Updates in renal and bladder cancer for the internist

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Disclosures/Confluence of Interests

- PI/research funding - Acerta, Novartis, Merrimack, Abbvie/StemCentrx, Merck, Regeneron, Mirati Therapeutics, Janssen, Astra Zeneca, Pfizer, OmniSeq, Personal Genome Diagnostics, Astellas
- Advisory Board – Merck, Exelixis, Sanofi-Aventis, Janssen, Astra Zeneca, Pfizer, Amgen, BMS, Pharmacyclics, SeaGen, Calithera, Dendreon, QED Therapeutics, Eisai, Aveo Pharmaceuticals, Bayer, Eli Lilly
- Consultant – Pfizer, MJH Associates, Vaniam, Aptitude Health, PeerView, Clinical Care Options
Outline

• Renal cell carcinoma
  • Combining immunotherapy and anti-angiogenic agents
  • Adjuvant and first-line metastatic treatment landscape

• Urothelial cancer
  • Immunotherapy, targeted therapies, antibody drug conjugates
  • Toxicities
Renal cell histologies: clear cell and non clear cell

<table>
<thead>
<tr>
<th>Type</th>
<th>Clear cell</th>
<th>Papillary type 1</th>
<th>Papillary type 2</th>
<th>Chromophobe</th>
<th>Oncocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated mutations</td>
<td>VHL, SDH, BAP1</td>
<td>MET</td>
<td></td>
<td>FH</td>
<td>BHD</td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>75</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Locus</td>
<td>3p25</td>
<td>7q31</td>
<td>1q42</td>
<td>17p11</td>
<td>17p11</td>
</tr>
</tbody>
</table>

- Sarcomatoid differentiation present ~5% of RCCs
  - Can occur with any histologic subtype
  - Spindle-like cells, high cellularity, and cellular atypia
  - More aggressive

Staging and natural history

Percent of cases by stage

- Localized (65%)
  Confined to Primary Site
- Regional (16%)
  Spread to Regional Lymph Nodes
- Distant (16%)
  Cancer Has Metastasized
- Unknown (3%)
  Unstaged

5-year relative survival

- Localized: 92.7%
- Regional: 71.0%
- Distant: 13.9%
- Unknown: 44.7%

Distribution of metastatic disease

- Lung: 29.5%
- Bone: 21.8%
- Lymph node: 20.3%
- Liver: 8.9%
- Adrenal: 8.1%
- Brain: 6.9%
- Other: 2.9%
- Digestive: 2.8%
- Other: 2.1%
- Urothelial: 1.4%
- Kidney: 1.3%
- Small intestine: 1.1%
- Other: 0.2%
- Ovary: 0.2%

SEER Cancer of the Kidney and Renal Pelvis Fact Sheet 2021
Renal cell carcinoma biology: angiogenesis and molecular pathogenesis


2019 Nobel Prize in Physiology or Medicine

Kaelin, Semenza, Ratcliffe

Brugarolas
Targeting angiogenesis:

**Small molecule tyrosine kinase inhibitors of VEGFR:**
- Sunitinib
- Pazopanib
- Sorafenib
- Axitinib
- Cabozantinib (off-target effects on MET and Axl)
- Lenvatinib (off-target effects on FGFRs)

**Monoclonal antibodies:**
- Bevacizumab

**Small molecule inhibitors of HIF2α:**
- PT2385
- Belzutifan (MK-6482)
Cytokine therapy era of 1990s-2000s

- High dose IL-2 very toxic but durable responses

Yang JC et al, JCO, 2003
International metastatic renal cell carcinoma database consortium (IMDC) prognostication

**Heng/IMDC Criteria**

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnofsky Performance Status &lt; 80%</td>
</tr>
<tr>
<td>Time from diagnosis to treatment &lt; 1 year</td>
</tr>
<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Neutrophilia</td>
</tr>
<tr>
<td>Thrombocytosis</td>
</tr>
</tbody>
</table>

**IMDC categories**

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable (0 risk factors)</td>
</tr>
<tr>
<td>Intermediate (1-2 risk factors)</td>
</tr>
<tr>
<td>Poor (≥3 risk factors)</td>
</tr>
</tbody>
</table>

**Markers of inflammation**

Initial prognosis publication 2009. Used as stratification & selection in trials, now strong implication for treatment selection.

