Global Breast Cancer Conference

Jeju Island, Korea – 20-22 April 2017

Can Anti-HER2 Treatment for Advanced Disease be Individualized in 2017?

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INSTITUT JULES BORDET

BIG against breast cancer

Relevant disclosures for this talk

- **Consultant (honoraria)** : Roche-Genentech
- **Research grants to my Institute** : most companies, including Roche-Genentech
- **Speakers bureau/stock ownership :** none

Anti-HER2 drugs for breast cancer

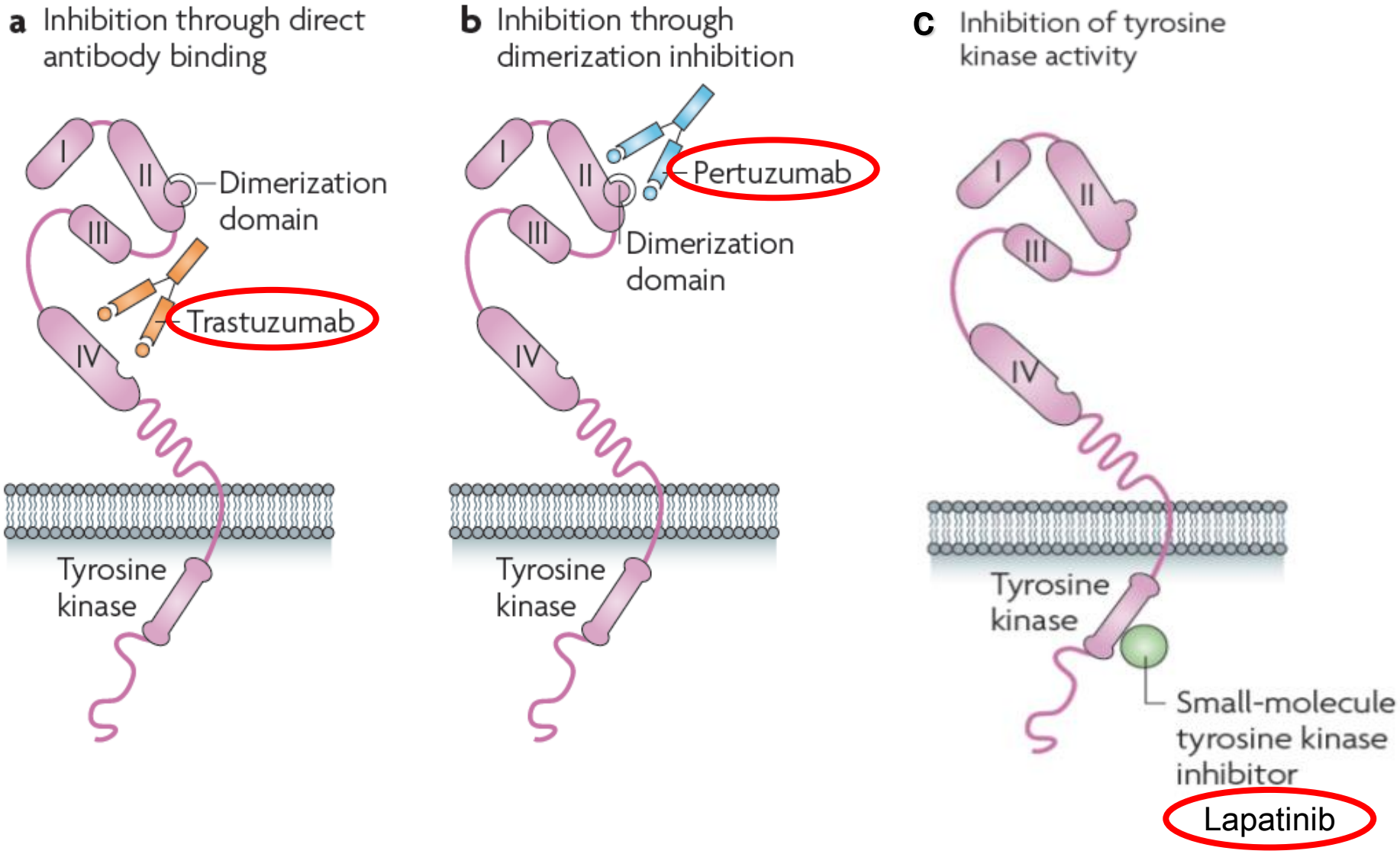
A plethora of divinities…

Trastuzumab = Zeus

Pertuzumab, Lapatinib, T-DM1… : who marries whom?

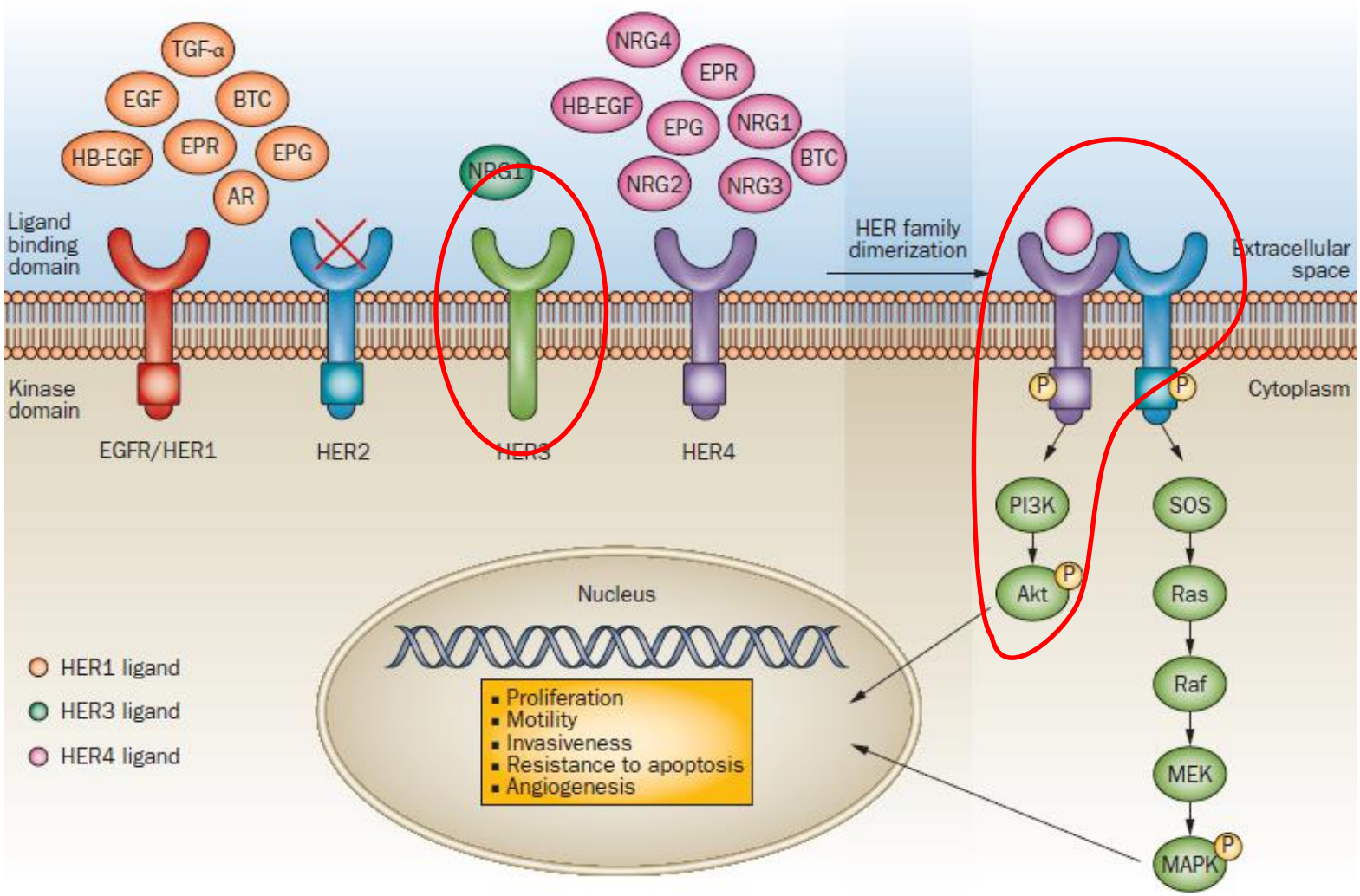
Who is allowed to set the scene first?

Anti-HER2 therapies



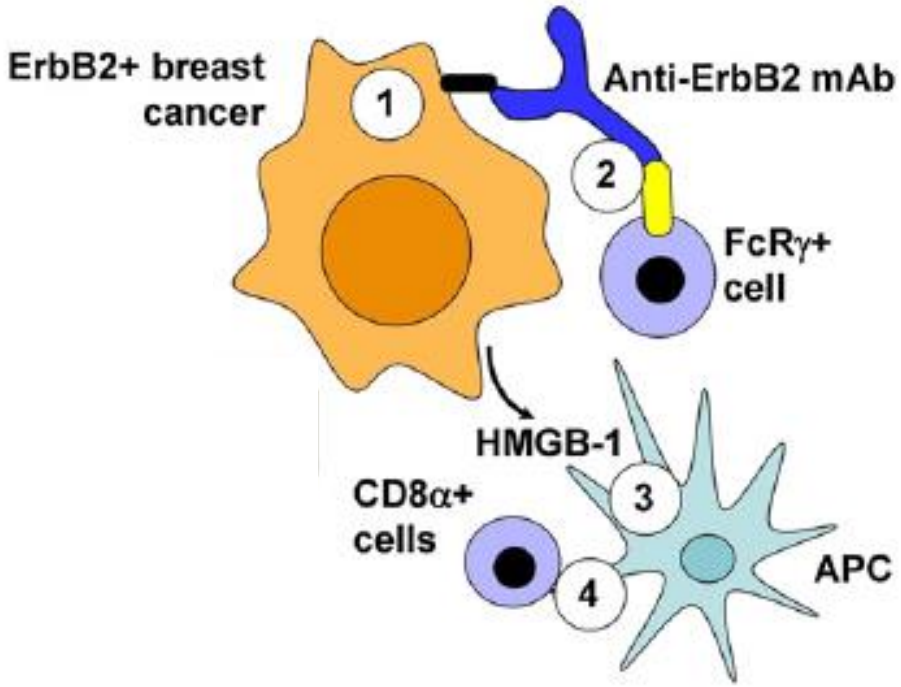
J Baselga, S Swain, Nature Reviews Cancer, 2009

HER2 signaling pathway



Arteaga CL et al. Treatment of HER2-positive breast cancer: current status and future perspectives. Nat Rev Clin Oncol 2011

A revised mechanism of action of Trastuzumab



HMGB-1 = High Mobility Group Box 1 Protein

(1+2)

Trastuzumab recruits Fc receptor expressing cells such as NK cells

(3)

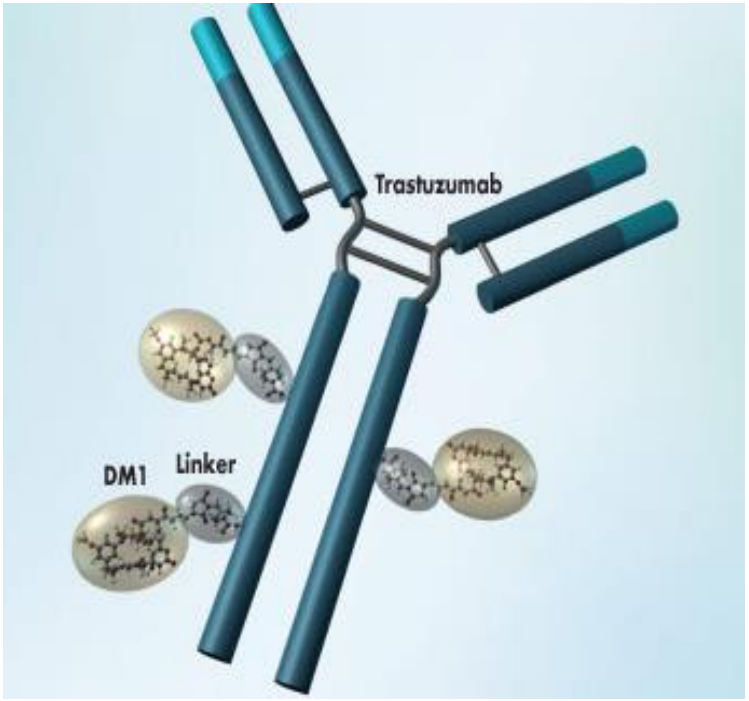
ADCC (or HER2 signaling blockade) causes cell death and the release of "death signals" such as HMGB-1, which triggers the activation of Antigen presenting cells (APC)

(4) As a result CD8-dependent adaptive anti-tumor immunity is generated

M. Smyth, Cancer Cell2010

Trastuzumab-DM1 in HER2+ MBC

Trastuzumab-DM1 → **Antibody Drug Conjugate (ADC)**

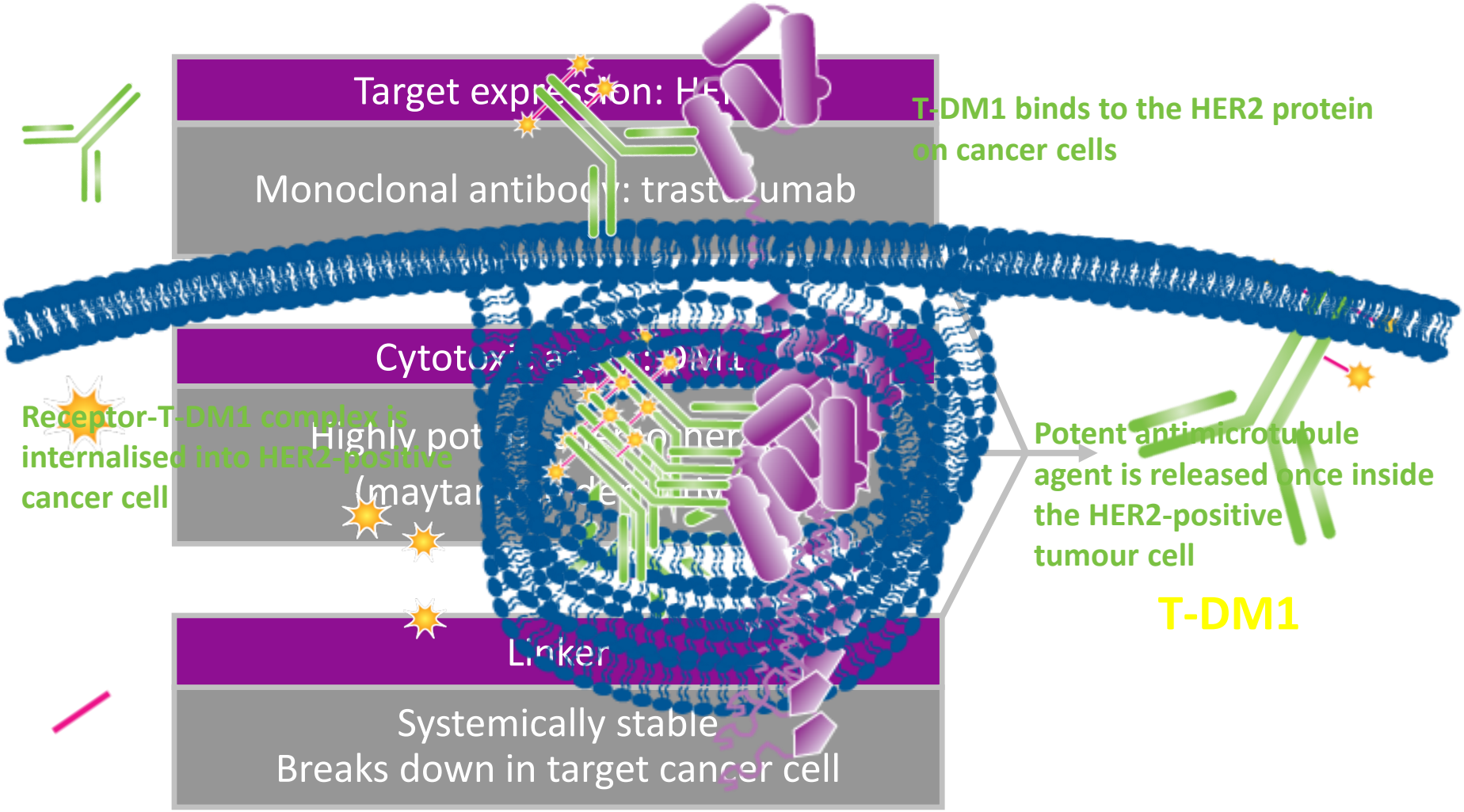


DM1 — **Maytansine (inhibitor of microtubule assembly)**

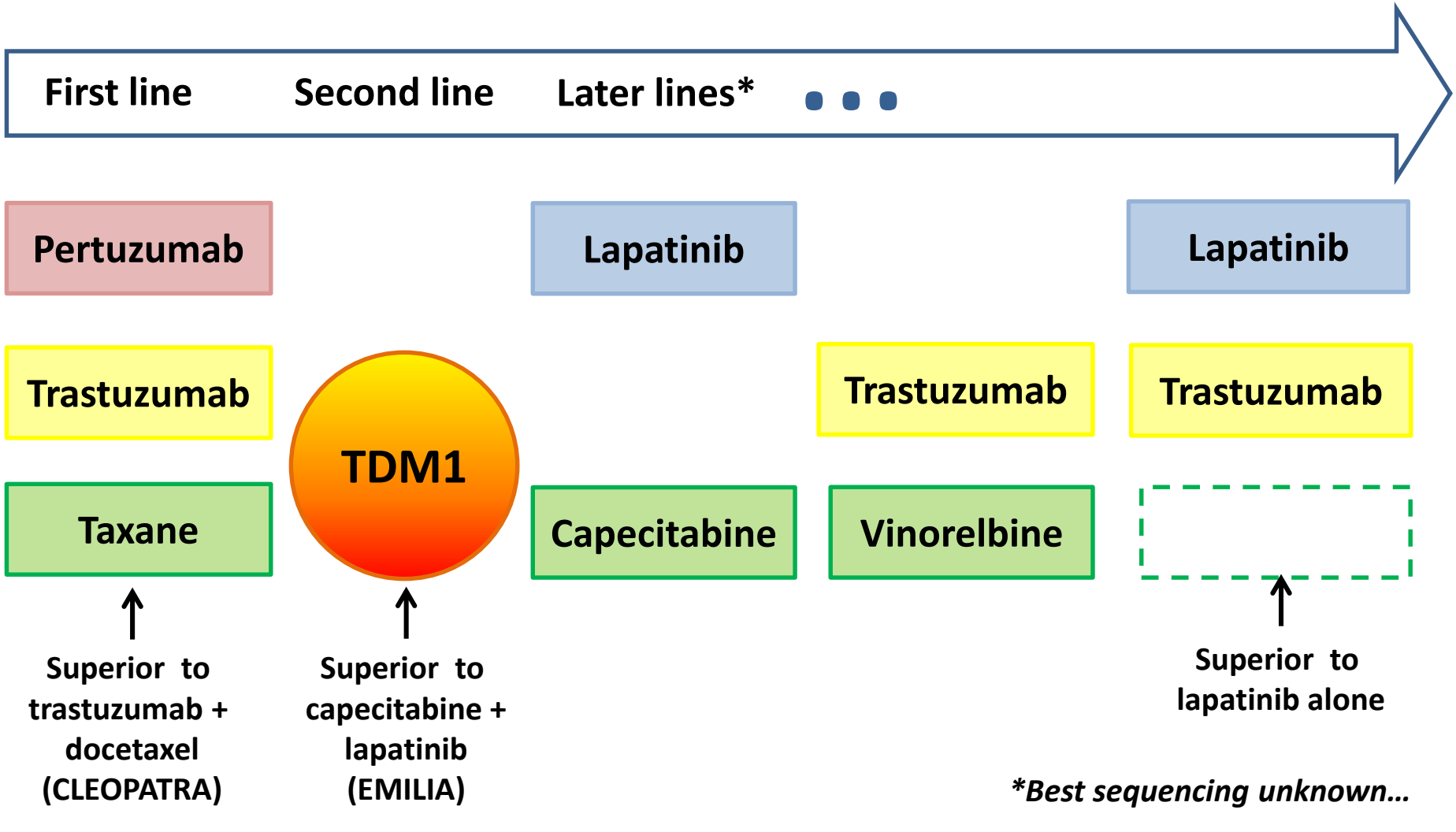
- **Potency > Vincristine or Vinblastine**
- **Maximal exposure of HER2+ tumors**
- **Minimal exposure of normal tissues**
- **Antitumor Properties of trastuzumab**

Lewis-Phillips GD et al., Cancer Res 68:9280-9290, 2008

T-DM1: 1st-in-class HER2 antibody-drug conjugate (ADC)

