Overview of Intralesional Therapy for Melanoma

Sanjiv S. Agarwala, MD
Professor of Medicine, Temple University
Chief, Oncology & Hematology
St. Luke’s Cancer Center
Bethlehem, PA, USA
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 Intralesional Therapy?

• Metastatic melanoma involves cutaneous metastases in a high percentage of patients accessible to injection
• Loco-regional control is clinically important
  – In transit disease
  – Symptom control
• Systemic Effect
• Backbone for future combinations
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
Melanoma intralymphatic metastasis
Spectrum of disease (AJCC IIIB/IIIC)

- 3 – 10% of primary melanoma develop local / in-transit recurrences
  - High risk groups: thick, ulcerated, positive SLN, lower extremity
- Source of significant morbidity
- Greater than 50% risk of distant disease and death

Courtesy of Robert Andtbacka, MD
Intralesional agents in development in melanoma

**Preclinical**
- Alpha-gal glycolipids
- HF-10 (HSV-1)
- OrienX010 (hGM-CSF HSV-1)
- Retroviral IFN-γ
- Canarypox virus expressing B7.1 and IL-12
- Adenovirus expressing IFN-γ
- Recombinant vaccinia virus expressing B7.1
- Ganglioside D2 mAb
- Plasmid encoding IL-12
- Alpha-immunoconjugate of vector 9.2.27 with 213Bi radioactive Ab
- Plasmid encoding IL-12
- Polylactic acid microspheres with IL-12 +/- IL-18

**Phase I**
- Coxsackievirus A21 (Cavatak)
- Adenovirus expressing IL-2
- GM-CSF
- BCG
- IL-2
- IL-12
- KORTUC II
- Monkey fibroblast Vero cells producing hu IL-2
- Intralesional GM-CSF + subcutaneous IL-2
- Intralesional IL-2 and topical imiquimod

**Phase II**
- Velimogene aliplasmid (Allovectin-7)

**Phase III**
- Talimogene laherparepvec (T-VEC, formerly OncoVEX GM-CSF)
- PV-10 (Rose Bengal)
Overview

• Introduction
• Current data with agents in development
  – TVEC (phase III reported, USFDA Approved)
  – PV-10 (phase III ongoing)
  – 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-macroage 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 intrallesional up to 4 mL Q2W* n = 295

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

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

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 intrallesional T-VEC was ≤ 4 mL x 10^8 pfu/mL once, then after 3 weeks, ≤ 4 mL x 10^8 pfu/mL every two weeks (Q2W).
Dosing of GM-CSF was 125 µg/m² 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% 95% CI (8.2, 19.2) P &lt; 0.0001 (unadjusted odds ratio 8.9)</td>
</tr>
</tbody>
</table>

<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>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>41% CR in T-VEC Responders</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.

Overview

• Introduction
• Current data with agents in development
  – TVEC (phase III reported)
  – PV-10 (phase III ongoing)
  – Others (phase II)
• Future prospects and perspective
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 transits plasmalemma of cancer cells
- Accumulation in lysosomes of cancer cells
- Excluded from normal cells

PV-10 accumulation elicits rapid autolysis of cancer cells
- Accumulation in lysosomal membrane triggers release of lysosomal contents
- Acute autolysis within 30-60 min
- Identical response in Hepa1-6 murine HCC, HTB-133 human breast carcinoma and H96Ar human multidrug resistant small cell lung carcinoma

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

Liu et al., AACR 2014
Ablation can Elicit T-cell Mediated Immune Response
PV-10 for Metastatic Melanoma

- **Phase 1 (Aug 2005 – Aug 2007)**
  - 20 subjects, treat 1-20 lesions once, 1-3 bystanders untreated
  - Follow up to 24 weeks
  - Primary EP ORR

- **Phase 2 (Oct 2007 – May 2010)**
  - 80 subjects, treat 1-20 lesions up to 4 times, up to 2 bystanders untreated
  - Follow up to 52 weeks
  - Primary EP ORR

- **Expanded Access (Jun 2009 – Present)**
  - Over 100 melanoma subjects treated to date

- Phase III Trial initiated April 2015
Phase 2: Demographics & Treatment Summary

Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subjects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>Female</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70 years</td>
<td>39</td>
<td>49</td>
</tr>
<tr>
<td>≥ 70 years</td>
<td>41</td>
<td>51</td>
</tr>
<tr>
<td>Disease Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>62</td>
<td>78</td>
</tr>
<tr>
<td>Stage IV</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Treatment History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Prior Systemic Therapy</td>
<td>46</td>
<td>58</td>
</tr>
<tr>
<td>Prior Systemic Therapy</td>
<td>34</td>
<td>42</td>
</tr>
<tr>
<td>Tumor Burden in Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 Lesions</td>
<td>44</td>
<td>55</td>
</tr>
<tr>
<td>≥ 10 Lesions</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td>Too Numerous to Count (TNC)</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>

- Substantial tumor burden: 6.3 cm sum diameter of study lesions (median)
- Refractory to a median of 6 previous interventions:
  - Excision (100% of patients)
  - Immunotherapy (21%)
  - Systemic Chemotherapy (13%)
  - Nodal biopsy (63%)
  - Radiotherapy (21%)
  - Amputation (9%)
  - Regional chemotherapy (24%)
  - Investigational Agents (14%)
  - Other (8%)
Clinical Examples

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.

