Phase I trials in oncology: a new era has started

The landscape of oncology drug development is currently undergoing fascinating revolutions and there is an urge to re-challenge many paradigms of early phase trials, which are currently becoming out-of-date. Needless to say, the advent of the first molecularly targeted therapies at the beginning of this millenium has opened this changing time, but this was only the wind before the tempest. Now, oncology faces the arrival of multiple new comers, including not only novel targeted therapies, but also active immune therapies, antibody-drug conjugates, and probably soon adoptive cell transfer using chimeric artificial T-cell receptors (CARs). Paradoxically, the need for rapid and efficient drug development has never been as significant, as illustrated by the advent of Food and Drug Administration (FDA) breakthrough designations based on phase I trials results, as well as FDA conditional approvals based on phase I and II data. As a result, phase I investigators are challenged by the need to conciliate efficiency with the implementation of novel drug development models for novel drugs that present unusual levels of activity and ad hoc specificities.

Which recent trials have presented the most successful drug development model? Examples include the ALK/ROS inhibitors crizotinib (PF-02341066, Pfizer) and ceritinib (LDK378, Novartis), as well as the programmed death 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors nivolumab (BMS-936558, Bristol-Myers Squibb), pembrolizumab (MK-3475, Merck) and MPDL3280A (Genentech-Roche). For the first two trials, thorough patient selection has been the key of success [1, 2]. In both studies, several thousands of patients were screened in order to eventually select 82 and 130 of them that fulfilled the eligibility criteria of presenting an ALK-rearranged disease (at least for non-small cell lung cancer patients). Interestingly, both phase I trials were amended to allow recruitment of hundreds of additional patients (n = 550 for crizotinib [3, 4] and n = 246 [3] for ceritinib). The impressive activity results observed in these trials have triggered an accelerated approval by the FDA in August 2011 for crizotinib and in April 2014 for ceritinib, <5 years after the first patient was enrolled in the corresponding phase I study. This starkly contrasts with previous drug development schedules, which presented a time-lapse of ~10 years between first-in-human studies and drug approval at the beginning of the century. Such successful stories strongly encourage the development of large-scale phase I trials enriched in molecularly selected patients—whenever a robust selection biomarker is available, thus implying the screening of several hundreds of patients and international collaborations. However, recent events have shadowed this impressive success of ceritinib. Indeed, despite the undisputable activity of the drug, uncertainties regarding the optimal dose and prandial conditions of administration were still unsolved at the end of that study [5, 6]. Although the drug was approved at the dose of 750 mg o.d., reviewers were concerned with the drug’s gastrointestinal (GI) tolerability and recommended investigating lower doses of 450 mg and 600 mg ceritinib taken with a meal, as a significant positive food effect was demonstrated for this drug and as this may improve the GI tolerability [6, 7]. How could have these issues been better addressed in phase I trials? One potential solution is the multiplication of expansion cohorts at doses below the maximum tolerated dose (MTD). In such design, dose levels that are known to be safe and at which pharmacodynamic parameters show a biological activity of the drug, can be expanded in parallel of the continuation of the dose escalation. This design, in which the patient could for example be its own control for food effect assessment in an expansion cohort, combines the advantage of collecting more data on PK data (including inter and intrapatient variability), as well as treating more patients when the drug is obviously active. This may help improving the ability of phase I trials of targeted agents to predict doses that will eventually be registered—as this ability has been reported to be poorer for targeted agents than for phase I trials evaluating conventional cytotoxic chemotherapies [8].

For immunotherapies, there is no doubt that the revolution is ongoing and that many drugs will flow through drug development processes to approval, considering the extremely promising levels of activity. One of the most recent examples of such successful drug development is the PD-L1 inhibitor MPDL3280A. Based on the results of the phase I trial only, this drug was granted a breakthrough therapy designation for urothelial bladder cancer. A large confirmatory phase II study has been mandated for confirmation (NCT02108652). However, the drug development model of immune therapies is often complex, as these agents challenge all previously established paradigms of cancer drug development even more deeply than targeted agents. As an illustration, after several phase I trials in monotherapy and combination, as well as phase II and phase III trials evaluating different schedules, it is still unclear what is the optimal dose of nivolumab to be administered [9–11]. Optimal patient selection is also a challenge, as there is no consensus on which technique, which antibody or which threshold should be used to assess PD-L1 positivity status. This obviously contrasts with a patient selection based on a specific mutation, as DNA sequencing is a robust and almost universal technique. If no consensus can be found soon on assessing PD-L1 positivity, this may become a worrying issue for a future large-scale administration of these drugs, as each compound currently has its own companion selection biomarker. More importantly, most phase I investigators
are not familiar with the mechanism of action of immune therapies and immunostimulatory agents—a mechanism that is still being explored and represents a matter of intense debate, sometimes even after a drug has been approved—as illustrated by the controversies on ipilimumab mechanism of action [12, 13]. In this context, establishing an optimal biological dose based on pharmacodynamics biomarker, when the MTD is not reached, becomes even more of a conundrum. And things can even become more complex, when considering the uncertainty regarding the optimal imaging techniques and criteria (irRECIST [14]) that should be used for assessing tumor response, at least in some tumor types (such as melanoma).