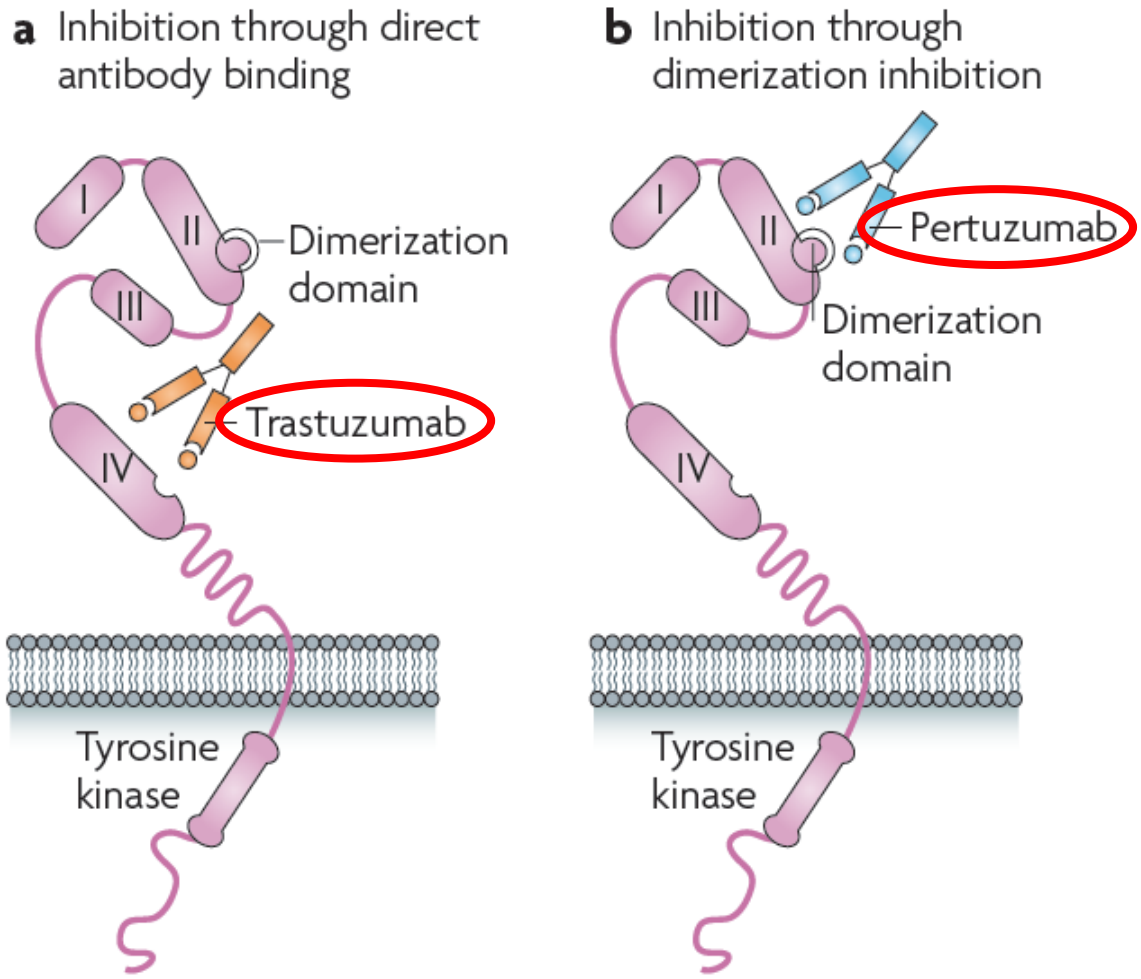


Systemic therapies for HER2+ advanced BC
Standards of care in 2017



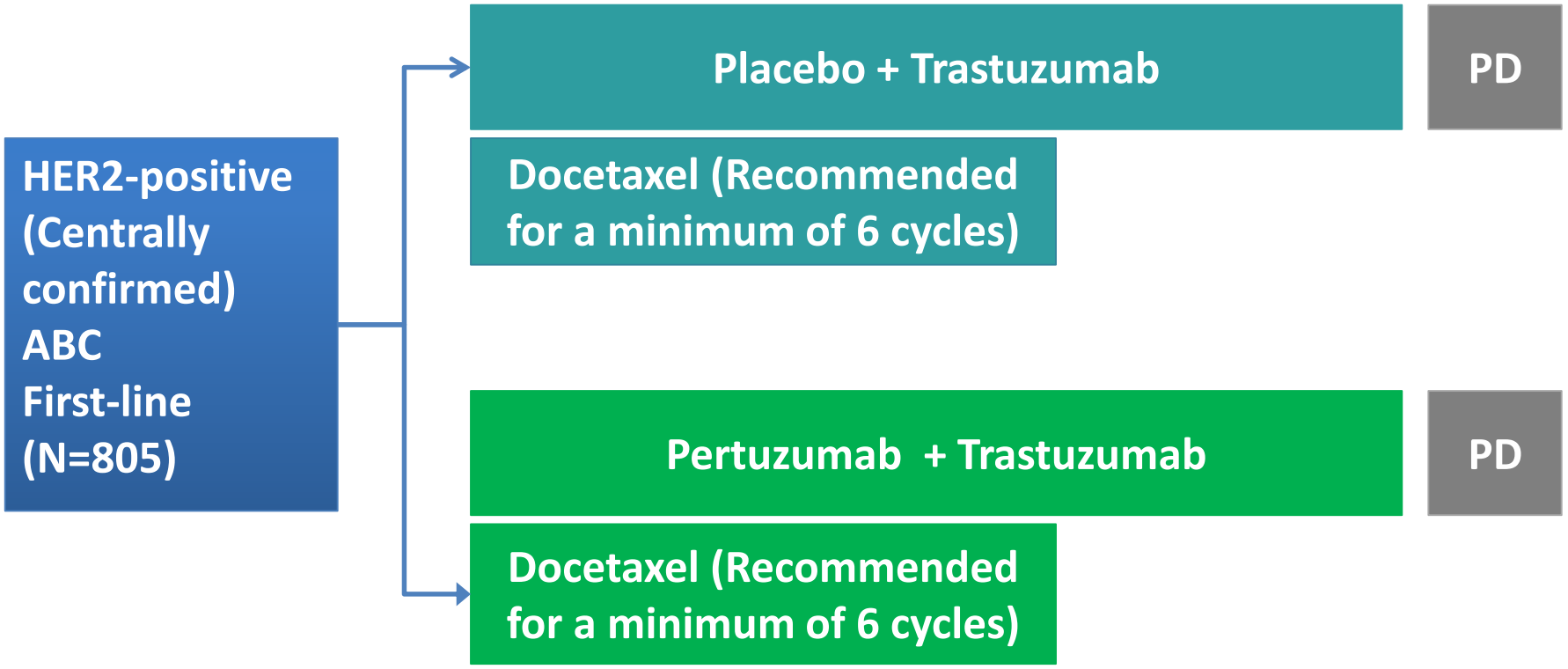
First line setting

Dual anti-HER2 blockade: Trastuzumab and Pertuzumab



J Baselga, S Swain, Nature Reviews Cancer, 2009

CLEOPATRA TRIAL



Primary endpoint: PFS (as determined by independent review facility)
Secondary endpoint: OS, PFS (investigator assessed), ORR, safety

Table 1. Baseline Characteristics of the Intention-to-Treat Population.*

Characteristic	Placebo plus Trastuzumab plus Docetaxel (N=406)	Pertuzumab plus Trastuzumab plus Docetaxel (N=402)
Female sex — no. (%)	404 (99.5)	402 (100.0)
Age — yr		
Median	54.0	54.0
Range	27–89	22–82
Race or ethnic group — no. (%)†		
Asian	133 (32.8)	128 (31.8)
Black	20 (4.9)	10 (2.5)
White	235 (57.9)	245 (60.9)
Other	18 (4.4)	19 (4.7)
Region — no. (%)		
Asia	128 (31.5)	125 (31.1)
Europe	152 (37.4)	154 (38.3)
North America	68 (16.7)	67 (16.7)
South America	58 (14.3)	56 (13.9)
ECOG performance status — no. (%)‡		
0	248 (61.1)	274 (68.2)
1	157 (38.7)	125 (31.1)
≥2	1 (0.2)	3 (0.7)
Disease type at screening — no. (%)		
Nonvisceral	90 (22.2)	88 (21.9)
Visceral	316 (77.8)	314 (78.1)
Hormone-receptor status — no. (%)		
ER-positive, PgR-positive, or both	199 (49.0)	189 (47.0)
ER-negative and PgR-negative	196 (48.3)	212 (52.7)
Unknown	11 (2.7)	1 (0.2)
HER2 status, assessed by immunohistochemistry — no. (%)		
0 or 1+	2 (0.5)	4 (1.0)
2+	32 (7.9)	47 (11.7)
3+	371 (91.4)	350 (87.1)
Data not available	1 (0.2)	1 (0.2)
HER2 status, assessed by FISH — no. (%)		
Positive	383 (94.3)	384 (95.5)
Negative	4 (1.0)	1 (0.2)
Data not available	19 (4.7)	17 (4.2)
Prior adjuvant or neoadjuvant chemotherapy — no. (%)		
No	214 (52.7)	218 (54.2)
Yes§	192 (47.3)	184 (45.8)
Anthracycline	164 (40.4)	150 (37.3)
Hormone	97 (23.9)	106 (26.4)
Taxane	94 (23.2)	91 (22.6)
Trastuzumab	41 (10.1)	47 (11.7)

* Baseline characteristics did not differ significantly between the two groups. ER denotes estrogen receptor, FISH fluorescence in situ hybridization, HER2 human epidermal growth factor receptor 2, and PgR progesterone receptor.
† Race or ethnic group was determined by the investigator. The category of "Other" includes American Indian and Alaska Native.
‡ The Eastern Cooperative Oncology Group (ECOG) performance status reflects the daily-living abilities of the patient, on a scale of 0 (fully active without symptoms) to 5 (dead).
§ Patients may have received more than one form of adjuvant or neoadjuvant chemotherapy.

Only 10-12% received prior adjuvant trastuzumab

Baselga et al. NEJM 2012

Trastuzumab + Pertuzumab: toxicities

Table 2. Adverse Events after the Discontinuation of Docetaxel in the Safety Population.*

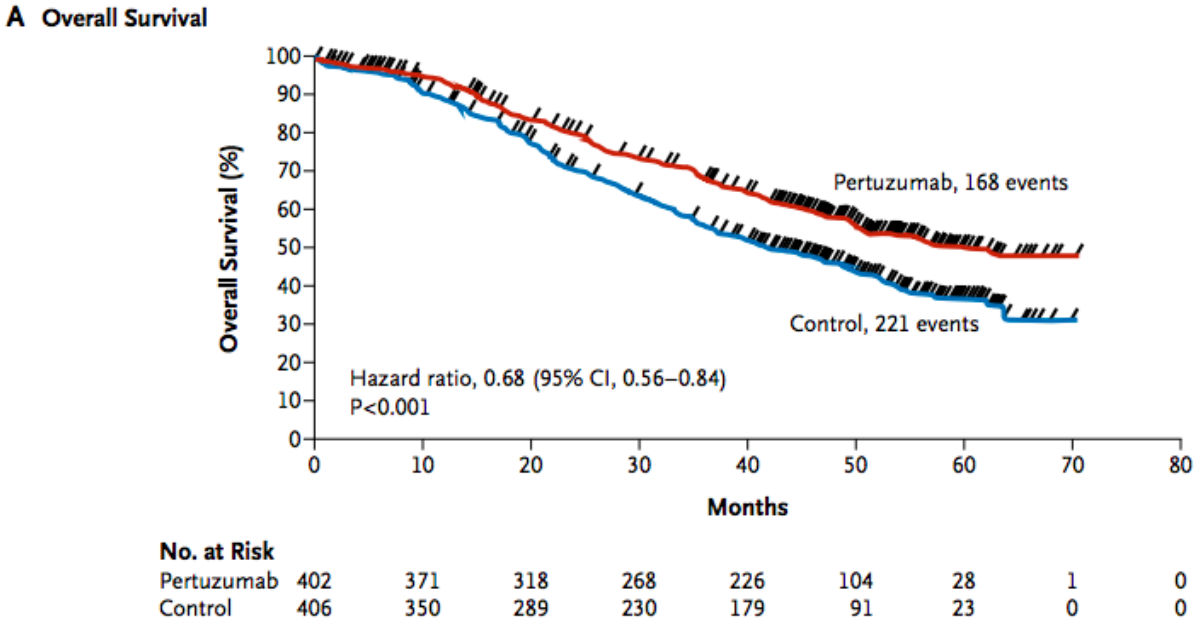
Adverse Event	Control Group (N=261)	Pertuzumab Group (N=306)
Most common events of any grade — no. of patients (%)†		
Alopecia	6 (2.3)	5 (1.6)
Diarrhea‡	37 (14.2)	86 (28.1)
Neutropenia	13 (5.0)	10 (3.3)
Nausea	30 (11.5)	39 (12.7)
Fatigue	25 (9.6)	41 (13.4)
Rash‡	21 (8.0)	56 (18.3)
Asthenia	23 (8.8)	41 (13.4)
Decreased appetite	14 (5.4)	22 (7.2)
Peripheral edema	32 (12.3)	28 (9.2)
Vomiting	17 (6.5)	30 (9.8)
Myalgia	19 (7.3)	25 (8.2)
Mucosal inflammation	4 (1.5)	11 (3.6)
Headache	32 (12.3)	52 (17.0)
Constipation	18 (6.9)	17 (5.6)
Upper respiratory tract infection‡	32 (12.3)	56 (18.3)
Pruritus‡	15 (5.7)	42 (13.7)
Febrile neutropenia	0	0
Dry skin	10 (3.8)	10 (3.3)
Muscle spasm‡	6 (2.3)	24 (7.8)

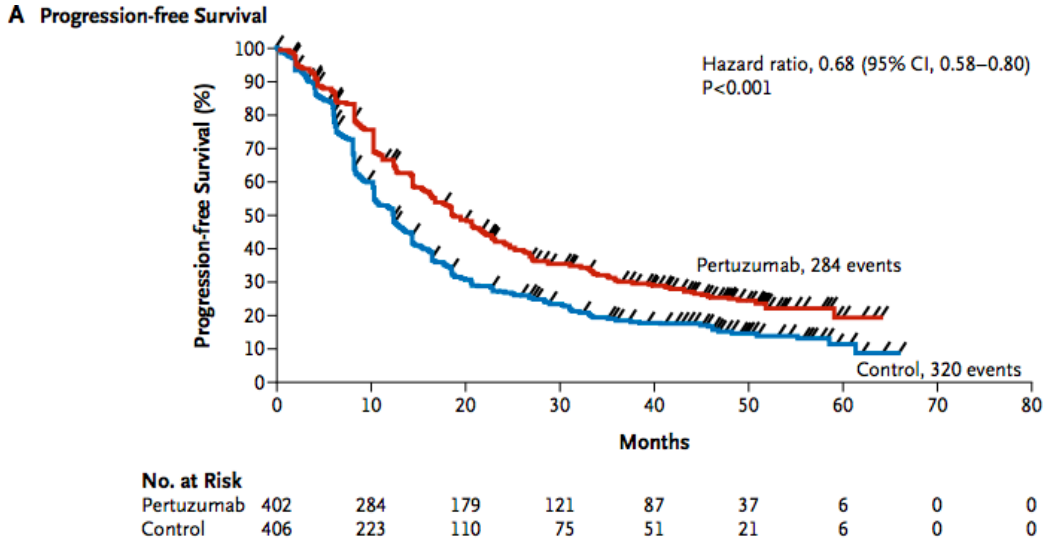
Combination generally well tolerated

No increase in cardiotoxicities

Swain et al. NEJM 2015

CLEOPATRA: RESULTS

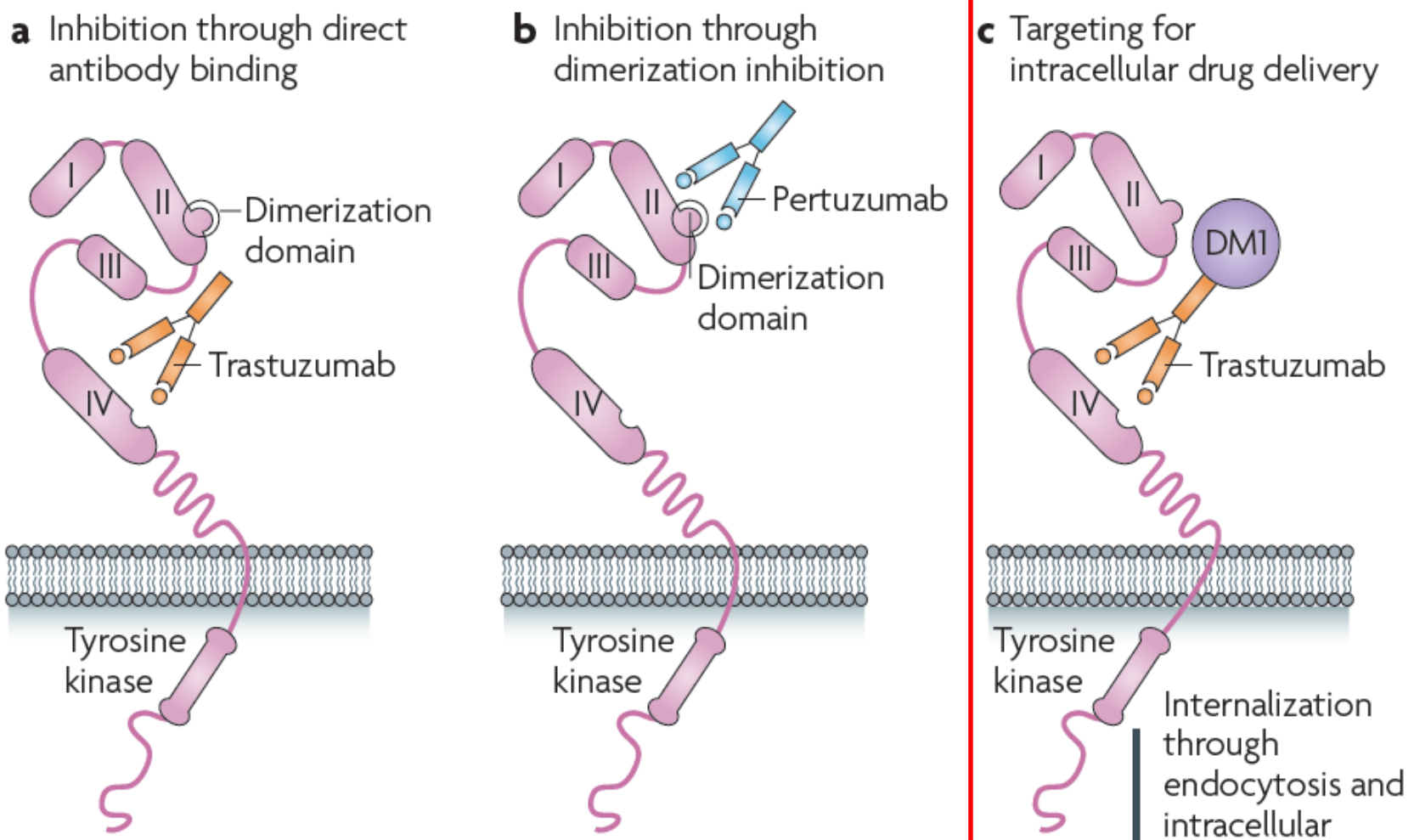




mOS 56.5 months in the pertuzumab group compared to 40.8 months in the control group

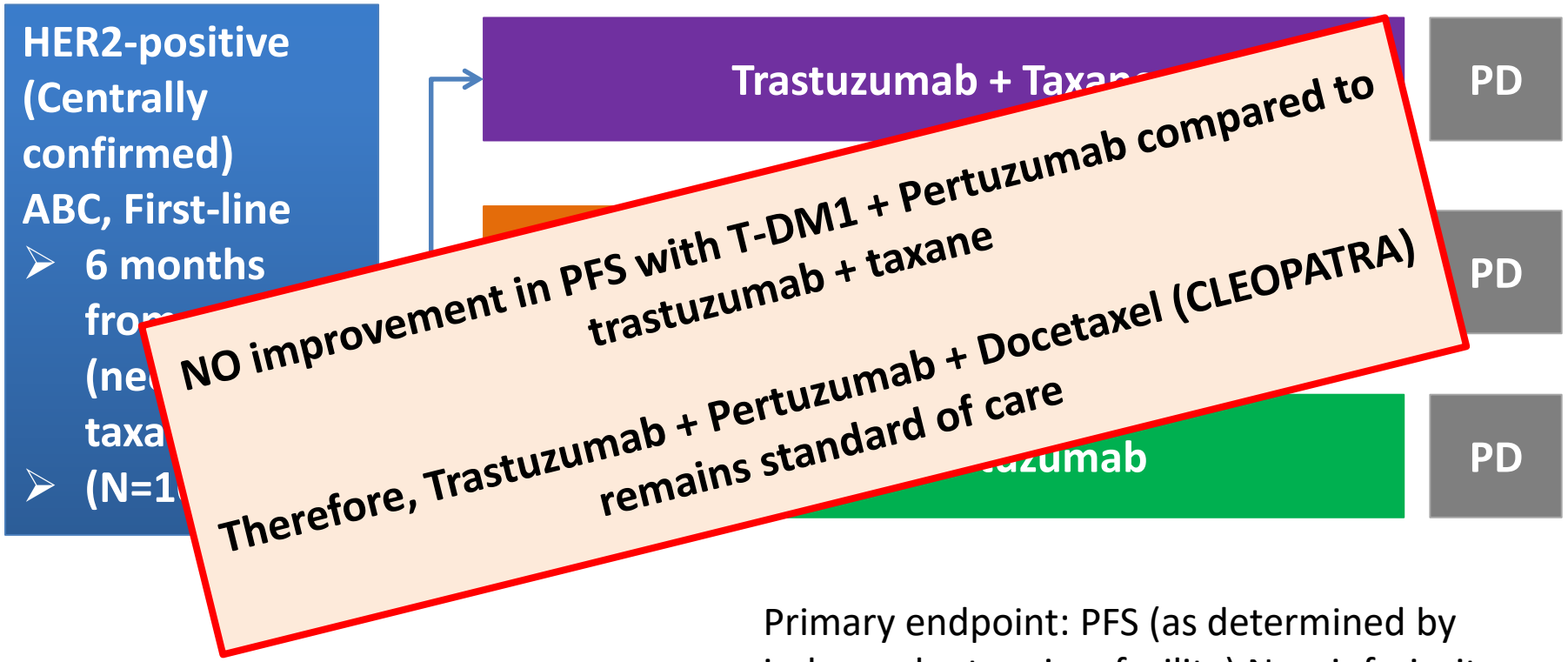
Swain et al. NEJM 2015

Dual anti-HER2 blockade in first line setting: Can we improve the results?



