Actualités en Sénologie

POST-ESMO 2024

10 Septembre 2024

L'atelier - Poitiers

Dr BAINAUD Matthieu

Liens d’intérêts

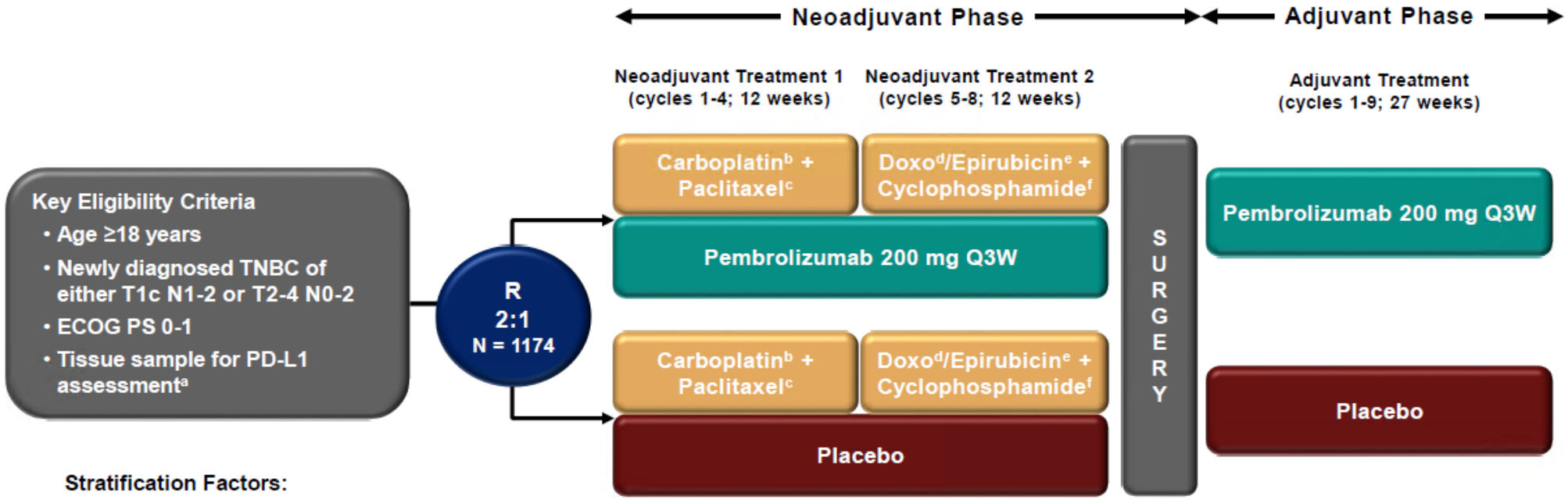
- Honoraria : Regeneron, MSD, Astra-Zeneca, Gilead
- Consulting or advisory role : Gilead
- Travel Support : Roche

Early Breast Cancer

- **OS KEYNOTE-522**
- NATALEE 4-years
- HypoG-01

KEYNOTE 522

Overall Survival Results



Stratification Factors:

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

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)

Schmid and al. NEJM 2024

KEYNOTE-522

Overall Survival Results

Baseline Characteristics, ITT Population

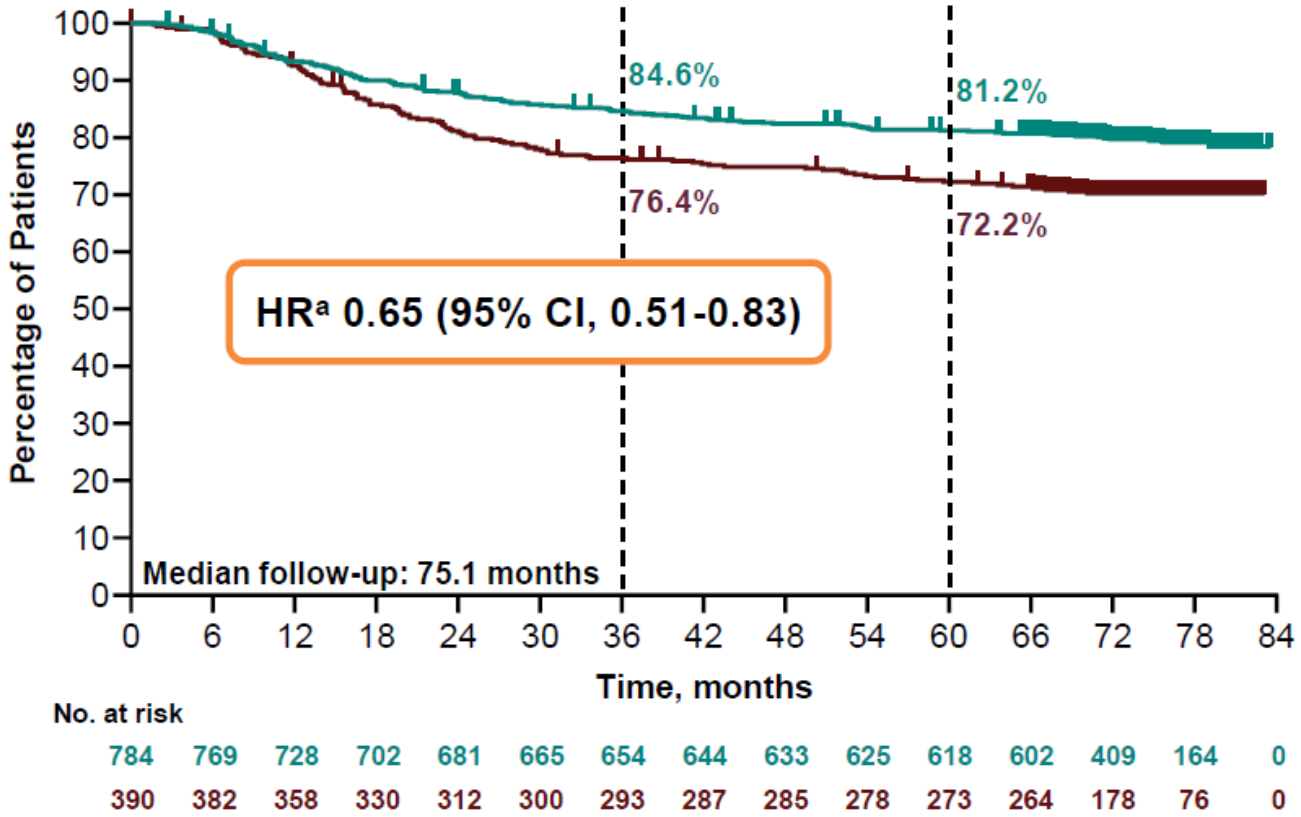
Characteristic, n (%)	All Patients, N = 1174	
	Pembro + Chemo/Pembro N = 784	Placebo + Chemo/Placebo N = 390
Age, median (range), yrs	49 (22-80)	48 (24-79)
ECOG PS 1	106 (13.5)	49 (12.6)
PD-L1 CPS ≥1[a]	656 (83.7)	317 (81.3)
Carboplatin schedule		
QW	449 (57.3)	223 (57.2)
Q3W	335 (42.7)	167 (42.8)
Tumor size		
T1/T2	580 (74.0)	290 (74.4)
T3/T4	204 (26.0)	100 (25.6)
Nodal involvement		
Positive	405 (51.7)	200 (51.3)
Negative	379 (48.3)	190 (48.7)

Schmid and al. NEJM 2024

KEYNOTE-522

Overall Survival Results

Updated Event-Free Survival



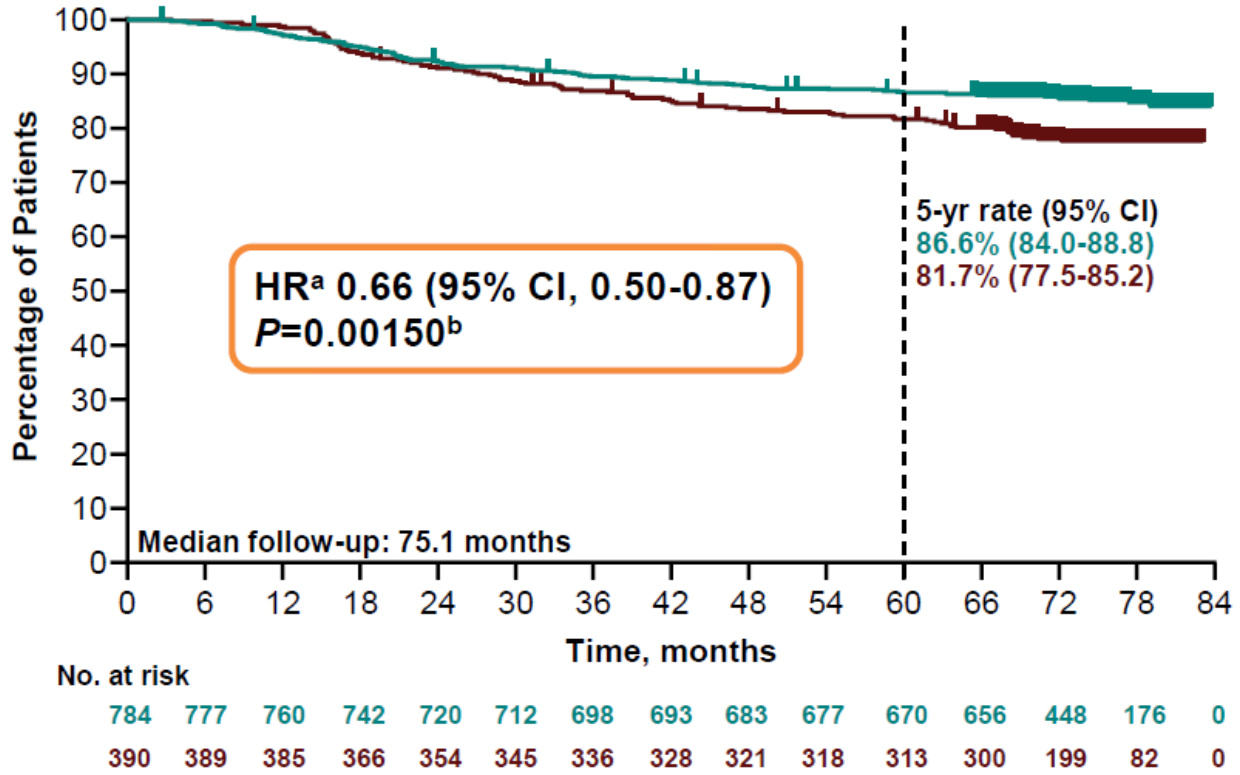
	Pts w/ Event
Pembro + Chemo/Pembro	20.3%
Placebo + Chemo/Placebo	29.2%

Schmid and al. NEJM 2024

KEYNOTE-522

Overall Survival Results

Key Secondary Endpoint: Overall Survival



	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

STANDARD OF CARE

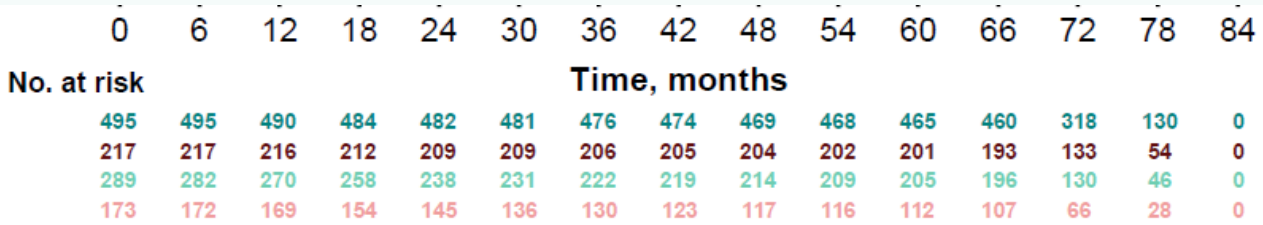
Schmid and al. NEJM 2024

KEYNOTE-522

Overall Survival Results

Overall Survival by Pathologic Complete Response (ypT0/Tis ypN0)

Variable	Pembrolizumab–Chemotherapy (N=401)	Placebo–Chemotherapy (N=201)	Estimated Treatment Difference†	P Value
			percentage points (95% CI)	
Pathological stage ypT0/Tis ypN0				
No. of patients	260	103		
Percentage of patients with response (95% CI)	64.8 (59.9–69.5)	51.2 (44.1–58.3)	13.6 (5.4–21.8)	P<0.001
Pathological stage ypT0 ypN0				
No. of patients	240	91		
Percentage of patients with response (95% CI)	59.9 (54.9–64.7)	45.3 (38.3–52.4)	14.5 (6.2–22.7)	
Pathological stage ypT0/Tis				
No. of patients	275	108		
Percentage of patients with response (95% CI)	68.6 (63.8–73.1)	53.7 (46.6–60.8)	14.8 (6.8–23.0)	



Schmid and al. NEJM 2020 ; Schmid and al. NEJM 2024

Association between clinicopathological characteristics and pathologic complete response in patients with triple negative breast cancer treated by neoadjuvant chemo-immunotherapy