Timeline of US FDA approved therapies in metastatic ccRCC

1L

- Sorafenib (12/05)
- Sunitinib (1/06)
- Temsirolimus (5/07)
- Bevacizumab + IFN-α (8/09)
- Pazopanib (10/09)
- Axitinib (1/12)
- Temsirolimus (5/07)
- Everolimus (3/09)
- Nivolumab (11/15)
- Ipilimumab/ Nivolumab (4/18)
- Cabozantinib (12/17)
- Pembrolizumab w/ cabozantinib (1/21)
- Avelumab with axitinib (5/19)
- Pembrolizumab w/ lenvatinib (5/19)

2L+

- Cabozantinib (4/16)
- Lenvatinib + Everolimus (5/16)
- Tivozanib (3/21)
First-line metastatic renal cell carcinoma phase 3 trial designs ~2014-2018

- Clear cell renal cell carcinoma
- Measurable metastatic disease, by RECIST criteria
- No prior systemic treatments
- Good performance status
- Archival tissue available

**Stratification factors:**
- IMDC criteria (favorable, intermediate, poor)
- Region (US vs outside US)
- Performance status

**Randomization**

- Checkmate 214, phase 3
  - n = 1096
- Javelin Renal 101, phase 3
  - n = 886
- Keynote 426, phase 3
  - n = 861
- IMMotion 151, phase 3
  - n = 915
- Checkmate 9ER
  - n = 638
- CLEAR
  - n = 1069

**Common control cohort in all trials**

- Sunitinib 50mg PO daily
  - 4 weeks on, 2 weeks off
- Ipilimumab 1mg/kg IV q3wk
  - Nivolumab 3mg/kg IV q3wk x4 cycles
  - Then nivolumab 3mg/kg IV q2wk
- Axitinib 5mg PO BID
  - Avelumab 10mg/kg IV q2wk
- Axitinib 5mg PO BID
  - Pembrolizumab 200mg IV q3wk
- Bevacizumab 15mg/kg IV q3wk
  - Atezolizumab 1200mg IV q3wk
- Cabozantinib 40mg PO daily
  - Nivolumab 240mg IV q2wk
- Lenvatinib 20mg PO daily
  - Pembrolizumab 200mg IV q3wk

**Primary endpoints:**
- Overall survival
- Progression free survival

**Secondary endpoints:**
- Objective response rates
- Duration of responses
- Patient-reported quality of life
- Safety of combinations

**Treat until disease progression or unacceptable toxicity**
First-line metastatic renal cell carcinoma trials: Overall Survival

**Checkmate 214: Overall Survival ITT (60-mo follow up)**

NIVO+PIN (N = 550)
SUN (N = 546)

- Median OS (95% CI), mo: 55.7 (46.3-64.6) vs 38.4 (32.0-45.6)
- HR (95% CI): 0.72 (0.62-0.85); P < 0.0001
- Overall survival (probability)
  - 60 months: 48% vs 37%
  - 54 months: 58% vs 52%

**Checkmate 9ER: Overall Survival**

- Median OS, months (95% CI): NIVO+CABO (NR-NE) vs SUN (22.6-NE)
- HR: 0.60 (98.9% CI, 0.40-0.89); P = 0.0010

**Keynote 426: Overall Survival ITT**

- HR, 0.72 (95% CI, 0.61-0.86); P < 0.0001

**Checkmate 214: Overall Survival ITT (60-mo follow up)**

- Events, n: pembrolizumab + axitinib 142 vs Nivo + axitinib 178
- Median OS (95% CI), mo: 36.7 (33.3-NR)

**CLEAR/Keynote 581: Overall Survival ITT**

- Lenvatinib + pembrolizumab vs lenvatinib + everolimus
- HR, 0.68 (95% CI, 0.55-0.85); P < 0.0014

References:
- Tannir N et al, GU ASCO 2020; Choueiri TK et al, NEJM, 2021
- Powles T et al, Lancet Oncol, 2020; Motzer RJ et al, NEJM, 2021
Survival benefit driven by patients with IMDC intermediate-poor risk/“clinically inflamed” disease

Checkmate 214 Overall survival by IMDC risk 60 mo followup

Intermediate/Poor risk

Favorable risk

Keynote 426: Overall survival by IMDC risk

Favorable risk

Intermediate/Poor risk

Tannir N et al, GU ASCO, 2020
Powles T et al, Lancet Oncol, 2020
PFS for ipilimumab-nivolumab – some responses durable
PFS for axitinib-pembrolizumab, axitinib-avelumab, cabozantinib-nivolumab, Lenvatinib-pembrolizumab significantly improved

**Checkmate 214 Progression free survival**

60-month update

**Checkmate 9ER Progression free survival**

**Keynote 426 Progression free survival**

**CLEAR/Keynote 581 Progression free survival**

Motzer RJ et al, ESMO, 2021


Choueiri TK et al, *NEJM*, 2021

Motzer RJ et al, *NEJM*, 2021
Objective responses – 8-16% complete responders, some delayed responses

Checkmate 214
GU ASCO 2020
48 month update

<table>
<thead>
<tr>
<th>Response per</th>
<th>Primary: Intermediate/poor risk</th>
<th>Secondary: ITT population</th>
<th>Exploratory: Favorable risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO+IPI</td>
<td>CR 32, PR 12</td>
<td>CR 42, PR 26</td>
<td>CR 29, PR 39</td>
</tr>
<tr>
<td>SUN</td>
<td>CR 30, PR 2</td>
<td>CR 29, PR 12</td>
<td>CR 14, PR 29</td>
</tr>
<tr>
<td>NIVO+IPI</td>
<td>CR 30, PR 2</td>
<td>CR 32, PR 2</td>
<td>CR 16, PR 31</td>
</tr>
<tr>
<td>SUN</td>
<td>CR 32, PR 2</td>
<td>CR 32, PR 2</td>
<td>CR 48, PR 45</td>
</tr>
</tbody>
</table>

