PD-L1 экспрессия – настоящее и будущее

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PD-1/PD-L1 ингибиторы, применяющиеся в клинической практике

	Nivolumab[1-3]	Pembrolizumab[4-6]	Cemiplimab[7,8]	Atezolizumab[9-11]	Durvalumab[12-14]	Avelumab[15-18]
Company	Bristol Myers Squibb	Merck & Co/ Merck Sharp & Dohme	Regeneron	Roche	AstraZeneca	Merck KGaA/Pfizer
Target	PD-1	PD-1	PD-1	PD-L1	PD-L1	PD-L1
Antibody type	Fully human IgG4	Humanized IgG4	Human IgG4	Humanized IgG1	Human IgG1	Human IgG1
IC_{50}	2.52 nM (PD-L1) 2.59 nM (PD-L2)	0.1–0.3 nM (PD-L1) 0.5–0.9 nM (PD-L2)	0.6 nM (PD-L1) 0.13 nM (PD-L2)	82.8 pM (PD-L1)	0.1 nM (PD-L1 to PD-1) 0.04 nM (PD-L1 to CD80)	0.07 nM (PD-L1)
Half-life	25 days	22 days	19 days	27 days	18 days	6.1 days
Monotherapy IV dosing[a]	240 mg over 30 min Q2W or 480 mg over 60 min Q4W[a] (EU); 240 mg over 30 min Q2W or 480 mg over 30 min Q4W[a] (US)	200 mg over 30 min Q3W (EU and US) or 400 mg Q6W (EU); 2 mg/kg (up to 200 mg) over 30 min Q3W for pediatrics (US)	350 mg over 30 min Q3W (US)	840 mg over 60 min (or 30 min if first infusion is tolerated) Q2W or 1200 mg Q3W or 1680 mg Q4W	10 mg/kg over 60 min Q2W (EU and US)	800 mg over 60 min Q2W (EU and US)
References	1. OPDIVO® (nivolumab) [package insert]. Princeton, NJ: Bristol Myers Squibb. 2. Wang C et al. *Cancer Immunol Res* 2014;2:846–856. 3. OPDIVO® (nivolumab) [summary of product characteristics]. Dublin, IR: Bristol Myers Squibb Ltd. 4. KEYTRUDA® (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck & Co, Inc. 5. KEYTRUDA® (pembrolizumab) [summary of product characteristics]. BN Harlem, The Netherlands: Merck Sharp & Dohme Ltd. 6. Chatterjee M et al. *Ann Oncol* 2016;27:1291–1298. 7. LIBTAYO® (cemiplimab) [package insert]. Tarrytown, NY: Regeneron. 8. NDA/BLA Multidisciplinary Review and Evaluation 761097. Published February 28, 2018. Accessed December 8, 2020. 9. TECENTRIQ® (atezolizumab) [package insert]. South San Francisco, CA: Genentech, Inc. 10. TECENTRIQ® (atezolizumab) [summary of product characteristics]. Grenzach-Wyhlen, Germany: Roche Registration GmbH. 11. TECENTRIQ® (atezolizumab) [assessment report]. London, UK: European Medicines Agency; March 2018. 12. IMFINZI® (durvalumab) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. 13. IMFINZI® (durvalumab) [summary of product characteristics] Södertälje, Sweden; AstraZeneca AB. 14. Planchard D et al. *Clin Lung Cancer* 2016;17:232–236. 15. BAVENCIO® (avelumab) [package insert]. New York, NY: EMD Serono, Inc, and Pfizer, Inc. 16. BAVENCIO® (avelumab) [summary of product characteristics]. MA Amsterdam, The Netherlands: Merck Europe BV. 17. Immuno-oncology news website. Updated March 1, 2018. Accessed December 8, 2020. 18. BLA Multidisciplinary Review and Evaluation 761049. Published February 1, 2016. Accessed December 8, 2020.					

[a]Depending on the approved indication. CD, cluster of differentiation; EU, European Union; IC_{50}, the half maximal inhibitory concentration; IgG, immunoglobulin G; IV, intravenous; PD-1, programmed death-1; PD-L1, programmed death ligand 1; Q#W, every # weeks; US, United States.

