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I-SPY 2: optimising cancer drug development in the 21st century

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Adjuvant phase III clinical trials in early-stage breast cancer are scientifically important, but sometimes they can be troublesome due to the amount of patients required as well as the long follow-up in order to get the expected number of events. While providing the highest level of evidence in oncology, conducting these trials may take several years or even decades and results may only be available once the question asked is no longer relevant. Furthermore, in recent adjuvant studies, lower than expected recurrence rates resulted in lower statistical power to demonstrate benefit with experimental therapies, thereby requiring alterations to the study design or joint analyses with parallel studies.[1 2] This suggests that further improvement in current treatment outcomes will eventually require even larger trials, making this practically impossible from a finance perspective. In contrast, with growing biological knowledge, breast cancer is understood as a heterogeneous disease and certain treatment approaches may only be relevant in relatively small patient subgroups. Given the plethora of novel substances currently under investigation in early phase clinical studies, it is highly unlikely that even all the most successful ones can be tested in studies of conventional adjuvant phase III design. This of course leads to the pertinent question: how can drug development be optimised and sped up in the era or personalised medicine?

Neoadjuvant treatment in general may be an important part of the solution to this problem as pathological complete remission (pCR) is an end point that is reached much earlier as compared to disease-free survival (DFS) or even overall survival (OS), thereby allowing for a faster appraisal of treatment efficacy. Of note, reaching pCR after neoadjuvant therapy has been demonstrated to correlate with favourable long-term outcome on an individual patient level in high-risk breast cancer subtypes.[3] This naturally may not translate automatically into a DFS or OS improvement on trial level—given the size of current neoadjuvant studies finding such a difference is rather unlikely.[4]

But even by focusing on the neoadjuvant setting and accepting pCR as surrogate end point, prescreening of drugs may be reasonable in order to focus on the most promising ones before moving towards larger phase III studies. The concept of graduating drugs in the Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2 (I-SPY 2) platform is indeed a successful example of such a prescreening programme.

This platform trial compares multiple experimental groups to a standard neoadjuvant chemotherapy backbone in high-risk breast cancer subtypes. Contrary to a conventional open-label phase II design, there is no fixed statistical assumption that determines the sample size. Instead, a biomarker assessment (based on HER2 receptor and hormone receptor expression status as well as the 70-gene assay) is performed at baseline, thus classifying patients into predefined groups. By using an adaptive randomisation approach based on incoming results, no more than 120 patients assigned to each experimental arm are required. An experimental regimen is deemed successful when there is an 85% Bayesian predictive probability of success in a simulated 300-patient phase III trial with a traditional statistical design while futility is reached if the probability of success is <10% for all 10 biomarker signatures. Therefore, I-SPY 2 allows for a prescreening of compounds in relatively small population with graduation of successful drugs to further clinical development in larger conventional trials. This approach can probably select the agents most likely to improve outcomes when tested in large randomised trials, thus saving time, money and avoiding exposing patients to unnecessary toxicities of a treatment that may not be efficacious.

Recently, two phase II studies from the I-SPY 2 platform were published in the *New*

England Journal of Medicine. The addition of veliparib and carboplatin to conventional chemotherapy increased the estimated pCR rates from 26% to 51% in triple negative tumours resulting in 88% probability of success in a phase III clinical trial. Of note, 72 patients were randomly assigned to experimental arm and 44 patients in the control arm.[5] Among patients with HER2-positive hormone receptor negative tumours, neratinib resulted in a higher estimated pCR rate as compared to trastuzumab (56% vs 33%) with 115 patients included into the experimental group.[6]

So where does this leave us? Obviously, the adaptive randomisation approach is interesting and allows for a quicker evaluation of compounds in relatively small patient population. However, there are some issues that need to be considered when using this adaptive approach. While the addition of veliparib and carboplatin increased pCR rates to a relevant extent, it is perfectly possible that this effect may be caused only by the platinum salt; therefore, appraisal of veliparib's role in this population may not be possible, and combinations of drugs may generally be difficult to be studied in this context. With regard to neratinib, this tyrosine kinase inhibitor apparently has an activity comparable[7] or even superior to trastuzumab.[6] Again, instead of trastuzumab alone, dual HER2-inhibition with a combination of trastuzumab and pertuzumab would usually be regarded as standard-of-care in the neoadjuvant setting today in many countries and should have been the control arm. Therefore, the same careful considerations of trial design and research question are required in I-SPY 2 as would be required in conventional studies.

Despite these pitfalls, I-SPY 2 provides us with an important research tool for fast-track evaluation of drug efficacy in relatively small patient subsets and may currently be regarded as the most promising pathway for optimising drug development in breast cancer. In the personalised medicine era, it is our duty to identify patients likely to respond to a given therapy in order to avoid costs in toxicities of therapies that may not be suitable for all patients. The concept of 'one size fits all' should no longer be applicable in oncology. The I-SPY platform may decrease the time to confirm or refute the activity of some drugs, but it does neither solve the problem of lack of biomarkers predicting the non-response of expensive treatments nor evaluates the de-escalation of drugs to be used in the treatment of patients with breast cancer. We made a lot of progress in the area of personalised medicine, now it is time to fine-tune these findings to really select the right drug to the right patient.

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REFERENCES

1. Pagani O, Regan MM, Walley BA, *et al*. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014;371:107–18.
2. 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;34:1034–42.
3. 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;384:164–72.
4. Hatzis C, Symmans WF, Zhang Y, *et al*. Relationship between complete pathologic response to neoadjuvant chemotherapy and survival in triple-negative breast cancer. *Clin Cancer Res* 2016;22:26–33.
5. Rugo HS, Olopade OI, DeMichele A, *et al*. Adaptive randomization of veliparib–carboplatin treatment in breast cancer. *N Engl J Med* 2016;375:23–34.
6. Park JW, Liu MC, Yee D, *et al*. Adaptive randomization of neratinib in early breast cancer. *N Engl J Med* 2016;375:11–22.
7. Awada A, Colomer R, Inoue K, *et al*. Neratinib plus paclitaxel vs trastuzumab plus paclitaxel in previously untreated metastatic ERBB2-positive breast cancer: the NEfERT-T randomized clinical trial. *JAMA Oncol* Published Online First: 14 Apr 2016. doi:10.1001/jamaoncol.2016.0237