Keynote 426
ASCO 2020
24-month update

Tannir N et al, GU ASCO, 2020; Motzer RJ et al, NEJM, 2021
Powles T et al, Lancet Oncol, 2020; Choueiri TK et al, NEJM, 2021

Checkmate 9ER

<table>
<thead>
<tr>
<th>ORR %</th>
<th>Pembrolizumab + Axitinib</th>
<th>Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>8% CR</td>
<td>8% CR (55.7%) (21.7-35.6)</td>
<td>27.1% (22.4-32.3)</td>
</tr>
<tr>
<td>11% CR</td>
<td>6% CR (50.1-61.2)</td>
<td>27.1% (22.4-32.3)</td>
</tr>
</tbody>
</table>

CLEAR Intention to treat

<table>
<thead>
<tr>
<th>ORR %</th>
<th>Lenalidomide + pembrolizumab</th>
<th>Lenalidomide + everolimus</th>
<th>Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>16% CR</td>
<td>16% CR (55.7%) (21.7-35.6)</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

P < 0.0001
Safety data: immune mediated adverse events

Checkmate 214: ipilimumab-nivolumab adverse events

<table>
<thead>
<tr>
<th>Category</th>
<th>Any grade</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea/colitis</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Nephritis and renal dysfunction</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Hypersensitivity/infusion reaction</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>19</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

CLEAR: Lenvatinib-pembrolizumab adverse events

Keynote 426: Axitinib-pembrolizumab adverse events

Checkmate 9ER: cabozantinib-nivolumab adverse events

CheckpointNow MD

Episode 2
Immune Related Thyroid Toxicities
Hosts: Join our hosts Dr. Afreen Shariff and Dr. Tian Zhang as they discuss challenges encountered in the diagnosis and management of commonly encountered immune related thyroid toxicities.

Episode 3
Breaking down the diagnosis and management of immune hypophysitis
Hosts: Join our hosts Dr. Afreen Shariff and Dr. Tian Zhang as they discuss all things immune hypophysitis and all you need to know to get better at managing this complex toxicity.

Episode 4
Immune mediated inflammatory arthritis: Challenges in diagnosis and management
Hosts: Join our hosts Dr. Afreen Shariff and Dr. Tian Zhang as they discuss with guest expert and rheumatologist Dr. Sophia Weinmann about the complex and challenging diagnosis of immune mediated inflammatory arthritis.

Episode 6
Rheumatic adverse events: Discussions on pre-existing rheumatic disease, biomarkers, collaborations and more.
Hosts: Join our hosts Dr. Afreen Shariff and Dr. Tian Zhang as they discuss with guest experts and rheumatologists Dr. Leonard Calabrese and Dr. Cassandra Calabrese from Cleveland Clinic and Dr. Alexa Meara from Ohio State University about budding collaborations and scientific discovery in immune mediated rheumatic adverse events.

Episode 7
Immune mediated colitis and lessons learnt from multidisciplinary team based management.
Hosts: Learn from the experts about the clinical diagnosis and multidisciplinary management of immune mediated colitis. Join our hosts Dr. Afreen Shariff and Dr. Tian Zhang as they discuss with guest experts - medical Oncologist Dr. Kerry Reynolds and Gastroenterologist/ Immunologist Dr. Micheal Dougan from Massachusetts General Hospital for an informative and high yield discussion.

Homegrown, self-supported podcast
19 Episodes available

Available on Spotify and Apple Podcasts; Hosts Drs. Afreen Shariff and Tian Zhang
Next Generation First-line phase 3 trial designs in mRCC

- Clear cell renal cell carcinoma
- Measurable metastatic disease, by RECIST criteria
- No prior systemic treatments
- Good performance status
- Archival tissue available

Stratification factors:
- IMDC criteria (favorable, intermediate, poor)
- Region (US vs outside US)
- Performance status

Randomization:
- Control cohort
- PDIGREE n=1046
- LITESPARK-012 n=1431
- COSMIC 313 n=840 Completed accrual
- PROBE n=364

Immunotherapy-based combination
- Nivolumab-cabozantinib
- Belzutifan-levalinib-pembro
- Quavonlimab-Lenvatinib-pembro
- Ipilimumab-Nivolumab-cabozantinib
- Consolidative nephrectomy

Primary endpoints:
- Overall survival
- Progression free survival

Secondary endpoints:
- Objective response rates
- Duration of responses
- Patient-reported quality of life
- Safety of combinations

Treat until:
- Disease progression
- Unacceptable toxicity
- Response endpoint

Consolidative nephrectomy PROBE n=364
PD-Inhibitor nivolumab and Ipilimumab followed by nivolumab vs VEGF TKI cabozantinib with nivolumab (PDIGREE, A031704) – schema

