Evolving Strategies to Overcome Resistance to HER2 Targeted Agents

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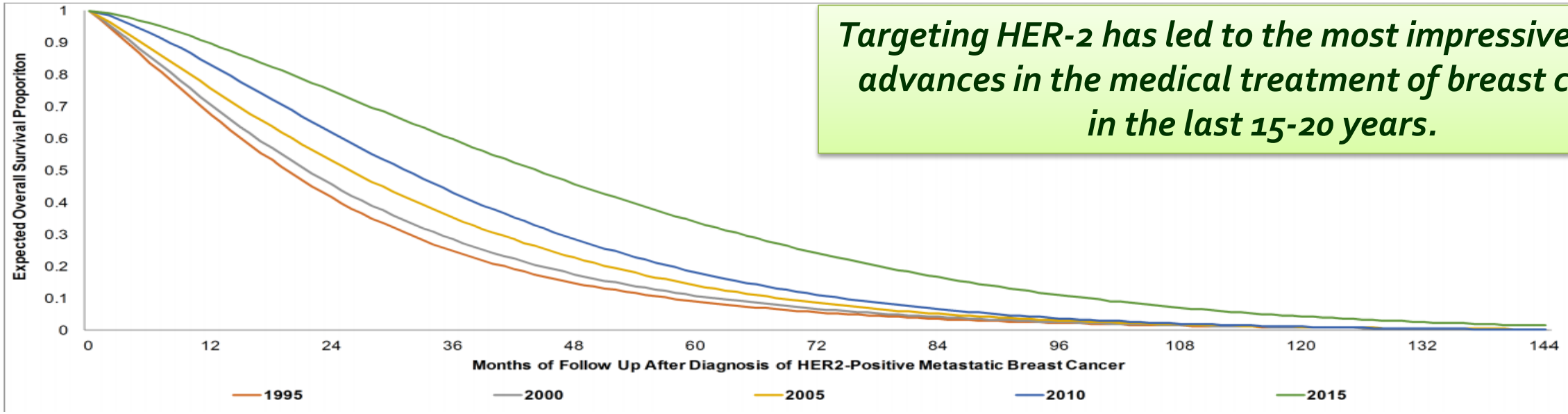
Advanced HER2+ Breast Cancer :
What have we accomplished ?

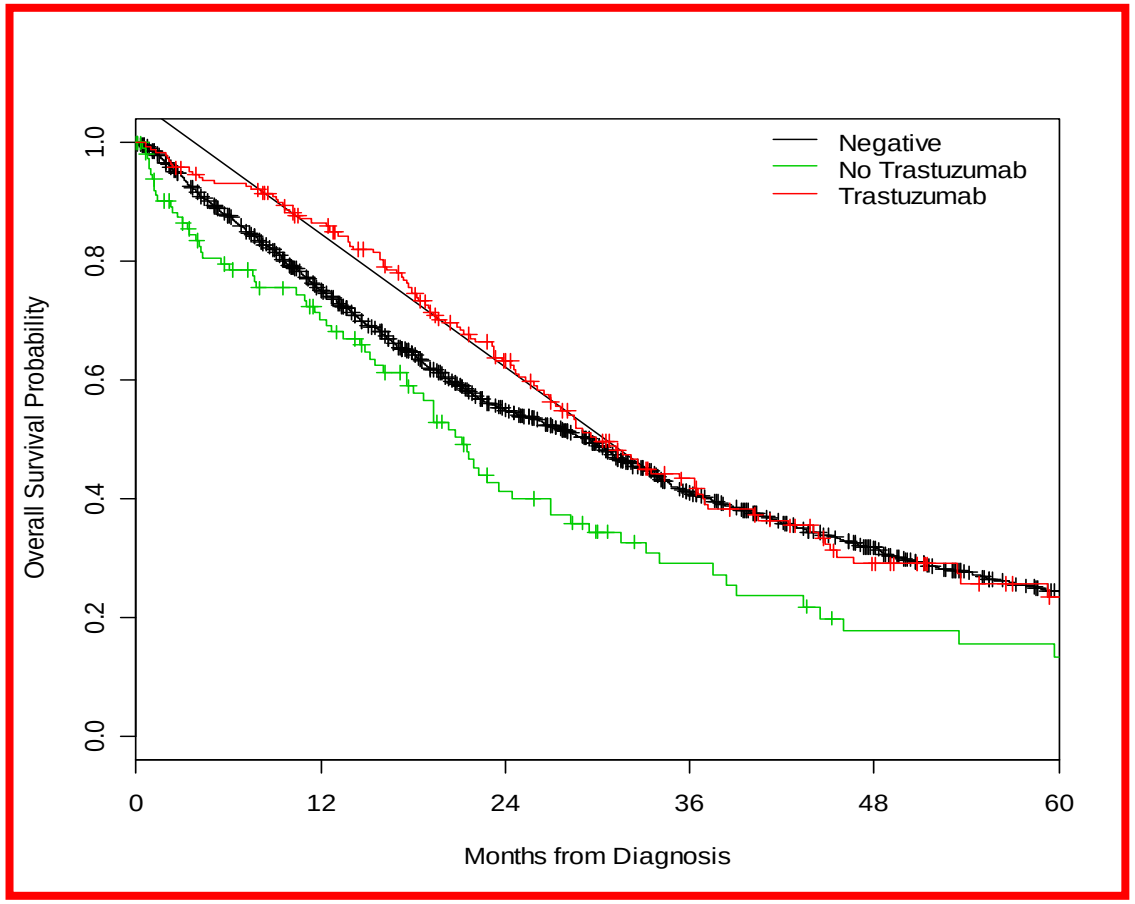


Targeting HER-2 has led to the most impressive clinical advances in the medical treatment of breast cancer, in the last 15-20 years.

Analysis Year	Expected: 5-Year Survival (%)	Expected: Mean Per-Patient Survival (Months)
1995	9.1%	26.6
2000	10.9%	28.7
2005	14.2%	32.6
2010	18.2%	37.3
2015	34.0%	50.8

Roth J et al ESMO 2017

Trastuzumab altered the natural history

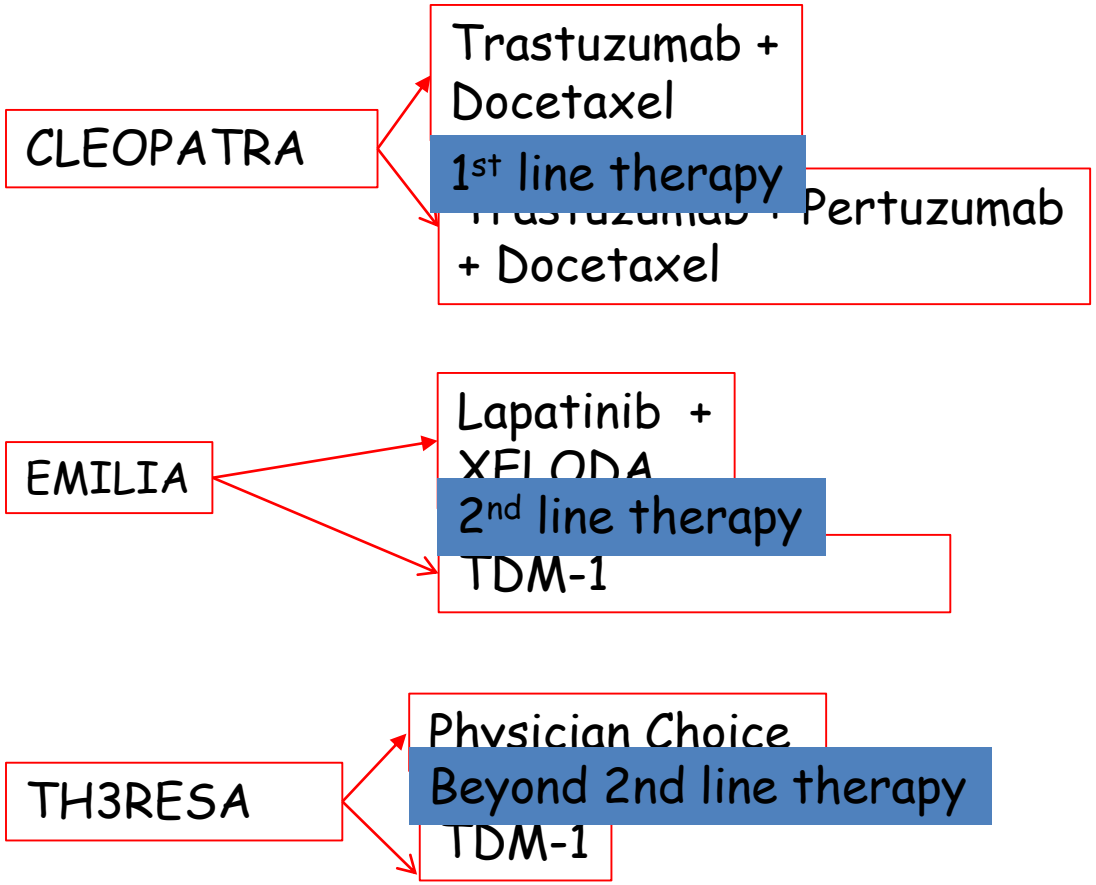


Treatment	Response rate	Time to Progression (months)	Median survival (months)
Chemotherapy	32%	4.6	20.3
Chemotherapy + Trastuzumab	50%	7.4	25.1
Difference	18%	2.8	4.8

Slamon et al. *N Engl J Med.* 2001;344:783

Dawood et al JCO 2010

Important trials to consider in the HER2 positive metastatic setting

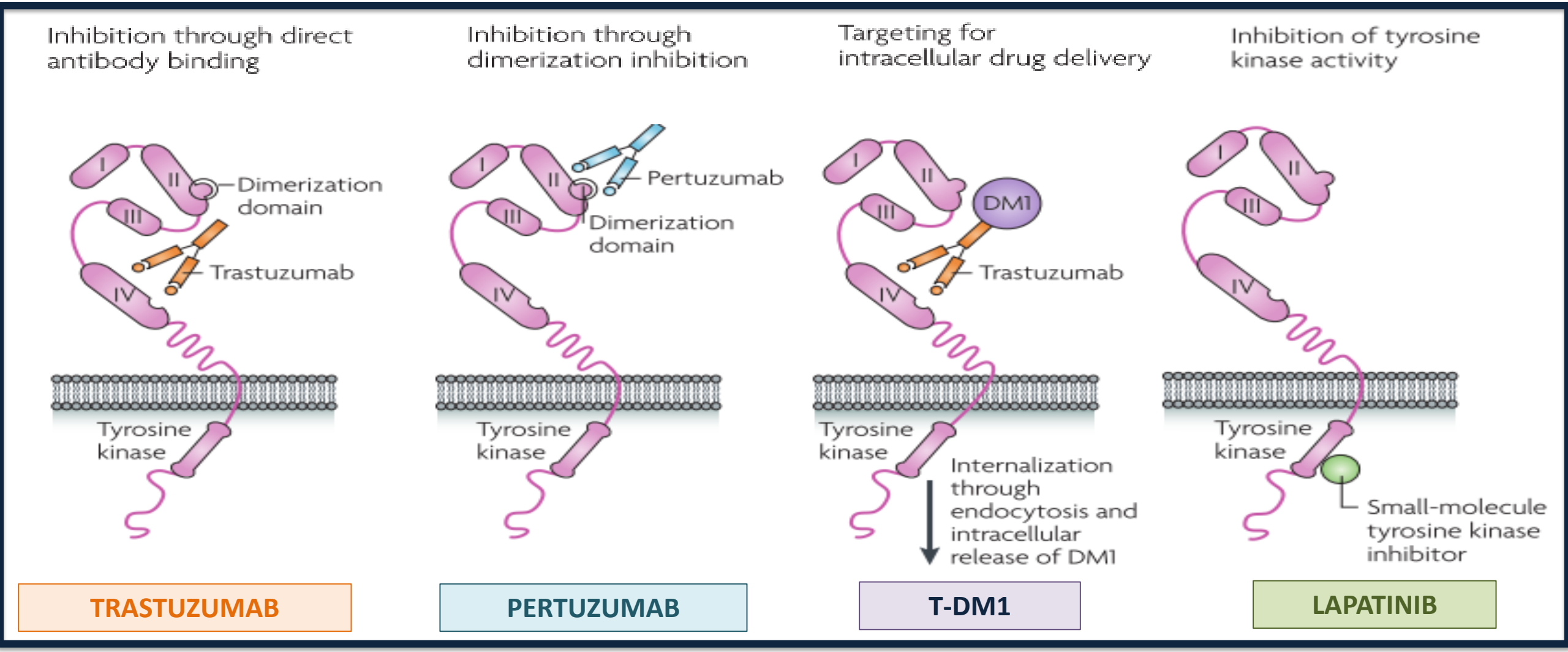


Swain et al NEJM 2015
Phase III
No prior treatment for metastatic disease
PFS 12.4 m vs 18.7 m
HR 0.68 (p=<0.0001)
OS 40.8 m vs. 56.5 m

Verma et al NEJM 2012
Phase III
Prior taxane/trastuzumab
Progression on metastatic therapy
PFS 6.4 m vs 9.6 m
HR 0.65 (p=<0.0001)
OS 25.9 vs. 29.9m
HR 0.75 p =0.0003

