

The background of the image is an abstract, fluid pattern of flowing waves. The colors range from deep, dark blue and purple on the left to bright, glowing cyan and light blue on the right. The waves are smooth and undulating, creating a sense of movement and depth. The overall effect is reminiscent of liquid light or a digital fluid simulation.

AmerisourceBergen



Filipa Lynce, MD

Dr. Lynce received her medical degree from the Universidade Nova de Lisboa, Portugal in 2004. She completed her residency in Internal Medicine and fellowship in Hematology and Medical Oncology at MedStar Washington Hospital Center/MedStar Georgetown University Hospital. She was faculty at MedStar Georgetown University Hospital from 2015 to 2020 where she served as the institutional PI for Alliance and the co-PI of the National Capital Area (NCA) Minority/Underserved NCORP. In 2020, she joined the staff of Dana-Farber Cancer Institute and Brigham and Women's Hospital, where she is a medical oncologist and clinical investigator in the Breast Oncology Center. Her research focuses on inflammatory breast cancer, triple-negative breast cancer, BRCA-associated breast cancers and novel therapies in the treatment of breast cancer.

Most Important Advances in Breast Cancer 2022

10.14.2022

Filipa Lynce, MD
Breast Medical Oncologist
Dana-Farber Cancer Institute
Harvard School of Medicine

Outline (2019)

- **Hormone Receptor (HR) Positive**
 - Alpelisib → SOLAR-1
- **HER2 Positive**
 - TDM1 in residual disease → KATHERINE
 - Trastuzumab, pertuzumab and docetaxel → CLEOPATRA updated OS
 - SAFE-HEART
- **Triple Negative Breast Cancer (TNBC)**
 - Atezolizumab and nabpaclitaxel → IMPASSION130

Outline (2020)

- **Hormone Receptor (HR) Positive**
- **HER2 Positive**
 - Trastuzumab Deruxtecan → DESTINY-Breast01
 - Tucatinib, trastuzumab and capecitabine → HER2CLIMB
 - Neratinib and capecitabine -> NALA trial
- **Triple Negative Breast Cancer (TNBC)**
 - Sacituzumab govitecan -> ASCENT trial
 - KEYNOTE-355
- **HR pathway genes mutations**
 - TBCRC 048

Outline (2021)

- **Hormone Receptor (HR) Positive**
 - Abemaciclib → monarchE
- **HER2 Positive**
 - Trastuzumab Deruxtecan → DESTINY-Breast03
- **Triple Negative Breast Cancer (TNBC)**
 - Pembrolizumab → KEYNOTE-522 and KEYNOTE-355
- **BRCA associated tumors**
 - Olaparib → OLYMPIA

Outline (2022)

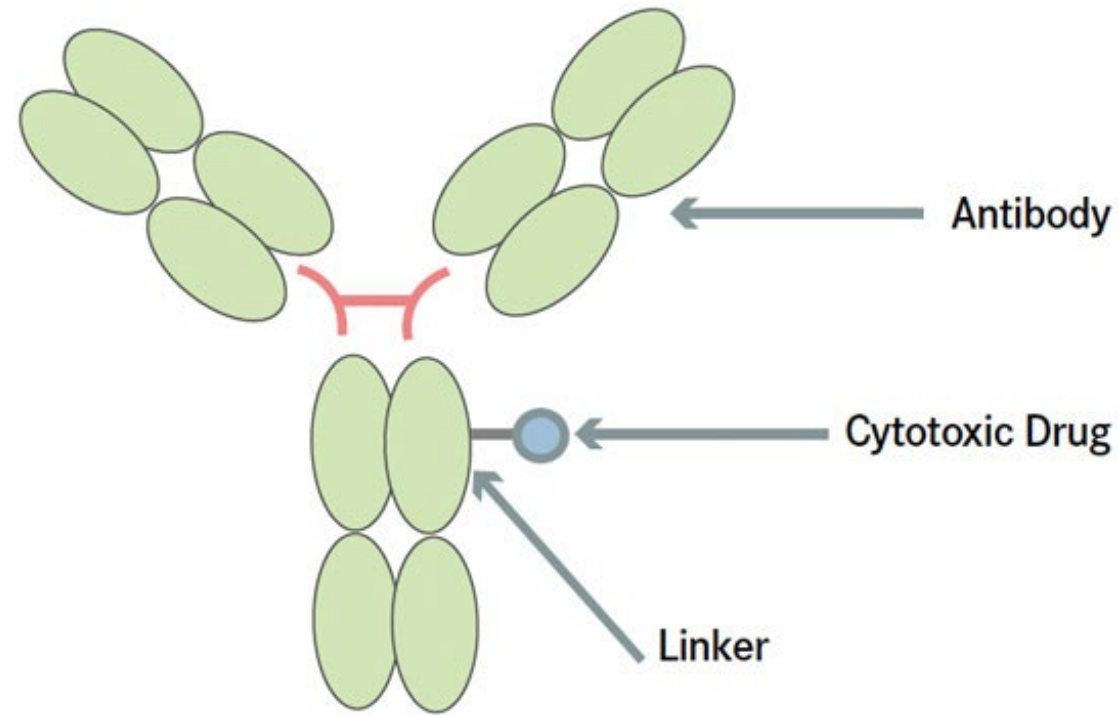
- **Hormone Receptor (HR) Positive**
 - DESTINY-Breast04
 - TROPICS-02
 - MAINTAIN
- **Triple Negative Breast Cancer (TNBC)**
 - DESTINY-Breast04
- **BRCA associated tumors**
 - OLYMPIA survival data
- **Local therapy**
 - E2108
 - NRG-BR002

Outline (2022)

- **Hormone Receptor (HR) Positive**
 - DESTINY-Breast04
 - TROPICS-02
 - MAINTAIN
- **Triple Negative Breast Cancer (TNBC)**
 - DESTINY-Breast04
- **BRCA associated tumors**
 - OLYMPIA survival data
- **Local therapy**
 - E2108
 - NRG-BR002

Antibody Drug Conjugates (ADCs)

- Deliver a toxic payload directly to the cancer cell
- Examples:
 - **Ado-trastuzumab emtansine**
 - **Trastuzumab deruxtecan**
 - **Sacituzumab govitecan**
 - **SGN-LIV1A**



Trastuzumab Deruxtecan

DESTINY-Breast01 (NCT03248492)

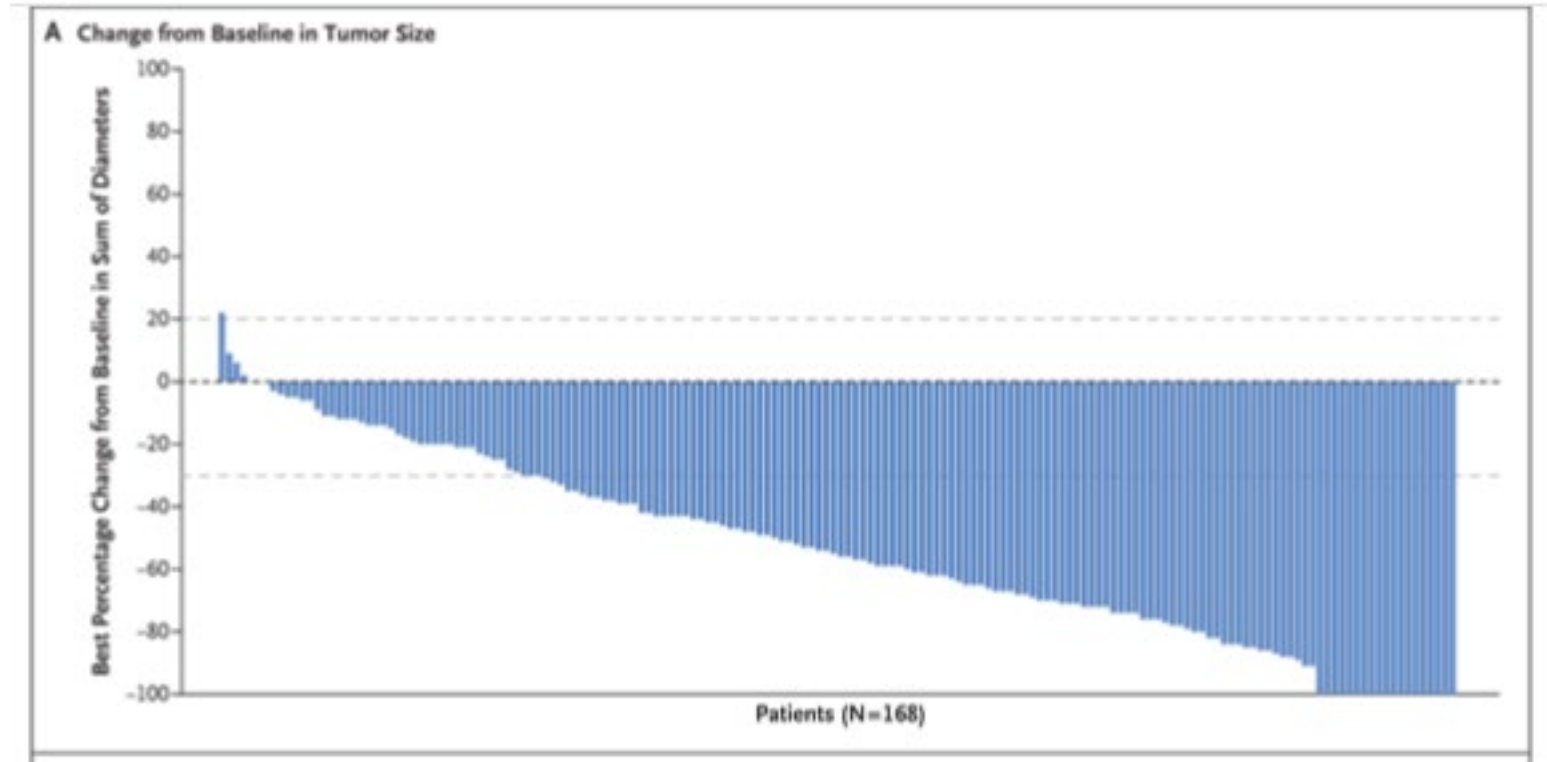
*2-part, open-label, single-group,
multicenter phase 2 study*

Patient Population (N = 184)

- ✓ *HER2+ metastatic breast cancer*
- ✓ *Previously received TDM1*
- ✓ *Median of 6 previous treatments*

ORR: 61%

PFS: 16.4 months



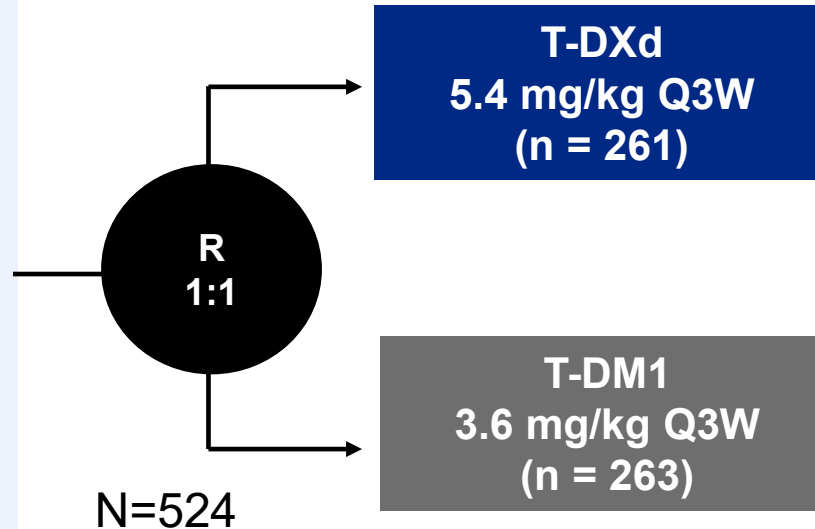
DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

Patients

- Unresectable or metastatic HER2-positive^a breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting^b
- Could have clinically stable, treated brain metastases

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS

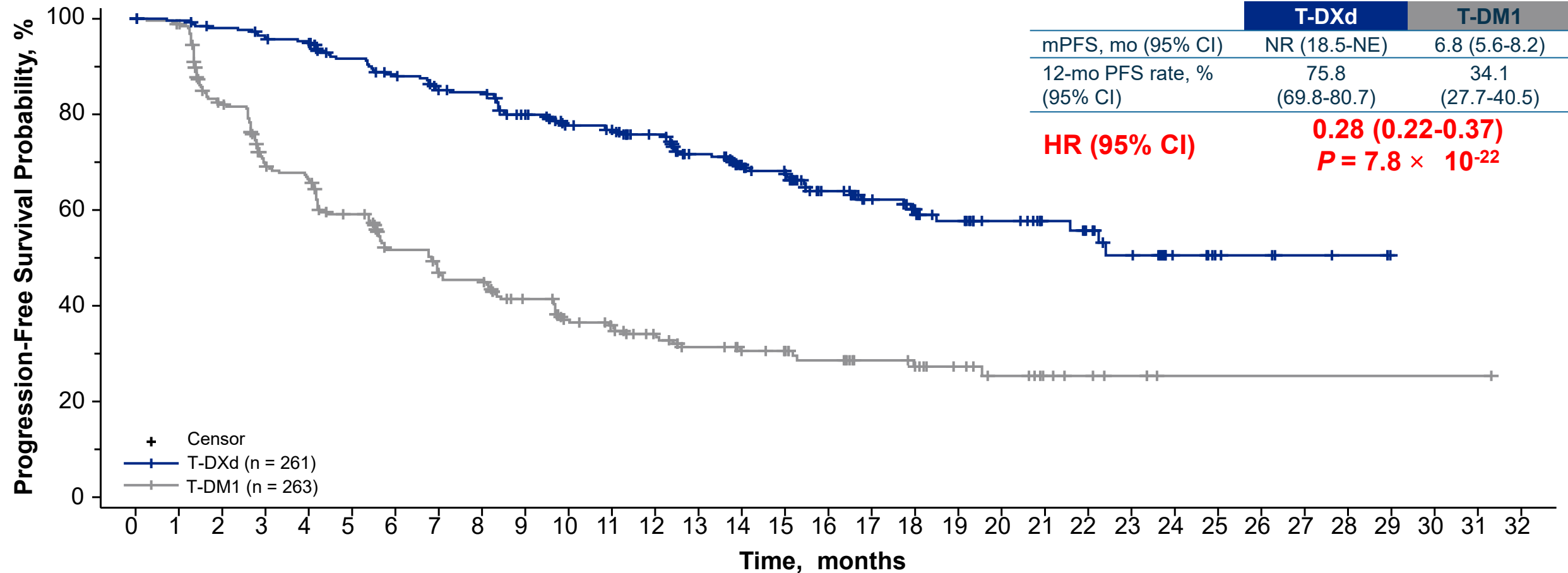
Secondary endpoints

- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Prior therapy for MBC:

