Роль набора PD-L1 IHC 22C3 pharmDx в диагностике немелкоклеточного рака легкого

В.А. Кушнарев,
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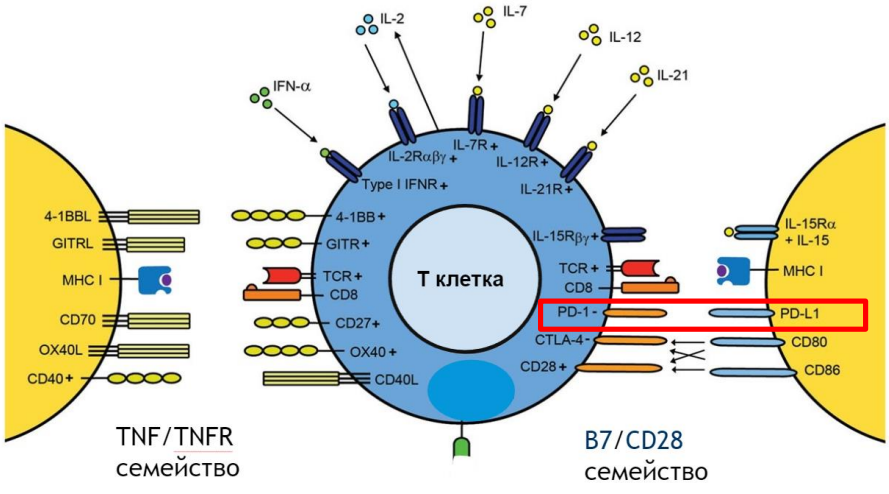
НМИЦ онкологии им.Н.Н.Петрова

Молекулы контрольных иммунных точек



Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2021

PD-L1 - предиктивный биомаркер

ORIGINAL ARTICLE

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., et al.

Published: 26 November 2014

Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients

Roy S. Herbst, Jean-Charles Soria, Marcin Kowanetz, Gregg D. Fine, Omid Hamid, Michael S. Gordon, Jeffery A. Sosman, David F. McDermott, John D. Powderly, Scott N. Gettinger, Holbrook E. K. Kohrt, Leora Horn, Donald P. Lawrence, Sandra Rost, Maya Leabman, Yuanyuan Xiao, Ahmad Mokatrin, Hartmut Koeppen, Priti S. Hegde, Ira Mellman, Daniel S. Chen & F. Stephen Hodi

Nature **515**, 563–567 (2014) | Cite this article

100k Accesses | **2964** Citations | **214** Altmetric | Metrics

Иммуногистохимическая экспрессия PD-L1, на опухолевых и иммунных клетках является полезным, но несовершенным прогностическим биомаркером ответа на анти-PD-1 или антитела против PD-L1 у пациентов с различными типами опухолей

Экспрессия PD-L1 может оцениваться на опухолевых клетках (TC) и инфильтрирующих опухоль иммунных клетках (IC), включая макрофаги, дендритные клетки, нейтрофилы, супрессорные клетки миелоидного происхождения и Т-клетки и / или В-клетки

Обязательная определения для назначения терапии

Assay	Dako PD-L1 IHC 28-8 pharmDx Assay[51]	Dako PD-L1 IHC 22C3 pharmDx Assay[53]	Ventana PD-L1 (SP142) Assay[52]	Ventana PD-L1 (SP263) Assay[73]
For use with (drug)	Nivolumab ± ipilimumab (Bristol Myers Squibb)	Pembrolizumab (Merck)	Atezolizumab (Roche or Genentech)	Durvalumab (AstraZeneca)
Manufacturer	Dako[a]	Dako[a]	Ventana[b]	Ventana[b]
Approved PD-L1 scoring algorithm(s)	% TC	TPS,[c] CPS[d]	% IC, % TC, or % IC[e]	% TC or % IC[f]
Approval status and cutoffs	Companion 1L NSCLC: ≥ 1%[g] Complementary 2L NSQ NSCLC: ≥ 1%, ≥ 5%, ≥ 10% 2L SCCHN: ≥ 1% 2L UC: ≥ 1%	Companion 1L or 2L NSCLC: TPS ≥ 1% 1L UC: CPS ≥ 10 3L+ gastric or GEJ: CPS ≥ 1 2L+ CC: CPS ≥ 1 2L+ ESCC: CPS ≥ 10 1L SCCHN: CPS ≥ 1 1L TNBC: CPS ≥ 10	Companion 1L UC[h]: ≥ 5% IC 1L TNBC: ≥ 1% IC 1L NSCLC: ≥ 50% TC or ≥ 10% IC Complementary 2L NSCLC: ≥ 50% TC or ≥ 10% IC	Complementary[i] 2L UC: ≥ 25% TC or ICP > 1% and IC+ ≥ 25% or ICP = 1% and IC+ = 100%