J Baselga, S Swain, Nature Reviews Cancer, 2009

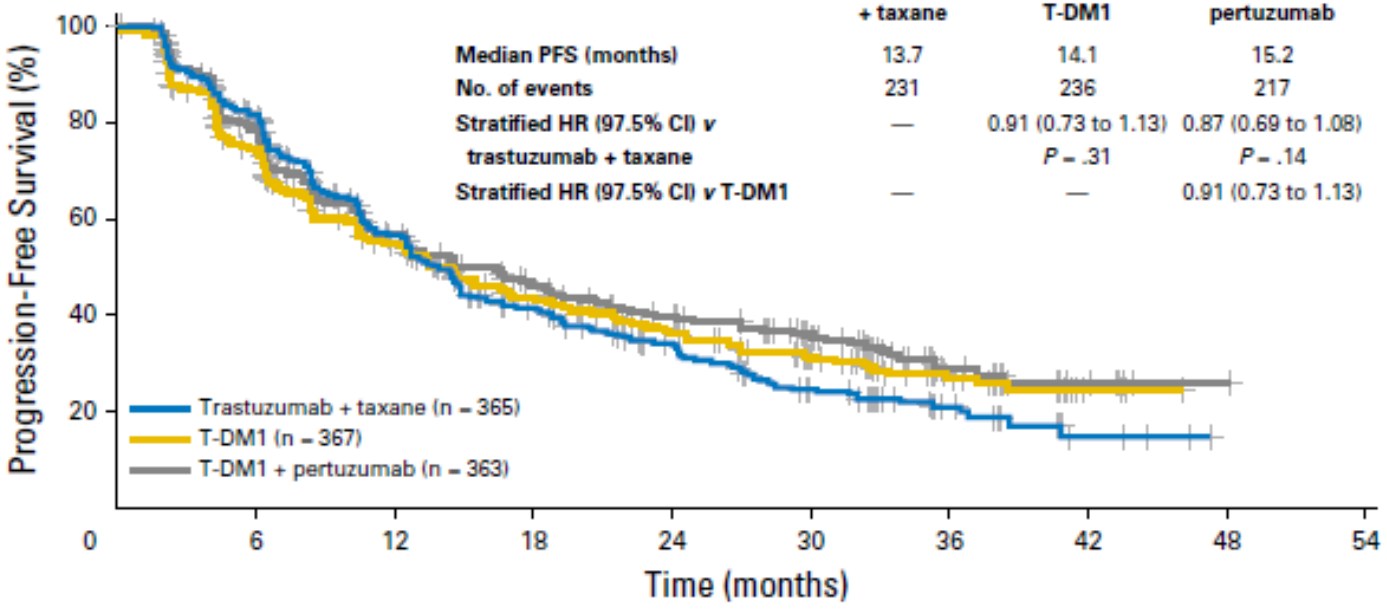
MARIANNE TRIAL



Primary endpoint: PFS (as determined by independent review facility) Non-inferiority and superiority assessed
Secondary endpoint: OS, PFS (investigator assessed), ORR, safety, patients-reported outcomes

Perez E. et al, JCO 35, 2016

Phase III MARIANNE Study

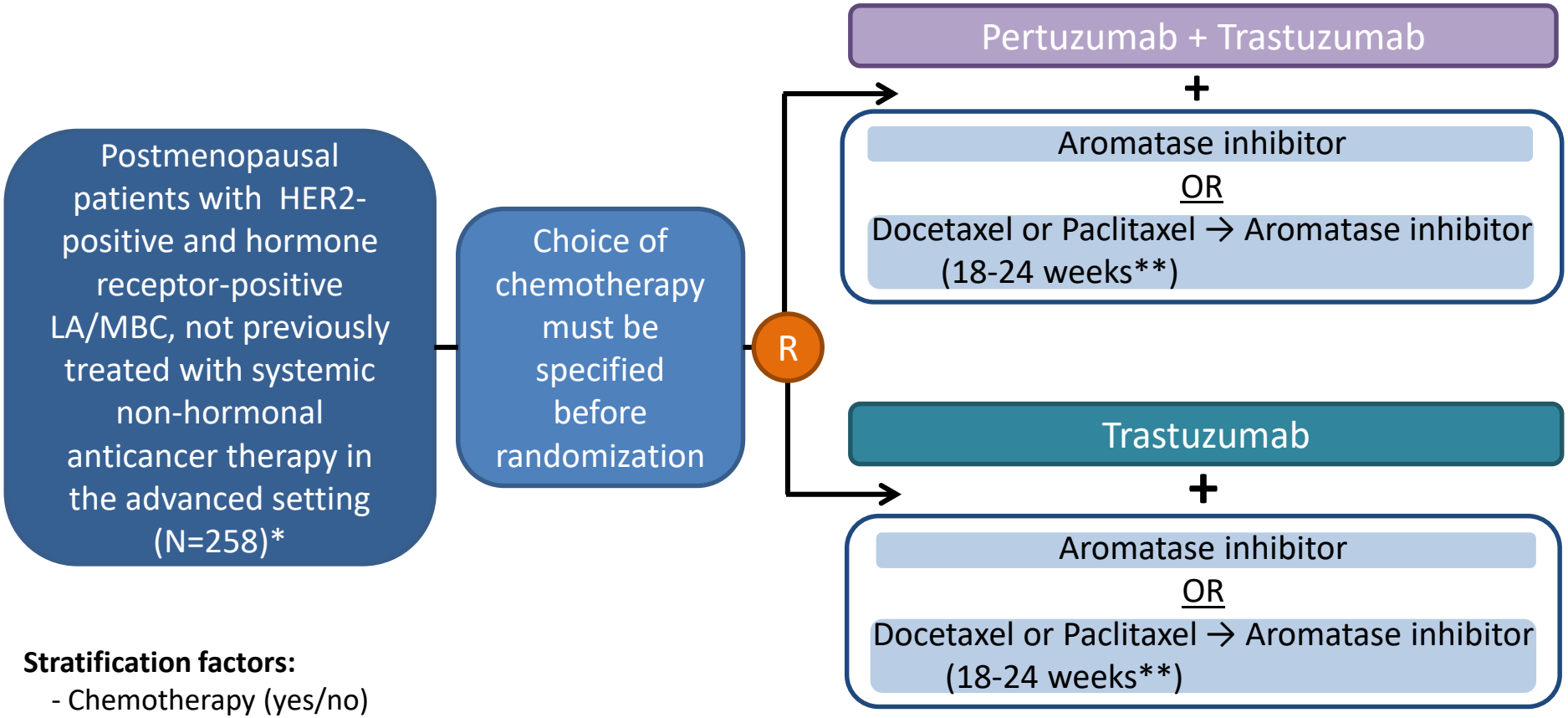


	Trastuzumab + taxane	T-DM1	T-DM1 + pertuzumab
Median PFS (months)	13.7	14.1	15.2
No. of events	231	236	217
Stratified HR (97.5% CI) *v* trastuzumab + taxane	—	0.91 (0.73 to 1.13) *P* = .31	0.87 (0.69 to 1.08) *P* = .14
Stratified HR (97.5% CI) *v* T-DM1	—	—	0.91 (0.73 to 1.13)

No. at risk:									
Trastuzumab + taxane	365	265	163	107	75	50	21	5	
T-DM1	367	257	176	133	104	67	28	3	
T-DM1 + pertuzumab	363	261	177	135	109	75	25	5	1

Perez E. et al, JCO 35, 2016

PERTAIN Study Design (Phase II Trial)



Stratification factors:

- Chemotherapy (yes/no)
- Time since adjuvant hormone therapy (<12 months/≥12 months/no prior therapy)

* 165 events to detect significant improvement in PFS from 7 months to 10.8 months (I.E. HR 0.645) with 80% power and a 2-sided log-rank test at an alpha level of 0.05.

** Choice of chemotherapy must be specified before randomization; administered per product labelling. LA, locally advanced; R, randomization)

Previous Systemic Therapy for Breast Cancer (ITT Population)

	Pertuzumab + Trastuzumab + AI (n=129)	Trastuzumab + AI (n=129)
Previous systemic therapy for BC, n (%)*	**67 (51.9)**	**67 (51.9)**
Chemotherapy, n(%)		
Neoadjuvant	**20 (15.5)**	**18 (14.0)**
Adjuvant	**51 (39.5)**	**41 (31.8)**
Anthracyclines	**53 (41.1)**	**36 (27.9)**
Taxanes	**33 (25.6)**	**36 (27.9)**
Trastuzumab, n(%)		
Neoadjuvant	**10 (7.8)**	**8 (6.2)**
Adjuvant	**30 (23.3)**	**24 (18.6)**
Hormonal therapy, n (%)		
Neoadjuvant	**1 (0.8)**	**1 (0.8)**
Adjuvant	**54 (41.9)**	**51 (39.5)**
Other**	**2 (1.6)**	**4 (3.1)**

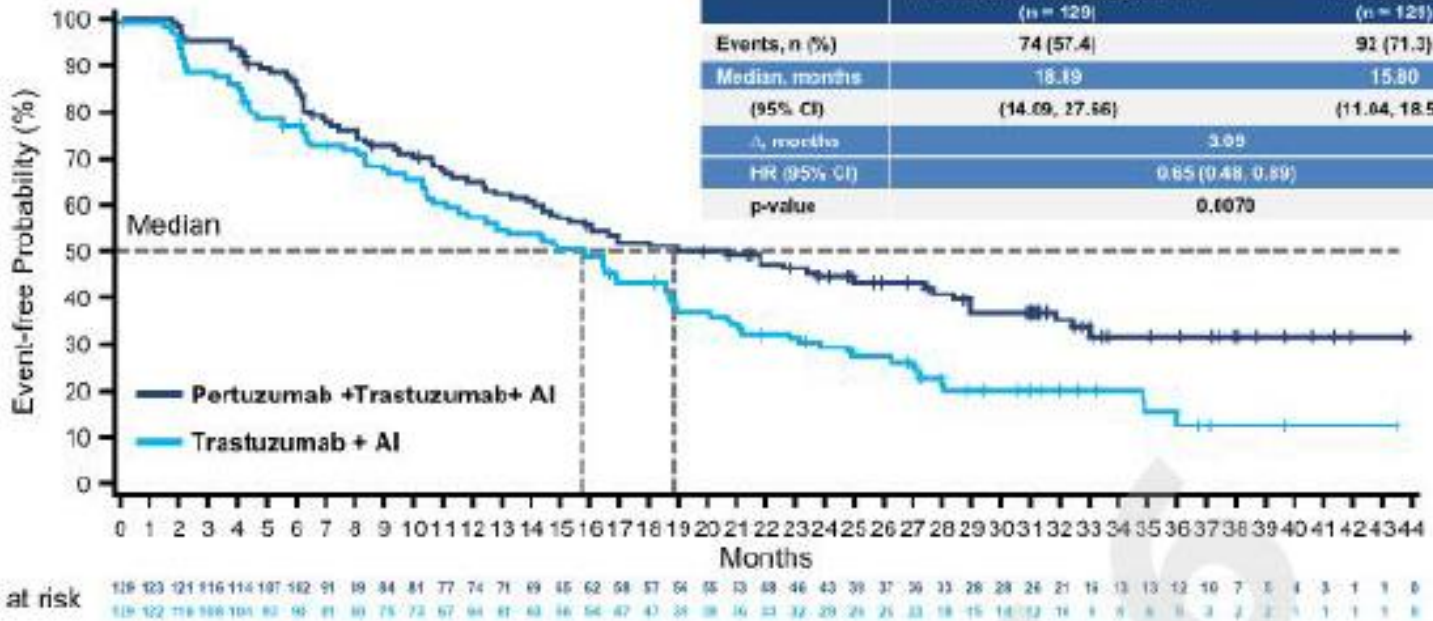
Patients could be counted under ≥ 1 treatment setting, e.g. neoadjuvant/adjuvant if they received > 1 treatment with a different purpose.

* Includes previous lapatinib (n=1 in each arm) and bevacizumab (n=1 in Arm A)

** Metastatic disease (n=3), bone metastasis (n=1), first-line metastasis (n=1), cancer treatment (n=1)

Primary Progression-Free Survival Analysis (Stratified, ITT Population)

	Pertuzumab + Trastuzumab + AI (n = 129)	Trastuzumab + AI (n = 128)
Events, n (%)	74 (57.4)	92 (71.3)
Median, months	18.89	15.80
(95% CI)	(14.09, 27.66)	(11.04, 18.56)
Δ, months	3.09	
HR (95% CI)	0.65 (0.48, 0.89)	
p-value	0.0070	

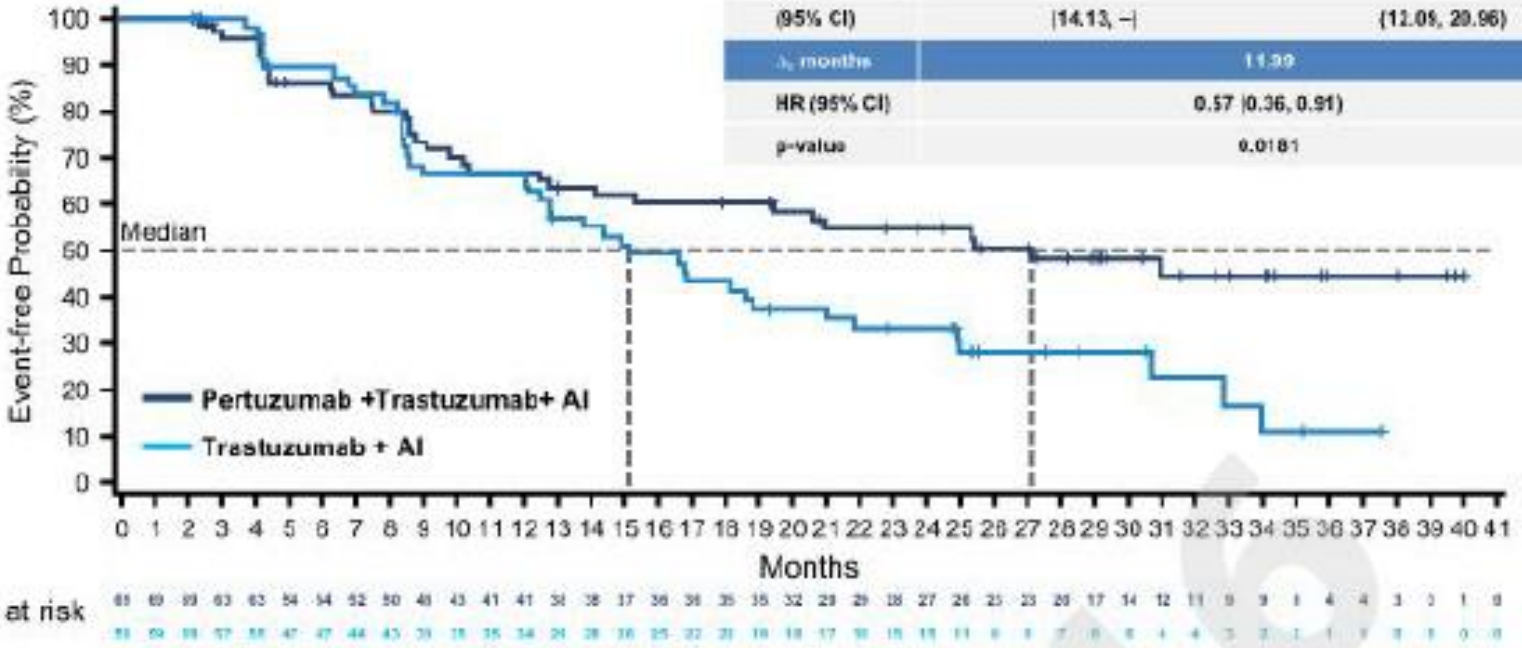


Analysis based upon Kaplan–Meier approach including stratification factors from IXRS. HR from a stratified Cox proportional hazards model including stratification factors from IXRS. Median time of follow-up: 31 months. CI, confidence interval; HR, hazard ratio.

Courtesy of SYNTHON

Duration of Response (Unstratified, ITT Responders)

	Pertuzumab + Trastuzumab + AI (n = 69)	Trastuzumab + AI (n = 59)
Median, months	27.10	15.11
(95% CI)	(14.13, –)	(12.06, 20.96)
Δ, months	11.99	
HR (95% CI)	0.57 (0.36, 0.91)	
p-value	0.0181	



Unstratified analysis based upon Kaplan–Meier approach. HR from a stratified Cox proportional hazards model including stratification factors from IXRS.

Courtesy of SYNTHON

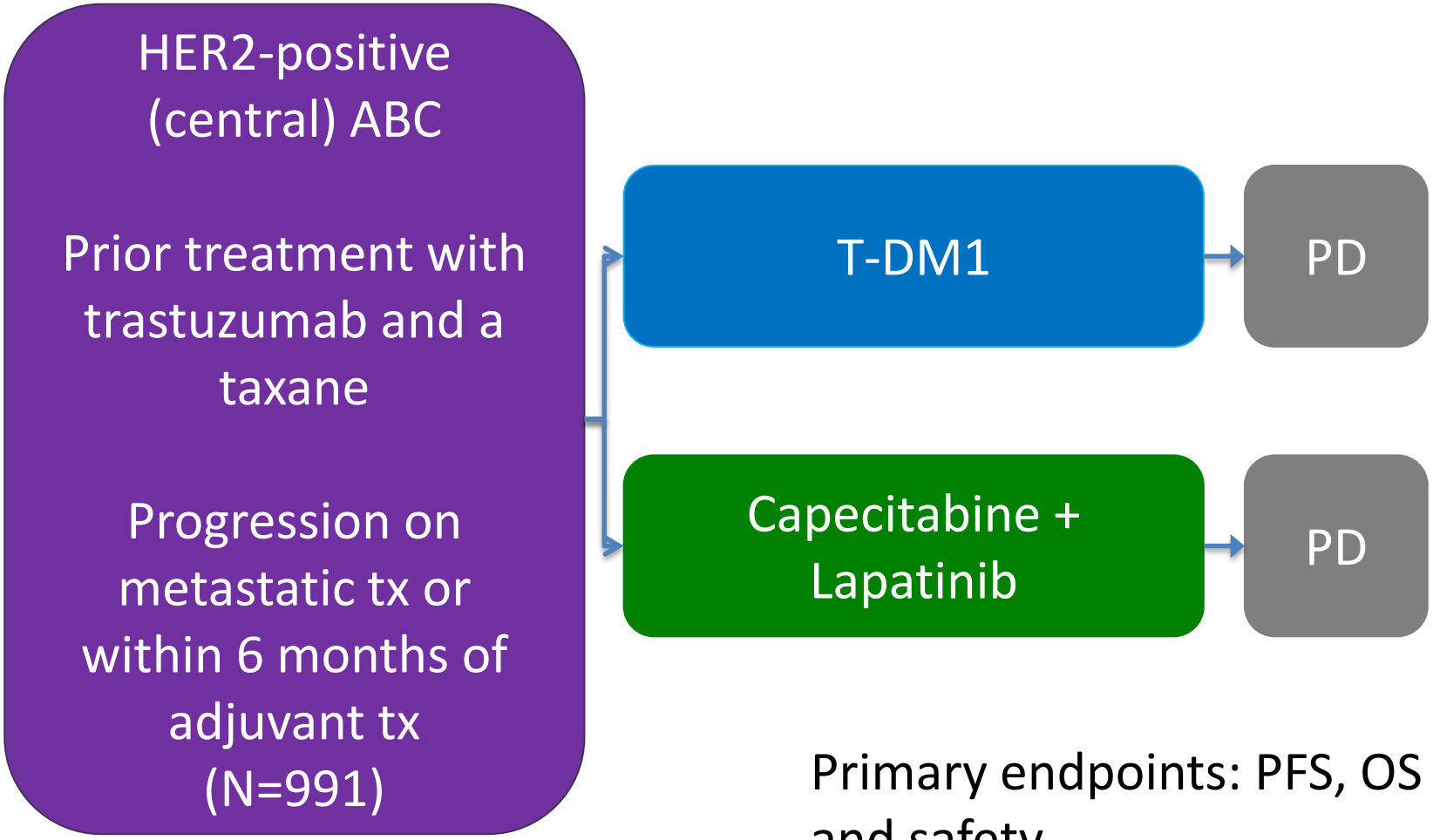
Messages from the PERTAIN trial

- **In a patient population with prior exposure to adjuvant CTX (45%) and adjuvant trastuzumab (30%), dual HER2 blockade (T+P) with a taxane (and endocrine therapy) is of added value, but its effect is less impressive than in CLEOPATRA**

- **There is a subgroup of patients at first relapse with more « indolent » disease that can be treated very efficiently with endocrine therapy (ET) and dual HER2 blockade (12m gain in PFS compared to ET + trastuzumab)**

After first-line with trastuzumab

EMILIA TRIAL DESIGN



Primary endpoints: PFS, OS and safety

Table 1. Selected Demographic and Baseline Characteristics of the Patients.*

Characteristic	Lapatinib plus Capecitabine (N=496)	T-DM1 (N=495)
Age — yr		
Median	53	53
Range	24–83	25–84
Race — no. (%)†		
White	374 (75)	358 (72)
Asian	86 (17)	94 (19)
Black	21 (4)	29 (6)
Other	10 (2)	7 (1)
Not available	5 (1)	7 (1)
World region — no. (%)		
United States	136 (27)	134 (27)
Western Europe	160 (32)	157 (32)
Asia	76 (15)	82 (17)
Other	124 (25)	122 (25)
ECOG performance status — no. (%)‡		
0	312 (63)	299 (60)
1	176 (35)	194 (39)
Not available	8 (2)	2 (<1)
Site of disease involvement — no. (%)		
Visceral	335 (68)	334 (67)
Nonvisceral	161 (32)	161 (33)
Hormone-receptor status — no. (%)		
ER-positive, PR-positive, or both	263 (53)	282 (57)
ER-negative and PR-negative	224 (45)	202 (41)
Unknown	9 (2)	11 (2)
Prior systemic therapy — no. (%)§		
Anthracycline	302 (61)	303 (61)
Other chemotherapy	382 (77)	385 (78)
Biologic agent other than trastuzumab or pertuzumab	21 (4)	13 (3)
Endocrine therapy	204 (41)	205 (41)
Prior chemotherapy regimens for locally advanced or metastatic disease — no. (%)		
0 or 1	305 (61)	304 (61)
>1	191 (39)	191 (39)
Prior trastuzumab treatment — no. (%)§		
For metastatic breast cancer, early breast cancer, or both	419 (84)	417 (84)
For early breast cancer only	77 (16)	78 (16)

