Prise en charge du cancer du sein Her2 positif

S.Sami

EHS Pierre & Marie Curie

14 NOVEMBRE 2021

HER2: facteur de mauvais pronostic

Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/*neu* Oncogene

DENNIS J. SLAMON,* GARY M. CLARK, STEVEN G. WONG, WENDY J. LEVIN,

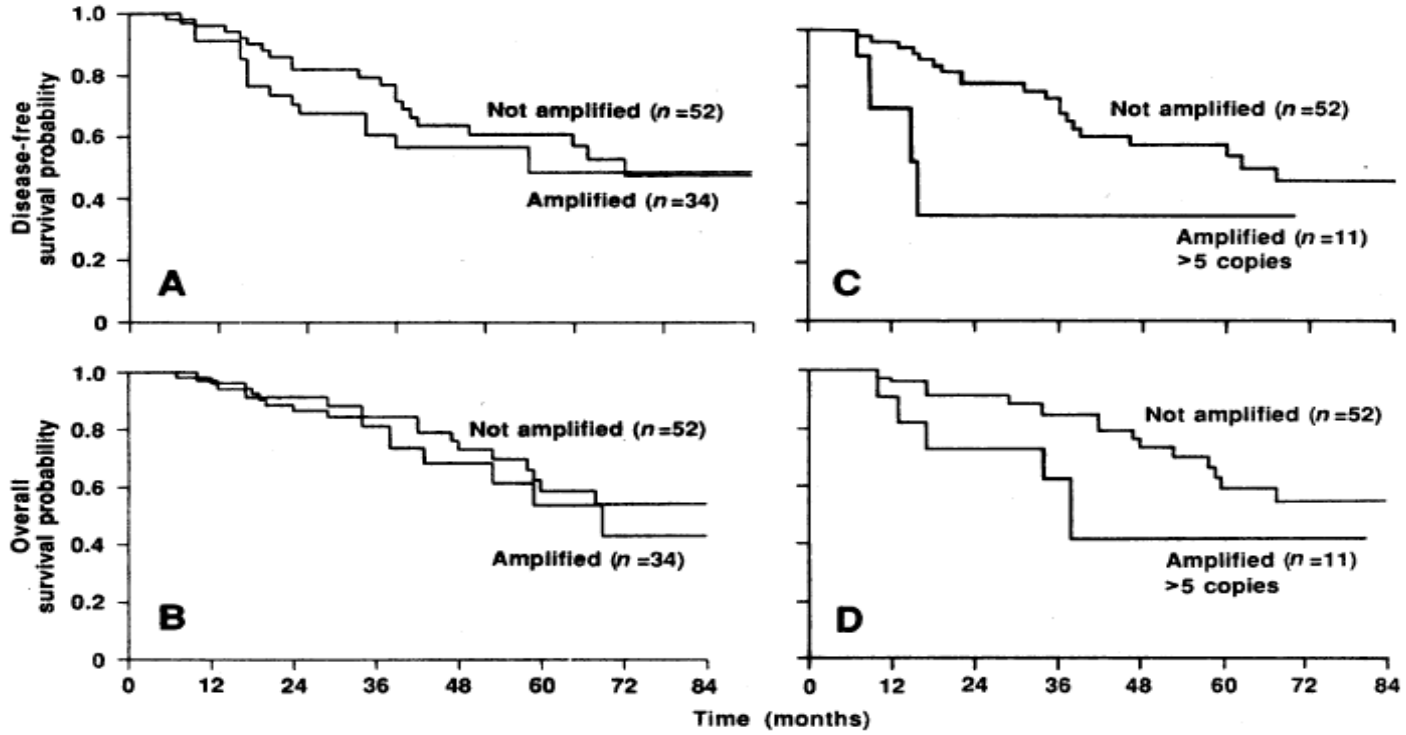


Table 3. Association between HER-2/*neu* amplification and disease parameters in combined surveys (189 patients).

Factor*	Single copy	2 to 5 copies	5 to 20 copies	>20 copies	Total	P†
Hormonal receptor status						
ER+	91	23	14	2	130	0.05
ER−	45	3	6	5	59	
PgR+	73	20	10	3	106	0.06
PgR−	63	6	10	4	83	
Tumor size (centimeters)						
≤2	31	9	4	0	44	0.19
2–5	62	13	7	2	84	
>5	23	4	6	3	36	
Unknown	20	0	3	2	25	
Age at diagnosis (years)						
≤50	37	13	8	2	60	0.11
>50	88	13	10	5	116	
Unknown	11	0	2	0	13	
Number of positive lymph nodes						
0	30	0	3	1	34	0.002
1–3	51	7	6	1	65	
>3	38	18	8	4	68	
Unknown	17	1	3	1	22	

*ER and PgR are as described in Table 1. †Statistical analyses for correlation of HER-2/*neu* amplification with various disease parameters were performed by the χ^2 test. *P* values were computed after combining the cases with 5 to 20 and >20 copies.

Science 1987; 235: 177-82.

- **Metastatic breast cancer**

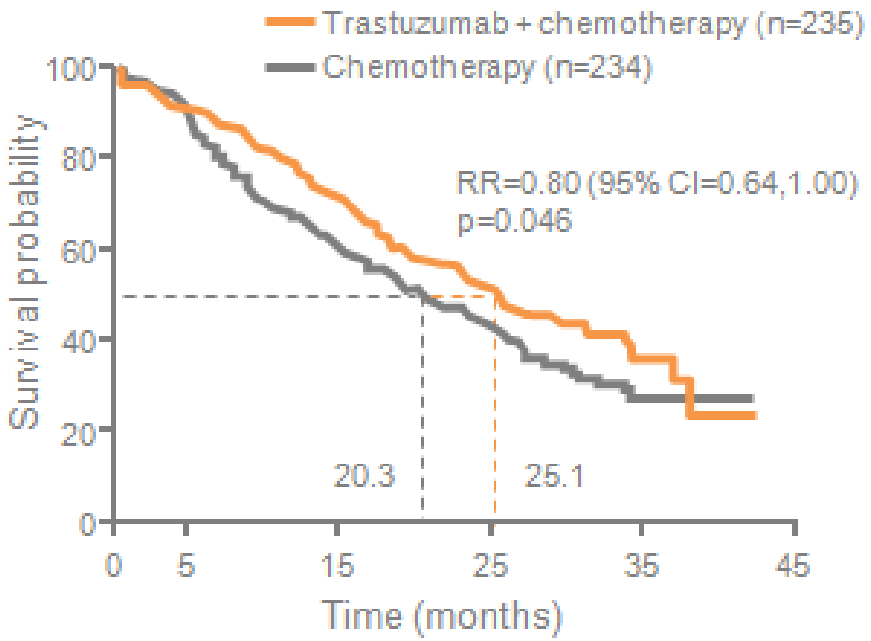
- **Metastatic breast cancer**

❑ **1ére ligne**

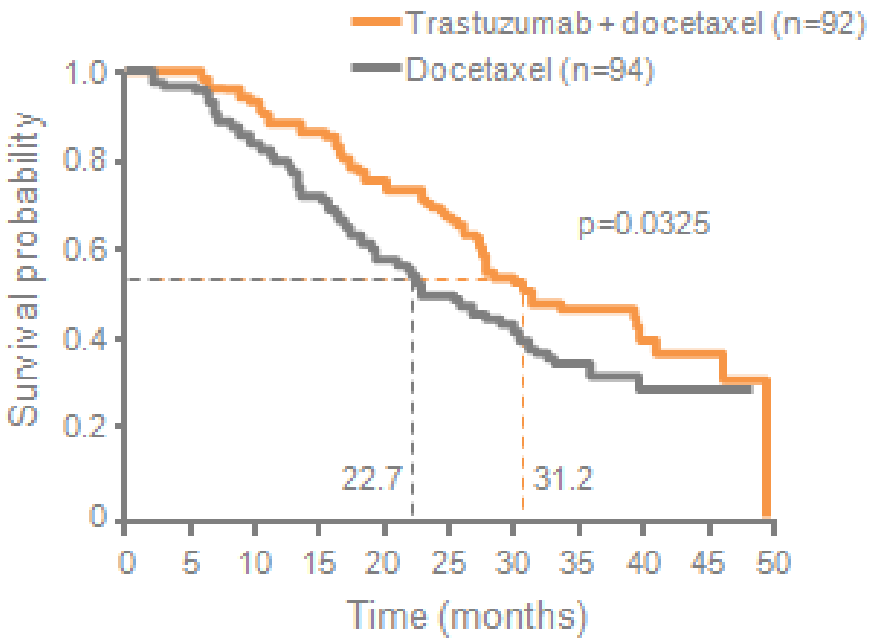
Premiers essais avec trastuzumab

Addition of trastuzumab to chemotherapy as a first-line therapy for HER2-positive mBC significantly increases OS

H0648g[1]



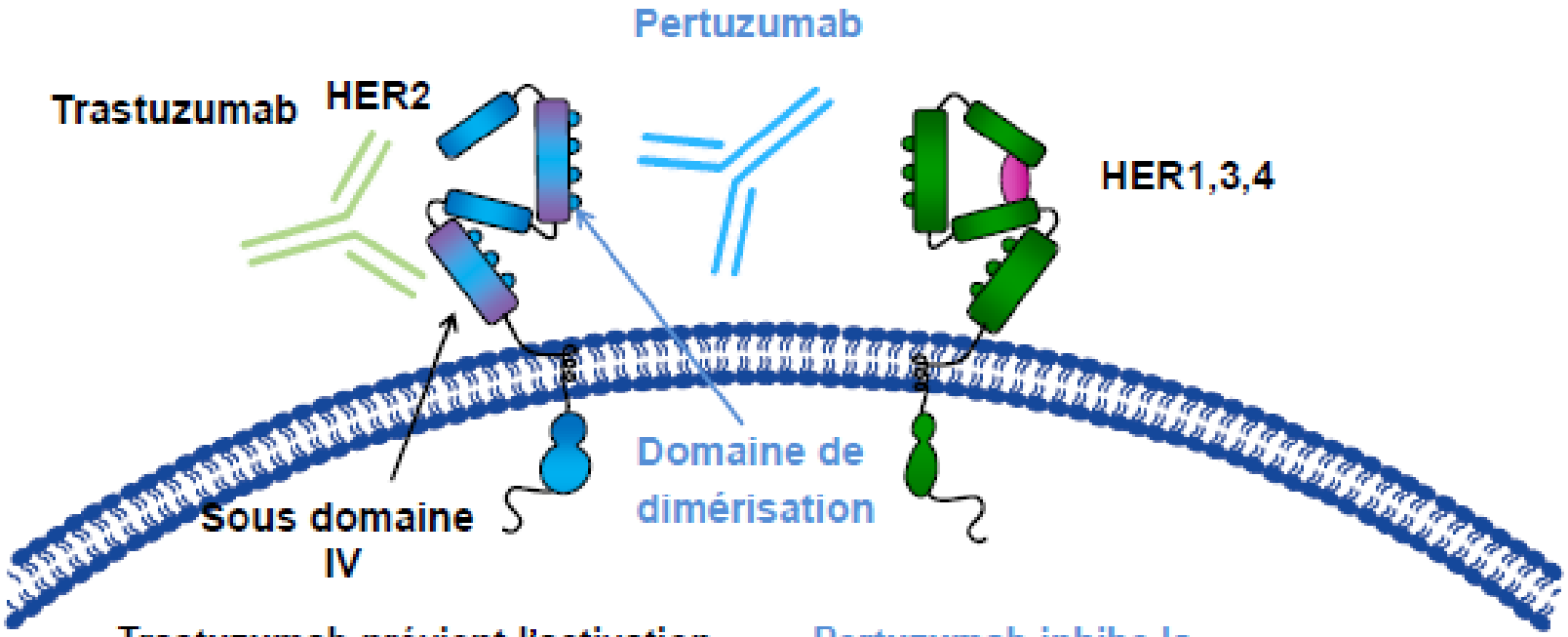
M77001[2]



1. Slamon DJ, *et al. N Engl J Med* 2001; **344**:783–792;

2. Marty M, *et al. J Clin Oncol* 2005; **23**:4265–4274**.**

PERTUZUMAB

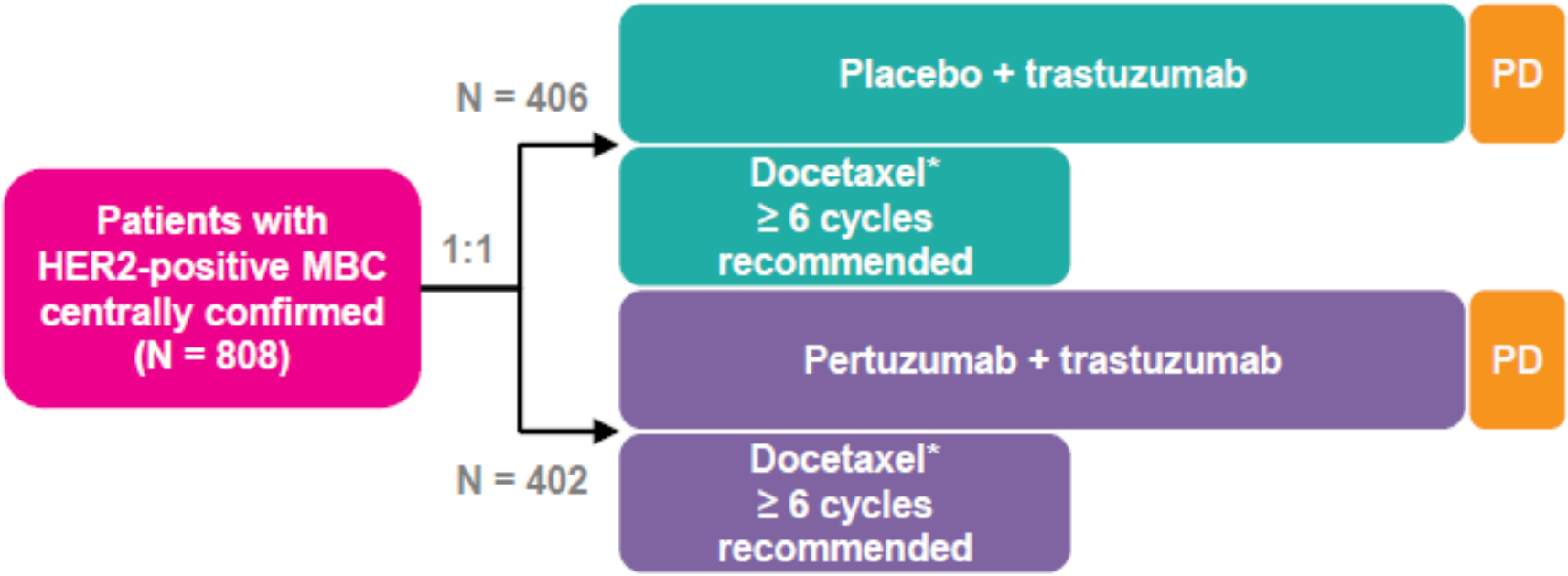


Trastuzumab prévient l'activation HER2 en masquant le domaine extracellulaire

Pertuzumab inhibe la dimérisation HER2 activée par le ligand

Cho et al. Nature 2003;421:756–760; Fendly et al. Cancer Cell 2004;5:317–328
Franklin et al. Cancer Cell 2004;5:317–328;. Nahta et al. Cancer Res 2004;64:2343–2346
Scheuer et al. Cancer Res 2009;69:9330–9336; Agus et al. Cancer Cell 2002;2:127–137

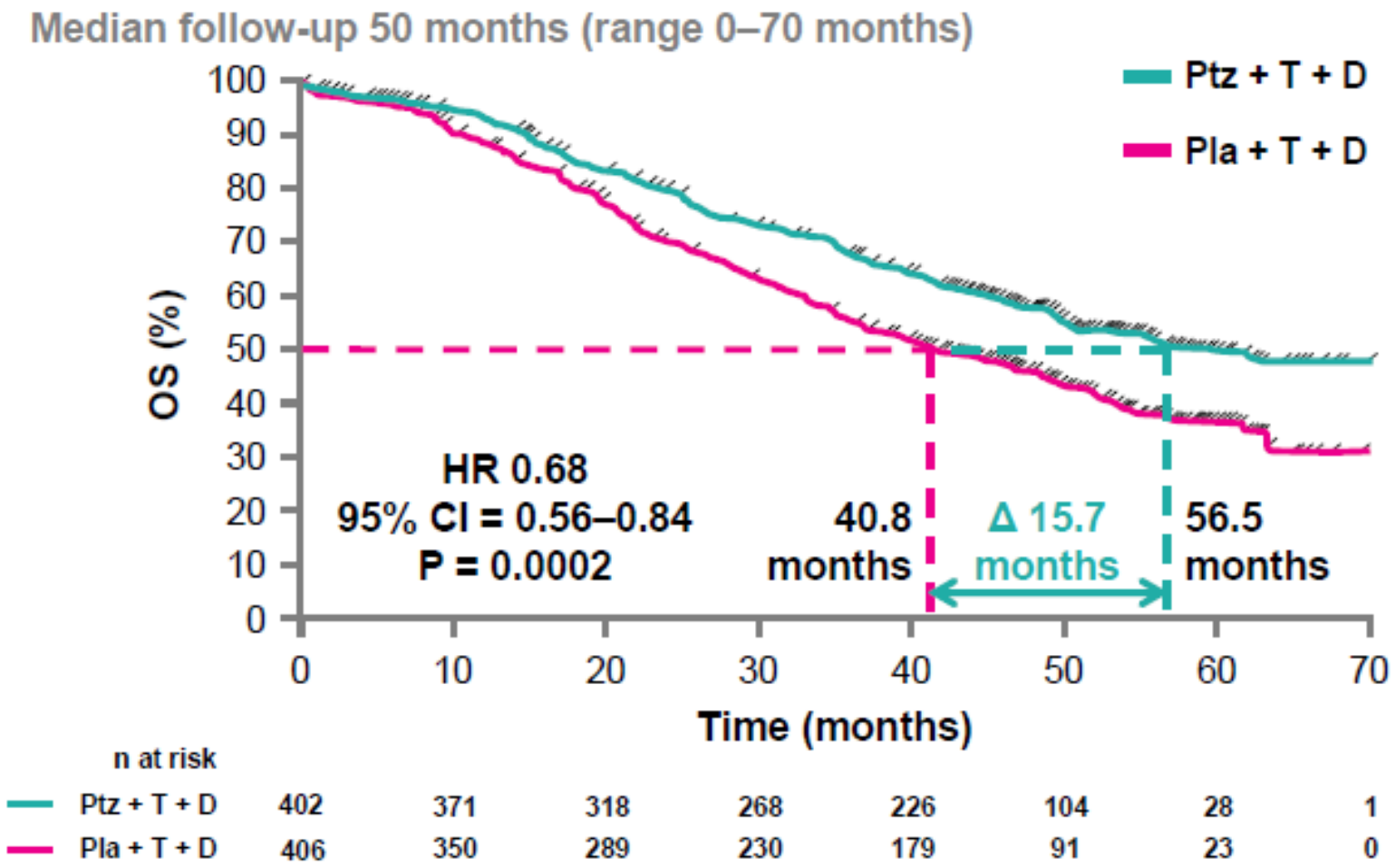
ETUDE CLEOPATRA



- Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)
- Study dosing q3w:
  - Pertuzumab/placebo: 840 mg loading dose, 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Docetaxel: 75 mg/m², escalating to 100 mg/m² if tolerated

Baselga J *et al. NEJM 2012*

ETUDE CLEOPATRA



Swain S *et al. ESMO 2014*

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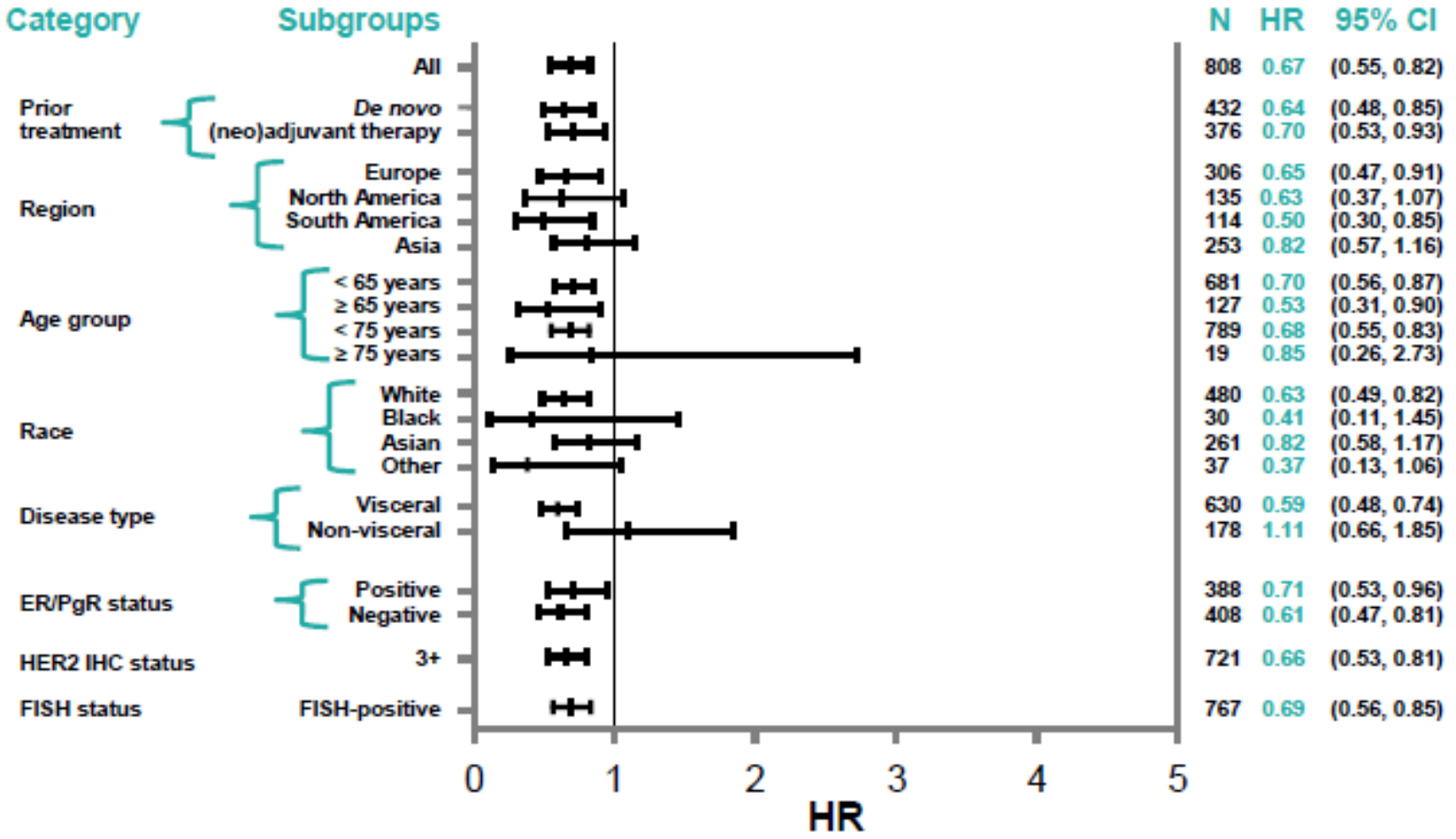

Swain S *et al. ESMO 2014*

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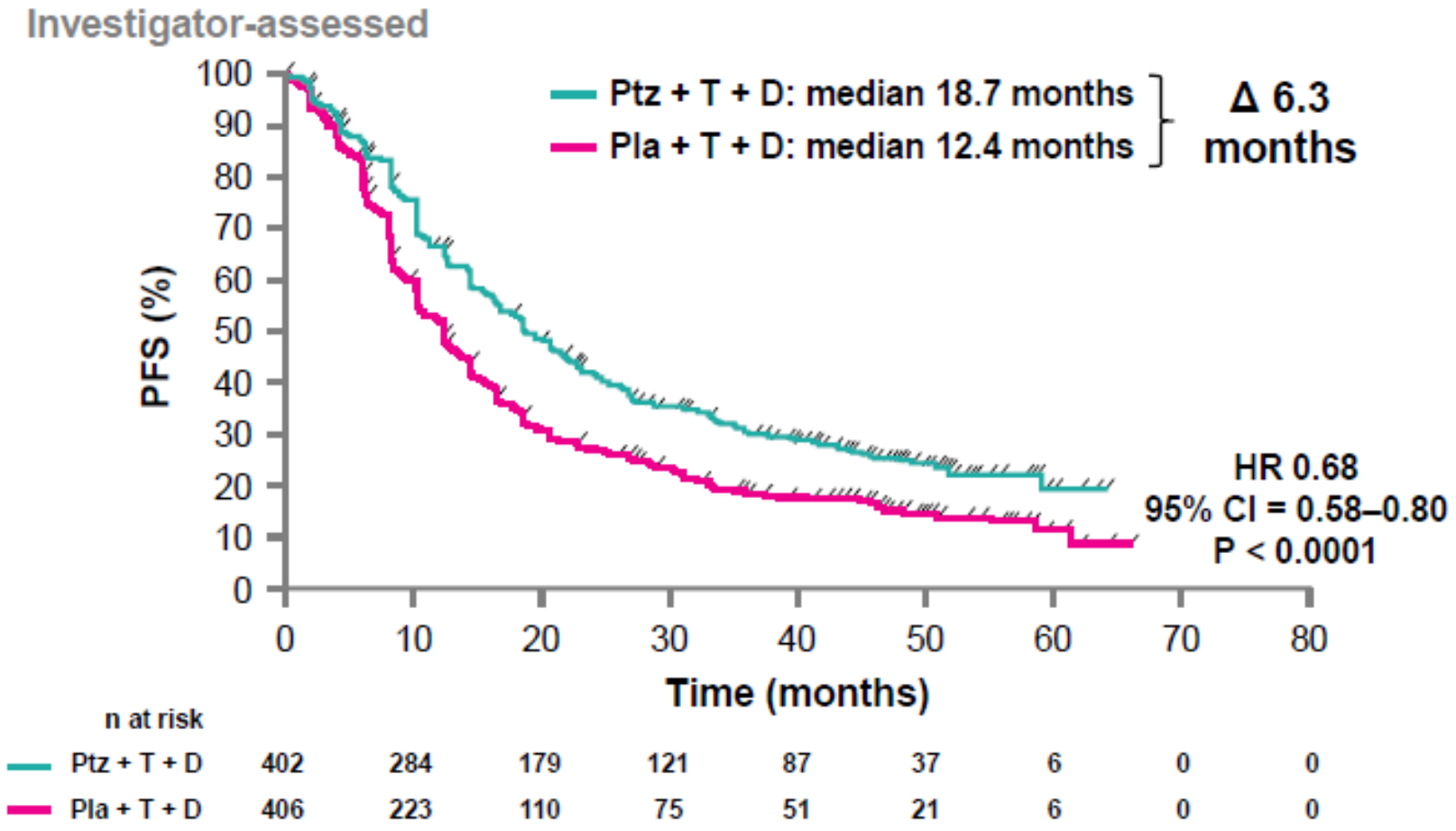


Swain S *et al. ESMO 2014*

ETUDE CLEOPATRA

Safety population	Placebo + T + D (N = 396), %	Pertuzumab + T + D (N = 408), %
Neutropenia	46.2	49.0
Leukopenia	14.9	12.3
Febrile neutropenia	7.6	13.7
Diarrhoea	5.1	9.3

- No cumulative toxicities

Swain S *et al. ESMO 2014*

ETUDE CLEOPATRA

Safety population	Placebo + T + D (N = 396), %	Pertuzumab + T + D (N = 408), %
sLVD	1.8	1.5
LVEF decline to <50% and by ≥10% points from baseline*	7.4	6.1

- One new sLVD event in the pertuzumab group after 40 months (resolved)
- LVEF declines reversed in 88% of pertuzumab patients

Swain S *et al. ESMO 2014*

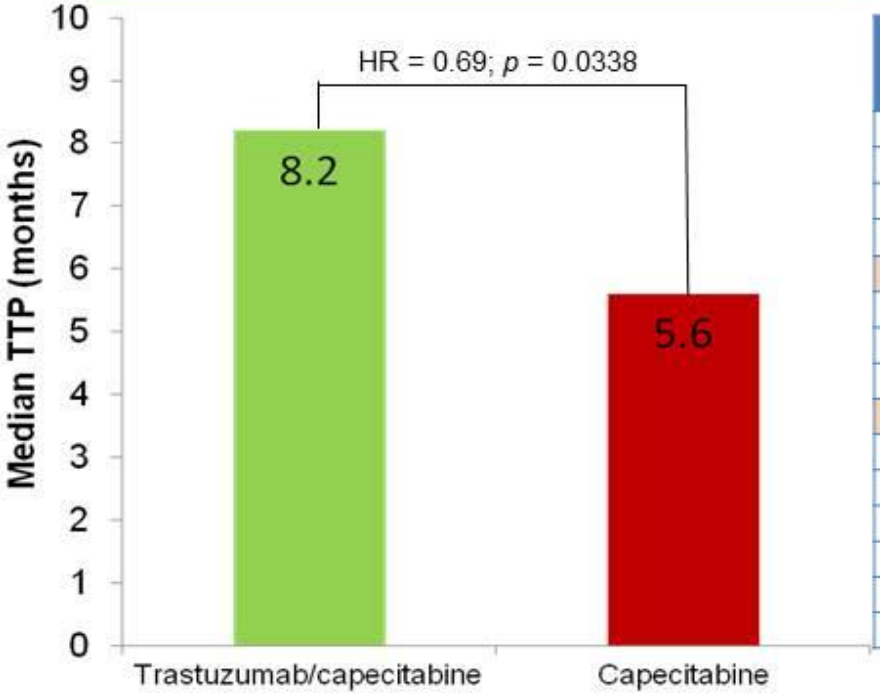
- **Metastatic breast cancer**

❑ **2éme ligne**

Trastuzumab/chemotherapy is also recommended for patients with MBC who have progressed on trastuzumab therapy for MBC[1]

GBG-26: Trastuzumab/capecitabine versus capecitabine alone[2]

TTP with trastuzumab/capecitabine compared with capecitabine



Adverse events associated with trastuzumab/capecitabine and capecitabine

Grade ≥3 adverse events (%)	Trastuzumab/ capecitabine	Capecitabine
Neutropenia	5.33	4.35
Febrile neutropenia	2.60	0
Anaemia	0	2.78
Vomiting	1.3	4.05
Diarrhoea	15.58	18.92
Mucositis	1.30	2.70
Oedema	0	1.35
Fatigue	3.9	5.41
Skin changes (incl. PPE)	32.47	24.32
Nail changes	3.90	0
Sensory neuropathy	2.60	5.41
Infection	2.60	8.11
Fever	1.30	0
Dyspnoea	2.60	6.76
CV disorder	5.19	2.7

1. Cardoso et al. Ann Oncol 2012; 2. von Minckwitz et al. *J Clin Oncol* 2009

TTP = time to progression; CV = cardiovascular

Trastuzumab/chemotherapy is also recommended for patients with MBC who have progressed on trastuzumab therapy for MBC[1]

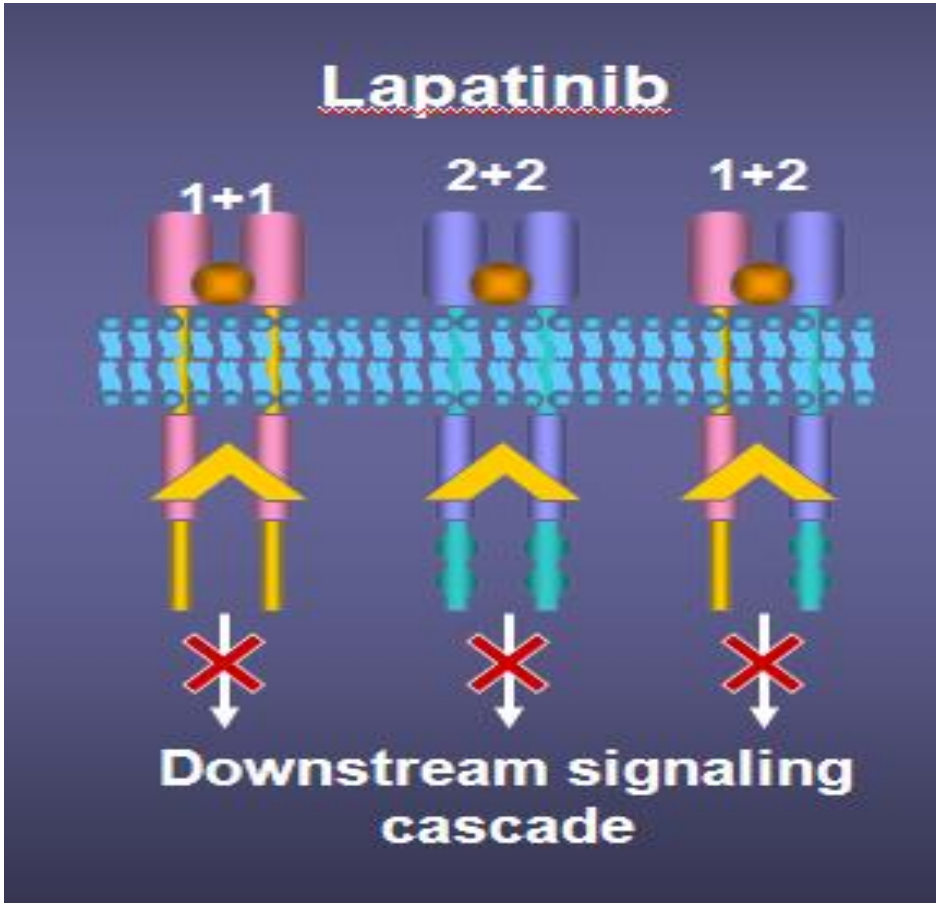
	CAPECITABINE + TRASTUZUMAB	CAPECITABINE	P
SG	25,5 mois	20,4 mois	0,257
RO	48,1 %,	27,0 %	0,0115

1. Cardoso et al. Ann Oncol 2012; 2. von Minckwitz et al. *J Clin Oncol* 2009

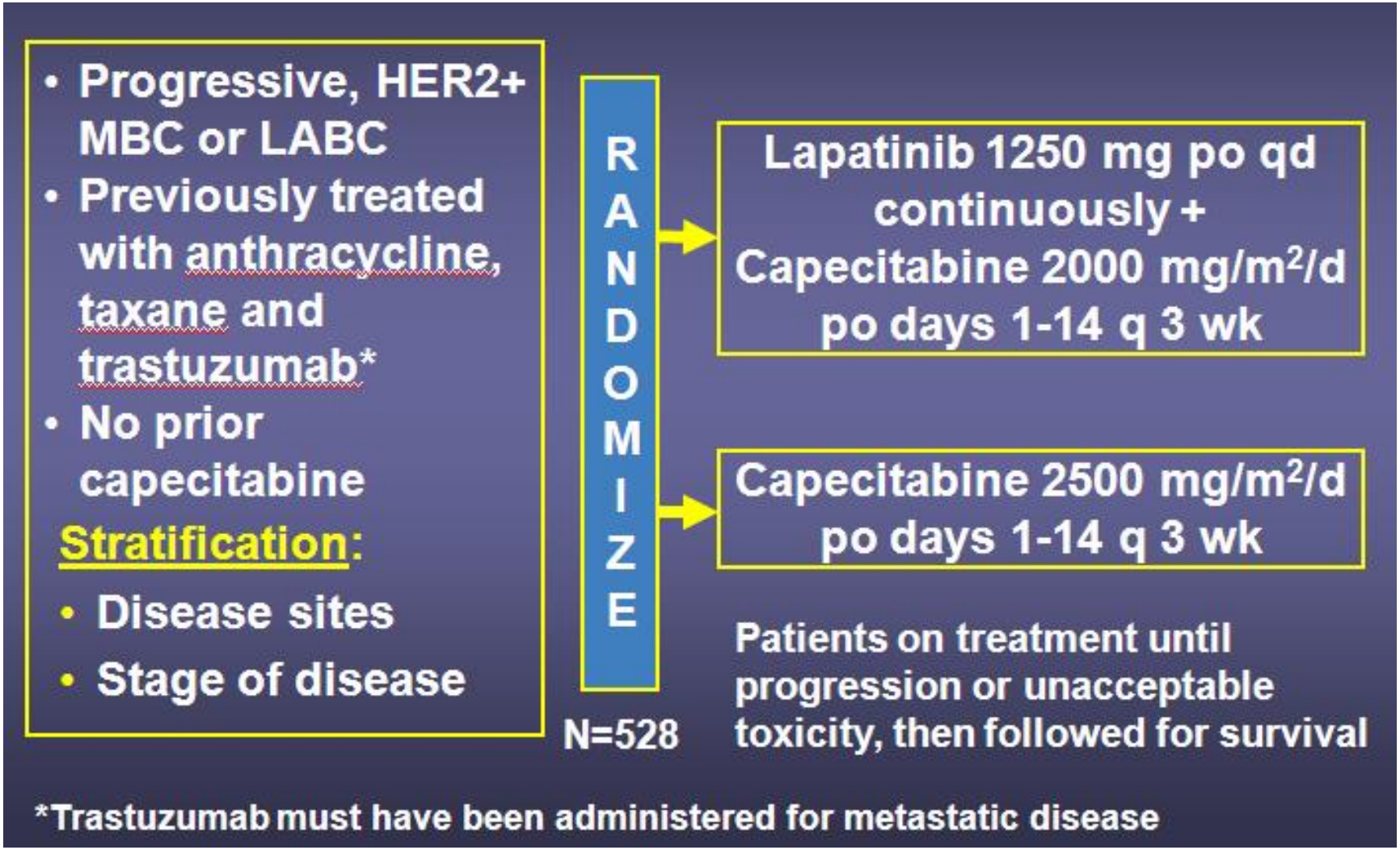
TTP = time to progression; CV = cardiovascu

Lapatinib

- Le lapatinib cible les domaines de la tyrosine kinase intracellulaire des récepteurs Her 1 & Her 2, induisant une apoptose et une inhibition de la croissance cellulaire tumorale.



