Management Renal Cell Cancer & Bladder Cancer

A/Prof Phillip Parente
Renal Cell Cancer
Overview

- 3% of all cancer cases, 2% of cancer death in US
- 15% of pt develops distant mets
- 8th most common ca in males, 9th in female
- Age 50-70yo
- Histology: Clear cell (75%), Urothelial (8-10%)
- Very vascular tumour, multidrug resistant efflux phenotype
- Generally chemo resistant, modest sensitive to immunotherapy
  - Chemo RR <6%, IFN RR 10%, HD IL2 RR <23%, median OS IFN 17.5m vs 13m in HD IL2. (McDermott JCO 2005;23:133)
- New era with targeted therapies since 2007 with VEGF inhibitors
Summary Recommendations for Treatment of Localised and locally Advanced RCC

- Partial nephrectomy is recommended for Treatment of all T1 tumours if negative margins obtained.
- Laparoscopic radical nephrectomy preferred option when partial nephrectomy not feasible.
- Routine adrenalectomy & lymph node dissection are not required for all radical nephrectomies.
- Open radical nephrectomy with negative margins is standard of care for locally advanced RCC.
- Ablative therapies in tumors <3cm & 70 years age with high surgical risk.
- Active surveillance in pts > 75 years, Significant risk factors & tumours < 4cm.
Summary Recommendations for Treatment of Localised and locally Advanced RCC

- No recommended adjuvant treatment
- 4 randomized TKI based adjuvant trials completed and waiting results
- Neoadjuvant approaches are still experimental for resectable tumors and should not be routinely proposed outside of a clinical trial
Cytoreductive Nephrectomy Trials

**CARMENA**
NCT00930033
Met ccRCC
No prior therapies
Nephrectomy → Sunitinib

**SURTIME**
NCT01099423
Met ccRCC
No prior therapies
Sunitinib → Nephrectomy
Nephrectomy → Sunitinib
Management Of Metastatic Disease
Role of Surgery

• Era of Immunotherapy – IFN - Cytoreductive nephrectomy was recommended in pts with good PS and improved PFS/OS

• Whether this recommendation remains with current TKIs currently being investigated 2 prospective randomised trials

• Routine Clinical Practice:
  • Cytoreductive nephrectomy recommended in pts good PS/large primary/limited mets
  • Symptomatic primary lesion
Management Of Metastatic Disease
Role of Surgery - Metastasectomy

- MDM discussion
- Selected pts with solitary/easily accessible mets/long disease free interval
- Lung/Liver/Brain/Lymph node/Adrenal/Bone
- Metastasectomy may provide a survival benefit for select group of pts
- No systemic therapy is recommended after metastasectomy
Management Of Metastatic Disease
Systemic Treatment – 1\textsuperscript{st} Line

- **1\textsuperscript{st} Line Treatment of Patients with Good or Intermediate Prognosis**

- Some RCC very indolent course

- Period of observation before starting treatment should be considered especially in pts with limited disease burden/lung mets/asymptomatic

- 3 Treatments demonstrated efficacy in pivotal phase 3 trials
• Phase 3 international multicenter trial involving 750 pts.
• 1:1 randomisation to Sunitinib 50mg or IFNa
• First line Rx in metastatic clear cell RCC
• ECOG 0-1, MSKCC low to intermediate
• Stratified based on LDH, ECOG and previous nephrectomy
• Primary EP: PFS
Figure 2. Kaplan–Meier Estimates of Progression-free Survival (Independent Central Review).

PFS: 11m v 4 m
Sunitinib vs IFN (OS analysis)

Fig 2. Kaplan-Meier estimates of overall survival. IFN-α, interferon alfa.