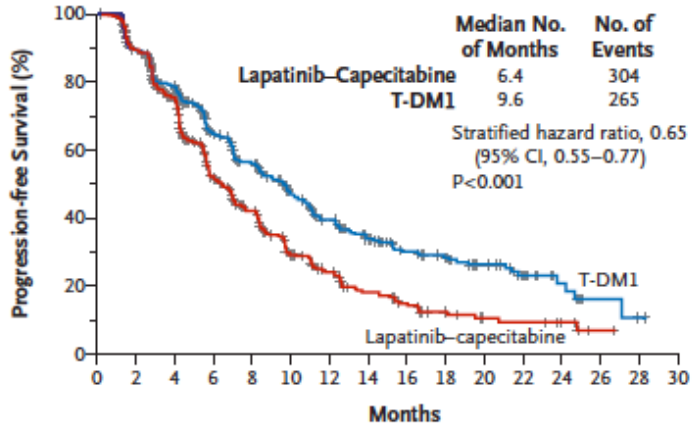
Majority of patients received only 0 to 1 prior therapy in the metastatic setting

100% received prior trastuzumab - 84% in the metastatic setting

Verma et al. NEJM 2012

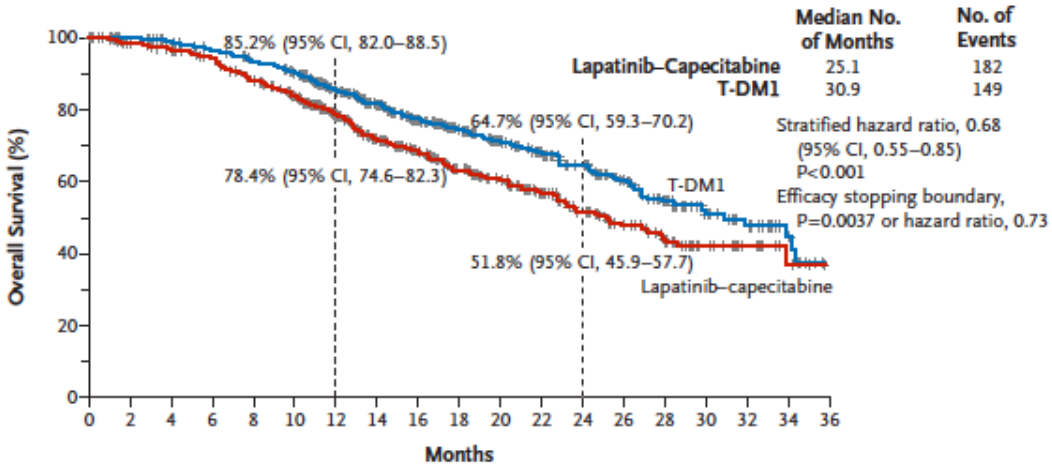
EMILIA RESULTS

PFS



No. at Risk																
Lapatinib–capecitabine	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

OS



No. at Risk																		
Lapatinib–capecitabine	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

mPFS 9.6 months (T-DM1) vs 6.4 months (p < 0.001)

OS 30.9 months (T-DM1) vs 25.1 months (p< 0.001)

Verma et al. NEJM 2012

T-DM1 vs Lapatinib + Capecitabine

Improved outcomes:

↑DFS

↑OS

Good safety profile:

↓Diarrhea

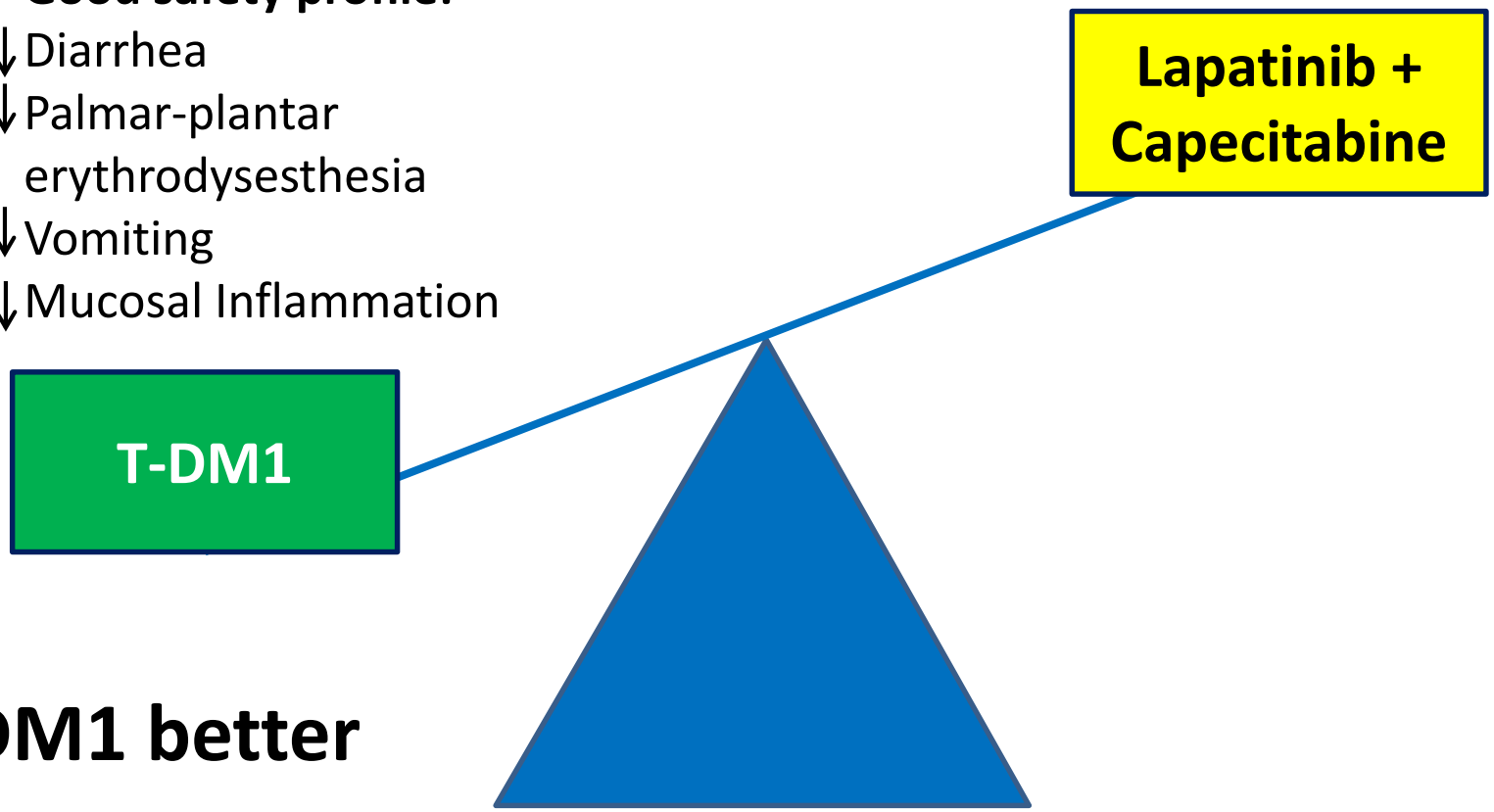
↓Palmar-plantar erythrodysesthesia

↓Vomiting

↓Mucosal Inflammation

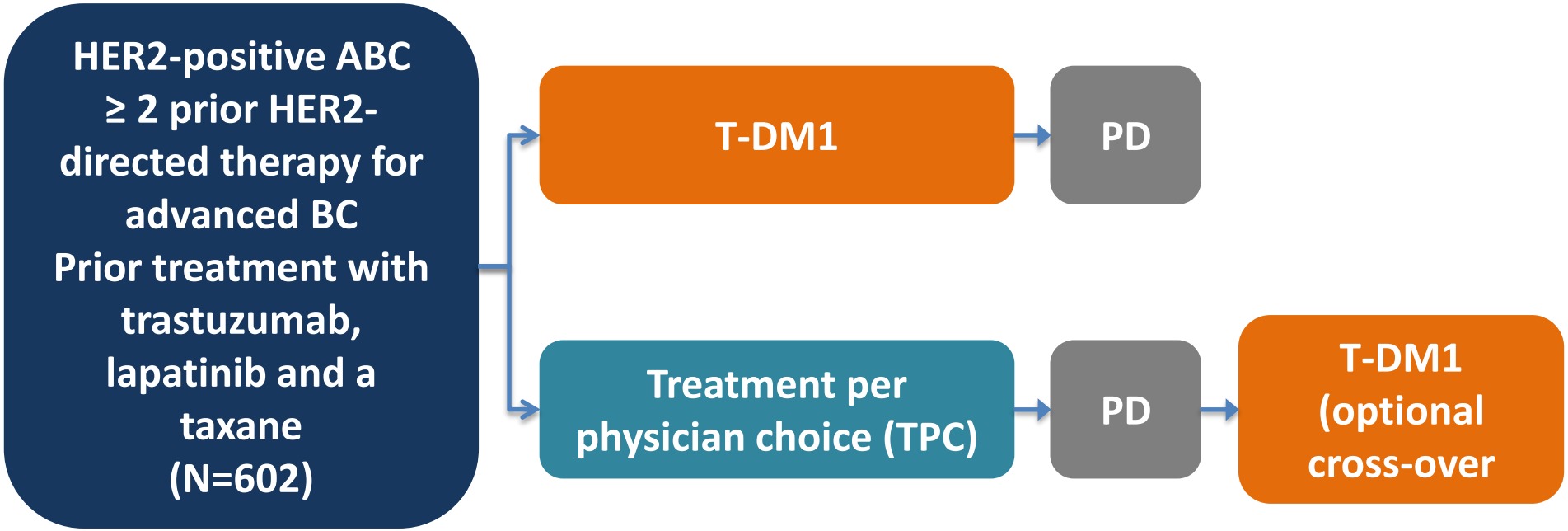
↓Thrombocytopenia

↓Elevated AST/ALT



T-DM1 better

TH3RESA TRIAL DESIGN



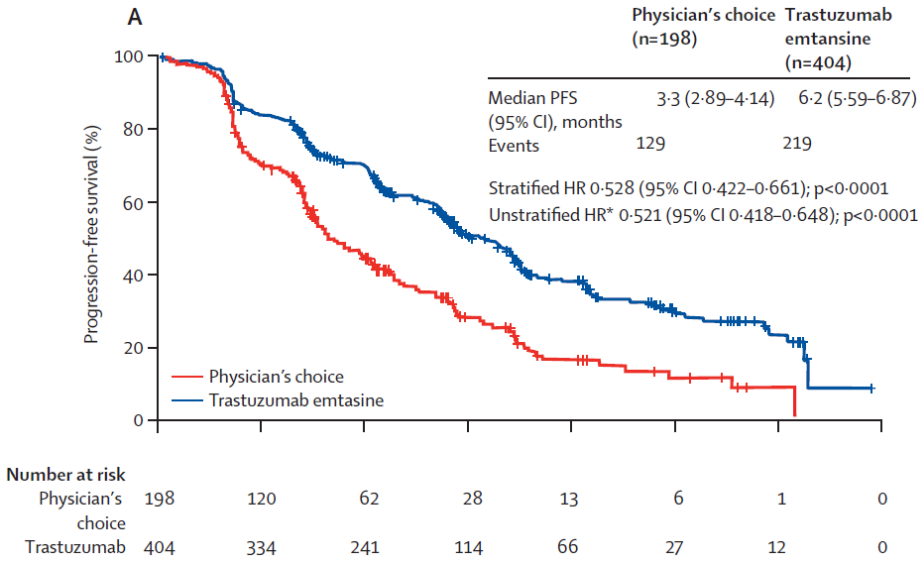
Co-primary endpoints: PFS and OS

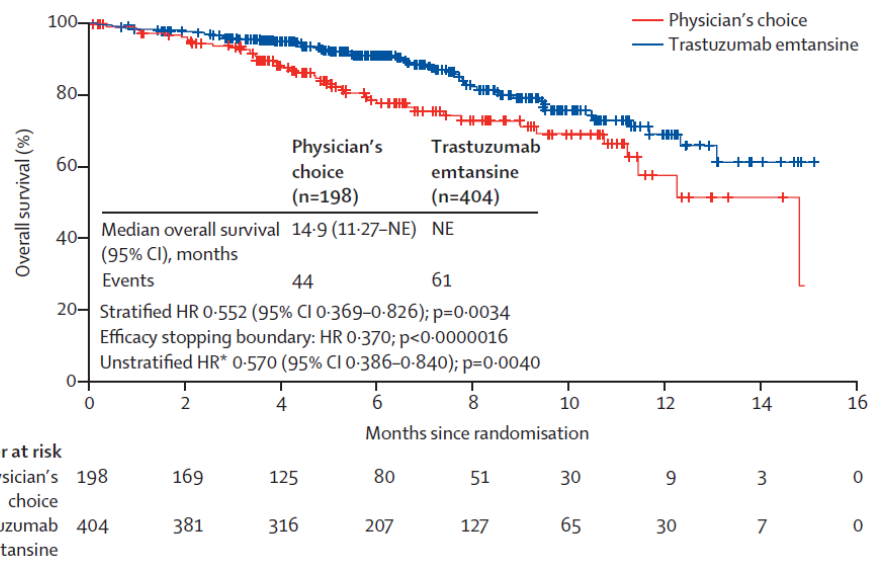
	Physician's choice (n=198)	Trastuzumab emtansine (n=404)
Age (years)	54 (28–85)	53 (27–89)
<65	164 (83%)	345 (85%)
65–74	28 (14%)	46 (11%)
≥75	6 (3%)	13 (3%)
World region		
USA	48 (24%)	99 (25%)
Western Europe	85 (43%)	171 (42%)
Other	65 (33%)	134 (33%)
Race		
White	161 (81%)	325 (80%)
Asian	24 (12%)	57 (14%)
Other*	13 (7%)	22 (5%)
ECOG PS†		
0	82 (41%)	180 (45%)
1	101 (51%)	200 (50%)
2	15 (8%)	22 (5%)
Hormone receptor status‡		
ER positive and/or PR positive	103 (52%)	208 (51%)
ER negative and PR negative	85 (43%)	185 (46%)
Unknown	10 (5%)	11 (3%)
Visceral disease involvement	150 (76%)	302 (75%)
Disease extent		
Metastatic	187 (94%)	391 (97%)
Unresectable locally advanced or recurrent	11 (6%)	13 (3%)
Measurable disease	163 (82%)	345 (85%)
Number of previous regimens for advanced breast cancer§¶	4 (1–19)	4 (1–14)
≤3	78 (39%)	131 (33%)
4–5	65 (33%)	149 (37%)
>5	55 (28%)	122 (30%)
Previous exposure to HER2-directed therapy		
Trastuzumab	198 (100%)	404 (100%)
Duration (months)	23·7 (0·7–508·8)	24·3 (1·4–140·5)
Lapatinib	198 (100%)	404 (100%)
Duration (months)	7·62 (0·1–48·0)	7·98 (0·1–71·2)
Previously treated asymptomatic brain metastasis	27 (14%)	40 (10%)

Very advanced disease: >60% of patients with more than 3 lines of therapy in the metastatic setting

100% received previous trastuzumab and lapatinib

THERESA results





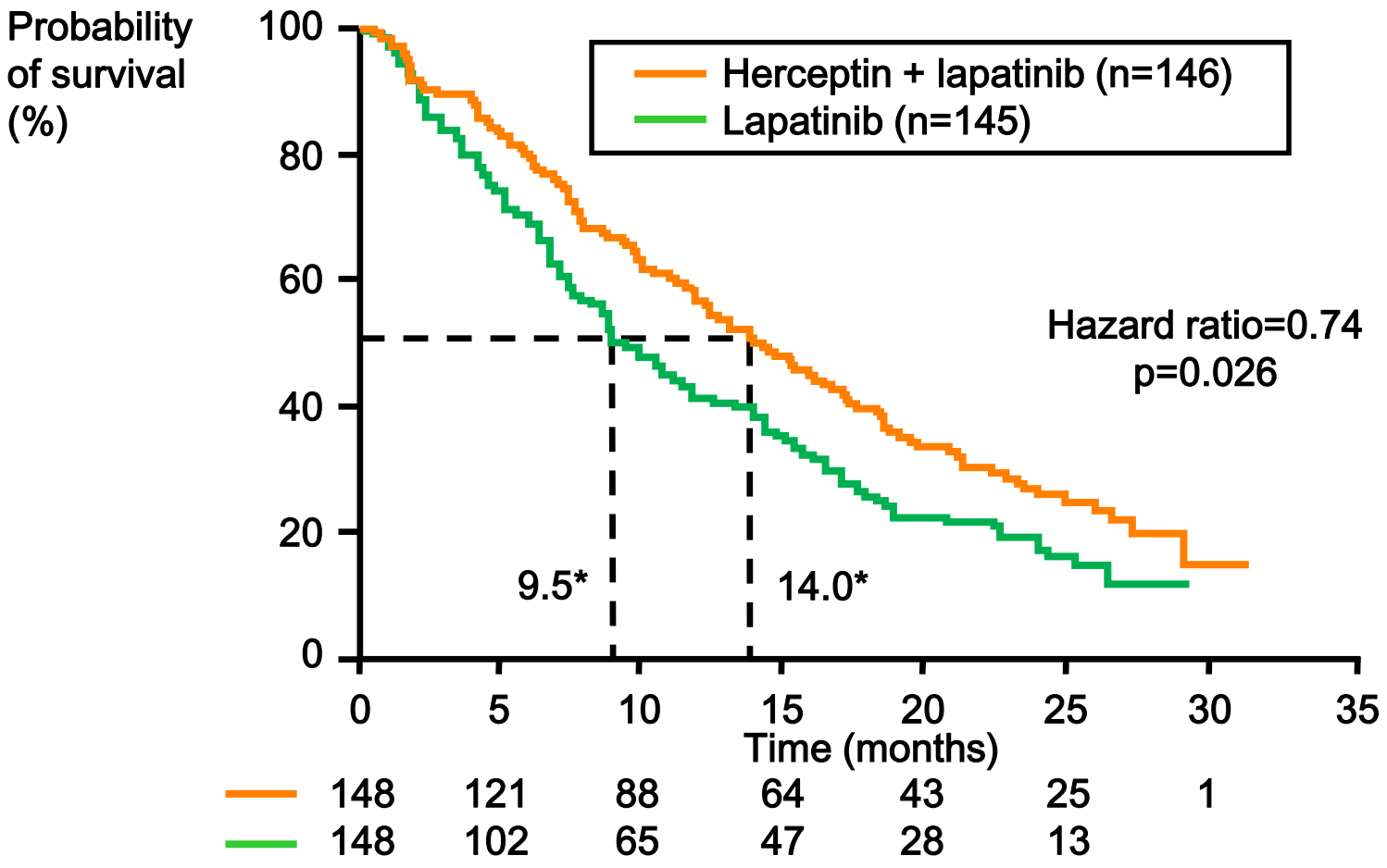
With results from TH3RESA + EMILIA, Trastuzumab emtansine should be considered as a new standard for patients with HER2-positive advanced breast cancer who have previously received anti-her2 therapy.

Ian E Krop, Lancet Oncol 2014

Recent clinical trials in advanced HER_2 positive B.C. that have shown a P.F.S. (primary endpoint) and O.S. gain

	First line setting (Cleopatra n=808)	Second line setting (Emilia n=991)	Third / Fourth line setting (EGF 104900 n=291)
	Trastuzumab + pertuzumab + docetaxel **vs** Trastuzumab + docetaxel	T-DM1 **vs** Capecitabine + lapatinib	Trastuzumab+ lapatinib **vs** Lapatinib
O.S. results	Median O.S. not reached (vs 37.6 mos)	Gain of 5.8 mos	Gain of 4.5 mos despite cross-over in 52%
Side effects?	Minimally increased	In favour of T-DM1	Minimally increased
Prior Trastuzumab exposure?	Minimal (10%) and interval of ≥12 mos required	100% [if adjuvant, free int < 6m] (= 16% of pts)	100% (≥ 3 regimens)
CNS disease?	Excluded	Absent or « controlled » (11%)	Absent or « controlled » (≈12%)

EGF104900: significant OS benefit with Herceptin + lapatinib following disease progression



* Median OS (months)

Not within EMEA-approved indication for Herceptin

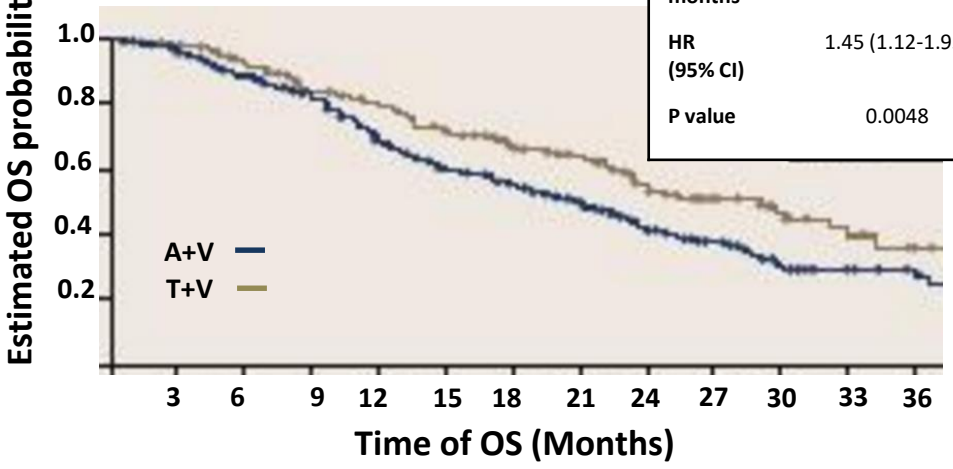
Blackwell et al 2010

Most likely trastuzumab needs to be kept “on board” while using an anti-HER2 TKI!

