

Chemoablation of Metastatic Melanoma with PV-10

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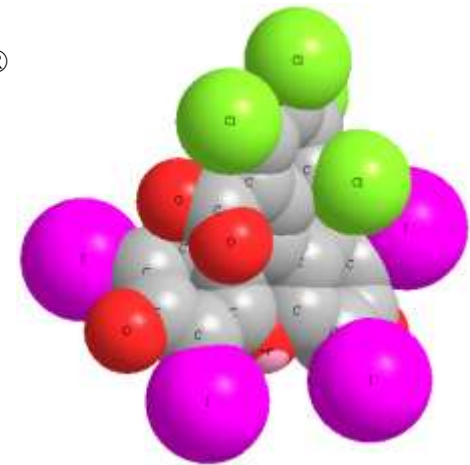
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7th EADO Congress
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Chemoablation with Intralesional PV-10

- *PV-10 is a sterile, non-pyrogenic solution of Rose Bengal disodium (10% RB) for intralesional 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[®]
 - Topical ophthalmic diagnostic: Rosettes[®] and Minims[®]
 - Established Safety History
 - Not metabolized
 - Short circulatory half-life (ca 30 min)
 - Excretion via bile

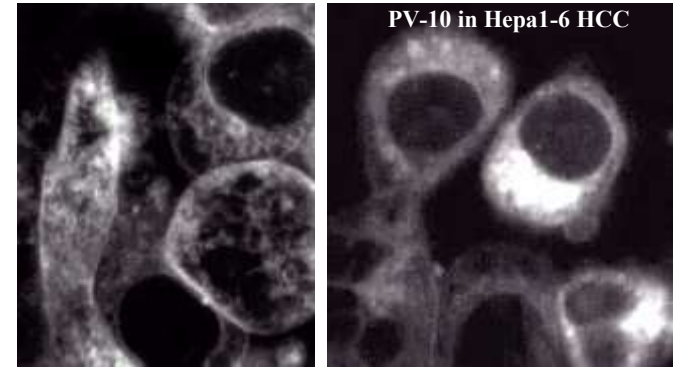


Rose Bengal Disodium (RB)

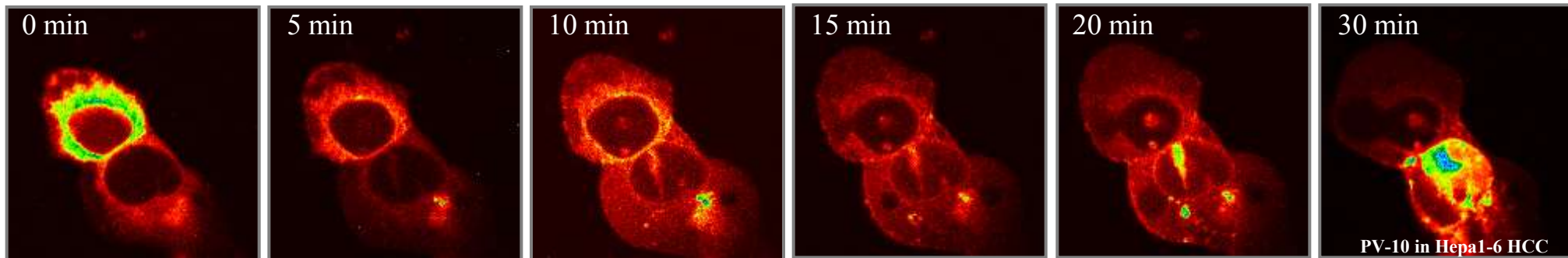
Chemoablative Mechanism of Action

□ *PV-10 transits plasmalemma of cancer cells*

- Accumulates in lysosomes of cancer cells
- Excluded from normal cells



Wachter et al., *SPIE Proceedings* 2002; 4622: 112–118
Mousavi, Zhang, Gillespie, Wachter and Hersey, *Mel. Res.* 2006; 16 (supl. 1): S8



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

□ *PV-10 accumulation elicits acute autophagy of cancer cells*

- Accumulation in lysosomal membrane triggers lysosomal release
- Complete autophagy within 30-60 min
- Identical response in cell cultures of Hepa1-6 HCC, HTB-133 human breast carcinoma and H96Ar human multidrug resistant small cell lung carcinoma

Chemoablation can Elicit Bystander Effect

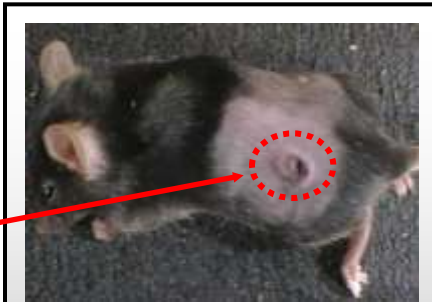
□ *IL PV-10 elicits acute necrosis of treated tumor*

