

CCR TRANSLATIONS COMMENTARY

Combining molecularly targeted agents: is more always better?

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Summary

The concurrent targeting of critical nodes along key signaling pathways with molecularly targeted agents is a rational antitumor strategy, which has had varying degrees of success. Combinatorial challenges include overcoming synergistic toxicities and establishing if combinations are truly active, to make “go, no-go” decisions to proceed to later phase trials.

In this issue of *Clinical Cancer Research*, Calvo and colleagues report a phase I trial combining dacomitinib, the small molecule irreversible pan-HER inhibitor and figitumumab, the insulin growth factor-1 receptor (IGF-1R) monoclonal antibody (1). Significant signaling crosstalk exists between the pan-HER family of receptor tyrosine kinase (TKI) pathways and IGF signaling network; therefore, combinatorial targeting of critical nodes along these pathways are a rational antitumor strategy (2) (**Figure 1**). There has been much hope placed on the development of rational combination regimens of molecularly targeted agents against key signaling pathways to overcome treatment resistance observed with single agent therapies (3). While we have had evidence of success with such targeted combinations, e.g. blockade of BRAF and MEK in *BRAF* V600E mutant melanoma (4), a major challenge has been synergistic toxicities observed with a number of targeted combinations, especially those involving the horizontal blockade of parallel signaling pathways (**Figure 1**). These toxicities have often hindered dose escalation of one or both drugs to single agent recommended phase 2 doses (RP2D), potentially resulting in the administration of subtherapeutic doses of either or both drugs, likely leading to poor pharmacokinetic exposures and lack of target modulation. A potential strategy around this may be to alter drug scheduling, e.g. with pulsatile dosing of one or both drugs to reduce such toxicities.

With regards to the study by Calvo and colleagues, this was essentially a dose de-escalation study, despite investigators starting dacomitinib and figitumumab at reasonable doses, which were below the RP2D of both drugs (1). However, dose-limiting toxicities (DLTs) and chronic intolerance prevented monotherapy RP2Ds of both

drugs from being reached. With the benefit of hindsight, this increased rate of serious toxicities should not be surprising, given the findings observed in the phase 3 trial of the epidermal growth factor receptor (EGFR) TKI erlotinib in combination with figitumumab in patients with non-adenocarcinoma non-small cell lung cancer (NSCLC). This combination failed to demonstrate a survival benefit, and significantly increased toxicities in the combination arm (5). Another issue with targeted combinations is the seemingly mild chronic toxicities, which are often not taken into consideration when establishing the RP2D as they do not constitute DLTs during phase I studies. However, such chronic adverse events have been found to lead to dose reductions and interruptions in phase 3 studies, potentially affecting the efficacy and regulatory approval of such drugs (6).

In this study, it is unclear if this is a truly synergistic combination of two drugs known to be active as monotherapies. Overall, antitumor activity was modest, with only 3 objective responses observed out of 61 evaluable patients, despite the investigators enriching the patient population with cancers known to respond to both drugs as single agents. Two of the three RECIST partial responses were also observed at intolerable doses of the combination (1). Furthermore, while suboptimal doses of pan-HER blockade may, in theory, interact favorably with IGF-1R inhibition to lead to responses, it is likely that the antitumor activity observed in these three patients were due to figitumumab, rather than dacomitinib or the combination since the doses of dacomitinib given to these responders were well below its monotherapy RP2D (1). Remarkably, the preclinical gene set enrichment studies suggested that low, rather than high, levels of

the target of figitumumab were associated with greater levels of tumor growth delay. Indeed, higher levels of IGF-1R pathway activation were associated with non-response. Although the authors suggested that this paradox might represent a “saturation effect”, this observation certainly deserves more detailed analysis before embarking on larger studies.

