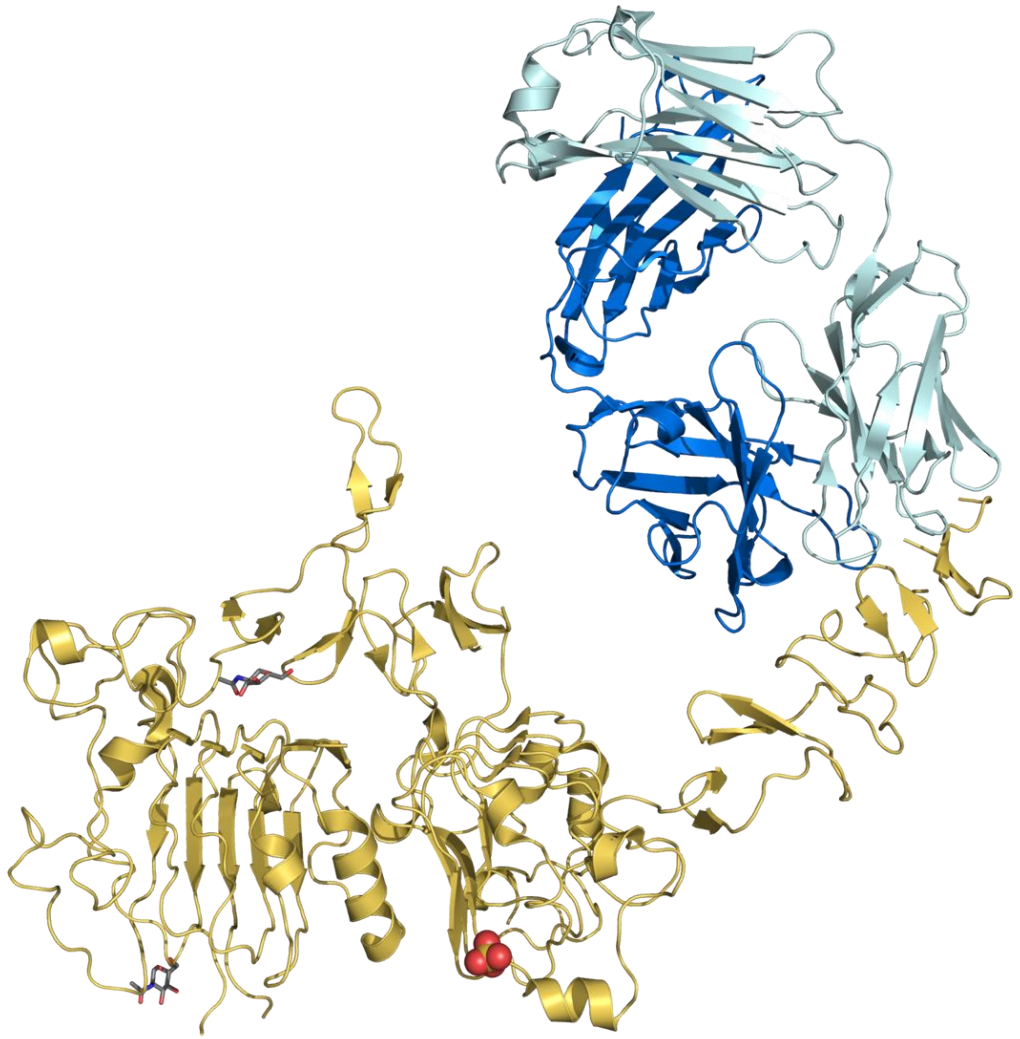
Post-ESMO 2024

BELLIO Hélène

15 octobre 2024



HER2 + METASTATIQUE

Les nouveautés

BARCELONA 2024 ESMO congress

DESTINY Breast12

Trastuzumab deruxtecan in patients with HER2+ advanced/metastatic breast cancer with or without brain metastases: DESTINY-Breast12 primary results

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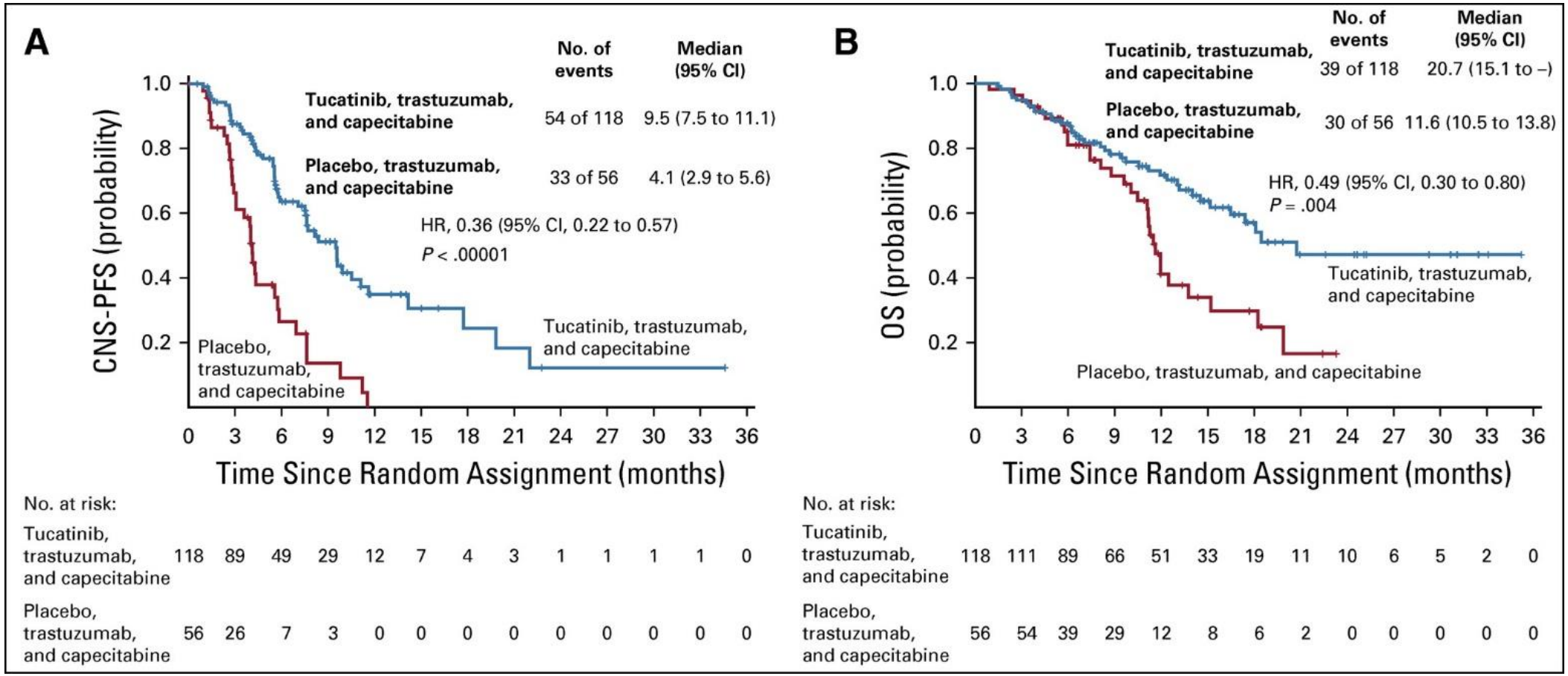
On behalf of the DESTINY-Breast12 investigators

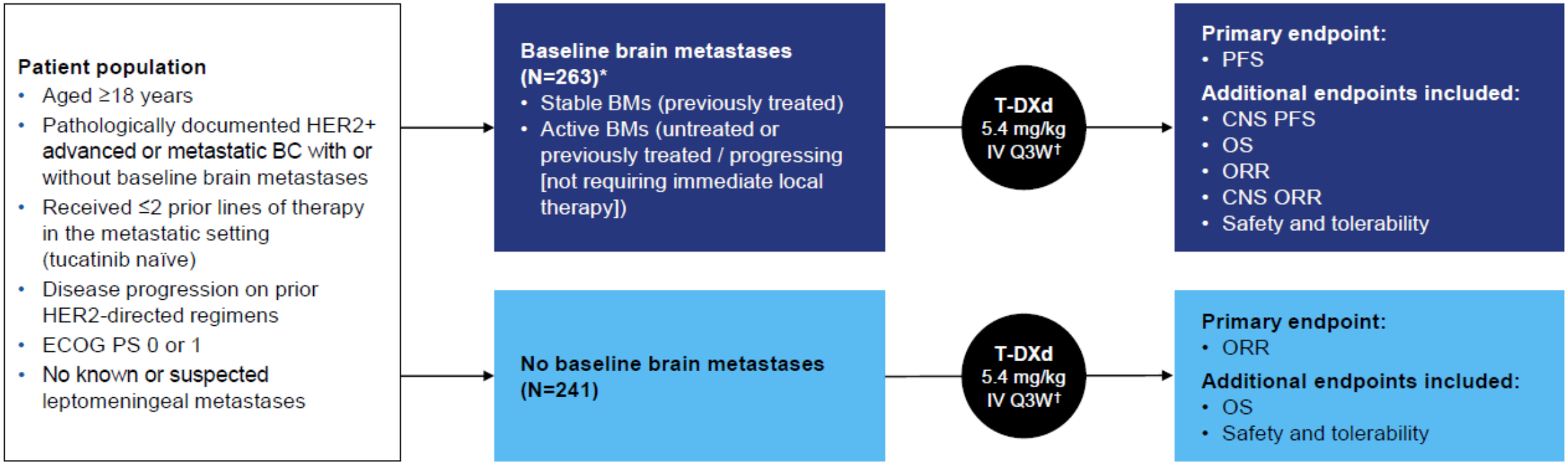
September 13, 2024

Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial



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



Data reported for the full analysis set (all patients enrolled in the study who received at least one treatment dose) and safety analysis set (identical to full analysis set). No hypothesis testing or comparison of cohorts. Response and progression assessed by ICR per RECIST 1.1 in both cohorts. Patients were enrolled from Australia, Canada, Europe, Japan, and United States

*Concomitant use of ≤3 mg of dexamethasone daily or equivalent allowed for symptom control of BMs (baseline BMs cohort only); †until RECIST 1.1-defined disease progression outside the CNS

BC, breast cancer; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; ICR, independent central review; IV, intravenous; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

NCT04739761. Updated. July 19, 2024. Available from: https://www.clinicaltrials.gov/study/NCT04739761 (Accessed September 9, 2024)

Demographics and baseline characteristics

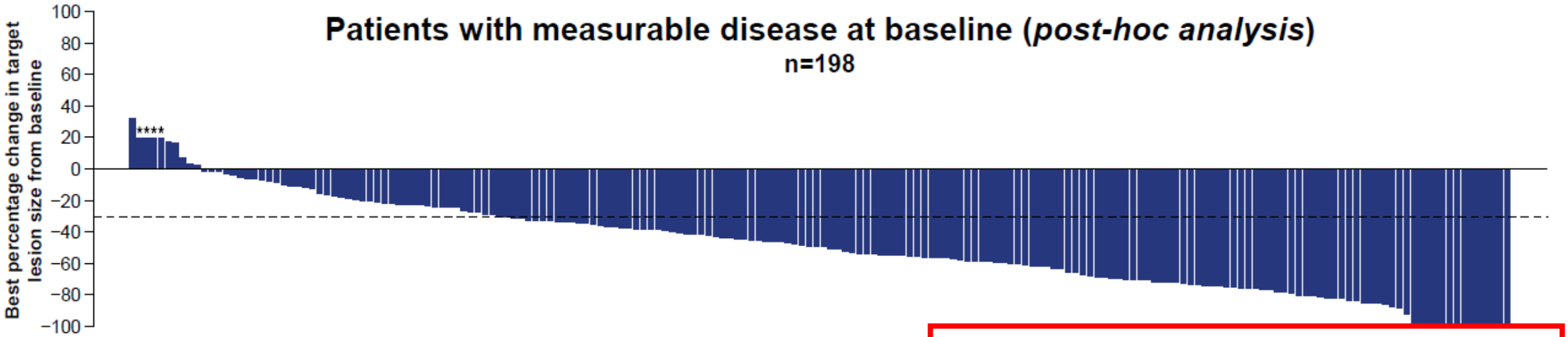
	Baseline BMs (N=263)	No baseline BMs (N=241)
Age, median (range), years	52 (28–86)	54 (24–87)
Female, n (%)	263 (100.0)	241 (100.0)
ECOG PS at baseline, n (%)		
0	163 (62.0)	194 (80.5)
1	100 (38.0)	47 (19.5)
HER2 status, n (%)		
2+	2 (0.8)	5 (2.1)
3+	187 (71.1)	141 (58.5)
Positive*	74 (28.1)	95 (39.4)
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: ORR

