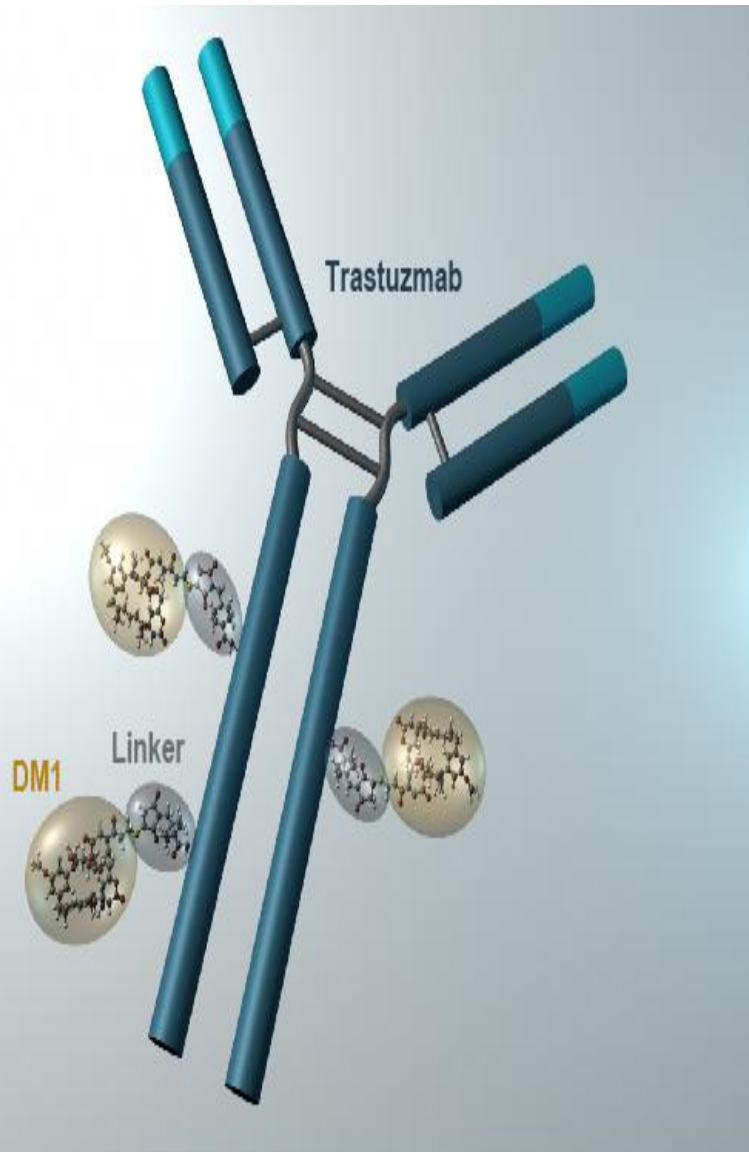


Clinical development of trastuzumab emtansine (T-DM1)

Ian Krop
Dana-Farber Cancer Institute
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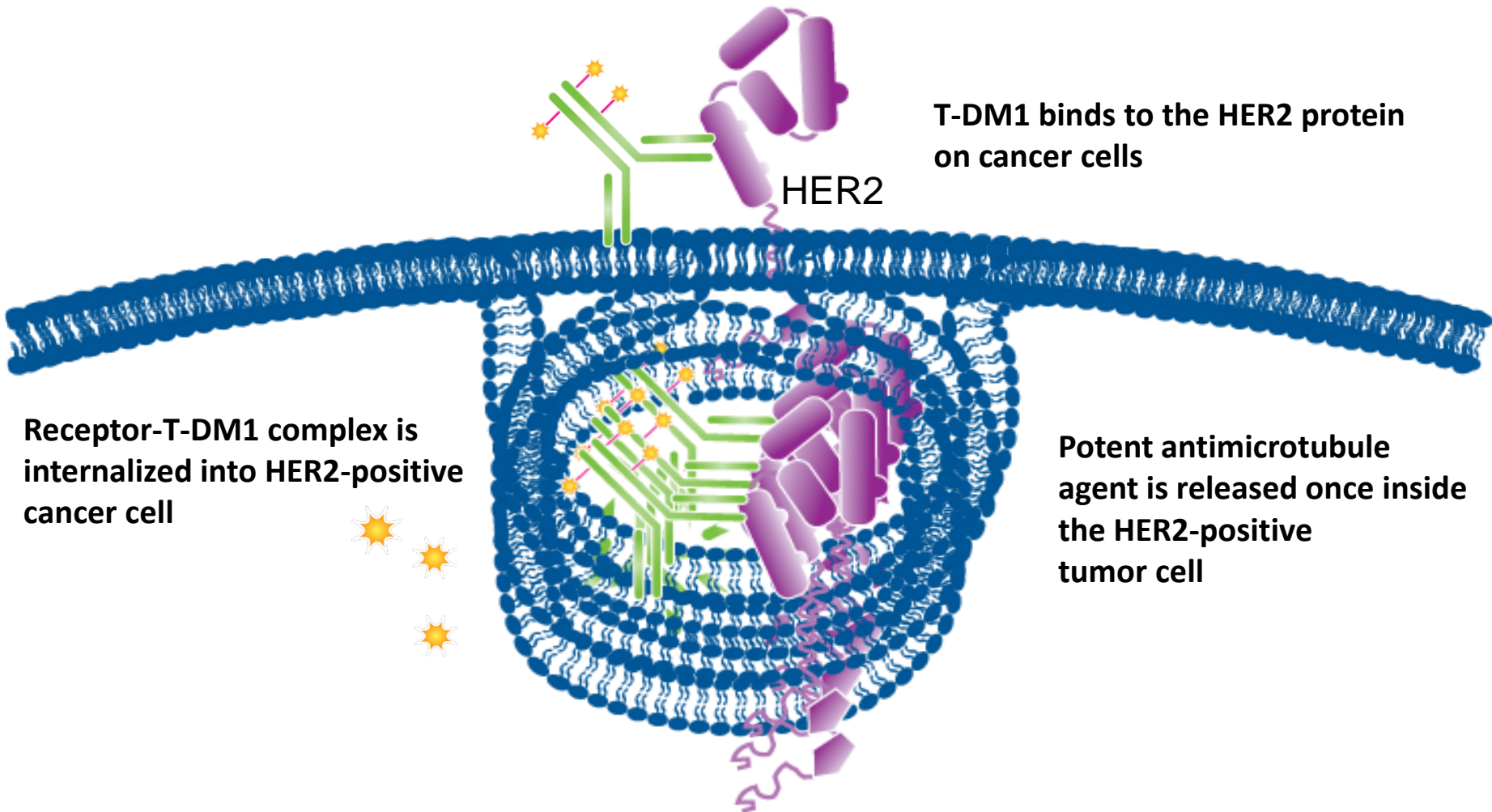
October 2011

Trastuzumab emtansine (T-DM1)



- Trastuzumab linked to potent cytotoxic agent
- DM1, a derivative of maytansine, is a microtubule inhibitor 25 to 500 fold more potent than taxanes
- Average of 3.5 DM1 per antibody

