Future Pathological IO-Biomarker: Pathologists beyond PD-L1

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Disclosure Information
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I will not discuss off label use and/or investigational use in my presentation.
The Tumor Immune Microenvironment

MIBC Intrinsic subtypes

The Tumor Immune Microenvironment

Summary: IT’S COMPLICATED

The PD-L1 Dilemma

Summary: IT'S COMPLICATED

Vs.

Bad Tumor
Metastasized

H&E, 200x

PD-L1 (SP263), 200x

PD-L1 Status ?
Happy Oncologist

Tons of positive IC and TC
Results for all algorithms far beyond any possible cut-off

Therapy Success?

The PD-L1 Dilemma: Example Urothelial Carcinoma

PD-L1 Status?

PD-L1 (SP263), 200x

Example Urothelial Carcinoma: **Inconsistent** PROGNOSTIC value of PD-L1-Status

**Therapy Success?**

The PD-L1 Dilemma: Example Urothelial Carcinoma

PD-L1 Status?

PD-L1 (SP263), 200x

PD-L1 status is PREDICTIVE for improved ORR

But: There are also responders in the PD-L1 low/absent group

Study 1108 (Durvalumab)
JAVELIN (Avelumab)
KN-052 (Pembrolizumab)
CM-275 (Nivolumab)
IMvigor 210 1L (Atezolizumab)
IMvigor 210 2L (Atezolizumab)

PD-L1 (SP263), 200x

ORR (%)
The PD-L1 Dilemma

What does PD-L1 positivity mean and is „PD-L1“ the right „question“?
The Tumor (Immune) Microenvironment

MIBC: Distant metastasis in the lung, liver and bones

TPS and TC-Score: appr. 50%
IC-Score: appr. 15%
IC-Area-Score: appr. 50%
CPS: appr. 90

Positive for all algorithms: Response to IO-therapy?
The Tumor (Immune) Microenvironment

MIBC: Distant metastasis in the lung, liver and bones

TPS and TC-Score: appr. 50%
IC-Score: appr. 15%
IC-Area-Score: appr. 50%
CPS: appr. 90

Positive for all algorithms: Response to IO-therapy?

Patient died two months later and showed progression under Pembrolizumab treatment
The Tumor (Immune) Microenvironment

What did we miss?
The Tumor (Immune) Microenvironment

What did we miss?

Type of "PD-L1" Positivity and other factors of the TIME
The TIME: PD-L1 = PD-L1?

**INDUCED** PD-L1 expression

- High T-Cell Infiltration
  - cGAS/Sting-Pathway
  - **INFG**

**MIXED** PD-L1 expression

- Adaptive/Regulatory Upregulation of Immune Checkpoints: PD-L1, PD-1, CTLA4, LAG3.....

**CONSTITUIVE** PD-L1 expression

- Molecular Driver?
  - e.g. genetic alterations
  - 3-UTR-disruption in ATL
  - Virus Integration in Merkel-Cell Carcinoma

Upregulation of PD-L1
The TIME: Example MIBC

Evasion-Phenotype
Induced and Constitutive
Predominantly on TC
Mechanism still unknown

Inflamed Phenotype
Induced PD-L1 expression
Predominantly on IC

Uninflamed Phenotype
Single Cases with constitutive expression
PD-L1

**Evasion-Phenotype**

- Induced and **Constitutive**
- Predominantly on TC
- Mechanism still unknown

**Inflammation (TIME): Example MIBC**

- **Inflamed Phenotype**
  - Induced PD-L1 expression
  - Predominantly on IC
- **Uninflamed Phenotype**
  - Single **constitutive** expression
  - Cases with PD-L1

**Huge Prognostic Impact**

**Predictive Potential?**
How to assess TIME status: CD8-Staining?

Digital Pathological Assessment (e.g. via QuPath)

PD-L1 Assessment + CD8-Staining

Spatial profiling:
- Invasion front
- Tumor center

- Positive Induced
- Positive Constitutive and induced
- Negative Constitutive

University Hospital Erlangen
How to assess TIME status: CD8-Staining?

CD8 could identify tumors with high inflammation without PD-L1 expression!

-> Additive value? Identification of additional immunotherapy responders?
The Tumor (Immune) Microenvironment

What did we miss?

Type of "PD-L1" Positivity and other factors of the TIME!!

Immunological Attractivity
Immunological Attractivity

Tumor
Mutational
Burden

Mutational Burden
APOBEC Mutational Load

Neoantigen Load ↑

Antigen presenting cells ↑

Bladder cancer cell

NK
CD8
NK
CD3
T reg
CD3
CD8
NK
CD3
T reg
CD3
CD8

Mutational Load ↑
APOBEC Mutational Load
Highly inflamed tumors associate with high TMB, neoantigen load and APOBEC Mutational Load

But: Many tumors exhibit high TMB, APOBEC-mutational burden and high neoantigen load, but no relevant immune infiltration!!!!
Quality of neoantigens >> absolute number (?)

MHC-I-Class Restriction:
→ Neoantigens have to be presented!!

Technical limitations:
→ WGS, Exome-Seq?

Where to do?
Companies vs. local molecular pathology?

→ Panels: Number of genes included, which genes are included? Infrastructure?

→ Cut-Off Problems: Panel A vs. B vs. WGS vs. Exome?
TMB: Problems?

NEPTUNE-Trial

Imfinzi-Tremelimimumab Combo Fails to Prolong Overall Survival in Metastatic NSCLC, Phase 3 Trial Shows

A combination of tremelimimumab plus Imfinzi (durvalumab) is no better than standard chemotherapy at extending the survival of people with metastatic non-small cell lung cancer (NSCLC) with a high tumor mutational burden, findings from a Phase 3 trial show.

Keynote 189-Trial

Keynote 189: Tumor mutational burden not significantly associated with efficacy of pembrolizumab

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

Keynote 21-Trial (Phase I)

BARCELONA — Tumor mutational burden did not appear significantly correlated with the effectiveness of chemotherapy alone or with pembrolizumab as first-line treatment for metastatic nonsquamous non-small cell lung cancer, according to results from an exploratory analysis of KEYNOTE-021 presented at International Association for the Study of Lung Cancer World Conference on Lung Cancer.
The Tumor (Immune) Microenvironment

What did we miss?

- Type of "PD-L1" Positivity and other factors of the TIME!!
- Immunological Attractivity of the tumor
- Other Resistance mechanisms
Other Resistance Mechanisms: Exclusion via ECM-remodeling

TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells

Active exclusion of immune cells due to ECM-remodeling via the TGF-beta pathway?
Other Resistance Mechanisms: Exclusion via ECM-remodeling

Useful to report stromal content?

Useful to report stromal aspect?
The Tumor (Immune) Microenvironment

What did we miss?

Type of "PD-L1" Positivity and other factors of the TIME!!

Immunological Attractivity of the tumor

Other Resistance mechanisms

Right Specimen?
TIME: Metastatic Heterogeneity

Primary Tumors

Metastasis: Liver Metastasis

Worse ORR towards IO-therapy
Absence of Immune Cells is frequent in liver metastasis

Switch to „Immune Desert“ phenotype occurs in 54% of LMs

→ Complete Loss of PD-1 and PD-L1 expression in the TIME
The Tumor (Immune) Microenvironment

What did we miss?

Integration of all variables to increase the likelihood of selecting patients with favorable response?

Type of "PD-L1" Positivity and other factors of the TIME!!

Other Resistance mechanisms

Immunological Attractivity of the tumor

Right Specimen?

A lot more ?!
Many thanks for your attention!