Best of ASCO 2019: Lung and Genitourinary Cancers

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Assistant Professor
University of North Carolina at Chapel Hill
August 28, 2019
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
2019 in GU Cancers

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**KEYNOTE-426 Study Design**

**Key Eligibility Criteria**
- Newly diagnosed or recurrent stage IV clear-cell RCC
- No previous systemic treatment for advanced disease
- Karnofsky performance status ≥70
- Measurable disease per RECIST v1.1
- Provision of a tumor sample for biomarker assessment
- Adequate organ function

**Prognostic Factors**
- IMDC risk group (favorable vs intermediate vs poor)
- Geographic region (North America vs Western Europe vs ROW)

**End Points**
- Dual primary: OS and PFS (RECIST v1.1, BICR) in ITT
- Key secondary: ORR (RECIST v1.1, BICR) in ITT
- Other secondary: DOR (RECIST v1.1), PROs, safety

Pembrolizumab 200 mg IV Q3W for up to 35 cycles
- N = 432

Axitinib 5 mg orally twice daily
- N = 429

Sunitinib 50 mg orally once daily for first 4 wks of each 6-wk cycle

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

HR 0.53 (95% CI 0.38-0.74) 
P < 0.0001

**Pembrolizumab plus Axitinib for mRCC**

- Other key findings from KEYNOTE-426\(^1\)
  - PFS: HR 0.69 (P < 0.001)
  - ORR: 59.3% 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

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IMDC Favorable Risk: OS, PFS, and ORR

- OS
  - HR: 0.64 (95% CI: 0.24–1.68)
- PFS
  - HR: 0.81 (95% CI: 0.53–1.24)
- ORR
  - 66.7% vs 49.6%

IMDC Intermediate/Poor Risk: OS, PFS, and ORR

- OS
  - HR: 0.52 (95% CI: 0.37–0.74)
- PFS
  - HR: 0.67 (95% CI: 0.53–0.85)
- ORR
  - 55.8% vs 29.5%
JAVELIN Renal 101: study design

Key eligibility criteria:
- Treatment-naïve aRCC with a clear cell component
- ≥ 1 measurable lesion as defined by RECIST v1.1
- Tumor tissue available for PD-L1 staining
- ECOG PS 0 or 1

Primary objective:
- To demonstrate the superiority of avelumab + axitinib compared with sunitinib for either PFS or OS in patients with PD-L1+ tumors

JAVELIN Renal 101 efficacy summary

<table>
<thead>
<tr>
<th></th>
<th>PD-L1+ group (N = 566)</th>
<th>Overall population (N = 886)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avelumab + axitinib</td>
<td>Sunitinib</td>
</tr>
<tr>
<td></td>
<td>(N = 270)</td>
<td>(N = 290)</td>
</tr>
<tr>
<td>PFS per IRC, months</td>
<td>13.8</td>
<td>7.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>11.1, NE</td>
<td>5.7, 9.7</td>
</tr>
<tr>
<td>Benefit vs sunitinib (HR; P value)</td>
<td>0.61; P &lt; .0001</td>
<td>-</td>
</tr>
<tr>
<td>ORR per IRC, %</td>
<td>55.2</td>
<td>25.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>49.0, 61.2</td>
<td>20.6, 30.9</td>
</tr>
<tr>
<td>PFS per investigator assessment, months</td>
<td>12.5</td>
<td>8.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>9.8, NE</td>
<td>6.9, 8.5</td>
</tr>
<tr>
<td>Benefit vs sunitinib (HR; P value)</td>
<td>0.51; P &lt; .0001</td>
<td>-</td>
</tr>
<tr>
<td>ORR per investigator assessment, %</td>
<td>55.9</td>
<td>30.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>55.6, 67.7</td>
<td>24.5, 35.3</td>
</tr>
</tbody>
</table>

HRNC, independent review committee; NE, not estimable; ORR, objective response rate.

data cutoff date: June 30, 2018

Presented By Toni Choueiri at 2019 Genitourinary Cancers Symposium
So which 1L treatment to pick?

