Escalation / de-escalation therapeutic strategies in the early setting: the example of breast cancer

Hans Wildiers

Medical oncology, University Hospitals Leuven, Belgium

UZ Leuven | Herestraat 49 B - 3000 Leuven | www.uzleuven.be tel. +32 16 33 22 11 | UNIVERSITY HOSPITALS LEUVEN

(Neo)-adjuvant systemic therapy

Possible **(NEO)ADJUVANT** chemotherapy regimens

Setting	HER2 neg ER pos	Triple neg	HER2 pos
Possible chemo-regimens	4xEC ➔ 12xPac qw 4xECdd ➔ 12xPac qw 3xFEC ➔ 3xDoc 6xTC (pN0 or pN1) 4xTC (elderly or lower risk)	4xECdd ➔ 12xPac qw 4xEC ➔ 12xPac qw 4xECdd ➔12xPac+Carbo(AUC2), (certainly an option if BRCA+, only data in neoadjuvant setting) 3xFEC ➔ 3x Doc 6xTC (pts at cardiac risk) 4xTC (elderly)	4xEC ➔12xPac+Trast 6xTCarboH 3xFEC ➔ 3xDoc+Trast 4xTC+Trast (elderly or low risk) 12xPac+Trast (elderly or low risk) Pertuzumab (P) can be combined with Trast in adjuvant or neoadjuvant setting in high risk patients* Possible regimens: 4xEC ➔12xPac+Tras+P 6xTCarboH-P 3xFEC➔3xDoc+Trast+P

E=epirubicine, C=cyclophosphamide, Carbo=carboplatin, Pac=paclitaxel, Doc or T =docetaxel, Trast or H=trastuzumab, P=pertuzumab, F=fluorouracil

* Pending Belgium approval and reimboursement

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ER+: De-escalation for chemo indication

Gene expression profiles (GEP)

MINDACT (Mammaprint®)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 25, 2016 VOL. 375 NO. 8

70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer

F. Cardoso, L.J. van't Veer, J. Bogaerts, L. Slaets, G. Viale, S. Delaloge, J.-Y. Pierga, E. Brain, S. Causeret, M. DeLorenzi, A.M. Glas, V. Golfinopoulos, T. Goulioti, S. Knox, E. Matos, B. Meulemans, P.A. Neijenhuis, U. Nitz, R. Passalacqua, P. Ravdin, I.T. Rubio, M. Saghatchian, T.J. Smilde, C. Sotiriou, L. Stork, C. Straehle, G. Thomas, A.M. Thompson, J.M. van der Hoeven, P. Vuylsteke, R. Bernards, K. Tryfonidis, E. Rutgers, and M. Piccart, for the MINDACT Investigators*

TAILOR-X (Oncotype DX®)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

Leads to decreased use of adjuvant chemotherapy without compromising outcome

But depends on how much chemo is given WITHOUT GEP !

ER+: TC (docetaxel cyclophosphamide) versus anthracycline taxane

	ABC trials	Hellenic Oncology Research Group	DBCG	Plan B
Regimens	6xTC vs 6xTaxAC	6xTC vs 4xddFEC -> 4xddDoc	6xTC vs 3xEC -> 3xDoc	6xTC vs 4xEC -> 4xDoc
Study characteristics	N=4156 59% N pos 31% TNBC	N=650 100% N pos 11% TNBC	N=2102 (TOP2A normal) 53% N pos 29% TNBC	N=2449 (genomic intermediate or high risk) 41% N pos 8% TNBC
Primary endpoint	4y-IDFS 88,2% vs 90,7% (p 0,04)	3y-DFS 91,1% vs 89.5% (p 0.57)	5y-DFS 88,3% vs 87,9% (p 1,0)	5y-DFS 89.9% vs 90.2% (ns)
Subgroup analysis	Anthracycline benefit mainly in ER neg and N pos	No difference	Grade 3 tumors more benefit from TC	Not reported
OS data	4y-OS 94,7% vs 95% (ns)	No difference	No difference	5y-OS 94.7% vs 94.6% (ns)
	J Clin Oncol 2017 Blum et al	Ann Oncol 2016 Mavroudis et al	JCO 2017 Ejlertsen et al	ASCO 2017 /JCO 2016 Harbeck et al

ER+: TC (docetaxel cyclophosphamide) versus anthracycline taxane

	HR positive		HR negative	
	TaxAC vs. TC difference in 4-year IDFS	Hazard ratio (95% CI)	TaxAC vs. TC difference in 4-year IDFS	Hazard ratio (95% CI)
Lymph node negative	−2.7%	0.69 (0.39–1.19)	2.5%	1.31 (0.86–1.99)
1–3 lymph nodes	2.0%	1.14 (0.77–1.69)	10.9%	1.58 (0.90–2.79)
4+ lymph nodes	5.8%	1.46 (0.95–2.26)	11.0%	1.34 (0.62–2.91)

Abbreviations: CI, confidence interval; HR, hazard ratio; IDFS, invasive disease-free survival; TaxAC, taxane- and anthracycline-containing regimen; TC, taxane, cyclophosphamide.

