Modulating the PD-1/PD-L1 axis in lymphoma

Dr. Adam Greenbaum

Faculty discussant Dr. Solomon Graf
Obligatory Slide

2 Easy Steps To Achieving a Driftwood Finish Fellowship Success
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Your favorite PD–1/PD–L1 inhibitor
Your favorite PD–1/PD–L1 inhibitor
Your favorite PD-1/PD-L1 inhibitor + Your favorite cancer
Your favorite PD-1 / PD-L1 inhibitor + Your favorite cancer =
Your favorite PD–1/PD–L1 inhibitor + Your favorite cancer =

The NEW ENGLAND JOURNAL of MEDICINE
Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck

Nivolumab for Recurrent Carcinoma of the Head and Neck

R.L. Ferris, G. Blumenschein, Jr., J. Fayette, J. Guigay,
K. Harrington, S. Kasper, E.E. Vokes, C. Even, F. W.
L.C. Iglesias Docampo, R. Haddad, T. Rordorf, N. Kiyota,
M. Lynch, W.J. Geese, J. Kopit, J.W. Shaw, and M.L.
Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer


Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma

Original Article

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Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Nina Hui, M.B., B.S.,
Natasha Leitl, M.D., Ami S. Balmanoukian, M.D., Matthew Gubens, M.D.,
Anita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Goldenberg, M.D.,
Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D.,
Enriqueta Felip, M.D., Dong-Seok Lee, M.D., Matthew D. Hellman, M.D.,
Omid Hamid, M.D., Jonathan W. Goldman, M.D., B.A., Jin Zhang, Ph.D.,
Marisa Dokal-Filhart, Ph.D., Ruth Z. Rutledge, M.D., Gregory M. Lubiniecki, M.D.,
Jared K. Lucey, Ph.D., Reshma Rangan, M.D., Kenneth Emanuel, M.D.,
Charlotte Roach, B.S., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators

Safety and Tumor Responses with Pembrolizumab (Anti-PD-1) in Melanoma

Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., Adil Daud, M.D.,
F. Stephen Hodi, M.D., Wenyen Hwu, M.D., Ph.D., Richard Kefford, M.D., Ph.D.,
David Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D.,
Roy S. Weber, M.D., Ph.D., Rosana Dromer, M.D., Tarah C. Gangadhar, M.D.,
Patrick G., Hassan Zarour, M.D., Anthony M. Joshwa, M.B., B.S., Ph.D.,
Gergich, M.A., Jeroen Elissass-Schaap, Ph.D., Alain Agazzi, B.S., Ph.D.,
Celine Mateus, M.D., Peter Boasberg, M.D., Paul C. Tumeh, M.D.,
Suzanne Chmielowski, M.D., Ph.D., and Antoni Ribas, M.D., Ph.D.

Original Article

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiariotto-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao,
D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill,
J. Wächter, M.S. Carliano, J.B. Haanen, M. Maio, I. Marquez-Rodas,
G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow,
K. Grossmann, M. Szol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak,
F.S. Hodi, and J.D. Wolchok

Original Article

 pued Cancer

O.E. Ready, L.O. Chow, W.J. O. Arieti, M.A. Burgio,
K.J. Antonia, C.M. Rudin,
Kiyota, M., and J.R. Pritchard,
and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators

Original Article

Cancer

D. E. McGovern, S. Cingolani, H.J. Haanen, S.
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Combined Nivolumab or Monotherapy


Safety and Tumor Responses with Pembrolizumab (Anti-PD-1) in Melanoma

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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., Cartronin McNeil, M.D., Ph.D., Michael Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Michal Lotem, 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., Michèle Koth, R.N., B.S.N., Honghong Zhou, Ph.D., C. H. Ibrahim, M.D., Scott Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma

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PD-1 Blockade in Tumors with Mismatch-Repair Deficiency


PD-1 Blockade with Pembrolizumab in Advanced Melanoma or Monotherapy

Combined Nivolumab and Pembrolizumab versus Ipilimumab in Advanced Melanoma

Lung Cancer Treatment
PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin’s Lymphoma

