Updated Overall Survival Results From EMILIA, a Phase 3 Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine and Lapatinib in HER2-Positive Locally Advanced or Metastatic Breast Cancer

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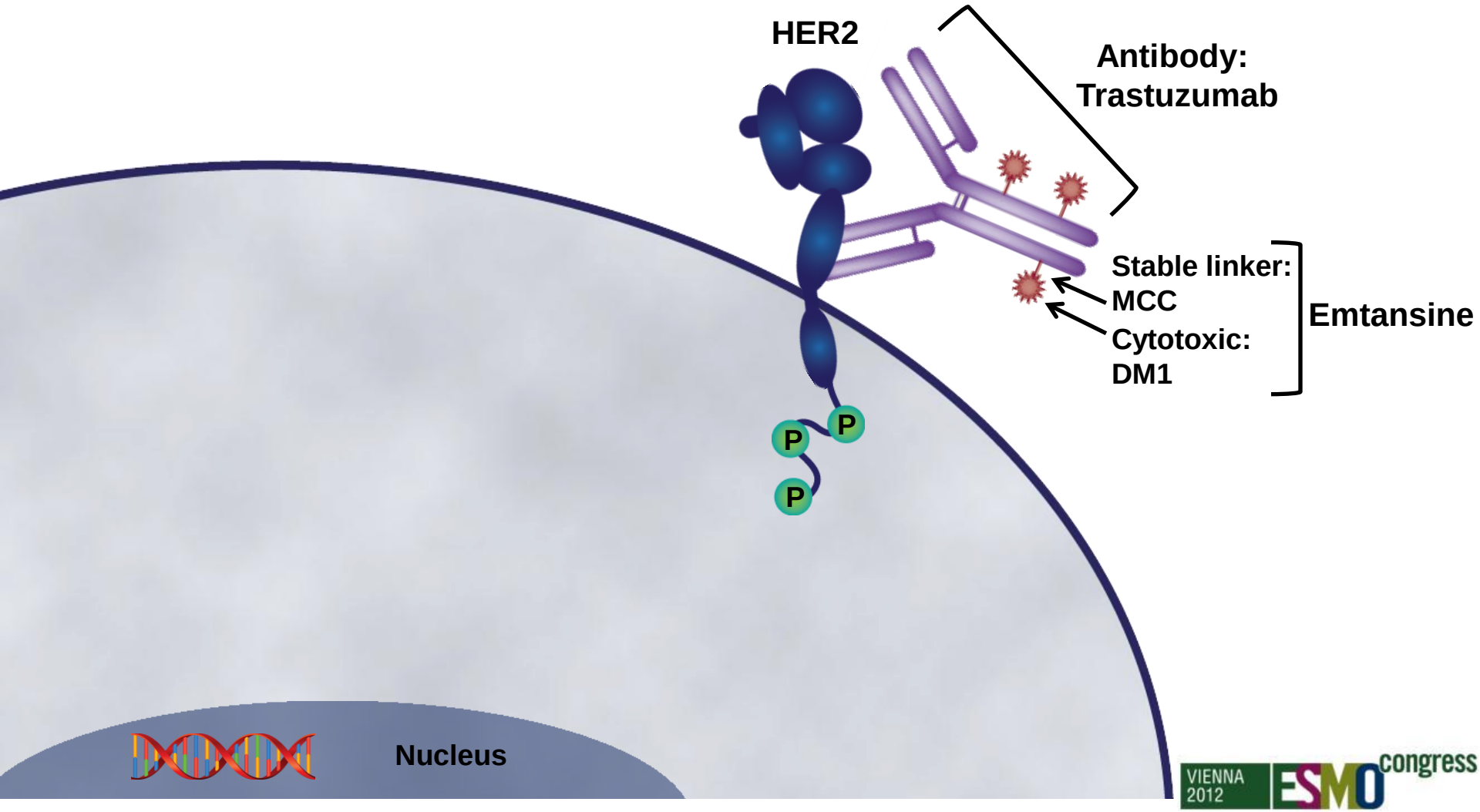
Disclosure Slide

- Verma: Compensated consultant/advisory relationship with Roche/GSK; honoraria from GSK/Roche; research funding from Genentech/Roche
- Miles: Compensated consultant/advisory relationship with Genentech/Roche; honoraria from Genentech/Roche
- Gianni: Compensated consultant/advisory relationship with Genentech/Roche, GSK, Pfizer
- Krop: Uncompensated consultant/advisory relationship with Novartis; research funding from Genentech/Roche
- Welslau: None
- Baselga: Compensated consultant/advisory relationship with Genentech/Roche
- Pegram: Compensated consultant/advisory relationship with Genentech/Roche; honoraria from Genentech/Roche
- Oh: None
- Dieras: Compensated consultant/advisory relationship with Genentech/Roche, Novartis, Sanofi, Amgen, Clovis, Pfizer, GSK; honoraria from Genentech/Roche, Novartis, Sanofi, Amgen, Clovis, Pfizer, GSK
- Guardino: Genentech employee; owns Roche stock
- Fang: Genentech employee; owns Roche stock
- Lu: Genentech employee; owns Roche stock
- Olsen: Genentech employee; owns Roche and Sanofi stock
- Blackwell: None