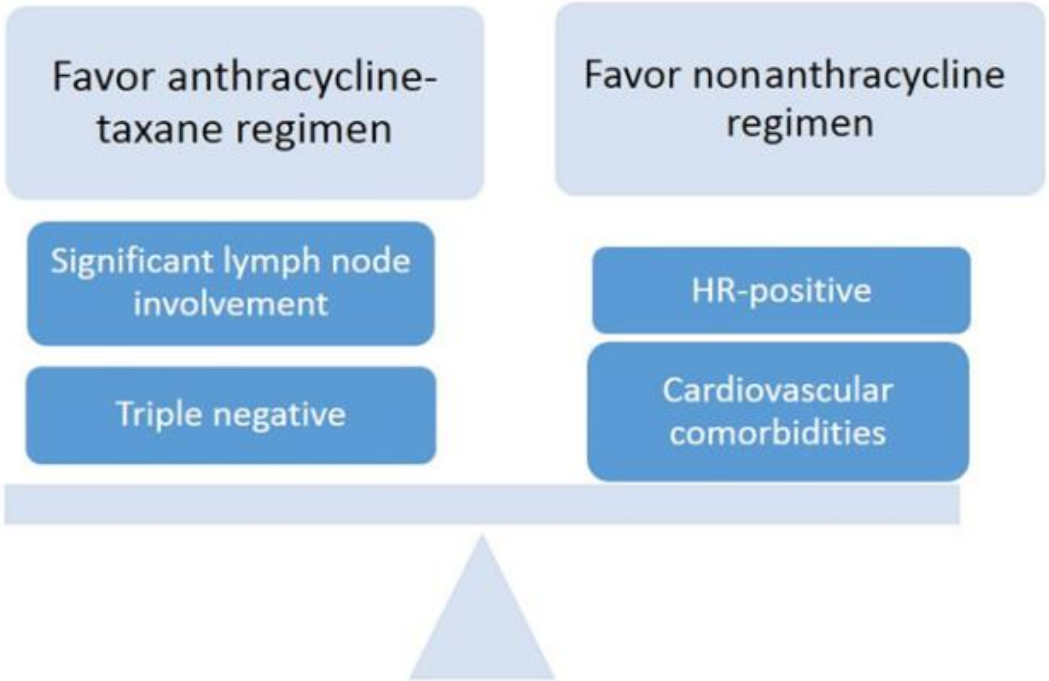

Figure 1. Factors influencing decisions regarding anthracycline use for adjuvant breast cancer therapy.
Abbreviation: HR, hormone receptor.

TC certainly an option in ER+/HER2- tumors pN0/pN1 requiring chemo

The oncologist 2018 Shah

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TNBC: Carboplatin neoadjuvant

Author (n)	Control arm	Experimental arm (+ **Carbo**)	**pCR** (breast and axilla)
Geparsixto (n=595) *53% triple neg*	18x NPLD 20mg/m2 + Pac(qw) + Bevacizumab if TN	18x NPLD20mg/m2 + Pac(qw) + **Carbo** (AUC1,5) + Bevacizumab if TN	pCR 37 -> 47%* (TN 37 -> 53%*)
CALGB 40603 (n=433) *100% Triple neg*	12xPac(qw) -> 4xddAC (+/- Bevacizumab)	12xPac(qw) + 4x **Carbo** (AUC6) -> 4xddAC (+/- Bevacizumab)	pCR 41 -> 54%* Febrile neutropenia 7 -> 12% Gr III-IV anemia 0 -> 4% Gr III-IV TCpenia 4 -> 20%
BrighTNess (n=634) *100% Triple neg*	12xPac(qw) -> 4xAC	12xPac(qw) + 4x **Carbo** (AUC 6) -> 4xAC	pCR 31 -> 58% Febrile neutropenia 0 -> 1% Gr III-IV anemia 0 -> 17% Gr III-IV TCpenia 0 -> 6% (also third arm with addition of veliparib: pCR 53%)

