

Current Clinical Trials with PV-10 (Rose Bengal)

The First Small Molecule Oncolytic Immunotherapy

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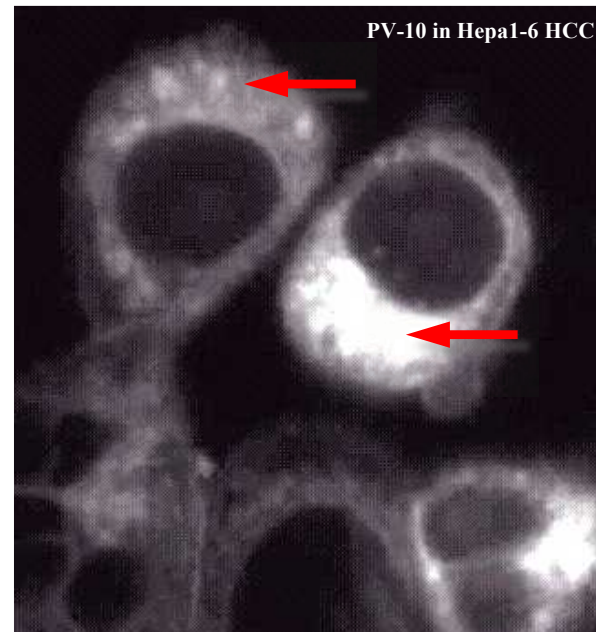
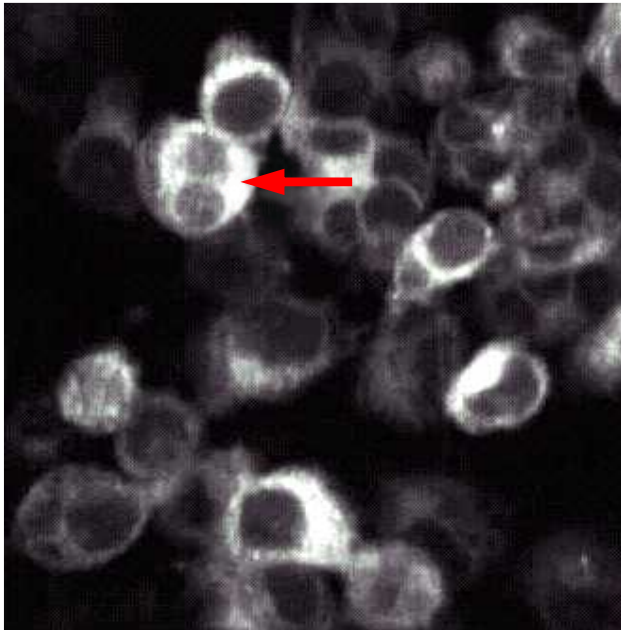
Oncolytic Immunotherapy with PV-10

- ❑ **PV-10 is an injectable formulation of rose bengal disodium (10% RB)**
 - 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®
 - Currently used as a food dye: FR-105 (Japan)
 - **Established safety history**
 - Not metabolized
 - Short circulatory half-life (ca 30 min)
 - Excreted via bile
 - **Stable at room temperature**
 - **Intralesional injection** can yield immunogenic cell death (ICD) resulting in tumor-specific reactivity in circulating CD8+ T cells



Lysosomal Targeting

- ❑ **PV-10 accumulation in lysosomes of cancer cells**
 - Lysosomal disruption yields Immunogenic Cell Death (ICD)



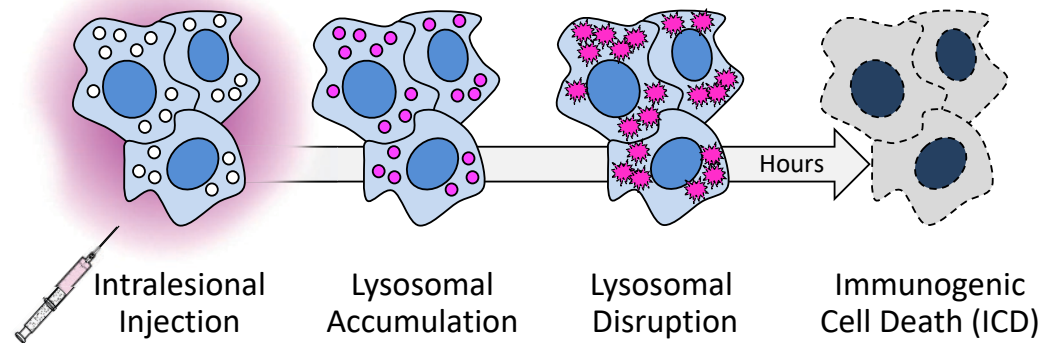
Wachter et al., *SPIE Proceedings* 2002; 4620: 143-147

Wachter et al., *SPIE Proceedings* 2002; 4622: 112-118

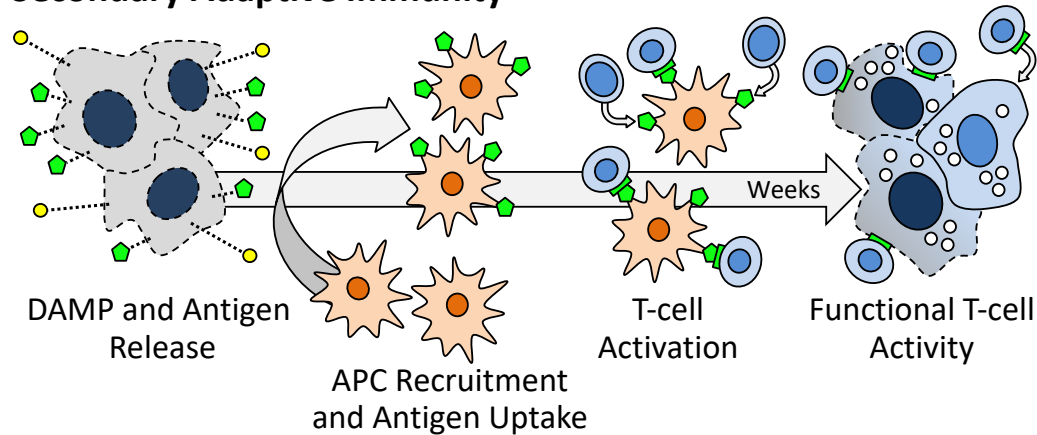
Mousavi, Zhang, Gillespie, Wachter and Hersey, *Mel. Res.* 2006; 16 (supl. 1): S8