EGF 100151



GEYER & al; ASCO 2006

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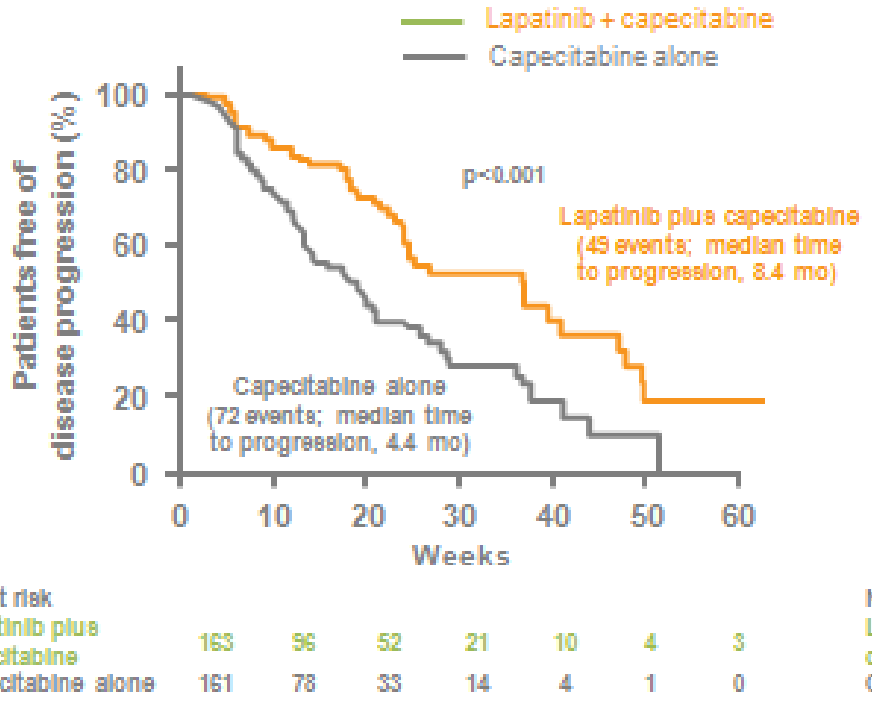
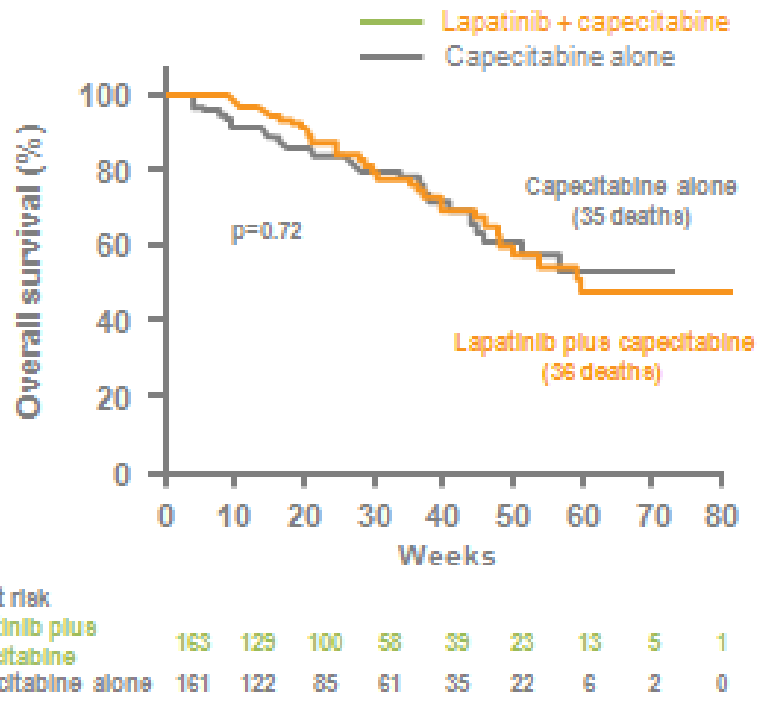
PFS



No. at risk							
Lapatinib plus capecitabine	163	96	52	21	10	4	3
Capecitabine alone	161	78	33	14	4	1	0

OS

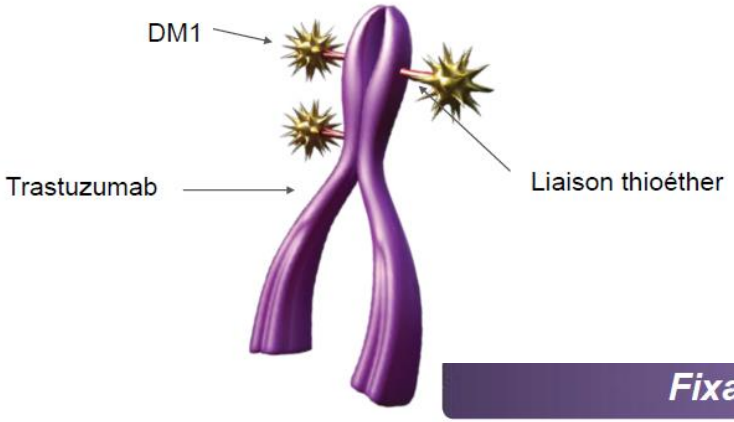


No. at risk									
Lapatinib plus capecitabine	163	129	100	58	39	23	13	5	1
Capecitabine alone	161	122	85	61	35	22	6	2	0

Geyer CE, *et al. N Engl J Med* 2006; **355**:2733–2743.

TDM1

Anticorps conjugué
Un nouvel agent pharmacologique



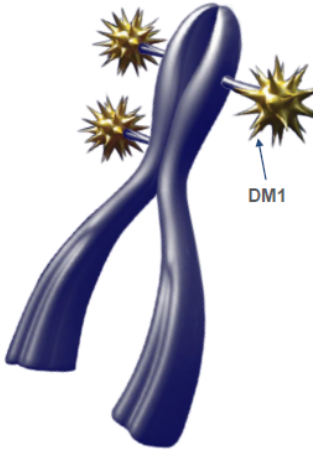
DM1
Un agent cytotoxique

Le DM1 est un dérivé de la maytansine

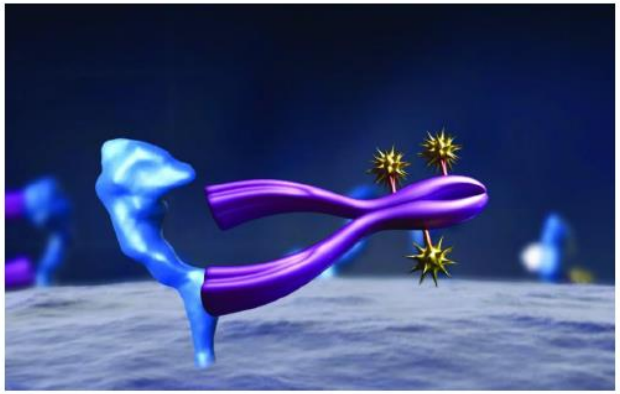
Les maytansinoïdes sont *in vitro* :

- de 20 à 200 fois plus puissants que le paclitaxel
- 2 à 3 fois plus puissants que la doxorubicine

Le DM1 se lie directement aux microtubules inhibant la polymérisation, causant ainsi l'arrêt du cycle cellulaire et la mort cellulaire

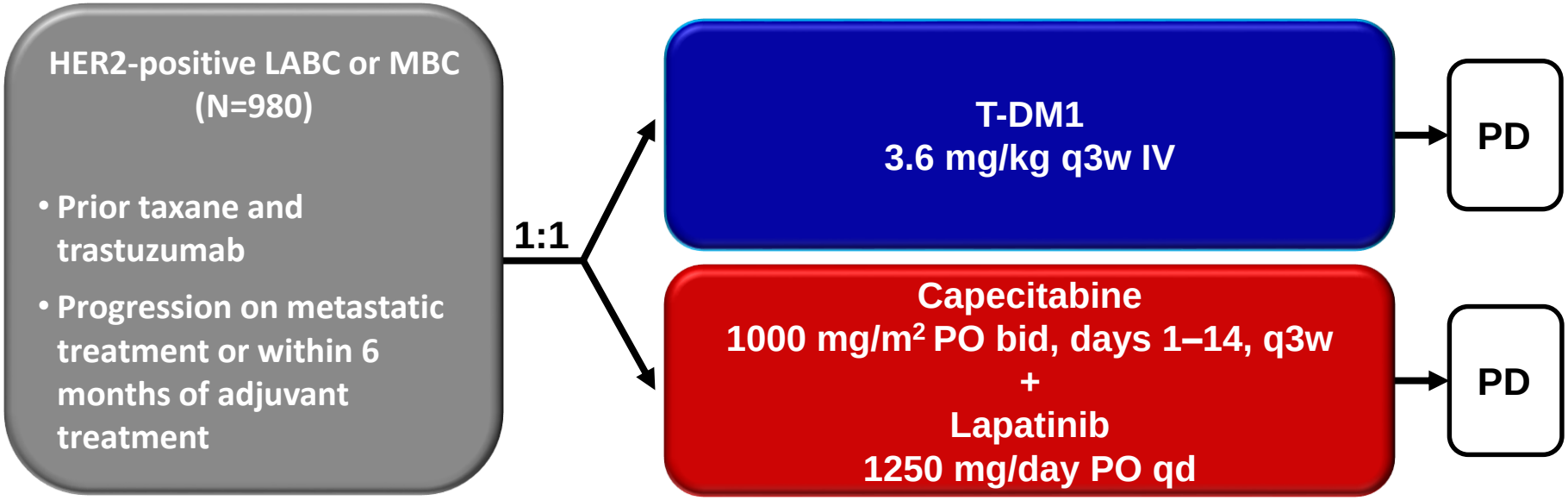


Fixation de Kadcyla



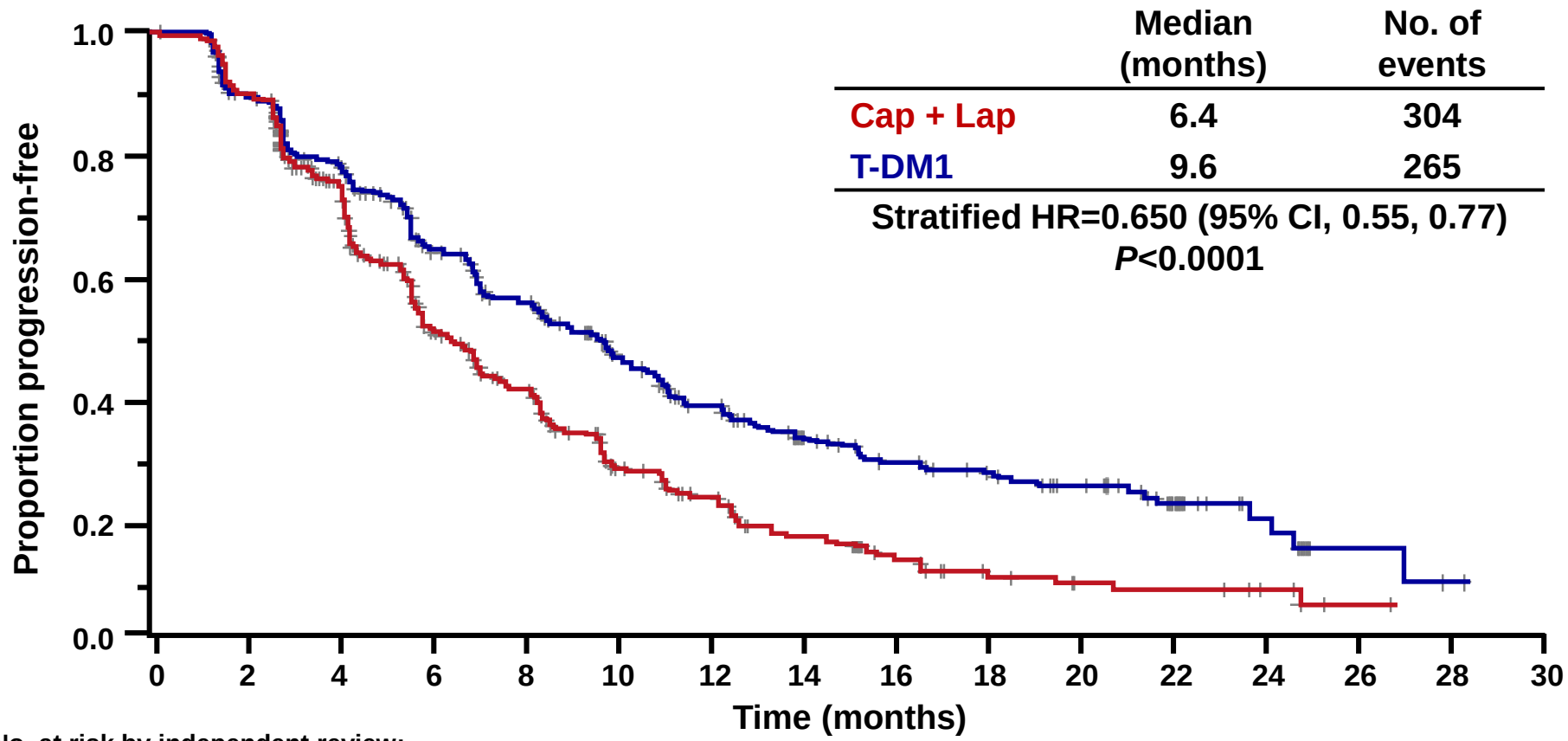
Le composant trastuzumab se lie aux récepteurs HER2

EMILIA Study Design



- **Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease
- **Primary endpoints:** PFS by independent review, OS, and safety
- **Key secondary endpoints:** PFS by investigator, ORR, DOR
- **Statistical considerations:** Hierarchical statistical analysis was performed in pre-specified sequential order: PFS by independent review → OS → secondary endpoints
  - PFS analysis: 90% power to detect HR=0.75; 2-sided alpha 5%
  - OS analyses: 80% power to detect HR=0.80; 2-sided alpha 5%

Progression-Free Survival by Independent Review



	Median (months)	No. of events
Cap + Lap	6.4	304
T-DM1	9.6	265

Stratified HR=0.650 (95% CI, 0.55, 0.77)
P<0.0001

No. at risk by independent review:

Cap + Lap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

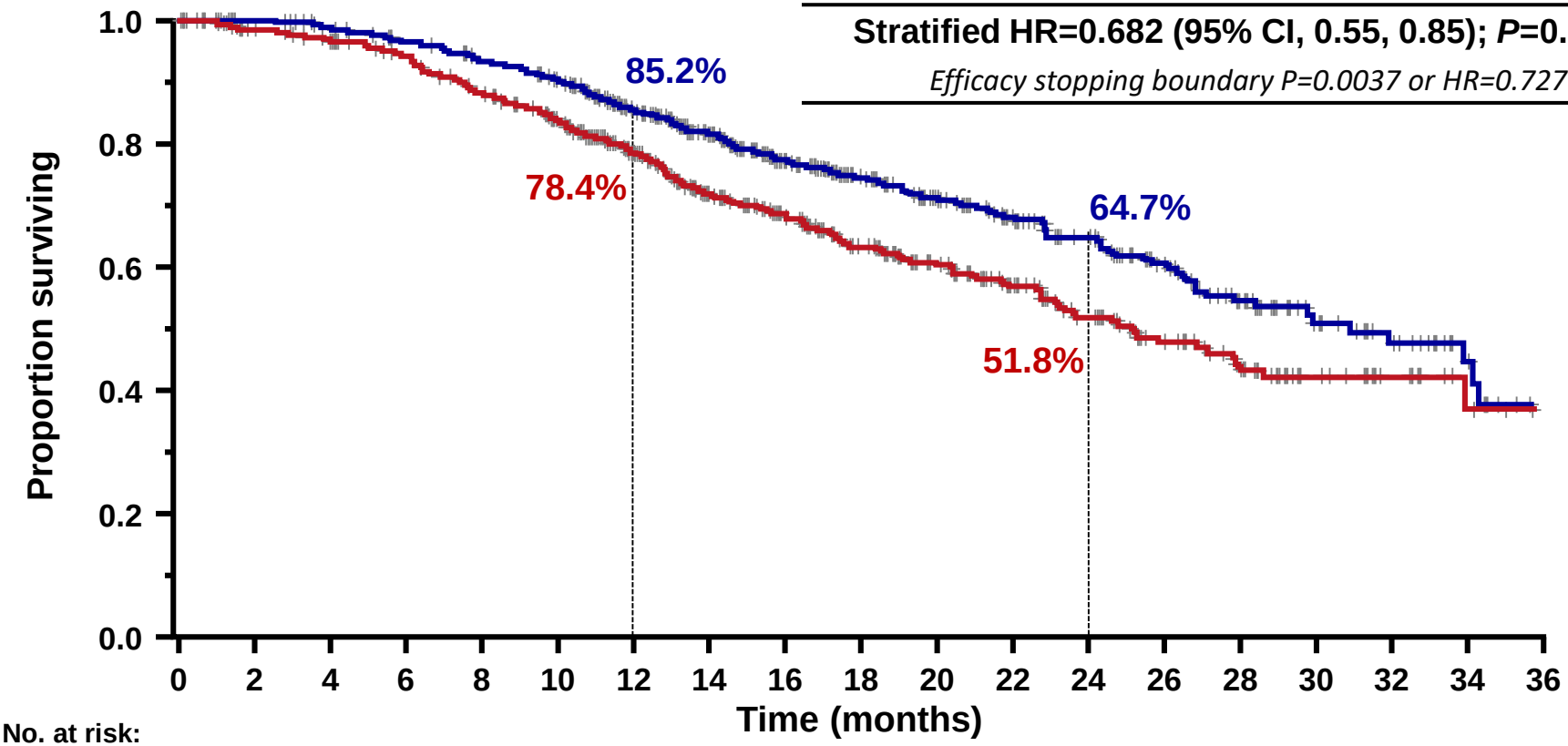
Unstratified HR=0.66 (*P*<0.0001).

Overall Survival: Confirmatory Analysis

	Median (months)	No. of events
Cap + Lap	25.1	182
T-DM1	30.9	149

Stratified HR=0.682 (95% CI, 0.55, 0.85); *P*=0.0006

Efficacy stopping boundary P=0.0037 or HR=0.727

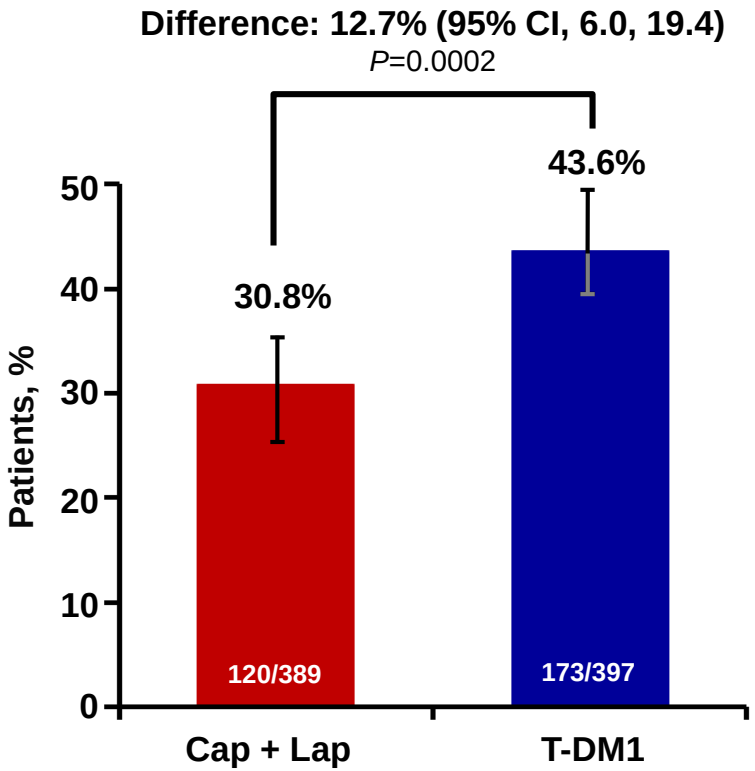


No. at risk:																			
Cap + Lap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

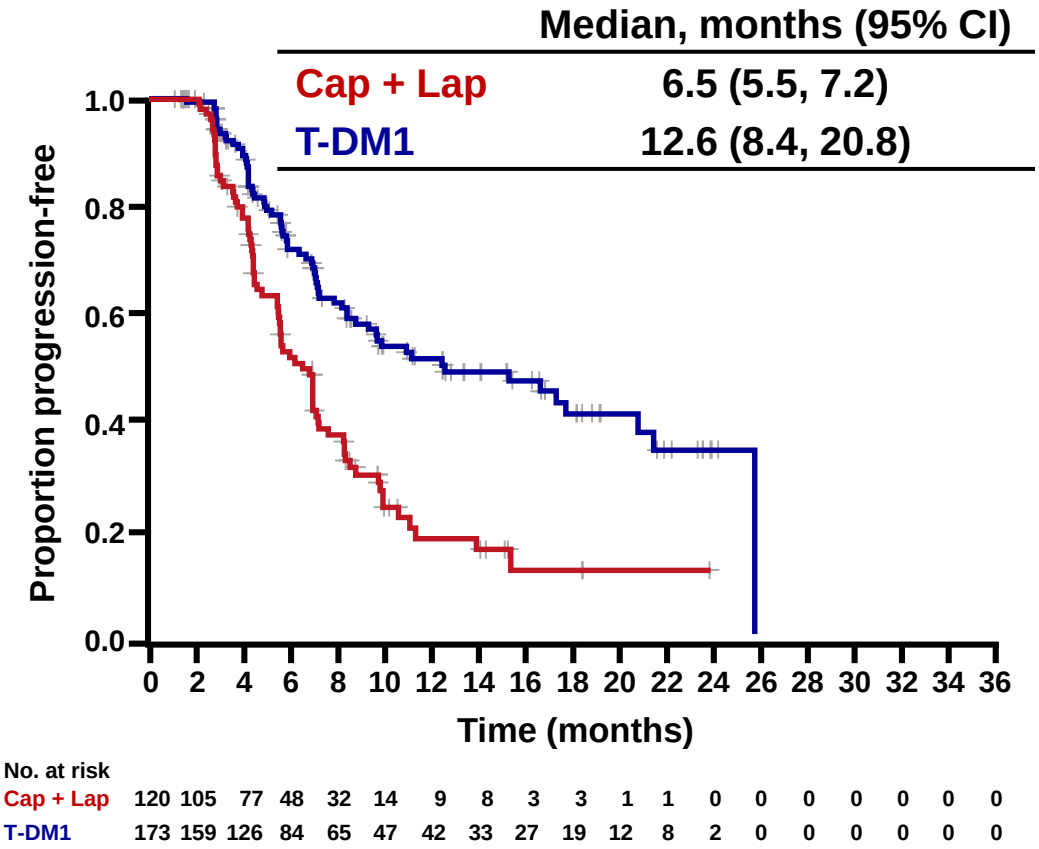
Data cut-off July 31, 2012; Unstratified HR=0.70 (*P*=0.0012).

ORR and DOR in Patients with Measurable Disease

Objective response rate (ORR)



Duration of response (DOR)



SAFETY

	Cap + Lap (n = 488)		T-DM1 (n = 490)	
Adverse event	All grades, %	Grade ≥3, %	All grades, %	Grade ≥3, %
Diarrhoea	79.7	20.7	23.3	1.6
Hand–foot syndrome	58.0	16.4	1.2	0.0
Vomiting	29.3	4.5	19.0	0.8
Neutropenia	8.6	4.3	5.9	2.0
Hypokalaemia	8.6	4.1	8.6	2.2
Fatigue	27.9	3.5	35.1	2.4
Nausea	44.7	2.5	39.2	0.8
Mucosal inflammation	19.1	2.3	6.7	0.2
Thrombocytopenia	2.5	0.2	28.0	12.9
Increased AST	9.4	0.8	22.4	4.3
Increased ALT	8.8	1.4	16.9	2.9
Anaemia	8.0	1.6	10.4	2.7

Verma S, et al. *N Engl J Med. 2012;367(19):1783-1791*

- **Metastatic breast cancer**

❑ **Au dela de la 2éme ligne**

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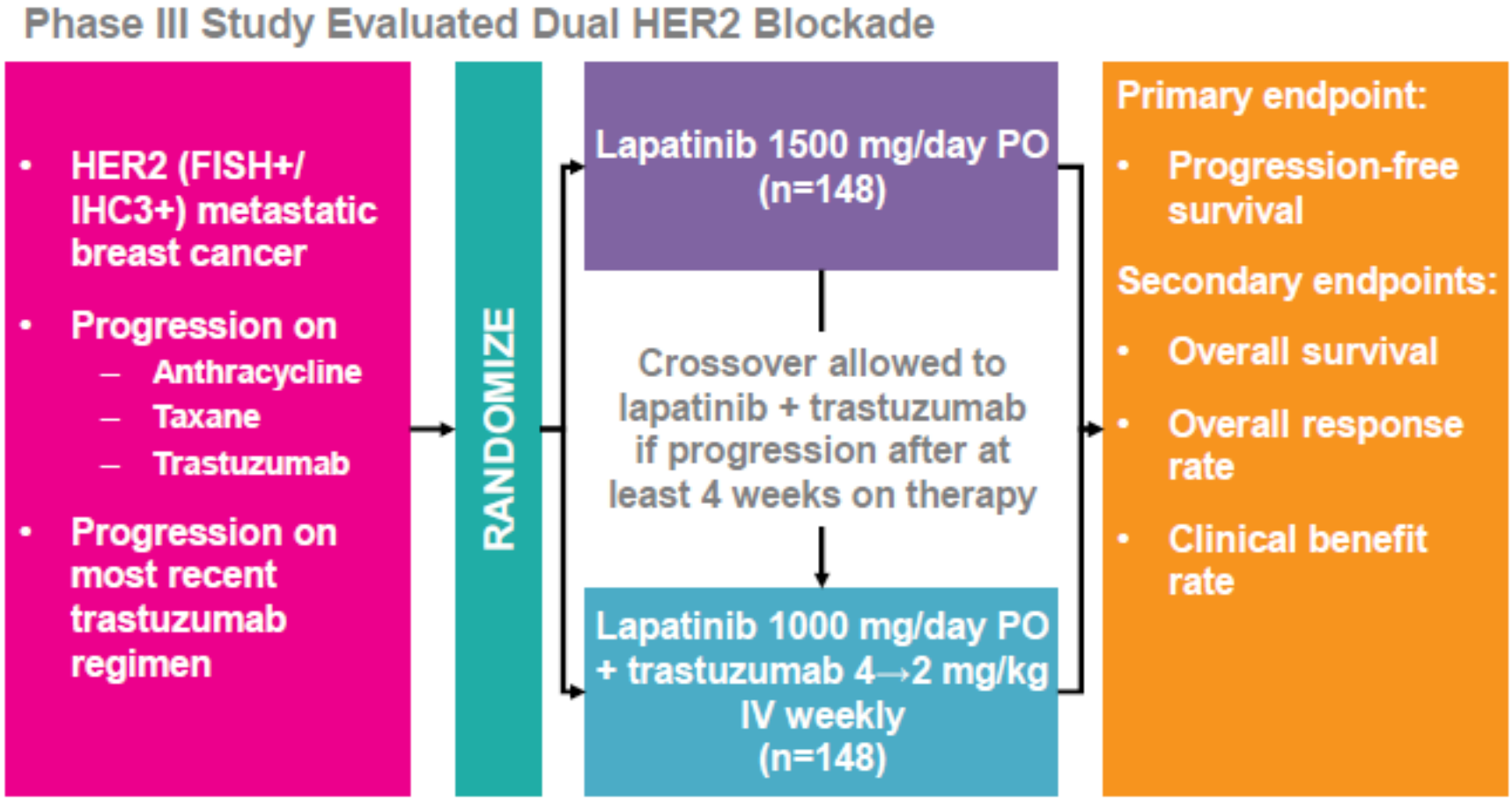


- Staging occurred at 4, 8, 12, 16 weeks and then every 8 weeks
- Steady state of single-agent lapatinib occurs at approximately 7 days

Blackwell K L *et al. JCO 2012;30:2585-2592*

Randomized Study of Lapatinib Alone or in Combination With Trastuzumab in Women With ErbB2-Positive, Trastuzumab-Refractory Metastatic Breast Cancer

Kimberly L. Blackwell, Harold J. Burstein, Anna Maria Storniolo, Hope Rugo, George Sledge, Maria Koehler, Catherine Ellis, Michelle Casey, Svetislava Vukelja, Joachim Bischoff, Jose Baselga, and Joyce O'Shaughnessy

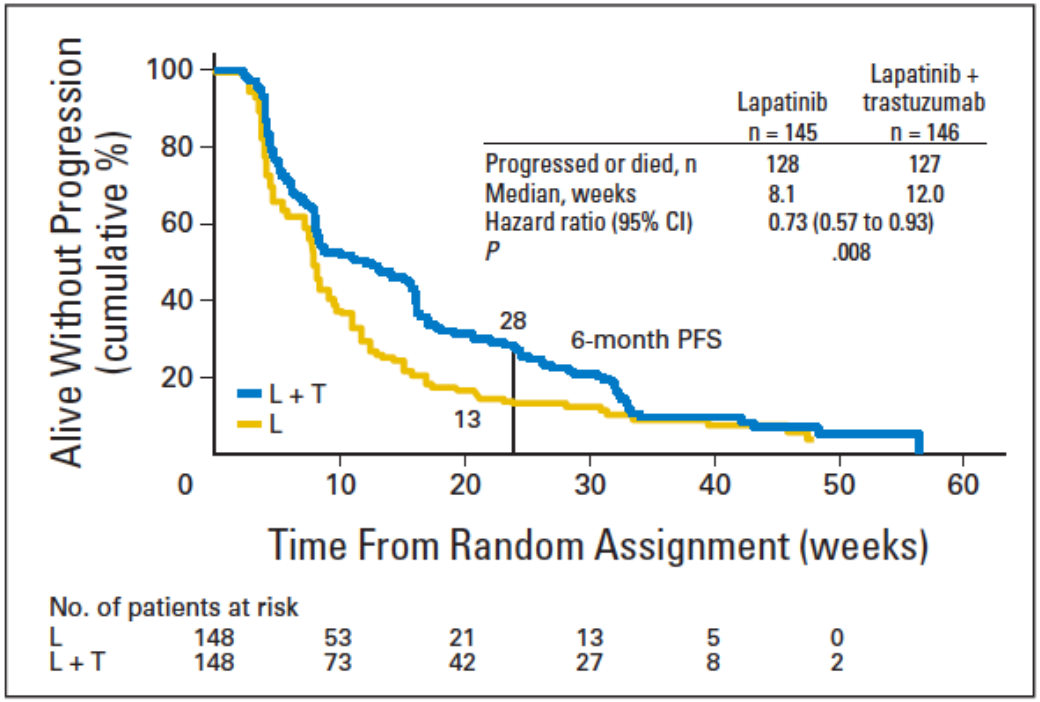


Fig 2. Kaplan-Meier estimates of progression-free survival (PFS) in the intent-to-treat population. L, lapatinib; L+T, lapatinib plus trastuzumab.

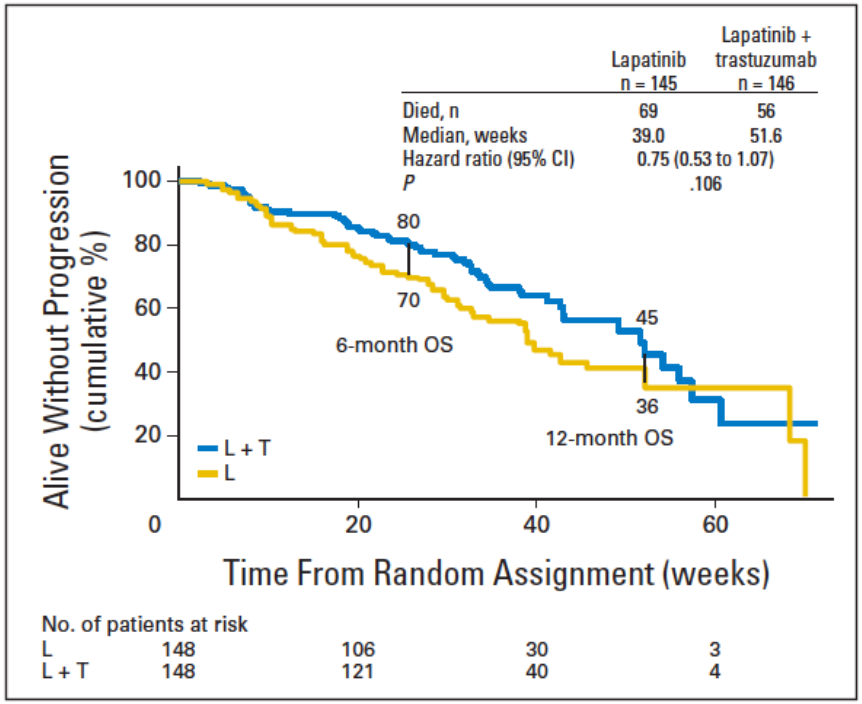
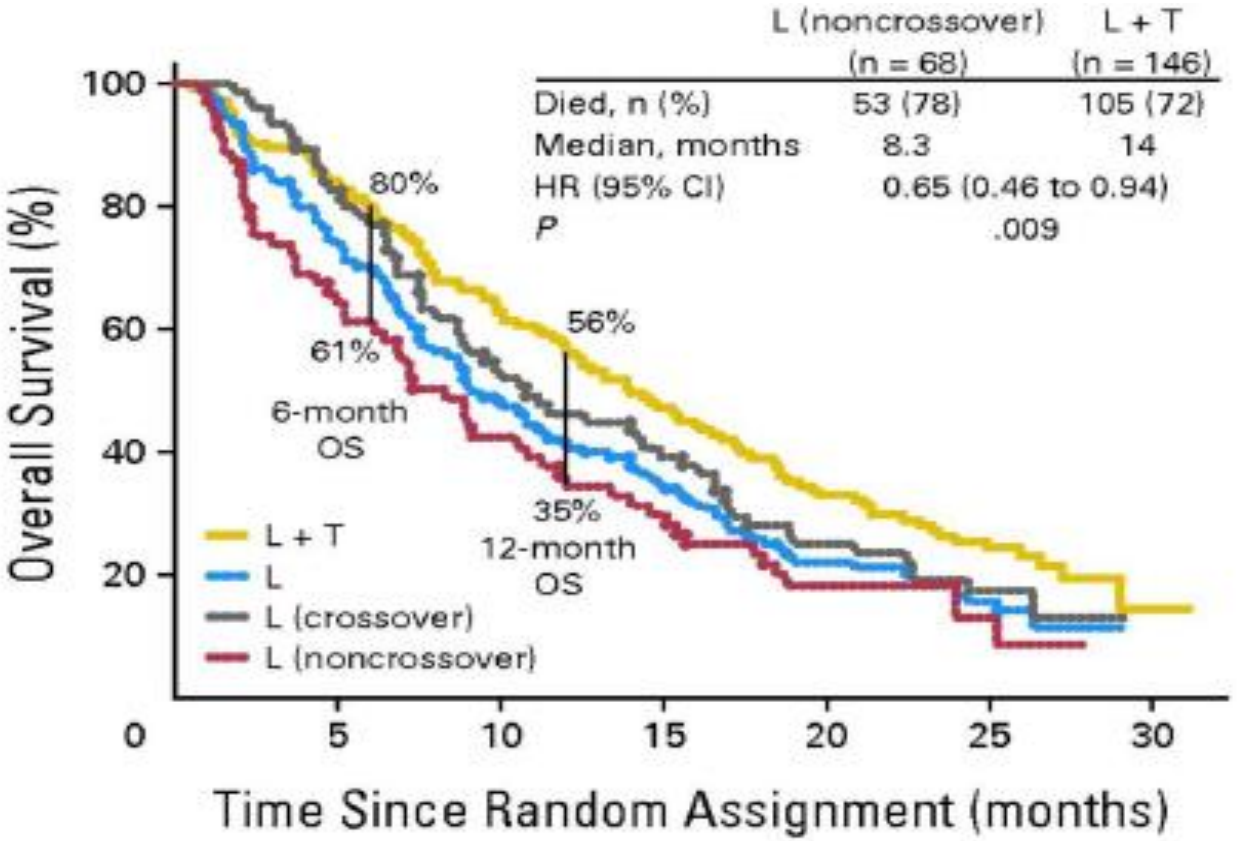


Fig 3. Kaplan-Meier estimates of overall survival (OS) in the intent-to-treat population. L, lapatinib; L+T, lapatinib plus trastuzumab.

J CLIN ONCOL 2010; 28: 1-7.