- Rapid necrosis of injected tumors and reduced tumor burden
- RB does not denature tumor antigens
- Acute exposure to antigenic tumor fragments to APCs
- Localized treatment does not compromise immune system

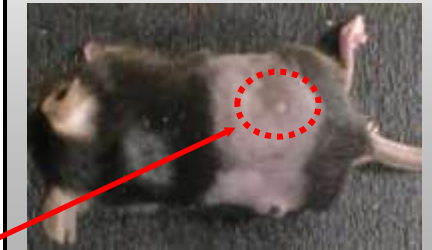
□ *Acute necrosis can trigger immunological response*

- Secondary tumors are rejected in immunocompetent animals
- No immune response in immune-compromised animals
- Response is tumor-specific
 - Secondary HCC rejected when primary HCC ablated
 - Melanomas not rejected when primary HCC ablated
- Adoptive transfer of spleen cells can convey immunity

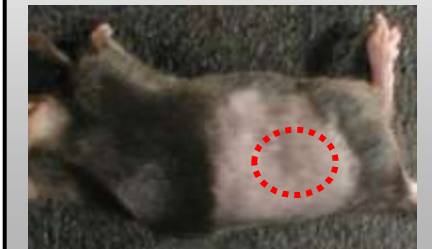
Treated
HCC



Untreated
HCC



• Day 4 Post-Treatment



• Day 10 Post-Treatment

C57BL/6 Immunocompetent Mouse

Phase 1 Clinical Testing

- ❑ *20 subjects with AJCC Stage III/IV melanoma at 2 centers in AUS*
 - John F Thompson, Sydney Melanoma Unit
 - Peter Hersey, Newcastle Melanoma Unit

- ❑ *Single intralesional injection into each study lesion*
 - Intralesional dosing of 1-20 lesions at 50% of calculated lesion volume
 - 1–3 additional lesions untreated to assess bystander response
 - 12–24 weeks observation
 - ORR assessed by modified RECIST

Phase 1 Clinical Testing

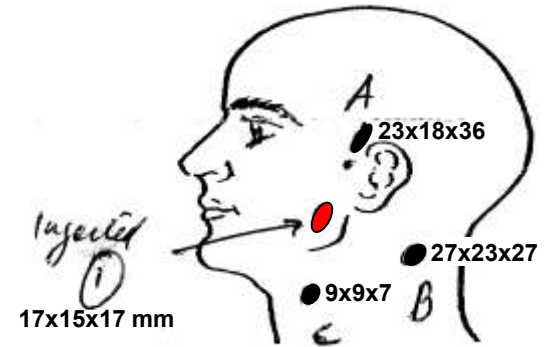
□ *Adverse Experiences*

- AEs generally mild to moderate grade (predominantly locoregional)
- Pain at injection site most common AE (reported by 75% of subjects)
- 1 instance each of Grade 3 pain and Grade 3 photosensitivity reaction
- No grade 4 or 5 AEs
- All AEs recovered without sequelae

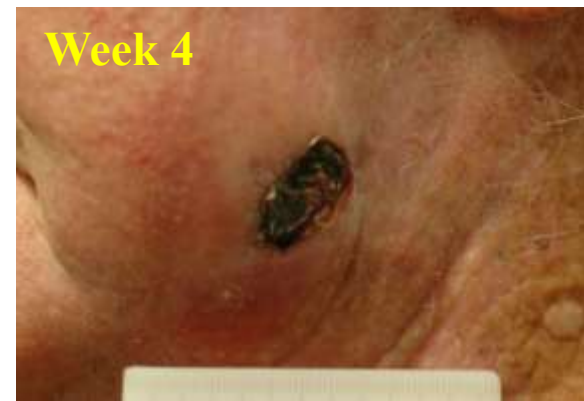
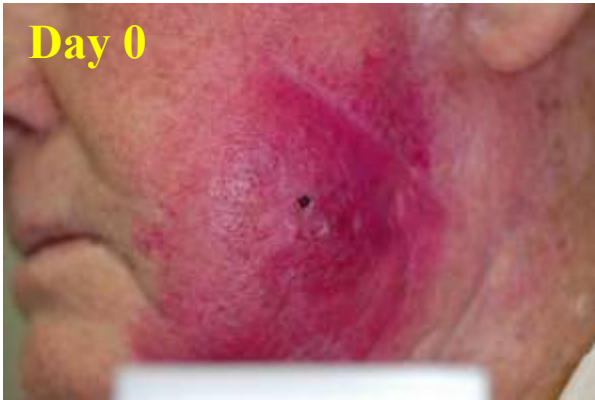
□ *Efficacy*

- Injected lesions: ORR = 40% (locoregional disease control in 75% of subjects)
- Bystander lesions: ORR = 15% (locoregional disease control 55% of subjects)

Male, age 86, Stage IIIC, onset 33 months prior.
Total parotidectomy, nodal dissection, multiple Sx of mets.
Single treatment with 1.2 mL PV-10 to 1 lesion;
3 untreated bystander lesions. NED @ 28 months.



