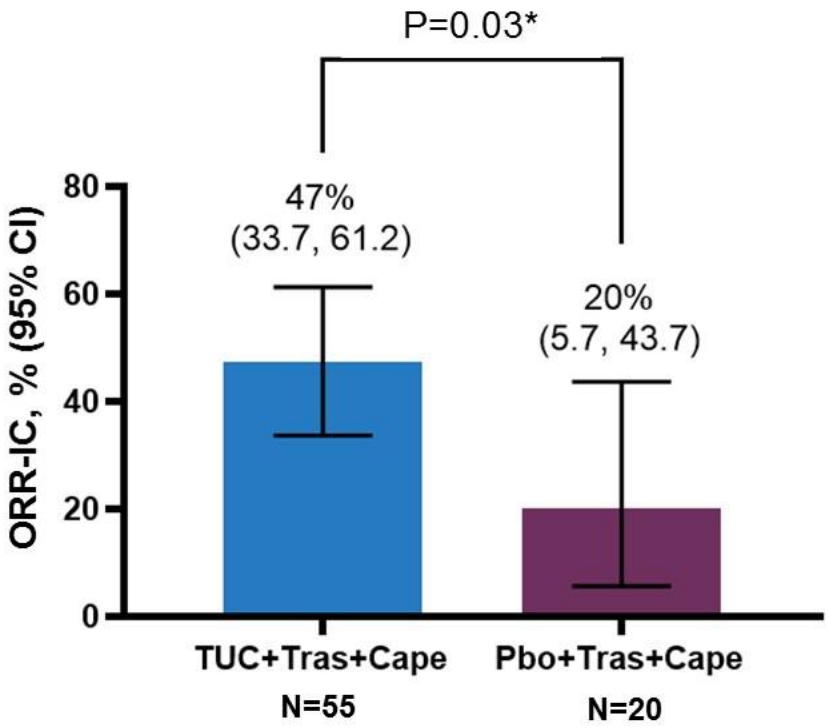
Intracranial Response Rate (ORR-IC) in Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline

Confirmed Objective Response Rate (RECIST 1.1)



*Stratified Cochran-Mantel-Haenszel P value

	TUC+Tras+Cape (N=55)	Pbo+Tras+Cape (N=20)
Best Overall Intracranial Response[a], n (%)		
Complete Response (CR)	3 (5.5)	1 (5.0)
Partial Response (PR)	23 (41.8)	3 (15.0)
Stable Disease (SD)	24 (43.6)	16 (80.0)
Progressive Disease (PD)	2 (3.6)	0
Not Available[b]	3 (5.5)	0
Subjects with Objective Response of Confirmed CR or PR, n	26	4
Duration of Intracranial Response (DOR-IC)[e] (95% CI)[f], months	6.8 (5.5, 16.4)	3.0 (3.0, 10.3)

(a) Confirmed Best overall response assessed per RECIST 1.1. (b) Subjects with no post-baseline response assessments. (c) Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934). (d Cochran-Mantel-Haenszel test controlling for stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. (e) As estimated using Kaplan-Meier methods. (f) Calculated using the complementary log-log transformation method (Collett, 1994).

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HER2CLIMB: ZNS-PFS u. OS bei ZNS-Mets

Phase III, n=612

HER2+ MBC

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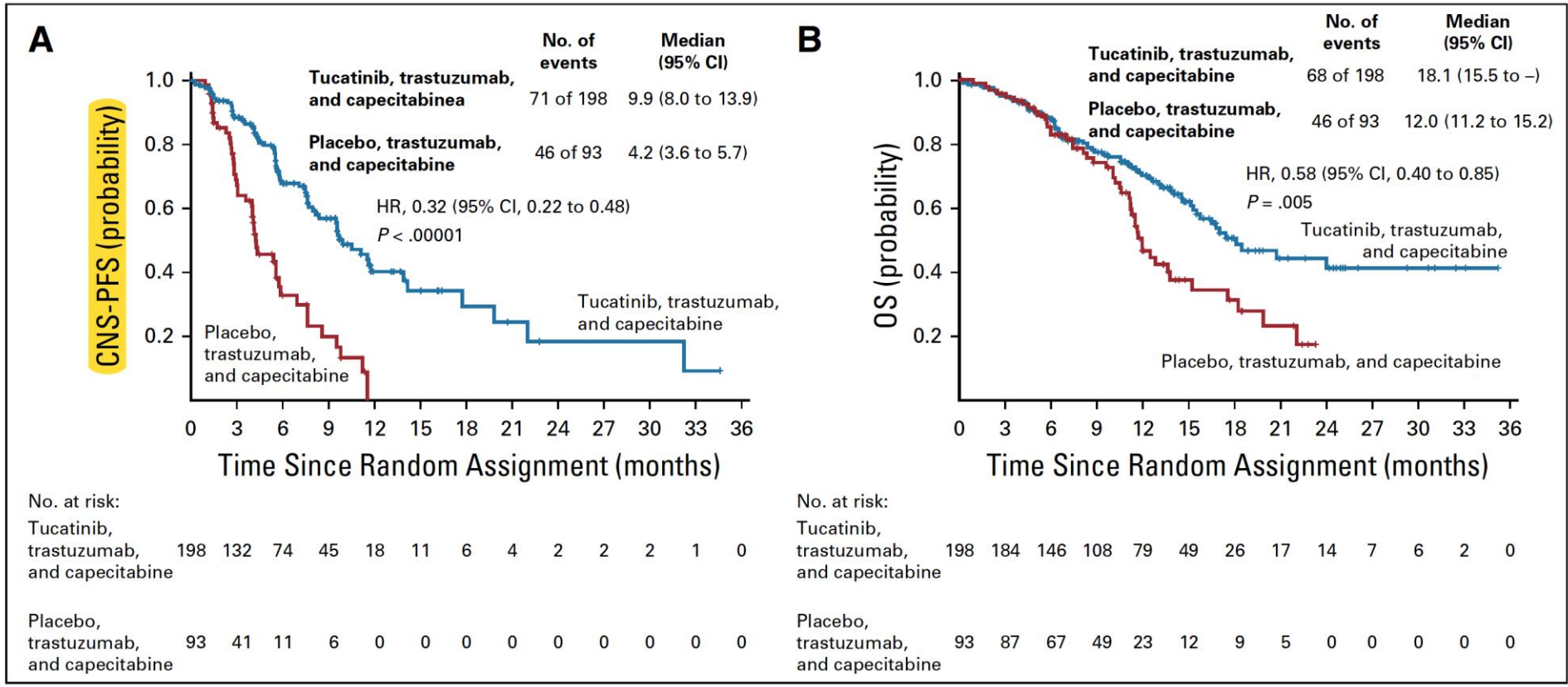

FIG 1. Kaplan-Meier curves for patients with brain metastases. (A) CNS progression-free survival (CNS-PFS) per investigator assessment. (B) Overall survival (OS). Hazard ratio (HR) computed from the Cox proportional hazards model using stratification factors (Eastern Cooperative Oncology Group performance status [0 or 1], region of world [North America or rest of world]) at random assignment. Two-sided *P* value calculated from stratified log-rank test.

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Lin N et al. | J Clin Oncol 38:2610-2619.

Medizinische Fakultät Mannheim der Universität Heidelberg

Universitätsklinikum Mannheim

HER2CLIMB: Tucatinib bei aktiven ZNS-Mets

Phase III, n=612

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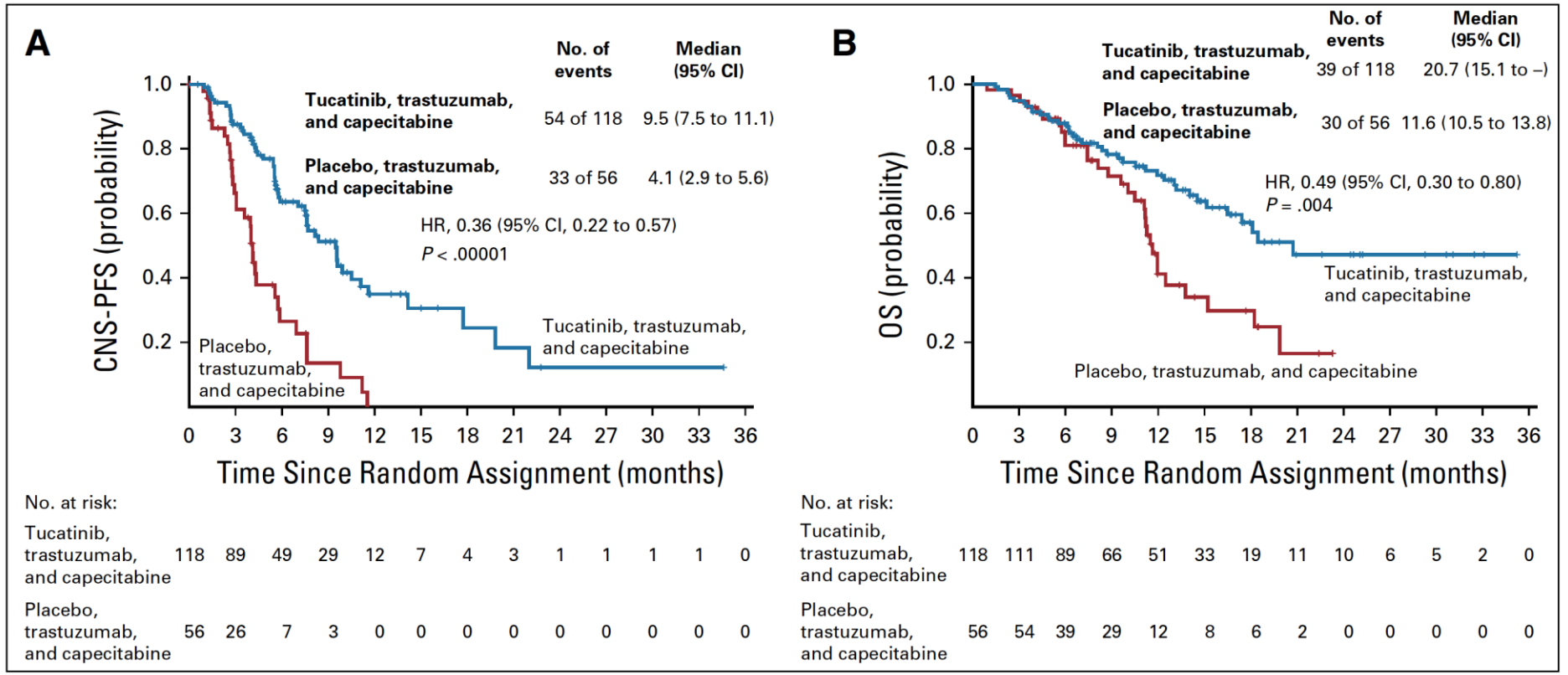

FIG 2. Kaplan-Meier curves for patients with active brain metastases. (A) CNS progression-free survival (CNS-PFS) per investigator assessment. (B) Overall survival (OS). Hazard ratio (HR) computed from the Cox proportional hazards model using stratification factors (Eastern Cooperative Oncology Group performance status [0 or 1], region of world [North America or rest of world]) at random assignment. Two-sided *P* value calculated from stratified log-rank test.

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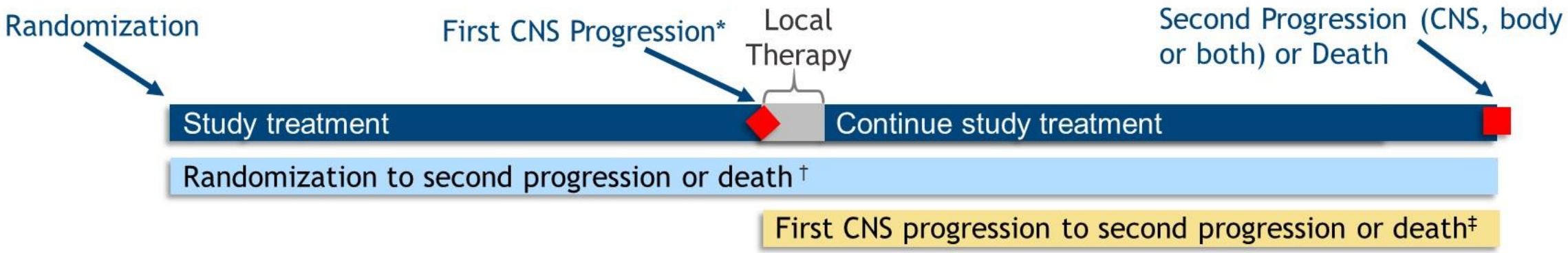
Universitätsklinikum Mannheim

PFS in Patients with Isolated Progression in the Brain Who Continued with Assigned Study Treatment



	Median time from randomization to second progression or death	HR	Median time from first CNS progression to second progression or death	HR
TUC+Tras+Cap N=21	15.9 months (11.7, 28.2)	0.292 (0.11, 0.77) P=0.009	7.6 months (3.9, 11.3)	0.332 (0.13, 0.85) P=0.02
Pbo+Tras+Cap N=9	9.7 months (4.9, 12.0)		3.1 months (1.2, 4.1)	

*Note: First CNS progression was captured as a PFS event in the primary analysis.
† Time from randomization to second progression or death among patients who received local therapy and continued study treatment after isolated CNS progression.
‡Time from first isolated CNS progression to second progression or death among patients who received local therapy and continued study treatment after isolated CNS progression.

PRESENTED BY: Nancy Lin, nlin@partners.org

Seagen®

Tukysa®

1. BEZEICHNUNG DES ARZNEIMITTELS

TUKYSA 50 mg Filmtabletten
TUKYSA 150 mg Filmtabletten

2. QUALITATIVE UND QUANTITATIVE ZUSAMMENSETZUNG

TUKYSA 50 mg Filmtabletten

Jede Filmtablette enthält 50 mg Tucatinib.

TUKYSA 150 mg Filmtabletten

Jede Filmtablette enthält 150 mg Tucatinib.

Sonstige Bestandteile mit bekannter Wirkung

Jede 150 mg Filmtablette enthält 27,64 mg Natrium und 30,29 mg Kalium.

Eine 300 mg Dosis TUKYSA enthält 55,3 mg Natrium und 60,6 mg Kalium.

Vollständige Auflistung der sonstigen Bestandteile, siehe Abschnitt 6.1.

3. DARREICHUNGSFORM

Filmtablette.

TUKYSA 50 mg Filmtabletten

Runde, gelbe Filmtablette mit der Prägung „TUC“ auf einer Seite und „50“ auf der anderen Seite. Die 50 mg Tablette hat einen Durchmesser von ca. 8 mm.

TUKYSA 150 mg Filmtabletten

Ovale, gelbe Filmtablette mit der Prägung „TUC“ auf einer Seite und „150“ auf der anderen Seite. Die 150 mg-Tablette ist ca. 17 mm lang und 7 mm breit.

4. KLINISCHE ANGABEN

4.1 Anwendungsgebiete

TUKYSA wird angewendet in Kombination mit Trastuzumab und Capecitabin zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem HER2-positivem Brustkrebs, die zuvor mindestens 2 gegen HER2 gerichtete Behandlungsschemata erhalten haben.

Dosisanpassung

Die empfohlenen Anpassungen der Tucatinib-Dosis für Patienten mit Nebenwirkungen (siehe Abschnitt 4.8) sind in den Tabellen 2 und 3 angegeben. Bezüglich Dosisanpassungen bei Toxizitäten, die mutmaßlich durch das gleichzeitig verabreichte Trastuzumab und Capecitabin hervorgerufen wurden, sind die Fachinformationen dieser Arzneimittel zu konsultieren.

Tabelle 1: Empfohlene Dosierung

Behandlung	Dosis	Behandlungstage	Zeitpunkt relativ zur Nahrungsaufnahme
Tucatinib	300 mg oral zweimal täglich	Kontinuierlich	Unabhängig von den Mahlzeiten
Capecitabin	1000 mg/m² oral zweimal täglich	Tag 1 bis 14 alle 21 Tage	Innerhalb von 30 Minuten nach einer Mahlzeit
Trastuzumab Intravenöse Gabe Initialdosis Nachfolgende Dosen ODER Subkutane Gabe	 8 mg/kg intravenös 6 mg/kg intravenös 600 mg subkutan	 Tag 1 Alle 21 Tage Alle 21 Tage	Nicht zutreffend

Tabelle 2: Empfohlene Reduktionen der Tucatinib-Dosis bei Nebenwirkungen

Dosisstufe	Tucatinib-Dosis
Empfohlene Anfangsdosis	300 mg zweimal täglich
Erste Dosisreduktion	250 mg zweimal täglich
Zweite Dosisreduktion	200 mg zweimal täglich
Dritte Dosisreduktion	150 mg zweimal täglich[1]

[1] Bei Patienten, die 150 mg oral zweimal täglich nicht vertragen, sollte TUKYSA dauerhaft abgesetzt werden.

