ESMO VIRTUAL PLENARY

Updated results of APHINITY at 8.4 years median follow up

A randomised multi-center, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer

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On behalf of the APHINITY Steering Committee and Investigators

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

July 14, 2022

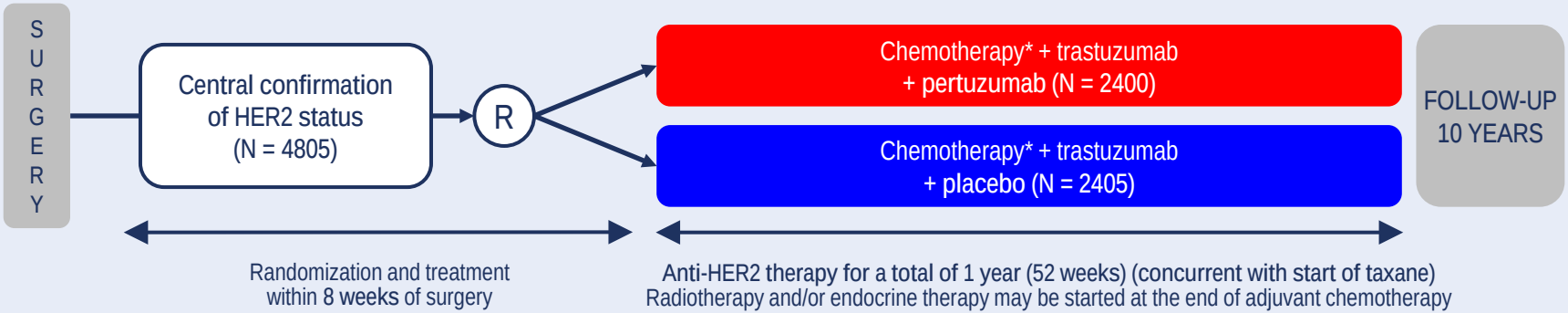
DECLARATION OF INTERESTS

Sibylle Loibl, MD, PhD

All paid to institution if not otherwise stated
Advisory boards: Amgen, AstraZeneca, BMS; DSI, Eirgenix, Eli Lilly, GSK, Gilead, Merck kG, Novartis, Pfizer, Pierre-Fabre, Relay Therapeutics, Sanofi, Seagen
Invited speaker: AstraZeneca, DSI, Novartis, Pfizer, Roche, SABCS 2021, ESMO 2020,21, ESMO Breast 2020,21,22, ASCO 2022,
Royalties: VM Scope
Medical Writing Support: AstraZeneca, DSI, Eirgenix, Gilead, Novartis, Pfizer, Roche, Seagen
Patents (Pending): EP14153692.0, EP21152186.9, EP15702464.7, EP19808852.8
Research grant: Abbvie, AstraZeneca, Celgene/BMS, DSI, Gilead, Molecular Health, Novartis, Pfizer, Roche,
Employment: GBG Forschungs GmbH
Non-financial: ESMO Guidelines Committee EC, AGO Guideline Group Mamma
Others: ABCSG, BMBF, EU grant, BIG, NSABP, AFT, Charité, Uni Marburg

BACKGROUND

APHINITY: A Phase III Adjuvant Study Investigating the Benefit of Pertuzumab when Added to Trastuzumab + Chemotherapy

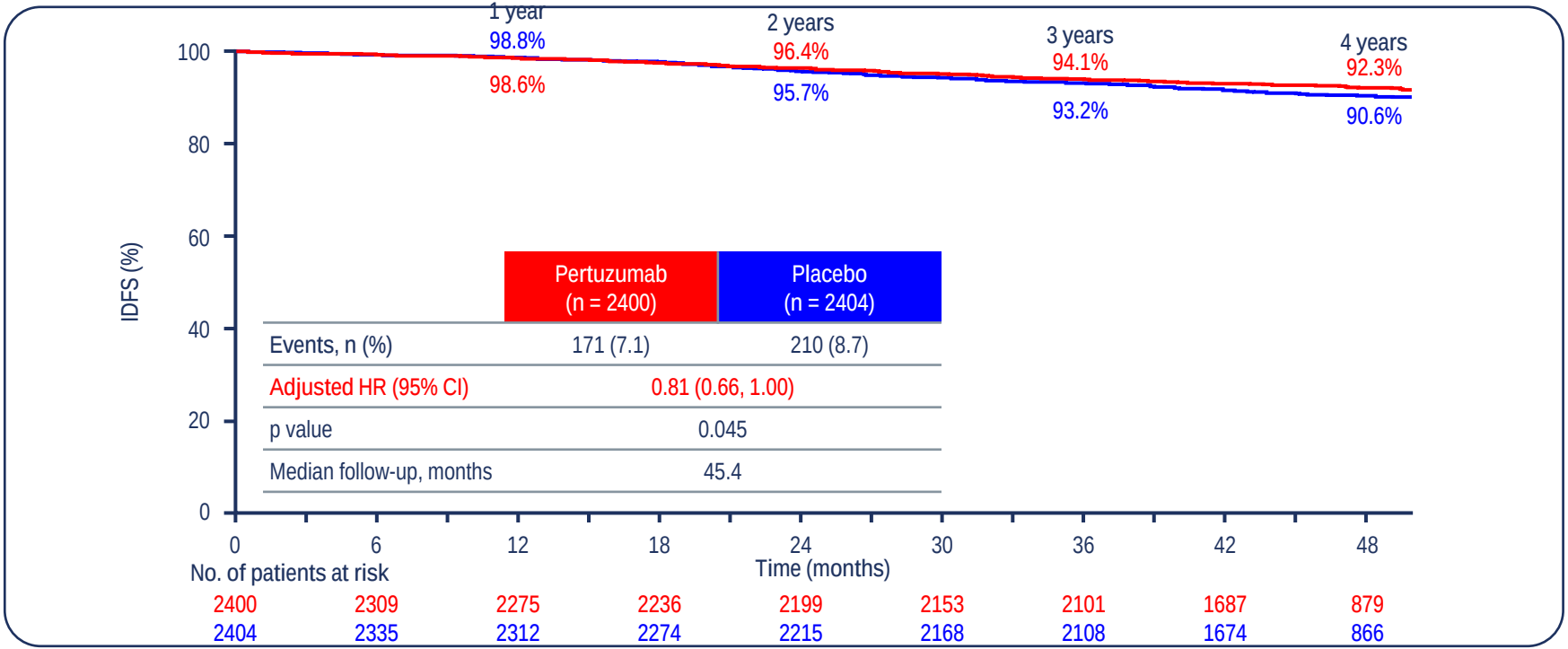


- **Primary endpoint:** IDFS (APHINITY definition differs from STEEP definition)
- **Secondary endpoint:** IDFS with 2nd primary non-breast primary cancers included, DFS, OS, RFI, DRFI, safety, and HRQoL
- **Stratification factors:** nodal status, HR status, chemotherapy regimen, geographic region, protocol version (A vs. B)
- **Clinical cut off date (CCOD)** at the time of primary analysis was 19 Dec 2016, 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.
DFS, disease-free survival; DRFI, distant relapse-free interval; HR, hormone receptor; HRQoL, health-related quality of life; IDFS, invasive disease-free survival; OS, overall survival; RFI, relapse-free interval.

