Clinical Management of the Immunotherapy Patient

ESMO Symposium on Immuno-Oncology
Geneva, Switzerland November 22\textsuperscript{nd}, 2014

Jeffrey Weber M.D. Ph.D.
Moffitt Cancer Center
Disclosures

• I have accepted honoraria for advisory boards and DSMBs from BMS, Merck, GSK and Genentech of less than $10,000 dollars per year

• Moffitt, but not me personally, receives funds from BMS, Merck, GSK and Genentech for the performance of trials

• I am not a member of any speaker’s bureau

• I have no other relevant disclosures
One approved agent for metastatic melanoma, high dose interleukin-2, and one for high risk resected melanoma, IFN-alpha; no phase III data for stage IV pts

Very poor penetration of the use of IL-2 due to toxicity and complexity

Not more than 50% use of interferon, again due to toxicity and perception of modest survival benefit
Immuno-Oncology: 2014

- Six drugs approved or about to be approved for melanoma
- All of the new drugs approved since 2011 are supported by data derived from phase III randomized trials
- First positive adjuvant data since IFN
- Combination data look promising enough to talk of “cure”
- Adoptive cell therapy has come into its own
Immunotherapy: 2014

• IL-2 was active in renal cell cancer, but competed with six other drugs and has not been commonly used outside a few centers.

• In 2014, PD-1/PD-L1 antibodies are active in renal cell, non-small cell lung, bladder, head and neck and ovarian cancer as well as non-Hodgkins lymphoma.

• The unique side effect profile of immuno-oncology drugs and their unusual kinetics of response will challenge oncologists.
Immunotherapy: Myth or Fact?

- One should take advantage of the “tail on the curve” and use immunotherapy as opposed to targeted therapy as front line treatment in melanoma to achieve prolonged survival and a “cure”
  - **Pro:** 177 ipilimumab patients treated at Surgery Branch NCI 2003-2009; 10% CR rate, all but one in remission up to ten years later\(^1\)
  - **Pro:** in the BMS EAP program, 20% plateau of OS from years 3-5 on over 3000 patients\(^2\)

Immunotherapy: Myth or Fact?

– Pro: At UCLA and MD Anderson, tremelimumab treated patients are alive 7-12 years later\(^1\)
– Con: The 20% OS tail with IPI is only 10% above the expected figure with chemotherapy
– Con: In the dabrafenib + trametinib phase II trial, median OS was 25 months, with patients on treatment > 4 years in remission\(^2\)
– Con: In the vemurafenib + cobemeticsinib phase III trial, estimated median OS is greater than 2 years\(^3\), compared to 12 mos for IPI, 20 mos for nivolumab

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Immunotherapy: Myth or Fact?

• PD-L1 staining is a predictive marker useful for choosing patients for PD-1/PD-L1 blockade
  • There appears to be an association between ORR and tumor PD-L1 positivity by IHC in most trials
  • Patients may still respond even if tumor PD-L1 staining is negative
  • Equivocal data on association of PD-L1 staining with overall survival.
## PD-L1 expression and response rate

<table>
<thead>
<tr>
<th>Study Description</th>
<th>N</th>
<th>PDL1 Positive</th>
<th>PDL1 Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (Topalian, NEJM, 2012)</td>
<td>42</td>
<td>9/25 (36%)</td>
<td>0/17 (0%)</td>
</tr>
<tr>
<td>Nivolumab (Weber #9011)</td>
<td>44</td>
<td>8/12 (67%)</td>
<td>6/32 (19%)</td>
</tr>
<tr>
<td>MPDL3280A (Hamid #9010)</td>
<td>30</td>
<td>4/15 (27%)</td>
<td>3/15 (20%)</td>
</tr>
<tr>
<td>Nivolumab/Ipilimumab (Callahan #3003)</td>
<td>27</td>
<td>4/10 (40%)</td>
<td>8/17 (47%)</td>
</tr>
<tr>
<td>Nivolumab (Grosso #3016)</td>
<td>34</td>
<td>7/16 (44%)</td>
<td>3/18 (17%)</td>
</tr>
</tbody>
</table>
Target Lesion Tumor Burden Change by PD-L1 Status: Nivolumab vs chemo

