Innovative Combination Strategies:
Oncolytic and Systemic Therapy

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Overview

• What is oncolytic therapy?
• What is the data with single agent oncolytic agents?
• What is the data with combinations?
• Future directions and prospects
What is Oncolytic Therapy?

- Direct injection of tumors with agents that produce regression
- Produce a local and systemic effect that is immunologically mediated
- Viral based
  - TVEC, HF-10, CAVATAK
- Non-viral based
  - PV-10, IL-12
Oncolytic Immunotherapy: Mechanisms of Action

- **Direct**
  - Cell lysis (viral replication, chemical and mechanical ablation)

- **Indirect “bystander response”**
  - Induction of innate immune response
  - Induction of adaptive immune response
Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects

The Cancer–Immunity Cycle

STEP 1
Tumor cell lysis and release of tumor-derived antigens

STEP 2
Uptake, process, and presentation of tumor antigens by APCs

STEP 3
• T-cell priming and activation
• Generation of memory T cells

STEP 4
Travel of activated T cells to tumors

STEP 5
T-cell infiltration into tumors

STEP 6
T-cell recognition of tumor cells

STEP 7
• Killing of tumor cells
• Memory-mediated control of tumor cell recurrence

APC, antigen-presenting cell
Soft Tissue/Skin Metastases
Role for Intraliesional Oncolytic Therapy

• Soft Tissue and Skin metastases occur frequently in melanoma
• Local-regional control is clinically important
• Systemic Therapy may not always be possible or appropriate
  – Newer IL agents produce systemic responses
  – Backbone for future combinations
Melanoma intralymphatic metastasis

Spectrum of disease (AJCC III B/III C)

- 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
Current Clinical Trials

• Single Agent (Monotherapy) Trials
  – PV-10 (phase III ongoing)
  – IL-12 electroporation
  – CAVATAK

• Combination Trials
  – TVEC
  – PV-10
  – HF-10
Rose Bengal Disodium 10% (PV-10)

- Small molecule fluorescein derivative
- Primary tumor lysis by entering lysosomes
- Tumor-infiltrating lymphocytes at local site and regression of distant tumors
- Necrotic tumor cells facilitate antigen presentation
- Secondary tumors are rejected in immuno-competent animals
- No immune response in immuno-compromised animals
- Response is tumor specific
- Adoptive transfer of spleen cells can convey immunity
  - T cell subsets have increased expression of Gamma IFN

Toomey P et al. SSO, 2012
### PV-10 Phase 2: Efficacy

**Objective Response of Study Lesions (n = 80)**

<table>
<thead>
<tr>
<th>Best Response (RECIST, n = 80 through Wk 52)</th>
<th>Target Lesions (n = 80)</th>
<th>Bystander Lesions (n = 38)</th>
</tr>
</thead>
<tbody>
<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 (22%)</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>PD</td>
<td>23 (29%)</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 (locoregional disease control)</td>
<td>57 (71%)</td>
<td>21 (55%)</td>
</tr>
</tbody>
</table>

PV-10 Response in Target Lesions

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

Robust response in Stage III subjects

NEV, not evaluable
Regression of bystander lesions strongly correlated with response in target lesions
Responses with PV-10 Occur Early

56% of lesions achieved CR after 1-2 injections

Agarwala et al., ASCO 2014
Phase III Design

Protocol PV-10-MM-31

Patients with Locally Advanced Cutaneous Melanoma

Randomize (2 : 1)\(^a\)

Active Arm PV-10 q4w

Comparator Arm DTIC or TMZ q4w or IMLYGIC q2w\(^c\)

RECIST q12w

PR/SD

CR/PD \(^b\)

Long-term Follow-up

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

Primary Objective:
- Overall Response Rate by modified “skin” RECIST within 180 days (ORR = CR + PR)

Secondary Objectives
- Disease Control Rate (DCR = CR + PR + SD)
- Distant Lesion Regression
- Duration of Response (DOR)
- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Safety

Max 4 Treatment Cycles
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.
Coxsackie virus A21 (CVA21)

Oncolytic immunotherapeutic modes of action

CALM Phase II study Design

**CAVATAK in Late stage Melanoma**

57 Stage IIIC and IV melanoma patients at least 1 injectable lesion

10 series of multi-intratumoral CVA21 injections
(up to 3x10^8 TCID<sub>50</sub>)
Day 1,3,5,8,22,43,64,85,106,127

- **YES**
  - Day 169 (w24) irPFS
  - Primary endpoint (≥ 22.5%)

- **NO**
  - Eligible for Extension study
  - 9 cycles of multi-intratumoral CVA21 injections
  (up to 3x10^8 TCID<sub>50</sub>) q21 days

  - **NO**
    - 6 Weeks later, confirm Disease progression
    - Planned Interim DMC analysis: 35 patients
    - Observation only
CALM Phase II

Best Percentage Change in Target Lesions*

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; PD, progressive disease

Andtbacka RHI et al. SSO Annual Cancer Symposium 2015.