Stephen M. Ansell, M.D., Ph.D., Alexander M. Lesokhin, M.D., Ivan Borrello, M.D., Ahmad Halwani, M.D., Emma C. Scott, M.D., Martin Gutierrez, M.D., Stephen J. Schuster, M.D., Michael M. Millenson, M.D., Deepika Cattray, M.S., Gordon J. Freeman, Ph.D., Scott J. Rodig, M.D., Ph.D., Bjoern Chapuy, M.D., Ph.D., Azra H. Ligon, Ph.D., Lili Zhu, M.S., Joseph F. Grosso, Ph.D., Su Young Kim, M.D., Ph.D., John M. Timmerman, M.D., Margaret A. Shipp, M.D., and Philippe Armand, M.D., Ph.D.
Nivolumab for classical Hodgkin’s lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial

Anas Younes, Armando Santoro, Margaret Shipp, Pier Luigi Zinzani, John M Timmerman, Stephen Ansell, Philippe Armand, Michelle Fanale, Voravit Ratanatharathorn, John Kuruvilla, Jonathon B Cohen, Graham Collins, Kerry J Savage, Marek Trneny, Kazunobu Kato, Benedetto Farsaci, Susan M Parker, Scott Rodig, Margaretha G M Roemer, Azra H Ligon, Andreas Engert

Programmed Death-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure

Philippe Armand, Margaret A. Shipp, Vincent Ribrag, Jean-Marie Michot, Pier Luigi Zinzani, John Kuruvilla, Ellen S. Snyder, Alejandro D. Ricart, Arun Balakumaran, Sheloniida Rose, and Craig H. Moskowitz
Nivolumab for classical Hodgkin’s lymphoma after failure of both autologous and allogeneic stem-cell transplantation: a phase 1 trial

Anas Younes, Armand Bex, Voravit Ratanatharit, Daniel Ganser, Susan M Parker, Stephanie Hellmann, David Schlenk, Marc de Botton, Justin D Flinn, Sebastian Trumper, John Kuruvilla, Barry J Powles, Jodi M Lerner, Claudia Kuhnt, Kathleen P Wright, Shirlayer Barlow, Derek E James, Paul D Buchdahn, Thomas Gadek, Giora M Rales, Carlos A Sanz-Gallego, and Stuart A Kamaras

Lancet Oncol 2016; 17: 1283-94
Online
http://dx.doi.org/10.1016/S1470-2045(16)0030167-X

VOLUME 17

FAILURE

WHEN YOUR BEST JUST ISN'T GOOD ENOUGH.
Response of HL

- ABVD: 70 – 90% cure
- Autologous transplant: 55% cure
- Brentuximab: PFS 5 – 10 months
- After brentuximab: PFS 3.5 months
Why Hodgkin’s Lymphoma?

- Hodgkin’s lymphoma characterized by massive infiltration of normal immune cells
- The immune response is ineffective
- This may be mediated by PD-L1 expression by the tumor cells
# PD-L1 expressed in HL

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Cytogenetic Alterations</th>
<th>IHC-positive HRS cells</th>
<th>Nuclear pSTAT3</th>
<th>EBER</th>
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<td>1</td>
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Alterations of 9p24.1

Figure. PD-L1 and PD-L2 genetic alterations and PD-L1 expression in tumor biopsy samples from 96 patients. (A) Distribution of 9p24.1 genetic alterations.* (B) Distribution of PD-L1 H-scores across cases with polysomy, copy gain and amplification.

*Amplification was defined as target:control probe ratio ≥3:1; copy gain, target:control probe ratio >1:1 and <3:1; polysomy, target:control probe ratio 1:1 and >2 copies of each probe

^H-score was calculated by multiplying the percentage of PAX5^+ (malignant) cells with positive staining (0–100%) and the average intensity of positive staining (1–3+; minimum 50 HRS cells counted)

ASH annual meeting, 2016. #2923 Chromosome 9p24.1/PD-L1/PD-L2 Alterations and PD-L1 Expression and Treatment Outcomes in Patients with Classical Hodgkin Lymphoma Treated with Nivolumab (PD-1 Blockade)
9p24.1 alterations associated with worse survival

J Clin Oncol. 2016 Aug 10;34(23):2690-7
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Nivolumab phase I

- 23 patients previously treated with at least one prior regimen
  - 87% with 3+ previous regimens
  - 78% received brentuximab
  - 78% received ABVD
## Table 3. Clinical Activity in Nivolumab-Treated Patients.