Motzer RJ. JCO 2009;27: 3584-3590
oral angiogenesis inhibitor targeting VEGF1,2,3 PDGF and c-KIT.
### Predefined subgrp analysis of PFS

<table>
<thead>
<tr>
<th>Baseline Factor</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td>435</td>
<td></td>
</tr>
<tr>
<td>Treatment naive</td>
<td>233</td>
<td></td>
</tr>
<tr>
<td>Cytokine pretreated</td>
<td>202</td>
<td></td>
</tr>
<tr>
<td>MSKCC risk: favorable</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>MSKCC risk: intermediate</td>
<td>236</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>307</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 65 yrs</td>
<td>281</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 65 yrs</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>183</td>
<td></td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>252</td>
<td></td>
</tr>
</tbody>
</table>
### Adverse Events

#### Any grade (predominantly low grade)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pazopanib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>52%</td>
<td>9%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40%</td>
<td>10%</td>
</tr>
<tr>
<td>Hair colour changes</td>
<td>38%</td>
<td>3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>26%</td>
<td>9%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>22%</td>
<td>10%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21%</td>
<td>8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19%</td>
<td>8%</td>
</tr>
<tr>
<td>Headache</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>AST rise</td>
<td>53%</td>
<td>19%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>34%</td>
<td>6%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>32%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Class effects AEs (proteinuria, hypothyroidism, hand-foot syndrome, and mucositis/stomatitis) occurred with an incidence of fewer than 10% each, with grade 3/4 events reported in less than 1% of patients.
COMPARZ: Overall Survival in RCC with Pazopanib vs. Sunitinib

Figure 1. Kaplan–Meier Curves for Overall Survival in the Intention-to-Treat Population.
The dashed line represents the median (0.5), and vertical lines represent 95% confidence intervals.
Management Of Metastatic Disease
Systemic Treatment – 1\textsuperscript{st} Line

- 1\textsuperscript{st} Line Treatment of Patients with Poor Prognosis

- **Temsirolimus** only drug level 1 evidence of activity in this pt population

- Pivotal Phase 3 trial showed improvement in OS

- **Sunitinib** - based on subgroup analysis of pivotal trials/EAPs reasonable

- **Sorafenib** – based on EAPs reasonable option
Management Of Metastatic Disease
Systemic Treatment – 2\textsuperscript{nd} Line

- **Post 1\textsuperscript{st} Line TKI**


Management Of Metastatic Disease
Systemic Treatment – 3rd Line

- Clinical trials recommended
- **Everolimus** – post 2 TKIs or Bev/TKI
- Previous TKI & mTOR inhibitor
  - Sorafenib
  - Another TKI
  - Rechallenge with same TKI at higher doses if no toxicities evident
Treatment of Metastatic Disease of Non Clear Cell Histology

- No prospective randomised data except subgroup analyses
- **Recommendation** – clinical trials
- Subgroup analyses benefit with sunitinib, sorafenib or temsirolimus
- Genetic mutations as possible targets
  - Papillary Type Tumors – cMET trials
- Chromophobe RCC – mTOR inhibitor Everolimus
- Collecting Duct Tumours/Medullary Carcinomas behave aggressively like Urothelial Tumours and require chemotherapy (Cisplatin + Gemcitabine)
Toxicities and role as predictive markers of response
## Side Effects May Be Related to the Target

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>VEGF, mTOR</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>mTOR</td>
</tr>
<tr>
<td>Everolimus</td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFr, PDGFR, c-KIT, Flt-3</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>VEGFr-2, VEGFr-3, PDGFR, c-KIT, Flt-3, RET, RAF-1</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>VEGFr, PDGFR, c-Kit, Flt-3</td>
</tr>
</tbody>
</table>

- Single target—specific VEGF-/mTOR-related side effects
- Multitargeted—potential for non-VEGF–related toxicity

Adapted from Bellmunt J. *Eur Urol Suppl.* 2007;6:484-491.
Overview of Common TKI-Associated Adverse Events (AEs)

- AEs commonly associated with VEGFr-TKIs are diarrhoea, fatigue, hypertension, hand-foot syndrome, stomatitis, hypothyroidism and hepatic/renal dysfunction\(^1\)\(^-\)\(^4\)

- Relative incidence of these AEs varies
  - Due to multitargeted nature and different pharmacological profiles of different VEGFR-TKIs\(^5\)
  - May also be a consequence of differences in patient populations and in study design (e.g. first-line vs second-line therapy)

