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Commentary

The case for a stratified application of targeted agents against pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis that has improved only marginally over the past decades [1]. The rising incidence of this disease and its unchanged poor outcome, has resulted in PDAC becoming a major cause of cancer-related deaths [2]. The vast majority of PDAC patients present with locally advanced or metastatic disease, and are no longer eligible for surgical removal of the tumour. In these cases, systemic therapies are given such as gemcitabine with Nab-paclitaxel or FOLFIRINOX (folinic acid, 5-FU, irinotecan, oxaliplatin) [3,4]. These regimens (in particular FOLFIRINOX) come at the cost of high toxicity, and several months of improved survival at best. The only treatment with curative intent is surgery, sometimes preceded by a neoadjuvant treatment. Despite this, recurrence rates in resected patients are high and also in this setting, long-term survival is limited. This has spurred the application of adjuvant therapies such as gemcitabine monotherapy, but this has not improved outcomes convincingly. In line with developments and progress in other cancer types, the expectation has been that improvements are likely to come from the application of novel targeted agents, in combination with classical cytotoxics against PDAC.

However, targeted therapies have been largely unsuccessful in PDAC. One example of this is Erlotinib, a small molecule receptor tyrosine kinase inhibitor with specificity against EGFR. Erlotinib shows significant but limited efficacy in the treatment of locally advanced and metastatic PDAC in combination with gemcitabine [5]. In the adjuvant setting however, results were negative: In the phase III CONKO-005 trial, 436 patients were enrolled and randomized to receive gemcitabine or gemcitabine with Erlotinib following a radical (R0) resection. However, no statistically significant improvement in survival (overall or disease-free) was achieved by the addition of Erlotinib [6].

The reasons for the disappointing outcomes of targeted agents in PDAC are not fully understood, but the failure to select those patients that are likely to respond to the experimental drug is a likely factor. In most cancers, a large degree of heterogeneity exists between cases, and PDAC is no exception. Despite being driven by a relatively limited number of driver mutations, large differences exist between pancreatic tumours at all levels of biological information. For targeted agents, this is particularly problematic as the heterogeneity is likely to impact on, for instance, the expression of targeted proteins, or the activity of associated signalling pathways. Failure to select for or against an experimental treatment based on the pertinent tumour characteristics, will negatively impact on the aggregate response rates in the trial cohort as a whole. With the advent of affordable genetic and transcriptomic analyses, researchers have obtained unprecedented insight into the heterogeneity that exists between cancers. Class discovery efforts have identified biologically different groups of cancers previously considered a single clinical entity, and have revealed that groups of patients can be identified that are likely to have a poor prognosis [7]. It is expected that this comprehensive tumour analysis will become an integral part of diagnostic routines in the future.

In the study recently published in *EBioMedicine* by Hoyer *et al.*, tumour samples from close to 300 CONKO-005 trial participants were analysed by targeted sequencing, copy number analysis, and transcriptomics on clinically available FFPE samples [8]. These data were then successfully used to chart the genomic landscape of PDAC, and to identify subgroups of tumours that associate with clinical outcome. In one of the subgroups identified, Erlotinib treatment associated with longer overall survival. This subgroup also featured relatively frequent alterations in the *SMAD4* gene. SMAD4 is part of the TGF-beta pathway and its loss is a tumour-promoting event. It is considered one of the main PDAC driver genes and its loss associates with specific tumour biology, for instance a tumour-stroma interaction that is specific to *SMAD4*-deficient tumours [9]. When grouped together based on *SMAD4* status, the CONKO-005 patients with *SMAD4* alterations showed a remarkable benefit from receiving Erlotinib. This signal was not discerned in the unselected cohort that had previously led to the conclusions on Erlotinib's inefficacy. Next, the authors incorporated a signalling molecule of which the expression was correlated to *SMAD4* status, and which was likely involved in the pathway targeted by Erlotinib; *MAPK9*. It was found that in the group of patients with *SMAD4* alterations, the response to Erlotinib was explained by the group of patients that also had low *MAPK9* expression. The combination of *SMAD4* alteration with low *MAPK9* was a highly predictive biomarker that identified a previously unrecognized group of patients who benefited from to the addition of Erlotinib.

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Studies such as the one by Hoyer *et al.* should urge us to reconsider targeted agents that have ostensibly failed in clinical trials. In addition, results from biomarker discovery studies can and should be used to properly design future studies to incorporate an up-front selection based on predictive biomarkers known at the time of study design. Several hurdles stand in the way of effectively doing so. One obvious problem with studies such as the one presented is that the discovery cohorts from clinical trials are often unique, meaning that validation of identified predictive signals is challenging. Conversely, it is rare for new stratified clinical trials to be initiated based on non-validated predictive biomarkers. The question is then how to break through this? The answers are threefold: One option that is gaining traction is the Trials within Cohorts design, in which eligible patients are enrolled from a larger study. However, this requires known markers for eligibility which may or may not become available during the course of the larger study. In lieu of known, relevant and validated predictive biomarkers to stratify patients with, trials should incorporate a solid translational framework from which predictive biomarkers and markers for therapy resistance will be rapidly identified, possibly even during the course of the study. In addition, the preclinical work leading up to clinical studies with targeted agents can be designed in such a way that it yields biomarkers with sufficient predictive power and relevance for direct application in the clinical studies (eg, NCT045547710 based on [10]). Whatever the options, it is fair to state that in PDAC, targeted agents are likely unsuccessful without adequate patient selection and that patients and caretakers are best spared the burden of such unstratified clinical studies.

Contributors

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Declaration of Competing Interest

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