Bladder and Renal Cancer

Chris Hocking
PCPA
29th April 2017
Overview

- Bladder Cancer
  - Neoadjuvant therapy
  - Adjuvant therapy
  - Bladder preservation
  - Advanced disease

- Renal Cell Cancer
  - Adjuvant therapy
  - Advanced disease

Practical Management
Australian Context
Current controversies
Bladder Cancer

Upper tract urothelial cancers
5-10%
60% are invasive

Bladder cancers
90-95%
20-25% are invasive

PCPA 2017 Chris Hocking
Non-muscle invasive

Muscle invasive

Risk Factors

1. Tobacco
2. Occupational chemical exposure
3. Radiation exposure
4. Bladder schistosomiasis and chronic UTI
5. Male
6. Family history (Lynch)
Bladder Cancer Overview

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival,[c] %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>98</td>
</tr>
<tr>
<td>I</td>
<td>88</td>
</tr>
<tr>
<td>II</td>
<td>63</td>
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<tr>
<td>III</td>
<td>46</td>
</tr>
<tr>
<td>IV</td>
<td>15</td>
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</table>

c. ACS website.
Controversies/Uncertainties in bladder cancer

1. Muscle invasive bladder cancer:
   a) Neoadjuvant cisplatin combination chemotherapy followed by radical cystectomy is current gold standard
   b) Multimodality treatment (Trimodality treatment) in select patients can achieve long-term survival comparable to cystectomy
      i. TURBT/EBRTx/Concurrent chemotherapy

2. Advanced disease:
   • Platinum based chemotherapy remains mainstay of treatment

3. Role of immunotherapy in bladder cancer
Neoadjuvant Chemotherapy

ABC Meta-analysis
Lancet 2003; 361(9373):1927

INT-0800 trial of neoadj MVAC not included in meta-analysis – a positive trial +++

HR for death
0.87

5 yr survival
50% vs 45%

5% absolute survival improvement
Neoadjuvant Chemo – which regimen? MVAC vs ddMVAC vs Cis/Gem

INT-0800 Grossman et al. NEJM 2003; 349(9):859
Neoadjuvant Chemo – which regimen? MVAC vs ddMVAC vs Cis/Gem

- **ddMVAC – 2 single arm phase II trials**
  - N=39, 4 x ddMVAC + G-CSF
    - pCR 26% (pRR 49%)
    - 10% grade 3 tox
  - N=40 3 x A-MVAC + G-CSF
    - pCR 38% (pRR 52%)
    - No grade 3 tox

- **Cis/Gem**
  - Based on equivalent efficacy and less toxicity cf MVAC in advanced disease

Choueiri et al. JCO 2014; 32(18): 1889
Pilmack et al. JCO 2014; 32(18): 1895
Neoadjuvant chemo

**YES**
- T2-T4a
- Cisplatin eligible
- <70
- Fit

**Maybe**
- >70
- Upper tract
- N1
- comorbidities

**No**
- Cisplatin ineligible*
- Frail
- Alternate histology

* If GFR <60 ensure hydronephrosis excluded

**ddMVAC requires G-CSF**
Adjuvant Chemotherapy

- Pathological staging available
  - Can select high risk patients (ie T3/T4 or N1)

- Individual trials have been low quality and underpowered
  - Neoadjuvant chemotherapy remains preferred

- Cisplatin combination chemotherapy
  - Medical fitness/cisplatin eligibility assessment if KEY
    - ECOG 0 or 1
    - GFR ≥ 60mls/min
    - Absence of hearing loss/neuropathy/heart failure
Adjuvant Chemotherapy – Meta-Analysis


940 patients, 9 RCTs
HR for OS 0.77 (p=0.049)

- <100 patients per trial
- All terminated early
- All negative studies
EORTC 30994

- T3-4 or N+
- Immediate (4x) versus delayed (6x) (84% Cis/Gem)
- Planned 664 patients – closed after 284 randomised