Trastuzumab Emtansine (T-DM1): Mechanism of Action

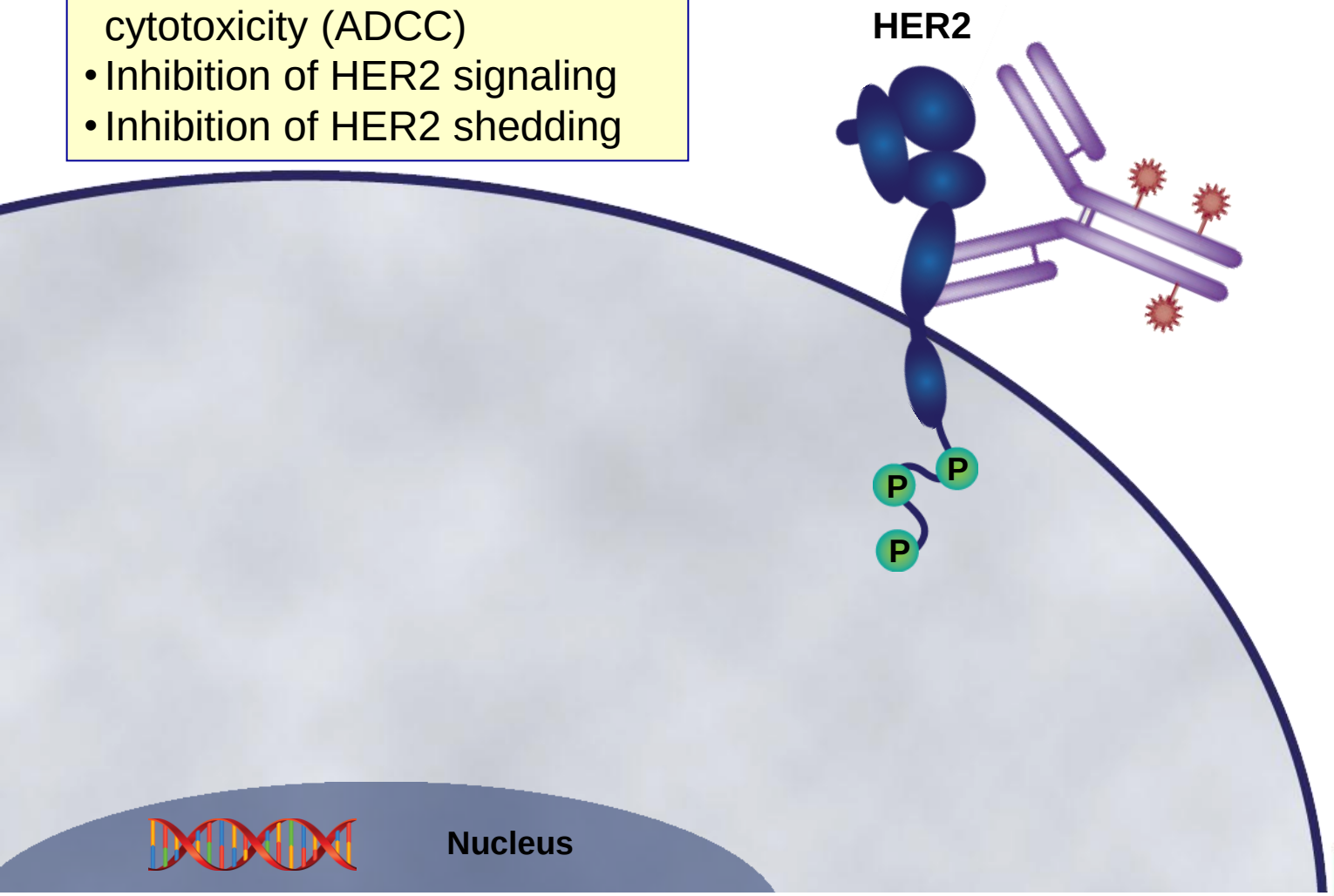


Adapted from LoRusso PM, et al. *Clin Cancer Res* 2011.

Trastuzumab Emtansine (T-DM1): Mechanism of Action

Trastuzumab-specific MOA

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



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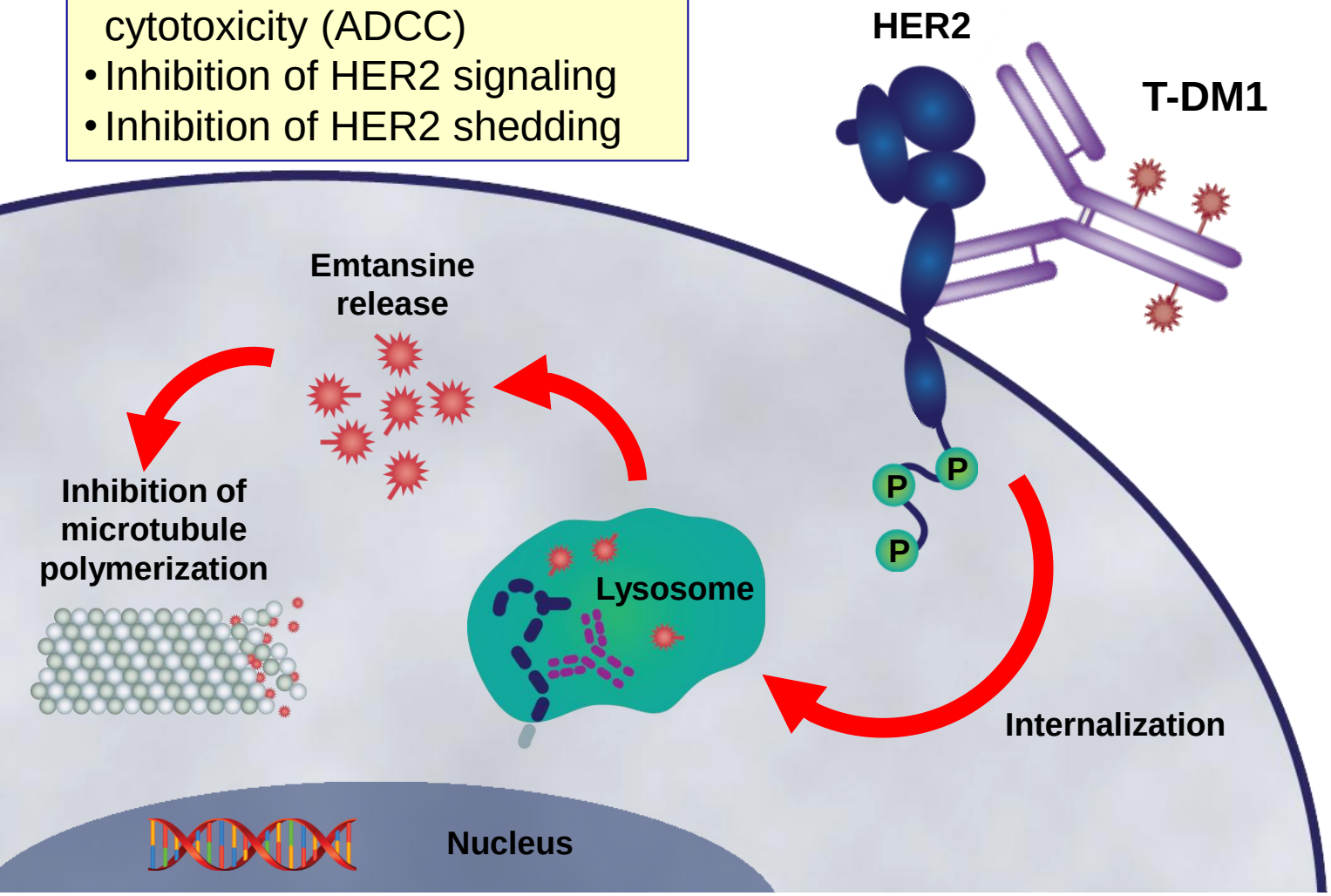

