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Commentary

BEZ235: When Promising Science Meets Clinical Reality

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In the July 2016 issue of ***The Oncologist***, Carlo et al. report the results of a phase I clinical trial [1] of BEZ235 in patients with advanced renal cell carcinoma (RCC). BEZ235 is a dual pan-class PI3K and mTOR inhibitor currently undergoing phase I/II clinical trials as a single agent or in combination in solid tumors and hematologic malignancies. The authors are to be congratulated for reporting the early termination of the BEZ235 trial due to toxicity and a lack of clinical efficacy.

PI3Ks are a family of kinases that regulate multiple hallmarks of cancer, including survival, proliferation, tumor metabolism, autophagy, and angiogenesis [2]. Many of these hallmarks are regulated through PI3K mediated regulation of the mTOR pathway [3, 4]. The genetic and molecular rationale of targeting the PI3K/Akt/mTOR pathway in RCC is supported by the existence of recurrent mutations of the pathway in clear cell RCC and elevation of the PI3K/Akt/mTOR proteomic signature in both clear cell and papillary RCC [5, 6]. Consistent with this, two mTOR inhibitors, temsirolimus and everolimus, have received U.S. Food and Drug Administration (FDA) approval in renal cell carcinoma. However, resistance to mTOR inhibitors is acquired early, possibly due to feedback activation of PI3K although upstream receptor tyrosine kinase signaling, providing the rationale for combined inhibition of PI3K and mTOR [7–9].

In the current study, Carlo et al. reported increased frequency of grade 3–4 adverse effects with BEZ235 in 50% of patients (5 of 10) without objective responses in the evaluable patients [1]. Most of the dose-limiting toxicities, including fatigue, diarrhea, nausea, and mucositis have been described with both PI3K and mTOR inhibitors, and thus, it is not surprising that combined pan-PI3K and mTOR blockade resulted in a high frequency of adverse events. Additionally, poor tolerability and modest clinical activity have been previously reported with BEZ235 in other solid tumors. In a phase II trial of advanced pancreatic neuroendocrine tumors (PNETs) comparing everolimus and BEZ235, adverse events led to treatment discontinuation in 39% and 16% of BEZ235- and everolimus-treated patients, respectively [10]. In another phase II trial in patients with PNETs whose disease progressed on everolimus, poor tolerance of BEZ235 with only modest activity led to study termination [11]. Finally, in metastatic RCC, apitolisib (GDC-0980), another dual pan-PI3K and mTOR inhibitor, also demonstrated a high incidence of grade 3–4 adverse effects and worrisomely shorter progression-free survival with a trend toward shorter overall survival compared with everolimus [12].

Overall, data from the aforementioned clinical trials make us question whether daily concurrent pan-PI3K and mTOR inhibition offers a viable strategy for treating cancer. It appears that full blockade of class I PI3K and mTOR cannot be tolerated due to multiple on-target adverse effects. While a pan-PI3K inhibitor aims to abolish total PI3K activity in the tumor, it fails to exploit dependency to a specific isoform that in turn could avoid unnecessary adverse effects from the inhibition of other "nonrelevant isoforms." Can we do better?

Isoform-specific PI3K inhibitors are currently under development. Early phase studies of PI3Kα and PI3Kβ inhibitors appear to show a more favorable adverse effect profile with preliminary evidence of responses in tumors harboring activating *PIK3CA* mutations or PTEN loss [13, 14]. Ongoing clinical trials are evaluating BYL719, an isoform specific PI3Kα inhibitor in combination with everolimus in patients with advanced RCC and PNETs [15]. Adverse events are likely to remain an issue, leaving open the question of how or if tolerability might be improved. In this regard, consideration will have to be given to the mTOR inhibitors and how critical is their use in these combinations, especially at the "approved" doses. Few drugs have proven more difficult to administer on a daily regimen than inhibitors of mTOR, and their activity, even in diseases for which regulatory approvals have been granted, have been modest [9, 16–19]. As regards toxicity, for example, even in pivotal trials everolimus has been discontinued or reduced by a high percentage of patients [17–21]. Even in the most recent everolimus approval, discontinuation for adverse events occurred in 29% of patients, and dose reductions or delays occurred in 70%, indicating that despite widespread experience, administration of everolimus remains very difficult and, in a majority of patients, not possible at a 10-mg dose [19, 22]. Temsirolimus, originally explored in patients with advanced RCC and shown in that pivotal trial to be relatively well tolerated, has also encountered tolerability issues in subsequent studies and has not been well tolerated at higher doses [23–28]. Thus, the issue of tolerability emerges in our minds as critical to the future of these drugs in any combination. We must ask whether the optimal drug or optimal schedule for mTOR inhibition has

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been explored or come to recognize that the mTOR pathway, shown in countless preclinical studies to be central to so many functions, cannot be inhibited continuously without inflicting intolerable toxicities [29–31]. A recent FDA approval of everolimus, in combination with lenvatinib, in RCC suggests that tolerability may be mitigated by lower doses, while possibly retaining activity, but the validity of this, especially in other diseases, and its clinical importance remain to be determined [32]. But might intermittent mTOR inhibition be better tolerated? While the temsirolimus clinical data suggest intermittent (weekly) administration can also be problematic, an intermittent schedule, especially in combination regimens, might improve tolerability. After all, do we have firm data in tumors that continuous 24/7 inhibition of mTOR is essential?

If we accept the limitations of our preclinical models and the even greater limitations of our speculations, then we realize only clinical trials in humans can give us answers. In the end, we must test our hypotheses, obtain results, and move forward. As the article by Carlo et al. shows, we can quickly establish tolerability and even a level of efficacy everyone would consider valuable—not one that is marginal in quantity [33]. And once we establish this, we must submit it for publication, rapidly and concisely, so that others can learn from it. Only by doing this, can we aspire to move forward to hopefully better outcomes for the many patients who still struggle with cancer.

Disclosures

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