Lesion 1: 1.2 mL PV-10; Lesions A, B and C Not Injected



Phase 2 Clinical Testing

□ *80 subjects with AJCC Stage III/IV melanoma*

- Open label, single-arm trial at 7 centers in AUS and USA
 - Sanjiv Agarwala, St Luke's Hospital and Health Network
 - Brendon Coventry, Royal Adelaide Hospital
 - David Minor, California Pacific Medical Center
 - Merrick Ross, MD Anderson Cancer Center
 - Charles Scoggins, University of Louisville
 - Mark Smithers, Princess Alexandra Hospital
 - John F Thompson, Melanoma Institute Australia
- Enrollment commenced Aug 2007, completed May 2009
- Final follow-up completed May 2010

Phase 2 – Protocol

- ❑ ***Treatment of 1-10 Target Lesions and up to 10 Non-Target Lesions***
 - Target Lesions must be ≥ 0.2 cm diameter
 - Biopsy confirmation of at least one Target Lesion
 - Intralesional dosing at 50% of calculated lesion volume

- ❑ ***Observe up to 1-2 untreated Bystander Lesions***
 - Typically small or difficult to access
 - Biopsy confirmation of each Bystander Lesion

- ❑ ***Retreatment (new or partially-responsive lesions)***
 - Allowed at weeks 8, 12 or 16 as necessary

Phase 2 – Protocol and Data Analysis

□ *Outcome Assessment*

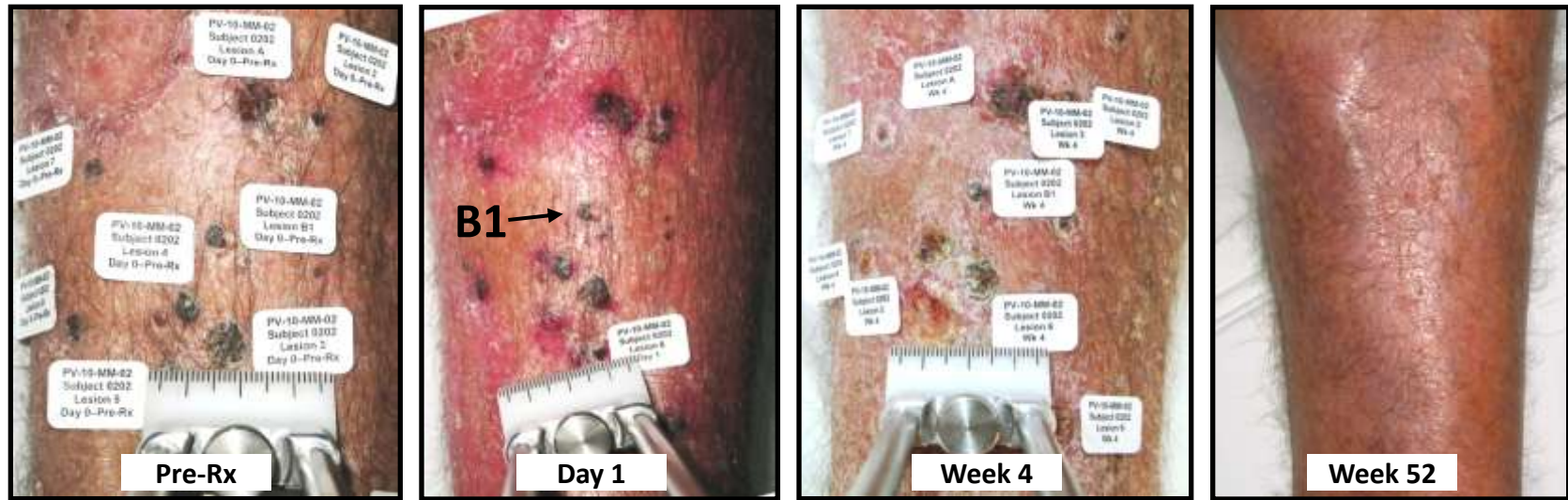
- Follow-up for 52 weeks
- Modified RECIST assessed on Target, Non-Target and Bystander Lesions
- Progression Free Survival
- Duration of Response (for CR + PR subjects)
- Overall Survival

□ *Preliminary Safety and Efficacy Data*

- Monitoring of all case report forms complete
- Final data validation underway
- Preliminary data available for full study cohort (N = 80 subjects)
- Subjects withdrawing prior to Week 8 assigned PD outcome

