2019台灣胸腔暨重症加護醫學會夏季會

2019 Summer Workshop of Taiwan Society of Pulmonary and Critical Care Medicine

PD-L1 and Immunotherapy

Real world data in Taiwan

23-JUN-2019 @ Yilan

台中榮總 胸腔內科

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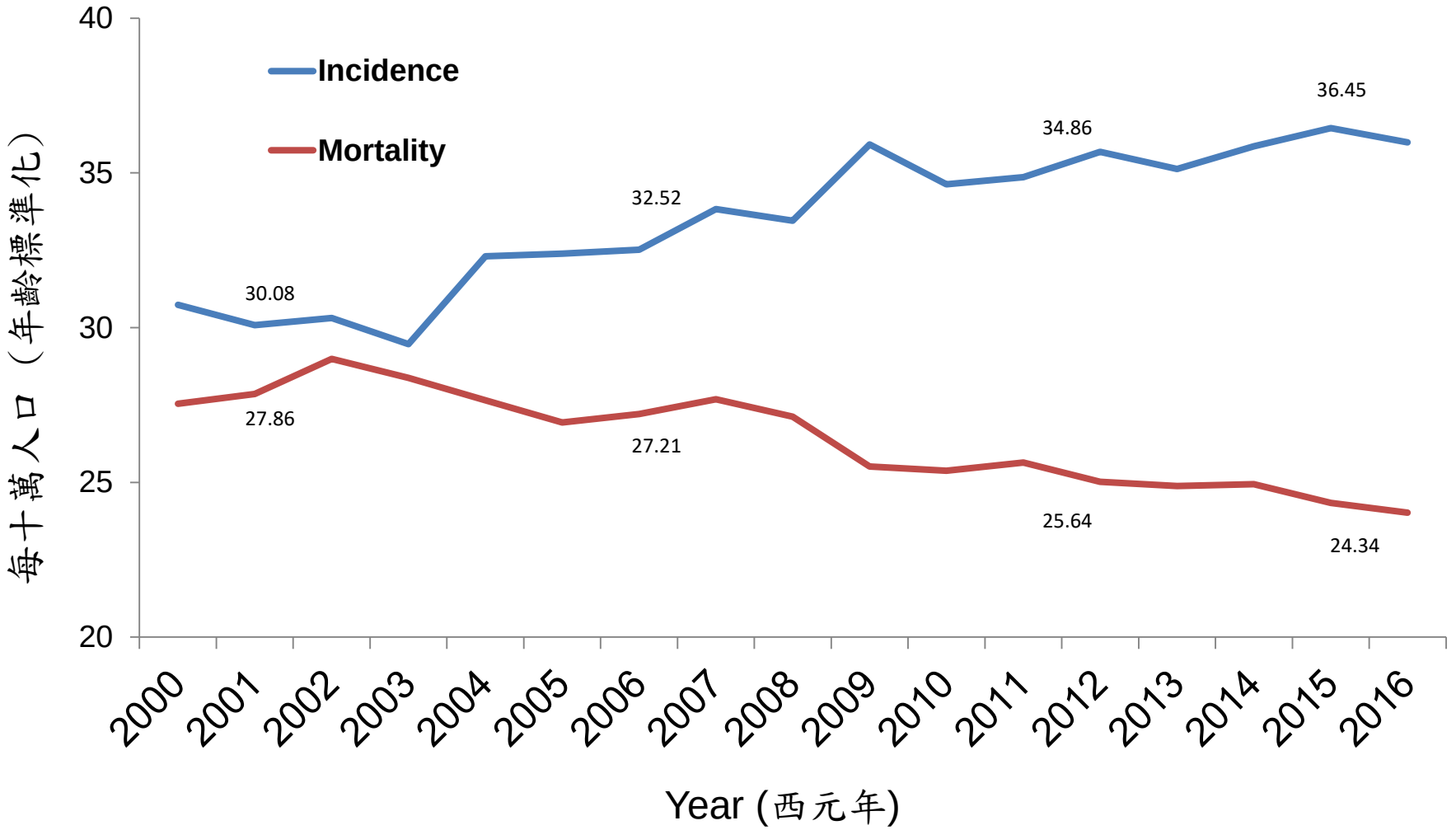
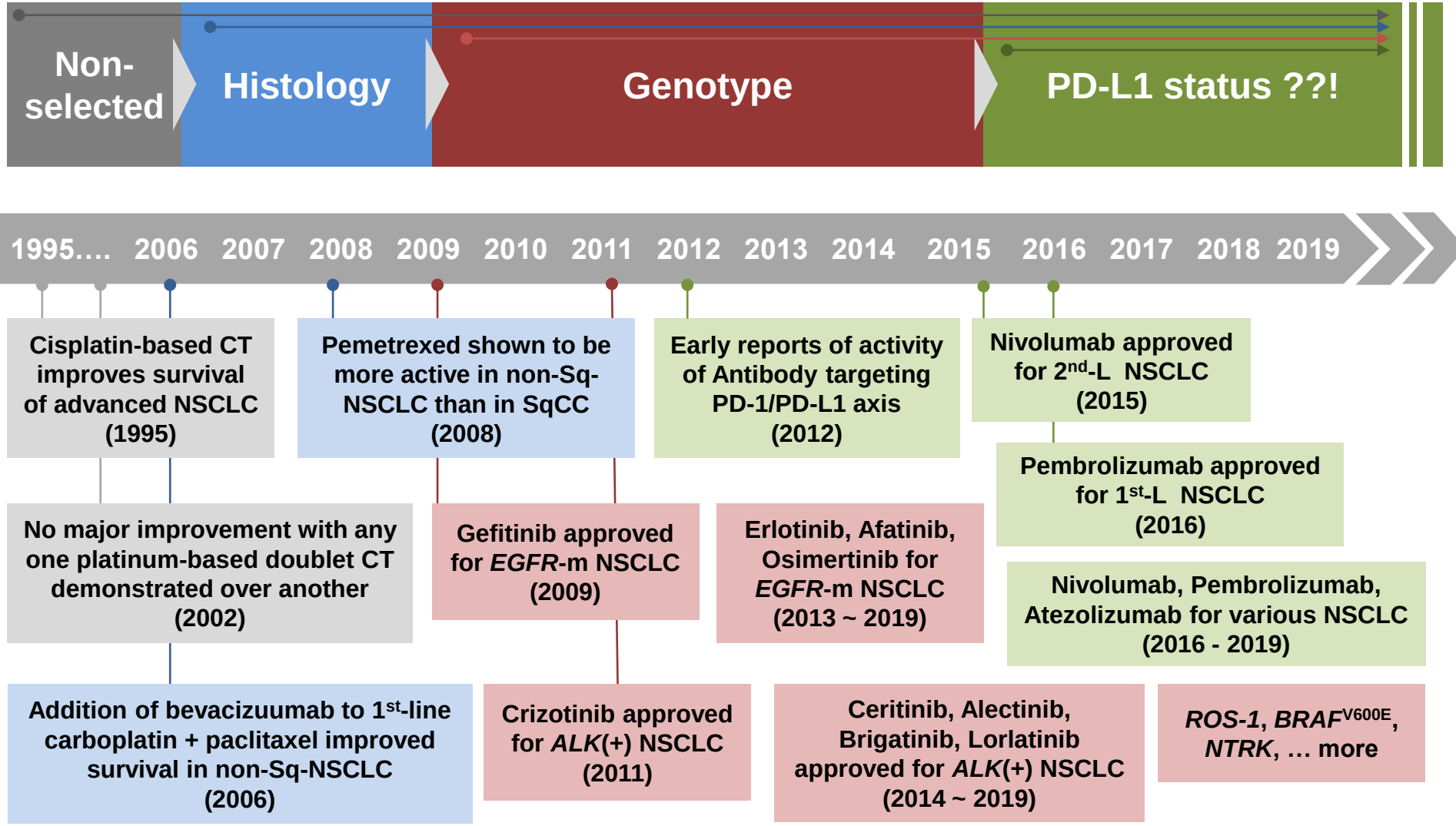
Trend of lung cancer incidence and mortality in Taiwan



資料來源：國健署

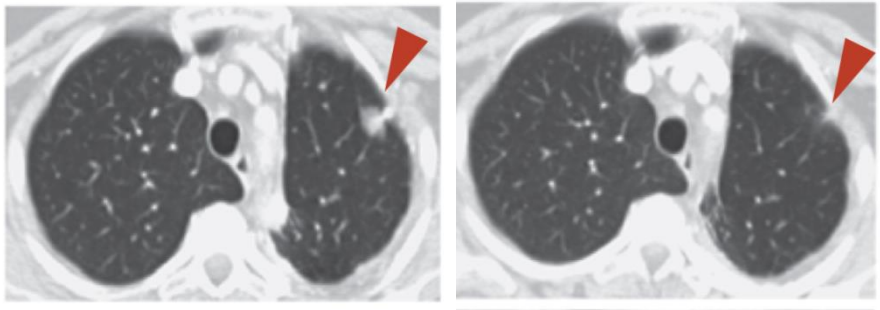
The way toward personalized therapy



The NEW ENGLAND JOURNAL of MEDICINE

Progress in Immunotherapy of Cancer

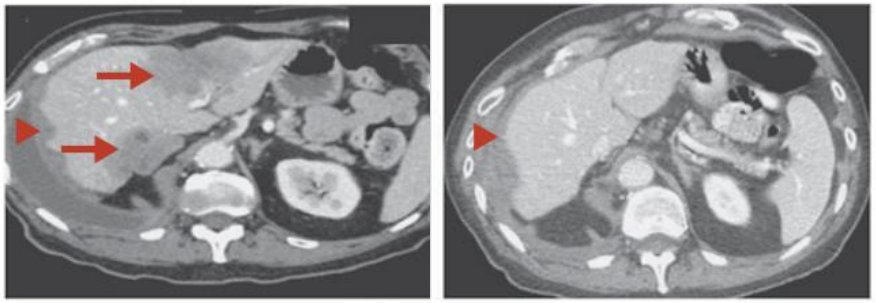
Before treatment | 4 months



An **anti-PD-1 antibody** developed by Bristol-Myers Squibb generates excitement with results from a phase I trial showing that, among 236 patients with various types of cancer, the treatment shrank tumors in 28 percent of melanoma patients, 30 percent of patients with kidney cancer, and **18 percent of patients with advanced non-small cell lung cancer**.

Topalian S et al. N Engl J Med 2012; 366:2443-54.

Before treatment | 15 months



An **anti-PD-L1 antibody** developed by Bristol-Myers Squibb generates excitement with results from a phase I trial showing that, among 207 patients with various types of cancer, the treatment shrank tumors in 17 percent of melanoma patients, 12 percent of patients with kidney cancer, 6 percent with ovarian cancer, and **10 percent of patients with advanced non-small cell lung cancer**.

Brahmer J et al. N Engl J Med 2012; 366:2455-65.

Integrate IO in lung cancer therapy

FDA indication

	Characters		NSCLC (wild type)			*EGFR*/ *ALK* Mutant	**IIIAB** CRT	SCLC ES
			1L		2L			
	Target	IHC	Mono	Combo				
Nivolumab	PD-1	28-8	-	-	✓	-	-	✓(3L)[3]
Pembrolizumab	PD-1	22C3	✓[P]	✓[1]	✓[P]	-	-	✓(3L)[3]
Atezolizumab	PD-L1	SP142	-	✓[2]	✓	-[E]	-	✓(1L)[4]
Durvalumab	PD-L1	SP263	-	-	-	-	✓	-

[1]Platinum/Pemetrexed/Pembrolizumab for non-Sq NSCLC and Platinum/Paclitaxel or albumin-bound Paclitaxel/ Pembrolizumab for SqCC.
[2]Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab (ABCP).
[3]After platinum-based therapy and at least one other prior line of therapy.
[4]Carboplatin/Etoposide/Atezolizumab.
[E]Approved by EMA.

[P]PD-L1 TPS ≥ 1% is required for Pembrolizumab monotherapy.

https://www.fda.gov/Drugs/ (Access on 19-JUN-2019)

Evidence to integrate IO in LC Tx.

First-Line Treatment

Study	Phase	Pt. No.	Pt.	ORR(%)	PFS(m)	OS(m)
KN-024[1]	III	154 vs. 151 (Pemb vs. CT)	PD-L1 ≥ 50% *E/A* Wild type	44.8*	10.3*	30.0*
KN-042[2]	III	637 vs. 637 (Pemb vs. CT)	PD-L1 ≥ 1% *E/A* Wild type	27.3	5.4	16.7*
KN-021G[3]	II	60 vs. 63 (Pemb/CaP vs. CaP)	Non-Sq NSCLC *E/A* Wild type	56.7*	19.0*	NR
KN-189[4]	III	410 vs. 206 (Pemb/CP vs. CP)	Non-Sq NSCLC *E/A* Wild type	47.6*	9.0*	22.0*
KN-407[5]	III	278 vs. 281 (Pemb/CaT vs. CaT)	Sq NSCLC	57.9*	6.4*	15.9*
IMP-150[6]	III	356 vs. 336 (A-BCP vs. BCP)	Non-Sq NSCLC *E/A* Wild type	63.5	8.3*	19.2*
IMP-133[7]	III	201 vs. 202 (A-CE vs. CE)	ES-SCLC	60.2	5.2*	12.3*

Pemb, Pembrolizumab; CT, Platinum-based chemotherapy; CaP, Carboplatin + Pemetrexed; CP, Cisplatin or Carboplatin + Pemetrexed; CaT, Carboplatin + Paclitaxel or albumin-bound Paclitaxel; A, Atezolizumab; BCP, Bevacizumab + Carboplatin + Paclitaxel; CE, Carboplatin + Etoposide; E/A, EGFR/ALK..

[1]Reck M et al. N Engl J Med 2016; 375:1823-33 & J Clin Oncol 2019; 37:537-46. [2]Mok T et al. Lancet 2019; 393:1819-30.
[3]Borghaei H et al. ESMO 2017. [4]Gandhi L et al. N Engl J Med 2018; 378:2078-92 & Gadgeel S et al. ASCO 2019.
[5]Paz-Ares L et al. N Engl J Med 2018; 379:2040-51. [6]Socinski MA et al. N Engl J Med 2018; 378:2288-301.
[7]Horn L et al. N Engl J Med 2018; 379:2220-9.

***Denote statistically significant.**

Evidence to integrate IO in LC Tx.