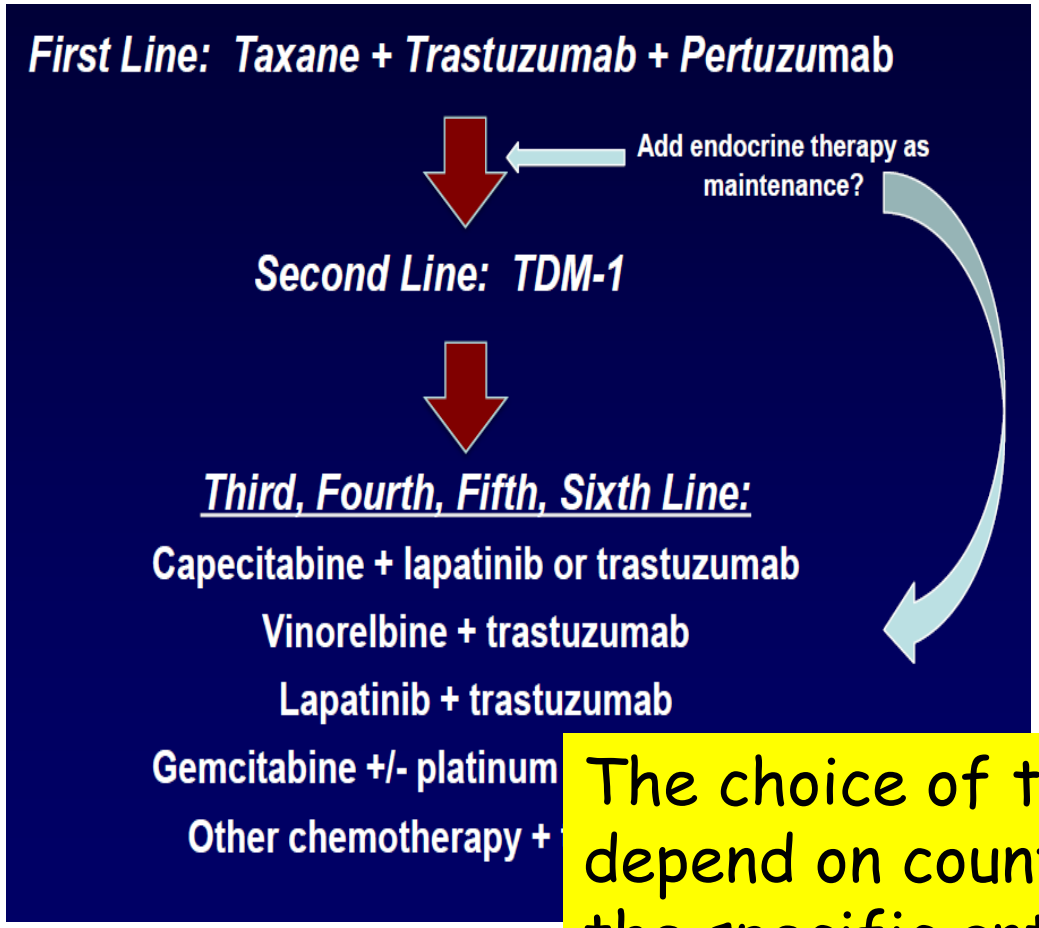
Krop et al Lancet Oncol 2014, 2017
Phase III
>=2 prior anti HER2 lines of therapy
60% >= lines of therapy
PFS 3.3 m vs 6.2 m
HR 0.55 (p=<0.0001)
OS 15.8 m vs22.7 M
HR 0.677 (p=0.0007)

Anti HER2 therapies available today



Baselga et al., Nat Rev Cancer 2009

Anti-HER2 Treatment:2018



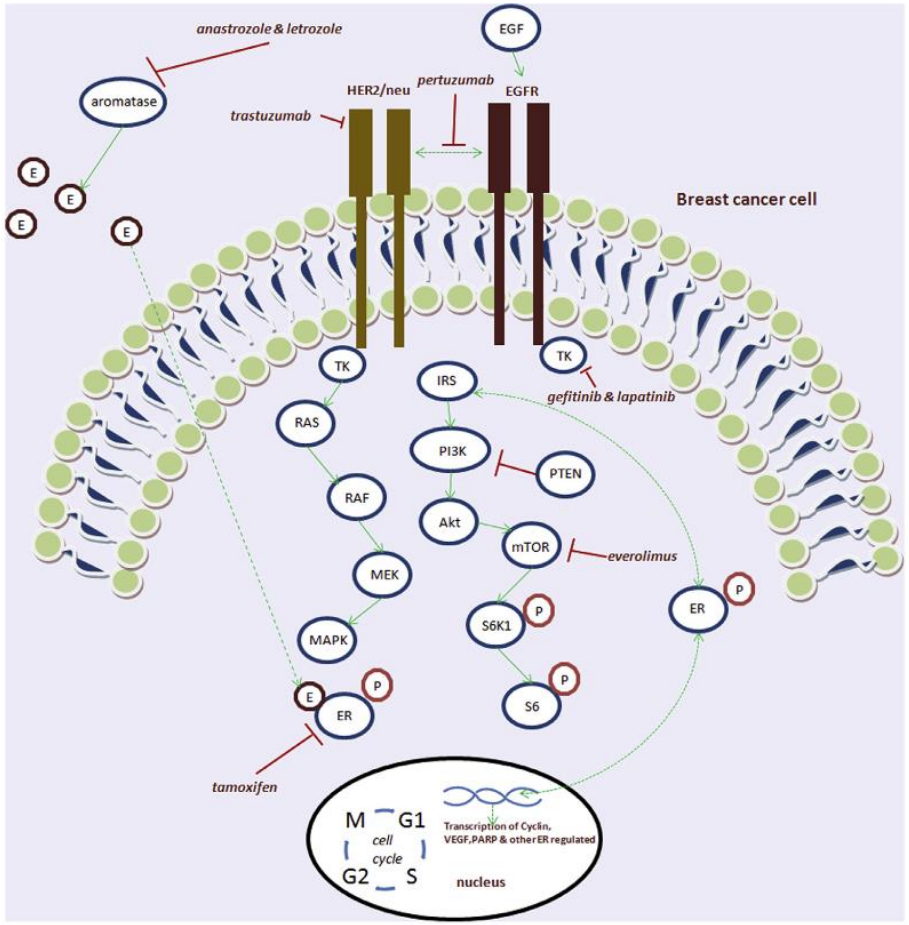
For patients with ER+/HER2+ MBC, for whom CT+anti-HER2 therapy was chosen as 1st line therapy and provided a benefit, it is reasonable to use ET+ anti-HER2 therapy as maintenance therapy, after stopping CT, although this strategy has not been studied in randomized trials.
LOE;1 C
Voters:39
Yes: 79% (31)
Abstain: 10% (4)

ABC3, Annals of Oncology 2016

The choice of the anti-HER2 agent will depend on country-specific availability, the specific anti-HER2 therapy previously administered, and the relapse free interval.

Adapted from Rugo H, et al. GBCC 2016 presentation

Do all women with HER2 positive MBC require chemotherapy? Can we de escalate therapy?"Triple Positive" Disease



The ER and HER2 signalling pathways are deeply interconnected

ER signalling plays a role in resistance to anti-HER2 Therapy

The unexciting nature of the results of early ET/anti-HER2 Trials have made CT -based combinations a more common standard

Mehta A et al Breast 2014 23(1):2-9

HER2+HR+ MBC

Regimen	ORR, %	PFS, Mo
Anastrozole+trastuzumab(n=103)[1]	20[a]	4.8
Anastrozole (n=104)[1]	7[a]	2.4
Lapatinib+letrozole (n=111) [2]	28	8.2
Letrozole (n=108) [2]	15	3.0

- Adding trastuzumab to endocrine therapy improved outcomes, presumably by eliminating the synergy between endocrine and HER2 signaling pathways.
-

1. Kaufman B, et al. J Clin Oncol 27(33): 5529, 2009
2. Johnston S, et al J Clin Oncol 27(33): 5538, 2009

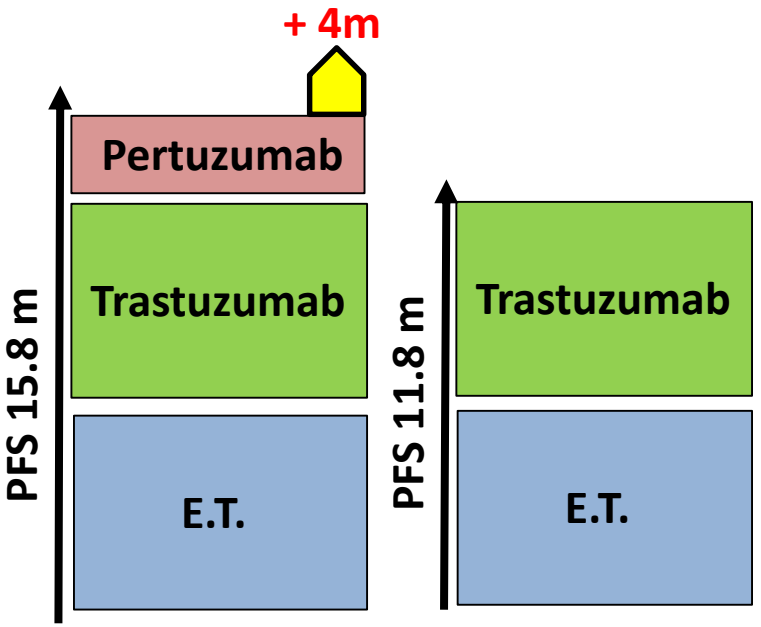
"Triple positive" Breast Cancer

Recent Randomized trials of endocrine therapy combined with single or dual HER2 blockade

Arpino G et al SABCS 2016 abstract S3-04

« FIRST LINE »

The « PERTAIN » trial (N=258)

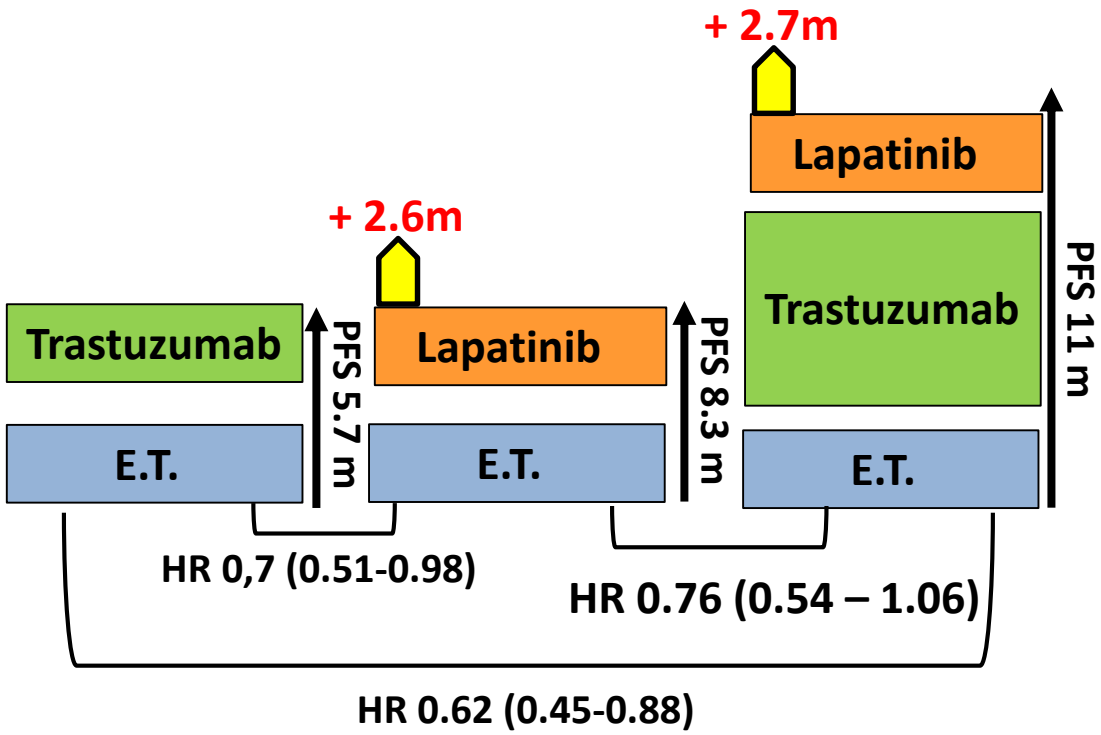


HR 0.65 (0.48 – 0.84)
Diarrhea 55 vs 36 %
Induction CTX in 57%

Gradishar et al ASCO 2017 abstract 1004

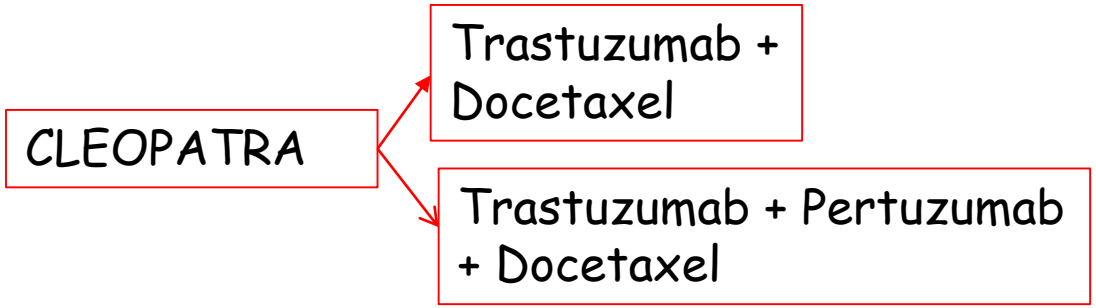
« SECOND+ LINE »

The « ALTERNATIVE» trial (N=355)



Questions in the first line setting

Addition of P clearly superior



Swain et al NEJM 2015
Phase III
No prior treatment for metastatic disease
PFS 12.4 m vs 18.7 m
HR 0.68 (p=<0.0001)
OS 40.8 m vs. 56.5 m

Should we use endocrine therapy+dual blockade for ER+/HER2+ disease?