adapted from von Minckwitz et al. N Engl J Med 2017; www.clinicaltrials.gov/ct2/show/NCT01358877.

APHINITY Demonstrated Significant Benefit of Adjuvant Pertuzumab in HER2 + Early Stage Breast Cancer After 45.5 Months Median FU



CI, confidence interval; FU, follow-up; HR, hazard ratio; IDFS, invasive disease-free survival.
adapted from von Minckwitz G, et al. N Engl J Med 2017.

2nd Interim Analysis of Overall Survival

- Limited information on overall survival (OS) at the time of the primary analysis
- 2nd interim analysis of OS – pre-planned, calendar-driven
  - Median follow-up time was 74.1 months
  - There were 272 deaths (42.5% required for definitive OS analysis)
  - 6-year overall survival (OS) per cents above 93% in both treatment groups; comparison of OS did not reach statistical significance
  - Confirmed IDFS benefit

Piccart M. et al. *J* Clin Oncol 2020.

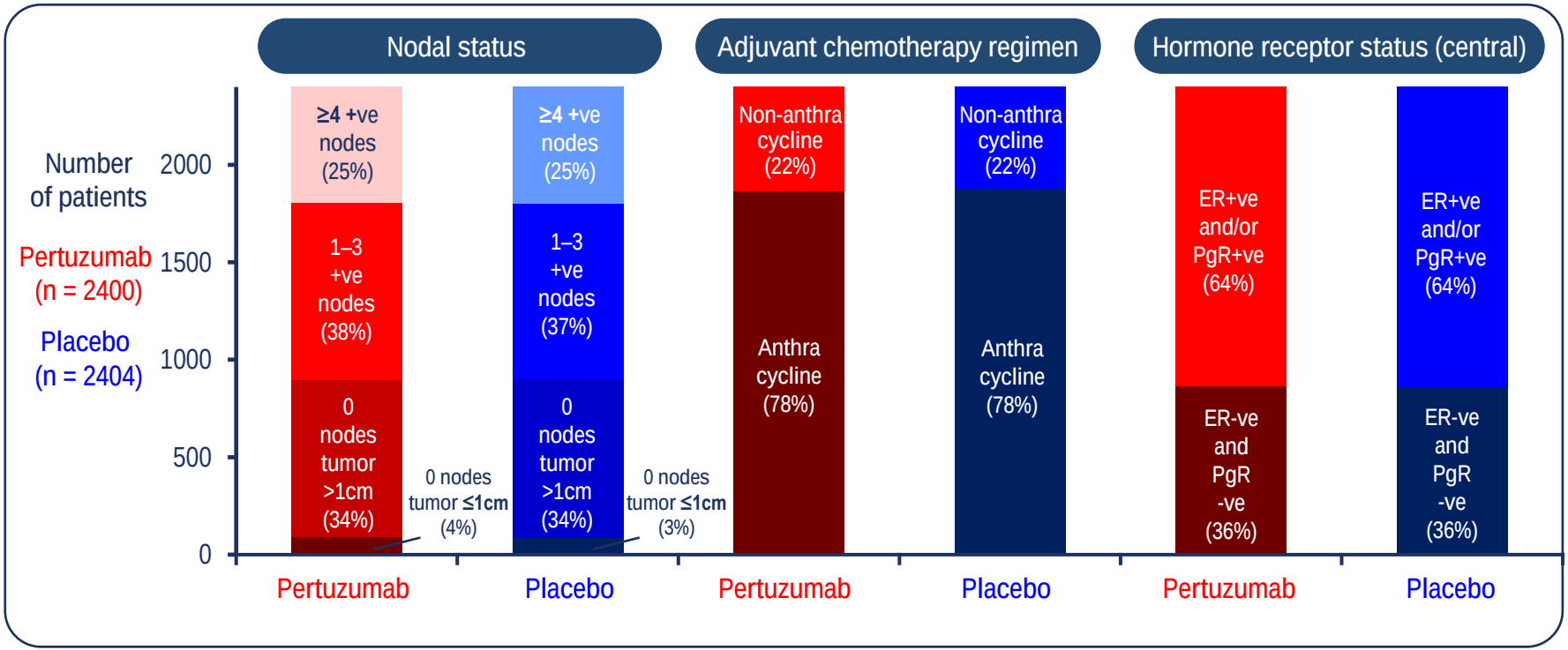
METHODS

Methods Third Interim Analysis

- We are now describing the 3rd interim analysis of OS
  - Median follow-up time is 8.4 years, 27 months longer than at the 2nd interim analysis.
  - There are now 370 deaths (98 more than at the 2nd interim analysis).
  - This is 57.8% of the 640 deaths needed for definitive OS analysis.
  - P-value of 0.0060 is required for statistical significance for this interim OS analysis.
- Updated descriptive analyses of IDFS and cardiac safety were also performed.
  - There are now 609 patients with an IDFS event (101 more than at the 2nd interim analysis).

