THE SEARCH FOR BIOMARKER IN RCC

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DISCLOSURE OF INTEREST

**Employment:** University Hospital Essen

**Honoraria for speaker engagements and advisory roles:** Art tempi, AstraZeneca, Astellas, BMS, Cerulean, COCS, ClinSol, EUSApharm, EISAI, Ipsen, MedUpdate, Merck Serono, MSD Merck, MedKomAkademie, Novartis, NewConceptOncology, Lilly, Johnson & Johnson, PharmaMar, PeerVoice, Pfizer, Roche, StreamedUp!, ThinkWired!

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**Ownership of any stocks and shares:** AstraZeneca, BMS, MSD
WHICH BIOMARKERS CAN BE USED FOR PREDICTION?

- **baseline marker (pre-therapeutic)**
  - RCC subtypes
  - TNM
  - IMDC
  - molecular marker (PBRM1, BAP1)
  - Immunogenicity (PD-L1, CD8 cells)

- **on-treatment marker**
  - CT changes (RECIST)
  - serum marker
DEFINITIONS

Marker can be predictive, prognostic or both

**Predictive**
- correlates with therapeutic outcome (PFS)

**Prognostic**
- correlates with overall survival (OS) upon standard intervention

Gore et al. ASCO 2007
ESTABLISHED CLINICAL PROGNOSTIC PARAMETERS

Clinical and laboratory parameters are standard prognostic factors

- Hypercalcemia
- Anemia
- LDH
- Performance status
- Thrombocytopenia
- Neutrophilia
GOOD RISK RCC HAVE A DISTINCT BIOLOGY

Selection of VEGF-driven tumors

Heng et al. (2009). JCO, 27(34), 5794–5799.

Rini et al. ESMO 2018: LBA31

Beuselinck et al. ESMO 2018: 869PD
CHROMATIN REMODELING IS KEY IN RCC CARCINOGENESIS

Bap1 is essential for kidney function and cooperates with Vhl in renal tumorigenesis

CCRCC - A DIVERSE DISEASE

POTENTIAL IMPROVEMENT OF CURRENT CLINICAL SCORE

BAP1, PBRM1 and TP53 may improve clinical risk systems - validation to be performed

negative prognosticators

TP53\textsuperscript{mt}  
BAP1\textsuperscript{mt}  
PBRM1\textsuperscript{wt*}  

*or mutated in combination with concurrent TP53 or BAP1 mutation

PBRM1, ALSO A PUTATIVE PREDICTIVE MARKER FOR PD-1I?

https://dx.doi.org/10.1126/science.aan5951
NOT CONFIRMED IN SUBGROUPS FROM PROSPECTIVE TRIAL

**NEITHER IN A SEPARATE COHORT**

Study did not show association in pts. treated with checkpoint inhibitors

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Intermediate</td>
<td>1.18 (0.6, 2.32)</td>
<td>0.627</td>
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<tr>
<td>Poor</td>
<td>4.05 (1.67, 9.85)</td>
<td>0.002</td>
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<tr>
<td>PBRM1 mutated (n = 65)</td>
<td>1.12 (0.62, 2.03)</td>
<td>0.714</td>
</tr>
<tr>
<td>1st Line Immunotherapy (n = 82)</td>
<td>0.3 (0.16, 0.55)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Hakimi et al. 2019 ASCO GU : abstr. 666

Total cohort N=2,152. RCC cohort: 143
PRECISION ONCOLOGY - ANY CHANCE IN MRCC?

Genetic differences may lead to molecular oncology

http://doi.org/10.1056/NEJMoa1113205

WHOLE EXOME SEQUENCING - WORK IN PROCESS
Always consider limitations of a given technique in the clinic

- intratumor heterogeneity difficult to distinguish from sequencing artifacts
- 69% of somatic mutations are false positive
- 34-80% of somatic mutation are background noise
- exclusion of mutations in low-mappable regions may help