Oncolytic Immunotherapy with PV-10

Primary Oncolysis



Secondary Adaptive Immunity



Wachter et al., SPIE 4620, 143, 2002 (lysosomal accumulation and rupture in tissue culture)

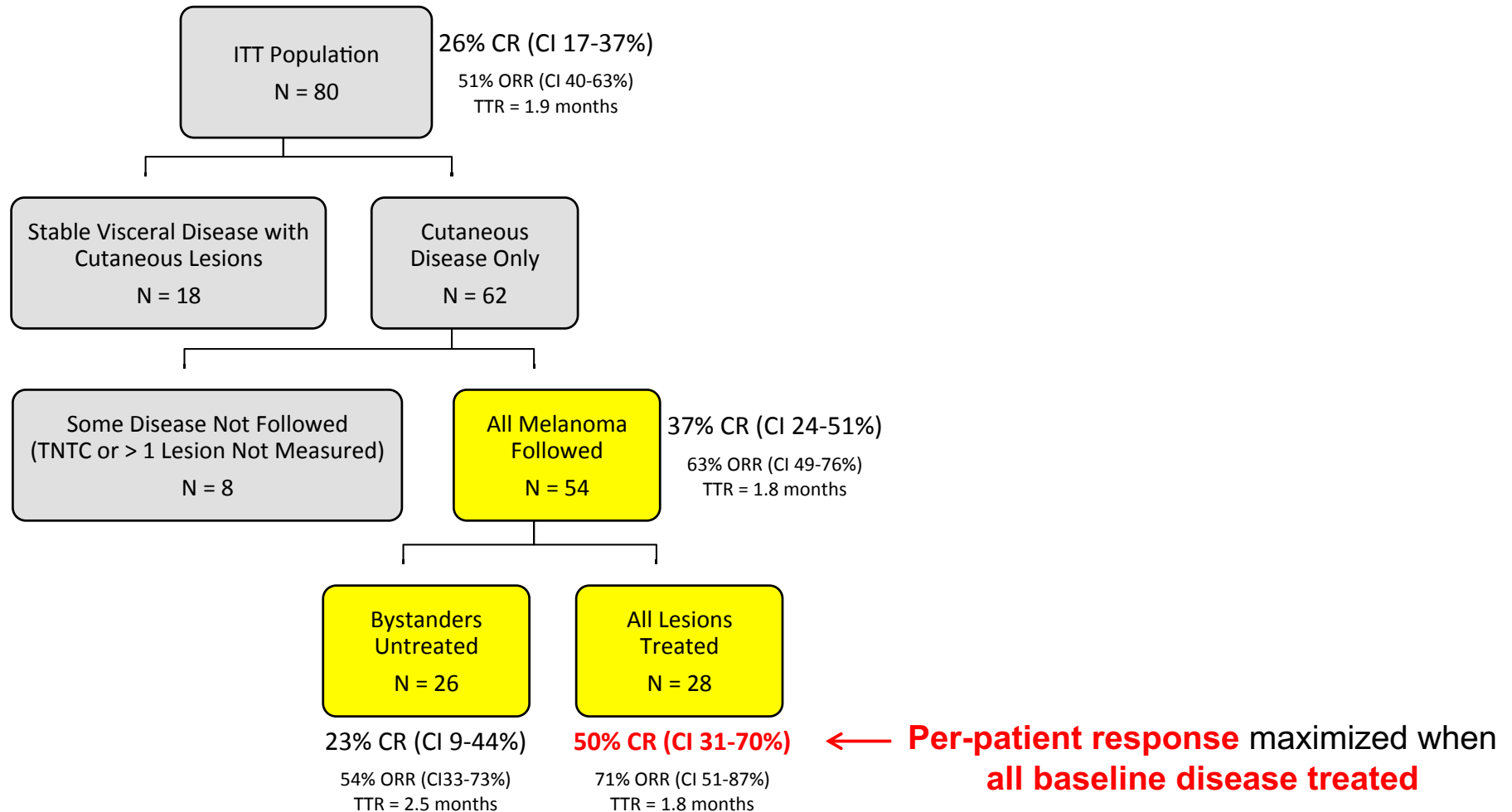
Thompson et al., Mel Res 18, 405, 2008 (ablation of injected tumors and bystander regression in recurrent patients)

Toomey et al., PLoS One 8, e68561, 2013 (tumor-specific immune response in mice)

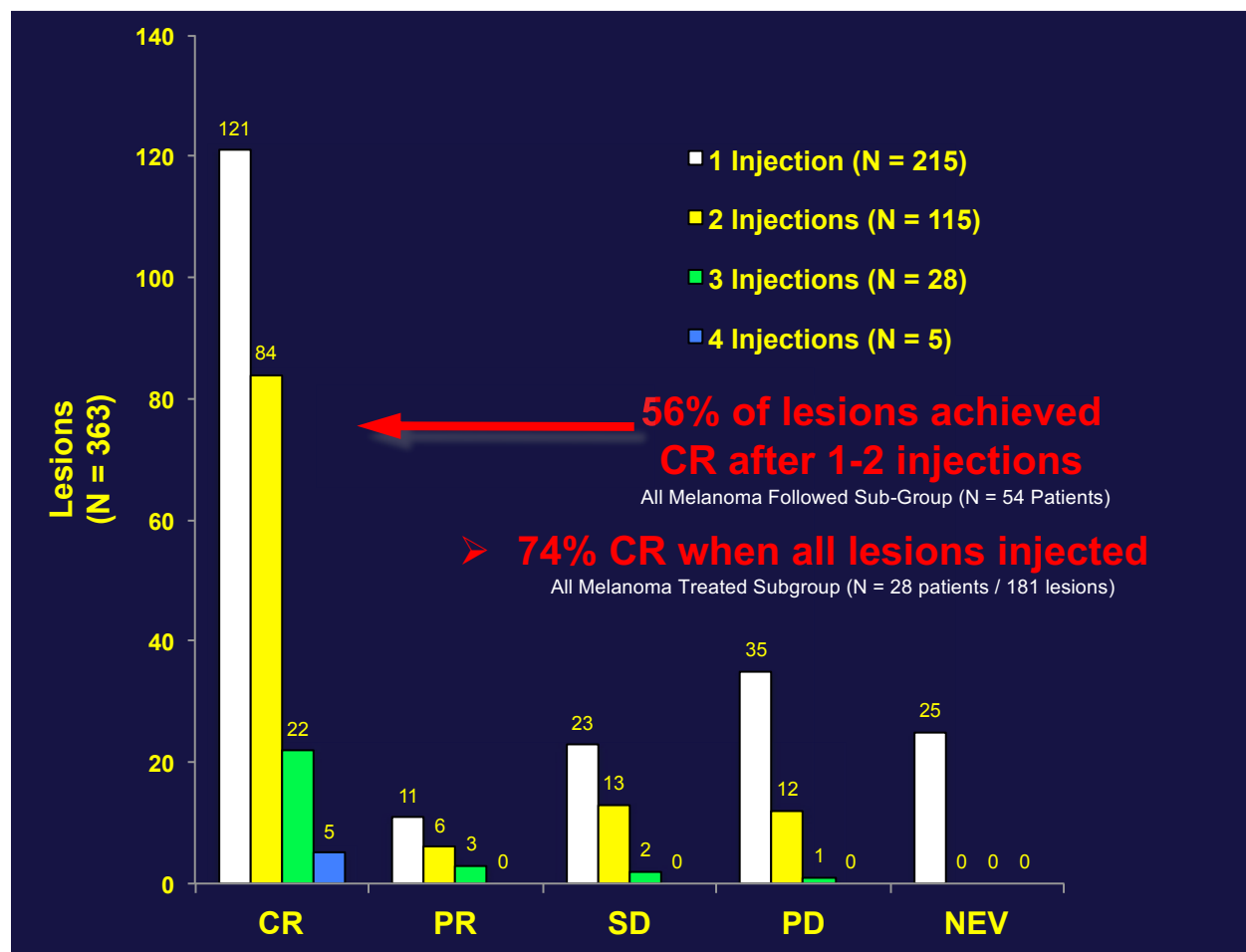
Liu et al., Oncotarget 7, 37893, 2016 (DAMPs, DC recruitment/activation, T-cell activation in mouse and man)