Abstract No. 109
San Antonio Breast Cancer Symposium®
December 8–11, 2020

HER2CLIMB-02: A Randomized, Double-Blind, Phase 3 Study of Tucatinib or Placebo with T-DM1 for Unresectable Locally-Advanced or Metastatic HER2+ Breast Cancer (Trial in Progress)

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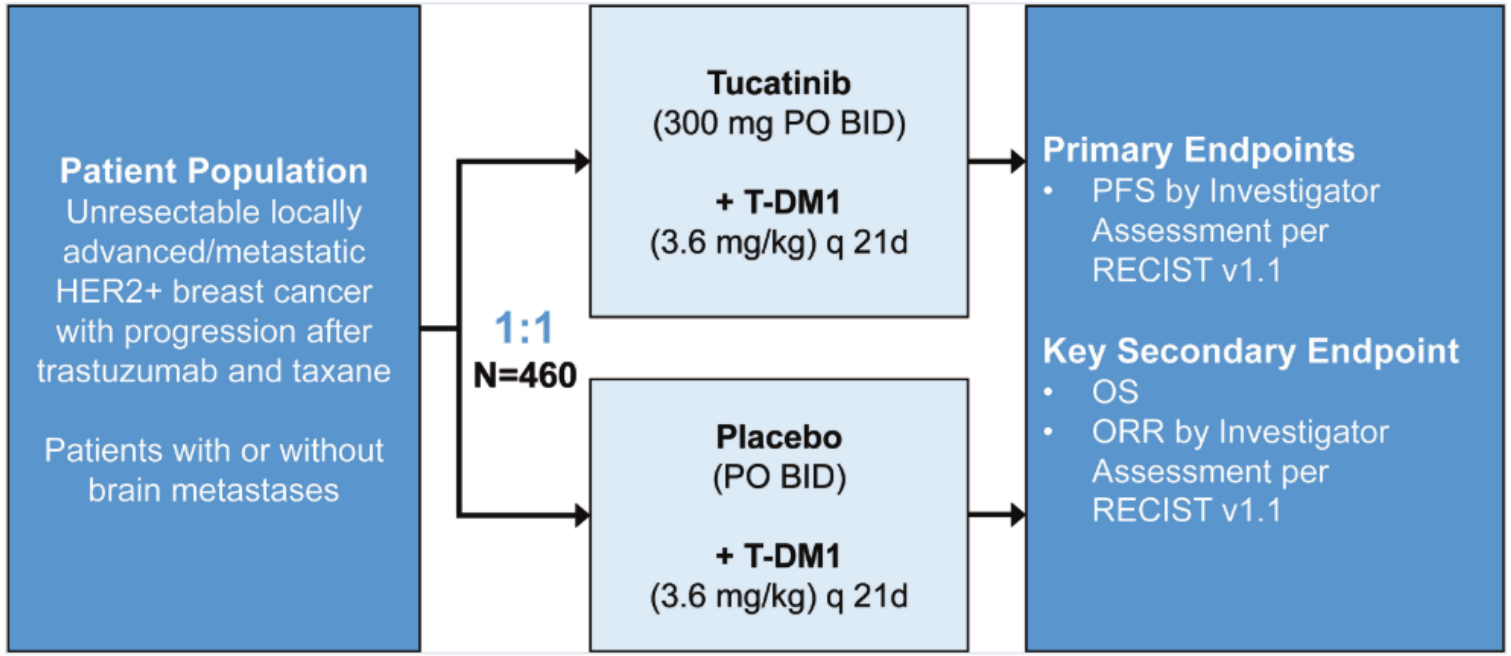
Study Design



- HER2CLIMB-02 (NCT03975647, EudraCT no. 2019-005017-39) is a randomized, double-blind, placebo-controlled phase 3 study to evaluate efficacy and safety of tucatinib in combination with T-DM1 in patients with unresectable locally advanced or HER2+ MBC who have had prior treatment with trastuzumab and taxane
- Approximately 460 patients will be randomized 1:1 to receive 21-day cycles of tucatinib (300 mg PO BID) or placebo in combination with T-DM1 (3.6 mg/kg IV)
- Randomization is stratified by line of treatment for metastatic disease, hormone receptor (HR) status, presence or history of brain metastases, and Eastern Cooperative Oncology Group (ECOG) performance status

Neues zu PARPi und DDR

TBCRC 048/Olaparib Expanded

ASCO 2020

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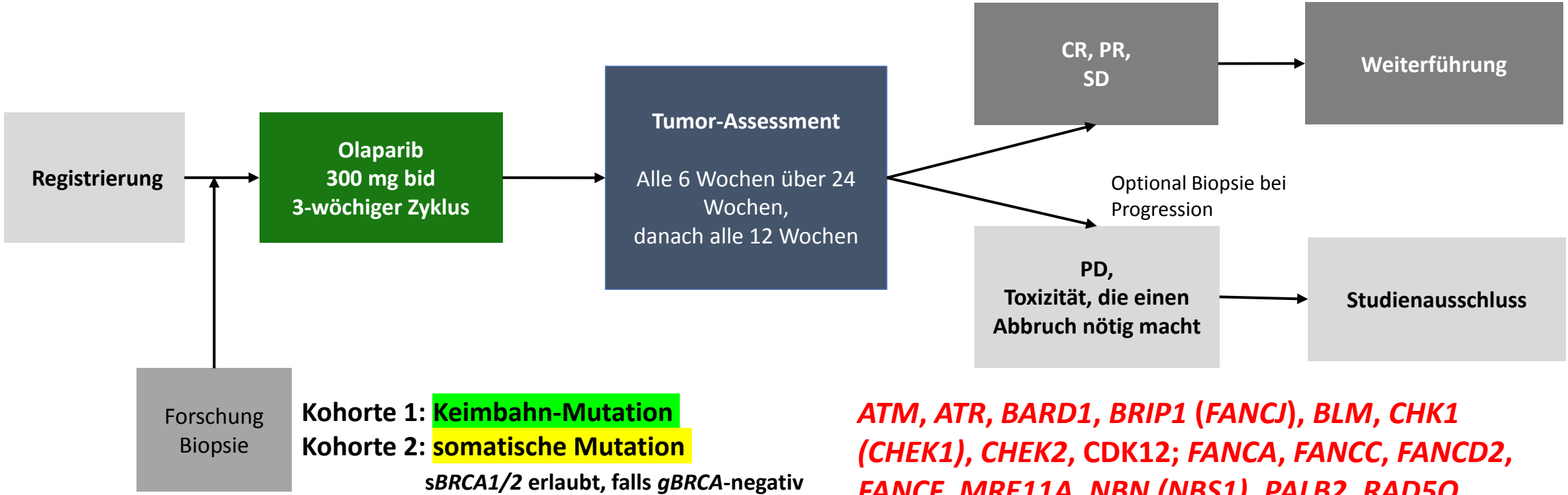
Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

TBCRC 048/Olaparib Expanded

Studiendesign – Einarmige Phase-2-Studie



Kohorte 1: Keimbahn-Mutation
Kohorte 2: somatische Mutation

s*BRCA1/2* erlaubt, falls *gBRCA*-negativ

ATM, ATR, BARD1, BRIP1* (*FANCJ*), *BLM*, *CHK1* (*CHEK1*), *CHEK2*, CDK12; *FANCA*, *FANCC*, *FANCD2*, *FANCF*, *MRE11A*, *NBN* (*NBS1*), *PALB2*, *RAD5O*, *RAD51C*, *RAD51D*, *WRN

bid: 2x täglich; CR: Komplettansprechen; PR: Teilansprechen; SD: Stabile Erkrankung; PD: Progression

Tung et al. | 2020 ASCO Annual Meeting | J Clin Oncol 38: 2020 (suppl; abstr 1002)

Patient and Tumor Characteristics

	Total N=53	Cohort 1 Germline N=27	Cohort 2 Somatic N=26
Age – median (range)- yrs	59 (30-87)	54 (30-87)	59 (34-79)
Subtype*			
ER+ HER2-neg#	75%	85%	65%
TNBC	19%	7%	31%
HER2+	5%	7%	4%
# lines chemo in met setting- mean (range)	1 (0-4)	0 (0-2)	1 (0-4)
No prior chemotherapy	19%	22%	15%
Prior platinum	5%	4%	8%
Prior CDK4/6i among ER+ HER2-neg	93%	96%	88%

* Subtype of primary tumor # ER, HER2 determined locally

TBCRC 048: Olaparib beyond gBRCA

Kohorte 1 – germline non-BRCA HRR gene mutations

ORR_{all}: 33%
CBR_{all}: 44%

ORR_{PALB2}: 82%
CBR_{PALB2}: 100%

A

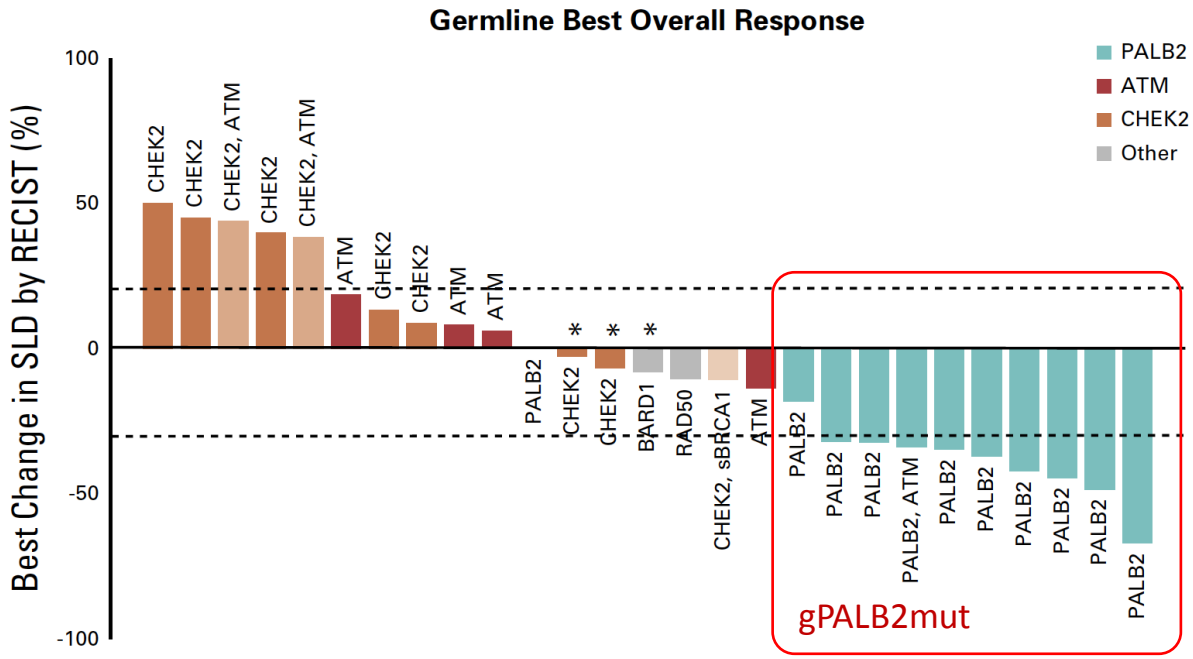
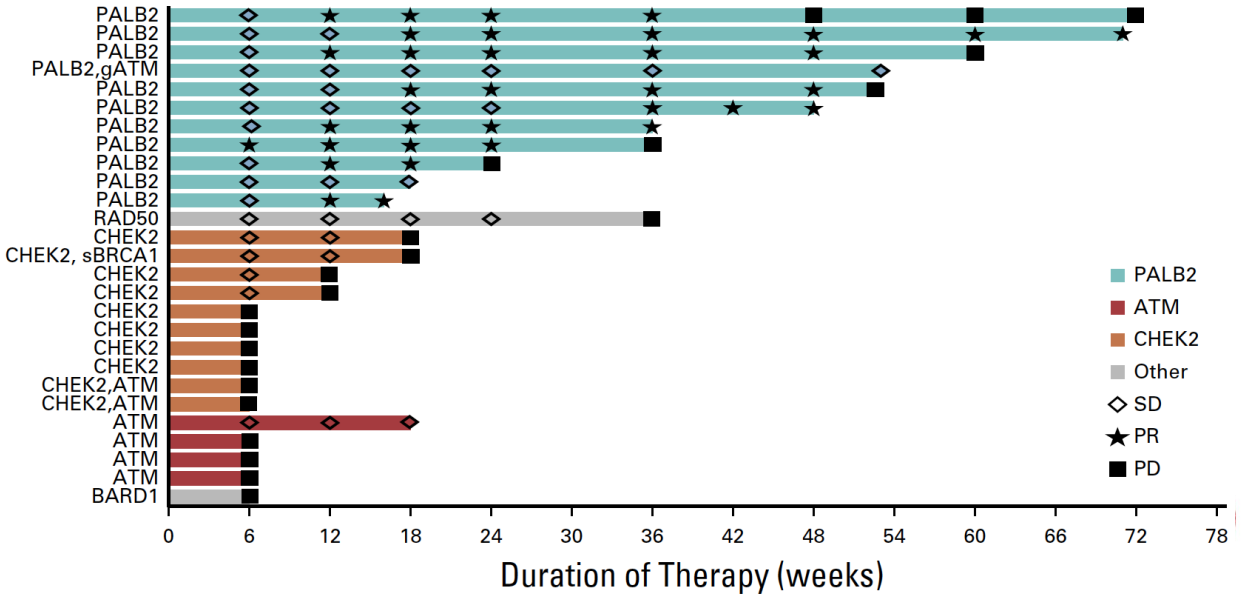


TABLE 3. Efficacy by Patient and Tumor Characteristics

Clinical Factor	g*PALB2* Responders of Total (n = 9 of 11)	s*BRCA1/2* Responders of Total (n = 8 of 16)[a]
Tumor subtype[b]		
ER+ HER2−	8 of 10	4 of 10
TNBC	—	4 of 6
HER2+	1 of 1	—
Any prior chemotherapy	7 of 8	7 of 15
No prior chemotherapy	2 of 3	1 of 1
Prior CDK 4/6 inhibitor	7 of 9	4 of 10

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; ER, estrogen receptor; g, germline; HER2, human epidermal growth factor receptor 2; s, somatic; TNBC, triple-negative breast cancer.
[a]Includes patient from cohort 1 with g*CHEK2* and s*BRCA1* mutations.
[b]Primary tumor.

B



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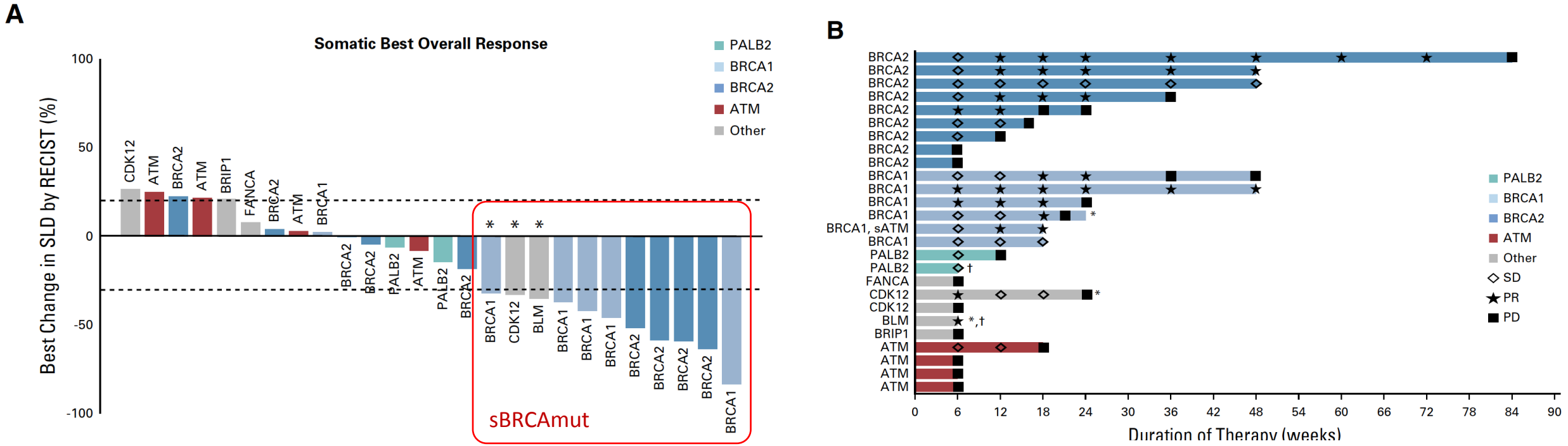
Tung et al. J Clin Oncol 2020

