2025 ESMO BREAST CANCER
Annual Congress

LBA1 – ADJUVANT PERTUZUMAB OR PLACEBO + TRASTUZUMAB + CHEMOTHERAPY (P OR PLA + T + CT) IN PATIENTS (PTS) WITH EARLY HER2-POSITIVE OPERABLE BREAST CANCER IN APHINITY: FINAL ANALYSIS AT 11.3 YEARS' MEDIAN FOLLOW-UP

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On behalf of the APHINITY Steering Committee and Investigators

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

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Sibylle Loibl, MD, PhD:

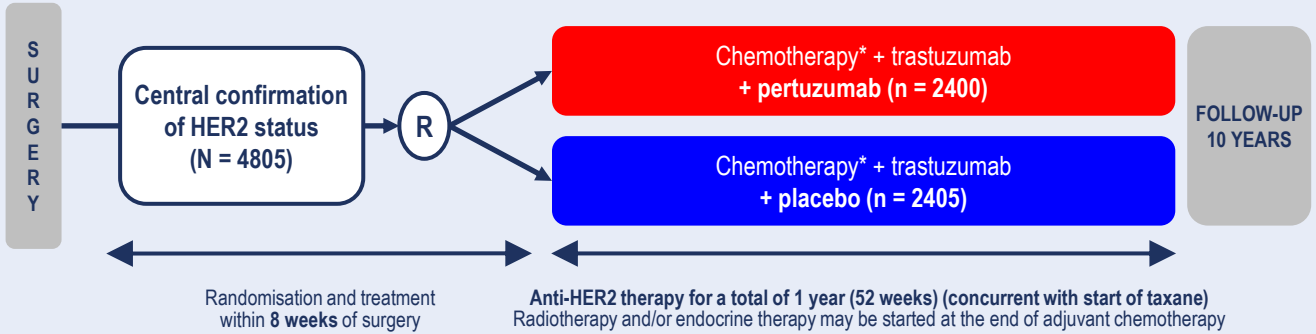
Grants and/or honoraria for advisory boards and/or contracts (financial, institutional): AstraZeneca, AbbVie, Agendia, Amgen, BioNTech, Celgene/BMS, Celcuity, DSI, Exact Science, Gilead, GSK, Incyte, Lilly, Medscape, Molecular Health, MSD, Novartis, Pierre Fabre, Pfizer, Relay, Roche, Sanofi, Seagen, Stemline/Menarini, Olema, Bayer, Bicycle, JAZZ Pharma, BeiGene
Support for attending meetings and/or travel (financial, personal): DSI, ESMO, SGBCC, ASCO, AGO Kommission Mamma
Patents planned, issued or pending (financial, personal): EP14153692.0/EP21152186.9/EP18209672/EP24210258
Royalties (financial, personal): VM Scope

Martine Piccart, MD, PhD:

Consulting or advisory role (financial, personal): AstraZeneca, Lilly, MSD, Novartis, Pfizer, Menarini, Seagen, Roche/Genentech, NBE Therapeutics, Frame Therapeutics, Gilead Sciences
Research funding (financial, institutional): AstraZeneca, Lilly, MSD, Novartis, Pfizer, Roche/Genentech, Radius Health, Synthon, Servier, Immunomedics/Gilead, Menarini
Member of Scientific Board (financial, personal): Oncolytics

All authors received research support in the form of third-party writing assistance
For all-author declarations of interest, please see abstract

APHINITY (NCT01358877): A PHASE III ADJUVANT STUDY INVESTIGATING THE BENEFIT OF PERTUZUMAB WHEN ADDED TO TRASTUZUMAB + CHEMOTHERAPY[1]



Primary IDFS analysis:

- Events:
  - Pertuzumab: 171/2400 (7.1%)
  - Placebo: 210/2404 (8.7%)
- Adjusted hazard ratio (95% CI): 0.81 (0.66, 1.00)
- p-value: 0.045