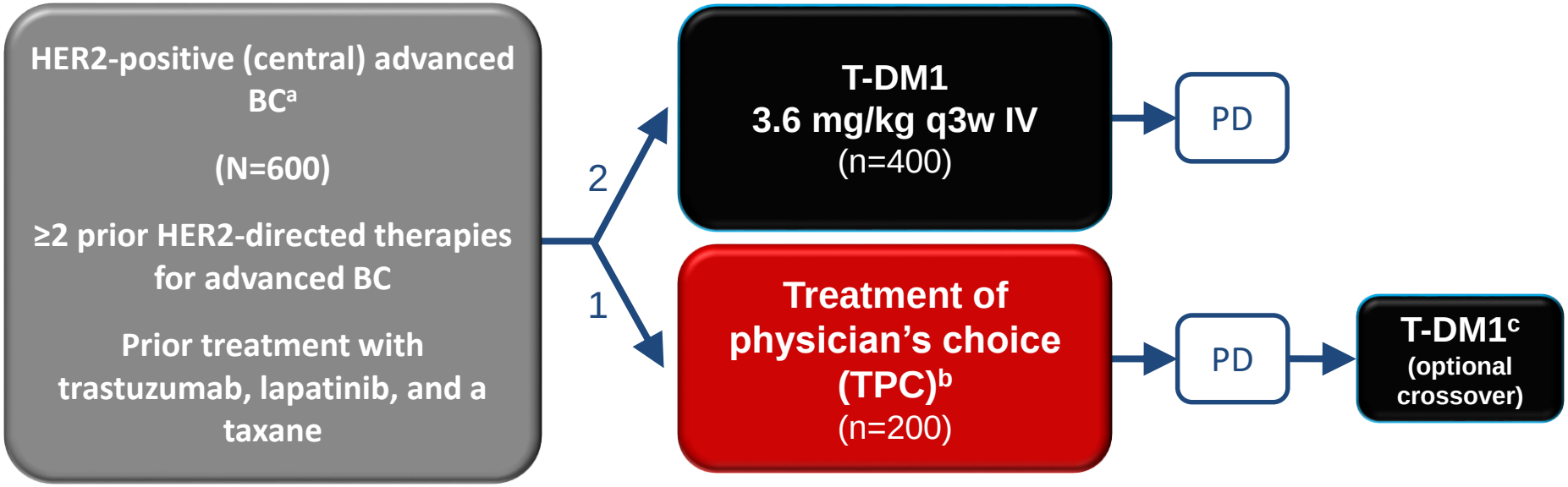
EGF 104900



No. at risk							
L + T	146	120	87	63	42	25	1
L	145	100	64	46	28	13	
L (crossover)	77	60	38	28	18	10	
L (noncrossover)	68	40	26	18	10	3	

Blackwell K L *et al. JCO 2012;30:2585-2592*

TH3RESA Study Schema



- **Stratification factors:** World region, number of prior regimens for advanced BC,[d] presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR by investigator and safety

[a] Advanced BC includes MBC and unresectable locally advanced/recurrent BC.
[b] TPC could have been single-agent chemotherapy, hormonal therapy, or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy.
[c] First patient in: Sep 2011. Study amended Sep 2012 (following EMILIA 2nd interim OS results) to allow patients in the TPC arm to receive T-DM1 after documented PD.
[d] Excluding single-agent hormonal therapy.
BC, breast cancer; IV, intravenous; ORR, objective response rate; PD, progressive disease; q3w, every 3 weeks.

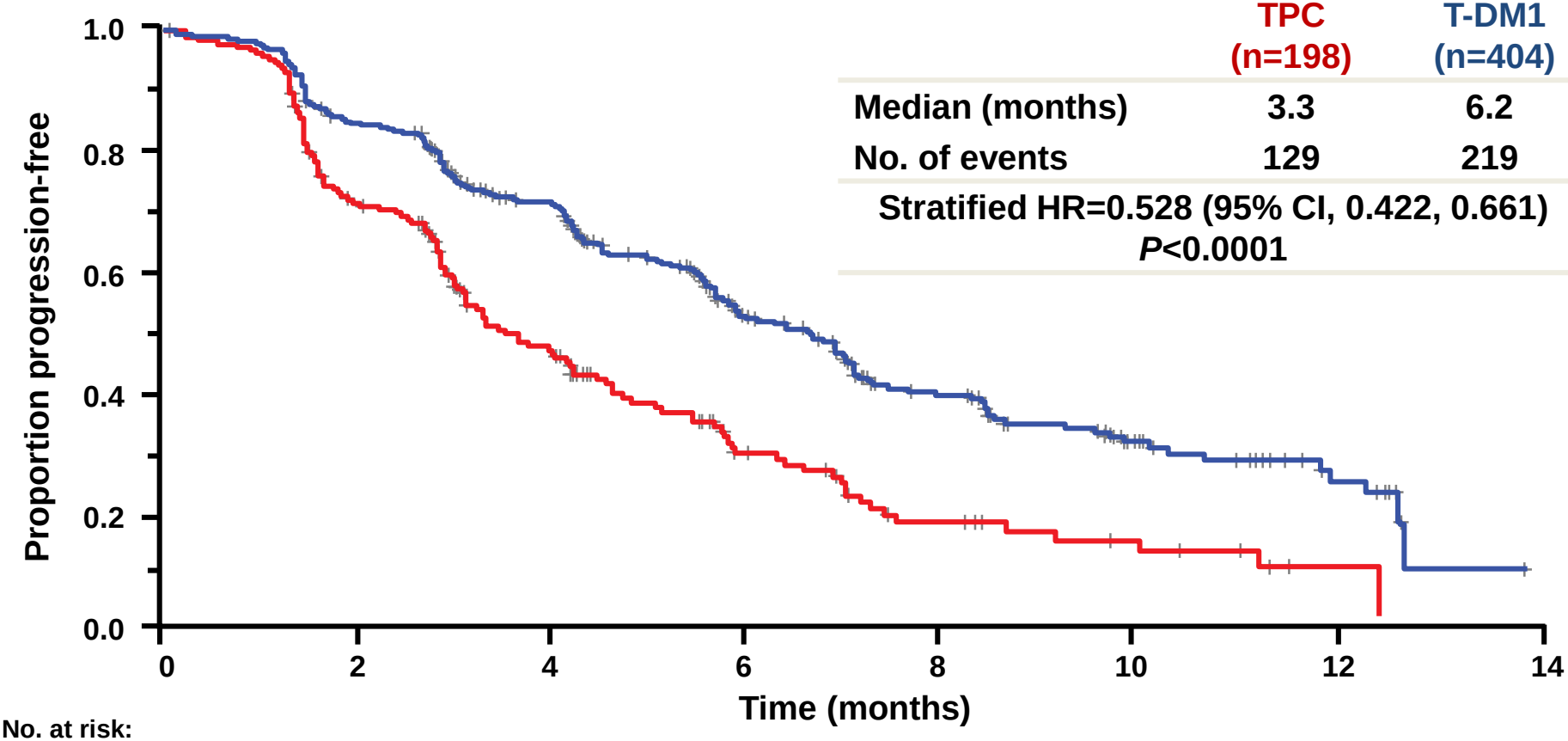
TPC Treatment Category

TPC treatment category	TPC (n=184[a])	
Combination with HER2-directed agent, %	**83.2**	
Chemotherapy[b] + trastuzumab	68.5	T-containing 80.4
Lapatinib + trastuzumab	10.3	
Hormonal therapy + trastuzumab	1.6	
Chemotherapy[b] + lapatinib	2.7	
Single-agent chemotherapy,[b] %	**16.8**	

[a] Includes patients who received study treatment.

[b] The most common chemotherapy agents used were vinorelbine, gemcitabine, eribulin, paclitaxel, and docetaxel.

PFS by Investigator Assessment



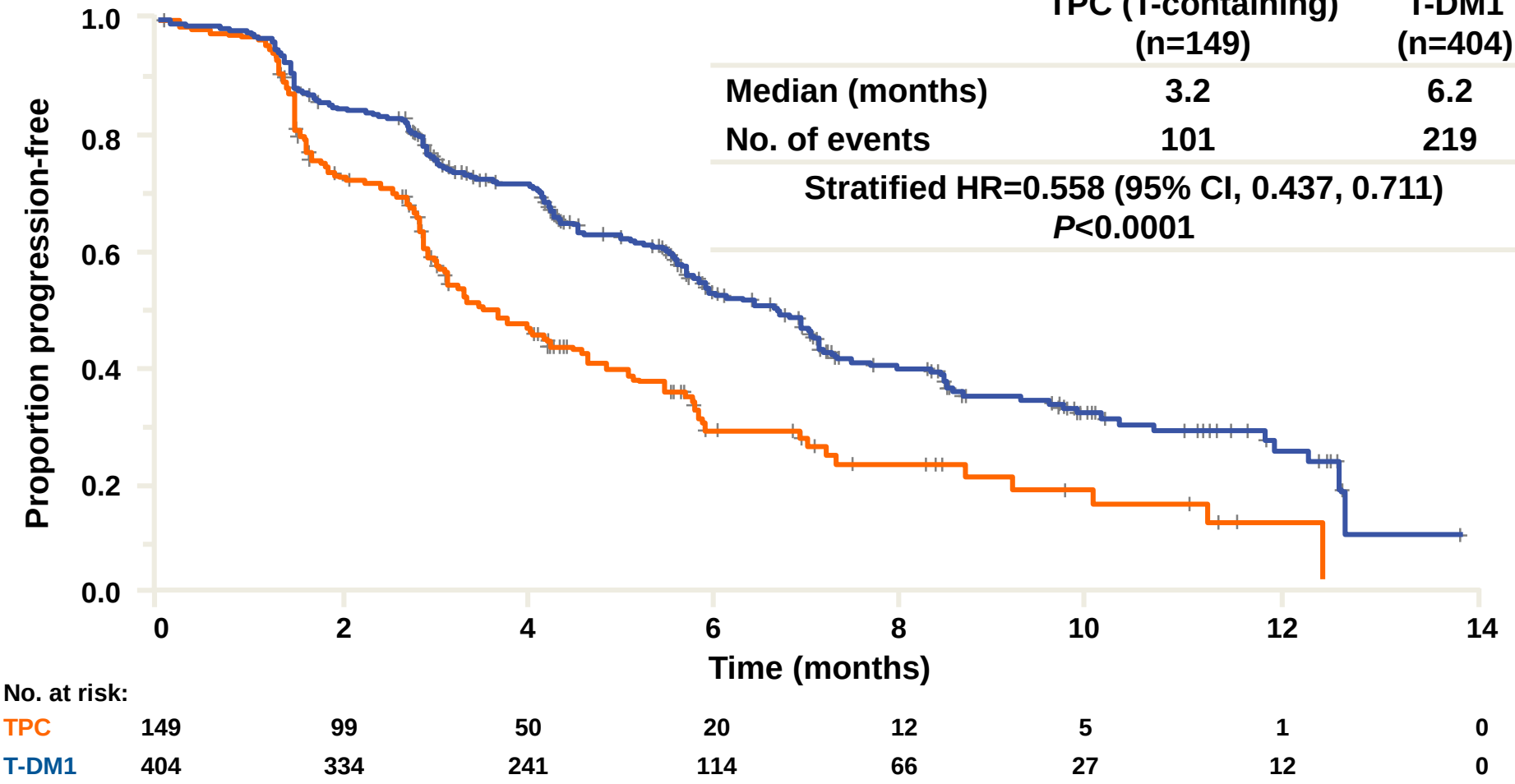
	TPC (n=198)	T-DM1 (n=404)
Median (months)	3.3	6.2
No. of events	129	219

Stratified HR=0.528 (95% CI, 0.422, 0.661)
P<0.0001

No. at risk:								
TPC	198	120	62	28	13	6	1	0
T-DM1	404	334	241	114	66	27	12	0

Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.
Unstratified HR=0.521 (*P*<0.0001).

PFS for Patients Treated With Trastuzumab-Containing Regimens



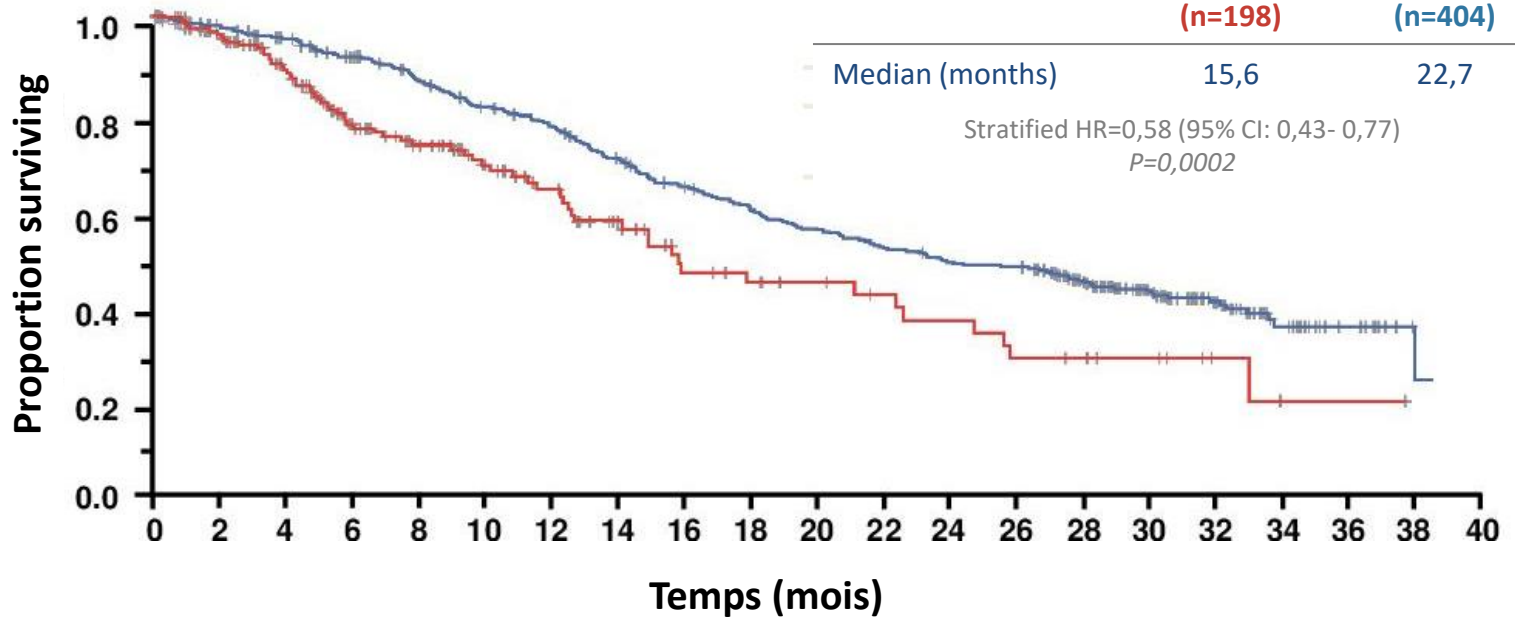
	TPC (T-containing) (n=149)	T-DM1 (n=404)
Median (months)	3.2	6.2
No. of events	101	219

Stratified HR=0.558 (95% CI, 0.437, 0.711)
P<0.0001

No. at risk:								
TPC	149	99	50	20	12	5	1	0
T-DM1	404	334	241	114	66	27	12	0

Unstratified HR=0.54 (*P*<0.0001).

OS (ITT analysis with 40 months of follow-up)



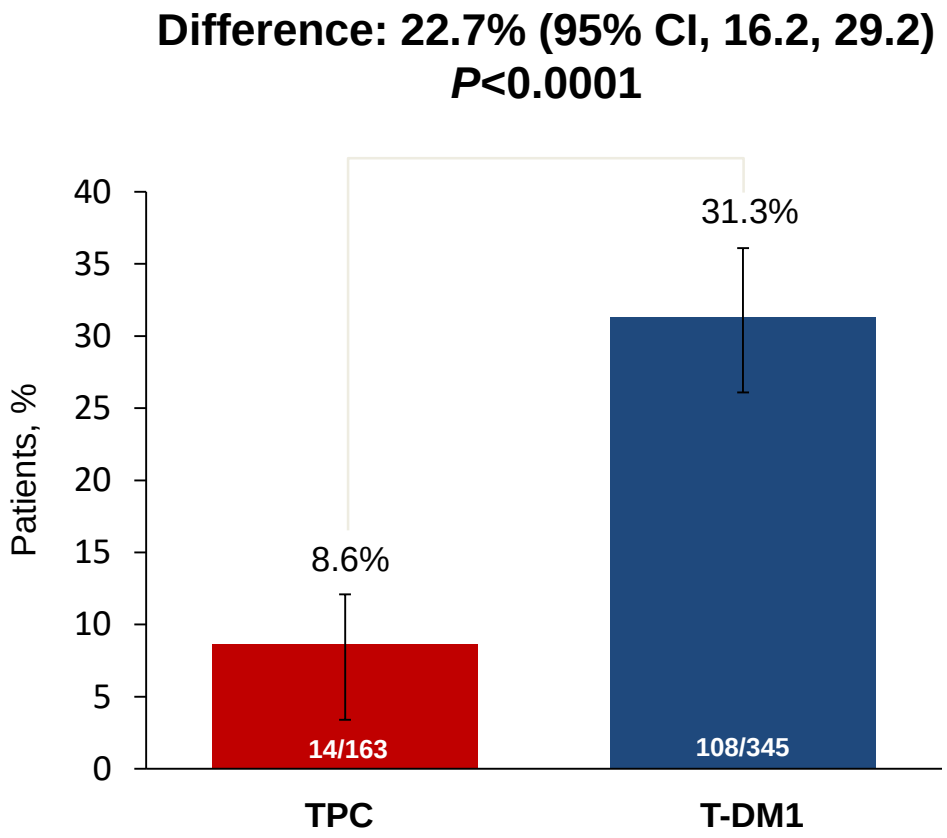
No. At risk

TPC	198	163	131	96	78	57	47	35	24	21	18	15	13	10	9	7	3	1	1	0	0
T-DM1	404	388	368	347	321	298	280	251	226	207	192	179	167	164	132	84	54	25	12	2	0

All 93 crossover patients were censored

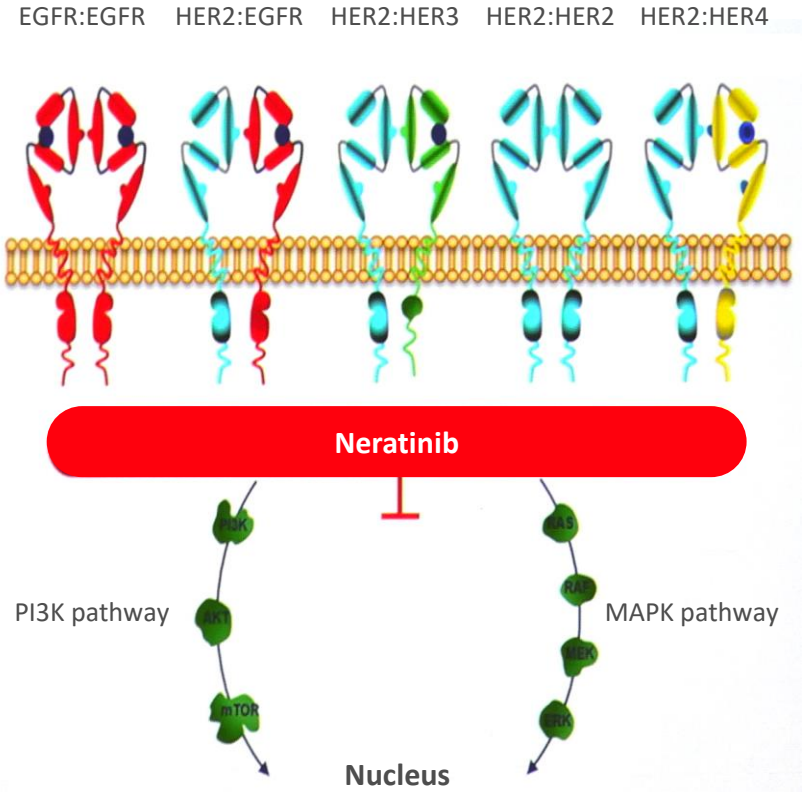
Wildiers H. *et al.*, SABCS 2013, S5-05

ORR in Patients With Measurable Disease



Neratinib : pan-HER TKI irréversible

Aberrant HER activation by:
- → Gene amplification
- → Receptor overexpression
- → Somatic mutations

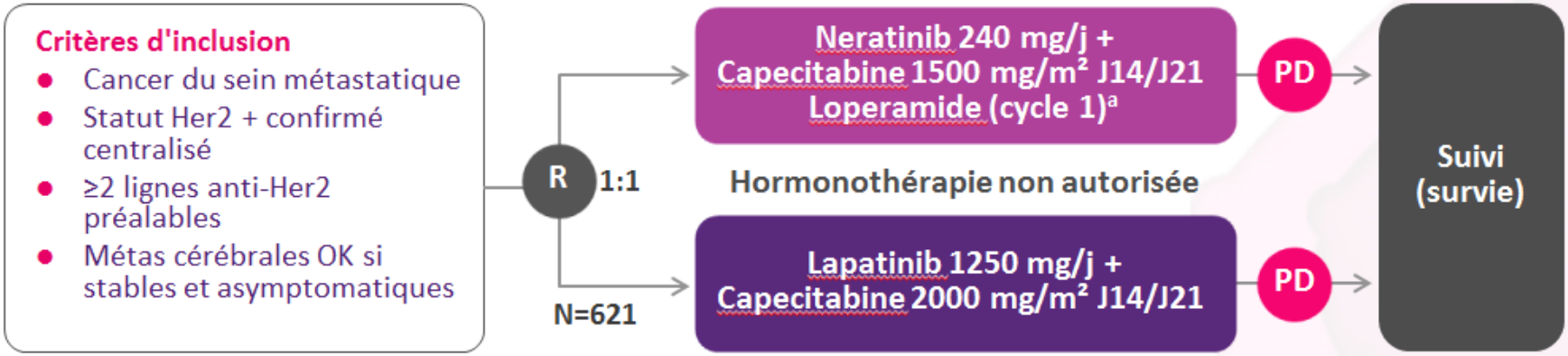


- Neratinib: pan-HER (HER1, 2, and 4) TKI
- Large Impact du neratinib sur la famille des récepteurs Her (HER1, 2, et 4 pour le neratinib; HER1 et 2 pour le lapatinib)
- Neratinib se lie de manière irréversible à HER1, 2, et 4; Liaison réversible avec lapatinib

- → Cell cycle control and proliferation
- → Cell survival and decreased apoptosis
- → Cellular migration and metastasis
- → Anglogenesis

C. Saura, et al., ASCO® 2019, Abs.#1002

Etude NALA



Stratification :

- Nombre de traitements antérieurs anti Her2
- Localisations des métastases
- Statut RH
- Localisation géographique

Critères de jugement :

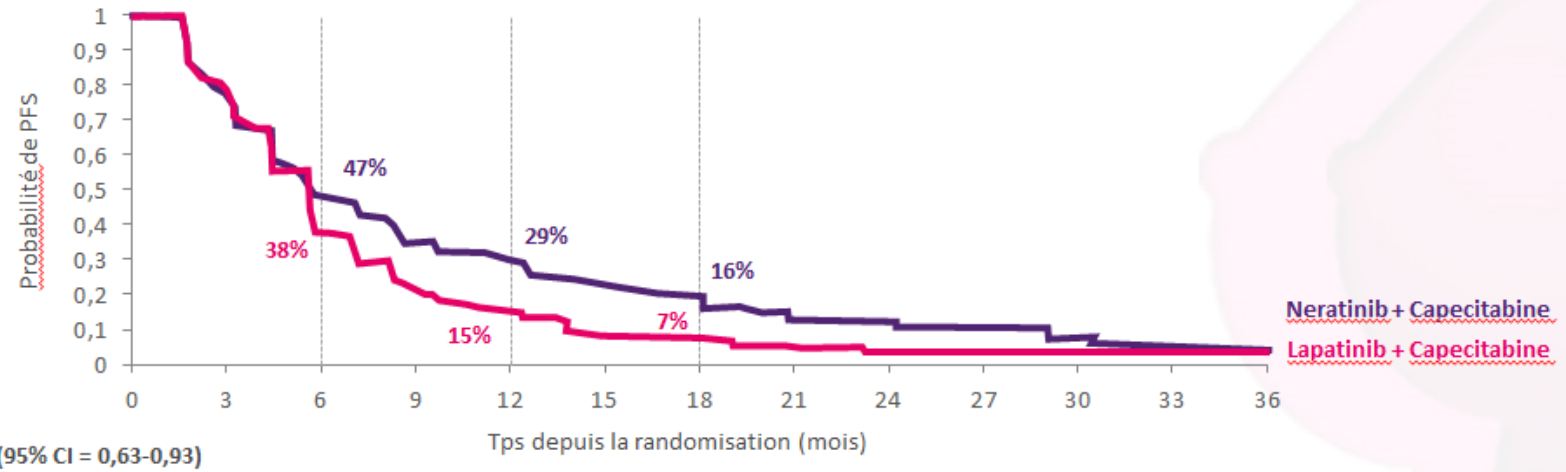
- Co-primaires : PFS et OS
- Secondaires : PFS (local), ORR, DoR, CBR, intervention pour métastases du SNC, tolérance

Lopéramide 4 mg avec la première dose de nératinib, suivie de 2 mg toutes les 4 h pendant 3 jours, puis de 2 mg toutes les 6-8 h jusqu'à la fin du cycle 1. Par la suite, au besoin

. Saura, et al., ASCO® 2019, Abs.#1002

Etude NALA

PFS centralisée (critère co-primaire)



HR 0,76 (95% CI = 0,63-0,93)
p : 0,0059

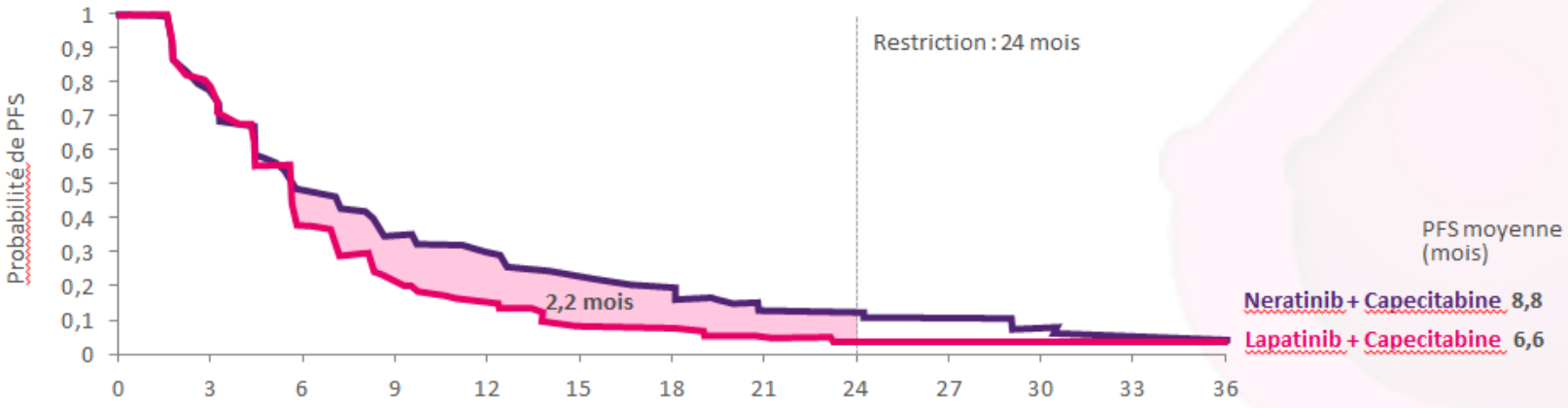
Nbre de risque

N + C	307	183	113	69	54	35	20	13	9	7	3	2	2
L + C	314	183	82	39	24	9	8	3	2	2	2	2	1

. Saura, et al., ASCO® 2019, Abs.#1002

Etude NALA

Analyse pré-sépicfiée restreinte à 24 mois – Moyenne des PFS



HR 0,76 (95% CI = 0,63-0,93)
p : 0,0003

Nbre à risque

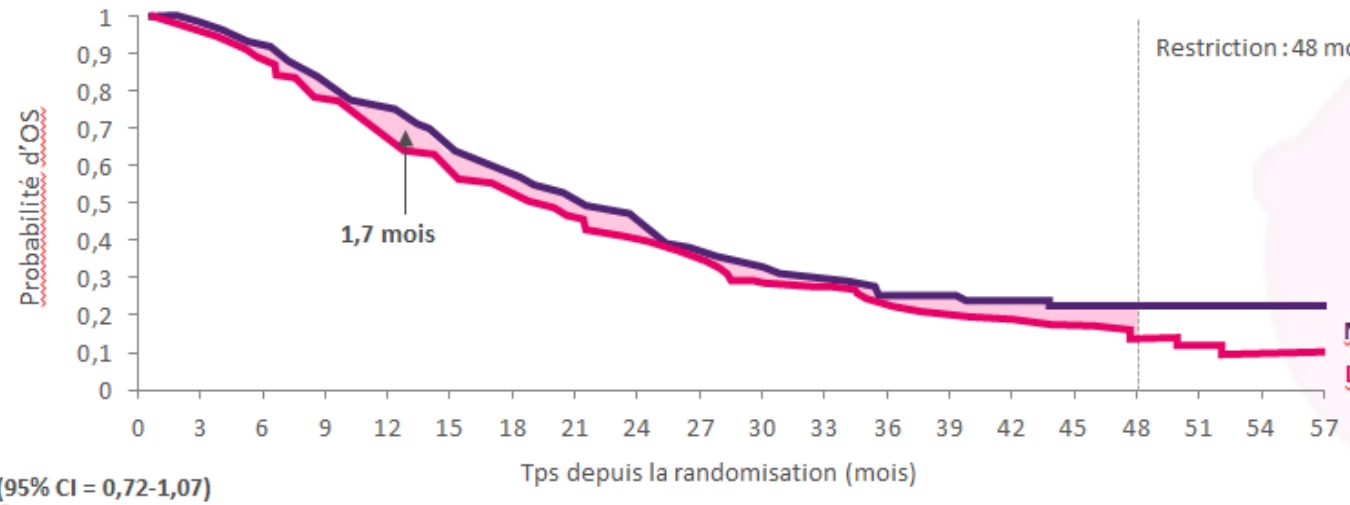
N + C	307	183	113	69	54	35	20	13	9	7	3	2	2
L + C	314	183	82	39	24	9	8	3	2	2	2	2	1

Gain en PFS de 2,2 mois avec le nératinib comparé au lapatinib : 8,8 versus 6,6 mois

. Saura, et al., ASCO® 2019, Abs.#1002

Etude NALA

Survie globale: critère co-primaire



HR 0,88 (95% CI = 0,72-1,07)
p : 0,2086

Nbre à risque

N + C	307	294	275	244	220	182	142	112	82	64	47	34	28	18	15	13	6	4	2	1
L + C	314	303	273	240	208	170	132	107	84	67	47	36	27	22	17	12	8	4	3	1

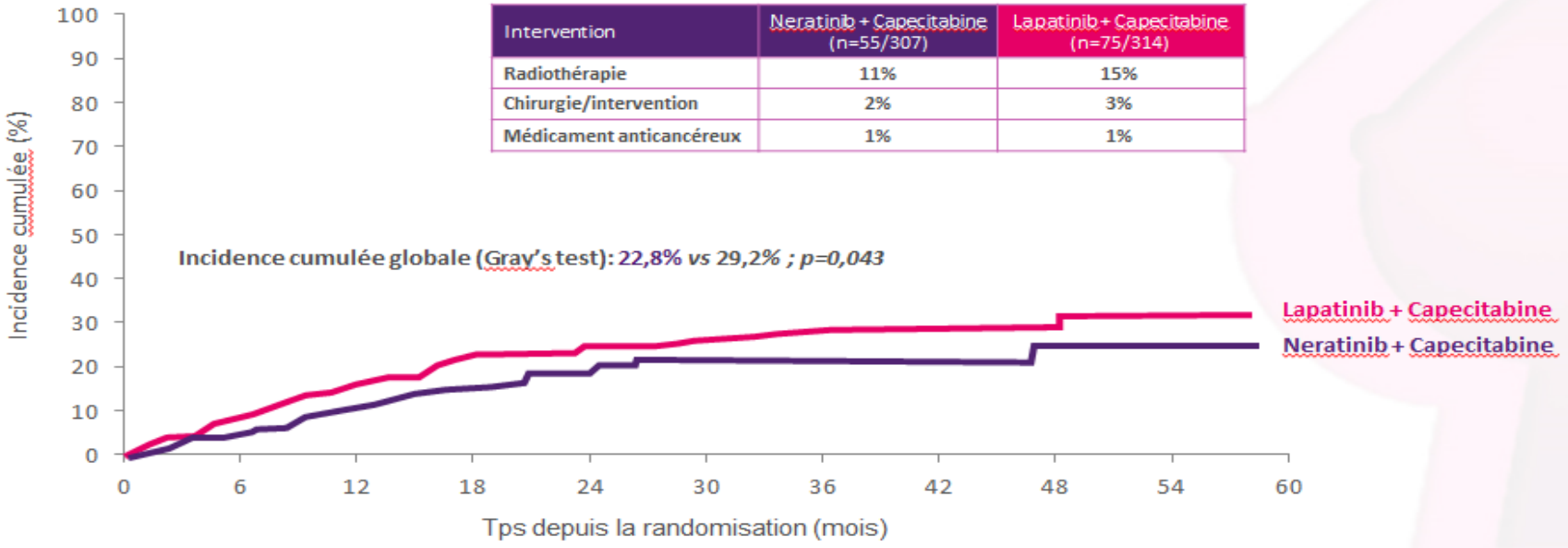
L'OS n'est pas encore tout à fait mature, mais légèrement en faveur du nératinib à ce stade du suivi avec un gain de 1,7 mois.

