Rose Bengal

Small Molecule Ablative Immunotherapy

A first-in-class halogenated xanthene
with unique therapeutic properties for fighting
cancer and inflammatory dermatoses

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for: The BIO International Convention (June 6-9)

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BIOPHARMACEUTICALS, INC.

Forward-Looking Statements

This presentation contains "forward-looking statements" as defined under U.S. federal securities laws. These statements reflect management's current knowledge, assumptions, beliefs, estimates, and expectations and express management's current views of future performance, results, and trends and may be identified by their use of terms such as "anticipate," "believe," "could," "estimate," "expect," "intend," "may," "plan," "predict," "project," "will," and other similar words. 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. Readers should not place undue reliance on forward-looking statements. Such statements are made as of the date hereof, and we undertake no obligation to update such statements after this date. Risks and uncertainties that could cause our actual results to materially differ from those described in forward-looking statements include those discussed in our filings with the U.S. Securities and Exchange Commission (including those described in items 1A of our Annual Report on 10-K for the year ended December 31, 2015). Provectus Biopharmaceuticals, Inc. ("Provectus") assumes no obligation to update any forward-looking statements or information that speaks as to their respective dates.

No claims with respect to Provectus' investigational drug PV-10 for solid tumor cancers and/or investigational drug PH-10 for inflammatory dermatoses are intended regarding safety or efficacy in the context of the forward-looking statements in this presentation.

Company presentations are made publicly available at the time of delivery, and may be found at www.pvct.com/presskit.html along with other presentations, including this one.

Presentation Contents

Investigational Oncology Compound PV-10

- **PV-10: A 10% solution of small molecule and halogenated xanthene Rose Bengal**
  - Administered by direct injection into solid tumor cancers (e.g., melanoma, liver, breast, etc.)
  - Not designed to rely on a single pathway, receptor or antigen to work; no known resistance
- **First-in-class ablative immunotherapy: Intended to kill only diseased cells upon injection into tumors; proper cell death would be the subsequent upstream trigger for a systemic anti-tumor response**
  - Potentially agnostic to disease presentation and orthogonal to other cancer treatments
- **Rose Bengal: A diagnostic agent for >100 years; long and established history of use in humans**
  - Original/first medicinal use: an intravenous hepatic diagnostic (^{131}I-radiolabeled Rose Bengal/Robengatope®) and topical ophthalmic diagnostic (Rosettes®, Minims®)
  - Physical chemistry properties; not metabolized; half-life of ~30 minutes in the blood stream
- **Therapeutic use: Advanced by Provectus Biopharmaceuticals in both oncology and dermatology**
  - Global intellectual property protection for the entire class of halogenated xanthenes
  - Second medicinal use (as a therapeutic), Method of use, Formulation (including trade secrets), Synthesis (to ICH Guidelines specification), Combination (with other cancer treatments)

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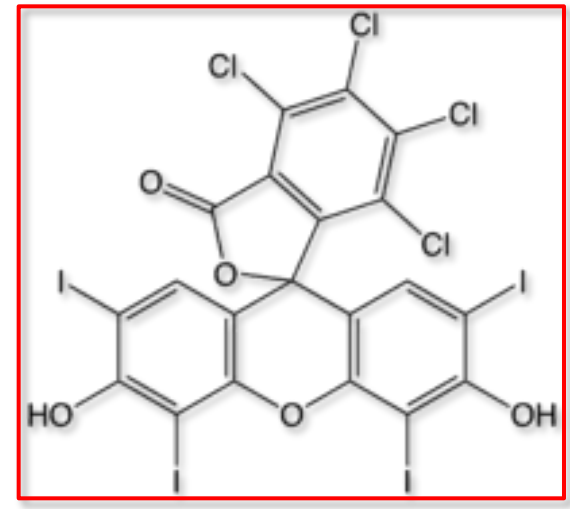
Bringing Small Molecule Nostalgia Back to Big Pharma

- **PV-10: Small molecule ablative immunotherapy**
  - Ablation: destruction of injected tumors
  - Immunotherapy: subsequent tumor-specific immune response
- **Rose Bengal weighs <1,000 g/mol**
  - Not a macromolecule, polymer or biomolecule; best classified as a small molecule, albeit a very heavy one
  - Good, consistent pharmacokinetic properties
  - May occupy "natural-product-like" chemical space



