HER2-positive Breast Cancer
The clinician‘s perspective

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Declaration of potential conflicts of interests

- Roche: Lecture honoraria, advisory role, travel support
- AstroPharma: Lecture honoraria
- Novartis: Lecture honoraria, advisory role, research support
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- Eliy-Lilly: Lecture honoraria, advisory role

The EMBO Journal vol.3 no.1 pp.159 – 163, 1984

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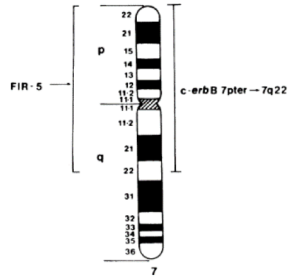
Chromosomal localisation of the human homologues to the oncogenes *erb*A and B



HER2: A Unique Story of Success

The *neu* oncogene encodes an epidermal growth factor receptor-related protein

Cornelia I. Bargmann, Mien-Chie Hung & Robert A. Weinberg

Whitehead Institute for Biomedical Research, 9 Cambridge Center, Cambridge, Massachusetts 02142 and Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA

- AVE (avian erythroblastosis virus) causes haematological malignancies and solid tumours in birds
- In the viral genome, two host-derived genes were identified: *v-erbA* and *v-erbB*
- *v-erbB* responsible for the malignant transformation of infected host cells
- 1983, 1984: Description of human homologues to AVE *erbA* and *erbB* [1,2]
- Human *c-erbB* localized on chromosome 7 (q22) – a *v-erB* homologue (*c-erbB2*) localized on chromosome 17 (q21) [3,4]

1 Spurr NK et al. EMBO J 1984;3:159-163.
2 Jansson M et al. EMBO J 1983;2:561-565.
3 Barschmann C et al. Nature 1986;319:226-230.
4 Yamamoto T et al. Nature 1986;319:230-234.

HER2: A Unique Story of Success

The HER-2/*neu* oncogene is a member of the *erb*B–like oncogene family, and is related to, but distinct from, the epidermal growth factor receptor. This gene has been shown to be amplified in human breast cancer cell lines.

Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/*neu* Oncogene

DENNIS J. SLAMON,* GARY M. CLARK, STEVEN G. WONG, WENDY J. LEVIN, AXEL ULLRICH, WILLIAM L. MCGUIRE

- Analysis of outcome in 189 primary breast cancer cases [1]
- *HER2/neu* amplification in 30%
- Significant correlation with DFS and OS
- Stronger prognosticator of outcome then the most relevant “conventional” markers such as nodal status and hormone-receptor status

- HER2 as prognostic marker

1 Slamon D et al. Science 1987;235:177-182.

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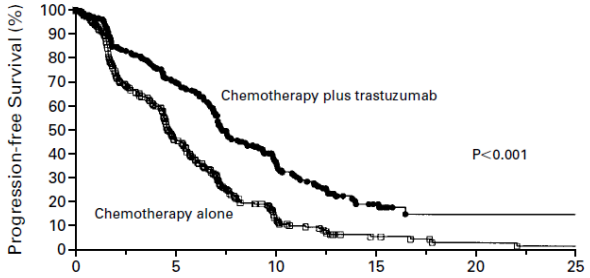
USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

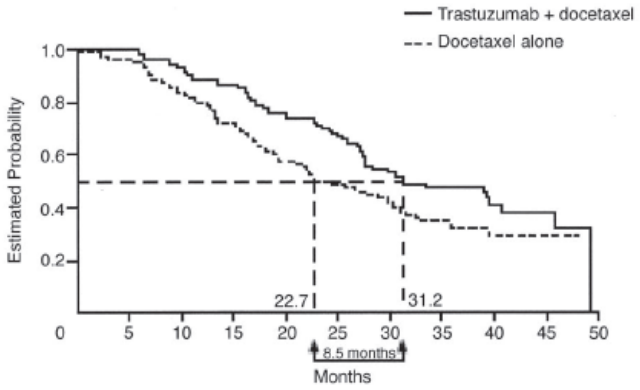
DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

Trastuzumab

- Phase III trial, 469 pts., MBC, HER2-pos., first-line
  AC +/- trastuzumab or paclitaxel +/- trastuzumab
  PFS: 7.4 *versus* 4.6 months; $p<0.001$
  OS: 25.1 *versus* 20.3 months; $p=0.046$ [1]



- Phase II trial, 186 pts., MBC, first-line
  Docetaxel +/- trastuzumab
  PFS: 11.7 *versus* 6.1 months; $p=0.0001$
  OS: 31.2 *versus* 22.7 months; $p=0.0325$ [2]

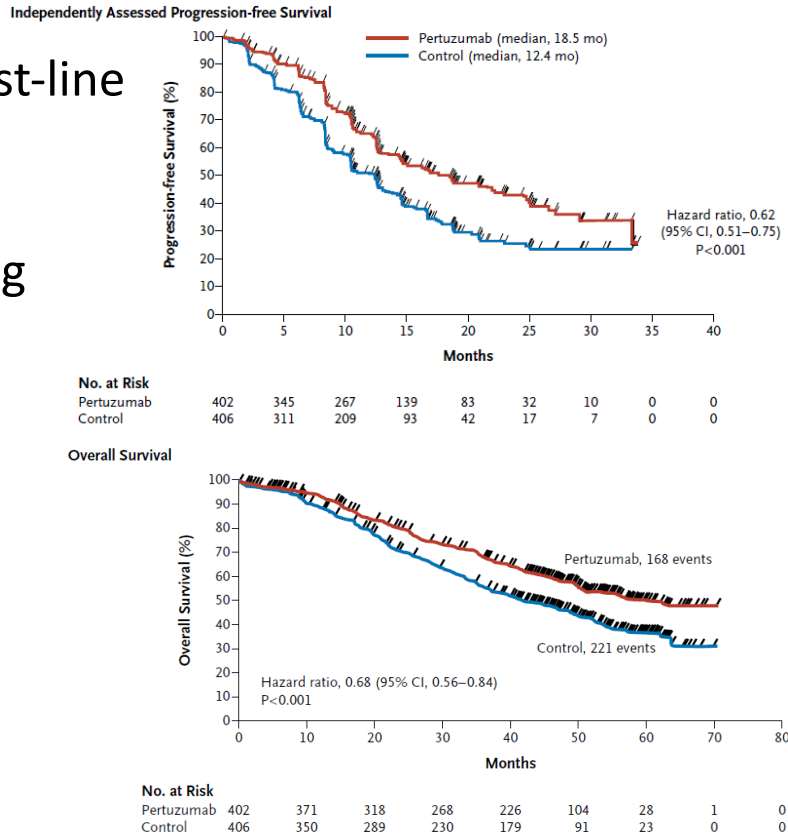


- HER2 as therapeutic target

1 Slamon D et al. N Engl J Med 2001; 344:783-792.
2 Marty M et al. J Clin Oncol 2005; 23:4265-4274.

Pertuzumab plus Trastuzumab[1-3]

- Phase III trial, 808 pts., MBC, HER2-pos., first-line
  Docetaxel + trastuzumab +/- pertuzumab
- Pertuzumab: Anti-HER2 antibody preventing
  HER2 / HER3 heterodimerization
- OS 37.6 months *vs*. not reached
  HR=0.66; 95% CI 0.52–0.84; *p*=0.0008
- 50 months median follow-up:
  D+TP 56.5 *vs*. D+T 40.8 months
  HR 0.68; 95% CI 0.56–0.84; *p*=0.0002

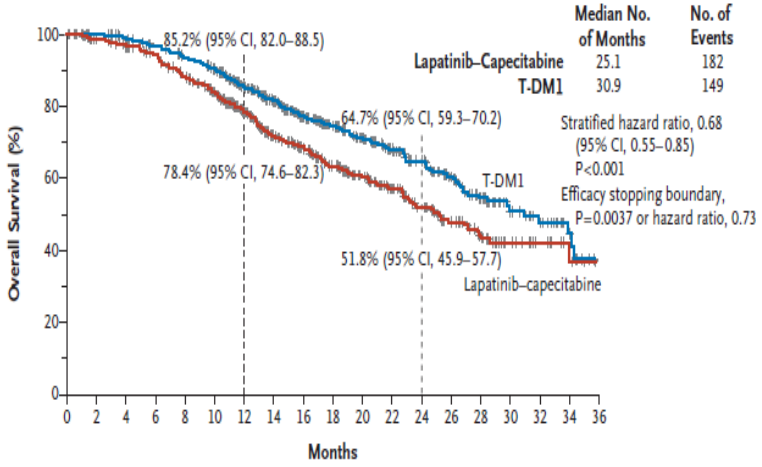


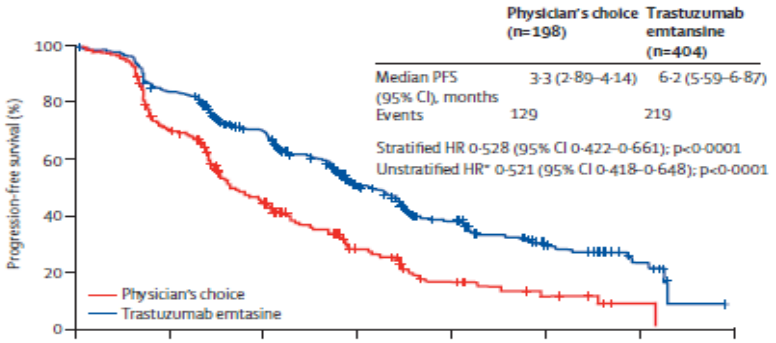
1 Baselga J et al. N Engl J Med 2012;366:109-119.
2 Swain SM et al. Lancet Oncol 2013;14:461-471.
3 Swain S et al. N Engl J Med 2015;372:724-734

T-DM1

- Phase III, randomized, T-DM1 *versus* capecitabine + lapatinib [1]
  137 pts., MBC, mainly second-line
  PFS 9.6 months *versus* 6.4 months
  (HR 0.65; 95% CI 0.55-0.77)

- TH3RESA: Randomized phase III [2]
  602 pts., heavily pretreated, 75% visceral metastases
  T-DM1 *versus* TPC (>80% trastuzumab)
  PFS 6.2 months *versus* 3.3 months
  (HR 0.53; 95% CI 0.42-0.66)





1 Verma S et al. H Engl J Med 2012;367:1783-1791.
2 Krop IE et al. Lancet Oncol 2014;15:689-699.

Lapatinib[1]

- Small molecule anti-HER2 TKI blocking HER2 and EGFR - diarrhoea relevant side-effect[1]

- Phase III, 324 pts., MBC, HER2-pos., prior trastuzumab; capecitabine +/- lapatinib[1]
- PFS 8.4 *vs.* 4.4 months ($p<0.001$); no OS difference

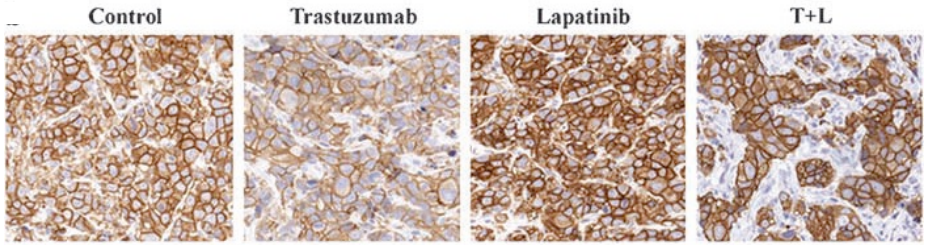
- Ma.31: Phase III, 652 pts. (537 confirmed HER2-pos.), MBC, first-line; lapatinib or trastuzumab plus taxane[2]
- PFS (HER2-pos.): 9.1 *vs.* 13.6 months (HR 1.48; 95% CI 1.20-1.83; $p<0.001$)
- OS (HER2-pos.): HR 1.47 (95% CI 1.03-2.09; $p=0.03$)

1 Geyer CE et al. N Engl J Med 2006;355:2733-2743.
2 Gelmon KA et al. J Clin Oncol 2015;33:1574-1583.

ORIGINAL ARTICLE

Lapatinib, a HER2 tyrosine kinase inhibitor, induces stabilization and accumulation of HER2 and potentiates trastuzumab-dependent cell cytotoxicity

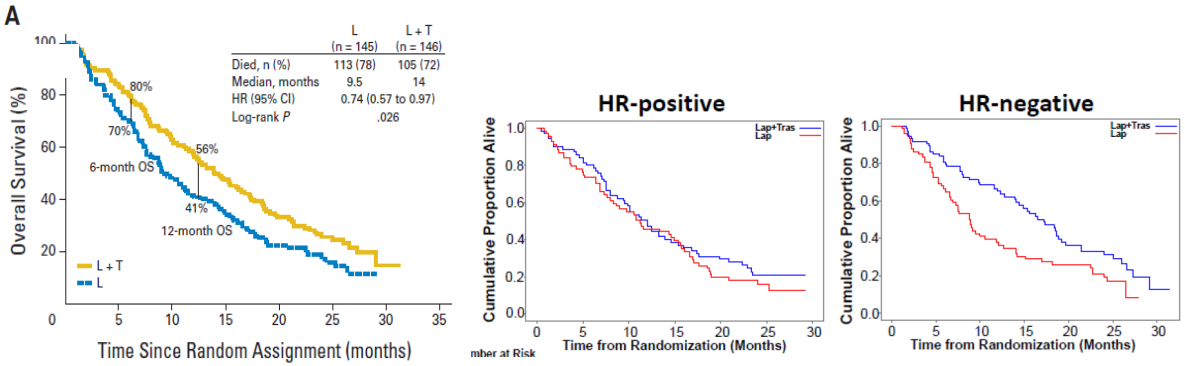
M Scaltriti[1], C Verma[2], M Guzman[1], J Jimenez[3], JL Parra[1], K Pedersen[1], DJ Smith[2], S Landolfi[3], S Ramon y Cajal[3], J Arribas[1] and J Baselga[1,4]