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Обзор платформ и пороговых значений PD-L1

Ab clone[a]	28-8[1-3]	22C3[4-6]	SP142[7-9]	SP263[10-14]	73-10[15,16]
Assay	PD-L1 IHC 28-8 pharmDx (Dako)	PD-L1 IHC 22C3 pharmDx (Dako)	PD-L1 (SP142) Assay (Ventana)	PD-L1 (SP263) Assay (Ventana)	PD-L1 (73-10) Bond RTU Primary
For use with (drug)	Nivolumab	Pembrolizumab	Atezolizumab	Nivolumab, pembrolizumab, durvalumab	Avelumab
IVD class III diagnostic partner	Dako[b] (Agilent)	Dako[b] (Agilent)	Ventana (Roche)	Ventana (Roche)	Abcam/Merck KGaA
PD-L1 scoring method[c]	% TCs	% TCs, TPS[d]; % TCs ± ICs, CPS[e] or MEL Score[f]	% TCs or ICs	% TCs or ICP ± ICs	% TC
Approval status and cutoffs specified in label (US)	**Complementary** **2L NSQ NSCLC** ≥ 1%, ≥ 5%, ≥ 10% **SCCHN** ≥ 1% **UC** ≥ 1% **Companion** **1L metastatic NSCLC**[f] ≥ 1%	**Companion** **1L NSCLC** ≥ 1% TPS **2L NSCLC** ≥ 1% TPS **UC**[g] ≥ 10 CPS **3L+ Gastric/GEJ** ≥ 1 CPS **2L+ CC** ≥ 1 CPS **2L+ ESCC** ≥ 10 CPS **1L SCCHN** ≥ 1 CPS **1L TNBC** ≥ 10 CPS **NSCLC** ≥ 1% TPS (China)[17]	**Complementary** **2L NSCLC** ≥ 50% TC or ≥ 10% IC **Companion** **UC**[g] ≥ 5% ICs **TNBC** ≥ 1% ICs **1L NSCLC** ≥ 50% or IC ≥ 10%	**Complementary** **UC** ≥ 25% TC or IC[h] (durvalumab)	Not approved
Approval status and cutoffs specified in label (EU)	**Complementary** **Melanoma**[i] ≥ 1%, ≥ 5% **NSQ NSCLC** ≥ 1%, ≥ 5%, ≥ 10% **SCCHN** ≥ 1% **UC** ≥ 1%	**Complementary** **Melanoma** ≥ 1% MEL Score[j] **Companion** **NSCLC** ≥ 1% TPS (2L), ≥ 50% TPS (1L)[k] **SCCHN** ≥ 50% TPS (2L)[l], ≥ 1 CPS (1L)[m] **UC**[g] ≥ 10 CPS	**Complementary** **2L NSCLC** ≥ 50% TC or ≥ 10% IC **Companion** **UC**[g] ≥ 5% ICs **TNBC** ≥ 1% ICs	**Complementary** **NSQ NSCLC** ≥ 1%, ≥ 5%, ≥ 10% TC (nivolumab) **UC** ≥ 25% TC or IC[h] (durvalumab)[i] **Companion** **NSCLC** ≥ 1% (2L), ≥ 50% TC (1L) (pembrolizumab) ≥ 1% TC (durvalumab – 1L[n,o])	Not approved

1L, first line; 2L, second line; 3L, third line; CC, cervical cancer; CPS, combined positive score; ESCC, esophageal squamous cell carcinoma; EU, European Union; GEJ, gastroesophageal junction; IC, immune cell; ICP, immune cells present; IHC, immunohistochemistry; IVD, in vitro diagnostic; MEL, melanoma; NSQ, nonsquamous; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; RTU, ready-to-use; SCCHN, squamous cell carcinoma of head and neck; TC, tumor cell; TNBC, triple-negative breast cancer; TPS, tumor proportion score; UC, urothelial carcinoma; US, United States. 1. PD-L1 IHC 28-8 pharmDx [package insert]. Santa Clara, CA: Agilent Company. 2. OPDIVO® (nivolumab) [package insert]. Princeton, NJ: Bristol Myers Squibb. 3. OPDIVO® (nivolumab) [summary of product characteristics]. Dublin, IR. 4. PD-L1 IHC 22C3 pharmDx [package insert]. Santa Clara, CA: Agilent Company. 5. KEYTRUDA® (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck & Co, Inc. 6. KEYTRUDA® (pembrolizumab) [summary of product characteristics]. BN Harlem, The Netherlands: Merck Sharp & Dohme Ltd. 7. VENTANA® PD-L1 (SP142) assay [package insert]. Tucson, AZ: Ventana Medical Systems, Inc. 8. TECENTRIQ® (atezolizumab) [package insert]. South San Francisco, CA: Genentech, Inc. 9. TECENTRIQ® (atezolizumab) [summary of product characteristics]. Grenzach-Wyhlen, Germany: Roche Registration GmbH. 10. VENTANA® PD-L1 (SP263) Assay [package insert]. Mannheim, Germany: Roche Diagnostics GmbH. 11. IMFINZI® (durvalumab) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. 12. Roche. Roche's VENTANA PD-L1 (SP263) Assay gains CE label expansion to inform treatment decisions in lung cancer patients being considered for KEYTRUDA (pembrolizumab) immunotherapy. Published May 5, 2017. Accessed December 9, 2020. 13. Roche. VENTANA PD-L1 (SP263) Assay (CE IVD). Accessed December 9, 2020. 14. IMFINZI® (durvalumab) [summary of product characteristics]. Södertälje, Sweden; AstraZeneca AB. 15. BAVENCIO® (avelumab) [package insert]. New York, NY: EMD Serono, Inc and Pfizer Inc. 16. Teixidó C et al. *Ther Adv Med Oncol* 2018;10:1-17. 17. Agilent. Agilent Receives Approval for First PD-L1 Companion Diagnostic in China. Accessed December 9, 2020.