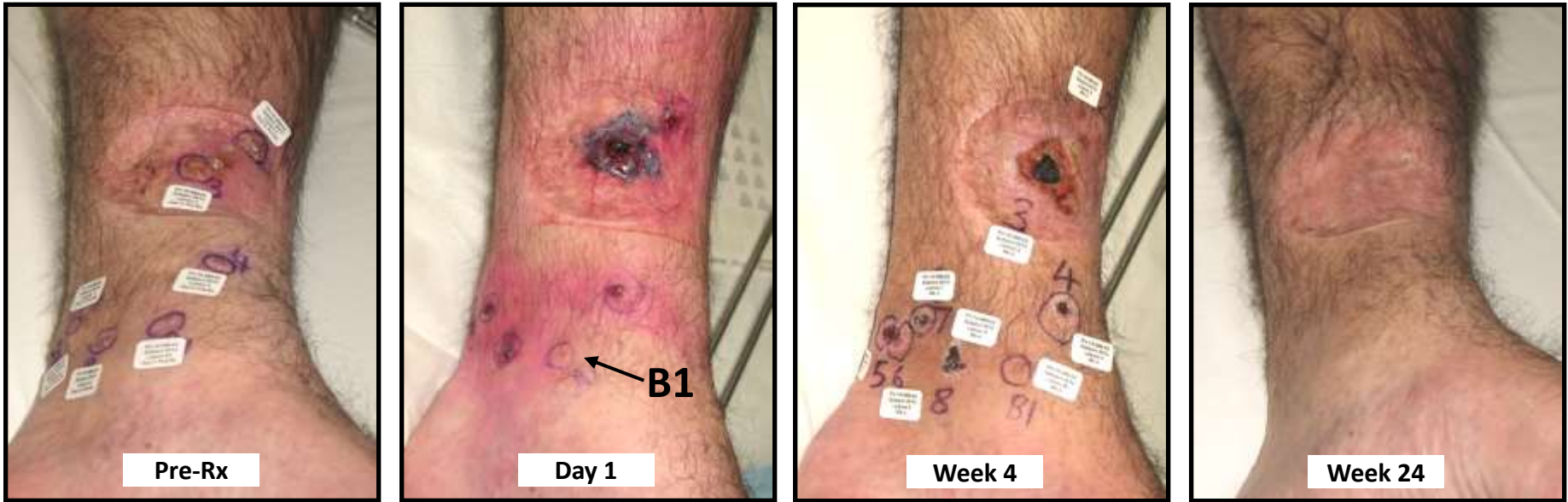
Phase 2 – Demographics & Treatment Summary

| | |
|---|------------------------|
| • Median Age (Range): | 70.0 yrs (33 – 97) |
| • Gender: | 49 M / 31 F |
| • Race / Ethnicity (White): | 40 (100%) |
| • AJCC Stage: | III (N=53) / IV (N=27) |
| • PV-10 Injections | 1142 |
| • Treatments per Subject, Median (Range): | 2 (1 – 4) |
| | 1 Course: 35 Subjects |
| | 2 Courses: 26 Subjects |
| | 3 Courses: 16 Subjects |
| | 4 Courses: 3 Subjects |
| • Dose PV-10 per Treatment, Median (Range): | 1.6 mL (0.1 – 15) |
| • Cumulative Dose, Median (Range): | 3.4 mL (0.3 – 26.0) |



Male, 73, Stage IIIB (N2c) since 2008, Sx of 1⁰ and mets.

Three treatments (Day 0, Wk 8 and Wk 16) with PV-10 to 11 lesions; 1 untreated bystander lesion.



**Male, 48, Stage IIIB (N2c) since 2008, Sx of 1^o and mets.
Single treatment with 1.3 mL PV-10 to 10 lesions; 1 untreated bystander lesion (B1).**



**Male, 79, Stage IV (M1b) since 2004, multiple Sx, CLND, 30 Gy XRT.
Three treatments (Day 0, Wk 10 and Wk 19) with PV-10 to 15 lesions; 2 untreated bystander lesions.**

Adverse Events At Least Possibly Related to PV-10 Administration

Protocol PV-10-MM-02 – 52 Weeks Follow-up, All Subjects (N=80)

