DGHO-Webinare 2024
Mammakarzinom

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Immanuel Klinik Märkische Schweiz
Immanuel Campus Rüdersdorf/Med. Hochschule Brandenburg Theodor Fontane

Offenlegung potentieller Interessenkonflikte

1. **Employment or Leadership Position: Keine.**
2. **Advisory Role or Expert Testimony: Amgen, AstraZeneca, BMS, Daiichi Sankyo, GSK, high5md, Loreal, MSD, Novartis, onkowissen.de, Pfizer, Roche, Seagen, TEVA**
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4. **Patent, Copyright, Licensing: Keine.**
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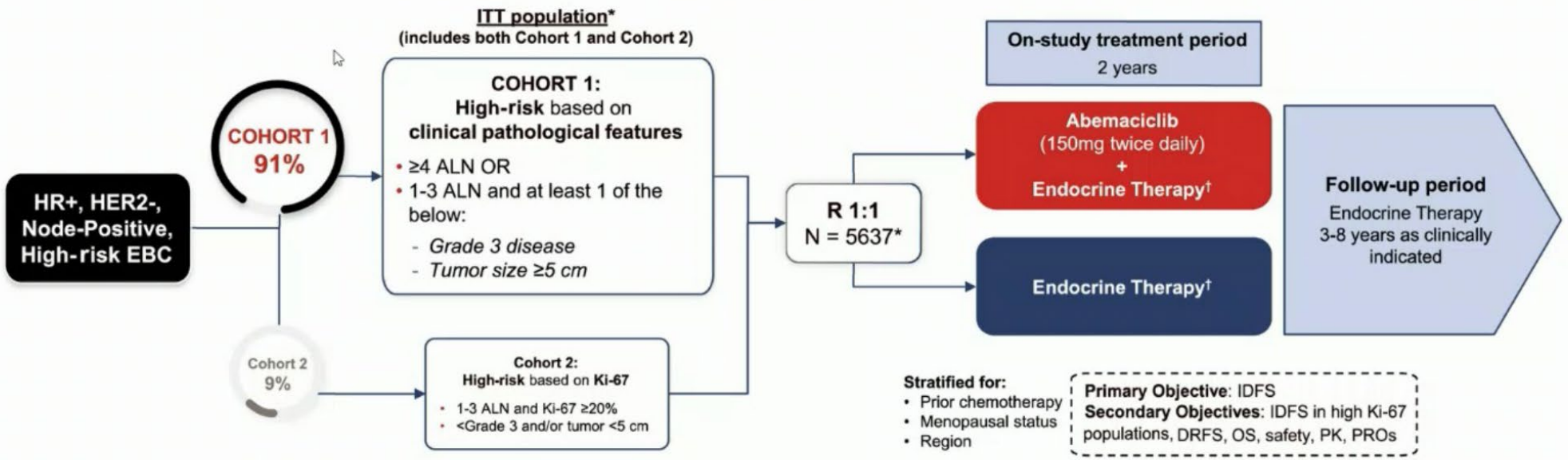
6. **Financing of Scientific Research: Amgen, Novartis**
7. **Other Financial Relationships: high1/5md**
8. **Immaterial Conflicts of Interest: Keine.**

Frühes Mammakarzinom

Frühes Mammakarzinom HR+

Adjuvante Therapie mit Abemaciclib bei high risk
Update der MonarchE-Studie

monarchE Study Design (NCT03155997)



*Recruitment from July 2017 to August 2019.
†Endocrine therapy of physician's choice [e.g., aromatase inhibitors, tamoxifen, GnRH agonist].

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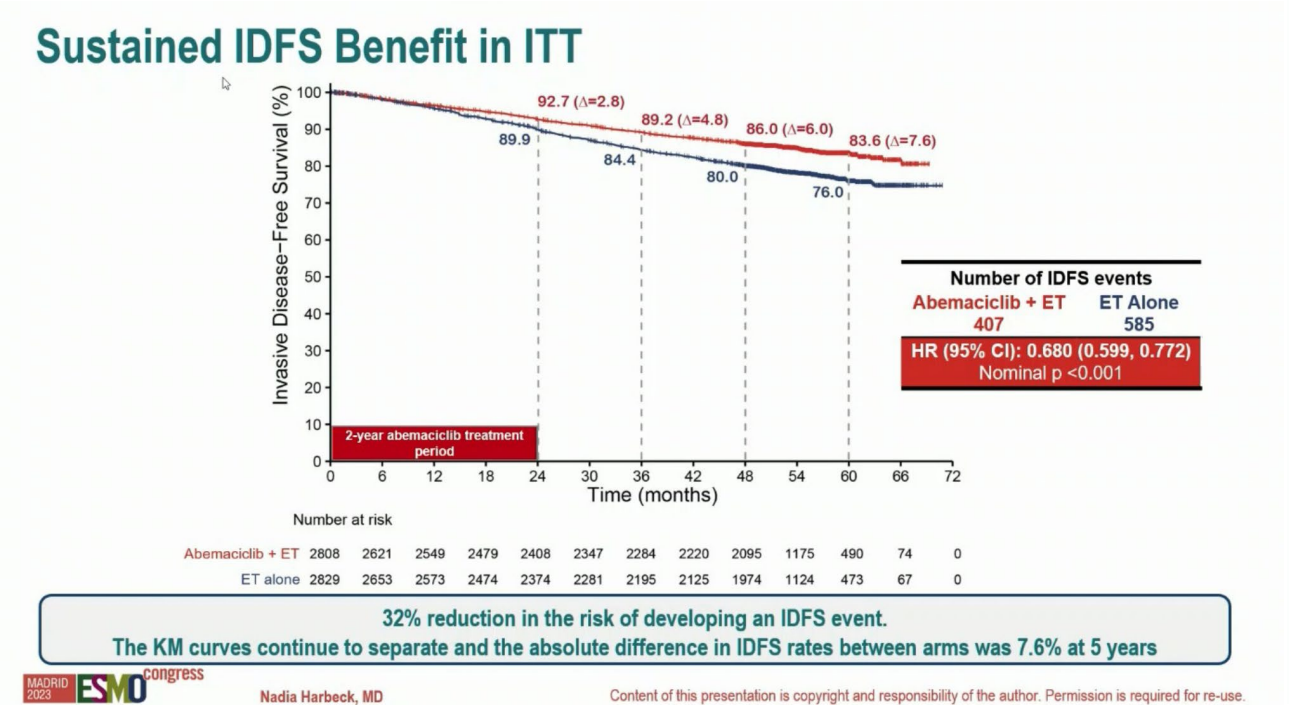
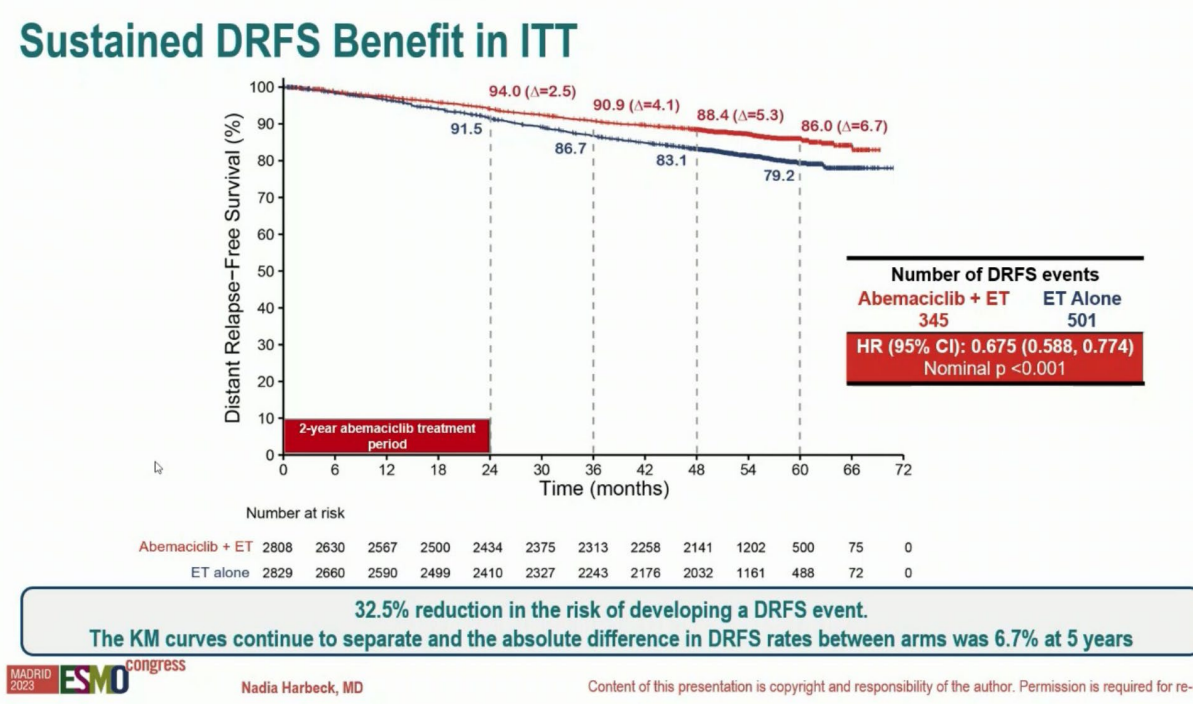
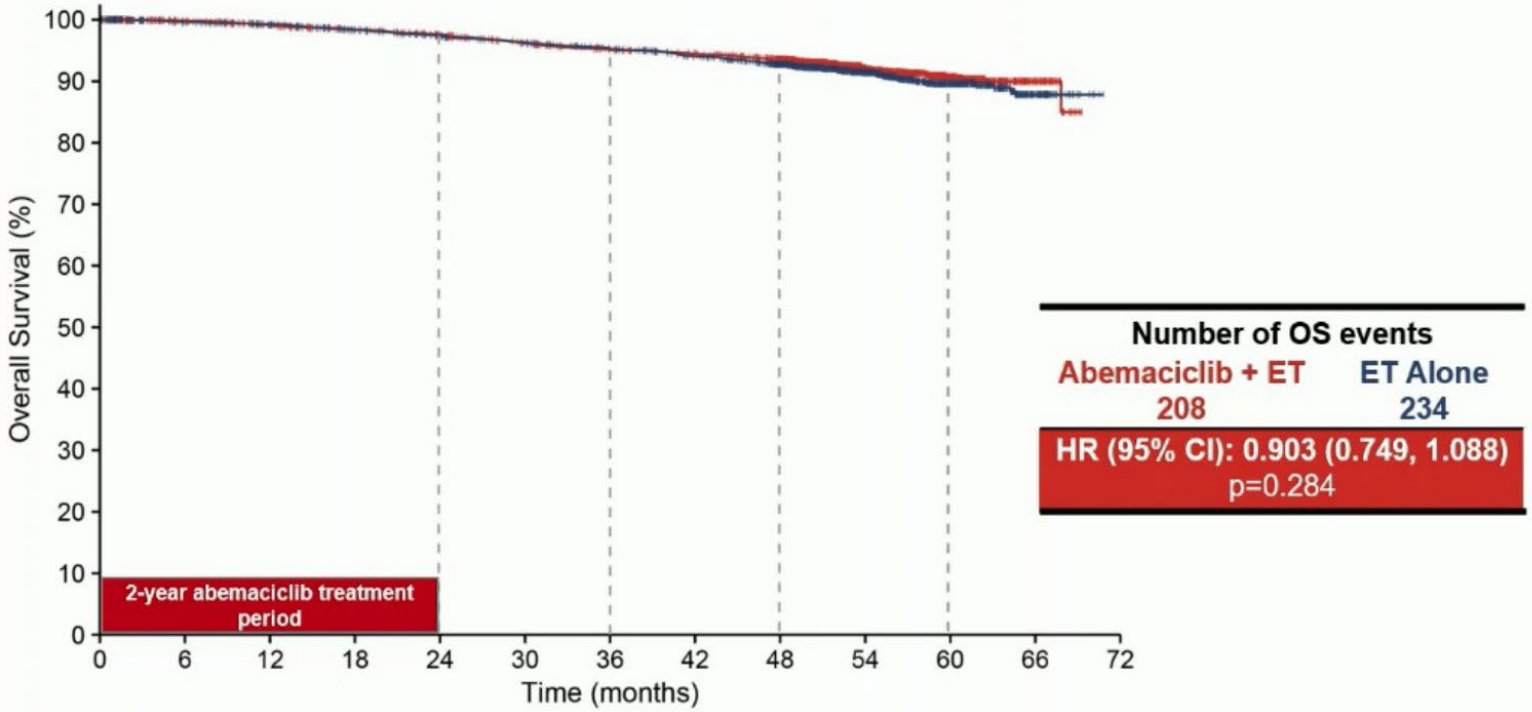
Adjuvante Therapie mit Abemaciclib bei high risk
Update der MonarchE-Studie





Adjuvante Therapie mit Abemaciclib bei high risk
Update der MonarchE-Studie

Fewer deaths in the Abemaciclib Arm in ITT



Number at risk

Abemaciclib + ET	2808	2666	2614	2566	2518	2455	2407	2373	2260	1271	528	80	0
ET alone	2829	2705	2664	2599	2545	2496	2440	2382	2243	1279	538	77	0

At OS IA3 statistical significance was not reached for OS

Nadia Harbeck, MD

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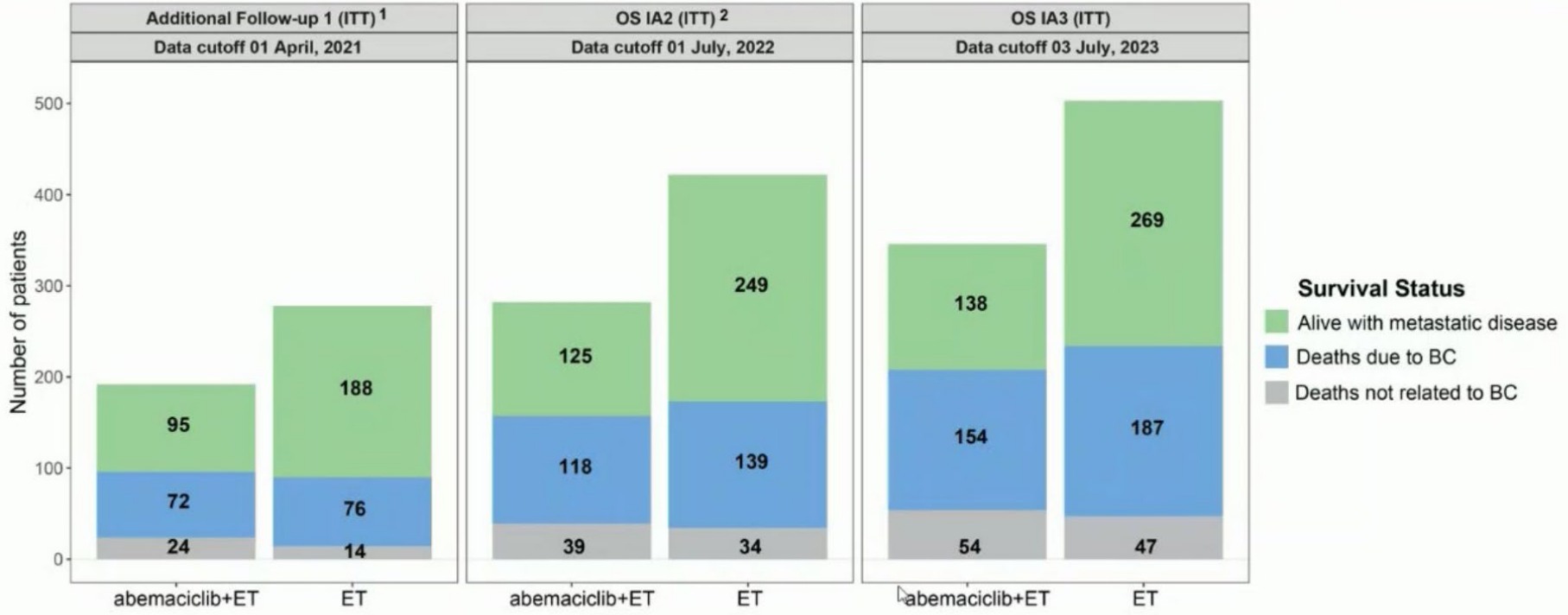
Adjuvante Therapie mit Abemaciclib bei high risk
Update der MonarchE-Studie

Fewer Patients with Metastatic Disease in the Abemaciclib Arm



The imbalance of incurable metastatic recurrence continues to be substantial at OS IA3

[1]Harbeck* N, Rastogi* P, et al. Ann Oncol. 2021;32(12):1571-1581 *co-first authors
[2]Johnston SRD, et al. Lancet Oncol. 2023;24:77-90

MADRID 2023 ESMO congress

Nadia Harbeck, MD

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Adjuvante Therapie mit Ribociclib
Update der NATALEE-Studie

Haupteinschlusskriterien

- Erwachsene Patient:innen mit HR+/HER2− EBC
- Vorherige ET bis zu 12 Monate erlaubt
- Anatomisches Stadium IIA*
  - N0 mit:
    - Grad 2 und Nachweis für hohes Risiko:
      - Ki67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26 oder
      - Hohes Risiko nach genomischem Risikoprofiling
    - Grad 3
  - N1
- Anatomisches Stadium IIB*: N0 oder N1
- Anatomisches Stadium III: N0, N1, N2 oder N3

N=5.101**

R 1:1***

Ribociclib
400 mg/Tag, 3 Wochen mit Ribociclib,
1 Woche Pause, über 3 Jahre
+
NSAI
Letrozol oder Anastrozol# für ≥5 Jahre
+ Goserelin bei Männern/prämenopausalen Frauen

NSAI
Letrozol oder Anastrozol für ≥5 Jahre
+ Goserelin bei Männern/prämenopausalen Frauen

Primärer Endpunkt

- iDFS nach STEEP-Kriterien

Sekundäre Endpunkte

- RFS
- dDFS
- OS
- PROs
- Sicherheit und Verträglichkeit
- Pharmakokinetik

Explorative Endpunkte

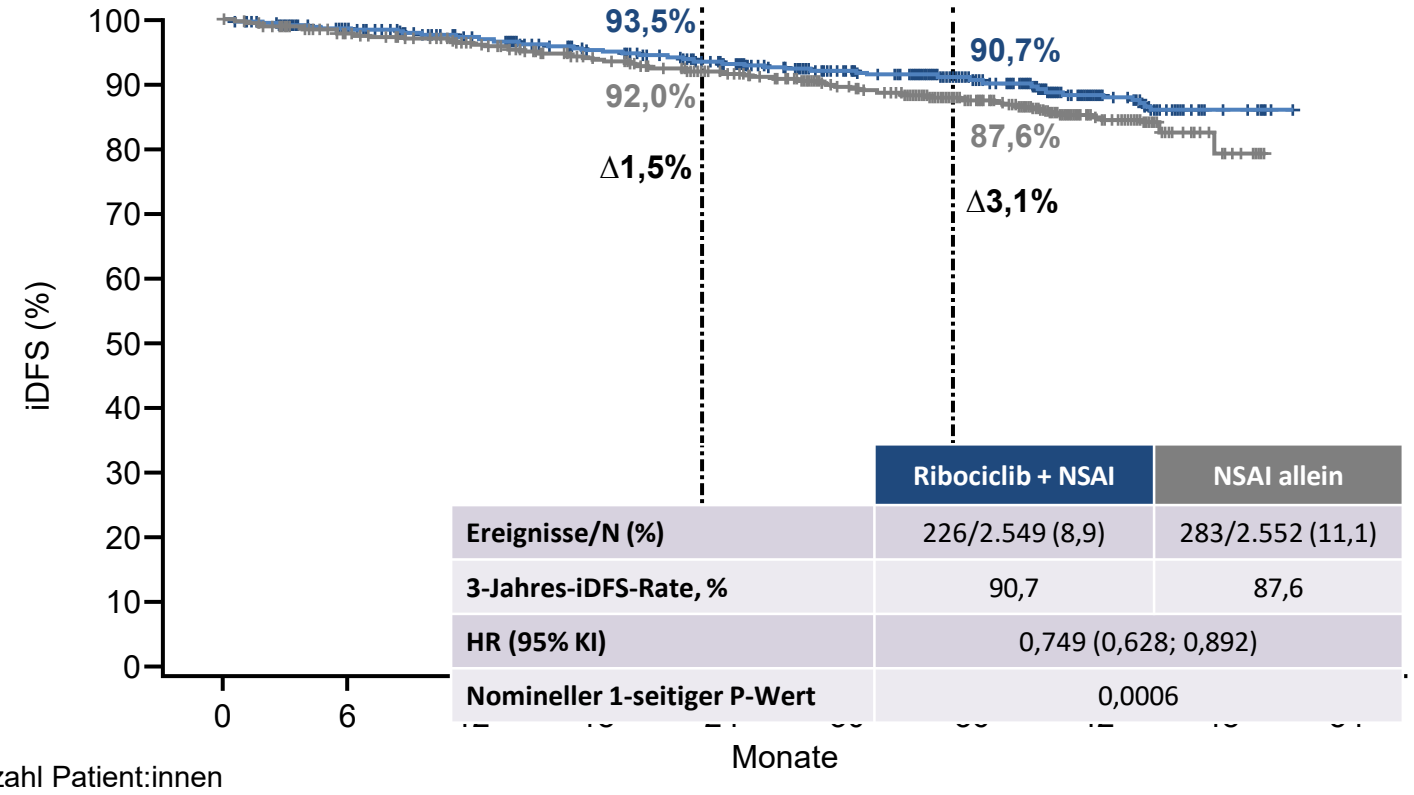
- Lokoregionales RFS
- Genexpression und Veränderungen der Tumor-ctDNA/ctRNA-Proben

Stratifizierungsfaktoren

- Anatomisches Stadium: II vs III
- Menopausenstatus: Männer und prämenopausale Frauen vs postmenopausale Frauen
- Vorherige (neo)adjuvante Chemotherapie: Ja vs Nein
- Geographische Lage: Nordamerika/Westeuropa/Ozeanien vs übrige Welt

Hortobagyi et al. | 2023 SABCS | GS03-03

Adjuvante Therapie mit Ribociclib
Update der NATALEE-Studie: iDFS



	Ribociclib + NSAI	NSAI allein
Ereignisse/N (%)	226/2.549 (8,9)	283/2.552 (11,1)
3-Jahres-iDFS-Rate, %	90,7	87,6
HR (95% KI)	0,749 (0,628; 0,892)	
Nomineller 1-seitiger P-Wert	0,0006	

Anzahl Patient:innen

Ribociclib + NSAI	2549	2350	2273	2204	2100	1694	1111	368	21	0
NSAI allein	2552	2241	2169	2080	1975	1597	1067	354	26	0