- 100% received prior trastuzumab
- 60% received prior pertuzumab
- 16% received HER2 TKI

DB03: Primary Endpoint - PFS by BICR



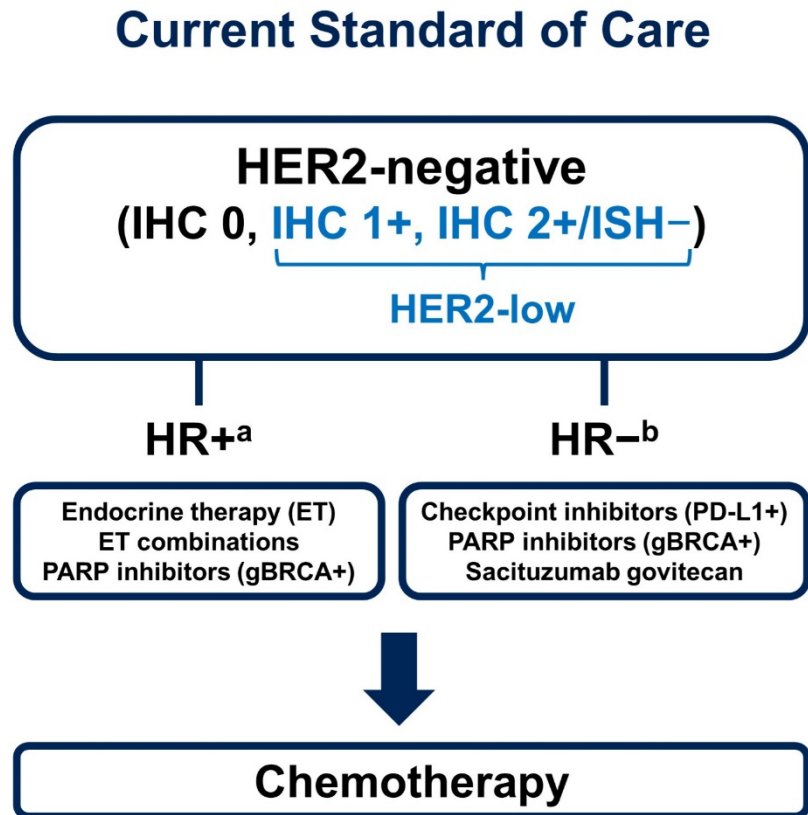
Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0		
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	0

FDA Approval: Trastuzumab Deruxtecan in mHER2+ Breast Cancer

- December 2019: fam-trastuzumab deruxtecan-nxki received accelerated approval for 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.
- May 4, 2022: the FDA approved fam-trastuzumab deruxtecan-nxki for adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy

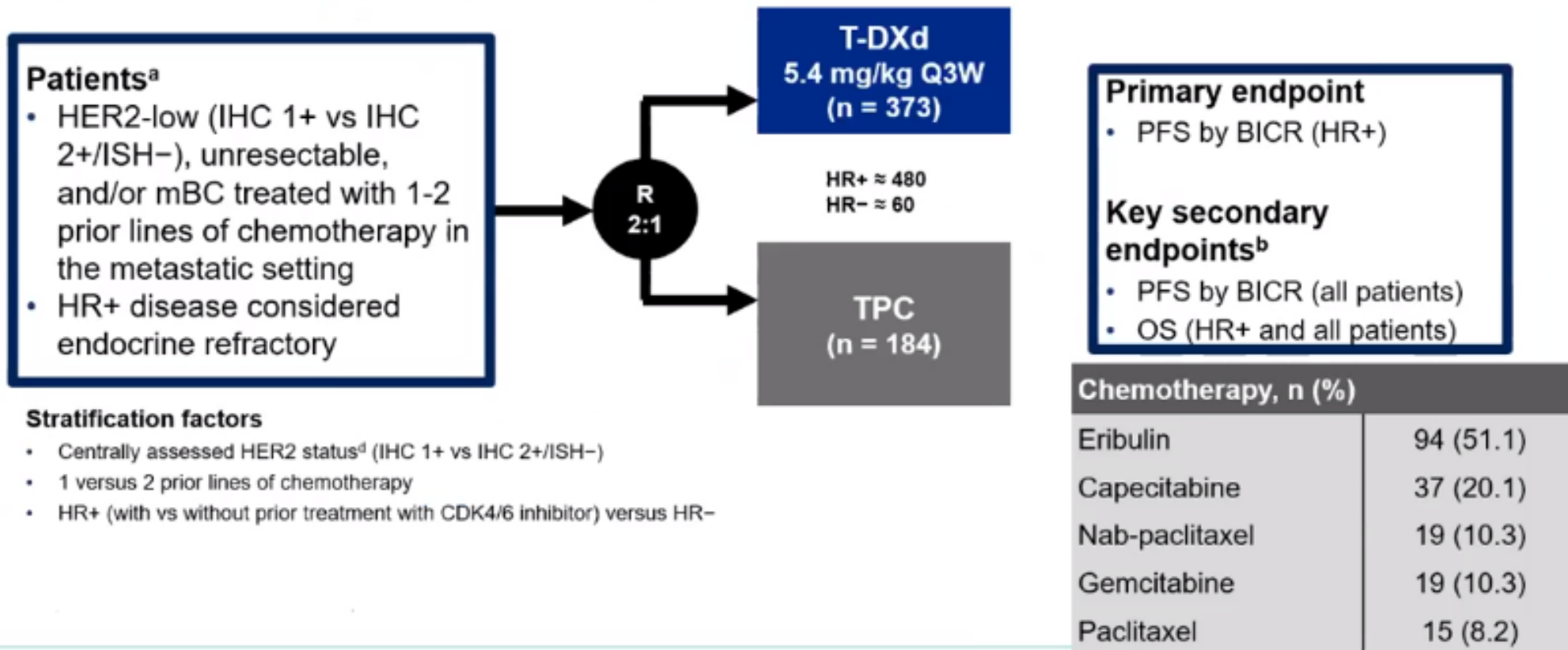
HER2 low: unmet need



- **HER2-low mBC is defined by IHC scores of 1+ or 2+/ISH-**
 - This is a heterogeneous population with a high prevalence of HR coexpression and without a distinct biology
- **HER2-low mBC is treated as HER2- mBC, with limited options for later lines of therapy¹⁻⁴**
 - Current HER2-targeted therapies are not effective for patients with tumors that express lower levels of HER2
- **Therapeutic options for patients with HR+/HER2- mBC after CDK4/6i progression have limited efficacy**
 - Real-world studies suggest a PFS of <4 months after progressive disease with CDK4/6i⁵
- **Limited benefit exists for patients who progress after multiple lines of chemotherapy**
 - In a pooled analysis of patients with HER2- mBC, eribulin and capecitabine provide minimal benefit, with a mPFS of ~4 months and mOS of ~15 months⁶

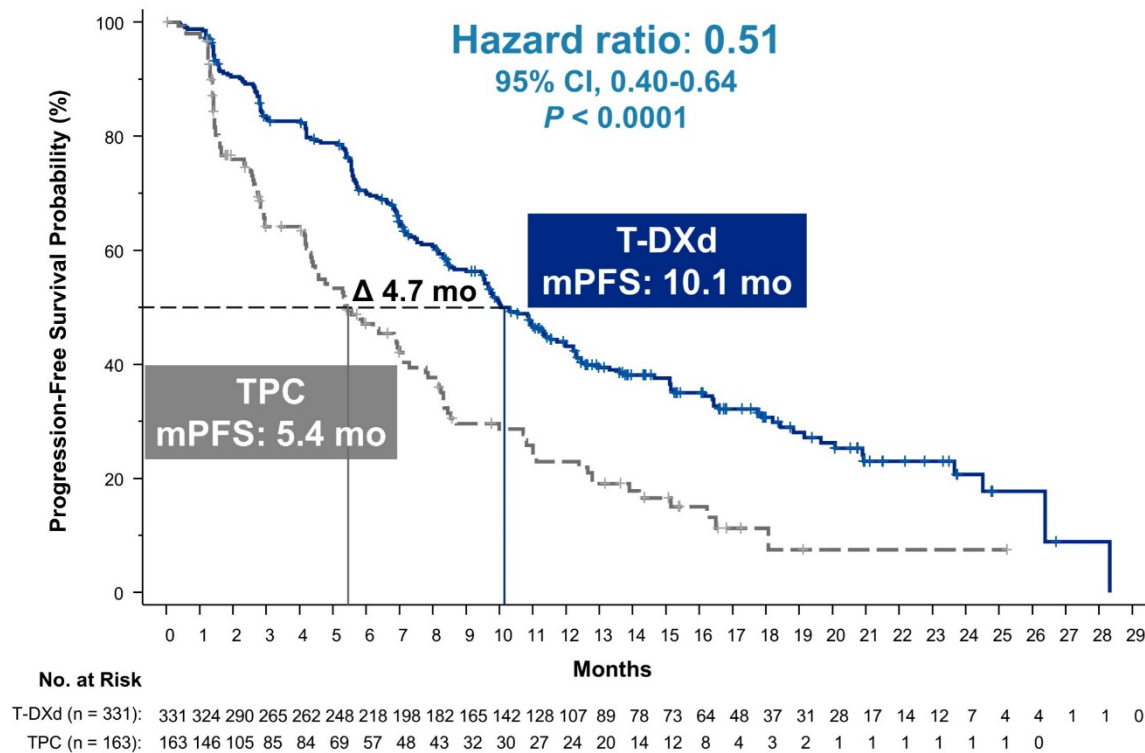
DESTINY-Breast04

An open-label, multicenter study (NCT03734029)

