KCRNC- ICUC Lecture – Multi-Disciplinary Care in Advanced Kidney Cancer – The Role for Adjuvant and Neo-Adjuvant Therapy in High-Risk for Recurrence Resected Kidney Cancer

Dr. Anil Kapoor
Professor of Surgery (Urology), McMaster University Chair, Kidney Cancer Research Network of Canada (KCRNC)
Disclosures

• Consultant – Novartis, Pfizer, Roche, Merck, BMS, Astellas, Janssen, Bayer, Amgen
Risk stratification for first-line therapy in mRCC: IMDC Criteria

<table>
<thead>
<tr>
<th>IMDC Criteria Risk Factors(^1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>&lt; 80%</td>
</tr>
<tr>
<td>Time from diagnosis</td>
<td>&lt; 12 mos</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&lt; LLN</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>&gt;ULN</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&gt;ULN</td>
</tr>
<tr>
<td>Corrected serum calcium</td>
<td>&gt;ULN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Group by No. of Risk Factors(^1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable (n=133)</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate (n=301)</td>
<td>1-2</td>
</tr>
<tr>
<td>Poor (n=152)</td>
<td>3-6</td>
</tr>
</tbody>
</table>

- >500 patients with mRCC treated with VEGF-targeted therapy: Sunitinib (61%); sorafenib (31%); bevacizumab (8%)

Debulking Nephrectomy: retrospective data from the targeted era – IMDC cohort (n=1,633)

<table>
<thead>
<tr>
<th>RF</th>
<th>No CN OS, mo (n)</th>
<th>CN OS, mo (n)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>insufficient number to compare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22.5 (n = 72)</td>
<td>30.4 (n = 178)</td>
<td>0.002</td>
</tr>
<tr>
<td>2</td>
<td>10.2 (n = 143)</td>
<td>20.2 (n = 253)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>10.0 (n = 113)</td>
<td>15.9 (n = 106)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>5.4 (n = 103)</td>
<td>6.0 (n = 67)</td>
<td>0.166</td>
</tr>
<tr>
<td>5</td>
<td>3.6 (n = 36)</td>
<td>2.8 (n = 14)</td>
<td>0.504</td>
</tr>
<tr>
<td>6</td>
<td>insufficient number to compare</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What are the approved standards for systemic first-line therapy?
Category 1

Sunitinib (Temsirilimus)
Bev+ IFNa
Pazopanib

FIRST-LINE THERAPY

Clinical trial or

Sunitinib (category 1)
or
Temsirilimus (category 1 for poor-prognosis patients, category 2B for selected patients of other risk groups)
or
Bevacizumab + IFN (category 1)
or
Pazopanib (category 1)
or
High dose IL-2 for selected patients
g
or
Axitinib
or
Sorafenib for selected patients
and
Best supportive care:
h
See NCCN Guidelines for Palliative Care

Relapse or Stage IV and surgically unresectable
Non-clear cell histology

See Systemic Therapy (KID-4)
### Canadian Kidney Cancer Forum 2015 Consensus Update

<table>
<thead>
<tr>
<th>Setting</th>
<th>Patients</th>
<th>Therapy (Level 1 Evidence)</th>
<th>Other Options (Less than Level 1 Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>Good/intermediate risk</td>
<td>Sunitinib, Pazopanib, Bevacizumab + IFN*</td>
<td>High-dose IL-2, Sorafenib, Observation</td>
</tr>
<tr>
<td></td>
<td>Poor risk</td>
<td>Temsirolimus**</td>
<td>Sunitinib, Pazopanib</td>
</tr>
<tr>
<td>Second-line</td>
<td>Cytokine refractory</td>
<td>Sorafenib, Pazopanib, Axitinib</td>
<td>Sunitinib, Bevacizumab + IFN*</td>
</tr>
<tr>
<td>Third-line***</td>
<td>Any</td>
<td>Everolimus, Axitinib</td>
<td>Targeted therapy not previously used</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VEGFr TKI</td>
</tr>
</tbody>
</table>

IFN, interferon; HD IL-2, high-dose interleukin-2; VEGF, vascular endothelial growth factor; VEGFr TKI, VEGF receptor-tyrosine kinase inhibitor; mTOR, mammalian target of rapamycin.