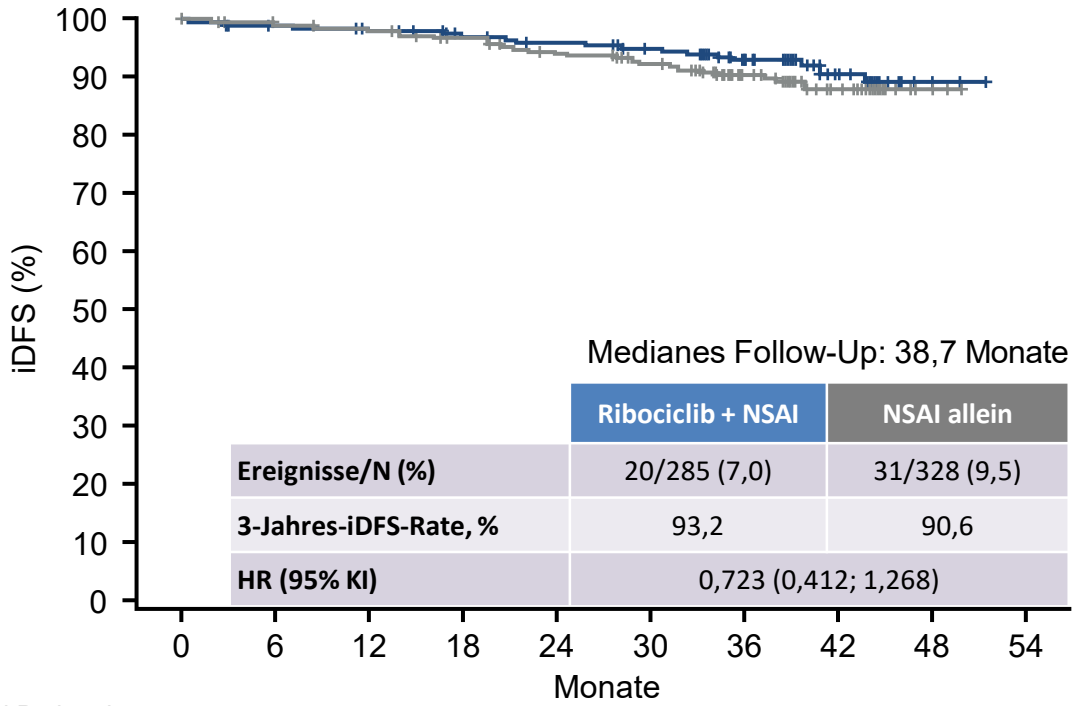
- Das mediane Follow-Up für iDFS betrug 33,3 Monate (maximal 51 Monate) - zusätzliche 5,6 Monate gegenüber der zweiten Interimsanalyse zur Wirksamkeit[1]
- Der absolute iDFS-Vorteil von Ribociclib plus NSAI betrug 3,1% nach 3 Jahren
- Das Risiko einer invasiven Erkrankung wurde mit Ribociclib plus NSAI im Vergleich zu NSAI allein um 25,1% gesenkt

Hortobagyi et al. | 2023 SABCS | GS03-03

Adjuvante Therapie mit Ribociclib

Update der NATALEE-Studie: iDFS nach Nodalstatus

N0

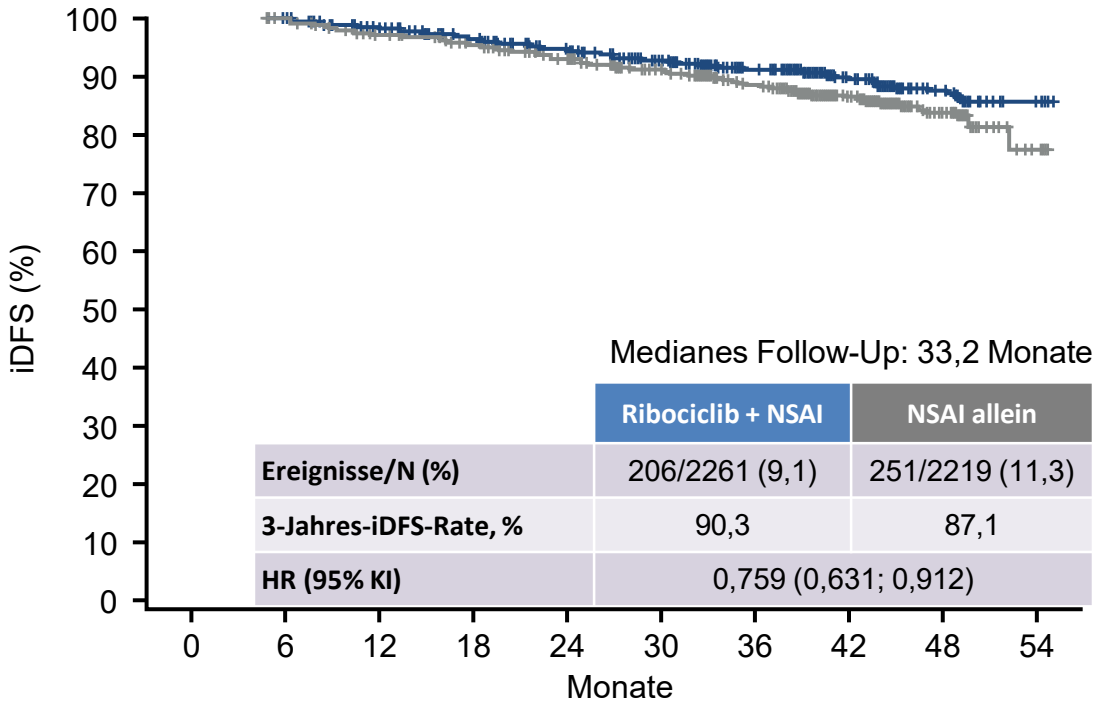


Medianes Follow-Up: 38,7 Monate

	Ribociclib + NSAI	NSAI allein
Ereignisse/N (%)	20/285 (7,0)	31/328 (9,5)
3-Jahres-iDFS-Rate, %	93,2	90,6
HR (95% KI)	0,723 (0,412; 1,268)	

Anzahl Patient:innen										
Ribociclib + NSAI	285	262	258	250	244	235	177	67	5	0
NSAI allein	328	300	294	287	276	258	188	80	5	0

N1-N3



Medianes Follow-Up: 33,2 Monate

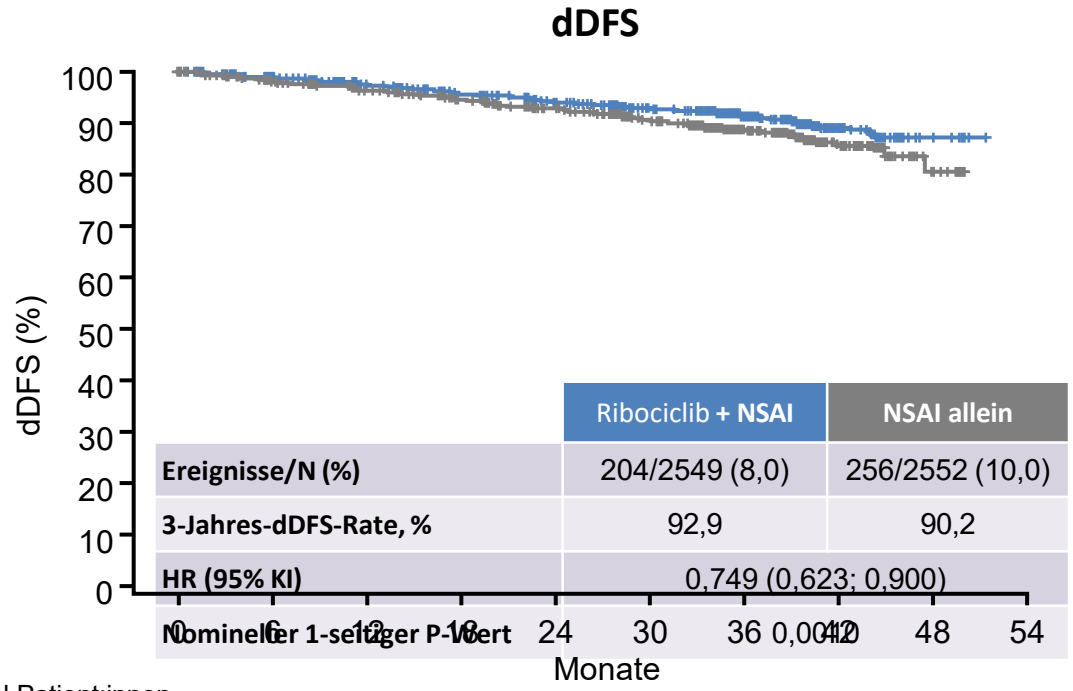
	Ribociclib + NSAI	NSAI allein
Ereignisse/N (%)	206/2261 (9,1)	251/2219 (11,3)
3-Jahres-iDFS-Rate, %	90,3	87,1
HR (95% KI)	0,759 (0,631; 0,912)	

Anzahl Patient:innen										
Ribociclib + NSAI	2261	2085	2012	1951	1853	1458	934	301	16	0
NSAI allein	2219	1938	1873	1791	1697	1337	877	273	21	0

Hortobagyi et al. | 2023 SABCS | GS03-03

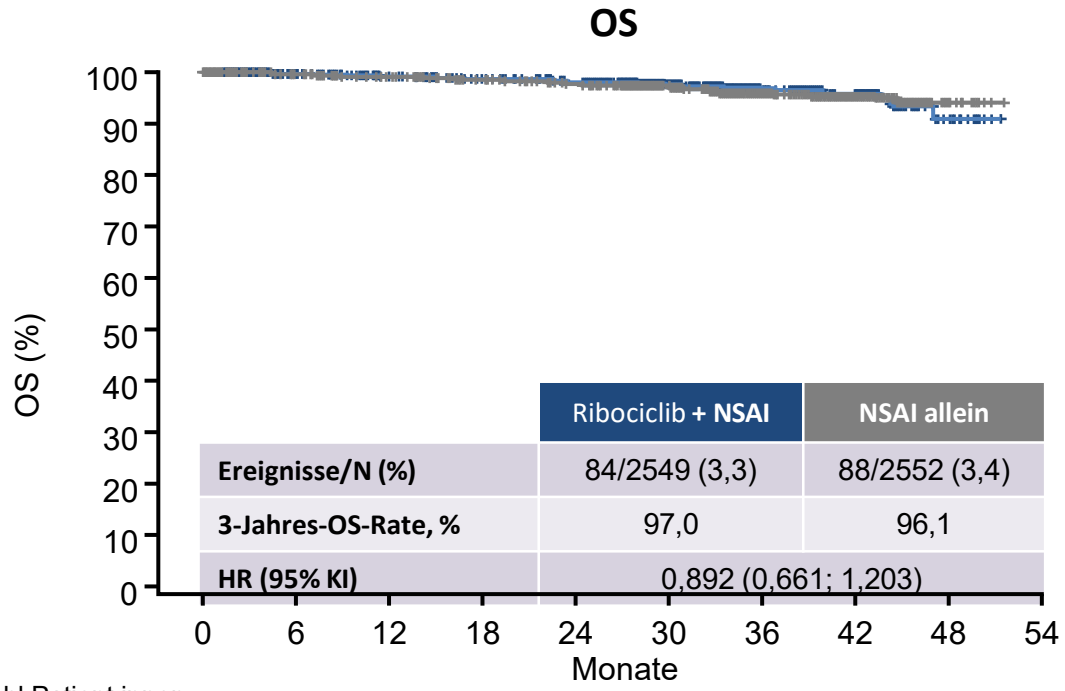
Adjuvante Therapie mit Ribociclib

Update der NATALEE-Studie: dDFS und OS



	Ribociclib + NSAI	NSAI allein
Ereignisse/N (%)	204/2549 (8,0)	256/2552 (10,0)
3-Jahres-dDFS-Rate, %	92,9	90,2
HR (95% KI)	0,749 (0,623; 0,900)	
Nomineller 1-seitiger P-Wert	0,0012	

Anzahl Patient:innen										
Ribociclib + NSAI	2549	2352	2280	2212	2113	1704	1119	369	21	0
NSAI allein	2552	2245	2171	2091	1990	1609	1080	356	26	0



	Ribociclib + NSAI	NSAI allein
Ereignisse/N (%)	84/2549 (3,3)	88/2552 (3,4)
3-Jahres-OS-Rate, %	97,0	96,1
HR (95% KI)	0,892 (0,661; 1,203)	

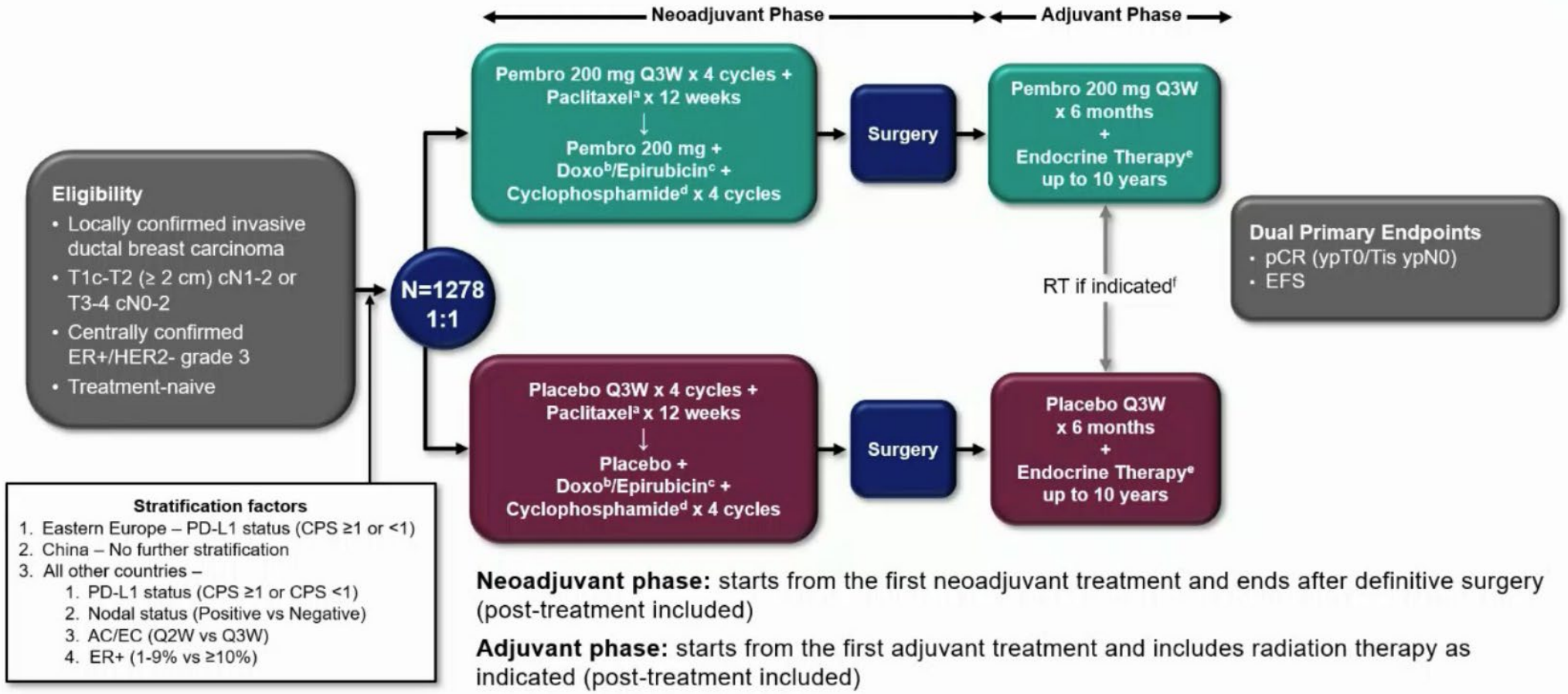
Anzahl Patient:innen										
Ribociclib + NSAI	2549	2405	2337	2305	2259	1902	1259	455	24	0
NSAI allein	2552	2302	2256	2209	2158	1815	1207	444	31	0

Hortobagyi et al. | 2023 SABCS | GS03-03

IO plus Chemotherapie auch bei HR+ high risk

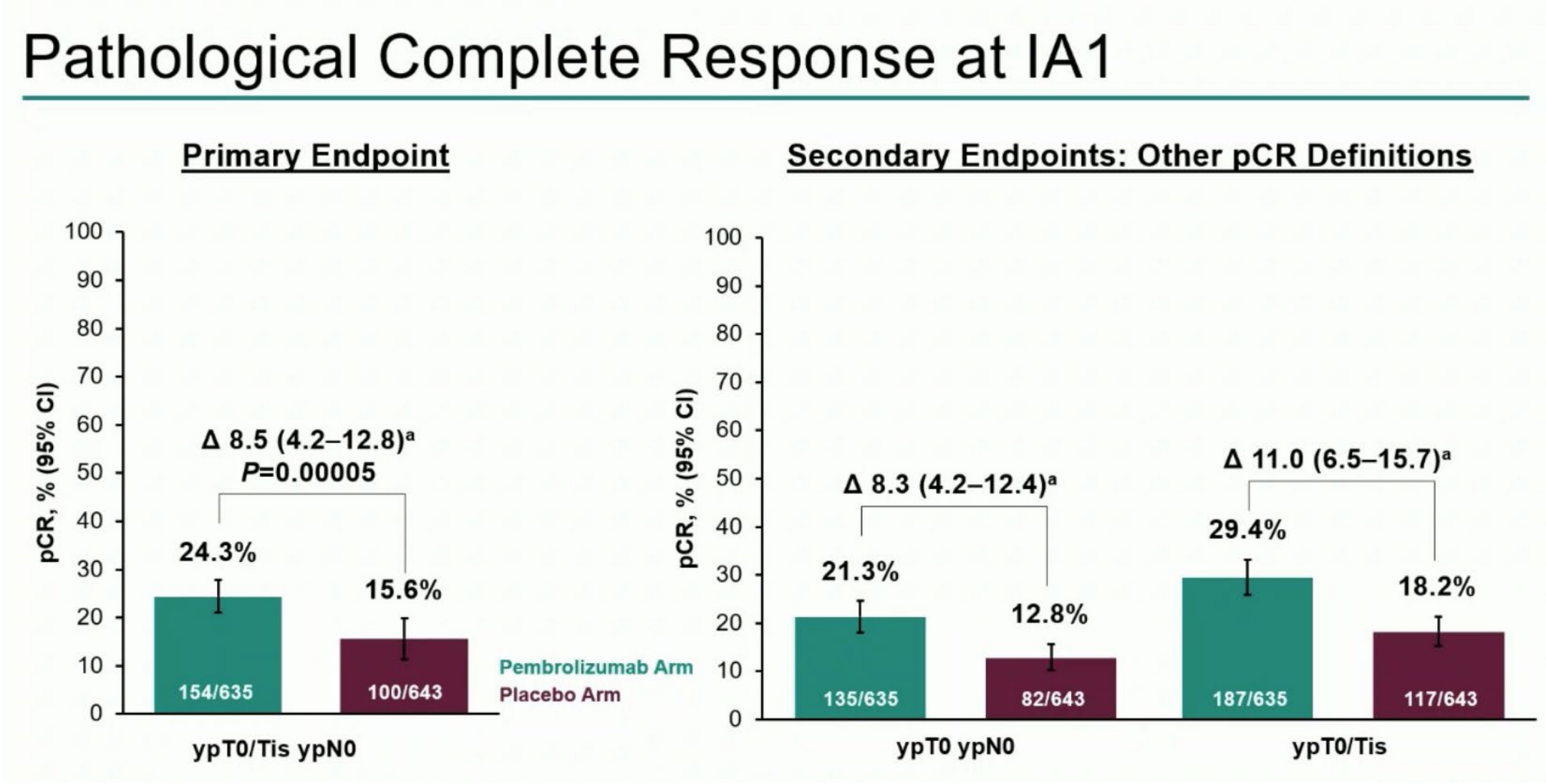
Erste Daten aus KEYNOTE-756

KEYNOTE-756 Study Design (NCT03725059)



IO plus Chemotherapie auch bei HR+ high risk

Erste Daten aus KEYNOTE-756

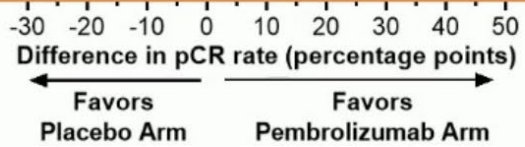


IO plus Chemotherapie auch bei HR+ high risk

Erste Daten aus KEYNOTE-756

Pathological Complete Response (ypT0/Tis ypN0) in Subgroups

Subgroup	No. with pCR/No. of Participants (%) Pembrolizumab Arm	Placebo Arm	pCR Rate Difference (95% CI)
Overall	154/635 (24.3)	100/643 (15.6)	8.5 (4.2 to 12.8)
Age category			
<65 years	135/546 (24.7)	89/567 (15.7)	9.0 (4.3 to 13.8)
≥65 years	19/89 (21.3)	11/76 (14.5)	6.9 (–5.2 to 18.6)
ECOG PS			
0	142/570 (24.9)	91/588 (15.5)	9.4 (4.8 to 14.1)
1	12/65 (18.5)	9/55 (16.4)	2.1 (–12.2 to 15.8)
PD-L1 status			
Positive (CPS ≥1)	143/482 (29.7)	96/489 (19.6)	9.8 (4.4 to 15.2)
Negative (CPS <1)	11/153 (7.2)	4/154 (2.6)	4.5 (–0.4 to 10.1)
Anthracycline schedule			
Every 3 weeks	97/415 (23.4)	55/425 (12.9)	10.4 (5.3 to 15.7)
Every 2 weeks	54/183 (29.5)	44/187 (23.5)	6.0 (–3.0 to 15.0)
Tumor size			
T1/T2	111/402 (27.6)	71/413 (17.2)	10.4 (4.7 to 16.1)
T3/T4	43/233 (18.5)	29/230 (12.6)	5.8 (–0.8 to 12.5)
Nodal status			
Positive	143/570 (25.1)	92/582 (15.8)	9.3 (4.6 to 13.9)
Negative	11/65 (16.9)	8/61 (13.1)	3.8 (–9.2 to 16.7)
ER positivity			
≥10%	135/601 (22.5)	87/600 (14.5)	8.0 (3.6 to 12.4)
<10%	19/34 (55.9)	13/43 (30.2)	25.6 (3.3 to 45.8)



IO plus Chemotherapie auch bei HR+ high risk

Daten aus der abgebrochenen CheckMate-7FL-Studie

CA209-7FL study design

Screening

Key inclusion criteria

- Newly diagnosed ER+ HER2− breast cancer
- Confirmed ER+ breast cancer
- T1c-T2, cN1-cN2 or T3-T4, cN0-cN2
- Grade 3 with ER ≥ 1% or grade 2 with ER 1-10%[a]
- Adequate organ function
- Tissue available for biomarker assessment
- ECOG PS 0-1

