Immunotherapy: Mechanism of Action and Efficacy

Dr. Megan Lyle
Medical Oncologist
Liz Plummer Cancer Care Centre – Cairns Hospital
- Honoraria and travel support from BMS, MSD, Novartis
- Advisory board for MSD

Some slides I will be presenting have been supplied by BMS and MSD
Checkpoint inhibitors: Mechanism of Action
- Checkpoint inhibitors in Melanoma
  - Clinical trial data
  - Future treatment directions
  - Special circumstances
- Checkpoint inhibitors in other cancers
- Atypical patterns of response
- Case studies
Checkpoint Inhibitors: Mechanism of Action
History of Immunotherapy

Enthusiasm Phase
1978 - 1985

Skepticism Phase
1985 - 2000

Renaissance Phase
2000 - current

Timeline

The history of cancer immunotherapy

Important basic immunological discoveries and key clinical trials are shown. BCG, bacille Calmette–Guérin; IFNα, interferon-α; IL-2, interleukin-2; MHC, major histocompatibility complex; TNF, tumour necrosis factor; VIN, vulvar intraepithelial neoplasia.


Weinberg, R. The Biology of Cancer
Components of Our Immune System

**Innate Immunity**
Using germline-encoded receptors, innate cells can recognize native structures of pathogens and tumor cells and eliminate them.

**Adaptive Immunity**
Using highly diverse antigen receptors (TCRs and BCRs), adaptive cells can recognize and eradicate pathogens and tumor cells.

- **NK cells**
- **Macrophages**
- **Dendritic cells**
- **Hematopoietic stem cell**
- **T cells**
- **B cells**

BCRs = B-cell receptors; NK = natural killer; TCRs = T-cell receptors.
Some Tumor Cells Express Multiple Antigens That Are Not Expressed by Normal Cells

Normal cells release molecules that are captured by antigen-presenting cells, but they don’t elicit an immune response.

Tumor cells release differentially expressed antigens that cause them to be recognized as foreign entities and therefore elicit an immune response.

Somatic mutations in cancer

More Mutations = Better Immune Response

Ref: Ludmil et al, Nature 2013
Checkpoint Blockade

Activation (cytokines, lysis, proliferation, migration to tumor)

CTLA-4 Blockade (ipilimumab)

PD-1 Blockade (nivolumab)
Checkpoint Blockade

Activation (cytokines, lysis, proliferation, migration to tumor)

CTLA-4 Blockade (ipilimumab)

PD-1 Blockade (nivolumab)
Mechanism of Action : The basics

- Work by making the bodies **own immune system more active** so that it fights the melanoma more effectively
- Stop T-cells from being **switched off**
- Stop melanoma cells from **hiding** from the immune system
- Immunotherapy drugs **do not** kill cancer cells directly
- Immunotherapy is **not** chemotherapy
Checkpoint Inhibitors in Melanoma
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.
Survival Rate

<table>
<thead>
<tr>
<th>Survival Rate</th>
<th>Ipi + gp100 N=403</th>
<th>Ipi + pbo N=137</th>
<th>gp100 + pbo N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>44%</td>
<td>46%</td>
<td>25%</td>
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<tr>
<td>2 year</td>
<td>22%</td>
<td>24%</td>
<td>14%</td>
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</tbody>
</table>
Ipilimumab (Yervoy)

- First checkpoint inhibitor developed
  - “Proof of concept”
- Objective response rate only 10—15%
- Durable responses (in some cases, 7-10 years)
- Intravenous infusion every 3 weeks x 4 treatments
- PBS approved in 2013
- New toxicity profile
  - 60% of people experience an immune-related adverse event
Long-term Efficacy of Pembrolizumab in a Pooled Analysis of 655 Patients With Advanced Melanoma Enrolled in KEYNOTE-001

Adil Daud,1 Antoni Ribas,2 Caroline Robert,3 F. Stephen Hodi,4 Jedd Wolchok,5 Anthony M. Joshua,6 Wen-Jen Hwu,7 Jeffrey S. Weber,8 Tara C. Gangadhar,9 Richard Joseph,10 Roxana Dronca,11 Amita Patnaik,12 Hassane Zarour,13 Richard Kefferd,14,15 Jill A. Lindia,16 Xiaoyun Nicole Li,16 Scot Ebbinghaus,16 S. Peter Kang,16 Omid Hamid17

