PATIENT SELECTION
IMMUNOGRAM, IMMUNOPROFILING, IMMUNOSCORES AND OTHER BIOMARKERS OF POTENTIAL USE

JOHN HAANEN, MD PHD
Unresectable or Metastatic Melanoma
• Previously untreated
• 945 patients

CHECKMATE 067: STUDY DESIGN

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone*

Randomize 1:1:1

Stratify by:
• BRAF status
• AJCC M stage
• Tumor PD-L1 expression <5% vs ≥5%*

N=314

NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W

N=316

NIVO 3 mg/kg Q2W + IPI-matched placebo

N=315

IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo

Treat until progression or unacceptable toxicity

Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

*The study was not powered for a comparison between NIVO and NIVO+IPI

Presented at AACR 2017 by Larkin
WHY DO WE NEED NEW BIOMARKERS FOR RESPONSE TO IMMUNOTHERAPY?

Wolchok et al., NEJM 2017
WHY DO WE NEED NEW BIOMARKERS FOR RESPONSE TO IMMUNOTHERAPY?

SOME PATIENTS BENEFIT LONG TERM FROM IPILIMUMAB

Progression-free Survival

No. at Risk
Nivolumab plus ipilimumab | 314 | 218 | 175 | 155 | 136 | 131 | 124 | 117 | 110 | 104 | 100 | 92 | 75 | 29 | 5 | 0
Nivolumab | 316 | 177 | 151 | 131 | 119 | 111 | 105 | 102 | 96 | 87 | 81 | 75 | 61 | 24 | 0 | 0
Ipilimumab | 315 | 136 | 78 | 58 | 46 | 42 | 34 | 32 | 30 | 28 | 26 | 23 | 15 | 8 | 2 | 0

Wolchok et al., NEJM 2017
WHY DO WE NEED NEW BIOMARKERS FOR RESPONSE TO IMMUNOTHERAPY?

SOME PATIENTS BENEFIT LONG TERM FROM NIVOLUMAB
SOME PATIENTS BENEFIT LONG TERM FROM IPILIMUMAB

Wolchok et al., NEJM 2017
WHY DO WE NEED NEW BIOMARKERS FOR RESPONSE TO IMMUNOTHERAPY?

SOME PATIENTS BENEFIT LONG TERM FROM COMBO
SOME PATIENTS BENEFIT LONG TERM FROM NIVOLUMAB
SOME PATIENTS BENEFIT LONG TERM FROM IPILIMUMAB

Wolchok et al., NEJM 2017
WHY DO WE NEED NEW BIOMARKERS FOR RESPONSE TO IMMUNOTHERAPY?

No long-term benefit from current checkpoint inhibitors

Wolchok et al., NEJM 2017
PERHAPS SOMETIMES COMBINATION IT IS JUST TOO MUCH…

ORR of 56.2% for NIVO+IPI and 42.3% for NIVO

ORR of 73.5% for NIVO+IPI and 58.8% for NIVO
MULTIPARAMETER BIOMARKERS ARE THE KEY!
THE CANCER IMMUNOGRAM

Tumor foreignness
Mutational load

Tumor sensitivity to immune effectors
MHC expression
IFN- sensitivity

General immune status
Lymphocyte count

Absence of inhibitory tumor metabolism
LDH, glucose utilization

Immune cell infiltration
Intratumoral T cells

Absence of soluble inhibitors
IL6->CRP/ESR

Absence of Checkpoints
PD-L1

Blank, Haanen et al. Science 2016
How often does the immune system ‘see’ neo-antigens in melanoma?

- The T cell based immune system frequently interacts with the consequences of DNA damage in human melanoma:

  **CD8 T cells**: 12 pts analyzed, neo-antigen specific reactivity in 10. Not all alleles covered, exome coverage incomplete, epitope predictions imperfect...

  **CD4 T cells**: 6 pts analyzed, neo-antigen specific reactivity in 5
Does the extent of DNA damage correlate with the clinical effects of cancer immunotherapy?

