Pertuzumab Trastuzumab e chemioterapia nel setting adiuvante- le evidenze scientifiche

-

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Overall survival for HER2+ trastuzumab-treated early disease similar to or better than HER2-normal

Study	Median F/U	HER2+/+tras	HER2+/-tras	HER2-
BCIRG 005[1]/006[2]	10 years	(1841/2149) **86%**	(870/1073) 81%	(2647/3298) **80%**
NOAH[3]	5 years	(87/117) **74%**	(74/118) 63%	(75/99) **76%**
Italian Registry[4]	4.1 years	(52/53) **98%**	(140/161) 87%	(1108/1186) **93%**
GeparQuattro[5]	5.4 years	(392/446) **88%**		(889/1049) **85%**
FinHer	5 years	(12/115) **90%**	(21/116) 82%	(61/778) **92%**

1. Mackey J, et al. Annals Oncol 2016;27:1041-1047
2. Slamon DJ, et al. Cancer Res 2015;76:Abs S5-04
3. Gianni L, et al. Lancet Oncol 2014;15:640-647
4. Musolino A, et al. Cancer, 2011;117:1837-1846
5. Von Minckwitz G, et al. Ann Oncol 2013;25:81-89

Mod da Hurvitz S, ASCO 2017

Four large initial adjuvant trastuzumab trials

Trial	Arms	N	DFS	OS	Median F/U	Crossover
NCCTG N9831 **NSABP B-31** Perez J Clin Oncol 2014	**N9831**	3351	10-year	10-year	8 year	20%
	AC→wP (Arm A)		Groups C/2 vs A/1	Groups C/2 vs A/1		
	AC→wP→wH (Arm B)					
	AC→wP→wH (Arm C)			84% AC-PH		
	B-31		73% AC-PH	75% AC-P		
	AC→P (Group 1)		62% AC-P	**HR 0.63**		
	AC→PwH (Group 2)		**HR 0.60**			
HERA Goldhirsch Lancet Oncol 2013:82:1021	**Std Chemo then**	5090	72% H 1 yr	84% H 1 yr	8 year	52%
	Observ vs.		66% obs	79% obs		
	H X 1 yr vs.					
	H X 2 yr		**HR 0.76**	**HR 0.76**		
BCIRG-006 Slamon Cancer Res 2016;76 (4 Suppl) Abs PD5-01	AC→T	3222	75% AC-TH	86% AC-TH	10.3 year	3.1%
	AC→TH		73% TCH	83% TCH		
	THC		68% AC-T	79% AC-T		
			HR: 0.72 ACTH	**HR 0.63 ACTH**		
			0.77 TCH	**0.76 TCH**		

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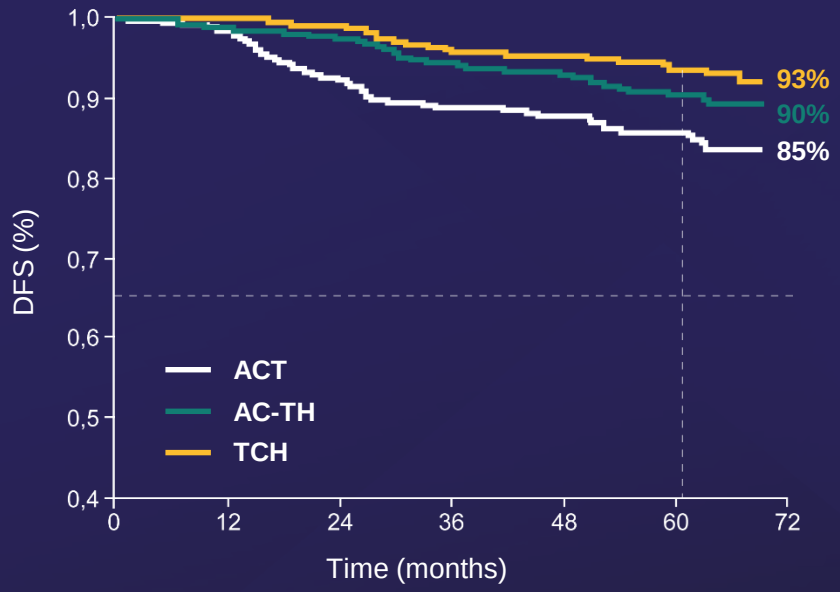
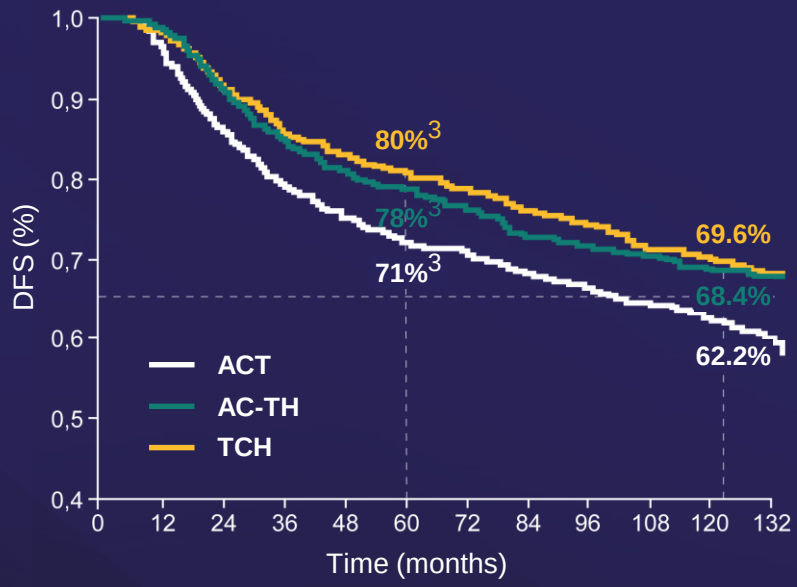
BCIRG 006 subgroups N

BCIRG 006: DFS in **node-negative** disease after 5 years' follow-up[1]



BCIRG 006: DFS in **node-positive** disease after 10 years' follow-up[2]

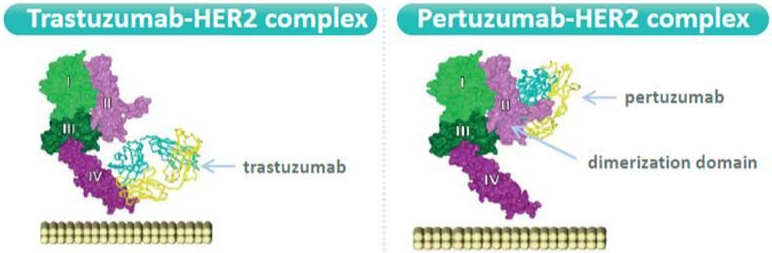


AC, doxorubicin/cyclophosphamide;
C, carboplatin; H, Herceptin; T, docetaxel

1. Slamon D, et al. SABCS 2009 2. Slamon D, et al. SABCS 2015
3. Slamon D, et al. N Engl J Med. 2011;365:1273-1283

APHINITY: Rationale

- Pertuzumab has complementary mechanisms of action with trastuzumab.[1-3]
  - Trastuzumab binds close to the transmembrane domain, inhibiting HER2 dimerization
  - Pertuzumab binds to the dimerization domain, inhibiting HER2 hetero-dimerization with other HER family receptors [4-7]
- In patients with HER2-positive metastatic breast cancer pertuzumab added to trastuzumab and docetaxel significantly improved both progression-free and overall survival.[8,9]
- In the neoadjuvant setting, the addition of pertuzumab to trastuzumab plus docetaxel significantly improved pathological complete response rate.[10,11]
- Recurrences of HER2-positive early breast cancer still occur for a significant proportion of patients in the long-term.[12]



