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REVIEW

Survival after neoadjuvant therapy with trastuzumab—lapatinib and chemotherapy in patients with HER2-positive early breast cancer: a meta-analysis of randomized trials

V. Guarneri[1,2*], G. Griguolo[1,2], F. Miglietta[1], P. F. Conte[1,2], M. V. Dieci[1,2] & F. Girardi[2]

[1]Department of Surgery, Oncology and Gastroenterology, University of Padua, Padova; [2]Oncology 2, Veneto Institute of Oncology - IOV — IRCCS, Padova, Italy

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Background: Studies testing the addition of lapatinib to neoadjuvant trastuzumab + chemotherapy reported an increase in pathologic complete response (pCR), with, nevertheless, discordant results in terms of survival, mainly due to suboptimal power. We here leverage the meta-analytic approach to resolve these inconsistencies.

Methods: We conducted a meta-analysis of randomized phase II/III studies testing lapatinib + trastuzumab in combination with neoadjuvant chemotherapy for human epidermal growth factor receptor (HER2)-positive early breast cancer (BC). Recurrence-free survival (RFS) and overall survival (OS) were adopted as survival endpoints. Pooled hazard ratios (HR) were obtained for the effect of lapatinib + trastuzumab versus trastuzumab, pCR versus no-pCR in the whole study populations and pCR versus no-pCR according to hormone receptor status.

Results: Four phase II/III randomized trials were included in the meta-analysis (CALGB 40601, Cher-LOB, NSABP-B41, NeoALTTO) for an overall population of 1410 patients receiving neoadjuvant chemotherapy in association with either trastuzumab, lapatinib or their combination. RFS was significantly improved with dual HER2 blockade as compared to trastuzumab [HR 0.62, 95% confidence interval (CI) 0.46-0.85]. Dual blockade also led to significantly improved OS (HR 0.65, 95% CI 0.43-0.98). For all treatments combined, patients achieving pCR had better RFS and OS than those with residual disease (HR 0.45, 95% CI 0.34-0.60, and HR 0.32, 95% CI 0.22-0.48, for RFS and OS, respectively). In patients with hormone receptor-negative tumors, pCR was associated with 65% and 73% relative reduction of risk of relapse and death, respectively. Patients with hormone receptor-positive tumors also experienced improved RFS if they achieved pCR; however, the benefit was smaller than that in hormone receptor-negative disease.

Conclusion: Findings from this meta-analysis further validate the role of pCR as a strong predictor of outcome in patients with HER2-positive BC, especially in hormone receptor-negative disease. Moreover, we provide robust evidence that dual blockade with lapatinib + trastuzumab in combination with neoadjuvant chemotherapy prolongs OS, suggesting that the role of lapatinib could be reconsidered in the early setting.

Key words: HER2-positive breast cancer, neoadjuvant treatment, lapatinib, trastuzumab, meta-analysis

INTRODUCTION

In the past decades, neoadjuvant treatment has been increasingly adopted given the acknowledged benefit from a patient perspective, especially in terms of expansion of locoregional treatment options and access to post-neoadjuvant strategies based on the pathologic response at surgery. In addition, the achievement of pathologic complete response (pCR) after neoadjuvant therapy represents a solid surrogate endpoint for improved long-term outcome at a single-patient level, within each breast cancer (BC) phenotypic subsets and baseline clinical stage categories.[1] However, the establishment of a trial-level association between pCR and drug efficacy is still formally lacking, thus challenging the role of pCR as a surrogate endpoint for regulatory purposes.[1] Indeed, this failure highlights the intrinsic paradox of the neoadjuvant platform, which, on one hand, may allow to make comparisons across treatments in a more cost-effective manner than the adjuvant setting, while, on the other, typically being inherently statistically underpowered to detect significant survival differences across treatment arms.

*Correspondence to: Prof. Valentina Guarneri, Department of Surgery, Oncology and Gastroenterology, University of Padova; Division of Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Via Gattamelata 64, 35128 Padova, Italy. Tel: +39-049-821-5291; Fax: +39-049-821-5932

E-mail: valentina.guarneri@unipd.it (V. Guarneri).

