Should treatment be prolonged indefinitely?

John Haanen MD PhD
IMMUNOTHERAPY IN MELANOMA

Anti-CTLA-4: ipilimumab
Anti-PD1: nivolumab or pembrolizumab
Anti-CTLA-4 + anti-PD1 combination: ipilimumab + nivolumab
Anti-CTLA-4
Ipilimumab: 4 infusions for the induction

Pre-treated-pts
 +/- gp100
 HLA-A2
 3mg/kg
 Re-induction possible

naive-pts
 + DTIC
 10 mg/kg
 Maintenance possible

Hodi et al 2010 NEJM
Robert et al NEJM 2011
Ipilimumab

- 4 Infusions in 12 weeks
- No way to predict the responders who will respond to this induction
- Re-induction can give new responses but few data
ANALYSIS OF RESPONSE AND SURVIVAL IN PATIENTS WITH IPILIMUMAB-REFRACTORY MELANOMA TREATED WITH PEMBROLIZUMAB IN KEYNOTE-002

A. Daud\textsuperscript{1}; I. Puzanov\textsuperscript{2}; R. Dummer\textsuperscript{3}; D. Schadendorf\textsuperscript{4}; O. Hamid\textsuperscript{5}; C. Robert\textsuperscript{6}; F. S. Hodi\textsuperscript{7}; J. Schachter\textsuperscript{8}; J. A. Sosman\textsuperscript{9}; A. C. Pavlick\textsuperscript{10}; R. Gonzalez\textsuperscript{11}; C. Blank\textsuperscript{12}; L. D. Cranmer\textsuperscript{13}; S. J. O’Day\textsuperscript{14}; A. K. Salama\textsuperscript{15}; K. A. Margolin\textsuperscript{16}; J. Yang\textsuperscript{17}; B. Homet Moreno\textsuperscript{17}; N. Ibrahim\textsuperscript{17}; A. Ribas\textsuperscript{18}

\textsuperscript{1}University of California, San Francisco, San Francisco, CA, USA; \textsuperscript{2}Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; (currently at Roswell Park Cancer Institute, Buffalo, NY, USA; \textsuperscript{3}University of Zürich, Zürich, Switzerland; \textsuperscript{4}University Hospital Essen, Essen, Germany; \textsuperscript{5}The Angeles Clinic and Research Institute, Los Angeles, CA, USA; \textsuperscript{6}Gustave Roussy and Paris-Sud University, Villejuif, France; \textsuperscript{7}Dana-Farber Cancer Institute, Boston, MA, USA; \textsuperscript{8}Ella Lemelbaum Institute of Melanoma, Sheba Medical Center, Tel Hashomer, Israel; \textsuperscript{9}Vanderbilt-Ingram Cancer Center, Nashville, TN, USA (currently at Northwestern University Feinberg School of Medicine, Chicago, IL, USA, USA); \textsuperscript{10}New York University Cancer Institute, New York, NY, USA; \textsuperscript{11}University of Colorado Denver, Aurora, CO, USA; \textsuperscript{12}Netherlands Cancer Institute, Amsterdam, Netherlands; \textsuperscript{13}currently at University of Washington and Seattle Cancer Care Alliance, Seattle, WA, USA; \textsuperscript{14}John Wayne Cancer Institute, Santa Monica, CA, USA; \textsuperscript{15}Duke Cancer Institute, Durham, NC, USA; \textsuperscript{16}City of Hope, Duarte, CA, USA; \textsuperscript{17}Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; \textsuperscript{18}University of California, Los Angeles, Los Angeles, CA, USA
Arrows indicate conversion from SD to CR; 5 patients converted from SD and 21 from PR to CR.

Median DOR in all treated patients was not reached (range 1.9 + mo to 43.5+ mo).

Of 20 patients without PD, 14 discontinued because of AEs (n = 3) or patient/physician decision (n = 11).