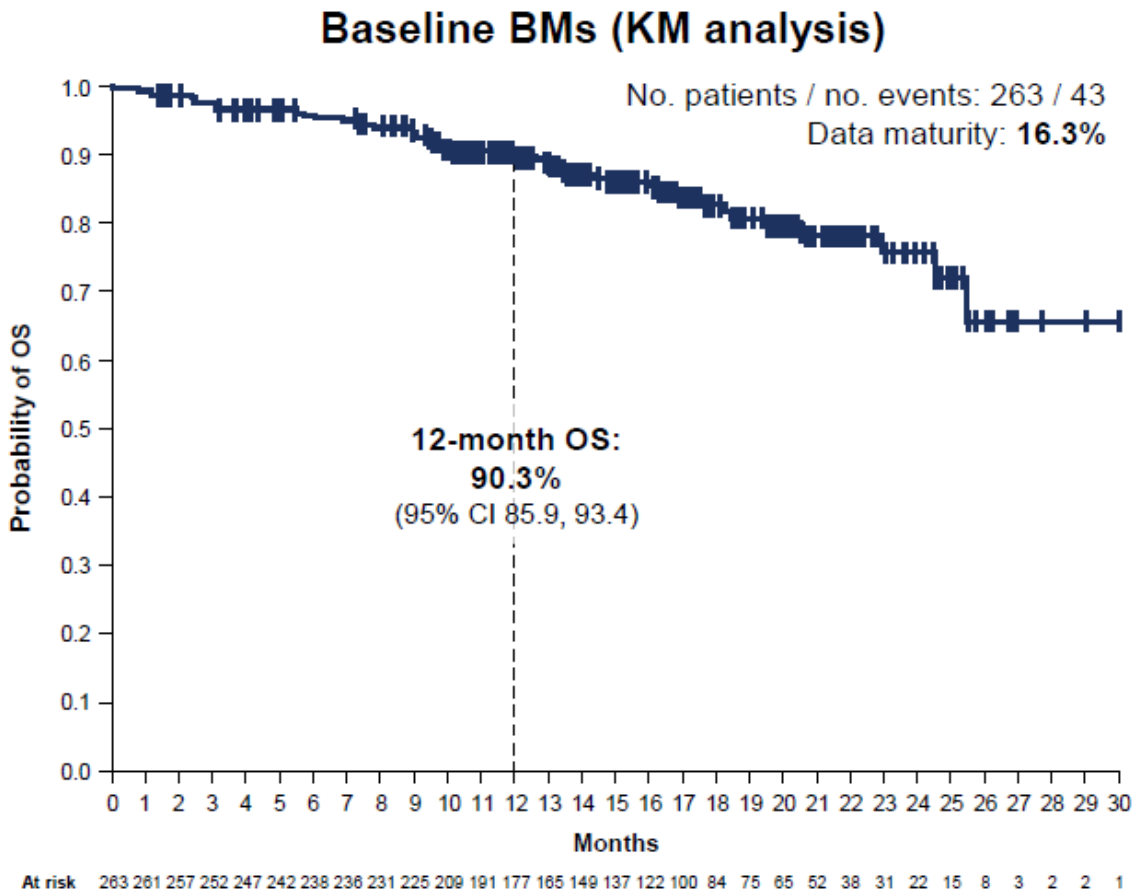


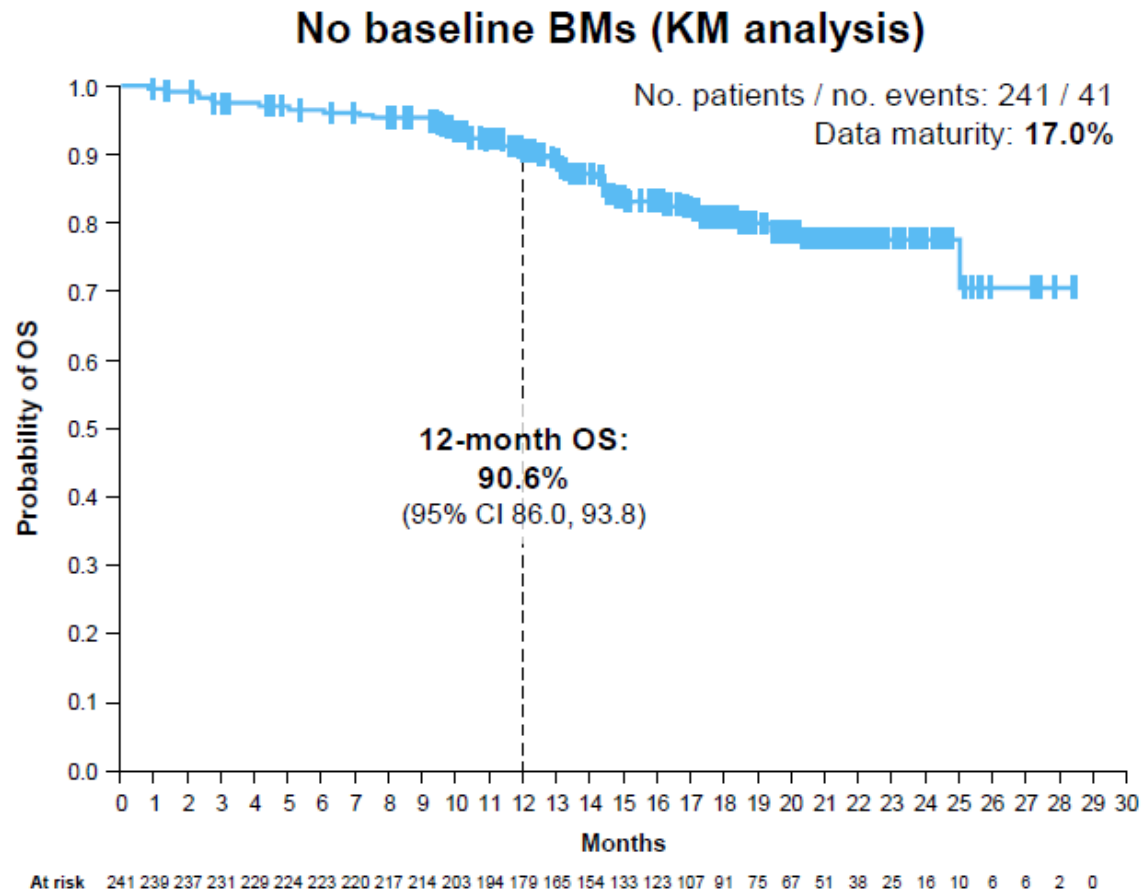
	Full analysis set†			Measurable disease at baseline (*post-hoc analysis*)		
	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)	All patients (n=198)	Stable BMs (n=109)	Active BMs (n=89)
Confirmed ORR, % (95% CI)	**51.7 (45.7, 57.8)**	49.7 (41.9, 57.5)	54.7 (45.2, 64.2)	**64.1 (57.5, 70.8)**	67.0 (58.1, 75.8)	60.7 (50.5, 70.8)
CR, n (%)	11 (4.2)	–	–	2 (1.0)	–	–
PR, n (%)	125 (47.5)	–	–	125 (63.1)	–	–

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

Median duration of response in the overall population was not calculated. Dashed line indicates a 30% decrease in target tumor size (PR). Response obtained by assessing target lesions, non-target lesions, and new lesions (extracranial and CNS)
*Imputed values: a value of +20% was imputed if best percentage change could not be calculated because of missing data if: a patient had a new lesion or progression of non-target lesions or target lesions, or had withdrawn because of PD and had no evaluable target lesion data before or at PD; †includes 65 patients with no measurable disease at baseline
BM, brain metastasis; CI, confidence interval; CNS, central nervous system; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; T-DXd, trastuzumab deruxtecan

OS in patients with and without baseline BMs





T-DXd showed consistent 12-month OS in patients with and without BMs

Median follow-up duration was 15.4 months in patients with BMs and 16.1 months in patients without BMs
BM, brain metastasis; CI, confidence interval; KM, Kaplan-Meier; no., number of; OS, overall survival; T-DXd, trastuzumab deruxtecan

LUMINAL METASTATIQUE

Les nouveautés

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Efficacy, safety and biomarker analysis of ICARUS-BREAST01: a phase 2 Study of Patritumab Deruxtecan (HER3-DXd) in patients with HR+/HER2- advanced breast cancer

B. Pistilli[1,15], L. Pierotti[2], M. Lacroix-Triki[3], C. Vicier[4], J.S. Frenel[5], V. D'Hondt[6], F. Dalenc[7], T. Bachelot[8], A. Ducoulombier[9], M.A Benderra[10], D. Loirat[11], D. Mayeur[12], G. Nachabeh[13], A. Sporchia[14], F.Suto[14], S.Michiels[2], N. Corcos[15], F. Mosele[1,16], F. André[1,16,17], G. Montagnac[15]

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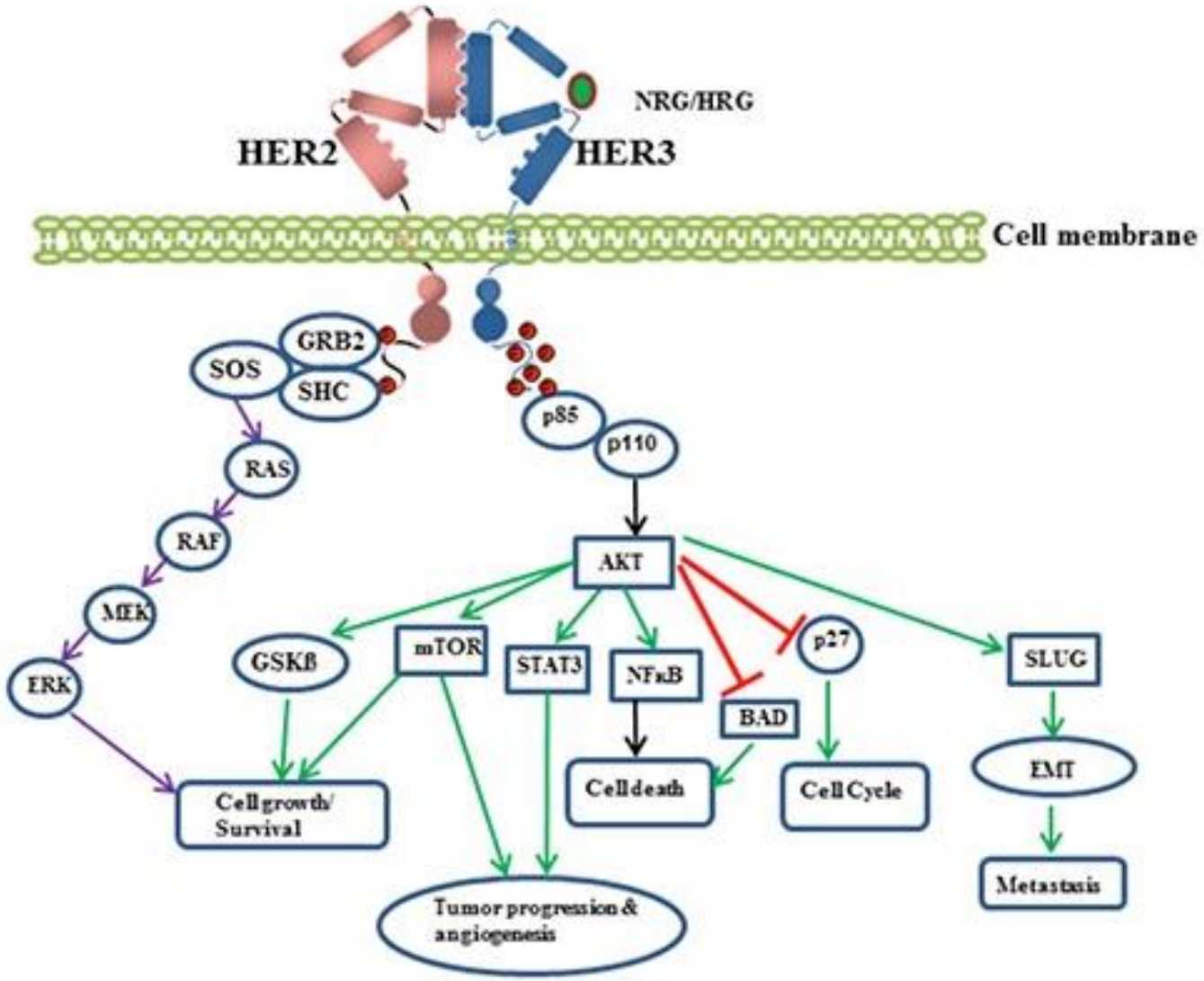
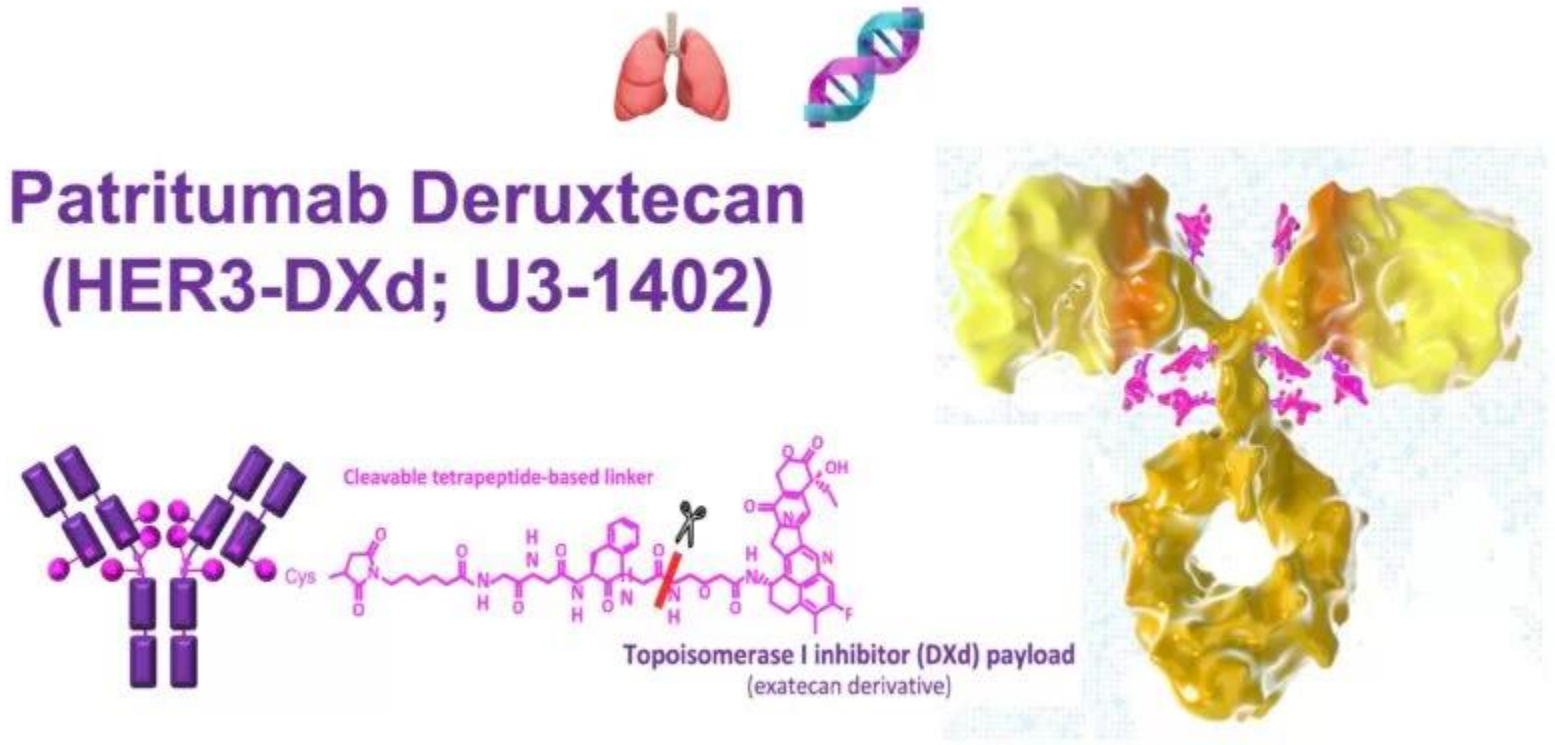
GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

ICARUS



Mishra R, Patel H, Alanazi S, Yuan L, Garrett JT. HER3 signaling and targeted therapy in cancer. Oncol Rev. 2018 May

Patritumab Deruxtecan (HER3-DXd)



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:

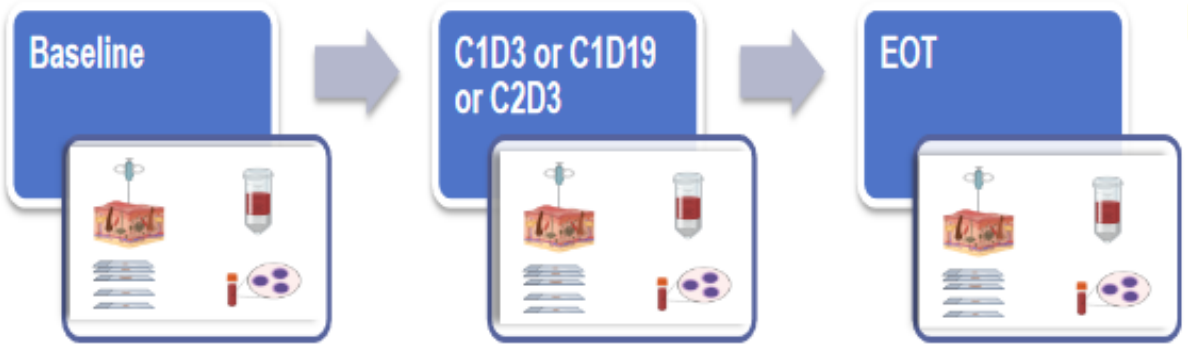
- Investigator-assessed confirmed ORR

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]**

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a. Either IHC2+ and in situ hybridization [ISH] negative, or IHC1+ or IHC0+; b. The study was initially designed to include only patients with HER3-membrane expression ≥ 75% with 10x in tumor biopsies at baseline, however this inclusion criterion was deleted by amendment on 21st of April, 2022, after including the first 29 patients, and afterwards recruitment proceeded regardless of HER3 expression. This decision was taken because of the lack of a clear correlation between HER3 expression and response in other datasets. ABC: advanced breast cancer; CBR: clinical benefit rate; CTC: circulating tumor cells; DOR: duration of response; ET: endocrine therapy, T-DXd: Trastuzumab deruxtecan; ORR: objective response rate; OS: overall survival; PFS: progression-free survival;

Demographics and baseline characteristics

ICARUS BREAST

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)

