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PRIMARY EFFICACY, SAFETY, SURVIVAL, AND INITIAL BIOMARKER DATA FROM THE REGISTRATION-INTENDED COHORT OF PATIENTS WITH ANTI–PD-1–FAILED MELANOMA FROM THE IGNYTE CLINICAL TRIAL WITH RP1 COMBINED WITH NIVOLUMAB

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Background: Treatment options for patients with advanced melanoma and disease progression on anti–PD-1 therapy are limited and associated with high toxicity. RP1 (vusolimogene oderparepvec) is an HSV-1–based oncolytic immunotherapy expressing GM-CSF and a fusogenic glycoprotein (GALV-GP-R−). The registration-intended cohort of the IGNYTE trial tested RP1 + nivolumab in patients with advanced melanoma that progressed on anti–PD-1 therapy.

Materials and methods: Melanoma patients with confirmed disease progression while undergoing anti–PD-1 treatment alone or in combination with anti–CTLA-4 for ≥8 weeks as the last prior treatment, including as adjuvant therapy, were enrolled. RP1 was given intratumorally at 1×10^6 plaque-forming units (PFU)/mL initially, then Q2W at 1×10^7 PFU/mL for up to 7 doses (≤10 mL/cycle) combined with nivolumab (240 mg IV); nivolumab was then given alone (240 mg Q2W or 480 mg Q4W IV) for up to 2 years, with further RP1 allowed if indicated. The primary endpoint was objective response rate (ORR) by independent central review (ICR) using modified RECIST (mRECIST) v1.1.

Results: Of 140 patients with advanced melanoma enrolled, 48.6% had stage IVb/c/d disease, 65.7% had primary anti–PD-1 resistance, 56.4% were PD-L1 negative, and 46.4% had prior anti–PD-1 + anti–CTLA-4 therapy. The confirmed ORR by ICR was 33.6% (15.0% CR) by mRECIST v1.1. Responses were observed in injected and non-injected lesions. Among responders, 98.7% of injected (n=79) and 98.4% of non-injected lesions (n=123) had reductions, with 93.7% and 79.7%, respectively, reduced by ≥30%. The median (range) DOR was 21.6 (1.2–43.5) months. The ORR was 35.9% in patients with primary anti–PD-1 resistance and 27.7% in patients who received prior anti–PD-1 + anti–CTLA-4. Landmark overall survival (OS) rates (95% CI) at 1,2 and 3 years were 75.3% (66.9–81.9) 63.3% (53.6–71.5), and 54.8% (42.7-65.3) respectively; median OS was not reached. Most treatment-related adverse events (TRAEs) were grade 1–2; the TRAE grade 3–4 rate was 12.8%. Initial biomarker assessment showed immune activation as measured by increased CD8+ T-cell infiltration (20/50) and PD-L1 levels (CPS; 26/49) vs baseline in available biopsies.

Conclusions: RP1 + nivolumab provided durable, clinically meaningful, antitumor activity with mostly grade 1–2 TRAEs in patients with advanced melanoma. Biomarker analysis from tumor biopsies showed

that RP1 + nivolumab increased CD8+ T-cell infiltration and PD-L1 expression, demonstrating that the combination can treat anti–PD-1–refractory disease.

Acknowledgements: This abstract was previously presented, in part, at the 2024 European Society for Medical Oncology (ESMO) Annual Meeting, FPN (Final Publication Number): LBA46, Caroline Robert et al. Reused with permission.

Trial registration: ClinicalTrials.gov, NCT03767348