Alexandrov et al, Nature 2013
Mutational load correlates with improved clinical benefit from CTLA-4 or PD-1 blockade

Van Allen et al., Science 2015
Rizvi et al., Science 2015
IMPACT OF TUMOR MUTATION BURDEN ON THE EFFICACY OF FIRST-LINE NIVOLUMAB IN STAGE IV OR RECURRENT NON-SMALL CELL LUNG CANCER: AN EXPLORATORY ANALYSIS OF CHECKMATE 026

Solange Peters,1 Benjamin Creelan,2 Matthew D. Hellmann,3 Mark A. Socinski,4 Martin Reck,5 Prabhu Bhagavatheeswaran,6 Han Chang,6 William J. Geese,6 Luis Paz-Ares,7 David P. Carbone8

1Oncology Department, Lausanne University Hospital, Lausanne, Switzerland; 2H. Lee Moffitt Cancer Center, Tampa, FL, USA; 3Memorial Sloan Kettering Cancer Center, New York, NY, USA; 4Florida Hospital Cancer Institute, Orlando, FL, USA; 5LungenClinic Grosshansdorf, Airway Research Center North (ARCN), German Center for Lung Research (DZL), Grosshansdorf, Germany; 6Bristol-Myers Squibb, Princeton, NJ, USA; 7Hospital Universitario Doce de Octubre, CNIO and Universidad Complutense, Madrid, Spain; 8Ohio State University Comprehensive Cancer Center, Columbus, OH, USA
Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC

Key eligibility criteria:
- Stage IV or recurrent NSCLC
- No prior systemic therapy for advanced disease
- No EGFR/ALK mutations sensitive to available targeted inhibitor therapy
- ≥1% PD-L1 expression

Randomize 1:1

Nivolumab 3 mg/kg IV Q2W
n = 271

Disease progression or unacceptable toxicity

Tumor scans Q6W until week 48 then Q12W

Chemotherapy (histology dependent)
Maximum of 6 cycles
n = 270

Disease progression

Crossover nivolumab (optional)

Stratification factors at randomization:
- PD-L1 expression (<5% vs ≥5%)
- Histology (squamous vs non-squamous)

Primary endpoint: PFS per BIRC (≥5% PD-L1+)
Secondary endpoints:
- PFS per BIRC (≥1% PD-L1+)
- OS
- ORR

Exploratory objective: Predictive biomarkers for outcomes with nivolumab

An exploratory analysis was conducted in CheckMate 026 to test the hypothesis that patients with high TMB may derive enhanced benefit from nivolumab
Exploratory TMB Methods
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

**Sample size throughout TMB determination**

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Tumor DNA</th>
<th>Germline DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>541 (100)</td>
<td>541 (100)</td>
</tr>
<tr>
<td>Samples available for DNA extraction&lt;sup&gt;a&lt;/sup&gt;</td>
<td>485 (90)</td>
<td>452 (84)</td>
</tr>
<tr>
<td>DNA available for sequencing</td>
<td>408 (75)</td>
<td>452 (84)</td>
</tr>
<tr>
<td>Successful preparation of next-generation sequencing library</td>
<td>402 (74)</td>
<td>452 (84)</td>
</tr>
<tr>
<td>Passed internal quality control&lt;sup&gt;b&lt;/sup&gt;</td>
<td>320 (59)</td>
<td>432 (80)</td>
</tr>
<tr>
<td>Matched tumor-germline exome sequences for TMB analysis&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>312 (58)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Samples were not available for various reasons, including but not limited to lack of patient pharmacogenetic consent, samples exhausted for PD-L1 testing, or poor tissue sampling.

<sup>b</sup>Internal quality control failure included factors such as discordance between tumor and germline DNA, too few sequence reads, and low or uneven target region coverage.

