findings. If a patient does well after surgery alone or with short-course radiotherapy and immediate surgery, we recommend discussion of the advantages and disadvantages of adjuvant chemotherapy. If the patient does not do well, the oncologist should not feel bad about not giving systemic therapy. If the patient had preoperative chemoradiotherapy, irrespective of response, we are as uncertain as other oncologists about what to recommend.

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1 Engelen SM, Maas M, Lahaye MJ, et al. Modern multidisciplinary treatment of rectal cancer based on staging with magnetic resonance imaging leads to excellent local control, but distant control remains a challenge. *Eur J Cancer* 2013; **49:** 2311–20.
2 Wolpin BM, Mayer RJ. Systemic treatment of colorectal cancer. *Gastroenterology* 2008; **134:** 1296–310.
3 Glimelius B, Tiret E, Cervantes A, Arnold D, Group EGW. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24** (suppl 6)**:** vi81–8.
4 van de Velde CJ, Boelens PG, Borras JM, et al. EURECCA colorectal: Multidisciplinary management: European consensus conference colon and rectum. *Eur J Cancer* 2014; **50:** 1; e1–e34.
5 Bosset J-F, Calais G, Mineur L, et al, for the EORTC Radiation Oncology Group. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014; published online Jan 17. http://dx.doi.org/10.1016/S1470-2045(13)70599-0.
6 Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355:** 1114–23.
7 Cionini L, Sainato A, De Paoli A, et al. Final results of randomized trial on adjuvant chemotherapy after preoperative chemoradiation in rectal cancer. *Radiother Oncol* 2010; **96** (suppl 1)**:** S113–14.
8 Breugom AJ, van den Broek CBM, van Gijn W, et al. The value of adjuvant chemotherapy in rectal cancer patients after preoperative radiotherapy or chemoradiation followed by TME-surgery: the PROCTOR/SCRIPT study. *Eur J Cancer* 2013; **49** (suppl 3)**:** S1.
9 Glynne Jones R, Counsell M, Meadows H, Sebag-Montefiore D. Chronicle: a phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine/oxaliplatin versus control. *Ann Oncol* 2013; **24** (suppl 4)**:** iv18.

Neoadjuvant chemotherapy for breast cancer: any progress?

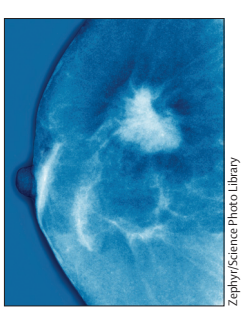
Neoadjuvant chemotherapy is a well established approach to treatment of locally advanced breast cancer. Preoperative therapy allows breast-conserving surgery in many patients and provides prognostic information that could guide the choice of treatments to maximise the degree of response (ie, towards pathological complete remission [pCR]).[1]

At present, about 20% of patients achieve pCR after an appropriate neoadjuvant chemotherapy regimen, including a taxane and an anthracycline, and an anti-HER2 drug for HER2-positive disease.[2] Improved pCR is reported in subgroups of patients (eg, patients with triple-negative and HER2-positive disease) and in the presence of targeted therapies.[3]

The next step is to improve these results. The neoadjuvant setting is a suitable scenario in which new regimens can be tested rapidly with pCR as an endpoint. The strategy was highlighted recently by regulatory agencies that might grant accelerated approval of new drugs on the basis of an endpoint such as pCR, which is reasonably likely to predict survival benefit.[4]

In the Neo-tAnGo study,[5] Helena Earl and colleagues addressed the value of addition of gemcitabine to paclitaxel, and the sequencing of epirubicin and cyclophosphamide and paclitaxel (with or without gemcitabine) blocks. The investigators concluded that no advantage was provided in terms of pCR rate by addition of gemcitabine: 70 (17%) of 404 patients given epirubicin and cyclophosphamide then paclitaxel had pCR compared with 71 (17%) of 408 patients who received additional gemcitabine (p=0·98). Conversely, improved pCR was seen with taxane-first sequencing for neoadjuvant chemotherapy: 82 (20%) of 406 patients given paclitaxel with or without gemcitabine followed by epirubicin and cyclophosphamide achieved pCR compared with 59 (15%) of 406 patients who received epirubicin and cyclophosphamide first (p=0·03).

