Third Quarter 2016

Business Update Conference Call

Peter Culpepper, MBA, CPA
Chief Operating Officer, and Interim Chief Executive Officer

November 14, 2016
Forward-Looking Statements

The statements contained in this presentation reflect management’s current knowledge, assumptions, beliefs, estimates and expectations, and express management’s current view of future performance results and trends. Such forward looking statements may be identified by the use of the terms such as anticipate, believe, should, could, estimate, expect, intend, may, plan, predict, project, will, and other similar terms. Forward looking statements are subject to a number of risks and uncertainties that could cause our actual results to materially differ from those described in the forward looking statements. You should not place undue reliance on forward looking statements. Such statements are made as of the date of this presentation. We undertake no obligation to update such statements after this date. Risks and uncertainties could cause our actual results to materially differ from those described in the forward looking statements, including those discussed in our filings with the Securities and Exchange Commission (SEC), including those in item 1A of our annual report on Form 10-K for the year ended December 31st filed with the SEC, as supplemented by the risk factors set forth in our Quarterly Reports on Form 10-Q filed with the SEC.
Presentation Agenda

- Actions While Waiting for Phase 3 Interim Results
- Five Pillars of Value
- Four Focus Areas
- Phase 3 Status and Combination Study
- Cancers of the Liver, Pancreas, Colon
- Conferences, Publications, Video
- Media and Public Relations Activities
- Relationships: FDA Big Pharma
- Financial Position & Proxy Issues
**Actions While Waiting**

We are waiting for the interim results of our phase 3 clinical trial examining the use of PV-10 as a treatment for melanoma. Waiting can be wearying, and we know the patience of most of you has been challenged. To be honest, our patience has been challenged as well.

But time spent waiting shouldn't be time wasted. We need to be ready for the arrival of those interim results. And Provectus has been busily preparing in the last year, including a revision of the protocol that increases the potential patient pool, which we will detail shortly.

Also, we have continued with our other studies of PV-10 and our researches into PH-10. We have taken the news of PV-10's promise to the scientific community through publications and presentations at international scientific conferences. We have expanded our portfolio of intellectual property. We have worked to develop relationships with other entities involved in the fight against cancer. We continue to develop our corporate structure and leadership so that we are ready to go from a development stage company to an enterprise with pharma partnerships.

To put these events into context, I want to briefly review the five clinical and business value proposition pillars of PV-10 and PH-10 that we have discussed over the last five years.
The first pillar is our intellectual property. We hold a number of patents covering both PV-10 and PH-10 in the U.S. and overseas. These help ensure that if and when these investigational agents are approved for commercial use, we expect to secure a significant revenue stream.
Second Pillar of Value – Control of the Drug and Drug Product Supply Chair

The second pillar is our control of the drug substance and drug product supply chain. Patents only protect drugs so much. By controlling the supply chain, and the intellectual property underlying that supply chain, we strive to minimize the risk of reverse engineering. We have already made and shipped PV-10 to a number of medical centers. Numerous medical organizations throughout the world have received similar shipments. Some of these are not yet public and we look forward to when they are made public.
Third Pillar of Value – Regulatory Guidance

Our third pillar is the regulatory guidance we receive from the FDA in the U.S. and its counterparts in other nations. Provectus works with our regulators to ensure the machinery of the bureaucracy keeps moving forward. Here, I point to our activities in China where Boehringer Ingelheim, our main Asian CRO and others are all working in tandem with us to steer the application for PV-10 to be available for clinical studies via the Chinese FDA. It is important to note that we have agreements with these firms to collaborate on this, and the terms of the arrangements have not changed.

We are also developing ties with Australia's Therapeutic Goods Administration. We have even opened an office in Australia to be able to work more closely with our collaborators there and to function better with regulators and pharmaceutical companies in Asia; it always helps to be in closer time zone and proximity.

Further, we are engaging regulators in other nations in Asia and Latin America in preparation for expansion of our activities there. As for Asia in general, we are seeking other local partners and are discussing memoranda of understanding to formalize these relationships.
Fourth Pillar of Value – Mechanisms of Action for PV-10 and PH-10

The fourth pillar is the mechanisms of action for both PV-10 and PH-10. Knowing much better how they work should help us better understand how to optimize their use and guide advanced development in oncology and dermatology, respectively.
Fifth Pillar of Value – Clinical Study Designs

Our fifth and final pillar are the clinical study designs that generate clinical data, as well as generation of other meaningful data in our preclinical work. Since we are waiting for data from various of these, we will spend some time talking about them shortly.
Four Focus Areas in Business and Development

In addition to the five pillars are our four focus areas of business and development, and I want to remind all of you about them as they add further context and color to our actions. They are:

1. a higher public profile for Pro vectus, PV-10 and PH-10;
2. co-development discussions with Big Pharma about drug combination work;
3. other strategic activities including regional licenses, collaborations, investments and so forth; and
4. grant programs that can help us further fund research.
Melanoma Studies

• Phase III Study: “PV-10 vs Chemotherapy or Oncolytic Viral Therapy for Treatment of Locally Advanced Cutaneous Melanoma,” Clinicaltrials.gov NCT02288897
  • Nine Listed Sites, 8 in USA, 1 in Australia
  • Eight actively recruiting, 1 preparing to recruit
  • Protocol Amended to expand the potential patient pool
  • Interim data expected during period of funding via the Rights Offering

• Phase 1b/2 Combination Study: “PV-10 in Combination With Pembrolizumab for Treatment of Metastatic Melanoma,” ClinicalTrials.gov Identifier NCT02557321
  • Being used in combination with Merck’s Keytruda
  • Potentially forming part of a cocktail of drugs similar to that realization of importance in HIV/AIDS treatment

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Liver, Pancreatic, Colo-Rectal Studies

• “A Phase 1 Study of PV-10 Chemoablation of Neuroendocrine Tumours (NET) Metastatic to the Liver,” ClinicalTrials.gov Identifier: NCT02693067.
  • Data forthcoming to be announced

• Separate Phase 1 Study -- “A Study to Assess PV-10 Chemoablation of Cancer of the Liver,” ClinicalTrials.gov Identifier: NCT00986661
  • Data forthcoming to be announced more near-term

• Intralresional injection with Rose Bengal and systemic chemotherapy induces anti-tumor immunity in a murine model of pancreatic cancer
  • Press release today, November 14th 2016

• "PV-10 Induces Potent Immunogenic Apoptosis in Colon Cancer Cells."
  • Ongoing work and expected data forthcoming to be announced in near-term
Recent & Upcoming Investor Presentations

• Third quarter, 2016
  • Sept 11-13: Rodman & Renshaw Annual Healthcare Conference, New York City
  • Sept 27-28: Biotech Investor Forum for Global Partnering and Investment, Basel, Switzerland

• Fourth quarter, 2016 (planned)
  • December 6th-8th LD Micro Main Event 2016 -- Los Angeles, CA
  • Road Show for Rights Offering throughout December -- New York, NY
  • December 16th - 19th ESMO Asia 2016 Congress -- Suntec City, Singapore
  • December 13th - 16th Investor Meetings – Philippines, Singapore, other SE Asian locations
Public and Media Relations Activities

• Radio news segment to run on 400 radio stations across the nation. The segment included quotes from Eric Watcher and Dr. Sanjiv Agarwala.

• Joya Dass of Small Cap Nation interview with Peter Culpepper to discuss the future of Provectus.