C.Helal, L.Djerroudi, T. Ramtohul, E. Laas, A. Vincent Salomon, M. Jin, R. David Seban, I. Bieche, D. Bello Roufai, FC Bidard, P. Cottu, D. Loirat, M. Carton, F. Lerebours, N. Kiavue, E. Romano, C. Bonneau, L. Cabel

ESMO 2024 Abstract #263P

BACKGROUND

- **15%** of breast cancer are **triple-negative** (TNBC)
- Definition of ER/PR positivity varies across countries

	ESMO	ASCO
IHC ER/PR	**< 10 %**	< 1%

- **Pathological complete response** (pCR) following **neo-adjuvant chemo-immunotherapy** (NACi) is associated with **improved patient outcomes** in high-risk early TNBC
- In the KEYNOTE-522 trial, pCR was achieved in 64.8% of the patients using NACi

OBJECTIVES

To **identify clin[ical] and pathological biomarkers** associated with [pCR] to NACi in a prospective real-life cohort of high[-risk] patients

METHODS

Institut Curie Hospitals, France

Early-stage II-III TNBC
- ER/PR expressed in <10%
- HER 2 negative (score 0, 1+, 2+ not amplified)
- Prescription of NACi

August 2021 – June 2023

KEYNOTE-522 treatment schedule

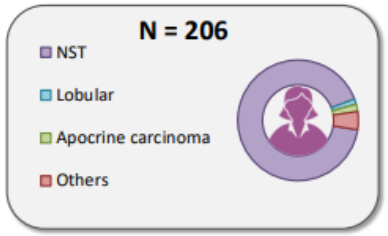
Pembrolizumab
Carboplatin + Paclitaxel → Doxorubicin Cyclophosphamide

Clinical and pathological biomarkers ?

pCR

- A logistic regression analysis was conducted for multivariate analysis, including only the significant variables identified in the univariate analysis
- Patient characteristics were reported using descriptive analyses and compared using the $\chi 2$ test, Fisher's exact test, or the Wilcoxon rank sum test
- The threshold for statistical significance was set at $p<0.05$
- Germline variants in the HR pathway include *BRCA1*, *BRCA2*, *PALB2*, *RAD51C* and *RAD51D*

RESULTS



Age – median (IQR)	49 (41–56)
Post menopausal status	69 %
Germline mutation in the HR pathway	16 %
Stage II	75 %
Stage III	25 %
ER < 1 %	86 %
ER 1-10%	14 %
Grade II	13 %
Grade III	87 %
No DCIS on pre-treatment biopsy	82 %
Ki-67 ≥ 30 %	89 %
PD-L1 CPS > 20%	23 %

Table 1.

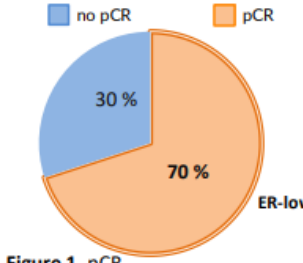


Figure 1. pCR

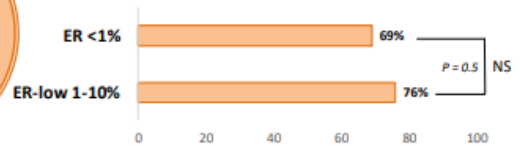


Figure 2. pCR according to ER status

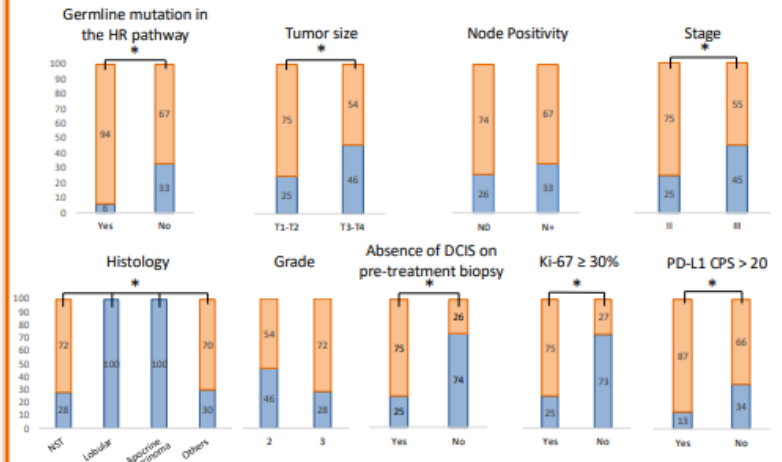


Figure 3. pCR according to clinico-pathological characteristics

RESULTS

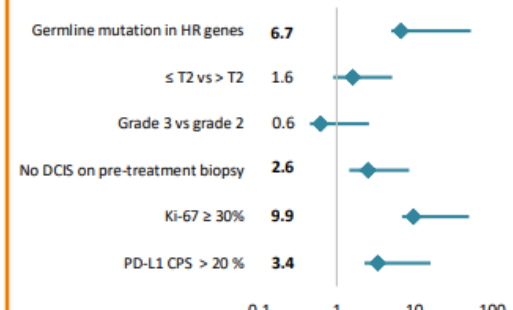


Figure 4. Multivariable Model for pCR

CONCLUSION

- We identified **biomarkers** of pCR after NACi:
  - ➤Germline mutation in HR genes
  - ➤ Ki-67 level
  - ➤ Histological subtype
  - ➤Absence of DCIS on pre-treatment biopsy
- This could **help to identify patients eligible for escalation or de-escalation therapy**
- **Patients with ER 1-10% have a similar pCR with NACi than patients with ER < 1%** and could benefit from the addition of carboplatin and pembrolizumab
- None of the lobular or apocrine cancers achieved pCR in this series

ER: estrogen receptor, PR: progesterone receptor ; DCIS: ductal carcinoma in situ ; HR: homologous recombination

AKNOWLEDGEMENTS

The authors thank the patients and their families as well as investigators and staff at Institut Curie Hospitals.

CONTACT

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COI : None declared

Helal and al. ESMO 2024

PROMENADE: PembROlizuMab for early ER-low/HER2- breast caNcer, reAlworlD frEnch cohort

F. Cherifi[1], L. Cabel[2], C. Bousrih[3], E. Volant[4], F. Dalenc[5], B. Mery[6], M. Auvray Kuentz[7], M. Alexandre[8], L. Benistant[9], M. Leheurteur[10], C. Bailleux[11], M. Debled[12], J-S. Frenel[13], D. Loirat[2], F.C. Bidard[2], S. Aho[14], A. Glenet[15], J.T.L. Ribeiro Mourato[3], F. Christy[16], G. Emile[1]

General characteristics

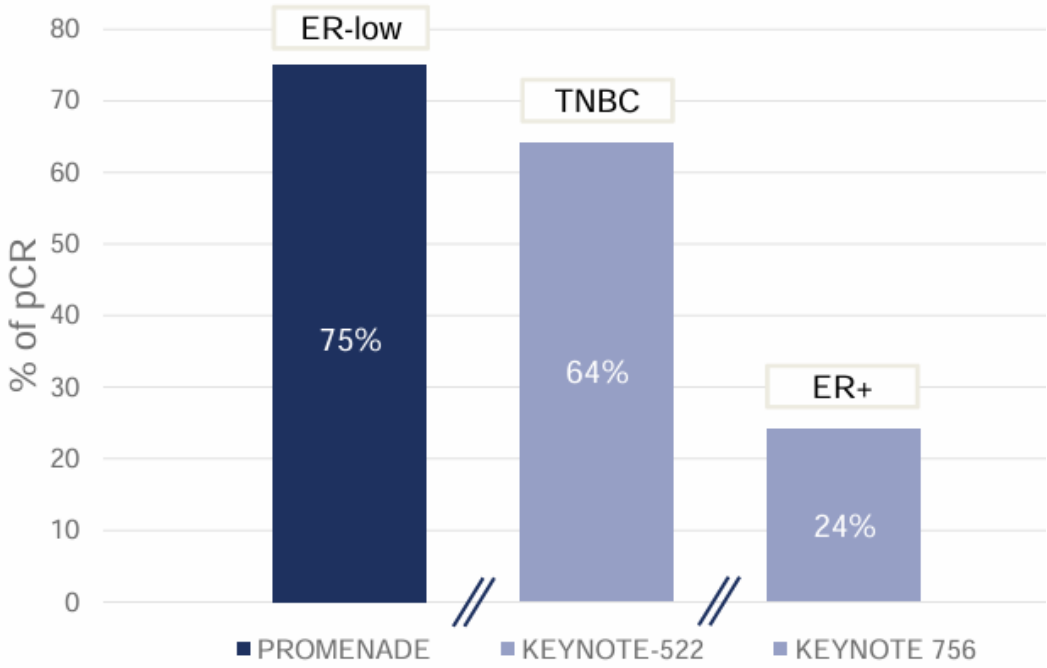
Number of patients	**114**
Age - Median (min-max)	49 (26-80)
Missing	*2 (1.8%)*
Menopausal status - n (%)	
Pre	64 (57%)
Post	48 (43%)
Missing	*2 (1.8%)*
Tumor size - n (%)	
<T2	12 (11%)
≥T2	102 (89%)
Node - n (%)	
N0	58 (51%)
N ≥1	56 (49%)

Pathology

Histology - n (%)	
Ductal	102 (90%)
Lobular	2 (2%)
Other	9 (8%)
Missing	*1 (0.9%)*
SBR grade - n (%)	
II	15 (14%)
III	95 (86%)
Missing	*4 (3.5%)*
KI67 - Mean (SD)	61 (24)
Missing	*15 (13.2%)*
Endocrine receptors - n (%)	
ER-/PR+	37 (32%)
ER+/PR-	66 (58%)
ER+/PR+	11 (10%)
HER2 – n (%)	
0	57 (50%)
1	35 (31%)
2 (ISH neg)	22 (19%)

Treatment

NACT* completed- n (%)	83 (75%)
Missing	*4 (3.5%)*
Surgery - n (%)	113 (99%)
Surgery type - n (%)	
Lumpectomy	62 (54.3%)
Mastectomy	50 (44%)
Not done (PD)	1 (0.8%)
Other	1 (0.8%)
Nodal intervention - n (%)	
Sentinel lymph node	57 (50%)
Axillary dissection	54 (47%)
Not done (PD)	1 (0.8%)
Other	2 (1.7%)