**PDIGREE**

Metastatic renal cell carcinoma
- Clear cell component
- No prior systemic therapy (HD IL-2 and adjuvant sunitinib allowed)
- IMDC Intermediate or poor risk
- Archival tissue available or fresh biopsy

N=1046

**PDGREE**

**Study chairs: Zhang & Choueiri**

Study activated in NCTN May 2019
Active enrollment across sites

**PDIGREE:** Alliance trial A031704
Clinicaltrials.gov: NCT03793166

**1º endpoint:**
3-year OS
(60% nivo vs 70% nivo-cabo, HR 0.70
85% power, 2-sided α =0.05)

**Key 2º endpoints:**
-- 1-year CR rate
-- PFS
-- ORR by RECIST
-- Toxicity of nivo-cabo

**Induction therapy**

Ipilimumab 1mg/kg IV every 3 weeks
Nivolumab 3mg/kg IV every 3 weeks

**CR**

Non-CR
Non-PD

3-month response (investigator assessed)

R

N=636

**PD**

Nivolumab 480mg IV every 4 weeks

cabo

Cabozantinib 60mg PO daily

Discontinue:
Progression of disease
Unacceptable toxicity
Complete response at 1 year
Two patients, same treatment, different outcomes

47yo man

- **Ipilimumab/Nivolumab**: 9/2017-11/2018
- **Treatment break**: 15 months
- **Nivolumab**: 2/2020-7/2021
- **Held for hematoma**
- **Liver abscess, sepsis hospice**: 10/2019
- **Death**: 11/2019
- **Innumerable symptomatic liver and lung mets**, Hgb 8.6, plt 550, <1 year from nephrectomy

70yo man

- **Ipilimumab/Nivolumab**: 6/2019-9/2019
- **Treatment break**: Ongoing
- **Liver abscess, sepsis hospice**: 10/2019
- **Death**: 11/2019
- **Hgb 9.0, plt 500**
- **De novo metastatic to lungs and liver**

2017 2019 2021
Sarcomatoid differentiation may predict for immunotherapy response – Progression Free Survival

CheckMate 214

- NIVO+IPI
- SUN

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>N = 60</th>
<th>N = 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO+IPI</td>
<td>37 (61.7)</td>
<td>40 (76.9)</td>
</tr>
<tr>
<td>Median PFS (95% CI), mo</td>
<td>8.4 (3.2–24.0)</td>
<td>4.9 (4.0–7.0)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.61 (0.38–0.97)</td>
<td></td>
</tr>
</tbody>
</table>

IMmotion151

- Median PFS (95% CI)
  - Atezo + bev: 8.3 mo (5.4, 12.9)
  - Sunitinib: 5.3 mo (3.3, 6.7)

KEYNOTE-426

- Pts w/ Event
- Median

<table>
<thead>
<tr>
<th>Pembrolizumab  + Axitinib</th>
<th>37%</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>63%</td>
<td>8.4</td>
</tr>
</tbody>
</table>

HR (95% CI) 0.54 (0.29–1.00)
## Sarcomatoid RCC: response to immunotherapy combinations

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab/Nivolumab Checkmate 214 (N=74)</th>
<th>Axitinib/Pembrolizumab Keynote 426 (N=51)</th>
<th>Axitinib/Avelumab Javelin Renal 101 (N=47)</th>
<th>Atezolizumab/Bevacizumab Immination 151 (N=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>61%</td>
<td>59%</td>
<td>47%</td>
<td>49%</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>19%</td>
<td>12%</td>
<td>4%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>26.5 months</td>
<td>NR</td>
<td>7.0 months</td>
<td>8.3 months</td>
</tr>
<tr>
<td>HR (95% CI) vs sunitinib</td>
<td>0.54 (0.3-0.9)</td>
<td>0.54 (0.29-1.00)</td>
<td>0.57 (0.33-1.00)</td>
<td>0.52 (0.34-0.79)</td>
</tr>
<tr>
<td><strong>12 month PFS</strong></td>
<td>57% (est.)</td>
<td>57%</td>
<td>35% (est.)</td>
<td>39%</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>NR</td>
<td>NR</td>
<td>NA</td>
<td>21.7 months</td>
</tr>
<tr>
<td>HR (95% CI) vs sunitinib</td>
<td>0.45 (0.3-0.7)</td>
<td>0.58 (0.21-1.59)</td>
<td>NA</td>
<td>0.64 (0.41-1.01)</td>
</tr>
<tr>
<td><strong>12 month OS</strong></td>
<td>84% (est.)</td>
<td>83%</td>
<td>83%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Pancreatic metastases: dependent on angiogenesis

- Highly vascular, looks like primary tumors

- Gene mutation panels with high proportion with loss of VHL and other angiogenesis pathways

Singla N et al, *JCI Insight*, 2020
Pancreatic metastases dependent on angiogenesis, respond to VEGF-targeted treatments, not to nivolumab

Singla N et al, *JCI Insight*, 2020
Gene expression clustering of 7 molecular subtypes from IMMotion 151 trial (atezolizumab-bevacizumab vs sunitinib)