Stratification factors

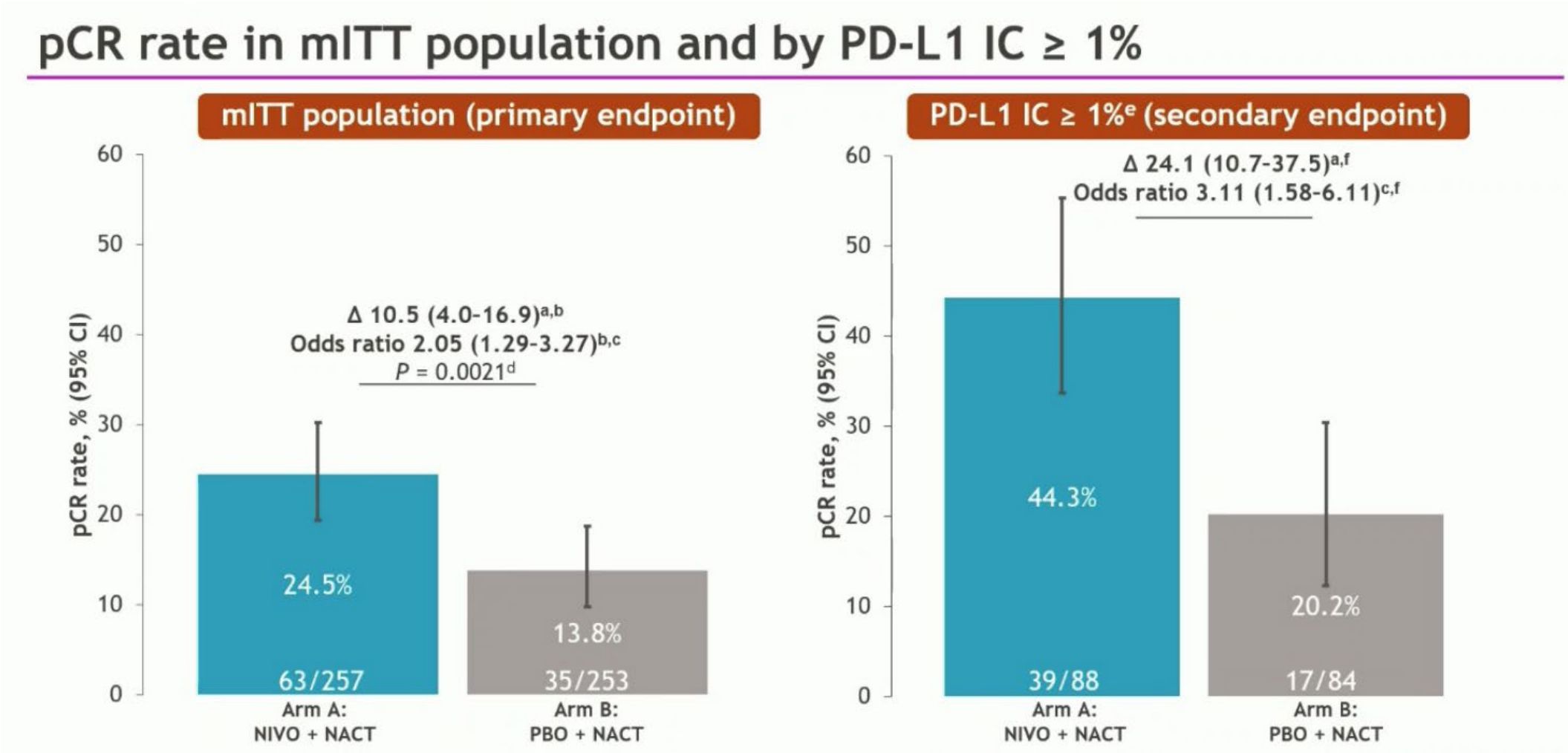
- PD-L1 IC (≥ 1% or < 1%)
- Tumor grade (3 or 2)
- Axillary nodal status (positive or negative)
- AC frequency (Q3W or Q2W)

Randomization 1:1

	Neoadjuvant phase (double blind)		Surgery	Adjuvant phase[c]	Follow-up
	PTX cycles 1-4 1 cycle = 3 wks	AC cycles 1-4 1 cycle = 2 or 3 wks[b]		Adjuvant cycles 1-7 1 cycle = 4 wks	
Arm A	NIVO 360 mg Q3W + PTX QW	NIVO 360 mg Q3W + AC Q3W or NIVO 240 mg Q2W + AC Q2W	Surgery	NIVO 480 mg Q4W + investigator's choice ET[d]	Safety follow-up 30 days 100 days Long-term follow-up (12 months post-surgery)
Arm B	NIVO PBO Q3W + PTX QW	NIVO PBO Q3W + AC Q3W or NIVO PBO Q2W + AC Q2W	Surgery	NIVO PBO + investigator's choice ET[d]	

IO plus Chemotherapie auch bei HR+ high risk

Daten aus der abgebrochenen CheckMate-7FL-Studie



Adjuvante endokrin-basierte Therapie in der Prämenopause

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Guidelines Breast
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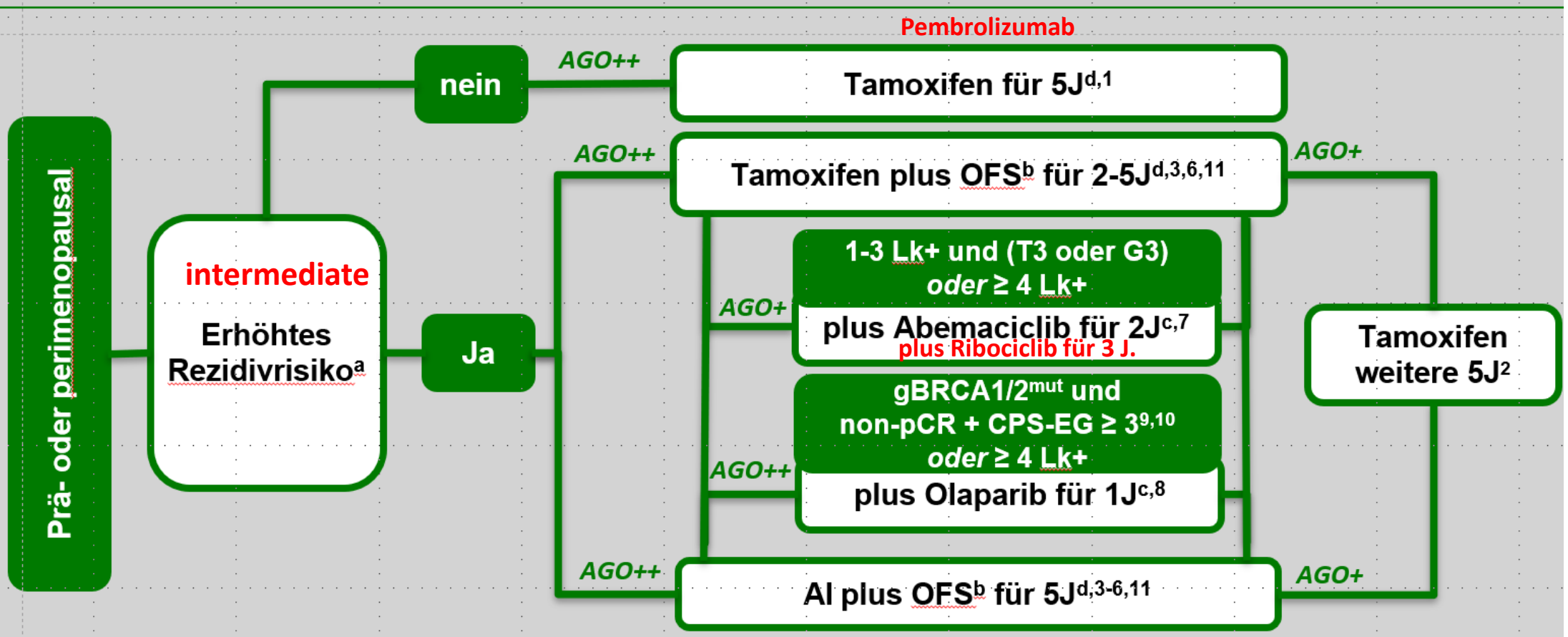

AI, Aromataseinhibitor; CPS-EG, Clinical-Pathological Stage + Estrogen receptor status and Grade Score; gBRCA[mut], Keimbahn BRCA1/2 Mutation; J, Jahre; Lk, Lymphknoten; OFS, ovarian function suppression; pCR, pathologische Komplettremission; [a]Die Applikation einer Chemotherapie war in den Studien ein Surrogatmarker für ein höheres Rezidivrisiko; [b]OFS bei erhaltener Ovarialfunktion bzw. Wiedereintritt der Ovarialfunktion innerhalb von 24 Monaten nach Chemotherapie-induzierter Ovarialinsuffizienz; [c]nur HER2-negativ; [d]Unterbrechung der adjuvanten endokrinen Therapie nach 18 Monaten für max. 2 Jahre bei Kinderwunsch ohne Überlebensnachteil mit einem medianen F/U von nur 3,5 Jahren möglich (AGO+).

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Frühes Mammakarzinom HER2+

KATHERINE – Studiendesign

- Prior neoadjuvant therapy consisting of:
  - Minimum 6 cycles of chemotherapy
  - Minimum 9 weeks of Trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

N=1486

R

1:1

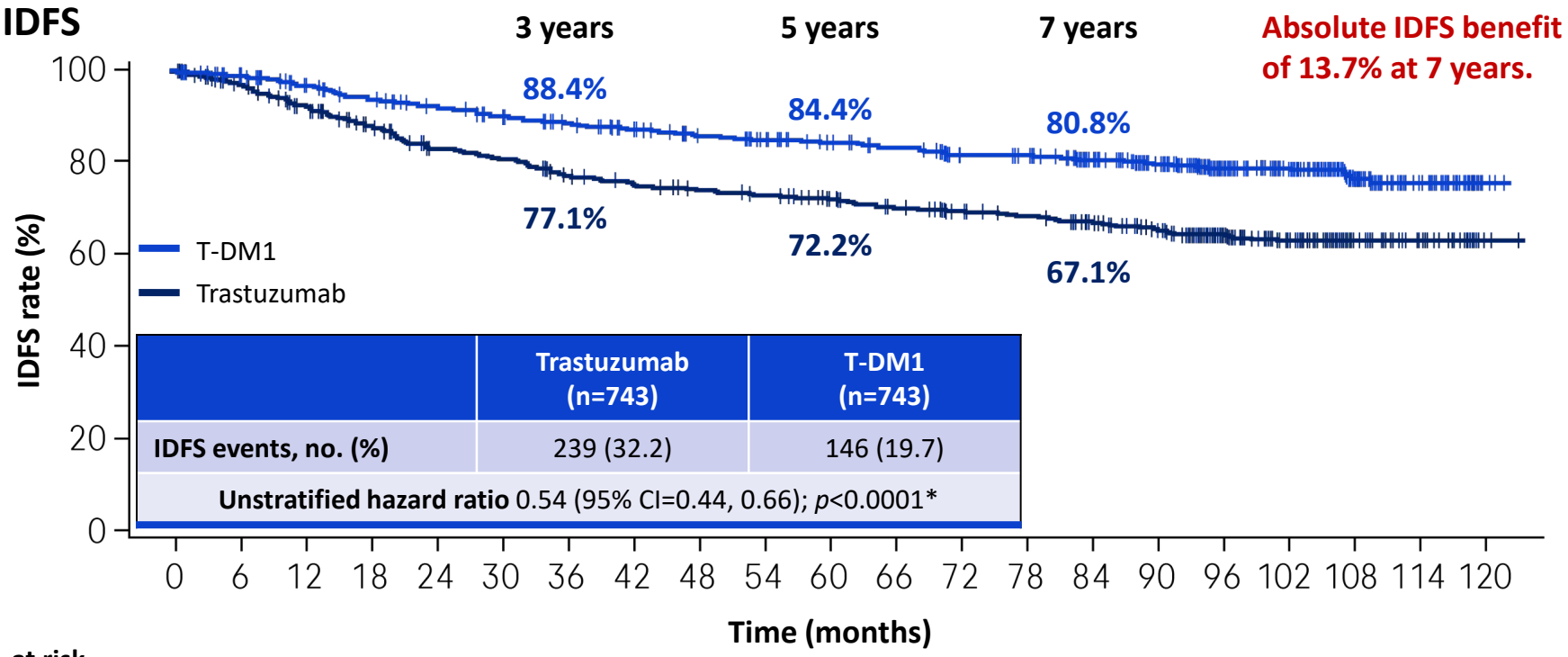
T-DM1
3.6 mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles

- Radiation and endocrine therapy per protocol and local guidelines
- Switch to Trastuzumab permitted if T-DM1 discontinued due to AEs

Mod. Loibl S et al. SABCS 2023, General Session – General Session 3, Abstract No. GS03-12

KATHERINE – Ergebnis für iDFS 2023: 13,7% Unterschied



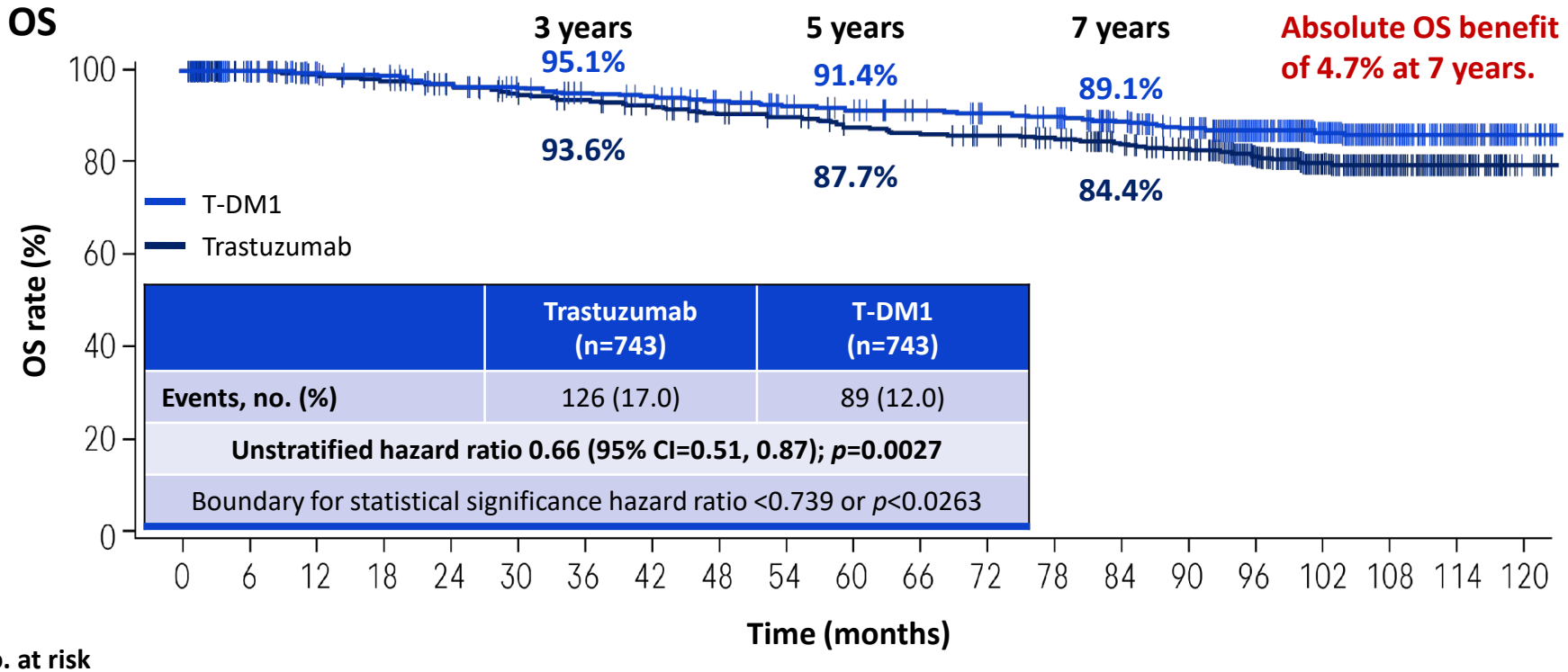
	Trastuzumab (n=743)	T-DM1 (n=743)
IDFS events, no. (%)	239 (32.2)	146 (19.7)
Unstratified hazard ratio 0.54 (95% CI=0.44, 0.66); *p*<0.0001*		

No. at risk																					
Trastuzumab	743	677	636	595	556	540	511	495	485	475	460	444	431	421	397	368	238	187	74	42	2
T-DM1	743	708	682	658	637	620	605	591	574	561	548	537	521	516	481	443	281	236	89	50	3

**p*-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, Ado-Trastuzumab Emtansine.

Mod. Loibl S et al. SABCS 2023, General Session – General Session 3, Abstract No. GS03-12

KATHERINE – Ergebnis für OS 2023



	Trastuzumab (n=743)	T-DM1 (n=743)
Events, no. (%)	126 (17.0)	89 (12.0)
Unstratified hazard ratio 0.66 (95% CI=0.51, 0.87); *p*=0.0027		
Boundary for statistical significance hazard ratio <0.739 or *p*<0.0263		

No. at risk

Trastuzumab	743	696	677	661	643	625	616	600	586	576	558	549	543	532	511	490	374	280	146	72	9
T-DM1	743	719	702	695	675	662	649	642	626	614	604	597	585	576	554	530	394	312	158	93	14

CI, confidence interval; OS, overall survival; T-DM1, Ado-Trastuzumab Emtansine.

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Therapie beim frühen HER2-positiven Mammakarzinom

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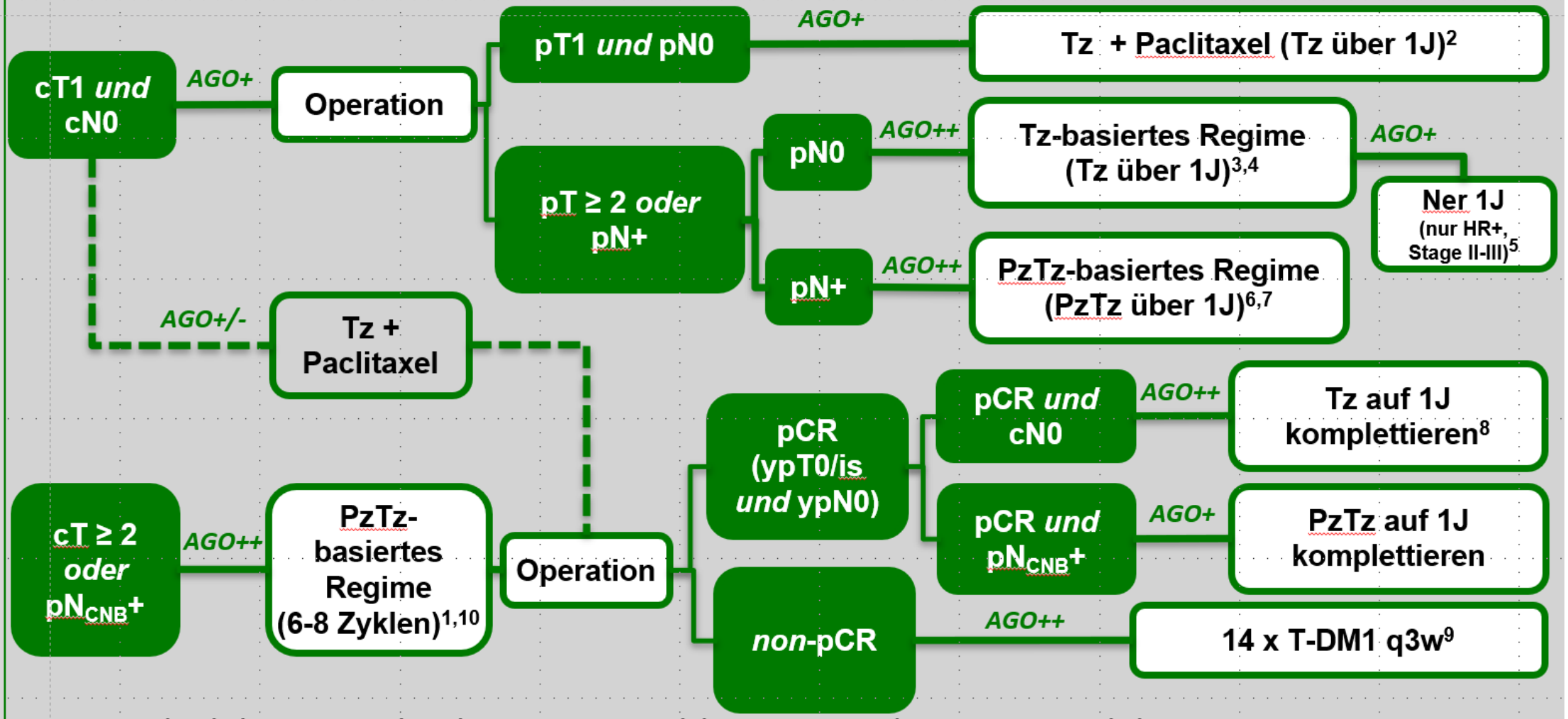

CNB, Stanzbiopsie (core needle biopsy); J, Jahr; Ner, Neratinib; pCR, pathologische Komplettremission; Pz, Pertuzumab; q3w, alle 3 Wochen; T-DM1, Trastuzumab Emtansin; Tz, Trastuzumab; bei Hormonrezeptor-positiv adjuvante endokrine Therapie.

