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Clinical trial design issues: Session 1

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ABSTRACT: Anticancer therapeutic intervention in patients with solid tumours still relies on the necessity of empirically treating many patients to obtain benefit for a limited few. The activity of a given drug in patients with advanced cancer is the result of a pharmacodynamic interaction with a pathway. Such putative pathways must be both prevalent in the cancer cells and relevant to the process of uncontrolled cell proliferation. Several examples have clearly demonstrated the value of measuring the molecular target and using it as inclusion criteria for clinical trials. Adaptive trial designs and the definition of clinical surrogate end-points can be helpful tools to further improve clinical drug development. In general go/no go decisions must be established prospectively.

Keywords: Target expression; Molecular signatures; Adaptive trial design; Surrogate end-points

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ROLE OF TARGET EXPRESSION AS INCLUSION CRITERIA

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Anticancer therapeutic intervention in patients with solid tumours still relies on the necessity of empirically treating many patients to obtain benefit for a limited few. The activity of a given drug in patients with advanced cancer is the result of a pharmacodynamic interaction with a pathway. Such putative pathways must be both prevalent in the cancer cells and relevant to the process of uncontrolled cell proliferation.

Many molecularly targeted anticancer agents have demonstrated limited effectiveness thus far. An example is the marginal impact on overall survival of erlotinib (Tarceva®), an epidermal growth factor receptor inhibitor, after first- or second-line treatment, compared to placebo. The respective study involved 731 patients with advanced non-small-cell lung cancer (NSCLC).[1] After adjusting for stratification factors and epidermal growth factor receptor (EGFR) status, the survival curves for the two treatments started to diverge after 2 or 3 months. At 1 year, 31% of patients treated with erlotinib were still alive, compared with 22% of those on placebo.

Similarly, new therapeutic schemes for treating hormone-refractory prostate cancer have shown only limited effects on overall survival. In one study involving 674 men, the median overall survival was 17.5 months in the group given docetaxel and estramustine, and 15.6 months in those given mitoxantrone and prednisone. The corresponding hazard ratio for death was 0.80.[2]

DESIGNING TRIALS: One way to streamline clinical trials of new anticancer agents is to use biomarkers rather than clinical end-points. Several examples of novel markers for assessing effectiveness and predicting response to therapy were discussed.

Methylation-dependent transcriptional silencing of 14-3-3σ, a major G2-M checkpoint control gene, could be a new, independent prognostic factor for survival in NSCLC patients receiving platinum-based chemotherapy.[3] 14-3-3σ methylation was observed in all histologic types of 39 patients (34%). And median survival was significantly longer in the methylation-positive group (15.1 versus 9.8 months). Median time to progression was 8 months in the methylation-positive group and 6.3 months in the methylation-negative group. Furthermore, 14-3-3σ methylation might be a prognostic marker. The estimated survival rate at 18 months was 64% amongst methylation-positive responders and 21% amongst methylation-negative responders. Methylation-negative responders had a fourfold greater risk of death during follow-up than those who were methylation-positive. Additionally, translational research studies in advanced NSCLC are limited by a lack of tumour biopsy tissue, but methylation of 14-3-3σ can be reliably and conveniently detected in the serum, thus obviating the need for tumour tissue analysis in translational studies.

As another example trabectedin (Yondelis) induced long lasting responses and tumour control in a clinically relevant proportion of sarcoma patients resistant or relapsed to conventional chemotherapy.[4] After the EMEA/CHPM positive opinion and

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approval from the European Commission, Yondelis is now the gold standard for patients with advance soft tissue sarcoma pre-treated with conventional therapy.[5] Its mechanism of action is based on binding to the DNA minor groove, causing the helix to bend. By interacting with transcription factors and other DNA-binding proteins, it interferes with DNA repair pathways through S-phase delay and G-2 blockade.[6]

In one large phase II study, durable objective responses to trabectedin were obtained in a subset of sarcoma patients with disease progression despite prior chemotherapy.[7] Such phase II results have been validated in a comparative trial that has been the basis of the EMEA positive opinion for Yondelis in advanced pre-treated soft tissue sarcoma.[8] Interestingly the antitumour activity of trabectedin might be the result of a molecular mechanism related to its interaction with an aberrant transcriptional regulator. In this context Mixoid round cell liposarcoma (MRCL) is representative example of a translocation, t 12:16, leading to a chimeric fusion protein (FUS-CHOP) that acts as a transcription factor to promote undifferentation and controlled proliferation.

