APPENDIX A: SEARCH STRATEGY

SYSTEMATIC REVIEWS

Search for current systematic reviews (limited to last 7 years) **Date Searched: 08-22-22**			
A. Bibliographic Databases:	**#**	**Search Statement**	**Results**
MEDLINE: Systematic Reviews Ovid MEDLINE(R) ALL 1946 to August 19, 2022	1	Carcinoma, Non-Small-Cell Lung/ or Lung Neoplasms/	250378
	2	(lung cancer or lung neoplasm* or lung carcinoma* or nsclc or lung tumor* or lung tumour*).ti,ab,kw.	218639
	3	(non small cell* or nonsmall cell*).ti,ab,kw.	82273
	4	2 and 3	79798
	5	1 or 4	270498
	6	Neoadjuvant Therapy/ or Chemotherapy, Adjuvant/	63639
	7	(neoadjuvant or adjuvant).ti,ab,kw.	189953
	8	6 or 7	211194
	9	Gefitinib/ or Afatinib/ or Nivolumab/ or Immune Checkpoint Inhibitors/ or Protein Kinase Inhibitors/	69196
	10	(gefitinib or erolotinib or afatinib or osimertinib or atezolizumab or durvalumab or nivolumab or pembrolizumab or cemiplimab or EGFR tyrosine kinase inhibitors or anti-PD-1 or anti-PD-L1 or checkpoint inhibitor* or check-point inhibitor*).ti,ab,kw.	45217
	11	9 or 10	98653
	12	5 and 8 and 11	781
	13	(systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best	535251

		practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt.	
	14	12 and 13	51
	15	limit 14 to english language	50
CDSR: Protocols and Reviews EBM Reviews - Cochrane Database of Systematic Reviews 2005 to August 17, 2022	1	(Non-Small-Cell Lung Carcinoma or Lung Neoplasms).kw.	45
	2	(lung cancer or lung neoplasm* or lung carcinoma* or nsclc or lung tumor* or lung tumour*).ti,ab,kw.	97
	3	(non small cell* or nonsmall cell*).ti,ab,kw.	53
	4	2 and 3	53
	5	1 or 4	72
	6	(Neoadjuvant Therapy or Chemotherapy, Adjuvant).kw.	91
	7	(neoadjuvant or adjuvant).ti,ab,kw.	296
	8	6 or 7	296
	9	(Gefitinib or Afatinib or Nivolumab or Immune Checkpoint Inhibitors or Protein Kinase Inhibitors).kw.	13
	10	(gefitinib or erolotinib or afatinib or osimertinib or atezolizumab or durvalumab or nivolumab or pembrolizumab or cemiplimab or EGFR tyrosine kinase inhibitors or anti-PD-1 or anti-PD-L1 or checkpoint inhibitor* or check-point inhibitor*).ti,ab,kw.	22
	11	9 or 10	29

	12	5 and 8 and 11	1

Search for current systematic reviews (limited to last 7 years) **Date Searched: 08-22-22**		
B. Non-bibliographic databases	**Evidence**	**Results**
AHRQ: evidence reports, technology assessments, U.S Preventative Services Task Force Evidence Synthesis	http://www.ahrq.gov/research/findings/evidence-based-reports/search.html Search: non-small-cell lung cancer AND (neoadjuvant OR adjuvant)	0
CADTH	https://www.cadth.ca Search: non-small-cell lung cancer AND (neoadjuvant OR adjuvant) Nivolumab-Ipilimumab for Non-Small Cell Lung Cancer – Details. 2021. https://www.cadth.ca/nivolumab-ipilimumab-non-small-cell-lung-cancer-details Keytruda for Non-Squamous NSCLC – Details. 2019. https://www.cadth.ca/keytruda-non-squamous-nsclc-details Keytruda for Squamous NSCLC – Details. 2020. https://www.cadth.ca/keytruda-squamous-nsclc-details	3
EPPI-Centre	http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=62 Search: lung cancer	0
NLM	http://www.ncbi.nlm.nih.gov/books Search: non-small-cell lung cancer AND (adjuvant OR neoadjuvant)	0
VA Products - VATAP, PBM and HSR&D publications	A. http://www.hsrd.research.va.gov/research/default.cfm B. http://www.research.va.gov/research_topics/ Search: lung cancer	0