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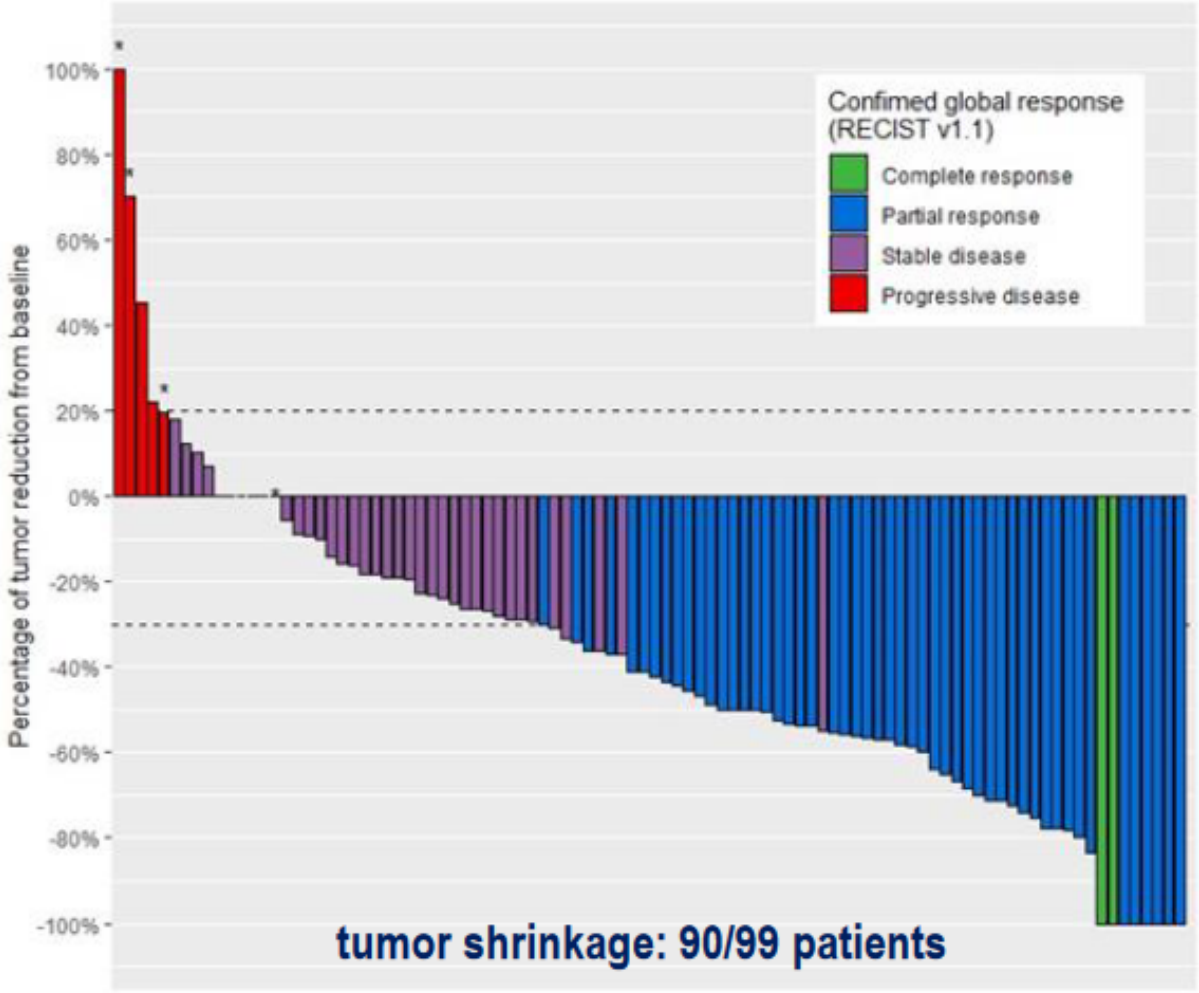
a. As assessed on initial tumor biopsy at diagnosis; b. Centrally assessed on tumor biopsy at study entry; c. Insufficient tumor sample available; d. 96 patients had CDK4/6inh for ABC, 2 patients for early breast cancer; 1 patient was enrolled by mistake as did not receive any prior treatment with CDK4/6inh; e. assessed in 73 patients; f. only 1 line of chemotherapyr allowed; *20 with HER2 membrane staining 1-10 %

Confirmed Objective Response Rate



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]

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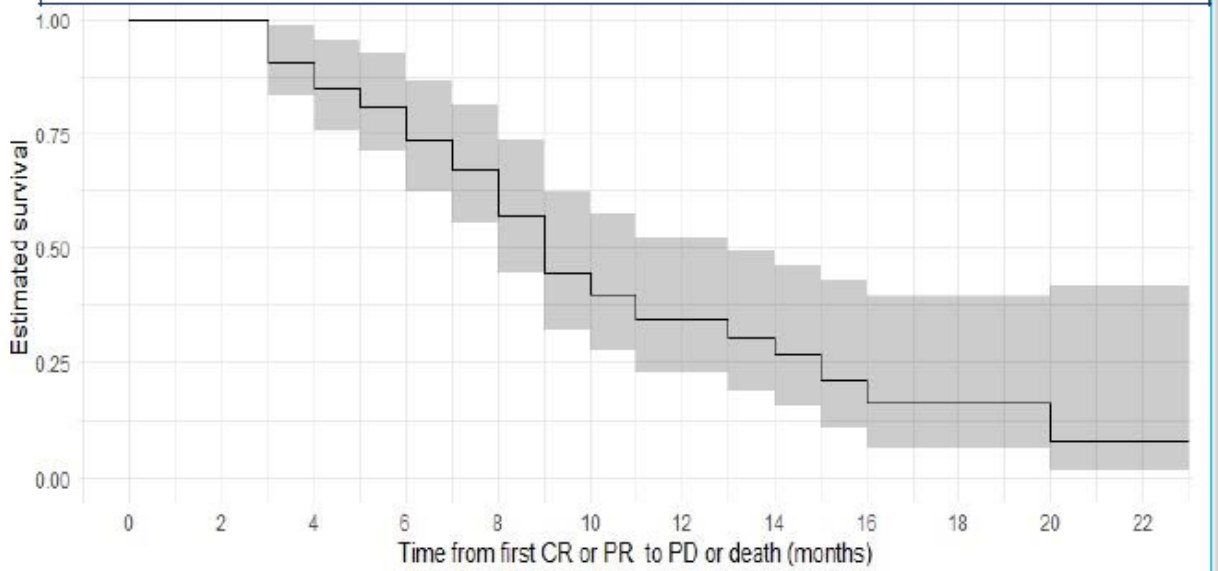
a. Clopper-Pearson (Exact) method was used for confidence interval; b. Confirmation of response must be demonstrated with a new tumor assessment 4 weeks or later from the initial response; c. 2 patients were not evaluable for ORR: one patient had only one tumor assessment with PR and then treatment discontinued due to clinical progression, a second patient had not evaluable as global response of target lesions. d. CBR is defined as the presence of at least a confirmed PR or CR, or a stable disease (SD) >6 months; e. logistic regression model was performed to estimate association between HER2 expression and ORR

Duration of Response and Progression-free Survival

DOR

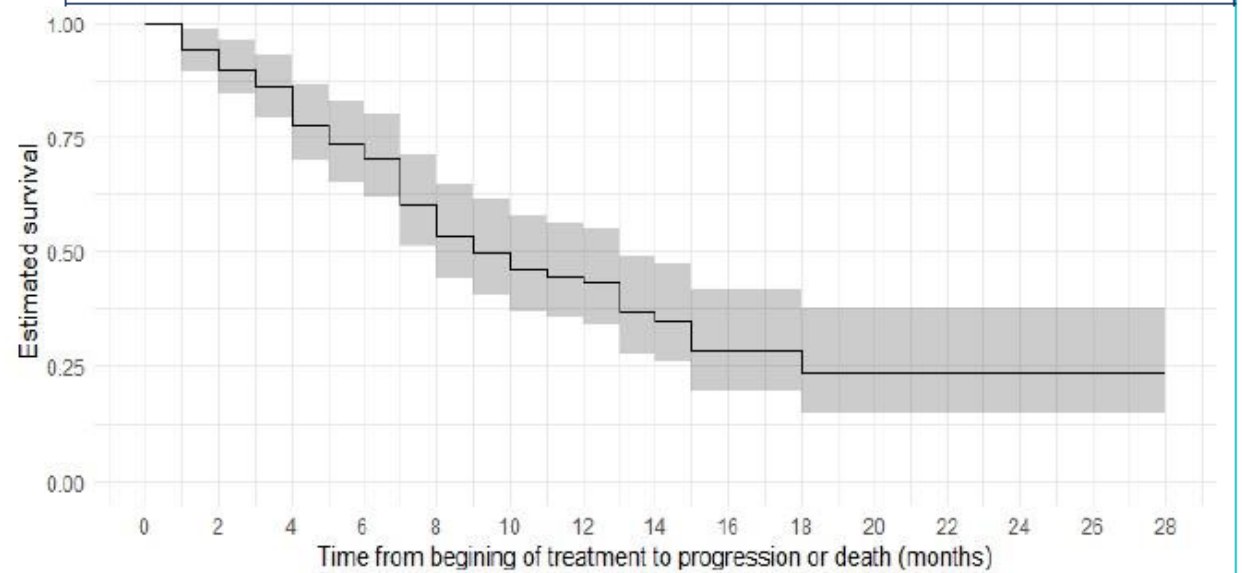
Median, months [95% CI] **8.7** [8.1; 12.5]



Overall												
At risk	53	53	44	36	23	15	9	5	3	2	1	1
Censored	0	0	1	3	9	10	14	16	16	17	17	17
Events	0	0	8	14	21	28	30	32	34	34	35	35

PFS

Median, months [95% CI] **9.4** [8.1; 13.4]



Overall															
At risk	99	88	74	64	44	35	26	17	12	9	5	3	2	2	0
Censored	0	1	3	6	11	14	21	25	27	28	32	34	35	35	37
Events	0	10	22	29	44	50	52	57	60	62	62	62	62	62	62

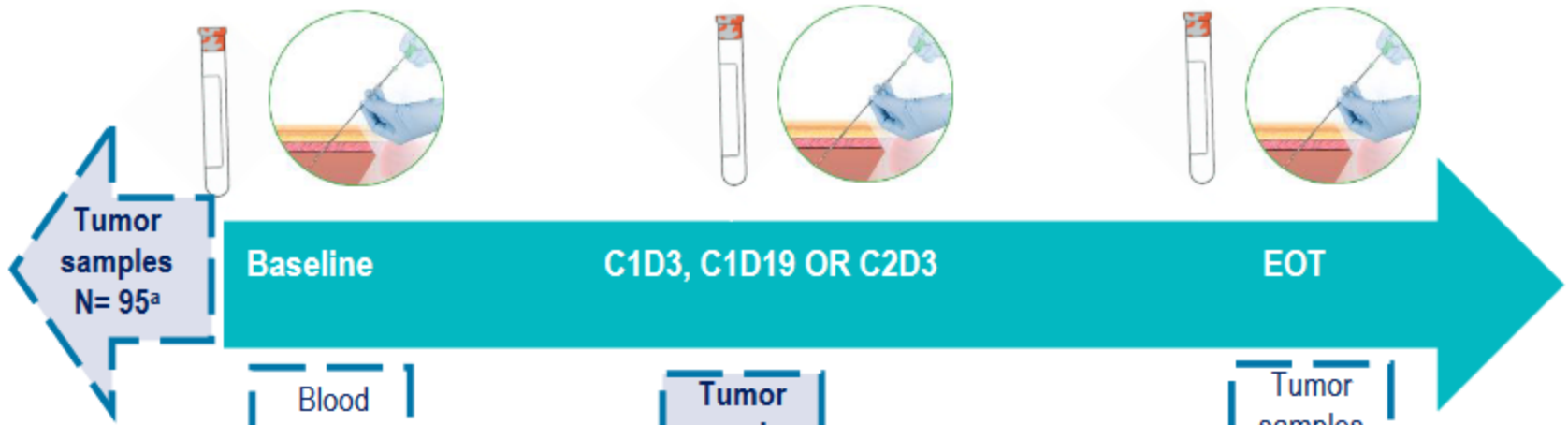
Median follow-up: 15.3 months [95%CI 13.0;17.2]

No significant association between HER2 expression and PFS (*p-value 0.6*)[a]

a. Cox regression model was performed to estimate association between HER2 expression and PFS

Exploratory biomarker analysis

- ***HER3 expression by IHC, n=72[b]***
- ***HER3 spatial distribution, ML, n=69[c]***
- ***Genomic alterations associated with response/resistance WES, n= 43[d]***
- ***Gene expression modulation, bulk RNA-seq, n=22[e]***
- ***Characterization of tumor/TME IMC, n=61[f]***



CTC (n=36), ctDNA (n=99) (Baseline, C1D3 or C2D3 or C2D19, C2D1, EOT)

HER3-DXd distribution, IMC, n= 57[g]

Gene expression modulation, bulk RNA-seq, n=22[h]

Genomic alterations associated with resistance, WES

HER3 expression, IHC

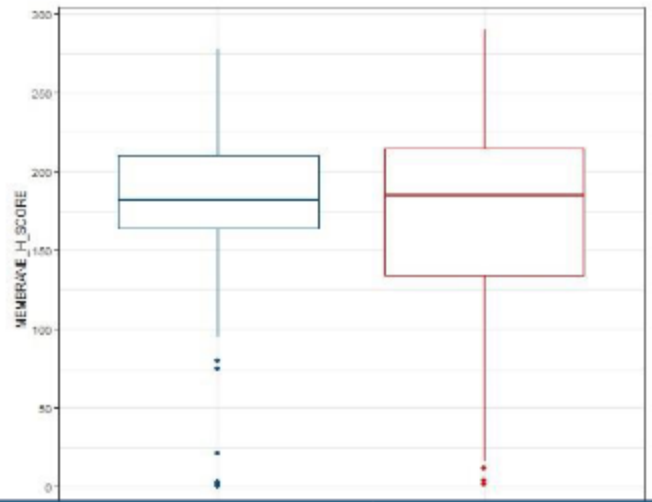
HER3-DXd distribution, remodeling TME, IMC

a.4 biopsies not performed/collected; b. 23 samples < 10%; c.25 excluded after pathologist's review; d. 15 fresh biopsies not collected/provided by centers, 28 < 200 ng DNA or < 10% tumor cell; 13 failed quality control; e. 15 fresh biopsies not provided by centers, 28 < 200 ng RNA or < 30% tumor cell, 5 failed quality control, 29 did not have the matched on-T sample; f. 15 fresh biopsies were not provided centers, 28 < 200 ng RNA or < 30% tumor cell, 5 failed the quality control, 29 did not have matched on-T sample; g. 12 samples inadequate staining; h. 22 fresh biopsies not provided by centers, 39 < 200 ng RNA or < 30% tumor cell, 1 sample failed the quality control, 15 did not have matched BL sample; *IHC: Immunohistochemistry, RNAseq: RNA Sequencing, IMC: Imaging Mass Cytometry, WES: Whole Exome Sequencing; ML: machine learning; HER3 IHC: clone SP438*

HER3 expression and outcome

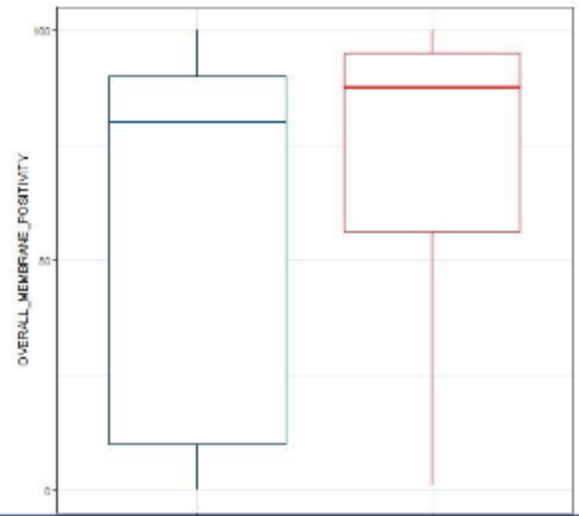
IHC analysis on tumor samples at baseline

HER3 membrane H-score



Non-responders (SD, PD) Median, [IQR]; n=34	Responders (CR,PR) Median, [IQR]. n=38
180.0 [165.0;210.0]	185.0 [134.0; 215.0]

HER3 membrane positivity 10x



Non-responders (SD, PD) Median, [IQR]; n=34	Responders (CR,PR) Median, [IQR]; n=38
80.0 [16.2;90.0]	87.5 [56.2;95.0]

No significant difference in HER3-membrane expression between responders and non-responders

(*p-value 0.8 and 0.4*, respectively with HER3 H-score and 10x membrane positivity) *