- **Potentially an understood mechanism of action**
  - Injection of Rose Bengal results in necrosis of tumor cells and the release of High Mobility Group Box 1 (HMGB1), with increased dendritic cell infiltration into draining lymph nodes and the activation of tumor-specific T cells[1]

[1] Liu et al., Oncotarget 2016

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An Opportunity for a Global Impact on Cancer

- Potentially viable for multiple cancer indications
- Potentially agnostic to disease presentation
- Intended to be synergistic in combination with other cancer treatments
- Intended to be orthogonal to other cancer treatments when combined
- Designed for ease of physician/provider use and/or re-use
- Designed to be supportive of patient compliance
- Designed for ease of shipment, storage and handling (all at room temperature)
- Globally affordable

Implications of Emerging Immunology Data

- **PV-10 has been implicated in each step of the *Cancer Immunity Cycle*[1,2]**
  - Release of cancer antigens–1; cancer antigen presentation–2; priming and activation–3; trafficking of T cells to tumors–4; infiltration of T cells into tumors–5; recognition of cancer cells by T cells–6; killing of cancer cells–7
  - PV-10 is as much about "starting the engine" and "stepping on the gas pedal" of the immune system as it is about "releasing the brakes"
  - International, pivotal, monotherapy trial-in-progress: PV-10 vs. Chemotherapy or Oncolytic Viral Therapy[3]
- **Potentially agnostic to disease presentation**
  - e.g., melanoma, cancers of the liver, breast cancer, colon cancer, pancreatic cancer, etc.
- **Potentially orthogonal to other cancer treatments when combined**
  - Synergistic: "induce and boost" an immune response (PV-10 would induce the immune response, and the partner treatment would boost it); minimal risk of clinically relevant drug-drug interaction[4]
  - Combination therapy trials-in-progress: PV-10 + anti-PD-1 pembrolizumab[5]; + radiotherapy[6]
  - Completed pre-clinical work: PV-10 + chemotherapy[7]; + anti-CTLA4[8,9]; + anti-PD-1[9,10]; + anti-PD-L1[9,10]

[1] Chen and Mellman, *Immunity* 2013. [2] Liu et al., Oncotarget 2016. [3] NCT02288897. [4] Kazmi et al., In vitro inhibition of human liver cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzymes by rose bengal: system-dependent effects on inhibitory potential, *Xenobiotica*, 2014 Jul; 44(7):606-14. [5] NCT02557321. [6] Foote et al., A phase 2 study of intralesional PV-10 followed by radiotherapy for localized in transit or recurrent metastatic melanoma, *J Clin Oncol* 34, 2016 (suppl; abstr e21072). [7] Dees et al., SITC 2012. [8] Wachter et al., AACR 2013. [9] Liu et al., SITC 2014. [10] Liu et al., AACR 2016.

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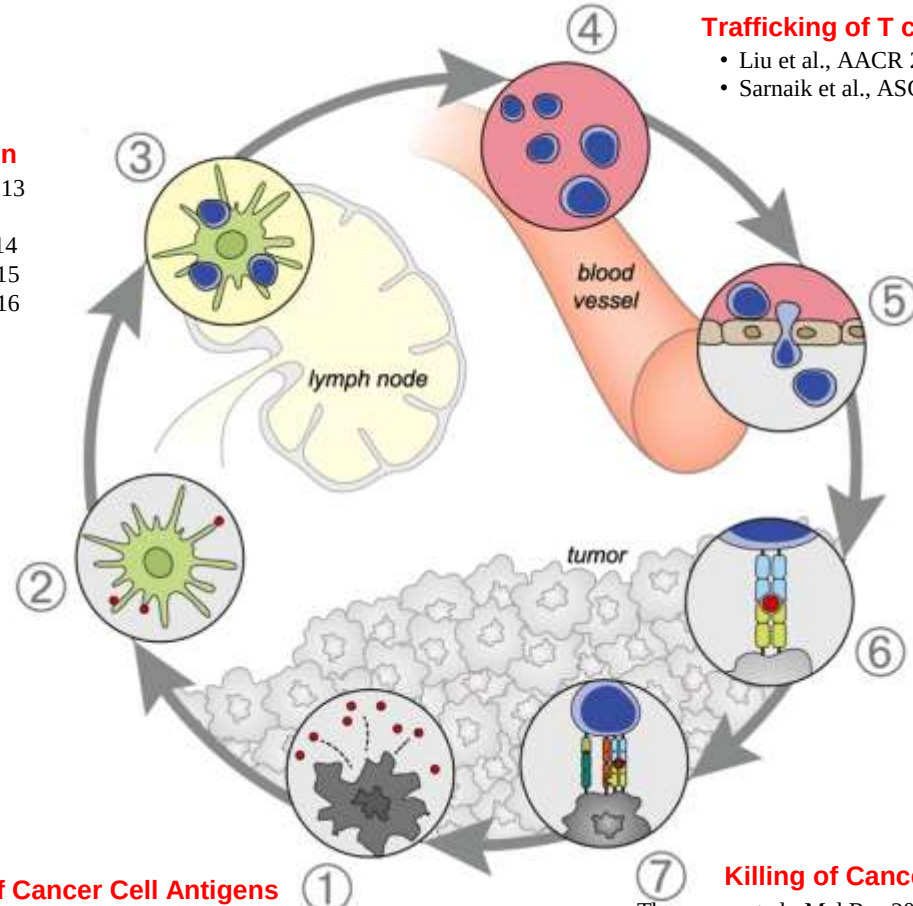
PV-10: Oncology Meets Immunology