YES : PFS prolongation, less toxicity
NO: No OS benefit, response rates higher with THP

Consider in patients with limited tumor burden or those not considered candidates for chemotherapy.

New Strategies

New Agents & New Combinations directed at the cancer cell

New Drugs	New Combinations
New anti-HER TKIs (Neratinib, Tucatinib, Pyrotinib, Poziotinb)	Anti-HER2 + mTOR Inhibitors
Antibody Drug Conjugates (ADCs) (SYD-985, DS 8201)	Anti-HER2 + PI3K Inhibitors
New anti-HER Antibodies (Margetuximab, Panitumumab)	Anti-HER2 + CDK 4/6 Inhibitors
Bi-specific Antibodies (ZW-25, MCLA-128, GBR1302)	Anti-HER2 + anti-PD(L)1

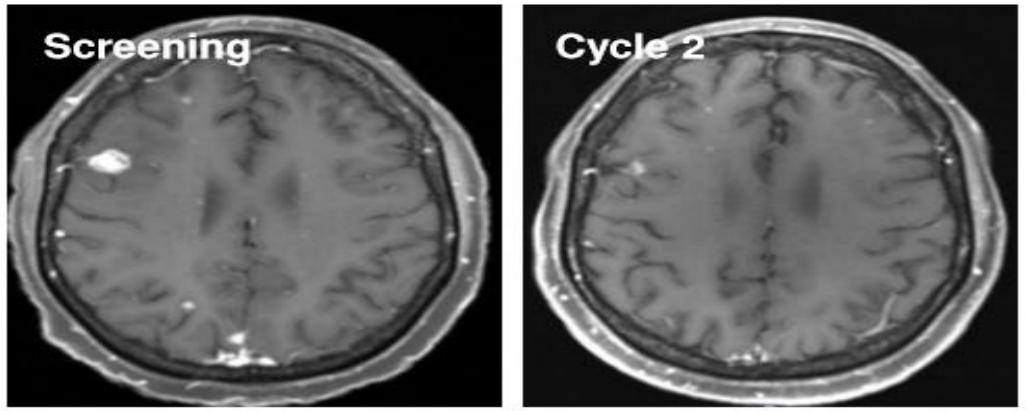
ClinicalTrials.gov

Second/third generation of HER inhibitors
Status of clinical development

Type of HER inhibitor	Drug	Development phase
HER1-2-4	Neratinib (N)	I → II → III
HER1-2-4	Afatinib (A)	I → II → III
HER2	Tucatinib (T)	I → II → III (dashed)
HER1-2-4	Pyrotinib (Py)	I → II (dashed)
HER1-2-4	Poziotinib (Po)	I → II (dashed)

NALA (NCT01808573) trial of Cape+N vs Cape+L in third line has completed accrual! (n=600)

(A) + vinorelbine not better than T + vinorelbine (2)

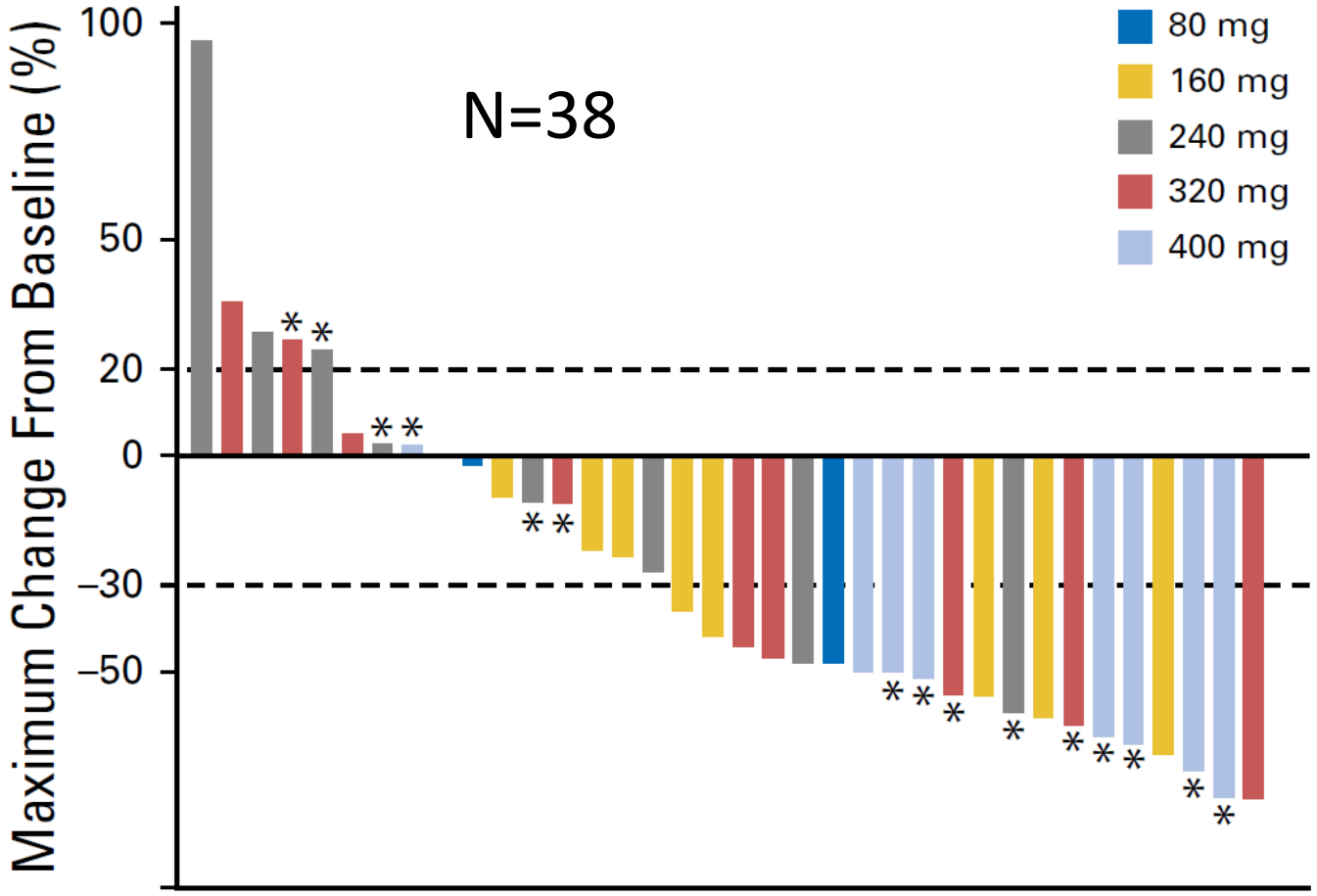


Single agent activity reported (6)

(12 mg poziotinib qd 14-day on/7-day off schedule)

(1) Awada A, JAMA Oncology 2016 2(12):1557-1564; (2) Harbeck H et al, Lancet Oncol 2016; 17 (3): 357-366; (3) Anders C et Al ASCO 2017 Abstracts TPS1107; (4) Murthi RK. et al SABCS 2015 P 4-14-19 , (5) Ma, F e tal JCO 35 (27) 2017; (6) Park YH et al ESMO 2017 abstract 2370 ,

Phase I Study and Biomarker Analysis of Pyrotinib, a Novel Irreversible Pan-ErbB Receptor Tyrosine Kinase Inhibitor, in HER2+ Metastatic Breast Cancer



- Dose limiting toxicity: diarrhea.
- MTD 400 mg/day
- ORR=50% ; CBR24w=61.1%
- ORR=33.3% in trastuzumab-treated
- ORR=83.3% in trastuzumab-naive

Ma et al. J Clin Oncol 2017

A randomized phase II trial of pyrotinib/capecitabine versus lapatinib/capecitabine in HER2+ metastatic breast cancer

This is an open label, multicenter, randomized phase II trial.

- HER2 positive metastatic breast cancer
- Age 18 – 70 years
- Previously treated with taxanes and anthracyclines
- With/without prior trastuzumab
- ≤2 lines of chemotherapy for advanced disease
- Previous treatment with capecitabine within 6 months is not permitted
- Brain metastasis is not permitted

RANDOMIZATION

PC: Pyrotinib (P) + Capecitabine (C)
pyrotinib 400mg, qd, d1-21, q3wks
capecitabine 1000mg/m^2, bid, d1-14, q3wks
until disease progression, intolerable toxicity or withdrawal of consent

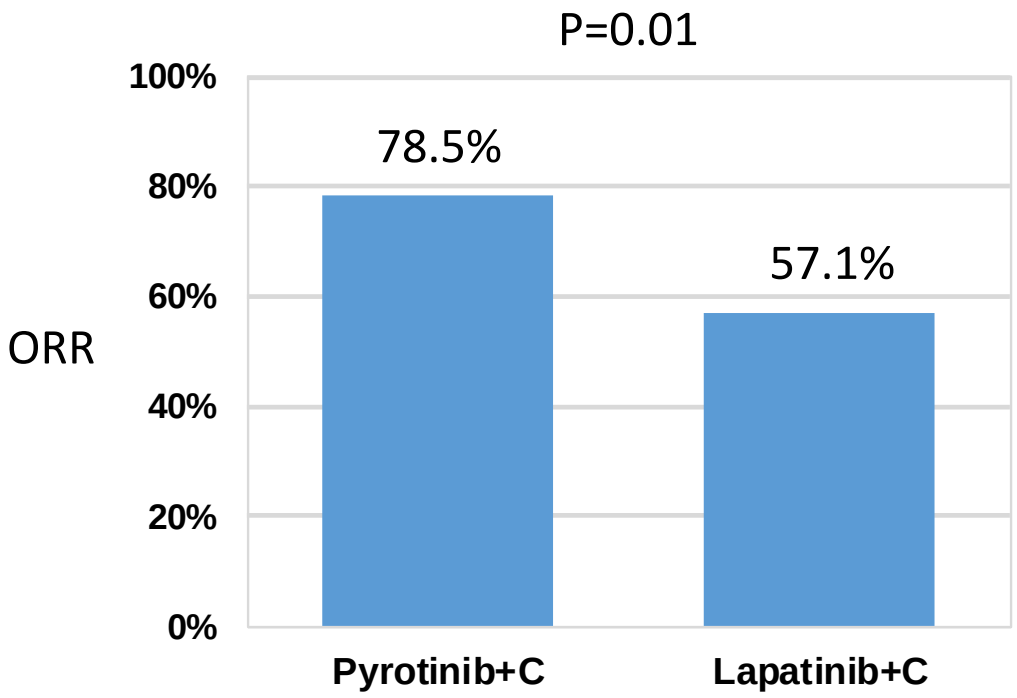
LC: Lapatinib (L) + Capecitabine (C)
Lapatinib 1250mg, qd, d1-21, q3wks
capecitabine 1000mg/m^2, bid, d1-14, q3wks
until disease progression, intolerable toxicity or withdrawal of consent

- Stratification: prior treatment with anti-HER2 monoclonal antibody (yes, no)
- Primary endpoint: overall response rate (ORR), as assessed by investigator

- Secondary endpoints:
  - Progression free survival (PFS)
  - Time to progression (TTP)
  - Duration of response (DoR)
  - Overall survival (OS)
  - Safety

Xu et al. SABCS 2017

A randomized phase II trial of pyrotinib/capecitabine versus lapatinib/capecitabine in HER2+ metastatic breast cancer

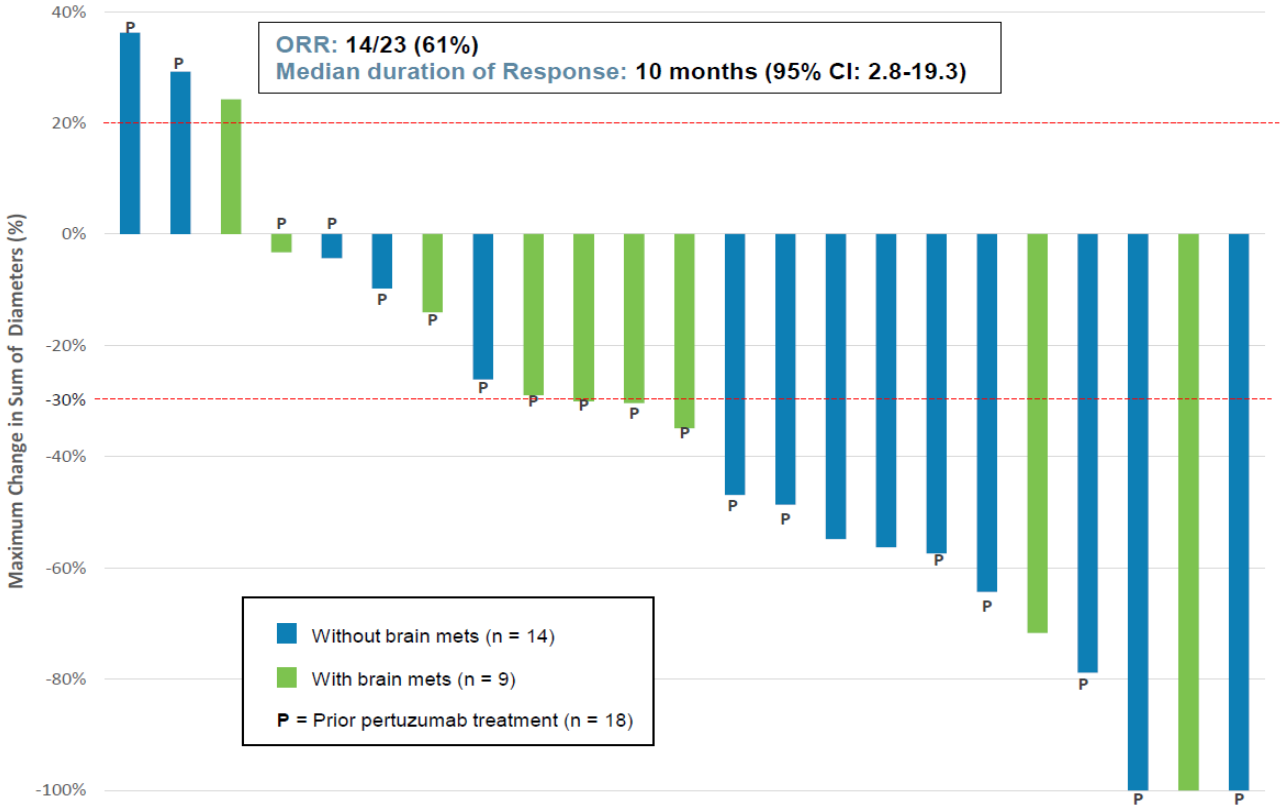


- Increased mPFS 18 vs. 7.0 months (HR=0.36 P<0.0001); irrespective of prior trastuzumab.
- Grade 3-4 toxicities higher in **PC** arm vs LC arm:
  - Hand-foot syndrome (24.6% vs 20.6%),
  - Diarrhea (15.4% vs 4.8%)
  - Decreased neutrophil (9.2% vs 3.2%)
  - Vomiting (4.6% vs 1.6%)
- Serious adverse events (SAEs): 7.7% vs. 6.3%.
- A Phase III trial is ongoing (NCT02973737).