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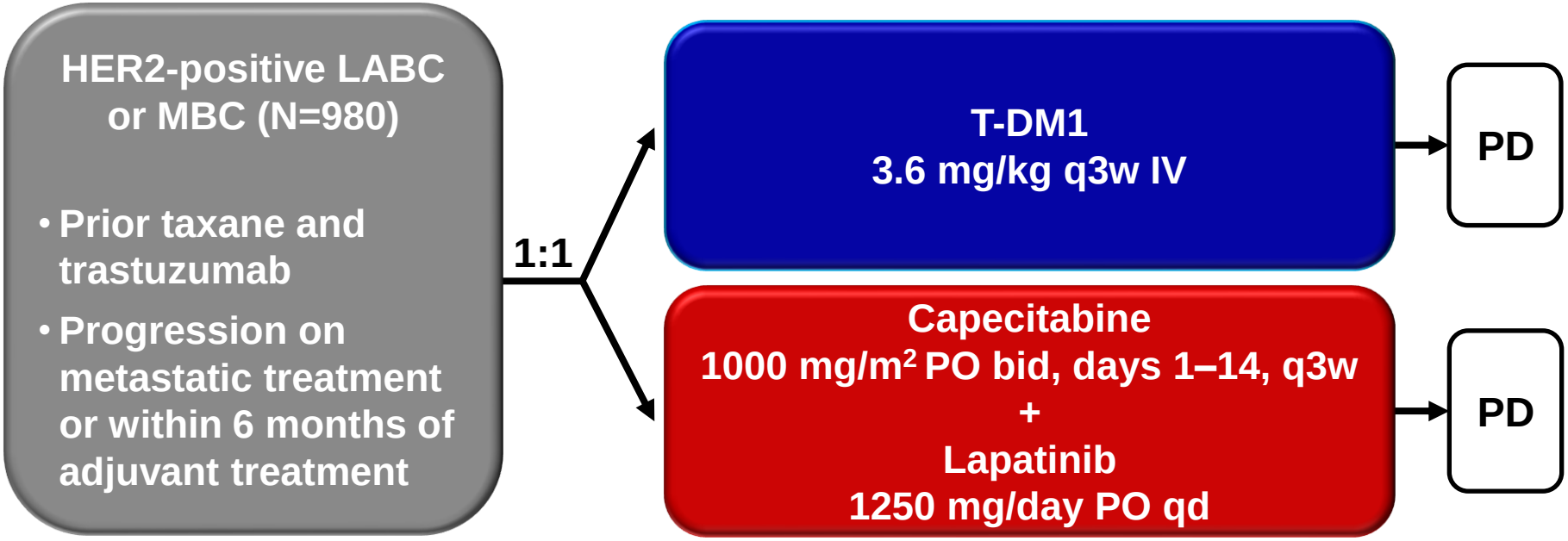
EMILIA Study Design



- **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%

EMILIA Analyses

Final PFS and 1st Interim OS Analysis
Data cut-off Jan 14, 2012

Presented at ASCO 2012

Final PFS analysis:
- Targeted number: 508 events
- Actual number: 569 events

1st Interim OS analysis:
- Preplanned at time of final PFS analysis
- Did not cross efficacy stopping boundary

Safety and Secondary Endpoint analysis

2nd Interim OS Analysis
Data cut-off July 31, 2012

Following health authority interactions
- 50% of targeted number of OS events (n=316)
- Actual number of OS events: 331 events

Final OS Analysis
Expected 2014

- Targeted number of events: 632

Patient Demographics and Baseline Characteristics (1)

	Cap + Lap (n=496)	T-DM1 (n=495)
Median age, years (range)	53 (24–83)	53 (25–84)
Race, n (%)		
White	374 (75)	358 (72)
Asian	86 (17)	94 (19)
Black/African American	21 (4)	29 (6)
Other	10 (2)	7 (1)
Not available	5 (1)	7 (1)
World region, n (%)		
United States	136 (27)	134 (27)
Western Europe	160 (32)	157 (32)
Asia	76 (15)	82 (17)
Other	124 (25)	122 (25)
ECOG PS, n (%)		
0	312 (64)	299 (61)
1	176 (36)	194 (39)

Patient Demographics and Baseline Characteristics (2)

	Cap + Lap (n=496)	T-DM1 (n=495)
Measurable disease by independent review, n (%)	389 (78)	397 (80)
Site of disease involvement, n (%)		
Visceral	335 (68)	334 (67)
Non-visceral	161 (32)	161 (33)
Metastatic sites, n (%)		
<3	307 (62)	298 (60)
≥3	175 (35)	189 (38)
Unknown	14 (3)	8 (2)
ER/PR status, n (%)		
ER+ and/or PR+	263 (53)	282 (57)
ER− and PR−	224 (45)	202 (41)
Unknown	9 (2)	11 (2)

Prior Systemic Treatment

	Cap + Lap (n=496)	T-DM1 (n=495)
Prior treatment type, n (%)		
Taxanes	494 (100)	493 (100)
Anthracyclines	302 (61)	303 (61)
Endocrine agents	204 (41)	205 (41)
Prior therapy for MBC, n (%)		
Yes	438 (88)	435 (88)
No	58 (12)	60 (12)
Prior trastuzumab treatment, n (%)	495 (100)	495 (100)
Early breast cancer only	77 (16)	78 (16)
Duration of trastuzumab treatment, n (%)		
<1 year	212 (43)	210 (42)
≥1 year	284 (57)	285 (58)
Median time since last trastuzumab, months (range)	1.5 (0–98)	1.5 (0–63)

