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Commentary

Development of Molecularly Driven Targeted Combination Strategies

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The development of molecularly targeted agents has undoubtedly led to multiple successes in cancer medicine, such as *BRAF* inhibitors in *BRAF* V600E mutant melanoma and epidermal growth factor receptor (EGFR) inhibitors in *EGFR* mutant non-small cell lung cancer (NSCLC) [1]. However, not all patients will respond, and drug resistance is inevitable with resulting disease progression in most if not all patients. Considering other key issues such as intratumor heterogeneity, clonal evolution, and the development of crosstalk and disruption of feedback loops, it is clear that targeted therapies are often inadequate when used in isolation as single agents, and rational combinatorial strategies are therefore predicted to be necessary to overcome compensatory escape mechanisms [2]. Combining diverse targeted therapies could optimally impact patient care by overcoming cancer resistance mechanisms, which may comprise multiple redundant signaling pathways (primary resistance) or involve the emergence of secondary mutations (acquired resistance). In the case of the trial presented in this issue by Leong et al. [3], combining EGFR and phosphatidylinositol-3 kinase (PI3K) inhibitors could enhance antitumor effects by cytotoxic enhancement (greater pathway inhibition using two agents against the same pathway, or "vertical inhibition"), biological cooperation (targeting different cell populations such as *EGFR* mutations and *PIK3CA* mutations), or temporal modulation (one target is upregulated when the other is inhibited; thus, the combined inhibition achieves a higher level of antitumor activity).

Despite their relative selectivity versus chemotherapy, it is now clear that the combination of targeted therapies is challenging, especially when overlapping toxicities are a barrier. Furthermore, while many chemotherapy-related toxicities may be effectively treated symptomatically with supportive measures, molecularly targeted agents bring a different portfolio of toxicities, including rash and elevated liver transaminases, which are more challenging to manage, especially when such therapies usually require continuous dosing until disease progression. A range of strategies have been employed to minimize the risk of such combination toxicities, such as the intermittent scheduling of the PI3K inhibitor pictilisib in combination with daily continuous doses of erlotinib, as undertaken in the study by Leong and colleagues [3]. In this trial, while there was only one dose-limiting toxicity of grade 3 facial edema and skin toxicity of the 11 patients treated at the recommended phase II combination dose, it is still unclear if this dose will be tolerable chronically, especially when other pictilisib combination trials have required dose reductions due to issues with long-term tolerability.

Some golden rules have typically been applied to the combination of chemotherapeutic agents in the past, including the use of drugs known to be active as single agents and combining compounds with complementary mechanisms of action, and/or additive or synergistic cytotoxic effects, but with nonoverlapping, dose-limiting toxicities and patterns of resistance. Although some of these considerations do not apply to targeted therapies today (e.g., the latter drugs in combination may result in synergistic effects without being highly active as single agents), two key issues that should be considered for the success of such targeted combinations include preclinical and clinical study designs and the selection of the most appropriate compounds for clinical testing (e.g., could an EGFR-targeting monoclonal antibody such as cetuximab be easier to combine with a small molecule? Is pictilisib the optimal PI3K inhibitor with the fewest off-target effects?). It is key to consider not only the pharmacology of each drug, routes of delivery, potential drug-drug interactions, and schedules, but also the degree of biological pharmacodynamic (PD) synergism. Potential strategies that should be considered to address these issues include broad preclinical modeling, with a large program to determine the optimal pharmacokinetic (PK) and PD relationship and treatment schedule, and the testing of these hypotheses clinically in biomarker-rich clinical trials.

Such a biology-driven approach will enable the direct testing of each combination at a molecular level and truly assess if there is synergy between two targeted therapies. Utilizing a PD biomarker-driven approach to direct dose and schedule will require prior animal modeling to establish the quantitative extent and duration of on-target and pathway inhibition necessary for both biological and therapeutic effects [4]. Such prior knowledge can then be utilized to correlate preclinical PK-PD profiles with toxicity and efficacy results. For example, preclinical studies of pictilisib indicated that >90% inhibition of AKT phosphorylation over several hours is required for 50% reduction in the number of proliferating cancer cells in vitro and subsequent growth arrest in tumor xenografts [5]. During the phase I single-agent trial of pictilisib, detailed PD studies were undertaken that demonstrated suppression of phosphorylated AKT levels by >90% in both platelet-rich plasma samples at 3

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hours after dosing and in tumor tissue at doses associated with PK area-under-curve levels >20 h/μmol/L [6]. Increased levels of plasma insulin and glucose levels, as well as >25% decrease in fludeoxyglucose (^{18}F) uptake by positron emission tomography scans in several patients, also provided evidence of target modulation in the clinic. While the recommended phase II dose (RP2D) was continuous dosing at 330 mg once daily, on-target PD activity was observed at dose levels ≥100 mg. Despite these positive PK and PD findings in multiple patients, single-agent antitumor activity with pictilisib was limited, thus leading to the development of rational combinatorial strategies with antitumor agents such as with erlotinib. During this combination trial by Leong et al. [3], grade ≥3 toxicities occurred in 38 patients (66.7%), with the most common including rash and elevated alanine transaminase levels in 6 patients (10.5%) each. The most common adverse events were diarrhea (70.2%), nausea (54.4%), fatigue (54.4%), and rash (49.1%), likely due to overlapping toxicities of both compounds.

