Highlights in GU 2015

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Conflict of Interest Disclosure

• Advisor
  • OncoGenex, Pierre Fabre, Astellas, Genentech, Merck

• Non-paid Advisor and/or Research Support
  • Sanofi, Novartis, Janssen, ImClone, Genentech, Merck, BMS
Outline Bladder

- Chemotherapy for Metastatic Disease
  - First line Cisplatin Fit
  - Maintenance after 1\textsuperscript{st} line
  - Second Line chemotherapy

- New Approaches
  - Predictive genomics
  - Targeted therapies
  - Immunotherapy
First-Line Randomized Phase 2 Study of Gemcitabine/Cisplatin plus Apatorsen or Placebo in Patients with Advanced Bladder Cancer: The International Borealis-1 Trial

Joaquim Bellmunt, Bernhard Eigl, Elżbieta Senkus, Yohann Loriot, Przemyslaw Twardowski, Daniel Castellano, Normand Blais, Srikala S. Sridhar, Cora N. Sternberg, Margitta Retz, Brent Blumenstein, Cindy Jacobs, Patricia S. Stewart, Daniel Petrylak
Study Design

Randomized, first-line, placebo-controlled, multinational phase 2 study in urothelial cancer conducted in 50 centers in 7 countries

Advanced bladder cancer
• Chemo-naive
• Stratified
  - PS
  - visceral disease

N = 179

Control (n=61)
• Gemcitabine/cisplatin
• Placebo

Apatorsen 600 mg (n=58)
• Gemcitabine/cisplatin
• Apatorsen 600 mg IV x 3 loading → 600 mg q1w

Apatorsen 1000 mg (n=60)
• Gemcitabine/cisplatin
• Apatorsen 600 mg IV x 3 loading → 1000 mg q1w

Endpoints
Primary
• Overall survival*

Secondary
• Safety
• Optimal dose for Phase 3
• Overall response rate
• Disease control rate
• Duration of response, PFS
• Biomarker effects

*Patients were to continue to receive weekly Study Drug maintenance until disease progression or the patient fulfills other reasons for withdrawal (tox, others)
Survival in 600 mg Apatorsen vs Control Arms by Risk

Good risk: HR = 1.44
Poor risk: HR = 0.72
Overview of study design

Endpoints
Primary: Progression free survival (PFS)
Secondary: Overall survival (OS) / adverse events.
Exploratory: subset analysis
Stratification: Chemotherapy response & PS

Eligibility criteria for randomisation
1. Metastatic or advanced UBC
2. HER1 or 2 positive transitional cell histology
3. Clinical benefit with first line chemotherapy
4. Normal ejection fraction

Screening phase
HER1/2 testing (n=446)

Treatment Phase
(n=232)

Chemotherapy

R

Lapatinib 1500mg OD

placebo
Randomised population: PFS for lapatinib vs. placebo (primary endpoint)

**HR 1.1**
(95%CI: 0.8-1.4)
P=0.62

**Median PFS**
- Lapatinib: 4.6 months (95%CI: 2.8-5.4)
- Placebo: 5.1 months (95%CI: 3.0-5.8)

**Response rate**
- Lapatinib: 14%
- Placebo: 8%
P=0.14
Randomised population:
OS for lapatinib vs. placebo

- Median PFS:
  - Lapatinib: 12.6 months (95%CI: 9-16.2)
  - Placebo: 12.0 months (95%CI: 10.6-15.8)

Further Therapy:
- Lapatinib: 58 (50%)
- Placebo: 64 (55%)

- HR 0.96
  (95%CI: 0.7-1.3)
  P=0.79
MAINTENANCE THERAPY IN BLADDER (after 1\textsuperscript{st} line)

• No role of maintenance therapy

• Ongoing Studies (vs observation)
  ◦ JASIMA, MAJA: Vinflunine
  ◦ MRC: Lapatinib in her1/2 +
Study Design

PD within 1 year of perioperative platinum chemotherapy OR after no more than 1 line of platinum chemotherapy for metastatic disease

Prior paclitaxel allowed

Primary Endpoint:
• Progression-free survival (PFS)

Secondary Endpoints:
• Overall survival, objective response rate, duration of response, safety, PK/PD and immunogenicity profile

Stratification factors:
• Visceral metastasis (yes vs. no)
• Prior anti-angiogenic therapy (yes vs. no)
Ramucirumab + docetaxel in pretreated patients

D.P. Petrylak, **Abs 295** ASCO-GU 2015

- Anti-VEGF-2 (ramucirumab) or anti-VEGF-1 (icrucumab) in combination with docetaxel
- In a 3 arm randomized phase II, pts PS 0-1 having progressed ≤ 12 months
  - Docetaxel 75 mg/m² on day 1 of a 21-day cycle
  - Docetaxel plus ramucirumab (10 mg/kg on day 1 of a 21-day cycle)
  - Docetaxel plus icrucumab (12 mg/kg on days 1 and 8 of a 21-day cycle)