[a]No head-to-head studies have been conducted, and comparisons cannot be made between these assays or antibodies used therein. [b]Dako, an Agilent Technologies, Inc company. [c]All assays score cells at any intensity. [d]TPS = % of viable TCs showing partial or complete membrane staining relative to all viable TCs present in the sample (positive and negative). [e]CPS = number of PD-L1–staining cells divided by the total number of viable TCs, multiplied by 100; PD-L1 expression is measured on both tumor and inflammatory cells. [f]With no EGFR or ALK genomic tumor aberrations, as 1L treatment in combination with ipilimumab. [g]UC ineligible for cisplatin-containing therapy. [h]When > 1% of the sample is composed of ICs, then PD-L1–expressing ICs must equal 25%. If only 1% of the sample is composed of ICs, then PD-L1–expressing ICs must equal 100. [i]As monotherapy or in combination with ipilimumab. [j]MEL Score includes partial or complete cell membrane staining of TCs and membrane and/or cytoplasmic staining of ICs. [k]≥ 50% TPS for first line only. [l]Progressing on or after platinum-containing chemotherapy. [m]Pembrolizumab monotherapy or in combination with chemotherapy in 1L metastatic/unresectable SCCHN. [n]Durvalumab is not licenced in the EU for UC. [o]Patients whose disease has not progressed following platinum-based chemoradiation therapy.

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How to evaluate PD-L1 expression score in ICs

Scoring method (antibody)	IC types evaluated	
CPS (22C3[1-4]; 28-8[5-7]): • Combined evaluation of TCs and ICs • Global assessment of PD-L1–positive cells	Lymphocytes and macrophages	$\text{CPS} = \frac{\text{Number of PD-L1-stained cells (TCs + ICs)}}{\text{Total number of viable TCs}} \times 100$
TCIC (22C3[8,a]): • Percentage PD-L1 expression in tumor-infiltrating ICs and invasive TCs	All immune cells (any staining)	$\%\ \text{TCIC} = \frac{\text{Number of PD-L1-stained cells (TCs [membranous] + ICs [any staining])}}{\text{Total number of invasive TCs}} \times 100$
MEL Score (22C3[9]): • Combined evaluation of TCs and ICs • Global assessment of PD-L1–positive cells	MICs	$\text{MEL Score} = \frac{\text{Number of PD-L1-stained cells (TCs + MICs)}}{\text{Total number of viable TCs + PD-L1-stained MICs}} \times 100$
% IC; ICP (SP263[10]): • Percentage of PD-L1–positive ICs • ICP is the area of the tumor occupied by ICs and should be ≥ 1% for positive scoring	All tumor-associated ICs	$\%\ \text{IC} = \frac{\text{Number of PD-L1-stained tumor-associated ICs}}{\text{Total number of tumor-associated ICs}} \times 100$ $\text{ICP} = \frac{\text{Tumor area occupied by tumor-associated ICs}}{\text{Total area of tumor scored}} \times 100$
% IC (SP142[11]): • Percentage of tumor area covered by PD-L1–positive ICs	All tumor-infiltrating ICs	$\%\ \text{IC} = \frac{\text{Tumor area covered by PD-L1-stained ICs}}{\text{Tumor area}} \times 100$
vCPS (SP263[12]): • Percentage of tumor area covered by PD-L1–positive TCs and ICs	Lymphocytes, macrophages, plasma cells, histocytes, reticular dendritic cells, and neutrophils	$\text{vCPS} = \frac{\text{Tumor area occupied by PD-L1-stained TCs and ICs}}{\text{Tumor area}} \times 100$
TAICs (28-8[13,14]): • The abundance of PD-L1–expressing TAICs in tumor area	All mononuclear cells	Qualitative assessment of mononuclear cell abundance in tumor area, classified as: • Numerous (presence of easily detected mononuclear cells) • Rare (few mononuclear cells detected) • Intermediate (mononuclear cell abundance between numerous and rare)