. Saura, et al., ASCO® 2019, Abs.#1002

Etude NALA

Temps jusqu'à nécessité d'intervention sur les métastases cérébrales

Intervention	Neratinib + Capecitabine (n=55/307)	Lapatinib + Capecitabine (n=75/314)
Radiothérapie	11%	15%
Chirurgie/intervention	2%	3%
Médicament anticancéreux	1%	1%



. Saura, et al., ASCO® 2019, Abs.#1002

Etude NALA: Toxicité

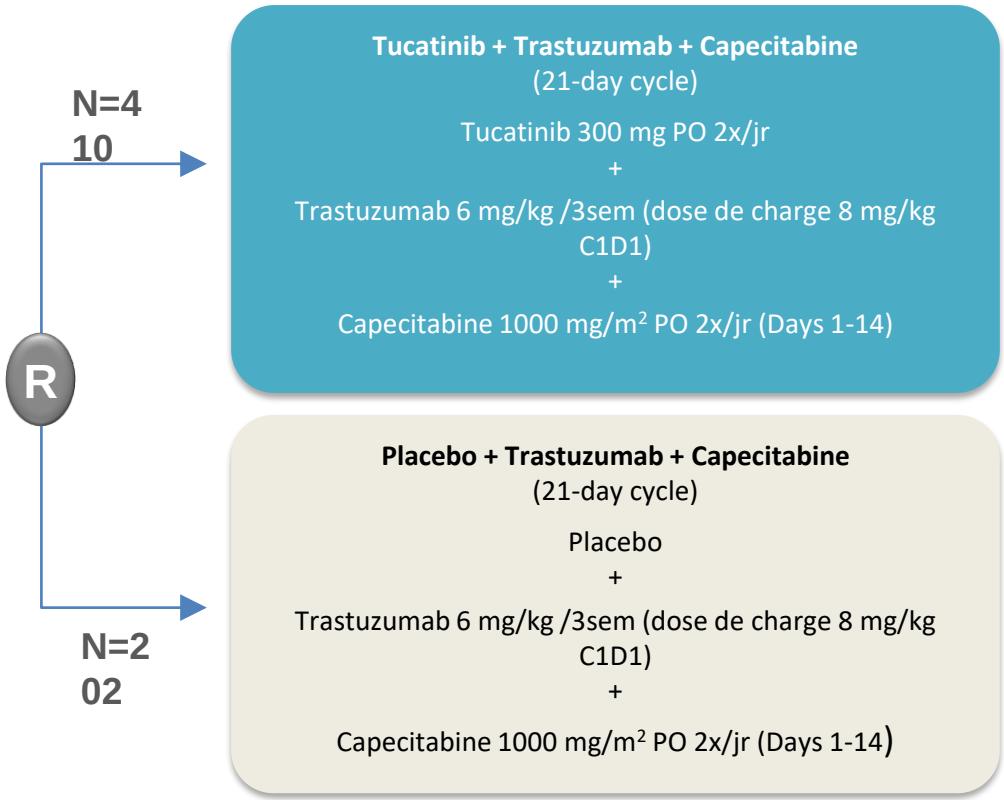
	Nératinib + Capécitabine (n=303)	Lapatinib + Capécitabine (n=311)
Toxicité maximale , n (%)		
Grade 1	91 (30)	111 (36)
Grade 2	87 (29)	56 (18)
Grade 3	74 (24)	39 (13)
Temps avant première apparition de la diarrhée, jours		
Grade 2 ou 3	9	18
Grade 3	11	38
Durée cumulative médiane par patient, jours		
Grade 2 ou 3	7	9
Grade 3	4	4
Arrêt du traitement en raison de diarrhée :	N+C : 2.6%	L+C : 2.3%

Saura, et al., ASCO® 2019, Abs.#1002

HER2CLIMB: design de l'étude

Critères d'éligibilité

- Cancer du sein métastatique HER2+
- Patients prétraités par trastuzumab, pertuzumab et T-DM1
- ECOG 0 où 1
- IRM cérébrale à l'inclusion
  - → Atteinte préalablement traitée et stable
  - → Atteinte de novo ne nécessitant pas de prise en charge locale immédiate
  - → Atteinte préalable et progressive mais ne nécessitant pas de prise en charge locale immédiate
  - → Pas d'arguments pour une atteinte cérébrale



*Facteurs de stratification : présence de métastases cérébrales (oui/non), ECOG (0 or 1), et région US ou Canada ou reste du monde)

Murthy R. et al, SABCS 2019 GS1-01

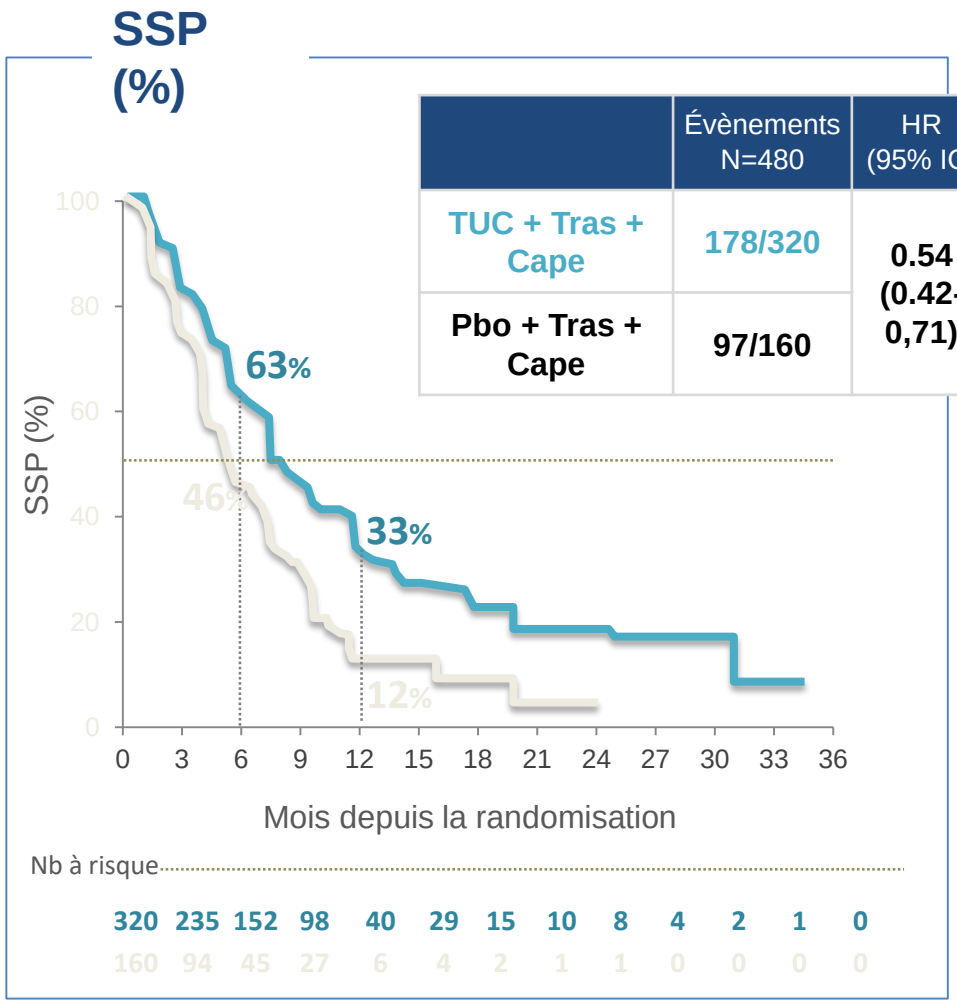
HER2CLIMB :Caractéristiques à l'inclusion

Distribution, n (%)		TUC+Tras+Cape N=410	Pbo+Tras+Cape N=202
Femme		**407 (99)**	**200 (99)**
Age (années), median (intervalle)		**55 (22-80)**	**54 (25-82)**
ECOG	0	**204 (49)**	**94 (47)**
	1	**206 (50)**	**108 (54)**
Statut RH	RE et/ou RP positifs	**143 (35)**	**77 (39)**
	RE et RP négatifs	**243 (60)**	**127 (63)**
Nb median de ignes précédentes de traitement, (intervalle)	Total	**4 (2-14)**	**4 (2-17)**
	Situation métastatique	**3 (1-14)**	**3 (1-3)**
Presence/histoire de metastases cérébrales		**198 (48)**	**93 (46)**
- Traitées, stables		**118 (59,6)**	**55 (59,1)**
- Non traitées		**44 (22,2)**	**22 (23,7)**
- Traitées en progression		**36 (18,2)**	**16 (17,2)**

Répartition bien équilibrée entre les bras de traitement

Murthy R. et al, SABCS 2019 GS1-01

HER2CLIMB :SSP



	Évènements N=480	HR (95% IC)	*valeure-p*
TUC + Tras + Cape	178/320	0.54 (0.42-0,71)	<0.00001
Pbo + Tras + Cape	97/160		

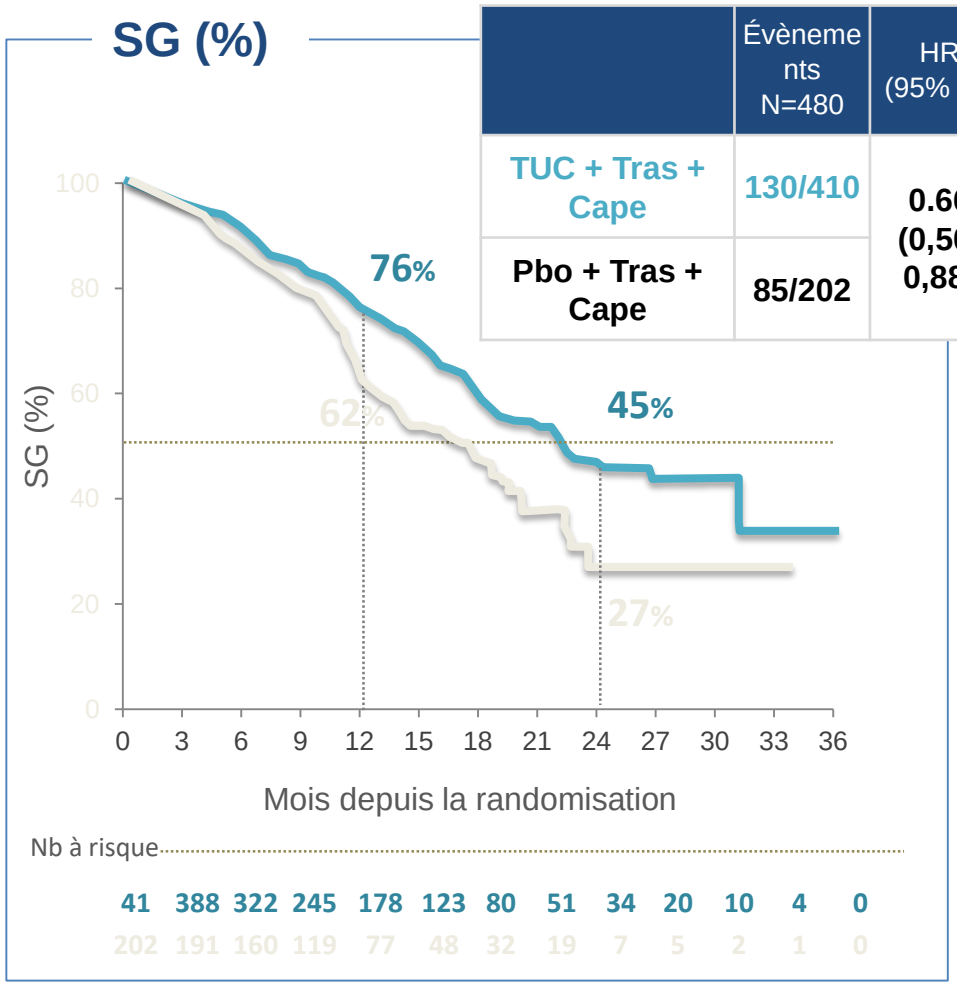
Le risque de progression ou de décès à été réduit de 46% dans la population initiale

	SSP à 1 an (95% IC)	SSP médiane (95% IC)
TUC + Tras + Cape	33% (27-40)	7,8 mois (7,5-9,6)
Pbo + Tras + Cape	12% (6-21)	5,6 mois (4,2-7,1)

Prespecified efficacy boundary for PFS: p=0.05
Data cut off : Sep 4, 2019

Murthy R. et al, SABCS 2019 GS1-01

SG



	Évènements N=480	HR (95% IC)	*valeure-p*
TUC + Tras + Cape	130/410	**0.66 (0,50-0,88)**	**0.00480**
Pbo + Tras + Cape	**85/202**		

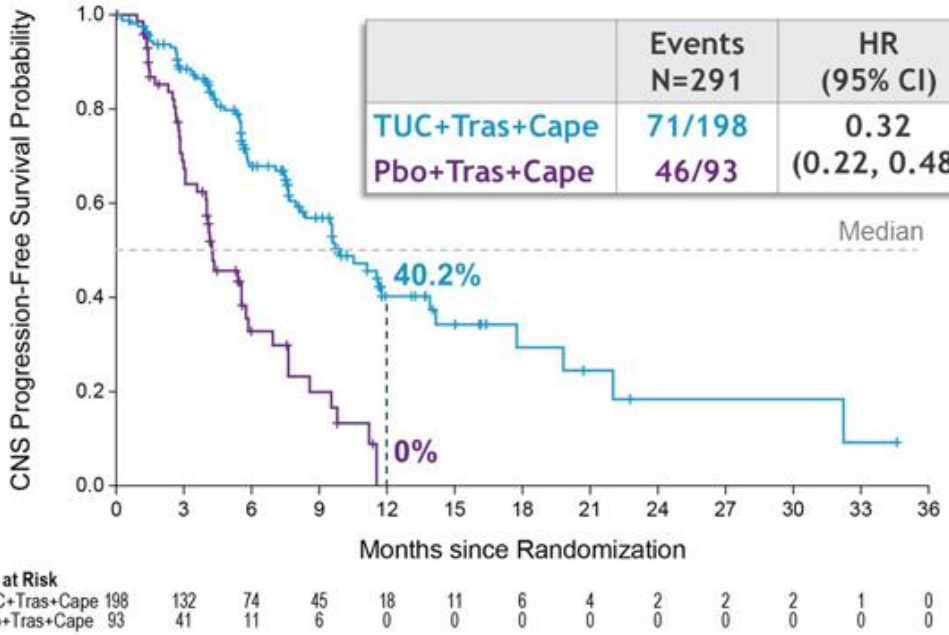
Le risque de décès à été réduit de 34% dans la population globale

	SG à 2 ans (95% IC)	SG médiane (95% IC)
TUC + Tras + Cape	45% (37-53)	21,9 mois (18,3-31,0)
Pbo + Tras + Cape	27% (20-39)	**17,4 mois (13,6-19,8)**

Prespecified efficacy boundary for OS: p=0.0074
Was met at the first interim analysis
Data cut off : Sep 4, 2019

Murthy R. et al, SABCS 2019 GS1-01

HER2CLIMB : SSP chez les patients avec métastases cérébrales



	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	71/198	0.32 (0.22, 0.48)	<0.00001
Pbo+Tras+Cape	46/93		

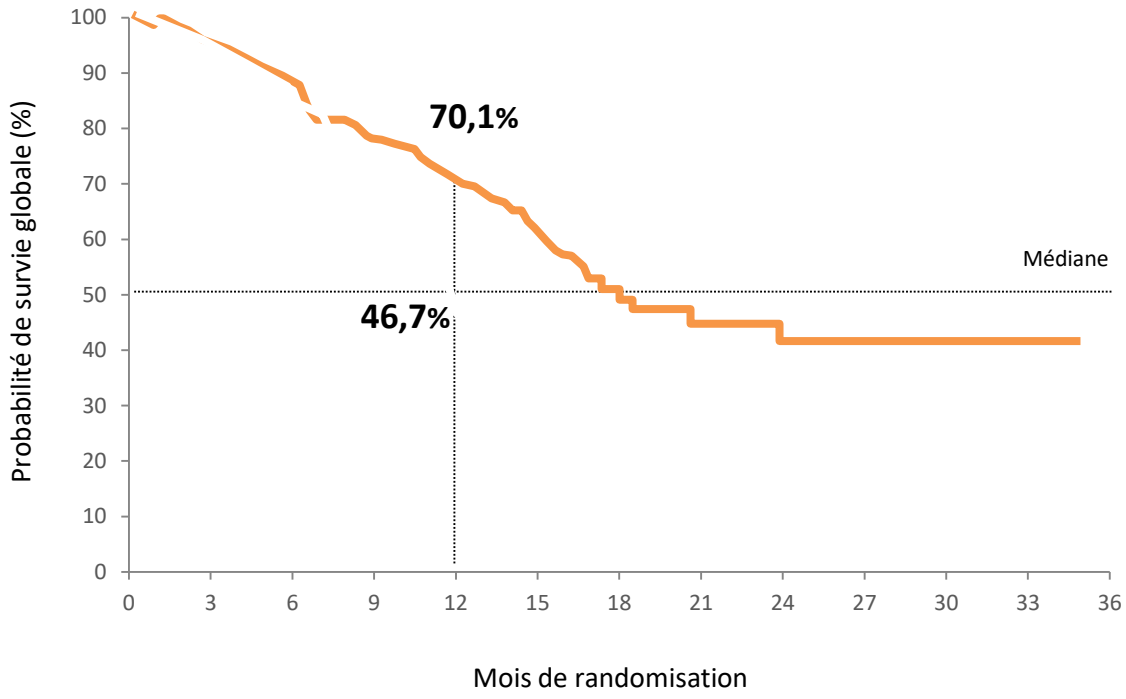
Risk of CNS progression or death was reduced by 68% in patients with brain metastases

One-year CNS-PFS (95% CI):	
TUC+Tras+Cape 40.2% (29.5, 50.6)	Pbo+Tras+Cape 0%
Median CNS-PFS (95% CI):	
TUC+Tras+Cape 9.9 months (8.0, 13.9)	Pbo+Tras+Cape 4.2 months (3.6, 5.7)

CNS-PFS: time from randomization to disease progression in the brain or death by investigator assessment.
HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

Lin N, *et al*., ASCO® 2020, Abs #1005

HER2CLIMB : SG chez les patients avec métastases cérébrales



Nbre Pts à risque

TUC+Tras+Cape	**198**	**184**	**146**	**108**	**79**	**49**	**26**	**17**	**14**	**7**	**6**	**2**	**0**
Pbo+Tras+Cape	**93**	**87**	**67**	**49**	**23**	**12**	**9**	**5**	**0**	**0**	**0**	**0**	**0**

	Evénements N=291	HR (IC95%)	*p*
TUC + Tras + Cape	**68/198**	**0,58 (0,40-0,85)**	**0,005**
	46/93		

Le risque de décès a été réduit de 42% chez les patients présentant des métastases cérébrales

	Survie globale à 1 an (IC95%)	Médiane de survie globale (IC95%)
TUC + Tras + Cape	**70,1% (62,1-76,7)**	**18,1 mois (15,5-NE)**
	46,7% (33,9-58,4)	**12,0 mois (11,2-15,2)**

NE : Non estimée

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and region of world: North America/Rest of world) at randomization.
All *p* values are nominal

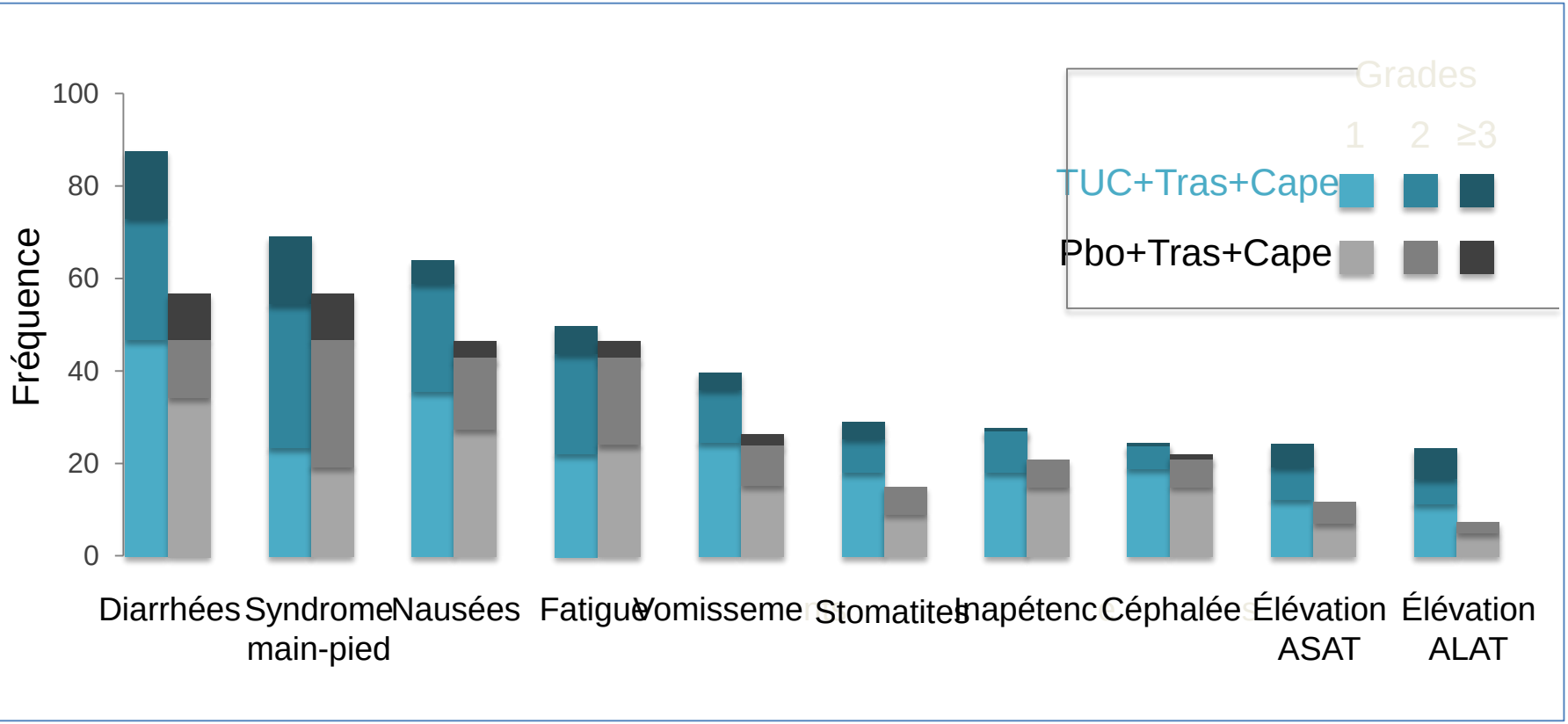
Lin N, *et al.*, ASCO® 2020, Abs #1005

HER2CLIMB: Efficacité

	Population générale		Patients avec métastases cérébrales		Métastases actives		Métastases stables	
	Tucatinib	Placebo	Tucatinib	Placebo	Tucatinib	Placebo	Tucatinib	Placebo
Taux de réponse objective (ORR)	41%	23%	-		47%	20%	-	
Durée de la réponse cérébrale, (DDR-IC)	-		-		6,8 mois	3,0 mois	-	
Survie sans progression (SSP)	HR=0,54		HR=0,48		-		-	
	7,8 mois	5,6 mois	7,6 mois	5,4 mois				
Survie sans progression cérébrale (SSP-SNC)	-		HR=0,32		HR=0,36		HR=0,31	
			9,9 mois	4,2 mois	9,5 mois	4,1 mois	13,9 mois	5,6 mois
Survie globale (SG)	HR=0,66		HR=0,58		HR=0,49		HR=0,88	
	21,9 mois	17,4 mois	18,1 mois	12,0 mois	20,7 mois	11,6 mois	15,7 mois	13,6 mois

Lin N, *et al*., ASCO® 2020, Abs #1005

Effets secondaires les plus fréquents (≥20% dans le bras Tucatinib)

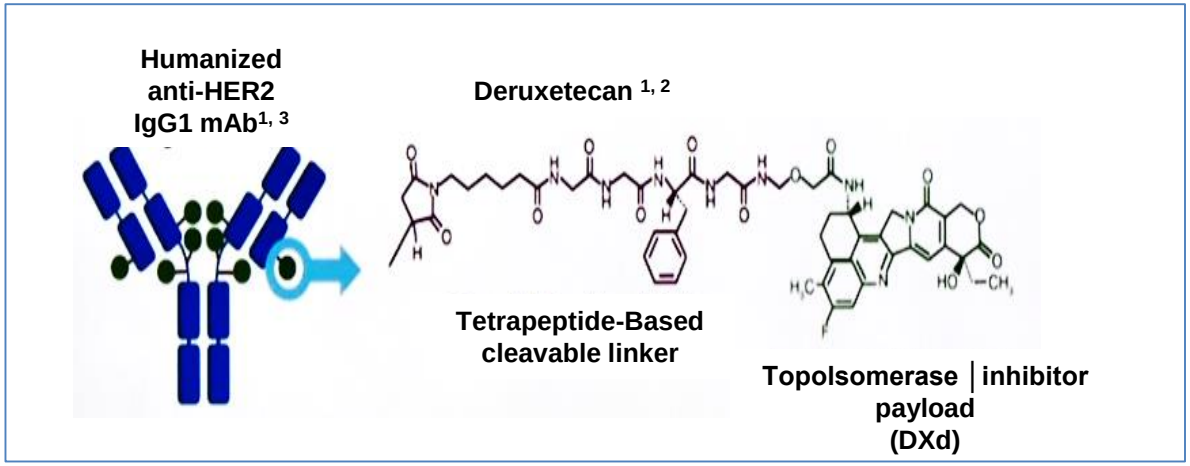


Murthy R. et al, SABCS 2019 GS1-01

Trastuzumab deruxtecan (DS-8201)

Le rastuzumab deruxtecan est un ADC ayant 3 composants:

- Une IgG1 monoclonale anti-HER2 avec la même séquence d'acides-aminés que le trastuzumab
- Une charge utile dérivée de l'exatecan et inhibiteur de topoisomerase
- Un linker tetrapeptidique



Mécanisme d'action de la charge utile: Inhibiteur de topoisomérase I
Effet anti-tumoral élevé de la chimiothérapie
Rapport médicament / anticorps élevé ≈ 8
Charge utile avec une demi-vie systémique courte
Linker-charge utile stable
Clivable sélectif pour les tumeurs
Charge utile perméable aux membranes

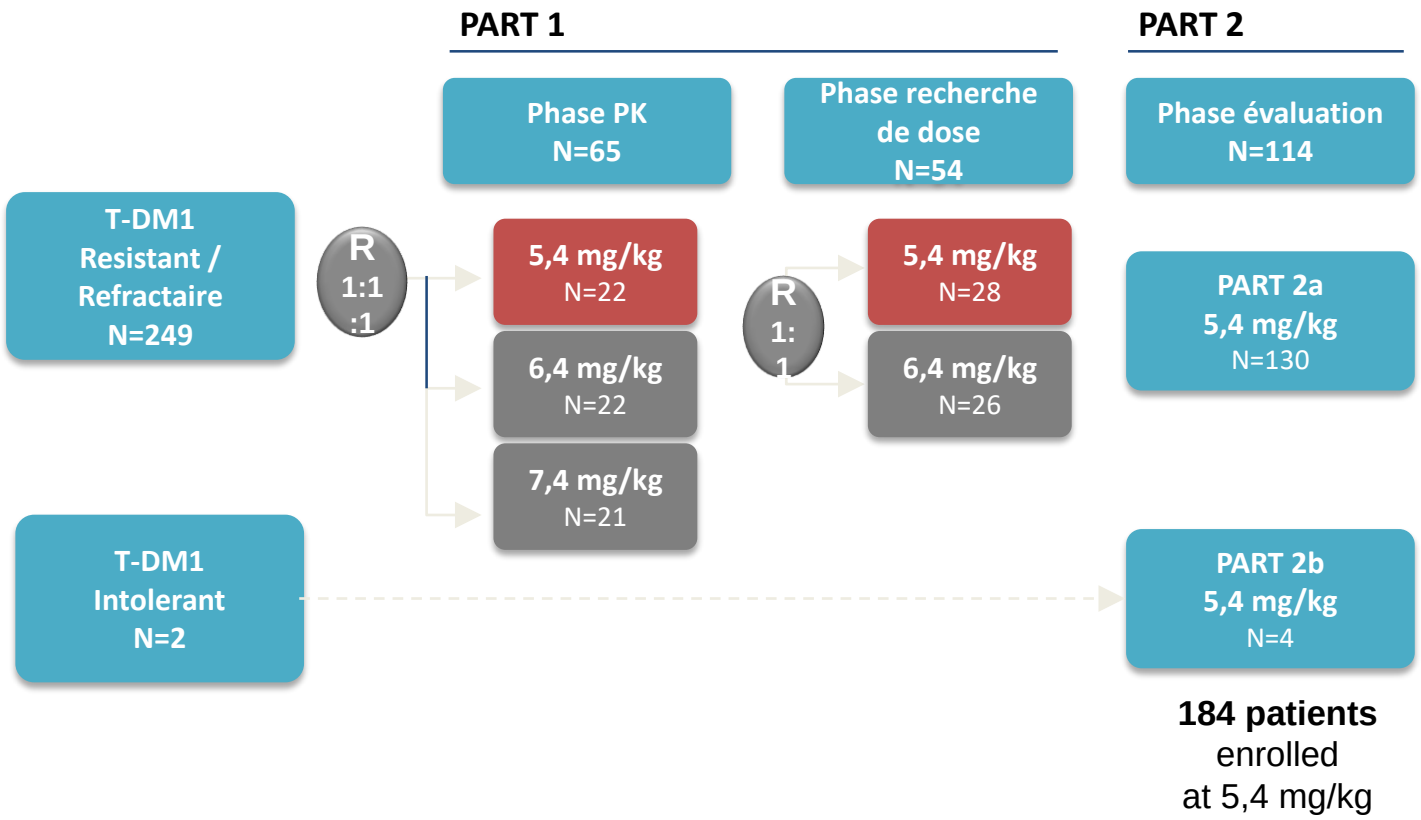
The clinic relevance of these features is under investigation.

[1] Nakade T, et al. Chem Pharma Bull (Tokyo). 2019,67(3):173-185. [2] Ogitani Y. Et al. Clin Cancer Res. 2016:22(20):5097-5108. [3] Trial PA et al. Pharmacol Ther. 2018:181:126-142.
[4] Ogitani Y, et al. Cancer Sci. 2016;107(7):1039-1046

DESTINY- breast 01 study design: An open-label, multicenter, Phase 2 study

Population

- ≥ 18 ans
- Maladie non résecable ou métastatique
- HER2-positive (confirmation centralisée)
- Pré-traité par T-DM1
- Pas d'ATCD de pneumopathie interstitielle
- Maladie métastatique cérébrale traitée et stable



Objectifs

- **Primaire:** ORR selon RECIST v1.1 (confirmation indépendante centralisée)
- **Secondaire:** par investigateurs ORR, DCR, DOR, CBR, PFS, OS, PK et toxicité

Data Cutoof: Aout 1-2019

- **79 patientes** (42,9%) encore en traitement
- **105 patients** (57,1%) ont fini le traitement essentiellement pour progression (28,8%)

Krop IE. et al, SABCS 2019 GS1-03

Caractéristiques des patients à l'inclusion

Nb médian de lignes antérieures de traitement : 6 [2-27]

Traitements préalables	Patients, % (T-DXd 5,4 mg/kg (n=184)
Trastuzumab	**100**
T-DM1	**100**
Pertuzumab	**65,8**
Autres traitements anti-HER2	**54,3**
Traitement anti-hormonal	**48,9**
Autres traitements systémiques	**99,5**

Incluant les traitements en situation non métastatique

Krop IE. et al, SABCS 2019 GS1-03

Objectif principal: Taux de réponse globale (ORR)

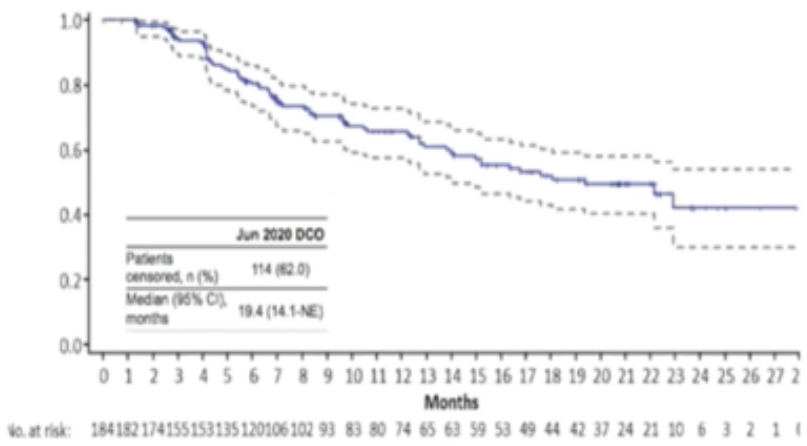
Analyse en ITT	Patients, % (T-DXd 5,4 mg/kg (n=184)
Confirmed ORR by ICR	**60,9% (n=112)** (95% CI: 53,4-68,0)
- Réponse complète	**6,0%** (n=11)
- Réponse partielle	**54,9%** (n=101)
- Maladie stable	**36,4%** (n=67)
- Maladie progressive	**1,6%** (n=3)
- Non évaluable	**1,1%** (n=2)
Réponse complète durable	**97,3%** (95% IC: 93,8-99,1)
Bénéfice Clinique (6 mois)	**76,1%** (95% IC: 69,3-82,1)
Durée de réponse (médiane)	**14, 8 mois** (95% IC: 13,8-16,9)

Krop IE. et al, SABCS 2019 GS1-03

Destiny Breast 01 : Efficacité

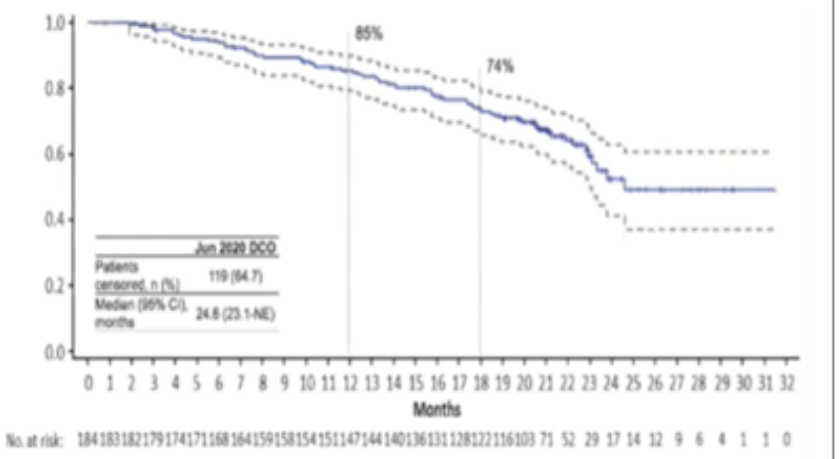
Median follow up 20.5 mo
ORR 61% (54-68.5%)

Probability of progression-free survival



➢ **Median PFS 19.4 mo** (14.1-NE)

Probability of survival



➢ **Median OS 24.6 mo** (23.1-NE)
only 35% of events

S. Modi, et al., SABCS® 2020, Abs #PD3-06

Effet secondaire d'intérêt particulier: Pneumopathie Interstitielle

Patients ayant reçu T-DXd 5,4 mg/kg (n=184)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Tout grade / Total
Pneumopathie interstitielle n,(%)	**5 (2,7)**	**15 (8,2)**	**1 (0,5)**	**0**	**4 (2,2)**	**25 (13,6)**

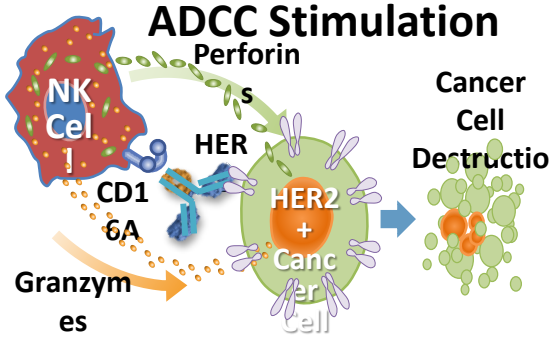
- Temps médian jusqu'à déclaration de la pneumopathie interstitielle : 193 jours [42-535]
- Parmi les 4 patients décédés, la maladie à débuté entre J 63 et J148, 3 ont reçu des stéroides et le décès est survenu 9 à 60 jours après le diagnostic de la maladie
- **Recommandations**: Surveiller les symptomes, suspendre le traitement, débuter les stéroides dés le diagnostic suspecté

Krop IE. et al, SABCS 2019 GS1-03

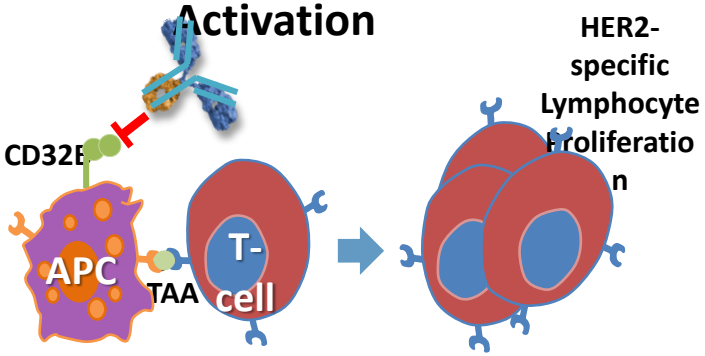
Margetuximab

- Même action antiproliférative sur les cellules HER2-surexprimées que le trastuzumab.
- Affinité de la fraction Fc pour ses récepteurs potentialisée.
- Améliore la stimulation du système immunitaire.
- Plus forte affinité pour CD16A et CD32B

Increased CD16A Affinity:
Enhance Innate Immunity/More Potent ADCC Stimulation



Decreased CD32B Affinity:
Enhance Adaptive Immunity/Increase Immune Activation



Nordstrom. Breast Cancer Res. 2011;13:R123. Nordstrom. ASCO 2019. Abstr 1030.

Etude SOPHIA

Cancer du sein avancé HER2+
- **≥2 traitements anti HER2 préalables, incluant pertuzumab**
- **1-3 lignes antérieures en métastatique**
- **Métas cérébrales acceptées si traitées et/ou stables**

Chimio au choix de l'investigateur (capecitabine, eribuline, gemcitabine, ou vinorelbine)

R **1:1**
N=536

bras 1
Margetuximab (15 mg/kg ttes 3 sem.)
+ CT cycles 3 sem.

bras 2
Trastuzumab
(8 mg/kg loading ➔ 6mg/kg ttes 3 sem.)
)+ CT cycles 3 sem

Objectifs Primaires séquentiels	• **PFS** (by CBA; n=257; HR=0,67; ∝=0,05; power=90%) • **OS** (n=385; HR=0,75; ∝=0,05; power=80%)
Objectifs secondaires	• PFS (Investigator assessed) • Objective response rate (by CBA)
Objectifs Tertiaires /Exploratoires	• Clinical benefit rate (CBR), duration of response (DoR) • Safety profile, antidrug antibody • Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

Stratification
- Chimiothérapie choisie
- Traitements antérieurs (≤2 *vs* >2)
- Nombre de sites métastatiques (≤2 *vs* >2)

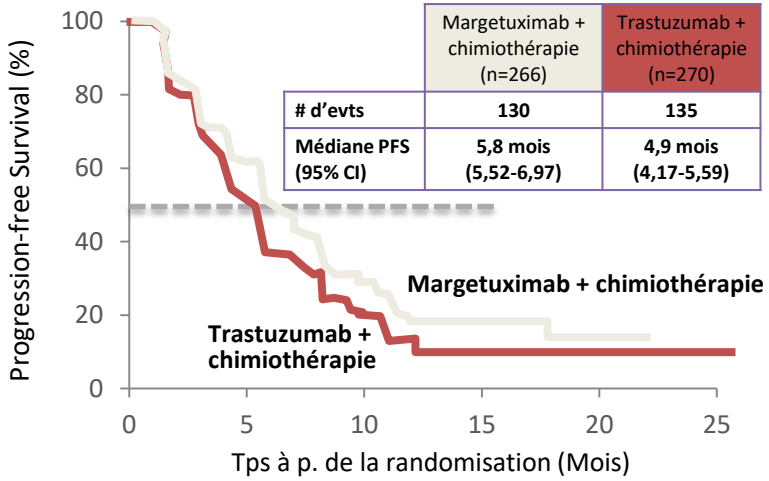
HR = hazard ratio; CBA=central blinded analysis.