TBCRC 048: Olaparib beyond gBRCA

Kohorte 2 – Somatic BRCA1/2 mutations

ORR_{all}: 31%
CBR_{all}: 44%

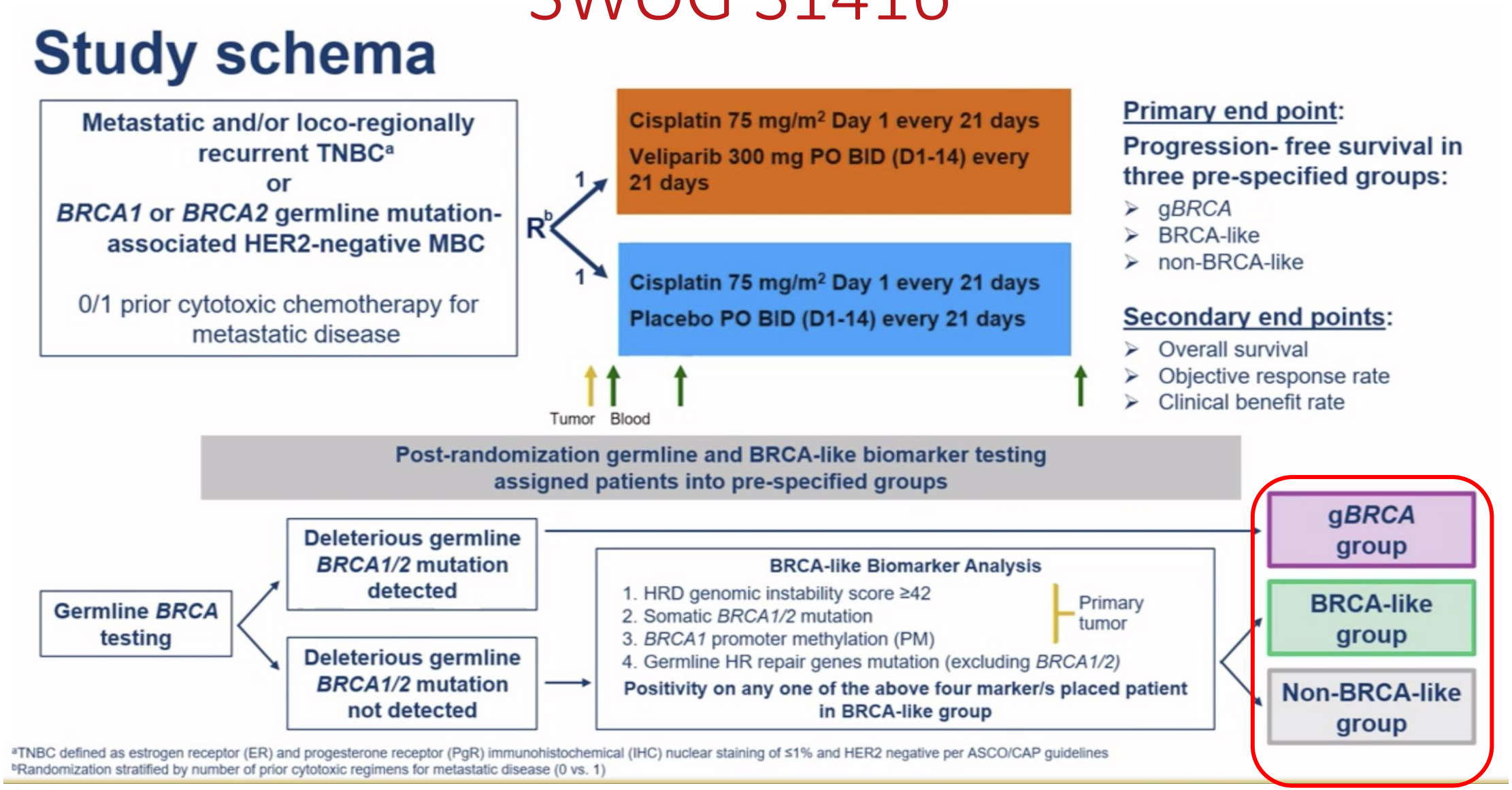
ORR_{sBRCA}: 50%
CBR_{sBRCA}: 66%



Tung et al. J Clin Oncol 2020

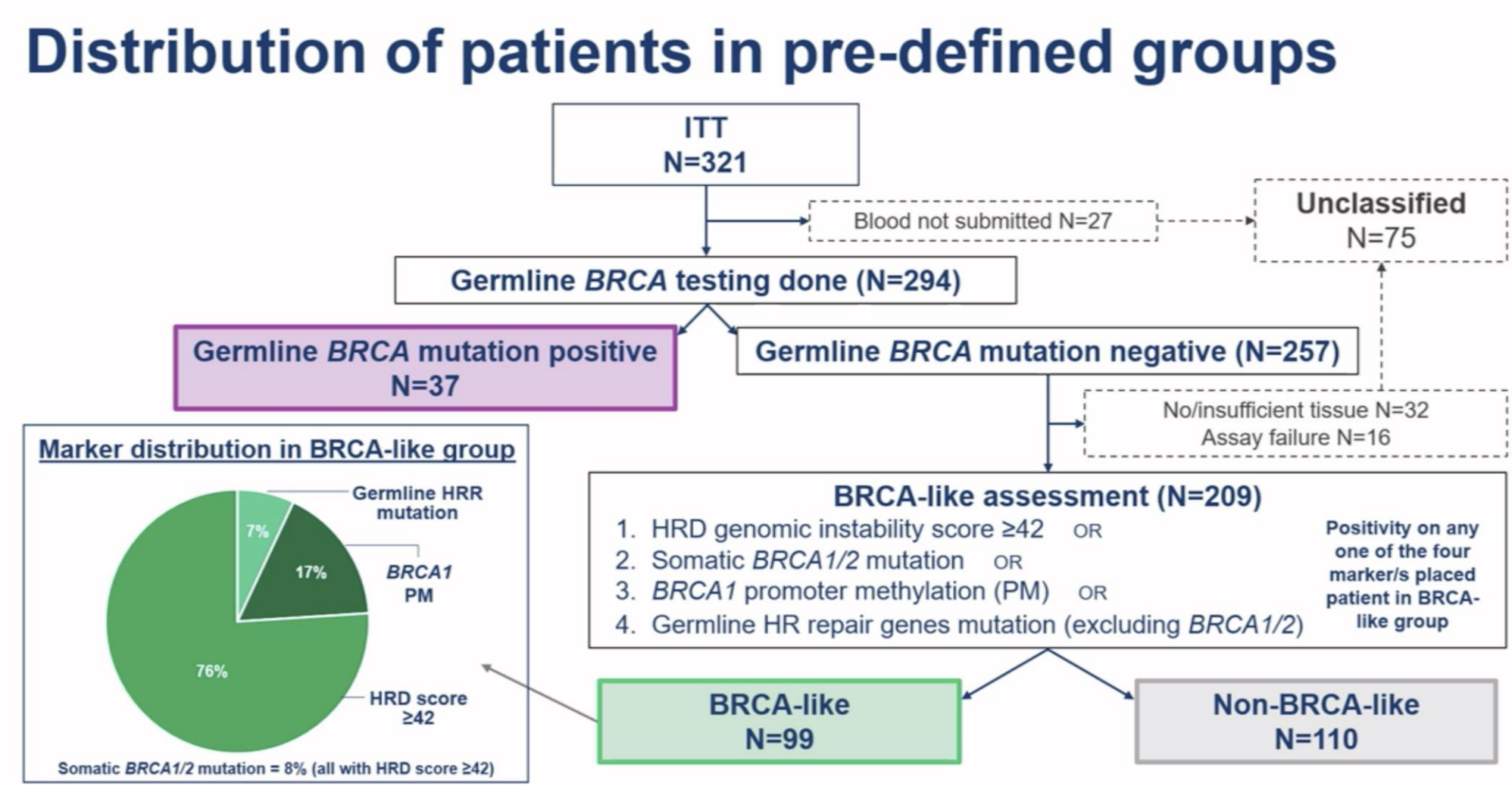
SWOG S1416 – Cisplatin +/- Veliparib

SWOG S1416



Sharma P et al. ASCO 2020 abstract #1001

SWOG S1416



Sharma P et al. ASCO 2020

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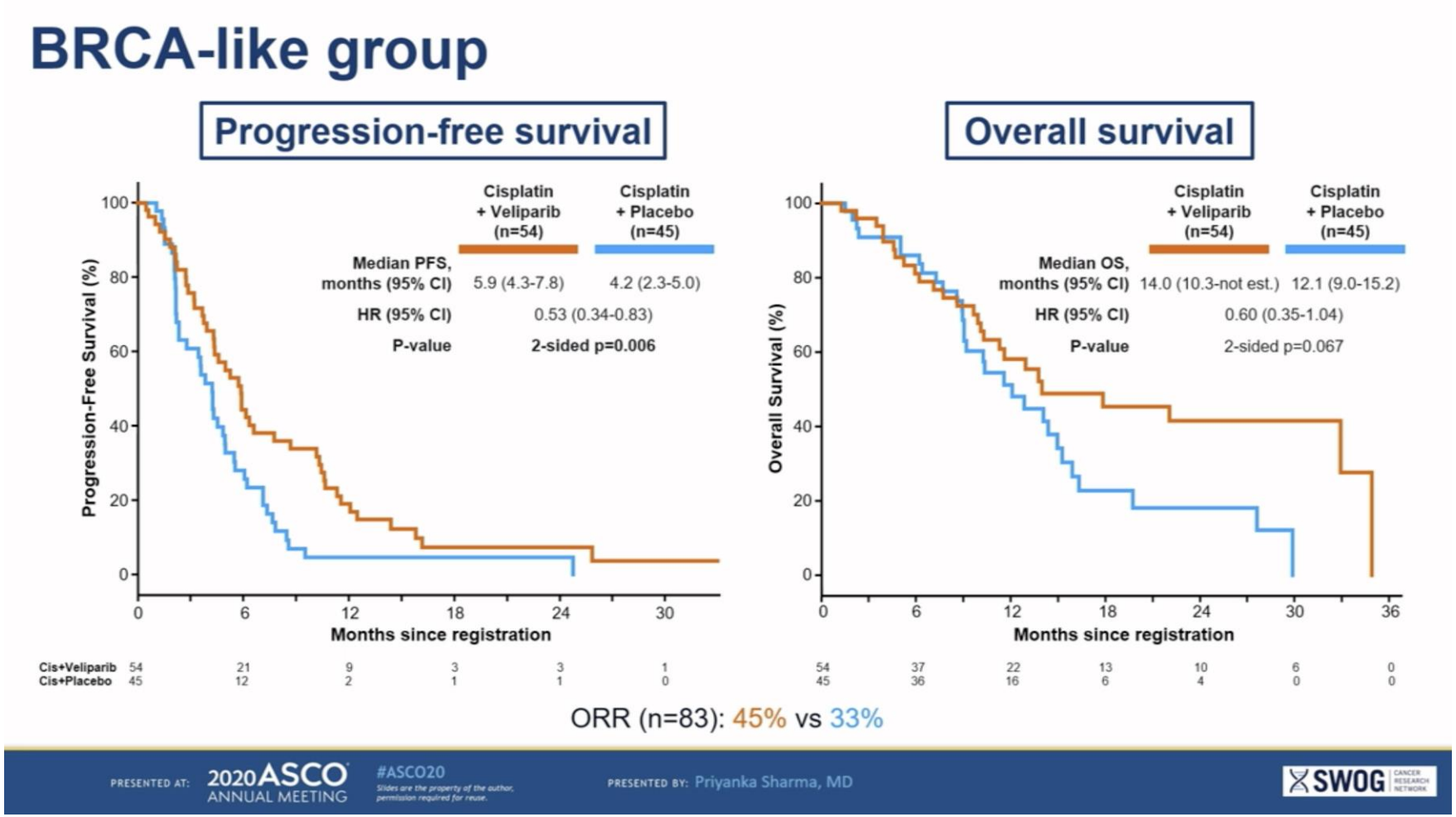

Sharma P et al. ASCO 2020

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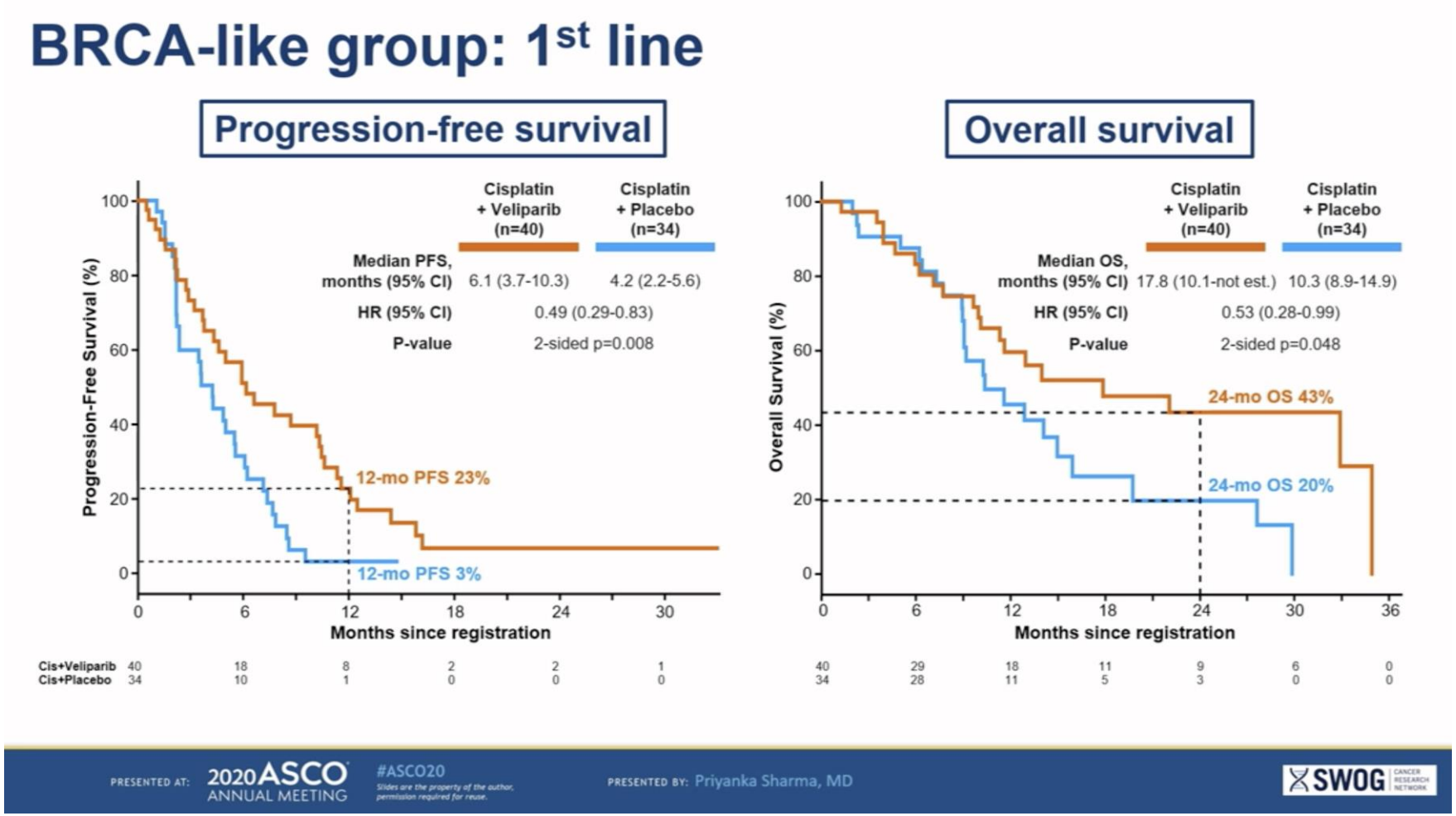
BRCA-like group: 1st line
Progression-free survival
Cisplatin + Veliparib (n=40)
Cisplatin + Placebo (n=34)
Median PFS, months (95% CI)
6.1 (3.7-10.3)
4.2 (2.2-5.6)
HR (95% CI)
0.49 (0.29-0.83)
P-value
2-sided p=0.008
12-mo PFS 23%
12-mo PFS 3%
Progression-Free Survival (%)
Months since registration
Cis+Veliparib 40 18 8 2 2 1
Cis+Placebo 34 10 1 0 0 0
Overall survival
Median OS, months (95% CI)
17.8 (10.1-not est.)
10.3 (8.9-14.9)
HR (95% CI)
0.53 (0.28-0.99)
P-value
2-sided p=0.048
24-mo OS 43%
24-mo OS 20%
Overall Survival (%)
Months since registration
40 29 18 11 9 6 0
34 28 11 5 3 0 0
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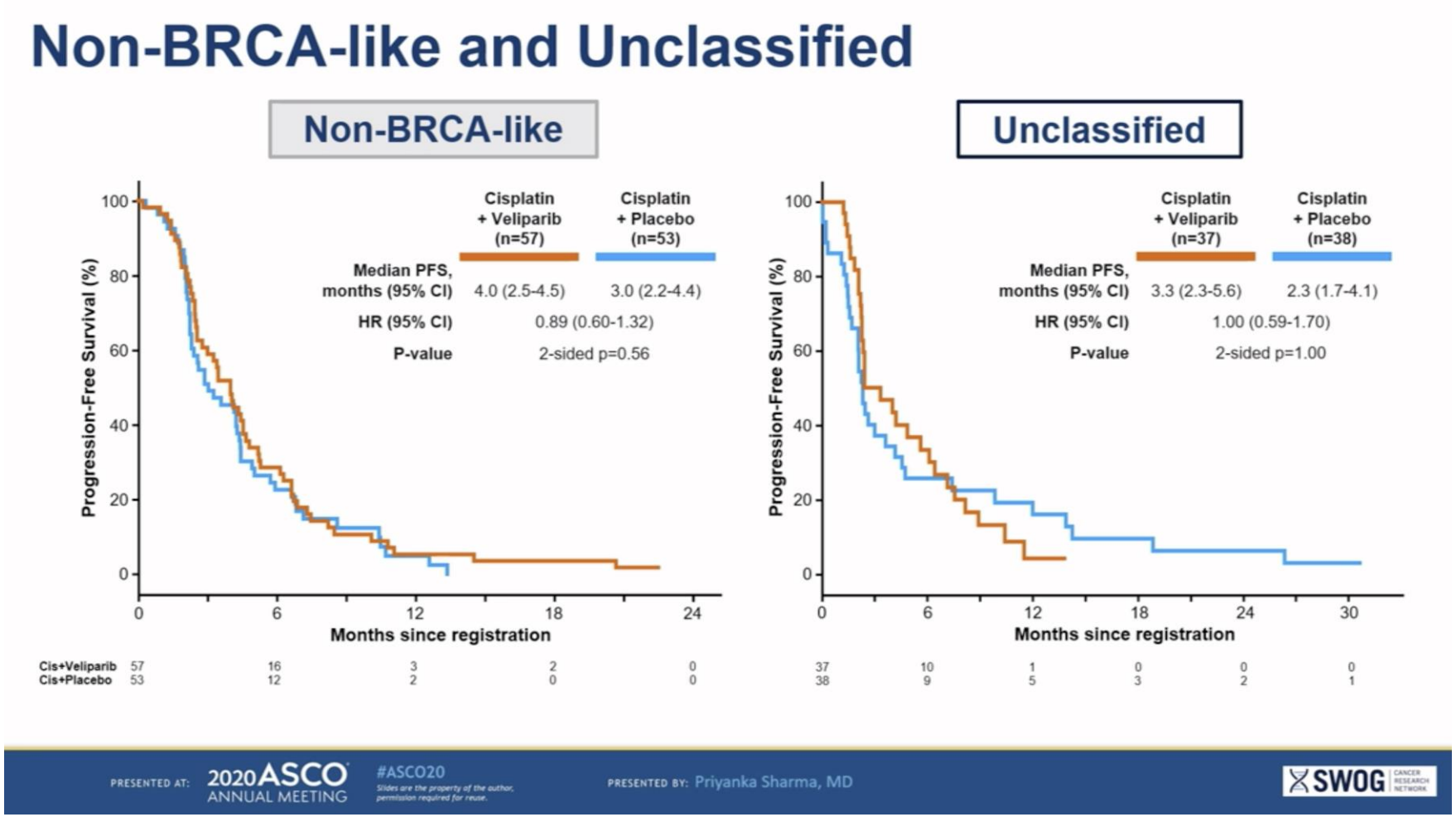
#ASCO20
PRESENTED BY: Priyanka Sharma, MD
SWOG

SWOG S1416


Non-BRCA-like and Unclassified
Non-BRCA-like
Cisplatin + Veliparib (n=57)
Cisplatin + Placebo (n=53)
Median PFS, months (95% CI)
4.0 (2.5-4.5)
3.0 (2.2-4.4)
HR (95% CI)
0.89 (0.60-1.32)
P-value
2-sided p=0.56
Progression-Free Survival (%)
Months since registration
Cis+Veliparib 57 16 3 2 0
Cis+Placebo 53 12 2 0 0
Unclassified
Cisplatin + Veliparib (n=37)
Cisplatin + Placebo (n=38)
Median PFS, months (95% CI)
3.3 (2.3-5.6)
2.3 (1.7-4.1)
HR (95% CI)
1.00 (0.59-1.70)
P-value
2-sided p=1.00
Progression-Free Survival (%)
Months since registration
37 10 1 0 0 0
38 9 5 3 2 1
PRESENTED AT: 2020 ASCO ANNUAL MEETING
#ASCO20
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PRESENTED BY: Priyanka Sharma, MD
SWOG CANCER RESEARCH NETWORK

PARPi 2021
Ausblick

GBG GERMAN BREAST GROUP

KONTAKT SITEMAP DI

LOGIN

HOME ÜBER UNS FORSCHUNG STUDIEN PATIENTINNEN

OlympiA trial crossed superiority boundary for invasive disease-free survival

17.02.2021

OlympiA
OLaparib in Adjuvant BRCAm breast cancer

IDMC has concluded that OlympiA trial crossed superiority boundary for invasive disease-free survival vs. placebo at planned interim analysis. OlympiA Phase III trial of Lynparza in the adjuvant treatment of BRCA-mutated HER2-negative high-risk early breast cancer will be analysed and reported early.

