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## NEOADJUVANT INTRATUMORAL TAVO-EP (PLASMID IL-12 ELECTRO GENE TRANSFER) IN COMBINATION WITH NIVOLUMAB; PRELIMINARY CLINICAL AND BIOMARKER DATA IN PATIENTS WITH OPERABLE LOCOREGIONALLY ADVANCED MELANOMA

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**Background** Intratumoral (IT) treatment with TAVO-EP (tavokinogene telseplasmid delivered by electroporation) results in localized expression of IL-12 in the tumor microenvironment. This study (NCT04526730) was designed to evaluate neoadjuvant TAVO-EP in combination with nivolumab followed by surgery and adjuvant nivolumab in patients with operable, locoregionally advanced melanoma.

**Methods** The neoadjuvant phase comprised up to 3 x4-week cycles of TAVO-EP on days 1, 8 and 15 (optional) concurrently with 480 mg nivolumab I.V. on day 8 of each cycle. Surgery followed and adjuvant nivolumab was initiated after recovery from surgery for up to one year. Longitudinal samples of tumor biopsies, PBMCs, serum, PAXgene® blood DNA/RNA, and fecal material were collected at screening, C1D8, C2D1, pre-surgery and during adjuvant phase. Patients provided an IRB-approved (Advarra-IRB Pro00041794) informed consent and were treated at Moffitt Cancer Center.

**Results** Ten patients (6 female, 4 male, 1 black, 9 white, 10 cutaneous primary including 1 acral), age 58–88, were treated. Five had Stage IIIB (4N1c, 1N2b), 3 IIIC (1N3b, 1N3c, 1N1c) and 2 IV (M1a). Treatment was well tolerated. Highest-grade treatment-related events to date were limited to one Gr3 hyponatremia possibly related to nivolumab. One patient is currently in the neoadjuvant phase. Among the nine patients who completed the neoadjuvant phase, median number of neoadjuvant cycles was 3; 2 patients received 2 cycles due to near complete clinical response. Preoperative response rate (RECIST, unconfirmed) was 7/9 (77.8%; 95%CI 40.0–97.2); 1PD, 1SD, 4CR, 3 PR. One patient with PR declined surgery. Among 8 patients who had surgery to date, 1 pathologic non-response (Surgery at 4 weeks after initiating treatment due to clinical progression), 1 pathologic major response (pMR; ≤10% viable tumor), 6 pathologic complete response (pCR). The overall pMR rate was 7/8 (87.5%; 95%CI 47.4–99.7), all with no disease recurrence to date, at a median follow up from the date of surgery of 7.08 months (range 0.2–17.5).

Transient on-treatment changes in systemic peripheral immune subsets were identified. At C2D1 (week 5), peripheral proliferating CD8+PD-1+ T cells were significantly increased. In addition, memory precursor effector cells (mPECs; CD8+KLRG1-CD127+) were transiently upregulated at same time-point, while short-lived effector cells (SLECs; CD8+KLRG1+CD127-) were significantly reduced. These peripheral T cell changes coincided with increased intratumoral CD8+ TIL.

**Conclusions** Neoadjuvant IT TAVO-EP in combination with nivolumab exhibited promising clinical activity and a favorable safety profile. There was evidence of significantly enhanced immune activation supporting the proposed immune mechanisms. Analyses of additional biomaterials are underway.

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**Trial Registration** NCT04526730

**Ethics Approval** All participating patients in this investigator-initiated clinical provided an IRB-approved (Advarra IRB Pro00041794) written informed consent and were treated at Moffitt Cancer Center.

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