Immunooncology-new possibilities in the fight against cancer: Clinical experience in melanoma

Christoph Höller
Dpt. Of Dermatology
Medical University of Vienna

Possible conflicts of interest:

• Advisor for Astra Zeneca
• Advisor and speaker honoraria for/from Amgen, BMS, MSD, Novartis and Roche
Question 1

Modern immunooncology-drugs block inhibitory receptors on immune cells.

Yes
No

Question 2

Modern immunotherapy is so great because it does not have any serious side-effects

Yes
No
Question 3

In the future immuno-oncology will be based on combinations of two or more drugs with PD-1 or PD-L1 inhibitors as the most frequent backbone drugs.

Yes
No

Immuno-Oncology trials of leading pharmaceutical companies
Why has Melanoma become the model tumor for IO-therapies?

Melanoma shows a high rate of spontaneous regression of primary lesions
Patients with unknown primary melanoma have a better prognosis


Immunotherapy of Melanoma

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Adoptive T-Cell Therapy</th>
<th>High-dose IL2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td>3-30%</td>
<td>49-72%</td>
</tr>
<tr>
<td>Overall Survival (months)</td>
<td>No overall survival benefit</td>
<td>NA (8-44% Complete Response)</td>
</tr>
<tr>
<td>Applicability</td>
<td>Peptide based good, DCs require specialized lab, HLA restriction</td>
<td>Low due to specialized technique and high cost</td>
</tr>
<tr>
<td>Current Status</td>
<td>experimental</td>
<td>experimental</td>
</tr>
</tbody>
</table>
Immunotherapy of Melanoma

Tumor-Vaccines

T-Cell Transfer

Breaks in the immune-response: “Checkpoints”

- Inhibitory checkpoints are important for limiting an inflammatory response
- Prevent tissue damage

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Blocking inhibitory check-points can start an immune response

Furthermore, this rejection resulted in immunity to a secondary exposure to tumor cells. These results suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effective immune responses against tumor cells.

**CTLA-4 counteracts early T-cell activation**

APC – antigen presenting cell  
TCR – T-cell receptor  
MHC – Major histocompatibility antigen  
CTLA-4 – Cytotoxic T-Lymphocyte Antigen 4  
B7 – Ligand for CD28  
CD28 – costimulatory receptor
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O’Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D.,
Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D.,
Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J. M. van den Eertwegh, M.D., Ph.D.,
Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D.,
Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D.,
Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D.,
Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

Ipilimumab – 3mg/kg
Long term survival is seen in up to 20% of patients on CTLA-4 inhibition.

CTLA-4 inhibition with Ipilimumab
Response during Therapy
Initial PD with delayed response and CR

Corresponding CT-Scans

Screening  Week 12  Week 16  CR for 7.5 years

Check point inhibitor induced T-Cell Activation

Efficacy: Anti-tumor response through T-cells infiltrating metastases

Safety: Immune related Adverse Events (IrAE) through T-cell activation
Side effects observed under treatment with checkpoint inhibitors

- Encephalitis
- Thyroiditis
- Fatigue
- Hypophysitis
- Pneumonitis
- Hepatitis
- Adrenal insufficiency
- Myositis, Myasthenia gravis
- Neuritis, Guillaine Barre Syndrome
- Pneumonitis
- Myositis, Myasthenia gravis
- Thrombopenia
- Nephritis
- Rash (including but not limited to Dermatomyositis, Bullous Pemphigoid, SJS/TEN, Psoriasis)

Stimulatory and inhibitory factors in the cancer immunity cycle
Blocking PD-1/PDL-1 (Programmed-death (Ligand) 1): the next break released

PD1 – Blockade: Mode of action

Recognition of tumour by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 upregulation on tumour

Priming and activation of T cells through MHC/antigen and CD28/B7 interactions with antigen-presenting cells
PD-1 Blockade is superior to chemotherapy: Nivolumab vs. DTIC

![Graph showing survival probabilities for Nivolumab (NVO) and DTIC over time, with median OS values and hazard ratios presented.]

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Blocking PD-1 is superior to blocking CTLA-4: Pembrolizumab vs. Ipilimumab

![Graph showing overall survival rates for Pembrolizumab (Pembro Q2W, Pembro Q3W) and Ipilimumab (Ipilimumab) over time, with event counts, hazard ratios, and confidence intervals presented.]