• Webinar with Melanoma Research Foundation led by Dr. Vern Sondak on November 14, 2016.
Relationships with Regulators and Big Pharma

- Regulators
  - FDA
  - Chinese FDA
  - Australian Regulators
  - Others

- Big Pharma
  - Merck
  - Pfizer
  - Boehringer Ingelheim
  - Others
3rd Quarter Results and Balance Sheet Highlights

• Monthly cash burn focus: $1.5 million
  • Reducing cash by focusing G&A activities and building on strengths in R&D
  • Wrapping up all outstanding lawsuits against Provectus
  • Initiating collection efforts against the former CEO
• Cash and cash equivalents: $5,178,076
• Shareholders’ equity: $5,309,712
• For additional information, see our quarterly report on Form 10-Q filed with the SEC on November 9th
Special Proxy Vote & Shareholder Meeting

• Currently scheduled for Monday, November 28th at 9 am EST at the law offices of Baker Donelson (265 Brookview Centre Way, Suite 600, Knoxville, Tennessee)

• Seek shareholder approval of two proposals:
  • To increase the number of shares of common stock authorized for issue from 400 million to 1 billion
  • To authorize the board of directors to effect a reverse stock split of our common stock at a ratio of between 1-for-10 and 1-for-50, where such ratio would be determined by the board at its discretion

• For additional information, see our preliminary proxy soliciting material on Schedule14-A filed with the SEC on October 21st
**Existing Investor Rights Offering**

- In connection with our proposed rights offering, we are planning to raise up to $21 million from existing shareholders
  - Most of proceeds expected to support generating randomized data from PV-10 in treating local melanoma in our phase 3, treating widely metastatic melanoma in our 1b/2 combo, and in treating ongoing cancers of the liver clinical work
- We have filed a Registration Statement on Form S-1 with the SEC, but it is not effective and not yet priced (must own stock to received rights for offering)
  - We expect to know more shortly after our November 28th special meeting of stockholders.
  - Stockholders participating in the rights offering will be entitled to purchase common stock and warrants to purchase common stock.
- For additional information, see our registration of securities on Form S-1/A filed with the SEC on November 1, 2016
NYSE Common Stock and Warrants Trading Suspension

- Due to the low trading price, the NYSE MKT has commenced proceedings to delist:
  - Our common stock under the symbol PVCT, and
  - Our class of warrants under the symbol PVCTWS
- Common stock currently trades over-the-counter under PVCT
- We are appealing the decision of the NYSE Regulation staff
- For additional information, see our October 14th press release *Trading in Proventus Biopharmaceuticals Common Stock and Warrants Suspended by NYSE MKT*
Business Summary
Clinical Development

Third Quarter 2016
Business Update Conference Call

Eric Wachter, Ph.D.
Chief Technology Officer

November 14, 2016
Forward-Looking Statements

These statements reflect management’s current knowledge, assumptions, beliefs, estimates, expectation, and express management’s current view of further performance, future performance results, and trends. And such forward looking statements may be identified by the use of the terms such as anticipate, believe, should, could, estimate, expect, intend, may, plan, predict, project, will, and other similar terms. Forward looking statements are subject to a number of risks and uncertainties that could cause our actual results to materially differ from those described in the forward looking statements. You should not place undue reliance on forward looking statements. Such statements are made as of the date of such statements. We undertake no obligation to update such statements after this date. Risks and uncertainties that could cause our actual results to material different from the described, from the described in forward looking statements including those discussed in our filings with the Securities and Exchange Commission including those in item 1A of our annual report on form, on the form 10K, the year ended December 31st filed with the SEC.
Safe Harbor Statements

- **PV-10 is an investigational drug** undergoing clinical study as an ablative immunotherapy for solid tumor cancers

- **PH-10 is an investigational drug** undergoing clinical study as a topical therapy for inflammatory dermatoses

- Neither PV-10 nor PH-10 have received approval for marketing in any country
Outline

• Breakthroughs in Oncology
• Introduction to PV-10
• Mechanism of PV-10
• Clinical Development of PV-10
• Supply Chain
• Overview of Clinical Trial Process
• Update on PH-10
• Some Personal Opinions
• Conclusions
Breakthroughs in Oncology

- Progress in any technology often follows a common path
Breakthroughs in Oncology

• Progress in any technology often follows a common path

Hope → Enthusiasm → Irrational Exuberance → Experience

Progress occurs in a non-linear manner

Realization → Rational Assessment and Use
• This pattern is evident in many megatrends in oncology
  
  • Therapeutic Vaccines
  • Targeted Therapy
  • Checkpoint Inhibitors (Immuno-oncology, or I-O)

  • Each has been hailed as the solution to melanoma
  • Each has been a major step forward
  • Each has failed to “solve” melanoma
Breakthroughs in Oncology

• James P Allison
  • Inventor of anti-CTLA-4
  • Father of modern immuno-oncology
  • Likely Nobel laureate in this decade

• “We’re in an era where we can occasionally discuss curing cancer.”
• “We need to find ways to routinely cure cancer.”

April 2016, Cellular Horizons: Third International Conference on the Progress of Regenerative Medicine and Its Cultural Impact
James Allison Says Rational Combinations Key to Immunotherapy Success in "Cold" Tumors

Immunotherapy has been a game changer in oncology, improving survival and providing long, durable responses in melanoma, lung, head and neck cancer, and others.

The success of immunotherapies in those cancers—which are likely seeing a better rate of response due to their high mutational burden—is now paving the way for what are known as "cold" tumors, those that don’t have a heavy mutational burden or significant T-cell infiltration, said James Allison, PhD.

“There is enough progress being made across the board that I think we can start thinking about some of the colder tumors responding if we just keep studying and making rational combination decisions,” said Allison, professor and chair of Immunology at MD Anderson Cancer Center.

“As we understand this better, we can rationally put two things together that won’t just duplicate or cancel each other out, but will do different things that can at least be additive, if not synergistic.”

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onclive.com, 31 Oct 2016
Breakthroughs in Oncology

• An important pattern in many megatrends in oncology

  • As immuno-oncology enters the “rational assessment and use” phase there is a notable push for combination of core I-O drugs with other classes of agent or other classes of therapy

  • Sanjiv Agarwala has been at the forefront of this push, recommending that oncologists “make the patient’s tumor his or her friend”

  • Intralesional therapies may have arrived at an opportune time

  • We are positioning PV-10 to capitalize on this new phase in oncology
Introduction to PV-10

- PV-10 is a sterile, non-pyrogenic solution of Rose Bengal disodium (10% RB) for injection
  - RB is a small molecule Fluorescein derivative attributed to Gnehm in 1882
  - Prior human use of RB
    - IV hepatic diagnostic, $^{131}$I radiolabeled RB: Robengatope®
    - Neonatal use for hepatobiliary diagnosis
    - Topical ophthalmic diagnostic: Rosettes® and Minims®
    - Food dye: FR-105
  - Established safety history of RB
    - Not metabolized
    - Short circulatory half-life (ca 30 min)
    - Excretion via bile
  - Stable at room temperature
  - Radiopaque
  - Intrallesional injection can yield ablative immunotherapy
Clinical Development Strategy

• PV-10 can yield
  • Rapid reduction in tumor burden
  • High rate of objective response
  • Tumor-specific immunologic activation
  • Potential prolongation of PFS
  • Potential synergy with other classes of therapy

• Locoregional intervention with a small molecule agent aligns with current care standards for many solid tumors
### Development Pipeline

<table>
<thead>
<tr>
<th>Indication</th>
<th>Pre-Clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma (Locoregional)</td>
<td><strong>PV-10</strong></td>
<td></td>
<td></td>
<td></td>
<td>• Orphan drug status obtained in January 2007</td>
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<td>• Phase 1 and 2 studies completed</td>
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<td></td>
<td></td>
<td>• Phase 3 study in progress: Opened recruitment in April 2015</td>
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<tr>
<td>Melanoma (Stage IV)</td>
<td><strong>PV-10 + Pembrolizumab</strong></td>
<td></td>
<td></td>
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<td>• Phase 1b/2 study initiated Sep 2015</td>
</tr>
<tr>
<td>Melanoma (Mechanism of Action)</td>
<td><strong>PV-10</strong></td>
<td></td>
<td></td>
<td></td>
<td>• Phase 1 study to detect immune cell infiltration into melanomas treated with PV-10</td>
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<td></td>
<td></td>
<td>• Comprehensive data published May 2016</td>
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<tr>
<td>Liver Metastasis</td>
<td><strong>PV-10</strong></td>
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<td></td>
<td></td>
<td>• Orphan drug status obtained in April 2011</td>
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<td>• Phase 1 patient accrual and treatment completed</td>
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<td>• Phase 1 protocol expansion (Sep 2012 to present)</td>
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<td>• Initial data communicated in mid-2015</td>
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<td>• Phase 1b/2 study planned for Asia / Pacific Rim</td>
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<tr>
<td>Breast Cancer</td>
<td><strong>PV-10</strong></td>
<td></td>
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<td></td>
<td>• Phase 1 study completed</td>
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<td></td>
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<td></td>
<td></td>
<td>• Further clinical development is planned</td>
</tr>
<tr>
<td>Other Solid Tumors</td>
<td><strong>PV-10</strong></td>
<td></td>
<td></td>
<td></td>
<td>• BCC, bladder, colorectal, NSCLC, pancreatic and prostate</td>
</tr>
</tbody>
</table>