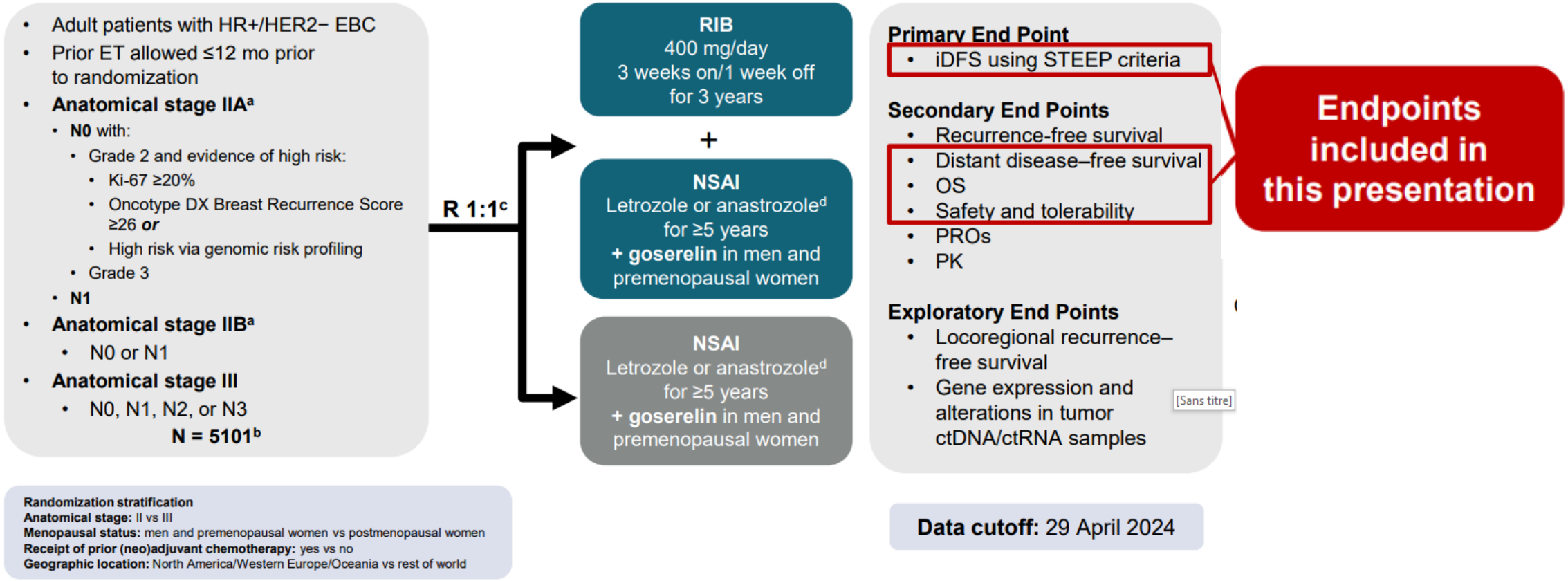
Cherifi and al. ESMO 2024

Early Breast Cancer

- OS KEYNOTE-522
- **NATALEE 4-years**
- HypoG-01

NATALEE

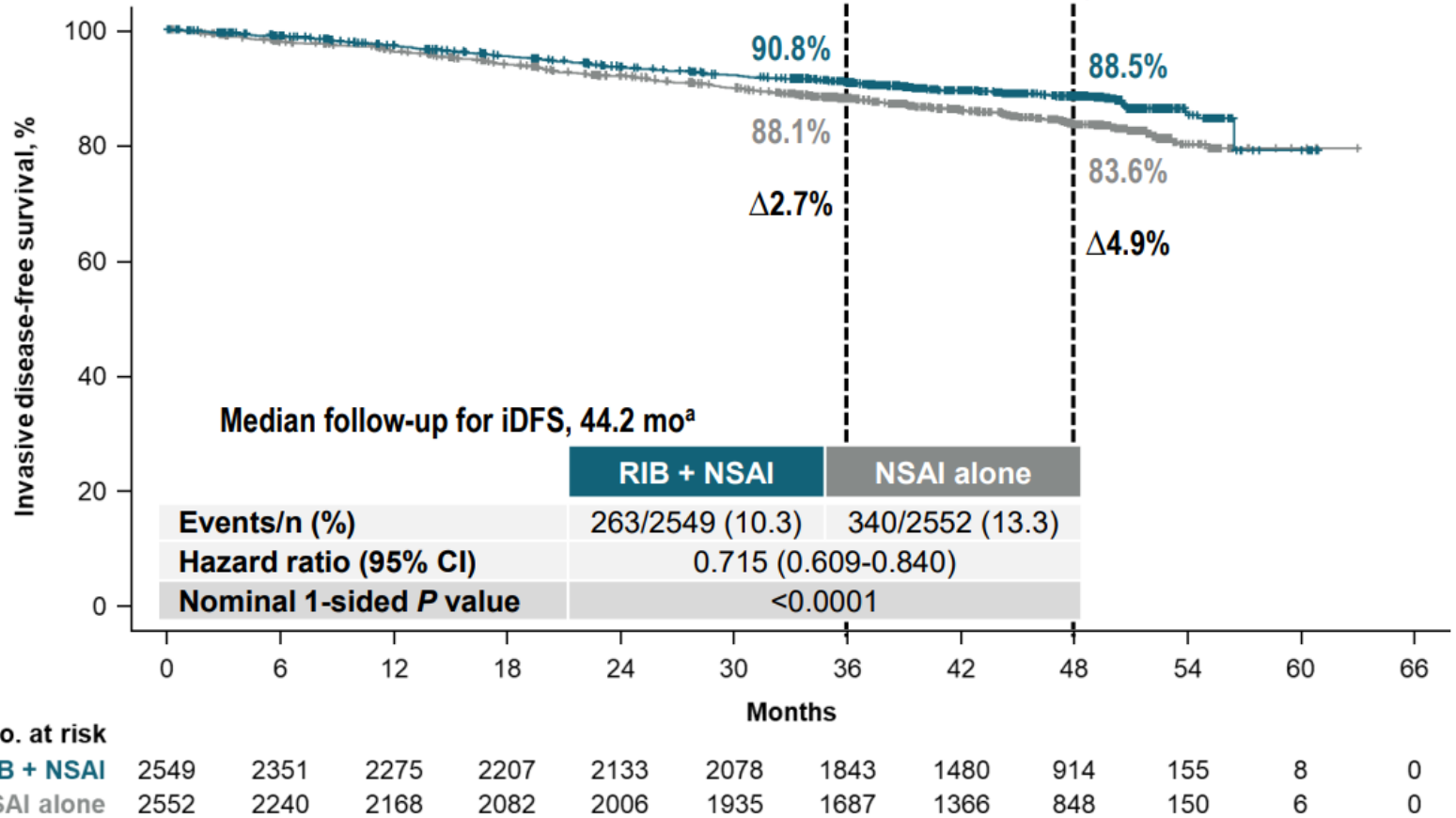
4 years analysis, all patients off RIBO (62,8% completed 3y)



Fasching and al. ESMO 2024

iDFS in ITT Population

Significant iDFS benefit with RIB + NSAI after the planned 3-year treatment

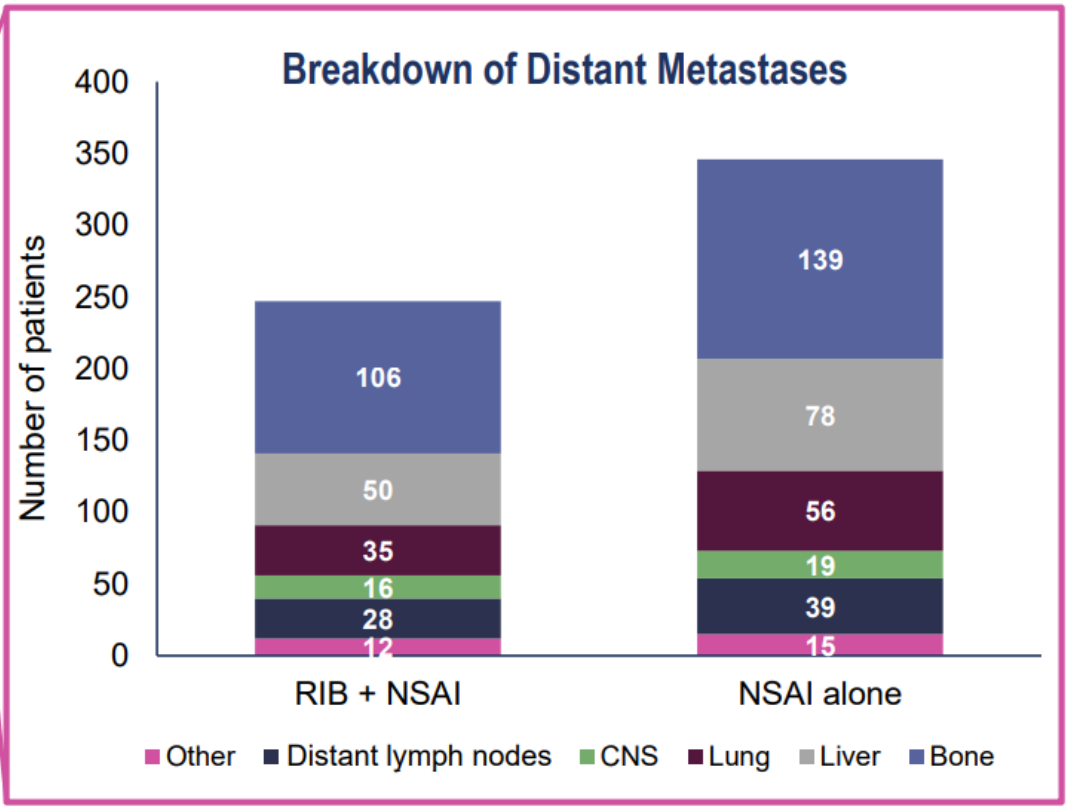


iDFS, invasive disease–free survival; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] An additional 10.9 months of follow-up compared with the protocol-specified final iDFS analysis.

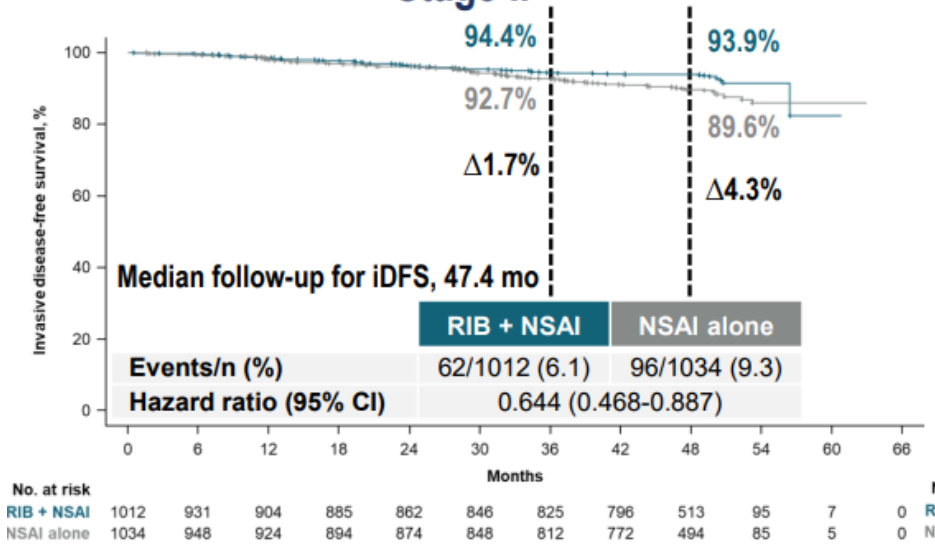
iDFS Events in ITT Population

The majority of iDFS events were distant recurrences, which were more common in the NSAI only arm

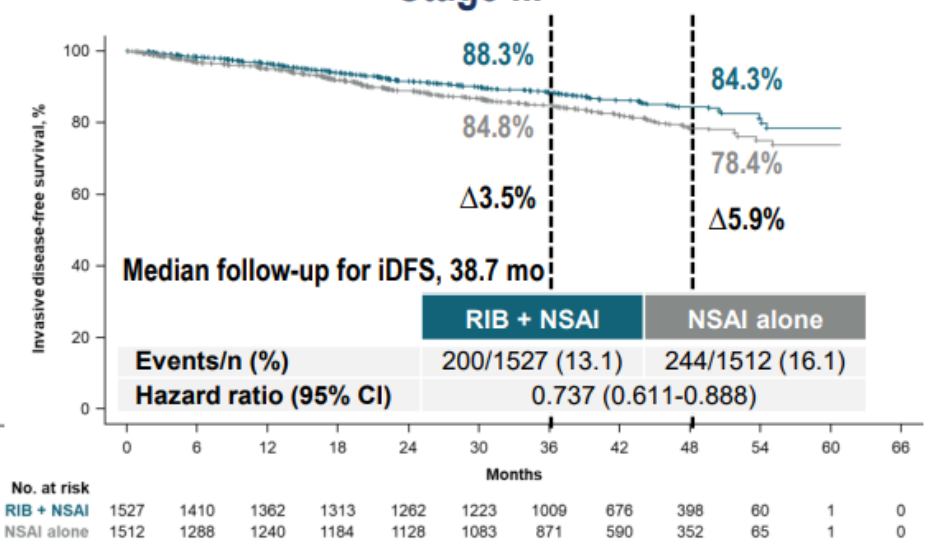
Type and site of first iDFS event, n (%)	RIB + NSAI n=2549	NSAI Alone n=2552
Distant recurrence	176 (6.9)	246 (9.6)
Local/regional invasive recurrence	25 (1.0)	49 (1.9)
Second primary nonbreast cancer	39 (1.5)	40 (1.6)
Death	17 (0.7)	11 (0.4)
Invasive contralateral breast tumor	11 (0.4)	10 (0.4)
Invasive ipsilateral breast tumor	8 (0.3)	9 (0.4)