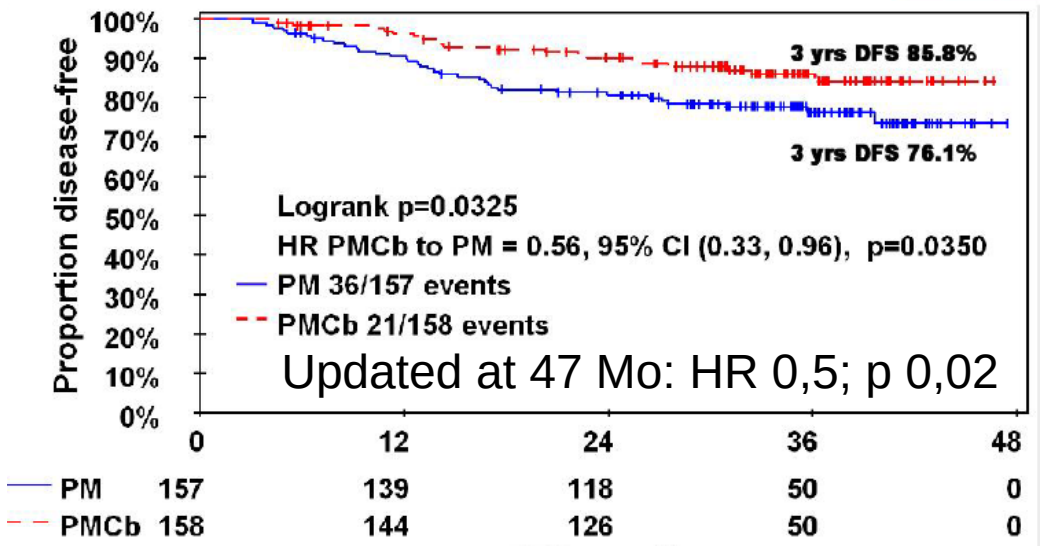
Lancet Oncol 2014 Von Minckwitz ; JCO 2015 Sikov : Lancet Oncol 2018 Loibl Meta-analysis Ann Oncol 2018 Lambertini

Carboplatin impact on longer term outcome

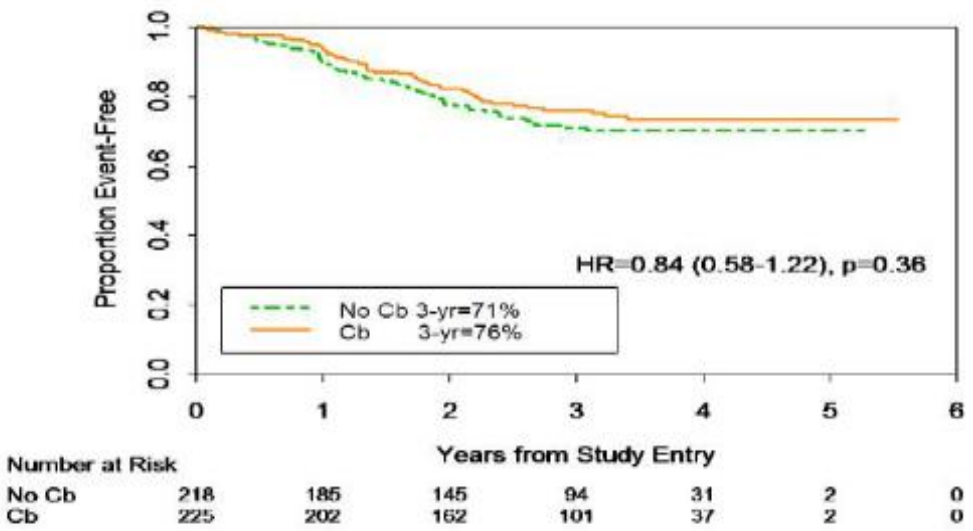
Geparxsixto: Triple neg cohort (n=315)

CALGB 40603

DFS



EFS



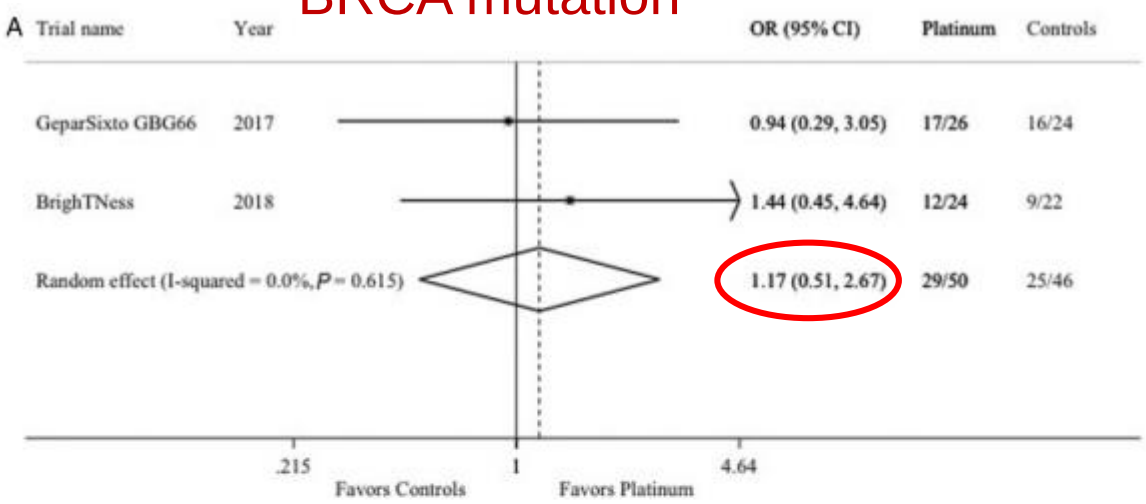
Why discordance ?