Events occurring in less than two subjects and with severity < 3 not shown

| System Organ Class Preferred Term | Adverse Events (by CTCAE Grade) | | | | | | |
|---|---------------------------------|----|---|---|---|-------|-----|
| | 1 | 2 | 3 | 4 | 5 | Total | % |
| Gastrointestinal disorders | | | | | | | |
| Nausea | 3 | 2 | 0 | 0 | 0 | 6 | 8% |
| Diarrhoea | 5 | 0 | 0 | 0 | 0 | 5 | 6% |
| Dysphagia | 0 | 1 | 1 | 0 | 0 | 2 | 2% |
| General disorders and administration site conditions | | | | | | | |
| Injection site pain | 29 | 30 | 7 | 0 | 0 | 66 | 82% |
| Injection site oedema | 22 | 13 | 0 | 0 | 0 | 35 | 44% |
| Injection site vesicles | 17 | 12 | 1 | 0 | 0 | 30 | 38% |
| Injection site discolouration | 13 | 12 | 0 | 0 | 0 | 25 | 31% |
| Injection site swelling | 14 | 7 | 1 | 0 | 0 | 22 | 28% |
| Injection site pruritus | 14 | 3 | 0 | 0 | 0 | 17 | 21% |
| Injection site erythema | 6 | 5 | 1 | 0 | 0 | 12 | 15% |
| Injection site inflammation | 0 | 7 | 0 | 0 | 0 | 7 | 9% |
| Injection site photosensitivity reaction | 3 | 3 | 0 | 0 | 0 | 6 | 8% |
| Injection site ulcer | 4 | 1 | 0 | 0 | 0 | 5 | 6% |
| Injection site infection | 4 | 1 | 0 | 0 | 0 | 5 | 6% |
| Injection site cellulitis | 1 | 1 | 2 | 0 | 0 | 4 | 5% |
| Injection site warmth | 2 | 2 | 0 | 0 | 0 | 4 | 5% |
| Injection site rash | 4 | 0 | 0 | 0 | 0 | 4 | 5% |
| Wound secretion | 1 | 1 | 0 | 0 | 0 | 2 | 2% |
| Oedema peripheral | 0 | 0 | 2 | 0 | 0 | 2 | 2% |
| Localised oedema | 0 | 0 | 1 | 0 | 0 | 1 | 1% |
| Palliative care | 0 | 0 | 1 | 0 | 0 | 1 | 1% |
| Nervous system disorders | | | | | | | |
| Headache | 11 | 2 | 0 | 0 | 0 | 13 | 16% |

- Adverse events predominantly locoregional and mild to moderate
- No grade 4 or 5 events

