2014 ANCO’s ASCO Highlights - Genitourinary Malignancies

Chong-Xian Pan, MD, PhD
Associate Professor of Medicine and Urology
Leader of the Urothelial Carcinoma Initiative
Department of Internal Medicine
UC Davis

DISCLOSURE

I have financial interest/arrangement or affiliation with

Name of Organization | Relationship
---------------------|-----------------
Accelerated Medical Diagnostics Inc | Co-founder and shareholder

Research support: Novartis and Abbott
Best of ASCO 2014
-Genitourinary Malignancies

1. Abstract LBA2: CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in prostate Cancer (C Sweeney) comments Michael Morris MSKCC

2. Abstract 5003: Immediate vs. deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study (Garcia-Albeniz)

3. Abstract 5008: Phase 3, randomized, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients (pts) with chemotherapy-naive metastatic castration-resistant prostate cancer (ELM-PC 4 trial). (R deWit)

4. Abstract 5011: Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic bladder cancer (T Powles)

5. Abstract 4500: International Intergroup Randomized Phase III trial comparing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4, and /or N+ M0 transitional cell carcinoma of the bladder (C Sternberg)
Newly diagnosed metastatic or recurrent CaP

First-line androgen deprivation therapy (ADT):
LHRH agonist, LHRH antagonist, or orchiectomy

AR modulators(-lutamide), abiraterone, sipuleucel-T, radium-223, ketoconazole

**docetaxel**

AR modulators(-lutamide), enzalutamide, abiraterone, radium-223, sipuleucel-T, cabazitaxel

Mitoxantrone, cyclophosphamide

---

E3805 CHAARTED Trial

First-line androgen deprivation therapy (ADT) + **Docetaxel**

AR modulators(-lutamide), abiraterone, sipuleucel-T, radium-223, ketoconazole

**docetaxel**

AR modulators(-lutamide), enzalutamide, abiraterone, radium-223, sipuleucel-T, cabazitaxel

Mitoxantrone, cyclophosphamide
The CHAARTED Hypothesis

- Docetaxel plus androgen deprivation therapy (ADT) will prolong overall survival of patients with hormone naïve metastatic prostate cancer

Presented by: Christopher J. Sweeney, MBBS

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

ARM A:
- ADT + Docetaxel 75mg/m2 every 21 days for maximum 6 cycles

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

ARM B:
- ADT (androgen deprivation therapy alone)

Evaluate every 12 weeks

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

Presented by: Christopher J. Sweeney, MBBS
Key Eligibility Criteria

• Metastatic prostate cancer
  – if clinical scenario c/w PrCa can enroll without tissue
• Prior ADT limited to
  – 120 days prior to randomization or adjuvant Rx < 24 months and no progression within 12 months of finish
• ECOG 0-2 (2 only if due to PrCa)
• Liver, bone marrow, renal, cardiac, pulmonary and neurological function suitable for docetaxel
• No prior docetaxel

Study Endpoints

• Primary Endpoint
  – Overall survival
• Secondary Endpoints
  – Rate of PSA < 0.2 ng/mL at 6 months and 12 months
  – Time to biochemical, radiographic or symptomatic PD
  – Time to radiographic or symptomatic progressive disease (PD)
  – Define adverse event profile and tolerability
  – Quality of life (FACT-P) until 12 months after randomization
Results:

- 790 men accrued 7/28/2006 to 11/21/2012
  - Planned interim analysis at 53% information, Oct 2013 met pre-specified criteria for significance and release of data
  - Jan 16, 2014 median follow-up of 29 months
    - 136 deaths ADT alone vs. 101 deaths ADT+D

Presented by: Christopher J. Sweeney, MBBS
Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>ADT + Doc (N=397)</th>
<th>ADT alone (N=393)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>Age (year)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>64</td>
<td>69.7%</td>
</tr>
<tr>
<td>Range</td>
<td>36-88</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>344</td>
<td>88.7%</td>
</tr>
<tr>
<td>Other</td>
<td>44</td>
<td>11.3%</td>
</tr>
<tr>
<td>Unknown</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>276</td>
<td>69.7%</td>
</tr>
<tr>
<td>1</td>
<td>114</td>
<td>28.8%</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>1.5%</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Presented by: Christopher J. Sweeney, MBBS

