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Cross-over—it's a feature, not a bug

A significant improvement of overall survival (OS) remains to be the most important goal in the treatment of advanced or metastatic cancer.

Historically, the additional benefit of a new oncology drug, as measured by time-to-event end points, has often been small because of (i) the relatively small number of sensitive tumors in the trial population, (ii) a toxicity profile that did not allow for longer term treatment, and/or (iii) lack of biomarkers. Hence, large trials were required to demonstrate a significant improvement over the established standard of care and, sometimes, the clinical meaningfulness of this benefit was debatable.

This traditional way of drug development still is the most reasonable approach in a scenario where an investigational drug or a new combination is intended to fully replace a standard of care in the same line of treatment, or represents a new last-line option. In such a scenario, OS remains a valid primary efficacy end point (Figure 1A and B). Ideally, the demonstration of an improvement of OS should also remain the major trial objective whenever a new combination partner is being added to a standard backbone therapy regimen, although this can be challenging when multiple poststudy options are available. The addition of monoclonal antibodies like cetuximab or bevacizumab to standard chemotherapy represents such a scenario (Figure 1B).

Advances in molecular cell biology have brought about a new era of drug development in oncology. Remarkable efficacy could be achieved by applying tailored treatments according to identified molecular driver alterations. Examples include the targeting of ALK fusion proteins or mutated epidermal growth factor receptor in nonsmall-cell lung cancer (NSCLC), mutated tyrosine kinase KIT in gastrointestinal stromal tumors, bcr-abl fusion proteins in chronic myelogeous leukemia, or mutated BRAF in melanoma.

As a result of the development of targeted agents in conjunction with predictive biomarkers, it has become apparent in recent years that the traditional drug development paradigm no longer assesses the added value for patients adequately. This holds particularly true for the end point of OS.

Since some of these drugs have proven striking antitumor activity for select patients in early clinical development, it was often deemed unethical to withhold them from patients in the control groups of randomized clinical trials. Therefore, cross-over was introduced to allow all patients access to the new active substance. As a consequence of cross-over and the influence of poststudy treatments, it became far more challenging to draw meaningful conclusions in terms of any OS benefit. In such cases, progression-free survival (PFS) is usually employed as the primary time-to-event measure, and OS is a secondary end point. It almost seems to be a paradox that it becomes increasingly difficult to prove an OS effect with increasing efficacy of a new compound. Of note, in such a case, no demonstrated statistically improvement of OS in an individual trial does not necessarily mean that a treatment is not providing an OS benefit overall to the study population.

In addition to cross-over, a second consideration is important in terms of the assessment of patient-relevant incremental benefit of highly active biomarker-driven treatments: if the new treatment is not going to fully replace a current standard treatment, but represents a new line of treatment in addition to existing options, the most important clinical question might be that of the new medicine's place in the treatment sequence. In such a scenario, it is questionable if the additional benefit of a new drug is represented by the delta of PFS or differences in the toxicity profile in head-to-head comparisons, since both options will remain available to the patients one after another. So, why should the valuation of the new treatment be based on such comparison when (i) the comparison is not relevant, and (ii) the ultimate goal of improving OS cannot formally be demonstrated?

This dilemma is nicely exemplified by the clinical development of the ALK inhibitor crizotinib in patients with ALK-positive NSCLC. Crizotinib is a small molecule inhibitor of the tyrosine kinases ALK, cMet, and ROS1, and is approved for the treatment of ALK-positive advanced NSCLC. ALK fusions occur in 3%–5% of all NSCLC cases and have been shown to be potent oncogenic drivers.

Marked efficacy of crizotinib in ALK-positive NSCLC was seen early in clinical development in an expanded cohort of a phase I study and a single-arm phase II study [1, 2]. Both studies enrolled patients in various lines of treatment and showed a response rate of ∼60%, a PFS of ∼8–10 months, and a generally manageable toxicity profile. Based on the results from treatment of 255 patients in these studies, the US FDA granted approval independent of the line of treatment of patients with ALK-positive NSCLC as detected with an FDA-approved test. Two already ongoing randomized phase III trials were required as postapproval commitments: A first-line study, comparing crizotinib to platinum doublet standard chemotherapy, and a second-line study, comparing crizotinib to either pemetrexed, or docetaxel.

