EMERGING BIOMARKERS OF IMMUNE CHECKPOINT INHIBITORS

Rodrigo Dienstmann
<table>
<thead>
<tr>
<th>(PERSONAL) CONFLICTS OF INTEREST</th>
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<tbody>
<tr>
<td>Advisory role:</td>
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<tr>
<td>Roche, Foundation Medicine</td>
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<td>Boehringer-Ingelheim</td>
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<td>Speaker's fee:</td>
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<td>Roche</td>
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<td>Amgen</td>
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<td>Sanofi</td>
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<td>Research grant:</td>
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<td>Merck</td>
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<td>Pierre Fabre</td>
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<td>BMS</td>
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INTEGRATED BIOMARKER ANALYSIS

IHC

PDL1/PD1 expression

Gene expression
Multiplex molecular pathology

Neoantigen prediction
NGS large panels, exome sequencing

Cytotoxic microenvironment

High neoantigen burden
MSI, high TMB
MULTI-OMICS PREDICTIVE MARKERS

Lee & Ruppin, JAMA Oncol 2019
MULTI-OMICS PREDICTIVE MARKERS

In-silico analysis
TCGA data vs. results clinical trials

Spearman $R = 0.9$

Model with PDL1 + CD8 + TMB explains 80% of ORR across tumor types

Lee & Ruppin, JAMA Oncol 2019
MULTI-OMICS PREDICTIVE MARKERS

Metanalysis KEYNOTE trials
300 patients, 22 tumors

TMB
GEP cytotoxicity signature (18 genes)
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Cristescu et al, Science 2018
MULTI-OMICS PREDICTIVE MARKERS

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Cristescu et al, Science 2018
MULTI-OMICS PREDICTIVE MARKERS

Systematic review and metanalysis
45 clinical trials

PD-L1 IHC
TMB
GEP cytotoxicity signature
Multiplex IHC/IF: quantitative CD8/PD-L1

Lu et al, JAMA Oncol 2019
MULTI-OMICS PREDICTIVE MARKERS

Systematic review and metanalysis
45 clinical trials

PD-L1 IHC
TMB
GEP cytotoxicity signature
Multiplex IHC/IF: quantitative CD8/PD-L1
Response

Clonal mutations, viral neoantigens
Hypermuation – MSI, POLE mut, high TMB, DDR alt
Upregulation of PDL1 (ampl)
Epigenetic events (PBMR1, SMARCA4, ARID1A, ARID2...)

Resistance

Single gene alterations – STK11 mut, PTEN loss, CDK4/CCND1 ampl
High levels of copy number loss
Alterations in Interferon and antigen presentation signaling
CLONAL NEOANTIGENS IN LUNG CANCER

McGranahan et al, Science 2016
VIRAL NEOANTIGENS AND APOBEC MUTATION SIGNATURE

Tamborero et al, Clin Cancer Res 2018
OPTIMIZING PANEL-BASED TMB MEASUREMENT

~ 33% misclassification rate across commercial panels

Important aspects:
- Cut-offs (tumor type/setting)
- Source (tissue, ctDNA)
- Harmonization
- Prognostic vs. predictive (OS gain)
DNA DAMAGE REPAIR ALTERATIONS

Teo et al, J Clin Oncol 2018
PD-L1 UPREGULATION

Hodgkin’s lymphoma – 9p24.1 gain

ORR 70%

Ansell et al, NEJM 2015

PDL1 amplification in solid tumors

ORR 67%

Goodman et al, JAMA Oncol 2018
EPIGENETIC ALTERATIONS IN RENAL CANCER

SWI/SNF alterations: 
*PBMR1* mut

Miao et al, Science 2018
EPIGENETIC ALTERATIONS ACROSS TUMORS

ARID1A deficiency promotes mutability and potentiates therapeutic antitumor immunity unleashed by immune checkpoint blockade

ARID1A mut
Nature Medicine 2018

A major chromatin regulator determines resistance of tumor cells to T cell–mediated killing

PBMR1 mut, ARID2 mut
Science 2018

Immune-Active Microenvironment in Small Cell Carcinoma of the Ovary, Hypercalcemic Type: Rationale for Immune Checkpoint Blockade

SMARCA4 mut
JNCI 2018
Response

- Clonal mutations, viral neoantigens
- Hypermutation – MSI, *POLE* mut, high TMB, DDR alt
- Upregulation of *PDL1* (ampl)
- Epigenetic events (*PBMR1, SMARCA4, ARID1A, ARID2...*)

Resistance

- High levels of copy number loss
- Alterations in Interferon and antigen presentation signaling
**STK11 MUTATIONS IN LUNG CANCER**

Cristescu et al, Science 2018

Skoulidis et al, Cancer Discov 2018
PTEN LOSS AND CDK4/CCND1 AMPL

Melanoma

Pan-tumor

Peng et al, Cancer Discov 2016

Miao et al, Nat Genet 2018
HIGH COPY NUMBER ALTERATIONS ACROSS TUMORS

Tamborero et al, Clin Cancer Res 2018
INTERFERON PATHWAY MUTATIONS IN MELANOMA AND MSI COLON CANCER

Responders

Non-responders

Shin et al, Cancer Discov 2017
ACQUIRED ANTIGEN PRESENTATION PATHWAY ALTERATIONS

Clin Cancer Res 2016
Response
Cytotoxic (CD8 T cell inflammation) microenvironment signatures

Resistance
Pathway alterations – WNT high, TGFB high
granzyrne A (GZMA) and perforin (PRF1)

- Lung squamous ($p = 0.089$)
- Cervical, HPV+ ($p = 0.038$)
- Lung adeno. (*$p = 0.0027$)
- Stomach, EBV− (*$p = 0.0016$)
- Colorectal (*$p = 0.014$)
- Uterine (*$p = 0.0081$)
- Bladder ($p = 0.062$)
- Melanoma ($p = 0.12$)
- Glioma (*$p = 8.5 \times 10^{-5}$)

Total mutation count vs. Cytolytic activity (CYT)

EBV

$p = 1.2 \times 10^{-8}$

193

23
Metanalysis
Melanoma, HNSCC, gastric
Pembrolizumab

GEP cytotoxicity signature (10 genes)
Nanostring nCounter

ABACUS trial Bladder Cancer
Atezolizumab neoadjuvant

PD-L1

TMB

DDR

GEP (CD8)

Keenan et al, Nat Med 2018
Response
Cytotoxic (CD8 T cell inflammation) microenvironment signatures

Resistance
Pathway alterations – WNT high, TGFB high
WNT AND TGFB HIGH SIGNATURES

Cristescu et al, Science 2018
B CATENIN POSITIVE/HIGH

Bladder

Melanoma


Spranger et al, Nature 2015
CONCLUSIONS

- Response to immune checkpoint inhibitors is multi-factorial

- PD-L1, TMB and CD8 signatures (and combinations) have highest potential
  ➢ Tumor type and disease setting matter

- There is room for further biomarker development (digital pathology, radiomics, patient genetics/phenomics)

- Design clinical trials with power for retrospective correlative analysis (not only “exploratory analysis”) in homogeneous populations.
CONCLUSIONS

- Response to immune checkpoint inhibitors is multi-factorial
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ARE THERE UNIVERSAL RESISTANCE MARKERS?

TIME TO MOVE TO NEGATIVE PREDICTIVE MARKERS?