Immune Conjugates in Breast Cancer

Hannah Linden MD FACP

“Prediction #1: “The era of HER2 is almost over.

We will always have patients relapsing with HER2-positive disease, and this will require novel therapies. But from a public health standpoint, I believe HER2 is almost over.”

George Sledge MD ASCO Past President, ASCO post reporting of ASCO Breast Symposium 2013

“Why your preferred targeted drugs may become unaffordable:

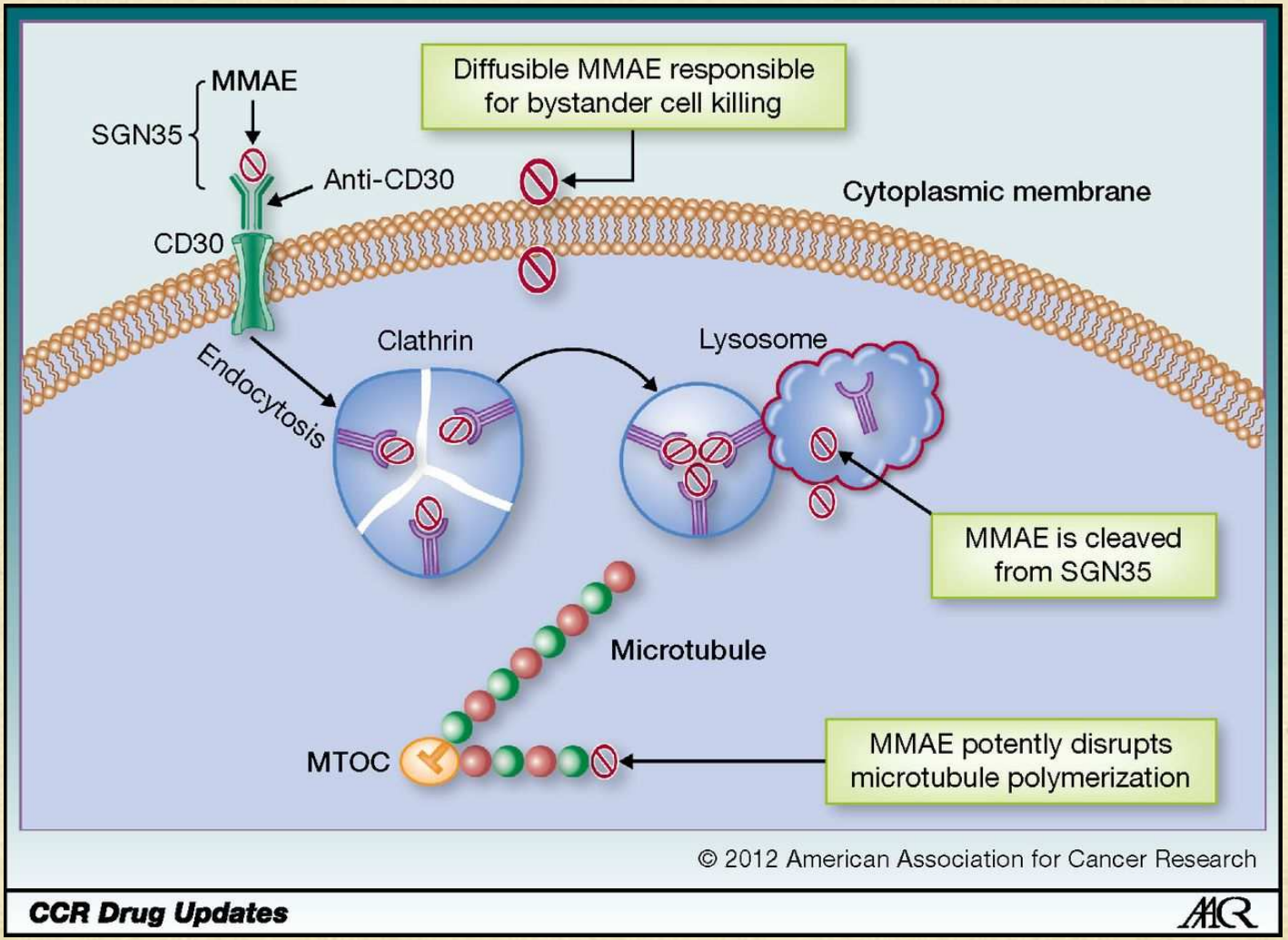
Optimal duration, [of Trastuzumab], is poorly defined… both in Advanced and Early disease… with a significant economic impact in the adjuvant setting where the drug is arbitrarily given for 1 year”

Martine J Piccart President European Society for Medical Oncology (ESMO) Cancer Res. 2013 Oct 1;73(19):5849-51

Outline

- Immune Conjugates in solid tumors
- Context in Breast Cancer
- Recent data
- Pending data
- Unanswered questions
- Future directions

Mechanism of action of Brentuximab Vedotin.



Deng C et al. Clin Cancer Res 2013;19:22-27

Brentuximab vedotin (SGN-35)

FDA approved indications

profoundly changes how we manage CD30-positive lymphoproliferative malignancies

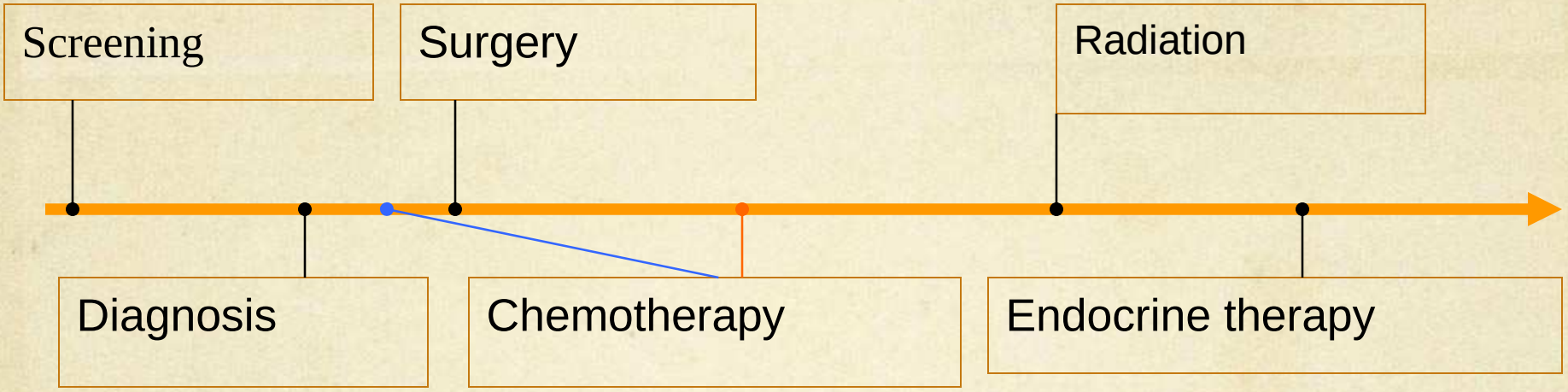
- 1. Relapsed Hodgkin lymphoma
  - Post autologous stem-cell transplantation (ASCT),
  - or after two multidrug regimens in patients with Hodgkin lymphoma who are not candidates for ASCT; and
- 2. patients with systemic anaplastic large cell lymphoma (ALCL) who failed at least one prior multidrug chemotherapy regimen.
- Markedly high response rates for a single agent, exceeding 70% and 80% for Hodgkin lymphoma and ALCL, respectively.
- Complete response rate was equally as impressive, at 34% and 57% for Hodgkin lymphoma and ALCL, respectively

Deng et al. Clin Cancer Res. 2013 Jan 1;19(1):22-7.

TDM-1, trastuzumab emtansine

- A potent, low toxicity “targeted” therapy for HER2 positive breast cancer
  - And probably other HER2 positive tumors
  - Promising data in gastric cancer
- Effective alone, and in synergy with other chemo and immune therapies
- Currently FDA approved for salvage treatment of HER2 positive breast cancer which has progressed on trastuzumab, and following taxane, anthracycline exposure
- Testing in earlier lines of therapy is underway to determine optimal timing, sequencing, synergies.

Diagnosis and Treatment



Neoadjuvant,

Adjuvant,

Preventative

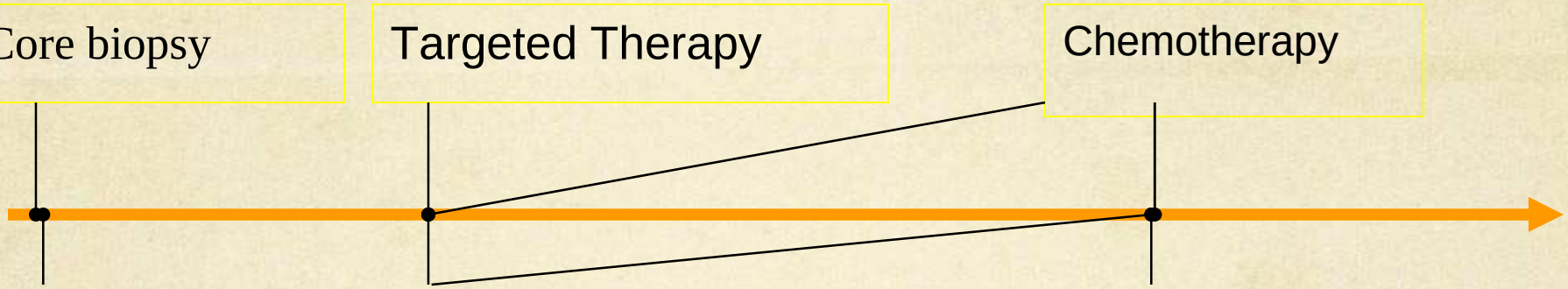
Exam,
Mammography
(Screening and
Diagnostic)
Genetic testing?
MRI

