Update on Immunotherapy in Advanced Melanoma

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Outline

• Adjuvant Therapy
• Combination Immunotherapy
• Single Agent Immunotherapy
• Overview of Adverse Events
IPI + NIVO vs IPI vs NIVO

CA209-067: Study Design

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

Randomize 1:1:1

N=314

Unresectable or Metastatic Melanoma

- Previously untreated
- 945 patients

Stratify by:

- PD-L1 expression
- BRAF status
- AJCC M stage

N=316

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

Treating until progression** or unacceptable toxicity

N=315

NIVO 3 mg/kg Q2W + IPI-matched placebo

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

*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.

Adjuvant therapy

DISCLOSURE: My slides are already behind the times – Data I can not disclose will change scope of adjuvant therapy. Be on the look out for presentations and publications after ESMO September 2017.
Adjuvant Interferon – May it rest in peace...

You are seeing a 75-year-old male with recently recurrent Stage III melanoma from a 4 mm primary of the RLE in 2013. One SNL was positive and no further disease was found on CLND. In 2015, he recurred in R groin with a palpable LN and repeat dissection demonstrated additional 2/7 lymph nodes involved.

You have recommended adjuvant ipilimumab. Which is the best treatment plan for this therapy?

a. 3 mg/kg q3weeks four doses

b. 10 mg/kg q3weeks for four doses

c. 3 mg/kg q3weeks, followed by maintenance of 3mg/kg q3months for three years

d. 10 mg/kg q3weeks, followed by maintenance of 3mg/kg q3months for three years

e. 10 mg/kg q3weeks, followed by maintenance of 10mg/kg q3months for three years

f. None of the above
CTLA4 Blockade
Taking the Brakes Off T Cell Activation

Adjuvant Ipilimumab

- Ipilimumab 10mg/kg
- Compared to placebo
  - 475 patients
    - IIIA 20%
    - IIIB 38%
    - IIIC 41%
- 53% discontinuation rate for AEs
- 5 year follow up data

Primary Endpoint: Recurrence-free Survival (IRC)

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>234/475</td>
<td>294/476</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>0.75 (0.64–0.90)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value*</td>
<td>0.0013</td>
<td></td>
</tr>
<tr>
<td>2-Year RFS rate (%)</td>
<td>51.5</td>
<td>43.8</td>
</tr>
<tr>
<td>3-Year RFS rate (%)**</td>
<td>46.5</td>
<td>34.8</td>
</tr>
</tbody>
</table>

*Stratified by stage. **Data are not yet mature.

### Immune-Related Adverse Events

**Table 3. Immune-Related Adverse Events.**

<table>
<thead>
<tr>
<th>Event</th>
<th>Ipilimumab (N = 471)</th>
<th>Placebo (N = 474)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Any immune-related adverse event</td>
<td>426 (90.4)</td>
<td>169 (35.9)</td>
</tr>
<tr>
<td>Any dermatologic event</td>
<td>298 (63.3)</td>
<td>20 (4.2)</td>
</tr>
<tr>
<td>Rash</td>
<td>161 (34.2)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Any gastrointestinal event†</td>
<td>217 (46.1)</td>
<td>70 (14.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>194 (41.2)</td>
<td>46 (9.8)</td>
</tr>
<tr>
<td>Colitis</td>
<td>73 (15.5)</td>
<td>32 (6.8)</td>
</tr>
<tr>
<td>Any endocrine-system event</td>
<td>178 (37.8)</td>
<td>34 (7.2)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>77 (16.3)</td>
<td>20 (4.2)</td>
</tr>
<tr>
<td>Any hepatic event</td>
<td>115 (24.4)</td>
<td>38 (8.1)</td>
</tr>
<tr>
<td>Increase in liver-enzyme levels</td>
<td>83 (17.6)</td>
<td>14 (3.0)</td>
</tr>
<tr>
<td>Any neurologic event</td>
<td>21 (4.5)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Other‡</td>
<td>111 (23.6)</td>
<td>34 (7.2)</td>
</tr>
</tbody>
</table>

* The safety analysis included all the patients who underwent randomization and received at least one dose of ipilimumab or placebo (945 patients). Immune-related adverse events that occurred in at least 10% of the patients are reported. Patients may have had more than one event. In the ipilimumab group, 5 patients died because of drug-related adverse events; 3 patients died from colitis (2 patients with gastrointestinal perforation), 1 from myocarditis, and 1 from multorgan failure associated with the Guillain–Barré syndrome.

