INSTITUT
JULES BORDET
INSTITUUT

Adjuvant and Extended-Adjuvant Therapy for Patients with Localized HER2-Positive Breast Cancer

Martine J Piccart-Gebhart, MD, PhD
Scientific Director
Jules Bordet Institute
Université Libre de Bruxelles
Brussels, Belgium

BIG
Breast International Group

ULB iris

Disclosures

Advisory Committee and Scientific Boards	Oncolytics Biotech Inc, Radius Health Inc
Consulting Agreements	AstraZeneca Pharmaceuticals LP, Camel-IDS, Crescendo Biologics, Debiopharm Group, G1 Therapeutics, Genentech, HUYA Bioscience International, Immunomedics Inc, Lilly, Menarini Group, Merck Sharp & Dohme Corp, Novartis, Odonate Therapeutics, PeriphaGen Inc, Pfizer Inc, Roche Laboratories Inc, Seattle Genetics
Contracted Research	AstraZeneca Pharmaceuticals LP, Genentech, Lilly, Merck Sharp & Dohme Corp, Novartis, Pfizer Inc, Radius Health Inc, Roche Laboratories Inc, Servier, Synthon

Case Presentation: Dr Brufsky

This is a 60-year-old woman who presented with a 1.5 cm left breast mass. Ultrasound guided core biopsy was remarkable for IDC, ER 50% PR 0% HER2 3+ by IHC. She underwent LSM SLNB which demonstrated a 1.3 cm IDC ER 50% PR 0% HER2 3+ by IHC, with 1 of 3 SLN positive for a 0.6 cm metastasis. Clinically she is without evidence of metastatic disease, and echo ER is 58%.

Questions:

1. Would you give her TCH (or AC-TH) or TCHP or (AC-THP)?
2. Would you give her adjuvant neratinib?

Case Presentation: Dr Carey

- A 45-year-old woman presents with an ER-negative, HER2-positive, node-negative 8.5 cm DCIS with 0.6-cm of IDC.
- Enrolled on the Phase II ATEMPT trial comparing adjuvant T-DM1 versus paclitaxel/trastuzumab; randomized to T-DM1
- Ran the Boston Marathon while receiving T-DM1

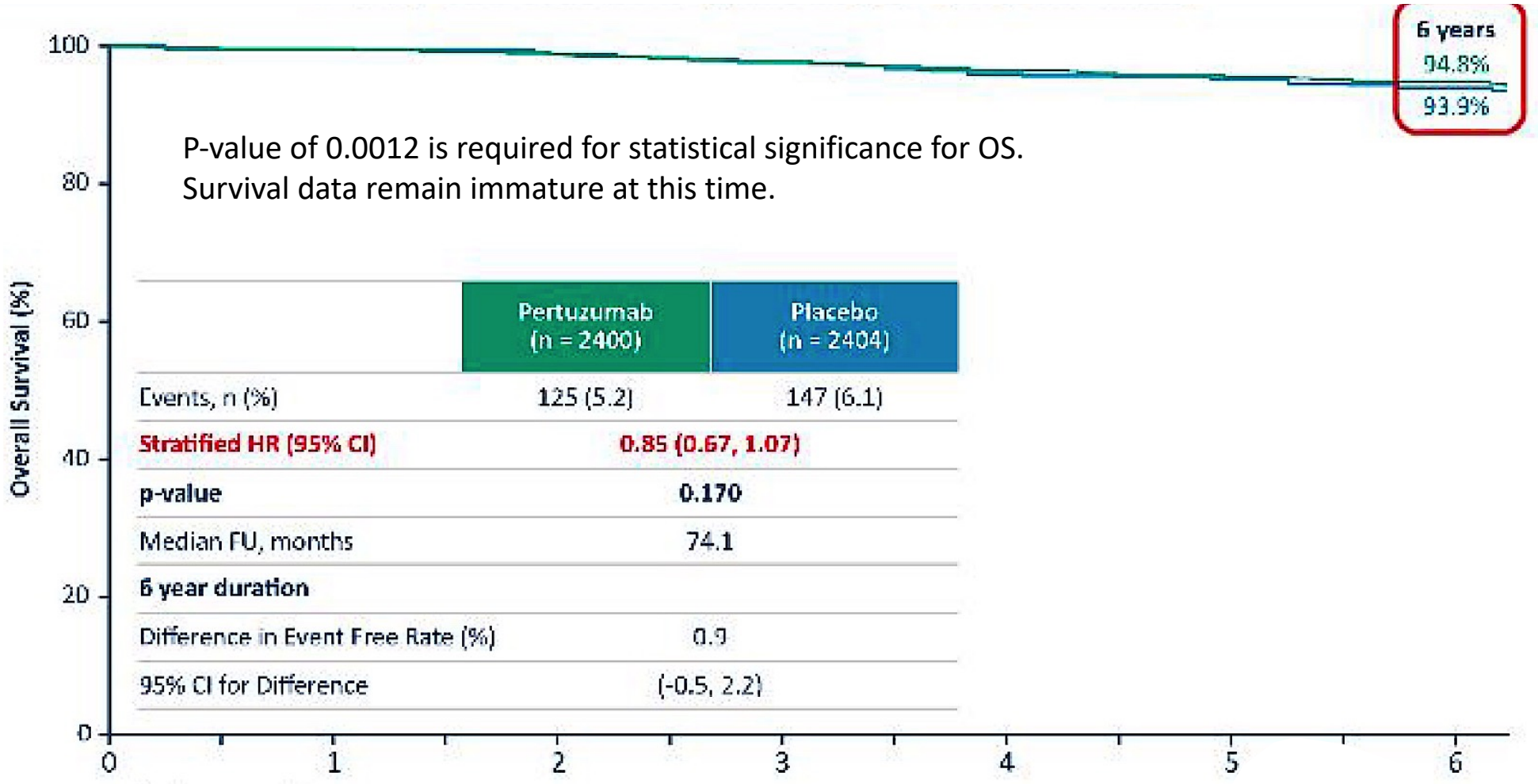
Interim overall survival analysis of APHINITY (BIG 4-11): A randomized multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer

Piccart M et al.

SABCS 2019; Abstract GS1-04.

General Session 1 – Wednesday, December 11, 2019: 9:30 AM

APHINITY Interim Overall Survival Analysis (ITT)
(74.1 months median FU)

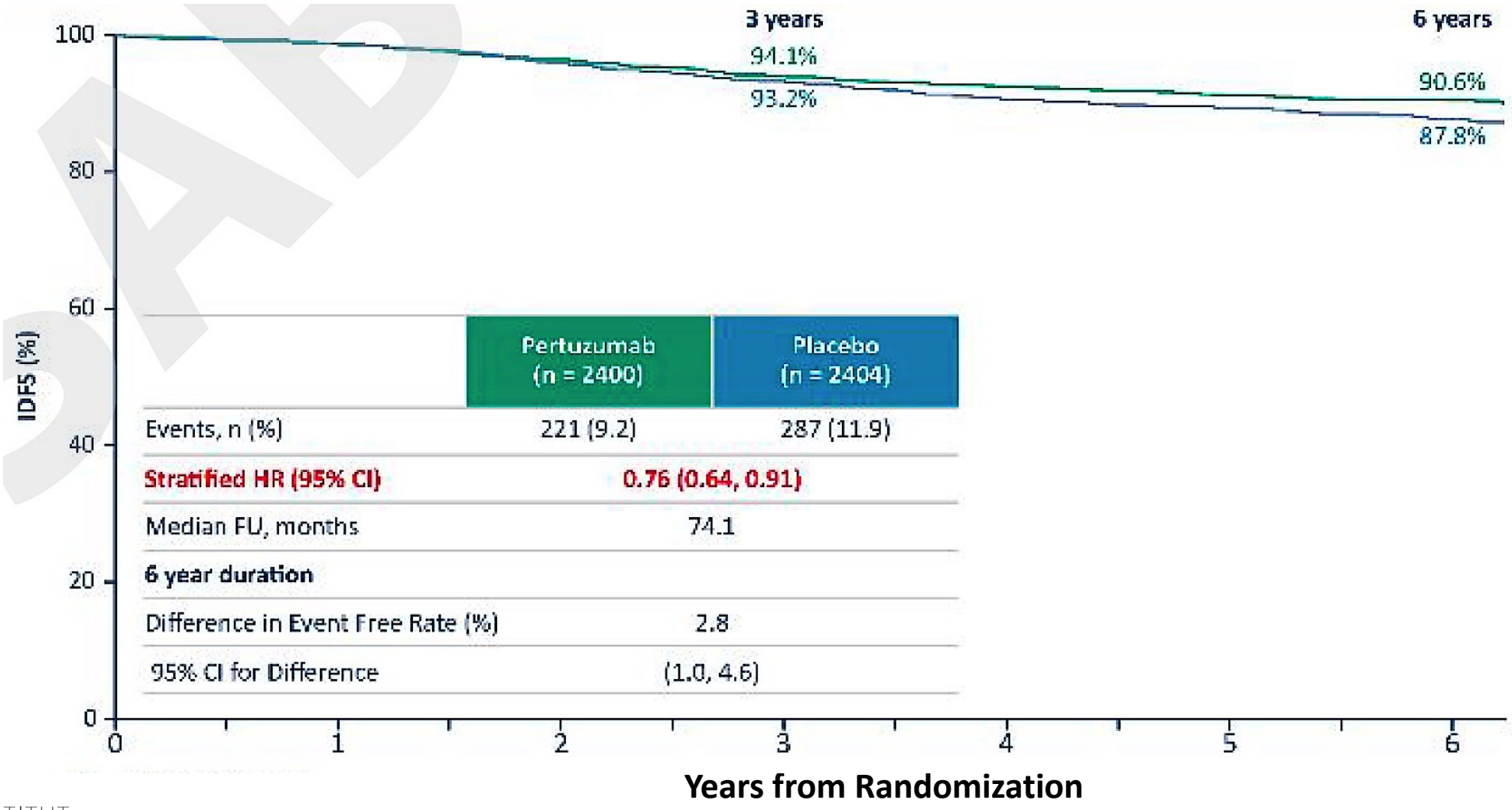


P-value of 0.0012 is required for statistical significance for OS.
Survival data remain immature at this time.

	Pertuzumab (n = 2400)	Placebo (n = 2404)
Events, n (%)	125 (5.2)	147 (6.1)
Stratified HR (95% CI)	**0.85 (0.67, 1.07)**	
p-value	**0.170**	
Median FU, months	74.1	
6 year duration		
Difference in Event Free Rate (%)	0.9	