RESULTS

Baseline Characteristics were Balanced Between 2 arms in APHINITY



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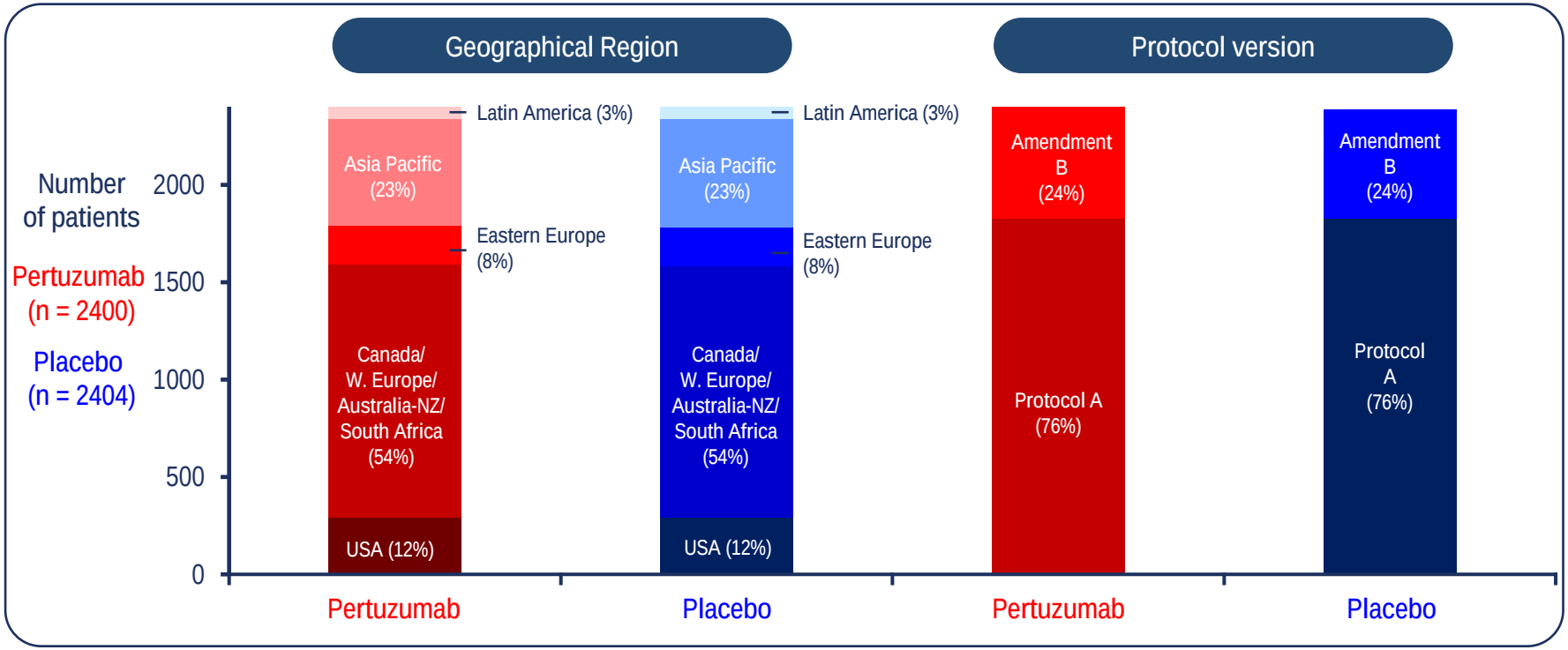
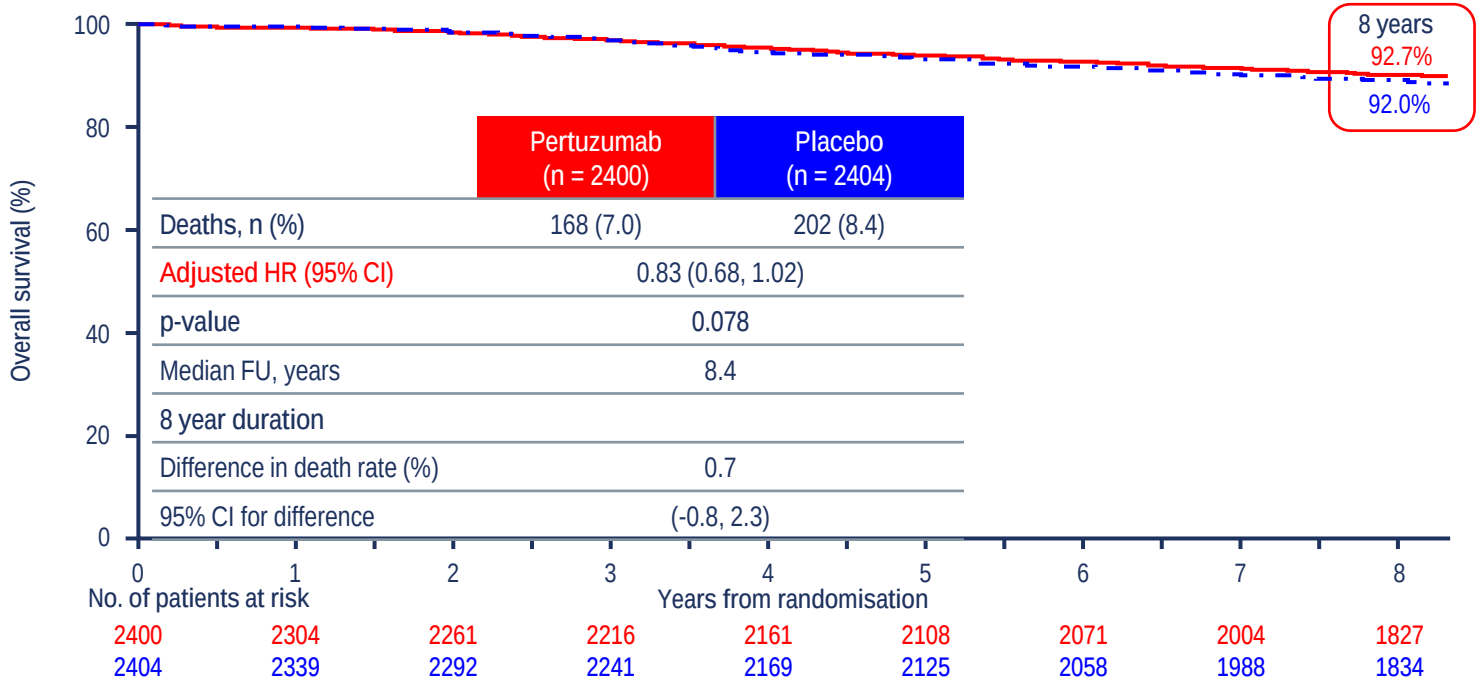
Baseline Characteristics were Balanced Between 2 arms in APHINITY