[1]Baselga J, Nat Rev Cancer 2009; [2]Scheuer W, Cancer Res 2009; [3]Hubbard SR Cancer Cell 2005; [4]Molina MA et al. Cancer Res 2001; [5]Junttila TT et al. Cancer Cell 2009; [6]Franklin MC et al. Cancer Cell 2004; [7]Agus DB et al. Cancer Cell 2002
[8]Baselga J, NEJM 2012; [9]Swain SM, NEJM 2015; [10]Swain SM, Oncologist 2013; [11]Gianni L, Lancet Oncol 2012; [12]Cameron D, Lancet 2017

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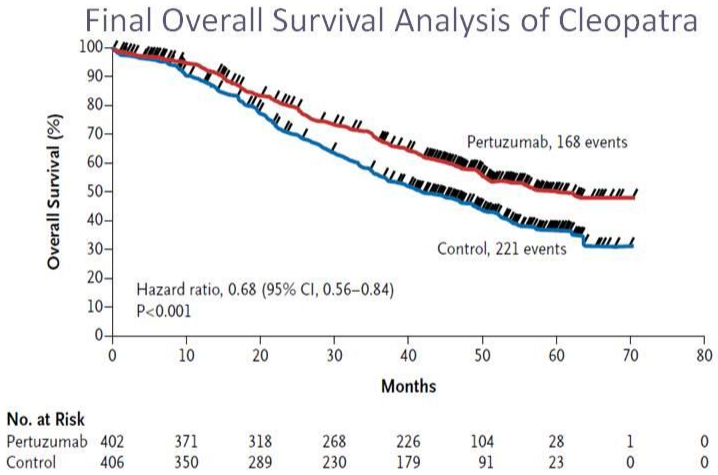

[1]Baselga J, Nat Rev Cancer 2009; [2]Scheuer W, Cancer Res 2009; [3]Hubbard SR Cancer Cell 2005; [4]Molina MA et al. Cancer Res 2001; [5]Junttila TT et al. Cancer Cell 2009; [6]Franklin MC et al. Cancer Cell 2004; [7]Agus DB et al. Cancer Cell 2002
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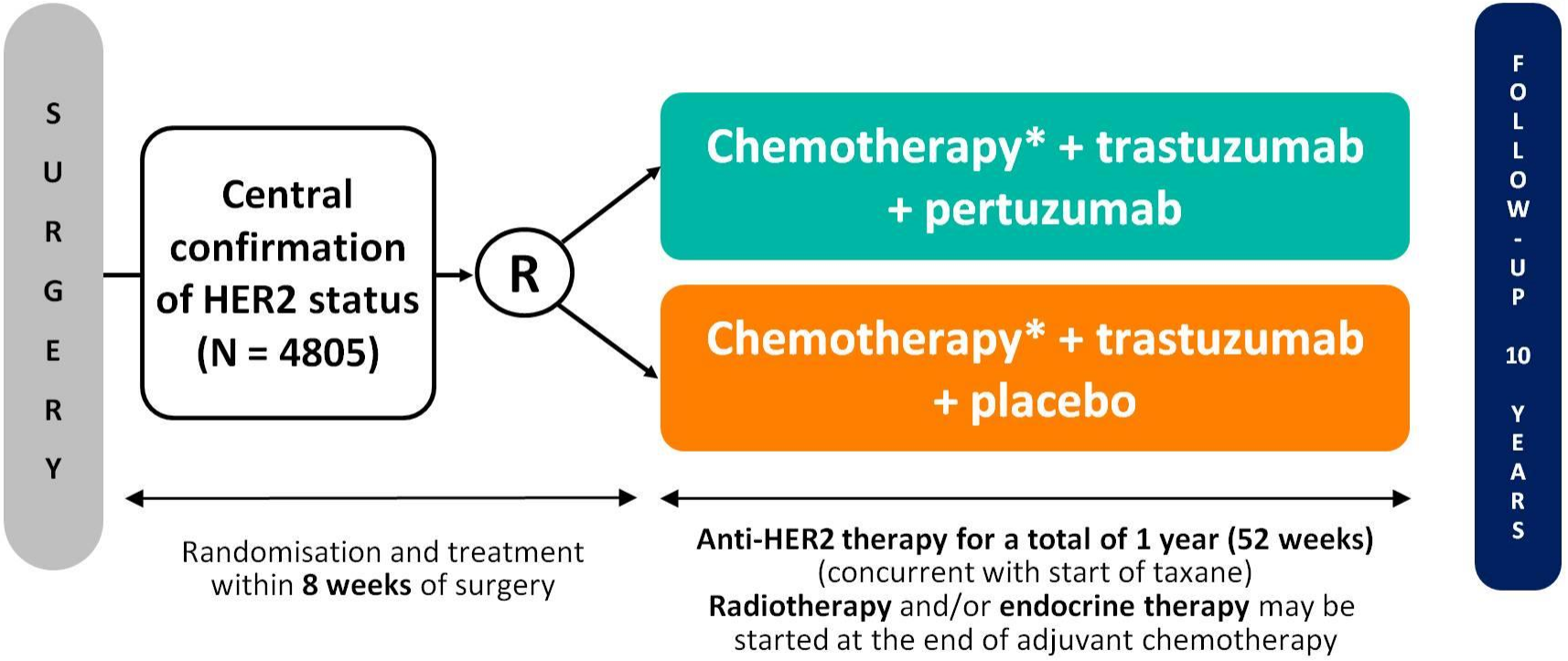
APHINITY: Trial Design



*A number of standard anthracycline-taxane-sequences or a non-anthracycline (TCH) regimen were allowed

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APHINITY: Key Eligibility Criteria

Inclusion Criteria

- HER2-positive status confirmed by a central review (IHC 3+ or FISH-/CISH-positive)*
- Node-positive, any tumour size except T0
- Node-negative
  - Tumour size >1 cm

  OR
  - For tumours >0.5 and ≤1 cm, at least 1 of:
    - histological/nuclear grade 3

    OR
    - ER- and PR-negative

    OR
    - age <35
- Baseline LVEF ≥55%

Exclusion Criteria

- Prior invasive breast cancer
- Non-operable breast cancer
- Metastatic disease (stage IV)
- Previous non-breast malignancies (except for the following: carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, and basal cell and squamous cell carcinomas of the skin)
- Previous or current anti-cancer therapy or previous radiotherapy for any malignancy
- Cardiac dysfunction or serious medical conditions

* Wolff A et al, J Clin Oncol 2013

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APHINITY: Primary Endpoint: Invasive Disease-Free Survival (IDFS)

Time from randomisation until the date of the first occurrence of one of the following events:

- Ipsilateral invasive breast tumour recurrence
- Ipsilateral local-regional invasive breast cancer recurrence
- Distant recurrence
- Contralateral invasive breast cancer
- Death attributable to any cause including breast cancer, non-breast cancer, or unknown cause

This IDFS definition

- **was the FDA's recommended definition for a trial intended to support a regulatory filing**
- **differs from the STEEP definition[1] of IDFS since it excludes second primary non-breast cancers as event**

[1] Hudis CA, J Clin Oncol 2007

APHINITY: Secondary Endpoints

- IDFS according to STEEP[1] definition, including second primary non-breast cancer
- Recurrence-free interval
- Distant recurrence-free interval
- Disease-free interval
- Overall survival
- Safety
- Cardiac safety
- Health-related quality of life

[1] Hudis CA, J Clin Oncol 2007

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APHINITY: Statistical Assumptions

	EXPECTED 3-year IDFS rate Placebo vs. Pertuzumab
HR=0.75	89.2% vs. 91.8% (Δ=2.6%)

- Placebo arm IDFS rate was based on BCIRG 006 data[1], assuming a 35% / 65% node-negative / node-positive split
- 379 events and 4800 patients required for 80% power and alpha of 5%

[1] Slamon D, NEJM 2011

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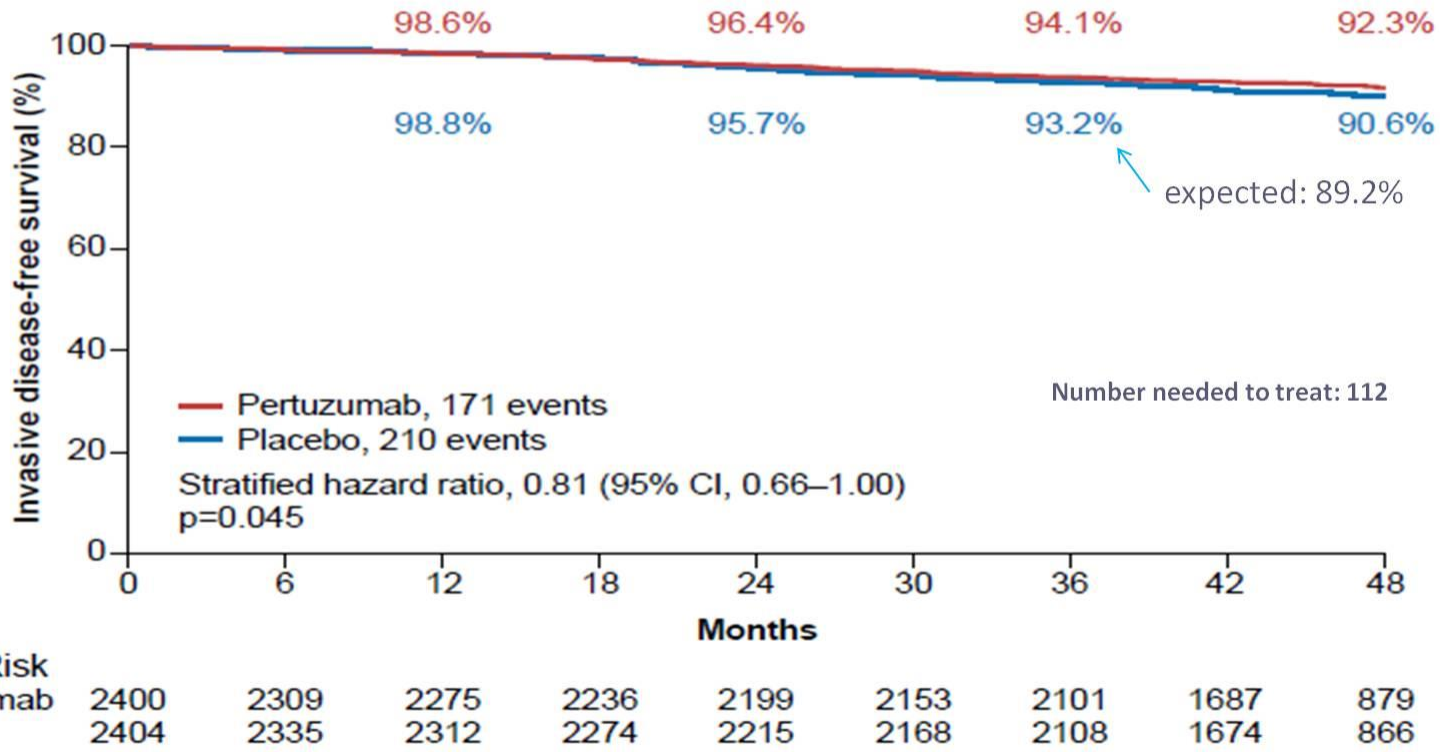
APHINITY: Randomization Stratification Factors by Treatment

	Pertuzumab n=2400	Placebo n=2404*
Nodal status, n (%)		
0 positive nodes and T ≤1 cm*	90 (3.8)	84 (3.5)
0 positive nodes and T >1 cm*	807 (33.6)	818 (34.0)
1–3 positive nodes	907 (37.8)	900 (37.4)
≥ 4 positive nodes	596 (24.8)	602 (25.0)
Adjuvant chemotherapy regimen (randomised), n (%)		
Anthracycline-containing regimen	1865 (77.7)	1877 (78.1)
Non-anthracycline-containing regimen	535 (22.3)	527 (21.9)
Hormone receptor status (central), n (%)		
Negative (ER- and PgR-negative)	864 (36.0)	858 (35.7)
Positive (ER- and/or PgR-positive)	1536 (64.0)	1546 (64.3)
Geographical region, n (%)		
USA	296 (12.3)	294 (12.2)
Canada/Western Europe/Australia – New Zealand/South Africa	1294 (53.9)	1289 (53.6)
Eastern Europe	200 (8.3)	200 (8.3)
Asia Pacific	550 (22.9)	557 (23.2)
Latin America	60 (2.5)	64 (2.7)
Protocol Version, n (%)		
Protocol A	1828 (76.2)	1827 (76.0)
Protocol Amendment B	572 (23.8)	577 (24.0)

* One patient was excluded from the ITT population due to her falsification of personal information

APHINITY: Intent-to-Treat Primary Endpoint Analysis Invasive Disease-free Survival



No. at Risk									
Pertuzumab	2400	2309	2275	2236	2199	2153	2101	1687	879
Placebo	2404	2335	2312	2274	2215	2168	2108	1674	866