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**Interim analysis**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>OR (%)</th>
<th>DCR (%)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCT</td>
<td>44</td>
<td>5</td>
<td>43</td>
<td>7,7*</td>
</tr>
<tr>
<td>DCT + RAM</td>
<td>46</td>
<td>20</td>
<td>67</td>
<td>11,3*</td>
</tr>
<tr>
<td>DCT + ICR</td>
<td>49</td>
<td>10</td>
<td>31</td>
<td>6,4*</td>
</tr>
</tbody>
</table>

* OS is not mature

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Ramucirumab enter in phase III (DCT + RAM vs DCT + plac), 524 pts ; end point is PFS
**RANGE (trial I4T-MC-JVDC): Study Design**

**1:1**

- **Screen**
  - **Randomize**
    - Docetaxel 75 mg/m² + Placebo 10 mg/kg I.V. on day 1 of a 21-day cycle
      - N = 262
    - Docetaxel 75 mg/m² + Ramucirumab 10 mg/kg I.V. day 1 of a 21-day cycle
      - N = 262
  - Oversight by an IDMC
  - Treat until disease progression or intolerable toxicity
  - **Primary Objective**
    - PFS
  - **Key Secondary Objectives**
    - OS and ORR

**Important Inclusion Criteria:**
- Locally advanced or unresectable or metastatic UC and ECOG PS 0 or 1
- Progression on or after first-line platinum-based chemotherapy (≤ 14 months; or ≤ 24 months if prior treatment with one immune checkpoint inhibitor)

**Key Exclusion Criteria:**
- Hemoglobin < 9 g/dL
- Uncontrolled bleeding or thrombotic disorder
- Known untreated brain metastasis

Presented by: Daniel P. Petrylak, MD
Pazopanib + paclitaxel in pretreated patients
S. Srinivas Abs 294 ASCO-GU 2015

• Single arm phase II study in patients PS 0-1 having progressed after ≤ 2 prior CT regimen
  – Paclitaxel 80 mg/m^2 on day 1, 8 & 15 of a 28-day cycle
  – Pazopanib 800 mg/day of a 28-day cycle

• Primary endpoint: ORR

<table>
<thead>
<tr>
<th>Response</th>
<th>OR (%)</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 32 (28 ev.)</td>
<td>50</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

- 59% received 2 prior regimen
- 12.5% node only, 2 patients PS 2
- 75% of patients required dose reduction
- 44% of patients received growth factors

Impressive ORR but OS is similar to many other trials, myelosuppression is significant
Sponsor cancelled the planned phase III study
Bladder Cancer is a molecularly heterogeneous disease

TP53 (49%)
MLL2 (27%)
ARID1A (25%)
KDM6A (24%)
PIK3CA (20%)
EP300 (15%)
CDKN1A (14%)
RB1 (13%)
ERCC2 (12%)
FGFR3 (12%)
STAG2 (11%)
ERBB3 (11%)
FBXW7 (10%)
Proof of Concept Established for Targeting FGFR3 in FGFR3-Mutant Metastatic Urothelial Cancer

BGJ398 has clinical activity in patients with FGFR3-mutated urothelial carcinoma

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Tumor</th>
<th>Schedule (125 mg/day)</th>
<th>Best Overall Response (% tumor change)</th>
<th>Duration on Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>88 ♀</td>
<td>FGFR3-mutated</td>
<td>Continuous</td>
<td>PR (−48%)</td>
<td>5 cycles</td>
</tr>
<tr>
<td>62 ♀</td>
<td>FGFR3-mutated</td>
<td>3 weeks on/1 week off</td>
<td>PR (−45%)</td>
<td>9+ cycles</td>
</tr>
<tr>
<td>53 ♂</td>
<td>FGFR3-mutated</td>
<td>3 weeks on/1 week off</td>
<td>SD (−28%)</td>
<td>4 cycles</td>
</tr>
<tr>
<td>77 ♂</td>
<td>FGFR3-mutated</td>
<td>Continuous</td>
<td>SD (−27%)</td>
<td>4 cycles</td>
</tr>
<tr>
<td>52 ♂</td>
<td>FGFR3-mutated</td>
<td>Continuous</td>
<td>SD (+11.4%)</td>
<td>3 cycles</td>
</tr>
<tr>
<td>80 ♀</td>
<td>FGFR1-amplified</td>
<td>3 weeks on/1 week off</td>
<td>PD</td>
<td>&lt; 2 weeks</td>
</tr>
</tbody>
</table>

In FGFR3-mutated urothelial carcinoma
- Overall response rate 40% (2/5)
- Disease control rate 100% (5/5)

Clinical Activities of JNJ-42756493 in Patients with FGFR Aberration in Tumor Treated at ≥ 6mg Dose

Sequist, AACR, 2014
Bahleda, ASCO, 2014
Molecular subtypes of bladder cancer. mRNA expression profiling studies.

a | Sjödahl et al five major subtypes urobasal A (UroA), UroB, genomically unstable (GU), squamous cell carcinoma-like (SCCL) and ‘infiltrated’.