---

Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>ADT + Doc (N=397)</th>
<th>ADT alone (N=393)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>Volume of Mets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>134</td>
<td>33.8%</td>
</tr>
<tr>
<td>High</td>
<td>263</td>
<td>66.2%</td>
</tr>
<tr>
<td><strong>Gleason Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>21</td>
<td>5.9%</td>
</tr>
<tr>
<td>7</td>
<td>96</td>
<td>26.9%</td>
</tr>
<tr>
<td>8-10</td>
<td>240</td>
<td>67.2%</td>
</tr>
<tr>
<td>Unknown</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td><strong>PSA (ng/mL) at time of ADT start</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>56.0</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.4-8540.1</td>
<td>0.1-8056.0</td>
</tr>
</tbody>
</table>

Presented by: Christopher J. Sweeney, MBBS
Patient characteristics

<table>
<thead>
<tr>
<th>Prior Treatment</th>
<th>ADT + Doc (N=397)</th>
<th>ADT alone (N=393)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No localized Rx</td>
<td>289 (72.8%)</td>
<td>286 (73.0%)</td>
</tr>
<tr>
<td>Primary radiation</td>
<td>27 (6.8%)</td>
<td>33 (8.4%)</td>
</tr>
<tr>
<td>Prostatectomy</td>
<td>81 (20.4%)</td>
<td>73 (18.6%)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Adjuvant ADT</td>
<td>21 (5.3%)</td>
<td>15 (3.8%)</td>
</tr>
</tbody>
</table>

Median time from start ADT to randomization

<table>
<thead>
<tr>
<th>Months (range)</th>
<th>ADT + Doc</th>
<th>ADT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ADT prior to randomization</td>
<td>1.1 (0-3.9)</td>
<td>1.2 (0-3.9)</td>
</tr>
<tr>
<td></td>
<td>46 (12%)</td>
<td>45 (11%)</td>
</tr>
</tbody>
</table>

Primary endpoint: Overall survival 13.6 month improvement

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

High tumor volume: visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column).

Presented by: Christopher J. Sweeney, MBBS
### Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>ADT + Doc (N=397)</th>
<th>ADT alone (N=393)</th>
<th>P-value</th>
<th>Hazard Ratio (95% CI*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA &lt;0.2 ng/mL at 6 months</td>
<td>27.5%</td>
<td>14.0%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>PSA &lt;0.2 ng/mL at 12 months</td>
<td>22.7%</td>
<td>11.7%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Median time to CRPC - biochemical, symptoms, or radiographic (months)</td>
<td>20.7</td>
<td>14.7</td>
<td>&lt;0.0001</td>
<td>0.56 (0.44, 0.70)</td>
</tr>
<tr>
<td>Median time to clinical progression - symptoms or radiographic (months)</td>
<td>32.7</td>
<td>19.8</td>
<td>&lt;0.0001</td>
<td>0.49 (0.37, 0.65)</td>
</tr>
</tbody>
</table>

*CI: confidence intervals

---

### Therapy beyond progression

<table>
<thead>
<tr>
<th></th>
<th>ADT + Docet (N=397)</th>
<th>ADT alone (N=393)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochem, Sympt, Radiog PD</td>
<td>145</td>
<td>174</td>
</tr>
<tr>
<td>Symptom or Radiograph PD</td>
<td>93</td>
<td>133</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>49</td>
<td>129</td>
</tr>
<tr>
<td>Other Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td>Mitoxantrone &amp;/or Platinum</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Hormonal Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abiraterone/Enzalutamide</td>
<td>92</td>
<td>79</td>
</tr>
<tr>
<td>Antiandrogen/ketoconazole</td>
<td>87</td>
<td>99</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sipuleucel T</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>54</td>
<td>67</td>
</tr>
</tbody>
</table>

Presented by: Christopher J. Sweeney, MBBS
### Non-Hematologic Toxicity (%)

<table>
<thead>
<tr>
<th>Grade</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reaction</td>
<td>2</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Colitis/Diarrhea</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neuropathy-motor</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neuropathy-sensory</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thrombo-embolism</td>
<td>&lt;1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Sudden death</td>
<td>-</td>
<td>-</td>
<td>1 patient</td>
</tr>
</tbody>
</table>

### Hematologic Toxicity (%)

<table>
<thead>
<tr>
<th>Grade</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>1</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>-</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Infection with neutropenia</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

**Worst grade heme and non-heme toxicity per patient**

|         | 16% | 12%  | 1 patient |

Presented by: Christopher J. Sweeney, MBBS
Conclusion

• The combination of standard ADT and 6 cycles of docetaxel significantly improved overall survival compared to standard ADT alone in men with hormone sensitive metastatic prostate cancer

Clinical interpretation

• 6 cycles of docetaxel in addition to ADT represents an appropriate option for men with metastatic prostate cancer commencing ADT who are suitable for docetaxel therapy

• The benefit in patients with a high volume of metastases is clear and justifies the treatment burden
  – longer follow-up is required for patients with low volume metastatic disease
What is high volume disease?

