Nouvel Immuno-conjugué T-DM1 Kadcyla® Cancers du Sein HER2+

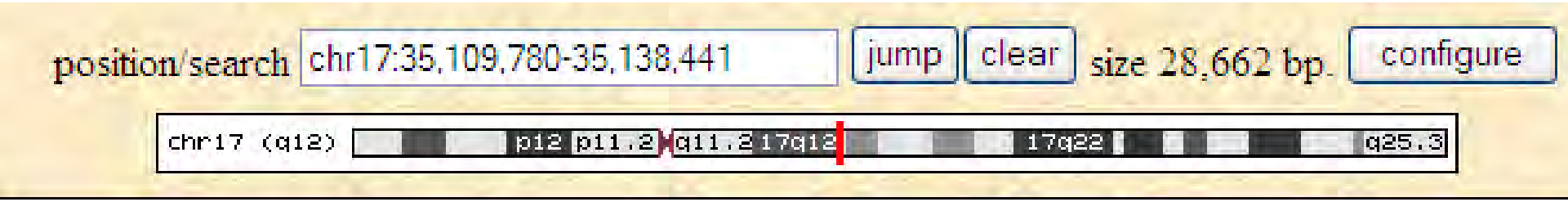
Véronique Diéras

Plan

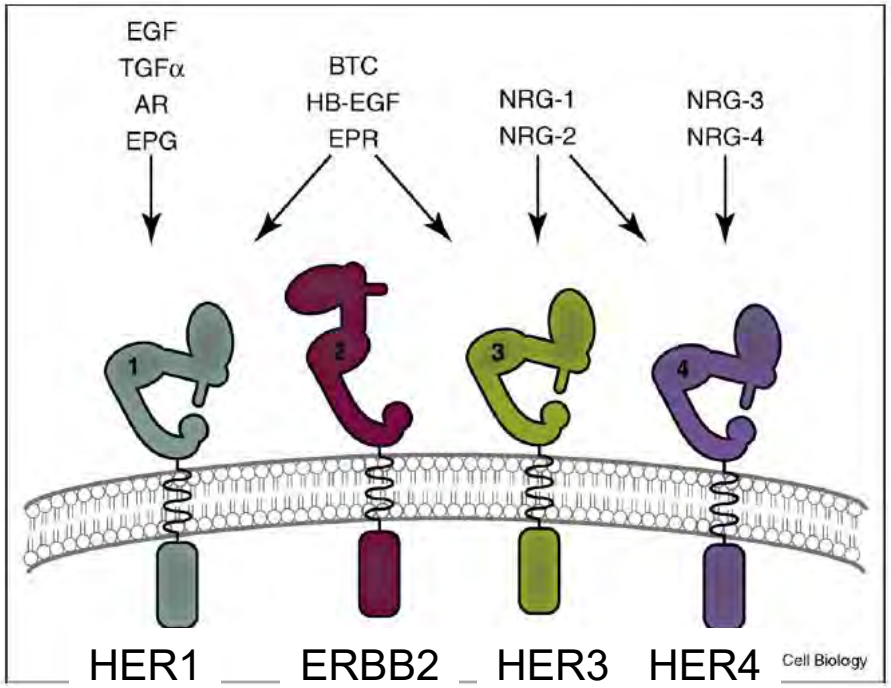
- Introduction
- Préclinique
- Phase I and Phase II
- Phase III situation métastatique
- Perspectives
- Conclusion

ERBB2/ Neu/HER2

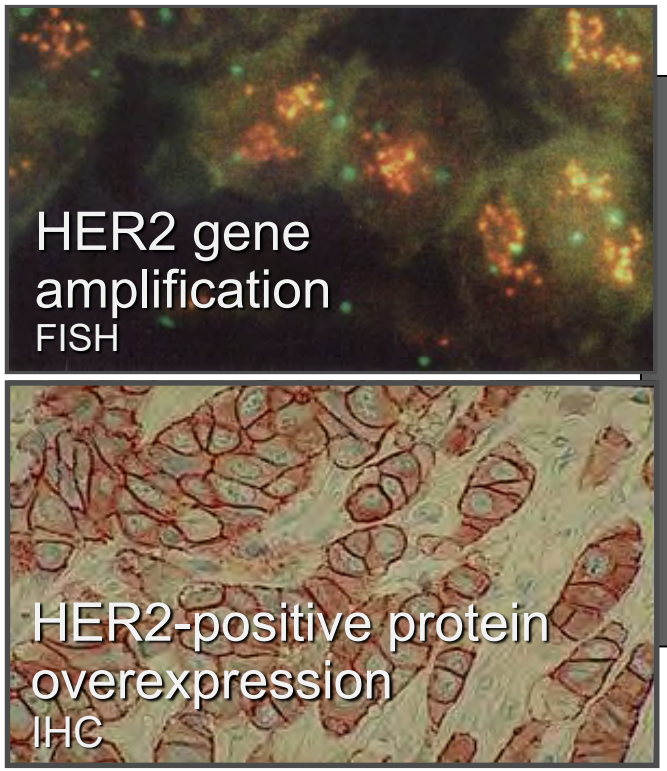
- Oncogene, chr17q12



- EGFR Family
- No ligand ERBB2
- Activation by heterodimerization
- Transduction of signal:
  - proliferation,
  - survival
  - angiogenesis …



Prognosis of HER2 positive breast cancers



Shortened Median Survival*	
HER2 positive	3 years
HER2 normal	6–7 years

Key Decision: Target the cell surface "constitutively active" HER2/ErbB2 protein with a monoclonal antibody

Slamon D, *et al*. *Science* 1987; **235**:177–182;

Pauletti, G *et al*. *J Clin Oncol* 2000; **18**:3651–3664.

* Combined metastatic and adjuvant patients.

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Trastuzumab dans les cancers du sein métastatiques

- **Association taxane (paclitaxel, docetaxel) standard première ligne**
- **Association avec de nombreux agents cytotoxiques (vinorelbine, capécitabine…)**
- **Après progression bénéfice de la prolongation du blocage anti-HER2Preclinical data**
  - Données précliniques
  - Nombreux données rétrospectives
  - Essai randomisé Phase III Capecitabine +/- Trastuzumab

Robert N JCO 2006, Wardley AM JCO 2010,
Chan BJC 2006, von Minckwitz G JCO 2009

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Trastuzumab: progrès majeur dans les cancers du sein HER2+
Cependant……

En situation métastatique, la progression est fréquemment observée dans les mois ou années

Des rechutes surviennent après trastuzumab adjuvant [4–6]

Relapses may also occur following adjuvant trastuzumab

→ **Nouveaux traitements**

1. Dieras V, *et al*. *Bull Cancer* 2007; **94:**259–266;
2. Vogel CL, *et al*. *J Clin Oncol* 2002; **20:**719–726;
3. Baselga J, *et al*. *J Clin Oncol* 2005; **23:**2162–2171;
4. Slamon DJ, *et al*. *N Engl J Med* 2001; **344:**783–792;
5. Marty M, *et al*. *J Clin Oncol* 2005; **23:**4265–4274;
6. Wardley AM, *et al*. *J Clin Oncol* 2010; **28:**976−983.

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Introduction

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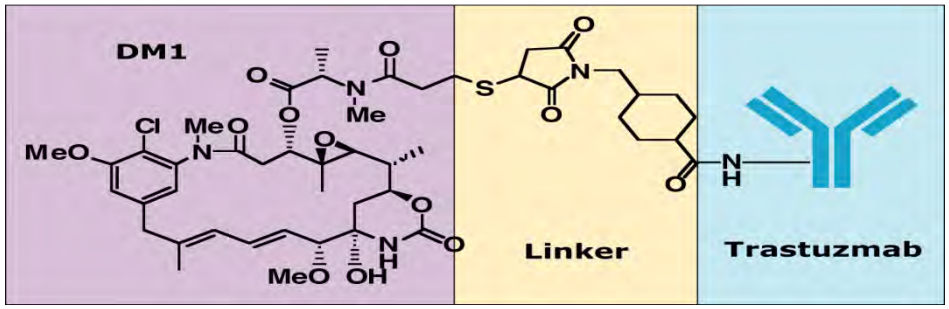


T-DM1 is a novel ADC

Target expression: HER2

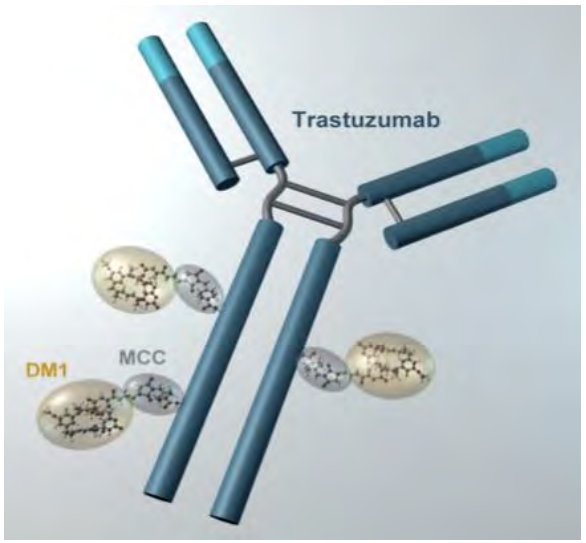
Monoclonal antibody: Trastuzumab

Cytotoxic agent: DM1

Highly potent cytotoxic agent

Linker: MCC

Systemically stable



T-DM1

Average drug:

- antibody ratio ≅3.5:1

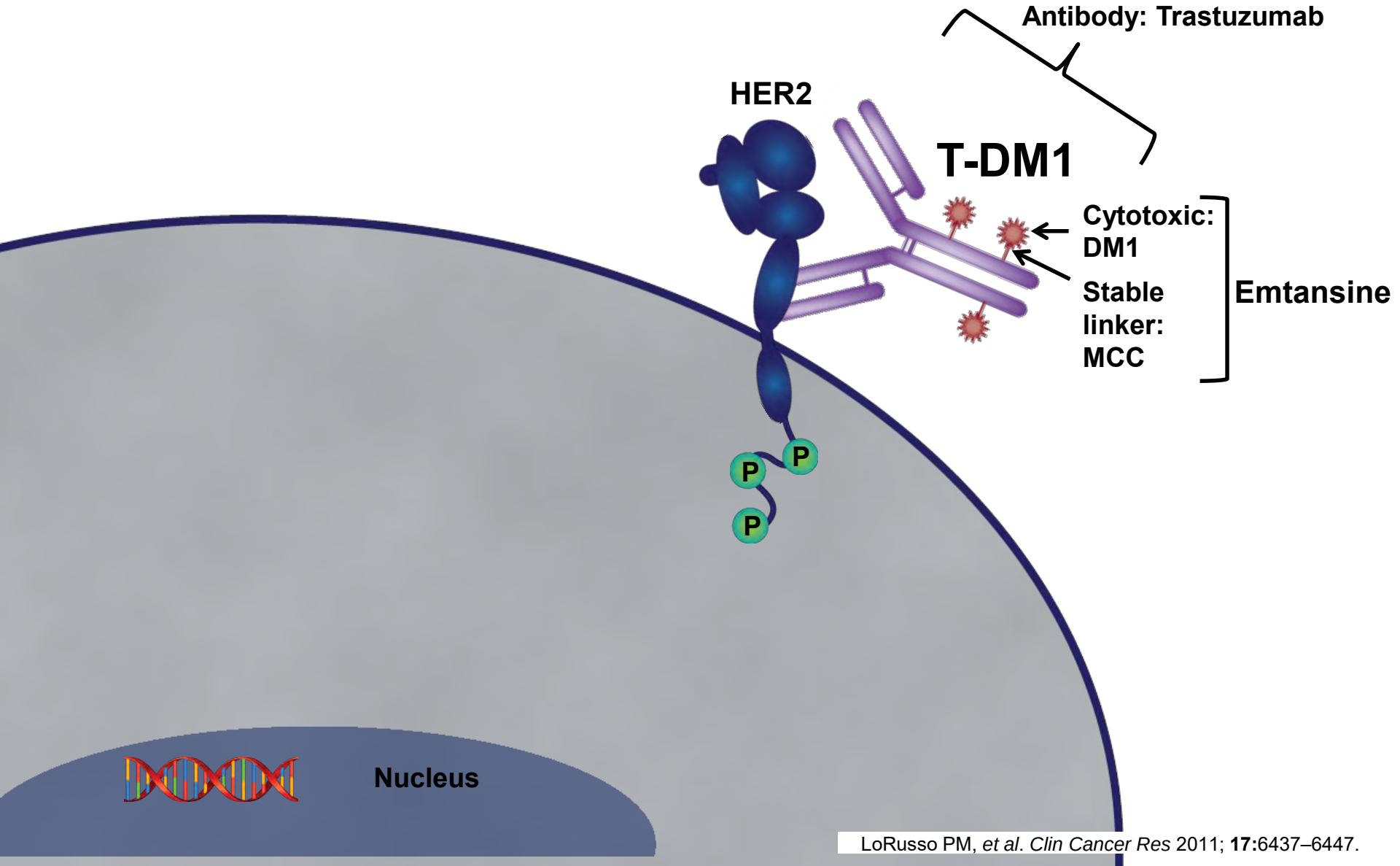
In vitro DM1

- 25-270 fold more potent than paclitaxel
- 180-4000 fold more potent than doxorubicin

Lewis Phillips Cancer Res 2008

Mechanism of action

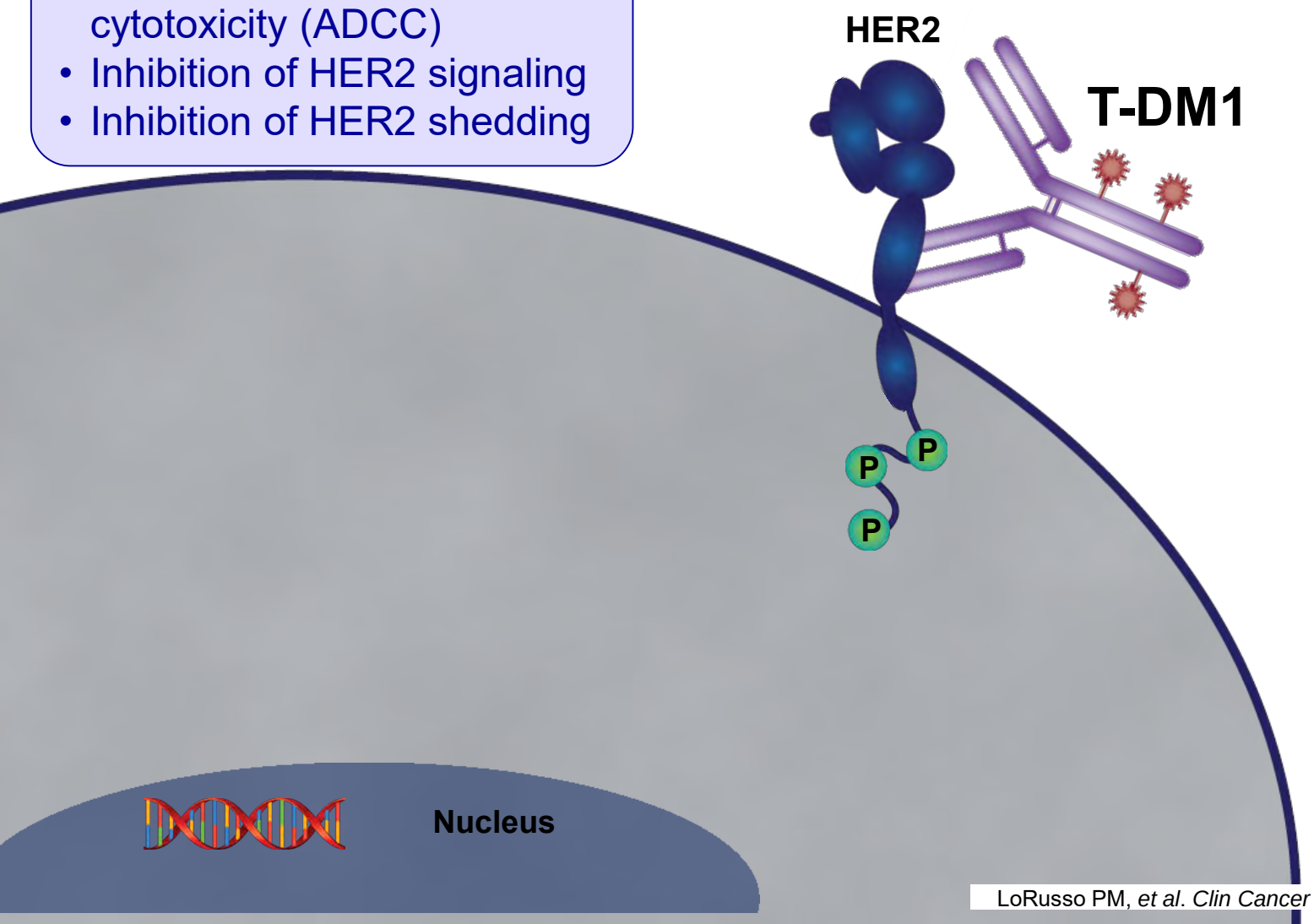
T-DM1 is a novel ADC that targets HER2



LoRusso PM, *et al. Clin Cancer Res* 2011; **17**:6437–6447.

