Efficacy Evaluation for Immune Checkpoint Blockade

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INSERM 1015

ESMO Advanced Course July 3rd 2019
Paradigm Shift in Cancer Therapy

Historical Paradigm: Targeting Tumor Cells

New Paradigm: Targeting Immune Cells

Tumor Cell

Lymphocyte
Rapid Response in an NSCLC Patient Treated With MPDL3280A Monotherapy

Baseline | Post C2 (Week 6) | Post C4 (Week 12)

64-year-old male with squamous NSCLC s/p R lobectomy, cisplatin + gemcitabine, docetaxel, erlotinib, PD-L1 positive

Images represent data from patient enrolled after Aug 1, 2012. Hospital Universitario Vall D’Hebron (Cruz/Tabernero).

Presented By Roy S. Herbst, MD, PhD at 2013 ASCO Annual Meeting
Long Duration of Responses

JCO, April 20, 2015.
Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study

Why Immune Targeted Therapies provide Survival Benefits?

Adaptive anti-tumor immunity is polyclonal: ➔ *better control of tumor heterogeneity*

Adaptive anti-tumor immunity has memory: ➔ *durable remissions*

*And immune cells can cross the BBB*

(*whereas most drugs can’t*)
Incidence of brain metastases

- Occur in 10-30% of all adult cancers
- Approx. 10 times more frequent than primary brain tumors
- Relative incidence increasing, due to
  - Effective systemic treatments → with longer survival
  - Improved imaging techniques and their increased availability
- Approx. half of all brain mets due to NSCLC, others:
  - Breast cancer
  - Melanoma
  - Unknown primary
  - Renal cell carcinoma

Barnholtz-Sloan... Sawaya RE. J Clin Oncol 22:2865-72, 2004

Courtesy of Prof M.Preusser
Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers

Anna S Berghoff, Sophie Schur, Lisa M Füreder, Brigitte Gatterbauer, Karin Dieckmann, Georg Widhalm, Johannes Hainfellner, Christoph C Zielinski, Peter Birner, Rupert Bartsch, Matthias Preusser

(Courtesy of Prof M. Preusser)
Response to Nivolumab in SQ NSCLC Brain Metastasis

- 73 year-old male, stage IIIb, former smoker
- Prior radiotherapy (mediastinal), 3 prior systemic regimens (cisplatin/gemcitabine, docetaxel, vinorelbine)
- No prior CNS-directed radiotherapy

Ramalingam et al

Pre-treatment

Week 14

Week 68
## Anti-PD-1 in NSCLC with Brain Mets

### Response outcomes.

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>CNS metastasis (n = 409)</th>
<th>All patients (n = 1588)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>68 (17)</td>
<td>290 (18)</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>164 (40)</td>
<td>704 (44)</td>
</tr>
<tr>
<td>Complete response</td>
<td>4 (1)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Partial response</td>
<td>64 (16)</td>
<td>278 (18)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>96 (23)</td>
<td>414 (26)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>192 (47)</td>
<td>688 (43)</td>
</tr>
<tr>
<td>Death</td>
<td>35 (9)</td>
<td>130 (8)</td>
</tr>
<tr>
<td>Not determined</td>
<td>18 (4)</td>
<td>66 (4)</td>
</tr>
</tbody>
</table>

New Types of Responses in Oncology

Immune-Related Response Criteria

Aurélien Marabelle MD, PhD, Gustave Roussy
Pseudo-Progression (PsPD) in NSCLC

Mixed Response in NSCLC

Impact of Atypical Responses on Survival in NSCLC

## Baseline Tumor assessment

<table>
<thead>
<tr>
<th>RECIST v1.1</th>
<th>irRC</th>
<th>irRECIST</th>
<th>iRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sum of longest diameters of target lesions (unidimensional)</td>
<td>• Sum of the products of the two largest perpendicular diameters (SPD) of each lesion ≥ 5 x 5 mm.</td>
<td>• Follows RECIST v1.1</td>
<td>• Follows RECIST v1.1</td>
</tr>
<tr>
<td>• Max 5 lesions (2 per organ)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Measurable lesions defined as:</td>
<td></td>
<td></td>
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<tr>
<td>✓ 10 mm by CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ 10 mm by caliper</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ 20 mm chest X-ray</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Lymph nodes ≥15 mm short axis</td>
<td></td>
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</tbody>
</table>
## New Lesions

<table>
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<tr>
<th>RECIST v1.1</th>
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<th>iRECIST</th>
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<tr>
<td>• Represents PD</td>
<td>• Tumor Burden = SPD_{index} lesions + SPD_{new} lesions</td>
<td>• Does not correspond to a formal progression.</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• The longest diameter will be added to the total measured tumour burden of all target lesions at baseline</td>
<td>• Is not incorporated into tumor burden</td>
</tr>
</tbody>
</table>
# Complete Response (CR)