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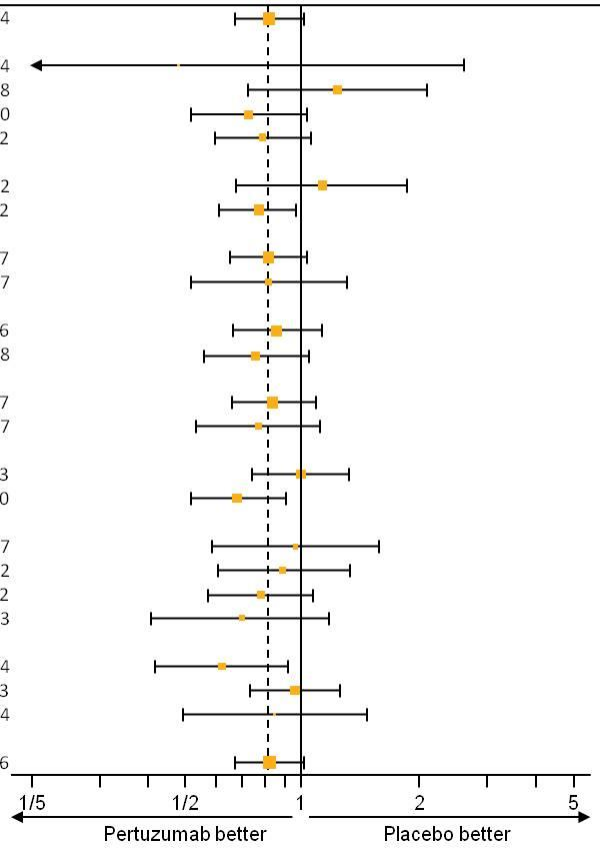
APHINITY: Summary of first Occurrence of an IDFS Event

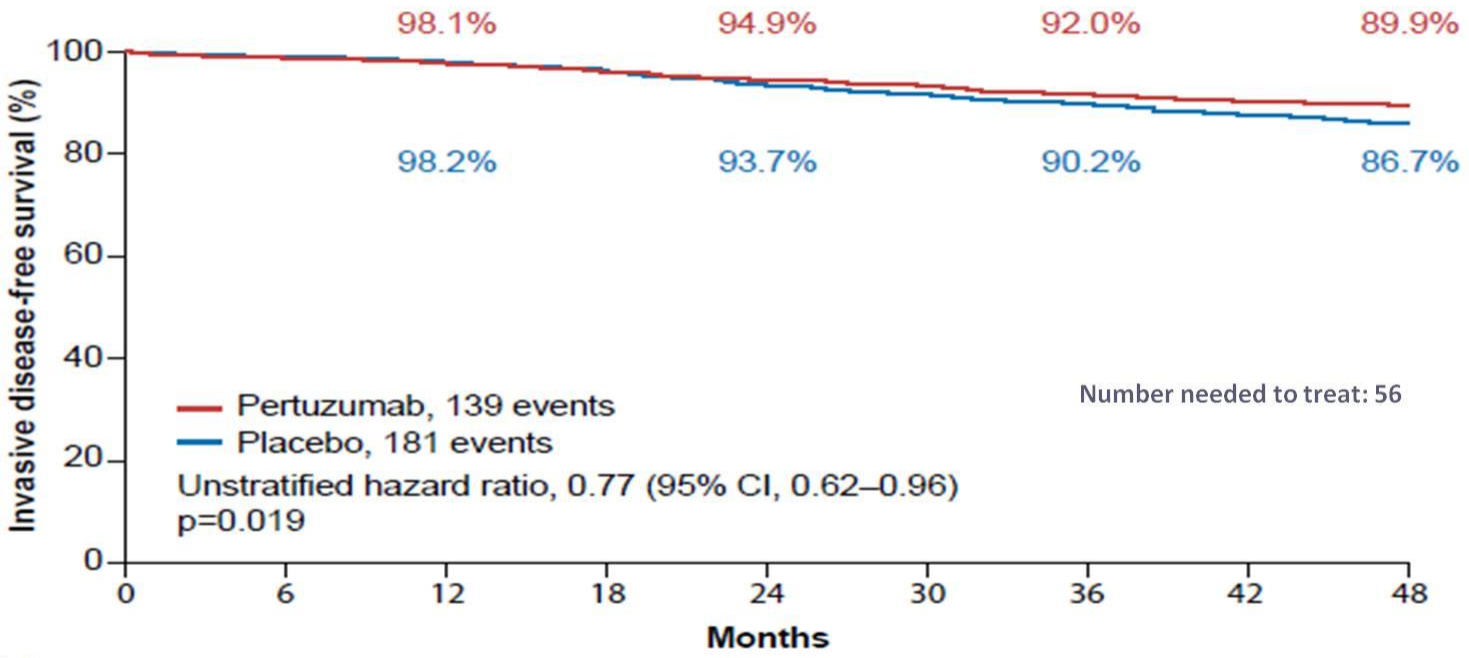
	Pertuzumab n=2400	Placebo n=2404
Total patients with IDFS event, n (%)	171 (7.1)	210 (8.7)
Category of first IDFS event, n (%)		
Distant recurrence	112 (4.7)	139 (5.8)
Locoregional recurrence	26 (1.1)	34 (1.4)
Contralateral breast cancer	5 (0.2)	11 (0.5)
Death without prior event	28 (1.2)	26 (1.1)
Site of first distant recurrence n (%)		
Lung/liver/pleural effusion	43 (1.8)	61 (2.5)
CNS	46 (1.9)	45 (1.9)
Other	9 (0.4)	9 (0.4)
Bone	21 (0.9)	30 (1.2)

APHINITY: IDFS Forest Plot by Subgroups

Subgroup	No. of Events / No. of Patients: Pertuzumab	No. of Events / No. of Patients: Placebo	Unstratified Hazard Ratio (95%CI)	3-year IDFS Rate, %: Pertuzumab	3-year IDFS Rate, %: Placebo	Interaction test p-value
All patients	171 / 2400	210 / 2404	0.82 (0.67–1.00)	94.1	93.2	NA
Nodal status						
0 positive nodes, tumor ≤1cm	2 / 90	4 / 84	0.48 (0.09–2.60)	97.7	97.5	0.374
0 positive nodes, tumor >1cm	30 / 807	25 / 818	1.23 (0.72–2.10)	97.5	98.5	
1–3 positive nodes	55 / 907	75 / 900	0.73 (0.52–1.04)	94.9	93.8	
≥4 positive nodes	84 / 596	106 / 602	0.79 (0.59–1.05)	87.5	84.7	
0 positive nodes	32 / 897	29 / 902	1.13 (0.68–1.86)	97.5	98.4	0.169
≥1 positive nodes	139 / 1503	181 / 1502	0.77 (0.62–0.96)	92.0	90.2	
Adjuvant chemotherapy regimen						
Anthracycline	139 / 1865	171 / 1877	0.82 (0.66–1.03)	93.8	93.0	0.996
Non-anthracycline	32 / 535	39 / 527	0.82 (0.51–1.31)	94.9	94.0	
Central hormone receptor status						
Positive (ER- and/or PgR-positive)	100 / 1536	119 / 1546	0.86 (0.66–1.13)	94.8	94.4	0.543
Negative (ER- and PgR-negative)	71 / 864	91 / 858	0.76 (0.56–1.04)	92.8	91.2	
Protocol version						
Protocol A	120 / 1828	143 / 1827	0.84 (0.66–1.08)	94.7	94.1	0.686
Protocol Amendment B	51 / 572	67 / 577	0.77 (0.53–1.11)	91.9	90.6	
Menopausal status at screening						
Pre-menopausal	93 / 1152	96 / 1173	0.99 (0.75–1.32)	93.5	93.7	0.069
Post-menopausal	78 / 1242	113 / 1220	0.68 (0.51–0.91)	94.5	92.7	
Age group (years)						
<40	30 / 326	32 / 327	0.96 (0.59–1.59)	93.4	93.1	0.781
40–49	48 / 708	53 / 702	0.89 (0.60–1.32)	94.5	94.3	
50–64	69 / 1051	91 / 1082	0.78 (0.57–1.07)	94.3	93.3	
≥65	24 / 315	34 / 293	0.70 (0.41–1.17)	92.9	90.6	
Tumor size (cm)						
<2	41 / 977	64 / 944	0.62 (0.42–0.92)	97.0	94.6	0.203
2–<5	108 / 1273	115 / 1283	0.96 (0.74–1.24)	92.5	93.0	
≥5	22 / 147	31 / 174	0.85 (0.49–1.47)	87.5	87.5	
Sex						
Female	171 / 2397	209 / 2396	0.82 (0.67–1.01)	94.1	93.2	NA



