Optimal adjuvant and neoadjuvant therapy in HER2 positive breast cancers

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Neoadjuvant therapy in HER2 positive

INDICATIONS

- Locally advanced breast c

T3 – Tumor >50 mm in greatest dimension.
T4 – Tumor of any size with direct extension to the chest wall and/or the skin (ulceration or macroscopic skin nodules)*.
T4a – Extension to chest wall, not including only pectoralis muscle adherence/invasion.
T4b – Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma.
T4c – Both (T4a and T4b).
T4d – Inflammatory carcinoma**.

T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB

Clinical classification of regional lymph nodes
cN1 – Metastasis to movable ipsilateral level I, II axillary lymph nodes(s).
•cN1mi** – Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm).
cN2 – Metastasis to ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary nodes in the absence of clinically evident axillary node metastases.
cN3 – Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement.

T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

Click for staging definitions

Neoadjuvant therapy in HER2 positive

- A higher pCR in HER2+ with chemotherapy
- Using targeted therapy → increasing the pCR rate

In comparison with Her2 -

Even without anti-Her2 therapy

In addition to ChT

Trastuzumab

- randomized studies and meta-analyses demonstrating improvements in
  - pCR rate
  - EFS
  - OS

JAMA Oncol. 2016;2(6):751-760

Research

Original Investigation

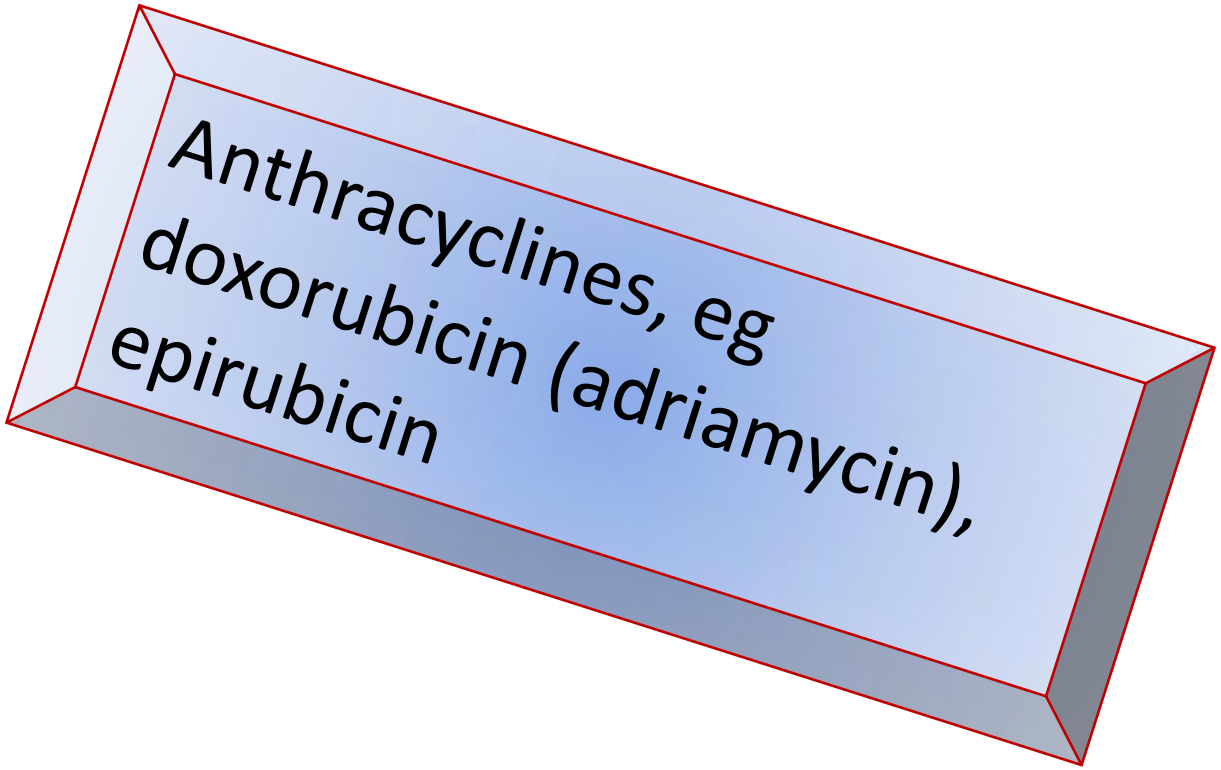
Association of Pathologic Complete Response to Neoadjuvant Therapy in HER2-Positive Breast Cancer With Long-Term Outcomes
A Meta-Analysis

