Efficacy of atezolizumab in the treatment of solid tumors with high tumor mutational burden (TMB): A MyPathway study cohort

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I will discuss the following off-label use and/or investigational use in my presentation:

*Atezolizumab treatment of patients with non-indicated tumor types and high tumor mutational burden*
Background

- High tumor mutational burden (TMB-H) is associated with higher neoantigen expression, potentially rendering TMB-H tumors more responsive to cancer immunotherapy.\(^1\) Recent studies have indicated that TMB-H status is associated with improved response to immune checkpoint inhibitors, including those targeting the PD-1/PD-L1 pathway\(^1,2\)

- The anti–PD-1 antibody pembrolizumab was recently FDA-approved for patients with TMB ≥10 mut/Mb solid tumors based on the KEYNOTE-158 study.\(^3\) However, the optimal TMB cutoff to maximize efficacy in the pan-tumor population has not been clearly delineated

- Retrospective studies suggest that TMB ≥16 mut/Mb may act as a threshold for enrichment of response to atezolizumab, an anti–PD-L1 antibody that enhances tumor-specific T-cell responses, in various tumor types\(^4–6\)

- We present a cohort analysis of atezolizumab treatment in patients with advanced solid tumors characterized by TMB ≥16 mut/Mb or TMB ≥10 and <16 mut/Mb from MyPathway (NCT02091141), an open-label, multicenter, non-randomized, multiple-basket phase 2a study assessing activity of FDA-approved therapies in non-indicated tumors with targetable alterations

MyPathway Atezolizumab Arm Study Design

Eligible patients had advanced solid tumors with TMB ≥10 mut/Mb by any CLIA assay

Patients without FoundationOne CDx (F1CDx)\(^a\) TMB data provided archival or fresh tumor tissue for central F1CDx retesting after enrollment
- Aged ≥18 years
- No satisfactory alternative treatment options
- Pan-tumor indications

Key exclusion criteria
- Prior therapy with CIT (PD-1, PD-L1/L2, CTLA-4)

Total patients: N=121

Primary endpoint
- IRF-assessed\(^b\) ORR by RECIST 1.1 in patients with F1CDx TMB ≥16 mut/Mb

Secondary endpoints
- DOR, DCR, PFS, OS, safety

Exploratory endpoints
- Clinical outcomes in other TMB testing groups: F1CDx TMB ≥10 and <16 mut/Mb, TMB by any CLIA assay, and TMB by blood
- Biomarker analysis

Atezolizumab 1200 mg q3w
Treatment until loss of clinical benefit

Study enrollment completed: August 2018–July 2020
Data cut-off date: January 19, 2021

\(^a\)F1CDx TMB testing was used for the primary analysis to limit variability in TMB measurements between different gene panels. \(^b\)Patients were assessed by the investigator until the last patient ended treatment, at which point scans would be submitted for IRF assessments. CIT, cancer immunotherapy; CLIA, Clinical Laboratory Improvement Amendments; CTLA, cytotoxic T-lymphocyte-associated protein; DCR, disease control rate; DOR, duration of response; F1CDx, FoundationOne Companion Diagnostic; IRF, independent review facility; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.
All patients enrolled with TMB $\geq 10$ mut/Mb by any CLIA assay (N=121)

- Any CLIA testing TMB $\geq 16$ mut/Mb
  - n=56

- Any CLIA testing TMB $\geq 10$ and <16 mut/Mb
  - n=65
TMB Local and Central Testing

All efficacy-evaluable patients with TMB $\geq 10$ mut/Mb by any CLIA assay (n=120)

One patient with TMB $\geq 10$ and $<16$ mut/Mb did not have a tumor evaluation reported by the data cut-off, and is not included in the efficacy population.
TMB Local and Central Testing

All efficacy-evaluable patients with F1CDx TMB ≥10 mut/Mb (n=90)

Patients without F1CDx TMB testing at enrollment submitted tissue for retrospective F1CDx re-testing

Any CLIA TMB ≥16 mut/Mb, n=56

Any CLIA TMB ≥10 and <16 mut/Mb, n=64

F1CDx testing
TMB ≥16 mut/Mb
n=42
Primary efficacy population

F1CDx testing
TMB ≥10 and <16 mut/Mb
n=48
All efficacy-evaluable patients with F1CDx TMB ≥10 mut/Mb (n=90)

Patients without F1CDx TMB testing at enrollment submitted tissue for retrospective F1CDx re-testing

- Any CLIA TMB ≥16 mut/Mb, n=56
- Any CLIA TMB ≥10 and <16 mut/Mb, n=64

F1CDx re-testing
- TMB <10 mut/Mb, n=13
- Failed F1CDx or insufficient tissue for re-testing, n=7

Primary efficacy population
- F1CDx testing TMB ≥16 mut/Mb, n=42
- Failed F1CDx or insufficient tissue for re-testing, n=6

F1CDx testing
- TMB ≥10 and <16 mut/Mb, n=48
Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All N=121</th>
<th>F1CDx TMB ≥16 mut/Mb n=42</th>
<th>F1CDx TMB ≥10 and &lt;16 mut/Mb n=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>67.0 (25–90)</td>
<td>67.0 (25–90)</td>
<td>66.0 (44–85)</td>
</tr>
<tr>
<td>Number of prior regimens, median (range)</td>
<td>3 (0–14)</td>
<td>2 (0–13)</td>
<td>3 (0–14)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>74 (61.2)</td>
<td>19 (45.2)</td>
<td>35 (71.4)</td>
</tr>
<tr>
<td>Male</td>
<td>47 (38.8)</td>
<td>23 (54.8)</td>
<td>14 (28.6)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>91 (75.2)</td>
<td>37 (88.1)</td>
<td>34 (69.4)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>13 (10.7)</td>
<td>3 (7.1)</td>
<td>7 (14.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>8 (6.6)</td>
<td>0</td>
<td>4 (8.2)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9 (7.4)</td>
<td>2 (4.8)</td>
<td>4 (8.2)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td>n=120</td>
<td>n=42</td>
<td>n=49</td>
</tr>
<tr>
<td>0</td>
<td>38 (31.7)</td>
<td>11 (26.2)</td>
<td>17 (34.7)</td>
</tr>
<tr>
<td>1</td>
<td>82 (68.3)</td>
<td>31 (73.8)</td>
<td>32 (65.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup>“Other” includes American Indian/Alaska Native and Other patients. ECOG PS, Eastern Cooperative Oncology Group performance status.
<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>F1CDx TMB ( \geq 16 \text{ mut/Mb} ) n=42</th>
<th>F1CDx TMB ( \geq 10 \text{ and } &lt;16 \text{ mut/Mb} ) n=48</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed objective response rate</strong>, ( n ) (%), 95% CI</td>
<td>16 (38.1) 23.6–54.4 3 CR(^b), 13 PR</td>
<td>1 (2.1) 0.1–11.1 1 PR</td>
</tr>
<tr>
<td><strong>Disease control rate</strong>, ( n ) (%), 95% CI</td>
<td>26 (61.9) 45.6–76.4</td>
<td>11 (22.9) 12.0–37.3</td>
</tr>
<tr>
<td><strong>Duration of confirmed response, median months</strong>, 95% CI</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td><strong>Progression-free survival, median months</strong>, 95% CI</td>
<td>5.7 2.7–8.5</td>
<td>1.8 1.4–2.6</td>
</tr>
<tr>
<td><strong>Overall survival, median months</strong>, 95% CI</td>
<td>19.8 11.9–NE</td>
<td>11.4 5.3–15.7</td>
</tr>
</tbody>
</table>

\(^a\)Includes patients with confirmed CR or PR. \(^b\)Patients with CR had biliary, colon, and head and neck cancers. \(^c\)Includes patients with CR, PR, or stable disease \( >4 \) months. CI, confidence interval; CR, complete response; NE, not evaluable; PR, partial response.
Median follow-up was 11.7 months in patients with F1CDx TMB ≥16 mut/Mb and 7.5 months in patients with F1CDx TMB ≥10 and <16 mut/Mb.
Exploratory Clinical Outcomes

