Immunotherapy

**Major finding:** A dimeric amidobenzimidazole (diABZI) STING agonist enhances adaptive immunity and antitumor activity.

**Concept:** The diABZI compound can be administered systemically to induce tumor regression in mice with colorectal cancer.

**Impact:** The possibility for systemic delivery of diABZI compounds may expand the use of STING agonists in cancer.

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**A DEVELOPED STING AGONIST HAS SYSTEMIC ANTITUMOR ACTIVITY**

Tumor-derived DNA activates the cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway to enhance adaptive antitumor immunity. DNA activates cGAS to produce cGAMP, the ligand for the endoplasmic reticulum receptor STING. Downstream signaling results in increased production of IFN and other proinflammatory cytokines to promote cross-presentation of tumor antigens and mobilization of tumor-specific CD8+ T cells. STING agonists are in clinical trials to treat patients with solid tumors. The available STING agonists are modified cyclic nucleotides that are delivered intratumorally and have achieved durable regressions in tumor models. However, STING agonists that can be delivered systemically in patients with cancer have not been developed, prompting Ramanjulu, Pesiridis, Yang, and colleagues to perform a high-throughput screen to identify ligands that compete with cGAMP for STING binding to modulate STING activity. This approach discovered two amidobenzimidazole (ABZI) compounds that inhibited cGAMP binding to STING. Crystal structures of each compound in complex with the STING C-terminal domain revealed binding to the cGAMP binding pocket, with two bound molecules per STING dimer. Based on these findings a linker was added between the two compounds to create a linked dimeric ABZI (diABZI), which exhibited enhanced binding to STING. Further optimization yielded compound 3, a more potent diABZI. Compound 3 functioned as a STING agonist, selectively activating STING. In vivo, compound 3 triggered a STING-dependent activation of type I IFN and proinflammatory cytokines. Further, intravenous injection of compound 3 induced durable tumor regression in a mouse model of colorectal cancer. Depletion of CD8+ T cells suppressed the antitumor activity, suggesting that compound 3 suppresses tumor growth by activating the adaptive immune response. The development of a non-nucleotide STING agonist that can be administered intravenously may expand the use of STING agonists in patients with cancer.


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**Clinical Trials**

**Major finding:** Targeting BCMA with the antibody–drug conjugate GSK2857916 is well tolerated in a phase I trial.

**Clinical relevance:** At the recommended phase II dose, GSK2857916 achieves responses in 21 of 35 patients.

**Impact:** GSK2857916 may be safe and effective in patients with relapsed or refractory multiple myeloma.

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**TARGETING BCMA ACHIEVES DEEP AND DURABLE RESPONSES IN MULTIPLE MYELOMA**

Treatment options are limited for patients with relapsed or refractory multiple myeloma, and new therapies are needed to improve outcomes. The B-cell maturation antigen (BCMA) has emerged as a potential therapeutic target. BCMA is expressed on late-stage B cells and malignant plasma cells, and inhibition of BCMA suppresses multiple myeloma cell growth and survival. GSK2857916, a humanized BCMA antibody conjugated to the tubulin polymerization inhibitor monomethylauristatin F (MMAF), exhibited activity against multiple myeloma cells and primary samples. Based on these preclinical findings, Trudel and colleagues evaluated the safety and efficacy of GSK2857916 in a first-in-human open-label phase I dose escalation and expansion study in 73 heavily pretreated patients with relapsed or refractory multiple myeloma, 38 patients in the dose-escalation phase and 35 patients in the dose-expansion phase. The primary endpoints were maximum tolerated dose and recommended phase II dose, and secondary endpoints included preliminary antitumor activity. In the dose-escalation phase there were no dose-limiting toxicities, and GSK2857916 was well tolerated at the determined recommended phase II dose. Overall, there were 12 treatment-related serious adverse events. Corneal events occurred in 57.5% of patients, most of which were grade 1–2. At the recommended phase II dose, 21 of 35 patients (60%) achieved a response, including 3 complete responses, 15 very good partial responses, and 3 partial responses. Responses were durable, with a median progression-free survival of 7.9 months. Taken together, the results of this phase I trial indicate that GSK2857916 is well tolerated and has preliminary antitumor activity in patients with relapsed or refractory multiple myeloma.

Targeting BCMA Achieves Deep and Durable Responses in Multiple Myeloma


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