Overview

• Introduction

• Current data with agents in development
  – TVEC (phase III reported)
  – PV-10 (phase III ongoing)
  – Others (phase II)

• Future prospects and perspective
Why Consider Intrallesional Therapy?

• Metastatic melanoma involves cutaneous metastases in a high percentage of patients accessible to injection

• Loco-regional control is clinically important
  – In transit disease
  – Local regional recurrence without distant metastases
Local/Satellite/In-transit metastases

Spectrum of Regional Metastases (AJCC IIIb/IIIc)

6%-12% of primary melanoma
- high risk groups: thick, ulcerated, and positive SLN, lower extremity
Source of significant morbidity
Greater than 50% risk for distant disease and death
(Courtesy: Merrick Ross, MD)
Treatment Options for Regional Disease

• Surgery
  – resection for limited disease
  – amputation

• Topical agents
  – imiquimod

• Extremity Regional Chemotherapy
  • Isolated limb perfusion/infusion

• Systemic therapy

• Intra-lesional therapy
Potential Goals of Intralesional Therapy

• Local disease control
  – Durable tumor shrinkage
  – Symptom control and palliation
• Systemic effect
  – Immune mediated
• Delay or prevent systemic therapy
• Neoadjuvant potential
## Intralesional agents in development in melanoma

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alpha-gal glycolipids</td>
<td>• HF-10 (HSV-1)</td>
<td>• Coxsackievirus A21 (Cavatak)</td>
<td>• Velimogene aliplasmid (Allovectin-7)</td>
</tr>
<tr>
<td>• OrienX010 (hGM-CSF HSV-1)</td>
<td>• Retroviral IFN-γ</td>
<td>• Adenovirus expressing IL-2</td>
<td>• Talimogene laherparepvec (T-VEC, formerly OncoVEX&lt;sup&gt;GM-CSF&lt;/sup&gt;)</td>
</tr>
<tr>
<td>• Canarypox virus expressing B7.1 and IL-12</td>
<td>• Adenovirus expressing IFN-γ</td>
<td>• GM-CSF</td>
<td>• Recombinant vaccinia virus expressing B7.1</td>
</tr>
<tr>
<td>• Adenovirus expressing IFN-γ</td>
<td>• Recombinant vaccinia virus expressing B7.1</td>
<td>• BCG</td>
<td>• Ganglioside D2 mAb</td>
</tr>
<tr>
<td>• Plasmid encoding IL-12</td>
<td>• Plasmid encoding IL-12</td>
<td>• IL-2</td>
<td>• Plasmid encoding IL-12</td>
</tr>
<tr>
<td>• Alpha-immunoconjugate of vector 9.2.27 with 213Bi radioactive Ab</td>
<td>• Polylactic acid microspheres with IL-12 +/- IL-18</td>
<td>• IL-12</td>
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</tr>
<tr>
<td>• Coxsackievirus A21 (Cavatak)</td>
<td>• PV-10 (Rose Bengal)</td>
<td>• PV-10 (Rose Bengal)</td>
<td>• VMIP-10 (Rose Bengal)</td>
</tr>
<tr>
<td>• KORTUC II</td>
<td>• Monkey fibroblast Vero cells producing human IL-2</td>
<td>• Intralrostal GM-CSF + subcutaneous IL-2</td>
<td>• Intralrostal GM-CSF + subcutaneous IL-2</td>
</tr>
<tr>
<td>• Intralrostal IL-2 and topical imiquimod</td>
<td>• Intralrostal IL-2 and topical imiquimod</td>
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</tr>
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</table>

Courtesy of Robert Andtbacka, MD
Overview

• Introduction

• Current data with agents in development
  – TVEC (phase III reported)
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  – Others (phase II)

• Future prospects and perspective
T-VEC: an HSV-1-derived oncolytic immunotherapy designed to produce both local and systemic effects

Local effect: tumour cell lysis

Systemic effect: tumour-specific immune response

Selective viral replication in tumour tissue

Tumour cells rupture for an oncolytic effect

Systemic tumour-specific immune response

Death of distant cancer cells

T-VEC key genetic modifications:
JS1/ICP34.5-/ICP47-/hGM-CSF

CMV, cytomegalovirus; hGM-CSF, human granulocyte-macrophage colony-stimulating factor; HSV-1, herpes simplex virus type 1; ICP, infected cell protein; pA, polyadenylation (from bovine growth hormone).

