Supplementary material

Addition of immune checkpoint inhibitors to chemotherapy vs chemotherapy alone as first-line treatment in extensive-stage small-cell lung carcinoma: a systematic review and meta-analysis

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Table S1. Search strategy for MEDLINE accessed through PubMed (1966 to 16 July 2020)

SEARCH	QUERY	RESULTS
#1	Search: (("Carcinoma, Small Cell"[Mesh] AND "Lung"[Mesh]) OR "Small Cell Lung Carcinoma"[Mesh]) OR (Small-Cell Lung Cancer OR SCLC OR "Lung neoplasm")	93,759
#2	Search: Chemo-naïve OR untreated OR "un-treated" OR "not treated" OR "first line" OR "1st line" OR "1st- line" Sort by: Most Recent	265,438
#3	Search: #1 AND #2	6,868
#4	Search: "atezolizumab" [Supplementary Concept] OR (anti-PDL1 OR immunoglobulin G1, anti-(human CD antigen CD274) (human monoclonal MDPL3280a heavy chain), disulfide with human monoclonal MDPL3280a kappa-chain, dimer OR MPDL3280A OR MPDL-3280A OR Tecentriq OR RG7446 OR RG-7446) Sort by: Most Recent	1,136
#5	Search: "durvalumab" [Supplementary Concept] OR (MEDI4736 OR MEDI-4736 OR Imfinzi) Sort by: Most Recent	545
#6	Search: "pembrolizumab" [Supplementary Concept] OR (SCH-900475 OR Keytruda MK-3475 OR lambrolizumab) Sort by: Most Recent	4,086
#7	Search: "Nivolumab" [Mesh] OR (Opdivo OR ONO-4538 OR ONO 4538 OR ONO4538 OR MDX-1106 OR MDX 1106 OR MDX1106 OR BMS-936558 OR BMS 936558 OR BMS936558) Sort by: Most Recent	5,147
#8	Search: "Ipilimumab" [Mesh] OR (Anti-CTLA-4 MAb Ipilimumab OR Anti CTLA 4 MAb Ipilimumab OR Ipilimumab, Anti-CTLA-4 MAb OR Yervoy OR MDX 010 MDX010 OR MDX-010 OR MDX-CTLA-4 OR MDX CTLA 4) Sort by: Most Recent	10,061
#9	Search: #4 OR #5 OR #6 OR #7 OR #8	16,32
#10	Search: #3 AND #9	383

SEARCH	QUERY	RESULTS
#1.	small cell lung cancer'/exp OR 'small cell lung cancer'	154,361
#2.	Scic	13,126
#3.	'pembrolizumab'/exp OR 'pembrolizumab'	15,875
#4.	'nivolumab'/exp OR 'nivolumab'	18,248
#5.	'ipilimumab'/exp OR 'ipilimumab'	14,42
#6.	'durvalumab'/exp OR 'durvalumab'	3,771
#7.	'atezolizumab'/exp OR 'atezolizumab'	5,578
#8.	chemo naïve' OR untreated OR 'un-treated' OR 'not treated' OR 'first line' OR '1st line' OR '1st-line'	394,911
#9.	#1 OR #2	155,621
#10.	#8 AND #9	13,699
#11.	#3 OR #4 OR #5 OR #6 OR #7	34,146
#12.	#10 AND #11	1,503
#13.	#12 AND 'randomized controlled trial'/de	320

Table S2. Search strategy for EMBASE (1980 to 17 July 2020)



Figure S1. PRISMA flow-chart of study selection

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): Overall survival	Blinding of participants and personnel (performance bias): Progression-free survival, response rate and adverse events	Blinding of outcome assessment (detection bias): Overall survival	Blinding of outcome assessment (detection bias): Progression-free survival, response rate and adverse events	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Horn 2018	•	?	•	•	•	?		•	•
Owonikoko 2019	?	?	÷	÷	•	?	•	•	•
Paz-Ares 2019	•	•	•	•	•		•		•
Reck 2013	?	?	•	•	•	?	•	?	•
Reck 2016	•	?	•	•	•	•	•	•	•
Rudin 2020	•	?	•	•	•	?	•	•	•

Figure S2. Risk of bias summary: authors' judgements about risk of bias for each included study

Figure S3. Subgroup analysis by age (age <65 years/≥65 years). Forest plot comparison of

adverse event rate in patients receiving chemotherapy plus immune checkpoint inhibitors

(ICIs) versus chemotherapy alone or combined with placebo. CI, confidence interval; IV,

inverse variance; SE standard error.