Search for systematic reviews currently under development (includes forthcoming reviews & protocols) **Date Searched: 08-22-22**		
D. Under development :	**Evidence:**	**Results :**
AHRQ topics in development (EPC Status Report)	KV emailed 08-22-22; CA responded 08-22-22, no duplication	0
PROSPERO (SR registry)	http://www.crd.york.ac.uk/PROSPERO/ Search: non-small-cell lung cancer AND (neoadjuvant OR adjuvant) Chunhua Xu, wei liu, Qian Zhang, Tiantian Zhang, Li Li, Chunhua Xu. A systematic review and meta-analysis of neoadjuvant chemoimmunotherapy in stage III non-small cell lung cancer.. PROSPERO 2022 CRD42022325531 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022325531 Xuhao Wang, Fanqi Meng. A systematic review and network meta-analysis protocol of neoadjuvant chemoimmunotherapy for patients with resectable non-small-cell lung cancer. PROSPERO 2022 CRD42022328166 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022328166 Xuhao Wang, Fanqi Meng. A systematic review and network meta-analysis protocol of neoadjuvant Immune Checkpoint Inhibitor therapy for patients with resectable non-small-cell lung cancer. PROSPERO 2021 CRD42021258132 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021258132 Guishi Wang, Tiantian Wang. A systematic review and network meta-analysis protocol of various neoadjuvant therapies Immune for patients with resectable non-small-cell lung cancer. PROSPERO 2021 CRD42021269087 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021269087 Rui-Lian Chen, Ling-Ling Sun, Yang Cao, Jie-Tao Lin, Ying Zhang, Jing-Xu Zhou, Si-Yu Wang, Wei Hou, Li-Zhu Lin. Adjuvant EGFR-TKI for EGFR-mutant patients with resected non-small cell lung cancer: a meta-analysis from randomized controlled trials. PROSPERO 2020 CRD42020181942 Available from:	22

	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020181942 Rui-Lian Chen, Han-Rui Chen, Ling-Ling Sun, Yang Cao, Jie-Tao Lin, Ying Zhang, Jing-Xu Zhou, Si-Yu Wang, Wei Hou, Li-Zhu Lin. Adjuvant EGFR-TKI for EGFR-mutant patients with resected non-small cell lung cancer: a meta-analysis from randomized controlled trials. PROSPERO 2020 CRD42020190776 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020190776 Ran Zhong, Wenhua Liang, Caichen Li, Jianxing He. Adjuvant EGFR-TKIs versus standard chemotherapy for patients with resected NSCLC: a meta-analysis. PROSPERO 2021 CRD42021240657 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021240657 Ye Zhao, Hai-ming Feng, Jin-hui Tian, Qin Yu, Long Ge, Bin Li, Cheng Wang, Ke-hu Yang, Jian-kai Wang. Adjuvant treatments after chemoradiotherapy in patients with locally advanced inoperable non-small cell lung cancer (NSCLC): a systematic review and network meta-analysis.. PROSPERO 2021 CRD42021239433 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021239433 Jessa Gilda Pandy,, Joanmarie Balolong, Marcelo Imasa. Adjuvant Tyrosinen Kinase Inhibitors in Nonsquamous non-small cell lung cancer with EGFR driver mutations: A Meta-analysis of randomized trials. PROSPERO 2020 CRD42020197421 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020197421 Yongxing Bao, Shuang Sun, Xu Yang, Yunsong Liu, Yang Wang, Zhouguang Hui. Comparation of Different adjuvant EGFR-TKIs for Resected Non small cell lung cancer – a Systematic Review and Network Meta-Analysis. PROSPERO 2022 CRD42022300589 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022300589 Yi Yang, Yingyao Chen, Dai Lian, Ying Tao. Comparative safety and efficacy of PD-1/PD-L1 inhibitors in the first-line treatment for locally advanced or metastatic non-squamous non-small cell lung cancer: A systematic review and network meta-analysis. PROSPERO 2021 CRD42021275631 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021275631 Manting Wang, Liang Hengrui, Liang Wenhua, He Jianxing. Comparison of immune-related adverse events (irAEs) of combination of PD-(L)1 inhibitors and chemotherapy versus PD-(L)1 inhibitors for non-small cell lung cancer: a meta-analysis of randomised controlled trials. PROSPERO 2020 CRD42020139923 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020139923	