Lumpectomy or
Mastectomy;
Sentinel Node
Biopsy +/- Axillary
Node dissection
Reconstruction

Breast Cancer Staging

- High risk
  - Atypical Ductal (or Lobular) Hyperplasia, Lobular Carcinoma in situ
- 0
  - Ductal Carcinoma in Situ (DCIS)
- I
  - No Lymph node involvement
  - >2cm
- II
  - Lymph node involvement
- III
  - Very large Tumor, Deep/fixed Nodes, or Skin involved
- IV
  - Cancer in sites other than Breast and Nodes, locally

Stage IV Diagnosis and Treatment



ER+ 65-75%
HER2+ 15-25%
"triple neg" ~20-30%

Endocrine Therapy/immune therapy

Radiation therapy as needed

Heterogeneity, between primary tumor and metastatic biopsy is seen in ~ 15-20%

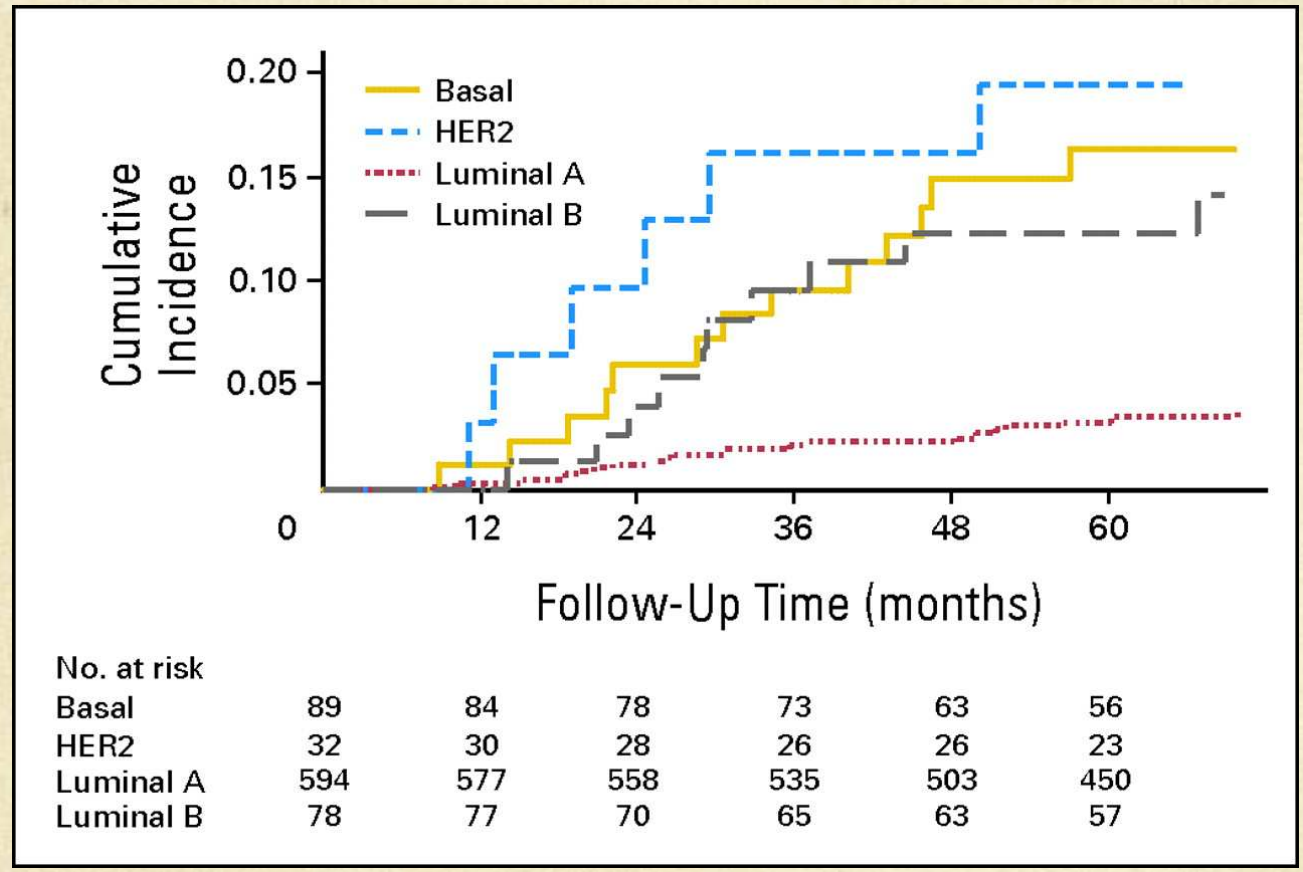
Amir et al JCO 30, 6, 2012

All Palliative

Can go through many lines of therapy

Surgery rarely indicated

Phenotype predicts outcome prognostic and predictive



HER2+=ER, PR-

Basal=ER, PR, H2-

LumB=ER or PR+ H2+

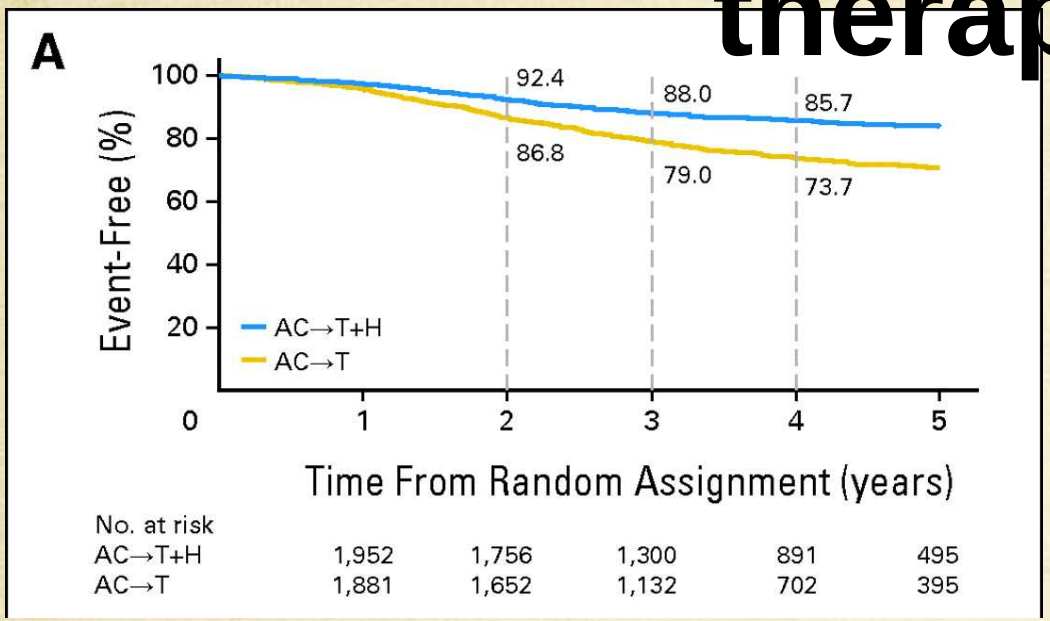
LumA=ER+ H2-

Protein expression to roughly describe genomic profile

Fig 2. Cumulative incidence of distant metastases by breast cancer subtype
Observational series of patients undergoing radiation therapy at DFCC
Pre-trastuzumab era

Nguyen, P. L. et al. J Clin Oncol; 26:2373-2378 2008

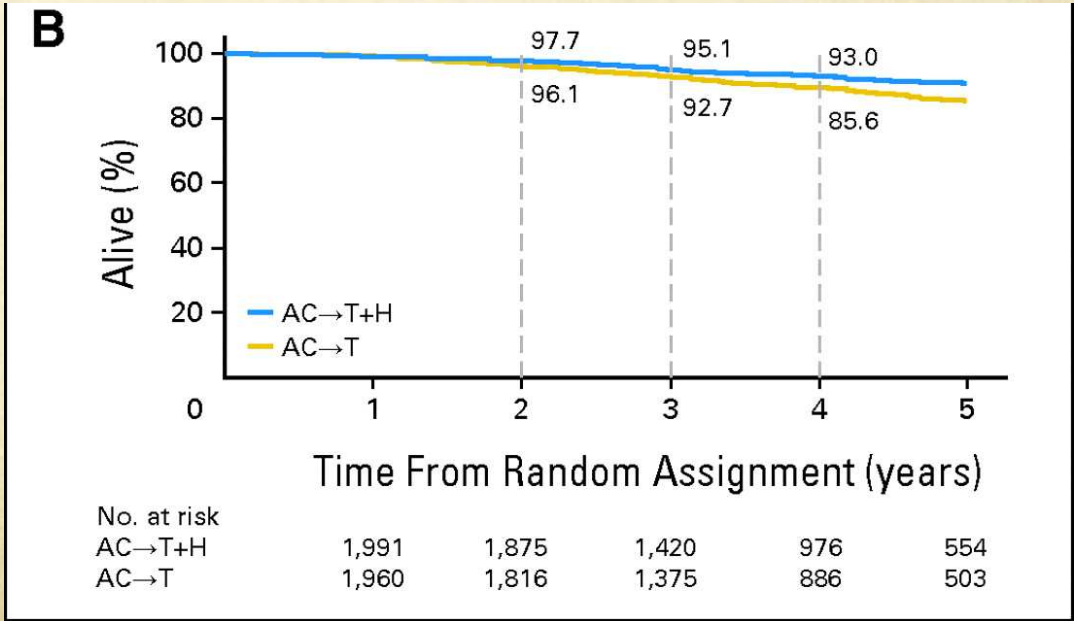
Durable benefit of Immune therapy



Kaplan-Meier estimates of (A) event-free survival and (B) overall survival.