* The combination of bevacizumab + IFN has not been approved in Canada but is approved in the United States and Europe.

** Temsirolimus is only an option in poorer risk patients as it was only studied in this population.

*** At the present time, there is no Health Canada–approved third-line systemic therapy.
Sunitinib and Pazopanib are standards in first-line RCC – registration data

- **Sunitinib**: 50 mg PO qd for 4 wk then 2 wk off for repeated 6-wk cycles (n=375)
- **IFN-α**: 9 MU SC 3x/wk (n=375)

**Eligibility Criteria**
- Locally advanced RCC or mRCC
- Predominant clear cell histology
- Measurable disease (≥1 lesion)
- No prior systemic treatment (cytokine based) for locally advanced or mRCC

**Primary Endpoint**: Progression Free Survival

**Randomization** 1:1 (N=750)

**Primary Endpoint**: PFS

COMPARZ: Phase III Non-Inferiority Trial of Pazopanib vs Sunitinib: Study Design

**Eligibility Criteria**
- aRCC or mRCC with clear cell histology
- Measurable disease
- No prior systemic treatment
- KPS ≥70

N = 1110

Randomise

- n = 557
  - Pazopanib 800 mg/day
- n = 553
  - Sunitinib 50 mg/day (schedule 4/2)

**Primary endpoint:** PFS for non-inferiority (independent review)

**Secondary endpoints:** OS, ORR, PRO, safety, QoL, and medical resource utilization

- KPS, Karnofsky performance status; QoL, quality of life.

COMPARZ: Secondary Efficacy Analyses – ORR and OS


Does immunotherapy have a role in the first-line treatment of advanced clear cell RCC?
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma


<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Median Overall Survival (95% CI)</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>410</td>
<td>25.0 (21.8–NE)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>411</td>
<td>19.6 (17.6–23.1)</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.73 (98.5% CI, 0.57–0.93)  
P=0.002

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>410</td>
<td>411</td>
</tr>
<tr>
<td>0</td>
<td>389</td>
<td>366</td>
</tr>
<tr>
<td>3</td>
<td>359</td>
<td>324</td>
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<td>6</td>
<td>337</td>
<td>287</td>
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<td>9</td>
<td>305</td>
<td>265</td>
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<td>12</td>
<td>275</td>
<td>241</td>
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<td>15</td>
<td>213</td>
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<td>18</td>
<td>139</td>
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<td>21</td>
<td>73</td>
<td>61</td>
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<td>24</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>27</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
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</tbody>
</table>
Checkpoint inhibitors and agonists being tested in advanced RCC

Nature Reviews Urology

Ongoing combination checkpoint inhibitor and targeted therapy trials in RCC

Bevacizumab

Sunitinib

Sorafenib

Axitinib

APC

$T_{reg}$ cell

MDSC

VEGF-A

Nature Reviews | Urology

Ongoing combination checkpoint inhibitor and targeted therapy trials in RCC

<table>
<thead>
<tr>
<th>Checkpoint inhibitor</th>
<th>Targeted therapy</th>
<th>Phase</th>
<th>Population</th>
<th>Identifier</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>Sunitinib</td>
<td>I</td>
<td>Advanced RCC, prior cytokine therapy allowed</td>
<td>NCT01472081 (CheckMate 016)</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Bevacizumab</td>
<td>Neoadjuvant pilot</td>
<td>Metastatic clear cell RCC, prior therapy allowed</td>
<td>NCT02210117</td>
<td>38</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Temsirolimus</td>
<td>Ib/II</td>
<td>Metastatic RCC, prior therapy allowed</td>
<td>NCT02423954</td>
<td>117</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Pazopanib</td>
<td>I/II</td>
<td>Untreated, advanced clear cell RCC</td>
<td>NCT02014636</td>
<td>65</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Axitinib</td>
<td>Ib</td>
<td>Untreated, advanced clear cell RCC</td>
<td>NCT02133742</td>
<td>67</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Bevacizumab</td>
<td>Ib/II</td>
<td>Metastatic clear cell RCC treated with failure of at least one prior therapy</td>
<td>NCT02348008</td>
<td>66</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Aflibercept</td>
<td>I</td>
<td>Metastatic RCC treated with at least one prior VEGF TKI</td>
<td>NCT02298959</td>
<td>118</td>
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<tr>
<td>Avelumab</td>
<td>Axitinib</td>
<td>Ib</td>
<td>Untreated, advanced clear cell RCC</td>
<td>NCT02493751</td>
<td>119</td>
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<tr>
<td>Atezolizumab</td>
<td>Bevacizumab</td>
<td>III</td>
<td>Untreated, advanced clear cell RCC</td>
<td>NCT02420821</td>
<td>45</td>
</tr>
</tbody>
</table>

RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Adjuvant therapy for High-Risk resected Localized RCC
65 y.o. patient with Solid Left Renal Mass 4.5 cm, Otherwise healthy
Pathology – T1b 4.5 cm ccRCC; grade 4/4, neg margin 20 percent sarcomatoid

His disease is likely going to recur!

Watch?

Adjuvant TKI?
Trials in Adjuvant Therapy for RCC

- ARISER - girentuximab - negative
- ASSURE – sunitinib vs sorafenib vs placebo - negative
- S-TRAC – adjuvant sunitinib – ESMO 2016 - Positive trial
  
- SORCE – adjuvant sorafenib (1 or 3 years)
- ATLAS – adjuvant axitinib (3 years) – 2017
- PROTECT – adjuvant pazopanib (1 year) – 2017
- EVEREST – adjuvant everolimus (1 year) - 2021
Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial


• Post-RN, R0, within 12 weeks from RN
• Clear cell or non-clear cell
• HIGH RISK defined as:
  • Intermediate, high or very high risk (UISS) $\geq$ High Grade T1b
• ECOG $\leq$ 2 before Nx
Registration (Pre-surgery) → Nephrectomy

Registration (Post-surgery) → Nephrectomy

Stratify

**TNM:**
- Intermediate High Risk Group
  - pT1bG3-4
  - pT2G1-2
  - pT2G3-4
  - pT3aG1-2 (as long as pT3a is not due to adrenal involvement)

- Very High Risk Group
  - pT3aG3-4 or any grade pT3a if due to adrenal involvement
  - pT3b-c G any
  - pT4 G any
  - pT any G any N+

- Histologic Subtype
  - Clear Cell
  - Non-Clear cell (except collecting duct or medullary)

- Performance Status
  - 0
  - 1

- Type of Nephrectomy
  - Laparoscopic or Open

**Randomize**

Arm A (Sunitinib)
- Sunitinib po daily x 4 weeks followed by rest x 2 weeks for 9 cycles
  - AND
  - Placebo sorafenib po daily x 6 weeks for 9 cycles.

Arm B (Sorafenib)
- Sorafenib po daily X 6 weeks for 9 cycles
  - AND
  - Placebo sunitinib po daily x 4 weeks followed by rest x 2 weeks for 9 cycles.

Arm C (Placebo)
- Placebo sorafenib po daily X 6 weeks for 9 cycles
  - AND
  - Placebo sunitinib po daily x 4 weeks followed by rest x 2 weeks for 9 cycles.

Accrual goal = 1923 patients
1 cycle = 6 weeks (42 days)
ASSURE

- Grade 3 toxicity significantly increased with both Sunitinib & Sorafenib compared to placebo

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib</th>
<th>Sorafenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade $\geq 3$ AE</td>
<td>63%</td>
<td>72%</td>
<td>25%</td>
</tr>
<tr>
<td>Treatment discontinuation d/t AE</td>
<td>34-44%</td>
<td>30-45%</td>
<td>10-11%</td>
</tr>
</tbody>
</table>
ASSURE

- No improvement in DFS

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>DFS (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>5.8</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>6.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.6y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arms compared</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib v Placebo</td>
<td>1.02, 97.5%CI 0.85-1.23</td>
</tr>
<tr>
<td>Sorafenib v Placebo</td>
<td>0.97, 97.5%CI 0.80-1.17</td>
</tr>
</tbody>
</table>