---

Common AEs (Any Grade) Associated With TKIs in Pivotal Trials

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Sunitinib(^1)</th>
<th>Sorafenib(^2,3)</th>
<th>Pazopanib(^4,5)</th>
<th>Axitinib(^6,7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>61</td>
<td>48</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>Fatigue</td>
<td>54</td>
<td>29</td>
<td>19</td>
<td>39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30</td>
<td>17</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>29</td>
<td>33</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>30</td>
<td>5</td>
<td>NR</td>
<td>15</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14</td>
<td>NR</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Haematological toxicity</td>
<td>≥79(^*)</td>
<td>≥44(^*)</td>
<td>≥37(^|$</td>
<td>≥35(^*)</td>
</tr>
<tr>
<td>Hepatic toxicity</td>
<td>≥56(^†)</td>
<td>NR</td>
<td>≥53(^**)</td>
<td>≥22(^**)</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>≥49(^‡)</td>
<td>≥45(^§)</td>
<td>≥34(^§)</td>
<td>≥55(^‡‡)</td>
</tr>
</tbody>
</table>

All data are presented as percentage of the total population; NR, not reported.
Percentage is for the most common toxicity: \(^*\)anaemia; \(^†\)increased aspartate aminotransferase; \(^‡\)increased creatine kinase; \(^§\)hypophosphataemia; \(^\|$\)leukopenia; \(^**\)increased alanine aminotransferase; \(^‡‡\)elevated creatinine.

# Common Grade ≥3 AEs Associated With TKIs in Pivotal Trials

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Sunitinib¹</th>
<th>Sorafenib²,³</th>
<th>Pazopanib⁴,⁵</th>
<th>Axitinib⁶,⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11</td>
<td>3</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>4</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>9</td>
<td>6</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1</td>
<td>0</td>
<td>NR</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2</td>
<td>NR</td>
<td>NR</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Haematological toxicity</td>
<td>≥16*</td>
<td>≥13§</td>
<td>≥4§</td>
<td>3§</td>
</tr>
<tr>
<td>Hepatic toxicity</td>
<td>≥2†</td>
<td>NR</td>
<td>12†</td>
<td>&lt;1†</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>14†</td>
<td>≥13¶</td>
<td>5**</td>
<td>4**</td>
</tr>
</tbody>
</table>

All data are presented as percentage of the total population; NR, not reported. Percentage is for the most common ≥3 toxicity; *neutropenia; †increased alanine aminotransferase; ‡increased uric acid; §lymphopenia; ¶hypophosphataemia; **hyponatremia.

Predictive Biomarkers

- **Prognostic factors** are disease or host characteristics that estimate the chance of disease death/progression/recurrence regardless of treatment
  - Examples: MSKCC criteria, Heng Criteria

- **Predictive factors** are disease or host characteristics that estimate the chance of improvements in outcome with a particular treatment
  - Examples: Treatment-induced hypertension or baseline IL-6 and HGF for VEGF inhibitors; baseline LDH for mTOR inhibition
Hypertension as a predictive marker

- Postulated mechanism of hypertension from VEGF inhibition:
  - Decreased nitric oxide and prostacyclins synthesis, hence inhibition of vasodilatation, increased peripheral vascular resistance and ultimately hypertension.
  - Decreased GFR leading to increased Na and H2O retention
  - Functional vascular rarefaction

- Treatment related HTN as a biomarker of clinical effect of anti-VEGF
  - Diastolic BP>90mmHg a/w better outcome with Axitinib
OS in patients with or without dBP ≥ 90 mmHg – all six studies combined