**High tumor volume:** visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column).

---

**Best of ASCO 2014**

1. Abstract LBA2: CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in prostate Cancer (C Sweeney) comments Michael Morris MSKCC
2. Abstract 5003: Immediate vs. deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study (Garcia-Albeniz)
3. Abstract 5008: Phase 3, randomized, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients (pts) with chemotherapy-naive metastatic castration-resistant prostate cancer (ELM-PC 4 trial). (R deWit)
4. Abstract 5011: Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic bladder cancer (T Powles)
5. Abstract 4500: International Intergroup Randomized Phase III trial comparing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4, and/or N+ M0 transitional cell carcinoma of the bladder (C Sternberg)
Background

- Many patients with localized prostate cancer receive curative treatment
- Many of these patients will have PSA recurrence without symptoms or detectable metastasis.
- Optimal timing to initiate ADT is unknown in those patients with PSA-only relapse.

Methods. Study population.

- CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavour). University of California, San Francisco.
  - Longitudinal observational study > 14,300 men with biopsy-proven prostate cancer.
  - Patients are treated and followed in usual practice setting.
  - Started in 1995, 43 study sites have enrolled patients nationwide.
- Baseline and sequential information on variables that determine treatment choices in routine practice.
  - Baseline variables: Gleason, % of positive biopsies, T-stage, type of primary treatment (radical prostatectomy vs. radiation), time from primary treatment to relapse, calendar year of relapse, age
  - Time-varying variables: PSA, Karnofsky performance status, bone pain, fatigue.
**Results**

**Inclusions**
9,748 patients with a histological diagnosis of prostate adenocarcinoma, PSA and imaging tests after diagnosis and no orchiectomy.

9,431 staged ≤ T3aN0M0.

7,311 treated with curative intention (5,023 with RP + EBRT and 2,286 with EBRT and/or brachitherapy).

2,247 relapsed by PSA.

**Exclusions**
21 patients underwent orchiectomy before PSA relapse.

148 patients received pharmacological ADT in the 12 months preceding PSA relapse.

64 patients presented overt relapse on bone scan, abdominopelvic CT scan or pelvic MRI.

12 patients suffered from cancer-related symptoms.

---

**2022 eligible patients (No rescue XRT)**

Immediate ADT strategy:
(ADT within 3 months of PSA relapse)

13,516 months of follow-up
30 deaths (15 due to prostate cancer)

Deferred ADT strategy:
(ADT ≥ 2 years after PSA relapse; metastasis, or symptoms, or short PSA DT)

84,716 months of follow-up
155 deaths (24 due to prostate cancer)

---

**Results**

**All cause mortality**

<table>
<thead>
<tr>
<th></th>
<th>Immediate ADT</th>
<th>Deferred ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio</td>
<td>0.94 (0.51-1.73)</td>
<td>Reference</td>
</tr>
<tr>
<td>5-year survival</td>
<td>85.1 (77.6-92.7)</td>
<td>87.2 (84.5-90.0)</td>
</tr>
<tr>
<td>10-year survival</td>
<td>71.6 (56.3-87.0)</td>
<td>71.6 (65.0-78.3)</td>
</tr>
</tbody>
</table>

**Prostate cancer-specific mortality**

<table>
<thead>
<tr>
<th></th>
<th>Immediate ADT</th>
<th>Deferred ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio</td>
<td>1.15 (0.33-3.97)</td>
<td>Reference</td>
</tr>
<tr>
<td>5-year survival</td>
<td>93.3 (85.3-100)</td>
<td>96.0 (88.7-100)</td>
</tr>
<tr>
<td>10-year survival</td>
<td>89.4 (80.6-98.1)</td>
<td>90.2 (82.7-97.7)</td>
</tr>
</tbody>
</table>
Results