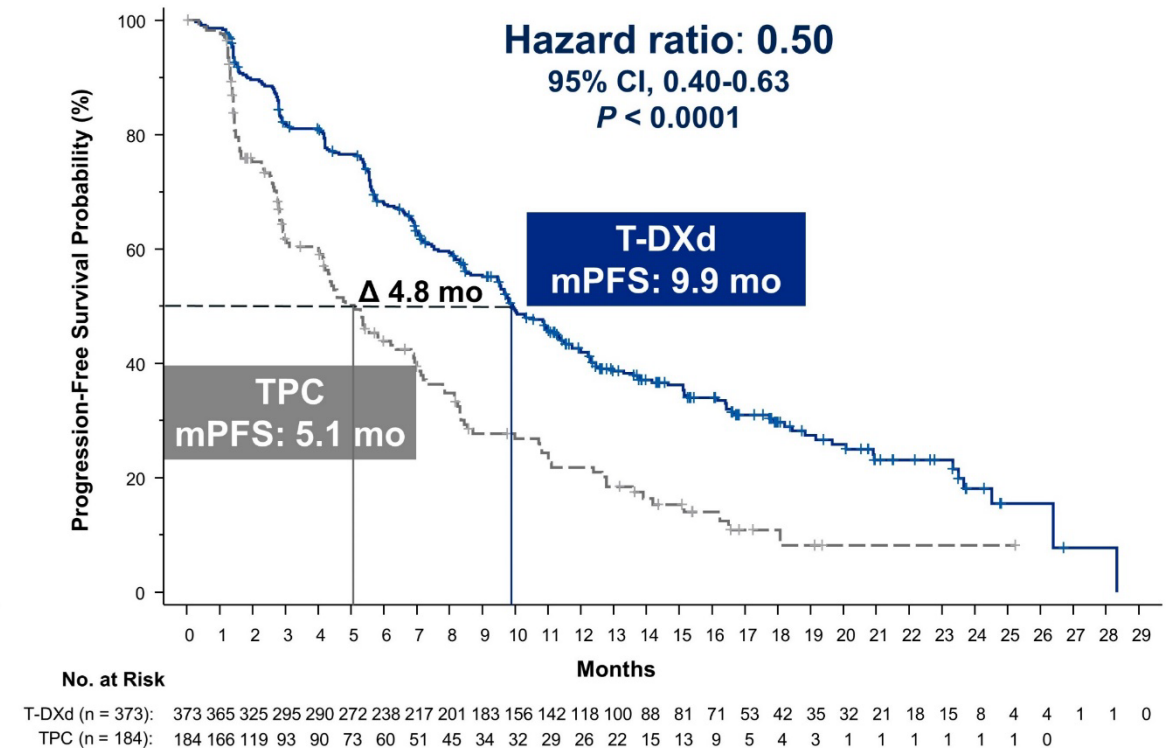


DESTINY-B04: PFS results

Hormone receptor–positive

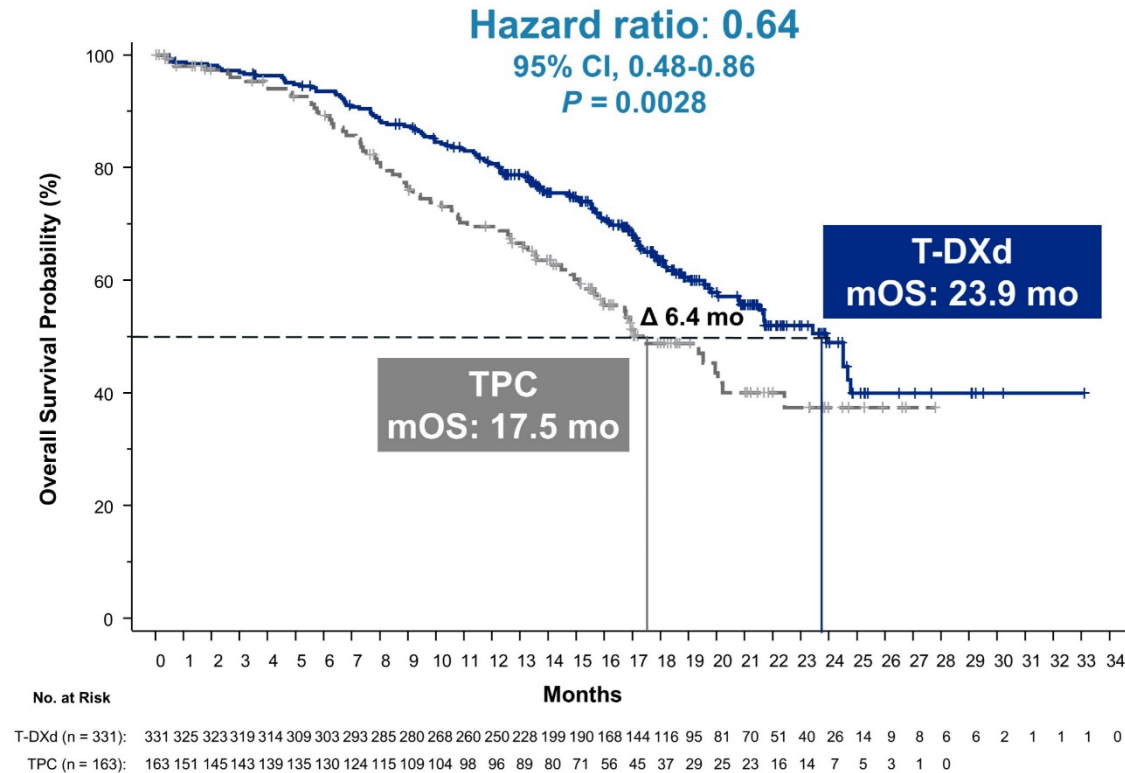


All patients

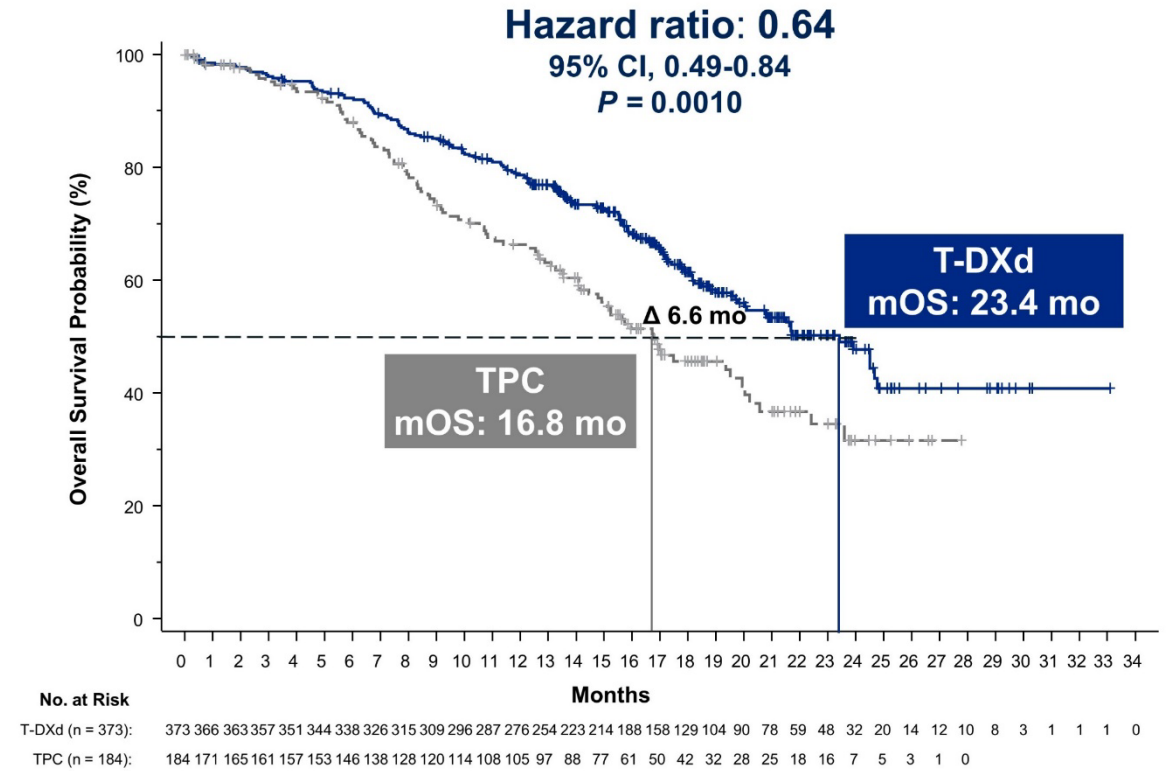


DESTINY-B04: OS results

Hormone receptor–positive

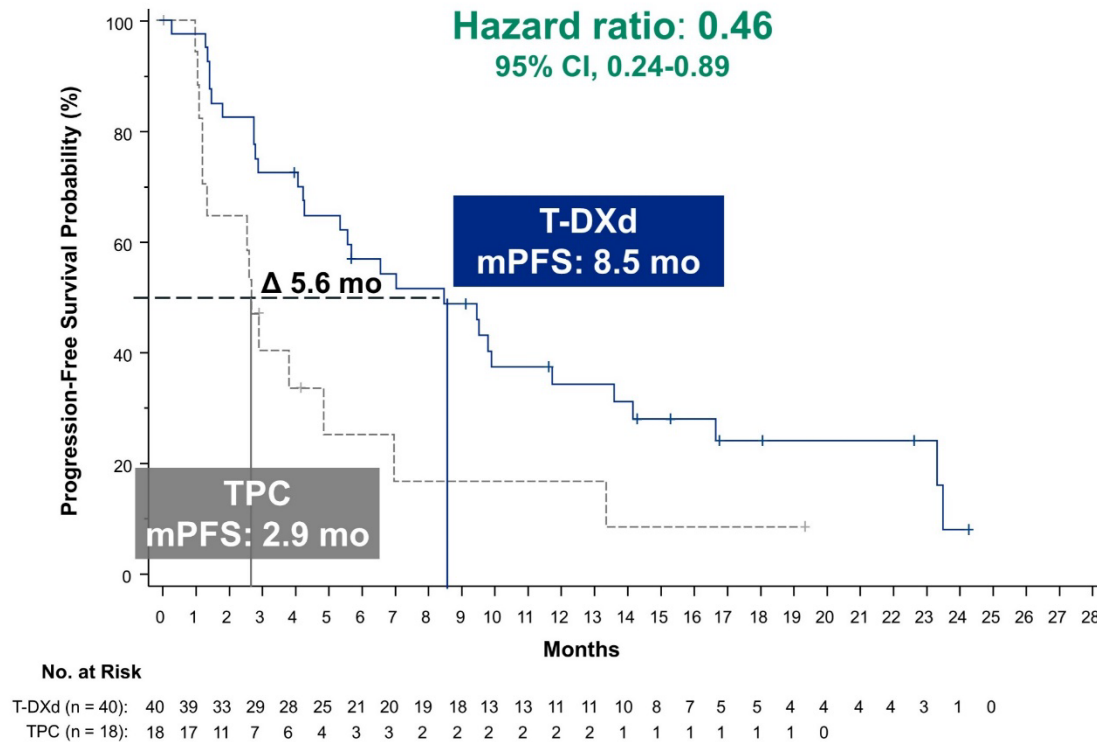


All patients

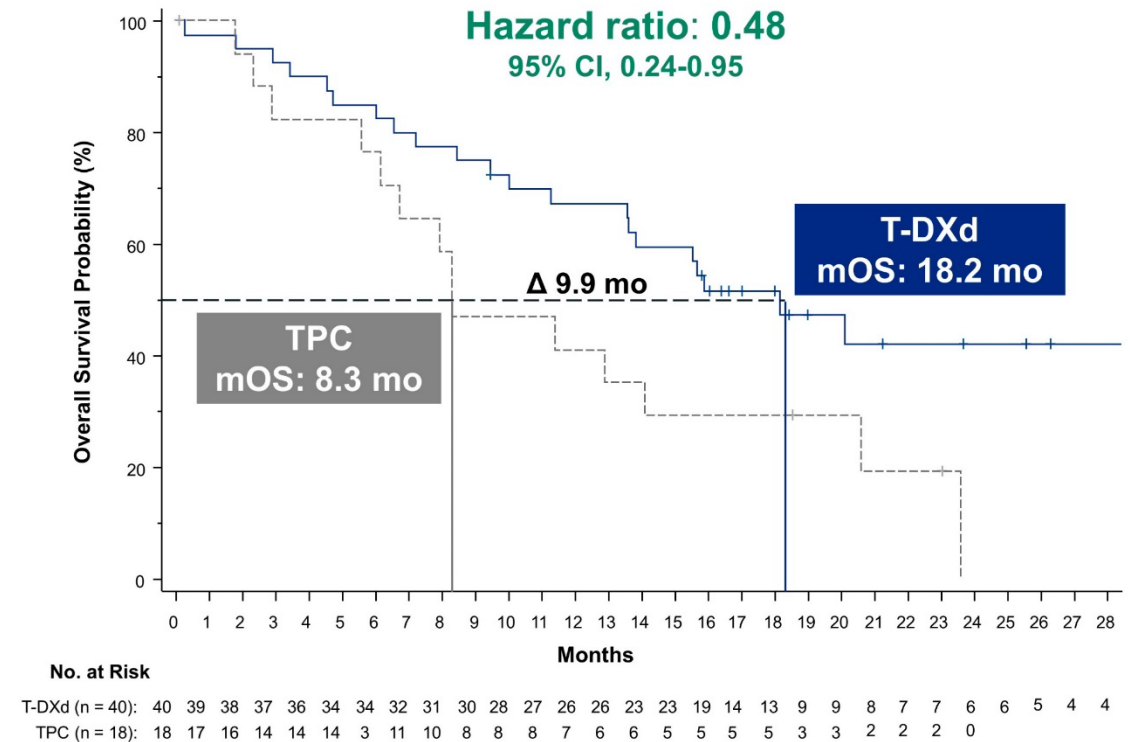


DESTINY-B04: Outcomes in ER neg

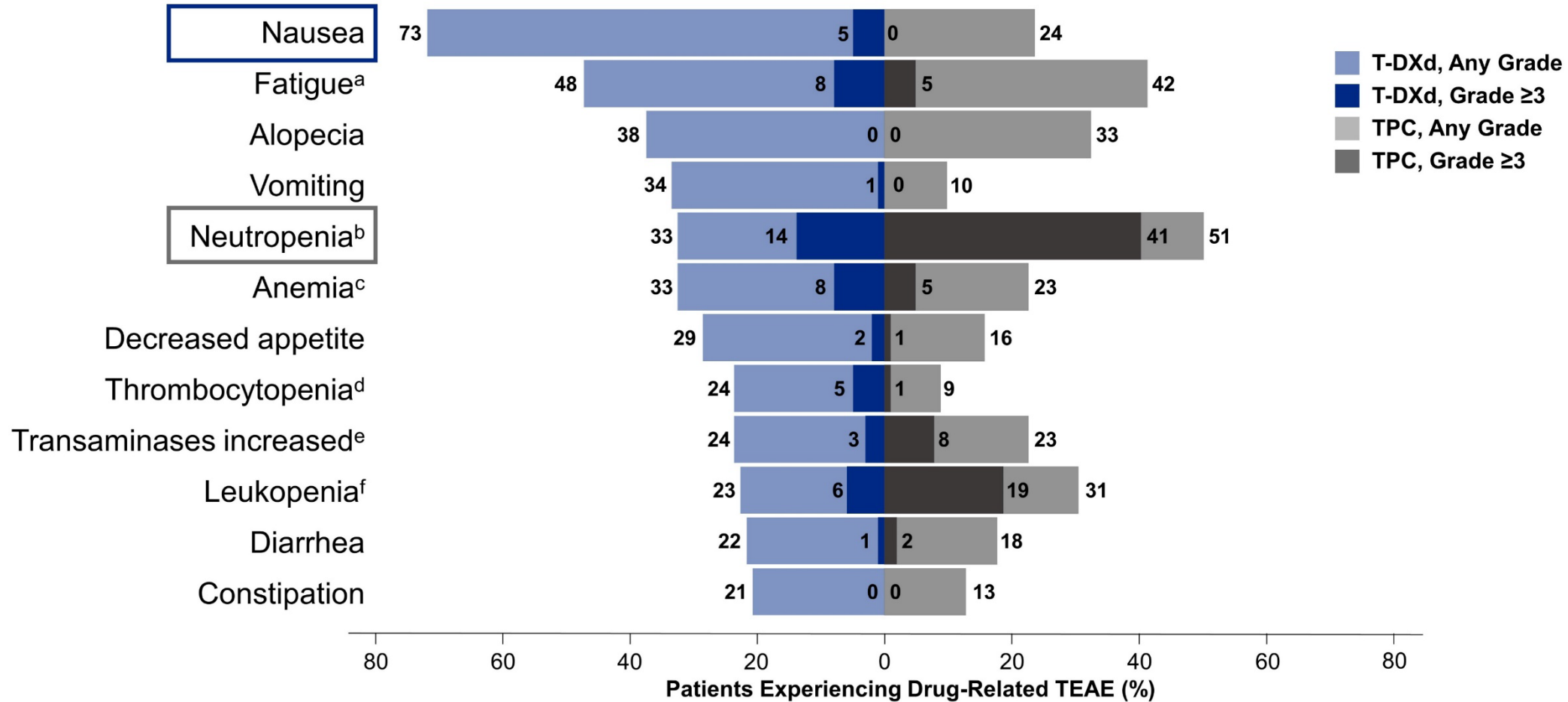
PFS



OS



DESTINY-B04: Drug-Related TEAEs in $\geq 20\%$ of Patients



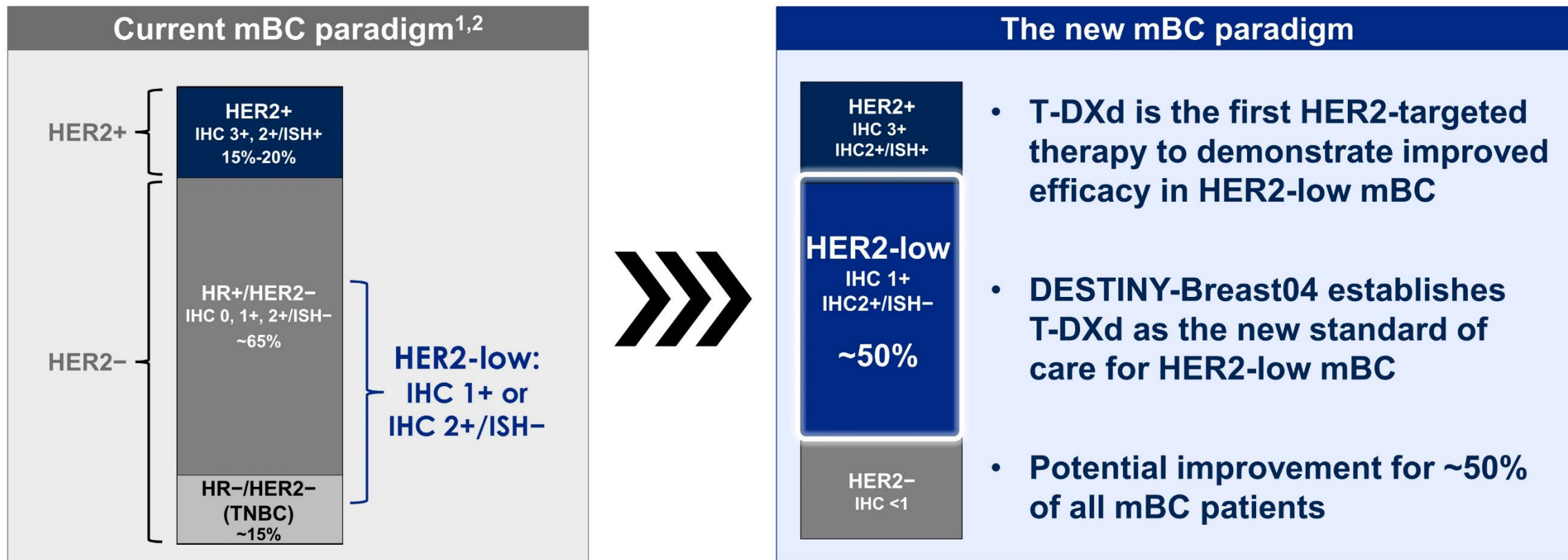
DESTINY-B04: Overall Safety Summary

n (%)	Safety analysis set ^a	
	T-DXd (n = 371)	TPC (n = 172)
Total patient-years of exposure, years ^b	283.55	63.59
TEAEs	369 (99)	169 (98)
Grade ≥3	195 (53)	116 (67)
Serious TEAEs	103 (28)	43 (25)
TEAEs associated with dose discontinuations	60 (16)	14 (8)
TEAEs associated with dose interruptions	143 (39)	72 (42)
TEAEs associated with dose reductions	84 (23)	66 (38)
TEAEs associated with deaths	14 (4)	5 (3)