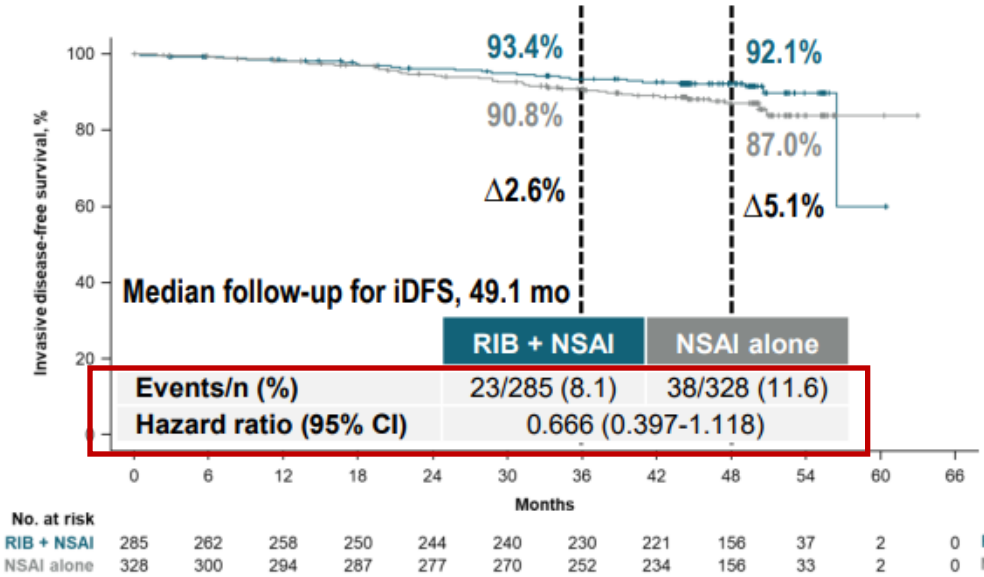
Stage II



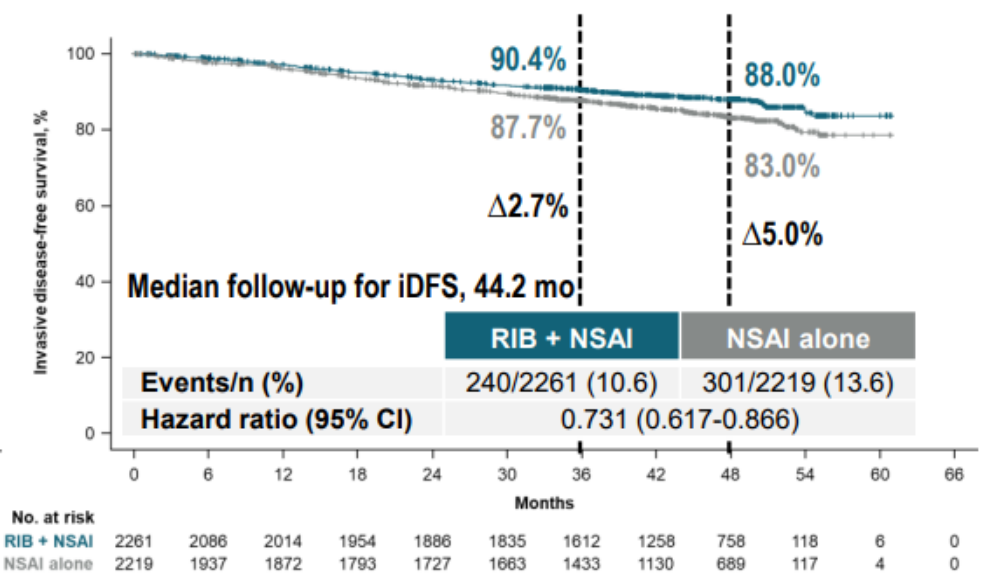
Stage III



N0



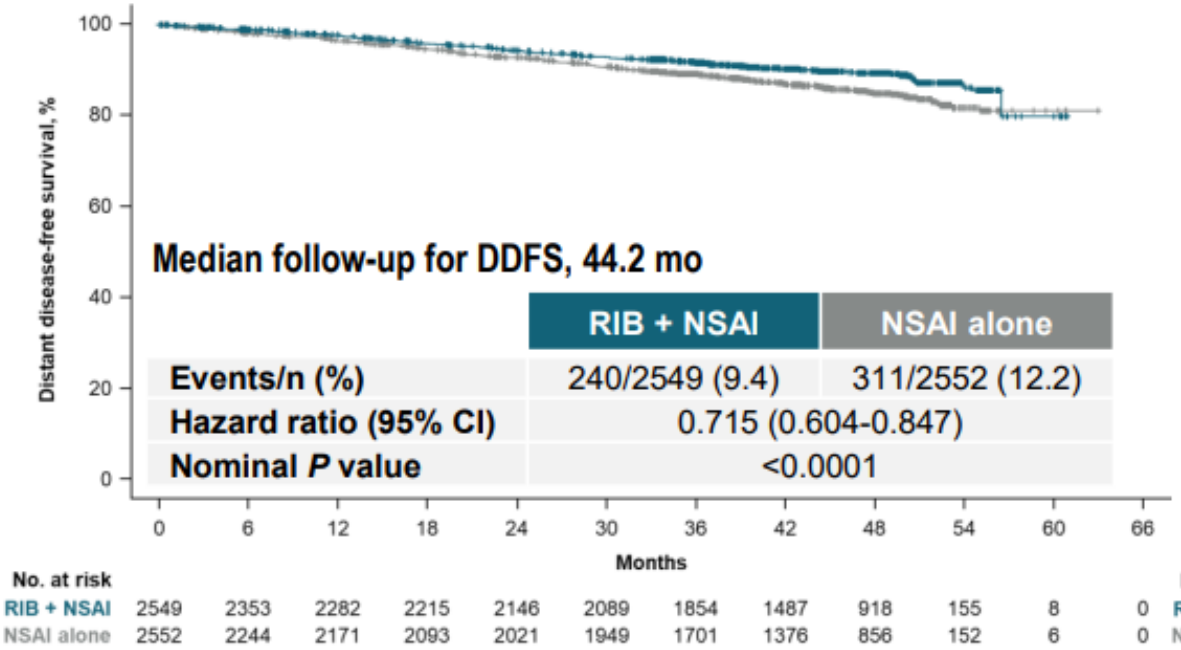
N1-3



NATALEE

4 years analysis, all patients off RIBO (62,8% completed 3y)

DDFS

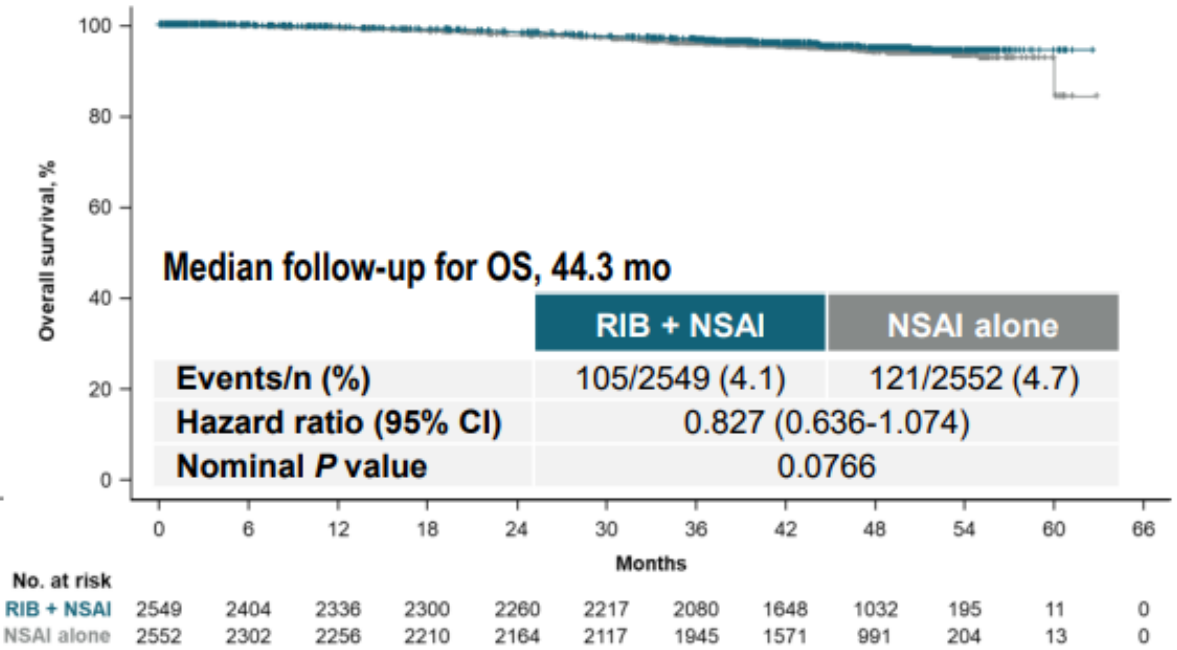


Median follow-up for DDFS, 44.2 mo

	RIB + NSAI	NSAI alone
Events/n (%)	240/2549 (9.4)	311/2552 (12.2)
Hazard ratio (95% CI)	0.715 (0.604-0.847)	
Nominal *P* value	<0.0001	

No. at risk												
RIB + NSAI	2549	2353	2282	2215	2146	2089	1854	1487	918	155	8	0
NSAI alone	2552	2244	2171	2093	2021	1949	1701	1376	856	152	6	0

OS



Median follow-up for OS, 44.3 mo

	RIB + NSAI	NSAI alone
Events/n (%)	105/2549 (4.1)	121/2552 (4.7)
Hazard ratio (95% CI)	0.827 (0.636-1.074)	
Nominal *P* value	0.0766	

No. at risk												
RIB + NSAI	2549	2404	2336	2300	2260	2217	2080	1648	1032	195	11	0
NSAI alone	2552	2302	2256	2210	2164	2117	1945	1571	991	204	13	0

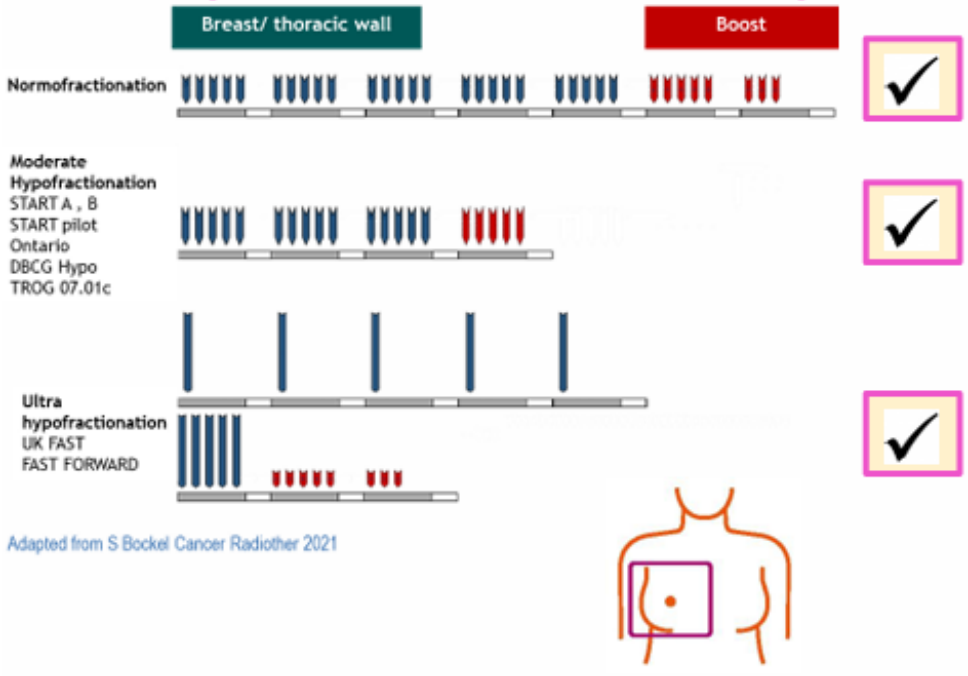
Early Breast Cancer

- OS KEYNOTE-522
- NATALEE 4-years
- **HypoG-01**

Locoregional hypo vs normofractionated radiation therapy in breast early cancer

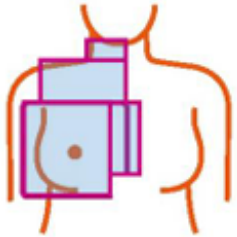
5 years results of the **HypoG-01** phase 3
UNICANCER trial

RT Breast only



Nodal RT

- **No previous randomized trial for nodal RT**
- **50 Gy/ 25 fractions/ 5 weeks** is the **standard** in most countries when **nodal RT**
- **Nodal RT= larger volumes**, fear of increased toxicities with higher dose per fraction



Rivera and al. ESMO 2024

Non inferiority, phase III, 29 centers

N= 1265 randomized patients

Woman≥18 years, operated for T1-3, N0-3, M0 breast cancer with an indication for **regional nodes RT**

R

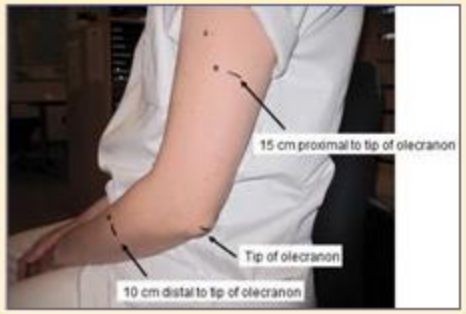
Hypofractionated RT: 40 Gy/ 15 fr/ 3 weeks +/- boost (investigator's choice)

Normofractionated RT: 50 Gy/ 25 fr/ 5 weeks +/- boost (investigator's choice)

Primary endpoint: 3-year cumulative incidence of **Arm lymphedema**

Primary endpoint

- **Arm lymphedema** defined as ≥10% increase in arm circumference 15 cm proximal and/or 10 cm distal of the olecranon relative to baseline, compared to the contralateral circumference



Secondary endpoints

- **Overall Survival (OS)**
- **Loco Regional-Free survival (LRFS)**
- **Distant disease-Free survival (DDFS)**
- **Breast cancer specific survival (BCSS)**
- **Shoulder range of motion** impairment defined as a reduction ≥25° in active abduction or flexion