Kristine R. Broglio, MS; Melanie Quintana, PhD; Margaret Foster, MS; Melissa Olinger, BA; Anna McGlothlin, PhD; Scott M. Berry, PhD; Jean-François Boileau, MD; Christine Brezden-Masley, MD; Stephen Chia, MD; Susan Dent, MD; Karen Gelmon, MD; Alexander Paterson, MD; Daniel Rayson, MD; Donald A. Berry, PhD

Anthracycline versus non anthracycline

- AC → TH

Taxol+ Herceptin



TRAIN-2/alternatives to anthracycline

- In a phase III trial of 438 patients with stage II to III
- Based on results, taxane-carboplatin-trastuzumab (with or without pertuzumab) regimens as preferable alternatives to anthracycline-containing regimens
- lesser toxicity and equivalent rates of pCR

- the rates of pCR did not differ between the arms (67% versus 68%) Patients who received the anthracycline
  - experienced higher rates of grade >3 febrile neutropenia (11 versus 2%)
  - grade >2 declines in left ventricular ejection fraction (29% versus 18%).

Pertuzumab

- Blocking the formation of HER2:HER3 heterodimers
- An important mechanism of resistance to trastuzumab

NeoSphere Trial

- 417 HER2-positive patients
- Those randomly assigned to
  - pertuzumab and trastuzumab had a pCR rate (46%)
  - just trastuzumab (29%)
  - just pertuzumab (24%)
- five-year PFS results do not demonstrate a benefit associated with the addition of pertuzumab to docetaxel and trastuzumab (HR 0.69, 95% CI 0.34-1.40)
- →for clinical stage I to IIA disease, the potential for added toxicity associated with pertuzumab may outweigh the benefit. For such patients, we engage in a risk-benefit discussion regarding the use of pertuzumab
- (Size<2 with N0, N1 / size 2-5 with N0)

Pertuzumab

- There is no demonstrated benefit to administration of additional chemotherapy or of pertuzumab in the adjuvant setting.

Trastuzumab emtansine (T-DM1) KRISTINE

Taxol- carboplatin-herceptin-pertusumab

- Patients who received TCHP had a higher pCR rate (56 versus 44 percent) and a higher rate of breast-conserving surgery (53 versus 42 percent) than those assigned to the T-DM1-based regimen

Neratinib
NSABP FB-7 trial

- An oral agent that binds irreversibly to and inhibits the tyrosine kinase domains of both EGFR and HER2.
- Comparing paclitaxel-neratinib versus paclitaxel-trastuzumab as neoadjuvant treatment
- The trastuzumab-based arm was associated with a higher pCR rate (38% versus 33%)

Adjuvant

Adjuvant

- Small HER2-positive tumors (tumor ≤10 mm)
  - higher risk of recurrence compared with similar patients with HER2-negative disease
- Early HER2-positive tumors
  - Low risk → 10 to 20 mm with N0
  - High risk → >20 mm or N1
- Locally advance HER2-positive tumors

small HER2-positive tumors

Paclitaxel=
Taxol

(Docetaxel= taxotere)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

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This article was updated on January 8, 2015, at NEJM.org.

ABSTRACT

BACKGROUND

No single standard treatment exists for patients with small, node-negative, human epidermal growth factor receptor type 2 (HER2)–positive breast cancers, because most of these patients have been ineligible for the pivotal trials of adjuvant trastuzumab.

METHODS

We performed an uncontrolled, single-group, multicenter, investigator-initiated

small HER2-positive tumors

- **CONCLUSIONS**
- Among women with predominantly stage I
- with adjuvant paclitaxel plus trastuzumab was associated with a risk of early recurrence of about 2%;
- (Single arm)

small HER2-positive tumors

VOLUME 27 · NUMBER 34 · DECEMBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

High Risk of Recurrence for Patients With Breast Cancer Who Have Human Epidermal Growth Factor Receptor 2–Positive, Node-Negative Tumors 1 cm or Smaller

Ana M. Gonzalez-Angulo, Jennifer K. Litton, Kristine R. Broglio, Funda Meric-Bernstam, Ronjay Rakkhit, Fatima Cardoso, Florentia Peintinger, Emer O. Hanrahan, Aysegul Sahin, Merih Guray, Denis Larsimont, Francesco Feoli, Heidi Stranzl, Thomas A. Buchholz, Vicente Valero, Richard Theriault, Martine Piccart-Gebhart, Peter M. Ravdin, Donald A. Berry, and Gabriel N. Hortobagyi

See accompanying editorial on page 5671 and articles on pages 5685, 5693, and 5838

small HER2-positive tumors

- Retrospective
- study of 965 patients
- T1a (>1 mm but ≤5 mm) or T1b (>5 mm but ≤10 mm)
- Compared with HER2-negative disease: significantly worse five-year rates of recurrence-free survival (77% versus 94%)

small HER2-positive tumors

- It is reasonable to offer trastuzumab-based adjuvant therapy to patients with small HER2-positive tumors