- Median treatment duration
 - T-DXd: 8.2 months (range, 0.2-33.3)
 - TPC: 3.5 months (range, 0.3-17.6)
- Most common TEAE associated with treatment discontinuation
 - T-DXd: 8.2%, ILD/pneumonitis^c
 - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction
 - T-DXd: 4.6%, nausea and fatigue^d
 - TPC: 14.0%, neutropenia^d
- Total on-treatment deaths^e
 - T-DXd: 3.8%
 - TPC: 4.7%

DESTINY-Breast04

T-DXd treatment showed unprecedented improvement in efficacy for patients with HER2-low mBC



FDA Approval: Trastuzumab Deruxtecan in mHER2+ Breast Cancer

- On August 5, 2022, the FDA approved fam-trastuzumab deruxtecan-nxki (brand name Enhertu®) for adult patients with unresectable or metastatic HER2-low breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy.
- HER2-low expression was defined as IHC 1+ or IHC 2+/ISH-, determined at a central laboratory.

Outline (2022)

- **Hormone Receptor (HR) Positive**
 - DESTINY-Breast04
 - TROPICS-02
 - MAINTAIN
- **Triple Negative Breast Cancer (TNBC)**
 - DESTINY-Breast04
- **BRCA associated tumors**
 - OLYMPIA survival data
- **Local therapy**
 - E2108
 - NRG-BR002

Outline (2022)

- **Hormone Receptor (HR) Positive**
 - DESTINY-Breast04
 - TROPICS-02
 - MAINTAIN
- **Triple Negative Breast Cancer (TNBC)**
 - DESTINY-Breast04
- **BRCA associated tumors**
 - OLYMPIA survival data
- **Local therapy**
 - E2108
 - NRG-BR002

Sacituzumab Govitecan

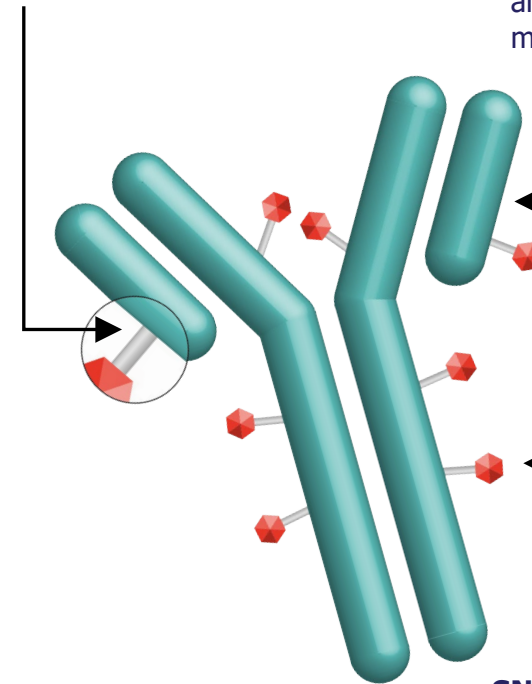
- Trop-2/EGP-1 -> pan-epithelial cancer antigen with broad expression in many cancers
- Sacituzumab govitecan -> Trop2-specific antibody (RS7), site-specifically conjugated with a SN-38, using a pH-sensitive linker

Linker for SN-38

- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7.6:1)⁶

Humanized anti-Trop-2 antibody

- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

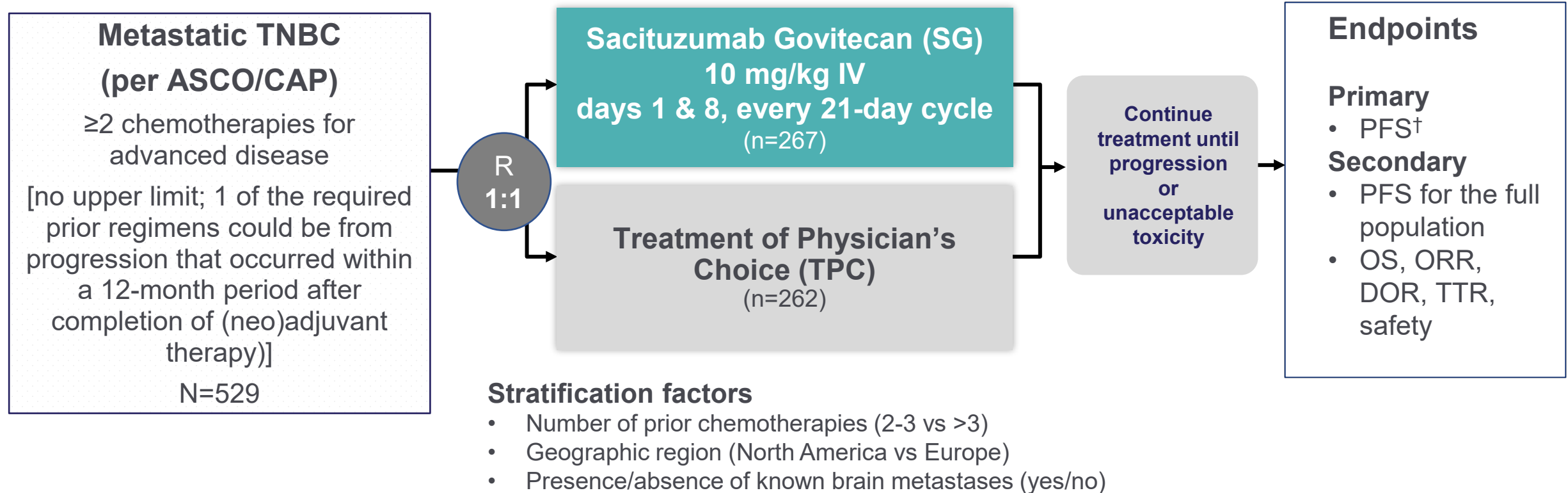


SN-38 payload

- SN-38 more potent than parent compound, irinotecan

ASCENT: Sacituzumab Govitecan in TNBC

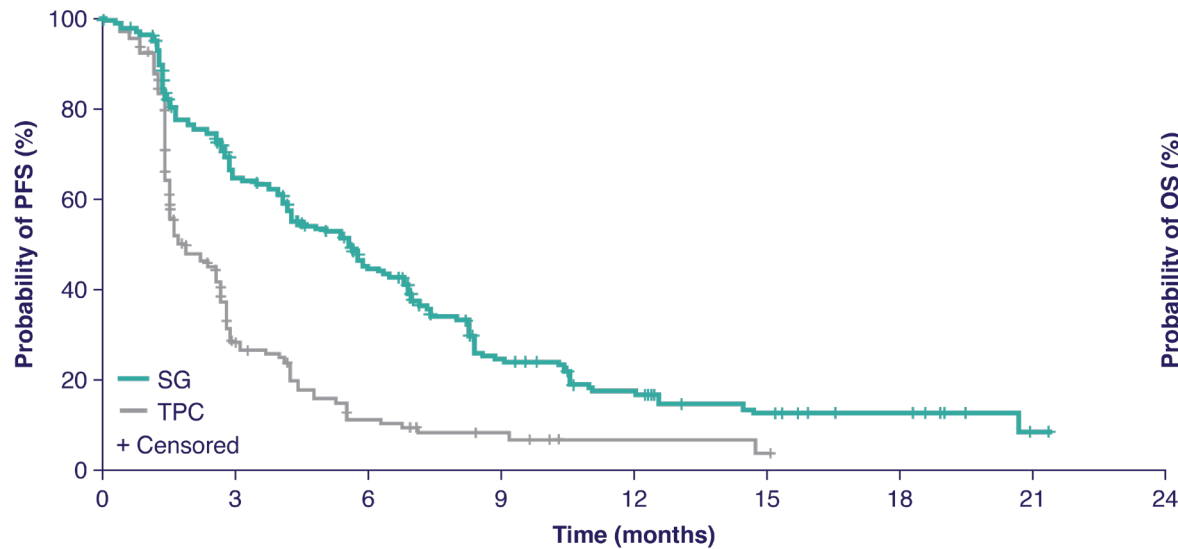
• Phase 3 Confirmatory Study



ASCENT: Results

PFS

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), <i>P</i> -value	0.41 (0.32-0.52), <i>P</i><0.0001	

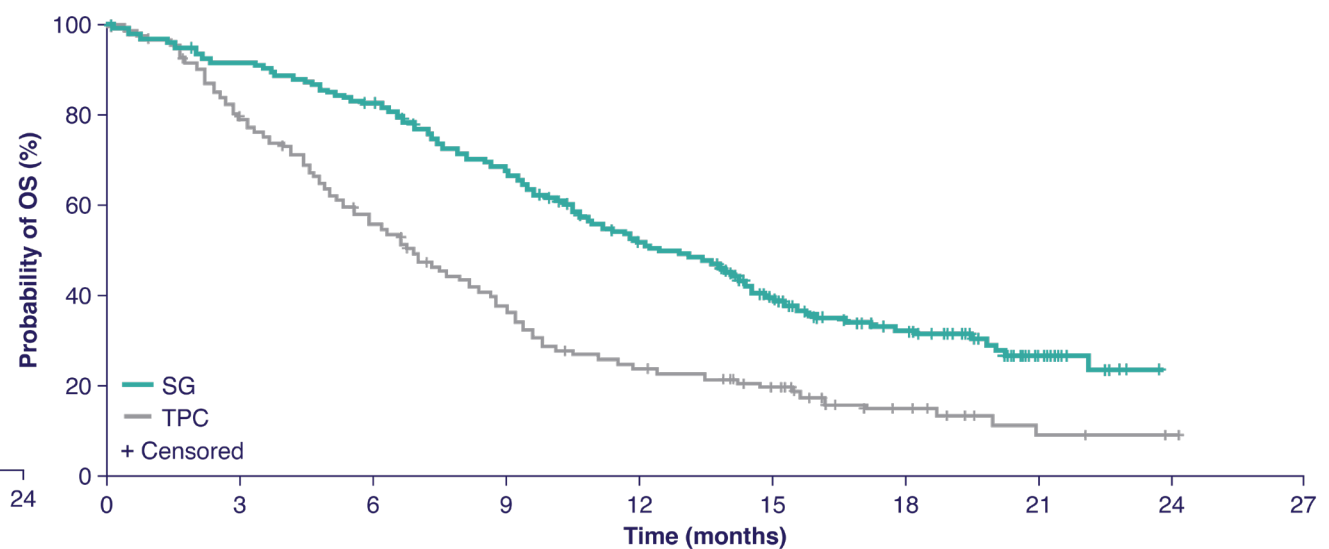


Number of patients at risk

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

OS

	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), <i>P</i> -value	0.48 (0.38-0.59), <i>P</i><0.0001	



Number of patients at risk

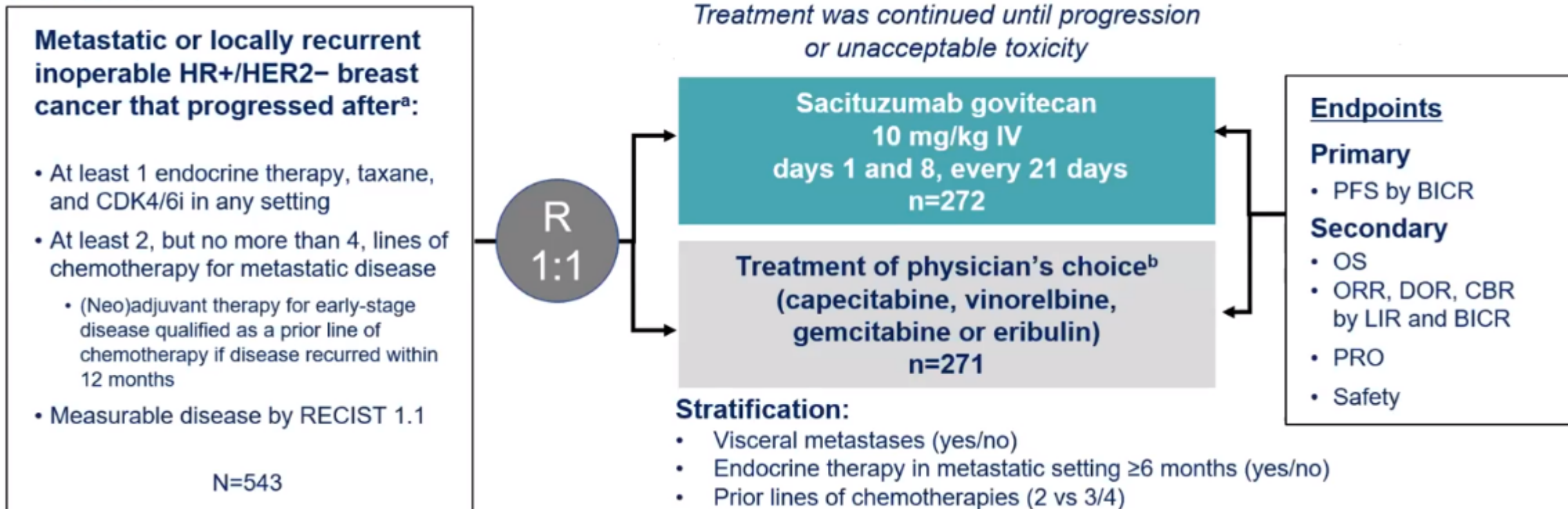
SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

FDA Approval: Sacituzumab Govitecan in mTNBC

- In April 2020, sacituzumab govitecan received accelerated approval for patients with mTNBC who have received at least two prior therapies for metastatic disease.
- On April 7, 2021, the Food and Drug Administration granted regular approval to sacituzumab govitecan (Trodelvy, Immunomedics Inc.) for patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.

