Immunotherapy – A New Treatment for Cancer

Michael Millward

University of WA
Sir Charles Gairdner Hospital
Linear Clinical Research
Disclosures

• Melanoma/Lung/Immuno-oncology advisory boards
  – Bristol Myers Squibb
  – Merck Sharp & Dohme
  – GlaxoSmithKline
  – Roche
  – AstraZeneca
Themes

• Cancer and the immune system
• Using drugs to change the immune response
• Where we are at....especially melanoma and lung cancer
• Where will we be in the years to come
Our Immune System

• Complex network of different cells and proteins that function together in a coordinated way.

• It is there to recognize ‘foreign’ proteins on ‘foreign’ cells that get into our bodies – ie infections with bacteria, viruses, parasites that we have evolved with.

• When, for example, a bacteria gets into our body, the immune system goes through multiple steps to recognize it, activate immune cells to destroy it, and (in some circumstances) remember it.
Cancer and the Immune System

- **Our immune system is not there to fight cancer. Cancer is a ‘recent’ event!**

- **Cancers arise from our own bodies cells, they are not ‘foreign’ like an infection BUT**

- **Cancers arise because of mutations in genes and these can result in abnormal proteins being produced on cancer cells, which the immune system could recognise...SO**

- **Does the immune system ‘recognize’ cancer and can it destroy cancer cells?**
Cancer and the Immune System

• **YES….and it probably is right now…**

• **But it doesn’t….**

• **WHY NOT?**
Immunotherapy

Presented by Julie Brahmer, M.D.
Presented by Julie Brahmer at 2014 ASCO Annual Meeting
The Immunotherapy Revolution

- **We know what is stopping the immune system - checkpoints (brakes)**
- **We can then make drugs that will block these – checkpoint inhibitors (release the brakes)**
- **These drugs are antibodies that bind to the ‘target’. Antibodies are given IV every 2-4 weeks.**
- **When you treat with these drugs, the immune system will then start attacking the cancer.**
Current Immunotherapy Drugs

- **Ipilimumab (Yervoy)** – anti CTLA4
  - Approved in Australia for unresectable / metastatic melanoma. PBS funded.

- **Pembrolizumab (Keytruda)** – anti PD-1
  - Approved in Australia for unresectable / metastatic melanoma. PBS funded.

- **Nivolumab (Opdivo)** – anti PD-1
  - Approved in Australia for unresectable / metastatic melanoma. PBS funded.
  - Approved in Australia for recurrent/metastatic NSCLC cancer (second line). Not yet PBS funded.
Current Immunotherapy Drugs

- **Ipilimumab (Yervoy)** – anti CTLA4
  - Approved in US for melanoma that has spread to lymph nodes (stage III)
- **Pembrolizumab (Keytruda)** – anti PD-1
  - Approved in US for NSCLC, head and neck cancer.
- **Nivolumab (Opdivo)** – anti PD-1
  - Approved in US for metastatic renal cancer, Hodgkin’s Disease
- **Atezolizumab** – anti PD-L1
  - Approved in US for metastatic/recurrent bladder cancer, NSCLC second line (Oct 20, 2016)
Current Checkpoint Inhibitors

- **Clinical Trials:**
  - *Tremelimumab (Anti CTLA4)*
  - *Durvalumab (Anti PD-L1)*
  - *Avelumab (Anti PD-L1)*

- >15 more drugs targeting PD-1 or PD-L1
- As of 16/10/16 there are >800 registered clinical trials of PD-1/PD-L1 inhibitors with expected accrual of >166,000 patients.

- **BUT WAIT**
>22,000 patients on pembrolizumab clinical trials since 2011

- Initial approval for metastatic melanoma
- Now approval for non-small-cell lung cancer, head and neck cancer
- Potential application in up to 30 different types of tumors
Current Checkpoint Inhibitors

• Some results in melanoma and lung cancer

• *Ipilimumab (Yervoy)* first approved checkpoint inhibitor in metastatic melanoma.

