**Background** Neoadjuvant PD-1 blockade produces major pathological response (MPR) in ~30% of patients (pts) with high-risk resectable MEL with durable relapse-free benefit, and increased circulating activated CD8+ T cells.1-2 Vidutolimod (vidu) comprises a CpG-A oligodeoxynucleotide packaged within a virus-like particle (VLP) and is designed to activate tumor-associated plasmacytoid dendritic cells (pDC) via TLR9, inducing an IFN-rich tumor microenvironment and anti-tumor CD8+ T cell responses. Vidu/anti-PD-1 resulted in durable tumor responses in PD-1 refractory MEL.3 This Phase II study evaluated the pathological, clinical and immunological activities of neoadjuvant vidu/nivo in high-risk stage III B/C/D resectable MEL.

**Methods** Vidu/nivo was administered over 7 weeks (vidu 10mg IT Q1W x7, nivo 240mg Q2W x3) pre-surgery. Post-surgery, vidu/nivo (vidu SC 5mg, nivo 480mg Q4W) was continued for 48 weeks. Primary endpoints included MPR rate, and incidence of DLT. Secondary endpoints were radiographic response, relapse-free survival (RFS), distant metastasis-free survival (DMFS) and overall survival (OS). Pathological response assessment was performed to evaluate % residual volume of tumor (RVT) per consensus criteria4-6 by 3 blinded dermatopathologists: 0% (pCR); 0%-50% (pNR). Radiographic response assessed using RECIST v1.1. Serial blood, tumor and stool were collected for correlative analyses.

**Results** 31 pts were enrolled, of whom 30 evaluable for per-protocol (PP) analyses as 1 pt progressed pre-surgery. No DLTs were observed. 8 Gr3 TRAE, including hypertension (7/8) and colitis (1/8) were observed; no delays in surgery occurred. ORR by BICR was 45% (all) and 47% (PP). In PP population, MPR was observed in 57% (17/30) including 47% pCR (14/30) and 10% pMR (3/30). With median follow-up of 26.5 months, median RFS was not reached (table 1). Post-treatment, MPR was associated with increased CD8+ tumor infiltrating lymphocytes (p<0.0001), and peripheral immune activation and pDC activation by multiparameter flow cytometry (p < 0.001). Spatial investigation of immune cell infiltrates by miHC revealed significantly immune cell infiltrates (p<0.05) and higher pDC (p=0.053) within tumor (but not stroma) of MPRs post-treatment (figure 1a,b). Deconvoluted RNAseq confirmed these findings compared to a control cohort of PD-1 treated MEL.

**Conclusions** Neoadjuvant vidu/nivo has minimal tox and demonstrated promising activity with 47% pCR rate and 57% MPR rate. MPR was associated with improved 1-2- year RFS (94%/88%), and 1-2- year DMFS (94%/94%) and 2-year OS (100%). MPR is associated with pDC and immune infiltrate (figure 1c). Further evaluation of this combination is ongoing in an ongoing randomized phase II trial (EA6194, NCT04708418).

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**Trial Registration** Clinical trial information: NCT03618641.

**REFERENCES**

**Ethics Approval** The study was approved by University of Pittsburgh’s Institutional Review Board, approval number MOD19040237-002.

**Consent** Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.
Abstract 605 Figure 1  Multiplex IHC (mIHC) Analysis of Post-treatment Samples by GeoMx Spatial Analysis