Second-Line Treatment or later

Study	Phase	Pt. No.	Pt.	ORR(%)	PFS(m)	OS(m)
CM-017[1]	III	135 vs. 137 (Nivo vs. Doc)	Sq NSCLC	20*	3.5*	9.2*
CM-057[2]	III	292 vs. 290 (Nivo vs. Doc)	Non-Sq NSCLC	19*	2.3	12.2*
KN-010[3]	II/III	345 vs. 343 (Pemb 2mg/kg vs. Doc)	NSCLC PD-L1 ≥ 1%	18*	3.9	10.4*
OAK[4]	III	425 vs. 425 (Atezo vs. Doc)	NSCLC	14	2.8	13.8*
CM-032[5]	I/II	109 (single arm) (Nivo mono)	ES-SCLC ≥ 2L of Tx.	12	1.4	5.6
KN-158[6] KN-028[7]	II Ib	83 (single arm) (Pemb mono)	ES-SCLC ≥ 2L of Tx.	19	-	-

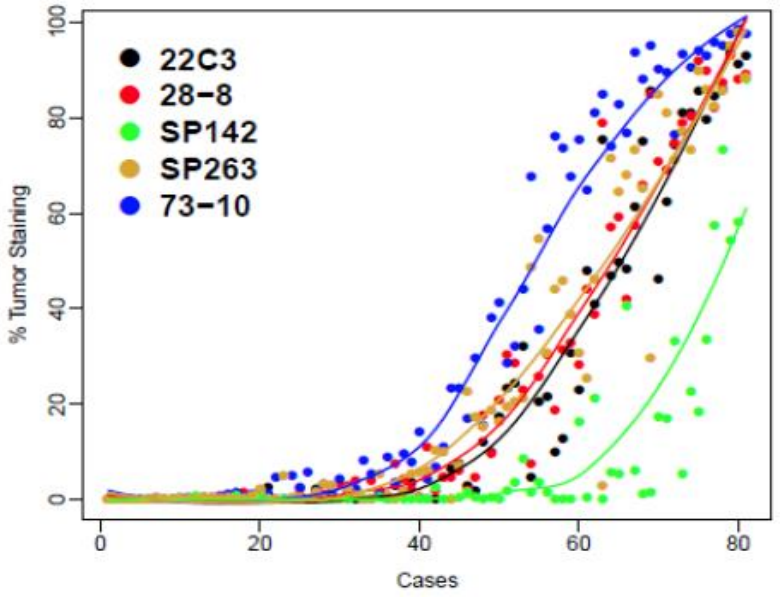
Nivo, Nivolumab; Pemb, Pembrolizumab; Atezo, Atezolizumab; Doc, Docetaxel; ***, denote statistically significant**.

[1]Brahmer J et al. N Engl J Med 2015;373: 123-35.
[2]Borghaei H. et al. N Engl J Med 2015;373:1627-39.
[3]Herbst RS et al. Lancet 2016;387:1540-50.
[4]Rittmeyer A et al. Lancet 2017;389: 255-65.
[5]Ready N et al. J Thorac Oncol 2019; 14:237-44.
[6]Chung HC et al. J Clin Oncol 2018; 36(Suppl; abstr 8506).
[7]Ott PA et al. J Clin Oncol 2017; 35:3823-9.

Assays of PD-L1 status

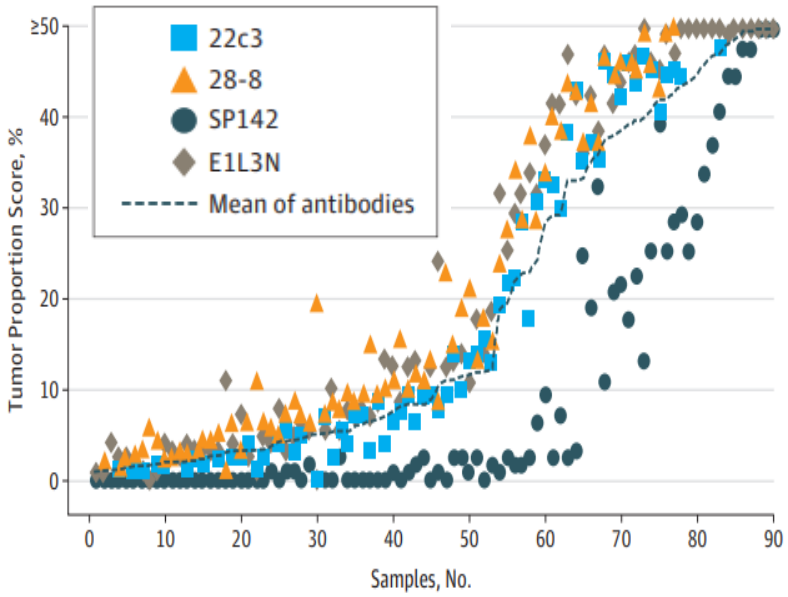
Drug/ Vendor	Nivolumab BMS	Pembrolizumab MSD	Atezolizumab Roche	Durvalumab Astra-Zeneca
Antibody	28-8	22C3	SP142	SP263
IVD partner	Dako	Dako	Ventana	Ventana
Scoring method	% cells with membrane staining at any intensity	% cells with membrane staining at any intensity	TC = tumor cells IC = immune cells Combine % and intensity	% cells with membrane staining at any intensity
Thresholds	1%, 5%, 10%	1%, 50%	TC3 = TC 50% IC3 = IC 10% TC2/IC2 = TC/IC 5% TC1/IC1 = TC/IC 1%	25%
Method	Pathologist/ subjective	Pathologist/ subjective	Pathologist/ subjective	Pathologist/ subjective
Regulatory	Complementary	Companion	Complementary	Complementary

Evidence of PD-L1 exam/comparability



Blueprint Phase 2 study

- **N = 81 lung tumors**
- **Larger cohort than BP-1.**
- **25 pathologists**
- **PD-L1 by 22C3, 28-8, and SP263 are comparable**



NCCN PD-L1 expression study

- **N = 90 lung tumors**
- **13 pathologists**
- **SP142 assay was an outlier, with a lower mean score of PD-L1 expression.**

Tsao MS et al. J Throac Oncol 2018; 13:1302-11; Rimm D et al. JAMA Oncol 2017; 3:1051-8.

“Real World Condition”

- **Characteristics of PD-L1**
- **Predictive value of PD-L1**
- **Efficacy of IO**

“Real World Condition”

- **Characteristics of PD-L1**
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PD-L1 expression in Taiwan LC

Author	Journal	Institute	Patients	IHC	Criteria	(+) %	Strong (+) %
Yang CY[1]	Eur J Cancer 2014	NTUH	Stage I ADC (n = 163)	Proteintech	≥ 5%	39.9	N/A
Chang YL[2]	Lung Cancer 2015	NTUH	LELC (n = 66)	Proteintech	≥ 5%	75.8	N/A
Yang CY [3]	Eur J Cancer 2016	NTUH	Stage I SqCC (n = 105)	Proteintech	≥ 5%	56.2	N/A
Chang YL[4]	Eur J Cancer 2016	NTUH	PPC (n = 122)	Proteintech	≥ 5%	70.5	N/A
Chang YL[5]	Oncotarget 2017	NTUH	SCLC (n = 186)	Proteintech	≥ 5%	78.0	N/A
Tseng JS[6]	J Immunother 2018	TCVGH	NSCLC (n = 211)	SP263 22C3	≥ 1% ≥ 50%	27.0 47.4	12.8 12.8
Lin SY[7]	J Cancer 2018	NTUH	Stage IIIB/IV NSCLC (n = 43)	22C3	≥ 1% ≥ 50%	76.7	39.5
Hsu JC[8]	PLoS One 2018	NCKUH	Stage IIIB/IV NSCLC (n = 24)	N/A	≥ 1%	16.7	N/A
Hsu KH & Huang YH[9]	Lung Cancer 2019	TCVGH	*EGFR*-m ADC (n = 123)	22C3	≥ 1% ≥ 50%	30.1	13.0
Kuo CH[10]	Thorac Cancer 2019	CGMH	Stage IIIB/IV NSCLC (n = 119)	22C3	≥ 50%	N/A	26.1

ADC, adenocarcinoma; LELC, lymphoepithelioma-like carcinoma; SqCC, squamous cell carcinoma, PPC, pleomorphic carcinoma.

[1]Yang CY et al. Eur J Cancer 2014; 50:1361-9.
[2]Chang YL et al. Lung Cancer 2015; 88:254-9.
[3]Yang CY et al. Eur J Cancer 2016; 57:91-103.
[4]Chang YL et al. Eur J Cancer 2016; 60:125-35.
[5]Chang YL et al. Oncotarget 2017; 8:18021-30.
[6]Tseng JS et al. J Immunother 2018; 41:292-9.
[7]Lin SY et al. J Cancer 2018; 9:1813-20.
[8]Hsu JC et al. PLoS One 2018; 13:e0202725.
[9]Hsu & Huang et al. Lung cancer 2019; 127:37-43.
[10]Kuo HS et al. Thorac Cancer 2019; 10:1158-66.

Patient characteristics	N = 211
Age (yr), median (range)	63 (35-90)
Gender, n (%)	
Male	136 (64.5)
Female	75 (35.5)
Smoking status, n (%)	
Non-smokers	92 (43.6)
Current/former smokers	119 (56.4)
Histology, n (%)	
Adenocarcinoma	156 (73.9)
Non-adenocarcinoma	55 (26.1)
- Squamous cell carcinoma	- 44
- Adenosquamous cell carcinoma	- 4
- Not otherwise specified (NOS)	- 7
Stage, n (%)	
I-IIIA	87 (41.2)
IIIB-IV	124 (58.8)
Actionable driver mutation[a], n (%)	
Positive[b]	95 (45.0)
Unfound/unknown/*KRAS*	116 (55.0)
Treatment history, n (%)	
Treatment-naïve	176 (83.4)
Post-treatment	35 (16.6)
Biopsy location, n (%)	
Primary tumor	143 (67.8)
Metastatic sites	68 (32.2)
Type of specimens, n (%)	
Histology	182 (86.3)
Cytology (cell block)	29 (13.7)

[a]Including *EGFR*, *ALK*, *HER2*, and $BRAF^{V600E}$ mutation(s).

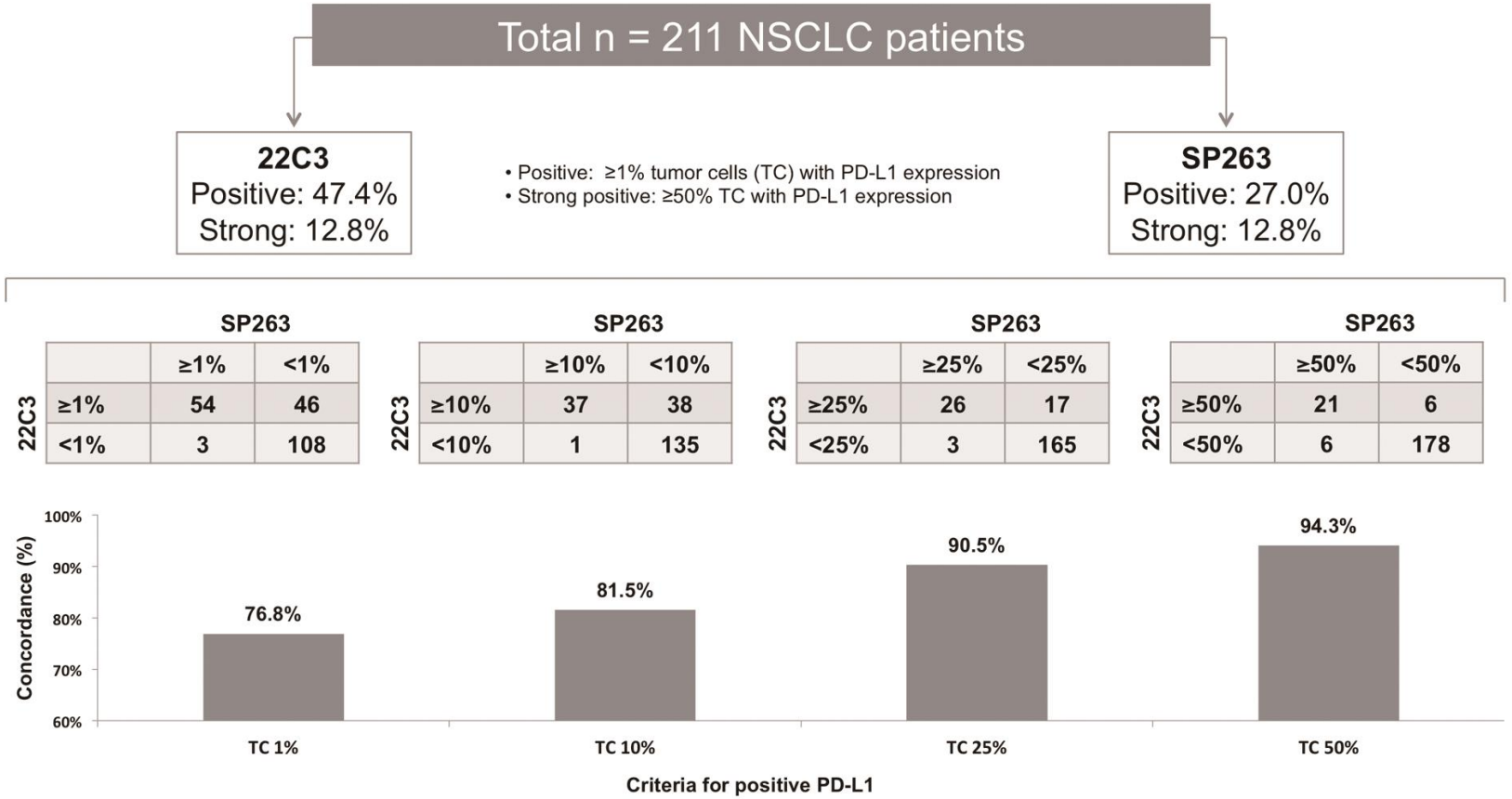
[b]Including one patient with *EGFR* and *KRAS* co-mutations.

PD-L1 assay at VGHTC

Total 211 NSCLC patients enrolled

Tseng JS et al. J Immunother 2018; 41:292-9.

Concordance of 22C3 and SP263



Tseng JS et al. J Immunother 2018; 41:292-9.

PD-L1 SP263 and Pt's characteristics

Characteristics	(+)[a] (%)	P value[c]	Strong (+)[b] (%)	P value[c]
Age		0.439		1.000
<65 years	29.3		12.9	
≥65 yrs	24.2		12.6	
Gender		0.196		0.017
Male	30.1		16.9	
Female	21.3		5.3	
Smoking status		0.019		0.001
Non-smokers	18.5		4.3	
C/F smokers	33.6		19.3	
Histology		0.008		0.032
Adenocarcinoma	21.8		9.6	
Non-adenocarcinoma	41.8		21.8	
Stage		0.042		0.037
I-IIIA	19.5		6.9	
IIIB-IV	32.3		16.9	
Actionable driver mutation[d]		0.020		0.003
Positive[e]	18.9		5.3	
Unfound/unknown/*KRAS*	33.6		19.0	
Treatment history		0.302		0.409
Treatment-naïve	25.6		11.9	
Post-treatment	34.3		17.1	
Biopsy location		0.032		0.185
Primary tumor	22.4		10.5	
Metastatic sites	36.8		17.6	
Type of specimens		0.369		0.771
Histology	25.8		12.6	
Cytology	34.5		13.8	

C/F smokers, current/former smokers; ADC.

[a]≥1% tumor cells with PD-L1 expression.

[b]≥50% tumor cells with PD-L1 expression.

[c]By Fisher's exact test.

[d]Including *EGFR*, *ALK*, *HER2*, and $BRAF^{V600E}$ mutation(s).

[e]Including one patient with *EGFR* and *KRAS* co-mutations.

Tseng JS et al. J Immunother 2018; 41:292-9.