Xu et al. SABCS 2017

A Phase 1b Study of Tucatinib (ONT-380) Combined With Capecitabine and/or Trastuzumab in HER2+ Metastatic Breast Cancer

N=23



- 300mg BID
- Encouraging anti-tumor activity seen in the triplet combination, in a heavily pre-treated population including those with brain mets
- ORR=61% ; Median PFS=7.8m
- Median DOR=10 months
- Orphan drug designation by FDA for the treatment of BC brain metastases

NCT02025192

Hamilton et al. SABCS 2016

EORTC 75111 – 10114 Trial Design

Primary endpoint:
PFS rate at 6 months

N=80

HER2+ MBC

≥ 70 Years (or ≥65/≥60y with co-morbidity)
No prior chemo for MBC
≤1 line of antiHER2 + endocrine therapy
Prior endocrine therapy allowed

1:1

Pertuzumab + Trastuzumab

Pertuzumab + Trastuzumab + Metronomic Cyclophosphamide

PD →

T-DM1 *(optional)*

Stratification: ER and/or PR pos vs both negative, previous HE R2 treatment (none vs adj only vs metastatic), G8< or equal 1 4 vs G8>14

Metronomic CT (chemotherapy): **cyclophosphamide 50 mg/d po continuously**
On progression: Option to have T-DM1 *(3.6 mg/kg iv q3w)* **till progression**

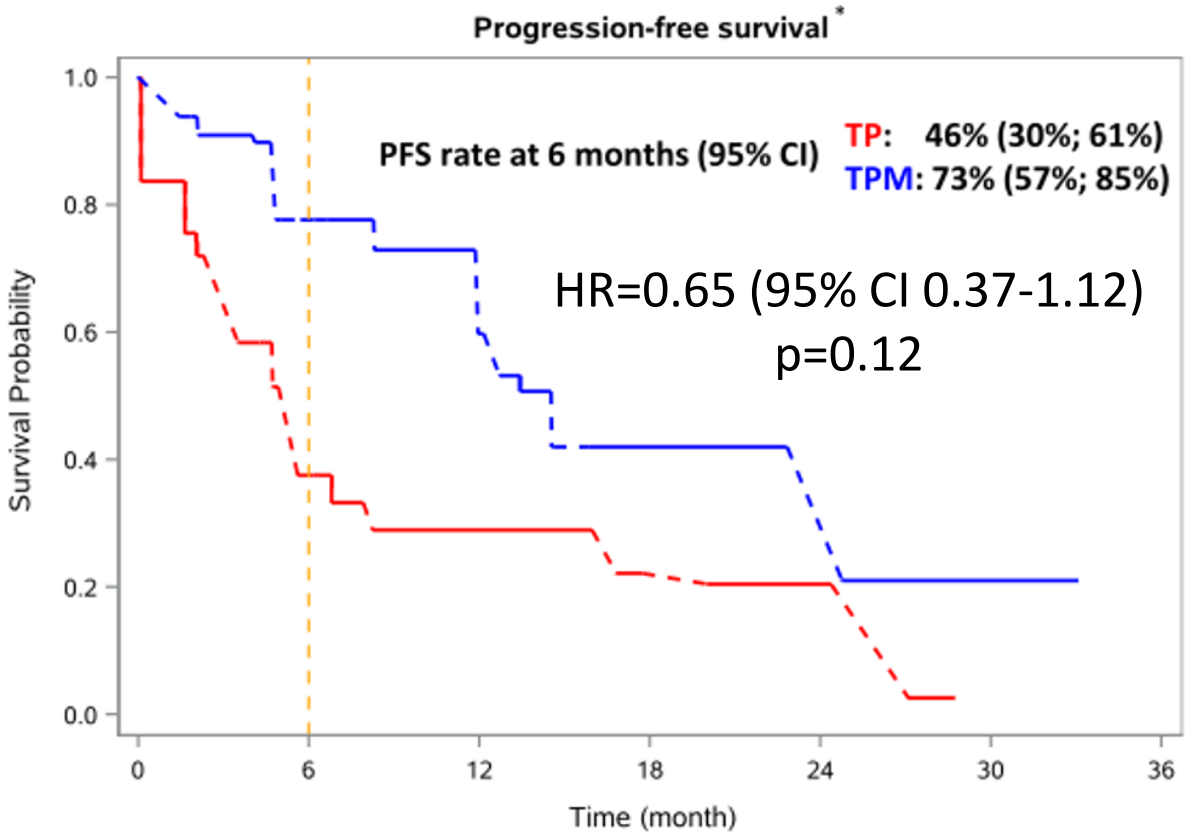
SABCS 2017 Wildiers et al ; Lancet Oncol 2017

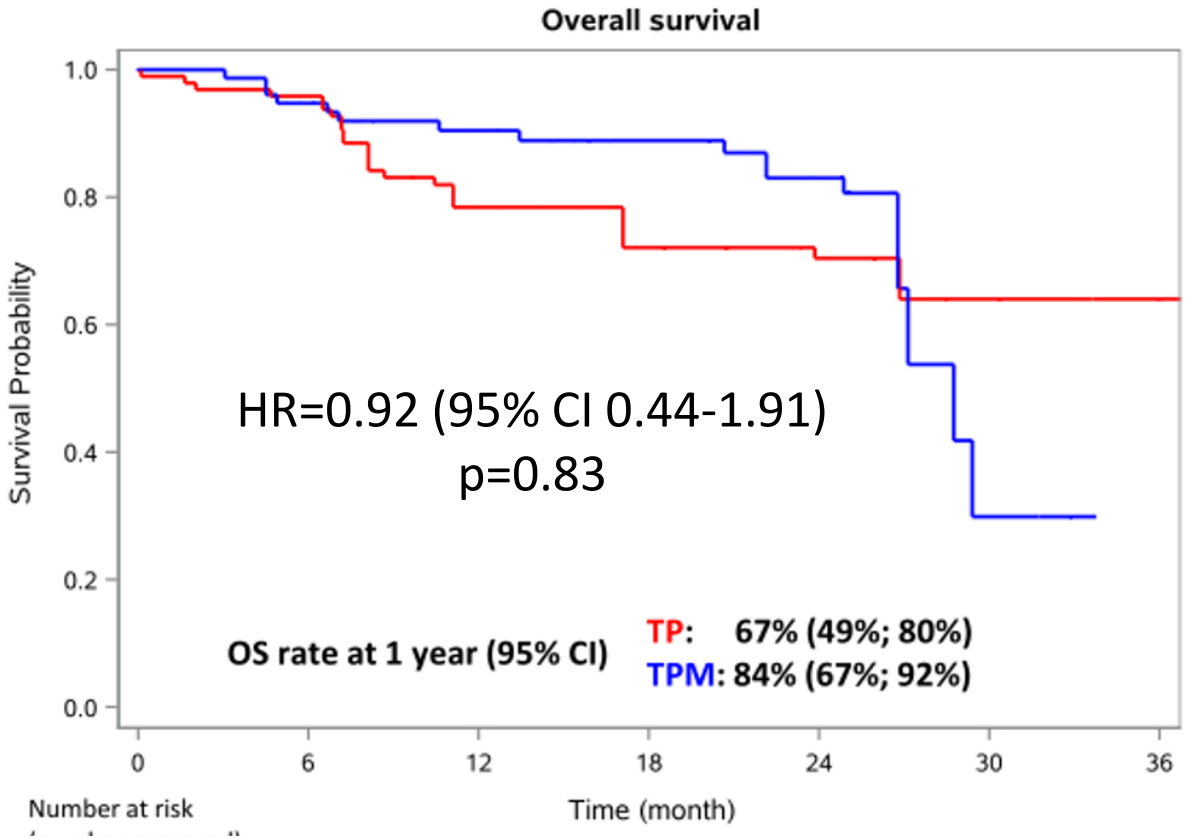
EORTC 75111 – 10114 Patient Characteristics

	N (%)
Age (years) – Median (Range)	**76.7 (61.4 - 91.4)**
WHO PS 2-3	19 (23.8)
ER and/or PgR positive	55 (68.8)
No prior anti-HER2 therapy for MBC	72 (91.1)
Prior adjuvant endocrine therapy	24 (30.4)
Visceral involvement	74 (93.3)
G8 score at baseline G8 ≤ 14	**56 (70.9)**
Frail (SPPB ≤ 7) **Short physical performance battery**	**37 (52.9)**

SABCS 2017 Wildiers et al ; Lancet Oncol 2017 in Press

EORTC 75111 – 10114 Trial Design





Median PFS was 5.6 months (95% CI 3.6-16.8) versus 12.7 months (95% CI 6.7-24.8)

SABCS 2017 Wildiers et al ; Lancet Oncol 2017 in Press

EORTC 75111 – 10114 vs. CLEOPATRA

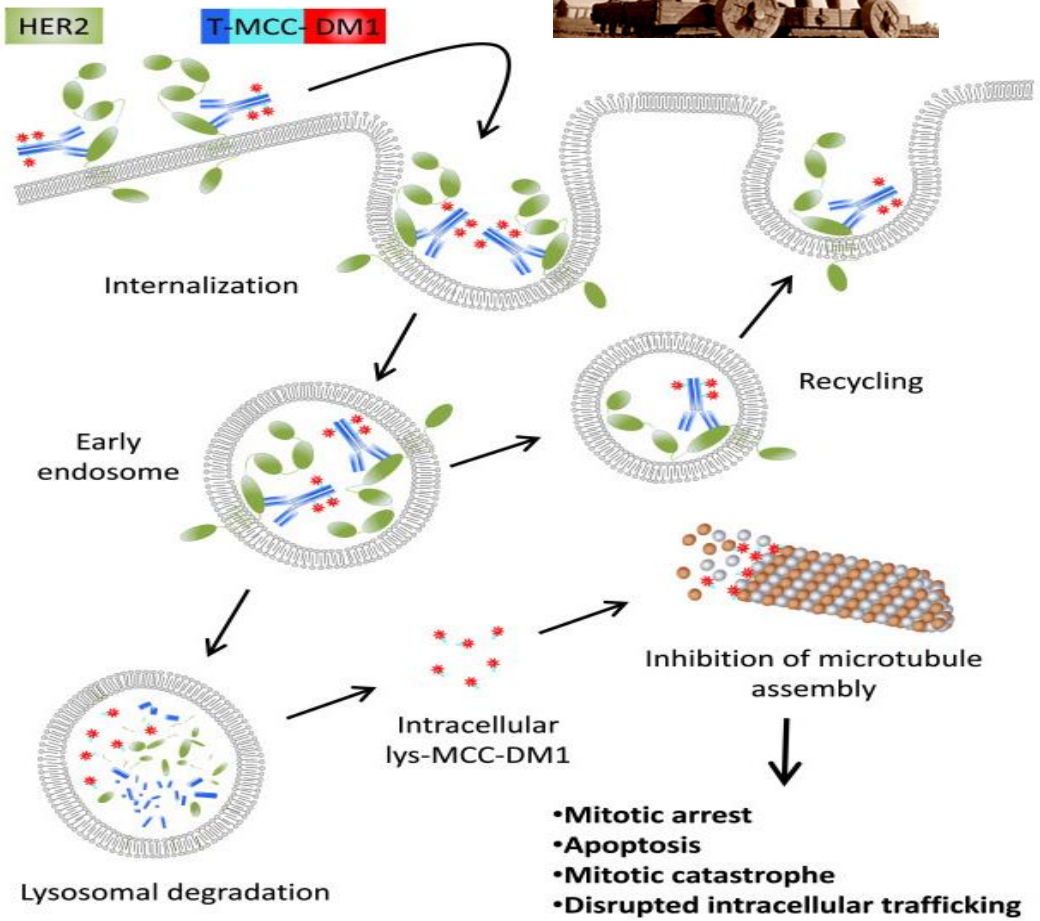
	Wilders et al. (N=80)			CLEOPATRA (N=808; NEJM 202)	
	Trastuzumab + Pertuzumab (TP)	Cyclophosphamide + Trastuzumab + Pertuzumab (CTP)	T-DM1 (following CTP)	Docetaxel + Trastuzumab	Docetaxel + Trastuzumab + Pertuzumab
ORR %	44.0%	53.0%	13.0%	69.3%	80.2%
Median PFS (months)	5.6	12.7	5.0	12.4	18.5

