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Expansion platform type II: testing a treatment strategy

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In *The Lancet Oncology*, Christophe Le Tourneau and colleagues report the results of SHIVA,[1] a next-generation clinical trial and the first example of a trial using the expansion platform design type IIB.[2] Several trial designs have emerged to address the challenges associated with the implementation of targeted therapies.[2,3] Briefly, so-called exploratory platform designs (eg, BATTLE and I-SPY2) start by randomly assigning patients to several treatment groups, and during the course of the trial, further test newly discovered biomarker–drug signals in an exploratory and adaptive fashion. Alternatively, expansion platform designs assign therapy immediately based on predefined biomarker–treatment pairings, thus expanding on a previously derived match. The expansion platform type IA design is histology dependent (eg, the conceptualised FOCUS4 colon cancer trial),[4] whereas the type IB design is histology agnostic (eg, NCI-MATCH).[3,5] Type I designs enable coordinated molecular profiling and treatment assignment, but each biomarker– treatment group must meet individual statistical endpoints, and hence large numbers of patients must be screened and profiled to adequately test low incidence groups. In a report of a type IB trial in which 647 patients were screened, the authors suggested that accrual, and hence this study design, would be infeasible for low incidence biomarkers,[5] as previously recognised.[2]

In anticipation of these accrual challenges for most groups within type I designs, type II designs concede the loss of statistical scrutiny within each biomarker– treatment group in favour of testing a predefined treatment strategy that pools multiple biomarker–drug pairings, ideally with comparison to a biomarker-stratified control group. Type IIA designs are histology dependent (eg, PANGEA, a gastroesophageal cancer trial)[6] whereas type IIB designs are histology agnostic (eg, SHIVA).[1]

SHIVA required 200 patients to be randomly assigned to receive either molecularly targeted agents matched to predefined molecular alterations or treatment at physicians' choice to meet the primary endpoint. Of 741 patients enrolled, samples were successfully profiled for 496 (67%) patients. Only 195 (26%) of these patients could be categorised into a predefined biomarker group and were randomly assigned to molecularly targeted agents (n=99) or treatment at physicians' choice (n=96). Treatment choices for patients who received molecularly targeted agents were assigned by an algorithm that allocated them 11 prespecified molecularly targeted agents divided into ten regimens in nine treatment groups (with one regimen used as a backup option). Some leeway existed for a molecular biology

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board to decide which molecular alteration was the most relevant and whether previous treatment considerations should be included in the decision. While practical, having a board assign therapy based on these provisions outside the algorithm can make the strategy challenging to reproduce by others. Nevertheless, the prespecified companion diagnostics used included a mixture of novel and previously approved assays, including next generation sequencing, assessment of copy number alterations with chip arrays, and immunohistochemistry.

SHIVA is a notable trial. It is the first to test, with a randomised control, the idea of whether off-label use of commercial drugs for matched molecular biomarkers confers a clinical benefit. This approach is often advocated on the basis of a few case reports, observational cohorts, and meta-analyses, all of which have no appropriate prospective randomised controls. Unfortunately, properly run clinical trials often disprove intuition—statistics and hypothesis testing can be sobering. This prospective randomised trial was negative, a common occurrence after the publication of several promising uncontrolled reports.

However, careful consideration of the variables embedded in this trial design is warranted. These include choice of the biomarker groups, the molecular profiling assays and positivity criteria,[7] the drugs, the treatment assignment algorithm, and the histology makeup, all of which contributed to the aggregated results of SHIVA. This is the nature of the type II expansion platform design. Therefore, the conclusions must be viewed in this context, with the specifics of these variables acknowledged within the overall personalised strategy. The generalisability of this SHIVA strategy to other potential trials is therefore limited.[2] But this fact does suggest that any other proposed strategies should be similarly tested before they are accepted as routine standard care. Importantly, although the treatment strategy for molecularly targeted agents in SHIVA was not significantly better than treatment at physicians' choice (defined as an HR of 0·625 in SHIVA), this finding does not exclude the possibility that one or more biomarker– drug pairings in one or all histologies was truly beneficial, an important shortcoming of the type-II design.

Irrespective of these limitations, SHIVA offers robust evidence for deficiencies in assigning therapy based on the various loose associations between biomarkers and inhibitors that are often provided in commercial clinical diagnostic reports. The results suggest that off-label use of molecularly targeted agents in this manner should be restricted. Instead, patients should be encouraged to participate in well-designed next-generation clinical trials that use an iterative and scientific approach to build on findings from trials such as SHIVA. Future revised treatment strategies could include best-in-class agents that are not necessarily already commercially available; combination therapies for specific biomarker groups; repeated molecular profiling with newly matched biological agents after the first tumour progression to address intrapatient tumour evolution and resistance; modified treatment assignment algorithms; histological considerations (ie, type IIA); novel biomarkers; treatment relegation groups for biomarker-negative groups such that all screened patients are included within the treatment algorithm; and novel companion diagnostics or definitions of biomarker-positivity.[2]

A negative type II trial such as SHIVA is straightforward—the treatment strategy failed and should be abandoned, amended then retested, or promising subsets should be investigated within classic population-enriched strategies if feasible. However, a type II trial that significantly meets the statistical endpoints remains problematic. A successful treatment strategy that encompasses multiple companion diagnostics, drugs, and even tumour histologies would challenge the existing regulatory infrastructure. Would 11 drugs in nine treatment groups, using various companion diagnostics, and for any histology, all be simultaneously approved for expanded indication if confirmed in a phase 3 trial? What if some drugs are not already commercially available? What should be done about development and approval pathways for multiple incorporated companion diagnostics? Thus, to pre-emptively tackle these issues in preparation for potential future positive type II trials, next-generation regulation must accompany next-generation trials through the integration of next-generation companion diagnostics and the concept of personalised treatment strategies, to continue to advance clinical cancer care.

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