Therapeutic Approaches to Metastatic Melanoma

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Objectives

• Introduction and Background
• Questions I ask myself in the clinic
• Future Directions
The Transformed Landscape of Melanoma Therapy: Approved Drugs Before 2011

• **Dacarbazine (DTIC), 1970s**
  - Response rate: <10% in unselected stage IV melanoma patients
  - No proven impact on survival

• **High-dose IL-2, 1998**
  - Response rate: 16% in highly selected stage IV melanoma patients
  - Durable responses: ~5%
  - Rarely used outside of specialized centers
  - Not used outside USA
The Pre-PD-1 Era: Survival for Metastatic Melanoma

Survival data from 42 Phase II trials with over 2,100 stage IV patients¹:
12 month OS: 25.5 %, median OS: 6.2 mos

Adapted from Korn 2008

New Paradigm in the Treatment of Cancer

Immunotherapy
Target: host

Targeted therapy
Target: tumor

Courtesy Axel Hauschild, MD
My Options in 2017

- Clinical Trials
- Immunotherapy
- Targeted therapy
In 2017
Immunotherapy for Cancer
= Checkpoint Inhibitors
T-Cell Activity Is Regulated By Immune Checkpoints to Limit Autoimmunity

Immune checkpoints, such as CTLA-4, PD-1, LAG-3, and TIM-3 function at different phases in the immune response to regulate the duration and level of the T-cell response.

CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed cell death protein 1; LAG-3 = lymphocyte activation gene 3; TIM-3 = T-cell immunoglobulin and mucin protein 3.

What is a “Checkpoint Inhibitor”? 
Checkpoint Inhibition

<table>
<thead>
<tr>
<th>Immune System</th>
<th>Cytokines</th>
<th>Antigens</th>
<th>Regulatory molecules (CTLA-4, PD-1)</th>
</tr>
</thead>
</table>
CTLA-4 Affects the Priming Phase of T-Cell Activation

- In healthy tissues, CTLA-4 is thought to function as a dominant “off switch” broadly shutting down T-cell activity to prevent autoimmunity.\(^1\)


CTLA-4 = cytotoxic T-lymphocyte antigen 4.
PD-1 affects Mainly the Effector Phase of T-cell Activity

Emerging research has identified PD-1 as an immune checkpoint pathway that tumor cells may exploit to evade immune surveillance.

Tumor cells may block immune responses via the PD-1 immune checkpoint pathway by expressing the dual PD-1 ligands, PD-L1 and PD-L2.


PD-1 = programmed cell death protein 1; TCR = T-cell receptor; MHC = major histocompatibility complex; PD-L1 = programmed cell death ligand 1; PD-L2 = programmed cell death ligand 2.

Overview

• Introduction and Background
• Questions I ask myself in the clinic
• Future Directions
Questions I Ask Myself in the Clinic

- What are my options for immunotherapy?
- Should I use PD-1 monotherapy or combination with CTLA-4?
- What are my options for targeted therapy?
- What should I choose between immunotherapy or targeted therapy for BRAF+ patients?
Immuno-Oncology Timeline

Clinical Developments

1882 | William Coley Mixed Toxins
1957 | Allogeneic BM transplantation
1967 | BCG Bladder Cancer
1973 | First trial with IL-2
1974 | First trial with IFNα Melanoma
1976 | First trial with IFNα Sarcoma
1983 | Non-myelosuppressive chemotherapy & adoptive T cell melanoma
1985 | TNFα Isolated limb perfusion melanoma & sarcoma
1991 | Interferons cloned
1992 | CTLA4 Identified
1995 | Discovery of TLRs
2002 | Imiquimod
2008 | 2009 | 2011-2015

Laboratory Discoveries

1970 | Zinkernagel & Doherty MHCI T cell recognition
1974 | Boon, Rosenberg Characterisation of Human Tumour Antigens
1983 | Sakaguchi Rediscovery of Tregs
1992 | First trial Adoptive T cells in cancer
1996 | 2002

2011
- Regulatory approvals
  - FDA: Brentuximab aCD30 HD&AnLC Lymphoma
  - FDA Ipi Melanoma