Agarwala et al., ASCO 2014
Clinical Examples

Target Lesion 1

Screening

Week 4
(mislabeled as “Day 7”)

Week 12

Provectus 2014
Phase 2: Subgroups by Baseline Disease Burden

### Table 2. Objective Response of Target Lesions (ITT Population and by Disease Burden)

<table>
<thead>
<tr>
<th>Response of Target Lesions</th>
<th>ITT Population</th>
<th>All Lesions Treated</th>
<th>Bystanders Untreated</th>
<th>Up to 10 Skin Lesions Untreated</th>
<th>TNTC or Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (Patients)</td>
<td>80 %</td>
<td>28 %</td>
<td>26 %</td>
<td>7 %</td>
<td>19 %</td>
</tr>
<tr>
<td>CR</td>
<td>21 26%</td>
<td>14 50%</td>
<td>6 23%</td>
<td>1 14%</td>
<td>0 0%</td>
</tr>
<tr>
<td>PR</td>
<td>20 25%</td>
<td>6 21%</td>
<td>8 31%</td>
<td>1 14%</td>
<td>5 26%</td>
</tr>
<tr>
<td>SD</td>
<td>14 18%</td>
<td>3 11%</td>
<td>8 31%</td>
<td>1 14%</td>
<td>2 11%</td>
</tr>
<tr>
<td>PD (PD + NEV) b</td>
<td>25 31%</td>
<td>5 18%</td>
<td>4 15%</td>
<td>4 57%</td>
<td>12 63%</td>
</tr>
<tr>
<td>CR + PR</td>
<td>41 51%</td>
<td>20 71%c</td>
<td>14 54%</td>
<td>2 29%</td>
<td>5 26%</td>
</tr>
<tr>
<td>CR + PR + SD (Locoregional Disease Control)</td>
<td>55 69%</td>
<td>23 82%</td>
<td>22 85%</td>
<td>3 43%</td>
<td>7 37%</td>
</tr>
<tr>
<td>Mean PFS (months) d</td>
<td>8.2</td>
<td>9.8e</td>
<td>8.9f</td>
<td>6.0</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Abbreviations: ITT, intent-to-treat; TNTC, too numerous to count; N, number; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NEV, non-evaluable; PFS, progression free survival.

a Median number of untreated lesions: 5.
b Patients that were non-evaluable were tracked separately but combined with PD for tabulation of outcome.
c $P = 0.006$ vs. TNTC or Stage IV subgroup, BORR by Chi-square test.
d PFS by mRECIST, maximum follow-up duration 12 months.
e $P < 0.001$ vs. TNTC or Stage IV subgroup, by log-rank test.
f $P = 0.04$ vs. TNTC or Stage IV subgroup, by log-rank test.
Minimal Intervention Required

56% of lesions achieved CR after 1-2 injections

All Melanoma Followed Sub-Group (N = 54 Patients)

Agarwala et al., ASCO 2014
Objective Response is Durable

Yellow = CR
White = PR
Grey = PR (Stage IV)

Thompson et al., Annals Surg Oncol
2014
Phase 2 – Efficacy

% Change in Target Lesion Diameter

PD
SD
PR
CR
Phase 2 – Efficacy

Regression of bystander lesions strongly correlated with response in target lesions.
Distant Bystander Effect

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

Agarwala et al., ESMO 2012
Table 2. Most Frequent Adverse Events at Least Possibly Related to Treatment

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>CTCAE Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
<td>1</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Injection Site Discoloration</td>
<td>13</td>
</tr>
<tr>
<td>Injection Site Erythema</td>
<td>6</td>
</tr>
<tr>
<td>Injection Site Edema</td>
<td>19</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>29</td>
</tr>
<tr>
<td>Injection Site Photosensitivity</td>
<td>3</td>
</tr>
<tr>
<td>Injection Site Pruritus</td>
<td>14</td>
</tr>
<tr>
<td>Injection Site Swelling</td>
<td>14</td>
</tr>
<tr>
<td><strong>Injection Site Vesicles</strong></td>
<td>17</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Photosensitivity Reaction</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: includes all CTCAE Grade 3 AEs, no treatment-related Grade 4 or 5 AEs were reported. Locoregional adverse events were coded to “injection site” preferred terms to differentiate these from systemic events. If a subject experienced an AE more than once during the study period, the greatest severity is tabulated.
Phase 3 Design

- **Randomized Controlled Trial**
  - PV-10 vs. DTIC or TMZ (2 : 1)
    - Proposed modification to include TVEC
  - Cross-over on documented progression
  - Sample size **225 patients**
  - Interim assessment

