Preclinical Optimization of T Cell Redirected Therapy in Multiple Myeloma

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BCMA-directed T cell therapies (TCEs and CAR T cells) have shown remarkable efficacy in relapsed/refractory multiple myeloma, but ~30% of patients exhibit primary resistance and most responders eventually relapse. Primary resistance is associated with high tumor burden, extramedullary disease, and elevated soluble BCMA (sBCMA), which may compete for TCE binding, while acquired resistance often involves BCMA loss. Using controlled, immunocompetent syngeneic Vk*MYC mouse models, we investigated how tumor burden and soluble BCMA influence TCE efficacy and explored rational combination strategies to overcome resistance while maintaining tolerability, and prevent relapses.

We found that baseline tumor burden, measured by M-spike levels, was sufficient to stratify responders from non-responders. Increasing TCE dose or inhibiting BCMA shedding with gamma secretase inhibitors provided only modest benefit. In contrast, combining TCEs with the IMiD pomalidomide enhanced T cell activation and improved initial responses, even in IMiD-resistant tumors, indicating a tumor-extrinsic effect of Ikaros degraders on T cell fitness. However, repeated dosing drove T cell exhaustion and failed to improve survival. Addition of the checkpoint inhibitor anti-PD-1 further amplified cytotoxic T cell expansion and drove complete responses, but resulted in lethal cytokine release syndrome (CRS) and poor tolerability. While dexamethasone (DEX) moderated acute T cell activation, but not its magnitude, it did not prevent CRS when added to hyperactivating combinations, though TCE plus DEX alone improved efficacy and survival without compromising cytotoxicity.

To overcome primary TCE resistance while limiting toxicity, we developed strategies to temper early T cell hyperactivation. Step-up TCE dosing with CELMoD (iberdomide or mezigdomide) plus dexamethasone pretreatment was well tolerated, reduced inflammatory cytokine production, limited T cell exhaustion, prevented Treg accumulation, and induced sustained complete responses with extended survival. As an alternative, combining TCEs with cyclophosphamide (Cy) enabled tumor debulking overcoming primary resistance, generated durable responses, and was curative in Cy-sensitive tumors. In Cy-refractory models, addition of PD-1 or TIGIT blockade safely overcame resistance and produced durable complete responses and cures across all treated mice. Mechanistically, these triple combinations rapidly remodeled the tumor microenvironment, depleting exhausted T cells and Tregs while promoting expansion of naive T cells in the tumor bed that can be readily reactivated by subsequent TCE dosing. Importantly, we noted for the first time a significant engagement of the CD4 T cell compartment, which can be essential for a complete anti-tumor response.

Finally, we examined how TCE dosing schedule, continual versus intermittent, influences relapse and resistance. Continuous TCE treatment promoted transient BCMA downregulation without loss of plasma cell identity, as retransplantation of relapsing tumor into new recipient mice restored sensitivity to TCE. In one case, however, we identified complete and irreversible loss of BCMA due to retrotransposition of IAP particles into the first intron of *Tnfrsf17*, disrupting transcription of downstream exons, representing a genomic mechanism of antigen escape. Intermittent TCE dosing preserved BCMA expression but allowed tumor-extrinsic resistance mechanisms currently under investigation. Together, these findings demonstrate that tumor burden is a dominant driver of primary TCE resistance, that controlled modulation of T cell activation is essential for efficacy and tolerability, and that rational combinations and dosing strategies can overcome resistance while limiting antigen escape.