- Both studies underpowered for DFS
- Geparsixto:
  - low anthracycline dose ?
  - no cyclophosphamide ?

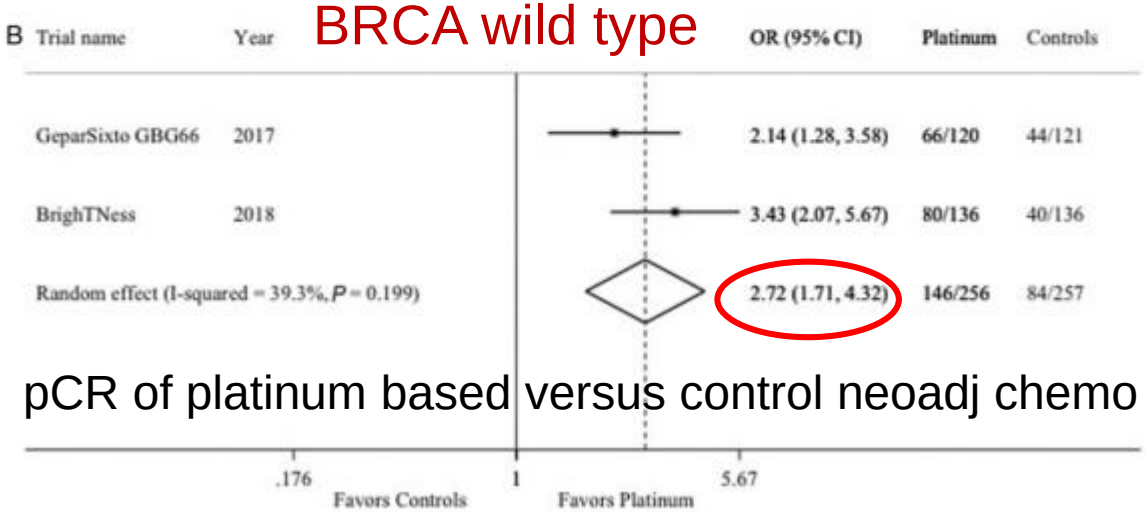
JAMA Oncol 2017 Hahnen et al ; ESMO 2017 Untch et al

Biomarkers for Carboplatin benefit?

BRCA mutation



BRCA wild type

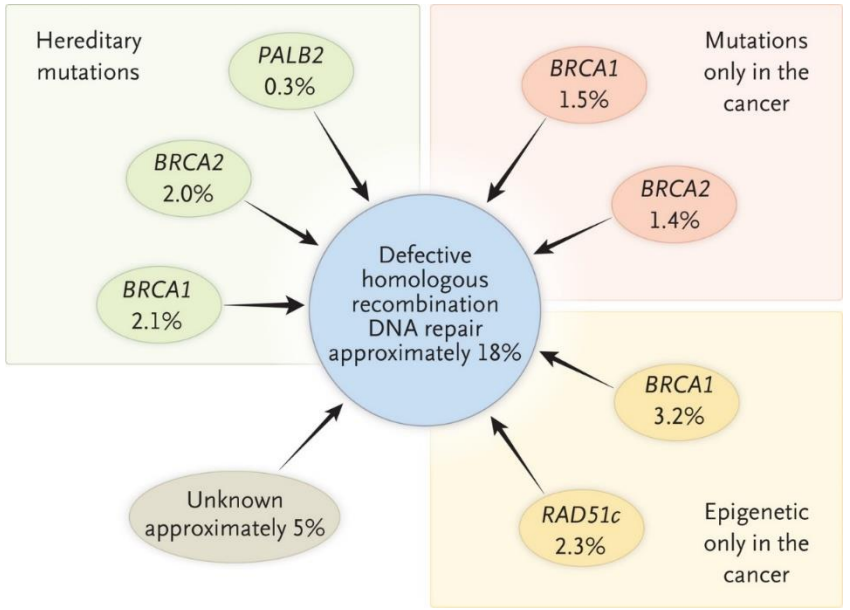


pCR of platinum based versus control neoadj chemo

Most benefit of Carbo in pts <u>without</u> BRCA mutation

Meta-analysis Ann Oncol 2018 Lambertini

HRD? (Homologous Recombination Deficiency)



But how to measure HRD optimally?