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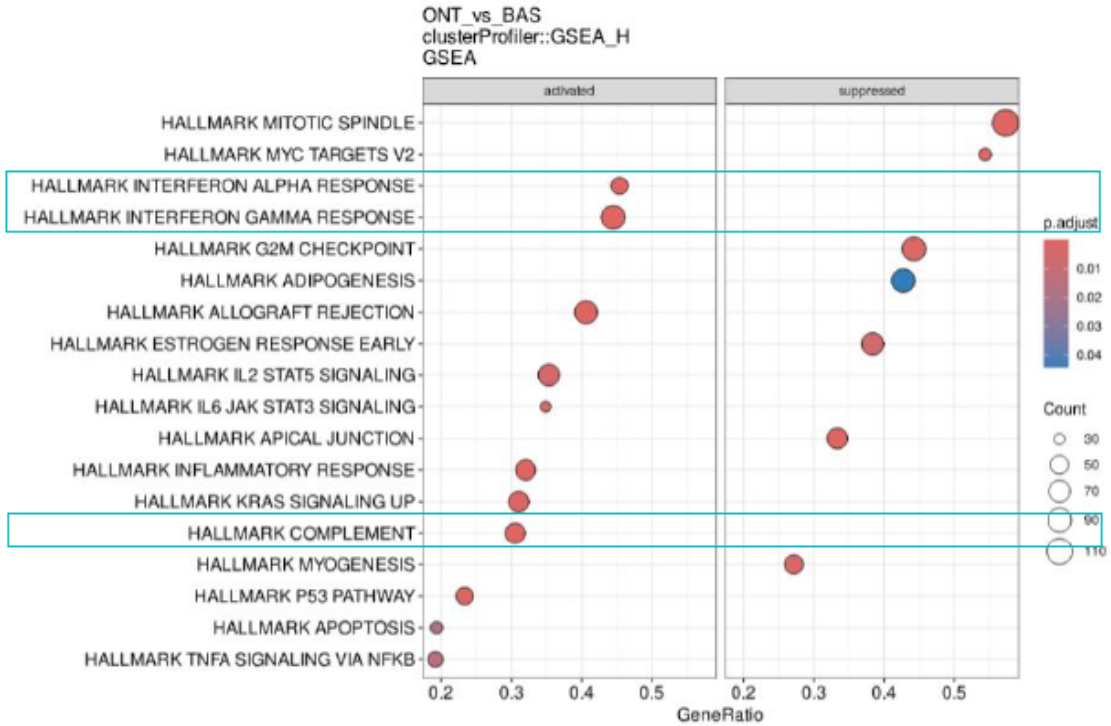
72 patients at baseline, of whom 29 enrollment before study amendment ; *Logistic regression models were used to estimate the association of ORR and HER3 expression as continuous or categorical variable; HER3 assessment made by Roche CDx CAP/CLIA Laboratory (Tucson) using clone SP438

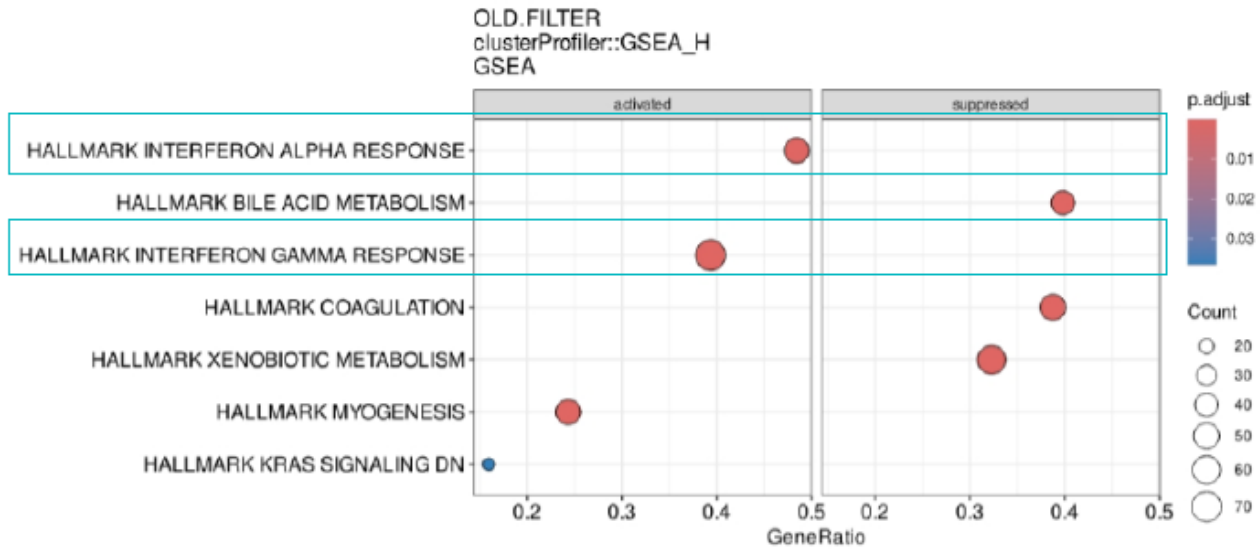
Gene expression modulation by HER3-DXd

- **22 pairs of baseline/on-treatment biopsies from <u>all analyzable samples</u>**
- Gene Set Enrichment Analysis (GSEA) using the Gene Sets "Hallmarks"*

Regardless of treatment response (n=22)



Responders (n=14)



Up-regulation of pathways involved in immune response, interferon alpha and gamma and complement signaling, enriched in the whole cohort and in responders (*adj p-value ≤0.05*)

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At baseline, 15 fresh biopsies not provided by centers, 28 were excluded due to < 200 ng RNA or < 30% tumor cell, 5 failed the quality control, 29 did not have the matched on-T sample. On-treatment (n=12 at C1D3, n=4 at C1D19, n=6 at C2D3), 22 fresh biopsies not provided by centers, 39 were excluded due to < 200 ng RNA or < 30% tumor cell, 1 sample failed the quality control, and 15 did not have the matched BL sample; "P_Value_Adj" by Benjamini-Hochberg method

LUMINAL LOCALISE

Les nouveautés

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Adjuvant Ribociclib Plus Nonsteroidal Aromatase Inhibitor in Patients With HR+/HER2− Early Breast Cancer: 4-Year Outcomes From the NATALEE Trial

Peter A. Fasching,[1] Daniil Stroyakovskiy,[2] Denise A. Yardley,[3] Chiun-Sheng Huang,[4] John Crown,[5] Aditya Bardia,[6] Stephen Chia,[7] Seock-Ah Im,[8] Miguel Martin,[9] Binghe Xu,[10] Sherene Loi,[11] Carlos Barrios,[12] Michael Untch,[13] Rebecca Moroose,[14] Frances Visco,[15] Gabriel N. Hortobagyi,[16] Dennis J. Slamon,[6] Yanina Oviedo,[17] Sorcha Waters,[18] Sara A. Hurvitz[19]

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September 16, 2024

Study Design and Methods

- Adult patients with HR+/HER2− EBC
- Prior ET allowed ≤12 mo prior to randomization
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26 ***or***
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

RIB
400 mg/day
3 weeks on/1 week off
for 3 years

+

NSAI
Letrozole or anastrozole[d]
for ≥5 years
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[d]
for ≥5 years
+ goserelin in men and premenopausal women

Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- Safety and tolerability
- PROs
- PK

Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Endpoints included in this presentation

Statistical comparisons were performed using a Cox proportional hazards model and the Kaplan-Meier method

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

Data cutoff: 29 April 2024

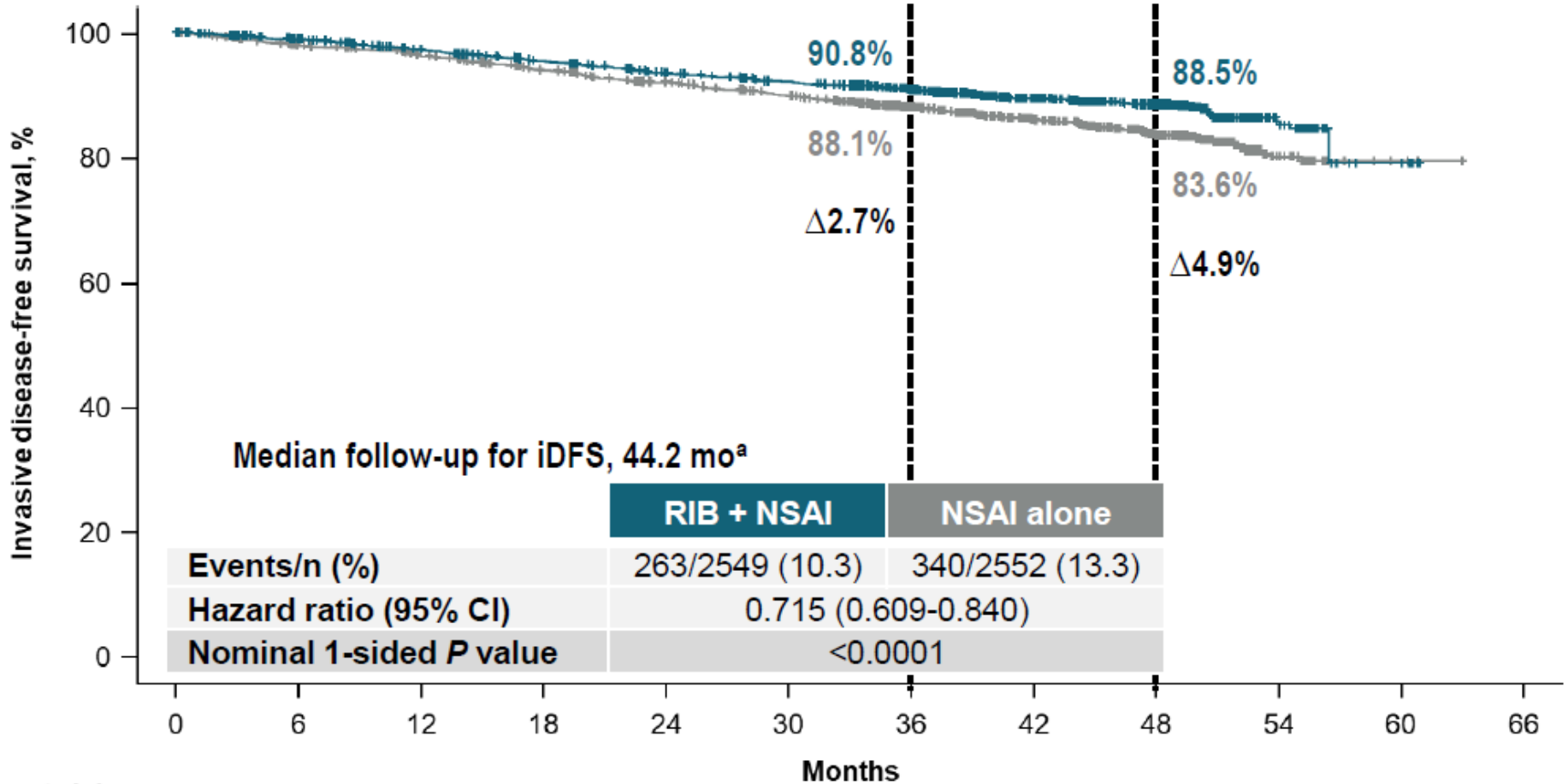
ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; RIB, ribociclib; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.

[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.

1. ClinicalTrials.gov. Accessed March 15, 2024. https://clinicaltrials.gov/ct2/show/NCT03701334. **2.** Slamon DJ, et al. Poster presented at: ASCO 2019. Poster TPS597. **3.** Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:1-16. **4.** Hortobagyi, G, et al. Oral presentation at: SABCS 2023. Oral GS03-03.

iDFS in ITT Population

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

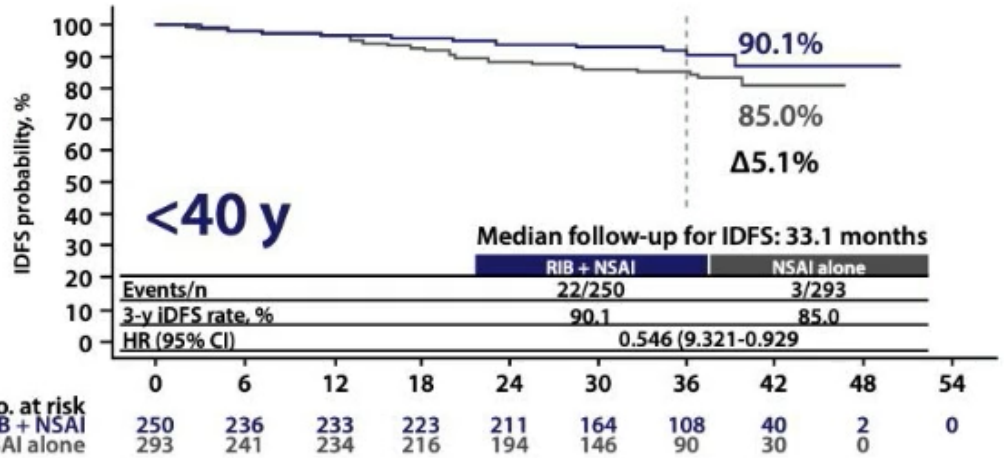


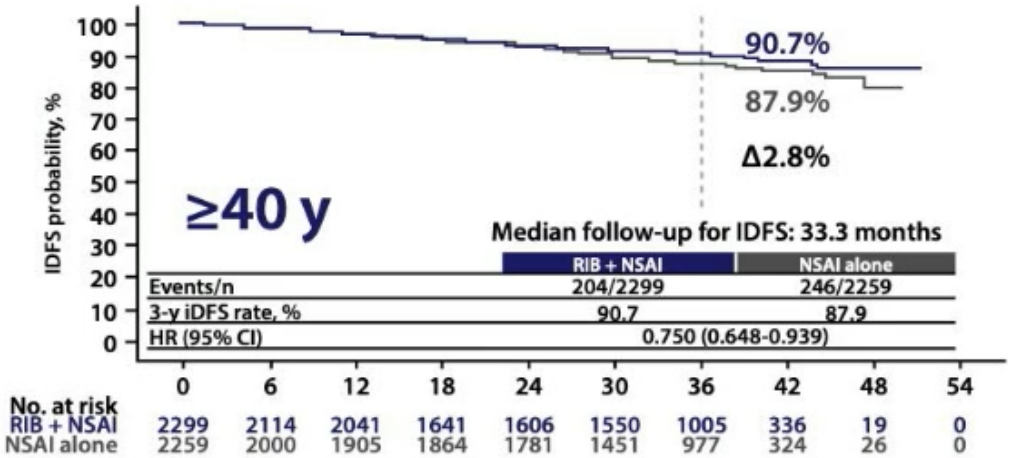
No. at risk												
RIB + NSAI	2549	2351	2275	2207	2133	2078	1843	1480	914	155	8	0
NSAI alone	2552	2240	2168	2082	2006	1935	1687	1366	848	150	6	0

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.