Qin et al., Cell Death and Disease 8, e2584, 2017 (immunogenic cell death in colon cancer)

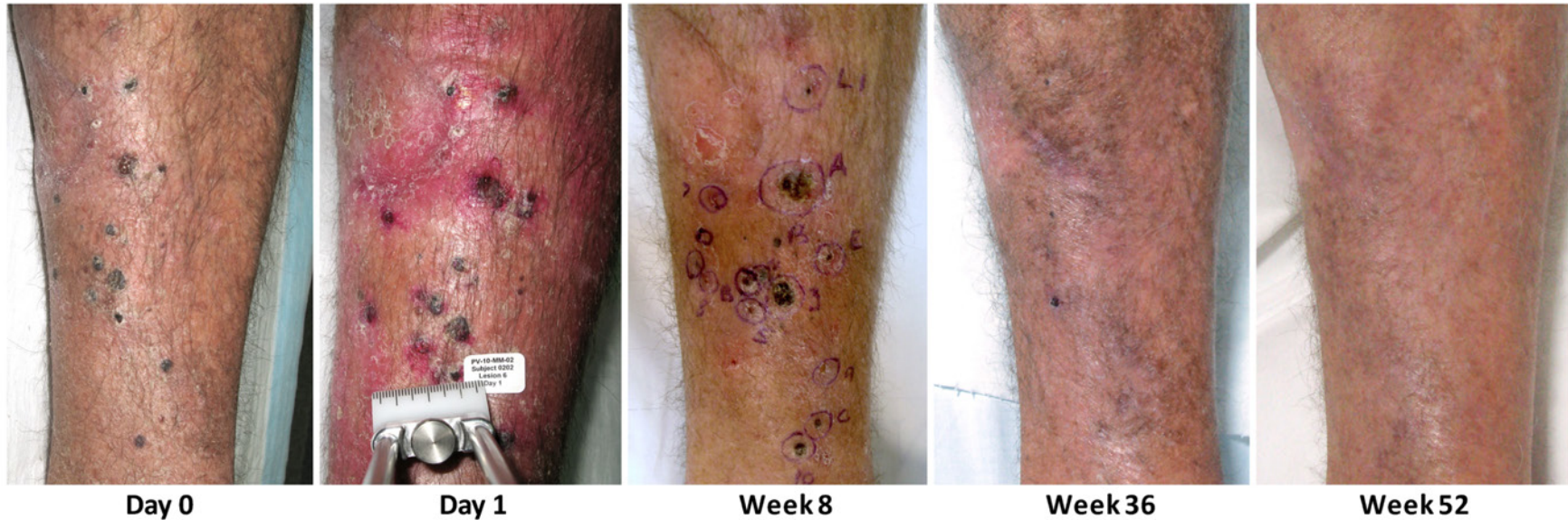
Phase 2: Subgroups by Baseline Disease Burden



Response of Injected Lesions

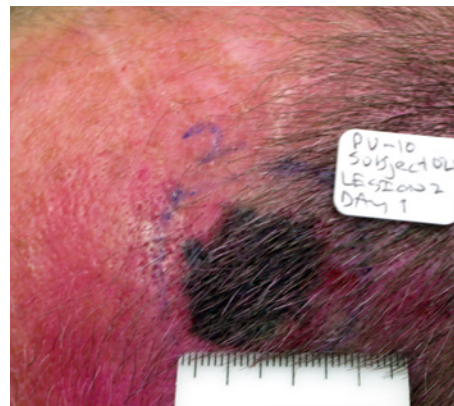
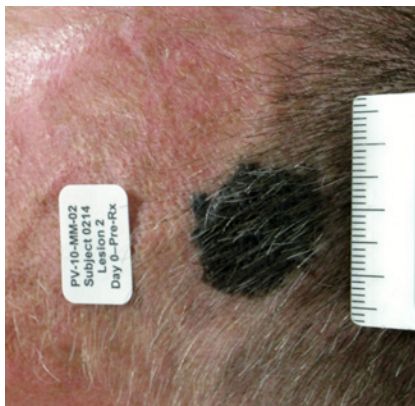


Clinical Examples



Male age 73, Stage IIIB 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.