1University of California, San Francisco, CA; 2University of California, Los Angeles, CA; 3Gustave-Roussy and Paris-Sud University, Villejuif, France; 4Dana-Farber Cancer Institute, Boston, MA; 5Memorial Sloan-Kettering Cancer Center, New York, NY; 6Princess Margaret Hospital, Toronto, Ontario; 7MD Anderson Cancer Center, Houston, TX; 8H. Lee Moffitt Cancer Center, Tampa, FL; 9Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; 10Mayo Clinic, Jacksonville, FL; 11Mayo Clinic, Rochester, MN; 12South Texas Accelerated Research Therapeutics, San Antonio, TX; 13University of Pittsburgh, Pittsburgh, PA; 14Crown Princess Mary Cancer Centre, Westmead Hospital and Melanoma Institute Australia, Sydney, Australia; 15Macquarie University, Sydney, Australia; 16Merck & Co., Inc., Kenilworth, NJ; 17The Angeles Clinic and Research Institute, Los Angeles, CA
## KEYNOTE-001: Melanoma Cohorts

<table>
<thead>
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<th>2012</th>
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<tr>
<td>11</td>
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<tr>
<td>Nonrandomized IPI Naive and IPI Treated</td>
<td>Randomized IPI Treated</td>
</tr>
<tr>
<td>2 Q3W, 10 Q3W, 10 Q2W</td>
<td>2 Q3W vs 10 Q3W</td>
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<tr>
<td>N = 135</td>
<td>N = 173</td>
</tr>
</tbody>
</table>

### Previous Pooled Analyses
- N = 411

### This Pooled Analysis
- N = 655

- 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; ≥2 IPI doses required
- **BRAF inhibitor required** for IPI-T, but not IPI-N, *BRAF*-mutant melanoma
Efficacy as First-Line Therapy\textsuperscript{a}

\textbf{Duration of Response in First Line}

- Median: Not reached
- Range: 2.7+ to 27.5+ months
- Patients without progression: 86%

\textsuperscript{a}Excludes patients with ocular melanoma.
Analysis cut-off date: October 18, 2014.
# Efficacy as First-Line Therapy

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 133)</th>
<th>(BRAF^{V600}) Wild Type (n = 109)</th>
<th>(BRAF^{V600}) Mutant (n = 22)</th>
</tr>
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<tbody>
<tr>
<td><strong>Complete response, % (95% CI)</strong></td>
<td>13.5 (8.2-20.5)</td>
<td>12.8 (7.2-20.6)</td>
<td>18.2 (5.2-40.3)</td>
</tr>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>45.1 (36.5-54.0)</td>
<td>45.0 (35.4-54.8)</td>
<td>50.0 (28.2-71.8)</td>
</tr>
<tr>
<td><strong>DCR, % (95% CI)</strong></td>
<td>60.9 (52.1-69.2)</td>
<td>60.6 (50.7-69.8)</td>
<td>63.6 (40.7-82.8)</td>
</tr>
</tbody>
</table>

\(a\)Excludes patients with ocular melanoma.

Analysis cut-off date: October 18, 2014.
Kaplan-Meier Estimates of PFS and OS in Treatment-Naive Patients (n = 152a)

- **PFS**
  - Median (95% CI): 13.8 months (6.7-17.4)
  - Rate at 12 months: 52%

- **OS**
  - Median (95% CI): 31.1 months (24.4-NR)
  - Rate at 12 months: 73%
  - Rate at 24 months: 60%

Excludes patients with ocular melanoma.
Analysis cut-off date: October 18, 2014.
Pembrolizumab versus Ipilimumab in Advanced Melanoma

Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*
KEYNOTE-006 (NCT01866319): International, a Randomized, Phase III Study

**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)

**Randomization Ratio:** 1:1:1

- **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

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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.
Patient Disposition at IA1

834 patients randomly assigned

Pembrolizumab 10 Q2W
- 279 allocated
- 278 received treatment\(^a\)
  - 128 ongoing
  - 150 discontinued
    - 111 progressive disease
    - 20 adverse events
    - 2 deaths
    - 17 other

Pembrolizumab 10 Q3W
- 277 allocated
- 277 received treatment
  - 125 ongoing
  - 152 discontinued
    - 103 progressive disease
    - 29 adverse events
    - 1 death
    - 1 complete response
    - 18 other

Ipilimumab
- 278 allocated
- 256 received treatment\(^a\)
  - 144 completed treatment as assigned
    - 100 discontinued\(^b\)
      - 41 progressive disease
      - 37 adverse events
      - 6 deaths
      - 16 other