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Frühes Mammakarzinom
TNBC

IO plus Chemotherapie auch bei HR+ high risk

KEYNOTE-522

KEYNOTE-522 Study Design (NCT03036488)

Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

Key Eligibility Criteria
- Age ≥18 years
- Newly diagnosed TNBC of either T1c N1-2 or T2-4 N0-2
- ECOG PS 0-1
- Tissue sample for PD-L1 assessment[a]

R
2:1
N = 1174

Primary Endpoints
- pCR (ypT0/Tis ypN0)
- EFS

Secondary Endpoints
- pCR (ypT0 ypN0 and ypT0/Tis)
- pCR, EFS, and OS in PD-L1+ population
- Safety

← Neoadjuvant Phase → ← Adjuvant Phase →

Neoadjuvant Treatment 1 (cycles 1-4; 12 weeks)	Neoadjuvant Treatment 2 (cycles 5-8; 12 weeks)		Adjuvant Treatment (cycles 1-9; 27 weeks)
Carboplatin[b] + Paclitaxel[c]	Doxo[d]/Epirubicin[e] + Cyclophosphamide[f]	SURGERY	Pembrolizumab 200 mg Q3W
Pembrolizumab 200 mg Q3W			
Carboplatin[b] + Paclitaxel[c]	Doxo[d]/Epirubicin[e] + Cyclophosphamide[f]		Placebo
Placebo			

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

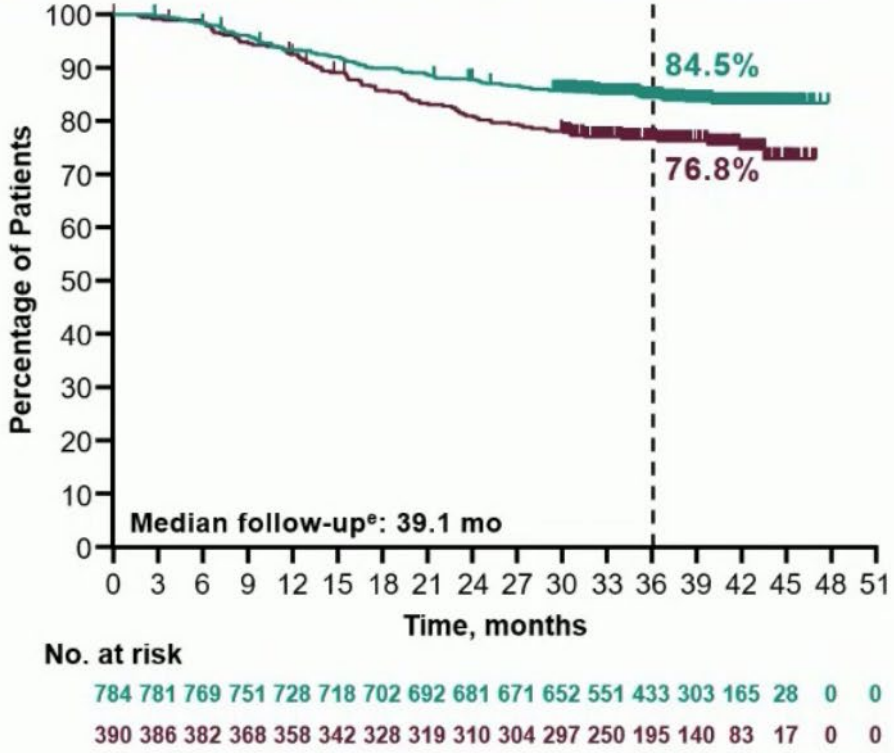
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m^2 QW. [d]Doxorubicin dose was 60 mg/m^2 Q3W. [e]Epirubicin dose was 90 mg/m^2 Q3W. [f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

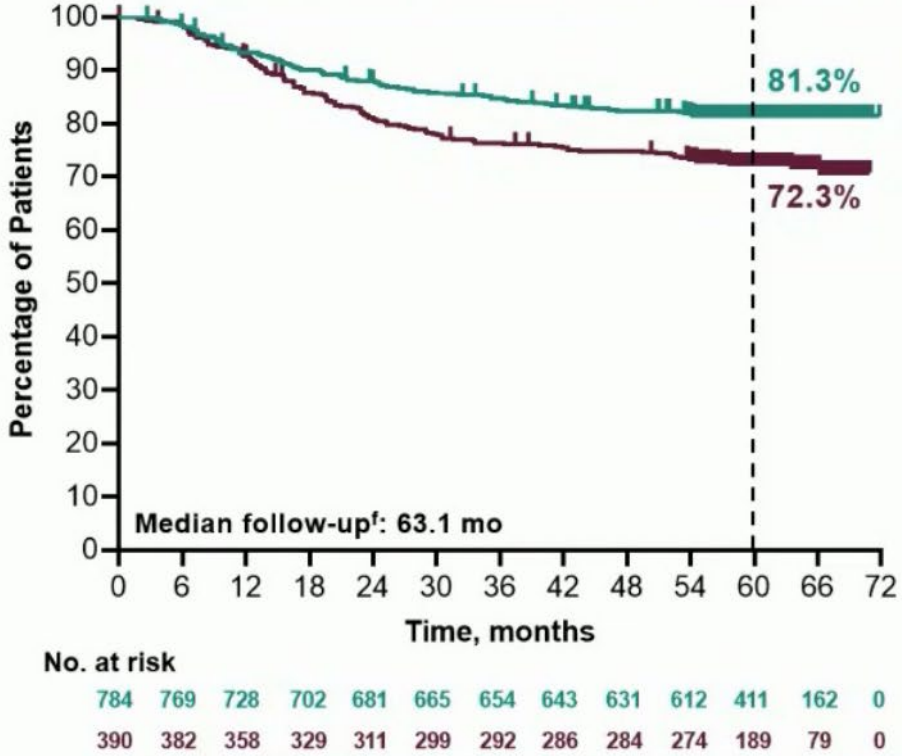
IO plus Chemotherapie auch bei HR+ high risk
KEYNOTE-522

EFS

IA4[a]	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[c] (0.48-0.82)	0.00031[d]
Placebo + Chemo/Placebo	23.8%		



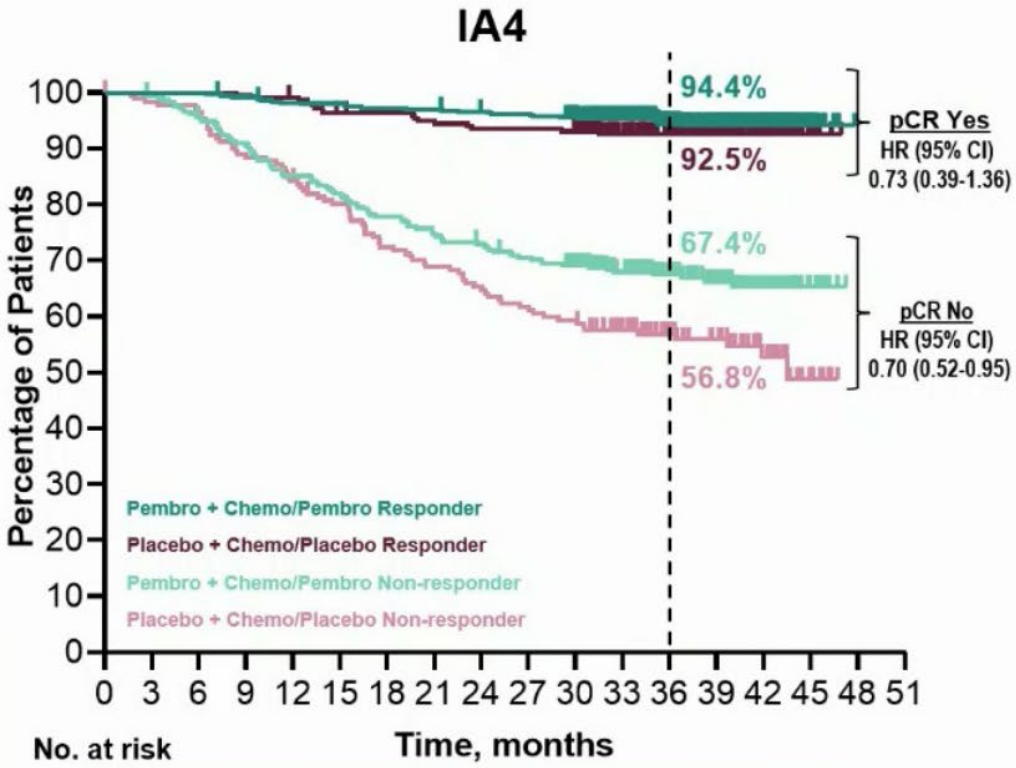
IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49-0.81)
Placebo + Chemo/Placebo	27.7%	



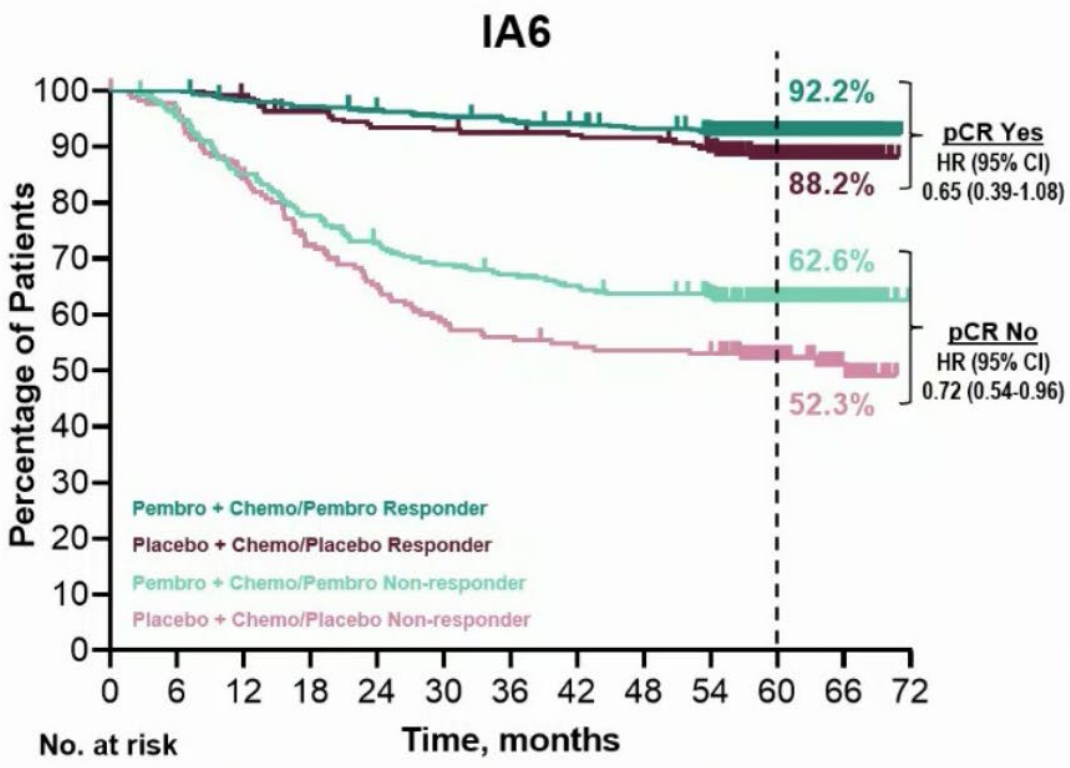
[a]The 4th prespecified interim analysis of EFS was calendar-driven planned to occur ~48 months after the first participant was randomized. [b]The 6th prespecified interim analysis of EFS was calendar-driven planned to occur ~72 months after the first participant was randomized. [c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary of 0.00517 was crossed. [e]Defined as the time from randomization to the data cutoff date of March 23, 2021. [f]Defined as the time from randomization to the data cutoff date of March 23, 2023.

IO plus Chemotherapie auch bei HR+ high risk
KEYNOTE-522

EFS by pCR (ypT0/Tis ypN0)



Data cutoff date: March 23, 2021.



Data cutoff date: March 23, 2023.

Postneoadjuvante Therapie triple-negativ

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	Oxford LoE	Oxford GR	AGO
pCR			
▪ Fortführung Pembrolizumab, wenn neoadj. begonnen (q3w für 9 Kurse)	1b	B	+
Non-pCR			
▪ Capecitabin (q3w bis zu 8 Kurse)*			
▪ Bei non-pCR nach A-T-haltiger Chemotherapie*	1a	A	++
▪ Bei non-pCR nach Platin +/- Pembrolizumab-haltiger Therapie	5	D	+/-
▪ Platinderivate (Carboplatin oder Cisplatin) q3w	1b	B	+/-
▪ Olaparib (*gBRCA*^{MUT})[1]	1b	A	++
▪ Fortführung Pembrolizumab, wenn neoadj. begonnen (q3w für 9 Kurse)	1b	B	++

[1] entsprechend Einschlußkriterien der OlympiA-Studie, Vorteil v.a. bei platin-freier NACT

* Studienlage bei Stadium II-III ohne Platin/Pembrolizumab-basierte Vortherapie

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Therapie beim frühen triple-negativen Mammakarzinom

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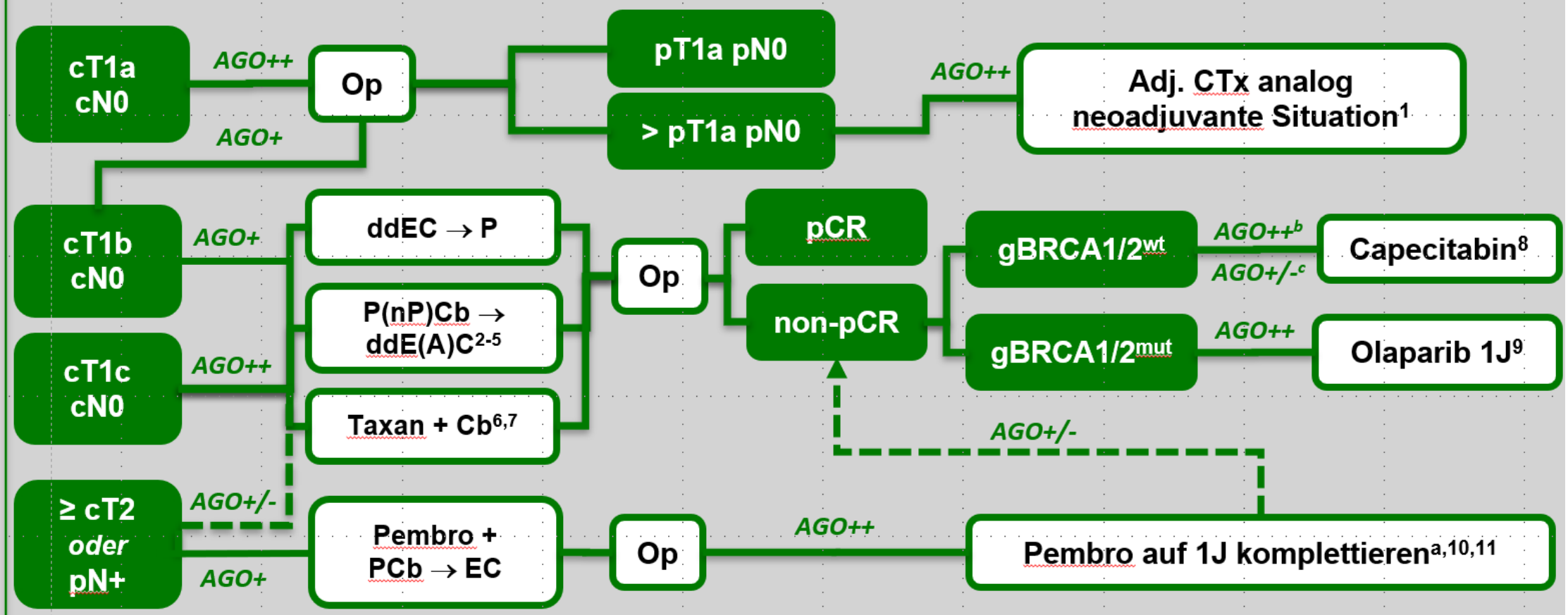

A, Doxorubicin; C, Cyclophosphamid; Cb, Carboplatin; CTx, Chemotherapie; dd, dosisdicht (alle 2 Wochen); E, Epirubicin; J, Jahr; mut, mutiert; nP, nab-Paclitaxel; Op, Operation; Pembro, Pembrolizumab; P, Paclitaxel; wt, wild type; [a] sofern Pembrolizumab neoadjuvant begonnen wurde; [b] nach A/T-haltiger Chemotherapie; [c] nach Chemotherapie mit Platin und/oder Pembrolizumab.

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Metastasiertes Mammakarzinom

Metastasiertes Mammakarzinom HR+

Endokrine Resistenz beim metastasierten Mammakarzinom

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Primäre endokrine Resistenz:

- Rezidiv innerhalb der ersten zwei Jahre unter einer adjuvanten endokrinen Therapie (ET)
- Progress innerhalb der ersten 6 Monate unter einer laufenden endokrinen first-line-Therapie beim metastasierten Mammakarzinom

Sekundäre (erworbene) endokrine Resistenz:

- Rezidiv unter einer adjuvanten ET, aber erst nach den ersten 2 Jahren oder innerhalb 12 Monate nach abgeschlossener adjuvanter ET
- Progression ≥ 6 Monate nach Initiierung einer ET in der metastasierten Situation

Kombination aus klinischer und molekularer Resistenzdefinition
INAVO120-Studie

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

Enrolment period: December 2019 to September 2023

N=325

R 1:1

Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Placebo (PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors:

- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints

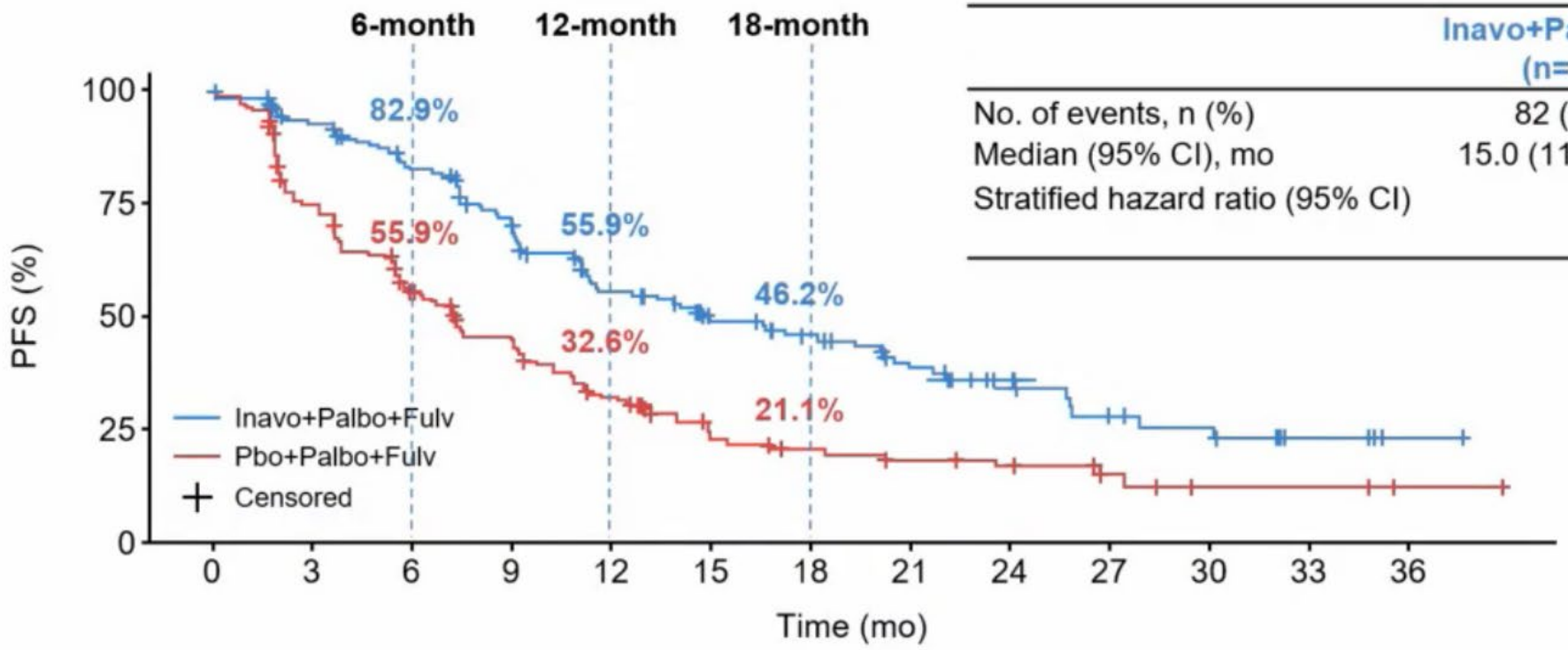
- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

* Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[1] Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis;
** Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, *et al. Ann Oncol* 2018;**29:**1634–1657.

San Antonio Breast Cancer Symposium 2023
The INAVO120 study [NCT04191499]

Kombination aus klinischer und molekularer Resistenzdefinition

INAVO120-Studie: PFS



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59)** **p<0.0001**	

Patients at risk:													
Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up:
21.3 months

CCOD: 29th September 2023
CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

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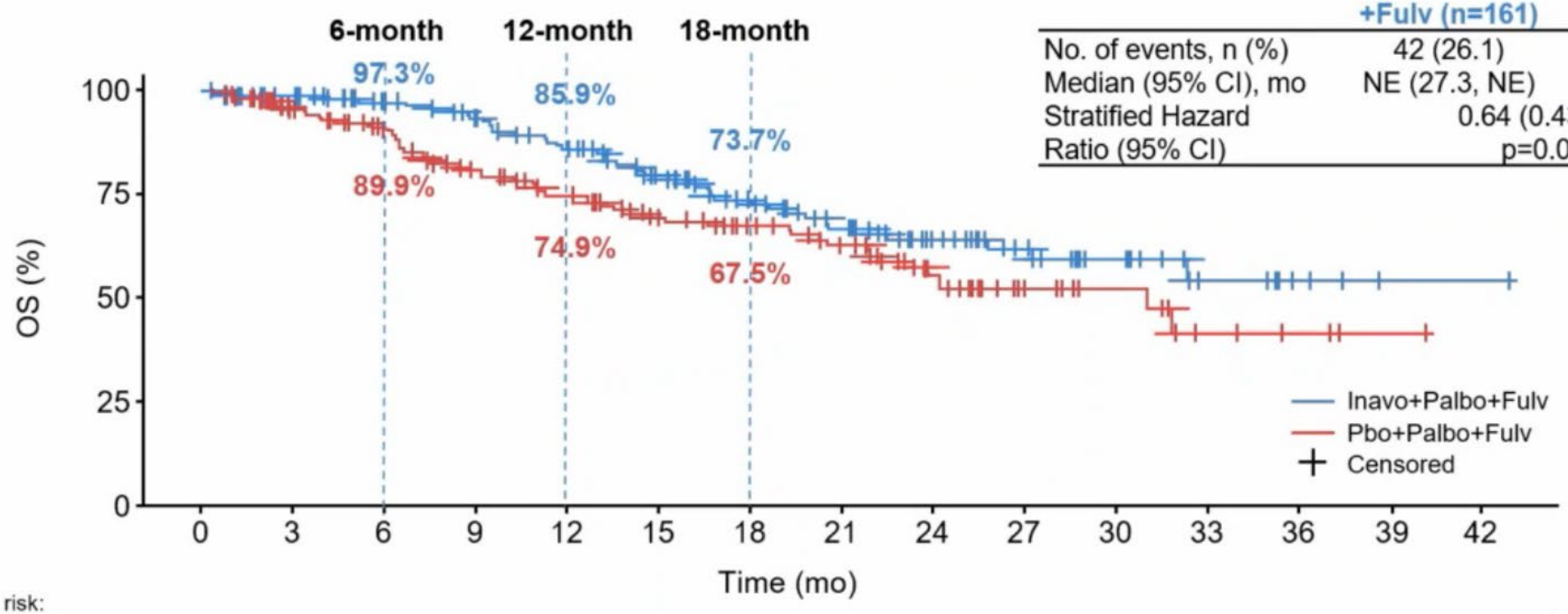
The INAVO120 study [NCT04191499]

Kombination aus klinischer und molekularer Resistenzdefinition

INAVO120-Studie: OS in der Interimsanalyse



	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified Hazard Ratio (95% CI)	0.64 (0.43, 0.97) p=0.0338	

Patients at risk:

Inavo+Palbo+Fulv	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Pbo+Palbo+Fulv	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

Median follow-up: **21.3 months**

The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; NE, not estimable; OS, overall survival; Palbo, palbociclib; Pbo, placebo.

San Antonio Breast Cancer Symposium 2023
The INAVO120 study [NCT04191499]

Neues anti Trop-2-ADC beim mHR+
Ergebnisse der TROPION-Breast01-Studie

Background: Dato-DXd

- **Dato-DXd** is a **TROP2-directed ADC**, that selectively delivers a potent Topo-I inhibitor payload directly into tumor cells,[1] and has several unique properties*:
  - Optimised drug to antibody ratio ≈ 4
  - Stable linker-payload
  - Tumour-selective cleavable linker
  - Bystander antitumour effect
- Dato-DXd previously demonstrated **promising antitumour activity** and a **manageable safety profile** with a convenient Q3W schedule in pre-treated patients with **metastatic HR+/HER2– breast cancer**[2]

Dato-DXd: Humanised anti-TROP2 IgG1 monoclonal antibody

Deruxtecan

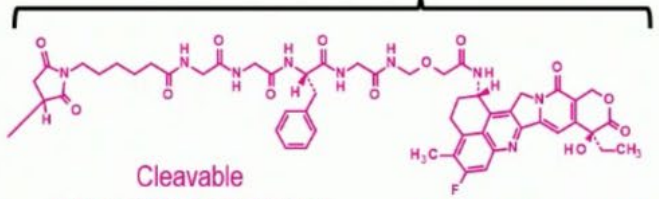


Image is for illustrative purposes only; actual drug positions may vary.

*The clinical relevance of these features is under investigation. Based on animal data.
Dato-DXd, datopotamab deruxtecan; IgG1, immunoglobulin G1; Q3W, every 3 weeks; Topo-I, topisomerase I.

1. Okajima D, et al. *Mol Cancer Ther* 2021;20:2329–40;
2. Meric-Bernstam F, et al. Poster presentation at SABCS 2022: abstract PD13-08.

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Neues anti Trop-2-ADC beim mHR+

Ergebnisse der TROPION-Breast01-Studie

TROPION-Breast01 Study Design[1]

Randomised, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety

Randomisation stratified by:

- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Detailed description of the statistical methods published previously.[1] *Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. †ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice); vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W. BICR, blinded independent central review; CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; IV, intravenous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world.