Clinical Examples



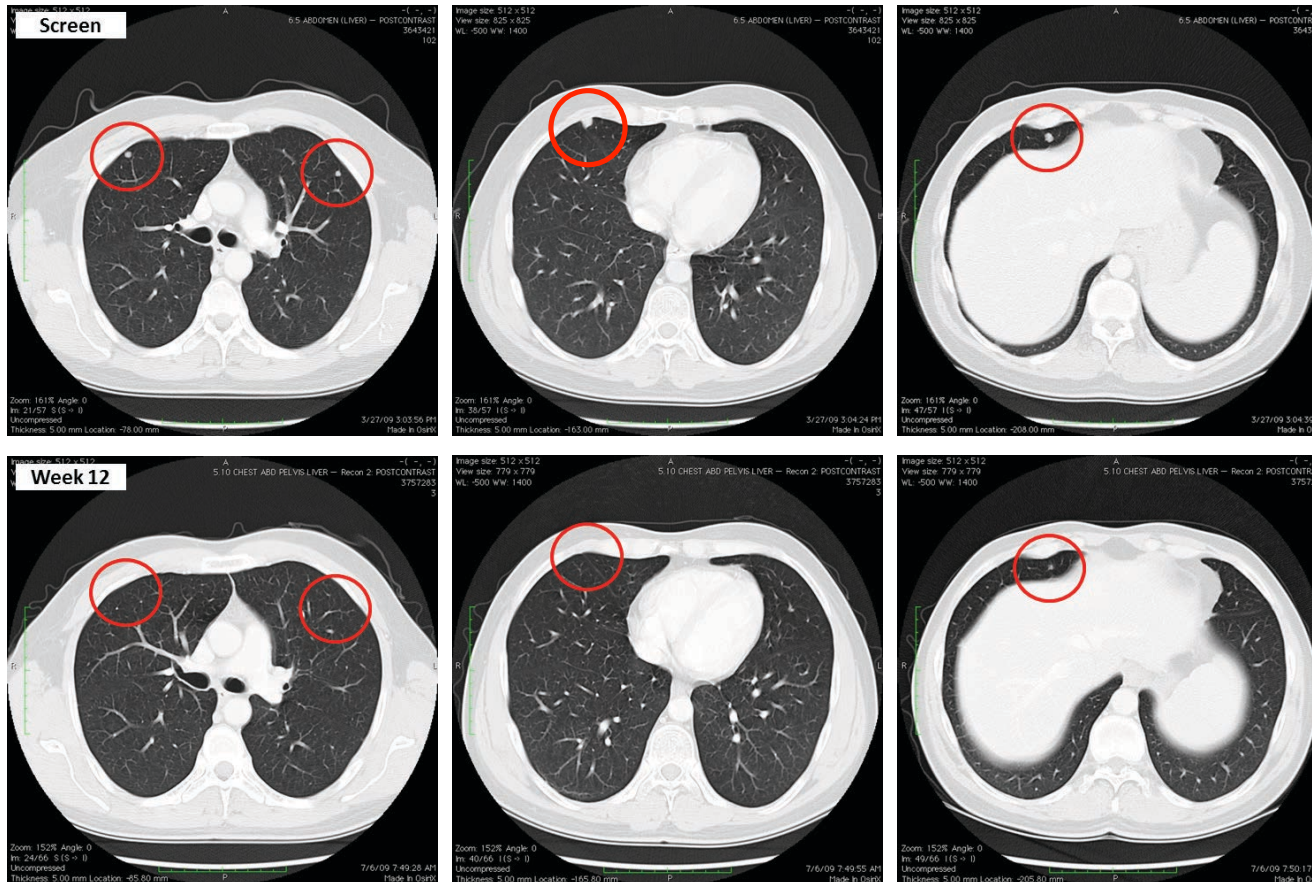
Day 0 – Pre-Rx

Day 1

Week 36

Male age 57, Stage IIIB melanoma recurrent after 3 interventions. Six lesions injected with PV-10 on Day 0, 3 lesions injected at Week 8 and 3 injected at Week 16. CR at Week 24 with NED at Week 52.

Distant Tumor 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)

Locoregional Adverse Events

System Organ Class ^a Preferred Term ^a	Adverse Events ^{b,c} (ITT Population, N = 80)				
	CTCAE Grade			Total	%
	1	2	3		
General Disorders and Administration Site Conditions					
Injection Site Pain	29	25	10	64	80%
Injection Site Edema	19	14	0	33	41%
Injection Site Vesicles	17	13	1	31	39%
Injection Site Discoloration ^d	13	12	0	25	31%
Injection Site Swelling	14	7	1	22	28%
Injection Site Pruritus	14	3	0	17	21%
Injection Site Erythema	6	4	1	11	14%
Injection Site Infection	3	2	1	6	8%
Peripheral Edema	3	0	1	4	5%
Injection Site Cellulitis	0	2	1	3	4%
Injection Site Necrosis	0	0	1	1	1%
Gastrointestinal Disorders					
Dysphagia	0	0	1	1	1%
Nervous System Disorders					
Headache	11	2	0	13	16%
Skin and Subcutaneous Tissue Disorders					
Photosensitivity Reaction	0	0	1	1	1%

^a System Organ Class and Preferred Term are based on the MedDRA[®] version 13.0 terminology dictionary. Locoregional adverse events were coded to "injection site" Preferred Terms to differentiate these from systemic events.

^b 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.

