

New Results Will Change the Paradigm for Phase I Trials and Drug Approval

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With the advent of targeted therapies in the past decade, the transition from cytotoxic treatments to highly selective molecules has radically altered and expanded options for cancer patients. Myelosuppression, mucositis, nausea, and hair loss are no longer the inevitable “partners” of antitumor drugs. For the right patient, a single oral medication may prove more beneficial than combination cytotoxic therapy. The attractiveness of this alternative and recent successes in early clinical trials have led to high patient interest in access to these new therapies even during phase I treatment, and the success of the approach promises to shorten and transform our long-established path of successive steps to drug approval.

In the past, phase I trials were pursued to establish the maximum tolerated dose (MTD), to identify organ toxicities that might limit further development, and to provide hints for the focus of phase II trials. The occasional response seen in phase I, although meaningful in terms of establishing the biological activity of the drug, often misled investigators regarding ultimate paths for approval [1]. Melanoma, a notoriously unresponsive tumor, often tantalized investigators with an occasional response to drugs such as carmustine (BCNU), trabectedin, pacli-

taxel, and others, during phase I studies. This phase I melanoma experience usually led to a dead end for drug approval in phase II trials [2].

Several recent phase I trials have disclosed startling evidence that, when patients are appropriately selected, convincing benefit can be realized in the earliest of trials, setting the stage for rapid drug approval. In a recent issue of the *New England Journal of Medicine*, investigators report dramatic evidence of response in melanoma patients to a bRAF inhibitor [3], and in a second paper, currently in press, similar results in non-small cell lung cancer (NSCLC) patients treated with an inhibitor of anaplastic lymphoma kinase (ALK) [4]. In each case, the response rate was >50% and the overall benefit rate (partial and complete responses, and minor responses and stable disease for at least 3 months) approached 90%. Conventional treatments for these indications are expected to produce brief responses in a minority of patients, and at the cost of severe toxicity. These findings are all the more impressive in that many of these patients had received prior conventional chemo- or immunotherapy, and their tumors, as a histological type, were notoriously unresponsive to treatment. Con-

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firmatory phase II and phase III trials are ongoing for both drugs, but the phase I success has created a strong demand for early access to them. The number of potential patients, particularly in the case of melanoma, vastly exceeds the number of available slots on trials. The respective pharmaceutical companies and the U.S. Food and Drug Administration are working diligently to establish compassionate treatment programs and to reach early approval for marketing.

What made the phase I experience so successful? The answer is simple: patient selection. In each of these trials, a biomarker for response was obvious. The *bRAF* inhibitor designed by Plexxikon (Berkeley, CA) specifically blocks the mutated form of *bRAF* (V600E), a mutation that affects $\geq 50\%$ of melanoma patients. The ALK inhibitor from Pfizer (New York), one of approximately 70 such ALK-directed drugs in preclinical or clinical development, blocks the function of a receptor tyrosine kinase that is activated by chromosomal translocation in about 4% of NSCLC patients, primarily nonsmokers. In each trial, an expansion cohort at the MTD accrued patients with tumors that had the specific mutation in question, and the results were spectacular. Toxicity, primarily diarrhea and reversible hepatotoxicity, was modest and reversible. A higher incidence of cutaneous squamous cell cancers of the skin was observed in patients treated with the *bRAF* inhibitor, but these tumors were easily removed surgically. Although confirmation of these results is important, the number of responders in the phase I trials is sufficiently impressive to convince both patients and oncologists that the drugs are valuable, and even preferable to existing treatments. Applications for marketing approval are likely to be completed in the next calendar year, even though the phase II and phase III trials are just now beginning. The phase II data should confirm the phase I findings and should be sufficient to allow drug registration.

These trials have profound implications for cancer drug development. They are notable for the speed with which convincing evidence of drug efficacy was obtained. However, in expanding the treatment cohort to patients with a molecular type of tumor, the participation of multiple institutions was required. Particularly for the ALK trials, >1,000 tumor biopsies from nine institutions worldwide were analyzed for the EML-4 ALK translocation to find the <10% who received treatment [4]. A second challenge, to analyze biopsies for the mutations in question, was accomplished through central research laboratories in each study, but rollout of these therapies for general use will require that easily accessible testing be established on a national basis.

This phase I experience has convinced knowledgeable investigators that tumor profiling and patient selection will

become a routine part of cancer drug development. My own hospital, the Massachusetts General in Boston, has established a tumor profiling laboratory that tests tumor specimens from all new patients with melanoma, NSCLC, colon cancer, and other tumors of interest, in order to assign patients to the appropriate clinical trial. A growing number of cancer centers are establishing such laboratories, because the capability is essential to performing clinical trials and will shortly become a necessary technology for routine patient care [5].

The earlier successes in targeted therapy were derived from the same rationale for patient selection, but the need for tumor profiling was not immediately apparent. Imatinib for chronic myeloid leukemia (CML) won approval after phase II [6], but patient selection was straightforward because all CML patients had the mutation in question. Everyone with CML was a candidate. The clinical development of trastuzumab depended on the demonstration of human epidermal growth factor receptor 2/*neu* amplification in tumor specimens, but clinical benefit was less obvious, with few responses, in its phase I trials [7]. For this drug, patient selection was complicated by uncertainties regarding the best method for demonstrating amplification (immunohistochemistry versus fluorescence in situ hybridization). The value of trastuzumab was not realized until its synergy in combination with cytotoxic chemotherapy (primarily taxanes) was demonstrated [8]. The oral epidermal growth factor receptor (EGFR) inhibitors were developed in NSCLC patients based on the misguided hypothesis that expression of EGFR would confer sensitivity. It is now apparent that these small molecules have their greatest activity against mutant *EGFR* NSCLC, but this relationship was established only after phase III trials in unselected patients were completed [8]. Later phase II–III trials clearly determined the response rate, which was >70%, in appropriately selected patients [9].

The development of these new drugs for ALK and *bRAF* tumors, even after their anticipated early approval, has only begun. Like other single agents in cancer treatment, they do not cure the disease. Drug resistance must be overcome with rationally designed combinations of drugs, incorporating either other targeted drugs, antibodies, or cytotoxics. Understanding mechanisms of resistance should lead to logical combination trials, and thus it is critical to obtain tumor biopsies in patients with progressive disease.

As was said many times in the past regarding cytotoxics, drug approval is only the first step toward developing effective therapy. Fortunately, that first step may become a more rapid process, thanks to patient selection.

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