Mechanism of action
T-DM1 is a novel ADC that targets HER2

- Antibody-dependent cellular cytotoxicity (ADCC)
- Inhibition of HER2 signaling
- Inhibition of HER2 shedding



LoRusso PM, *et al*. *Clin Cancer Res* 2011; **17**:6437–6447.

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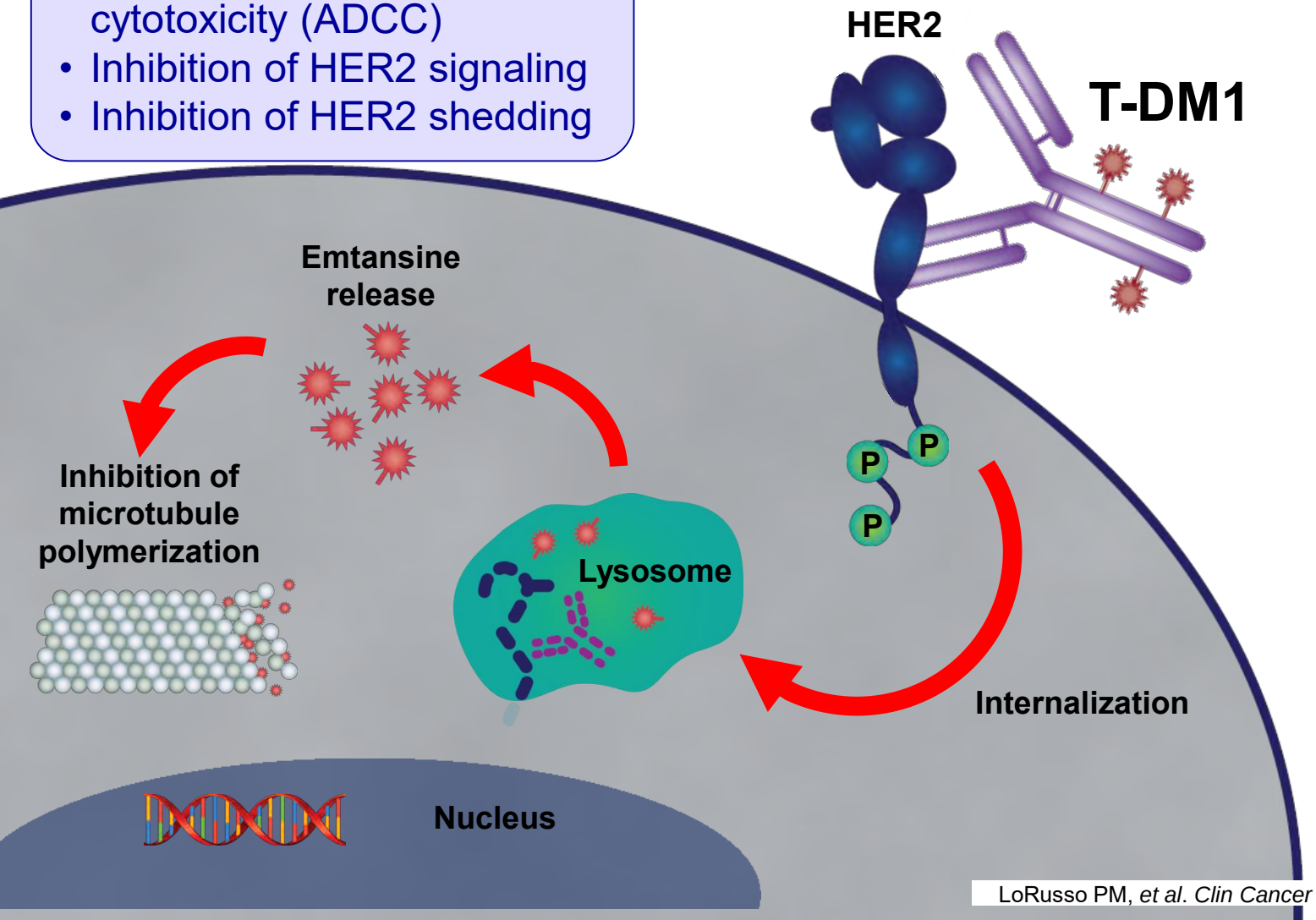

LoRusso PM, *et al. Clin Cancer Res* 2011; **17**:6437–6447.

Etudes de Phase I et Phase II

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T-DM1 Phase I
Schémas: hebdomadaire et toutes les 3 semaines

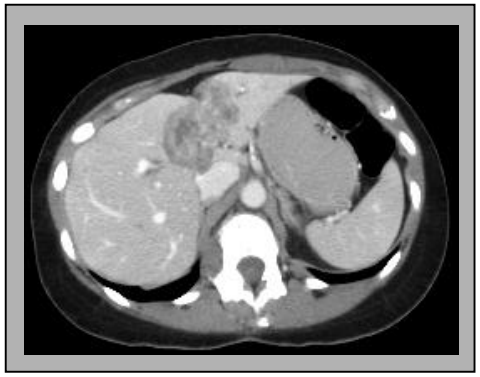
Toxicité

- Toxicité dose-limitante: thrombopénie transitoire
- Effets secondaires Grade 1-2: élévation transaminases, fatigue et anémie
- Absence de nausée, vomissements, diarrhée, alopécie ou neuropathie Grade ≥2

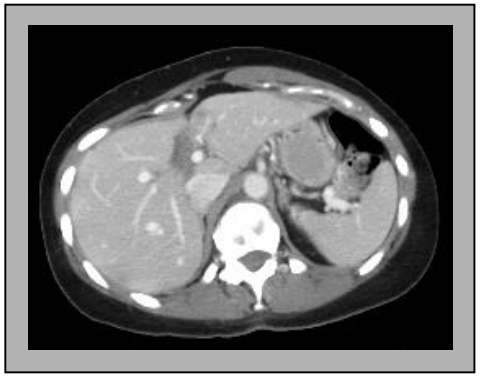
Activitée

- Schéma 3-sem : RO 44%
- Hebdomadaire RO 40%

DMT
3,6mg/3 sem



Inclusion



Après 2 cycles

Krop I JCO 2010
Beeram M Cancer 2012

Etudes de Phase II
Activité

	TDM4258g	TDM4374g
	N=112	N=110
Réponse objective RO %	**26 %**	**35%**
Bénéfice clinique, %	**39.3%**	**48.2%**
Durée de réponse (mois)	**9.4**	**9.7**
Survie sans progression	**4.6**	**6.9**
RO HER2+ confirmé rétrospectivement	**32.1%**	**40.3%**

Burris HA JCO 2011, Krop IE JCO 2012

Pharmacocinétique

- Analyse chez 288 patientes traitées par T-DM1
- Demi-vie 3.5 – 4 jours
- Absence d'accumulation significative du T-DM1 dans le schéma toutes les trois semaines
- Taux plasmatique DM1 très bas (<5ng/ml)
- Anticorps anti-T-DM1 détectés 4.5% des patientes (13/286)

Etudes de Phase III en situation métastatique

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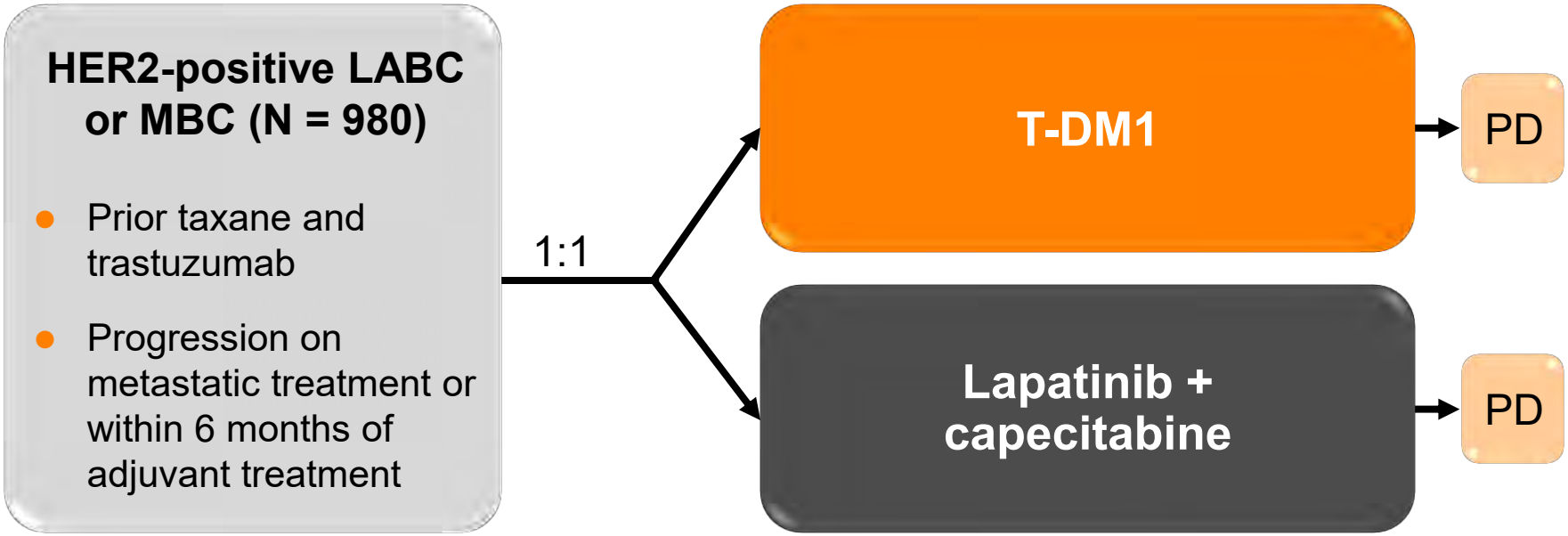
EMILIA: Phase III study of T-DM1 vs. lapatinib plus capecitabine in MBC

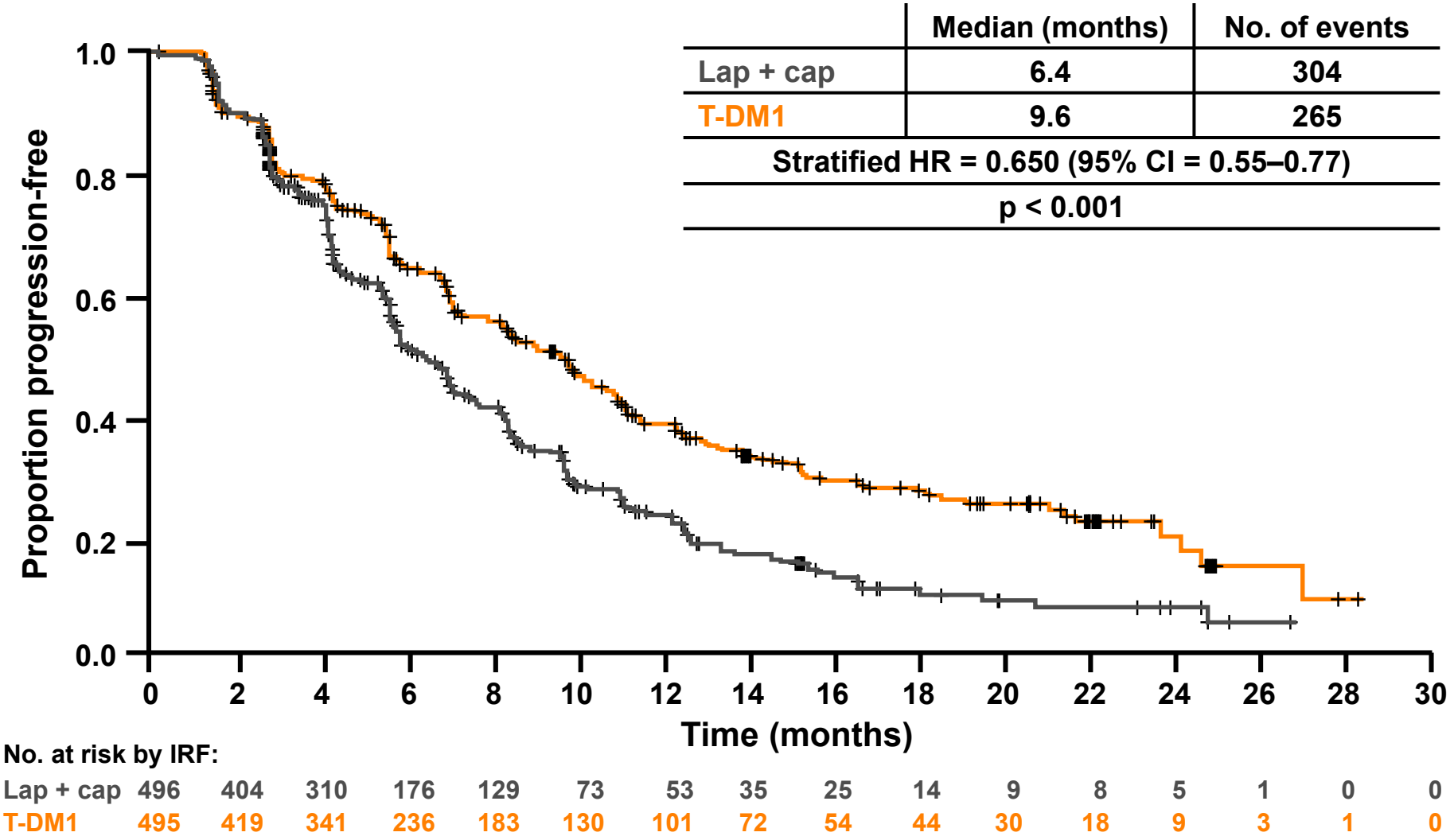


- **Stratification factors:** world region, number of prior chemotherapy regimens for MBC or unresectable LABC, presence of visceral disease
- **Primary endpoints:** PFS by independent review, OS and safety
- **Key secondary endpoints:** PFS by investigator, ORR, DoR

Verma S, *et al. N Engl J Med* 2012; **367:**1783–1791.

EMILIA: PFS was improved with T-DM1 treatment

PFS by IRF



	Median (months)	No. of events
Lap + cap	6.4	304
T-DM1	9.6	265
Stratified HR = 0.650 (95% CI = 0.55–0.77)		
p < 0.001		

No. at risk by IRF:

Lap + cap	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 <0.001)

Cap, capecitabine; IRF, independent review facility; Lap, lapatinib.

Verma S, *et al. N Engl J Med* 2012; **367:**1783–1791.

