Updated Results of a Phase 1/2a, Dose Escalation Study of PVX-410 Multi-Peptide Cancer Vaccine in Patients with Smoldering Multiple Myeloma (SMM)

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INTRODUCTION

Smoldering Multiple Myeloma

Smoldering multiple myeloma (SMM) is an asymptomatic, plasma cell proliferative disorder characterized by monoclonal plasma cell proliferation in the bone marrow and monoclonal proteins in the blood and/or urine. The diagnosis of SMM, as defined in this study, requires 2 of the 3 risk factors: abnormal FLC ratio, a serum monoclonal (M) protein level ≥3 g/dL and/or bone marrow clonal plasma cells (BMPC) >10%, and the absence of end-organ damage (i.e., hypercalcemia, renal insufficiency, anemia, or bone lesions [CRAB]). Although asymptomatic, SMM is associated with a high risk of progression to symptomatic multiple myeloma (MM) or amyloidosis.

At present, it has been estimated that SMM accounts for approximately 15% of all newly diagnosed cases of MM. The median time to progression from diagnosis of moderate to high risk smoldering myeloma to symptomatic myeloma ranges from 2 to 5 years and the annual risk of progression from SMM to symptomatic MM requiring treatment is estimated to be 10%. The standard of care for these patients has been "watchful waiting."

PVX-410

PVX-410 (OncoPep, Inc.) is a clinical stage, multi-peptide therapeutic cancer vaccine for subcutaneous (SC) administration to patients diagnosed with SMM. The goal of treatment with PVX-410 is to induce immunity against MM cells by selectively stimulating tumor-associated antigen-specific cytotoxic T lymphocytes (CTLs). The rationale for the use of multiple peptides is to 1) target the tumor cell heterogeneity observed in all cancers, particularly MM, and 2) decrease the likelihood of tumor cells developing resistance to CTLs by targeting multiple antigens simultaneously. Furthermore, targeting multiple antigens increases the probability of an immune response against all subsets of MM.

PVX-410 consists of 4 human leukocyte antigen (HLA)-A2 restricted, synthetic 9-mer peptides from unique regions of 3 MM-associated antigens (XBP1 US$^{184-192}$; XBP1 SP$^{367-375}$; CD138$^{260-268}$; and CS1$^{239-247}$) emulsified in Montanide® ISA-720 VG (Seppic, Inc.). XBP1 is a basic leucine zipper-containing transcription factor required for the terminal differentiation of B lymphocytes to plasma cells. Splicing of XBP1 occurs in terminal B cell differentiation and correlates with plasma cell differentiation. XBP1 is highly expressed in plasma cells, with regulation through both transcriptional and post-transcriptional mechanisms. The unique tissue expression profile of XBP1 provides an opportunity to develop an antigen-specific immunotherapy for SMM. CD138 is an integral membrane protein acting as a receptor for the extracellular matrix. Within the normal hematopoietic compartment, CD138 is expressed on differentiated plasma cells and is a primary diagnostic marker of MM. Antibody responses to CD138 *in vitro* indicate it is a clinical target for an immunotherapeutic. CS1 is a member of the immunoglobulin gene super-family and is universally present and highly expressed on MM cells. These characteristics support the choice of these peptides as appropriate target antigens for this vaccine.

DISCLOSURES

Nooka – *Spectrum Pharmaceuticals:* Consultancy; *Onyx Pharmaceuticals:* Consultancy. **Off Label Use:** Off label use of lenalidomide.

Wang – *Janssen:* Honoraria; *Pharmacyclics, Janssen, Celgene, Oncopep, Kite, Juno:* Research Funding.

Thomas – *Novartis, Celgene, Acerta Pharmaceuticals, Idera Pharmaceuticals:* Research Funding.

O'Donnell – *Millennium:* Consultancy.

Shah – *Millenium:* Research Funding; *Onyx:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Array:* Research Funding; *Bristol-Myers Squibb:* Research Funding; *Celgene:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Merck:* Membership on an entity's Board of Directors or advisory committees.

Kaufman – *Millenium, Celgene, Novartis, Onyx, Spectrum:* Consultancy.

Lonial – *Onyx:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding; *Bristol-Myers Squibb:* Consultancy, Research Funding; *Millennium:* Consultancy, Research Funding; *Celgene:* Consultancy, Research Funding; *Janssen:* Consultancy, Research Funding.

Richardson – *Millennium Takeda:* Membership on an entity's Board of Directors or advisory committees; *Gentium S.p.A.:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Jazz Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Celgene Corporation:* Membership on an entity's Board of Directors or advisory committees.

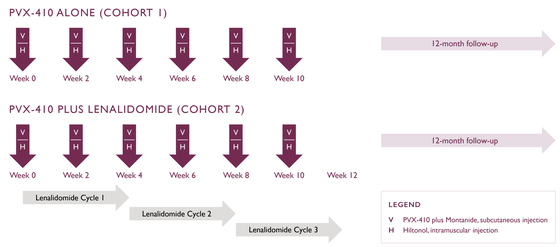
Raje – *Celgene Corporation:* Consultancy; *Amgen:* Consultancy; *Takeda:* Consultancy; *BMS:* Consultancy; *AstraZeneca:* Research Funding; *Eli Lilly:* Research Funding.