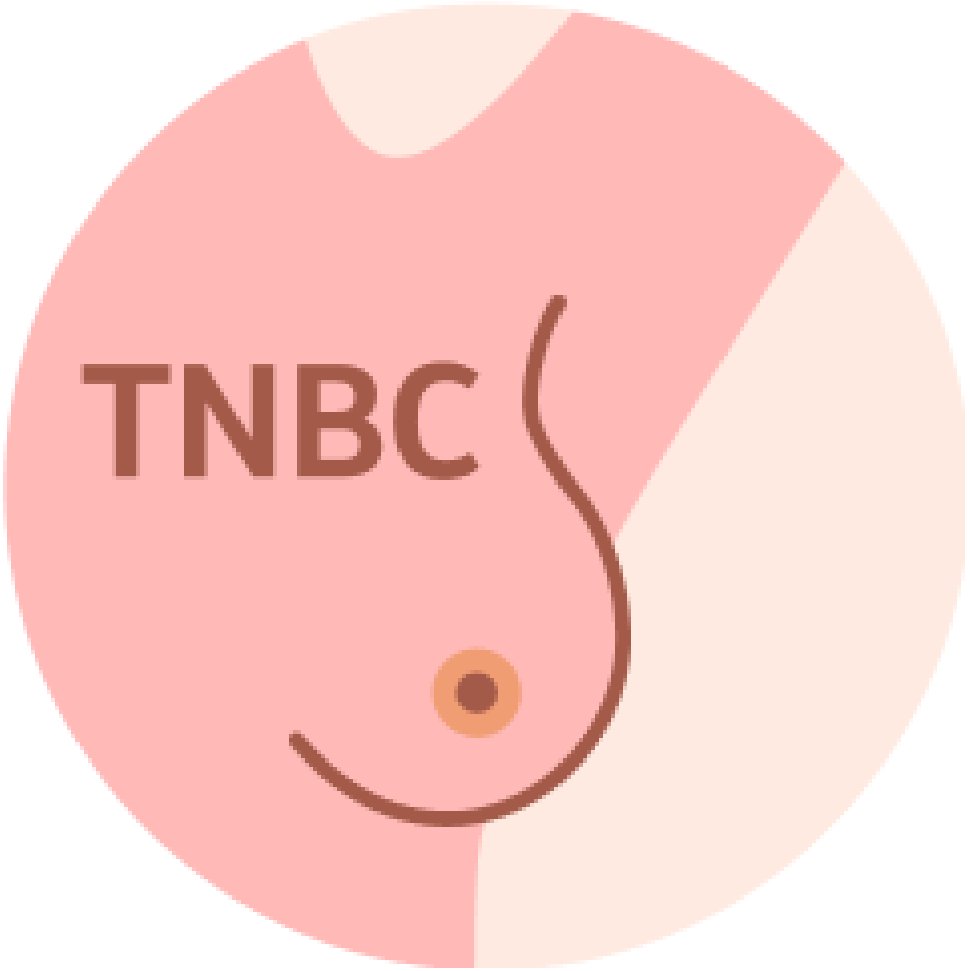
Bénéfice en termes de iDFS selon l'âge

RIB + NSAI showed iDFS benefit in pts aged <40 and ≥40 y





- iDFS benefit of RIB + NSAI was observed regardless of menopausal status[a]
  - <40 y: premenopausal (n=513)-HR, 0.592 (95% CI, 0.345-1.015); postmenopausal (n=30)-not estimable due to small size
  - ≥40 y: premenopausal (n=1744)-HR, 0730 (95% CI, 0.522-1.019); postmenopausal (n=2814)-HR, 0.812 (95% CI, 0.649-1.016)
- The absolute differences in 3-y iDFS rates between the RIB + NSAI and NSAI-only arms, when adjusted for menopausal status and prior neoadjuvant CT, were similar to those without adjustment (Δ4.0% for pts <40 y and Δ2.9% for pts ≥40 y)



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Les nouveautés

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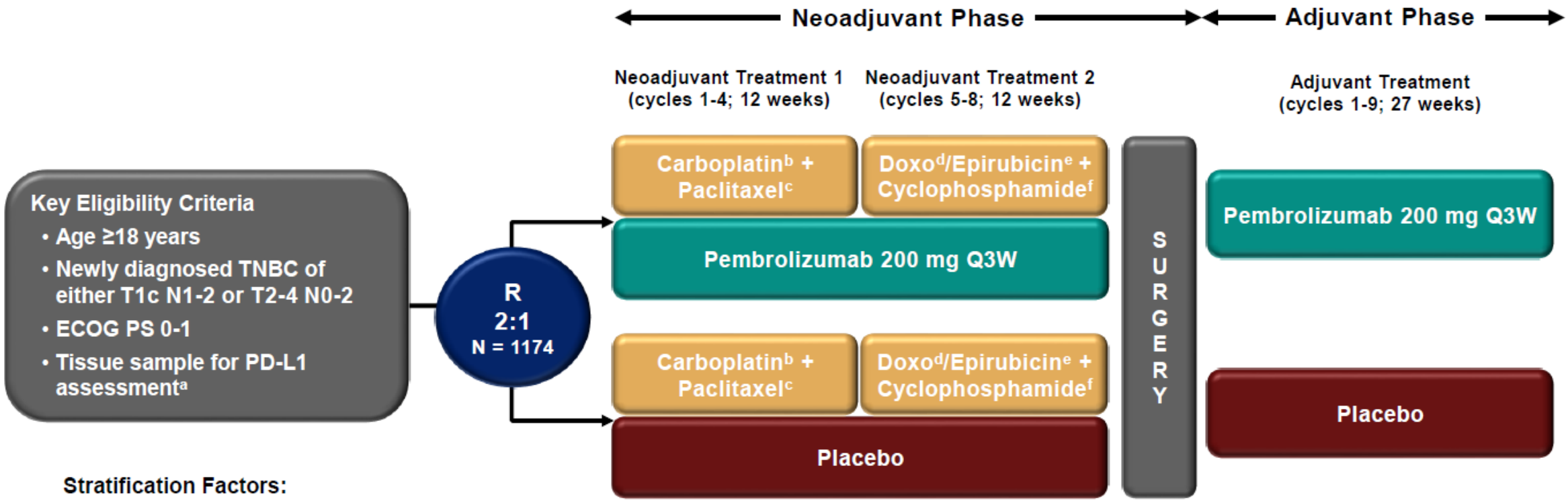
Neoadjuvant Pembrolizumab or Placebo + Chemotherapy Followed by Adjuvant Pembrolizumab or Placebo for High-Risk Early-Stage Triple-Negative Breast Cancer: Overall Survival Results from the Phase 3 KEYNOTE-522 Study

Peter Schmid,[1] Javier Cortes,[2] Rebecca Dent,[3] Heather McArthur,[4] Lajos Pusztai,[5] Sherko Kümmel,[6] Carsten Denkert,[7] Yeon Hee Park,[8] Rina Hui,[9] Nadia Harbeck,[10] Masato Takahashi,[11] Seock-Ah Im,[12] Michael Untch,[13] Peter A. Fasching,[14] Fatima Cardoso,[15] Jing Zhao,[16] Xuan Zhou,[16] Konstantinos Tryfonidis,[16] Gursel Aktan,[16] Joyce O'Shaughnessy[17]

[1]Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University London, London, UK; [2]International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Barcelona, Spain; Medical Scientia Innovation Research (MedSIR), Barcelona, Spain; Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Spain; [3]National Cancer Centre Singapore, Duke – National University of Singapore Medical School, Singapore; [4]University of Texas Southwestern Medical Center, Dallas, TX, USA; [5]Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA; [6]Breast Unit, Kliniken Essen-Mitte, Essen, Germany and Charité – Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Berlin, Germany; [7]Institute of Pathology, Philipps-University Marburg and University Hospital Marburg, Marburg, Germany; [8]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [9]Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia and Centre of Cancer Medicine, School of Clinical Medicine, University of Hong Kong, Hong Kong; [10]Breast Center, Dept. OB&GYN, LMU University Hospital, Munich, Germany; [11]Hokkaido University Hospital, Sapporo, Japan; [12]Seoul National University Hospital, Cancer Research Institute, Seoul National University, Seoul, Republic of Korea; [13]Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; [14]University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany; [15]Breast Unit, Champalimaud Clinical Center/ Champalimaud Foundation, Lisbon, Portugal; [16]Oncology, Merck & Co., Inc., Rahway, NJ, USA; [17]Baylor University Medical Center, Texas Oncology, Sarah Cannon Research Institute, Dallas, TX, USA

KEYNOTE-522 Study Design (NCT03036488)



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)

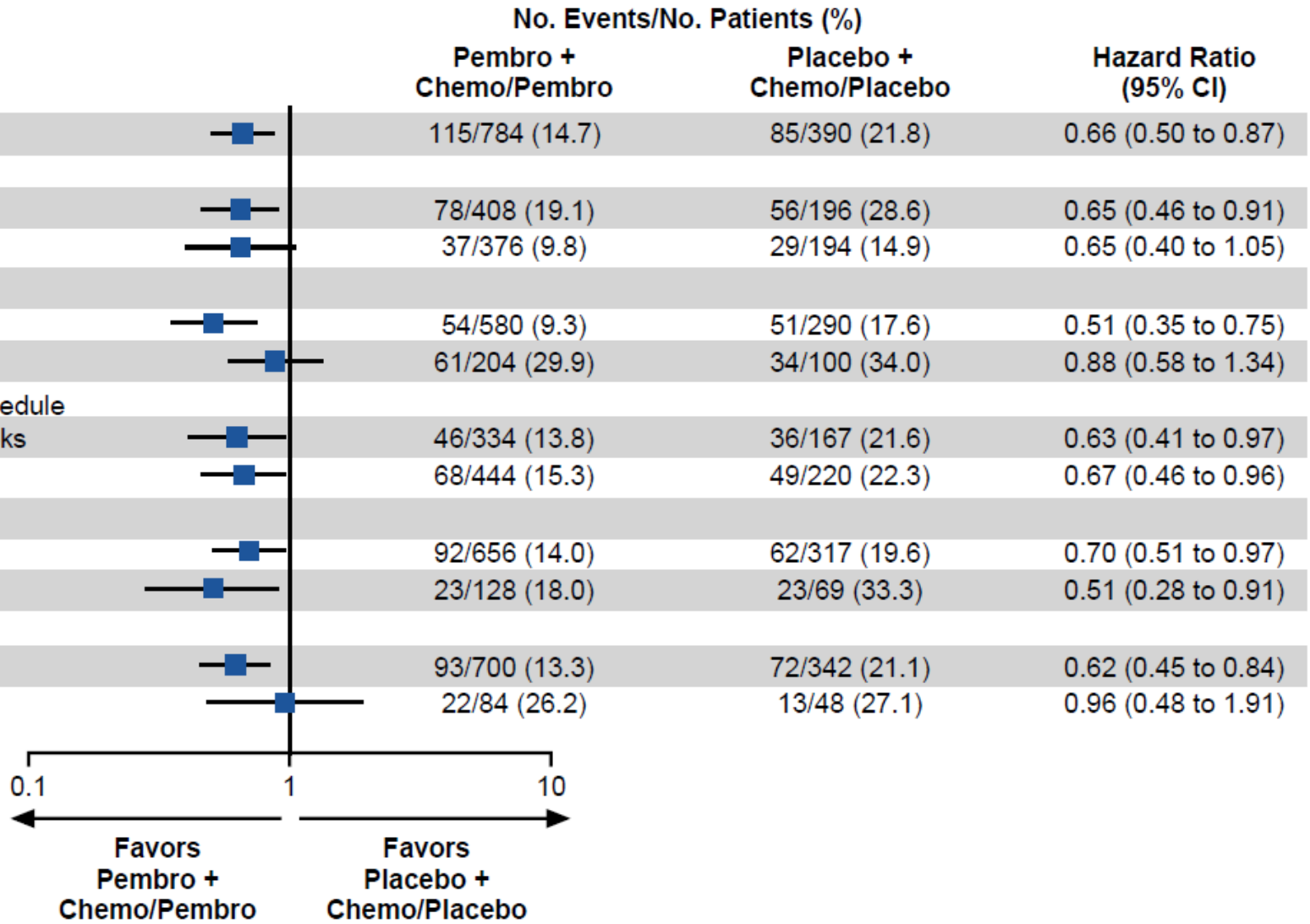
[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m^2 QW. [d]Doxorubicin dose was 60 mg/m^2 Q3W. [e]Epirubicin dose was 90 mg/m^2 Q3W. [f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

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)

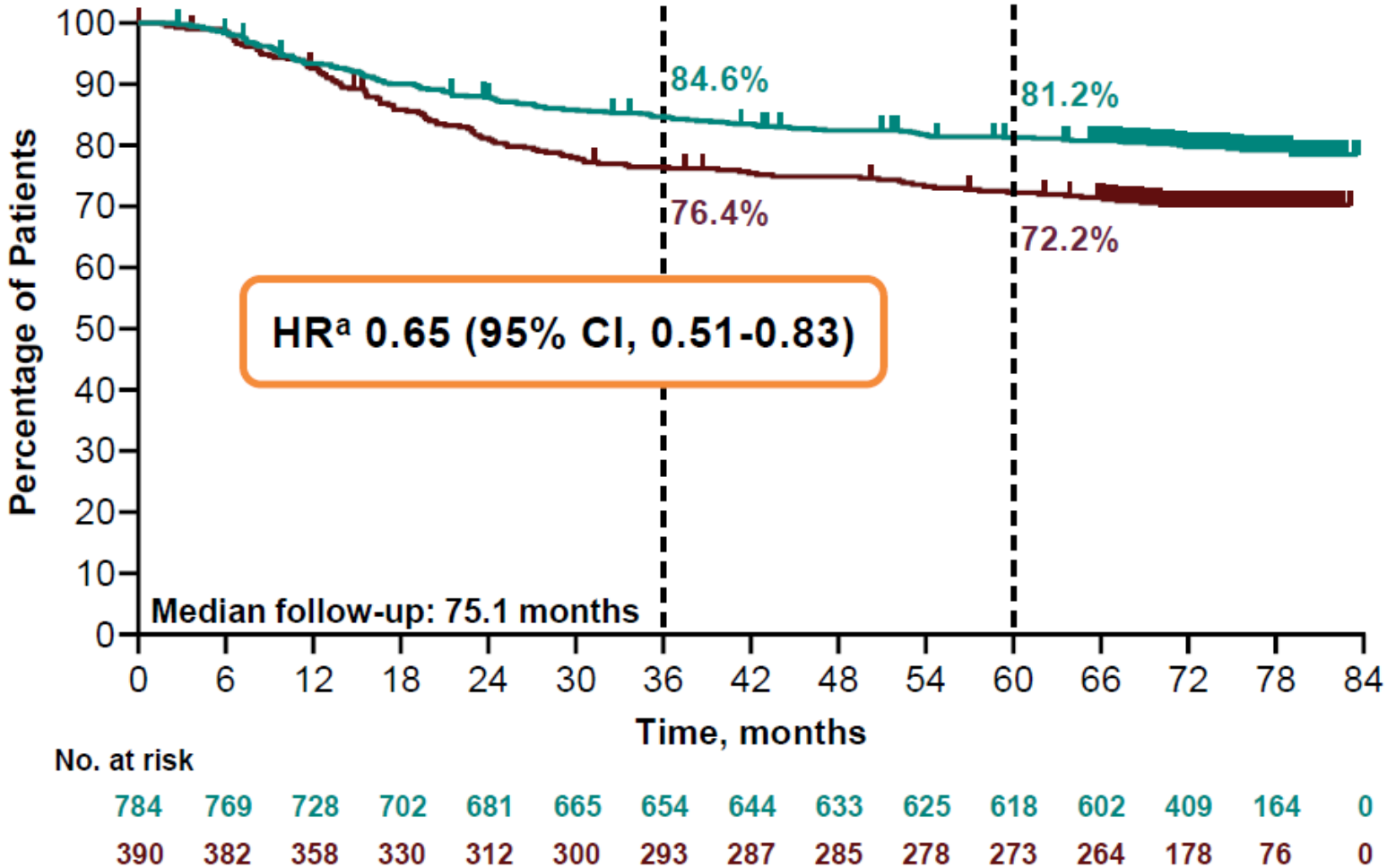
[a]PD-L1 assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by the total number of tumor cells x 100). Data cutoff date: March 22, 2024.