Time to and Duration (RECIST v1.1, INV) of Partial Response to Pembrolizumab

Patients with PR, n = 70

- Median, mo (range)
  - Time to PR: 2.9 (1.9-27.9)
  - Time from SD to PR (n = 28): 2.7 (0.9-25.2)
  - Duration of PR: Not reached (1.9+ to 43.5+)

Arrows indicate conversion from SD to PR; 28 patients converted from SD to PR. Median DOR in all treated patients was not reached (range 1.9+ mo to 43.5+ mo).

Of 25 patients without PD, 24 discontinued because of AEs (n = 11) or patient/physician decision (n = 13). Data cut-off: February 3, 2017.

Duration (RECIST v1.1, INV) of Stable Disease to Pembrolizumab

Patients with SD, n = 88

- Median, mo (range)
  - Duration of SD: 6.9 (0.8+ to 38.8+)

Of 25 patients without PD, 24 discontinued because of AEs (n = 11) or patient/physician decision (n = 13). Duration of SD is from randomization to progression. Data cut-off: February 3, 2017.
PFS AND OS in All Pembrolizumab-Treated Patients and Those With Best Response of CR, PR, or SD

<table>
<thead>
<tr>
<th>Group</th>
<th>Events, n</th>
<th>Median, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>29</td>
<td>41.0 (38.9-NR)</td>
</tr>
<tr>
<td>PR</td>
<td>70</td>
<td>35.8 (27.9-NR)</td>
</tr>
<tr>
<td>SD</td>
<td>88</td>
<td>7.0 (5.8-9.7)</td>
</tr>
<tr>
<td>All treated</td>
<td>361</td>
<td>4.2 (3.3-5.6)</td>
</tr>
</tbody>
</table>

PFS was assessed by RECIST v1.1 per investigator.
Conclusions

- Responses to pembrolizumab are durable and associated with prolonged OS in ipilimumab-refractory melanoma
- Even in these heavily pretreated patients, best response can evolve over time, with late conversions from SD to PR/CR and PR to CR observed
- No new safety signals with longer term follow-up
Keynote 001: phase I study of pembrolizumab in 655 metastatic melanoma patients. Median follow-up of 43 months

Robert et al EADO 2017
Pembrolizumab phase 1: Keynote 001:
Median Follow-Up 43 Months for 655 patients

Consent withdrawal: 5%
Discontinue for AEs: 25%
Discontinue for PD: 42%
On treatment: 16%
Discontinue for physician Decision: 11%

Range of follow-up: 36-57 months.
Analysis cutoff date: September 1, 2016.

Robert et al EADO 2017
Complete Responders: Disposition
Median follow-up: 43 months

92 (88%) remained in CR

105 (16%) patients had CR per irRC by investigator review

14 (13%) remained on pembrolizumab
24 (23%) discontinued for AEs (n = 12), PD (n = 2), or other reason (n = 10)
67 (64%) stopped pembrolizumab for observation

Patient was alive and without disease progression.
Analysis cutoff date: September 1, 2016.

Robert et al EADO 2017
Complete Responders Who Stopped Pembrolizumab for Observation (N = 67)

- Median time to CR: 13 mo (3-36 mo)
- 61 (91%) responses were maintained
- Median response duration: NR (6+ to 56+ mo)

Total bar length represents the time to the last scan.
Analysis cutoff date: September 1, 2016.
Complete Responders Who Stopped Pembrolizumab for Observation (N = 67)

- 2 patients died; causes unrelated to pembrolizumab (3,6)
- Only 4 patients experienced PD
  - 2 received commercial pembrolizumab, and had PD (1, 4)
  - 2 received 2nd course pembrolizumab
    - 1 had PR and is ongoing (2)
    - 1 had PD (5)

Robert et al EADO 2017
How long to treat with anti-PD1?