- No significant difference in OS
ASSURE TRIAL - Conclusions

• First and largest trial reporting on efficacy of VEGF inhibitors as adjuvant therapy for patients with locally advanced kidney cancer who are at high risk of recurrence

• Median time to disease recurrence did not differ between those who received sorafenib or sunitinib after surgery (median 5.8 years) and those treated with placebo (median 6 years)

• Findings from this study suggest that patients with locally advanced kidney cancer should not be treated with either adjuvant sorafenib or sunitinib

Presented by: Naomi B. Haas, MD
Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy

• Post-RN within 3-12 weeks from RN
• Clear cell RCC
• Loco-regional RCC
  • Tumor stage $\geq 3$ and/or
  • Regional LN mets
  • Basis of UISS criteria (Int. or high)
• ECOG $\leq 2$ before Nx
S-TRAC

• Randomized to:
  • Sunitinib 50mg OD – 4 weeks on, 2 weeks off
  • Placebo – 4 weeks on, 2 weeks off

• Treatment duration:
  • 1 year or
  • Disease recurrence or
  • Unacceptable toxicity

• Sept 2007 – April 7, 2011
• 615 pts

• Primary endpoint:
  • DFS

• Secondary endpoints:
  • Investigator assessed DFS
  • OS
  • Safety
Median f/u: 5.4y

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Sunitinib (N = 309)</th>
<th>Placebo (N = 306)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients in central review: primary analysis</td>
<td>6.8 (5.8–NR)</td>
<td>5.6 (3.8–6.6)</td>
<td>0.76 (0.59–0.98)†</td>
</tr>
<tr>
<td>Secondary analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients in investigator review</td>
<td>6.5 (4.7–7.0)</td>
<td>4.5 (3.8–5.9)</td>
<td>0.81 (0.64–1.02)</td>
</tr>
<tr>
<td>Higher-risk patients in central review</td>
<td>6.2 (4.9–NR)</td>
<td>4.0 (2.6–6.0)</td>
<td>0.74 (0.55–0.99)†</td>
</tr>
<tr>
<td>Higher-risk patients in investigator review</td>
<td>5.9 (4.4–7.0)</td>
<td>3.9 (2.8–5.6)</td>
<td>0.76 (0.58–1.01)</td>
</tr>
</tbody>
</table>
Secondary Endpoints

• Overall Survival:
  • Data not mature at time of cut-off

• QoL
  • Did not meet pre-specified criteria for minimally important difference

• Safety

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade $\geq$ 3 AE</td>
<td>63.4%</td>
<td>21.7%</td>
</tr>
<tr>
<td>Dose reductions d/t AE</td>
<td>34.3%</td>
<td>2%</td>
</tr>
<tr>
<td>Dose interruptions d/t AE</td>
<td>46.4%</td>
<td>13.2%</td>
</tr>
<tr>
<td>Treatment discontinuation d/t AE</td>
<td>28.1%</td>
<td>5.6%</td>
</tr>
</tbody>
</table>
Conclusion

- Patients in sunitinib had a longer median duration of DFS 6.8 years vs 5.6 years

- Further study to determine if effect is maintained at 10y

- Overall Survival results pending
S-TRAC vs ASSURE Trials - Comments

- Period of follow up similar to (5.4y S-TRAC vs 5.8y ASSSURE)
- Rate of discontinuation of Sunitinib or Sorafenib d/t AE was high (28-45%)
- Difference in results:

<table>
<thead>
<tr>
<th></th>
<th><strong>ASSURE</strong></th>
<th><strong>S-TRAC</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>Many stage I-II tumours (35%)</td>
<td>Loco-regional</td>
</tr>
<tr>
<td></td>
<td>Only 50% were very high risk</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>Non-clear cell allowed (20%)</td>
<td>Clear cell</td>
</tr>
<tr>
<td>Dosing</td>
<td>Starting doses changed mid-trial</td>
<td>Starting dose consistent</td>
</tr>
<tr>
<td></td>
<td>Allowed dose reductions to 25mg</td>
<td>Dose reduction to 37.5mg</td>
</tr>
<tr>
<td>DF status on entry</td>
<td>Investigators</td>
<td>Investigators and blinded central review</td>
</tr>
</tbody>
</table>
Trials in Adjuvant Therapy for RCC