1. Bardia A, et al. *Future Oncol* 2023; doi: 10.2217/fon-2023-0188.

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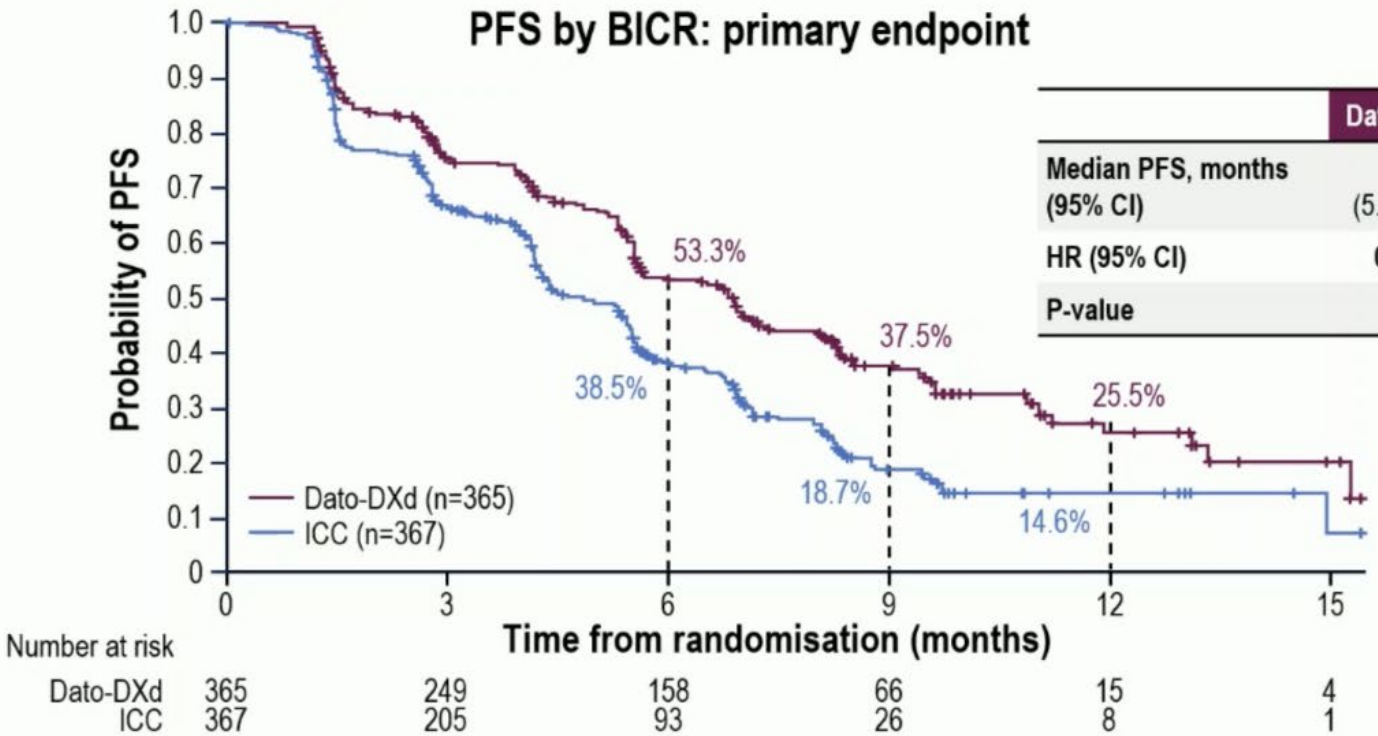
Neues anti Trop-2-ADC beim mHR+
Ergebnisse der TROPION-Breast01-Studie

Progression-Free Survival



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	0.63 (0.52–0.76)	
P-value	<0.0001	

PFS by investigator assessment: Median 6.9 vs 4.5 months; HR 0.64 (95% CI 0.53–0.76)

CI, confidence interval; HR, hazard ratio

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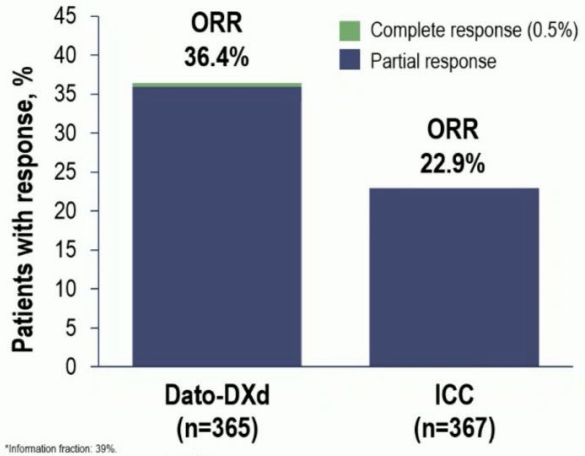
Neues anti Trop-2-ADC beim mHR+

Ergebnisse der TROPION-Breast01-Studie

Response and Interim OS

Response Rate



*Information fraction: 39%.
ORR, confirmed objective response rate by BICR

OS: Dual Primary Endpoint

- OS data not mature:*
  - Median follow-up 9.7 months
- A trend favouring Dato-DXd was observed:
  - HR 0.84 (95% CI 0.62–1.14)
- The study is continuing to the next planned analysis for OS

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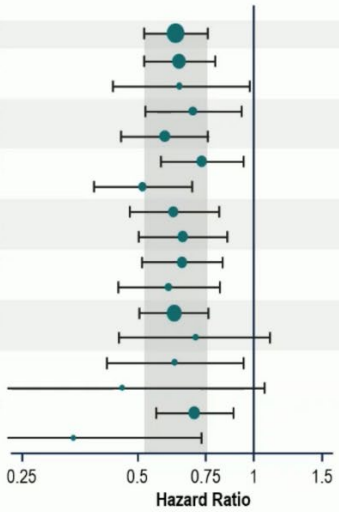
PFS by BICR Across Subgroups

		Events/n Dato-DXd	Events/n ICC	Hazard ratio
All patients		212/365	235/367	0.63
Age at randomisation	<65 years	163/274	190/295	0.64
	≥65 years	49/91	45/72	0.65
Race	Asian	88/146	101/152	0.70
	Non-Asian	109/187	119/183	0.59
ECOG performance status	0	119/197	136/220	0.73
	1	91/165	98/145	0.52
Geographic region	US, Canada, Europe	110/186	112/182	0.62
	Rest of World*	102/179	123/185	0.66
Number of previous lines of chemotherapy	1	128/229	145/225	0.65
	2	84/135	90/141	0.60
Prior use of CDK4/6 inhibitor	Yes	177/299	190/286	0.62
	No	35/66	45/81	0.70
Prior use of taxane and/or anthracycline	Taxane alone	48/80	47/71	0.62
	Anthracycline alone	9/14	16/21	0.46
	Both taxane and anthracycline	141/236	155/247	0.70
	Neither taxane nor anthracycline	14/35	17/28	0.34



Size of circle is proportional to the number of events across both treatment groups.
*Three patients from Canada were incorrectly stratified to Rest of World.

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HR-positives, HER2-negatives, metastasiertes Mammakarzinom: Endokrin-basierte Erstlinientherapie

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HR+ / HER2- MBC

- **Prämenopause Standardtherapie**
  - *AGO++* GnRHa + Fulvestrant + CDK4/6i[1,2,6]
  - *AGO++* GnRHa + AI + Ribociclib[4,5]
  - *AGO+* GnRHa + AI + Palbociclib oder Abemaciclib[3]
  - *AGO+* GnRHa + Tamoxifen[7,8]
  - *AGO+* GnRHa + AI *oder* GnRHa + Fulvestrant[9-12]
- **Postmenopause Standardtherapie**
  - *AGO++* Ribociclib + nsAI[20,21] oder Fulvestrant[32,33]
  - *AGO++* Abemaciclib + Fulvestrant[34,35]
  - *AGO+* Abemaciclib + nsAI[22,23]
  - *AGO+* Palbociclib + nsAI[16-18] oder Fulvestrant[30,31]

AI, Aromataseinhibitor; CDK4/6i, CDK4/6-Inhibitor; GnRHa, GnRH Agonist; HER2, humaner epithelialer Wachstumsfaktor-Rezeptor 2; HR, Hormonrezeptor; ; ns, nicht-steroidal; MBC, metastasiertes Mammakarzinom; Mo, Monate; TFI, Therapie-freies Intervall.

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HR-positives, HER2-negatives, metastasiertes Mammakarzinom: Strategien

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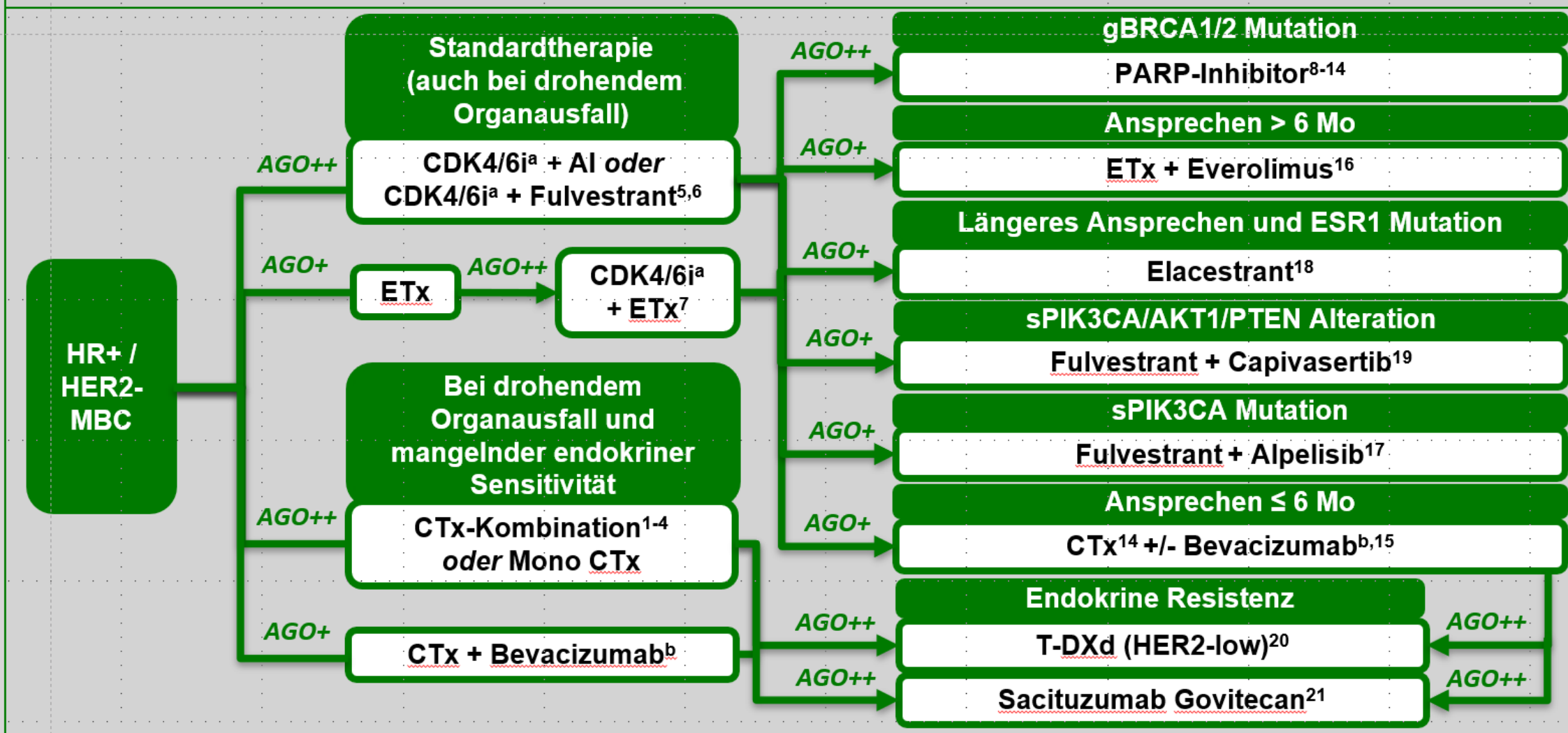

AI, Aromataseinhibitor; CDK4/6i, CDK4/6 Inhibitoren; CTx, Chemotherapie; ETx, endokrine Therapie; gBRCA1/2 Mutation, BRCA1/2-Keimbahnmuatation; HER2, humaner epidermaler Wachstumsfaktor-Rezeptor 2; HR, Hormonrezeptoren; MBC, metastasiertes Mammakarzinom; Mo, Monate; sPIK3CA Mutation, somatischer PIK3CA-Mutation; sPIK3CA/AKT1/PTEN Alteration, somatische PIK3CA/AKT1/PTEN Alteration; T-DXd, Trastuzumab Deruxtecan; [a]in Prämenopause zusätzlich ovarielle Suppression; [b]Bevacizumab + Paclitaxel oder + Capecitabin.

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Metastasiertes Mammakarzinom HER2 low

HER2 low und Trastuzumab Deruxtecan

Update zur Destiny Breast 04-Studie

DESTINY-Breast04

DESTINY-Breast04 Study Design:

An open-label, multicenter study (NCT03734029)[1-3]

Patients[a]

- HER2-low (IHC 1+ or IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Stratification factors

- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) vs HR−

Primary endpoint

- PFS by BICR (HR+)

Key secondary endpoints[d]

- PFS by BICR (all patients)
- **OS (HR+ and all patients)**

Secondary endpoints[d]

- **PFS by investigator**
- ORR by BICR and investigator
- DOR by BICR
- **Safety**
- Patient-reported outcomes (HR+)[e]

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI, 31.0-32.8 months)

ASCO, American Society of Clinical Oncology; BICR, blinded independent central review; CAP, College of American Pathologists; CDKi, cyclin-dependent kinase 4/6 inhibitors; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational-use-only [IUO] assay system, at the time of study. [c]TPC was administered according to the label. [d]Efficacy in the HR− cohort was an exploratory endpoint. [e]The patient-reported outcomes analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.

1. Modi S et al. *N Engl J Med*. 2022;387:9-20. 2. Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3. Prat A et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

Shanu Modi, MD

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HER2 low und Trastuzumab Deruxtecan

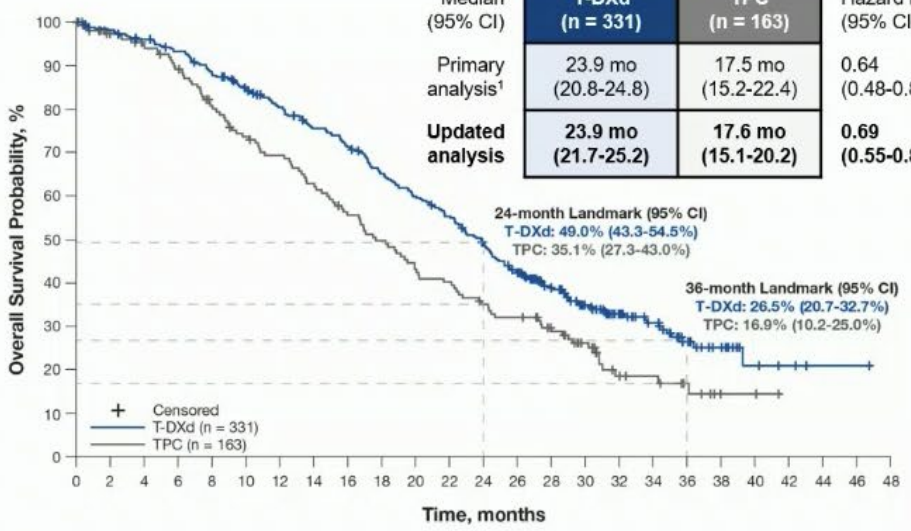
Update zur Destiny Breast 04-Studie

DESTINY-Breast04

Overall Survival

HR+ Cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**



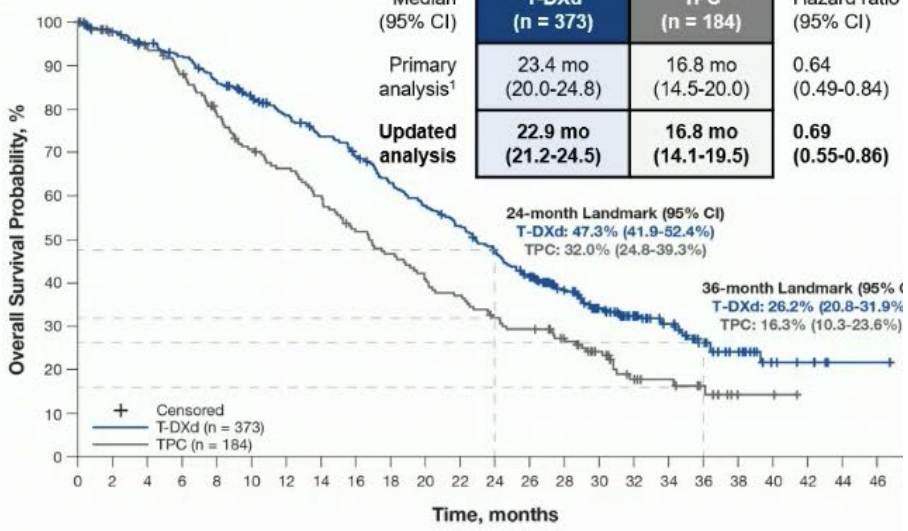
Patients still at risk:

T-DXd (n = 331) 331 325 323 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 155 147 135 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 138 134 129 123 114 108 103 97 96 92 87 82 76 71 68 64 59 56 55 50 47 43 43 42 36 31 25 16 13 11 11 9 7 5 2 2 2 1 0

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**



Patients still at risk:

T-DXd (n = 373) 373 366 363 355 350 342 337 325 314 308 295 285 276 269 257 254 240 231 217 205 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0

TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

- In the HR+ cohort and all patients, median OS was consistent with results from the primary analysis,[1] showing a 31% reduction in risk of death for patients receiving T-DXd compared with those receiving TPC

HR, hormone receptor; mo, month; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

MADRID 2023 ESMO congress

Shanu Modi, MD

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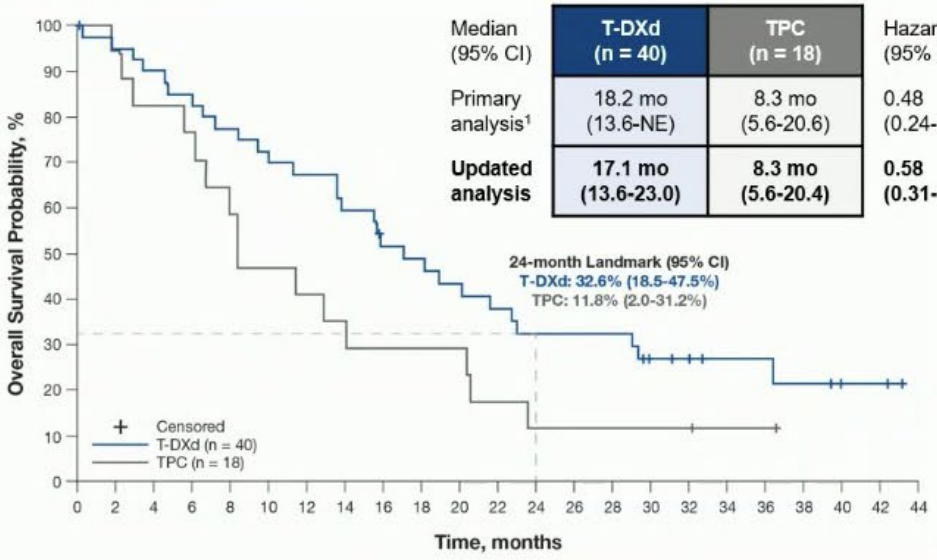
HER2 low und Trastuzumab Deruxtecan

Update zur Destiny Breast 04-Studie

DESTINY-Breast04

Efficacy in the HR− Cohort (Exploratory Analyses)

Overall Survival

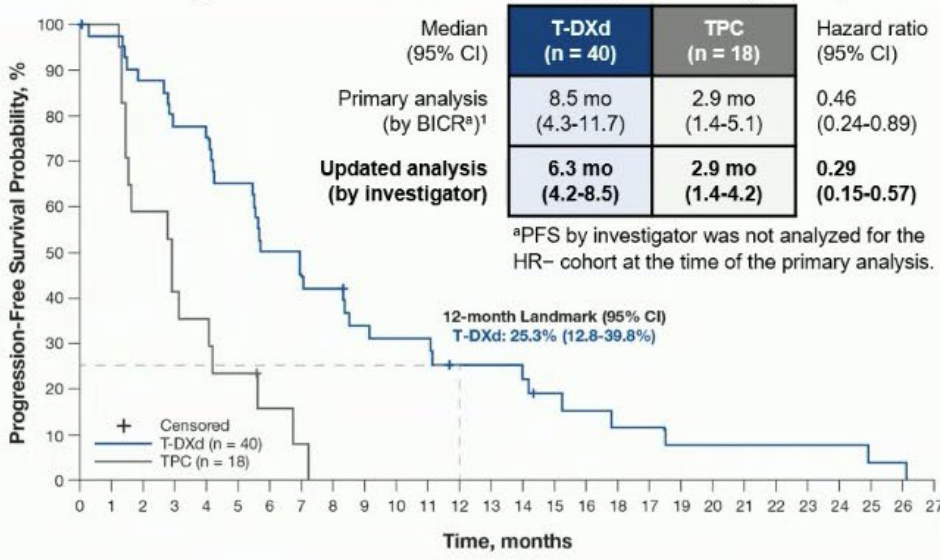


Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**

Patients still at risk:

T-DXd (n = 40)	40	38	36	34	31	28	26	23	19	18	16	14	12	12	12	8	7	5	5	4	2	2	0	
TPC (n = 18)	18	16	14	13	10	8	7	6	5	5	5	3	2	2	2	2	2	1	1	0	0	0	0	

Progression-Free Survival (by Investigator)



Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.