METHODS & TRIAL DESIGN

Adults with SMM at moderate and high risk of progression to active MM (i.e., ≥2 of the following risk factors: serum monoclonal [M]-protein ≥3 g/dL; bone marrow clonal plasma cells >10%; and/or abnormal serum free light chain ratio [0.26-1.65]) and HLA-A2$^+$were eligible to participate in the study.

PVX- 410 initially was investigated as a single agent, as reported previously (ASH, 2014). Patients received 6 doses of PVX-410 emulsified in Montanide 720 VG (Seppic, Inc.) subcutaneously plus 0.5 mL (1 mg) Hiltonol® (poly-ICLC, Oncovir, Inc.) intramuscularly over 10 weeks. Patients initially received PVX-410 0.4 mg (3 patients, 0.1 mg/peptide / 0.4 mg total dose; low-dose) with escalation to 0.8 mg (9 patients, 0.2 mg/peptide / 0.8 mg total dose; target-dose).

Figure 1: Study Schema



Immunogenicity data at Week 0 (Baseline or pre-dose), Weeks 4 and 8, and post-treatment Month 1 showed that PVX-410 alone was immunogenic in the initial 12 patients treated, with all 12 having positive immune response to at least 1 peptide at at least 1 time point (enzyme-linked immunospot, interferon [IFN]-γ). Clinical response data showed that with PVX-410 alone, 5 patients (2 of 3 with the low-dose of 0.4 mg [0.1 mg/peptide] and 3 of 9 at the target-dose [0.2 mg/peptide]), experienced progression to active disease within 9 months post-treatment, and 6 had stable disease (SD) at Month 12, the last follow-up visit (Table 1). Furthermore, PVX-410 alone was well-tolerated, with all adverse events (AEs) being ≤Grade 2 and non-serious and consisting of systemic symptoms and local reactions commonly seen with vaccines (e.g., fever, chills, fatigue, nausea, and other flu-like symptoms / localized erythema, induration, pain, rash, and pruritus).

Predicated by these positive findings, PVX-410 is similarly being evaluated when co-administered with lenalidomide (Celgene Corp). Given its immunomodulatory properties, it was hypothesized that co-administration of lenalidomide would enhance the specific T cell-mediated immune response induced by PVX-410.

In the PVX-410 + lenalidomide cohort, patients received PVX-410 at the target dose (0.8 mg; 0.2 mg/peptide or 0.8mg total) plus three, 28-day cycles of lenalidomide, with each cycle consisting of lenalidomide 25 mg orally (PO) daily for 21 days (Days 1-21) followed by a 7-day rest period.

Patients are being followed for 12 months post-treatment. Whole blood samples for immune response evaluation are collected at Week 0 (Baseline; pre-dose), 2, 4, and 8 during treatment and at Months 1, 3, 6, 9, and 12 post-treatment; disease response is assessed at the same timepoints, except Weeks 0 and 2. Peripheral blood mononuclear cells (PBMCs) are isolated and stored for batch analysis (see Figure 1).

A flow cytometry (FACS) based assay is being used to detect antigen (Ag) specific CD3+CD8+ T cell responses to PVX-410 in the patient derived PBMCs. After a 6-day in vitro stimulation (IVS) culture in the presence of PVX-410, 20 U/ml interleukin (IL)-2, and 20 U/ml IL-15, PBMCs are stimulated with the PVX-410 peptide cocktail overnight, followed by the detection of specific cell surface markers, intracellular cytokines (IFN-γ, IL-2 and TNF), and binding capacity to A2/PVX-410 tetramers. A positive immune response to the vaccine is defined as a minimum increase from baseline of 1.5-fold for IFN-γ and 2-fold for tetramer measurements for any time point.

RESULTS

Ten patients were enrolled in the PVX-410 + lenalidomide cohort, of whom 6 were female. Median age at enrollment was 56.5 years (range 45 to 82 years). Eight patients were white; of the remaining 2, 1 each was American-Indian/Alaskan native and African-American. All patients had at least 2 risk factors for progression to MM, with 1 having 3.

Nine of 10 patients each received 6 injections of 0.8 mg PVX-410, 1 mg Hiltonol® and 3 cycles of lenalidomide, per protocol. One patient was withdrawn from the study due to a protocol violation, which rendered their outcome measurements as unevaluable. One patient required a 20% lenalidomide dose reduction due to lenalidomide-related neutropenia, but completed all 3 lenalidomide cycles thereafter.

Nine of 10 patients were evaluable for efficacy. Of these 9 patients, 5 experienced partial or minimal responses (PR or MR), and 4 experienced SD. One patient who had achieved a MR response later progressed to active disease at 5 months post treatment and their participation in the study was discontinued (see Table 2).

