Lung cancer PD-L1 testing clinical impact

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Immune therapy with checkpoint-inhibitors
- overview -

	NSCLC	
	1st	2nd
Ipilimumab (anti-CTLA-4)		
Nivolumab (anti-PD-1)		+
Pembrolizumab (anti-PD-1)	+3,7	+2
Atezolizumab (anti-PD-L1)		+
Durvalumab (anti-PD-L1)	+	
Avelumab (anti-PD-L1)		

[1] = also in combination with Ipilimumab
[2] = only for PD-L1 positive tumors (TPS ≥ 1%)
[3] = only for PD-L1 positive tumors (TPS ≥ 50%)
[4] = FDA: 4. line or refractar (also pediatric pat.)
[5] = if Cisplatin is inapplicable
[6] = EMA: after BV-therapy+ auto-SZT; Pembro additionally after BV-Behandlung, if auto-SZT is not possible
[7] = in combination with Pemetrexed und Carboplatin in non-squamous NSCLC
[8] = only for PD-L1 positive Tumore (CPS ≥ 1)

Until now only FDA

MSD

PD-L1-testing

standardisation and harmonization in PD-L1-testing im NSCLC:

PD-L1-expression on tumor cells stained with the antibodies 28-8, 22-C3 und SP263 show similar results

Scheel et al, Harmonized PD-L1 immunohistochemistry for pulmonary squamous-cell and adenocarcinomas **Modern Pathology** 2016 Oct;29(10):1165-72.

Scheel et al, [Predictive PD-L1 immunohistochemistry for non-small cell lung cancer : Current state of the art and experiences of the first German harmonization study]. **Der Pathologe** 2016 Nov;37(6):557-567.

Hirsch et al, PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. **Journal of thoracic oncology** 2017 Feb;12(2):208-222.

Ratcliffe et al, A Comparative Study of PD-L1 Diagnostic Assays in Head and Neck Squamous Cell Carcinoma, Poster presented at the European Society for Medical Oncology (**ESMO**) Annual Meeting; Copenhagen, Denmark; 7–11 October 2016

Adam et al, Multicentric French harmonization study for PD-L1 IHC testing in non-small cell lung cancer, PL04.04a, presented at IASLC 17th World Conference On Lung Cancer, 4-7 December 2016, Vienna,Austria

the „International Association for the Study of Lung Cancer (IASLC)" has created an PD-L1-atlas with examples und practical recommendation (https://www.iaslc.org/sites/default/files/keytakeaways/pdl1_atlas_book_lo-res.pdf).

BMS

Conclusion of PD-L1 testing in NSCLC

	Atezolizumab	Nivolumab	Pembrolizumab	
Assay	SP 142	28-8	22C3	
Indication	2L	2L	1L	2L
PD-L1 required	No[ł]	No[ł]	≥ 50%	≥ 1%
Regimen	Single agent	Single agent	Single agent	Single agent

*With carboplatin and pemetrexed for adenocarcinomas only
ł Responses enriched when positive

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Ref.: Mod. Mansfield A, ASCO 2017

Overview of studies in 1. line therapy metastatic NSCLC

Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab	Avelumab
CheckMate 026 PhIII (N=541) 1L PD-L1-selected NSCLC Nivolumab monotherapy NCT02041533	**KEYNOTE-024** PhIII (N=305) 1L PD-L1-selected NSCLC Pembrolizumab monotherapy NCT02142738	**IMpower110** PhIII (N=570) 1L PD-L1-selected NSCLC Atezolizumab monotherapy NCT02409342	**MYSTIC** PhIII (N=1092) 1L NSCLC Durvalumab ± tremelimumab NCT02453282	**JAVELIN Lung 100** PhIII (N=1095) 1L PD-L1-selected NSCLC Avelumab monotherapy NCT02576574
CheckMate 227 PhIII (N=2220) 1L NSCLC Nivolumab monotherapy Nivolumab + ipilimumab Nivolumab + chemotherapy NCT02477826	**KEYNOTE-042** PhIII (N=1240) 1L PD-L1-selected NSCLC Pembrolizumab monotherapy NCT02220894	**IMpower150** PhIII (N=1202) 1L non-squamous NSCLC Atezolizumab + chemotherapy ± bevacizumab NCT02366143	**NEPTUNE** PhIII (N=960) 1L NSCLC Durvalumab + tremelimumab NCT02542293	
CheckMate 568 PhII (N=730) 1L NSCLC Nivolumab + ipilimumab Nivolumab + ipilimumab + chemotherapy NCT02659059	**KEYNOTE-021 Cohort G** PhII (N=123) 1L NSCLC Pembrolizumab + chemotherapy NCT02039674	**IMpower130** PhIII (N=650) 1L non-squamous NSCLC Atezolizumab + chemotherapy NCT02367781	**Study-006** PhIb (N=459) 1L NSCLC Durvalumab + tremelimumab NCT02000947	
CheckMate 012 PhI (N=412) 1L NSCLC Nivolumab monotherapy Nivolumab + chemotherapy targeted therapy/ipilimumab NCT01454102	**KEYNOTE-407** PhIII (N=560) 1L squamous NSCLC Pembrolizumab + chemotherapy NCT02775435	**IMpower131** PhIII (N=1025) 1L squamous NSCLC Atezolizumab + chemotherapy NCT02367794	**POSEIDON** PhIII (N=801) 1L NSCLC Durvalumab + tremelimumab NCT03164616	
	KEYNOTE-189 PhIII (N=570) 1L non-squamous NSCLC Pembrolizumab + chemotherapy NCT02578680	**IMpower132** PhIII (N=568) 1L non-squamous NSCLC Atezolizumab + chemotherapy NCT02367794		