BCC, basal cell carcinoma; NSCLC, non-small cell lung cancer
Selective Tumor Ablation

• Consistent ablation in multiple murine models
  • Murine HCC (HePa 1-6)
  • Murine RAG (CCL-142)
  • Murine Melanoma (MeWo, A375 and B16F10)
  • Murine Breast (MT-901)
  • Murine Colon (COLON 26 / CT26)
  • Murine Pancreatic (PANC 02)
  • Human Breast (MCF-7 and HTB-133/T-47D)
  • Human Gall Bladder
  • Human Lung (H69Ar – small cell, multidrug resistant)
  • Human Prostate (PC-3)

“PV-10 is agnostic to tumor type”
Dr. Vernon Sondak, Moffitt Cancer Center
Accumulation in Cancer Cells

- PV-10 transits plasmalemma of cancer cells
  - Accumulation in lysosomes of cancer cells
  - Excluded from normal cells

**Figure 5.** Composite MPE image showing a cross-section of murine tissue spanning the transition from normal skin (leftmost edge of image) to a subcutaneously implanted hepatoma tumor (area at right hand third of image). The sample was prepared by fresh frozen sectioning following systemic administration of RB.

Wachter et al., SPIE Proceedings 2002; 4622: 112-118
Accumulation in Cancer Cells

- PV-10 accumulates in lysosomes of cancer cells

Wachter et al., SPIE Proceedings 2002; 4620: 143-147
Wachter et al., SPIE Proceedings 2002; 4622: 112–118
Mousavi, Zhang, Gillespie, Wachter and Hersey, Mel. Res. 2006; 16 (supl. 1): S8
Accumulation in Cancer Cells

- **Lysosomal accumulation elicits rapid autolysis of cancer cells**
  - Accumulation in lysosomal membrane triggers release of lysosomal contents
  - Acute autolysis within 30-60 min
  - Identical response in Hepa1-6 murine HCC, HTB-133 human breast carcinoma and H96Ar human multidrug resistant small cell lung carcinoma
  - Chronology consistent with pharmacodynamics observed in murine models
Selective Toxicity to Cancer Cells

- Selective toxicity observed across multiple cancer cell lines
- Data consistent with selective ablation observed in murine models
Necrotic Cell Death in Cancer Cells

- Necrosis predominates in cancer cells

Liu et al., Oncotarget 2016

Incubation with 50 uM RB for 48 hrs

Murine Melanoma  B16
Human Melanoma  888
Human Melanoma (Primary)  P1, P2, P3
Human Embryonic Kidney  293T
Mouse Fibroblast  3T3

Mousavi, Zhang, Gillespie, Wachter and Hersey, Mel. Res. 2006, 16(supl. 1): S8
Ablative Immunotherapy

- IL PV-10 elicits acute necrosis of treated tumor
  - Rapid necrosis of injected tumors and reduced tumor burden

- Induction of tumor-specific immunity ("abscopal" or "bystander" effect)
  - Regression of untreated tumor in immunocompetent animals
  - No effect in immunodeficient animals
  - Response is tumor-specific
Ablative Immunotherapy

Primary Ablation and Secondary Tumor-Specific Immune Response

1. Intralesional Injection
2. Lysosomal Accumulation
3. Lysosomal Disruption
4. Autolytic Cell Death
5. T-cell Activation
6. Bystander Tumor Regression

Rapid Tumor Ablation Systemic Immune Stimulation

References:
- Wachter et al., SPIE 4630, 147, 2002 (lysosomal accumulation and rupture in tissue culture)
- Thompson et al., Mel Res 18, 405, 2008 (ablation of injected tumors and bystander regression in recurrent patients)
- Toomey et al., PLoS One 8, e68561, 2013 (tumor-specific immune response in mice)
- Liu et al., AACR 2014 Abstract 0630 (DC recruitment/activation and T-cell activation in mice)
- Sarnaik et al., ASCO 2014 Abstract 9028 (pCR and T-cell activation in refractory patients)
The Cancer-Immunity Cycle

- Murine and Human Melanoma
- Murine Breast
- Murine CRC
- Murine PANC

1. Release of Cancer Cell Antigens

High Mobility Group Box 1 (HMGB1) Elevated in Cell Supernatants

Detection of HMGB1 in tumor cell supernatants (via ELISA) after 48 hrs incubation. HSP90 unchanged, HSP70 and IL-1α not detected.

Liu et al., Oncotarget 2016
1. Release of Cancer Cell Antigens

High Mobility Group Box 1 (HMGB1) Elevated in Patient Sera

HMGB1 elevated in sera of melanoma patients after IL PV-10 (N = 14).

Liu et al., Oncotarget 2016
2. Cancer Antigen Presentation

IL PV-10 Leads to DC Infiltration of Draining Lymph Nodes

DC (CD11c\(^+\) MHC II\(^+\)) from tumor draining LNs (DLN) or nondraining LNs (NDLN) measured by flow cytometry.

FITC\(^+\) DC infiltrate when FITC-OVA injected intratumorally 4 hrs after PV-10 injection.

Liu et al., AACR 2014
Liu et al., Oncotarget 2016
2. Cancer Antigen Presentation

DC from DLN Exhibit Increased Activation Markers

Liu et al., Oncotarget 2016
3. Priming and Activation of T Cells

IL PV-10 Elicits Tumor-Specific T Cell Response

MT-901 Breast Ca Flank Model

M05 Melanoma Flank Model

CT26 Colorectal Flank Model

Figure 2. PV-10 treatment leads to tumor-specific IFN-gamma responses in mice bearing MT-901 breast cancer. Splenocytes were plated at 2 × 10^6, co-cultured with 2 × 10^7 irradiated MT-901 tumor cells, and incubated for 48 hours. Culture supernatants were analyzed for IFN-γ production using commercially available ELISA kit. Data shows the mean ± SD of triplicates. *indicates p<0.05.

Toomey et al., PLoS One 2013

References

3. ASCO meeting 2010.
4. Trafficking of T Cells to Tumors

T Cells in PBMC of Melanoma Patients

A. CD8+  
B. CD4+  
C. NKT

Supplementary Figure S2: Increased circulating T and NKT cells after IL-PV-10 treatments. A. CD8+ T cells, B. CD4+ T cells, and C. NKT cells in PBMCs of patients increased after IL-PV-10 treatment (n=14 patients). Data show the absolute numbers of live cells per ml of peripheral blood. \( P \) values were determined by Wilcoxon matched-pairs signed rank test. \( * \), \( P<0.05 \), statistically significant versus pre-treatment; n.s., not significant.

Liu et al., Oncotarget 2016
5. Infiltration of T Cells into Tumors

IL PV-10 can boost T cell infiltration into Tumors

Bilateral M05 melanoma flank tumors in C57BL/6 Mice, CD3+ in bystander tumor 96 hrs after injection

\[ \text{CD}^+ \text{cells per million} \]

\[ \begin{align*}
\text{PBS} & : & 1 \\
\text{PV-10} & : & 4 \times 10^5 \\
\end{align*} \]

Liu et al., Oncotarget 2016
6. Recognition of Cancer Cells

IL PV-10 Elicits Functional T Cell Response in Melanoma Patients

Supplementary Figure S3: Increased tumor-specific T cell response after IL PV-10 treatment. IFN-γ production from CD8+ T cells purified from PBMCs from 5 patients and re-stimulated with autologous melanoma cells A, or HLA- matched or HLA-mismatched melanoma cells B-E. Data were measured in 3 independent experiments with triplicates for each experiment. P values were determined by an unpaired student t-test. *, p<0.05 statistically significant versus pre-treatment; **, p<0.01; n.s., not significant.