Motzer et al, Cancer Cell, 2020
Molecular clusters have differing responses to sunitinib vs atezolizumab/bevacizumab

Motzer et al, Cancer Cell, 2020
Future trials with molecular selection

Proposed trial from Rini et al
Multicenter study from Vanderbilt

Need strategies for rapid gene expression testing to improve clinical utility
First-line metastatic clear cell RCC treatment summary

- Overall survival benefit for ipilimumab-nivolumab, pembrolizumab-axitinib, cabozantinib-nivolumab, and lenvatinib-pembrolizumab
  - No head-to-head trial of VEGF-IO combinations versus ipilimumab-nivolumab
  - Better outcomes of VEGF-IOs vs sunitinib in favorable risk disease
- Treatment selection depends on patient in front of us:
  - IMDC status
  - Prior nephrectomy?
  - Bone metastases?
  - Symptomatic disease?
  - Burden of metastatic disease?
  - Goals of treatment?
- Opportunities in molecular patient selection and treatment sequencing
Timeline of US FDA approved therapies

Adjuvant

1L
- Sorafenib (12/05)
- Sunitinib (1/06)
- Temsirolimus (5/07)
- Pazopanib (10/09)
- Bevacizumab + INF-α (8/09)

2L+
- Everolimus (3/09)
- Axitinib (1/12)
- Nivolumab (11/15)
- Cabozantinib (4/16)
- Lenvatinib + Everolimus (5/16)
- Tivozanib (3/21)

- Cabozantinib (12/17)
- Sunitinib (11/17)
- Pembrolizumab (11/21)
- Nivolumab (4/18)
- Pembrolizumab + cabozantinib (1/21)
- Ipilimumab + nivolumab (4/19)
- Nivolumab w/ cabozantinib (5/19)
- Avelumab w/ lenvatinib (8/21)
- Pembrolizumab w/ lenvatinib (8/21)
- Pembrolizumab (11/21)
- Nivolumab (4/19)
- Avelumab (5/19)
- Pembrolizumab (11/21)

- Bevacizumab + IFN-α (8/09)
- Axitinib (1/12)
- Temsirolimus (5/07)
- pazopanib (10/09)
- Sorafenib (12/05)
- Sunitinib (1/06)
- Cabozantinib (12/17)
- Everolimus (3/09)
- Axitinib (1/12)
- Nivolumab (11/15)
- Cabozantinib (4/16)
- Lenvatinib + Everolimus (5/16)
- Tivozanib (3/21)
Balancing Risk/Benefit: Sunitinib in the Adjuvant Setting

November 16, 2017: FDA approved 1 year of sunitinib in the adjuvant setting
Not used often in clinical care because toxicity outweighs potential benefit

If/when recommended, adjuvant sunitinib likely more for younger patients with a high anxiety about disease recurrence and a high threshold for toxicity.
### Completed and Ongoing Phase 3 Adjuvant Trials With Immune Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Trial</th>
<th>Neoadjuvant</th>
<th>Adjuvant</th>
<th>Eligible Histology</th>
<th>Primary Endpoint</th>
<th>Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMmotion010</td>
<td></td>
<td>Atezolizumab, Placebo</td>
<td>ccRCC</td>
<td>DFS</td>
<td>778 (actual)</td>
</tr>
<tr>
<td>KEYNOTE-564</td>
<td></td>
<td>Pembrolizumab, Placebo</td>
<td>ccRCC</td>
<td>DFS</td>
<td>994 (actual)</td>
</tr>
<tr>
<td>PROSPER</td>
<td></td>
<td>Nivolumab, Observation</td>
<td>ccRCC, nccRCC</td>
<td>EFS</td>
<td>766 (estimated)</td>
</tr>
<tr>
<td>RAMPART</td>
<td></td>
<td>Durvalumab, Durvalumab + tremelimumab, Observation</td>
<td>ccRCC, nccRCC</td>
<td>DFS, OS</td>
<td>1,750 (estimated)</td>
</tr>
<tr>
<td>CheckMate -914</td>
<td></td>
<td>Nivolumab + ipilimumab, Placebo</td>
<td>ccRCC</td>
<td>DFS</td>
<td>1,600 (estimated)</td>
</tr>
</tbody>
</table>

**Dosing Relative to Surgery**

-1 0 6 9 12

**Time, mo**

- DFS: Disease-Free Survival
- EFS: Event-Free Survival
- OS: Overall Survival
With a median follow-up of 24 months, the primary endpoint of DFS was met; ongoing DFS benefit at 30-mo follow up (HR 0.63; GU ASCO 2022)

Not enough events for OS - Additional follow-up planned for key secondary endpoint of OS

Safety results as expected for immune checkpoint inhibitors, and no new safety signals were observed

No clinically meaningful changes from baseline in HRQOL or symptom scores were observed
High risk: pT4, any grade, N0, M0 or any T/grade, N+, M0
M1 NED: s/p metastasectomy within 1 year nephrectomy

Choueiri TK et al, GU ASCO 2022
Balancing Risk/Benefit: Pembrolizumab in the Adjuvant Setting