† Gastrointestinal perforation occurred in seven patients (1.5%) in the ipilimumab group (all such events were considered to be related to ipilimumab) and in three patients (0.6%) in the placebo group (none of these events were considered to be related to placebo).

‡ In the ipilimumab group, 26 patients had a grade 3 or 4 lipase level, 4 had a grade 3 or 4 immune-system disorder (hypersensitivity, autoimmune disorder, anaphylactoid reaction, or drug hypersensitivity), 4 had grade 3 lung infiltration, pneumonitis, or interstitial lung disease, 1 had arthritis, and 1 had uveitis.
Ipilimumab 3mg/kg versus 10mg/g E1609*

- 1670 patients: 511 ipi10, 636 HDI, 523 ipi3

- No difference in 3-year RFS
  - IPI10 56%
  - IPI3 54%

- Grade 3-5 AEs
  - IPI10 57%
  - IPI3 36.4%

*Unplanned analysis

Should IPI replace Interferon for adjuvant therapy?

• Yes from me but others differ in opinion…S1404 trial: 40% oncologist using interferon

• Questions
  • Is ipilimumab now better than treatment at recurrence?
  • Is the risk worth the benefit?

• How do we interpret E1609 IPI 3mg/kg vs IPI 10mg/kg?

• Future trials
  • How will PD-1 antibodies fair?
    • Nivolumab vs Ipilimumab 10mg/kg (accrued, DATA AVAILABLE AT ESMO Sept 2017)
    • S1404: SOC (IPI or IFN) vs Pembrolizumab (Accrual ends 8/01/2017)
    • CA206-915 Nivo vs IPI vs Nivo + IPI (Just opened in US)
Bristol-Myers Squibb Press Release

Phase 3 Study Evaluating the Safety and Efficacy of Adjuvant Opdivo in Resected High-Risk Melanoma Patients Meets Primary Endpoint

Opdivo (nivolumab) demonstrates superior recurrence-free survival versus Yervoy (ipilimumab) in Adjuvant Setting in CheckMate -238
Immunotherapy for stage IV melanoma
Reminder of the Past

• 1 year overall survival 25%
• 2 year overall survival 10%

PROGRESSION-FREE SURVIVAL ON COOPERATIVE GROUP PHASE II TRIALS BY DECADE AND PRETREATMENT ALLOWED
Case 1

• 40 year old Caucasian female with a history of a intermediate risk melanoma 2 years ago presents with increasing severe back pain. Imaging demonstrates bulky retroperitoneal lymphadenopathy as well as axillary, supraclavicular lymphadneopathy. Biopsy confirms metastatic melanoma and is found to harbor the BRAF V600E mutation
What are your systemic treatment options?

• Ipilimumab + nivolumab, followed by maintenance nivo
• Nivolumab alone
• Pembrolizumab alone
• Dabrafenib plus Trametinib
• Vemurafenib plus Cobimetinib
• HD-IL2
• Chemotherapy
# Metastatic disease: 1st line therapy

- **Goals:** survival, palliation, quality of life

<table>
<thead>
<tr>
<th></th>
<th>Immune Therapy (CTLA-4/PD1 blockade, IL-2, trials)</th>
<th>Targeted Therapy (BRAF, MEK, trials)</th>
<th>Cytotoxic Chemotherapy (dacarbazine, trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance of response</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Predictive marker</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Response duration</td>
<td>Long</td>
<td>Short**</td>
<td>Short</td>
</tr>
<tr>
<td>Time to response</td>
<td>Long*</td>
<td>Short</td>
<td>Short</td>
</tr>
<tr>
<td>Toxicity (potential)</td>
<td>Moderate/High</td>
<td>Moderate/Low</td>
<td>Moderate/Low</td>
</tr>
<tr>
<td>Survival benefit</td>
<td>Yes (phase III trial)</td>
<td>Yes (phase III trial)</td>
<td>No</td>
</tr>
</tbody>
</table>

- *Rapid responses seen in CTLA4/PD1 combinations
- **20-30% 5 year survival noted on DT trials
Combination Immunotherapy
Ipilimumab + Nivolumab
Unresectable or Metastatic Melanoma
• Previously untreated
• 945 patients

CheckMate 067: Study Design

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

N=314
Stratify by:
• BRAF status
• AJCC M stage
• Tumor PD-L1 expression <5% vs ≥5%*

