Chemoablation of Metastatic Melanoma with PV-10

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SMR 2010
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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
Chemoablative Mechanism of Action

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

- **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
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**
  - Intraleisonal 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 III-C, 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.
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 $\geq 0.2$ 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

<table>
<thead>
<tr>
<th>Demographic/Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (Range):</td>
<td>70.0 yrs (33 – 97)</td>
</tr>
<tr>
<td>Gender:</td>
<td>49 M / 31 F</td>
</tr>
<tr>
<td>Race / Ethnicity (White):</td>
<td>40 (100%)</td>
</tr>
<tr>
<td>AJCC Stage:</td>
<td>III (N=53) / IV (N=27)</td>
</tr>
<tr>
<td>PV-10 Injections</td>
<td>1142</td>
</tr>
<tr>
<td>Treatments per Subject, Median (Range):</td>
<td>2 (1 – 4)</td>
</tr>
<tr>
<td>1 Course:</td>
<td>35 Subjects</td>
</tr>
<tr>
<td>2 Courses:</td>
<td>26 Subjects</td>
</tr>
<tr>
<td>3 Courses:</td>
<td>16 Subjects</td>
</tr>
<tr>
<td>4 Courses:</td>
<td>3 Subjects</td>
</tr>
<tr>
<td>Dose PV-10 per Treatment, Median (Range):</td>
<td>1.6 mL (0.1 – 15)</td>
</tr>
<tr>
<td>Cumulative Dose, Median (Range):</td>
<td>3.4 mL (0.3 – 26.0)</td>
</tr>
</tbody>
</table>
Male, 73, Stage IIIB (N2c) since 2008, Sx of 1° and mets.
Three treatments (Day 0, Wk 8 and Wk 16) with PV-10 to 11 lesions; 1 untreated bystander lesion.
## 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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Adverse Events (by CTCAE Grade)</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
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<tr>
<td>Nausea</td>
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<td>3</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Diarrhoea</td>
<td></td>
<td>5</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Dysphagia</td>
<td></td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site pain</td>
<td></td>
<td>29</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>Injection site oedema</td>
<td></td>
<td>22</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Injection site vesicles</td>
<td></td>
<td>17</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Injection site discolouration</td>
<td></td>
<td>13</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td></td>
<td>14</td>
<td>7</td>
<td>1</td>
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<tr>
<td>Injection site pruritus</td>
<td></td>
<td>14</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td></td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Injection site inflammation</td>
<td></td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Injection site photosensitivity reaction</td>
<td></td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Injection site ulcer</td>
<td></td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Injection site infection</td>
<td></td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Injection site cellulitis</td>
<td></td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Injection site warmth</td>
<td></td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Injection site rash</td>
<td></td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wound secretion</td>
<td></td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Oedema peripheral</td>
<td></td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Localised oedema</td>
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<td>0</td>
<td>1</td>
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<td>Palliative care</td>
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<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>11</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

- 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)**

<table>
<thead>
<tr>
<th>Best Response</th>
<th>Target Lesions</th>
<th>Bystander Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (Subjects)</td>
<td></td>
</tr>
<tr>
<td>N (Subjects)</td>
<td>80</td>
<td>38</td>
</tr>
<tr>
<td>CR</td>
<td>19 (24%)</td>
<td>9 (24%)</td>
</tr>
<tr>
<td>PR</td>
<td>20 (25%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>SD</td>
<td>18 (18%)</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>PD</td>
<td>23 (23%)</td>
<td>17 (45%)</td>
</tr>
<tr>
<td>ND</td>
<td>--</td>
<td>42</td>
</tr>
<tr>
<td>CR + PR</td>
<td>39 (49%)</td>
<td>14 (37%)</td>
</tr>
<tr>
<td>CR + PR + SD</td>
<td>57 (71%)</td>
<td>21 (55%)</td>
</tr>
</tbody>
</table>

*(Locoregional Disease Control)*
Phase 2 – Preliminary Efficacy

% Change in Target Lesion Diameter

PD
SD
PR
CR
Phase 2 – Preliminary Efficacy

Regression of bystander lesions strongly correlated with response in target lesions
Objective Response of Bystander Lesions
Grouped According to Subject Objective Response of Target Lesions
All Subjects (N=80)

<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>20</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>5</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>ND</td>
<td>(21)</td>
<td>(21)</td>
<td></td>
</tr>
<tr>
<td>CR + PR</td>
<td>12</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CR + PR + SD</td>
<td>13</td>
<td>7</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 of response rates tested using the Chi-Square and Fisher Exact tests. Forty two subjects had no designated bystander lesion (or no assessable lesion) to assess (ND) and were censored.
### Phase 2 – Response by Disease Stage

#### Objective Response of Target Lesions (by AJCC Stage)

All Subjects (N=80)

<table>
<thead>
<tr>
<th>Best Response (RECIST, N=80, through Week 52)</th>
<th>Unresectable Stage III</th>
<th>Stage IV M1a</th>
<th>Stage IV M1b</th>
<th>Stage IV M1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (Subjects)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>CR</td>
<td>15 (34%)</td>
<td>1 (50%)</td>
<td>3 (21%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>PR</td>
<td>13 (26%)</td>
<td>1 (50%)</td>
<td>3 (21%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>SD</td>
<td>13 (24%)</td>
<td>0 (0%)</td>
<td>2 (14%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>PD</td>
<td>12 (16%)</td>
<td>0 (0%)</td>
<td>6 (43%)</td>
<td>5 (45%)</td>
</tr>
<tr>
<td>CR + PR</td>
<td>28 (53%)</td>
<td>2 (100%)</td>
<td>6 (43%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>CR + PR + SD</td>
<td>41 (77%)</td>
<td>2 (100%)</td>
<td>8 (57%)</td>
<td>6 (55%)</td>
</tr>
</tbody>
</table>

- Early systemic progression of M1b and M1c subjects led to early withdrawal and PD score
- OR for Stages III–IV (M1a) = 55% vs 49% for all subjects
Phase 2 – Survival

Progression Free Survival

All Subjects (N=80)

IIIB - IV (M1a) (N = 55)
Mean = 8.8 mo

IV (M1b-M1c) (N = 25)
Mean = 6.2 mo

P = 0.114

Time (months)

0 2 4 6 8 10 12 14

0.0 0.2 0.4 0.6 0.8 1.0

Majority of subjects censored due to progression of disease other than target lesions

- 6 subjects withdrawn at 4 wks or less, 18 prior to week 8
- Stage IIIB – IV(M1a) cohort: 67% of subjects censored
- Stage IV (M1b-M1c) cohort: 54% of subjects censored
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.
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
    - 30 subjects have been enrolled
      - 29 melanoma + 1 rSCC
      - Enrollment continuing, anticipate up to 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
  - Study approved for enrollment

- **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 1H-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 accepted comparator
  - 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
  - Durable response as primary endpoint
    - 12 month follow-up
    - Treatment regimen similar to ongoing expanded access protocol
  - Study duration ca. 30 months
  - Commence enrollment in 2011

- Investigators needed in AUS, USA and EU
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