## TYPE 1 PAPILLARY RCC - A MET-DRIVEN DISEASE?

<table>
<thead>
<tr>
<th>Type 1</th>
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<tr>
<td>Papillary</td>
<td>Chromophobe</td>
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<td>Gain Chr. 7, 17</td>
<td>Del Chr. 8p</td>
<td>Del Chr. 1, 2, 6, 10, 13, 17</td>
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<td>Del Chr. 8p, 16p, 1p, 9p</td>
<td>Gain Chr. 10q</td>
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### Cytogenetic Alterations

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<tr>
<td>MET</td>
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<td>Cdkn2a/Braf</td>
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### Molecular Alterations

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<td>SETD2/SMARCB1</td>
<td>TFE3</td>
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<tr>
<td>PTEN/DEK</td>
<td>TFE3</td>
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<tr>
<td>TFE3 fusion</td>
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<td>MET/MTOR</td>
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<td>SMARCB1</td>
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<td>Cdkn2a/Braf</td>
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### Pathway Deregulations

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<tr>
<td>Cell cycle</td>
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<td>MAPK kinase</td>
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<td>Deregulation</td>
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<tr>
<td>Chromatin remodeling</td>
<td>Chromatin remodeling</td>
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<tr>
<td>Metabolism</td>
<td>Metabolism</td>
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</tbody>
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Albiges, et al. J Clin Oncol 2018
MOLECULAR ONCOLOGY IN MRCC

Crizotinib is active in MET+ papillary type 1 mRCC

TSC MUTATIONS
A putative predictor for mTOR inhibition?


Voss, M., Chen, D., Reising, A. et al. (2019). PTEN Expression, Not Mutation Status in TSC1, TSC2, or mTOR, Correlates with the Outcome on Everolimus in Patients with Renal Cell Carcinoma Treated on the Randomized RECORD-3 Trial. Clinical cancer research : an official journal of the American Association for Cancer Research 25(2), 506 - 514. https://dx.doi.org/10.1158/1078-0432.ccr-18-1833
PTEN EXPRESSION

Instead PTEN level predicts PFS for mTORi, but not for TKI

Voss, M., Chen, D., Reising, A. et al. (2019). PTEN Expression, Not Mutation Status in TSC1, TSC2, or mTOR, Correlates with the Outcome on Everolimus in Patients with Renal Cell Carcinoma Treated on the Randomized RECORD-3 Trial. Clinical cancer research : an official journal of the American Association for Cancer Research 25(2), 506 - 514. https://dx.doi.org/10.1158/1078-0432.ccr-18-1833
BASELINE QOL IS PROGNOSTIC
Poor QoL scores correlate with poor OS

Grünwald et al. ESMO 2016: 817P
IS QOL IMPROVEMENT PROGNOSTIC IN MRCC?

Patients who improve in QoL achieve a better OS

EARLY TUMOR SHRINKAGE IS PROGNOSTIC IN MRCC

Patients with $\geq 10\%$ tumor shrinkage have favorable outcome


DIFFERENCES IN RESPONSE PATTERN BETWEEN CPI AND TKI EXIST

\[ \geq 50\% \text{ tumor shrinkage is prognostic with CPI treatment} \]
HYPERPROGRESSION IS A CLINICAL REALITY (CPI THERAPY)

Patient selection may help to decrease this risk

INTERPLAY OF PD-L1 AND TILS
PD-L1 is only 1 component of a complex system

N=146 paired lesions, 73 cases. Discrepancies: 14% (tumor), 26% (TILs)

http://doi.org/10.1093/annonc/mdw289
**PD-L1 IS A REASONABLE PREDICTOR IN 1ST LINE**

Enrichment for CR can be achieved by PD-L1 status in mRCC

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab(^1)</th>
<th>Atezolizumab(^2)</th>
<th>Ipilimumab + nivolumab(^3)</th>
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<tr>
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<td>PD-L1+</td>
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<td>ORR</td>
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<td>PR</td>
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PD-L1 STATUS IS PREDICTIVE FOR IPI-NIVO

**PD-L1 <1% (n = 562)**

- **Median PFS, months (95% CI)**
  - NIVO + IPI: 11.0 (8.1–14.9)
  - SUN: 10.4 (7.5–13.8)