95% CI for Difference	(-0.5, 2.2)	

Piccart M et al. SABCS 2019; Abstract GS1-04.

APHINITY Updated Descriptive Analysis of Time to First iDFS Event by Treatment Regimen (ITT) (74.1 months median FU)



	Pertuzumab (n = 2400)	Placebo (n = 2404)
Events, n (%)	221 (9.2)	287 (11.9)
Stratified HR (95% CI)	**0.76 (0.64, 0.91)**	
Median FU, months	74.1	
6 year duration		
Difference in Event Free Rate (%)	2.8	
95% CI for Difference	(1.0, 4.6)	

SAD

INSTITUT JULES BORDET INSTITUUT

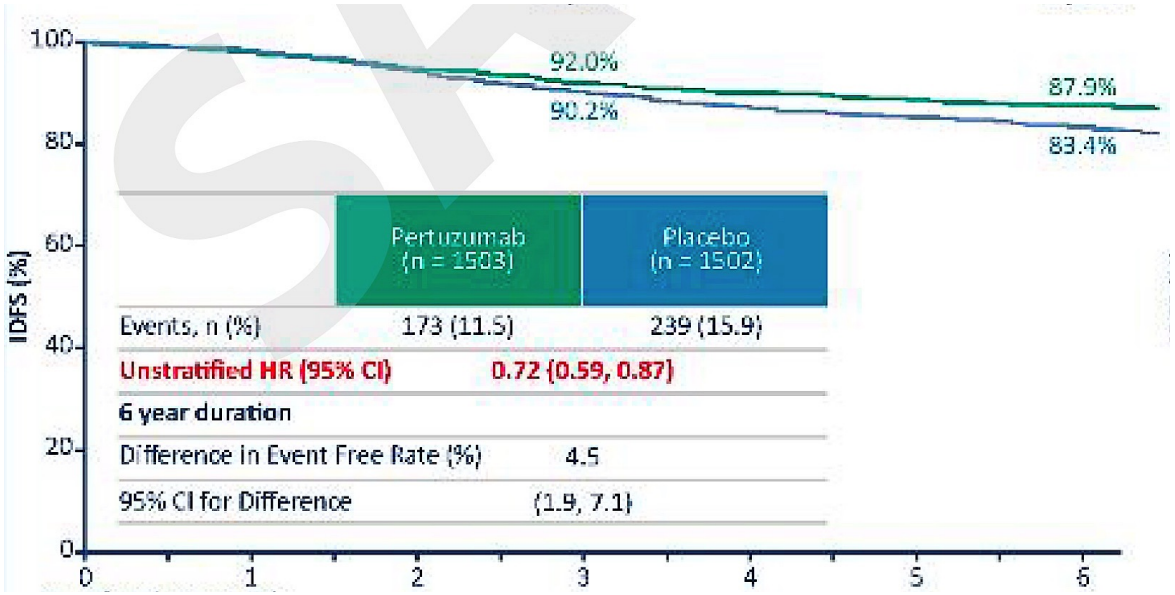
Piccart M et al. SABCS 2019; Abstract GS1-04.