Trials showing « loss of survival » with trastuzumab interruption in advanced disease

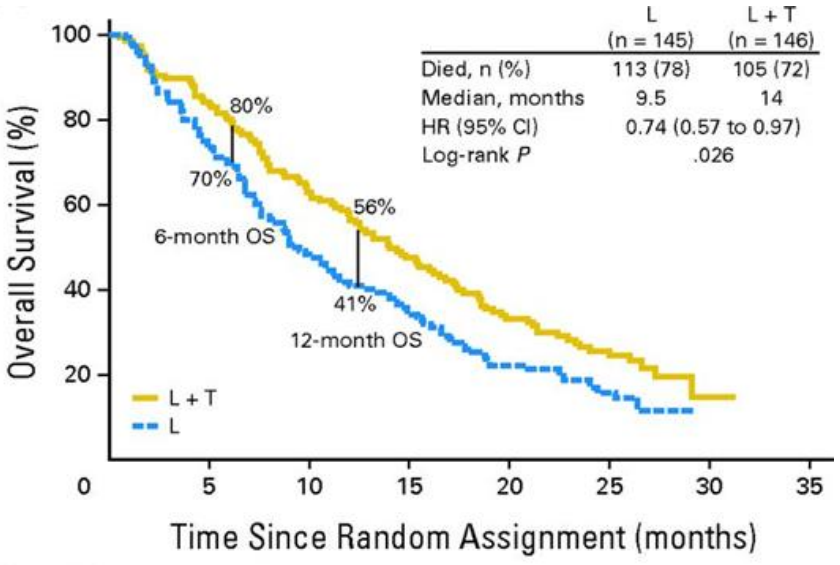
LUX BREAST 1

	A + V (N=330)	T + V (N=169)
Events, n (%)	180 (53.1)	74 (43.8)
Median, months	20.5	28.6
HR (95% CI)	1.45 (1.12-1.95)	
P value	0.0048	



Harbeck N, Presented at SABCS 2014, poster P5-19-01

EGF104900 trial



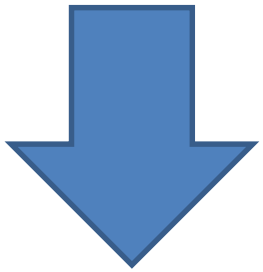
	L (n = 145)	L + T (n = 146)
Died, n (%)	113 (78)	105 (72)
Median, months	9.5	14
HR (95% CI)	0.74 (0.57 to 0.97)	
Log-rank *P*	.026	

Blackwell KL, JCO 2012 Jul 20; 30(21):2585-92

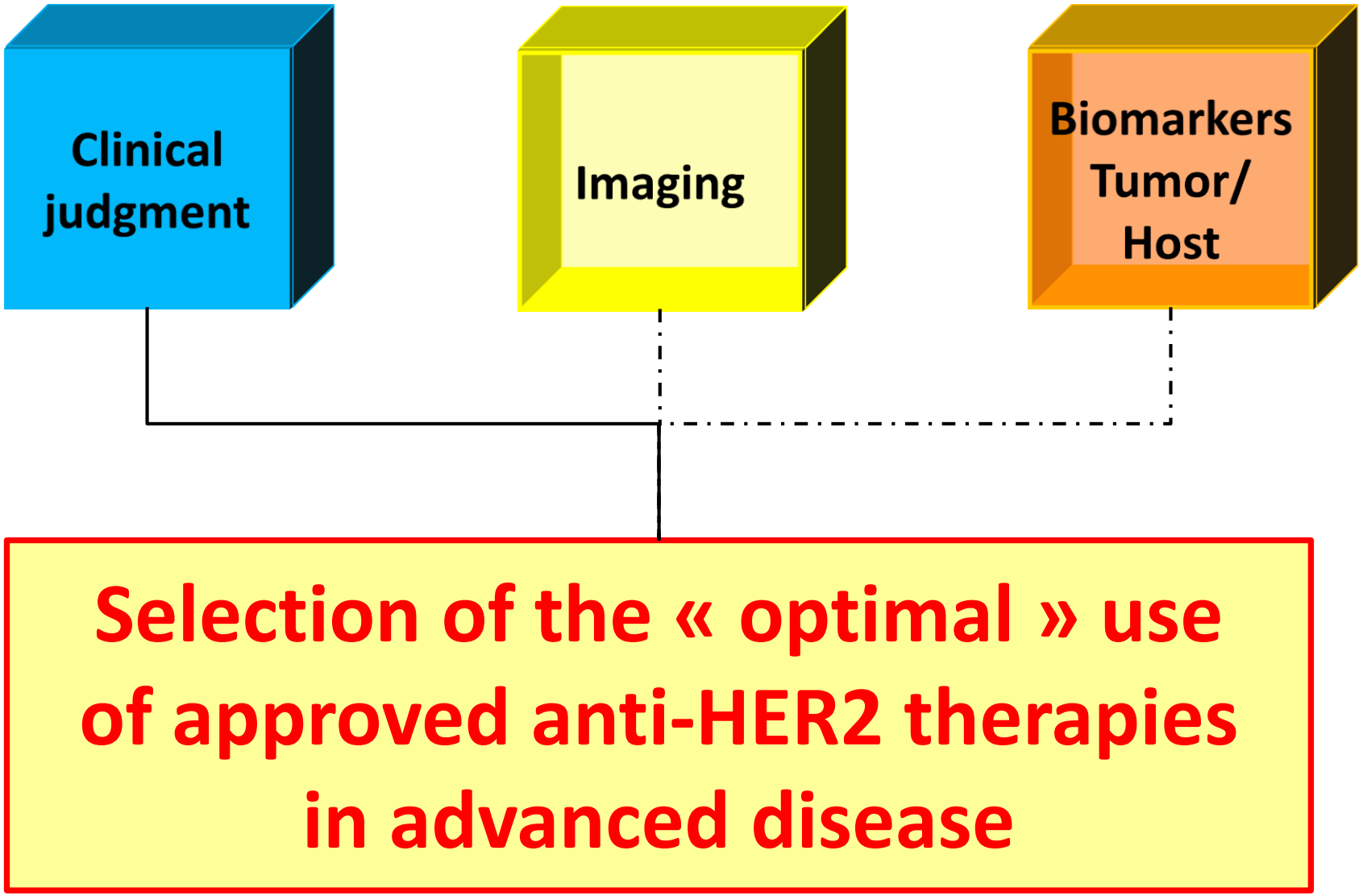
PFS identical

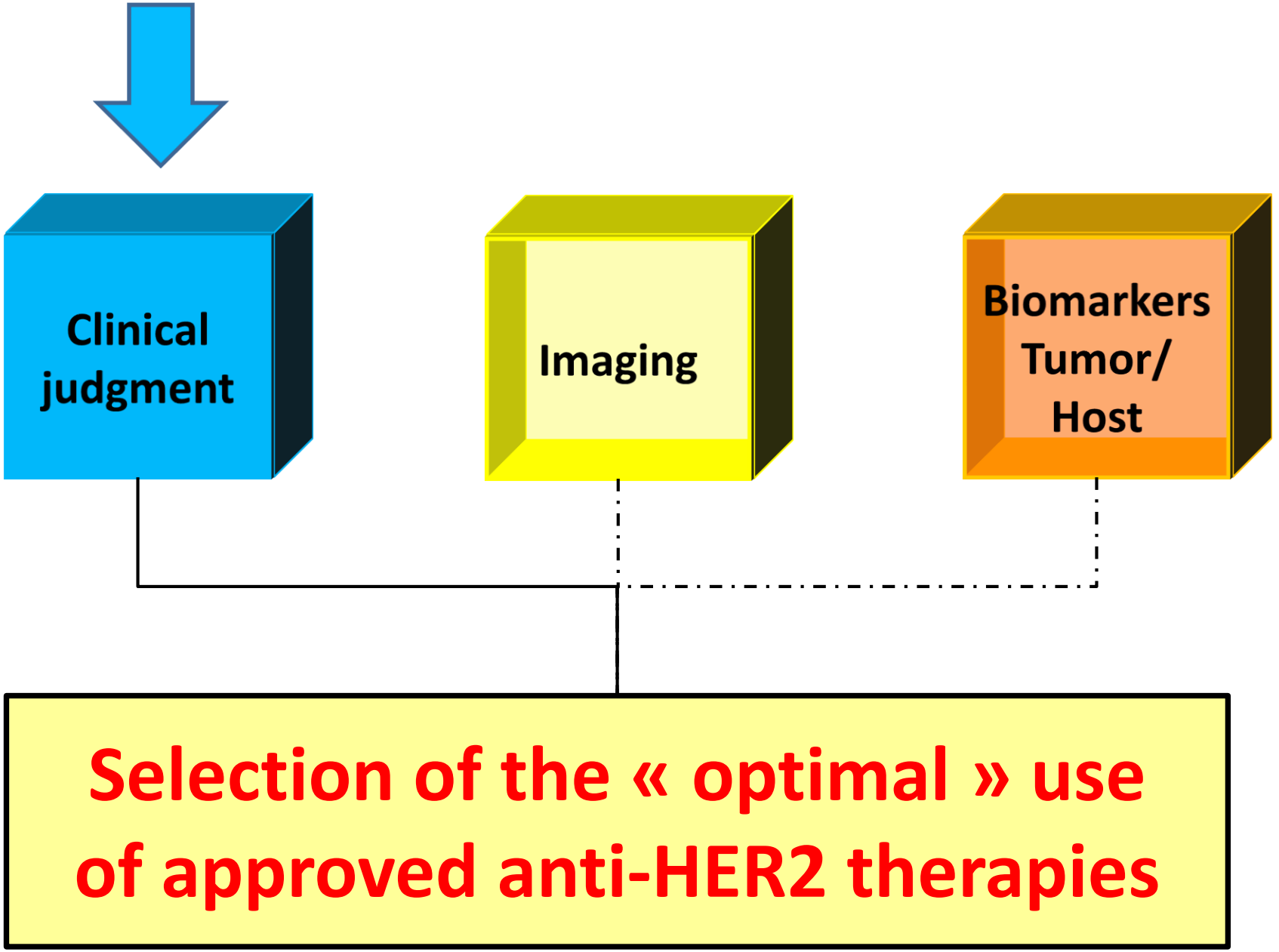
OS worse for the non trastuzumab-containing arm

Beyond Guidelines



How can we improve treatment tailoring in advanced HER2+ BC?


Clinical judgment
Imaging
Biomarkers Tumor/ Host
Selection of the « optimal » use of approved anti-HER2 therapies in advanced disease


Clinical judgment
Imaging
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Selection of the « optimal » use of approved anti-HER2 therapies

Optimizing the use of new HER2 targeted agents in advanced disease :

No known brain metastases

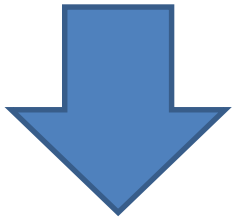
	Trastuzumab (T) naive or T-« sensitive » population (adj. T- free interval ≥ 1y)	Trastuzumab (T) pretreated and doubt about T- « sensitivity » (adj. T- free interval < 1y)
1rst line	Taxane + T + Pertuzumab	T-DM1
2nd line	T-DM1	Lapatinib + Capecitabine
3rd line	Lapatinib + Capecitabine	Lapatinib + Trastuzumab
4th line	Lapatinib + Trastuzumab	Trastuzumab + Chemo

With input from L. Dirix, M.D.

Optimizing the use of new HER2 targeted agents in advanced disease :

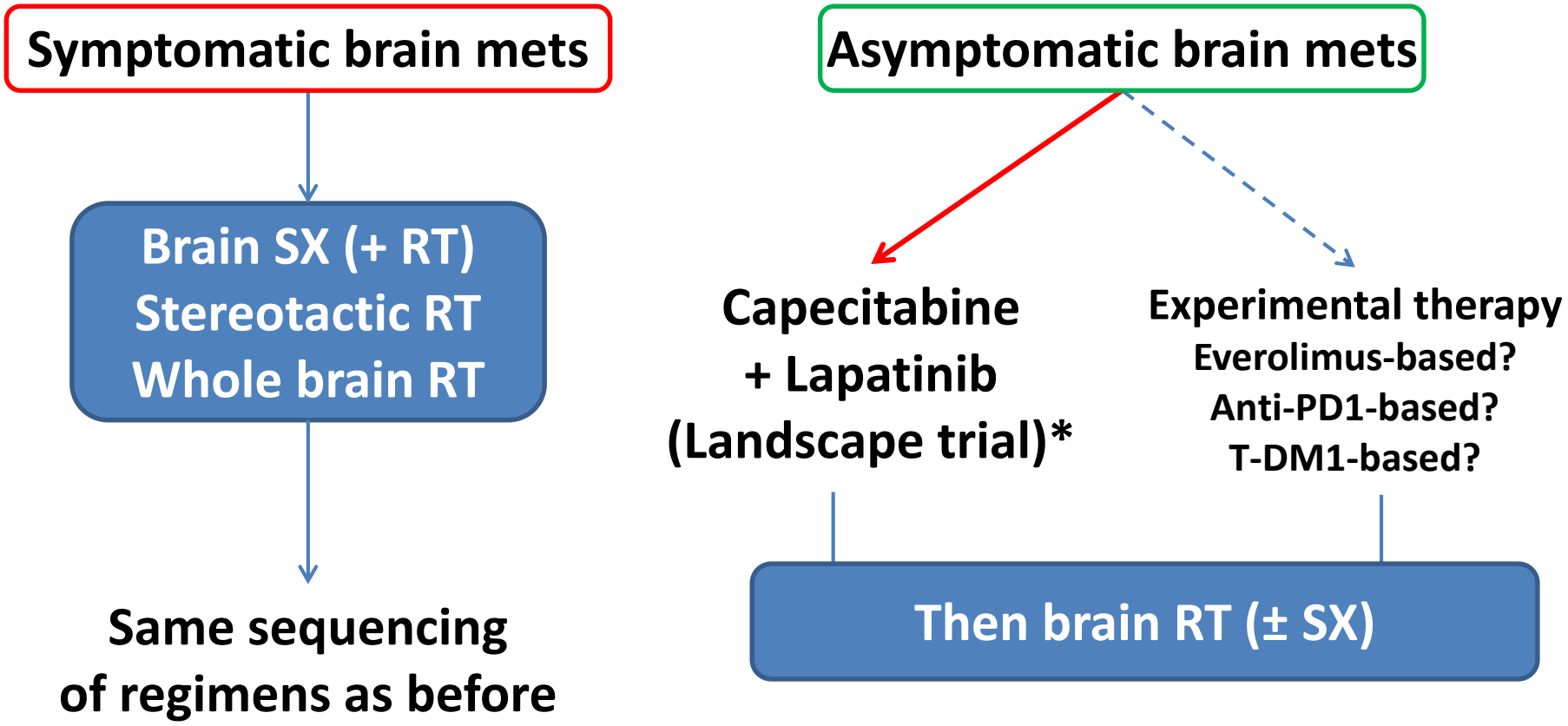
No known brain metastases

“Indolent” disease
Patient “chemotherapy adverse”
and trastuzumab pre-treated
HER2+ HR+ disease



Endocrine therapy
+
Trastuzumab and Pertuzumab

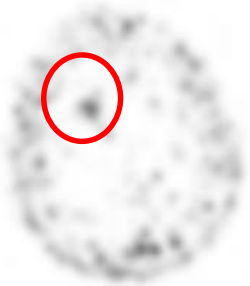
Optimizing the use of new HER2 targeted agents in advanced disease : What if there are known brain metastases as well as distant metastases?



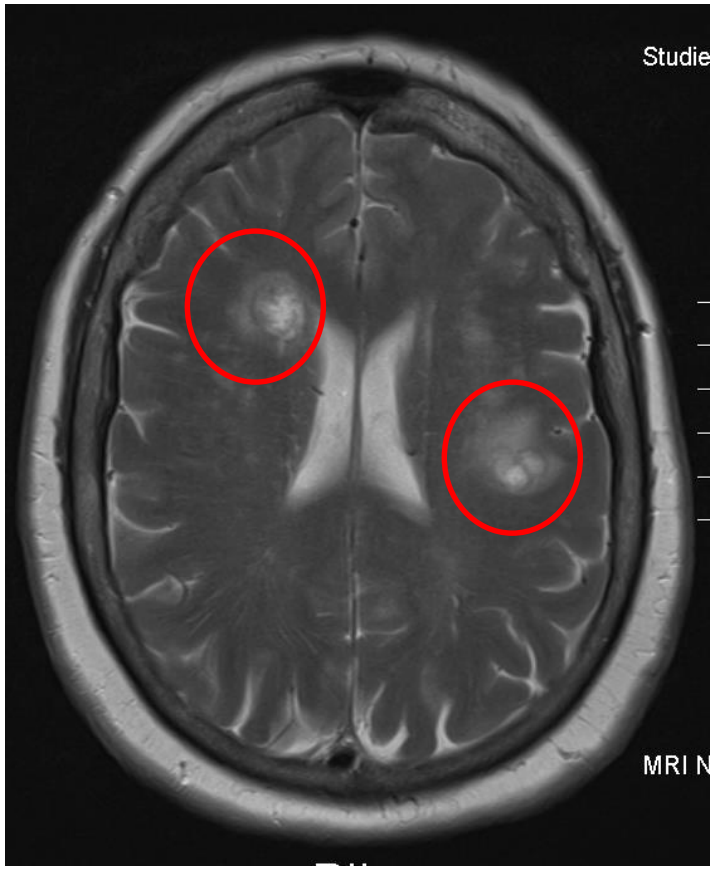
* 66% RR, most progressions (78%) in CNS after a median time of 5,5m, significant toxicities

Ramakrishna et al, ASCO Guidelines 2014

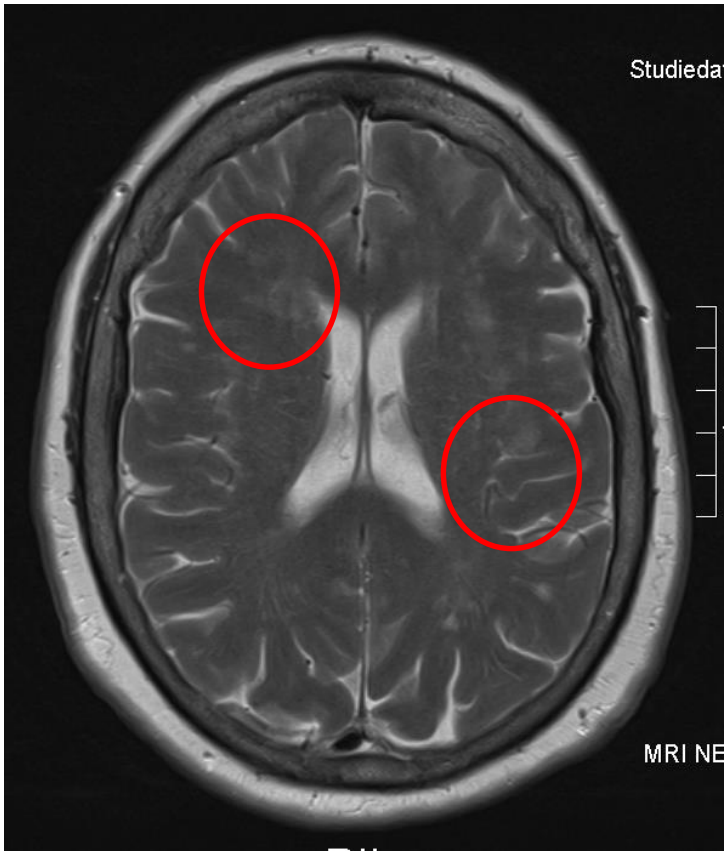
Courtesy E. de Vries



Patient 202: response of brain metastases to T-DM1

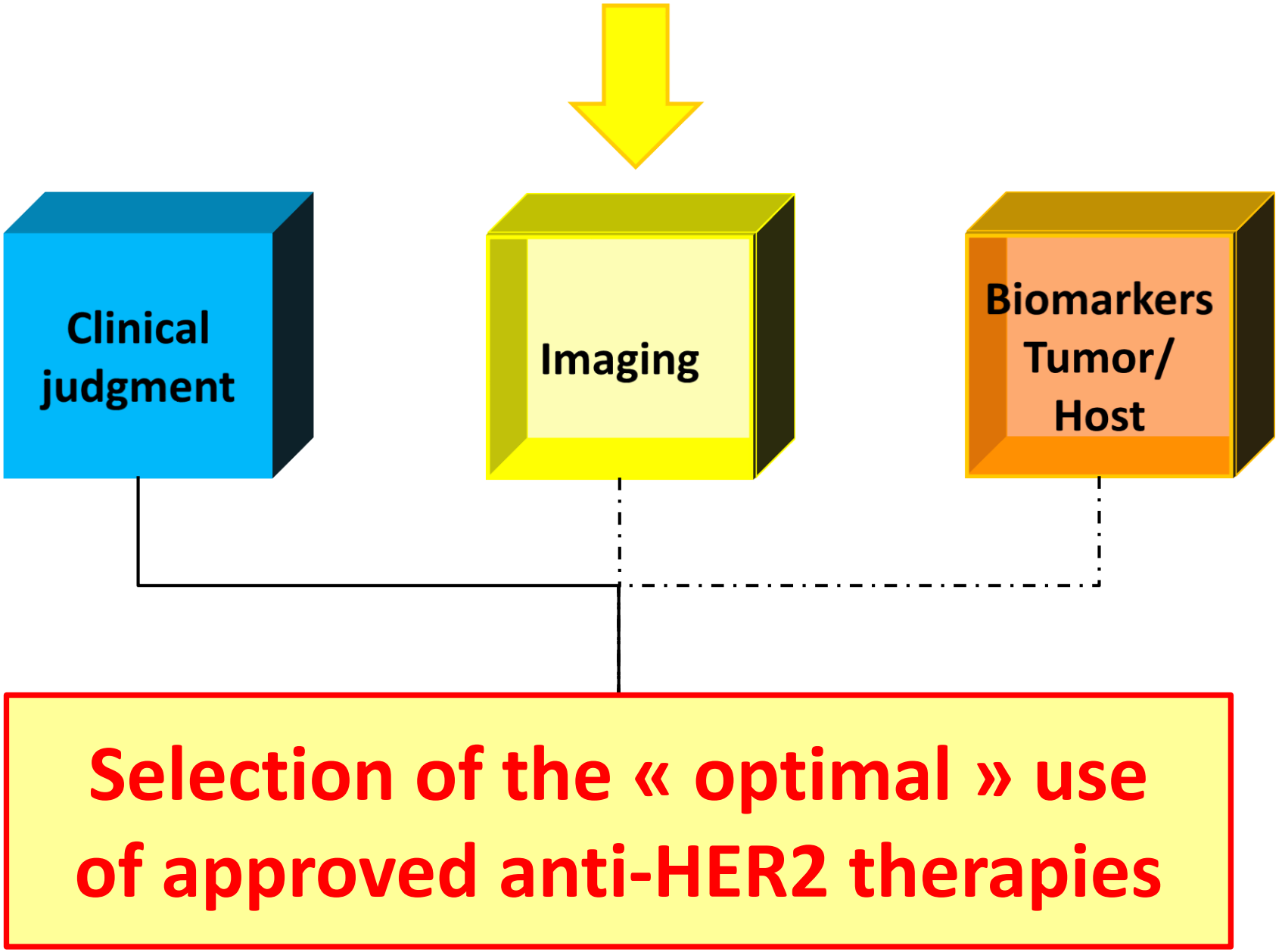


3 Cycles of T-DM1



Before: 1-AUG-2012

After 3 cycles: 28-SEP-2012

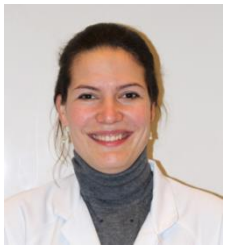

Clinical judgment
Imaging
Biomarkers Tumor/ Host
Selection of the « optimal » use of approved anti-HER2 therapies