b | Damrauer et al. classified bladder cancer into basal and luminal subtypes.

c | The Cancer Genome Atlas (TCGA) study defined four expression clusters (I–IV).

d | Choi et al. defined a ‘p53-like’ luminal subtype
A Prognostic Gene Expression Signature in the Molecular Classification of Chemotherapy-naïve Urothelial Cancer is Predictive of Clinical Outcomes from Neoadjuvant Chemotherapy: A Phase 2 Trial of Dose-dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin with Bevacizumab in Urothelial Cancer

Paradigm Shift in Urothelial Cancer

- **Urothelial cancer is no longer just 1 disease:**

  **“Basal”**
  - Chemo-sensitive
  - Immune signature
  - Angiogenesis
  
  **Therapies:**
  - GC/DDMVAC
  - CTLA4/PD1/PDL-1?
  - VEGF inhibitors?

  **“p53-like”**
  - Chemo-resistance
  - Stromal enrichment
  - Bone mets
  
  **Therapies:**
  - Met inhibitors?
  - Initial surgery?

  **“Luminal”**
  - Still some chemo-sensitivity
  - “FGFR” signature
  
  **Therapies:**
  - GC/DDMVAC
  - FGFR inhibitors?
Somatic ERCC2 Mutations Correlate with Cisplatin Sensitivity in Muscle-Invasive Urothelial Carcinoma

Eliezer M. Van Allen1,2, Kent W. Mau2,3, Philip Kim5, Gopa Iyer7,7, Nikhil Wagle1,2, Nihmat Ahmed4,5, Cong Zhu, Irina Ostrovskaya1, Gregory V. Kryukov3, Kevin W. O’Connor1, John Stakianos1, Ilana Garcia-Grossman1, Joegil Kim1, Elizabeth A. Guancial9, Richard Bambury1, Samira Bahl1, Namrata Gupta1, Deborah Farlow1, Angela Qu1, Sabina Signoretti1,11, Justine A. Barletta1,11, Victor Reuter11, Jesse Boehm1, Michael Lawrence1, Gad Getz1,2, Philip Kantoff1, Bernard H. Bochner1, Tani K. Choueiri1, Dean F. Bjoerheim5, David B. Splitt2,11, Stacey Gabrieli1, Alan D’Andrea1, Levi A. Garraway1,11, and Jonathan E. Rosenberg8,7

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B

- **Syn.**
- **Nonsyn.**

**Responder** • **Nonresponder**

- Missense
- Splice site
- In-frame indel
- Nonsense
- Frame shift
- Other nonsyn.

**# Mutations/Mb**

- 30
- 20
- 10
- 0

**# Cases with mutations**

- 56%
- 24%
- 24%
- 26%
- 18%

**TP53**

**RB1**

**KDM6A**

**ARID1A**

**ERCC2**

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Published Online First August 5, 2014; DOI: 10.1158/2159-8890.CD-14-0523
Defects in DNA Repair Genes Predict Response to Neoadjuvant Cisplatin-based Chemotherapy in Muscle-invasive Bladder Cancer

Elizabeth R. Plimack\(^a\), Roland L. Dunbrack\(^a\), Timothy A. Brennan\(^b\), Mark D. Andrade\(^a\), Yan Zhou\(^a\), Ilya G. Serebriskii\(^a\), Michael Silfker\(^a\), Katherine Alpaugh\(^a\), Essel Dulaimi\(^a\), Norma Palma\(^b\), Jean Hoffman-Censits\(^c\), Marijo Bilusic\(^a\), Yu-Ning Wong\(^a\), Alexander Kutikov\(^a\), Rosalia Viterbo\(^a\), Richard E. Greemberg\(^a\), David Y.T. Chen\(^a\), Costas D. Lallas\(^c\), Edouard J. Trabulsi\(^f\), Roman Yelensky\(^b\), David J. McConkey\(^d\), Vincent A. Miller\(^b\), Erica A. Golemis\(^a\), Eric A. Ross\(^a\)

\(^a\)Fox Chase Cancer Center, Philadelphia, PA, USA; \(^b\)Foundation Medicine Inc., Cambridge, MA, USA; \(^c\)Thomas Jefferson University Hospital, Philadelphia, PA, USA; \(^d\)MD Anderson Cancer Center, Houston, TX, USA

Results and limitations: Patients with a pathologic complete response had more alterations than those with residual tumor in both the discovery (\(p = 0.024\)) and validation (\(p = 0.018\)) sets. In the discovery set, alteration in one or more of the three DNA repair genes ATM, RB1, and FANCC predicted pathologic response (\(p < 0.001\); 87% sensitivity, 100% specificity) and better overall survival (\(p = 0.007\)). This test remained predictive for pathologic response in the validation set (\(p = 0.033\)), with a trend towards better overall survival (\(p = 0.055\)). These results require further validation in additional sample sets.