Overall Survival in Patient Subgroups



Subgroup	No. Events/No. Patients (%) Pembro + Chemo/Pembro	Placebo + Chemo/Placebo	Hazard Ratio (95% CI)
Overall	115/784 (14.7)	85/390 (21.8)	0.66 (0.50 to 0.87)
Nodal status			
Positive	78/408 (19.1)	56/196 (28.6)	0.65 (0.46 to 0.91)
Negative	37/376 (9.8)	29/194 (14.9)	0.65 (0.40 to 1.05)
Tumor size			
T1/T2	54/580 (9.3)	51/290 (17.6)	0.51 (0.35 to 0.75)
T3/T4	61/204 (29.9)	34/100 (34.0)	0.88 (0.58 to 1.34)
Carboplatin schedule			
Every 3 weeks	46/334 (13.8)	36/167 (21.6)	0.63 (0.41 to 0.97)
Weekly	68/444 (15.3)	49/220 (22.3)	0.67 (0.46 to 0.96)
PD-L1 status			
CPS ≥1	92/656 (14.0)	62/317 (19.6)	0.70 (0.51 to 0.97)
CPS <1	23/128 (18.0)	23/69 (33.3)	0.51 (0.28 to 0.91)
Age category			
<65 years	93/700 (13.3)	72/342 (21.1)	0.62 (0.45 to 0.84)
≥65 years[a]	22/84 (26.2)	13/48 (27.1)	0.96 (0.48 to 1.91)

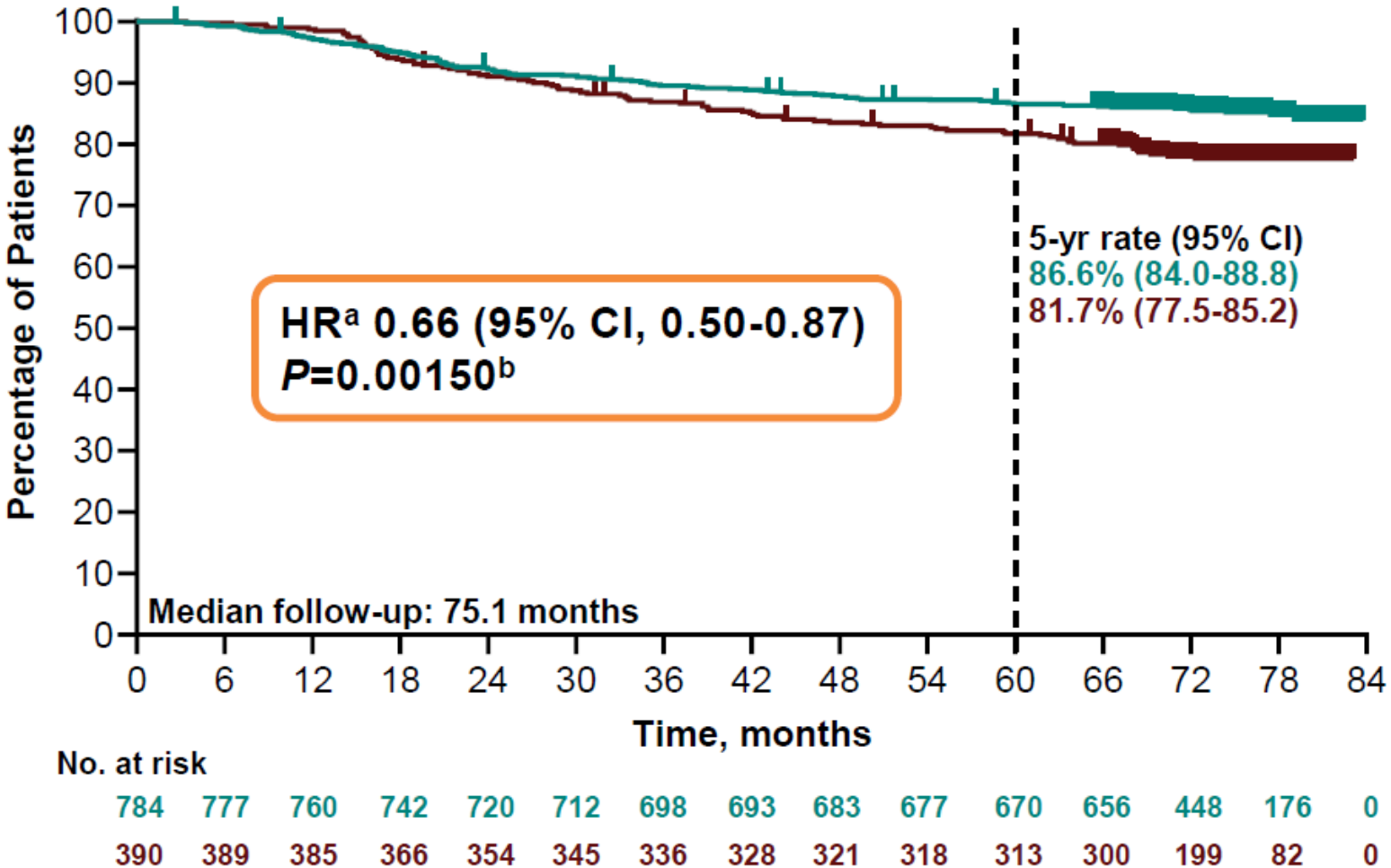
Updated Event-Free Survival



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

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 22, 2024.

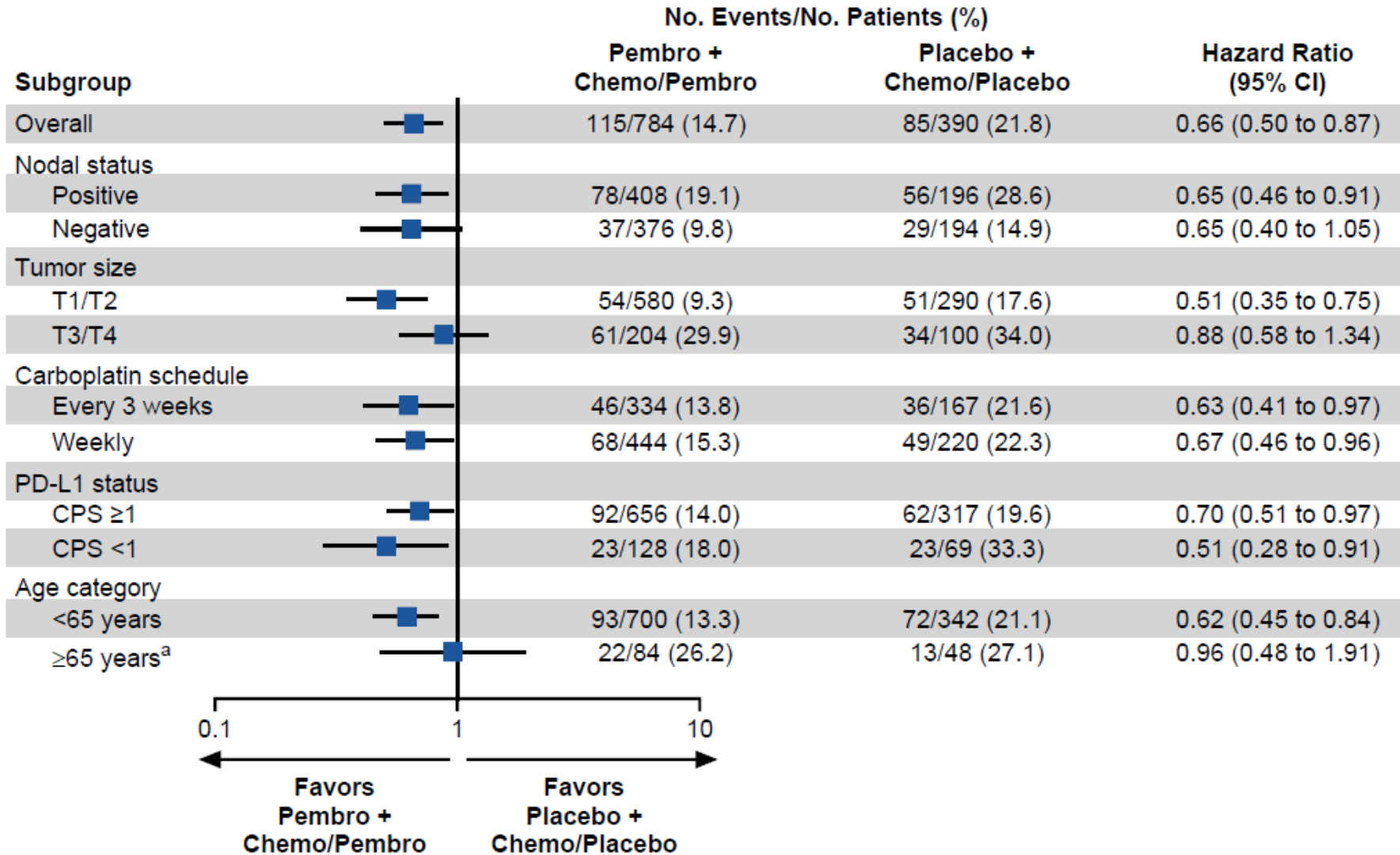
Key Secondary Endpoint: Overall Survival



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

[a]The unstratified piecewise HR was 0.87 (95% CI, 0.57-1.32) before the 2-year follow-up and 0.51 (95% CI, 0.35-0.75) afterwards. The weighted average HR with weights of number of events before and after 2-year follow-up was 0.66. With 200 events (67.3% information fraction), the observed *P*-value crossed the prespecified nominal boundary of 0.00503 (1-sided) at this interim analysis.
Data cutoff date: March 22, 2024.

Overall Survival in Patient Subgroups



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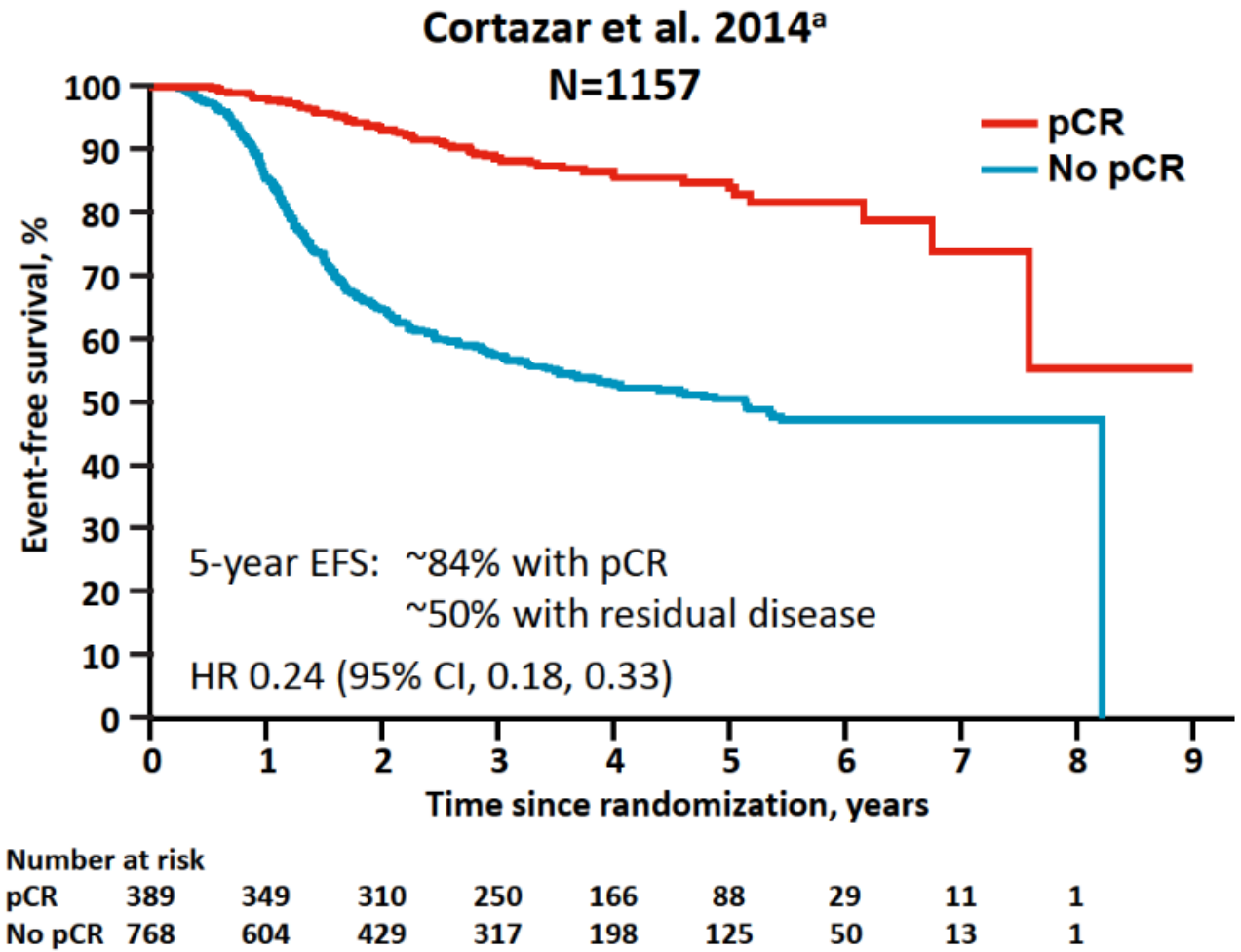
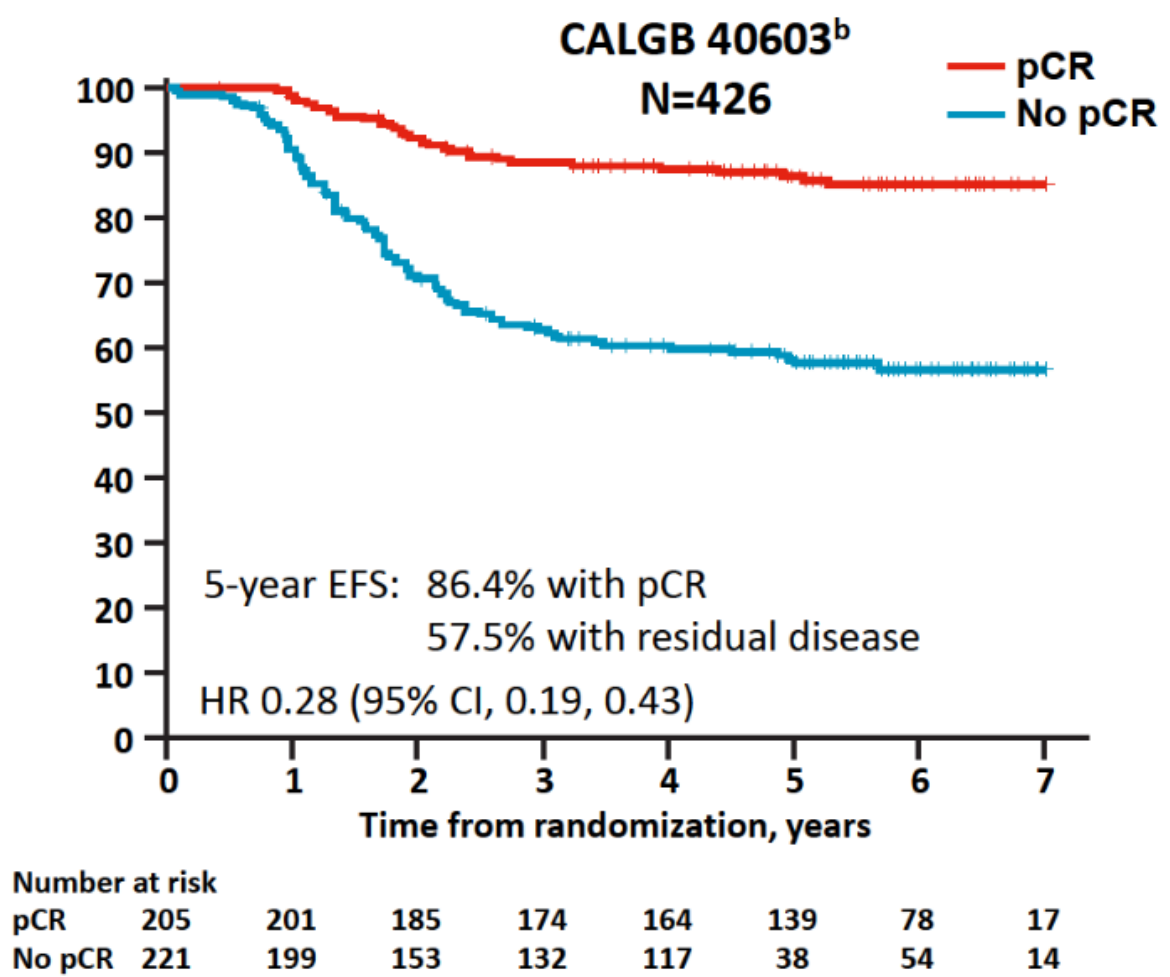
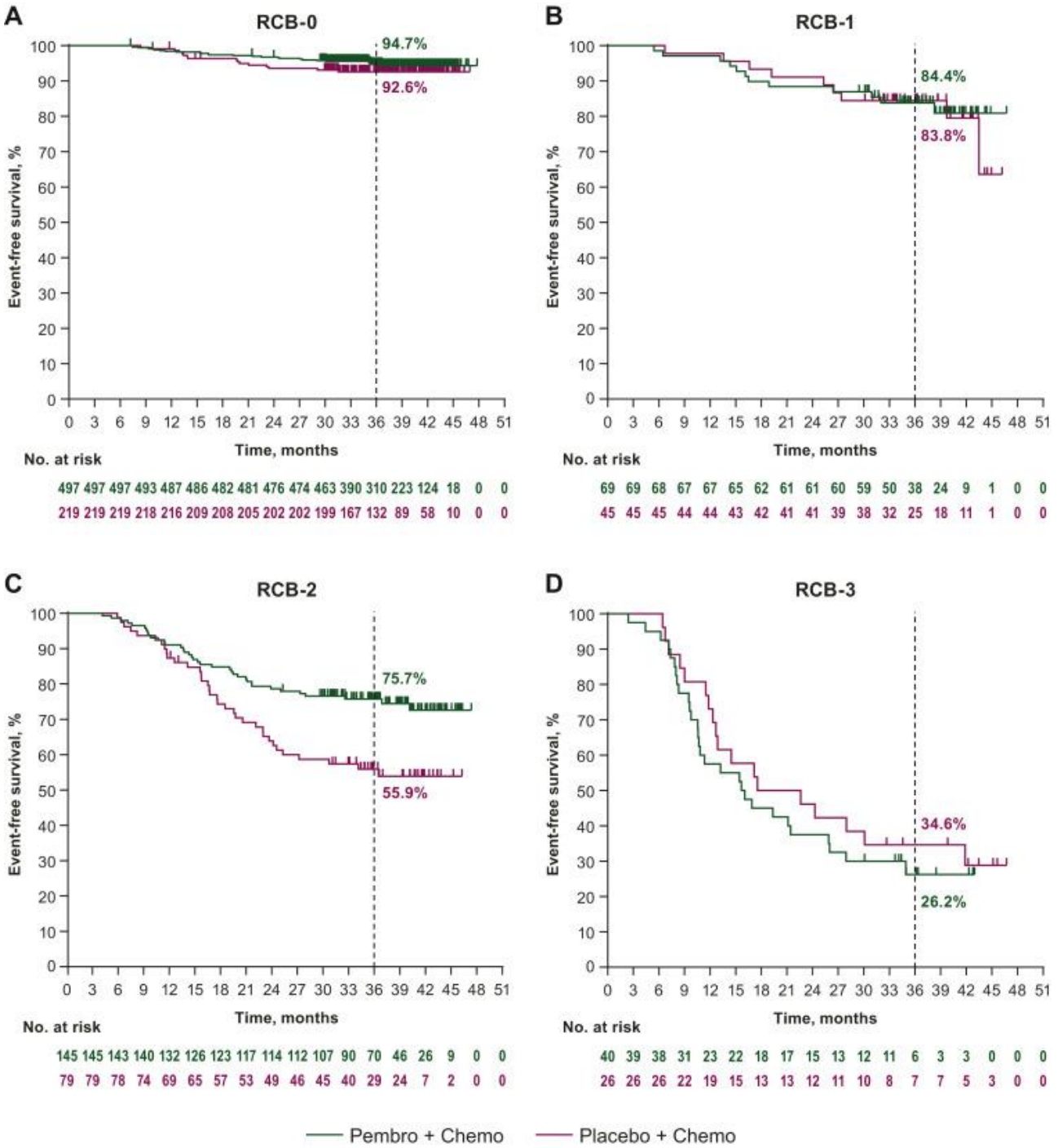
For overall population and PD-L1 subgroups, analyses based on Cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4), and frequency of carboplatin (once weekly vs once every 3 weeks); for other subgroups, analysis based on unstratified Cox model. [a]Based on the small sample size and few events, results should be interpreted with caution. Data cutoff date: March 22, 2024.


