Evaluation of Programmed Death Ligand-1 Expression and Efficacy Outcomes in Patients With Squamous Cell Carcinoma of the Head and Neck From KEYNOTE-040 Using Two Scoring Techniques

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Disclosures

- Kenneth Emancipator
  - Employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA
  - Stockholder of Bayer AG, Johnson & Johnson, and Merck & Co., Inc., Kenilworth, NJ, USA
  - Spouse is an employee of and owns stock in Celgene
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Introduction

- Emerging challenges for pathologists measuring PD-L1 expression for HNSCC include the following:
  - Pembrolizumab was first approved by the EMA as a second-line therapy based on TPS 50%[1]
  - First-line approval may be based on CPS for pembrolizumab monotherapy as a result of data from the phase 3 KEYNOTE-048 trial in patients with CPS ≥1 and CPS ≥20[2]
- TPS[a] measures PD-L1 expression in tumor cells; CPS[b] measures PD-L1 expression in tumor and immune cells[3]
- The phase 3 KEYNOTE-040 trial evaluated pembrolizumab versus SOC in patients with HNSCC stratified by PD-L1 expression (TPS ≥50% vs TPS <50%)[4]
- Post hoc analysis of KEYNOTE-040 (NCT02252042) was performed to determine whether CPS is a suitable alternative for TPS in patients with HNSCC

CPS, combined positive score; EMA, European Medicines Agency; HNSCC, head and neck squamous cell carcinoma; TPS, tumor proportion score.

[a]TPS is defined as the percentage of viable tumor cells with partial or complete membrane staining at any intensity. [b]CPS is defined as the ratio of the number of PD-L1–expressing cells (tumor cells, lymphocytes, macrophages) to the number of all viable tumor cells multiplied by 100.

1. Keytruda (pembrolizumab) 50 mg powder for concentrate for solution for infusion (summary of product characteristics). Hoddesdon, UK: Merck Sharp & Dohme Limited; June 3, 2019.
2. Rischin D et al. *J Clin Oncol.* 2019;37(suppl):6000. 3. Kulangara K et al. *Arch Pathol Lab Med.* 2019;143:330-337. 4. Cohen EEW et al. *Lancet.* 2019;393:156-167.

Phase 3 KEYNOTE-040 Study (NCT02252042)

Key Eligibility Criteria

- SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- PD after platinum-containing regimen for R/M HNSCC or recurrence of PD within 3-6 months of multimodal therapy using platinum[a]
- ECOG PS 0 or 1
- Known p16 status (oropharynx)[b]
- Tissue sample[c] for PD-L1 assessment[d]

Stratification Factors

- ECOG PS (0 vs 1)
- p16 status[b] (positive vs negative)
- PD-L1 TPS[d] (≥50% vs <50%)

R (1:1)

Pembrolizumab
200 mg IV Q3W
for 2 years

Methotrexate 40 mg/m^2 QW[e]
OR
Docetaxel 75 mg/m^2 Q3W
OR
Cetuximab 250 mg/m^2 QW[f]

- Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 weeks later confirmed PD
- Crossover not permitted

ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; PD, progressive disease; QW, every week; Q3W, every 3 weeks; R, randomized; R/M, recurrent/metastatic; SCC, squamous cell carcinoma.

[a]Limit of 2 prior therapies for R/M HNSCC. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutoff for positivity = 70%. [c]Newly collected preferred. [d]Assessed using the PD-L1 IHC 22C3 PharmDx assay (Agilent Technologies). [e]Could be increased to 60 mg/m^2 QW in the absence of toxicity. [f]Following a loading dose of 400 mg/m^2.