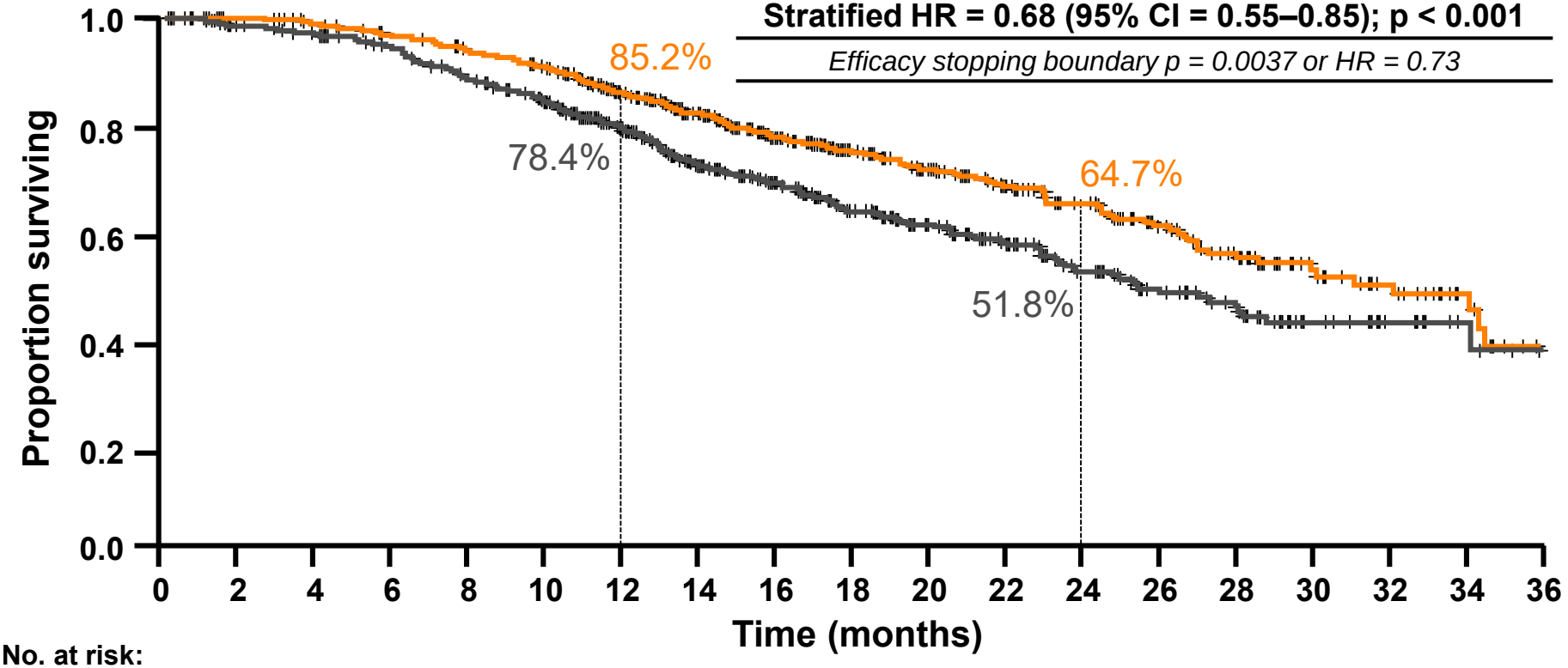
EMILIA: OS was improved with T-DM1 treatment

Confirmatory analysis

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

Stratified HR = 0.68 (95% CI = 0.55–0.85); p < 0.001

Efficacy stopping boundary p = 0.0037 or HR = 0.73



No. at risk:

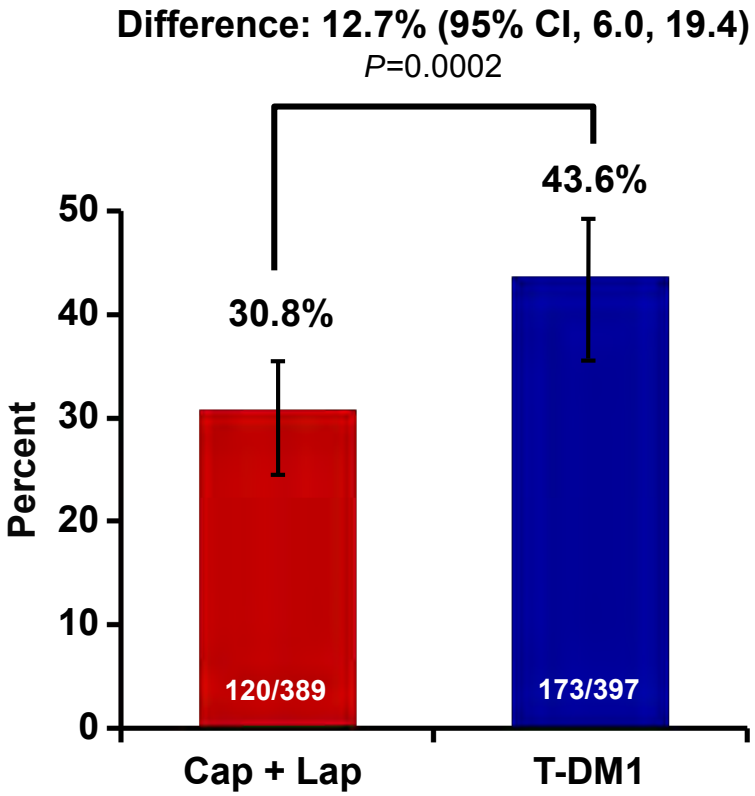
Lap + cap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

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

Verma S, *et al. N Engl J Med* 2012; 367: 1783–1791 (supplementary material available with the publication online); Verma S, *et al.* ESMO 2012 (Abstract LBA12; oral presentation).

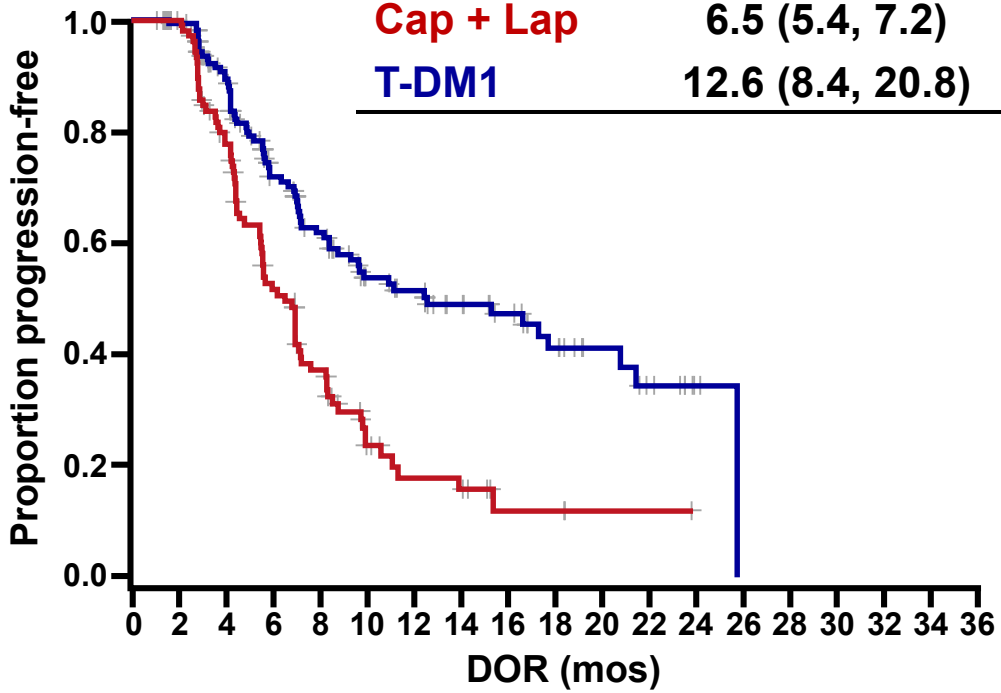
Objective Response Rate (ORR) and Duration of Response (DOR) in Patients with Measurable Disease

ORR



DOR

	Median, mos (95% CI)
Cap + Lap	6.5 (5.4, 7.2)
T-DM1	12.6 (8.4, 20.8)



No. at risk:

Cap + Lap	120	105	77	48	32	14	9	8	3	3	1	1	0	0	0	0	0	0	0
T-DM1	173	159	126	84	65	47	42	33	27	19	12	8	2	0	0	0	0	0	0

EMILIA: Overall incidence of AEs (grade ≥3) was lower in the T-DM1 arm

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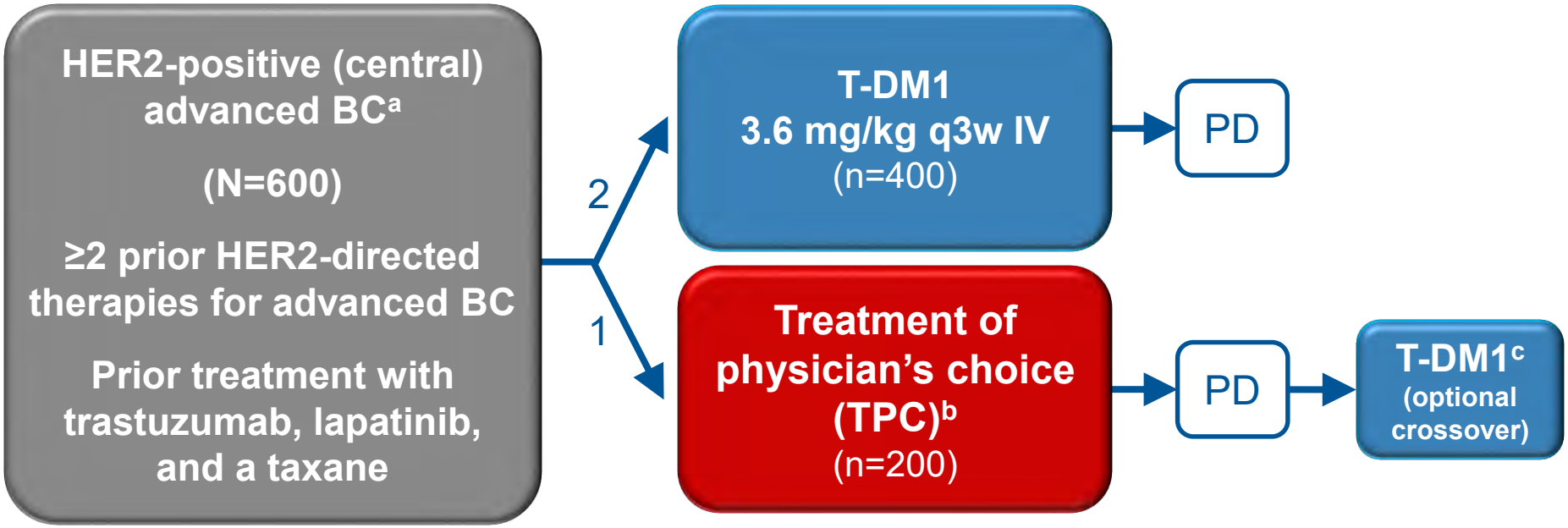
	Lap + cap (n = 488)	T-DM1 (n = 490)
All-grade AE, n (%)	477 (97.7)	470 (95.9)
Grade ≥3 AE, n (%)	278 (57.0)	200 (40.8)
AEs leading to treatment discontinuation (for any study drug), n (%)	52 (10.7)	29 (5.9)
AEs leading to death within 30 days of last dose of study drug, n (%)*	4 (0.8)	1 (0.2)

* Lap + cap: coronary artery disease, multi-organ failure, coma, and hydrocephalus; T-DM1: metabolic encephalopathy

Verma S, *et al*. *N Engl J Med* 2012; **367:**1783–1791;
Verma S, *et al*. ESMO 2012 (Abstract LBA12; oral presentation).

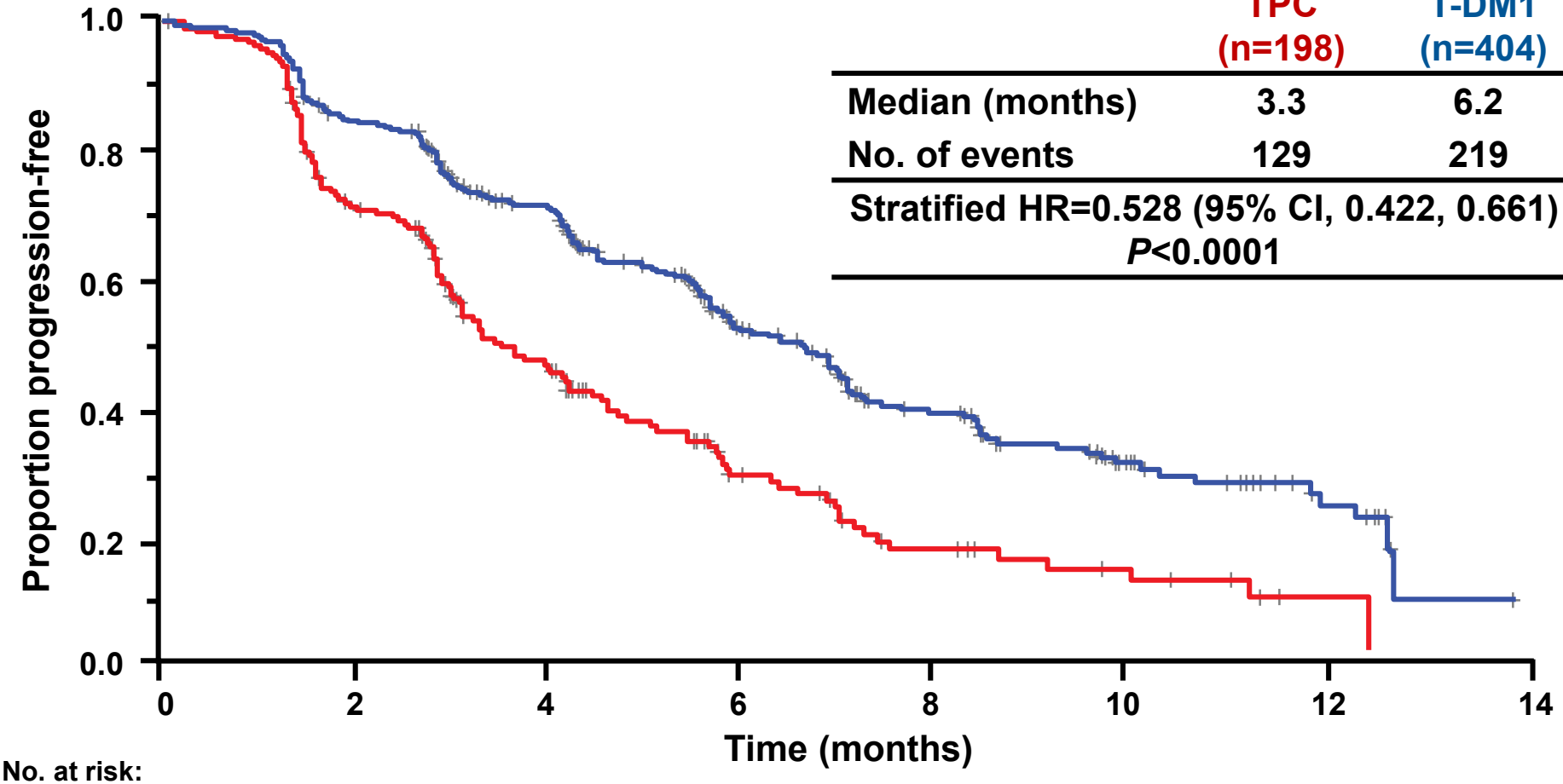
TH3RESA Study Schema



- **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.

PFS by Investigator Assessment



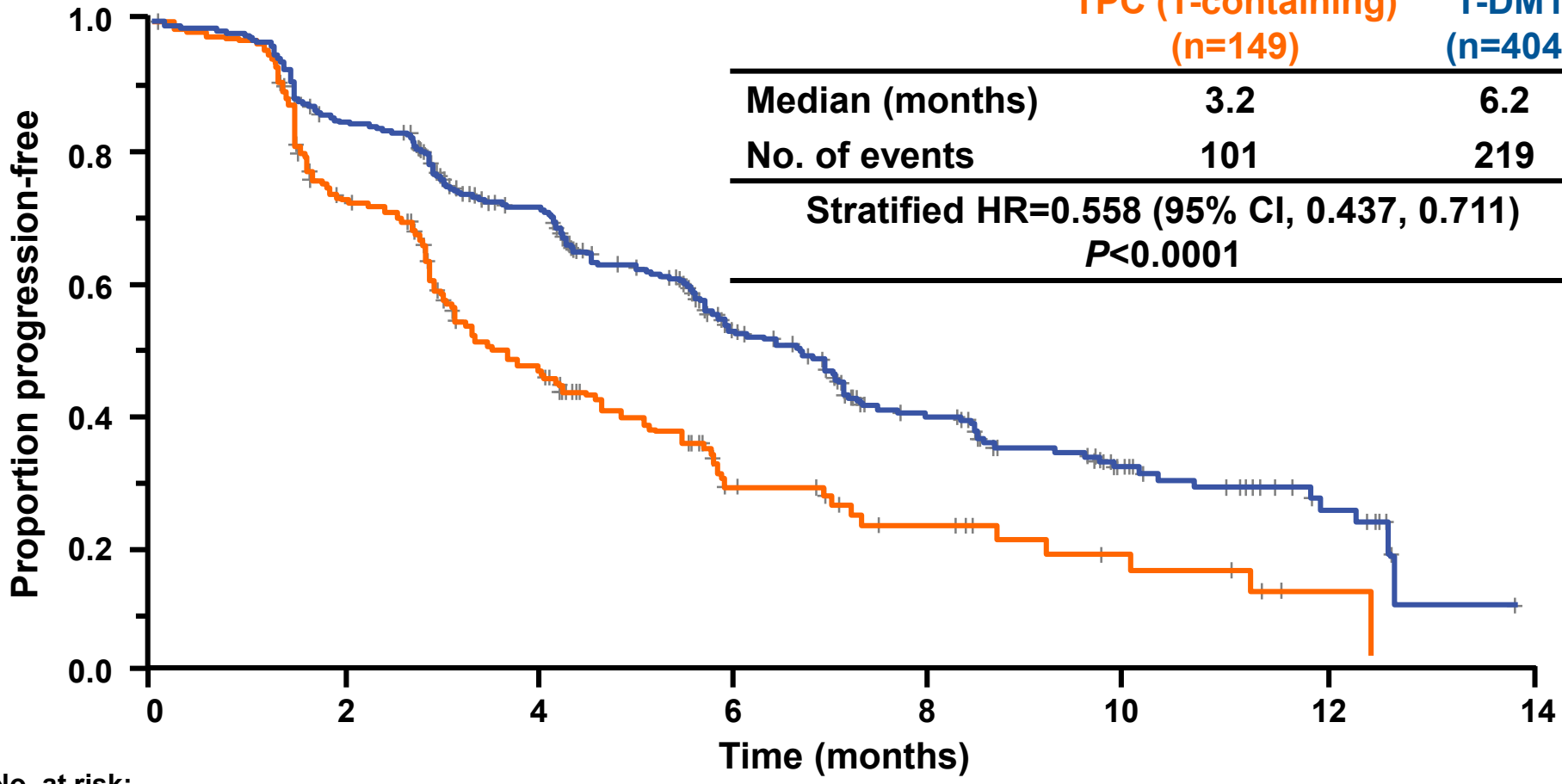
	TPC (n=198)	T-DM1 (n=404)
Median (months)	3.3	6.2
No. of events	129	219