T-DM1 selectively delivers DM1 to HER2-positive tumor cells



T-DM1: Dual Mechanisms of Action

Combined Targeted Therapy



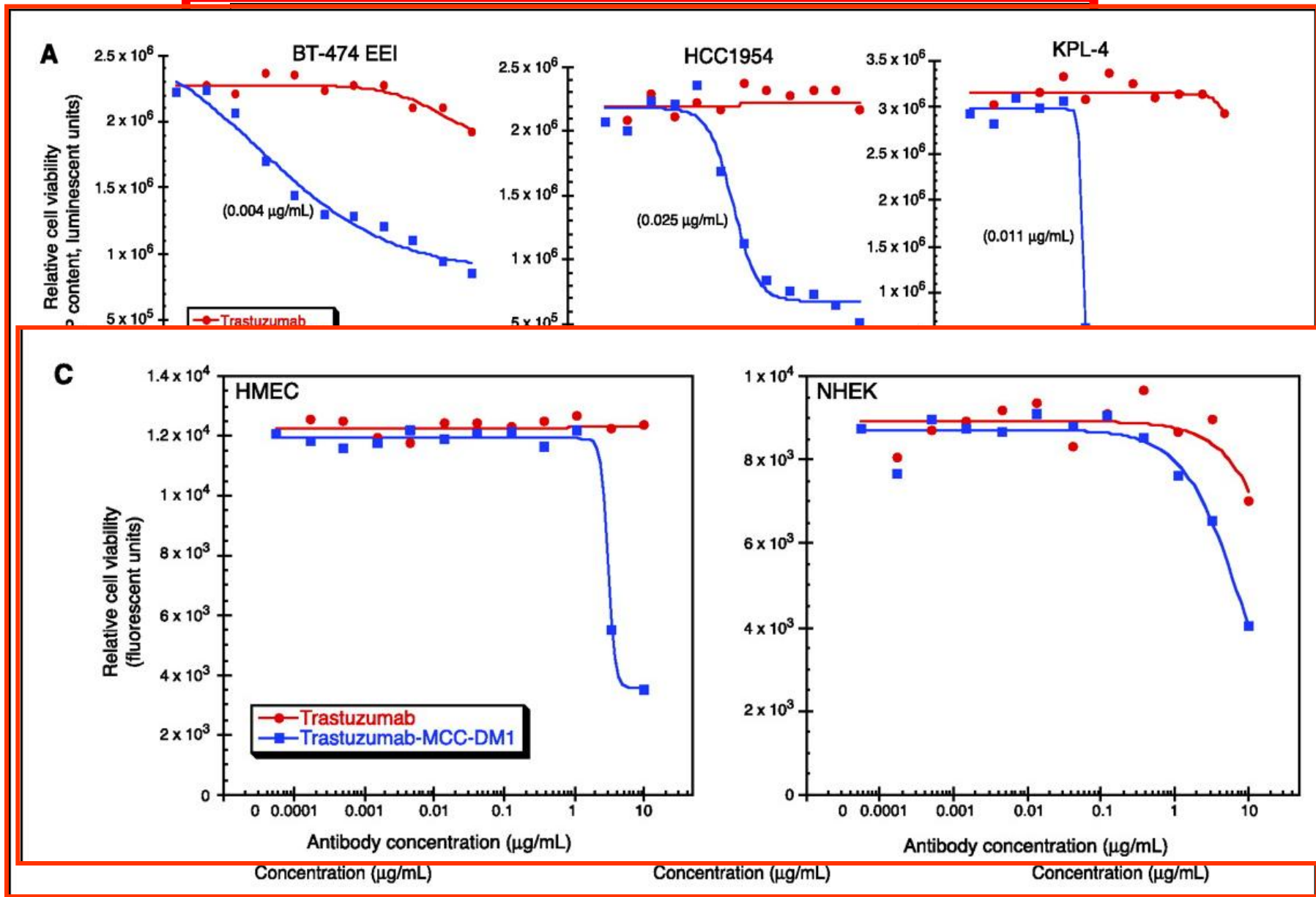
Targeted Intracellular Delivery of DM1

- T-DM1 specifically delivers high concentrations of DM1 to the tumor cell
- Systemic toxicity is limited due to low HER2 expression in normal tissues

Trastuzumab Biologic Activity

- Inhibits HER2 signaling
- Flags HER2-positive tumor cells for destruction via antibody-dependent cell-mediated cytotoxicity (ADCC)
- Inhibits HER2 shedding

T-DM1 inhibits growth of trastuzumab-resistant tumor cells but not HER2 normal cells



First in human Phase I study of T-DM1

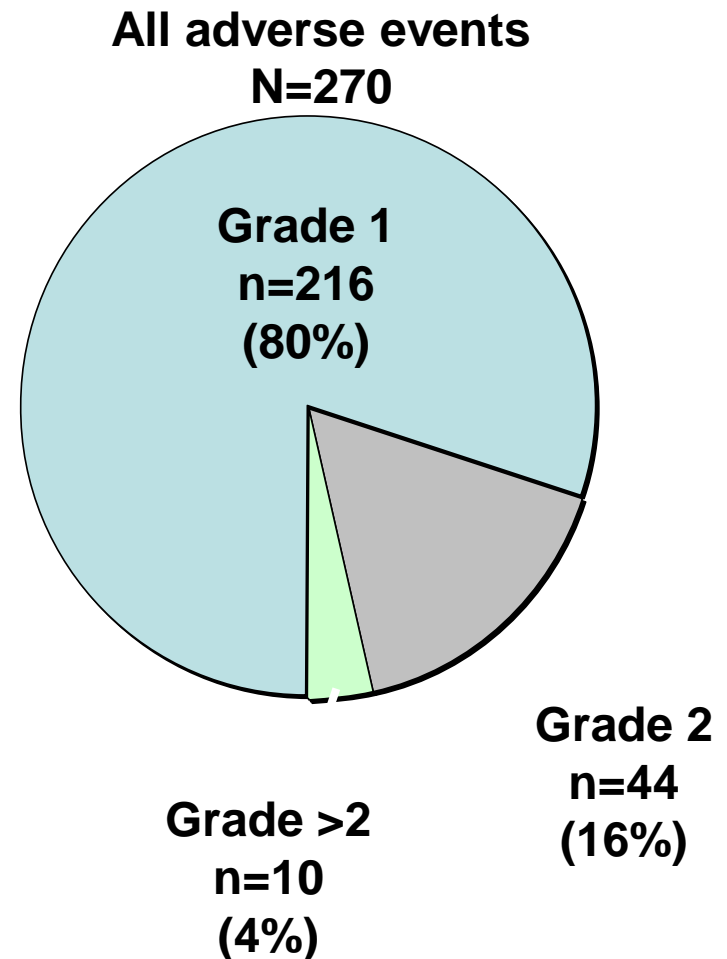
- Objective: Assess safety and define MTD
- Population: HER2+ MBC with progression on at least one trastuzumab + chemotherapy regimen
- Accelerated dose escalation design

The MTD of q3 week dosing of T-DM1 was established at 3.6 mg/kg

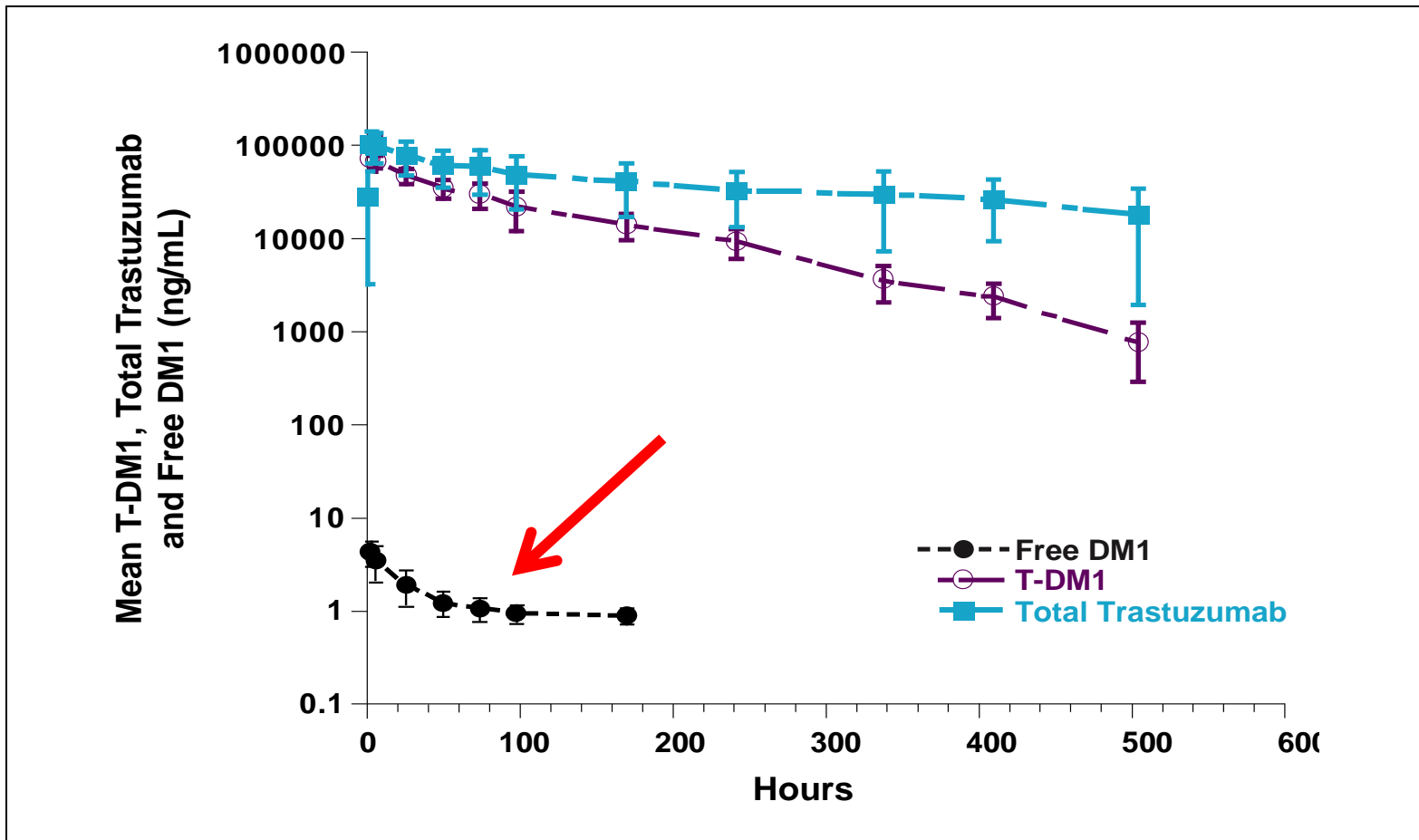
- Maximum tolerated dose (MTD) every 3 weeks is 3.6 mg/kg
- Dose-limiting toxicity is rapidly reversible thrombocytopenia at 4.8 mg/kg
- Thrombocytopenia at MTD generally Grade 1, rapidly reversible, non-cumulative