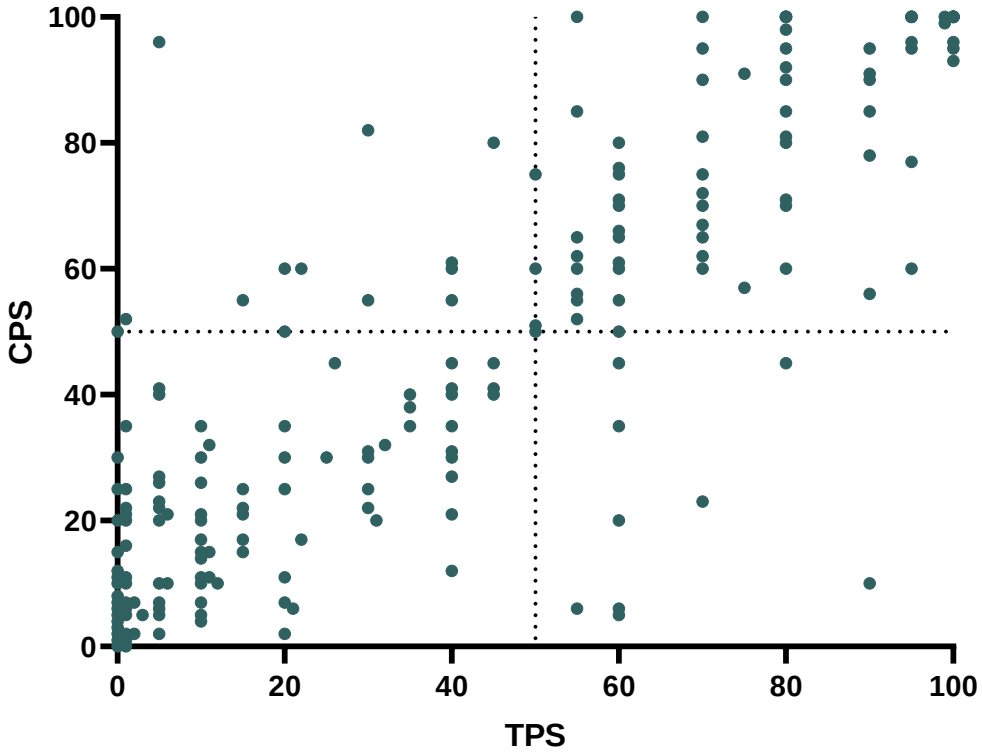
Current Post Hoc Analysis

- Pathologists scored tumor samples for TPS and CPS using the PD-L1 IHC 22C3 PharmDx assay[1]
  - Samples were scored for TPS and CPS at different times and without knowledge of the other score
  - Of 495 patients randomly assigned, 475 samples were evaluated for PD-L1 expression
    - 15 samples were removed because those patients were not treated
    - An additional 5 samples had no PD-L1 scoring
    - 475 samples were available for this PD-L1 analysis
- Efficacy end points were compared between the scoring methods
  - ORR per RECIST v1.1
  - OS
  - PFS per RECIST v1.1
- Cutoffs were evaluated by tandem ROC analysis using ORR

IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; ROC, receiver operating characteristic.

[1]PD-L1 IHC 22C3 pharmDx [package insert]. Carpinteria, CA: Dako, Agilent Pathology Solutions; 2019.