ULB iris

APHINITY Updated Analysis of Time to First iDFS Event by Treatment Regimen and Nodal Status (74.1 months median FU)

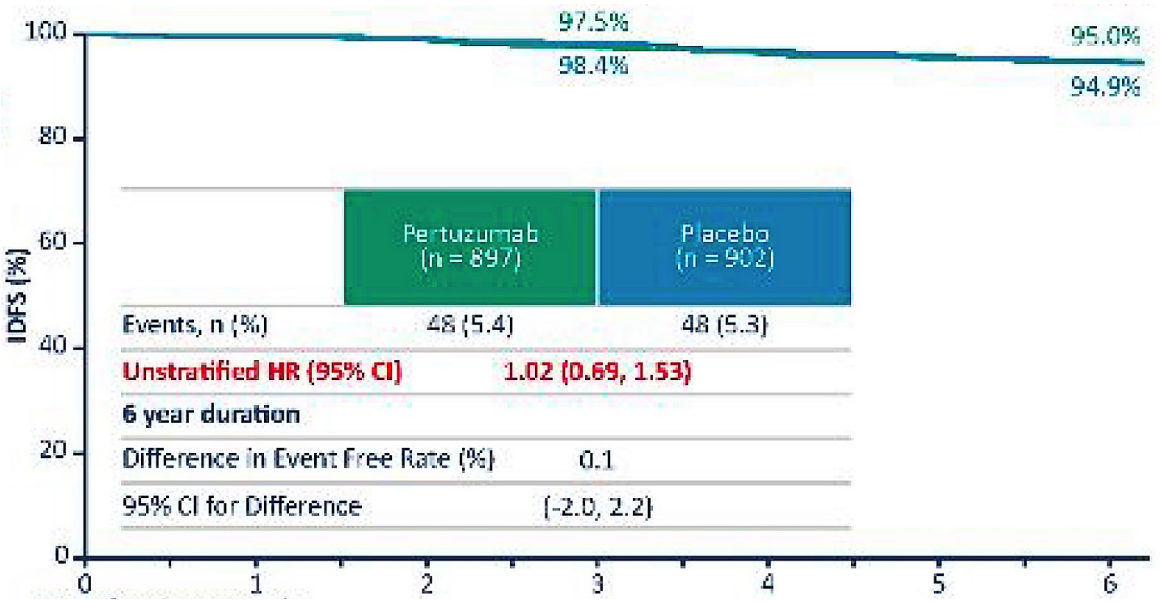
The node-positive cohort continues to derive clear benefit from addition of pertuzumab

Node-positive cohort, ITT population



Years from Randomization

Node-negative cohort, ITT population



Years from Randomization

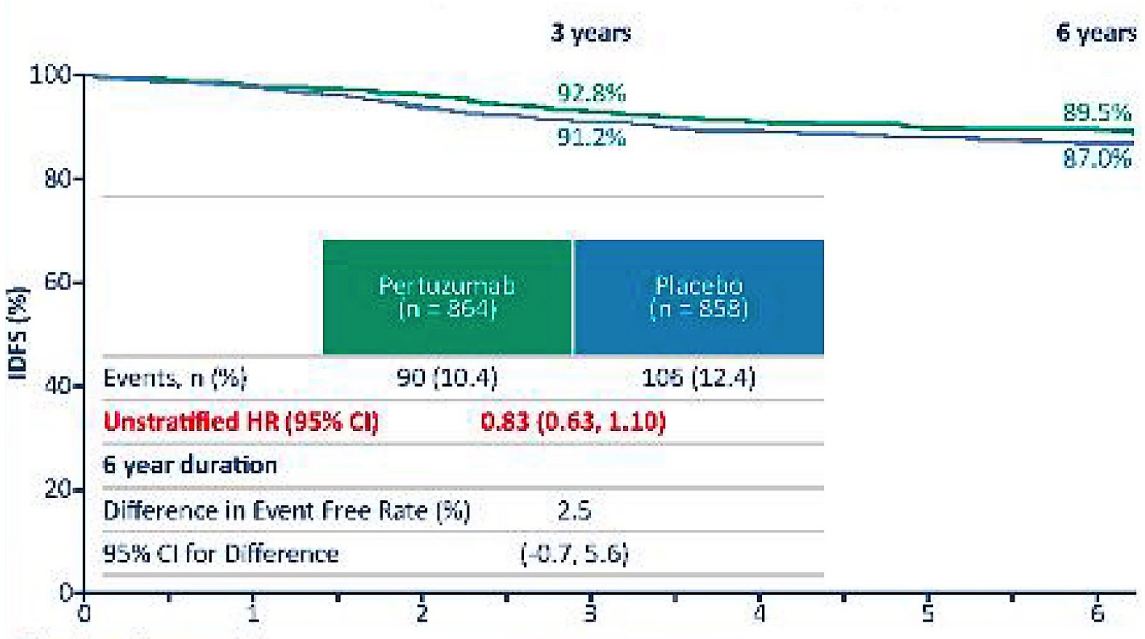
INSTITUT JULES BORDET INSTITUUT

Piccart M et al. SABCS 2019; Abstract GS1-04.