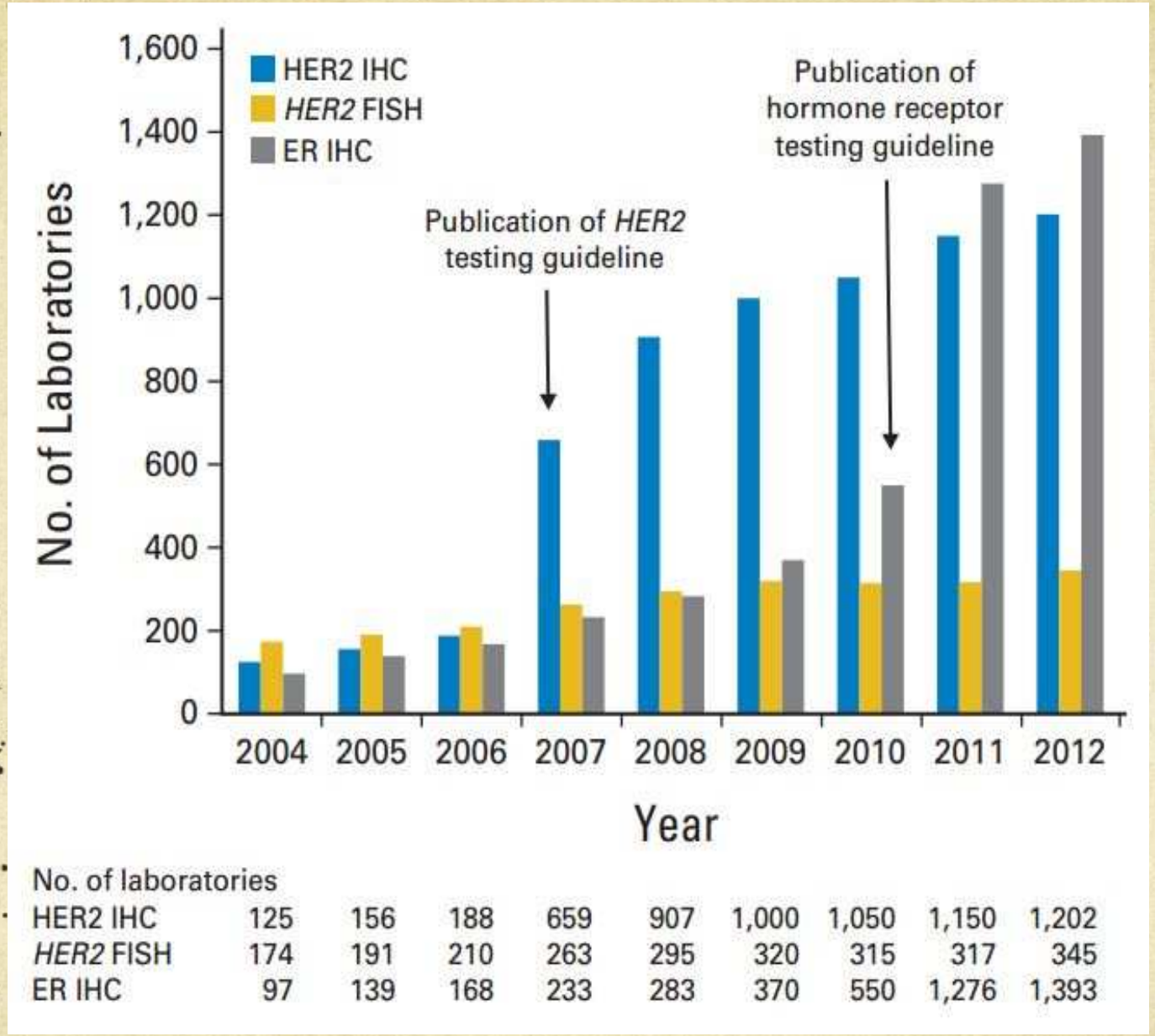
Joint Analysis of Data From NCCTG N9831 and NSABP B-31

JOURNAL of CLINICAL ONCOLOGY ASCO
Perez E A et al. JCO 2011;29:3366-3373



HER2 directed therapy

- Requires expression of HER2
  - by the tumor at the time of therapy
  - *Biopsy to confirm phenotype of metastasis is indicated*
- Many ‘targeted agents’
  - Trastuzumab,
  - Pertuzumab
  - TKIs e.g. lapatinib
- Difficult to test all sequences, synergies
  - Chemotherapy synergy with trastuzumab is PROVEN to be ongoing
  - Continued immune therapy *with* chemotherapy is indicated
    - The ability to give chemo with trastuzumab, nth line, delayed approval of TDM-1
- Like lymphoma, less *may* be better

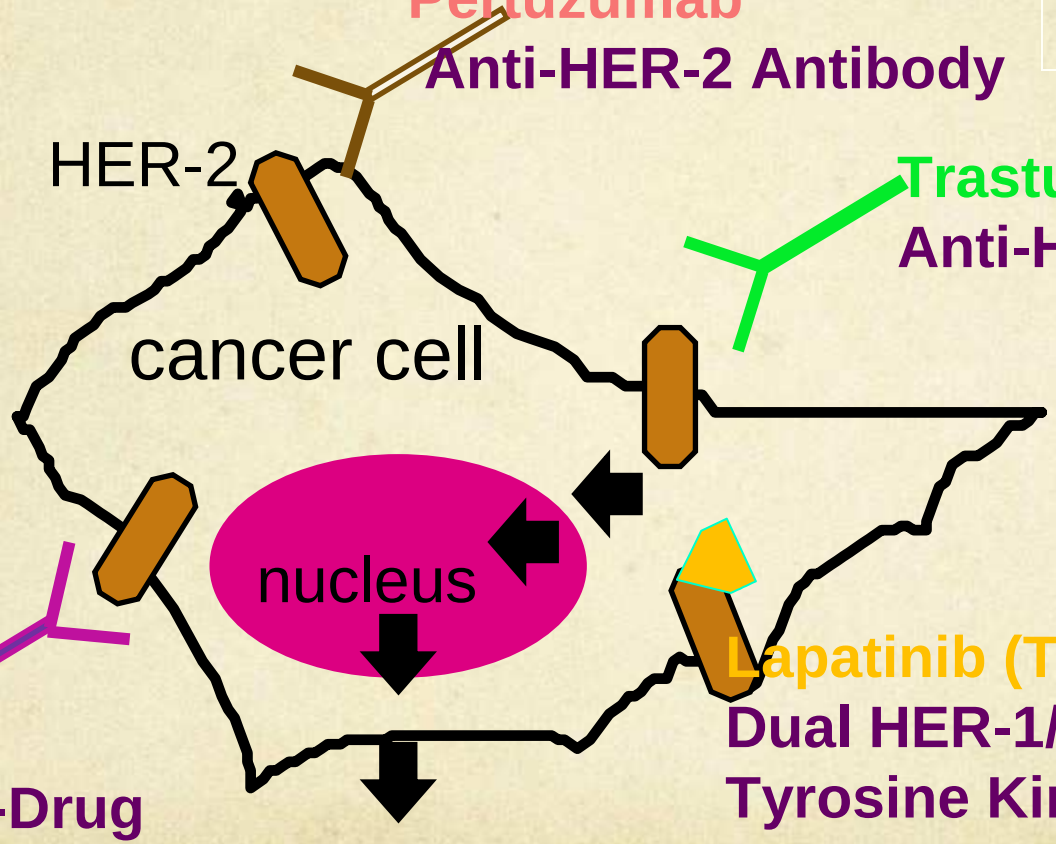


No. of laboratories									
HER2 IHC	125	156	188	659	907	1,000	1,050	1,150	1,202
HER2 FISH	174	191	210	263	295	320	315	317	345
ER IHC	97	139	168	233	283	370	550	1,276	1,393

Krop I, Winer EP. Trastuzumab emtansine: a novel antibody-drug conjugate for HER2-positive breast cancer. Clin Cancer Res. Published OnlineFirst October 17,

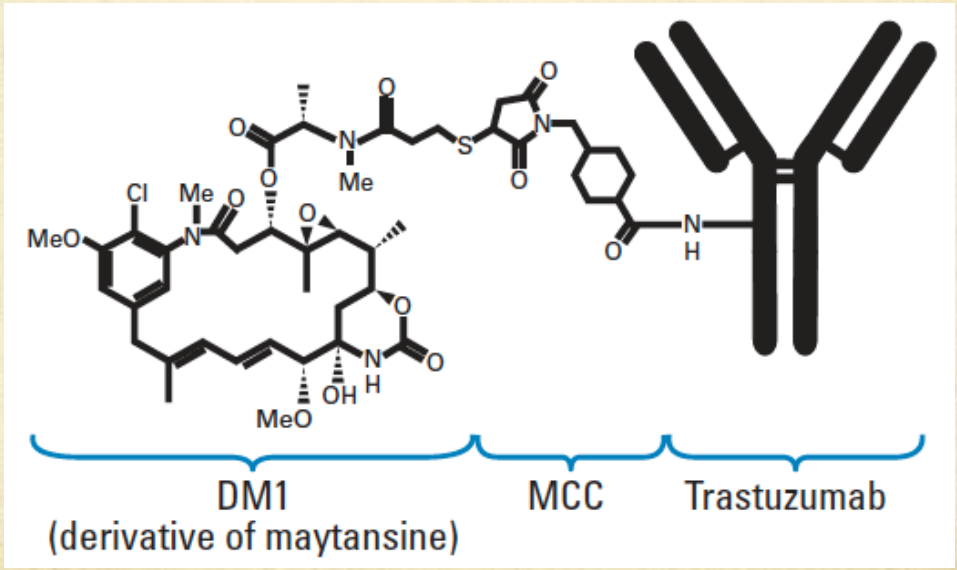
Four FDA-Approved Drugs with HER-2 as a Target