q3 week dosing of T-DM1 was well tolerated with toxicity generally \leq grade 1

- Other common related adverse events are Grade 1–2 transaminitis, fatigue, anemia
- No Grade \geq 2 nausea, vomiting, alopecia, or neuropathy events
- No significant cardiac toxicity



Pharmacokinetics at MTD (Q3week)



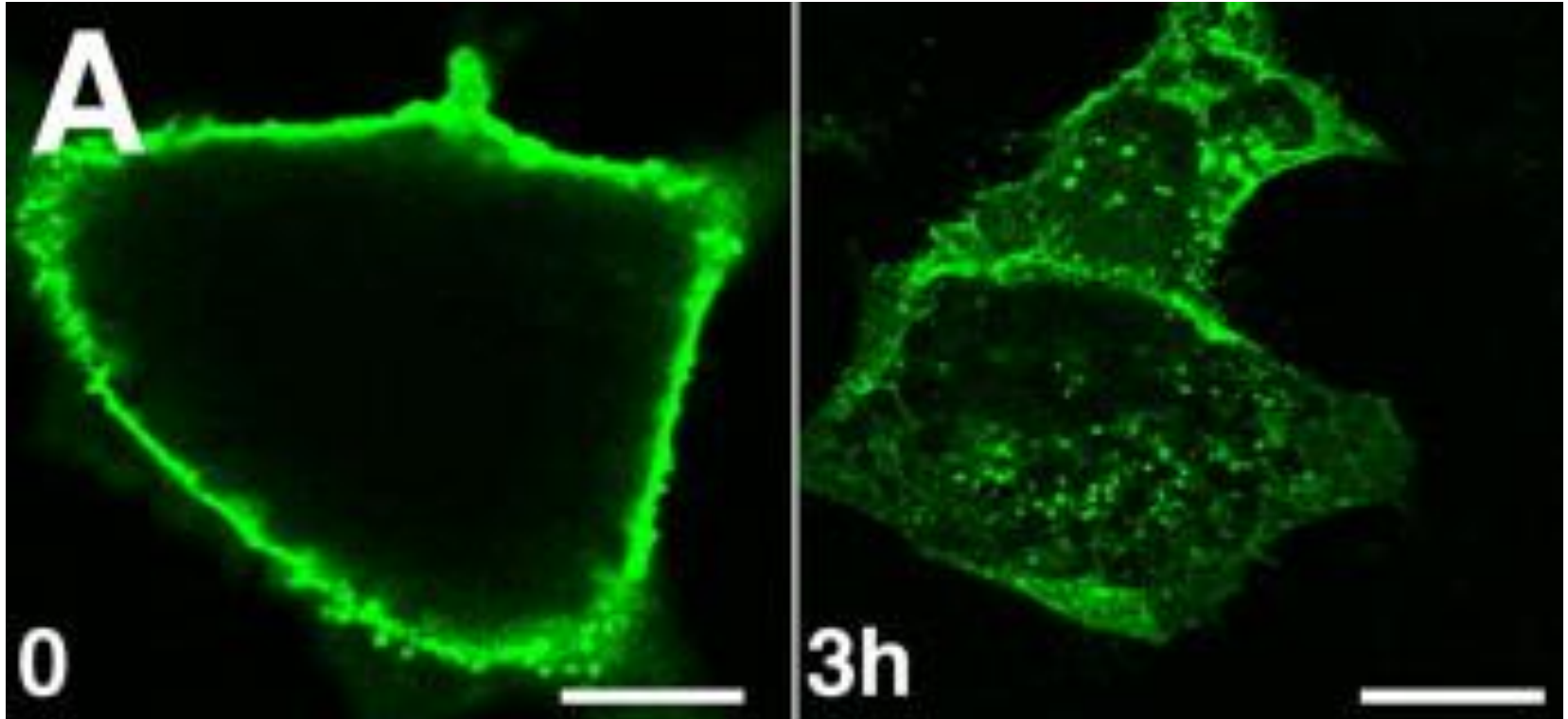
- Half life of intact T-DM1 is 3.5 days
- Exposure to free DM1 very low

Anti-tumor activity in q3 week dosing

- Efficacy evaluated in 15 patients treated q3 weeks at MTD of 3.6mg/kg
 - Clinical benefit rate (CR + PR + SD x 6 months) was 73%,
 - Confirmed RR was 44% in the 9 patients with measurable disease
 - Responses durable (PFS 9.8mo)

HER2 – An Ideal ADC Target

- Tumor expression >>> Normal-tissue expression
- Absolute Expression levels very high
- Internalized without down regulation
- Function important for cell (oncogene addiction)



Phase II study of T-DM1 in HER2+ MBC (Study TDM4258g)

- Objective:
 - Assess objective response rate of q3 week T-DM1 in patients with HER2+ MBC after progression on trastuzumab based therapy
- Study Logistics:
 - 113 patients enrolled between 7/07 and 7/08
 - Patients received T-DM1 3.6mg/kg IV q3w until progression