- Enrollment period: September 2013 to March 2014
- Data cutoff date, first interim analysis: September 3, 2014 (median follow-up, 7.9 months)
- Data cutoff date, second interim analysis: March 3, 2015 (median OS follow-up, 13.8 months)

\(^a\)Patients withdrew consent.
\(^b\)There was no ipilimumab completion or study discontinuation form for 12 patients in the ipilimumab arm.
PFS at the First Interim Analysis (IA1)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 6 mo</th>
<th>HR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Pembrolizumab Q2W</td>
<td>5.5 (3.4-6.9)</td>
<td>47.3%</td>
<td>0.58</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Pembrolizumab Q3W</td>
<td>4.1 (2.9-6.9)</td>
<td>46.4%</td>
<td>0.58</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>2.8 (2.8-2.9)</td>
<td>26.5%</td>
<td>—</td>
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No. at risk

<table>
<thead>
<tr>
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<th>279</th>
<th>231</th>
<th>147</th>
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<td>235</td>
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<td>278</td>
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<td>42</td>
<td>18</td>
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Analysis cut-off date: September 3, 2014.
OS at the Second Interim Analysis (IA2)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 12 mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab Q2W</td>
<td>NR (NR-NR)</td>
<td>74.1%</td>
<td>0.63</td>
<td>(0.47-0.83)</td>
</tr>
<tr>
<td>Pembrolizumab Q3W</td>
<td>NR (NR-NR)</td>
<td>68.4%</td>
<td>0.69</td>
<td>(0.52-0.90)</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>NR (12.7-NR)</td>
<td>58.2%</td>
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No. at risk

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<tr>
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<th>248</th>
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<th>212</th>
<th>177</th>
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Analysis cut-off date: March 3, 2015.
# Tumor Response at the First Interim Analysis (RECIST v1.1, Central Review)

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab Q2W n = 279</th>
<th>Pembrolizumab Q3W n = 277</th>
<th>Ipilimumab n = 278</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR (95% CI)</strong></td>
<td>33.7% (28.2-39.6)</td>
<td>32.9% (27.4-38.7)</td>
<td>11.9% (8.3-16.3)</td>
</tr>
</tbody>
</table>

- \( P = 0.00013 \) for pembrolizumab Q2W vs ipilimumab
- \( P = 0.00002 \) for pembrolizumab Q3W vs ipilimumab

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab Q2W n = 279</th>
<th>Pembrolizumab Q3W n = 277</th>
<th>Ipilimumab n = 278</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable disease</td>
<td>13.3%</td>
<td>14.1%</td>
<td>16.5%</td>
</tr>
<tr>
<td>NonCR/nonPD(^a)</td>
<td>4.7%</td>
<td>5.1%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>38.0%</td>
<td>41.2%</td>
<td>48.9%</td>
</tr>
<tr>
<td>Not evaluable(^b)</td>
<td>7.2%</td>
<td>5.4%</td>
<td>18.3%</td>
</tr>
<tr>
<td>No assessment(^c)</td>
<td>3.2%</td>
<td>1.4%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab Q2W n = 279</th>
<th>Pembrolizumab Q3W n = 277</th>
<th>Ipilimumab n = 278</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing responses</td>
<td>89.4%</td>
<td>96.7%</td>
<td>87.9%</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab Q2W n = 279</th>
<th>Pembrolizumab Q3W n = 277</th>
<th>Ipilimumab n = 278</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of response (range), days</td>
<td>251 (42+ to 251)</td>
<td>NR (42+ to 246+)</td>
<td>NR (33+ to 239+)</td>
</tr>
</tbody>
</table>

\(^a\)Patients without measurable disease per central review at baseline who did not experience complete response or disease progression.

\(^b\)Target lesion not captured by postbaseline scans or for whom a target lesion was surgically removed.

\(^c\)No postbaseline scan performed or were not able to be evaluated.