Conclusions: Genomic alterations in the DNA repair-associated genes ATM, RB1, and FANCC predict response and clinical benefit after cisplatin-based chemotherapy for MIBC. The results suggest that defective DNA repair renders tumors sensitive to cisplatin.
MPDL3280A (anti–PD–L1) treatment leads to clinical activity in metastatic bladder cancer

Thomas Powles¹, Joseph Paul Eder², Gregg D. Fine³, Fadi S. Braiteh⁵, Yohann Loriot⁶, Cristina Cruz⁷, Joaquim Bellmunt⁸, Howard A. Burris³, Daniel P. Petrylak⁵, Siew-Y leng Teng⁵, Xiaodong Shen⁵, Zachary Boyd⁷, Priti S. Hegde³, Daniel S. Chen⁸ & Nicholas J. Vogelzang⁹
A Phase Ia Study of Atezolizumab (MPDL3280A/Anti-PDL1):
Updated Response and Survival Data in Urothelial Bladder Cancer (UBC)

Daniel P. Petrylak,¹ Thomas Powles,² Joaquim Bellmunt,³
Fadi Braiteh,⁴ Yohann Loriot,⁵ Cristina Cruz,⁶ Howard A. Burris III,⁷
Joseph W. Kim,¹ Howard M. Mackey,⁸ Zachary S. Boyd,⁸ Priti S. Hegde,⁸
Oyewale Abidoye,⁸ Nicholas J. Vogelzang⁹

¹Yale Cancer Center, New Haven, CT; ²Barts Cancer Institute, Queen Mary University of London, London, UK;
³Bladder Cancer Center, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA;
⁴Comprehensive Cancer Centers of Nevada, Las Vegas, NV; ⁵Gustave Roussy, Villejuif, France;
⁶Vall d'Hebron University Hospital, Barcelona, Spain; ⁷Sarah Cannon Research Institute, Nashville, TN;
⁸Genentech, Inc., South San Francisco, CA; ⁹University of Nevada School of Medicine, Las Vegas, NV,
and US Oncology/Comprehensive Cancer Centers of Nevada, Las Vegas, NV
Pembrolizumab (MK-3475) for Advanced Urothelial Cancer: Updated Results and Biomarker Analysis from KEYNOTE-012

Elizabeth R. Plimack,1 Joaquim Bellmunt,2 Shilpa Gupta,3 Raanan Berger,4 Bruce Montgomery,5 Karl Heath,6 Jonathan Juco,6 Kenneth Emancipator,6 Kumudu Pathiraja,6 Jared Lunceford,6 Rodolfo Perini,6 Peter H. O’Donnell7

1Fox Chase Cancer Center, Philadelphia, PA, USA, 2Dana-Farber Cancer Institute, Boston, MA, USA
3H.Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA, 4Sheba Medical Center, Tel hashomer, Israel
5University of Washington, Seattle, WA, USA, 6Merck & Co, Inc., Kenilworth, NJ, USA,
7University of Chicago, Chicago, IL, USA
Anti-PD-1/PD-L1 in Heavily Pretreated Metastatic Urothelial Cancers Including Bladder Carcinoma

Atezolizumab (MPDL3280A)¹

- ORR: IC2/3: 50%; IC0/1: 17%
- Median PFS: IC2/3: 6 months; IC0/1: 1 month
- Median OS: IC2/3: Not reached; IC0/1: 8 months

Pembrolizumab²

- ORR: 28%
- Median PFS: 2 months
- Median OS: 12.7 months

1. Petrylak DP et al. J Clin Oncol 33, 2015 (suppl; abstractI4501)
2. Plimack ER et al. J Clin Oncol 33, 2015 (suppl; abstr 4502)
## Atezo and Pembro Fast Facts

<table>
<thead>
<tr>
<th></th>
<th>^Atezolizumab</th>
<th>^Pembrolizumab</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>PD-L1</td>
<td>PD-1</td>
<td>Cytotoxics and TKIs</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>q3wk</td>
<td>q2wk</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Grade 3-4 Toxicity</strong></td>
<td>8%</td>
<td>15%</td>
<td>~40-50%</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>35%</td>
<td>28%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>10-14 months</td>
<td>13 months</td>
<td>7 months</td>
</tr>
</tbody>
</table>

^ASCO 2015; abst 4501 / ^ASCO 2015; abst 4502.
Atezolizumab in Patients with Locally-Advanced or Metastatic Urothelial Carcinoma (mUC): Results from a Pivotal Multicenter Phase II Study (IMvigor 210)

Jonathan E. Rosenberg,1 Daniel P. Petrylak,2 Oyewale Abidoye,3 Michiel S. van der Heijden,4 Jean Hoffman-Censits,5 Andrea Necchi,6 Peter H. O’Donnell,7 Ani Balmanoukian,8 Yohann Loriot,9 Margitta Retz,10 Jose Luis Perez-Gracia,11 Nancy A. Dawson,12 Arjun V. Balar,13 Matthew D. Galsky,14 Mark T. Fleming,15 Thomas Powles,16 Na Cui,3 Sanjeev Mariathasan,3 Gregg D. Fine,3 Robert Dreicer17