H. S. Rugo, et al., ASCO® 2019, Abs #1000

PFS enITT

24% Risk Reduction of Disease Progression

Central Blinded Analysis (Primary Endpoint)



	Margetuximab + chimiothérapie (n=266)	Trastuzumab + chimiothérapie (n=270)
# d'evts	130	135
Médiane PFS (95% CI)	5,8 mois (5,52-6,97)	4,9 mois (4,17-5,59)

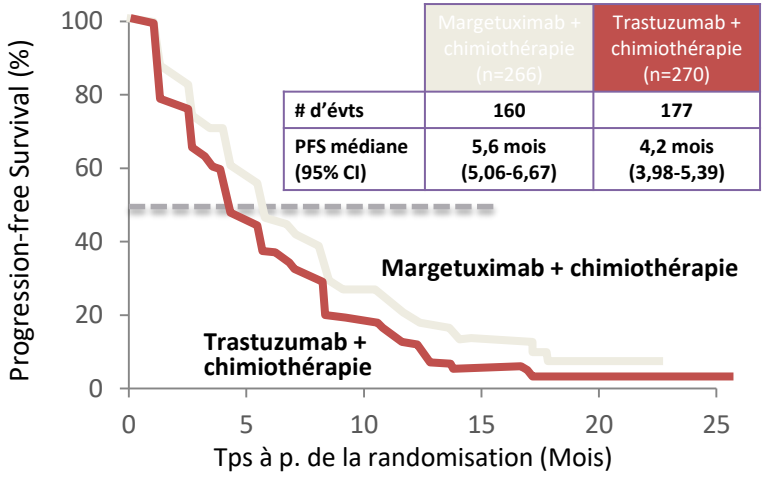
HR by stratified Cox model, 0.76 (95% CI = 0,59- 0,98)
Stratified log-rank *p=0,033*

Nbre de risque

Margetuximab	266	174	94	45	21	8	6	4	2	0	
Trastuzumab	270	159	74	33	13	2	2	1	1	1	1

30% Risk Reduction of Disease Progression

Investigator Assessed (Secondary Endpoint)



	Margetuximab + chimiothérapie (n=266)	Trastuzumab + chimiothérapie (n=270)
# d'évts	160	177
PFS médiane (95% CI)	5,6 mois (5,06-6,67)	4,2 mois (3,98-5,39)

HR by stratified Cox model, 0.70 (95% CI = 0,56- 0,87)
Stratified log-rank *p=0,001*

Nbre de risque

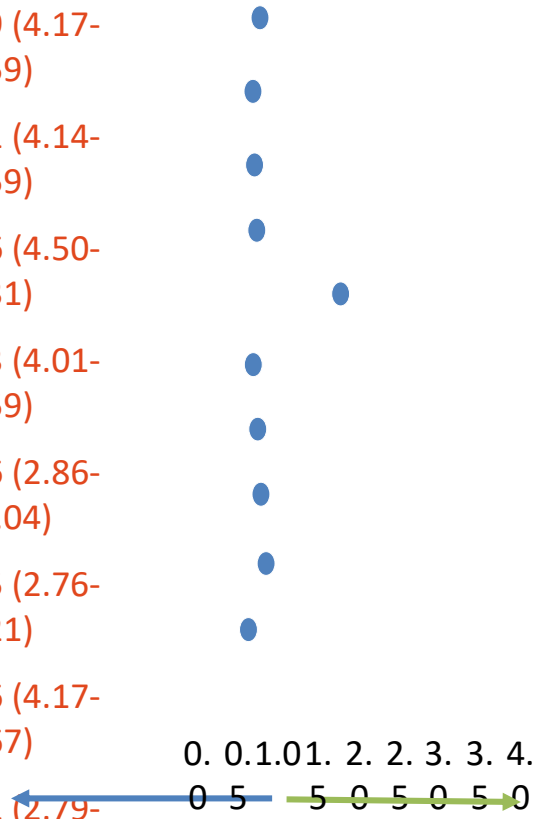
Margetuximab	266	206	155	112	72	61	33	32	16	13	8	7	3	2	2	0	
Trastuzumab	270	184	130	87	59	45	25	21	10	5	4	3	1	1	1	1	0

H. S. Rugo, et al., ASCO® 2019, Abs #1000

Etude SOPHIA

Certaines patientes avec un génotype particulier du fragment Fc (allèle 158F de CD16A) semblent particulièrement bénéficier du margetuximab.

	Median PFS* Mos (95% CI) Margetuximab + CT	Trastuzumab + CT	HR by Unstratified Cox Model	95% CI	Unstratified Log-Rank *P* Value
All patients	5.8 (5.52-6.97)	4.9 (4.17-5.59)	0.78	0.61-0.99	.044
CD16A/F carrier (FV or FF) (n = 437)	6.9 (5.55-8.15)	5.1 (4.14-5.59)	0.68	0.52-0.90	.005
CD16A/FF (n = 192)	8.2 (5.52-10.51)	5.6 (4.50-8.31)	0.69	0.46-1.05	.080
CD16A/FV (n = 245)	6.3 (5.52-7.23)	4.3 (4.01-5.59)	0.71	0.50-1.01	0.55
CD16A/VV (n = 69)	4.8 (2.46-5.65)	5.6 (2.86-11.04)	1.78	0.87-3.62	.110
CD32A/RR (n = 122)	5.7 (4.80-10.55)	5.5 (2.76-8.21)	0.69	0.41-1.17	.166
CD32A/RH (n = 247)	6.9 (5.55-8.15)	5.6 (4.17-6.67)	0.74	0.52-1.06	.102
CD32A/HH (n = 137)	5.6 (3.29-8.28)	4.1 (2.79-5.59)	0.80	0.49-1.30	.365
CD32B/II (n = 380)	5.8 (5.55-7.66)	5.5 (4.17-5.65)	0.85	0.64-1.13	.265
CD32B/IT (n = 117)	6.0 (4.14-NA)				



*Assessed by central blinded analysis.

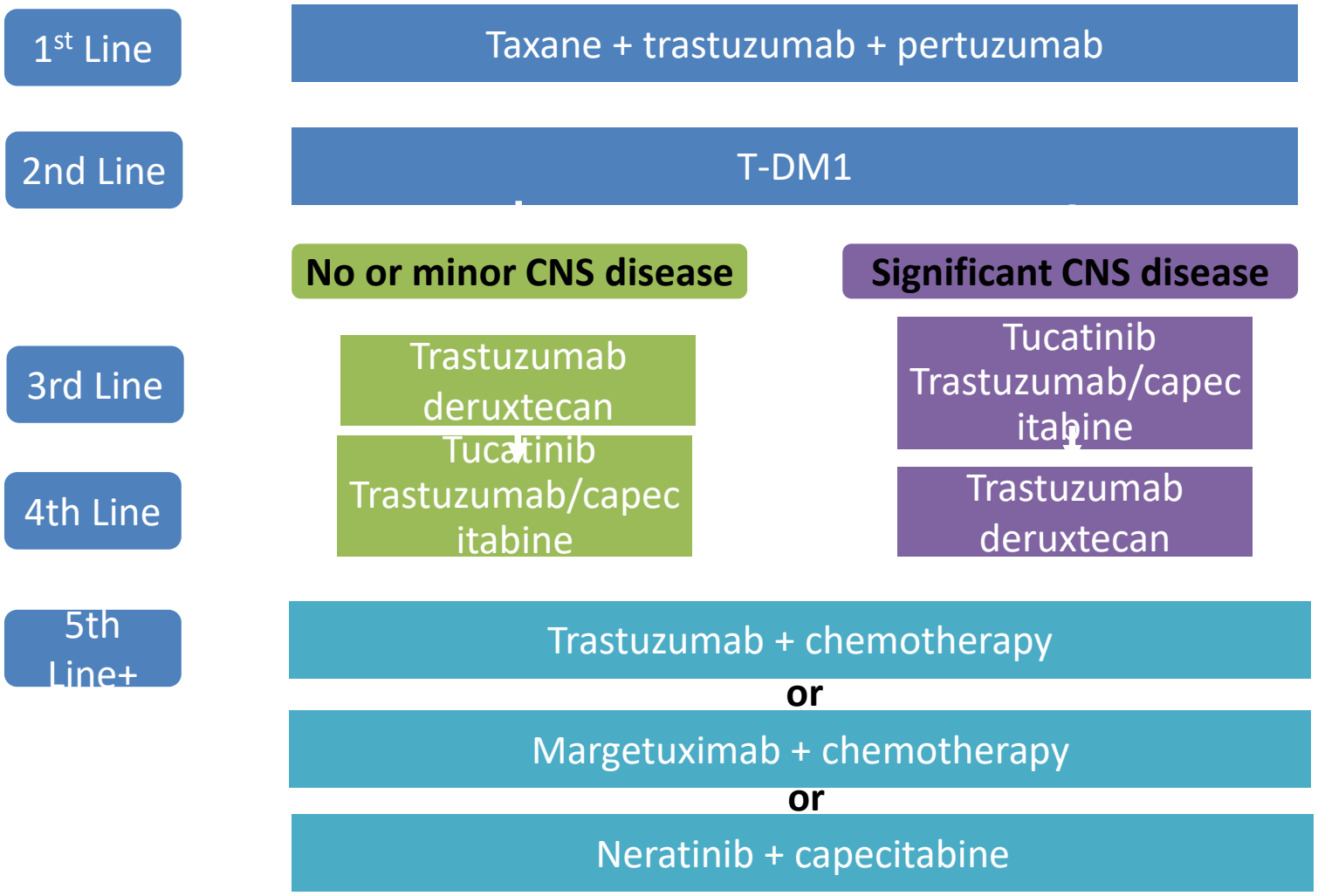
Rugo. ASCO 2019. Abstr 1000.

Current Approach for Sequencing Therapy

First line	Second line	≥ Third Line
▪ Trastuzumab + pertuzumab + taxane	▪ T-DM1	▪ Tucatinib + capecitabine + trastuzumab ▪ Lapatinib + capecitabine ▪ CT + trastuzumab (eribulin, vinorelbine, gemcitabine, or capecitabine, CMF..) ▪ Lapatinib + trastuzumab ▪ Hormonal therapy + anti-HER2 (for HR+) ▪ Trastuzumab/Pertuzumab or T-DM1, if not received prior ▪ Trastuzumab deruxtecan ▪ Neratinib/Capecitabine ▪ Margetuximab

1. Giordano. JCO. 2018;36:2736. 2. NCCN. Breast Cancer. V5.2020. July 15, 2020.

Approach to Therapy for Metastatic HER2+ disease: Move to Personalization



Etude DESTINY-Breast03

Essai phase III multicentrique, en double aveugle (NCT03529110)

Patientes

- Cancer du sein HER2+ non opérable ou métastatique
- Précedemment traitée par trastuzumab et taxane
  au stade métastatique
- Incluable si metastases cérébrales stables et traitées

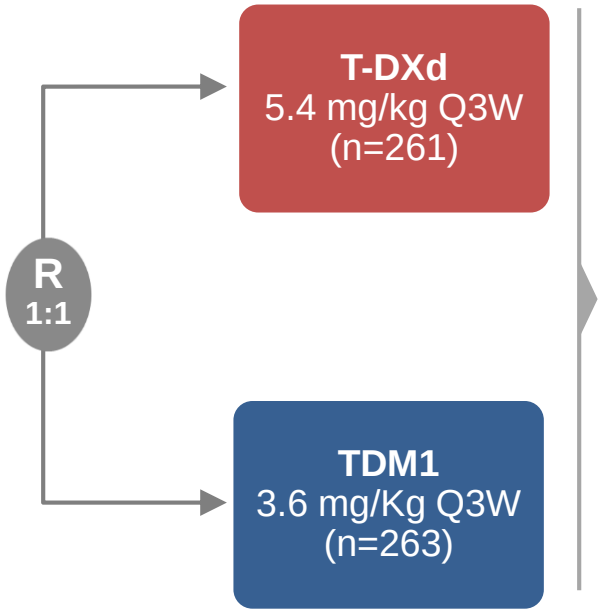
Stratification

- Expression des RH
- Traitement antérieur par pertuzumab
- Atteinte viscérale

Analyse intermédiaire de la SSP

- Limite pour détection de la supériorité : P<0.000204 (245 évenements)

Objectifs secondaires : limite pour détection de
la supériorité (SG) P<0.000265 (86 évenements)



Objectif principal

- SSP (relecture centralisée)

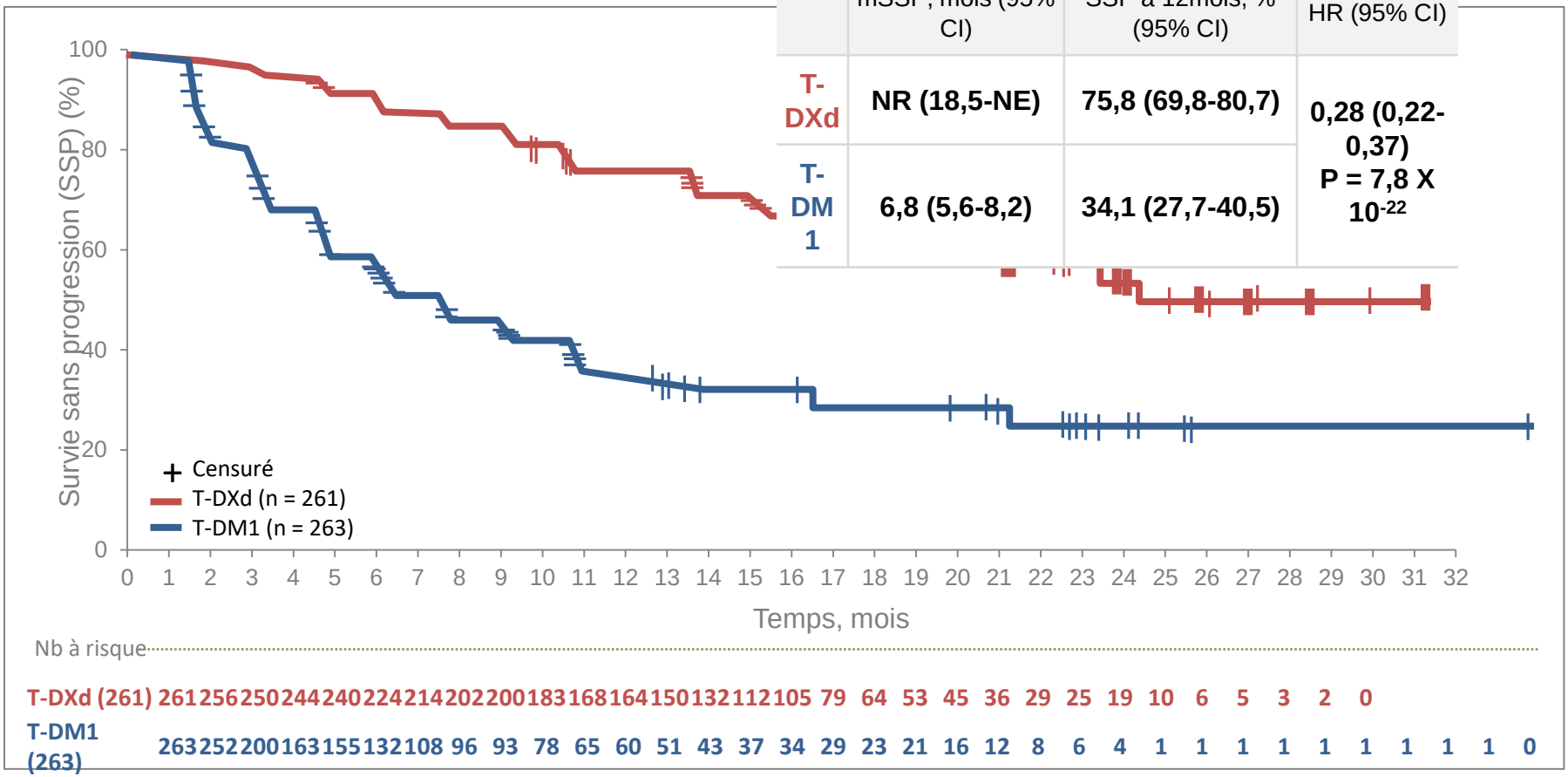
Objectifs secondaires

- SG
- Taux de réponse objective (centralisée et investigateur)
- Durée de réponse (centralisée)
- SSP (investigateur)
- Toxicité

J. Cortés, et al., ESMO® 2021, Abs LBA1

SSP (relecture centralisée)

	mSSP, mois (95% CI)	SSP à 12mois, % (95% CI)	HR (95% CI)
T-DXd	NR (18,5-NE)	75,8 (69,8-80,7)	0,28 (0,22-0,37) P = 7,8 X 10^{-22}
T-DM 1	6,8 (5,6-8,2)	34,1 (27,7-40,5)	

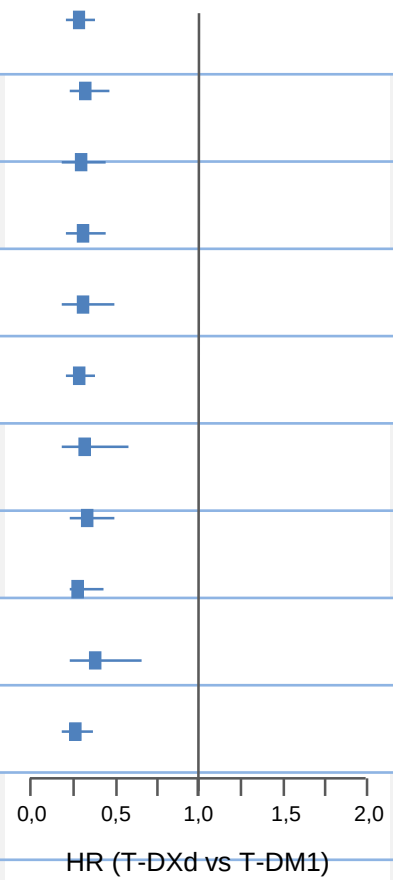


Suivi médian pour le T-DXd : 15.5 mois (15.1-16.6) et pour le T-DM1 : 13.9 mois (II .8-15.1)

J. Cortés, et al., ESMO® 2021, Abs LBA1

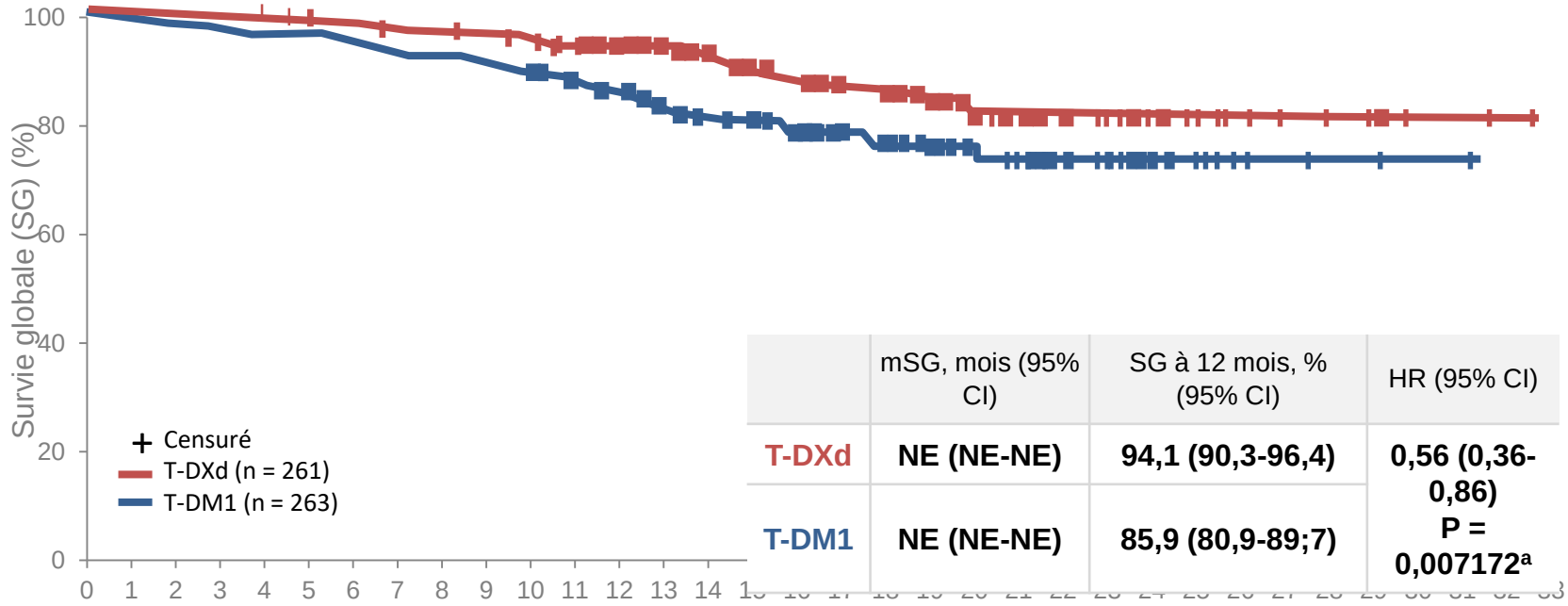
SSP en sous-groupes

		Evénements/N		SSP médiane (mois, IC95%)		HR (IC95%)
		T-DXd	T-DM1	T-DXd	T-DM1	
Population globale		87/261	158/263	NE (18,5-NE)	6,8 (5,6-8,2)	0,2840 (0,2165-0,3727)
RH	Positifs (n = 272)	46/133	84/139	22,4 (17,5-NE)	6,9 (4,2-9,8)	0,3191 (0,2217-0,4594)
	Negatifs (n = 248)	41/126	73/122	NE (18,0-NE)	6,8 (5,4-8,3)	0,2965 (0,2008-0,4378)
Traitement par pertuzumab	Oui (n = 320)	57/162	98/158	NE (18,5-NE)	6,8 (5,4-8,3)	0,3050 (0,2185-0,4257)
	Non (n = 204)	30/99	60/105	NE (16,5-NE)	7,0 (4,2-9,7)	0,2999 (0,1924-0,4675)
Atteinte viscérale	Oui (n = 384)	72/195	123/189	22,2 (16,5-NE)	5,7 (4,2-7,0)	0,2806 (0,2083-0,3779)
	Non (n = 140)	15/66	35/74	NE (NE-NE)	11,3 (6,8-NE)	0,3157 (0,1718-0,5804)
Nb de lignes antérieures	0-1 (n = 258)	46/132	75/126	22,4 (17,9-NE)	8,0 (5,7-9,7)	0,3302 (0,2275-0,4794)
	≥ 2 (n = 266)	41/129	83/137	NE (16,8-NE)	5,6 (4,2-7,1)	0,2828 (0,1933-0,4136)
Métastases cérébrales	Oui (n = 114)	31/62	31/52	15,0 (12,6-22,2)	5,7 (2,9-7,1)	0,3796 (0,2267-0,6357)
	Non (n = 410)	56/199	127/211	NE (22,4-NE)	7,0 (5,5-9,7)	0,2665 (0,1939-0,3665)



J. Cortés, et al., ESMO® 2021, Abs LBA1

SG



	mSG, mois (95% CI)	SG à 12 mois, % (95% CI)	HR (95% CI)
T-DXd	NE (NE-NE)	94,1 (90,3-96,4)	0,56 (0,36-0,86) P = 0,007172[a]
T-DM1	NE (NE-NE)	85,9 (80,9-89;7)	

Nb à risque

T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	&!	11	5	4	3	3	1	1	0	

Données en SG précoce (nombre d'événements faible : 33 dans le bras T-DXd et 53 dans le bras T-DM1)
[a]P= .007172, pour une limite pré-définie à P < .000265

J. Cortés, et al., ESMO® 2021, Abs LBA1

Tolérance

n (%)	T-DXd (n=261)	T-DM1 (n=263)
Effets indésirables (EI) – tous grades	252 (98.1)	226 (86.6)
EI – Grade >3	116 (45.1)	104 (39.8)
EI – Sévères	28 (10.9)	16 (6.1)
EI responsables d'un arrêt de traitement	33 (12.8)	13 (5.0)
EI responsables d'une réduction de dose	55 (21.4)	33 (12.6)
EI responsables d'un décès	0 (0.0)	0 (0.0)

J. Cortés, et al., ESMO® 2021, Abs LBA1

Tolérance : toxicité pulmonaire et cardiaque ?

Pneumopathie interstitielle, n (%)

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2,7)	18 (7,0)	2 (0,8)	0	0	27 (10,5)
T-DM1 (n = 261)	4 (1,5)	1 (0,4)	0	0	0	5 (1,9)

Pas de grade 4 or 5 dans le bras T-DXd

Diminution de la FEVG, n (%)

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	1 (0,4)[b]	6 (2,3)[c]	0	0	0	7 (2,7)
T-DM1 (n = 261)	0	1 (0,4) [c]	0	0	0	1 (0,4)

Dans le bras T-DXd arm, toutes les altérations de la FEVG sont restées asymptomatiques

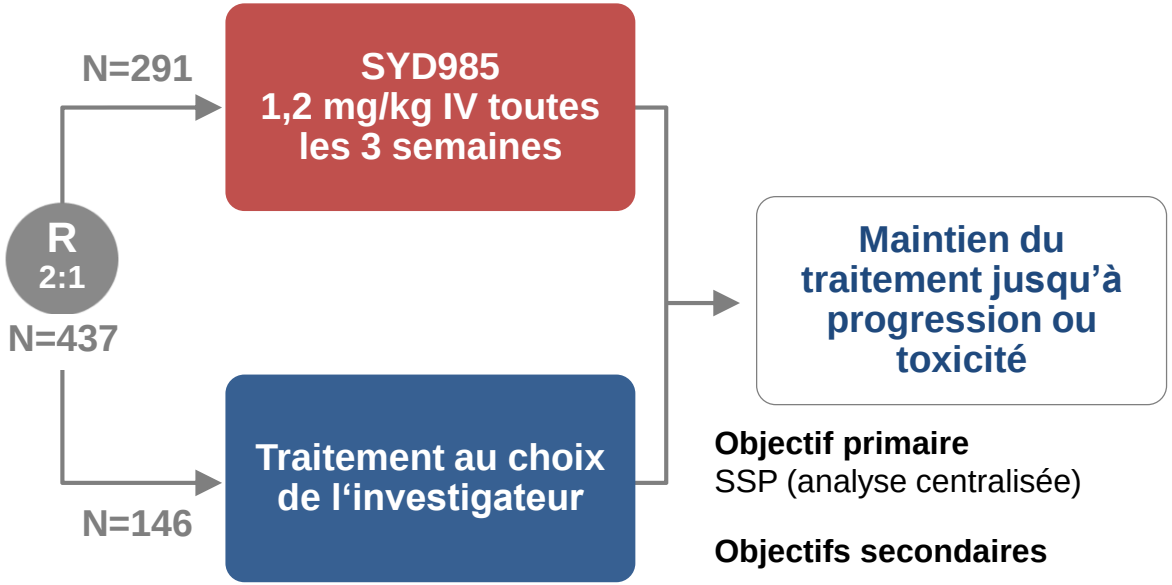
J. Cortés, et al., ESMO® 2021, Abs LBA1

Etude TULIP: trastuzumab duocarmazine

- Essai de phase III, multicentrique

Cancer du sein métastatique ou localement avancé HER2+

- ≥ 2 lignes en situation métastatique
- ou T-DM1 en situation métastatique
- Métastases cérébrales autorisées si traitées



Objectif primaire
SSP (analyse centralisée)

Objectifs secondaires

- SSP (investigateur)
- SG
- Taux de réponse objective
- QOL

Stratification

- Region (EU+Singapore vs Amérique du Nord)
- Nombre de lignes thérapeutiques antérieures (1-2 vs >2)
- Traitement préalable par pertuzumab (oui/non)

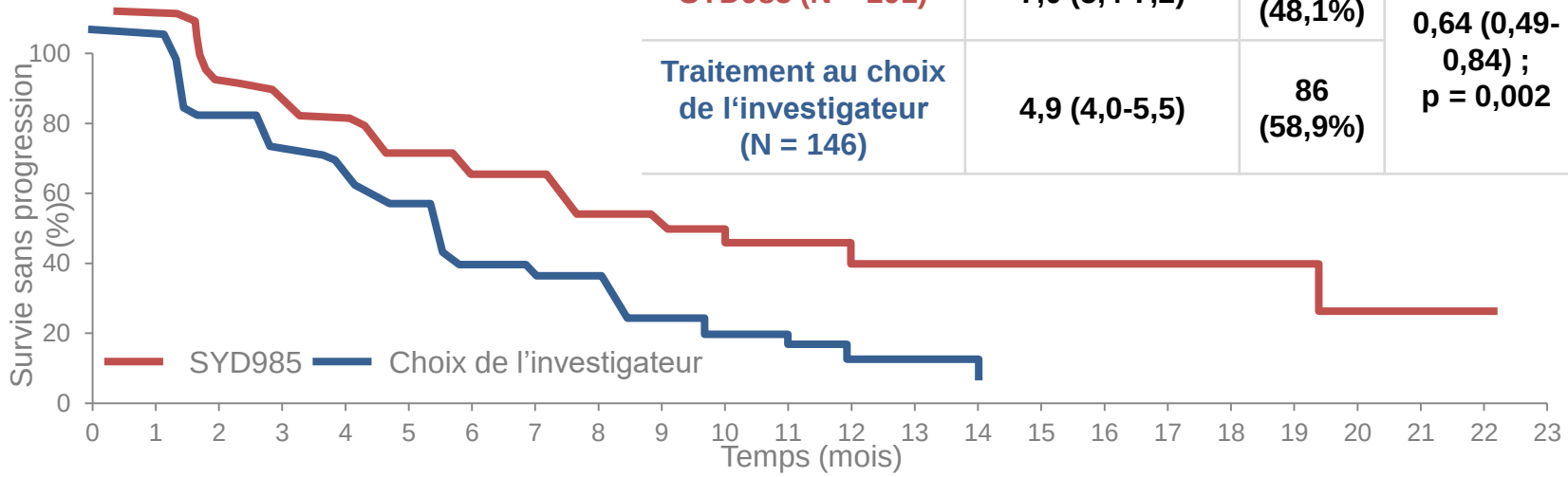
Traitement au choix de l'investigateur

- Lapatinib + Capecitabine
- Trastuzumab + Capecitabine
- Trastuzumab + Vinorelbine
- Trastuzumab + Eribuline

C. Saura Manich, et al., ESMO® 2021, Abs LBA15

Etude TULIP – SSP (relecture centralisée)

	mSSP (IC95%) mois	Évènements	HR (IC95%)
SYD985 (N = 291)	7,0 (5,4-7,2)	140 (48,1%)	0,64 (0,49-0,84) ; p = 0,002
Traitement au choix de l'investigateur (N = 146)	4,9 (4,0-5,5)	86 (58,9%)	



Nb à risque

SYD985	291	278	208	167	150	109	83	59	51	35	28	24	13	12	9	8	6	5	3	2	1	1	0
Choix de l'investigateur	146	125	86	69	64	44	26	22	19	10	6	6	3	2	1	0							

C. Saura Manich, et al., ESMO® 2021, Abs LBA15

Early breast cancer

Updated Results (Primary Endpoint)

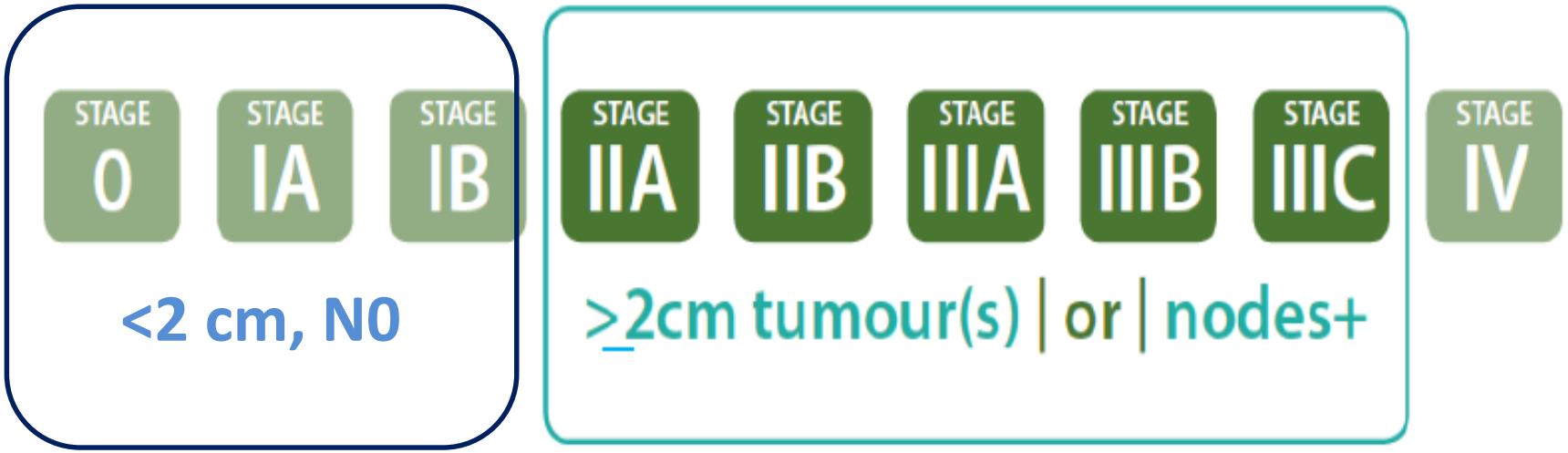
Clinical Trial	Population	Primary Endpoint/FU	Crossover	Results (Primary endpoint)
HERA[1]	Node-positive Node-negative • D >1 cm	DFS/ 11 years	52%	**63% (no T) vs 69% (1 year T) vs 69% (2 yrs T)** HR = 0.76; *P*<.0001 (No T / 1 year T) HR = 1.02; *P* not reported (1 year T / 2 years T)
BCIRG-006[2]	Node-positive Node-negative D >2 cm • HR – • Grade 2-3 • Age <35 years	DFS/ 10 years	2.1%	**67.9% (no T) vs 74.6% (T) vs 73% (TCH)** (HR = 0.72; *P*<.0001) (No T/T) (HR = 0.77; *P* = .0011) (No T/TCH)
N9831[3]	Node-positive Node-negative • D >1 cm; HR – • D >2 cm; HR +	DFS/ 72 months	Not reported	**71.8% (no T) vs 80.1% (T Se) vs 84.4 % (T Co)** (HR = 0.69; *P*<.001) (No T/T Se) (HR = 0.77; *P* = .022) (T Se/T Co)
NSABP B-31 + N9831[4]	Node-positive Node-negative • D >1 cm; HR – • D >2 cm; HR +	DFS/ 8.4 years	21%	**62.2% (no T) vs 73.7% (T)** (HR = 0.6; *P*<.0001)

1. Cameron D, et al. *Lancet.* 2017;389(10075):1195-1205. 2. Slamon DJ, et al. *Cancer Res.* 2016;76(4 Suppl): Abstract S5-04. 3. Perez EA, et al. *J Clin Oncol.* 2011;29(34):4491-4497. 4. Perez EA, et al. *J Clin Oncol.*

- **Early breast cancer**

High-Risk HER2-Positive EBC Tumors Are ≥2 cm or Node-Positive

Treatment guidelines define high risk in the context of neoadjuvant treatment:[1,2]



In early-stage breast cancer, tumor size, grade, hormone-receptor status, and lymph node metastases should be taken into account[3]

1. Coates AS, et al. *Ann Oncol.* 2015;26(8):1533-1546. 2. American Joint Committee on Cancer. AJCC Breast Cancer Staging Manual. 7th Ed. Chicago, IL; 2010. 3. Pertuzumab [prescribing information]. Grenzach-Wylen, Germany: Genentech, Inc.; 2018.