## HTN as a biomarker in VEGF-targeted Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor (N)</th>
<th>Therapy</th>
<th>HTN definition</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rini et al.¹</td>
<td>Multiple solid Tumors (n=230)</td>
<td>Axitinib</td>
<td>dBP ≥ 90 mmHg</td>
<td>OS: 30.1 vs. 10.2 months (p&lt;0.001)</td>
</tr>
<tr>
<td>Rini et al.²</td>
<td>RCC (n=544)</td>
<td>Sunitinib</td>
<td>sBP &gt; 140 mmHg and dBP ≥ 90 mmHg</td>
<td>OS: 30.9 vs. 7.2 months (p&lt;0.0001)</td>
</tr>
<tr>
<td>Harzstark et al.³</td>
<td>RCC (n=366)</td>
<td>Bevacizumab (+IFN)</td>
<td>≥ CTC Grade 2</td>
<td>OS: 41.6 vs. 16.2 months (p&lt;0.0001)</td>
</tr>
<tr>
<td>Escudier et al.⁴</td>
<td>RCC (n=337)</td>
<td>Bevacizumab (+IFN)</td>
<td>≥ CTC Grade 2</td>
<td>PFS: 10.2 vs. 8.4 months (p=ns)</td>
</tr>
<tr>
<td>Schneider et al.⁵</td>
<td>Breast Ca (n=345)</td>
<td>Bevacizumab (+chemo)</td>
<td>≥ CTC Grade 3</td>
<td>OS: 38.7 vs. 25.3 months (p=0.002)</td>
</tr>
<tr>
<td>Dahlberg et al.⁶</td>
<td>NSC Lung Ca (n=741)</td>
<td>Bevacizumab (+chemo)</td>
<td>&gt; 150/100 mmHg, OR &gt; 20 mmHg in increase</td>
<td>OS: 15.9 vs. 11.5 months (p=0.0002)</td>
</tr>
<tr>
<td>Goodwin et al.⁷</td>
<td>NSC Lung Ca (n=148)</td>
<td>Cediranib (+chemo)</td>
<td>New onset HTN, OR Worsening HTN</td>
<td>HR for death in HTN pts 0.62 (p=0.06)</td>
</tr>
</tbody>
</table>

¹ CCR (submitted); ² JNCI (in press); ³ ASCO GU 2010; ⁴ ASCO 2008; ⁵ JCO 26:4672-4678 2008 ⁶ JCO 28:949-54, 2010; ⁷ Ann Onc 21:2220-6, 2010
The impact of Angiotensin System Inhibitors (ASIs) on outcomes in patients with mRCC: pooled clinical trials database (Pfizer)

Presented by Toni K. Choueiri at 2015 Genitourinary Cancers Symposium

McKay, Simantov et al, GU-ASCO 2014, and CCR online Feb 27th
Other potential predictive markers for response to anti-VEGF
Hypothyroidism as a predictive marker of treatment outcome in patients with mRCC

- Exploratory analysis of 87 patients receiving sunitinib or sorafenib
- Patients who had an increase in TSH within 2 months of starting treatment had significantly longer OS versus patients without hypothyroidism

OS Kaplan Meier Estimates

Schmidinger Cancer 2/2011

p=0.016
# Hand foot syndrome any grade

<table>
<thead>
<tr>
<th>Drug</th>
<th># pts</th>
<th>Incidence</th>
<th>Tumor</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>sunitinib</td>
<td>1186</td>
<td>22%</td>
<td>RCC 770</td>
<td>66.5 v 31.8%</td>
<td>11 v 5.5 mo</td>
<td>35.7 v 16.6 mo</td>
</tr>
<tr>
<td>sunitinib</td>
<td>770</td>
<td>23%</td>
<td>RCC</td>
<td>55.6 v 32.7%</td>
<td>14.4 v 8.3 mo</td>
<td>38.3 v 18.9 mo</td>
</tr>
</tbody>
</table>

*Same group of RCC pts in both analyses*
Sorafenib Adverse Events: Hand-foot Skin Reaction

At: http://www.nexavar.com/wt/page/safety
Toxicity & Predictive Markers mTOR Inhibitors - Toxicity

- Mouth ulcers
- Stomatitis
- Rash
- Fatigue
- Hypertension
- Hand & Foot Syndrome
- Diarrhoea
- Infections
- Pneumonitis (can be rapidly fatal)
Serum LDH is Predictive of OS for Temsirolimus in RCC

NORMAL LDH (<1x ULN)