Multivariate analysis

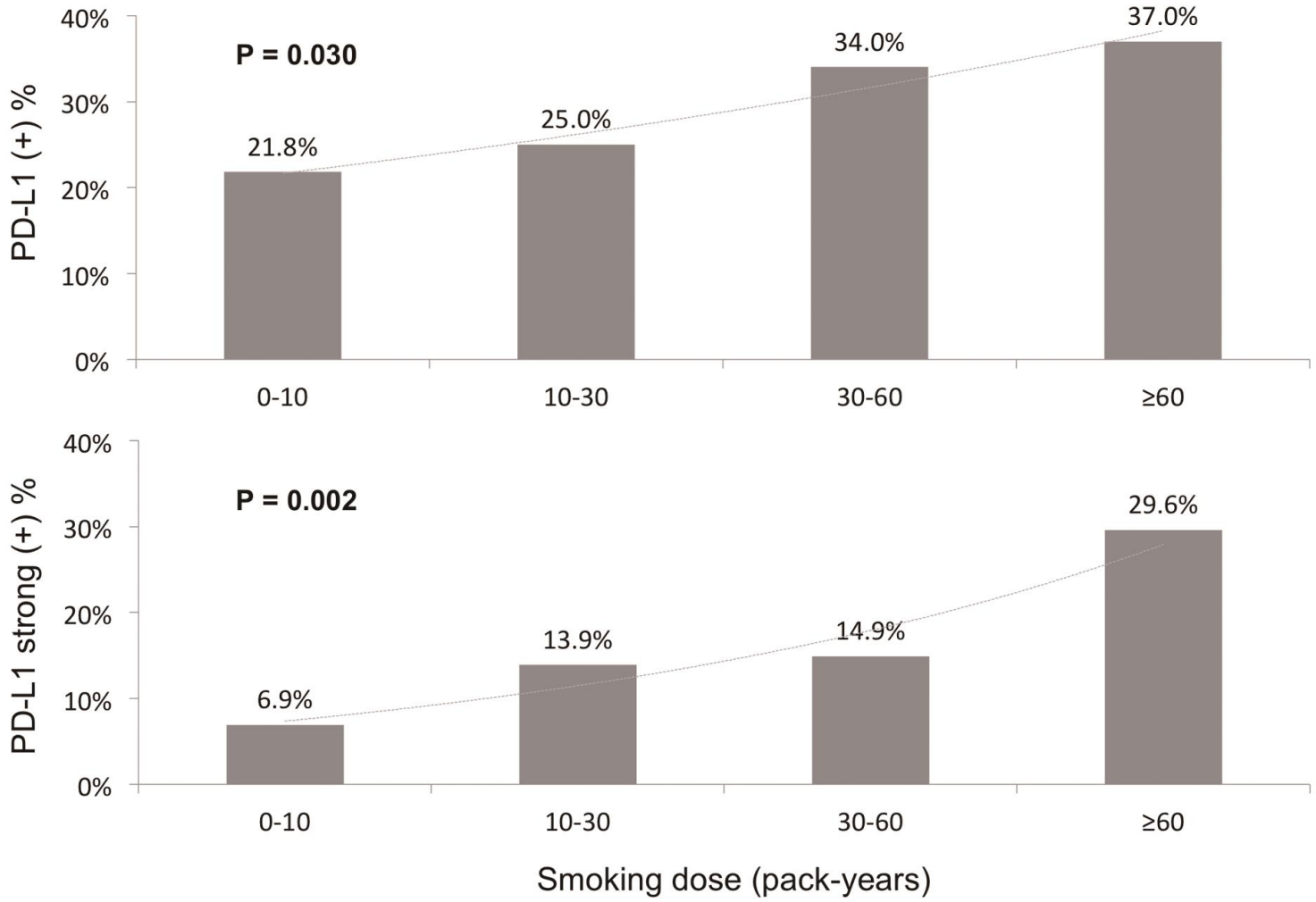
Strong PD-L1 expression

Factor	Adjusted OR	95% CI	P value
Smoking status C/FS *vs.* NS	5.00	1.60-15.64	0.006
Actionable driver mutation(s)* Unfound/unknown/*KRAS vs.* With	3.59	1.25-10.33	0.018
Tumor stage Stage IIIB/IV *vs.* I-IIIA	3.83	1.41-10.43	0.009

C/FS, current/former smokers; NS, non-smokers.
*Include *EGFR*, *ALK*, *HER2*, and *BRAF*^{V600E}.

Tseng JS et al. J Immunother 2018; 41:292-9.

Smoking dose and SP263 PD-L1



Tseng JS et al. J Immunother 2018; 41:292-9.

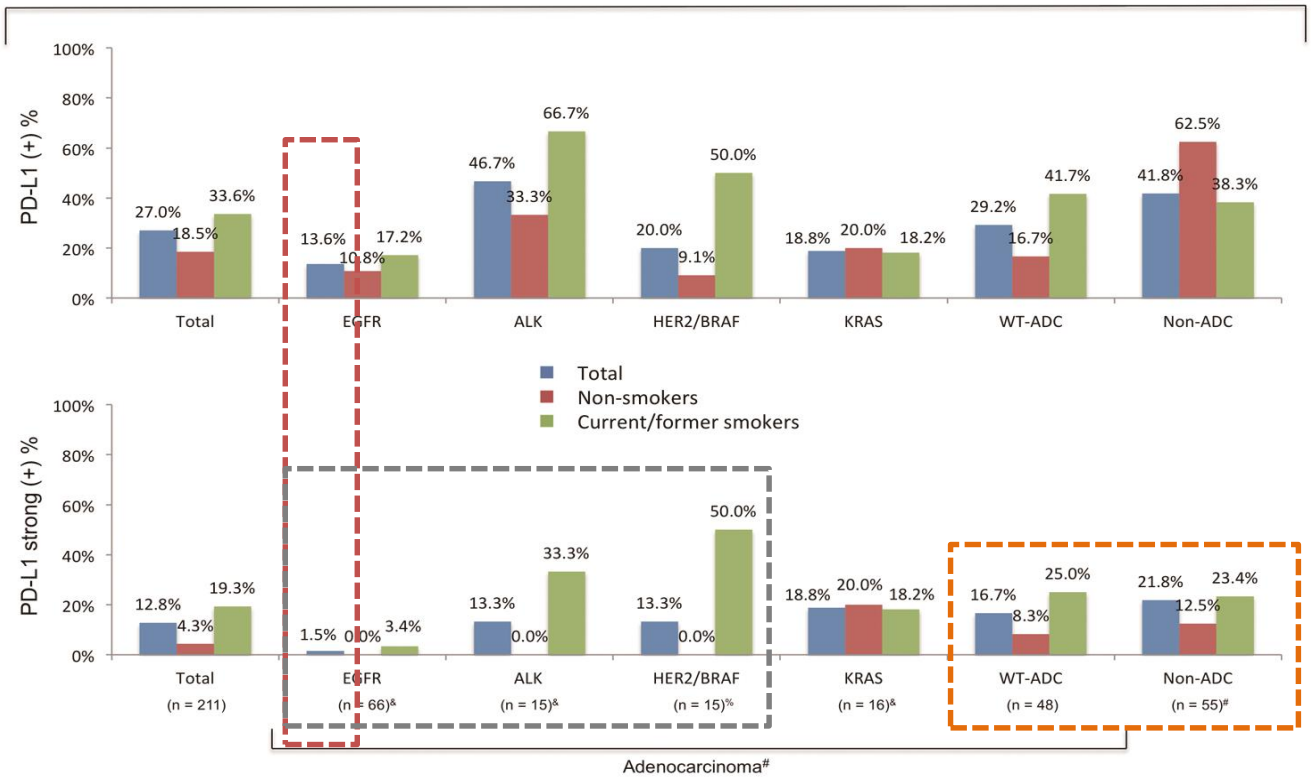
Integrated analysis of smoking, histology, driver mutation(s)

NSCLC patients
at VGHTC, n = 211
(2009/12 ~ 2017/3)

Smoking status
(NS [92] *vs.* C/FS [119])
- Positive: 18.5 *vs.* 33.6%*
- Strong: 4.3 *vs.*19.3%*

Histology
(ADC [156] *vs.* non-ADC [55])
- Positive: 21.8 *vs.* 41.8%*
- Strong: 9.6 *vs.* 21.8%*

Actionable driver mutation$
([+] [95] *vs.* [-]/unknown/*KRAS* [116])
- Positive: 18.9 *vs.* 33.6%*
- Strong: 5.3 *vs.* 19.0%*



PD-L1 status by SP263 IHC ([+]: ≥1% tumor cells with positive staining; strong [+]: ≥50% tumor cells with positive staining).
NS, non-smokers; C/FS, current/former smokers; ADC, adenocarcinoma; WT, wild type.
$Include *EGFR*, *ALK*, *HER2*, and *BRAF* mutation(s).
&Include 1 patients with *EGFR*/*ALK* co-mutation and 1 patient with *EGFR*/*KRAS* co-mutation.
%Include 12 *HER2* mutation and 3 *BRAF* mutation; PD-L1 (+)/strong (+) rate were 8.3%/0.0% in *HER2* and 66.7%/66.7% in *BRAF*.
#Include 2 patients with adenosquamous cell carcinoma (1 with *EGFR* mutation and 1 with *KRAS* mutation).
*P value < 0.05.

Tseng JS et al. J Immunother 2018; 41:292-9.

“Real World Condition”

- **Characteristics of PD-L1**
- Predictive value of PD-L1
- Efficacy of IO

- Current data were NOT yet enough to illustrate the whole picture of PD-L1 expression in Taiwan lung cancer patients.
- Higher criteria of PD-L1 positivity was associated with a higher concordance rate between 22C3 and SP263 assays.
- Driver mutation(s), smoking status (dose), tumor stage, and possible histology are associated with PD-L1 expression.
- Roughly, 15-20% of wild type ADC patients and 20-25% non-ADC patients had strong PD-L1 expression.

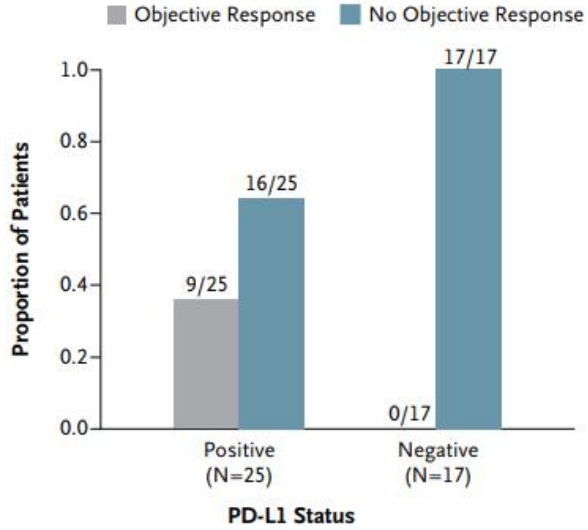
“Real World Condition”

- Characteristics of PD-L1
- **Predictive value of PD-L1**
- Efficacy of IO

Is PD-L1 a useful biomarker for IO?

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

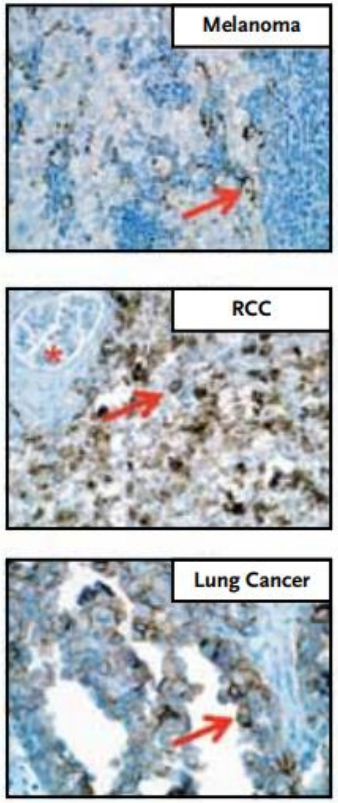
Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D.,



Association between Pretreatment Tumor PD-L1 Expression and Clinical Response

Response Status	PD-L1–Positive	PD-L1–Negative	Total
		number (percent)	
Objective response	9 (36)	0	9 (21)
No objective response	16 (64)	17 (100)	33 (79)
All	25	17	42

P=0.006 for association by Fisher's exact test



Nivolumab (BMS-936558); PD-L1 status by monoclonal Ab 5H1 (5% as threshold)

Topalian S et al. NEJM 2012.

RESEARCH ARTICLE

Effectiveness and safety of immune checkpoint inhibitors: A retrospective study in Taiwan

Jason C. Hsu[1]*, Jia-Yu Lin[2], May-Ying Hsu[2], Peng-Chan Lin[3]

PLOS ONE

- NCKUH cohort
- N = 50; of them, 24 patients (48%) were NSCLC.
- Median PFS and OS were 4.9 months and 13 months, respectively.

Table 4. Effectiveness of immuno-therapies.

Cancer Type			n	Overall Survival (Months)			Progression Free Survival (Months)		
				Mean	Median	Log Rank p-value	Mean	Median	Log Rank p-value
Overall Cancer Types			50	23.37	Didn't reach		15.00	4.90	
Non-Small Cell Lung Cancer (NSCLC)			24	11.73	13.00		9.17	4.90	
	Gender	Male	11	11.97	Didn't reach	0.801	10.13	11.53	0.672
		Female	13	9.70	13.00		7.13	4.43	
	Age	≧65	10	14.07	Didn't reach	0.175	10.67	5.37	0.416
		<65	14	8.50	11.53		6.27	4.43	
	Histological subtype	squamous cell	2	1.00	0.63	0.010	1.37	1.37	0.272
		non-squamous cell	22	12.70	Didn't reach		9.47	4.90	
	Stage	IV	20	12.07	Didn't reach	0.794	9.77	5.37	0.451
		III	4	7.10	2.23		4.57	2.03	
	EGFR mutation	mutation	7	12.13	11.53	0.969	9.90	11.53	0.949
		non-mutation	17	9.67	13.00		7.30	4.90	
	PD-L1	positive	4	13.00	13.00	0.378	10.40	Didn't reach	0.186
		negative	20	10.80	11.53		8.03	2.60	
	Hepatitis B virus	carriers	4	11.53	11.53	0.453	9.03	11.53	0.559
		non-carriers	20	10.90	13.00		8.50	4.43	
	Timing of treatment	first line treatment	3	9.43	Didn't reach	0.673	9.43	Didn't reach	0.446
		second or third line treatment	21	11.50	13.00		8.67	4.90	

Hsu JC et al. PLoS One 2018; 13:e0202725.

IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2018; 9(10): 1813-1820. doi: 10.7150/jca.24985

Research Paper

Tumor PD-L1 Expression and Clinical Outcomes in Advanced-stage Non-Small Cell Lung Cancer Patients Treated with Nivolumab or Pembrolizumab: Real-World Data in Taiwan

Characteristic	n	
Age, median (range)	62.1	34.1-86.7
Male, %	43	58.1%
Stage IIIB/IV	2/72	
Smokers, %	31/71	52.7%
Histology, %		
Adenocarcinoma	48	64.9%
Squamous cell carcinoma	14	18.9%
Pleomorphic carcinoma	4	5.4%
Lymphoepithelioma-like carcinoma	6	8.1%
Poorly differentiated carcinoma	2	2.7%
ECOG ≥ 2 before anti-PD-1 treatment	36	48.6%
Radiotherapy before anti-PD-1 treatment	47	63.5%
Nivolumab/Pembrolizumab	24/50	
Anti-PD-1 as ≥ 3L treatment	51	68.9%
Previous lines of treatment, median (range)	3	0-10
Brain metastasis, %	33	44.6%
EGFR mutation, %	25/61	41%
KRAS mutation. %	10/40	25%
PD-L1 status,%		
≥50%	17/43	39.5%
1-50%	16/43	37.2%
<1%	10/43	23.3%

Abbreviations: 3L: third line. ECOG: Eastern Cooperative Oncology Group performance status. EGFR: epidermal growth factor receptor. KRAS: Kirsten rat sarcoma virus oncogene homolog.