[a]In this study, TCIC scores were equivalent to CPS scores used in a range of pembrolizumab studies, eg, 5% TCIC was equivalent to CPS 5. CPS, combined positive score; IC, immune cell; ICP, immune cells present; MEL, melanoma; MIC, mononuclear inflammatory cell; PD-L1, programmed death ligand 1; TAIC, tumor-associated immune cell; TC, tumor cell; TCIC, tumor infiltrating immune cells and invasive tumor cells; vCPS, visually-estimated combined positive score. 1. PD-L1 IHC 22C3 pharmDx [interpretation guide for cervical cancer]. Santa Clara, CA: Agilent Company. 2. PD-L1 IHC 22C3 pharmDx [package insert]. Santa Clara, CA: Agilent Company. 3. PD-L1 IHC 22C3 pharmDX [interpretation guide for urothelial carcinoma]. Santa Clara, CA: Agilent Company. 4. PD-L1 IHC 22C3 pharmDx [interpretation guide for gastric or gastroesophageal junction adenocarcinoma]. Santa Clara, CA: Agilent Company. 5. Lei M et al. Oral presentation at the 110th American Association for Cancer Research Annual Meeting; March 29-April 3, 2019; Atlanta, GA, USA. Abstract 2673. 6. Moehler M et al. Oral presentation at the European Society for Medical Oncology Annual Meeting (Virtual); September 19-21, 2020. Abstract 3047. 7. Motzer RJ et al. Oral presentation at the 56th American Society of Clinical Oncology Annual Meeting (Virtual); May 29-31, 2020. Abstract 5009. 8. Guo H et al. *Breast Cancer Res* 2020;22:69. 9. PD-L1 IHC 22C3 pharmDx [interpretation manual for melanoma]. Santa Clara, CA: Agilent Company. 10. VENTANA® PD-L1 (SP263) Assay [package insert]. Mannheim, Germany: Roche Diagnostics GmbH. 11. VENTANA® PD-L1 (SP142) Assay [package insert]. Mannheim, Germany: Roche Diagnostics GmbH. 12. Chao Y et al. Poster presentation at the European Society for Medical Oncology Annual Meeting (Virtual); September 19-21, 2020. Abstract 154P. 13. Ferris RL et al. Oral presentation at the 108th American Association of Cancer Research Annual Meeting; April 1-5, 2017; Washington DC, USA. Abstract CT021. 14. Overman MJ et al. *Lancet Oncol* 2017;18:1182-1191.

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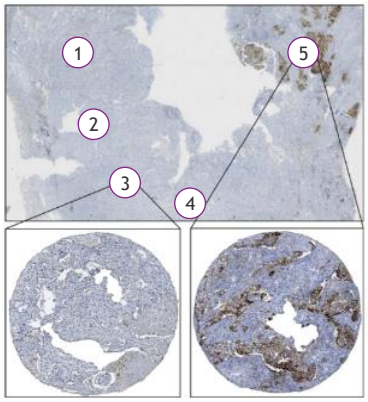
Внутриопухолевая гетерогенность PD-L1 экспрессии

- Between 13% and 70% of tumor cells and/or immune cells within the tumor microenvironment may express PD-L1[1]
- PD-L1 expression can vary within and across tumor types or histologies and can change by line of therapy[1-8]



Heterogeneity of PD-L1 expression in NSCLC[9]

Whole section of squamous NSCLC stained with PD-L1 shows spots corresponding to TMA cores numbered 1 to 5. TMA core numbers 1 to 4 are sampled randomly in an area with a negative result, whereas core number 5 is positive in more than 50% of neoplastic cells

