Rationale to Combine Immunotherapy with “Physical” Therapy

Kevin Harrington
Conflicts of Interest

- Advisory Board member for Amgen, Merck, Viralytics
- Honoraria from Amgen, Merck
- Research funding from Viralytics
The Power of the New Immunotherapies

BRAF^{wt}
Biochemo
HD IL-2
Ipi

Baseline
Day 90

CD8^{+}

CD8^{+}

N_Engl_J_Med_369;2  NEJM.ORG  July 11, 2013
MK3475 (Pembrolizumab) in Melanoma

Individual patients treated with MK-3475

- Yellow: Previous ipilimumab treatment
- Blue: No previous ipilimumab treatment

Percentage change from baseline in longest diameter of target lesion

<table>
<thead>
<tr>
<th>Cohort</th>
<th>ORR by RECIST, %</th>
<th>No previous ipilimumab</th>
<th>Previous ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/kg Q2W (n = 52)</td>
<td>49</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg Q3W (n = 45)</td>
<td>26</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>2 mg/kg Q3W (n = 20)</td>
<td>25</td>
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Q3W, every 3 weeks.
MK3475 (Pembrolizumab) in Melanoma

Can we use combination therapies to reduce number of non-responders?

Can we use combination therapies to convert SD to responders?

Can we use combination therapies to increase number and durability of CR?
Points to Consider

- Not all patients present initially with disseminated metastatic disease
- “Local” therapies are frequently curative against locoregional disease
- Delayed systemic failure is a significant problem in many tumours that are apparently “cured” by locoregional therapies
- Not all solid tumours will respond to immunotherapy like melanoma
- The toxic effects of single- and combination-agent immunotherapies are significant
- The costs of long-term single- and combination-agent immunotherapies are significant
- The long-term effects of chronic checkpoint blockade remain to be elucidated
Local “Physical” Therapies Combined with Immunotherapy

- Radiation therapy
- Oncolytic immunotherapy
- High-intensity focused ultrasound
- Hyperthermia
- Cryotherapy
- Radiofrequency ablation
- Electrochemotherapy
Local “Physical” Therapies Combined with Immunotherapy

- Radiation therapy

- Oncolytic immunotherapy
Systemic effects of local radiotherapy

Silvia C Formenti, Sandra Demaria

- Patient with thymic carcinoma
- 2 Lung lesions, one irradiated, one not irradiated
Abscopal response in unirradiated lesion

Ab = away from Scopus = the target
Steps in Generating Immune Responses

Tesniere et al. Cell Death & Differentiation 2008
Potential Therapeutic Modulation of Immune Responses

1. Release of cancer cell antigens
   - Chemotherapy
   - Radiation therapy
   - Targeted therapy

2. Cancer antigen presentation
   - Vaccines
   - IFN-α
   - GM-CSF
   - Anti-CD40 (agonist)
   - TLR agonists

3. Priming and activation
   - Anti-CTLA4
   - Anti-CD137 (agonist)
   - Anti-OX40 (agonist)
   - Anti-CD27 (agonist)
   - IL-2
   - IL-12

4. Trafficking of T cells to tumors

5. Infiltration of T cells into tumors
   - Anti-VEGF

6. Recognition of cancer cells by T cells
   - CARs

7. Killing of cancer cells
   - Anti-PD-L1
   - Anti-PD-1
   - IDO inhibitors
Potential Radiotherapeutic Modulation of Immune Responses

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Radiation as a Form of Active Immunotherapy

- Increased expression of MHCI
- Generation of novel peptides
  - Increased CD8 T-cell recognition and lysis
- Induction of apoptosis
- Expression of calreticulin, phosphatidylserine
- Release of endogenous danger signals eg. HMGB1, HSP, uric acid
- Maturation/activation
- Cross-presentation of tumour antigen

Radiation

- Irradiated tumour cell
  - Increased expression of NKG2D ligands
  - NK-cell recognition and lysis
- T-cell activation, tumour targeting and destruction; generation of protective immunity

- NK-cell activation
- CD8 T-cells
- DC
Preclinical Therapeutic Data

- Potential of combination immunotherapy and (chemo)radiation is great, but current data largely pre-clinical.
Primary but Not Single-Dose Radiotherapy Induces an Immune-Mediated Abscopal Effect when Combined with Anti-CTLA-4 Antibody

M. Zahidunnabi Dewan, Ashley E. Galloway, Noriko Kawashima, J. Keith Dewyngaert, James S. Babb, Silvia C. Formenti, and Sandra Demaria

Diagram:
- IR: 9H10 mAb 200 μg ip for 3 times
- Primary tumor
- Secondary tumor
- Day 0 2 12 13 14 15 16 35
- Tumor cells sc (Primary)
- Tumor cells sc (Secondary)
- Sacrificed
- 9H10: - + - + - + - +
- IR: 0 0 20x1 20x1 8x3 8x3 6x5 6x5
- Tumor weight (g ± SEM)