November 17, 2021: FDA approved pembrolizumab for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

- **Grade ≥3 toxicity is low**
- **Extend OS?**
- **Prevent disease recurrence**
- **Severe toxicities can be life-threatening**
- **Cost to patient and payers**
- **Inconvenience: IV treatment every 3 or 6 weeks**

*Depends on patient preferences/priorities, tolerance for toxicity, and goals for treatment—shared decision-making*
Recurrence prediction: ASSURE nomogram

Assure RCC Prognostic Nomogram
A post-operative prediction model which provides a comprehensive review of expected oncological outcomes in patient with renal cell carcinoma

Main features:
- Age
- Tumor size
- Histology
- Grade
- Necrosis
- LN involvement
- Vascular invasion
- Sarcomatoid features

Output:
Landmark disease free survival & overall survival (1-10yr) rates

https://studies.fccc.edu/nomograms/492
Completed accrual: PROSPER Study

**Step 0**
- **Arm H**: Histology confirmation required

**Step 1**
- **Arm A**: Nivolumab 480 mg x 1 dose
  - Partial or radical nephrectomy
- **Arm B**: Partial or radical nephrectomy followed by observation

**Stratification**
- Clinical T stage: cT1 or 2 vs cT3 or 4
- Clinical N stage: cN0 vs cN+
- Clinical metastatic stage: cM0 vs cM1

**Preregistration and randomization**
- Arm H: Histology confirmation required
- Arm O: Histology confirmation not required

**Registration**
- Arm A: Nivolumab 480 mg every 4 wk x 9 doses
- Arm B: Partial or radical nephrectomy followed by observation

**Long-term follow-up**

**N = 805**

Fully accrued summer 2021

Allaf ME et al. ASCO 2021. Abstract TPS4596
Adjuvant clear cell RCC takeaways

- Pembrolizumab now approved as adjuvant option with tolerable toxicity profile
- Balancing risks of toxicities with decreasing recurrence risk
- Depends on patient in front of us:
  - Pathologic features at time of nephrectomy, risk of recurrence
  - Discussion point whether benefit is meaningful for that patient
• Renal cell carcinoma
  • Combining immunotherapy and anti-angiogenic agents
  • Adjuvant and first-line metastatic treatment landscape
• Urothelial cancer
  • Immunotherapy, targeted therapies, antibody drug conjugates
  • Toxicities
Urothelial cancer staging and prognosis

Non-muscle-invasive bladder cancer (NMIBC)
- Tis
- Ta
- T1

Muscle-invasive bladder cancer (MIBC)
- T2a
- T2b
- T3
- T4

Tumor invades subepithelial connective tissue
Tumor invades superficial muscle
Tumor invades deep muscle
Tumor invades perivesical tissue
Tumor invades adjacent tissues and organs

Node (N)
Metastasis (M)

5-year relative survival

Platinum-based chemotherapy
- MVAC
- Gem/cis
- Gem/carbo

Refractory chemotherapy
- Paclitaxel
- Docetaxel
- Pemetrexed

Clinical trials:
- Immune checkpoint inhibitors
  - Enfortumab vedotin
  - Sacituzumab govitecan
- Novel targets, immunomodulating agents

Zhang T, adapted from discussion, ASCO Annual Meeting, 2020
Phase 1/2 PD-1 inhibitors

Atezolizumab


Pembrolizumab


Avelumab


Nivolumab


Durvalumab

**Pivotal trials Immune checkpoint inhibitors**

- Urothelial cancer
- Measurable metastatic disease, by RECIST criteria
- Prior platinum-based chemotherapy
- Good performance status
- Archival tissue available

**Stratification factors:**
- IMDC criteria (favorable, intermediate, poor)
- Region (US vs outside US)
- Performance status

**Common control cohort in all trials**

- Keynote 045, phase 3
  - n = 542
- IMVigor 211, phase 3
  - n = 931
- Checkmate 275, phase 3
  - n = 270
- DANUBE, phase 3
  - n = 1032
- Javelin, Phase 2
  - n = 44

**Chemotherapy**

- Pembrolizumab 200mg IV q3 weeks
- Atezolizumab 1200mg IV q3 weeks
- Nivolumab 3mg/kg IV q2 weeks
- Durvalumab 10mg/kg IV q2 weeks
- Durvalumab with temelimumab
- Avelumab 10mg/kg IV q2 weeks

**Treat until disease progression or unacceptable toxicity**

**Primary endpoints:**
- Overall survival
- Progression free survival

**Secondary endpoints:**
- Objective response rates
- Duration of responses
- Patient-reported quality of life
- Safety of combinations

---

Apolo AB et al, *JCO*, 2017
Phase 3 Immune checkpoint inhibitors

**Keynote 045**

**Pembro vs chemo**

**IMVigor 211**

Atezolizumab vs chemo

- **Overall survival**
  - Median OS 8.6 mo vs 8.0 mo
  - HR 0.85 (95% CI 0.73-0.99)

- **Progression Free Survival**
  - HR 0.98 (95% CI 0.81-1.19, p=0.42)