- Nivolumab/Pembrolizumab = 24/50
- ECOG PS ≥ 2: 48.6%
- IO as ≥ 3L treatment: 68.9%
- Brain metastasis: 44.6%

- ORR: 32% in 47 evaluable patients

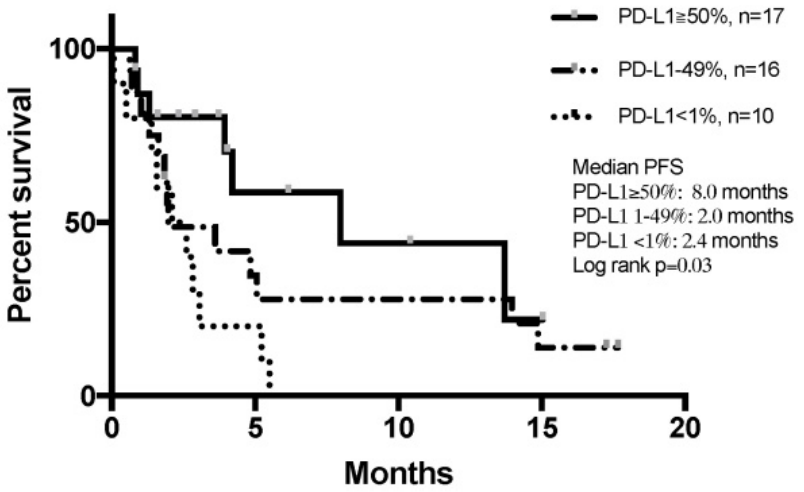
- PFS: 1.8m (1yr PFS rate 14%)
- OS: 7.9m (1yr OS rate 46%)

Lin SY et al. J Cancer 2018; 9:1813-20.

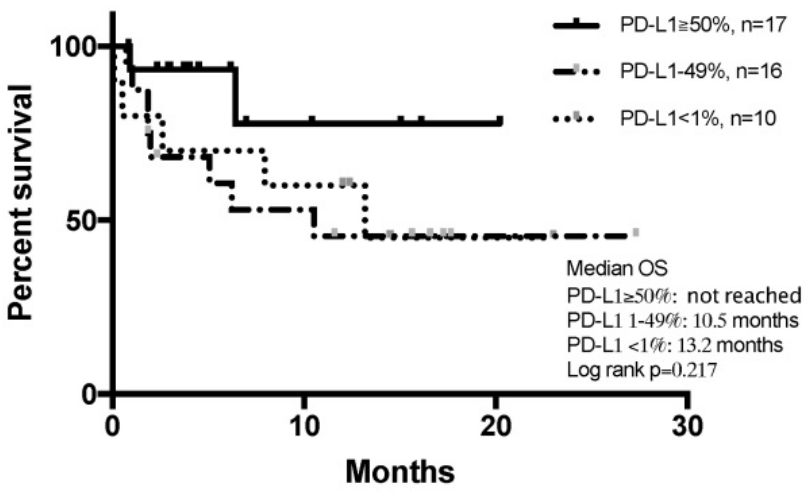
PD-L1 as a predictor of IO - NTUH

	ORR (%)	P value
PD-L1 < 1%	25.0%	0.195
PD-L1 1-49%	28.6%	
PD-L1 ≥ 50%	**46.7%**	

E: Progression free survival stratified by PD-L1



F: Overall survival stratified by PD-L1



Lin SY et al. J Cancer 2018; 9:1813-20.

Patient characteristics	N = 34
Age (yr), median (range)	57 (45-89)
Gender, n (%)	
Male	24 (70.6)
Female	10 (29.4)
Smoking status, n (%)	
Non-smokers	16 (47.1)
Current/former smokers	18 (52.9)
Histology, n (%)	
Adenocarcinoma	24 (70.6)
Non-adenocarcinoma	10 (29.4)
- Squamous cell carcinoma	- 7
- Adenosquamous cell carcinoma	- 2
- Not otherwise specified (NOS)	- 1
Stage, n (%)	
IIIB-IV(M1A)	10 (29.4)
IV(M1B)	24 (70.6)
ECOG PS	
0-1	17 (50.0)
2	9 (26.5)
3-4	8 (23.5)
Actionable driver mutation, n (%)	
Positive[a]	5 (14.7)
Unfound/unknown/*KRAS*[b]	29 (85.3)
Treatment history, n (%)	
<3 regiments	15 (44.1)
≥3 regiments	19 (55.9)

ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]Including 3 with *EGFR* mutation, 1 with *EGFR-ALK* co-mutations, and 1 with *HER2* mutation.

[b]Including 4 with *KRAS* mutation.

IO Efficacy and PD-L1

(n = 34)

- IO: Nivolumab=8 and Pembrolizumab=26
- Monotherapy=23 and Combined Tx.=11
- Thoracic R/T: without=27, with=7

- PD-L1 status (SP263):
  - ≥1%: 14 (41.2%) positive
  - ≥50%: 6 (17.6%) positive

Tseng JS et al. J Immunother 2018; 41:292-9.

Efficacy of IO

Outcome	Result
Objective response rate	15.2%
Disease control rate	33.3%
Progression-free survival	1.8 (95% CI 1.5-2.1) months

Strong PD-L1 expression as predictive factor of IO

Outcome	PD-L1 High	PD-L1 (-)/low	P value
ORR	66.7%	3.7%	0.002
DCR	83.3%	22.2%	0.010
PFS	7.2m (2.0-12.5)	1.6m (1.2-2.1)	0.008
	aHR 0.15 (95% CI 0.03-0.71)		0.017

- **PD-L1 positivity (1%) did not correlate with ORR and PFS (P = 0.138 and 0.247, respectively).**
- **ECOG PS correlated with PFS and OS, too (aHR 0.25 [95% CI 0.10-0.63], P = 0.003 and aHR 0.07 [95% CI 0.02-0.28], P < 0.001).**

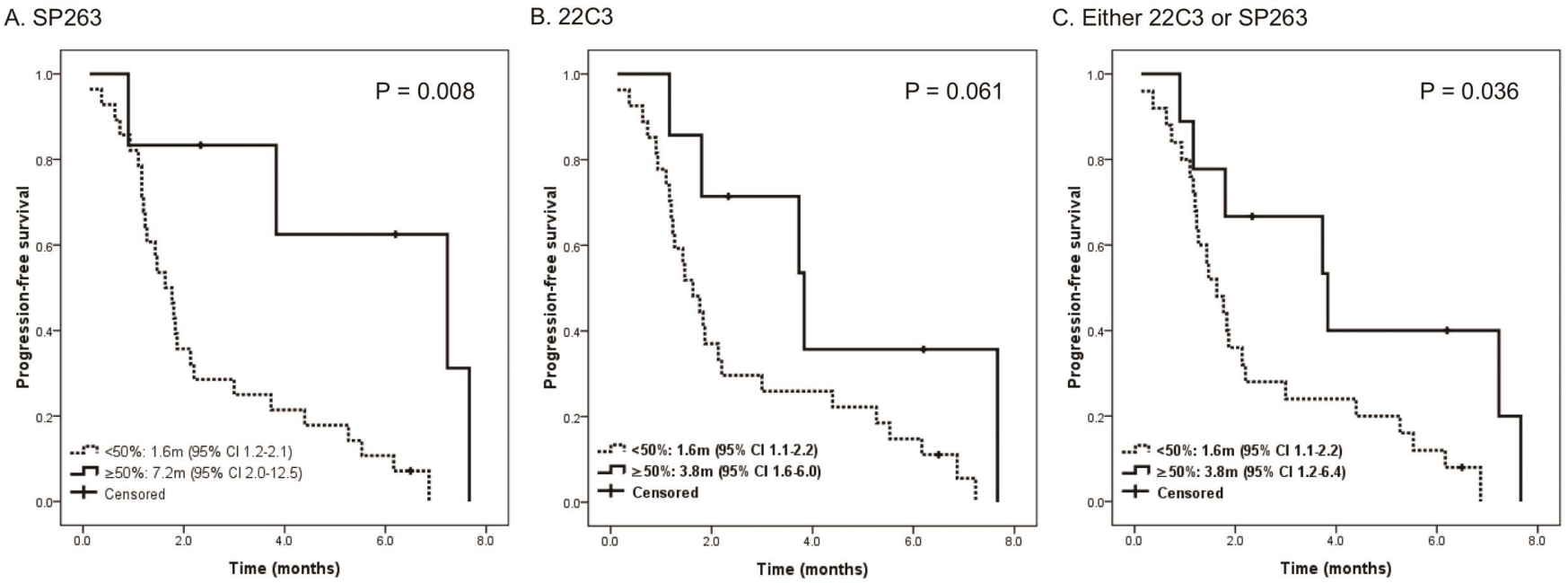
Tseng JS et al. J Immunother 2018; 41:292-9.

PD-L1 status by 22C3 and SP263

PD-L1 assay	Strong PD-L1, n	(%)
SP263	6	17.6
22C3	7	20.6
Either assay(s)	9	26.5

*Total 7 patients with discordant PD-L1 results by 22C3 and SP263 assays.

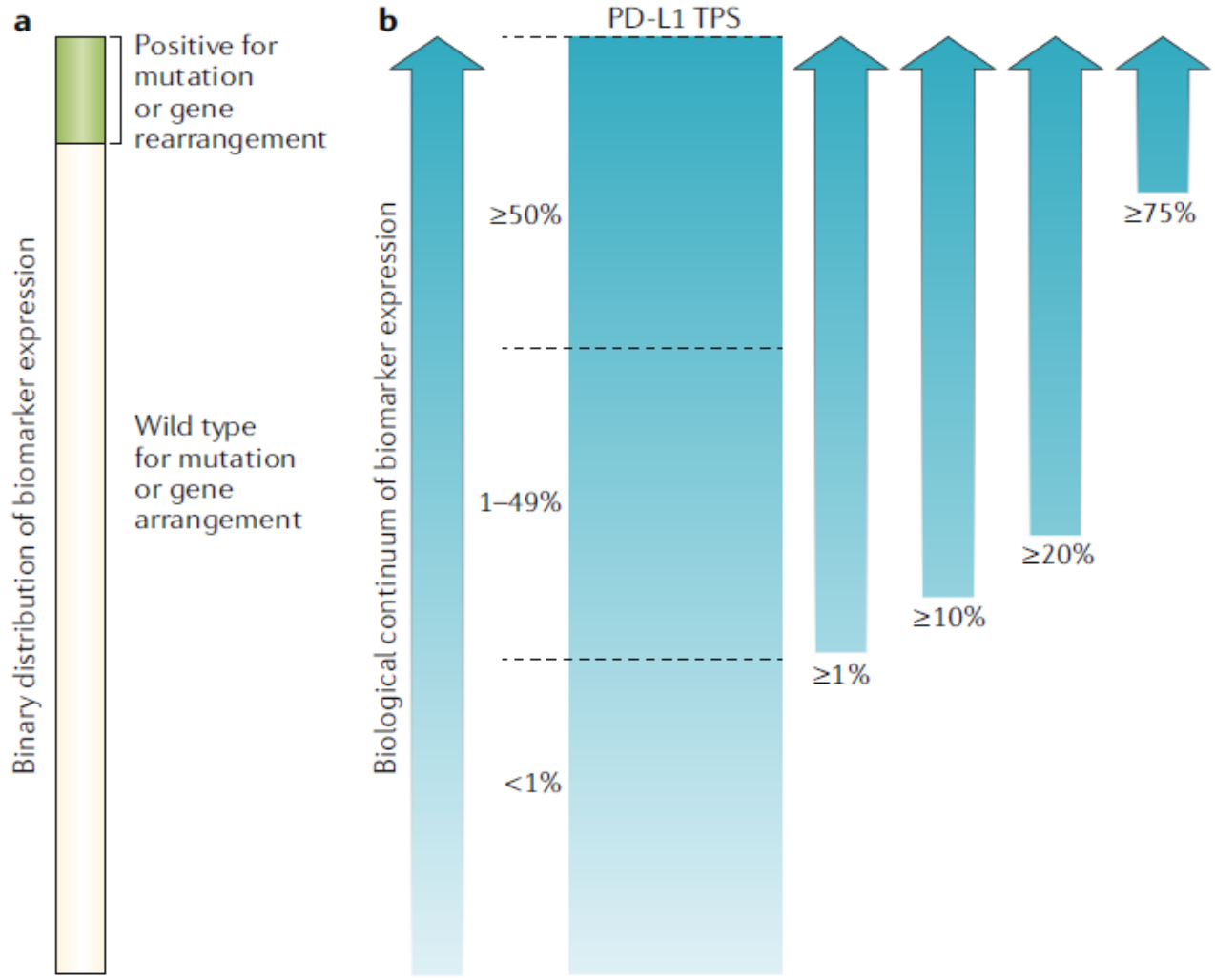
PFS and various PD-L1 assays



PD-L1 status by 22C3 and SP263 assay with ≥50% as positivity criteria.
N = 34 lung cancer patients receiving PD-1/PD-L1 inhibitors.
P value by log-rank test.

Tseng JS et al. J Immunother 2018; 41:292-9.

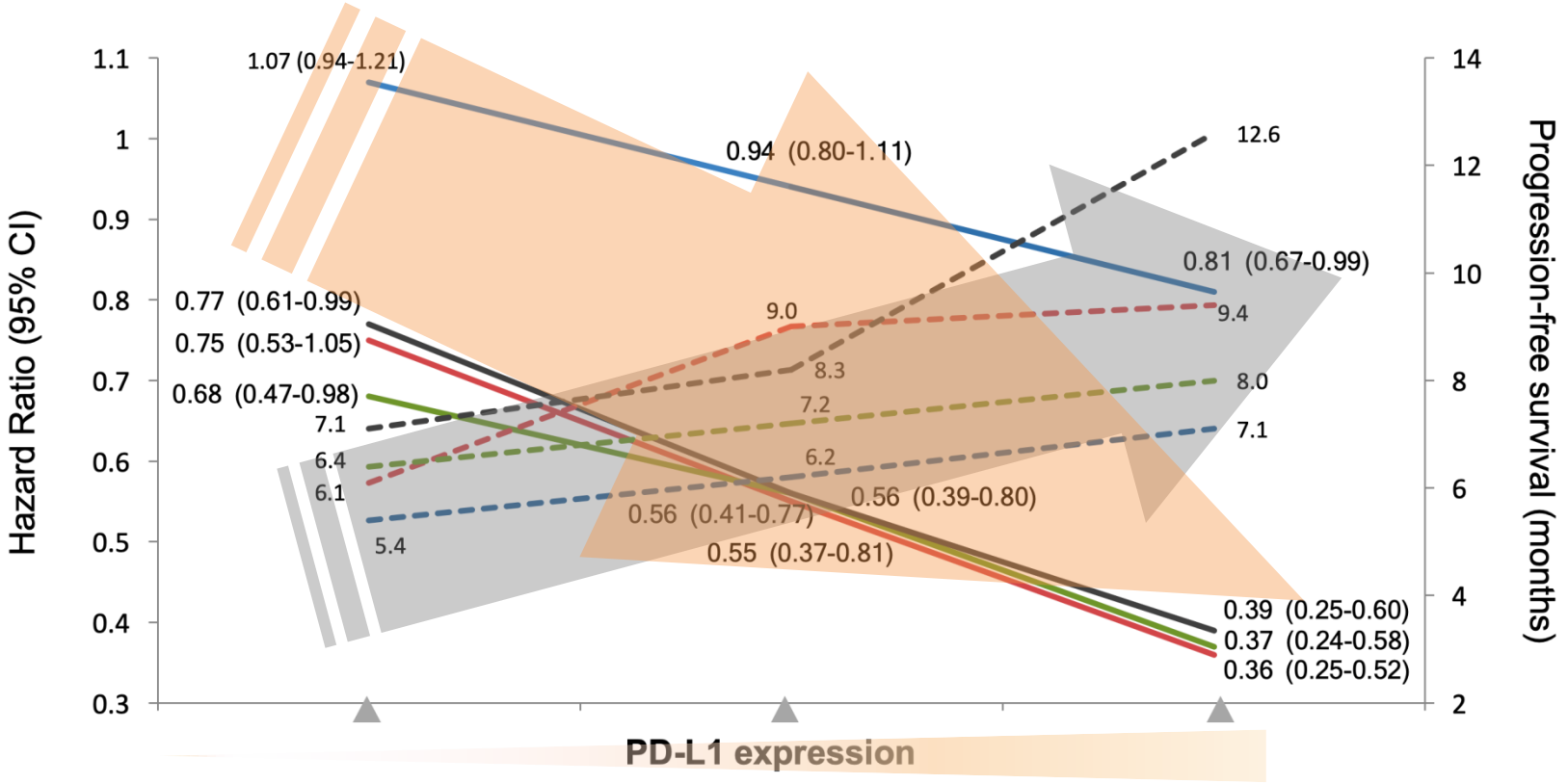
PD-L1 as a biomarker ?