Lapatinib plus Trastuzumab

- Trastuzumab binding to the cell surface results in HER2 downregulation [2]
- Lapatinib stabilizes HER2 in the membrane – may improve trastuzumab-binding

- Phase III, 291 pts., MBC, HER-pos., heavily pretreated, lapatinib *vs*. L+T [3]
- OS 9.5 *vs*. 14 months (HR 0.74; 95% CI 0.57-0.97; *p*=0.026)



	Lap+Tras N=71	Lap N=70	OS HR (95% CI)
Median OS, mos	12.0	11.2	0.84 (0.5-1.23)
	Lap+Tras N=75	**Lap N=75**	**OS HR (95% CI)**
Median OS, mos	17.2	8.9	0.62 (0.42-0.90)

1 Scaltriti M et al. Oncogene 2009;28:803-814.
2 Blackwell KL et al. J Clin Oncol 2012;30:2585-2592.

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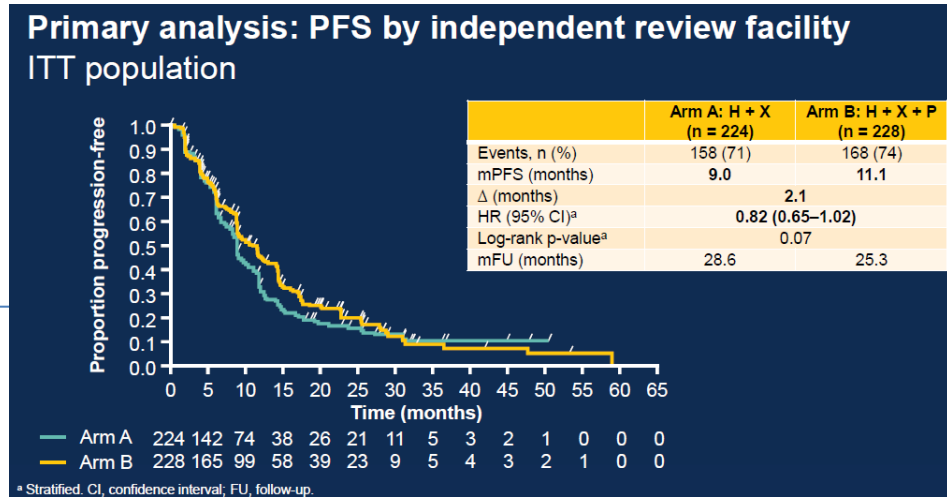
Caveats in Current Data



	Arm A: H + X (n = 224)	Arm B: H + X + P (n = 228)
Events, n (%)	158 (71)	168 (74)
mPFS (months)	9.0	11.1
Δ (months)	2.1	
HR (95% CI)[a]	0.82 (0.65–1.02)	
Log-rank p-value[a]	0.07	
mFU (months)	28.6	25.3

- The EMILIA trial was conducted in a population without prior exposure to dual inhibition with trastuzumab and pertuzumab - currently only data from restrospective studies available suggesting that T-DM1 is active even after TP
- Median duration of T-DM1 therapy after progression on TP 7.1 (CLEOPATRA) and 4.2 months (PHEREXA) [1]
- Case-series, 82 pts., T-DM1, heavily pretreated (31.7% 1st-line and 2nd-line)
  Treatment duration ≥6 months 30.8% (95% CI 20.6-41.1)
  Median treatment duration 4 months (95% CI 2.7-5.1) [2]
- PHEREXA: Formally no benefit for dual inhibition with TP plus capecitabine over trastuzumab plus capecitabine in pretreated patients [3]

1 Urruticoechea M et al. Abst. #1023; presented at the 2017 ASCO Annual Meeting, June 2017, Chicago, USA.
2 Dzimitrowicz H et al. J Clin Oncol 2016;34:3511-3517.
3 Urruticoechea A et al. J Clin Oncol 2017;35:3030-3038.

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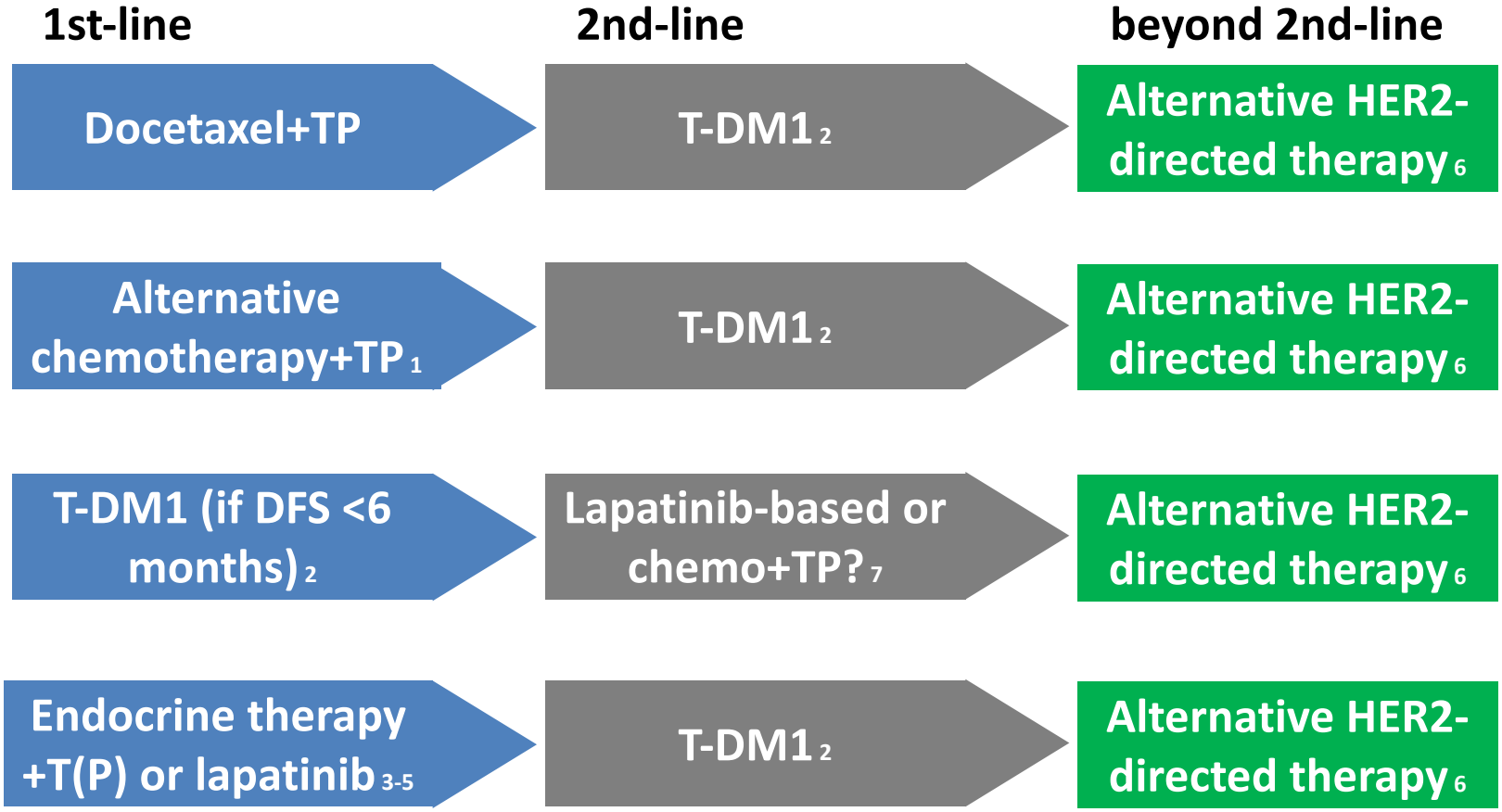
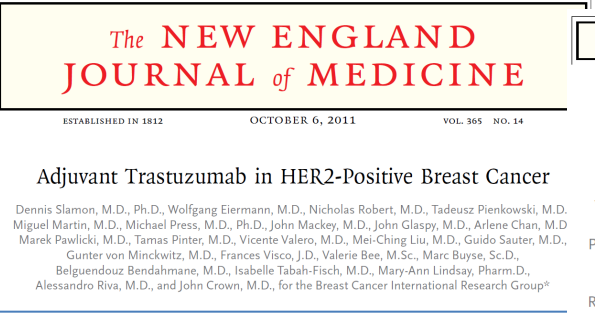
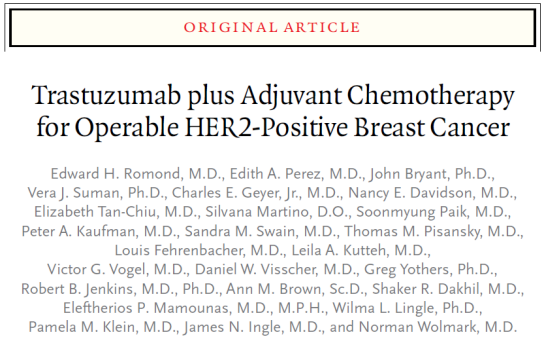
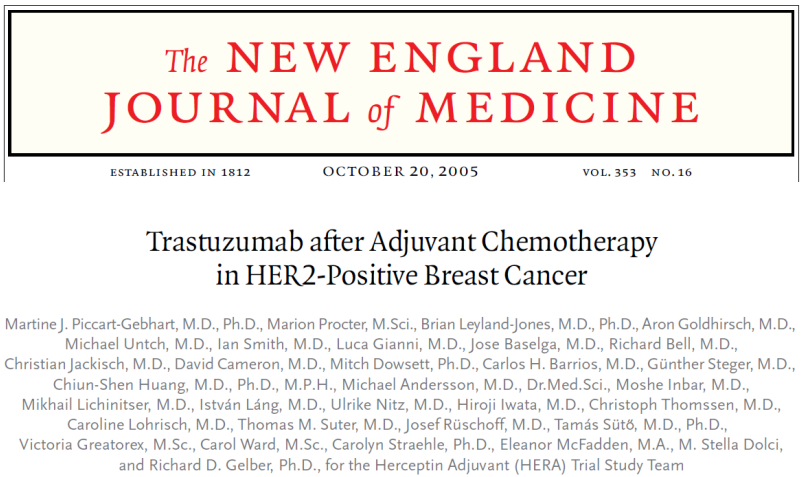
Current standards in HER2-positive MBC



1 VELVET
2 EMILIA
3 TanDem
4 ALTERNATE
5 PERTAIN
6 HERMINE
7 PHEREXA







Adjuvant Trastuzumab

- One year of adjuvant trastuzumab as standard-of-care in the adjuvant setting [1-4]
- Cut-off for adjuvant therapy?
- Biology more relevant than size – retrospective data, 1,000 pts, T <1 cm [5,6]
- Recurrence risk:
  HR 5.09 (95% CI 2.56-10.14; $p<0.0001$)
- Risk for distant recurrences:
  HR 7.81 (95% CI 3.17-19.22; $p<0.0001$)

1 Piccart-Gebhart M et al. N Engl J Med 2005;353:1659-1672.
2 Romond HE et al. N Engl J Med 2005;353:1673-1684.
3 Slamon D et al. N Engl J Med 2011;365:1273-1283.
4 Goldhirsch A et al. Lancet 2013;382:1021-1028.
5 Joerger M et al. Ann Oncol 2011;22:17-23.
6 Rakkhit R et al. Cancer Res 2008;69(Suppl. 2):97S.

ORIGINAL ARTICLE

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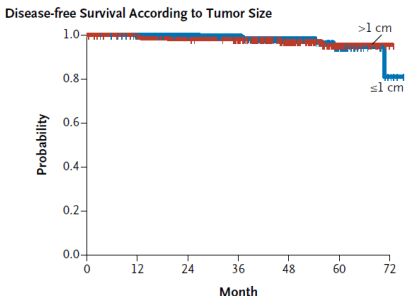
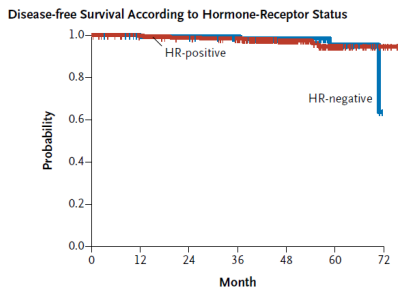
Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Sara M. Tolaney, M.D., M.P.H., William T. Barry, Ph.D., Chau T. Dang, M.D., Denise A. Yardley, M.D., Beverly Moy, M.D., M.P.H., P. Kelly Marcom, M.D., Kathy S. Albain, M.D., Hope S. Rugo, M.D., Matthew Ellis, M.B., B.Chir., Ph.D., Iuliana Shapira, M.D., Antonio C. Wolff, M.D., Lisa A. Carey, M.D., Beth A. Overmoyer, M.D., Ann H. Partridge, M.D., M.P.H., Hao Guo, M.S., Clifford A. Hudis, M.D., Ian E. Krop, M.D., Ph.D., Harold J. Burstein, M.D., Ph.D., and Eric P. Winer, M.D.