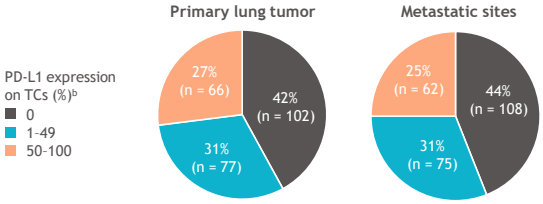
PD-L1 expression was assessed with the VENTANA PD-L1 SP263 automated staining platform

Reproduced with permission from *J Thorac Oncol*.[9]

NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1. TMA, tissue microarray.
1. Kerr KM et al. *J Thorac Oncol* 2015;10:985-989. 2. Gatalica Z et al. *Cancer Epidemiol Biomarkers Prev* 2014;23:2965-2970. 3. Sharpe K et al. *Clin Cancer Res* 2013;19:6924-6934. 4. Brown JA et al. *J Immunol* 2003;170:1257-1266. 5. Callea M et al. *Cancer Immunol Res* 2015;3:1158-1164. 6. Calles A et al. *J Thorac Oncol* 2015;10:1726-1735. 7. Dong H et al. *Nat Med* 2002;8:793-800. 8. Rehman JA et al. *Mod Pathol* 2017;30:340-349. 9. Munari E et al. *J Thorac Oncol* 2018;13:1113-1120.

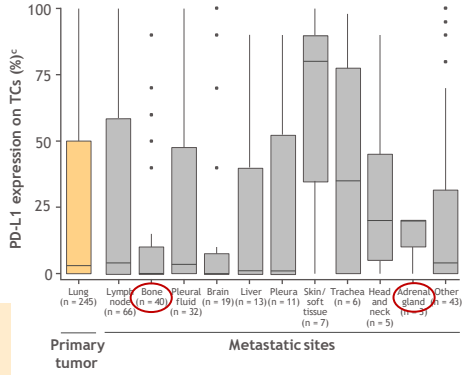
PD-L1 экспрессия при НМРЛ: первичная опухоли vs метастазы

- Comparison of PD-L1 expression[a] between 245 paired biopsies from primary tumor and metastatic sites in a real-world cohort of 44,407 patients with lung cancer[1]



The proportion of patients in each PD-L1 expression category was similar in the primary tumor and metastatic sites

PD-L1 expression levels were variable within and across biopsy sites

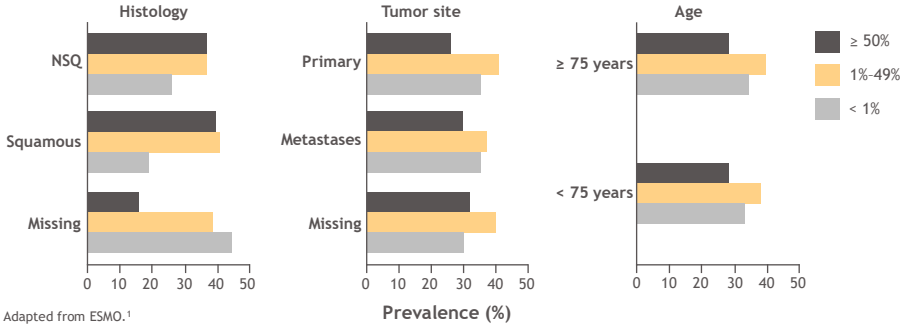


Reproduced with permission from E. Prince.[1]

[a]Inclusion criteria: Patients with only 2 biopsy sites (1 from primary lung tumor, 1 from a metastasis) collected ≤ 3 months apart, both tested with either the Dako PD-L1 IHC 28-8 or 22C3 pharmDx assays, with test ordered dates ≤ 3 months apart. PD-L1 tests performed October 2015-January 2020. [b]The number and proportion of patients is indicated for each PD-L1 expression cutoff.
[c]Each box shows the IQR. The line is the median value. Whiskers represent values 1.5 × the upper and lower limits of the IQR. Enlarged data points are outlying values more than 1.5 × the IQR above the third quartile or below the first quartile. IHC, immunohistochemistry; IQR, interquartile range; PD-L1, programmed death ligand 1; TC, tumor cell.
1. Prince E et al. Poster presentation at the 111th American Association for Cancer Research Annual Meeting (Virtual); June 22-29, 2020. Abstract 2004.