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<td>30–50</td>
</tr>
</tbody>
</table>
### Table 3. Clinical Activity in Nivolumab-Treated Patients.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N=23)</th>
<th>Failure of Both Stem-Cell Transplantation and Brentuximab (N=15)</th>
<th>No Stem-Cell Transplantation and Failure of Brentuximab (N=3)</th>
<th>No Brentuximab Treatment (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>4 (17)</td>
<td>1 (7)</td>
<td>0</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Partial response</td>
<td>16 (70)</td>
<td>12 (80)</td>
<td>3 (100)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3 (13)</td>
<td>2 (13)</td>
<td>0</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Objective response</td>
<td>20</td>
<td>13</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>No. of patients</td>
<td>87 (66—97)</td>
<td>87 (60—98)</td>
<td>100 (29—100)</td>
<td>80 (28—99)</td>
</tr>
<tr>
<td>Percent of patients (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression-free survival at 24 wk — % (95% CI)</td>
<td>86 (62—95)</td>
<td>85 (52—96)</td>
<td>NC‡</td>
<td>80 (20—97)</td>
</tr>
<tr>
<td>Overall survival — wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Range at data cutoff</td>
<td>21—75</td>
<td>21—75</td>
<td>32—55</td>
<td>30—50</td>
</tr>
</tbody>
</table>
All patients failed, ineligible for, or refused ASCT
Pembrolizumab phase I

ORR 65%
Phase 1: Collect underpants

Phase 2: ?

Phase 3: Profit
Nivolumab for classical Hodgkin’s lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial

Anas Younes, Armando Santoro, Margaret Shipp, Pier Luigi Zinzani, John M Timmerman, Stephen Ansell, Philippe Armand, Michelle Fanale, Voravit Ratanatharathorn, John Kuruvilla, Jonathon B Cohen, Graham Collins, Kerry J Savage, Marek Trneny, Kazunobu Kato, Benedetto Farsaci, Susan M Parker, Scott Rodig, Margaretha G M Roemer, Azra H Ligon, Andreas Engert
Nivolumab phase 2

Progression-free survival at 6 months 76.9% (95% CI 64.9–85.3)
Pembrolizumab phase 2 (only presented)

- **Three arms**
  - Failure of both autologous transplant and brentuximab
  - Ineligible for transplant, failure of brentuximab
    - ORR 70-80%
    - CR 20-30%
    - PR 50%
    - SD 10-20%
  - Third arm (not reported): Failure of autologous transplant, no brentuximab
Adverse events

- Fatigue, rash, nausea, diarrhea, pyrexia, hypothyroidism, infusion reaction, cytopenias
- Serious (~6%)
  - Choose your own “itis”
    - Pneumonitis
    - Pancreatitis
    - Stomatitis
    - Colitis
    - Meningitis
    - Thyroiditis
    - Hypophysitis
Adverse events

- Fatigue, rash, nausea, diarrhea, pyrexia, hypothyroidism, infusion reaction, cytopenias
- Serious (~25%)
  - Choose your own “itis”
    - Pneumonitis
    - Pancreatitis
    - Stomatitis
    - Colitis
    - Meningitis
    - Thyroiditis
    - Hypophysitis

Mefitis is the Samnite Goddess of the foul-smelling gases of the earth. The Samnites occupied central Italy before the rise of Rome. Mefitis was worshipped in central and southern Italy before Roman times, with her main shrine in the volcano Ampsanctus in Samnium. There was a temple dedicated to her in Cremona, and another on the Esquiline Hill in Rome. It is theorized that Mefitis was originally a Goddess of underground sources, such as natural springs—the fact that many of these springs were sulfurous led to her association with noxious gases. She is almost always identified with volcanoes, having been worshipped at Pompeii. Her name, which likely means “one who smokes in the middle,” is also seen as Mephitis.
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    - Pancreatitis
    - Meningitis
    - Hypophysitis
FDA approval pending phase 3

Immunotherapeutic Use Expanded to Hodgkin Lymphoma

The U.S. Food and Drug Administration approval provides a new option for patients with the most common type of Hodgkin lymphoma.