1Memorial Sloan Kettering Cancer Center, New York, NY, USA; 2Yale Cancer Center, New Haven, CT, USA; 3Genentech, Inc., South San Francisco, CA, USA; 4Netherlands Cancer Institute, Amsterdam, the Netherlands; 5Thomas Jefferson University Hospital, Philadelphia, PA, USA; 6Istituto Nazionale dei Tumori, Milan, Italy; 7University of Chicago, Chicago, IL USA; 8The Angeles Clinic and Research Institute, Los Angeles, CA, USA; 9Gustave Roussy, Villejuif, France; 10Urologische Klinik und Poliklinik, Technische Universität München, Munich, Germany; 11Clinica Universidad de Navarra, Pamplona, Spain; 12Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA; 13Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY, USA; 14Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; 15Virginia Oncology Associates, Norfolk, VA, USA; 16Barts Cancer Institute, Queen Mary University of London, London, UK; 17Division of Hematology/Oncology, University of Virginia, Charlottesville VA USA
**IMvigor 210: Efficacy**

**Changes in Target Lesions by PD-L1 Subgroup**

111/258 (43%) patients with tumor assessments had SLD reduction

<table>
<thead>
<tr>
<th>PD-L1 Status</th>
<th>ORR&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC2/3</td>
<td>27%</td>
</tr>
<tr>
<td>IC1</td>
<td>10%</td>
</tr>
<tr>
<td>IC0</td>
<td>9%</td>
</tr>
</tbody>
</table>

SLD, sum of longest diameters. <sup>a</sup> > 100% increase. <sup>b</sup>Per confirmed RECIST v1.1 (independent review).

Data cutoff May 5, 2015. Follow up ≥ 24 weeks. Patients without post-baseline tumor assessments not included.

Several patients with CR had < 100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

Rosenberg JE, et al.: IMvigor 210: Phase II Atezolizumab in mUC
**IMvigor 210: Efficacy**

**Preliminary Analyses of Overall Survival**

<table>
<thead>
<tr>
<th>Survival</th>
<th>IC2/3 n = 100</th>
<th>IC0/1 n = 211</th>
<th>All N = 311</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>NR (7.6, NE)</td>
<td>6.7 (5.7, 8.0)</td>
<td>7.9 (6.7, NE)</td>
</tr>
</tbody>
</table>

**Median follow up:** 7 mo (range, 0-11 mo)

NR, not reached; NE, not estimable. Data cutoff May 5, 2015. Follow up ≥ 24 weeks.

Rosenberg JE, et al.: IMvigor 210: Phase II Atezolizumab in mUC
Outline Kidney

• Adjuvant TKI (Assure)
• First line:
  • Failure of peptide vaccines IMA901
  • Non Clear Cell histology (ASPEN)
• Second Line: Nivo and Cabo
Dose analysis of ASSURE (E2805): Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma, an ECOG-ACRIN-led, NCTN Phase 3 Trial

Naomi B. Haas¹ MD

• Co-authors: J Manola², K Flaherty³, R Uzzo⁴, C Wood⁵, C Kane⁶, M Jewett⁷, J Dutcher⁸, M Atkins⁹, M Pins¹⁰, G Wilding¹¹, D Cella¹², L Wagner¹², S Matin⁵, T Kuzel¹², W Sexton¹³, Y Wong³, T Choueiri¹⁴, R Pili¹⁵, R Puzanov¹⁶, M Koli¹⁷, W Stadler¹⁸, B Coomes¹⁹, R DiPaola²⁰

¹Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; ²Dana-Farber Cancer Institute, ³Boston; Massachusetts General Hospital, Boston; ⁴Fox Chase Cancer Center, Philadelphia; ⁵The University of Texas MD Anderson Cancer Center, Houston; ⁶Moores Cancer Center, University of California, San Diego, La Jolla; ⁷Princess Margaret Hospital, University of Toronto, Toronto; ⁸Cancer Research Foundation, NY; ⁹Lombardi Comprehensive Cancer Center, Washington, DC; ¹⁰University of Illinois College of Medicine, Chicago; ¹¹University of Wisconsin Carbone Cancer Center, Madison; ¹²Northwestern University Feinberg School of Medicine, Chicago; ¹³Moffitt Cancer Center, Tampa; ¹⁴Dana Farber Cancer Institute, Boston; ¹⁵Roswell Park Cancer Institute, Buffalo; ¹⁶Vanderbilt-Ingram Cancer Center, ¹⁷Mayo Clinic, Rochester; ¹⁸University of Chicago, Chicago; ¹⁹Cancer Research Patient Advocate, Atlanta; ²⁰Rutgers Cancer Institute of New Jersey, New Brunswick
Disease-Free Survival