Trafficking of T cells to Tumors

- Liu et al., AACR 2014
- Sarnaik et al., ASCO 2014
- Liu et al., Oncotarget 2016
- Melanoma (p, c)

Priming and Activation

- Toomey et al., PLoS1 2013
- Liu et al., AACR 2014
- Sarnaik et al., ASCO 2014
- Pardiwala et al., SSO 2015
- Liu et al., Oncotarget 2016
- Melanoma (p, c)
- Colon cancer (p)

Infiltration of T cells into Tumors

- Liu et al., Oncotarget 2016
- Melanoma (p, c)

Cancer Antigen Presentation

- Liu et al., AACR 2014
- Liu et al., SITC 2015
- Liu et al., Oncotarget 2016
- Melanoma (p, c)

Recognition of Cancer Cells by T Cells

- Liu et al., AACR 2014
- Sarnaik et al., ASCO 2014
- Liu et al., SITC 2015
- Liu et al., Oncotarget 2016
- Melanoma (p, c)

Release of Cancer Cell Antigens

- Thompson et al., Mel Res 2008
- Agarwala et al., ASCO 2009
- Toomey et al., PLoS1 2013
- Liu et al., AACR 2014
- Sarnaik et al., ASCO 2014
- Pardiwala et al., SSO 2015
- Thompson et al., Ann Surg Oncol 2015
- Liu et al., SITC 2015
- Liu et al., Oncotarget 2016
- Melanoma (p, c)
- Breast cancer (p)
- Colon cancer (p)

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
- Wachter et al., AACR 2013
- Toomey et al., PLoS1 2013
- Liu et al., AACR 2014
- Sarnaik et al., ASCO 2014
- Goldfarb et al., ESMO World GI 2015
- Thompson et al., Ann Surg Oncol 2015
- Liu et al., Oncotarget 2016
- Melanoma (p, c)
- Breast cancer (p)
- Colon cancer (p)
- Hepatocellular carcinoma (p, c)
- Pancreatic cancer (p)

Diagram: Chen D.S., Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 39:1–10 (2013). **Key:** p = preclinical, c = clinical.

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Ablative Immunotherapy: A Two-Prong Approach to Fighting Cancer

Local Effect:
Tumor destruction
(ablation)

- Intended for a patient's tumor burden to be rapidly reduced after injection of PV-10 into his or her cancerous lesions/tumors
- Rose Bengal's selective targeting of diseased cells is intended to minimize side effects
- PV-10 is not designed to rely on a single immunologic signaling pathway, cell receptor or tumor antigen to work
- Rose Bengal/PV-10 has no known resistance

Systemic Effect:
Tumor-specific immune response
(immunotherapy)

- PV-10 intended to cause regression of untreated (i.e., non-injected) tumors
- Potentially prolongs progression-free survival (PFS)
- PV-10 is designed to be combined with different immunotherapies, targeted therapies, chemotherapy and radiotherapy for lesions/tumors not accessible to injection
- A recent study demonstrated PV-10 may have potential positive implications for overall survival (OS) and other clinical measures for the treatment of cutaneous melanoma metastses[1]

[1] Read et al., Intralesional PV-10 Chemoablation Therapy for the Treatment of Cutaneous Melanoma Metastases – Results of a Prospective, Non-Randomised, Single Centre Study. *ANZ J Surg*. 2016; 86 (S1).