A multi-institutional integrated analysis of a cohort of 34 patients, heavily pretreated with standard therapies for advanced MRCL was highlighted.[9] Amongst patients who received trabectedin, 86% achieved long-lasting objective remissions and tumour control. The median progression-free survival (duration of tumour control) was 14 months. The molecular basis of these impressive results are active under investigation. Both the clinical impact and the pattern of response noted suggested a targeted mediated effect. This warrants further investigation in other tumour types, such as prostate cancer, in which a similar molecular signature, translocation leading to a transcription factor can be identified as a proportion of cases.

In such retrospective analysis[9] Grosso and colleagues also reported on the utility of a measure of tissue response combined with standard dimensional criteria in the initial assessment of patients with advanced MRCL treated with trabectedin.[1] Tissue response (i.e. initial tumour response) was defined as either a decrease in contrast enhancement on magnetic resonance imaging (MRI) or a decrease in contrast uptake or in density measured in Hounsfield units on computed tomography (CT). Tissue response is often followed by delayed response. This pattern of response, that mimicks the one applicable to imatinib in GIST, has to be considered in the incorporation of response criteria into prospective studies with trabectin.

Of note patients with advanced MRCL, treated with trabectedin and who had the type III FUS-CHOP fusion protein variant resulting from a translocation mutation (13% of patients in the study reported by Grosso et al.[9]) were more likely to have disease progression than those with other FUS-CHOP translocations. They also had much shorter median progression-free survival times.[9] The clinical impact of Trabectin in unselected pre-treated, non MRCL, soft tissue sarcoma patients have been also reported.[10] The data showed a 19% rate of tumour response, with remissions noted in different sarcoma subtypes. Long-lasting tumour control was reported in 21% if patients studied. These findings support the conclusion that trabectin efficacy is not testricted to MRCL patients.

POTENTIAL ROLE OF DNA REPAIR MECHANISMS: In experimental models the functionality of DNA repair mechanisms influences the cytotoxicity of trabectin and, hence, its efficacy.[6] If either the nucleotide excision repair (NER) is *proficient* or the double-stranded break (DSB) repair mechanism is *deficient*, the cytotoxicity of trabectedin is generally increased. Schöffski et al. selected *ERCC1* and *XPD* as key genes for NER and *BRCA1* for DSB and characterised their mRNA expression levels as potential biomarkers for patient outcome in tumour tissues from advanced, pretreated sarcoma patients exposed to trabectedin.[11] Patients with higher levels of ERCC1 or XPD expression showed a trend toward better clinical outcomes. Low expression of BRCA1 correlated with better relative risk, tumour control, progression-free survival at 6 months and median survival. Co-expression of BRCA1 and ERCC1 increased the accuracy of treatment outcome prediction, identifying the most sensitive subpopulation. Those with low BRCA1 and high ERCC1 expression demonstrated the best response and had longer median survival. This group accounted for 25% of the whole population. Co-expression of BRCA1 and XPD produced an equivalent prediction of response to trabectedin. Co-expression of all three markers further refined

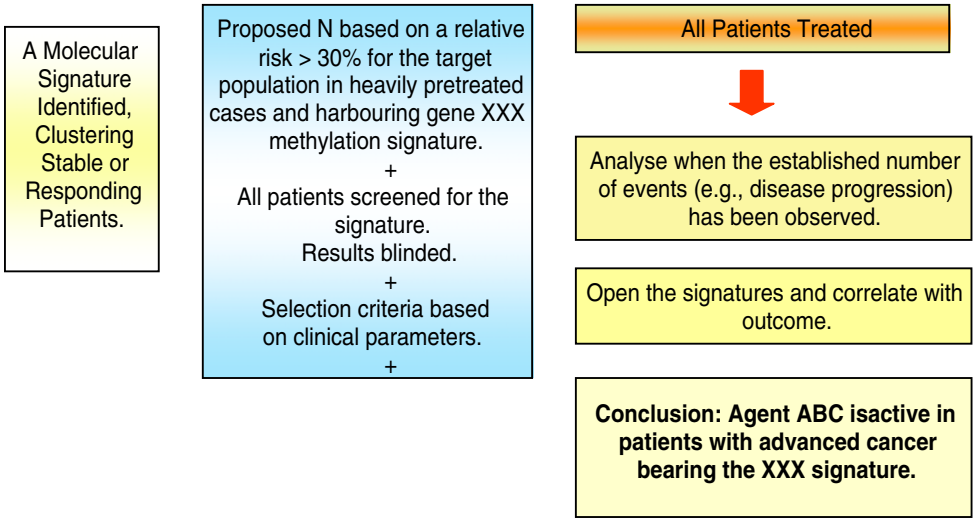

Fig. 1 – A potential design for a phase II trial for a given drug in a particular tumour type based on a molecular signature.