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Overview: 2. line therapy in metastatic NSCLC

Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab	Avelumab
CheckMate 017 PhIII (N=272) 2L squamous NSCLC Nivolumab monotherapy NCT01642004	**KEYNOTE-010** PhII/III (N=1033) ≥2L PD-L1-selected (TPS ≥1%) NSCLC Pembrolizumab monotherapy NCT01905657	**POPLAR** PhII (N=287) ≥2L NSCLC Atezolizumab monotherapy NCT01903993	**ATLANTIC** PhII (N=1980) ≥3L NSCLC Durvalumab monotherapy NCT02087423	**JAVELIN Lung 200** PhIII (N=792) 2L NSCLC Avelumab monotherapy NCT02395172
CheckMate 057 PhIII (N=582) 2/3L non-squamous NSCLC Nivolumab monotherapy NCT01673867		**OAK** PhIII (N=850) ≥2L NSCLC Atezolizumab monotherapy NCT02008227	**ARCTIC** PhIII (N=730) ≥3L NSCLC Durvalumab ± tremelimumab NCT02352948	
CheckMate 078 PhIII (N=500) 2L NSCLC Nivolumab monotherapy NCT02613507				

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Overview of PD-L1 antibody clones, immunogenic and epitope region

- For all five PD-L1-antibody clones are different epitopes described

PD-L1 Ab clone	Immunogen [adapted from *datasheet or ** patent]	Epitope location
28-8	Purified recombinant human PD-L1 containing the extracellular domain of huPD-L1 (Phe19-Thr239).[1]	intracellular & extracellular
SP142	Synthetic peptide derived from the C-terminus of human PD-L1 protein.* (aa 279-290; SKKQSDTHLEET).**	intracellular & extracellular
SP263	Human PD-L1 (aa 272-290; CGIQDTNSKKQSDTHLEET).**	intracellular
E1L3N	Synthetic peptide corresponding to residues carboxy terminus of human PD-L1 protein.*	intracellular
22C3	Human extracellular domain of PD-L1 (Phe19-Thr239) fused to a human IgG1 fragment.**	extracellular 156-178 & 196-206; Not tested

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Ref.: Mod. Schats et al., ASCO 2017, Poster Display 3038
1. Phillips et al. Appl. Immunohistochem. Mol. Morphol. 2015 Mol. Morphol

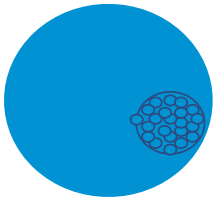
Overview of the differences between PD-L1 assay scoring algorithms in NSCLC

Antibody	company	TC	IC
SP263	AstraZeneca	X	
22C3	Merck	X	
28-8	BMS	X	
SP142	Roche	X	X
73-10	Pfizer	unknown	

Algorithm TC/IC

- TC: proportion of tumor cells positive for PD-L1 of any staining
- IC: proportion of tumor area occupied by PD-L1expressing ICs of any intensity
- Cut-offs for PD-L1 high:
  - TC ≥ 50% or
  - IC ≥ 10%

Calculation of the tumor status



100% of this area PD-L1

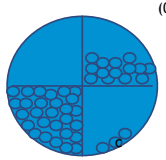
positive

overall percentage of positive cells

10%

Determination of the tumor status

(0%+10%+50%+100)/4=40%



Conclusion: OAK and POPLAR-study

- Results from the OAK und POPLAR study show, that all patients, independent from the PD-L1 status, can benefit from Atezolizumab-therapy
- A correlation of the PD-L1 status regarding Atezolizumab could be confirmed in both NSCLC-studies. Besides PD-L1 + tumor cells also PD-L1+ immune cells in the tumor were predictive regarding the clinical outcome of an Atezolizumab-therapy.
- Independent from PD-L1 test (SP142 or 22C3) NSCLC patients with no or less PD-L1 expression (<1%) could benefit from Atezolizumab-therapy.