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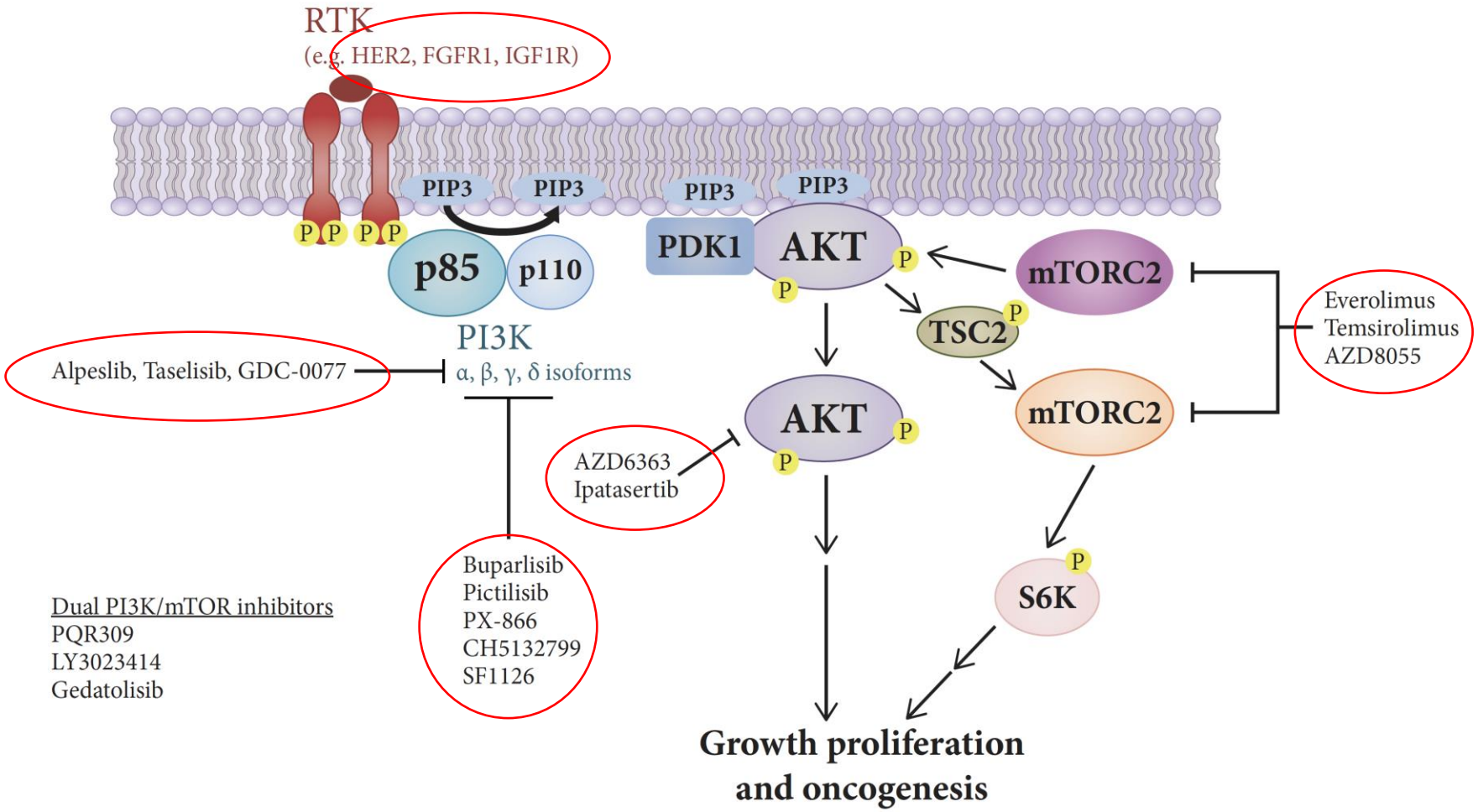
FAZIT – PARPi

- gute Hinweise für Wirksamkeit von Olaparib als Monotherapie bei
  - Somatischen BRCA Mutationen
  - sPALB2 Mutationen (überwiegend HR+!)
- Auch Veliparib + Cisplatin zeigt Wirksamkeitsignal bei gBRCAwt – BRCA-Like mTNBC
- vgl. GeparOla-Studie (HRD+)

- Priorität: Wirksamkeit von PARPi beyond BRCAmut in Zulassungsrelevanten Studien überprüfen
- **Olympia-Studie wird frühzeitig ausgewertet (wg. Wirksamkeit)**

Wichtiges update zum PIK3CA/AKT/mTOR pathway

PI3K-AKT-mTOR Signalling



Vasan N et al., Annals of Oncology 30 (Supplement 10): x3–x11, 2019

MBC

PIK3CA INHIBITOREN

SOLAR1:

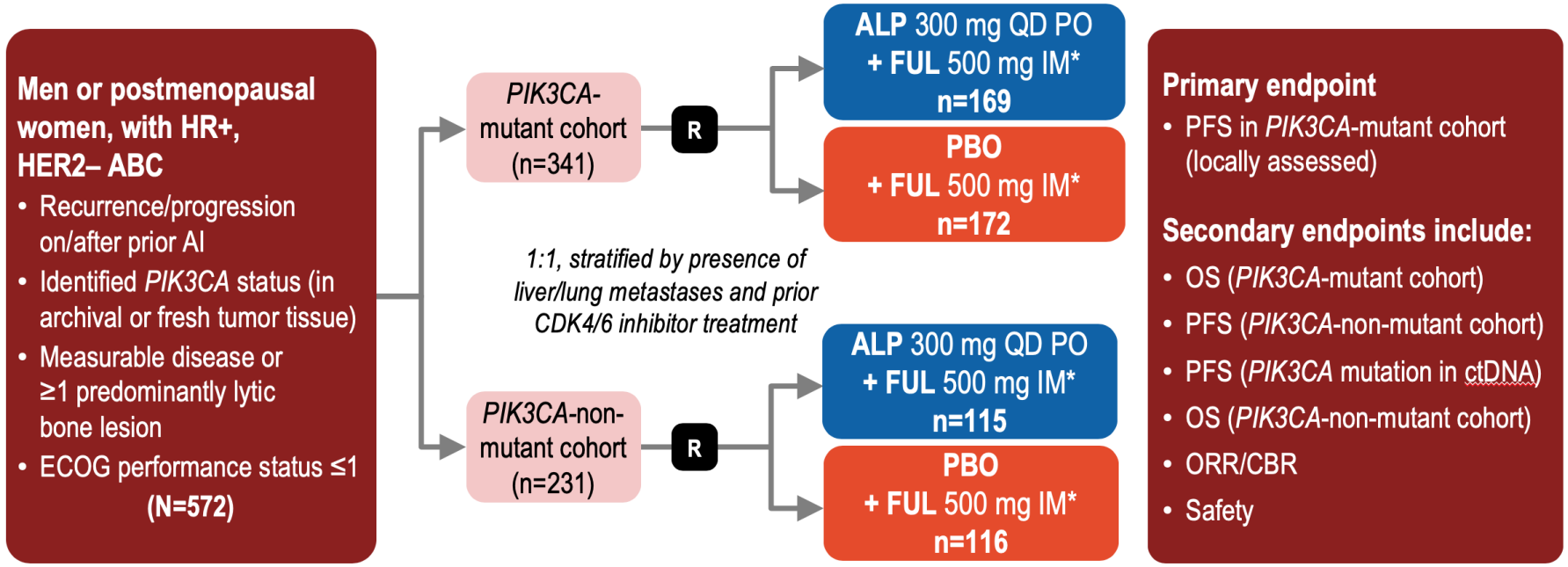
Fulvestrant +/- ALPELISIB in PIK3CA^{mt} ER+/HER2- MBC (Phase III)

Selektiver PI3K Inhibitor (alpha-specific)

- N=572
- PIK3CA mutant (small non mutant cohort)
- 1:1 Rando
- Postmenopausal
- Progression on/after AI
- Ca. 6% prior CDK4/6

F. André et al., LBA3, ESMO 2018; CBYL719C2301

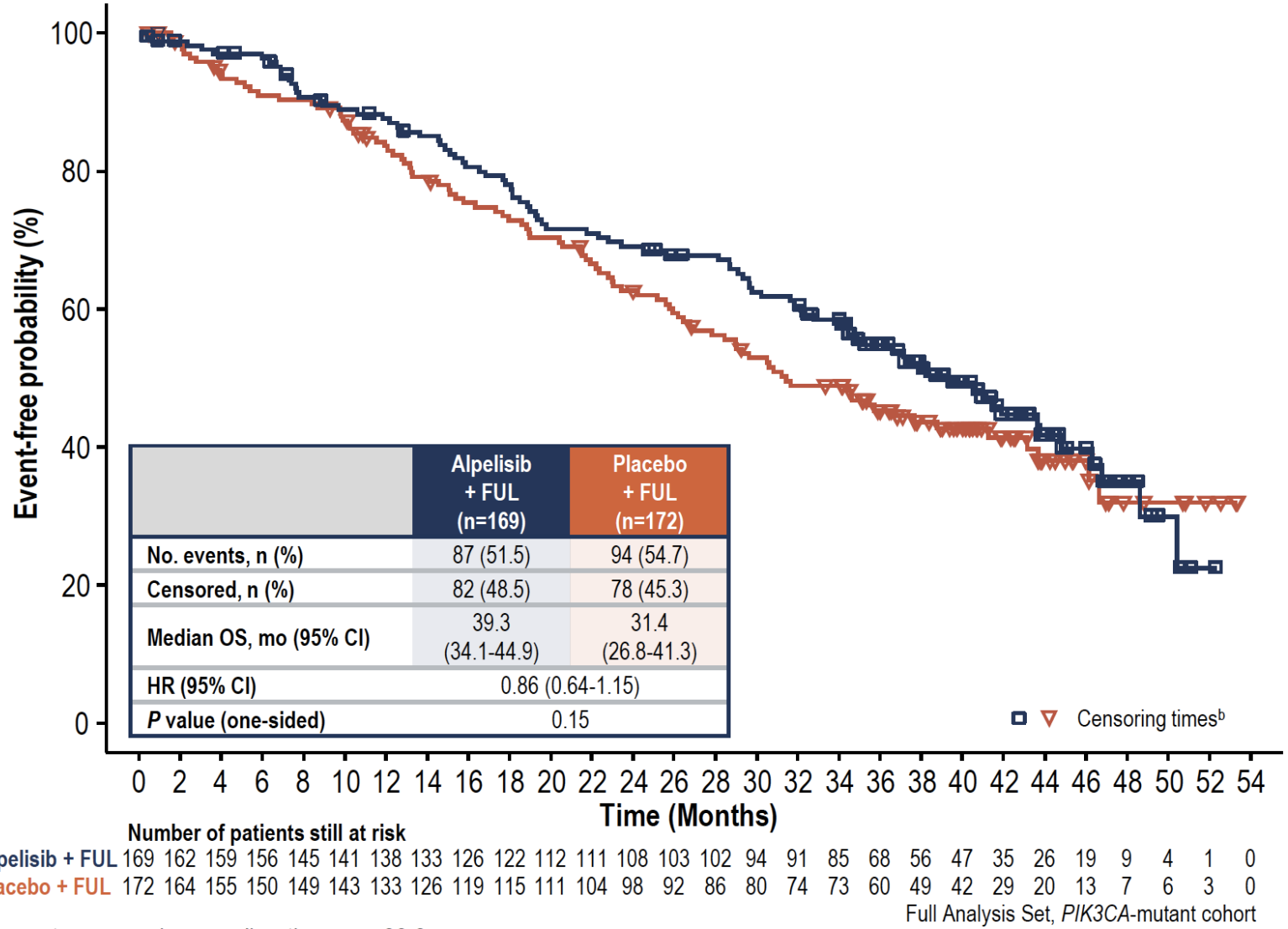
SOLAR-1: A Phase III randomized, controlled trial (NCT02437318)



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

SOLAR-1: OS in Patients in *PIK3CA*-mutant Cohort[a]

- mOS was prolonged by 7.9 mo for patients in the alpelisib + fulvestrant arm
- Final OS analysis in the *PIK3CA*-mutant cohort did not cross the prespecified O'Brien-Fleming efficacy boundary (1-sided $P \leq 0.0161$)

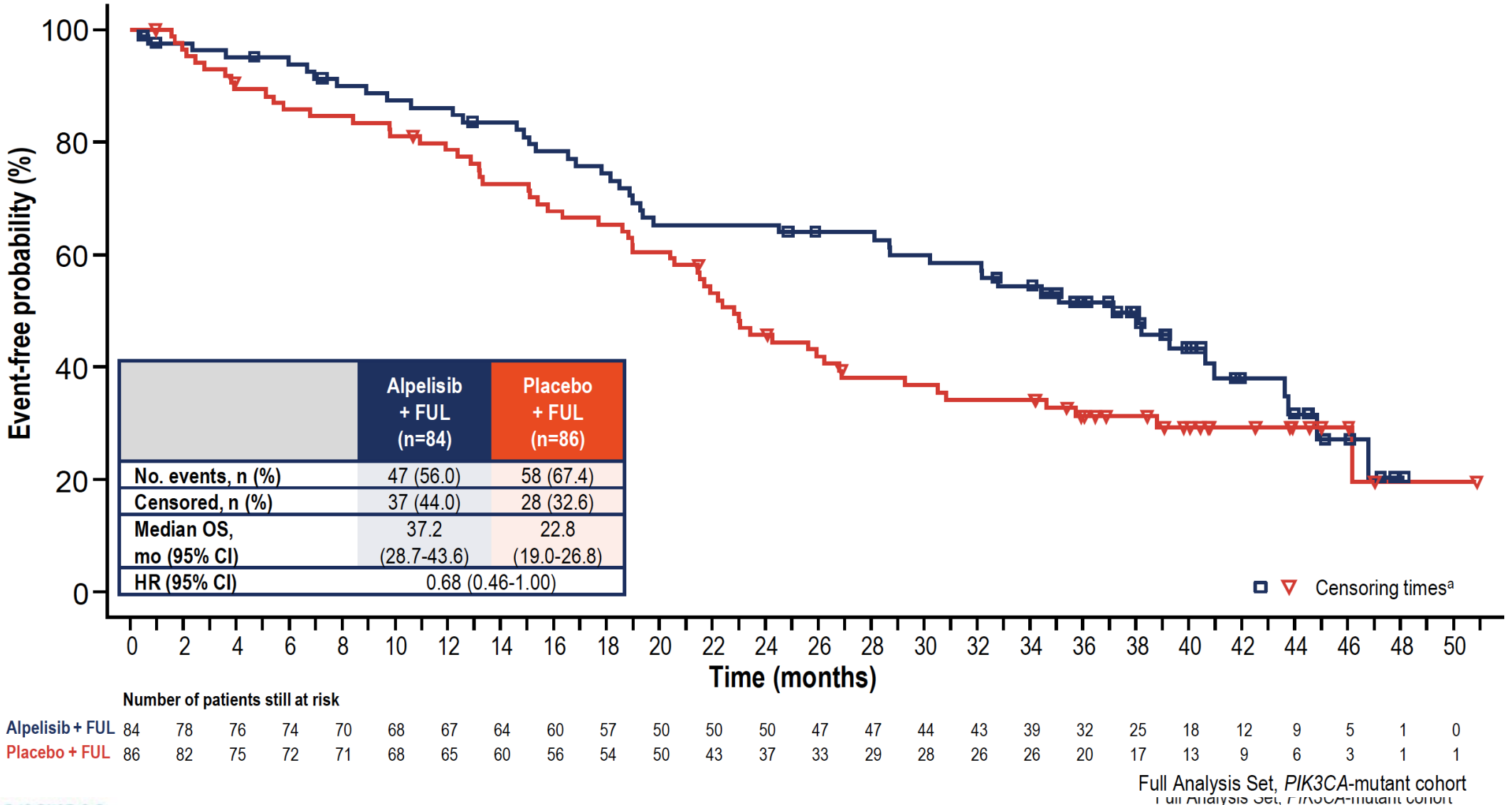


	Alpelisib + FUL (n=169)	Placebo + FUL (n=172)
No. events, n (%)	87 (51.5)	94 (54.7)
Censored, n (%)	82 (48.5)	78 (45.3)
Median OS, mo (95% CI)	39.3 (34.1-44.9)	31.4 (26.8-41.3)
HR (95% CI)	0.86 (0.64-1.15)	
P value (one-sided)	0.15	

Full Analysis Set, *PIK3CA*-mutant cohort

[a]Between randomisation to OS event or censoring, median time was 30.8 mo.
[b]Date of censoring is defined as the last contact date for OS.

SOLAR-1: OS in Patients With Lung and/or Liver Metastases



	Alpelisib + FUL (n=84)	Placebo + FUL (n=86)
No. events, n (%)	47 (56.0)	58 (67.4)
Censored, n (%)	37 (44.0)	28 (32.6)
Median OS, mo (95% CI)	37.2 (28.7-43.6)	22.8 (19.0-26.8)
HR (95% CI)	0.68 (0.46-1.00)	

Number of patients still at risk

Alpelisib + FUL	84	78	76	74	70	68	67	64	60	57	50	50	50	47	47	44	43	39	32	25	18	12	9	5	1	0
Placebo + FUL	86	82	75	72	71	68	65	60	56	54	50	43	37	33	29	28	26	26	20	17	13	9	6	3	1	1

Full Analysis Set, *PIK3CA*-mutant cohort

[a]Between randomisation to OS event or censoring, median time was 30.8 mo.
[b]Date of censoring is defined as the last contact date for OS.

SOLAR1:

Fulvestrant +/- ALPELISIB in PIK3CA^{mt} ER+/HER2- MBC (Phase III)

Selektiver PI3K Inhibitor (alpha-specific)

- N=572
- PIK3CA mutant (small non mutant cohort)
- 1:1 Rando
- Postmenopausal
- Progression on/after AI
- Ca. 6% prior CDK4/6

F. André et al., LBA3, ESMO 2018; CBYL719C2301

Adverse events in the total population

AEs ≥20% in either arm, %	Alpelisib + fulvestrant N=284			Placebo + fulvestrant N=287		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash*	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Decreased weight	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0

- Eighteen patients (6.3%) discontinued alpelisib due to hyperglycemia and 9 patients (3.2%) due to rash; no patients discontinued placebo due to either hyperglycemia or rash
- Maculopapular rash was observed in 14.1% of patients (all-grade) and 8.8% (grade 3) in the alpelisib arm, vs 1.7% and 0.3%, respectively, in the placebo arm
- The safety profile of the alpelisib group and the placebo group was similar in *PIK3CA*-mutant and *PIK3CA*-non-mutant cohorts

*Single preferred term of "rash" does not include preferred term of "maculopapular rash".