HypoG-01: Baseline and Treatment characteristics

Treatment		HF-RT* n = 614 (%)	NF-RT** n = 607 (%)
Breast surgery	Mastectomy	276 (45.0)	274 (45.1)
	Lumpectomy	338 (55.0)	333 (54.9)
Axillary exploration	Axillary clearance	505 (82.2)	499 (82.2)
	Sentinel node(s) biopsy	304 (49.5)	281 (46.3)
Radiotherapy technique	IMRT	324 (52.8)	314 (51.7)
	RT3D	290 (47.2)	293 (48.3)
Tumour bed boost	n (%)	293 (47.8)	303 (50.0)
	Integrated (SIB)	97 (33.1)	95 (31.4)
	Sequential	196 (66.9)	208 (68.6)
Systemic treatment	Preoperative chemotherapy	130 (21.2)	155 (25.5)
	Adjuvant Chemotherapy	389 (63.4)	386 (63.6)
	Preoperative endocrine therapy	13 (2.1)	7 (1.2)
	Adjuvant endocrine therapy	496 (80.8)	498 (82.0)

*HF-RT: 40 Gy/15F/3-weeks +/- tumor bed boost
**NF-RT: 50 Gy/25F/5-weeks +/- tumor bed boost

Per Protocol population		HF-RT* n = 614 (%)	NF-RT** n = 607 (%)
Age	Mean (sd)	58.5 (13.1)	58.2 (12.8)
Breast size	Small	69 (11.1)	82 (13.5)
	Medium	241 (39.5)	230 (37.9)
	Large	257 (41.9)	236 (38.9)
	Unknown	47 (7.5)	59 (9.7)
Laterality	Left	309 (50.3)	324 (53.4)
	Right	305 (49.7)	283 (46.6)
Tumour (mm)	n (%)	607 (98.9)	600 (98.8)
	Mean (sd)	26.2 (18.1)	26.1 (18.6)
Histology	Ductal	491 (80.0)	493 (81.2)
	Lobular	87 (14.2)	78 (12.9)
	Other	35 (5.7)	32 (5.3)
	Unknown	1 (0.2)	4 (0.7)
Grade	I	63 (10.3)	57 (9.4)
	II	319 (52.0)	351 (57.8)
	III	223 (36.3)	191 (31.5)
	Unknown	9 (1.4)	8 (1.3)
Breast cancer subtype	HER2+	114 (18.7)	125 (20.6)
	HER2-, ER+ or PR+	426 (70.0)	420 (69.2)
	HER2-, ER-, PR-	69 (11.3)	61 (10.0)
	Unknown	5 (0.8)	1 (0.2)
cT	0	19 (3.1)	17 (2.8)
	1	205 (33.4)	202 (33.3)
	2	293 (47.7)	285 (46.9)
	3	80 (13.0)	83 (13.7)
	4	5 (0.9)	4 (0.7)
	Unknown	12 (1.9)	16 (2.6)
cN	0	255 (41.5)	236 (38.9)
	1	292 (47.6)	297 (48.9)
	2	40 (6.5)	41 (6.8)
	3	15 (2.4)	16 (2.6)
	Unknown	12 (2.0)	17 (2.8)

Non inferiority of hypofractionated RT

In per protocol analysis :

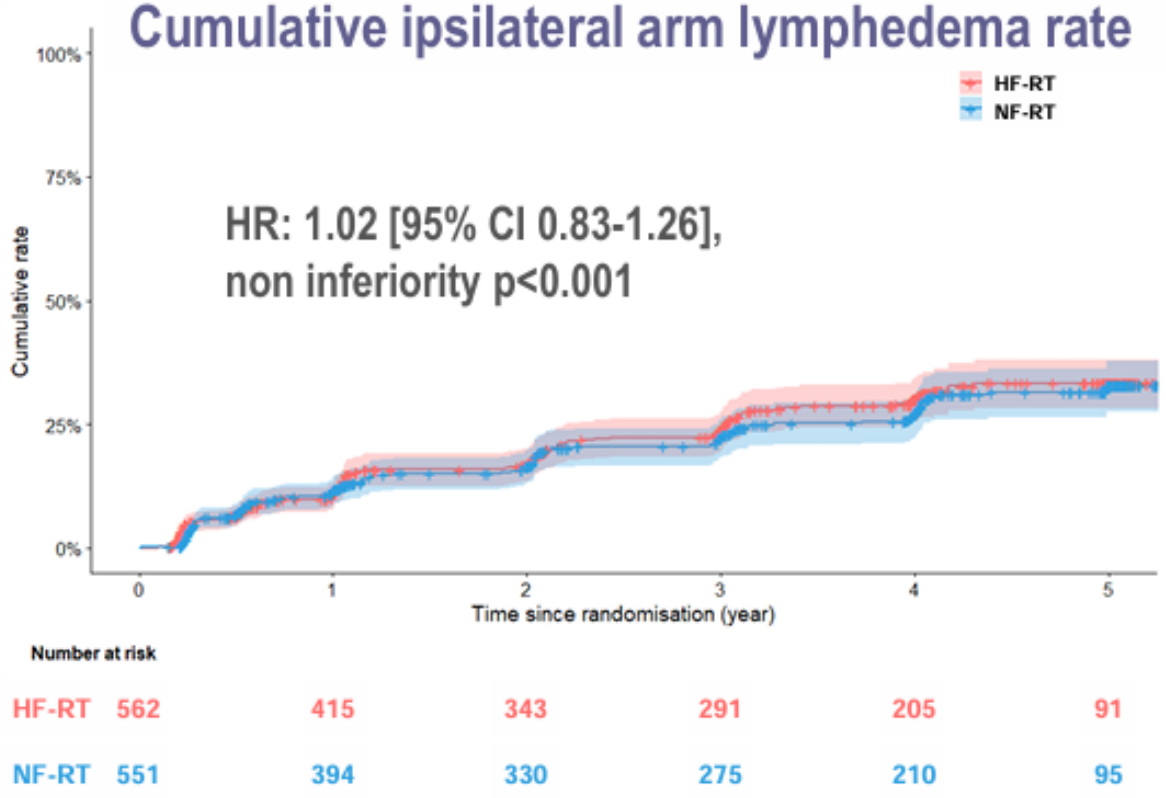
Median follow up: **4.8 years**

Arm lymphedema occurred in 275/ 1113 pts with baseline and end of RT measurements

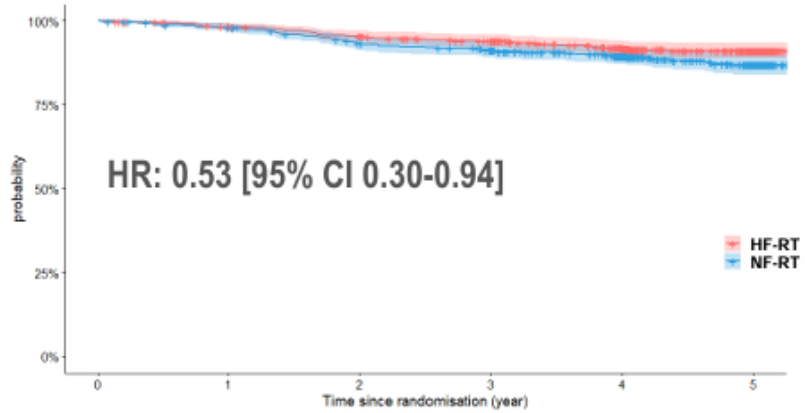
Non inferiority in cumulative ipsilateral arm lymphedema rate p<0.001

Cumulative 5-year rate (PP):

- **33.3%** (95% CI: 28.7 - 38.4) in HF
- **32.8%** (95% CI: 27.9 - 38.1) in NF



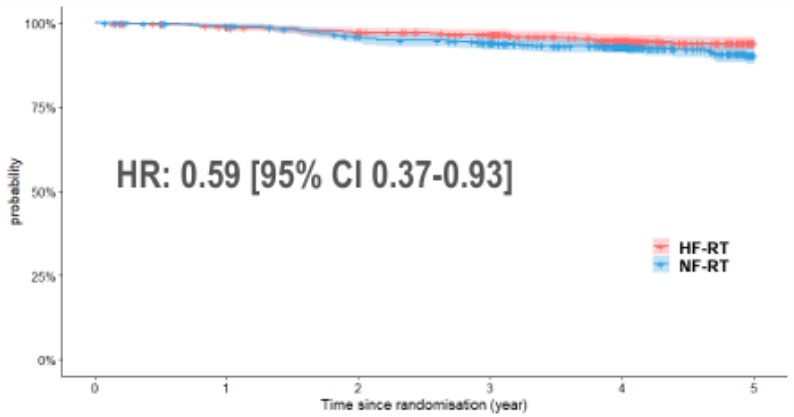
Breast Cancer-Specific Survival



Number at risk

HF-RT	614	590	567	541	438	201
NF-RT	607	586	550	526	433	172

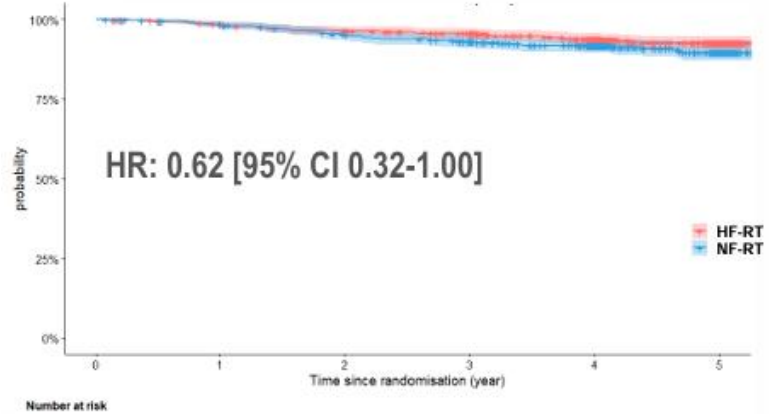
Overall Survival



Number at risk

HF-RT	614	593	577	555	444	200
NF-RT	607	591	564	537	437	170

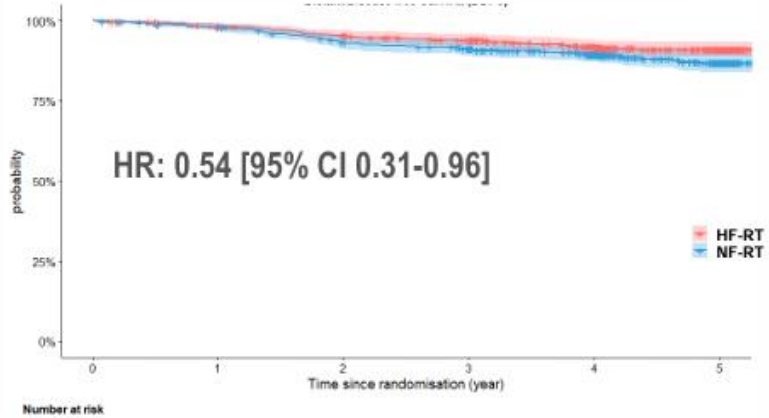
Local Recurrence-free Survival



Number at risk

HF-RT	614	591	573	550	447	223
NF-RT	607	585	560	532	438	176

Distant Disease-free Survival



Number at risk

HF-RT	614	590	567	541	438	201
NF-RT	607	586	550	526	433	172

Limited adverse events and no sign of detrimental effect of hypofractionated RT

32 (2.6%)patients with any SAEs :

17 in HF

15 in NF

3 RT-related

No grade 5

Adverse Events (AE)	HF-RT (n=614)				NF-RT(n=607)				
ITT population	*total*	Grade I	Grade II	Grade III	*total*	Grade I	Grade II	Grade III	Grade IV
Any grade ≥3 AE	*80 (12.7%)*				*79 (12.6%)*				
AE of interest									
Brachial plexopathy	*18(3%)*	15(2%)	2(0%)	1(0%)	*17 (3%)*	15 (2%)	2(0%)		
Cardiac disorders	*13(2%)*	7(1%)	3(0%)	3(0%)	*4 (1%)*	2 (0%)	1(0%)		1(0%)
Endocrine disorders	*43(7%)*	29(5%)	14(2%)		*27 (4%)*	15 (2%)	12 (2%)		
Fatigue	*401(64%)*	**318(50%)**	**75(12%)**	**8(1%)**	*401 (64%)*	**315 (50%)**	**80 (13%)**	**6(1%)**	
Fibrosis	*306(48%)*	**236(37%)**	**61(10%)**	**9(1%)**	*277 (44%)*	**210 (33%)**	**60 (10%)**	**7(1%)**	
Dysphagia	*132(21%)*	116(18%)	16(3%)		*154 (24%)*	142 (23%)	12 (2%)		
Pain	*412(65%)*	294(47%)	108(17%)	10(2%)	*434 (69%)*	327 (52%)	97 (15%)	10(2%)	
Radiation skin injury	*520(82%)*	**428(68%)**	**83(13%)**	**9(1%)**	*561 (89%)*	**363 (58%)**	**183 (29%)**	**15(2%)**	
Breast/nipple edema	*71(11%)*	61(10%)	10(2%)		*72 (11%)*	65 (10%)	7 (1%)		
Respiratory disorders	*147(23%)*	125(20%)	21(3%)	1(0%)	*175 (28%)*	157 (25%)	14 (2%)	3(0%)	1(0%)
Dyspigmentation	*165(26%)*	147(23%)	16(3%)	2(0%)	*179 (28%)*	152 (24%)	22 (3%)	5(1%)	