OPTiM phase III study design

**Injectable, unresectable Stage IIIB-IV melanoma**

T-VEC intralesional up to 4 mL Q2W*  
\( n = 295 \)

GM-CSF Subcutaneous  
14 days of every 28-day cycle*  
\( n = 141 \)

**Primary Endpoint:**
- Durable response rate  
  (Defined as objective response lasting for at least 6 months)

**Key Secondary Endpoints**
- OS  
- ORR  
- Time to treatment failure (TTF)  
- Safety

**Randomization stratification:**
1. Disease substage  
2. Prior systemic treatment  
3. Site of disease at first recurrence  
4. Presence of liver metastases

- Patients enrolled between May 2009 and July 2011  
- Patients enrolled at 64 sites in USA, UK, Canada, and South Africa

* Dosing of intralesional T-VEC was \( \leq 4 \text{ mL} \times 10^6 \text{ pfu/mL} \) once, then after 3 weeks, \( \leq 4 \text{ mL} \times 10^8 \text{ pfu/mL} \) every two weeks (Q2W).
Dosing of GM-CSF was 125 \( \mu \text{g/m}^2 \) subcutaneous daily x 14 days of every 28 day cycle.

### OPTiM phase III study results

**Primary endpoint: durable response rate per EAC***

**Secondary endpoint: objective response per EAC**

<table>
<thead>
<tr>
<th>ITT set</th>
<th>GM-CSF (n = 141)</th>
<th>T-VEC (n = 295)</th>
<th>Treatment difference (T-VEC – GM-CSF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durable response rate</td>
<td>2.1%</td>
<td>16.3%</td>
<td>14.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI (8.2, 19.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.0001 (unadjusted odds ratio 8.9)</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>ITT Set</th>
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<th>T-VEC (n = 295)</th>
<th>Treatment difference (T-VEC – GM-CSF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective overall response (95% CI)</td>
<td>5.7% (1.9, 9.5)</td>
<td>26.4% (21.4, 31.5)</td>
<td>20.8% (14.4, 27.1) P &lt; 0.0001 descriptive</td>
</tr>
<tr>
<td>CR</td>
<td>0.7%</td>
<td>10.8%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>5.0%</td>
<td>15.6%</td>
<td></td>
</tr>
</tbody>
</table>

*Rate of CR or PR that began at any point within 12 months of initiation of therapy and lasted continuously for 6 months or longer.

Determined using modified WHO criteria by an independent, blinded endpoint assessment committee (EAC).

ITT, intention to treat; CI, confidence interval.

Secondary endpoint: primary overall survival

<table>
<thead>
<tr>
<th>Survival</th>
<th>T-VEC (%)</th>
<th>GM-CSF (%)</th>
<th>Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-mo</td>
<td>73.7%</td>
<td>69.1%</td>
<td>4.6 (-4.7, 13.8)</td>
</tr>
<tr>
<td>24-mo</td>
<td>49.8%</td>
<td>40.3%</td>
<td>9.5 (-0.5, 19.6)</td>
</tr>
<tr>
<td>36-mo</td>
<td>38.6%</td>
<td>30.1%</td>
<td>8.5 (-1.2, 18.1)</td>
</tr>
<tr>
<td>48-mo</td>
<td>32.6%</td>
<td>21.3%</td>
<td>11.3 (1.0, 21.5)</td>
</tr>
</tbody>
</table>

Events/n (%)  
T-VEC: 189/295 (64)  
GM-CSF: 101/141 (72)  
Median, months  
T-VEC: 23.3 (19.5, 29.6)  
GM-CSF: 18.9 (16.0, 23.7)  
HR = 0.79 (95% CI: 0.62, 1.00)  
Unadjusted log-rank P = 0.051

Kaplan–Meier percent

Median follow-up: 44.4 months (range: 32.4–58.7)

PV-10 (Rose Bengal)

- 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
  - **Radiopaque** with prolonged retention in tumors
PV-10 (Rose Bengal)

Mechanism of action

- PV-10
  - Accumulates in lysosomes of cancer cells
  - -> acute autophagy
  - -> acute exposure of antigenic tumor fragments to APCs.
- Excluded from normal cells

PV-10 Phase II Trial

• 80 patients, open label, single arm
• Stage III and IV melanoma (Aug 2007 – May 2009)
• Response (all patients):
  – Target lesions: 51% (26% CR, 25% PR)
  – Non-target lesions: 33% (26% CR, 7% PR)
• PFS:
  – Responders 11.4 mo
  – Non-responders 4.1 mo
  – Local / regional disease longer PFS compared to distant metastases
• Adverse reactions mild / moderate