Распределение PD-L1 при НМРЛ в зависимости от возраста, локализации опухоли и гистологии

- PD-L1 IHC was carried out on 4784 samples from patients with advanced NSCLC (KEYNOTE-001, KEYNOTE-010, KEYNOTE-024)
  - PD-L1 IHC 22C3 pharmDx assay was used to assess TPS
  - PD-L1 expression was stratified by the TPS cutoffs: < 1%, 1%–49%, and ≥ 50%
  - Prevalence was assessed using disease characteristics and patient demographics



Adapted from ESMO.[1]

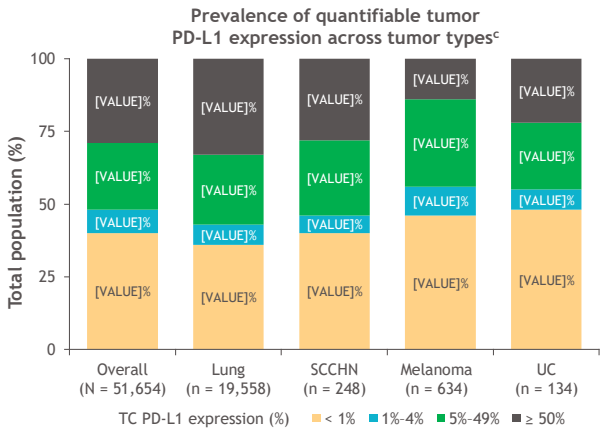
Despite missing data for some samples, PD-L1 prevalence seemed to be similar across age, tumor site and histology

IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; PD-L1, programmed death ligand 1; TPS, tumor proportion score.
1. Aggarwal C et al. Poster presentation at the 41st European Society for Medical Oncology Annual Meeting; October 7–11, 2016; Copenhagen, Denmark. Abstract 1060P.

Совокупный анализ экспрессии PD-L1 при разных опухолях

- Pooled analysis of 62,180 PD-L1 tests from 55,652 patients performed at a single reference laboratory between October 2015 and March 2018
  - Available samples included 55,217 and 6081 tested using the 22C3 and 28-8 assays, respectively[a]
- Proportion of samples with PD-L1 expression ≥ 1% was similar across tumor types (52%–64%)
- Highest proportion of samples with PD-L1 expression ≥ 50% was seen in lung cancer (33%),[b] and the lowest in melanoma (14%)

PD-L1 prevalence was similar across tumor types at all investigated cutoffs, although data may be confounded by small sample sizes for SCCHN, melanoma, and UC

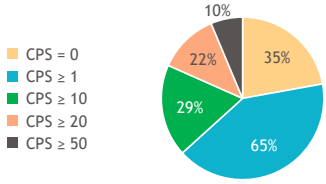


[a]882 samples tested with the SP142 assay were not included in analyses. [b]Data for non-small cell lung cancer and small cell lung cancer were pooled due to limitations in the ability of the coding method used to establish tumor type. [c]Data represent patients with a single test result or ≥ 2 identical 22C3 or 28-8 assay results.
PD-L1, programmed death ligand 1; SCCHN, squamous cell carcinoma of the head and neck; TC, tumor cell; UC, urothelial carcinoma.
1. Krigsfeld G et al. *J Clin Pathol* 2020;73:656–664.

Совокупный анализ PD-L1 методом CPS при 9 видах опухолей

- Pooled retrospective pan-tumor analysis of samples from 3769 patients enrolled in single-arm and randomized clinical trials investigating the efficacy of pembrolizumab monotherapy
- Tumor types investigated: cervical cancer, EC, GC/GEJC, HCC, RCC, SCCHN, SCLC, TNBC, and UC
- PD-L1 prevalence was determined in pembrolizumab-treated patients (n = 2678) at a range of cutoffs using the CPS algorithm
  - Further analyses in this subgroup assessed association between PD-L1 expression and ORR across CPS cutoffs to determine cutoff sensitivity and specificity

PD-L1 prevalence in patients receiving pembrolizumab monotherapy



Sensitivity and associations with ORR across CPS cutoffs

	Population					
	Overall	CPS = 0	CPS ≥ 1	CPS ≥ 10	CPS ≥ 20	CPS ≥ 50
ORR, %	17.6	**11.1**	21.0	27.7	30.4	**33.1**
Sensitivity	1.00	0.22	**0.78**	0.45	0.33	0.19
Specificity	0	NA	0.38	0.75	0.84	**0.92**

CPS, combined positive score; EC, esophageal cancer; GC, gastric cancer; GEJC, gastroesophageal cancer; HCC, hepatocellular carcinoma; NA, not applicable; ORR, objective response rate; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer; UC, urothelial carcinoma. 1. Huang L et al. Poster presentation at the Society for Immunotherapy of Cancer Annual Meeting (Virtual); November 10–15, 2020. Abstract 282.