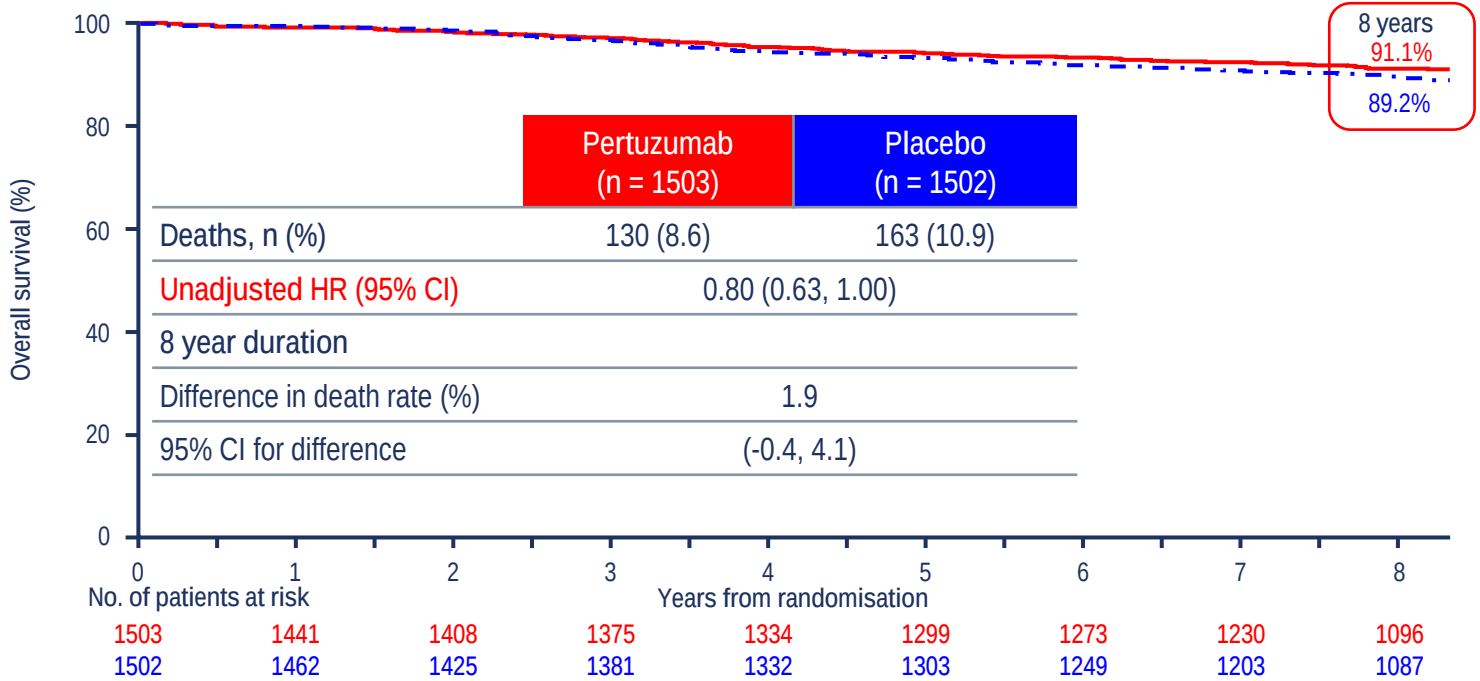


APHINITY Interim Overall Survival Analysis at 8.4 years Median FU by Treatment Regimen (ITT Population)



APHINITY Interim Overall Survival Analysis at 8.4 Years Median FU by Treatment Regimen

Node-positive Cohort



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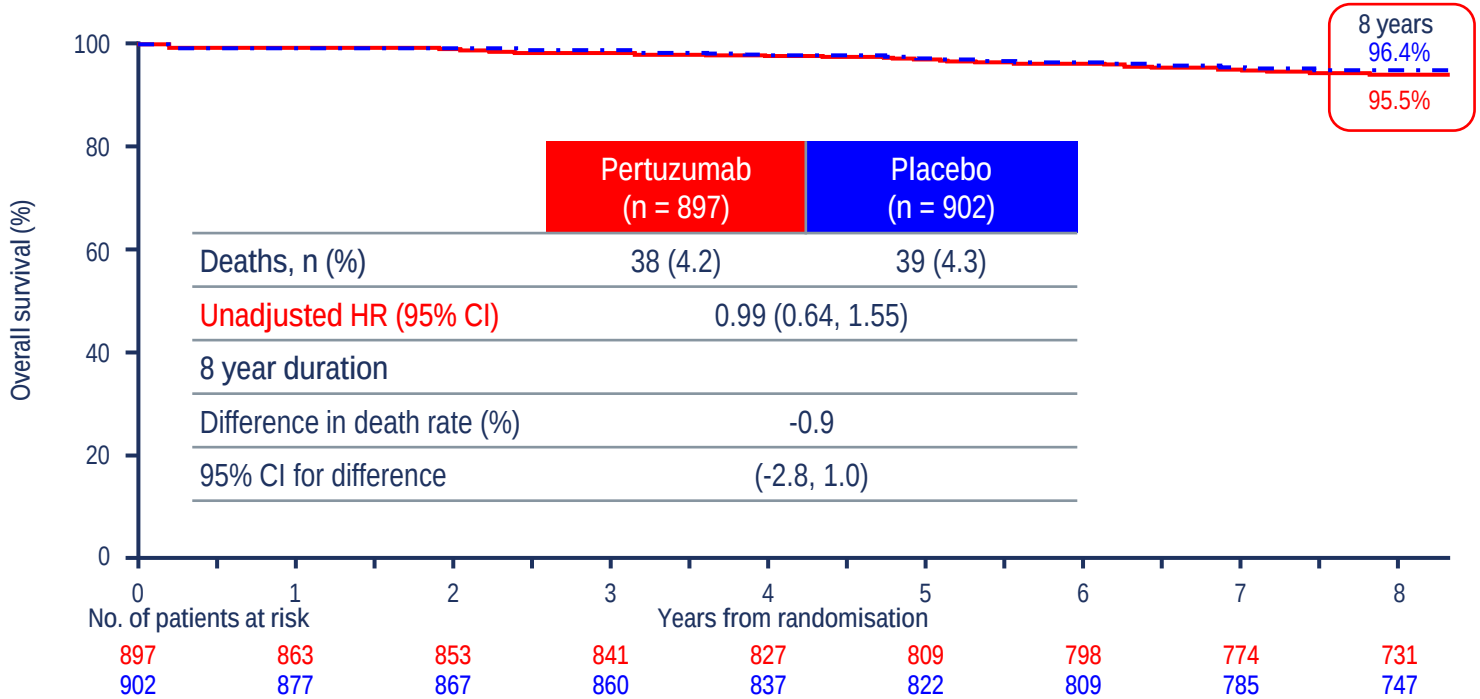
APHINITY Interim Overall Survival Analysis at 8.4 Years Median FU by Treatment Regimen