- **Primary endpoint:** IDFS (APHINITY definition differs from STEEP definition)
- **Secondary endpoints:** IDFS with 2nd primary non-breast primary cancers included, DFS, OS, RFI, DRFI, safety, HRQoL
- **Stratification factors:** Nodal status, hormone receptor status, chemotherapy regimen, geographical region, protocol version (A vs B)
- **CCOD** at the time of the primary analysis was 19 Dec 2016, with a median follow-up of 45.4 months

* Standard anthracycline or non-anthracycline (TCH) regimens were allowed: 3–4 x FEC (or FAC) → 3–4 x TH; 4 x AC (or EC) → 4 x TH; 6 x TCH.
AC, doxorubicin and cyclophosphamide; CCOD, clinical cutoff date; CI, confidence interval; DFS, disease-free survival; DRFI, distant relapse-free interval; EC, epirubicin and cyclophosphamide; FAC, fluorouracil, doxorubicin and cyclophosphamide; FEC, fluorouracil, epirubicin and cyclophosphamide; HRQoL, health-related quality of life; IDFS, invasive disease-free survival; OS, overall survival; R, randomised; RFI, relapse-free interval; STEEP, Standardized Definitions for Efficacy End Points; TCH, docetaxel, carboplatin and trastuzumab; TH, docetaxel and trastuzumab.

Adapted from von Minckwitz G, *et al*. ASCO 2017;Abstract LBA500, with permission. 1. von Minckwitz G, *et al*. *New Engl J Med* 2017;**377:**122–31.

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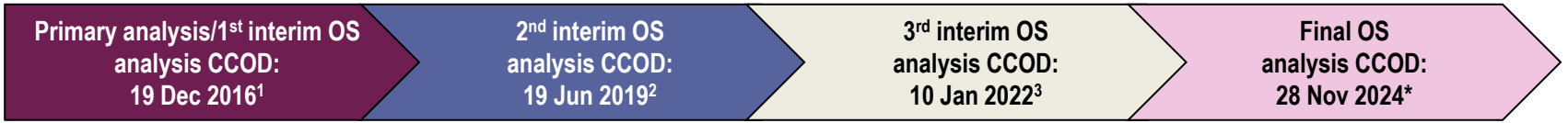
METHODS: FINAL ANALYSIS OF OS



- We are now describing the **final analysis of OS**
  - Median follow-up time was 11.3 years; 34 months longer than the 3rd interim analysis[3]
- There were 452 deaths; 62 more than at the 3rd interim analysis[3] and 188 less than the original target of 640[1]
- p-value of ≤0.0496 was required for statistical significance for this final OS analysis

- Updated **descriptive analyses of IDFS and cardiac safety** were also performed
  - There were 682 patients with an IDFS event; 73 more than at the 3rd interim analysis[3]

* Following the 3rd interim OS analysis, the timing of the final OS analysis was changed from event-driven to calendar-driven due to a lower than anticipated overall death rate.

CCOD, clinical cutoff date; IDFS, invasive disease-free survival; OS, overall survival. 1. von Minckwitz G, *et al. New Engl J Med* 2017;**377:**122–31; 2. Piccart M, *et al. J Clin Oncol* 2021;**39:**1448–57; 3. Loibl S, *et al. J Clin Oncol* 2024;**42:**3643–51.

