Abstract CT112

Artificial Intelligence–Powered and Manual Assessment of PD-L1 Are Comparable in Predicting Response to Neoadjuvant Atezolizumab in Patients With Resectable Non-Squamous, Non-Small Cell Lung Cancer

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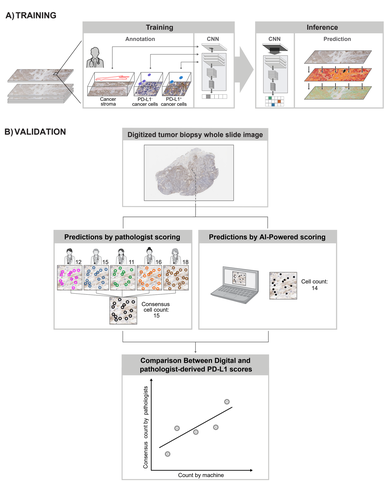
BACKGROUND

- Immunohistochemistry (IHC) evaluation of programmed death-ligand 1 (PD-L1) expression is a reliable predictor of the efficacy of anti–PD-L1/programmed cell death protein 1 (PD-1) cancer immunotherapy in patients with resected and metastatic non-small cell lung cancer (NSCLC)[1,2]
- Exploratory analyses in patients with metastatic NSCLC suggest a potentially limited enrichment for the efficacy of anti–PD-L1/PD-1 therapy in patients with high PD-L1 expression and squamous histology.[2] Data in early NSCLC are limited to date[3]
- Preoperative treatment with atezolizumab (anti–PD-L1 antibody) in patients with untreated early-stage resectable NSCLC resulted in a 20% major pathologic response (MPR) rate in the LCMC3 Phase II study[4]
- Computer vision can be used on pathology slides to identify biological entities, including cell types, tissue types, and biomarker expression, and to compute slide-level scores or digitally quantify pathology features
- Using manual and digital PD-L1 scoring methods, we assessed PD-L1 expression in tumor cells as a potential predictor of pathologic response to neoadjuvant atezolizumab treatment in patients with non-squamous and squamous NSCLC tumors

METHODS

- Clinical data were obtained from 181 patients with NSCLC who participated in LCMC3. The primary efficacy population was defined as patients with no *EGFR* or *ALK* genetic alterations and who had surgery (n=143). Overall survival (OS) and disease-free survival (DFS) data were available for all 143 patients
- PD-L1 status on pre-treatment tissue biopsy samples that fulfilled assay requirements was determined centrally using IHC (tumor proportion score (TPS), anti–PD-L1 22C3 antibody, Dako). Local results were used if central results were not available. Categorical results were associated with MPR and stratified by non-squamous or squamous histology
- To produce a continuous PD-L1 TPS, an automated digital pathology workflow was developed
- Convolutional neural networks, developed using pathologist annotations, were trained to detect tumor and stromal regions and distinguish PD-L1–positive or –negative cells within the tumor microenvironment in PD-L1–stained NSCLC tissue samples
- Cell type predictions were used to compute the digital PD-L1 TPS, defined as the percentage of all cancer epithelial cells that were PD-L1 positive[5] (**Figure 1**)
- Samples with available manual and digital PD-L1 scores in LCMC3 were then used to assess the role of PD-L1 expression in predicting MPR by histological subtype

Figure 1. Developing machine learning algorithms for digital assessment of cell type and PD-L1 positivity, which requires training (A) and validation (B)[5]



AI, artificial intelligence; CNN, convolutional neural networks.

RESULTS

- At data cutoff (October 15, 2021), 108 of 143 patients had manual and digital PD-L1 scores and were included in the TPS-evaluable (TPSE) population (**Table 1**).
- The baseline characteristics were similar between all patients and the TPSE