Analysis cut-off date: September 3, 2014.
CheckMate 066

Nivolumab in previously untreated melanoma without BRAF mutation

CheckMate 066: Phase 3, randomised, double-blind study in treatment-naïve advanced melanoma\(^1,2\)

- **Nivolumab**
  - monotherapy 3 mg/kg IV q2w + dacarbazine-matched placebo IV q3w
  - (n=210)

- **Dacarbazine**
  - 1000 mg/m\(^2\) IV q3w + nivolumab-matched placebo IV q2w
  - (n=208)

**PRIMARY ENDPOINT**
- Overall survival

**SECONDARY ENDPOINTS**
- Investigator-assessed progression-free survival
- Objective response rate\(^3\)
- PD-L1 expression as a predictive biomarker of overall survival

Treatment continued until disease progression or unacceptable toxicity

- Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial adverse effects with the study drug, as determined by the investigator\(^1,2\)

Adapted from Robert C et al. and OPDIVO Product Information.\(^1,2\)

\(^1\)Randomisation was stratified according to tumour PD-L1 status and American Joint Committee on Cancer metastasis stage.

\(^2\)Tumour response was assessed according to RECIST v1.1.

ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed death ligand 1; q2w=every 2 weeks; q3w=every 3 weeks

CheckMate 066: Overall survival in treatment-naïve, BRAF wild-type, advanced melanoma (primary endpoint; updated analysis)\(^1,2\)

Overall survival in BRAF WT advanced melanoma: Kaplan-Meier estimate\(^1\)

- Nivolumab reduced the risk of death by 57% vs. dacarbazine – median overall survival not reached (95% CI 23.1–NR) vs. 11.2 months (95% CI 9.6–13.0; HR=0.43; 95% CI 0.33–0.57; p<0.001)\(^1\)

Adapted from Atkinson V et al. (SMR 2015).\(^1\) Phase III study of nivolumab monotherapy (3 mg/kg; q2w) vs. dacarbazine (1000 mg/kg; q3w) in 418 treatment-naïve BRAF wild-type advanced (unresectable stage III or metastatic stage IV) melanoma patients. Median follow-up for overall survival was 18.5 months for nivolumab vs. 10.9 months for dacarbazine.\(^1,2\)

\(\text{CI} = \text{confidence interval}; \text{HR} = \text{hazard ratio}; \text{NIVO} = \text{nivolumab}; \text{NR} = \text{not reached}; \text{WT} = \text{wild-type}.

**References:**
CheckMate 066: Progression-free survival in treatment-naïve, *BRAF* wild-type, advanced melanoma (secondary endpoint; updated analysis)¹,²

Progression-free survival in *BRAF* WT advanced melanoma: Kaplan-Meier estimate¹

- Median progression-free survival was 5.4 months (95% CI 3.7–12.2) with nivolumab — vs. 2.2 months (95% CI 2.1–2.5) with dacarbazine (HR=0.42; 95% CI 0.32–0.53; p<0.0001)¹

![Graph showing progression-free survival](image)

*No. at risk*

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Dacarbazine</th>
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<tbody>
<tr>
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</table>

*Nivolumab vs. dacarbazine* ¹

*P-value for 12-month and 24-month progression-free survival not reported.

Adapted from Atkinson V *et al.* (SMR 2015).¹ Phase III study of nivolumab monotherapy (3 mg/kg; q2w) vs. dacarbazine (1000 mg/kg; q3w) in 418 treatment-naïve *BRAF* wild-type advanced (unresectable stage III or metastatic stage IV) melanoma patients.¹,²

CI = confidence interval; DTIC = dacarbazine; HR = hazard ratio; NC = not calculable; NIVO = nivolumab.

**References:**
1. Atkinson V *et al.* Two-year survival and safety update in patients with treatment-naïve advanced melanoma receiving nivolumab or dacarbazine in CheckMate 066. Presented at the 12th International Congress of the Society forMelanoma Research; 18–21 November 2015; San Francisco, CA, USA (abstract).
CheckMate 066: Objective response rate in treatment-naïve, \textit{BRAF} wild-type, advanced melanoma (secondary endpoint; updated analysis)\textsuperscript{1,2}

**Objective response rate in \textit{BRAF} WT advanced melanoma\textsuperscript{1†}**

- 43\% of patients in the nivolumab group had an objective response
  - vs. 14\% in the dacarbazine group (p-value not reported)\textsuperscript{1}

- Median duration of response was not reached with nivolumab
  - vs. 7.2 months (range 3.9–NR) for dacarbazine (p-value not reported)\textsuperscript{1}

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Adapted from Atkinson V et al. (SMR 2015).\textsuperscript{1} Phase III study of nivolumab monotherapy (3 mg/kg; q2w) vs. dacarbazine (1000 mg/kg; q3w) in 418 treatment-naïve \textit{BRAF} wild-type advanced (unresectable stage III or metastatic stage IV) melanoma patients.\textsuperscript{1,2}

\textsuperscript{1}Objective response rate was assessed by the investigator using RECIST, v1.1.