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

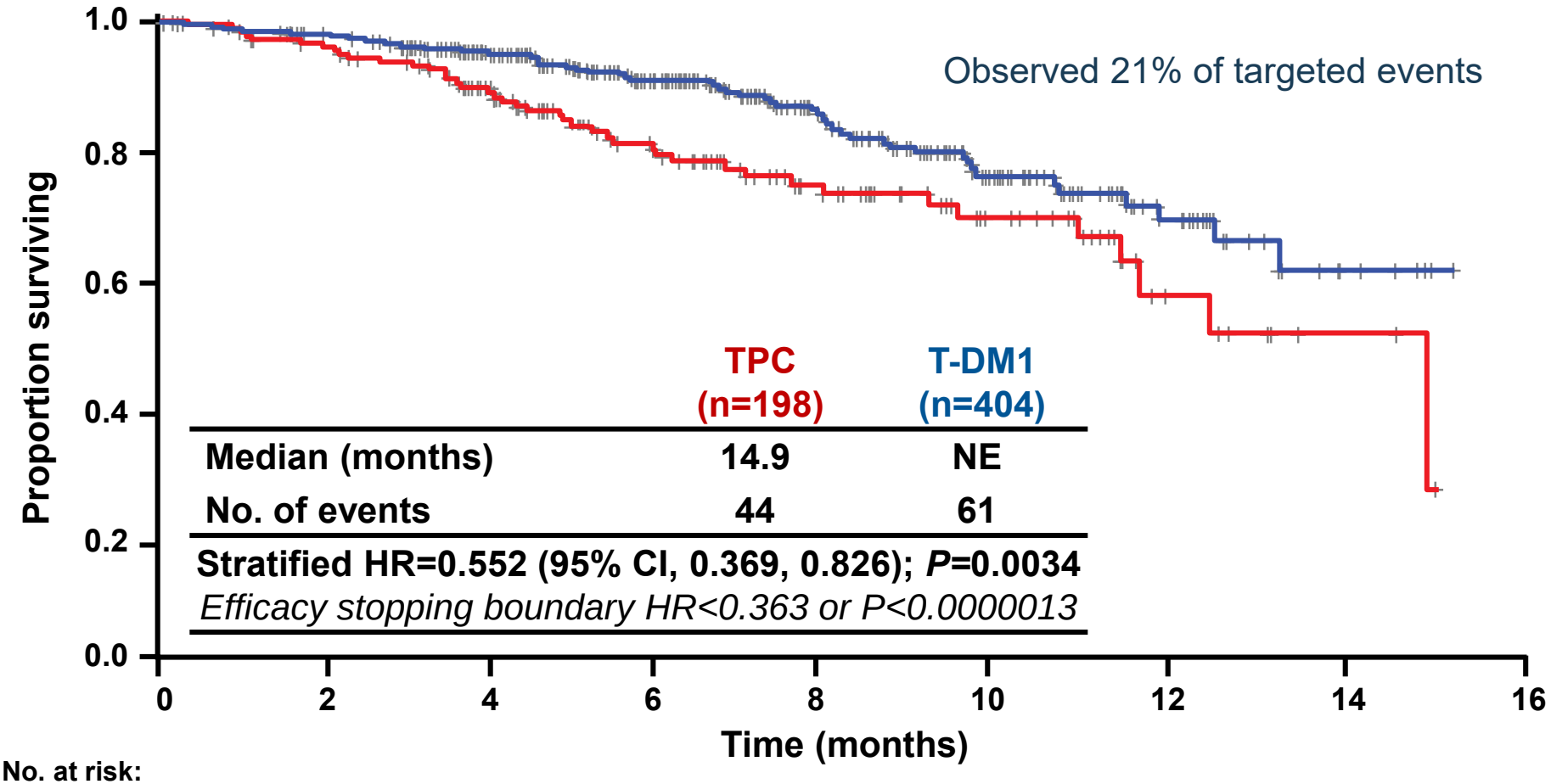
Stratified HR=0.558 (95% CI, 0.437, 0.711)
P<0.0001

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).

First Interim OS Analysis

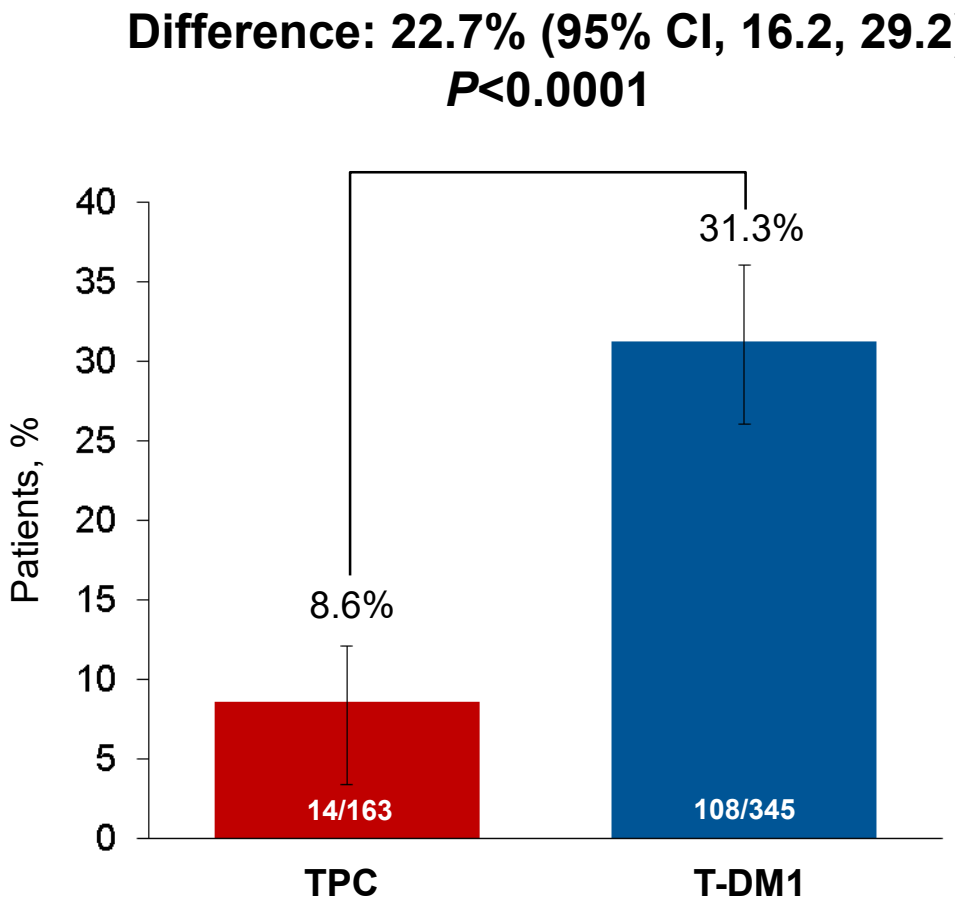


No. at risk:

TPC	198	169	125	80	51	30	9	3	0
T-DM1	404	381	316	207	127	65	30	7	0

44 patients in the TPC arm received crossover T-DM1 treatment after documented progression.
Unstratified HR=0.57 (*P*=0.004).

ORR in Patients With Measurable Disease
By Investigator Assessment



T-DM1 en première ligne métastatique

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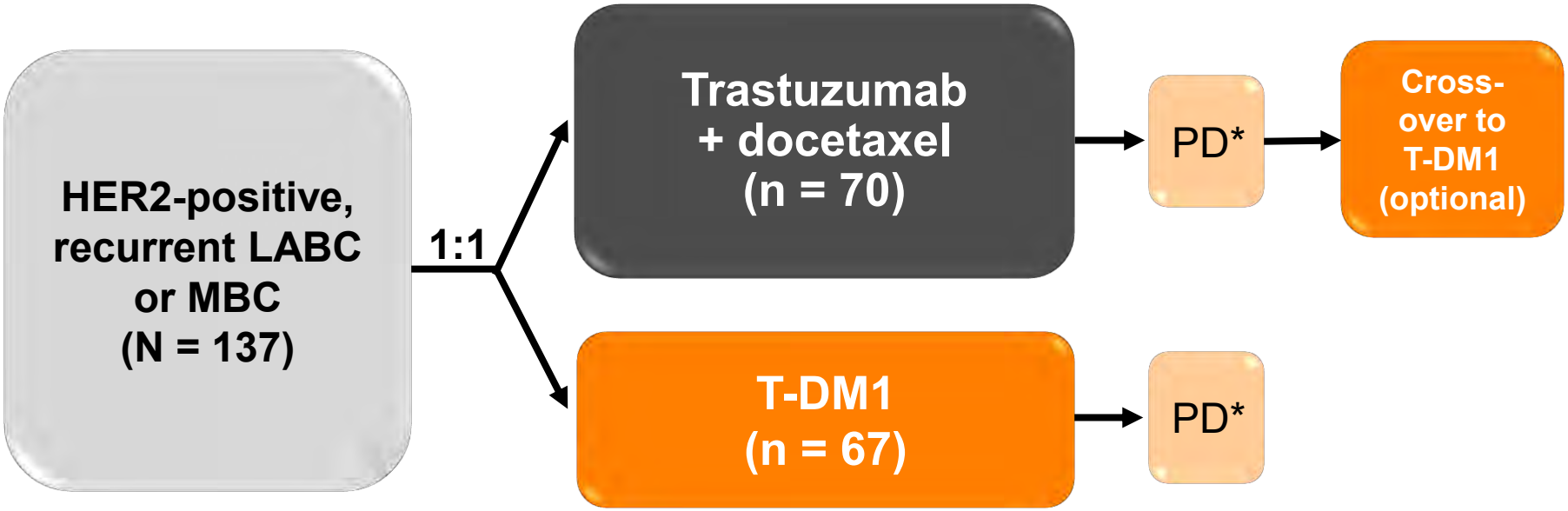
TDM4450g: First randomised, open-label, Phase II, hypothesis-generating study of T-DM1 in 1st-line MBC



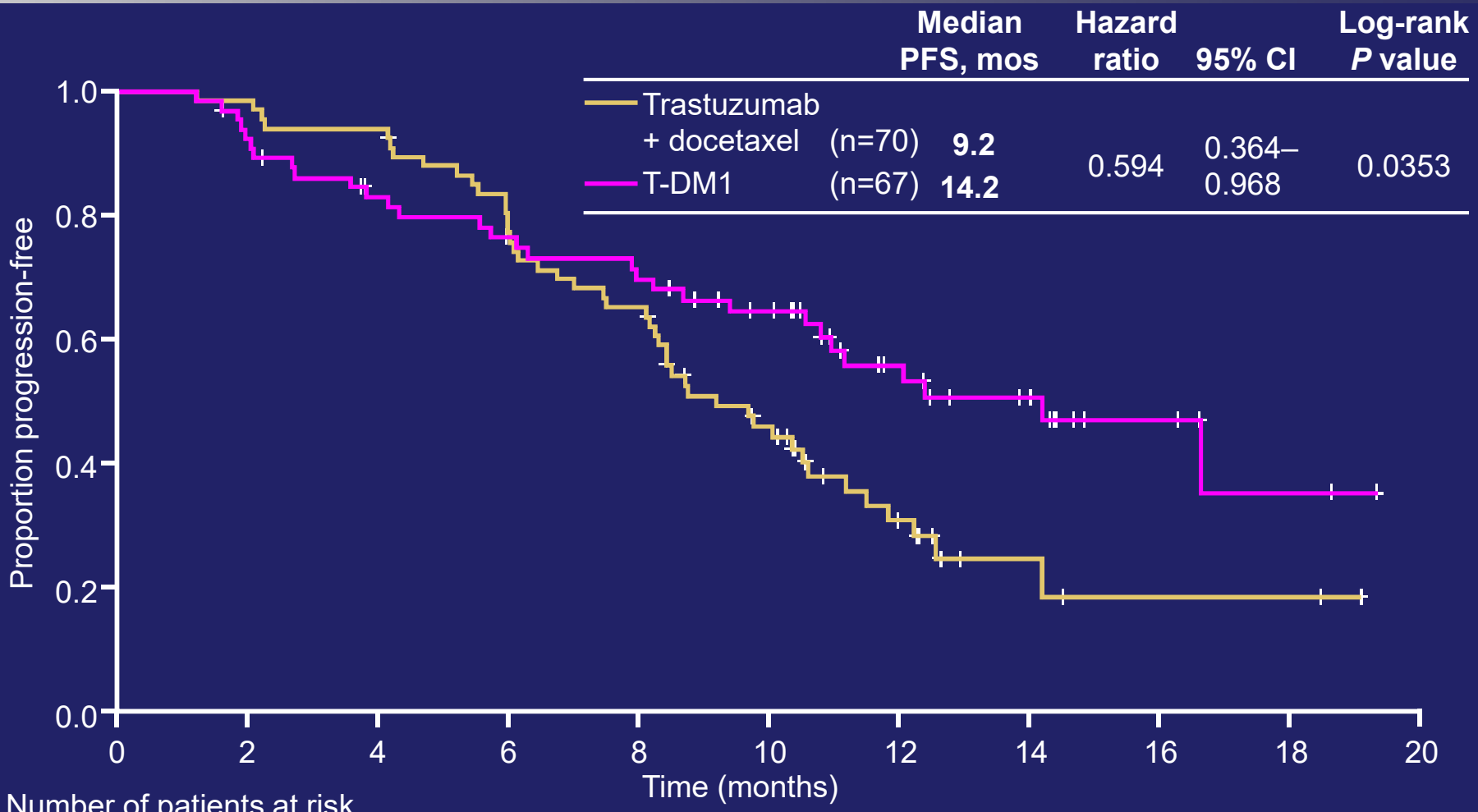
- **Stratification factors:** world region, prior adjuvant trastuzumab therapy, disease-free interval
- **Primary endpoints:** PFS by INV, and safety
- **Key secondary endpoints:** OS, ORR, DoR, CBR and quality of life

* Patients were treated until PD or unacceptable toxicity
DoR, duration of objective response; INV, investigator; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; ORR, objective response rate; PD, progressive disease.

Hurvitz SA, *et al*. *J Clin Oncol* 2013; **31**:1157–1163.