ORR Δ 11.0%
PFS Δ 7.1 months

ORR Δ 10.9%
PFS Δ 6.1 months

- Lower median PFS with CTP than in taxane + TP (12.7 vs. 18.5 months)
- **Adding cyclophosphamide achieves a similar magnitude of clinical benefit as pertuzumab on top of taxane + trastuzumab.**
- T-DM1 might help prolong progression in second-line in this elderly population.
- **More clinical trials are needed in elderly and/or frail patients!**

New Strategies : New Antibody Drug Conjugates

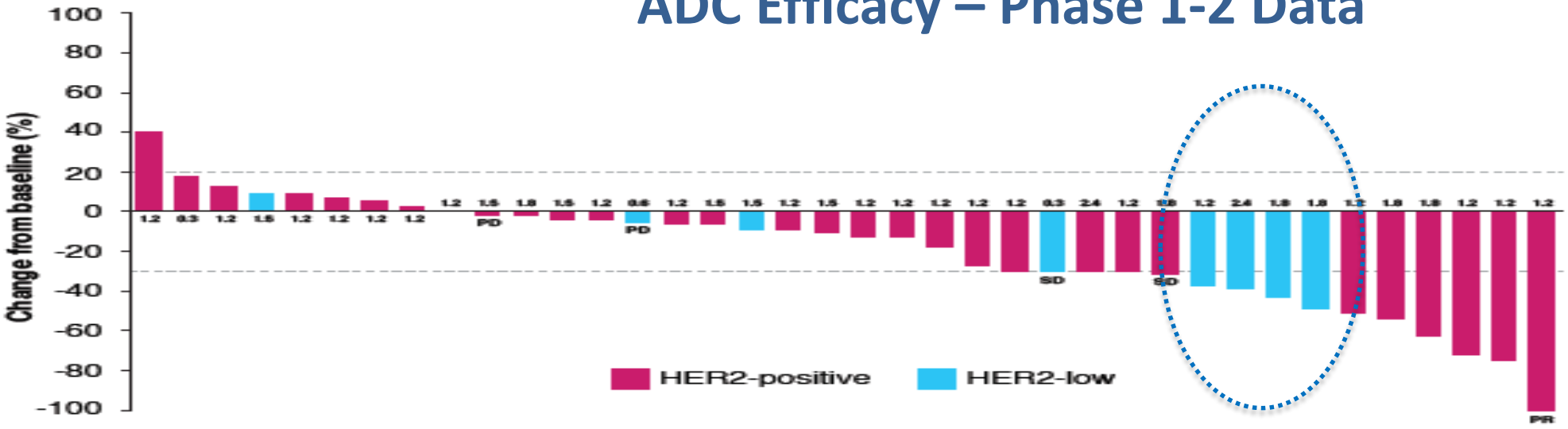


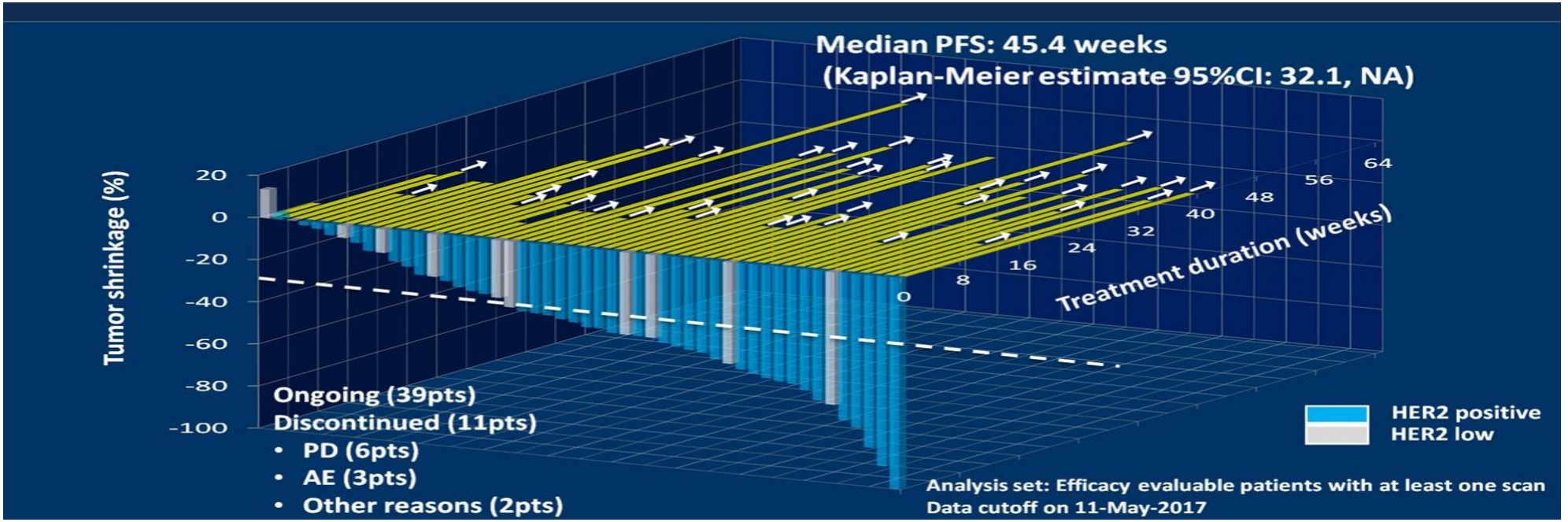
The success of T-DM1 has created a lot of excitement around ADCs

Drug Name	Antibody	Chemotherapy
MM - 302[2]	Humanized anti-HER2 antibody	Liposomal doxorubicin
DS – 8201a[3]	Humanized anti-HER2 antibody	**Exatecan**
SYD- 0985[4]	Trastuzumab	Duocarmycin
XMT - 1522[5]	HT-19 (Humanized anti-HER2 antibody)	Auristatin
MEDI 4276[6]	Bispecific anti-HER2/HER2 antibody	Tubulysin

1. Barok M. Breast Cancer Res. 2014; 16(2): 209; 2. Espelin CW et al Cancer Res 2016 76(6):1517-27; 3. Ogitani Y et Al Clin Cancer Res 2016 22 (20) 5097-5108; 4. Dokter W. et al Mol Cancer Ther 2014;13(11): 2618–29; 5. Bergstrom DA et al AACR Abstract 6716; 6. Li J et al Abstract 2970

ADC Efficacy – Phase 1-2 Data





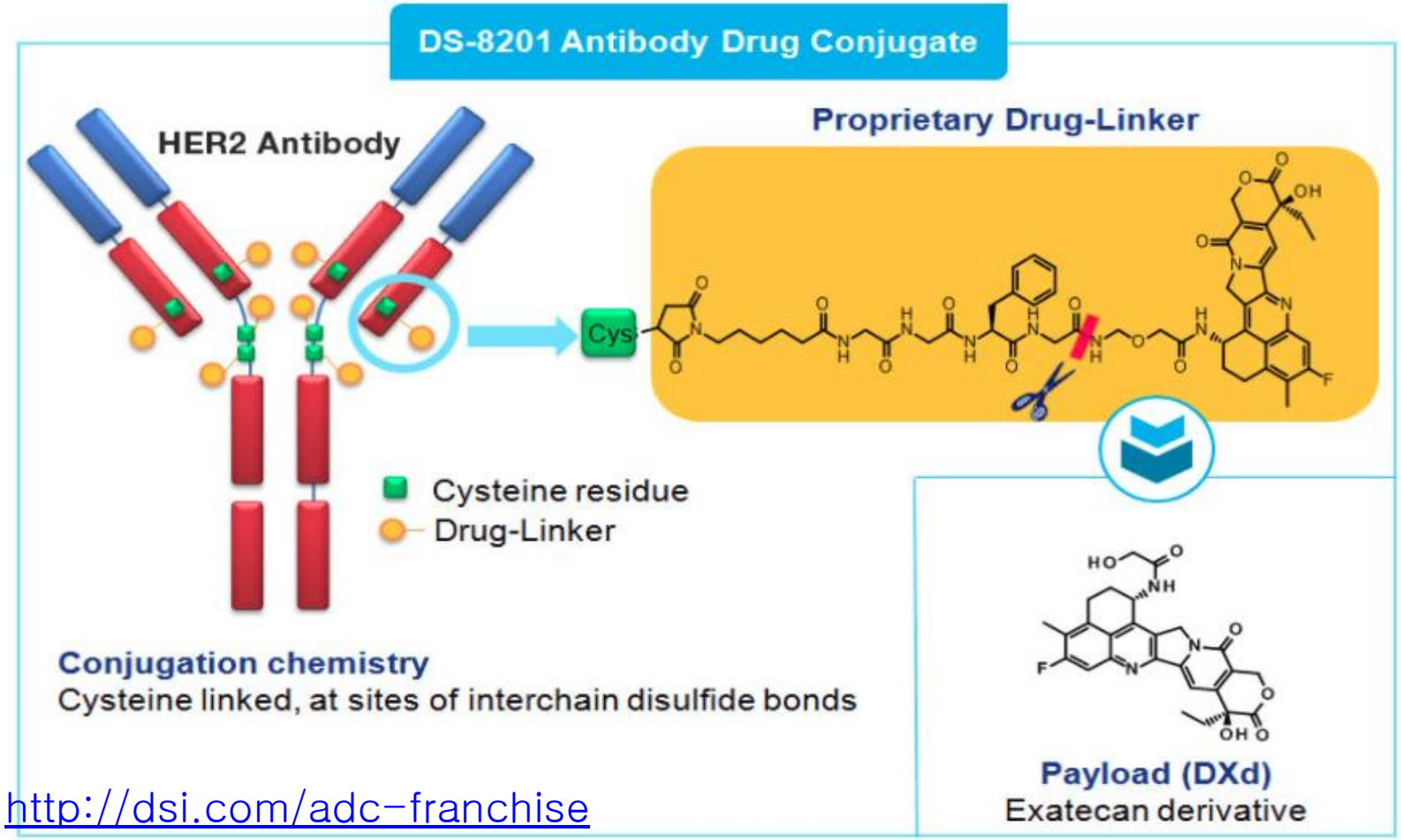
SYD-985 *(1)*

Responses seen in heavily pretreated patients !

DS-8201a *(2)*

1. Aftimos P et al SABCS 2016 P6-12-02; 2. Doi T et al ASCO 2017 Abstract 108

Trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody–drug conjugate

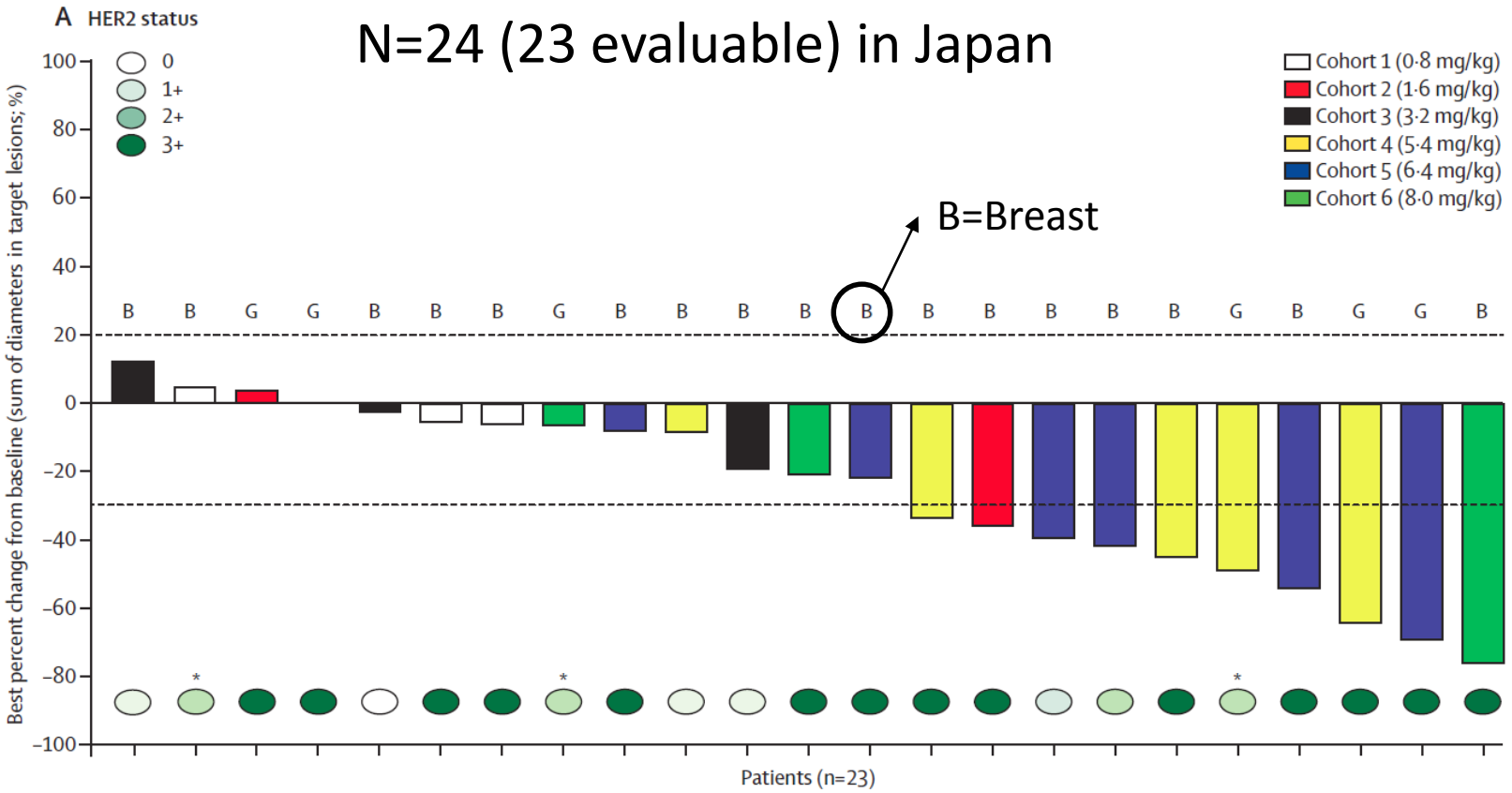


http://dsi.com/adc-franchise

- **Highly potent: Drug-to-antibody ratio = 7.8 vs 3.5 for T-DM1.**
- **Topoisomerase I inhibitor vs. tubulin inhibitor (T-DM1)**
- **Preclinically, DS-8201a has a potent bystander effect due to a highly membrane-permeable payload**