• *Despite efficacy in melanoma, trials in other malignancies failed to show benefit.*
In a pooled analysis of 12 studies, an OS plateau starts at approximately 3 years with follow-up of up to 10 years in some patients.

Median OS, months (95% CI): 11.4 (10.7–12.1)\(^a\)

3-year OS rate, % (95% CI): 22 (20–24)\(^a\)

\(^a\)Ipilimumab was given at different doses and lines of therapy, and using different schedules across the 12 studies.

Schadendorf D, et al. ECC Congress. 2013 Abs 124LBA

Hodi, et al JCO 2015
3-Year Overall Survival For Patients With Advanced Melanoma Treated With Pembrolizumab in KEYNOTE-001

Caroline Robert, 1 Antoni Ribas, 2 Omid Hamid, 3 Adil Daud, 4 Jedd D. 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 Peter Hersey, 15 Xiaoyun Nicole Li, 16 Scott J. Dieder, 16 Scot Ebbinghaus, 16 F. Stephen Hodi 17

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

Presented By Caroline Robert at 2016 ASCO Annual Meeting
Pembrolizumab Versus Ipilimumab For Advanced Melanoma: Final Overall Survival Analysis of KEYNOTE-006

Jacob Schachter,1 Antoni Ribas,2 Georgina V. Long,3 Ana Arance,4 Jean-Jacques Grob,5 Laurent Mortier,6 Adil Daud,7 Matteo S. Carlino,8 Catriona McNeil,9 Michal Lotem,10 James Larkin,11 Paul Lorigan,12 Bart Neyns,13 Christian Blank,14 Teresa M. Petrella,15 Omid Hamid,16 Honghong Zhou,17 Scot Ebbinghaus,17 Nageatte Ibrahim,17 Caroline Robert18

1Ella Lemelbaum Institute for Melanoma, Sheba Medical Center, Tel Hashomer, Israel; 2University of California, Los Angeles, Los Angeles, CA; 3Melanoma Institute Australia, The University of Sydney, Mater Hospital, and Royal North Shore Hospital, Sydney, Australia; 4Hospital Clinic de Barcelona, Barcelona, Spain; 5Aix Marseille University, Hôpital de la Timone, Marseille, France; 6Université Lille, Centre Hospitalier Régional Universitaire de Lille, Lille, France; 7University of California, San Francisco, San Francisco, CA; 8Westmead and Blacktown Hospitals, Melanoma Institute Australia, and The University of Sydney, Sydney, Australia; 9Chris O'Brien Lifehouse, Royal Prince Alfred Hospital, and Melanoma Institute Australia, Camperdown, Australia; 10Sharett Institute of Oncology, Hadassah Hebrew Medical Center, Jerusalem, Israel; 11Royal Marsden Hospital, London, UK; 12University of Manchester and the Christie NHS Foundation Trust, Manchester, UK; 13Universitair Ziekenhuis Brussel, Brussel, Belgium; 14Netherlands Cancer Institute, Amsterdam, Netherlands; 15Sunnybrook Health Sciences Center, Toronto, ON; 16The Angeles Clinic and Research Institute, Los Angeles, CA; 17Merck & Co., Inc., Kenilworth, NJ; 18Gustave Roussy and Paris-Sud University, Villejuif, France

Presented By Jacob Schachter at 2016 ASCO Annual Meeting
Overall Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Pembro Q2W</td>
<td>122</td>
<td>0.68 (0.53-0.87)</td>
<td>0.00085</td>
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<tr>
<td>Pembro Q3W</td>
<td>119</td>
<td>0.68 (0.53-0.86)</td>
<td>0.00083</td>
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<tr>
<td>Ipi</td>
<td>142</td>
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No. at risk

