Programmed Cell Death Protein-(Ligand) 1 Inhibitors for Treatment of Locally Advanced or Metastatic Non-Small Cell Lung Cancer in Asian and Non-Asian Patients: A Meta-Analysis

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CONCLUSIONS

- Data from this meta-analysis of randomised phase 3 clinical studies support the global use of programmed cell death protein-(ligand) 1 (PD-[L]1) inhibitors as first-line (1L) monotherapy or combination therapy and second-line/later (2L/2L+) monotherapy in Asian and non-Asian patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC)
- The consistency in clinical benefit shown in this meta-analysis is important when considering the use of drugs that were initially developed in an Asian population, such as tislelizumab, in a wider population, or for global regulatory and reimbursement submissions

INTRODUCTION

- Lung cancer is the leading cause of cancer mortality worldwide, with 1.1 million deaths in Asia vs ~0.5 million deaths in Europe and North America combined in 2022[1]
- Treatment for metastatic NSCLC depends on PD-(L)1 tumour cell (TC) expression and/or clinically relevant oncogene translocations. PD-(L)1 inhibitor monotherapy or combination therapy with platinum-based chemotherapy or cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibitors are 1L options, and PD-(L)1 inhibitor monotherapy is a 2L option[2-4]
- Survival data for metastatic NSCLC in Asian vs non-Asian populations are limited[5]
- We assessed the efficacy and safety of PD-(L)1 inhibitor monotherapy or combination therapy in Asian and non-Asian patients with unresectable, locally advanced or metastatic NSCLC

METHODS

- A systematic literature review and meta-analysis were conducted in accordance with published guidance[6-8] from January 1, 2010, to October 25, 2024
- Literature searches were performed primarily using the Ovid SP® platform

Selection

- Patients aged ≥18 years with unresectable, locally advanced or metastatic squamous/nonsquamous NSCLC who received 1L or 2L/2L+ PD-(L)1 inhibitor monotherapy or combination therapy (with platinum-based chemotherapy or CTLA-4 inhibitors) were included; comparators included chemotherapy or placebo
- Randomised, phase 3, controlled studies that included subgroup analyses for Asian patients by ethnicity or region were selected
- Only the intent-to-treat populations or PD-L1 subgroups were included; patients were excluded if they were not suitable for chemotherapy or had positive *EGFR* mutations or *ALK* translocations

Extraction

- Data were extracted using DistillerSR© literature review software and Microsoft Excel®
- Quality was evaluated using the Cochrane Risk of Bias tool (RoB 2.0),[9] and publication bias was evaluated using a funnel plot and Begg's test

Outcomes

- Overall survival (OS) and progression-free survival (PFS) hazard ratios (HRs) were extracted using random effects models based on line of therapy, PD-(L)1 inhibitor monotherapy or combination therapy, and high PD-L1 TC expression (≥50%)
- Safety outcomes were described if reported

RESULTS

Study Population

- Twenty-one 1L and 10 2L/2L+ phase 3 studies were included; 10,233 patients received PD-(L)1 inhibitors as 1L (63%) and 2L/2L+ (37%) therapy, and 8498 patients received comparator as 1L (65%) and 2L/2L+ (35%) therapy. Most studies showed low risk of bias
- Asian patients ranged from 2% to 100% (1L) and from 3% to 100% (2L/2L+); nine 1L studies and one 2L/2L+ study enrolled only Asian (China) patients
- Most studies enrolled males (52%-94%), smoking prevalence was high (62%-100%), and baseline Eastern Cooperative Oncology Group performance score was ≥1 in 56%-90% of patients

RESULTS (CONT.)