Ogitani Y et al. Cancer Sci 2016
Marcoux-J et al. Protein Sci 2015

Safety, pharmacokinetics, and antitumor activity of DS-8201 in advanced breast/gastric cancer: a Phase 1 study



- No dose-limiting toxic effects or deaths.
- ORR=43% ; DCR=91%
- Responses observed at higher doses
- Antitumor activity observed in previously treated with T-DM1 or trastuzumab, and **in patients with HER2-low tumors**

Doi et al. Lancet Oncol 2017

Safety and efficacy results from a phase 1 study of DS-8201a in patients with HER2+ breast cancers

TABLE 3. Efficacy – Confirmed ORR, DCR, and PFS

Population	ORR, n/N (%)*	DCR, n/N (%)*	PFS (months), median (range)†
HER2-positive			
All	35/57 (61.4)	54/57 (94.7)	10.4 (1.2+, 16.8+)
HR-positive	22/39 (56.4)	36/39 (92.3)	NR (1.2+, 16.8+)
HR-negative	12/16 (75.0)	16/16 (100.0)	10.4 (1.2+, 14.1+)
Prior pertuzumab-treated	31/50 (62.0)	47/50 (94.0)	10.3 (1.2+, 16.8+)
HER2-low			
All	6/19 (31.6)	16/19 (84.2)	NR (0.5, 12.2+)
HR-positive	5/16 (31.3)	14/16 (87.5)	NR (1.2+, 12.2+)
HR-negative	0/2 (0.0)	1/2 (50.0)	7.6 (0.5, 7.6)

*Analysis set for ORR (CR+PR) and DCR (CR+PR +SD): efficacy evaluable for confirmed overall response, at least 2 postbaseline scans or progressive disease at the first scan.
†Minimum and maximum of PFS include "+" after value indicates censoring.
CR, complete response; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NR, not recorded; ORR, objective response rate; PFS, progression-free survival; SD, stable disease.

N=130 (76 evaluable)

- The dose levels of **5.4** and **6.4 mg/kg IV** every 3 weeks were chosen for Part 2.
- Grade 3 toxicities occurred in <10% of the patients.
- Most frequent grade 3 toxicity was nausea.

breakthrough therapy designation

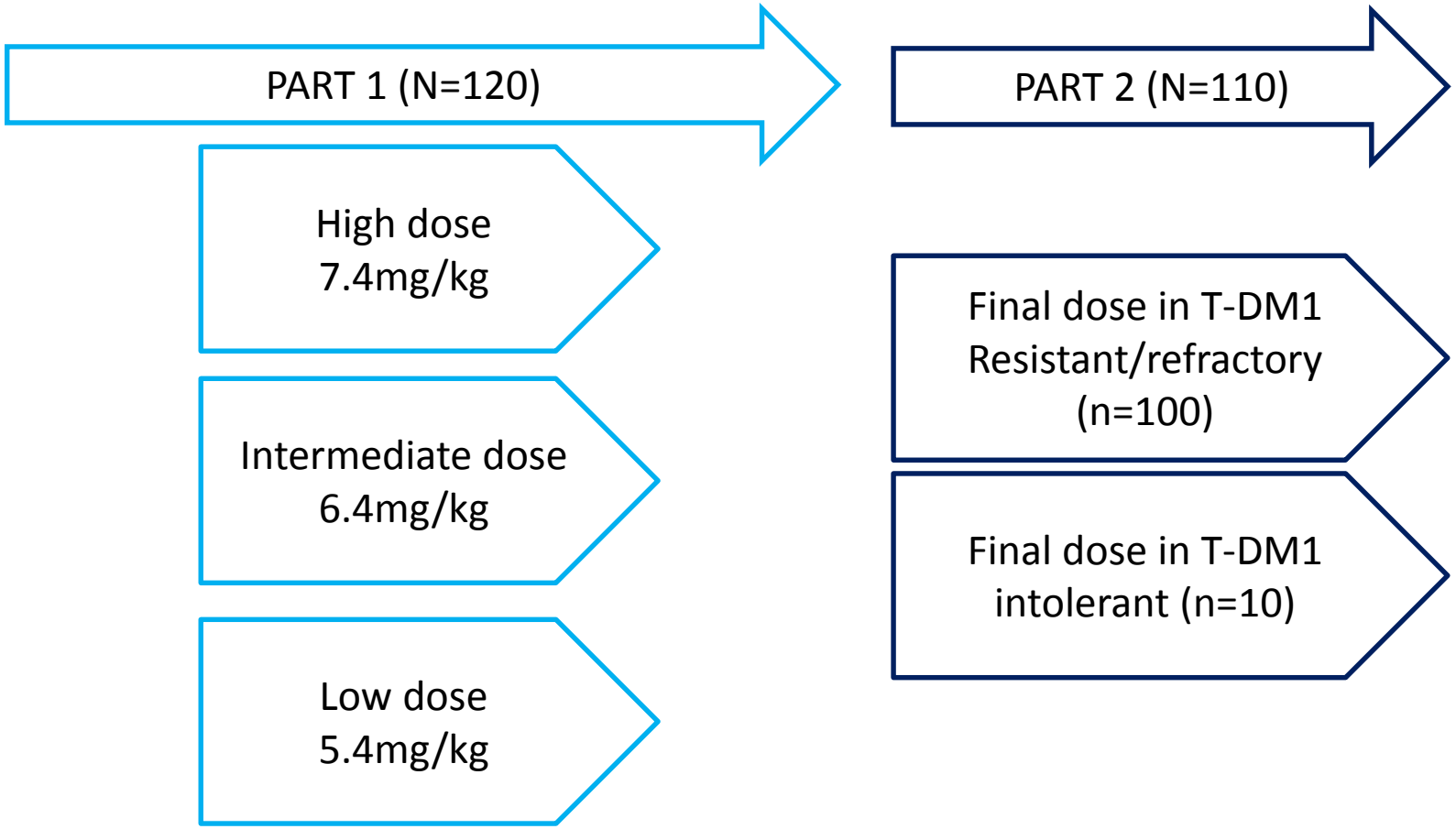
Modi et al. SABCS 2017

A Phase 2, Multicenter, Open-Label Study of DS-8201a in HER2+ Metastatic Breast Cancer Resistant/Refractory to T-DM1 (DESTINY-Breast01)

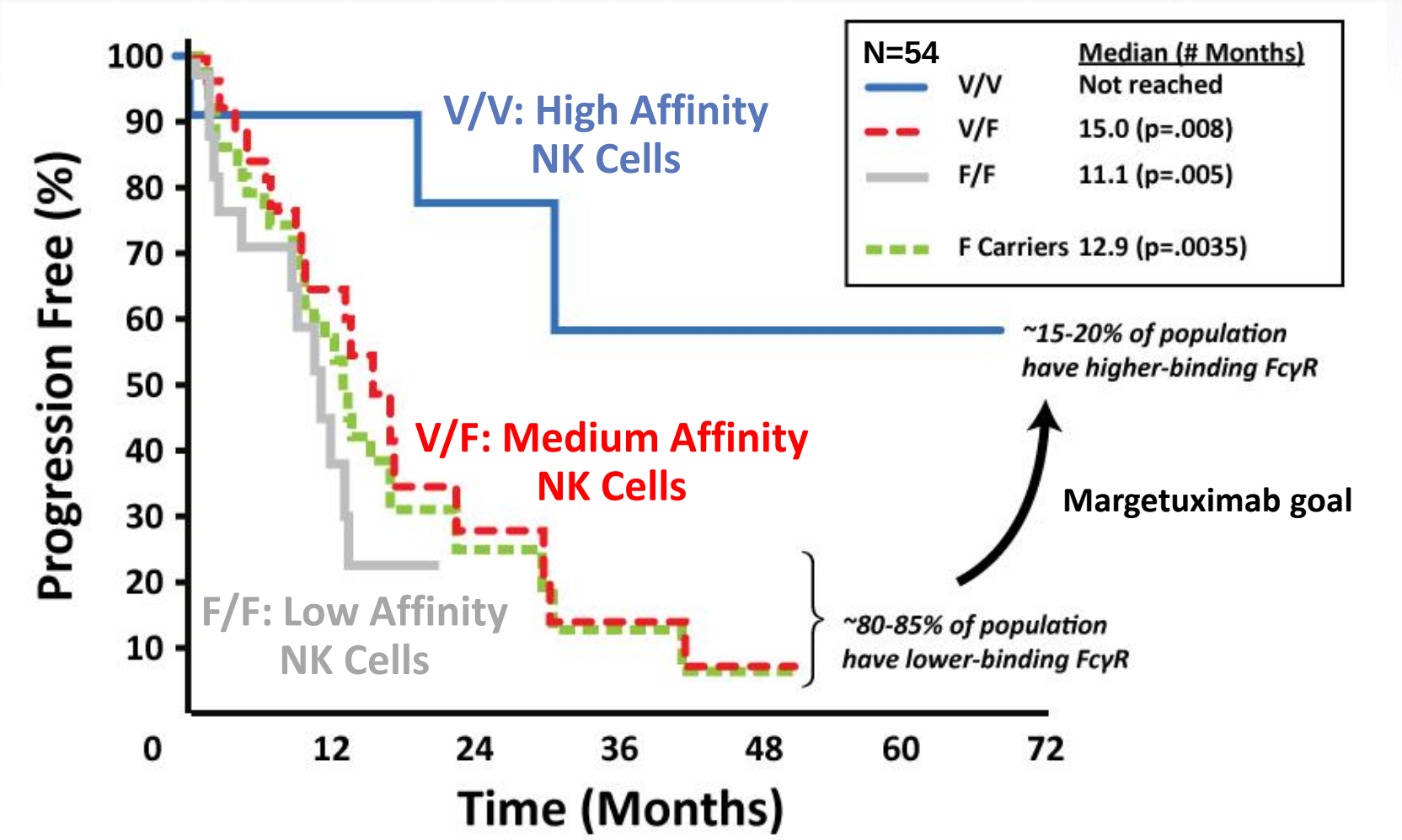
- N=230
- Primary objective: ORR

- Men or women
- Unresectable or metastatic
- HER2 positive expression
- ≥1 measurable lesion

NCT03248492



Trastuzumab Progression-Free Survival ~ CD16A (FcγRIIIA) genotype

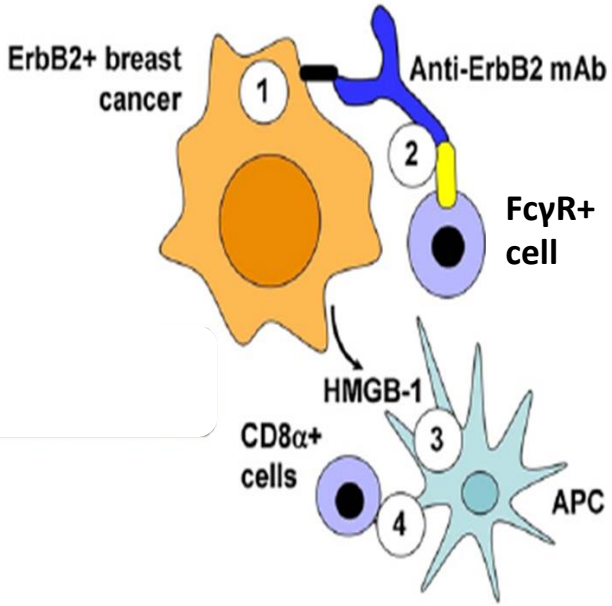


Better Outcomes in Patients with Sticky Natural Killer Cells (CD16A V/V)

Musolino et al., J Clin Oncol 26: 1789-96 (2008)

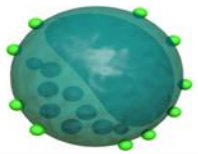
New Strategies

New Anti-HER Antibodies - Margetuximab



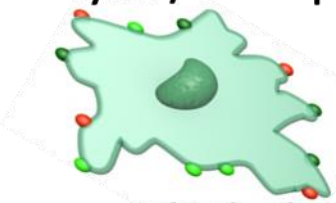
- Optimized IgG1 Fc domains: 5 amino acid substitutions
  - ↑ binding to **activating CD16A** (FcγRIIIA); ↓ binding to **inhibitory CD32B** (FcγRIIB)