http://ascopubs.org/doi/full/10.1200/PO.20.00412

Клон PD-L1 22C3

Dako Link 48

Dako IHC 22C3 PD-L1

Анализатор Dako (22C3) оптимизирован для использования с системами детекции, разработанными для системы окрашивания Dako Link 48. Закрытый протокол

- Фиксация в 10 % нейтральном формалине в течение 6-72 часов
- Архивные или свежие образцы ткани взятые из первичного очага или метастаза,
- Достаточный объем материала: не менее 100 жизнеспособных опухолевых клеток
- Контроль - миндалина. Сильное окрашивание участков эпителия крипт и слабое или умеренное окрашивание макрофагов в зародышевых центрах фолликулов

NB! Прежде чем попасть на анализ на PD-L1 образец проходит гистологическое иммуногистохимическое исследования

Цитологические образцы и ткань после декальцинации **не должны использоваться** для анализа

Руководство по интерпретации результатов 22C3 DAKO

Системы оценки - визуальный анализ патологом

$$\text{TPS (\%)} = \frac{\text{Число PD-L1 окрашенных опухолевых клеток}}{\text{Общее число опухолевых клеток}} \times 100\%$$ Для 22C3 или SP263

$$\text{TC (\%)} = \frac{\text{Число PD-L1 окрашенных опухолевых клеток}}{\text{Общее число опухолевых клеток}} \times 100\%$$ Для SP142

$$\text{IC (\%)} = \frac{\text{Площадь опухоли, инфильтрированная PD-L1 + иммунными клетками}}{\text{Общая площадь опухоли}} \times 100\%$$ Для SP142

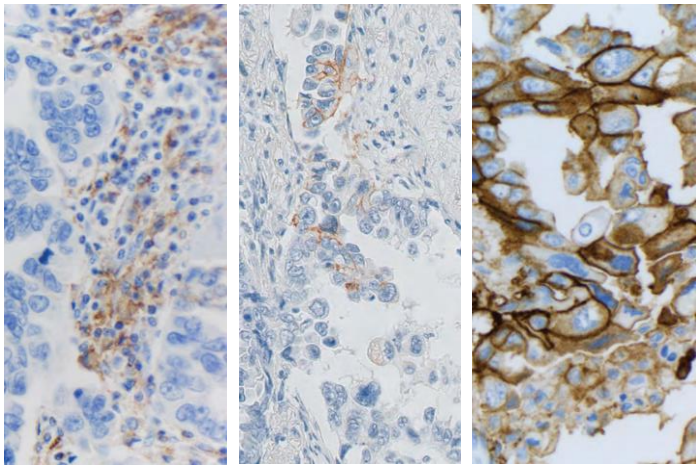
$$\text{CPS} = \frac{\text{Число PD-L1 окрашенных клеток (опухолевые клетки, лимфоциты, макрофаги)}}{\text{Общее число опухолевых клеток}} \times 100$$ Для 22C3

Соблюдение критериев оценки - ключ к успеху

Требования к окрашиванию:

- полное или частичное окрашивание мембраны опухолевой клетки
- любая степень интенсивности окрашивания

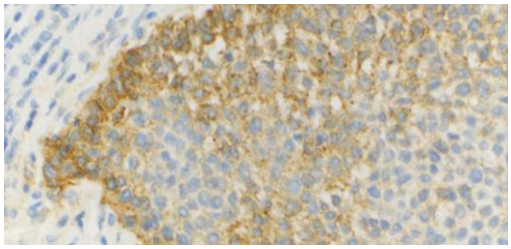
PD-L1 статус: устанавливается на основе *Tumour Proportion Score* (TPS) - процент живых опухолевых клеток с полным или частичным окрашиванием мембраны любой интенсивности