*Investigator assessed
Current Clinical Trials

• Single Agent (Monotherapy) Trials
  – PV-10 (phase III ongoing)
  – IL-12 electroporation
  – CAVATAK
  – HF10

• Combination Trials
  – TVEC
  – PV-10
  – HF-10
T-VEC: an HSV-1-derived oncolytic immunotherapy designed to produce both local and systemic effects

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

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

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

**T-VEC intrallesional 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

**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 x10⁶ pfu/mL once, then after 3 weeks, ≤ 4 mL x10⁸ 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 rate 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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(unadjusted odds ratio 8.9)</td>
</tr>
</tbody>
</table>

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<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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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.

T-VEC + ipilimumab Phase Ib trial

Unresectable Stage IIIIB-IV Melanoma
- Injectable
- Treatment naïve
- ECOG PS 0 or 1
- No evidence of CNS mets

T-VEC Intralesional
$10^6$ PFU/mL, after 3 weeks $10^8$ PFU/mL Q2W

Ipilimumab 3mg/kg IV Q3W x 4

Week 1
Week 6

N = 19

- T-VEC dosing until CR, all injectable tumors disappear, PD per irRC, or intolerance, whichever is first
- Safety follow-up occurs 30 (+7) days after last dose of T-VEC or 60 (+7) days after last dose of ipilimumab, whichever is later

Primary Endpoint: Incidence of dose-limiting toxicities (DLTs)
Key Secondary Endpoints: ORR$^{irRC}$, Safety

The waterfall plot shows best reductions in tumor burden at a single time point.

For the irRC response table, CR, PR, and PD needed to be confirmed by consecutive assessments no less than 4 weeks apart to be considered confirmed with the following exception: if PD was the last tumor assessment, it was considered as confirmed.

\*\*≤ -98%, but > -100% , †Unconfirmed CR

Puzanov I et al Clin Oncol 2016; JCO671529
**T-VEC + ipilimumab Phase II trial (20110264)**

**Unresectable Stage IIIB-IV Melanoma**
- Injectable
- ≤ 1 line of systemic therapy for BRAF wt, or ≤ 2 lines of systemic therapy including BRAFi regimen for BRAF mutated
- ECOG PS 0 or 1
- No evidence of active CNS mets

**Primary Endpoint**
- **ORR**

**Secondary Endpoints**
- **PFS, OS, DRR, BOR, DCR, DoR, TTR, resection rate**

**Week 1**
- T-VEC Intralosonal
  - $10^6$ PFU/mL, after 3 weeks $10^8$ PFU/mL Q2W
  - Ipilimumab 3mg/kg IV Q3W x 4

**Week 6**
- Ipilimumab 3mg/kg IV Q3W x 4

- T-VEC dosing until CR, all injectable tumors disappear, PD per irRC, or intolerance, whichever is first
- Safety follow-up occurs 30 (+7) days after last dose of T-VEC or 60 (+7) days after last dose of ipilimumab, whichever is later

**N = 100**
## T-VEC + ipilimumab Phase II trial (20110264)

### Initial results

<table>
<thead>
<tr>
<th></th>
<th>Confirmed&lt;sup&gt;a&lt;/sup&gt; n (%)</th>
<th>Unconfirmed&lt;sup&gt;b&lt;/sup&gt; n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T-VEC+ IPI (N=42)</td>
<td>IPI (N=40)</td>
</tr>
<tr>
<td>ORR – n (%)</td>
<td>15 (35.7)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(21.6, 52.0)</td>
<td>(7.3, 32.8)</td>
</tr>
<tr>
<td>CR</td>
<td>4 (9.5)</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>PR</td>
<td>11 (26.2)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>SD</td>
<td>13 (31.0)</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (14.3)</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>UE*</td>
<td>5 (11.9)</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>Odds ratio (95% CI) for ORR</td>
<td>2.6 (0.9, 7.3)</td>
<td>2.6 (1.0, 6.6)</td>
</tr>
<tr>
<td>DCR (%) – n (%)</td>
<td>28 (66.7)</td>
<td>18 (45.0)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(50.5, 80.4)</td>
<td>(29.3, 61.5)</td>
</tr>
<tr>
<td>Odds ratio (95% CI) for DCR</td>
<td>2.4 (1.0, 6.0)</td>
<td>2.4 (1.0, 6.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Confirmation of initial CR/PR/PD by subsequent assessment by ≥ 4 w apart. A CR/PR without confirmation is classified as SD and *an unconfirmed PD is classified as UE. Further follow up is ongoing.

