

## Dual inhibition of HER2 in breast cancer treatment



In *The Lancet*, José Baselga and colleagues<sup>1</sup> present results from the phase 3 NeoALLTO trial, a pivotal investigation of dual anti-HER2 therapy for neoadjuvant treatment of breast cancer. The investigators used a straightforward approach to assess whether combination treatment with the antibody trastuzumab and the tyrosine kinase inhibitor lapatinib was better than single-agent treatment. 455 women were randomised to treatment with trastuzumab, lapatinib, or both drugs combined for 6 weeks, followed by addition of paclitaxel for 12 weeks and subsequent surgery. In terms of the primary endpoint, pathological complete response (pCR) at the time of surgery, dual blockade was significantly more efficacious (51.3% [95% CI 43.1–59.5]) than was lapatinib (24.7% [18.1–32.3]) or trastuzumab (29.5% [22.4–37.5]) alone. Because targeting of HER2 and molecules important in downstream signalling is a paradigm for targeted anticancer therapy, NeoALLTO is a model for future research and clinical trial design.

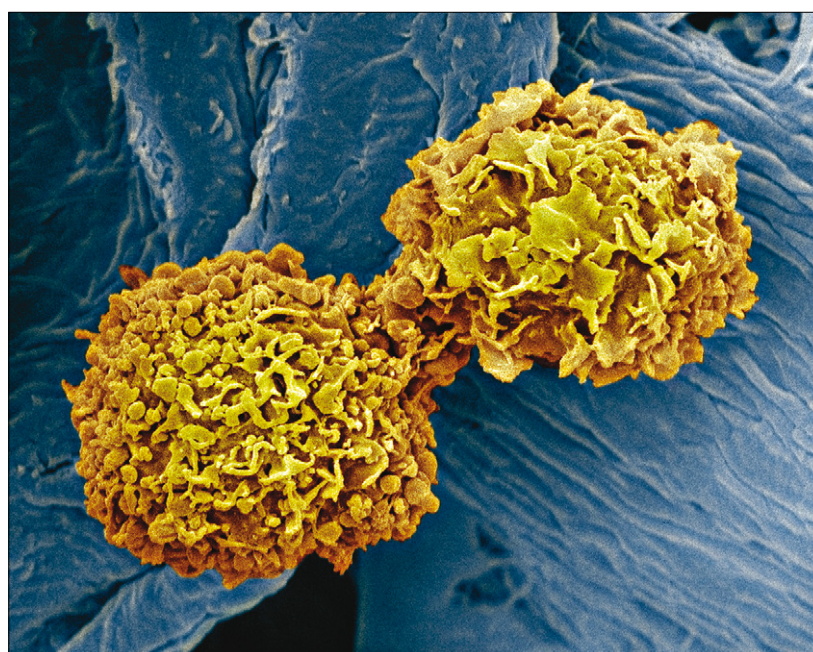
A crucial scientific strength of NeoALLTO is the study's design. During the initial 6 week biological window, targeted anti-HER2 treatment was given without chemotherapy, enabling collection of samples for translational research, and early tumour response to be assessed without confounding by cytotoxic therapy. Such approaches should be used more often in pivotal trials of new drugs that target specific biological pathways, to enable unbiased efficacy assessments to be made. Equally important, such trials could help to identify clinically useful markers of early response, with the ultimate goal of tailoring neoadjuvant treatments for individual patients.

In NeoALLTO,<sup>1</sup> after 6 weeks the dual treatment strategy already had higher efficacy (tumour response rate 67%) than did treatment with lapatinib (53%) or trastuzumab (30%) alone. Differences in early tumour response had diminished by the time of surgery, however, potentially because of the addition of taxane or continuation of treatment. Factors such as optimum assessment timepoints and different mechanisms of action (eg, antibodies or tyrosine kinase inhibitors) are important to bear in mind, and careful consideration will be needed as to whether the best predictor of clinical outcomes is early or definite response, pCR, residual cancer burden, or all these together in a combined algorithm.