Human epidermal growth factor receptor 2 (HER2)-positive BC accounts for approximately 20% of all breast tumors. Its intrinsic high biological aggressiveness has been mitigated by the implementation of HER2 blockade, whereby, over the past decades, HER2-positive BC patients' outcome has been widely improved in all disease settings.[2-4] Focusing on the neoadjuvant setting, which currently represents the standard approach for stage II-III[5] HER2-positive breast patients, the incorporation of trastuzumab into the chemotherapy backbone resulted in a substantial improvement in pCR rates as compared to chemotherapy alone, thus laying the groundwork to test escalated anti-HER2 strategies with the ultimate goal of further enhancing pCR rates.[6-8] In this regard, one of the most successful attempts is represented by the dual blocking of HER2 signaling, either with pertuzumab or lapatinib (both added to trastuzumab + chemotherapy). In particular, accumulating evidence supports the combination of lapatinib to trastuzumab (+chemotherapy) as an effective escalated neoadjuvant approach, since it has been consistently reported to be capable of significantly improving pCR rates as compared to single HER2-blockade in several randomized trials.[9-13] However, survival analyses of the same trials,[9,14-16] while all being consistent in reporting a trend of survival benefit in favor of the lapatinib-containing arms, failed to report statistically significant differences, with the exception of the CALGB 40601[9,10] which represents the only trial succeeding, so far, in this regard.

To overcome the limitation in terms of sample size of individual neoadjuvant studies, we carried out a meta-analysis of survival data of randomized trials evaluating neoadjuvant dual HER2 targeting with trastuzumab and lapatinib versus single HER2 blockade with trastuzumab, in association with neoadjuvant chemotherapy.

METHODS

Identification of eligible studies

The systematic review focused on phase II and III randomized studies testing lapatinib in combination with neoadjuvant trastuzumab + chemotherapy for HER2-positive early BC. We queried three electronic databases (Embase, Medline and PubMed) from database inception to 30 July 2021. We used a pre-specified search strategy (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100433) including terms for the disease domain and the study design domain. We did not set language or time restrictions.

Methods for the meta-analysis

The meta-analysis was based on aggregated data from phase II or phase III randomized studies on neoadjuvant lapatinib added to trastuzumab + chemotherapy. Pooled hazard ratios (HRs) were obtained for the effect of trastuzumab + lapatinib compared to trastuzumab only, pCR compared to no-pCR in the whole study populations and pCR compared to no-pCR in the hormone receptor-negative or hormone receptor-positive cohorts. HRs for recurrence-free survival (RFS) and overall survival (OS) were considered separately. Event-free survival estimates were analyzed together with RFS estimates as we assumed the long study follow-ups made these outcome measures broadly comparable. We log-transformed HRs to correct for possible asymmetry of confidence intervals (CIs). Point estimates and corresponding CIs were graphically displayed in the logarithmic scale, but they were reported in the original, exponential scale. To allow for heterogeneity between studies, a random-effects meta-analysis was used.

RESULTS

Eligible studies

The database search yielded 1794 records. We screened these records for eligibility from the title and the abstract. We then assessed the full text of the remaining 54 studies (reasons for exclusion are reported in Figure 1). This process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[17] The PRISMA flowchart is shown in Figure 1. Four international neoadjuvant trials comparing dual HER2 blockade with trastuzumab + lapatinib versus trastuzumab only (in association with chemotherapy) with survival analysis results available were therefore included in the quantitative synthesis: CALBG 40601 ($n = 305$),[9] Cher-LOB ($n = 121$),[14] NSABP B-41 ($n = 522$)[15] and NeoALTTO ($n = 455$).[16]

Study characteristics

Characteristics of the four eligible neoadjuvant trials are summarized in Table 1.

In summary, in all of the trials, HER2-positive BC patients were randomized to receive neoadjuvant chemotherapy in association with either trastuzumab, lapatinib or the combination of trastuzumab + lapatinib. In the Cher-LOB and NSABP B41 trials, anthracyclines were administered sequentially to paclitaxel in the preoperative setting, while in the CALBG 40601 and NeoALTTO trials anthracyclines were recommended post-operatively. In all but the NeoALTTO trial, adjuvant anti-HER2 treatment consisted of trastuzumab given to complete 1 year of HER2 blockade. In the NeoALTTO trial all patients received the same anti-HER2 strategy according to the previous random assignment to complete 1 year of anti-HER2 treatment. In addition, all patients with hormone receptor-positive disease were recommended to receive at least 5 years of hormonal therapy as per local guidelines after the completion of neoadjuvant therapy and surgery. Similarly, post-operative radiation therapy was administered as per local policy, when indicated.