STANDARD OF CARE

Metastatic / Locally Advanced Breast Cancer

- **Capitello-290**
- ICARUS B-01
- DB-12

CAPItello-290: Study overview

Phase 3, randomised, double-blind, placebo-controlled study (NCT03997123)

Patients with locally advanced or mTNBC

- Men and pre-/post-menopausal women
- Eligible for taxane monotherapy
- No prior (neo)adjuvant chemotherapy within 6 months (12 months for taxanes)
- No prior systemic therapy for inoperable locally advanced or metastatic disease
- ECOG performance status 0 or 1
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumour sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1
N=812

Capivasertib–paclitaxel[a]

Placebo–paclitaxel[a]

Stratification factors:
- Visceral vs non-visceral disease
- (Neo)adjuvant chemotherapy (yes/no)
- Region[b]

- First patient randomised: July 2019
- Last patient randomised: February 2022

Dual primary endpoints

OS
- Overall population
- *PIK3CA*/*AKT1*/*PTEN*-altered population

Key secondary endpoints

PFS
- Overall population
- *PIK3CA*/*AKT1*/*PTEN*-altered population

Safety

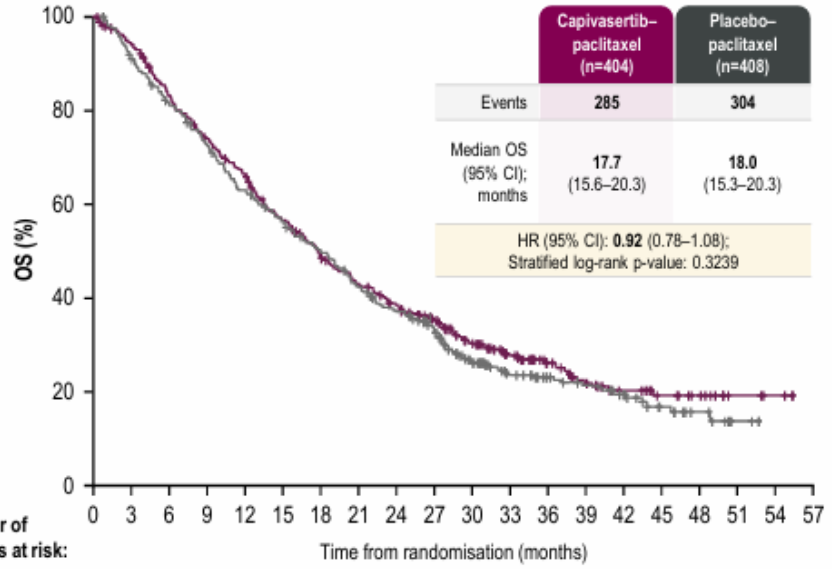
McArthur and al. ESMO 2024

Alterations; n (%)	Capivasertib–paclitaxel (n=404)	Placebo–paclitaxel (n=408)
Any alteration	124 (30.7)	125 (30.6)
PIK3CA only	52 (12.9)	49 (12.0)
PIK3CA and *AKT1*	0	1 (0.2)
PIK3CA and *PTEN*	12 (3.0)	8 (2.0)
AKT1 only	16 (4.0)	15 (3.7)
PTEN only	44 (10.9)	52 (12.7)
Non-altered	280 (69.3)	283 (69.4)
Confirmed (no alteration detected)	228 (56.4)	237 (58.1)
Unknown[b]	52 (12.9)	46 (11.3)

PIK3CA/AKT1/PTEN alterations were analysed by retrospective central molecular testing of primary or recurrent FFPE tumour sample. [b]Reasons for unknown status include no sample available, preanalytical failure, or post-analytical failure. The non-altered analysis subgroup includes patients with confirmed non-altered and unknown next-generation sequencing results.

No statistically significant OS difference between treatment arms in either population

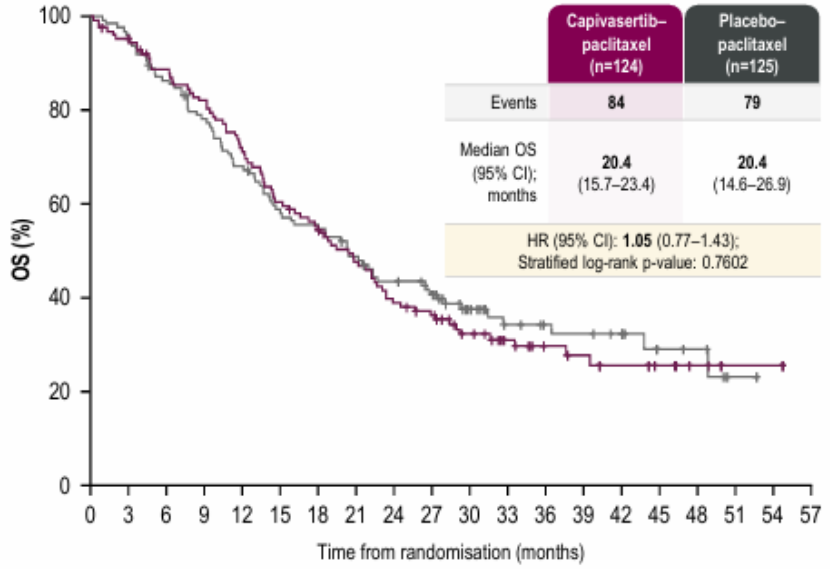
Overall population



Number of patients at risk:

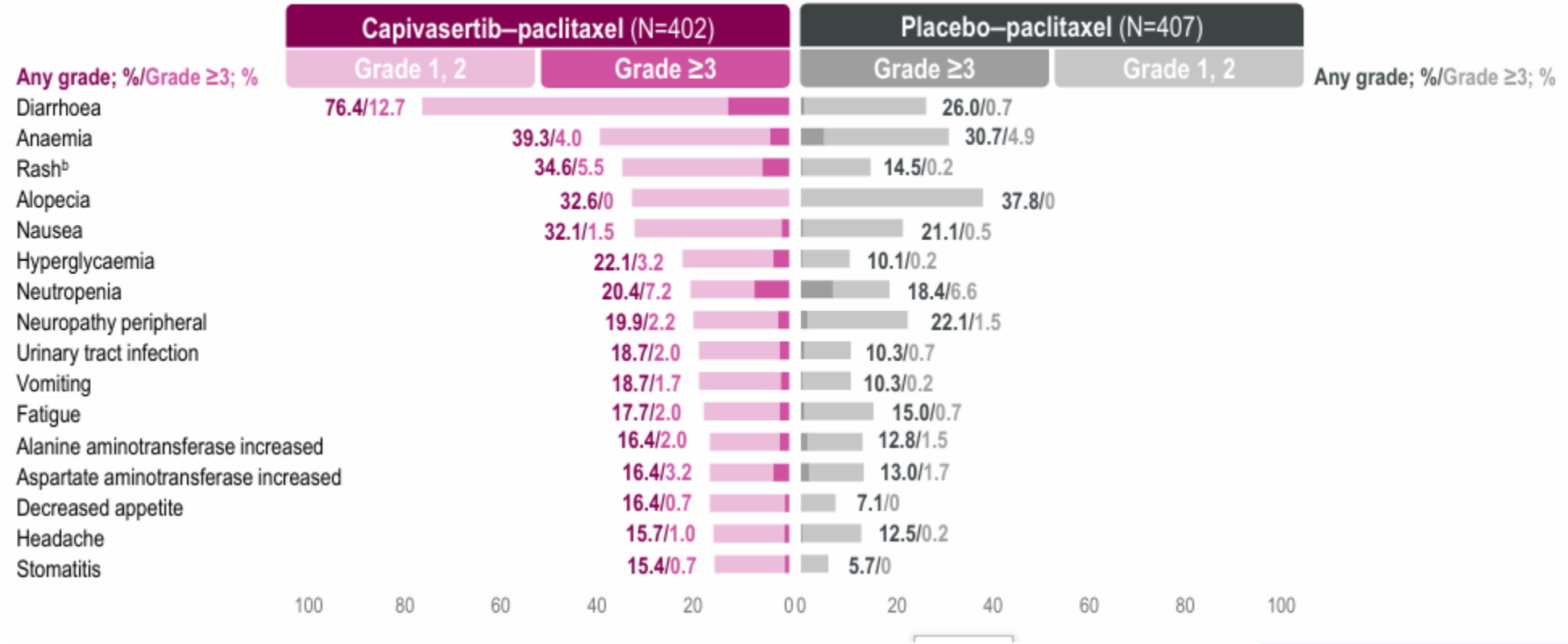
Capivasertib–paclitaxel	404	376	328	290	259	218	184	160	140	118	88	66	45	31	23	16	12	4	2	0
Placebo–paclitaxel	408	369	325	290	250	221	196	165	140	114	77	53	43	36	27	15	9	2	0	0

PIK3CA/AKT1/PTEN-altered population



Capivasertib–paclitaxel	124	117	107	99	86	73	65	55	45	40	30	22	15	13	10	7	4	1	1	0
Placebo–paclitaxel	125	119	106	94	82	69	66	57	50	44	30	20	17	16	14	7	6	1	0	0

Diarrhoea was the most frequent AE at any grade and Grade ≥3 in the capivasertib–paclitaxel group
The AE profile of capivasertib–paclitaxel was broadly consistent with the known profiles of the agents



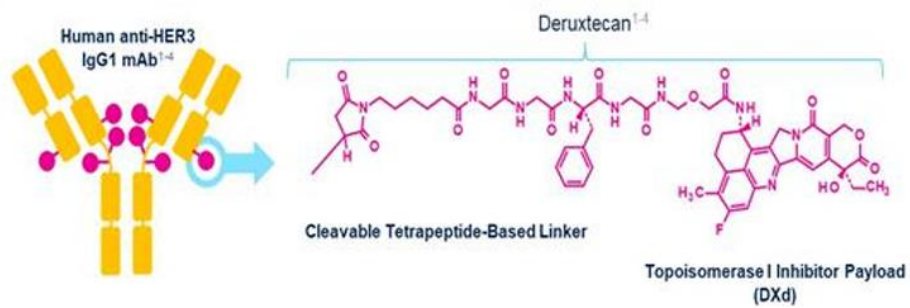
→ **Pas de CAPI**

Metastatic / Locally Advanced Breast Cancer

- Capitello-290
- **ICARUS B-01**
- DB-12

ICARUS BREAST01: Study Design

Multi-center, single-arm, phase 2 study (NCT04965766)



KEY ELIGIBILITY CRITERIA*:

-unresectable locally advanced/metastatic BC
-HR+/HER2-neg[a]
-progression on CDK4/6inh + ET
-progression on 1 prior chemotherapy for ABC
-prior PI3K/AKT/mTORinh allowed
-no prior T-DXd

HER3-DXd 5.6 mg/kg every 3 weeks until PD or unacceptable toxicity

Primary Endpoint:

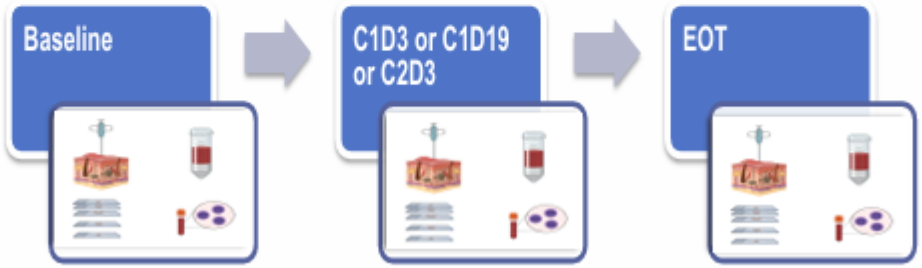
- Investigator-assessed confirmed ORR

Secondary Endpoints:

- DOR, PFS, CBR, OS
- Safety and tolerability

Mandatory:

-tumor biopsy (1 frozen + 3 FFPE)
-blood (whole blood + serum)



Exploratory Endpoints:

- Predictors of response/resistance
- Dynamics of HER3 expression before and after treatment
- CTCs levels during treatment