ULB iris

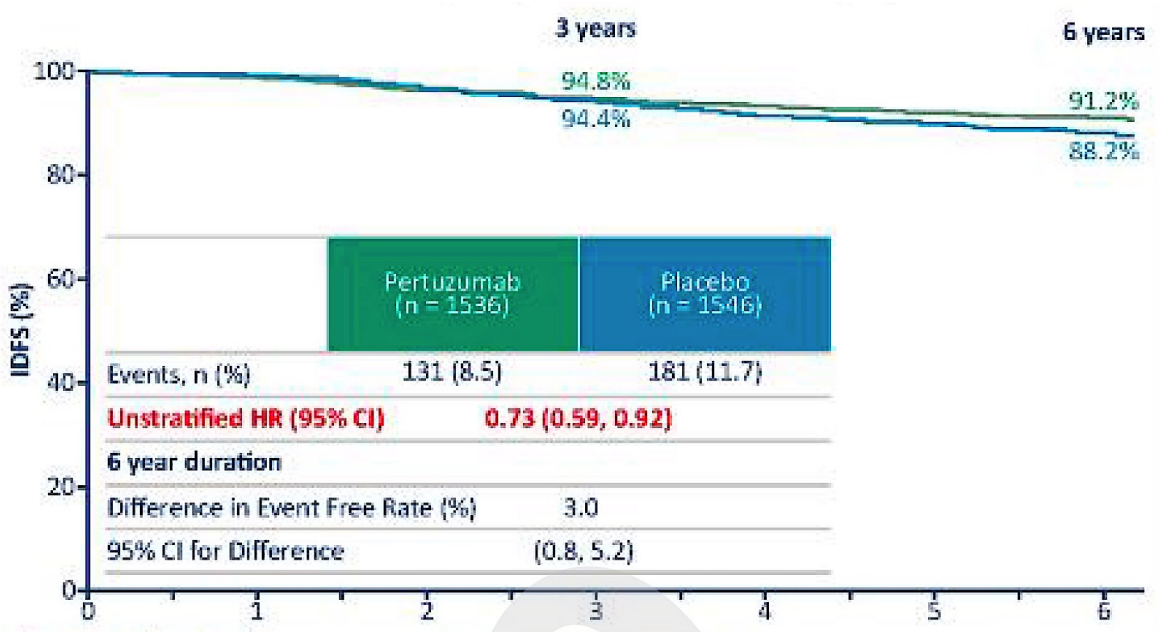
APHINITY Updated Analysis of Time to First iDFS Event by Treatment Regimen and Hormone Receptor Status (74.1 months median FU)

Hormone receptor-negative cohort, ITT population



Years from Randomization

Hormone receptor-positive cohort, ITT population



Years from Randomization

INSTITUT JULES BORDET INSTITUUT

Piccart M et al. SABCS 2019; Abstract GS1-04.

ULB iris

Clinical Benefit of Adjuvant Dual-HER2 Blockade with Chemotherapy

Hazard ratio (95% CI) for IDFS in the ITT population and subgroups based on lymph node & hormone receptor status			IDFS at 6 years from randomisation (APHINITY Updated descriptive analysis)		
Population	**Primary Analysis** median FU 45.4 months; 2017	**Updated Analysis** median FU 74.1 months; 2019	Pertuzumab arm	Placebo arm	**Absolute benefit (95% CI)**
ITT	0.81 (0.66-1.00)	0.76 (0.64-0.91)	90.6%	87.8%	2.8% (1.0, 4.6)
LN-positive	0.77 (0.62-0.96)	0.72 (0.59-0.87)	87.9%	83.4%	4.5% (1.9, 7.1)
LN-negative	1.13 (0.68-1.86)	1.02 (0.69-1.53)	95.0%	94.9%	0.1% (-2.0, 2.2)
HR-positive	0.86 (0.66-1.13)	0.73 (0.59-0.92)	91.2%	88.2%	3.0% (0.8, 5.2)
HR-negative	0.76 (0.56-1.04)	0.83 (0.63-1.10)	89.5%	87.0%	2.5% (-0.7, 5.6)

LN = lymph-node; HR = hormone receptor

OS difference after 74.1 months of median FU did not yet reach statistical significance

INSTITUT JULES BORDET INSTITUUT

Piccart M et al. SABCS 2019; Abstract GS1-04.

