RESEARCH WATCH

UMBRALISIB INHIBITS PI3Kδ WITH LESS TOXICITY THAN PREVIOUS INHIBITORS

Class I phosphatidylinositol 3-kinases (PI3K) regulate cell proliferation, differentiation, and survival, and thus represent potential therapeutic targets in cancer. Expression of the PI3Kδ isoform is largely restricted to hematopoietic cells and it is often aberrantly activated in B-cell malignancies, supporting the development of isoform-selective PI3K inhibitors. However, despite promising antitumor activity, the PI3Kδ-selective inhibitors idelalisib and duvelisib exhibited substantial toxicity, including autoimmune-like complications in clinical studies, thought to be due in part to off-target effects, suggesting the need for more specific inhibitors. Umbralisib, a structurally distinct next-generation PI3Kδ-selective inhibitor, which also inhibits casein kinase-1ε, exhibits potent antitumor activity in preclinical studies, and Burris and colleagues assessed its safety and efficacy in an open-label phase I dose-escalation study. Ninety patients with relapsed or refractory lymphoma were enrolled and treated with umbralisib. The primary endpoints were determination of safety, maximum tolerated dose, and pharmacokinetic profile of umbralisib. Secondary endpoints included objective response rate and the duration of response. The maximum tolerated dose was determined to be 1,200 mg. Umbralisib was well tolerated and exhibited fewer autoimmune-like toxicities (such as colitis) than previous PI3Kδ-selective inhibitors, although serious adverse events potentially related to treatment occurred in 8% of patients. Overall, 33 of 90 (37%) patients had an objective response, including 3 complete and 30 partial responses. Further, there was an 85% response rate in the 20 patients with relapsed or refractory chronic lymphocytic leukemia. The mean duration of response was 13.4 months in 16 patients with chronic lymphocytic leukemia, 6.4 months in 4 patients with diffuse large B-cell lymphoma, and 9.3 months in 9 patients with follicular lymphoma. In addition to suggesting umbralisib is safe and has antitumor activity in patients with relapsed or refractory hematologic malignancies, these findings demonstrate that umbralisib has a distinct safety profile from other PI3Kδ-selective inhibitors, supporting its further clinical investigation.


THE ONCOLYTIC ADENOVIRUS DNX-2401 HAS ANTITUMOR ACTIVITY IN GliOBlastOMA

Despite standard treatment with surgery, radiochemotherapy, and adjuvant chemotherapy, glioblastomas have a poor survival rate and generally recur. Oncolytic adenoviruses have emerged as a potential therapeutic modality, and in preclinical studies the tumor-selective oncolytic adenovirus DNX-2401 induced tumor regression via direct oncolysis of tumor cells and by inducing an antitumor immune response. Lang and colleagues evaluated the safety and efficacy of DNX-2401 in a phase I dose-escalation study enrolling 37 patients with recurrent malignant glioma in two groups. Group A (25 patients), the treatment-only group, received a single intratumoral injection of DNX-2401, and group B (12 patients), the treat-resect-treat group, received intratumoral DNX-2401 followed 14 days later by tumor resection. DNX-2401 was well tolerated; no dose-limiting toxicities occurred, and no study drug-related grade 3+ adverse events occurred. Immunostaining of tumors from group B patients revealed that 55% (6/11) tumors had continued oncolytic adenovirus replication 14 days after treatment with DNX-2401, indicative of direct lysis of tumor cells. Further, post-treatment tumor sites exhibited inflammation, necrosis, and immune cell infiltration including CD8+ and T-BET+ T cells. In group A, tumor reductions were observed in 72% (18/25) of patients. The median overall survival was 9.5 months. In group A, three patients achieved complete and durable responses and two patients experienced sustained stable disease, and these patients (20%) survived for more than 3 years after treatment. Taken together, these findings reveal that DNX-2401 is safe and has antitumor activity in patients with glioma. Further, DNX2401 exhibited robust viral replication and direct killing of tumor cells in addition to producing an antitumor immune response, supporting further clinical investigation of DNX-2401.

Umbralisib Inhibits PI3Kδ with Less Toxicity Than Previous Inhibitors

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