Durable responses and immune activation with intratumoral electroporation of pIL-12 plus pembrolizumab in actively progressing anti-PD-1 refractory advanced melanoma: KEYNOTE 695 interim data


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KEYNOTE-695 Trial Design

Figure 1. pIL-12 Gene Electro Transfer Immunotherapy

Figure 2. Overall Best Response

Figure 3. Percent Change in Tumor Size Over Time

Figure 4. Treated and Untreated Lesions from 16 Responding Patients

Figure 5. Activity Progressing Patients and Short Interval Between the Last Dose of Anti-PD-1 and Study Treatment

Figure 6. Actively Growing Lesions Significantly Reduce in Size After pIL-12 + Pembrolizumab Treatment

Figure 7. Pseudo Progression in Target Lesion Followed by Tumor Response (Stage IVB; PR [2/3]–)

Figure 8. Progression on Ipi/Nivo Followed by Tumor Response (Stage IVB; PR [1/3])

Figure 9. Progression on Ipi/Nivo Followed by Tumor Response (Stage IVB; PR [2/3])

Figure 10. Patients Have Immunologically Quiescent Lesions at Screen That Quickly Inflame With a Productive Immune Infiltrate

Figure 11. On-treatment Increase of CD8+ T-cells in TME is Associated With an Active Transcriptomic Profile With Increased Intratumoral Clonality After a Single Cycle of Treatment

Figure 12. Productive Modulation of Systemic Peripheral Immune Subsets and Microbiota Is Evident in Responding Patients

Summary

This phase 1b/2 trial assessed intratumoral electroporation of pIL-12 plus pembrolizumab in anti-PD-1 refractory melanoma (NCT03432085). We report data from 20 patients who received pIL-12 and pembrolizumab on an every 2 weeks q4w schedule for 24 weeks. We assessed primary endpoints of clinical and immune responses; secondary endpoints included immunogenomics, transcriptomic, and genomic analyses. We observed durable responses in 11/20 (55%) patients, with 8 ongoing responses at the time of data cut-off. The median duration of response (mDOR) is 12.2 months (95% CI: 5.6–NE; n = 11). Importantly, we report the first systemic durable responses (≥12 months) in a PD-1 refractory patient that were associated with intratumoral clonality. Additionally, we observed 23/200 (11.5%) tumor-infiltrating lymphocytes (TILs) during the first cycle of therapy, which were significantly increased (p = 0.0127) compared with pretreatment (baseline) levels. Patients with a large increase in TILs demonstrated higher objective response rate (ORR) of 40% (9/23 patients). Last responders and non-responders after 1 cycle of treatment were analyzed using transcriptomic and genomic signatures. These analyses were performed on genomic DNA isolated from fixed tumor biopsies obtained at screen and after one cycle of therapy. The number of differentially expressed genes (DEGs) with a fold-change greater than or equal to 2 (C2D1) was significantly increased in responding patients compared with non-responding patients (fold-change C2D1/Screen). On-treatment biomarker signatures demonstrate that this combination treatment licenses immunologically quiescent tumors to yield productive local and systemic immune responses.