N=316
NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W

N=315
IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo

Treat until progression or unacceptable toxicity

*The study was not powered for a comparison between NIVO and NIVO+IPI

Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

Checkmate 067

- 945 patients
- IPI/NIVO NIVO vs vs IPI
- mPFS 11.5 v 6.9 v 2.9m
- Grade 3,4 AEs: 55% v 16.3% vs 27.3%
- PDL-1 status
  - Pos: ipi/nivo = nivo alone (14 m)
  - Neg: 11.2m vs 5.3

## PFS Checkmate 067

<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>Median PFS, mo (95% CI)</td>
<td>11.7 (8.9–21.9)</td>
<td>6.9 (4.3–9.5)</td>
<td>2.9 (2.8–3.2)</td>
</tr>
<tr>
<td>HR (95% CI) vs. IPI</td>
<td>0.42 (0.34–0.51)</td>
<td>0.54 (0.45–0.66)</td>
<td>--</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.76 (0.62–0.94)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>


Database lock: Sept 13, 2016, minimum f/u of 28 months
Checkmate 067

- **Nivo**
  - RR 43.7%
  - Tumor change -34.5%
  - CR 8.9%

- **IPI/NIVO**
  - RR 57.6%
  - Tumor Change -51.9%
  - CR 11.5%

- **IPI alone**
  - IPI 19.0%
  - Tumor Change – 5.9%
  - CR 2.2%

OS Checkmate 067

<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>Median OS, mo (95% CI)</td>
<td>NR (29.1–NR)</td>
<td>20.0 (17.1–24.6)</td>
<td></td>
</tr>
<tr>
<td>HR (98% CI) vs. IPI</td>
<td>0.55 (0.42–0.72)*</td>
<td>0.63 (0.48–0.81)*</td>
<td>--</td>
</tr>
</tbody>
</table>
| HR (95% CI) vs. NIVO | 0.88 (0.69–1.12) | -- | **P<0.0001**

What about QOL? No meaningful difference seen in Checkmate 067

## Summary Checkmate 067

<table>
<thead>
<tr>
<th></th>
<th>IPI/NIVO</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year OS (%)</td>
<td>• 64%</td>
<td>• 59%</td>
<td>• 45</td>
</tr>
<tr>
<td>mPFS (m)</td>
<td>• 11.5</td>
<td>• 6.9</td>
<td>• 2.9</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>• 57.6%</td>
<td>• 43.7</td>
<td>• 19</td>
</tr>
<tr>
<td>CR (%)</td>
<td>• 11.5</td>
<td>• 8.9</td>
<td>• 2.2</td>
</tr>
<tr>
<td>Gr3+ AEs (%)</td>
<td>• 55%</td>
<td>• 16</td>
<td>• 27.3</td>
</tr>
</tbody>
</table>

- 12% risk of death reduction of IPI/NIVO vs NIVO
- Is it worth the toxicity?
- Is CR rate important?
- Will the OS hold up at 5 or 10 years?

You elect treat a patient with the combination ipilimumab and nivolumab. Which of the following is false about this treatment?

A. Responses can be rapid and deep
B. Overall response rate is 50%, but in patients with autoimmune toxicity the RR is 67%
C. If a patient experiences an autoimmune toxicity, it is likely he or she will experience other toxicities
D. Delayed responses are never seen
Single Agent Immunotherapy
Phase I Study of Nivolumab

- Melanoma Responses
  - 26 of 94 patients
  - At 3mg/kg 7/17 41% RR

- PDL-1 staining
  - All tumor types
  - Positive 9/25
  - Negative 0/17
  - Results have not held true in other studies
    - PDL1 positive respond at a higher rate, but PDL1 negative can respond

In nivolumab-treated pts:
  - 1-yr OS 62%
  - 2-year OS 43%

Topalian et al JCO 2014

Phase III
Nivolumab vs chemotherapy

Phase III
pembrolizumab vs ipilimumab

Decrease in the risk of death 58% vs chemotherapy
And 31 to 37% vs ipilimumab

Update of the phase III Keynote 006 pembrolizumab vs ipilimumumab
Median Follow-Up, 33.9 Mo

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>Median, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>278</td>
<td>0.70 (0.58-0.86)</td>
<td>32.3 (24.5-NR)</td>
</tr>
<tr>
<td>Ipili</td>
<td>155</td>
<td>—</td>
<td>15.9 (13.3-22.0)</td>
</tr>
</tbody>
</table>

