Targeting the PI3K/AKT/mTOR Pathway in Renal Cell Carcinoma

Signalling Pathways in Cancer 2014

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Disclosures

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Overview

- Progress in advanced RCC 2007-2014
- Randomised trials of mTORi in RCC
- How can the role of mTORi in RCC be expanded?
- Predictive biomarkers for mTORi
- Intratumour heterogeneity: implications for predictive biomarkers
Progress in Advanced Kidney Cancer 2007-2014

Neoadjuvant / Pre-operative

Adjuvant

1st Line Relapse
SUNITINIB
PAZOPANIB
IFN-α + BEVACIZUMAB
TEMSIROLIMUS
Median PFS 9 months

2nd Line Relapse
EVEROLIMUS (post-VEGFR-TKI)
AXITINIB (post-VEGFR-TKI/immunoRx)
SORAFENIB (post-immunoRx)
SUNITINIB (post-immunoRx)
PAZOPANIB (post-immunoRx)
Median PFS 4-5 months

3rd Line Relapse
SORAFENIB (post-VEGFR-TKI + mTORi)
EVEROLIMUS (post-VEGFR-TKI ×2)
Median PFS 4-5 months
Randomised trials of mTORi in RCC

- TEM vs IFN vs TEM + IFN in poor risk 1st line
- EVE vs sunitinib 1st line
- EVE + BEV vs IFN + BEV 1st line
- TEM + BEV vs IFN + BEV 1st line
- EVE vs placebo post sunitinib/sorafenib
- TEM vs sorafenib post sunitinib

Hudes NEJM 2007; Motzer Lancet 2008 and ASCO 2013; Hutson JCO 2013; Rini JCO 2013; Ravaud ASCO 2013
Randomised trials of mTORi in RCC

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- EVE vs sunitinib 1\textsuperscript{st} line
- EVE + BEV vs IFN + BEV 1\textsuperscript{st} line
- TEM + BEV vs IFN + BEV 1\textsuperscript{st} line
- EVE vs placebo post sunitinib/sorafenib
- TEM vs sorafenib post sunitinib

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Randomised trials of mTORi in RCC

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- TEM vs sorafenib post sunitinib

Hudes NEJM 2007; Motzer Lancet 2008 and ASCO 2013; Hutson JCO 2013; Rini JCO 2013; Ravaud ASCO 2013
Randomised trials of mTORi in RCC

- TEM vs IFN vs TEM + IFN in poor risk 1\textsuperscript{st} line
- *Choice of comparator arm controversial*
- *No other trials in poor risk group*
- *No yardstick for anti-VEGF activity*
- EVE vs placebo post sunitinib/sorafenib
- *Placebo control arm reasonable when trial recruited*

Hudes NEJM 2007; Motzer Lancet 2008
mTORi have a diminishing role in RCC

- How can this be reversed?
- Increase dose? Neither EVE or TEM are given at MDT in RCC so possible, but not likely
- Use other inhibitors of pathway e.g. PI3K or dual TORC inhibitors: also possible and RP2 studies of GDC0980 and AZD2014 open
- Combinations? In RCC to date these result in increased toxicity and reduced dose
mTORi have a diminishing role in RCC

- How can this be reversed?
- Define predictive biomarkers
- Non-clear cell histology is a clinical candidate
- This is not homogeneous: papillary, chromophobe, medullary, collecting duct etc
- Sunitinib is active in papillary / chromophobe
- Our group became interested in trying to develop predictive markers in clear cell RCC for anti-VEGF and mTORi a few years ago...
The Intratumour Heterogeneity Question

• A fundamental question for personalised medicine:
  • Does the putative driver identified from tissue x at time y really drive the metastatic disease in the patient in front of you in the clinic?
  • Are image-guided biopsies of large tumours representative of the entire primary, never mind metastatic disease?
• We set out to investigate this
Radiographic Intratumour Heterogeneity
### A Biopsy Sites