It now seems like an age-old debate – and remains a continued challenge - how one actually determines, in phase I studies, if a combination potentially has superior antitumor activity to either single agent, so as to make robust “go, no-go” decisions to proceed to later phase trials (3). This is particularly relevant when one or both drugs are known to be potentially efficacious – as is the case with this trial - since it will be challenging to assess the synergistic value of the combination without a large and suitably powered randomized trial. Although a randomized phase 2 trial would seem like the ideal next step, such a study may be associated with high false-positive and/or false-negative rates, complicating interpretation of the results. A more novel strategy involves a “reversal-of-resistance” approach, where patients are initially exposed to one drug (usually the active one) until disease progression, when the second drug is added to assess if drug resistance is “reversed” (3).

Aligning clinical and pre-clinical drug testing in co-clinical trials is an emerging strategy for early drug development and appears to be a sound approach to explore adaptive therapies aimed at overcoming drug resistance, especially in rare tumor types (7). The authors used avatar mouse models of adenoid cystic carcinoma (ACC) to explore the

synergic effects of figitumumab and dacomitinib. The results from these avatar studies were expressed as percentage tumor growth inhibition relative to control, without data provided on absolute tumor volumes and their changes over time, making it difficult to interpret these data and draw inferences on the relative roles of the two agents in mediating the observed therapeutic effects. Regardless, there appears to be little synergistic activity between the two drugs since the tumor growth inhibition achieved with the combination is comparable to single agent figitumumab in most of the patient-derived xenografts (PDXs).

It would have been interesting if tumor specimens for PDXs and molecular profiling had been obtained at baseline and at disease progression from patients with ACC enrolled in the trial, instead of an independent cohort, so as to add biological insights into the development of predictive biomarkers of response. While obtaining sequential biopsies from phase I trial patients poses potential safety, logistical and ethical issues, they represent an opportunity to define changes in the molecular profile of the tumor during treatment, so as to dissect mechanisms of synergy and to influence decision-making in proceeding to phase II trials. Organoid technologies have made rapid advances in recent years (8), and may represent a cost-effective alternative to genetically-engineered mouse models and PDXs, providing a timely and financially sustainable platform to understand tumor heterogeneity, predict resistance mechanisms, and enable high-throughput drug discovery.

Both dacomitinib and figitumumab were developed with relatively high expectations, but have unfortunately not found their niche areas of unmet need to achieve regulatory approval (9,10). Pfizer has discontinued figitumumab development, while dacomitinib is currently being assessed in a phase III trial versus gefinitib (AstraZeneca) for the first line treatment of advanced *EGFR* mutant NSCLC. However, in a rapidly evolving and crowded treatment landscape in *EGFR* mutant NSCLC, even if this is a positive trial and dacomitinib is approved, its role in this space remains unclear given its toxicity profile and potential fiscal burden (11).

Ultimately, with some combinations, it may simply not be feasible to block two or more key signaling pathways involved in critical malignant and normal cellular functions. In such situations, one should consider a sequential rather than concurrent use of such agents, as guided by molecular profiling of tumor re-biopsies or circulating tumor DNA (12). Finally, in the advent of immuno-oncology and the emergence of novel epigenetic inhibitors, one should also widen the spectrum of rational combination regimens to include other exciting classes of antitumor agents.

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FIGURE LEGEND

Figure 1. Combination studies of molecularly targeted agents against critical targets along the IGF-1R and HER family signaling pathways.

The combination of inhibitors against RAF and MEK along the MAPK signaling pathway is now Food and Drug Administration (FDA)-approved for clinical application (green line). Several other combinations have successfully completed phase I/II trials, suggesting that these regimens are potentially feasible with early signals of antitumor responses observed (orange lines). However, other combinations have been found to be intolerable in phase I trials (solid red lines), or have failed to meet their endpoints of survival or response in phase II/III studies (dotted red lines). While this list of combinations - based on peer-reviewed publications and/or international conference abstracts - is not exhaustive, it does suggest that combining molecularly targeted therapies against critical targets along these key signaling pathways is fraught with potential pitfalls and challenges. Nevertheless, there has been evidence of success, providing proof-of-concept for this antitumor strategy. Combination approaches involving other classes of antitumor agents, e.g. angiogenesis and DNA repair, are also currently being explored (not shown in figure).

DISCLOSURES

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Figure 1:

