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A RANDOMIZED, CONTROLLED, MULTICENTER, PHASE 3 STUDY OF VUSOLIMOGENE ODERPAREPVEC COMBINED WITH NIVOLUMAB VS TREATMENT OF PHYSICIAN'S CHOICE IN PATIENTS WITH ADVANCED MELANOMA THAT HAS PROGRESSED ON ANTI-PD-1 AND ANTI-CTLA-4 THERAPY (IGNYTE-3)

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Background: Melanoma is the fifth most common cancer, with ~100,000 new cases and ~8,000 related deaths estimated in the US for 2024 [1]. First-line systemic treatment with immune checkpoint inhibitors improves the objective response rate (ORR) and extends progression-free survival (PFS) and overall survival (OS) for patients with advanced disease. Among available treatments, combination anti-PD-1 (nivolumab) + anti-CTLA-4 (ipilimumab) therapy is associated with the highest ORR and best PFS and OS. However, only ~50% of patients respond to treatment and limited options exist for patients whose melanoma progresses following anti-PD-1-based therapy. Vusolimogene oderparepvec (VO; also known as RP1), is a selectively replication-competent herpes simplex virus type 1-based oncolytic immunotherapy that expresses human granulocyte-macrophage colony-stimulating factor and a fusogenic glycoprotein (GALV-GP-R-) [2]. Data from a registration-intended cohort of the IGNYTE study showed that intratumoral (IT) VO + intravenous (IV) nivolumab was well tolerated and demonstrated durable, clinically meaningful antitumor activity (ORR, 33.6% per independent central review using modified Response Evaluation Criteria in Solid Tumors [mRECIST] 1.1) in patients with advanced melanoma and confirmed progression on prior anti-PD-1 therapy. This phase 3 study will evaluate the OS and clinical benefit of VO + nivolumab for patients with advanced melanoma whose disease has

progressed after anti-PD-1 and anti-CTLA-4 therapy (or who are ineligible for anti-CTLA-4 therapy) vs physician's choice.

Materials and methods: IGNYTE-3 is a global, randomized, controlled, multicenter, phase 3 trial. Key eligibility criteria include age ≥ 12 years; stage IIIb-IV/M1a-M1d cutaneous melanoma; confirmed disease progression on an anti-PD-1 and anti-CTLA-4 treatment (administered in combination or in sequence, with anti-PD-1 last); ≥ 1 measurable and injectable tumor (≥ 1 cm); and adequate hematologic, hepatic, and renal function. Patients who are not candidates for anti-CTLA-4 therapy may enroll if they have confirmed progression on anti-PD-1 therapy. Patients with BRAF V600-mutant melanoma must have received anti-BRAF \pm anti-MEK targeted therapy prior to enrollment. Patients (N = ~400) will receive VO + nivolumab or physician's choice (nivolumab + relatlimab, anti-PD-1 monotherapy rechallenge [nivolumab or pembrolizumab], or single-agent chemotherapy [dacarbazine, temozolomide, or paclitaxel/albumin-bound paclitaxel]). The primary endpoint of the study is OS; the key secondary endpoints are PFS and ORR per RECIST 1.1.

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Trial registration: ClinicalTrials.gov, NCT06264180

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