Correlation of Patient TPS vs CPS



Spearman ρ = 0.88

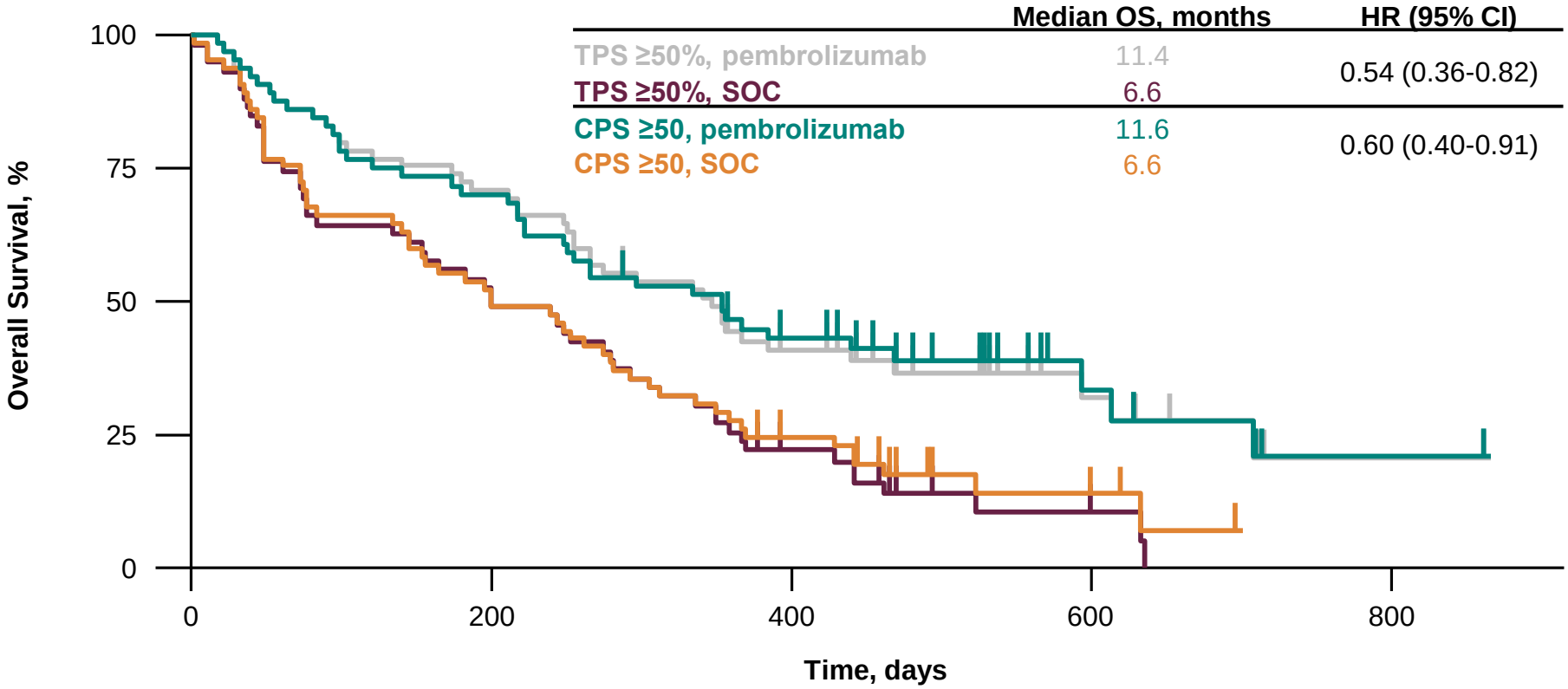
Database cutoff date: May 15, 2017.

ORR Based on PD-L1 Scoring Method

PD-L1 Subgroup	Treatment Group	Responses, n	Nonresponses,[a] n	ORR, %	Odds Ratio[b] (95% CI)
TPS ≥50%	Pembrolizumab	17	48	26.2	3.83 (1.31-11.15)
	SOC	5	54	8.5	
CPS ≥50	Pembrolizumab	18	46	28.1	4.70 (1.62-13.59)
	SOC	5	60	7.7	
TPS <50%	Pembrolizumab	19	160	10.6	0.90 (0.46-1.76)
	SOC	20	152	11.6	
CPS <50	Pembrolizumab	18	162	10.0	0.81 (0.41-1.59)
	SOC	20	146	12.0	