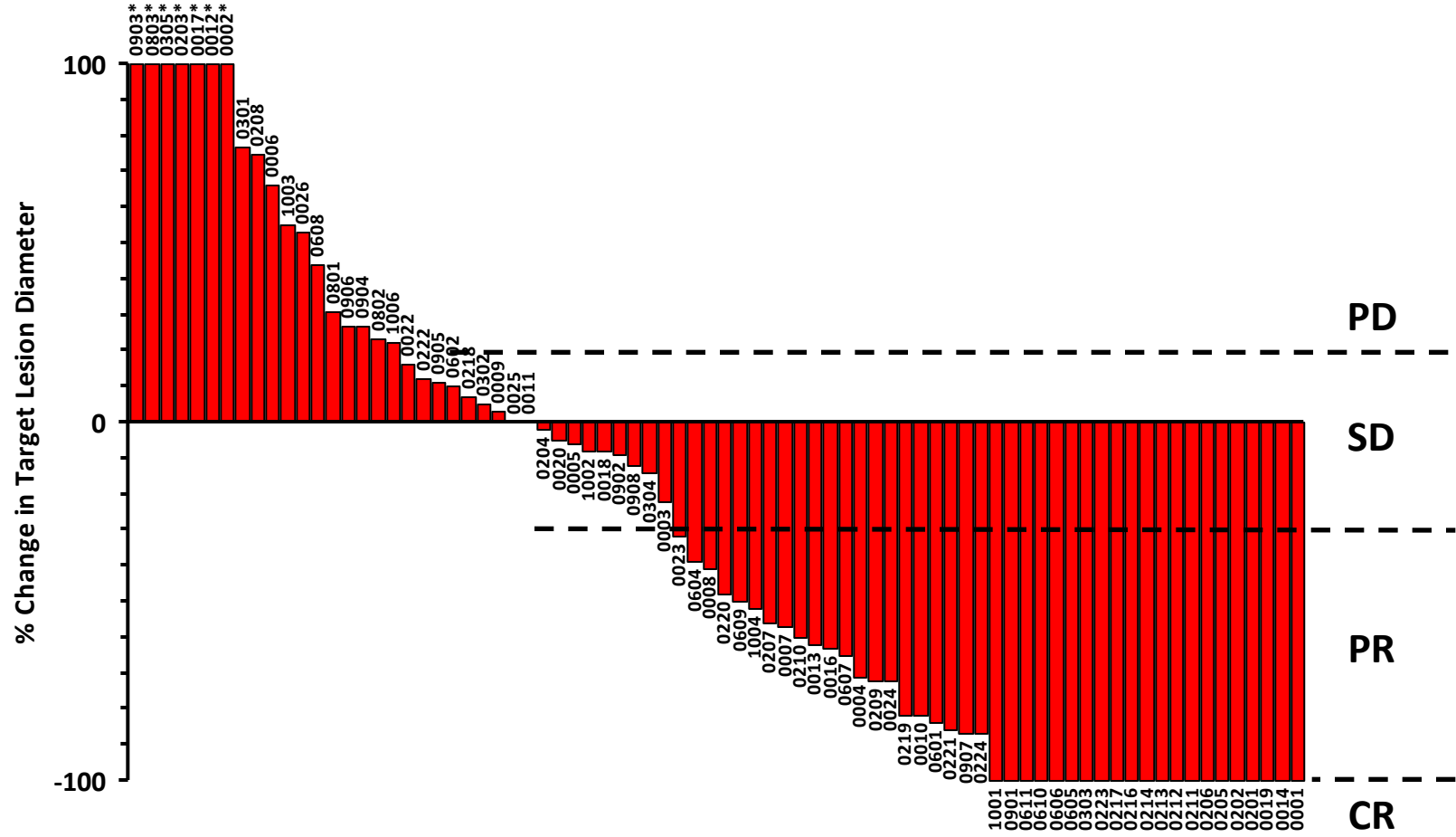
Phase 2 – Preliminary Efficacy

Objective Response of Study Lesions

All Subjects (N=80)

| Best Response (RECIST, N = 80 Subjects through Week 52) | Target Lesions | | Bystander Lesions | |
|--|----------------|-----|-------------------|-----|
| | N | | N | |
| N (Subjects) | 80 | | 38 | |
| CR | 19 | 24% | 9 | 24% |
| PR | 20 | 25% | 5 | 13% |
| SD | 18 | 22% | 7 | 18% |
| PD | 23 | 29% | 17 | 45% |
| ND | -- | -- | 42 | |
| | | | | |
| CR + PR | 39 | 49% | 14 | 37% |
| CR + PR + SD (<i>Locoregional Disease Control</i>) | 57 | 71% | 21 | 55% |

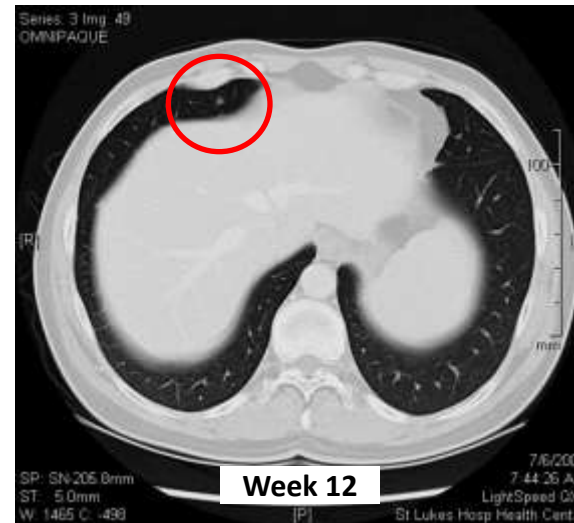
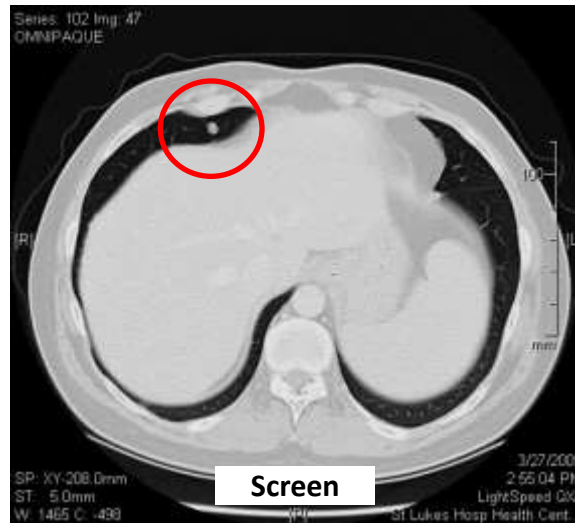
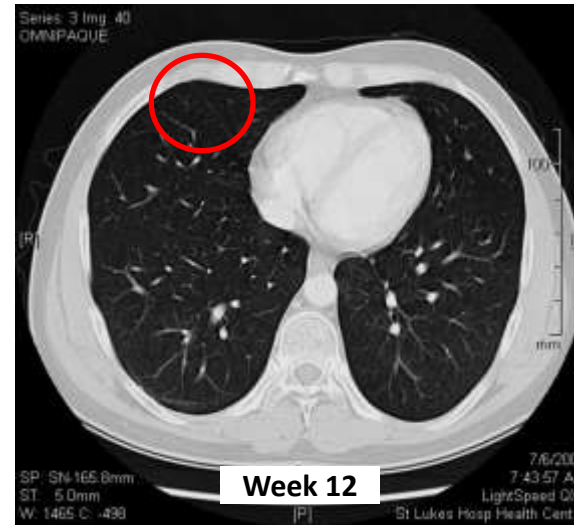
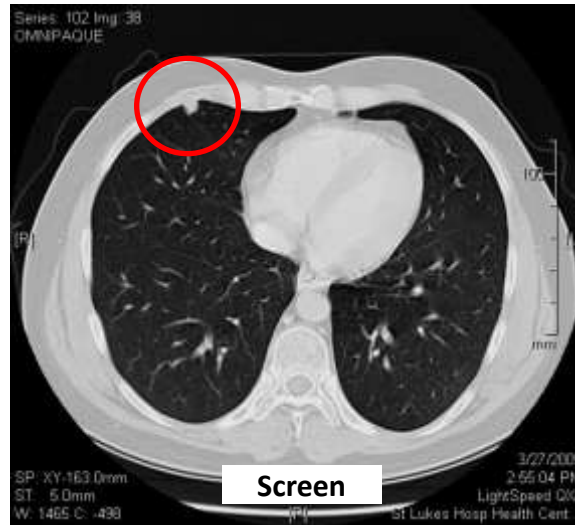
Phase 2 – Preliminary Efficacy



