Biomarkers for immunotherapy

John Haanen MD PhD
Clear value of mobilizing endogenous tumor-specific T cell responses

1. TIL therapy

1. Checkpoint blockade
Where are we trying to get to…

Treat unselected patients
Treat selected patients
Select treatment for patients

Ref. Lawrence Fong at 2016 ASCO Annual Meeting
Biomarker research

Melero, .., Haanen, Nat Rev Canc 2015
Combination therapy guided by biomarkers

Co-stimulatory mAbs targeting:
- CD137
- OX40
- CD40
- GITR

Conventional agents inducing immunogenic cell death:
- Chemotherapy
- Radiotherapy
- Anti-angiogenics
- Targeted therapies

Other checkpoint inhibitory molecules:
- CTLA4
- LAG3
- TIM3
- BTLA
- TIGIT

Cancer vaccines considering individual neoantigens

Functional modification of immunosuppressive enzymes such as:
- IDO1
- iNOS

TReg cell targeting or inhibition

Adoptive cell therapy

Myeloid cell modulation

Personalized combinations guided by biomarkers

PD1 or PDL1 blockade

Melero, .., Haanen, Nat Rev Canc 2015
The Cancer Immunogram

Describing the state of Cancer - Immune interaction

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

Blank et al. Science 2016
The Cancer Immunogram

Tumor foreignness

Mutational load

Blank et al., Science 2016
What could tumor-specific cytotoxic T cells detect on human cancer?

1. Self antigens (to which tolerance is incomplete)
   *Shared between patients*

2. Viral antigens
   *Shared between patients*

3. ‘Neo-antigens’, epitopes that arise as a consequence of tumor-specific mutations
   *In large part patient-specific, hence generally ignored*
Generation of pMHC multimers by UV-induced peptide exchange

Toebes et al. Nat. Med. 2006
Bakker et al. PNAS 2008
Self-assembling molecular codes

Generate fluorochrome conjugated MHC multimers

Mix to create a collection of differentially encoded MHC multimers

Assembly of combinatorial codes on T cell surfaces

Analysis by flow cytometry

Allows detection of 47 T cell responses in parallel

What could tumor-specific cytotoxic T cells detect on human cancer?

1. Self antigens (to which tolerance is incomplete)
   *Shared between patients*

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   *In large part patient-specific, hence generally ignored*
Predictions:

1). If recognition of neo-antigens is an important ingredient to cancer immunotherapy, one would expect that, in tumor types that are responsive to immunotherapy, the immune system is often able to recognize mutant antigens.
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1). If recognition of neo-antigens is an important ingredient to cancer immunotherapy
   one would expect that, in tumor types that are responsive to immunotherapy, the immune system is often able to recognize mutant antigens

2). If recognition of neo-antigens is an important ingredient to cancer immunotherapy
   one would expect that the extent of DNA damage correlates with the clinical effects of cancer immunotherapy
Analyzing the neo-antigen-specific T cell repertoire in human cancer

- Generate map of tumor-specific mutations (ExomeSeq)
- Determine which mutated genes are expressed (RNASeq)
- Predict epitopes for each mutation/each HLA-allele *in silico*
- Screen for T cell recognition of mutated epitopes
Pt 010: complete response upon TIL therapy

- Isolate tumor cells
- Isolate tumor-infiltrating T cells
- Resected tumor material
- Screen with MHC multimer technology
- Identify tumor-specific mutations
- Predict potential epitopes

Graph shows reduction in tumor burden post infusion of TIL with time.
Strong T cell responses against neo-antigens in the infusion product

TIL infusion product

- \( \text{VARS}_{T>M} \)
- \( \text{MYLK}_{G>V} \)
- \( \text{WDR1}_{N>K} \)
- \( \text{LRP3}_{T>S} \)
- \( \text{RBM12}_{S>L} \)
Profound effect of TIL therapy on the neo-antigen specific T cell pool

TIL infusion product

Peripheral blood

>450 fold increase in neo-antigen specific T cell reactivity upon TIL therapy
Evidence for neo-antigen reactive CD4 T cells?