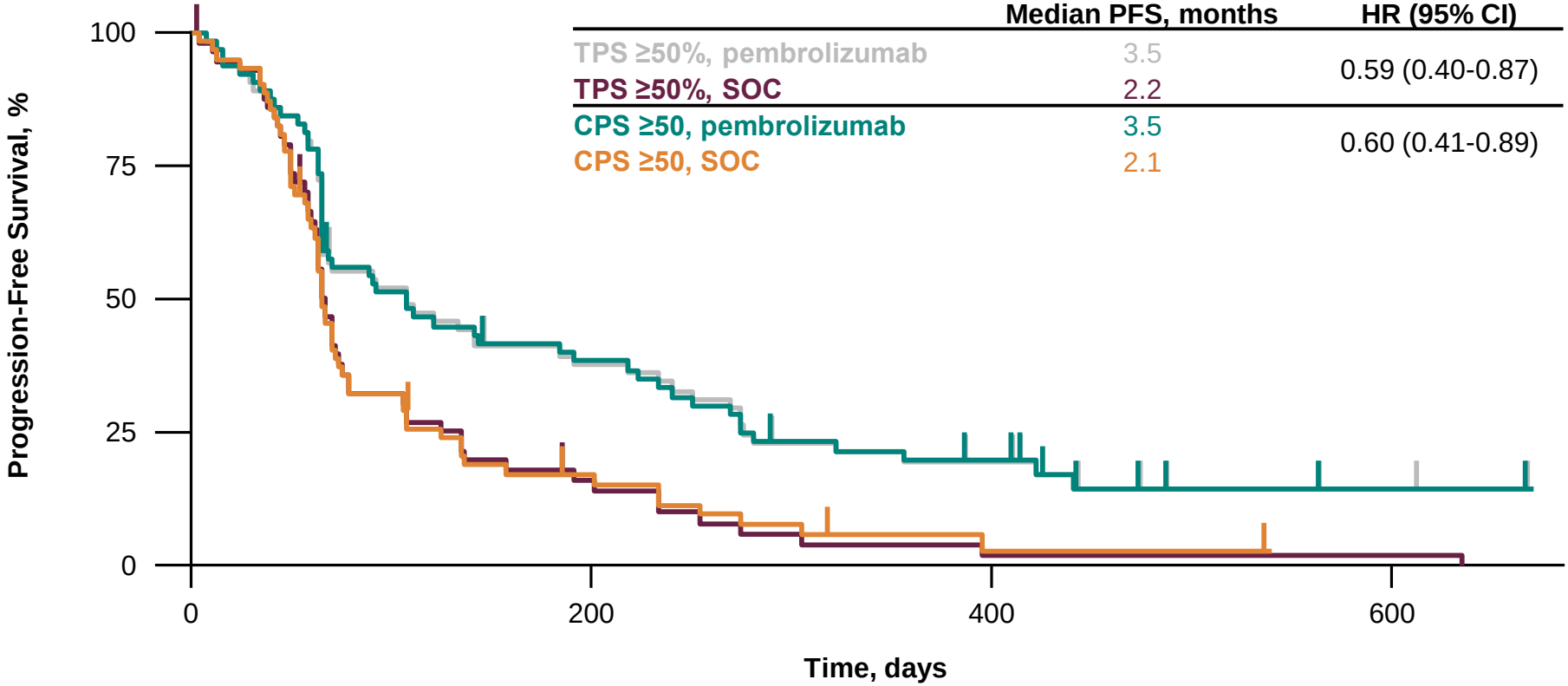
SOC, standard of care.
Database cutoff date: May 15, 2017.
[a]Patients without a confirmed or unconfirmed response.
[b]Ratio of odds of pembrolizumab response to odds of SOC response; a ratio >1 favors pembrolizumab whereas a ratio <1 favors SOC.

Overall Survival in Patients With TPS ≥50% or CPS ≥50



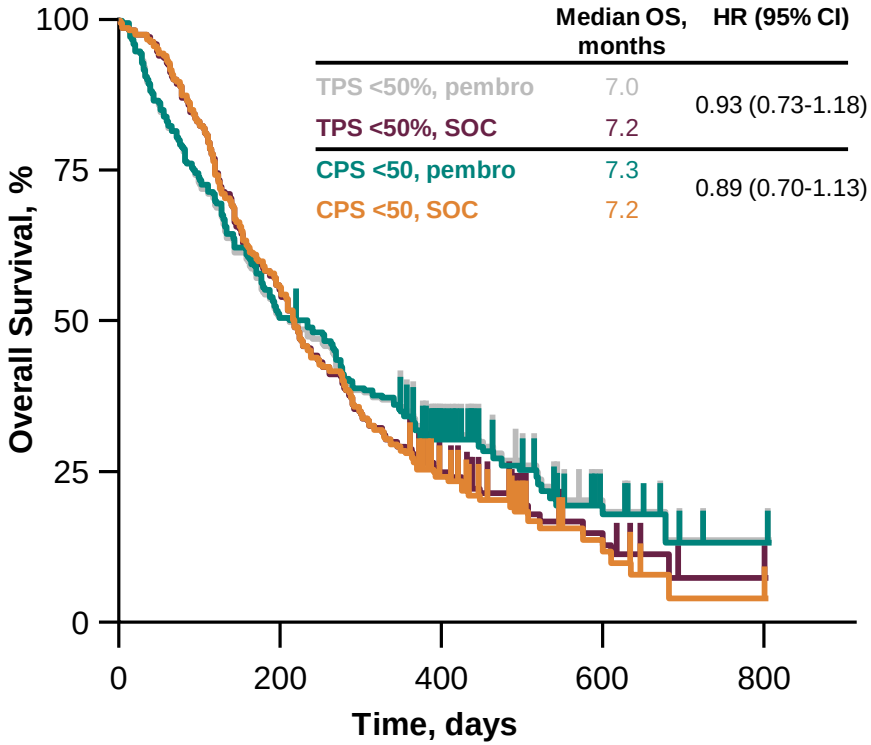
HR, hazard ratio.
Database cutoff date: May 15, 2017.