![Graph showing all cause and prostate cancer mortality over time with immediate and delayed ADT]

5-year difference: -2.1% (95% CI -10.2% to 6.0%)
10-year difference: 0% (95% CI -16.4% to 16.4%)

5-year difference: -2.7% (95% CI -7.4% to 2.0%)
10-year difference: -0.9% (95% CI -8.2% to 6.4%)

Conclusions

• This analysis suggests that patients undergoing immediate ADT at PSA-only relapse had similar survival to those who deferred ADT initiation at progression or two or more years after PSA relapse in the absence of clinical progression

• Limitations: those of an observational study. Imprecise estimates.

• Preliminary answer: an ongoing phase III trial ("A Collaborative Randomized Phase III Trial: the Timing of Intervention with Androgen Deprivation in Prostate Cancer Patients with Rising PSA", clinicaltrials.gov ref: NCT00110162) will serve as gold standard.

XGA is a 2012-13 CaPSURE scholar and also a recipient of an "ASISA Fellowship" and a SEOM (Sociedad Española de Oncología Médica) grant. This work was partly funded by NIH grant P01-CA134294. CaPSURE is supported in part by an independent, educational grant from Abbott.
Best of ASCO 2014

1. Abstract LBA2: CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in prostate Cancer (C Sweeney) comments Michael Morris MSKCC

2. Abstract 5003: Immediate vs. deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study (Garcia-Albeniz)

3. Abstract 5008: Phase 3, randomized, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients (pts) with chemotherapy-naive metastatic castration-resistant prostate cancer (ELM-PC 4 trial). (R deWit)

4. Abstract 5011: Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic bladder cancer (T Powles)

5. Abstract 4500: International Intergroup Randomized Phase III trial comparing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4, and/or N+ M0 transitional cell carcinoma of the bladder (C Sternberg)

Phase 3, randomized, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients (pts) with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC) (ELM-PC 4 trial)

Ronald de Wit¹, Karim Fizazi², Viorel Jinga³, Eleni Efstathiou⁴, Peter Fong⁵, Manfred Wirth⁶, Kazuhiro Suzuki⁷, Ling Wang⁸, Hideyuki Akaza⁹, Joel Nelson¹⁰, Howard I. Scher¹¹, Robert Dreicer¹², Niels Borgstein¹², Fred Saad¹³

¹Erasmus University Medical Center, Rotterdam, The Netherlands; ²Institut Gustave Roussy, University of Paris Sud, Villejuif, France; ³Universitatea de Medicina Si Farmacie, Bucharest, Romania; ⁴University of Athens Medical School, Athens, Greece; ⁵Auckland City Hospital, Auckland, New Zealand; ⁶University Hospital Carl Gustav Carus Dresden, Dresden, Germany; ⁷Gifu University Graduate School of Medicine, Gifu, Japan; ⁸Takeda Pharmaceuticals International Co., Cambridge, MA, USA; ⁹The University of Tokyo Research Center for Advanced Science and Technology, Tokyo, Japan; ¹⁰University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; ¹¹Memorial Sloan-Kettering Cancer Center, New York, NY, USA; ¹²Cleveland Clinic, Cleveland, OH, USA; ¹³University of Montreal Hospital Center, Montreal, QC, Canada

Presented by: Dr Ronald de Wit
Patients with chemotherapy-naive mCRPC and asymptomatic without opioid use at screening

Enrolled
N = 1560

Visceral metastases were allowed.

Randomized 1:1

Orteronel 400mg BID
Prednisone 5mg BID
n = 781

Placebo BID
Prednisone 5mg BID
n = 779

Endpoints
Primary:
• OS
• rPFS

Key Secondary:
• PSA response
• Change in CTCs
• Time to pain progression

• Recruitment in 324 centers from 43 countries across 6 continents, October 2010 through June 2012

Primary Endpoint: Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>O+P</th>
<th>PL+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median rPFS</td>
<td>13.8 Mo</td>
<td>8.7 Mo</td>
</tr>
<tr>
<td>HR: 0.7; 95%CI: 0.6-0.8; p&lt;0.00001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P=0.31421

Median: Orteronel + Prednisone 31.4 mo vs Prednisone 29.5 mo

Events: Orteronel + Prednisone 294 vs Prednisone 317

# of subjects at risk:

Orteronel + Prednisone: 781, 779, 744, 709, 666, 620, 581, 533, 397, 234, 149, 68, 23, 4