Sternberg et al. Lancet Oncology 2015; 16(1):76
Adjuvant chemotherapy

- Consider in patients:
  - No neoadjuvant chemotherapy
  - Cisplatin eligible and fit
  - High risk = T3/T4 or N+
  - Informed re lack of definitive OS data
Bladder Preservation
Tri-Modality Therapy

- Medically unfit for cystectomy
- Patient desires bladder preservation

Important factors for optimal patient selection:
- Urothelial histology
- Maximal TURBT
- Earlier T stage (T2/3)
- Good renal function
- Absence of tumour associated hydronephrosis
- Good bladder function/capacity
- Absence of extensive CIS
Bladder Preservation Tri-Modality Therapy

Mak et al. JCO 2014; 32(34): 3801

Cisplatin

MMC + 5FU

James et al. NEJM 2014; 32(34): 3801
<table>
<thead>
<tr>
<th>Treatment</th>
<th>2 yr local DFS</th>
<th>Muscle invasive recurrence</th>
<th>Salvage Cystectomy</th>
<th>5yr OS</th>
<th>5yr DSS</th>
<th>5 yr distant met</th>
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<tr>
<td>CRT (Cisplatin) N=468</td>
<td></td>
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<td>57%</td>
<td>71%</td>
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<tr>
<td>CRT (MMC + 5FU) N=182</td>
<td>67%</td>
<td>11%</td>
<td>11.4%</td>
<td>48%</td>
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<td>39%</td>
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<td>RTx N=178</td>
<td>54%</td>
<td>19%</td>
<td>16.8%</td>
<td>35%</td>
<td>51%</td>
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<tr>
<td></td>
<td>HR 0.66</td>
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<td></td>
<td>p=0.03</td>
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<td></td>
<td>HR 0.82</td>
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<td></td>
<td>p=0.16</td>
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</table>
Tri-modality therapy

- Maximal TURBT
- Chemoradiotherapy
  - Cisplatin
  - MMC + 5FU
- Careful post treatment surveillance
Advanced disease

- **Prognostic factors**
  - ECOG PS > 1
  - Visceral (including bone) metastasis

- Long term survival (>5 yrs) is possible in those with LN only disease
  - 15-20%

- Cisplatin combination chemotherapy is preferred 1st line therapy in those assessed as “medically fit”

**ECOG ≥ 2**
- CrCl ≤ 60mL/min
- Significant hearing loss
- Grade ≥2 neuropathy
- Class III heart failure
Advanced Disease – first line

- 1992: MVAC **superior** to Cisplatin monotherapy
  - mOS 13 vs 8 months

- 2000: CG **less toxic** than MVAC
  - mOS 14 vs 15 months, **ORR** 49 vs 46%
  - Neutropenic sepsis (1 vs 12%), Grade ≥ 3 mucositis (1 vs 22%)

- 2001: ddMVAC (+G-CSF) **less toxic** than classic MVAC
  - mOS 15.1 vs 14.9 months, 2yr OS 21 vs 13%

- 2012: PGC **more ‘active’** and **more toxic** than CG
  - mOS 16 vs 13 months (NS), RR 56 vs 44%
  - Febrile neutropenia 13 vs 4%

- 2012: Carbo/Gem **less toxic** than M-CAVI (patients with GFR 30-60mls/min)
  - mOS 9.3 vs 8.1, RR 30 vs 21%
  - Grade ≥3 toxicity 9 vs 21%
Eligible for Cisplatin?

Y

Cisplatin-based combination

N

Candidate for combination chemotherapy?

