Nature Reviews Clinical Oncology **10**, 65 (2013); published online 11 December 2012; doi:10.1038/nrclinonc.2012.226

HAEMATOLOGY

PONATINIB—THE NEXT TKI CHALLENGE

Patients with chronic myeloid leukaemia (CML) and other haematological cancers—including multiple myeloma, acute lymphoblastic leukaemia and myelofibrosis—often develop resistance to tyrosine kinase inhibitors (TKIs). A new agent, ponatinib, has shown promise in a phase I study in patients with these conditions who have developed resistance to existing treatments, with even heavily pretreated patients producing a response.

"Ponatinib is an important new agent because it is clinically active in the setting of patients who have tried multiple prior therapies with no good response," explains lead investigator Jorge Cortes. More than half of the 81 patients enrolled in the trial had been challenged with all three approved TKIs (imatinib, nilotinib and dasatinib) for their haematological cancers. The primary objective of the study was to determine the maximum tolerated dose of ponatinib, which was found to be 45 mg. Common adverse events included rash, myelosuppression and constitutional symptoms, such as fatigue. Dose-related pancreatitis was a common occurrence, but most cases resolved in a median of 6 days.

The secondary objectives included response. Of the 43 patients with CML, 98% had a complete haematological response and 72% had a major cytogenetic response. Patients with identifiable mutations that included the BCR–ABL T3151 mutation responded equally well, if not better, than those in other cohorts. "Importantly, responses were observed in very high rates whether patients had mutations or not, and regardless of the specific mutation," explains Cortes. Also, patients with CML achieved cytogenetic responses in a median of 16 weeks, with responses lasting 12–105 weeks. "Ponatinib is an important new addition for the treatment of patients with CML, and offers new hope for those who have not responded well to prior therapies," comments Cortes.

The researchers have also conducted a phase II study with more than 440 patients in all stages of the disease, the results of which confirm the high rate of response and the favourable toxicity profile. Cortes continues, "The results of that trial will be released soon." Future work will examine combination therapies of ponatinib and its use as a first-line treatment.

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Original article Cortes, J. E. *et al.* Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N. Engl. J. Med.* **376**, 2075–2088 (2012)