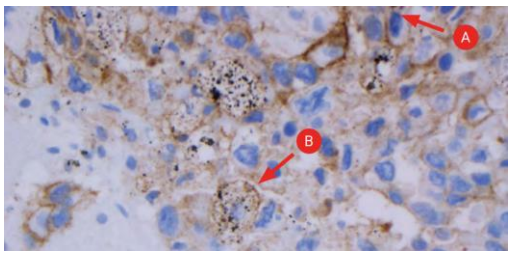
PD-L1 непрерывный, вариабельный и гетерогенный биомаркер

Руководство по интерпретации результатов 22C3 DAKO

Сложности интерпретации



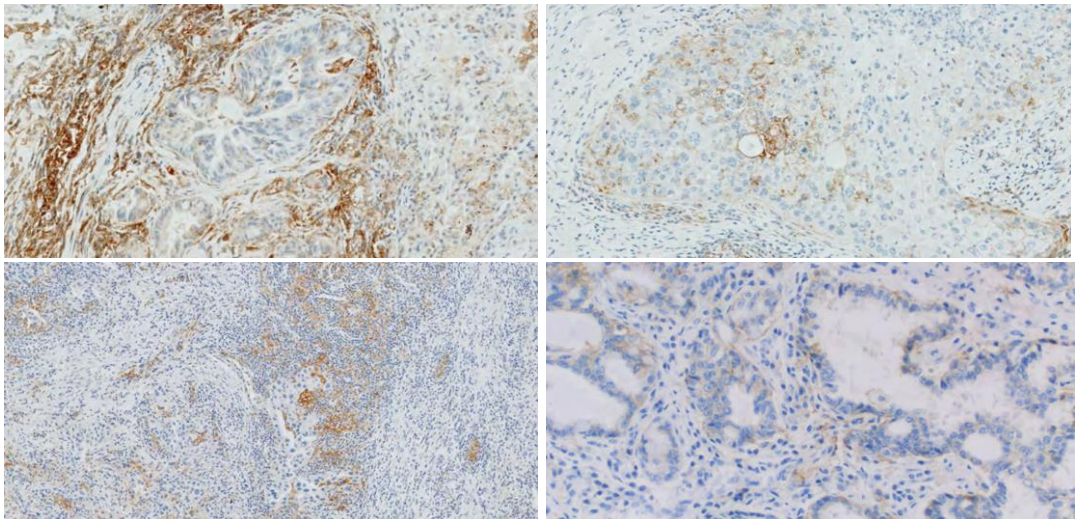
Гранулярное окрашивание



Антракоз и иммунные клетки

Руководство по интерпретации результатов 22C3 DAKO

Границы оценки TPS 0-49%



Руководство по интерпретации результатов 22C3 DAKO

Оценка экспрессии - визуальный или цифровой анализ?

Оригинальные исследования Original Investigations
Архив патологии 2020, т. 82, №6, с. 24-28 https://doi.org/10.17116/patol20208206124
Russian Journal of Archive of Patology = Arkhiv patologii 2020, vol. 82, no 6, pp. 24-28 https://doi.org/10.17116/patol20208206124

Оценка в биоптатах немелкоклеточных карцином легкого экспрессии PD-L1 с применением алгоритма нейросетевого анализа

© В.А. КУШНАРЕВ[1], Н.А. МАТЯШИНА[2], В.А. ШАПКИНА[1], Е.А. КУШНАРЕВА[3], Ю.А. КРИВОЛАПОВ[4], А.С. АРТЕМЬЕВА[1]

Таблица 2. **Распределение по группам коэффициентов согласия результатов оценки экспрессии визуальным и нейросетевым методами**

Группа	Коэффициент согласия, %	Коэффициент Максвелла
1-я	58	0,53
2-я	71	0,76
3-я	96	0,92

Таблица 1. **Сравнительная характеристика оценки уровня экспрессии PD-L1 по данным визуального и нейросетевого анализа в группах**

Тип анализа	1-я группа (отсутствие экспрессии), %	2-я группа (низкая экспрессия), %	3-я группа (высокая экспрессия), %
Визуальный	42	37	21
Нейросетевой	32	49	19