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab + Axitinib vs Sunitinib</th>
<th>Avelumab + Axitinib vs Sunitinib</th>
<th>Ipilimumab + Nivolumab vs Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMDC risk group</td>
<td></td>
<td></td>
<td></td>
</tr>
<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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR for death</td>
<td>0.53</td>
<td>0.78</td>
<td>0.68</td>
</tr>
<tr>
<td>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>15.1</td>
<td>13.8</td>
<td>12.4</td>
</tr>
<tr>
<td>Combo therapy</td>
<td>11.1</td>
<td>8.4</td>
<td>12.3</td>
</tr>
<tr>
<td>Sunitinib</td>
<td></td>
<td></td>
<td></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

2019 in GU Cancers

- Kidney Cancer
  - First-line IO/VEGF combinations
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- Prostate Cancer
  - The explosion of options for hormone sensitive metastatic prostate cancer
  - M0 CRPC
Pazopanib did not improve disease-free survival

Median follow-up
30 months

36 month DFS:
Pazopanib 26%
Placebo 22%

RCC M1
Resected
To NED
No Prior
Systemic
Therapy

RANDOMIZATION
Stratification:
DFI < or > 1yr
1 or > 1 site resected

Endpoints
DFS
OS
AEs
PROs
Lab Correl.

Pazopanib 800 mg qd
Placebo 800 mg qd

52 weeks Rx
CT q3mo

DFI: disease-free interval
DFS: disease-free survival
PRO: patient reported outcome
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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EV-201: Single-Arm, Pivotal Phase 2 Trial

- Cohort 1: Prior PD-1/L1 inhibitor and platinum-based therapy
  - Enrollment completed July 2018
  - N=120

- Cohort 2: Prior PD-1/L1 inhibitor, platinum naive, cisplatin ineligible
  - Enrollment ongoing

Enfortumab vedotin
- 1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle
- Primary endpoint: ORR per RECIST v1.1 as determined by IRC
- Select secondary endpoints: DOR, PFS, OS, Safety

Enfortumab Vedotin: Nectin-4 Targeted Therapy
Proposed Mechanism of Action
2019 in GU Cancers

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ENZAMET Treatment

STRATIFICATION
- Volume of metastases*: High vs Low
- Planned Early Docetaxel: Yes vs No
- ECOG PS: 0-1 vs 2
- Anti-resorptive therapy: Yes vs No
- Comorbidities: ACE-27**: 0-1 vs 2-3
- Study site

RANDOMIZE

ARM A: Testosterone Suppression + standard NSAA
Evaluate every 12 weeks

CRPC therapy at investigator’s discretion at progression

Follow for time to progression and overall survival

ARM B: Testosterone Suppression + Enzalutamide (160 mg/d)
Evaluate every 12 weeks

- Prior to randomization testosterone suppression up to 12 weeks and 2 cycles of docetaxel was allowed
- Intermittent ADT and cyproterone were not allowed
- NSAA: bicalutamide; nilutamide; flutamide
- *High volume: visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column)
- **Adult Co-morbidity Evaluation-27

Primary endpoint: Overall survival

Proportion alive at 36 months (95% CI)
- NSAA: 0.72 (0.68 to 0.76)
- Enzalutamide: 0.80 (0.75 to 0.83)

Hazard ratio: 0.67 (95% CI: 0.52 to 0.86)
Log-rank p=0.002
Secondary Endpoints: Progression-free survival (PCWG2)

Time to PSA rise, clinical progression or death

Time to clinical progression

(Imaging, symptoms, signs, change of therapy or death)

Hazard ratio = 0.39 (0.33 to 0.47)

Log-rank p < 0.001

Hazard ratio = 0.40 (0.33 to 0.48)

Log-rank p < 0.001

Number at risk

Number at risk

Enzalutamide

NSAA

Enzalutamide

NSAA

Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

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

Kim N. Chi,1 Neeraj Agarwal,2 Anders Bjartell,3 Byung Ha Chung,4 Andrea Juliana Pereira-de Sampaio Gomes,5 Robert W. Given,6 Álvaro Juárez Soto,7 Axel S. Merseburger,8 Mustafa Özgür,9,10 Hirotsugu Uemura,11 Dingwei Ye,12 Kris Deprince,13 Vahid Nains,12 Jinhui Li,13 Shinta Cheng,13 Margaret K. Yu,13 Ke Zhang,13 Julie S. Larsen,13 Sharon A. McCarthy,13 Simon Chowdhury14 on behalf of the TITAN Investigators

1BC Cancer and Vancouver Prostate Centre, Vancouver, BC, Canada; 2Thornton Cancer Institute, University of Utah, Salt Lake City, UT; 3Stockholm University, Stockholm, Sweden; 4University of Washington School of Medicine, Seattle, WA; 5Ohio State University, Columbus, OH; 6Johns Hopkins University, Baltimore, MD; 7Icahn School of Medicine at Mount Sinai, New York, NY; 8University of Bern, Bern, Switzerland; 9St. Jude Children's Research Hospital, Memphis, TN; 10Zhejiang University School of Medicine, Hangzhou, China; 11University of Tokyo, Tokyo, Japan; 12Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada; 13Eli Lilly; 14AstraZeneca