2014
- Regulatory approvals
  - FDA Nivo Melanoma
  - FDA Blinotumomab (BiTE) ALL
  - FDA Pembo Melanoma
  - Japan: Nivo melanoma

2015
- Regulatory approvals
  - FDA Nivo Renal Cancer
  - FDA Daratumumab (aCD38) Myeloma
  - FDA Tvec melanoma
  - FDA Nivo NonSQ NSCLC
  - FDA: pembrol NSCLC
  - FDA Ipi Nivo Combination Melanoma
  - FDA: Nivo NSCLC
  - Austr: Pembro: Melanoma

accc-iclio.org
Rationale for targeting checkpoint pathways as a therapeutic option: Cancer Immunotherapy
Checkpoint Inhibitors
Approved for Melanoma

• Anti CTLA-4 antibody: ipilimumab
• Anti PD-1 inhibitors: pembrolizumab, nivolumab
• Combination anti CTLA-4 and anti-PD-1 (ipilimumab and nivolumab)
Clinical Results with Ipilimumab (2\textsuperscript{nd} and 1\textsuperscript{st} line)

Ipilimumab vs vaccine and Ipi + DTIC vs DTIC

HR: 0.66 and 0.68
Pre-treated pts
Ipi 3 mg/kg +/- gp100


HR: 0.72
First line
Ipi 10 mg/kg + DTIC

Ipilimumab became the standard of care for advanced melanoma in 2011.

But can we do better?
# KEYNOTE-001: Melanoma Cohorts

This Pooled Analysis  
\[N = 655\]

<table>
<thead>
<tr>
<th>11</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
</table>
| Nonrandomized IPI Naive and IPI Treated  
2 Q3W, 10 Q3W, 10 Q2W  
\[N = 135\] | Randomized IPI Treated  
2 Q3W vs 10 Q3W  
\[N = 173\] | Randomized IPI Naive and Treated  
10 Q3W vs 10 Q2W  
\[N = 244\] |

- IPI-T defined as **unequivocal PD** within 6 mo of first IPI dose
- BRAF inhibitor **not required** for BRAF-mutant melanoma
- IPI-T defined as **confirmed PD** within 24 wk of last IPI dose; \(\geq 2\) IPI doses required
- BRAF inhibitor **required** for IPI-T, but not IPI-N, BRAF-mutant melanoma

Presented By Adil Daud at 2015 ASCO Annual Meeting
KN-001: Pembrolizumab All Pts (n=655)

**Progression-free Survival**
- Median (95% CI): 4.4 months (3.1-5.5)
- Rate at 12 months: 35%

**Overall Survival**
- Median (95% CI): 22.8 months (19.8-28.7)
- Rate at 12 months: 66%
- Rate at 24 months: 49%

**Change From Baseline**
- Median Change: -36%

**Response Duration**
- N = 681*
- CR, % (95% CI): 8 (6-11)
- ORR, % (95% CI): 33 (30-37)

**Exposure and AEs Summary**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>IPI-T (n = 342)</th>
<th>IPI-N (n = 313)</th>
<th>Total (N = 655)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of therapy, mean (range), weeks</td>
<td>31.9 (0.1-116.3)</td>
<td>35.1 (0.1-123.1)</td>
<td>33.4 (0.1-123.1)</td>
</tr>
<tr>
<td>No. of doses, median (range)</td>
<td>8 (1-59)</td>
<td>11 (1-58)</td>
<td>10 (1-59)</td>
</tr>
<tr>
<td>Any grade treatment related</td>
<td>82%</td>
<td>85%</td>
<td>83%</td>
</tr>
<tr>
<td>Grade 3-4 treatment related</td>
<td>14%</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Discontinuation due to treatment-related AE</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>


**KEYNOTE-001:** Pembrolizumab in Total Population (n=655)
KEYNOTE-001: Pembrolizumab in First Line (1L) Population (n=133)
KEYNOTE-002 (NCT01704287): Pembrolizumab post ipilimumab

Patients
- Advanced melanoma
- PD within 24 weeks after ≥2 IPI doses
- Previous BRAF or MEK inhibitor (if BRAF mutant)
- ECOG PS 0-1
- Resolution of IPI-related AEs
- No chronic systemic steroid therapy (>10 mg/day prednisone or equivalent)
- No active autoimmune disease

Stratification factors:
- ECOG PS (0 vs 1)
- LDH (normal vs elevated)
- BRAF status (mutant vs wild type)

Primary end points: PFS and OS
Secondary end points: ORR, duration of response, safety
Keynote 002: Progression-Free Survival
(Post ipilimumab, RECIST v1.1, Central Review)

Analysis cut-off date: May 12, 2014.