Survival analysis

A total of 1410 patients were analyzed for each meta-analysis outcome. Pooled HR were stratified by treatment arm, pCR and hormone receptor status.

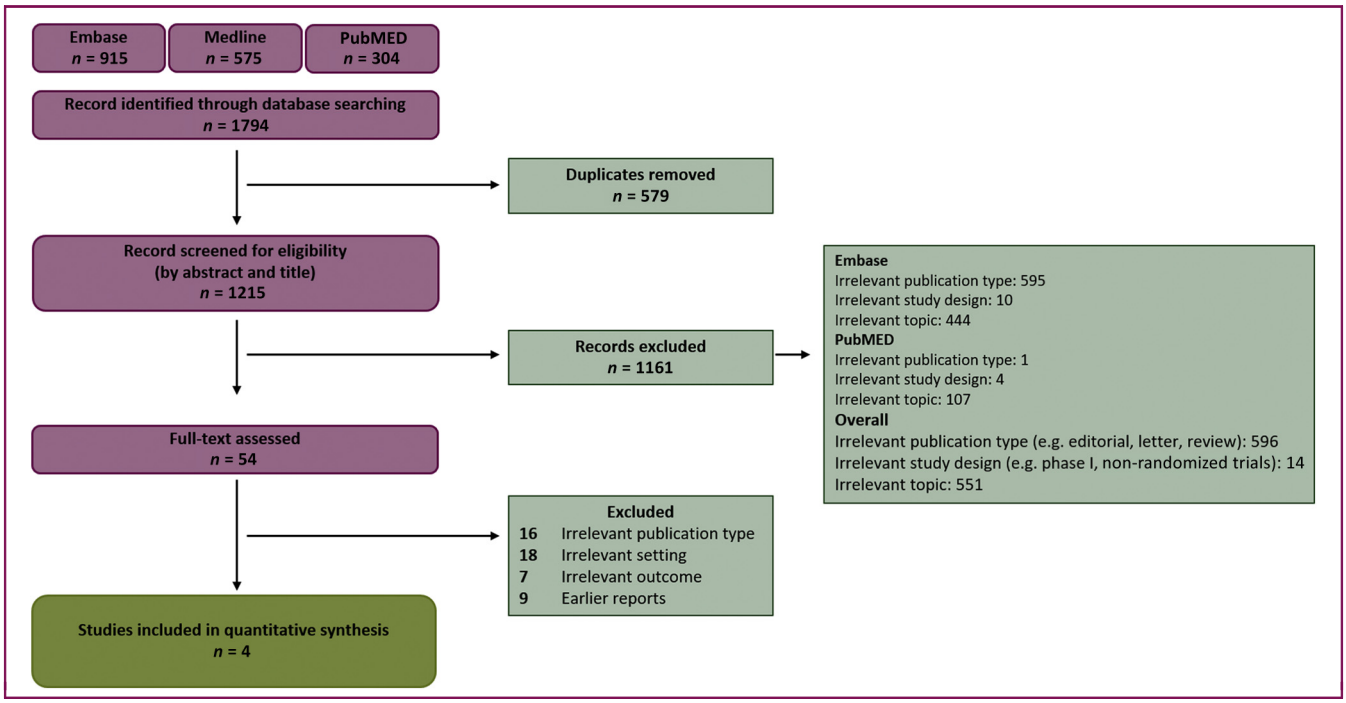

Figure 1. PRISMA flowchart.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Overall, dual HER2 blockade with trastuzumab and lapatinib was significantly associated with improved RFS (pooled HR 0.62, 95% CI 0.46-0.85), as shown in Figure 2A. In addition, dual blockade with lapatinib and trastuzumab in combination to neoadjuvant chemotherapy led to a significant OS improvement as compared to trastuzumab alone (pooled HR 0.65, 95% CI 0.43-0.98), as shown in Figure 2B.

pCR was found to be significantly and highly associated with survival. In particular, patients achieving pCR experienced improved RFS (HR 0.45, 95% CI 0.34-0.60) and OS (HR 0.32, 95% CI 0.22-0.48) as compared to those with residual disease evidence at surgery (Figures 3A and 4A). When evaluating the association between pCR and survival according to hormone receptor status, the positive relationship between pCR and both RFS and OS was particularly evident in the hormone receptor-negative subgroup (RFS: HR 0.35, 95% CI 0.23-0.53; OS: HR 0.27, 95% CI 0.15-0.47, Figures 3B and 4B). Although to a lesser extent, pCR was