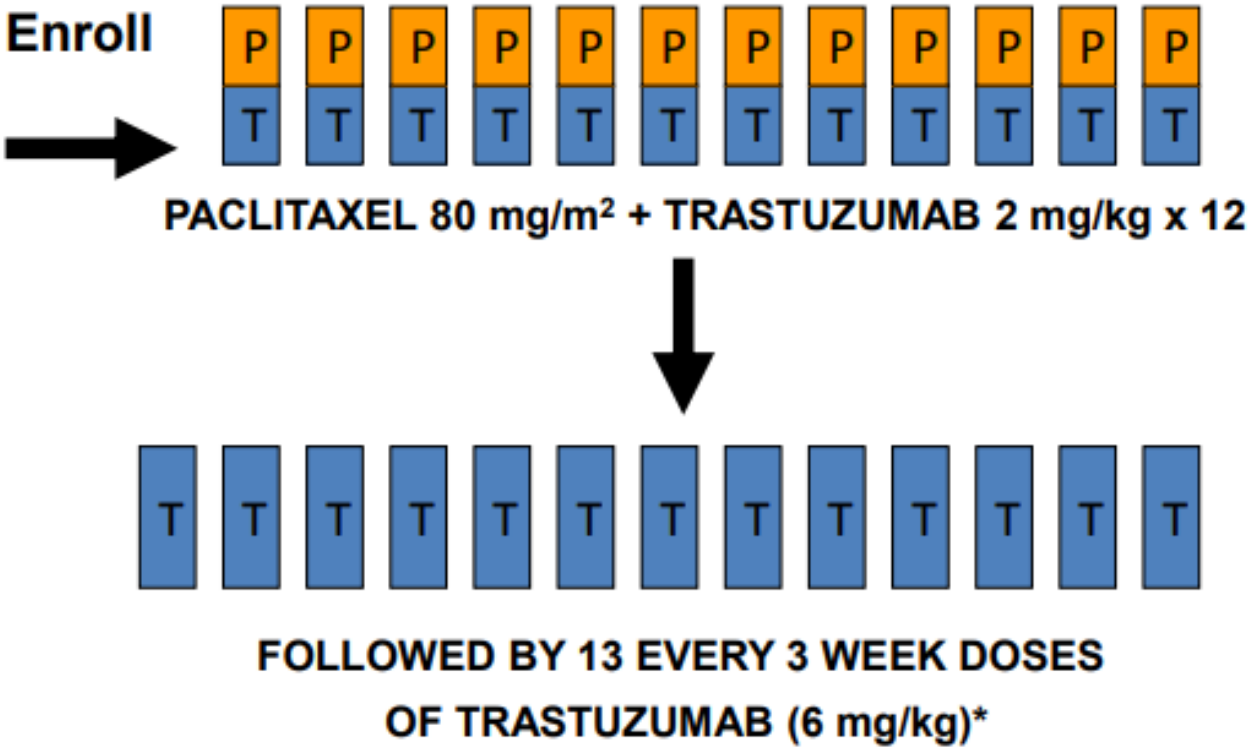
- **Early breast cancer**

  STADE I: Desescalade du TRT

APT Trial: Study Design

HER2+
ER+ or ER-
Node Negative
≤ 3 cm

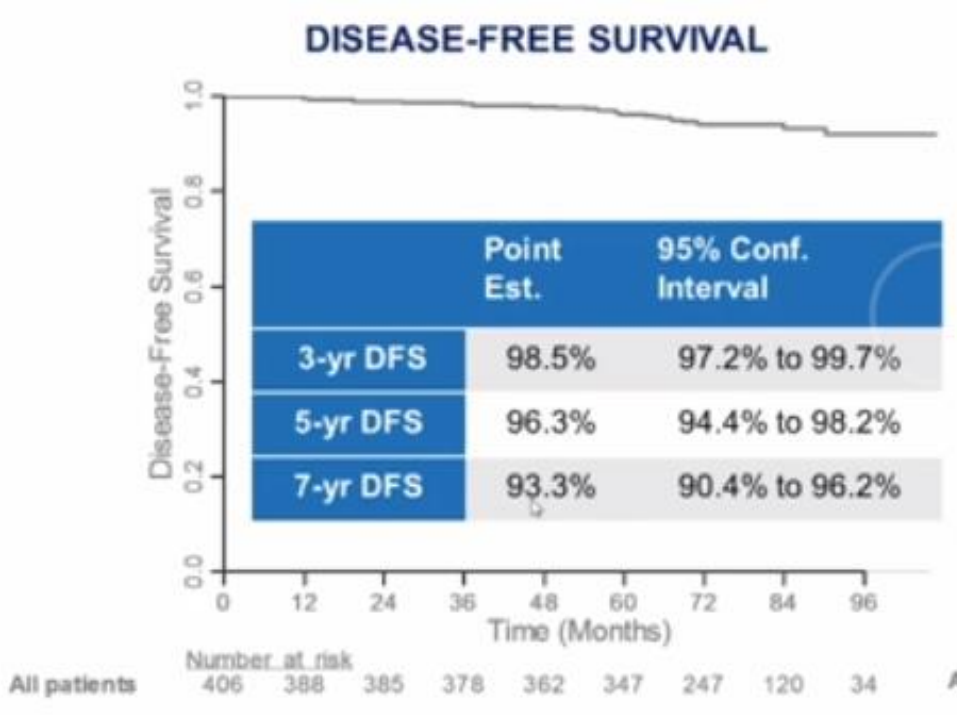
Planned N=400



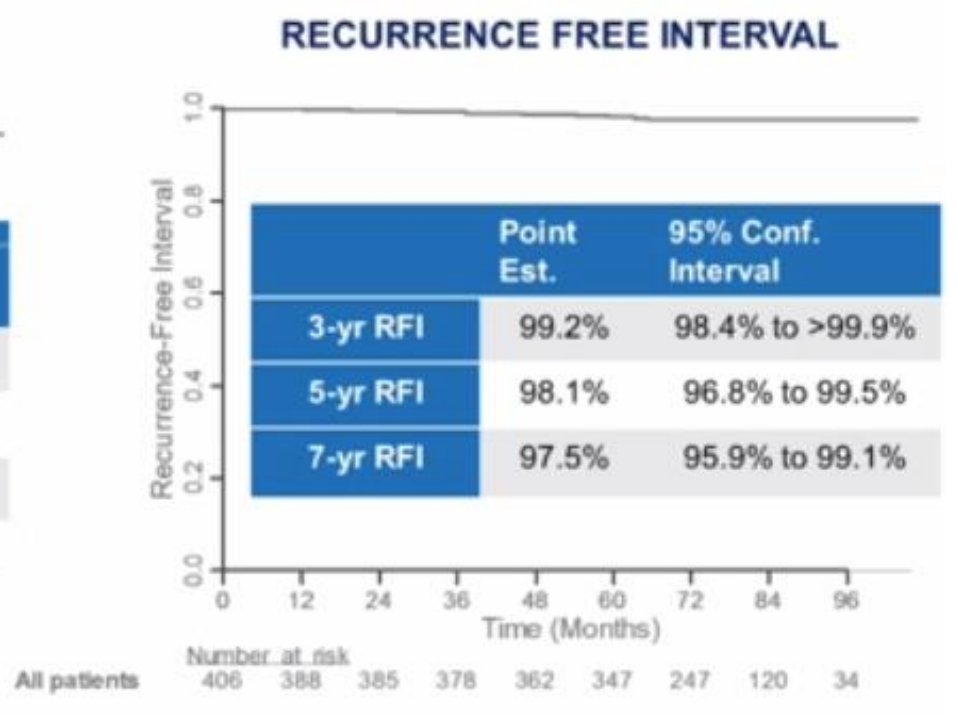
*Dosing could alternatively be 2 mg/kg IV weekly for 40 weeks
** Radiation and hormonal therapy was initiated after completion of paclitaxel

Tolaney SM et al, ASCO 2017

APT Trial: 7 years outcomes



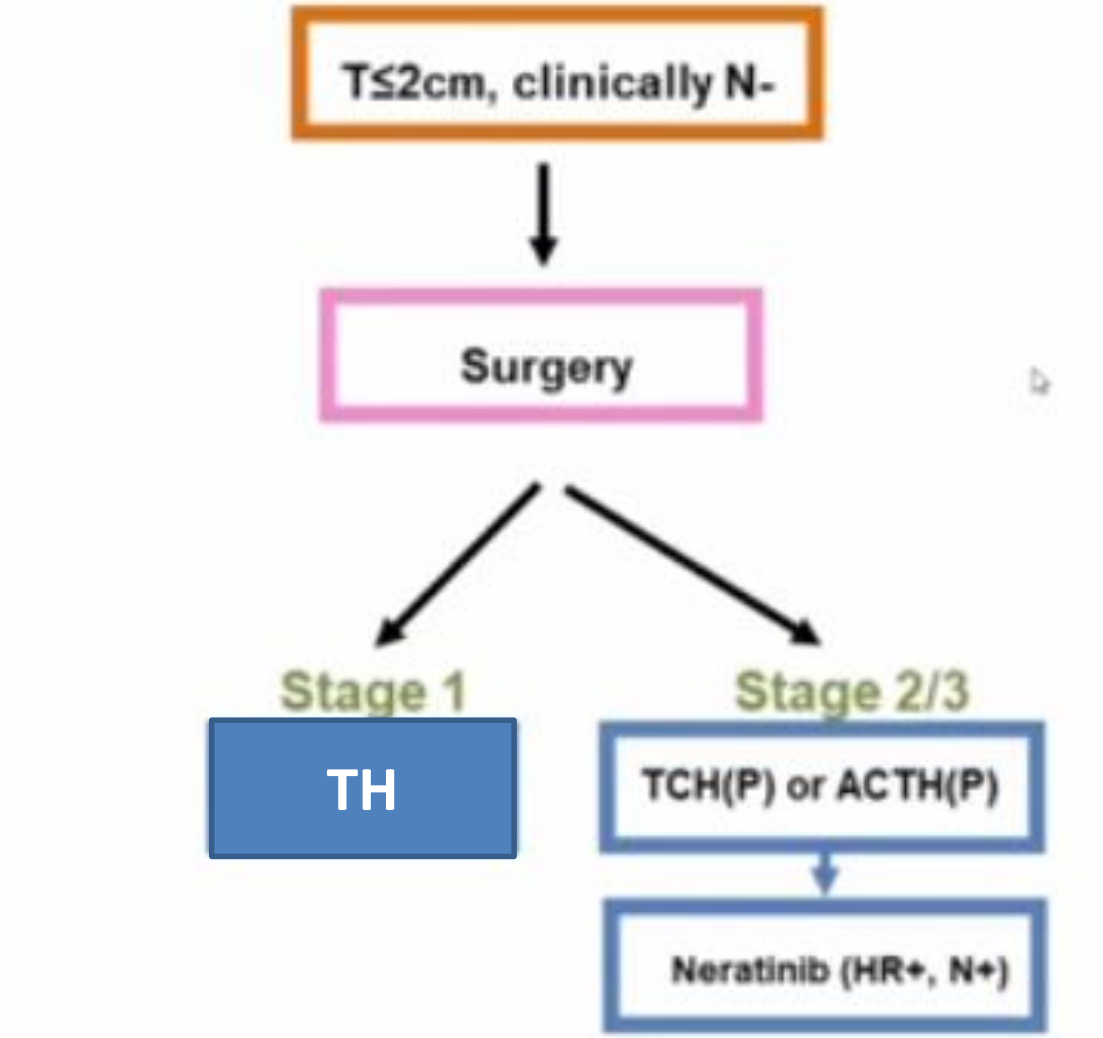
	Point Est.	95% Conf. Interval
3-yr DFS	98.5%	97.2% to 99.7%
5-yr DFS	96.3%	94.4% to 98.2%
7-yr DFS	93.3%	90.4% to 96.2%



	Point Est.	95% Conf. Interval
3-yr RFI	99.2%	98.4% to >99.9%
5-yr RFI	98.1%	96.8% to 99.5%
7-yr RFI	97.5%	95.9% to 99.1%

Tolaney SM & al. JCO 2019

Current treatment algorithm

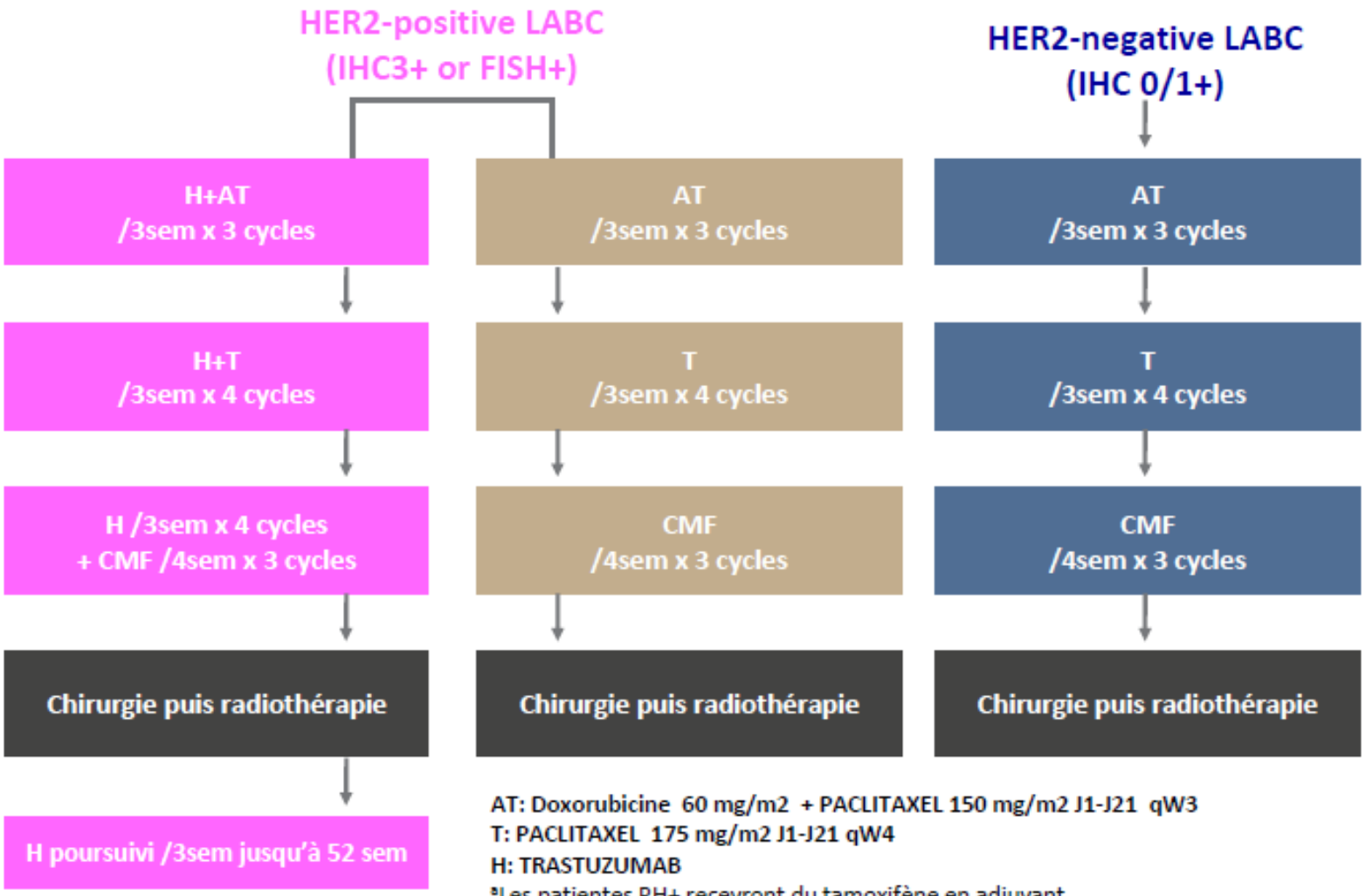


Adapted from Sara Tolaney ESMO Breast 2020

- **Early breast cancer**

  STADE II- III

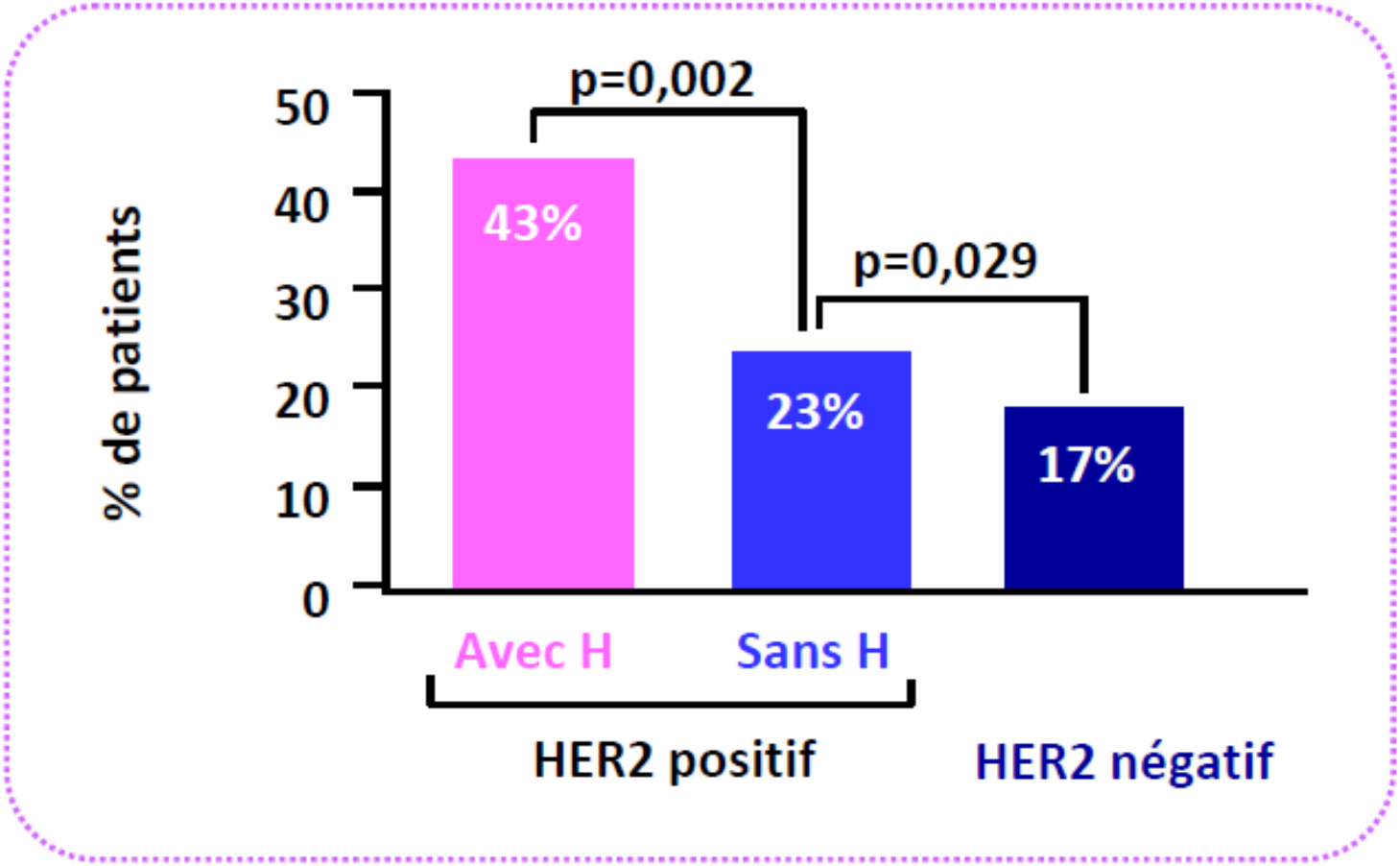
Etude NOAH



AT: Doxorubicine 60 mg/m2 + PACLITAXEL 150 mg/m2 J1-J21 qW3
T: PACLITAXEL 175 mg/m2 J1-J21 qW4
H: TRASTUZUMAB
[a]Les patientes RH+ recevront du tamoxifène en adjuvant

Gianni L. et al. Lancet 2010;375:377-84

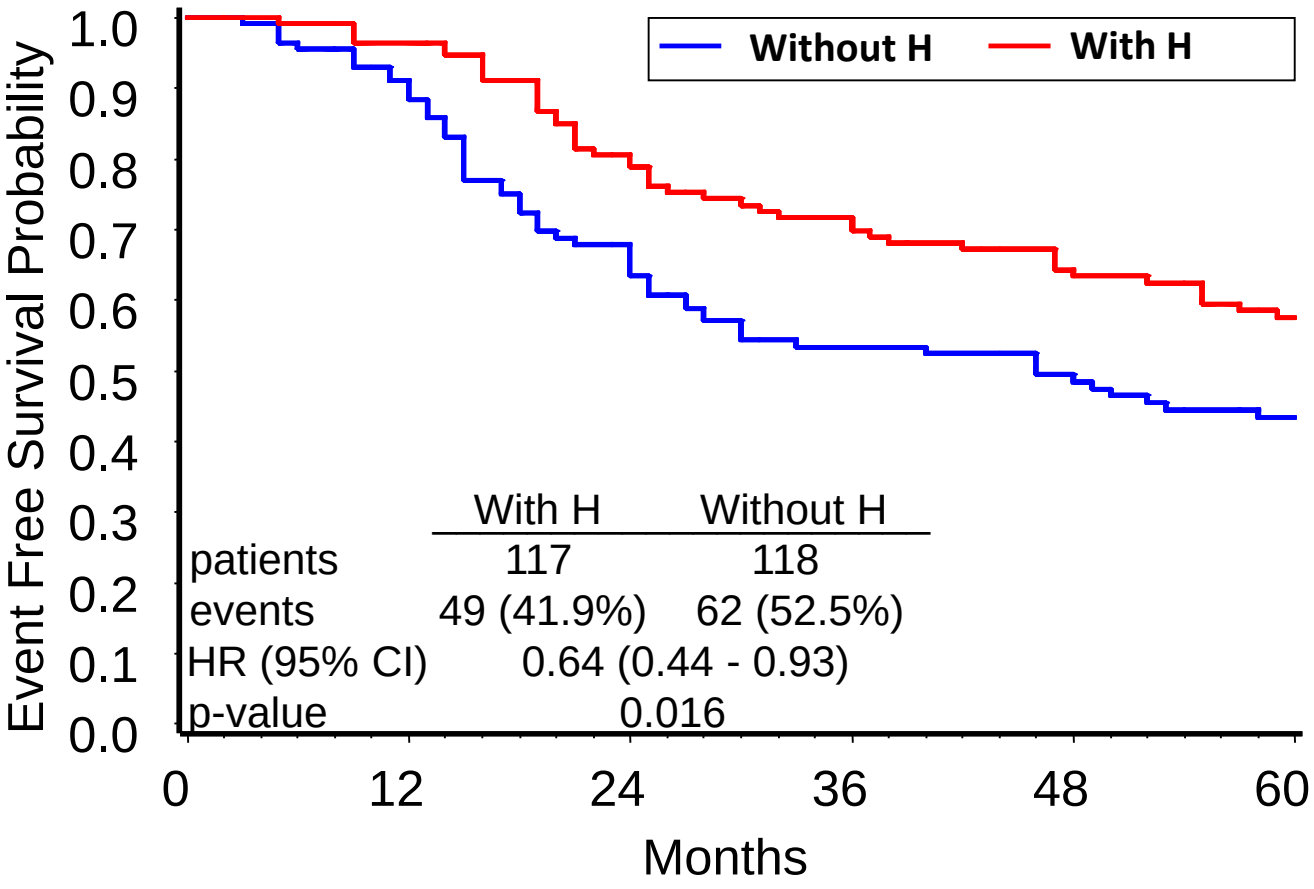
Etude NOAH



Gianni L. et al. Lancet 2010;375:377-84

EFS in HER2-positive ITT population

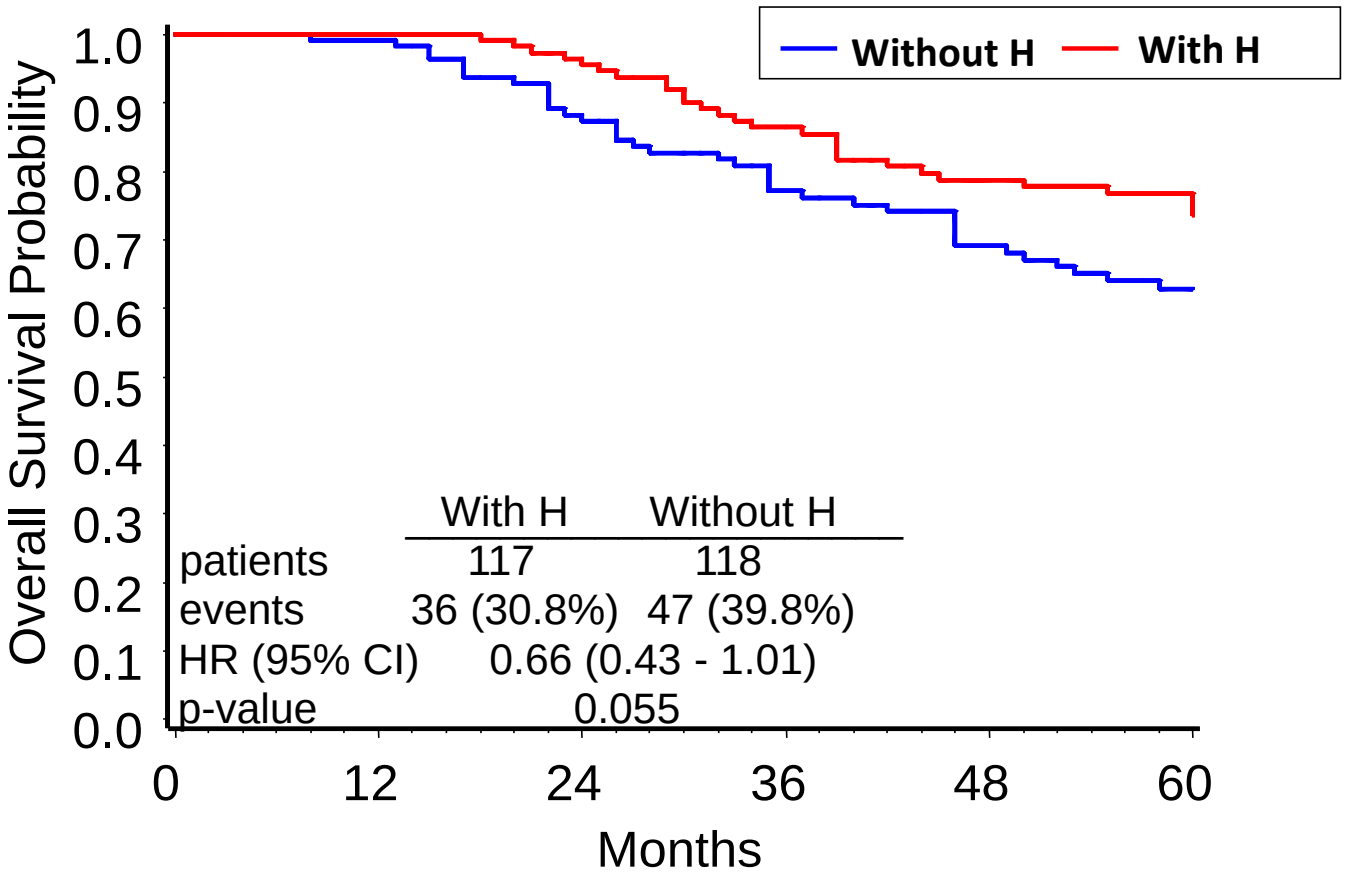
Median follow-up 5,4 years



GIANNI L. Lancet Oncol 2014

OS in HER2-positive ITT population

Median follow-up 5,4 years

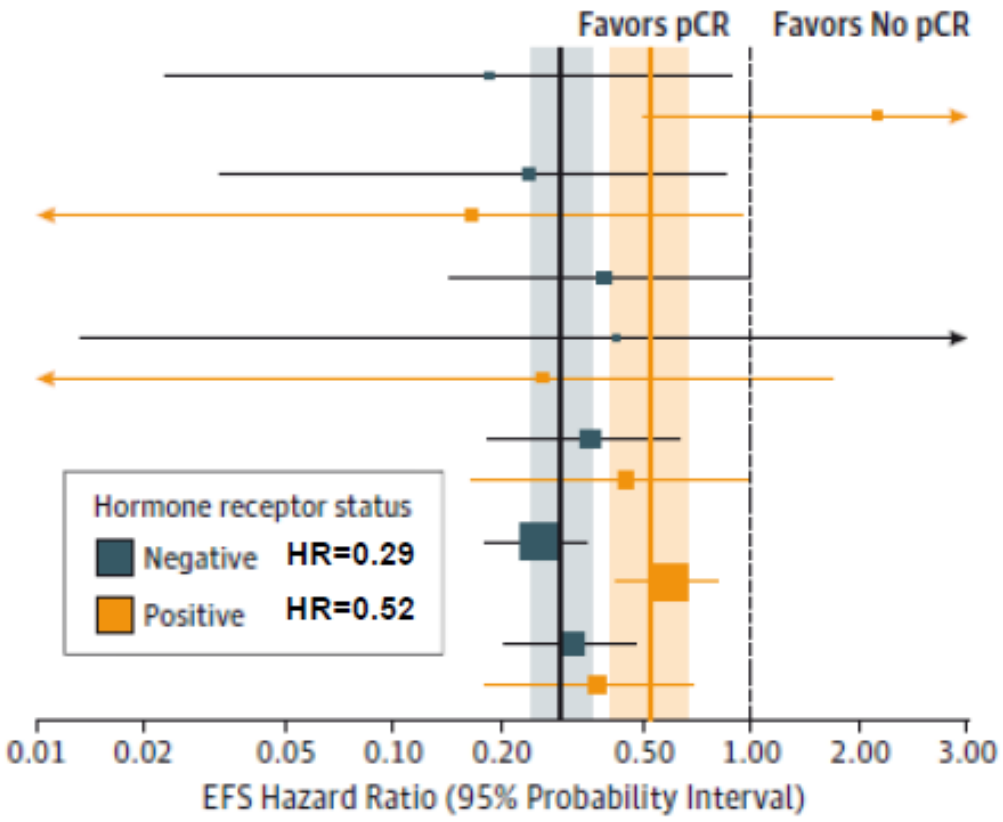


GIANNI L. Lancet Oncol 2014

Association of pCR With EFS in HER2+ Subtypes

A EFS by hormone receptor status groups

Source	pCR Events/N	No pCR Events/N
Esserman et al,[6] 2012	2/19	6/14
	4/11	4/22
Krishnan et al,[51] 2013	2/13	22/42
	1/9	17/38
Natoli et al,[33] 2013	7/44	13/36
Sánchez-Muñoz et al,[46] 2013	1/8	2/8
	1/5	9/17
de Azambuja et al,[53] 2014	14/87	47/124
	6/50	36/150
Cortazar et al,[5] 2014	48/325	223/510
	43/247	243/839
Takada et al,[30] 2014	35/281	62/158
	11/120	54/214



Broglio K, et al. *JAMA Oncol.* 2016;2(6):751-760.

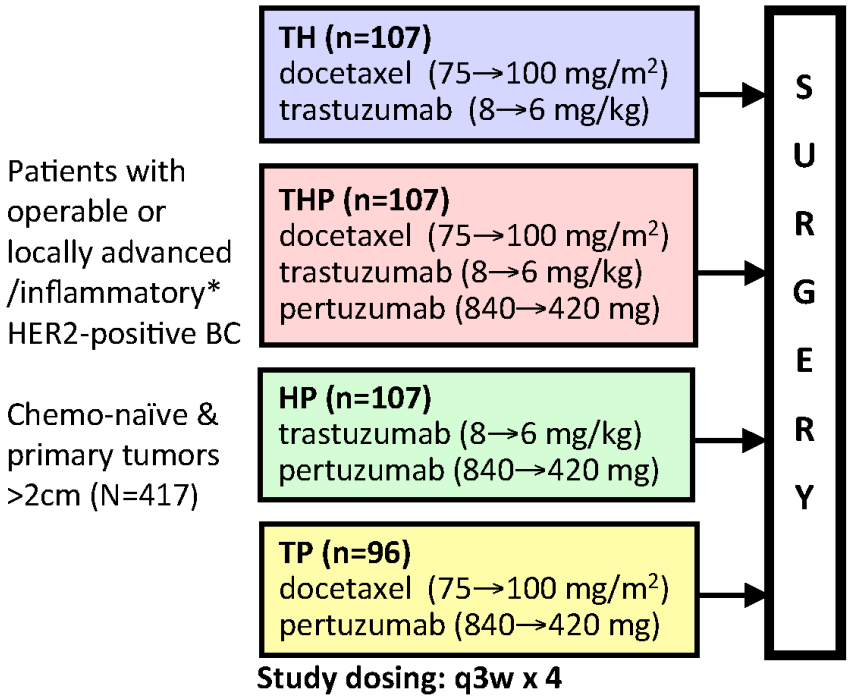
Trastuzumab+pertuzumab en néoadjuvant

Neoadjuvant Pertuzumab/Trastuzumab (3 regimens FDA/EMA approved)

	NEOSPHERE[1]	TRYPHAENA[2]	TRYPHAENA[2]
Treatment	Pertuzumab, Trastuzumab, Docetaxel THP x 4 FEC x 3 post-op	Docetaxel/Carbo/ Trastuzumab/ Pertuzumab TCHP x 6	FEC x 3 → THP x 3
N	107	77	75
ypT0/is ypN0 (%)	39.3	63.6	54.6

1. Gianni L et al. Lancet Oncol 2012; 2. Schneeweiss A et al. Ann Oncol 2013

Etude Neosphere

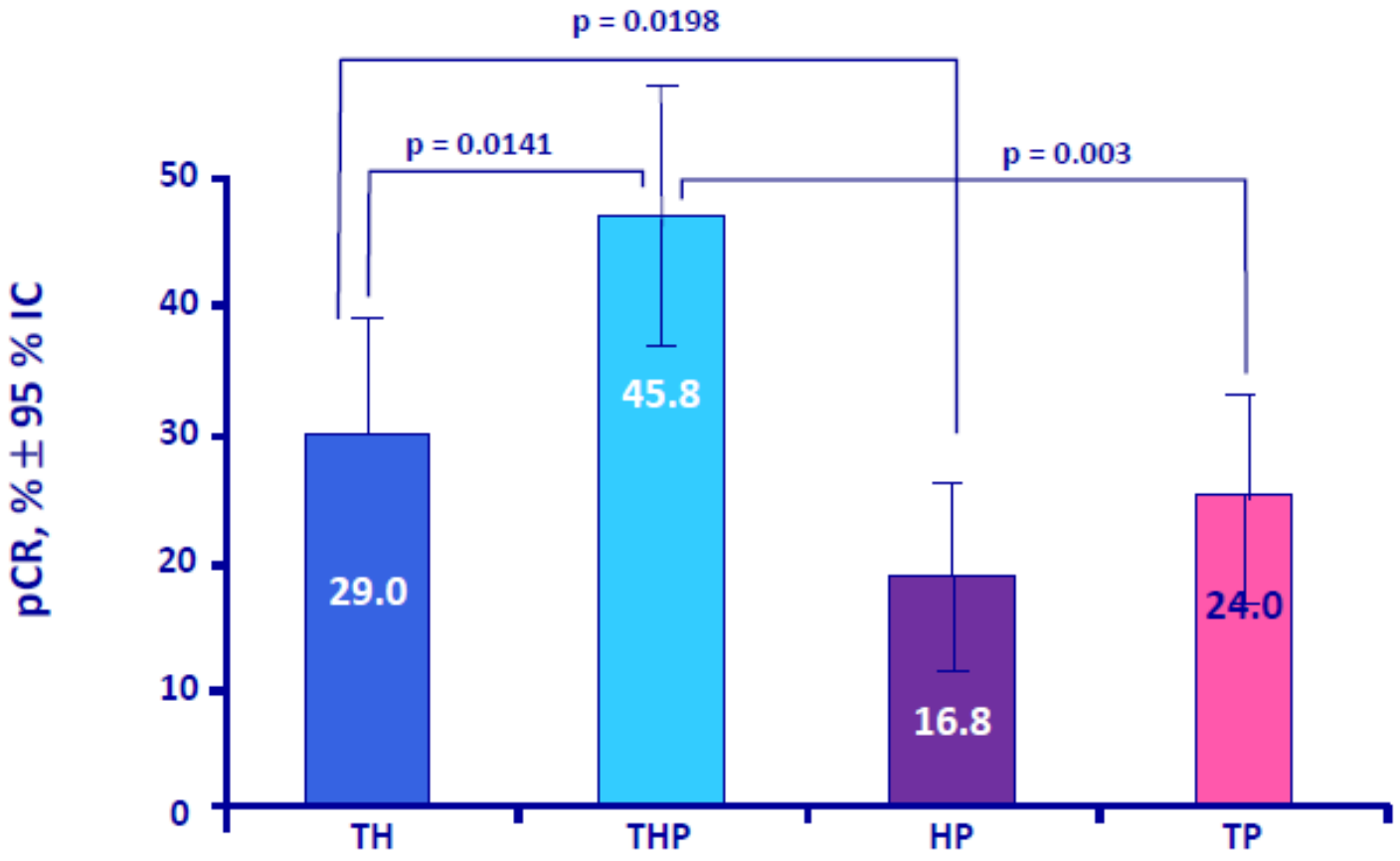


- **Phase II design**
- **Primary endpoint:**
  - **comparison of pCR rates**
    - **TH vs THP**
    - **TH vs HP**
    - **THP vs TP**
- **Secondary endpoints:**
  - Clinical response
  - DFS
  - Breast conservation rate
  - Biomarker evaluation

BC, breast cancer; FEC, 5-fluorouracil, epirubicin and cyclophosphamide
*Locally advanced=T2–3, N2–3, M0 or T4a–c, any N, M0; operable=T2–3, N0–1, M0; inflammatory = T4d, any N, M0
H, trastuzumab; P, pertuzumab; T, docetaxel

Gianni L, *et al*. *Lancet Oncol* 2012.