Table 1: Patient Status – Cohort 1

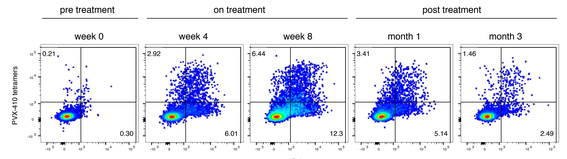
Patient Number	Treatment	No. Risk Factors	Last Study Visit	Best Clinical Response/ Status Last Study Visit
03-004	Low Dose PVX-410	3	6 month post-vaccine	Stable/PD
04-006	Low Dose PVX-410	3	1 month post-vaccine	Stable/Stable
04-008	Low Dose PVX-410	2	12 month post-vaccine	Stable/Stable
01-034	Target Dose PVX-410	2	12 month post-vaccine	Stable/Stable
01-042	Target Dose PVX-410	2	12 month post-vaccine	Stable/Stable
03-012	Target Dose PVX-410	3	12 month post-vaccine	Stable/Stable
03-013	Target Dose PVX-410	2	12 month post-vaccine	Stable/Stable
04-028	Target Dose PVX-410	2	9 month post-vaccine	Stable/PD
04-031	Target Dose PVX-410	3	6 month post-vaccine	Stable/PD
01-010	Target Dose PVX-410	3	12 month post-vaccine	Stable/Stable
01-017	Target Dose PVX-410	3	3 month post-vaccine	Stable/PD
01-018	Target Dose PVX-410	2	12 month post-vaccine	Stable/Stable

Table 2: Patient Status – Cohort 2

Patient Number	Treatment	No. Risk Factors	Last Study Visit	Best Clinical Response/ Status Last Study Visit
03-052	Target Dose PVX-410 + Lenalidomide	2	12 month post-vaccine	Stable/Stable
03-054	Target Dose PVX-410 + Lenalidomide	2	12 month post-vaccine	MR/MR
03-059	Target Dose PVX-410 + Lenalidomide	2	9 month post-vaccine	Stable/Stable
03-063	Target Dose PVX-410 + Lenalidomide	2	3 month post-vaccine	MR/PD
03-061	Target Dose PVX-410 + Lenalidomide	2	6 month post-vaccine	Stable/Stable
03-071	Target Dose PVX-410 + Lenalidomide	3	6 month post-vaccine	MR/MR
01-075	Target Dose PVX-410 + Lenalidomide	2	6 month post-vaccine	PR/PR
04-072	Target Dose PVX-410 + Lenalidomide	2	6 month post-vaccine	MR/MR
06-069	Target Dose PVX-410 + Lenalidomide	2	3 month post-vaccine	Stable/Stable

Preliminary immunogenicity data are available for 4 of 9 evaluable patients from Cohort 2 through the Month 3 follow-up time point. Ag-specific CD8$^+$ T cell responses are detectable in all patients by IFN-γ production and HLA-A2/PVX-410 binding (see Figure 2), as well as TNF production, though response magnitudes vary among patients. Preliminary analyses support the hypothesis that, in most cases, the addition of lenalidomide would yield a more robust T cell-mediated immune response to PVX-410 compared to PVX-410 alone. This is most notable in the frequency of TNF$^+$ cells, indicating that lenalidomide potentially increases the proportion of multi-functional cells.

Figure 2: IFN-γ Production and HLA-A2/PVX-410 Tetramer Binding



Note: *PBMC samples from Patient 03-054 were drawn pre-treatment (Week 0), at Weeks 4 and 8 of treatment, and at 1 and 3 months following the last vaccination with PVX-410 + lenalidomide. Following a 6-day IVS culture in the presence of PVX-410, IL-2 and IL-15, cells were tested for the production of IFN-γ, as well as their HLA-A2/PVX-410 tetramer binding capacity following an overnight stimulation with PVX-410.*

PVX-410 was well tolerated in the combination. All 10 (100%) patients had at least 1 AE, with most being ≤Grade 2 and non-serious. All 10 (100%) patients had local reactions at the injection site, including pain (100%), swelling (90%), erythema (80%), pruritus (70%), irritation and induration (each 30%), discomfort (20%), and rash (10%). The most common systemic AEs were myalgia (70%), fatigue (50%), and chills, headache, pruritus, and pyrexia (each 40%). The incidence of these AEs was increased with PVX-410 + lenalidomide compared to PVX-410 alone. Neutropenia, which was not reported with PVX-410 alone, occurred in 4 patients (Grade 1 for 2 patients, Grade 3 for 2 patients).

Two patients in the PVX-410 + lenalidomide cohort experienced one serious adverse event, (fatigue and pneumonia), which were both considered unrelated to the study vaccine.

No deaths or other reportable events have occurred. Furthermore, no clinically significantly abnormal clinical laboratory test results have been seen.

CONCLUSION

PVX-410 is well tolerated when administered in combination with lenalidomide, with most AEs being ≤Grade 2 and non-serious and no AEs leading to treatment discontinuation. Preliminary immunogenicity data support the hypothesis that lenalidomide would enhance the specific T cell response to PVX-410 as well as clinical effect. Based on the promising findings to date, additional studies are planned to start in 2016 evaluating PVX-410 in combination with an antibody to the programmed cell-death-1-ligand complex (PD1/PDL1).