Cortazar et al. 2014[a]
N=1157
pCR
No pCR
Event-free survival, %
100
90
80
70
60
50
40
30
20
10
0
5-year EFS: ~84% with pCR
~50% with residual disease
HR 0.24 (95% CI, 0.18, 0.33)
0 1 2 3 4 5 6 7 8 9
Time since randomization, years
Number at risk
pCR 389 349 310 250 166 88 29 11 1
No pCR 768 604 429 317 198 125 50 13 1

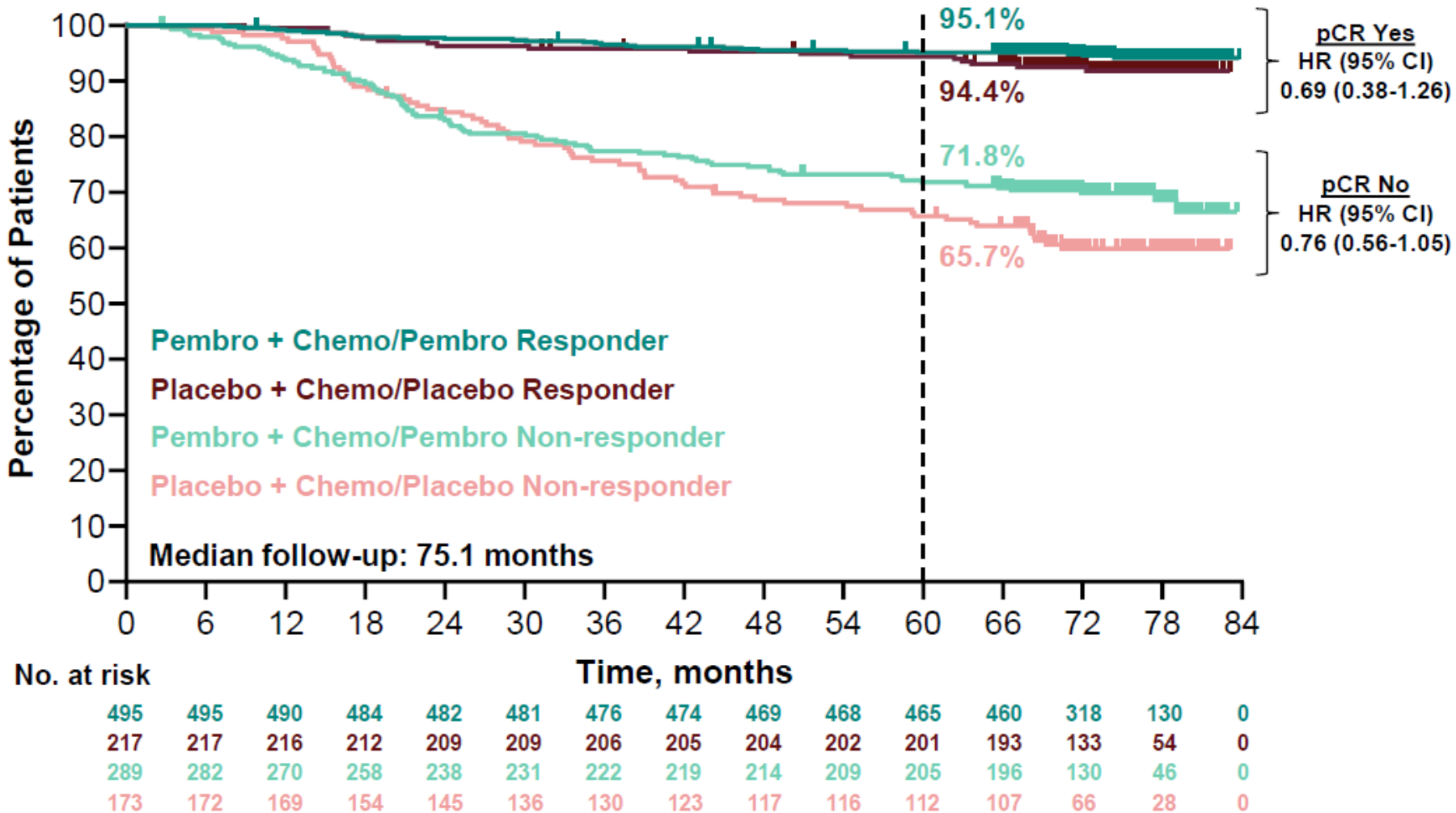

CALGB 40603[b]
N=426
pCR
No pCR
100
90
80
70
60
50
40
30
20
10
0
5-year EFS: 86.4% with pCR
57.5% with residual disease
HR 0.28 (95% CI, 0.19, 0.43)
0 1 2 3 4 5 6 7
Time from randomization, years
Number at risk
pCR 205 201 185 174 164 139 78 17
No pCR 221 199 153 132 117 38 54 14

KEYNOTE 522

Analyse exploratoire

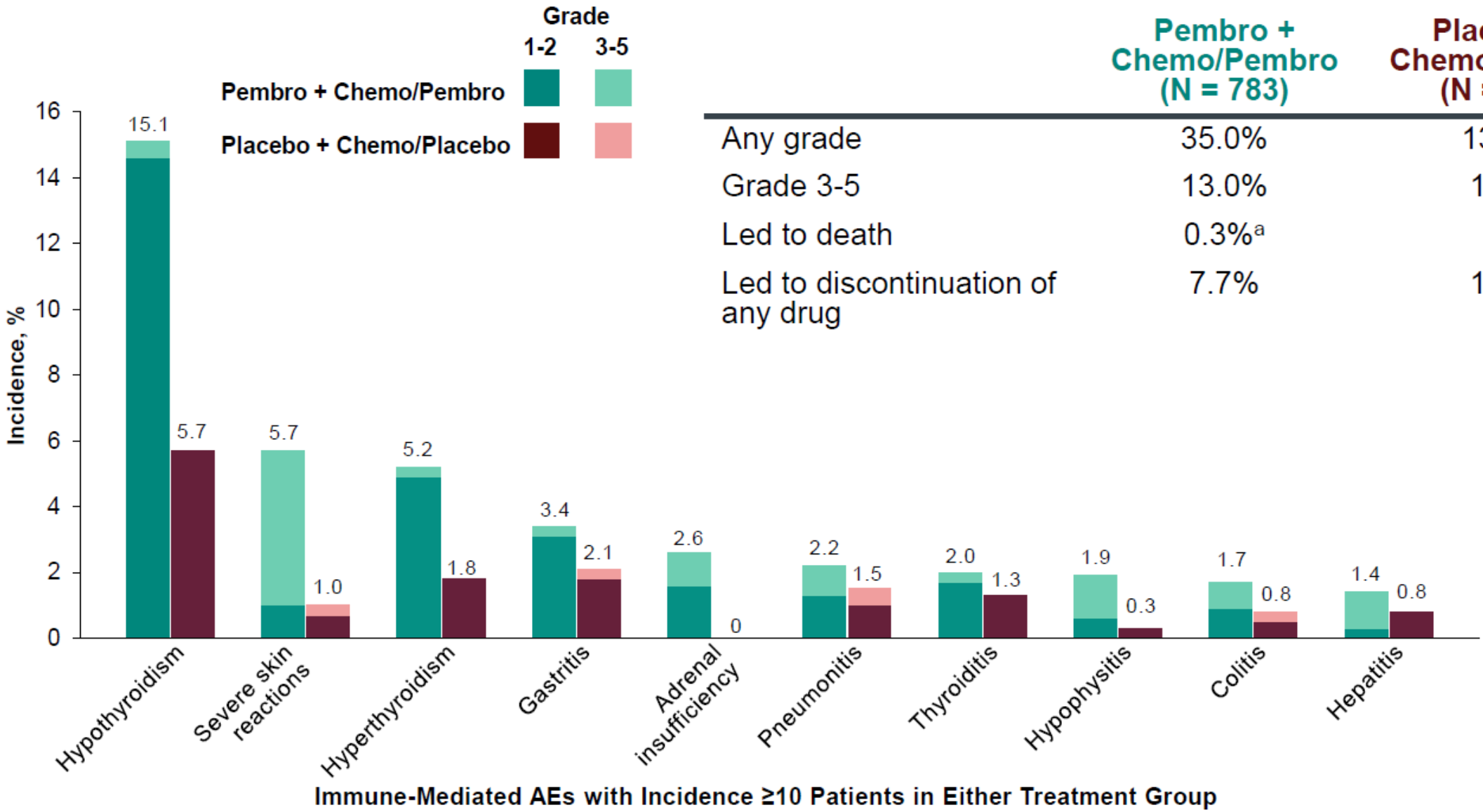


Overall Survival by Pathologic Complete Response (yp T0/Tis ypN0)



This is a non-randomized subgroup analysis based on the post-treatment outcome of pCR and HRs should therefore be interpreted with caution. Data cutoff date: March 22, 2024.

Immune-Mediated Adverse Events



	Pembro + Chemo/Pembro (N = 783)	Placebo + Chemo/Placebo (N = 389)
Any grade	35.0%	13.1%
Grade 3-5	13.0%	1.5%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	7.7%	1.0%

Immune-Mediated AEs with Incidence ≥10 Patients in Either Treatment Group

[a]1 patient from pneumonitis and 1 patient from autoimmune encephalitis. Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed.
Data cutoff date: March 22, 2024.

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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]

[1]Breast Cancer Unit, Centre Francois Baclesse, Caen, CEDEX 4, France [2]Medical Oncology, Institut Curie, Paris, CEDEX 14, France, [3]Breast unit, Gustave Roussy - Cancer Campus, Villejuif, France [4]Oncology, Cancéropôle Grand Ouest - CHU Nantes Immeuble Deurbroucq, Nantes, France, [5]Medical oncology, Oncopole Claudius Regaud- IUCT, Toulouse, France, [6]Oncology, Center Leon Berard, Lyon, France, [7] Oncology Center Eugène Marquis, Rennes, France, [8]Medical Oncology, ICM - Institut du Cancer de Montpellier, Montpellier, France, [9]Oncology, ICANS - Institut de Cancérologie Strasbourg Europe, Strasbourg, France, [10]Oncology, Centre Henri Becquerel, Rouen, CEDEX 1, France, [11]Oncology, Centre Anticancer Antoine Lacassagne, Nice, France, [12]Institute Bergonié - Centre Régional de Lutte Contre le Cancer Bordeaux,France [13]Medical Oncology Department, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain,France, [14]Institut de Cancérologie de Lorraine, Nancy, France [15]Oncology, IUCT Oncopole, Toulouse, France, [16]Clinical Research, Centre Francois Baclesse, Caen, Cedex, France,

RESULTS

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

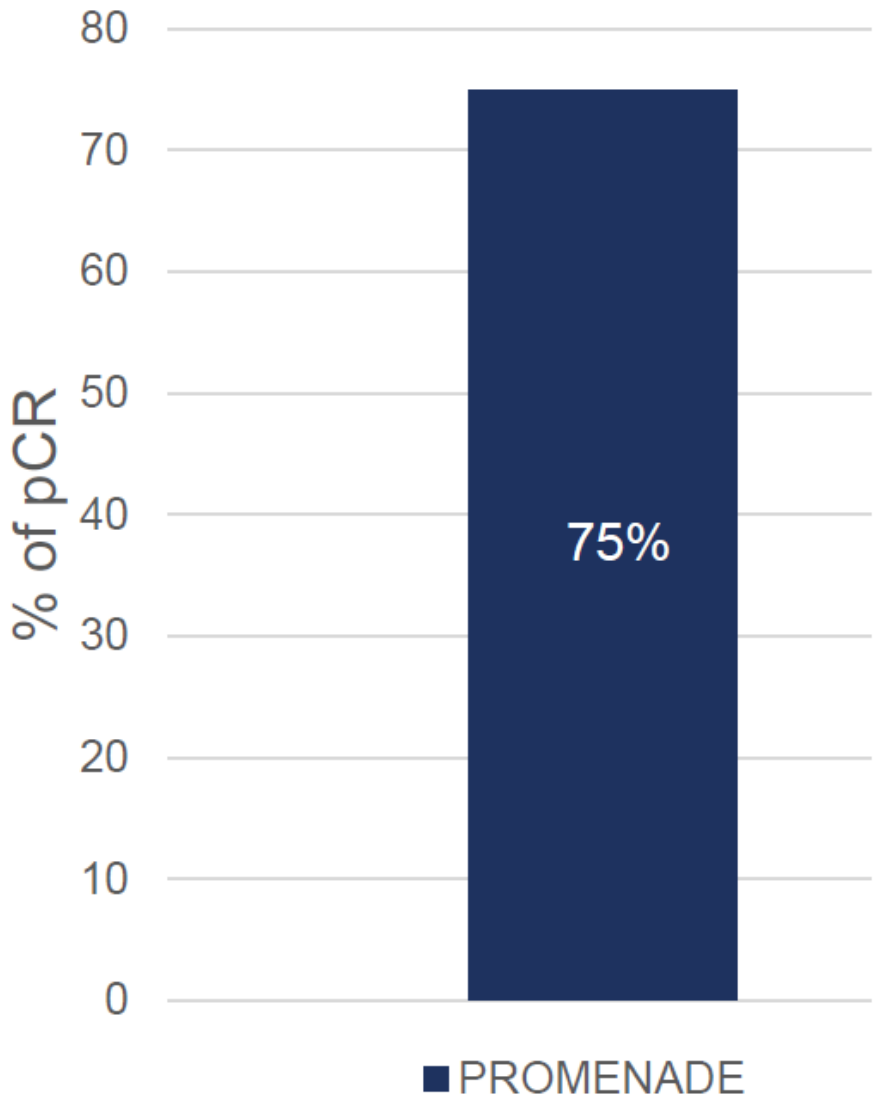
Histology - n (%)	
Ductal	102 (90%)
Lobular	2 (2%)
Other	9 (8%)
Missing	*1 (0.9%)*
SBR grade - n (%)	
II	15 (14%)
III	95 (86%)
Missing	*4 (3.5%)*
KI67 - Mean (SD)	61 (24)
Missing	*15 (13.2%)*
Endocrine receptors - n (%)	
ER-/PR+	37 (32%)
ER+/PR-	66 (58%)
ER+/PR+	11 (10%)
HER2 – n (%)	
0	57 (50%)
1	35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