Presented By Kim Chi at 2019 ASCO Annual Meeting
**TITAN Study Design**

- "All-comer" patient population
- Key Eligibility Criteria:
  - Castration resistant
  - Distant metastatic disease by ≥ 1 lesion on bone scan
  - ECOG PS 0 or 1
- On-Study Requirement: Continuous ADT
- Permitted:
  - Prior docetaxel
  - ADT ≤ 6 mo for mSMPC or ≤ 3 yr for local disease
  - Local treatment completed ≥ 1 yr prior
- Stratifications:
  - Gleason score at diagnosis (≤ 7 vs > 7)
  - Region (NA and EU vs all other countries)
  - Prior docetaxel (yes vs no)

**Dual primary end points**
- OS
- rPFS

**Secondary end points**
- Time to cytotoxic chemotherapy
- Time to pain progression
- Time to chronic opioid use
- Time to skeletal-related event

**Exploratory end points**
- Time to PSA progression
- Second progression-free survival (PFS2)
- Time to symptomatic progression

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**TITAN rPFS: Apalutamide Significantly Reduced Risk of Radiographic Progression or Death by 52%**

- Blinded independent central imaging review confirmed investigator assessment of radiographic progression (concordance, 85%)

- **Results**: 22.1 vs 18.0-32.9 (HR 0.39-0.66, 0.0001)

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Presented By: Kim Chi at 2019 ASCO Annual Meeting
TITAN OS: Apalutamide Significantly Reduced the Risk of Death by 33%

What to use in hormone sensitive disease?

<table>
<thead>
<tr>
<th></th>
<th>CHAARTED (docetaxel)</th>
<th>LATTITUDE (abiraterone/P)</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>1.04 (0.7-1.6)</td>
<td>N/A</td>
<td>0.43 (0.26-0.72)</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>0.66 (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>29.6%</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
Enzamet, 2019 ASCO Annual Meeting
Titan, 2019 ASCO Annual Meeting
2019 in GU Cancers

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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
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 (HR 0.28 (0.23-0.35))</td>
<td>36.6 (HR 0.29 (0.24-0.35))</td>
<td>40.4 (HR 0.41 (0.34-0.50))</td>
</tr>
<tr>
<td>Time to PSA progression, mos</td>
<td>NR (HR 0.06 (0.05-0.08))</td>
<td>37.2 (HR 0.07 (0.05-0.08))</td>
<td>33.2 (HR 0.13 (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
KEYNOTE-042 Study Design: Pembrolizumab vs. chemotherapy

Key Eligibility Criteria
- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 tumor proportion score (TPS) ≥ 1% stage I or II
- No sensitizing EGFR or ALK alterations
- ECOG PS 0 or 1

Pembrolizumab
- 200 mg Q3W for up to 33 cycles

Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m² Q3W
- OR
Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m² Q3W
- for up to 6 cycles

No crossover allowed!

Stratification Factors
- Region (East Asia vs rest of the world)
- PD-L1 TPS (≥50% vs 1–49%)

KEYNOTE 42

Overall Survival: TPS ≥ 1%

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>0.81</td>
<td>0.0018</td>
</tr>
<tr>
<td>Chemo</td>
<td>(0.71-0.93)</td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI)
- 15.7 mo (13.9-19.7)
- 12.1 mo (11.3-13.3)

Data cutoff date: Feb 26, 2018

For Educational Use Only
Table 3. Adverse Events of interest in the As-Treated Population.

<table>
<thead>
<tr>
<th>Event</th>
<th>Pembrolizumab Combination (N = 278)</th>
<th>Placebo Combination (N = 280)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3, 4, or 5</td>
</tr>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td>number of patients (percent)</td>
</tr>
<tr>
<td>Any event</td>
<td>80 (28.8)</td>
<td>30 (10.8)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>22 (7.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>20 (7.2)</td>
<td>1 (0.4)</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>Colitis</td>
<td>7 (2.5)</td>
<td>6 (2.2)</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>Hypophysitis</td>
<td>3 (1.1)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>3 (1.1)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Nephritis</td>
<td>2 (0.7)</td>
<td>2 (0.7)</td>
</tr>
</tbody>
</table>

Mean Change from BL in QLQ-C30

![Graph showing mean change from baseline in QLQ-C30 scores over time.](image)
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.

Hope of Good Biomarkers, at last?

