Best of ASCO 2019: Lung and Genitourinary Cancers

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Disclosures

- Research Funding: Merck, GeneCentric, Bristol-Myers Squibb, X4 Pharmaceuticals
2019 in GU Cancers

• Kidney Cancer
  – First-line IO/VEGF combinations
  – “Adjuvant” pazopanib after metastasectomy
• Bladder Cancer
  – Post-platinum, post-checkpoint options
• Prostate Cancer
  – The explosion of options for hormone sensitive metastatic prostate cancer
  – M0 CRPC

KEYNOTE-426 Study Design

Presented By Brian Rini at 2019 ASCO Annual Meeting
KEYNOTE-426: OS in the ITT Population

Pembrolizumab plus Axitinib for mRCC

- Other key findings from KEYNOTE-426:
  - PFS: HR 0.89 (P < 0.001)
  - ORR: 55.3% vs 35.7% (P < 0.001)
  - Benefit observed across subgroups, including the IMDC favorable, intermediate, and poor risk groups and in PD-L1-expressing and non-expressing tumors
  - Manageable safety profile

- Combination of pembrolizumab and axitinib approved by the FDA for first-line treatment of advanced RCC

IMDC Favorable Risk: OS, PFS, and ORR
So which 1L treatment to pick?

<table>
<thead>
<tr>
<th>IMDC risk group</th>
<th>Pembrolizumab + Axitinib vs Sunitinib</th>
<th>Avelumab + Axitinib vs Sunitinib</th>
<th>Avelumab + Nivolumab vs Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>31.2%</td>
<td>21.4%</td>
<td>23%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>56.2%</td>
<td>61.8%</td>
<td>61%</td>
</tr>
<tr>
<td>Poor</td>
<td>12.6%</td>
<td>16.2%</td>
<td>17%</td>
</tr>
<tr>
<td>PDL1 “positive”</td>
<td>60.5%</td>
<td>63.2%</td>
<td>63.2%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>0.53</td>
<td>0.78</td>
<td>0.68</td>
</tr>
<tr>
<td>HR for death P value</td>
<td>&lt;0.0001</td>
<td>0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>Combo therapy</td>
<td>Sunitinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.1</td>
<td>13.8</td>
<td>12.4</td>
</tr>
<tr>
<td></td>
<td>11.1</td>
<td>8.4</td>
<td>12.3</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>59.3%</td>
<td>51.4%</td>
<td>39.0%</td>
</tr>
<tr>
<td>CR (%)</td>
<td>5.8%</td>
<td>3.4%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Median f/u (mo)</td>
<td>12.8</td>
<td>11.6</td>
<td>25.2</td>
</tr>
</tbody>
</table>

Adapted from Escudier, NEJM 380;12 March 21, 2019

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E2810 STUDY SCHEMA

- RGC M1
  - No Prior Systemic Therapy
  - NACOB Obst: Staging: DFS > 1yr T > 1 site measured
  - 600 mg qd
  - 52 weeks Rx
  - CT Qtr
  - Placebo 100 mg qd
  - Endpoints
    - DFS
    - OS
    - AEs
    - QOL

Presented by Leonard Appelman, 2019 ASCO Annual Meeting
Pazopanib did not improve disease-free survival

Median follow-up 30 months

36 month DFS:
Pazopanib 26%
Placebo 22%

Overall survival by blinded treatment arm

Hazard Ratio for OS was 2.65 (1.02, 6.9) in favor of placebo (p=0.05)

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ENZAMET Treatment

**Primary endpoint: Overall survival**

![Graph showing overall survival comparison between Enzalutamide and NSAA](image)
Secondary Endpoints: Progression-free survival (PCWG2)

Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

Abstract 5006

First Results From TITAN: a Phase 3 Double-Blind, Randomized Study of Apalutamide Versus Placebo in Patients With Metastatic Castration-Sensitive Prostate Cancer Receiving Androgen Deprivation Therapy

Presented By Kim Chi at 2019 ASCO Annual Meeting

TITAN Study Design

Presented By Kim Chi at 2019 ASCO Annual Meeting
TITAN rPFS: Apalutamide Significantly Reduced Risk of Radiographic Progression or Death by 52%

Presented By Kim Chi at 2019 ASCO Annual Meeting

TITAN OS: Apalutamide Significantly Reduced the Risk of Death by 33%

Presented By Kim Chi at 2019 ASCO Annual Meeting

What to use in hormone sensitive disease?