In case of a partial response or stable disease?
KEYNOTE-006 (NCT01866319) Study Design

**Patients**
- Unresectable, stage III or IV melanoma
- ≤1 previous therapy, excluding anti–CTLA-4, PD-1, or PD-L1 agents
- Known *BRAF* mutation status\(^a\)
- 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\(^b\) (positive vs negative)

**Pembrolizumab**
- 10 mg/kg intravenous Q2W for 2 years

**Pembrolizumab**
- 10 mg/kg intravenous Q3W for 2 years

**Ipilimumab**
- 3 mg/kg intravenous Q3W × 4 doses

\(^a\) 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.

\(^b\) Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).
Keynote 006: Patients Who Completed Protocol-Specified Time on Pembrolizumab\textsuperscript{a} (median follow-up, 9.7 mo)

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 SD
- 2 deaths\textsuperscript{b,c}

\textsuperscript{a}Includes patients completing ≥21.6 months of treatment.
\textsuperscript{b}From end of pembrolizumab treatment.
\textsuperscript{c}Both deaths were a result of PD. Data cutoff date: Nov 3, 2016.
PFS (irRC, investigator) from last Pembrolizumab dose in patients who completed protocol-specified time on treatment (n = 104)

102 (98%) patients were alive after a median of 9.7 months after completing pembrolizumab treatment.
Ipilimumab + nivolumumab

Overall Survival (%)

Months

Patients at risk:
- NIVO+IPI: 314, 292, 265, 247, 226, 221, 209, 200, 198, 192, 170, 49
- NIVO: 316, 292, 265, 244, 230, 213, 201, 191, 181, 175, 157, 55
- IPI: 315, 285, 254, 228, 205, 182, 164, 149, 136, 129, 104, 34

Larkin et al AACR 2016
Ipilimumab + nivolumab: pooled data from Checkmate 067 and 69

Pooled patients randomly assigned to nivolumab plus ipilimumab (N = 409; 407 treated)
- CheckMate 067 (n = 314 randomly assigned; 313 treated)
- CheckMate 069 (n = 95 randomly assigned; 94 treated)

Patients who discontinued because of an AE at any time* (safety analyses; n = 176)
- Did not continue study treatment (n = 176)
- Disease progression (n = 1)
- Study drug toxicity (n = 173)
- AE unrelated to study drug (n = 1)
- Not reported (n = 1)

Treated patients who did not discontinue because of an AE (n = 231)
- Did not continue study treatment (n = 150)
  - Disease progression (n = 97)
  - Study drug toxicity (n = 1)
  - Death (n = 4)
  - AE unrelated to study drug (n = 18)
  - Patient request (n = 14)
  - Withdrew consent (n = 4)
  - Maximum clinical benefit (n = 7)
  - Poor/noncompliance (n = 1)
  - No longer met study criteria (n = 1)
  - Other (n = 3)

Patients who discontinued because of an AE during the induction phase† (efficacy analyses; n = 96)
Ipilimumab + nivolumab: pooled data from Checkmate 067 and 09

- PFS and OS not significantly different between the patients who discontinued for AE during the induction period and those who did not discontinue

Schadendorf et al J Clin Oncol 2017
Ipilimumab + nivolumab: pooled data from Checkmate 067 and 09

Patients who discontinued treatment because of adverse events during the induction phase of treatment.

<table>
<thead>
<tr>
<th>Response</th>
<th>Patients Who Discontinued Because of AEs During Induction Phase (n = 96)</th>
<th>Patients Who Did Not Discontinue Because of AEs (n = 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>56 (58.3)</td>
<td>117 (50.2)</td>
</tr>
<tr>
<td>95% CI</td>
<td>47.8 to 68.3</td>
<td>43.6 to 56.8</td>
</tr>
<tr>
<td><strong>Best overall response, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>11 (11.5)</td>
<td>28 (12.0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>45 (46.9)</td>
<td>89 (38.2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>18 (18.8)</td>
<td>25 (10.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>19 (19.8)</td>
<td>63 (27.0)</td>
</tr>
<tr>
<td>Unable to determine*</td>
<td>3 (3.1)</td>
<td>28 (12.0)</td>
</tr>
<tr>
<td><strong>Median time to response, months (range)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.7 (1.9-10.3)</td>
<td>2.8 (1.4-17.1)</td>
</tr>
<tr>
<td><strong>Median duration of response, months (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NR (8.6 to NR)</td>
<td>NR (NR to NR)</td>
</tr>
<tr>
<td><strong>Ongoing responders, No. of No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36 of 56 (64.3)</td>
<td>94 of 117 (80.3)</td>
</tr>
</tbody>
</table>
Do we treat for too long? What is the risk?