Liu et al., Oncotarget. 2016
Assessment of Immune and Clinical Efficacy after Intralesional PV-10 in Injected and Uninjected Metastatic Melanoma Lesions


H. Lee Moffitt Cancer Center, Tampa, FL

Prior Treatment Abstract (updated)

Summary

• IL PV-10 can induce regression of injected and uninjected metastatic melanoma
• IL PV-10 can enhance tumor-specific reactivity in circulating T cells
• IL PV-10 leads to responses in treatment-refractory tumors
• IL PV-10 may be rationally combined with systemic immunotherapy for the treatment of metastatic melanoma

Intralesional (IL) therapy is under investigation to treat dermal and subcutaneous metastatic cancer. In our murine model, IL injection of PV-10 (10% Rose Bengal) induced regression of injected and uninjected "bystander" melanomas. We observed a consistent increase in anti-tumor T cell responses following IL PV-10. We translated these findings into a pilot clinical trial that enrolled 13 patients with dermal and/or subcutaneous metastatic melanoma. Two study lesions in each patient were sampled by biopsy pre-treatment; one of the two lesions was injected with IL PV-10, then both residual sites were completely excised. We compared tumors before and after treatment with H&E staining to determine pathologic complete response (pCR), and we confirmed results with MelanA immunohistochemistry.

Peripheral blood mononuclear cells (PBMC) before and after IL PV-10 were phenotyped for activation markers by flow cytometry. Of the evaluable patients to date, treatment with IL PV-10 led to pCR in the post-treatment biopsies of both PV10-injected and uninjected study lesions in 4 of the 8 patients, and all 8 exhibited at least partial regression of the injected lesion. IL PV-10 was associated with an increase in circulating cytotoxic CD3+/CD8+ T cells (n=10, paired t test, p=0.03). Pre and post PV-10 treated CD8+ PBMC from one patient were re-stimulated with autologous tumor in vitro. Compared to pre-treatment, PV-10 treatment produced an increase in tumor-specific interferon-gamma release by ELISA. Six of 8 patients had metastatic disease refractory to previous ipilimumab, anti-PD-1 and/or vemurafenib therapy. Four of these 6 patients exhibited pCR to PV10 in both the injected and uninjected lesions.

IL PV-10 treatment can lead to systemic anti-melanoma immunity and pCR in injected and uninjected lesions including treatment-refractory tumors. Further studies are ongoing to determine the mechanism by which PV-10 increases tumor-specific T cell responses as well as to establish the interaction of intralesional PV-10 with combination checkpoint protein inhibition.

Change in Melanin A IHC (cont)

Clinical Trial Design

Partial biopsy of two lesions and PBMC collection pretreatment

Excision of 2 lesions and PBMC collection post treatment

IL PV-10 of one of the two lesions

PBMC collection post treatment

patients

Day 7 Day 14 Day 28

PV-10 alters T cell immunity

Of the 13 consented patients, 5 had no previous treatment, 6 received IPI or ipilimumab, and 2 received PD-1 blocking antibody; 6 received two or more prior systemic therapy.

PV001

Change in Melanin A IHC

PV10-Injected Lesion Uninjected Lesion

PV002

PV003

PV004

PV005

PV006

PV007

PV008

Loss of viability of injected and non-injected cutaneous melanoma tumors within 7-14 days of PV-10 injection (N = 14 patients)

Liu et al., AACR 2014
Sarnaik et al., ASCO 2014
Liu et al., Oncotarget 2016
Implications of Immunology Data

• Tumor ablation can elicit a functional, tumor-specific T cell response

• This T cell response is implicated in
  • Regression of untreated tumors
  • Potential prolongation of Progression Free Survival (PFS)
  • Rational design of combinatorial strategies
Putting T Cells to Work

1. Release of cancer cell antigens
   - Thompson et al., Mel Res 2008
   - Agarwala et al., ASCO 2009
   - Toomey et al., PLoS1 2013
   - Liu et al., AOCR 2014
   - Sarinaik et al., ASCO 2014
   - Pardiwala et al., SSO 2015
   - Liu et al., SITC 2015
   - Weber et al., AOCR 2016
   - Liu et al., Oncotarget 2016

2. Cancer antigen presentation
   - Liu et al., AOCR 2014
   - Liu et al., SITC 2015
   - Liu et al., Oncotarget 2016

3. Priming and activation
   - Toomey et al., PLoS1 2013
   - Liu et al., AOCR 2014
   - Sarinaik et al., ASCO 2014
   - Pardiwala et al., SSO 2015
   - Weber et al., AOCR 2016
   - Liu et al., Oncotarget 2016
   - Pilon-Thomas et al., SITC 2016

4. Trafficking of T cells to tumors
   - Liu et al., AOCR 2014
   - Sarinaik et al., ASCO 2014
   - Liu et al., Oncotarget 2016

5. Infiltration of T cells into tumors
   - Liu et al., Oncotarget 2016

6. Recognition of cancer cells by T cells
   - Liu et al., AOCR 2014
   - Sarinaik et al., ASCO 2014
   - Liu et al., SITC 2015
   - Weber et al., AOCR 2016
   - Liu et al., Oncotarget 2016

7. Killing of cancer cells
   - Thompson et al., Mel Res 2008
   - Agarwala et al., ASCO 2009
   - Toomey et al., SSO 2012
   - Dees et al., SITC 2012
   - Toomey et al., PLoS1 2013
   - Wachter et al., AOCR 2013
   - Liu et al., AOCR 2014
   - Sarinaik et al., ASCO 2014
   - Pardiwala et al., SSO 2015
   - Weber et al., AOCR 2016
   - Liu et al., Oncotarget 2016
   - Pilon-Thomas et al., 2016

Efficacy of Intralesional Injection with PV-10 in Combination with Anti-CTLA4 in B16-OVA bearing mice

**Results**

- Treatment with anti-CTLA4 antibodies in combination with IL PV-10 results in smaller B16-OVA tumors
- Treatment with anti-PD-1 antibodies in combination with IL PV-10 results in reduced growth of B16-OVA tumor
- Treatment with anti-PD-L1 antibodies alone or in combination with IL PV-10 leads to the induction of B16-specific T cells

**Conclusion**

These murine studies support the idea that anti-CTLA4 antibodies and IL PV-10 combination therapy can enhance anti-tumor immunity and regression of melanoma. Further studies are needed to confirm these findings in human patients.

**Acknowledgement**

Provectus Pharmaceuticals, Inc.

**Author Information**

Shari Pilon-Thomas, Hao Liu, Krithika Kodumudi, Ellen Moore, Amy Weber, and Amod A. Sarnaik

H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL
Combination Therapy with IL PV-10 and anti-PD-1 antibodies in B16-OVA bearing mice

Treatment with anti-PD-1 antibodies in combination with IL PV-10 results in reduced growth of B16-OVA tumor

Treatment with anti-PD-1 antibodies in combination with IL PV-10 leads to the induction of B16-OVA-specific T cells

Combination therapy with IL PV-10 and anti-PDL1 antibodies slows growth of B16-OVA bearing mice

Combination therapy with IL PV-10 and anti-PDL1 antibodies leads to reduced tumor growth and increased tumor-specific T cell activity.

Combination therapy with IL PV-10 and NrIgG antibodies led to a trend in tumor reduction and increased tumor-specific T cell activity.

Combination therapy with IL PV-10 and anti-CTLA4 antibodies led to a reduction in tumor growth and increased tumor-specific T cell activity.

Combination therapy with IL PV-10 and anti-CTLA4 antibodies led to a trend in tumor reduction and increased tumor-specific T cell activity.