Median Survival Time:
- Temsirolimus: 11.7 mo
- IFN-α: 10.4 mo

HR 0.90 (95% CI 0.67-1.22)

Log rank p-value = 0.5138

ELEVATED LDH (≥1x ULN)

Median Survival Time:
- Temsirolimus: 6.9 mo
- IFN-α: 4.2 mo

HR 0.56 (95% CI 0.38-0.81)

Log rank p-value = 0.0017
<table>
<thead>
<tr>
<th>Histology/Setting</th>
<th>Risk Group</th>
<th>Standard</th>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear Cell/1\textsuperscript{st} Line</td>
<td>Good/Intermediate</td>
<td>\textbf{Sunitinib}</td>
<td>High Dose IL2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bevacizumab/IFN</td>
<td>Sorafenib</td>
</tr>
<tr>
<td></td>
<td>Poor Risk</td>
<td>\textbf{Pazopanib}</td>
<td>Bev/IFN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temsirolimus</td>
<td>\textbf{Sunitinib}</td>
</tr>
<tr>
<td>Clear Cell/2\textsuperscript{nd} Line</td>
<td>Post Cytokines</td>
<td>Axitinib</td>
<td>Sorafenib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sorafenib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>\textbf{Pazopanib}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post TKIs</td>
<td>Axitinib</td>
<td>\textbf{Sorafenib}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>\textbf{Everolimus}</td>
<td></td>
</tr>
<tr>
<td>Clear Cell/3\textsuperscript{rd} Line</td>
<td>Post 2 TKIs</td>
<td>\textbf{Everolimus}</td>
<td>Other TKI</td>
</tr>
<tr>
<td></td>
<td>Post TKI &amp; mTOR</td>
<td>\textbf{Sorafenib}</td>
<td>Rechallenge TKI</td>
</tr>
<tr>
<td>Non Clear Cell</td>
<td></td>
<td></td>
<td>Sunitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sorafenib</td>
</tr>
</tbody>
</table>
Management Of Metastatic Disease
Radiotherapy

- No role in neoadjuvant/adjuvant – 4 negative trials

- Indications:
  - Unresectable local or recurrent local disease to improve local control
  - Palliation
  - Spinal Cord Compression
  - Brain Metastases
Bladder Cancer
Bladder Cancer Stats - 2014

New cases in 2014
74,690
Deaths in 2014
15,580

Median age at diagnosis 73
Death 78

571,518 men and women are living with bladder cancer

Annual cost $4B

Survival:
71% (New Cases)
81% (Deaths)

Age distribution of new cases:
- <20: 0.1%
- 20-34: 0.4%
- 35-44: 1.5%
- 45-54: 7.1%
- 55-64: 18.5%
- 65-74: 27.9%
- 75-84: 30.5%
- >84: 14.0%
The Faces of Bladder Cancer
Muscle Invasive Bladder Cancer (MIBC)

- Radical cystectomy with extended lymphadenectomy considered standard treatment in MIBC
- Extended lymph node dissection beneficial/potentially curative with mets/micro mets to nodes
- PFS & OS directly correlated to number of lymph nodes removed surgically
- Chemo/radiotherapy curative in pts not fit for surgery
Neoadjuvant Chemotherapy + Radical Cystectomy for Muscle-Invasive Bladder Cancer cT2-T4a
Muscle Invasive Bladder Cancer (MIBC) Neoadjuvant/Adjuvant Therapy

- Use of cisplatin based neoadjuvant chemotherapy supported by meta analysis
  11 randomised trials 3005 pts

- 5% increase OS & 9% increase DFS compared to Surgery

- Adjuvant chemotherapy – meta analysis 9 randomised clinical trials of 945 pts

- Statistically significant improvement DFS/OS esp. in lymph node positive disease

- Issue – post surgery because of morbidity of procedure unfit adjuvant chemotherapy medically or new renal impairment excludes them for chemotherapy
Management Metastatic Disease – 1st Line