### Maximum Change from Baseline in Target Lesion (%)

**Nivolumab**

- **PD-L1+**
  - ORR* 9%

- **PD-L1-**
  - ORR* 13%

**ICC**

- **PD-L1+**
  - ORR* 9%

- **PD-L1-**
  - ORR* 13%

*ORR among treated patients in the ORR population; D’Angelo, S et al SMR 2014
Efficacy Based on Tumor PD-L1 Expression (Central Review, RECIST v1.1)

- Overall Response Rate:
  - Unselected: 40
  - PD-L1+: 49
  - PD-L1−: 13
  - $P = 0.0007^a$

- Progression-Free Survival (PFS, %):
  - PD-L1+: 100
  - PD-L1−: 80
  - $P = 0.0051$

- Overall Survival (OS, %):
  - PD-L1+: 100
  - PD-L1−: 80
  - $P = 0.3165$

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*a*1-sided $P$ values calculated by logistic regression, adjusting for dose/schedule.

PD-L1 positivity defined as staining in ≥1% of tumor cells.

Analysis cut-off date: 18 October 2013.

Daud A et al. Presented at: 2014 Annual AACR Meeting; April 5-9, 2014; San Diego, CA.

Presented by: Richard Kefford, ASCO 2014
Overall survival based on tumor PD-L1 expression by IHC does appear to favor PD-L1+ tumors.
What sets immunotherapy apart from other therapies?

- Late responses and unconventional kinetics of response
- Immune related adverse events and unusual late patterns of toxicity
- Law of unforeseen consequences
- Long duration of remissions
- Ability to re-respond to therapy after progression
UNIQUE KINETICS OF RESPONSE WITH I-O AGENTS
Patients Treated Beyond RECIST v1.1 progression; nivolumab vs DTIC

Nivolumab Group, n = 54

Dacarbazine Group, n = 49

Change from Baseline in Target Lesion Size (%)

Time Since Treatment Initiation (Weeks)

Patients with RECIST v1.1 progression, but achieved or maintained a ≥ 30% reduction in the target lesion tumor burden

- Nivolumab = 17 (8% of all 210 randomized)
- Dacarbazine = 8 (4% of all 208 randomized)

Robert, C et al NEJM 2014
Patients Treated Beyond RECIST v1.1 progression; pembrolizumab

• 4% of pembrolizumab patients experienced regression after RECIST progression.

Ribas, A et al SMR 2014
6 of 192 patients (3.1%) showed ≥25% increase in tumor burden at a time point beyond week 12 followed by reduction at a later assessment.
Early Pseudoprogression: 56-Year-Old Woman With Advanced Melanoma Treated With MK-3475

Case courtesy of C. Robert, Gustave Roussy, Villejuif, France.

Presented by: F. Stephen Hodi ESMO 2014
irRC criteria with pembrolizumab?

- There appears to be a clear association of OS with the amended irRC definition of SD and PR/CR

Ribas, A et al SMR 2014
Immune-related Response Criteria (irRC) Identifies Survivors with Otherwise mWHO PD with ipilimumab

Pooled data from Phase 2 studies CA 184-008: ipilimumab monotherapy 10 mg/kg

Hodi S et al ASCO 2008
Unusual kinetics of response after XRT: The “abscopal effect” with ipilimumab

Postow, M et al NEJM 2012
LONG DURATION OF RESPONSES
Time and Duration of Response by Central Review, RECIST 1.1: nivolumab vs. chemo

36/38 (95%) of nivolumab responses ongoing

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median time to response, (range), mo</th>
<th>Median duration of response, (range), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>2.1 (1.6, 7.4)</td>
<td>NR (1.4+, 10.0+)</td>
</tr>
<tr>
<td>ICC</td>
<td>3.5 (2.1, 6.1)</td>
<td>3.6 (1.3+, 3.5)</td>
</tr>
</tbody>
</table>

Data report date: 30 Apr 2014
“+” denotes patients who are censored (still in response);
NR = not reached

Weber, J et al ESMO 2014
## Time to, and Durability of Response: Nivolumab vs DTIC

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to response,</td>
<td>2.1 (1.6–7.6)</td>
<td>2.1 (1.8–3.6)</td>
</tr>
<tr>
<td>median (range), <em>mo</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of response,</td>
<td>NR</td>
<td>6.0 (3.0–NR)</td>
</tr>
<tr>
<td>median (range), <em>mo</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing response</td>
<td>72/84 (86%)</td>
<td>15/29 (52%)</td>
</tr>
<tr>
<td>among responders*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*At the time of the last follow-up; NR=Not reached