Node-negative Cohort



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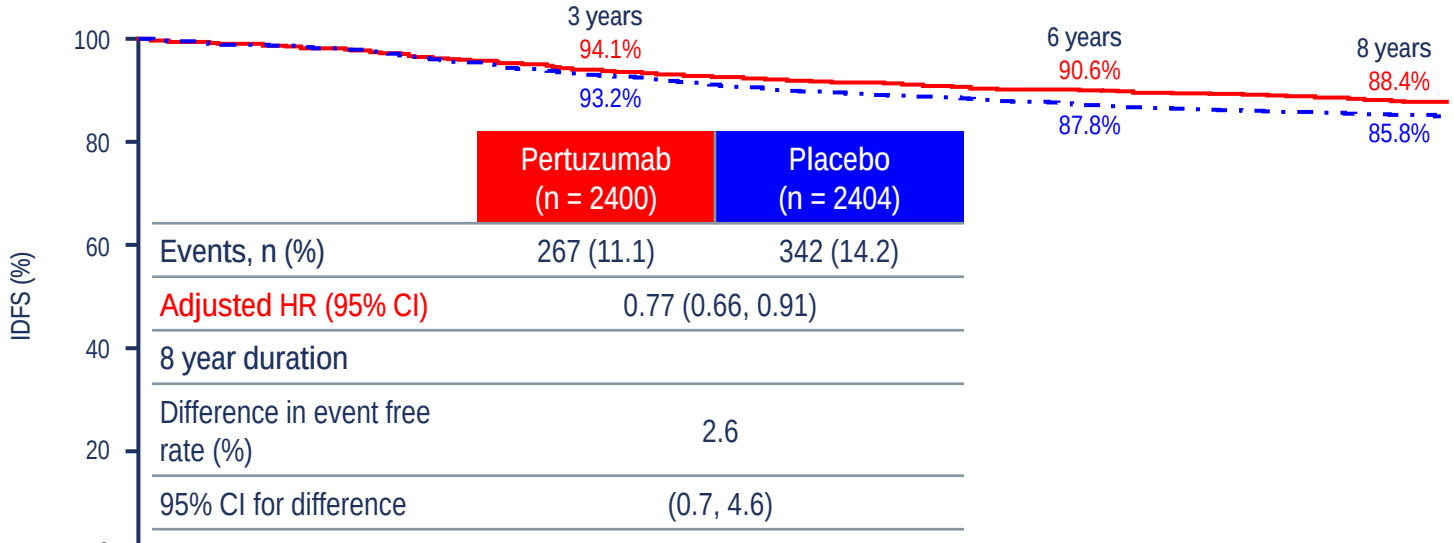
APHINITY Updated Descriptive IDFS Analysis at 8.4 Years Median FU by Treatment Regimen - ITT population



APHINITY Updated Descriptive Analysis 8.4 year Median FU, Site of First Occurrence of an IDFS event

	Pertuzumab N=2400	Placebo N=2404
Total patients with IDFS event: n (%)	267 (11.1%)	342 (14.2%)
Category of IDFS event: n (%)		
• Distant recurrence	149 (6.2%)	204 (8.5%)
• CNS metastases	51 (2.1%)	53 (2.2%)
• Locoregional BC recurrence	32 (1.3%)	57 (2.4%)
• Contralateral invasive BC recurrence	28 (1.2%)	22 (0.9%)
• Death without prior event	58 (2.4%)	59 (2.5%)

Hierarchy applied if a patient experiences additional IDFS event(s) within 61 days of their 1st IDFS event

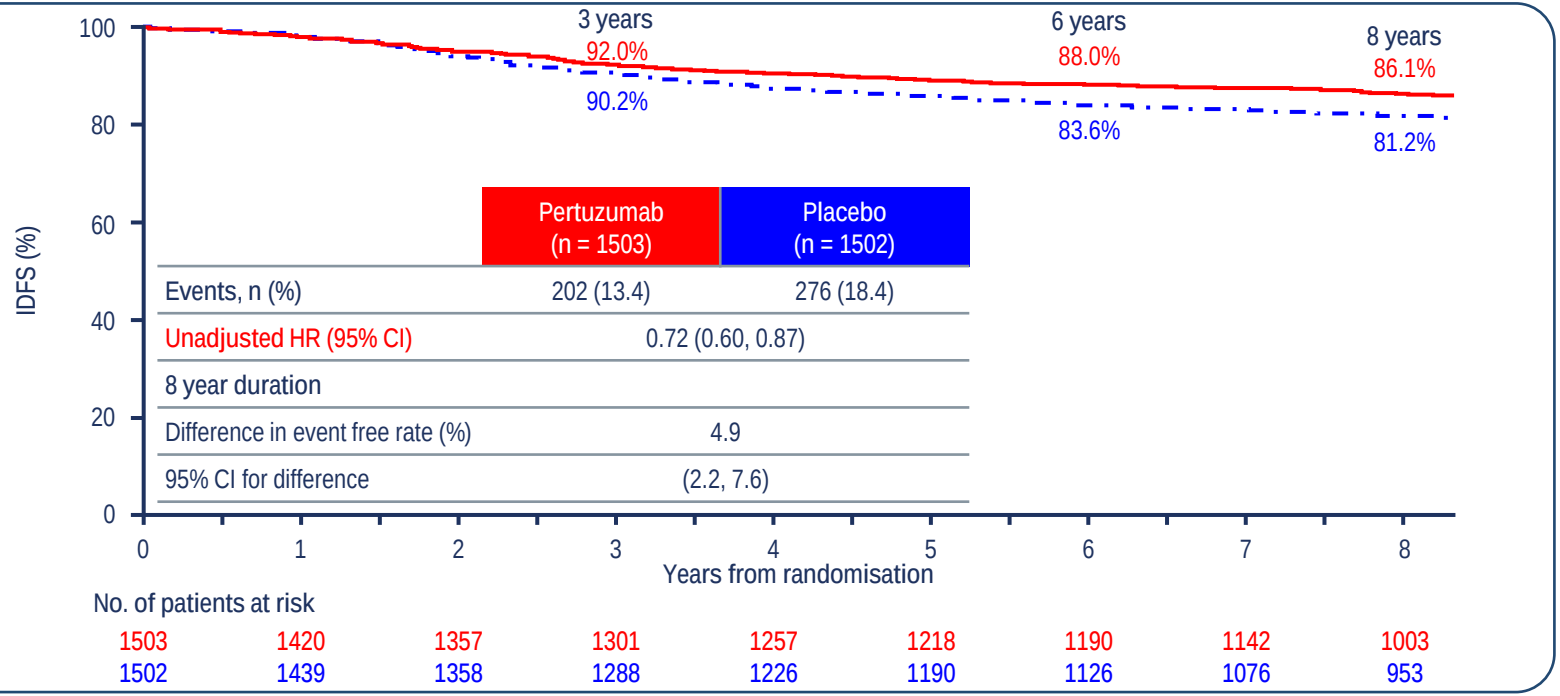
APHINITY Updated Descriptive Analysis 8.4 year median FU, Site of First Occurrence of an IDFS Event by Nodal Status