<sup>b</sup>Unconfirmed is response or PD without confirmation requirement. CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; UE = unable to evaluate; DCR = disease control rate (SD or better).

Chesney J., et al. ESMO 2016
T-VEC + Pembrolizumab Phase 1b Trial (Masterkey – 265)

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

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

T-VEC Intrallesional
- 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

T-VEC: talimogene laherparepvec
Amgen study 20110265.

Long, et al. ECC 2015
Long, et al. SMR 2015

30 (+7) days after end of treatment
Best overall response

The waterfall plot shows best reductions in tumor burden at a single time point. For the irRC response table, CR, PR, and PD needed to be confirmed by consecutive assessments no less than 4 weeks apart to be considered confirmed with the following exception: if PD was the last tumor assessment, it was considered as confirmed. *

≤ -98%, but > -100% , †Unconfirmed CR

Puzanov I,....Andtbacka, RHA J Clin Oncol 2016; JCO671529. [Epub ahead of print]
MASTERKEY-265 Phase 3 Study Design

- 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 x 4, then Q3W

T-VEC Intralesional
Pembrolizumab 200mg IV Q3W

1:1

T-VEC placebo Intralesional
Pembrolizumab 200mg IV Q3W

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

T-VEC: talimogene laherparepvec
PV-10 + Pembrolizumab

- **Phase 1b**

**Treatment Phase**
(PV-10 and Pembro q3w)

- Screening
- Cycle 1
- Cycle 2
- Cycle 3
- Cycle 4
- Cycle 5

**Response Follow-up**
(Pembro q3w)

- Cycle 6
- Cycle 7
- Cycle ...
- Survival

**RECIST Assessment**
(q12w)

- Patients receive up to 5 cycles of PV-10 and Pembro (q3w)
- Patients continue to receive treatment until PD (q3w)
- Patients remain on active portion of study for up to 24 months
HF10 – Oncolytic HSV-1

- 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.
Since 1988, DNA all base sequence
UL: 65, US: 14, Inverted repetitive sequence: 10 (Total 89)
Accessory genes: 45

Partial deletion and insertion of inverted repetitive sequence at the left end in L component
Stability of genome in transfer of cultured cells

Lack of UL56 gene decreases HSV-1 pathogenicity without affecting viral replication ability
HF10 + Ipilimumab Phase II trial in unresectable stage IIIB – IV melanoma

- Multicenter trial
- **Primary objective:** Best Overall Response Rate (BORR) at week 24
- **Secondary objective:** safety, tolerability, ORR, PFS, DRR, 1-year OS, correlative studies

Andtbacka, RHA et al. ASCO 2016 Abstract 9543 (and poster presentation)
HF10 + Ipilimumab Phase II trial in unresectable stage IIIB – IV melanoma

Patient demographics N=46

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
<th>Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td></td>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>67</td>
<td>Male</td>
<td>27 (59%)</td>
</tr>
<tr>
<td>Range</td>
<td>29-92</td>
<td>Female</td>
<td>19 (41%)</td>
</tr>
<tr>
<td>ECOG Status</td>
<td></td>
<td>Disease Stage</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>34 (74%)</td>
<td>IIIB</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>1</td>
<td>12 (26%)</td>
<td>IIIC</td>
<td>20 (43%)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0%)</td>
<td>IV</td>
<td>17 (37%)</td>
</tr>
<tr>
<td>HSV-1 antibody</td>
<td></td>
<td>≥ 1 Prior Cancer Therapy</td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>30 (65%)</td>
<td>Yes</td>
<td>20 (43%)</td>
</tr>
<tr>
<td>(-)</td>
<td>16 (35%)</td>
<td>No</td>
<td>26 (57%)</td>
</tr>
</tbody>
</table>

Andtbacka, RHA et al. ASCO 2016 Abstract 9543 (and poster presentation)
HF10 + Ipilimumab Phase II trial in unresectable stage IIIB – IV melanoma

Maximum change in index lesions

Andtbacka, RHI et al. Int. Meeting on Replicating Oncolytic Virus Therapeutics, 2016 (abstract and oral presentation)
# 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

• Soft tissue and cutaneous metastases are a major clinical problem in melanoma
• Oncolytic intralesional approaches may have value
  – Local direct effect
  – Systemic immune effect
  – Low toxicity
• Several agents in development appear promising
  – TVEC approved by US and EU regulators
• Combination therapies are likely to be the future and may be the best way to integrate them into clinical practice