15-25% of breast cancers overexpress HER2

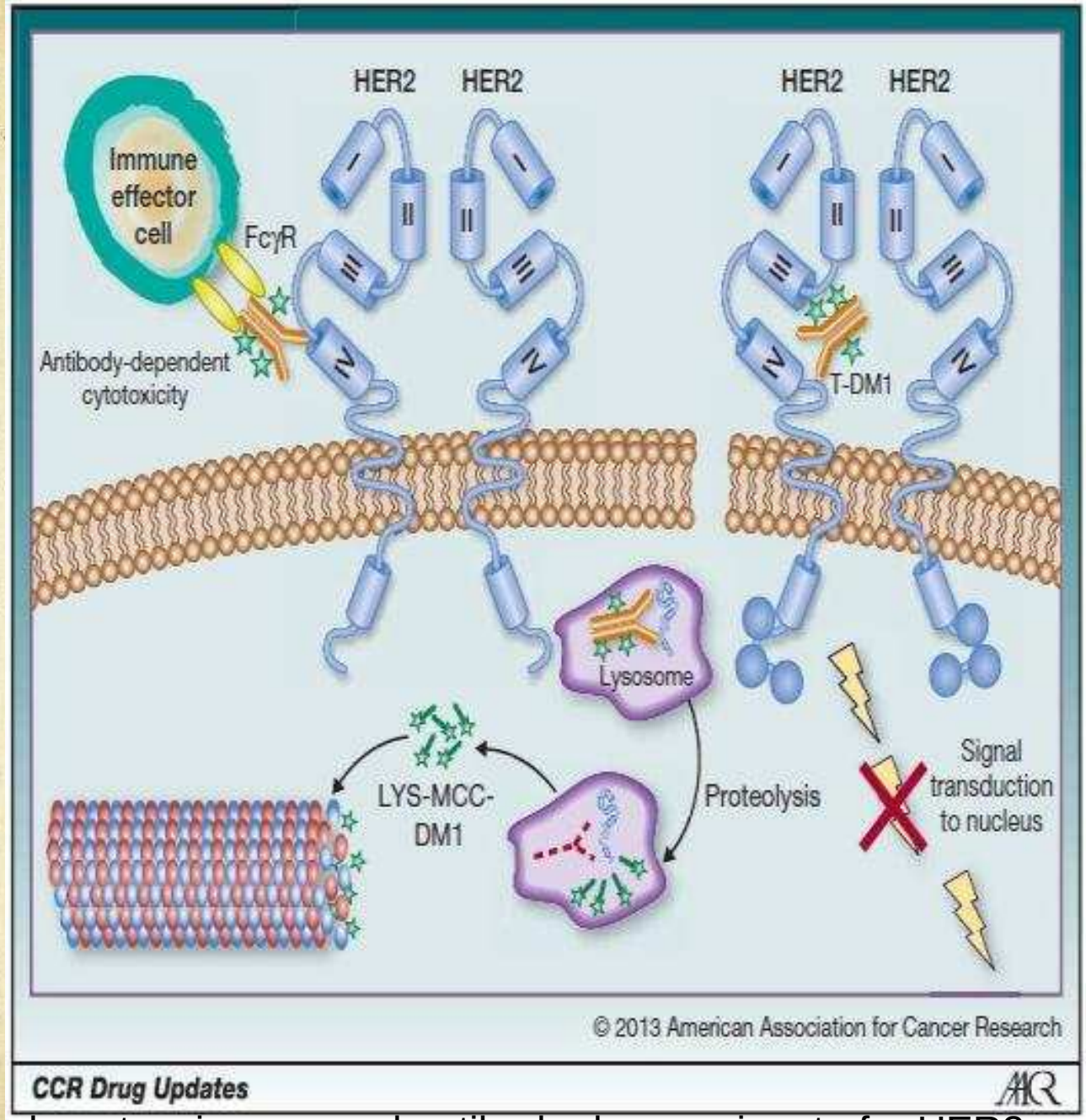


Immunoconjugate/ADC

- TDM-1: Trastuzumab Emtansine
  - Antibody Drug Conjugate (ADC)
  - Trastuzumab is linked to an antimicrotubule drug (maytansine or DM1) for a targeted and antineoplastic effect
  - Trastuzumab binds to HER2 cancer cells, is absorbed, and then releases DM1



Burris H, et al . JCO 2011;29(4):398-405



Krop I, Winer EP. Trastuzumab emtansine: a novel antibody-drug conjugate for HER2-positive breast cancer. Clin Cancer Res. Published OnlineFirst October 17, 2013

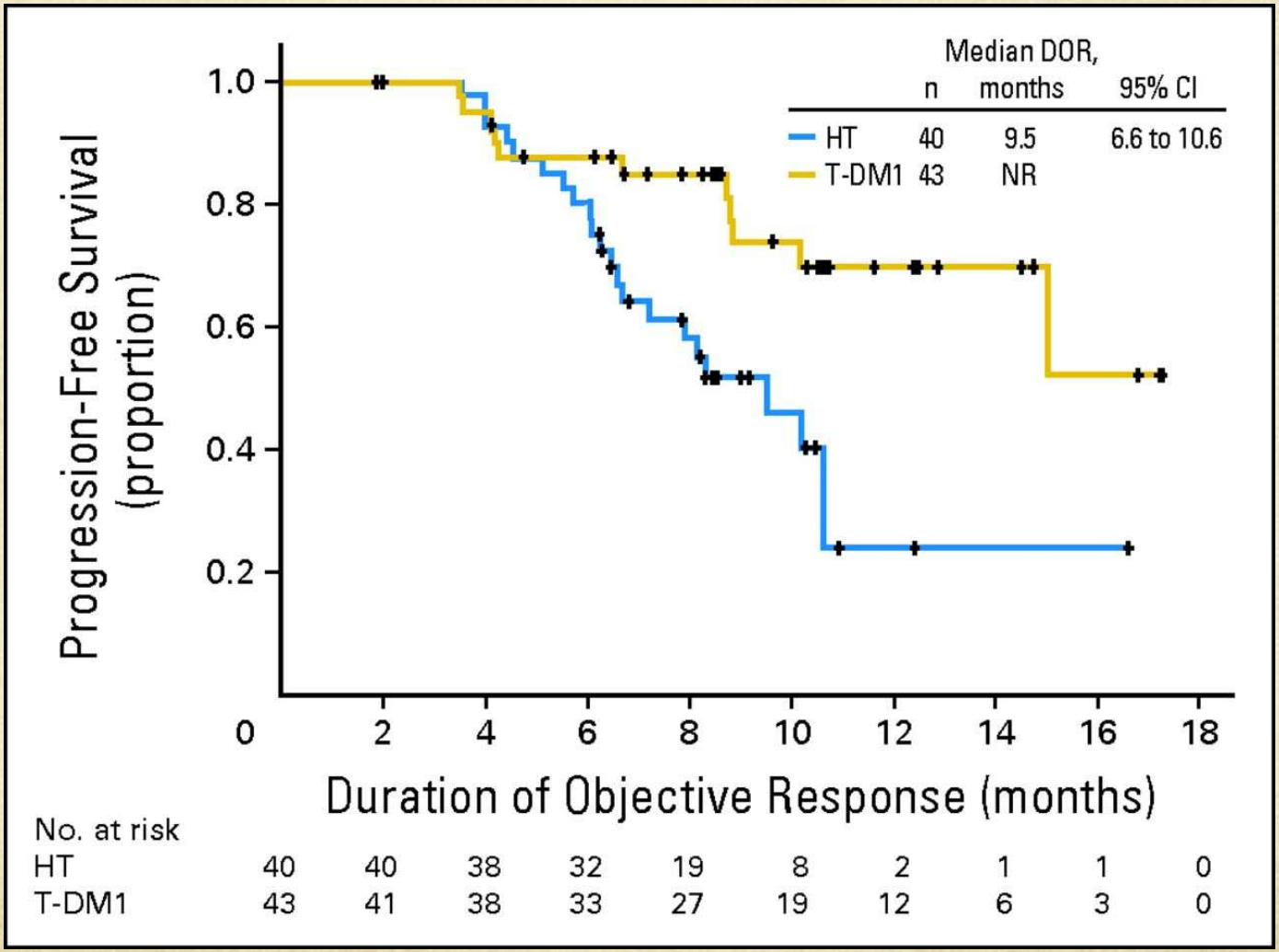
1st line MBC: TDM-1 vs Docetaxel + Trastuzumab