Prednisone: 779, 751, 700, 661, 609, 564, 516, 372, 239, 149, 81, 26, 4
Conclusions

- Orteronel + prednisone demonstrated statistically significant improvement in rPFS in men with chemotherapy-naive mCRPC
- Improvement in OS was not demonstrated
- Median testosterone levels in both treatment groups were drastically reduced by 12 weeks and through 24 weeks
- Improvements in rates of PSA response and CTC conversion, as well as delay in time to docetaxel and other subsequent therapies, were observed

Best of ASCO 2014

1. Abstract LBA2: CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in prostate Cancer (C Sweeney) comments Michael Morris MSKCC
2. Abstract 5003: Immediate vs. deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study (Garcia-Albeniz)
3. Abstract 5008: Phase 3, randomized, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients (pts) with chemotherapy-naive metastatic castration-resistant prostate cancer (ELM-PC 4 trial). (R deWit)
4. Abstract 5011: Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic bladder cancer (T Powles)
5. Abstract 4500: International Intergroup Randomized Phase III trial comparing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4, and /or N+ M0 transitional cell carcinoma of the bladder (C Sternberg)
Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic urothelial bladder cancer (UBC)

Thomas Powles,1 Nicholas J. Vogelzang,2 Gregg Fine,3 Joseph Paul Eder,4 Fadi Braiteh,5 Yohann Loriot,6 Cristina Cruz,6 Joaquim Bellmunt,7 Howard Burris,8 Siew-leng Melinda Teng,9 Xiaodong Shen,3 Hartmut Koeppen,2 Priti S. Hegde,3 Daniel S. Chen,3 Daniel P. Petrylak4

1Barts Cancer Institute, Queen Mary University of London; 2US Oncology Research; 3Genentech, Inc.; 4Yale Cancer Center; 5Gustave Roussy, University of Paris-Sud; 6Vall d’Hebron Institute of Oncology (VHIO) and Vall d’Hebron University Hospital; 7Bladder Cancer Center, Dana-Farber/Brigham and Women’s Cancer Center; Harvard Medical School; 8Sarah Cannon Research Institute

MPDL3280A: UBC Baseline Characteristics

Efficacy-evaluable population with UBC in Phase I expansion

<table>
<thead>
<tr>
<th>Characteristics of Patients With UBC</th>
<th>PD-L1+ (IHC) n = 30</th>
<th>PD-L1− (IHC) n = 35</th>
<th>All n = 67a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>67 (42-86)</td>
<td>63 (36-81)</td>
<td>65 (36-86)</td>
</tr>
<tr>
<td>Male</td>
<td>83%</td>
<td>60%</td>
<td>72%</td>
</tr>
<tr>
<td>ECOG PS 0 / 1</td>
<td>48% / 52%b</td>
<td>37% / 63%c</td>
<td>41% / 59%d</td>
</tr>
<tr>
<td>Metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral / liver</td>
<td>63% / 30%</td>
<td>83% / 34%</td>
<td>75% / 33%</td>
</tr>
<tr>
<td>Prior treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystectomy</td>
<td>67%</td>
<td>31%</td>
<td>48%</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>93%</td>
<td>66%</td>
<td>79%</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>23%</td>
<td>43%</td>
<td>34%</td>
</tr>
<tr>
<td>≤ 3 months from last prior chemo</td>
<td>31%b</td>
<td>52%a</td>
<td>42%</td>
</tr>
</tbody>
</table>

a 2 pts have unknown IHC (IC) status.
b n = 29; c n = 35; d n = 66; e n = 31; f n = 62.

diag-pos: PD-L1+ (IHC ≥ 10% of ICs PD-L1+) and IHC ≥ 1% but < 10% of ICs PD-L1+
diag-pos: PD-L1− (IHC ≥ 1% but < 5% of ICs PD-L1+) and IHC < 1% of ICs PD-L1+

Patients dosed by Nov 20, 2013 (≥ 6 wk follow-up) with measurable disease at baseline. Clinical data cut-off was Jan 1, 2014.