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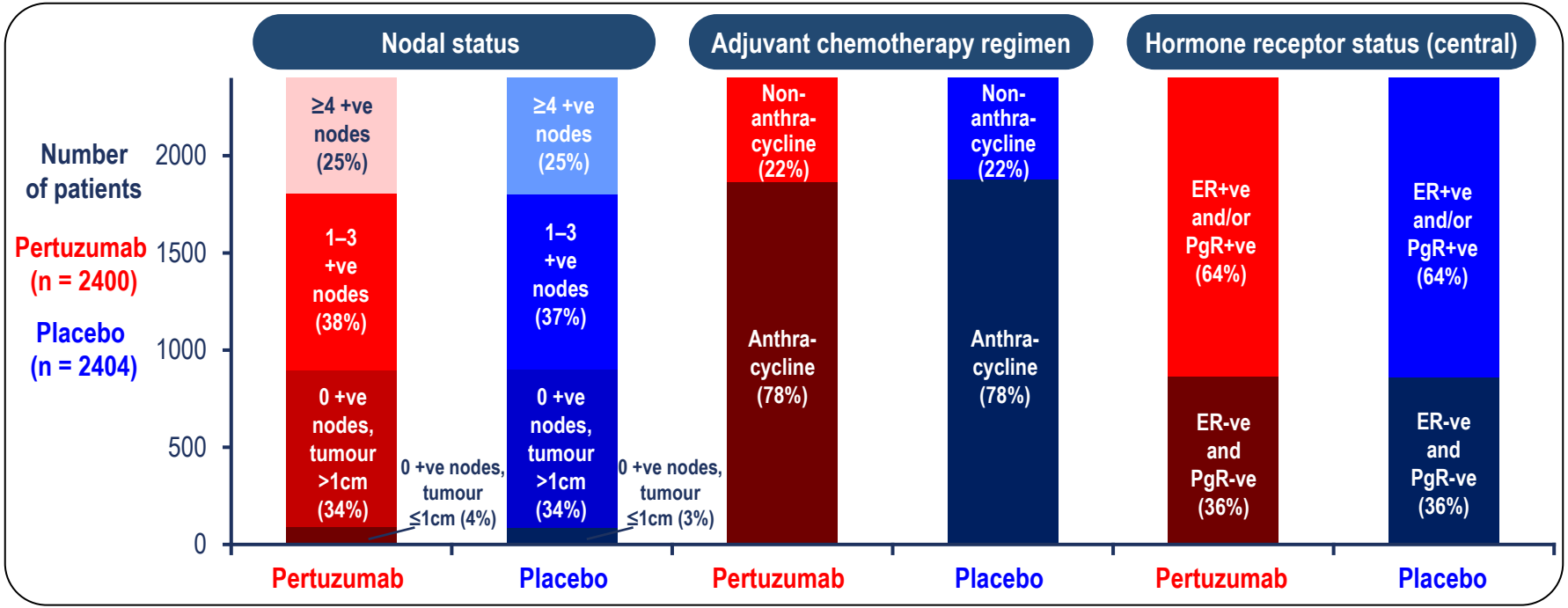
BASELINE CHARACTERISTICS WERE BALANCED BETWEEN THE TWO ARMS IN APHINITY[1]



ER, oestrogen receptor; PgR, progesterone receptor.

Adapted from Piccart M, *et al.* SABCS 2019:Abstract GS1-04, with permission. 1. von Minckwitz G, *et al. New Engl J Med* 2017;**377:**122–31.