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<th>6</th>
<th>8</th>
<th>10</th>
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<tr>
<td>Pembro Q2W</td>
<td>279</td>
<td>266</td>
<td>249</td>
<td>234</td>
<td>221</td>
<td>215</td>
<td>202</td>
<td>188</td>
<td>176</td>
<td>163</td>
<td>156</td>
<td>96</td>
<td>44</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Pembro Q3W</td>
<td>277</td>
<td>266</td>
<td>251</td>
<td>238</td>
<td>215</td>
<td>201</td>
<td>184</td>
<td>179</td>
<td>174</td>
<td>164</td>
<td>156</td>
<td>93</td>
<td>43</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ipi</td>
<td>278</td>
<td>242</td>
<td>213</td>
<td>189</td>
<td>170</td>
<td>159</td>
<td>145</td>
<td>132</td>
<td>122</td>
<td>113</td>
<td>110</td>
<td>69</td>
<td>28</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

NR (22.1-NR)
NR (23.5-NR)
16.0 (13.5-22.0)
ORR at Each Analysis

- **Pembrolizumab Q2W**
  - IA1: 33.7%
  - IA2: 36.2%
  - Final: 36.9%

- **Pembrolizumab Q3W**
  - IA1: 32.9%
  - IA2: 36.1%
  - Final: 36.1%

- **Ipilimumab**
  - IA1: 11.9%
  - IA2: 12.9%
  - Final: 13.3%

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*Assessed per RECIST v1.1 by independent central review. Interim analysis 1 (IA1) data cutoff date: Sep 3, 2014 (median follow-up, 7.8 months). Interim analysis 2 (IA2) data cutoff date: Mar 3, 2015 (median follow-up, 13.8 months). Final analysis data cutoff date: Dec 3, 2015 (median follow-up, 22.9 months).*

Presented By Jacob Schachter at 2016 ASCO Annual Meeting
3-Year Overall Survival For Patients With Advanced Melanoma Treated With Pembrolizumab in KEYNOTE-001

Caroline Robert, 1 Antoni Ribas, 2 Omid Hamid, 3 Adil Daud, 4 Jedd D. 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 Peter Hersey, 15 Xiaoyun Nicole Li, 16 Scott J. Dieder, 16 Scot Ebbinghaus, 16 F. Stephen Hodi 17

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Presented By Caroline Robert at 2016 ASCO Annual Meeting
Complete Responders: Disposition

85 (89%) remained in CR\textsuperscript{a}

95 (15%) patients had CR per irRC by investigator review

18 (19%) remained on pembrolizumab

16 (17%) discontinued for AEs (n = 9), PD (n = 2), or other reason (n = 5)

61 (64%) stopped pembrolizumab for observation

\textsuperscript{a}Patient was alive and without disease progression. Analysis cutoff date: Sep 18, 2015.
Complete Responders Who Stopped Pembrolizumab for Observation (N = 61)

- 59 (97%) of responses were maintained
Complete Responders Who Stopped Pembrolizumab for Observation (N = 61)

- Only 2 patients experienced disease progression

Unconfirmed progression; patient remains in follow-up

Confirmed progression; patient started second pembrolizumab course

Time on therapy, Complete response, Time to last scan, Partial response, Last dose, Progressive disease

Total bar length represents the time to the last scan. Analysis cutoff date: Sep 18, 2015.
Updated Results From a Phase III Trial of Nivolumab Combined With Ipilimumab in Treatment-naïve Patients With Advanced Melanoma (Checkmate 067)

Jedd D. Wolchok,1 Vanna Chiarion-Sileni,2 Rene Gonzalez,3 Piotr Rutkowski,4 Jean-Jacques Grob,5 C. Lance Cowey,6 Christopher D. Lao,7 Dirk Schadendorf,8 Pier Francesco Ferrucci,9 Michael Smylie,10 Reinhard Dummer,11 Andrew Hill,12 John Haanen,13 Michele Maio,14 Grant McArthur,15 Dana Walker,16 Joel Jiang,16 Christine Horak,16 James Larkin,17 F. Stephen Hodi18