Randomized 1:1, phase II, international, open-label trial

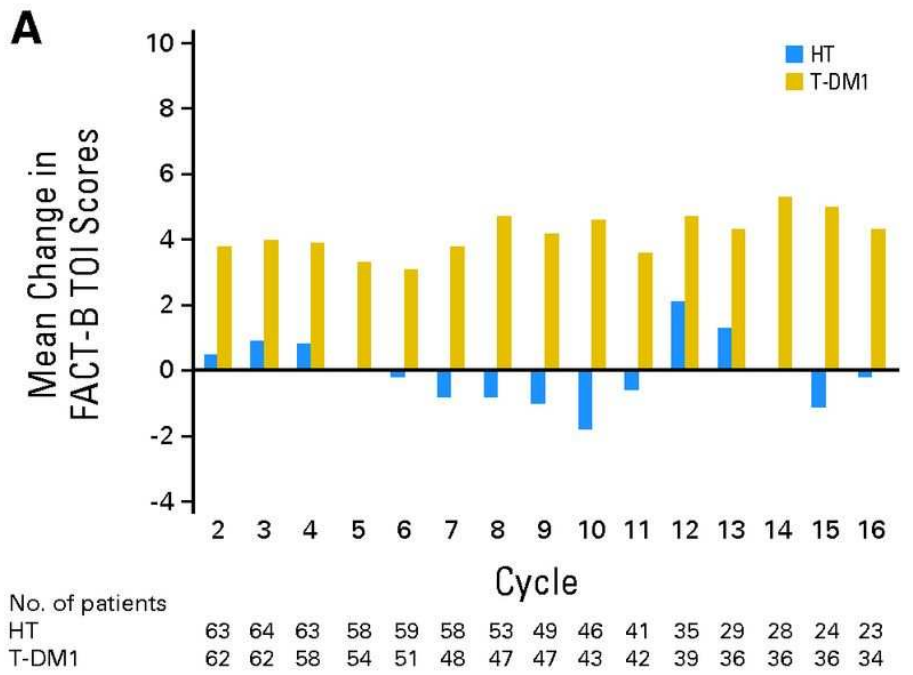
- Primary end points
  - PFS by Investigator
  - Safety
- Secondary end points
  - ORR, clinical benefit
  - OS
  - QOL, symptom control

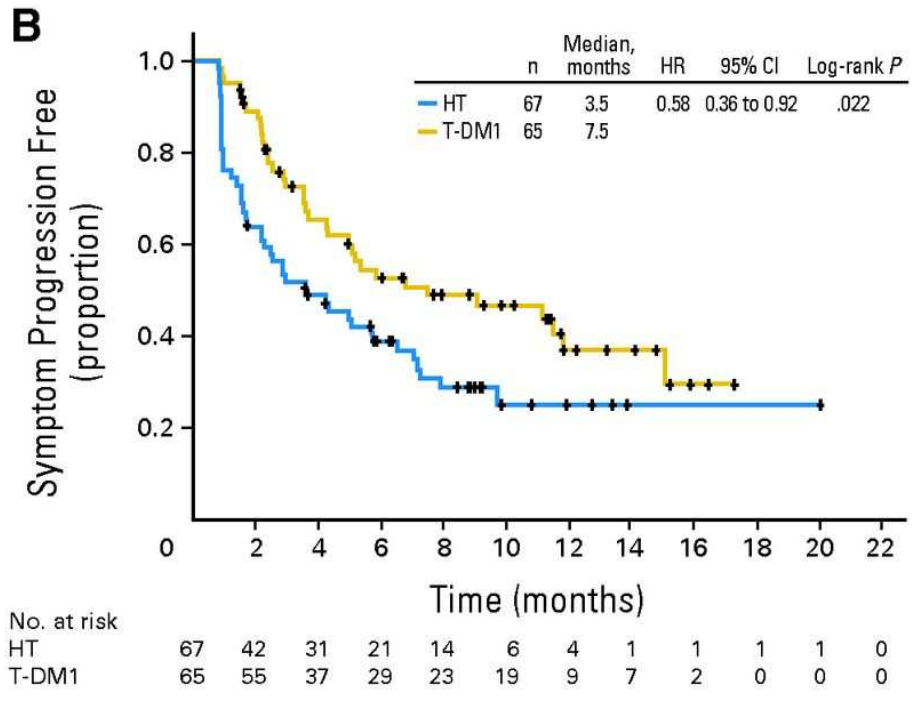
Perez EA, et al. Abstr LBA3. ESMO 2010
Hurvitz S, et al. ESMO 2011

Kaplan-Meier estimates of duration of response (DOR) by investigator.



Hurvitz S A et al. JCO 2013;31:1157-1163





(A) Mean change in Functional Assessment of Cancer Therapy-Breast (FACT-B) Trial Outcome Index (TOI) scores from baseline.

Hurvitz S A et al. JCO 2013;31:1157-1163

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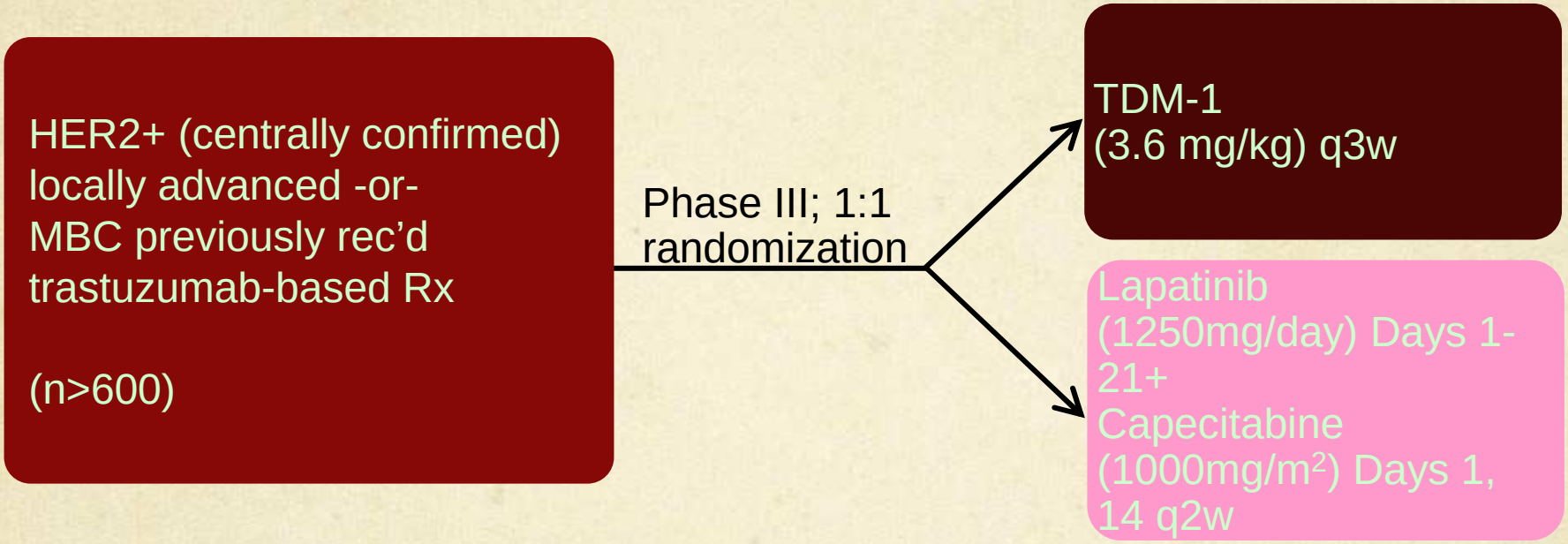
Refractory: TDM-1 vs. Capecitabine + Lapatinib in HER2+ MBC (EMILIA)