1L PD-(L)1 Inhibitor Combinations

- Beneficial and comparable effect on **OS** for Asian (HR=0.70; 95% confidence interval [CI]: 0.63, 0.76) and non-Asian (HR=0.70; 95% CI: 0.62, 0.79) patients treated with 1L PD-(L)1 inhibitor combination therapy (**Figure 1**)
- Similar effects on **PFS** observed for Asian (HR=0.53; 95% CI: 0.47, 0.60) and non-Asian (HR=0.60; 95% CI: 0.53, 0.68) patients (**Figure 2**)

2L/2L+ PD-(L)1 Inhibitor Monotherapy

- Beneficial and comparable effect on **OS** with 2L/2L+ PD-(L)1 inhibitor monotherapy in Asian (HR=0.73; 95% CI: 0.64, 0.83) and non-Asian (HR=0.71; 95% CI: 0.64, 0.78) patients (**Figure 3**)
- Greater effect on **PFS** for Asian (HR=0.57; 95% CI: 0.49, 0.67) than non-Asian (HR=0.73; 95% CI: 0.56, 0.95) patients (**Figure 4**); this may be due to differences in regional treatment patterns, additional maintenance therapy, prior treatment, or prior surgery

1L PD-(L)1 Inhibitor Monotherapy or Combination Therapy by PD-(L)1 Status

- Highly efficacious treatment effect on **OS** in Asian (HR=0.50; 95% CI: 0.39, 0.64) and non-Asian (HR=0.64; 95% CI: 0.55, 0.76) patients with high PD-(L)1 TC expression (**Figure 5**)
- Slightly greater magnitude of effect on **PFS** in Asian (HR=0.38; 95% CI: 0.32, 0.44) than non-Asian (HR=0.46; 95% CI: 0.37, 0.56) patients; heterogeneity was moderate in the non-Asian analysis, which may reflect fewer studies included (**Figure 6**)

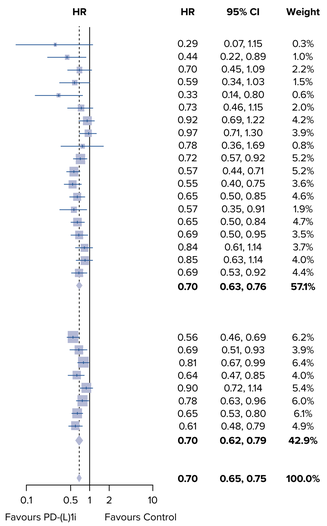
Safety

- Data were obtained from six 1L and two 2L/2L+ PD-(L)1 inhibitor studies
- Trend towards higher rates of grade 3-5 treatment-related adverse events in Asian than non-Asian subpopulations in 6 of 8 studies, eg, KEYNOTE-407: 82% China, 57% overall; CheckMate 227: 55% Japan, 33% overall; IMPower132: 73% Japan, 65% China, 58% overall

Limitations

- Several limitations inherent with meta-analysis design
- Lack of data for some subgroups, including biomarkers and genetic profiles
- Outcomes impacted by variations in patient numbers, follow-up time, and regional adverse event reporting practices

Figure 1. OS for Asian and Non-Asian Patients With NSCLC Treated With 1L PD-(L)1 Inhibitor Combination Therapy