1Memorial Sloan Kettering Cancer Center, Ludwig Institute for Cancer Research and Weill Cornell Medical College, New York, NY, USA; 2Oncology Institute of Veneto IRCCS, Padua, Italy; 3University of Colorado Cancer Center, Denver, CO, USA; 4Maria Sklodowska-Curie Memorial Cancer Center & Institute of Oncology, Warsaw, Poland; 5Hospital de la Timone, Marseille, France; 6Texas Oncology-Baylor Charles A. Sammons Cancer Center, US Oncology Research, Dallas, TX, USA; 7University of Michigan, Ann Arbor, MI, USA; 8Department of Dermatology, University of Essen, Essen, Germany; 9European Institute of Oncology, Milan, Italy; 10Cross Cancer Institute, Edmonton, Alberta, Canada; 11Universitäts Spital, Zurich, Switzerland; 12Tasman Oncology Research, QLD, Australia; 13Netherlands Cancer Institute, Amsterdam, The Netherlands; 14University Hospital of Siena, Siena, Italy; 15Peter MacCallum Cancer Centre, Victoria, Australia; 16Bristol-Myers Squibb, Princeton, NJ, USA; 17Royal Marsden Hospital, London, UK; 18Dana-Farber Cancer Institute, Boston, MA, USA. *Contributed equally to the study

Presented By Jedd Wolchok at 2016 ASCO Annual Meeting
Progression-Free Survival (Intent-to-Treat Population)

Presented By Jedd Wolchok at 2016 ASCO Annual Meeting
Original Article

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.

N Engl J Med
Volume 373(2):123-135
July 9, 2015
Kaplan–Meier Curves for Overall Survival.

Median Overall Survival
mo (95% CI)        1-Yr Overall Survival
% of patients (95% CI)

Nivolumab (N=135)  9.2 (7.3–13.3)  42 (34–50)
Docetaxel (N=137)  6.0 (5.1–7.3)   24 (17–31)

Hazard ratio for death, 0.59 (0.44–0.79)
P<0.001

No. at Risk
Nivolumab 135 113 86 69 52 31 15 7 7 0
Docetaxel 137 103 68 45 30 14 7 2 0

Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (N=131)</th>
<th>Docetaxel (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Any event</td>
<td>76 (58)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (16)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14 (11)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>13 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1 (1)</td>
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</tr>
<tr>
<td>Leukopenia</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Neutropenia</td>
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</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Safety analyses included all the patients who received at least one dose of study drug. No treatment-related deaths occurred in patients treated with nivolumab. Treatment-related deaths were reported in three patients treated with docetaxel (one death each from interstitial lung disease, pulmonary hemorrhage, and sepsis).
KEYNOTE-024: Pembrolizumab vs Platinum-Based Chemotherapy as First-Line Therapy for Advanced NSCLC With a PD-L1 TPS ≥50%

Martin Reck,¹ Delvys Rodríguez-Abreu,² Andrew G. Robinson,³ Rina Hui,⁴ Tibor Csősz,⁵ Andrea Fülöp,⁶ Maya Gottfried,⁷ Nir Peled,⁸ Ali Tafreshi,⁹ Sinead Cuffe,¹⁰ Mary O’Brien,¹¹ Suman Rao,¹² Katsuyuki Hotta,¹³ Melanie A. Leiby,¹⁴ Gregory M. Lubiniecki,¹⁴ Yue Shentu,¹⁴ Reshma Rangwala,¹⁴ and Julie R. Brahmer¹⁵ on behalf of the KEYNOTE-024 investigators

