



Adding pertuzumab to adjuvant therapy for high-risk HER2-positive early breast cancer in APHINITY: a GRADE analysis

Alberto Zambelli^{*1}, Giovanni Pappagallo² & Paolo Marchetti^{3,4}

¹Oncology Unit, ASST Papa Giovanni XXIII, 24127 Bergamo, Italy

²Epidemiology & Clinical Trials Office, General Hospital, 30035 Mirano VE, Italy

³Department of Clinical & Molecular Medicine, Sant'Andrea Hospital, Sapienza University of Rome, 00189 Rome, Italy

⁴Istituto Dermopatico dell'Immacolata, IDI-IRCCS, 00167 Rome, Italy

*Author for correspondence: alberto.zambelli@asst-pg23.it

Aim: Adding pertuzumab to standard trastuzumab-based adjuvant therapy significantly improved invasive disease-free survival (IDFS) in the APHINITY trial. However, the magnitude of benefit was marginal in the overall population. **Methods:** We used GRADE (Grading of Recommendations Assessment, Development and Evaluation) analysis on data from APHINITY to build summary-of-findings tables to evaluate the efficacy, safety and quality of evidence of predefined clinical outcomes for the addition of pertuzumab to trastuzumab-based adjuvant therapy in patients with high-risk HER2-positive early breast cancer. **Results:** Pertuzumab significantly improved 3-year, event-free, absolute benefit in disease-free survival, IDFS and distant relapse-free interval (DFRI) in patients with node-positive or hormone receptor-negative disease. The analysis provides strength of evidence supporting the addition of pertuzumab in this patient population.

First draft submitted: 12 November 2019; Accepted for publication: 20 January 2020; Published online: 14 February 2020

Keywords: APHINITY trial • breast cancer • GRADE • HER2-positive • pertuzumab

The advent of anti-HER2 therapies has dramatically improved the prognosis of patients with HER2-positive early breast cancer (eBC) [1]. One year of adjuvant trastuzumab added to chemotherapy is the current standard of care. In a meta-analysis of pivotal trials, adding trastuzumab to chemotherapy resulted in 40 and 34% reduction in the relative risk of relapse and death, respectively [2]. Notwithstanding the positive results, the proportion of patients with HER2-positive eBC who still relapse and eventually die is not negligible, despite having received optimal treatment.

A recent update of the HERA (HERceptin Adjuvant) trial showed a 10-year disease-free survival (DFS) of 69% in patients treated with 1 year of trastuzumab, with distant recurrences in 18% [3].

In the joint analysis of two pivotal adjuvant trials – NCCTG (North Central Cancer Treatment Group) N9831 (Alliance) and NSABP (National Surgical Adjuvant Breast and Bowel Project) B-31 (NRG) – the patients treated with trastuzumab experienced a 10-year cumulative hazard of relapse (or death) of 29 and 24%, respectively, in patients with HR-negative and HR-positive tumors, with an increasing risk associated with the extent of lymph node (LN) involvement [4].

In the trastuzumab arms of the BCIRG-006 (Breast Cancer International Research Group 006) trial, 25% of patients eventually developed a 10-year DFS event (30% in case of LN+ disease) [5]. Moreover, it has been observed that pathological primary tumor size, LN involvement, and hormone receptor status have the greatest independent effect on recurrence risk [6].

From the above, the need for more effective therapies to improve the clinical outcomes of patients at high risk of relapse appears to be clear.

In this scenario, the Phase III APHINITY trial (Adjuvant Pertuzumab and Herceptin in Initial Therapy in Breast Cancer; NCT01358877) [7] was a very large (n = 4804), randomized, placebo-controlled trial of 1 year of adjuvant pertuzumab added to standard adjuvant chemotherapy plus trastuzumab in patients with HER2-positive eBC. In