- In patients with a local non-F1CDx TMB assay and subsequent central F1CDx TMB testing, overall agreement for TMB subgroups (<16 mut/Mb or ≥16 mut/Mb) was 74.4% (29/39 patients)

- No confirmed responses were observed among:
  - Patients with TMB <10 mut/Mb by F1CDx (n=17)
  - Patients with TMB ≥16 mut/Mb by any CLIA assay and TMB <16 mut/Mb by F1CDx (n=9)

- ORR was higher in patients with TMB ≥16 mut/Mb by any CLIA test than those with TMB ≥10 and <16 mut/Mb

<table>
<thead>
<tr>
<th></th>
<th>Any CLIA test</th>
<th>Any CLIA test</th>
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<tbody>
<tr>
<td></td>
<td>≥16 mut/Mb</td>
<td>≥10 and &lt;16 mut/Mb</td>
</tr>
<tr>
<td>Confirmed objective response rate, n (%)</td>
<td>16 (28.6)</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>95% CI</td>
<td>17.3–42.2</td>
<td>0.4–10.8</td>
</tr>
<tr>
<td></td>
<td>3 CR, 13 PR</td>
<td>2 PR</td>
</tr>
</tbody>
</table>
### Association of ORR with F1CDx TMB Cutoff in MyPathway

- A statistically significant association of ORR with F1CDx TMB cutoff was observed (log odds ratio of response for an increase of 1 mut/Mb to the cutoff: slope 0.119, 95% CI 0.078–0.160)

<table>
<thead>
<tr>
<th>F1CDx TMB cutoff mut/Mb</th>
<th>n/n</th>
<th>ORR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>17/90</td>
<td>18.9 (11.4–28.5)</td>
</tr>
<tr>
<td>13</td>
<td>16/56</td>
<td>28.6 (17.3–42.2)</td>
</tr>
<tr>
<td>16</td>
<td>16/42</td>
<td>38.1 (23.6–54.4)</td>
</tr>
<tr>
<td>19</td>
<td>15/34</td>
<td>44.1 (27.2–62.1)</td>
</tr>
<tr>
<td>22</td>
<td>15/29</td>
<td>51.7 (32.5–70.6)</td>
</tr>
<tr>
<td>25</td>
<td>15/25</td>
<td>60.0 (38.7–78.9)</td>
</tr>
<tr>
<td>28</td>
<td>15/24</td>
<td>62.5 (40.6–81.2)</td>
</tr>
<tr>
<td>31</td>
<td>12/20</td>
<td>60.0 (36.1–80.9)</td>
</tr>
<tr>
<td>34</td>
<td>11/19</td>
<td>57.9 (33.5–79.7)</td>
</tr>
<tr>
<td>37</td>
<td>10/16</td>
<td>62.5 (35.4–84.8)</td>
</tr>
<tr>
<td>40</td>
<td>10/15</td>
<td>66.7 (38.4–88.2)</td>
</tr>
</tbody>
</table>

Statistical analysis was based on a marginal structural model (MSM) estimate for ORR at various F1CDx TMB cut-offs. Red line represents the MSM estimate; ie, the estimated logistic linear trend. Grey boundaries represent 95% CI.
Clinical Outcomes by MSI Status

One patient with F1CDx TMB ≥10 and <16 mut/Mb + MSI-H and a PR is not shown. Whiskers represent 95% CI.

- One patient had a CR (colon cancer).
- MSI-NH includes microsatellite stable, low, or intermediate tumors.
- Two patients had a CR (biliary and head and neck cancer). MSI-H, high microsatellite instability; MSI-NH, microsatellite instability not high.