Progression-Free Survival by Investigator

Randomized Patients

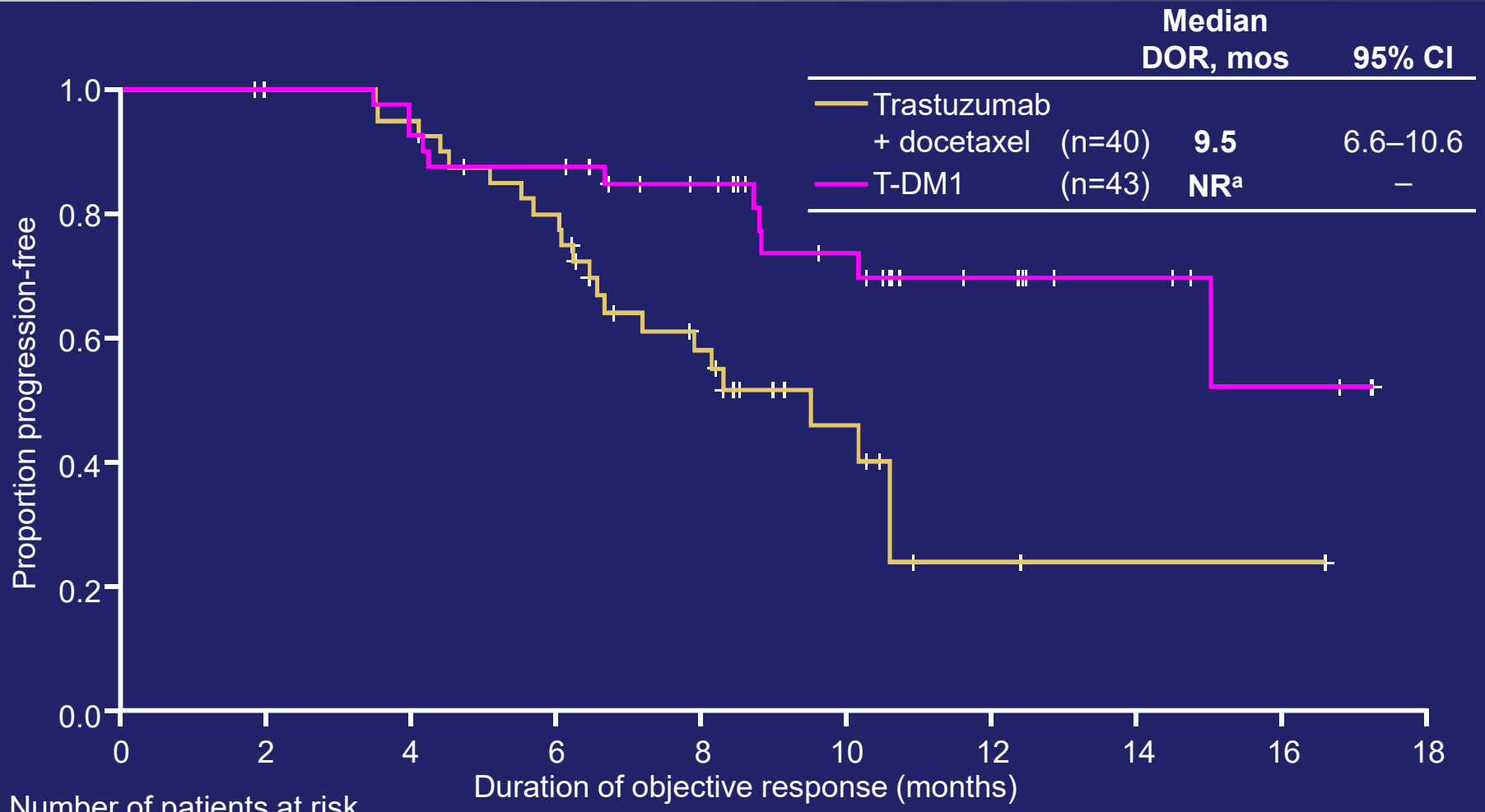


Hazard ratio and log-rank *P* value were from stratified analysis.

Hurwitz ESMO 20111

Duration of Response by Investigator

Patients with Measurable Disease at Baseline with an Objective Response



Number of patients at risk

T+D	40	40	38	32	19	8	2	1	1	0
T-DM1	43	41	38	33	27	19	12	6	3	0

Kaplan-Meier estimates are shown.

[a]NR, not reached; longer follow-up is needed to estimate the duration of response in the T-DM1 arm

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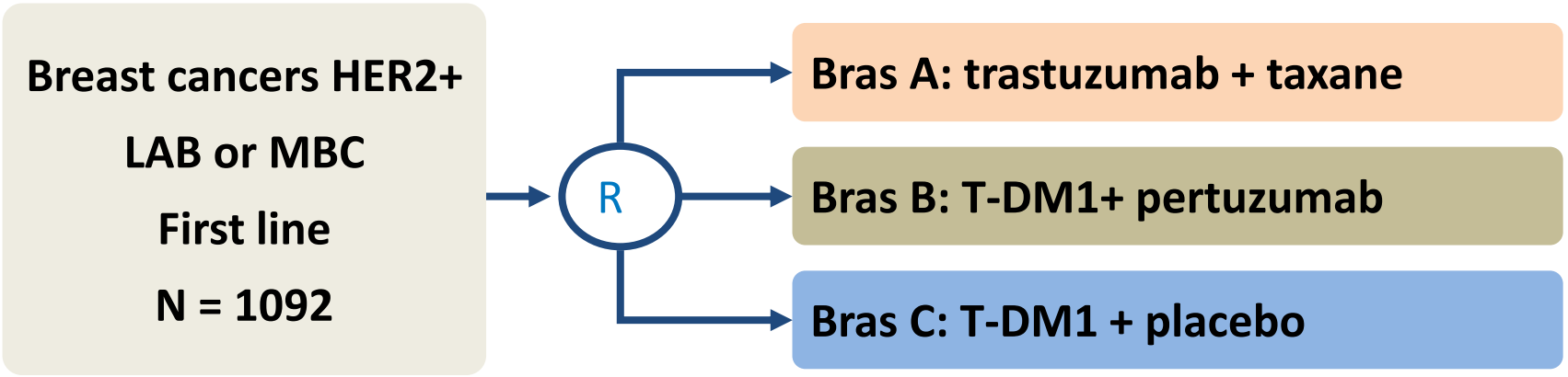

Primary objectives

- DFS
- Tolerability

Secondary objectives: ORR, Overall survival, clinical benefit, duration of response

Tolérance

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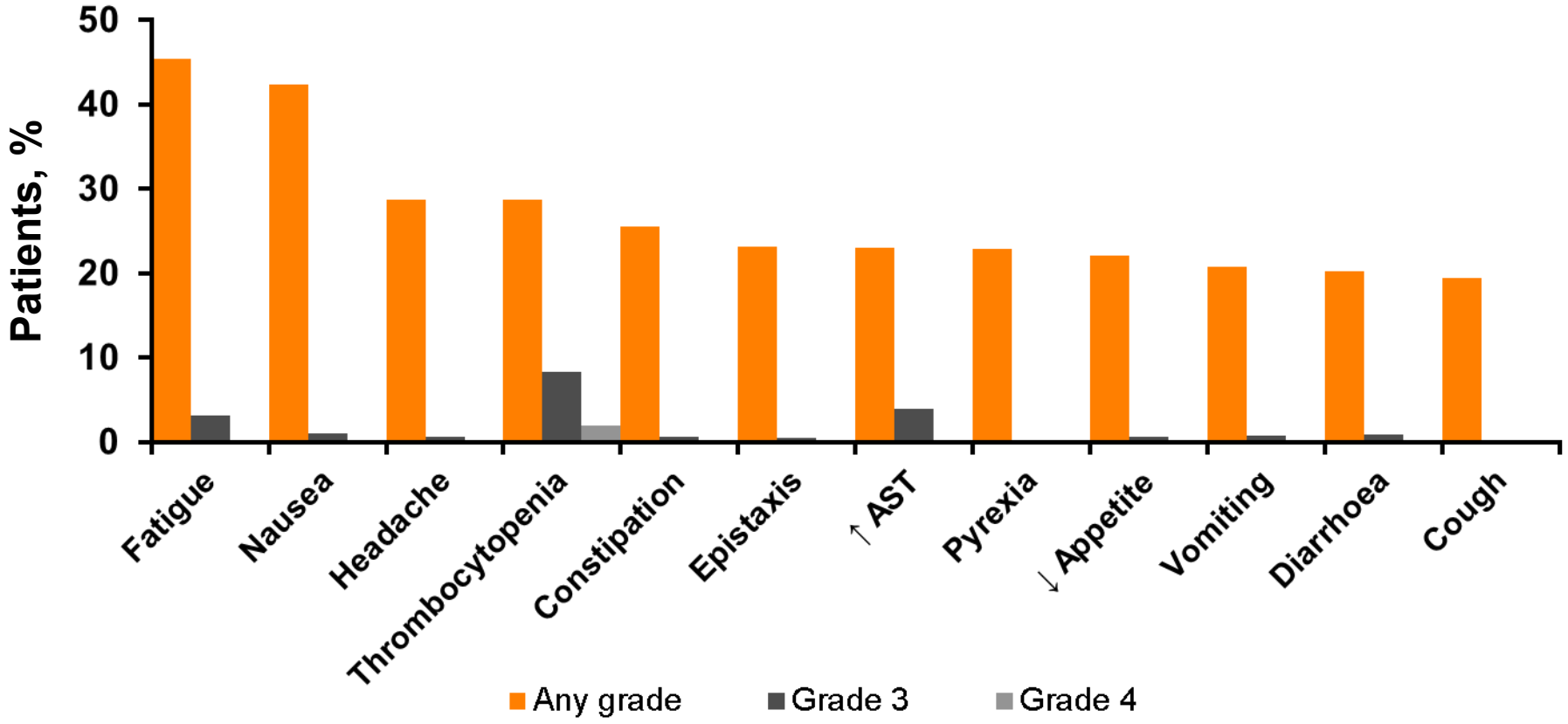
Overview of T-DM1 safety

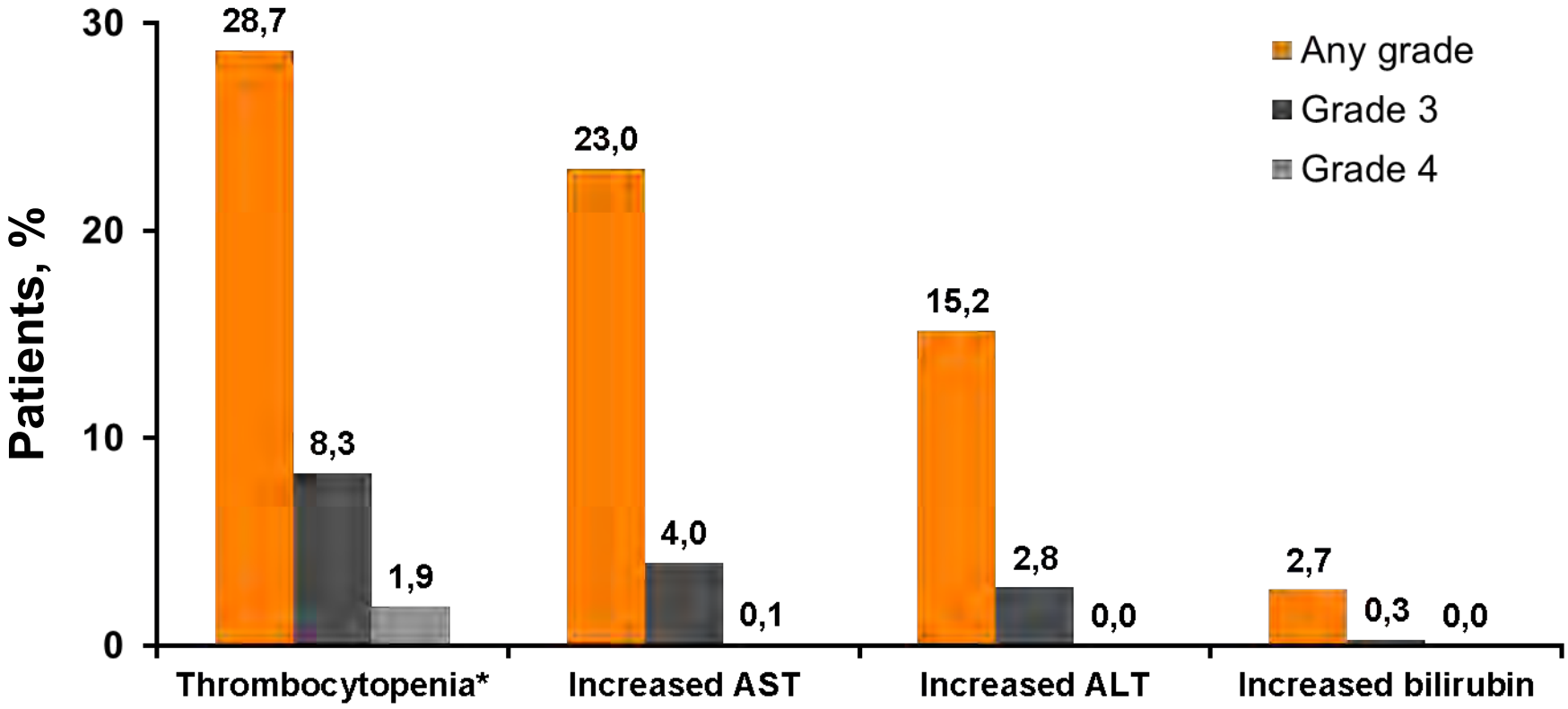
Integrated safety analysis from seven clinical trials (AEs with incidence ≥20%)



Data included from: EMILIA, TDM4450g/BO21976, TDM4374g, TDM4258g, TDM4688g, TDM3569g and TDM4529g/BO25430. N = 882
ALT, alanine transaminase; AST, aspartate transaminase

Diéras V, *et al*. J Clin Oncol 2014

Thrombocytopenia and hepatotoxicity
Combined incidence in seven clinical trials



* Six (0.7%) patients had both grade 3/4 thrombocytopenia events and grade 3/4 haemorrhage events, but these did not occur concurrently in any patients.
Data included from: EMILIA, TDM4450g/BO21976, TDM4374g, TDM4258g, TDM4688g, TDM3569g and TDM4529g/BO25430. N = 882

Diéras V, *et al*. J Clin Oncol 2014

Tolérance cardiaque: *incidence dans 7 essais cliniques*

- **4 patientes (0.5%) qvec LVEF <40%[1]**
  - Sixteen (1.8%) patients had an LVEF decline of ≥15 percentage points from baseline to below 50%[1]
- **A total of three (0.3%) patients discontinued T-DM1 because of cardiac disorders:**
  - One atrial fibrillation, one left ventricular dysfunction, one decreased ejection fraction[1]
- **T-DM1 safety in patients will be further explored in the global safety study, KAMILLA[2]**

Diéras V, *et al*. J Clin Oncol 2014

* Standardised MedDRA query (SMQ) term “cardiac failure”
LVEF, left ventricular ejection fraction.