CR=complete response; ORR=objective response; PR=partial response; NR=not reached.

**References:** 1. Atkinson V et al. Two-year survival and safety update in patients with treatment-naïve advanced melanoma receiving nivolumab or dacarbazine in CheckMate 066. Presented at the 12th International Congress of the Society for Melanoma Research; 18–21 November 2015; San Francisco, CA, USA (abstract).

CheckMate 067

Combined nivolumab and ipilimumab or monotherapy in untreated melanoma†


†OPDIVO, in combination with YERVOY (ipilimumab) is only indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH).
CheckMate 067: Phase 3, randomised, double-blind study in treatment-naïve, advanced melanoma¹,²†

†OPDIVO, in combination with YERVOY (ipilimumab) is only indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH)¹

- Nivolumab patients could be treated after progression, provided that they had a clinical benefit and did not have substantial adverse effects, as assessed by the investigator¹

Adapted from Larkin J et al. and OPDIVO Product Information.¹,²

†Randomisation was stratified according to PD-L1 status, BRAF mutation status and American Joint Committee on Cancer metastasis stage.

¹Tumour response was assessed according to RECIST V1.1.

ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed death ligand 1; q2w=every 2 weeks; q3w=every 3 weeks.

CheckMate 067: Objective response rate in treatment-naïve, advanced melanoma (secondary endpoint)$^{1,2+}$

$^+$OPDIVO, in combination with YERVOY (ipilimumab) is only indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH)$^{1}$

Objective response rate in advanced melanoma$^{1,2+}$

- Significantly more complete responses with nivolumab + ipilimumab combination regimen vs. ipilimumab monotherapy – 11% vs. 2%; p-value not reported$^{1,2}$

Adapted from Larkin J et al. and OPDIVO Product Information.$^{1,2}$ Phase III study of nivolumab (1 mg/kg; q3w) plus ipilimumab (3 mg/kg; q3w) for four doses followed by nivolumab monotherapy (3 mg/kg; q2w) or nivolumab (3 mg/kg, q2w) vs. ipilimumab monotherapy (3 mg/kg, q3w, 4 doses) in 945 treatment-naïve advanced (unresectable stage III or metastatic stage IV) melanoma patients. Study was not designed for statistical analysis between nivolumab + ipilimumab combination regimen vs. nivolumab monotherapy.$^{1,2}$

$^+$Coprimary endpoints were progression-free survival and overall survival, overall survival data not mature at time of analysis.

CI=confidence interval; CR=complete response; ORR=objective response; PR=partial response

CheckMate 067: ORR across predefined subgroups in treatment-naïve, advanced melanoma (secondary endpoint)¹,²

<table>
<thead>
<tr>
<th></th>
<th>ORR (Patients)</th>
<th>NIVO + IPI</th>
<th>NIVO</th>
<th>Unweighted ORR difference vs IPI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>57.6% (314)</td>
<td>43.7% (316)</td>
<td>38.6% (31.3–45.2)</td>
<td>24.6% (17.9–31.4)</td>
</tr>
<tr>
<td>BRAF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild-type</td>
<td>53.3% (212)</td>
<td>46.8% (218)</td>
<td>35.6% (26.3–43.6)</td>
<td>28.1% (20.5–37.1)</td>
</tr>
<tr>
<td>Mutant</td>
<td>66.7% (102)</td>
<td>36.7% (88)</td>
<td>44.7% (31.5–55.6)</td>
<td>14.7% (2.0–26.8)</td>
</tr>
<tr>
<td>M stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1c</td>
<td>51.4% (185)</td>
<td>38.9% (185)</td>
<td>37.1% (27.3–45.4)</td>
<td>24.6% (15.8–33.0)</td>
</tr>
<tr>
<td>Baseline LDH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ULN</td>
<td>65.3% (199)</td>
<td>51.6% (194)</td>
<td>48.6% (31.1–48.9)</td>
<td>26.6% (17.1–33.6)</td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>44.7% (114)</td>
<td>39.4% (112)</td>
<td>36.2% (24.1–45.2)</td>
<td>20.8% (10.5–30.7)</td>
</tr>
<tr>
<td>&gt;2x ULN</td>
<td>37.5% (37)</td>
<td>25.8% (37)</td>
<td>37.8% (20.4–53.9)</td>
<td>21.6% (6.3–37.2)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 and &lt;75</td>
<td>57.4% (84)</td>
<td>48.1% (79)</td>
<td>35.9% (25.3–51.0)</td>
<td>30.1% (16.0–42.8)</td>
</tr>
<tr>
<td>≥75</td>
<td>54.3% (35)</td>
<td>43.5% (39)</td>
<td>27.6% (5.3–45.8)</td>
<td>16.3% (4.1–35.2)</td>
</tr>
<tr>
<td>PD-L1 expression level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>54.8% (216)</td>
<td>41.3% (208)</td>
<td>36.9% (28.3–45.0)</td>
<td>23.5% (14.5–31.6)</td>
</tr>
<tr>
<td>≥5%</td>
<td>72.1% (88)</td>
<td>67.7% (80)</td>
<td>56.7% (35.0–62.8)</td>
<td>36.2% (21.9–48.0)</td>
</tr>
</tbody>
</table>

