III International Symposium on Immuno-Oncology
Saturday, October 7th 9:30 – 10:00 am

Melanoma, o status da imunoterapia e o futuro próximo

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Chair, Melanoma Committee at SWOG
High LDH
High tumour volume
More metastatic sites
Brain metastases
PD-L1 negative/lack of immune signature

Normal LDH
Low tumour volume
Fewer metastatic sites
CR to treatment

Dabrafenib + trametinib¹ (n = 352)
Vemurafenib + cobimetinib⁵ (n = 247)
Nivolumab² (n = 210)
Nivolumab³ (n = 316)
⁴Pembrolizumab⁴ (n = 279)
Nivo + ipi³ (n = 314)

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CTLA-4 and PD-1 Checkpoint Blockade
Checkmate 067: Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>11.7 (8.9–21.9)</td>
<td>6.9 (4.3–9.5)</td>
<td>2.9 (2.8–3.2)</td>
</tr>
<tr>
<td>HR (95% CI) vs. IPI</td>
<td>0.42 (0.34–0.51)</td>
<td>0.54 (0.45–0.66)</td>
<td>--</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.76 (0.62–0.94)</td>
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</tr>
</tbody>
</table>

Grade 3/4 tox: 59% NIVO+IPI, 21% NIVO, 28% IPI

Database lock: Sept 13, 2016, minimum f/u of 28 months

Larkin et al. AACR 2017, Wolchok et al. NEJM 2017
Checkmate 067: Overall Survival

<table>
<thead>
<tr>
<th>Patients at risk:</th>
<th>NIVO+IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
</table>
| Months           | Median OS, mo (95% CI) | HR (98% CI) vs. IPI | HR (95% CI) vs. NIVO | *
|                  | NR (29.1–NR) | 0.55 (0.42–0.72) * | 0.88 (0.69–1.12) -- | P<0.0001 |
|                  | 20.0 (17.1–24.6) | 0.63 (0.48–0.81) * | 0.88 (0.69–1.12) -- | -- |

*NIVO+IPI (N=314)
NIVO (N=316)
IPI (N=315)

*P < 0.0001

Larkin et al. AACR 2017, Wolchok et al. NEJM 2017

Database lock: Sept 13, 2016, minimum f/u of 28 months
CTLA-4 and PD-1 Checkpoint Blockade

Abril-Rodriguez and Ribas, Snapshot, Cancer Cell 2017
Melanoma response to PD-1 blockade is mediated by pre-existing infiltrates of CD8s inhibited by reactively expressed PD-L1.

Tumeh et al., Nature 2014
PD-1 blockade induces responses by inhibiting adaptive immune resistance

Hypothesis formulated based on quantitative IHC analyses of 46 cases from UCLA

Adapted from Tumeh et al. Nature 2014
What differentiates anti-PD-1-responsive from non-responding melanomas?

ORR: 33%
ORR in previously untreated: 45%

Ribas et al. JAMA 2016
What differentiates anti-PD-1-responsive from non-responding melanomas?

Pembrolizumab Keynote 001 trial. Central radiology review by RECIST v1.1

Ribas et al. JAMA 2016

Ayers et al, JCI 2017
What differentiates anti-PD-1-responsive from non-responding melanomas?

Pembrolizumab Keynote 001 trial. Central radiology review by RECIST v1.1

Ribas et al. JAMA 2016

Le et al, NEJM 2015

Rizvi et al, Science 2015

Mutational load and response to anti-PD-1 in NSCLC

Mutational load and response to anti-PD-1 in MSI high colon cancer

Mutational load and response to anti-PD-1 in melanoma

McGranahan et al. Science 2016
What differentiates anti-PD-1-responsive from non-responding melanomas?


IPRES (Innate anti-PD-1 Resistance) signature

Pembrolizumab Keynote 001 trial. Central radiology review by RECIST v1.1

Ribas et al. JAMA 2016
The Cancer Immunogram

- Tumor foreignness
  - Mutational load
- Tumor sensitivity to immune effectors
  - MHC expression
  - IFN-γ sensitivity
- General immune status
  - Lymphocyte count
- Immune cell infiltration
  - Intratumoral T cells
- Absence of soluble inhibitors
  - IL6 > CRP/ESR
- Absence of inhibitory tumor metabolism
  - LDH, glucose utilization
- Absence of Checkpoints
  - PD-L1

Desmoplastic melanoma: Defined by a dense collagenous fibrous tissue

A rare subtype of melanoma (less than 4%)
A dense fibrous reaction
A known relationship to UV light damage
High NF1 mutation rate and no known actionable genes for targeted therapies.

Zeynep Eroglu
Siwen Hu-Lieskovan
Jesse Zaretsky
(submitted)
High response rate and high mutational load in Desmoplastic melanoma

70% overall response rate
18% complete response rate

Tumor Mutational Load
p=0.015

Extended Data Figure 1

n=57 (out of 1054 cases Reviewed*)
1 slllc
3 M1a
20 M1b
35 M1c

*Retrospective Review

Estimated 2 year OS 73% (CI 62-88).