<sup>c</sup>8 patients with available tumor DNA sequences did not have matched germline DNA sequences.
TMB in The Cancer Genome Atlas\(^1\) and CheckMate 026 Samples\(^a\)

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

![Graph showing TMB analysis by sample type and clinic](image)

- **Non-squamous**
  - TCGA\(^1\) (n = 533)
  - CheckMate 026\(^a\) (n = 243)
- **Squamous**
  - TCGA\(^1\) (n = 177)
  - CheckMate 026\(^a\) (n = 69)

\(^a\)Samples were from whole exome sequencing

### BASELINE CHARACTERISTICS
(ALL RANDOMIZED PATIENTS AND TMB-EVALUABLE PATIENTS)
CHECKMATE 026 TMB ANALYSIS: NIVOLUMAB IN FIRST-LINE NSCLC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All randomized patients (n = 541)</th>
<th>TMB-evaluable patients (n = 312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>64 (29, 89)</td>
<td>65 (32, 89)</td>
</tr>
<tr>
<td>Female, %</td>
<td>38.6</td>
<td>40.1</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32.9</td>
<td>32.1</td>
</tr>
<tr>
<td>1/2</td>
<td>66.0/0.9</td>
<td>66.7/1.0</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/former smoker</td>
<td>19.8/68.0</td>
<td>17.9/71.5</td>
</tr>
<tr>
<td>Never smoker</td>
<td>10.9</td>
<td>9.3</td>
</tr>
<tr>
<td>Disease stage, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>92.2</td>
<td>93.3</td>
</tr>
<tr>
<td>Recurrent</td>
<td>7.6</td>
<td>6.4</td>
</tr>
<tr>
<td>Tumor histology, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>24.0</td>
<td>22.8</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>76.0</td>
<td>77.2</td>
</tr>
<tr>
<td>PD-L1 expression level, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5%</td>
<td>77.3</td>
<td>80.8</td>
</tr>
<tr>
<td>≥50%</td>
<td>39.6</td>
<td>41.7</td>
</tr>
</tbody>
</table>
PFS (All Randomized Patients and TMB-Evaluable Patients)
CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

Nivolumab Arm

All randomized TMB-evaluable
n = 271 n = 158
Median PFS, months 4.2 4.8
(95% CI) (3.1, 5.5) (3.3, 6.5)

Chemotherapy Arm

All randomized TMB-evaluable
n = 270 n = 154
Median PFS, months 5.8 6.5
(95% CI) (5.4, 6.9) (5.4, 7.4)

- OS in each treatment arm was also similar in patients with evaluable TMB data and all randomized patients
PFS by Tumor Mutation Burden Tertile
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

Nivolumab Arm

<table>
<thead>
<tr>
<th>Tertile</th>
<th>n</th>
<th>Median PFS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>62</td>
<td>4.2 (1.5, 5.6)</td>
</tr>
<tr>
<td>Medium</td>
<td>49</td>
<td>3.6 (2.7, 6.9)</td>
</tr>
<tr>
<td>High</td>
<td>47</td>
<td>9.7 (5.1, NR)</td>
</tr>
</tbody>
</table>

Months

PFS (%)

0 3 6 9 12 15 18 21 24

Low

Medium

High

0 10 20 30 40 50 60 70 80 90 100

Median PFS, months

(95% CI)
Data for patients with low and medium TMB were pooled in subsequent analyses.
There was no association between TMB and PD-L1 expression in patients with ≥1% PD-L1 tumor expression.

All patients had ≥1% PD-L1 tumor expression.
PFS by TMB Subgroup and PD-L1 Expression

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

No. at Risk

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Months</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>High TMB, PD-L1 ≥50%</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>High TMB, PD-L1 1–49%</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>Low/medium TMB, PD-L1 ≥50%</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Low/medium TMB, PD-L1 1–49%</td>
<td>70</td>
<td>53</td>
</tr>
</tbody>
</table>
TOTAL EXOME MUTATIONS VS GENES IN FOUNDATIONONE PANEL

CHECKMATE 026 TMB ANALYSIS: NIVOLUMAB IN FIRST-LINE NSCLC

Based on in silico analysis filtering on 315 genes in FoundationOne comprehensive genomic profile (Foundation Medicine, Inc, Cambridge, MA, USA)