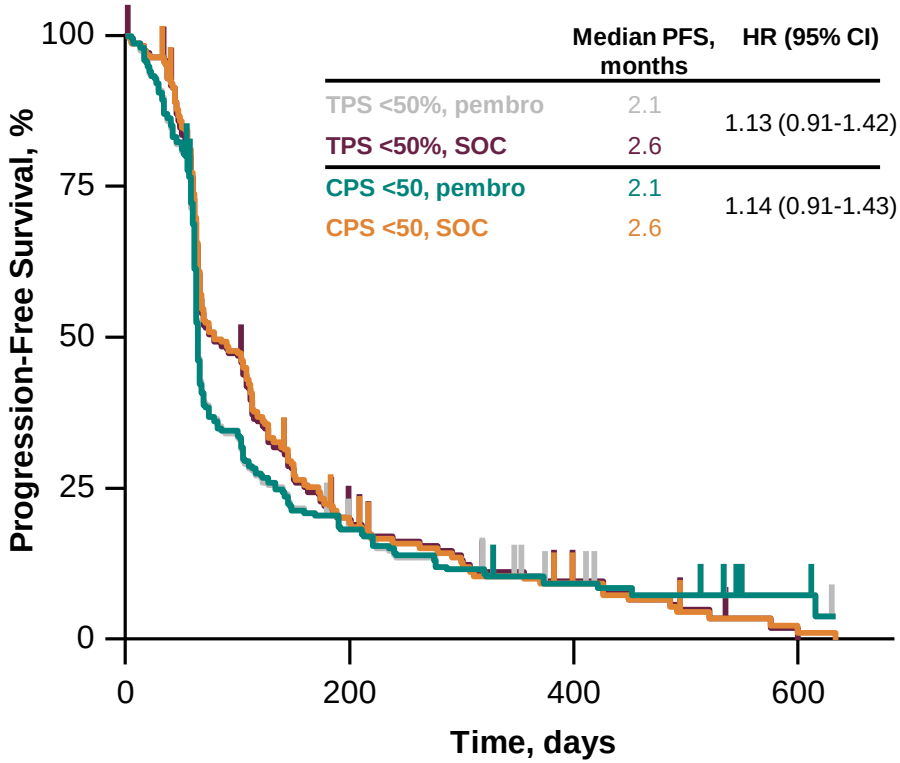
Progression-Free Survival in Patients With PD-L1 TPS ≥50% or CPS ≥50



Database cutoff date: May 15, 2017.