Combinations

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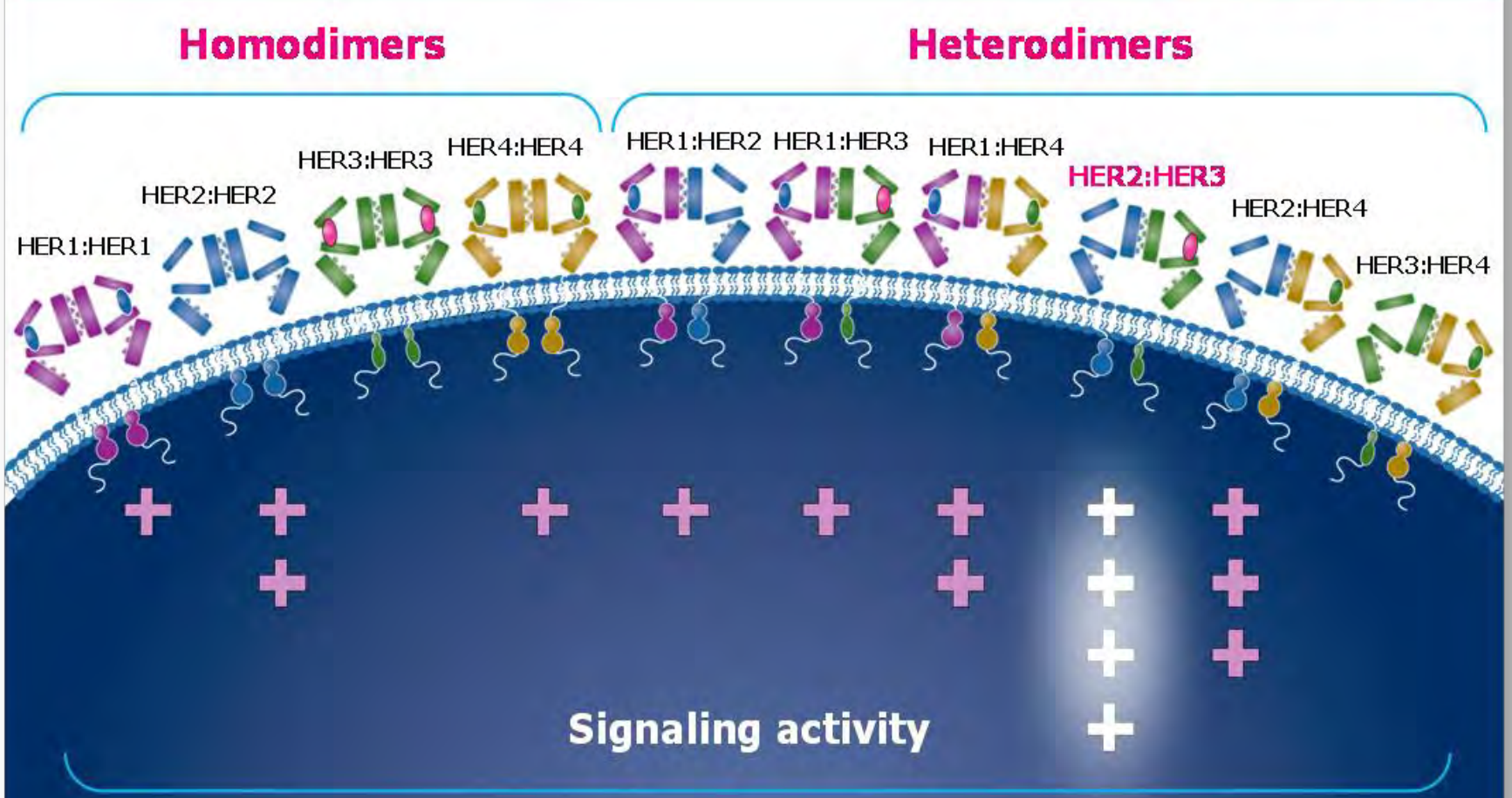
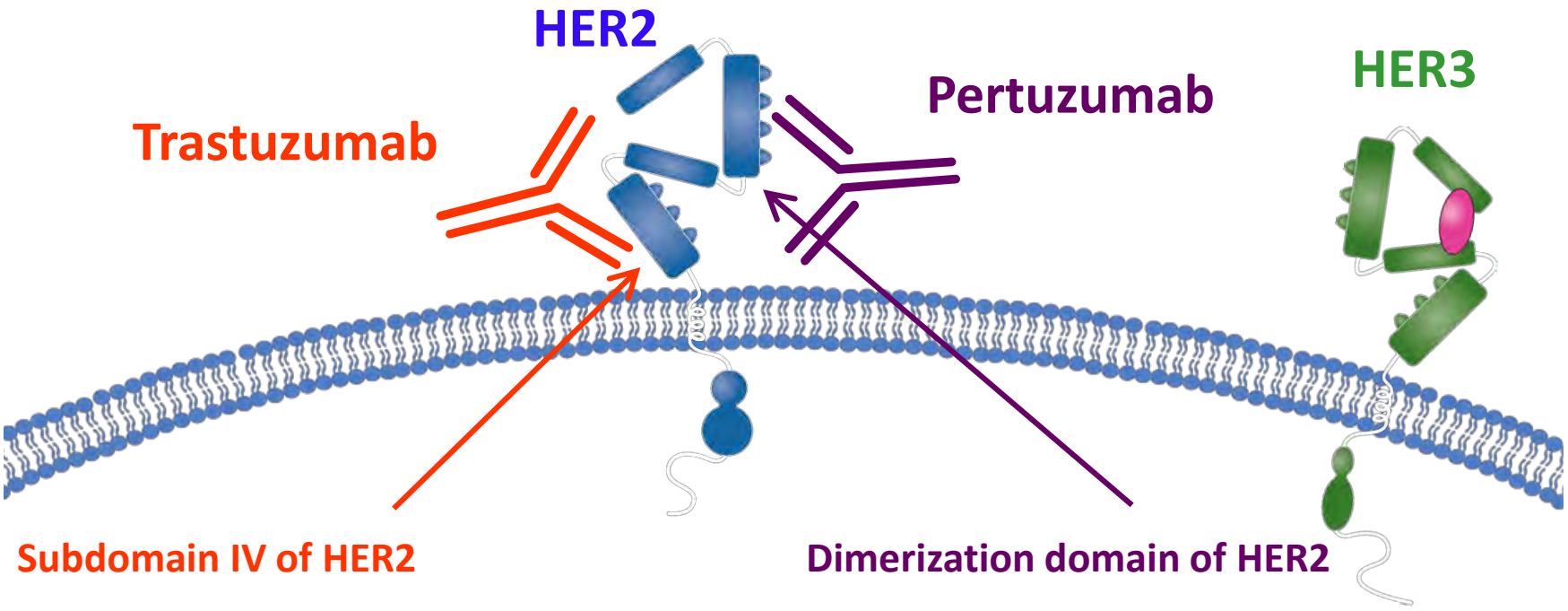
HER2:HER3 dimers have the strongest mitogenic signaling



Tzahar et al. Mol Cell Biol. 1996;16:5276-5287.

Binding on different epitopes and synergism of the two antibodies



Subdomain IV of HER2

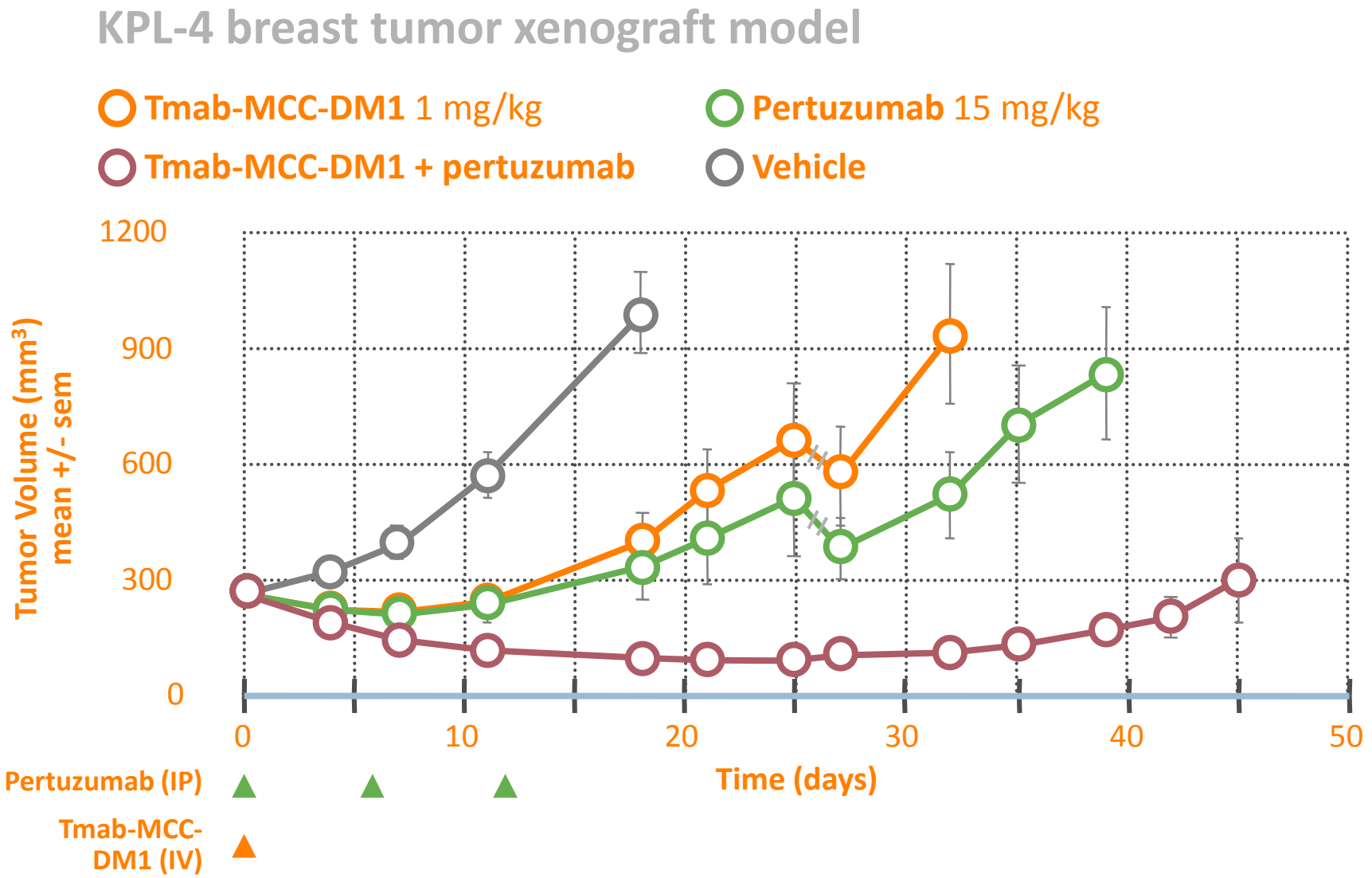
- Trastuzumab disrupts ligand-independent HER2-HER3-PI3K complex
- Trastuzumab prevents HER2 receptor shedding
- Trastuzumab blocks HER2 signaling and flags cells for destruction by the immune system via ADCC

Dimerization domain of HER2

- Pertuzumab prevents ligand-induced HER2-HER3 dimerization
- Pertuzumab does not prevent HER2 receptor shedding
- Flags cells for destruction by the immune system via ADCC

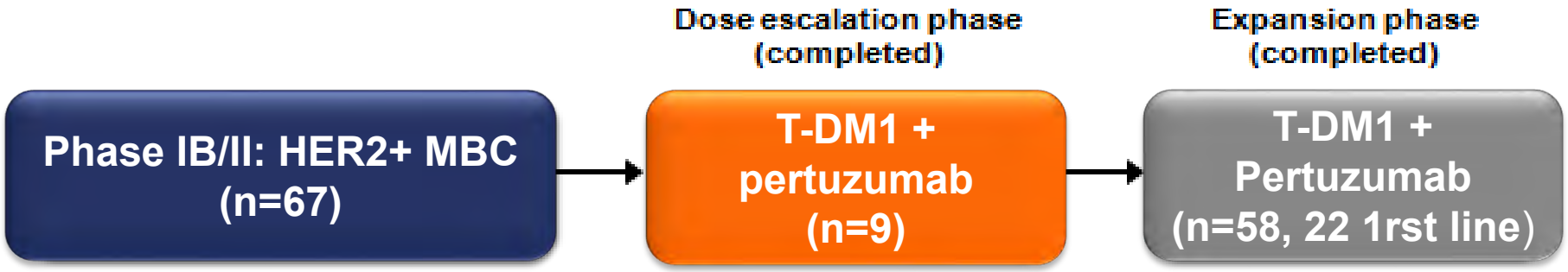
Junttila et al. Cancer Cell. 2009;15:429-440; Hynes et al. Nat Rev Cancer. 2005;5:341-354. Rowinsky. Annu Rev Med. 2004;55:433-457.

T-DM1 in combo with anti-HER2 MAb pertuzumab



Lewis Phillips GD CCR 2013

T-DM1 Pertuzumab
Etude de PHASE I/II



Primary endpoints

- Safety
- ORR by RECIST 1.0

Secondary endpoints

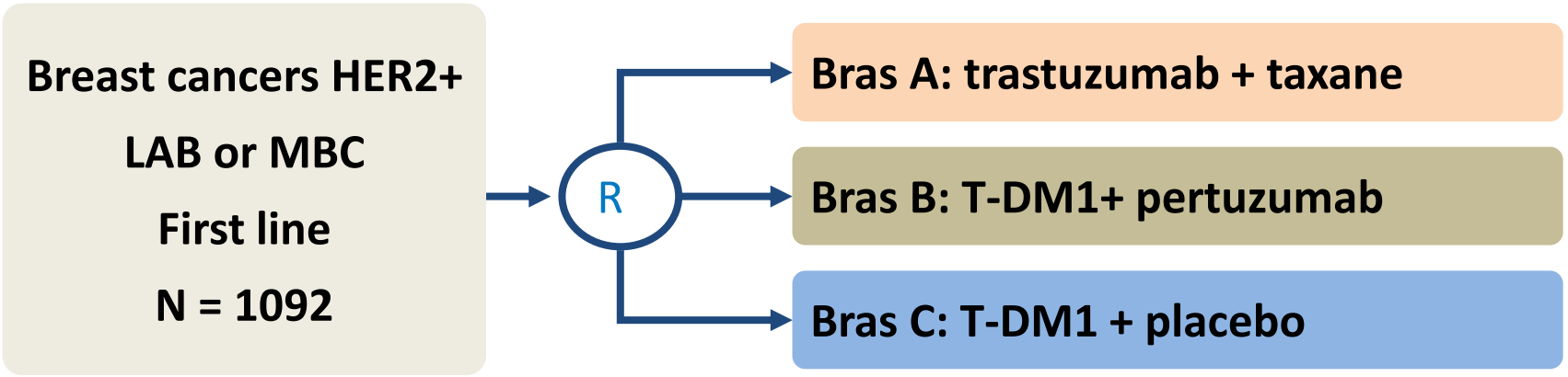
- PFS
- DoR

Results	Total, n (%) (n=28)
PR	10 (35.7)
SD	13 (46.4)
PD	4 (14.3)
Missing	1 (3.6)

Encouraging safety and tolerability profile

Miller K Diéras V J Clin Oncol 2013

MARIANNE



Primary objectives

- DFS
- Tolerability

Secondary objectives: ORR, Overall survival, clinical benefit, duration of response

Combinations with cytotoxic agents

- Rational
  - Enhanced activity
  - Heterogeneity HER2 disease
  - Blood brain barrier
- Taxane + T-DM1
  - Paclitaxel + T-DM1
  - Docetaxel + T-DM1
- Capecitabine + T-DM1
- Phase Ib/II ongoing

Perspectives

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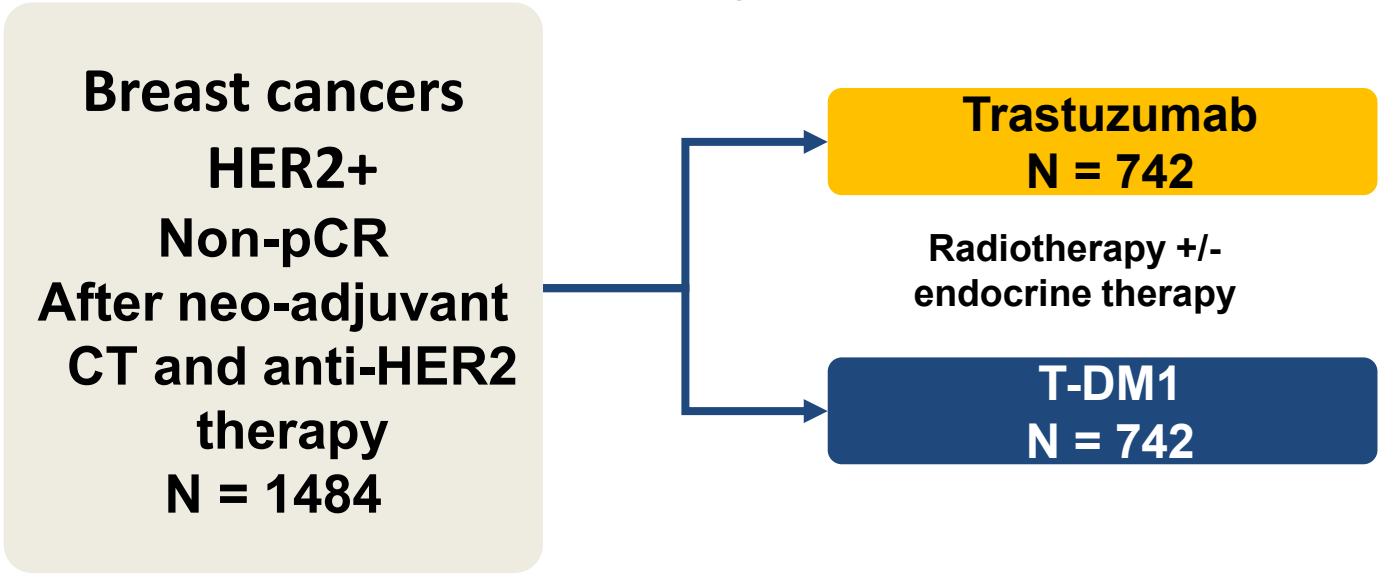
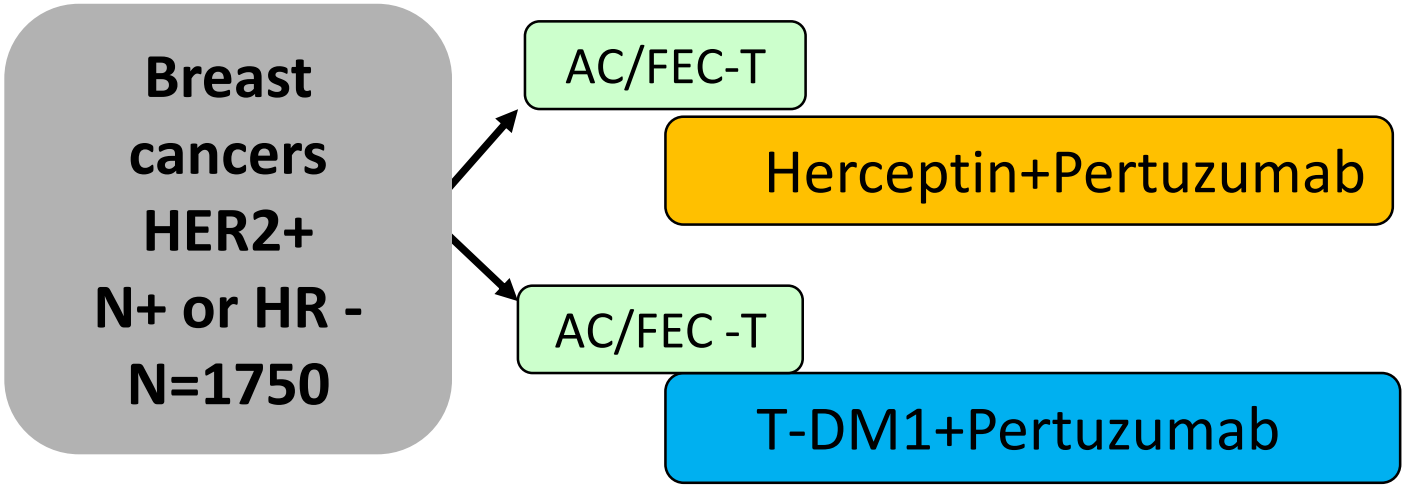
BO27938 / KATHERINE