Subject 0907: Male, 40, Stage IV (M1c) since 2006

Multiple Sx, CLND, whole brain XRT, stereotactic radiosurgery, DTIC, IV- and SQ-IFN.

Three treatments (Day 0, Wk 8 and Wk 12) with PV-10 to 10 cutaneous lesions: PR of injected lesions.



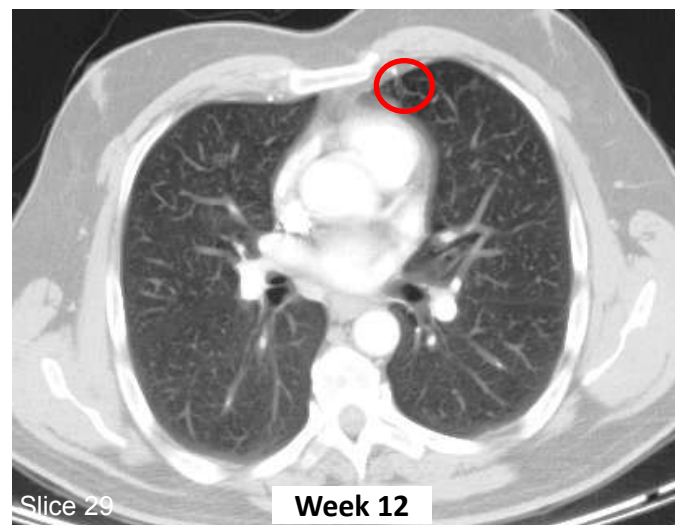
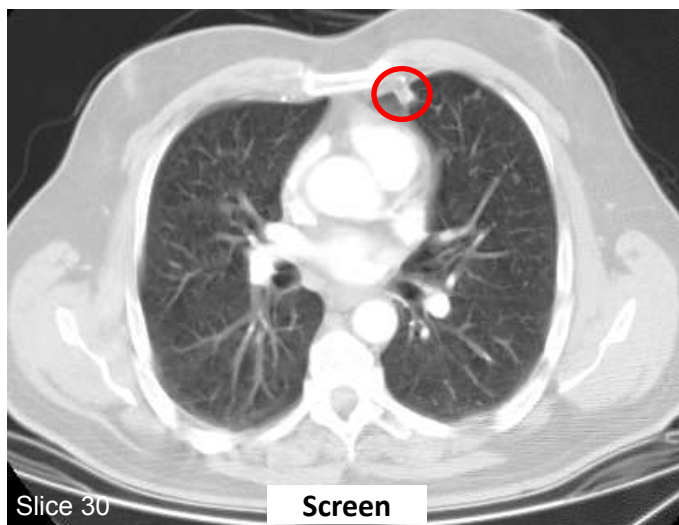
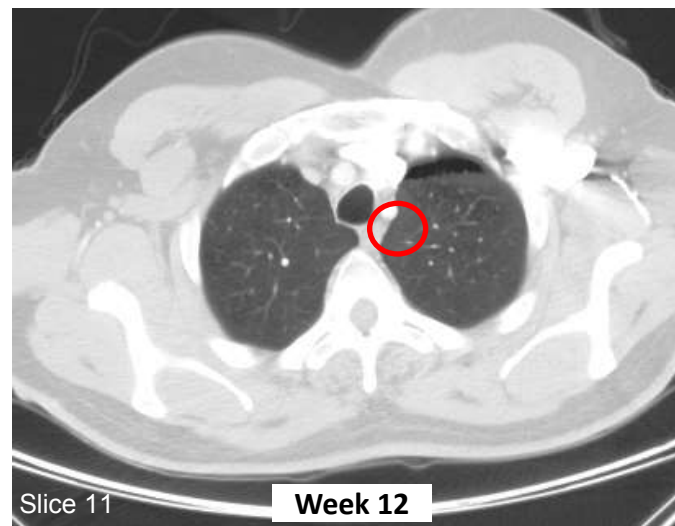
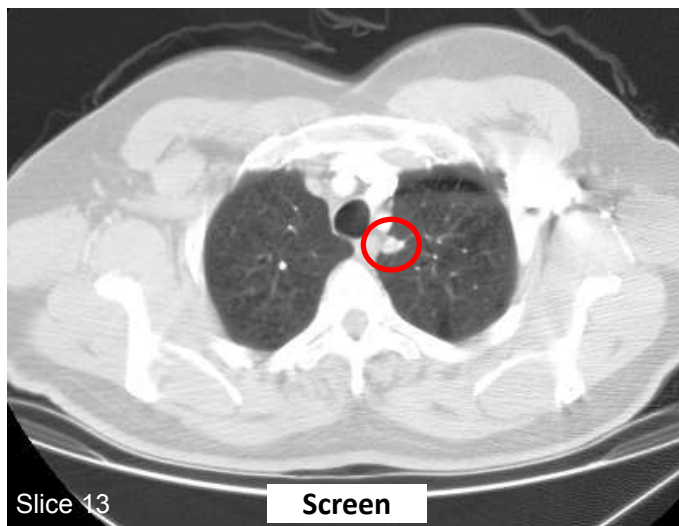
Interval progression of widespread 6–9 mm pulmonary mets at screening.