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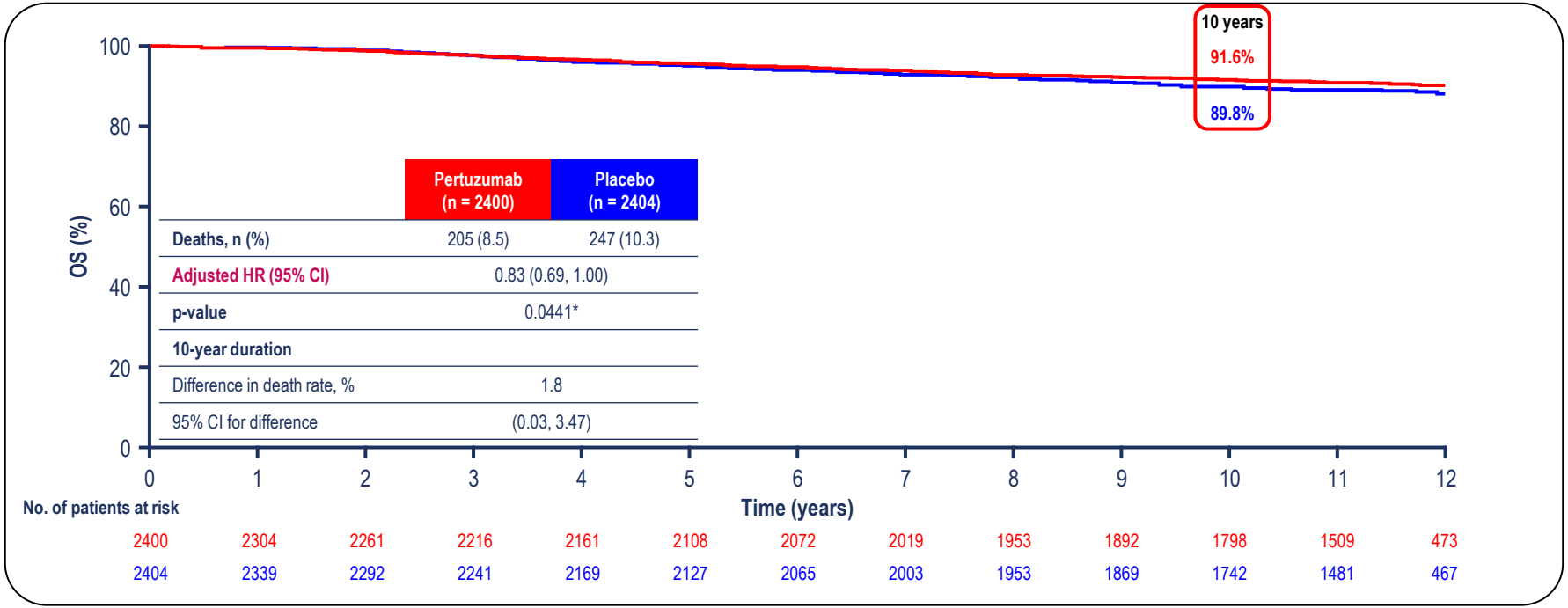
APHINITY FINAL OS ANALYSIS AT 11.3 YEARS' MEDIAN FOLLOW-UP BY TREATMENT REGIMEN (ITT POPULATION)



* p≤0.0496 required for statistical significance.

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival.

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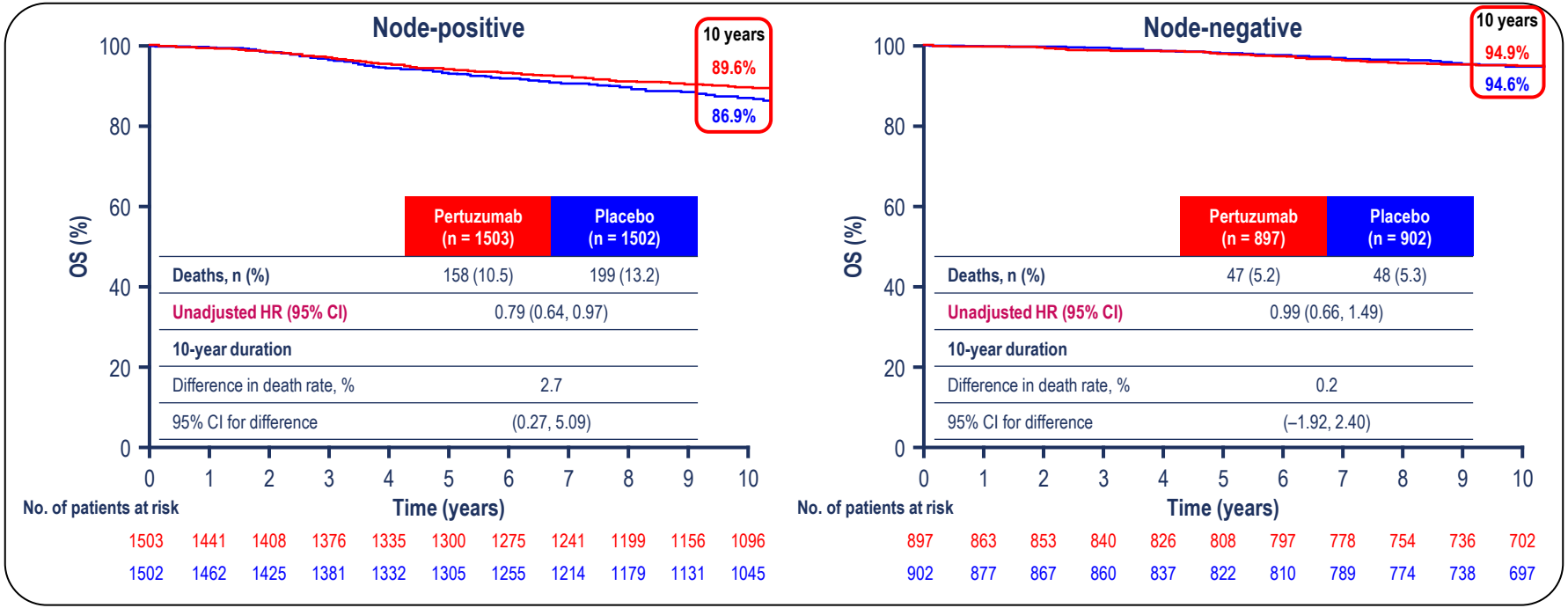
APHINITY FINAL OS ANALYSIS AT 11.3 YEARS' MEDIAN FOLLOW-UP BY TREATMENT REGIMEN AND NODAL STATUS