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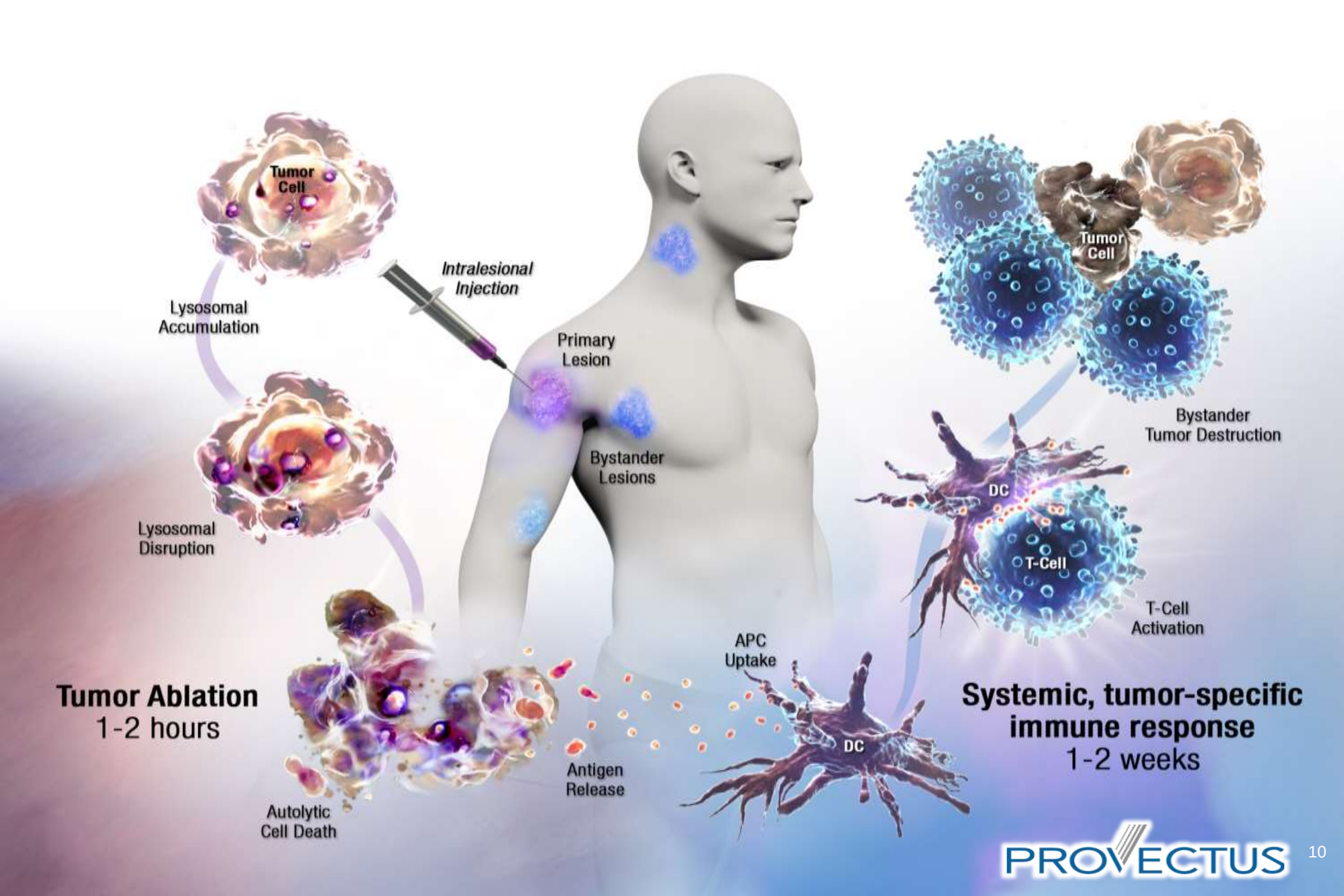
Tumor Cell
Intralesional Injection
Lysosomal Accumulation
Primary Lesion
Bystander Lesions
Lysosomal Disruption
Tumor Cell
Bystander Tumor Destruction
DC
T-Cell
T-Cell Activation
APC Uptake
Tumor Ablation
1-2 hours
Antigen Release
DC
Systemic, tumor-specific immune response
1-2 weeks
Autolytic Cell Death

