Transcriptional Regulation

**Major finding:** The BET degrader dBET6 induces global BRD4 depletion, whereas JQ1 preferentially affects superenhancers.

**Mechanism:** dBET6 induces a P-TEFb/CDK9-independent disruption of transcription elongation.

**Impact:** Therapeutic agents that degrade BET proteins warrant further investigation in patients with cancer.

**BET DEGRADATION IS MORE EFFECTIVE THAN COMPETITIVE INHIBITION IN T-ALL**

Inhibitors of the bromodomain and extra-terminal domain (BET) family proteins disrupt chromatin-dependent transcriptional signaling, which is often dysregulated in cancer. Competitive BET inhibitors, such as JQ1, bind the bromodomain of the BET protein BRD4 to promote its release from chromatin, predominantly at superenhancers, to selectively suppress transcription of target genes. A small-molecule BET degrader (dBET1) has recently been developed that has a more robust antiproliferative effect than competitive BET inhibition in models of acute myeloid leukemia, but the underlying mechanism is unknown. Winter, Mayer, Buckley, and colleagues explored the mechanism underlying the differences between competitive BET inhibition and BET degradation in models of T-cell acute lymphoblastic leukemia (T-ALL). Chemical optimization of dBET1 led to the identification of a more potent compound called dBET6, which was more cell-permeable and exhibited greater cytotoxicity than dBET1. In a panel of 20 T-ALL cell lines, dBET6 also more potent than dBET1 and induced BRD4 degradation, c-MYC downregulation, and apoptosis. Further, dBET6 reduced tumor burden and extended survival in a mouse model of T-ALL to a greater extent than JQ1. JQ1 preferentially displaced BRD4 from superenhancers and downregulated a discrete set of superenhancer-regulated genes, whereas dBET6 induced a global depletion of BRD4 from regulatory elements and strong downregulation of the T-ALL core regulatory circuitry transcription factors. Mechanistically, dBET6 induced a global disruption in transcription elongation that was independent of P-TEFb and its kinase subunit CDK9, which control the release of promoter-proximal pausing. In addition to suggesting that the BET proteins are master regulators of productive transcription elongation, these findings indicate that inhibitors that degrade BET proteins may be more effective than competitive inhibitors and merit further development for the treatment of patients with cancer.


**Clinical Trials**

**Major finding:** Gilteritinib was well tolerated in a phase I/II dose-escalation and dose-expansion study.

**Clinical relevance:** Gilteritinib achieved responses in 49% of patients with relapsed or refractory FLT3-mutant AML.

**Impact:** Gilteritinib may be effective in patients with FLT3-mutant AML in single-agent or combination therapy.

**THE FLT3 INHIBITOR GILTERITINIB HAS ACTIVITY IN PATIENTS WITH AML**

Internal tandem duplications in FLT3 occur frequently in patients with acute myeloid leukemia (AML) and are associated with aggressive disease, rapid relapse, and poor overall survival. FLT3 inhibitors have had limited success, but rapid resistance generally develops, often due to FLT3**ITD** mutations. Gilteritinib is an oral FLT3 inhibitor that has demonstrated activity against FLT3 internal tandem duplications and D835 point mutations in vitro, suggesting that it might overcome resistance to other FLT3 inhibitors. Perl, Alfman, and colleagues performed an open-label, first-in-human, phase 1/II, dose-escalation and dose-expansion study to assess the safety, tolerability, and pharmacokinetic profile of gilteritinib. Secondary endpoints included overall response, duration of response, and overall survival. Gilteritinib treatment inhibited FLT3 phosphorylation at all dose levels. Gilteritinib was well tolerated, and the maximum tolerated dose was determined to be 300 mg/day. The most common grade 3–4 adverse events were febrile neutropenia (39%), anemia (24%), thrombocytopenia (13%), sepsis (11%), and pneumonia (11%). Of 249 evaluable patients, 100 (40%) achieved responses, including 19 complete remissions, 10 complete remissions with incomplete platelet recovery, 46 complete remissions with incomplete hematologic recovery, and 25 partial remissions. The median duration of response was 17 weeks, and median overall survival was 25 weeks. In the 191 patients with FLT3 mutations, 93 (49%) achieved an overall response, whereas only 7 of 58 (12%) FLT3 wild-type patients achieved responses. Collectively, the results of this trial suggest that gilteritinib monotherapy is well tolerated and has antileukemia activity in patients with relapsed or refractory FLT3-mutant AML, supporting further clinical investigation, and trials of gilteritinib in combination with other therapies are ongoing.


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