* * *
Efficacy of Intralesional Injection with PV-10 in Combination with Co-Inhibitory Blockade in a Murine Model of Melanoma

Shari Pilon-Thomas, Hao Liu, Krithika Kodumudi, Ellen Moore, Amy Weber, and Amod A. Sarnaik

Combination Therapy with IL PV-10 and anti-PD-L1 antibodies in B16 bearing mice

Treatment with anti-PD-L1 antibodies in combination with IL PV-10 results in reduced growth of B16 tumor

Combination Therapy with IL PV-10 and anti-PD-1 antibodies in

Treatment with anti-PD-L1 antibodies alone or in combination with PV-10 leads to the induction of B16-specific T cells

PV-10 leads to the induction of B16-OVA-specific T cells

Mean Tumor Weight (mg)

PV-10 results in reduced growth of B16-OVA tumor

Mean Tumor Size (mm²)

PV-10 + anti-PDL1

1000

2500

IFN-gamma (pg/ml)

PBS

3000

p<0.05 compared to PV-10 treated mice

PBS + NrIgG

PV10

PV10 + anti-PD1

PBS + anti-PD1

PV10 + anti-CTLA4

PBS + anti-CTLA4

PV10 + NrIgG

PBS + NrIgG

* * *

*p<0.05 compared to PV-10 treated mice

Pilon-Thomas et al., SITC 2014

Days

p<0.05 compared to PV-10 treated mice

*p<0.05 compared to PV-10 treated mice

IFN-gamma (pg/ml)

Days

PBS

PV10

anti-PDL1

PV10 + anti-PDL1

* * *

*p<0.05 compared to PV-10 treated mice

Pilon-Thomas et al., SITC 2014

Days

PBS

PV10

anti-PDL1

PV10 + anti-PDL1

* * *

*p<0.05 compared to PV-10 treated mice

Pilon-Thomas et al., SITC 2014

Days

PBS

PV10

anti-PDL1

PV10 + anti-PDL1

* * *

*p<0.05 compared to PV-10 treated mice

Pilon-Thomas et al., SITC 2014

Days

PBS

PV10

anti-PDL1

PV10 + anti-PDL1

* * *

*p<0.05 compared to PV-10 treated mice

Pilon-Thomas et al., SITC 2014

Days

PBS

PV10

anti-PDL1

PV10 + anti-PDL1

* * *

*p<0.05 compared to PV-10 treated mice

Pilon-Thomas et al., SITC 2014
Combinations: What We Know So Far

• **Additive or Better Response in Multiple Models**
  - HCC when combined with 5-FU ( antimetabolite) \(^1\)
  - Melanoma when combined with anti-CTLA-4 \(^2\)
  - Melanoma when combined with anti-PD-1 \(^2,3\)
  - Melanoma when combined with anti-PD-L1 \(^2\)
  - Pancreatic adenocarcinoma when combined with gemcitabine (nucleoside analog that depletes myeloid-derived suppressor cells) \(^4\)

  • In each case the combination appears to be T cell mediated

---

\(^1\) Dees et al., SITC 2016  
\(^2\) Pilon-Thomas et al., SITC 2014  
\(^3\) Weber et al., AACR 2016  
\(^4\) Pilon-Thomas et al., SITC 2016
Implications for Clinical Development

Locoregional Progression

Metastatic Progression

- Draining Nodal Basin
- In-Transit Candidates for Single Agent Rx
- Primary
- Stage IV-M1c
- Stage IV-M1b
- Stage IV-M1c

Candidates for Combination Rx

- Primary

Survival: 7 yrs (IIIB) to 1.8 yrs (M1a)
Survival: 1.2 yrs (M1b) to 7 mon (M1c)

➢ This general approach appears applicable to melanoma and other solid tumors
Melanoma Clinical Development

• **Phase 1 (Aug 2005 – Aug 2007)**
  - 20 subjects, treat 1-20 lesions once, 1-3 bystanders untreated
  - Follow up to 24 weeks
  - Primary EP ORR (mRECIST)

• **Phase 2 (Oct 2007 – May 2010)**
  - 80 subjects, treat 1-20 lesions up to 4 times, up to 2 bystanders untreated
  - Follow up to 52 weeks
  - Primary EP ORR (mRECIST)

• **Expanded Access (Jun 2009 – Jun 2016)**
  - 177 melanoma patients treated
  - 10 non-melanoma patients treated
Melanoma Clinical Data
Melanoma Clinical Data

Subject 0014: Male, age 48, Stage III (N2c) since 2008, Sx of 1° and mets Single treatment with 1.3 mL PV-10 to 10 lesions; 1 untreated bystander lesion (B1) CR of Target and Bystander Lesions at Week 24

Agarwala et al., ASCO 2010
Male age 73, Stage IIIIB in-transit melanoma of the left lower extremity recurrent after surgical intervention (PV-10 started 1.6 months after resection). Eleven lesions (6.0 cm sum diameter) injected with 1.1 mL PV-10 at Day 0 (single bystander lesion not injected); 7 lesions injected with 1.0 mL PV-10 at Week 8 (5.1 cm sum diameter); and 3 lesions injected with 1.3 mL PV-10 at Week 16 (3.4 cm sum diameter). Subject achieved CR in all injected lesions at Week 36 and confirmed CR in all lesions (including uninjected bystander) at Week 52. Reproduced with permission of Provectus Biopharmaceuticals, Inc.

Agarwala et al., ASCO 2010
# Phase 2 Patients

## Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subjects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>Female</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70 years</td>
<td>39</td>
<td>49</td>
</tr>
<tr>
<td>≥ 70 years</td>
<td>41</td>
<td>51</td>
</tr>
<tr>
<td><strong>Disease Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>62</td>
<td>78</td>
</tr>
<tr>
<td>Stage IV</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td><strong>Treatment History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Prior Systemic Therapy</td>
<td>46</td>
<td>58</td>
</tr>
<tr>
<td>Prior Systemic Therapy</td>
<td>34</td>
<td>42</td>
</tr>
<tr>
<td><strong>Tumor Burden in Skin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 Lesions</td>
<td>44</td>
<td>55</td>
</tr>
<tr>
<td>≥ 10 Lesions</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td>Too Numerous to Count (TNC)</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>

- Substantial tumor burden: 6.3 cm sum diameter of skin lesions (median)
- Refractory to a median of 6 previous interventions:

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excision (100% of patients)</td>
<td></td>
</tr>
<tr>
<td>Nodal biopsy (63%)</td>
<td></td>
</tr>
<tr>
<td>Regional chemotherapy (24%)</td>
<td></td>
</tr>
<tr>
<td>Immunotherapy (21%)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy (21%)</td>
<td></td>
</tr>
<tr>
<td>Investigational Agents (14%)</td>
<td></td>
</tr>
<tr>
<td>Systemic Chemotherapy (13%)</td>
<td></td>
</tr>
<tr>
<td>Amputation (9%)</td>
<td></td>
</tr>
<tr>
<td>Other (8%)</td>
<td></td>
</tr>
</tbody>
</table>
# Response of Injected Lesions

## Table 2. Objective Response of Target Lesions

<table>
<thead>
<tr>
<th>Response of Target Lesions</th>
<th>ITT Population</th>
<th>Subjects Categorized by Disease Burden at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All Lesions Treated</td>
</tr>
<tr>
<td>N (Subjects)</td>
<td>80 %</td>
<td>28 %</td>
</tr>
<tr>
<td>CR</td>
<td>21 26</td>
<td>14  50</td>
</tr>
<tr>
<td>PR</td>
<td>20 25</td>
<td>6   21</td>
</tr>
<tr>
<td>SD</td>
<td>14 18</td>
<td>3   11</td>
</tr>
<tr>
<td>PD (PD + NEV)†</td>
<td>25 31</td>
<td>5   18</td>
</tr>
<tr>
<td>(NEV: Progression Prior to Week 8)</td>
<td>(13)</td>
<td>(2)</td>
</tr>
<tr>
<td>CR + PR</td>
<td>41 51</td>
<td>20   71</td>
</tr>
<tr>
<td>CR + PR + SD (Locoregional Disease Control)</td>
<td>55 69</td>
<td>23   82</td>
</tr>
<tr>
<td>Mean PFS (months)‡</td>
<td>8.2</td>
<td>9.8§</td>
</tr>
</tbody>
</table>

*Median number of untreated lesions: 5. †Non-evaluable subjects were combined with PD for tabulation of outcome. ‡PFS by mRECIST, maximum follow-up duration 12 months. §P < 0.01 vs. TNTC or Stage IV subgroup. ¶P = 0.04 vs. TNTC or Stage IV subgroup.