The absence of a significant effect for addition of gemcitabine is not surprising and is in line with results already reported in large phase 3 randomised studies in the neoadjuvant setting.[6] These results however confirm the value of neoadjuvant trials for anticipation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of results of large adjuvant trials, which yielded much the same outcomes.[7]

The improved pCR reported in Neo-tAnGo[5] with the taxane-first sequence did not translate into improved disease-free survival and overall survival. This finding might be related to the small, albeit significant, difference noted in the pCR (20% *vs* 15%). The overall low pCR (17%) was possibly related to the heterogeneous population, which included patients with inflammatory breast cancer.

Interpretation of efficacy of neoadjuvant treatments might be improved by a selective focus on specific subtypes of breast cancer. The Neo-tAnGo study,[5] as is the case with most studies done in the neoadjuvant setting in the past few years, took no account of potential heterogeneity of tumour biology, which has been widely studied since such studies began.[2] The magnitude of the therapeutic effect on pCR in patients with favourable and unfavourable prognosis might differ according to the intrinsic breast cancer subtype. von Minckwitz and colleagues[3] explored, according to selected subtypes, the value of pCR in 6377 patients with primary breast cancer who received neoadjuvant chemotherapy with an anthracycline and a taxane in seven randomised trials. They concluded that pCR is a good surrogate endpoint for patients with triple negative, luminal B (HER2-negative), and non-luminal (HER2-positive) disease, but not for patients with luminal A and luminal B/HER2-positive disease.

pCR according to subtypes should be taken into consideration when results of Earl and colleagues' trial are interpreted. Although results were adjusted for HER2 and oestrogen receptor status, information on the taxane-first sequence was restricted in some subgroups (eg, HER2-positive disease). The regimen used in the study cannot be regarded as a present standard for patients with HER2-positive disease, because no targeted anti-HER2 agent was used. In the ACOSOG Z1041 trial,[8] the value of a taxane-first sequence was not shown in patients with HER2-positive disease in the neoadjuvant setting. pCR rates obtained in breast or nodes did not differ between two regimens in the analysis of anthracyclines followed by taxane plus trastuzumab compared with taxanes plus trastuzumab followed by anthracyclines plus trastuzumab.

Overall, a taxane-first sequence can be regarded as a reasonable option in neoadjuvant chemotherapy for locally advanced breast cancer. The results of Earl and colleagues' study[5] reinforce available evidence on the efficacy of this sequence.[9] In future trials, breast cancer should be regarded as a homogeneous disease until new evidence supports a different approach. However, we favour consideration of available information suggesting the biological heterogeneity of the disease. Therefore, investigations of tailored neoadjuvant treatments should aim at specific groups of patients selected according to criteria of hypothetical responsiveness through international collaboration. This strategy will be key for progress to be made in the treatment of individual patients with locally advanced breast cancer.

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1 Kaufmann M, von Minckwitz G, Mamounas EP, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. *Ann Surg Oncol* 2012; **19:** 1508–16.
2 Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol* 2013; **24:** 2206–23.
3 von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012; **30:** 1796–804.
4 Prowell TM, Pazdur R Pathological complete response and accelerated drug approval in early breast cancer. *N Engl J Med* 2012; **366:** 2438–41.
5 Earl HM, Vallier A-L, Hiller L, et al, for the Neo-tAnGo Investigators. Neoadjuvant sequential epirubicin, cyclophosphamide, and paclitaxel, with or without gemcitabine, for women with high-risk early breast cancer (Neo-tAnGo): an open-label, factorial, randomised phase 3 trial. *Lancet Oncol* 2013; pubilshed online Dec 19. http://dx.doi.org/10.1016/S1470-2045(13)70554-0.
6 Bear HD, Tang G, Rastogi P, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. *N Engl J Med* 2012; **366:** 310–20.
7 Poole CJ, Hiller L, Howard HC, et al. tAnGo: a randomised phase III trial of gemcitabine (gem) in paclitaxel-containing, epirubicin/cyclophosphamide-based, adjuvant chemotherapy (CT) for women with early stage breast cancer (EBC). *Proc Am Soc Clin Oncol* 2008; **26:** abstr 506.
8 Buzdar A, Suman V, Meric-Bernstam F, et al. Fluorouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab as neoadjuvant treatment for patients with HER2-positive breast cancer (Z1041): a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; **14:** 1317–25.
9 Wildiers H, Forceville K, Paridaens R, et al. Taxanes and anthracyclines in early breast cancer: which first? *Lancet Oncol* 2010; **11:** 219–20.