Neoadjuvant Therapy: Where are we in 2016?

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Disclosure:

Investigator-Pfizer
Outline

• Neoadjuvant-definition
• Justification and rationale
• Assessment of response
• State of the data
• Future directions
Background

• Important to draw distinctions

• Primary therapy
  – Large volume metastatic disease
  – Poor performance status

• Neoadjuvant
  – Curative intent/disease control (loco-regional disease, metastatic disease)
  – “Litmus test”
Evolving Role of Neoadjuvant Therapy

• Metastatic Disease—
  • facilitate cytoreductive nephrectomy and metastatectomy

• Loco-regional advanced Disease—
  • facilitate complete resection

• Large and Complex renal mass with imperative indication for nephron sparing surgery:
  • Facilitation of partial nephrectomy
Neoadjuvant targeted therapy and advanced kidney cancer: observations and implications for a new treatment paradigm

Brian Shuch*, Stephen B. Riggs*, Jeff C. LaRochelle*, Fairouz F. Kabbinavar*,
Raffi Avakian†, Allan J. Pantuck*, Jean-Jacques Patard* and
Arie S. Beldegrun*

Response of the Primary Tumor to Neoadjuvant Sunitinib in Patients With Advanced Renal Cell Carcinoma

Anil A. Thomas, Brian I. Rini, Brian R. Lane, Jorge Garcia, Robert Dreicer,
Eric A. Klein, Andrew C. Novick and Steven C. Campbell*

Neoadjuvant (Presurgical) Therapy for Renal Cell Carcinoma: A New Treatment Paradigm for Locally Advanced and Metastatic Disease*

Christopher G. Wood, MD* and Vitaly Margulis, MD

Feasibility and efficacy of neoadjuvant sunitinib before nephron-sparing surgery

Jonathan L. Silberstein, Frederick Millard*, Reza Mehrzad†, Ryan Kopp,
Wassim Bazzi, Christopher J. DiBlasio†, Anthony L. Patterson†,
Tracy M. Downs, Furhan Yunus†, Christopher J. Kane and Ithaa H. Derweesh
Objective methods of measuring response

- Reduction in maximum diameter
- RECIST
- Morphometric Score (RENALE, PADUA, C-index)
  - Correlates with type of surgery (Lane)
  - Surgical approach (Stroup)
  - Complications (Leibovich, Stroup)
  - Oncologic Outcomes (Uzzo, Kopp)
# RENAL Nephrometry Score
*(Kutikov and Uzzo, 2009)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1 pt</th>
<th>2 pts</th>
<th>3 pts</th>
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</thead>
<tbody>
<tr>
<td>Radius (maximal diameter in cm)</td>
<td>≤ 4</td>
<td>&gt; 4 but &lt; 7</td>
<td>≥ 7</td>
</tr>
<tr>
<td>Exophytic/endophytic properties</td>
<td>≥ 50%</td>
<td>&lt; 50%</td>
<td>Entirely endophytic</td>
</tr>
<tr>
<td>Earness of the tumor to the collecting system or sinus (mm)</td>
<td>≥ 7</td>
<td>&gt; 4 but &lt; 7</td>
<td>≤ 4</td>
</tr>
<tr>
<td>Anterior/Posterior</td>
<td>No points given. Mass assigned a descriptor of a, p, or x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location relative to the polar lines*</td>
<td>Entirely above the upper or below the lower polar line</td>
<td>Lesion crosses polar line</td>
<td>&gt;50% of mass is across polar line (a) or mass crosses the axial renal midline (b) or mass is entirely between the polar lines (c)</td>
</tr>
</tbody>
</table>

*suffix “h” assigned if the tumour touches the main renal artery or vein*
Can we do more or better? Predictors of Response

Changes in Platelet Count

Change in platelet count as a prognostic indicator for response to primary tyrosine kinase inhibitor therapy in metastatic renal cell carcinoma

Zachary Hamilton*, Hak J. Lee*, Juan Jimenez†, Brian R. Lane‡, Song Wang*, Alp T. Bekszács*, Kyle Gillis*, Amy Alagh*, Conrad Tobiert‡, James M. Randall*, Christopher J. Kane*, Frederick Millard*, Steven C. Campbell† and Ithaar H. Derweesh*

Diffusion-Weighted/Multiphase Contrast Enhanced MRI

Diffusion-weighted and multiphase contrast-enhanced MRI as surrogate markers of response to neoadjuvant sunitinib in metastatic renal cell carcinoma

N Bharwani*, M E Miquel2,3, T Powles4, P Dilks3, A Shawyer1, A Sahdev1, P D Wilson5, S Chowdhury6, D M Berney7 and A G Rockall1

Need to correlate with tumor tissue
STATE of the Literature: 2016

- **No** published randomized clinical trials to support neoadjuvant therapy
- 6 Phase II studies overall with various TMT
- By potential indication for Neoadjuvant
  - In setting of metastatic disease: 3 Studies (Phase II), 2 retrospective analyses
  - In *loco*-regional disease/facilitation of partial nephrectomy: 3 studies (Phase II), 2 retrospective series
  - For thrombi: 2 retrospective series, multiple case reports
Neoadjuvant Prior to Renal Vein/IVC Thrombectomy

Neoadjuvant targeted molecular therapies in patients undergoing nephrectomy and inferior vena cava thrombectomy: is it useful?