**Note:**

- Time (Week)
- Patients (no. of responders/no. randomized)

**Legend:**
- On treatment
- Off treatment
- First response
- Ongoing response
- Death

Robert, C. et al NEJM 2014
Durability of Response (Central Review, RECIST v1.1)

- 88% of responses ongoing\(^a\)
- Median response duration not reached (range, 8+ to 76+ weeks)

\(^a\)Ongoing response defined as alive, progression free, and without new anticancer therapy. Analysis cut-off date: October 18, 2013.

Presented by: Antoni Ribas, ASCO 2014
Durability of Response: pembrolizumab

• Comparison of 2 mg/kg every 3 weeks versus 2 mg/kg every 2 weeks

PLATEAU ON THE OS, PFS CURVES
Ipilimumab leads to durable anti-tumor responses with a plateau at 3 years in OS.

Median OS (95% CI): 9.5 (9.0–10.0)

3-year OS Rate (95% CI): 21% (20–22%)

Schadendorf et al, Eur J Cancer 2013;49(2) [Abstract 24LBA]
Primary End Point: PFS (RECIST v1.1, Central Review)

<table>
<thead>
<tr>
<th>Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 6 mo</th>
<th>Rate at 9 mo</th>
<th>Mean, a mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 Q3W</td>
<td>2.9 (2.8-3.8)</td>
<td>34%</td>
<td>24%</td>
<td>5.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pembro 10 Q3W</td>
<td>2.9 (2.8-4.7)</td>
<td>38%</td>
<td>29%</td>
<td>5.8</td>
<td>0.91 (0.71-1.16)</td>
<td>0.44</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>2.7 (2.5-2.8)</td>
<td>16%</td>
<td>8%</td>
<td>3.6</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Pembrolizumab 10 mg/kg vs 2 mg/kg

*aRestricted mean PFS time based on 12 months of follow-up. Ribas A et al SMR 2014; Robert, C et al Lancet 2014
Analysis cut-off date: May 12, 2014.
Secondary Endpoint: PFS for Nivolumab vs chemotherapy

Based on 5 August 2014 database lock
Robert, C et al NEJM 2014

<table>
<thead>
<tr>
<th>Death or disease progression, n/N</th>
<th>Median PFS mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab 108/210</td>
<td>5.1 (3.5–10.8)</td>
</tr>
<tr>
<td>Dacarbazine 163/208</td>
<td>2.2 (2.1–2.4)</td>
</tr>
</tbody>
</table>

HR 0.43 (95% CI, 0.34–0.56; P < 0.0001)

Patients without Progression (%)

<table>
<thead>
<tr>
<th>Months</th>
<th>Patients at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Nivolumab 210</td>
</tr>
<tr>
<td>3</td>
<td>116</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>Dacarbazine 208</td>
</tr>
<tr>
<td>3</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

Based on 5 August 2014 database lock
Robert, C et al NEJM 2014
Primary endpoint: overall survival for nivolumab vs chemotherapy

HR 0.42 (99.79% CI, 0.25–0.73; P < 0.0001)
(Boundary for statistical significance 0.0021)

Patients who died, n/N

Nivolumab: 50/210
Dacarbazine: 96/208

Median OS mo (95% CI)
Nivolumab: NR
Dacarbazine: 10.8 (9.3–12.1)

Follow-up since randomization: 5.2–16.7 months
NR=not reached. Robert C et al NEJM 2014
PFS and OS for pembrolizumab: plateau?

• Comparison of PFS and OS in patients receiving pembrolizumab at 2 mg/kg q2 vs q3 weeks

UNIQUE SIDE EFFECT PROFILE
Immune-Related Adverse Events (irAE) with checkpoint protein inhibition

• irAE = any adverse event associated with drug exposure and consistent with an immune-mediated mechanism of action.