- Nivolumab + ipilimumab combination regimen showed numerically greater ORR than either agent alone across predefined subgroups, including patients with elevated LDH and stage M1c (p-value not reported)¹,³

Adapted from Larkin J et al. (ECC 2015)¹ Phase III study of nivolumab (1 mg/kg; q3w) plus ipilimumab (3 mg/kg; q3w) for four doses followed by nivolumab monotherapy (3 mg/kg; q2w) or nivolumab (3 mg/kg; q2w) vs. ipilimumab monotherapy (3 mg/kg, q3w, 4 doses) in 945 treatment-naïve advanced (unresectable stage III or metastatic stage IV) melanoma patients. Study was not designed for statistical analysis between nivolumab + ipilimumab combination regimen vs. nivolumab monotherapy. ³ Coprimary endpoints were progression-free survival and overall survival; overall survival data not mature at time of analysis.¹⁻³

LDH=lactate dehydrogenase; ORR=objective response rate; NIVO=Nivolumab; NIVO+IPI=Nivolumab + ipilimumab Combination Regimen; PD-L1=programmed death ligand 1; ULN=upper limit of normal.

References: 1. Larkin J et al. Efficacy and safety in key patient subgroups of nivolumab alone or combined with ipilimumab vs. ipilimumab alone in treatment-naïve patients with advanced melanoma. Presented at European Cancer Congress 2015; September 25–29, 2015; Vienna, Austria (abstract).
CheckMate 067: Progression-free survival in treatment-naïve, advanced melanoma (coprimary endpoint)\(^1,2\)

\(^1\)OPDIVO, in combination with YERVOY (ipilimumab) is only indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH)\(^1\)

Progression-free survival in advanced melanoma: Kaplan-Meier estimate\(^1,2\)

- **Nivolumab + ipilimumab reduced the risk of death or progression by 58% vs. ipilimumab monotherapy**
  - HR=0.42; 99.5% CI 0.31–0.57; p<0.0001\(^1,2\)
- **Median PFS was numerically higher with nivolumab + ipilimumab vs. nivolumab monotherapy**
  - 11.5 months (95% CI 8.9–16.7) vs. 6.9 months (95% CI 4.3–9.5; p-value not calculated)\(^1,2\)

Adapted from Larkin J \textit{et al.} and OPDIVO Product Information.\(^1,2\) Phase III study of nivolumab (1 mg/kg; q3w) plus ipilimumab (3 mg/kg; q3w) for four doses followed by nivolumab monotherapy (3 mg/kg, q2w) or nivolumab (3 mg/kg, q2w) vs. ipilimumab monotherapy (3 mg/kg, q3w, 4 doses) in 945 treatment-naïve advanced (unresectable stage III or metastatic stage IV) melanoma patients. Study was not designed for statistical analysis between nivolumab + ipilimumab combination regimen vs. nivolumab monotherapy.\(^1,2\)

\(^2\)Coprimary endpoints were progression-free survival and overall survival; overall survival data not mature at time of analysis.

CI=confidence interval; HR=hazard ratio; PFS=progression-free survival.

