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HAEMATOLOGICAL CANCER

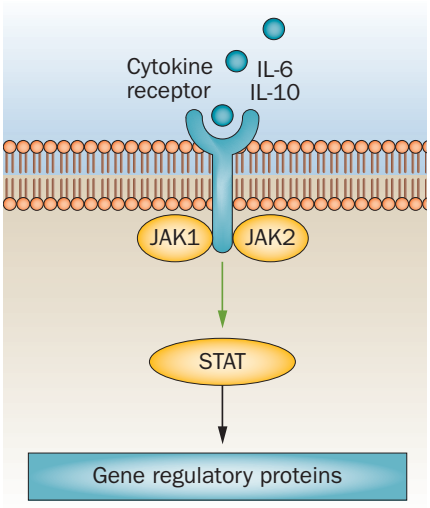
Hit the lymphoma, JAK

The Janus kinases (JAK) are a family of kinases that act downstream of a range of cytokine and growth factor signals, and are involved in the phosphorylation of the signal transducers and activators of transcription (STAT) proteins. The JAK/STAT pathway has been shown to be deregulated in a number of cancers, including lymphomas and, as such, has emerged as a rational target for anticancer therapy. Now, a phase I clinical trial has shown for the first time that it is possible to effectively target this pathway in patients with lymphoma.

The study, led by Anas Younes, assessed the efficacy of treatment with the oral pyrimidine-based small-molecule JAK2 kinase inhibitor SB1518. Younes describes the rationale: "there is accumulating evidence that a variety of lymphoma subtypes express the activated JAK/STAT pathway, which contributes to their growth and survival." He continues, "this activation is linked with rare genetic and epigenetic defects, but in the majority of cases it is driven by autocrine and paracrine cytokine loops. With this background, we hypothesized that interrupting JAK/STAT signalling might lead to growth arrest and clinical responses in patients with relapsed lymphoma."

Patients with relapsed or refractory lymphoma of most subtypes (except Burkitt's or CNS lymphoma) were recruited, and 34 patients received at least one dose of SB1518. The doses ranged from 100 mg per day to 600 mg per day, and the median time on the study drug was 88 days.

The study was a dose-escalation trial, but it did not continue until a maximum-tolerated dose was achieved. Rather, dose escalation was halted based on the dose that demonstrated activity against progressive disease. An intermediate dose of 400 mg per day was selected to avoid adverse events—of which gastrointestinal effects were the most common—when SB1518 is combined with a chemotherapy regimen.



Three patients (two with mantle-cell lymphoma and one with follicular lymphoma) achieved a partial response when receiving SB1518 with a progression-free survival ranged from 120 days to 249 days. When considering all evaluable patients, the median progression-free survival was 120 days.

Although the results are modest, Younes underlines the importance of this trial: "this is the first clinical proof of concept that targeting JAK2 can lead to clinical responses across different types of lymphomas." He continues, "future work will evaluate the clinical activity of SB1518 and other JAK/STAT-targeted agents in phase-II studies in patients with relapsed lymphoma. Rationally designed combination strategies, and predictive biomarkers will be explored."

Rebecca Kirk

Original article Younes, A. *et al*. Phase I study of a novel Janus kinase inhibitor, SB1518, in patients with relapsed lymphoma: evidence of clinical and biologic activity in multiple lymphoma subtypes. *J. Clin. Oncol*. doi:10.1200/JCO.2012.42.5223

Further reading Younes, A. & Berry, D. A. From drug discovery to biomarker-driven clinical trials in lymphoma. *Nat. Rev. Clin. Oncol*. doi:10.1038/nrclinonc.2012.156