Key Eligibility Criteria

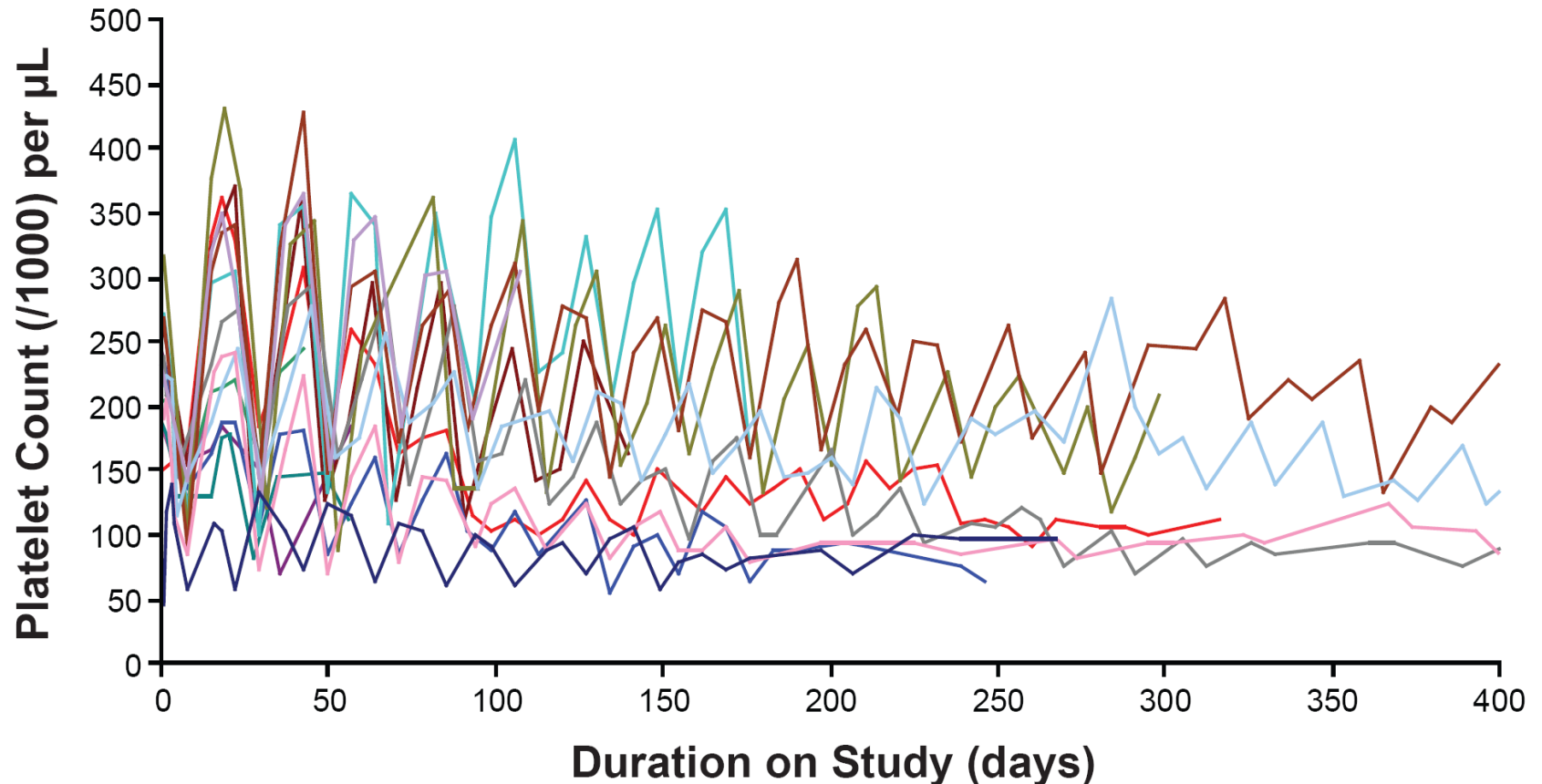
- HER2-positive disease by FISH or 3+ IHC
- Measurable disease
- Progression on HER-directed therapy or up to 60 days after receiving trastuzumab (≥ 6 weeks exposure to HER2-directed therapy)
- Prior treatment with one or more chemotherapy regimens
- LVEF $\geq 50\%$

Most Common Grade 3 or 4 Adverse Events (AEs) (n=112)

AE	Grade 3	Grade 4
Thrombocytopenia	5	3
Hypokalemia	6	0
Fatigue	4	0
Infection	3	0
Musculoskeletal chest pain	2	0
Convulsions	2	0
Thrombosis	2	0
Dyspnea	3	0
Pleural effusion	3	0
Epistaxis	2	0

Platelet counts at the MTD: consistent effects over time

Platelet count by study day for 3.6 mg/kg cohort

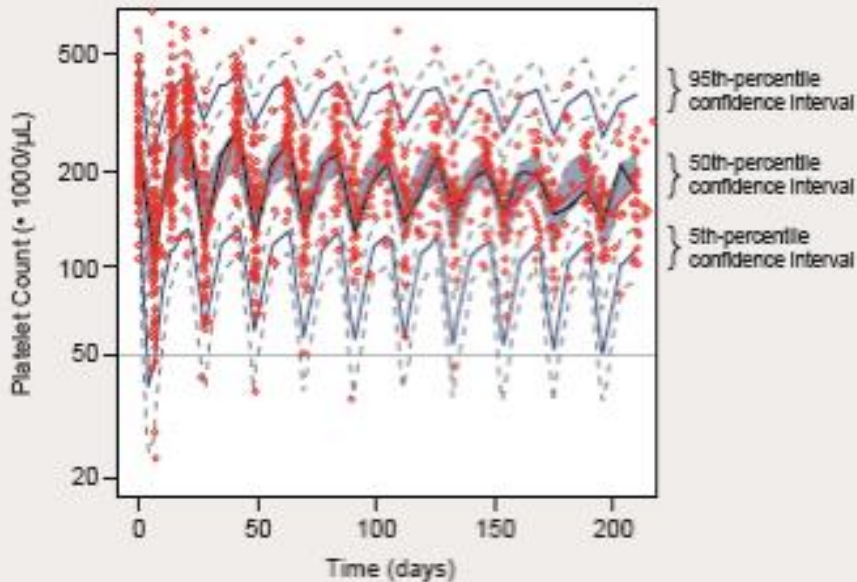


T-DM1 administered on Day 21 of each cycle.