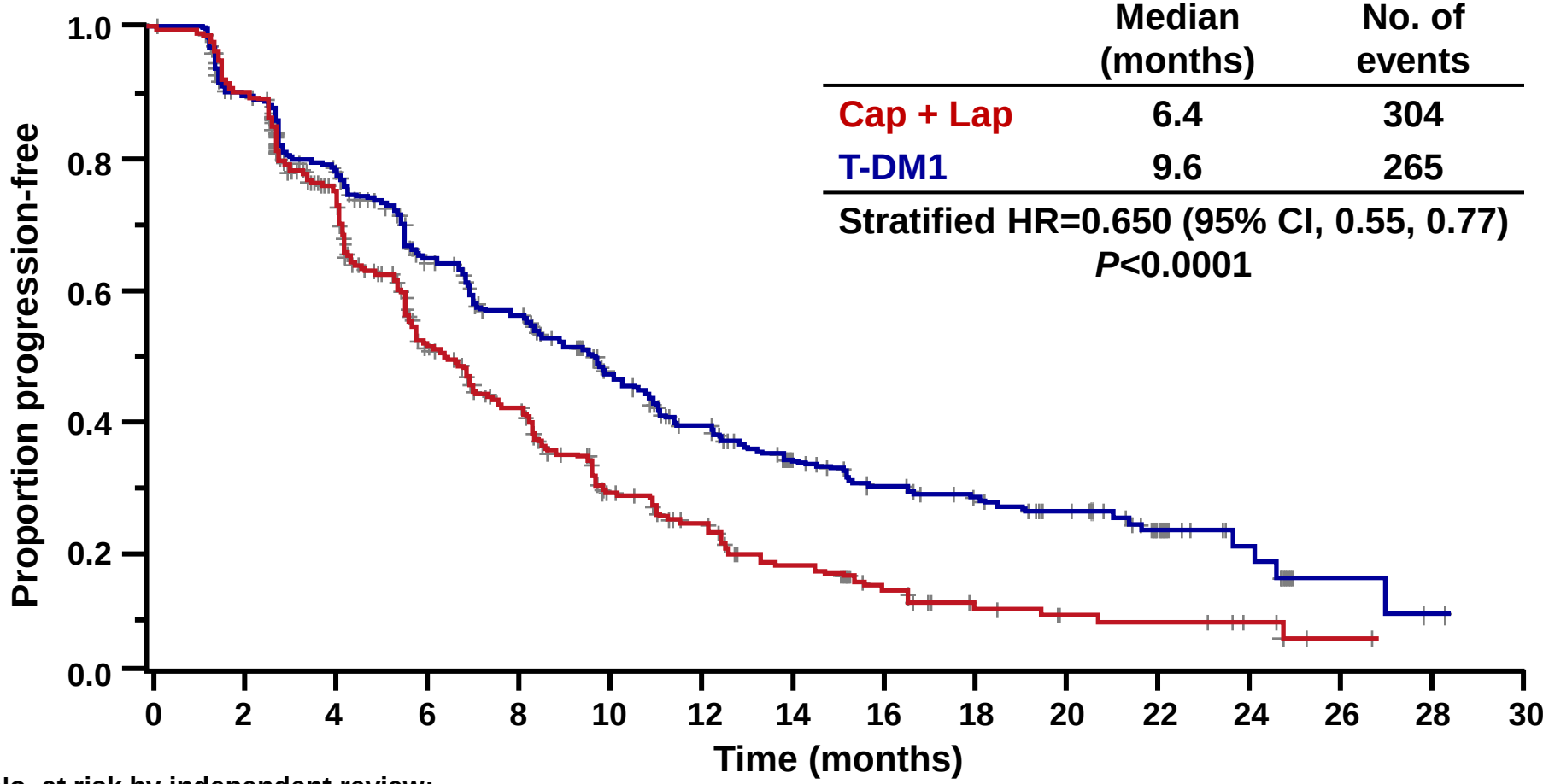
Patient Disposition

	Primary analysis data cut-off Jan 14, 2012		Updated OS data cut-off July 31, 2012	
	Cap + Lap	T-DM1	Cap + Lap	T-DM1
Randomized, n	496	495	496	495
Treated, n	488	490	488	490
Median follow-up, months	12.4	12.9	18.6	19.1
On study at data cut-off date, n	316	366	262	308
On treatment, n	125	182	55	106
Deaths, n	129	94	182	149

Drug Exposure

	Cap (n=487)	Lap (n=488)	T-DM1 (n=490)
Median dose intensity, %	77.2	93.4	99.9
Pts with dose reduction, n (%)	260 (53.4)	133 (27.3)	80 (16.3)
T-DM1 decreased to 3.0 mg/kg, n (%)	—	—	58 (11.8)
T-DM1 decreased to 2.4 mg/kg, n (%)	—	—	22 (4.5)

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:

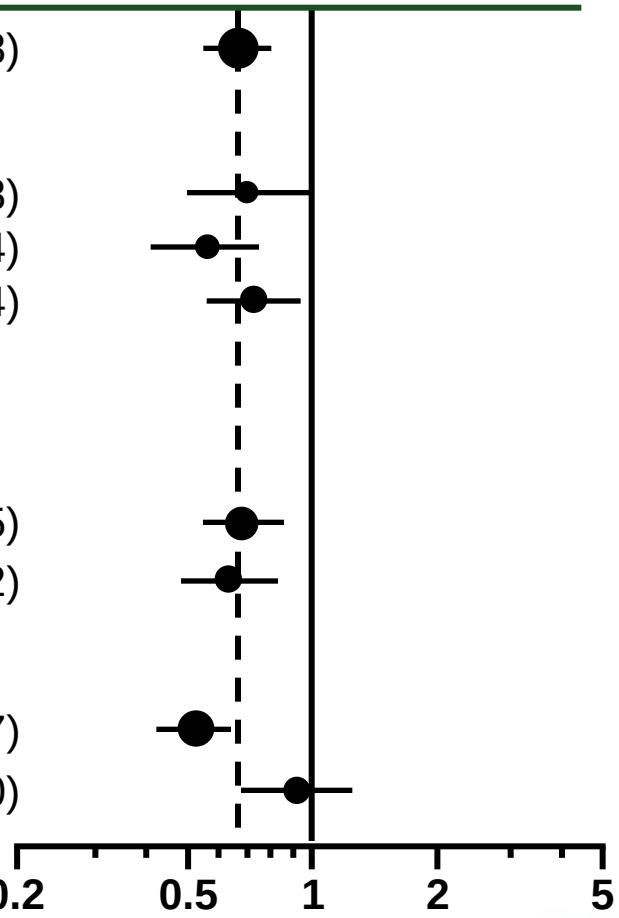
Cap + Lap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