Camidge DR et al. Nature Rev Clin Oncol 2019.

PD-L1 as a predictor of IO

First-line studies

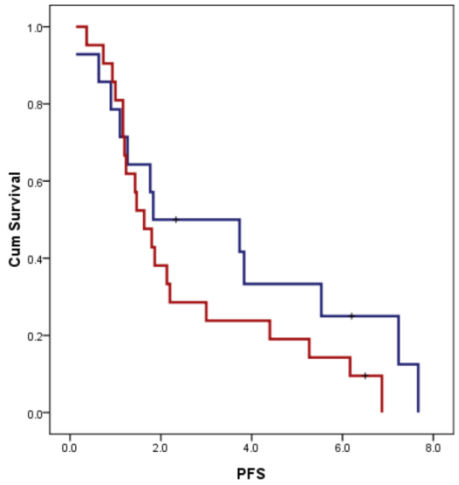
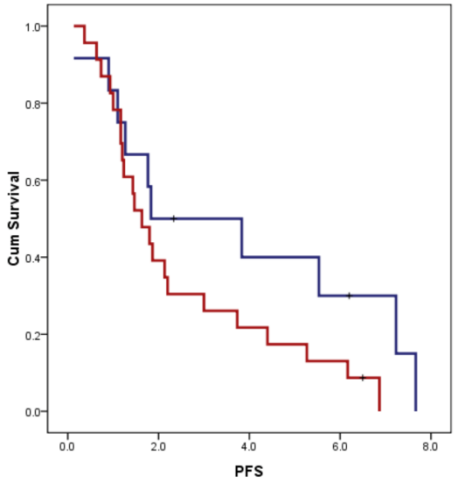
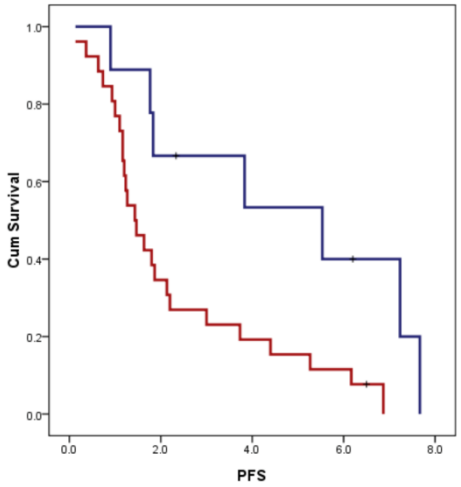
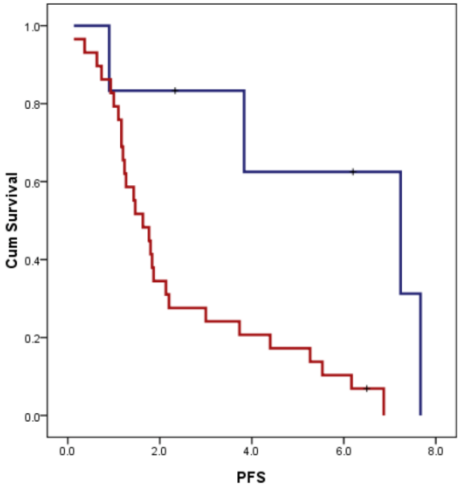


Study	Patients	Patient No.	Treatment	PD-L1 cutoff	Mark (HR / PFS)
KN-042[1]	NSCLC (TPS≥1%)	1274	Pembrolizumab vs. CT	TPS ≥ 1, 20, 50	
KN-189[2]	Non-SqCC	616	Platinum/Pemetrexed ± Pembrolizumab	TPS <1, 1-49, ≥50	
KN-407[3]	SqCC	559	Carboplatin/Paclitaxel ± Pembrolizumab	TPS <1, 1-49, ≥50	
IMP-150[4]	Non-SqCC	692	Carbo/Paclitaxel/Bev ± Atezolizumab	TC/IC 0, 1/2, 3	

[1]Lopes G et al. ASCO 2018. [2]Gandhi L et al. N Engl J Med 2018; 378:2078-92.
[3]Paz-Ares L et al. N Engl J Med 2018; 379:2040-51. [4]Socinski MA et al. N Engl J Med 2018; 378:2288-301.

PFS and various PD-L1 criteria

-- Positive -- Negative

≥1% or not	≥10% or not	≥25% or not	≥50% or not
			
P = 0.210	P = 0.118	P = 0.014	P = 0.008

PD-L1 status by SP263 assay.
N = 34 lung cancer patients receiving PD-1/PD-L1 inhibitors.
P value by log-rank test.

Higher PD-L1, better IO efficacy

- Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, and Massachusetts General Hospital (**n = 172**).
- NSCLC and a PD-L1 tumor proportion score (TPS) ≥ 50%.
- Pembrolizumab as first line therapy.
- ORR 33.9%, PFS 4.8 months, OS 20.6 months.

PD-L1 expression

75% as cutoff

PD-L1	50-74%	75-100%	P value
ORR (%)	20.6	45.2	0.001
PFS (m)	2.5	5.3	0.008
OS (m)	20.6	33.6	0.056

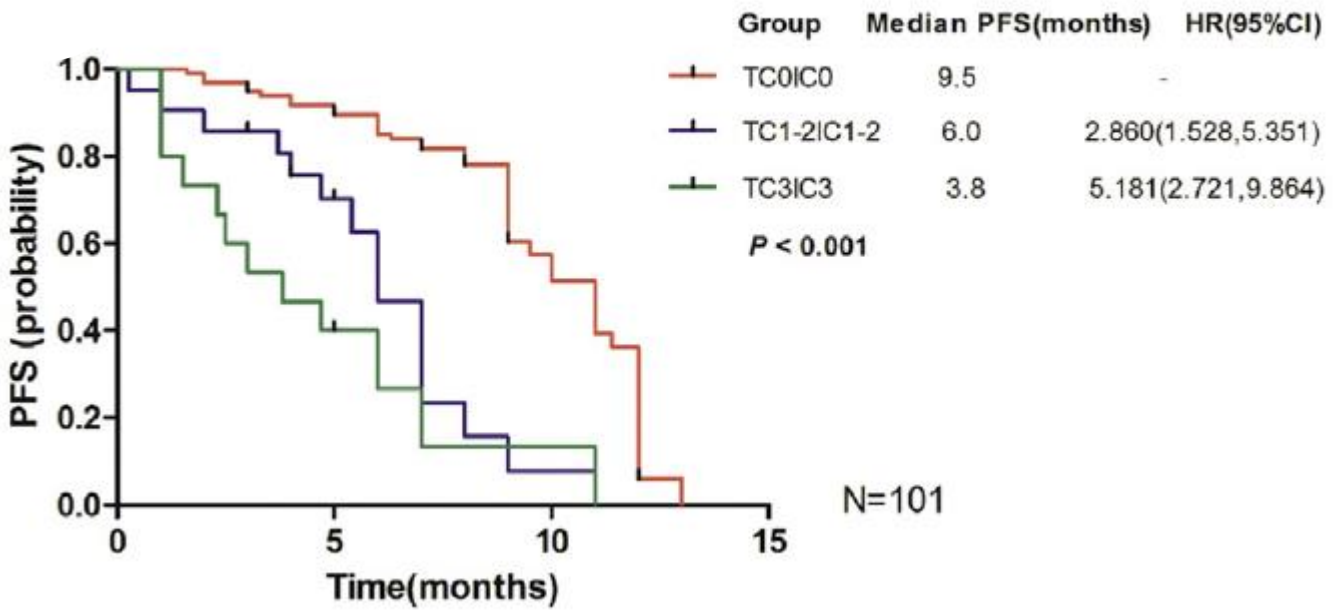
90% as cutoff

PD-L1	50-89%	90-100%	P value
ORR (%)	24.2	50.7	<0.001
PFS (m)	2.8	6.4	<0.001
OS (m)	18.0	33.6	0.008

Aguilar EJ et al. J Thorac Oncol 2018; 13:S367-8.

Predictive role of PD-L1 status in *EGFR*-m patients

	TC3/IC3	TC1-2/IC1-2	TC0/IC0	P value
Patient No.	14	18	52	
ORR (%)	35.7	63.2	67.3	0.001

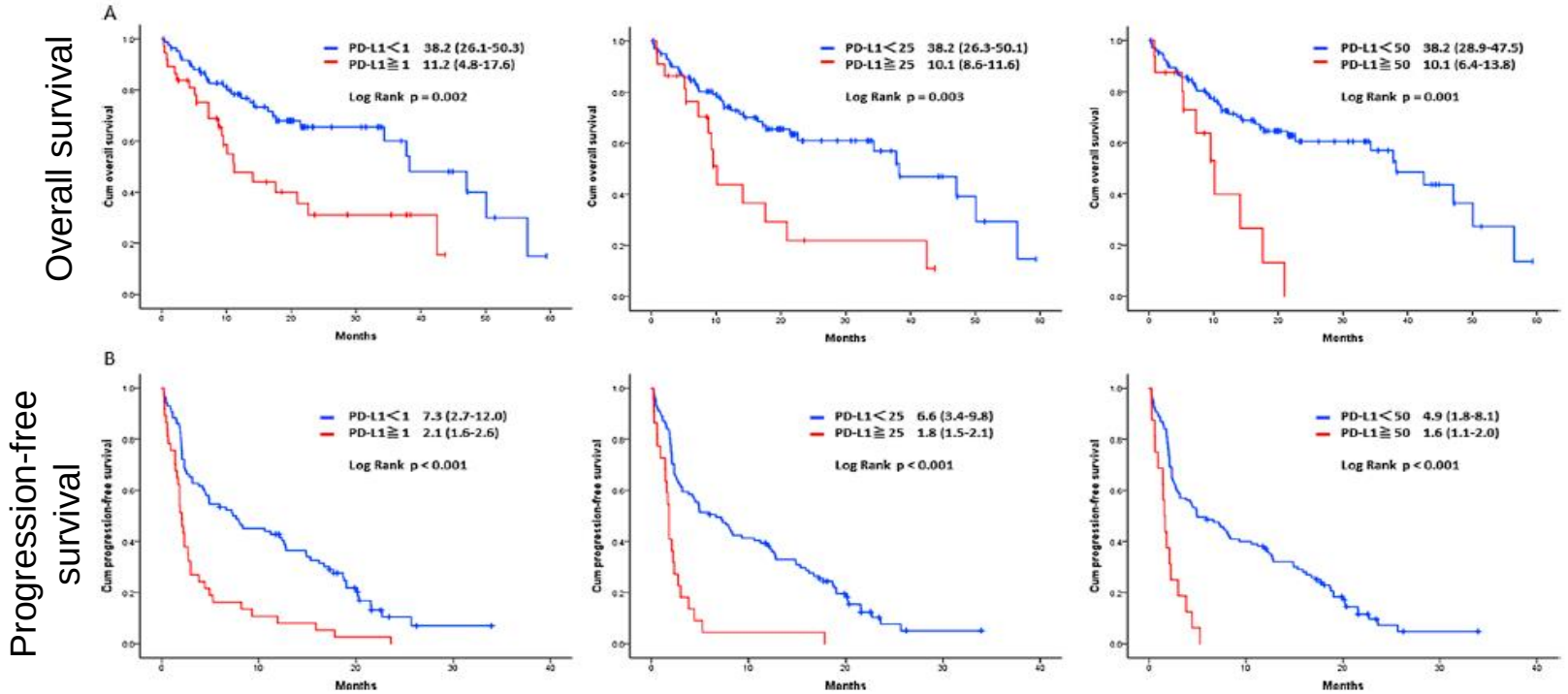


N = 101 *EGFR*-m NSCLC (84 measurable); PD-L1 by SP142.

Su S et al. J Thorac Oncol 2018; 13:1668-75.

Predictive role of PD-L1 status in *EGFR*-m patients

	Primary resistance	Disease control	P value
PD-L1 ≥ 1%, n (%)	30 (45.5)	7 (12.3)	< 0.001
PD-L1 ≥ 25%, n (%)	20 (30.3)	2 (3.5)	< 0.001
PD-L1 ≥ 50%, n (%)	15 (22.7)	1 (1.8)	0.001



N = 66 primary resistance group and 57 disease control group
PD-L1 by SP263.

Hsu & Huang et al. Lung cancer 2019; 127:37-43.

“Real World Condition”

- Characteristics of PD-L1
- **Predictive value of PD-L1**
- Efficacy of IO

- PD-L1 expression (especially ≥ 50%) remains an important predictor of immunotherapy efficacy.
- Since the concordance rate between 22C3 and SP263 is high at ”50%” cutoff, both IHC assays could well predict the outcome of IO.
- Because of the biological continuum of PD-L1 expression, the higher PD-expression seems to associate with better outcome. IDEAL cutoff ??
- In *EGFR*-mutant population, high PD-L1 expression predicts poor response to EGFR-TKI.