- Cisplatin based Combination Chemotherapy
  - MVAC (methotexate, vinblastine, adriamycin, cisplatin)
  - GC (Gemcitabine/cisplatin) – less toxic
  - HDMVAC – better tolerated with GCSF

- Median survival 14mths

- Long tern DFS 15% (20.9% LN disease Vs 6.8% visceral mets)

- Pts poor PS/Comorbid status/impaired renal function (50% all pts) – Carboplatin based regimens/single agent Taxanes/Gemcitabine
Management Metastatic Disease – 2\textsuperscript{nd} Line

- Progression < 12 mths
  - Second Line chemotherapy
    - Taxane based
    - Clinical trial
    - Vinflunine

- Progression > 12 mths
  - Platinum based rechallenge
### Second-Line Single Agent Targeted Therapies Reported in Metastatic Urothelial Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Agent</th>
<th>Target</th>
<th>Study type</th>
<th>n</th>
<th>OS (months)</th>
<th>RR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomez-Abuin</td>
<td>2007</td>
<td>Bortezomib</td>
<td>Proteasome inhibitor</td>
<td>Phase II</td>
<td>20</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Rosenberg</td>
<td>2008</td>
<td>Bortezomib</td>
<td>Proteasome inhibitor</td>
<td>Phase II</td>
<td>25</td>
<td>5.7</td>
<td>0</td>
</tr>
<tr>
<td>Wulffing</td>
<td>2009</td>
<td>Lapatinib</td>
<td>HER1 and HER2</td>
<td>Phase II</td>
<td>59</td>
<td>4.5</td>
<td>3</td>
</tr>
<tr>
<td>Petrylak</td>
<td>2009</td>
<td>Gefitinib</td>
<td>EGFR</td>
<td>Phase II</td>
<td>31</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dreicer</td>
<td>2009</td>
<td>Sorafenib</td>
<td>B-Raf, c-Raf, VEGFR-2/3, PDGFR-b, VEGFR-1/2, C-KIT, PDGFR a/b, FLT3 and RET</td>
<td>Phase II</td>
<td>27</td>
<td>6.8</td>
<td>0</td>
</tr>
<tr>
<td>Gallagher</td>
<td>2010</td>
<td>Sunitinib</td>
<td>VEGF, PDGF</td>
<td>Phase II</td>
<td>45</td>
<td>6.9</td>
<td>7</td>
</tr>
<tr>
<td>Twardowski</td>
<td>2010</td>
<td>Aflibercept</td>
<td>VEGF, PDGF</td>
<td>Phase II</td>
<td>22</td>
<td>NR</td>
<td>4.5</td>
</tr>
<tr>
<td>Cheung</td>
<td>2010</td>
<td>Vorinostat</td>
<td>SAHA: histone deacetylase</td>
<td>Phase II</td>
<td>14</td>
<td>4.3</td>
<td>0</td>
</tr>
<tr>
<td>Stadler</td>
<td>2011</td>
<td>Volasertib</td>
<td>Polo-like kinase 1</td>
<td>Phase II</td>
<td>31</td>
<td>NR</td>
<td>19</td>
</tr>
<tr>
<td>Milowsky</td>
<td>2011</td>
<td>Everolimus</td>
<td>PI3K/Akt/mTOR</td>
<td>Phase II</td>
<td>45</td>
<td>10.5</td>
<td>5</td>
</tr>
<tr>
<td>Piti</td>
<td>2011</td>
<td>Pazopanib</td>
<td>VEGFR1/2/3, PDGFR a/b, c-Kit</td>
<td>Phase II</td>
<td>19</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Necchi</td>
<td>2012</td>
<td>Pazopanib</td>
<td>VEGFR1/2/3, PDGFR a/b, c-Kit</td>
<td>Phase II</td>
<td>41</td>
<td>4.7</td>
<td>17</td>
</tr>
<tr>
<td>Lerner</td>
<td>2012</td>
<td>Tamoxifen</td>
<td>ER-B</td>
<td>Phase II</td>
<td>28</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Milowsky</td>
<td>2013</td>
<td>Dovitinib</td>
<td>FGFR3</td>
<td>Phase II</td>
<td>44</td>
<td>NR</td>
<td>0</td>
</tr>
</tbody>
</table>

Ghosh M. and Apolo, AB. Curr Opin Oncol. 2014
We are in the beginning of an immunotherapy revolution in oncology

- Immune check point therapy has demonstrated significant clinical activity in multiple solid tumors
- PD-L1 is highly expressed in urothelial cancer of the bladder


Presented at the Genitourinary Cancers Symposium
Slides are the property of the author. Permission required for reuse.