Individualization of T-DM1 therapy in advanced HER2+ BC

ZEPHIR trial (NCT01565200)
Belgium and Holland
Coordination : Nuclear Medicine Department
(P. Flamen, G. Gebhart - J. Bordet Institute)

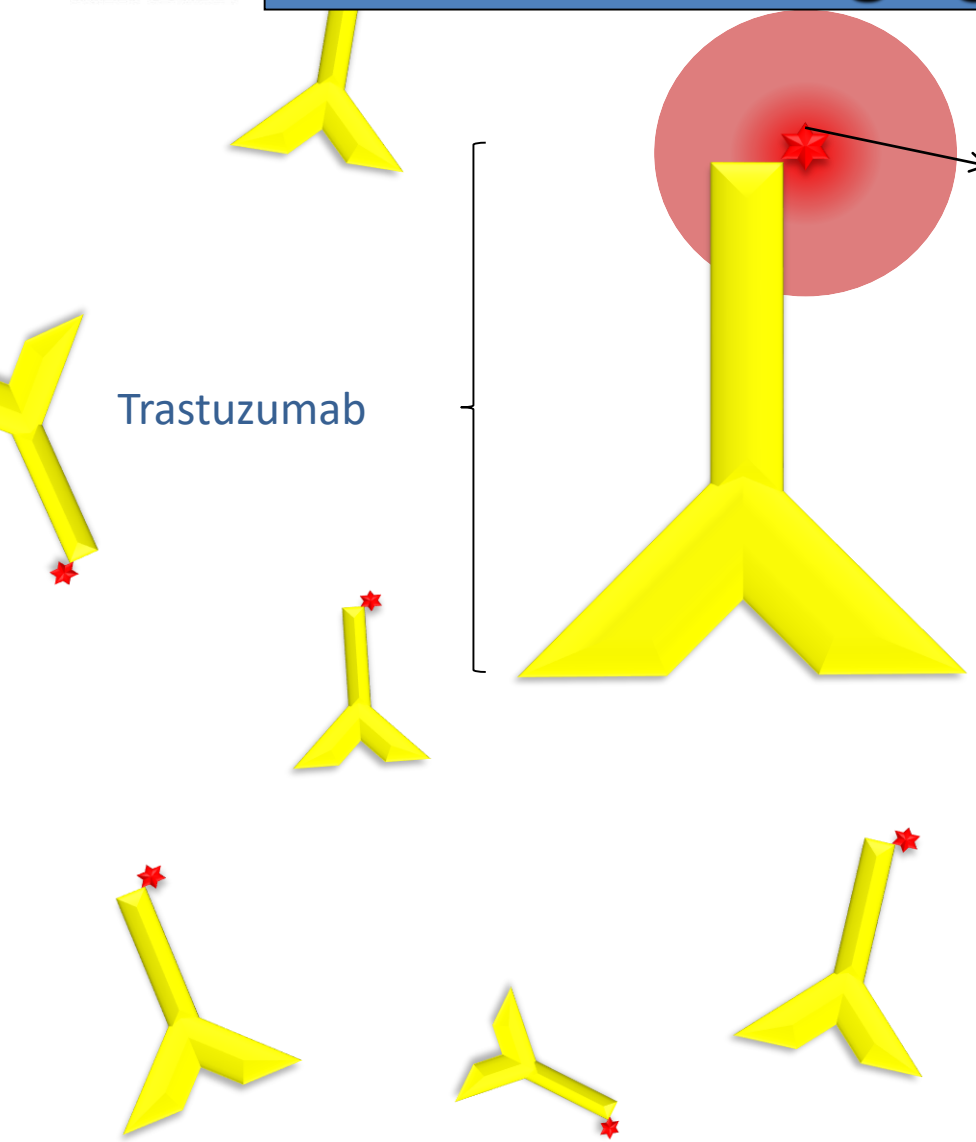
INSTITUT JULES BORDET

HER2 imaging

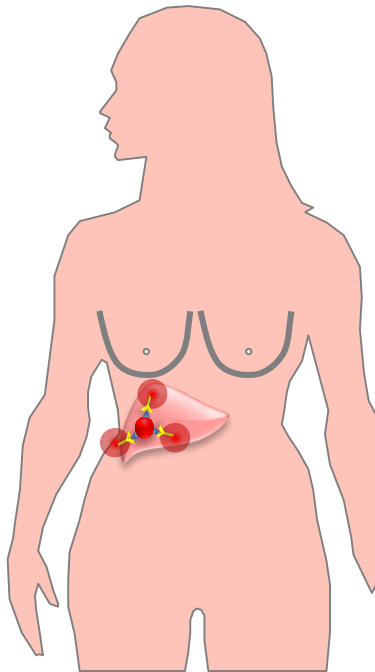

G. Gebhart


P. Flamen


E. de Vries



Zirconium^{89}
- positron emitting isotope ➔ PET
- compatible physical characteristic
  (Half-life 78.4 h)



The ZEPHIR Trial: Optimizing T-DM1 Administration in Advanced HER2+ BC Rationale

1. **For TDM1 to be active, the presence of an intact HER2 receptor is "key“.**

   The zirconium 89 labelled trastuzumab PET/CT is a non invasive test which shows promise in evaluating HER2 expression (extracellular domain) for the <u>entire disease burden</u>

2. **It is desirable to identify early on, which patients are <u>unlikely</u> to benefit.**

The ZEPHIR Trial: Optimizing T-DM1 Administration in Advanced HER2+ BC

The ZEPHIR Trial	
Primary Objective	**To show that pre-treatment 89Zr-trastuzumab PET/CT is able to select lesions not responding from treatment with T-DM1**
Primary Endpoint	**NPV of the 89Zr-trastuzumab PET/CT**
Secondary Objective	**To show that early FDG PET/CT (performed after one cycle of T-DM1) is able to select lesions not responding from treatment with T-DM1**
Secondary Endpoint	**NPV of the early FDG PET/CT**

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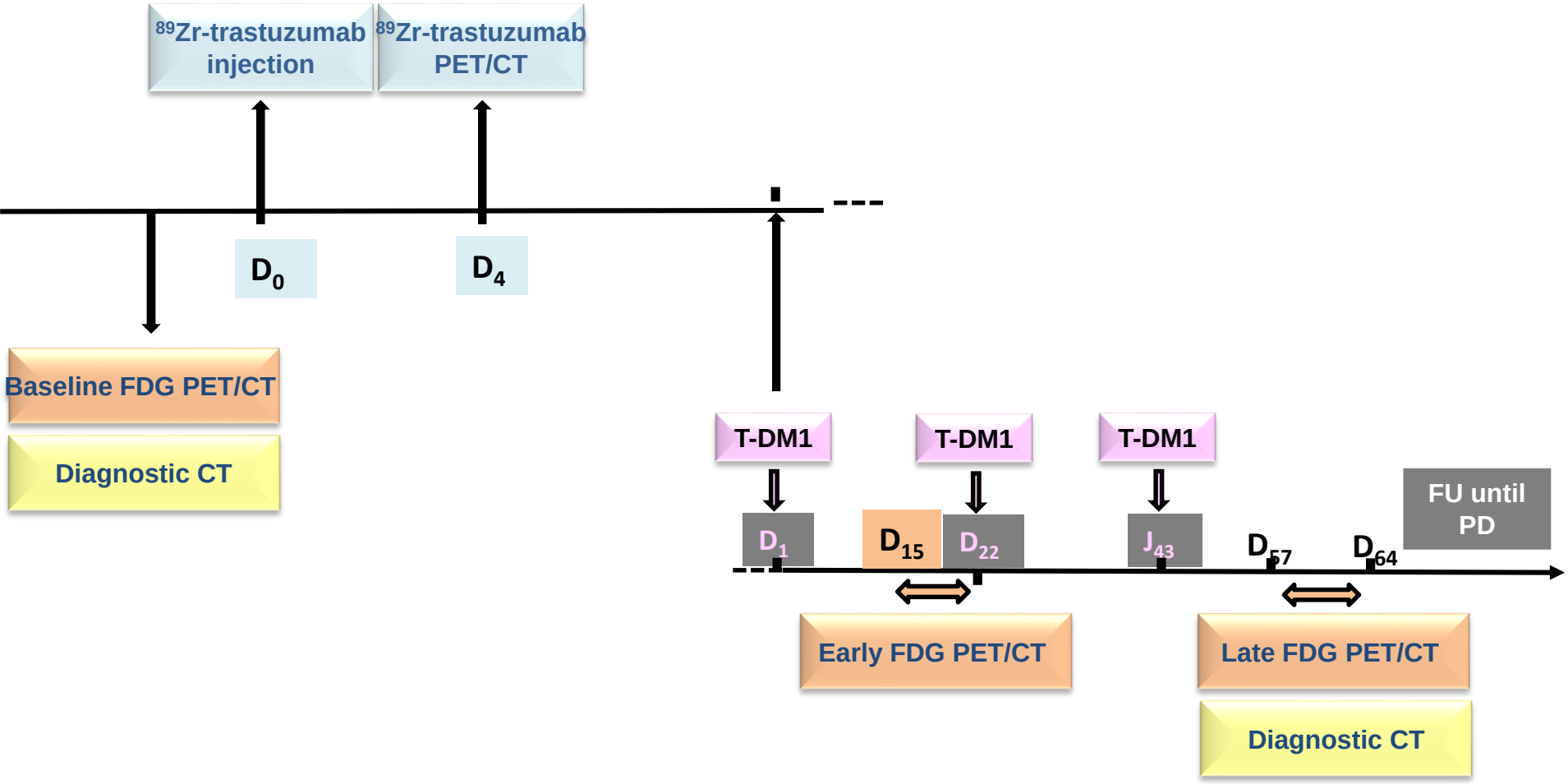
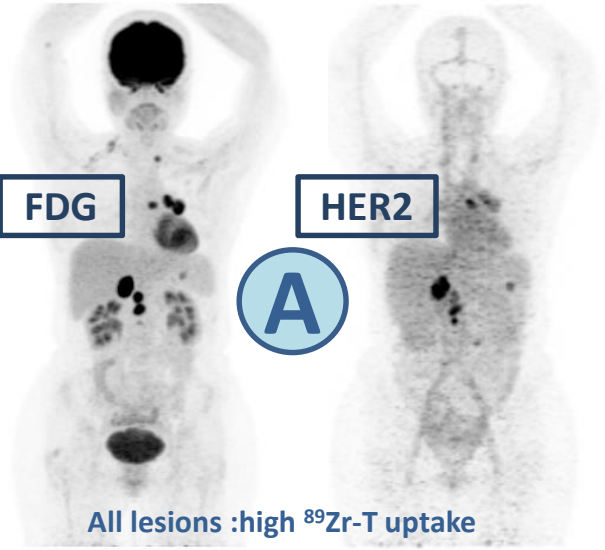
ZEPHIR trial design



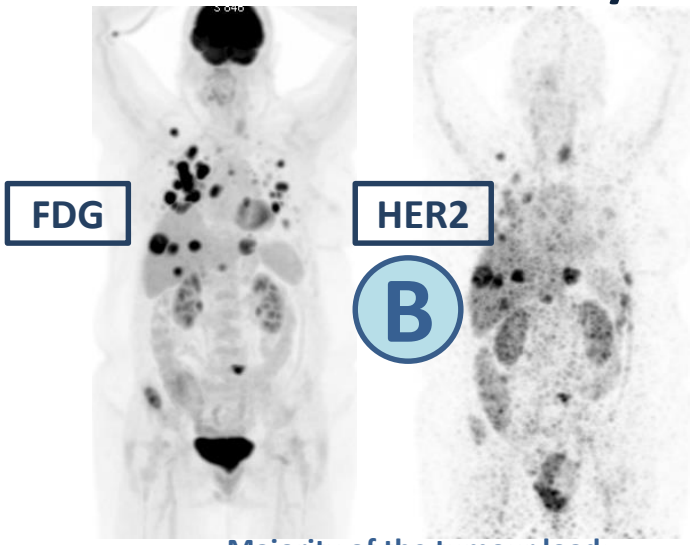
G. Gebhart et al., Annals of Oncology, published online Nov 23, 2015

Patterns of ^{89}Zr-trastuzumab PET/CT confronted with FDG-PET/CT



All lesions :high ^{89}Zr-T uptake

All (A) or most (B) of the metastatic lesions are seen on the HER2 PET

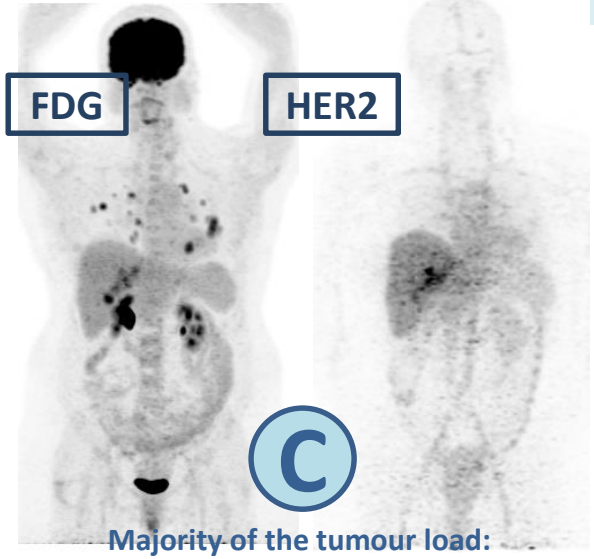


Majority of the tumour load: high ^{89}Zr-T

+

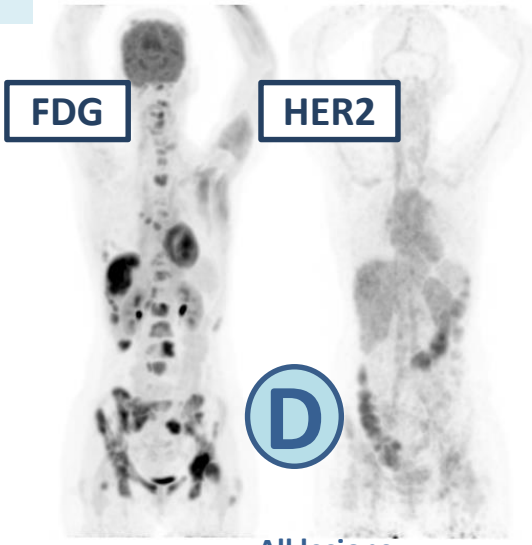
HER2 IMAGING METHODOLOGY

−



Majority of the tumour load: low/no ^{89}Zr-T uptake

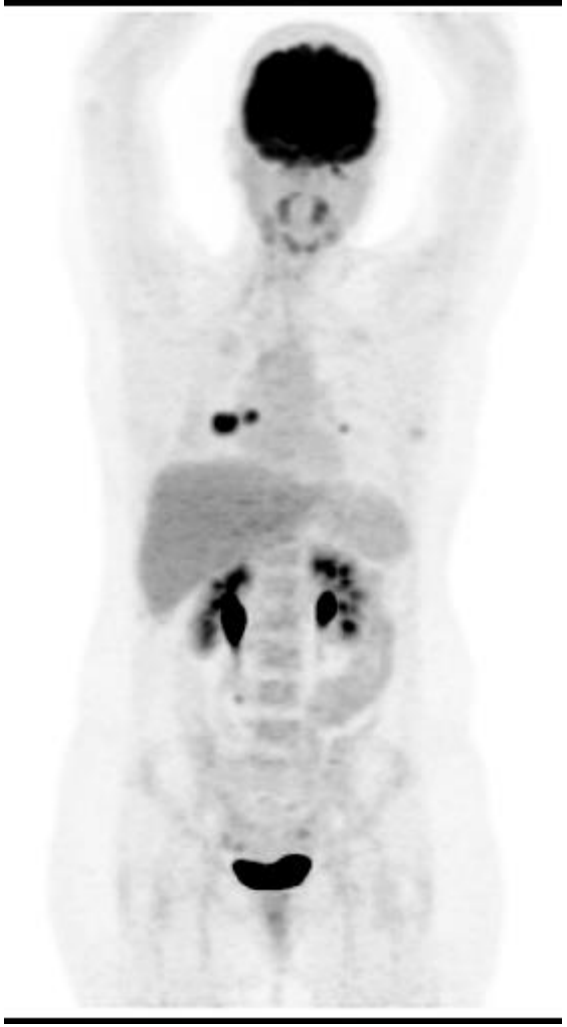
None (D) or very few (C) metastatic lesions are seen on the HER2 PET