Despite beginning with a starting dose of 60 mg daily of pictilisib on days 1–21 of a 28-day cycle, which is less than a fifth of the RP2D of pictilisib monotherapy, and erlotinib at a dose of 150 mg daily from day 2 of the first cycle in cohort 1, the maximum tolerated dose was exceeded at the first dose level. This led to a switch to a 5-days-on, 2-days-off (5/2) intermittent schedule of pictilisib, followed by a subsequent decrease in erlotinib dosing to 100 mg daily, again because of overlapping toxicities. While the investigators were able to escalate doses of pictilisib to 340 mg in a 5/2 schedule, it had to be administered with 100 mg daily of erlotinib, which is lower than the recommended monotherapy dose of 150 mg daily given to patients with NSCLC. Nevertheless, 100 mg daily of erlotinib is still considered a biologically active dose of drug and is the recommended dose when given in combination with gemcitabine to patients with advanced pancreatic cancers. Regardless, it would have been helpful to have had PD biomarker studies incorporated into this phase I trial to assess the underlying target and pathway modulation with this different dose and schedule of both drugs and to guide the exploration of other schedules if appropriate. For example, one could use such PD biomarker analyses of patient specimens undertaken prospectively in real time to quantify target and pathway modulation of both inhibitors in combination. These PD data from the combination study could be compared with single agent data to gauge the relative contribution of each drug to the combination. This could in turn inform appropriate dose escalation or schedule modification, contingent on safety and tolerability, to optimize target and pathway inhibition. Alternatively, preclinical PK/PD modeling for the combination could indicate PK exposure levels in which erlotinib and pictilisib robustly inhibit the pathway and lead to antitumor activity. Such a model could help in the interpretation of the relevance of drug PK exposure levels achieved at the RP2D of the combination trial presented here.

While appropriate patient selection through the use of predictive biomarkers of response and resistance have been established for multiple targeted monotherapies, a new challenge will be to determine the optimal selection of patients for combination regimens, which may be different from single agent regimens. In the study by Leong and colleagues, while sensitizing *EGFR* mutations are a well-established predictive biomarker of response in patients with *EGFR* mutant NSCLC, biomarkers for PI3K inhibitors remain less established. Although aberrations of key components of the PI3K pathway, such as *PIK3CA*, *PTEN*, and *AKT*, have already been implicated as promising putative predictive biomarkers of response, they have not been shown to predict strongly for patient benefit for PI3K/AKT pathway inhibitors. Reasons for this are multifactorial and include likely differences in variant-level drug sensitivity and a lack of sufficiently potent and robust PI3K/AKT pathway inhibitors with tolerable safety profiles. Another important consideration is whether *RAS* mutations represent negative predictors of activity for EGFR and PI3K inhibitors. This is especially salient because 9 of 40 (22.5%) patients molecularly profiled in this trial were found to harbor somatic *RAS* mutations. None of these patients achieved an objective response to this combination.

Pictilisib is a pan-class I PI3K inhibitor, with varying levels of potency against different PI3K isoforms. While promising antitumor activity with pictilisib and other PI3K inhibitors has been observed in preclinical studies, the transition to the clinic has been generally disappointing despite the progression of more than 30 small molecule PI3K inhibitors into clinical trials [7]. A more promising strategy in targeting PI3K appears to be through the development of isoform-specific PI3K inhibitors, such as PI3Kδ inhibitors—idelalisib was recently approved for use in relapsed hematological B-cell cancers, although there are concerns over serious gastrointestinal, pulmonary, and infective toxicities. There are also promising data supporting the use of p110α-specific PI3K inhibitors, such as alpelisib and taselisib in *PIK3CA* mutant malignancies; p110δ-specific PI3K inhibitors, including GSK-2636771 and AZD8186 in cancers with PTEN loss; and p110γ-specific PI3K inhibitors [8]. Similarly, the third-generation *EGFR* mutant-specific inhibitor osimertinib recently demonstrated a statistically significant and clinically meaningful progression-free survival benefit in first-line *EGFR* mutant NSCLC compared with current standard-of-care treatments, including erlotinib, in the phase III FLAURA trial [9]. An alternate combination to the one used in the study by Leong and colleagues, which targets the same pathways, may thus include the combination of osimertinib with an isoform-specific PI3K inhibitor, the latter of which may be determined based on the molecular profile of the patient, especially with regard to coexisting aberrations. In this study, objective responses were observed in only 3.5% of patients, and prospective patient selection was not undertaken for either molecular or tumor type, stressing the importance of upfront molecular testing and the appropriate matching of patients with this drug combination.

In conclusion, during the development of targeted combinations, it is imperative that due consideration be given to the incorporation of PK-PD profiling, as well as putative predictive biomarkers, so as to increase the odds of success in impacting patient benefit and accelerating oncological drug development.

Disclosures

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Editor's Note:

See the related article, "A Phase I Dose-Escalation Study of the Safety and Pharmacokinetics, of Pictilisib in Combination with Erlotinib in Patients with Advanced Solid Tumors," by Stephen Leong et al., on page 1491 of this issue.