Both pembrolizumab and nivolumab as single agents are more effective than ipilimumab

- Objective response rate 30-40%
- 1 year OS ~70-80%, 2 year OS ~60%
- Intravenous infusion every 2 or 3 weeks, indefinite?
- Side effects are less common and milder
- Available on PBS now as first treatment for metastatic melanoma
Summary: Ipilimumab + Nivolumab

- **Combined** checkpoint blockade
- Even more effective
  - *But we are still waiting for overall survival* data
- **Much** more toxicity
  - 55% severe or life threatening side effects
- Many patients don’t **“need”** the combination
  - Can we choose the right people?
- Not available on PBS (but is TGA approved)
Case study

- 60yo man
- Bulky, highly symptomatic metastatic melanoma in abdomen Dec 2014
- Commenced ipilimumab (2 doses)
  - Disease progression
- March 2015 - Commenced Nivolumab
- Marked symptomatic improvement, clinical response, and drop in LDH after only 1 dose
Progress

Feb 2015

May 2015
Progress

Feb 2015

May 2015
Future of immunotherapy in Melanoma?
Current research

- Other **combination** immunotherapies
  - Epacadostat plus pembrolizumab
  - Pembrolizumab plus ipilimumab (different dosing)
  - Pembrolizumab plus T-Vec

- Effective combination with less toxicity?
Current research

- Immunotherapy combined with **other treatments**
  - BRAF inhibitors
  - Chemotherapy
  - Radiotherapy

- Stimulate and then enhance an immune response?
“Special circumstances”
BRAF mutated melanoma

- Dabrafenib and Trametinib
  - Must be “first PBS-subsidised therapy”

- Melanoma specialists disagree with this restriction
  - Choice of immunotherapy versus targeted therapy should be made on a case-by-case basis
Stage 3 Melanoma

- Melanoma has spread to regional lymph nodes
- All melanoma has been removed with surgery but possible “micro-metastases” in the blood stream
- High risk of the melanoma returning
- Adjuvant Treatment:
  - Is there a treatment that can be given to these high risk patients soon after surgery to stop the melanoma coming back?
Stage 3 Melanoma

Ref: Balch et al, JCO 2009
Adjuvant Immunotherapy

- Ipilimumab trial
  - Improved relapse free survival
  - Higher dose and significant concerns regarding toxicity
  - No overall survival data yet – does it actually cure people or just delay recurrence?
  - **Not** available in Australia in this setting

- PD-1 Antibodies
  - Recently completed and ongoing trials
- Ipilimumab – some activity, but not if symptomatic/steroid requiring (phase 2 study)
- PD-1 antibodies – anecdotally show promising activity
- Trials underway, results pending
- Immunotherapy combined with SRS
  - Radionecrosis does occur
Case study

- 63yo man
- High risk stage 3 melanoma Dec 2014
- May 2015 – metastatic disease involving subcutaneous tissue, LN, bone and peritoneum
- Staging CT – 2 small brain metastases (asymptomatic)
- Commenced pembrolizumab June 2015
Progress

Baseline – May 2015

Scan 1 – Sept 2015
Checkpoint Inhibitors in Other Cancers
Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.
**Figure 1. Kaplan–Meier Curves for Overall Survival.**

The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.
Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

A Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>No. of Deaths/Total No. of Patients</th>
<th>Median Overall Survival (95% CI)</th>
<th>1-Yr Overall Survival Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>190/292</td>
<td>12.2 (9.7–15.0)</td>
<td>51 (45–56)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>223/290</td>
<td>9.4 (8.1–10.7)</td>
<td>39 (33–45)</td>
</tr>
</tbody>
</table>

Hazard ratio for death, 0.73 (95% CI, 0.59–0.89)
P = 0.002

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>292</td>
<td>290</td>
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<tr>
<td></td>
<td>232</td>
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<td>5</td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>
Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D., Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D., Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D., Jared K. Luneford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D., Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*
So what does this mean for lung cancer?

- RCT in 2\textsuperscript{nd} line patients both squamous and non-squamous histology comparing PD-1 based therapy to Docetaxel demonstrating improved response rate, PFS, OS.
- Nivolumab is better tolerated than second line Docetaxel and for those that respond the response can be prolonged.
- TGA approved but not available on PBS.
- More data pending on pembrolizumab.
- The need for increasing response rates (only 20-25\%) and choosing predictive biomarkers remains.
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

Figure 1. Kaplan–Meier Curve for Overall Survival.
CI denotes confidence interval, and NE not estimable.
So what does this mean for Renal-cell Carcinoma?