APHINITY: Node-positive Subgroup



No. at Risk									
Pertuzumab	1503	1444	1419	1387	1358	1327	1283	912	423
Placebo	1502	1453	1439	1408	1359	1319	1264	882	405

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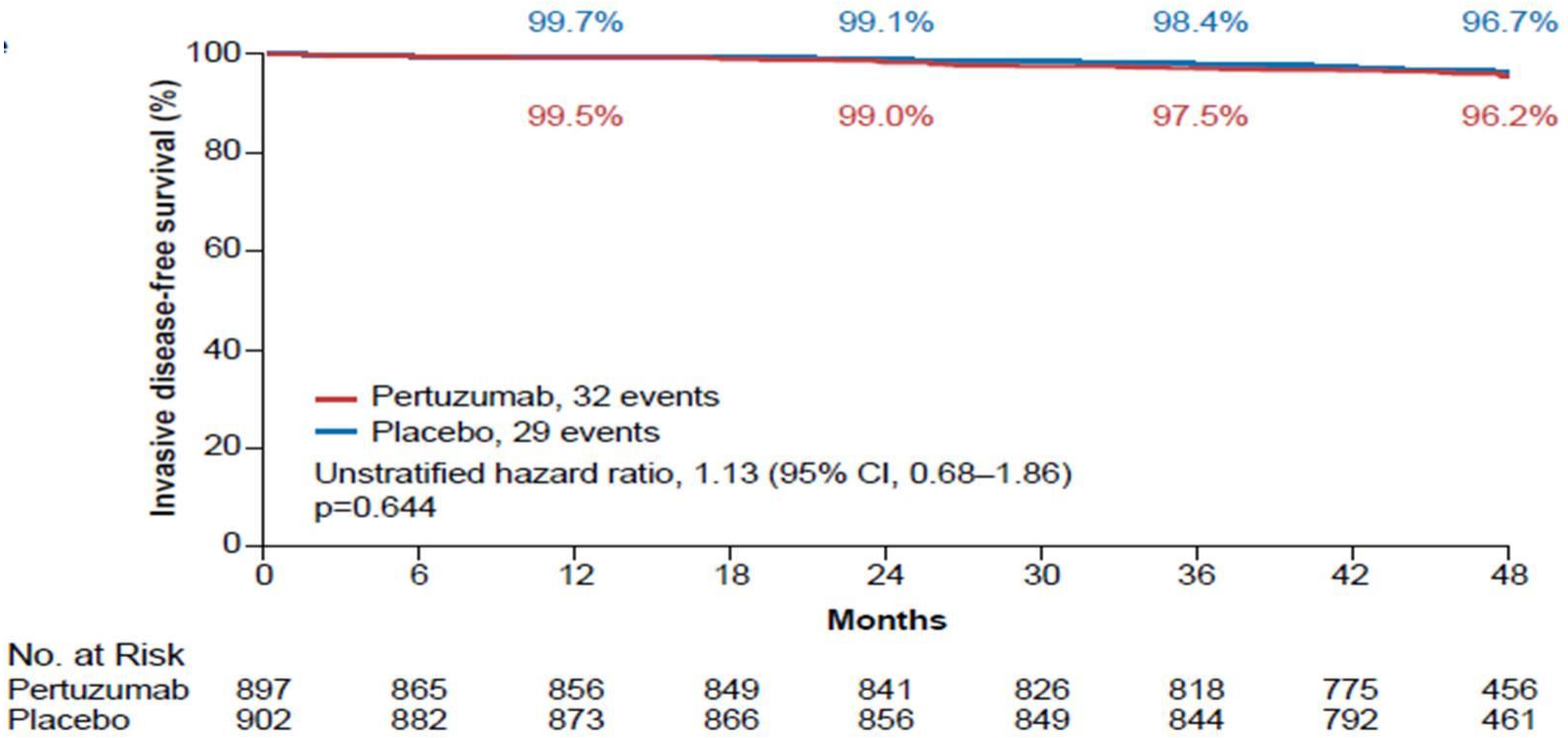
APHINITY: Node-negative Subgroup



No. at Risk

Pertuzumab	897	865	856	849	841	826	818	775	456
Placebo	902	882	873	866	856	849	844	792	461

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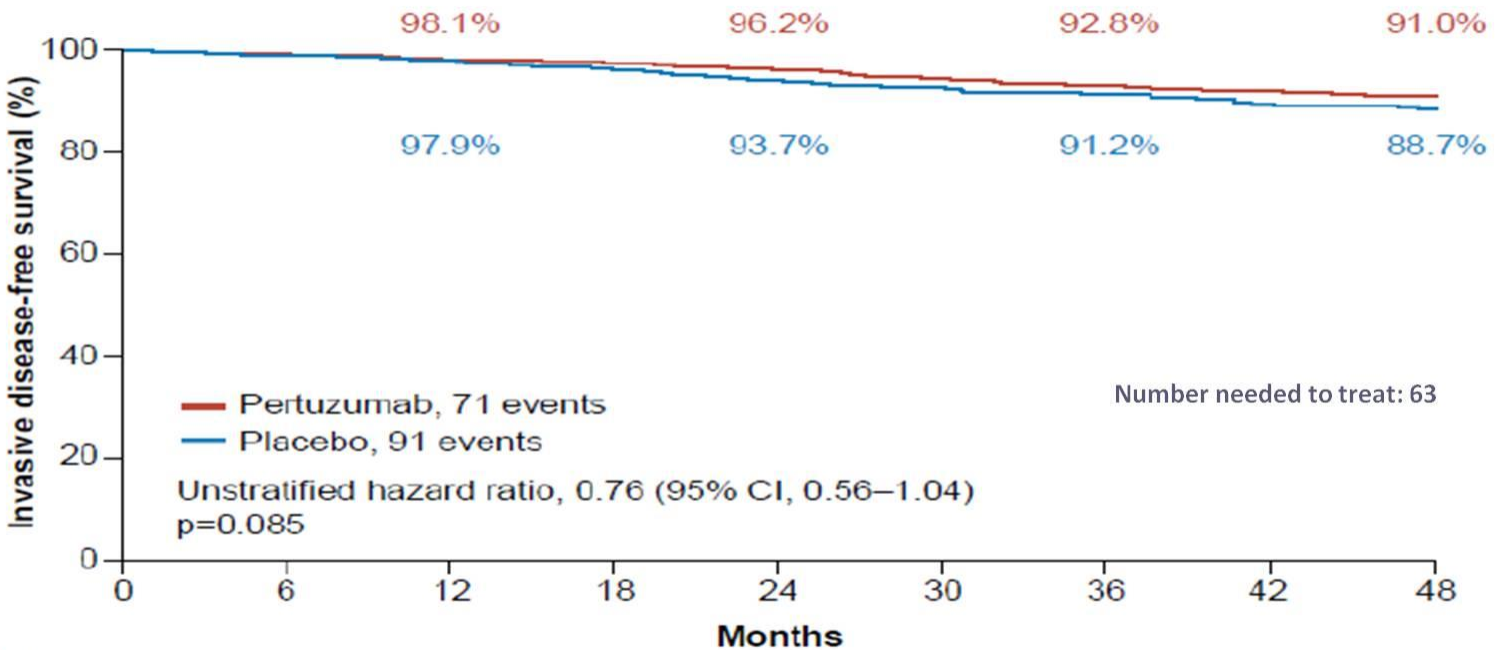
APHINITY: Hormone Receptor-negative Subgroup