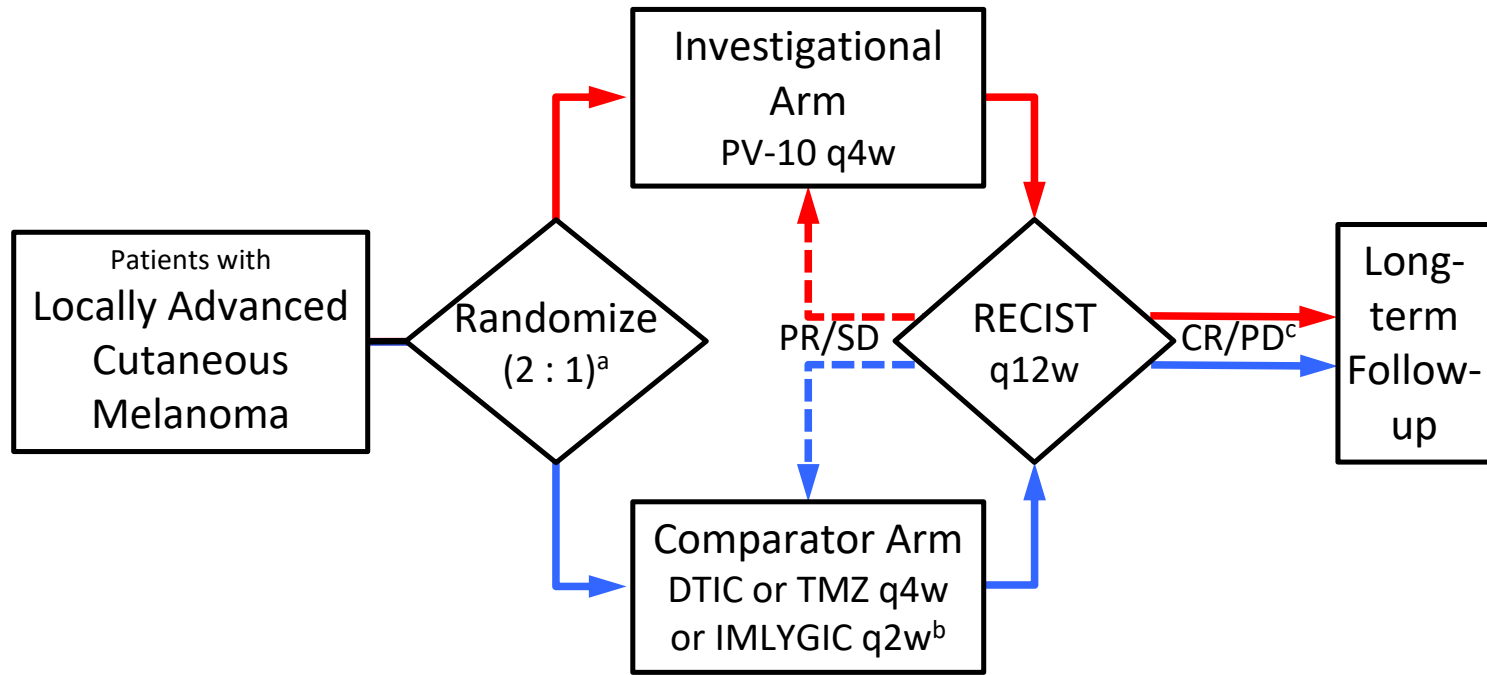
^c If a patient experienced an AE more than once during the study the greatest severity is presented.

^d Discoloration locoregional to injected lesions.

Phase 3 Design

- **PV-10-MM-31: International Pivotal RCT**
 - 225 patients with locally advanced cutaneous melanoma
 - Stage IIIB - IVM1a
 - Randomized 2 : 1 to PV-10 or comparator
 - Investigator's choice of Imlygic or DTIC / TMZ
 - RECIST 1.1 by Independent Review Committee (IRC)
 - Primary: PFS
 - Secondary: Complete Response Rate, Duration of Complete Response
 - Exploratory: QoL, Investigator-Assessed Lesion Symptoms
 - Competent Authority (CA) approval in USA, AUS, Germany, Italy, France, Mexico and Argentina

Phase 3 Schematic



- a. 225 patients randomized 2:1 (stratified for prior immune checkpoint inhibition)
- b. IMLYGIC repeated after 3 weeks then q2w
- c. Cross-over allowed upon documented PD in comparator arm

Phase 1b / 2 Combination Study

- **Protocol PV-10-MM-1201**
- **Phase 1b**
 - Safety of PV-10 + pembrolizumab in up to 24 subjects with unresectable metastatic melanoma (i.e., Stage IV) having at least 1 injectable cutaneous melanoma lesion and who are candidates for pembrolizumab.
 - PV-10 administered by intralesional injection to all injectable cutaneous and subcutaneous lesions (up to 5 cycles); pembrolizumab administered by intravenous infusion (up to 24 mo).
 - Preliminary efficacy (best objective response rate and progression free survival at week 16 based on RECIST 1.1; and overall survival).
 - Phase 1 accrual completed May 2018 (24 subjects in ITT population).
- **Phase 2**
 - Expanded phase 2 RCT of PV-10 + pembrolizumab vs. pembrolizumab alone (i.e., PV-10 + Standard of Care vs. Standard of Care).
 - PFS, ORR and OS key endpoints.

Phase 1b / 2 Combination Study

Subject Characteristics

(Safety Population, N = 12)

ID / Age / Gender	Stage	Number of CUT/SQ Lesions	Location(s) of Target Lesions	Site(s) of Non-Target Lesions
0101 / 81 / M	M1c	3	SQ (x2), Axillary LN	Liver, Lung
0102 / 47 / M	M1b	4	Scalp	Lung
0104 / 79 / M	M1b	3	LLE	Bilateral Lung
0105 / 69 / M	M1c	4	RUE	Bone, Liver, Lung
0106 / 78 / M	M1a	1	RLE (x2)	In-transit or satellite with nodal mets (N3)
0202 / 52 / M	M1a	1	Chest Wall	Chest Wall, Axillary LN
0203 / 76 / M	M1b	2	RLE (x2)	Lower Extremity and Lung
0204 / 28 / M	M1a	40	Jaw, LUE	Scalp, Face, Neck, Torso, Upper Extremity, LN (x20)
0205 / 50 / F	M1a	3	Chest Wall	Back
0206 / 73 / M	M1b	1	RUE	Lung
0401 / 70 / M	M1c	1	Lung, Shoulder	Liver, Lung
0402 / 79 / M	M1c	2	Axilla, Flank	Liver

**Patients had extensive
uninjected tumor burden**

Preliminary Safety Results

Treatment-Emergent Adverse Events (TEAEs) Occurring in >1 Subject, or Any Grade 3 or Higher (Safety Population, N = 12)	All TEAEs		TEAEs Related to PV-10		TEAEs Related to Pembrolizumab	
	All	≥ G3	All	≥ G3	All	≥ G3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Injection site pain	7	0	7	0	0	0
Fatigue	4	0	0	0	3	0
Injection site discolouration	3	0	3	0	0	0
Chest pain	2	0	0	0	0	0
Injection site discharge	2	0	2	0	0	0
Injection site haemorrhage	2	0	2	0	0	0
Injection site photosensitivity reaction	2	0	2	0	0	0
Oedema peripheral	2	0	2	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Rash	2	0	0	0	2	0
Rash maculo-papular	2	0	0	0	2	0
ENDOCRINE DISORDERS						
Hypothyroidism	2	0	0	0	2	0
GASTROINTESTINAL DISORDERS						
Diarrhoea	3	0	0	0	2	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
Arthralgia	3	0	0	0	2	0
METABOLISM AND NUTRITION DISORDERS						
Hyperglycaemia	1	1	0	0	1	1 ^a
NERVOUS SYSTEM DISORDERS						
Myasthenia gravis	1	1	0	0	1	1 ^a