REVIEW ARTICLE

IASLC

PD-L1 Testing for Lung Cancer in 2019: Perspective From the IASLC Pathology Committee

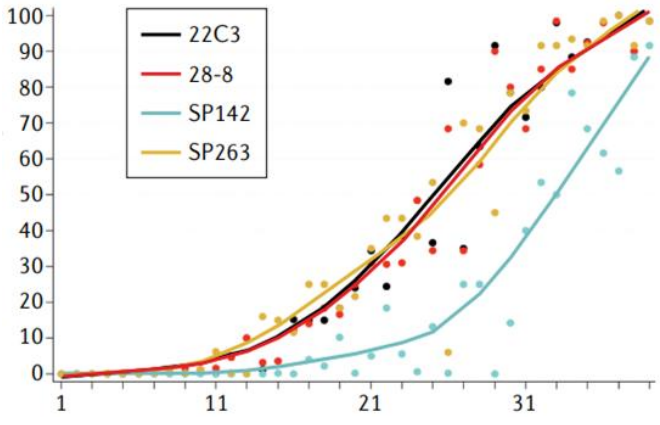
Check for updates

Table 1. Regulatory Approval Status of Pembrolizumab and Required PD-L1 Immunohistochemistry Assays in Selected Countries or Regions

	Pembrolizumab												
	Monotherapy										Combination (With Chemo) Therapy		
	First-Line for NSCLC				>Second-line for NSCLC				≥Third-Line for SCLC		First-Line		
Country	Approval Status[a]	PD-L1 Testing[b]	22C3 (TPS)	SP263 (TPS)	Approval Status[a]	PD-L1 Testing[b]	22C3 (TPS)	SP263 (TPS)	Approval Status[a]	PD-L1 Testing[b]	Approval Status[a]	Indication	PD-L1 Testing[b]
US	A	Companion	≥50%/ ≥1%	–	A	Companion	≥1%	–	A	NR	A	NSCLC	NR
EU	A	Companion	≥50%	≥50%	A	Companion	≥1%	≥1%	NA	–	A	NSCLC	NR
Canada	A	Companion	≥50%	–	A	Companion	≥1%	–	NA	–	A	NSCLC	NR
Japan	A	Companion	≥50%/ ≥1%	–	A	Companion	≥1%	–	NA	–	A	NSCLC	NR
Australia	A	Companion	≥50%	≥50%	A	Companion	≥1%	≥1%	NA	–	A[c]	non-SQC NSCLC	NR

[a]A, approved; A[c], approved, but not yet reimbursed; NA, not approved.
[b]Companion, companion diagnostic; NR, not required.
PD-L1; programmed death ligand 1; TPS, Tumor Proportion Score; EU, European Union; SQC, squamous cell carcinoma.

Разные клоны - разные цели?



Clinical Trial > J Thorac Oncol. 2017 Feb;12(2):208-222. doi: 10.1016/j.jtho.2016.11.2228. Epub 2016 Nov 29.

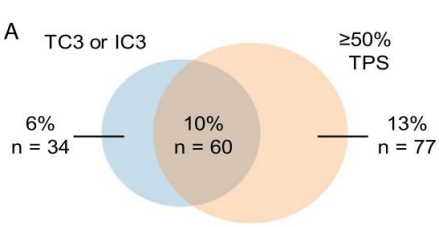
PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project

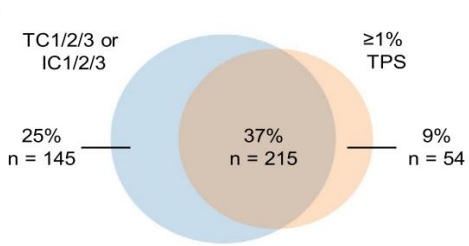
Doroshow, D.B., Bhalla, S., Beasley, M.B. *et al.* PD-L1 as a biomarker of response to immune-checkpoint inhibitors. *Nat Rev Clin Oncol* 18, 345–362 (2021). https://doi.org/10.1038/s41571-021-00473-5

Table 6. Studies Conducted to Assess the Analytical Comparability of FDA-Approved Commercial PD-L1 Immunohistochemistry Assays