No. at Risk									
Pertuzumab	864	836	821	813	797	774	755	600	314
Placebo	858	827	811	793	771	758	730	569	302

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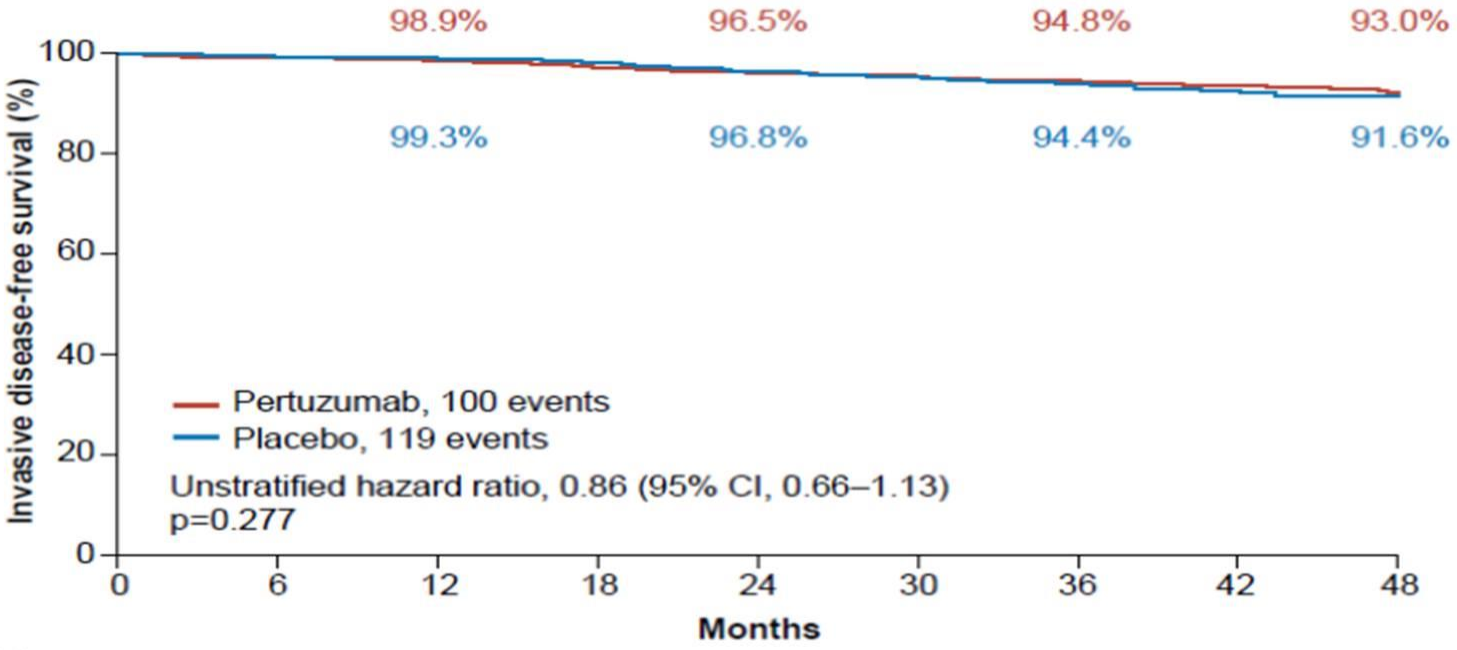
APHINITY: Hormone Receptor-positive Subgroup



No. at Risk									
Pertuzumab	1536	1473	1454	1423	1402	1379	1346	1087	565
Placebo	1546	1508	1501	1481	1444	1410	1378	1105	564

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APHINITY: Secondary Efficacy Endpoints

3-year	Pertuzumab n=2400	Placebo n=2404	Hazard ratio (95% CI)	p value
IDFS (primary endpoint), %	94.1	93.2	**0.81 (0.66, 1.00)**	**0.045**
Secondary efficacy endpoints, %				
IDFS incl. second primary non-BC events (STEEP definition)	93.5	92.5	**0.82 (0.68, 0.99)**	**0.043**
Disease-free interval	93.4	92.3	**0.81 (0.67, 0.98)**	**0.033**
Recurrence-free interval	95.2	94.3	**0.79 (0.63, 0.99)**	**0.043**
Distant recurrence-free interval	95.7	95.1	**0.82 (0.64, 1.04)**	**0.101**
Overall survival (first interim analysis)*	97.7	97.7	**0.89 (0.66, 1.21)**	**0.467**

*** 1st interim analysis at 26% of the target events for the final overall survival analysis**

APHINITY: Cardiac Endpoints

N (%)	Pertuzumab n=2364	% Treatment difference (95% CI)	Placebo n=2405
Primary cardiac endpoint	**17 (0.7)**	**0.4 (0.0, 0.8)**	**8 (0.3)**
• Heart failure NYHA III/IV + LVEF drop* • Cardiac death**	15 (0.6) 2 (0.08)		6 (0.2) 2 (0.08)
• Recovered according to LVEF	7		4
Secondary cardiac endpoint Asymptomatic or mildly symptomatic LVEF drop*	**64 (2.7)**	**-0.1 (-1.0, 0.9)**	**67 (2.8)**