	Node-positive Cohort		Node-negative Cohort	
	Pertuzumab N=1503	Placebo N=1502	Pertuzumab N=897	Placebo N=902
Total patients with IDFS event: n (%)	202 (13.4%)	276 (18.4%)	65 (7.2%)	66 (7.3%)
Category of IDFS event: n (%)				
• Distant recurrence	131 (8.7%)	184 (12.3%)	18 (2.0%)	20 (2.2%)
• CNS metastases	43 (2.9%)	48 (2.9%)	8 (0.9%)	5 (0.6%)
• Locoregional BC recurrence	23 (1.5%)	39 (2.6%)	9 (1.0%)	18 (2.0%)
• Contralateral invasive BC recurrence	13 (0.9%)	16 (1.1%)	15 (1.7%)	6 (0.7%)
• Death without prior event	35 (2.3%)	37 (2.5%)	23 (2.6%)	22 (2.4%)

Hierarchy applied if a patient experiences additional IDFS event(s) within 61 days of their 1st IDFS event

APHINITY Updated Descriptive IDFS Analysis at 8.4 Years Median FU by treatment regimen

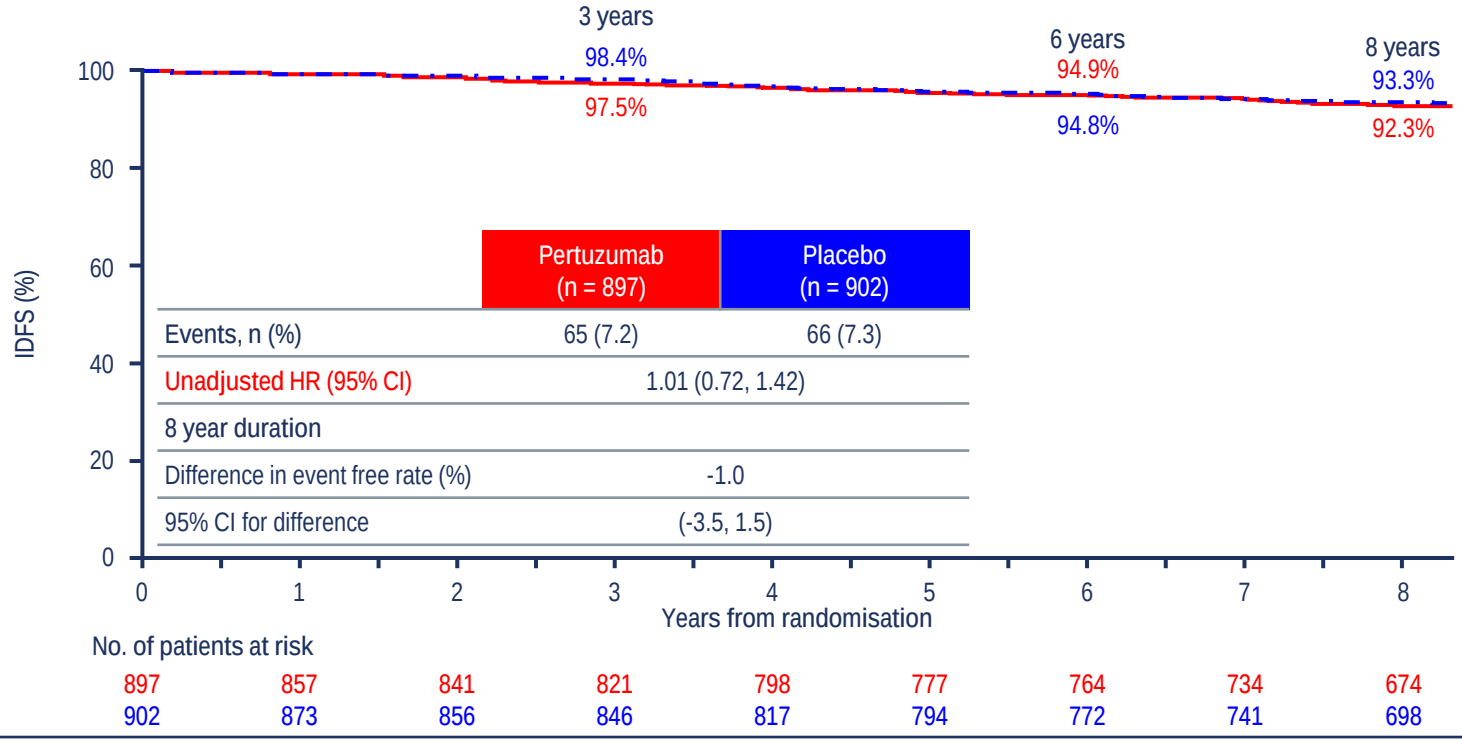
Node-positive Cohort



The node positive cohort continues to derive clear benefit from addition of pertuzumab.