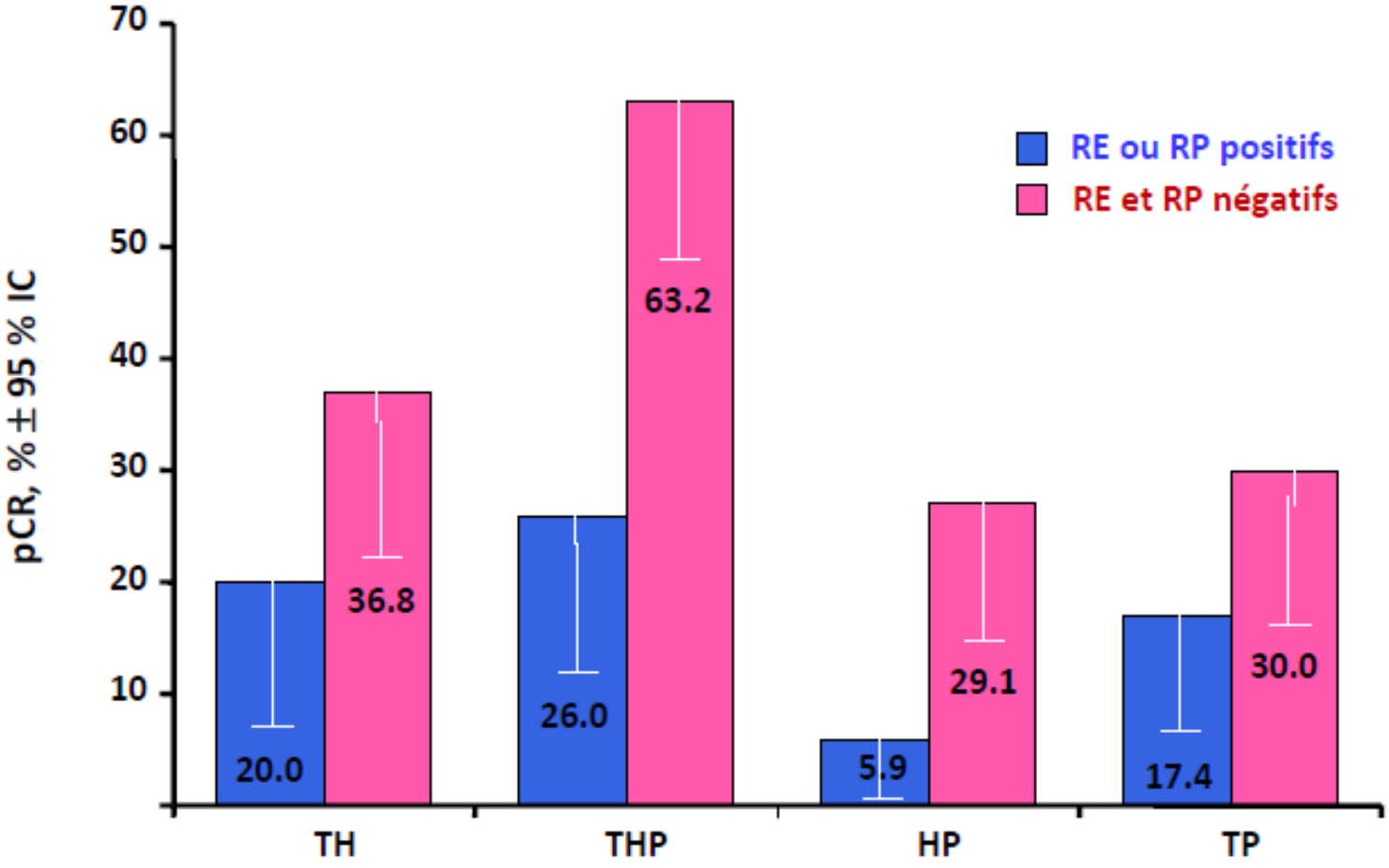
Etude Neosphere



H, trastuzumab; P, pertuzumab; T, docetaxel

Gianni L et al. SABCS 2010

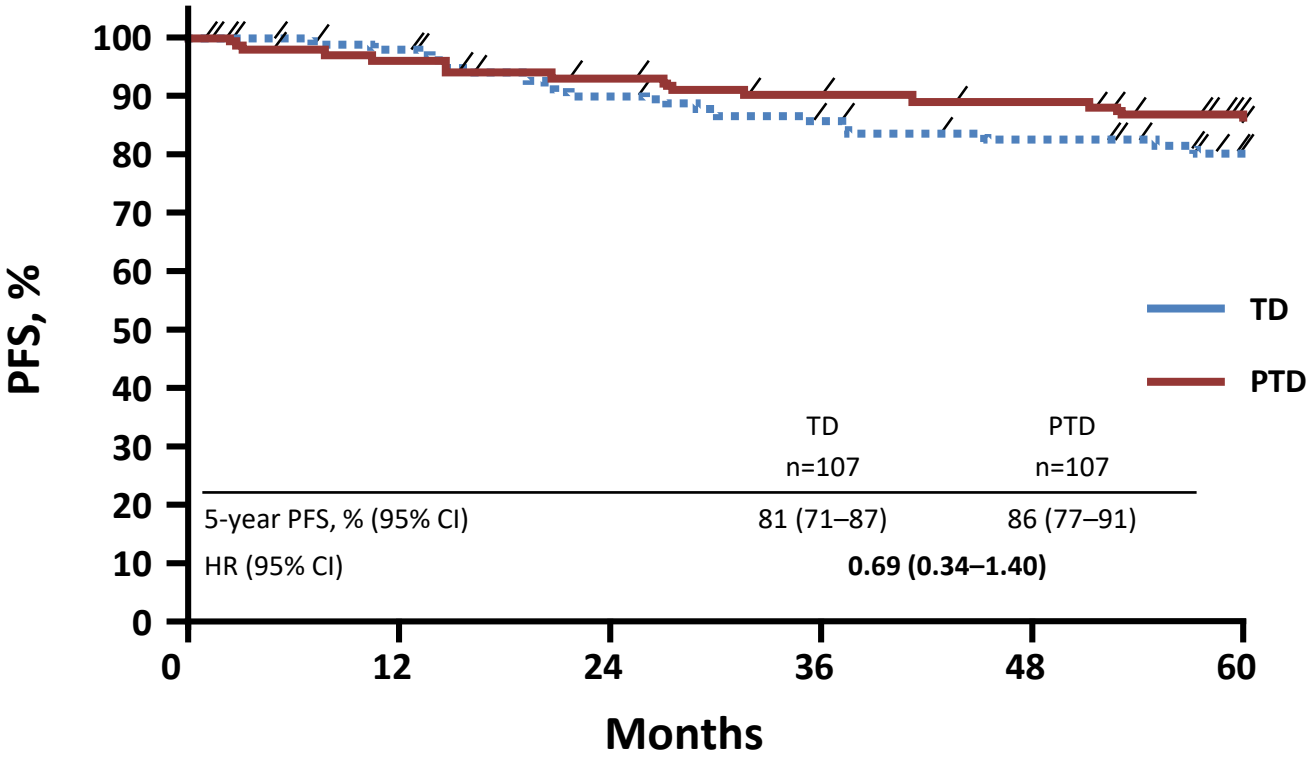
Etude Neosphere



H, trastuzumab; P, pertuzumab; T, docetaxel

Gianni L, Lancet Oncol. 2012 Jan;13(1):25-32.

PFS for TD vs PTD, ITT population

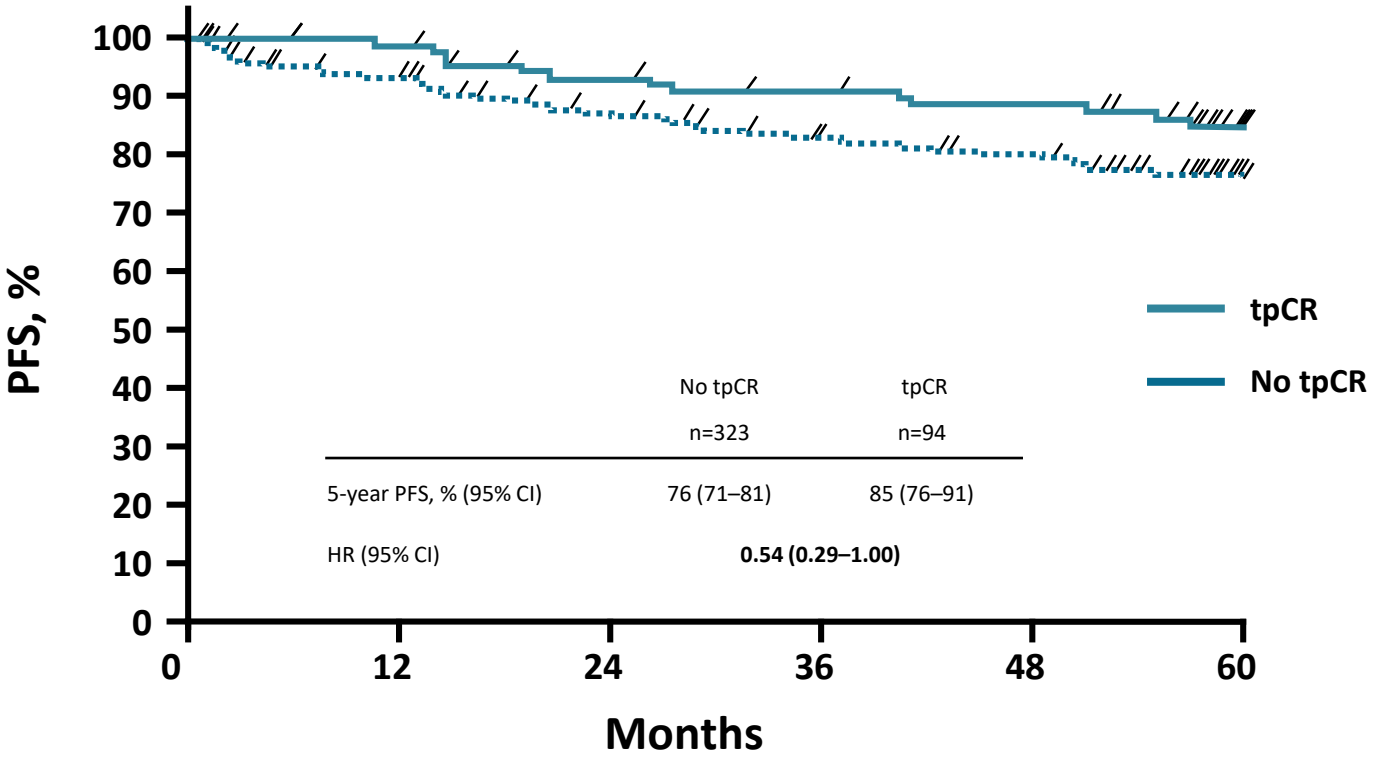


n at risk						
TD	107	101	89	83	78	58
PTD	107	99	94	88	86	63

Gianni L, *et al*. *ASCO 2015*

Kaplan–Meier curves are truncated at 60 months (the end of scheduled follow-up). However, summary statistics shown here take into account all follow-up
Three late events occurred with PTD: two cases of PD at 63 and 71 months, and one death due to an unrelated cerebrovascular accident without PD at 76 months

PFS by tpCR: all treatment arms combined, ITT population:

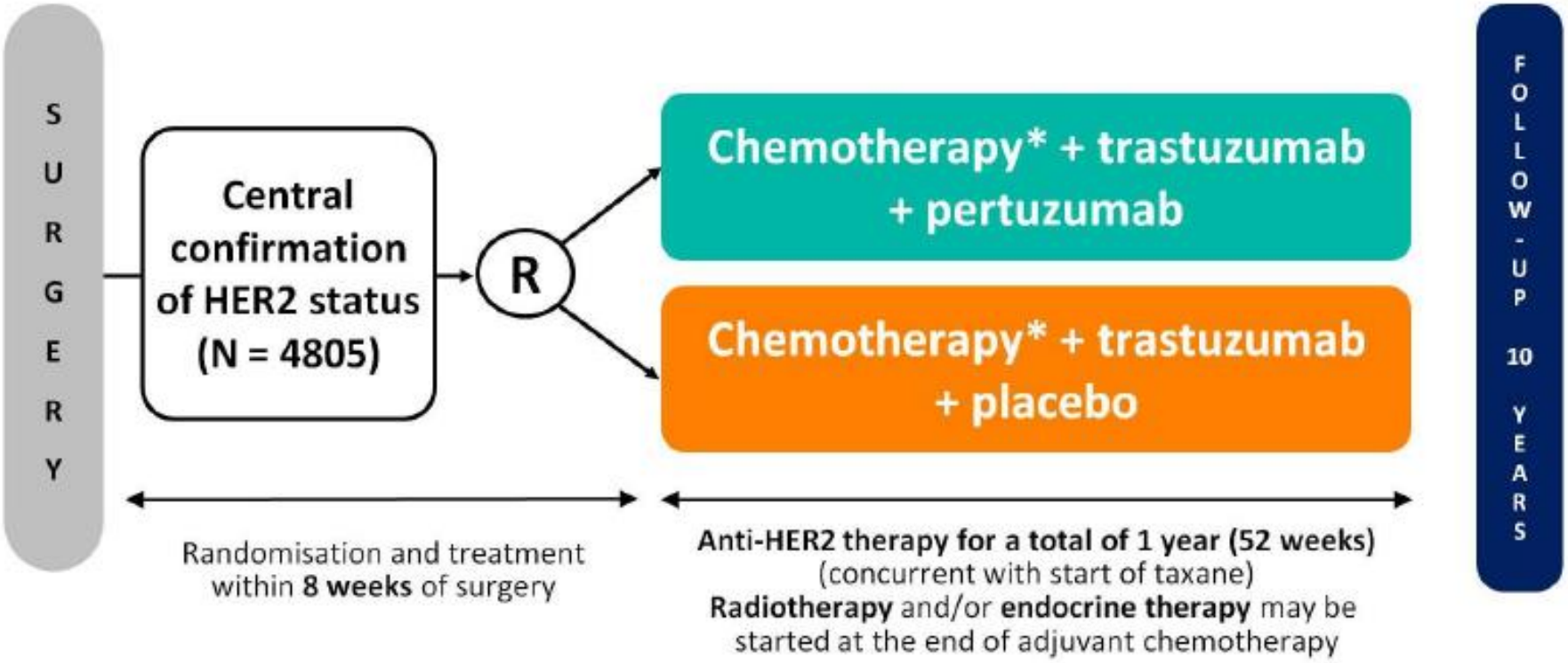


n at risk						
tpCR	94	91	83	79	76	55
No tpCR	323	287	262	244	234	178

Gianni L, *et al*. *ASCO 2015*

Kaplan–Meier curves are truncated at 60 months (the end of scheduled follow-up). However, summary statistics shown here take into account all follow-up. One late event occurred in the No tpCR group due to PD at 71 months; one late event occurred in the tpCR group, a death due to an unrelated cerebrovascular accident without PD at 76 months

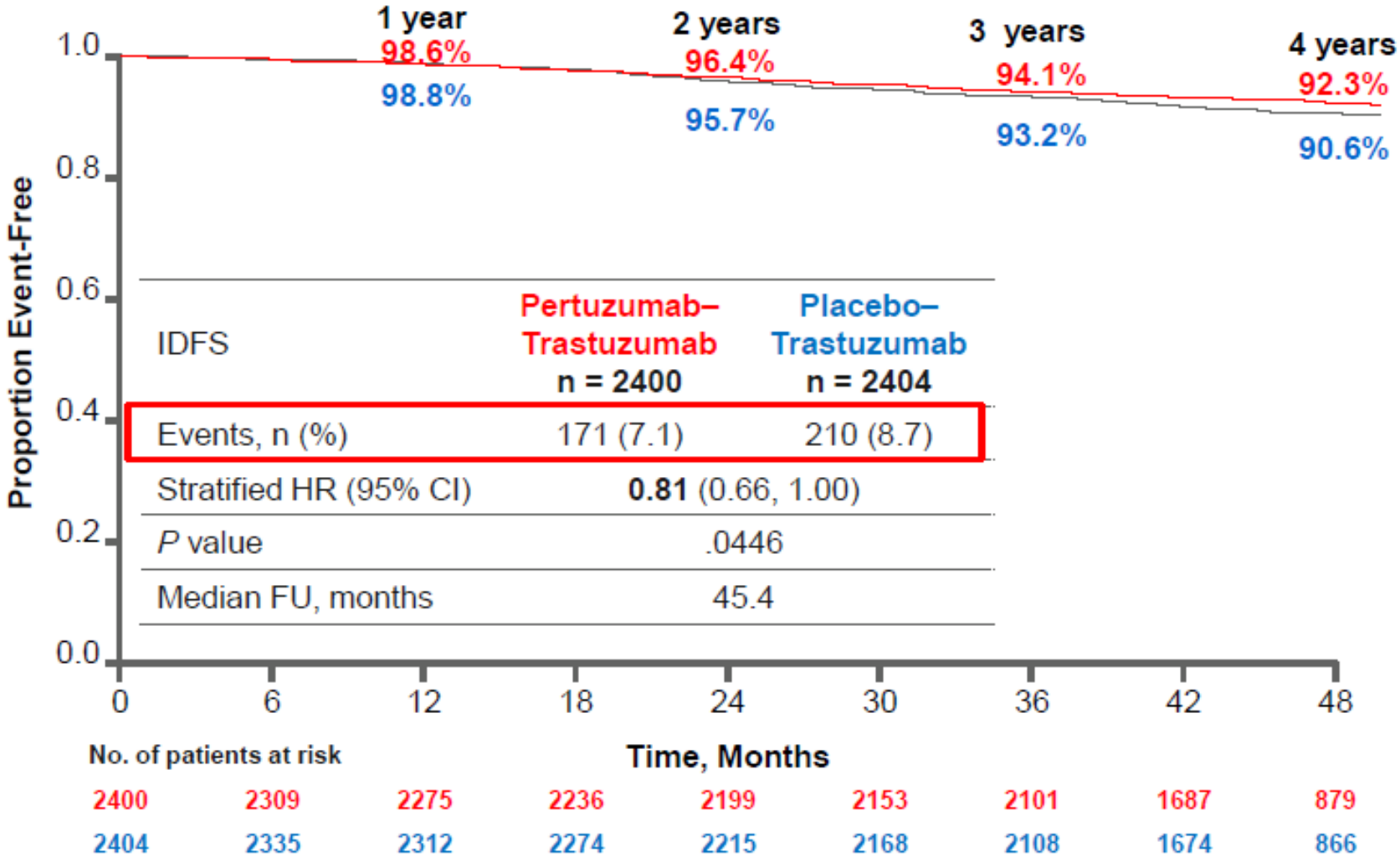
APHINITY: Trial Design



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

von Minckwitz G, et al. *N Engl J Med.* 2017;377(2):122-131.

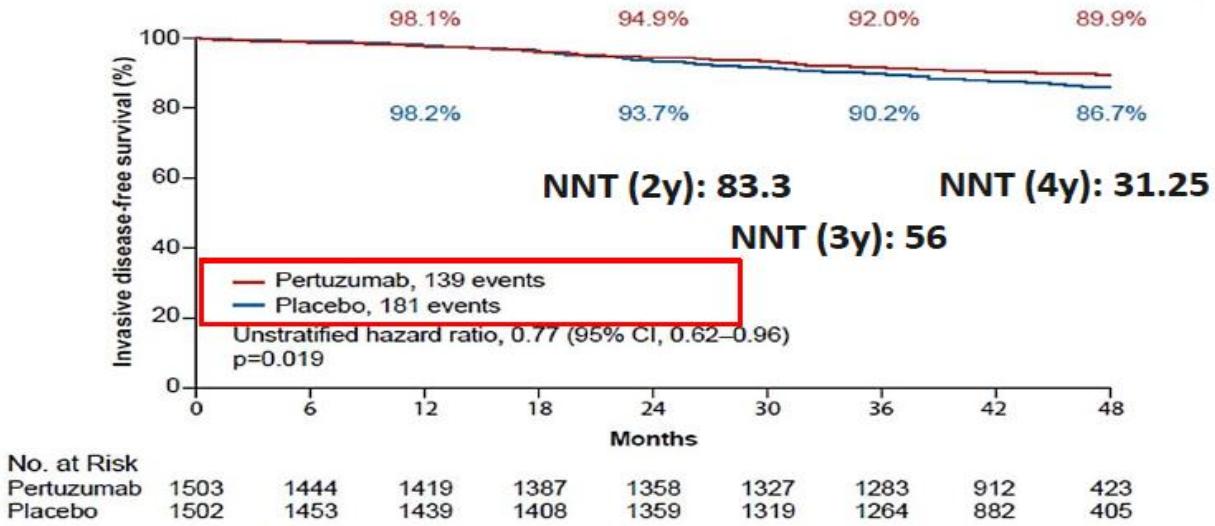
APHINITY: ITT Primary Endpoint Analysis
Invasive Disease-Free Survival



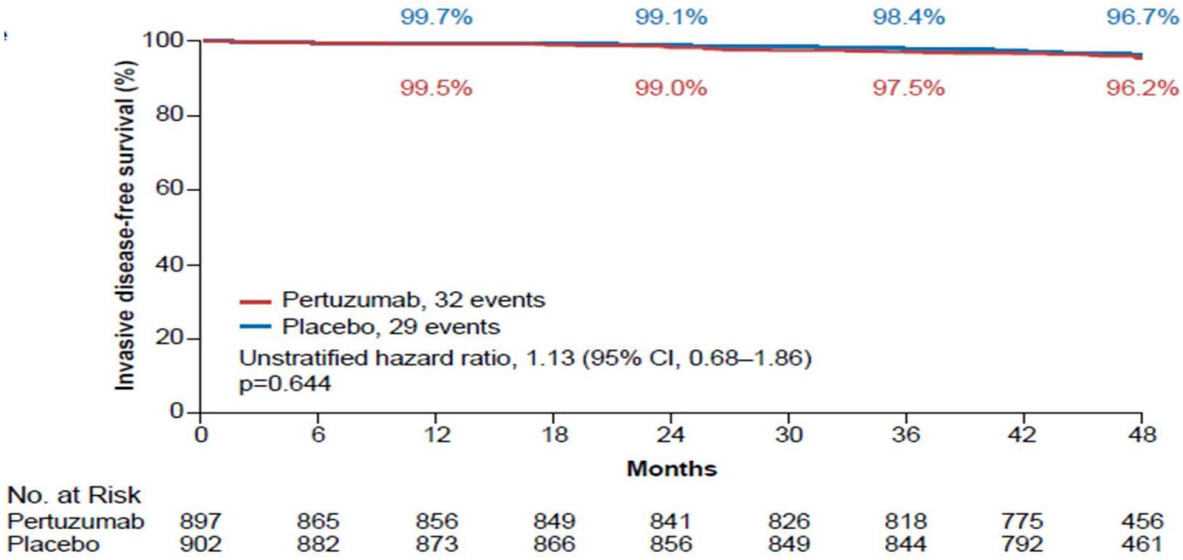
IDFS	Pertuzumab–Trastuzumab n = 2400	Placebo–Trastuzumab n = 2404
Events, n (%)	171 (7.1)	210 (8.7)
Stratified HR (95% CI)	**0.81** (0.66, 1.00)	
P value	.0446	
Median FU, months	45.4	

von Minckwitz G, et al. *N Engl J Med.* 2017;377(2):122-131.

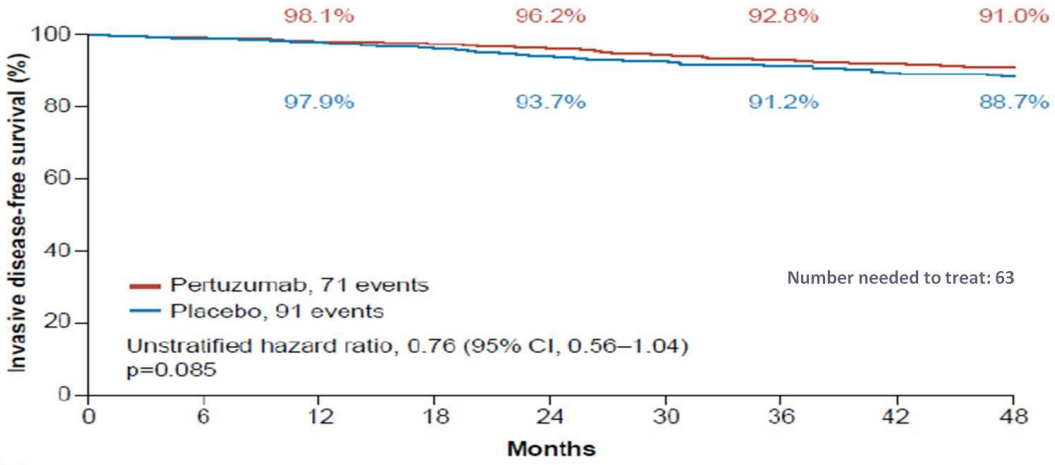
APHINITY: Node-Positive Subgroup



APHINITY: Node-negative Subgroup

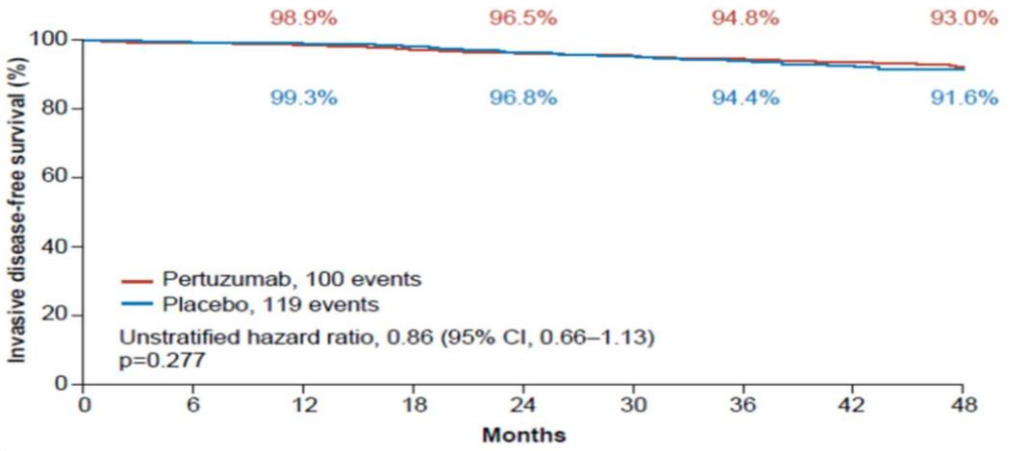


APHINITY: Hormone Receptor-negative Subgroup



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

APHINITY: Hormone Receptor-positive Subgroup



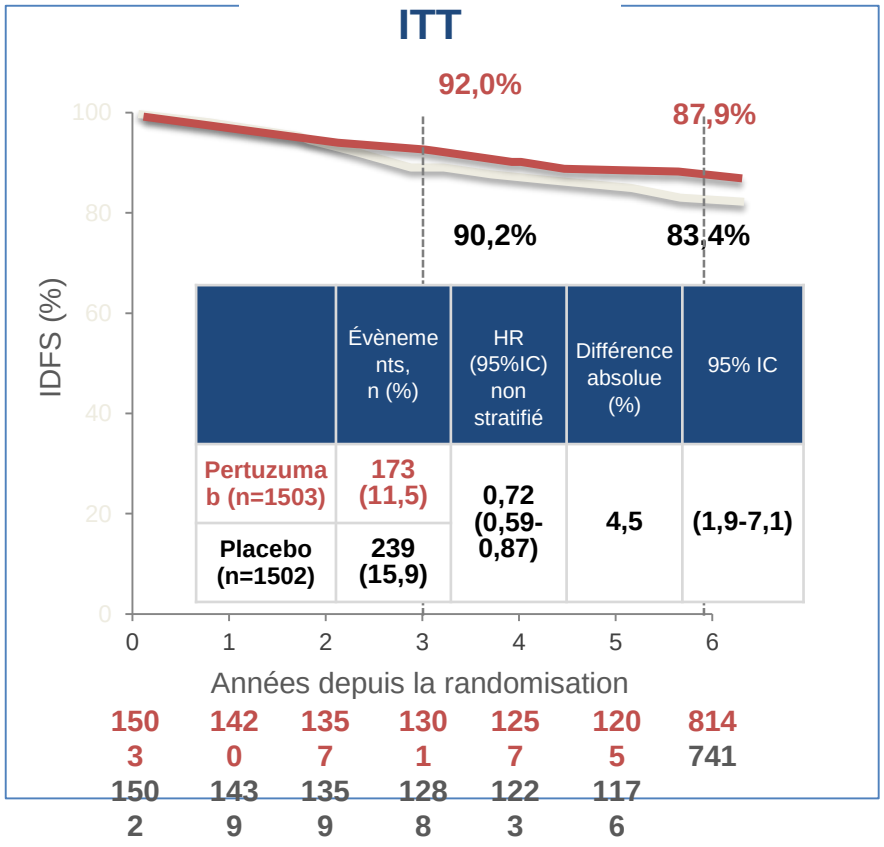
No. at Risk									
Pertuzumab	1536	1473	1454	1423	1402	1379	1346	1087	565
Placebo	1546	1508	1501	1481	1444	1410	1378	1105	564

Presented By Gunter Von Minckwitz at 2017 ASCO Annual Meeting

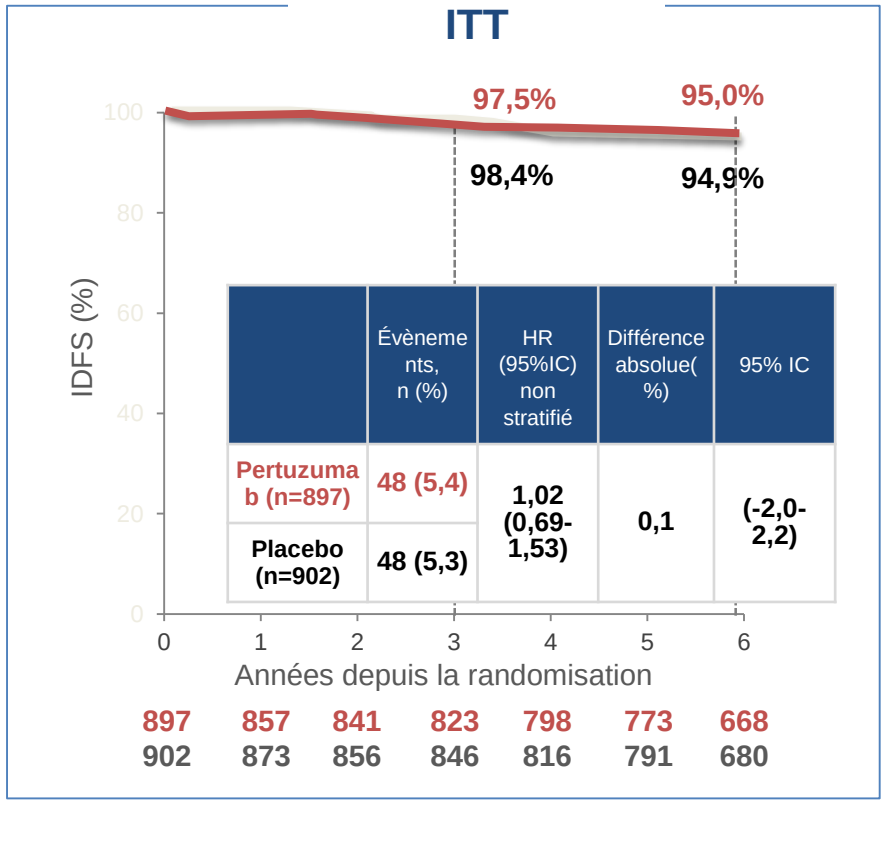
APHINITY: analyse descriptive actualisée de l'IDFS

- 74,1 mois de suivi médian
- **La cohorte pN+ continue à bénéficier de l'adjonction du pertuzumab**

Cohorte pN+, en ITT



Cohorte pN0, en ITT

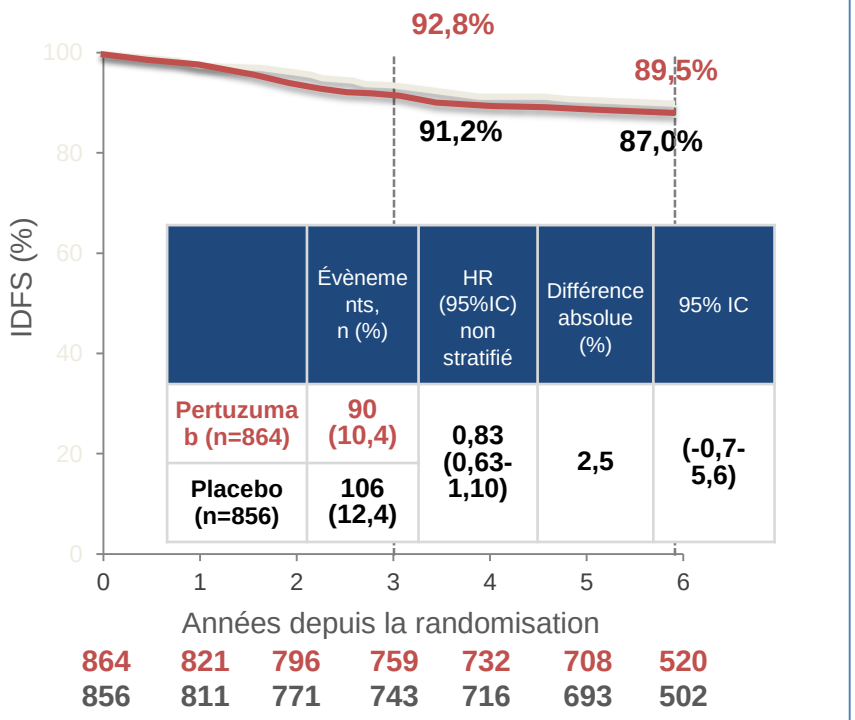


Piccart M. et al, SABCS 2019 GS1-04

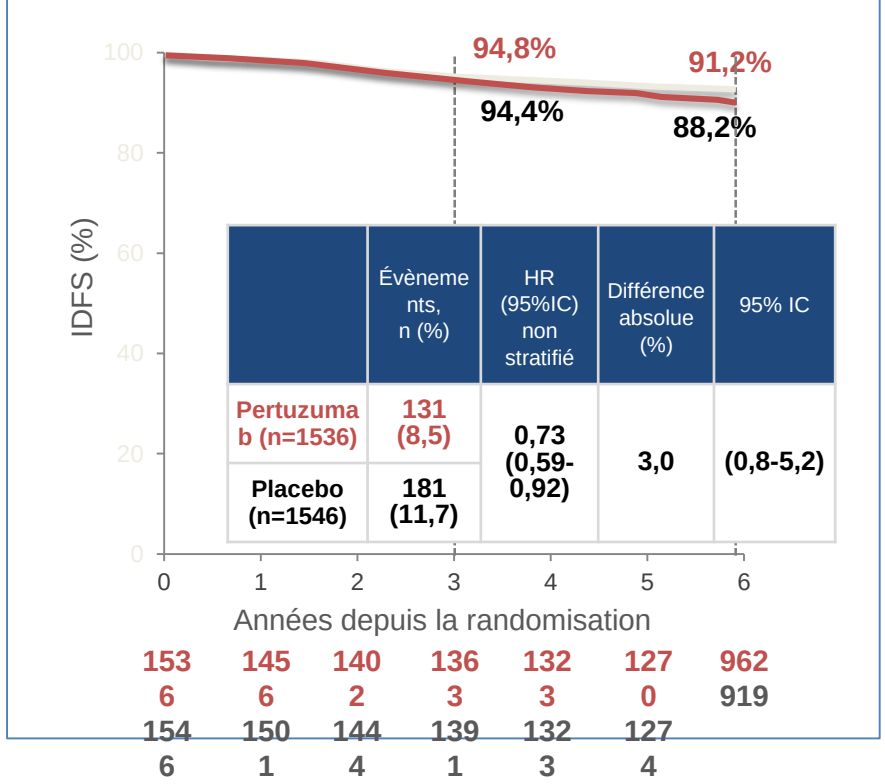
APHINITY: analyse descriptive actualisée de l'IDFS

- 74,1 mois de suivi médian
- **Le bénéfice est également observé dans la population RH+**

Cohorte HR neg , en ITT



Cohorte HR pos, en ITT



Piccart M. et al, SABCS 2019 GS1-04

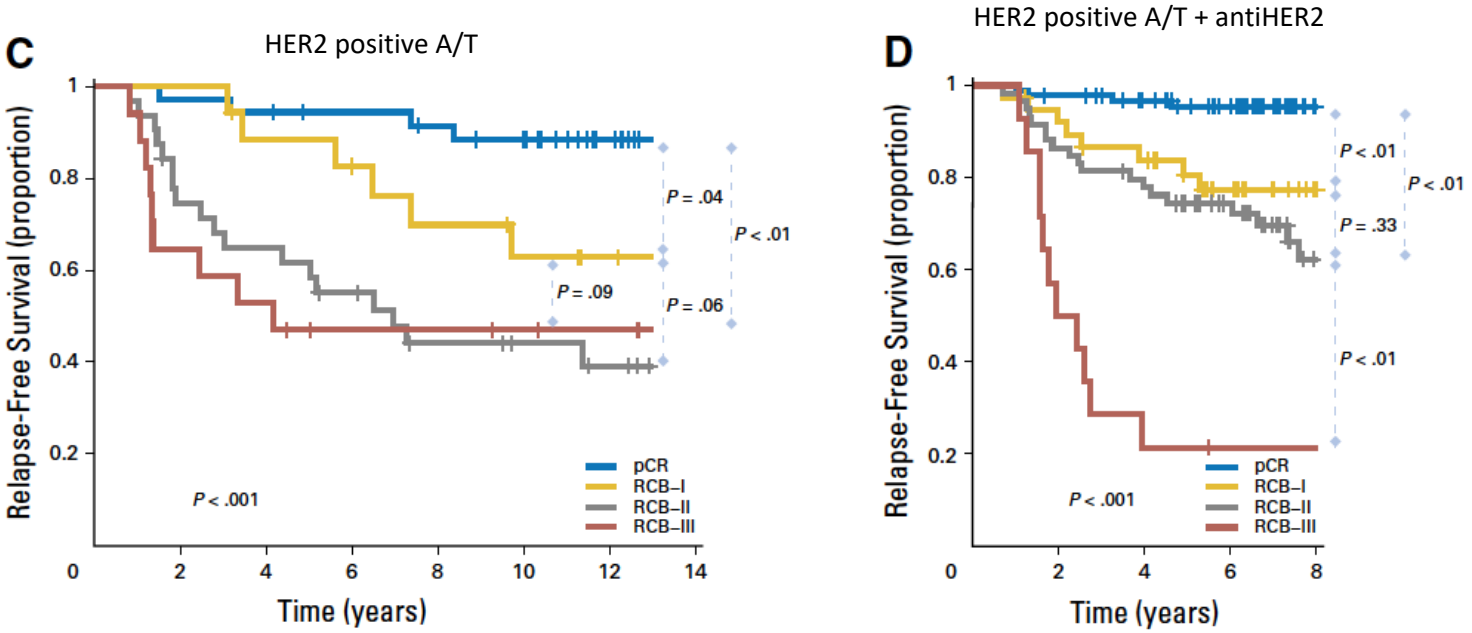
APHINITY: Cardiac Endpoints

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

Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype

W. Fraser Symmans, Caimiao Wei, Rebekah Gould, Xian Yu, Ya Zhang, Mei Liu, Andrew Walls, Alex Bousamra, Maheshwari Ramineni, Bruno Sinn, Kelly Hunt, Thomas A. Buchholz, Vicente Valero, Aman U. Buzdar, Wei Yang, Abenaa M. Brewster, Stacy Moulder, Lajos Pusztai, Christos Hatzis, and Gabriel N. Hortobagyi



J Clin Oncol 2017; 35: 1049-61

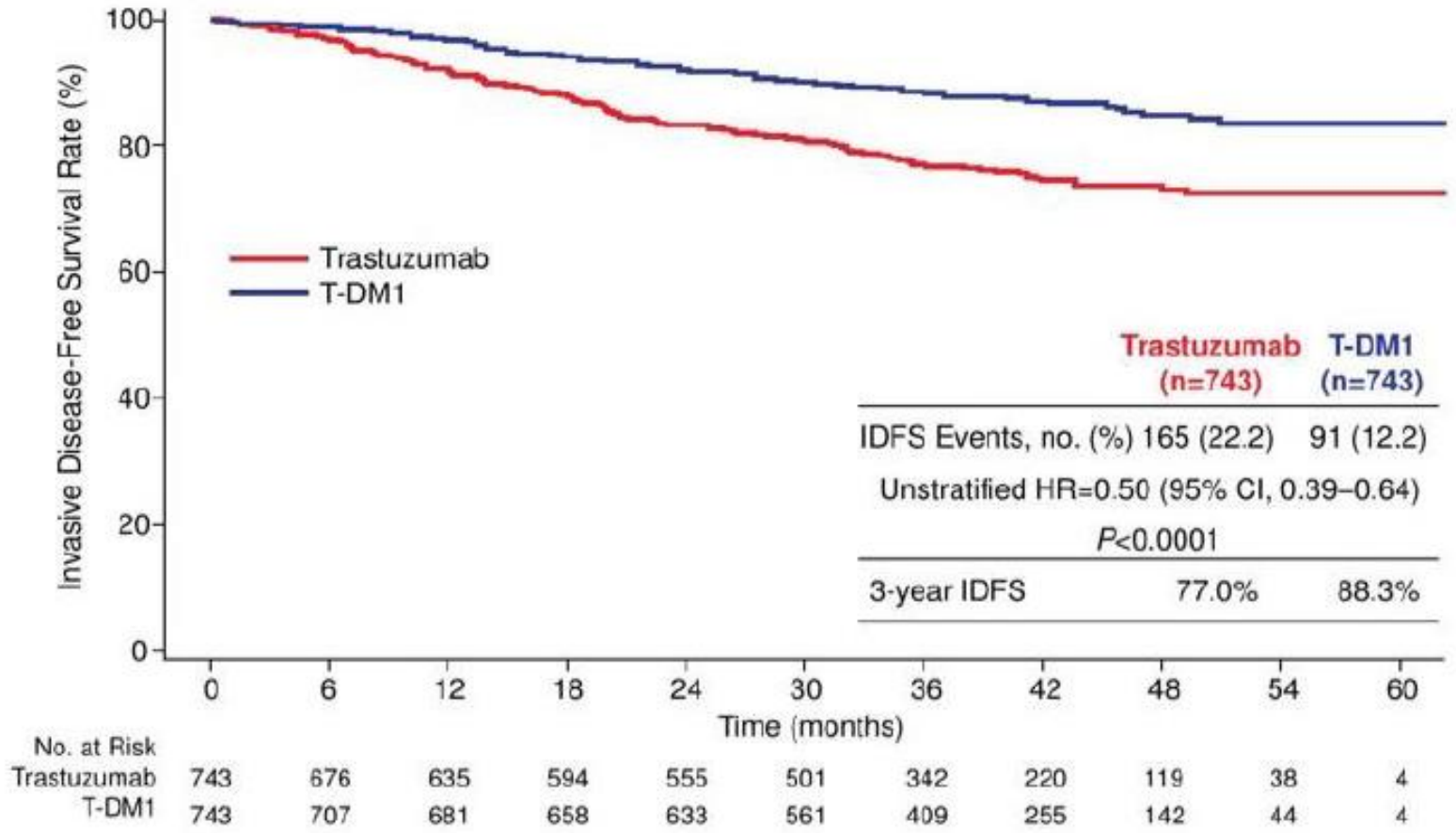
Katherine

Primary endpoint : IDFS

≈ 900/1400 patients recruited as of today

KATHERINE: iDFS

Invasive Disease–Free Survival

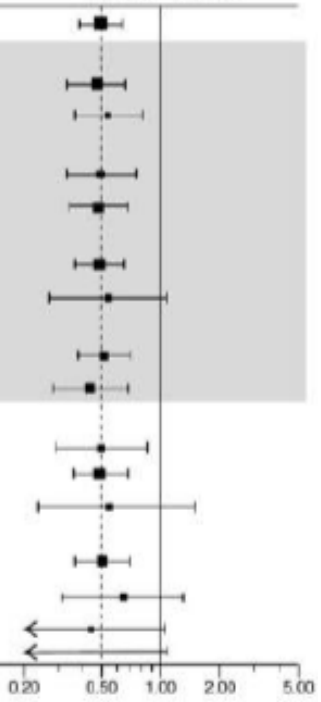


Geyer CE, et al. *Cancer Res.* 2019;79(4): Abstract GS1-10. von Minckwitz G, et al. *N Engl J Med.* 2019;380(7):617-628.

