529 IMPACT OF HISTOLOGY AND PD-L1 STATUS ON IMMUNE CHECKPOINT INHIBITORS IN THE TREATMENT OF NON-SMALL CELL LUNG CANCER

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Background Immune checkpoint inhibitors (IO) have revolutionized the treatment of advanced non-small cell lung cancer (NSCLC). In the pre-IO era, patients (pts) with squamous cell carcinoma (SCC) had worse survival outcomes than non-squamous (nSCC) pts.[1] Landmark trials comparing IO to chemotherapy in SCC[2] and nSCC[3] suggest a numerical survival advantage for pts with nSCC irrespective of PD-L1 status. However, no head-to-head comparison of the effect of histology on response to IO, and with respect to PD-L1 status has been done.

Methods A systematic search of the PubMed and EMBASE databases (January 1, 2010- December 31, 2022) with additional search of ASCO and ESMO conferences, identified relevant randomized control trials (RCTs). Eligible studies included phase II/III RCTs in NSCLC pts (≥ 18 years; clearly defined subtype: SCC *vs.* nSCC) treated with IO (monotherapy/combination), irrespective of treatment lines. In a meta-analysis, hazard ratios (HR) and 95% confidence intervals (CI) were pooled to estimate overall survival (OS) and progression-free survival (PFS). Heterogeneity was tested and when substantial, a random-effect model was used.

Results In total, 23 studies were identified [N= 14,171 pts (SCC: 4,398; nSCC: 9,773); table 1**]**. Overall, as will be reported at the World Conference on Lung Cancer, there was no difference in these outcomes between nSCC and SCC [**OS** (HR 1.06; *P=0.406*); **PFS** (HR 1.09; *P=0.506*)], irrespective of the line of therapy (1st, *P=0.341 vs.* ≥ 2nd line, *P=0.625*) or IO regimen (monotherapy, *P=0.268 vs.* chemo-IO, *P=0.864;* table 2).

Here we report subset analysis based on PD-L1 expression. There was no difference in OS between SCC and nSCC based on PD-L1 status (**PD-L1+ pts:** HR 1.05; *P=0.598*; **PD-L1- pts**: HR 1.01; *P=0.945*). Similarly, both subgroups did not significantly differ in PFS (**PD-L1+:** HR 1.40; *P=0.068*; **PD-L1-**: HR 0.90; *P=0.685*). Within the same histology subgroup, no difference in OS was seen between PD-L1+ and PD-L1- (**SCC:** HR 0.995; *P=0.965*; nSCC: HR 1.04; *P=0.749*). PD-L1 status did not affect PFS across histologies (**SCC:** HR 0.68; *P=0.096*; nSCC: HR 1.06; *P=0.841*) (table 3).

Conclusions Despite distinct molecular landscapes and poorer survival for SCC pts in the pre-IO era, outcomes from IO-based therapy in NSCLC did not differ based on histology, and irrespective of PD-L1 status. While previous differences may be explained by higher prevalence of targeted mutations in nSCC, the introduction of IO to the landscape of NSCLC may have helped bridge the gap between both subtypes, by targeting a shared immune mechanism.

REFERENCES

1. Socinski MA, Obasaju C, Gandara D, Hirsch FR, Bonomi P, Bunn P, Kim ES, Langer CJ, Natale RB, Novello S, Paz-Ares L, Pérol M, Reck M, Ramalingam SS, Reynolds CH, Spigel DR, Stinchcombe TE, Wakelee H, Mayo C, Thatcher N. Clinicopathologic Features of Advanced Squamous NSCLC. *Journal of Thoracic Oncology*. 2016; **11** (9):1411–22.
2. Novello S, Kowalski DM, Luft A, Gümüş M, Vicente D, Mazières J, Rodríguez-Cid J, Tafreshi A, Cheng Y, Lee KH, Golf A, Sugawara S, Robinson AG, Halmos B, Jensen E, Schwarzenberger P, Pietanza MC, Paz-Ares L. Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. *JCO* .2023; **41** (11):1999–2006.
3. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, Hui R, Hochmair MJ, Clingan P, Powell SF, Cheng SYS, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Garon EB, Novello S, Rubio-Viqueira B, Boyer M, Kurata T, Gray JE, Yang J, Bas T, Pietanza MC, Garassino MC. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2020; **38** (14):1505–17.

Abstract 529 Table 1 Totoal number of subjects by histology, PD-L1 status, and treatment received. IO: Immune checkpoint inhibitors; SCC: squamous cell carcinoma; nSCC: non-squamous cell carcinoma; OS: overall survival; PFS: progression-free survival.