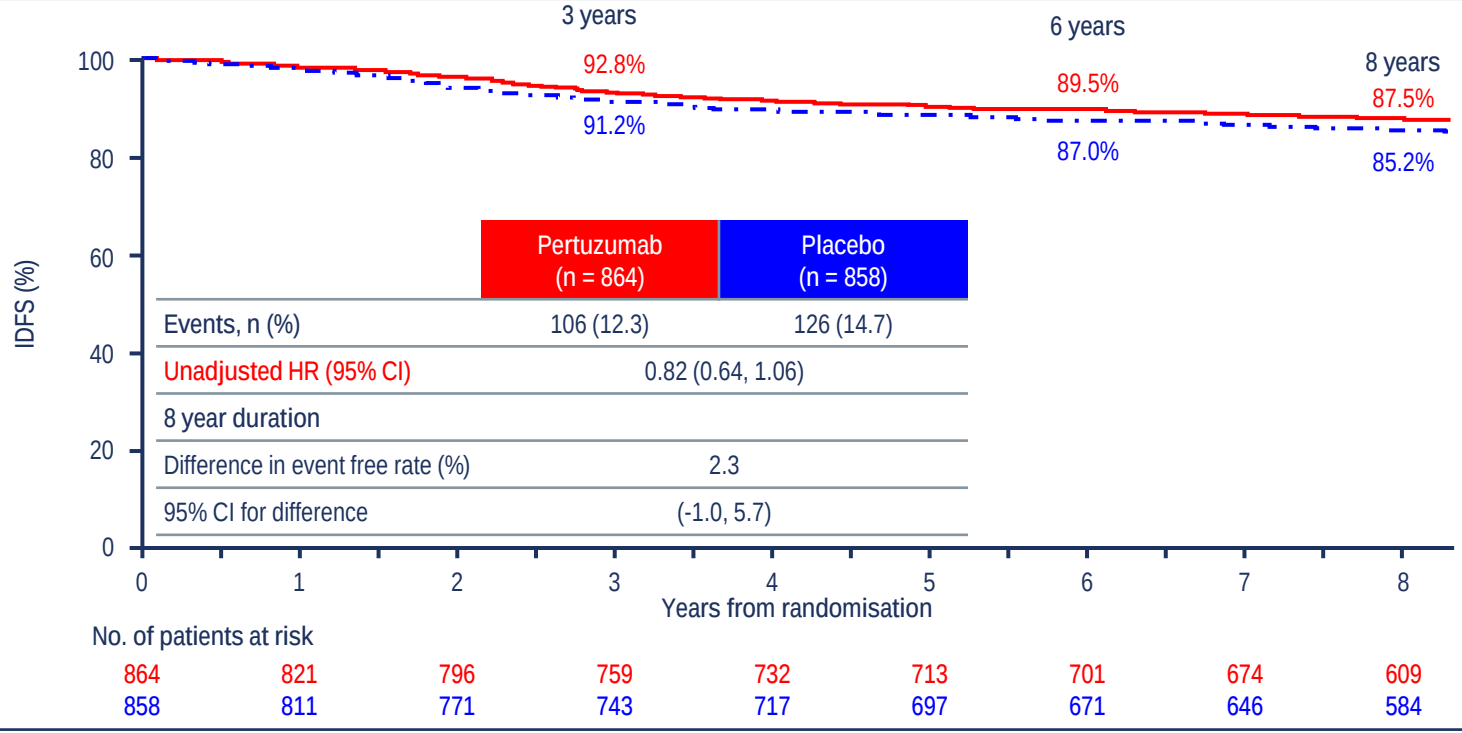
APHINITY Updated Descriptive IDFS Analysis at 8.4 Years Median FU by treatment regimen

Node-negative Cohort



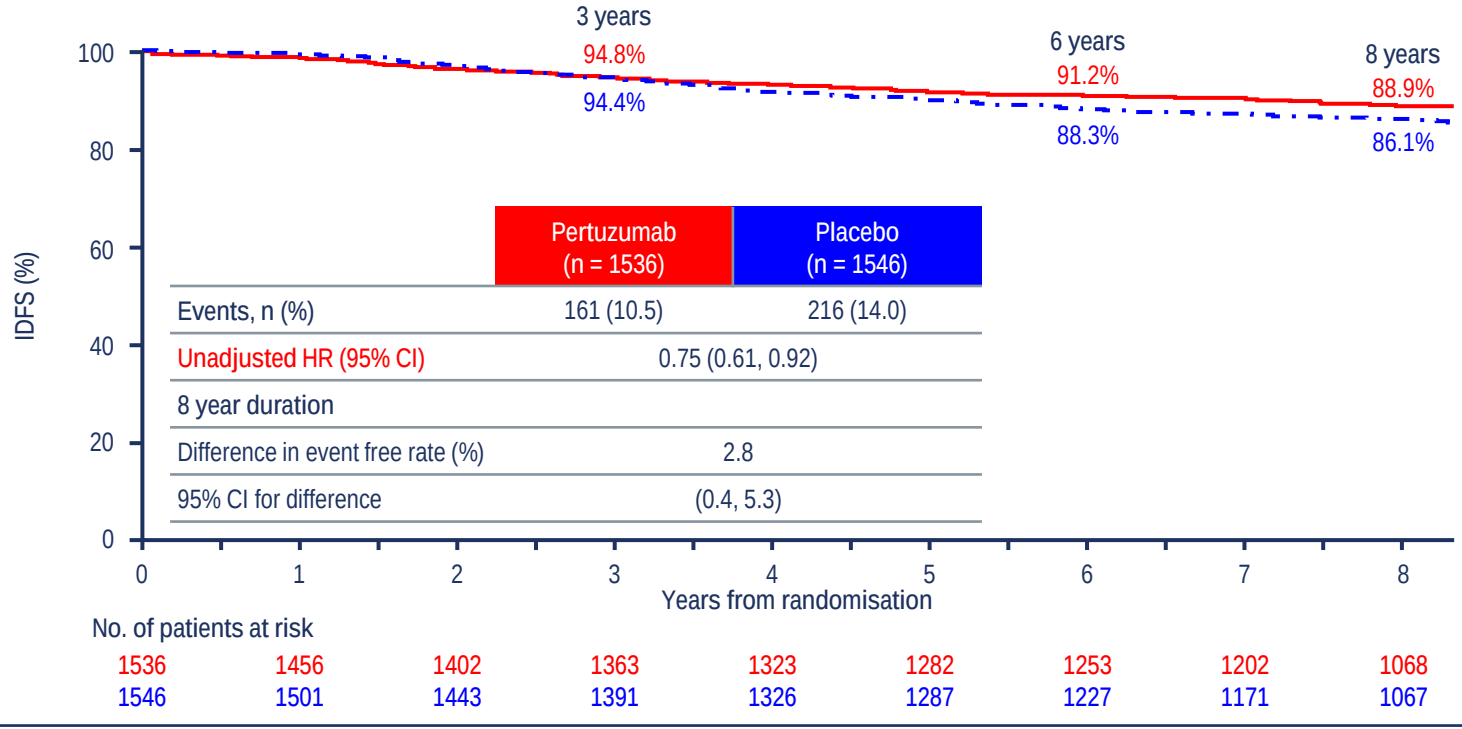
APHINITY Updated Descriptive IDFS Analysis at 8.4 Years Median FU by treatment regimen