Reproducibility: The Hallmark of Western Science

- **Key collaborators:** H. Lee Moffitt Cancer Center and Research Institute (Moffitt), Maker Laboratory at the University of Illinois at Chicago (UIC)
- Moffitt and UIC independently reproduced and also expanded upon Provectus' original work; did so independently of the company and each other[1,2,3]:
  - Tumor ablation, the local effect of destroying (ablating) injected tumors
  - A tumor-specific immune response, the systemic effect of destroying untreated (non-injected) tumors
  - Tumor-specific IFN-γ production
  - Multi-indication viability in solid tumor cancers (melanoma, breast cancer and colorectal cancer)
- **Mouse-to-man-to-mouse: An exemplary demonstration of translational medicine**[4,5]
  - Moffitt identified important immunologic markers in model systems; verified key facets in humans
  - Similarly identified other markers in humans; substantiated these in mouse models

[1] Toomey et al., SSO 2012. [2] Toomey et al., PLoS1 2013. [3] Pardiwala et al., SSO 2015. [4] NCT01760499. [5] Liu et al., Intralesional rose bengal in melanoma elicits tumor immunity via activation of dendritic cells by the release of high mobility group box 1, *Oncotarget* (2016).

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Valuation Drivers: Clinical Development Program

- **Melanoma:**
  - **Ongoing Pivotal Phase 3:** PV-10 vs. Chemotherapy or Oncolytic Viral Therapy for Treatment of Locally Advanced Cutaneous Melanoma
  - **Ongoing Phase 1b:** PV-10 in Combination With Pembrolizumab for Treatment of Metastatic Melanoma
- **Cancers of the liver:**
  - **Ongoing expanded Phase 1:** PV-10 Chemoablation of Cancer of the Liver
  - **Ongoing Phase 1:** PV-10 Chemoablation of Neuroendocrine Tumors (NET) Metastatic to the Liver
  - **Planned:** A Phase 1b/2 study of PV-10 and standard of care(s) for Hepatocellular carcinoma (HCC) in Asia
- **Inflammatory dermatoses:**
  - **Ongoing Phase 2:** Cellular and Immunologic Changes in the Skin of Subjects Receiving PH-10
  - **Planned:** Potentially pivotal Phase 3 trials for atopic dermatitis and psoriasis

Intralesional (IL) Therapy: Increasing Awareness & Acceptance

- Until 2015, there was no history of clinical success and regulatory approval for nearly 40 years
  - Before Amgen's IL drug talimogene laherparepvec (Imlygic®) was approved in October 2015 for advanced melanoma, recent failure included Vical's velimogene aliplasmid (Allovectin-7®)
  - Before Allovectin-7®'s failure in 2013 (advanced melanoma), bacillus Calmette-Guérin (BCG) failed in 1978 for advanced melanoma too
- As a result of Imlygic® and PV-10's positive clinical data to date, there is more regulatory, medical and pharmaceutical community acceptance and awareness of the category of IL treatment; clinical studies and data to date have demonstrated:
  - Notable and lengthy tumor destruction upon injection
  - Loco-regional and systemic immune responses
  - Minimal toxicity
  - Use in earlier disease settings of cancer
  - Immune system priming to allow other immunomodulatory drugs to boost and sustain its response