Late Adverse events with anti-PD1?

Weber et al J Clin Oncol 2017
No Significant increase in AE incidence between 2 and 3 years with anti-PD1

**TREATMENT-RELATED AE INCIDENCE OVER TIME**

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Pembrolizumab N = 555</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median FU (months)</strong></td>
<td>7.9</td>
</tr>
<tr>
<td>Any grade %</td>
<td>76.2</td>
</tr>
<tr>
<td>Grade 3/4 %</td>
<td>11.7</td>
</tr>
<tr>
<td>Led to death %</td>
<td>0</td>
</tr>
<tr>
<td>Led to discontinuation %</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Data from Ribas et al, AACR 2015; Robert et al ASCO 2016; Robert et al ASCO 2017

Analysis includes all randomized patients who received ≥1 pembrolizumab dose.

*a* As designated by the investigator. *b* Because of sepsis.

Data cutoff date: Nov 3, 2016.
When can we stop anti-PD1?
Help from PFS curve

Ugurel S et al Eur J Cancer 2017
Keynote 006 PFS Total Population (Median Follow-Up, 33.9 mo)

Progression-Free Survival, %

- Pembrolizumab
- Ipilimumab

<table>
<thead>
<tr>
<th>Time, months</th>
<th>Pembrolizumab</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>12</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>16</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>20</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>24</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>28</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>32</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No. at risk

<table>
<thead>
<tr>
<th>Time, months</th>
<th>Pembrolizumab</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>556</td>
<td>278</td>
</tr>
<tr>
<td>4</td>
<td>347</td>
<td>110</td>
</tr>
<tr>
<td>8</td>
<td>269</td>
<td>64</td>
</tr>
<tr>
<td>12</td>
<td>231</td>
<td>40</td>
</tr>
<tr>
<td>16</td>
<td>211</td>
<td>32</td>
</tr>
<tr>
<td>20</td>
<td>182</td>
<td>27</td>
</tr>
<tr>
<td>24</td>
<td>155</td>
<td>23</td>
</tr>
<tr>
<td>28</td>
<td>138</td>
<td>20</td>
</tr>
<tr>
<td>32</td>
<td>88</td>
<td>14</td>
</tr>
<tr>
<td>36</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Stop pembro
Conclusion

• The optimal duration of immunotherapy is presently unknown
• Encouraging data: documentation of long term benefit after discontinuation
  – in CR or after two years of treatment with anti-PD1 monotherapy (pembrolizumab)
• Randomized discontinuation trial needed but challenging to organize
• Practically: decision should be based upon patient’s clear information and decision
  – In case discontinuation due to toxicity and when the disease is not progressing, we advise not to rechallenge
  – In case of confirmed CR after at least 6 months of therapy, if patients agree, we propose to stop
  – In case of PR or SD, if patients agree, we propose to stop after 2 years
CheckMate 153: Randomized Results of Continuous vs 1-Year Fixed-Duration Nivolumab in Patients With Advanced Non-Small Cell Lung Cancer


*Immuno-Oncology Integrated Community Oncology Network (IO ICON) member
CheckMate 153: Continuous vs 1-Year Nivolumab

Study Design

Key eligibility criteria
• Advanced/metastatic NSCLC
• ≥1 prior systemic therapy\(^a\)
• ECOG PS 0–2
• Treated CNS metastases allowed

Exploratory endpoints\(d\): safety/efficacy\(e\) with continuous vs 1-year treatment, efficacy, other (eg, biomarkers, PK)

- At database lock (May 15, 2017), minimum/median follow-up time post-randomization was 10.0/14.9 months