- **Patient Eligibility**
  - Cutaneous and subcutaneous disease (Stage IIIB or IIIC) with no active nodal disease
  - Failed or not candidates for at least one immune checkpoint inhibitor
  - BRAF wild-type
  - Cutaneous only target disease (critical for photodocumentation and IRC review)
  - All disease must be injectable on Day 1
  - No lesion > 3 cm, no more than 20 lesions at baseline
Phase 3 Design

• **Endpoints**
  – Primary: PFS
  – Secondary
    • Complete Response Rate (CRR)
    • Duration of Complete Response
    • OS
    • Safety
  – Exploratory
    • Change in Domain Scores on Skindex-16
    • Change in Patient Reported Pain and Pain Medication Use
    • Change in Investigator Assessed Lesion Bleeding, Ulceration and Infection (CTCAE)
Overview

- Introduction
- Current data with agents in development
  - TVEC (phase III reported)
  - PV-10 (phase III ongoing)
  - Others (phase II)
- Future prospects and perspective
Intratumoral DNA-encoded IL-12 Electroporation (IT-pIL12-EP)

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)

Daud AI, et al. ASCO 2014, Abstract 9025
Phase 2 Efficacy: pIL-12 EP Monotherapy Demonstrates Anti-tumor Activity in Advanced Melanoma

**Response Category**  |  **N (%)**  
--- | ---  
Complete Response (CR) | 4 (14%)  
Partial Response (PR) | 5 (17%)  
**Stable Disease (SD)** | 5 (17%)  
Progressive Disease (PD) | 15 (52%)  
Overall Response Rate (CR + PR) | 9 (31%)  
Disease Control Rate (CR + PR + SD) | 14 (48%)  

*by Modified “Skin” RECIST  
**SD required to last for at least 90 days
Coxsackievirus A21 (CVA21) 
Oncolytic immunotherapeutic modes of action

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

- CR, PR or SD = 80.6%
- CR or PR = 35.5%

*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
CALM Phase II trial
Current analysis: Response data

Primary endpoint (≥ 10 pts with irPFS 6 months from 54 evaluable pts)

irPFS 6 months+
(CR+PR+SD) 37.3% (19 / 51 pts)

Secondary endpoint

Overall response rate*
(CR+PR, irRECIST 1.1) 26.3 % (15 / 57 pts)

Safety
No grade 3 or 4 toxicity

+ analysis excludes patients satisfying protocol criteria but not on study long enough for 6 months evaluation
* ongoing overall response continually assessed at ≥ 12 weeks up to 48 weeks.

Andtbacka RHI, et al. ESMO 2014 Abstract 1103P
Overview

• Introduction

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

• Future prospects and perspective
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?
The future of intra-lesional therapy probably lies in combinations
T-VEC + ipilimumab Phase Ib trial (20110264)

- **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)

F-UP, follow up.

Stage IIIIB/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 x4 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.

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

Maximal change in tumor burden

Patients (N = 17)\textsuperscript{b}

Investigator-assessed responses
\( N = 18 \)\textsuperscript{a}

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

\textsuperscript{a}Efficacy analysis set includes only the patients who received both T-VEC and ipilimumab.

\textsuperscript{b}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.

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


F-UP, follow up.
Phase 1b Study Schema

N=21

- Unresectable stage III or IV melanoma
- Treatment naive
- Injectable lesions
- No clinically active brain mets
- No active herpetic skin lesions or prior complications from herpetic infection

T-VEC intralesional
- Up to 4 mL per treatment
- 1st dose $10^6$ PFU/mL
- Then $10^8$ PFU/mL Q2W

Pembrolizumab 200mg IV Q2W

Wk -5  Wk -2  Wk 0  DLT Window  Wk 6

Treatment until whichever occurs first:
- Progressive disease (PD) per irRC
- Intolerance
- All injectable tumors disappeared (T-VEC only)
- 2 Years

T-VEC: talimogene laherparepvec
Best Change in Tumor Burden

N=16

Includes all patients who received at least 1 dose of talimogene laherparepvec or pembrolizumab. Include patients who had at least 2 assessments with bi-dimensional measurements.
**MASTERKEY-265 Phase 3 Study Design**

**N = 660**

- Unresectable stage III or IV melanoma
- Treatment naive
- Injectable lesions
- No clinically active brain mets
- No active herpetic skin lesions or prior complications from herpetic infection

**T-VEC intralesional**
- Up to 4 mL per treatment
- 1st dose $10^6$ PFU/mL
- Then $10^8$ PFU/mL Q2W

**N = 330**

**Pembrolizumab 200mg IV Q3W**

**T-VEC Intralesional**

**1:1**

**T-VEC placebo Intralesional**

**Pembrolizumab 200mg IV Q3W**

**SAFETY FOLLOW-UP**

Treatment until whichever occurs first:
- Complete Response (CR)
- Progressive disease (PD) per irRC-RECIST
- Intolerance
- All injectable tumors disappeared (T-VEC only)
- 2 Years

30 (+7) days after end of treatment

T-VEC: talimogene laherparepvec
**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