PV-10: An NDA-stage, Wholly-owned, IL Cancer Asset

Intralesional agent	Proprietary name	Company	+ Medical device	As a monotherapy			In combination with				
				Phase 1	*Phase 2*	*Phase 3*	*Ipilimumab*	*Pembro*	*Nivolumab*	*Radiation*	*Other*
bacillus Calmette-Guerin (BCG)		n.a.	No								
+ melanoma					1967-74	1974-1978	P1, 2013-				
Velimogene aliplasmid	**Allovectin-7**	Vical	No								
+ melanoma					2002-11	2006-14					
talimogene laherparepvec (T-Vec)	**Imlygic**	Amgen (BioVex)	No								
+ melanoma					2006-15	2008-15	P1b/2, 2012-	P1b/3, 2014-			
+ melanoma, neoadjuvant to surgery					2014-						
+ pancreatic cancer				2006-16							
+ HCC, liver mets				2015-							
+ breast cancer					2016-						
+ head & neck cancer								P1, 2015-			
+ soft tissue sarcoma										P1/2, 2015-	P3, 2010-16
+ pediatric non-CNS tumors				2015-							
+ expanded access program, melanoma					2014-16						
Rose bengal	**PV-10**	Provectus Bio	No								
+ melanoma				2005-7	2007-14	2015-		P1b/2, 2015-		P2, 2010-	
+ HCC, liver mets				2009-							
+ NET liver mets				2016-							
+ breast cancer				2005-8							
+ expanded access program					2009-						
Electroporation of plasmid interleukin-12	**ImmunoPulse**	OncoSec	Yes								
+ melanoma					2011-			P2, 2015-			
+ cutaneous lymphoma				2012-2016							
+ breast cancer				2015-							
+ head & neck cancer					2015-						
coxsackievirus A21	**CAVATAK, CVA21**	Viralytics	No								
+ melanoma				2007-9	2010-15		P1, 2014-	P1, 2015-			
+ head & neck cancer				2009-12							
Herpes simplex virus type 1	**HF10**	Takara Bio	No								
+ melanoma, breast cancer, head & neck cancer				2009-15							
+ melanoma				2015-			P2, 2014-				

Dates (years) above from ClinicalTrials.gov: *First received-Last updated*, except for investigator-initiated (Australia) study of PV-10 + radiation

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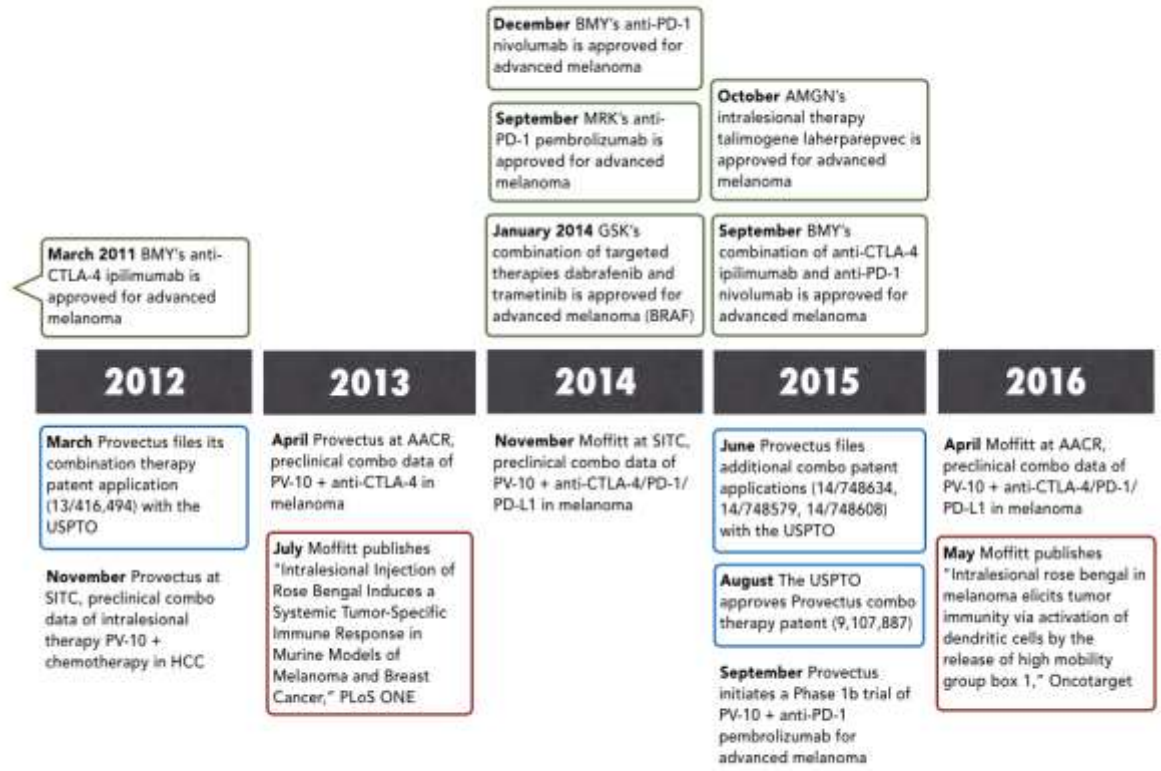
Combination Therapy: 'Induce and Boost' the Immune Response