**PV-10 AEs
Equivalent to
Single-Agent**

**Pembro AEs
Non-overlapping**

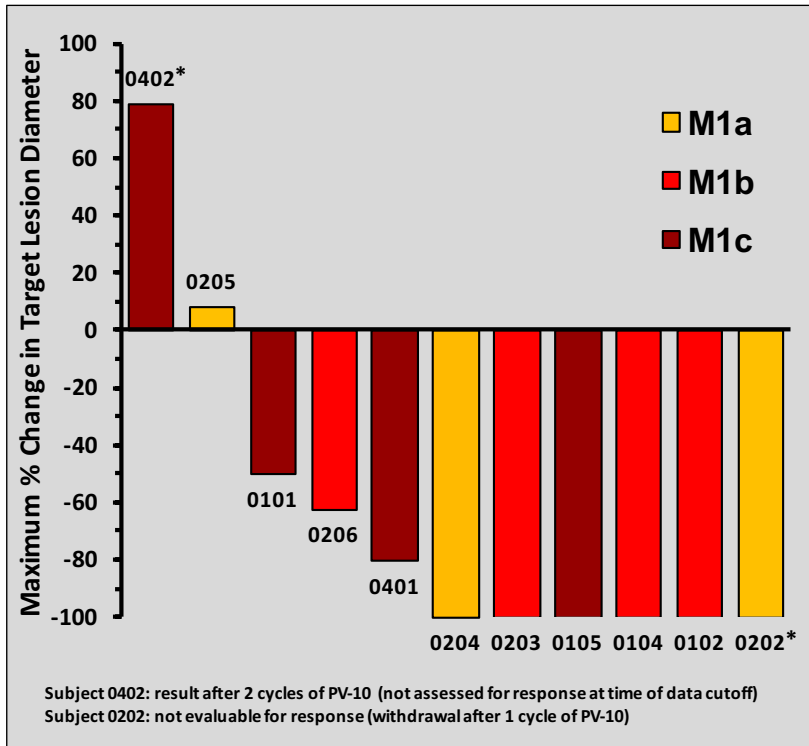
AEs coded using MedDRA v19.0 for system organ class (SOC) and preferred term (PT).

Subjects with more than one occurrence of the same AE are counted once based on maximum severity.

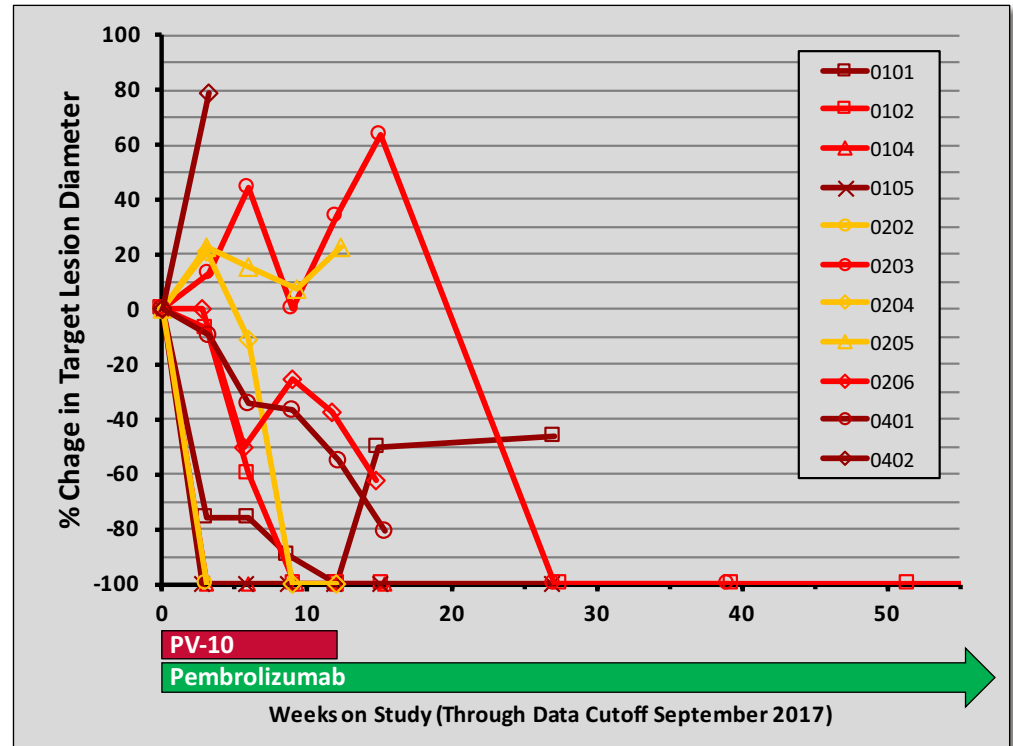
Single occurrences of decreased appetite (Grade 1) and fatigue (Grade 1) were deemed possibly related to the combination.

^aSingle occurrences of hyperglycemia (Grade 3) and exacerbation of myasthenia gravis (Grade 5) were deemed possibly related and certain related to pembrolizumab, respectively.

Preliminary Efficacy Results



- Most subjects had robust response in their Target Lesions
- These included injected cutaneous / subcutaneous lesions and non-injected nodal / visceral lesions



- Response of Target Lesions coincided with combination regimen
- Subjects received a median of 5 cycles of PV-10 (mean 3.8, range 1 – 5)

Patients had rapid, deep response

Beyond Melanoma: Hepatic Tumors

❑ Percutaneous PV-10 to Hepatic Tumors

- Protocol PV-10-LC-01
 - “Basket study” design allows assessment in HCC and metastatic tumors
- PV-10-NET-01
 - Symptomatic gastrointestinal neuroendocrine tumors (GI-NET) metastatic to liver



**PV-10 is radiopaque,
facilitating delivery and follow-up**

Beyond Melanoma: Hepatic Tumors

❑ Protocol PV-10-LC-01 (Phase 1): Initial 18 Subjects

- “Basket study” design allows assessment in HCC and metastatic tumors
 - Currently enrolling cutaneous and uveal melanoma patients
- Single intralesional injection into center of a single study lesion
 - Percutaneous delivery
 - CT or U/S guided
- Follow-up
 - 23 hour admission for initial safety observation
 - Primary follow-up at 28 days to 3 months
 - Extended follow-up every 3 months beginning at Month 6
- Observe treated lesion and any untreated lesions
 - Outcome scored using RECIST (amended to 2D EASL)

Beyond Melanoma: Hepatic Tumors

□ 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)