<u>Footnotes</u>

(1) Subgroup with age higher or equal to 75 years

(2) Subgroup with age higher or equal to 65 years and <75 years

Figure S4. Subgroup analysis by sex (male/female). Forest plot comparison of adverse event

rate in patients receiving chemotherapy plus immune checkpoint inhibitors (ICIs) versus

chemotherapy alone or combined with placebo. CI, confidence interval; IV, inverse variance;

SE, standard error.

				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
9.1.1 Male					
Horn 2018	-0.3011	0.1608	12.0%	0.74 [0.54, 1.01]	
Paz-Ares 2019	-0.2744	0.1292	14.9%	0.76 [0.59, 0.98]	
Reck 2016	0.0677	0.094	18.8%	1.07 [0.89, 1.29]	
Rudin 2020	-0.2744	0.1292	14.9%	0.76 [0.59, 0.98]	
Subtotal (95% CI)			60.5 %	0.84 [0.69, 1.03]	
Heterogeneity: Tau² =	: 0.03; Chi² = 8.05, df	f= 3 (P =	0.05); l² =	: 63%	
Test for overall effect:	Z = 1.71 (P = 0.09)				
9.1.2 Female					
Horn 2018	-0.4308	0.2228	7.9%	0.65 [0.42, 1.01]	
Paz-Ares 2019	-0.462	0.2318	7.5%	0.63 [0.40, 0.99]	
Reck 2016	0.0583	0.1372	14.1%	1.06 [0.81, 1.39]	
Rudin 2020	-0.1278	0.187	10.0%	0.88 [0.61, 1.27]	
Subtotal (95% CI)			39.5%	0.82 [0.64, 1.06]	
Heterogeneity: Tau² =	: 0.03; Chi² = 5.72, df	'= 3 (P =	0.13); I² =	: 48%	
Test for overall effect:	Z = 1.49 (P = 0.14)				
Total (95% CI)			100.0%	0.84 [0.72, 0.97]	•
Heterogeneity: Tau² =	: 0.02; Chi ^z = 13.78, (df = 7 (P =	= 0.06); I ^z	= 49%	
Test for overall effect:	Z = 2.39 (P = 0.02)				0.5 0.7 1 1.5 Z ICIs+Chemotherany Chemotherany slope
Test for subgroup diff	ferences: Chi² = 0.01	tota - one notiferapy - one notiferapy alone			

Figure S5. Subgroup analysis by baseline functional status. Forest plot comparison of adverse

event rate in patients receiving chemotherapy plus immune checkpoint inhibitors (ICIs) versus

chemotherapy alone or combined with placebo. CI, confidence interval; ECOG, Eastern

Cooperative Oncology Group; IV, inverse variance; SE, standard error; WHO, World Health

Organization.

				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
10.1.1 ECOG/WHO 0					
Horn 2018 (1)	-0.2357	0.2437	7.4%	0.79 [0.49, 1.27]	
Paz-Ares 2019 (2)	-0.3425	0.1997	9.5%	0.71 [0.48, 1.05]	
Reck 2016 (3)	0.2469	0.1363	14.0%	1.28 [0.98, 1.67]	
Rudin 2020 (4)	-0.3857	0.2221	8.3%	0.68 [0.44, 1.05]	
Subtotal (95% CI)			39.3%	0.86 [0.61, 1.21]	
Heterogeneity: Tau² =	= 0.08; Chi² = 9.74, df	'= 3 (P =	0.02); l² =	: 69%	
Test for overall effect:	Z = 0.86 (P = 0.39)				
10.1.2 ECOG/WHO 1					
Horn 2018 (5)	-0.3857	0.1569	12.4%	0.68 [0.50, 0.92]	
Paz-Ares 2019 (6)	-0.2744	0.1292	14.6%	0.76 [0.59, 0.98]	
Reck 2016 (7)	-0.0101	0.0899	18.3%	0.99 [0.83, 1.18]	_ _
Rudin 2020 (8)	-0.1508	0.1198	15.5%	0.86 [0.68, 1.09]	
Subtotal (95% CI)			60.7 %	0.84 [0.71, 0.99]	•
Heterogeneity: Tau² =	= 0.01; Chi² = 5.61, df	'= 3 (P =	0.13); l² =	: 46%	
Test for overall effect:	Z = 2.13 (P = 0.03)				
Total (95% CI)			100.0%	0.85 [0.73, 1.00]	•
Heterogeneity: Tau ² =	= 0.03; Chi ² = 15.99, (:f=7(P	= 0.03); I ^z	= 56%	
Test for overall effect:	Z = 2.02 (P = 0.04)				U.S U.7 I I.S Z ICIs+Chemotherany Chemotherany alone
Test for subgroup diff	ferences: Chi ² = 0.02	, df = 1 (F	P = 0.90),	I² = 0%	icis chemotherapy chemotherapy alone
<u>Footnotes</u>					
(1) According to ECO	G performance statu				
(2) According to WHO) performance status				
(3) According to ECO	G performance statu	s			
(4) According to ECO	G performance statu	s			
(5) According to ECO	G performance statu	s			

