RECHALLENGE WITH BRAF AND MEK INHIBITORS HAS ANTITUMOR ACTIVITY

Activating BRAF<sup>V600</sup> mutations drive tumor progression by constitutively activating MAPK signaling in approximately half of patients with melanoma. Patients with BRAF<sup>V600</sup>-mutant tumors initially respond well to combination therapies targeting BRAF and MEK, but in most patients acquired resistance leads to disease progression. Resistance to BRAF inhibitors occurs via BRAF-independent reactivation of the MAPK pathway, not by mutations that preclude BRAF inhibitor binding. This suggests the possibility for effective rechallenge with BRAF and MEK inhibitors after disease progression, and preclinical and early clinical data support this notion. Thus, Schreuer and colleagues performed a prospective, open-label, single-arm, phase II trial to evaluate the antitumor activity of rechallenge with BRAF and MEK inhibitors in patients with advanced BRAF<sup>V600</sup>-mutant melanoma who had previously progressed on BRAF-inhibitor regimens. A total of 25 patients were treated with the BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib for at least 12 weeks off BRAF inhibitor treatment. The primary endpoint was overall response, and secondary endpoints included safety and progression-free survival. Partial responses were achieved in 8 of 25 patients (32%), 6 of whom had previously progressed on dabrafenib plus trametinib and two of whom had progressed on BRAF inhibitor monotherapy. Stable disease was observed in 10 of 25 patients (40%). The median progression-free survival was 4.9 months. Rechallenge with dabrafenib plus trametinib was well tolerated; there were no unexpected adverse events and the majority of adverse events were grades 1–2. Treatment-related grade 3 adverse events occurred in 2 patients. Taken together, these findings demonstrate that resistance to BRAF and MEK inhibitors may be reversible, and rechallenge with dabrafenib plus trametinib warrants further investigation in patients with BRAF<sup>V600</sup>-mutant melanoma who have previously progressed on BRAF inhibitors.


RESEARCH WATCH

Clinical Trials

**Major finding:** Resistance to BRAF plus MEK inhibitors may be reversible in patients with BRAF<sup>V600</sup>-mutant melanoma.

**Approach:** Rechallenge with the BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib was evaluated.

**Impact:** Patients who have progressed on BRAF inhibitors may respond to rechallenge with dabrafenib plus trametinib.

Multiple Myeloma

**Major finding:** T-cell bispecific antibodies (TCB) targeting BCMA or FcRH5 induce T cell-mediated myeloma cell death.

**Concept:** TCBs are well tolerated in animals and exhibit antitumor activity alone and with PD-L1 blockade.

**Impact:** TCBs exhibit promising activity in animal models and may be effective in patients with multiple myeloma.

T-CELL BISPECIFIC ANTIBODIES SUPPRESS MULTIPLE MYELOMA

Multiple myeloma is a hematologic malignancy characterized by abnormal plasma cell accumulation in the bone marrow. Although several therapies are available, the majority of patients eventually develop refractory disease or discontinue treatment due to toxicities. One potential immunotherapeutic strategy is the development of T-cell bispecific antibodies (TCB), which bind simultaneously to a surface tumor cell antigen and a T-cell receptor (TCR) to induce T-cell-mediated killing of tumor cells harboring the target surface antigen. Seckinger, Delgado, and colleagues generated a TCB (EM801) targeting the B-cell maturation antigen (BCMA), a receptor required for the survival of long-lived bone marrow plasma cells. The constructed BCMA-CD3 TCB, EM801, promoted CD4+ and CD8+ T-cell activation and release of IFNγ, granzyme B, and perforin, resulting in T-cell-mediated killing of myeloma cell lines. Further, EM801 induced autologous T-cell–mediated cell death in 34 of 43 bone marrow aspirates from patients with myeloma, including those with relapse or refractory disease. In vivo, EM801 was well tolerated, induced tumor regression in 6 of 9 myeloma xenograft models, and depleted BCMA+ cells in cynomolgus monkeys. In a related study, Li and colleagues developed a TCB targeting FcRH5, a B-cell lineage marker that is broadly expressed in myeloma. TCBs induced T-cell receptor activation by clustering the tumor target and excluding inhibitory CD45 from the synapse. FcRH5-CD3 TCB killed human plasma cells and patient-derived myeloma cells. In vivo, FcRH5-CD3 TCB reduced the growth of multiple myeloma xenografts and eliminated FcRH5-expressing B cells and bone marrow plasma cells in cynomolgus monkeys at well-tolerated doses. PD-L1 blockade enhanced the activity of FcRH5-CD3 TCB, suggesting the possibility for combination therapy. Together, these studies show that TCBs targeting myeloma antigens can induce antitumor activity and warrant further clinical investigation in patients with multiple myeloma alone and in combination with other therapies.