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Presented By Jacob Schachter at 2016 ASCO Annual Meeting
Lower rate of important immune-related adverse events with PD-1 inhibition

PD-1 Blockade vs. CTLA-4 Blockade: do we see the plateau move up?


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Hodi et al., presented at AACR 2016
Activity of Pembrolizumab across tumor types

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Talimogene Laherparepvec (TVEC)

Talimogene laherparepvec is an oncolytic herpes simplex virus type 1 (HSV-1) strain engineered to selectively replicate in tumor cells and to express human GM-CSF

- ICP34.5 deletion (neurovirulence factor)
- ICP47 deletion
- Insertion of GM-CSF
- Created in JS1 virus strain

Talimogene laherparepvec (JS1/ICP34.5-/-ICP47-/-hGM-CSF)

HSV: Herpes simplex virus; ICP: Infected cell protein; CMV: Cytomegalovirus promoter

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T-VEC – a HSV1 based oncolytic Immunotherapy

Exploratory subgroup analysis – OS in the Stage IIIB/C, IV M1a subpopulation*

Due to the exploratory nature of the analysis and based on the current evidence, it has not been established that T-VEC is associated with an effect on OS.
Where to from here?

- Adjuvant use
- Neo-adjuvant use
- New targets
- Combining therapies

Combining therapies - the new standard
Combined CTLA-4 & PD-1 Blockade
Checkmate-067

Randomized, double-blind, phase III study
to compare NIVO + IPI or NIVO alone to IPI alone

Unresectable or
Metastatic Melanoma
- Previously untreated
- 946 patients

Randomize
1:1

N=314

Stratify by:
- PD-L1 expression*
- BRAF status
- AJCC M stage

N=316

N=315

Treat until progression**
or unacceptable
toxicity.

*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

Nivo = Nivolumab = PD-1 blockierender Antikörper
Ipi = Ipilimumab = CTLA-4 blockierender Antikörper


Checkmate 067: Response Rates

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)*</td>
<td>57.6 (52.0–63.2)</td>
<td>43.7 (36.1–49.3)</td>
<td>19.0 (14.0–23.8)</td>
</tr>
<tr>
<td>Two-sided P value vs IPI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>--</td>
</tr>
<tr>
<td>Best overall response --- %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>12.1</td>
<td>9.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Partial response</td>
<td>45.5</td>
<td>33.9</td>
<td>16.8</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13.1</td>
<td>10.4</td>
<td>21.9</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>22.6</td>
<td>38.0</td>
<td>49.9</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.7</td>
<td>7.9</td>
<td>10.2</td>
</tr>
<tr>
<td>Median duration of response, months (95% CI)</td>
<td>NR (20.5–NR)</td>
<td>22.3 (20.7–NR)</td>
<td>14.4 (8.3–NR)</td>
</tr>
<tr>
<td>Ongoing response among responders, %</td>
<td>72.5</td>
<td>72.4</td>
<td>51.7</td>
</tr>
</tbody>
</table>

*By RECIST v1.1. NR = not reached.

Checkmate 067: Progression-free survival

Progression-Free Survival (Intent-to-Treat Population)

- **Median PFS** months (95% CI): NIVO + IPI (N=216) 11.5 (8.9-18.7), NIVO (N=313) 6.9 (4.3-8.8), IPI (N=311) 2.9 (2.6-3.4)
- **HR (95% CI) vs. IPI**: 0.42 (0.31-0.57), NIVO 0.55 (0.43-0.69), IPI -
- **HR (95% CI) vs. NIVO**: NIVO + IPI 0.67 (0.50-0.92), NIVO -

*Stratified log-rank P=0.0001 vs. IPI
**Expiratory endpoint

Number of patients at risk:
- NIVO + IPI: 314, 239, 156, 133, 126, 110, 49, 8, 0
- NIVO: 314, 157, 140, 127, 114, 104, 94, 46, 8, 0
- IPI: 313, 267, 196, 99, 46, 40, 26, 15, 3, 0