Case Report: Malignant Melanoma

• 33 year old woman
• 2004 – 1.53 mm melanoma: Resected with clear margins, 0/5 LN
• 2008 – 2 cm lung metastasis: Chemotherapy and surgical removal (2009)
• August 2009 – Progressive pleural disease
• September 2009 – Commenced ipilimumab
RT Delivery

- 6-field image-guided IMRT
- 28.5 Gy in 3 fractions over 7 days, 6 MV photons
Clinical Course

Evolution of local AND abscopal response

RT Delivery
Immune Endpoints

Spike in CD4+ ICOS^{hi} T Cells

Spike in MHC Class II on monocytes

Fall in immune suppressive cells (CD14+ HLA-DR^{lo})
Future Challenges

• Modes of tumour cell death have different immunogenicity: apoptosis, necrosis, necroptosis, autophagy, mitotic catastrophe
• Can we be sure that radiation is inducing the ‘right’ sort of death?
• Radiation toxicity to immune effector cells
• Poorly understood in context of activatory vs suppressive immune cells against cancer
• Will anti-CTLA4/PD1/PDL1 etc inhibitors all behave the same way?
• How will concomitant/adjuvant chemotherapy affect activity?
• Dose fractionation and scheduling critical
Local “Physical” Therapies Combined with Immunotherapy

- Radiation therapy

- Oncolytic immunotherapy
Selective viral replication in tumour tissue

Local effect: tumour cell lysis

Tumour cells rupture for an oncolytic effect

Systemic effect: tumour-specific immune response

Systemic tumour-specific immune response

Death of distant cancer cells

T-VEC: HSV-1-derived oncolytic immunotherapy
Phase II Clinical Trial of a Granulocyte-Macrophage Colony-Stimulating Factor–Encoding, Second-Generation Oncolytic Herpesvirus in Patients With Unresectable Metastatic Melanoma

Phase III Study: OS by Stage

Stage IIIB/C, IV M1a

HR: 0.57 (95% CI: 0.40, 0.80)
Log rank: P < 0.001 (descriptive)

Stage IV M1b/c

HR: 1.07 (95% CI: 0.75, 1.52)
Log rank: P = 0.71 (descriptive)

**T-VEC + Ipilimumab Phase Ib**

- **Primary endpoint:** DLT
- **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, ulceration)

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**Stage IIIB/C–IV M1c melanoma**

Talimogene laherparepvec

up to 4 mL

$10^6$ pfu/mL Wk1 D1,

$10^8$ pfu/mL Wk4 D1 & then Q2W

+ ipilimumab 3 mg/kg

Q3W x4 starting Wk6 D1

N = 19

**Screening**

Screening 28 days prior to enrollment

**Enrollment**

**End of Treatment**

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

**Safety Follow-Up**

Up to 24 months after end of randomization


## Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 19)</th>
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<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Women</td>
<td>11 (58)</td>
</tr>
<tr>
<td><strong>Age, median (min, max) – years</strong></td>
<td>61 (29, 84)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14 (74)</td>
</tr>
<tr>
<td>1</td>
<td>5 (26)</td>
</tr>
<tr>
<td><strong>Disease stage, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>1 (5)</td>
</tr>
<tr>
<td>IIIC</td>
<td>3 (16)</td>
</tr>
<tr>
<td>IV M1a</td>
<td>4 (21)</td>
</tr>
<tr>
<td>IV M1b</td>
<td>5 (26)</td>
</tr>
<tr>
<td>IV M1c</td>
<td>6 (32)</td>
</tr>
<tr>
<td><strong>BRAF mutation status</strong></td>
<td></td>
</tr>
<tr>
<td>Mutant</td>
<td>11 (58)</td>
</tr>
<tr>
<td>Wild-type</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (11)</td>
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</table>
Maximal Change in Tumour Burden

Patients (N = 17)\(^b\)

<table>
<thead>
<tr>
<th>Percentage change from baseline</th>
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<tbody>
<tr>
<td>-100</td>
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Investigator-assessed responses
N = 18\(^a\)

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

\(^a\)Efficacy analysis set includes only the patients who received both T-VEC and ipilimumab.
\(^b\)One patient assessed to have PD by the investigator was not shown in the plot because tumour burden could not be accurately calculated based on missing post-baseline data.

Conclusions

• Immunotherapies have changed the treatment paradigm for a limited number of tumours (so far)

• Local/Loco-regional therapies will remain important in a large number of solid tumours

• There are sound reasons to combine immunotherapy with radiation therapy

• Oncolytic viral immunotherapy represents an exciting approach to inducing local immune activation with systemic effects

• Combining oncolytic immunotherapy with immune checkpoint blockade deserves active evaluation