Conclusions

1). Neo-antigen recognition is frequent in melanoma

2). Mutational load correlates with response to checkpoint blockade in a way that is consistent with a probabilistic ‘neo-antigen lottery’ model

Note: NO clear threshold

Not (very) useful as a predictor of response for individual patients
Useful to understand biology of tumor control
Useful to identify tumor types that are attractive targets for immunotherapy
Incentive to develop therapies that boost neo-ag. specific T cell responses
The Cancer Immunogram

Tumor foreignness
Mutational load

General immune status
Lymphocyte count

Blank et al., Science 2016
General immune status – lymphocyte count

**ipilimumab**

- Relative lymphocytes $\geq 10.5\%$
- Relative lymphocytes $< 10.5\%$

\[ p = 3.3 \times 10^{-12} \]

**pembrolizumab**

- Relative lymphocyte counts $\geq 17.5\%$
- Relative lymphocyte counts $< 17.5\%$

\[ P < 0.001 \]

Martens et al., CCR 2016

Weide et al., CCR 2016
PRETREATMENT PERIPHERAL BLOOD T CELL CLONALITY ANALYSIS
T cell repertoire assessment by TCRβ sequencing

(adapted from Aaron Logan, UCSF)
PATIENTS WITH CLINICAL BENEFIT TO IPILIMUMAB HAD A RICHER AND MORE EVENLY DISTRIBUTED TCR REPERTOIRE

Postow et al., J Immunother Cancer 2015
TRANSLATIONAL RESEARCH ON PATIENTS TREATED IN THE PHASE II IMVIGOR 210 STUDY OF ATEZOLIZUMAB (ANTI-PD-L1) IN METASTATIC UROTHELIAL CARCINOMA

- Atezolizumab 1200 mg IV q3weeks
- PD-L1 expression on tumor-infiltrating immune cells (PD-L1 IC score) assessed prospectively
  - IC0 (<1%)
  - IC1 ≥1% but <5%
  - IC2/3 ≥5%
- Objective Response Rate (RECIST 1.1) % (95% CI)
  - All (310): 15% (11-19)
  - IC2/3 (100): 26% (18-36)
  - IC1 (107): 10% (5-18)
  - IC0 (103): 8% (3-15)

Rosenberg et al., Lancet 2016
PRETREATMENT T CELL CLONALITY IN BLOOD INVERSELY CORRELATED WITH OVERAL SURVIVAL (N=29)

Presented by Samuel Funt, ASCO 2016

* Log Rank
The Cancer Immunogram

- Tumor foreignness
- Mutational load
- General immune status
  - Lymphocyte count
- Immune cell infiltration
  - Intratumoral T cells

Blank et al., Science 2016
RESPONSE TO ANTI-PD1 IS ASSOCIATED WITH BASELINE T CELL INFILTRATION IN MELANOMA

Tumeh et al., Nature 2014
WHY ARE SOME TUMOR “HOT” AND SOME “COLD”?

Diffuse infiltration with CD8+ TILs in HNSCC

Absence of TILs in HNSCC

Keck et al., Clin Canc Res 2014
Higher T cell infiltration and clonality are associated with higher PD-L1 expression

Presented by Samuel Funt at 2016 ASCO Annual Meeting

**TIL Infiltration and PD-L1 IC Score**

- TIL Infiltrate (TCR rearrangements/genome)
- PD L1 Score
  - IC0
  - IC1
  - IC2

\[ p = 0.01^* \]
\[ \rho = 0.48 \]

**TIL Clonality and PD-L1 IC Score**

- Clonality
- PD L1 Score
  - IC0
  - IC1
  - IC2

\[ p = 0.02^* \]
\[ \rho = 0.51 \]
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 Checkpoints
PD-L1

Blank et al., Science 2016
Understanding tumor cell resistance to T cell attack by haploid screening

Carette et al., Science 2009
Understanding tumor cell resistance to T cell attack by haploid screening

Red => sensitive cells
Green => resistant cells

T cells are added

Resistant cells are enriched
Understanding tumor cell resistance to T cell attack by haploid screening