- R1 (G3)
- R2 (G3)
- R3 (G4)
- R4 (G1)
- R5 (G4)
- R6 (G1)
- R7 (G4)
- R8 (G4)
- R9
- Hilum

10 cm

### B Regional Distribution of Mutations

<table>
<thead>
<tr>
<th>Ubiquitous</th>
<th>Shared primary</th>
<th>Shared metastasis</th>
<th>Private</th>
</tr>
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<tbody>
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</table>

Gerlinger NEJM 2012
65% mutations are heterogeneous and not present in every biopsy
Evidence for Parallel Evolution
SETD2 Loss of Function: H3K36 tri-methylation

KDM5C missense and F/S

SETD2 (frameshift)

SETD2 (splice site)

KDM5C splice site
Branched Evolution in ccRCC

Gerlinger Nature Genetics 2014
## Branched Evolution in ccRCC

<table>
<thead>
<tr>
<th>Gene</th>
<th>Prevalence in TCGA samples (n = 218 samples)</th>
<th>Prevalence in all M-seq samples (n = 79 samples)</th>
<th>Prevalence in cases based on M-seq (n = 10 cases)</th>
<th>Prevalence cases/prevalence M-seq samples</th>
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</thead>
<tbody>
<tr>
<td>PBRM1</td>
<td>42%</td>
<td>39%</td>
<td>60%</td>
<td>1.5</td>
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<tr>
<td>SETD2</td>
<td>18%</td>
<td>27%</td>
<td>30%</td>
<td>1.1</td>
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<tr>
<td>BAP1</td>
<td>21%</td>
<td>24%</td>
<td>40%</td>
<td>1.7</td>
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<tr>
<td>KDM5C</td>
<td>7%</td>
<td>11%</td>
<td>10%</td>
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<tr>
<td>TP53</td>
<td>5%</td>
<td>5%</td>
<td>40%</td>
<td>8.0</td>
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<tr>
<td>ATM</td>
<td>3%</td>
<td>4%</td>
<td>10%</td>
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<tr>
<td>ARID1A</td>
<td>6%</td>
<td>1%</td>
<td>10%</td>
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<tr>
<td>PTEN</td>
<td>5%</td>
<td>10%</td>
<td>20%</td>
<td>2.0</td>
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<tr>
<td>MTOR</td>
<td>9%</td>
<td>8%</td>
<td>10%</td>
<td>1.3</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>3%</td>
<td>4%</td>
<td>20%</td>
<td>5.0</td>
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<tr>
<td>TSC2</td>
<td>2%</td>
<td>4%</td>
<td>10%</td>
<td>2.5</td>
</tr>
<tr>
<td>PI3K-mTOR pathway</td>
<td>18%</td>
<td>28%</td>
<td>60%</td>
<td>2.2</td>
</tr>
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Gerlinger Nature Genetics 2014
Branched Evolution in Cancer


Renal (Gerlinger et al 2012)  Medulloblastoma (Wu et al 2012)

Colon Adenoma-Carcinoma (Thirlwell et al 2010)
Clonal Architecture as a Biomarker?

- Palm
- Chestnut
- Baobab Tree
Clonal Architecture as a Biomarker?

Successful Biomarkers eg EGFR/KRAS/HER2/BRAF
Trunk not branches?
BRAF in Melanoma: ‘Truncal Driver’

48% confirmed response rate
(2 complete responses)

5% confirmed response rate
(0 complete responses)
Target Tumour Phylogenetic Trunks and Resolve Branches

Trunk Genetic Events Present in Every Cancer Cell

DEFINE TRUNK DRIVERS

Branched Genetic Events Present in Some Cancer Cells not others Dynamic during disease course

Monitor subclonal events to define drug resistance mechanisms

Trunk Genetic Events Present in Every Cancer Cell

DEFINE TRUNK DRIVERS
Conclusions

- mTORi active in RCC but less (on average in unselected patients) than anti-VEGF therapy
- No predictive biomarkers for drugs in RCC
- mTOR pathway aberrations not infrequent
- Are they ‘truncal drivers’ though?
- Further study, particularly of metastatic sites / non-invasive technologies needed
- Understanding this could transform the use of mTORi in RCC
Acknowledgements

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- Professor Martin Gore
- Professor David Nicol
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- Dr Steve Hazell
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Thank you