**RECIST v1.1**
- Disappearance of all target lesions
- Lymph nodes must have reduction in short axis of <10mm
- No new lesions

**irRC**
- Complete disappearance of all lesions
- Confirm after 4 weeks

**irRECIST**
- Same as RECIST 1.1

**iRECIST**
- Same as RECIST 1.1
### Partial Response (PR)

<table>
<thead>
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<th>irRECIST</th>
<th>iRECIST</th>
</tr>
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<tr>
<td>• ≥30% decrease in sum of diameters of target lesions relative to baseline</td>
<td>• Decrease in tumor burden ≥50% relative to baseline</td>
<td>• Same as RECIST1.1</td>
<td>• Same as RECIST1.1</td>
</tr>
<tr>
<td>• Non progression of non-target lesions</td>
<td>• Confirm after 4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No new lesions</td>
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Aurélien Marabelle MD, PhD, Gustave Roussy
## Stable Disease (SD)

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Neither PR or PD
# Progressive Disease (PD)

<table>
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<th>iRECIST</th>
</tr>
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</table>
| • At least 20% increase in the sum of longest diameters of target lesions compared to nadir (absolute increase of at least 5mm)  
• Progression of non target lesions  
• New lesions | • Increase in tumor burden $\geq 25\%$ relative to nadir  
• Confirm after 4 weeks. | **irPD**  
• Same as RECIST 1.1 **BUT** confirm after 4 weeks after the first irPD | **iUPD**  
• Same as RECIST 1.1 **BUT** confirm after 4 weeks after the first iUPD |

**Confirmation not required**
Resolving Initial iUPD

Any original cause of PD worsens
OR another cause of PD appears

TLs were a cause of iUPD,
now still >PD, but no worse
AND no other driver of iCPD
(new cause of PD or worsening of existing cause)

TLs are not above PD threshold*
AND no other driver of iCPD
(new cause of PD or worsening of existing cause)
All lesions resolved

Note: Only target lesion PD, if present at iUPD, must resolve to achieve iSD/iPR.
  e.g. PR in TLs + unequivocal PD of NTLs + new lesions \(\rightarrow\) unchanged = iPR

* Courtesy of Gregory Goldmacher (MSD)
In Summary

- **RECIST 1.1** does not take atypical immune responses into account
- **irRC**: more complex and no standardized definition of PsPD (threshold, timing)
- **irRECIST**: unidimensional, confirmation of PD at 4 weeks, *addition of new lesions to sum of target lesions*
- **iRECIST**: same as irRECIST *without addition of new lesions to sum of target lesions*
Could Anti-PD-(L)1 Immunotherapy be detrimental for some patients?

Hyperprogressive Prostate Cancer under Anti-PD-L1 Therapy
Urothelial carcinoma 49 yo male
anti-PDL1 combo with other immunotherapy
Urothelial carcinoma, 40yo female, anti-PD-1

22 MAR 2017

17 APR 2017

C1D1
31 MAR 2017
Endometrial Stromal Sarcoma, anti-PD-1

Is HPD an unexpected pattern of progression?

HPD?

Tumor Size

1. Progressive Disease
2. Stable Disease
3. Partial/Complete Responses

* pseudoprogressions, mixed responses

Aurélien Marabelle MD, PhD, Gustave Roussy
Can HPD Explain Early Crossing of Survival Curves?


Pembro
Chemo

Excess of Death in first 3 months of nivolumab in NSCLC

Excess of Death in first 3 months 

**atezolizumab in UC**

What is a Hyperprogression?

Acceleration of Cancer Growth

Triggered by the initiation of anti-PD(L)1 Treatment

(Clinical Definition)

- Detrimental effect
- At the beginning of the treatment
Evaluating Tumor Kinetics in Clinical Practice

What is needed?

What is needed? Evaluating Tumor Kinetics in Clinical Practice

Evaluating Tumor Kinetics in Clinical Practice

What is needed?
Tumor Growth Rates (TGR) vs Kinetics (TGK)

\[
TGR_{t+1} = 100 \left[ \exp \left( 3 \log \left( \frac{R_0}{R_{t+1}} \right) \right) - 1 \right]
\]

\[
TGR_{t-1} = 100 \left[ \exp \left( 3 \log \left( \frac{R_0}{R_{t-1}} \right) \right) - 1 \right]
\]

\[
TGK_{t+1} = \frac{R_{t+1} - R_0}{t_{t+1}}
\]

\[
TGK_{t-1} = \frac{R_0 - R_{t-1}}{t_{t-1}}
\]

Delta TGR: \( TGR_{t+1} - TGR_{t-1} \)

TGK ratio:

Champiat et al.
Ferrara et al.
Saada-Bouzid et al.
RECISt 1.1 evaluation of primary resistant tumors

