KIDNEY CANCER

Reversal of fortunes
for TKI resistance

New data show that resistance to tyrosine kinase inhibitors (TKIs) can be overcome by targeting HDAC-mediated overexpression and stabilization of HIF-1 α using the HDAC inhibitor abexinostat. This strategy enables prolonged treatment exposure and improves patient responses.

Aggarwal and colleagues enrolled participants to a phase Ib, open-label, dose-escalation and expansion trial of abexinostat in combination with pazopanib. The trial included 55 patients, 22 of whom had RCC and 30 of whom had received VEGF-targeted therapy. Two dosing schedules were assessed: schedule A consisted of oral abexinostat administered twice a day on days 1 to 5, 8 to 12, and 15 to 19, and schedule B involved oral abexinostat administered twice a day on days 1 to 4, 8 to 11, and 15 to 18. Pazopanib was given orally once a day in both schedules. The primary end points were determining the maximum tolerated dose, recommended dose, and schedule for phase II assessment. Secondary aims included characterization of the pharmacodynamic profile and analysis of safety and efficacy.

Of 20 evaluable patients receiving schedule A, 25% experienced dose-limiting toxicities, which resulted in schedule B being devised; only 8% of patients on this regimen experienced a dose-limiting toxicity. Regarding safety, no grade 5 adverse events were reported, but dose interruptions or reductions were common; however, only two patients discontinued treatment.

Overall, nine of 43 evaluable participants achieved an objective response. Of the 10 patients whose disease had progressed on previous pazopanib monotherapy, seven experienced tumour regression using combination therapy. Of 28 patients who had experienced disease progression whilst receiving one or more VEGF-targeted therapies, 19 experienced tumour regression, and six had an objective response. For patients with RCC, six of 22 had an objective response and median duration of response was 10.5 months; eight patients had a durable response, five of whom had experienced progression whilst on VEGF-targeted therapy. For patients with pazopanib-refractory RCC, three had minor or partial durable responses. Pharmacodynamic analyses showed that peripheral blood mononuclear cell histone acetylation and *HDAC2* expression were associated with durable response to treatment.

These results show that reversing TKI resistance using HDAC inhibitors is possible and can result in durable responses for patients when used as part of a combination therapy regimen.

Louise Stone

ORIGINAL ARTICLE Aggarwal R, et al. Inhibiting histone deacetylase as a means to reverse resistance to angiogenesis inhibitors: phase I study of abexinostat plus pazopanib in advanced solid tumor malignancies. *J. Clin. Oncol.* <http://dx.doi.org/10.1200/JCO.2016.70.5350> (2017)

For patients with pazopanib-refractory RCC, three had minor or partial durable responses”

P Morgan/Macmillan Publishers Limited