- **Primary objective:** IDFS
- **Secondary objectives :**DFS , overall survival, cardiac tolerability, tolerance,

BO28407 / KAITLIN : phase III adjuvant



Primary objective: DFS

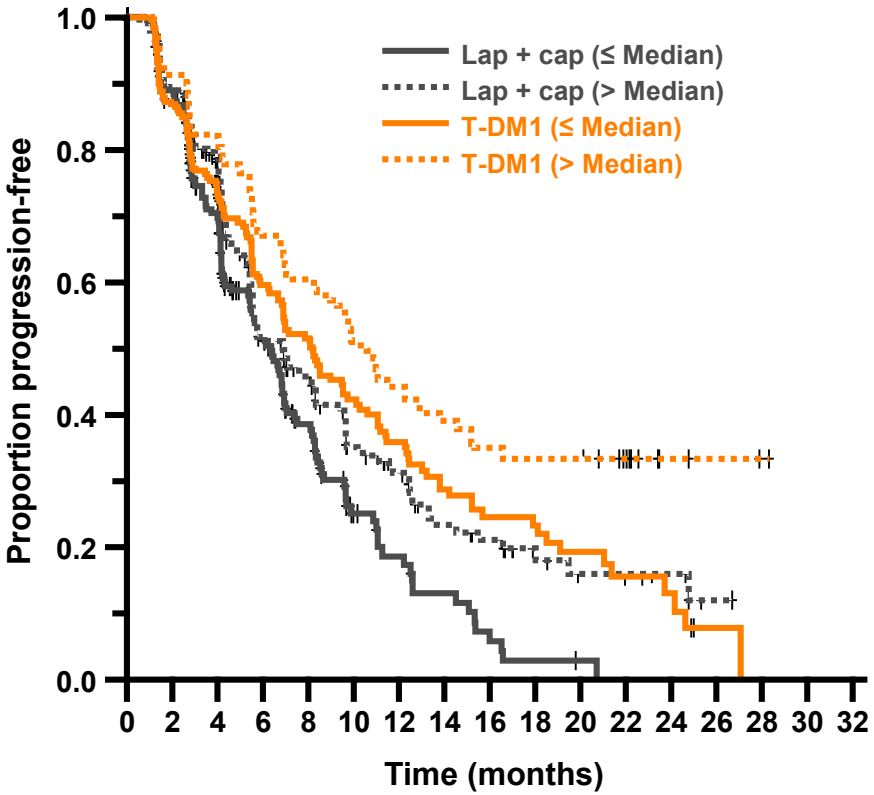
Secondary objective: OS, tolerance

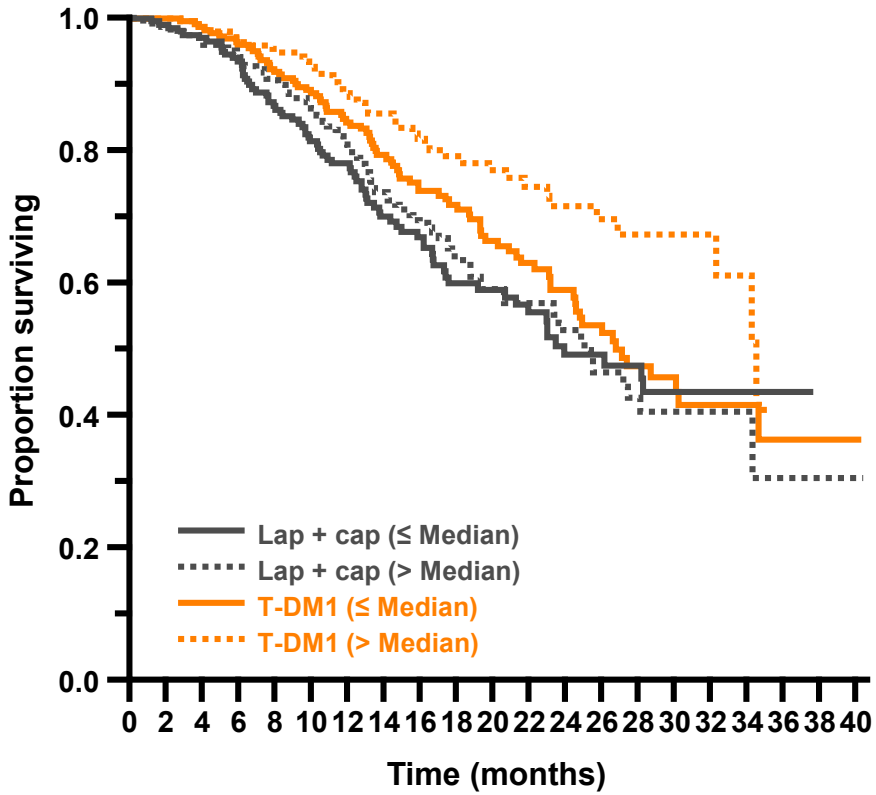
AC= adriamycine/cyclophosphamide
FEC = 5FU/épirubicine/cyclophosphamide
T = docetaxel Q3W ou paclitaxel QW

Biomarkers and mechanisms of resistance

- Predictive biomarkers ?
  - Exploratory study in EMILIA
- Mechanisms of resistance ?
  - Not associated with PI3K mutation
  - Loss HER2 expression
  - Up regulation drug efflux MDR1
  - RTK ligands
- Biopsies

EMILIA: Tumours expressing high HER2 mRNA may derive greater PFS/OS benefit compared to those with low HER2 mRNA expression





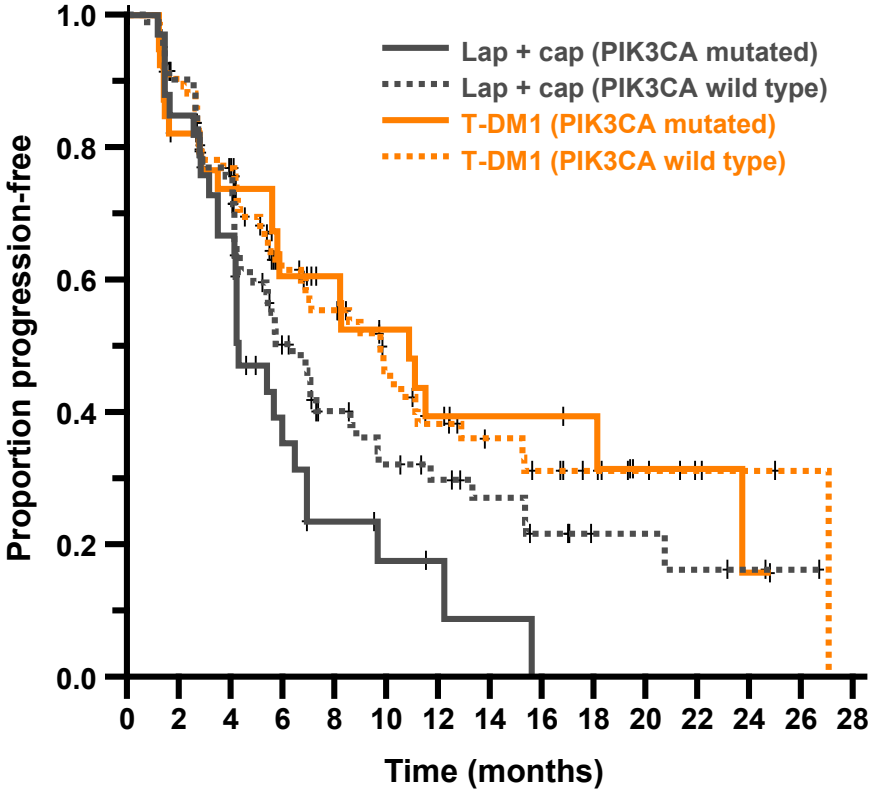
PFS	Lap + cap		T-DM1			
HER2 median mRNA conc. ratio = 13.3	n	Median (months)	n	Median (months)	Hazard ratio[a]	95% CI
≤ Median	204	6.4	230	8.2	0.64	0.50–0.82
> Median	235	6.9	197	10.6	0.65	0.50–0.85

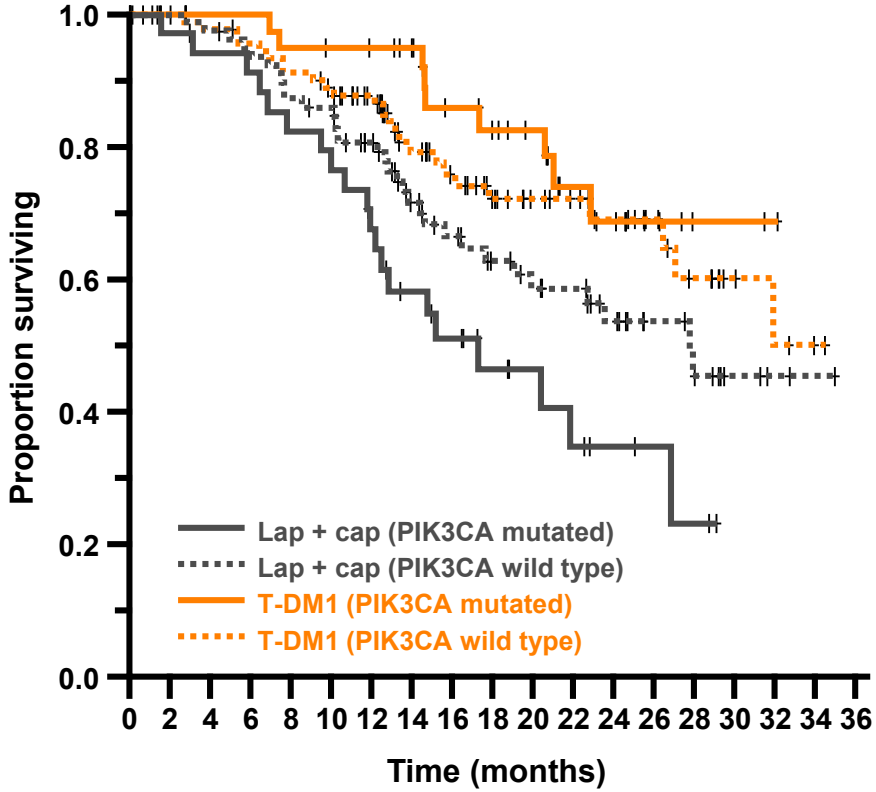
OS	Lap + cap		T-DM1			
HER2 median mRNA conc. ratio = 13.3	n	Median (months)	n	Median (months)	Hazard ratio[a]	95% CI
≤ Median	204	23.7	230	26.5	0.80	0.59–1.09
> Median	235	24.8	197	34.1	0.53	0.37–0.76

[a]Hazard ratios are based on unstratified analyses.

Baselga J, *et al*. AACR 2013 (Abstract LB-63).

EMILIA: Patients with PIK3CA mutations had worse outcomes in the lap + cap arm than those with wild type PIK3CA





PFS	Lap + cap		T-DM1			
PIK3CA mutation status	n	Median (months)	n	Median (months)	Hazard ratio[a]	95% CI
Mutated	39	4.3	40	10.9	0.45	0.25–0.82
Wild type	87	6.4	93	9.8	0.74	0.50–1.10

OS	Lap + cap		T-DM1			
PIK3CA mutation status	n	Median (months)	n	Median (months)	Hazard ratio[a]	95% CI
Mutated	39	17.3	40	NE	0.26	0.12–0.57
Wild type	87	27.8	93	NE	0.68	0.40–1.15

[a]Hazard ratios are based on unstratified analyses.

Baselga J, *et al*. AACR 2013 (Abstract LB-63).

Biomarkers and mechanisms of resistance

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Lewis Phillips GD World ADC Summit 2011

Biomarkers and mechanisms of resistance

- Predicitive biomarkers ?
  - Exploratory study in EMILIA
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Conclusion

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T-DM1

- **Anticorps drogue-conjugué**
- **Etudes précliniques, double mécanisme d'action:**
  - Activité du trastuzumab
  - Distribution sélective de la chimiothérapie dans les cellules tumorales HER2+
- **Etudes de phase III**
  - Amélioration de la survie sans progression (EMILIA , THERESA)
  - Amélioration de la survie globale (EMILIA)
- **Profil de tolérance très favorable**
- **Standard pour les patientes progressant sous trastuzumab et taxanes**
- **Perspectives**
  - Première ligne M+
  - Essais en phase précoce (neo-adjuvant/adjuvant)

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Back-up

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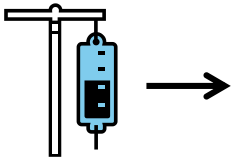
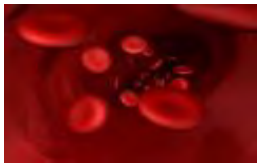
Devenir catabolique du T-DM1





Distribution du T-DM1 dans le plasma

Fixation sur les cellules HER2-positives

Endocytose

Catabolisme lysosomal

La majorité du T-DM1 reste sous forme conjuguée

Faible quantité de DM1 libre est détectée dans le sang

trastuzumab

↓

Protéolyse

↓

Excrétion

Catabolites du DM1

Plasma

↓

DM1

↓

Métabolisme hépatique

↓

Bile, fèces, urine

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Catabolisme du T-DM1 et Métabolisme du DM1

Le T-DM1 est internalisé dans les cellules et subit une protéolyse lysosomale, il est ainsi dégradé en:

Trastuzumab:

- **dégradé par protéolyse**

DM1 (un composant du T-DM1):

- **Suite à l'action pharmacologique (inhibition de la polymérisation des microtubules)**
- **Métabolisé dans le foie: par le cytochrome P450 3A4 (CYP3A4) et moins fréquemment par le cytochrome P450 3A5 (CYP3A5)**
- **N'induit pas et n'inhibe pas le métabolisme médié par le cytochrome P450**
- **Excrétion: majoritairement dans la bile et les fèces (faible élimination dans les urines)**

En conséquence:

Faible exposition systémique au DM1

Pas d'implication significative du cytochrome P450 et par conséquent faible risque d'interactions médicameneuses

L'insuffisance hépatique peut engendrer l'accumulation des métabolites du DM1

Aucun impact de l'insuffisance rénale sur la pharmacocinétique du T-DM1

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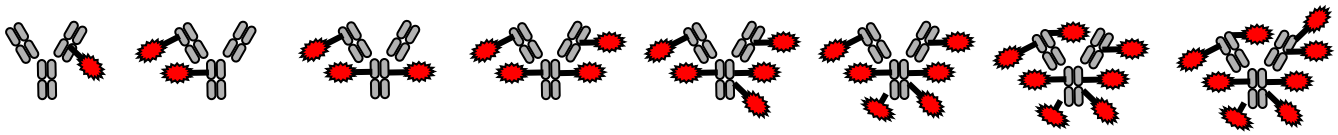
Analytes du T-DM1: Que mesure-t-on et comment ?