• Infections and other etiologies should be ruled out or deemed unlikely as contributing to the irAE

• 4 main categories: GI, liver, endocrine, skin

• At 3 mg/kg dose level in melanoma:
  – High grade (grades 3/4) irAE rate is ~14%

• At 10 mg/kg dose level in melanoma
  – Overall (grade 1-4) irAE rate is ~70%
  – High-grade (grades 3/4) irAE rate is ~25%
Immune Related Adverse Events with checkpoint protein inhibition

• Unique potential side effect profile first observed with ipilimumab

• While frequent, primarily low grade

• Most cases of > grade 3 easily managed with steroids: suggestions/algorithms/communication

• Treatment does not significantly compromise anti-tumor activity
Uncommon irAEs with checkpoint protein inhibition

• Pancreatitis
  – Amylase/lipase elevation, abdominal pain low, and out of proportion to elevation of lab tests

• Uveitis
  – Redness, change in vision; ophtho evaluation
  – Topical corticosteroid eye drops

• Neuropathy (rare)
  – Mono- and Poly-neuropathies, ascending motor neuropathy
  – Rule-out cord compression and leptomeningeal disease
  – Consider steroids
Skin

Colon

Colon: CD3^+

Liver

Biopsies Revealing Inflammation Following CTLA-4 Blockade

Phan et al. PNAS 2003
# Time to Onset of irAEs

<table>
<thead>
<tr>
<th>Type</th>
<th>Grade 2-5</th>
<th>Grade 3-5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median Time to Onset, Weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n, 95% CI)</td>
<td>(n, 95% CI)</td>
</tr>
<tr>
<td>Skin</td>
<td>3.6 (61, 3.1–4.1)</td>
<td>4.4 (9, 3.1–4.4)</td>
</tr>
<tr>
<td>GI</td>
<td>6.6 (76, 5.1–8.0)</td>
<td>6.9 (40, 5.7–8.9)</td>
</tr>
<tr>
<td>Liver</td>
<td>6.7 (23, 6.1–9.3)</td>
<td>6.7 (23, 6.1–9.7)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>9.2 (16, 6.7–11.1)</td>
<td>10.1 (8, 7.0–11.4)</td>
</tr>
</tbody>
</table>

Time to Resolution of Grade 2-4 irAEs (ipilimumab 10 mg/kg)

- **GI**
  - Monotherapy 10mg/kg treated subjects
  - Censored
  - Median: 2.29 weeks

- **Liver**
  - Monotherapy 10mg/kg treated subjects
  - Censored
  - Median: 4.00 weeks

- **Endocrine**
  - Monotherapy 10mg/kg treated subjects
  - Censored
  - Median: 20.1 weeks

- **Skin**
  - Monotherapy 10mg/kg treated subjects
  - Censored
  - Median: 6.14 weeks
Management of irAEs

- Patient education for early recognition of irAE symptoms
- Awareness, early work-up, and management are essential
- Low-grade irAEs:
  - Established symptomatic therapies or oral corticosteroids, if needed
- Moderate/high-grade irAEs:
  - Established therapies are effective
    - Majority respond to oral or IV corticosteroids
    - Rarely, alternative immunosuppressive agents are needed
    - Algorithms are available for the management of common irAEs
- Non-specific complaints may reflect endocrine (eg, pituitary) toxicity
## Treatment-related adverse events by age: nivolumab vs chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th></th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 65 yrs</td>
<td>≥ 65 yrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=175)²</td>
<td>(N=93)²</td>
<td></td>
</tr>
<tr>
<td>Drug-related AE, n (%)</td>
<td>117 (67)</td>
<td>64 (69)</td>
<td>47 (78)</td>
</tr>
<tr>
<td>Any grade</td>
<td>9 (5)</td>
<td>15 (16)</td>
<td>19 (32)</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (3)</td>
<td>11 (12)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Serious drug-related AE, n (%)</td>
<td>5 (3)</td>
<td>7 (8)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Any grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>1 (1)</td>
<td>5 (5)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Drug-related AE leading to</td>
<td>1 (1)</td>
<td>5 (5)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>discontinuation, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>1 (1)</td>
<td>5 (5)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

- Younger patients reported grade 3–4 nivolumab treatment-related adverse events less frequently
- Grade 3–4 treatment-related adverse events were less frequent in the nivolumab arm compared with the ICC arm regardless of age subgroup

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²Safety analysis included all treated patients. Only includes adverse events that occurred within 30 days of last dose. Angelo, D et al SMR 2014
LAW OF UNINTENDED CONSEQUENCES
Unexpected toxicity of CAR in solid tumors

- Fatal toxicity with rapid pulmonary edema, hypoxia and lung injury when ERBB2 was targeted with a CAR.
- Liver injury associated with CAR-T-cells against carbonic anhydrase IX in clear cell kidney cancer.
- A MAGE-A3 TCR modified to enhance avidity, recognized an epitope from titin, a protein present in cardiomyocytes. Two patients treated with this CAR had fatal cardiac toxicity.
- A murine TCR against MAGE-A3 recognized a similar epitope in MAGE-A12, also presented by HLA-A0201. MAGE-A12 was expressed in the brain and two patients suffered irreversible CNS injury.