Ribas A, et al. SMR 2014
After ipilimumab, anti-PD-1 is better than chemotherapy.
Keynote-006 Pembro vs Ipilimumab

**Patients**
- Unresectable, stage III or IV melanoma
- ≤1 prior therapy, excluding anti-CTLA-4, PD-1, or PD-L1 agents
- Known **BRAF** status\(^b\)
- ECOG PS 0-1
- No active brain metastases
- No serious autoimmune disease

**Stratification factors:**
- ECOG PS (0 vs 1)
- Line of therapy (first vs second)
- PD-L1 status (positive\(^c\) vs negative)

**Treatments**
- **Pembrolizumab** 10 mg/kg IV Q2W
- **Pembrolizumab** 10 mg/kg IV Q3W
- **Ipilimumab** 3 mg/kg IV Q3W x 4 doses

**Primary end points:** PFS and OS
**Secondary end points:** ORR, duration of response, safety

\(^a\) Patients enrolled from 83 sites in 16 countries.

\(^b\) Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.

\(^c\) Defined as membranous PD-L1 expression in ≥1% of tumor cells as assessed by IHC using the 22C3 antibody.
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pembrolizumab Q2W (N = 279)</th>
<th>Pembrolizumab Q3W (N = 277)</th>
<th>Ipilimumab (N = 278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>61 (18-89)</td>
<td>63 (22-89)</td>
<td>62 (18-88)</td>
</tr>
<tr>
<td>Men</td>
<td>161 (58%)</td>
<td>174 (63%)</td>
<td>162 (58%)</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>196 (70%)</td>
<td>189 (68%)</td>
<td>188 (68%)</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>81 (29%)</td>
<td>98 (35%)</td>
<td>91 (33%)</td>
</tr>
<tr>
<td><strong>BRAF&lt;sup&gt;V600&lt;/sup&gt; mutant</strong></td>
<td>98 (35%)</td>
<td>97 (35%)</td>
<td>107 (38%)</td>
</tr>
<tr>
<td>PD-L1 positive&lt;sup&gt;a&lt;/sup&gt;</td>
<td>225 (81%)</td>
<td>221 (80%)</td>
<td>225 (81%)</td>
</tr>
<tr>
<td>M1c disease</td>
<td>179 (64%)</td>
<td>189 (68%)</td>
<td>178 (64%)</td>
</tr>
<tr>
<td>1 previous therapy</td>
<td>96 (34%)</td>
<td>92 (33%)</td>
<td>97 (35%)</td>
</tr>
</tbody>
</table>

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**Presented By Jacob Schachter at 2016 ASCO Annual Meeting**

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<sup>a</sup>Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody)

<sup>b</sup>1 patient had 2 lines of previous therapy

Final analysis data cutoff date: Dec 3, 2015.
Overall Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab Q2W</td>
<td>122</td>
<td>0.68 (0.53-0.87)</td>
<td>0.00085</td>
</tr>
<tr>
<td>Pembrolizumab Q3W</td>
<td>119</td>
<td>0.68 (0.53-0.86)</td>
<td>0.00083</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>142</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

No. at risk

| Pembrolizumab Q2W | 279 | 266 | 249 | 234 | 221 | 215 | 202 | 188 | 176 | 163 | 156 | 96  | 44  | 4   | 0   |
| Pembrolizumab Q3W | 277 | 266 | 251 | 238 | 215 | 201 | 184 | 179 | 174 | 164 | 156 | 93  | 43  | 1   | 0   |
| Ipilimumab     | 278 | 242 | 213 | 189 | 170 | 159 | 145 | 132 | 122 | 113 | 110 | 69  | 28  | 1   | 0   |

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Progression-Free Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro Q2W</td>
<td>181</td>
<td>0.61 (0.50-0.75)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Pembro Q3W</td>
<td>183</td>
<td>0.61 (0.50-0.75)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Ipi</td>
<td>202</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Assessed per RECIST v1.1 by independent central review. P values are nominal only because no statistical alpha was applied to the comparison at final analysis. Final analysis data cutoff date: Dec 3, 2015.