Adjuvant Trastuzumab: Deescalation?

- Single-arm phase II trial, paclitaxel weekly x12 plus trastuzumab [1]
- 406 pts, node-negative, tumour size <3 cm
- 3-years invasive DFS: 98.7% (95% CI 97.6-99.8)
- Effect independent of size and hormone-receptor status
- First data suggesting that deescalation my be possible even in a high-risk subtype

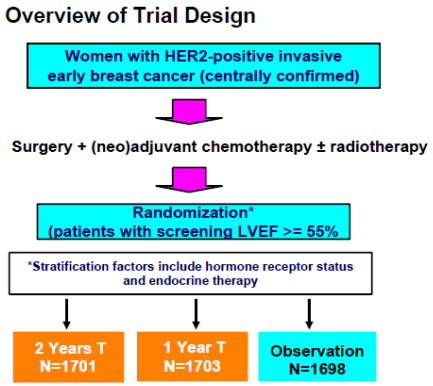


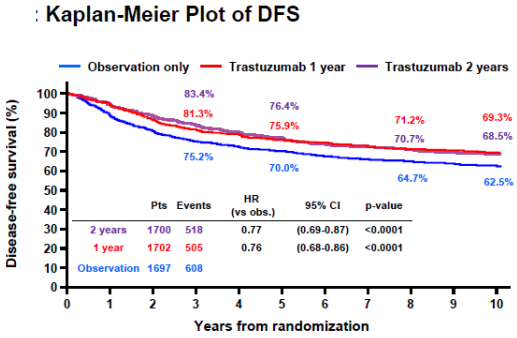


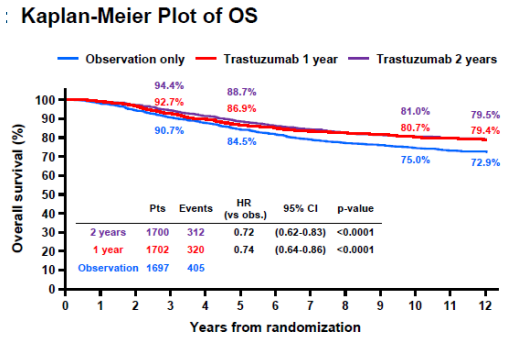
1 Tolaney SM et al. N Engl J Med 2015;372:134-141.

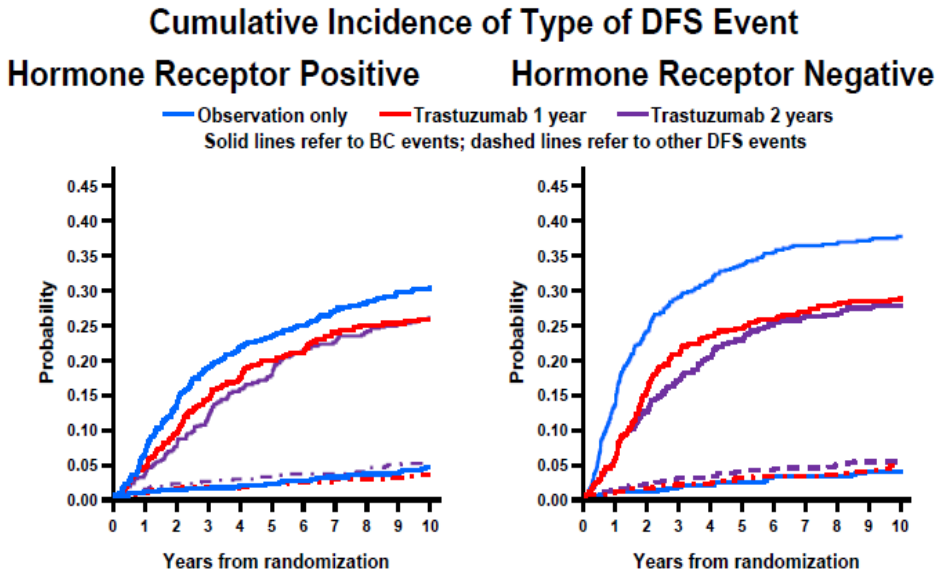
Are All HER2-positive Tumours the Same?

- 10-years Follow-Up update HERA (median follow-up 11 years)





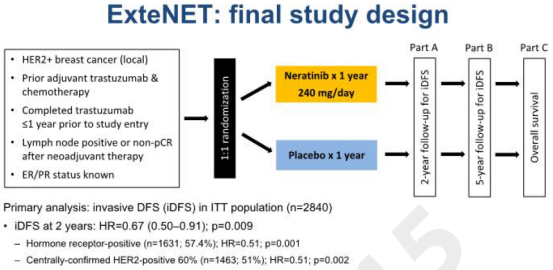


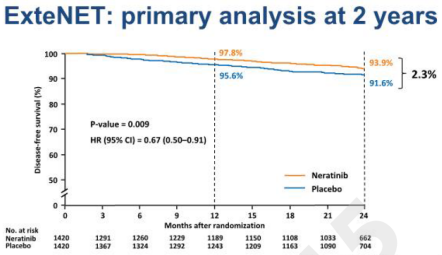


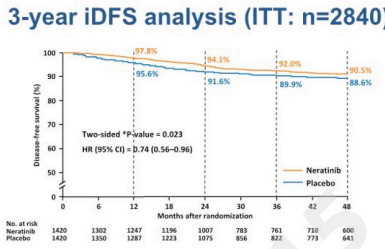
1 Jackisch C et al. PD5-01. Presented at the 2015 SABCS.

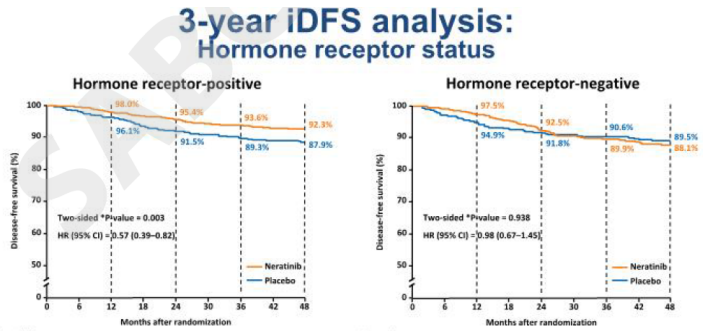
Are All HER2-positive Tumours the Same?

- Recurrence in up to 26.3% even after adjuvant trastuzumab – EXTENET [1-6]
- Discussion: Effect apparetnly limted to luminal B / HER2-positive tumours, toxicity, compliance









1 Chan A et al. S5-02. Presented at the 2015 SABCS.
2 Perez EA et al. J Clin Oncol 2014;32:3744-3752.
3 Goldhirsch A et al. Lancet 2013;382:1021-1028.
4 Joensuu H et al. J Clin Oncol 2009;27:5685-5692.
5 Slamon D et al. N Engl J Med 2011;365:1273-1283.
6 Chan A et al. Lancet Oncol 2016;17:367-377.

[CANCER RESEARCH 52, 2127–2137, April 15, 1992]

Perspectives in Cancer Research

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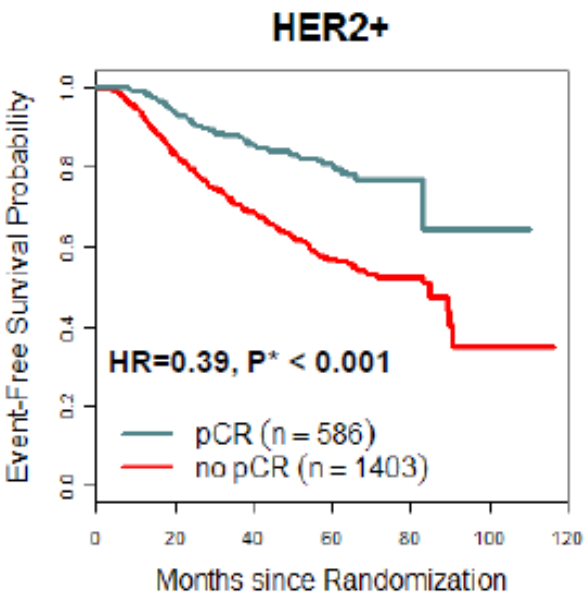
Evolving Concepts in the Systemic Adjuvant Treatment of Breast Cancer

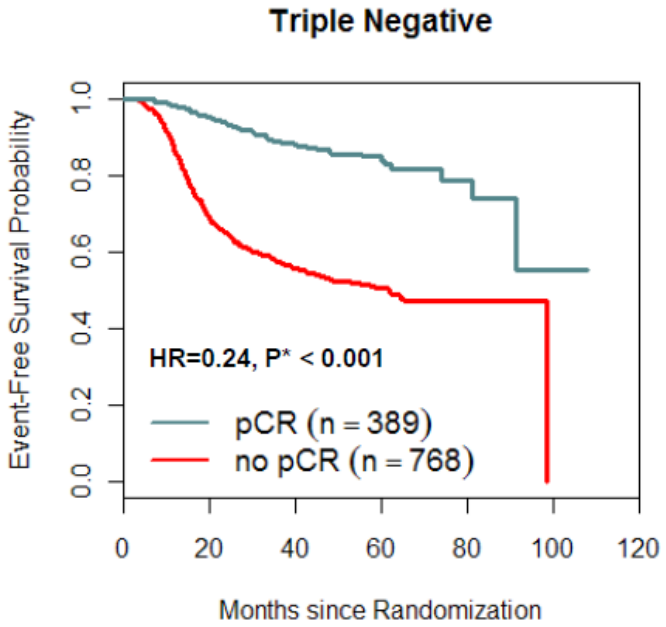
Gianni Bonadonna[1]

Division of Medical Oncology, Istituto Nazionale Tumori, Via Venezian, 1, Milan, Italy

Neoadjuvant Therapy and Outcome

- Neoadjuvant treatment preferred in high-risk breast cancer subtypes [1]
- pCR predicts OS on an individual patient level [2,3]





1 Curigliano G et al. Ann Oncol 2017;28(1700-1712 .
2 Von Minckwitz G et al. J Clin Oncol 2012;30:1796-1804.
3 Cortazar P et al. Lancet 2014;384:164-172.

Neoadjuvant Trastuzumab[1]

- Randomized phase III, neoadjuvant, 650 pts., HER2-positive
- EC x4 - docetaxel x4 with either trastuzumab or lapatinib
- Primary EP: pCR (no invasive BC in breast or axilla):
  Chemotherapy plus trastuzumab: 30.3%
  Chemotherapy plus lapatinib: 22.7%
  OR 0.68 (95%CI 0.47-0.97; *p*=0.04)
- Higher pCR rates in non-luminal HER2-positive tumours

1 Untch M et al. Lancet Oncol 2012;13:135-144.

Annals of Oncology 24: 2278–2284, 2013
doi:10.1093/annonc/mdt182
Published online 22 May 2013

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Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA)

A. Schneeweiss[1*], S. Chia[2], T. Hickish[3], V. Harvey[4], A. Eniu[5], R. Hegg[6], C. Tausch[7], J. H. Seo[8], Y.-F. Tsai[9], J. Ratnayake[10], V. McNally[10], G. Ross[10] & J. Cortés[11]

Neoadjuvant Pertuzumab[1]

- TRYPHENA: Randomized phase II, 225 pts, HER2-positive, neoadjuvant,
- Primary end-point: cardiac safety
- T+P and anthracyclines either concomitantly or sequentially, arm C anthracycline-free

pCR	ypT0/is	ypT0 ypN0
FEC-T+P+H	61.6%	50.7%
FEC+T+P-T+P+H	57.3%	45.3%
TC+P+H	66.2%	51.9%

- Effect dominant in non-luminal HER2-positive tumours

1 Schneeweiss A et al. Ann Oncol 2013;24:2278-2284.

Neoadjuvant *versus* Adjuvant

- Approval of neoadjuvant dual inhibition based-upon phase II studies [1]
- NeoSphere Inclusion Criteria: T2 and/oder N+ [2]
- Limited pCR improvements in luminal B / HER2-positive tumours
- Currently, no formally significant improvement of DFS and OS with dual HER2-blockade in the neoadjuvant setting [3]
- Individualized treatment decision in small, node-negative tumours – either neoadjuvant chemotherapy + TP or weekly paclitaxel + T adjuvant. Decision based upon patient specific factors and additional clinical risk-factors?

1 Avaiable at: http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/002547/WC500140980.pdf. Last accessed January 3rd, 2017.
2 Gianni L et al. Lancet Oncol 2012;13:25-32.
3 Gianni L et al. Lancet Oncol 2016;17:791-800.