ULB iris

TBCRC 033: A randomized phase II study of adjuvant trastuzumab emtansine (T-DM1) vs paclitaxel (T) in combination with trastuzumab (H) for stage I HER2-positive breast cancer (BC) (ATEMPT)

Tolaney SM et al.

SABCS 2019; Abstract GS1-05.

General Session 1 – Wednesday, December 11, 2019: 9:45 AM

ATEMPT: Disease-Free Survival

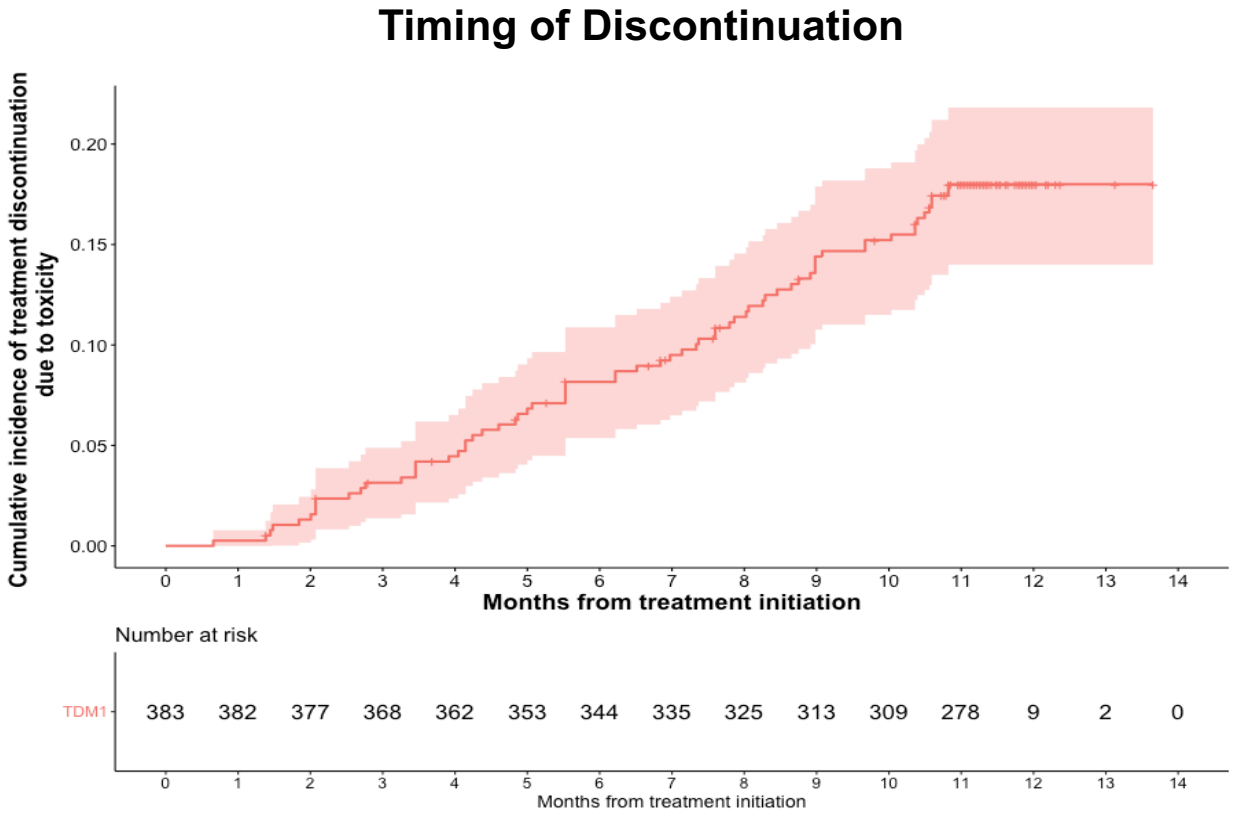
	T-DM1			TH		
	N	No. of events	3-yr DFS	N	No. of events	3-yr DFS
Overall	**383**	**10**	**97.7%**	**114**	**7**	**92.8%**
Hormone Receptor Status						
HR+	289	8	97.5%	Not Reported		
HR-	94	2	98.5%			
Tumor Size						
T<1cm	163	2	98.5%	Not Reported		
T≥1cm	220	8	97.1%			

INSTITUT JULES BORDET INSTITUUT

Tolaney SM et al. SABCS 2019; Abstract GS1-05.