Y

Carboplatin based combination

N

Single agent chemo or BSC

Carboplatin Gemcitabine Taxane
Immunotherapy in bladder cancer
PD-1/PD-L1 Inhibition in Platinum-Pretreated Patients

Atezolizumab[^a]
- IMvigor210; FDA-approved in United States

Nivolumab[^b]
- Checkmate 275; FDA-approved in United States

Pembrolizumab[^c]
- Keynote 045

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### Outcomes

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<tr>
<th>Treatment</th>
<th>ORR</th>
<th>mPFS</th>
<th>mOS</th>
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<tr>
<td>Atezolizumab n=316</td>
<td>15%</td>
<td>2.1 months</td>
<td>7.9 months</td>
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<tr>
<td>Nivolumab n=270</td>
<td>19.6%</td>
<td>2 months</td>
<td>8 months</td>
</tr>
<tr>
<td>Pembrolizumab (n=270) vs chemo</td>
<td>21%</td>
<td>2.1 vs 3.3 months (p=0.42)</td>
<td>10.3 vs 7.4 months (p=0.02)</td>
</tr>
</tbody>
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**Outcomes improved in those with higher PDL-1 staining**
Advanced disease – second line

- PD-1/PD-L1 checkpoint inhibitor therapy (likely to be) the new standard of care
  - KEYNOTE-045 – first Phase III trial demonstrating OS improvement in 2nd line
  - 1st line trials awaited – including combination checkpoint inhibitor therapy

- Will immunotherapy replace chemotherapy?
  - RR to 1st line platinum based chemo are very good
  - ?combinations or maintenance immunotherapy

- Biomarkers
  - PD-L1 staining ???
  - Mutational load

- Chemotherapy
  - Paclitaxel, Docetaxel, Pemetrexed, Vinflunine, Abraxane
Renal Cell Carcinoma

- Local disease
  - 30% recur after nephrectomy

- Metastatic RCC
  - 20% synchronous metastasis
  - mOS 28-32 months, 5 yr survival ≈ 12%

Choueiri T, Motzer R. NEJM 2017; 376: 354
Controversies in RCC

1. Adjuvant therapy
2. Cytoreductive nephrectomy
3. Sunitinib vs Pazopanib in first line
4. Sequence
5. Role of immunotherapy
6. Non-clear cell histology
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Freq</th>
<th>Genetic insult</th>
<th>Notes</th>
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<tr>
<td>Clear Cell</td>
<td>75-85%</td>
<td>Loss of VHL (deletion 3p, mutation, methylation)</td>
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<tr>
<td>Papillary – type 1</td>
<td>10-15%</td>
<td>Activated MET • amplification Chromosome 7 • germ line mutation</td>
<td>Typically stage I/II Favorable prognosis</td>
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<tr>
<td>Papillary - type 2</td>
<td></td>
<td>Germline FH mutation</td>
<td>Stage III/IV Poor prognosis</td>
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<tr>
<td>Chromophobe</td>
<td>5-10%</td>
<td>P53, PTEN</td>
<td>Earlier stage, improved prognosis</td>
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<tr>
<td>Collecting Duct</td>
<td>1%</td>
<td></td>
<td>Younger patients, aggressive</td>
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Sarcomatoid differentiation
• can occur in any subtype
• Poor prognosis
Adjuvant therapy

- No RCT has demonstrated OS benefit

- ASSURE (Sunitinib vs Sorafenib vs Placebo)
  - n=1943
  - No difference in DFS or OS

- S-TRAC (Sunitinib vs placebo)
  - n=615, ≥T3 or N+
  - DFS 6.8 vs 5.6 years (HR 0.76, p < 0.05)
  - OS not mature

Ravaud A et al. NEJM 2016; 375: 2246
Prognostic Models

MSKCC
- Karnofsky PS < 80%
- Hb < LLN
- Calcium > 2.50 mmol/L
- LDH > 1.5 x ULN
- Time from diagnosis to systemic treatment < 1 year

International Metastatic RCC Database Consortium (Heng Score)
- LD removed
- Neutrophils > ULN
- Platelets > ULN