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer

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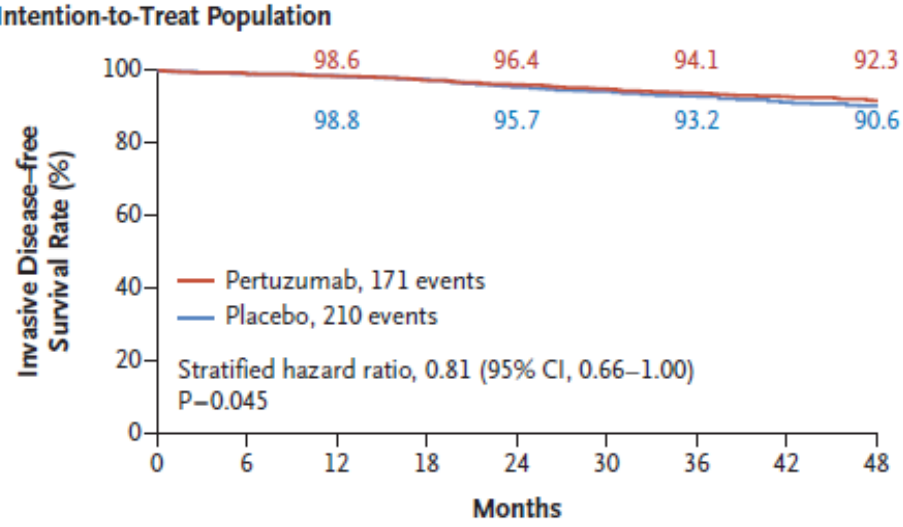
Adjuvant Pertuzumab[1]

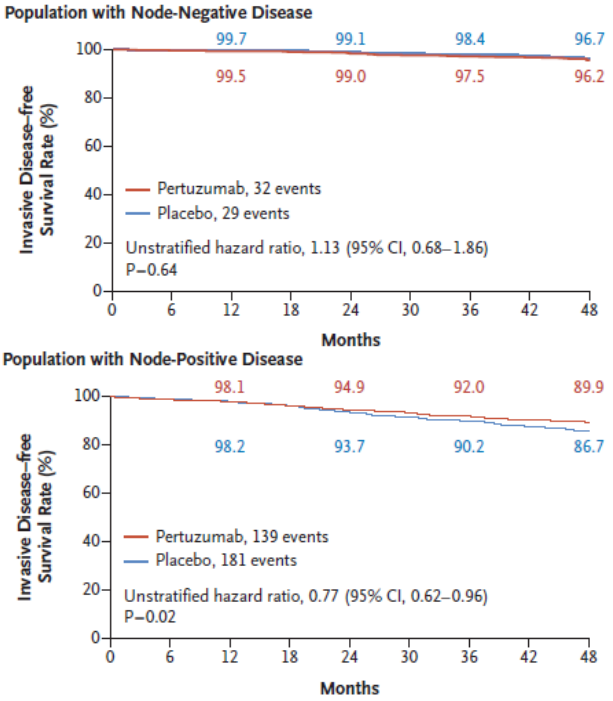
- APHINITY: Prospective, randomized, placebo-controlled phase III
- Adjuvant chemotherapy pus trasutzmab plus/minus pertuzumab
- 2,805 pts., node-positive or high-risk node negative
- Primary endpoint: 3-year invasive-disease-free suvival
- Assumption: placebo 89,2%; pertuzumab 91,8%
- 63% node-positive, 36% hormone-receptor negative

1 von Minckwitz G et al. N Engl J Med 2017;377:122-131.

Adjuvant Pertuzumab[1]

- Results





- Lower recurrence-rate than anticipated in the placebo group
- Effect limited to node-positive pts.
- How to treat after neoadjuvant dual blokade – decision based upon initial node-status?

1 von Minckwitz G et al. N Engl J Med 2017;377:122-131.

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Subcutanous Trastuzumab[1]

- HannaH: Prospective randomized open-label phase III trial
- 596 pts., early breast cancer, HER2 pos., indication for neoadjuvant treatment

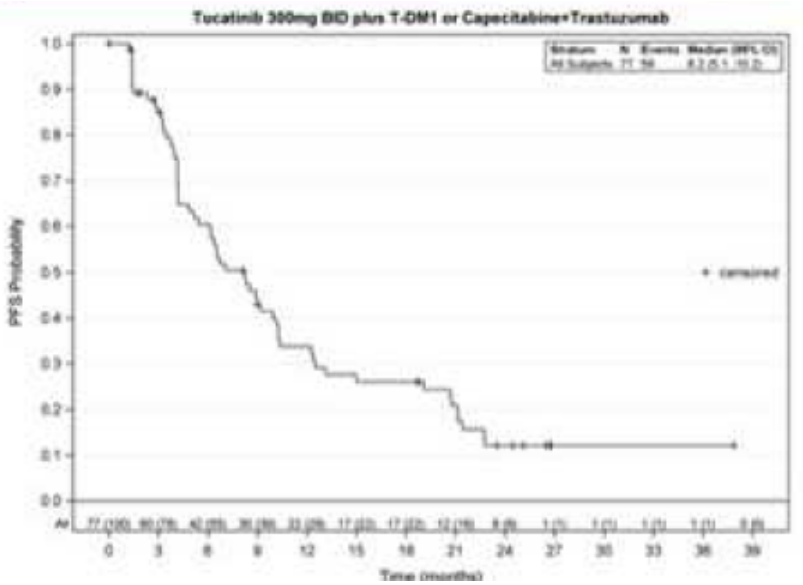
- Neoadjuvant chemotherapy (docetaxel x4 -> FEC x4) in combination with trastuzumab i.v. or s.c. (600 mg fixed-dose)
- Co-primary endpoints: serum trough concentration at pre-dose cycle 8 and pCR (non-inferiority design)

- pCR rates: 40.7% (i.v.) and 45.4% (s.c.)
- The geometric mean pre-surgery C(trough): 51.8 µg/mL (i.v.) and 69.0 µg/mL (s.c.)
- Potential benefits in terms of time-saving

1 Ismael G et al. Lancet Oncol 2012;13:869-878.

Outlook: Tucatinib[1]

- Tucatinib (ONT-380) – third-generation HER2-TKI; 500-fold activity against HER2 as compared to EGFR – lower diarrhoea rate[1]
- Joint analysis of two phase Ib trials[2]
- Primary endpoint: identification of pts. with prolonged PFS (double the median PFS)
- Tucatinib as ≥3-line treatment: >70%
- 22% with prolonged PFS (≥17 months), no predictive factors identified;
- 41% of pts. with prolonged PFS had stable BM at baseline



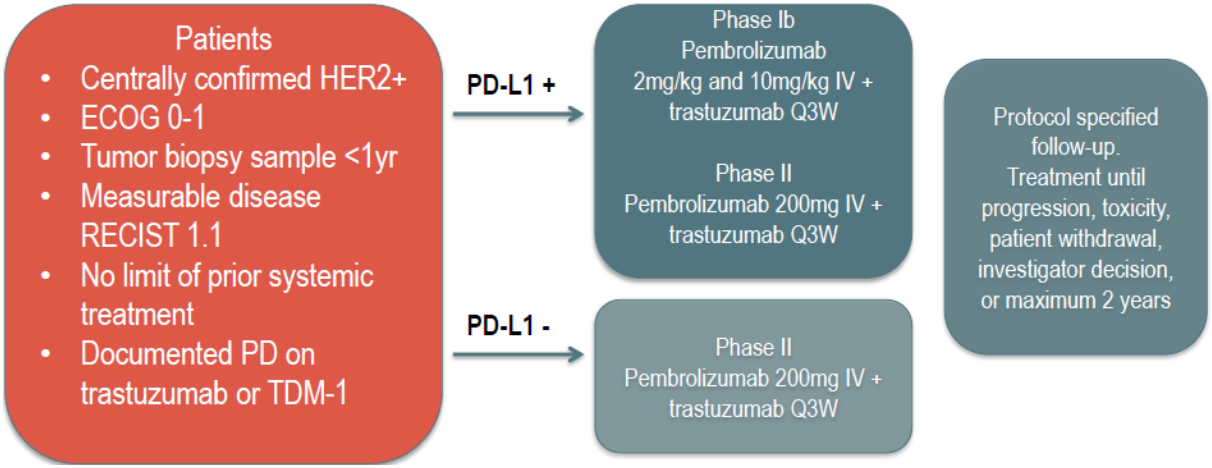
1 Hamilton E et al. P5-20-01; presented at the 2017 SABCS, December 2017, San Antonio, USA.
2 Borges VF et al. Abstr.#513; ASCO 2016

Outlook: KEYnote-14 / PANACEA[1]

- Growing evidence regarding activity of immune-checkpoint inhibitors in breast cancer, trials focusing on TNBC
- No well defined standard option upon progression on trastuzumab plus pertuzumab, T-DM1, lapatinib
- Higher rate of TIL infiltration correlates with trastuzumab activity indicating an immunological effect[2,3]
- Trastuzumab resistance conveyed via immunological effects, preclinical data suggest reversal of resistance with checkpoint inhibitor combination[4]

1 Loi S et al. GS2-06; SABCS 2017.
2 Loi S et al. J Clin Oncol 2013;31:860-867.
3 Loi S et al. Ann Oncol 2014;25:1544-1550.
4 Stagg J et al. Proc Natl Acad Sci U S A 2011;108:7142-7147.

PANACEA[1]



Characteristic N (%)	Overall n=58
Age yrs. median (range)	50.5 (28-72)
ER negative	33 (56.9%)
positive (≥ 1%)	25 (43.1%)
Prior trastuzumab-containing therapy	58 (100%)
Additional anti-HER2 therapy	
No	7 (12.1%)
Yes	51 (87.9%)
T-DM1	42
Pertuzumab	17
Other	26
Prior chemotherapy (Anth/Taxane)	58 (100%)

- Phase Ib/II trial, main cohort PD-L1 positive tumours
- Primary endpoint phase II: Dafety and efficacy of trasuztumab plus pembrolizumab in PD-L1 expressing tumours

1 Loi S et al. GS2-06; SABCS 2017.

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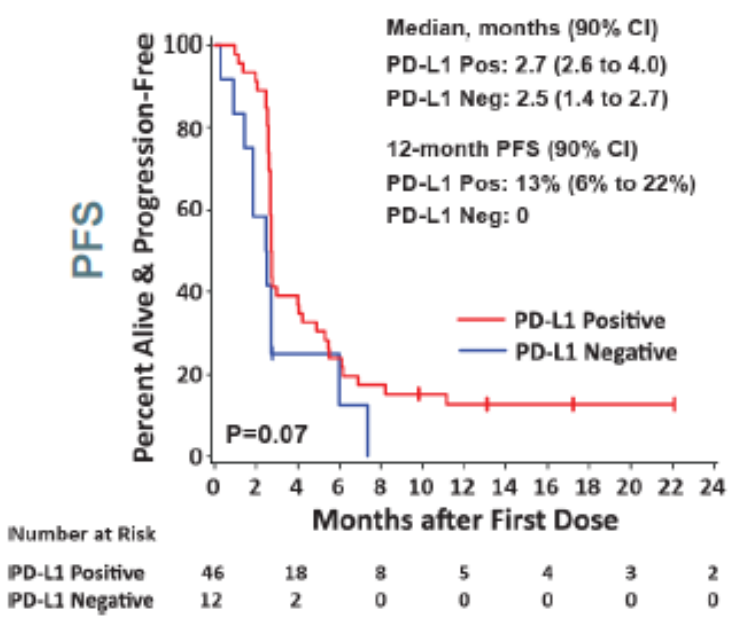
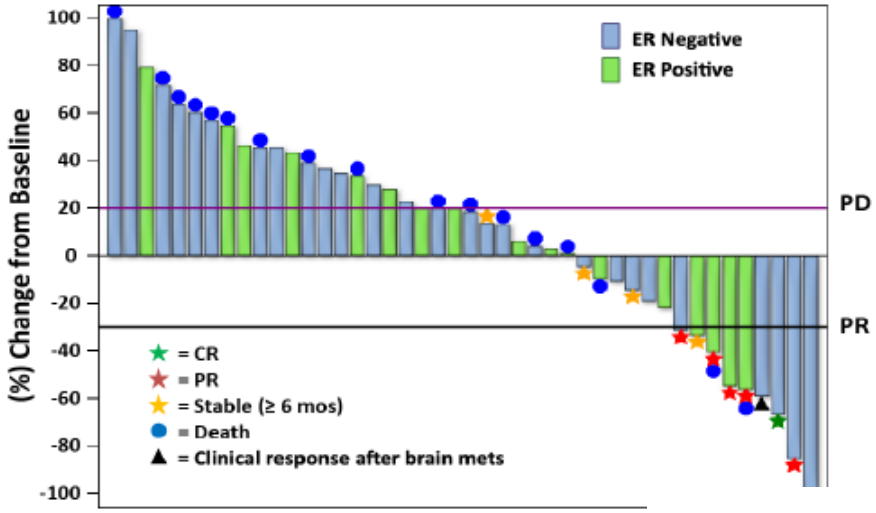
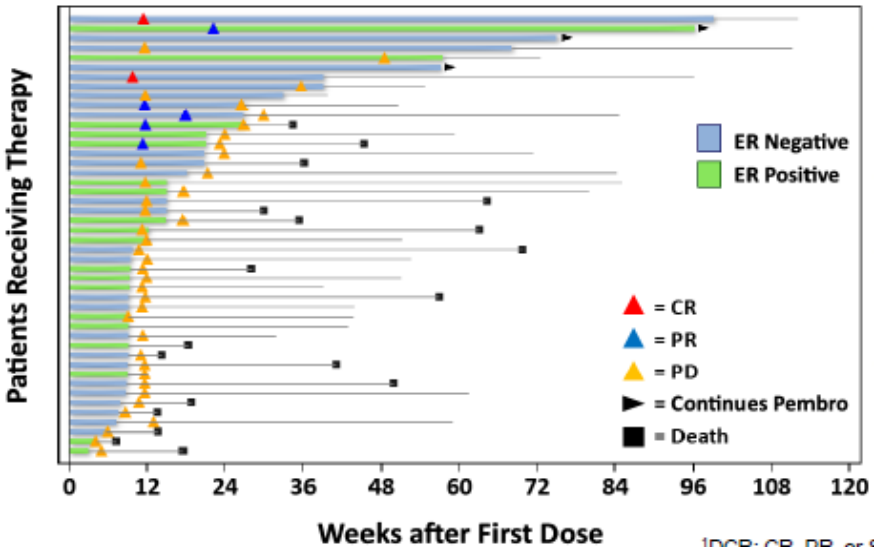
PANACEA[1]



