Supplementary Online Content

Association of Smoking Status with Efficacy of First-line Immune Checkpoint Inhibitors in Advanced Non-small Cell Lung Cancers: A Systematic Review and Meta-analysis

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eMethods. Search strategies for PubMed, EMBASE, Cochrane database

eFig.1. Risk of bias of included studies

eFig.2. Forest plots of meta-analysis comparing checkpoint inhibitor-based treatment versus chemotherapy for overall survival by smoking status, which confined to trials with FDA-approved regimens.

eMethods. Search strategies for PubMed, EMBASE, Cochrane database

PubMed search details: 270 results

(("carcinoma, non-small-cell lung"[Mesh] OR "NSCLC"[Title/Abstract] OR "Non-Small Cell Lung Cancer"[All Fields]) AND ("checkpoint inhibitor"[Title/Abstract] OR "pembrolizumab"[Title/Abstract] OR "nivolumab"[Title/Abstract] OR "atezolizumab"[Title/Abstract] OR "durvalumab"[Title/Abstract] OR "ipilimumab"[Title/Abstract] OR "cemiplimab"[Title/Abstract])) AND (("random allocation"[MeSH Terms] OR "randomized"[All Fields] OR "randomised"[All Fields] OR "randomly"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR "trial"[Title/Abstract] OR "study"[Title/Abstract]))

EMBASE: 1,572 results

('non-small cell lung cancer'/exp OR 'nsclc':ab,ti OR ('lung':ab,ti AND ('non small cell':ab,ti OR 'non-small-cell':ab,ti OR 'non-small cell':ab,ti))) AND ('checkpoint inhibitor':ab,ti OR 'pembrolizumab':ab,ti OR 'nivolumab':ab,ti OR 'atezolizumab':ab,ti OR 'durvalumab':ab,ti OR 'ipilimumab':ab,ti OR 'cemiplimab':ab,ti) AND 'human'/de AND ('clinical trial'/de OR 'randomized controlled trial'/exp)
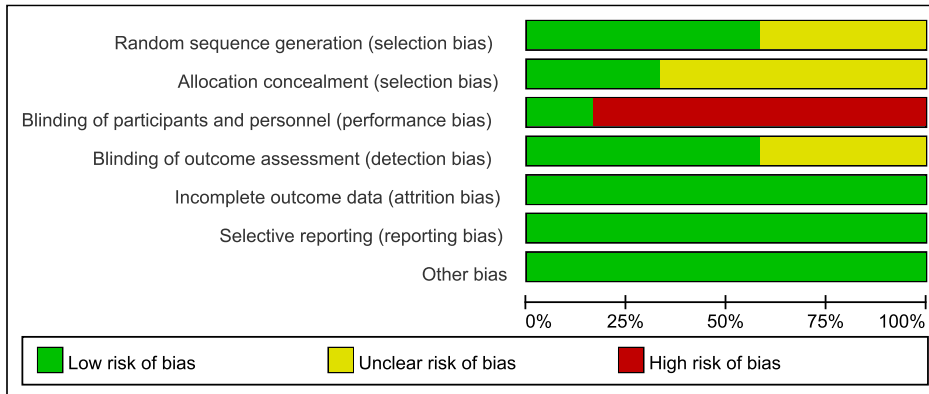
Cochrane database: 1,301 results

#1 "carcinoma, non- small-cell lung" OR "non-small cell lung cancer" OR "nsclc"

#2 "checkpoint inhibitor" OR "pembrolizumab" OR "nivolumab" OR "atezolizumab" OR "durvalumab" OR "ipilimumab" OR "cemiplimab"

#3 trials

#1 AND #2 AND #3

eFigure 1. Risk of bias of included studies

eFigure 2. Forest plots of meta-analysis comparing checkpoint inhibitor-based treatment versus chemotherapy for overall survival by smoking status, which confined to trials with FDA-approved regimens. (A) never-smoker group; (B) current/former smoker group. The size of the squares corresponds to the weight of the study in the meta-analysis. The treatment effects were calculated using a random-effects model.

A

Study or Subgroup	ICI Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
ICI+Chemotherapy				
IMpower-130	48	17	30.0%	0.55 [0.26, 1.18]
Keynote-189	48	25	27.8%	0.23 [0.10, 0.53]
Keynote-407	22	19	42.2%	0.80 [0.59, 1.08]
Subtotal (95% CI)	**118**	**61**	**100.0%**	**0.51 [0.25, 1.03]**

Heterogeneity: Tau² = 0.29; Chi² = 7.76, df = 2 (P = 0.02); I² = 74%
Test for overall effect: Z = 1.88 (P = 0.06)

Study or Subgroup	ICI Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
ICI only				
Checkmate-227	56	51	43.3%	1.23 [0.76, 1.99]
IMpower-110	9	15	8.7%	1.83 [0.63, 5.31]
Keynote-024	5	19	2.2%	0.90 [0.11, 7.48]
Keynote-042	64	67	45.8%	1.10 [0.69, 1.75]
Subtotal (95% CI)	**134**	**152**	**100.0%**	**1.20 [0.88, 1.65]**

Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 3 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.14 (P = 0.25)

Test for subgroup differences: Chi² = 4.77, df = 1 (P = 0.03), I² = 79.0%

Favors [ICI]   Favors [Chemotherapy]

B

Study or Subgroup	ICI Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
ICI+Chemotherapy				
IMpower-130	403	211	37.0%	0.81 [0.65, 1.01]
Keynote-189	362	181	32.0%	0.54 [0.41, 0.71]
Keynote-407	256	262	31.0%	0.64 [0.48, 0.85]
Subtotal (95% CI)	**1021**	**654**	**100.0%**	**0.66 [0.52, 0.84]**

Heterogeneity: Tau² = 0.03; Chi² = 5.19, df = 2 (P = 0.07); I² = 61%
Test for overall effect: Z = 3.34 (P = 0.0008)

Study or Subgroup	ICI Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
ICI only				
Checkmate-227	334	340	43.3%	0.77 [0.64, 0.92]
IMpower-110	98	83	10.0%	0.53 [0.34, 0.83]
Keynote-024	149	132	18.0%	0.63 [0.46, 0.87]
Keynote-042	235	233	28.7%	0.62 [0.49, 0.79]
Subtotal (95% CI)	**816**	**788**	**100.0%**	**0.67 [0.58, 0.78]**

Heterogeneity: Tau² = 0.00; Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 5.25 (P < 0.00001)

Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%

Favors [ICI]   Favors [Chemotherapy]