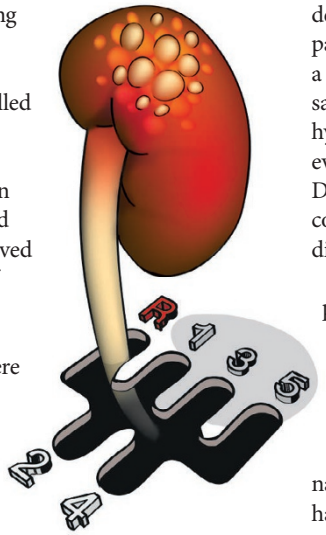
Nature Reviews Clinical Oncology | Published online 7 Mar 2017; doi:10.1038/nrclinonc.2017.33

TARGETED THERAPIES

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-1α using the HDAC inhibitor abexinostat. This strategy was shown to prolong treatment exposure and improve patient responses.

Aggarwal and colleagues enrolled patients to a phase Ib, open-label, dose-escalation and expansion trial of abexinostat in combination with pazopanib. The trial included 55 patients, 30 of whom had received VEGF-targeted therapy and 10 of whom had experienced disease progression on pazopanib monotherapy. Two dosing schedules were assessed: schedule A consisted of oral abexinostat administered twice daily on days 1 to 5, 8 to 12, and 15 to 19, and schedule B involved oral abexinostat administered twice daily 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 to determine the maximum tolerated dose and RP2D. Secondary aims included characterization of the pharmacodynamic profile and analysis of safety and efficacy.



P. Morgan/Macmillan Publishers Limited

Of 20 evaluable patients receiving schedule A, 25% experienced dose-limiting toxicities, prompting the development of schedule B; only 8% of patients on this regimen experienced a dose-limiting toxicity. Regarding safety, one patient had grade 3 hypertention and reported adverse events were mainly of grades 1–3. 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 with disease that 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. 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

This article is modified from the original in *Nat. Rev. Urol.* (http://dx.doi.org/10.1038/nrurol.2017.37)

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)