Patterns of thrombocytopenia with T-DM1

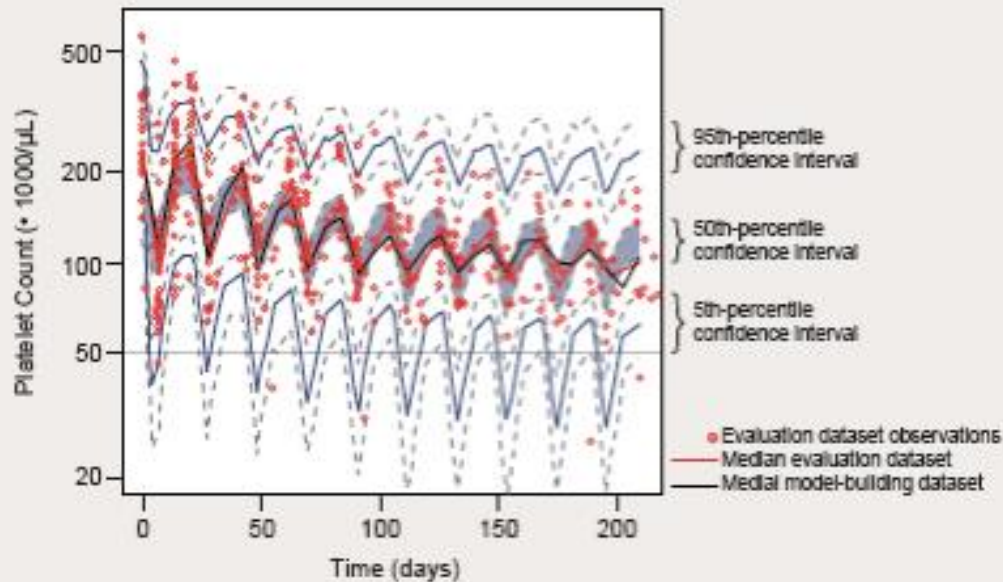
Stable effects over time

≈80% of patients

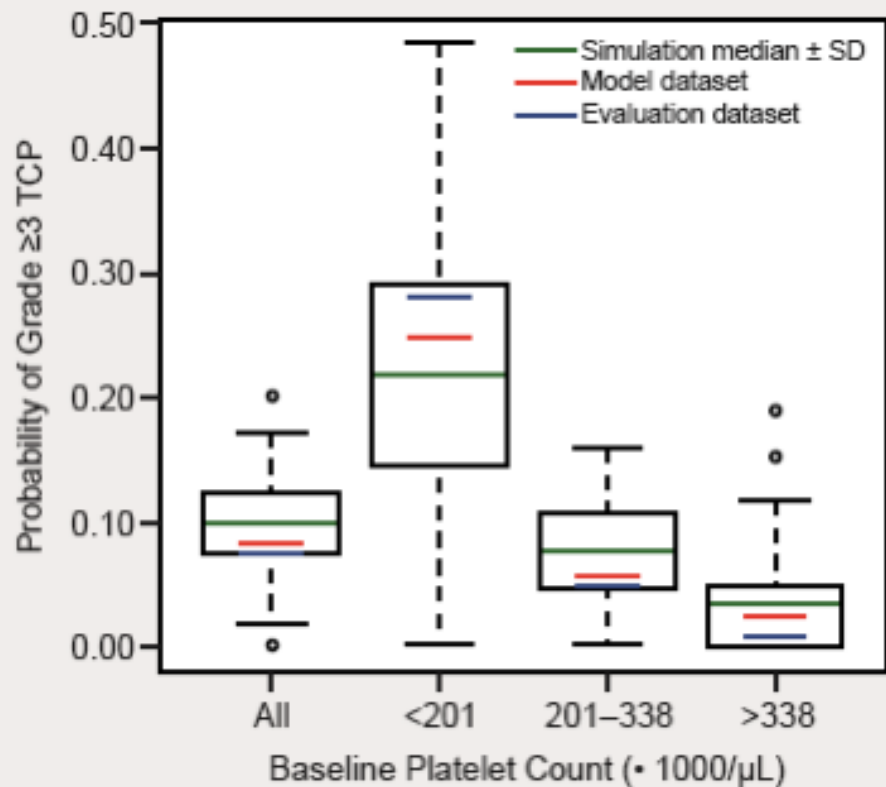


Cumulative loss of platelets

≈20% of patients



Predictors of thrombocytopenia in patients receiving T-DM1



- Lower pretreatment platelet count associated with greater risk of TCP
- T-DM1 exposure (AUC) or prior chemotherapy history not predictive

TDM4258g: encouraging efficacy demonstrated for single-agent T-DM1

	Population		
	All efficacy evaluable patients	Lapatinib pretreated patients	Patients with centrally confirmed HER2-positive disease
n	112	67	75
ORR* (%)	38.4	35.8	48
PFS (months)	4.9	Not available	7.4

After 8.5 months' follow-up

* Investigator assessment

T-DM1 second Phase II Study Design (TDM4374g)

- Multi-institutional, open-label, single-arm Phase II trial (N=110)
- HER2+ MBC pts:
 - Prior exposure to an anthracycline, a taxane, capecitabine, lapatinib and trastuzumab
 - Two HER2-directed regimens in the metastatic setting
 - Progressive disease on last regimen received
- T-DM1 at 3.6 mg/kg IV Q3W
- Primary endpoint: ORR assessed by IRF

Prior Chemotherapy and Anti-HER2 Therapy

Median number of agents for metastatic disease (range)*	7.0 (1–15)
Median number of agents in all therapy setting (range)*	8.0 (1–19)
Number of patients with 5 prior agents, n(%)**	109 (99.1)
Prior trastuzumab Median duration of prior trastuzumab in metastatic setting, months (range)	19.4 (2–116)
Prior lapatinib Median duration of prior lapatinib in metastatic setting, months (range)	6.9 (0–23)

* Includes all agents intended for the treatment of breast cancer except hormonal therapy

** One patient did not receive a taxane.

Phase II Study (TDM4374g): Common Adverse Events

Adverse event, %	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All grades
Fatigue	30.0	26.4	2.7	0	0	59.1
Nausea	26.4	10.0	0.9	0	0	37.3
Thrombocytopenia	10.9	12.7	3.6	1.8	0	29.1
AST increased	10.9	10.9	2.7	0	0	24.5
Pyrexia	12.7	8.2	0.9	0	0	21.8
Constipation	17.3	2.7	0.9	0	0	20.9
Dry mouth	17.3	3.7	0	0	0	20.0
Headache	17.3	2.7	0	0	0	20.0
Back pain	13.6	1.8	2.7	0.9	0	19.1
Hypokalemia	16.4	0.9	0.9	0	0	18.2
Anemia	5.5	10.0	1.8	0	0	17.3
Decreased appetite	10.9	6.4	0	0	0	17.3
Cough	12.7	4.5	0	0	0	17.3
Epistaxis	13.6	2.7	0.9	0	0	17.3

AST=aspartate aminotransferase.

Krop et al. Presented at: 32nd Annual SABCS Meeting. December 10–13, 2009; San Antonio, TX. Poster 710.

Phase II Study (TDM4374g): LVEF (Local Assessment)

Lowest post-baseline value, n (%)	N=110
≥45%	107 (97.3)
≥40 – <45%	0 (0)
<40%	0 (0)
Missing	3 (2.7)

Maximum decrease from baseline, n (%)	
Increase	25 (22.7)
0 – <15%	80 (72.7)
≥15 – <25%	2 (1.8)
≥25%	0 (0)
Missing	3 (2.7)

Baselga et al. Discussion of Krop et al poster 710. Presented at 32nd Annual SABCS Meeting. December 10–13, 2009; San Antonio, TX.

Antitumor Activity in Treated Patients

Tumor Response	IRF (N=110)	Investigator (N=110)
Objective Response Rate, % (95% CI)	34.5 (26.1–43.9)	32.7 (24.1–42.1)
CR	0	4.5
PR	34.5	28.2
SD*	44.5	50.9
PD	18.2	14.5
Clinical Benefit Rate, % (95% CI)	48.2 (38.8–57.9)	46.4 (37.1–56.1)

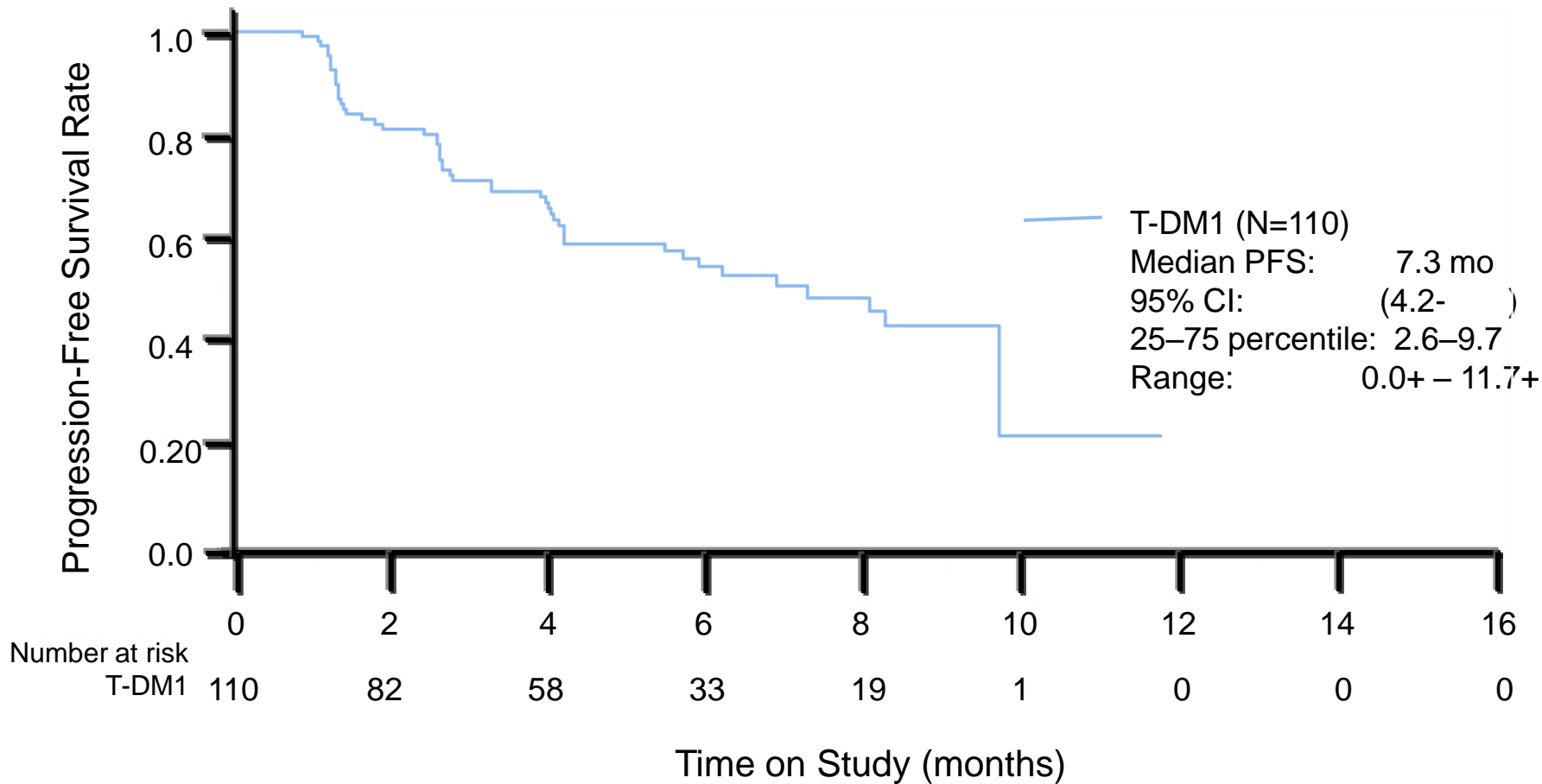
IRF - Independent Review Facility

Objective Response - CR or PR determined by two consecutive tumor assessments at least 28 days apart.