The ultimate aim of breast cancer treatment is to save lives, not just to achieve responses to treatment. With targeted therapies being used in pathway-orientated trials such as NeoALLTO, what matters most in early response assessment needs to be established with respect to prediction of long-term survival under adjuvant treatment. The randomised postsurgery phase of NeoALLTO in progress could inform that issue in the future. Whether additional biomarkers other than HER2 could be helpful in identification of how much specific patients benefit from one treatment remains to be established; the conceptually related NeoSphere trial<sup>2</sup> did not resolve this question.

In NeoALLTO, the 12 week duration of targeted treatment combined with paclitaxel was short compared with other trials of neoadjuvant treatment involving one or two targeted agents in HER2-overexpressing primary breast cancer. In the NOAH,<sup>3</sup> GEICAM 2006-14,<sup>4</sup> CHERLOB,<sup>5</sup> and GeparQuinto trials,<sup>6</sup> and in the investigation by Holmes and colleagues,<sup>7</sup> at least 24 weeks of preoperative combination therapy were used. The short duration of targeted treatment in NeoALLTO apparently did not compromise efficacy. For biological therapies, this finding suggests a qualitative rather than quantitative mechanism of action—ie, drugs that interfere with pathways that control cancer cell replication duly prevent

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Dividing breast cancer cells

tumour cell growth and survival. Therefore, tremendous possibilities for clinical use might exist, and there is a clear difference from cytotoxic therapy in which long treatment duration is usually most effective.<sup>8</sup>

A 12 week treatment duration was also used in NeoSphere,<sup>9</sup> a randomised phase 2 trial of neoadjuvant trastuzumab, docetaxel, pertuzumab (another HER2-directed antibody interfering with receptor dimerisation), and combination therapy. As in NeoALLTO,<sup>1</sup> the dual-targeted strategy combined with a taxane resulted in a significantly higher pCR rate than did either antibody alone. These results are in agreement with findings in advanced breast cancer.<sup>10</sup> NeoSphere also yielded a pCR rate of 16.8% (95% CI 10.3–25.3) when the two antibodies were combined without chemotherapy, suggesting a potential role of treatment that does not include chemotherapy for HER2-positive breast cancer, an option which was not assessed in NeoALLTO.

The development of biological therapies for breast cancer will have to be viewed in the context of treatments for all stages of the disease. On the basis of neoadjuvant trials such as NeoALLTO,<sup>1</sup> the traditional sequence of drug testing (first in advanced disease, then neoadjuvant, then adjuvant settings) could be revised, both from a scientific and a regulatory perspective. In the future, assessment of a pathway-directed therapeutic intervention in rigorous neoadjuvant trials might be sufficient for validity in a biomarker-defined population of patients to be accepted. Trials in the neoadjuvant setting based on research-based hypotheses (after establishment of drug safety) could lead to a saving of enormous sums in drug development costs, and promising new drugs for treatment of early breast cancer could become available much more quickly than at present.

For the present generation of anti-HER2 drugs, such a resource-saving concept is not yet accepted. The adjuvant combination of lapatinib and trastuzumab is being tested in the ALLTO trial (NCT00490139), which has already finished recruitment. The addition of pertuzumab to trastuzumab will be assessed in the adjuvant APHINITY trial (NCT01358877). Neoadjuvant findings can predict outcomes in adjuvant trials; indeed, results from NeoALLTO<sup>1</sup> and the GeparQuinto trial (in which lapatinib was not as successful as trastuzumab)<sup>6,10</sup> anticipated a modification of ALLTO. The lapatinib group was closed in the adjuvant ALLTO trial after a

recommendation based on futility from the independent data monitoring committee.<sup>11</sup>

The optimum duration of targeted therapies remains unclear. In most trials, overall treatment duration is 1 year,<sup>12</sup> but this arbitrary period has been challenged.<sup>13</sup> Although undertreatment or withholding of potential benefits should be avoided, clinicians also have the obligation to avoid overtreatment, not only with traditional chemotherapy,<sup>14</sup> but also with costly targeted therapies. Therefore, questions about duration of treatment and possible differential efficacy in biomarker-selected patient subcohorts need to be incorporated into clinical trials of targeted therapies.<sup>15</sup> Standard-defining trials should not be left to drug manufacturers, with their economic incentive towards protracted treatment durations, alone; such trials are best governed by collaborative academic groups and should be accompanied by translational research enterprises.