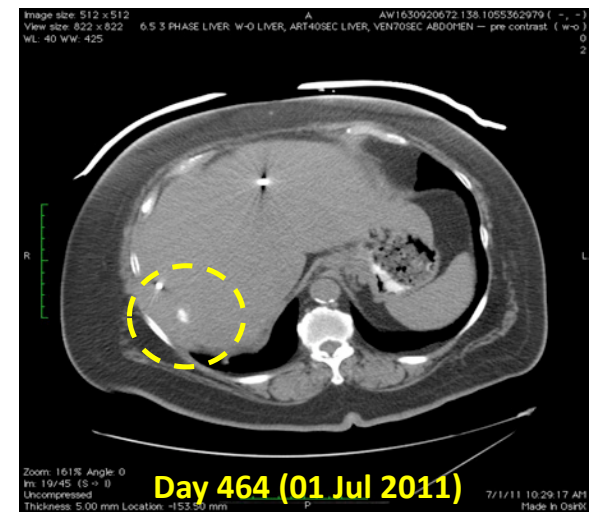
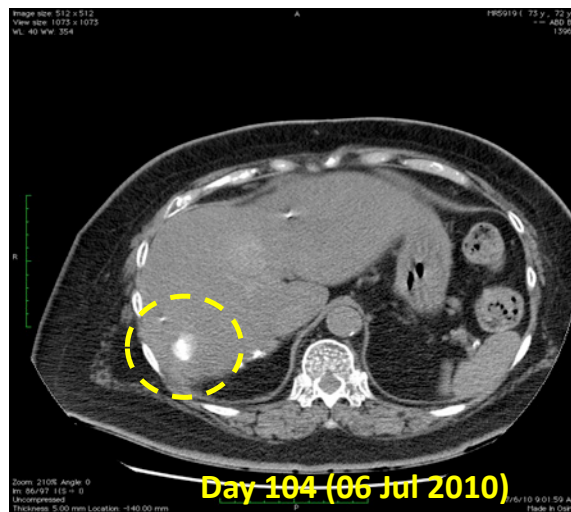
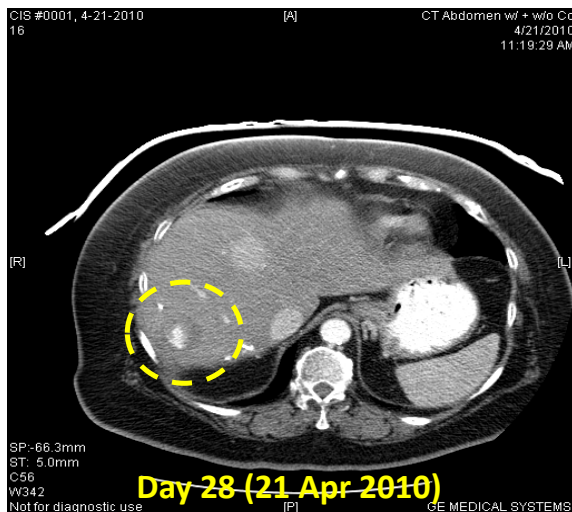
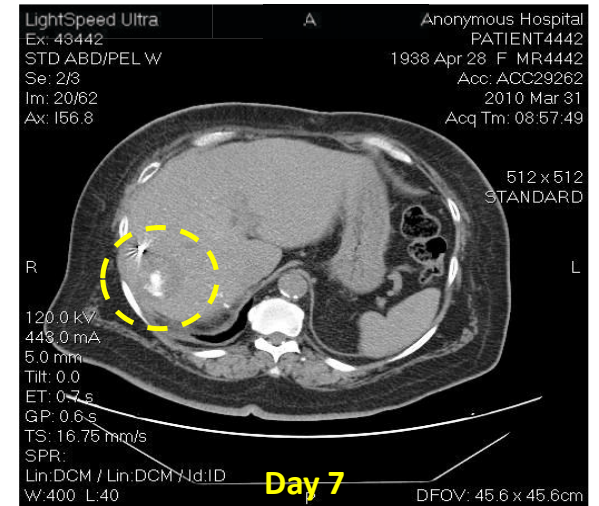
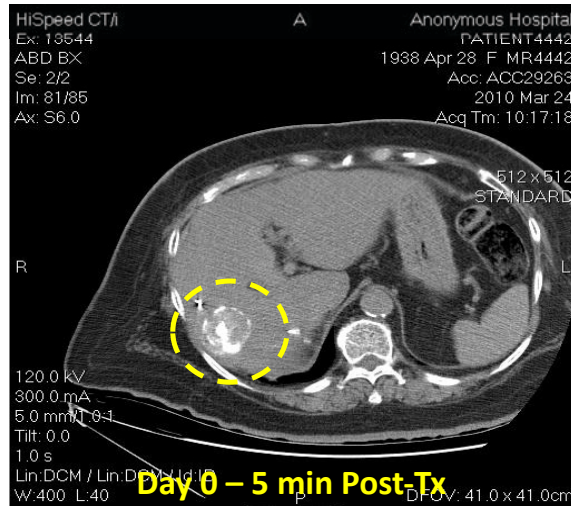
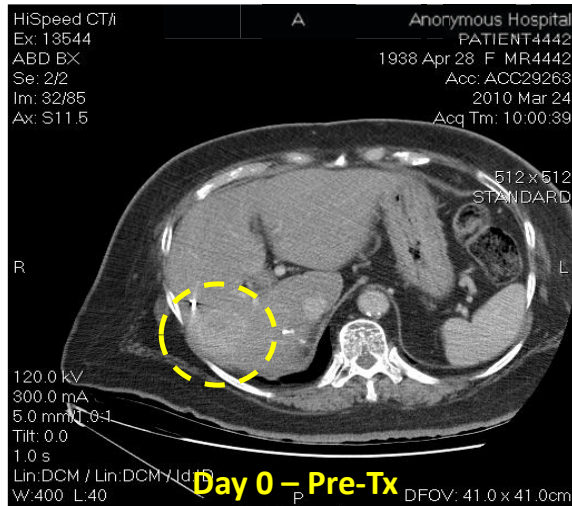
Subject	Disease and History	Survival Status
0005 M 68	HCC (3 tu + Chest Wall and Adrenal Mets, HBV and Cirrhosis)	Alive (NED, 75 mon) ^a
0001 F 71	HCC (3 tu, Lobectomy, RFA) ^b	Alive (with Disease, 58 mon, lost to follow-up)
0004 F 73	HCC (4 tu, HCV, Cirrhosis, Portal Hypertension, RFA, TACE)	Expired (DP, 48 mon)
0008 F 66	HCC (3 tu, HCV, Cirrhosis, Portal Hypertension, TACE)	Expired (DP, 12 mon)
0007 M 67	HCC (1 tu Penetrating Diaphragm)	Expired (Cardiac Comorbidity, 2 mon)
0101 F 89	HCC (1 tu 8.9 cm)	Expired (SAE, suspected thromboembolism)
0006 M 61	mCRC (3 tu + Extensive Abdominal Mets, FOLFOX, Avastin, Erbitux)	Alive (NED, 73 mon)
0204 F 67	mCRC (2 tu, RFA, FOLFOX, Liver Resections)	Alive (24 mon)
0009 M 85	mCRC (Numerous Metabolically Active Hepatic tu)	Alive (18 mon) ^c
0010 F 53	mCRC (3 tu, FOLFOX, Avastin, Irinotecan, Partial Hepatectomy)	Alive (9 mon)
0206 F 67	mCRC (≥ 6 tu, FOLFOX, FOLFIRI, ZALTRAP, Regorafenib)	Expired (DP, 3 mon)
0203 M 69	Lung (≥ 4 tu, Nivo, SNX-5422 and Carbo/Paclitaxel)	Expired (DP, 12 mon)
0202 M 83	Lung (≥ 6 tu, Carbo/Abraxane)	Expired (DP, 4 mon)
0205 M 83	Pancreatic (2 tu)	Alive (12 mon)
0102 F 53	Melanoma (≥ 4 tu + Lung Mets, Hepatitis, Biochemo, Nivo + Ipi) ^b	Expired (DP, 18 mon)
0201 F 51	Ovarian (≥ 35 tu, Carbo/Paclitaxel)	Expired (DP, 15 mon)