- ORR (PD-L1 pos.) 15% (90% CI 7-29)
- DCR (CR+PR+SD≥6 Monate) 25% (90% CI 14-49)
- No activity observed in the PD-L1 negative cohorts





1 Loi S et al. GS2-06; SABCS 2017.

PANACEA[1]

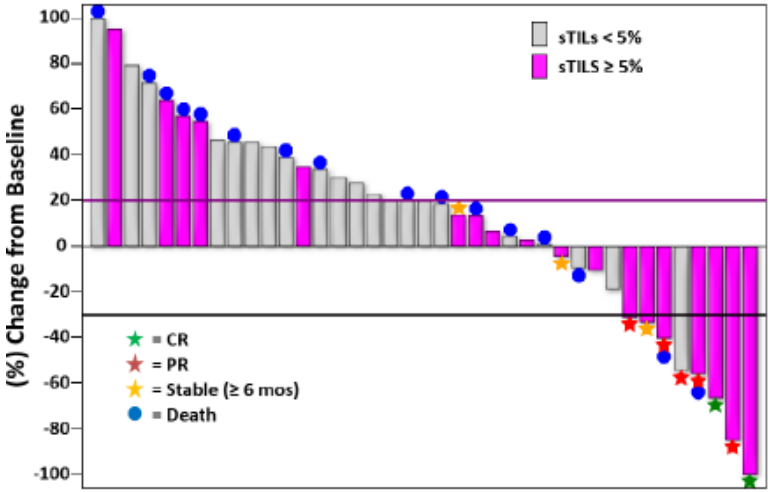
- Toxicity:
- No DLTs in phase Ib; any grade IrAEs 19%
- No cardiac events
- Greatest activity in tumours with sTILs ≥5% at base-line

Immune-related AEs

- Any grade, n=11 (19.0%)
- Grade ≥ 3, n=6 (10.3%)
- Led to discontinuation, n=4 (6.9%)

Most common Immune AEs

- Any grade thyroid, n=4 (6.9%)
- Pneumonitis
  - All grades, n=4 (6.9%)
  - Grade≥3, n=2 (3.4%)



1 Loi S et al. GS2-06; SABCS 2017.

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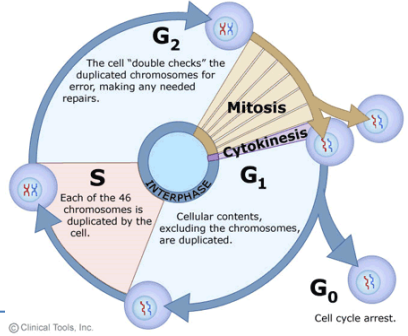
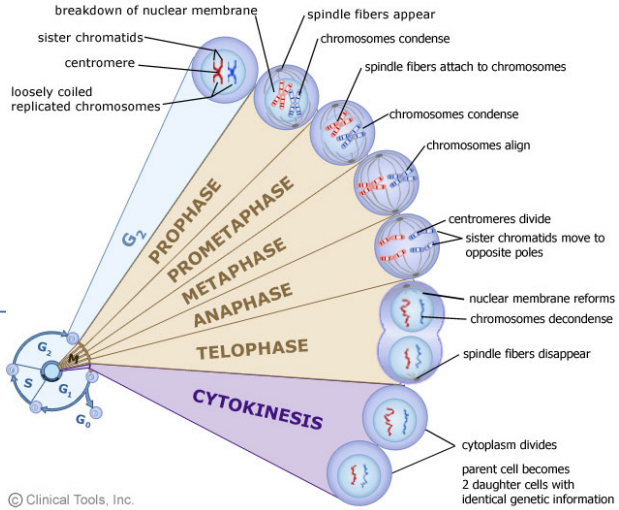
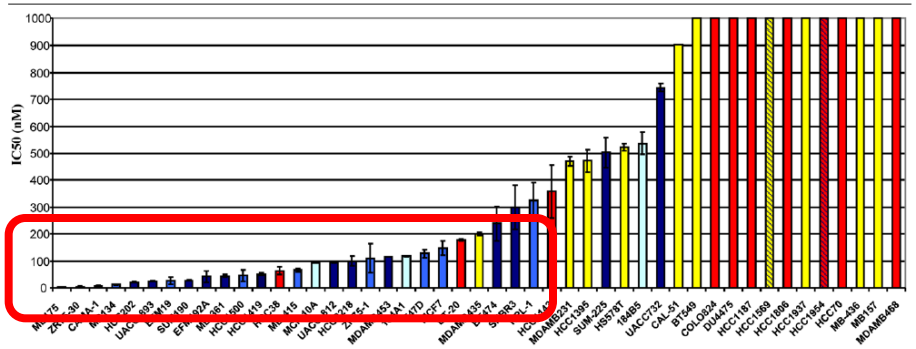




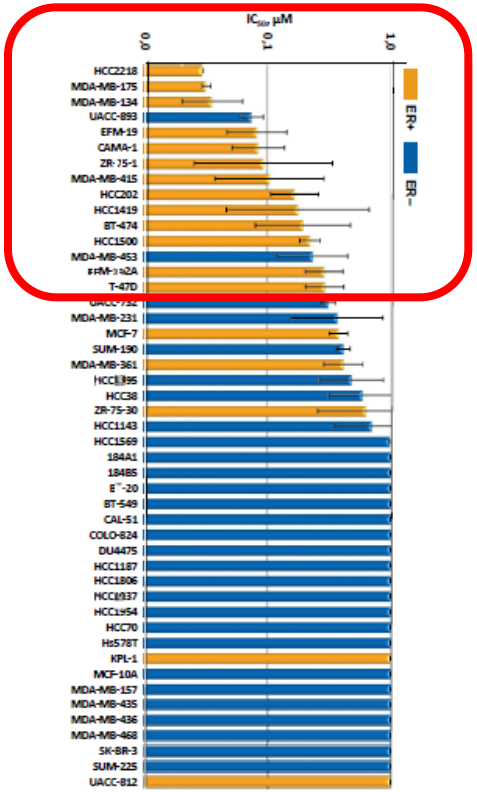
CDK4/6-Inihibitors[1-3]

- CDK4/6 decisive role in the passage of cells through the cell cycle by regulating the progression from the G1 to the S phase

- *In vitro* studies; activity of CDK4/6-inhibitors mainly in luminal and HER2-positive cell lines



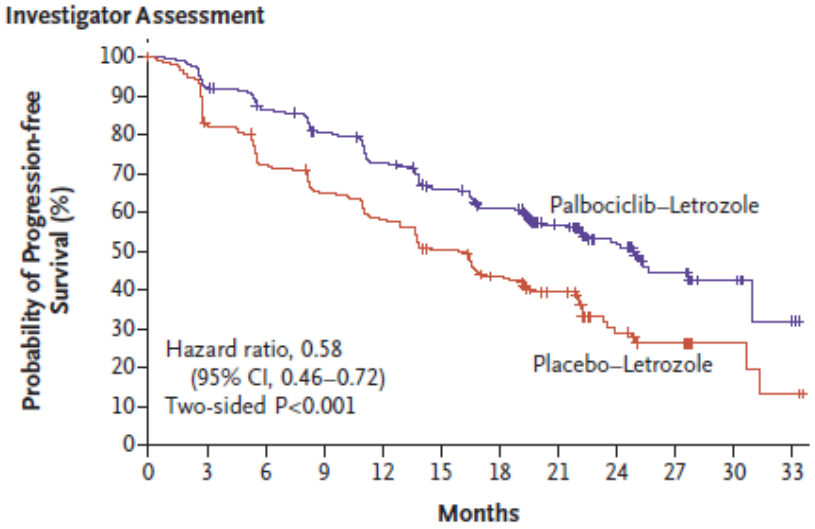
Inhibitory concentration and cell type. Bar graph of IC_{50} values (nM) and cell type. Cell lines are color coded by subtype: light blue, luminal; dark blue bars or stripes, HER2 amplified; yellow, nonluminal/undergone an epithelial-to-mesenchymal transition; red, nonluminal; turquoise, immortalized.



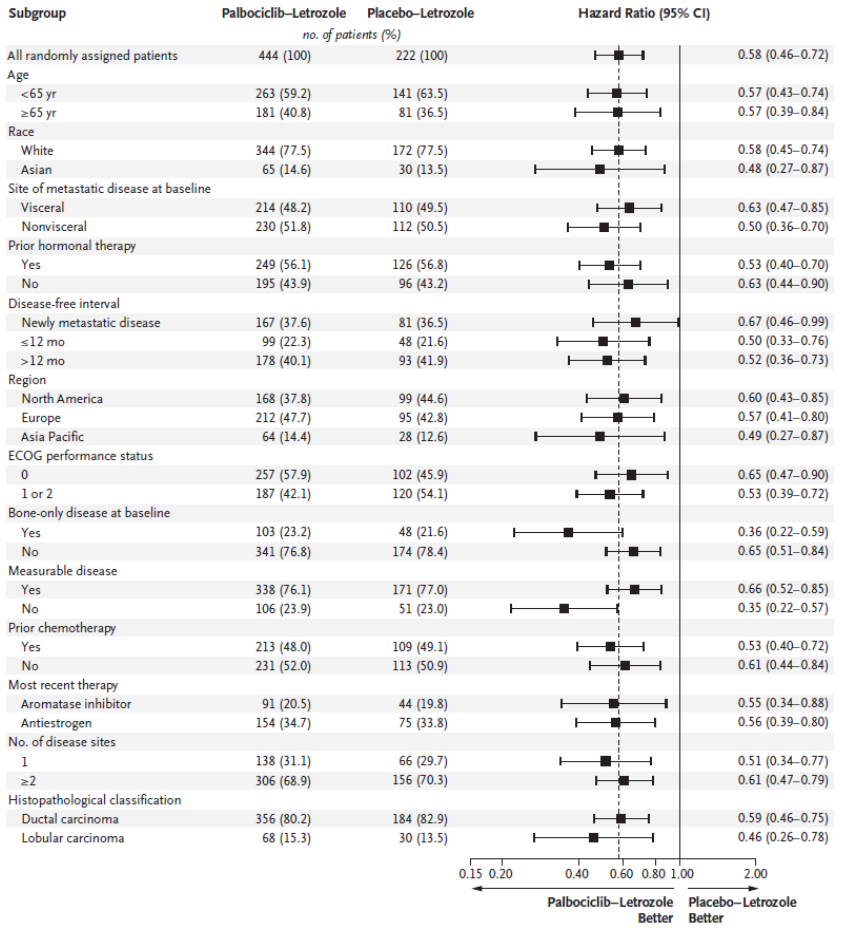
1 Caldon CE et al. J Cell Biochem 2006;97:261-274.
2 Sherr CJ and Rpberts JM. Genes Dev 2004;18:2699-2711.
3 Tlsty TD et al. J Mammary Gland Biol Neoplasia 2004;9:263-274.