Reference	Assays Included in Study				Major Observation/Conclusion on Assay Comparability	
	28-8	22C3	SP263	SP142	TC Staining	IC Staining
Scheel 2016[69]	√	√	√	√	• 28-8 and 22C3 reported comparable sensitivity • SP142 stained lower proportions to others by 36% 59% • SP263 stained higher proportions to others by 44% 59%	• SP142 and SP263 stained more intense
Kim 2017[70]	-	√	√	√	• 22C3 reported similar TPS at low cutoffs when compared with SP263, but higher TPS at high cutoffs (≥10%) • SP142 reported lowest TPS	• 22C3 and SP263 reported higher IC staining than SP142
Hirsch 2017[71]	√	√	√	√	• 28-8, 22C3, SP263 reported similar staining • SP142 reported weaker and fewer TC staining	• All four assays detected IC
Rimm 2017[72]	√	√	-	√	• 22C3 stained slightly less TC than 28-8 • SP142 detected significantly less PD-L1+ TC	• SP142 detected less PD-L1+ IC than 22C3 and 28-8
Ratcliffe 2017[78]	√	√	√	-	• All three assays reported comparable PD-L1 expression across all cutoffs	• Not assessed
Brunnström 2017[73]	√	√	√	√	• 22C3 and 28-8 reported highest weighted κ (0.89) • SP263 reported more PD-L1 + TC than 28-8 or 22C3 at both 1% and 50% cutoffs • SP142 reported lower PD-L1+ TC and κ (0.56 0.63) compared with all others	• Not assessed
Marchetti 2017[79]	-	√	√	-	• Very high concordance at 50% (Light's κ 0.99) and 1% (κ 0.80) cutoffs	• Not assessed
Fujimoto 2018[74]	√	√	√	√	• 22C3, 28-8, and SP263 reported good concordance (weighted κ 0.64-0.71) at 1% and 50% cutoffs • SP142 reported lower concordance vs other assays • 28-8, 22C3, and SP263 reported moderate • Accuracy and SP142 lower accuracy for clinical response to nivolumab	• Not assessed
Tsao 2018[75]	√	√	√	√	• 22C3 and 28-8 reported closest approximation • SP263 reported slightly greater sensitivity compared with 22C3 and 28-8. • SP142 reported less sensitivity to detect PD-L1 on TC	• 22C3, 28-8, and SP263 reported comparable IC staining distribution • SP142 reported lesser staining than the other three assays
Adam 2018[76]	√	√	√	√	• Very high concordance between 22C3, 28-8, and SP263 (weighted κ 0.71-0.89)	• Poor overall agreement between 22C3, 28-8, SP263
Hendry 2018[77]	√	√	√	√	• Highest concordance between 22C3 and 28-8 • SP263 consistently reported higher PD-L1+ TC than 22C3 and 28-8 • SP142 consistently reported lower PD-L1+ TC than all others	• Differences in IC staining mirrored TC staining • SP142 consistently reported lower IC staining • 28-8 consistently reported higher IC staining
Munari 2018[81]	-	√	√	-	• SP263 stained significantly more cases than 22C3 at both 1% and 50% cutoffs	• Not assessed
Fujimoto 2018[80]	-	√	√	-	• No difference between 22C3 and SP263 at various cutoffs ($p = 0.455$), with 88% 97% agreement rates	• Not assessed
Condé 2019[86]			√	√	• High concordance between SP263 and SP142: ICC of 0.97 and 0.97 (validation cohort)	• Lower correlation between SP263 and SP142 (0.74 0.68) • ICCs of 0.81 and 0.76 for SP263 and SP142