“Real World Condition”

- Characteristics of PD-L1
- Predictive value of PD-L1
- **Efficacy of IO: subgroups !?**

Characteristics	N = 270
Age (years), median (range)	60 (27-90)
Gender, n (%)	
Male	175 (64.8)
Female	95 (35.2)
Smoking status, n (%)	
Never-smokers	129 (47.8)
Former and current -smokers	141 (52.2)
Cell type, n (%)	
Adenocarcinoma	184 (68.1)
Squamous cell carcinoma	62 (23.0)
Others	24 (8.9)
PD-L1 status, n (%)	
Unknown	75 (27.8)
＜1%	71 (26.3)
1-49%	54 (20.0)
≧50%	70 (25.9)
Diver mutation	
Wild type	198 (73.3)
Targetable*	51 (18.9)
Non-targetable	21 (7.8)
Medication	
Pembrolizumab	175 (64.8)
Nivolumab	49 (18.1)
Atezolizumab	46 (17.1)
Best response of immunotherapy, n (%)	
Progressive disease	154 (57.0)
Stable disease	62 (23.0)
Partial response	54 (20.0)
Combination, n (%)	
No	152 (56.3)
Yes	118 (43.7)
Treatment line, n (%)	
First line	66 (24.4)
≧ secondary line	204 (75.6)

*1 BRAF, 2 G719S, 3 ALK, 3 ALK+EGFR, 4 HER2, 38 EGFR

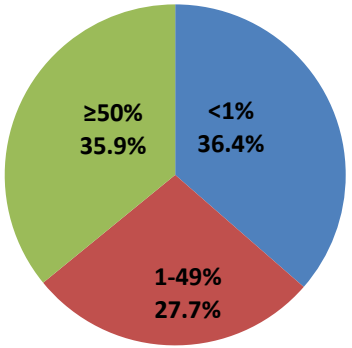
長庚紀念醫院
Chang Gung Memorial Hospital

臺中榮民總醫院
Taichung Veterans General Hospital

- Patients: advanced stage NSCLC
- Source: CGMH and TCVGH
- N = 270

- ECOG PS
  0-1 = 166 (61.5%)
  2 = 50 (18.5%)
  3-4 = 54 (20.0%)

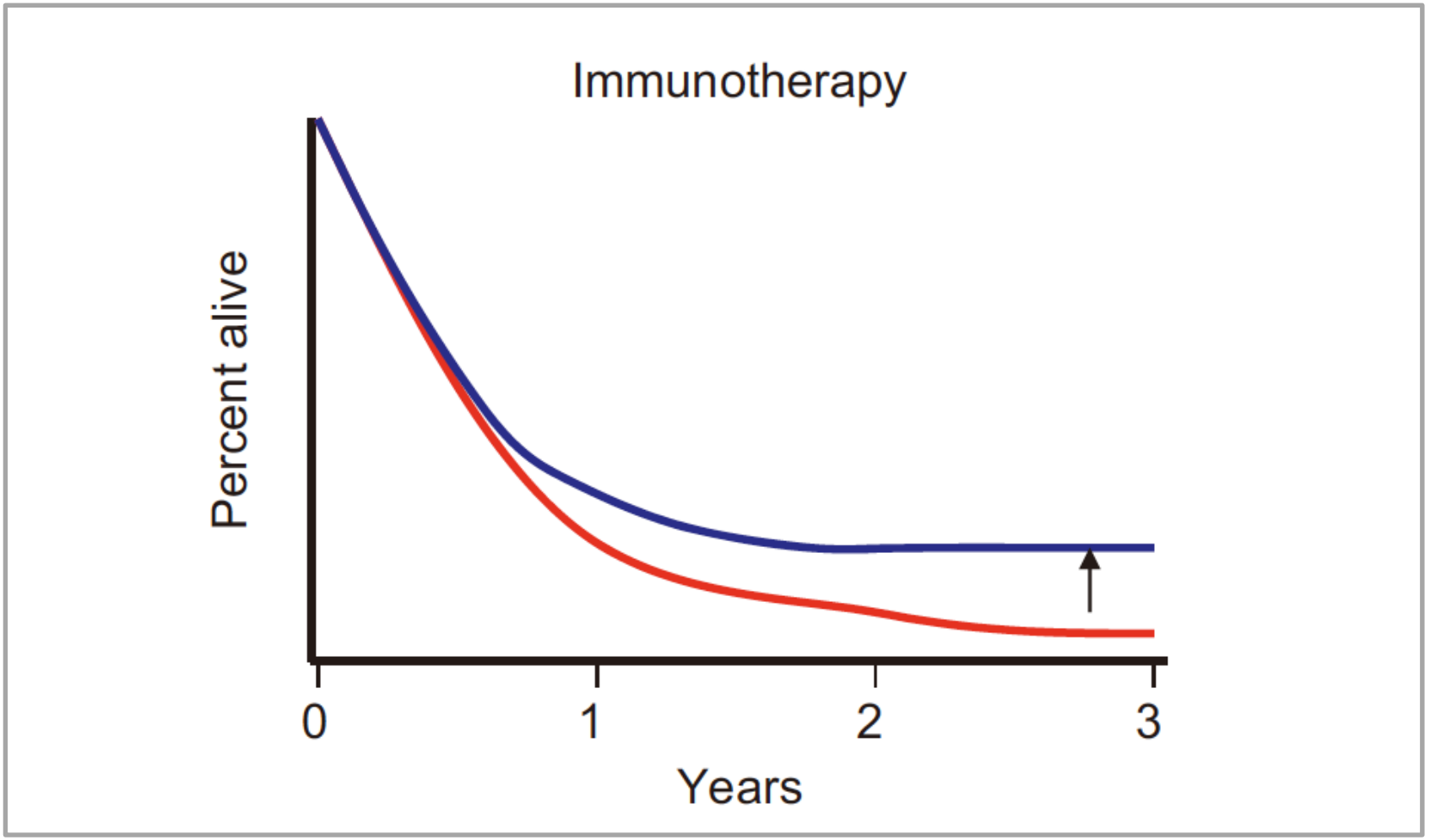
- PD-L1 IHC: 22C3 or SP263
- PD-L1 status available: 195 (72.2%)



Huang YH and Wang CL et al. Unpublished Data.

IO: a dream to cure cancer

Seven years have passed ….?!



Ribas A et al. CCR 2012; 18:336-41.

Pure 1L, no driver mutation

The expected efficacy?

Study	Phase	Pt. No.	Pt.	ORR(%)	PFS(m)	OS(m)
KN-024[1]	III	154 vs. 151 (Pemb vs. CT)	PD-L1 ≥ 50% *E/A* Wild type	44.8*	10.3*	30.0*
KN-042[2]	III	637 vs. 637 (Pemb vs. CT)	PD-L1 ≥ 1% *E/A* Wild type	27.3	5.4	16.7*
KN-021G[3]	II	60 vs. 63 (Pemb/CaP vs. CaP)	Non-Sq NSCLC *E/A* Wild type	~~56.7*~~	~~19.0*~~	~~NR~~
KN-189[4]	III	410 vs. 206 (Pemb/CP vs. CP)	Non-Sq NSCLC *E/A* Wild type	47.6*	9.0*	22.0*
KN-407[5]	III	278 vs. 281 (Pemb/CaT vs. CaT)	Sq NSCLC	57.9*	6.4*	15.9*
IMP-150[6]	III	356 vs. 336 (A-BCP vs. BCP)	Non-Sq NSCLC *E/A* Wild type	63.5	8.3*	19.2*
IMP-133[7]	III	201 vs. 202 (A-CE vs. CE)	ES-SCLC	~~60.2~~	~~5.2*~~	~~12.3*~~

Pemb, Pembrolizumab; CT, Platinum-based chemotherapy; CaP, Carboplatin + Pemetrexed; CP, Cisplatin or Carboplatin + Pemetrexed; CaT, Carboplatin + Paclitaxel or albumin-bound Paclitaxel; A, Atezolizumab; BCP, Bevacizumab + Carboplatin + Paclitaxel; CE, Carboplatin + Etoposide; E/A, EGFR/ALK..

[1]Reck M et al. N Engl J Med 2016; 375:1823-33 & J Clin Oncol 2019; 37:537-46. [2]Mok T et al. Lancet 2019; 393:1819-30.
[3]Borghaei H et al. ESMO 2017. [4]Gandhi L et al. N Engl J Med 2018; 378:2078-92 & Gadgeel S et al. ASCO 2019..
[5]Paz-Ares L et al. N Engl J Med 2018; 379:2040-51. [6]Socinski MA et al. N Engl J Med 2018; 378:2288-301.
[7]Horn L et al. N Engl J Med 2018; 379:2220-9.

***Denote statistically significant.**

Efficacy of IO in real world

N = 270 NSCLC

ORR = 20.0%

DCR = 43.0%

PFS = 3.0m (95% CI 2.6-3.3)

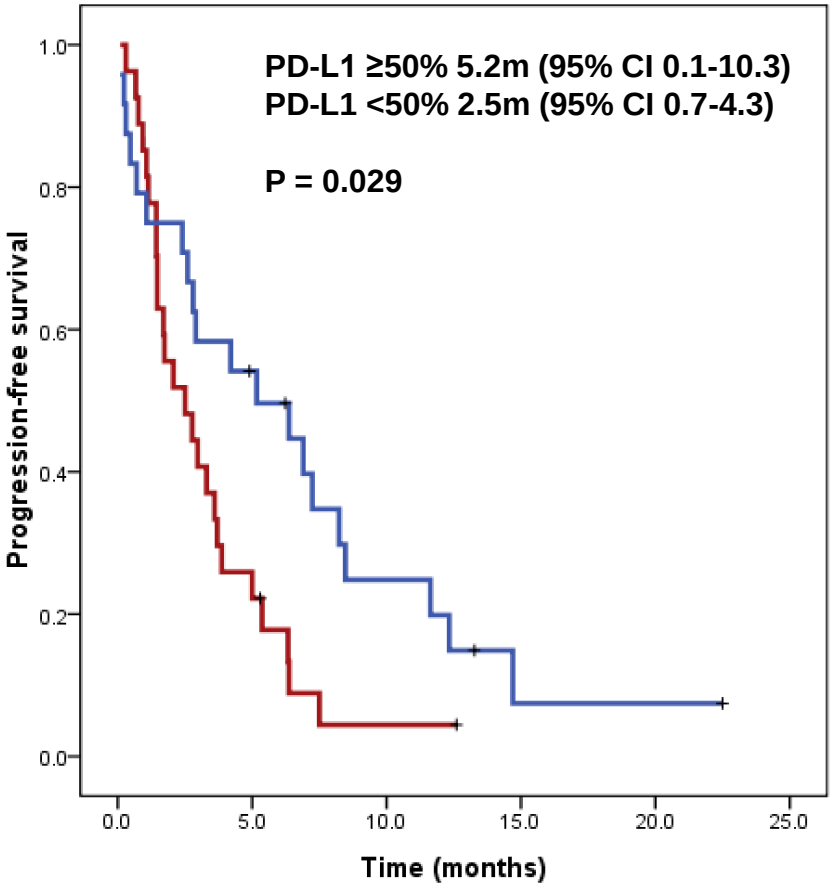
OS = 8.7 m (95% CI 5.7-11.8)

Pure 1L, known PD-L1, no driver mutation (n = 51)

- N = 51
- Combo 26 and IO mono 25
- **11 (21.6%) with ECOG PS 3-4**

- Pembrolizumab (43)
- Nivolumab (2)
- Atezolizumab (6)

- PFS = 3.0m (95% CI 1.9-4.1)
- OS = 16.7m (95% CI 5.7-27.6)
- ORR = 33.3%
- DCR = 52.9%



OS NR vs. 5.4 months, respectively.

What is “REAL”?

PD-L1 ≥ 50%

Study	Patients	Patient No.	PFS (m)	OS (m)
KN-024[1]	Clinical trial Multicenter	154	10.3	30.0
Alguilar EJ[2]	DFCI MSKCC MGH	172	4.8	20.6
Huang/Wang[3*]	TCVGH CGMH	24	5.2	NR

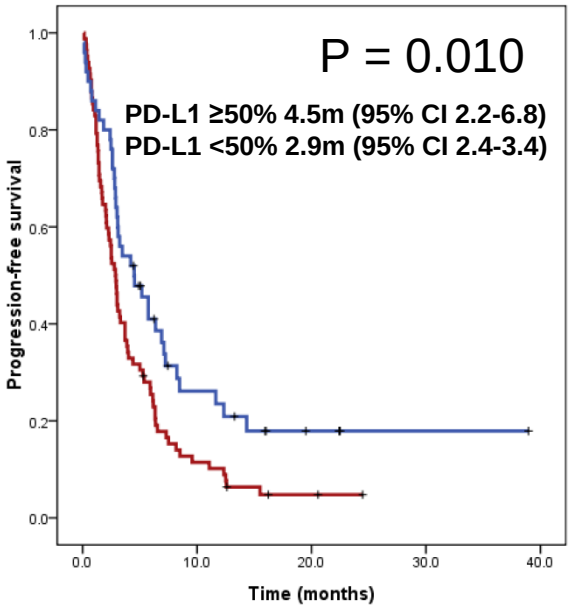
*First line IO treatment, PD-L1 ≥ 50%, 21 pembrolizumab and 3 atezolizumab.

[1]Reck M et al. N Engl J Med 2016; 375:1823-33 & J Clin Oncol 2019; 37:537-46.
[2]Alguilar EJ et al. J Thorac Oncol 2018; 13:S367-8.
[3]Huang YH and Wang CL et al. TCVGH & CGMH; unpublished data.

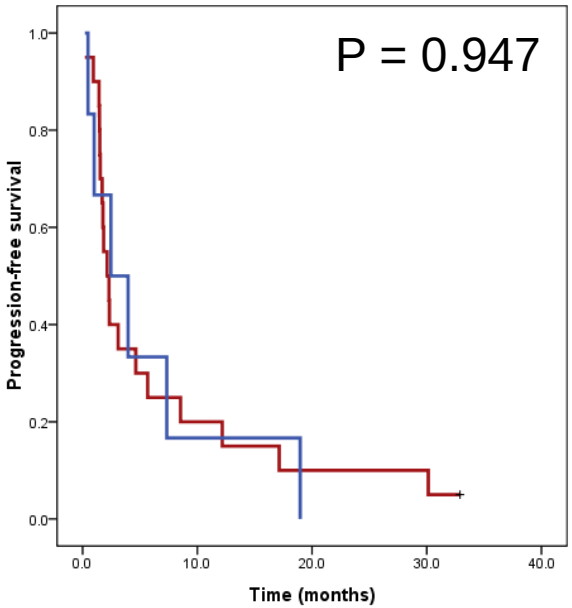
Predictive role of PD-L1 in individual IO regimen

N = 195

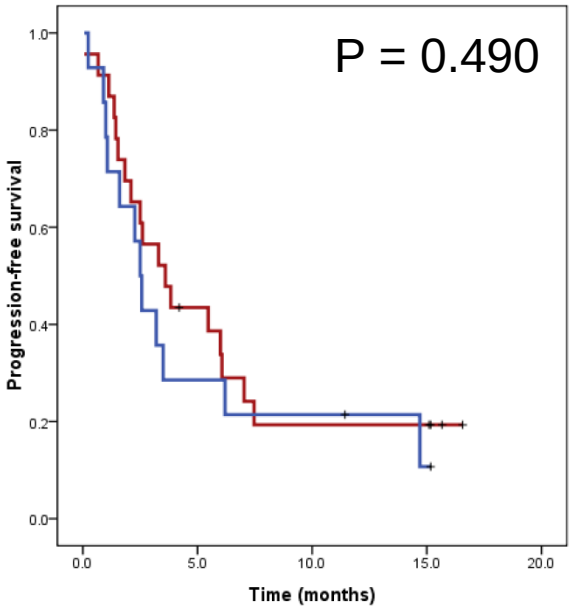
-- Positive -- Negative



Pembrolizumab
(n = 132)



Nivolumab
(n = 26)



Atezolizumab
(n = 37)

PD-L1 by SP263 or 22C3; OS: non-significant.

Why ?

- CM-026: Even in PD-L1 strong expression subgroup (PD-L1 ≥ 50%), nivolumab was not associated with survival benefit.[1]

  → **TMB?, other biomarker?**

- BP-1, 2, NCCN: High concordance was noted between PD-L1 assays, except "SP142".[2,3,4]

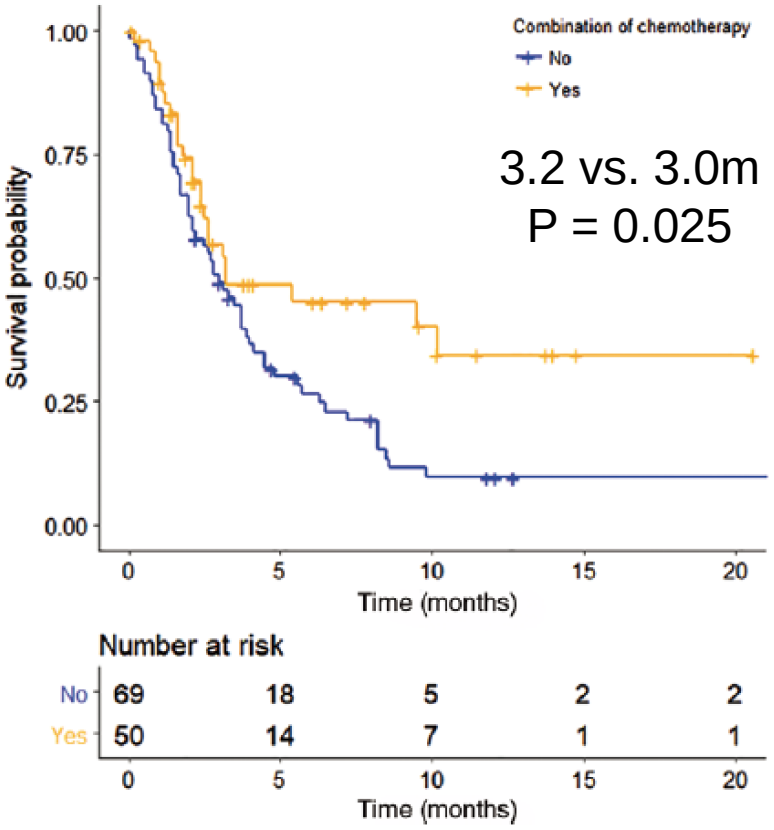
  → **SP142 should be "companion"?**

[1]Carbone DP et al. N Engl J Med 2017; 376:2415-26.
[2]Hirsch FR et al. J Throac Oncol 2017; 12:208-22.
[3]Tsao MS et al. J Throac Oncol 2018; 13:1302-11.
[4]Rimm D et al. JAMA Oncol 2017; 3:1051-8.