<table>
<thead>
<tr>
<th></th>
<th>MSKCC/Motzer</th>
<th>mOS</th>
<th>IMDC score</th>
<th>mOS</th>
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<tbody>
<tr>
<td>Good</td>
<td>0 points</td>
<td>20 months</td>
<td>≤ 1 point</td>
<td>43 months</td>
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<tr>
<td>Intermediate</td>
<td>1-2 points</td>
<td>10 months</td>
<td>2 point</td>
<td>22 months</td>
</tr>
<tr>
<td>Poor</td>
<td>&gt; 2 points</td>
<td>4 months</td>
<td>≥ 3 points</td>
<td>8 months</td>
</tr>
</tbody>
</table>
An Era of Discovery in RCC: Drugs and FDA-Approved Indications

Mechanisms of action
- Anti-VEGF TKI; Anti-VEGF monoclonal antibody; mTOR inhibitor; PD-1 inhibitor

January 2006
Sunitinib (Sustiva)
- Previously untreated advanced RCC based on PFS

December 2005
Sorafenib (Nexavar)
- First targeted therapy in RCC, approved for recurrent, advanced disease after prior treatment based on PFS

May 2007
Temozolomide (Temodal)
- Advanced RCC based on OS benefit vs interferon

July 2009
Bevacizumab (Avastin)
- In combination with interferon-alfa in mRCC based in PFS vs interferon-alfa

October 2009
Pazopanib (Votrient)
- Advanced RCC based on PFS vs placebo

March 2009
Everolimus (Afinitor)
- Recurrent or progressive RCC after sunitinib therapy based on PFS vs placebo

January 2012
Axitinib (Inlyta)
- Advanced RCC after failure of 1 prior systemic regimen based on PFS vs sorafenib

April 2016
Cabozantinib (Cabometyx)
- Advanced RCC after prior antiangiogenic therapy based on PFS vs everolimus

May 2016
Lenvatinib (Lenvima)
- In combination with everolimus for advanced RCC after prior antiangiogenic therapy

November 2015
Nivolumab (Opdivo)
- Advanced RCC after prior antiangiogenic therapy
mOS in First Line RCC Trials

Nephrectomy + IFNα

Sunitinib

Pazopanib

Sunitinib - Everolimus

IFNα

Median Overall Survival (months)

1999: 8.5
2001: 11.1
2003: 17.5
2007: 26.4
2010: 23
2013: 29.1
2014: 32
Important lessons from the past

- Cytokines
  - High dose bolus IL-2
  - Interferon α

- Surgery:
  - Resection of oligometastasis
  - Cytoreductive nephrectomy
High dose IL-2

Case series (1986-2006) - 259 patients
  • CR 23 (9%)

Phase III RCT (2003) n = 304
  • high dose vs low dose IL-2
  • PR 21% (CR: 7%)
  • “No difference in survival”
  • Toxicity: 36% severe hypotension
Cytoreductive Nephrectomy

- 2 RCTs – published in 2001
  - Cytoreductive Nephrectomy + IFNa vs IFNa
  - n=331, ECOG 0/1
    - mOS 13.6 vs 7.8 months (HR 0.69, p=0.002)

- Retrospective series 2006-2013
  - n=15390 patients with mRCC treated with targeted therapies
  - 5374 (35%) Cytoreductive nephrectomy (88% prior to targeted therapy)
  - mOS 17.1 vs 7.7 months

- CARMENA – phase III RCT

- Patient selection is KEY
  - Good PS
  - Large/symptomatic primary
  - Small volume metastatic disease

Hanna N et al. JCO 2016; 34;(27): 3267
Resection of oligometastasis

5 yr survival
44% - ‘curative resection’
14% - ‘non-curative resection’
11% - no metastasectomy

Factors associated with benefit:  
- DFS >12 months from nephrectomy  
- Single site metastasis  
  - esp lung  
- ECOG 0/1  
- No weight loss
Systemic therapy