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

Progression-Free Survival Subgroup Analyses

Pre-specified Stratification Factors

Baseline characteristic	Total n	Cap + Lap Median, mos	T-DM1 Median, mos	HR (95% CI)
All patients	991	6.4	9.6	0.66 (0.56, 0.78)
World region				
US	270	5.7	8.5	0.70 (0.51, 0.98)
Western Europe	317	6.4	10.9	0.56 (0.41, 0.74)
Other	404	6.9	9.6	0.73 (0.56, 0.94)
Number prior chemo regimens for MBC or unresectable LABC				
0–1	609	6.7	10.3	0.68 (0.55, 0.85)
>1	382	5.7	8.5	0.63 (0.49, 0.82)
Disease involvement				
Visceral	669	5.7	9.6	0.55 (0.45, 0.67)
Nonvisceral	322	10.2	8.5	0.96 (0.71, 1.30)

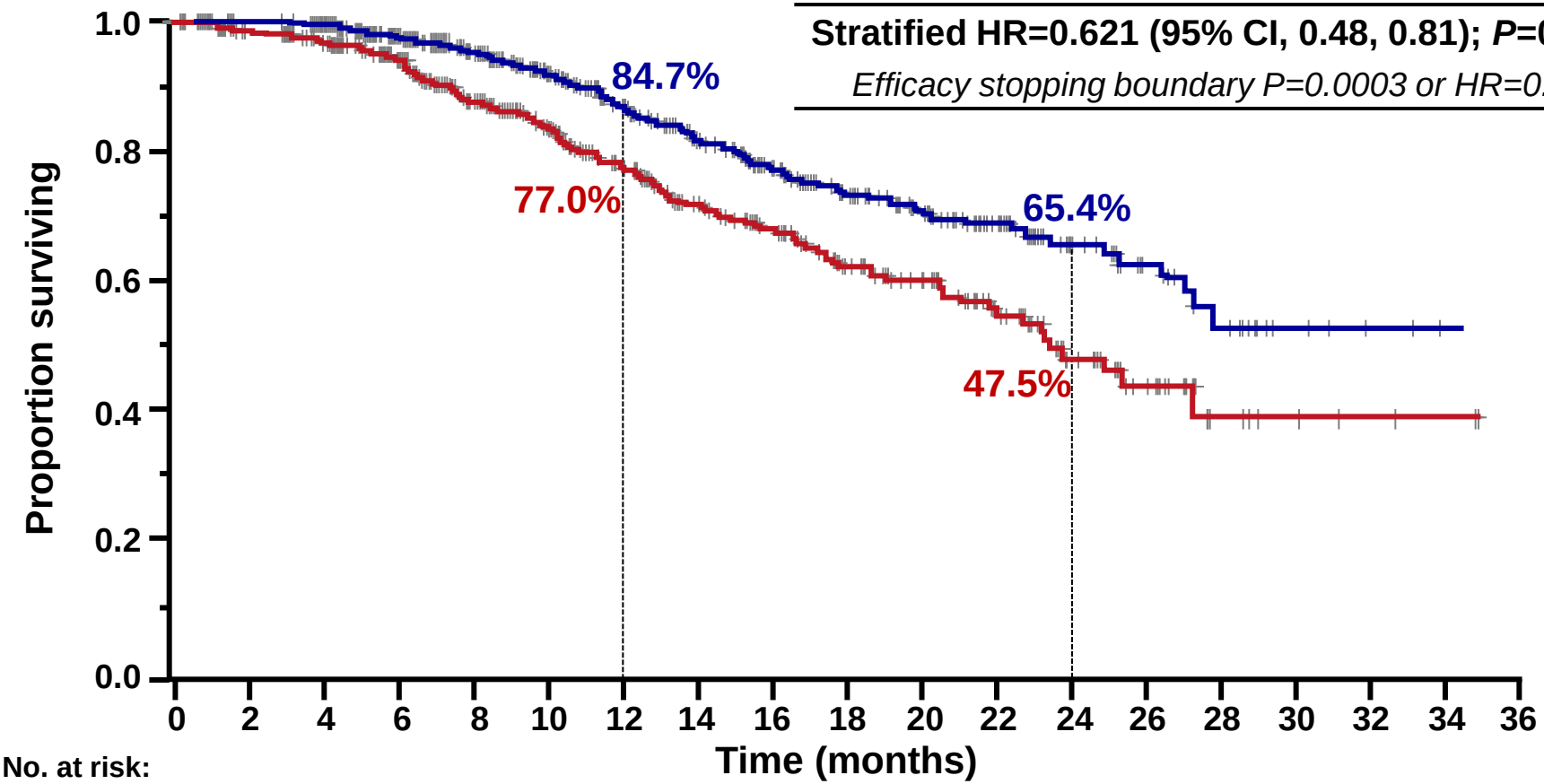


Overall Survival: First Interim Analysis

	Median (months)	No. of events
Cap + Lap	23.3	129
T-DM1	NR	94

Stratified HR=0.621 (95% CI, 0.48, 0.81); *P*=0.0005

Efficacy stopping boundary P=0.0003 or HR=0.617



No. at risk:

Cap + Lap	496	469	438	364	296	242	195	155	129	97	74	52	31	17	7	3	2	1	0
T-DM1	495	484	461	390	331	277	220	182	149	123	96	67	46	29	16	5	2	0	0