- Myriad: not predictive in TNT trial
- HRD mutation signature (WGS)?

No reliable biomarker yet to predict the benefit of Carboplatin in TNBC

NEJM 2017 Turner et al ; CCR 2017 Zhao et al

Conclusion Carbo Neoadjuvant in TNBC

Carbo for nobody	Carbo for all	Carbo dependent on risk factors
• No carbo ‘burden’ • Risk of undertreatment	• Additional toxicity from Carbo • Risk of overtreatment	~~• BRCA positive?~~ • Signs of HRD? • Able to tolerate carbo side effects (young)? • High volume • Suboptimal response after 4 cycles of EC?

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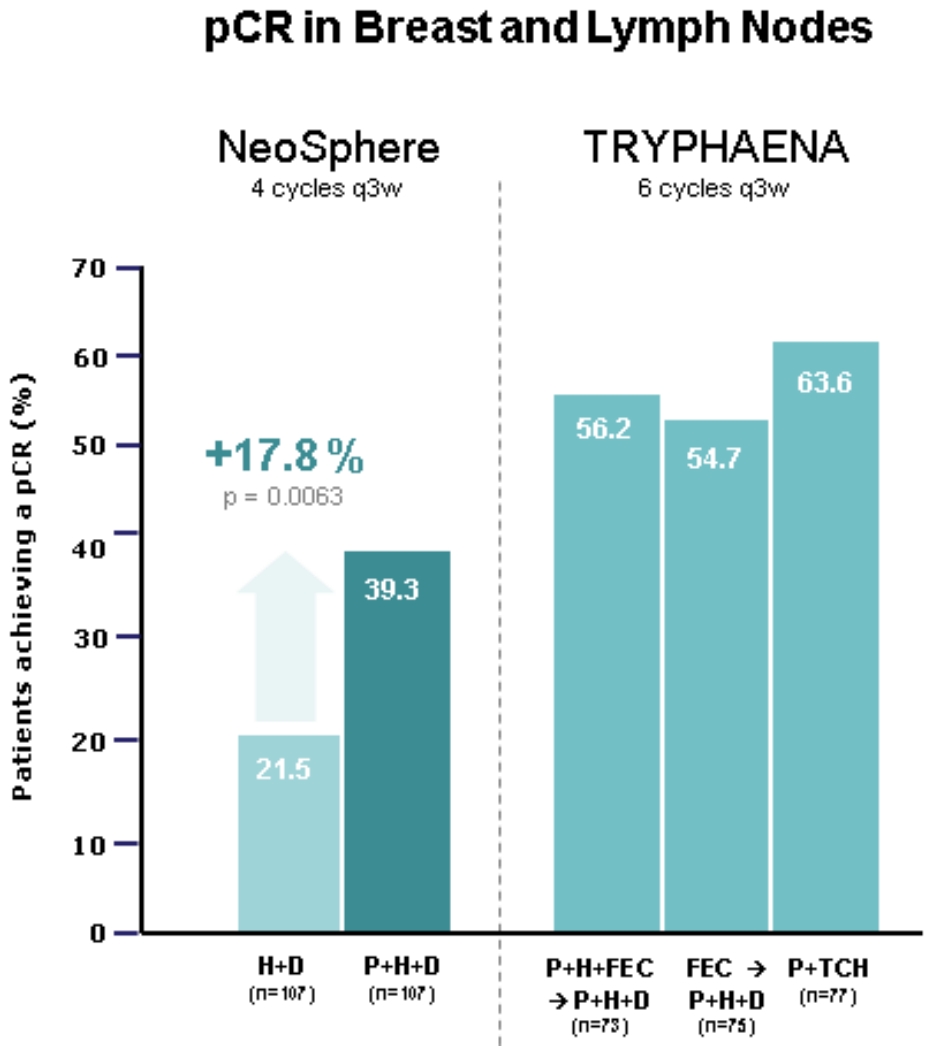
HER2+: Escalation neoadjuvant