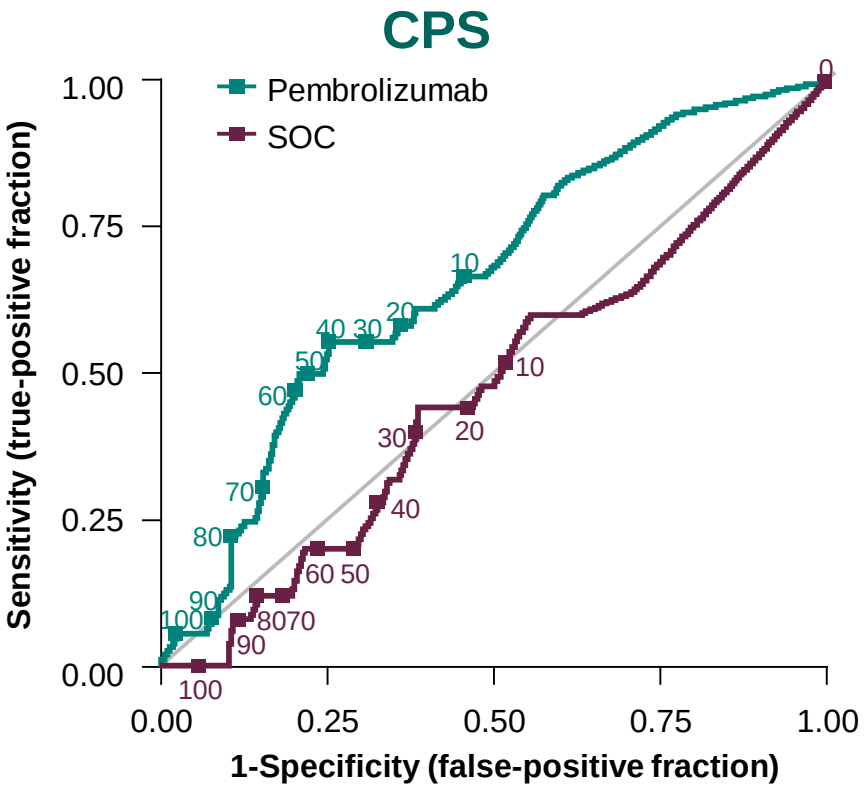
Overall Survival and Progression-Free Survival in Patients With TPS <50% or CPS <50

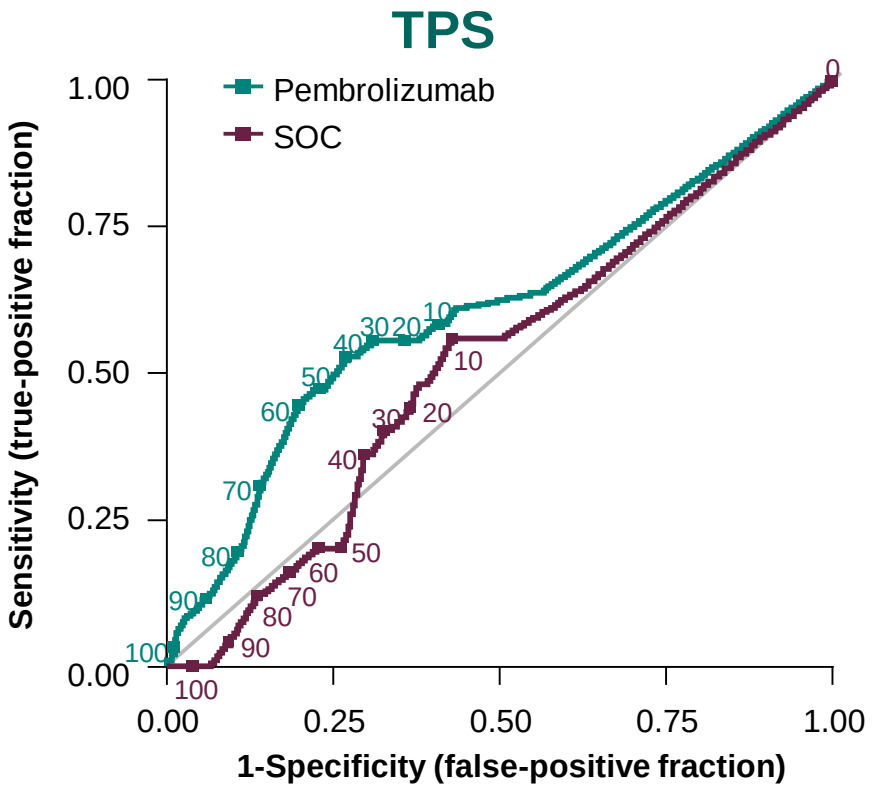




Database cutoff date: May 15, 2017.

ROC Curves for CPS and TPS by Treatment





Database cutoff date: May 15, 2017.
Based on objective response per RECIST v1.1.