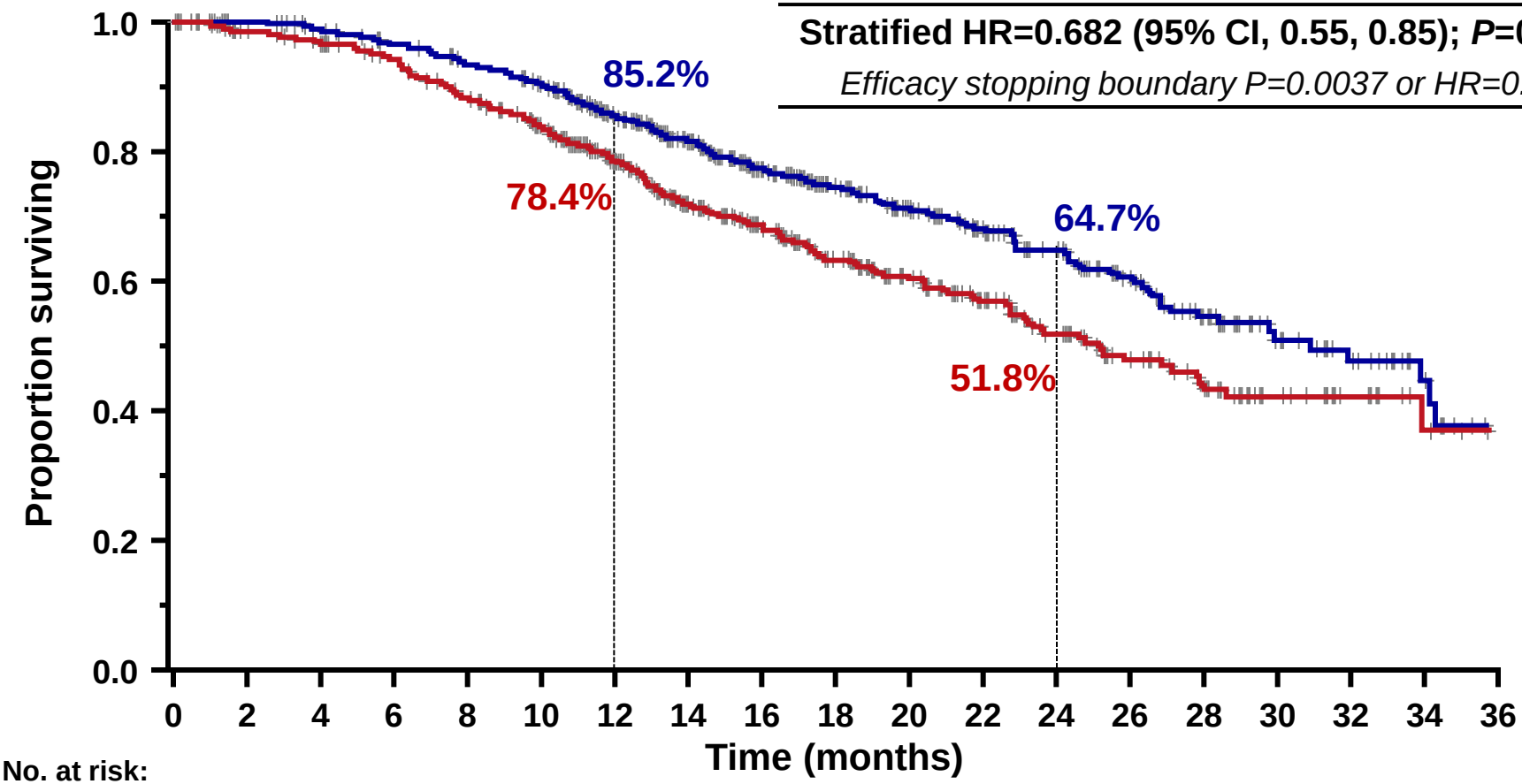
Unstratified HR=0.63 (*P*=0.0005).
NR, not reached.

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

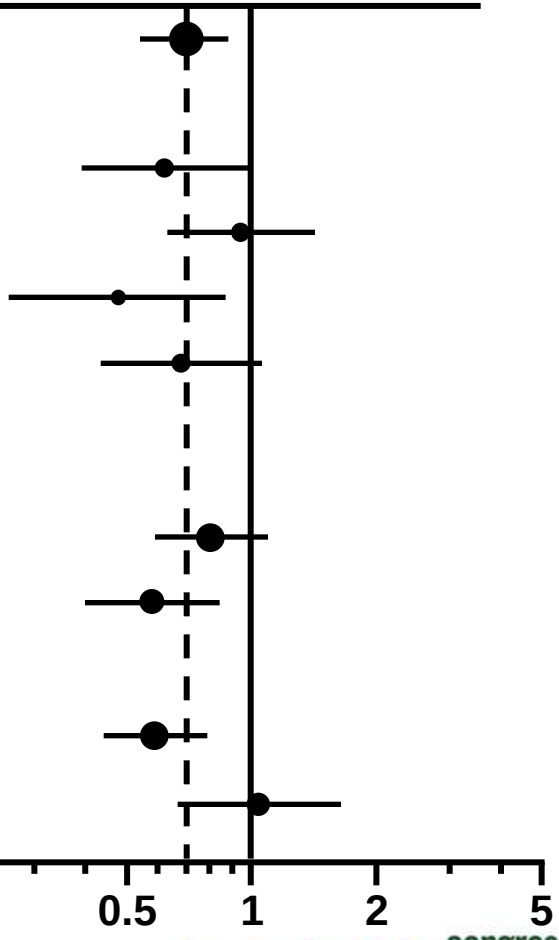


No. at risk:																			
Cap + Lap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