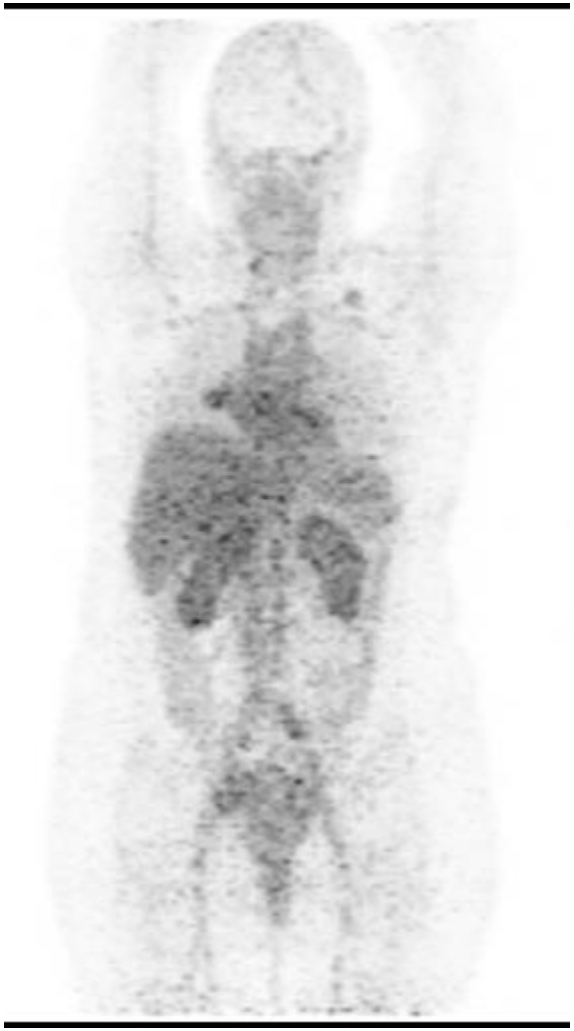
All lesions: low/no ^{89}Zr-T uptake

G. Gebhart et al., Annals of Oncology, published online Nov 23, 2015

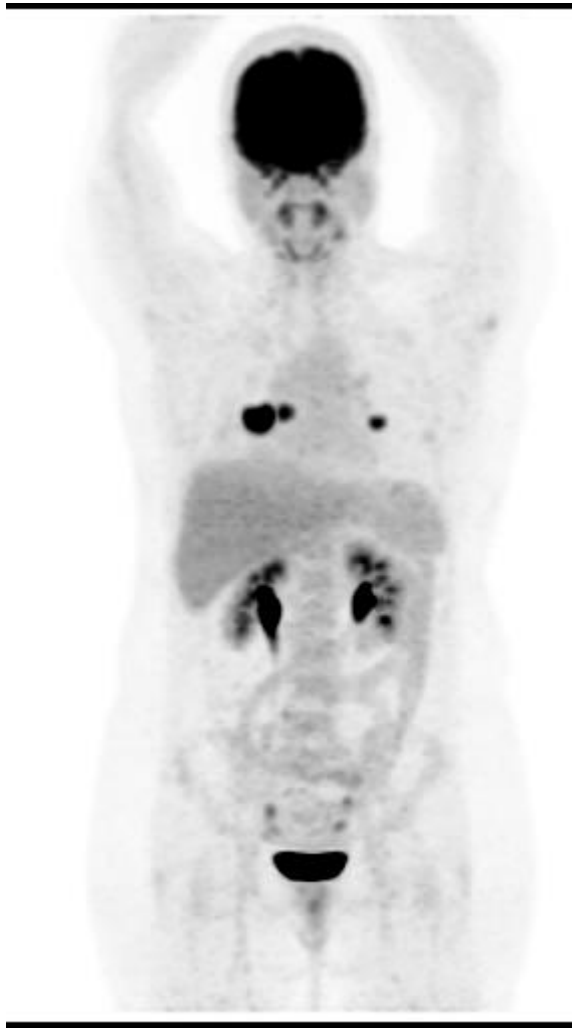
PET



Baseline
FDG PET

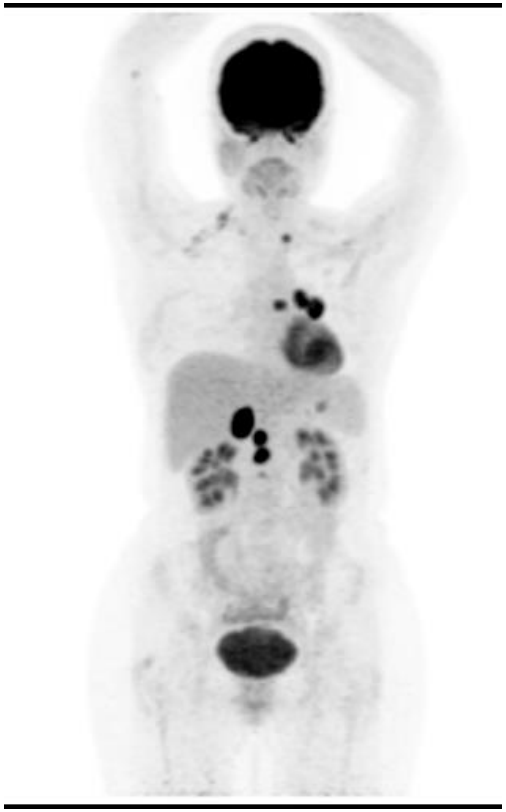


^{89}Zr-Trastuzumab PET

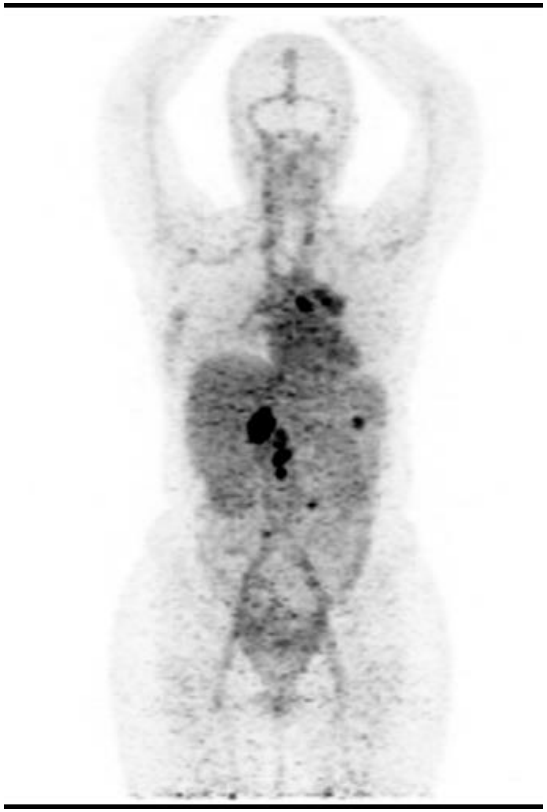


Post 3 cycles TDM1 FDG PET

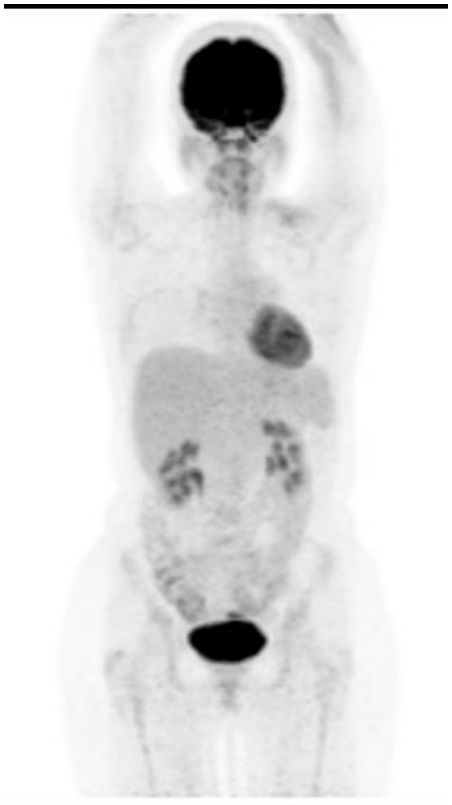
PET



Baseline FDG PET



^{89}Zr-Trastuzumab
PET



Post 3 cycles TDM1
FDG PET

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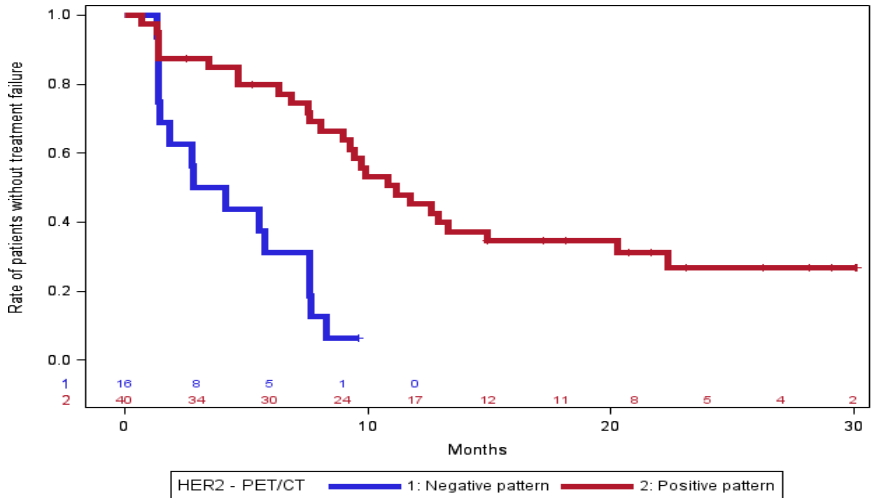
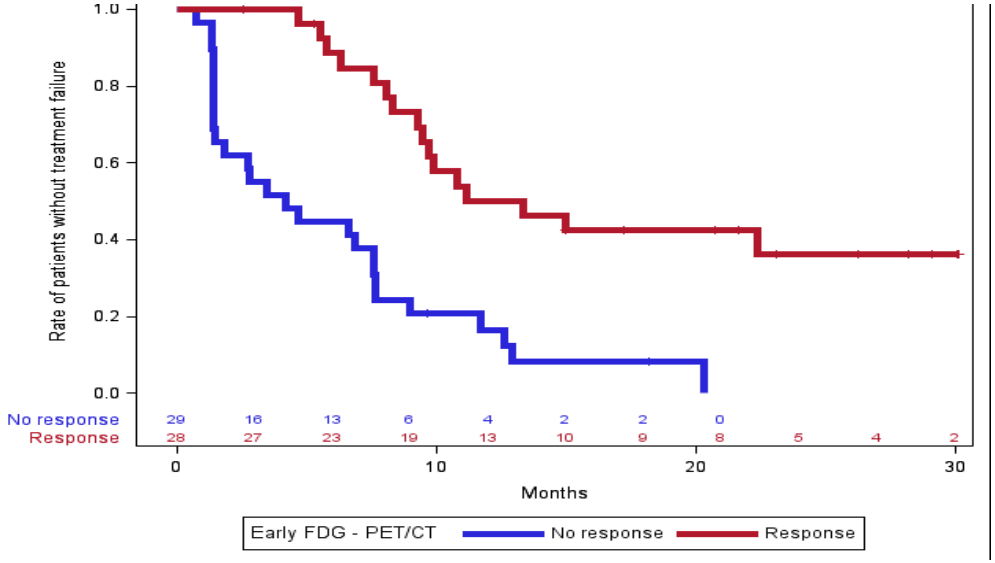
Heterogeneity in HER2 « mapping » and early FDG-PET predict time to treatment failure (TTF) under T-DM1 Therapy

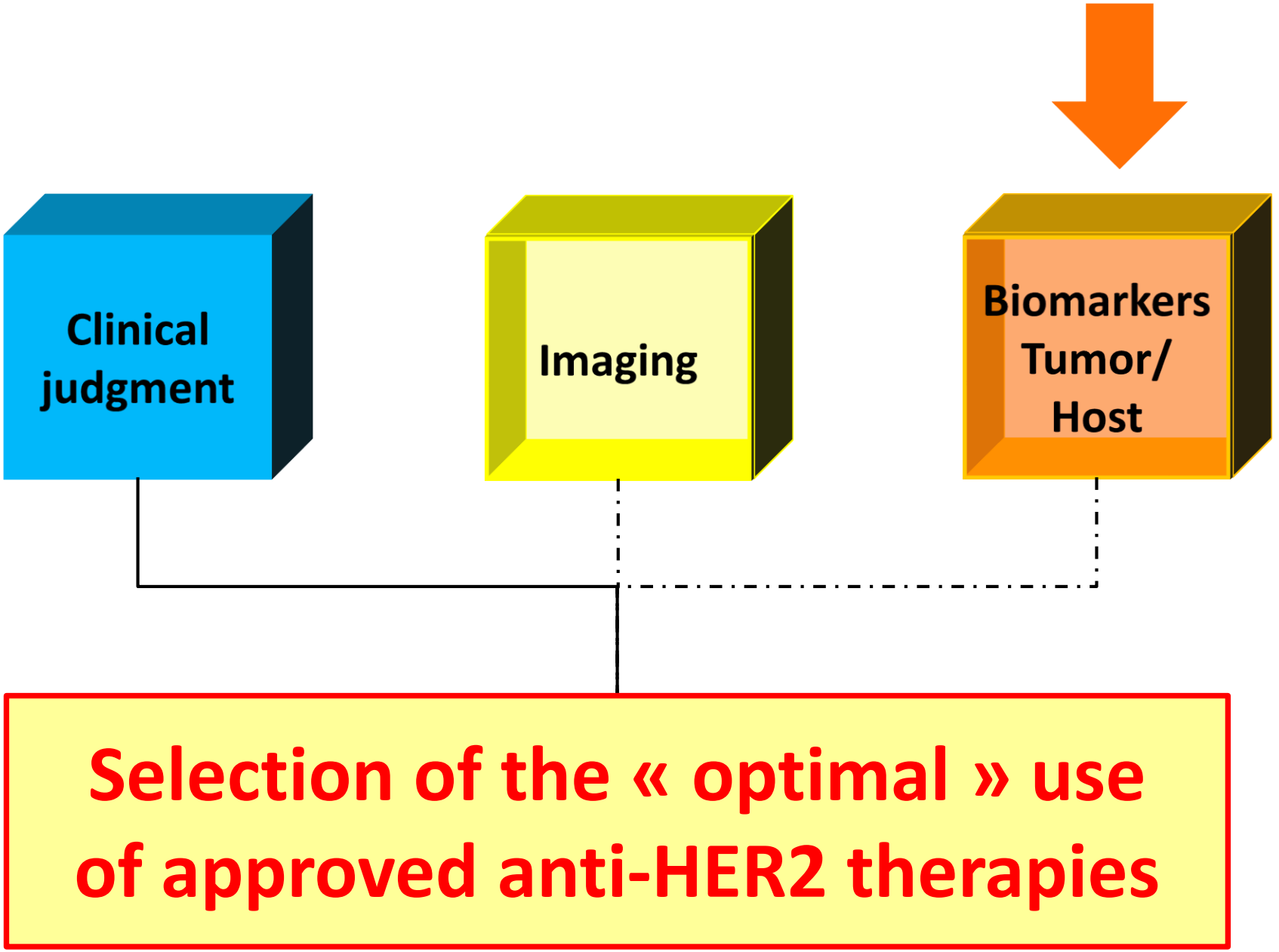


Short TTF with HER2 PET patterns C+D

Short TTF if no early FDG-PET response



G. Gebhart et al., Annals of Oncology, published online Nov 23, 2015


Clinical judgment
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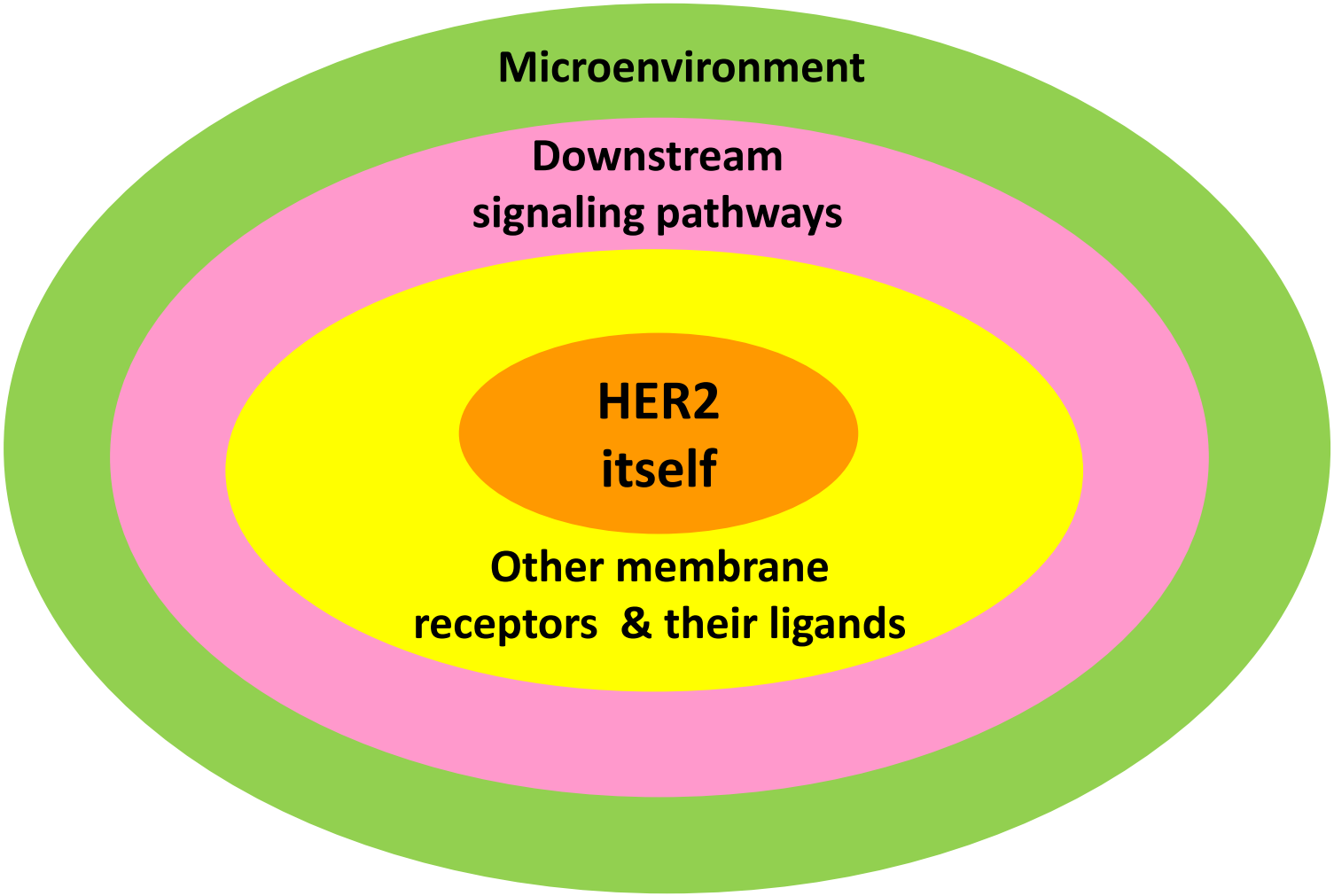
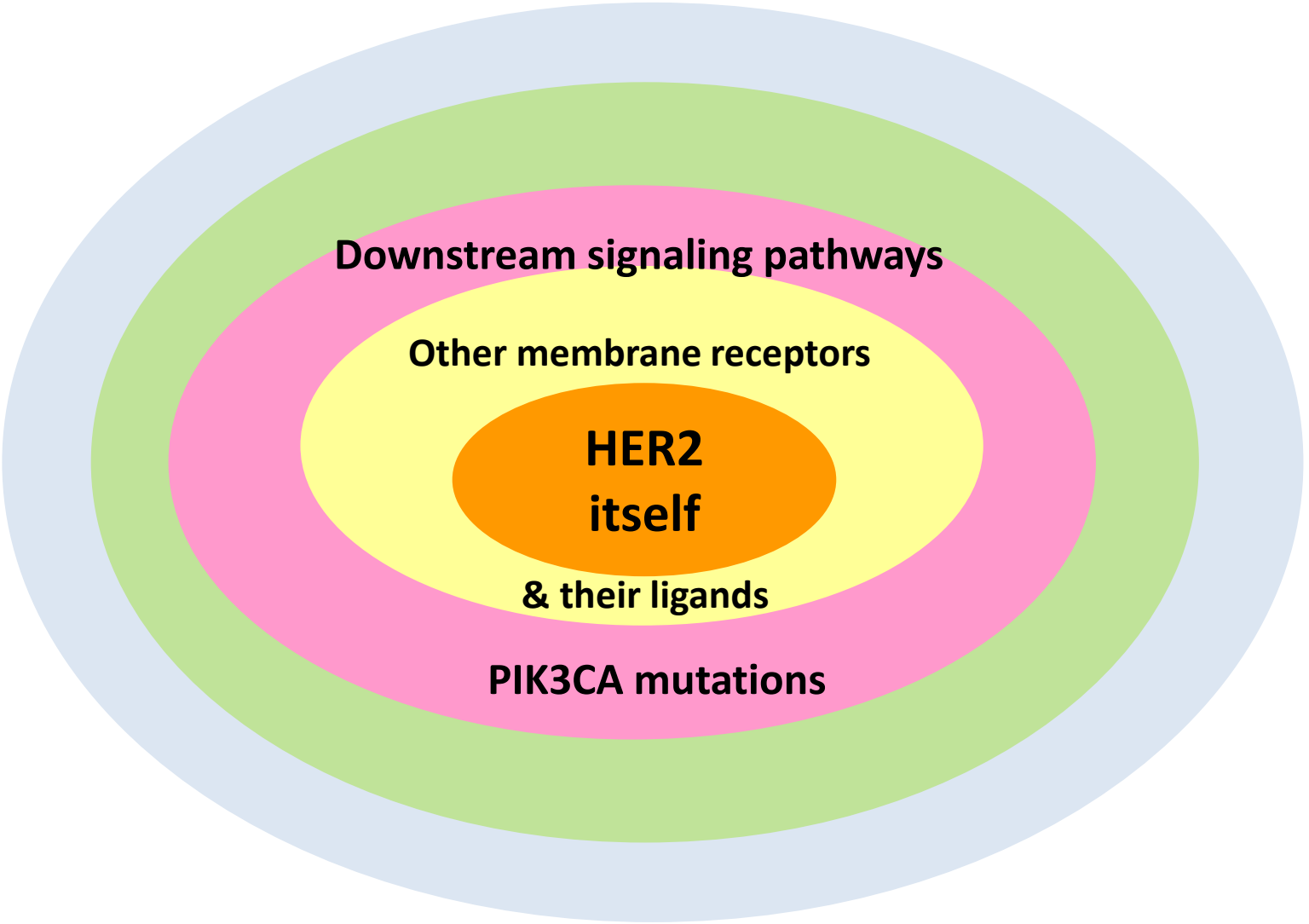
Translational Research efforts in HER2+ BC



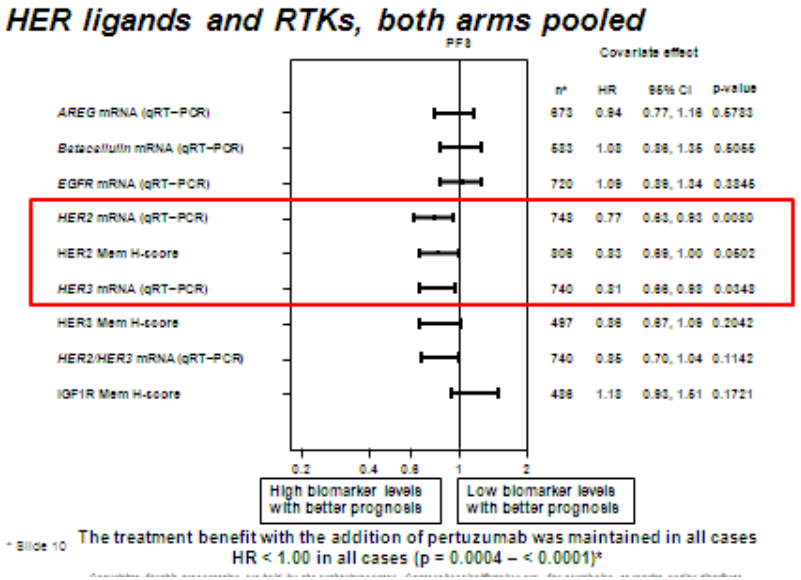
Translational Research efforts in HER2+ BC
I. Advanced disease



High tumor HER2 mRNA means a better prognosis

Cleopatra :