Presented by: Prof. Thomas Powles

Presented at the 2014 ASCO Annual Meeting. Presented data is the property of the author.
MPDL3280A: Treatment-Related AEs

Safety-evaluable population with UBC in Phase I expansion

- MPDL3280A: 15 mg/kg, iv q3w up to one year.
- Well tolerated in patients with UBC, including patients with impaired renal function.
- MPDL3280A was not associated with renal toxicity.
- No treatment-related grade 4 or 5 AEs.
- No investigator-assessed immune-related toxicities were reported as of the clinical cutoff.

Additional treatment-related Grade 3/4 AEs: thrombocytopenia and decrease in blood phosphorus (1 each).

Clinical data cutoff was Jan 1, 2014.
Includes events occurring in ≥3 patients.

<table>
<thead>
<tr>
<th>Patients With UBC N = 68</th>
<th>All Grade n (%)</th>
<th>Grade 3-4(^a) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>39 (57%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Chills</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Lethargy</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

• MPDL3280A: 15 mg/kg, iv q3w up to one year.
• Well tolerated in patients with UBC, including patients with impaired renal function.
• MPDL3280A was not associated with renal toxicity.
• No treatment-related grade 4 or 5 AEs.
• No investigator-assessed immune-related toxicities were reported as of the clinical cutoff.

Additional treatment-related Grade 3/4 AEs: thrombocytopenia and decrease in blood phosphorus (1 each).

Clinical data cutoff was Jan 1, 2014.
Includes events occurring in ≥3 patients.

Presented by: Prof. Thomas Powles

---

MPDL3280A: Summary of ORR in UBC

Efficacy-evaluable population with UBC in Phase I expansion

<table>
<thead>
<tr>
<th>PD-L1 IHC Tumor-infiltrating immune cells (ICs)</th>
<th>ORR % (95% CI)</th>
<th>Dx+ vs Dx− ORR % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC 3 (n = 10)</td>
<td>50% (22-78)</td>
<td>43% (26-63)</td>
</tr>
<tr>
<td>IHC 2 (n = 20)</td>
<td>40% (21-64)</td>
<td></td>
</tr>
<tr>
<td>IHC 1 (n = 23)</td>
<td>13% (4-32)</td>
<td>11% (4-26)</td>
</tr>
<tr>
<td>IHC 0 (n = 12)</td>
<td>8% (0.4-35)</td>
<td></td>
</tr>
</tbody>
</table>

- 2 CRs (1 IHC 2, 1 IHC 3).
- 16 of 17 responding patients had ongoing responses at the time of data cutoff.
- ORR = 52% (95% CI, 32-70) for Dx+ with ≥12 weeks of follow-up.

Investigator-assessed ORRs unconfirmed per REGIST v.1.
2 pts with unknown IHC status are not included in table.
Diagnostic DxPD-L1+: IHC 3 (≥10% of ICs PD-L1+) and IHC 2 (≥5% but < 10% of ICs PD-L1+).
Diagnostic DxPD-L1−: IHC 1 (≥1% but < 5% of ICs PD-L1+) and IHC 0 (< 1% of ICs PD-L1+).
Patients dosed by Nov 20, 2013 (≥6 wk follow-up) with measurable disease at baseline. Clinical data cutoff was Jan 1, 2014.

Presented by: Prof. Thomas Powles
MPDL3280A: Tumor Burden Over Time in UBC

- Median time to first response was 42 days (range, 38 to 85 days)
- Median duration of response has not been reached
  - 0.1+ to 30.3+ weeks for IHC (IC) 2 or 3 and 0.1+ to 6.0+ weeks for IHC (IC) 0 or 1
- Median follow-up was 4.2 months (1.1+ to 8.5) for Dx+ and 2.7 months (0.7+ to 3.6) for Dx−

Figure does not include 7 pts without any post-baseline tumor assessment.
Patients dosed by Nov 20, 2013 (≥6 wk follow-up) with measurable disease at baseline and at least 1 post-baseline measurement. Clinical data cutoff was Jan 1, 2014.