• ARISER - girentuximab - negative
• ASSURE – sunitinib vs sorafenib vs placebo - negative
• S-TRAC – adjuvant sunitinib – ESMO 2016 -Positive trial

• SORCE – adjuvant sorafenib (1 or 3 years)
• ATLAS – adjuvant axitinib (3 years)– 2017
• PROTECT – adjuvant pazopanib (1 year) – 2017
• EVEREST – adjuvant everolimus (1 year) - 2021
What about Neo-Adjuvant therapy for RCC
A randomized phase III study comparing perioperative PD-1 blockade vs. placebo in unfavorable resectable renal cell carcinoma

EA8121 (E1812)
Phase III Perioperative PD-1 Blockade
Non-metastatic RCC: 2 Arm Alternative Design

• N=1000 patients of all histologies (85% clear cell, 15% non-clear cell)
• Stratify: T2 or >T2, PS 0 vs. 1, clinical node positive vs. negative
• Primary endpoint: Recurrence-free survival (RFS)

Clinical stage: ≥T2 (7cm renal mass) or N any

1:1 Randomize

Nivolumab q 2 wks x 2 doses
Nephr.
Nivolumab q 2 wks x 6 months

IV Placebo q 2 wks x 2 doses
Nephr.
X

IV Placebo q 2 wks x 6 months

Biopsy (select centers):
• Histology
• PD-L1 expression
• Immune cell infiltration

Nivolumab at relapse
Potential for Partial Nephrectomy

- Retrospective study of 72 patients treated with neoadjuvant sunitinib demonstrated a PN rate of 63%
- Phase II study enrolled 25 patients in which surgery would likely yield a GFR <30, high-risk PN given high RENAL score (10-12), tumor adjacent to hilar vessels
  - Received 8-16 weeks of pazopanib
  - RENAL scores decreased by 71%
  - 92% experienced reduction of tumor volume
  - 6/13 for whom PN was not possible at baseline were able to undergo PN

Presented at: 2016 Genitourinary Cancers Symposium
Presented by: Rana McKay, MD
Slides are the property of the author. Permission required for reuse.
Neoadjuvant Targeted Therapy: Downsizing of the Kidney Tumors Allowed to Perform PN

Two tumours in solitary right kidney unfeasible for PN

Neoadjuvant sunitinib (50 mg daily, 4/2)
6 cycles

Downsizing of kidney tumours following by successful right-side PN

Pre-surgical TKI Therapy

Baseline 8 Weeks of Therapy

Surgical plane
Multi-Disciplinary Care in RCC

- Urologist will see the RCC patient initially
- Decision regarding low-risk, high-risk, or metastatic after staging
- Medical Oncology opinion regarding neo-adjuvant, adjuvant therapy, or treatment for metastatic disease
- Radiation Oncology opinion for oligo-metastatic disease or oligo-progression
Patient Case

66 yo lawyer
Post nephrectomy for grade ¾ RCC with 5% sarcomatoid features
Metastases - Retroperitoneal nodes
On Pazopanib – regression of retroperitoneal nodes
Side effects of Fatigue, difficulty working
Stopped Pazopanib
Growth of Nodes

Options ?
Restart Pazopanib
Palliate
Case: Radiotherapy to Retroperitoneal nodes
Conclusions – management of advanced RCC

• TKI therapy remains the first-line standard of care for the majority of patients with metastatic disease.

• Sunitinib and pazopanib have similar efficacy in the first-line setting. The COMPARZ and PISCES trials suggest that pazopanib is better tolerated by most patients.
Conclusions – management of advanced RCC

- Checkpoint-inhibitor combination regimens are intensely studied in the first-line space and are already challenging sunitinib on numerous phase III trials.
- Adjuvant Sunitinib increases DFS post resection of high-risk for recurrence RCC – OS?
- Neo-Adjuvant? – clinical trial setting
- Role of Urologist/Med Onc/ Rad Onc team optimizes patient outcomes
Thank you!

Dr. Anil Kapoor

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