Pierre Bigot · Tarek Fardoun · Jean Christophe Bernhard · Evanguelos Xylinas · Julien Berger · Morgan Rouprét · Jean-Baptiste Beauval · Samuel Lagabrielle · Souhil Lebdai · Myriam Ammi · Hervé Baumert · Bernard Escudier · Nicolas Grenier · Jean-François Hétel · Jean-Alexandre Long · Philippe Paparel · Nathalie Rioux-Leclercq · Michel Soulé · Abdel-Rahmène Azzouzi · Karim Bensalah · Jean-Jacques Patard

- Retrospective analysis, N=14 (Sunitinib n=3, Sorafenib N=3)
- 6 (43%) patients had decrease, 6 (43%) had no change, and 2 (14%) had an increase in thrombus.
- One patient (7%) had a downstage of thrombus level, 12 (85%) had stable thrombi, and 1 (7%) had an upstage.

Neoadjuvant prior to Nephron Sparing Surgery

• Indications: Downsizing renal mass to permit partial nephrectomy in imperative indications.

• Current State: Retrospective series and Phase II Trials demonstrating feasibility

• Reduction in Tumor Size: 18-28%

• RECIST PR rate: 19-45.8%

• Partial Nephrectomy success rate: 50-75%
Phase 2 Trial of Neoadjuvant Axitinib in Patients with Locally Advanced Nonmetastatic Clear Cell Renal Cell Carcinoma

Jose A. Karam, Catherine E. Devine, Diana L. Urbauer, Marisa Lozano, Tapati Maity, Kamran Ahrar, Pheroze Tamboli, Nizar M. Tannir, Christopher G. Wood

- single-institution, single-arm phase 2 clinical trial-axitinib prior to partial or radical nephrectomy in **cT3a disease**
- N=24.
- Median reduction of primary renal tumor diameter was **28.3%**.
- RECIST PR: **11/24**, stable disease **13/24**
- 23 patients underwent surgery-19 radical nephrectomy, 5 partial nephrectomy

A Phase II Study of Pazopanib in Patients with Localized Renal Cell Carcinoma to Optimize Preservation of Renal Parenchyma

Brian I. Rini,* Elizabeth R. Plimack,† Toshio Takagi, Paul Elson, Laura S. Wood, Robert Dreicer,‡ Timothy Gilligan, Jorge Garcia, Zhiling Zhang, Jihad Kaouk,§ Venkatesh Krishnamurthi, Andrew J. Stephenson, Amr Fergany, Eric A. Klein, Robert G. Uzzo, David Y. T. Chen and Steven C. Campbell†,||

- Phase II, neoadjuvant Pazopanib in patients at high risk for severe CKD or high complexity partial nephrectomy
- N=25
- R.E.N.A.L. score decreased in 71% of tumors
- 92% experienced reduction in tumor volume.
- 20/25 partials performed; 6/13 patients for whom partial nephrectomy was not possible at baseline were able to undergo partial nephrectomy

Presurgical sunitinib reduces tumor size and may facilitate partial nephrectomy in patients with renal cell carcinoma

Brian R. Lane, M.D., Ph.D., F.A.C.S. a,*, Ithaa H. Derweesh, M.D. c, Hyung L. Kim, M.D. b,d, Rebecca O’Malley, M.D. d,e, Joseph Klink f, Cesar E. Ercole f, Kerrin L. Palazzi, M.P.H. c, Anil A. Thomas f, Brian I. Rini, M.D. f, Steven C. Campbell, M.D., Ph.D. f

• 72 patients, 78 renal units
• Tumor size decrease from 7.2 cm to 5.3 (p<0.001).
• 32% reduction in tumor bidirectional area
• Downsizing occurred in 65 tumors (83%)
• RECIST: 15 partial responses (19%).
• Tumor complexity per R.E.N.A.L. score reduced in 59%.
• PN success rate: 49 (63%).

So Where are we and where do we go from here?
Clinical Trial to Assess Role of Primary Cytoreductive Nephrectomy vs. Systemic Therapy

CARMENA (Assistance Publique - Hôpitaux de Paris/Pfizer): phase III study 700 m-RCC patients with the primary tumor in situ randomize them to either nephrectomy plus sunitinib or sunitinib alone (NCT00930033).