1. Cytoreductive Nephrectomy?

2. Metastatectomy?

3. Watch and wait?
   - Asymptomatic
   - Limited disease burden
   - Good risk disease
Systemic therapy

Key questions

1. First line therapy
   • Sunitinib vs Pazopanib

2. How to sequence available agents?

3. How to access immunotherapy?
<table>
<thead>
<tr>
<th>Reference and Agents</th>
<th>Patients</th>
<th>Median Progression-free Survival</th>
<th>Hazard Ratio for Disease Progression (95% CI)</th>
<th>P Value</th>
<th>Median Overall Survival</th>
<th>Hazard Ratio for Death (95% CI)</th>
<th>P Value</th>
<th>Objective Response Rate</th>
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<tbody>
<tr>
<td><strong>First-line treatment</strong></td>
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<tr>
<td>Motzer et al.</td>
<td>375</td>
<td>11</td>
<td>0.42 (0.32–0.54)</td>
<td>&lt;0.001</td>
<td>26.4</td>
<td>0.82 (0.67–1.00)</td>
<td>0.05</td>
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<tr>
<td>Sunitinib</td>
<td>375</td>
<td>5</td>
<td>0.46 (0.34–0.62)</td>
<td>&lt;0.001</td>
<td>21.8</td>
<td>0.91 (0.71–1.16)</td>
<td>0.22</td>
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<tr>
<td>Interferon alfa</td>
<td>290</td>
<td>9.2</td>
<td>0.54 (0.34–0.82)</td>
<td>&lt;0.001</td>
<td>22.9</td>
<td>0.86 (0.72–1.04)</td>
<td>0.13</td>
<td>30</td>
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<tr>
<td>Placebo</td>
<td>145</td>
<td>4.2</td>
<td>0.61 (0.51–0.73)</td>
<td>&lt;0.001</td>
<td>20.5</td>
<td>0.96 (0.76–1.20)</td>
<td>0.07</td>
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<tr>
<td>Escudier et al.</td>
<td>327</td>
<td>10.2</td>
<td>0.71 (0.61–0.81)</td>
<td>&lt;0.001</td>
<td>23.3</td>
<td>0.86 (0.72–1.01)</td>
<td>0.07</td>
<td>26</td>
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<td>Bevacizumab–interferon alfa</td>
<td>369</td>
<td>8.5</td>
<td>0.61 (0.51–0.73)</td>
<td>&lt;0.001</td>
<td>18.3</td>
<td>0.96 (0.76–1.20)</td>
<td>0.07</td>
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<tr>
<td>Interferon alfa</td>
<td>363</td>
<td>5.3</td>
<td>0.71 (0.61–0.81)</td>
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<td>17.4</td>
<td>0.86 (0.72–1.01)</td>
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<td><strong>Second-line treatment</strong></td>
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<tr>
<td>Motzer et al.</td>
<td>553</td>
<td>9.5</td>
<td>1.05 (0.90–1.22)</td>
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<td>10.9</td>
<td>0.73 (0.58–0.92)</td>
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<td>Temsirolimus</td>
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<td>4.7</td>
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<td>7.3</td>
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<td>4.8</td>
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COMPARZ –

- Phase III open-label RCT
  - n=1110
  - Pazopanib non-inferior PFS vs Sunitinib
  - HR 1.05 (CI 0.90-0.22)

  • Tolerability
    • Sunitinib: fatigue, hand-foot syndrome, myelosuppression
    • Pazopanib: LFTs

  • PISCES trial – 169 patients
    • Randomised double-blind cross-over
      • S vs P
    • Pt preference – 70% Pazopanib, 22% Sunitinib
73 yr old, met clear cell RCC

Poor risk – severe hypercalcaemia, anaemia, hip pain

June 2014          Oct 2014          Feb 2015
75 yr old woman, met clear cell RCC
Poor risk – severe hypercalcaemia, anorexia, abdominal pain