Table 1. Characteristics of studies included in the meta-analysis

Study (design)	Anti-HER2 treatment arm	Primary endpoint		Survival analysis		
		Definition	pCR rates	Median follow-up	Survival rates	HR (95% CI) for T versus TL
Cher-LOB (phase II R)	T	pCR: ypT0/is ypN0	25%	9 years	5-year RFS: 77.8%	EFS: 0.52 (0.23-1.15)
	L		26.3%		5-year RFS: 77.1%	OS: 1.00 (0.31-3.27)
	TL		46.7%		5-year RFS: 85.8%	
NSABP B41 (phase III)	T	pCR: ypT0/is	52.5%	5 years	5-year RFI: 84.3% 5-year OS: 94.5%	EFS: 0.66 (0.34-1.25) OS: 1.00 (0.24-1.67)
	L		53.2%		5-year RFI: 78.6% 5-year OS: 89.4%	
	TL		62%		5-year RFI: 90% 5-year OS: 95.7%	
NeoALTTO (phase III)	T	pCR: ypT0/is	29.5%	6.7 years	6-year EFS: 67% 6-year OS: 82%	EFS: 0.98 (0.64-1.91) OS: 0.85 (0.49-1.86)
	L		24.7%		6-year EFS: 67% 6-year OS: 79%	
	TL		51.3%		6-year EFS: 74% 6-year OS: 85%	
CALGB 40 601 (phase III)	T	pCR: ypT0/is	46%	7 years	7-year EFS: 79% 7-year OS: 88%	EFS: 0.32 (0.14-0.71) OS: 0.34 (0.12-0.94)
	L		32%		7-year EFS: 69% 7-year OS: 84%	
	TL		56%		7-year EFS: 93% 7-year OS: 96%	

CI, confidence interval; EFS, event-free survival; T, trastuzumab; HR, hazard ratio; L, lapatinib; OS, overall survival; pCR, pathologic complete response; R, randomized; RFI, recurrence-free interval; RFS, recurrence-free survival.

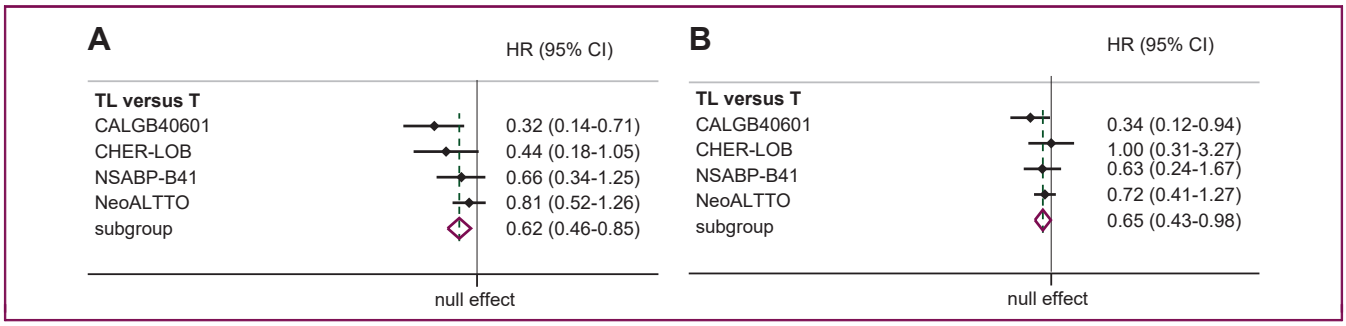

Figure 2. Hazard ratios according to treatment arm (chemotherapy + trastuzumab versus chemotherapy + trastuzumab + lapatinib).
(A) Recurrence-free survival analysis. (B) Overall survival analysis.
CI, confidence interval; HR, hazard ratio; TL, trastuzumab+lapatinib; T, trastuzumab.

significantly associated with RFS also in the hormone receptor-positive subgroup (HR 0.60, 95% CI 0.37-0.97, Figure 3C), with a relationship of borderline significance in terms of OS (HR 0.52, 95% CI 0.23-1.15, Figure 4C).