Thompson et al., Ann Surg Oncol 2015
Response of Injected Lesions

56% of lesions achieved CR after 1-2 injections
All Melanoma Followed Sub-Group (N = 54 Patients)

74% CR when all lesions injected
All Melanoma Treated Subgroup (N = 28 patients / 181 lesions)

Agarwala et al., ASCO 2014
Bystander Response

Objective Response of BYSTANDER LESIONS
Grouped According to Subject Objective Response of Target Lesions
All Evaluable Subjects (N=67)

<table>
<thead>
<tr>
<th>Bystander Lesion Response</th>
<th>Subjects with POSITIVE Objective Response of Target Lesions</th>
<th>Subjects with NEGATIVE Objective Response of Target Lesions</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (Subjects)</td>
<td>18</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>10 (56%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>1 (6%)</td>
<td>2 (12%)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2 (11%)</td>
<td>5 (29%)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>5 (28%)</td>
<td>9 (53%)</td>
<td></td>
</tr>
<tr>
<td>ND</td>
<td>(23)</td>
<td>(9)</td>
<td></td>
</tr>
<tr>
<td>CR + PR</td>
<td>11 (61%)</td>
<td>3 (18%)</td>
<td></td>
</tr>
<tr>
<td>SD + PD</td>
<td>7 (39%)</td>
<td>14 (82%)</td>
<td></td>
</tr>
<tr>
<td>CR + PR + SD</td>
<td>13 (72%)</td>
<td>8 (47%)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>5 (28%)</td>
<td>9 (53%)</td>
<td></td>
</tr>
</tbody>
</table>

Response of each subject’s bystander lesions (overall subject response) as a function of the subject’s objective response of target lesions (POSITIVE Objective Response = CR + PR subjects; NEGATIVE Objective Response = SD + PD subjects). Statistical significance tested using the Chi-Square test. Thirty one evaluable subjects had no designated bystander lesion (or no assessable lesion) to assess (ND) and were censored. Thirteen subjects were not evaluable for either target or bystander lesion response (NEV) and were excluded from this analysis.

Agarwala et al., ESMO 2012
**Distant Bystander Response**

Subject 0216: Male, age 57, Stage IV (M1b) since 2002
Primary left lower extremity, multiple Sx, limb XRT, ILI
Two treatments (Day 0 and Week 16) with PV-10 to 5 cutaneous lesions in calf

CR of injected cutaneous lesions at Week 52
Generalized improvement of pulmonary lesions at Week 12 with “no focal parenchymal pathology” at Week 52

Agarwala et al., ESMO 2012
Distant Bystander Response

Subject 0907: Male, age 40, Stage IV (M1c) since 2006
Multiple Sx, CLND, whole brain XRT, stereotactic radiosurgery, DTIC, IV- and SQ-IFN
Four treatments (Day 0, Week 8, Week 12 and Week 16) with PV-10 to cutaneous lesions

PR of injected cutaneous lesions; 9 of 10 pulmonary lesions resolved at Week 12 (PR of 10th nodule)

Agarwala et al., ESMO 2012
# Adverse Events

<table>
<thead>
<tr>
<th>System Organ Class&lt;sup&gt;a&lt;/sup&gt; Preferred Term&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Adverse Events&lt;sup&gt;b,c&lt;/sup&gt; (ITT Population, N = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>CTCAE Grade</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td></td>
</tr>
<tr>
<td>Injection Site Edema</td>
<td></td>
</tr>
<tr>
<td>Injection Site Vesicles</td>
<td></td>
</tr>
<tr>
<td>Injection Site Discoloration&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Injection Site Swelling</td>
<td></td>
</tr>
<tr>
<td>Injection Site Pruritus</td>
<td></td>
</tr>
<tr>
<td>Injection Site Erythema</td>
<td></td>
</tr>
<tr>
<td>Injection Site Infection</td>
<td></td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td></td>
</tr>
<tr>
<td>Injection Site Cellulitis</td>
<td></td>
</tr>
<tr>
<td>Injection Site Necrosis</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Photosensitivity Reaction</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> System Organ Class and Preferred Term are based on the MedDRA<sup>®</sup> version 13.0 terminology dictionary. Locoregional adverse events were coded to “injection site” Preferred Terms to differentiate these from systemic events.

<sup>b</sup> Includes all AEs with an incidence of 10% or higher and all CTCAE Grade 3 and higher AEs; there were no treatment-related Grade 4 or 5 AEs reported.

<sup>c</sup> If a patient experienced an AE more than once during the study the greatest severity is presented.

<sup>d</sup> Discoloration locoregional to injected lesions.

Thompson et al., Ann Surg Oncol 2015
Implications for Clinical Development

Locoregional Progression

Metastatic Progression

Draining Nodal Basin

In-Transit Candidates for Single Agent Rx

Primary

Survival: 7 yrs (IIIB) to 1.8 yrs (M1a)

Stage IV-M1c

Stage IV-M1b

Stage IV-M1c

Candidates for Combination Rx

Primary

Phase 3 Protocol PV-10-MM-31

Phase 1b/2 Protocol PV-10-MM-1201

Survival: 1.2 yrs (M1b) to 7 mon (M1c)
Clinical Development Strategy

- Despite major advances, clinical trial remains a primary treatment recommendation for patients with locoregional disease
Clinical Development Strategy

- Clinical trial is also recommended for patients with recurrent disease
Clinical Development Strategy

• Today there are at least 13 IL drugs in melanoma clinical trials

Melanoma+ (Intratumoral or Intralesional):

• PV-10
• Imlygic
• Cavatak
• IMO-2125
• LL37
• SD-101
• Ipilimumab
• IL19
• INGN 241
• Hiltonol
• MGN1703
• TTI-621
• Toca 511

➢ In 2014 there were 4 drugs in clinical trials

1 www.ClinicalTrials.gov, November 12, 2016
Clinical Development Strategy

• And there are at least 7 IL drugs in combination clinical trials¹

  Melanoma + (Intratumoral or Intralesional) + (pembro/nivo/ipi):
  • PV-10
  • Imlygic
  • Cavatak
  • IMO-2125
  • SD-101
  • Ipilimumab
  • MGN1703

➢ In 2014 there was 1 drug in combination clinical trials

¹ www.ClinicalTrials.gov, November 12, 2016
Clinical Development Strategy

• This growth of the sector represents a dual-edged sword:
  • There’s little doubt that our IL approach with PV-10 is sound
  • There is growing competition for investigators and patients
  • This is reflected in our development activities and timelines
    • Maximize patient eligibility
    • Pursue opportunities in regions with less competition
Phase 3 Design

• PV-10-MM-31: Protocol History
  • Ver 1.1: 06 Mar 2015
  • Ver 1.2: 16 Feb 2016
    • Added IMLYGIC as comparator
    • Clarified eligibility WRT immune checkpoint inhibitors
    • Clarified and expanded eligibility WRT targeted therapy
    • Expanded eligibility to include Stage IV M1a
  • Ver 1.3: 25 Jun 2016
    • Modified size requirements for Target Lesions
    • Increased total number of lesions
  • Ver 1.4: Late 2016
    • Allow subcutaneous Target Lesions
    • Increase maximum lesion size
    • Additional eligibility optimization
Phase 3 Execution

• **PV-10-MM-31: Protocol Rollout**
  
  • 2015: Anticipated about 1/3 each USA, AUS, EU
  
  • 2016: Expand outreach in EU and extend to LATAM, Russia, Asia
    • 60 centers expected
    • 16+ in Germany, Italy, France and Poland
      • Half in Germany where Imlygic is available
      • Regulatory review underway in Germany and Italy
      • Study uptake expected to be high in Germany (ver 1.2 amendment focused on requirements for Germany)
    • 4 in Russia
    • 7 in Argentina
    • 5 in Mexico
    • 5+ in Brazil
    • 1+ in China
Phase 3 Execution