Thompson JF, Agarwala, SS et al., Ann Surg Oncol, 2014
PV-10 response in Target lesions (Phase II)

Rapid early progression led to PD/NEV assignment in 13 subjects

Robust response in Stage III subjects

PV-10 Phase III Trial

 Patients with Locally Advanced Cutaneous Melanoma

 Randomize (2 : 1)<sup>a</sup>

 Active Arm
 PV-10 q4w

 Comparator Arm
 DTIC or TMZ q4w

 RECIST q12w
 PR/SD

 Long-term Follow-up

 CR/PD<sup>b</sup>

 a. 225 patients randomized 2:1 (stratified for prior immune checkpoint inhibition)
b. Cross-over allowed upon documented PD in comparator arm
Intratumoral DNA-encoded IL-12 Electroporation

1. Cancer Cells
2. DNA IL-12 Injected
3. Electroporation
4. DNA IL-12 Enters
5. IL-12 Protein Expression
6. Initiation of Local Pro-Inflammatory Process
7. Targeted Anti-Tumor Immune Response & Lymphocyte Education
8. Systemic Anti-Tumor Immune Response
Plasmid encoded DNA IL-12 Electroporation

Phase II study (interim analysis, n=28)

- Primary endpoint ORR 24 wks
  - OR 32% (9/28)
  - CR 11% (3/28)

- Lesion responses (n=85)
  - SD 31% (26/85)
  - PR 8% (7/85)
  - CR 45% (38/85)

- Response untreated lesions
  - 59% (13/22 patients)

Responses in electroporated and non-electroporated lesions

Daud AI, et al. ASCO 2014, Abstract 9025
Phase 2 Efficacy: pIL-12 EP Monotherapy

**Response Category**

<table>
<thead>
<tr>
<th>Category</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td><strong>Stable Disease (SD)</strong></td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>15 (52%)</td>
</tr>
<tr>
<td>Overall Response Rate (CR + PR)</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>Disease Control Rate (CR + PR + SD)</td>
<td>14 (48%)</td>
</tr>
</tbody>
</table>

*by Modified “Skin” RECIST

**SD required to last for at least 90 days

Coxsackievirus A21 (CVA21)

CALM Phase II trial: Best percentage change in target lesions* (investigator assessed)

- Analysis excludes patients satisfying protocol criteria but not on study long enough for 6 week tumor response assessment;
- CR=Complete response, PR= Partial response, SD= Stable disease and PD= Progressive disease

Andtbacka et al. World Melanoma Congress 2013
Spontaneous mutant strain of HSV-1 with no external gene.

- Greater replication ability = effective dose is lower
- No toxicity to be caused by exogenous gene (ex. GM-CSF) inserted.

- Attenuation of neurovirulence to be attributable to the lack of the UL56 gene.

- In addition to local oncolytic tumor destruction, systemic anti-tumor immune response observed.
**Title of the study**
A Phase II Study of Combination Treatment with HF10, a Replication-competent HSV-1 Oncolytic Virus, and Ipilimumab in Patients with Stage IIIB, Stage IIIC, or Stage IV Unresectable or Metastatic Malignant Melanoma

**Objectives**
To assess efficacy and safety with repeated administration of intratumoral injections of HF10 at $1 \times 10^7$ TCID$_{50}$/mL in combination with intravenous infusions of 3mg/kg ipilimumab and evaluate the following objectives:

Primary Objective:
Best overall response rate (BORR) at Week 24

Secondary Objectives:
Safety and tolerability, ORR, PFS, DRR, 1-year survival rate, Evaluation of correlative studies

**# of patients**
Planned 43 patients

**Methodology**
single arm, open label Phase II trial

**Investigators**
Robert Andtbacka, University of Utah, Huntsman Cancer Institute
Sanjiv S. Agarwala, St. Luke's University Hospital and Temple University
and 6 other sites
Overview

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• Current data with agents in development
  – TVEC (phase III reported)
  – PV-10 (phase III ongoing)
  – Others (phase II)

• Future prospects and perspective
The future of intra-lesional therapy probably lies in combinations
How do we assess IL monotherapy?