\(^a\)Conventional systemic therapies, excluding immuno-oncology therapies; \(^b\)Treatment until PD, unacceptable toxicity, or withdrawal of consent; treatment beyond investigator-assessed PD permitted; \(^c\)All patients on treatment at 1 year were randomized regardless of response status; \(^d\)Primary endpoint was incidence of high-grade select treatment-related AEs\(^1,2\); \(^e\)Responses were investigator-assessed every 8 weeks ± 5 days from week 9

CheckMate 153: Continuous vs 1-Year Nivolumab

Patient Flow and Analysis

Populations

1,245 patients treated

220 patients on treatment at 1 year

Continuous nivolumab

76 had response or SD at randomization

Stop nivolumab

87 had response or SD at randomization

Efficacy analyses

\textsuperscript{a}Main US cohort; 1,025 patients discontinued prior to 1 year due to progression, death, study withdrawal, toxicity, or other reasons;

\textsuperscript{b}All 220 patients continuing on treatment at 1 year were randomized regardless of response status; 57 of these 220 patients had PD and were randomized as allowed per protocol; safety analyses were based on all 220 patients, 107 in the continuous arm and 113 in the stop arm; 8 patients discontinued treatment due to patient request or withdrawal of consent;

\textsuperscript{c}12 patients discontinued treatment due to patient request or withdrawal of consent.
## CheckMate 153: Continuous vs 1-Year Nivolumab

### Baseline Patient Characteristics (Efficacy Analyses)\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Continuous treatment (n = 76)</th>
<th>1-year treatment\textsuperscript{b} (n = 87)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70 years, %</td>
<td>67 (50–92) 41</td>
<td>67 (49–86) 40</td>
</tr>
<tr>
<td><strong>Female, %</strong></td>
<td>51</td>
<td>45</td>
</tr>
<tr>
<td><strong>ECOG PS, c %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td><strong>Current or former/never smoker, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>96/4</td>
<td>97/3</td>
</tr>
<tr>
<td><strong>Squamous histology, %</strong></td>
<td>34</td>
<td>47</td>
</tr>
<tr>
<td><strong>PD-L1 status, d %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantifiable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%e</td>
<td>53</td>
<td>60</td>
</tr>
<tr>
<td>≥1%e</td>
<td>68</td>
<td>75</td>
</tr>
<tr>
<td>≥50%e</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td><strong>Prior lines of therapy, f %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>≥3</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td><strong>CR or PR prior to randomization, g %</strong></td>
<td>70</td>
<td>56</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Patients who did not have PD at randomization; \textsuperscript{b}With optional retreatment allowed at PD; \textsuperscript{c}Not reported: continuous, n = 1; 1-year, n = 2; \textsuperscript{d}Using Dako PD-L1 IHC 28-8 pharmDx assay; \textsuperscript{e}Percentage of patients with quantifiable PD-L1 expression; \textsuperscript{f}Not reported: continuous, n = 0; 1-year, n = 3; \textsuperscript{g}CRs: continuous, n = 8; 1-year, n = 2
CheckMate 153: Continuous vs 1-Year Nivolumab

PFS From Randomization\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Median, months (95% CI)</th>
<th>PFS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-month</td>
<td>1-year</td>
</tr>
<tr>
<td>Continuous tx</td>
<td>NR (NR)</td>
<td>80</td>
</tr>
<tr>
<td>1-year tx\textsuperscript{b}</td>
<td>10.3 (6.4, 15.2)</td>
<td>69</td>
</tr>
</tbody>
</table>

HR: 0.42 (95% CI: 0.25, 0.71)

\textsuperscript{a}Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months
\textsuperscript{b}With optional retreatment allowed at PD
NR = not reached; tx = treatment
CheckMate 153: Continuous vs 1-Year Nivolumab