Clinical Benefit - objective response or SD maintained for at least 6 months.

*Including unconfirmed PRs.

Progression-Free Survival

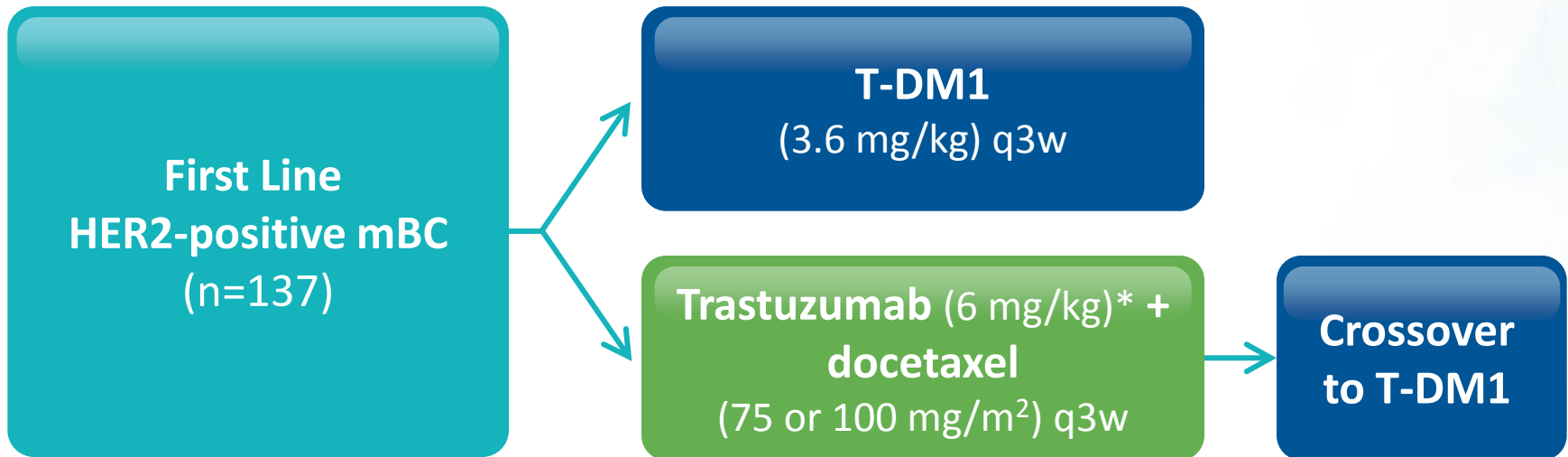


N	110
Number progressed	50 (45.5%)
Number censored	60 (54.5%)

T-DM1 vs trastuzumab + docetaxel

Phase II Study: TDM4450g/BO21976

Randomized 1:1, 2-arm, open-label, multicenter trial



Primary endpoints: PFS, Safety

- **137 patients enrolled:** 9/08-12/09

**Trastuzumab dose in cycle 1 is 8 mg/kg*

Objective Response by Investigator

Patients With Measurable Disease at Baseline

	Trastuzumab + docetaxel (n=69) ^a	T-DM1 (n=67)
Patients with an objective response, ^b n (%)	40 (58.0)	43 (64.2)
95% CI	45.5–69.2	51.8–74.8
Objective responses, n (%)		
Complete response	3 (4.3)	7 (10.4)
Partial response	37 (53.6)	36 (53.7)
Stable disease	23 (33.3)	13 (19.4)
Progressive disease	4 (5.8)	8 (11.9)
Unable to evaluate or missing	2 (2.9)	3 (4.5)
Patients with clinical benefit, ^c n (%)	56 (81.2)	50 (74.6)
95% CI	70.7–89.1	63.2–84.2

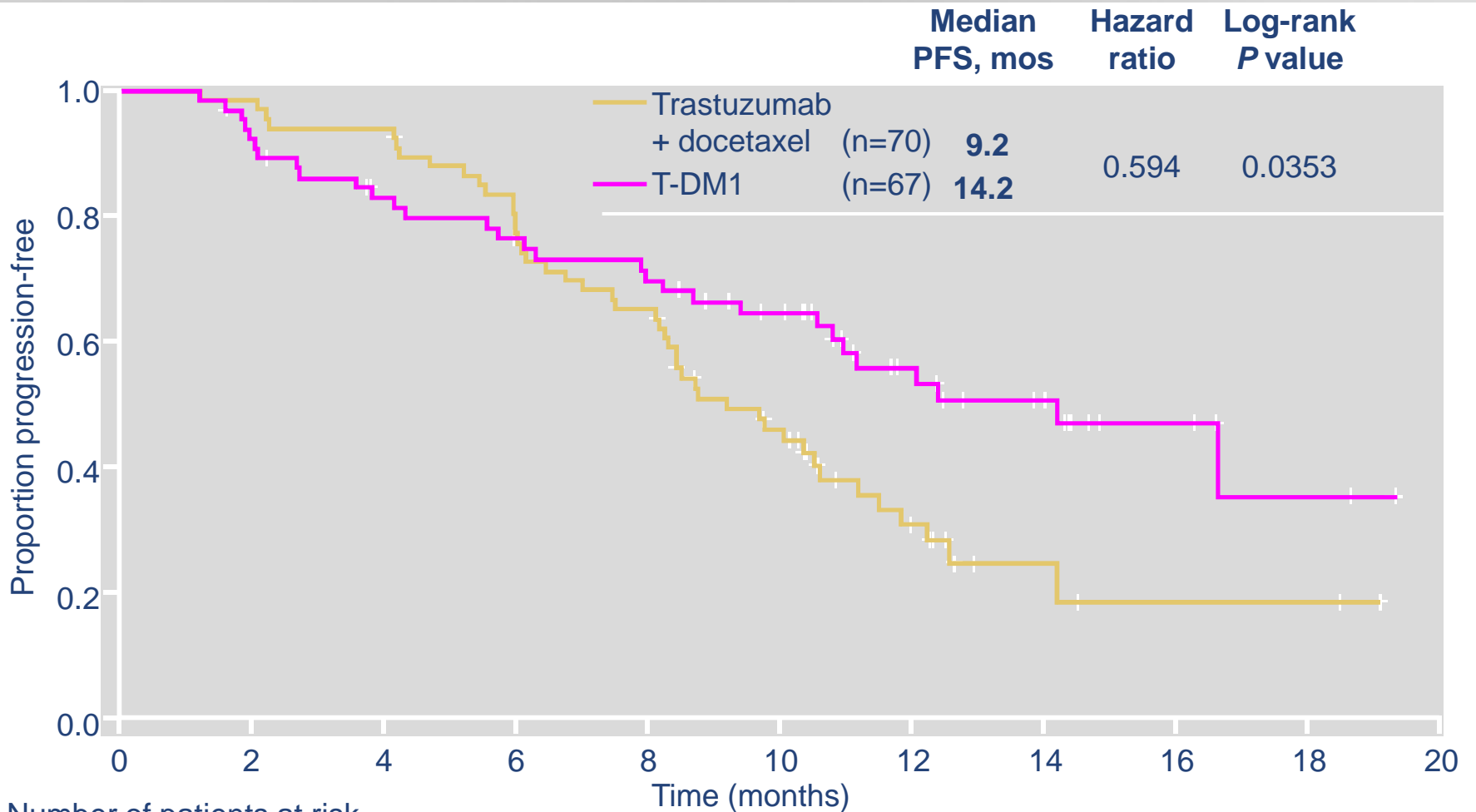
^aOne patient was not included in the efficacy analysis due to study site withdrawal.