***HER3-expression prescreening (75% of membrane positivity at 10x) was removed by amendment on April 21st 2022[b]**

Pistilli and al. ESMO 2024

PATIENTS N=99

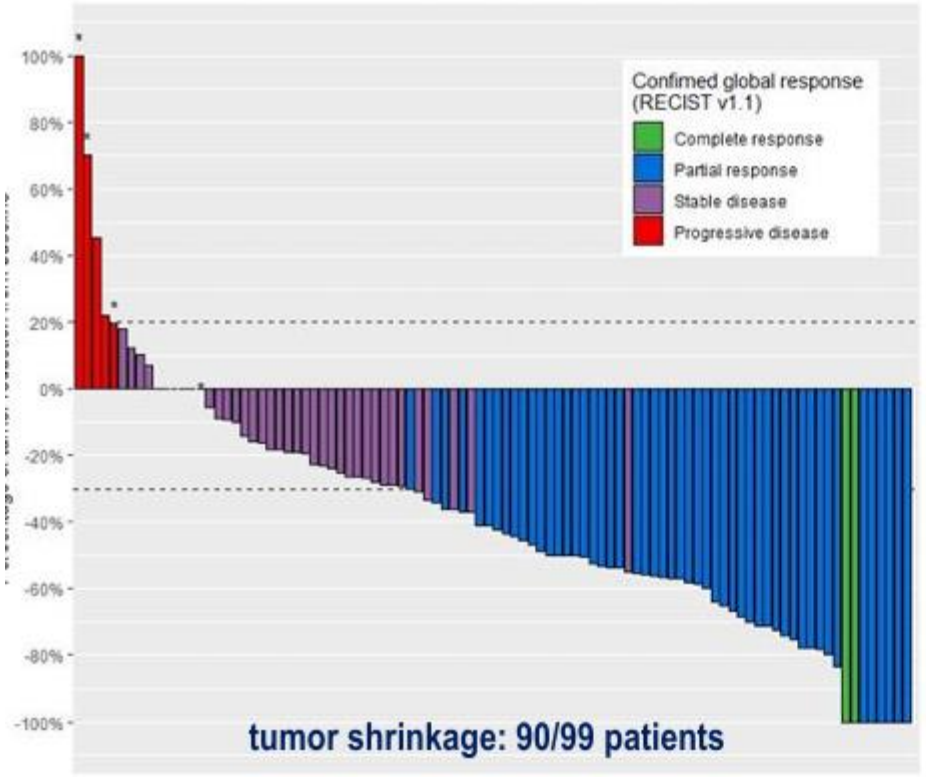
Age	
Median [range], years	57.0 (48.0;66.0)
Sex, n (%)	
Female	99 (100.0)
HR status, n (%)[a]	
ER+	94 (94.9)
PR+	42 (42.4)
HER2 expression, n (%)[b]	
IHC 0*	39 (39.4)
IHC 1+	22 (22.2)
IHC 2+	7 (7.1)
IHC 3+	1 (1.0)
Unknown	30 (30.3)[c]

HER3 expression[b]	
Membrane H-score, median (IQR)	180 (144;215)
Overall membrane positivity at 10x, n (%):	
<25%	16 (16.2)
25-74%	7 (7.1)
≥75%	49 (49.4)
Unknown	27 (27.3)
Median number of systemic therapies for ABC, n [range]	2 [1;4]
Prior treatment with CDK4/6inh, n (%)	98 (99.0)[d]
Median duration, months [range]	13.7 [6.5;19.7][e]
Prior PI3K/AKT/mTOR inh for ABC, n (%)	35 (35.4)
Prior chemotherapy for ABC, n (%)[f]	99 (100.0)

HER3-DXd treatment status, n (%)	
Ongoing	19 (19.2)
Discontinued	80 (80.8)
Primary reason for discontinuation, n (%)	
Disease progression	64 (64.6)
Adverse events	8 (8.1)[a]
Other	7 (7.1)
Number of HER3-DXd cycles, median [IQR]	11.0 [6.0;18.0]
Median treatment duration, days [IQR]	251.0 [144.5;402.0]

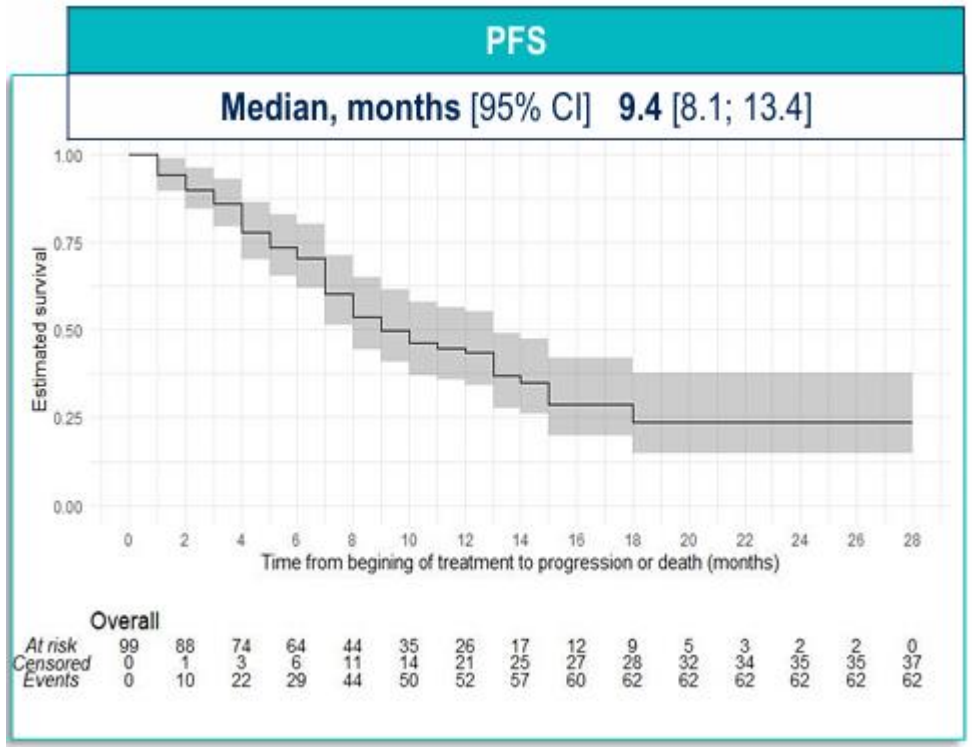
Confirmed Objective Response Rate

ICARUS BREAST



	N=99 n	% [95%CI][a]
Confirmed ORR[b]	**53**	**53.5** [43.2; 63.6]
CR	2	2.0 [0.2;7.1]
PR	51	51.5 [41.3; 61.7]
SD	37	37.4 [27.8; 47.7]
PD	7	7.1 [2.9; 14.0]
NE[c]	2	2.0 [0.2;7.1]
CBR[d]	**62**	**62.6** [52.3;72.1]

No significant association between HER2 expression and ORR (*p-value 0.8*)[e]



TRAEs occurring in ≥ 10% of patients

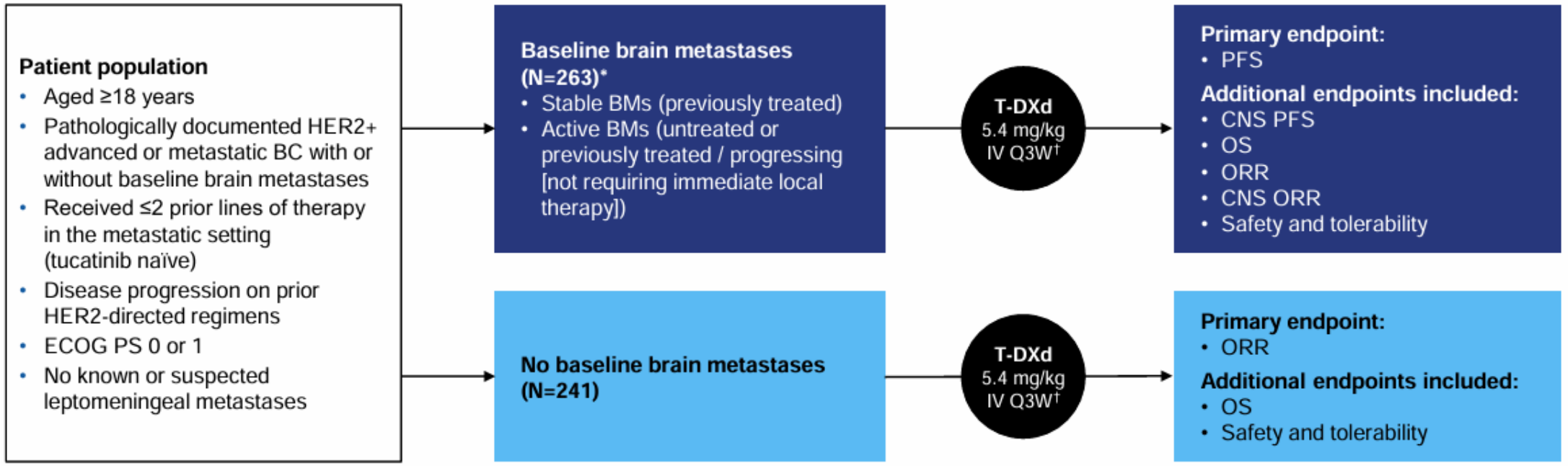
	Any grade, n (%)	Grade ≥ 3, n (%)
Fatigue	82 (82.8)	10 (10.1)
Nausea	74 (74.7)	14 (14.1)
Diarrhea	52 (52.5)	10 (10.1)
Alopecia	40 (40.4)	0
Constipation	21 (21.2)	0
Vomiting	18 (18.2)	3 (3.0)
Anorexia	16 (16.2)	1 (1.0)
Neutrophil count decrease	14 (14.1)	12 (12.1)
Abdominal pain	11 (11.1)	0
Stomatitis	10 (10.1)	0
Anemia	10 (10.1)	0

Metastatic / Locally Advanced Breast Cancer

- Capitello-290
- ICARUS B-01
- **DESTINY BREAST-12**

DESTINY-Breast12 study design

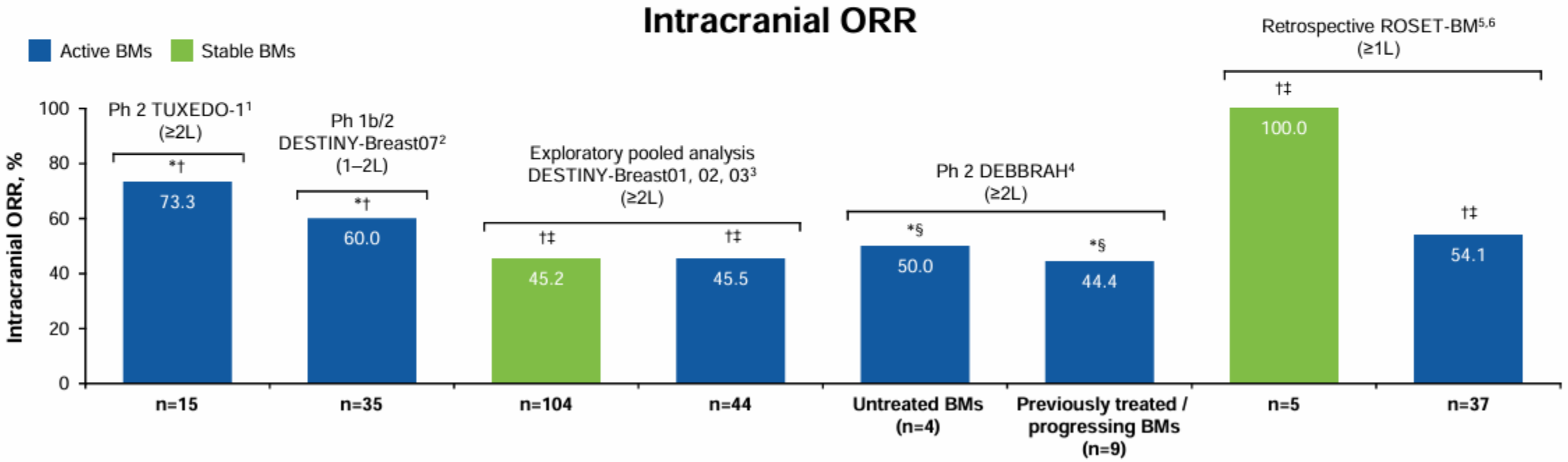
Phase 3b/4, multicenter, single-arm, two-cohort, open-label study of T-DXd in previously treated HER2+ mBC with and without brain metastases (BMs); the largest prospective study of T-DXd in patients with stable or active BMs



Harbeck and al. Nat Med 2024

Current evidence base for T-DXd benefit in patients with HER2+ mBC and BMs

Promising preliminary evidence of T-DXd intracranial activity in HER2+ mBC has been observed in small prospective patient cohorts, retrospective studies, and exploratory analyses:[1–6]