1. Addition of pertuzumab



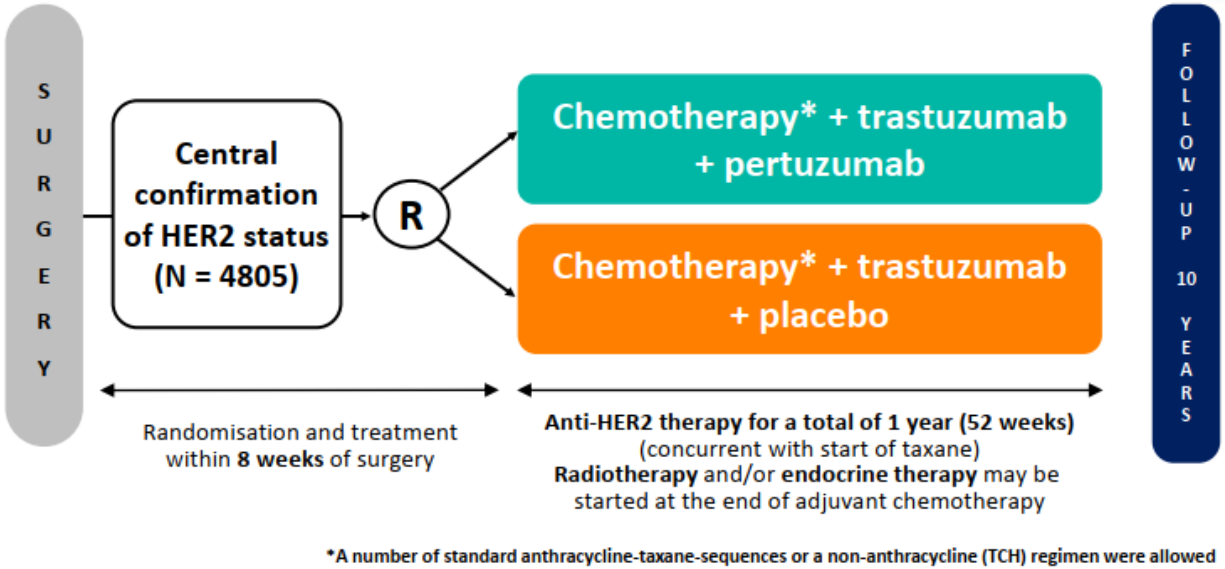
pCR significantly increased by Pertuzumab

Lancet Oncol 2012 Gianni
Ann Oncol 2013 Schneeweiss

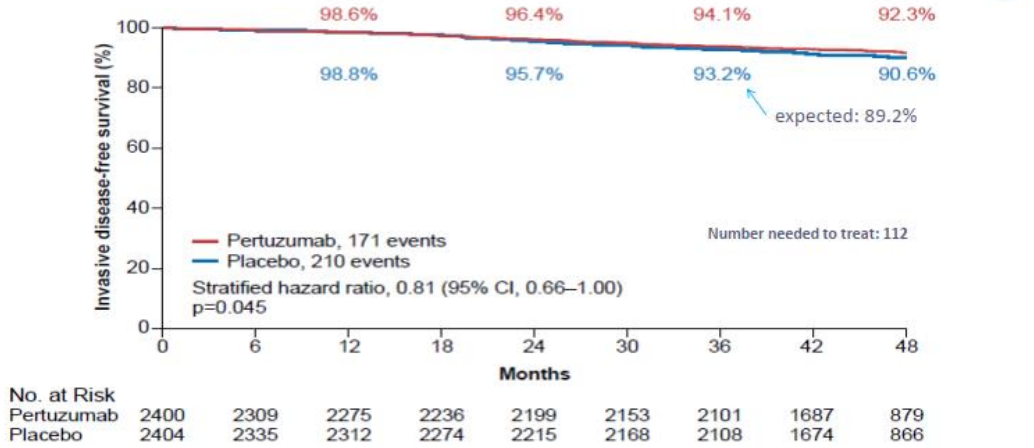
HER2+: Escalation adjuvant

2. Addition of pertuzumab

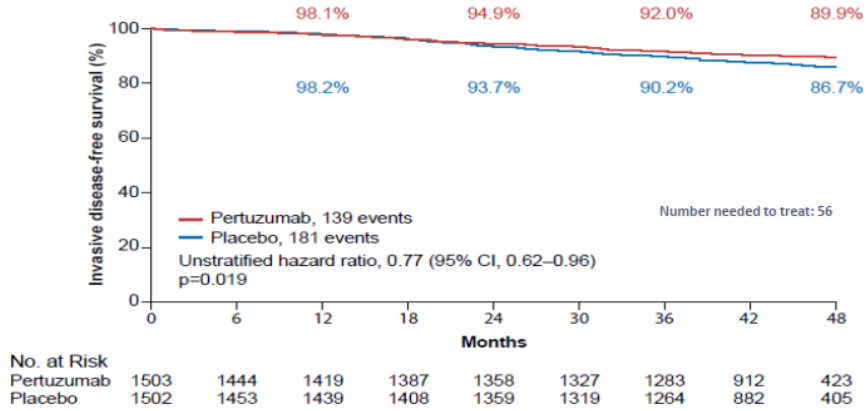
APHINITY trial



APHINITY: Intent-to-Treat Primary Endpoint Analysis Invasive Disease-free Survival