PALOMA-2[1]

- PFS 24.8 *vs*. 14.5 months



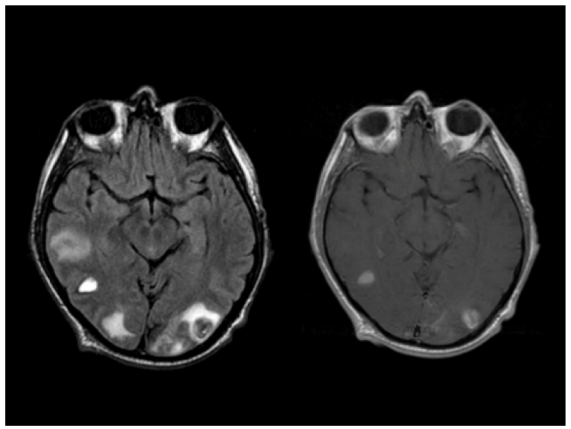
- RR 42.1% *vs*. 34.7%
- RR (measurable disease) 55.3% *vs*. 44.4%
- CBR 84.9% *vs*. 70.3%



1 Finn RS et al. N Engl J Med 2016;375:1925-1936.

Brain Metastases in Breast Cancer

- Breast cancer is the second most common cause for BM among solid tumors
  Incidence increasing since 2000 [1,2]
- Brain metastases (BM) increase morbidity, reduce Quality-of-Life, shorten survival [3-5]
- Greatest conceivable threat for pts. at risk [4]



- Prolonged survival of pts. with BM – issue of WBRT-associated late toxicity [6,7]
- Lapatinib: Relevant activity as primary systemic therapy for BM; no reduction of BM incidence [8-10]

1 Weil RJ et al. Am J Pathol 2005;167:913-920.
2 Clyton AJ et al. Br J Cancer 2004;91:639-643.
3 Slimane K et al. Ann Oncol 2004;15:1640-1644.
4 Mayer M. Clin Cancer Res 2007;13:1623-1624.
5 Bartsch R et al. BMC Cancer 2009; 9:367
6 Bartsch R et al. Br J Cancer 2012;106:25-31.
7 Chang EL et al. Lancet Oncol 2009;10:1037-1044.
8 Bachelot T et al. Lancet Oncol 2013;14:64-71.
9 Bartsch R and Preusser M. Lancet Oncol 2013;14:8-9.
10 Pivot X et al. J Clin Oncol 2015;33:1564-1573

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A Place for Biosimilars?

- What will decide the success of biosimilars in HER2-positive breast cancer?
- Clinicians may accept the extrapolation from neoadjuvant data to the metastatic BC setting easier then *vice versa*
- Extrapolation of chemotherapy plus biosimilar trastuzumab data to combination with other biologicals and targeted therapies (e.g. pertuzumab, lapatinib)
- In the adjuvant setting, the success of trastuzumab biosimilars ay depend upon the uptake of subcutaneous trastuzumab

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Alexander de Vries
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Backup

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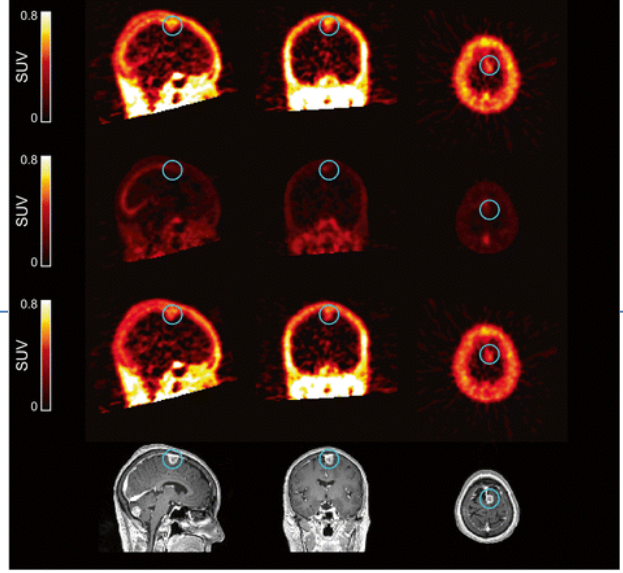
Neuro-Oncology

Neuro-Oncology 17(2), 289–295, 2015
doi:10.1093/neuonc/nou141
Advance Access date 11 July 2014

Capecitabine and lapatinib uptake in surgically resected brain metastases from metastatic breast cancer patients: a prospective study

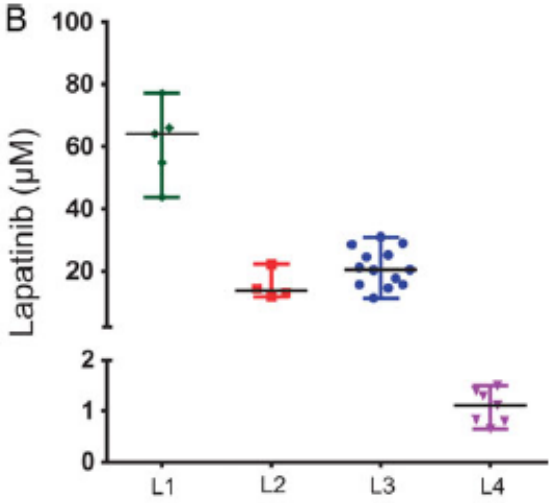
Aki Morikawa, David M. Peereboom, Helen R. Thorsheim, Ramakrishna Samala, Rajiv Balyan, Conleth G. Murphy, Paul R. Lockman, Ahkeem Simmons, Robert J. Weil, Viviane Tabar, Patricia S. Steeg, Quentin R. Smith, and Andrew D. Seidman



The Blood-Brain-Barrier

- [^{11}C]lapatinib as PET-Tracer in HER2-positive MBC patients with or without BM [1]
- Three patients with BM, three patients control
- No siginificant uptake of [^{11}C]lapatinib in normale brain tissue, signifcant uptake in BM (A)

- Clinical relevant concentration of lapatinib and capecitabine in resected BM without prior WBRT (*n*=12) – high variability (B) [2]



1 Sallem A et al. EJNMMI Research 2015;5:30.
2 Morikawa A et al. Neuro Oncol 2015;17:289-295.

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Multicenter Phase II Study of Lapatinib in Patients with Brain Metastases from HER2-Positive Breast Cancer

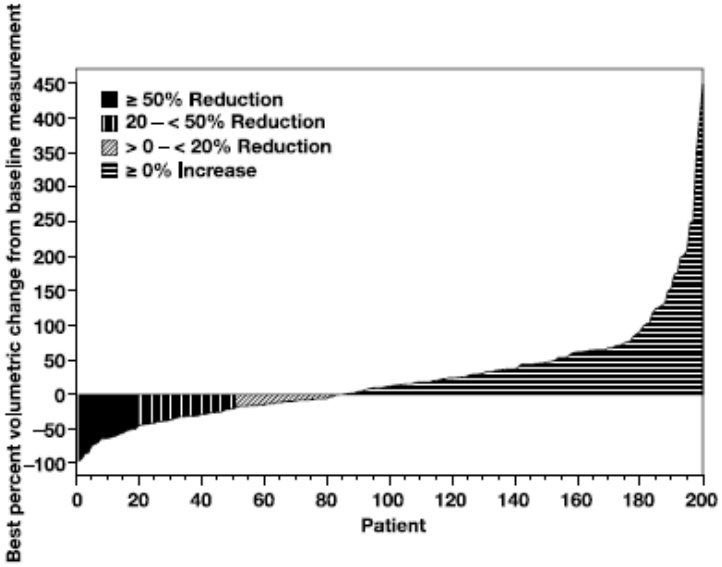
Nancy U. Lin,[1] Véronique Diéras,[2] Devchand Paul,[3] Dominique Lossignol,[4] Christos Christodoulou,[5] Hans-Joachim Stemmler,[6] Henri Roché,[7] Minetta C. Liu,[8] Richard Greil,[9] Eva Ciruelos,[10] Sibylle Loibl,[11] Stefania Gori,[12] Andrew Wardley,[13] Denise Yardley,[14] Adam Brufsky,[15] Joanne L. Blum,[16] Stephen D. Rubin,[17] Bernie Dharan,[17] Klaudia Steplewski,[17] Denise Zembryki,[17] Cristina Oliva,[18] Debasish Roychowdhury,[17] Paolo Paoletti,[17] and Eric P. Winer[1]

Brain Metastases: Systemic Therapy

- Prospective single-arm phase II trial
- 242 pts., HER2-positive MBC, progressing after local therapy (~95% WBRT); amandment: Lap+Cap upon PD on lapatinib (50 Pat.)

- RR lapatinib 6%; minor response 21%;
- RR lapatinib+capecitabine 20%, minor response 40%

- PFS lapatinib: 2.40 months (95% CI 1.87-2.79)
- PFS Lap+Cap: 3.65 months (95% CI 2.43-4.37)



1 Lin NU et al. Clin Cancer Res 2009;15:1452-1459.

THELANCETONCOLOGY-D-12-01226 939
S1470-2045(12)70449-7
Embargo: Nov 2, 2012—00:01 (GMT)

Comment

DM

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Primary systemic treatment of breast-cancer brain metastases

Brain Metastases: Systemic Therapy

- LANDSCAPE: Primary treatment with lapatinib plus capecitabine in HER2-positive patients with brain metastases – aiming to delay WBRT [1,2]

- Single-arm phase II trial
- Primary endpoint RR (CNS): 66%
- Secondary endpoint time-to-WBRT: 8.3 months

- Caveat: non-randomized, 40% of pat. asymptomatic, 95% ECOG <2, no data regarding QoL

- Potential standard? [3]

1 Chang EL et al. Lancet Oncol 2009;10:1037-1044.
2 Bachelot T et al. Lancet Oncol 2013;14:64-71.
3 Bartsch R and Preusser M. Lancet Oncol 2013;14:8-9.

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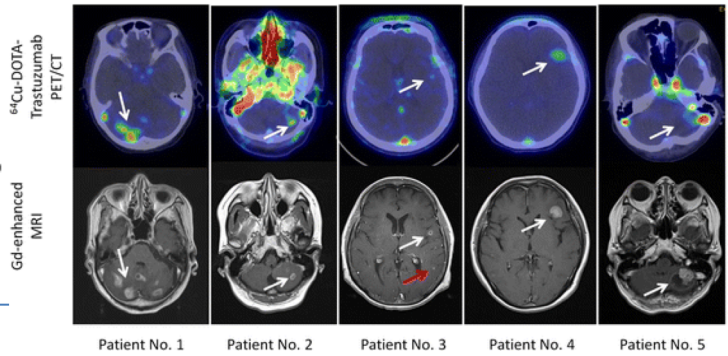
Chemotherapy Induces Regression of Brain Metastases in Breast Carcinoma

DUTZU ROSNER, MD, TAKUMA NEMOTO, MD, AND WARREN W. LANE, PhD

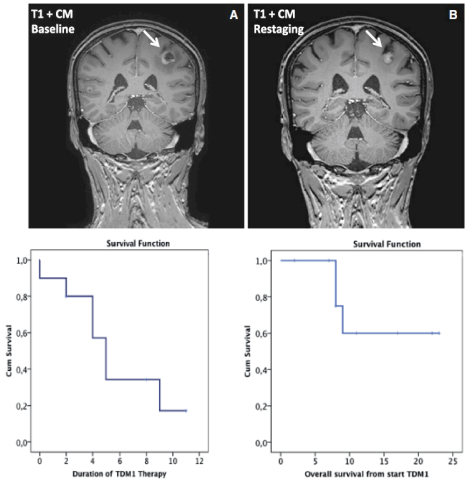


The Blood-Brain-Barrier

- Decreased concentration of anti-cancer drugs in brain metastases as compared to extracranial lesions even with small molecules [1]

- Impaired BBB in metastases allows for penetration of larger molecules and activity of conventional cytotoxics in BM – response rate 50% [2,3]

- T-DM1: Newly diagnosed or progressive BM [4,5]
- *n*=10; 60% prior lapatinib
- RR: PR 30% (RANO); SD 40%
- PFS: median 5 mo. (95% CI 3.69-6.32)
- OS: not reached at 8.5 mo. median FU



1 Taskar KS et al. Pharm Res 2012;29:770-781.
2 Rosner D et al. Cancer 1986;58:832-839.
3 Kurihara H et al. EJNMMI Research 2015;5:8.
4 Bartsch R et al. J Neurooncol 2014;116:205-206.
5 Bartsch R et al. Clin Exp Metastasis 2015;32:729-737.