DISCUSSION

The neoadjuvant platform is currently endorsed by the Food and Drug Administration[18] for the investigation of experimental interventions since it may allow to compare treatments more cost-effectively than the adjuvant setting. However, pCR being usually the primary endpoint, these trials are generally underpowered to formally demonstrate significant survival differences across treatment arms. In order to overcome this limitation, we carried out a meta-analysis of survival analysis of phase II and III randomized clinical trials comparing dual HER2 blockade with lapatinib and trastuzumab versus either trastuzumab or lapatinib given as single HER2 agents, in association with neoadjuvant chemotherapy (CALGB 40601, Cher-LOB, NSABP B41 and NeoALTTO) with a total of 1410 patients included in the pooled analysis.

As expected, in the present meta-analysis, we confirmed pCR to be strongly associated with prognosis, with a 55% and 68% relative reduction in the risk of RFS and OS events, respectively, for patients achieving pCR as compared to those with residual disease after neoadjuvant therapy. This finding strengthens the already solid evidence supporting the role of pCR as a prognostic biomarker for single patients with HER2-positive BC receiving chemotherapy + HER2-targeted agents in the neoadjuvant setting.[1,7,9,15,16,19] Notably, although pCR was found to be positively associated with long-term outcome in both hormone receptor-positive and hormone receptor-negative patients, the strength of the association was greater in this latter subgroup. These data confirm the observations of the CtNeoBC meta-analysis in a large population of HER2-positive BC patients homogeneously treated with taxane (+/− anthracycline)-based chemotherapy + anti-HER2 blockade.

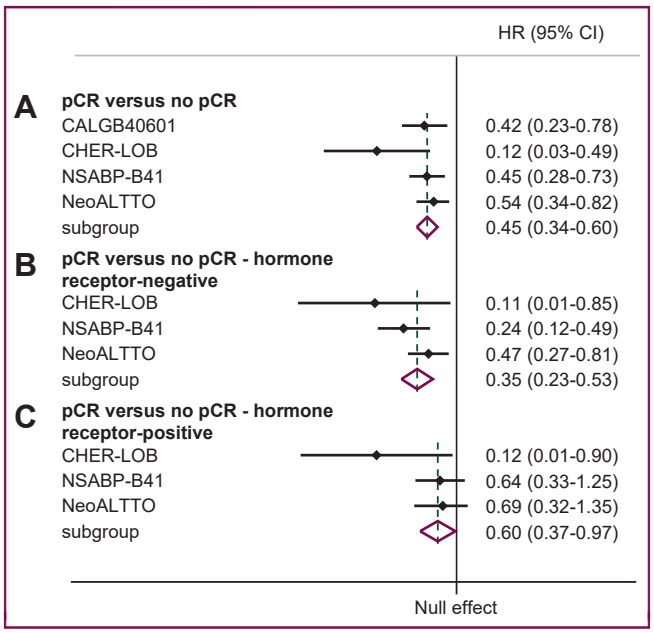

Figure 3. Hazard ratios for recurrence-free survival according to pCR (pCR versus no-pCR).
(A) Overall population. (B) Hormone receptor-negative subgroup. (C) Hormone receptor-positive subgroup.
CI, confidence interval; HR, hazard ratio; pCR, pathologic complete response.

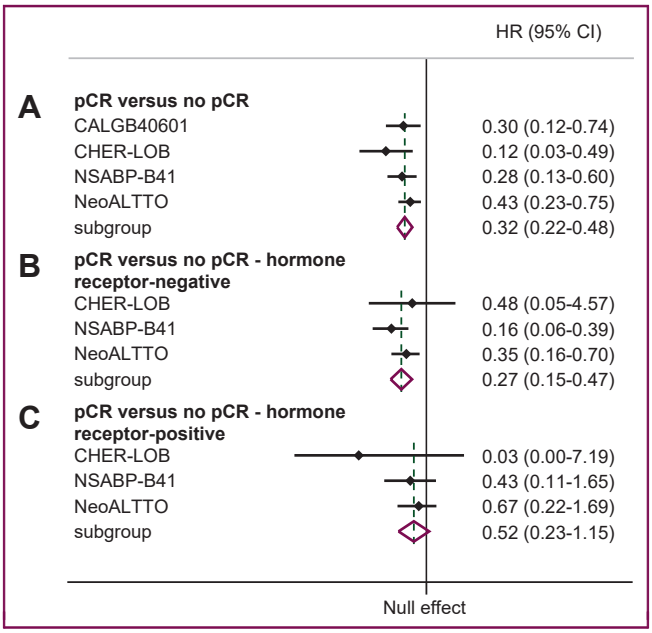

Figure 4. Hazard ratios for overall survival according to pCR (pCR versus no-pCR).
(A) Overall population. (B) Hormone receptor-negative subgroup. (C) Hormone receptor-positive subgroup.
CI, confidence interval; HR, hazard ratio.