Presented by: Naomi B. Haas, MD

0 12 24 36 48 60 72 84
0.0 0.2 0.4 0.6 0.8 1.0
Sunitinib
Sorafenib
Placebo

Events | Patients | 5-yr DFS | 97.5% CI | HR | 97.5% CI
--- | --- | --- | --- | --- | ---
Sunitinib | 265 | 647 | 53.8% | 49.0 – 59.1% | 1.01 | 0.83 – 1.23
Sorafenib | 272 | 649 | 52.8% | 48.0 – 58.0% | 0.98 | 0.81 – 1.19
Placebo | 270 | 647 | 55.8% | 51.2 – 60.9% |

Median 5.8 yrs
Median 5.8 yrs
Median 6.0 yrs
Overall Survival

Presented by: Naomi B. Haas, MD

Time (Months)

Proportion Alive

0.0 0.2 0.4 0.6 0.8 1.0

Sunitinib
Sorafenib
Placebo

Events Patients 5-yr OS 97.5% CI HR 97.5% CI

Sunitinib 138 647 76.9% 72.9 – 81.2% 1.10 0.83 – 1.45

Sorafenib 121 649 80.7% 77.0 – 84.6% 0.93 0.69 – 1.23

Placebo 130 647 78.7% 74.8 – 82.8%
Study Design

- 1,171 pts screened → 366 started 1\textsuperscript{st} sunitinib cycle (HLA-A2-negativity main exclusion) → 339 pts randomized
- Study was \textbf{not} blinded (HLA match peptide based vaccine)
Overall Survival

HR: 1.34  p = 0.08*

Control: Median OS: n.r.#
Vaccine: Median OS: 33.1 mo

# n.r. = not reached
* logRank stratified on risk group
** unstratified logRank
Metastatic RCC

- Non-clear cell pathology: papillary, chromophobe, unclassified
- No prior therapy
- Measurable disease

Stratified by Histology, MSKCC Risk Group

EVEROLIMUS 10 mg orally once daily
Days 1-42
Cycle = 6 weeks

SUNITINIB 50 mg orally
Days 1-28
Cycle = 6 weeks

Radiographic PFS Primary Endpoint

No planned crossover

Duke Cancer Institute was coordinating center and central biorepository for this multinational randomized open label trial, monitoring by inVentiv Health clinical

NCT01108445 Andrew J. Armstrong
Summary and Conclusions

- Patients with metastatic NC-RCC treated with sunitinib had a statistically significantly prolonged PFS duration than patients treated with everolimus.
  - Sunitinib resulted in improved PFS in good/intermediate risk, papillary, and unclassified subtypes.
  - Everolimus resulted in improved PFS in poor risk and chromophobe subtypes.
- Both agents resulted in short PFS times and low response rates.
- Sunitinib and everolimus resulted in different rates of expected toxicities; more severe toxicities with sunitinib, but more discontinuations due to toxicity from everolimus.
Randomized phase 2 three-arm trial of lenvatinib (LEN), everolimus (EVE), and LEN+EVE in patients (pts) with metastatic renal cell carcinoma (mRCC)

**Study Design**

**Key eligibility criteria:**
- Advanced or metastatic RCC
- Measurable disease
- Progression on/after 1 prior VEGF-targeted therapy
- Progression within 9 mos of stopping prior treatment
- ECOG PS ≤1

**Stratification factors:**
- Hemoglobin (normal vs low)
- Corrected serum calcium (≥ vs < 10 mg/dL)

**Patients were treated until:**
- Disease progression
- Unacceptable toxicity

**Randomization**

- **Lenvatinib** 18 mg PO qd + **Everolimus** 5 mg PO qd
- **Lenvatinib** 24 mg PO qd
- **Everolimus** 10 mg PO qd
Conclusions

- Progression-free survival was longer for lenvatinib/everolimus and lenvatinib compared with everolimus.

- Response rate was higher in both lenvatinib-containing arms.
  - The highest rate and longest duration of response was observed with the combination.

- Study results suggest an overall survival benefit for lenvatinib/everolimus over everolimus.
Cabozantanib versus Everolimus in Advanced Renal-Cell Carcinoma

Study Design

Advanced RCC (N=650)
- Clear cell histology
- Measurable disease
- Progression on prior VEGFR TKI within 6 months of enrollment
- No limit to the number of prior therapies
- Antibodies targeting PD-1/PD-L1 allowed
- Brain metastases allowed if treated

Stratification:
- MSKCC\(^1\) risk groups: favorable, intermediate, poor
- Number prior VEGFR-TKIs: 1, 2 or more

\(^1\) Motzer R. et al., J Clin Oncol, 2004

Tumor assessment by RECIST 1.1 every 8 weeks
Treatment until loss of clinical benefit or intolerable toxicity

Randomization 1:1
No cross-over allowed

* Cabozantinib 60 mg qd orally
* Everolimus 10 mg qd orally
Progression-Free Survival
Independent Central Radiology Review

Median PFS mo (95% CI)  
- Cabozantinib (N=187) 7.4 (5.6-9.1) 121  
- Everolimus (N=188) 3.8 (3.7-5.4) 126  
Hazard ratio, 0.58 (95% CI 0.45-0.75, P<0.001)