Выделение группы пациентов по типам экспрессии



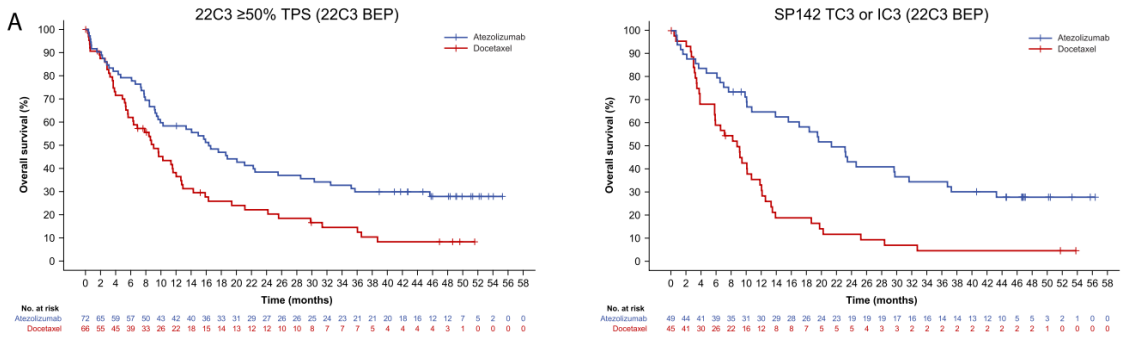


BEP, n = 576		22C3 TPS <50	22C3 TPS ≥50
SP142	TC0/1/2 or IC0/1/2	70% (405)	13% (77)
	TC3 or IC3	6% (34)	10% (60)

BEP, n = 575		22C3 TPS <1%	22C3 TPS ≥1%
SP142	TC0 and IC0	28% (161)	9% (54)
	TC1/2/3 or IC1/2/3	25% (145)	37% (215)

Shirish Gadgeel et al, Comparison of SP142 and 22C3 Immunohistochemistry PD-L1 Assays for Clinical Efficacy of Atezolizumab in Non–Small Cell Lung Cancer: Results From the Randomized OAK Trial, Clinical Lung Cancer

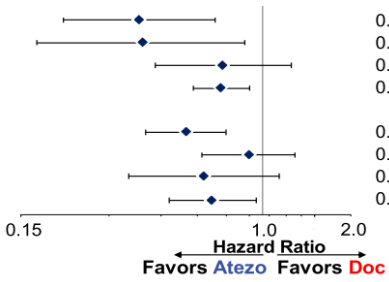
Выделение группы пациентов с высокой экспрессией



Shirish Gadgeel et al, Comparison of SP142 and 22C3 Immunohistochemistry PD-L1 Assays for Clinical Efficacy of Atezolizumab in Non–Small Cell Lung Cancer: Results From the Randomized OAK Trial, Clinical Lung Cancer

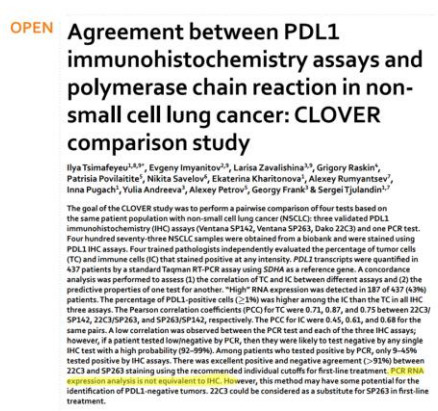
Выделение группы пациентов с высокой экспрессией

Subgroup	Atezo, n	Doc, n	OS HR (95% CI)	Median OS, mo: Atezo	Median OS, mo: Doc
22C3-BEP					
DP TC3 or IC3 AND TPS ≥50%	28	32	0.38 (0.21-0.69)	22.4	8.4
SP TC3 or IC3 AND TPS <50%	21	13	0.39 (0.17-0.87)	19.6	7.8
SP TC0/1/2 or IC0/1/2 AND TPS ≥50%	43	34	0.73 (0.43-1.25)	14.1	12.7
DN TC0/1/2 or IC0/1/2 AND TPS <50%	202	203	0.72 (0.58-0.90)	10.5	7.9
DP TC1/2/3 or IC1/2/3 AND TPS ≥1%	114	101	0.55 (0.40-0.75)	15.7	9.0
SP TC1/2/3 or IC1/2/3 AND TPS <1%	77	68	0.90 (0.62-1.29)	12.5	8.4
SP TC0 and IC0 AND TPS ≥1%	26	28	0.63 (0.35-1.14)	13.3	6.0
DN TC0 and IC0 AND TPS <1%	77	84	0.67 (0.48-0.95)	9.4	7.3



Shirish Gadgeel et al, Comparison of SP142 and 22C3 Immunohistochemistry PD-L1 Assays for Clinical Efficacy of Atezolizumab in Non–Small Cell Lung Cancer: Results From the Randomized OAK Trial, Clinical Lung Cancer

ПЦР, RNAseq или иммуногистохимия для PD-L1?