In Europe, crizotinib received a conditional approval by the European Medicines Agency for the treatment of adults with previously treated ALK-positive advanced (NSCLC) based on the two single-arm studies [1, 2], but not before results from the second-line phase III trial became available.

The two phase III trials confirmed the results from early studies. Response rates for crizotinib were 74% for first line and 65% in second line, and PFS was 10.9 months for first line and 7.7 months for second line, respectively [3, 4]. Cross-over to

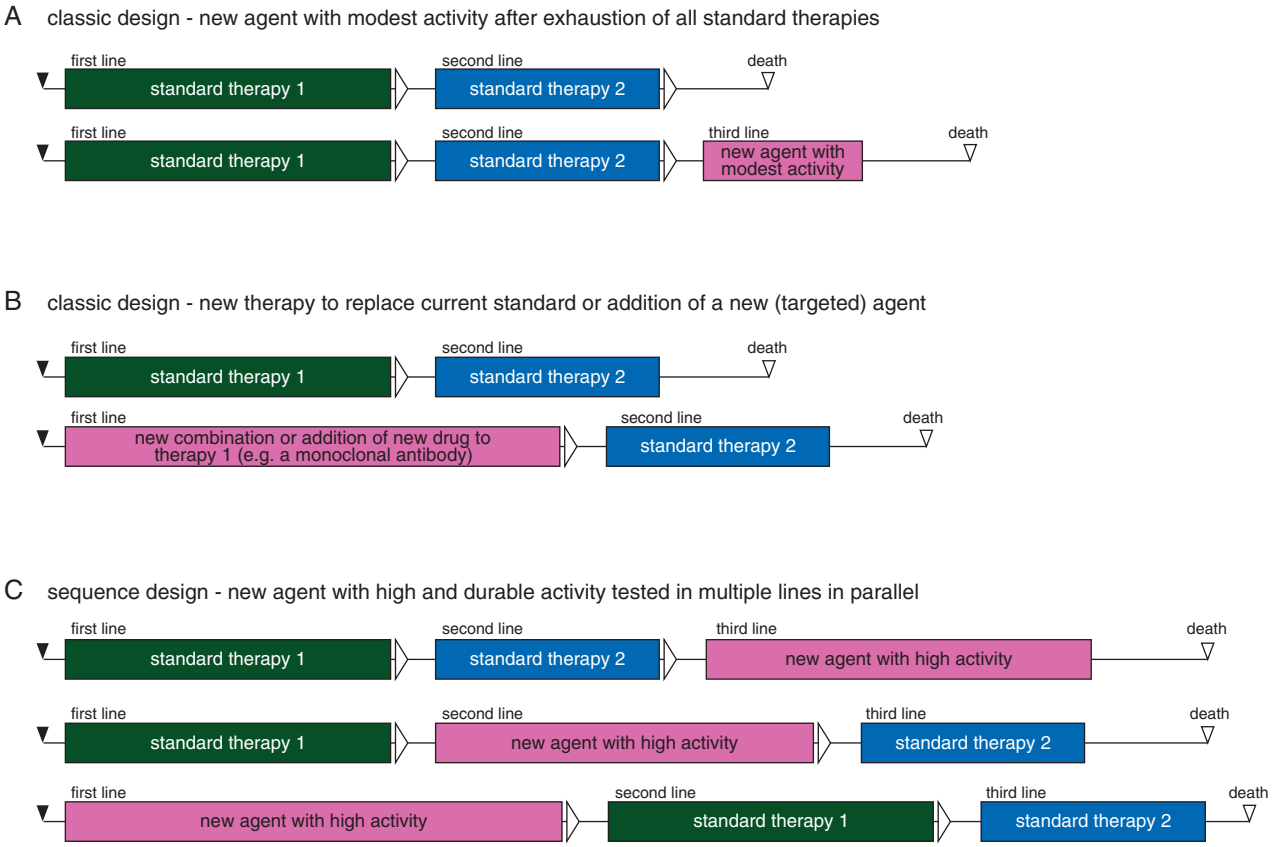

Figure 1. Drug development strategies for three different clinical scenarios. (A) A new drug with modest activity is added as last-line treatment and tested versus placebo or best supportive care. (B) Either a new drug or a novel combination is intended to replace an existing standard of care. The figure illustrates this approach for the first-line setting but it is also applicable to later lines of treatment. (C) The sequence approach aims at establishing the most appropriate line of treatment of a highly active new drug. No standard regimen is being replaced; instead, the new treatment is being added to the existing options.