TROPiCS-02

NCT03901339



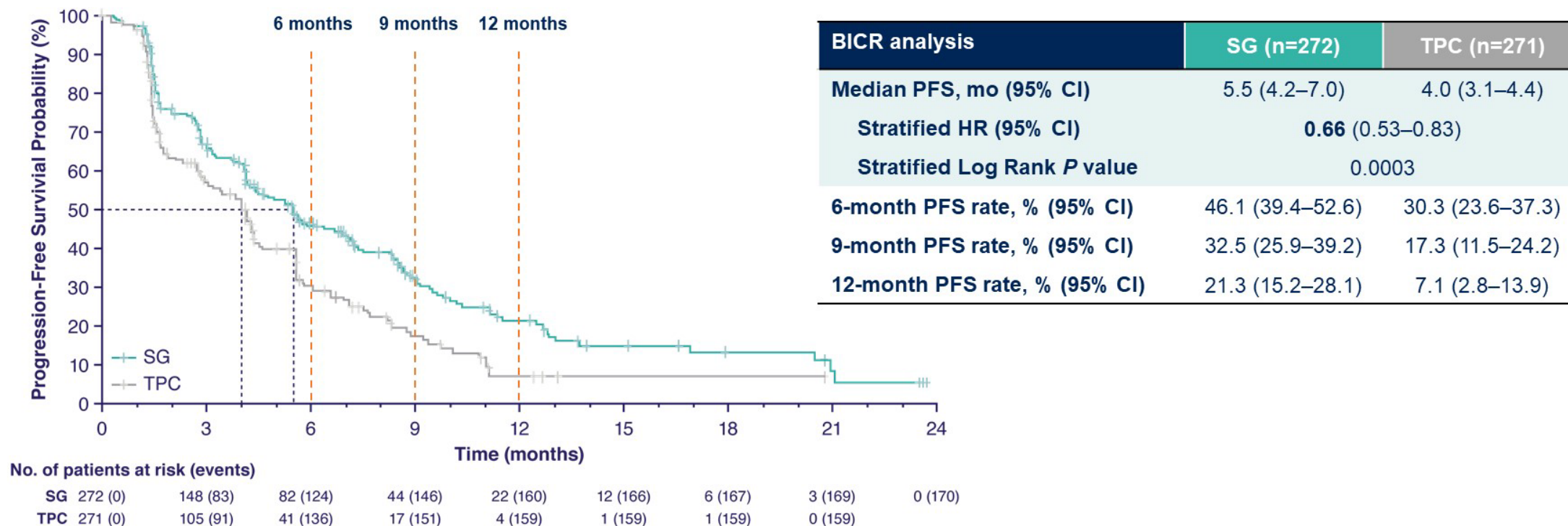
Key all Grade and Grade ≥ 3 Treatment Related AEs

TRAEs, n (%)		SG (n=268)		TPC (n=249)	
		All grade	Grade ≥ 3	All grade	Grade ≥ 3
Hematologic	Neutropenia ^b	188 (70)	136 (51)	134 (54)	94 (38)
	Anemia ^c	91 (34)	17 (6)	62 (25)	8 (3)
	Leukopenia ^d	37 (14)	23 (9)	23 (9)	13 (5)
	Lymphopenia ^e	31 (12)	10 (4)	25 (10)	8 (3)
	Febrile neutropenia	14 (5)	14 (5)	11 (4)	11 (4)
Gastrointestinal	Diarrhea	152 (57)	25 (9)	41 (16)	3 (1)
	Nausea	148 (55)	3 (1)	77 (31)	7 (3)
	Vomiting	50 (19)	1 (<1)	30 (12)	4 (2)
	Constipation	49 (18)	0	36 (14)	0
	Abdominal pain	34 (13)	2 (1)	17 (7)	0
Other	Alopecia	123 (46)	0	41 (16)	0
	Fatigue	100 (37)	15 (6)	73 (29)	6 (2)
	Asthenia	53 (20)	5 (2)	37 (15)	2 (1)
	Decreased appetite	41 (15)	1 (<1)	34 (14)	1 (<1)
	Neuropathy ^f	23 (9)	3 (1)	38 (15)	6 (2)

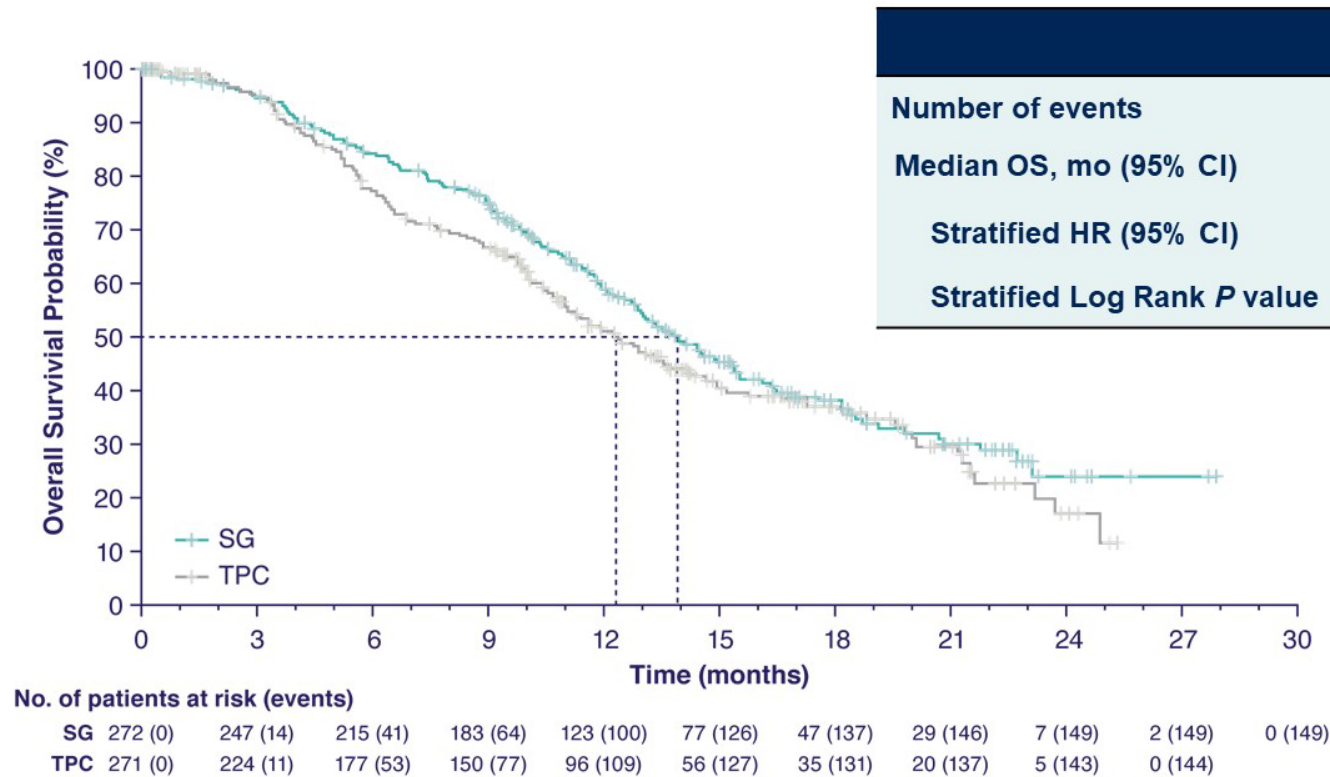
There were no events of interstitial lung disease in the SG arm (vs 1% in the TPC arm) and no TRAEs of cardiac failure or left ventricular dysfunction in either arm

TROPiCS-02: Primary Endpoint

SG demonstrated a statistically significant improvement in PFS vs TPC with a 34% reduction in the risk of disease progression/death; a higher proportion of patients were alive and progression-free at all landmark timepoints



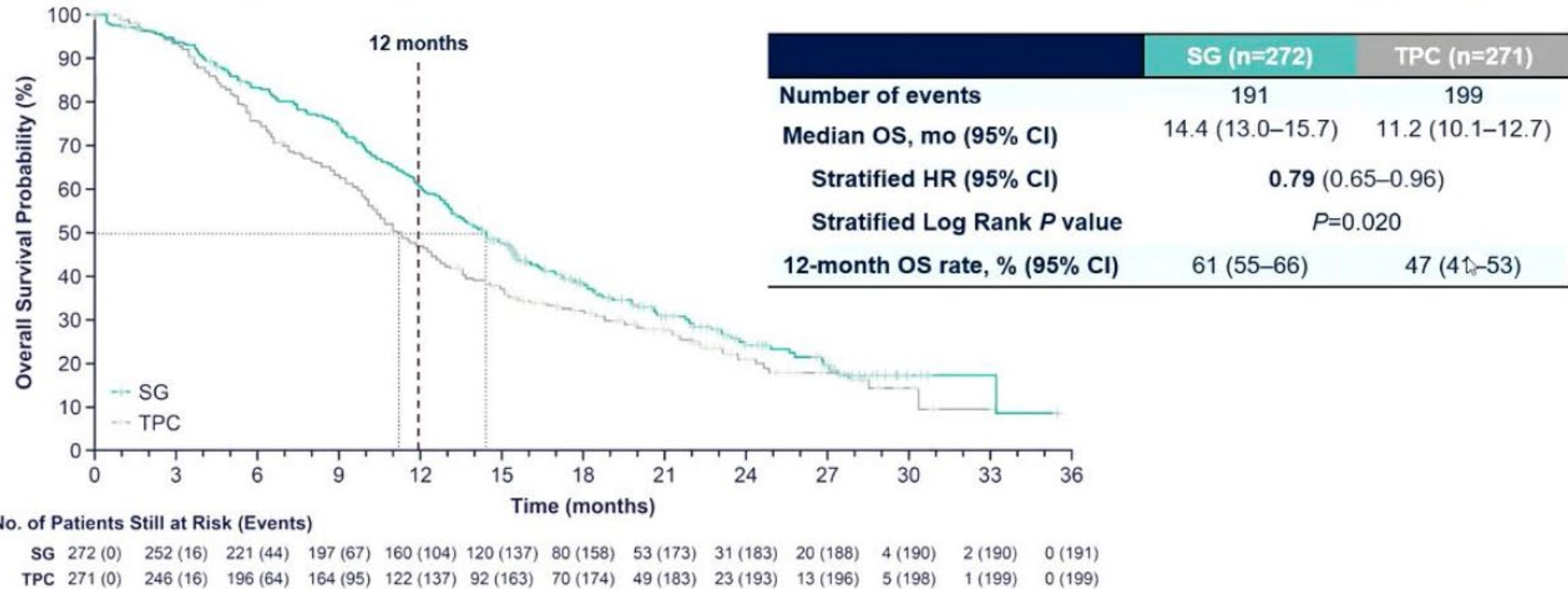
TROPiCS-02: Overall Survival



	SG (n=272)	TPC (n=271)
Number of events	149	144
Median OS, mo (95% CI)	13.9 (12.7-15.4)	12.3 (10.8-14.2)
Stratified HR (95% CI)	0.84 (0.67-1.06)	
Stratified Log Rank <i>P</i> value	<i>P</i> =0.14	

- OS data is not yet mature at the first of three planned OS analyses
- Further follow-up is ongoing

TROPiCS-02: Overall Survival (2nd Interim Analysis)



- SG demonstrated a statistically significant improvement in OS vs TPC with 21% reduction in the risk of death; having met statistical significance, no further formal statistical testing of OS will occur
- Patients who received SG survived a median of **3.2 months longer** than those who received TPC

Median follow-up was 12.5 months.
OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Outline (2022)

- **Hormone Receptor (HR) Positive**
 - DESTINY-Breast04
 - TROPICS-02
 - MAINTAIN
- **Triple Negative Breast Cancer (TNBC)**
 - DESTINY-Breast04
- **BRCA associated tumors**
 - OLYMPIA survival data
- **Local therapy**
 - E2108
 - NRG-BR002

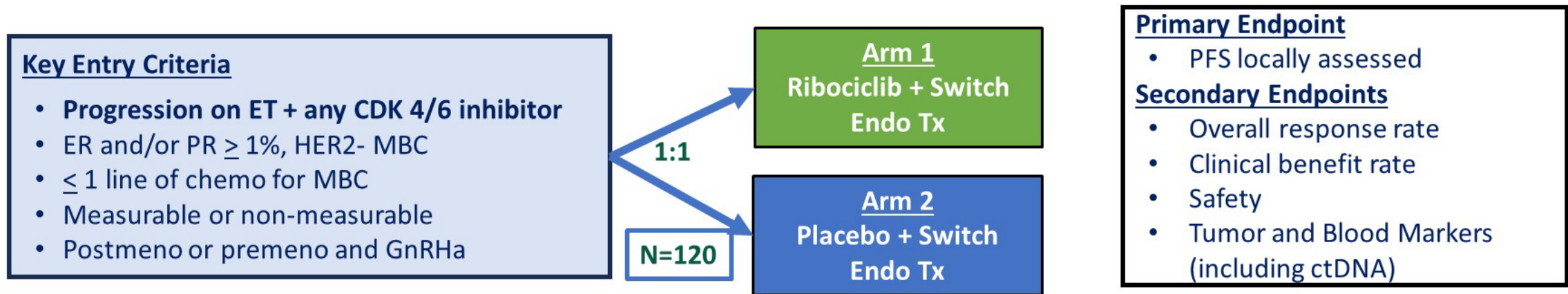
Outline (2022)

- **Hormone Receptor (HR) Positive**
 - DESTINY-Breast04
 - TROPICS-02
 - MAINTAIN
- **Triple Negative Breast Cancer (TNBC)**
 - DESTINY-Breast04
- **BRCA associated tumors**
 - OLYMPIA survival data
- **Local therapy**
 - E2108
 - NRG-BR002