1a: Isolation & immortalization of B cells
1b: Tumor excision
2a: Identifying tumor-specific mutations
2b: Isolation of TIL
3: Sorting & expanding of CD4+ T cells
4: Synthesizing mutated long peptides
5: Loading of autologous B cells with long peptides
6: Culture with autologous CD4 T cells
7: Analyze cytokine production

Oncogene-immortalized autologous APC platform

Linnemann et al Nat Med 2015
Neo-antigen reactive CD4 T cells in clinically effective ACT products? (>7yr CR upon T cell therapy)

Tumor-reactive T lymphocytes are grown by culture of PB T cells with autologous melanoma

Expansion

Infusion of T cells + IFNα


Control  TNIK_{S>F}  RPS12_{G>A}  ZC3H18_{G>R}

CD4

0.77%  2.21%  7.89%  2.02%
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?

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
Induction of neo-antigen specific T cell reactivity in a patient with NSCLC upon PD-1 blockade
Induction of neo-antigen specific T cell reactivity in a patient with NSCLC upon PD-1 blockade

Rizvi et al, Science 2015
Conclusions

A neo-antigen repertoire may only be common in some human cancers.

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**
  - Survival probability over years.
  - Years: 0, 1, 2, 3, 4, 5.
  - Survival probability: 1.0, 0.8, 0.6, 0.4, 0.2, 0.0.
  - $p = 3.3 \times 10^{-12}$.
  - **Martens et al., CCR 2016**

- **pembrolizumab**
  - Survival probability over months.
  - Months: 0, 6, 12, 18, 24.
  - Survival probability: 1.0, 0.8, 0.6, 0.4, 0.2, 0.0.
  - $P < 0.001$.
  - **Weide et al., CCR 2016**
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)

Pretreatment peripheral blood T cell clonality analysis
Pretreatment T cell clonality in blood inversely correlated with overall survival (n=29)
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
WNT/β-catenin pathway activation correlates with immune exclusion across most human cancers

Jason J. Luke, MD, FACP
Assistant Professor of Medicine
Melanoma and Developmental Therapeutics Clinics

Probably accounts for <10% of “cold” tumors
TIL clonality and outcome in melanoma and bladder cancer

- T cell repertoire assessment by TCRβ sequencing
- High TIL clonality associated with improved outcome
The Cancer Immunogram

- Tumor foreignness
  - Mutational load

- General immune status
  - Lymphocyte count

- Immune cell infiltration
  - Intratumoral T cells

- Absence of Checkpoints
  - PD-L1

Blank et al., Science 2016
PD-L1 Expression and Relationship With Response

- Among first 411 patients enrolled, 67% evaluable for PD-L1 status
- Correlation between PD-L1 expression and ORR ($P < 0.0001$)

ORR, RECIST v1.1

- APS, Allred proportion score.
- Analysis cut-off date: October 18, 2014.
Checkmate-067: Study Design

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

Unresectable or Metastatic Melanoma
- Previously untreated
- 945 patients

Randomize 1:1:1

Stratify by:
- Tumor PD-L1 expression*
- BRAF mutation status
- AJCC M stage

N=314

NIVO 3 mg/kg Q2W + IPI-matched placebo

N=316

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

N=315

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

Treat until progression** or unacceptable toxicity

*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

Larkin et al., NEJM 2015
Progression-free Survival by Tumor PD-L1 Expression

For the original PD-L1 PFS analysis, the descriptive hazard ratio comparing NIVO+IPI vs NIVO was 0.96, with a similar median PFS in both groups (14 months).

Database lock Nov 2015

<table>
<thead>
<tr>
<th>Tumor PD-L1 Expression Level &lt;5%</th>
<th>NIVO + IPI (N=210)</th>
<th>NIVO (N=208)</th>
<th>IPI (N=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.1 (8.0–22.2)</td>
<td>5.3 (2.8–7.1)</td>
<td>2.8 (2.8–3.1)</td>
</tr>
<tr>
<td>HR (95% CI) vs NIVO</td>
<td>0.74 (0.58–0.96)*</td>
<td>–</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor PD-L1 Expression Level ≥5%</th>
<th>NIVO + IPI (N=212)</th>
<th>NIVO (N=218)</th>
<th>IPI (N=215)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR (9.7–NR)</td>
<td>22.0 (8.9–NR)</td>
<td>3.9 (2.8–4.2)</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.87 (0.54–1.41)*</td>
<td>–</td>
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</tbody>
</table>