Database lock Nov 2015

Checkmate 067: Side effects

- Updated safety information with 9 additional months of follow-up were consistent with the initial report

<table>
<thead>
<tr>
<th>Event Type</th>
<th>NIVO + IPI (N=313)</th>
<th>NIVO (N=313)</th>
<th>IPI (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>Any Grade</td>
<td>Any Grade</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>Grade 3-4</td>
<td>Grade 3-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Treatment-related adverse event (AE)</td>
<td>95.6</td>
<td>56.5</td>
<td>84.0</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>38.7</td>
<td>30.7</td>
<td>10.5</td>
</tr>
<tr>
<td>Treatment-related death*</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)

Database lock Nov 2015
Pooled analysis of patients who discontinued (DC) therapy due to AEs on Nivolumab + Ipilimumab

**PFS per Investigator**

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPT DC (n = 175)</th>
<th>NIVO+IPI no DC (n = 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium PFS, months (95% CI)</td>
<td>18.7 (10.2, NA)</td>
<td>10.8 (5.9, 23.6)</td>
</tr>
<tr>
<td>HR (99.5% CI)</td>
<td>0.74 (0.56, 0.98), <em>P</em> &lt; 0.04</td>
<td></td>
</tr>
</tbody>
</table>

- Minimum follow-up of 18 months, median length of follow-up = 21.3 months

DC = patients who discontinued due to an AE; NA = not available; no DC = patients who did not discontinue due to an AE.

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**Blocking PD1 and PDL-1**

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Schaden et al. Presented at EADO 2016, Vienna
Indoleamine 2-3 Dioxygenase (IDO)

Poster presented at ESMO 2016

TVEC & Check-point Inhibitors
Melanoma Therapies 2017

Targeted therapies have an impact on immunity
Potential improvement through combinations of immunotherapy and targeted therapy

Current treatment options for BRAF<sup>V600</sup> mutated melanoma include:
- BRAF alone or BRAF/MEK inhibitors → rapid clinically significant responses usually with limited durability
- Immunotherapy → less frequent objective responses but clinically significant durability

**Hypothesis:** Combining anti-PD-L1 with BRAF and MEK inhibitors may result in higher frequency of long-lasting responses in patients with advanced BRAF<sup>V600</sup> mutated melanoma

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**PD-1/PD-L1 + B-RAF/MEK inhibition**

**Phase 1 study combining anti-PD-L1 (MEDI4736) with BRAF (dabrafenib) and/or MEK (trametinib) inhibitors in advanced melanoma**

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**Safety and Clinical Activity of Atezolizumab + Cobimetinib + Vemurafenib in BRAF V600 Mutant Metastatic Melanoma**

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**Pembrolizumab in Combination With Dabrafenib and Trametinib for BRAF-Mutant Advanced Melanoma: Phase 1b KEYNOTE-022 Study**

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Atezolizumab + Vemurafenib + Cobimetinib: Reduction in Tumor Burden

- 5 patients had a 100% reduction in tumor burden
  - 3 of these patients were considered PRs due to the lack of confirmatory scans or remaining target lesions
- Due to limited follow-up time at data cutoff, the median DOR and median PFS was not estimable

Atezolizumab + Vemurafenib + Cobimetinib: Reduction in Tumor Burden
“Landmark-OS” of current melanoma therapies

Important: The patient populations are not equivalent and data from different trials cannot be compared directly

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Question 1

Modern immunooncology-drugs block inhibitory receptors on immune cells.

Yes
No
Question 2

Modern immunotherapy is so great because it does not have any serious side-effects

Yes
No

Question 3

In the future immuno-oncology will be based on combinations of two or more drugs with PD-1 or PD-L1 inhibitors as the most frequent backbone drugs.

Yes
No
Take home messages

• Immuno-oncology drugs will become the principal therapy for the majority of malignant tumors with drugs targeting the PD-1/PD-L1 axis as the main group.

• Knowledge of the mode of action as well as the management of immune mediated adverse events is a prerequisite for the safe use of these drugs.

• Novel targets, use as adjuvant or neo-adjuvant therapy and most importantly combinations of IO- with IO- or other anti-tumor agents are the major strategies currently in clinical development.

Thank you for your attention!