CI, confidence interval; HR, hazard ratio; OS, overall survival.

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APHINITY UPDATED DESCRIPTIVE ANALYSIS AT 11.3 YEARS' MEDIAN FOLLOW-UP: SITE OF FIRST OCCURRENCE OF AN IDFS EVENT

	Pertuzumab (n = 2400)	Placebo (n = 2404)
Total patients with an IDFS event, n (%)	303 (12.6)	379 (15.8)
Category of 1st IDFS event, n (%)		
• Distant recurrence	150 (6.3)	211 (8.8)
• CNS metastases	51 (2.1)	53 (2.2)
• Locoregional BC recurrence	35 (1.5)	61 (2.5)
• Contralateral invasive BC recurrence	43 (1.8)	29 (1.2)
• Death without prior event	75 (3.1)	78 (3.2)

Hierarchy applied if a patient experienced additional IDFS event(s) within 61 days of their first IDFS event. Fewer patients randomised to the pertuzumab arm received HER2-targeted therapy as a first-line treatment for distant recurrence than those randomised to the placebo arm (50.4% [57/113] vs 54.7% [93/170], respectively). BC, breast cancer; CNS, central nervous system; IDFS, invasive disease-free survival.

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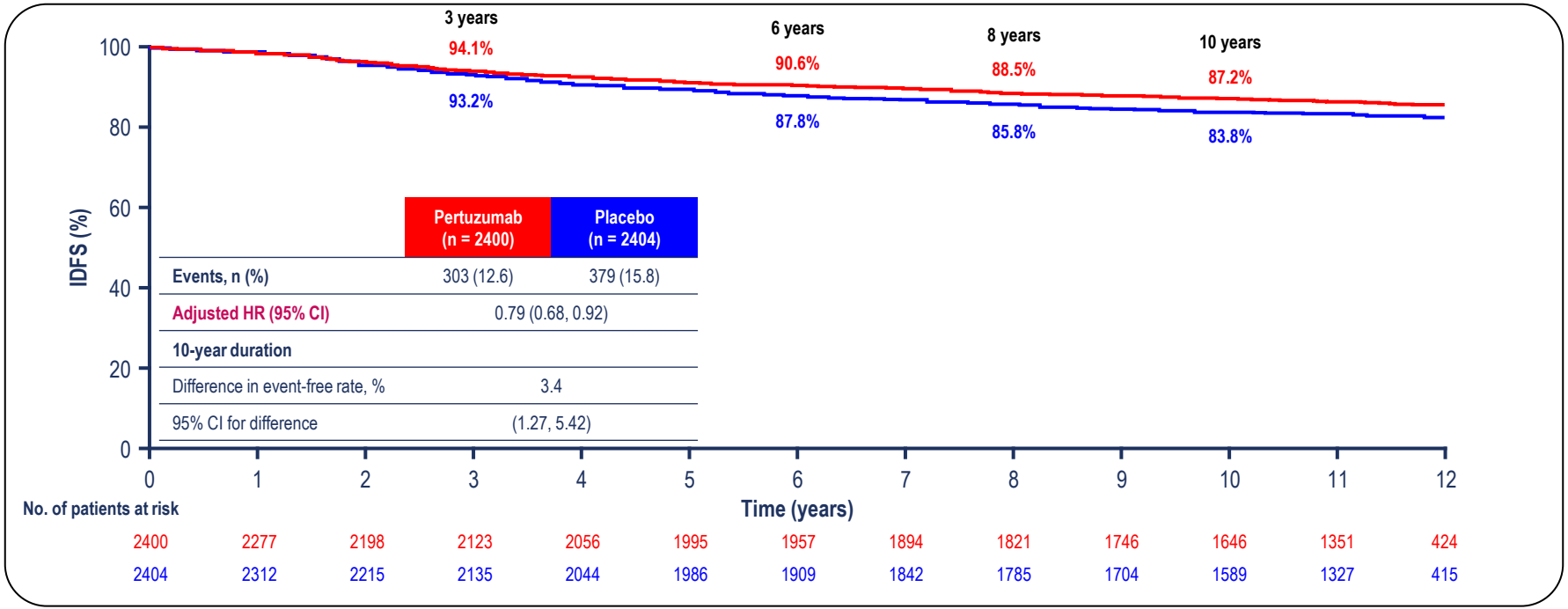
APHINITY UPDATED DESCRIPTIVE IDFS ANALYSIS AT 11.3 YEARS' MEDIAN FOLLOW-UP BY TREATMENT REGIMEN (ITT POPULATION)