Remarkably, when comparing treatment arms, we found dual HER2 targeting with trastuzumab and lapatinib to be associated with significantly improved survival as compared to single HER2 blockade with trastuzumab. In particular, patients receiving the escalated strategy experienced a significant 38% and 35% relative decrease in the risk of recurrence or death, respectively, as compared to those receiving the standard approach with trastuzumab + chemotherapy. We believe that this finding may question the actual lack of positioning of lapatinib for the management of HER2-positive disease in the early setting. The ALTTO trial failed to establish the superiority of dual HER2 blockade with lapatinib + trastuzumab over trastuzumab alone as adjuvant strategy for HER2-positive BC, while raising concerns regarding lapatinib safety profile, mainly in terms of diarrhea.[20] These findings ultimately limited the implementation of lapatinib use in the context of early-stage HER2-positive disease. On the other hand, the APHINITY trial, which evaluated the addition of adjuvant pertuzumab to trastuzumab and chemotherapy, reported a statistically significant improvement in terms of invasive disease-free survival (iDFS) with the escalated approach,[21] thus offering an effective and relatively less toxic escalation alternative to lapatinib, further consolidated by the enhanced pCR rates observed with this dual HER2 blockade approach in the corresponding neoadjuvant NeoSphere trial.[22] However, it should be highlighted that the 3-year and 6-year iDFS absolute differences observed between the placebo and pertuzumab arms in the APHINITY trial were 0.9%[20] and 3%,[23] respectively. Subset analyses revealed higher benefit for node-positive patients, but there is still room for improvement.[22] Despite formally not significant, possibly because of a too ambitious trial design testing four arms, the ALTTO trial reported a 2% 4-year DFS absolute difference between chemotherapy + trastuzumab and lapatinib versus chemotherapy + trastuzumab.[20] Of course, toxicity is an important issue, and the rate of grade 3-4 diarrhea reported in adjuvant and neoadjuvant trials (10%-20%) surely mitigated the enthusiasm for the use of lapatinib in the early setting. However, it should be noted that the improvement of iDFS observed with the adjuvant escalation treatment with neratinib in the ExteNET trial[24] has been considered to outweigh the reported 40% rate of grade 3 diarrhea in the risk—benefit ratio, thus leading to neratinib approval as extended treatment after adjuvant trastuzumab in HER2-positive/hormone receptor-positive BC. Under this scenario, the significant impact in terms of RFS and—remarkably—OS, observed with dual HER2 blockade within the present meta-analysis, deserves a more tight re-thinking of the future positioning of lapatinib in the evolving landscape of HER2-positive BC treatment. Indeed, we demonstrated that the consistent pCR enhancement reported across neoadjuvant trials finally translates into a significant survival benefit. This acquires further relevance considering the current scenario where neoadjuvant pertuzumab is still associated with reimbursement restrictions on a country-specific basis.

Certainly, this meta-analysis presents some limitations. Firstly, this represents a study-level meta-analysis, thus it has not included individual patient data. This approach precluded the possibility to explore heterogeneity in terms of treatment effect across patient-level subgroups, as well as to uniform outcome measures. However, in this specific regard, it should be noted that the long study follow-ups made RFS and event-free survival (EFS) measures broadly comparable, as already discussed earlier, thereby downsizing the impact of this flaw. In addition, survival data extrapolated from the meta-analyzed studies have been obtained after varying median follow-up lengths, and this might have biased the relative contribution of each study to the pooled HR computation. However, it is reasonable to assume that this limitation may have had an impact, if any, more on OS rather than RFS/EFS estimates. Indeed, it should be noted that the shortest median follow-up duration across included trials is 5 years (in the NSABP B41 trial), which is long enough to be considered reliable in terms of capture capacity of RFS/EFS events in HER2-positive BC subtype.