“Near complete resolution” of pulmonary nodules observed at Wk 12.

Subject 0216: Male, 57, Stage IV (M1b) since 2002

Primary left lower extremity. Multiple Sx, limb XRT, ILI.

Two treatments (Day 0 and Wk 16) with PV-10 to 5 cutaneous lesions in calf: CR at Wk 52.



Multiple bilateral pulmonary mets at screening.

Generalized improvement of pulmonary mets at Wk 12 with "no focal parenchymal pathology" at Wk 52.

Leveraging Phase 2 – Expanded Access Protocols

□ *PV-10-MM-02X*

- Continuation protocol available to Phase 2 subjects
 - Evidence of response to PV-10
 - Disease not completely controlled under phase 2 design
 - Allows multiple treatments NLT 28 days apart
 - 10 subjects have crossed over from phase 2 study
 - Dose regimen similar to anticipated phase 3 RCT

□ *PV-10-EA-02*

- Expanded access for solid cutaneous or subcutaneous tumors
 - Trial program at existing Phase 2 centers
 - AUS: Sydney, Brisbane, Adelaide
 - USA: Bethlehem, Houston, Louisville
 - Dose regimen identical to PV-10-MM-02X protocol
 - 45 subjects have been enrolled
 - 44 melanoma + 1 rSCC
 - Enrollment continuing, anticipate approximately 50 participants

Additional Phase 2 Studies

□ *PV-10+XRT-01*

- Follow-up to observations reported by Foote et al., Mel. Res. 2009
 - Unexpectedly robust response to XRT in refractive lesions 6-12 weeks after PV-10 treatment
- Single center investigator-initiated study of PV-10 chemoablation followed by XRT
- Single intralesional PV-10 dosing
 - If CR not achieved 6 fractions x 5 Gy at 6-10 weeks post-PV-10
- Up to 25 subjects
- Enrollment commenced 1Q-2011

□ *Mechanism of Action*

- Phase 2B study to fully validate bystander effect
 - Response in untreated proximal and visceral lesions consistent with immunologic process
 - PV-10 chemoablation yields immediate reduction in tumor burden
 - Ablation appears to recruit immune cells to exposed tumor antigens
- Assess immune markers in peripheral blood and tumor tissue
- Commence 2H-2011

Planned Phase III Trial

□ *Phase 3 Randomized Controlled Trial (RCT)*

- Incorporate guidance from FDA and TGA meetings for pivotal trial under SPA
- PV-10 vs DTIC / TMZ / Paclitaxel
- Approximately 300 subjects
 - Stage IIIB to IV (M1a) based on phase 2 response data
- Treatment of all injectable lesions to maximize response rate and long-term outcome
- PFS as primary endpoint
- Study duration ca. 30 months
- Commence enrollment late 2011

- Investigators needed in AUS, USA, EU, ROW

Conclusions

PV-10 is well tolerated, eliciting a robust response in a majority of patients

- The safety and efficacy profile compare favorably with existing and emerging therapies
- Suitable for repeat treatment to maximize OR, ablate new lesions and enhance long-term outcome
- Non-responsive patients are quickly evident, avoiding delay in transition to alternate therapy
- Treatment of all injectable lesions likely to improve response rate and long-term outcome

Locoregional treatment may yield systemic benefit via the bystander effect

- PV-10 offers potential locoregional control of metastatic disease
- Bystander effect in untreated cutaneous lesions correlates closely with response of injected lesions
- Stasis or regression of visceral lesions evident in several subjects (“remote bystander effect”)
- Immunologic mechanism of action study planned to fully validate the bystander effect