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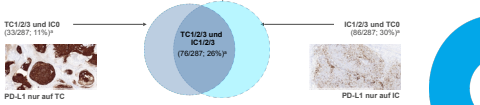
PD-L1expression on immune and tumor cells is predictive regarding the effect of Atezolizumab in NSCLC

- The PD-L1expression in immune cells or tumor cells is independently predictive for the overall survival (OS) with Atezolizumab vs. Docetaxel (POPLAR-study)

tumor cells are predictive:
>1% PD-L1 tumor cell expression (TC1/2/3) and <1% immune cell expression (IC0): HR = 0.37 (33 Pts)

Immune cells are predictive:
>1% immune cell expression (IC1/2/3) and <1% tumor cell expression (TC0): HR = 0.63 (86 Pts)



PD-L1 nur auf TC

PD-L1 nur auf IC

PD-L1 Status	OS HRb (95% CI)
TC1/2/3 and IC0	0,37 (0,12, 1,13)
IC1/2/3 and TC0	0,63 (0,36, 1,12)
TC1/2/3 and IC1/2/3	0,60 (0,34, 1,08)
TC1/2/3 or IC1/2/3	0,59 (0,40, 0,85)

a Number of patients within subgroup/total study population; Percentage of total study population. b Unstratified HR

Rittmeyer et al., DGP 2016; Data cutoff: 8th of May 2016

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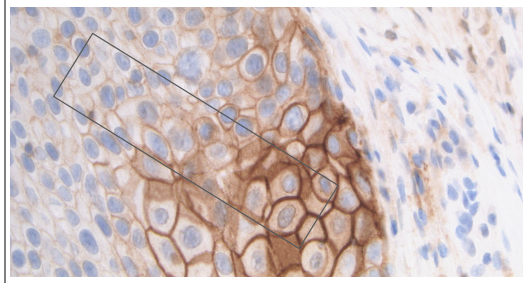
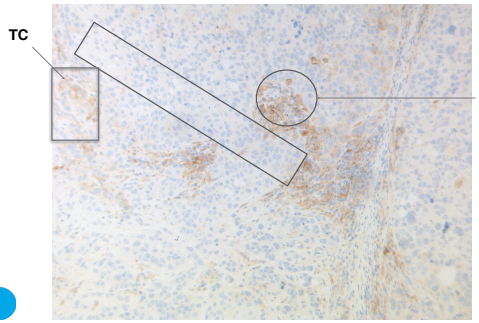
Herbst: Personalized targeted therapy for lung cancer (see Herbst 2018 in Nature)

tumor heterogeneity

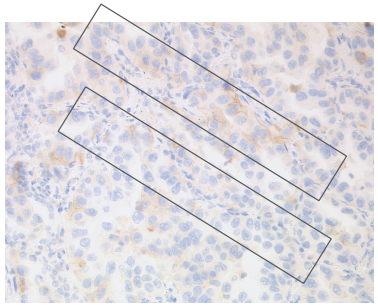
expression pattern: tumor cells



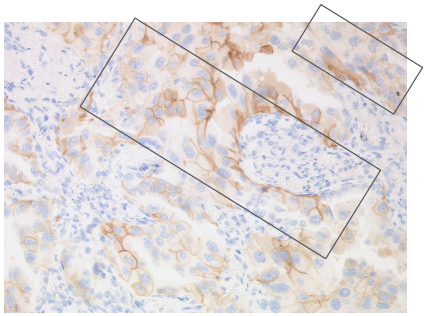
expression pattern: tumor cells



expression pattern: tumor cells



expression pattern: tumor cells



Questions

1. The cut-off of the PD-L1 expression pattern for the therapy with Pembrolizumab is

   A) none
   B) >1%
   C) >25
   D) ≥ 50%

2. Which statement is correct?

   A) the tumor-heterogeneity is not relevant regarding the interpretation of PD-L1 expression
   B) the tumor-heterogeneity is important regarding the interpretation of PD-L1 expression pattern
   C) the importance of tumor-heterogeneity depends on different PD-L1 antibodies

3. Which statement is correct?

   A) independent from PD-L1 test (SP142 or 22C3) NSCLC patients with no or less PD-L1 expression (<1%) could benefit from Atezolizumab-therapy.
   B) independent from PD-L1 test (SP142 or 22C3) NSCLC patients with no or less PD-L1 expression (<1%) do n
benefit from Atezolizumab-therapy.