*Exploratory endpoint

For the original PD-L1 PFS analysis, the descriptive hazard ratio comparing NIVO+IPI vs NIVO was 0.96, with a similar median PFS in both groups (14 months).
# Response to Treatment by Tumor PD-L1 Expression*

<table>
<thead>
<tr>
<th>PD-L1 (≥5%)</th>
<th>NIVO+IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>72.1 (59.9–82.3)</td>
<td>57.5 (45.9–68.5)</td>
<td>21.3 (12.7–32.3)</td>
</tr>
<tr>
<td>Median Duration of Response (months)</td>
<td>NR</td>
<td>20.7</td>
<td>NR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD-L1 (&lt;5%)</th>
<th>NIVO+IPI</th>
<th>NIVO</th>
<th>IPI</th>
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</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>54.8 (47.8–61.6)</td>
<td>41.3 (34.6–48.4)</td>
<td>17.8 (12.8–23.8)</td>
</tr>
<tr>
<td>Median Duration of Response (months)</td>
<td>NR</td>
<td>22.3</td>
<td>18.2</td>
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</table>

*Pre-treatment tumor specimens were centrally assessed by PD-L1 immunohistochemistry (using a validated BMS/Dako assay).

Presented by Wolchok at ASCO 2016

Database lock Nov 2015
Higher T cell infiltration and clonality are associated with higher PD-L1 expression

Presented By Samuel Funt at 2016 ASCO Annual Meeting
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
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:

- IFNGR1
- IFNGR2
- JAK1
- JAK2
- STAT1
- IFN inducible gene
- IFN unrelated genes, part of the same complex.
Tumors may lose MHC expression
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>
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<tbody>
<tr>
<td><strong>Total population</strong></td>
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<td></td>
<td>57.6% (314)</td>
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<td>38.6% (31.3–45.2)</td>
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<td></td>
<td>43.7% (316)</td>
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<td>24.6% (17.5–31.4)</td>
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<tr>
<td><strong>BRAF</strong></td>
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<td>Wild-type</td>
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<td></td>
<td>53.3% (212)</td>
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<td>35.6% (26.8–43.6)</td>
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<td></td>
<td>46.8% (218)</td>
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<td>29.1% (20.5–37.1)</td>
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<tr>
<td>Mutant</td>
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<td></td>
<td>66.7% (102)</td>
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<td>44.7% (31.5–55.6)</td>
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<td>36.7% (98)</td>
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<td>14.7% (2.0–26.8)</td>
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<td><strong>M Stage</strong></td>
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<td>M1c</td>
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<td>51.4% (185)</td>
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<td>37.1% (27.9–45.4)</td>
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<td></td>
<td>38.9% (185)</td>
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<td>24.6% (15.8–33.0)</td>
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<td><strong>Baseline LDH</strong></td>
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<td>≤ULN</td>
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<td>65.3% (199)</td>
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<td>40.6% (31.1–48.9)</td>
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<tr>
<td></td>
<td>51.5% (196)</td>
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<td>26.8% (17.3–35.6)</td>
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<td>&gt;ULN</td>
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<td>44.7% (114)</td>
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<td>30.4% (112)</td>
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<td>20.8% (10.5–30.7)</td>
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<td>&gt;2x ULN</td>
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<td>37.8% (37)</td>
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<td>21.6% (37)</td>
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<td>21.6% (6.3–37.2)</td>
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<td><strong>Age (yr)</strong></td>
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<td>≥65 and &lt;75</td>
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<td>57.4% (94)</td>
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<td>39.5% (25.8–51.0)</td>
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<td>48.1% (79)</td>
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<td>30.1% (16.0–42.8)</td>
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<td>≥75</td>
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<td>54.3% (35)</td>
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<td>43.6% (39)</td>
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<td>16.3% (-4.1–35.2)</td>
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<tr>
<td><strong>PD-L1 Expression Level</strong></td>
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<td>&lt;5%</td>
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<td>54.8% (210)</td>
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<td>41.3% (208)</td>
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<td>23.5% (14.8–31.8)</td>
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<tr>
<td>≥5%</td>
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<td>72.1% (68)</td>
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<td>50.7% (35.0–62.8)</td>
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<tr>
<td></td>
<td>57.5% (80)</td>
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<td>36.2% (21.0–49.0)</td>
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</tbody>
</table>
The Cancer Immunogram