• Is there a role for monotherapy in today’s melanoma landscape?
• What is the correct endpoint for clinical trials?
• What should be the control arm?
T-VEC + ipilimumab Phase Ib trial (20110264)

Stage IIIB/C–IV M1c melanoma not suitable for surgical resection, no prior systemic treatment (except adjuvant treatment)

Talimogene laherparepvec up to 4 mL
10⁶ pfu/mL Wk1 D1,
10⁸ pfu/mL Wk4 D1 & then Q2W
+ ipilimumab 3 mg/kg
Q3W x 4 starting Wk6 D1
N = 19

Screening 28 days prior to enrollment

T-VEC dosing until CR, all injectable tumours disappeared, PD per immune-related response criteria, or intolerance for treatment, whichever comes first.

Primary endpoint: Incidence of dose-limiting toxicities
Secondary endpoints: ORR, safety: all AEs, Grade ≥ 3 AEs, serious AEs, events requiring discontinuation of study drug, events with local effects on tumours (pain, inflammation, and ulceration)

30 (+7) days after last dose of T-VEC or
60 (+7) days after last dose of ipilimumab

Up to 24 months after end of randomization

TVEC + ipi: Maximal change in tumor burden

Patients (N = 17)<sup>b</sup>

Investigator-assessed responses

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>%</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>10</td>
<td>56%</td>
<td>31–79%</td>
</tr>
<tr>
<td>Complete response</td>
<td>6</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>4</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>3</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5</td>
<td>28%</td>
<td></td>
</tr>
</tbody>
</table>

Efficacy analysis set includes only the patients who received both T-VEC and ipilimumab.

One patient assessed to have PD by the investigator was not shown in the plot because tumor burden could not be accurately calculated based on missing post-baseline data.

NCT02263508: Phase Ib/II Study of Pembrolizumab + T-VEC

**Key Objective:** Evaluate the safety (phase Ib) and efficacy (phase II) of pembrolizumab + T-VEC in patients with previously untreated, unresected, Stage IIIB to IVM1c melanoma.

**Primary Outcome Measures:**
- Incidence of DLTs (Phase Ib)
- Confirmed ORR (Phase II)

**Secondary Outcome Measures:**
- Incidence of AEs
- ORR (Phase Ib)
- Best ORR
- Durable response rate
- DoR
- PFS
- OS

**Phase Ib**
- Pembrolizumab Q2W + T-VEC

**Phase II, Part 1**
- Pembrolizumab Q2W + T-VEC

**Phase II, Part 2**
- Pembrolizumab Q2W

**Progression**
- Pembrolizumab Q2W + T-VEC*

**Estimated Enrollment:** 110
**Study Start Date:** October 2014
**Estimated Study Completion Date:** February 2019
**Estimated Primary Completion Date:** November 2016 (Final data collection date for primary outcome measure)

T-VEC Neoadjuvant Treatment with Surgery vs. Surgery Alone
Phase 2 surgically resectable stage IIIB/C/IVM1a melanoma (20110266)

Arm 1
Talimogene laherparepvec up to 4 mL $10^6$ PFU/mL week 1 followed by $10^8$ PFU/mL week 4 then every 14 (± 3) days until week 12 followed by surgical resection of melanoma lesion(s) anytime during weeks 13 to 18*

N = 75

Arm 2
Immediate surgical resection of melanoma lesion(s) any time during weeks 1 to 6

N = 75

Primary endpoint: Recurrence-Free Survival (RFS)
Secondary endpoints: OS, overall tumor response and tumor response in injected and uninjected lesions (T-VEC arm only), Rates of R0 resection and pathological CR, Local RFS, Distant metastases-free survival, safety

Current Melanoma Landscape: Is there a role for IL monotherapy?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not all patients candidates for systemic therapy (co-morbidities, toxicity)</td>
<td>Systemic therapies in 2015 are safe and effective</td>
</tr>
<tr>
<td>After progression on other therapies</td>
<td>Melanoma is a systemic disease</td>
</tr>
<tr>
<td>Alternative to surgery?</td>
<td>Surgery is an instant CR</td>
</tr>
<tr>
<td>Neoadjuvant potential</td>
<td>Not yet proven</td>
</tr>
</tbody>
</table>
Summary & Conclusions

• In the new and current era of melanoma therapy, intralesional approaches may have value
  – Local direct effect
  – Systemic immune effect
• Several agents in development appear promising
  – Recent ODAC vote on TVEC
• Combination therapies are likely to be the future and may be the best way to integrate them into clinical practice