BYLieve: A Phase 2, Open-Label, 3-Cohort, Noncomparative Trial (NCT03056755)

BYLieve
Alpelisib (BYL719) In patients with PIK3CA mutant, HR+, HER2- adVanced brEast cancer

Goal: In the post-CDKi setting, assess the efficacy and safety of alpelisib + ET (fulvestrant or letrozole) in patients with *PIK3CA*-mutated HR+, HER2– ABC

Men or pre-/postmenopausal[a] women with HR+, HER2– ABC with a *PIK3CA* mutation

- Last line of prior therapy: CDKi + ET, systemic chemotherapy or ET
- ECOG PS ≤2
- Measurable disease (per RECIST v1.1) or ≥1 predominantly lytic bone lesion

Patients who received CDKi + AI as immediate prior treatment (N=112)[b]
(Cohort A)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Patients who received CDKi + fulvestrant as immediate prior treatment (N=112)
(Cohort B)
Alpelisib 300 mg oral QD + letrozole 2.5 mg[d]

Patients who progressed on/after AI and received chemotherapy or ET as immediate prior treatment (N=112)
(Cohort C)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Treatment crossover between cohorts is not permitted

Primary endpoint

- Proportion of patients alive without PD at 6 months (RECIST v1.1) in each cohort
- **Secondary endpoints include**

(assessed in each cohort)

- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

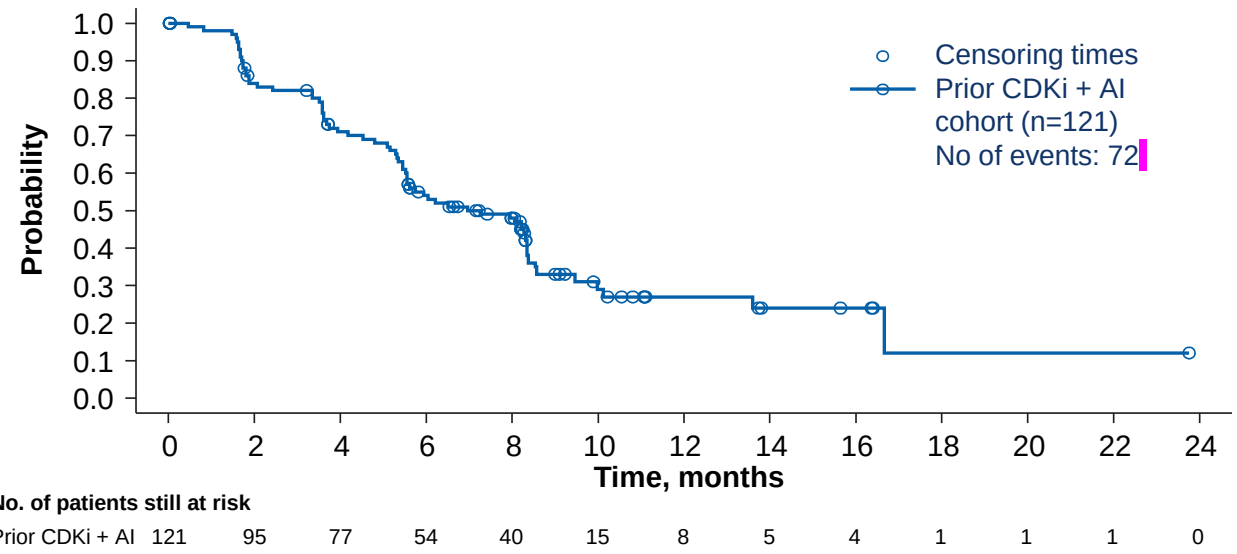
[a]Men in the letrozole cohort and premenopausal women also received goserelin 3.6 mg SC every 28 days or leuprolide 7.5 mg IM every 28 days for adequate gonadal suppression. [b]Enrollment in each cohort continued until at least 112 patients with a centrally confirmed *PIK3CA* mutation was reached. [c]IM on D1 and D15 of Cycle 1 and D1 for all other cycles thereafter. [d]Oral QD.
ABC, advanced breast cancer; AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; CBR, clinical benefit rate; D, day; DOR, duration of response; IM, intramuscularly; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, PFS on next-line treatment; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RECIST, Response Evaluation Criteria In Solid Tumors; SC, subcutaneously; QD, once daily.

Rugo HS et al., Alpelisib + Fulvestrant in Patients With PIK3CA-Mutated Hormone-Receptor Positive (HR+), Human Epidermal Growth Factor Receptor-2-Negative (HER2-) Advanced Breast Cancer (ABC) Previously Treated With Cyclin-Dependent Kinase 4/6 Inhibitor (CDKi) + Aromatase Inhibitor (AI): BYLieve Study Results, ASCO 2020, (Abstract #1006), NCT03056755.

Efficacy: Primary Endpoint and PFS Results

BYLieve
Alpelisib (BYL719) In patients with PIK3CA mutant, HR+, HER2- adVanced brEast cancer

Endpoint	Prior CDKi + AI (Cohort A) (n=121)
Primary endpoint: Patients who were alive without disease progression at 6 mo	**50.4%** (n=61; 95% CI, 41.2-59.6)
Secondary endpoint: Median PFS	**7.3 mo** [n=72 (59.5%) with event]; 95% CI, 5.6-8.3)



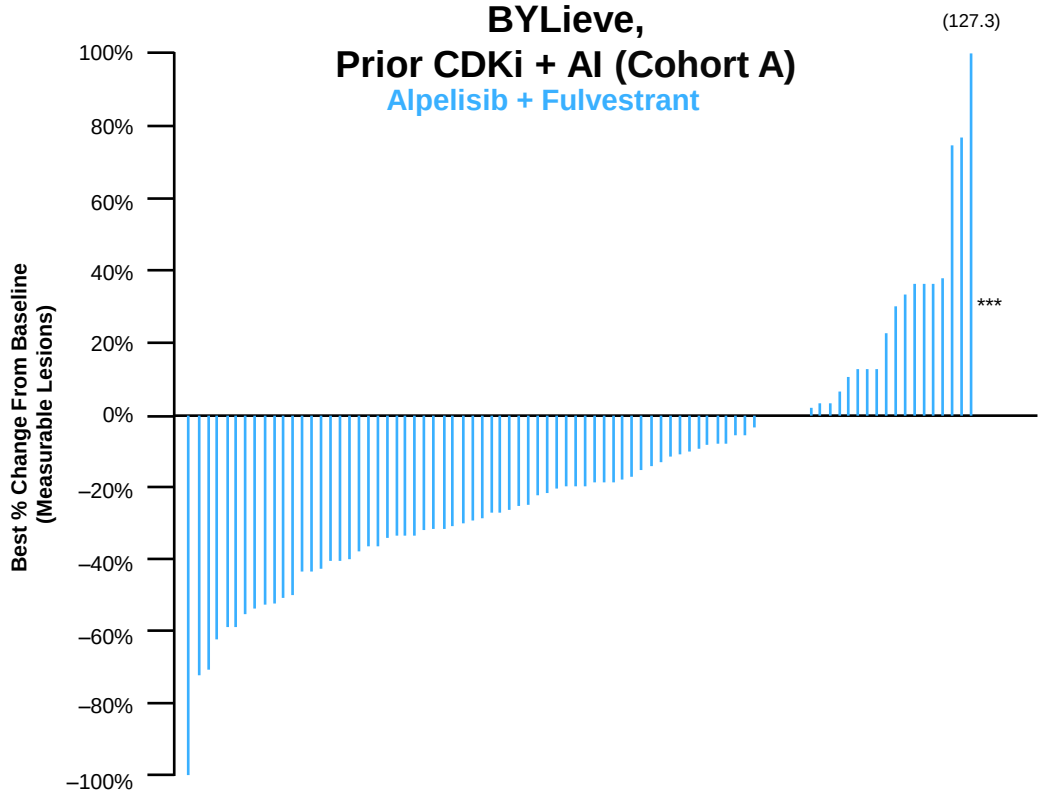
The primary endpoint for the prior CDKi + AI cohort was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months

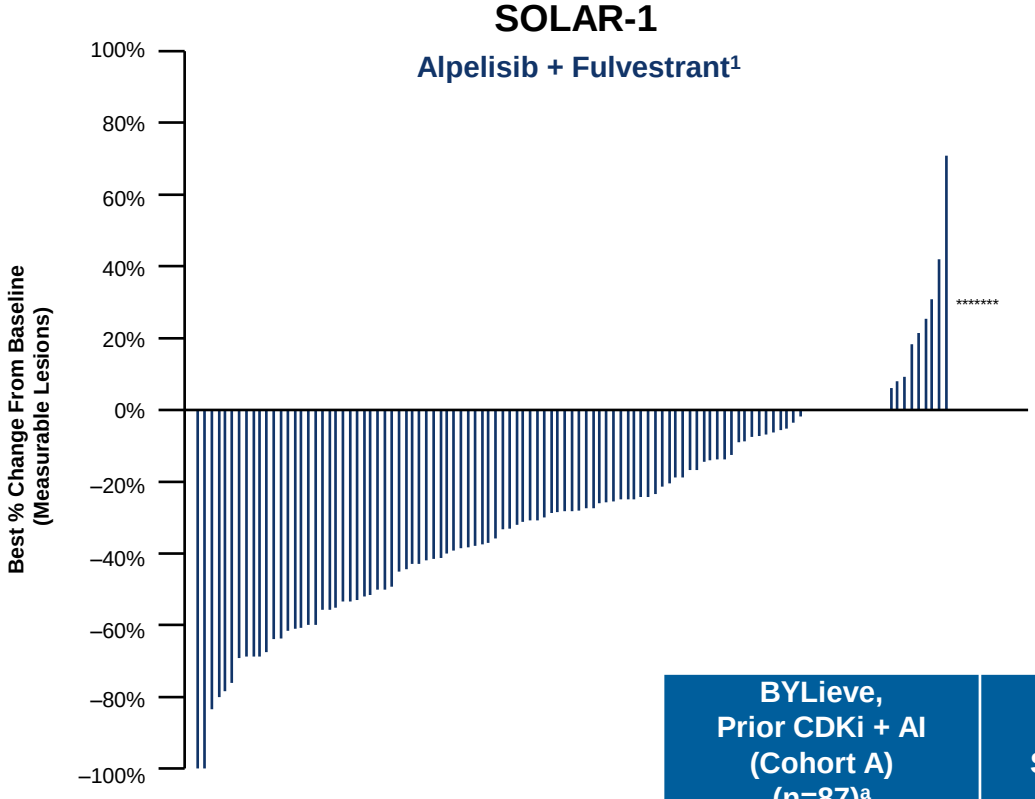
- In SOLAR-1, 44.4% of patients in the *PIK3CA*-mutant cohort with prior CDKi treated with alpelisib plus fulvestrant were alive without disease progression at 6 months

AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; CI, confidence interval; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Rugo HS et al., Alpelisib + Fulvestrant in Patients With PIK3CA-Mutated Hormone-Receptor Positive (HR+), Human Epidermal Growth Factor Receptor-2-Negative (HER2-) Advanced Breast Cancer (ABC) Previously Treated With Cyclin-Dependent Kinase 4/6 Inhibitor (CDKi) + Aromatase Inhibitor (AI): BYLieve Study Results, ASCO 2020, (Abstract #1006), NCT03056755.

Efficacy: Best Percent Change From Baseline in Tumor Size





	BYLieve, Prior CDKi + AI (Cohort A) (n=87)[a]	SOLAR-1 (n=116)[1]
Decrease in best % change from baseline	70.1%	75.9%
Increase/zero change in best % change from baseline	26.4%	18.1%

SOLAR-1 data cutoff date: June 12, 2018; BYLieve data cutoff date: December 17, 2019.
*Best percentage change in sum of diameters per investigator assessment, for patients with measurable disease at baseline.
[a]Patients with missing best percentage change or those with best percentage change in target lesion but overall response of Unknown are excluded'
1. Reprinted from Juric D, et al. SABCS 2018. Abstract GS3-08 (oral).

Rugo HS et al., Alpelisib + Fulvestrant in Patients With PIK3CA-Mutated Hormone-Receptor Positive (HR+), Human Epidermal Growth Factor Receptor-2-Negative (HER2-) Advanced Breast Cancer (ABC) Previously Treated With Cyclin-Dependent Kinase 4/6 Inhibitor (CDKi) + Aromatase Inhibitor (AI): BYLieve Study Results, ASCO 2020, (Abstract #1006), NCT03056755.

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

Guidelines Breast
Version 2020.1D

	Oxford LoE	GR	AGO
▪ CDK4/6-Inhibitor (Abemaciclib, Palbociclib, Ribociclib)			
▪ + nicht-steroidaler AI	1b	B	++
▪ + Fulvestrant	1b	B	++
▪ Abemaciclib Monotherapie	3	C	+/-
▪ Alpelisib + Fulvestrant (bei PIK3CA Mutation)	1b	B	+
▪ CDK4/6i beyond progression	5	D	-
▪ CDK4/6i-Wechsel aufgrund Toxizität	5	D	+/-

- Wirksamkeit nach CDK4/6 auch prospektiv gezeigt (BYLieve-Studie)

MBC

AKT INHIBITOREN

FAKTION:
Capivasertib + Fulvestrant bei **HR+ MBC** (Phase II)

No selection on AKT pathway activation

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

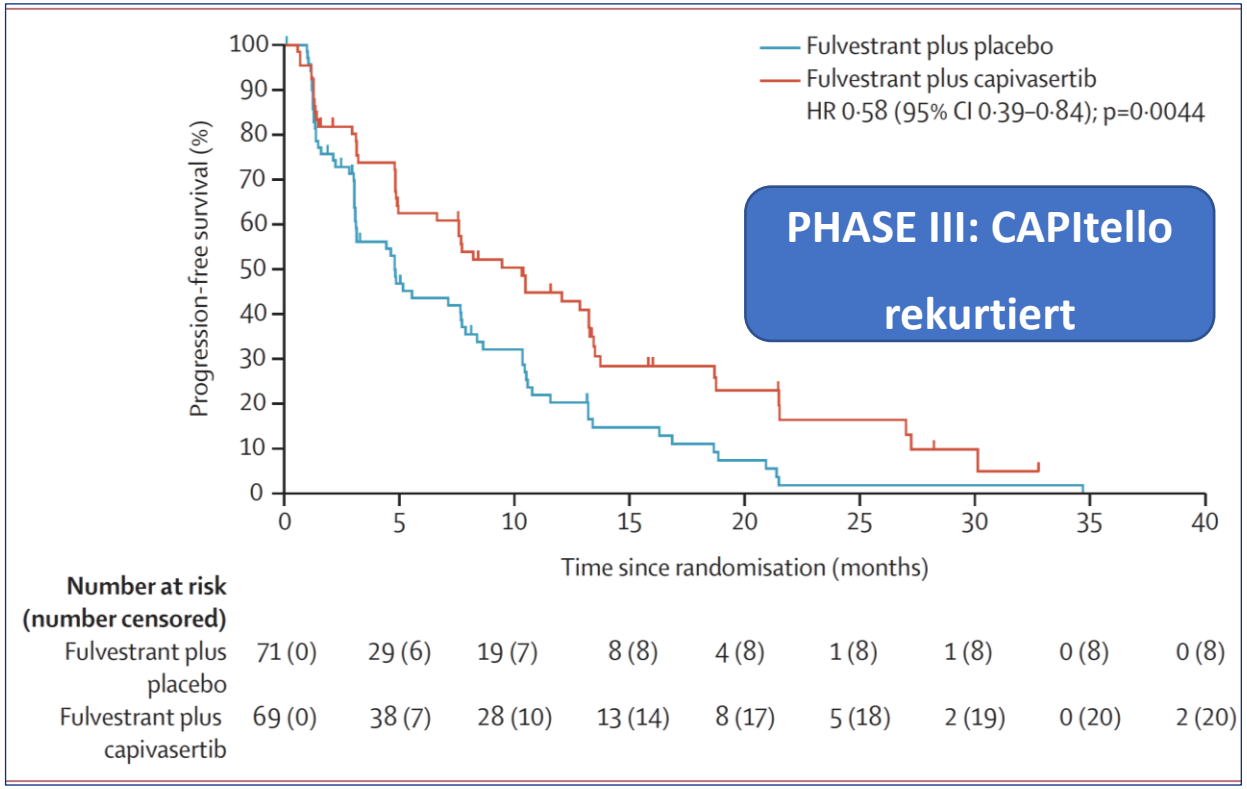
N = 140

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



ORR **12%** *vs* **41%**
OS **20 mo.** *vs* **26 mo.**
HR 0.6
p=0.07

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Jones R et al., ASCO 2019 annual meeting, oral presentation abstr. # 1005
Jones R et al., Lancet Oncol. 2020 Mar;21(3):345-357

AKTi + Paclitaxel in 1st Line mTNBC: PAKT trial: CAPIVASERTIB (AZD5363)