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- 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; published online Jan 17. DOI:10.1016/S0140-6736(11)61847-3.
- Gianni L, Bianchini G, Kiermaier A, et al. Neoadjuvant pertuzumab (P) and trastuzumab (H): biomarker analyses of a 4-arm randomized phase II study (NeoSphere) in patients (pts) with HER2-positive breast cancer (BC). San Antonio Breast Cancer Symposium; San Antonio, TX, USA; Dec 6–10, 2011. S5–1.
- 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**: 377–84.
- Alba E, Albanell J, de la Haba J, et al. Lapatinib vs trastuzumab in combination with standard EC-D chemotherapy in the neoadjuvant treatment of HER2+ patients: results from the GEICAM 2006-14 phase II randomized trial. *Cancer Res* 2011; **71** (suppl 24): PD07–04.
- Guarneri V, Frassoldati A, Cagossi K, et al. CHER-LOB: preoperative chemotherapy plus trastuzumab, lapatinib or both in HER2-positive operable breast cancer—preliminary safety report with focus on cardiac tolerability. *J Clin Oncol* 2011; **29** (suppl): 507 (abstr).
- Untch M, Loibl S, Bischoff J, et al, for the German Breast Group (GBG) and the Arbeitsgemeinschaft Gynäkologische Onkologie-Breast (AGO-B) study group. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG44): a randomised phase 3 trial. *Lancet Oncol* 2012; published online Jan 17. DOI:10.1016/S1470-2045(11)70397-7.

- 7 Holmes FA, Nagarwala YM, Espina VA, et al. Correlation of molecular effects and pathologic complete response to preoperative lapatinib and trastuzumab, separately and combined prior to neoadjuvant breast cancer chemotherapy. *J Clin Oncol* 2011; **29** (suppl): 506 (abstr).
- 8 Steger GG, Galid A, Gnant M, et al. Pathologic complete response with six compared with three cycles of neoadjuvant epirubicin plus docetaxel and granulocyte colony-stimulating factor in operable breast cancer: results of ABCSG-14. *J Clin Oncol* 2007; **25**: 2012-18.
- 9 Gianni L, Pienkowski T, Im Y-H, 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* 2011; **13**: 25-32.
- 10 Baselga J, Cortes J, Kim S-B, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2011; published online Dec 7. DOI:10.1056/NEJMoa1113216.
- 11 Bozovic I, Capelan M, de Azambuja E. Breast International Group Newsletter: accrual target reached and changes after IDMC recommendation. December, 2011. <http://www.breastinternationalgroup.org/Portals/BIG//Eloket/7077/BIG%20NL%20Vol.%2013.2%20December%202011.pdf> (accessed Jan 11, 2011).
- 12 Garnock-Jones KP, Keating GM, Scott LJ. Trastuzumab: a review of its use as adjuvant treatment in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. *Drugs* 2010; **70**: 215-39.
- 13 Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. *J Clin Oncol* 2009; **27**: 5685-92.
- 14 Gnant M, Steger GG. Fighting overtreatment in breast cancer therapy. *Lancet* 2009; **374**: 2029-30.
- 15 Hall PS, Hulme C, McCabe C, Oluboyede Y, Round J, Cameron DA. Updated cost-effectiveness analysis of trastuzumab for early breast cancer: a UK perspective considering duration of benefit, long-term toxicity and pattern of recurrence. *Pharmacoeconomics* 2011; **29**: 415-32.