ROC and Youden Index for CPS by Treatment

CPS	Pembrolizumab			SOC			ΔYI
	TPR	FPR	YI	TPR	FPR	YI	
0	1.0000	1.0000	0.0000	1.0000	1.0000	0.0000	0.0000
1	0.9444	0.7740	0.1704	0.7600	0.8058	-0.0458	0.2162
10	0.6667	0.4567	0.2099	0.5200	0.5194	0.0006	0.2094
20	0.5833	0.3606	0.2228	0.4400	0.4612	-0.0212	0.2439
30	0.5556	0.3077	0.2479	0.4000	0.3835	0.0165	0.2314
40	0.5556	0.2500	0.3056	0.2800	0.3252	-0.0452	0.3508
50	0.5000	0.2212	0.2788	0.2000	0.2913	-0.0913	**0.3701**
60	0.4722	0.2019	0.2703	0.2000	0.2379	-0.0379	0.3082
70	0.3056	0.1538	0.1517	0.1200	0.1845	-0.0645	0.2162
80	0.2222	0.1058	0.1165	0.1200	0.1456	-0.0256	0.1421
90	0.0833	0.0769	0.0064	0.0800	0.1165	-0.0365	0.0429
100	0.0556	0.0240	0.0315	0.0000	0.0583	-0.0583	0.0898

FPR, false-positive rate; TPR, true-positive rate; YI, Youden Index.
Database cutoff date: May 15, 2017.

ROC and Youden Index for TPS By Treatment

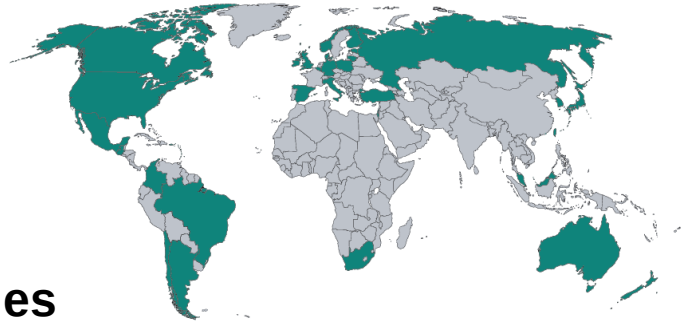
TPS	Pembrolizumab			SOC			ΔYI
	TPR	FPR	YI	TPR	FPR	YI	
0	1.0000	1.0000	0.0000	1.0000	1.0000	0.0000	0.0000
1	0.6389	0.5625	0.0764	0.6400	0.6165	0.0235	0.0529
10	0.5833	0.4087	0.1747	0.5600	0.4272	0.1328	0.0419
20	0.5556	0.3558	0.1998	0.4400	0.3641	0.0759	0.1239
30	0.5556	0.3077	0.2479	0.4000	0.3252	0.0748	0.1731
40	0.5278	0.2692	0.2585	0.3600	0.2961	0.0639	0.1947
50	0.4722	0.2308	0.2415	0.2000	0.2621	-0.0621	**0.3036**
60	0.4444	0.1971	0.2473	0.2000	0.2282	-0.0282	0.2755
70	0.3056	0.1394	0.1661	0.1600	0.1845	-0.0245	0.1906
80	0.1944	0.1058	0.0887	0.1200	0.1359	-0.0159	0.1046
90	0.1111	0.0577	0.0534	0.0400	0.0922	-0.0522	0.1057
100	0.0278	0.0096	0.0182	0.0000	0.0388	-0.0388	0.0570

Database cutoff date: May 15, 2017.

Conclusions

- Post hoc analysis of KEYNOTE-040 demonstrated that CPS is useful for evaluating PD-L1 expression in patients with HNSCC
  - CPS 50 can be used interchangeably with TPS 50%
- Clinical benefit, OS and PFS curves, and ORR showed congruence between treatment groups by TPS and CPS
- Data from the ROC analyses further suggest that CPS may be more sensitive than TPS at lower cutoffs (CPS ≥1)

Acknowledgments



PATIENTS AND THEIR FAMILIES

Investigators and site personnel from 20 countries

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