- **PV-10:** Intended to kill only diseased cells upon injection into tumors; proper cell death would be the subsequent upstream trigger for a systemic anti-tumor response
- **Immune activation after PV-10 injection:** Immunogenic cell death and signaling via release of HMGB1, dendritic cell recruitment and infiltration into draining lymph nodes, activation of tumor-specific T cells, and killing of non-injected tumors upon infiltration by these T cells[1]
- **In combination:** PV-10 is designed to provide the requisite pre-existing anti-tumor immunity for co-inhibitory blockade (i.e., checkpoint inhibitors) to potentially improve their clinical benefit



[1] Liu et al., Oncotarget 2016

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Compassionate Use (Expanded Access) Program

- Began in Australia in 2009 (special access scheme), and later expanded to the U.S. in the same year
  - Available for cancer indications that did/do not involve visceral organs, and to patients who were/are not subject to enrollment in on-going clinical trials
  - **Eight participating sites:** St. Luke's Hospital & Health Network (Bethlehem, PA), MD Anderson Cancer Center (Houston, TX), University of Louisville (Louisville, KY), Sharp Memorial Hospital (San Diego, CA), Melanoma Institute Australia (Sydney), Princess Alexandra Hospital (Brisbane, Australia), Royal Adelaide Hospital (Adelaide), Peter MacCallum Cancer Centre (Melbourne)
- Originally designed for 115 patients; an initial target of 25-30 patients
  - Approximately 160 patients treated through 2015; more treated in 2016
- The program will be wound down at the end of this year
  - **Rationale:** Two clinical trials[1,2] are underway (currently recruiting) for a substantial fraction of Stage III/IV melanoma patients; reached and exceeded the program's accrual design and targets

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[1] NCT02288897. [4] NCT02557321.

Publications: Compassionate Use (Expanded Access) Program

- Data publications in 2016 for >65 patients from two Australian sites' experiences: Princess Alexandria (Brisbane)[1], Peter MacCallum (Melbourne)[2]
- "PeterMac:" Lippey et al., Intralesional PV-10 for in-transit melanoma-A single-center experience, *J Surg Oncol*, 2016 May 30
  - 68% disease control (complete or partial response or disease stability); 26% complete response; N = 19
  - **Patient population:** Unresectable local recurrence and in-transit metastasis of cutaneous melanoma, or American Joint Committee on Cancer (AJCC) Stage IIIB and IIIC — Pivotal trial population: Stage IIIB-IVM1a[3]
  - **Treatment with PV-10:** Most patients received only one course of treatment; a majority of patients did not have all of their lesions injected because of the number of lesions present — Pivotal trial treatment: Designed to treat all disease (i.e., all of a patient's lesions)
  - **Predictors of response:** Predictors of complete response were age and lesion size; the presence of ulceration, blistering, eschar, or pain following injection also was predictive of response; the number of injected lesions and time from primary diagnosis to treatment were not predictive — Pivotal trial efficacy measures: PFS (primary), complete response rate (CRR) (secondary), duration of complete response (secondary), OS (secondary)

[1] Read et al., Intralesional PV-10 Chemoablation Therapy for the Treatment of Cutaneous Melanoma Metastases - Results of a Prospective, Non-Randomised, Single Centre Study, *ANZ J Surg* 2016, 86 (S1). [2] Lippey et al., Intralesional PV-10 for In-Transit Melanoma - A Single Centre Experience. *ANZ J Surg*. 2016, 86 (S1). [3] NCT02288897.

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Globally-Protected Intellectual Property

- **Protection (through at least 2031):** Second medicinal use, Method of use, Formulation, Synthesis, Combination
- **Synthesis:** Process for the synthesis of 4,5,6,7-tetrachloro-3',6'-dihydroxy-2',4',5',7'-tetraiodo-3H-spiro[isoben- zofuran-1,9'-xanthen]-3-one (rose bengal) and related xanthenes
  - The process under which pharmaceutical-grade Rose Bengal and related xanthenes are produced per International Conference on Harmonisation (ICH) Guidelines; covers the use of alternative raw material when manufacturing Rose Bengal
  - Approved in the U.S. (#8,530,675); allowed in China; filed in multiple other global jurisdictions
  - Supported by Cambrex Comporation
- **Combination:** Combination of local and systemic immunomodulative therapies for enhanced treatment of cancer
  - The treatment combination of PV-10 and immunomodulatory therapeutic agents, including anti-CTLA-4, PD-1 and PD-L1 compounds
  - Approved in the U.S. (#9,107,887); filed in multiple other global jurisdictions
  - Jointly owned with Pfizer Inc.

