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POSTER ABSTRACTS

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

Immune Profiling and Responses of Smoldering Multiple Myeloma Patients Treated in a Phase Ib Study of Pvx-410 Vaccine Targeting XBP1/CD138/CS1 Antigens, and Citarinostat, a Histone Deacetylase Inhibitor (HDACi) with and without Lenalidomide

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BACKGROUND AND SIGNIFICANCE

Immunoparesis plays an important role in the progression of smoldering multiple myeloma (SMM). Therapies that augment the immune response may prevent or slow the progression to symptomatic multiple myeloma. We have previously shown that PVX-410, a multi-peptide cancer vaccine (OncoPep., Inc.) targeting XBP1/CD138/CS1, is immunogenic in SMM, as a single therapy and in combination with lenalidomide. Here, we investigated whether co-administration of PVX-410 with an oral HDAC inhibitor, citarinostat, +/- lenalidomide enhances vaccine specific immune response in patients with SMM.

STUDY DESIGN AND METHODS

This 2-cohort phase 1b multicenter study accrued 16 adults (≥18 years) with HLA-A2 $^{+}$ SMM and high risk of progression to active MM. Patients received citarinostat in combination with PVX-410 (double combination cohort) and with PVX-410 and lenalidomide (triple combination cohort). PVX-410 was given as six doses of 0.8 mg biweekly (weeks 0, 2, 4, 6, 8, and 10) via subcutaneous injection followed by a single dose of PVX-410 during follow-up visits at month 1, 2, 3, 6, and 9; 3 cycles of citarinostat (180 mg QD PO for 21 days every 28 days) and lenalidomide (25 mg on Days 1-21 every 28 days) were given to patients in the double and triple combination cohorts respectively in conjunction with the initial 6 doses of PVX-410. Patients were followed post-treatment for 12 months. Peripheral blood (PB) and bone marrow (BM) samples at baseline and month one after treatment were analyzed by single-cell RNA sequencing. T-cell receptor and B-cell receptor sequencing were also performed to investigate T cell and B-cell clonal expansion before and after treatment. Flow cytometric analyses of anti-MM functionality of the XBP1/CD138/CS1-specific CD8 $^{+}$ cytotoxic T lymphocytes (CTL) was performed at various timepoints from baseline up to 12-month post-treatment. The development of antigen-specific memory CD8 $^{+}$ CTL through upregulation of 41BB and production of Th1-type of cytokines (IFN-g, IL-2, TNF-a) were evaluated by flow cytometry. Deep whole genome sequencing was performed on subsets of CD138 $^{+}$ cells from BM isolates to corroborate our findings.

RESULTS

We screened 16 SMM patients; 15 (94%) received treatment (7 with the double and 8 with the triple combination). By the end of the 12-month post-treatment follow-up period no patients progressed to symptomatic myeloma in the double combination cohort; one patient in the triple combination cohort withdrew by month 3 for disease progression. Most patients receiving the double combination had stable disease (SD) as their best clinical response (n=5), one had partial response (PR) and one minimal response (MR). Triple combination therapy resulted in better clinical response including PR (n=2), MR (n=4) and SD (n=2). Single-cell transcriptomic analyses of 21 PB samples from 13 patients and 15 BM samples from 11 patients at baseline and month one after treatment is in progress. Immune monitoring studies on 125 samples from 15 different patients at various timepoints from baseline up to 12-month post-treatment are ongoing. Fourteen patients (100%) had at least one treatment-

related adverse event (trAEs), mostly grade 1-2 in severity. The most common trAEs among patients receiving double vs triple combination were fatigue (71% vs 63%), injection site reactions (43% vs 50%), neutropenia (57% vs 38%), anemia (29% vs 38%), and diarrhea (0% vs 50%). There was one grade 3 trAE: specifically, a thromboembolic event in one patient who was receiving lenalidomide and despite aspirin prophylaxis, but who fully recovered.

DISCUSSION

The combination of PVX-410 with citarinostat, with and without lenalidomide is generally safe in this patient population. The objective clinical response was relatively modest given the short duration of therapy: longer follow up is needed to assess the impact on progression to active myeloma. PB and marrow transcriptome profiling along with the immunogenicity studies are in progress and will be presented. We will evaluate whether PB mononuclear cells have the potential to replace BM as a surrogate for genetic and immunological surveillance in SMM, as we anticipate that further understanding of the immune alterations among patients with SMM and the response to immunomodulatory therapy may provide insight on early intervention and prevention of progression to symptomatic disease.

Disclosures Duvallet: *OncoPep Inc:* Current Employment. **Joyce:** *OncoPep Inc:* Current Employment. **Moyo:** *OncPep.,Inc.:* Current Employment, Current holder of *stock options* in a privately-held company. **Yee:** *Sanofi:* Consultancy; *Regeneron:* Consultancy; *Prothena:* Consultancy; *Pfizer:* Consultancy; *Karyopharm:* Consultancy; *Janssen:* Consultancy, Research Funding; *GSK:* Consultancy; *Adaptive Biotechnologies:* Consultancy; *AbbVie:* Consultancy; *Amgen:* Consultancy, Research Funding; *BMS:* Consultancy, Research Funding. **Malek:** *Cumberland Inc.:* Research Funding; *Amgen:* Speakers Bureau; *Medpacto Inc.:* Research Funding; *BMS:* Consultancy; *Sanofi Inc.:* Consultancy; *Karyopharm:* Speakers Bureau. **Richardson:** *Takeda:* Research Funding; *AstraZeneca Pharmaceuticals LP, Bristol-Myers, Squibb Company, Celgene Corporation, GlaxoSmithKline, Janssen Biotech Inc, Karyopharm Therapeutics, Oncopeptides, Sanofi, Secura Bio, Takeda Pharmaceuticals USA Inc;:* Consultancy; *GSK:* Consultancy; *Bristol Myers Squibb:* Consultancy, Other: Contracted research, Research Funding; *Oncopeptides:* Consultancy, Research Funding; *Karyopharm:* Consultancy, Research Funding; *Sanofi:* Consultancy. **Raje:** *K36 Therapeutics:* Consultancy; *Caribou Bioscience:* Consultancy; *Janssen:* Consultancy; *Amgen:* Consultancy; *Abbvie:* Consultancy; *2seventy Bio:* Consultancy, Research Funding; *Roche:* Consultancy; *Pfizer:* Consultancy, Research Funding; *Immuneel:* Consultancy; *GSK:* Consultancy; *Sanofi:* Consultancy.

OffLabel Disclosure: Lenalidomide is FDA approved for newly diagnosed and relapse/refractory multiple myeloma. In this trial lenalidomide was used in smoldering multiple myeloma patients in combination with PVX-410 vaccine and citarinostat.

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