IO: mono or combo

Variable, N (%)	Total (*n* = 119)
Age, median (range), year	59 (53–65)
Gender (male)	87 (73.1)
Smoker/ex-smoker	73 (61.3)
ECOG PS (0,1)	92 (77.3)
Stage	
III	16 (13.4)
IV	103 (86.6)
Histology	
Adenocarcinoma	76 (63.9)
Squamous cell carcinoma	33 (27.7)
NSCLC-PD	10 (8.4)
EFGR mutation	21 (17.6)
ALK mutation	6 (5.0)
Brain metastasis	25 (21.0)
First-line treatment	36 (30.3)
PD-L1 TPS, median (range)	30 (2–75)
Immunotherapy agent	
Pembrolizumab	53 (44.5)
Non-pembrolizumab	66 (55.5)

More 1st-L in combo group
(52.0 vs. 14.5%, P < 0.001)



CGMH cohort

Kuo CH et al. Thorac Cancer 2019.

IO in 1L (PD-L1 ≥ 50%)

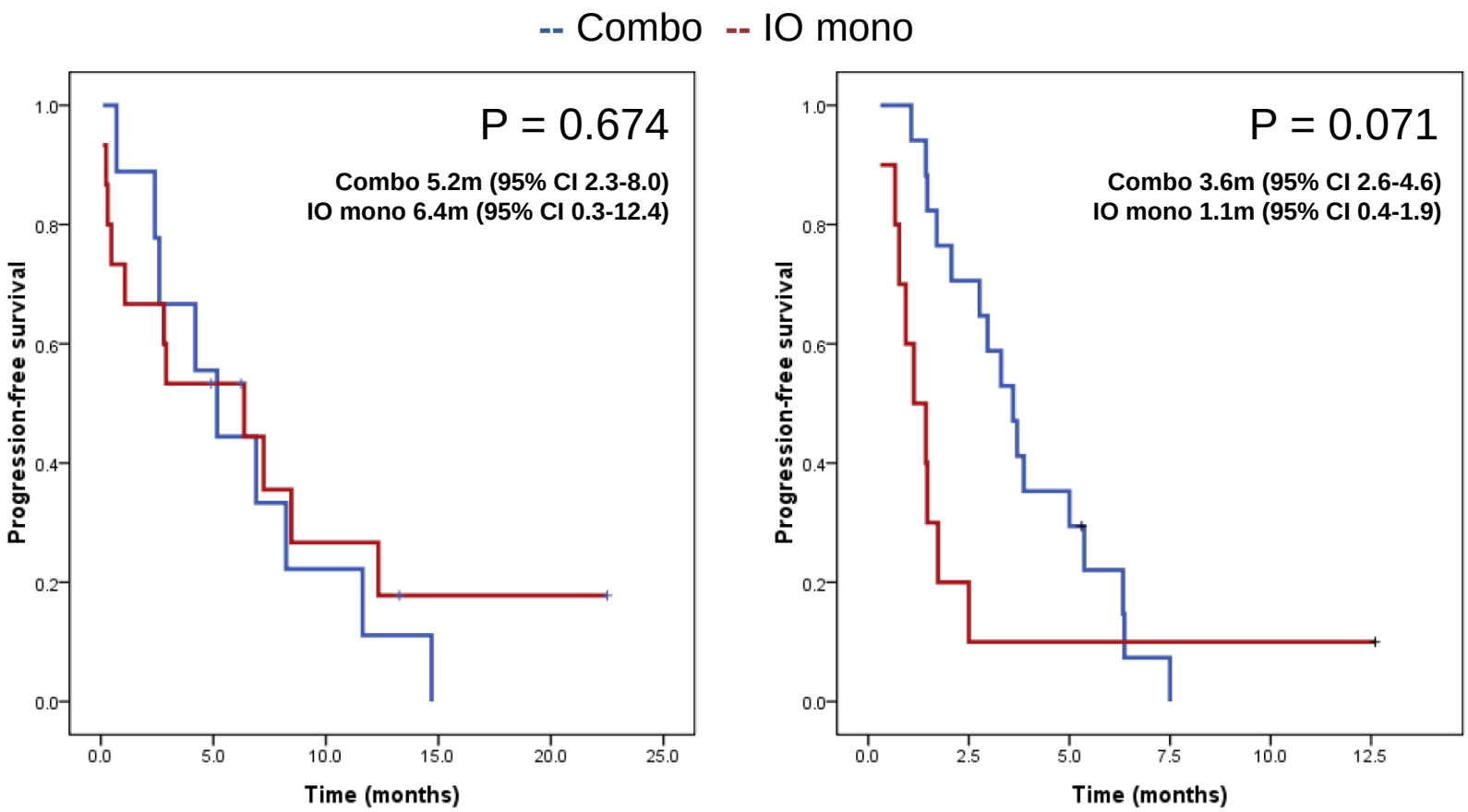
Mono or combo ?!

Study	Patients	IO	PFS	OS
KN-024[1]	NSCLC	Mono	10.3	30.0
KN-042[2]	NSCLC	Mono	7.1	20.0
KN-189[3]	Non-Sq-NSCLC	Combo	9.4	NR
KN-407[4]	Sq-NSCLC	Combo	8.0	NR

[1]Reck M et al. N Engl J Med 2016; 375:1823-33 & J Clin Oncol 2019; 37:537-46.
[2]Lopes G et al. ASCO 2018.
[3]Gandhi L et al. N Engl J Med 2018; 378:2078-92 & Gadgeel S et al. ASCO 2019.
[4]Paz-Ares L et al. N Engl J Med 2018; 379:2040-51.

Pure 1L, known PD-L1, no driver mutation (n = 51)

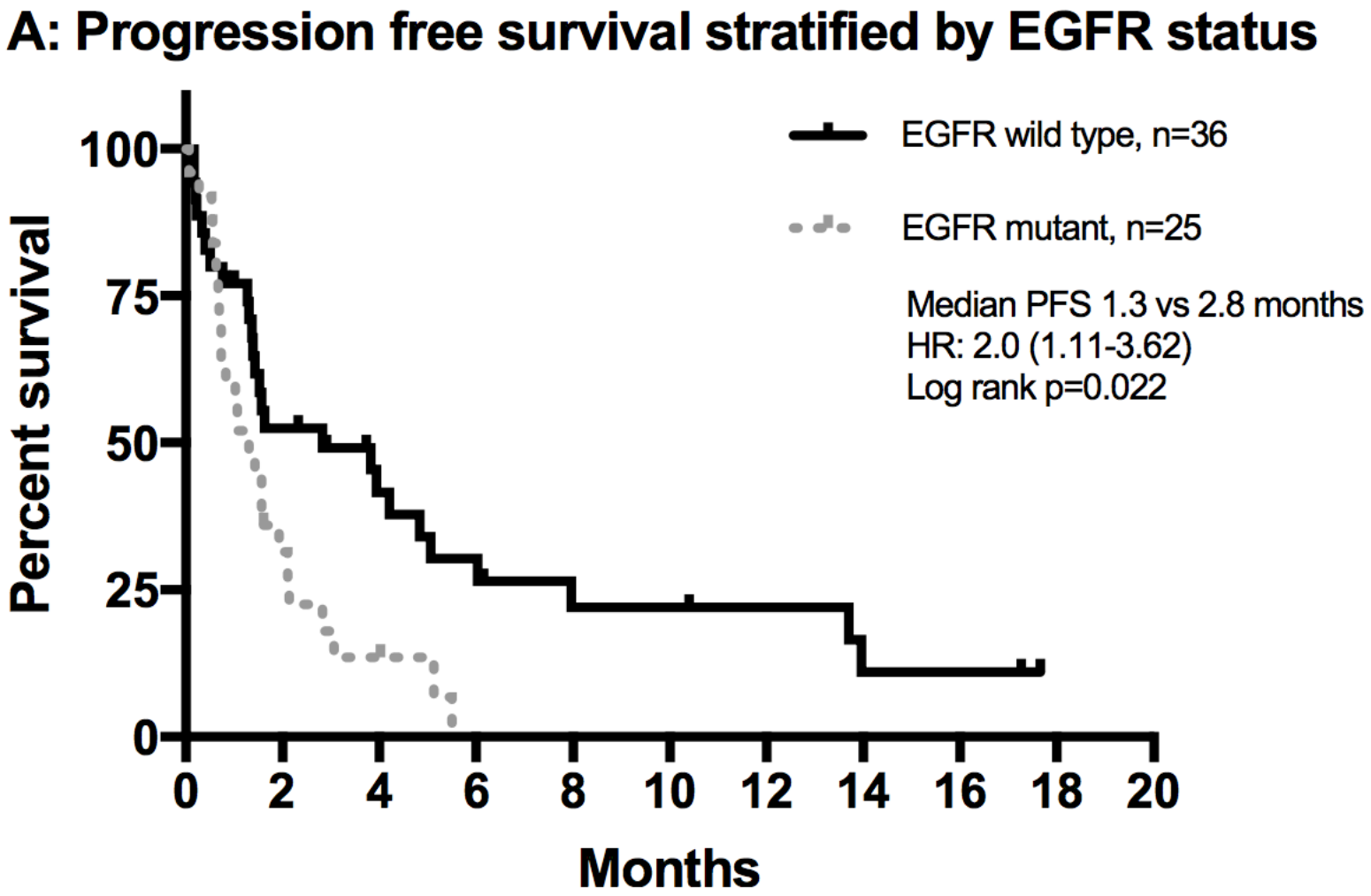
Combo or NOT



PD-L1 ≥ 50% (n =24)

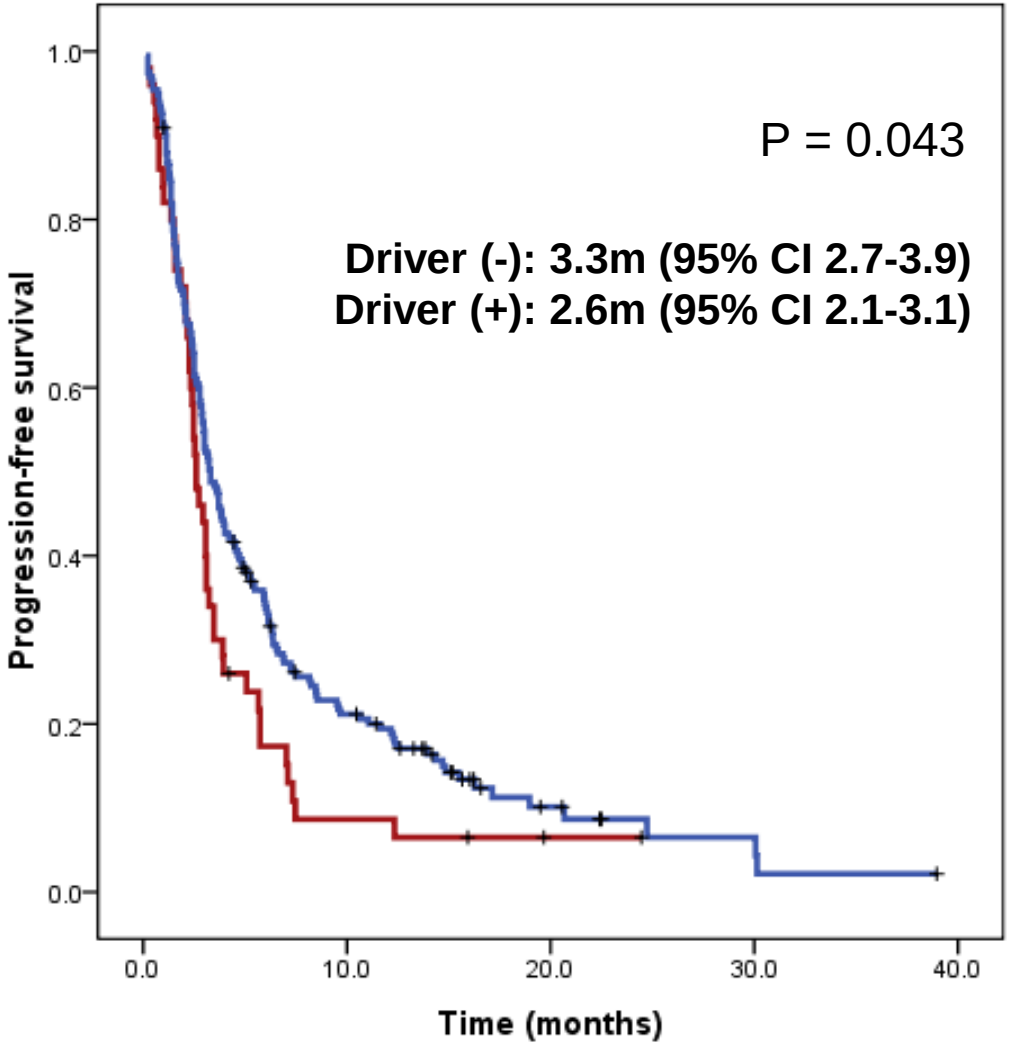
PD-L1 < 50% (n = 27)

IO in *EGFR*-m subgroup



Lin SY et al. J Cancer 2018; 9:1813-20.

IO in driver-mutant subgroup



N = 248 (exclude ECOG PS=4 patients); 50 (20.2%) with drivers.
Drivers: *EGFR* 42, *ALK* 3, *HER2* 4, *BRAF*^{V600E} 1.

IO in *EGFR*-m subgroup

Atezolizumab can work ?

- 37 patients received atezolizumab treatment.
- 8 with *EGFR* mutation (4 with 19Del and 4 with L858R).
- 2 of them with strong PD-L1 expression.
- 1 patient as first line therapy.
- 6 combined with CT (no ABCP) and 2 monotherapy.

	***EGFR*-m (n = 8)**	***EGFR*-wt (n = 29)**
ORR (%)	0	13.8
PFS (m, 95% CI)	2.3 (1.6-3.0)	3.3 (1.7-4.9)

*Both ORR and PFS were not statistically significant.