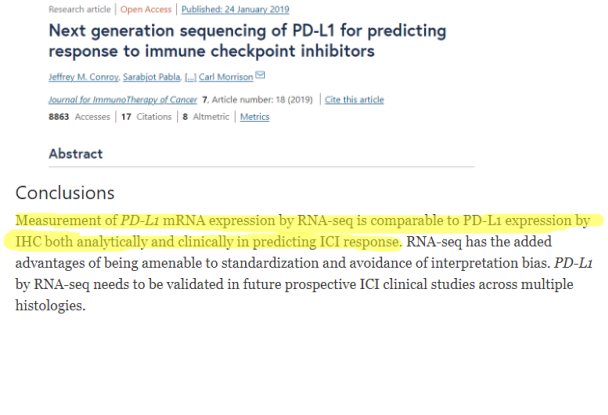


OPEN

Agreement between PDL1 immunohistochemistry assays and polymerase chain reaction in non-small cell lung cancer: CLOVER comparison study

Ilya Tsimafeyeu[1,8,9*], Evgeny Imyanitov[2,3], Larisa Zavalishina[3,9], Grigory Raskin[4], Patrisia Povilaitite[5], Nikita Savelov[6], Ekaterina Kharitonova[1], Alexey Rumyantsev[7], Inna Pugach[1], Yulia Andreeva[1], Alexey Petrov[1], Georgy Frank[1] & Sergei Tjulandin[1,7]

The goal of the CLOVER study was to perform a pairwise comparison of four tests based on the same patient population with non-small cell lung cancer (NSCLC): three validated PDL1 immunohistochemistry (IHC) assays (Ventana SP142, Ventana SP263, Dako 22C3) and one PCR test. Four hundred seventy-three NSCLC samples were obtained from a biobank and were stained using PDL1 IHC assays. Four trained pathologists independently evaluated the percentage of tumor cells (TC) and immune cells (IC) that stained positive at any intensity. *PDL1* transcripts were quantified in 437 patients by a standard Taqman RT-PCR assay using SDHA as a reference gene. A concordance analysis was performed to assess (1) the correlation of TC and IC between different assays and (2) the predictive properties of one test for another. "High" RNA expression was detected in 187 of 437 (43%) patients. The percentage of PDL1 positive cells (≥1%) was higher among the IC than the TC in all IHC three assays. The Pearson correlation coefficients (PCC) for TC were 0.71, 0.87, and 0.75 between 22C3/SP142, 22C3/SP263, and SP263/SP142, respectively. The PCC for IC were 0.45, 0.61, and 0.68 for the same pairs. A low correlation was observed between the PCR test and each of the three IHC assays; however, if a patient tested low/negative by PCR, then they were likely to test negative by any single IHC test with a high probability (92–99%). Among patients who tested positive by PCR, only 9–45% tested positive by IHC assays. There was excellent positive and negative agreement (>91%) between 22C3 and SP263 staining using the recommended individual cutoffs for first-line treatment. PCR RNA expression analysis is not equivalent to IHC. However, this method may have some potential for the identification of PDL1-negative tumors. 22C3 could be considered as a substitute for SP263 in first-line treatment.



Research article | Open Access | Published: 24 January 2019

Next generation sequencing of PD-L1 for predicting response to immune checkpoint inhibitors

Jeffrey M. Conroy, Sarabjot Pabla, [...] Carl Morrison

Journal for ImmunoTherapy of Cancer 7, Article number: 18 (2019) | Cite this article

8863 Accesses | 17 Citations | 8 Altmetric | Metrics

Abstract

Conclusions

Measurement of *PD-L1* mRNA expression by RNA-seq is comparable to PD-L1 expression by IHC both analytically and clinically in predicting ICI response. RNA-seq has the added advantages of being amenable to standardization and avoidance of interpretation bias. *PD-L1* by RNA-seq needs to be validated in future prospective ICI clinical studies across multiple histologies.

Спасибо за внимание