¹Lung Clinic Grosshansdorf, Airway Research Center North (ARCN), member of the German Center for Lung Research (DZL), Grosshansdorf, Germany; ²Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; ³Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON, Canada; ⁴Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; ⁵Jász-Nagykun-Szolnok County Hospital, Szolnok, Hungary; ⁶Országos Korányi TBC és Pulmonológiai Intézet, Budapest, Hungary; ⁷Meir Medical Center, Kfar-Saba, Israel; ⁸Davidoff Cancer Center, Tel Aviv University, Petah Tikva, Israel; ⁹Southern Medical Day Care Centre, Wollongong, NSW, Australia; ¹⁰St. James’s Hospital and Cancer Trials Ireland (formerly ICORG – All Ireland Cooperative Oncology Research Group), Dublin, Ireland; ¹¹The Royal Marsden Hospital, London, UK; ¹²MedStar Franklin Square Hospital, Baltimore, MD, USA; ¹³Okayama University Hospital, Okayama, Japan; ¹⁴Merck & Co., Inc., Kenilworth, NJ, USA; ¹⁵Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

esmo.org
PD-L1 Expression and Pembrolizumab

- PD-L1 TPS cutpoint of 50% was identified in KEYNOTE-001 using independent training and validation sets\(^1\)
- FDA-approved and CE-marked companion diagnostic: PD-L1 IHC 22C3 pharmDx (Dako)

KEYNOTE-024 Study Design (NCT02142738)

Key Eligibility Criteria
- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

R (1:1) N = 305

Pembrolizumab
- 200 mg IV Q3W (2 years)

Platinum-Doublet Chemotherapy
- (4-6 cycles)

PD

Pembrolizumab
- 200 mg Q3W for 2 years

Key End Points
- Primary: PFS (RECIST v1.1 per blinded, independent central review)
- Secondary: OS, ORR, safety
- Exploratory: DOR

*To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.*
PD-L1 Screening

- 1934 patients entered screening
- 1729 submitted samples for PD-L1 assessment
- 1653 samples evaluable for PD-L1
  - 500 TPS ≥50% (30%)
  - 1153 TPS <50%
Disposition of Study Treatment

305 patients randomly allocated

Pembrolizumab
- 154 allocated
- 154 treated
- 74 ongoing
- 80 discontinued
  - 51 progressive disease
  - 17 AEs
  - 6 deaths
  - 4 patient withdrawal
  - 1 physician decision
  - 1 complete response

Chemotherapy
- 151 allocated
- 150 treated
- 15 ongoing
- 29 completed treatment
- 106 discontinued
  - 69 progressive disease
  - 16 AEs
  - 9 deaths
  - 5 patient withdrawal
  - 7 physician decision

66 crossed over to pembro on study +
9 received anti-PD-1 outside of crossover =
  - 50% (75/151) in ITT population
  - 54% (75/136) excl. those ongoing

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\(^a\) Reasons for screen failure were untreated brain metastases (n = 59), EGFR or ALK aberration (n = 30), ECOG PS 2 or 3 (n = 27), inadequate organ function (n = 19), prohibited intercurrent condition (n = 16), NSCLC not confirmed (n = 13), and other (n = 33).

\(^b\) 46 patients received pemetrexed maintenance therapy.

Data cut-off: May 9, 2016.
Progression-Free Survival

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<th>Events, n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Pembrolizumab</td>
<td>73</td>
<td>10.3</td>
<td>0.50</td>
<td>&lt;0.001</td>
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<tr>
<td>Chemo</td>
<td>116</td>
<td>6.0</td>
<td>0.37-0.68</td>
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No. at risk:
- Pembrolizumab: 154, 104, 89, 44, 22, 3, 1
- Chemo: 151, 99, 70, 18, 9, 1, 0

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.
Overall Survival

<table>
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<th>Events, n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Pembro</td>
<td>44</td>
<td>NR</td>
<td>0.60</td>
<td>0.005</td>
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<tr>
<td>Chemo</td>
<td>64</td>
<td>NR</td>
<td>(0.41-0.89)</td>
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DMC recommended stopping the trial because of superior efficacy observed with pembrolizumab

