RESEARCH WATCH

Clinical Trials

**Major finding:** PD-1 blockade with pembrolizumab achieves responses in 53% of patients with MMR-deficient tumors.

**Concept:** The frequency of mutant neoantigens in MMR-deficient tumors renders them sensitive to pembrolizumab.

**Impact:** MMR deficiency be a biomarker for response to PD-1 blockade in patients with diverse solid tumor types.

MISMATCH-REPAIR DEFICIENCY CONFER S SENSITIVITY TO CHECKPOINT BLOCKADE

Checkpoint blockade therapies, including the anti–PD-1 antibody pembrolizumab, achieve robust and durable responses in a subset of patients with a variety of tumor types. However, biomarkers that can predict response across tumor types have not been identified. A small phase II study in patients with colorectal cancer indicated that PD-1 blockade was effective in patients with mismatch repair (MMR) deficiency, which can result in many mutation-associated neoantigens (MANA) that may be recognized by the adaptive immune response, prompting Le and colleagues to evaluate the efficacy of pembrolizumab in 85 patients with 12 different MMR-deficient tumor types. Pembrolizumab treatment was tolerable and adverse events were similar to those previously reported. In total, 74% of patients experienced an adverse event, but most were low grade. Responses were observed in 46 of 86 patients (53%), including 18 complete and 28 partial responses. Further, 20 patients experienced stable disease. The overall response rate was similar in patients with colorectal cancers compared with patients with other tumor types, 52% (21 of 40 patients) and 54% (25 of 46), respectively. Median progression-free survival (PFS) had not yet been reached, but the estimated 1-year PFS was 64% and estimated 2-year PFS was 53%. Of the 18 patients who achieved a complete response and were taken off therapy, 11 exhibited no evidence of cancer recurrence after a median of 8.3 months, and 7 showed residual disease, but discontinued therapy due to intolerance. None of these patients experienced disease progression after discontinuation of pembrolizumab. Functional studies in a responding patient revealed that pembrolizumab induced a rapid expansion of MANA-specific T-cell clones. In addition to suggesting that MANA in MMR-deficient tumors render them sensitive to immune checkpoint blockade, these findings raise the possibility that testing for MMR deficiency may identify patients likely to benefit from pembrolizumab.


Drug Evaluation

**Major finding:** Click chemistry-based modification of BET inhibitors allows use as molecular probes in vitro and in vivo.

**Concept:** These probes may be used to evaluate the toxicity and efficacy of BET inhibitors or other drugs.

**Impact:** Click chemistry provides a framework to characterize the mechanisms of action of targeted therapies.

A CLICK-CHEMISTRY APPROACH REVEALS THE BET INHIBITOR MECHANISM OF ACTION

Targeted cancer therapeutics have shown great promise in preclinical research, but relatively few have had clinical success, in part due to a poor understanding of the molecular and cellular effects of the targeted agents. Tyler, Vappiani, and colleagues used a click-chemistry approach to chemically modify BET bromodomain inhibitors, which are under investigation in multiple malignancies, for use as molecular probes to allow assessment of the cellular localization, protein and genomic targets, and effects of the drug in animal models without impairing cellular drug uptake or drug-target interactions. This approach aimed to preserve the functional integrity of BET inhibitors and allowed fluorochromes or affinity tags to be reacted with the BET inhibitors within cells. Clickable derivatives of the BET inhibitors JQ1 and IBET-762 were synthesized [JQ1-Propargyl Amide, JQ1-trans-cyclooctene (JQ1-TCO), and IBET-762-TCO]. The clickable BET inhibitors phenocopied the parental compounds, resulting in displacement of BET proteins from chromatin, reduced proliferation, and nearly identical gene expression signatures. Using click sequencing to discover drug-chromatin target interactions within cells revealed that genes downregulated by BET inhibition exhibited higher chromatin occupancy of the drug, indicating that this approach can identify drug-responsive genes. Further, the JQ1 and IBET derivatives associated with the same protein complexes, demonstrating that these compounds have an overlapping molecular activity. In vivo in a mouse model of acute myeloid leukemia (AML), the activity of JQ1-TCO was higher in AML cells in the spleen compared with the bone marrow, providing a possible explanation for the development of refractory leukemic stem cells in the bone marrow, and suggesting that BET inhibitor efficacy may be improved by increased bone marrow penetration. Moreover, intracellular drug levels were higher in AML cells compared with normal hematopoietic cells. This click-chemistry approach provides insight into the mechanism of action of BET inhibitors and may allow for preclinical characterization of a wide range of targeted cancer therapies.

A Click-Chemistry Approach Reveals the BET Inhibitor Mechanism of Action


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