Conclusions

To conclude, besides the established role of lapatinib for HER2-positive advanced BC management,[25] the present meta-analysis demonstrated significant survival benefit of an escalated approach including neoadjuvant dual HER2 blockade with lapatinib and trastuzumab for HER2-positive, high-risk BC patients. Also in view of the maturity of the follow-up of the studies included, our results get the basis for reconsidering the role of lapatinib in the early setting.

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DISCLOSURE

VG reports personal fees from Roche, Novartis, Eli Lilly, MSD, GSK and Gilead, all outside the submitted work. GG reports personal fees from Novartis and Eli Lilly all outside the submitted work. MVD reports personal fees from Lilly, Genomic Health, Novartis and Celgene, all outside the submitted work. PFC reports personal fees from Novartis, Eli Lilly, AstraZeneca, Tesaro, BMS and Roche, all outside the submitted work.All other authors have declared no conflicts of interest.

REFERENCES

1. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384(9938):164-172.
2. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev*. 2012;2012(4):CD006243.

3. Balduzzi S, Mantarro S, Guarneri V, et al. Trastuzumab-containing regimens for metastatic breast cancer. *Cochrane Database Syst Rev*. 2014;2014(6):CD006242.
4. Guarneri V, Frassoldati A, Giovannelli S, Borghi F, Conte P. Primary systemic therapy for operable breast cancer: a review of clinical trials and perspectives. *Cancer Lett*. 2007;248(2):175-185.
5. Giuliano A, Edge SB, Hortobagyi GN. Eighth Edition of the AJCC cancer staging manual: breast cancer. *Breast Oncol*. 2018.
6. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol*. 2005;23(16):3676-3685.
7. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet*. 2010;375(9712):377-384.
8. Guarneri V, Barbieri E, Dieci MV, Piacentini F, Conte P. Anti-HER2 neoadjuvant and adjuvant therapies in HER2 positive breast cancer. *Cancer Treat Rev*. 2010;36(suppl 3):S62-S66.
9. Fernandez-Martinez A, Krop IE, Hillman DW, et al. Survival, pathologic response, and genomics in CALGB 40601 (alliance), a neoadjuvant phase III trial of paclitaxel-trastuzumab with or without lapatinib in HER2-positive breast cancer. *J Clin Oncol*. 2020;38(35):4184-4193.
10. Carey LA, Berry DA, Cirrincione CT, et al. Molecular heterogeneity and response to neoadjuvant human epidermal growth factor receptor 2 targeting in CALGB 40601, a randomized phase III trial of paclitaxel plus trastuzumab with or without lapatinib. *J Clin Oncol*. 2016;34(6):542-549.
11. Robidoux A, Tang G, Rastogi P, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2013;14(12):1183-1192.
12. Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2012;379(9816):633-640.
13. Guarneri V, Frassoldati A, Bottini A, et al. Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHER-LOB study. *J Clin Oncol*. 2012;30(16):1989-1995.
14. Guarneri V, Dieci MV, Griguolo G, et al. Trastuzumab-lapatinib as neoadjuvant therapy for HER2-positive early breast cancer: survival analyses of the CHER-lob trial. *Eur J Cancer*. 2021;153:133-141.
15. Robidoux A, Tang G, Rastogi P, et al. Evaluation of lapatinib as a component of neoadjuvant therapy for HER2+ operable breast cancer: 5-year outcomes of NSABP protocol B-41. *J Clin Oncol*. 2016;34(suppl 15):501.
16. de Azambuja E, Holmes AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol*. 2014;15(10):1137-1146.
17. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
18. Pathological complete response in neoadjuvant treatment of high-risk early-stage breast cancer: use as an endpoint to support accelerated approval guidance for industry. U.S: Department of Health and Human Services Food and Drug Administration Oncology Center of Excellence Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER); 2020.
19. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol*. 2016;17(6):791-800.
20. Piccart-Gebhart M, Holmes E, Baselga J, et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. *J Clin Oncol*. 2016;34(10):1034-1042.
21. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377(2):122-131.
22. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(1):25-32.
23. Piccart M, Procter M, Fumagalli D, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer in the APHINITY trial: 6 years' follow-up. *J Clin Oncol*. 2021;39(13):1448-1457.
24. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2016;17(3):367-377.
25. Guarneri V. Lapatinib plus letrozole for postmenopausal patients with advanced HER2(+)/HR(+) breast cancer. *Expert Rev Anticancer Ther*. 2009;9(11):1549-1557.