No. at Risk  
- Cabozantinib 187 152 92 68 20 6 2  
- Everolimus 188 99 46 29 10 2 0
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

Checkmate-25 Study design

Previously treated mRCC

Stratification factors
- Region
- MSKCC risk group
- Number of prior anti-angiogenic therapies

Randomize 1:1

Nivolumab
3 mg/kg intravenously every two weeks

Everolimus
10 mg orally once daily

• PRIMARY EDNPOINT: OS
• Treatment beyond progression was permitted if drug was tolerated and clinical benefit was noted

MSKCC, Memorial Sloan-Kettering Cancer Center.
Progression-free survival

<table>
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<th>Months</th>
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<th>Everolimus</th>
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Median PFS, months (95% CI)

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<th>Everolimus</th>
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</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>4.6 (3.7–5.4)</td>
<td>4.4 (3.7–5.5)</td>
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HR (95% CI): 0.88 (0.75–1.03)

\[ P = 0.1135 \]

- In a post-hoc analysis of patients who had not progressed or died at 6 months, median PFS was 15.6 months for nivolumab vs 11.7 months for everolimus (HR (95% CI): 0.64 (0.47–0.88))
Overall survival

<table>
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<th>Median OS, months (95% CI)</th>
<th>HR (98.5% CI):</th>
<th>P</th>
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<tr>
<td>Nivolumab</td>
<td>25.0 (21.8–NE)</td>
<td>0.73 (0.57–0.93)</td>
<td>0.0018</td>
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<tr>
<td>Everolimus</td>
<td>19.6 (17.6–23.1)</td>
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Minimum follow-up was 14 months.

NE, not estimable.

Motzer, NEJM 2015
Outline Prostate

- Chemotherapy for HSPC
- COMET trial CRPC
- PCWG3
- Genomics
  - TCGA
  - StandUp2 Cancer: DNA repair and MSH mutations
- PARP inh in PCa
E3805 – CHAARTED Treatment

**STRATIFICATION**

- **Extent of Mets**
  - High vs Low
- **Age**
  - ≥70 vs < 70yo
- **ECOG PS**
  - 0-1 vs 2
- **CAB> 30 days**
  - Yes vs No
- **SRE Prevention**
  - Yes vs No
- **Prior Adjuvant ADT**
  - ≤12 vs > 12 months

**RANDOMIZE**

- **ARM A:** ADT + Docetaxel 75mg/m² every 21 days for maximum 6 cycles
- **ARM B:** ADT (androgen deprivation therapy alone)

**Evaluate every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks**

- Follow for time to progression and overall survival
- Chemotherapy at investigator’s discretion at progression

- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone
Primary endpoint: Overall survival

HR = 0.61 (0.47-0.80) p = 0.0003
Median OS:
ADT + D: 57.6 months
ADT alone: 44.0 months

Sweeney et al. The NEW ENGLAND JOURNAL of MEDICINE
AUGUST 20, 2015
In patients with **high volume** metastatic disease, there is a **17 month improvement in median overall survival** from 32.2 months to 49.2 months. We projected 33 months in ADT alone arm with collaboration of SWOG9346 team.
STAMPEDE

1184 men with metastatic (~75%) or high risk disease (~25%): randomized to ADT + docetaxel or ADT alone.

- OS: median 77 vs 67 months, hazard ratio [HR] 0.76, 95% CI 0.63-0.91. A similar benefit was observed for DFS.
- OS in M1 subset: median 65 versus 43 months, HR 0.73, 95% CI 0.59-0.89.
- Failure-free survival in M1: HR 0.62, 95% CI 0.54-0.71; in M0 HR 0.57, 95% CI 0.42-0.76.

James et al, ASCO 2015, abstr 5001
GETUG-AFU 15

192 men randomized to ADT + docetaxel and 193 to receive ADT alone.

Median follow-up 50 months:
- Median OS 58.9 vs 54.2 months
- HR 1.01, 95% CI 0.75-1.36.
- 72 serious adverse events ADT + docetaxel
- Four treatment-related deaths in ADT + docetaxel

Median follow-up 83 months:
- Median OS 61 versus 47 months
  - HR 0.9, 95% CI 0.7-1.2
- PFS median 22.9 versus 12.9 months
  - HR 0.7, 95% CI 0.6-0.9
- PFS benefit seen in both high and low volume disease

Gravis et al, ASCO 2015, (suppl 7; abstr 140)
Cabozantinib (XL 184)

Bone effects

<table>
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<th>Bone scan evaluable (N=108)</th>
<th>n (%)</th>
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<td>Complete resolution</td>
<td>21 (19)</td>
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<tr>
<td>Partial resolution</td>
<td>61 (56)</td>
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<td>Stable</td>
<td>23 (21)</td>
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<td>Progressive disease</td>
<td>3 (3)</td>
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</table>