PFS From Randomization by Response Status\textsuperscript{a}

<table>
<thead>
<tr>
<th>Response Status</th>
<th>Median, months (95% CI)</th>
<th>Continuous tx</th>
<th>1-year tx\textsuperscript{b,c}</th>
<th>HR: 0.45 (95% CI: 0.24, 0.85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR</td>
<td>NR (NR)</td>
<td>10.6 (4.8, NA)</td>
<td>HR: 0.45 (95% CI: 0.24, 0.85)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>NR (5.6, NA)</td>
<td>9.6 (4.5, 12.6)</td>
<td>HR: 0.44 (95% CI: 0.17, 1.09)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Best overall response prior to randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months; \textsuperscript{b}With optional retreatment allowed at PD; \textsuperscript{c}Two patients who stopped treatment had CR prior to randomization; both patients lost CR (6 and 13 months after stopping treatment) with progression due to new lesions; NA = not available
CheckMate 153: Continuous vs 1-Year Nivolumab
OS From Randomization

<table>
<thead>
<tr>
<th></th>
<th>Median, months (95% CI)</th>
<th>OS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6- month</td>
<td>1-year</td>
</tr>
<tr>
<td>Continuous tx</td>
<td>NR (NR)</td>
<td>97</td>
</tr>
<tr>
<td>1-year txb</td>
<td>23.2 (23.2, NA)</td>
<td>95</td>
</tr>
</tbody>
</table>

HR: 0.63 (95% CI: 0.33, 1.20)

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a Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months
b With optional retreatment allowed at PD
CheckMate 153: Continuous vs 1-Year Nivolumab
Retreatment in 1-Year Treatment Arm

1,245 patients treated
220 patients on treatment at 1 year

Continuous nivolumab
76 had response or SD at randomization

Stop nivolumab
87 had response or SD at randomization

43 (49%) had PD after stopping nivolumab
34 (79%) were retreated with nivolumab

Data at time of analysis (database lock May 15, 2017)

a Main US cohort: 1,025 patients discontinued prior to 1 year due to progression, death, study withdrawal, toxicity, or other reasons;
b All 220 patients continuing on treatment at 1 year were randomized regardless of response status; 57 of these 220 patients had PD and were randomized as allowed per protocol; safety analyses were based on all 220 patients, 107 in the continuous arm and 113 in the stop arm;
c 8 patients discontinued treatment due to patient request or withdrawal of consent;
d 12 patients discontinued treatment due to patient request or withdrawal of consent
CheckMate 153: Continuous vs 1-Year Nivolumab

Summary

- CheckMate 153 is the first randomized study to evaluate duration of therapy with a PD-1/PD-L1 inhibitor

- Among patients still on nivolumab at 1 year, PFS was significantly improved for those treated continuously vs stopping: PFS HR = 0.42 (95% CI: 0.25, 0.71)

- OS HR = 0.63 (95% CI: 0.33, 1.20), showing a trend favoring continuous nivolumab; follow-up for OS is ongoing

- The frequency of treatment-related AEs was numerically higher with continuous vs 1-year treatment, but overall, few new-onset events occurred after 1 year
Remaining questions

• When is the best moment to stop?
  – At a definite time point after start of therapy?
  – After first response (CR or PR)?
  – After maximal response?
  – After AE occurrence?
  – Biological dynamic marker?
• Will stopping rules differ between tumortypes?
• Efficacy of re-treatment with anti-PD1 in case of relapse after discontinuation?
Conclusion

- The optimal duration of immunotherapy is presently unknown
- Encouraging data in melanoma: documentation of long term benefit after discontinuation
  - in CR or after two years of treatment with anti-PD1 monotherapy (pembrolizumab)
  - for toxicity for IPI + NIVO combination
- Randomized discontinuation trial needed but challenging to organize (performed in NSCLC with surprising outcome)
- Practically: decision should be based upon patient’s clear information and decision
  - In case discontinuation due to toxicity and when the disease is not progressing, we advise not to rechallenge
  - In case of confirmed CR after at least 6 months of therapy, if patients agree, we propose to stop
  - In case of PR or SD, if patients agree, we propose to stop after 2 years