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

Overall Survival Subgroup Analyses

Baseline characteristic	Total n	Cap + Lap Median (mos)	T-DM1 Median (mos)	HR (95% CI)
All patients	991	25.1	30.9	0.70 (0.56, 0.87)
World region				
United States	270	23.7	NR	0.62 (0.41, 0.96)
Western Europe	317	28.6	27.8	0.95 (0.65, 1.39)
Asia	158	22.7	34.3	0.48 (0.27, 0.85)
Other	246	22.7	26.1	0.68 (0.45, 1.04)
Number of prior chemotherapeutic regimens for LABC or MBC				
0–1	609	28.0	29.8	0.80 (0.61, 1.07)
>1	382	22.7	31.9	0.58 (0.41, 0.81)
Disease involvement				
Visceral	669	21.9	28.4	0.59 (0.46, 0.76)
Nonvisceral	322	NR	33.9	1.05 (0.69, 1.61)

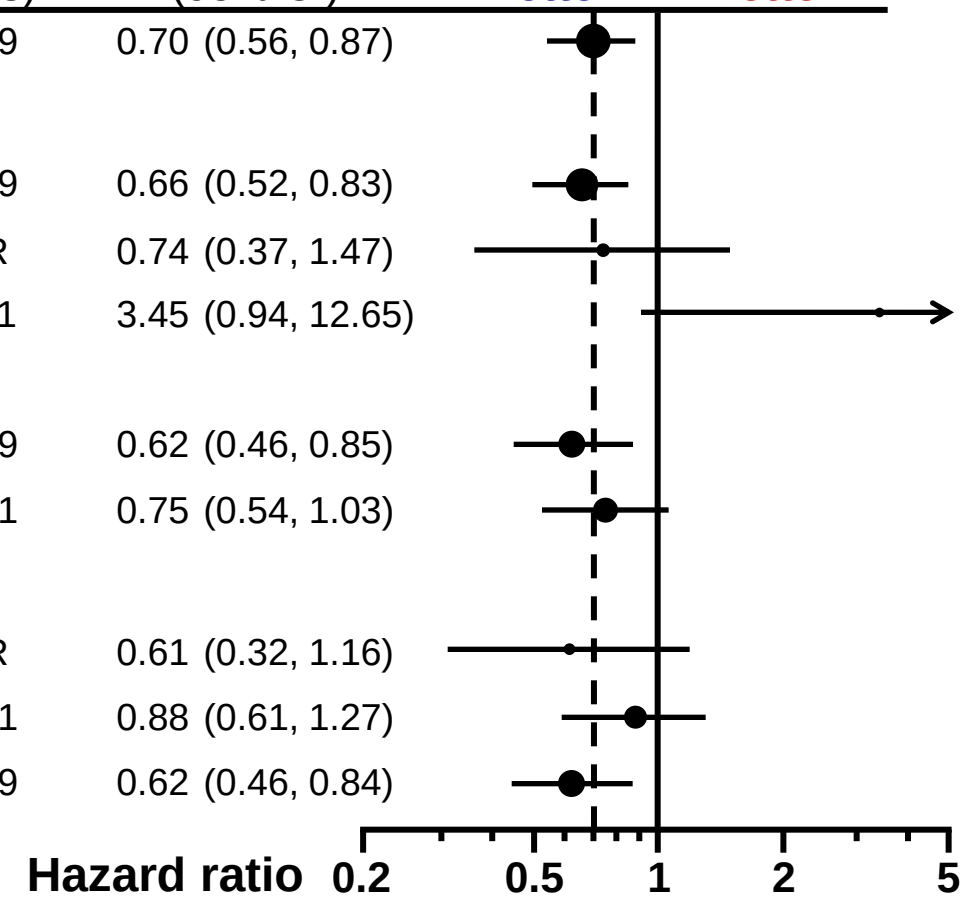


NR, not reached.

From confirmatory OS analysis; data cut-off July 31, 2012.

Overall Survival Subgroup Analyses

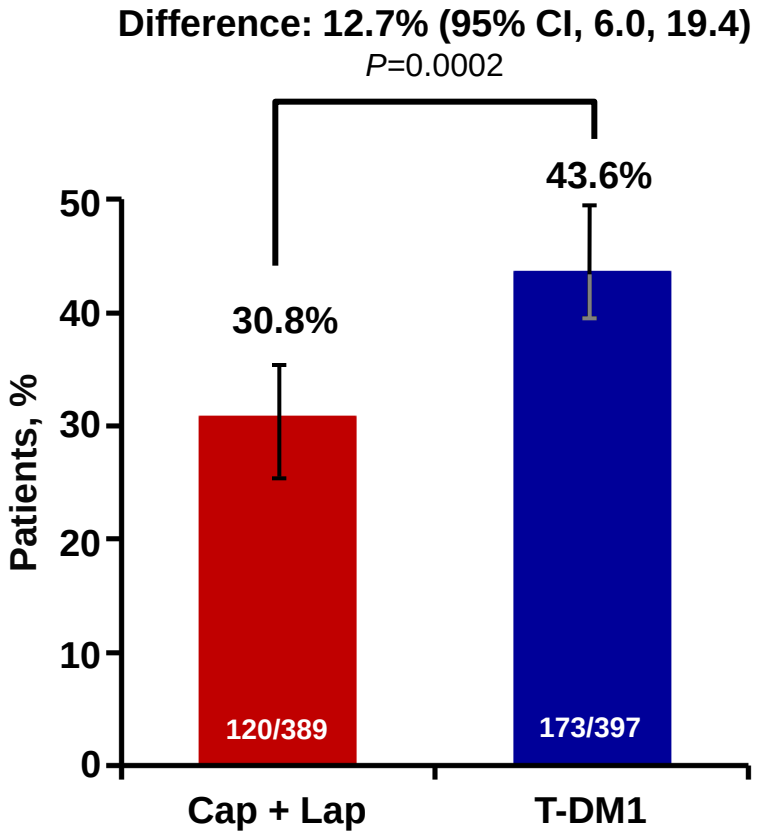
Baseline characteristic	Total n	Cap + Lap Median (mos)	T-DM1 Median (mos)	HR (95% CI)
All patients	991	25.1	30.9	0.70 (0.56, 0.87)
Age group				
<65 years	853	24.6	30.9	0.66 (0.52, 0.83)
65–74 years	113	27.1	NR	0.74 (0.37, 1.47)
≥75 years	25	NR	11.1	3.45 (0.94, 12.65)
ER and PR status				
ER+ and/or PR+	545	25.3	31.9	0.62 (0.46, 0.85)
ER– and PR–	426	23.7	27.1	0.75 (0.54, 1.03)
Line of therapy[a]				
First-line	118	27.9	NR	0.61 (0.32, 1.16)
Second-line	361	NR	27.1	0.88 (0.61, 1.27)
Third- and later-line	512	23.3	33.9	0.62 (0.46, 0.84)