MAINTAIN – P2 RCT

Role of continuing CDK4/6i post PD on CDK4/6i

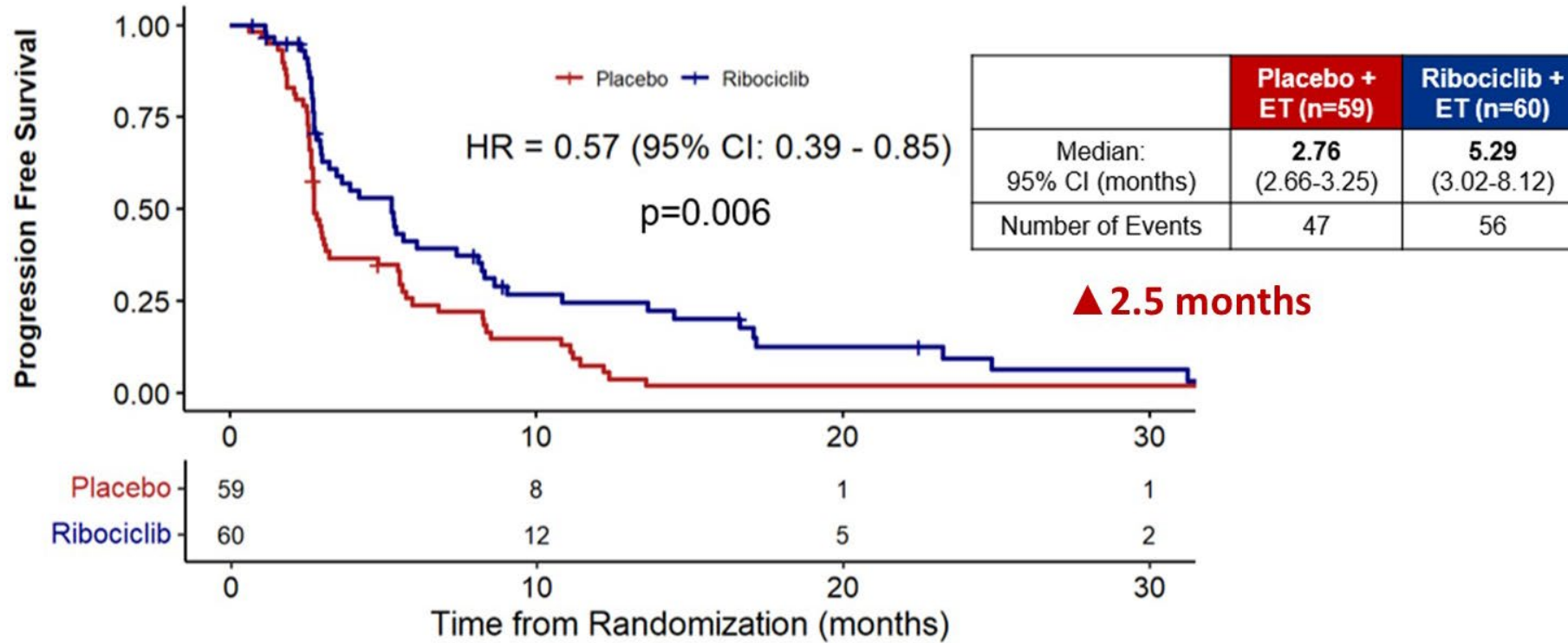
6



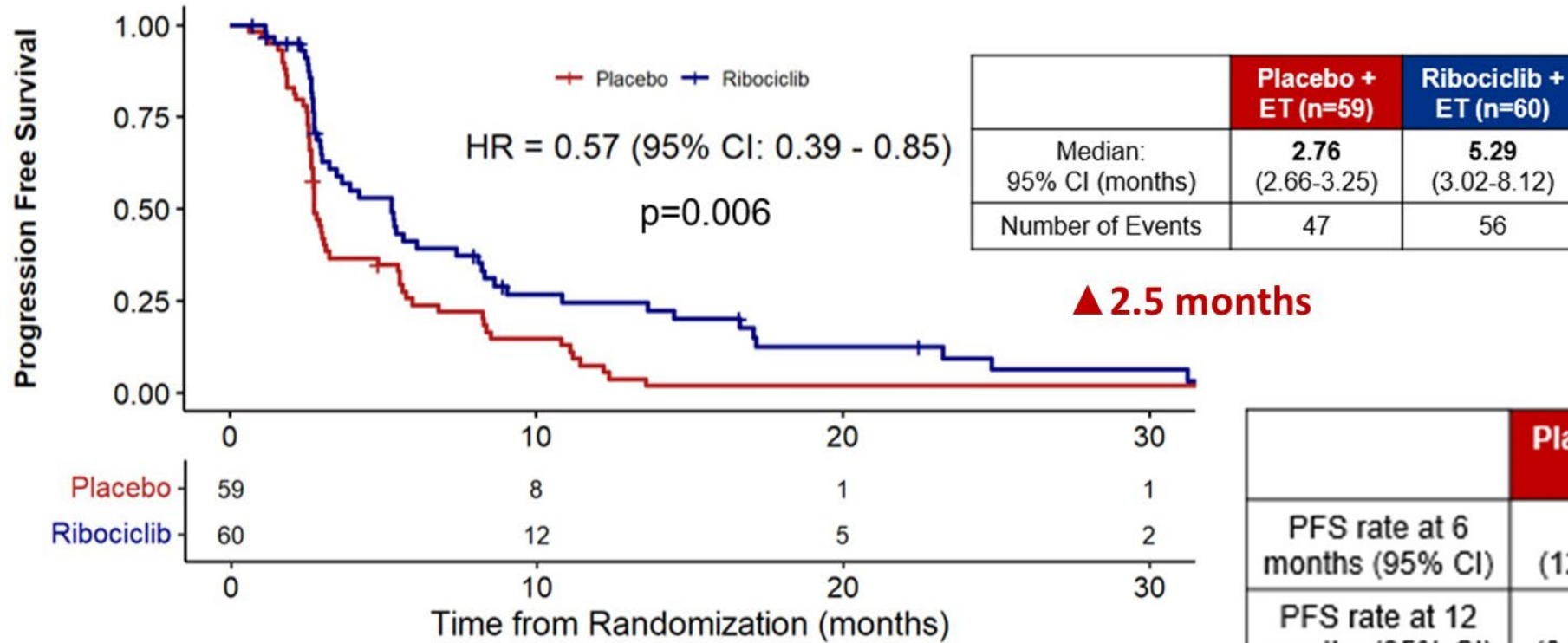
Demographic characteristics:

- Most patients had no intervening therapy after PD on CDK4/6i (90%+)
- Most received prior palbociclib (87%)
- Duration (median) prior CDK4/6i: ~16 months
- Endo therapy – Fulvestrant 83%; Exemestane 17%

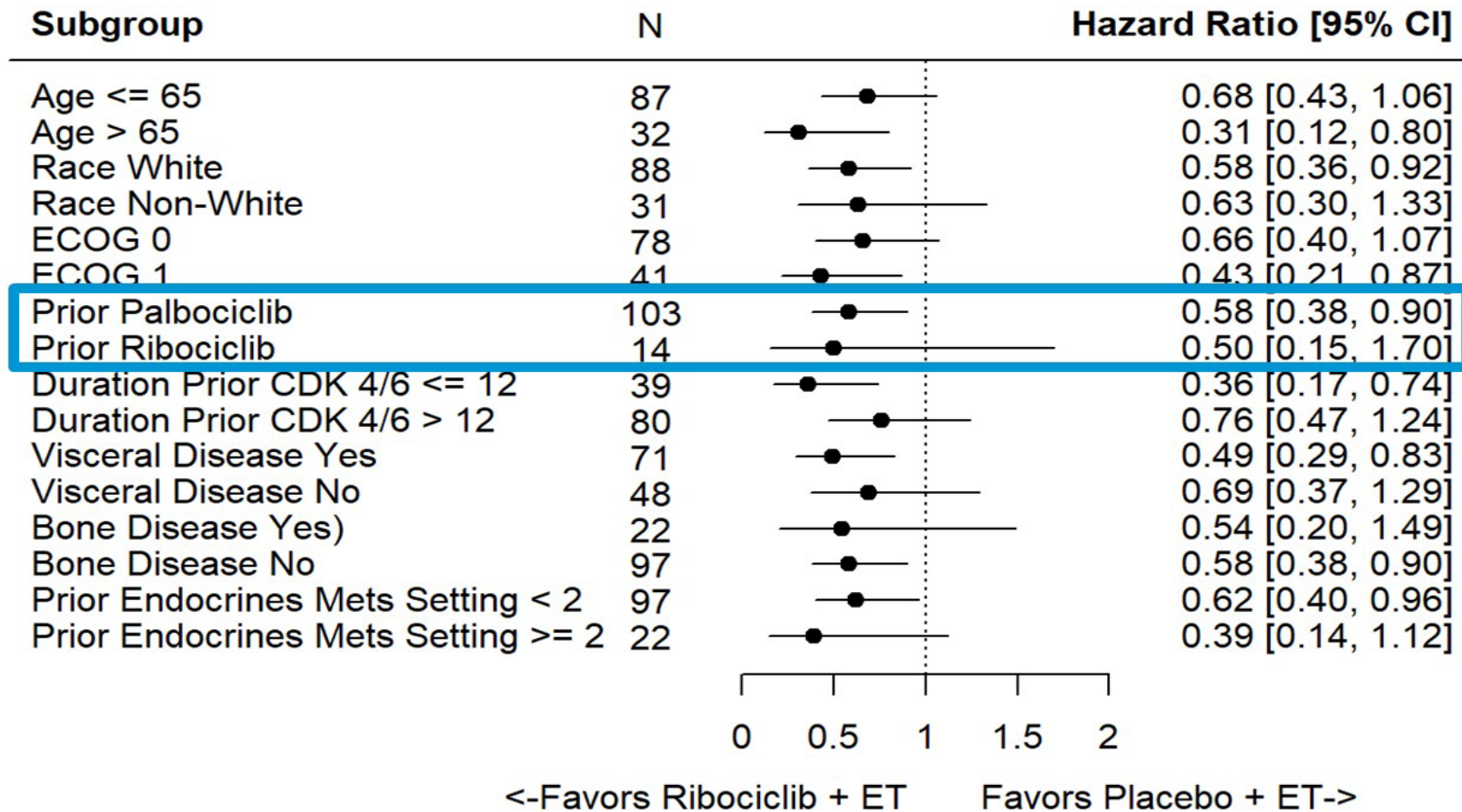
MAINTAIN: PFS



MAINTAIN: PFS



MAINTAIN: PFS by Subgroup



MAINTAIN – CDK4/6i post PD CDK4/6i

Strengths

- First randomized trial addressing this important question
- Well designed phase 2 trial

Limitations

- Unclear if need to switch both ET and CDK4/6i
- Small study – not practice changing need additional data
 - Other trials evaluating this question underway

PALMIRA - P2 RCT (NCT03809988)	ET vs ET/Palbo (post PD Palbo)
PACE - P2 RCT (NCT03147287)	Fulv vs Fulv/Palbo vs Fulv/Palbo/Avelumab (post PD any CDK4/6i)
EMBER-3 (P3 RCT) (NCT04975308)	Oral SERD vs ET PC vs oral SERD/Abema (post PD any CDK4/6i)
PostMONARCH (P3 RCT) (NCT05169567)	Fulv/Placebo vs Fulv/Abema (post PD any CDK4/6i)

- While encouraging, still leaves room for additional improvement in outcome

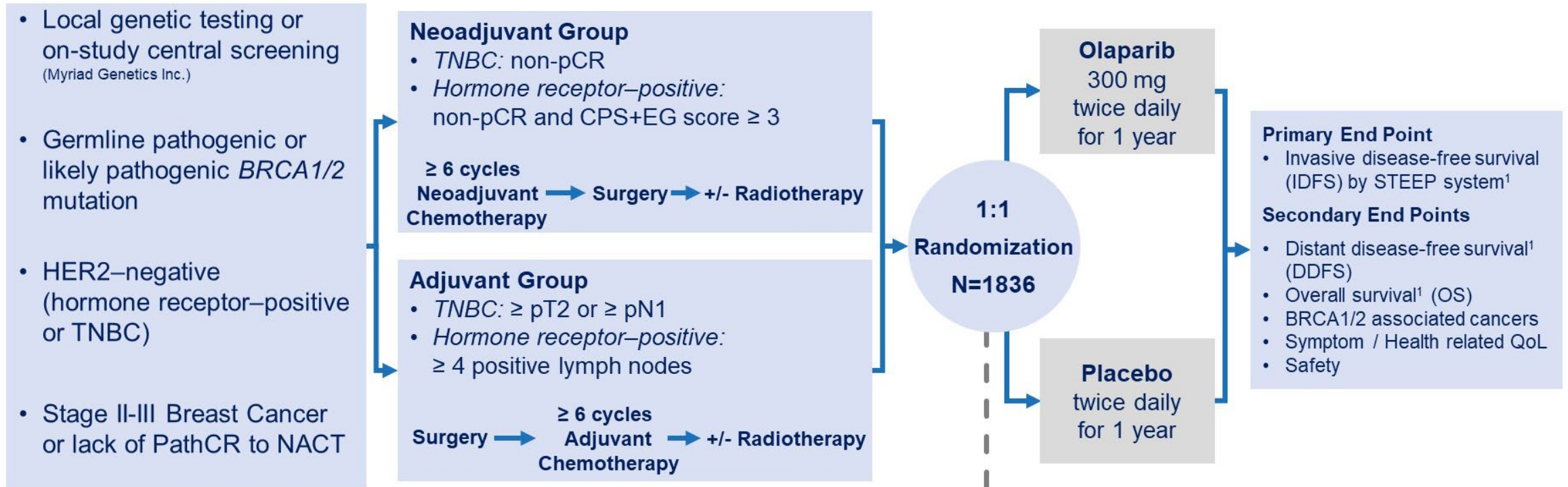
Outline (2022)

- **Hormone Receptor (HR) Positive**
 - DESTINY-Breast04
 - TROPICS-02
 - MAINTAIN
- **Triple Negative Breast Cancer (TNBC)**
 - DESTINY-Breast04
- **BRCA associated tumors**
 - OLYMPIA survival data
- **Local therapy**
 - E2108
 - NRG-BR002

Outline (2022)

- **Hormone Receptor (HR) Positive**
 - DESTINY-Breast04
 - TROPICS-02
 - MAINTAIN
- **Triple Negative Breast Cancer (TNBC)**
 - DESTINY-Breast04
- **BRCA associated tumors**
 - OLYMPIA survival data
- **Local therapy**
 - E2108
 - NRG-BR002