^bDefined as complete or partial response based on RECIST 1.0 determined on 2 consecutive tumor assessments at least 4 weeks apart.

^cDefined as objective response any time during the study or maintained stable disease for at least 6 months from randomization.

Progression-Free Survival by Investigator

Randomized Patients



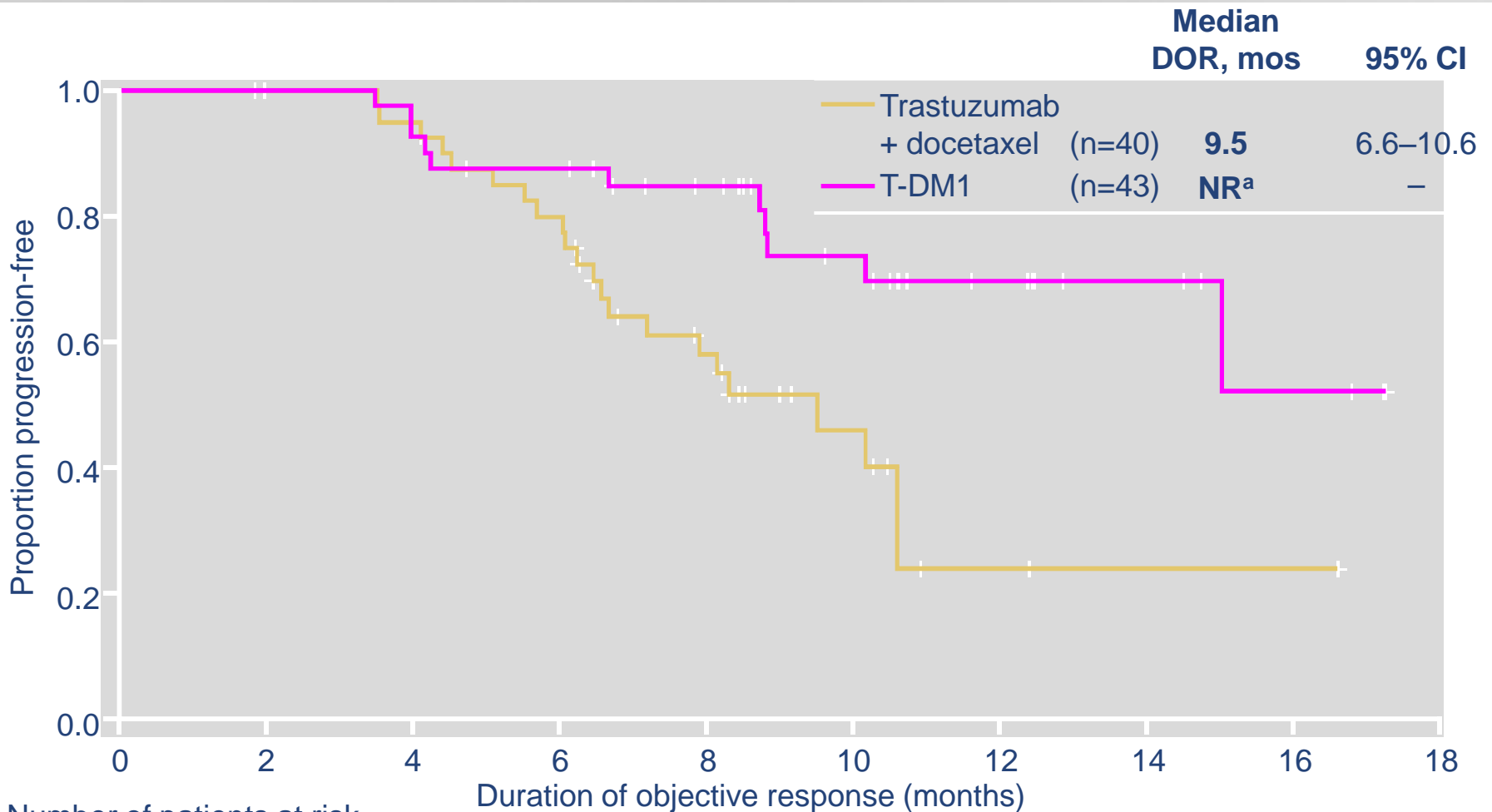
Number of patients at risk

T+D	70	66	63	53	43	27	12	4	2	2	0
T-DM1	67	60	51	46	42	35	22	15	6	3	0

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

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.

^aNR, not reached; longer follow-up is needed to estimate the duration of response in the T-DM1 arm.

Summary of Adverse Events

Safety Evaluable Patients

	Trastuzumab + docetaxel (n=66) ^a , n (%)	T-DM1 (n=69) ^{a,b} , n (%)
Any grade ≥3 AE	59 (89.4)	32 (46.4)
AE leading to discontinuation of any study treatment component (any grade)	19 (28.8)	5 (7.2)
AE leading to death	1 (1.5) ^c	1 (1.4) ^d
Serious AEs (any grade)	17 (25.8)	13 (18.8)

^aTwo patients mistakenly received a dose of T-DM1 and were thus included in the T-DM1 arm for safety analyses.

^bIncludes 3 patients who received at least 1 dose of trastuzumab alone or trastuzumab plus docetaxel.

^cDue to cardiopulmonary failure.

^dDue to sudden death.

Incidence of Common Hematologic Adverse Events

AE	All grade, n (%)		Grade $\geq 3^b$, n (%)	
	Trastuzumab + docetaxel (n=66)	T-DM1 (n=69)	Trastuzumab + docetaxel (n=66)	T-DM1 (n=69)
Neutropenia	42 (63.6)	12 (17.4)	40 (60.6)	4 (5.8)
Febrile neutropenia	9 (13.6)	0	9 (13.6)	0
Thrombocytopenia	4 (6.1)	21 (30.4)	2 (3.0)	6 (8.7)
Leukopenia	18 (27.3)	6 (8.7)	17 (25.8)	0

Incidence of Common Non-hematologic Adverse Events

AE	All grade, n (%)		Grade ≥3, n (%)	
	Trastuzumab + docetaxel (n=66)	T-DM1 (n=69)	Trastuzumab + docetaxel (n=66)	T-DM1 (n=69)
Alopecia	44 (66.7)	3 (4.3)	NA	NA
Fatigue	30 (45.5)	34 (49.3)	3 (4.5)	3 (4.3)
Nausea	29 (43.9)	33 (47.8)	0	2 (2.9)
Diarrhea	30 (45.5)	11 (15.9)	2 (3.0)	0
Peripheral edema	29 (43.9)	7 (10.1)	3 (4.5)	0
Increased AST	4 (6.1)	27 (39.1)	0	6 (8.7)
Pyrexia	15 (22.7)	27 (39.1)	1 (1.5)	0
Headache	12 (18.2)	25 (36.2)	0	0
Back pain	20 (30.3)	18 (26.1)	3 (4.5)	1 (1.4)
Increased ALT	4 (6.1)	16 (23.2)	0	6 (8.7)
Pneumonia	1 (1.5)	6 (8.7)	0	4 (5.8)

Cardiac Safety

LVEF assessment	Trastuzumab + docetaxel	T-DM1
Local assessment		
Patients assessed	65	67
Patients with post-baseline LVEF \leq 40%	2 ^a	0
Central assessment		
Patients assessed	60	65
Patients with post-baseline LVEF \leq 40%	1 ^b	0

No clinically significant cardiac events reported

Unanswered questions

- How do we identify which patients will benefit from T-DM1?
 - Are these the same patients who benefit from all HER2-targeted therapies
- What is the mechanism for T-DM1 induced thrombocytopenia and can it be overcome?
- Can T-DM1 be combined with other agents to improve its efficacy?