Randomized Phase II

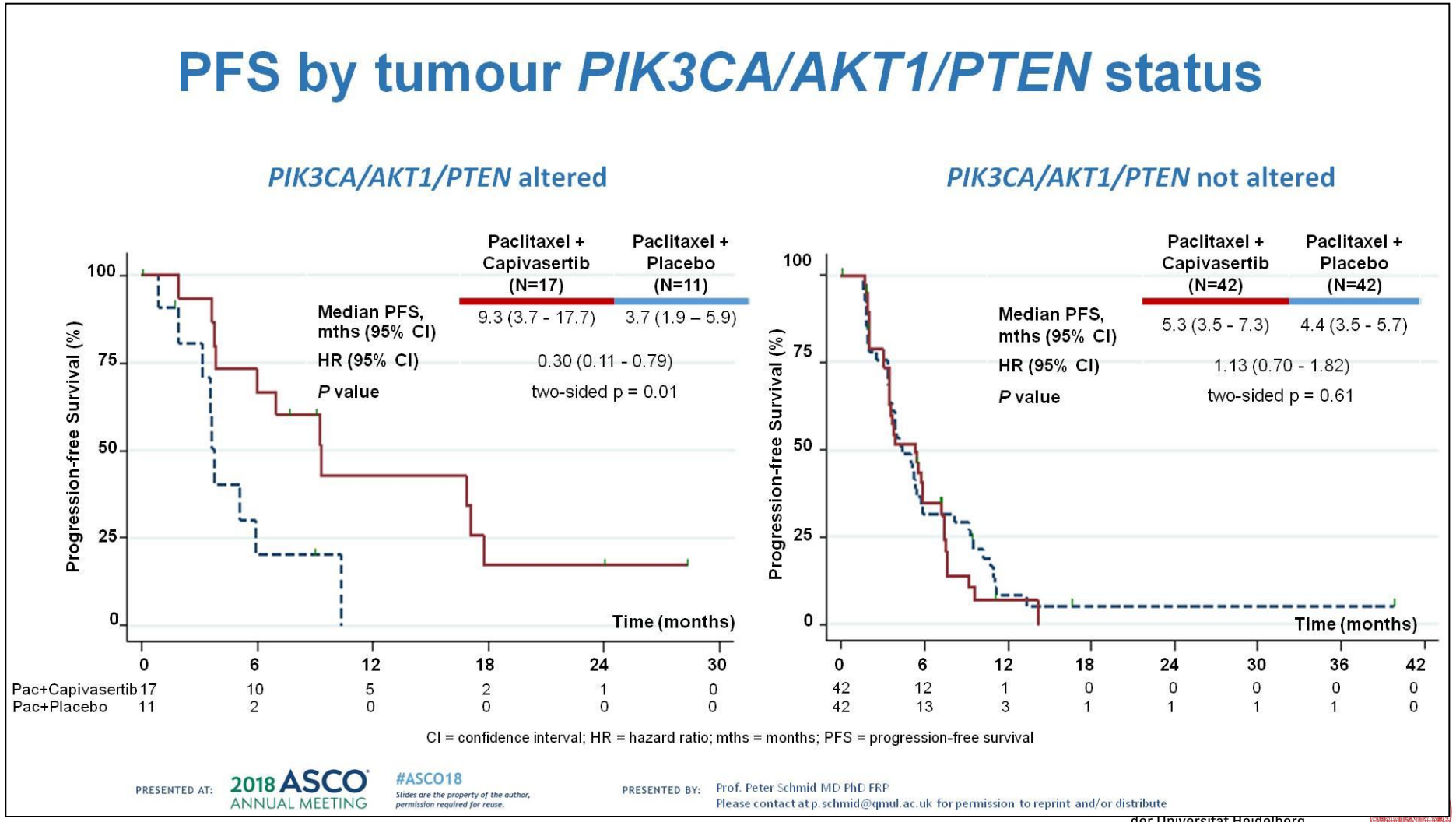
N=140

mTNBC 1st Line

Prior taxan: 57%

- **No biomarker preselection**
  - 1° EP: PFS
  - 2° EP: PFS in PIK3CA/AKT1/PTEN altered tumors
- **Pathway alteration:**
  - 25% (28/112)

- ***80% power for HR 0.67***
- ***1-sided alpha=10%***



Schmid P et al., 2018 ASCO Annual Meeting oral session, abstract # 1007

AKTi + Paclitaxel in 1st Line mTNBC: LOTUS trial: IPATASERTIB

Randomized Phase II

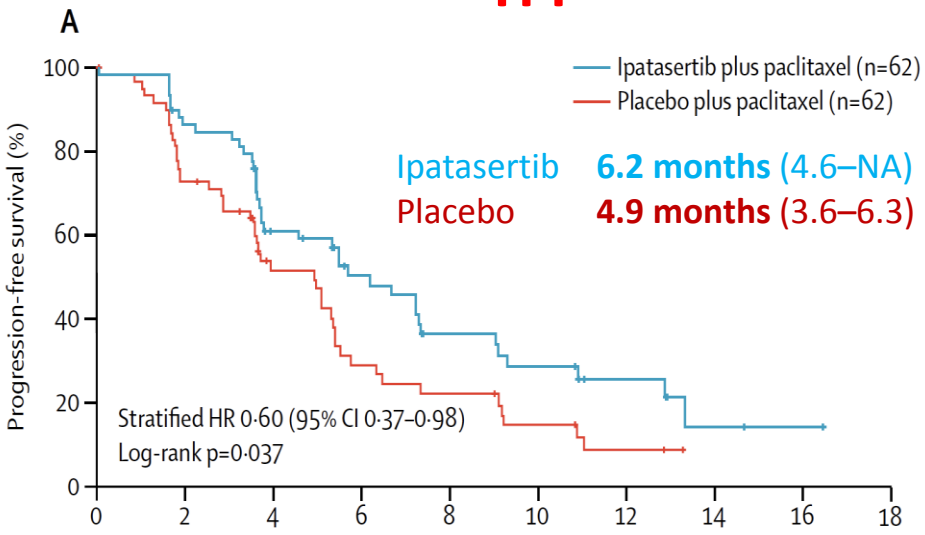
n=124

mTNBC 1st Line

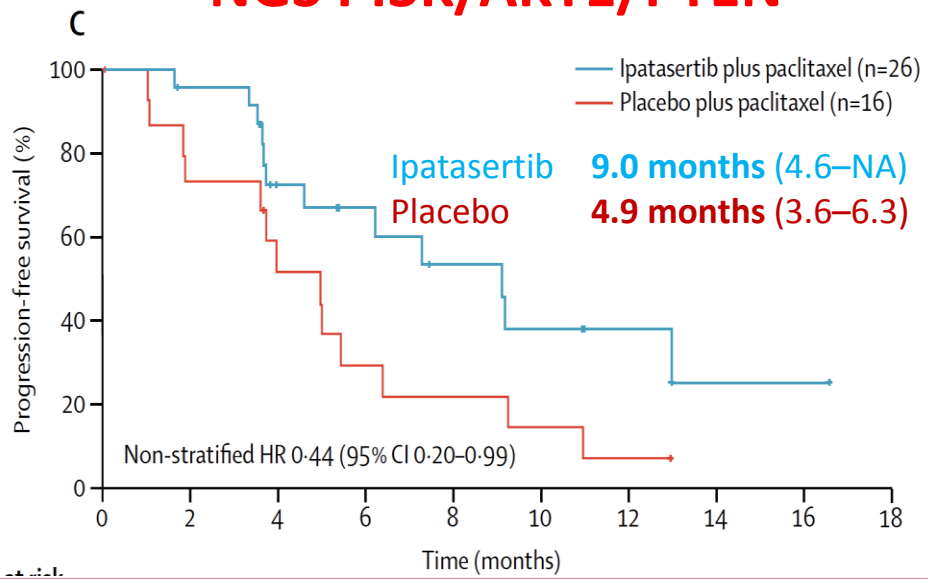
Prior taxan: >50%

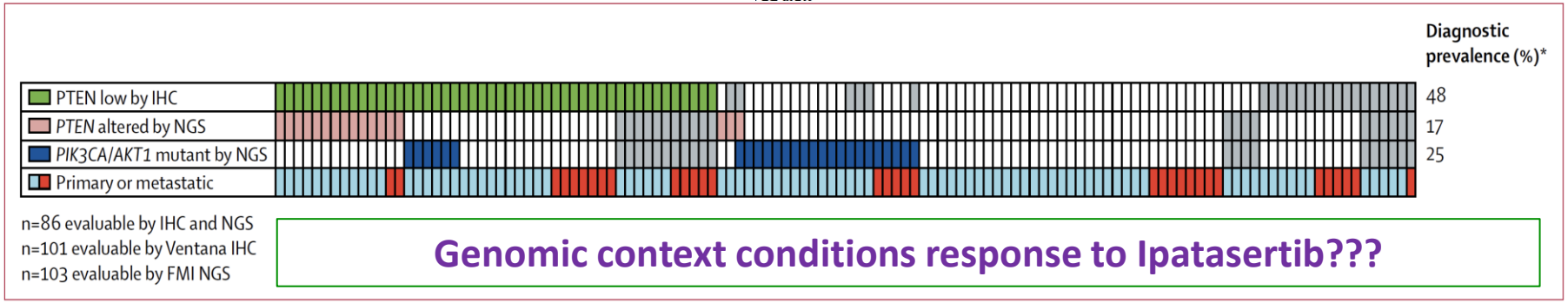
- **No biomarker preselection**
- Co-1° EP: PFS in IIT & $TPEN_{low}$
- 2°: PIK3CA/AKT pathway activated population
- **Pathway alteration:**
  - 41% (42/103)

ITT



NGS PI3K/AKT1/PTEN





Genomic context conditions response to Ipatasertib???

Kim SB et al., Lancet Oncology 2017

AKTi + Paclitaxel in 1st Line mTNBC: LOTUS trial: IPATASERTIB

Randomized Phase II

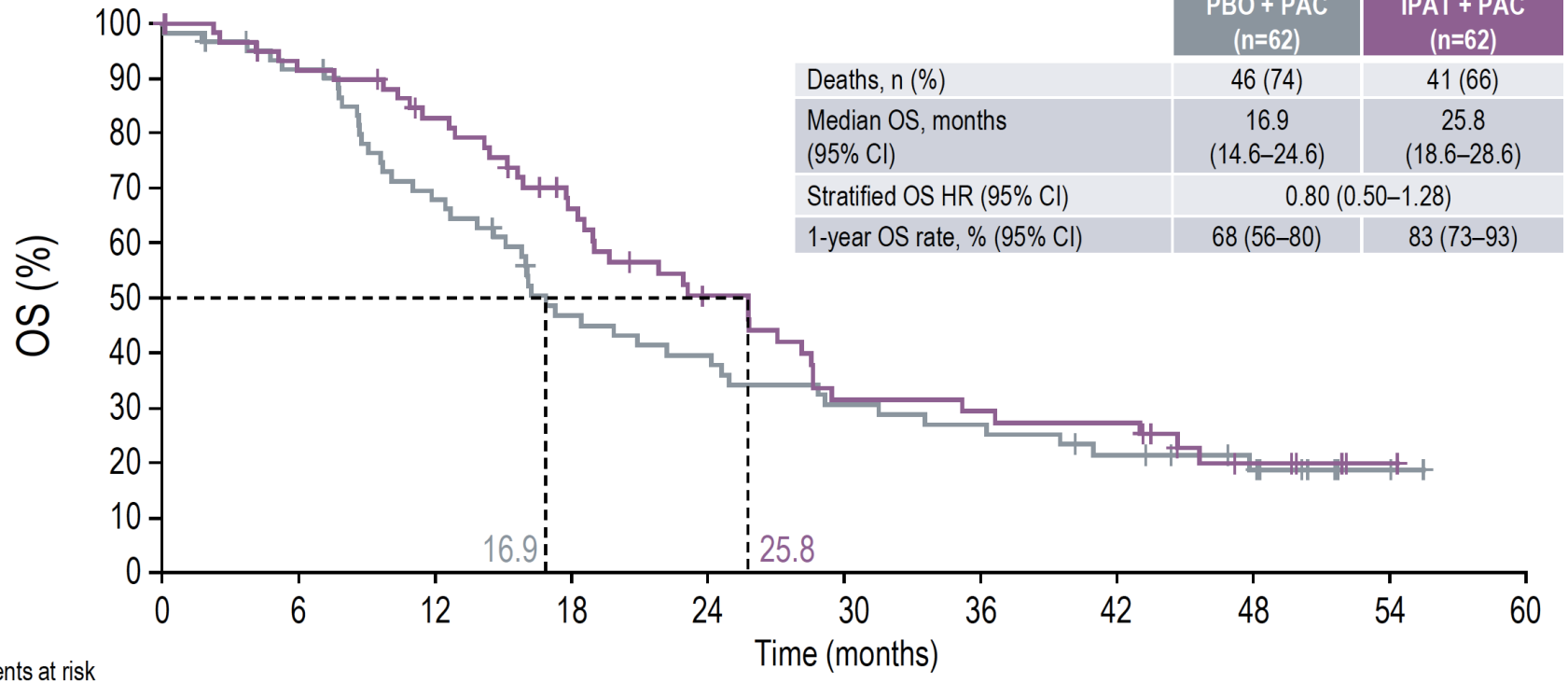
n=124

mTNBC 1st Line

Prior taxan: >50%

- **No biomarker preselection**
- Co-1° EP: PFS in IIT & $TPEN_{low}$
- 2°: PIK3CA/AKT pathway activated population
- **Pathway alteration:**
  - 41% (42/103)

Final OS in the ITT population



	PBO + PAC (n=62)	IPAT + PAC (n=62)
Deaths, n (%)	46 (74)	41 (66)
Median OS, months (95% CI)	16.9 (14.6–24.6)	25.8 (18.6–28.6)
Stratified OS HR (95% CI)	0.80 (0.50–1.28)	
1-year OS rate, % (95% CI)	68 (56–80)	83 (73–93)

Patients at risk

IPAT + PAC	62	54	46	34	24	15	14	13	5	1
PBO + PAC	62	55	40	26	22	17	15	11	7	1

ESMO BREAST CANCER VIRTUAL MEETING

Data cut-off: 3 September 2019

Dent R et al., 2020 ESMO Breast abstract #

IPATunity130 Cohort B (NCT03337724): Double-blinded placebo-controlled randomised trial[a]

- HR+ (≥1%) HER2-negative measurable aBC
- *PIK3CA/AKT1/PTEN* alteration[b]
- Not considered appropriate for endocrine-based therapy
- No prior chemotherapy for aBC
- Prior CDK4/6 inhibitor and/or mTOR inhibitor permitted
- Candidate for taxane therapy
- ECOG performance status 0/1

222 patients enrolled between 6 Jan 2018 and 29 Mar 2019 (50% Europe, 26% Asia-Pacific)

R 2:1

PAC 80 mg/m^2 days 1, 8 & 15 + IPAT 400 mg od days 1–21 q28d

PAC 80 mg/m^2 days 1, 8 & 15 + PBO days 1–21 q28d

Treatment until disease progression, intolerable toxicity[c] or elective withdrawal

Crossover from PBO to IPAT is not permitted

Analysis of primary endpoint (investigator-assessed PFS) planned after ~150 PFS events

- 80% power to detect an increase in median PFS from 8.5 → 13.8 months with the addition of IPAT to PAC
- Target hazard ratio = 0.62 at 2-sided 5% significance level

[a]Cohort A comparing the same two regimens in triple-negative breast cancer will be analysed independently. Cohort C (safety and efficacy signal seeking) is evaluating IPAT + PAC + atezolizumab in patients with *PIK3CA/AKT1/PTEN*-non-altered tumours. [b]Centrally or locally tested archival or newly obtained tumour tissue; activating alterations in *PIK3CA* and/or *AKT1* and/or inactivating alterations in *PTEN*.[1] [c]Patients discontinuing PAC or IPAT/PBO due to toxicity can continue single-agent treatment

CDK = cyclin-dependent kinase; ECOG = Eastern Cooperative Oncology Group; mTOR = mammalian target of rapamycin; od = once daily; PAC = paclitaxel; PBO = placebo; PFS = progression-free survival; q28d = once every 28 days; R = randomisation

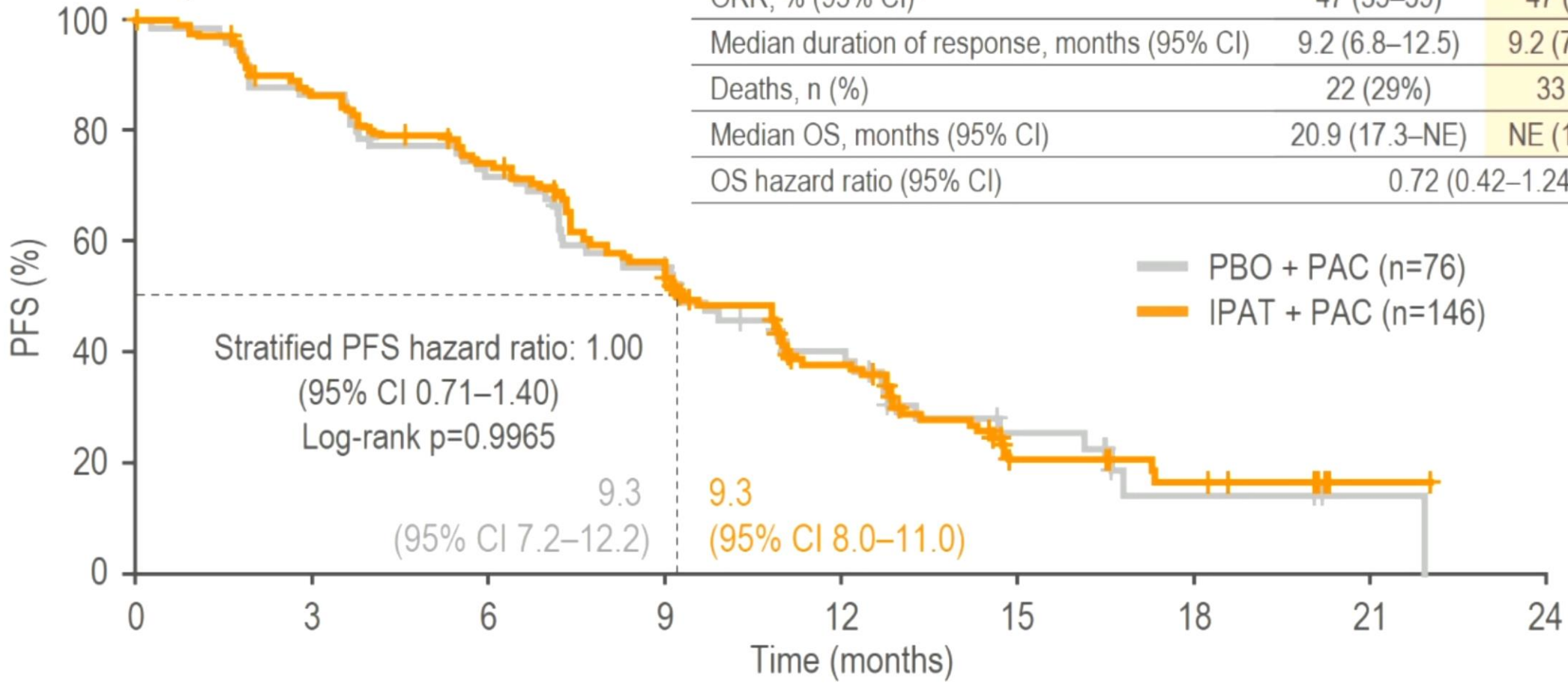
[1]Wongchenko M, et al. AMP 2019

VIRTUAL 2020 ESMO congress

Summary of efficacy

Primary endpoint: investigator-assessed PFS

Median follow-up: 12.9 months



Secondary endpoints	PBO + PAC (n=76)	IPAT + PAC (n=146)
ORR, % (95% CI)[a]	47 (35–59)	47 (38–55)
Median duration of response, months (95% CI)	9.2 (6.8–12.5)	9.2 (7.2–11.3)
Deaths, n (%)	22 (29%)	33 (23%)
Median OS, months (95% CI)	20.9 (17.3–NE)	NE (19.2–NE)
OS hazard ratio (95% CI)	0.72 (0.42–1.24)	