ULB iris

T-DM1 discontinuations



	n (%)
Discontinuations for any reason	90 (23.5%)
Discontinuations for toxicity	67 (17.0%)
Discontinuations for toxicity that were protocol mandated	33 (9%)

***66% of patients who discontinued T-DM1 early for toxicity received further therapy with trastuzumab**

- **Probability of discontinuing within 6 months: 8.2%**
- **Probability of discontinuing between months 6-12: 10.7%**

Tolaney SM et al. SABCS 2019; Abstract GS1-05.

Clinically Relevant Toxicity

Clinically Relevant Toxicity	T-DM1 (n = 383) N (%)	TH (n = 114) N (%)
Grade ≥3 non-hematologic toxicity	37 (10%)	13 (11%)
Grade ≥ 2 neurotoxicity	42 (11%)	26 (23%)
Grade ≥4 hematologic toxicity	4 (1%)	0 (0%)
Febrile neutropenia	0 (0%)	2 (2%)
Any toxicity requiring dose delay	106 (28%)	30 (26%)
Any toxicity requiring early discontinuation	67 (17%)	7 (6%)
Total	176 (46%)	53 (46%)

p=0.91

Tolaney SM et al. SABCS 2019; Abstract GS1-05.

Treatment Related Adverse Events: Grade ≥2 by Arm

	T-DM1 (n = 383)	TH (n = 114)
Fatigue	84 (22%)	26 (23%)
Neuropathy	44 (11%)	27 (24%)
Neutropenia	13 (3%)	15 (13%)
Thrombocytopenia	43 (11%)	1 (1%)
Nausea	39 (10%)	8 (7%)
Hypertension	35 (9%)	7 (6%)
ALT increase	33 (9%)	5 (4%)
Headache	24 (6%)	4 (4%)
Bilirubin increase	21 (5%)	1 (1%)
Infusion related reaction	19 (5%)	12 (11%)
Arthralgia	18 (5%)	2 (2%)
Anemia	18 (5%)	2 (2%)

Tolaney SM et al. SABCS 2019; Abstract GS1-05.

Treatment Related Adverse Events: Grade ≥2 by Arm

	T-DM1 (n = 383)	TH (n = 114)
Fatigue	84 (22%)	26 (23%)
Neuropathy	44 (11%)	27 (24%)
Neutropenia	13 (3%)	15 (13%)
Thrombocytopenia	43 (11%)	1 (1%)
Nausea	39 (10%)	8 (7%)
Hypertension	35 (9%)	7 (6%)
ALT increase	33 (9%)	5 (4%)
Headache	24 (6%)	4 (4%)
Bilirubin increase	21 (5%)	1 (1%)
Infusion related reaction	19 (5%)	12 (11%)
Arthralgia	18 (5%)	2 (2%)
Anemia	18 (5%)	2 (2%)

Tolaney SM et al. SABCS 2019; Abstract GS1-05.

Cardiac Toxicity

ECHO or MUGA

	Arm 1: T-DM1 (n = 383)	Arm 2: TH (n = 114)
Symptomatic Congestive Heart Failure	3 (0.8%)	1 (0.9%)
Asymptomatic declines in LVEF (≥15%)	5 (1.3%)	7 (6.1%)

Tolaney SM et al. SABCS 2019; Abstract GS1-05.

Effect of prophylaxis or neratinib dose escalation on neratinib-associated diarrhea and tolerability in patients with HER2-positive early-stage breast cancer: Phase II CONTROL trial