<table>
<thead>
<tr>
<th></th>
<th>CHAARTED (docetaxel)</th>
<th>LATITUDE (abiraterone)</th>
<th>ENZAMET (enzalutamide)</th>
<th>TITAN (apalutamide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High volume disease, %</td>
<td>66%</td>
<td>100%</td>
<td>52%</td>
<td>62%</td>
</tr>
<tr>
<td>rPFS, HR (95%CI)</td>
<td>0.62 (0.5-0.8)</td>
<td>0.47 (0.4-0.6)</td>
<td>0.40 (0.33-0.49)</td>
<td>0.48 (0.39-0.60)</td>
</tr>
<tr>
<td>OS, low vol disease, HR (95%CI)</td>
<td>1.94 (1.3-1.6)</td>
<td>N/A</td>
<td>0.43 (0.28-0.72)</td>
<td>0.67 (0.34-1.32)</td>
</tr>
<tr>
<td>OS, HR (95%CI)</td>
<td>0.72 (0.6-0.9)</td>
<td>0.86 (0.6-0.8)</td>
<td>0.67 (0.52-0.86)</td>
<td>0.67 (0.51-0.89)</td>
</tr>
<tr>
<td>Discontinuation rate for AE</td>
<td>12%</td>
<td>6%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Grade &gt;=3% AE</td>
<td>29%</td>
<td>63% vs 48%</td>
<td>57% vs 43%</td>
<td>42% vs 41% (but rash)</td>
</tr>
<tr>
<td>QoL scores</td>
<td>Worse at 3mos, better at 12 mos</td>
<td>Better than placebo</td>
<td>Not reported</td>
<td>Not different than placebo</td>
</tr>
</tbody>
</table>

CHAARTED, Sweeney et al, NEJM 2015
Latitude, Fizazi et al, NEJM 2017
Enzalutamide, 2019 ASCO Annual Meeting
Titan, 2019 ASCO Annual Meeting
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### ARAMIS: Darolutamide in non-metastatic castration-resistant prostate cancer

- Androgen receptor inhibitor
- Structurally distinct from enza/apalutamide – less CNS toxicity since doesn’t cross BBB and fewer drug interactions (not a CYP-inhibitor)
- Taken with food

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**ARAMIS trial design**

What to use in M0 CRPC?

<table>
<thead>
<tr>
<th></th>
<th>SPARTAN (apalutamide)</th>
<th>PROSPER (enzalutamide)</th>
<th>ARAMIS (darolutamide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median pre-trial PSA/DT, mos</td>
<td>4.4</td>
<td>3.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Metastasis free survival, mos</td>
<td>40.5 (0.28-0.35)</td>
<td>36.6 (0.24-0.35)</td>
<td>40.4 (0.34-0.50)</td>
</tr>
<tr>
<td>Time to PSA progression, mos</td>
<td>NR</td>
<td>37.2 (0.05-0.08)</td>
<td>33.2 (0.11-0.16)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>HR 0.70 (0.47-1.04)</td>
<td>HR 0.80 (0.58-1.09)</td>
<td>HR 0.71 (0.50-0.99)</td>
</tr>
<tr>
<td>Discontinuation rate for AE</td>
<td>11%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Grade &gt;=3% AE</td>
<td>45% vs 34%</td>
<td>31% vs 23%</td>
<td>25% vs 20%</td>
</tr>
</tbody>
</table>

Note: Men with PSA DT of >10 months excluded from all these trials

SPARTAN, Smith et al, NEJM 2018
PROSPER, Hussain et al, NEJM 2018
ARAMIS, 2019 GU Cancers Symposium
### Table 3. Adverse Events of Interest in the Av interacted Population

<table>
<thead>
<tr>
<th>Event</th>
<th>Pembrolizumab Arm (N=278)</th>
<th>pembrolizumab Arm (N=290)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3, 4, or 5</td>
</tr>
<tr>
<td>Any event</td>
<td>80 (29.0)</td>
<td>28 (10.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (10.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>21 (7.6)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>18 (6.5)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>8 (2.9)</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>Cutis</td>
<td>7 (2.5)</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>5 (1.8)</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>Severe skin reaction</td>
<td>5 (1.8)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Hypophosphatidosis</td>
<td>3 (1.1)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>3 (1.1)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>No photos</td>
<td>2 (0.7)</td>
<td>2 (0.7)</td>
</tr>
</tbody>
</table>

### Mean Change from BL in QLQ-C30

- Lung Cancer Initiative of North Carolina
- A Network of Hope and Action
- Manuscript: ESMO 2018

### Pembrolizumab @ 5 years

- Hope, Summarized:
  - 5y OS 15.5% in previously treated
  - 5y OS 23.2% in 1L

- Top: Garon, ASCO 2019
- Bottom: Garon, Personal Comm.
Tumor shrinkage per BIRC

Deep responses observed in a majority of patients across both cohorts

Progression-free survival per BIRC

Median PFS was 3.02 months in Cohort 1 (1/2) and 9.97 months in Cohort 10 (1/2)

Safety summary

Key adverse events observed:
- Grade 3 or 4 events: none
- Grade 1 or 2 events:
  - Hematologic
  - Non-hematologic

* Censored events indicated by lower-right corner dot. Events removed in subsequent cycles.