Hits obtained:

- IFNγR1
- IFNγR2
- JAK1
- JAK2
- STAT1
- IFN inducible gene
- IFN unrelated genes, part of the same complex.
The Cancer Immunogram

- Tumor foreignness
  - Mutational load

- Tumor sensitivity to immune effectors
  - MHC expression
  - IFN-γ sensitivity

- General immune status
  - Lymphocyte count

- Absence of inhibitory tumor metabolism
  - LDH, glucose utilization

- Immune cell infiltration
  - Intratumoral T cells

- Absence of Checkpoints
  - PD-L1

Blank et al., Science 2016
High LDH and poor survival to ipilimumab in melanoma

Kelderman et al., CII 2014
High LDH and poor survival in melanoma treated with pembrolizumab

- Response rate
- Overall survival

- Daud et al., ASCO 2015
- Weide et al., CCR 2016
## ORR IN PATIENT SUBGROUPS

<table>
<thead>
<tr>
<th>Subgroup</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><strong>Total population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57.6% (314)</td>
<td></td>
<td></td>
<td>38.6% (31.3–45.2)</td>
</tr>
<tr>
<td></td>
<td>43.7% (316)</td>
<td></td>
<td></td>
<td>24.6% (17.5–31.4)</td>
</tr>
<tr>
<td><strong>BRAF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild-type</td>
<td>53.3% (212)</td>
<td></td>
<td></td>
<td>35.6% (26.8–43.6)</td>
</tr>
<tr>
<td></td>
<td>46.8% (218)</td>
<td></td>
<td></td>
<td>29.1% (20.5–37.1)</td>
</tr>
<tr>
<td>Mutant</td>
<td>66.7% (102)</td>
<td></td>
<td></td>
<td>44.7% (31.5–55.6)</td>
</tr>
<tr>
<td></td>
<td>36.7% (98)</td>
<td></td>
<td></td>
<td>14.7% (2.0–26.8)</td>
</tr>
<tr>
<td><strong>M Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1c</td>
<td>51.4% (185)</td>
<td></td>
<td></td>
<td>37.1% (27.9–45.4)</td>
</tr>
<tr>
<td></td>
<td>38.9% (185)</td>
<td></td>
<td></td>
<td>24.6% (15.8–33.0)</td>
</tr>
<tr>
<td><strong>Baseline LDH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ULN</td>
<td>65.3% (199)</td>
<td></td>
<td></td>
<td>40.6% (31.1–48.9)</td>
</tr>
<tr>
<td></td>
<td>51.5% (196)</td>
<td></td>
<td></td>
<td>26.8% (17.3–35.6)</td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>44.7% (114)</td>
<td></td>
<td></td>
<td>35.2% (24.1–45.2)</td>
</tr>
<tr>
<td>&gt;2x ULN</td>
<td>30.4% (112)</td>
<td></td>
<td></td>
<td>20.8% (10.5–30.7)</td>
</tr>
<tr>
<td></td>
<td>37.8% (37)</td>
<td></td>
<td></td>
<td>37.8% (20.0–53.9)</td>
</tr>
<tr>
<td></td>
<td>21.6% (37)</td>
<td></td>
<td></td>
<td>21.6% (6.3–37.2)</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 and &lt;75</td>
<td>57.4% (94)</td>
<td></td>
<td></td>
<td>39.5% (25.8–51.0)</td>
</tr>
<tr>
<td></td>
<td>48.1% (79)</td>
<td></td>
<td></td>
<td>30.1% (16.0–42.8)</td>
</tr>
<tr>
<td>≥75</td>
<td>54.3% (35)</td>
<td></td>
<td></td>
<td>27.0% (5.3–45.8)</td>
</tr>
<tr>
<td></td>
<td>43.6% (39)</td>
<td></td>
<td></td>
<td>16.3% (-4.1–35.2)</td>
</tr>
<tr>
<td><strong>PD-L1 Expression Level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>54.8% (210)</td>
<td></td>
<td></td>
<td>36.9% (28.0–45.0)</td>
</tr>
<tr>
<td></td>
<td>41.3% (208)</td>
<td></td>
<td></td>
<td>23.5% (14.8–31.8)</td>
</tr>
<tr>
<td>≥5%</td>
<td>72.1% (68)</td>
<td></td>
<td></td>
<td>50.7% (35.0–62.8)</td>
</tr>
<tr>
<td></td>
<td>57.5% (80)</td>
<td></td>
<td></td>
<td>36.2% (21.0–49.0)</td>
</tr>
</tbody>
</table>
The Cancer Immunogram