- Not that long ago- for RCC it was Interferon or BSC
- Now:
  - 1st line therapy for RCC-(outside of trials) Pazopanib or Sutent,
  - 2nd line Everolimus or Axitinib currently listed on PBS for second line therapy
- This trial demonstrates improve response rates, tolerability and OS compared with standard second line therapy
- Not currently approved or reimbursed
- Further immune therapy based trials to improve response rate are in the pipeline
PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma

Paul T. Nghiem, M.D., Ph.D., Shailender Bhatia, M.D., Evan J. Lipson, M.D.,
Ragini R. Kudchadkar, M.D., Natalie J. Miller, B.A.,
Lakshmanan Annamalai, D.V.M., Ph.D, Sneha Berry, M.S.,
Elliot K. Chartash, M.D., Adil Daud, M.B., B.S., Steven P. Fling, Ph.D.,
Philip A. Friedlander, M.D., Harriet M. Kluger, M.D.,
Holbrook E. Kohrt, M.D., Ph.D.,* Lisa Lundgren, M.S., Kim Margolin, M.D.,
Alan Mitchell, M.Sc., Thomas Olencki, D.O., Drew M. Pardoll, M.D., Ph.D.,
Sunil A. Reddy, M.D., Erica M. Shantha, M.D., William H. Sharfman, M.D.,
Elad Sharon, M.D., M.P.H., Lynn R. Shemanski, Ph.D., Michi M. Shinohara, M.D.,
Joel C. Sunshine, M.D., Ph.D., Janis M. Taube, M.D., John A. Thompson, M.D.,
Steven M. Townson, Ph.D., Jennifer H. Yearley, D.V.M., Ph.D.,
Suzanne L. Topalian, M.D., and Martin A. Cheever, M.D.
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

B Radiographic Response

- Mismatch repair–proficient colorectal cancer
- Mismatch repair–deficient colorectal cancer
- Mismatch repair–deficient noncolorectal cancer

Change from Baseline in the Sum of Longest Diameters (%)

- 20% increase (progressive disease)
- 30% decrease (partial response)
Atypical Patterns of Response
Patient With Melanoma Treated in KEYNOTE-001

Baseline | Week 12 | Week 24 | Week 52
--- | --- | --- | ---

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

Presented By Jedd Wolchok at 2015 ASCO Annual Meeting
Responses to Immunotherapy Captured by RECIST\textsuperscript{1}

- **Most** immunotherapy-related responses are captured by RECIST v1.1


In very few cases, **atypical responses** may be the result of tumors becoming heavily infiltrated by T cells and inflammatory cells that initially increase the tumor’s size\(^1,2\)

## RECIST and irRC Differ in Their Assessment of Tumor Burden

<table>
<thead>
<tr>
<th>Category</th>
<th>RECIST v1.1</th>
<th>irRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement of tumor burden</td>
<td>Unidimensional</td>
<td>Bidimensional</td>
</tr>
<tr>
<td>Complete response</td>
<td>Disappearance of all target and nontarget lesions; lymph nodes must regress to &lt;10 mm short axis; no new lesions; requires confirmation</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>≥30% decrease in tumor burden compared with baseline; requires confirmation</td>
<td>≥50% decrease in tumor burden compared with baseline; requires confirmation</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>&gt;20% + 5 mm absolute increase in tumor burden compared with nadir; progression of nontarget lesions and/or appearance of new lesions (at any single time point)</td>
<td>&gt;25% increase in tumor burden compared with most recent prior evaluation; new lesions added to tumor burden; requires confirmation</td>
</tr>
<tr>
<td>Stable disease</td>
<td>Any response pattern that does not meet criteria for complete response, partial response, or progressive disease</td>
<td></td>
</tr>
</tbody>
</table>

RECIST v1.1 = Response Evaluation Criteria In Solid Tumors 1.1.

- Using the irRC criteria, new lesions are included in the assessment of total tumor burden but are not considered an indication of progressive disease unless confirmed later by follow-up radiographic findings.

Case study

- 76yo man
- Primary melanoma May 2015
  - 12mm Breslow thickness, not ulcerated, TMR 5/mm²
- Left axillary LN July 2015
- Staging showed metastases in LN’s and single liver lesion
- BRAF wild type
- Commenced pembrolizumab July 2015
Baseline scan - July 2015
Progress

Scan 1 – Oct 2015

Scan 3 – March 2016
Conclusions

- Checkpoint Inhibitors represent a major breakthrough in our approach to cancer treatment.
- Now standard of care for metastatic melanoma – and other cancers not far behind.
- We need to get better at **predicting** which treatments work best for which patients.
  - Biomarker research.
- Immunotherapy requires a unique approach to monitoring, assessing response and managing toxicity.
Questions?