- **Duration of responses**
  - mDOR 15.9mo vs 8.3 mo
  - HR 0.57, 95% CI 0.26-1.26

Maintenance avelumab for mUC

- CR, PR, or SD with standard 1st-line chemotherapy (4-6 cycles)
  - Cisplatin + gemcitabine or
  - Carboplatin + gemcitabine
- Unresectable locally advanced or metastatic UC

Treatment-free interval 4-10 weeks
N=700

All endpoints measured post randomization (after chemotherapy)

Avelumab 10 mg/kg IV Q2W
+ BSC*
N=350

Until PD, unacceptable toxicity, or withdrawal

BSC alone*
N=350

Primary endpoint
- OS

Primary analysis populations
- All randomized patients
- PD-L1+ population

Secondary endpoints
- PFS and objective response per RECIST 1.1
- Safety and tolerability
- PROs

Stratification
- Best response to 1st-line chemo (CR or PR vs SD)
- Metastatic site (visceral vs non-visceral)

Powles T et al, NEJM, 2020
Maintenance avelumab for mUC

Progression free survival

Overall survival

Powles T et al, NEJM, 2020
Antibody drug conjugates (ADCs) in mUC

**Enfortumab vedotin**
Target: Nectin 4
Payload: MMAE – microtubule disrupter

**Sacituzumab govitecan**
Target: Trop 2
Payload: SN38

*Linker for SN-38*
- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7:6:1)

*Humanized anti-Trop-2 antibody*
- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

*SN-38 payload*
- SN-38 more potent than parent compound, irinotecan
Enfortumab vedotin for mUC post-platinum & post-checkpoint inhibitor

**EV-201: Single-arm, 2-cohort Phase 2 trial**

- **Cohort 1**: Prior PD-1/L1 inhibitor and platinum-based therapy
  - Enrollment completed July 2018 N=12⁷
- **Cohort 2**: Prior PD-1/L1 inhibitor, platinum naive, cisplatin ineligible
  - Enrollment ongoing

**Enfortumab vedotin**
- 1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle
- **Primary endpoint**: ORR per RECIST v1.1 as determined by BICR
- **Select secondary endpoints**: DOR, PFS, OS, Safety

**Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>88 (70)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>69 (40, 84)</td>
</tr>
<tr>
<td>≥75 years, n (%)</td>
<td>34 (27)</td>
</tr>
<tr>
<td>ECOG PS of 1, n (%)</td>
<td>85 (68)</td>
</tr>
<tr>
<td>Primary tumor location, n (%)</td>
<td></td>
</tr>
<tr>
<td>Bladder/other</td>
<td>81 (65)</td>
</tr>
<tr>
<td>Upper tract</td>
<td>44 (35)</td>
</tr>
<tr>
<td>Number of prior systemic therapies¹, median (range)</td>
<td>3 (1, 6)</td>
</tr>
<tr>
<td>≥2 Bellmunt adverse prognostic factors</td>
<td>52 (42)</td>
</tr>
<tr>
<td>Metastasis sites, n (%)</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes only</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Visceral disease</td>
<td>112 (90)</td>
</tr>
<tr>
<td>Liver</td>
<td>50 (40)</td>
</tr>
<tr>
<td>PD-L1 status by combined positive score²</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>78/120 (65)</td>
</tr>
<tr>
<td>≥10</td>
<td>42/120 (35)</td>
</tr>
</tbody>
</table>

¹ 3 patients did not receive enfortumab vedotin treatment: one each due to clinical deterioration, patient decision, and low hemoglobin after enrollment

BICR=b blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

Enfortumab vedotin for mUC post-platinum

Radiographic responses

84%

n=110 patients with target lesions and adequate post-baseline assessment
- 10 patients had no post-baseline assessment
- 4 patients had no target lesions identified at baseline
- 1 patient had an uninterpretable post-baseline assessment

Overall Survival

Median OS: 11.7 mo

Progression free survival

Median PFS: 5.8 mo

Enfortumab vedotin for mUC post-IO (cisplatin-ineligible)

**EV-201: Single-Arm, Pivotal Phase 2 Trial**

- **Cohort 1**
  - Prior PD-1/L1 inhibitor and platinum-based therapy
  - Enrollment completed July 2018

- **Cohort 2**
  - Prior PD-1/L1 inhibitor, platinum naive, cisplatin ineligible
  - Enrollment ongoing

**Enfortumab vedotin**
- 1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle
- Primary endpoint: ORR per RECIST v1.1 as determined by BICR
- Select secondary endpoints: DOR, PFS, OS, Safety

**Radiographic changes**
- 52% objective response rate

**Progression free survival**
- Median PFS: 5.8 mo

**Overall survival**
- Median OS: 14.7 mo

Sacituzumab govitecan phase 2 post-platinum

- Urothelial cancer
- Measurable metastatic disease, by RECIST criteria
- Prior platinum-based chemotherapy
- Prior immune checkpoint inhibitors
- Good performance status
- Archival tissue available