Zeynep Eroglu
Siwen Hu-Lieskovan
Jesse Zaretsky
(submitted)
Primary and Acquired Resistance to PD-1 Blockade

Waterfall plot of RECIST responses in 510 patients treated with pembrolizumab in the Keynote 001 trial

KM of duration of response in patients treated with pembrolizumab or ipilimumab in the Keynote 006 trial

Ribas et al. JAMA 2016

Robert et al. ASCO 2017
How does the cancer sense IFN-gamma and reactively expresses PD-L1?

Tumeh et al., Nature 2014
Interferon gamma receptor pathway regulating reactive PD-L1 expression

Adapted from Shin et al. Cancer Discovery 2017 and Garcia-Diaz et al. Cell Reports 2017
Primary resistance to PD-1 blockade by disabling PD-L1 adaptive expression

Would be useless to try to inhibit PD-1:PD-L1

Adapted from Shin et al. Cancer Discovery 2017 and Garcia-Diaz et al. Cell Reports 2017
Is JAK loss associated with primary resistance to PD-1 blockade?

1/23 melanoma cases with high-allele frequency JAK1 mutation

1/16 colorectal cases with high-allele frequency JAK1 mutation

data from Le DT et al. NEJM 2015

Shin et al, Cancer Discovery 2017
Interferon-gamma Sensitivity Model:

- Initially, benefits of PD-L1 suppression outweigh immune sensitizing effects.
- PD-L1 expression is of no benefit after PD-1/L1 blockade; selective pressure is flipped.
- The cancer has an incentive to lose INF-γ sensitivity, avoid apoptosis, enhanced antigen presentation.

Adapted from Zaretsky et al. NEJM 2016
In 8 additional paired biopsies:
• One additional $B2M$ LoF mutation
• No additional $JAK1/2$, $IFNGR$, $IRF1$ or $STAT1/3/5$ LoF mutations

How prevalent are $JAK$ and $B2M$ loss-of-function mutations?

Jesse Zaretsky, Antoni Ribas (unpublished)
Confirmation of $B2M$ and $JAK$ as genetic mechanisms of resistance to anti-PD-1 using CRISPR/Cas9 knock out sublines

Davis Torrejon, Gabriel Abril Rodriguez, Siwen Hu-Lieskován (unpublished)
Defects in the IFNγ pathway induce resistance

Loss of Ptpn2 increases IFNγ sensing by tumour cells

Genome-wide CRISPR mutagenesis reveals essential genes for the effector function of T cells in a target cell.

Functional loss of APLNR reduces efficacy of cancer Immunotherapy, which IPs with JAK1
Conclusions

• Inhibiting adaptive immune resistance is the mechanistic basis of the antitumor activity of PD-1 blockade therapies

• Combination therapies aimed at increasing T cell infiltration in tumors may improve the antitumor activity of PD-1 blockade

• Loss of function mutations in IFN-gamma receptor signaling or antigen presenting machinery mediate some cases of primary resistance and acquired resistance to PD-1 blockade therapy
Intervalo
Combinação em Imunoterapia: Deve ser o standard?
Qual o melhor parceiro para combinar com imunoterapia?

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Intrinsic or primary resistance to immune checkpoint therapies - cellular microenvironment

Intrinsic or primary resistance to immune checkpoint therapies—cellular microenvironment

2 out of 48 melanoma cell lines had JAK1/2 LOF mutations and did not respond to IFN-gamma by expressing PD-L1.
Management of cancer in the anti-PD-1/L1 era

Generate T cells:
- + anti-CTLA4
- + immune activating antibodies or cytokines
- + TLR agonists or oncolytic viruses
- + IDO or macrophage inhibitors
- + targeted therapies

Bring T cells into tumors:
- Vaccines
- TCR engineered ACT
- CAR engineered ACT

Modified from Ribas, Cancer Discovery 2016
T cell mediated INFγ release triggers both:
- PD-L1 expression
- IDO expression
in tumor cells and in the μ-environment
# Efficacy data: ECHO-202, Keynote-006, Checkmate 067