	SCC	nSCC	Total
Overall (N= 23 studies)	**4398**	**9773**	**14171**
IO-based therapy	2301	5351	7652
Non-IO therapy	2097	4422	6519
OS analysis by PD-L1 status			
PD-L1+	**2696**	**4665**	**7361**
PD-L1+/IO-based therapy	1406	2555	3961
PD-L1+/non-IO therapy	1290	2110	3400
PD-L1-	**723**	**1653**	**2376**
PD-L1-/IO-based therapy	355	929	1284
PD-L1-/non-IO therapy	368	724	1092
Unknown/unreported	**979**	**3455**	**4434**
PFS analysis by PD-L1 status			
PD-L1+	**1648**	**2947**	**4595**
PD-L1+/IO-based therapy	882	1691	2573
PD-L1+/non-IO therapy	766	1256	2022
PD-L1-	**631**	**988**	**1619**
PD-L1-/IO-based therapy	309	597	906
PD-L1-/non-IO therapy	322	391	713
Unknown/unreported	**2119**	**5838**	**7957**

Abstract 529 Table 2 Pooled hazard ratio of overall and progression-free survival and comparison between SCC and nSCC. OS: overall survival; PFS: progression-free survival; SCC: squamous cell carcinoma; nSCC: non-squamous cell carcinoma; HR: hazard ratio; 95% CI; 95% confidence interval; Ratio: ratio of HR between SCC and nSCC with SCC as a reference (Ref.); IO: immune checkpoint inhibitor; chemo-IO: chemotherapy/immune checkpoint inhibitor combination

Endpoint	Group		Pooled HR (95% CI)	*P-value*	Ratio (95% CI)	*P-value*
OS	SCC		0.73 (0.68-0.79)	<0.001	Ref.	
	nSCC		0.78 (0.71-0.85)	<0.001	1.06 (0.92-1.23)	0.406
	1st line:	SCC	0.71 (0.63-0.81)	<0.001	Ref.	
		nSCC	0.78 (0.70-0.88)	<0.001	1.10 (0.91-1.33)	0.341
	≥ 2nd line:	SCC	0.71 (0.61-0.83)	<0.001	Ref.	
		nSCC	0.75 (0.68-0.82)	<0.001	1.05 (0.87-1.25)	0.625
	IO monotherapy:	SCC	0.73 (0.67-0.80)	<0.001	Ref.	
		nSCC	0.81 (0.72-0.90)	<0.001	1.11 (0.92-1.33)	0.268
	Chemo-IO:	SCC	0.74 (0.65-0.84)	<0.001	Ref.	
		nSCC	0.73 (0.63-0.84)	<0.001	0.98 (0.78-1.23)	0.864
PFS	SCC		0.63 (0.54-0.72)	<0.001	Ref.	
	nSCC		0.69 (0.59-0.80)	<0.001	1.09 (0.84-1.42)	0.506
	1st line:	SCC	0.57 (0.48-0.69)	<0.001	Ref.	
		nSCC	0.65 (0.55-0.77)	<0.001	1.13 (0.84-1.52)	0.415
	≥ 2nd line:	SCC	0.71 (0.57-0.87)	0.001	Ref.	
		nSCC	0.89 (0.78-1.01)	0.078	1.26 (0.98-1.61)	0.067
	IO monotherapy:	SCC	0.63 (0.48-0.83)	<0.001	Ref.	
		nSCC	0.81 (0.64-1.03)	0.083	1.29 (0.84-1.99)	0.245
	Chemo-IO:	SCC	0.64 (0.56-0.72)	<0.001	Ref.	
		nSCC	0.59 (0.54-0.64)	<0.001	0.93 (0.80-1.08)	0.339

Abstract 529 Table 3 Pooled hazard ratio of overall and progression-free survival and comparison between SCC and nSCC and PD-L1-positive (+) and negative (-). OS: overall survival; PFS: progression-free survival; SCC: squamous cell carcinoma; nSCC: non-squamous cell carcinoma; HR: hazard ratio; 95% CI; 95% confidence interval; Ratio: ratio of HR between SCC and nSCC (SCC as a reference-Ref.) and between PD-L1 + and negative (PD-L1 - as a Ref.)

Endpoint	Group		Pooled HR (95% CI)	*P.value*	Ratio (95% CI)	*P.value*
OS	SCC vs. nSCC					
	PD-L1+	*SCC*	0.71 (0.64-0.78)	<0.001	Ref.	
		nSCC	0.75 (0.65-0.86)	<0.001	1.05 (0.86-1.29)	0.598
	PD-L1-	*SCC*	0.71 (0.60-0.85)	<0.001	Ref.	
		nSCC	0.72 (0.63-0.82)	<0.001	1.01 (0.80-1.28)	0.945
	PD-L1 – vs. PD-L1+					
	SCC	*PDL1-*	0.71 (0.60-0.85)	<0.001	Ref.	
		PDL1+	0.71 (0.64-0.78)	<0.001	0.995 (0.81-1.23)	0.965
	nSCC	*PD-L1-*	0.72 (0.63-0.82)	<0.001	Ref.	
		PD-L1+	0.75 (0.65-0.86)	<0.001	1.04 (0.81-1.34)	0.749
PFS	SCC vs. nSCC					
	PD-L1+	*SCC*	0.51 (0.40-0.64)	<0.001	Ref.	
		nSCC	0.71 (0.55-0.91)	0.007	1.40 (0.98-2.00)	0.068
	PD-L1-	*SCC*	0.74 (0.62-0.89)	0.001	Ref.	
		nSCC	0.67 (0.45-0.98)	0.041	0.90 (0.54-1.49)	0.685
	PD-L1 – vs. PD-L1+					
	SCC	*PD-L1-*	0.74 (0.62-0.89)	0.001	Ref.	
		PD-L1+	0.51 (0.40-0.64)	<0.001	0.68 (0.44-1.07)	0.096
	nSCC	*PD-L1-*	0.67 (0.45-0.98)	0.041	Ref.	
		PD-L1+	0.71 (0.55-0.91)	0.007	1.06 (0.60-1.88)	0.841

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