Active BM : patients with untreated and previously treated / progressing BMs

* Use of <3mg DEXA daily or equivalent allowed for symptom control of BMs

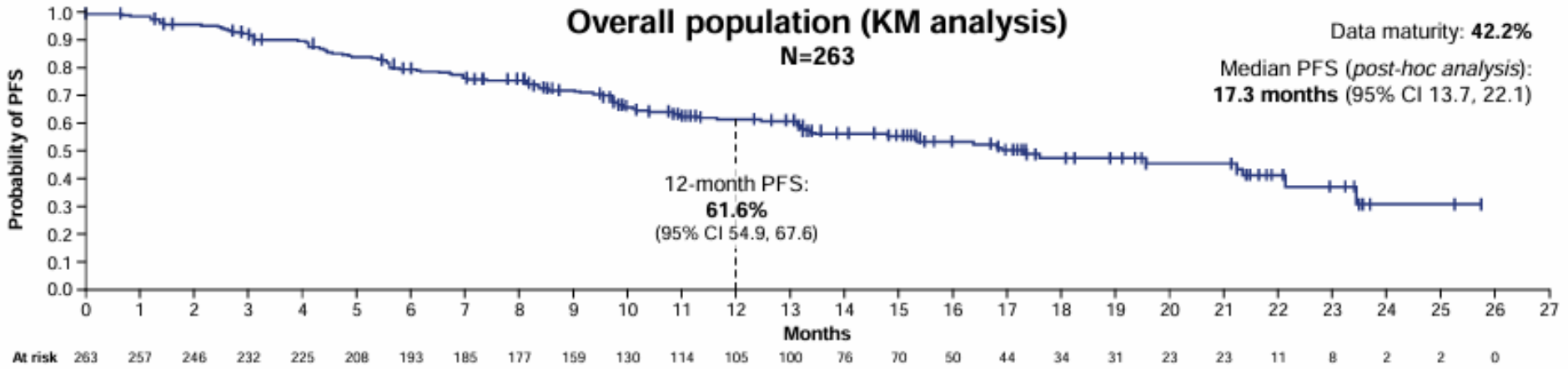
Demographics and baseline characteristics

	Baseline BMs (N=263)	No baseline BMs (N=241)
Age, median (range), years	52 (28–86)	54 (24–87)
Female, n (%)	263 (100.0)	241 (100.0)
ECOG PS at baseline, n (%)		
0	163 (62.0)	194 (80.5)
1	100 (38.0)	47 (19.5)
HER2 status, n (%)		
2+	2 (0.8)	5 (2.1)
3+	187 (71.1)	141 (58.5)
Positive*	74 (28.1)	95 (39.4)
HR status, n (%)		
Positive†	165 (62.7)	150 (62.2)
Liver metastases, n (%)	58 (22.1)	66 (27.4)
Lung metastases, n (%)	67 (25.5)	67 (27.8)
Measurable disease, n (%)	198 (75.3)	215 (89.2)

	Baseline BMs (N=263)	No baseline BMs (N=241)
Prior regimens of anticancer therapies for metastatic disease		
Number of regimens, median (range)	1.0 (0–4)	1.0 (0–4)
Number of regimens, n (%)		
0	20 (7.6)	18 (7.5)
1	132 (50.2)	124 (51.5)
2	109 (41.4)	96 (39.8)
≥3	2 (0.8)	3 (1.2)
Prior HER2 inhibitor agents, n (%)	262 (99.6)	240 (99.6)
Trastuzumab	258 (98.1)	233 (96.7)
Pertuzumab	228 (86.7)	207 (85.9)
T-DM1	106 (40.3)	94 (39.0)
Tucatinib‡	2 (0.8)	0
Other TKIs§	15 (5.7)	15 (6.2)
T-DXd	1 (0.4)	0
Specific agent not reported	1 (0.4)	0
Prior therapies for BMs, n (%)		
Intracranial radiotherapy¶	158 (60.1)	–
Whole brain radiation therapy	40 (15.2)	–
Stereotactic radiosurgery	15 (5.7)	–
Time from last intracranial radiotherapy to treatment initiation, median (range), days	164 (9–2115)	–

*Specific HER2 status unknown; †HR status positive if either or both of ER/PR status had a positive result; ‡the two patients with prior tucatinib use were recorded as protocol deviations; §lapatinib and neratinib; ¶the type of intracranial radiotherapy was not always recorded by investigators, and only whole brain radiation therapy and stereotactic radiosurgery were reported
BM, brain metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PR, progesterone receptor; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

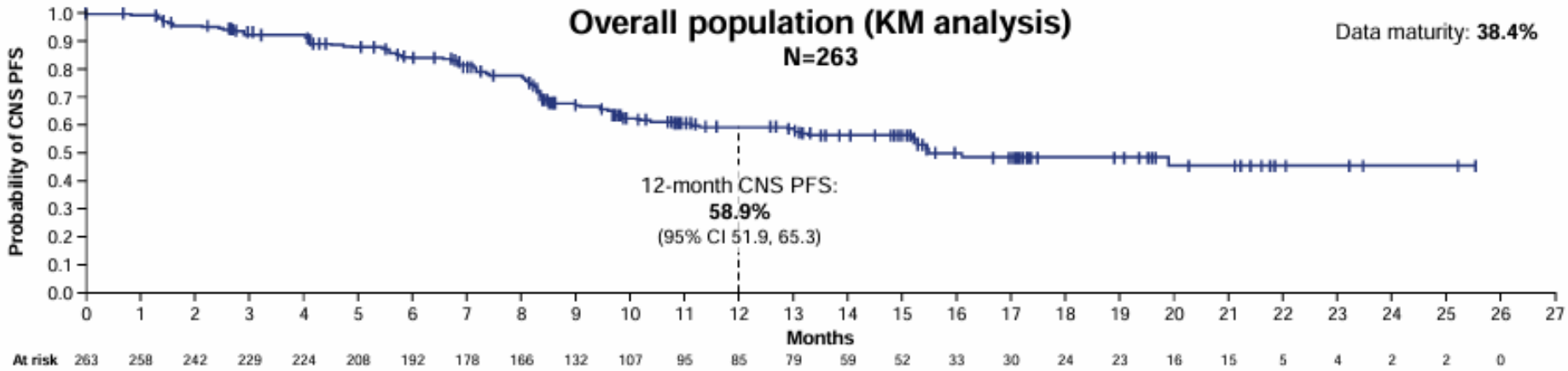
Baseline BMs: PFS (primary endpoint)



	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)	Active BM subgroups: Untreated (n=39) *Post-hoc analysis*	Active BM subgroups: Previously treated / progressing (n=67) *Post-hoc analysis*
Overall no. events	**111**	64	47	20	27
12-month PFS, % (95% CI)	**61.6 (54.9, 67.6)**	62.9 (54.0, 70.5)	59.6 (49.0, 68.7)	47.0 (29.6, 62.7)	66.7 (53.4, 76.9)

T-DXd showed consistent 12-month PFS in patients with stable and active BMs

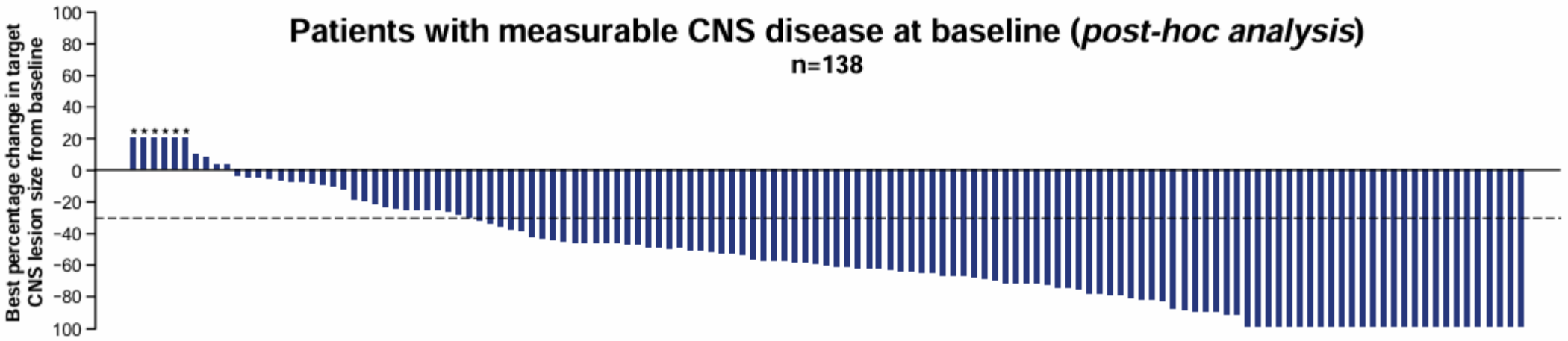
Baseline BMs: CNS PFS



	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)
Overall no. events	**101**	61	40
12-month CNS PFS, % (95% CI)	**58.9 (51.9, 65.3)**	57.8 (48.2, 66.1)	60.1 (49.2, 69.4)

T-DXd showed consistent 12-month CNS PFS in patients with stable and active BMs

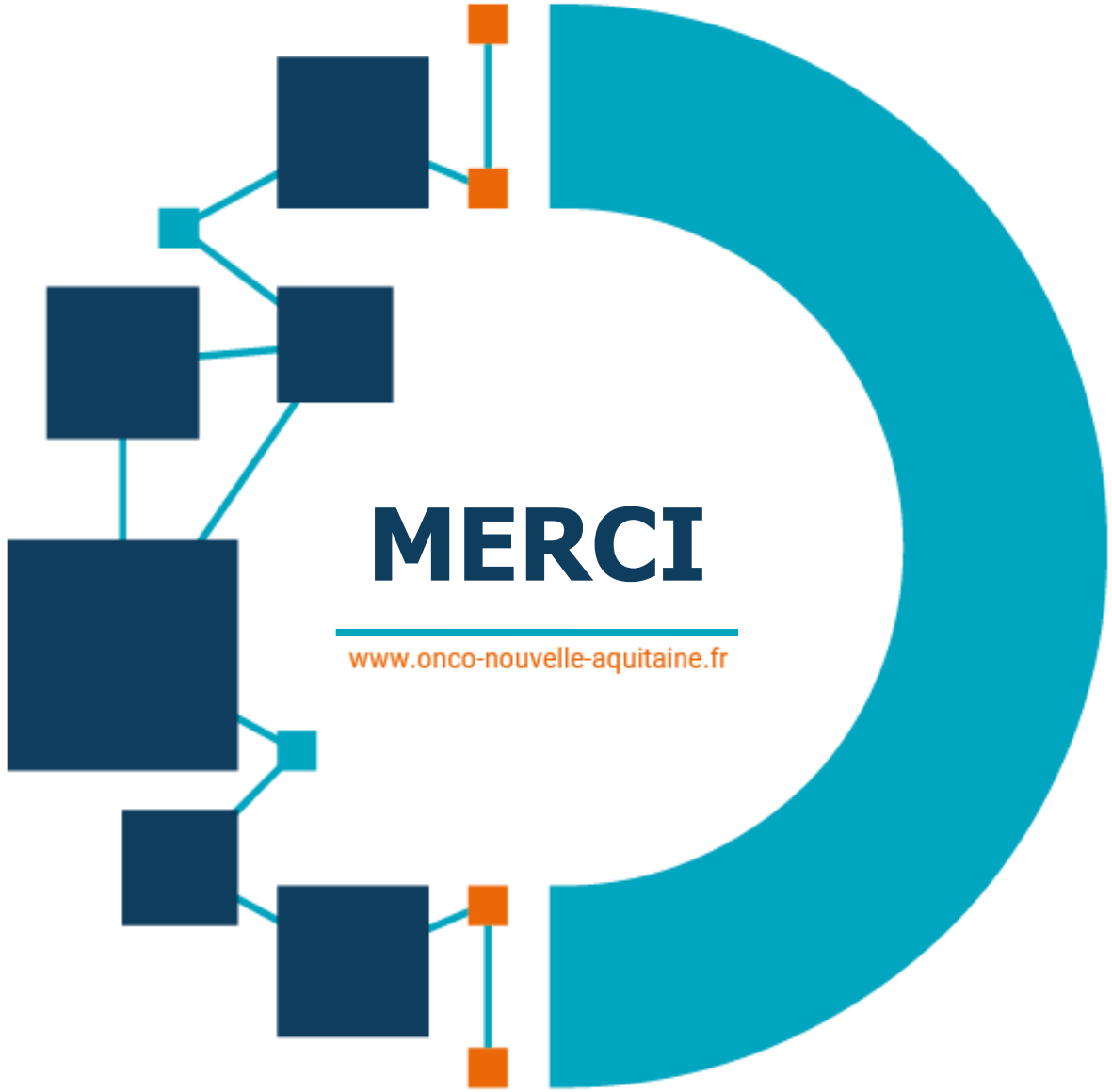
Baseline BMs: CNS ORR



Measurable CNS disease at baseline	All patients (n=138)	Stable BMs (n=77)	Active BMs (n=61)	Active BM subgroups: Untreated (n=23) *Post-hoc analysis*	Active BM subgroups: Previously treated / progressing (n=38) *Post-hoc analysis*
Confirmed CNS ORR, % (95% CI)	**71.7 (64.2, 79.3)**	79.2 (70.2, 88.3)	62.3 (50.1, 74.5)	82.6 (67.1, 98.1)	50.0 (34.1, 65.9)

T-DXd showed substantial CNS responses in the overall BMs population, including patients with stable and active BMs

Dashed line indicates a 30% decrease in target tumor size (PR)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