the intent-to-treat population, invasive disease-free survival (IDFS) was significantly improved by the addition of pertuzumab to adjuvant chemotherapy and trastuzumab, with estimated 3-year IDFS rates of 94.1 versus 93.2% for pertuzumab versus placebo (hazard ratio [HR]: 0.81; 95% CI: 0.66–1.00). However, although this result met statistical significance, the magnitude of the benefit is arguably clinically marginal in the overall population. Indeed, based upon the predefined stratification (nodal status, adjuvant chemotherapy regimen, hormone-receptor status, geographic region and protocol version), the treatment effect was most detectable among patients who were at higher risk for relapse because of LN involvement (LN+) or HR negativity (HR-). These findings highlighted a selected setting of patients with a greater benefit from the treatment escalation. In line with these results, the recent update of the American Society of Clinical Oncology guidelines [8] and the St Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer [9] recommends the incorporation of pertuzumab in that setting of patients. Accordingly, the EMA approved the use of pertuzumab in combination with trastuzumab/chemotherapy as adjuvant treatment for LN+ or HR- high-risk HER2 eBC patients.

To support physicians in their clinical practice, we conducted a GRADE (Grading of Recommendations Assessment, Development and Evaluation) [10] methodology analysis on APHINITY to ascertain the strength of the emerging recommendations for the treatment of high-risk HER2-positive eBC.

Methods

The GRADE analysis was conducted on the available data from the APHINITY study, concerning the addition of pertuzumab to the standard adjuvant treatment, consisting of trastuzumab plus chemotherapy, in high-risk HER2-positive eBC [7]. According to the approved indication of the EMA, patients with high-risk HER2-positive eBC were identified based on nodes involvement (LN+) or hormone receptor negativity (HR-).

The GRADE method was applied [10], using the GRADEpro Guideline Development Tool (GRADEpro GDT) [11], to build summary-of-findings tables for the evaluation of effects (both efficacy and safety) and quality of evidence of selected clinical outcomes.

Ranking outcomes by their relative importance (critical vs important or noncritical) can help focus on those parameters that are considered most clinically important and help to resolve or clarify disagreements. As required by GRADE analysis, ‘critical’ outcomes will be the primary factors influencing the closing remarks of this paper and will be used to determine the overall quality of evidence supporting the remarks.

An expert panel of medical oncologists and Health Technology Assessment experts involved in the management of breast cancer was in charge for the determination of the relative importance (critical vs important) [12] of both outcomes of benefit and outcomes of harm. Thus, outcomes were ranked as follows:

- DFS, IDFS, DFRI and overall survival were ‘critical’ outcomes of benefit;
- Any adverse event leading to permanent discontinuation of treatment, any adverse event of grade ≥ 3 (according to Common Toxicity Criteria [CTC]-AE v.4.0), diarrhea of grade ≥ 3 (according to CTC-AE v.4.0), primary cardiac events (heart failure of New York Heart Association [NYHA] class III or IV and a substantial decrease in left ventricular ejection fraction, defined as a decrease of at least 10 percentage points from baseline and to below 50%, or cardiac death) were critical outcomes of harm;
- IDFS including second primary nonbreast cancer, per the STEEP [13] definition (IDFS-SPNBC), relapse-free interval (RFI), health-related quality of life, secondary cardiac events (asymptomatic or mildly symptomatic – NYHA class II – substantial decrease in left ventricular ejection fraction, as assessed by multigated acquisition scanning or echocardiography, confirmed by a second left ventricular ejection fraction assessment conducted within approximately 3 weeks also showing a substantial decrease or as confirmed by the cardiac advisory board), neutropenia of grade ≥ 3 (according to CTC-AE v.4.0) and anemia of grade ≥ 3 (according to CTC-AE v.4.0) were considered as important (noncritical) outcomes.

In the GRADE system, the quality of evidence reflects the extent to which a panel’s confidence in an estimate of the effect is adequate to support a particular treatment proposal. The system classifies quality of evidence as high, moderate, low, or very low according to factors that include risk of bias (selection, performance, detection, attrition, reporting), inconsistency (inhomogeneity of effects between studies in a meta-analysis), precision (i.e., wide 95% confidence limits) and directness (applicability of evidence to the clinical question) [10]. GRADE’s conceptualization includes a focus on outcome specificity (i.e., not the individual study but rather the individual outcome), and quality can differ across outcomes in individual trials or a series of trials. As suggested by the GRADE Working Group [14],

Table 1. Relative and (anticipated) absolute effects of the addition of pertuzumab (vs. placebo) to chemotherapy plus trastuzumab. Critical outcomes of benefit.