Presented By Jacob Schachter at 2016 ASCO Annual Meeting
## Tumor Response

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pembro Q2W N = 279</th>
<th>Pembro Q3W N = 277</th>
<th>Ipilimumab N = 278</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>37% (30%-42%)</td>
<td>36% (30%-42%)</td>
<td>13% (10%-18%)</td>
</tr>
<tr>
<td><strong>Best overall response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>33 (12%)</td>
<td>36 (13%)</td>
<td>14 (5%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>70 (25%)</td>
<td>64 (23%)</td>
<td>23 (8%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>30 (11%)</td>
<td>30 (11%)</td>
<td>43 (15%)</td>
</tr>
<tr>
<td>NonCR/NonPD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12 (4%)</td>
<td>14 (5%)</td>
<td>9 (3%)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>107 (38%)</td>
<td>115 (42%)</td>
<td>137 (49%)</td>
</tr>
<tr>
<td>Not evaluable&lt;sup&gt;c&lt;/sup&gt;</td>
<td>19 (7%)</td>
<td>15 (5%)</td>
<td>50 (18%)</td>
</tr>
<tr>
<td>No assessment&lt;sup&gt;d&lt;/sup&gt;</td>
<td>8 (3%)</td>
<td>3 (1%)</td>
<td>2 (&lt;1%)</td>
</tr>
</tbody>
</table>

*Presented at: ASCO Annual Meeting ‘16*

Virtual meeting: June 29 - July 2, 2020

Presented By Jacob Schachter at 2016 ASCO Annual Meeting

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<sup>a</sup> Assessed per RECIST v1.1 by independent central review.
<sup>b</sup> Patients without measurable disease per central review at baseline who did not experience CR or disease progression.
<sup>c</sup> Target lesion not captured by postbaseline scan or for whom a target lesion was surgically removed.
<sup>d</sup> No postbaseline scan performed or scan not able to be evaluated. Final analysis data cutoff date: Dec 3, 2015.
Duration of Response

Arm | Responders, n | Median (range), mo | Ongoing Response
--- | --- | --- | ---
Pembro Q2W | 103 | NR (1.8 to 22.8+) | 69 (67%)
Pembro Q3W | 100 | NR (2.0 to 22.8+) | 60 (60%)
Ipi | 37 | NR (1.1+ to 23.8+) | 23 (62%)

Presented By Jacob Schachter at 2016 ASCO Annual Meeting
Anti-PD-1 is better than ipilimumab front line and has less toxicity.
Questions I Ask Myself in the Clinic

• What are my options for immunotherapy?
• Should I use PD-1 monotherapy or combination with CTLA-4?
• What are my options for targeted therapy?
• What should I choose between immunotherapy or targeted therapy for BRAF+ patients?
CA209-067: Study Design

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

Unresectable or Metastatic Melanoma
- Previously untreated
- 948 patients

Randomize 1:1:1

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

N=314

NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W

N=316

NIVO 3 mg/kg Q2W + IPI-matched placebo

N=315

IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo

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.

Presented By Jedd Wolchok at 2015 ASCO Annual Meeting
Progression-Free Survival (Intent-to-Treat Population)

<table>
<thead>
<tr>
<th>Number of patients at risk:</th>
<th>Nivolumab + Ipilimumab</th>
<th>Nivolumab</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>314</td>
<td>219</td>
<td>174</td>
<td>156</td>
</tr>
<tr>
<td>316</td>
<td>177</td>
<td>148</td>
<td>127</td>
</tr>
<tr>
<td>315</td>
<td>137</td>
<td>78</td>
<td>58</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PFS per Investigator (months)</th>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>49%</td>
<td>42%</td>
<td>46%</td>
</tr>
<tr>
<td>6 months</td>
<td>42%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 months</td>
<td>39%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Presented By Jedd Wolchok at 2016 ASCO Annual Meeting
Checkmate 067: Progression-Free Survival
N= 945

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.5 (8.9–16.7)</td>
<td>6.9 (4.3–9.5)</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.74 (0.60–0.92)**</td>
<td>--</td>
</tr>
</tbody>
</table>