APHINITY: Node-positive Subgroup



DFS slightly increased by Pertuzumab

NEJM 2017 Von Minckwtiz

HER2+: Escalation adjuvant

3. Addition of T-DM1 adjuvant if no pCR obtained after neoadjuvant chemotherapy

KATHERINE study

Adjuvant T-DM1 Improves iDFS in Phase III HER2+ Breast Cancer Trial

Gina Columbus @ginacolumbusonc
Published: Monday, Oct 15, 2018

Sandra Horning, MD

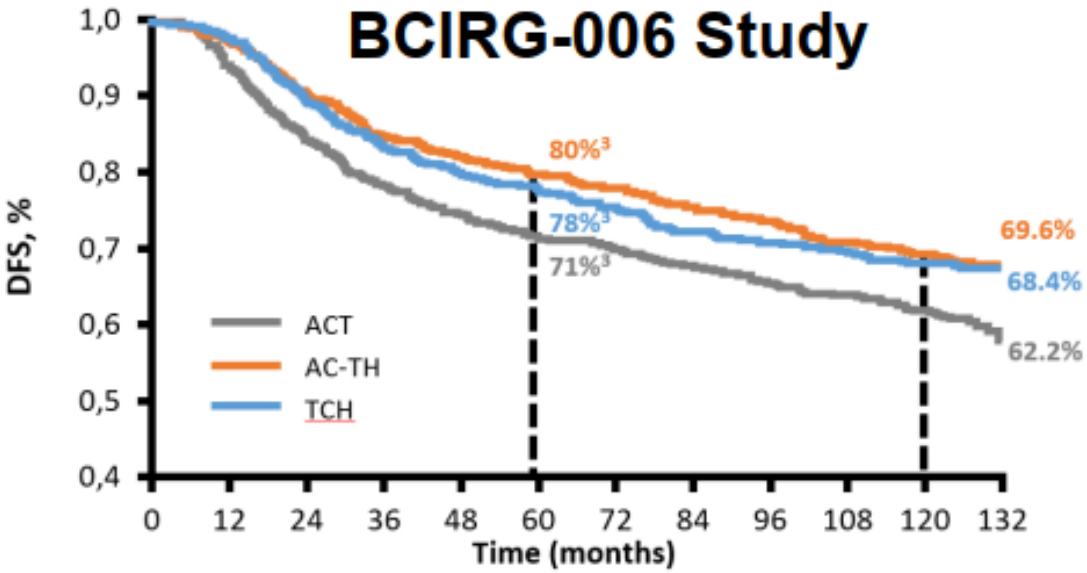
Ado-trastuzumab emtansine (T-DM1; Kadcyla) was found to significantly reduce the risk of invasive disease recurrence or death compared with trastuzumab (Herceptin) as an adjuvant treatment in patients with HER2-positive early breast cancer who have residual disease following neoadjuvant therapy, according to topline findings of the phase III KATHERINE study.

Moreover, no new safety signals with T-DM1 were reported and the safety profile was consistent with prior studies of the agent. Full data will be presented at the 2018 San Antonio Breast Cancer Symposium and will be submitted to the FDA and European Medicines Agency, Genentech (Roche), the developer of the antibody-drug conjugate, stated in a news release.

HER2+: De-escalation

1. Taxane only as chemobackbone adjuvant?

- **TCH**: Docetaxel Carboplatin Trastuz.



- **Paclitaxel weekly** x12 + 1y trastuz.
  - 410 women N0
    max 3 cm
    67% ER+
    20% pT1a, 9% pT2
  - 7y IDFS 99,3%
    23 relapses
    4 distant metastases (1%)