PV-10: Oncology Meets Immunology – References

Author	Affiliation	Title	Venue & Year	Indication	Pre-/Clinical
Thompson et al.	Clinical trial investigators, Provectus	Chemoablation of metastatic melanoma using intralesional Rose Bengal [Phase 1 study]	Melanoma Research (Mel Res) 2008	Melanoma	Clinical
Agarwala et al.	Clinical trial investigators, Provectus	Chemoablation of Melanoma with Intralesional Rose Bengal (PV-10)	American Society of Clinical Oncology (ASCO) 2009	Melanoma	Clinical
Toomey et al.	Moffitt Cancer Center	Intralesional Injection of Melanoma with Rose Bengal Induces Regression of Untreated Synchronous Melanoma In a Murine Model	Society of Surgical Oncology (SSO) 2012	Melanoma	Pre-clinical
Dees et al.	Provectus	Generation of an Antitumor Response and Immunity Using a Small Molecule Drug (PV-10)	Society for Immunotherapy of Cancer (SITC) 2012	HCC, Melanoma, Pancreatic cancer, Colon cancer	Pre-clinical
Wachter et al.	Provectus	Combination of PV-10 Immuno-chemoablation and Systemic anti-CTLA-4 Antibody Therapy in Murine Models of Melanoma	American Association for Cancer Research (AACR) 2013	Melanoma	Pre-clinical
Toomey et al.	Moffitt Cancer Center	Intralesional Injection of Rose Bengal Induces a Systemic Tumor-Specific Immune Response in Murine Models of Melanoma and Breast Cancer	PLoS ONE (PLoS1) 2013	Melanoma, Breast Cancer	Pre-clinical

References /2

Author	Affiliation	Title	Venue & Year	Indication	Pre-/Clinical
Liu et al.	Moffitt Cancer Center	Induction of anti-melanoma immunity after intralesional ablative therapy	AACR 2014	Melanoma	Pre-clinical
Sarnaik et al.	Moffitt Cancer Center	Assessment of immune and clinical efficacy after intralesional PV-10 in injected and uninjected metastatic melanoma lesions	ASCO 2014	Melanoma	Clinical
Pilon-Thomas et al.	Moffitt Cancer Center	Efficacy of Intralesional Injection with PV-10 in Combination with Co-Inhibitory Blockade in a Murine Model of Melanoma	SITC 2014	Melanoma	Pre-clinical
Pardiwala et al.	University of Illinois at Chicago	Intralesional Injection of Rose Bengal Induces an Anti-tumor Immune Response and Potent Tumor Regressions in a Murine Model of Colon Cancer	SSO 2015	Colon cancer	Pre-clinical
Goldfarb et al.	Clinical trial investigators, Provectus	"Phase 1 Study of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver"	ESMO World GI 2015	HCC, Liver mets	Clinical
Thompson et al.	Clinical trial investigators, Provectus	Phase 2 Study of Intralesional PV-10 in Refractory Metastatic Melanoma	Ann Surg Oncol 2015	Melanoma	Clinical

References /3

Author	Affiliation	Title	Venue & Year	Indication	Pre-/Clinical
Liu et al.	Moffitt Cancer Center	Intralesional Rose Bengal in Melanoma Elicits Tumor Immunity via High Mobility Group Box 1	SITC 2015	Melanoma	Clinical
Liu et al.	Moffitt Cancer Center	T cell Mediated Immunity After Combination Therapy with Intralesional PV-10 and Co-Inhibitory Blockade in a Melanoma Model	AACR 2016	Melanoma	Pre-clinical
Liu et al.	Moffitt Cancer Center	Intralesional Rose Bengal in Melanoma Elicits Tumor Immunity Via Activation of Dendritic Cells by the Release of High Mobility Group Box 1	Oncotarget 2016	Melanoma	Pre-clinical, Clinical