Effects on osteoblast (t-ALP) and osteoclast (CTX) activity

Smith, et al JCO 2012
COMET-1: Final Analysis
Abstr #139

- N = 1028, dose 60mg po
- Plan for 578 deaths to provided 90% power to detect HR 0.75
- Bone scan response at wk 12
  - Based on 614 deaths: OS 11 mo vs 9.8, P=0.212
  - BSR 41% for Cabo vs 3% for Pred
  - Median PFS per investigator: 5.5 vs 2.8 mo, P<0.001
- Visceral dz*: OS 7.1 vs 4.8 mo
333 primary prostate cancers

- mutations
- copy-number alterations
- mRNA expression
- fusions
- DNA methylation
- microRNA expression
- protein expression

molecular subtypes

Percent of tumors

DNA hypermethylation
AR pathway activity
DNA repair defects
PI3K/RAS/RAF pathway alterations

Figure 1. The Molecular Taxonomy of Primary Prostate Cancer

Comprehensive molecular profiling of 333 primary prostate cancer samples revealed seven genomically distinct subtypes, defined (top to bottom) by ERG fusions (46%), ETV1/ETV4/ETV14 fusions or overexpression (8%, 4%, 1%, respectively), or by SPOP (11%), FOXA1 (3%), and IDH1 (1%) mutations. A subset of these subtypes was correlated with clusters computationally derived from the individual characterization platforms (somatic copy-number alterations, methylation, mRNA, microRNA, and protein levels from reverse phase protein arrays). The heatmap shows DNA copy-number for all cases, with chromosomes shown from left to right. Regions of loss are indicated by shades of blue, and gains are indicated by shades of red.

See also Figures S1, S2, S3, S4, S5, S6, and S7 and Tables S1A, S1B, S1C, and S2.
Integrative Clinical Genomics of Advanced Prostate Cancer

Dan Robinson, 1,3,4,5 Eliezir M. Van Allen, 3,4,5 Y-Mi Wu, 3,4,5 Nikolaus Schultz, 3,4,5 Robert J. Lonigro, 3,4,5
Jean-Miguel Messing, 3,4,5 Bruce Montgomery, 3,4,5 Mary-Ellen Taplin, 3,4,5 Colie C. Pritchard, 3,4,5 Gerhardth Attendt, 1,3,4
Himaha Reddy, 3,4,5 Grigorios Papanastassiou, 3,4,5 Robert K. Bradley, 3,4,5 Jake Vinson, 3,4,5 Xuefang Diao, 3,4,5 Panagis Yanta, 3,4,5
Lakshmi P. Kurup, 3,4,5 Maha Hansen, 3,4,5 Felix Y. Feng, 3,4,5 Scott A. Tomlin, 3,4,5 Kathleen A. Cooney, 3,4,5
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Michael J. Morris, 3,4,5 Stephen B. Solomon, 3,4,5 Jeremy G. Durack, 3,4,5 Victor E. Routier, 3,4,5 Anuradha Gopalas, 3,4,5
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Elisabeth l. Heath, 3,4,5 Howard I. Scher, 3,4,5 Kenneth J. Pieloa, 3,4,5 Philip Kantoff, 3,4,5 Johann S. de Bono, 3,4,5
Mark A. Rubin, 3,4,5 Peter G. Nelson, 3,4,5 Leslie S. Gleave, 3,4,5 and Arul M. Chennaham

Figure 1. Overview of the SU2C-PCF IDT Multi-Institutional Clinical Sequencing of the mCRPC Project
(A) Schema of the multi-institutional clinical sequencing project workflow.
(B) Clinical trials associated with the SU2C-PCF mCRPC project.
(C) Copy number changes of the cohort, Representative images of morphological analysis of mCRPC are shown along with prevalence in our cohort.

Figure 2. Integrative Landscape Analysis of Somatic and Germline Aberrations in Metastatic CRPC Obtained through DNA and RNA Sequencing of Clinically Obtained Biopsies
Columns represent individual affected individuals, and rows represent specific genes grouped into pathways. Mutations per MB are shown in the upper histogram, and incidence of alterations in the cohort is in the right histogram. Copy number variations (CNV) common to mCRPC samples are shown on the lower matrix, with pink representing gain and light blue representing loss. Color legend of the aberrations represented including amplification, loss (red box), one copy loss, co-copy loss, heterozygous loss (light green), missense mutation, frameshift mutation, nonsense mutation, in-frame indel, and gene fusion. Cancers with more aberrations in a gene are represented by split colors.
Antitumor Activity of Olaparib and Association with Defects in DNA-Repair Genes, According to Biomarker Status.
Genomic Aberrations in DNA Repair in Patients with Metastatic, Castration-Resistant Prostate Cancer.

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Radiologic Evidence of Tumor Responses to Olaparib at Week 12.
GU Highlights 2015

- Failed role of lapatinib in maintenance
- Check point inhibitors are promising in bladder cancer
- Expression signatures might help to identify the best treatment option (chemo vs immuno)

- Adjuvant therapy in RCC an open question
- Nivolumab FDA approved for renal second line
- New promising role of cabozantanib in second line

- Established role of docetaxel in HSPC
- Genomic profiling in early and advance disease
- Translation to treatment with Olaparib