Outcome		Relative effect HR (95% CI)	Anticipated absolute effect events/100 subjects (95% CI)
LN+	DFS	0.77 (0.62–0.95)	3 fewer (5 fewer to 1 fewer)
	IDFS	0.77 (0.62–0.96)	3 fewer (4 fewer to 0 fewer)
	DRFI	0.79 (0.61–1.02)	2 fewer (3 fewer to 0 fewer)
	OS	0.85 (0.61–1.18)	1 fewer (2 fewer to 1 more)
HR-	DFS	0.80 (0.60–1.07)	3 fewer (5 fewer to 1 fewer)
	IDFS	0.76 (0.56–1.04)	3 fewer (4 fewer to 0 fewer)
	DRFI	0.72 (0.49–1.04)	2 fewer (3 fewer to 0 fewer)
	OS	0.85 (0.62–1.41)	1 fewer (2 fewer to 1 more)

DFS: Disease-free survival; DRFI: Distant relapse-free interval; HR: Hazard ratio; HR-: Negativity for estrogen and progesterone receptors; IDFS: Invasive disease-free survival; LN+: Node-positive disease; OS: Overall survival.

Table 2. Relative and (anticipated) absolute effects of the addition of pertuzumab (vs. placebo) to chemotherapy plus trastuzumab. Critical outcomes of harm.

Outcome	Relative effect RR (95% CI)	Anticipated absolute effect events/100 subjects (95% CI)
Any adverse event leading to permanent discontinuation of treatment	1.12 (1.07–1.17)	7 more (4 more to 10 more)
Any adverse event of grade [†] ≥3	1.21 (0.98–1.51)	1 more (0 fewer to 3 more)
Diarrhea of grade [†] ≥3	2.62 (2.07–3.22)	6 more (4 more to 8 more)
Primary cardiac events [‡]	2.16 (0.93–5.00)	0 more (0 fewer to 1 more)

[†] Common Toxicity Criteria (CTC)-AE v.4.0.
[‡] Heart failure of New York Heart Association class III or IV and a substantial decrease in left ventricular ejection fraction, defined as a decrease of at least 10 percentage points from baseline and to below 50%, or cardiac death.
RR: Risk ratio.

the lowest quality of evidence for any of the outcomes that are critical to making a decision should provide the basis for rating the overall quality of evidence.

Results

In the trial population [7], 63% of the patients who were randomly assigned to receive pertuzumab (2400 patients) or placebo (2405 patients) had LN+ disease, and 36% had HR- disease. One year of treatment was completed by 84.5% of the patients in the pertuzumab group and 87.4% of the patients in the placebo group. Treatment was discontinued for safety reasons by 7.8% of the patients in the pertuzumab group and 6.4% of the patients in the placebo group. The median follow-up period in the intention-to-treat population was 45.4 months.

Relative and (anticipated) absolute effects of the addition of pertuzumab (vs placebo) to chemotherapy plus trastuzumab are presented in [Tables 1](#) (critical outcomes of benefit) and [2](#) (critical outcomes of harm).

Efficacy

In APHINITY [7], the addition of pertuzumab resulted in a >20% relative improvement in all relapse-related end points, with an absolute benefit of approximately 3 relapse-events fewer/100 patients treated ([Table 1](#)). Thus, pertuzumab was found to be associated with a significantly better 3-year, event-free, landmark benefit (defined as difference in Kaplan–Meier estimates at time [t]) in DFS (2.1% for LN+; 1.4% for HR-), IDFS (1.8% for LN+; 1.6% for HR-) and DFRI (1.2% for LN+; 1.5% for HR-) compared with placebo.

There was no significant treatment effect with regard to mortality at the first interim overall survival analysis, when only 26% (169 deaths) of the expected events had been observed. Nonetheless, a point estimate of 0.85 (relative benefit) and an anticipated absolute benefit of 1 death event fewer/100 patients treated were observed ([Table 1](#)). The final (event-driven) overall survival analysis is planned to be conducted when 640 deaths have occurred.

A >20% relative improvement in IDFS-SPNBC and RFI was also observed, with comparable European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 Global Health Status scores between treatment groups, in both LN+ and HR- populations (Supplementary Tables 4 & 5).