The benefits of adding trastuzumab

- A 2012 meta-analysis of eight trials of chemotherapy plus trastuzumab versus chemotherapy alone involving nearly 12,000 patients
- 12 months in the adjuvant setting improvement in OS
- ≤6 months also showed a trend towards an improvement in OS
- The benefit in OS was associated with concurrent administration

durable survival benefits

VOLUME 32 · NUMBER 33 · NOVEMBER 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Trastuzumab Plus Adjuvant Chemotherapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Planned Joint Analysis of Overall Survival From NSABP B-31 and NCCTG N9831

Edith A. Perez, Edward H. Romond, Vera J. Suman, Jong-Hyeon Jeong, George Sledge, Charles E. Geyer Jr, Silvana Martino, Priya Rastogi, Julie Gralow, Sandra M. Swain, Eric P. Winer, Gerardo Colon-Otero, Nancy E. Davidson, Eleftherios Mamounas, Jo Anne Zujewski, and Norman Wolmark

Listen to the podcast by Dr Burstein at www.jco.org/podcasts

Edith A. Perez, Gerardo Colon-Otero, the Mayo Clinic, Jacksonville; Eleftherios Mamounas, University of Florida Health Cancer Center-Orlando Health.

ABSTRACT

- With a median on-study time of 8.4 years,
- 37% improvement in overall survival
- 40% improvement in disease-free survival

Early HER2-positive tumors and Dual anti-HER2 therapy

- for high-risk disease → Dual anti-HER2 therapy
  - node-positive
  - tumors >2 cm

ORIGINAL ARTICLE

Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer

Gunter von Minckwitz, M.D., Marion Procter, Ph.D., Evandro de Azambuja, M.D., Dimitrios Zardavas, M.D., Mark Benyunes, M.D., Giuseppe Viale, M.D., Thomas Suter, M.D., Amal Arahmani, Ph.D., Nathalie Rouchet, M.Sc., Emma Clark, M.Sc., Adam Knott, Ph.D., Istvan Lang, M.D., Christelle Levy, M.D., Denise A. Yardley, M.D., Jose Bines, M.D., Richard D. Gelber, Ph.D., Martine Piccart, M.D., and Jose Baselga, M.D., for the APHINITY Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Pertuzumab increases the rate of pathological complete response in the preoperative context and increases overall survival among patients with metastatic disease when it is added to trastuzumab and chemotherapy for the treatment of human epidermal growth factor receptor 2 (HER2)–positive breast cancer. In this trial, we investigated whether pertuzumab, when added to adjuvant trastuzumab and chemotherapy, improves outcomes among patients with HER2-positive early breast cancer.

METHODS

We randomly assigned patients with node-positive or high-risk node-negative HER2-positive, operable breast cancer to receive either pertuzumab or placebo added to standard adjuvant chemotherapy plus 1 year of treatment with trastuzumab. We assumed a 3-year invasive-disease–free survival rate of 91.8% with pertuzumab and 89.2% with placebo.

RESULTS

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. von Minckwitz at the German Breast Group, GBG Forschungs, Martin-Behaim-Str. 12, 63263 Neu-Isenburg, Germany, or at gunter.vonminckwitz@gbg.de, or to Dr. Baselga at Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065, or at baselgaj@mskcc.org.

*A complete list of the members of the APHINITY Steering Committee and Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 5, 2017, and last updated on October 1, 2018, at NEJM.org.

APHINITY trial

APHINITY Trial: Adjuvant Pertuzumab and Trastuzumab

- phase III
- 4800 patients
- median follow-up of approximately 45 months,
- improved three-year DFS (94.1% versus 93.2%; HR 0.81, 95% CI 0.66-1.00).
- node-positive disease (92% versus 90.2%; HR 0.77, 95% CI 0.62-0.96).
- greater among ER negative (2.4% versus 1.2%) but not significant.

Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial

*Miguel Martin, Frankie A Holmes, Bent Ejlertsen, Suzette Delaloge, Beverly Moy, Hiroji Iwata, Gunter von Minckwitz, Stephen K L Chia, Janine Mansi, Carlos H Barrios, Michael Gnant, Zorica Tomašević, Neelima Denduluri, Robert Šeparović, Erhan Gokmen, Anna Bashford, Manuel Ruiz Borrego, Sung-Bae Kim, Erik Hugger Jakobsen, Audrone Ciceniene, Kenichi Inoue, Friedrich Overkamp, Joan B Heijns, Anne C Armstrong, John S Link, Anil Abraham Joy, Richard Bryce, Alvin Wong, Susan Moran, Bin Yao, Feng Xu, Alan Auerbach, Marc Buyse, Arlene Chan, for the ExteNET Study Group**

Lancet Oncol 2017; 18: 1688–700

Published Online November 13, 2017

http://dx.doi.org/10.1016/S1470-2045(17)30717-9

Summary

Background ExteNET showed that 1 year of neratinib, an irreversible pan-HER tyrosine kinase inhibitor, significantly improves 2-year invasive disease-free survival after trastuzumab-based adjuvant therapy in women with HER2-positive breast cancer. We report updated efficacy outcomes from a protocol-defined 5-year follow-up sensitivity analysis and long-term toxicity findings.