- Tumor foreignness
  - Mutational load

- Tumor sensitivity to immune effectors
  - MHC expression
  - IFN-γ sensitivity

- General immune status
  - Lymphocyte count

- Absence of inhibitory tumor metabolism
  - LDH, glucose utilization

- Absence of soluble inhibitors
  - IL6->CRP/ESR

- Immune cell infiltration
  - Intratumoral T cells

- Absence of Checkpoints
  - PD-L1

Blank et al., Science 2016
Cyclooxygenase-Dependent Tumor Growth through Evasion of Immunity

CRP

Zelenay et al. Cell 2015
CRP, LDH AND ALC ARE STRONG OUTCOME PARAMETERS FOR IPILIMUMAB AND ANTI-PD1 (PEMBROLIZUMAB) IN MELANOMA

Kelderman et al., Cll Jansen et al., Poster 1127, ESMO 2016
Extension to other malignancies

NSCLC: Immunogram of cancer immunity cycle

Extension to other malignancies

NSCLC: Immunogram of cancer immunity cycle

Not only the presence of immune infiltrates, but their spatial relationship will be crucial.
Not only the presence of immune infiltrates, but their spatial relationship will be crucial.
Not only the presence of immune infiltrates, but their spatial relationship will be crucial.
Multiparameter biomarkers are key-Cancer Immunogram

Tumor sensitivity to immune effectors
- MHC expression
- IFN- sensitivity

Absence of inhibitory tumor metabolism
- LDH, glucose utilization

Absence of soluble inhibitors
- IL6->CRP/ESR

Absence of Checkpoints
- PD-L1

Immune cell infiltration
- Intratumoral T cells

Spatial correlations

Absence of inhibitory tumor metabolism
- LDH, glucose utilization

Tumor sensitivity to immune effectors
- MHC expression
- IFN- sensitivity

Absence of soluble inhibitors
- IL6->CRP/ESR

Absence of Checkpoints
- PD-L1

Immune cell infiltration
- Intratumoral T cells

Spatial correlations

Blank, Haanen et al. Science 2016
Tumor-resident T cell clones that proliferate upon a-PD-1 show an exhausted phenotype

Huang, et al. Nature 2017
T cell reinvigoration in context of tumor burden predicts outcome to anti-PD-1

Huang, et al. Nature 2017
New biomarkers within the Cancer Immunogram

- Tumor sensitivity to immune effectors
  - MHC expression
  - IFN- sensitivity

- Absence of inhibitory tumor metabolism
  - LDH, glucose utilization

- Absence of soluble inhibitors
  - IL6->CRP/ESR

- General immune status
  - Lymphocyte count
  - Ki67 PD1+ CD8

- Immune cell infiltration
  - Intratumoral T cells
    - Shared T cell clones

- Absence of Checkpoints
  - PD-L1

- Absence of Checkpoints
  - Immune cell infiltration
  - General immune status
  - Tumor sensitivity to immune effectors
THE HUMAN MICROBIOME

- 100 trillion microbes
- 3% human body mass
- 10-100X microbial : human genes
- 1-10X microbes : human cells
- largest # microbes – GI tract

Presented by: Jennifer Wargo
There is a growing appreciation of the role of the microbiome in cancer.
ANTI-TUMOR IMMUNE RESPONSES WERE ASSESSED AND WERE COMPARED TO THE COMPOSITION OF THE GUT (FECAL) MICROBIOME IN PATIENTS ON ANTI-PD-1