Conclusions (1)

- Trastuzumab emtansine (T-DM1) demonstrates significant clinical activity
- Trastuzumab emtansine is well tolerated
 - Transient thrombocytopenia is only common significant toxicity
 - No typical chemotherapy related toxicity
 - No cardiac toxicity has been observed
- These data support further testing of T-DM1 in confirmatory phase III studies

1st Line mBC Phase III MARIANNE Study: BO22589/TDM4788g

n=1092

FPI July 6 2010

Arm A

Trastuzumab + taxane (until PD)
n=364

Arm B

T-DM1 + pertuzumab (until PD)
n=364

Arm C

T-DM1 + pertuzumab placebo (until PD)
n=364

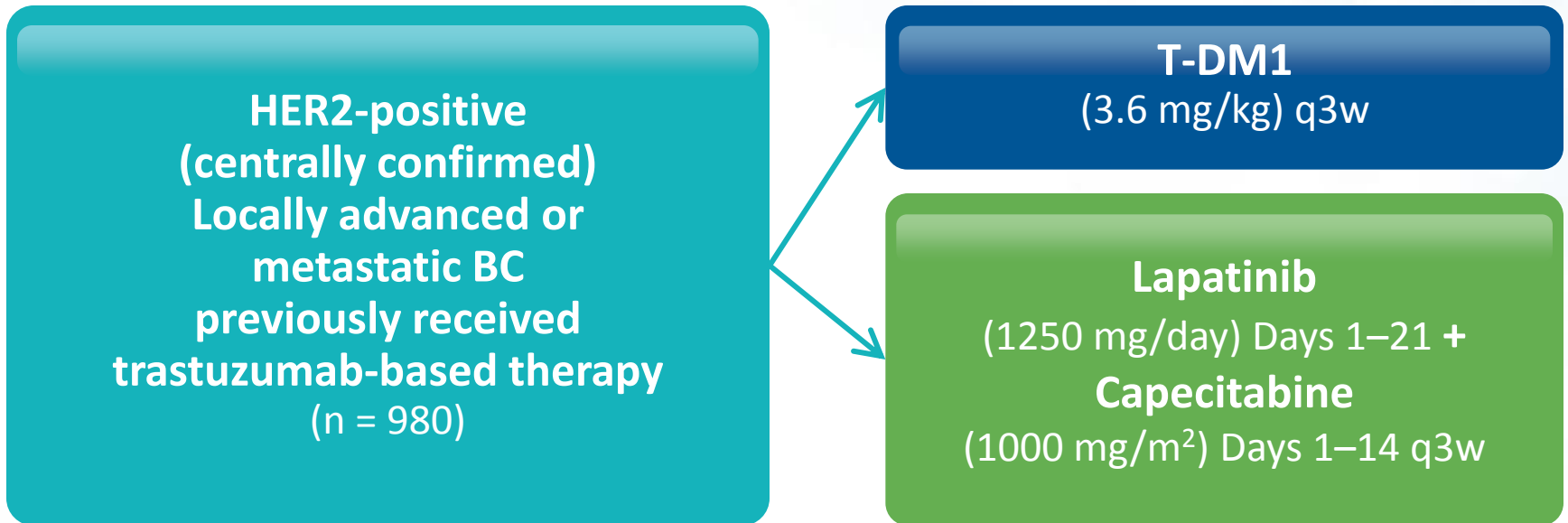
Patients stratified by:

- World region
- Neo/Adjuvant therapy (Y/N)
 - Trastuzumab and/or lapatinib based therapy (Y/N)
- Visceral disease (Y/N)

Patients with HER2 positive progressive or recurrent locally advanced breast cancer or previously untreated metastatic breast cancer

- **Primary endpoints:** PFS as assessed by IRF; Safety
- **Secondary endpoints:** OS; PFS by investigator; PRO analyses; Biomarkers
- Superiority design with a Non-inferiority analysis between each of the experimental arms and the control arm
- **Interim futility analysis:** Option to drop experimental arm

T-DM1 vs capecitabine + lapatinib in HER2+ mBC Phase III Study (EMILIA): TDM4370g/BO21977



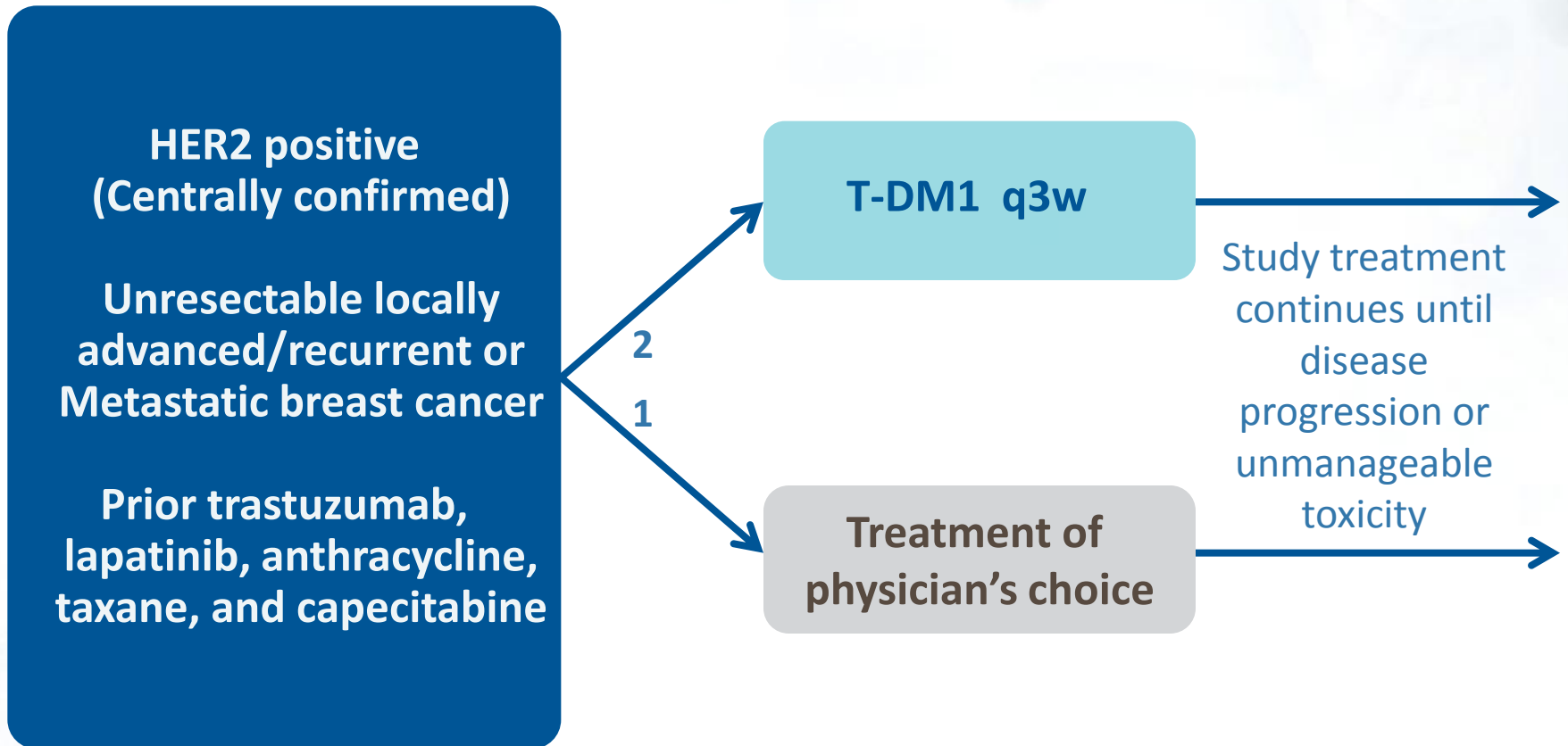
Primary end points: PFS by IRF, OS
Secondary end points: Quality of life

Treatment continues until disease progression or unmanageable toxicity

Key inclusion criteria

- Prior treatment to include a taxane and trastuzumab in adjuvant, locally advanced or metastatic setting
- Documented progression of disease during or after treatment for advanced/metastatic disease or within 6 months of completing adjuvant therapy

Th3RESA: Study Schema



N = 795
2:1 randomization

Conclusions (2)

- HER2 remains a valid therapeutic target in a heavily pretreated patient population
- The efficacy and tolerability of T-DM1 validates the hypothesis that antibody drug conjugates can significantly improve the therapeutic index of a cytotoxic agent (e.g. DM1)
- The results with T-DM1 suggest that trastuzumab-toxin conjugates may be a new paradigm for treating HER2+ cancers