In this context, the future of drug development faces the challenge of combining an efficient and rapid drug development—ideally leading to breakthrough designations and accelerated approvals—with a profound renewal of the drug development process, of which many facets are still unknown. This is obviously a risky and tricky situation. One first step is to envision larger-scale trials and more flexible designs allowing the recruitment of numerous molecularly selected patients at doses where the drug is known to be safe and active [15]. Second, cancer treatment of numerous molecularly selected patients at doses where the mechanism of action of the drug in human bodies and whether biomarkers should focus on noninvasive exploratory procedures, using notably imaging and sampling on treatment and at tumor progression, and favor companion biomarkers for response, repeated tumor or blood sampling on treatment and at tumor progression, and favor noninvasive exploratory procedures, using notably imaging and circulating biomarkers. For immune therapies, this challenge is even more relevant, as a lot remains to be discovered about their mechanism of action and whether biomarkers should focus on tumor cells, immune cells or both. Most importantly, phase I clinicians should always exploit at best exceptional responders or unexpected prolonged responses, in order to better understand the mechanism of action of the drug in human bodies and improve patient selection. In this regard, protocols should be flexible and make provisions for allowing the realization of extra translational sampling and analysis on these patients who are the most informative cases.

The era of small and unselected phase I trials is definitely over and oncology drug development is currently being revolutionized with the advent of extremely promising and potent therapies that lead to massive phase I trials enrolling hundreds if not thousands of patients (Figure 1). Recent successes show that, if we want to go further faster and expedite efficiently drug development, it is time for a profound re-think of the strategy. This will be a hard and difficult task. But as Sir W. Churchill said, ‘a pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty’. Let’s be optimistic, and take the challenge.

In that regard, *Annals of Oncology* welcomes the publication of phase I trials [18]. Such studies will only be considered when clinical data is enriched with additional ‘translational research components’ i.e. biomarkers analysis. In exceptional cases, for example where a ‘remarkable response rate’ or a very unique pattern of toxicity is observed, translational research will not be required.

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**disclosure**

The authors have declared no conflicts of interest.

**references**


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**Figure 1.** Number of patients enrolled in recent phase I trials having led to conditional approval or breakthrough designations (based on [www.clinicaltrial.gov](http://www.clinicaltrial.gov); last accessed on October 2014).
Challenges in combining novel molecularly targeted agents in cancer medicine

Combining novel molecularly targeted agents is probably one of the most critical and complex challenges in cancer medicine today [1]. Although we currently have a burgeoning armamentarium of targeted agents in early phase clinical trials, it is clear that when administered as single agents, patient benefit is limited by the inevitable development of drug resistance. There are multiple reasons for this, including the disruption of signaling feedback loops and development of crosstalk and compensatory mechanisms of resistance. Recent studies have highlighted issues of intra- and intertumoral heterogeneity, indicating that monotherapy-targeted approaches are unlikely to result in durable antitumor efficacy [2, 3]. In light of this, recent drug development efforts have focused on combining novel targeted agents, with the primary aims of circumventing early drug resistance mechanisms and prolonging patient benefit [4].

The importance of such combinatorial approaches is reflected in the release of recommendations from the US Food and Drug Administration (FDA) on the co-development of investigational agents [5]. Several criteria have been proposed for the selection of individual drugs for such combination strategies. These include the existence of compelling biological evidence for the use of the combination, data that the novel agents cannot be developed individually, and preclinical studies showing that the combination not only has substantial activity, but is also associated with greater and more durable antitumor response or a better toxicity profile than the individual agents.

In the article by Tolcher et al. [6], the investigators have undertaken a phase I/II trial involving the combination of the mitogen-activated protein kinase kinase (MEK) inhibitor trametinib and mammalian target of rapamycin (mTOR) inhibitor everolimus. Both drugs are approved targeted therapies that have been shown to benefit patients as single agents in multiple cancers, including BRAF V600-mutation-positive melanoma [7] and renal cell carcinoma [8], respectively. This rational combination involves the horizontal blockade of mitogen-activated protein kinases (MAPK) and phosphoinositide 3-kinase (PI3K) signaling pathways, which are involved in the regulation of multiple key cellular functions. Importantly, there are strong preclinical data to support the simultaneous blockade of both pathways in cancers that harbor genetic aberrations along these signaling trunks [9].

While this is essentially a negative clinical trial for failing to establish a recommended phase II combination dose and schedule with acceptable tolerability and adequate drug exposure, the study clearly showcases the current challenges associated with combining targeted agents. It also dispels the notion that targeted therapy combinations are associated with minimal normal tissue toxicities, and clearly demonstrates that two great drugs do not always make a good combination. Such observations with targeted therapy combinations are not new, with previous studies involving other approved molecular agents also leading to ‘supra-additive toxicities’ [10, 11]. Although no obvious pharmacokinetic drug interactions were observed with this study combination, there were clear overlapping toxicities with both drugs, including mucosal inflammation, stomatitis, fatigue and diarrhea, which prohibited the achievement of clinically relevant drug exposures. Significantly, treatment-related grade 3 toxicities were observed in 24 out of 67 (36%) patients, with mucosal inflammation and liver function derangement frequently observed, necessitating dose interruptions and reduction. Rash was surprisingly not frequently observed, compared with previously undertaken studies of both drugs as single agents. Relatively high rates of drug-related toxicities have also been observed in other studies involving the combined targeting of other key MAPK and PI3K pathway substrates, such as the inhibition of MEK with PI3K or AKT [12, 13].

The study by Tolcher and co-workers also demonstrates that in such scenarios where the single-agent maximum tolerated dose (MTD) of each targeted therapy component has already been well delineated in previous phase I trials, drug scheduling appears to be more critical than dose finding. Since the MTD range has already been established, starting doses may be selected close to the previously established MTDs, thus reducing the need for multiple dose escalation cohorts. For example in this study, Tolcher and co-workers used 25% of the 2 mg recommended monotherapy trametinib dose used in melanoma treatment, and 50% of the 10 mg recommended single-agent dose of everolimus utilized in renal cell cancers. With regards to drug scheduling, the use of intermittent schedules may improve tolerability and potentially widen the therapeutic window of combinatorial regimens. The pulsatile dosing of drugs will also permit a higher degree, albeit shorter duration, of target and pathway blockade compared with continuous dosing, and may