Data cut-off: May 9, 2016.
Immune-Mediated AEs With Pembrolizumab

Overall incidence
- 29% any grade
- 10% grade 3-4
- No grade 5 events

Incidence, %

Hypothyroidism  Hyperthyroidism  Pneumonitis  Infusion reactions  Severe skin toxicity  Thyroiditis  Colitis  Myositis  Hypophysitis  Nephritis  Pancreatitis  T1DM

Grade
1-2  3-4

Data cut-off: May 9, 2016.
Novel immunotherapy combinations

<table>
<thead>
<tr>
<th>Study</th>
<th>H&amp;N</th>
<th>Lung</th>
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<td>SHR 3162 PARPi</td>
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<tr>
<td>GSK3359609 ICOS+PD1i</td>
<td>✓</td>
<td>NCSLC</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X Mesothelioma, esophage sqcc, Bladder, Prostate, Melanoma</td>
</tr>
<tr>
<td>BMS-986156 GITR +PD1i</td>
<td>X</td>
<td>NSCLC</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>(more cohorts to open shortly including HNSCC, bladder, cervix...)</td>
</tr>
<tr>
<td>BMS 986148 Mesothelin+</td>
<td>X</td>
<td>Adeno</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>Mesothelioma: pleural or peritoneal, not sarcomatoid, Gastric adenoca</td>
</tr>
<tr>
<td>GO29674 OX40+PDL 1i (PDL1 +ve)</td>
<td>X</td>
<td>NSCLC B</td>
<td>X</td>
<td>X</td>
<td>TNBC B</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Prior chkpt Urothelial bladderB Melanoma+prior chkpt B</td>
</tr>
<tr>
<td>BGB - A317 PD1i</td>
<td>closed</td>
<td>NSCLC closed</td>
<td>X</td>
<td>TNBC</td>
<td>X</td>
<td>MSI-h or dMMR</td>
<td>✓</td>
<td></td>
<td>Esophageal, GastricB, HCCB (will open all tumour types shortly pt 3)</td>
</tr>
<tr>
<td>BGB-290, PARPi (A)</td>
<td>X</td>
<td>SCLC</td>
<td>HGSC</td>
<td>X</td>
<td>TNBC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>HR def-Prostate, fallopian, Primary peritoneal, BRCA1/2 anything, ATM-gastric ca</td>
</tr>
<tr>
<td>(B)</td>
<td>X</td>
<td>X</td>
<td>BRCA1/2</td>
<td>X</td>
<td>BRCA1/2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X Any with susceptible tumor</td>
</tr>
<tr>
<td>BGB COMBO PARPi+PD1i</td>
<td>X</td>
<td>SCLC</td>
<td>HGSC</td>
<td>X</td>
<td>TNBC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Fallopian, Primary peritoneal: BRCA1/2 + Platinum sensitive</td>
</tr>
</tbody>
</table>
Why do PD-1 pathway inhibitors work in some patients but not others?

- **Something simple** (tumour volume/LDH)
- **Something solvable** (PD-L1)
- **Something much more complex** (tumour/immune interaction, T cell infiltration, gene signature, DNA repair deficiencies, mutation burden, gut microbiome....)
- ....?something that can be overcome
Patient With Gastric Cancer Treated In KEYNOTE-012

- PD by central review per RECIST 1.1 at week 16

- PR has been achieved at week 28 and confirmed at week 32 per tumor burden and improved non-target disease but cannot be captured per RECIST 1.1

Case presented by K Muro at 2015 Gastrointestinal Cancer Symposium (abstract 03).
Practical Issues with Patients on new Immune Drugs

• **How long to treat?**

• **Volume of work in day chemotherapy units**
  – Not chemotherapy
  – Not cytotoxic
  – *Routine pre-treatment medical review may not be necessary*
  – *Blood monitoring not immediate like chemotherapy*
  – Home administration
  – Remote patients

• **Nurse practitioner/coordinator important**

• **How do we deal with the long term survivors?**

• **Cost and Value**