Use of the immunotherapeutic nivolumab (Opdivo) was recently expanded by the U.S. Food and Drug Administration (FDA) to include certain patients with Hodgkin lymphoma.

The expanded nivolumab approval means the drug can be used for patients with classical Hodgkin lymphoma that has relapsed or progressed despite treatment with an autologous hematopoietic stem cell transplant and post-transplantation brentuximab vedotin (Adcetris).

The approval of nivolumab for classical Hodgkin lymphoma was based on results from the phase II KEYNOTE-087 clinical trial, according to Merck, the company that develops pembrolizumab. In brief, the results showed that 69 percent of the 210 adult patients who received pembrolizumab had an objective response for an estimated median of 11.1 months. Of the 145 patients who responded, 46 had a complete response and 99 had a partial response.

FDA Expands Use of Pembrolizumab to Fourth Cancer Type

Posted on March 23, 2017 by Karen Honey, PhD

Last week, the U.S. Food and Drug Administration (FDA) announced that it had approved expanding the use of the immunotherapeutic pembrolizumab (Keytruda) to include the treatment of certain patients with Hodgkin lymphoma. Specifically, the FDA approved pembrolizumab for treating adults and children with classical Hodgkin lymphoma that has not responded to treatment or that has relapsed after three or more different treatments.
IF WE HIT THAT BULLSEYE, THE REST OF THE DOMINOES WILL FALL LIKE A HOUSE OF CARDS.

CHECKMATE.
PD-L1 and checkpoint inhibitors

[Diagram showing distribution of stable disease, progressive disease, complete remission, and partial remission across different PD-L1 H score quartiles (Q1 to Q4).]
PD-L1 and checkpoint inhibitors

![Bar chart showing responses to PD-L1 and checkpoint inhibitors]

**P-VALUE INTERPRETATION**
- 0.001: Highly significant
- 0.01: Significant
- 0.02: Highly suggestive
- 0.03: On the edge of significance
- 0.04: Significant
- 0.05: On the edge of significance
- 0.06: Redo calculations
- 0.07: Hey, look at this interesting subgroup analysis
- 0.08: Significant
- 0.09: Hey, look at this interesting subgroup analysis
- 0.1: Hey, look at this interesting subgroup analysis

xkcd.com
Role of allogeneic transplant

- High TRM in initial reports
  - Myeloablative, TRM > 50%
  - Reduced intensity, TRM 15-25%
- Concern that prior immune priming may worsen GvHD
  - In phase 1 trial of nivolumab, 5 patients proceeded to allogeneic transplant with TRM of 80%
  - In phase 2 trial, 17 patients proceeded to allogeneic transplant, with TRM 25%, 82% with acute GvHD
    - Strange manifestations such as encephalitis and steroid refractory fevers
    - No relapse in those who survived
- Allogeneic transplant is category 3 recommendation per NCCN guidelines
Interesting Combinations

Panobinostat in Patients With Relapsed/Refractory Hodgkin’s Lymphoma After Autologous Stem-Cell Transplantation: Results of a Phase II Study

Anas Younes, Anna Sureda, Dina Ben-Yehuda, Pier Luigi Zinzani, Tee-Chuan Ong, H. Miles Prince, Simon J. Harrison, Mark Kirschbaum, Patrick Johnston, Jennifer Gallagher, Christophe Le Corre, Angela Shen, and Andreas Engert
Panobinostat modulates PD-1

Combination with chemotherapy/radiation
Conclusions

- The vast majority of Hodgkin’s lymphoma express PD-L1
- A subset of Hodgkin’s lymphoma over-express PD-L1 which appears to correlate with outcome with conventional therapy
- Nivolumab is FDA approved after failure of ASCT and brentuximab
- Pembrolizumab is FDA approved for treatment after failing 3+ lines of therapy
- Phase 3 studies are pending
- Studies investigating checkpoint inhibitors in combination with chemotherapy/small molecules/radiation are coming
Questions?

- Thanks
  - Dr. Solomon Graf
  - New England Journal of Medicine