Patients still at risk:

T-DXd (n = 40)	40	39	35	31	30	26	19	17	16	12	11	11	8	8	7	5	4	3	3	2	2	2	2	2	2	1	1	0
TPC (n = 18)	18	17	10	7	6	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- There was a 42% reduction in risk of death and 71% reduction in risk of disease progression or death for HR− patients receiving T-DXd compared with TPC

BICR, blinded independent central review; HR, hormone receptor; mo, month; NE, not evaluable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

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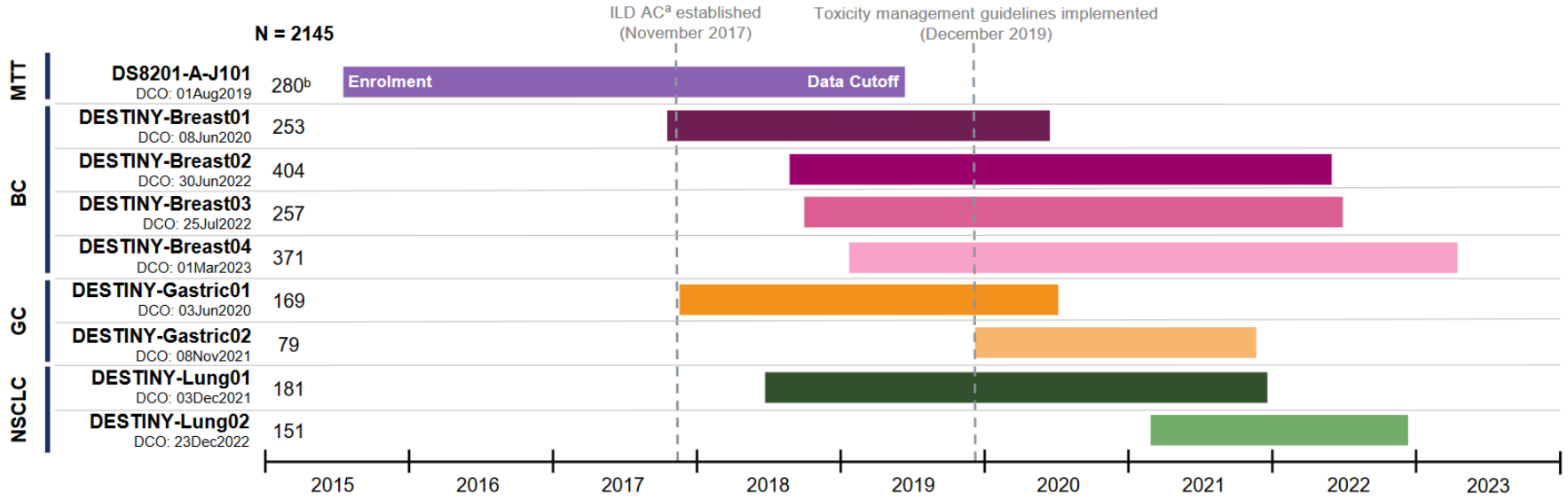
Trastuzumab Deruxtecan und Retreatment bei ILD

Gepoolte Daten aus allen Tumorentitäten

DESTINY-Pooled Trials

Methods



- Data were pooled from 9 clinical trials to identify patients with Gr 1 ILD as assessed by the investigators and confirmed by the adjudication committee (AC) who were retreated with T-DXd
  - All patients received at least 1 dose of T-DXd (5.4-8.0 mg/kg) monotherapy
- *T-DXd toxicity management guidelines recommend a dose reduction for retreatment if ILD takes longer than 28 days to resolve. At the time of study inclusions, guidelines recommended discontinuation of T-DXd if ILD had not resolved within 49 days from the last T-DXd dose[c]*

AC, adjudication committee; BC, breast cancer; DCO, data cutoff ; GC, gastric cancer; ILD, interstitial lung disease/pneumonitis; MTT, multiple tumor types; NSCLC, non–small cell lung cancer.
[a]Each AC session included an oncologist, a radiologist, and a pulmonologist. [b]Only patients who received at least 1 dose of T-DXd 5.4-8.0 mg/kg are included. The color bar for each study indicates the time from patient enrollment to data cut-off. [c]Guidelines have subsequently been updated to recommend discontinuation of T-DXd if ILD has not resolved within 126 days from the date of last drug dose.

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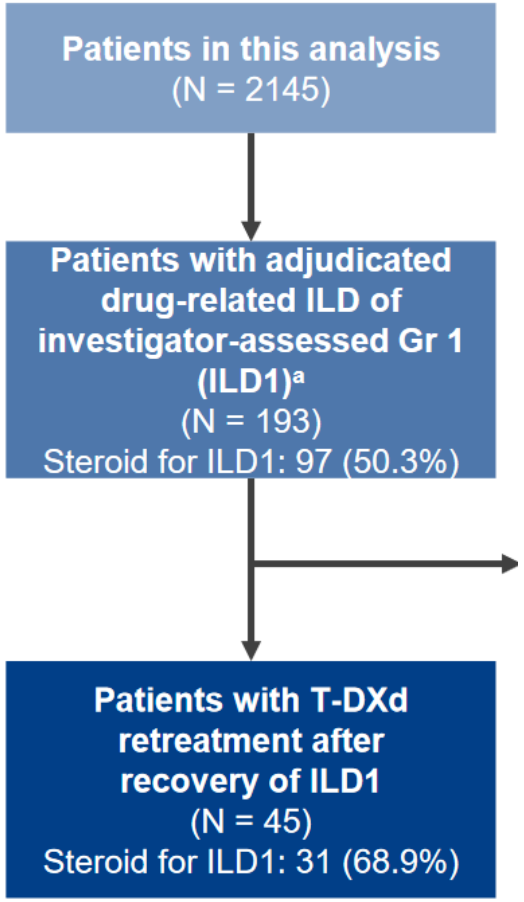
Trastuzumab Deruxtecan und Retreatment bei ILD

Gepoolte Daten aus allen Tumorentitäten



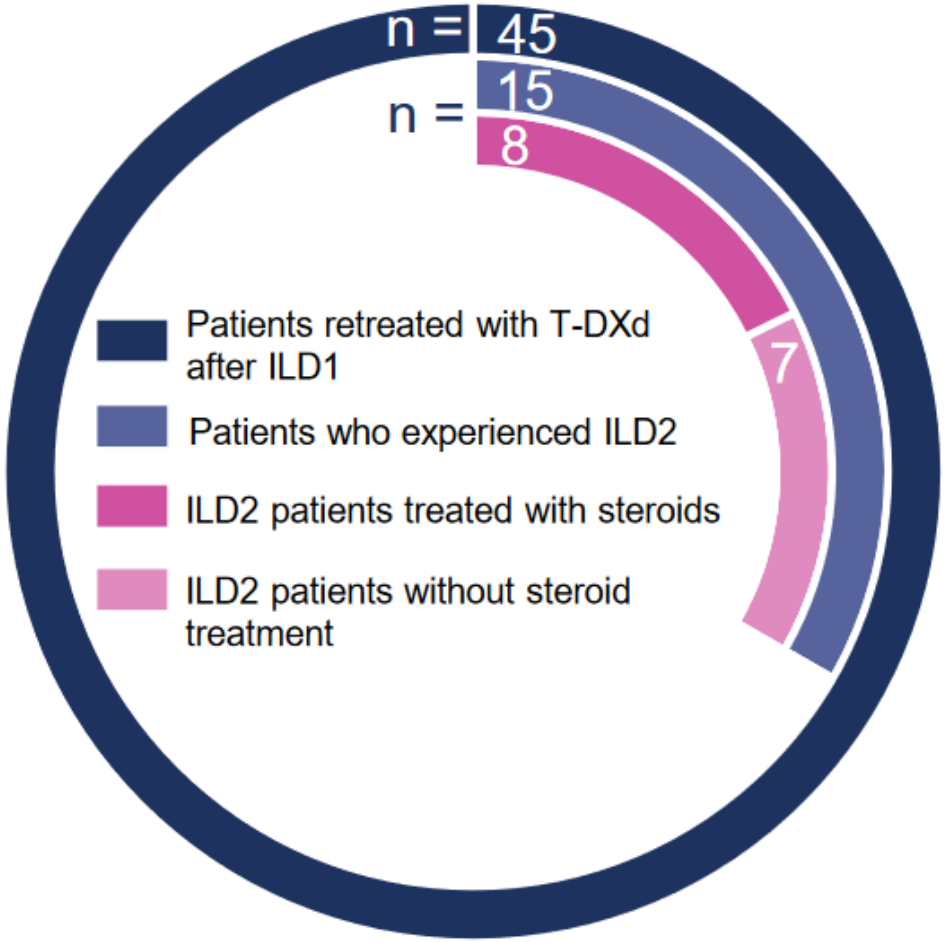
Demographics and Baseline Characteristics

Baseline characteristics	All Tumor Types Pool (N = 2145)	ILD1 (N = 193)	T-DXd retreatment (N = 45)
Age, median (range), years	58.0 (20-96)	60.0 (30-88)	59.1 (30-79)
<65 years, n (%)	1524 (71.0)	130 (67.4)	27 (60.0)
≥65 years, n (%)	621 (29.0)	63 (32.6)	18 (40.0)
Sex, n (%)			
Female	1756 (81.9)	157 (81.3)	36 (80.0)
Country, n (%)			
Japan	586 (27.3)	89 (46.1)	17 (37.8)
Non-Japan	1559 (72.7)	104 (53.9)	28 (62.2)
ECOG PS, n (%)			
0	1100 (51.3)	115 (59.6)	22 (48.9)
1	1043 (48.6)	78 (40.4)	23 (51.1)
Tumor type, n (%)			
Breast cancer	1462 (68.2)	131 (67.9)	27 (60.0)
Gastric cancer	294 (13.7)	20 (10.4)	3 (6.7)
Lung cancer	350 (16.3)	39 (20.2)	15 (33.3)
Colorectal cancer	20 (0.9)	1 (0.5)	0
Other	19 (0.9)	2 (1.0)	0
Lung comorbidities,[a] n (%)			
No	2023 (94.3)	183 (94.8)	42 (93.3)

Trastuzumab Deruxtecan und Retreatment bei ILD

Gepoolte Daten aus allen Tumorentitäten

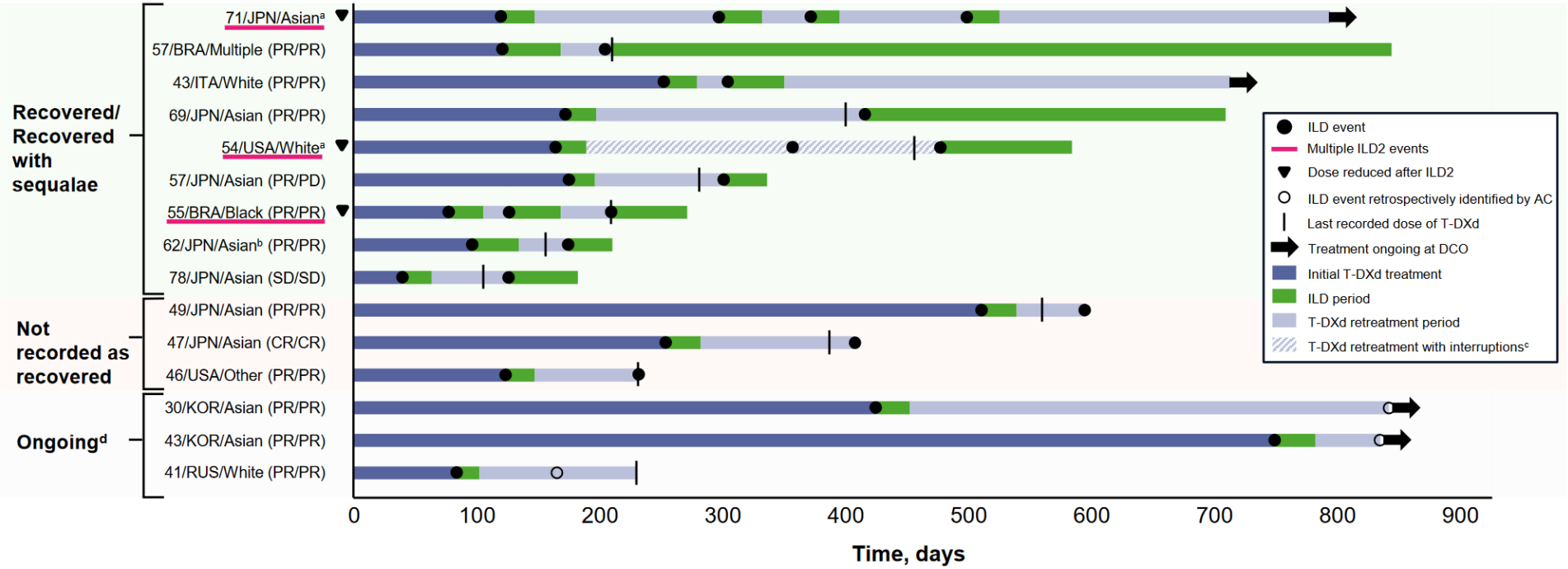
	T-DXd retreatment (N = 45)
Dose level of T-DXd retreatment	
Same dose, n (%)	31 (68.9)
Reduced dose, n (%)	14 (31.1)
Median time to retreatment after ILD1 onset (range), days	28 (8-48)
Median retreatment cycles (range)	5.0 (1-37)
Patients with ILD2 (n = 15)	5.0 (2-23)
Patients without ILD2 (n = 30)	4.5 (1-37)
Median retreatment duration (range), days	85.0 (1-848)
Patients with ILD2 (n = 15)	85.0 (22-648)
Patients without ILD2 (n = 30)	82.5 (1-848)



Trastuzumab Deruxtecan und Retreatment bei ILD

Gepoolte Daten aus allen Tumorentitäten

n (%)	With Steroid Treatment for ILD2[a] (n = 8)	Without Steroid Treatment for ILD2 (n = 7)	Total (n = 15)
Adjudicated Worst-Grade of ILD2			
1	2 (25.0)	4 (57.1)	6 (40.0)
2	6 (75.0)	3 (42.9)	9 (60.0)
≥3	0	0	0
Outcome of ILD2[b]			
Recovered/Recovered with sequalae	6 (75.0)	3 (42.9)	9 (60.0)
Not marked as recovered[c]	2 (25.0)	1 (14.3)	3 (20.0)
Ongoing[d]	0	3 (42.9)	3 (20.0)
Fatal	0	0	0



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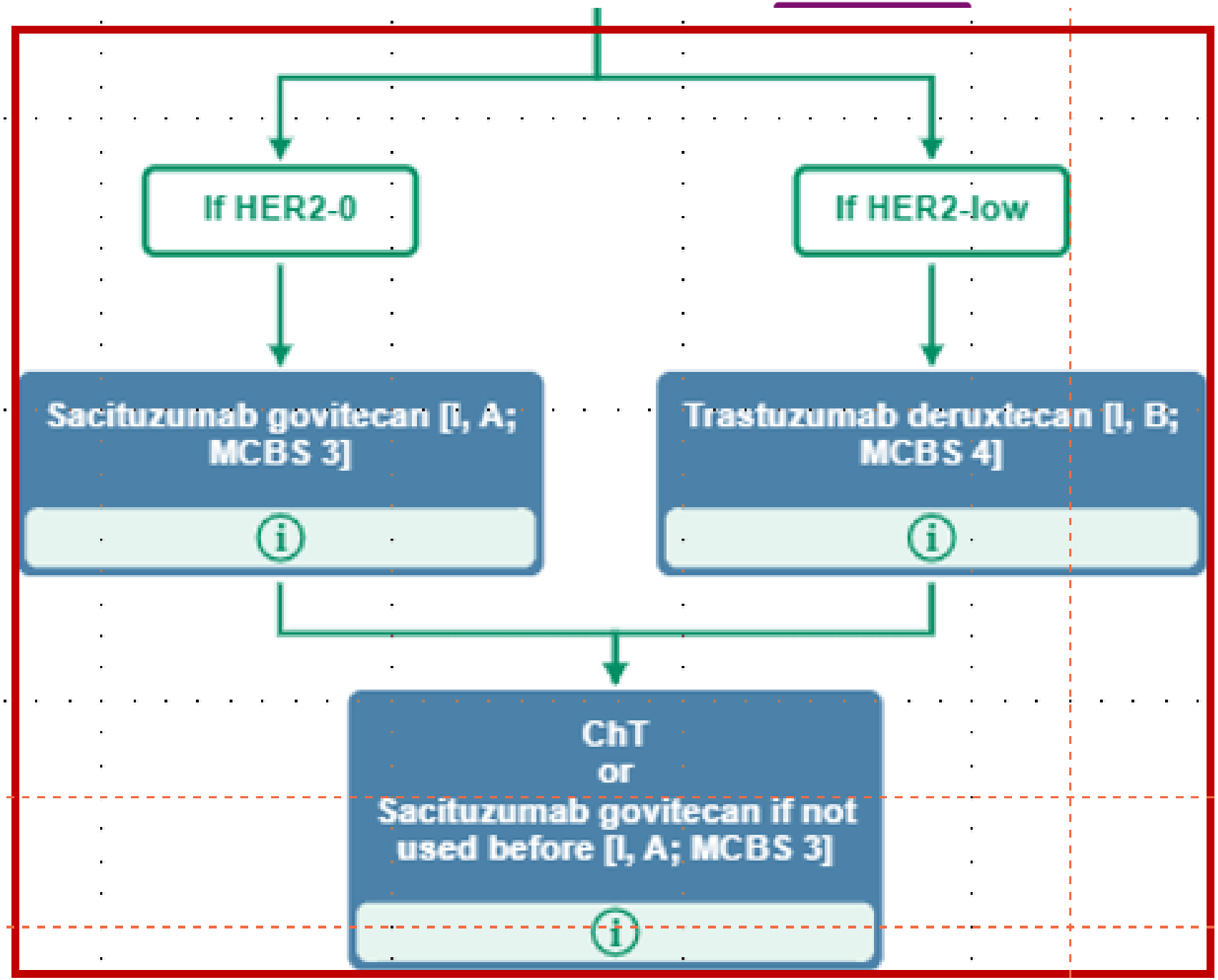

Metastasiertes Mammakarzinom HER2+

Datengenerierung für T-DXd bei Hirnmetastasen
Joint Analysis von DB01, DB02 und DB03

DESTINY-Breast01, -02, and -03

BM Eligibility Criteria Evolution in Each Trial

Inclusion Criteria	
DESTINY-Breast01[1]	**DESTINY-Breast02 and DESTINY-Breast03[2-4]**
• Patients with asymptomatic, previously locally treated, and stable BMs	• Initially, patients with previously untreated and asymptomatic BM were eligible • After protocol amendments, only patients with treated, asymptomatic BMs were allowed

- Per FDA criteria, patients with untreated BMs from DESTINY-Breast02 and -03 would be considered to have active BMs[5]
  - The population of patients with baseline BMs from DESTINY-Breast02 and -03 therefore consists of a mix of treated/stable and untreated/active metastases

BM, brain metastasis; FDA, Food and Drug Administration.

1. Modi S et al. *N Engl J Med*. 2020; 382:610-621. 2. Cortes J et al. *N Engl J Med*. 2022; 368(12):1143-1154. 3. André F et al. *The Lancet*. 2023. https://doi.org/10.1016/S0140-6736(23)00725-0. 4. Hurvitz SA et al. *Lancet*. 2023;401(10371):105-117. 5. U.S. Department of Health and Human Services – Food and Drug Administration. Cancer Clinical Trial Eligibility Criteria: Brain Metastases. 2020.

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Datengenerierung für T-DXd bei Hirnmetastasen

Joint Analysis von DB01, DB02 und DB03

DESTINY-Breast01, -02, and -03

Retrospective Exploratory Pooled Analysis Plan[1-3]

DESTINY-Breast01 (N = 253)[a,b]
- Phase II study
- Patients previously treated with T-DM1
- Patients with asymptomatic and previously locally treated BM eligible
- Prior BM therapy within 60 days prohibited

DESTINY-Breast02 (N = 608)[a,c]
- Phase III study
- Patients previously treated with T-DM1
- Patients with asymptomatic and previously treated/untreated BM eligible
- Prior BM therapy within 14 days of randomization prohibited

DESTINY-Breast03 (N = 524)[a,d]
- Phase III study
- Patients previously treated with trastuzumab and a taxane in metastatic or (neo)adjuvant setting with recurrence within 6 months of therapy
- Patients with asymptomatic and previously treated/untreated BM eligible
- Prior BM therapy within 14 days of randomization prohibited

R 2:1

R 1:1

T-DXd[e] (Total n = 184) (With BM n = 19)

T-DXd[e] (Total n = 406) (With BM n = 83)

TPC per label Trastuzumab/Capecitabine or Lapatinib/Capecitabine (Total n = 202) (With BM n = 41)

T-DXd[e] (Total n = 261) (With BM n = 46)

T-DM1[f] (Total n = 263) (With BM n = 42)

T-DXd pool (N = 851)

T-DXd BM pool (n = 148)

T-DXd non-BM pool (n = 703)

Comparator pool (N = 465)

Comparator BM pool (n = 83)

Comparator non-BM pool (n = 382)

Endpoints:
- IC-ORR (CR+PR in brain) per BICR per RECIST v1.1
- IC-DoR per BICR
- CNS-PFS per BICR
- Safety and tolerability

- **The BM and non-BM pools were determined by BICR at baseline among all patients based on mandatory brain CT/MRI screening**

BICR, blinded independent central response; BM, brain metastasis; CNS, central nervous system; CR, complete response; CT, computed tomography; DB, DESTINY-Breast; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IC, intracranial; mBC, metastatic breast cancer; MRI, magnetic resonance imaging; ORR, objective response rate; PFS, progression-free survival; PR, partial response; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice (trastuzumab/capecitabine or lapatinib/capecitabine).
Data for patients in the 5.4 mg/kg T-DXd arms were pooled from the DB-01, DB-02, and DB-03 trials. Comparator data were pooled from the DB-02 and DB-03 trials. All three studies were conducted in unresectable/mBC; HER2 status was confirmed centrally; and a documented radiographic progression after most recent treatment was required.
[a]The presence of BMs was not a stratification factor. [b]Data Cutoff: March 26, 2021. [c]Data Cutoff: June 30, 2022. [d]Data Cutoff: May 21, 2021. [e]5.4 mg/kg Q3W. [f]3.6 mg/kg Q3W.

1. Modi S et al. *N Engl J Med.* 2020; 382:610-621 [article and supplementary appendix]. 2. André F et al. *The Lancet.* 2023. https://doi.org/10.1016/S0140-6736(23)00725-0 [article and supplementary appendix]. 3. Cortes J et al. *N Engl J Med.* 2022; 368(12):1143-1154 [article and supplementary appendix].

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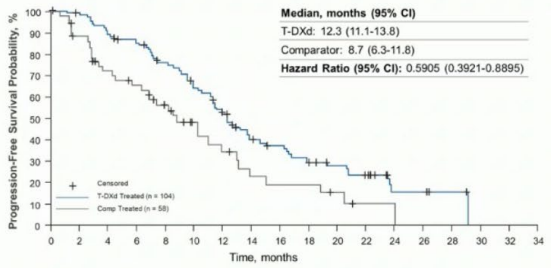
Datengenerierung für T-DXd bei Hirnmetastasen

Joint Analysis von DB01, DB02 und DB03

DESTINY-Breast01, -02, and -03

Exploratory CNS-PFS per BICR

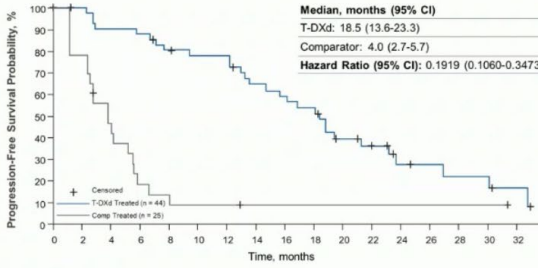
Treated/Stable BMs



Patients still at risk

T-DXd Treated (n = 104)	104	100	89	83	72	58	46	32	28	21	18	12	4	4	2	0	0	0
Comparator Treated (n = 58)	58	44	33	29	22	14	10	6	5	5	3	1	0	0	0	0	0	0

Untreated/Active BMs



Patients still at risk

T-DXd Treated (n = 44)	44	41	37	36	32	30	30	24	22	20	13	11	6	5	4	4	2
Comparator Treated (n = 25)	25	18	11	5	3	2	2	1	1	1	1	1	1	1	1	1	0

- **T-DXd demonstrated a trend towards prolonged CNS-PFS over comparator, with a noticeably greater advantage for patients with untreated/active BMs**

BICR, blinded independent central review; BM, brain metastasis; CNS, central-nervous system; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.
CNS-PFS was defined by BICR as only radiological progression.