### Clinical Outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1CDx TMB ≥16 mut/Mb + MSI-H</td>
<td>54.5</td>
<td>72.7</td>
</tr>
<tr>
<td>F1CDx TMB ≥16 mut/Mb + MSI-NH</td>
<td>30.0</td>
<td>56.7</td>
</tr>
<tr>
<td>F1CDx TMB ≥10 and &lt;16 mut/Mb + MSI-NH</td>
<td>3.3</td>
<td>22.2</td>
</tr>
</tbody>
</table>

One patient with F1CDx TMB ≥10 and <16 mut/Mb + MSI-H and a PR is not shown. Whiskers represent 95% CI.

- One patient had a CR (colon cancer).
- MSI-NH includes microsatellite stable, low, or intermediate tumors.
- Two patients had a CR (biliary and head and neck cancer). MSI-H, high microsatellite instability; MSI-NH, microsatellite instability not high.

Access slides at: https://bit.ly/30xu8se
Objective Response Rate by PD-L1 Status in Patients With F1CDx TMB ≥16 mut/Mb

The PD-L1 subgroup analysis was post-hoc and exploratory. Whiskers represent 95% CI.

- a n=5 responders (all CRC).
- b n=2 responders (prostate and adrenocortical).
- c n=3 responders (cervical, head and neck, and biliary tract).
- d n=1 responder (CRC).
- e n=5 responders (CRC [n=3], prostate, and adrenocortical).
- f n=2 responders (head and neck, and biliary tract).
- g Three patients had a TPS score, but did not have a CPS score.

CPS, Combined Positive Score; CRC, colorectal cancer; TPS, Tumor Proportion Score.
Tumor Groups in Efficacy-Evaluable Patients With F1CDx TMB Testing

In patients with TMB ≥16 mut/Mb by F1CDx:

- Among 10 patients with colorectal cancer, ORR was 70.0% (7/10, 95% CI 34.8–93.3)
  - Three of seven responders had tumors characterized as MSI-NH
- In two patients with biliary tract cancer, one with an MSI-NH tumor had a CR
- Responses were observed in patients with MSI-NH breast cancer (1/7), CUP (2/3), head and neck cancer (1/3), and adrenocortical cancer (1/1)
- Responses were also observed in patients with MSI-H tumors in the pancreas (1/1), cervix (1/1), and prostate (1/2)

CUP, carcinoma of unknown primary.
Among all patients (N=121), treatment-emergent adverse events (TEAEs) led to:
  • Withdrawal from study drug: 5.0% (6/121)
  • Study drug reduction: 0
  • Study drug interruption: 19.0% (23/121)
  • Death: 4.1% (5/121; none related to study drug)

TEAEs were reported in 90.9% (110/121) of patients
  • Serious TEAEs: 33.1% (40/121)
  • Grade 3–5 TEAEs: 47.9% (58/121)

Treatment-related TEAEs were reported in 56.2% (68/121) of patients
  • Serious related TEAEs: 6.6% (8/121)
  • Grade 3–4 related TEAEs: 12.4% (15/121)

TEAE, treatment-emergent adverse event.
### Most common treatment-related TEAEs

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Any grade related TEAE, %</th>
<th>Grade 3–4 related TEAE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Analysis in safety population (N=121).

*Includes treatment-related TEAEs in ≥5% of the population (any grade) and ≥2% of the population (grade 3–4).*
Conclusions

- Atezolizumab monotherapy conferred a confirmed ORR of 38.1% in patients with F1CDx TMB ≥16 mut/Mb (n=42)
  - Responses were observed across a broad spectrum of advanced solid tumor types

- Limited efficacy was observed in patients with F1CDx TMB ≥10 and <16 mut/Mb (n=48), with a confirmed ORR of 2.1%

- Meaningful clinical activity was observed in patients with F1CDx TMB ≥16 mut/Mb tumors regardless of MSI status, suggesting that there are genomic mechanisms other than microsatellite instability that drive response to atezolizumab in patients with TMB-H tumors

- Significant enrichment for response to atezolizumab was observed with higher F1CDx TMB cutoffs
Acknowledgments

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