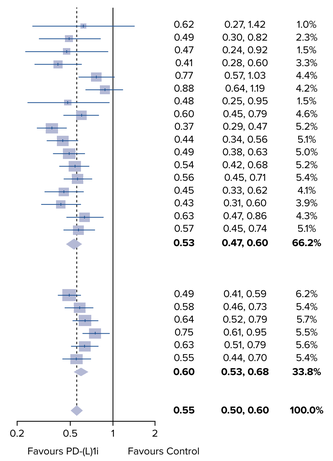
Study	HR	95% CI	Weight
Ethnicity: Asian			
KN-189	0.29	0.07, 1.15	0.3%
KN-407	0.44	0.22, 0.89	1.0%
CM-227 (PD-L1 ≥1%)	0.70	0.45, 1.09	2.2%
CM-227 (PD-L1 <1%)	0.59	0.34, 1.03	1.5%
CM-9LA	0.33	0.14, 0.80	0.6%
IMPower132	0.73	0.46, 1.15	2.0%
POSEIDON (D+CT vs CT)	0.92	0.69, 1.22	4.2%
POSEIDON (D+T+CT vs CT)	0.97	0.71, 1.30	3.9%
EMPOWER-Lung 3 part 2	0.78	0.36, 1.69	0.8%
CameL	0.72	0.57, 0.92	5.2%
CameL-sq	0.57	0.44, 0.71	5.2%
AK105-302	0.55	0.40, 0.75	3.6%
ORIENT-11	0.65	0.50, 0.85	4.6%
ORIENT-12	0.57	0.35, 0.91	1.9%
GEMSTONE-302	0.65	0.50, 0.84	4.7%
RN-307-Pac	0.69	0.50, 0.95	3.5%
RN-307-nPac	0.84	0.61, 1.14	3.7%
RN-304	0.85	0.63, 1.14	4.0%
CHOICE-01	0.69	0.53, 0.92	4.4%
Random effects model	**0.70**	**0.63, 0.76**	**57.1%**
Heterogeneity: I^2=25%, τ^2=0.0096, P=.1553			
Ethnicity: non-Asian			
KN-189	0.56	0.46, 0.69	6.2%
KN-407	0.69	0.51, 0.93	3.9%
CM-227 (PD-L1 ≥1%)	0.81	0.67, 0.99	6.4%
CM-227 (PD-L1 <1%)	0.64	0.47, 0.85	4.0%
IMPower132	0.90	0.72, 1.14	5.4%
POSEIDON (D+CT vs CT)	0.78	0.63, 0.96	6.0%
POSEIDON (D+T+CT vs CT)	0.65	0.53, 0.80	6.1%
EMPOWER-Lung 3 part 2	0.61	0.48, 0.79	4.9%
Random effects model	**0.70**	**0.62, 0.79**	**42.9%**
Heterogeneity: I^2=51.5%, τ^2=0.0147, P=.0439			
Random effects model	**0.70**	**0.65, 0.75**	**100.0%**

Heterogeneity: I^2=32.4%, τ^2=0.0108, P=.0551

Test for subgroup differences: χ^2_1=0.01, df=1, P=.9344

Abbreviations: CM, CheckMate; CT, chemotherapy; D, durvalumab; KN, KEYNOTE; PD-(L)1i, programmed cell death protein-(ligand) 1 inhibitor; RN, RATIONALE; T, tremelimumab.

Figure 2. PFS for Asian and Non-Asian Patients With NSCLC Treated With 1L PD-(L)1 Inhibitor Combination Therapy

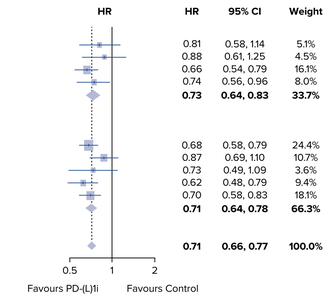


Study	HR	95% CI	Weight
Ethnicity: Asian			
KN-189	0.62	0.27, 1.42	1.0%
KN-407	0.49	0.30, 0.82	2.3%
CM-9LA	0.47	0.24, 0.92	1.5%
IMPower132	0.41	0.28, 0.60	3.3%
POSEIDON (D+CT vs CT)	0.77	0.57, 1.03	4.4%
POSEIDON (D+T+CT vs CT)	0.88	0.64, 1.19	4.2%
EMPOWER-Lung 3 part 2	0.48	0.25, 0.95	1.5%
CameL	0.60	0.45, 0.79	4.6%
CameL-sq	0.37	0.29, 0.47	5.2%
AK105-302	0.44	0.34, 0.56	5.1%
ORIENT-11	0.49	0.38, 0.63	5.0%
ORIENT-12	0.54	0.42, 0.68	5.2%
GEMSTONE-302	0.56	0.45, 0.71	5.4%
RN-307-Pac	0.45	0.33, 0.62	4.1%
RN-307-nPac	0.43	0.31, 0.60	3.9%
RN-304	0.63	0.47, 0.86	4.3%
CHOICE-01	0.57	0.45, 0.74	5.1%
Random effects model	**0.53**	**0.47, 0.60**	**66.2%**
Heterogeneity: I^2=53.9%, τ^2=0.0316, P=.0043			
Ethnicity: non-Asian			
KN-189	0.49	0.41, 0.59	6.2%
KN-407	0.58	0.46, 0.73	5.4%
IMPower132	0.64	0.52, 0.79	5.7%
POSEIDON (D+CT vs CT)	0.75	0.61, 0.95	5.5%
POSEIDON (D+T+CT vs CT)	0.63	0.51, 0.79	5.6%
EMPOWER-Lung 3 part 2	0.55	0.44, 0.70	5.4%
Random effects model	**0.60**	**0.53, 0.68**	**33.8%**
Heterogeneity: I^2=48.9%, τ^2=0.0114, P=.0816			
Random effects model	**0.55**	**0.50, 0.60**	**100.0%**