More detailed information is available in Supplementary Tables 1–3, together with complete efficacy and safety data concerning important (noncritical) outcomes (Supplementary Tables 4–6).

Safety

The safety analysis population included 2364 patients who were treated with at least one dose of pertuzumab and 2405 patients who received study medication (including chemotherapy or trastuzumab) but no pertuzumab (placebo group) [7]. The rate of treatment discontinuation due to adverse events was 1.4 percentage points higher with pertuzumab than with placebo, with 7 discontinuation events more/100 patients treated (Table 2). A 6.9% absolute difference (64.2% in the pertuzumab group and 57.3% in the placebo group) in any adverse event of grade ≥ 3 was also observed, with a 21% relative increase in the pertuzumab group; however, resulting in only 1 event more/100 patients (Table 2). Among grade ≥ 3 toxicities, the largest absolute difference between the treatment groups was found for diarrhea (9.8% in the pertuzumab group and 3.7% in the placebo group – 6 events more/100 patients; Table 2), a 2.9% absolute increase was observed in anemia, while no difference was found for neutropenia. Primary cardiac events were uncommon, occurring in 17 patients (0.7%) in the pertuzumab group and in 8 patients (0.3%) in the placebo group. Secondary cardiac events were also uncommon, and of similar magnitude in both treatment groups (Supplementary Table 6).

Quality of evidence

Supplementary Tables 1–6 present (in a summary-of-findings format) the assessment of the quality (certainty) of the evidence for each outcome considered.

The APHINITY trial was a randomized, double-blind, well-conducted study; stratification included both LN status and hormone receptor status; thus, no serious risk of bias (selection, performance, detection and attrition) [12] was evident at this analysis.

In selected cases (see footnotes of Supplementary Tables 1–6), a downgrade for imprecision was decided when a wide 95% CI of an anticipated absolute effect [12] was consistent with opposite clinical recommendations.

Regarding the directness of evidence, a formal downgrade was decided because safety information was not stratified per LN status and hormone receptor status.

When the quality of evidence differs across outcomes, the GRADE system demands that the lowest grade of quality of available evidence for any of the outcomes deemed critical determines the overall quality of evidence [14]. Thus, as can be seen in Supplementary Tables 1–3, the overall quality of evidence for this analysis is ‘moderate’.

Discussion

HER2-positive eBC patients relapsing despite receiving standard adjuvant treatment still represent an unmet medical need. According to the 10-years update of the 4 pivotal trials, at least 1 patient out of 4, treated with optimal chemotherapy plus 1 year of trastuzumab, eventually experiences a breast cancer recurrence. There is an increasing need to risk stratify HER2+ eBC and to optimize HER2-directed therapy, possibly considering treatment-escalation to improve the long-term cure rates in high-risk patients. This is the main goal obtained by APHINITY, in which the addition of pertuzumab to the optimal adjuvant therapy demonstrated an overall advantage in IDFS, with magnified effect in the subgroups of high-risk eBC because of nodes involvement (LN+) or HR negativity (HR-). The extensive clinical routine use of pertuzumab in the adjuvant setting remains a matter of debate. One of the reasons lies with the questionable ability to translate, at the individual level, the finite advantage of pertuzumab, as observed in the study population of the APHINITY trial [15].

In fact, the positive results of the study have been perceived to be of only moderate success mainly because the expectations regarding the effect of pertuzumab in the adjuvant setting were so high. The survival results observed in the APHINITY study had already been predicted in the neoadjuvant models [16,17]. In particular, the HR of 0.81 (95% CI: 0.66–1.00; $p = 0.045$) for disease recurrence reported in the APHINITY study, represents exactly what could have been anticipated, based on the rate of pathological complete response in the neoadjuvant models [18]. In this scenario, the high expectations of the oncology community regarding the role of pertuzumab in the adjuvant setting should have been at least aligned with the actual predictions and ultimately recalibrated. Actually, the APHINITY study has shown a long-term survival benefit, in line with the expectation provided by neoadjuvant models, especially in the subgroups of patients at higher risk of relapse, where the relative-risk reduction rate magnifies the absolute benefit of the escalating treatment.