**Exploratory endpoint

Highly Censored – many pts still ongoing

Safety Summary

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

<table>
<thead>
<tr>
<th>Patients reporting event, %</th>
<th>NIVO+IPI (N=313)</th>
<th>NIVO (N=313)</th>
<th>IPI (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3-4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Treatment-related adverse event (AE)</td>
<td>95.8</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>

- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

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

Database lock Nov 2015

Presented By Jedd Wolchok at 2016 ASCO Annual Meeting
Checkmate 067: Safety
Onset Grade 3–4 Treatment-Related Select AEs

Toxicity Earlier
Longer Time to Resolution

Circles represent medians; bars signify ranges

Larkin J, et al. ECC 2015
Keynote 001 Pembrolizumab
PD-L1 Expression and Response

APS, Allred proportion score.
Analysis cut-off date: October 18, 2014.

ORR, RECIST v1.1

PD-L1 Negative
0% Staining
APS = 0

PD-L1 Positive
1-10% Staining
APS = 2

PD-L1 Positive
10-33% Staining
APS = 3

PD-L1 Positive
66-100% Staining
APS = 5

ORR, % (95% CI)

APS 0
n = 28

APS 1
n = 24

APS 2
n = 72

APS 3
n = 54

APS 4
n = 32

APS 5
n = 34

Negative
Positive

Daud A, et al. ASCO 2015
Phase III: Nivolumab versus DTIC
Overall Survival by PD-L1 Status

Atkinson V, et al. SMR 2015
Checkmate 067: PFS by PD-L1 Expression

**PD-L1 ≥5%***

N= 223

<table>
<thead>
<tr>
<th></th>
<th>mPFS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO + IPI</td>
<td>14.0</td>
<td>0.40</td>
</tr>
<tr>
<td>NIVO</td>
<td>14.0</td>
<td>0.40</td>
</tr>
<tr>
<td>IPI</td>
<td>3.9</td>
<td>--</td>
</tr>
</tbody>
</table>

**PD-L1 <5%***

N=620

<table>
<thead>
<tr>
<th></th>
<th>mPFS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO + IPI</td>
<td>11.2</td>
<td>0.42</td>
</tr>
<tr>
<td>NIVO</td>
<td>5.3</td>
<td>0.60</td>
</tr>
<tr>
<td>IPI</td>
<td>2.8</td>
<td>--</td>
</tr>
</tbody>
</table>

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100

Wolchok J, et al. ASCO 2015; Larkin et al. NEJM 2015
Checkmate 067: PFS by PD-L1 Expression (1%)

**PD-L1 ≥1%***

- **NIVO + IPI**: mPFS 12.4, HR 0.44
- **NIVO**: mPFS 12.4, HR 0.46
- **IPI**: mPFS 3.9, --

**PD-L1 <1%***

- **NIVO + IPI**: mPFS 11.2, HR 0.38
- **NIVO**: mPFS 2.8, HR 0.67

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

Wolchok J, et al. ASCO 2015; Larkin et al. NEJM 2015
Questions I Ask Myself in the Clinic

• What are my options for immunotherapy?
• Should I use PD-1 monotherapy or combination with CTLA-4?
• What are my options for targeted therapy?
• What should I choose between immunotherapy or targeted therapy for BRAF+ patients?
BRAF inhibitors
- dabrafenib
- vemurafenib
- encorafenib (LGX 818)

MEK inhibitors
- trametinib
- cobimetinib
- binimetinib (MEK162)
Vemurafenib Improves Overall Survival in Previously Untreated Stage IV BRAF V600 Mutant Melanoma

MAPK Pathway Targeted Therapy

BRAFi (dabrafenib)
- PFS HR, 0.37 vs DTIC\(^1\)
- Hyperproliferative skin AEs

BRAFi (vemurafenib)
- PFS HR, 0.38 vs DTIC\(^2\)
- Hyperproliferative skin AEs

MEKi (trametinib)
- PFS HR, 0.45 vs chemotherapy\(^3\)