Heterogeneity: I^2=54.7%, τ^2=0.0254, P=.0009

Test for subgroup differences: χ^2_1=1.99, df=1, P=.1585

Figure 3. OS for Asian and Non-Asian Patients With NSCLC Treated With 2L/2L+ PD-(L)1 Inhibitor Monotherapy

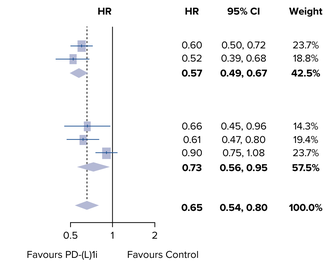


Study	HR	95% CI	Weight
Ethnicity: Asian			
KN-010	0.81	0.58, 1.14	5.1%
JAVELIN-Lung 200	0.88	0.61, 1.25	4.5%
RN-303	0.66	0.54, 0.79	16.1%
ORIENT-3	0.74	0.56, 0.96	8.0%
Random effects model	**0.73**	**0.64, 0.83**	**33.7%**
Heterogeneity: I^2=0%, τ^2=0.0002, P=.4769			
Ethnicity: non-Asian			
KN-010	0.68	0.58, 0.79	24.4%
JAVELIN-Lung 200	0.87	0.69, 1.10	10.7%
RN-303	0.73	0.49, 1.09	3.6%
CM-017	0.62	0.48, 0.79	9.4%
CM-057	0.70	0.58, 0.83	18.1%
Random effects model	**0.71**	**0.64, 0.78**	**66.3%**
Heterogeneity: I^2=8.8%, τ^2=0, P=.3560			
Random effects model	**0.71**	**0.66, 0.77**	**100.0%**

Heterogeneity: I^2=0%, τ^2 =0, P=.5369

Test for subgroup differences: χ^2_1=0.12, df=1, P=.7271

Figure 4. PFS for Asian and Non-Asian Patients With NSCLC Treated With 2L/2L+ PD-(L)1 Inhibitor Monotherapy

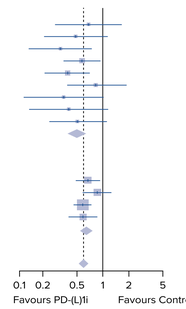


Study	HR	95% CI	Weight
Ethnicity: Asian			
RN-303	0.60	0.50, 0.72	23.7%
ORIENT-3	0.52	0.39, 0.68	18.8%
Random effects model	**0.57**	**0.49, 0.67**	**42.5%**
Heterogeneity: I^2=0%, τ^2=0, P=.3988			
Ethnicity: non-Asian			
RN-303	0.66	0.45, 0.96	14.3%
CM-017	0.61	0.47, 0.80	19.4%
CM-057	0.90	0.75, 1.08	23.7%
Random effects model	**0.73**	**0.56, 0.95**	**57.5%**
Heterogeneity: I^2=68.7%, τ^2=0.0350, P=.0410			
Random effects model	**0.65**	**0.54, 0.80**	**100.0%**