The opportunity of a targeted escalation of the anti-HER2 treatment has been recently highlighted by the positive results of the KATHERINE study, that clearly demonstrated that trastuzumab cannot any longer be regarded as the single optimal adjuvant treatment in all cases of HER2+ eBC [19]. Moreover, the positive results of the EXTEnet study, conducted in women who had completed standard trastuzumab-based adjuvant treatment, further support the possibility for improvement in selected cases of HER2+ eBC [20].

In the APHINITY study, the subgroups of patients at higher risk of relapse because of LN+ or HR- achieved the largest treatment effect of pertuzumab. This *post hoc*, subgroup analyses should be interpreted with caution [21,22], even if LN and HR status were stratification factors.

Accordingly, the overall result was evident in the whole study population, mainly driven by the subgroups of LN+ and/or HR- patients, as expected. Indeed, after a median follow-up duration of 45.4 months, the proportion of IDFS events for patients with LN+ disease was 9.2% (n = 139) and 12.1% (n = 181) in the pertuzumab and placebo arms, respectively (HR: 0.77; 95% CI: 0.62–0.96), with an absolute benefit of 2.9%. Moreover, the proportion of IDFS events in patients with HR- disease was 8.2% (n = 71) and 10.6% (n = 91) in the pertuzumab and placebo arms, respectively (HR: 0.76; 95% CI: 0.56–1.04), with an absolute benefit of 2.4% [23]. The general safety profile of treatments was acceptable with a slight increase (6.9%) of any reported grade 3 adverse events (particularly diarrhea) in the pertuzumab arm, compared with placebo. Heart failure, cardiac death and cardiac dysfunction were infrequent in both the treatment groups.

The number needed to treat (NNT) is the reciprocal of the absolute benefit and, in the present case, represents the number of patients needed to be treated with pertuzumab to prevent one additional IDFS event over the benefit provided by standard therapy. The NNT for pertuzumab was 33 for both LN+ and HR- patients. The magnitudes of these NNTs are of the same order to that observed for the use of aromatase inhibitors instead of tamoxifen, with an NNT of 33 (calculated on the overall number of observed events) for anastrozole–letrozole to avoid 1 additional DFS event in the postmenopausal adjuvant setting, for a median follow-up of 69.6 months [24]. Similarly, for the addition of taxanes to anthracycline-based adjuvant chemotherapy, the NNT to avoid 1 additional DFS was 25, for a median follow-up of 59 months [25]. Thus, according to our analysis, the addition of pertuzumab in high-risk LN+ and/or HR- patients has been shown to provide magnitudes of DFS benefit similar to those practice-changing modern adjuvant therapies, aromatase inhibitors and taxanes.

Conclusion

The application of the GRADE methodology to prespecified subgroups in the APHINITY study provided the magnitude of the effects and the quality of evidences about the benefit and the safety profile of the addition of pertuzumab to the standard trastuzumab-based adjuvant treatment. Patients are best served when treatment recommendations are supported by the strength of evidence, and the GRADE analysis we performed can support the therapeutic decisions in daily clinical practice in HER2 eBC patients at higher risk of recurrence because of LN+ or HR-.

Future perspective

Considering the results of observational studies that confirm the results from clinical studies on its effectiveness in early stage HER2-positive breast cancer patients, it can be expected that the use of adjuvant trastuzumab will continue to increase in clinical practice. The addition of pertuzumab to standard trastuzumab-based adjuvant therapy for early HER2-positive breast cancer has provided a clinically meaningful benefit in terms of invasive disease-free, event-free, distant relapse-free survival in patients at high risk of recurrence because of nodes involvement of hormone receptor negativity. However, questions remaining to be answered include the optimal duration of adjuvant pertuzumab, and whether additional benefit in the early setting will be gained by combining trastuzumab and pertuzumab HER2 blockade with immunotherapy agents designed to further engage the immune system against the tumor block. A challenge for investigating combination treatments with immunotherapy is the sheer number of potential combinations, which will require critical selection of appropriate breast cancer patients who can be expected to benefit most. In this regard, the identification of additional predictive biomarkers of response for specific therapeutic approaches is ongoing. As breast cancer biology and resistance mechanisms become better understood, research will continue, or be initiated, into expanding current adjuvant therapy in early HER2-positive breast cancer by adding PI3K/Akt/mTOR inhibitors, anti-PD(L)1 antibodies, or CDK4/6 inhibitors, as well as endocrine therapy and new anti-HER2 agents. It can be expected that trastuzumab–pertuzumab adjuvant therapy

in combination with different agents will be studied in this setting to further improve clinical outcomes and quality of life, while avoiding unnecessary treatment and toxicity.