Anthracycline free regimen is an option

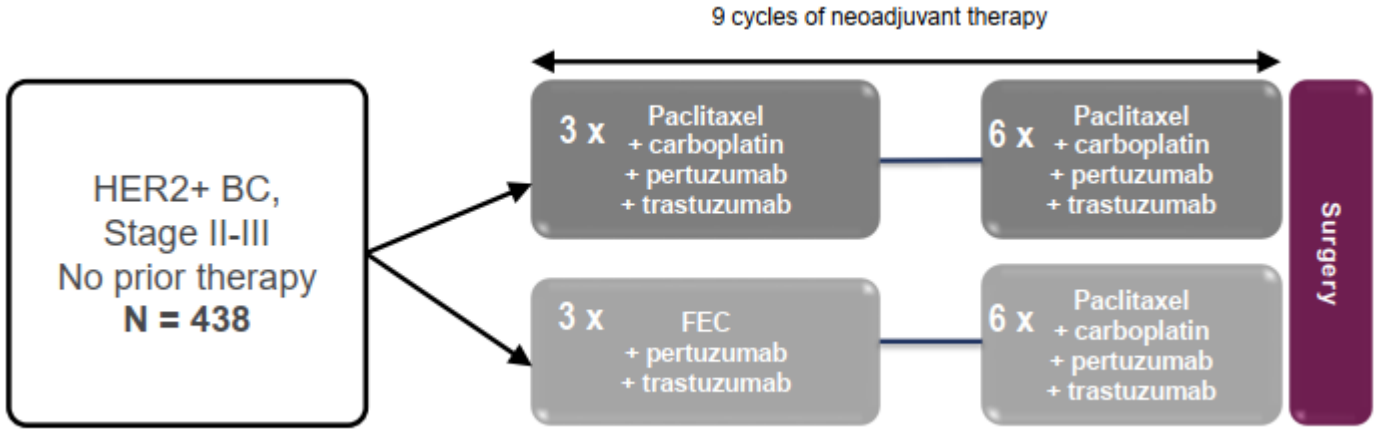
NEJM 2011 Slamon

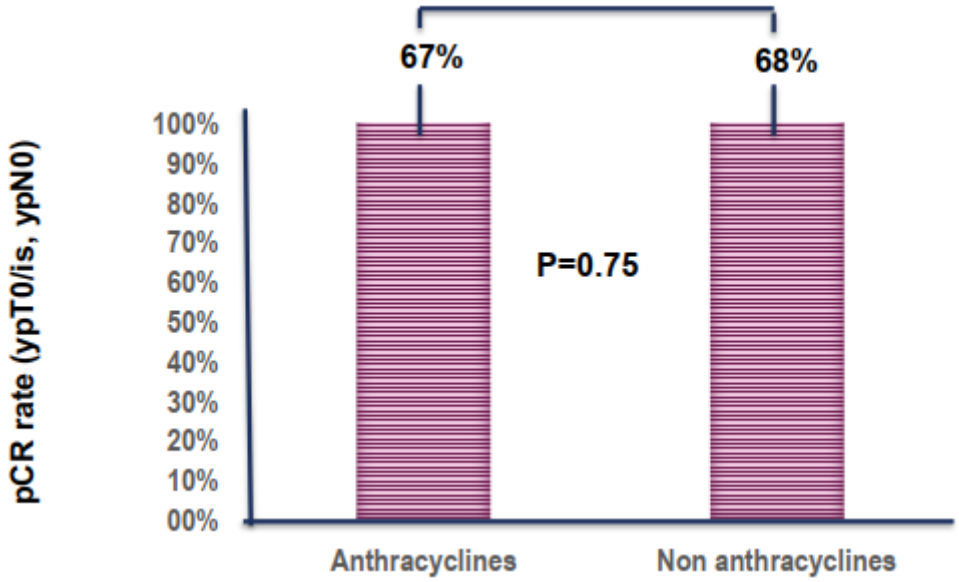
NEJM 2015 Tolaney ; ASCO 2017 Tolaney

HER2+: De-escalation attempts:

2. Taxane only as chemobackbone neoadjuvant?

TRAIN study





Anthracycline free regimen is an option

SABCS 2017 Van Ramshorst

HER2+: De-escalation attempts:

3. Duration of trastuzumab adjuvant

Study	N pts	Regimen	Outcome
Short-Her	627	3xDoc+Trast (9w) -> 3xFEC 4xAC/EC -> 4xTax/trast (1y)	HR DFS 1,15 (0,91-1,46) HR OS 1,06 (0,73-1,55)
SOLD	2176	3xDoc+Trast(9w)->3xFEC 3xDoc+Trast(9w)->3xFEC->Trast(1y)	HR DFS 1,39 (1,12-1,72) HR OS 1,36 (0,98-1,89)
HORG	241	4xFEC -> Doc+trast(6 Mo) 4xFEC -> Doc+trast(12 Mo)	HR DFS 1,57 (0,86-2,10) HR OS 1,45 (0,57-3,67)
Phare	1690	Chemo+Trast(12Mo) Chemo+Trast(6Mo)	HR DFS 1,28 (1,05-1,56) HR OS 1,46 (1,06-2,01)
Persephone	4089	Chemo+Trast(12Mo) Chemo+Trast(6Mo)	HR DFS 1,07 (ns) (4y 89,9% vs 89,4%) Stop for cardiac reasons 8% vs 4% (p<0,001)

1 year trastuzumab still standard, but subgroups may benefit from shorter duration.

Short duration not tested with ‘Tolaney’ regimen.

HER2+: De-escalation attempts:

4. Omission of classical chemotherapy neoadjuvant

Study	N pts	Regimen	pCR
ADAPT	375	T-DM1 T-DM1 + endocrine R/ Trastuzumab + endocrine R/	41,0% 41,5% 15,1%
KRISTINE	444	TCHP T-DM1+Pertuzumab	55,7% 44,4%

Subgroups can probably skip classical chemotherapy, but more research needed to identify those patients

JCO 2017 Harbeck ; Lancet Oncol 2018 Hurvitz

Conclusion

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