WHICH IMMUNOTHERAPY IS THE STANDARD 1ST LINE THERAPY IN mRCC – IMMUNE COMBOS WITH A TKI

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## C. PORTA: DISCLOSURE OF INTEREST

<table>
<thead>
<tr>
<th>CONSULTANCY</th>
<th>SPEAKER</th>
<th>STEERING COMMITTEES</th>
<th>EXPERT TESTIMONY</th>
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<td>BMS</td>
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<td>MSD</td>
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<td>Eisai</td>
<td>EUSA Pharma (AIFA)</td>
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THE THIRD REVOLUTION IN MRCC TREATMENT

HOW TO MAKE A CHOICE

We should avoid to make direct comparisons between these 3 studies because they are extremely different in terms of:

- immune agent(s) used,
- study end-points,
- primary efficacy patients’ population,
- distribution of patients between different prognostic groups
POSSIBLE DRIVERS OF OUR DECISION

- Biology
- IMDC prognostic class
- The shape of survival curves (tails and heads)
- PD-L1 expression
- Sequential approach (which data for selecting subsequent therapies?)
POSSIBLE DRIVERS OF OUR DECISION

• Biology
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TARGETING WHAT IS KEY IN mRCC

POSSIBLE DRIVERS OF OUR DECISION

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IPILIMUMAB + NIVOLUMAB AND IMDC RISK CATEGORIES

PEMBROLIZUMAB + AXITINIB AND IMDC RISK CATEGORIES

Keynote 426 (Pembro + Axi)

AVELUMAB + AXITINIB AND IMDC RISK CATEGORIES

JAVELIN Renal 101 (Ave + Axi)

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"ONCOLOGY IS A MATTER OF TAILS"\textsuperscript{1}

BUT... separation of curves and survival impact occurs thereafter – and median OS is thus increased

... AND after few years a survival plateau is observed, and we start to see long-term survivors (cured?)


1. Prof. Pieter De Mulder
LET’S TAKE A LOOK AT THE HEADS OF THE CURVES, INSTEAD …

In CheckMate-214, PFS curves start separating at about 6 months, while in the Keynote-426 trial, curves’ separation appears to be anticipated by almost 3 months; as far as JAVELIN Renal 101, the different timing of first diseases assessment do not allow any relevant comparison.

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• **PD-L1 expression**
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IN CHECKMATE 214, PD-L1 EXPRESSION SEEMS TO BE PREDICTIVE …

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

<table>
<thead>
<tr>
<th>Median PFS, months (95% CI)</th>
<th>NIVO + IPI</th>
<th>11.0 (8.1–14.9)</th>
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<tbody>
<tr>
<td></td>
<td>SUN</td>
<td>10.4 (7.5–13.8)</td>
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<tr>
<td>HR (95% CI)</td>
<td>1.00 (0.74–1.36)</td>
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<tr>
<td>( P )</td>
<td>0.9670</td>
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**PD-L1 ≥1% (n = 214)**

<table>
<thead>
<tr>
<th>Median PFS, months (95% CI)</th>
<th>NIVO + IPI</th>
<th>22.8 (9.4–NE)</th>
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<tbody>
<tr>
<td></td>
<td>SUN</td>
<td>5.9 (4.4–7.1)</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.48 (0.28–0.82)</td>
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<tr>
<td>( P )</td>
<td>0.0003</td>
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**Progression-Free Survival (Probability)**

- **NIVO**: 284, 202, 155, 119, 102, 90, 70, 23, 9, 1, 0
- **SUN**: 278, 200, 138, 105, 83, 67, 43, 25, 11, 1

... BUT NOT ENOUGH

Ventana PD-L1 IHC SP263 assay

Positive immune cells within the tumor area

Ave + Axi  Sun

<table>
<thead>
<tr>
<th>PD-L1 status:</th>
<th>Ave + Axi</th>
<th>Sun</th>
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<tbody>
<tr>
<td>Positive</td>
<td>108/270</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>54/132</td>
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<tr>
<td>Not evaluable</td>
<td>18/40</td>
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Agilent PD-L1 22C3 pharmDX assay

Combined score (no. of PD-L1+ cells/total no. of tumor cells)

Pembro + Axi  Sun

<table>
<thead>
<tr>
<th>PD-L1 combined positive score</th>
<th>Pembro + Axi</th>
<th>Sun</th>
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</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>54/325</td>
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<tr>
<td>≥1</td>
<td>90/497</td>
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</table>

Dako PD-L1 IHC 28-8 pharmDx test

Positive tumor cells

Ipi + Nivo  Sun

<table>
<thead>
<tr>
<th>Baseline PD-L1 expression</th>
<th>Ipi + Nivo</th>
<th>Sun</th>
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</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td>93/284</td>
<td></td>
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<tr>
<td>≥1%</td>
<td>28/100</td>
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<tr>
<td>Not reported</td>
<td>19/41</td>
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</tbody>
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WHAT TO DO AFTER I-O/VEGFR-TKIS COMBINATIONS?

Almost everything, including:
• Cabozantinib
• Lenvatinib + Everolimus
• Tivozanib
... if allowed in Your Country
BECAUSE ANGIogenesis REMAINS KEY THROUGHOUT MRCC WHOLE NATURAL HISTORY

Evolution of Circulating Tumor DNA Profile from First-line to Subsequent Therapy in Metastatic Renal Cell Carcinoma


TAKE HOME MESSAGES

The combinations of ICIs plus a VEGFR-TKI targets two of the most important biologic drivers of mRCC growth, i.e. angiogenesis and immune suppression.

These combination, differently from the immune doublet, acts irrespective of the IMDC risk categories; this is not the case for the Ipilimumab + Nivolumab.

The use of the VEGFR-TKI within the combination leads to a quicker activity, i.e. saves the lives of few patients who cannot wait for the late effect of immunotherapy.

The combinations of ICIs plus a VEGFR-TKI, differently from the immune doublet, act irrespective of PD-L1 expression, which indeed is (and by far) really a poor biomarkers.

After the failure of these combinations, one can use almost everything (and in particular other VEGFR-targeting agents), because angiogenesis remains a key driver of mRCC growth along its whole natural history.
THANK YOU VERY MUCH FOR YOUR KIND ATTENTION!!!

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