BRAFi + MEKi ph III studies
- + trametinib (D + T)
  - PFS HR, 0.67 vs dabrafenib\(^4\)
  - OS HR, 0.71 vs dabrafenib\(^4\)
  - PFS HR, 0.56 vs vemurafenib\(^5\)
  - OS HR, 0.69 vs vemurafenib\(^5\)

Vemurafenib + cobimetinib
- PFS HR, 0.58 vs vemurafenib\(^6\)
- OS HR, 0.70 vs vemurafenib\(^6\)

Decreased hyperproliferative skin AEs\(^4,5,6\)

---

coBRIM: Overall Survival

Vem + Cobi
Med OS 22.3 mo (20.3-NE)

Vem + placebo
Med OS 17.4 mo (15.0-19.8)

HR 0.70 (0.55-0.90), p = 0.005

Atkinson V, et al. SMR 2015
Questions I Ask Myself in the Clinic

• What are my options for immunotherapy?
• Should I use PD-1 monotherapy or combination with CTLA-4?
• What are my options for targeted therapy?
• What should I choose between immunotherapy or targeted therapy for BRAF+ patients?
Phase III KEYNOTE-006: PFS in Prespecified Subgroups

Hazard Ratio

Overall
Male
Female
Age <65 y
Age ≥65 y
White race
US
Rest of world
ECOG PS 0
ECOG PS 1

First-line therapy
Second-line therapy
PD-L1 positive
PD-L1 negative
BRAF wild type
BRAF mutant, prior anti-BRAF
BRAF mutant, no prior anti-BRAF
No prior immunotherapy

0.1  1  10  0.1  1  10
Favors Pembro  Favors IPI  Favors Pembro  Favors IPI

Pembrolizumab Q2W vs ipilimumab
Pembrolizumab Q3W vs ipilimumab

Analysis cut-off date: September 3, 2014.
KEYNOTE-001: Phase I
RECIST Response (v1.1)

Total population n=581
ORR 33%
CR 8%

Median Change: 
-36%

IPI-T
IPI-N

Treatment naïve n=152
ORR 45%
CR 14%

Median Change: 
-54%

Analysis cut-off date: October 18, 2014; Median follow up 21 mo

Daud A, et al. ASCO 2015
# BRAF Inhibitors

<table>
<thead>
<tr>
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<th>Vemurafenib&lt;sup&gt;1&lt;/sup&gt;</th>
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COMBI-d: Normal LDH$^a$ and < 3 Disease Sites$^b$

**PFS**
- Dabrafenib + Trametinib (n = 76)
  - 3-y PFS, 38%
- Dabrafenib + Placebo (n = 96)
  - 3-y PFS, 15%

**OS**
- Dabrafenib + Trametinib (n = 76)
  - 2-y OS, 68%
  - 3-y OS, 62%
- Dabrafenib + Placebo (n = 96)
  - 2-y OS, 61%
  - 3-y OS, 45%

---

$^a$ Baseline LDH ≤ ULN; $^b$ Any organ at baseline with ≥ 1 metastasis could be counted as a single disease site; +, censored.

Presented by Keith Flaherty, ASCO 2016
EA6134: Ipi/Nivo to D/T vs D/T to Ipi/Nivo

ECOG PS
1. 0
2. 1

LDH
1. Normal
2. Elevated

RANDOMIZE

Arm 1:
Ipi 3/Nivo 1 mg/kg/ q 3wks x 4 +Maint Nivo

PD

D 150 BID / T 2 mg Qd

Arm 2:
D 150 BID / T 2 mg Qd

PD

Ipi 3/Nivo 1 mg/kg q 3wks x 4 +Maint Nivo

ECOG and SWOG protocol – Atkins, Chmielowski
Anticipated opening 6/2015

Presented By Michael Atkins at 2015 ASCO Annual Meeting

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How I Treat Metastatic Melanoma

Diagnosis of metastatic melanoma

BRAF mutation test

BRAF\textsuperscript{V600} mutation positive
- BRAF/MEK combo
  - Anti PD-1
  - Combo anti CTLA4/anti PD-1
  - Ipilimumab

BRAF\textsuperscript{V600} mutation negative
- Anti PD-1
- Combo anti CTLA4/anti PD-1
- Ipilimumab
Overview

- Introduction and Background
- Questions I ask myself in the clinic
- Future Directions
How Can Immunotherapy be Optimized and Improved?