*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

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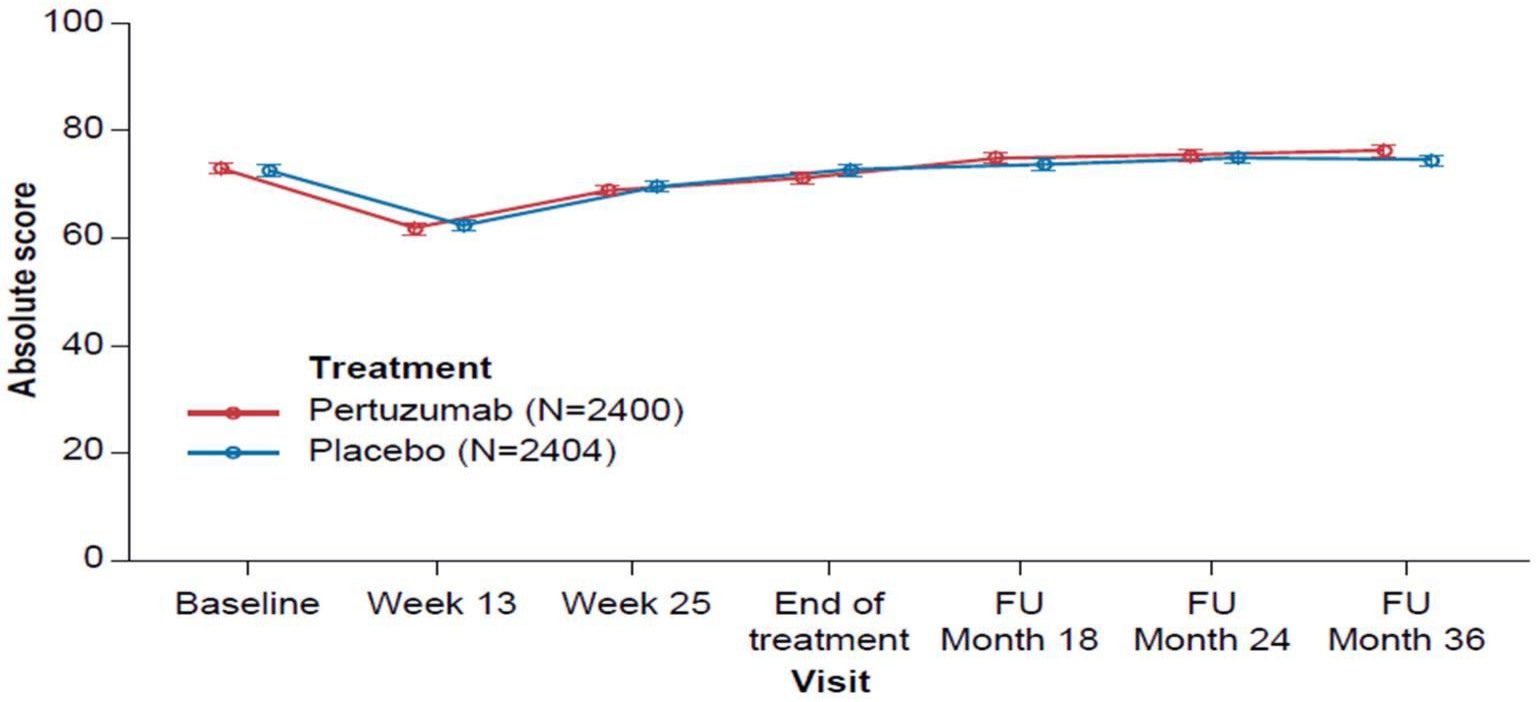
APHINITY: Common Grade ≥ 3 Adverse Events

	Pertuzumab n=2364	Placebo n=2405
Neutropenia	**385 (16.3%)**	**377 (15.7%)**
Febrile Neutropenia	**287 (12.1%)**	**266 (11.1%)**
Anaemia	**163 (6.9%)**	**113 (4.7%)**
Diarrhoea	**232 (9.8%)**	**90 (3.7%)**
- with chemotherapy and targeted therapy	232 (9.8%)	90 (3.7%)
- with targeted therapy (post-chemotherapy)	12 (0.5%)	4 (0.2%)
- with AC->T (N=1834; 1894)	137 (7.5%)	59 (3.1%)
- with TCH (N= 528; 510)	95 (18.0%)	31 (6.1%)

APHINITY: Health-related Quality of Life

Plot of Mean EORTC QLQ-C30 global health status by treatment regimen, ITT population



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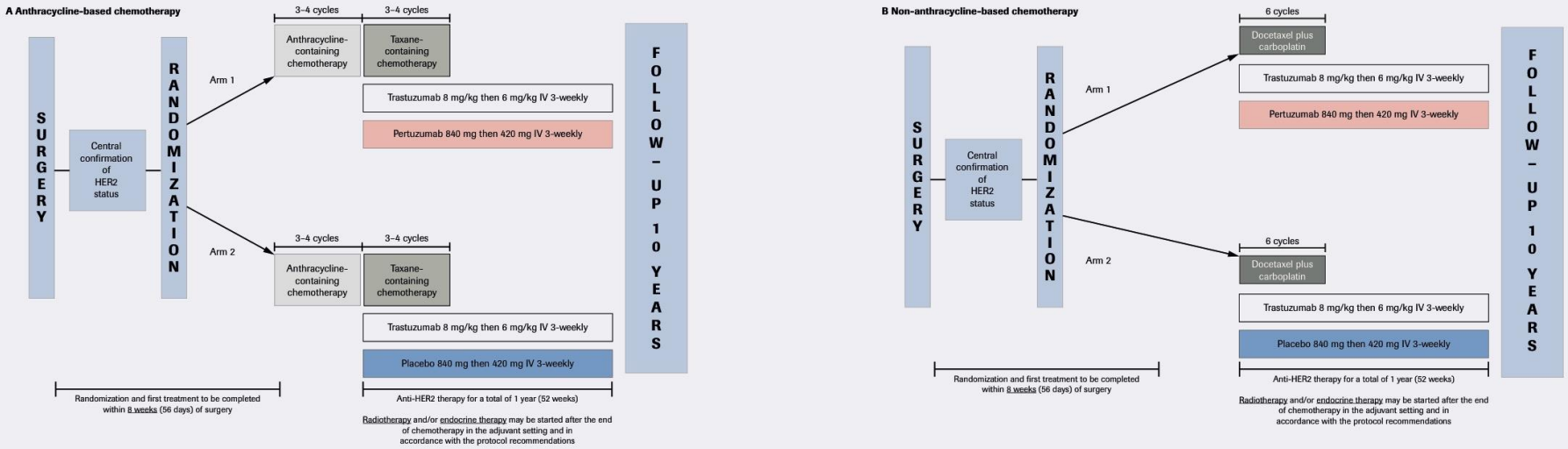
Incidenza e management della diarrea con pertuzumab e trastuzumab adiuvante in pazienti con tumore della mammella adiuvante



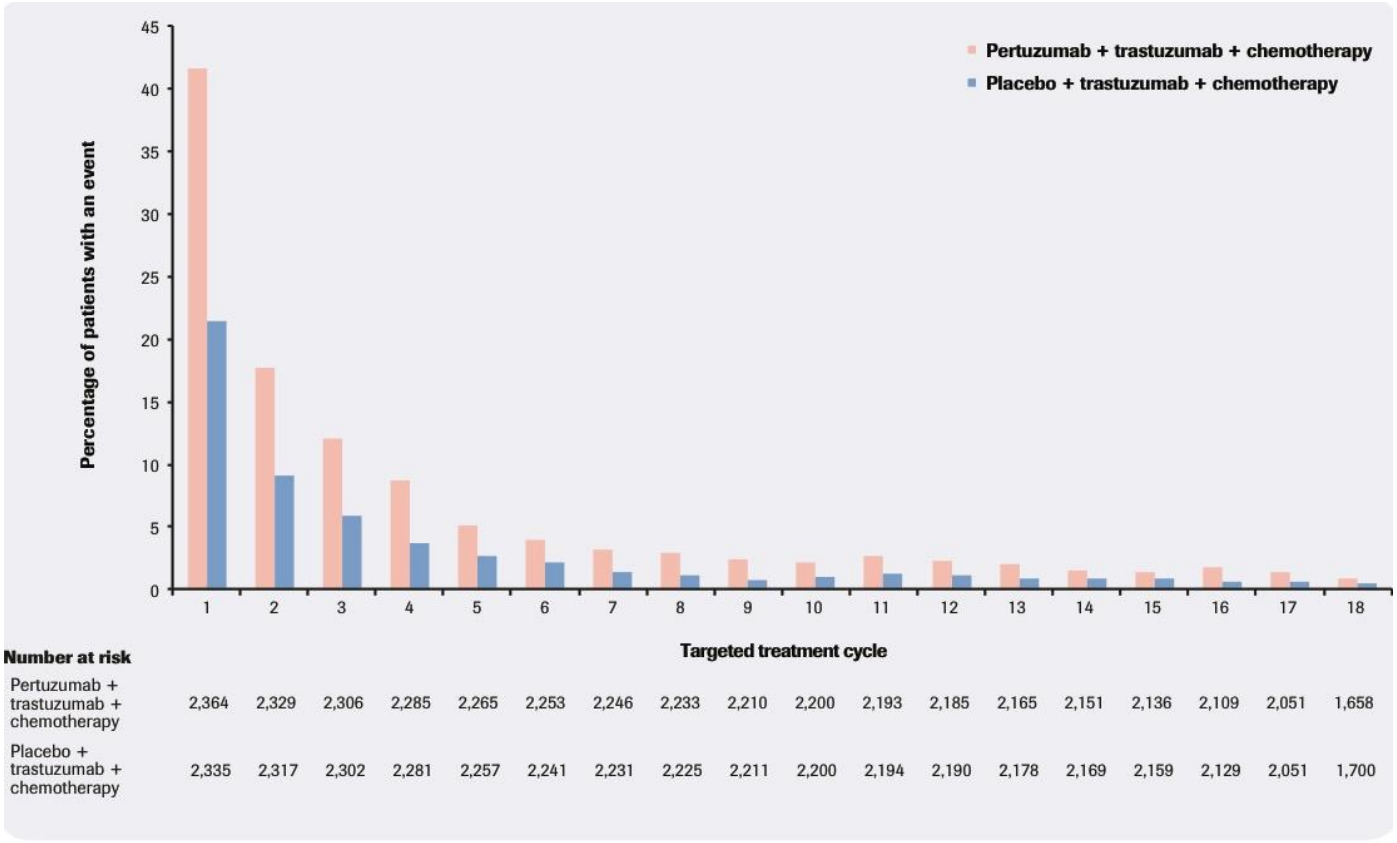
IV, intravenous.

From the New England Journal of Medicine, von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, Suter T, Arahmani A, Rouchet N, Clark E, Knott A, Lang I, Levy C, Yardley DA, Bines J, Gelber RD, Piccart M, and Baselga J, for the APHINITY Steering Committee and Investigators, Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer, 377, 122–131. Copyright © (2017) Massachusetts Medical Society. Reprinted with permission.

	Pertuzumab + trastuzumab + chemotherapy n = 2,364	Placebo + trastuzumab + chemotherapy n = 2,405
Incidence and severity		
Total number of patients with at least one event	1,683 (71.2)	1,086 (45.2)
Total number of events	3,411	1,790
Age subgroups		
< 40 years	222/325 (68.3)	144/324 (44.4)
40–64 years	1,228/1,737 (70.7)	796/1,788 (44.5)
≥ 65 years	233/302 (77.2)	146/293 (49.8)
Race subgroups		
White	1,233/1,680 (73.4)	792/1,691 (46.8)
Asian	370/580 (63.8)	248/605 (41.0)
Black	28/32 (87.5)	19/39 (48.7)
Other	47/66 (71.2)	25/68 (36.8)
NCI-CTCAE grade (highest grade per patient)		
Any grade	1,683 (71.2)	1,085 (45.1)
Grade 1	829 (35.1)	690 (28.7)
Grade 2	622 (26.3)	305 (12.7)
Grade 3	229 (9.7)	90 (3.7)
Grade 4	3 (0.1)	0
Onset and duration		
Median time (days) from first HER2-targeted treatment to onset (min–max)	7 (1–358)	10 (1–384)
Median duration (days) of each event (min–max)	8 (1–811)	6 (1–1,022)
Management		
Antidiarrheals as treatment	898 (38.0)	385 (16.0)
Dose modification of any study drug*	210 (8.9)	74 (3.1)
Dose modification of HER2-targeted treatment†	69 (2.9)	18 (0.7)
Discontinuation of any study drug	38 (1.6)	7 (0.3)
Discontinuation of HER2-targeted treatment	20 (0.8)	2 (< 0.1)

All presented data based on the preferred term "diarrhea."
Data are patients, n (%) unless specified.
* Includes dose reductions, delays, or interruptions during infusion.
† Includes dose delays or interruptions during infusion.

Incidenza della diarrea durante i differenti cicli di trattamento Anti HER2



Incidenza della diarrea in dipendenza dei regimi chemioterapici amministrati

	Anthracycline-based chemotherapy		Non-anthracycline-based chemotherapy	
	Pertuzumab + trastuzumab n = 1,834	Placebo + trastuzumab n = 1,894	Pertuzumab + trastuzumab n = 528	Placebo + trastuzumab n = 510
Incidence and severity				
Total number of patients with at least one event (%)	1,235 (67.3)	772 (40.8)	447 (84.7)	314 (61.6)
Total number of events	2,527	1,282	883	508
Total number of patients with at least one NCI-CTCAE grade ≥ 3 event (%)	137 (7.5)	59 (3.1)	95 (18.0)	31 (6.1)
Total number of NCI-CTCAE grade ≥ 3 events	147	60	113	35
Treatment period, total number of patients with at least one event (%)				
Anthracycline*	296 (16.1)	278 (14.7)	–	–
HER2-targeted therapy + taxane†	1,006 (54.9)	513 (27.1)	444 (84.1)	301 (59.0)
HER2-targeted treatment post-chemotherapy	373 (20.3)	175 (9.2)	55 (10.4)	46 (9.0)

All presented data based on the preferred term "diarrhea."
* The incidence of diarrhea is based on anthracycline-based chemotherapy only as no pertuzumab or placebo was given concurrently with an anthracycline.
† Docetaxel only in the non-anthracycline groups.

APHINITY: Conclusions

- **The APHINITY study met its primary objective**
  - **Pertuzumab reduced the risk of an IDFS event by 19% compared with placebo (HR 0.81; 95% CI 0.66, 1.00; p=0.045) at a median follow up of 45.4 months (3 years IDFS of 94.1% with pertuzumab and 93.2% with placebo)**
- Treatment effect was homogenous throughout all subgroups, however the N+ and HR-negative cohorts appeared to derive most benefit at the current point of time
  - with a relative risk reduction of 23% and 24%, respectively and
  - a 3-year IDFS absolute increase of 1.8% and 1.6% respectively
- Cardiac toxicity was low and not different between the two arms.
- The incidence of diarrhea was increased in the pertuzumab arm and occurred predominantly during chemotherapy and with TCH.
- Continued follow up for up to 10 years is important for overall survival, longer-term IDFS and safety analyses. Next analysis will be time-driven in 2.5 years.

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