N=113

Sacituzumab govitecan 10mg/kg IV d1/d8 every 3 weeks

Disease control 77%
Objective responses 27%

Progression Free Survival
Median PFS 5.4 mo

Overall Survival
Median OS 10.9 mo

Tagawa ST et al, JCO, 2021
Targeted: Erdafitinib for FGFR-altered mUC

Baseline patient characteristics

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>8 mg continuous dose (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (range)</td>
<td>68 (36-87)</td>
</tr>
<tr>
<td>ECOG performance status 0</td>
<td>50 (51)</td>
</tr>
<tr>
<td>1</td>
<td>42 (42)</td>
</tr>
<tr>
<td>2</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Pre-treatment Progressed or relapsed after chemo</td>
<td>87 (88)</td>
</tr>
<tr>
<td>Chemo-naive</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Prior immunotherapy</td>
<td>22 (22)</td>
</tr>
<tr>
<td>Number of lines of prior treatment 0</td>
<td>11 (11)</td>
</tr>
<tr>
<td>1</td>
<td>45 (46)</td>
</tr>
<tr>
<td>2</td>
<td>29 (29)</td>
</tr>
<tr>
<td>3+</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Visceral metastases Present</td>
<td>18 (19)</td>
</tr>
<tr>
<td>Absent</td>
<td>21 (21)</td>
</tr>
<tr>
<td>Hemoglobin Level ≥10</td>
<td>84 (85)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Tumor location Upper tract</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Lower tract</td>
<td>76 (77)</td>
</tr>
<tr>
<td>Creatinine clearance rate &gt;60 mL/min</td>
<td>52 (53)</td>
</tr>
<tr>
<td>≤60 mL/min</td>
<td>47 (47)</td>
</tr>
<tr>
<td>FGFR alterations FGFR2 or FGFR3 fusion</td>
<td>25 (25)</td>
</tr>
<tr>
<td>FGFR3 mutation</td>
<td>74 (75)</td>
</tr>
</tbody>
</table>

Radiographic responses

40% objective response rate

Progression free survival

Overall survival

Loriot Y et al, NEJM, 2019
Overlapping Toxicities of mUC treatments

Immune Checkpoint Inhibitors
- Immune Mediated Hepatitis
- Thyroiditis
- Hypophysitis
- Myositis
- Pneumonitis

Non-CSR Ocular Disorders
- Cytopenias
- Neuropathy
- Diarrhea
- Fatigue
- Rashes
- Hyperglycemia
- Alopecia

Antibody Drug Conjugates

CSR: central serous retinopathy

FGFR Inhibitors
- Hyperphosphatemia
- Hand Foot Syndrome
- Central Serous Retinopathy
- Stomatitis

Atiq S et al, Urol Oncol, 2021
The current treatment landscape for mUC: April 2022

Platinum-based chemotherapy
MVAC
Gem/cis
Gem/carbo

Switch
Maintenance
Or 2nd line
Immunotherapy
targeting
PD-1 or PD-L1

Enfortumab vedotin

Sacituzumab govitecan

FGFR2 & FGFR3
genomic alterations:
Erdafitinib

Clinical trials:
Sitravatinib-
nivolumab
PARP inhibitors
HDAC inhibitors
Novel targets,
immunomodulating agents

First line treatment
Maintenance avelumab after chemotherapy
Javelin bladder 100

Zhang T, adapted from discussion, ASCO Annual Meeting, 2020
Additive benefit of sequential treatment

2015
- Gemcitabine/cisplatin (9/2015 - 1/2016)

2016
- Atezolizumab (6/2016 - 9/2016)

2017
- Pembrolizumab (9/2017 - 11/2017)
- Trial: FGFR inhibitor (12/2017 - 8/2018)

2018

2019
- Pembrolizumab (9/2017 - 11/2017)
- Trial: FGFR inhibitor (12/2017 - 8/2018)
- Expanded access Enfortumab vedotin (12/2019 - 9/2020)

2020
-试: Sitravatinib-nivolumab (9/2020 - 5/2021)

2021
- Sacituzumab govitecan (5/2021 - 7/2021)

Treatment break:
5 months

Treatment break:
13 months for skin/nail toxicities

NGS testing from LN biopsy:
- FGFR3 S249C
- PI3K, MLL2, CDKN2A/B loss
- NOTCH amp, TERT alteration

R inguinal LN: metastatic urothelial cancer

Oncology Goals:
Live longer, while maintaining quality of life

65yo man, Professor

Grandson born

Death 8/2021

71yo

Another grandbaby

Daughter Oscars nomination

Death 8/2021
New advances in immunotherapies, ADCs, and FGFR targeted therapies
- Maintenance avelumab, enfortumab vedotin, sacituzumab govitecan, & erdafitinib (first genomically selected treatment)
- All improving clinical outcomes in mUC

Learning from our patients - cohorts and the individual
- Unanswered questions in treatment resistance, novel combinations, sequencing
- As long as good performance status, novel treatments and trials should be available

To cure sometimes, to relieve often, to comfort always

~ Edward Trudeau
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