- Addition of other checkpoint modulators
- BRAF/MEK Combination
- Reduce toxicity of combination therapy
  - Lower dose ipilimumab
- Can we “injure” the tumor to render it more vulnerable to systemic immune attack?
  - Oncolytic therapy
  - Radiation/Chemotherapy
T-Cell Immune Checkpoints

Presented By Scott Gettinger at 2014 ASCO Annual Meeting

IDO and T Cells

IDO
Tryptophan
Kynurenine
Switch to T reg

TCR
Macrophages
APC

T reg
FOXP3+

PD-1
CTLA-4
GITR

IL2
CD28

CD8 T cells apoptosis

↑CD8

↓T reg
KEYNOTE 252//ECHO 501: Trial Design

Subjects with unresectable or metastatic MEL have baseline biopsy to identify PD-L1 status

Stratified by PD-L1 expression status, BRAF mutation status

Randomization

Pembrolizumab 200 mg + Epacadostat

Survival Follow up*

Pembrolizumab 200 mg + Placebo

*Survival follow up will include post treatment imaging for subjects who discontinue treatment for reasons other than PD until documented PD, death, withdraw consent, or start of a new anti-cancer treatment.
Pembrolizumab in Combination With Dabrafenib and Trametinib for BRAF-Mutant Advanced Melanoma: Phase 1/2 KEYNOTE-022 Study

Figure 2. Part 2: dose expansion.

- Dabrafenib 150 mg BID
- Trametinib 2 mg QD
- Pembrolizumab 2 mg/kg Q3W

BID = twice daily; Q3W = once every 3 weeks; QD = once daily.
KEYNOTE 022: Pembrolizumab in Combination With Dabrafenib and Trametinib

Longitudinal Change From Baseline in Tumor

Maximum Percentage Change From Baseline in Tumor

aAssessed in all patients who received ≥1 dose of study treatment (n = 13). bOnly patients with measurable disease per RECIST v1.1 by investigator review at baseline and ≥1 post-baseline tumor assessment were included (n = 13). 4In patients with confirmed response only. Data cutoff date

KEYNOTE-029: Study Design

Dose Run-In (Part 1A)

Patients
- Advanced melanoma, any number of prior therapies OR
- Advanced clear cell RCC, ≥1 prior therapy
- No prior anti-CTLA4 or anti-PD1/PDL1
- ECOG PS 0 or 1

Pembro 2 mg/kg Q3W up to 24 months + Ipi 1 mg/kg Q3W x 4 doses

Tolerable Based on DLT Rate

Yes

No

Stop development of pembro + ipi

Dose Expansion (Part 1B)

Patients
- Advanced melanoma
- Any number of prior therapies
- No prior anti-CTLA4 or anti-PD1/PDL1
- ECOG PS 0 or 1

Primary end point:
- Safety

Secondary end points:
- ORR, DOR, and PFS (per RECIST v1.1) and OS

ClinicalTrials.gov identifier NCT02089685.
Immune-Mediated AEs: Incidence

Any: 58%
Grade 3-4: 25%

Presented By Georgina Long at 2016 ASCO Annual Meeting
Best Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)

81%  

ORR = 57%

Median change:  
-54.5%

Presented By Georgina Long at 2016 ASCO Annual Meeting
Intralesional Oncolytic Therapy
“Injuring the Tumor”

- TVEC (FDA approved)
- PV-10
- IL-12
- HF-10
- Cavatak
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

N = 330
• Pembrolizumab 200mg IV Q3W

1:1

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

Pembrolizumab 200mg IV Q3W

T-VEC placebo intralesional

Pembrolizumab 200mg IV Q3W

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

T-VEC: talimogene laherparepvec

30 (+7) days after end of treatment
Summary & Conclusions

• Checkpoint inhibitors and MAPK targeted agents have revolutionized the treatment of advanced melanoma.
• First line immunotherapy in the US is either anti-PD-1 monotherapy or combination with anti-CTLA4.
• BRAF+ patients may receive targeted therapy or immunotherapy.
• Future directions will exploit adding new agents and lowering toxicity of combinations
Questions?
Thank you for participating in the ICLIO Webinar. Presentation slides and archived recording will be available at accc-icl.io.org