Background Interleukin(IL)-12 and -2 are recognized as potent anti-tumor molecules; yet, balancing effective dosing while mitigating systemic toxicity presents a significant hurdle for their use clinically. A targeted delivery system that provides sustained local cytokine levels in the tumor microenvironment, while minimizing systemic exposure and its associated toxicities, may effectively tip the balance to overcome the recognized limitations of IL-12 and -2 therapies. Krystal Biotech, Inc. has developed KB707, a replication-defective herpes simplex virus type 1 (HSV-1)-derived vector encoding human IL-12 and -2, for redosable treatment of solid tumors.

Methods As the human cytokines are only partially cross-reactive in mice, surrogate vectors were constructed to express murine Il12 and Il2, termed KB703 and KB704, respectively, for nonclinical development. For efficacy studies, C57BL/6 mice were inoculated with B16-F10 tumors, a checkpoint inhibitor-refractory melanoma line, subcutaneously on day 0, and cohorts were treated by intratumoral injection with vehicle, single, or combined vectors on days 7, 14, and 21.

Results Studies indicated that once weekly intradermal injection of the vectors was well tolerated in healthy mice and induced detectable cytokine expression in the skin for at least 7 days post-administration. Systemic cytokine exposure was limited with vector treatment compared to clinically relevant doses of intravenous recombinant proteins. In efficacy studies, all control animals succumbed to tumor burden by day 28; combined KB703/KB704 therapy resulted in 40% survival by day 70, the highest survival rate of all treatment groups. In a rechallenge study, KB703/KB704 dosed animals were re inoculated with B16-F10 tumors 55 days post-initial inoculation. >60% of these animals survived to the study’s endpoint, 45 days post-rechallenge, without additional intervention. These results suggest that vector-derived IL-12 and -2 treatment induces a durable anti-tumor memory response. To test the robustness of this approach, a bilateral tumor model was employed where animals were inoculated with primary B16-F10 tumors on day 0 and secondary tumors at a distal site on day 0, 4, or 10. Primary tumors were treated with either vehicle control or KB703/KB704 as described above. Vector treatment resulted in at least some degree of secondary (untreated) tumor growth inhibition, suggesting an abscopal effect, the magnitude of which was directly proportional to the interval between primary and secondary tumor instillation.

Conclusions Overall, these results highlight the potential of Krystal’s platform for sustained delivery of IL-12 and IL-2 into the tumor microenvironment as a novel immunotherapy for the treatment of local and distal solid tumors, including cutaneous malignancies.

Ethics Approval The studies described here were performed in an AAALAC accredited facility, and protocols were IACUC approved prior to initiation.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1065