388 A TRIAL TO EVALUATE THE SAFETY, IMMUNOGENICITY, AND CLINICAL ACTIVITY OF A HELPER PEPTIDE VACCINE PLUS PD-1 BLOCKADE (MEL64, PATHVACS: PD-1 ANTIBODY AND T-HELPER VACCINE AND CORRELATIVE STUDIES)

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Background A multipeptide vaccine containing 6 melanoma-associated peptides to stimulate helper T cells (6MHP) is safe and immunogenic and has clinical activity. A phase I/II trial was designed to evaluate safety and immunogenicity of 6MHP vaccines plus PD1 blockade.

Methods Participants with measurable advanced melanoma, age ≥ 18 years, and ECOG performance status 0–1 were administered 6MHP vaccine intradermally and subcutaneously in an incomplete Freund's adjuvant on days (D) 1, 8, 15, 43, 64, and 85. Pembrolizumab 200 mg was administered intravenously every 3 weeks for up to two years. Biopsies of accessible tumors at baseline and D22 were analyzed by multiparameter immunofluorescence histology. Primary endpoints were safety (CTCAE 4.03) and immunogenicity (ex vivo IFNγ ELIspot assay). Secondary and exploratory endpoints included changes in the tumor microenvironment (TME), and clinical outcomes.

Results Twenty-two eligible participants were enrolled and treated, including 6 naïve to PD-1 Ab and 16 anti-PD-1 Ab-experienced. Median follow-up was 20 months. Treatment-related adverse events (any grade) experienced by >20% were injection site reactions, fatigue, anemia, nausea, fever, bruising, and rash. Treatment-related dose limiting toxicities (grade 3 elevated AST, skin ulcer, or uveitis) were observed in 3 (14%), which did not cross the study safety bound. Objective clinical responses were observed in 23% (1 CR, 4 PR), including 4/6 anti-PD-1 Ab-naive (67%) and one 1/16 anti-PD1 Ab-experienced (6%). Four participants (18%) had SD as best radiographic response (18%), all in the Ab-experienced cohort. T cell responses to 6MHP were detected in seven participants (32%) by week 13 and were associated with clinical response (CR/PR 80% vs. SD/PD 18%; p = 0.01). Overall survival was prolonged for anti-PD-1 Ab naïve vs experienced (p = 0.0048), for those with T cell response (p = 0.045, landmark analysis after week 13), and for those with objective response (p = 0.0148). TME evaluation in 12 participants revealed significant increases by D22 in the densities (per mm2) of CD8 + T cells (p = 0.0186), CD20+ B cells (P = 0.002), and Tbet+ cells (p = 0.034).

Conclusions In patients with advanced melanoma, combined treatment with the 6MHP vaccine plus pembrolizumab was safe, increased intratumoral T and B cells, as well as Th1 (Tbet+) cells, and induced T cell responses that were associated with objective response and with overall survival. The promising objective response rate and overall survival in patients naive to PD1 blockade supports consideration of a larger study to assess definitive benefit in that clinical setting.

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Trial Registration The clinical trial Mel64 (PATHVACS) is registered with Clinicaltrials.gov (NCT02515227).

Ethics Approval The clinical trial Mel64 (PATHVACS) was performed with IRB (#18174) and FDA approval (IND #10825) and is registered with Clinicaltrials.gov (NCT02515227). Written informed consent was obtained from each participant prior to participation in the study.

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