• PV-10-MM-31: Protocol Rollout

  • 2016-2017: Expand outreach to new investigators in USA and AUS
    • Expanded eligibility criteria expected to attract initial declines
  
  • 2017: Slow uptake by USA and AUS investigators
    • Set timelines back by an additional 6-9 months
    • Simultaneous launch of sites in Germany, immediately followed by Italy, will stabilize timelines
    • Adding more USA and AUS sites will also stabilize timelines
    • Q2 opening of sites in LATAM, France, Russia accelerate progress
    • Reviewing selected other regions for possible study expansion
    • No fundamentally competitive threats evident (patient population remains underserved)
    • Overall playing field improved substantially 2H-2016 (reducing headwinds going into 2017)
Phase 3 Execution

• PV-10-MM-1201: Protocol Rollout

  • 2015: Anticipated 4-6 centers in USA and AUS
  • 2016: 4 centers opened
    • 2 additional centers to open Q1-2017
    • Contemplating 1 further center for phase 1b
  • 2017: Initial phase 1b data available for prospective partners
    • No significant impact on timeline for initial safety results
    • Preliminary efficacy data not expected to be impacted
    • ASCO / ESMO initial public readout
    • Preparing for expansion of study to phase 2
Melanoma in the USA

Melanoma Incidence and Deaths in the USA

Data source: Cancer Facts & Figures 2004 - 2016, American Cancer Society
Hepatic Tumors

- **Protocol PV-10-LC-01 (Phase 1)**
  - Single intralesional injection into center of a single study lesion
  - Follow-up
    - 23 hour admission for initial safety observation
    - Primary follow-up at 28 days (amended to add Month 3)
    - Extended follow-up for 6 – 15 months (amended to every 3 months beginning at Month 6)
  - Observe treated lesion and any untreated lesions
    - Outcome scored using RECIST (amended to 2D EASL)
  - “Basket study” design allows assessment in HCC and metastatic tumors
Subject 0001 (HCC #1)

- Female, age 71, 3.4 cm HCC lesion injected once with 5.1 mL PV-10
Initial Results

- **Protocol PV-10-LC-01 (Phase 1):** Initial 18 Lesions (16 Patients)
  - Median Age 68 years (range 51 – 89)
  - HCC – 7 lesions (6 patients) / Metastases – 11 lesions (10 patients)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Disease and History</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0005</td>
<td>M, age 68 HCC (HepB and Cirrhosis)</td>
<td>Alive (NED, 66 mon)</td>
</tr>
<tr>
<td>0001</td>
<td>F, age 71 HCC (2 lesions treated with PV-10, RFA)</td>
<td>Alive (with Disease, 57 mon, lost to follow-up)</td>
</tr>
<tr>
<td>0004</td>
<td>F, age 73 HCC (HepC, Cirrhosis, Portal Hypertension, RFA, TACE)</td>
<td>Expired (DP, 48 mon)</td>
</tr>
<tr>
<td>0008</td>
<td>F, age 66 HCC (HepC, Cirrhosis, Portal Hypertension)</td>
<td>Expired (DP, 12 mon)</td>
</tr>
<tr>
<td>0007</td>
<td>M, age 67 HCC</td>
<td>Expired (Cardiac Comorbidity, 2 mon)</td>
</tr>
<tr>
<td>0101</td>
<td>F, age 89 HCC (8.9 cm)</td>
<td>Expired (SAE, suspected thromboembolism)</td>
</tr>
<tr>
<td>0006</td>
<td>M, age 61 mCRC (3 tu, FOLFOX, Avastin, Erbitux)</td>
<td>Alive (NED, 57 mon)</td>
</tr>
<tr>
<td>0204</td>
<td>F, age 67 mCRC (RFA, FOLFOX)</td>
<td>Alive (21 mon)</td>
</tr>
<tr>
<td>0009</td>
<td>M, age 85 mCRC</td>
<td>Alive (15 mon)</td>
</tr>
<tr>
<td>0010</td>
<td>F, age 53 mCRC</td>
<td>Alive (DP, 3 mon)</td>
</tr>
<tr>
<td>0206</td>
<td>F, age 67 mCRC (≥ 6 tu, FOLFOX)</td>
<td>Expired (DP, 3 mon)</td>
</tr>
<tr>
<td>0203</td>
<td>M, age 69 Lung (≥ 4 tu, nivo)</td>
<td>Expired (DP, 12 mon)</td>
</tr>
<tr>
<td>0202</td>
<td>M, age 83 Lung (≥ 6 tu, carbo/Abraxane)</td>
<td>Expired (DP, 12 mon)</td>
</tr>
<tr>
<td>0205</td>
<td>M, age 83 Pancreatic</td>
<td>Alive (9 mon)</td>
</tr>
<tr>
<td>0102</td>
<td>F, age 53 Melanoma (≥ 4 tu, 2 lesions treated with PV-10, nivo + ipi)</td>
<td>Expired (DP, 18 mon)</td>
</tr>
<tr>
<td>0201</td>
<td>F, age 51 Ovarian (≥ 35 tu, paclitaxel/carbo)</td>
<td>Expired (DP, 15 mon)</td>
</tr>
</tbody>
</table>
HCC Management Guidelines

Management of Hepatocellular Carcinoma: An Update

Jordi Bruix¹ and Morris Sherman²

WHERE DOES PV-10 FIT?

1. If the patient has one HCC nodule <2 cm or no HCC, the treatment is Resection or Transplantation.
2. If the patient has one HCC nodule between 2 cm and 3 cm, the treatment is Ablation.
3. If the patient has three HCC nodules <3 cm, the treatment is TACE.
4. If the patient has three HCC nodules >3 cm, the treatment is Sorafenib.

HCC Development Plan

- **Asia/Pacific Development Strategies**

  - **Phase 1b / 2 Options**
    - Phase 1b SAT: Neoadjuvant PV-10 + local SOC (Sorafenib)
    - Phase 2 RCT: Neoadjuvant PV-10 + local SOC vs local SOC
    - Phase 1b SAT: PV-10 + Checkpoint Inhibition (PD-1 / PD-L1)
    - Phase 2 RCT: PV-10 + Checkpoint Inhibition vs Checkpoint Inhibition

  - Sorafenib study to be advanced pending resource availability

  - Checkpoint combination pending nonclinical validation
    - Immunologic characterization in Singapore to start Q4-2016
    - Supports collaboration with BI and possible Merck / BMS / others
HCC in USA

Hepatic Cancer Incidence and Deaths in USA

Data source: Cancer Facts & Figures 2004 - 2016, American Cancer Society
Development Plan for Metastatic Disease

- **Continue Basket Study**
  - Open Additional Centers in USA and AUS
    - All-comers to expand numbers for important tumor types
    - Focused enrollment of high-priority tumor types (e.g., uveal melanoma)
    - Next data reporting expected Feb 2017 (China)

- **Explore Leveraging LC-01 and MM-1201 Protocols**
  - Combination therapy for demonstrated combinations
    - PV-10 + Gemcitabine for pancreatic adenocarcinoma
      - Leverage QoL experience gained in MM-31
    - PV-10 + PD-1 for hepatic metastases of melanoma
Overall Development Plan

- Balance Primary Focus with High Potential Opportunities
Supply Chain

• Priority Date: September 2010
• CIP and Divisional Issued
• Allowed or Issued in Canada, Mexico, EU, China, HK, Japan, Korea
  (awaiting OA in India)
• Applies Quality-by-Design Principals to Meet Global Purity and Reproducibility Standards
Supply Chain

- New synthetic process supplants 1880’s Gnehm process
- Tightly controls impurities characteristic of historic process to meet ICH standards
  - Related substances
  - Solvents
  - Inorganics
- RBL and PV-10 manufactured in USA by established drug manufacturers
- PV-10 specifications meet FDA and EMA requirements for injectable drug
- First of 3 NDA stability lots manufactured H2-2016 (8,000 vials / lot)
Clinical Trial Process

All Clinical Work is Guided by ICH Principals

• The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities and pharmaceutical industry to standardize scientific and technical aspects of drug registration.