Methods In this ongoing randomised, double-blind, placebo-controlled, phase 3 trial, eligible women aged 18 years or

ExteNET

- academic institutions in 40 countries
- phase III trial of 2840 eligible women
- stage 1–3c (modified to stage 2–3c in February, 2010) operable
- oral neratinib 240 mg/day or matching placebo
- The 5-year DFS 90·2% Vs 87·7%
- nonsignificant trend toward greater improvements in ER+ (HR of 0.60 and 0.95, respectively).

Treatment duration

- the standard course of adjuvant trastuzumab is one year
- no improvement with extension to two years
  - In HERA trial,
  - over 5000 women with HER2-positive breast cancer
  - observation or trastuzumab for one or two years
  - With 11-year follow-up

Treatment duration / de-escalation

- 6 versus 12 months

6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial

*Xavier Pivot, Gilles Romieu, Marc Debled, Jean-Yves Pierga, Pierre Kerbrat, Thomas Bachelot, Alain Lortholary, Marc Espié, Pierre Fumoleau, Daniel Serin, Jean-Philippe Jacquin, Christelle Jouannaud, Maria Rios, Sophie Abadie-Lacourtoisie, Nicole Tubiana-Mathieu, Laurent Cany, Stéphanie Catala, David Khayat, Iris Pauporté, Andrew Kramar, and the PHARE trial investigators**

Summary

Background Since 2005, 12 months of adjuvant trastuzumab has been the standard treatment for patients with HER2-positive early-stage breast cancer. However, the optimum duration of treatment has been debated. We did a non-inferiority trial of a shorter exposure of 6 months versus the standard 12 months of trastuzumab for patients with early breast cancer.

Lancet Oncol 2013; 14: 741–48

Published Online
June 11, 2013
http://dx.doi.org/10.1016/S1470-2045(13)70225-0

PHARE

- 3380 women were randomly assigned
- median follow-up of 42.5 months,
- shorter two-year DFS rate compared with 12 months of therapy (91 versus 94%)
- more deaths (93 versus 66%)
- distant recurrences as first events (141 versus 108 events).

original articles

Annals of Oncology 26: 1333–1340, 2015
doi:10.1093/annonc/mdv213
Published online 1 May 2015

Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG)

D. Mavroudis[1]*, E. Saloustros[2], N. Malamos[3], S. Kakolyris[4], I. Boukovinas[5], P. Papakotoulas[6], N. Kentepozidis[7], N. Ziras[8] & V. Georgoulias[9], on behalf of the Breast Cancer Investigators of the Hellenic Oncology Research Group (HORG), Athens, Greece

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Received 19 January 2015; revised 13 April 2015; accepted 23 April 2015

Conclusions: Our study failed to show noninferiority for the 6-month arm. The results further support the current standard of care that is administration of adjuvant trastuzumab for 12 months.

PERSEPHONE (J Clin Oncol 2018; 36S: ASCO#506)

- **6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): Randomised phase 3 non-inferiority trial with definitive 4-year (yr) disease-free survival (DFS) results.**
- 4089/ early breast cancer/ 85 percent of whom received adjuvant chemotherapy,
- **Conclusions:** PERSEPHONE has demonstrated 6m of trastuzumab as non-inferior to 12m (3% non-inferiority margin). Given cardiac and other toxicities during months 7-12 of treatment, our results would support a reduction of standard trastuzumab duration to 6 months

Take home messages

- Neoadjuvant chemotherapy and anti HER2
  - A higher pCR with chemotherapy → and more with Trastuzumab → and more with pertuzumab
  - But not survival benefit with pertuzumab
  - No recommend additional chemotherapy or of pertuzumab in the adjuvant setting
  - Anthracycline  Non Anthracycline
  - Dual target No recommend for clinical stage I to IIA (Size<2 with N0, N1 / size 2-5 with N0)
  - Neratinib No recommend
  - T-DM 1 No recommend

Take home messages

- Adjuvant chemotherapy and anti HER2
  - Addition of adjuvant pertuzumab for node-positive disease, or node-negative tumors >2 cm in size (Grade 2C)
  - Neratinib for ER positive and high risk
  - Do not offer neratinib if pertuzumab or for smaller tumors or those that are ER negative