CI, confidence interval; HR, hazard ratio; IDFS, invasive disease-free survival; ITT, intention-to-treat.

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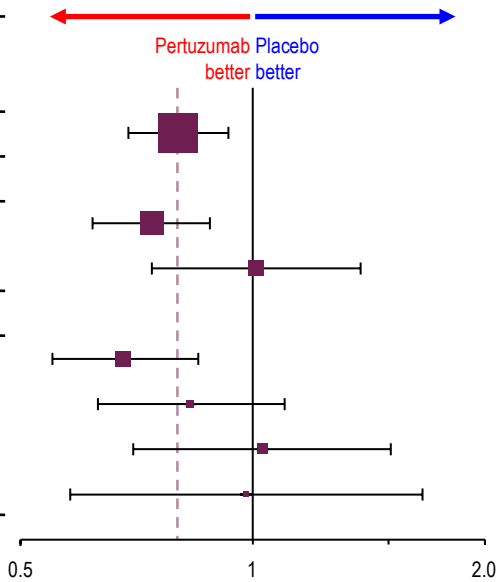
APHINITY UPDATED DESCRIPTIVE IDFS ANALYSIS AT 11.3 YEARS' MEDIAN FOLLOW-UP BY TREATMENT REGIMEN, NODAL STATUS AND HORMONE RECEPTOR STATUS

		Pertuzumab (n = 2400)		Placebo (n = 2404)		
Baseline risk factors	**Total patients, n**	**Patients per group, n**	**Events, n**	**Patients per group, n**	**Events, n**	**HR (95% CI)**
All patients*	4804	2400	303	2404	379	0.80 (0.69, 0.93)
Nodal status						
Node-positive	3005	1503	224	1502	299	0.74 (0.62, 0.88)
Node-negative	1799	897	79	902	80	1.01 (0.74, 1.38)
Nodal and hormone receptor status						
Node-positive, hormone receptor-positive	1912	947	131	965	193	0.68 (0.55, 0.85)
Node-positive, hormone receptor-negative	1093	556	93	537	106	0.83 (0.63, 1.10)
Node-negative, hormone receptor-positive	1170	589	52	581	52	1.03 (0.70, 1.51)
Node-negative, hormone receptor-negative	629	308	27	321	28	0.98 (0.58, 1.66)



Hormone receptor status was centrally assessed. * Unadjusted analysis of the ITT population.
CI, confidence interval; HR, hazard ratio; IDFS, invasive disease-free survival; ITT, intention-to-treat.

