Aska-SS (Synovial Sarcoma)

Early attempts at using Tfh efficacy may vary among members for anti-tumor therapies. Tfh and Fas are not in the same class of molecules, as the discovery of tumor necrosis factor-related death receptor 5 (TRAIL) has identified an agonist capable of killing tumor cells without the side effects observed with Fas. In a phase 2 trial of MM-201b (dulanermin), a clinical candidate, 4/18 patients (22%) in patients with relapsed or refractory Ewing's sarcoma had a partial response (PR). In both patients, the initial clinical results were poor. The first-generation TRAIL agonists were limited by poor pharmacokinetics (PK) and systemic toxicities. However, the discovery of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has led to the development of molecules that are capable of killing tumor cells via apoptosis without the side effects observed with TNF.

The viability of the SW Synovial sarcoma cell line was determined using MTSA2 assay to compare MM-201b, MM-201a and other antibody-FC vaccines. MM-201b and MM-201a were more potent than both MM-201a and ABBV-621, with up to 11-fold lower IC50 across a panel of 12 CRC cell lines. MM-201b shows improved PK relative to native ligand. MM-201b is more potent than ABBV-621 against CRC in vitro. MM-201 shows improved PK relative to native ligand. MM-201 is more potent than both MM-201a and ABBV-621 in all cell lines. MM-201b was more potent than both MM-201a and ABBV-621 (p<0.0001 for both comparisons after ANOVA with Tukey posthoc testing).

The activity of three second generation trail agonists was determined in vitro against a panel of CRC cell lines using both a DR4 and DR5 ELISA. The concentration of either MM-201a or MM-201b was measured in serum after a single injection in a mouse. However, MM-201b was significantly more active than all comparators, including the TRAIL cytokine and both DR4 and DR5 agonist antibodies. Despite some isolated responders, the initial clinical results were poor. The first-generation TRAIL agonists were limited by poor pharmacokinetics (PK) and systemic toxicities. However, the discovery of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has led to the development of molecules that are capable of killing tumor cells via apoptosis without the side effects observed with TNF.

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