MPDL3280A: Conclusions in UBC

- MPDL3280A has noteworthy activity in heavily pretreated patients with metastatic UBC
  - 43% response rate in PD-L1-positive UBC. Rapid responses seen
  - 16 of 17 responding patients had ongoing responses at the time of data cutoff
- MPDL3280A was well tolerated
  - Only 4% of patients experienced a Grade 3-4 treatment-related AE
  - There were no Grade 4 or 5 treatment-related AEs
  - No evidence of renal toxicity
- Elevations in circulating biomarkers represent pharmacodynamic effects
- Additional studies of MPDL3280A in UBC are planned and ongoing (including NCT02108652)
- Breakthrough therapy designation has been granted by the FDA
1. Abstract LBA2: CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in prostate Cancer (C Sweeney) comments Michael Morris MSKCC

2. Abstract 5003: Immediate vs. deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study (Garcia-Albeniz)

3. Abstract 5008: Phase 3, randomized, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients (pts) with chemotherapy-naïve metastatic castration-resistant prostate cancer (ELM-PC 4 trial). (R deWit)

4. Abstract 5011: Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic bladder cancer (T Powles)

5. Abstract 4500: International Intergroup Randomized Phase III trial comparing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4, and/or N+ M0 transitional cell carcinoma of the bladder (C Sternberg)

---

**EORTC TRIAL 30994**

International Intergroup Randomized Phase III trial comparing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4, and/or N+ M0 transitional cell carcinoma (TCC) of the bladder

Study coordinated by the EORTC GU Cancers Group, with collaboration from GETUG, NCRI, NCIIC and AUO

Cora N. Sternberg1, Iwona Skoneczna2, J.M. Kerst3, Sophie Fossa4, Peter Albers5, Mads Agerbaek6, Herlinde Dumez7, Maria De Santis8, Christine Theodore9, Michael Leahy10, J.D. Chester11, Antony Verbaeys12, Armelle Caty13, Gedske Daugaard14, Sandrine Marreaud14, Samantha Cambier14, Richard Sylvester14

1San Camillo and Forlanini Hospitals, Rome, Italy, 2Maria Sklodowska-Curie Memorial Cancer Centre, Warsaw, Poland, 3The Netherlands Cancer Institute, Amsterdam, The Netherlands, 4Oslo University Hospital, Oslo, Norway, 5Klinikum Kassel, Kassel, Germany and University Clinic Bonn, Bonn, Germany, 6Aarhus University Hospital, Aarhus, Denmark, 7U.Z. Gastrohosp, Leuven, Belgium, 8Kaiser Franz Josef Spathl, Vienna, Austria, 9Institut Gustave Roussy, Villejuif, France, 10St James’s University Hospital, Leeds, United Kingdom, 11University Hospital Gent, Gent, Belgium, 12Centre Oscar Lambret, Lille, France, 13Rigshospitalet, University of Copenhagen, Denmark, 14EORTC Headquarters, Brussels, Belgium.
Background
- Neoadjuvant chemo is the standard care for MIBC

**MRC EORTC-CMV**

- 10-y OS: 36% vs 30%; p=0.037

**INT-0800 trial-MVAC**

- 5-y OS: 57% vs 43%; p=0.06

In practice, <15% of eligible pts receive neoadjuvant chemo.

**EORTC 30994 TRIAL**: will adjuvant chemotherapy improve treatment outcomes?

---

**Trial Design**

- **Eligibility**
  - pT3-pT4, and/or any pTN+M0
  - Within 90 days after cystectomy:

- **Randomize**

- **Immediate therapy**
  - Gem-Cis or M-VAC or HD-M-VAC
  - 4 cycles

- **Deferred therapy at relapse**
  - 6 cycles

**Pt accrual**: 284/660 pts from 63 sites in 13 countries from 4/2002 to 8/2008

- **Primary endpoint**: Overall survival
- **Secondary endpoint**: Progression free survival
A Significant Improvement in PFS (ITT)

- 5 Year PFS rates: 46.8% Immediate, 29.5% Deferred
- HR = 0.52 (95% CI: 0.39 – 0.71)
- P < 0.0001

Overall Survival (ITT)

- A non-significant reduction of 22.2% in the risk of death
- 5 Years OS rates: 53.6% Immediate, 47.7% Deferred
- HR = 0.78 (CI*: 0.56 - 1.08)
- P = 0.13

*95.09%, adjusted for interim analysis
Conclusions

✓ Largest randomized trial ever reported of adjuvant chemotherapy in patients with muscle invasive bladder cancer

✓ Immediate adjuvant cisplatin based combination chemotherapy after radical cystectomy led to
  ✓ a statistically significant improvement in PFS
  ✓ a non-significant reduction of 22.2% in the risk of death

Thank you very much.

Questions?