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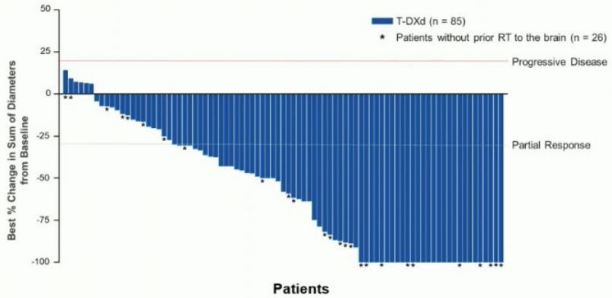
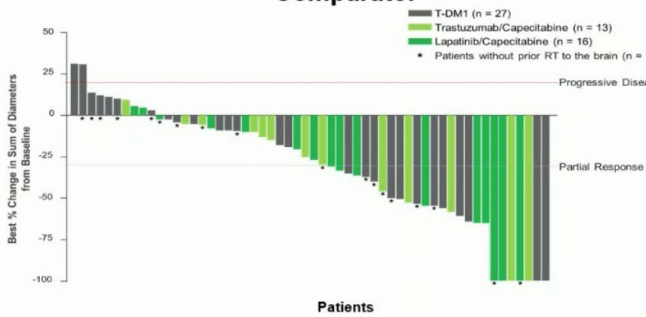
DESTINY-Breast01, -02, and -03

Best Percentage Change from Baseline in Sum of Diameters of Brain Tumors

T-DXd



Comparator



- **The shrinkage of BMs in response to T-DXd was more prominent, whereas in the comparator pool, BMs showed less of a response**

BM, brain metastases; RT, radiotherapy; T-DXd, trastuzumab deruxtecan.
For patients with measurable brain lesion(s) at baseline and at least one post-baseline assessment.

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HER2CLIMB-02 – Studiendesign

- HER2+ LA/MBC with progression after Trastuzumab and Taxane in any setting[a]
- ECOG PS ≤1
- Previously treated stable, progressing, or untreated brain metastases not requiring immediate local therapy

N≈460

R

1:1

T-DM1 + Tucatinib
T-DM1 3.6 mg/kg IV and Tucatinib 300 mg PO BID

T-DM1 + Placebo
T-DM1 3.6 mg/kg IV and Placebo PO BID

Outcomes

Primary
- PFS by investigator assessment per RECIST v1.1

Key Secondary (hierarchical)
- OS
- PFS in patients with brain metastases
- cORR per RECIST v1.1
- OS in patients with brain metastases

Stratification factors
-
-
-
-

The primary analysis for PFS was planned after ≈331 PFS events to provide 90% power for hazard ratio of 0.7 at two-sided alpha level of 0.05. The first of two interim analyses for OS was planned at the time of the primary PFS analysis, if the PFS result was significantly positive[b].

[a]Patients who received prior Tucatinib, Afatinib, T-DXd, or any investigational anti-HER2, anti-EGFR, or HER2 TKIs were not eligible. Patients who received Lapatinib and Neratinib were not eligible if the drugs were received within 12 months of starting study treatment, and patients who received Pyrotinib for recurrent or metastatic breast cancer were not eligible. These patients were eligible if the drugs were given for ≤21 days and were discontinued for reasons other than disease progression or severe toxicity.
[b]Subsequent OS analyses are planned upon 80% and 100% of required events for the final OS analysis.

Mod. Hurvitz S et al. SABCS 2023, General Session – General Session 1, Abstract No. GS01-10

HER2CLIMB-02 – Studiendesign

- HER2+ LA/MBC with progression after Trastuzumab and Taxane in any setting[a]
- ECOG PS ≤1
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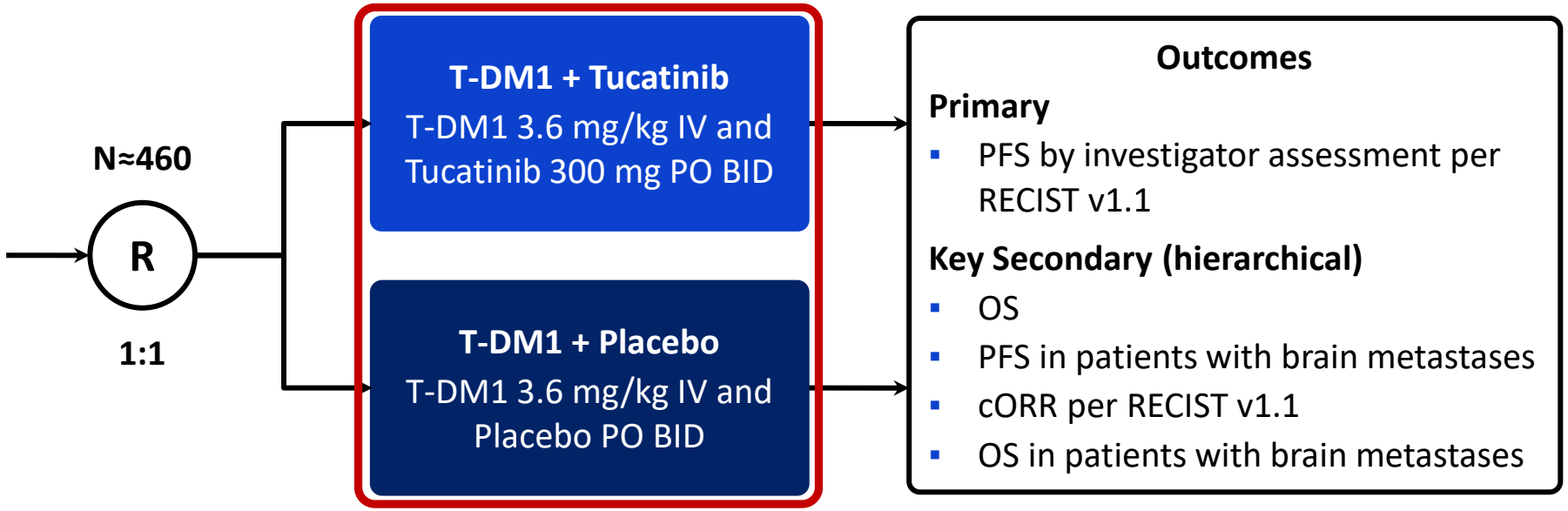

Stratification factors

-
-
-
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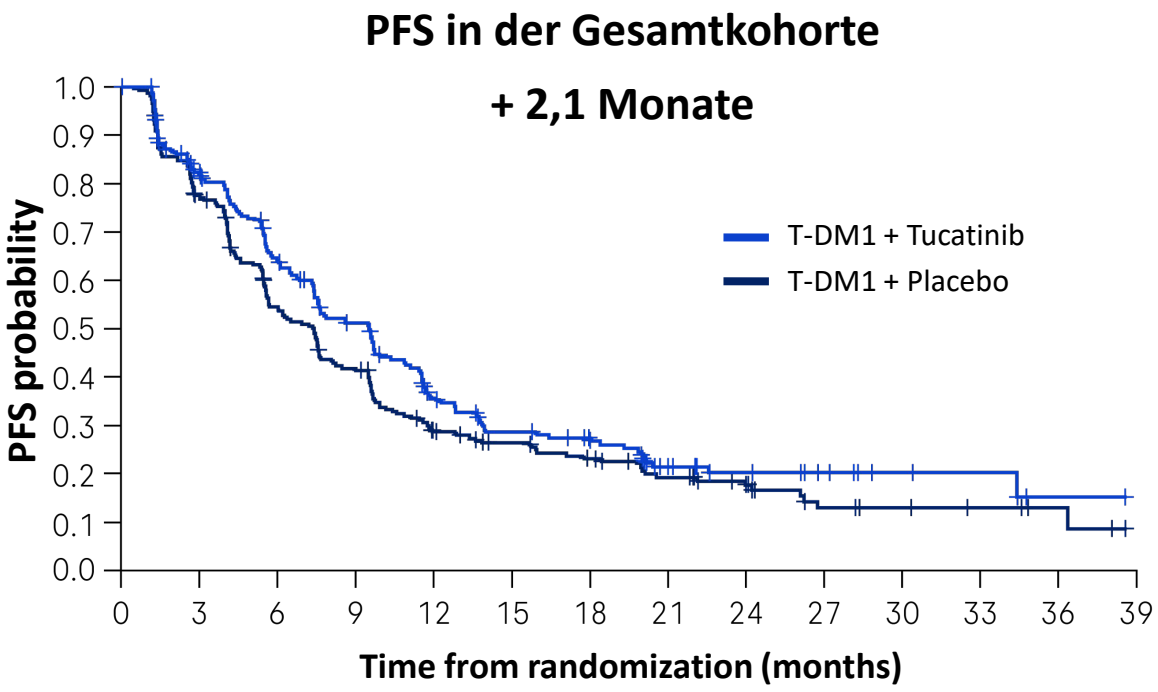
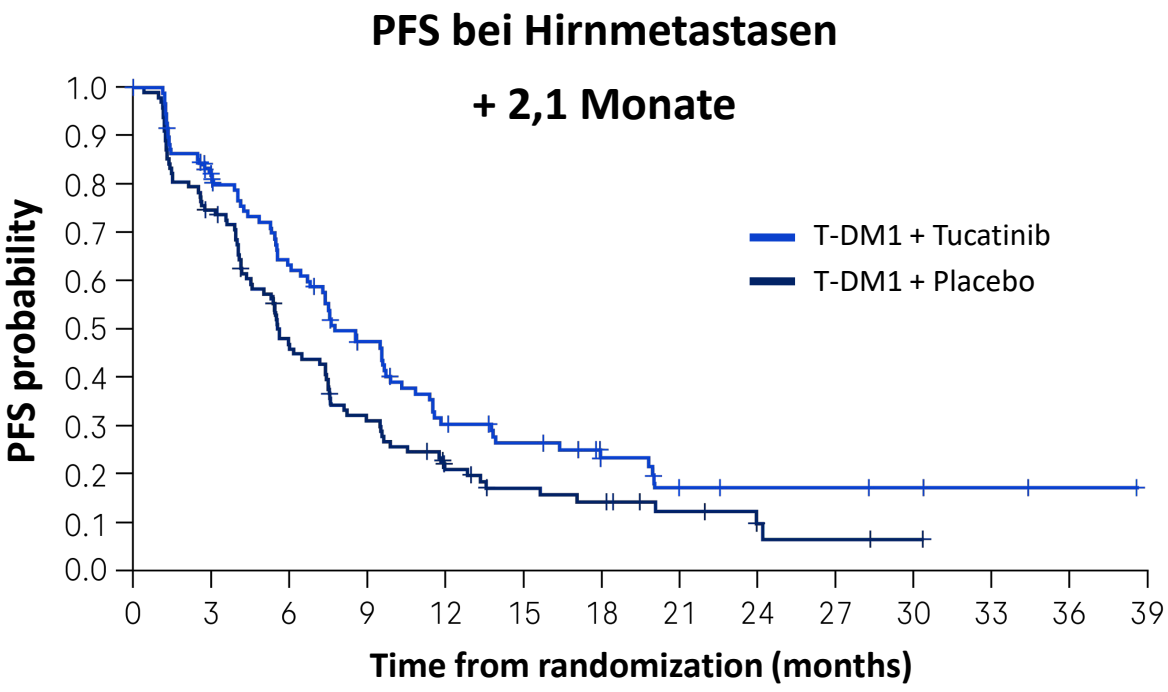
[b]Subsequent OS analyses are planned upon 80% and 100% of required events for the final OS analysis.

Mod. Hurvitz S et al. SABCS 2023, General Session – General Session 1, Abstract No. GS01-10

HER2CLIMB-02 – PFS in der Gesamtpopulation & bei Hirnmetastasen





	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	151	182
Median PFS (95% CI)	9.5 months (7.4, 10.9)	7.4 months (5.6, 8.1)
HR (95% CI): 0.76 (0.61, 0.95); *p*=0.0163		

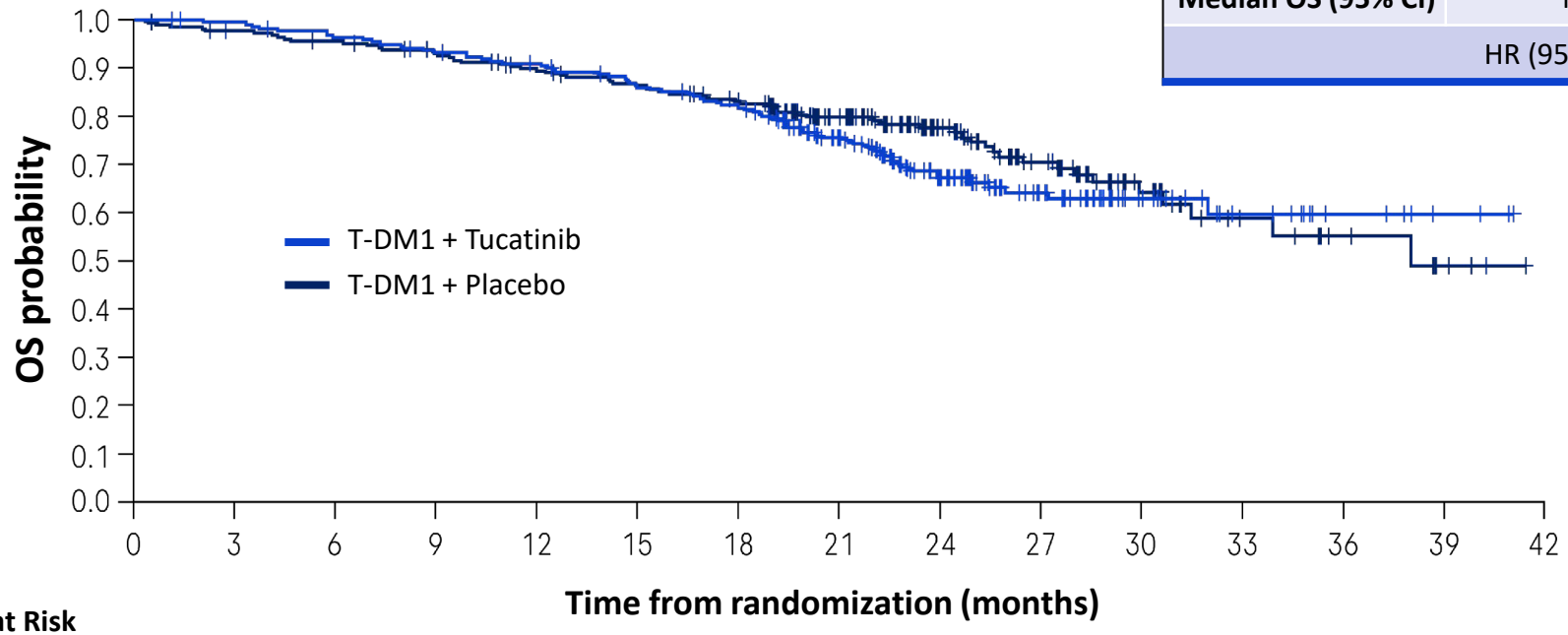
	T-DM1 + Tucatinib (N=99)	T-DM1 + Placebo (N=105)
# of events	70	85
Median PFS (95% CI)	7.8 months (6.7, 10.0)	5.7 months (4.6, 7.5)
HR (95% CI)[a]: 0.64 (0.46, 0.89)		

[a]The outcome was not formally tested.

Mod. Hurvitz S et al. SABCS 2023, General Session – General Session 1, Abstract No. GS01-10

HER2CLIMB-02 – Gesamtüberleben

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	71	63
Median OS (95% CI)	NR (NR, NR)	38.0 months (31.5, NR)
HR (95% CI)[a]: 1.23 (0.87, 1.74)		



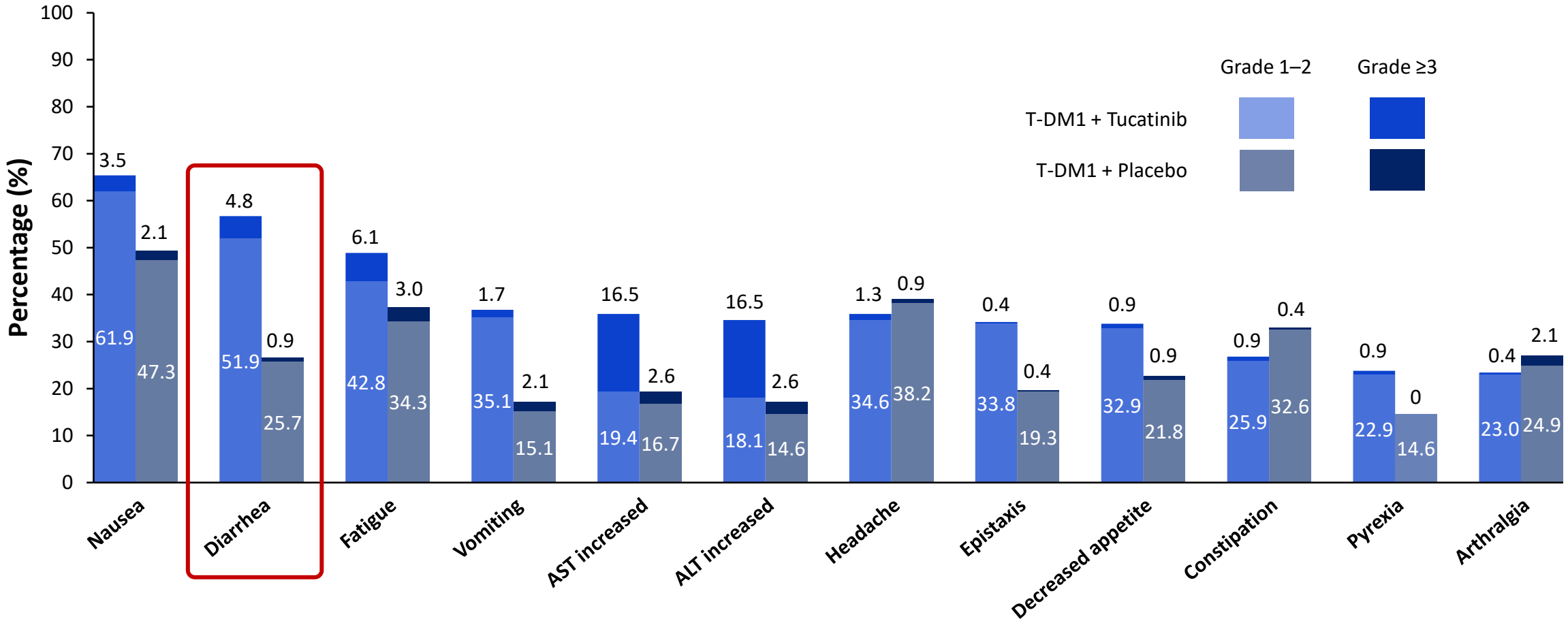
No. at Risk															
T-DM1 + Tucatinib	228	225	217	209	202	189	180	132	89	55	30	16	7	3	0
T-DM1 + Placebo	235	227	221	212	201	191	180	135	90	58	32	16	10	4	0

Median follow-up was 24.4 months. As of data cutoff, 134 out of 253 (53%) prespecified events for the OS final analysis were observed. Interim OS results did not meet the prespecified crossing boundary of *p*≤0.0041.

[a]The proportional hazard assumption was not maintained post-18 months, with extensive censoring on both arms.

Mod. Hurvitz S et al. SABCS 2023, General Session – General Session 1, Abstract No. GS01-10

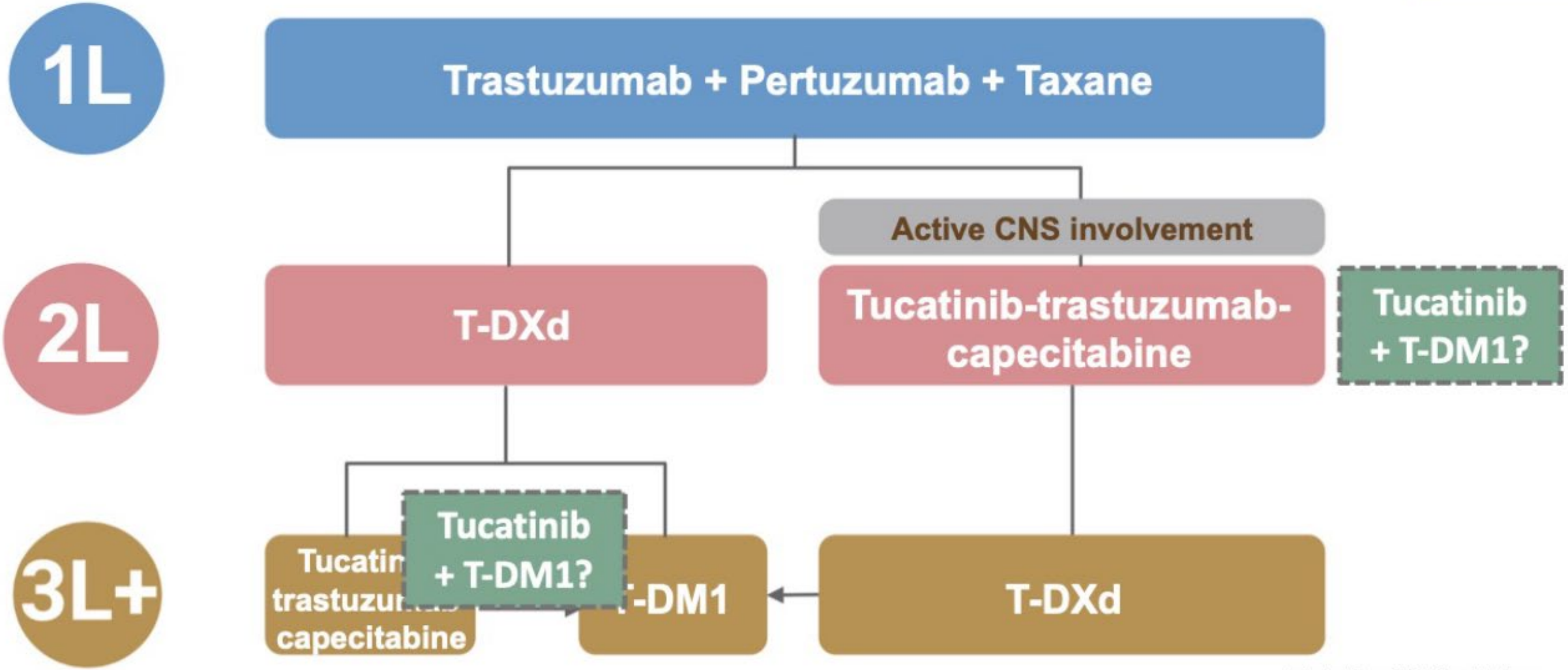
HER2CLIMB-02 – Nebenwirkungsprofil



[1]Curigliano et al. *Ann Onc* 2022.

Mod. Hurvitz S et al. SABCS 2023, General Session – General Session 1, Abstract No. GS01-10

Current algorithm: where will HER2CLIMB-02 fit in?