Press Release March 30, 2012: Positive for PFS

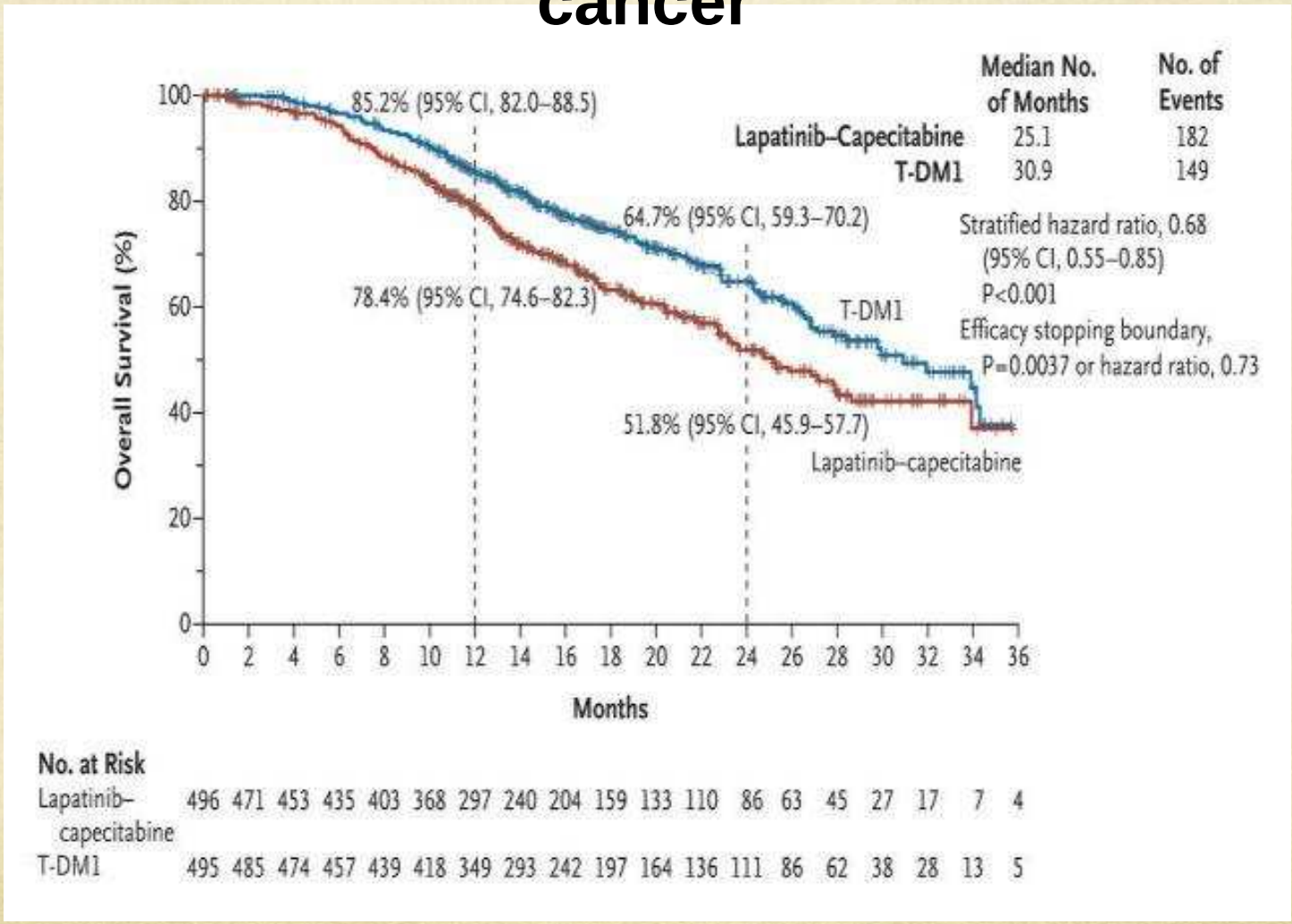


Key inclusion criteria

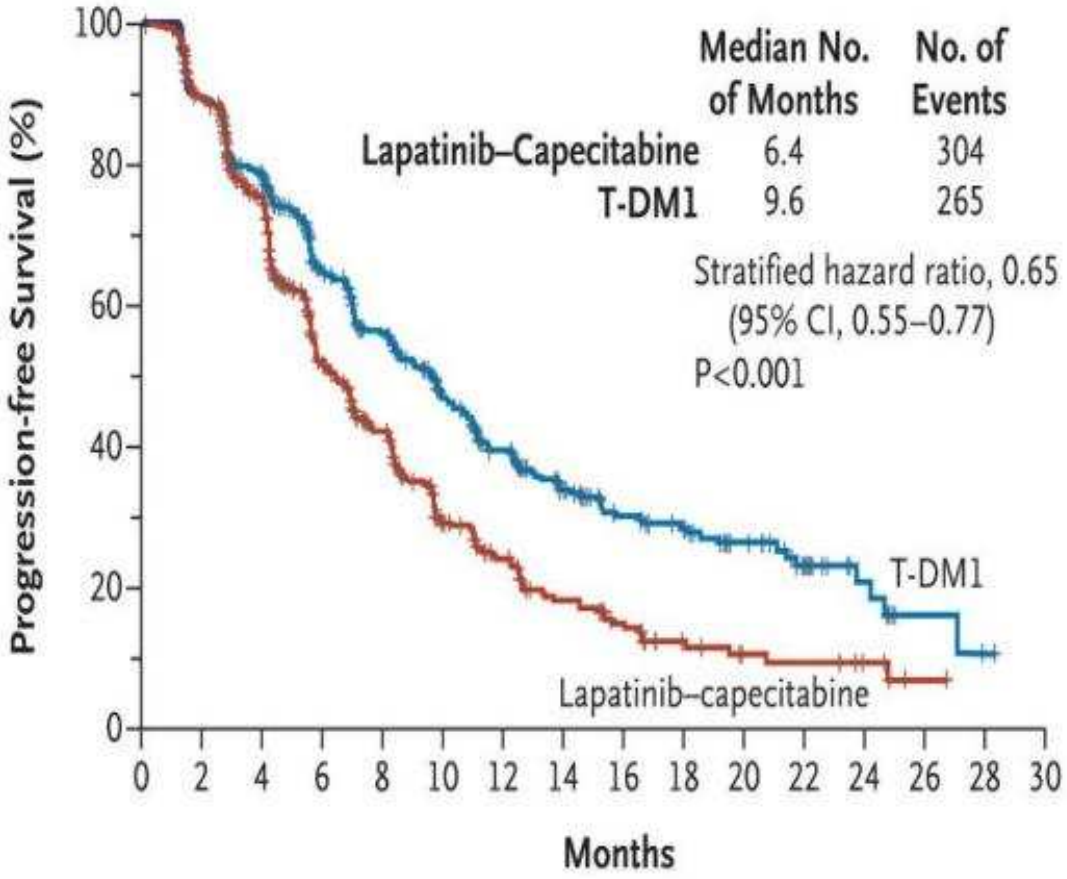
- Prior treatment to include taxane and trastuzumab in adjuvant, locally advanced ,or metastatic setting
- Documented progression of disease during or after treatment for advanced/metastatic disease or within 6 months of completing adjuvant therapy

- Primary end points
  - Overall Survival
  - PFS by IRF
  - Safety
- Secondary end point
  - Quality of life

Overall Survival Favors TDM-1 over Standard Therapy in salvage treatment of metastatic breast cancer



Verma S et al, NEJM 367:1783-1791, 2012



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

Progression Free survival also superior for TDM-1

TDM-1 (ado-trastuzumab emtansine) FDA approved March, 2013

Verma S et al, NEJM 367:1783-1791, 2012

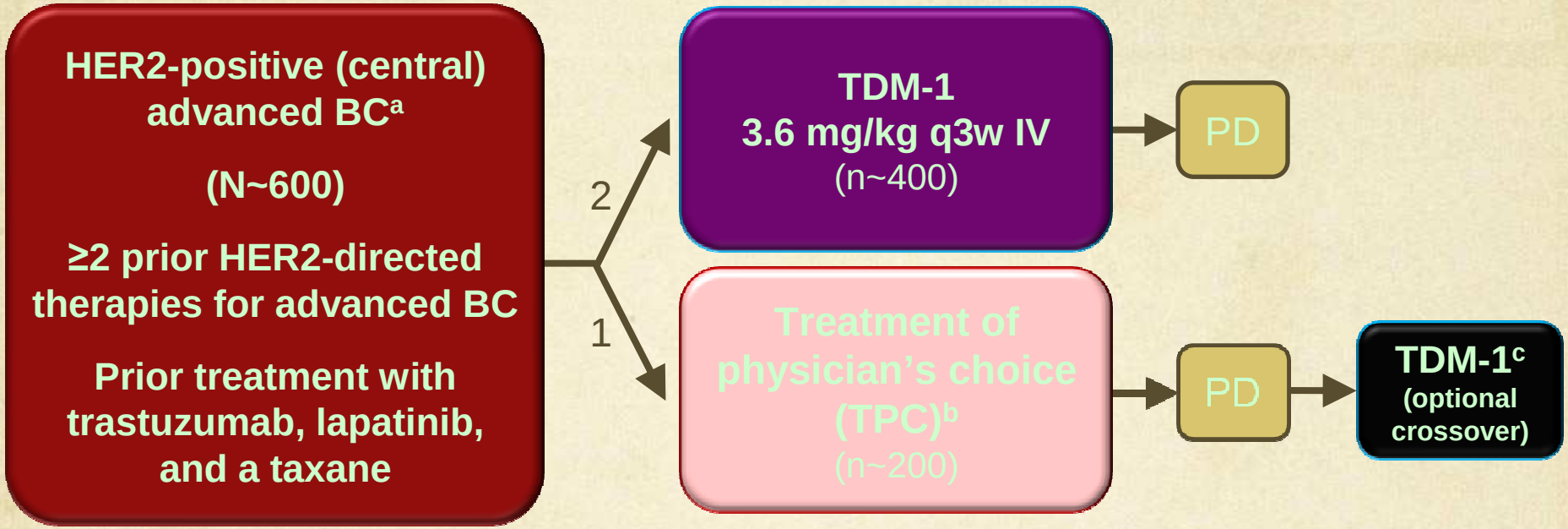
EMELIA: Adverse Events

Table 2. Adverse Events of Any Grade Occurring in ≥ 25% and/or Grade ≥ 3 Occurring in ≥ 5% of Patients in Either Treatment Group

	All Grade				Grade ≥ 3*			
	HT (n = 66)†		T-DM1 (n = 69)†‡		HT (n = 66)†		T-DM1 (n = 69)†‡	
Adverse Event	No.	%	No.	%	No.	%	No.	%
Hematologic								
Neutropenia§	**43**	**65.2**	**11**	**15.9**	**41**	**62.1**	**4**	**5.8**
Thrombocytopenia§	**4**	**6.1**	**19**	**27.5**	2¶	3.0	5¶	7.2
Leukopenia§	17	25.8	7	10.1	**16**	**24.2**	**0**	
Febrile neutropenia	9	13.6	0		9	13.6	0	
Anemia	18	27.3	9	13.0	3	4.5	2	2.9
Nonhematologic								
Alopecia	**44**	**66.7**	**3**	**4.3**	—‖		—‖	
Fatigue	30	45.5	34	49.3	3	4.5	3	4.3
Nausea	29	43.9	34	49.3	0		2	2.9
Diarrhea	**30**	**45.5**	**11**	**15.9**	2	3.0	0	
Peripheral edema	**29**	**43.9**	**7**	**10.1**	4	6.1	0	
Increased AST	**4**	**6.1**	**30**	**43.5**	0		6	8.7
Pyrexia	15	22.7	28	40.6	1	1.5	0	