Presented by: Andrea B. Apolo
Checkpoint Inhibition in Urothelial Carcinoma

MPDL3280A
Summary of ORR

Pembrolizumab
Summary of ORR


Presented by: Andrea B. Apolo

Presented at the Genitourinary Cancers Symposium
Slides are the property of the author. Permission required for reuse.
Agents that can enhance the immune response

- Immunotherapies
  - Vaccines
  - CTLA-4 inhibitors
  - Adoptive cell transfer
- Radiation
- Chemotherapy
- Tyrosine kinase inhibitors
## Response rates in reported combination therapies

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Nivolumab (all dose levels)</th>
<th>Nivolumab + Ipilimumab</th>
<th>Nivolumab + Sunitinib or pazopanib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>RR</td>
<td>N</td>
</tr>
<tr>
<td>Melanoma</td>
<td>94</td>
<td>28%1</td>
<td>53</td>
</tr>
<tr>
<td>Renal Cell Carcinoma</td>
<td>168</td>
<td>21%2</td>
<td>44</td>
</tr>
</tbody>
</table>

*21% in N=17 in nivolumab 3mg/Kg
*41% in N=17 in nivolumab 3mg/Kg
*53% in N=23 in ipilimumab 3mg/Kg

2. Motzer R. et al., JCO.2014.59.0703
4. Hammers HJ et al., J Clin Oncol 32:5s, 2014 (suppl; abstr 4504)
5. Amin. et al., J Clin Oncol 32:5s, 2014 (suppl; abstr 5010)
### Response rates by baseline PD-L1 expression

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Nivolumab (all dose levels)</th>
<th>Nivolumab + Ipilimumab</th>
<th>Nivolumab + Sunitinib or pazopanib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>RR</td>
<td>RR</td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1+</td>
<td>28% ^1</td>
<td>40% ^2</td>
<td>N/R</td>
</tr>
<tr>
<td>7/17</td>
<td>6/13</td>
<td>PD-L1+</td>
<td></td>
</tr>
<tr>
<td>41%</td>
<td>46%</td>
<td>PD-L1-</td>
<td></td>
</tr>
<tr>
<td>3/21</td>
<td>9/22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14%</td>
<td>41%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal Cell Carcinoma</strong></td>
<td>21% ^5</td>
<td>45% ^3</td>
<td>49% ^4</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>9/29</td>
<td>PD-L1+</td>
<td></td>
</tr>
<tr>
<td>31%</td>
<td>6/13</td>
<td>PD-L1-</td>
<td></td>
</tr>
<tr>
<td>14/78</td>
<td>9/22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18%</td>
<td>56%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1-</td>
<td>1/4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25%</td>
<td>18/32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56%</td>
<td>54%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Hammers HJ et al., J Clin Oncol 32:5s, 2014 (suppl; abstr 4504)
4. Amin. et al., J Clin Oncol 32:5s, 2014 (suppl; abstr 5010)
5. Motzer R. et al., JCO. 2014 S9.0703
## Treatment-Related Adverse Events in reported combination therapies

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Events</th>
<th>Nivolumab(^1) (Melanoma and RCC) N=296</th>
<th>Nivolumab + Ipilimumab(^2) (Melanoma) N=53</th>
<th>Nivolumab + Ipilimumab(^2) (RCC) N=44</th>
<th>Nivolumab + Sunitinib or pazopanib(^3) (RCC) N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>2 (1%)</td>
<td>7 (13%)</td>
<td>6 (14%)</td>
<td>10 (19%)</td>
</tr>
<tr>
<td>AST</td>
<td>2 (1%)</td>
<td>6 (11%)</td>
<td>12 (28%)</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>Lipase</td>
<td>N/A</td>
<td>7 (13%)</td>
<td>12 (28%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>2 (4%)</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (1%)</td>
<td>3 (6%)</td>
<td>4 (9%)</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>0</td>
<td>2 (4%)</td>
<td>0</td>
<td>3 (6%)*</td>
</tr>
</tbody>
</table>