Clinical cut-off date: 17 January 2020. [a]Patients with measurable disease (n=75 PBO + PAC, n=144 IPAT + PAC)

ORR = objective response rate; NE = not estimable

IPATunity130 Cohort A (NCT03337724): Double-blind placebo-controlled randomized trial

- Measurable aTNBC
- *PIK3CA/AKT1/PTEN* alteration[a]
- No prior chemotherapy for aTNBC (≥12 months since last [neo]adjuvant chemotherapy)
- Candidate for taxane therapy
- ECOG performance status 0/1

R 2:1

- PAC 80 mg/m^2 days 1, 8 & 15 + IPAT 400 mg qd days 1–21 q28d
- PAC 80 mg/m^2 days 1, 8, & 15 + PBO days 1–21 q28d

Treatment until disease progression, intolerable toxicity,[b] or elective withdrawal

Crossover from PBO to IPAT is not permitted

255 patients enrolled between Feb 6, 2018, and Apr 8, 2020

Stratification factors:

- Prior (neo)adjuvant chemotherapy (yes vs no)
- Geographic region (Asia-Pacific vs Europe vs North America vs rest of world)
- Tumor alteration status (*PIK3CA/AKT1*-activating mutation vs *PTEN* alteration without *PIK3CA/AKT1*-activating mutation)

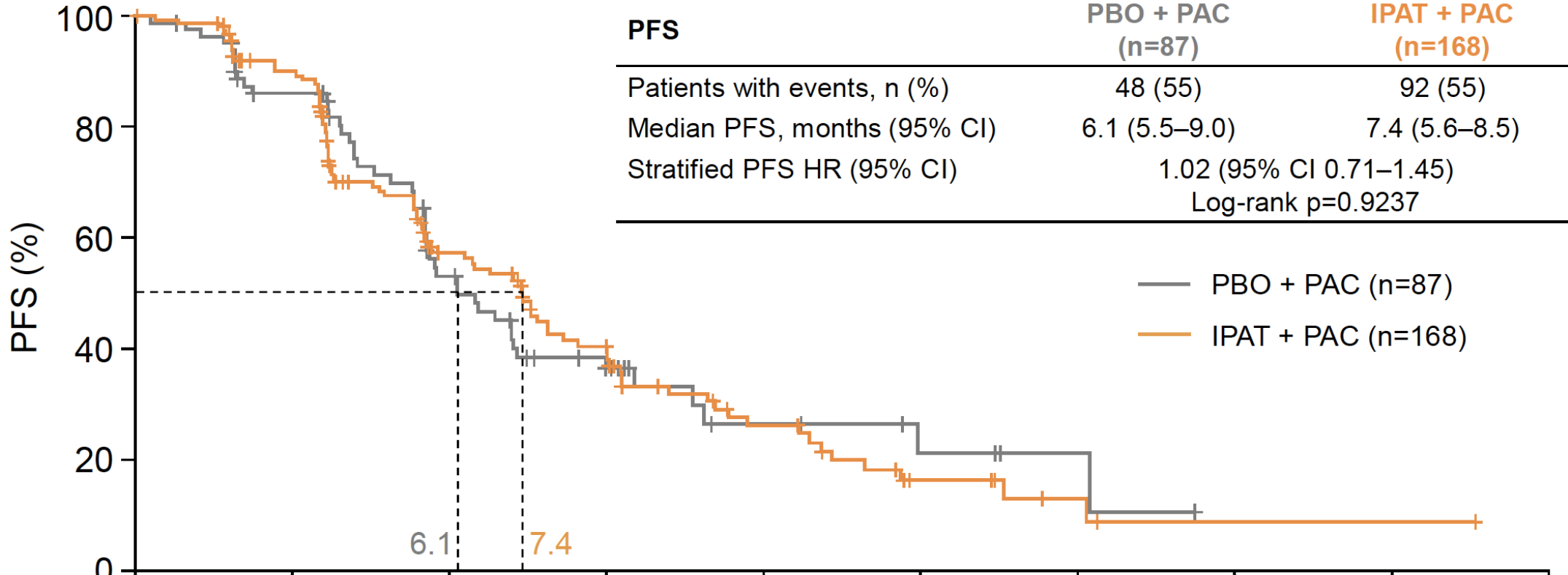
Analysis of primary endpoint (investigator-assessed PFS) planned after 125 PFS events

- 95.5% power to detect an increase in median PFS of 6 → 12 months with addition of IPAT to PAC
- Target HR = 0.50 at 2-sided 5% significance level

[a]Centrally or locally tested archival or newly obtained tumor tissue. [b]Patients discontinuing PAC or IPAT/PBO due to toxicity can continue on single-agent treatment

Primary endpoint: Investigator-assessed PFS
Data cut-off: May 7, 2020 (median follow-up: 8.3 months)

PFS	PBO + PAC (n=87)	IPAT + PAC (n=168)
Patients with events, n (%)	48 (55)	92 (55)
Median PFS, months (95% CI)	6.1 (5.5–9.0)	7.4 (5.6–8.5)
Stratified PFS HR (95% CI)	1.02 (95% CI 0.71–1.45) Log-rank p=0.9237	



Patients at risk

PBO + PAC	87	63	34	20	7	4	2	NE	NE
IPAT + PAC	168	126	59	36	18	7	3	1	1

FAZIT – AKT-Inhibition

- Capivasertib + Fulvestrant vielversprechend, aktuell keine post CDK4/6
- Phase III Capitello-Studie validiert Daten der FAKTION Studie post CDK4/6

- Ipatasertib konnte Wirksamkeit in Phase III IPATunity130 Studie nicht bestätigen
  - Gänzlich negativ
  - sowohl TNBC als auch HR+/HER2-
  - Trotz PIK3CA/AKT-pathway Aktivierung

- Hoffnungen für die AKTi ruhen auf der Kombi mit ET (Fulvestrant; Capitello)

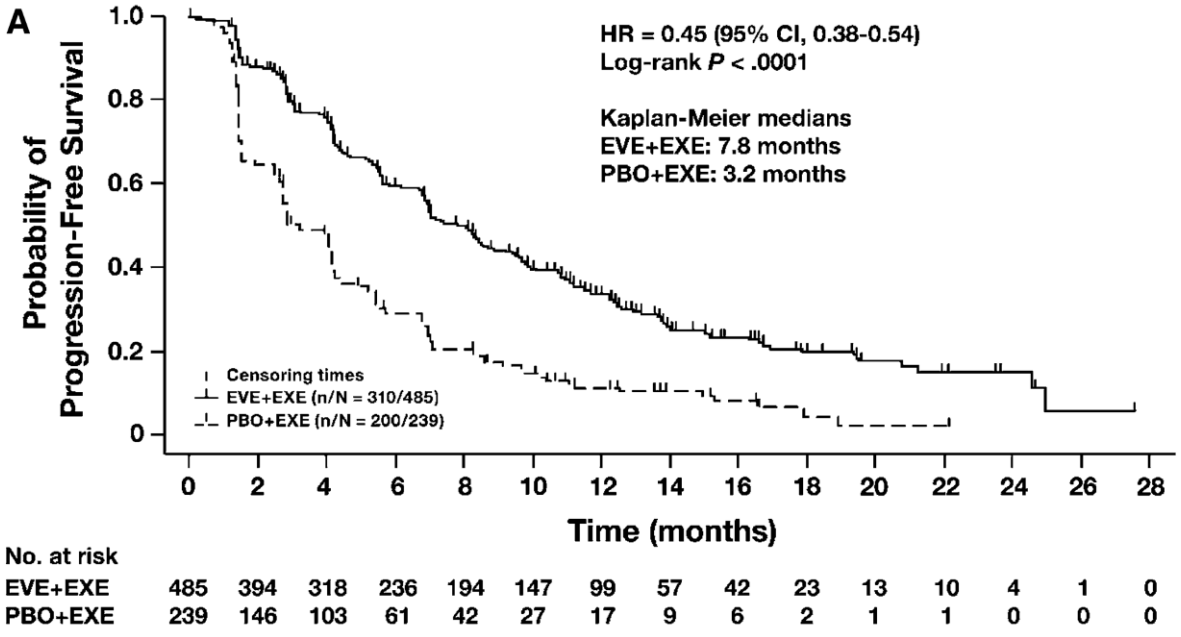
MBC

mTORi – Neustes zu Bewährtem!

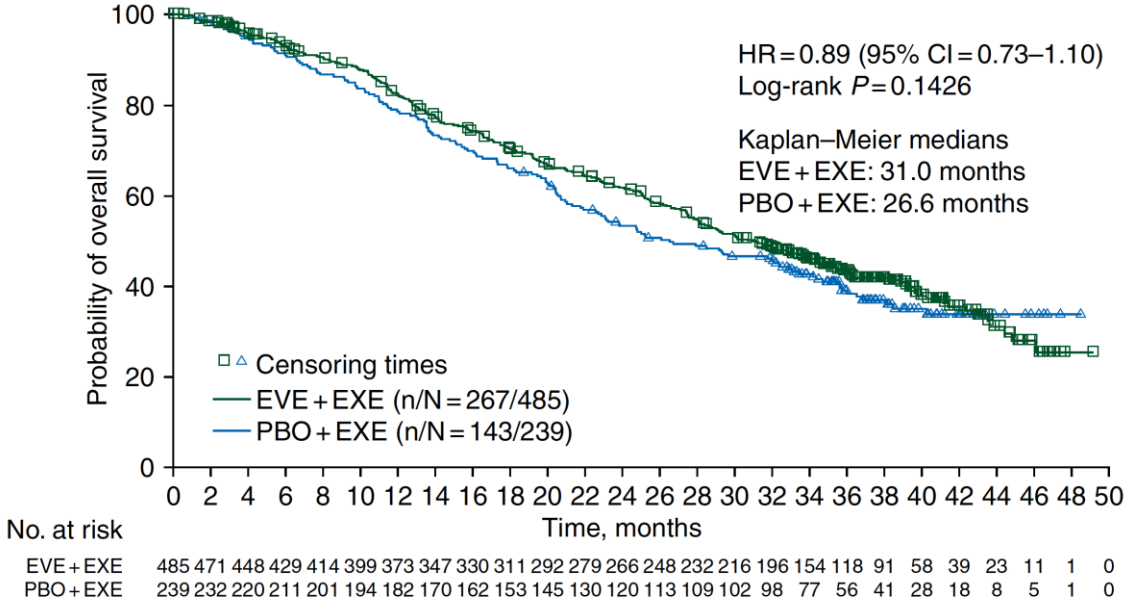
BOLERO-2:
Everolimus + Exemestan nach PD unter NSAIDs

PFS

(investigator = primary endpoint; final analsis)



OS



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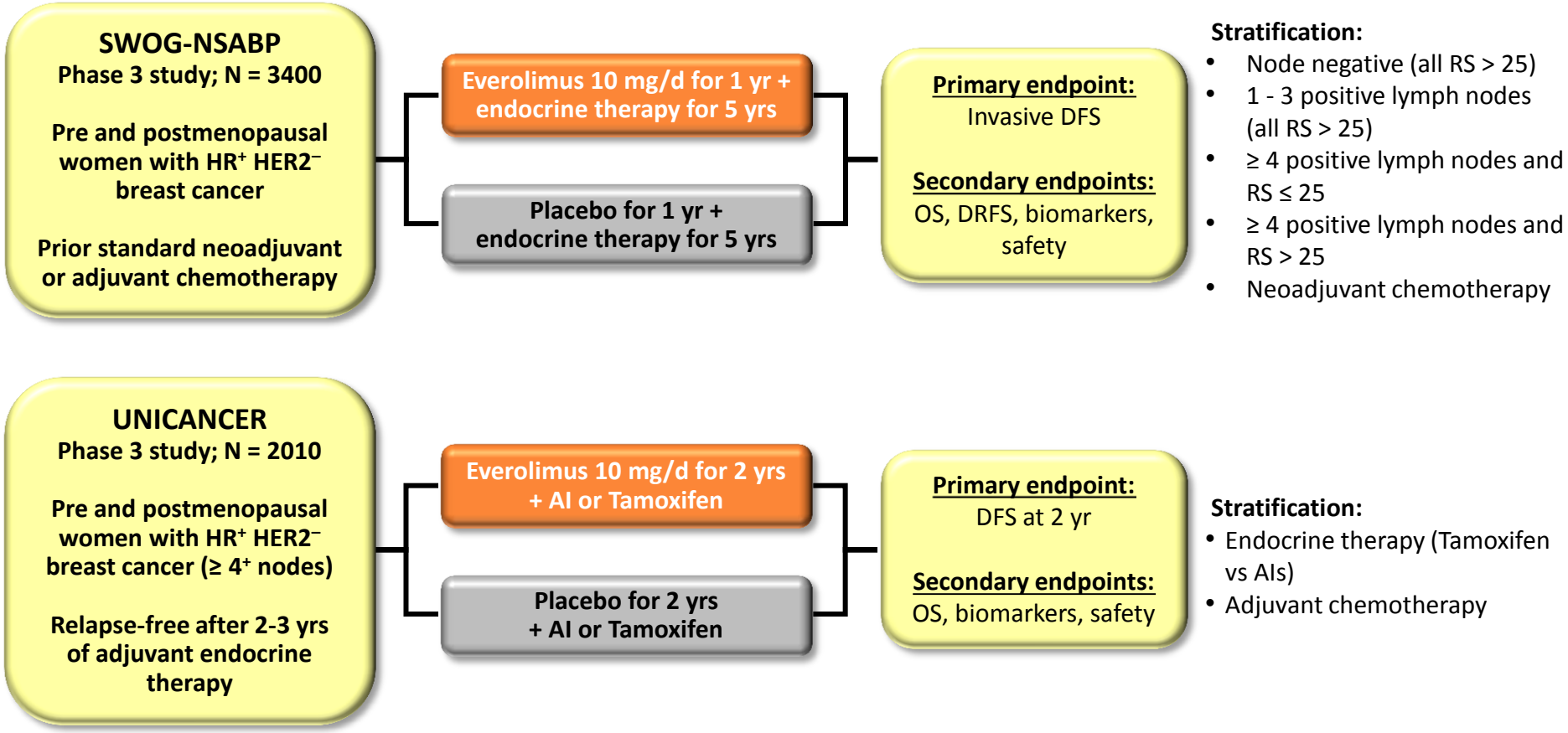
Yardley et al., Adv Ther. 2013 Oct;30(10):870-84
Piccart M et al., Ann Oncol. 2014 Dec;25(12):2357-62

Medizinische Fakultät Mannheim der Universität Heidelberg
Universitätsklinikum Mannheim

Everolimus in Breast Cancer: Expanding Into the Adjuvant High-Risk Setting



Abbreviations: AI, aromatase inhibitor; DFS, disease-free survival; DRFS, distant recurrence-free survival; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; SWOG-NSABP, Southwest Oncology Group-National Surgical Adjunct Breast and Bowel Project; OS, overall survival; vs, versus; yr, year.

ESMO VIRTUAL PLENARY

UNIRAD: A UCBG RANDOMIZED, DOUBLE BLIND, PHASE III INTERNATIONAL TRIAL EVALUATING THE ADDITION OF EVEROLIMUS TO ADJUVANT HORMONE THERAPY IN WOMEN WITH HIGH RISK HR+ AND HER2- PRIMARY BREAST CANCER

Thomas BACHELOT, Florence DALENC, Sylvie CHABAUD, Paul COTTU, Djelila ALLOUACHE, Etienne BRAIN, Jean-Philippe JACQUIN, Julien GRENIER, Laurence VENAT BOUVET, Murray BRUNT, Mario CAMPONE, Francesco DEL PIANO, Marc DEBLED, Anne-Claire HARDY BESSARD, Sylvie GIACCHETTI, Judith BLISS, Jean-Luc CANON, Jérôme LEMONNIER, David CAMERON, Fabrice ANDRE

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

UCBG

unicancer

UNIRAD : STUDY DESIGN

NCT018505271

ER+/HER2 neg early Breast cancer, High risk of relapse: any T and:

- ≥ 4N+
  or
- ≥ 1N+ after NAC/HT
  or
- ≥ 1N+ and EPclin score ≥ 3.3

Could have received up to 4 years of adjuvant HT

Stratification:

- Tamoxifen vs. AI
- Previous adj vs. neoadj CT/HT
- PR: positive vs. negative
- Duration of HT: ≤ 3 years vs >3 years
- ≥ 4 N+ and ≥ 1N+ after NAC/HT vs ≥ 1N+ and EPclin