• Since its inception in 1990, ICH has gradually evolved to respond to the increasingly global face of drug development.

• ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.

  ➢ Provectus conforms to ICH principals to assure safe and efficient execution of each clinical study.

  ➢ This is critical to meet global regulatory requirements and assure portability of study data.
Clinical Trial Process

Competent Authority: Clinical Trial Authorization

Application
- IND
- CTN
- CTA

Clinical Site
- Site / National SRC
- Site Contract
- Site ICF
- Site / National IRB / EC

Supporting Documents
- Tox
- Pharm
- PK
- CMC
- IB

- Pharmacy
- Radiology
- Local Lab

x N
x M
Clinical Trial Process

Clinical Site

Site Contract

Protocol

Site Patient Population

Investigational Team

Potential Subjects

Site ICF

Eligible Subjects
Clinical Trial Process

Clinical Site

Investigational Team

Study Subject

Sponsor Monitor

Protocol

IMP and Supply Logistics

Raw Study Data

CRFs / eCRFs
Local / Central Labs
Photo-documentation
Image Core Lab
PRO / ePRO

Central Study Database
Clinical Trial Process

Data Analysis


Statistical Analysis (per SAP)

→ Study Efficacy EP(s)
Clinical Trial Process

Safety Analyses

Study Subject → CRFs / eCRFs → Local / Central Labs → Statistical Analysis (per SAP) → Study Safety EP(s)
Clinical Trial Process

Study Reporting

- Study Safety EP(s)
- Study Efficacy EP(s)
- Study Tables and Listings

→ CSR

Study PV-10-PK-01
- 8 subject pharmacokinetic study
- 884 pages
Clinical Trial Process

Study Management – USA and AUS

Core Regulatory Dossier

Protocol

Study Sites
- Contracting
- Local Approval
- SRC / IRB Interface
- Study Monitoring
- Coordinating with Study Vendors (Central Lab, Photography, etc)
- Coordinate Study Supplies

Investigator Brochure
Clinical Trial Process

Study Management – Europe, LATAM, Asia

- Core Regulatory Dossier
- Protocol
- Investigator Brochure

CRO
- Local Regulatory Dossier
- Protocol (Translated)
- IB (Translated)

Study Sites
- Contracting
- Local Approval
- SRC / IRB Interface
- Study Monitoring
- Coordinating with Study Vendors (Central Lab, Photography, etc)
- Coordinate Study Supplies

➢ Sponsor retains ultimate responsibility for safe and efficient execution of study
# Clinical Trial Process

## Study Monitoring

### Sponsor Monitors (CRAs)
- Regularly Visit Each Site
- Verify Protocol Compliance
- Review ALL DATA Reported vs Source Records
- Follow-up to Assure Errors are Corrected

### Clinical Trial Data Monitoring Committee

**Independent Committee Managed by Lead CRO**
- Lead Project Manager
- Study Medical Monitor
- Study Biostatistician
- Three Independent Oncologists
  - Separate from Sites, IRCs, etc
- Periodic Review of Safety and Efficacy Data

![PROJECTUS BIOPHARMACEUTICALS, INC.](image)
Clinical Trial Process

Study Execution

• A large, pivotal trial (such as the phase 3 study) will contain all of these elements

• An earlier phase trial (such as the phase 1b combination study) will contain many of these elements
  • Using the full model early allows the study to expand quickly into more advanced phases
  • Selecting only those components necessary controls cost during initial testing

• Exploratory trials (such as the hepatic study) contain many of these elements
  • For a small study data management may be efficiently addressed using traditional methods
    (such as paper CRFs, in-house data aggregation, etc)

• In each case, the necessary elements are used to assure ICH compliance

• This assures regulatory compliance and data portability for regulatory submission globally
Update on PH-10

- Advanced Immunologic Analysis of Biopsy Specimens Underway
  - Expect these additional MoA data Dec 2016
Warning: Personal Opinions Ahead

• Anyone who has interacted with me knows that I avoid giving personal opinions about Provectus and the company’s prospects.

• In light of recent trends, I take a pause from this policy and offer my personal opinion on the following slides.

• It is important to note that as a major shareholder I am heavily vested in the success of the company.
Why You Should Head for the Exit

• The time to readout of the melanoma phase 3 study cannot be quantified with certainty
  • Oncology is changing rapidly and very large players are aggressively staking claims
  • Changing SoC and “de facto” SoC pose difficult challenges
    • Investigator interest and center opening
    • Competition for patients in a very active era of clinical development
    • Study timelines
    • Total study cost

• We may fail to achieve crucial clinical milestones
  • Many drugs fail in phase 3
  • We may not receive adequate capital to reach key milestones
  • Our secondary and tertiary indications may not be successful
Why You Should Head for the Exit

• We’ve made missteps, and are likely to make more in the future
  • We may not recognize new landmines before it’s too late
  • As a small organization we are susceptible to death by a thousand cuts
  • We are susceptible to disruptive change in management (“house cleaning”) that could alter course of technology and/or capital structure
  • We may fail to manage transition to a larger organization (growth precipitating collapse)
Why You Shouldn’t Head for the Exit

• The news about our technology gets consistently better
  • Work by high-quality third parties continues to build credibility for core indications and supports broad “multi-indication” promise for PV-10
  • “Basket study” data from our hepatic trial is closely paralleling work in the lab
  • Asia path forward is clear, and the advanced path (I-O) could be a game changer there and in the West
  • Phase 3 interim assessment and Phase 1b preliminary assessment will occur if we stay the course
  • PV-10 has a novel MoA in a crowded field hungry for novelty

• The same could apply to PH-10...
Why You Shouldn’t Head for the Exit

• We have technology that leverages megatrends in oncology
  • The latest period of irrational exuberance in oncology seems to be ending
  • PV-10 addresses an opportunity to build on current I-O backbone
  • PV-10 appears to “make the patient’s tumor his or her friend”
  • PV-10 could be a breakthrough for immunologically “cold” tumors
  • PV-10 could be a compelling value proposition for big pharma
  • PV-10 can be a global play (“it can be hauled in a backpack to the farthest reaches”)

• PH-10 may fit many of these parameters as well
Why You Shouldn’t Head for the Exit

• We’ve addressed key structural challenges in clinical development
  • Our supply chain is robust
  • The first NDA stability lot of PV-10 has been manufactured
  • We’ve implemented quality systems necessary for phase 3 testing
  • We’ve built a global clinical development team
  • We’ve fostered corporate collaborations to smooth globalization of programs
Why You Shouldn’t Head for the Exit

• Drug development is slow and expensive
  • A typical drug takes over 10 years and $2.5B to develop \(^1\)

![Cost, $ millions](image)

• Despite missteps, we’ve spent a tiny fraction of what is typically required to bring a new drug to market

\(^1\) Scientific American, November 24, 2014
Why You Shouldn’t Head for the Exit

• Drug development is slow and expensive
  • We have consistently advanced clinical development of PV-10 from initial IND filing in 2004 to phase 1, phase 2 and now phase 3
  • While we were charting a course for melanoma through the end of the targeted therapy era and start of the I-O era we continued to advance clinical understanding via expanded access, MoA, XRT, and hepatic programs
  • This experience provided the necessary foundation for a dual path forward in melanoma (single agent and combination) that we are advancing today
  • Our primary EP in phase 3 (PFS) is now being advanced by industry as the preferred EP for oncology studies
  • We remain at the forefront of non-cutaneous clinical development for IL agents
Conclusions

- PV-10 is a unique small molecule investigational oncolytic immunotherapy
  - Stable at room temperature
  - No biosafety restrictions
  - Predominantly local toxicity
  - Capable of high response rate
  - Often with minimal intervention
  - Rapid reduction in tumor burden
  - Can produce a systemic immune effect
  - Single-agent or combination use

- PH-10 is under investigation as a potential topical immunomodulatory agent for inflammatory dermatoses
  - Emerging data may be crucial in demonstrating market niche
Conclusions

• Thank you for your attention today and your support of this work