Heterogeneity: I^2=73.5%, τ^2=0.0349, P=.0045

Test for subgroup differences: χ^2_1=2.39, df=1, P=.1221

Figure 5. OS for Asian and Non-Asian Patients With NSCLC and PD-L1 TC Expression ≥50% Treated With 1L PD-(L)1 Inhibitor Monotherapy or Combination Therapy

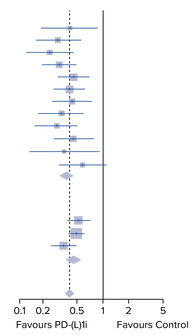


Study	HR	95% CI	Weight
Ethnicity: Asian			
CameL	0.68	0.28, 1.63	2.2%
CameL-sq	0.48	0.21, 1.12	2.4%
AK105-302	0.32	0.14, 0.73	2.5%
GEMSTONE-302	0.57	0.35, 0.93	7.1%
RN-304	0.39	0.21, 0.70	4.7%
CHOICE-01	0.82	0.39, 1.90	2.7%
KN-024	0.35	0.12, 1.01	1.5%
IMPower110	0.40	0.14, 1.14	1.6%
EMPOWER-Lung 1	0.51	0.24, 1.10	2.9%
Random effects model	**0.50**	**0.39, 0.64**	**27.7%**
Heterogeneity: I^2=0%, τ^2=0, P=.7961			
Ethnicity: non-Asian			
KN-024	0.67	0.49, 0.93	16.6%
IMPower110	0.86	0.59, 1.25	12.1%
EMPOWER-Lung 1	0.58	0.46, 0.73	32.0%
KN-189	0.59	0.40, 0.86	11.6%
Random effects model	**0.64**	**0.55, 0.76**	**72.3%**
Heterogeneity: I^2=9.9%, τ^2=0.0023, P=.3437			
Random effects model	**0.60**	**0.52, 0.68**	**100.0%**

Heterogeneity: I^2=0%, τ^2=0, P=.5295

Test for subgroup differences: χ^2_1=3.03, df=1, P=.0817

Figure 6. PFS for Asian and Non-Asian Patients With NSCLC and PD-L1 TC Expression ≥50% Treated With 1L PD-(L)1 Inhibitor Monotherapy or Combination Therapy



Study	HR	95% CI	Weight
Ethnicity: Asian			
CameL	0.42	0.19, 0.87	2.7%
CameL-sq	0.30	0.17, 0.55	4.3%
AK105-302	0.24	0.13, 0.45	3.9%
ORIENT-11	0.31	0.20, 0.49	6.7%
ORIENT-12	0.46	0.30, 0.69	7.8%
GEMSTONE-302	0.41	0.27, 0.62	7.8%
RN-307-Pac	0.44	0.26, 0.75	5.2%
RN-307-nPac	0.33	0.18, 0.59	4.2%
RN-304	0.29	0.16, 0.50	4.6%
CHOICE-01	0.45	0.27, 0.78	5.2%
KN-024	0.35	0.14, 0.91	1.8%
EMPOWER-Lung 1	0.58	0.31, 1.09	3.8%
Random effects model	**0.38**	**0.32, 0.44**	**58.1%**
Heterogeneity: I^2=0%, τ^2=0, P=.7143			
Ethnicity: non-Asian			
KN-024	0.52	0.38, 0.72	11.7%
EMPOWER-Lung 1	0.49	0.40, 0.61	19.5%
KN-189	0.35	0.25, 0.49	10.8%
Random effects model	**0.46**	**0.37, 0.56**	**41.9%**
Heterogeneity: I^2=41.9%, τ^2=0.0135, P=.1790			
Random effects model	**0.41**	**0.36, 0.46**	**100.0%**

Heterogeneity: I^2=4.6%, τ^2 =0.0107, P=.4008

Test for subgroup differences: χ^2_1=2.02, df=1, P=.1551

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