Natural Killer (NK) Cell



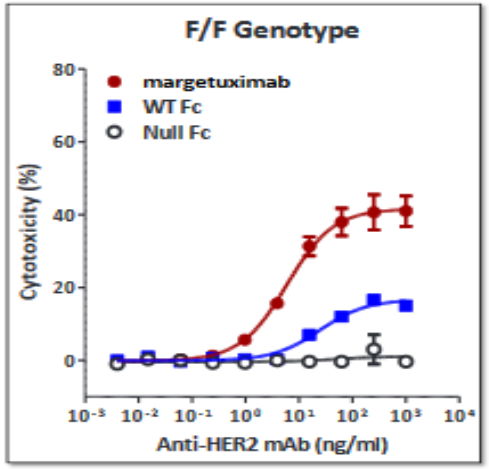
CD16A (Activating)

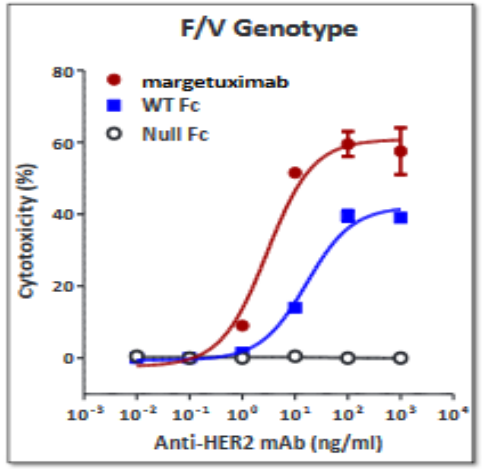
Monocytes / Macrophages

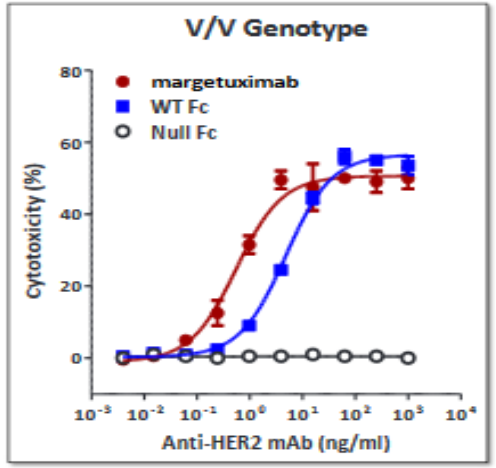


CD16A (Activating)
CD32B (Inhibitory)

Enhanced ADCC of the Fc optimized chimeric Mab Margetuximab, irrespective of the FcγR isoform



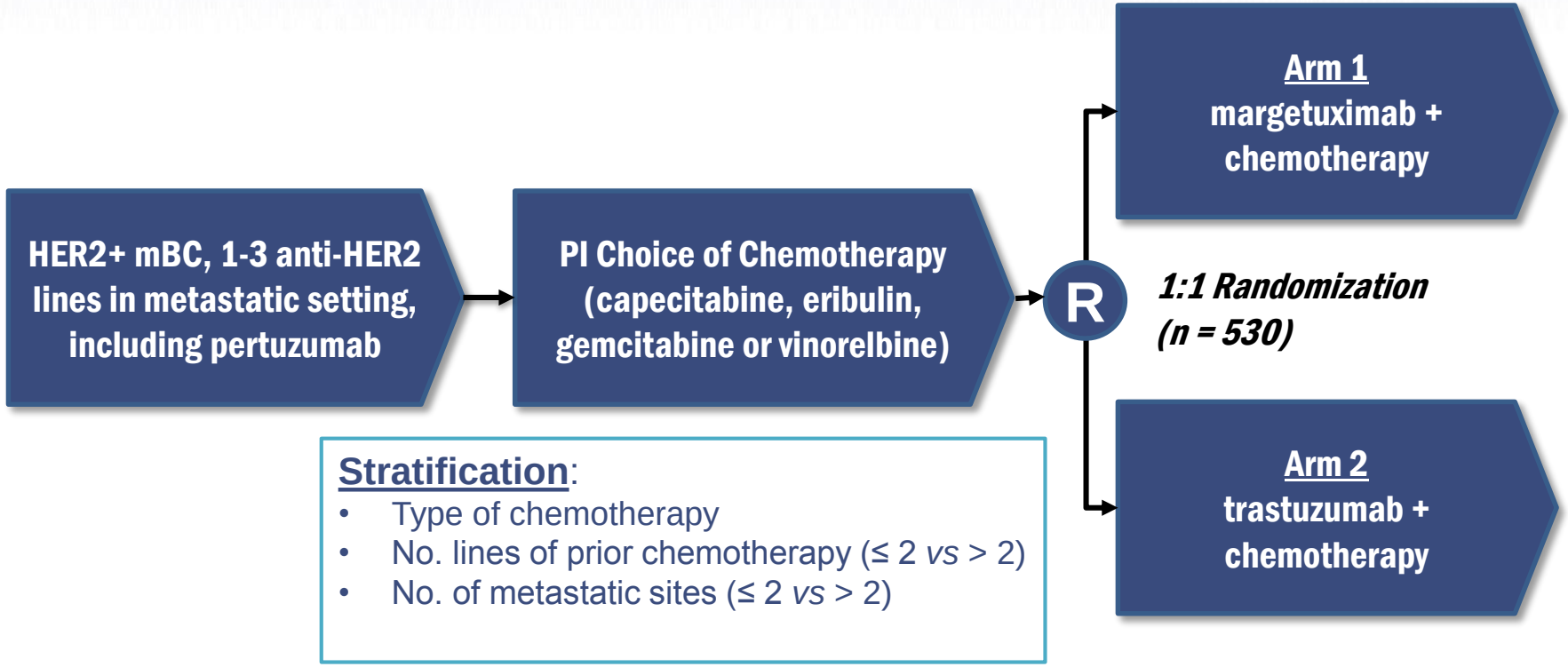




Burris H et al ASCO 2015

SOPHIA Study to Establish Superiority Over Trastuzumab

Phase 3 – Randomized Trial of Margetuximab in Third-Line Metastatic Breast Cancer



Sequential Primary Endpoints:

Progression-Free Survival (PFS, N=257, HR=0.67, α=0.05, power=90%)

then Overall Survival (OS, N=385, HR=0.75, α=0.05, power=80%)

SOPHIA

MacroGenics

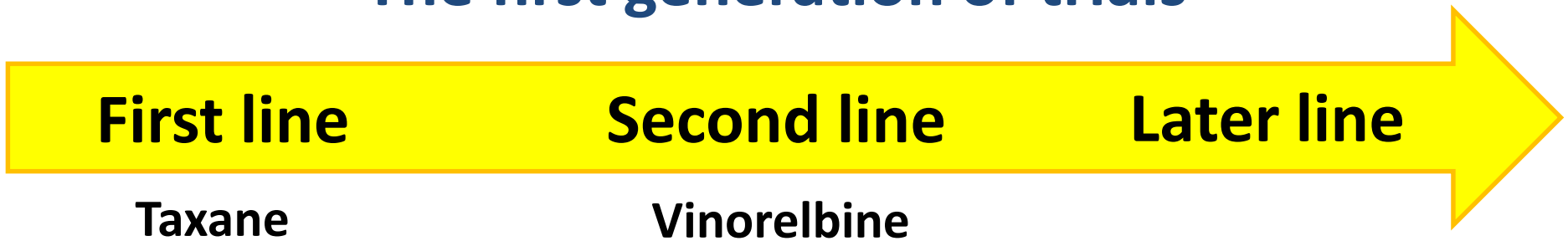
New Strategies

New Agents & New Combinations directed at the cancer cell

New Drugs	New Combinations
New anti-HER TKIs (Neratinib, Tucatinib, Pyrotinib, Poziotinb)	Anti-HER2 + mTOR Inhibitors
Antibody Drug Conjugates (ADCs) (SYD-985, DS 8201)	Anti-HER2 + PI3K Inhibitors
New anti-HER Antibodies (Margetuximab, Panitumumab)	Anti-HER2 + CDK 4/6 Inhibitors
Bi-specific Antibodies (ZW-25, MCLA-128, GBR1302)	Anti-HER2 + anti-PD(L)1

ClinicalTrials.gov

Strategies antagonizing the Pi3K-mTOR pathway
The first generation of trials

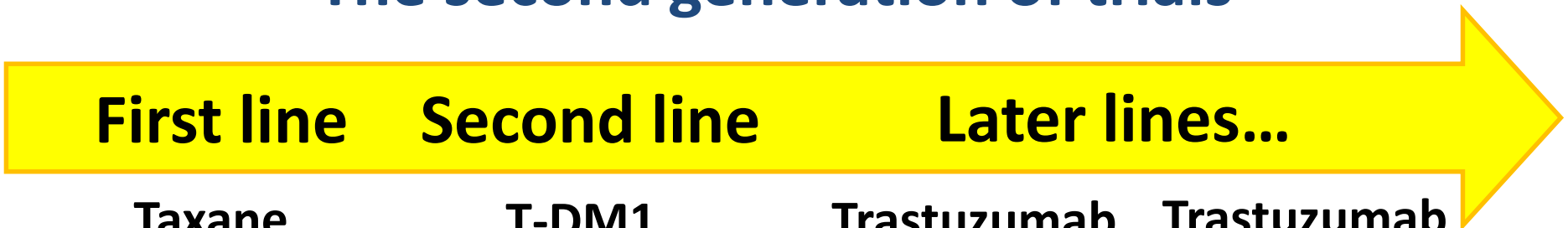


First line	Second line
Taxane + Trastuzumab	Vinorelbine + Trastuzumab
? + Everolimus	? + Everolimus
Bolero-1 **trial** *(1)*	***Bolero-3*** **trial** *(2)*
Negative trial (Signal in HR- subgroup)	**Marginal ↑ PFS**

(1) Hurvitz S et al Lancet Oncol 2015 16 (7) 816-29

(2) Andre F Lancet Oncol 2014 15 (6) p-580-591

Strategies antigonizing the Pi3K-mTOR pathway
The second generation of trials



First line	Second line	Later lines…	
Taxane + Trastuzumab + Pertuzumab	T-DM1	Trastuzumab LJM716*	Trastuzumab

? + Taselisib *(3)*

? + Alpelisib *(2)*

+ Buparlisib
+ Pilaralisib *(1)*

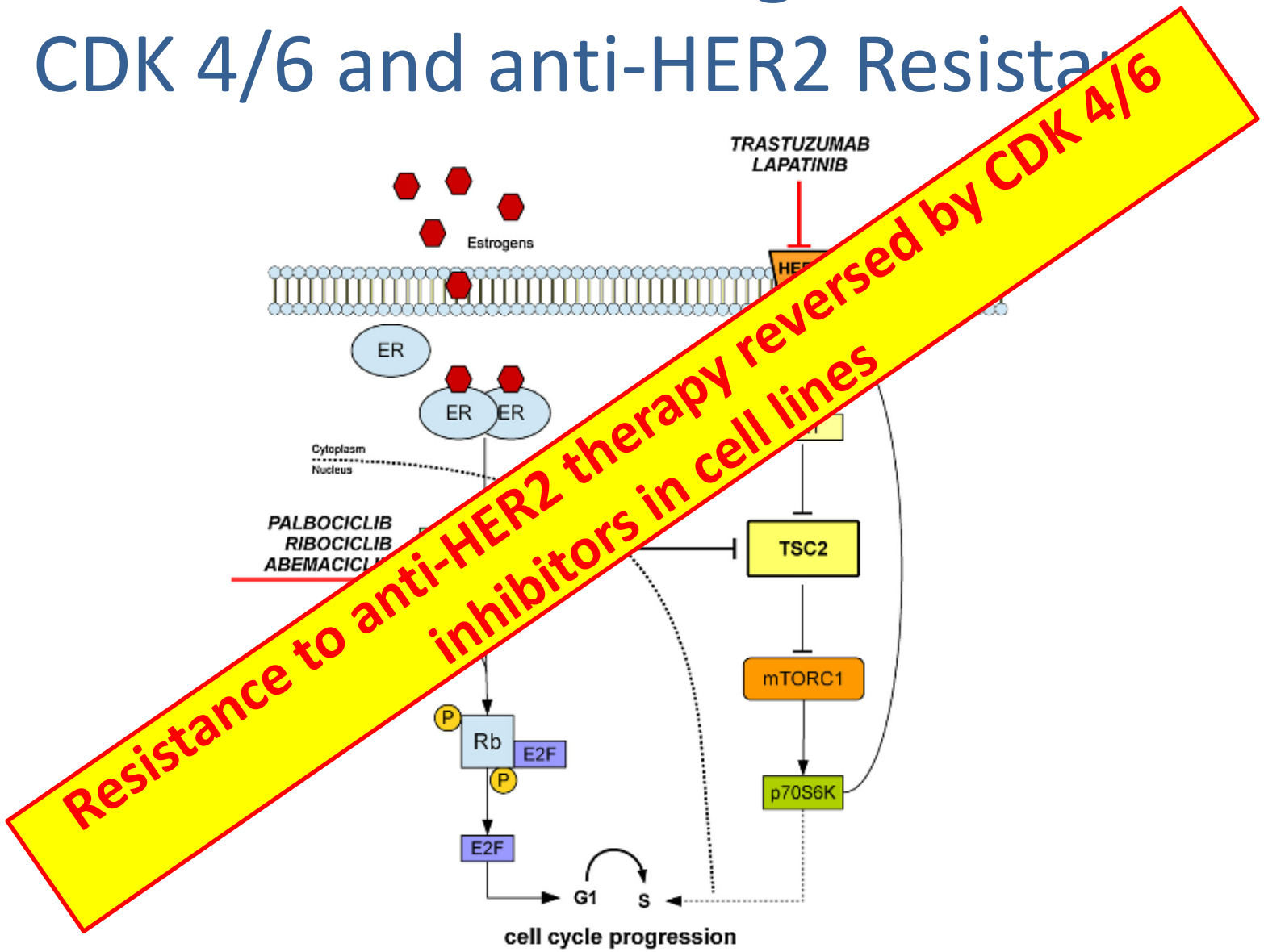
Very modest activity and significant toxicity