STK11/LKB1 genomic alterations are a mediator of the cold tumor immune microenvironment and a major driver of primary resistance to PD-1 axis blockade in non-squamous NSCLC

A. 30-59%  LKB1  LKB1 in NSCLC patients D. 35.7% 28.6% 7.4%
B.  UBER (stabilized) 5072 LKB1-BGC (UBER/14)
C.  UBER Stabilized WI

References:
- Staudt et al. ASCO Annual Meeting, 2015
- Staudt et al. J Cancer Res, 2018

Prepared by: [Your Name]
Presented at: [Meeting Name, Year]
Lack of benefit from addition of pembrolizumab to CP chemotherapy in STK11 and/or KEAP1-mutant non-squamous NSCLC

STK11MUT and/or KEAP1MUT

Progression-free survival (%)

Overall survival (%)

BLU-667 Demonstrates Substantial Antitumor Activity in RET Fusion+ Advanced NSCLC

BLU-667 Starting Dose 400 mg QD

Best Response

BLU-667: High kinome selectivity for RET®

BLU-667 vs. pharmacologically relevant kinases
- 50-fold more selective for RET than VEGFR2
- 20-fold more selective for RET than JAK1

Gainor,
ASCO
2019
AMG 510 is a First in Class KRAS\textsuperscript{G12C} Inhibitor

- KRAS is a GTP-binding protein that links receptor tyrosine kinase activation to intracellular signaling.\textsuperscript{1,2}
- Mutation of KRAS favors the GTP-bound active state and constitutive activation of downstream effects (differentiation, proliferation, survival).\textsuperscript{3}
- KRAS\textsuperscript{G12C} mutation has been identified as an oncogenic driver of tumorigenesis.\textsuperscript{4}
- KRAS\textsuperscript{G12C} mutation is found in approximately 13% of lung cancer, 3% of colorectal (CRC)\textsuperscript{5} and appendix cancer, and 1-3% of other solid tumors.\textsuperscript{6}
- Currently there is no approved therapy targeting this mutation.
- AMG 510 is a novel, first in class, small molecule that specifically and irreversibly inhibits KRAS\textsuperscript{G12C} by locking it in an inactive GDP-bound state.

---

**Patient Incidence of Treatment Related TEAE**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Gr 1 n</th>
<th>Gr 2 n</th>
<th>Adverse Event</th>
<th>Gr 1 n</th>
<th>Gr 2 n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td></td>
<td>Proteinuria</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2</td>
<td></td>
<td>Dry mouth</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td></td>
<td>Flatulence</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Elevated creatine phosphokinase</td>
<td>2</td>
<td></td>
<td>Vomiting</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Elevated or change in AST</td>
<td>1</td>
<td>1</td>
<td>Fatigue</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Elevated or change in ALT</td>
<td>1</td>
<td>1</td>
<td>WBC Decrease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated alkaline phosphatase</td>
<td>1</td>
<td>1</td>
<td>Pyrexia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cheilitis</td>
<td>1</td>
<td></td>
<td>Arthralgia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td></td>
<td></td>
<td>Presented By Marwan Fekrat 2019 ASCO Annual Meeting</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Grade 3 Adverse Event**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia\textsuperscript{a}</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea\textsuperscript{a}</td>
<td>1</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Patient had grade 2 anemia at baseline
\textsuperscript{b}Lasting 3 days
**TAK-788 Antitumor Activity in Patients With EGFR Exon 20 Insertions**

- Median (range) best percent change: -32.5% (-100%, 26.3%)
- Three patients were excluded from the waterfall plot: 1 patient had nonmeasurable baseline target lesions, and 2 patients had no follow-up scans.
- PD, progressive disease.

<table>
<thead>
<tr>
<th>Exon 20 Insertion Variant</th>
<th>No. of Patients</th>
<th>No. of Confirmed Responses</th>
<th>Confirmed ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>768 ASV</td>
<td>5</td>
<td>2</td>
<td>40%</td>
</tr>
<tr>
<td>773 SPM</td>
<td>4</td>
<td>3</td>
<td>75%</td>
</tr>
<tr>
<td>frame variant unknown</td>
<td>4</td>
<td>2</td>
<td>50%</td>
</tr>
<tr>
<td>Other Exon 20 Insertions</td>
<td>15</td>
<td>6</td>
<td>40%</td>
</tr>
</tbody>
</table>

**MET Del 14**

- **Background**
  - **MET** exon 14 skipping mutations (**METdel**14) are reported in 3–4% of patients with NSCLC and associated with both poor prognosis and poor responses to standard therapies including immunotherapy.
  - Capmatinib is a highly selective MET inhibitor with in vitro and in vivo activity seen against preclinical cancer models with MET activation.
  - Capmatinib is the most potent inhibitor against MET compared to other inhibitors.