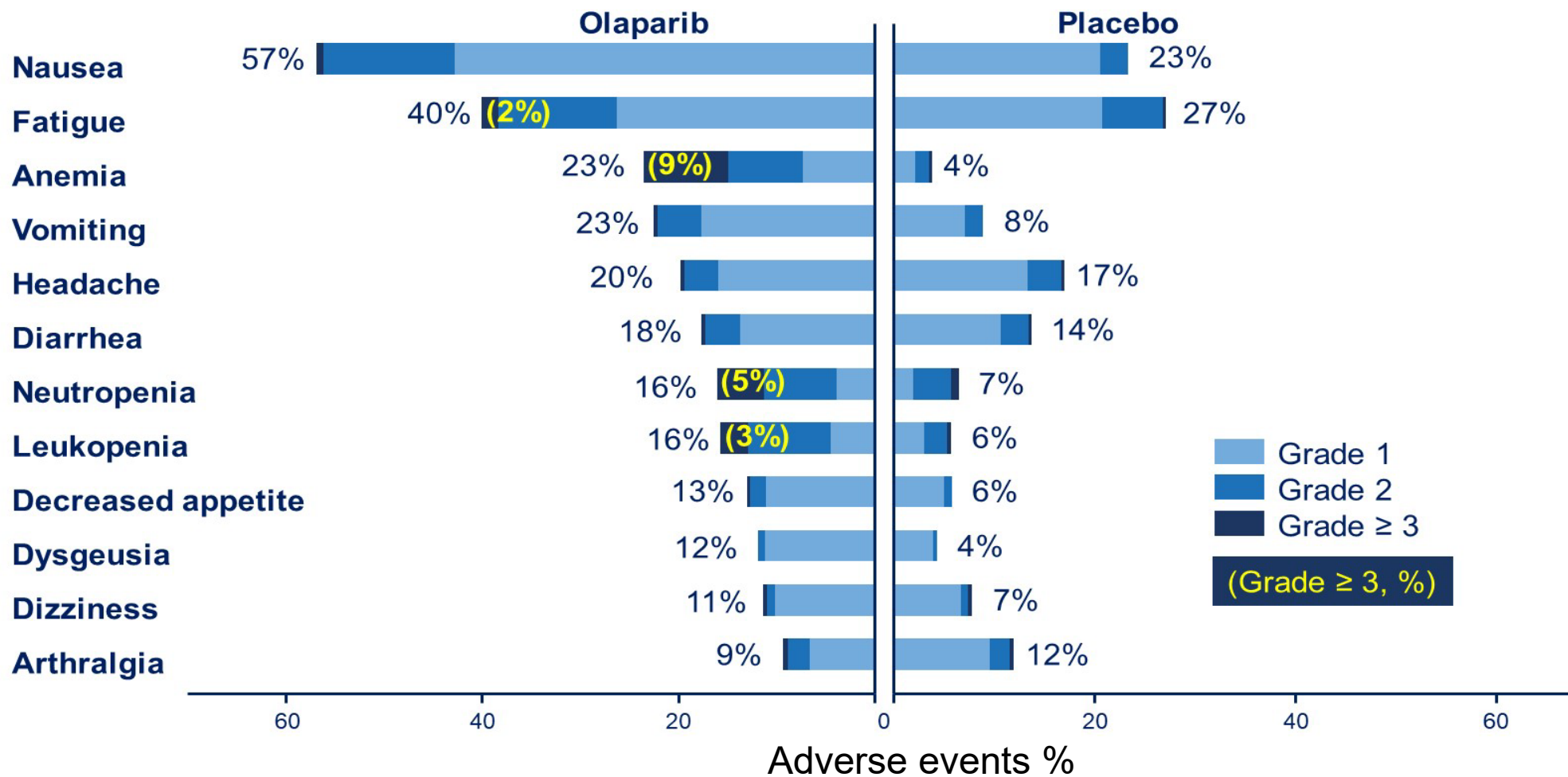
OlympiA: Study Design



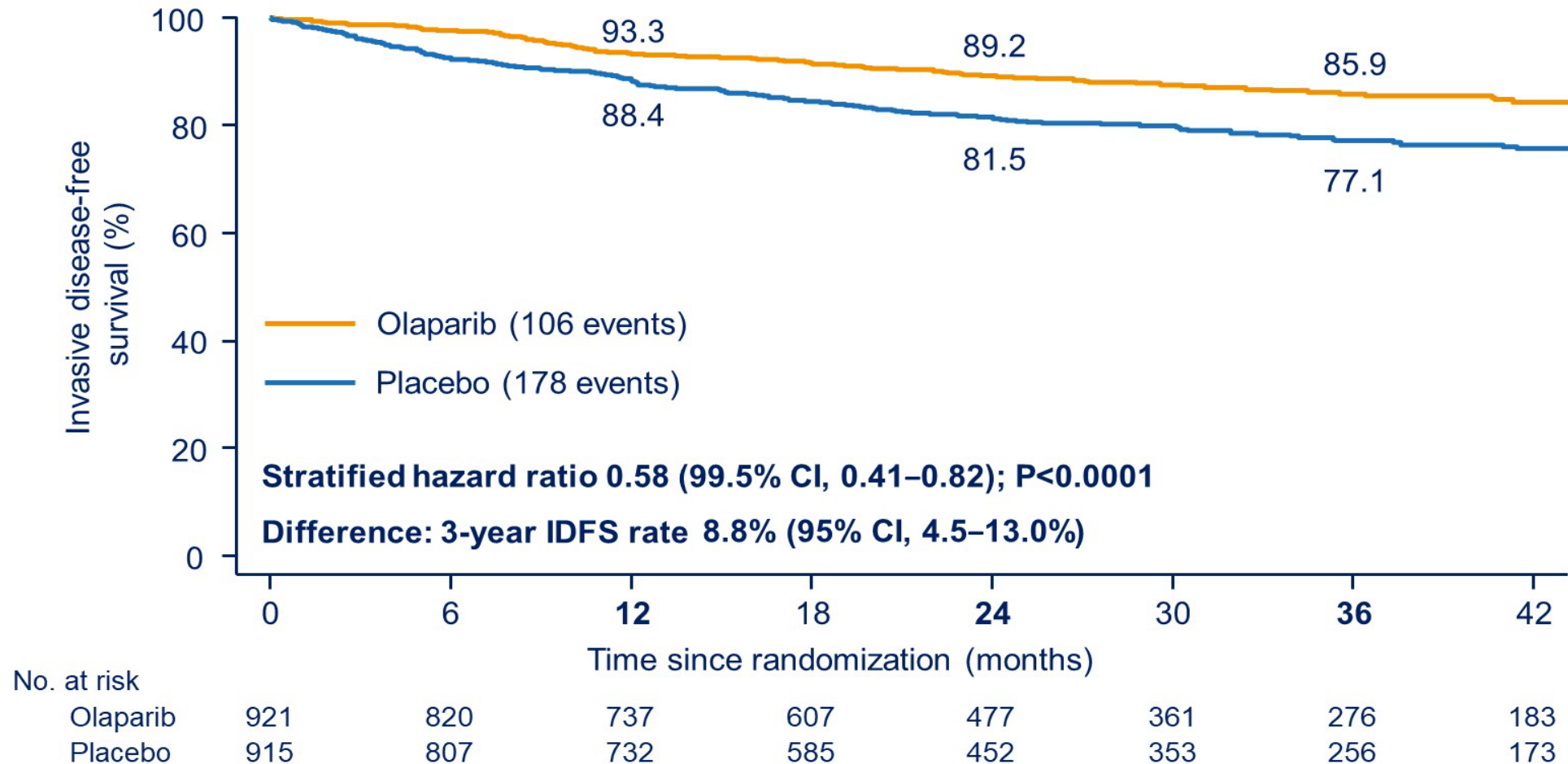
OlympiA: Patient Characteristics

	Olaparib (N=921)	Placebo (N=915)
BRCA gene affected in germline		
<i>BRCA1</i>	657 (71.3%)	670 (73.2%)
<i>BRCA2</i>	261 (28.3%)	239 (26.1%)
<i>BRCA1</i> and <i>BRCA2</i>	2 (0.2%)	5 (0.5%)
Hormone receptor status		
HR ≥ 1% / HER2-	168 (18.2%)	157 (17.2%)
TNBC	751 (81.5%)	758 (82.8%)
Prior chemotherapy		
Adjuvant	461 (50.1%)	455 (49.7%)
Neoadjuvant	460 (49.9%)	460 (50.3%)
Anthracycline and taxane regimen	871 (94.6%)	849 (92.8%)
Neo(adjuvant) platinum-based therapy	247 (26.8%)	239 (26.1%)
Concurrent endocrine therapy (HR-positive only)	146/168 (86.9%)	142/157 (90.4%)

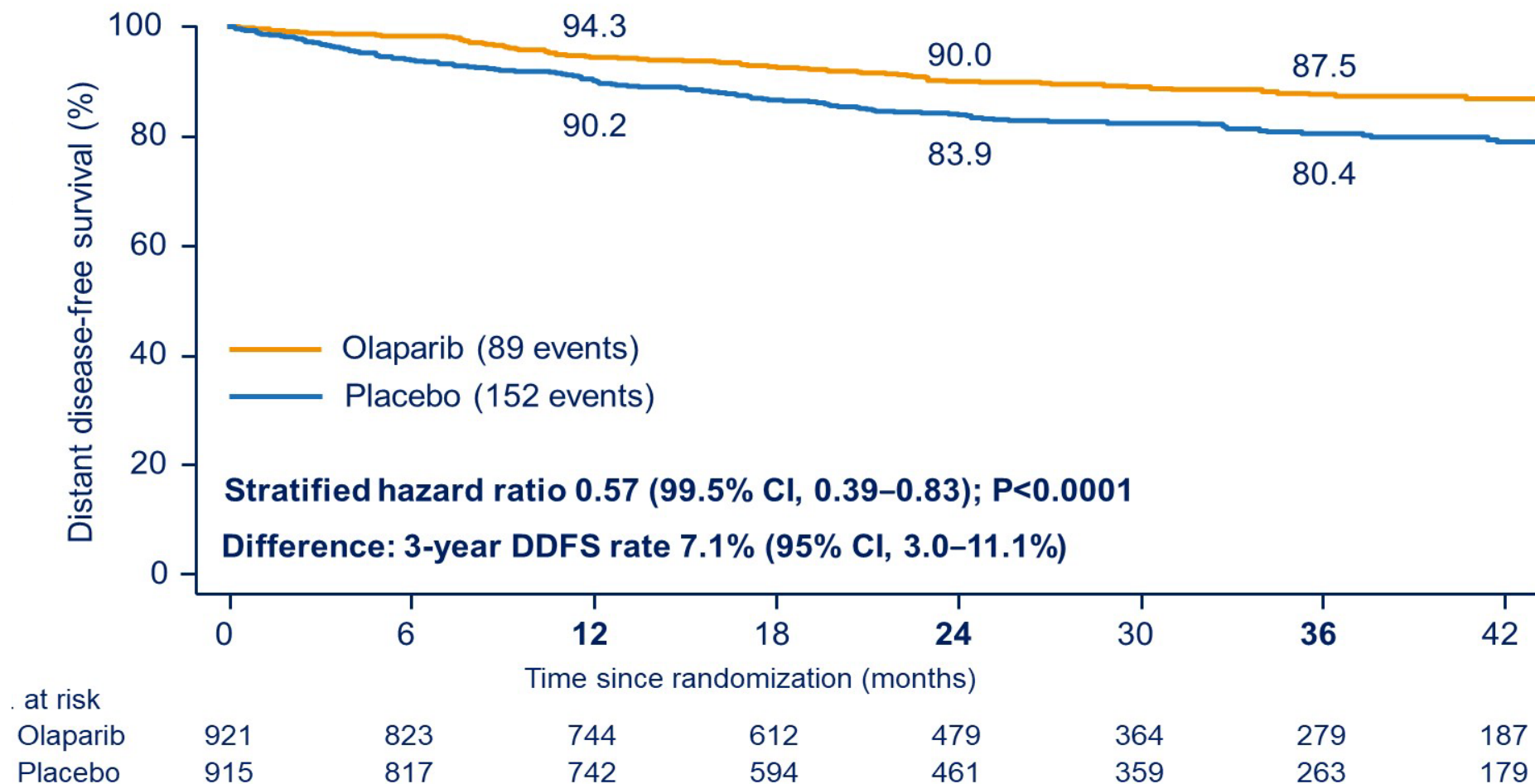
OlympiA: Toxicity



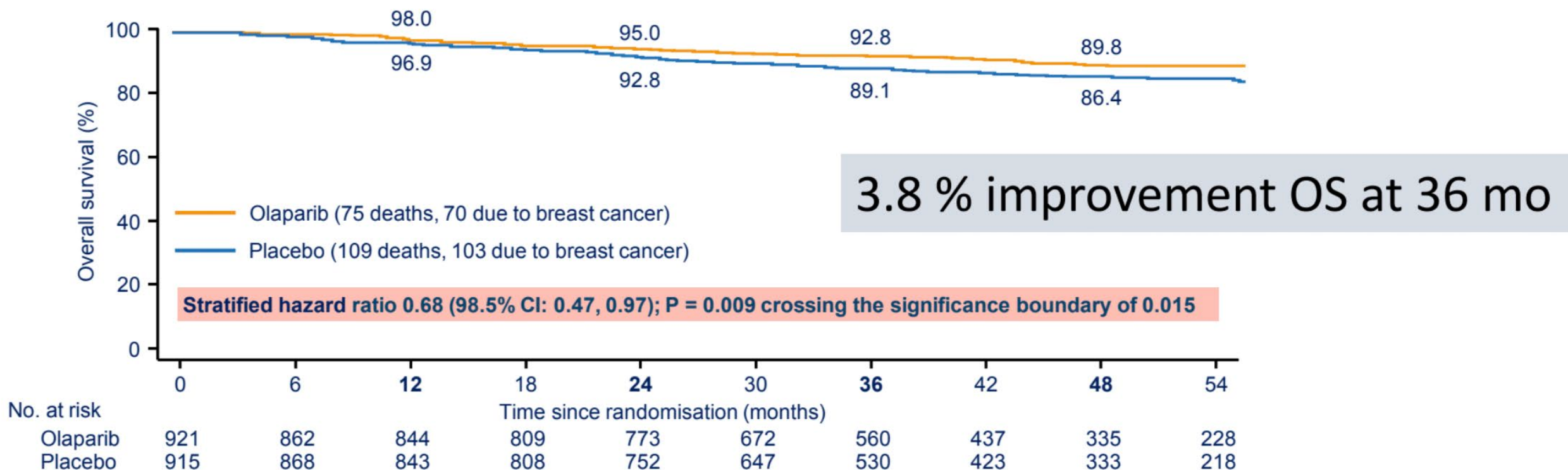
OlympiA: IDFS



OlympiA: DDFS



OlympiA: Second Overall Survival Interim Analysis



FDA approval

- On March 11, 2022, the Food and Drug Administration approved olaparib (Lynparza[®], AstraZeneca Pharmaceuticals, LP) for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy.