Sept 2013  April 2014
Sunitinib dosing schedule

Phase III trials - 50mg 4-weeks-on, 2-weeks-off

Commonly used - 2-week-on, 1-week-off schedule
• supported by phase II studies – less toxic than 4 on/2 off

Monitoring

Pazopanib
• LFTs – fortnightly for first 2 months

For both Sunitinib and Pazopanib regular
• TFTs
• CBE
• Urinalysis (PCR)
• BPs – home monitoring ideally
### Second line options

<table>
<thead>
<tr>
<th>Second-line or later treatment</th>
<th>mPFS</th>
<th>HR for disease progression</th>
<th>mOS</th>
<th>HR for death</th>
<th>ORR</th>
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<tr>
<td>Motzer et al. 49,50*†</td>
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<td>Everolimus</td>
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<td>4.9</td>
<td>14.8</td>
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<td>138</td>
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<td>Escudier et al. 51,52*†</td>
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<td>Sorafenib</td>
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<td>5.5</td>
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<td>Placebo</td>
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<td>15.2</td>
<td>0.88 (0.74–1.04)</td>
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*ORR for disease progression*
### Second line options

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<td>5.5</td>
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<td>17.8</td>
<td>0.15</td>
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<tr>
<td>Placebo</td>
<td>452</td>
<td>2.8</td>
<td></td>
<td>0.88 (0.74–1.04)</td>
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<tr>
<td>Rini et al.53†</td>
<td></td>
<td></td>
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<tr>
<td>Axitinib</td>
<td>361</td>
<td>6.7</td>
<td></td>
<td>20.1</td>
<td>19</td>
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<tr>
<td>Sorafenib</td>
<td>362</td>
<td>4.7</td>
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<td>0.97 (0.80–1.17)</td>
<td>0.37</td>
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</tbody>
</table>

PCPA 2017 Chris Hocking
Second line options

<table>
<thead>
<tr>
<th>Study</th>
<th>mPFS</th>
<th>HR for disease progression</th>
<th>mOS</th>
<th>HR for death</th>
<th>ORR</th>
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<tr>
<td>Motzer et al. 2015</td>
<td>51</td>
<td>12.8</td>
<td>0.45 (0.22–0.79)</td>
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<tr>
<td>Lenvatinib–everolimus</td>
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<td>0.62 (0.37–1.04)</td>
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<td>Lenvatinib</td>
<td>50</td>
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<tr>
<td>Everolimus</td>
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<tr>
<td>Choueiri et al. 2015</td>
<td>330</td>
<td>7.4</td>
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<td>Cabozantinib</td>
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<td>3.9</td>
<td>0.51 (0.41–0.62)</td>
<td>&lt;0.001</td>
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<tr>
<td>Motzer et al. 2015</td>
<td></td>
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<tr>
<td>Nivolumab</td>
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<tr>
<td>Everolimus</td>
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<td>4.4</td>
<td>0.88 (0.75–1.03)</td>
<td>0.11</td>
<td>19.6</td>
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</tbody>
</table>
Checkmate-025

![Graph showing the Kaplan-Meier Curve for Overall Survival.](image)

- **Nivolumab**
  - No. of Patients: 410
  - Median Overall Survival (95% CI): 25.0 (21.8–NE)
  - No. of Deaths: 183

- **Everolimus**
  - No. of Patients: 411
  - Median Overall Survival (95% CI): 19.6 (17.6–23.1)
  - No. of Deaths: 215

**Hazard ratio, 0.73 (95% CI, 0.57–0.93) P=0.002**

**Figure 1.** Kaplan–Meier Curve for Overall Survival. CI denotes confidence interval, and NE not estimable.
RCC – treatment algorithm

First line
- Pazopanib (preferred)
- Sunitinib

Second line
- Axitinib (preferred)

Third line
- Everolimus
- Sorafenib
Bladder Cancer

Throughout disease course
Chemotherapy
Lack of high quality data
Immunotherapy

Renal Cancer

Advanced disease
Targeted therapy
High quality data