1 **T-DM1 (Sérum: ELISA)**

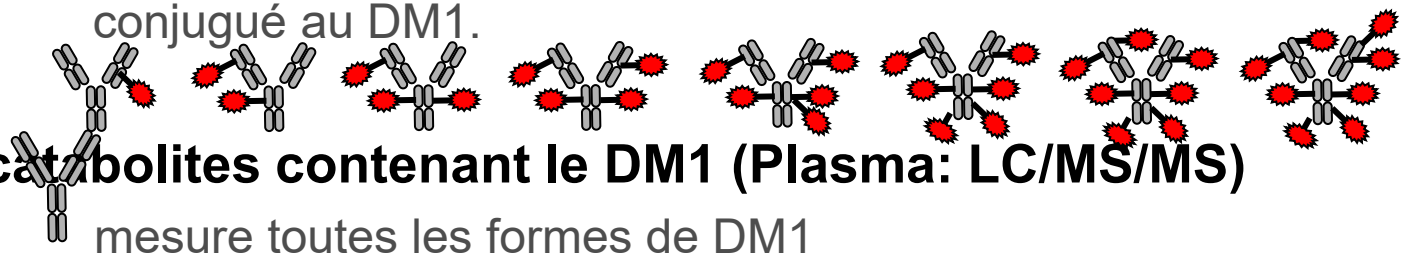
quantifie toutes les molécules de trastuzumab conjuguées à au moins un DM1. La médiane du ratio trastuzumab/DM1 égale à 1:3



trastuzumab total (Sérum: ELISA)

2

quantifie le trastuzumab seul et toutes les formes de trastuzumab conjugué au DM1.



catabolites contenant le DM1 (Plasma: LC/MS/MS)

3

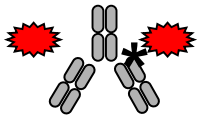
mesure toutes les formes de DM1

dimère de DM1

DM1

autre DM1-S-S-X

DM1-albumine



DM1 connecté par une liaison disulfure à l'anticorps

Pharmacocinétique du T-DM1: Mesure de 3 analytes

T-DM1

1 T-DM1 (Conjugué)

Demi-vie: 3,1 à 4,5 jours
Clairance: 7,3 à 12,7 mL/jr/kg
Pas d'accumulation

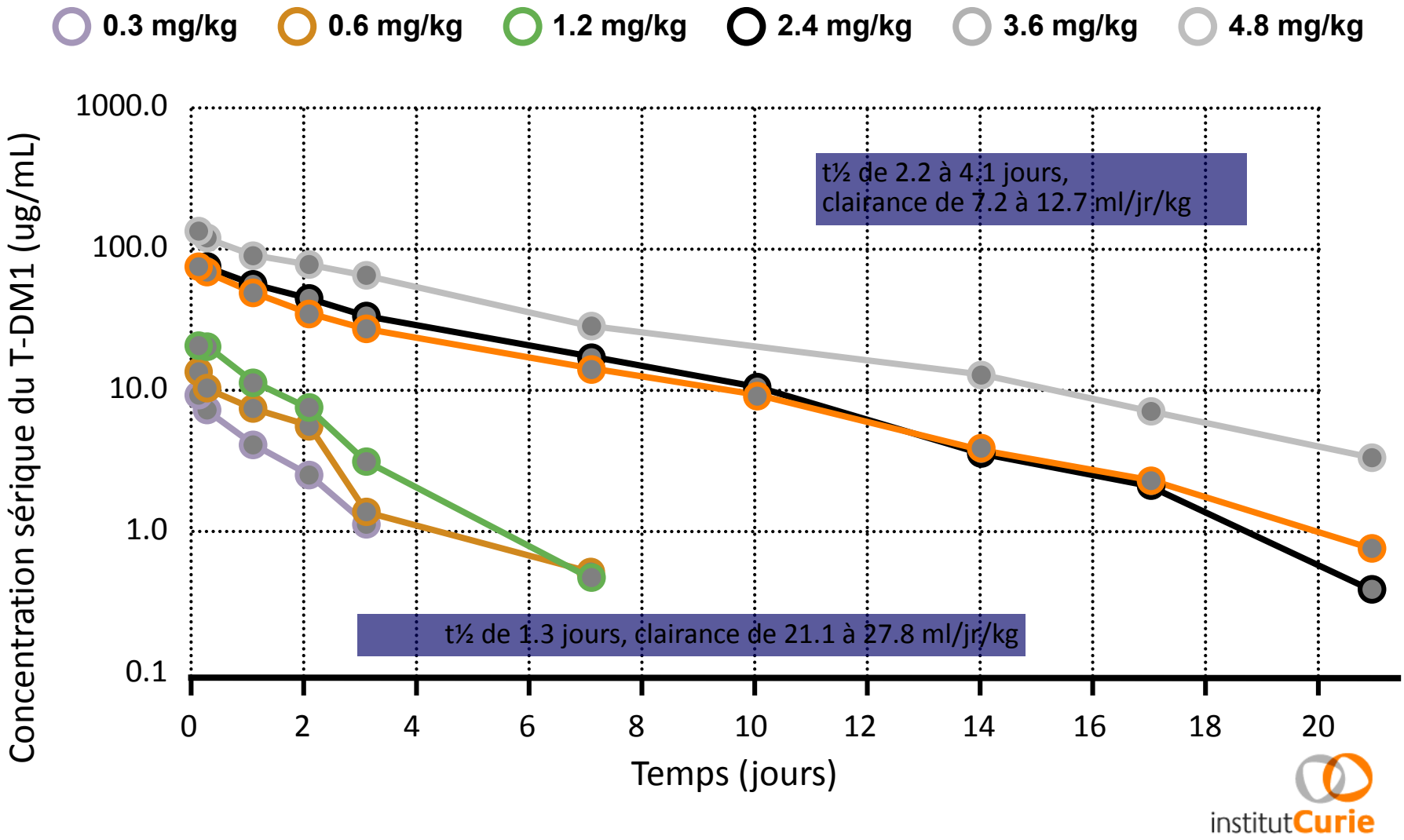
2 trastuzumab total

Demi-vie: 10,3 jours
Clairance: 4,21 mL/jr/kg
Accumulation moyenne

3 catabolites du DM1

Demi-vie: identique au T-DM1
Cmax: ~6 ng/mL
Pas d'accumulation

La pharmacocinétique dépend de la dose : Clairance plus rapide à des doses faibles



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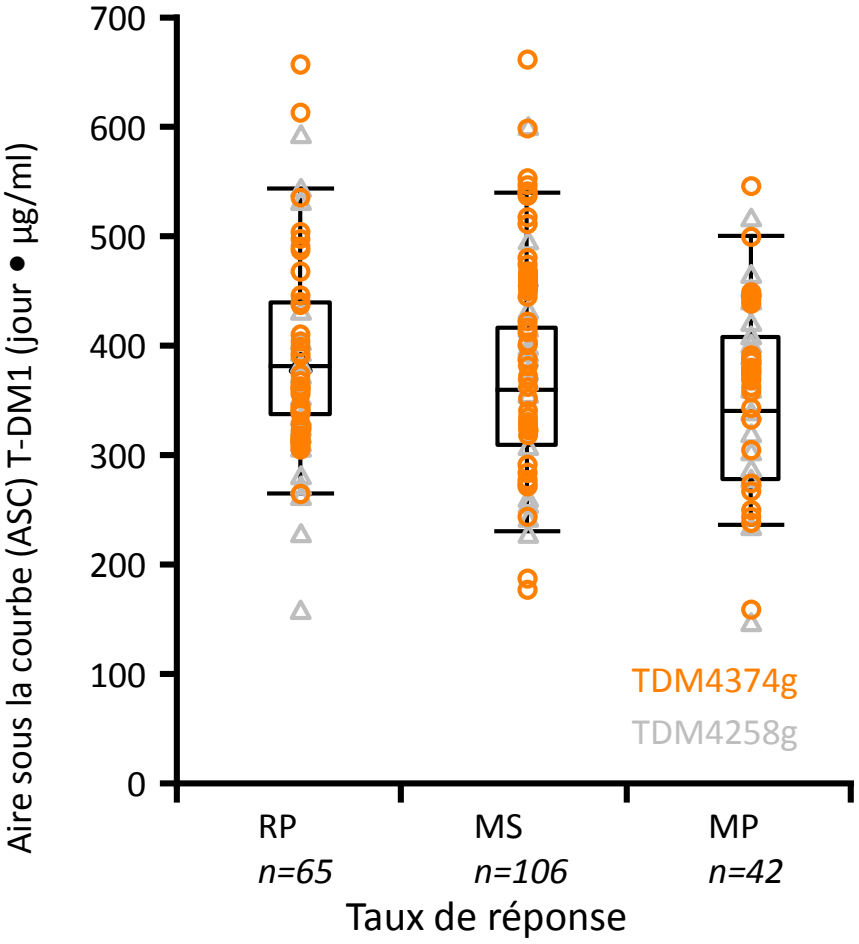
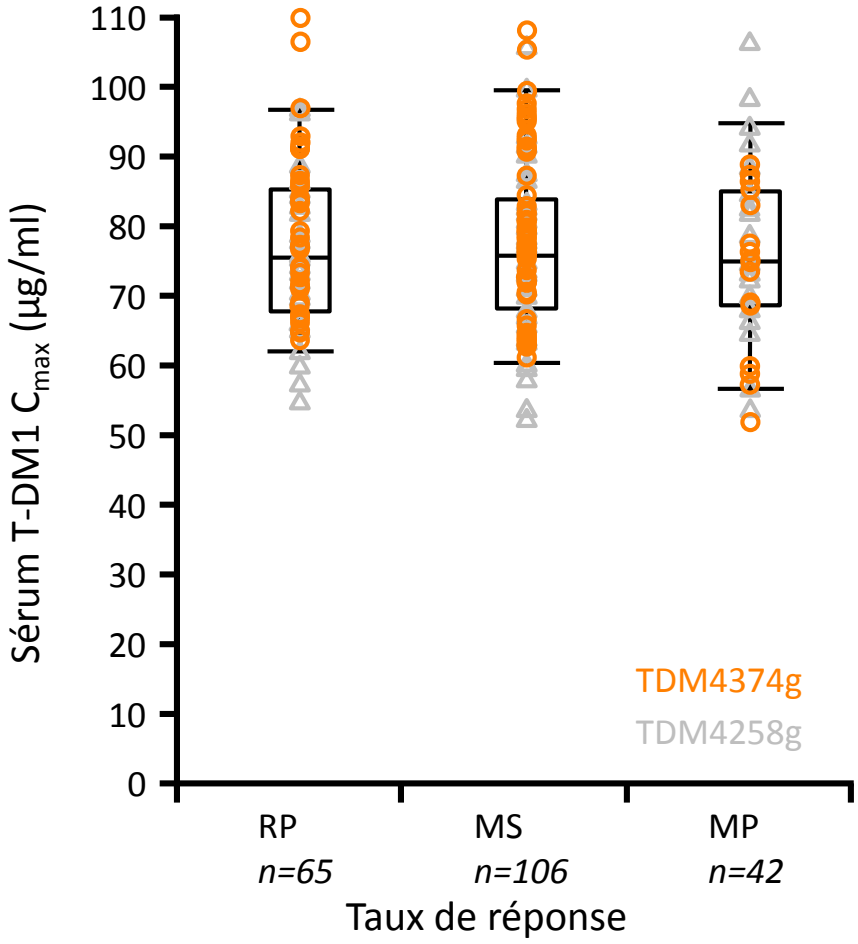
Pas de corrélation significative entre l'exposition au T-DM1 et l'efficacité





Girish S, Gupta M, Wang B, Lu D, Krop I, Vogel CL, Burris HA, Yi JH, Saad O, Tong B, Chu W, Joshi A. Presenté à l'ASCPT Dallas Mars 2011.

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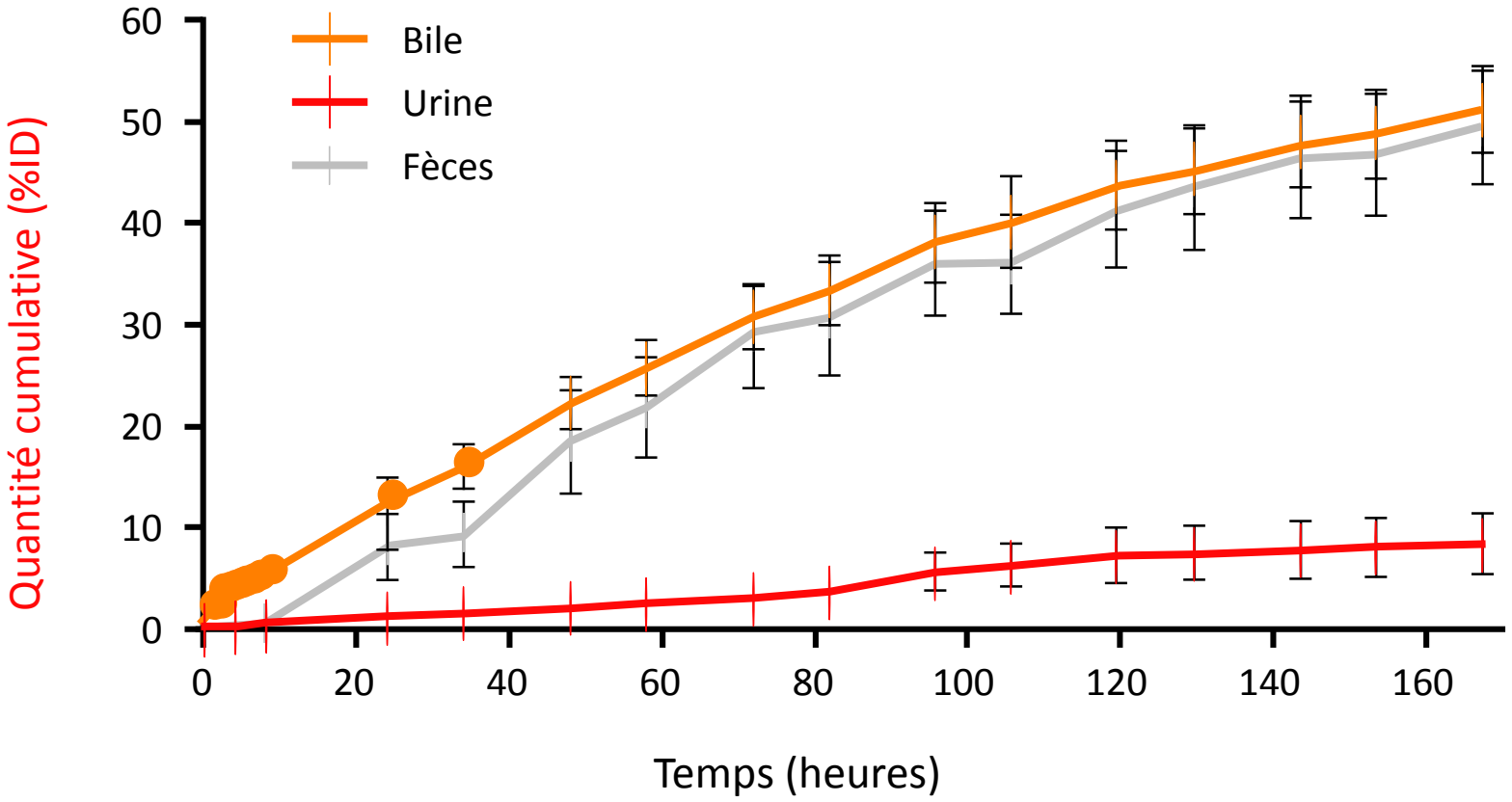
Catabolites du DM1: la voie biliaire est la voie principale d'excrétion



Shen B-Q, Bumbaca D, Saad O, Yue Q, Pastuskovas CV, Khojasteh C, Tibbitts J, Kaur S, Wang B, Chu Y-W, LoRusso PM, Girish S. Presenté à l'ASCPT Dallas Mars 2011.

Pharmacocinétique du T-DM1: Résumé

Une dose de 3,6 mg/kg de T-DM1 est administré en intraveineuse toutes les 3 semaines, sa demie-vie est d'environ 4,5 jours

Le T-DM1 conjugué est le composant principal pour la caractérisation de la pharmacocinétique

Pas d'accumulation de T-DM1 ou de DM1 dans le sérum/plasma après administration répétée de T-DM1.

Faibles concentrations plasmatiques de DM1 grâce à une liaison stable et un faible taux de catabolisme plasmatique

Le catabolisme du T-DM1 s'effectue dans la cellule, où il sera dégradé en trastuzumab et en catabolites contenant le DM1

Le trastuzumab est catabolisé par protéolyse intracellulaire

Le DM1 est catabolisé par métabolisme hépatique

Le DM1 métabolisé est excrété par voie biliaire (majoritairement)

l'augmentation de la clairance de la créatinine n'affecte pas la pharmacocinétique du T-DM1.