^a commenced sorafenib 11 months after PV-10 for residual adrenal and chest wall nodules (continued for 28 months until NED)

^b 2 lesions injected with PV-10 (requiring re-enrollment under separate subject number)

^c commenced Avastin, 5-FU and Fusilev two months after PV-10

PV-10-LC-01 – Subject 0001/0003 (HCC #1) – CT



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

Beyond Melanoma: Hepatic mNETs

❑ Protocol PV-10-NET-01 (Phase 1)

- Patients with Symptomatic Neuroendocrine Tumors (mNET) metastatic to liver
- Study design similar to PV-10-LC-01 protocol
- Assessment of multiple dimensions of response
 - Objective Response of Injected and Bystander Tumors
 - Ga-DOTATA PET/CT
 - Change in Tumor Biomarkers (CgA and LFT)
 - Change in Tumor Symptoms (QoL and Symptom Log)
- Single intralesional injection into center of study lesion
 - Percutaneous delivery
 - CT or U/S guided
 - Repeat injection of additional tumors allowed after 6 weeks
 - Cohort 1: single lesion injected / treatment
 - Cohort 2: 1-3 lesions injected / treatment

Beyond Melanoma: Hepatic mNETs

SUV max 37.5 (Injected Tumor)

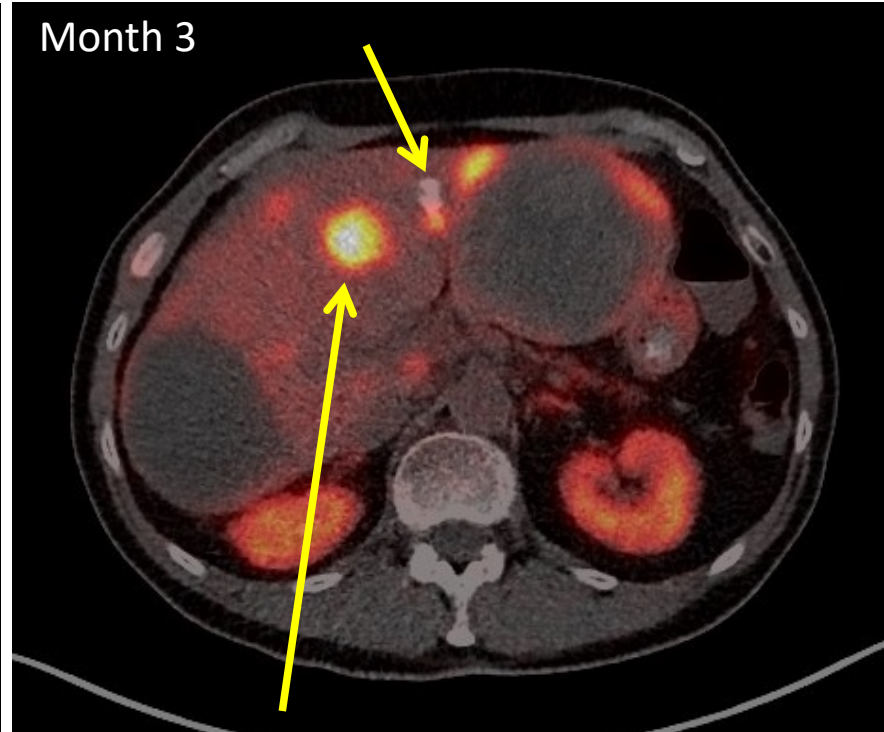
Baseline



SUV max 34.5 (Non-injected Tumor)

SUV max 16.7

Month 3



SUV max 31.2

Planned Studies for Metastatic Disease

❑ Continue Basket and NET Studies

- Open Additional Centers
 - All-comers to expand numbers for important tumor types
 - Focused enrollment of high-priority tumor types (e.g., uveal melanoma, CRC)
 - Expand NET program within AUS and to USA and/or EU

❑ Leverage LC-01 and MM-1201 Protocols

- Combination therapy for demonstrated combinations
 - PV-10 + Gemcitabine for pancreatic adenocarcinoma ¹
 - PV-10 + PD-1 ²
 - PV-10 + PD-L1 ²
 - Path to relevance for lagging class of checkpoint inhibitor

¹ Pilon-Thomas et al., SITC 2016. ² Liu et al., PLoS ONE 2018.

Conclusions

- PV-10 is a non-viral oncolytic immunotherapy with activity in multiple tumor types
- PV-10 shows robust responses as a monotherapy in a large melanoma phase II trial
- Randomized Phase III international trial underway
- Combination data with PV-10 and anti-PD1 (pembrolizumab) appears promising
- Non-melanoma data is intriguing and warrants further investigation