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APHINITY UPDATED DESCRIPTIVE ANALYSIS AT 11.3 YEARS' MEDIAN FOLLOW-UP: CARDIAC SAFETY

Patients, n (%)	Pertuzumab (n = 2364)	Placebo (n = 2405)
Primary cardiac event • Heart failure NYHA class III or IV + LVEF drop* • Cardiac death†	21 (0.9)	11 (0.5)
Heart failure NYHA class III or IV + LVEF drop*	18 (0.8)	7 (0.3)
Cardiac death†	3 (0.1)	4 (0.2)

No new cardiac safety issues emerged

Three further patients with a primary cardiac event since the 3rd interim analysis;[1] two (heart failure) in the pertuzumab arm and one (heart failure) in the placebo arm. * LVEF drop = ejection fraction drop ≥10% from baseline AND to below 50%. † identified by the Cardiac Advisory Board for the trial according to a prospective definition. LVEF, left ventricular ejection fraction; NYHA, New York Heart Association. 1. Loibl S, *et al. J Clin Oncol* 2024;**42:**3643–51.

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APHINITY UPDATED DESCRIPTIVE ANALYSIS AT 11.3 YEARS' MEDIAN FOLLOW-UP: CARDIAC SAFETY IN THE ANTHRACYCLINE COHORT

Patients, n (%)	Pertuzumab (n = 1834)	Placebo (n = 1894)
Primary cardiac event • Heart failure NYHA class III or IV + LVEF drop* • Cardiac death†	18 (1.0)	10 (0.5)
Heart failure NYHA class III or IV + LVEF drop*	15 (0.8)	6 (0.3)
Cardiac death†	3 (0.2)	4 (0.2)

No new cardiac safety issues emerged

Two further patients with a primary cardiac event since the 3rd interim analysis;[1] one (heart failure) in the pertuzumab arm and one (heart failure) in the placebo arm. * LVEF drop = ejection fraction drop ≥10% from baseline AND to below 50%. † identified by the Cardiac Advisory Board for the trial according to a prospective definition. LVEF, left ventricular ejection fraction; NYHA, New York Heart Association. 1. Loibl S, *et al. J Clin Oncol* 2024;**42:**3643–51.

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CONCLUSIONS

- In this prespecified OS analysis with longer follow-up (median, 11.3 years), a statistically significant OS improvement was observed by adding adjuvant pertuzumab to trastuzumab + chemotherapy
- The IDFS benefit was maintained, remaining clinically meaningful in the node-positive subgroup, while no benefit was observed in the node-negative subgroup
- No new cardiac safety concerns emerged

These final OS results, with long-term follow-up, further support the benefit of pertuzumab in the early BC setting

BC, breast cancer; IDFS, invasive disease-free survival; OS, overall survival.

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ACKNOWLEDGEMENTS

Our patients and their families

Participating Investigators from the Breast International Group network and other independent groups

The Principal Investigators

Members of the APHINITY Study Committees (Steering Committee, Joint Study Management Team, Translational Advisory Committee, Scientific Review Team, Cardiac Advisory Board)

The sponsor: F. Hoffmann-La Roche Ltd, Basel, Switzerland

Breast International Group, Brussels, Belgium

The statistical centre: Frontier Science Scotland, UK

The data centre: Institute Jules Bordet, Brussels, Belgium

The central laboratory: European Institute of Oncology, Milan, Italy

This study was funded by F. Hoffmann-La Roche Ltd in collaboration with the Breast International Group

Research support in the form of third-party medical writing assistance for this presentation, furnished by Daniel Clyde, PhD, of Nucleus Global, an Inizio Company, was provided by F. Hoffmann-La Roche Ltd

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Thank you!

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