**anti-HER3 antibody*

(1) Tolaney S et al. Breat Cancer Res Treat 2015 149 (1) 151-161; (2) NCT02167854 (3) Metzger O et al ASCO 2017

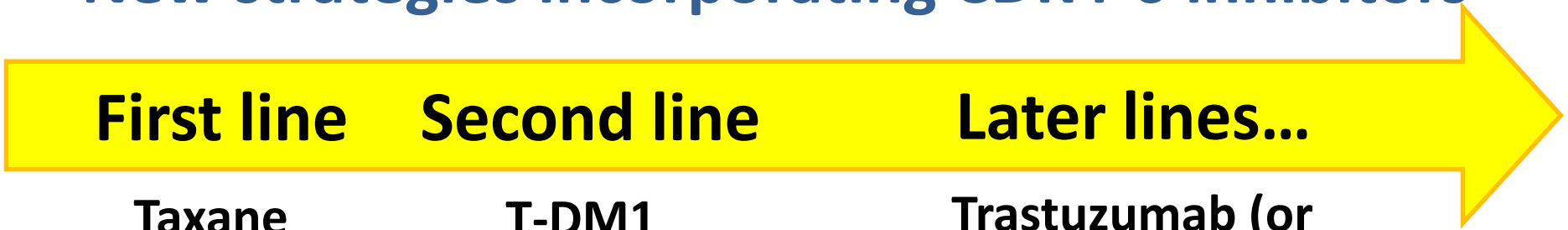
New Strategies

CDK 4/6 and anti-HER2 Resistan



Corona SP et al Crit Rev in Oncol/Hematol 2017 112: 208-2014; Goel S et al Cancer Cell 2016 29 (3):255-269

Advanced HER2+ Breast Cancer : New strategies incorporating CDK4-6 inhibitors



Taxane + Trastuzumab + Pertuzumab

T-DM1

Trastuzumab (or Lapatinib)-based therapies

+ Palbociclib or Ribociclib *(3)*

+ Abemaciclib *(1)*

+ Abemaciclib + Fulvestrant (2)

(1) Beeram M et al ESMO 2016 LBA18

(2) NCT02675231 *(3) NCT02657343*

New Strategies

Palbociclib - Phase 2 PATRICIA Design

BOTH ER- (Arm A) and ER+ (B & C arms)

Patient Population
- HER2+ locally advanced/MBC
- 2-4 previous lines of treatment
- at least 2 forms of anti-HER2 therapy
- At least one taxane or capecitabine containing regimen
- Tumour samples for biomarker research (preferably from metastasis)

RANDOMISATION

ARM A (ER-) Palbo/Trastuzumab

ARM B1 (ER+) Palbo/Trastuzumab

ARM B2 (ER+) Palbo/Trastuzumab/Letrozole

Endpoints

Primary
- PFS at 6 months

Secondary
- CBR
- ORR
- PFS
- Safety
- OS
- Biomarker of response based on 110 genes expression panel

Palbociclib regimen: 200mg 14 days/7 days rest

Clinical Trials.gov NCT02448420

What's New in 2017 (immunotherapy)

2016 2017 2018

KEYNOTE-12 (Nanda et al, JCO 2016)

JAVELIN (Dirix et al, Breast Ca Res Treat 2017)

Multiple phase 1/2 IO + chemo reported/ongoing

KEYNOTE-110 *accrual completed*

IMpassion-130 *accrual completed*

I-SPY2 (preop ER+/TNBC; Nanda et al ASCO 2017)

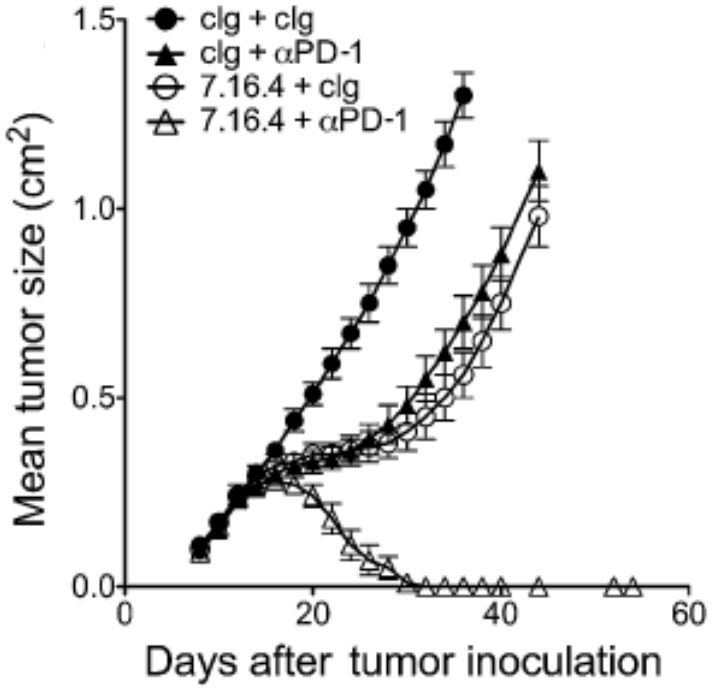
PANACEA (Loi et al, SABCS 2017)

IO combinations

IO + targeted tx

Background: Anti-tumor immunity & HER2-positive breast cancer

- HER2-positive breast cancer has high levels of T cell infiltration
- TILs are associated with improved prognosis and response to trastuzumab and chemotherapy[1,2]
- Trastuzumab has been shown to have immune mediated mechanisms of action[3,4]
- Preclinical studies suggest immune-mediated mechanisms of trastuzumab resistance that can be overcome with checkpoint inhibition combinations[5]



[1] Loi et al, J Clin Oncol 2013; [2] Loi et al, Ann Oncol 2014 [3] Clynnes et al Nat Med 2002
[4] Park et al, Cancer Cell 2011; [5] Stagg, Loi et al, PNAS 2011

Anti-PD(L) 1 Strategies explored in advanced HER2+ BC

Taxane + Trastuzumab + Pertuzumab

? + anti PD(L) 1

Pembrolizumab *(5)*
Atezolizumab *(6)*

T-DM1

? + anti PD(L) 1

Atezolizumab *(3)*
Pembrolizumab *(4)*

Trastuzumab

? + anti PD(L) 1

Pembrolizumab *(1)*
Durvalumab *(2)*

(1) NCT02129556 (2) NCT02649686 (3) NCT02924883 (4) NCT03032107 (5) NCT03199885 (6) NCT03125928

New Strategies
PANACEA TRIAL

S. Loi

ABC
Prior progression while on trastuzumab based

Central testing HER2 by IHC

HER2 -

Non Eligible

HER2 +

Central PD-L1 testing

PD-L1 -

Non Eligible *

PD-L1 +

Enroll

Phase Ib (dose finding Pembrolizumab in 3+3 design) /Phase II at RP2D
Treatment in 3 weeks cycles

Trastuzumab 6 mg/kg q 3 w

Pembrolizumab

PD

* **PDL1 negative cohort added later**

Clinical Trials.gov: NCT02129556

Baseline Characteristics

Characteristic N (%)	Phase Ib PD-L1 positive; n=6	Phase II PD-L1 positive; n=40	Phase II PD-L1 negative; n=12	Overall n=58
Age yrs. median (range)	49 (38-57)	49 (28-72)	56.5 (43-61)	**50.5 (28-72)**
ER negative	4 (66%)	23 (57.5%)	6 (50%)	**33 (56.9%)**
positive (≥ 1%)	2 (33%)	17 (42.5%)	6 (50%)	**25 (43.1%)**
Prior trastuzumab-containing therapy	6 (100%)	40 (100%)	12 (100%)	**58 (100%)**
Additional anti-HER2 therapy				
No	1 (16.7%)	6 (15%)	0 (0%)	**7 (12.1%)**
Yes	5 (83.3%)	34 (85%)	12 (100%)	**51 (87.9%)**
T-DM1	4	29	9	**42**
Pertuzumab	3	10	4	**17**
Other	1	17	8	**26**
Prior chemotherapy (Anth/Taxane)	6 (100%)	40 (100%)	12 (100%)	**58 (100%)**
Median time from Dx met disease to enrolment; months (range)	15.5 (6-83.6)	40.8 (1.1-111)	71.5 (9.9-179.1)	**40 (1.1-179.1)**

Best Overall Response (RECIST 1.1)

	PD-L1 Positive Phase Ib, n=6	PD-L1 Positive Phase II, n=40	PD-L1 Negative Phase II, n=12
ORR n (%) [90%CI]	**1 (17%) [1-58]**	**6 (15%) [7-29]**	**0 (0%) [0-18]**
DCR[1] n (%) [90%CI]	1 (17%) [1-58]	10 (25%) [14-49]	0 (0%) [0-18]
Best overall response, n (%)			
Complete Response	**1 (17%)**	**1 (2.5%)**	**-**
Partial Response	**-**	**5 (12.5%)**	**-**
Stable Disease	**-**	**7 (17.5%)**	**2 (16.7%)**
Progressive Disease	**5 (83%)**	**25 (62.5%)**	**9 (75.0%)**
Not Evaluable	**-**	**2 (5.0%)**	**1 (8.3%)**

Overall PD-L1 + cohort **ORR 15.2% [7-27]** **DCR 25% [14-36]**

PD-L1: assessed centrally by Merck
QualTek PD-L1 IHC Assay changed to 22C3 Q^2 Solutions
Positive was QualTek ≥1% tumor or stroma; $Q^{2:}$ CPS ≥1%

[1]DCR: CR, PR, or SD ≥ 6 months

PANACEA Trial: Summary and Conclusions

- PANACEA study of pembrolizumab with trastuzumab in trastuzumab-resistant mHER2+ patients met its primary endpoint in the PD-L1 positive cohort **(ORR 15%, DCR 25%)**
  - No responses observed in PD-L1 negative patients
  - Stromal TIL levels associated with responses: sTILs ≥ 5% patients (ORR 39%, DCR 47%)
  - For responders: combination offers durable control without chemotherapy

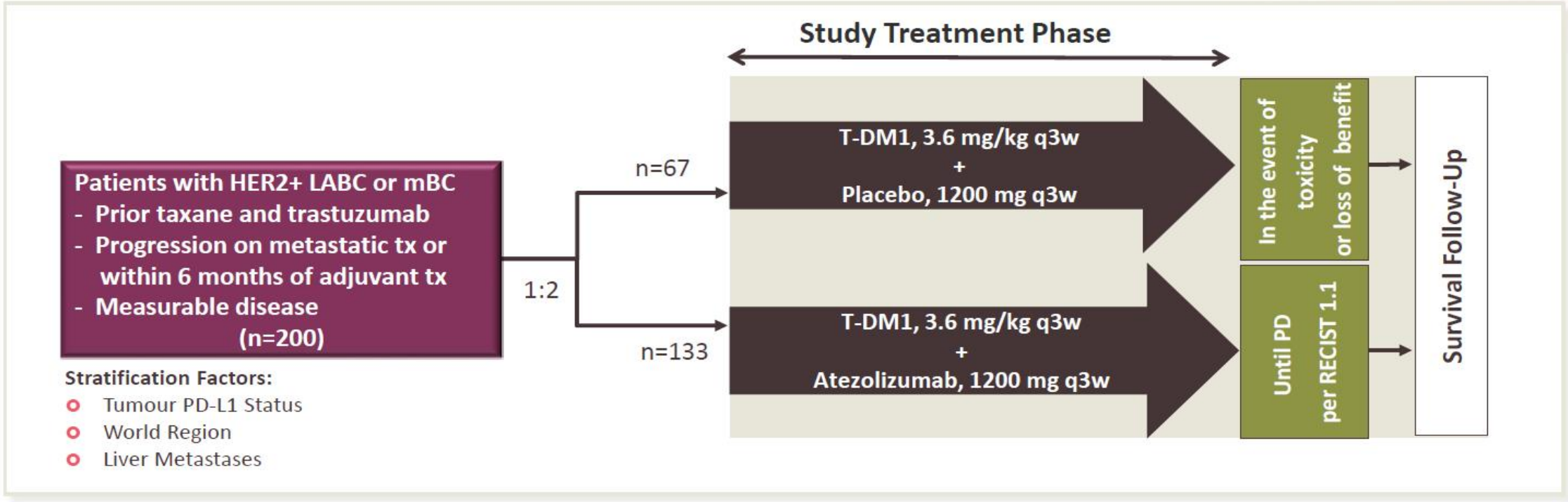
- Metastatic HER2+ disease in the heavily pretreated setting is ***poorly immunogenic*** (majority of patients had low TILs in their metastatic lesions)

- Future directions in IO in mHER2+ should focus on combinations with effective anti-HER2 therapy, especially in low TIL patients

KATE2 Study Overview

DESIGN: PHASE II | DOUBLE-BLIND | MULTICENTRE | RANDOMIZED | PLACEBO-CONTROLLED

Total study duration: 28 months – Recruitment: 9 months



T-DM1: Trastuzumab-emtansine

Kate2 WO30085

Concluding Remarks

The next decade will see numerous drugs & combinations come to Phase III (and hopefully clinical practice).



Coming together is a beginning
Keeping together is progress
Working together is success
- Henry Ford-