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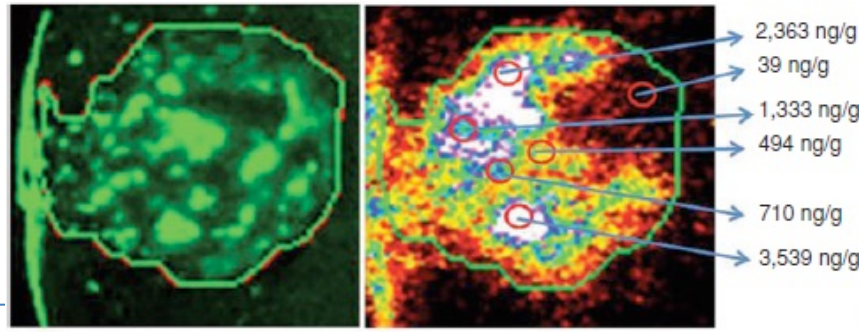
Clinical Cancer Research

Cancer Therapy: Preclinical
See commentary p. 5605

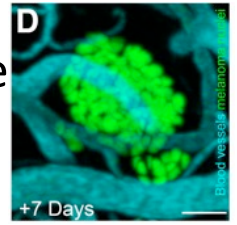
Heterogeneous Blood–Tumor Barrier Permeability Determines Drug Efficacy in Experimental Brain Metastases of Breast Cancer

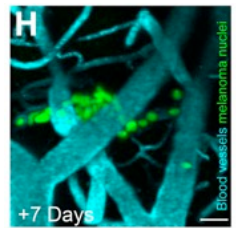
Paul R. Lockman[1], Rajendar K. Mittapalli[1], Kunal S. Taskar[1], Vinay Rudraraju[1], Brunilde Gril[2], Kaci A. Bohn[1], Chris E. Adkins[1], Amanda Roberts[1], Helen R. Thorsheim[1], Julie A. Gaasch[3], Suyun Huang[4], Diane Palmieri[2], Patricia S. Steeg[2], and Quentin R. Smith[1]

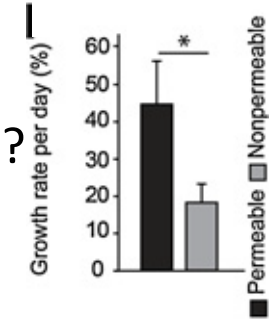


Systemic Therapy of BM: Considerations

- Reduction of BM volume with conventional systemic therapy possible
- Remaining BBB function present in BM – great variance regarding the extent of the BBB disturbence in each BM and in between different BM causing a heterogenous distribution of the concentration of cytotoxics in BM (e.g. Paclitaxel) [1]
- Higher growth rate in BM with defect BBB – diffuse growth along small vessels in BM with intact BBB. Cells behind the BBB cannot be reached by conventional anticancer drugs. [2]
- Reduction of BM volume of BM without stopping organ destruction?



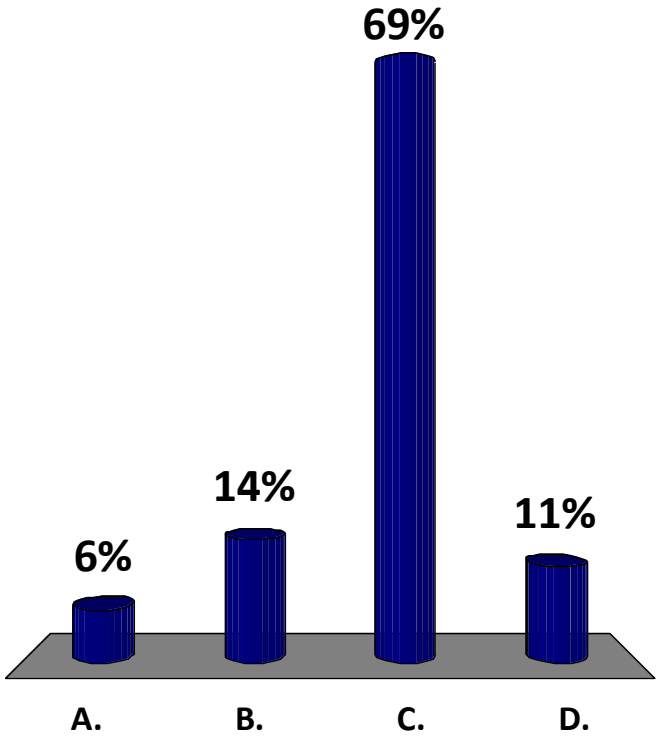


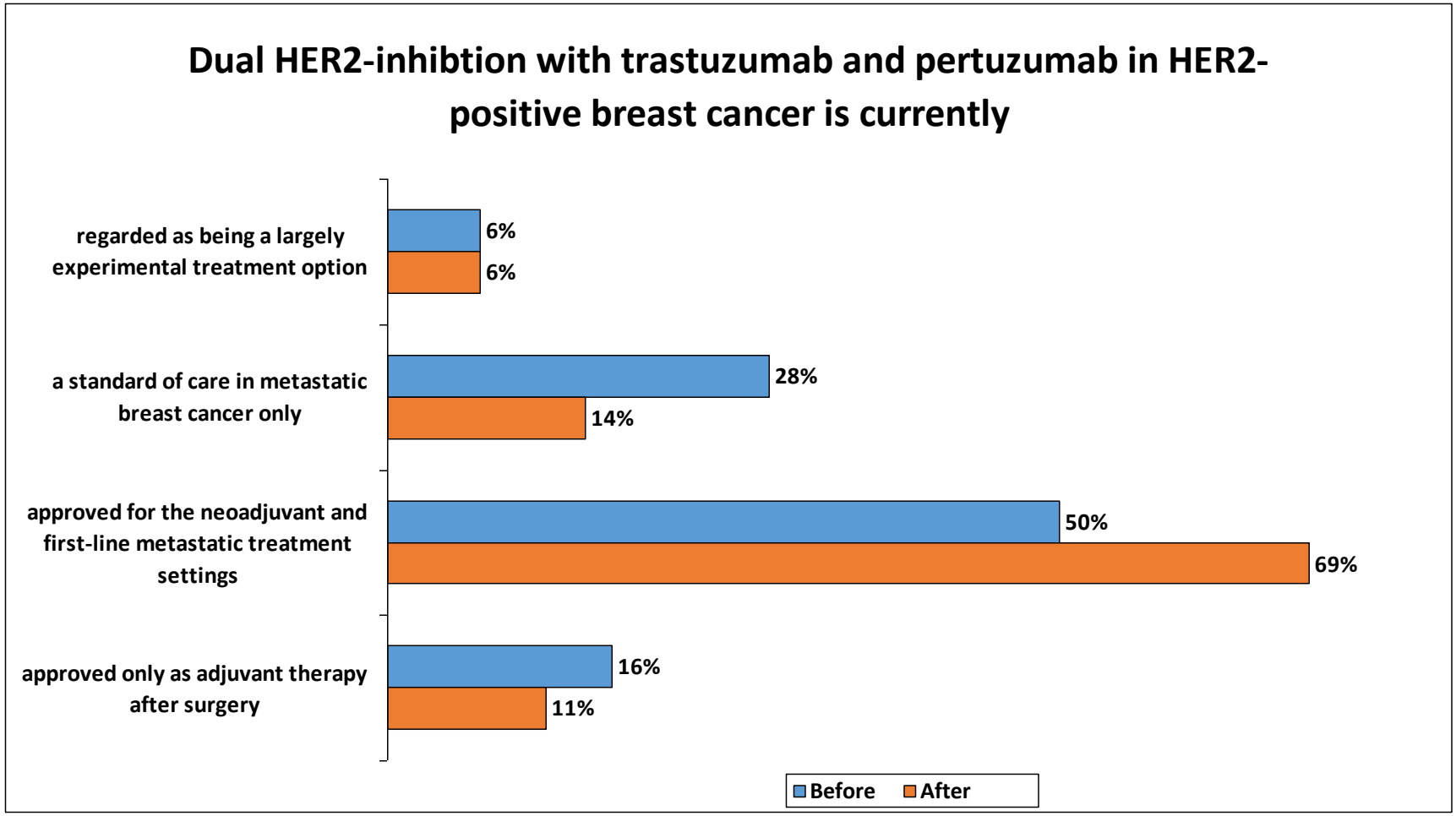


1 Lockman PR et al. Clin Cancer Res 2010;16:5664-5678.
2 Osswald M et al. Clin Cancer Res 2016;22:6078-6087.

Dual HER2-inhibtion with trastuzumab and pertuzumab in HER2-positive breast cancer is currently

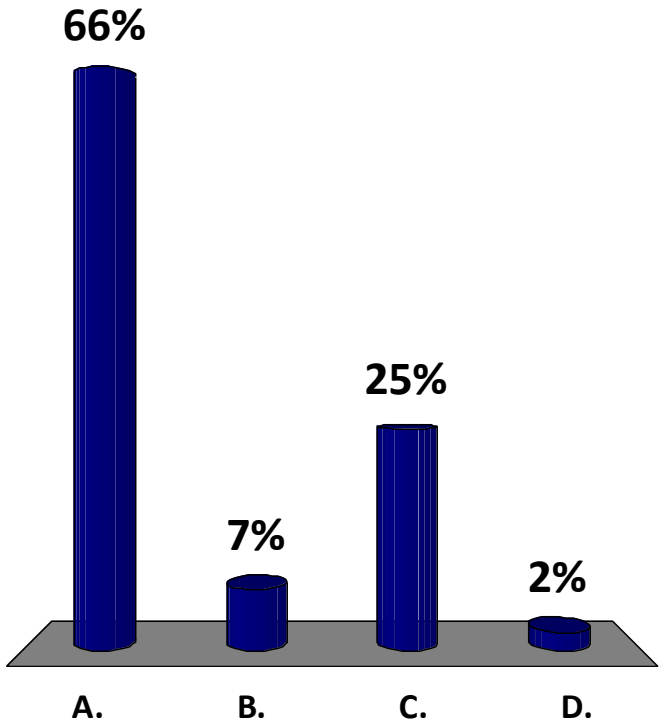
A. regarded as being a largely experimental treatment option
B. a standard of care in metastatic breast cancer only
✓ C. approved for the neoadjuvant and first-line metastatic treatment settings
D. approved only as adjuvant therapy after surgery

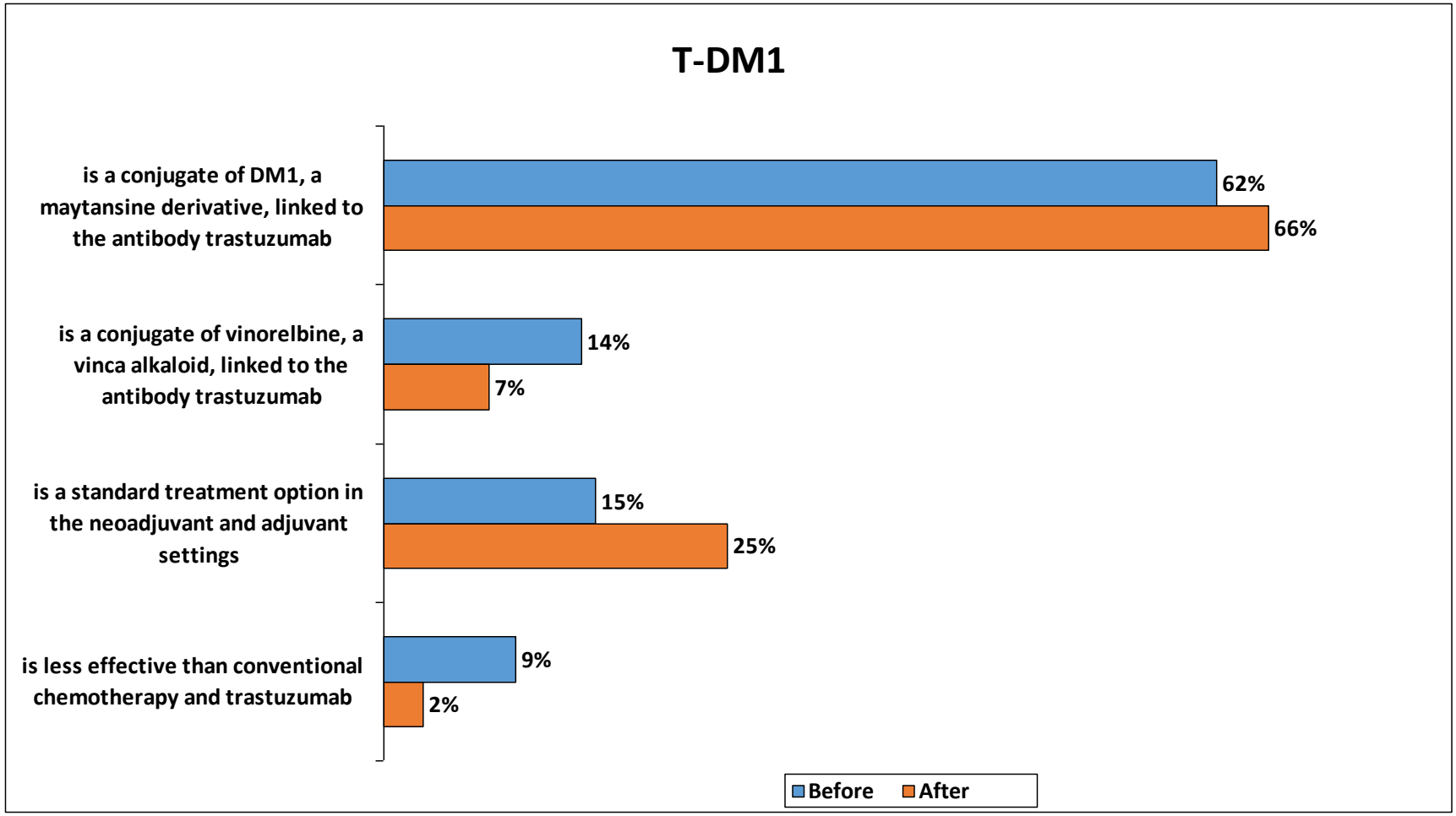



Dual HER2-inhibtion with trastuzumab and pertuzumab in HER2-positive breast cancer is currently
regarded as being a largely experimental treatment option
6%
6%
a standard of care in metastatic breast cancer only
28%
14%
approved for the neoadjuvant and first-line metastatic treatment settings
50%
69%
approved only as adjuvant therapy after surgery
16%
11%
Before
After