Summary points

- Anti-HER2 therapies have dramatically improved the prognosis of patients with HER2-positive early breast cancer.
- However, some patients still relapse despite receiving optimal treatment.
- In the large Phase III APHINITY trial, the addition of 1 year of adjuvant pertuzumab to standard trastuzumab-based adjuvant therapy significantly improved invasive disease-free survival (IDFS), although the magnitude of benefit was arguably marginal in the overall patient population.
- GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology provides a framework for evaluating the effects (both efficacy and safety) and quality of evidence of selected clinical outcomes in clinical trials.
- We used the GRADE approach on data from APHINITY to build summary-of-findings tables to evaluate the efficacy and safety effects and quality of evidence of predefined clinical outcomes for the addition of pertuzumab to trastuzumab-based adjuvant therapy in patients with high-risk HER2-positive early breast cancer.
- The addition of pertuzumab was associated with a clinically significant better 3-year, event-free, absolute benefit in disease-free survival, IDFS and distant relapse-free interval in patients with node-positive or hormone receptor-negative disease.
- There was a >20% relative improvement in all relapse-related end points, with an absolute benefit of approximately 3 relapse-events fewer/100 patients treated.
- Although data from APHINITY are not yet mature, there were indications of an absolute benefit in mortality, compared with placebo (standard adjuvant chemotherapy plus trastuzumab), which should be confirmed when the overall survival analysis is conducted.
- The overall quality of evidence for this GRADE analysis is 'moderate'.
- A good safety profile was confirmed.
- The application of the GRADE methodology to the APHINITY study provides a strength of evidence in support of the addition of pertuzumab in the adjuvant treatment of HER2-positive early breast cancer patients at higher risk of recurrence because of nodes involvement or hormone receptor-negativity.
- These data can be useful to guide therapeutic decisions in daily clinical practice.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2019-0168

Author contributions

Concept and design of the analysis and drafting of manuscript were done by G Pappagallo and A Zambelli. Critical revision of the manuscript was done by all the authors. Final approval of the manuscript was given by all the authors.

Acknowledgments

The authors thank Ray Hill, an independent medical writer, who provided medical writing support on behalf of Health Publishing & Services Srl. This assistance was supported by Roche SpA Italy.

Financial & competing interests disclosure

The GRADE analysis was made possible by an educational grant from Roche S.p.A. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Presented in part at the ISPOR Europe 2019 meeting, Copenhagen, Denmark, 2–6 November 2019.

Medical writing support from Ray Hill, on behalf of Health Publishing & Services Srl.

Ethical conduct of research

As the study involved analysis of anonymized published data from a clinical trial, no institutional review board approval was required.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