R 1:1

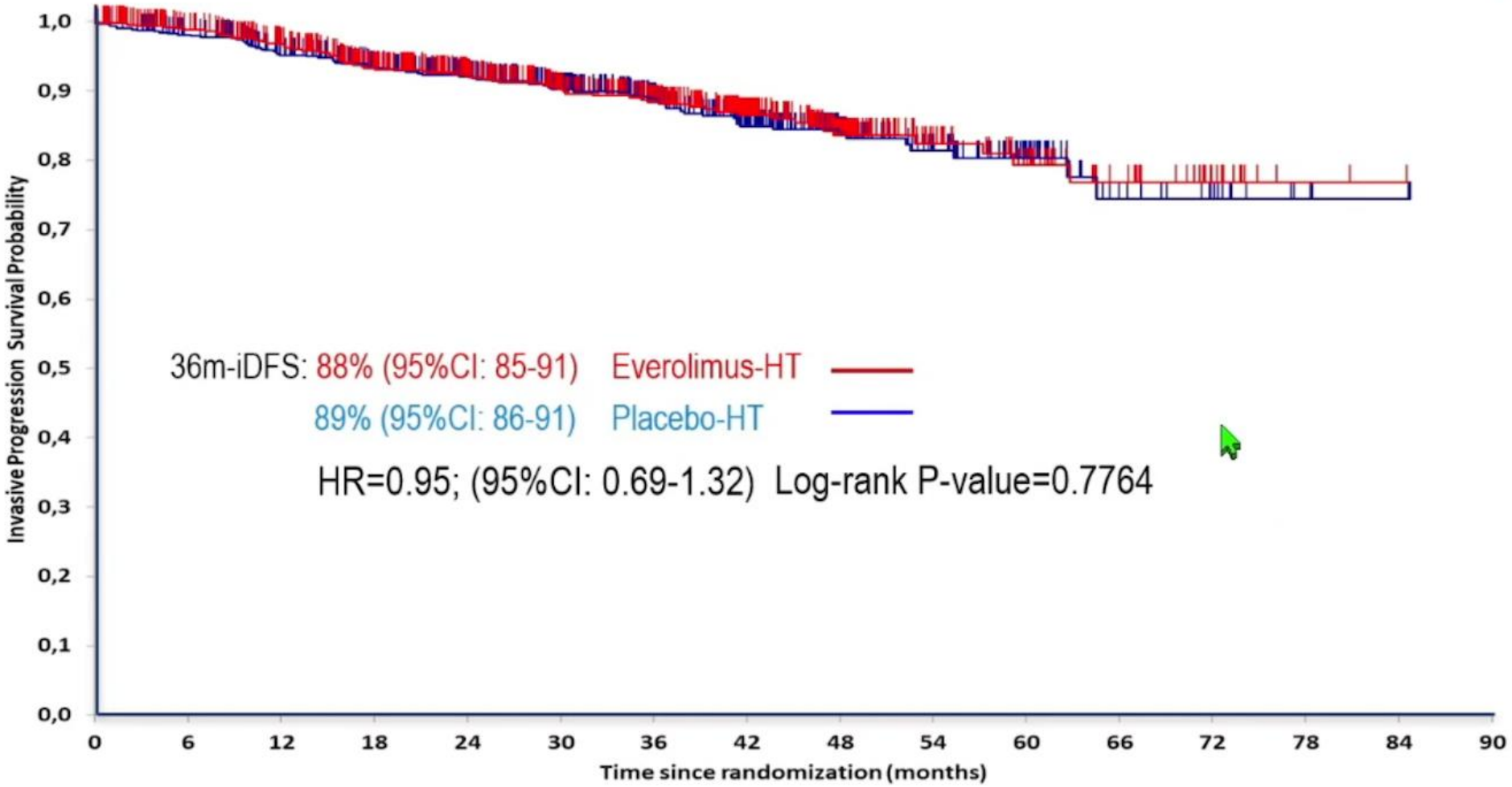
2 years everolimus and HT (E-HT Arm)

2 years placebo and HT (P-HT Arm)

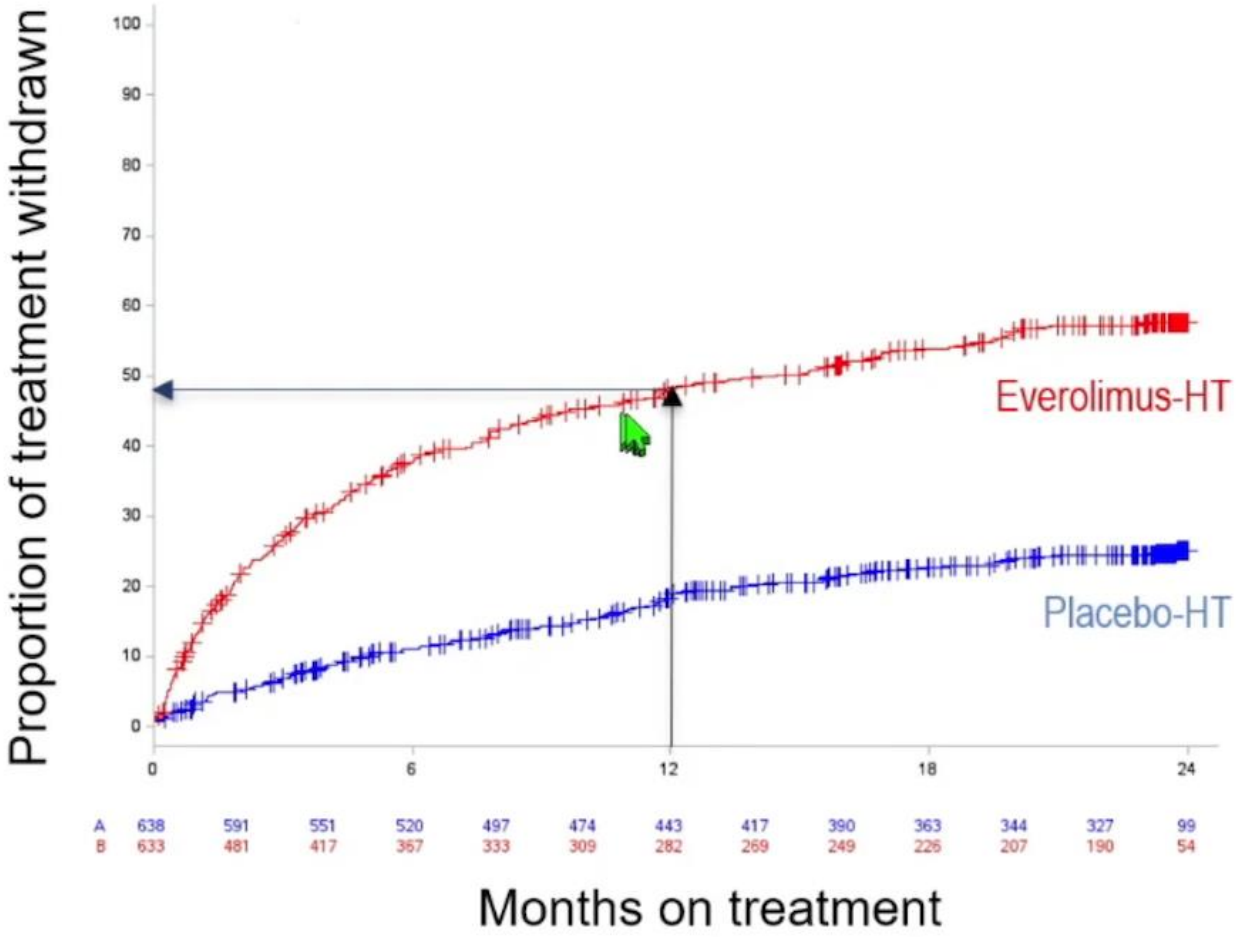
- End of HT
- Follow up

NAC : neoadjuvant chemotherapy; HT: Hormone therapy; CT: Chemotherapy

Primary end-point: iDFS



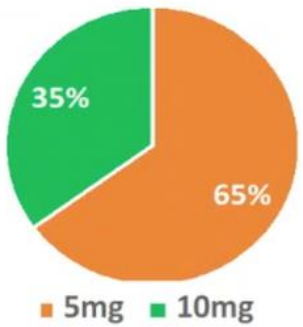
EXPERIMENTAL TREATMENT: DRUG DISCONTINUATION



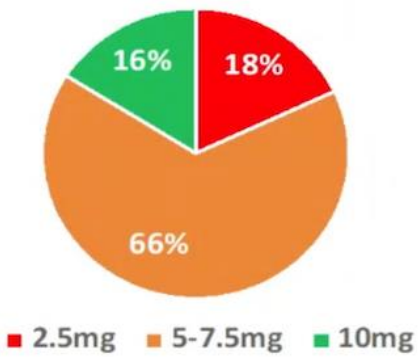
Characteristics	Placebo-HT arm (n=641)	Everolimus-HT arm (n=637)
All patients Median Treatment duration (Q1-Q3)	**22.5 (9.7 – 23.9)**	**9.2 (2.1-23.4)**
Patients stopping early (n, %)	**143/641 (22.3%)**	**340/637 (53.4%)**
Reason to stop		
Adverse Event	64 (10.0%)	225 (35.3%)
Withdrawal by subject	46 (7.2%)	97 (15.2%)
Disease recurrence	33 (5.1%)	18 (2.8%)

UNIRAD: Low dose and dose intensity of Everolimus

Start dose of EVE

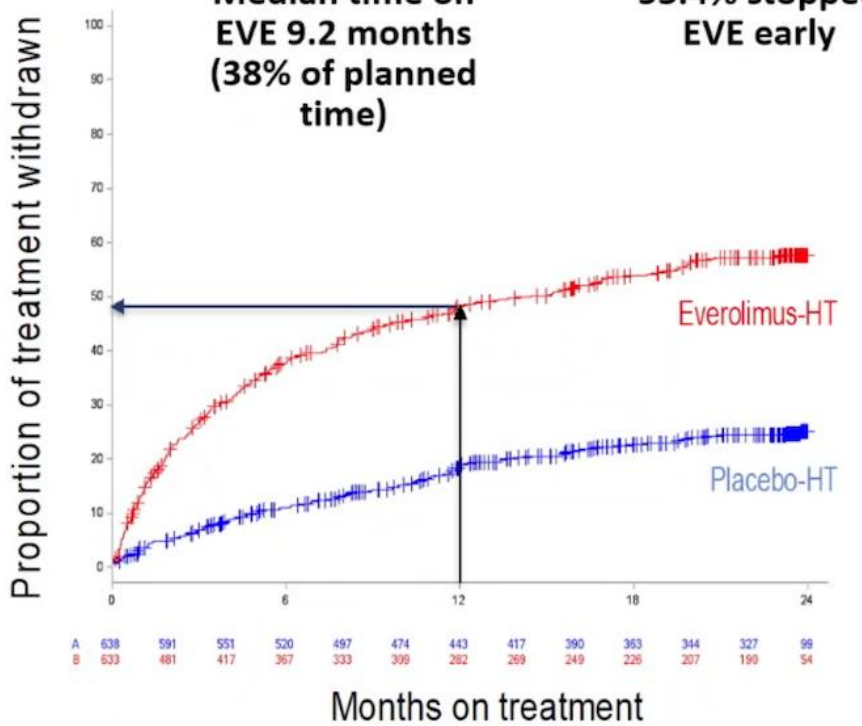


End dose of EVE



Median time on EVE 9.2 months (38% of planned time)

53.4% stopped EVE early



MBC Trials

Bolero2- EVE 10mg:
86%
dose intensity

Adjuvant Trials

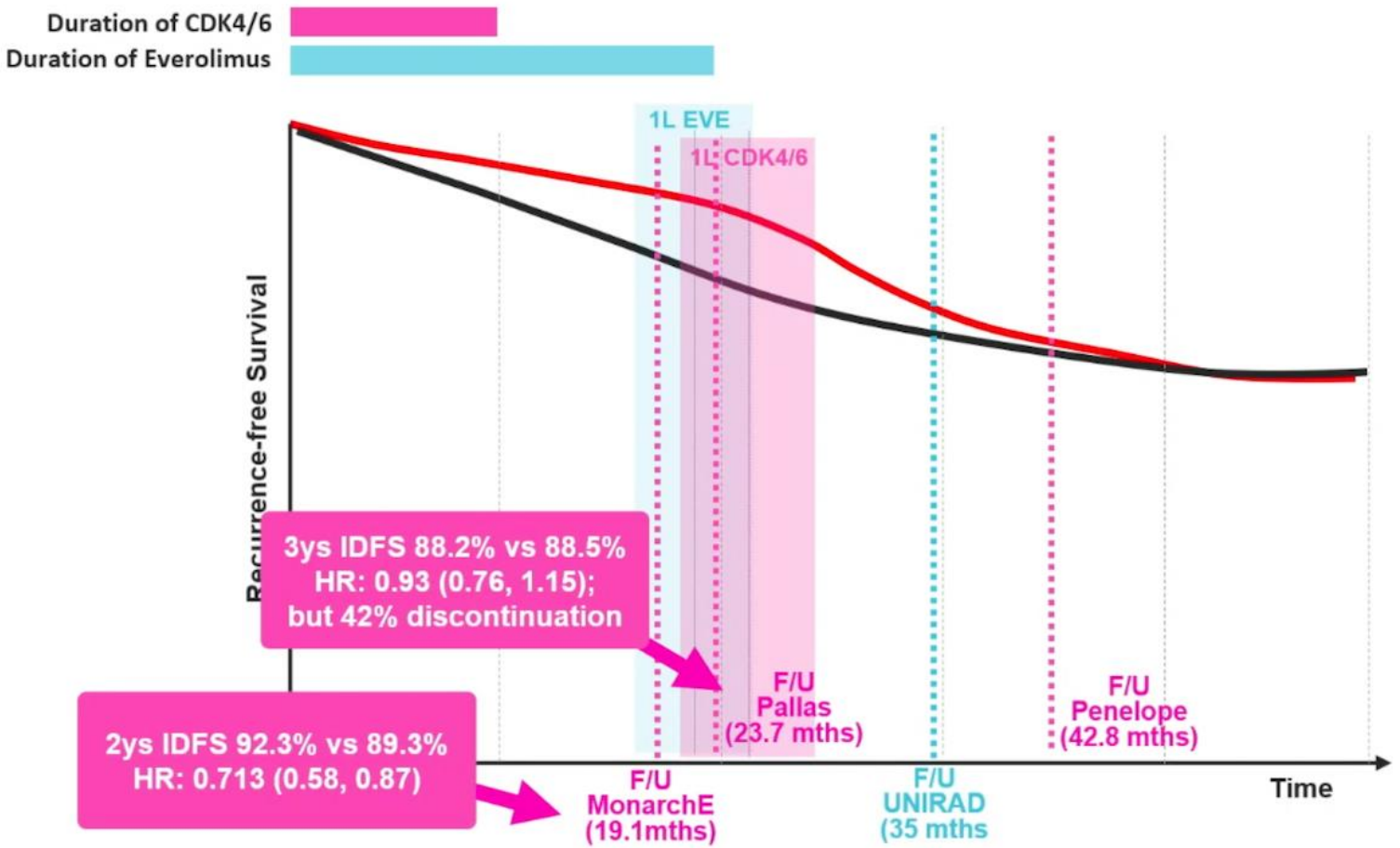
UNIRAD Everolimus
53%
Discontinuation

MonarchE Abemaciclib
27%
Discontinuation

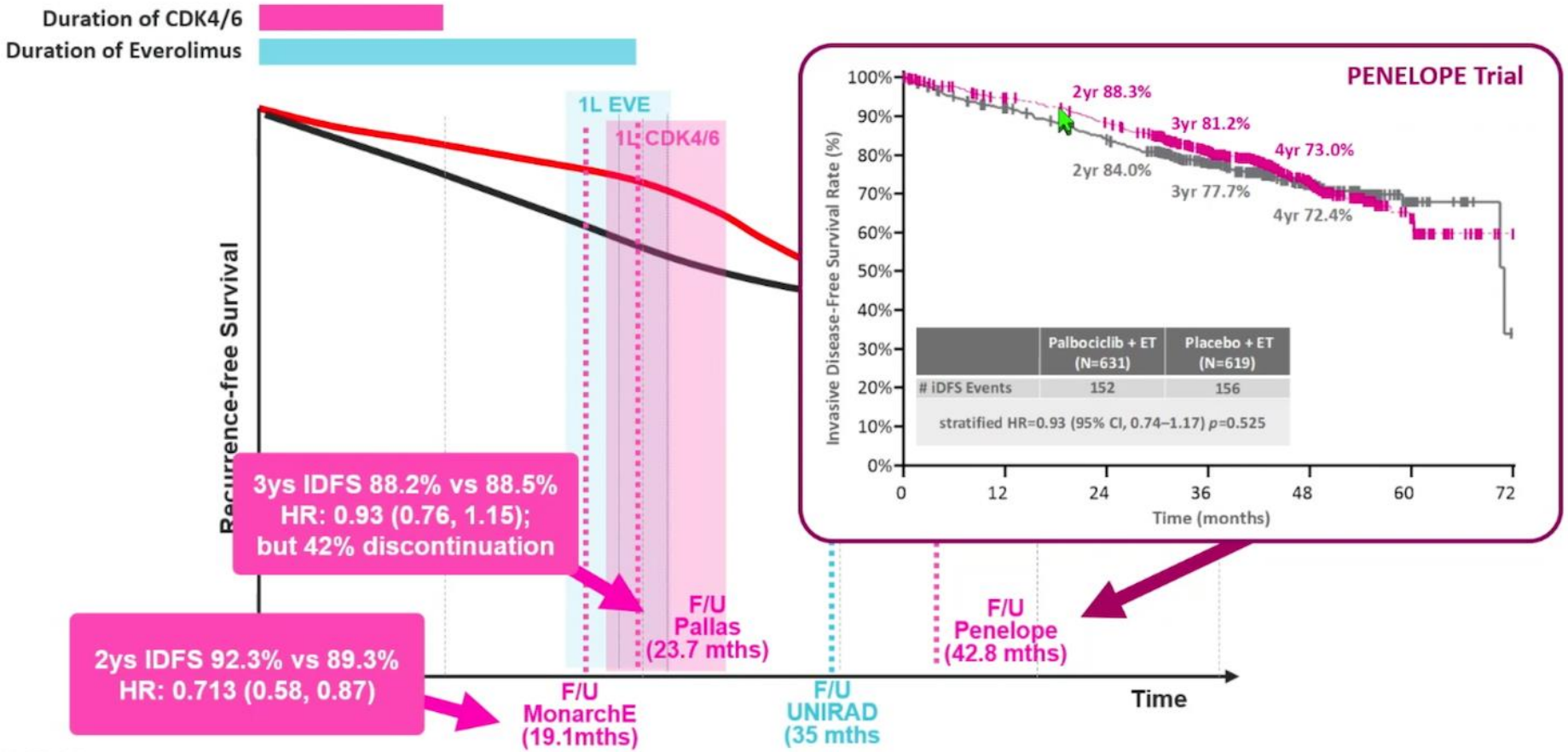
Pallas Palbociclib
42%
Discontinuation

Penolope Palbociclib
19%
Discontinuation

ET plus targeted therapy in high-risk HR+/HER2- EBC



ET plus targeted therapy in high-risk HR+/HER2- EBC



FAZIT – UNIRAD

- UNIRAD Studie im Kontext mit PALLAS, PENELOPE B und MonarchE
  - Siehe Vortrag Prof. Loibl
- geringe Therapieadhärenz und Dosisintensität
  - Vgl. PALLAS (Everolimus vermeintlich schlechter verträglich)
- Endokrin-basierte Therapien adjuvant:
  - Zytostatisch vs zytotoxisch?
- Dauer des FU entscheidend?
- Bislang nur Penelope-Studie mit ausreichendem FU!

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MANNHEIM

Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

Herzlichen Dank für die Aufmerksamkeit!

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