3. Hammers HJ et al., J Clin Oncol 32:5s, 2014 (suppl; abstr 4504)

* N/A not reported
* sunitinib arm
Checkpoint Clinical trials in Bladder Cancer

Non Muscle Invasive Bladder Cancer
- Low Grade
- High Grade

Muscle-Invasive Bladder Cancer
- Neoadjuvant
- Adjuvant

Metastatic Bladder Cancer
- Cisplatin-eligible
- Cisplatin-ineligible
  - 1st line
  - Maintenance
  - 2nd line & beyond
  - Cisplatin-refractory

Presented at the Genitourinary Cancers Symposium
Presented by: Andrea B. Apolo
Checkpoint Clinical trials in Bladder Cancer

Non Muscle-Invasive Bladder Cancer
- Low Grade
- High Grade

Muscle-Invasive Bladder Cancer
- Neoadjuvant
- Adjuvant

Metastatic Bladder Cancer
- Cisplatin-eligible
  - Pembrolizumab
  - MPDL3280A
  - MEDI4736
  - AMP-514
  - MSB0010718C
  - MGA271
- Cisplatin-refractory
  - Pembrolizumab (Phase III)
  - MPDL3280A (Phase III)

1st line
- Maintenance

2nd line & beyond
Checkpoint Clinical trials in Bladder Cancer

Non Muscle Invasive Bladder Cancer
- Low Grade
  - Pembrolizumab / BCG
- High Grade
  - Pembrolizumab / BCG
  - Neoadjuvant
  - Adjuvant
  - BCG-refractory
    - Pembrolizumab / BCG

Muscle-Invasive Bladder Cancer
- Neoadjuvant
- Adjuvant

Metastatic Bladder Cancer
- 1st line
  - Cisplatin-eligible
    - Pembrolizumab
    - MPDL3280A
  - Cisplatin-ineligible
    - Maintenance
    - Pembrolizumab
    - MPDL3280A

2nd line & beyond
- Cisplatin-refractory
  - Pembrolizumab (Phase III)
  - MPDL3280A (Phase III)
  - MEDI4736
  - AMP-514
  - MSBO010718C
  - MGA271
  - Nivolumab ± ipilimumab
  - Nivolumab/cabozantinib ± ipilimumab
  - Pembrolizumab/radiation
  - MPDL3280A+Bevacizumab
  - MEDI0680+MEDI4736

Presented at the Genitourinary Cancers Symposium
Slides are the property of the author. Permission required for reuse.

Presented by: Andrea B. Apolo
Checkpoint Clinical trials in Bladder Cancer

Non Muscle-Invasive Bladder Cancer
- Low Grade: In development
- High Grade: Pembrolizumab / BCG
  - BCG-refractory: Pembrolizumab / BCG

Muscle-Invasive Bladder Cancer
- Neoadjuvant: In development
- Adjuvant: In development

Metastatic Bladder Cancer
- 1st line: Cisplatin-eligible
  - Pembrolizumab / MPDL3280A
- Maintenance: In development
- 2nd line & beyond: Cisplatin-refractory
  - Pembrolizumab (Phase III)
  - MPDL3280A (Phase III)
  - MEDI4736
  - AMP-514
  - MSB0010718C
  - MGA271

- Cisplatin-ineligible
  - Nivolumab ± ipilimumab
  - Nivolumab / cabozantinib ± ipilimumab
  - Pembrolizumab / radiation
  - MPDL3280A + Bevacizumab
  - MEDI0680 + MEDI4736

Presented at the Genitourinary Cancers Symposium
Slides are the property of the author. Permission required for reuse.