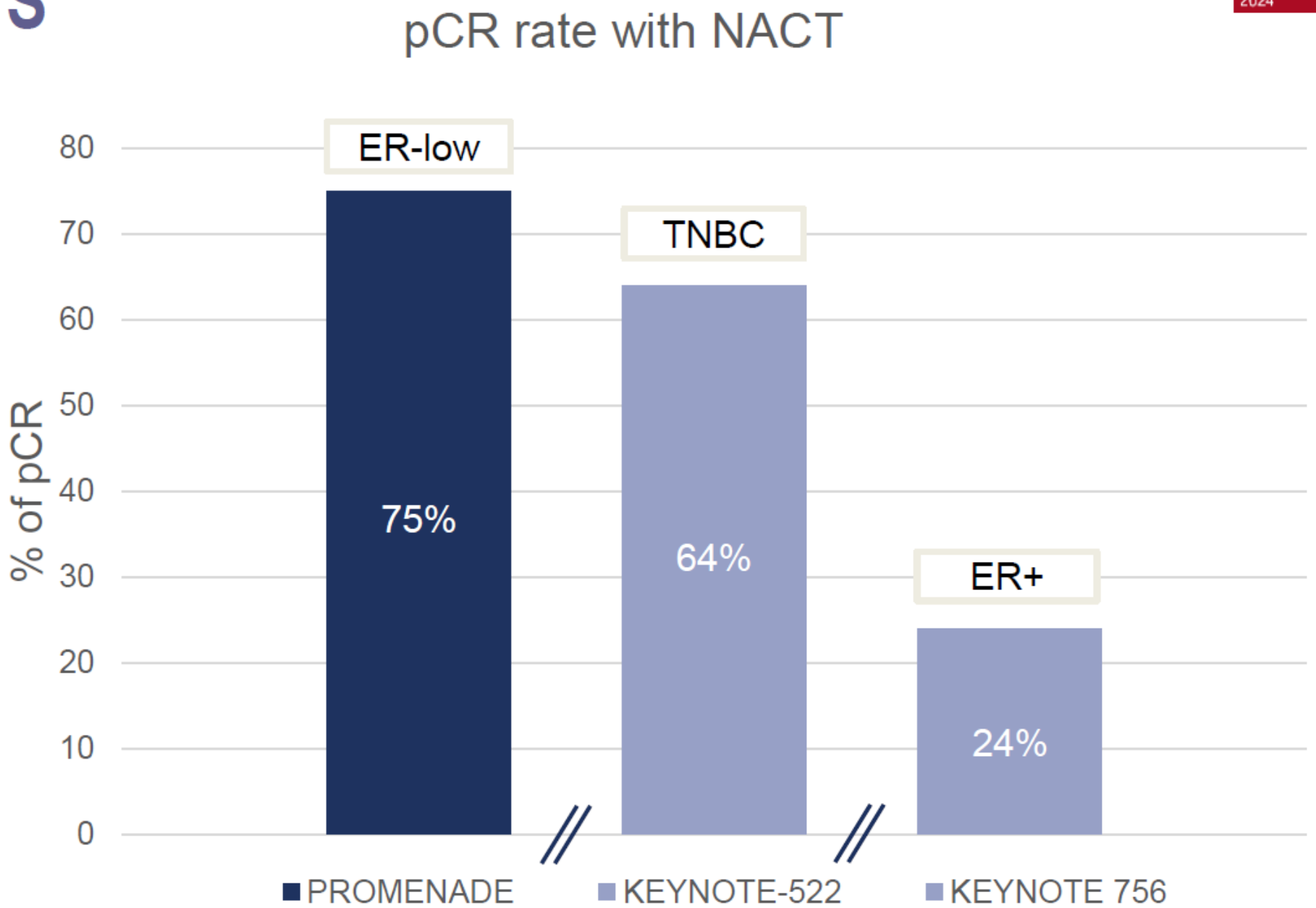
RESULTS

pCR rate with KEYNOTE-522 regimen in ER-low BC

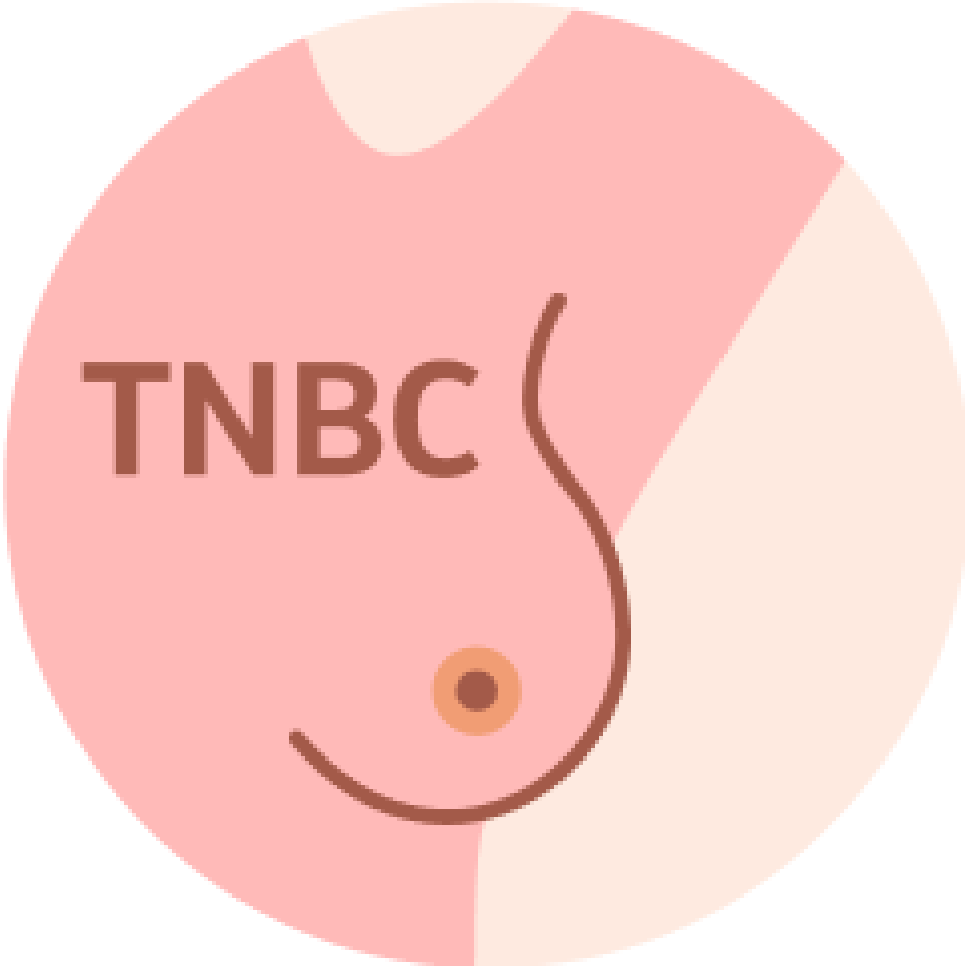


RCB	n (%)
0	85 (75 %)
1	9 (8 %)
2	12 (11 %)
3	7 (6 %)
Progressive disease	1 (1 %)

RESULTS



Data are not intended to be directly comparative



TNBC METASTATIQUE

Les nouveautés

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Capivasertib + paclitaxel as first-line treatment of metastatic triple-negative breast cancer: the CAPItello-290 Phase 3 trial

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Friday, 13 September 2024

CAPItello-290: Study overview

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

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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

HER2-negative was defined as IHC 0 or 1+, or IHC 2+/ISH–. [a]Paclitaxel: 80 mg/m^2, Day 1 of Weeks 1–3 of each 4-week cycle, capivasertib: 400 mg twice daily, Days 2–5 of Weeks 1–3 of each 4-week cycle, placebo: twice daily, Days 2–5 of Weeks 1–3 of each 4-week cycle; [b]China, Asia-Pacific (excluding China), United States, Rest of the World.

ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin-embedded; HbA1c, glycosylated haemoglobin A1c; IHC, immunohistochemistry; ISH, *in situ* hybridisation; R, randomisation.

CAPItello-290: *PIK3CA/AKT1/PTEN* alterations[a]

Alteration frequency consistent with literature[1,2] and balanced across treatment arms

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)

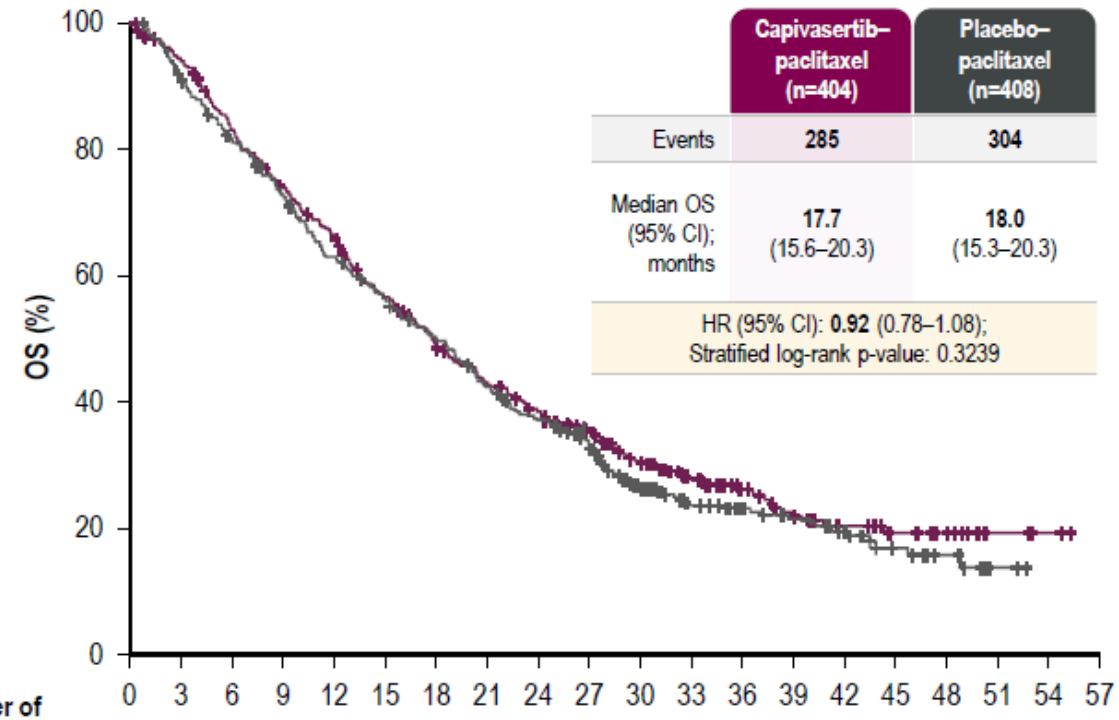
[a]*PIK3CA/AKT1/PTEN* alterations were analysed by retrospective central molecular testing of primary or recurrent FFPE tumour sample. [b]Reasons for unknown status include no sample available, preanalytical failure, or post-analytical failure. The non-altered analysis subgroup includes patients with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

1. Razavi P, et al. *Cancer Cell* 2018; 34:427–38; 2. Wilson TR, et al. *Mol Cancer Res* 2019;17:97–108.

CAPItello-290: Dual primary endpoints: OS in the overall population and in patients with *PIK3CA/AKT1/PTEN*-altered tumours (DCO2)

No statistically significant OS difference between treatment arms in either population

Overall population



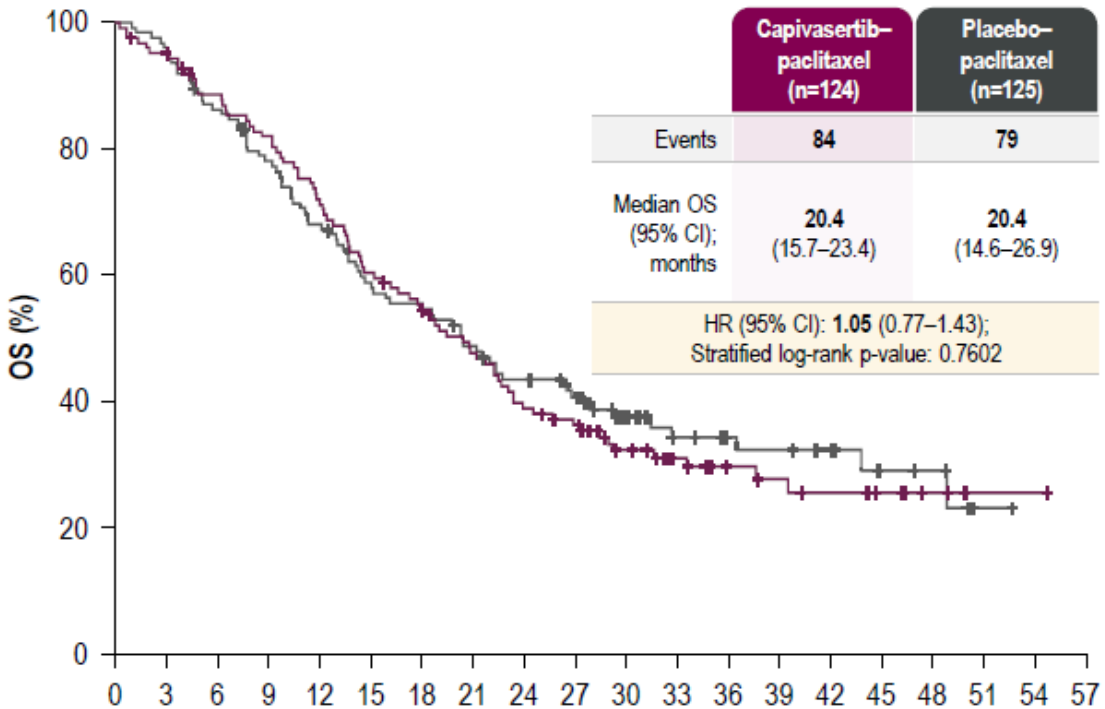
	Capivasertib–paclitaxel (n=404)	Placebo–paclitaxel (n=408)
Events	285	304
Median OS (95% CI); months	17.7 (15.6–20.3)	18.0 (15.3–20.3)

HR (95% CI): **0.92** (0.78–1.08);
Stratified log-rank p-value: 0.3239

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 (n=124)	Placebo–paclitaxel (n=125)
Events	84	79
Median OS (95% CI); months	20.4 (15.7–23.4)	20.4 (14.6–26.9)

HR (95% CI): **1.05** (0.77–1.43);
Stratified log-rank p-value: 0.7602

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

Exploratory analyses: No significant OS difference between treatments in patients with *PIK3CA/AKT1/PTEN*-non-altered tumours (n=563, hazard ratio 0.88 [95% CI 0.72–1.06]; patients with confirmed non-altered tumours [n=465], hazard ratio 0.90 [95% CI 0.73–1.11]).
Data cutoff: 18 March 2024 (DCO2). Tick marks indicate censored observations. Median (range) duration of follow-up in censored patients: Overall population: Capivasertib–paclitaxel: 31.8 (0.5–55.4) months, placebo–paclitaxel: 30.8 (0.3–52.7) months; *PIK3CA/AKT1/PTEN*-altered population: Capivasertib–paclitaxel: 32.6 (0.9–54.8) months, placebo–paclitaxel: 30.3 (3.0–52.7) months. Cox proportional hazards model stratified by (yes vs no): *PIK3CA/AKT1/PTEN*-altered (overall population only), visceral metastases, prior (neo)adjuvant chemotherapy. CI, confidence interval.

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Merci à tous

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