<table>
<thead>
<tr>
<th>Response</th>
<th>ECHO-202 Epacadostat + Pembro&lt;sup&gt;1&lt;/sup&gt;</th>
<th>PD-1 single agent Checkmate 067&lt;sup&gt;2&lt;/sup&gt; / Keynote-006&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Ipi + Nivo Checkmate 067&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR+PR)</td>
<td>56%</td>
<td>44% / 42%</td>
<td>58%</td>
</tr>
<tr>
<td>CR</td>
<td>14%</td>
<td>16% / 13%</td>
<td>19%</td>
</tr>
<tr>
<td>PR</td>
<td>41%</td>
<td>30% / 29%</td>
<td>42%</td>
</tr>
<tr>
<td>SD</td>
<td>16%</td>
<td>10% / 21%</td>
<td>11%</td>
</tr>
<tr>
<td>PD</td>
<td>29%</td>
<td>38.6 / 29%</td>
<td>23.6</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3%</td>
<td>7% / -</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td><strong>12.4 months</strong></td>
<td><strong>6.9 / 8.3 months</strong></td>
<td><strong>11.5 months</strong></td>
</tr>
<tr>
<td>PFS @ 18 months</td>
<td>52%</td>
<td>43% / -</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Grade 3/4 toxicity</strong></td>
<td><strong>20%</strong></td>
<td><strong>21% / 17.5%</strong></td>
<td><strong>59%</strong></td>
</tr>
</tbody>
</table>

<sup>1</sup> Hamid, ESMO 2017; <sup>2</sup> Larkin, AACR 2017 and Wolchok, NEJM 2017; <sup>3</sup> Robert, ASCO 2017 (2 pembro arms pooled) Note: data not randomized head to head, comparison only for indication
Double immune checkpoint inhibition: PD-1 plus LAG-3

CTLA-4 Blockade

PD-1 Blockade + LAG-3 Blockade

ASCO 2017-Ascierto et al

Nivolumab + BMS-986016 (anti-LAG3)

*Patients refractory or resistant to anti-PD-1*
Metastatic Melanoma with Prior-IO Cohort

LAG-3 ≥1%*

n = 22

ORR, 20%

LAG-3 <1%*

n = 12

ORR, 7.1%

LAG-3 Unknown

n = 8

ORR, 0

• LAG-3 expression enriched for responses in IO-experienced patients

• Nearly a 3-fold increase in ORR was observed in patients with LAG-3 ≥1% vs LAG-3 <1% (20% vs 7.1%)

• Overall response rate was 13%

6 PRs: 2 prior PD; 3 prior PR; 1 unk

DCR, disease control rate; ORR, objective response rate.

*LAG-3 expression (percent of positive cells within invasive margin, tumor, and stroma) evaluated using immunohistochemistry (IHC) assays on formalin-fixed, paraffin-embedded tumor sections. Immune cell LAG-3 expression (≥1% or <1%) determined using mouse antibody clone 17B4. *Response-evaluable patients (n = 48; all progressed on prior anti–PD-1/PD-L1 therapy). Six patients had clinical progression prior to their first scan and are not included in the plot. One patient with best change from baseline >30% had an unconfirmed best response of SD.

Ascierto et al. ASCO 2017
Adding intralesional therapies to anti-PD-1/L1

...the benefit should only be in the patients who were unlikely to respond to anti-PD-1/L1 alone because their T cells were not in the tumor + Anti-PD-1/anti-PD-L1
MASTERKEY-265: T-Vec + pembrolizumab

62% objective response rate
33% complete response rate

Ribas et al. Cell 2017
T-VEC increases tumor CD8 and PD-L1 in patients responding to combination with pembrolizumab.
Adding BRAF targeted therapies to anti-PD-1/L1

BRAFi+MEKi

Anti-PD-1/anti-PD-L1

Wilmott et al. CCR 2013
Frederick et al. CCR 2013

BRAFi+MEKi + anti-PD-1/L1
Combination of BRAFi+MEKi+Anti-PD-1

**RESEARCH ARTICLE**

**CANCER**

Improved antitumor activity of immunotherapy with BRAF and MEK inhibitors in BRAF^V600E melanoma

Siwen Hu-Lieskovan,1 Stephen Mok,1 Blanca HomeT Moreno,2,4 Jennifer Tsai,2,4 Lidia Robert,1 Lucas Goedert,3 Elaine M. Pinheiro,5 Richard C. Koya,5a Thomas G. Graeber,1,2,4,6 Begoña Comín-Andújar,6,7 Antoni Ribas1,2,4,7a

NIH Director’s Blog*

Knocking Out Melanoma: Does This Triple Combo Have What It Takes?
 Posted on March 31, 2015 by Dr. Francis Collins


Clinical trials combining BRAFi+MEKi+anti-PD-1/L1

dabrafenib+trametinib +durvalumab

Ribas et al. J Clin Oncol 33, 2015 (suppl, abstr 3003 ASCO)

dabrafenib+trametinib +pembrolizumab

Ribas et al. ESMO, 2017

vemurafenib+cobimetinib +atezolizumab

Hwu et al. Annals of Oncology 27; 2016 (supp 6; abstr 1109PD ESMO)
Conclusions

• Inhibiting adaptive immune resistance is the mechanistic basis of the antitumor activity of PD-1 blockade therapies

• Combination therapies aimed at increasing T cell infiltration in tumors may improve the antitumor activity of PD-1 blockade

• Loss of function mutations in IFN-gamma receptor signaling or antigen presenting machinery mediate some cases of primary resistance and acquired resistance to PD-1 blockade therapy