crizotinib upon disease progression was allowed for patients in both trials, and no significant OS difference has been detected at the time of final PFS analysis. Arguably, both phase III trials did not reveal significant new information in terms of antitumor efficacy or the safety profile of crizotinib. Thus, besides new results pertaining to quality of life, the only relevant new insight from the phase III studies was the performance of standard chemotherapy in patients with ALK-positive NSCLC, since this had not been investigated prospectively before. The clinically most relevant question of the optimal place of a highly effective new line of therapy in the treatment course however remained unanswered by these studies.

Interestingly, a phase III study of a new ALK inhibitor, ceritinib, is now comparing ceritinib to—again—docetaxel or pemetrexed after failure of crizotinib and platinum doublet chemotherapy (NCT01828112). Hence, the conclusion that docetaxel or pemetrexed have not been replaced by crizotinib in the second-line setting, instead they were displaced from second to third line.

Following the two above considerations, one could argue that whenever a new line of a highly active treatment is introduced in addition to the existing standards, its assessment does not necessarily require a direct comparison with an established treatment. Investigating various treatment sequences in a single trial could be an appealing alternative option for phase II or potentially for phase III trials for select new drugs and would better address the clinical problem (Figure 1C).

Which prerequisites must be fulfilled to pursue such a development strategy, and is it possible to identify criteria that make it highly likely that a new drug/treatment line extends OS without a formal proof? Here are some thoughts and proposed assumptions:

(i) A new treatment option is added—a displacement rather than a replacement of an existing standard of care
(ii) The new investigational treatment offers a long PFS that makes it likely to have an impact on OS—e.g. if results from early studies suggest that PFS exceeds 50% of the total OS observed with standard therapy in this patient population. In contrast, a small incremental benefit would be suggestive of a more traditional development approach starting in last line (Figure 1A)
(iii) Without the rigid statistics of a traditional comparative study, assumptions have to be made about when an OS benefit can be assumed from the integration of the new treatment, e.g. if the OS in at least one of the study arms exceeds the OS in retrospective analyses of the studied population by one-third
(iv) If a biomarker-defined patient population is studied, the assessment of the efficacy of established treatments can be helpful in extrapolating if this particular patient population has a different prognosis *per se*, or in other words: whether or not the biomarker is also prognostic

(v) Besides OS, time to progression of every treatment line has to be assessed individually to determine whether the new treatment has an impact on existing treatments, and if resistance occurs

Applying these factors to the above crizotinib example reveals that crizotinib would have been a good candidate for the sequence approach: (i) as outlined above, crizotinib does not replace a standard treatment, it is an add-on to existing options for patients with advanced ALK-positive NSCLC. (ii) The PFS with crizotinib was between 8 and 10 months through all treatment lines in early single-arm studies [1, 2] whereas the absolute life expectancy for advanced or metastatic NSCLC is in the range of 12 months. (iii) In the second-line phase III trial of crizotinib, median OS with crizotinib exceeded 20 months. Of note, this was measured from randomization to the second-line treatment until death and does not include any first-line treatment benefit [3]. (iv) PFS with chemotherapy of patients with ALK-positive NSCLC was in the range of the general NSCLC population.

The marked advances in tumor biology and the development of targeted drugs make it necessary to change the way we run trials and how we assess the value of new drugs. The traditional sole comparison between two treatments does not always seem to be ideal to address problems in oncology, and to valuate new treatments. In the case of ALK-positive NSCLC, the first next-generation ALK inhibitor ceritinib has just been approved in the United States for patients with disease progression on or who are intolerant to crizotinib, and in Europe for patients previously treated with crizotinib. Other ALK inhibitors including alectinib, brigatinib, or PF-06463922 are currently investigated in clinical trials and the question of how to sequence these treatments becomes even more relevant. The activity of these drugs is evident, yet the open question concerns the best way to apply them one after another, and it is unlikely that this question will be addressed by traditional comparative trials. Pharmaceutical companies, investigators, regulators, and payers need to work together to adapt standards for drug development that meet the needs of all stakeholders, but first and foremost, benefit cancer patients in the most appropriate way.

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The author is a Pfizer employee, holds Pfizer stock and Pfizer stock options.

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