1. Cossetti RJ, Tyldesley SK, Speers CH, Zheng Y, Gelmon KA. Comparison of breast cancer recurrence and outcome patterns between patients treated from 1986 to 1992 and from 2004 to 2008. *J. Clin. Oncol.* 33(1), 65–73 (2015).
- **Interesting paper illustrating the changing patterns over time of relapse according to estrogen receptor and HER2 status.**
2. Moja L, Tagliabue L, Balduzzi S *et al.* Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst. Rev.* (4), CD006243 (2012).
3. Cameron D, Piccart-Gebhart MJ, Gelber RD *et al.* 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 389(10075), 1195–1205 (2017).
- **Updated data from the pivotal randomized trial that led to the first approval for a HER2-targeted therapy.**
4. Perez EA, Romond EH, Suman VJ *et al.* 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. *J. Clin. Oncol.* 32(33), 3744–3752 (2014).
5. Slamon D, Eiermann W, Robert N, Giermek J, Martin M, Jasnowska M. Ten-year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab with docetaxel, carboplatin and trastuzumab in HER2-positive early breast cancer patients [Abstract S5-04]. Presented at *San Antonio Breast Cancer Symposium December 11*. TX, USA, 76(suppl. 4), S5–04 (2016).
6. Dall P, Koch T, Gohler T *et al.* Trastuzumab in human epidermal growth factor receptor 2-positive early breast cancer: results of a prospective, noninterventional study on routine treatment between 2006 and 2012 in Germany. *Oncologist* 22(2), 131–138 (2017).
7. Von Minckwitz G, Procter M, De Azambuja E *et al.* Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N. Engl. J. Med.* 377(2), 122–131 (2017).
- **The sole trial of the addition of pertuzumab to trastuzumab in the adjuvant setting in early HER2-positive breast cancer. The focus of the GRADE analysis carried out in this paper.**
8. Denduluri N, Chavez-Macgregor M, Telli ML *et al.* Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO Clinical Practice Guideline Focused Update. *J. Clin. Oncol.* 36(23), 2433–2443 (2018).
- **Current clinical practice guidelines detailing recommendations for the use of pertuzumab in early breast cancer.**
9. Curigliano G, Burstein HJ, Winer EP *et al.* De-escalating and escalating treatments for early-stage breast cancer: The St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann. Oncol.* 28(8), 1700–1712 (2017).
- **Current clinical practice guidelines detailing recommendations for the use of pertuzumab in early breast cancer.**
10. Guyatt GH, Oxman AD, Vist GE *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 336(7650), 924–926 (2008).
11. GRADEpro GDT. *GRADEpro Guideline Development Tool* (2018). <http://gdt.gradepro.org>
- **Methodology of the GRADE method for ranking the effects and quality of evidence for clinical outcomes.**
12. Guyatt GH, Oxman AD, Kunz R *et al.* GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J. Clin. Epidemiol.* 64(4), 395–400 (2011).
13. Hudis CA, Barlow WE, Costantino JP *et al.* Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: The STEEP system. *J. Clin. Oncol.* 25(15), 2127–2132 (2007).
14. Brozek JL, Akl EA, Alonso-Coello P *et al.* Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy* 64(5), 669–677 (2009).
15. Miller KD. Questioning our APHINITY for More. *N. Engl. J. Med.* 377(2), 186–187 (2017).
- **Interesting editorial discussing the challenges of translating, at the individual level, the finite advantage of pertuzumab in the setting.**
16. 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 II trial. *Lancet Oncol.* 13(1), 25–32 (2012).
- **A Phase II randomized trial that provides the first evidence for the benefit of pertuzumab in early HER2-positive breast cancer. Further trials in the same setting followed to investigate strategies to improve pathological responses with pertuzumab.**
17. Cortazar P, Zhang L, Untch M *et al.* Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. *Lancet* 384(9938), 164–172 (2014).
18. Broglio KR, Quintana M, Foster M *et al.* Association of pathologic complete response to neoadjuvant therapy in HER2-positive breast cancer with long-term outcomes: a meta-analysis. *JAMA Oncol.* 2(6), 751–760 (2016).
19. Von Minckwitz G, Huang CS, Mano MS *et al.* Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N. Engl. J. Med.* 380(7), 617–628 (2019).

20. Martin M, Holmes FA, Ejlertsen B *et al.* Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, Phase III trial. *Lancet Oncol.* 18(12), 1688–1700 (2017).
21. Lagakos SW. The challenge of subgroup analyses – reporting without distorting. *N. Engl. J. Med.* 354(16), 1667–1669 (2006).
22. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine – reporting of subgroup analyses in clinical trials. *N. Engl. J. Med.* 357(21), 2189–2194 (2007).
23. Howie LJ, Scher NS, Amiri-Kordestani L *et al.* FDA approval summary: pertuzumab for adjuvant treatment of HER2-positive early breast cancer. *Clin. Cancer Res.* 25(10), 2949–2955 (2018).
24. Dowsett M, Cuzick J, Ingle J *et al.* Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J. Clin. Oncol.* 28(3), 509–518 (2010).
25. De Laurentiis M, Cancelli G, D’Agostino D *et al.* Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. *J. Clin. Oncol.* 26(1), 44–53 (2008).