60 USE OF THE COMBINED POSITIVE SCORE (CPS) WITH THE COMPANION DIAGNOSTIC PD-L1 IHC 22C3 PHARMDX PROVIDES PRECISE EVALUATION OF PD-L1 EXPRESSION ACROSS MULTIPLE TUMOR INDICATIONS AND CUTOFFS

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Background The Combined Positive Score (CPS)[1] algorithm includes tumor and immune cells for determination of Programed Death-Ligand 1 (PD-L1) protein expression in tumor tissues and has been analytically and clinically validated for use with PD-L1 IHC 22C3 pharmDx across multiple indications and cutoffs.[2] PD-L1 22C3 IHC pharmDx is a qualitative immunohistochemical assay using anti-PD-L1, Clone 22C3 to detect PD-L1 in formalin-fixed, paraffin-embedded (FFPE) tumor tissues using Autostainer Link 48. PD-L1 IHC 22C3 pharmDx is FDA-approved as an aid in identifying patients for treatment with KEYTRUDA® for six tumor indications at clinically validated CPS diagnostic cutoffs[2]: gastric or gastroesophageal junction (GC/GEJ) adenocarcinoma (CPS $\geq$ 1), cervical cancer (CPS $\geq$ 1), urothelial carcinoma (CPS $\geq$ 10), head and neck squamous cell carcinoma (HNSCC) (CPS $\geq$ 1), esophageal squamous cell carcinoma (ESCC) (CPS $\geq$ 10)[3], and triple-negative breast cancer (TNBC) (CPS $\geq$ 10).

Methods Precision of PD-L1 IHC 22C3 pharmDx using CPS was assessed for all six indications at the corresponding clinically validated diagnostic cutoffs and at additional exploratory cutoffs under normal, day-to-day testing conditions. Precision testing included Combined Precision (inter-instrument/operator/run (day)), Intra-Run Repeatability, and Observer (inter-/intra-) Scoring Reproducibility studies. FFPE specimens were stained with PD-L1 IHC 22C3 pharmDx and scored using CPS as described in the package insert.[2] Four CPS cutoffs were evaluated: CPS $\geq$ 1 (GC/GEJ, urothelial carcinoma, ESCC, cervical cancer, HNSCC, TNBC), CPS $\geq$ 10 (GC/GEJ, urothelial carcinoma, ESCC, TNBC), CPS $\geq$ 20 (HNSCC), and CPS $\geq$ 50 (HNSCC). Data were analyzed using negative percent agreement (NPA), positive percent agreement (PPA), and overall agreement (OA) with two-sided 95% percentile bootstrap confidence intervals (CIs) based on PD-L1 binary status at the applicable cutoff(s). For each study, data from each CPS cutoff-indication pair were individually analyzed. Meta-analyses were also performed by pooling data from all indications per (i) study and cutoff, and (ii) per study for all tested cutoffs.

Results Nearly all agreement analyses (142/144) for each CPS cutoff-indication pair showed NPA/PPA/OA point estimates (PE) $\geq$ 90% and CI lower bounds (CILB) $\geq$ 85%. Meta-analyses showed PE $\geq$ 90% for NPA/PPA/OA and CILB $\geq$ 85% per study and cutoff, and per study for all tested cutoffs. Discordant comparisons accounted for <5% of total comparisons performed for each study type.

Conclusions CPS used with PD-L1 IHC 22C3 pharmDx provides precise evaluation of PD-L1 expression across multiple tumor indications and cutoffs under normal, day-to-day testing conditions.

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Trial Registration N/A

REFERENCES

1. CPS = (# PD-L1 staining cells (tumor cells, lymphotcytes, macrophages))/(Total # viable tumor cells)×100
2. PD-L1 IHC 22C3 pharmDx [Instructions for Use]. Available at: www.agilent.com/library/eifu. Code SK006. Accessed July 2, 2021
3. ESCC was analytically validated as a subtype of esophageal cancer [2].

Ethics Approval N/A
Consent N/A

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