Atezolizumab in *EGFR*-m patients

	IMpower-150[1,2]	OAK[3,4]
Treatment line	1st-L	2nd- or 3rd-L
Comparison	ABCP vs. BCP	Monotherapy vs. D
Driver mutation	*EGFR* or *ALK*	*EGFR*
Patient No.	108 (14%)	85 (10%)
PFS, m	9.7 vs. 5.1	N/A
Hazard ratio (PFS)	**0.59 (0.37-0.94)**	**1.21 (0.77-1.93)**
OS, m	NR vs. 17.5	10.5 vs. 16.2
Hazard ratio (OS)	**0.54 (0.29-1.03)**	**1.24 (0.71-2.18)**

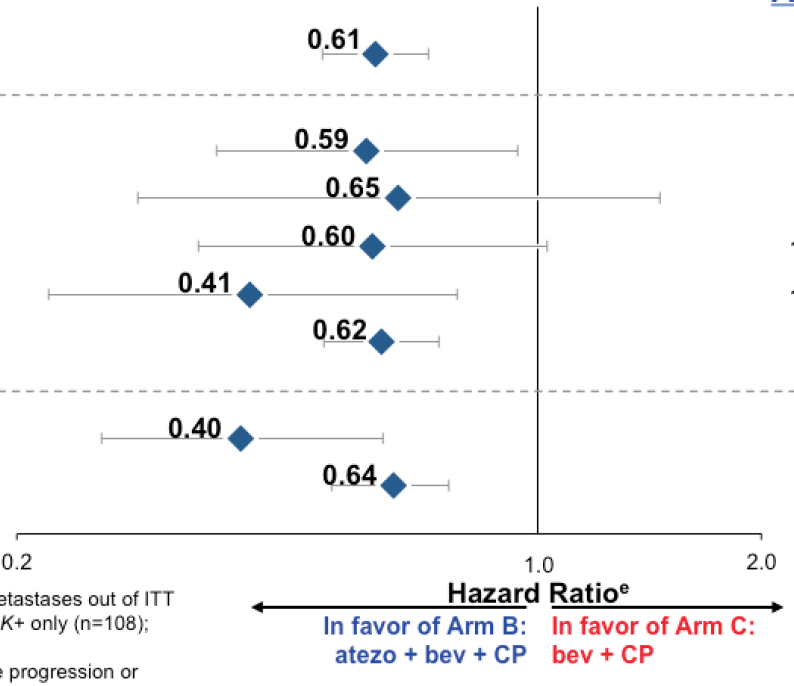
[1]Socinski MA et al. N Engl J Med 2018; 378:2288-301.
[2]IMpower 150 Socinski MA et al. ASCO 2018.
[3]Rittmeyer A et al. Lancet 2017;389: 255-65.
[4]Gadgeel SM et al. WCLC 2016.

Atezolizumab in *EGFR*-m patients

IMpower-150 (1st-L)

PFS Benefit in Arm B was Observed in Key Populations

Populations	n (%)[a]	Median PFS, mo Arm B	Median PFS, mo Arm C
ITT (including *EGFR*/*ALK*+)	800 (100%)	8.3	6.8
EGFR/*ALK*+ only[b]	108 (14%)	9.7	6.1
ALK rearrangement[c]	34 (31%)	8.3	5.9
EGFR mutation[c]	80 (74%)	10.2	6.9
Exon 19 deletion or L858R[d]	59 (74%)	10.2	6.1
ITT-WT	692 (87%)	8.3	6.8
Liver metastases	110 (14%)	8.2	5.4
No liver metastases	690 (86%)	8.3	7.0



Atezo, atezolizumab; bev, bevacizumab; CP, carboplatin + paclitaxel.
[a] Prevalence % for ITT, *EGFR/ALK*+ only, ITT-WT, liver metastases, and no liver metastases out of ITT (n=800); prevalence % for *ALK* rearrangement and *EGFR* mutation out of *EGFR/ALK*+ only (n=108); prevalence % for exon 19 deletion of L858R out of *EGFR* mutation (n=80).
[b] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or

Kowanetz M et al. AACR 2018.

Will IO rescue life in very ill patients?

ECOG PS eligible for clinical trials

Study	Therapy	Investigated regimen	Eligible ECOG PS
KN-024[1]	1L	Pembrolizumab mono	0 or 1
KN-042[2]	1L	Pembrolizumab mono	0 or 1
KN-189[3]	1L	Pembrolizumab/CT	0 or 1
KN-407[4]	1L	Pembrolizumab/CT	0 or 1
IMP-150[5]	1L	Atezolizumab/CT/Bev	0 or 1
CM-017[6]	2L	Nivolumab mono	0 or 1
CM-057[7]	2L	Nivolumab mono	0 or 1
KN-010[8]	2L~	Pembrolizumab mono	0 or 1
OAK[9]	2L~	Atezolizumab mono	0 or 1

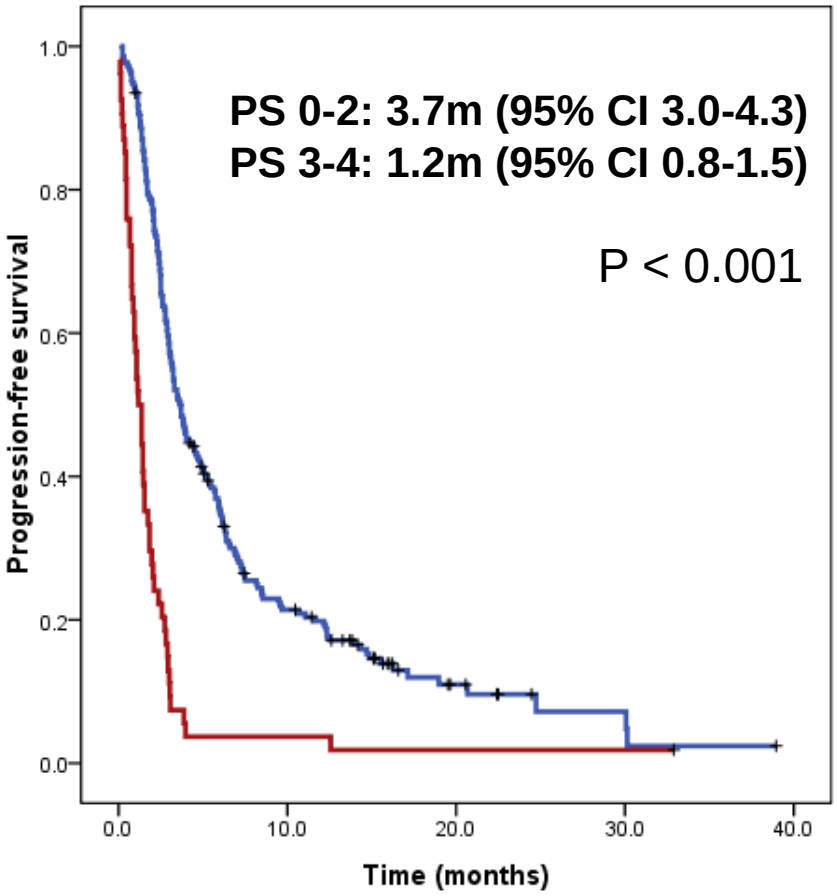
Cohort	ECOG PS	PFS HR	OS HR
NTUH[10]	2 -4 vs. 0-1	9.53 (4.23-21.51)	14.72 (6.01-36.05)
TCVGH[11]	0-1 vs. 2-4	0.25 (0.10-0.63)	0.07 (0.02-0.28)

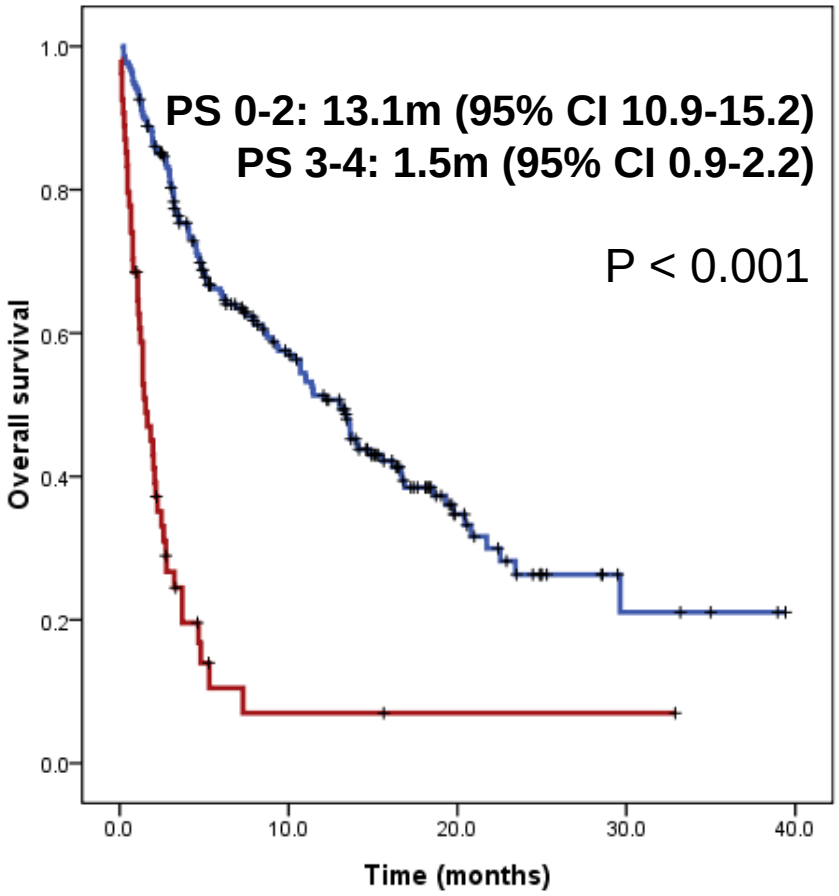
[10]Lin SY et al. J Cancer 2018; 9:1813-20; [11]Tseng JS et al. J Immunother 2018; 41:292-9.

[1]Reck M et al. N Engl J Med 2016; 375:1823-33 & J Clin Oncol 2019; 37:537-46. [2]Mok T et al. Lancet 2019; 393:1819-30 .
[3]Gandhi L et al. N Engl J Med 2018; 378:2078-92. [4]Paz-Ares L et al. N Engl J Med 2018; 379:2040-51.
[5]Socinski MA et al. N Engl J Med 2018; 378:2288-301. [6]Brahmer J et al. N Engl J Med 2015;373: 123-35.
[7]Borghaei H. et al. N Engl J Med 2015;373:1627-39. [8]Herbst RS et al. Lancet 2016;387:1540-50. [9]Rittmeyer A et al. Lancet 2017;389: 255-65.

IO in ECOG PS 3-4, rescue life?

-- ECOG PS 0-2 (n = 216, 80%) – ECOG PS 3-4 (n = 54, 20%)





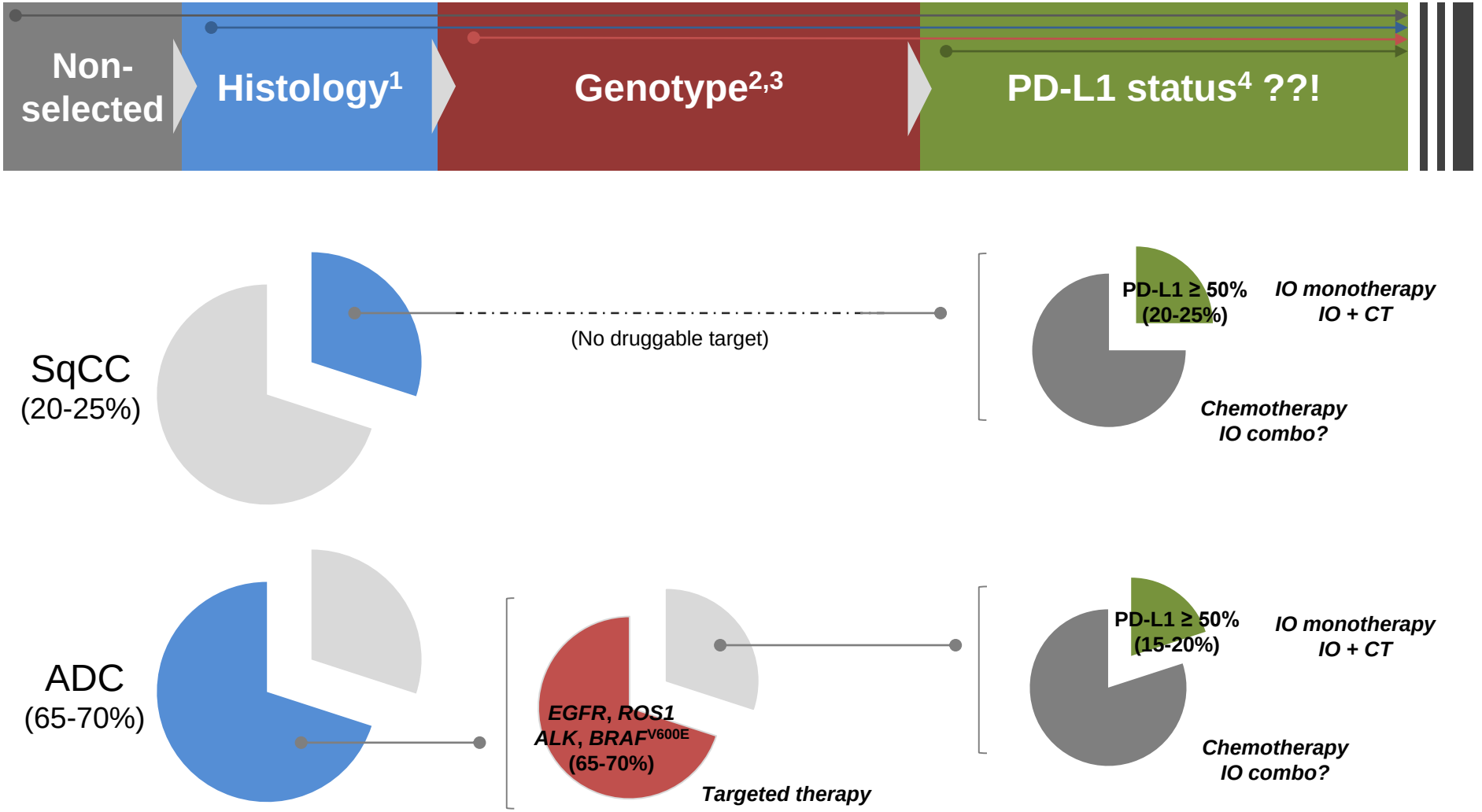
ORR: 23.6% vs. 5.6%, P = 0.002

“Real World Condition”

- Characteristics of PD-L1
- Predictive value of PD-L1
- **Efficacy of IO: subgroup !?**

- Efficacy of IO seemed not as good as clinical trials’ results.
- PD-L1 as predictor of IO efficacy: acceptable, **NOT** universal/enough.
- In 1L, PD-L1 ≥ 50% subgroup, combo/mono has similar efficacy.
- The role of IO in *EGFR*-m patients remains doubtful.
- IO CANNOT rescue life in patients with poor performance status.
- Patients with **good performance status** and **high PD-L1 expression** are more likely to benefit from IO.

Potential 1L treatment for NSCLC in Taiwan



[1]國健署 (https://www.hpa.gov.tw/); [2]Hsu KH et al. PLoS One 2015; 10:e0120852;
[3]Chen YF et al. J Thorac Oncol 2014; 9:1171-9; [4]Tseng JS et al. J Immunother 2018; 41:292-9.

Brief conclusions

- Immunotherapy is opening a new chapter of lung cancer treatment and some patients did benefit from immunotherapy.
- Smokers and patients without known actionable driver mutation were more likely to present strong positive PD-L1.
- PD-L1 acts as a biomarker: acceptable but not enough.
- “Gap” between clinical trials and real world results: many unanswered questions remain (patient selection/better biomarker?, best regimen?, best combination?, IO retreatment?, ….????)
- Currently, patients with high PD-L1 expression and good PS may be more suitable for immunotherapy.

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Thanks for your attention!

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