<table>
<thead>
<tr>
<th>Caspematinib</th>
<th>Savolitinib</th>
<th>Tepotinib</th>
<th>Cabozantinib</th>
<th>Crizotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IC_{50} (nM)</strong></td>
<td>0.6</td>
<td>2.1</td>
<td>3.0</td>
<td>7.8</td>
</tr>
</tbody>
</table>

- Preliminary efficacy data from the phase 2, multi-cohort, multicenter GEOMETRY mono-1 study showed deep responses with capmatinib irrespective of the line of treatment as well as activity in the brain lesions in patients with **METdel**14 mutated advanced NSCLC.

---

**Tumor shrinkage per BIRC**

*Deep responses observed in a majority of patients across both cohorts*

- **Cohort 4 (2/3L)**
- **Cohort 5b (1L)**

*patients still on treatment*

**Progression-free survival per BIRC**

*Median PFS was 5.42 months in Cohort 4 (2/3L) and 9.69 months in Cohort 5b (1L)*

- **Cohort 4 (2/3L)**
  - Kaplan-Meier median (95% CI, months): 5.42 (4.62, 6.97)
  - Event-free rate at 12 months (95% CI): 25.4% (15.9, 34.9)

- **Cohort 5b (1L)**
  - Kaplan-Meier median (95% CI, months): 9.67 (5.85, 13.88)
  - Event-free rate at 12 months (95% CI): 49.7% (29.6, 67.6)

*Median PFS per investigator was 4.80 months (95% CI: 4.11, 7.75) in Cohort 4 and 11.14 months (95% CI: 5.52, 13.24) in Cohort 5b*
Capmatinib

Safety summary
Favorable and manageable safety profile

<table>
<thead>
<tr>
<th>Most common adverse events</th>
<th>Treatment-related (33%, all grades)</th>
<th>N = 334</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3/4</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>282 (84.4)</td>
<td>119 (35.4)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>139 (41.6)</td>
<td>25 (7.5)</td>
</tr>
<tr>
<td>Nausea*</td>
<td>111 (33.2)</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>Increased blood creatinine</td>
<td>65 (19.5)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting*</td>
<td>63 (18.9)</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>46 (13.8)</td>
<td>10 (3.0)</td>
</tr>
<tr>
<td>Decreased appetite*</td>
<td>42 (12.6)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38 (11.4)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

- Safety determined in the largest dataset of MET dysregulated NSCLC patients (N=334).
- Median treatment exposure time: 14.9 weeks
- Capmatinib was well tolerated with few Grade 3/4 events (only 15 patients (4.5%) had Grade 4 events)
- Dose adjustment due to treatment-related AE: 73 (21.9%)
- Discontinuation due to treatment-related AE: 37 (11.1%)
  - Most frequent (≥ 1%): peripheral edema (n=6, 1.8%), pneumonitis (n=5, 1.5%) and fatigue (n=5, 1.5%)
- Serious treatment-related AEs: 43 (12.9%)

Capmatinib administered in fasting conditions; food restriction removed in new cohorts 6 and 7
Capmatinib is known to inhibit creatinine transporters
MET mutated/amplified

Targeting ROS1 Fusion Positive Non-Small Cell Lung Cancer

- ROS1 rearrangement is an oncogenic driver in 1-2% of NSCLC
- Crizotinib is the only approved targeted therapy for patients with advanced ROS1+ NSCLC
- G2032R is the most common ROS1 resistance mutation after crizotinib treatment
- Repotrectinib is a next-generation ROS1/FGFR1-CAK inhibitor, designed to overcome TKI resistance mutations, especially solvent front ROS1 G2032R

Repotrectinib is a Small, Rigid Macrocycle Designed to Overcome the ROS1 G2032R Solvent Front Mutation

<table>
<thead>
<tr>
<th>CD74-ROS1 BA/F3 Cell Proliferation IC50 (nM)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WTN</td>
</tr>
<tr>
<td>G2032R</td>
</tr>
</tbody>
</table>

*Data based on evaluation of comparable proxy chemical/simulations purchase from commercial sources except repotrectinib
Repotrectinib in TKI Naïve ROS1+ NSCLC

LUNG CANCER INITIATIVE of North Carolina

Overall Response (N=11)  Intracranial Response (N=3)

Future Oncologists

LUNG CANCER INITIATIVE of North Carolina

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