Verma S et al, NEJM 367:1783-1791, 2012

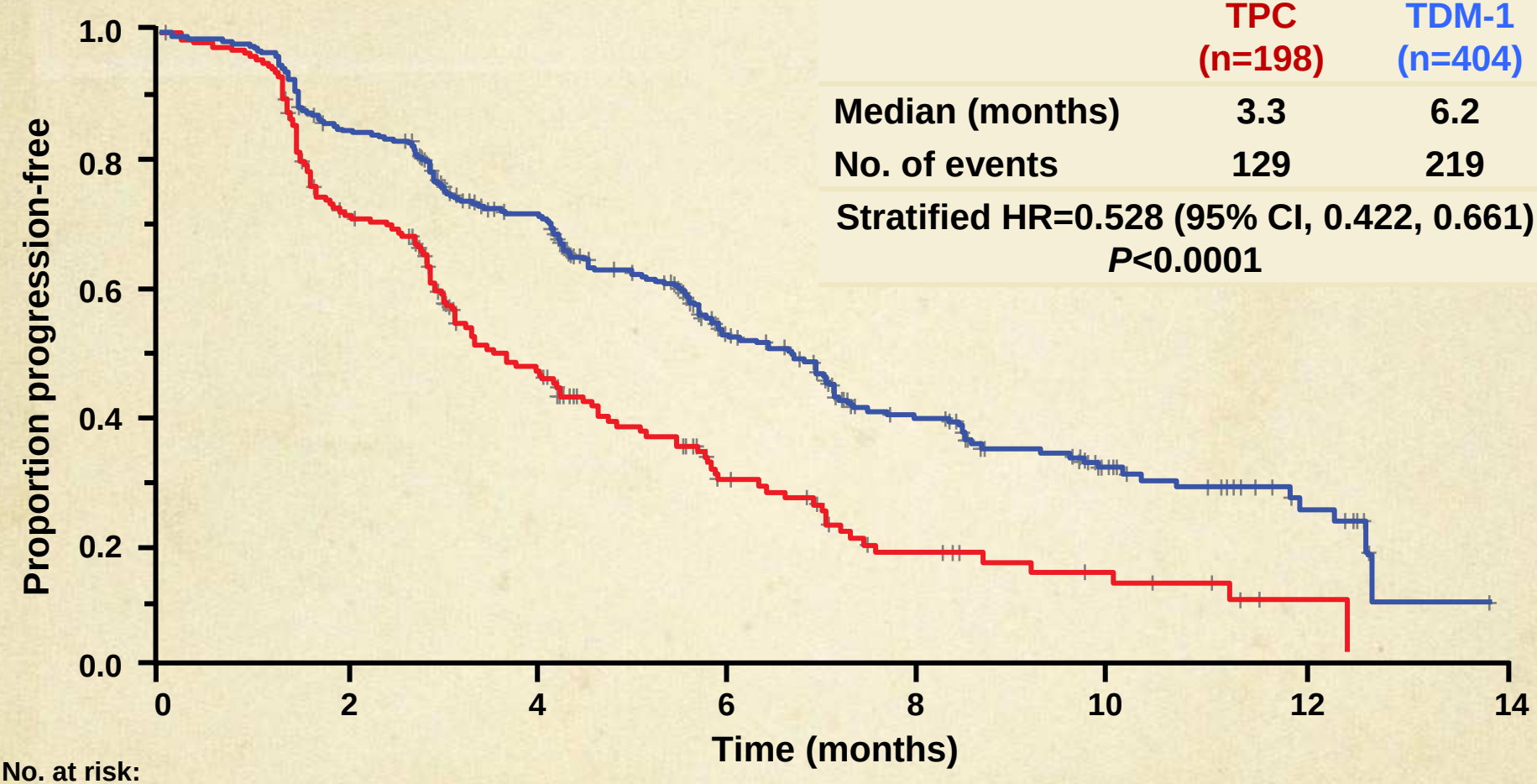
TH3RESA Study Schema



- **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] Study amended Sep 2012 (following EMILIA 2nd interim OS results) to allow patients in the TPC arm to receive TDM-1 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)	TDM-1 (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
TDM-1	404	334	241	114	66	27	12	0

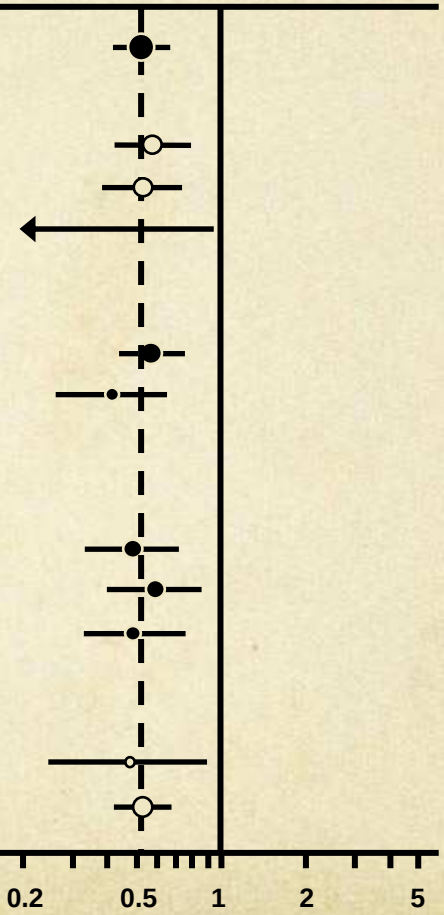
Median follow-up: TPC, 6.5 months; TDM-1, 7.2 months.
Unstratified HR=0.521 (*P*<0.0001).

ESMO 2013

By Investigator Assessment

PFS Subgroup Analyses (2)

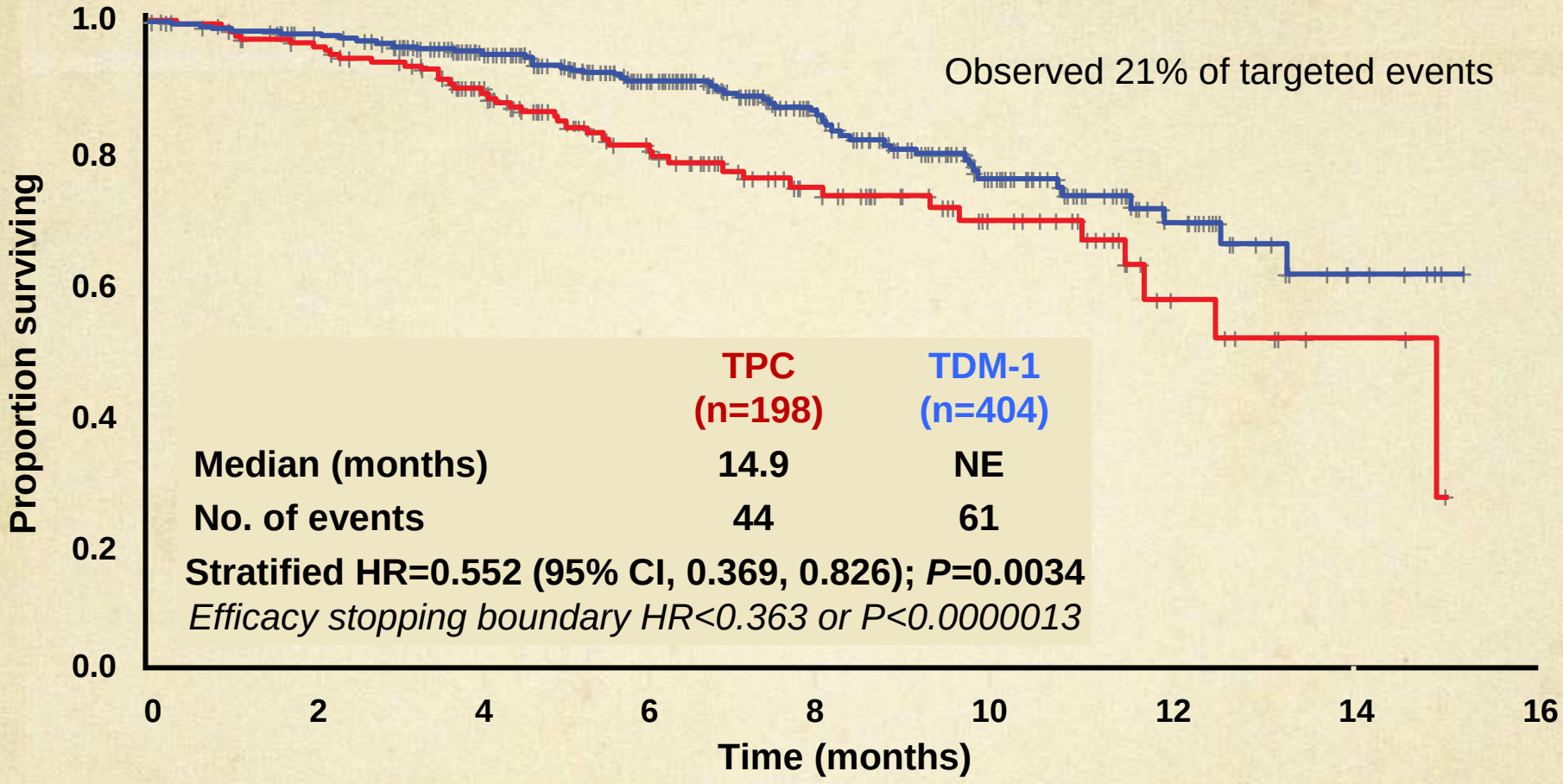
Baseline characteristic	Total n	TPC n	TPC Event	TPC Median (months)	TDM-1 n	TDM-1 Event	TDM-1 Median (months)	HR[a] (95% CI)
All patients	602	198	129	3.3	404	219	6.2	0.52 (0.42, 0.65)
ER and PR status								
ER+ and/or PR+	311	103	66	3.9	208	109	5.9	0.56 (0.41, 0.76)
ER– and PR	270	85	58	2.9	185	105	6.0	0.51 (0.37, 0.71)
Unknown	21	10	5	3.9	11	5	8.3	0.17 (0.03, 0.93)
Disease involvement								
Visceral	452	150	95	3.4	302	168	6.2	0.56 (0.44, 0.72)
Nonvisceral	150	48	34	3.1	102	51	6.7	0.41 (0.26, 0.64)
Number of prior regimens for advanced BC								
≤3	209	78	49	3.3	131	60	6.9	0.48 (0.33, 0.70)
4–5	214	65	45	3.7	149	83	6.2	0.58 (0.40, 0.83)
>5	177	55	35	2.9	122	75	5.8	0.48 (0.32, 0.73)
Brain metastasis at baseline								
Yes	67	27	16	2.9	40	24	5.8	0.47 (0.24, 0.89)
No	535	171	113	3.6	364	195	6.2	0.53 (0.42, 0.67)



ESMO 2013

[a] Unstratified HR.