T-DM1

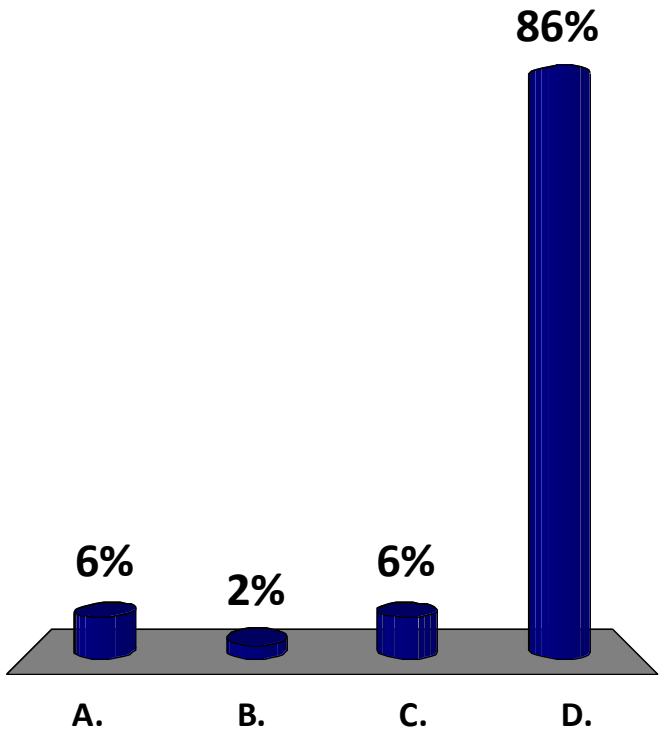
- ✓ A. is a conjugate of DM1, a maytansine derivative, linked to the antibody trastuzumab
- B. is a conjugate of vinorelbine, a vinca alkaloid, linked to the antibody trastuzumab
- C. is a standard treatment option in the neoadjuvant and adjuvant settings
- D. is less effective than conventional chemotherapy and trastuzumab

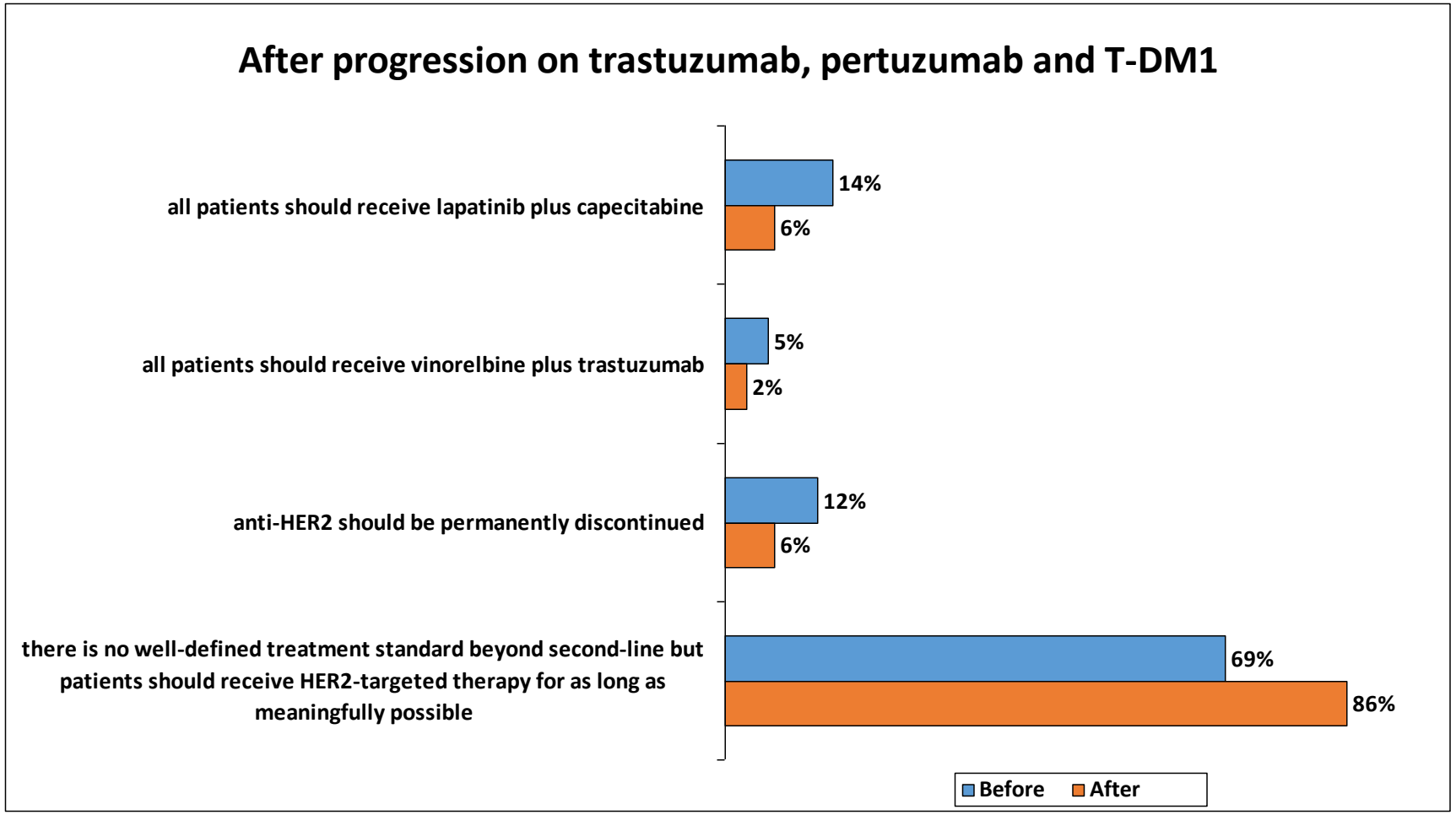



T-DM1
is a conjugate of DM1, a maytansine derivative, linked to the antibody trastuzumab
62%
66%
is a conjugate of vinorelbine, a vinca alkaloid, linked to the antibody trastuzumab
14%
7%
is a standard treatment option in the neoadjuvant and adjuvant settings
15%
25%
is less effective than conventional chemotherapy and trastuzumab
9%
2%
Before
After

After progression on trastuzumab, pertuzumab and T-DM1

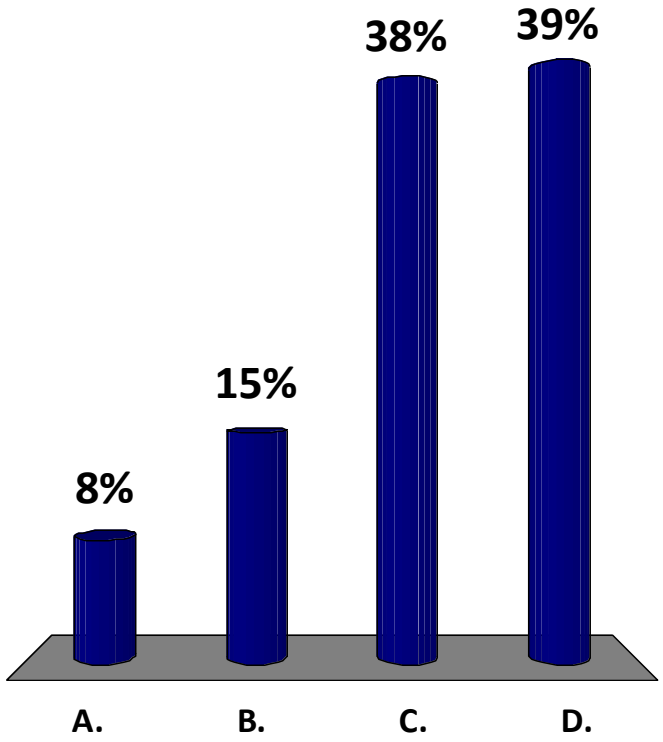
A. all patients should receive lapatinib plus capecitabine
B. all patients should receive vinorelbine plus trastuzumab
C. anti-HER2 should be permanently discontinued
✓ D. there is no well-defined treatment standard beyond second-line but patients should receive HER2-targeted therapy for as long as meaningfully possible

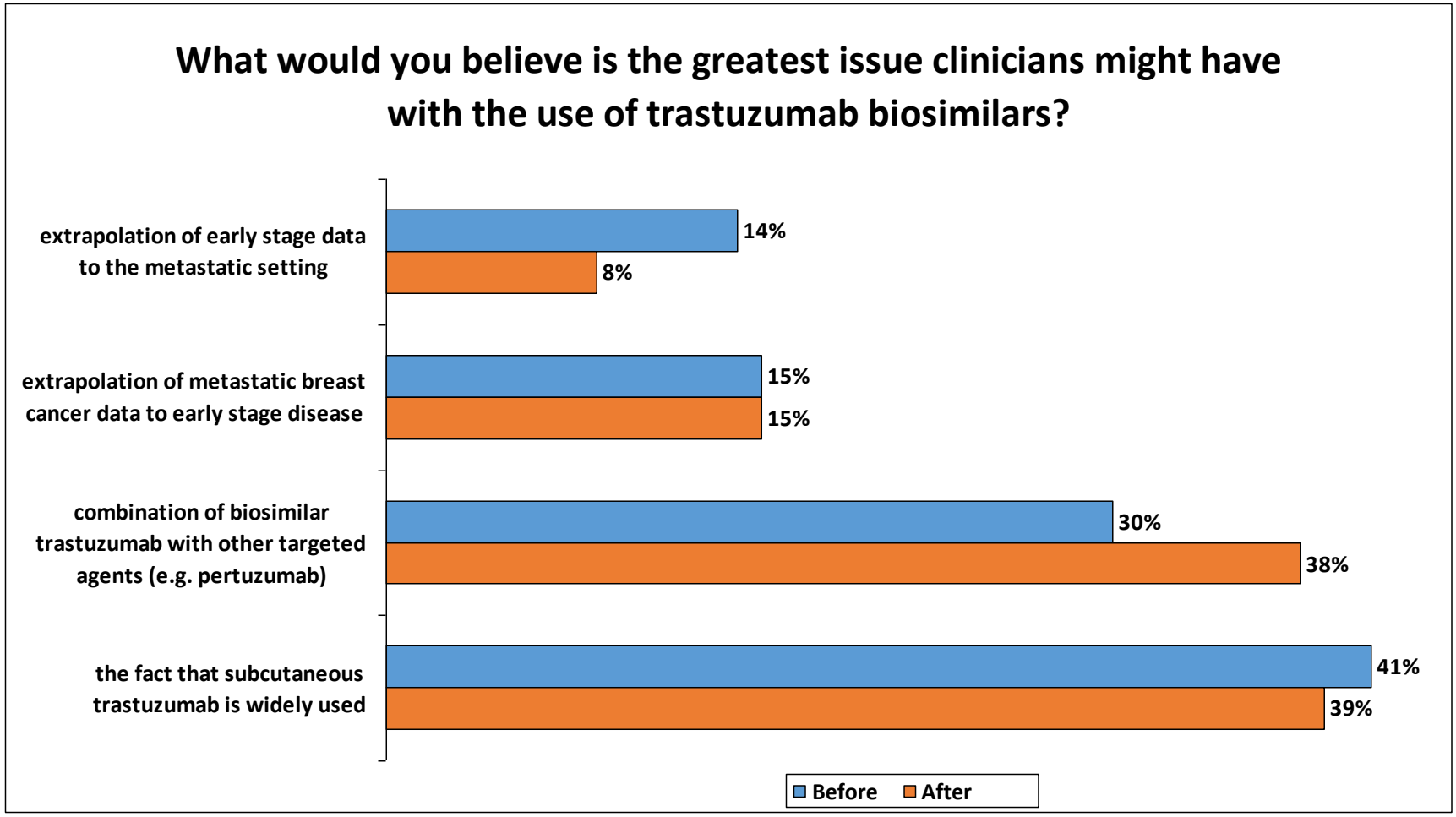



After progression on trastuzumab, pertuzumab and T-DM1
all patients should receive lapatinib plus capecitabine
14%
6%
all patients should receive vinorelbine plus trastuzumab
5%
2%
anti-HER2 should be permanently discontinued
12%
6%
there is no well-defined treatment standard beyond second-line but patients should receive HER2-targeted therapy for as long as meaningfully possible
69%
86%
Before
After

What would you believe is the greatest issue clinicians might have with the use of trastuzumab biosimilars?

A. extrapolation of early stage data to the metastatic setting
B. extrapolation of metastatic breast cancer data to early stage disease
C. combination of biosimilar trastuzumab with other targeted agents (e.g. pertuzumab)
D. the fact that subcutaneous trastuzumab is widely used




What would you believe is the greatest issue clinicians might have with the use of trastuzumab biosimilars?
extrapolation of early stage data to the metastatic setting
14%
8%
extrapolation of metastatic breast cancer data to early stage disease
15%
15%
combination of biosimilar trastuzumab with other targeted agents (e.g. pertuzumab)
30%
38%
the fact that subcutaneous trastuzumab is widely used
41%
39%
Before
After