Adapted from ESMO guidelines

Mod. Guarneri V SABCS 2023, General Session – General Session 1, discussion No. GS01-10

HER2-positives, metastasiertes Mammakarzinom: 1st-3rd-line

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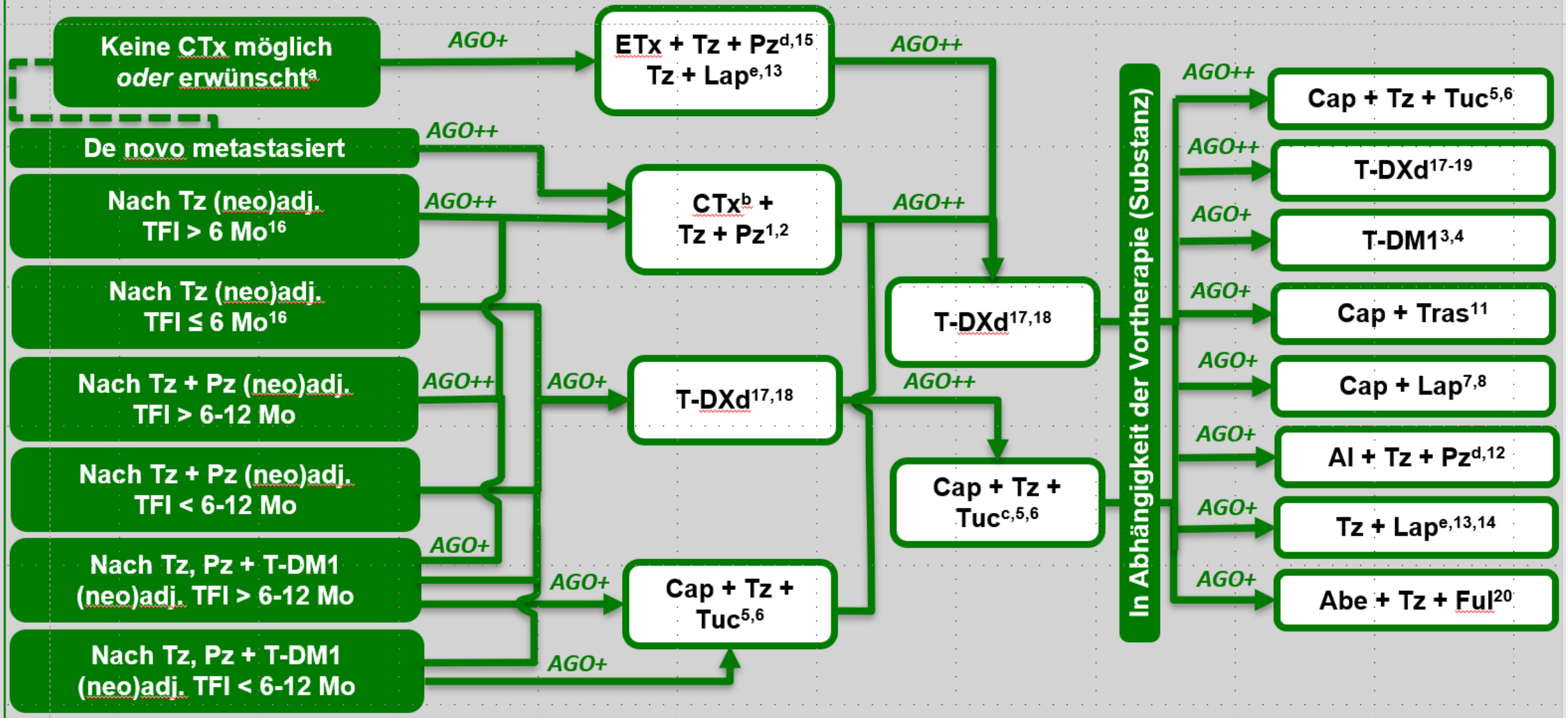

Abe, Abemaciclib; AI, Aromatasehemmer; Cap, Capecitabin; CTx, Chemotherapie; ETx, endokrine Therapie; Ful, Fulvestrant; HER2, humaner epithelialer Wachstumsfaktor-Rezeptor 2; HR, Hormonrezeptor; Lap, Lapatinib; Mo, Monate; Pz, Pertuzumab; T-DM1, Trastuzumab Emtansin; T-DXd, Trastuzumab Deruxtecan; TFI, treatment-free interval; Tuc, Tucatinib; Tz, Trastuzumab; [a]kein Überlebensvorteil, CTx in Erwägung ziehen; [b]Docetaxel (++), Paclitaxel (++), nab-Paclitaxel (+), Vinorelbin (+, nur sekundär metastasiert); [c]nur nach T-DM1; [d]nur HR pos; [e]nur HR neg.

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Metastasiertes Mammakarzinom TNBC

Trop2-ADC plus IO bei mTNBC

BEGONIA: Dato-DXd plus Durvalumab

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The BEGONIA Study (NCT03742102)

Rationale

- Immune checkpoint inhibitors + chemotherapy is the standard of care for patients with PD-L1 positive a/mTNBC; still, most progress within a year (median PFS ~9–10 months)[1,2]
- BEGONIA is evaluating combinations of durvalumab (D), an anti–PD-L1 antibody, with other novel therapies in first-line a/mTNBC
- Dato-DXd is a TROP2-directed ADC with a TOPO I inhibitor payload and a tumour-selective cleavable linker[3]
- At median 7.2 months follow-up, ORR was 74% for patients treated with Dato-DXd + D in BEGONIA[4]

Study Design

Eligibility criteria

- Females aged ≥18 years
- Unresectable a/mTNBC
- No prior treatment for Stage IV TNBC
- ≥12 months since prior taxane therapy
- ECOG PS 0-1
- Adequate organ function
- Measurable disease per RECIST v1.1
- No prior treatment with checkpoint inhibitor
- No prior treatment with TOPO I-based ADC[a]

Treatment arms

- Arm 1: Paclitaxel (P) + D (N=20)
- Arm 2: Capivasertib + P + D (N=30)
- Arm 5: Oleclumab + P + D (N=30)
- Arm 6: T-DXd + D (N=30)
- **Arm 7: Dato-DXd 6 mg/kg + D 1120 mg** (N=30) Q3W until PD
- Arm 8: Dato-DXd + D, PD-L1 positive (N=30)[b]

Part 1

Safety run-in (up to 6 patients)

Simon 2-stage futility analysis for Part 2 expansion[c]

1° endpoint: Safety and tolerability
2° endpoints: ORR, PFS, DoR, OS

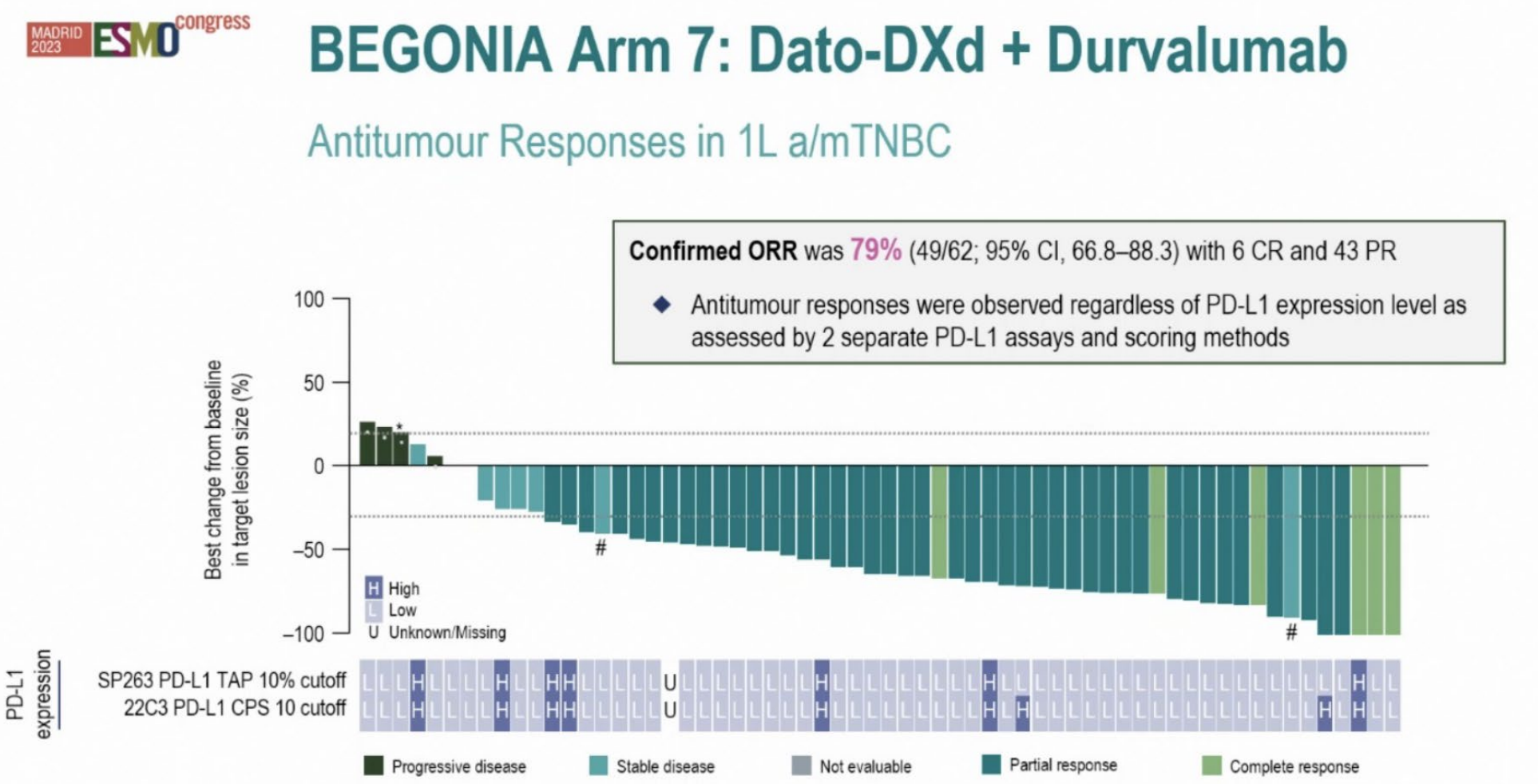
Part 2 expansion

Arms that meet expansion criteria enrol additional 27 patients

1° endpoint: ORR
2° endpoints: PFS, DoR, PFS6, OS

Trop2-ADC plus IO bei mTNBC

BEGONIA: Dato-DXd plus Durvalumab



Dotted lines indicate thresholds for partial response (−30%) and progressive disease (20%). PD-L1 expression was assessed by 1) immunohistochemistry using the VENTANA PD-L1 (SP263) Assay with expression defined as the percentage of the tumour area populated by tumour or immune cells with membranous staining (TAP), or 2) immunohistochemistry using the 22C3 antibody with expression defined as the number of PD-L1–staining tumour cells, lymphocytes, and macrophages, divided by the total number of viable tumour cells, multiplied by 100 (CPS). [#]If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. "•" Patients with PD as best overall response. [#]Unconfirmed response.

1L, first line; a/m TNBC, advanced/metastatic triple–negative breast cancer; CI, confidence interval; CPS, combined positive score; CR, complete response; Dato-DXd, datopotamab deruxtecan; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PR, partial response; TAP, tumour area positivity.

Data cutoff: 02 Feb 2023

Trop2-ADC plus IO bei mTNBC

BEGONIA: Dato-DXd plus Durvalumab

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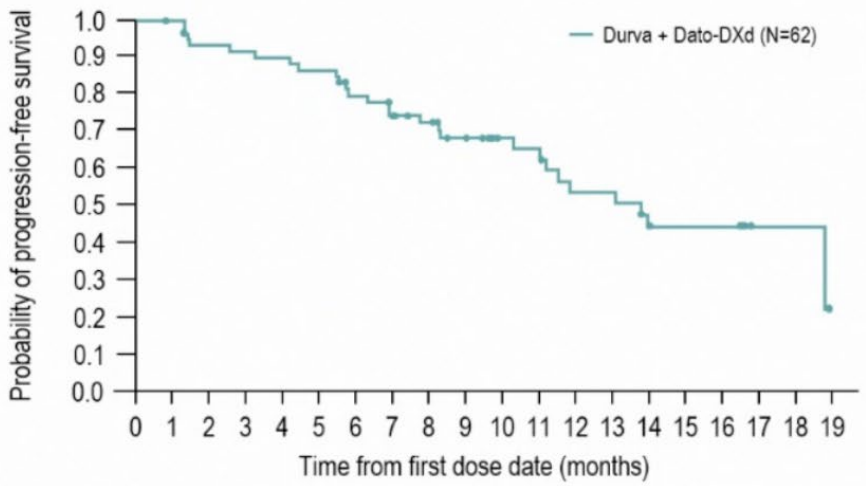
BEGONIA Arm 7: Dato-DXd + Durvalumab

Progression-Free Survival and Duration of Response

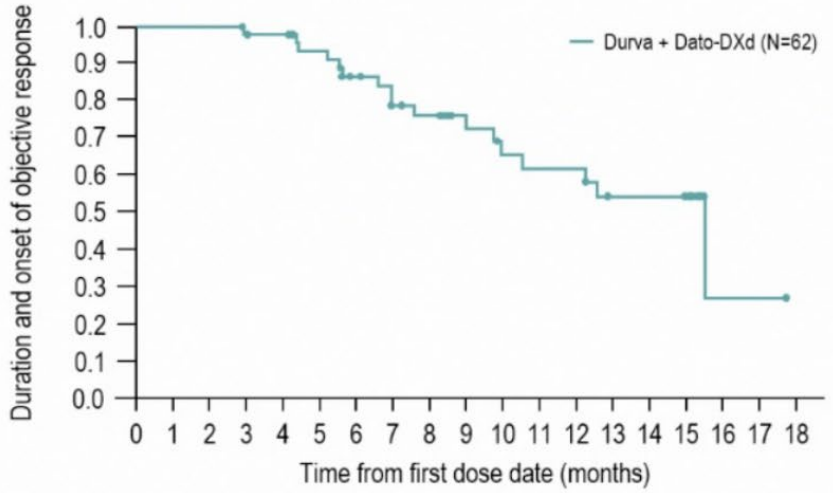
Median PFS was 13.8 months (95% CI, 11.0–NC)



Number of patients at risk

Durva + Dato-DXd	62	61	56	55	54	52	45	40	37	32	24	23	18	18	14	13	13	2	2	0

Median DoR was 15.5 months (95% CI, 9.92–NC)



Number of patients at risk

Durva + Dato-DXd	49	49	49	47	46	42	35	30	28	21	18	17	17	13	13	12	1	1	0

Kaplan-Meier analysis was performed. Circles indicate censored observations.
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; NC, not calculable; PFS, progression-free survival.

Data cutoff: 02 Feb 2023

Triple-negatives, metastasiertes Mammakarzinom

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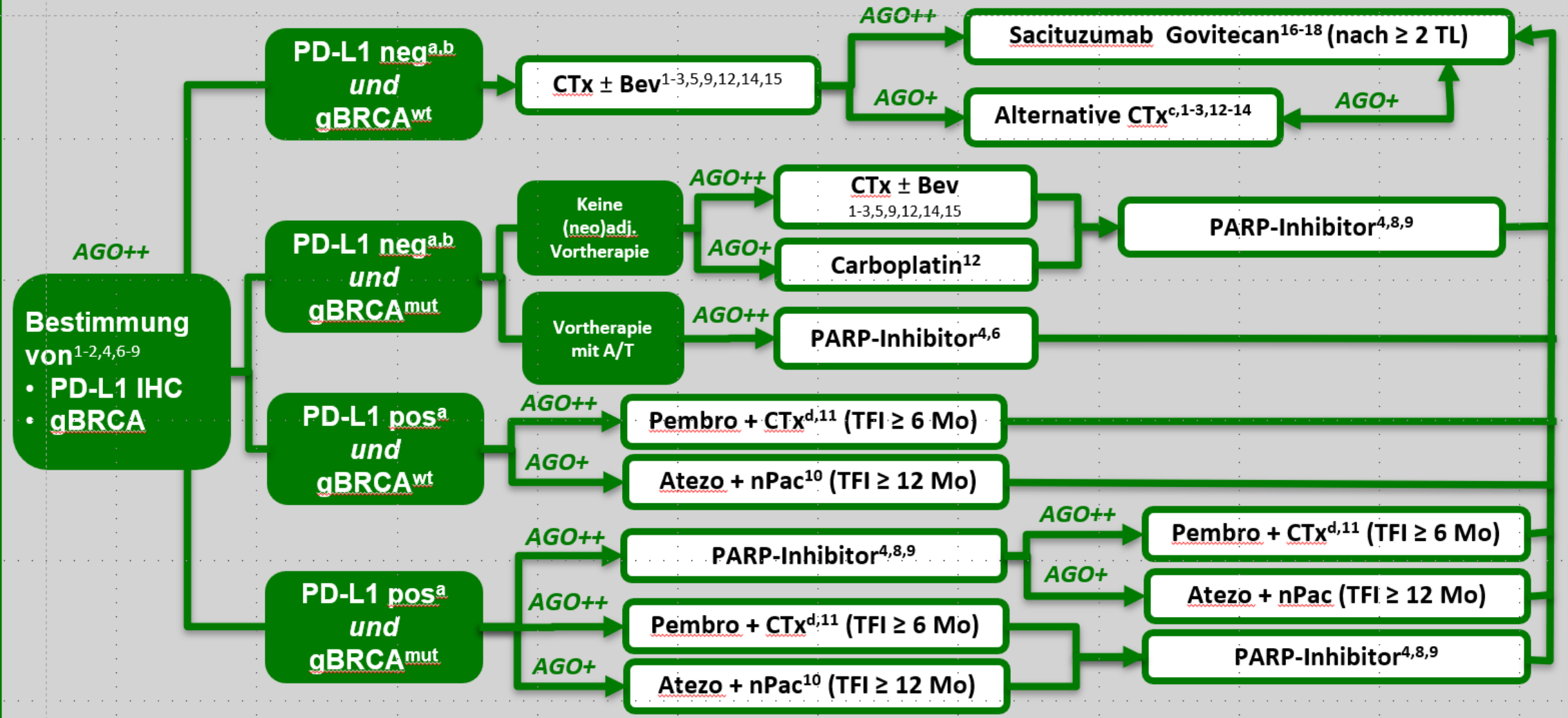

A, Anthrazyklin; Atezo, Atezolizumab; Bev, Bevacizumab; CTx, Chemotherapie; gBRCA, BRCA Keimbahnstatus; IHC, Immunhistochemie; Mo, Monate; mut, mutiert; neg, negativ; nPac, nab-Paclitaxel; Pembro, Pembrolizumab; PD-L1, programmed cell death ligand 1; pos, positiv; T, Taxan; TFI, Therapie-freies Intervall; wt, wild type; TL, Therapielinie; [a]Pembro: CPS < 10 (neg) oder CPS ≥ 10 (pos), Atezo: IC < 1% (neg), IC ≥ 1% (pos); [b]PD-L1 pos mit einem TFI < 6-12 Mo; [c]Einsatz bisher nicht genutzter Substanzen oder Regime ; [d]nPac, Pac oder Carboplatin+Gemcitabin.

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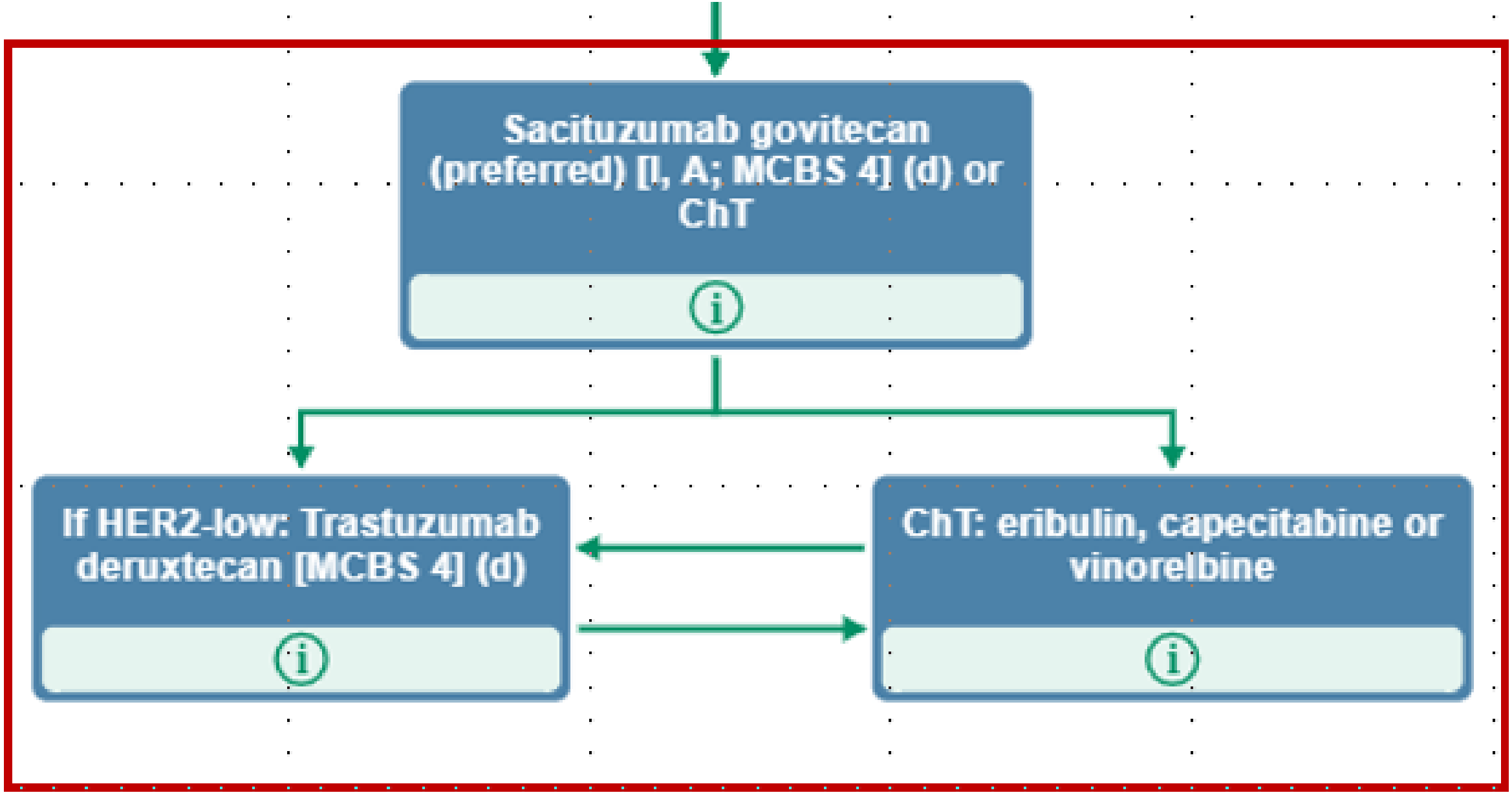
Sacituzumab govitecan (preferred) [I, A; MCBS 4] (d) or ChT
If HER2-low: Trastuzumab deruxtecan [MCBS 4] (d)
ChT: eribulin, capecitabine or vinorelbine

Gedanken für den Nach-Hause-Weg

Update Mammakarzinom

Gedanken für den Nach-Hause-Weg

- eHR+: CDK4/6-Inhibitoren und ICI im Vormarsch
- eHER2+: TDM-1 in der Postneoadjuvanz mit OS-Daten bestätigt
- Endokrine Resistenz wird zunehmend molekular definiert
- mER+ HER2low: ADC-Sequenz T-DXd → SG
- mTNBC HER2low: ADC-Sequenz SG → T-DXd

IMMANUEL ALBERTINEN DIAKONIE
IMMANUEL KLINIK MÄRKISCHE SCHWEIZ

Herzlichen Dank für Ihre Aufmerksamkeit

In besten Händen, dem Leben zuliebe.

Prof. Dr. med. Diana Lüftner

Immanuel Klinik Märkische Schweiz & Immanuel Campus Rüdersdorf/Med. Hochschule Brandenburg