(6) According to WHO performance status (7) According to ECOG performance status

(8) According to ECOG performance status

Figure S6. Subgroup analysis by serum lactate dehydrogenase (LDH). Forest plot comparison of

adverse event rate in patients receiving chemotherapy plus immune checkpoint inhibitors

(ICIs) versus chemotherapy alone or combined with placebo. CI, confidence interval; IV,

inverse variance; SE, standard error.



Figure S7. Subgroup analysis by brain metastasis at baseline. Forest plot comparison of

adverse event rate in patients receiving chemotherapy plus immune checkpoint inhibitors

(ICIs) versus chemotherapy alone or combined with placebo. CI, confidence interval; IV,

inverse variance; SE, standard error.



Figure S8. Subgroup analysis by baseline liver metastasis. Forest plot comparison of adverse

event rate in patients receiving chemotherapy plus immune checkpoint inhibitors (ICIs) versus

chemotherapy alone or combined with placebo. CI, confidence interval; IV, inverse variance;

SE, standard error.



Figure S9. Subgroup analysis in longer-term survival. Forest plot comparison of adverse event

rate in patients receiving chemotherapy plus immune checkpoint inhibitors (ICIs) versus

chemotherapy alone or combined with placebo. CI, confidence interval; M-H, Mantel-

Haenszel.

	ICIs+Chemoth	nerapy	Chemothera	y only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
14.5.1 Pembrolizum	ab						
Rudin 2020 Subtotal (95% Cl)	103	228 228	89	225 225	14.7% 14.7%	1.14 [0.92, 1.42] 1.14 [0.92, 1.42]	
Total events	103		89				
Test for overall effect	:Z=1.21 (P=0.	23)					
14.5.2 Ipilimumab							
Reck 2016 Subtotal (95% CI)	226	566 566	226	566 566	21.5% 21.5 %	1.00 [0.87, 1.15] 1.00 [0.87, 1.15]	—
Total events	226		226				
Heterogeneity: Not a Test for overall effect	pplicable : Z = 0.00 (P = 1.	.00)					
14.5.3 Durvalumab							
Paz-Ares 2019 Subtotal (95% CI)	145	268 268	108	269 269	17.5% 17.5 %	1.35 [1.12, 1.62] 1.35 [1.12, 1.62]	
Total events	145		108				
Heterogeneity: Not a Test for overall effect	pplicable : Z = 3.20 (P = 0.	001)					
14.5.4 Atezolizumab							
Horn 2018 Subtotal (95% CI)	104	201 201	77	202 202	14.3% 14.3%	1.36 [1.09, 1.69] 1.36 [1.09, 1.69]	-
Total events	104		77				
Heterogeneity: Not a Test for overall effect	pplicable : Z = 2.71 (P = 0.	007)					
14.5.5 Nivolumab							
Owonikoko 2019	114	279	110	275	15.8%	1.02 [0.83, 1.25]	_
Owonikoko 2019 Subtotal (95% CI)	123	280 559	110	275 550	16.3% 32.1 %	1.10 [0.90, 1.34] 1.06 [0.92, 1.22]	•
Total events	237		220				
Heterogeneity: Tau ² = Test for overall effect	= 0.00; Chi ^z = 0.2 : Z = 0.82 (P = 0.	25, df = 1 41)	(P = 0.61); I ² =	0%			
Total (95% CI)		1822		1812	100.0%	1.14 [1.02, 1.28]	◆
Total events	815		720				
Heterogeneity: Tau² :	= 0.01; Chi ² = 10	.08, df = 5	5 (P = 0.07); I ² =	= 50%		-	
Test for overall effect	: Z = 2.38 (P = 0.	02)					Chemotherapy alone ICIs+Chemotherapy
rest for subgroup dif	ierences: Uni*=	9.82, df=	= 4 (P = 0.04), I	-= 59.3%	, ,		