CTLA-4 is ectopically expressed in the pituitary gland. (A) RT-PCR showing CTLA-4 mRNA expression in pituitary, spleen, and thyroid using two different primer pairs (primers 1 and 2). Upper and lower bands indicate full-length and soluble CTLA-4, respectively. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expression was used as loading control. (B) Quantitative real-time PCR for CTLA-4 in pituitary, spleen, thymus, and thyroid. C4 values for CTLA-4 are expressed as means ± SE after adjusting for Ct for GAPDH. *P < 0.0001; **P = 0.001. (C and D) Protein extracts from murine pituitary (male and female) and spleen (C), as well as from human pituitary (D), were analyzed by Western blotting with an antibody directed against CTLA-4. The chimeric protein CTLA-4 Ig served as the experimental control. (E and F) Protein extracts from murine pituitary and spleen were probed with an antibody against CD3ε (E) or CD45 (F). (G) Actin loading control.
ABILITY TO RE-RESPOND TO THERAPY AFTER PROGRESSION
Re-response to checkpoint protein inhibition and TIL

- Re-response rates of 30-50% and OS at 5 years of 15-18% at 3 mg/kg and 20-25% at 10 mg/kg with second line of ipilimumab
- Report of clear response after failing prior nivolumab with an initial sustained PR
- Multiple anecdotal reports of second responses to TIL after an initial response

I-O AGENTS ARE ACTIVE IN A BROAD SPECTRUM OF MALIGNANCIES
PD-1 blockade in lung cancer

- MK-3475 (Pembolizimab, anti PD-1): 38 patients, previously treated, 21% ORR, median OS 11.7 months
- Nivolumab (anti PD-1): 129 patients, previously treated, 17% ORR, 9.9 months median OS, similar for squamous and non-squamous
- BMS 936559 (anti PD-L1): 49 pts, 10% ORR
- MPDL 3280A (anti PD-L1): 53 pts, 23% ORR

Clin Pharm Ther, 2013, Harvey, R.
PD-L1 antibody in bladder cancer

• MPDL 3280A is a human, engineered anti PD-L1 ab given at 15 mg/kg Q 3 weeks
• 31 patients treated, 30 had prior CDDP chemo
• 1 CR, 9 PR, and of the PD-L1 positive patients, 50% ORR
• Transient increases in CD8+/KI-67+ T cells
• 3% rate of grade 3-4 AEs, no irAES seen
• Responses seen by first evaluation, all ongoing

Powles et al ASCO 2014  abstr 5011
Nivolumab in renal cell cancer

- Phase I trial of nivolumab with pazopanib or sunitinib; nivolumab at 2 mg/kg
- Grade 3-4 irAEs: S + N 9% GI, 18% ALT, 3% lung, 3% skin; P + N: 20% GI, 20% ALT, 0 lung, 0 skin
- 48 pts evaluable; median PFS S + N 48 wks, P + N 31 weeks
- S+N: 17/28 60% ORR, P+N 9/19 55% ORR; 13 of the 26 responders ongoing

Amin et al ASCO 2014 abstr 5010
Conclusions: Immuno-oncology for the practitioner

- This is a new era in immuno-oncology, in that many different histologies now respond to I-O drugs
- Slow regression, progression prior to regression are common in immuno-oncology and require new response criteria to accommodate irRC responses
- Immune related adverse events are a new field for toxicity management and require a learning curve
- Prolonged duration of response and plateauing of survival curves suggest that cures are possible
- The Law of Unintended Consequences suggests that new and unexpected toxicities will occur
Acknowledgements

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- Jonathan Zager
- Ricardo Gonzalez
- Melissa Thebeau
- Jennifer Diehl
- Donna Lawless

- And all of our patients and their families.....