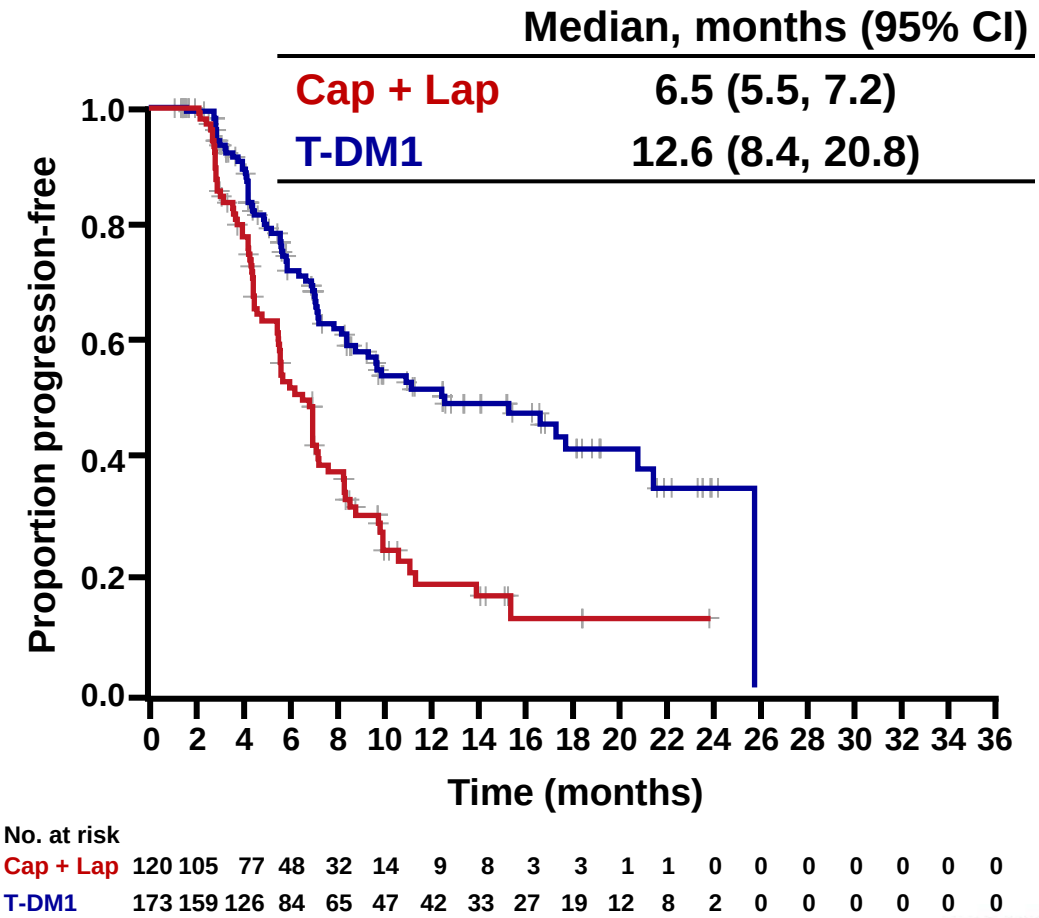
[a]Defined as any systemic therapy including endocrine and chemotherapy.
NR, not reached.
From confirmatory OS analysis; data cut-off July 31, 2012.

ORR and DOR in Patients with Measurable Disease

Objective response rate (ORR)



Duration of response (DOR)



Overview of Adverse Events

	Cap + Lap (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 (%)[a]	4 (0.8)	1 (0.2)

[a]Cap + Lap: coronary artery disease, multi-organ failure, coma, and hydrocephalus; T-DM1: metabolic encephalopathy.

Adverse Events

Grade ≥3 AEs With Incidence ≥2%

	Cap + Lap (n=488)		T-DM1 (n=490)	
Adverse Event	**All Grades, %**	**Grade ≥3, %**	**All Grades, %**	**Grade ≥3, %**
Diarrhea	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
Hypokalemia	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**
Anemia	8.0	1.6	10.4	**2.7**

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Cardiac Dysfunction

	Cap + Lap	T-DM1
Cardiac dysfunction AEs,[a] n (%)	(n=488)	(n=490)
All grades	15 (3.1)	9 (1.8)
Grade 3	2 (0.4)	1 (0.2)
Lowest post-baseline LVEF value, n (%)	(n=461)	(n=482)
≥45%	454 (98.5)	476 (98.8)
≥40 to <45%	4 (0.9)	3 (0.6)
<40%	3 (0.7)	3 (0.6)
LVEF <50% and ≥15-point decrease from baseline, n (%)	(n=445) 7 (1.6)	(n=481) 8 (1.7)

[a]Includes preferred terms 'decreased ejection fraction' and 'left ventricular dysfunction'; Does not include cardiac AEs (e.g. myocardial infarction, atrial fibrillation).

Conclusions

In the EMILIA study, T-DM1 achieved:

- **Significant improvement in PFS**
  - **Median PFS: Cap + Lap 6.4 mos; T-DM1 9.6 mos**
  - **HR=0.650; *P*<0.0001**
- **Significant improvement in OS**
  - **Median OS: Cap + Lap 25.1 mos; T-DM1 30.9 mos**
  - **HR=0.682; *P*=0.0006**

Key secondary efficacy endpoints including time to symptom progression[1] were also significantly improved with T-DM1

The safety profile of T-DM1 was favorable to that of Cap + Lap

T-DM1 should offer an important therapeutic option in the treatment of HER2-positive metastatic breast cancer

[1]Welslau et al. ESMO 2012, Poster 329P.

Thanks

To the scientists

To the investigators, clinicians and research staff at the 213 sites in 26 countries

To all of the patients who participated in the trial and their families

EMILIA
A clinical trial of trastuzumab emtansine (T-DM1) in HER2+ MBC