KATHERINE: iDFS Subgroup Analysis

IDFS Subgroup Analysis (1)

Group	Total N	Trastuzumab (n=743) 3-Year IDFS	T-DM1 (n=743) 3-Year IDFS	Hazard Ratio	95% CI
All	1486	77.0	88.3	0.50	(0.39–0.64)
Clinical stage at presentation					
Operable	1111	82.8	92.3	0.47	(0.33–0.66)
Inoperable	375	60.2	76.0	0.54	(0.37–0.80)
Hormone receptor status					
Negative (ER negative and PgR negative/unknown)	412	66.6	82.1	0.50	(0.33–0.74)
Positive (ER and/or PgR positive)	1074	80.7	90.7	0.48	(0.35–0.67)
Preoperative HER2-directed therapy					
Trastuzumab alone	1196	75.9	87.7	0.49	(0.37–0.65)
Trastuzumab plus additional HER2-directed agent(s)	290	81.8	90.9	0.54	(0.27–1.06)
Pathological nodal status after preoperative therapy					
Node positive	689	67.7	83.0	0.52	(0.38–0.71)
Node negative/not done	797	84.6	92.8	0.44	(0.28–0.68)
Age group (years)					
<40	296	74.9	86.5	0.50	(0.29–0.86)
40–64	1064	77.1	88.8	0.49	(0.36–0.67)
≥65	126	81.1	87.4	0.55	(0.22–1.34)
Race*					
White	1082	79.1	88.8	0.51	(0.37–0.69)
Asian	129	71.9	82.5	0.65	(0.32–1.32)
American Indian or Alaska Native	86	60.3	81.8	0.44	(0.16–1.03)
Black or African American	40	66.0	94.7	0.13	(0.02–1.10)

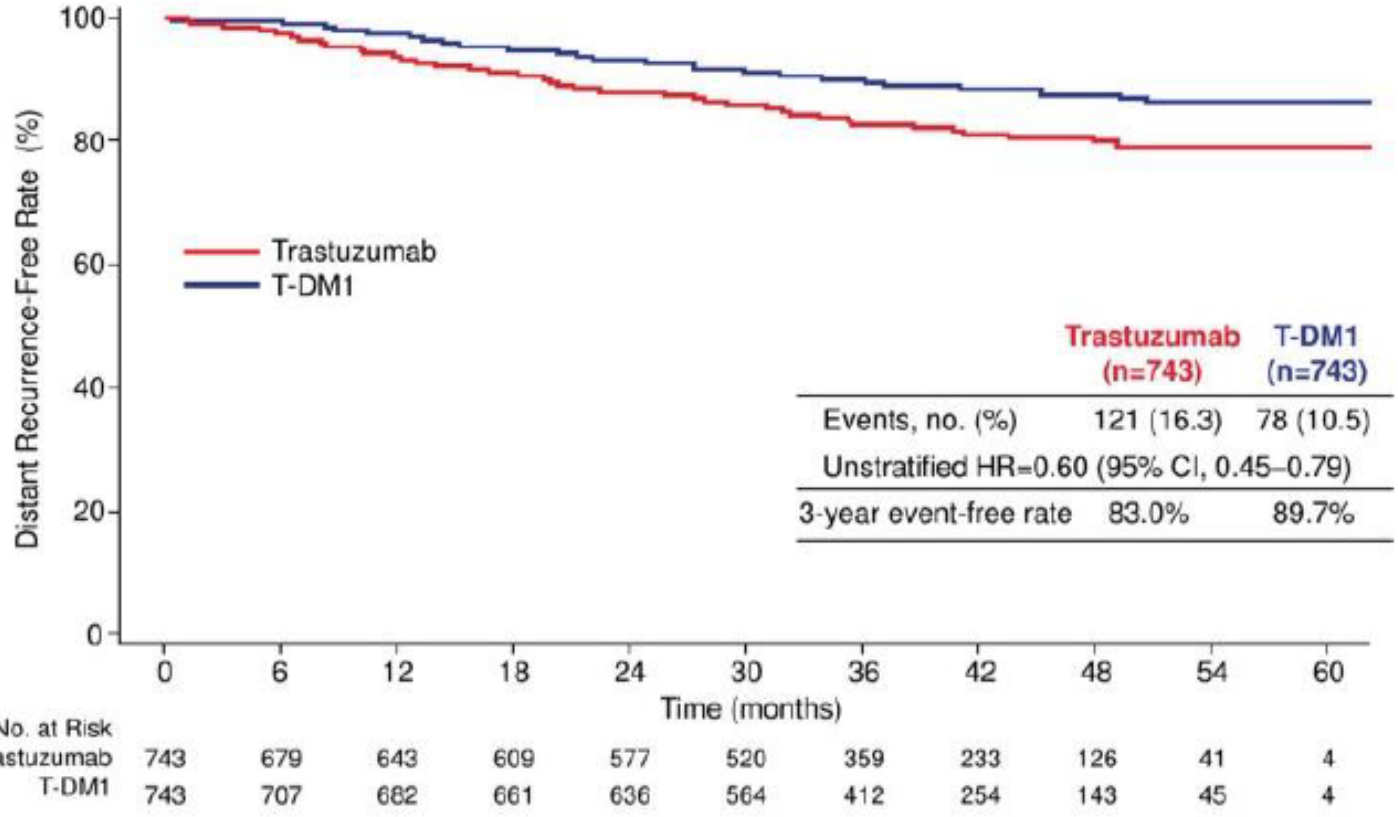


*149 were of multiple races or unknown race.

Geyer CE, et al. *Cancer Res.* 2019;79(4): Abstract GS1-10. von Minckwitz G, et al. *N Engl J Med.* 2019;380(7):617-628.

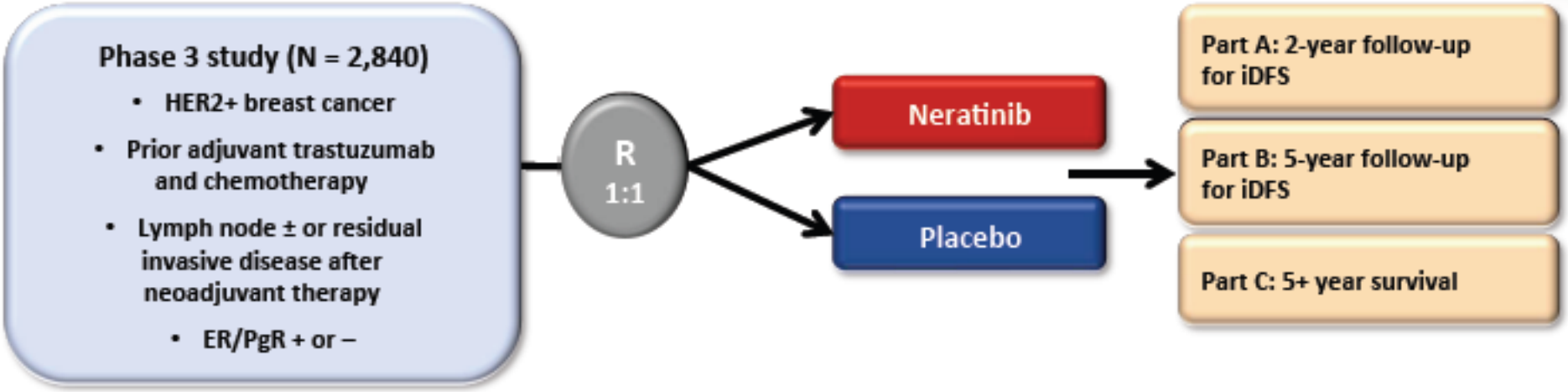
KATHERINE: Distant Recurrence

Distant Recurrence



Geyer CE, et al. *Cancer Res.* 2019;79(4): Abstract GS1-10. von Minckwitz G, et al. *N Engl J Med.* 2019;380(7):617-628.

ExteNET study

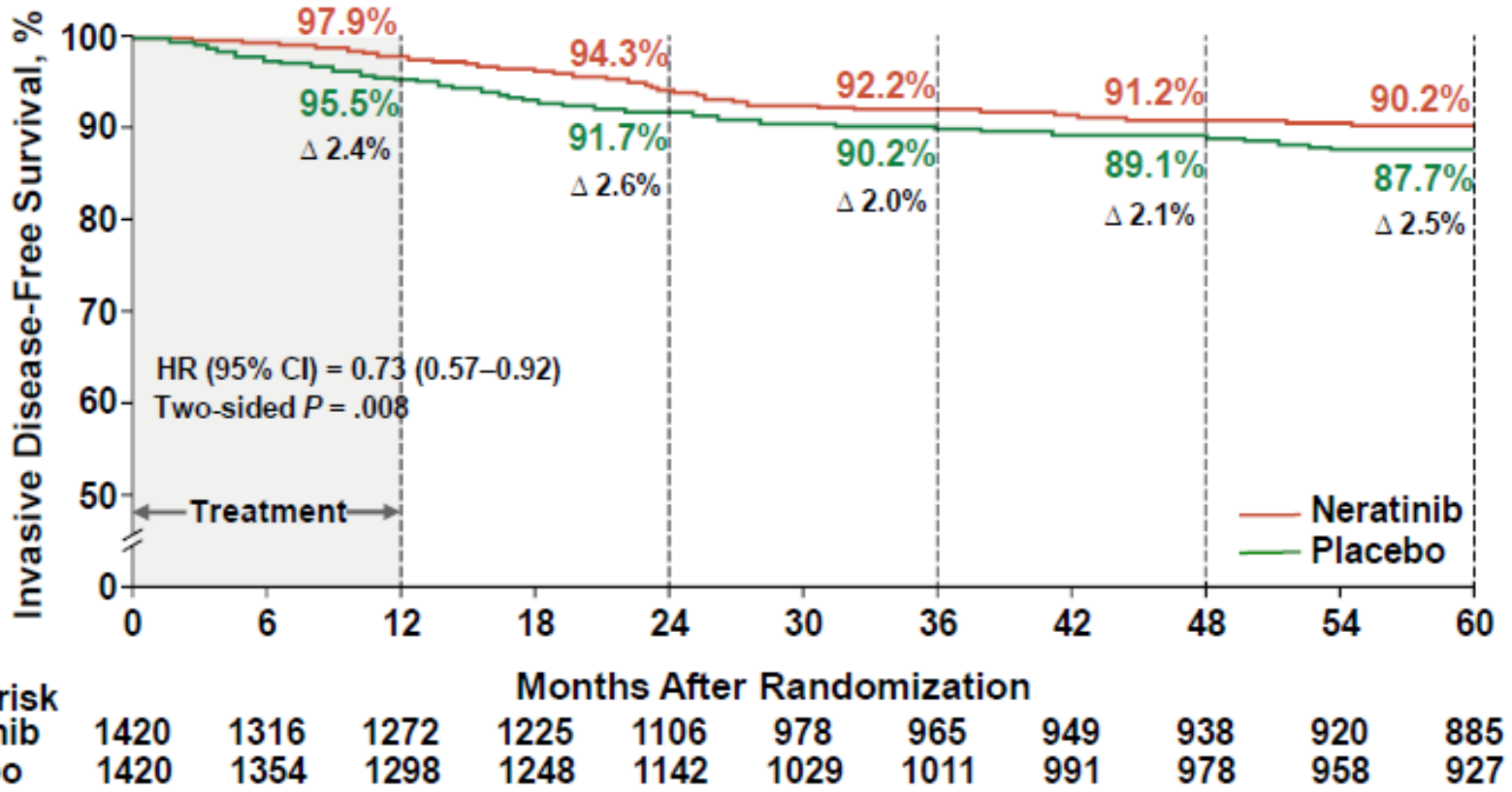


- **Primary endpoint:** invasive disease-free survival (iDFS)
- **Secondary endpoints:** DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, OS, safety

CNS, central nervous system; DFS-DCIS, disease-free survival including ductal carcinoma in situ; ER, estrogen receptor; HER2+, human epidermal growth factor receptor 2-positive; OS, overall survival; PgR, progesterone receptor; R, randomization.

Adapted from Chan A, et al. ASCO 2015, Abst 508 [oral presentation].

ExteNET: 5-Year Analysis—iDFS

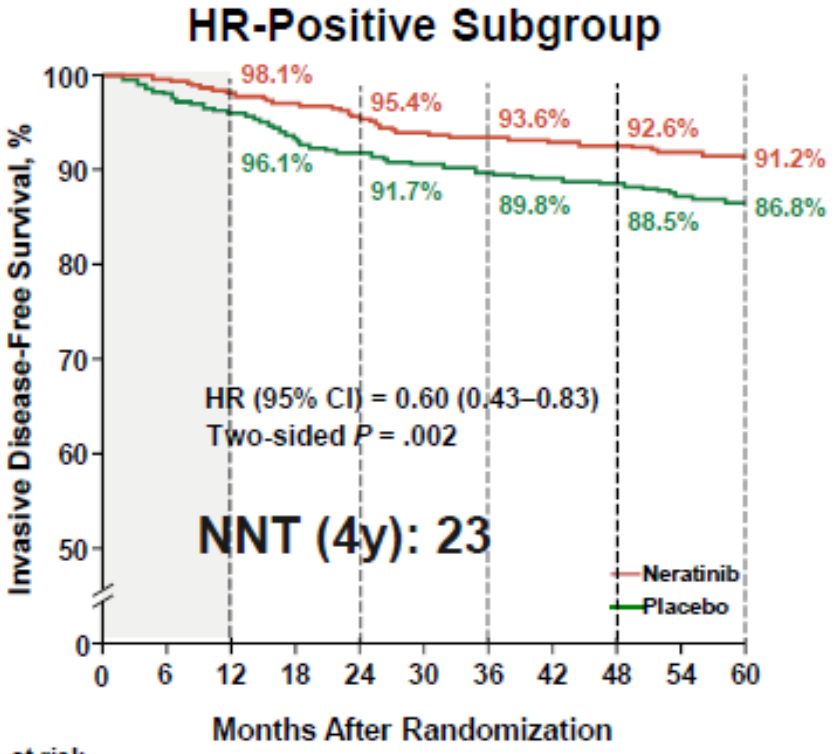


No. at risk											
Neratinib	1420	1316	1272	1225	1106	978	965	949	938	920	885
Placebo	1420	1354	1298	1248	1142	1029	1011	991	978	958	927

Intention-to-treat population. Cut-off date: March 1, 2017

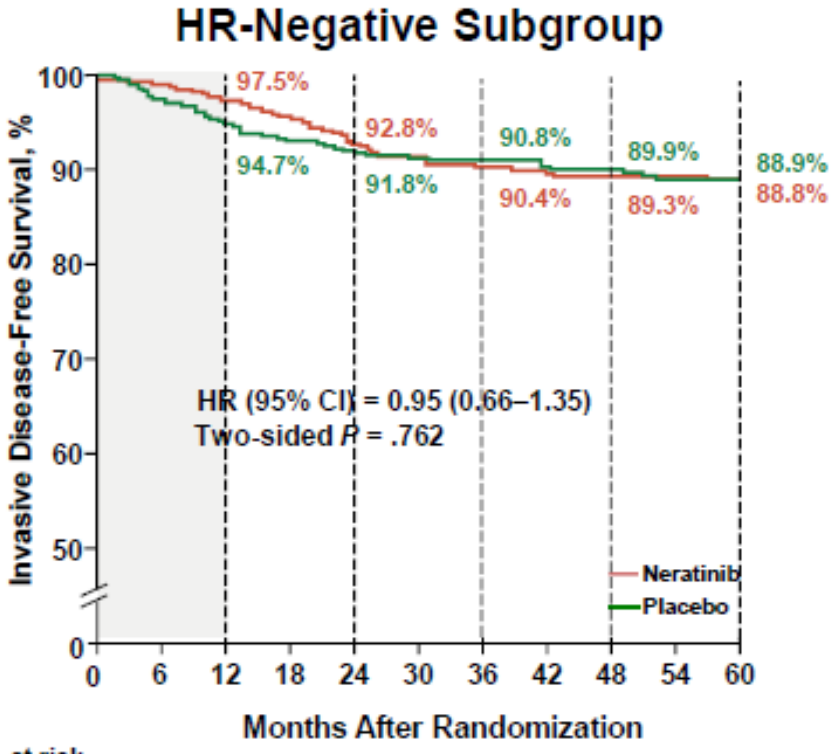
Martin M, et al. *Lancet Oncol.* 2017;18(12):1688-1700.

ExteNET: iDFS By Hormone-Receptor Status



No. at risk

Neratinib	816	757	731	705	642	571	565	558	554	544	523
Placebo	815	779	750	719	647	581	567	556	551	542	525



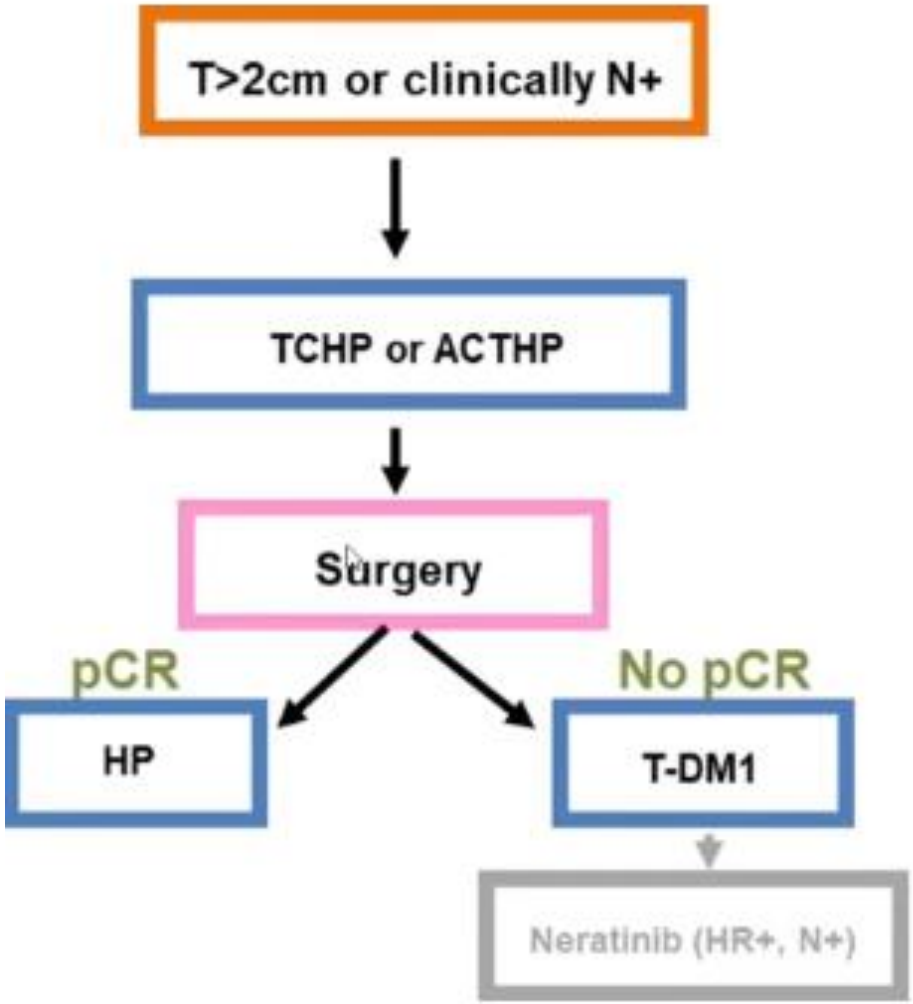
No. at risk

Neratinib	604	559	541	520	464	407	400	391	384	376	362
Placebo	605	575	548	529	495	448	444	435	427	416	402

Intention-to-treat population. Cut-off date: March 1, 2017

Martin M, et al. *Lancet Oncol.* 2017;18(12):1688-1700.

Current treatment algorithm



Adapted from Sara Tolaney ESMO Breast 2020

- **HER2-low: A New Subtype?**

HER2 Testing by IHC: 2018 ASCO/CAP Guidelines

HER2 testing (invasive component) by validated IHC assay

Batch controls and on-slide controls show appropriate staining

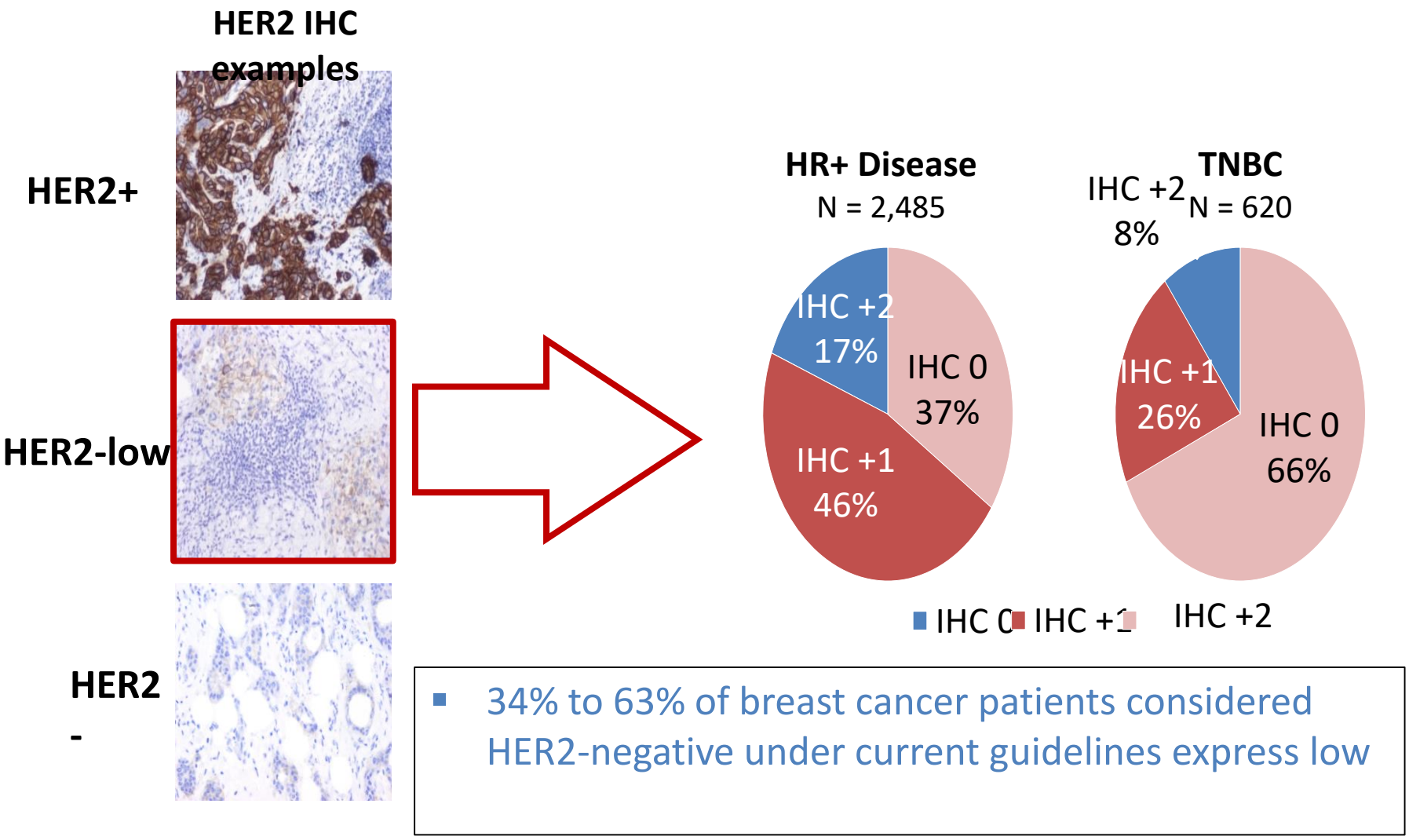
Circumferential membrane staining that is complete, intense, and in > 10% of tumor cells	Weak to moderate complete membrane staining observed in > 10% of tumor cells	Incomplete membrane staining that is faint/barely perceptible and in > 10% of tumor cells	No staining is observed *or* membrane staining that is incomplete and is faint/barely perceptible and in ≤ 10% of tumor cells
IHC 3+ positive	IHC 2+ equivocal	IHC 1+ negative	IHC 0 negative
			HER2-low

Must order a reflex test (same specimen using ISH) or order a new test (new specimen if available, using IHC or ISH)

- 2007, 2013/2014, and 2018 guidelines largely ignore both the IHC 0/1+ false-negative and the IHC 3+ false-positives

Wolff. Arch Pathol Lab Med. 2018;142:1364.

Prevalence of HER2-low by HR-status



- 34% to 63% of breast cancer patients considered HER2-negative under current guidelines express low

Schettini. ESMO Breast Cancer Virtual Meeting 2020. Abstr 23P. Slide courtesy of Aleix Prat.

NSABP B-47: Adjuvant Trastuzumab in Patients With Normal/Low HER2 Expression Breast Cancer

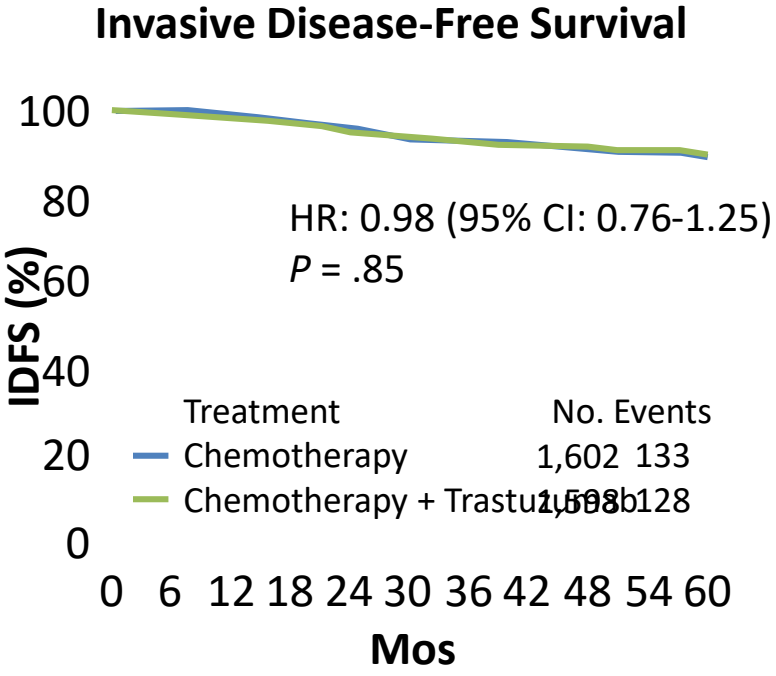
Patients with node positive or node negative high-risk primary breast cancer; IHC 1+ or 2+ for HER2; FISH negative and HER2 copy number < 4
(N = 3270)

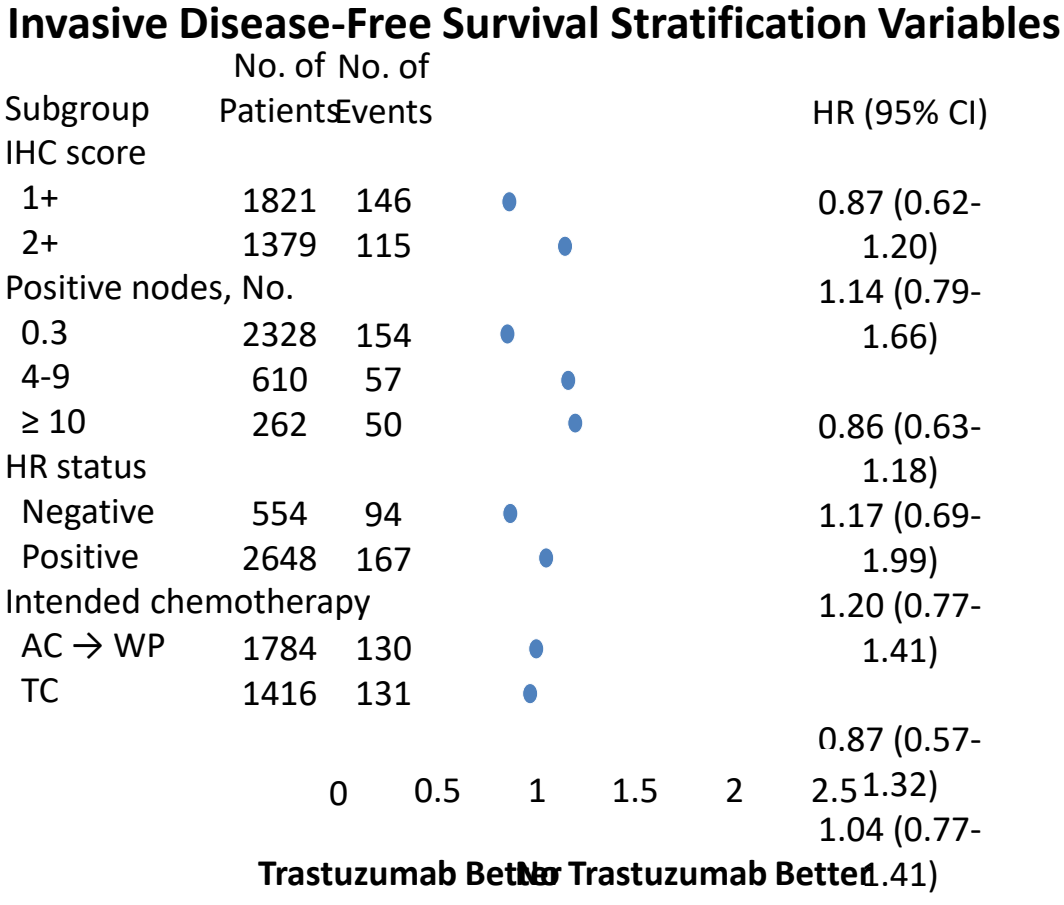
Anthracycline + Taxane + Trastuzumab
(n = 1599)

Anthracycline + Taxane
(n = 1603)

Fehrenbacher. SABCS 2017. Abstr GS1-02. Fehrenbacher. JCO. 2020;38:444.

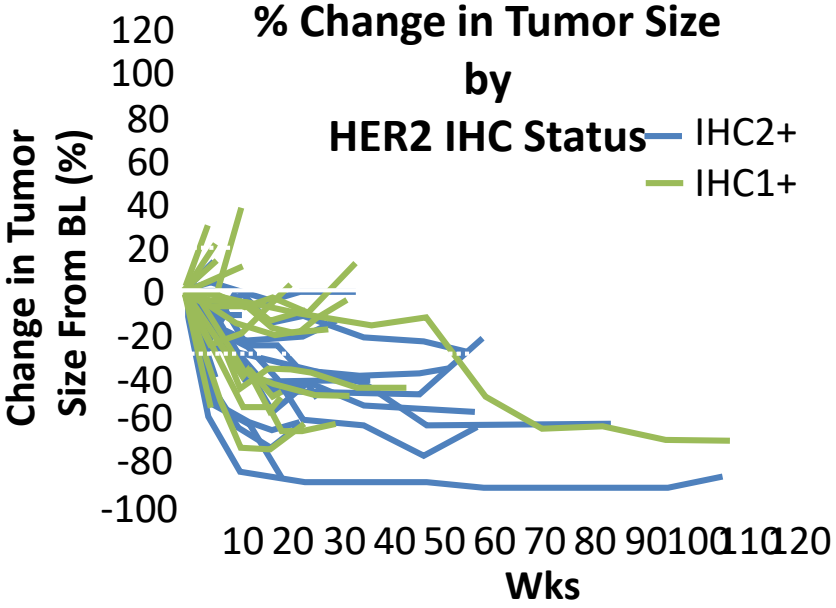
NSABP B-47: Invasive Disease-Free Survival

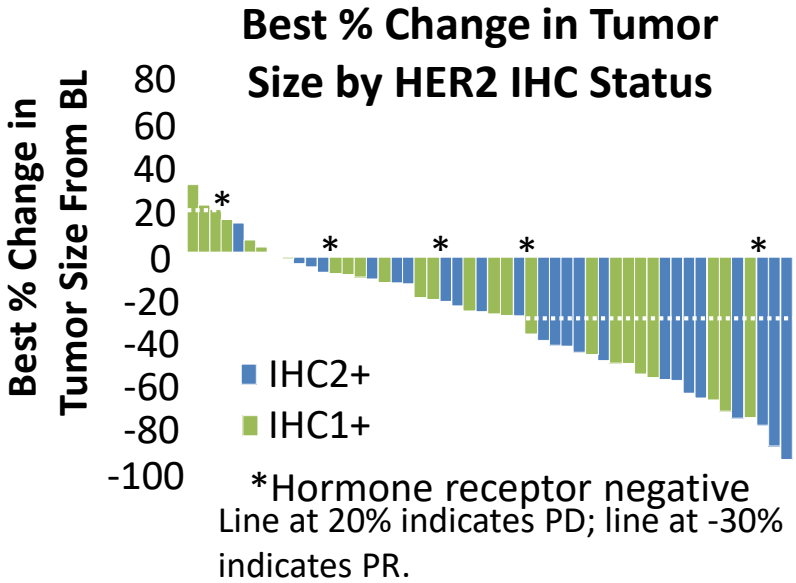




Fehrenbacher. JCO. 2020;38:444.

Efficacy of Trastuzumab Deruxtecan in HER2-Low MBC





Efficacy in HER2-Low MBC	Confirmed ORR, %	Median DoR, Mos	Median PFS, Mos
All (N = 51)	44.2	9.4	7.6
IHC 2+ (n = 24)	**54.5**	11.0	**13.6**
IHC 1+ (n = 27)	**33.3**	7.9	**5.7**
HR+ (n = 45)	47.4	11.0	7.9
Prior CDK4/6 inhibitor (n = 15)	33.3	NR	7.1

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