- Tumor foreignness
- Mutational load
- Tumor sensitivity to immune effectors
  - MHC expression
  - IFN-γ sensitivity
- Absence of inhibitory tumor metabolism
  - LDH, glucose utilization
- Absence of soluble inhibitors
  - IL6->CRP/ESR
- General immune status
  - Lymphocyte count
- 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
Tumor microenvironment-associated biomarkers – IFN gene signatures (pembrolizumab in melanoma)

Presented by Antoni Ribas at 2015 ASCO Annual Meeting

Correlation Matrix of Top Significant Genes in the Discovery Set Evaluated in the Validation Set

“Preliminary Expanded Immune” (28-gene) signature: coherent set correlated with the 10-gene “Preliminary IFNγ” signature genes (in red)
How to use the Cancer Immunogram?

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

Blank et al., Science 2016
Case 1: a patient with PD-L1 positive tumor, normal LDH

solution: anti-PD-1/PDL1

- Tumor foreignness
  - Mutational load
- Tumor sensitivity to immune effectors
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  - IFN-γ sensitivity
- Absence of inhibitory tumor metabolism
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  - IL6→CRP/ESR
- General immune status
  - Lymphocyte count
- Immune cell infiltration
  - Intratumoral T cells
- Absence of Checkpoints
  - PD-L1

Blank et al., Science 2016
Case 2: a patient with multiple unfavorable parameters
possible solution: BRAFi+MEKi followed by aPD-1

Blank et al., Science 2016
Tumor foreignness
Mutational load

Tumor sensitivity to immune effectors
MHC expression
IFN-γ sensitivity

Absence of inhibitory tumor metabolism
LDH, glucose utilization

Absence of soluble inhibitors
IL6->CRP/ESR

Absence of Checkpoints
PD-L1

General immune status
Lymphocyte count

Immune cell infiltration
Intratumoral T cells

Case 3: tumor with few mutations and no TIL
Possible solution: adoptive T cell therapy

Blank et al., Science 2016
Case 4: a patient initially responding to PD-1 blockade

Tumor foreignness
Mutational load

Tumor sensitivity to immune effectors
MHC expression
IFN-γ sensitivity

Absence of inhibitory tumor metabolism
LDH, glucose utilization

Absence of soluble inhibitors
IL6→CRP/ESR

Absence of Checkpoints
PD-L1

General immune status
Lymphocyte count

Immune cell infiltration
Intratumoral T cells

Blank et al., Science 2016
Case 4: a patient responding to PD-1 blockade

Tumor foreignness
Mutational load

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

Absence of inhibitory tumor metabolism
- LDH, glucose utilization

Absence of soluble inhibitors
- IL6->CRP/ESR

Absence of Checkpoints
- PD-L1

General immune status
Lymphocyte count

Immune cell infiltration
Intratumoral T cells

Blank et al., Science 2016
Case 4: a patient escaping from PD-1 blockade
possible solution: NK cell activation?

Blank et al., Science 2016
conclusions

• The Cancer – Immunogram is a framework to help to describe the cancer – immune system interaction for individual patients and predict which aspect to target.

• LDH (< 2x ULN) appears to be a solid biomarker of response to select melanoma patients for ipilimumab treatment.

• Many biomarkers of response to CIT are in development. Linking all this information to create a large database will rapidly increase our understanding of immune resistance and escape.
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Ellen Kapiteijn
Jan Willem de Groot
Edward Fiets
Rutger Kornstra
Wim Kruijt

Royal Marsden and Christie Hospital
Paul Lorigan
Martin Gore
James Larkin

MIA Sydney
Georgina Long

University of Tübingen
Benjamin Weide

University of Essen
Dirk Schadendorf

University of Regensburg
Marina Kreutz
Wolfgang Herr

UCLA
Toni Ribas