Outline (2022)

- **Hormone Receptor (HR) Positive**
 - DESTINY-Breast04
 - TROPICS-02
 - MAINTAIN
- **Triple Negative Breast Cancer (TNBC)**
 - DESTINY-Breast04
- **BRCA associated tumors**
 - OLYMPIA survival data
- **Local therapy**
 - E2108
 - NRG-BR002

Outline (2022)

- **Hormone Receptor (HR) Positive**
 - DESTINY-Breast04
 - TROPICS-02
 - MAINTAIN
- **Triple Negative Breast Cancer (TNBC)**
 - DESTINY-Breast04
- **BRCA associated tumors**
 - OLYMPIA survival data
- **Local therapy**
 - E2108
 - NRG-BR002

E2108: randomized phase III trial of systemic therapy +/- early local therapy in women with de novo stage IV breast cancer

Diagnosis of de novo stage IV breast cancer

Registration

Optimal systemic therapy based on patient and disease features

No progression of distant disease following 4-8 months of therapy

R

Continued systemic therapy (CST) alone

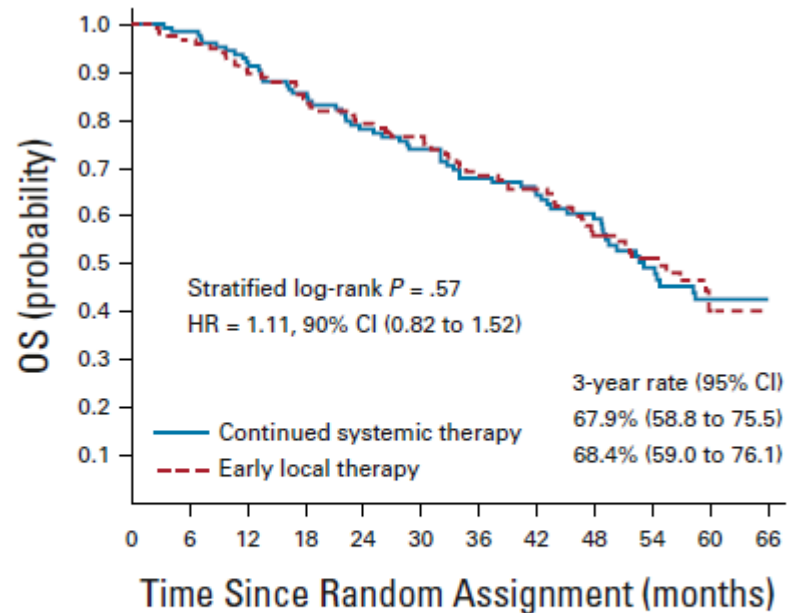
Early local therapy (ELT)

Follow up for 5 years

Complete tumor resection with free surgical margins
Post-operative radiotherapy per standard of care (SOC)

E2108: randomized phase III trial of systemic therapy +/- early local therapy in women with de novo stage IV breast cancer

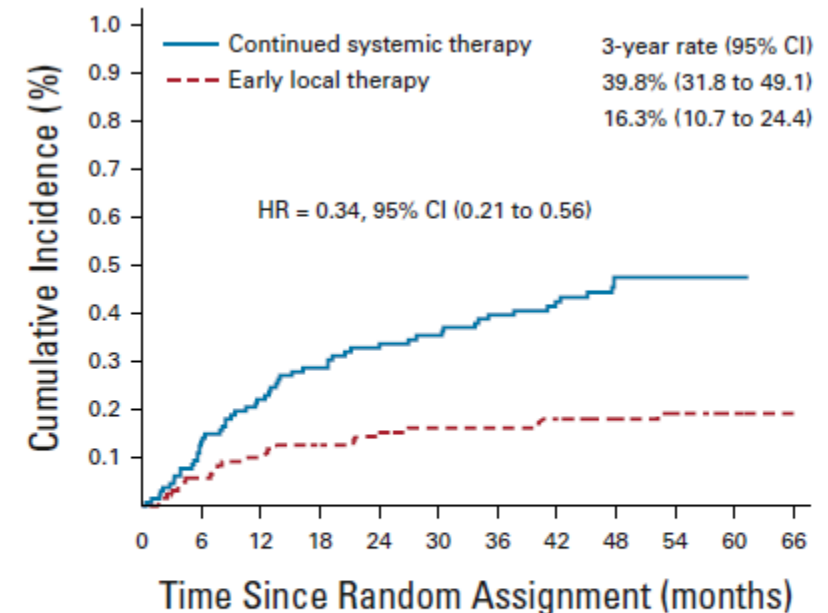
Overall Survival (Primary Endpoint)



No. at risk:

Continued systemic therapy	131	125	115	105	93	87	77	71	58	40	12	3
Early local therapy	125	112	103	97	91	85	75	70	54	36	8	2

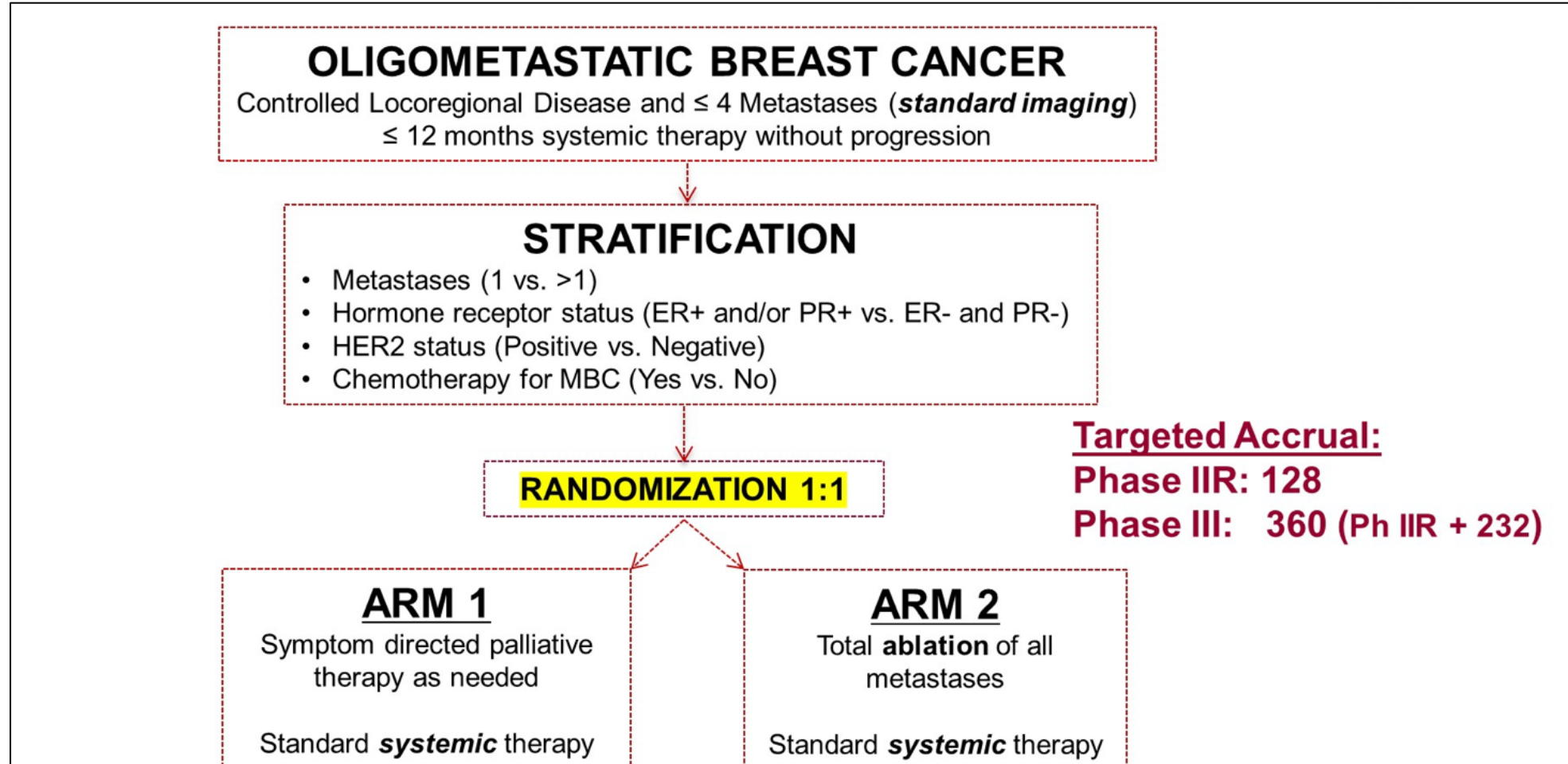
Locoregional Progression (Secondary Endpoint)



No. at risk:

Continued systemic therapy	131	108	89	75	67	59	50	44	30	21	3	1
Early local therapy	125	107	95	89	80	74	67	61	47	33	9	3

NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without SBRT and/or surgical resection for newly oligometastatic breast cancer



NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without SBRT and/or surgical resection for newly oligometastatic breast cancer

Phase IIR (n=128):

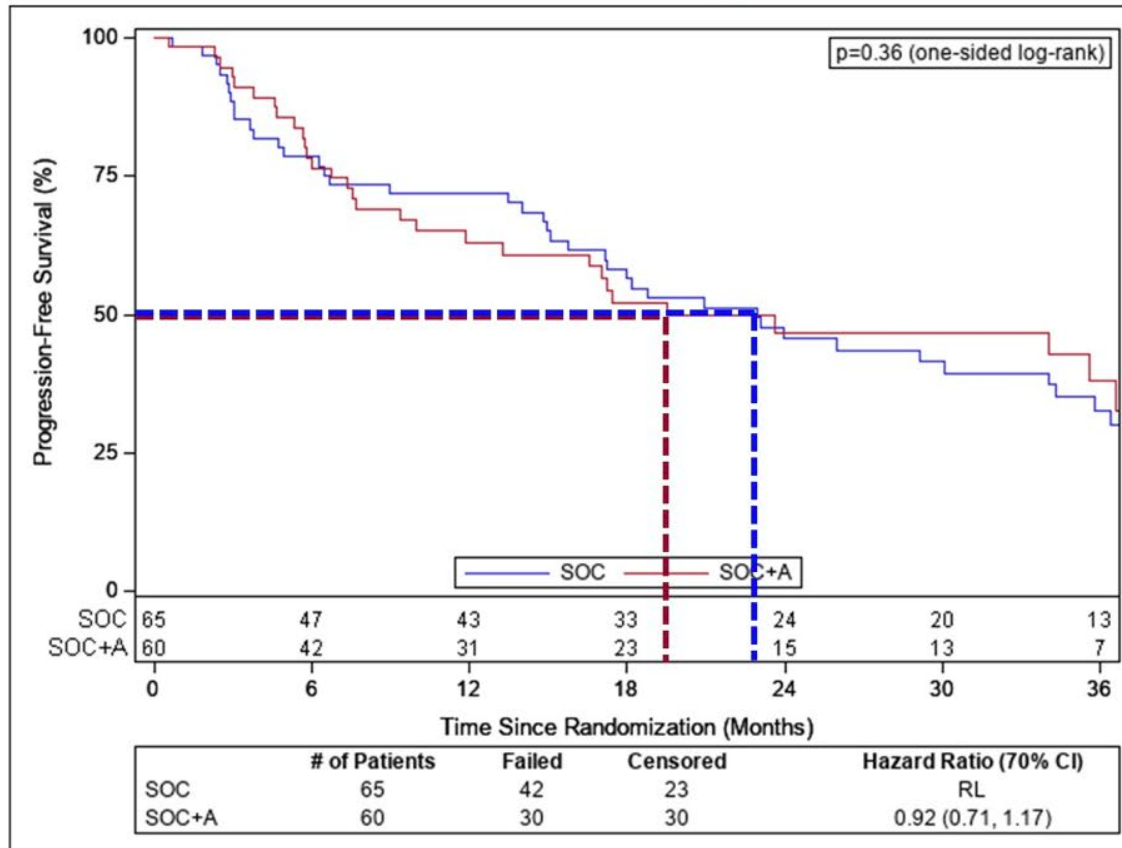
- **Hypothesis:** Metastasis-directed therapy of all **VISIBLE** lesions with systemic therapy will provide a **signal** for improved **PFS** (hazard ratio [HR]=0.55, corresponding to median PFS from 10.5 to 19 months).
 - Failure defined as: progression of metastases, new metastases, or death
 - Log-rank test statistic; 1-sided significance level = 0.15 (70% CI); 92% power; 69 events
 - If PFS “Go Signal”, trial continues to answer Ph III overall survival (OS)

Phase III (n=+232):

- **Hypothesis:** Metastasis-directed therapy of all **VISIBLE** lesions with systemic therapy will improve **OS** (HR=0.67, corresponding to 5-year OS from 28% to 42.5%).

NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without SBRT and/or surgical resection for newly oligometastatic breast cancer

PFS by Treatment Arm



	SOC (n=65)	SOC+A (n=60)
24-month estimate (70% CI)	45.7% (38.9%, 52.5%)	46.8% (39.2%, 54.3%)
36-month estimate (70% CI)	32.8% (26.0%, 39.5%)	38.1% (29.7%, 46.6%)
mPFS		
Design	10.5 months	19 months
Observed	23 months	19.5 months

HR [SOC+A/SOC] (70% CI): 0.92 (0.71, 1.17)

Median Follow-up = 35 months
(min-max: 0.03-62.74)

Conclusions

- First approved drug in HER2 low breast cancer
- First approval of PARPi in the early-stage setting
- No role for breast surgery or ablation of metastases for most patients with de novo metastatic breast cancer

The image features a central white rectangular area containing the text "Q&A". This central area is framed by a decorative border at the top and bottom. The border consists of fluid, wavy lines in various shades of blue and purple, creating a sense of motion and depth. The colors transition from deep purples on the left to bright blues on the right.

Q&A