Comparison of digital vs manual PD-L1 tumour cell scoring on SP263-stained whole imaging slides from IMpower110

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Background

• Pathologist-assessed PD-L1 expression has been shown to be predictive of response to anti–PD-L1/PD-1 therapies but the ability to improve such assays may be fundamentally limited by known inter-observer variability\(^1\)

• The use of artificial intelligence (AI) tools and digital pathology may address this challenge\(^1\)

• We applied a clone-agnostic model for AI-based measurement of PD-L1 (AIM-PD-L1; PathAI, Inc)\(^2\) for exploratory analysis in the Phase III IMpower110 study (NCT02409342)

• Digital and manual SP263 PD-L1 tumour cell (TC) scoring was compared to evaluate digital pathology as an unbiased, automated method to identify patients with NSCLC benefiting from atezolizumab

• Human interpretable features (HIFs) of the tumour microenvironment (TME) were also quantified from SP263-stained slides and evaluated as novel candidate biomarkers for survival benefit

IMpower110 study design

- IMpower110 was a randomised, open-label, Phase III study of first-line atezolizumab vs chemotherapy in PD-L1+ (PD-L1 ≥1% on TC or tumour-infiltrating immune cell [IC] by SP142) metastatic NSCLC.¹

- Atezolizumab showed statistically significant OS improvement vs chemotherapy in the high PD-L1 expression (PD-L1 ≥50% on TC or ≥10% on IC) wild-type population,¹ leading to approval of atezolizumab monotherapy for patients with metastatic NSCLC whose tumours have high PD-L1 expression with no EGFR or ALK alterations.

- The dataset for AI-based pathology analysis included 509 slides: 350 non-squamous, 123 squamous and 36 of indeterminate histology.

- Primary endpoint: OS in the wild-type population.

- Key secondary endpoints: investigator-assessed PFS, ORR and DOR (per RECIST v1.1)

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IC, tumour-infiltrating immune cells; nsq, non-squamous; PD, progressive disease; q3w, every 3 weeks; R, randomised; sq, squamous. ¹ VENTANA SP142 assay. ² TC1/2/3 and any IC vs TCO and IC1/2/3. ³ Cisplatin 75 mg/m² or carboplatin area under the curve (AUC) 6 + pemetrexed 500 mg/m² q3w. ⁴ Cisplatin 75 mg/m² + gemcitabine 1250 mg/m² or carboplatin AUC 5 + gemcitabine 1000 mg/m² q3w. ⁵ Excludes patients with EGFR+ and/or ALK+ NSCLC. ¹ Herbst RS, et al. N Engl J Med 2020;383(14):1328-1339.
• AIM PD-L1 is a clone-agnostic machine learning model for the quantification of PD-L1 in NSCLC\(^1\)
• AIM-PD-L1 was used on SP263-stained slides for continuous digital PD-L1 scoring and survival analysis
• Survival analysis was performed for PD-L1+ populations, comparing patients treated with atezolizumab vs chemotherapy

121 of 122 patients who were manually scored as PD-L1− (<1%) on TC by SP263 were PD-L1+ (≥1%) only on IC by SP142.

Concordance between manual and digital scoring was high at the 50% cutoff (OPA: 90%) but suboptimal at the 1% cutoff (OPA: 78%).

Digital scoring identified 114 (22%) and 22 (4%) additional patients with PD-L1+ NSCLC at the TC ≥1% and ≥50% cutoffs, respectively, compared with manual scoring.

Pathologist review of discrepant cases noted various causes of disagreement: model overcalled positive cancer cells with cytoplasmic but incomplete membrane staining, model confusion with positive immune cells and cases where manual scores were incorrect.

Presented by: Roy S. Herbst
IMpower110 Manual vs Digital PD-L1 Scoring

Digital

<table>
<thead>
<tr>
<th></th>
<th>&lt;1%</th>
<th>≥1%</th>
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<tbody>
<tr>
<td>Manual</td>
<td>8 (2%)</td>
<td>114 (22%)</td>
</tr>
<tr>
<td>≥1%</td>
<td>0 (0%)</td>
<td>387 (76%)</td>
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</table>

Manual

<table>
<thead>
<tr>
<th></th>
<th>&lt;50%</th>
<th>≥50%</th>
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<tbody>
<tr>
<td>Manual</td>
<td>209 (41%)</td>
<td>36 (7%)</td>
</tr>
<tr>
<td>≥50%</td>
<td>14 (3%)</td>
<td>250 (49%)</td>
</tr>
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PPA: 100%
NPA: 7%
OPA: 78%

PPA: 95%
NPA: 85%
OPA: 90%

CCC, concordance correlation coefficient; NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agreement; r, Pearson coefficient.