- **HR (95% CI)**: 1.00 (0.74–1.36)  
  - **P = 0.9670**

**PD-L1 ≥1% (n = 214)**

- **Median PFS, months (95% CI)**
  - NIVO + IPI: 22.8 (9.4–NE)
  - SUN: 5.9 (4.4–7.1)

- **HR (95% CI)**: 0.48 (0.28–0.82)  
  - **P = 0.0003**

**Progression-Free Survival (Probability)**

<table>
<thead>
<tr>
<th>Months</th>
<th>NIVO</th>
<th>NIVO + IPI</th>
<th>SUN</th>
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No. at Risk:
- NIVO: 284
- SUN: 278

Escudier et al ESMO 2017 LBA5
HOWEVER, IT LACKS PROGNOSTIC ABILITY

OS by tumor PD-L1 expression: IMDC intermediate/poor risk

PD-L1 <1% (n = 562)

PD-L1 ≥1% (n = 214)

Motzer et al. SITC 2017: O38
BEST OF BOTH WORLDS - TIME TO RE-THINK

VEGFi-CPI combos dilute predictivity of risk categories

Motzer et al, ESMO 2018 LBA6_PR

Mod. Motzer R et al. ASCO-GU 2018, Abstract No. 578
CAN WE DO BETTER?

Genetic signatures may dissect treatment strategies

Mod. Rini BI et al. ESMO 2018, Proffered paper session – Genitourinary tumours, non prostate, Abstract No. LBA31
IMMOTION151: ANGIOGENIC SIGNATURE

Impact is not exclusive to sunitinib treatment

<table>
<thead>
<tr>
<th>Angiogenesis (High vs. Low)</th>
<th>Sunitinib</th>
<th>Atezo + Bev</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>0.59 (0.47, 0.75)</td>
<td>0.86 (0.67, 1.1)</td>
</tr>
</tbody>
</table>

Mod. Rini BI et al. ESMO 2018, Proffered paper session – Genitourinary tumours, non prostate, Abstract No. LBA31
**IMMOTION151: T-EFFECTOR CELLS**

$T_{eff}$ high RCC are more responsive to ATEZO-BEV

### PFS Rates

- **T-effector$^{Low}$**
  - Sunitinib (n=234)
  - Atezo + Bev (n=243)
  - HR (95% CI): 0.91 (0.73, 1.14)

- **T-effector$^{High}$**
  - Sunitinib (n=182)
  - Atezo + Bev (n=164)
  - HR (95% CI): 0.76 (0.59, 0.99)

### Details

- **T-effector gene signature did not differentiate PFS within the Sunitinib or Atezolizumab + Bevacizumab treatment arms**
Angiogenesis Gene Expression Is Higher in Favourable MSKCC Risk Group

Angiogenesis Gene Signature

- Angio\textsuperscript{Low} (Favourable): 74%
- Angio\textsuperscript{High} (Intermediate/Poor): 43%
- Angio\textsuperscript{Low} (Intermediate/Poor): 26%
- Angio\textsuperscript{High} (Favourable): 57%

T-effector Gene Signature

- T\textsubscript{eff}\textsuperscript{Low} (Favourable): 36%
- T\textsubscript{eff}\textsuperscript{High} (Intermediate/Poor): 43%
- T\textsubscript{eff}\textsuperscript{Low} (Intermediate/Poor): 64%
- T\textsubscript{eff}\textsuperscript{High} (Favourable): 57%

PD-L1 Expression

- Negative (Favourable): 39%
- Positive (Intermediate/Poor): 43%
- Negative (Intermediate/Poor): 61%
- Positive (Favourable): 57%

P = 8.26e-05
P = 0.1
P = 0.35

CONCLUSIONS

• pre-therapeutic marker guide treatment choice in mRCC
• Current clinical risk categories are both, predictive and prognostic
• QoL, PBRM1, TP53 and BAP1 are candidate markers for further advancement
• On-treatment markers are more difficult to interpret
• Improvement in QoL or quality of response correlate with better prognosis
• PD-L1 enriches for complete responses during CPI treatment
• Combinations of TKI + CPI require novel marker for prediction