Table 1. Baseline demographics and characteristics

Characteristic		All patients (N=181)	TPSE (n=108)	Non-squamous TPSE (n=66)	Squamous TPSE (n=42)
Age, median (range), y		65 (37-83)	65 (39-83)	65 (39-82)	67 (42-83)
Male, n (%)		88 (49)	59 (55)	31 (47)	28 (67)
Race, n (%)	Asian	9 (5)	4 (4)	3 (5)	1 (2)
	Black	13 (7)	3 (3)	3 (5)	0
	White	145 (81)	92 (86)	55 (83)	37 (90)
	Unknown	12 (7)	8 (8)	5 (8)	3 (8)
Histology, n (%)	Non-squamous	112 (62)	66 (61)	66 (100)	0
	Squamous	69 (38)	42 (39)	0	42 (100)
Stage, n (%)	IB	18 (10)	10 (9)	5 (8)	5 (12)
	IIA	16 (9)	9 (8)	4 (6)	5 (12)
	IIB	55 (30)	36 (33)	19 (29)	17 (41)
	IIIA	70 (39)	42 (39)	33 (50)	9 (21)
	IIIB	22 (12)	11 (10)	5 (8)	6 (14)
Tobacco use, n (%)	Current	35 (19)	19 (18)	12 (18)	7 (17)
	Previous	128 (71)	81 (75)	49 (74)	32 (76)
	Never	18 (10)	8 (7)	5 (8)	3 (7)
Node status, n (%)	Positive	106 (59)	64 (59)	43 (65)	21 (50)
	Negative	75 (41)	44 (41)	23 (35)	21 (50)
***EGFR* mutation, n (%)**	Y	11 (6)	0	0	0
	N	150 (83)	104 (96)	66 (100)	38 (91)
	Unknown	20 (11)	4 (4)	0	4 (10)
***ALK* status, n (%)**	Y	6 (3)	0	0	0
	N	154 (85)	100 (93)	62 (94)	38 (91)
	Unknown	21 (12)	8 (7)	4 (6)	4 (10)
PD-L1 expression, n (%)	TPS <1	69 (38)	51 (47)	29 (44)	22 (52)
	TPS 1-50	30 (17)	16 (15)	11 (17)	5 (12)
	TPS ≥50	52 (29)	41 (38)	26 (39)	15 (36)
	Unknown	30 (17)	0	0	0
ECOG PS, n (%)	0	104 (57)	62 (57)	41 (62)	21 (50)
	1	77 (43)	46 (43)	25 (38)	21 (50)
Pack years, mean (SD)		30.33 (30.17)	28.3 (23.5)	23.6 (20.8)	35.5 (25.8)

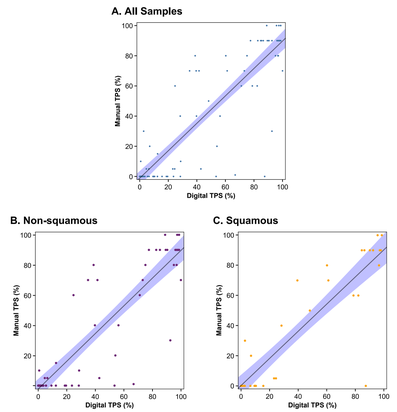
- 41/108 (38%) had tumors that were TPS ≥50% (non-squamous, 26/66 [39%]; squamous, 15/42 [36%]), which was associated with MPR in non-squamous histology (odds ratio [OR], 28.6; *P*<0.001; Fisher exact test) but not squamous histology (OR, 1.27; *P*=1.0) (**Table 2**)
- In TPSE, no significant difference in MPR rates was seen between histological subtypes

Table 2. MPR rate according to histology and PD-L1 status

Histology	PD-L1 expression	n	MPR, n (%)	Exact test OR (*P*)
Non-squamous n=66	TPS ≥50%	26	11 (42)	**28.6 (<0.001)**
	TPS <50%	40	1 (2)	
	Any	66	12 (24)	1.41 (0.62)
Squamous n=42	Any	42	10 (18)	
	TPS ≥50	15	4 (27)	1.27 (1.0)
	TPS <50%	27	6 (22)	

- Digital continuous PD-L1 scores (median, 5; range, 0-100) were well correlated with manual PD-L1 scores (median, 23.4; range, 0-100): n=108, Pearson r=0.90, *P*<0.001. Correlation was also high for non-squamous (n=66, Pearson r=0.90, *P*<0.001) and squamous (n=42, Pearson r=0.90, *P*<0.001) histology (**Figure 2**)

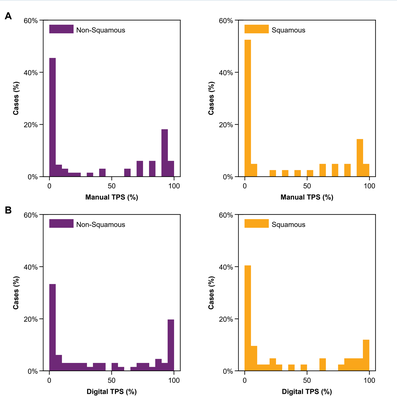
Figure 2. Correlation of manual vs digital PD-L1 TPS score in all-histology (A), non-squamous (B) and squamous (C) tissues



Diagonal black lines in each graph indicate ordinary least squares regression, with the 95% CI shown in the blue-shaded region.

