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TARGETED THERAPIES

Juggling combinations—not the way forward

The therapeutic landscape for the treatment of advanced-stage renal cell carcinoma (RCC) has changed considerably over recent years, as a result of molecular targeted therapies. Specific inhibitors of the mTOR signalling pathway, such as temsirolimus, and inhibitors targeting VEGF, such as bevacizumab, are standard therapies for patients with advanced-stage RCC. Both temsirolimus and bevacizumab have demonstrated single-agent activity in early phase trials. As both agents target different mechanisms of the carcinogenesis process, a randomized phase III multicentre trial (INTORACT) was initiated to assess whether combining both agents would improve clinical outcome.

Patients with previously untreated metastatic RCC were randomly assigned to receive either temsirolimus with bevacizumab or interferon with bevacizumab. Surprisingly, "the combination of temsirolimus and bevacizumab did not improve progression-free survival (PFS) or overall survival compared with bevacizumab and interferon—a standard of care in this setting," explains Brian Rini, lead investigator of the trial. Importantly, a greater toxicity was noted for the bevacizumab combination. Although an improvement in functional index scores (FKSI-15 and FKSI-DRS) was noted with the temsirolimus and bevacizumab combination, no differences in global health outcome measures were observed.

Rini concludes, "this trial confirms that these combinations remain experimental and can have substantial toxicity. This drug combination will not be further tested. The implications are that combinations of mTOR and VEGF inhibition are not a viable way to advance the care of patients with RCC."

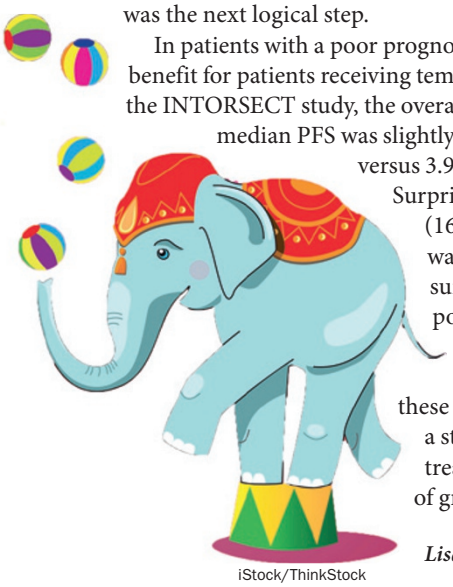
Another phase III, open-label study (INTORSECT) compared temsirolimus with the oral multi-tyrosine kinase inhibitor sorafenib—which, similar to bevacizumab, also targets VEGF—as second-line therapy in patients with metastatic RCC who have experienced disease progression after receiving treatment with sunitinib. Patients on the trial were stratified according to histology and duration of prior sunitinib therapy. As in the case of the INTORACT study, because both agents had different mechanisms of action, comparing them was the next logical step.

In patients with a poor prognosis, an earlier study had shown an overall survival benefit for patients receiving temsirolimus compared with those receiving interferon. In the INTORSECT study, the overall response rate was similar for both arms. Although the median PFS was slightly longer for patients treated with temsirolimus (4.3 months versus 3.9 months), this difference was not statistically significant. Surprisingly, the overall survival was much longer with sorafenib (16.6 months versus 12.3 months). It is not clear why there was a discrepancy in the correlation between PFS and overall survival, but the most likely reason relates to the use of post-study anticancer therapy that was not prespecified in the study protocol.

Bernard Escudier, coinvestigator on both trials, puts these study findings into context: "The results imply that there is a stronger rationale to use VEGF inhibitors in the second-line treatment of RCC compared with an mTOR inhibitor, which is of great value for oncologists."

Lisa Hutchinson

> "...[these combinations] are not a viable way to advance the care of patients with RCC"



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Original articles Rini, B. I. *et al*. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. *J. Clin. Oncol*. doi:10.1200/JCO.2013.50.5305 | Hutson, T. E. *et al*. Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. *J. Clin. Oncol*. doi:10.1200/JCO.2013.50.3961