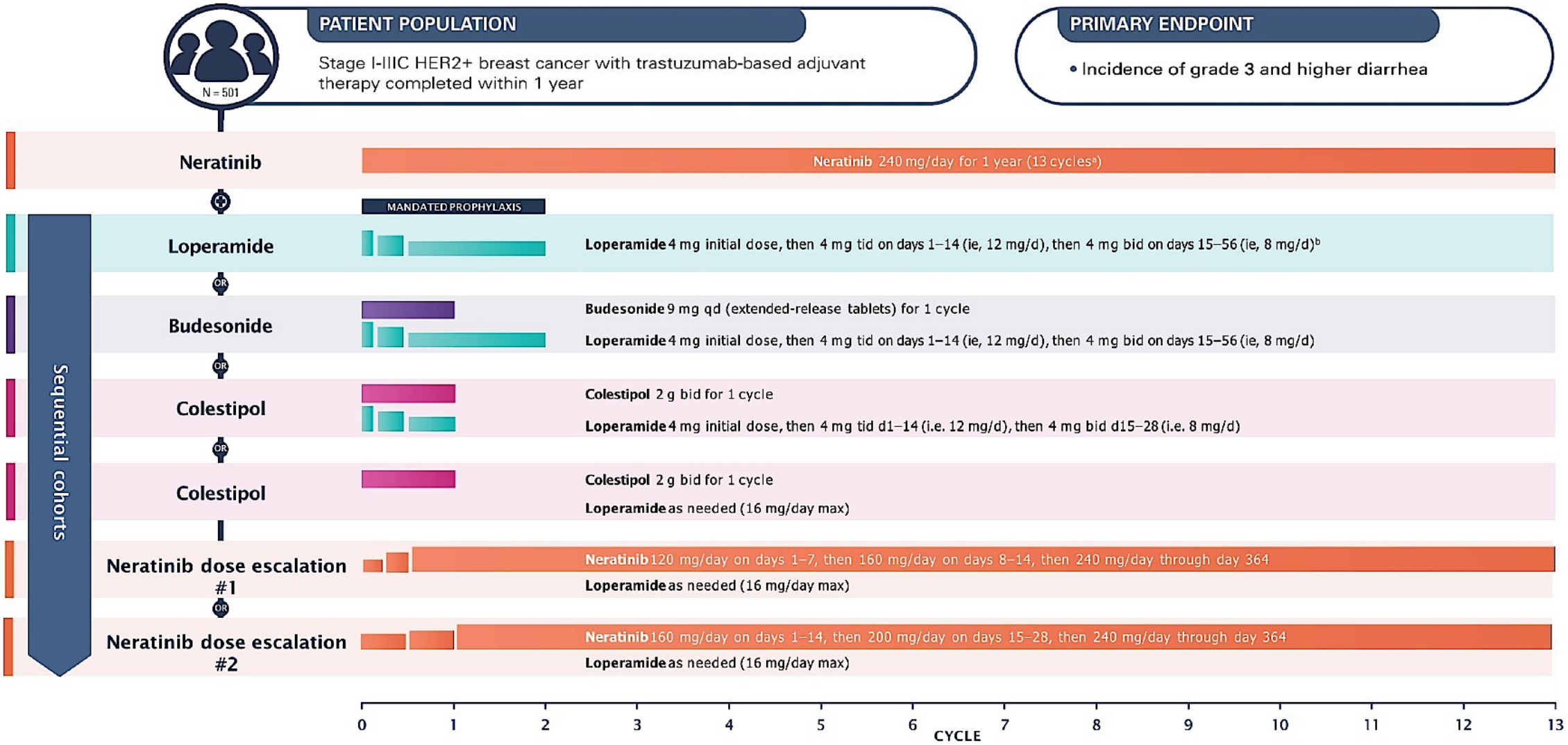
Chan A et al.

SABCS 2019; Abstract P5-14-03.

Poster Session 5 – Friday, December 13, 2019: 5:00 pm – 7:00 pm

CONTROL (Study 6201) Study Design

An Open-Label Study to Characterize the Incidence and Severity of Diarrhea in Patients with Early-Stage HER2+ Breast Cancer Treated with Neratinib and Proactive Management



Barcenas CH et al. Proc ASCO 2019; Abstract 548.

CONTROL: Characteristics of Treatment-Emergent Diarrhea

	Loperamide (n=137)	Budesonide + loperamide (n=64)	Colestipol + loperamide (n=136)	Colestipol + loperamide prn (n=104)	Neratinib dose escalation scheme 1 (n=60)	Neratinib dose escalation scheme 2 (n=13)
On neratinib, %	0	0	0	1.0[a]	85.0	84.6
Diarrhea, %						
Grade 1	24.1	25.0	27.9	30.8	41.7	23.1
Grade 2	24.8	32.8	34.6	32.7	38.3	46.2
Grade 3	30.7	28.1	20.6	31.7	15.0	7.7
Grade 4	0	0	0	0	0	0
Median cumulative duration, days (range)						
Grade ≥2	5.0 (1-400)	6.0 (1-117)	4.0 (1-371)	8.0 (1-375)	5.0 (1-28)	2.0 (1-6)
Grade 3	3.0 (1-93)	2.5 (1-6)	3.5 (1-22)	3.0 (1-55)	2.0 (1-5)	5.0 (5-5)
Discontinuation (due to a diarrhea TEAE), %	20.4	10.9	4.4	7.7	3.3	0
Hospitalization (due to a diarrhea TEAE), %	1.5	0	0	0	0	0

[a]As of the data cut-off, the final pt in the colestipol + loperamide prn cohort had completed 1y of neratinib but had not yet had the final study visit.

Chan A et al. SABCS 2019; Abstract P5-14-03.