First Interim OS Analysis



	TPC (n=198)	TDM-1 (n=404)
Median (months)	14.9	NE
No. of events	44	61

Stratified HR=0.552 (95% CI, 0.369, 0.826); *P*=0.0034

Efficacy stopping boundary HR<0.363 or P<0.0000013

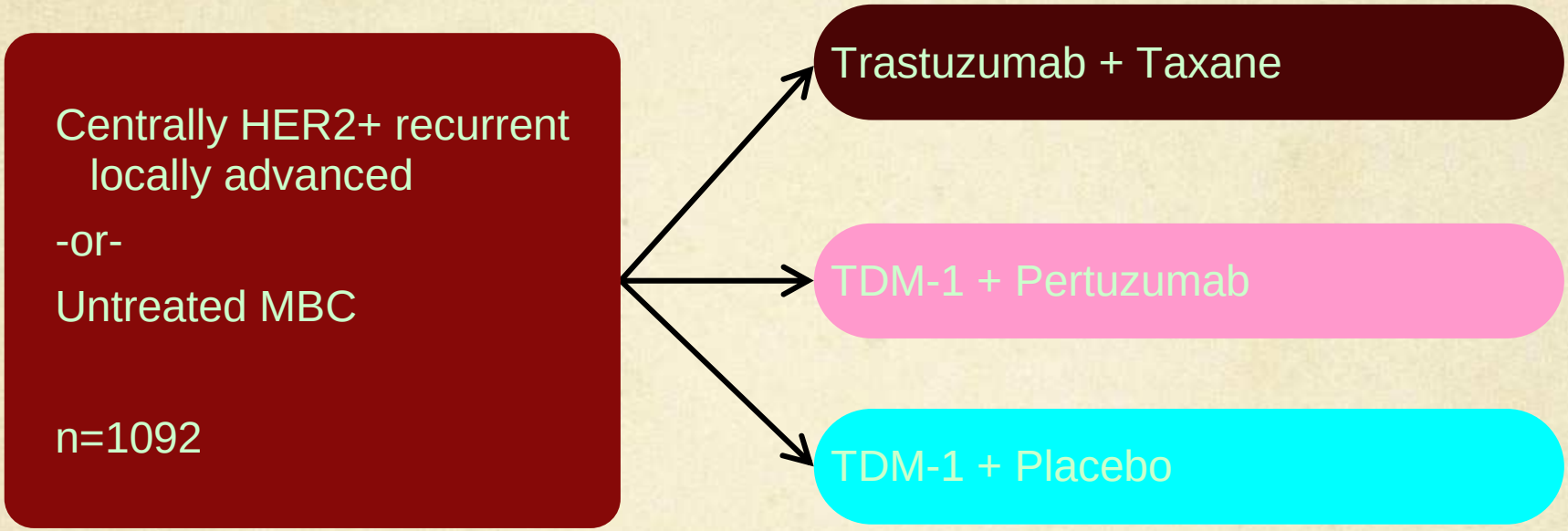
TPC	198	169	125	80	51	30	9	3	0
TDM-1	404	381	316	207	127	65	30	7	0

44 patients in the TPC arm received crossover TDM-1 treatment after documented progression.
Unstratified HR=0.57 (*P*=0.004).

ESMO 2013

MARIANNE Phase III Study: 1st-Line HER2+ MBC

Closed to Accrual



Rx until progressive disease

- Stratification factors
  - World region
  - Prior neo/adjuvant trastuzumab
  - Visceral disease
- Primary end points
  - Overall Survival
  - PFS by IRF
  - Safety
- Secondary end points
  - PFS by Investigator
  - Biomarkers

Summary

- TDM-1 is an effective therapy in metastatic breast cancer
  - Outstanding therapeutic index,
  - Displaces lapatinib
- Precise role is under study, but all trials reported look promising
  - Proven in advanced, salvage setting, following exposure to standard toxic regimens
  - Promising “first line”
  - Under testing in adjuvant/neoadjuvant
- Role in gastric cancer also looks promising

Summary II

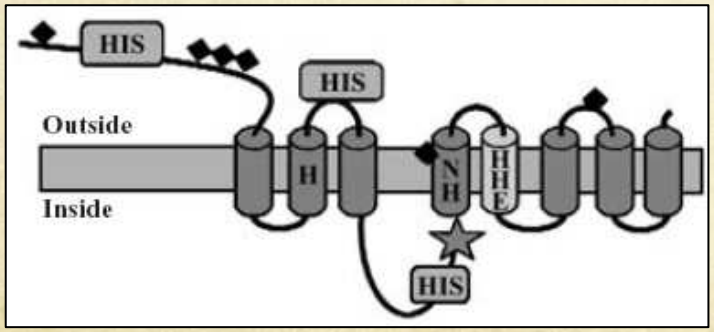
- Questions remain about “how little” we can give to HER2 positive patients
  - Synergy of trastuzumab/lapatinib given with endocrine therapy
  - What is ideal therapy for “triple positive” tumors? (ER, PR, HER2 all positive)
  - Can other synergistic agents displace standard cytotoxic therapy
  - This challenge is similar to curable lymphomas, testicular ca
- Unclear how effective TDM-1 will be in some patients
  - with loss of HER2 neu expression,
  - or with significant heterogeneity of HER2 expression
  - Or with poor tolerance for therapy
  - Cardiac or other issues which precluded from study of

Promising future agents in breast cancer

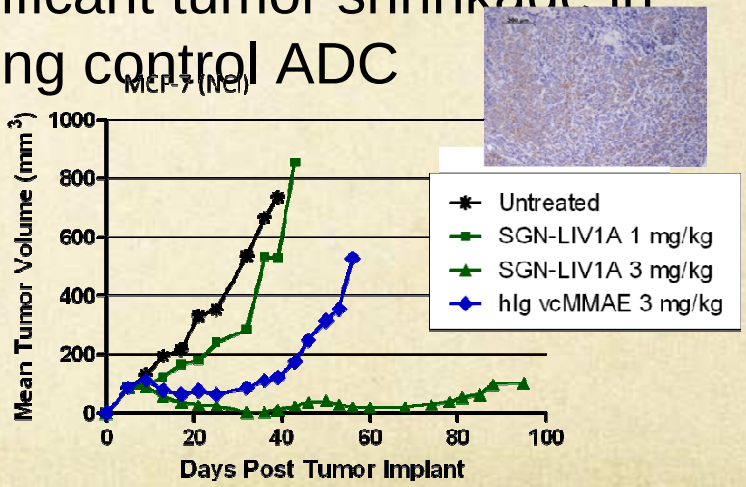
- Novel targets
- Immune targets
- Old – established targets with refined precision
- In various solid tumors

SGN-LIV1A: anti-LIV1-vc-MMAE

- LIV-1 (SLC39A6) is overexpressed in breast, prostate, ovarian, endometrial cancers and melanoma[1]
- Estrogen-inducible gene
- May function as zinc transporter and have metalloproteinase activity
- Preclinical data demonstrate significant tumor shrinkage in all models compared to non-binding control ADC



Taylor et al, Biochem J (2003) 375, 51-59



SCID mice were implanted subcutaneously with MCG-7 cells. Once tumors were ~100mm^3, treatment with SGN-LIV1A of control was initiated and repeated q4dx4.[1]

[1] Sussman D, et al. AACR 2013

The toxicity of TDM-1 (trastuzumab emtansine) is

- Similar to that of single agent chemotherapy
- Similar to potent immune therapy
- Low and manageable, with a minority of patients experiencing increases in transaminases or thrombocytopenia
- Minimal with steroid premedication
- Managed with hospitalization for first dose for supportive medications.

HER2 expression is

- Seen in many solid tumors, a common oncogene which when over-expressed drives proliferatione
- Necessary for effectiveness of TDM-1
- Easily measured by routine testing in Breast, Lung and Colon cancers
- Appreciated in nearly half of slow growing breast cancers
- Not routinely tested

TDM-1, trastuzumab emtansine, is effective in

- All patients with aggressive breast cancer, eg stage III, inflammatory tumors
- HER2 positive (early) stage 0 breast cancer, DCIS
- HLA A2 positive patients
- Patients with breast and gastric cancers which over-express HER2
- Patients who have not been exposed to trastuzumab