36 patients that are digital high positive/manual negative – 14 patients that are digital negative high/manual high positive.
Despite differences in PD-L1+ prevalence, OS and PFS were similar for manual and digital scoring at both cutoffs\(^a\)

<table>
<thead>
<tr>
<th>TC (\geq 1%)</th>
<th>Total, n (%)</th>
<th>Atezolizumab, n</th>
<th>Chemotherapy, n</th>
<th>HR (95% CI)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual OS</td>
<td>387 (76)</td>
<td>205</td>
<td>182</td>
<td>0.84 (0.64, 1.08)</td>
<td>0.18</td>
</tr>
<tr>
<td>Digital OS</td>
<td>501 (98)</td>
<td>260</td>
<td>241</td>
<td>0.85 (0.68, 1.05)</td>
<td>0.16</td>
</tr>
<tr>
<td>Manual PFS</td>
<td>387 (76)</td>
<td>205</td>
<td>182</td>
<td>0.72 (0.57, 0.9)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Digital PFS</td>
<td>501 (98)</td>
<td>260</td>
<td>241</td>
<td>0.74 (0.61, 0.88)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
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<tr>
<th>TC (\geq 50%)</th>
<th>Total, n (%)</th>
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<th>HR (95% CI)</th>
<th>(P) value</th>
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</thead>
<tbody>
<tr>
<td>Manual OS</td>
<td>264 (52)</td>
<td>144</td>
<td>120</td>
<td>0.83 (0.62, 1.13)</td>
<td>0.24</td>
</tr>
<tr>
<td>Digital OS</td>
<td>286 (56)</td>
<td>158</td>
<td>128</td>
<td>0.83 (0.62, 1.11)</td>
<td>0.2</td>
</tr>
<tr>
<td>Manual PFS</td>
<td>264 (52)</td>
<td>144</td>
<td>120</td>
<td>0.66 (0.5, 0.85)</td>
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<tr>
<td>Digital PFS</td>
<td>286 (56)</td>
<td>158</td>
<td>128</td>
<td>0.68 (0.53, 0.87)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

\(^a\) All biomarker-evaluable cases. There was an increase in prevalence by 114 (22%) and 22 (4%) patients at the TC \(\geq 1\%\) and TC \(\geq 50\%\) cutoffs by digital and manual scoring, respectively.
Survival benefit for atezolizumab vs chemotherapy in patients with PD-L1+ (TC ≥1%) tumours by digital scoring only (TC <1% by manual scoring)

**PFS in PD-L1 TC ≥1% by digital scoring only**

- PFS HR, 0.79 (0.53, 1.18)
- P = 0.24

**OS in PD-L1 TC ≥1% by digital scoring only**

- OS HR, 0.88 (0.54, 1.41)
- P = 0.58

**No. at risk**

- Atezolizumab: 55, 22, 8, 2, 1
- Chemotherapy: 59, 14, 3, 0, 0

**No. at risk**

- Atezolizumab: 55, 40, 26, 7, 2
- Chemotherapy: 59, 42, 24, 4, 0
AI-based quantification of the TME and PD-L1 expression enables biomarker exploration beyond TC score

Exploratory analysis for candidate biomarkers was conducted by searching for features associated with survival.

One feature was identified as nominally significant ($P=0.03$, FDR=0.21; 78 comparisons) with survival benefit for squamous samples:

- Density of PD-L1+ TILs for patients with squamous tumours in the cancer epithelium.

FDR, false discovery rate; TIL, tumour-infiltrating lymphocyte. Figure: Baxi V, et al. SITC 2019. Oral O65.
PFS by histology in patients with high (above median) PD-L1+ TILs in cancer epithelium

- TILs in the TME may contribute to differences in survival benefit in histology subtypes
- Although improved PFS was also observed in patients with non-squamous disease and a high density of PD-L1+ TILs in the cancer epithelium, benefit was greater in the squamous population
Conclusions

- In the exploratory analysis comparing manual and digital PD-L1 scoring in SP263-stained slides from IMpower110, AIM-PD-L1 scoring found 22% and 4% greater PD-L1+ prevalence at TC ≥1% and ≥50%, respectively, relative to manual scoring.

- AIM-PD-L1 scoring was as effective as manual scoring at predicting survival outcomes.

- Based on HIF analysis, improved PFS was observed in patients with a high density of PD-L1+ TILs in the cancer epithelium, with higher benefit in those with squamous vs non-squamous histology.

- The results of this analysis further support the potential for digital pathology to optimise PD-L1 scoring for clinical trial conduct.
Acknowledgements

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