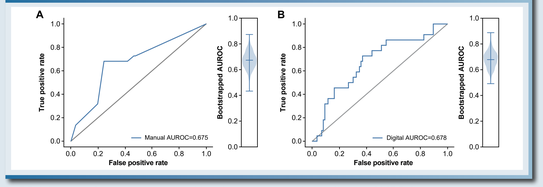
- PD-L1 scores were distributed widely for both histologies (**Figure 3**)
  - Non-squamous
    - Manual: range, 0-100; median, 7.5
    - Digital: range, 0-100; median, 28.6
  - Squamous
    - Manual: range, 0-100; median, 0.0
    - Digital: range, 0-98.7; median, 10.1

Figure 3. Manual (A) and digital (B) PD-L1 score distribution in non-squamous and squamous tissue



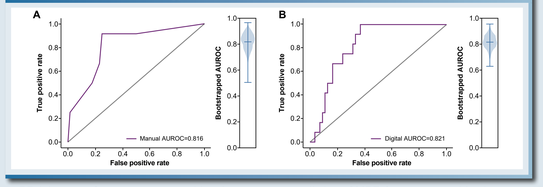
- The continuous manual and digital PD-L1 TPS determined for pre-treatment biopsies (n=108) were moderately predictive of MPR (manual: area under the receiver operating curve (AUROC)=0.675, logistic regression [LR] *P*=0.003; digital: AUROC=0.678, LR *P*=0.010; **Figure 4**). Continuous scores may be used to establish optimal cutoffs

Figure 4. Manual (A) and digital (B) continuous PD-L1 scoring was predictive of MPR for combined non-squamous and squamous histology



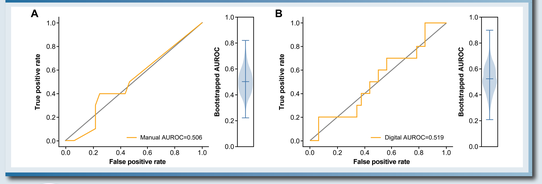
- PD-L1 scores from pre-treatment biopsies were strongly predictive of MPR for non-squamous histology (n=66; manual: AUROC=0.816,LR *P*=0.001; digital: AUROC=0.821, LR *P*=0.002; **Figure 5**)

Figure 5. Manual (A) and digital (B) continuous PD-L1 scoring was predictive of MPR for non-squamous histology



- PD-L1 scores from pre-treatment biopsies were not predictive of MPR for squamous histology (n=42; manual: AUROC=0.506, LR *P*=0.90; digital: AUROC=0.519, LR *P*=0.93; **Figure 6**)

Figure 6. Manual (A) and digital (B) continuous PD-L1 scoring was not predictive of MPR for squamous histology



CONCLUSIONS

- In pre-treatment biopsies from patients with NSCLC, cellular expression of PD-L1 was associated with a 42% (n=26) MPR rate with atezolizumab for non-squamous samples, but not for squamous; however, the overall MPR rate was similar between histologic subtypes
- Continuous manual PD-L1 and digital PD-L1 scoring were largely concordant, supporting the use of digitally assessed PD-L1 IHC as a streamlined method to evaluate TPS
- Consistent with observations in metastatic NSCLC, our results suggest that the tumor histological subtype may be an important factor in the utility of PD-L1 as a biomarker for patients with early NSCLC being considered for cancer immunotherapy[3]
- Considering the broad use of PD-L1 as a diagnostic tool to select patients for immunotherapy in metastatic and adjuvant settings, these data indicate that further studies are warranted to improve our understanding of the predictive prognostic value of PD-L1 expression stratified by histological subtype

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