% variation of the SLD of target lesions

+ 51%

+ 42%

+ 10%

Time

BEFORE treatment

ON treatment

No change on tumor kinetics
ON treatment TGR = TGR BEFORE treatment

Slow progressors may be confused with tumor benefiting from therapy

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RECIST 1.1 evaluation of primary resistant tumors

% variation of the SLD of target lesions

Time

BEFORE treatment

ON treatment

Fast progressors may be confused with HPD

No change on tumor kinetics
ON treatment TGR
= TGR BEFORE treatment

Slow progressors may be confused with tumor benefiting from therapy
RECEIT 1.1 evaluation of HPD tumors

% variation of the SLD of target lesions

+ 30%  
+ 17%  

HPD may be confused with non-HPD progressive disease

ON treatment TGR >> TGR BEFORE treatment

HPD may be confused with stable disease at early time points

Before treatment  
On treatment  

Time
Some Patient Increase Their TGR/TGK Under Anti-PD(L)1


# Incidence of HPD?

<table>
<thead>
<tr>
<th>HPD definition</th>
<th>Patients</th>
<th>HPD rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPD rate</strong></td>
<td><strong>Patients</strong></td>
<td><strong>Metastatic cancers</strong></td>
</tr>
<tr>
<td><strong>RECIST PD at first evaluation and TGR EXP/TGR Ratio ≥ 2</strong></td>
<td><strong>N = 131</strong></td>
<td><strong>N = 155</strong></td>
</tr>
<tr>
<td><strong>Metastatic cancers phase 1 trials</strong></td>
<td><strong>Metastatic cancers with molecular profiling</strong></td>
<td><strong>Metastatic HNSCC</strong></td>
</tr>
<tr>
<td><strong>Anti-PD(L)1 monotherapy</strong></td>
<td><strong>Anti-CTLA-4, PD-1/PD-L1 or other investigational agents</strong></td>
<td><strong>Anti-PD(L)1 monotherapy</strong></td>
</tr>
<tr>
<td>9% (12/131)</td>
<td>6% (6/102)</td>
<td>29% (10/34)</td>
</tr>
<tr>
<td><strong>RECIST PD at first evaluation and TGR EXP/TGR Ratio &gt; 1.5</strong></td>
<td><strong>N = 34</strong></td>
<td><strong>N = 406</strong></td>
</tr>
<tr>
<td><strong>Recurrent and/or Metastatic HNSCC</strong></td>
<td><strong>Advanced NSCLC</strong></td>
<td><strong>recurrent and/or metastatic NSCLC</strong></td>
</tr>
<tr>
<td><strong>Anti-PD(L)1 monotherapy</strong></td>
<td><strong>Anti-PD(L)1 +/- IO combo</strong></td>
<td><strong>Anti-PD(L)1 monotherapy</strong></td>
</tr>
<tr>
<td>29% (10/34)</td>
<td>14% (56/406)</td>
<td>21% (55/263)</td>
</tr>
</tbody>
</table>
HPD Patients Have a Worse Prognosis


HPD Patients Don’t Have Time For Next Line of Therapy

HPD is not limited to anti-PD(L)1

(Pseudo-Prog = 5%)

HPD is **Not Associated with**: 

- sex, ECOG, smoking, histology, drug/isotype albumin, NLR 
- tumor burden 
- tumor PD-L1, EGFR, ALK, ROS status 
- tumor mutational burden (TMB) 
- number or type of previous therapeutic lines 
- baseline corticosteroid use 
- presence of inflammatory markers at baseline 

*Saâda-Bouzid et al. Annals of Oncology 2017*  
HPD has been associated with:

- Age > 65y.o
- LDH > ULN
- Number of mets > 2
- Liver mets

Saâda-Bouzid et al. Annals of Oncology 2017
Limitations of TGR/TGK:
- HPD on Metastatic Mode
- HPD on non target lesions
- HPD in first line therapy

HPD patients have low circulating CCR7-CD45RA-CD8+ T-cells

HPD patients have high circulating TIGIT+PD-1+ CD8+ T-cells

Impact of Intratumoral PD-1+ Tregs?

Intratumoral Tregs Proliferate in HPD Pts upon αPD1 therapy

HPD by FcγR engagement by anti-PD-1 on TAMs

Do we need HPD biomarkers or Better Clinical Practice?

- Anti-PD(L)1
  - C1D1
  - W3-4
  - W6-9

First CT-scan

Look at all lesions
Switch to chemo if HPD
Imaging Assessment Criteria: RECIST is not Adapted to Intratumoral Immunotherapy

Clinical Benefit?
Intra Tumoral RECIST (itRECIST)

Goldmacher G et al. International Consensus Manuscript in Preparation
Waterfall Plots for Intratumoral Immunotherapy

Take Home Messages

• iRECIST criteria to confirm PD and take into consideration atypical responses
• Do not delay treatment onset if asymptomatic CNS mets
• Early CT-assessment to allow switch to chemo in case of fast/hyper-progression
Efficacy Evaluation for Immune Checkpoint Blockade

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