Gopalakrishnan et al, confidential unpublished data, manuscript under review

Wargo, ASCO 2017
Fecal microbiome transplant (FMT) alters response to aPD-L1

Germ-free mice receiving FMT from responders versus non-responders were injected with melanoma and treated with aPD-L1

Wargo, ASCO 2017
New biomarkers within the Cancer Immunogram

Tumor foreignness
Mutational load

Tumor sensitivity to immune effectors
MHC expression
IFN- sensitivity

General immune status
Lymphocyte count

Ki67 PD1+ CD8

Microbiome
Low bacteroides
High faecalibacteria prausnitzi

Immune cell infiltration
Intratumoral T cells

Shared T cell clones
Spatial correlations

Absence of inhibitory tumor metabolism
LDH, glucose utilization

Absence of soluble inhibitors
IL6->CRP/ESR

Absence of Checkpoints
PD-L1

Low bacteroides
High faecalibacteria prausnitzi

New biomarkers within the Cancer Immunogram
IFN-γ-related mRNA profile as response predictor for PD-1 blockade

Ayers et al., JCI 2017
Multi-compartment relevance of the IFN-g-related mRNA profile

Ayers et al., JCI 2017
New biomarkers within the Cancer Immunogram

Tumor foreignness
Mutational load

Tumor sensitivity to immune effectors
MHC expression
IFN- sensitivity

General immune status
Lymphocyte count
Ki67 PD1+ CD8
LAG3, TIGIT, CD27

Microbiome
Low bacteroides
High faecalibacteria prausnitzi

Absence of inhibitory tumor metabolism
LDH, glucose utilization
IDO1, tumor acidity

Immune cell infiltration
Intratumoral T cells
Shared T cell clones
B7-H3/CD276 macrophages
CCL5 attracting T cells
CCR5 expressing BATF3 DC

Absence of soluble inhibitors
IL6-->CRP/ESR

Absence of Checkpoints
PD-L1

Spatial correlations
CD73 as possible biomarker for combination therapy with Adenosine Receptor 2A blockade

- Increased VEGF, IL6, IL10, TGFβ, and IDO
- Modulation of MHC-I and -II antigen presentation
- M2 macrophage polarization, MDSC expansion

- Increased Polarization to CD4+ Treg
- Proliferation
- Immunosuppression

- Reduced T1 CD4+ polarization
- IFNγ, IL2, TNFα production

- Reduced Adhesion to tumor cells
- Cytotoxicity
- TCR signaling
- Activity leading to induced anergy

Adenosine receptors
- A1 and A2A inhibit cAMP release
- A2A and A2B stimulate cAMP signaling

- Decreased
  - Granule exocytosis-induced cytotoxicity
  - Perforin and CD99L molecule expression
  - Cytokine production IFNγ, TNFα, IL2, IL12, MIP1α
  - NK cell maturation

- Increased
  - Production of VEGF, IL8, angiopeitin-2
  - Neovascularization and proliferation

Pro-tumor survival
- Enhanced migration and metastasis
- Chemoresistance
- Immune evasion and proliferation

Anti-tumor survival
- Inhibited proliferation
- Enhanced caspase expression
- Cell death

Young et al., Cancer Discovery 2017
Beavis et al., CIR 2015
Summary - new biomarkers

Tumor foreignness
Mutational load
Neo-antigen load

Tumor sensitivity to immune effectors
MHC expression
IFN- sensitivity

General immune status
Lymphocyte count
Ki67 PD1+ CD8
, LAG3, TIGIT, CD27

Microbiome
Low bacteroides
High faecalibacteria prausnitzii

Absence of inhibitory tumor metabolism
LDH, glucose utilization
IDO1, tumor acidity

Absence of soluble inhibitors
IL6->CRP/ESR
CD73 → adenosine

Immune cell infiltration
Intratumoral T cells
Shared T cell clones
B7-H3/CD276 macrophages
CCL5 attracting T cells
CCR5 expressing BATF3 DC

Absence of Checkpoints
PD-L1

Spatial correlations

Neo-antigen load