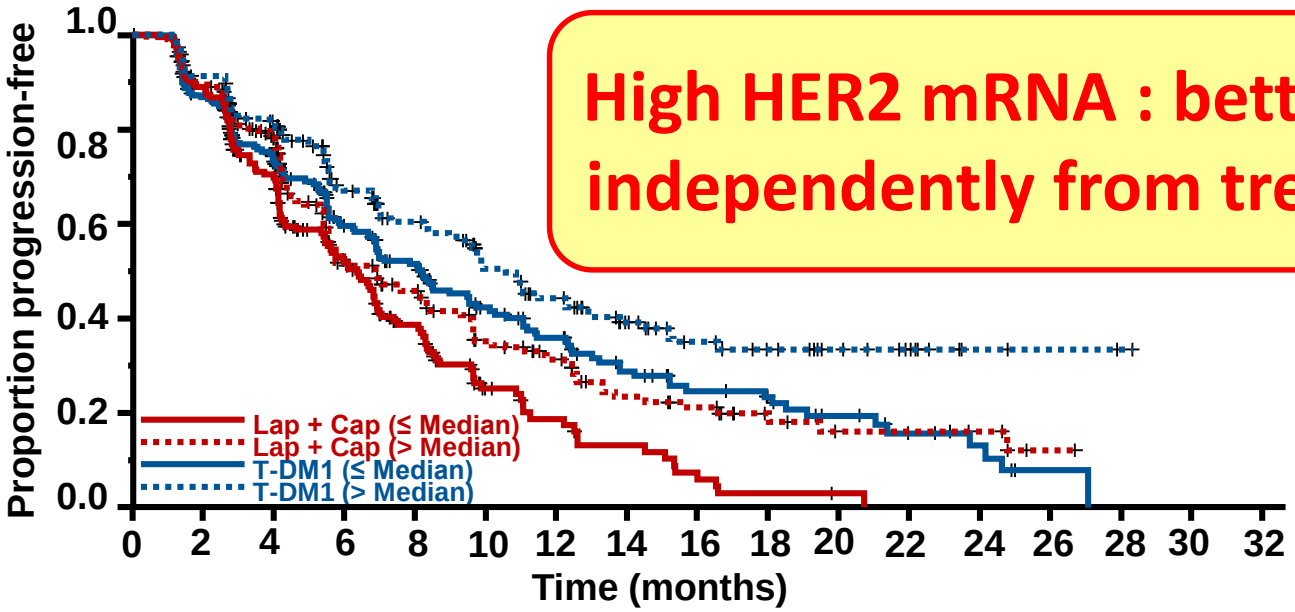
docetaxel + trastuzumab + pertuzumab > docetaxel + trastuzumab



Emilia:

T-DM1 > lapatinib + capecitabine

PFS

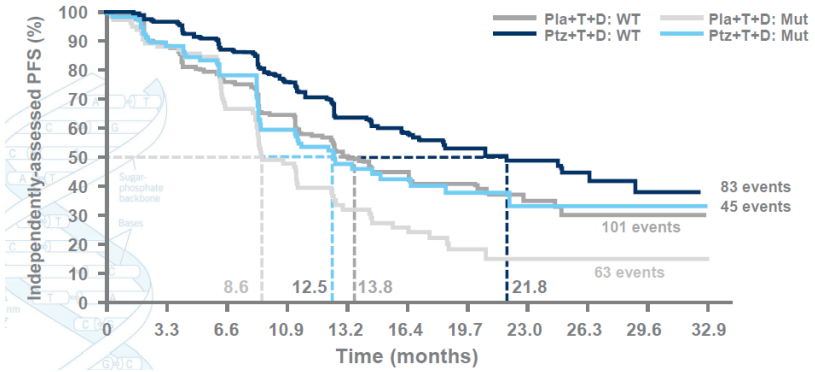


High HER2 mRNA : better prognosis independently from treatment arm

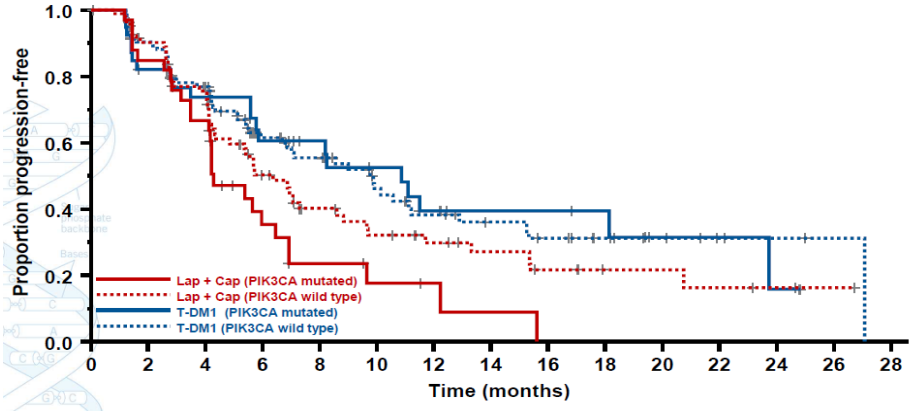
Courtesy J. Baselga

PiK3CA mutations (32% incidence): worse prognosis but still a benefit from treatment

Cleopatra trial



Emilia trial

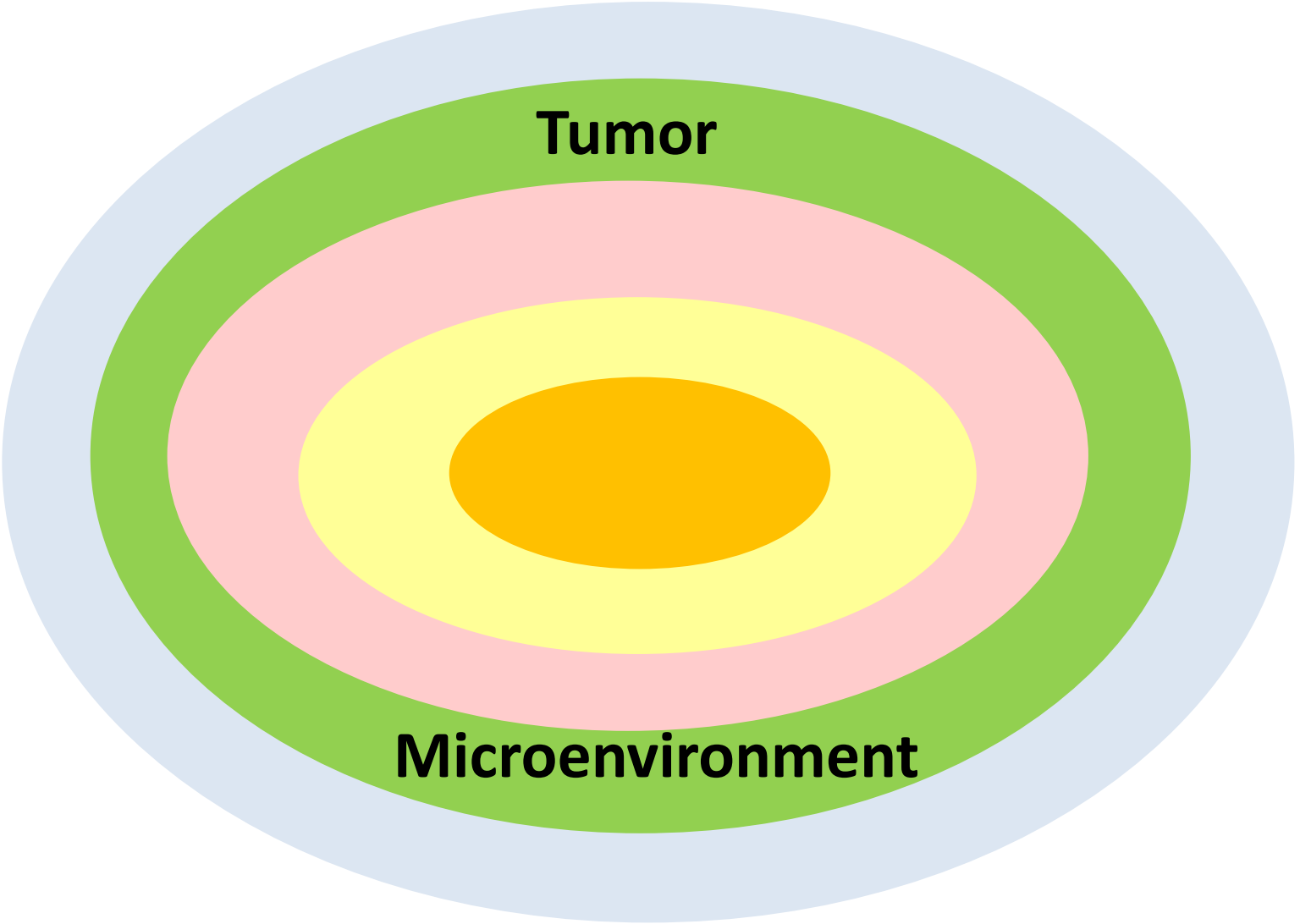


	Single blockade med PFS	Dual blockade med PFS	H.R.	Lap + Cap med PFS	T-DM1	H.R.
piK3CA stats mutant	8.6 m	12.5 m	0.64	4.3 m	10.9 m	0.45
Wild type	13.8 m	21.8 m	0.67	6.4 m	9.8 m	0.74

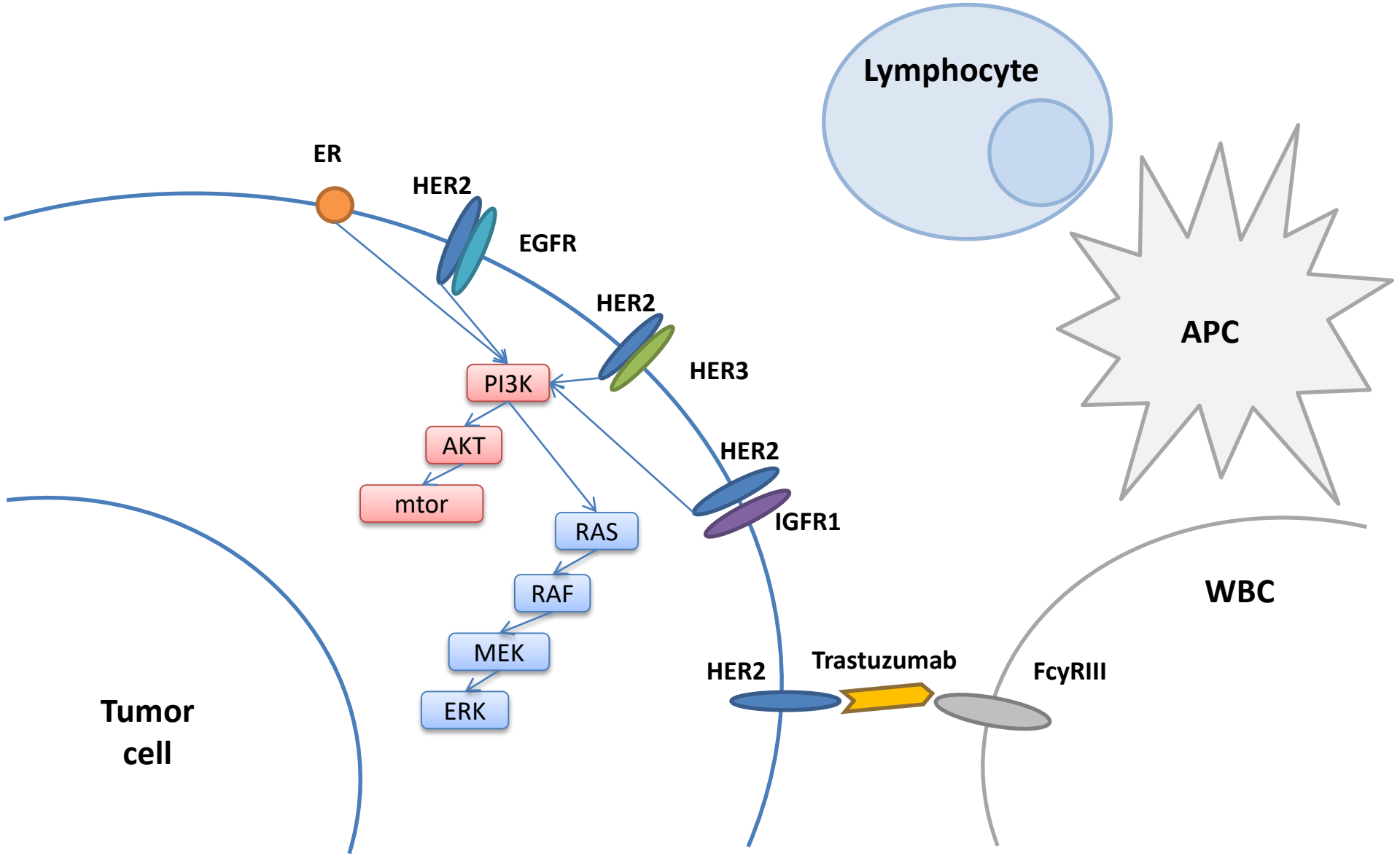
Dual blockade works in both cohorts… but larger magnitude of benefit in wild type cohort

T-DM1 works in both cohorts… but larger magnitude of benefit in mutated cohort

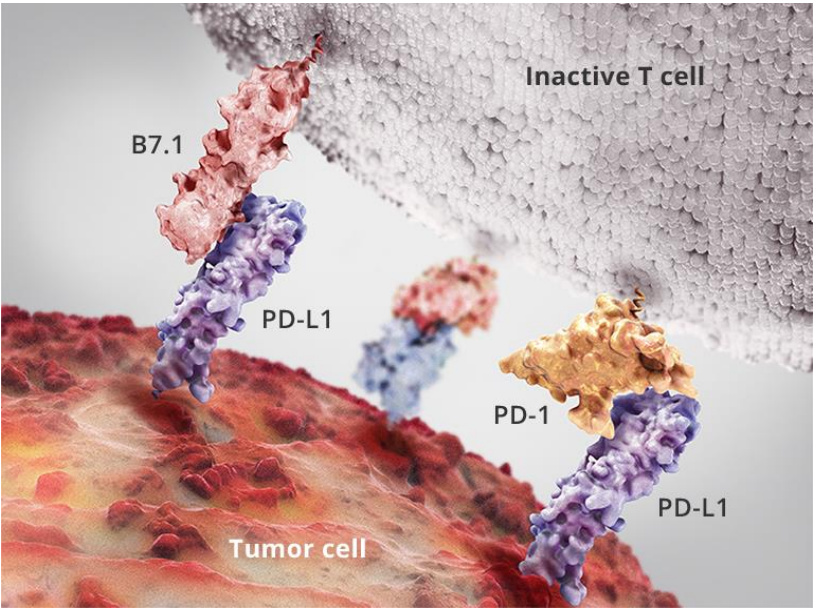
Translational Research efforts in advanced HER2+ BC



Translational Research efforts in HER2+ BC



HER2+ BC: The importance of the tumor microenvironment



Are TILs prognostic or predictive in the context of advanced disease treated with anti-HER2 therapies?

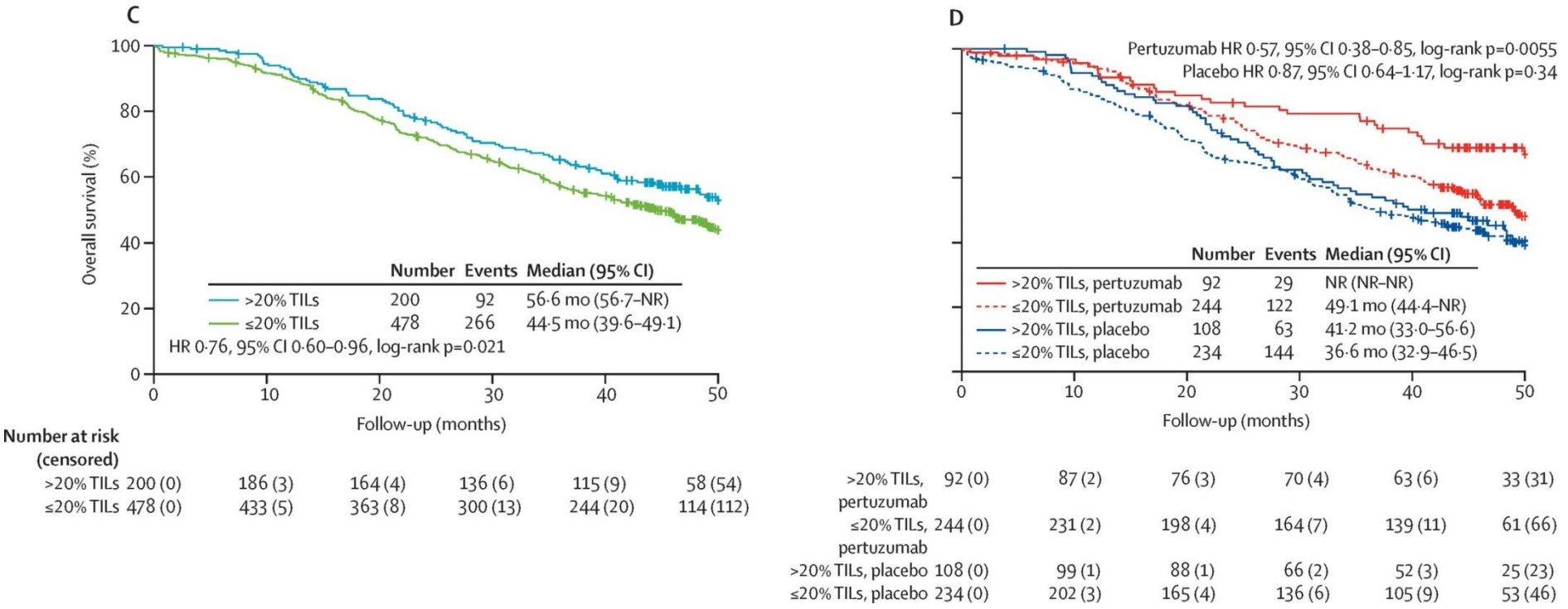
TIL's are prognostic in the context of advanced HER2 positive Breast Cancer treated with anti-HER2 MAbs

- **Clinical trial = CLEOPATRA (adding pertuzumab to trastuzumab + docetaxel improves PFS by 6.3m and OS by 15.7m in the first line setting)**
- **Tissue collected from 678 out of 808 patients (N=155 fresh samples, 519 archival samples, only 20 "paired" samples)**
- **Stromal TILs: median = 10%, range 1-95% (significantly higher in ER negative tumors)**

Each 10% increase in TILs is associated with an 11% decrease in the risk of death

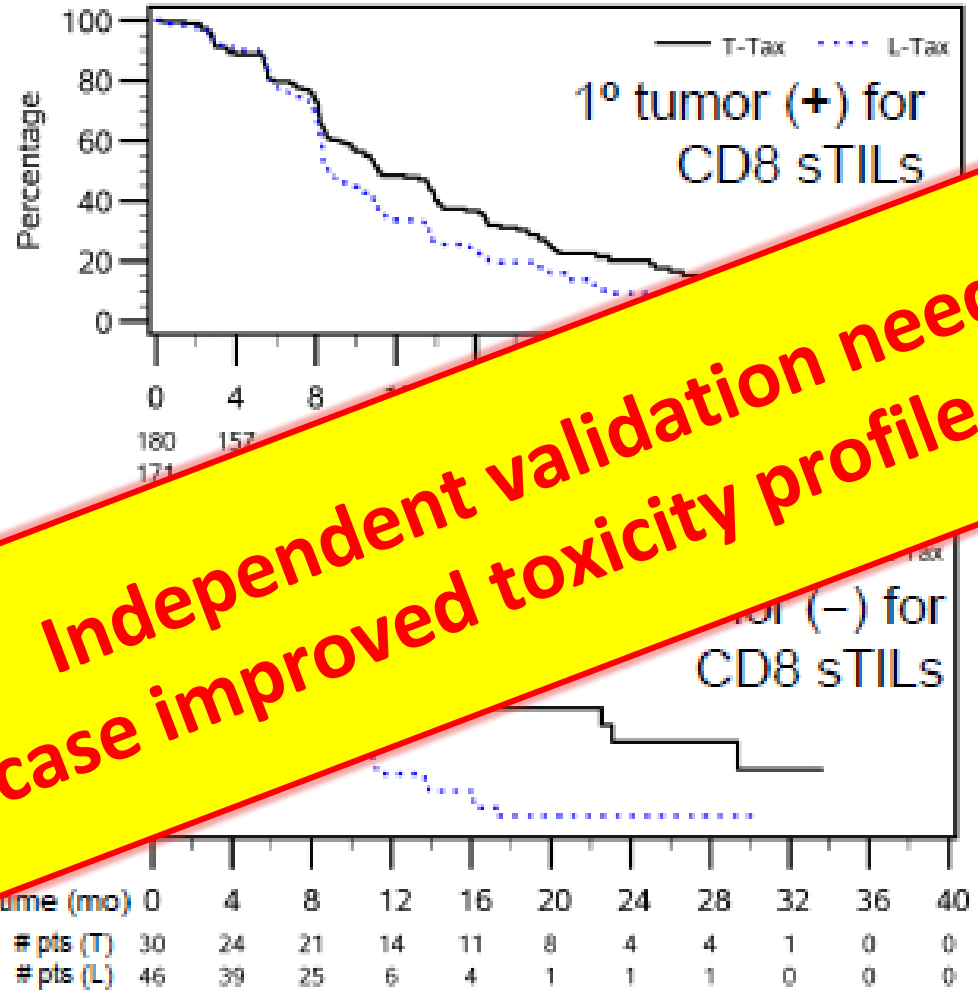
Luen, S.J. et al, Lancet Oncology, 2017; 18:52-62

TIL's are prognostic in CLEOPATRA



Luen, S.J. et al, Lancet Oncology, 2017, 18:52-62

CCTTG MA.31: Predictive effect of cytotoxic tumor infiltrating lymphocytes for PFS in HER2+ M.B.C.



Independent validation needed… but in any case improved toxicity profile of Trastuzumab

A lack of cytotoxic CD8 + TILs predicts greatest benefit from trastuzumab over lapatinib

! No demonstration of a prognostic effect

Liu S et al., P1-09-08

When should we use TKI inhibitors?

- Unfortunately p95-HER2 not validated as a biomarker of preferential activity of lapatinib

- Lapatinib (or other TKI) to be explored in Zirconium PET “negative” patients?

Winning the battle against HER2 positive BC !

THANK YOU

BREAST Data Center Team

BIG Headquarters Team

Institut Jules Bordet Team

BIG Executive Board 2014-2018

THANK YOU