Hormone Receptor-negative Cohort



APHINITY Updated Descriptive IDFS Analysis at 8.4 Years Median FU by treatment regimen

Hormone Receptor-positive Cohort



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APHINITY Updated Descriptive Analysis Cardiac Safety, 8.4 years Median FU

	Pertuzumab (N = 2364)	Placebo (N = 2405)
Primary cardiac event • Heart failure New York Heart Association class III or IV + LVEF drop* • Cardiac death**	19 (0.8%)	10 (0.4%)
Heart failure NYHA class class III or IV + LVEF drop*	16 (0.7%)	6 (0.2%)
Cardiac death ** Three further patients with a primary cardiac event (cardiac death) were reported; 1 in the pertuzumab arm and 2 in the placebo arm	3 (0.1%)	4 (0.2%)

No new cardiac safety issues emerged.

*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.

APHINITY Updated Descriptive Analysis Cardiac Safety by Chemotherapy Cohort, 8.4 years median FU

	Anthracycline Cohort		Non-Anthracycline Cohort	
	Pertuzumab (N = 1834)	Placebo (N = 1894)	Pertuzumab (N = 528)	Placebo (N = 510)
Primary cardiac event • Heart failure New York Heart Association class III or IV + LVEF drop* • Cardiac death**	17 (0.9%)	9 (0.5%)	2 (0.4%)	1 (0.2%)
Heart failure NYHA class class III or IV + LVEF drop*	14 (0.8%)	5 (0.3%)	2 (0.4%)	1 (0.2%)
Cardiac death **	3 (0.2%)	4 (0.2%)	0	0

*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.

CONCLUSIONS

APHINITY 3rd Interim Analysis of Overall Survival

Fewer deaths seen in pertuzumab (P) compared to placebo arm.

- After 8.4 years median FU, 8-year OS per cents were 92.7% (P) vs. 92.0% (placebo).
- 0.7% difference (95% CI [-0.8, 2.3]; hazard ratio 0.83 [0.68, 1.02]).
- The trend towards a benefit of OS was influenced by the node positive cohort (8-year OS per cents 91.1% vs 89.2%; hazard ratio 0.80).
- Follow-up is very important to determine OS benefit of P.

Definitive OS analysis
Event-driven, after 640 deaths

APHINITY Updated Descriptive Analysis of IDFS and Safety

The node-positive cohort derives benefit from adding pertuzumab.

- An improvement in IDFS at 8 years of 4.9% (86.1% vs. 81.2%)
- Hazard ratio 0.72 (0.60-0.87)
- The node – negative cohort does well without the addition of pertuzumab; IDFS 93.3% at 8 years; OS 96.4% at 8 years

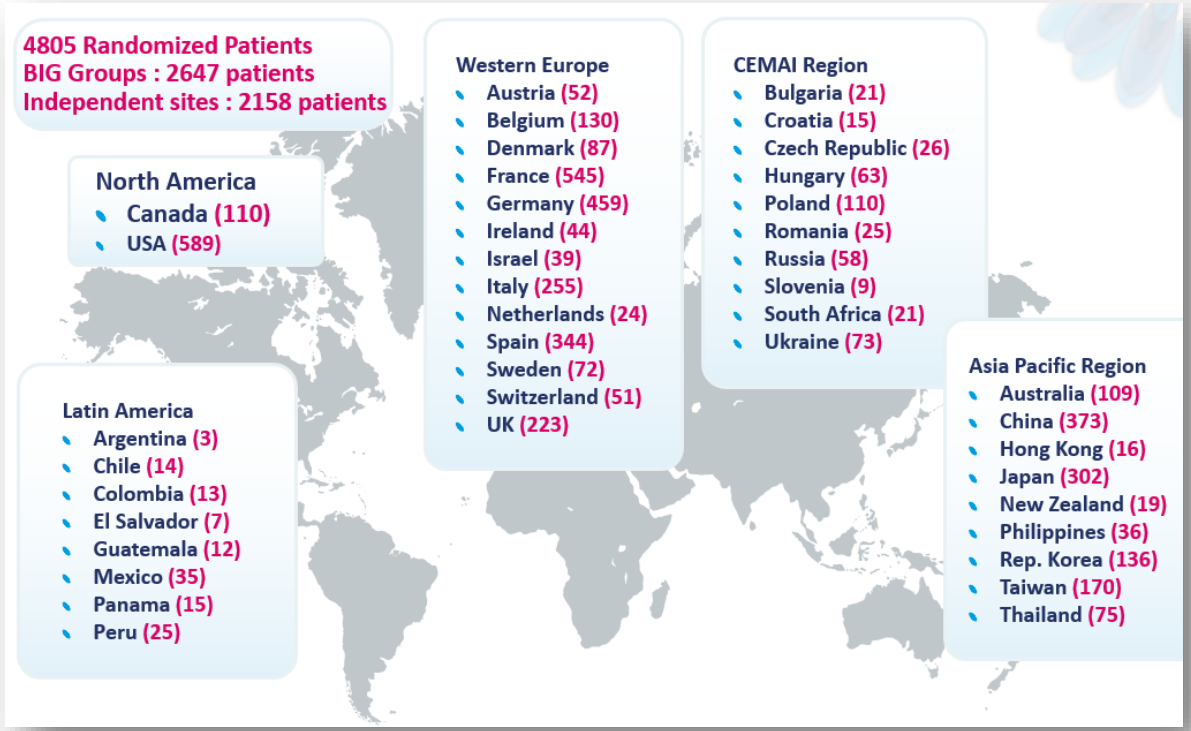
Hormone receptor status should not guide pertuzumab treatment decisions.

- 0.82 (0.64 – 1.06) – Hazard ratio for HR – negative cohort
- 0.75 (0.61 – 0.92) – Hazard ratio for HR – positive cohort

No new cardiac safety issues emerged at this interim analysis.

- Incidence of primary cardiac event remains <1% in both arms (0.8% P vs. 0.4% placebo)
- Three additional cardiac deaths reported

Thank you to our patients and their families…



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Thank you to Angela Hackworthy (Synaptic Digital) for supporting the formatting of slides for this presentation.

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Thank you!

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