Overall Survival, %

Progression-Free Survival, %

## Tumor Response (irRC, investigator)

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab (N = 556)</th>
<th>Ipilimumab (N = 278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>42 (38-46)</td>
<td>16 (12-21)</td>
</tr>
<tr>
<td>Best overall response, % (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>13 (11-16)</td>
<td>3 (1-6)</td>
</tr>
<tr>
<td>PR</td>
<td>29 (25-33)</td>
<td>14 (10-18)</td>
</tr>
<tr>
<td>SD</td>
<td>21 (18-25)</td>
<td>25 (20 -31)</td>
</tr>
<tr>
<td>PD</td>
<td>29 (26-33)</td>
<td>39 (33-45)</td>
</tr>
</tbody>
</table>

Robert et al, ASCO 2017

Complete Responders Who Stopped Pembrolizumab for Observation in Keynote 001 (N = 61)

- Median time on treatment: 23 mo (range, 8-44)
- Median time off treatment: 10 mo

Disposition of Patients Who Completed Protocol-Specified Time on Pembrolizumab (median follow-up, 9 months)

556 patients received pembrolizumab

104 (19%) completed pembrolizumab

24 (23%) CR
- 23 ongoing responses
- 1 PD\textsuperscript{b}
  - 1 received second course of pembrolizumab

68 (65%) PR
- 64 ongoing responses
- 4 PD\textsuperscript{b}
  - 3 received second course of pembrolizumab

12 (12%) SD
- 10 ongoing responses
- 2 deaths\textsuperscript{b,c}

Survival Rate Ipi + gp100
N=403
1 year 44%
2 year 22%

Ipi + pbo
N=137
1 year 46%
2 year 24%

gp100 + pbo
N=136
1 year 25%
2 year 14%

Remaining Question

• Why every 3 weeks vs. 2 weeks?
• Is there a difference between nivo and pembro?
• How much treatment does a patient need?
• What is the right sequence and combination of treatments?

Immune-related Adverse events
Immunotherapy adverse events

Autoimmune Toxicity

Treatment-Related Select AEs Reported in ≥10% of Patients

<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>Skin</td>
<td>59.1</td>
<td>5.8</td>
<td>41.9</td>
</tr>
<tr>
<td>Pruritus</td>
<td>33.2</td>
<td>1.9</td>
<td>18.8</td>
</tr>
<tr>
<td>Rash</td>
<td>28.9</td>
<td>2.9</td>
<td>21.7</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>11.8</td>
<td>1.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>46.3</td>
<td>14.7</td>
<td>19.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44.1</td>
<td>9.3</td>
<td>19.2</td>
</tr>
<tr>
<td>Colitis</td>
<td>11.8</td>
<td>7.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Hepatic</td>
<td>30.0</td>
<td>10.0</td>
<td>6.4</td>
</tr>
<tr>
<td>Increase in ALT</td>
<td>17.6</td>
<td>8.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Increase in AST</td>
<td>15.3</td>
<td>6.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Endocrine</td>
<td>30.0</td>
<td>4.8</td>
<td>14.4</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15.0</td>
<td>0.3</td>
<td>8.6</td>
</tr>
</tbody>
</table>

- With immune modulatory agents, resolution rates for the majority of grade 3–4 select AEs were: 85-100% for NIVO + IPI, 50-100% for NIVO, and 83-100% for IPI
- As observed in prior studies, most endocrine events did not resolve
TOXCITY PEARLS

• Patient education for early recognition of irAEs
• Nonspecific complaints might reflect endocrine (pituitary) toxicity
• Corticosteroids are effective – do not taper too quickly
• Consider Infliximab or MMF in refractory cases
• Combination therapies are showing higher toxicity rates, but similar types of toxicities are seen
• Watch out for multiple IRAEs in one patient, especially on combination (CTLA4/PD1) therapy
• Quicker onset of IRAEs in combination treatment
• Consider prophylaxis if prolonged steroids are required
Immunotherapy in Melanoma

FACTS
• PD-1 antibodies as single agents should be first-line over CTLA-4 antibodies
• PD-L1 testing is not ready for prime time
• Long term survival is seen with immunotherapy
• Alternative agents such as HD-IL2 and chemotherapy should no longer be front-line

QUESTIONS
• Should immunotherapy be first-line over BRAF inhibitors in BRAF-mutant melanoma?
• Is combination ipilimumab/nivolumab preferred over single agent PD-1 antibody?
• How long to continue PD-1 antibody treatment in responders?
• Pseudoprogression or real progression?
• Where does T-VEC fit in?
What will be the next big story in melanoma?

PD-1 Pathway Base

- IDO inhibitor
- MEK inhibitors
- BRAF/MEK inhibitors
- Intrallesional Therapies
- HD-IL2
- STAT-3 Inhibitors
- LAG-3 antibody
- TIM-3 antibody