Primary Endpoint: Overall Survival Est enrollment 576, Estimated completion date May 2016
Clinical Trial to Assess Role Neoadjuvant Therapy vs. Primary Cytoreductive Nephrectomy

- EORTC (European Organisation for Research and Treatment of Cancer): Immediate Surgery or Surgery After Sunitinib in Treating Patients With Metastatic Kidney Cancer (SURTIME) (NCT01099423)

- Primary outcome: Progression free survival. Est enrollment 458; Est primary completion date Oct 2014.
The dawn of a new era for neoadjuvant therapy in RCC?

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma


• Rationale: immunotherapy is more effective in eliminating circulating tumor cells or micrometastases than inhibitors of angiogenesis

• How will it work in the neoadjuvant setting? - metastatic vs. presurgical
Future Directions: Checkpoint inhibitor neoadjuvant therapy

- Phase 2, Neoadjuvant and adjuvant for mRCC, no prior Rx
- Primary endpoint: Safety profile
- Secondary endpoint: Response rate
Future Directions: Checkpoint inhibitor neoadjuvant therapy

Primary Outcome Measures: Safety and Tolerability
Secondary Outcome Measures:
Objective **Tumor Response Rate (by RECIST)**
Percentage of patients achieving CR or PR by **RECIST**

**ClinicalTrials.gov**
A service of the U.S. National Institutes of Health

Now Available: Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting

Trial record 1 of 2 for: Nivolumab neoadjuvant kidney cancer
Previous Study | Return to List | Next Study

Study of Neoadjuvant Nivolumab in Patients With Non-metastatic Stage II-IV Clear Cell Renal Cell Carcinoma

*This study is currently recruiting participants. (see Contacts and Locations)*
Verified August 2016 by Sidney Kimmel Comprehensive Cancer Center

Sponsor:
Sidney Kimmel Comprehensive Cancer Center

Collaborator:
Bristol-Myers Squibb

ClinicalTrials.gov Identifier:
NCT02575222
First received: October 6, 2015
Last updated: August 22, 2016
Last verified: August 2016

**Fifteenth International Kidney Cancer Symposium**
November 4-5, 2016
Marriott Miami Biscayne Bay, Miami, Florida, USA

KidneyCancer.org
www.kidneycancersymposium.com
Future Directions: Checkpoint inhibitor neoadjuvant therapy

Primary Outcome Measures:
Feasibility of a patient to receive at least 3 doses of nivolumab and complete surgery without significant delay attributable to nivolumab

Secondary Outcome Measures:
Incidence of toxicity.
Overall response rate (ORR) measured by RECIST
Recurrence free survival
Phase II Clinical Trial: “PADRES” (Prior Axitinib as a Determinant of Outcome of Renal Surgery)

• Goal: Targeted molecular therapy (Axitinib) to downsize large Kidney Cancers in previously unsalvageable kidneys in order to enable kidney preserving treatment of kidney cancer to keep a patient off dialysis.

• Investigator initiated
  • Funding from Pfizer

• Co-Principal Investigators: Ithaar H. Derweesh, MD; Steven C. Campbell, M.D., PhD; Brian Rini, M.D.

• Lead Site: Moores UC San Diego Cancer Center
“PADRES” Phase II Clinical Trial for Presurgical Targeted Therapy in Kidney Cancer

Study Protocol

• Well-tolerated targeted oral agent (Axitinib)-twice a day

• 2 (4 week) cycles of treatment prior to surgery

• N=50.

Participating Institutions

• Target for 10.

UC San Diego Moores Cancer Center
Outcomes/Assessment of Response

• Efficacy
  • primary efficacy endpoint is the proportion of patients able to undergo successful partial nephrectomy with negative margins
  • Reduction of Primary Tumor Size
  • RECIST Criteria
  • Change in RENAL (morphometry) Score
  • Renal Functional Assessment (avoidance

• Safety
  • Avoidance of Major Complications
  • Avoidance of Blood Transfusion
Conclusions

• No Level I Data is Present to support neoadjuvant approaches

• Neoadjuvant for localized or locally advanced disease is controversial. Phase II studies demonstrate feasibility in primary tumor shrinkage to:
  • Facilitate nephron sparing surgery
  • Resection of locally advanced disease
Conclusions

- Most studies looking at presurgical/neoadjuvant sunitinib in the setting of localized/locally advanced disease are small and single center. Larger multicenter studies are necessary.

- Phase III Clinical Trials assessing role of cytoreductive nephrectomy and timing of systemic therapy have closed and we await results.

- Advent of checkpoint inhibitor therapy and neoadjuvant studies.