	Michela Febbraro, Arani Sathiyapalan, Rosalyn Juergens. Effects of anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) in the first-line treatment of metastatic ALK positive non-small cell lung cancer (NSCLC): A systematic review and meta-analysis. PROSPERO 2021 CRD42021247914 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021247914 Pengfei ZHAO, Hongchao ZHEN, Hong ZHAO, Lei ZHAO, Bangwei CAO. Efficacy and safety of adjuvant EGFR-TKIs for resected non-small cell lung cancer: A systematic review and meta-analysis based on randomized control trials. PROSPERO 2022 CRD42022309877 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022309877 Dongyu Li, Nan Sun, Jie He. Efficacy and safety of adjuvant therapy for epidermal growth factor receptor mutated, non-small cell lung cancer: systematic review and network meta-analysis.. PROSPERO 2022 CRD42022334185 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022334185 Chris Dickhoff, Idris Bahce, Suresh Senan, Ezgi Ulas. Efficacy and safety of neoadjuvant immune checkpoint inhibitors in operable non-small cell lung cancer: a systematic review. PROSPERO 2021 CRD42021235759 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021235759 Peng Xie, Xiaolin Li, Wenjie Tang, Jinming Yu, Xindong Sun, Xueqi Xie, Haiyan Zeng, Jie Liu, Yinjun Dong, Guanglei Zhao, Chungang Wang, Dongdong Du. EGFR inhibitors as adjuvant therapy for resected non-small cell lung cancer harboring EGFR mutations: a meta-analysis. PROSPERO 2018 CRD42018093144 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018093144 Boxue He, Qidong Cai, Pengfei Zhang. EGFR-TKIs as neoadjuvant therapy for non-small cell lung cancer: a meta-analysis. PROSPERO 2020 CRD42020197989 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020197989 Jun Dang, He Wang, Jun Chen, Tingting Liu, Guang Li. Neoadjuvant immunotherapy and neoadjuvant chemotherapy in resectable non-small cell lung cancer: A systematic review and hypothesis-generating meta-analysis. PROSPERO 2021 CRD42021278661 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021278661 Dong Chen, Jianfei Shen. Neoadjuvant treatments of EGFR-Mutated IIIa NSCLC： A meta-analysis. PROSPERO 2021 CRD42021221136 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021221136	

	Xiaohui Jia, Hong Xu. Safety and efficacy of neoadjuvant immune checkpoint inhibitors in resectable non-small cell lung cancer：a Meta analysis. PROSPERO 2020 CRD42020173557 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020173557 Xiaoshun Shi, Xiaoying Dong, Jianxue Zhai, Zhen Ni. The efficacy and safety of neoadjuvant EGFR-TKIs for patients with non-small cell lung cancer (NSCLC)：a meta analysis. PROSPERO 2020 CRD42020187031 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020187031	

PRIMARY STUDIES

Search for primary literature **Date searched: 08-22-22**		
MEDLINE		
#	**Search Statement**	**Results**
1	Carcinoma, Non-Small-Cell Lung/ or Lung Neoplasms/	250378
2	(lung cancer or lung neoplasm* or lung carcinoma* or nsclc or lung tumor* or lung tumour*).ti,ab,kw.	218639
3	(non small cell* or nonsmall cell*).ti,ab,kw.	82273
4	2 and 3	79798
5	1 or 4	270498
6	Neoadjuvant Therapy/ or Chemotherapy, Adjuvant/	63639
7	(neoadjuvant or adjuvant).ti,ab,kw.	189953
8	6 or 7	211194
9	Gefitinib/ or Afatinib/ or Nivolumab/ or Immune Checkpoint Inhibitors/ or Protein Kinase Inhibitors/	69196
10	(gefitinib or erolotinib or afatinib or osimertinib or atezolizumab or durvalumab or nivolumab or pembrolizumab or cemiplimab or EGFR tyrosine kinase inhibitors or anti-PD-1 or anti-PD-L1 or checkpoint inhibitor* or check-point inhibitor*).ti,ab,kw.	45217
11	9 or 10	98653
12	5 and 8 and 11	781
	limit 12 to English language	725
CINAHL		
#	**Search Statement**	**Results**
1	(MH "Carcinoma, Non-Small-Cell Lung") OR (MH "Lung Neoplasms")	49649
2	lung cancer or lung neoplasm* or lung carcinoma* or nsclc or lung tumor* or lung tumour*	68650
3	non small cell* or nonsmall cell*	26497
4	S2 and S3	25890
5	S1 or S4	55949
6	(MH "Neoadjuvant Therapy") OR (MH "Chemotherapy, Adjuvant")	17798
7	neoadjuvant or adjuvant	46413

8	S6 or S7	46413
9	(MH "Gefitinib") OR (MH "Afatinib") OR (MH "Nivolumab") OR (MH "Immune Checkpoint Inhibitors") OR (MH "Protein Kinase Inhibitors")	8518
10	gefitinib or erolotinib or afatinib or osimertinib or atezolizumab or durvalumab or nivolumab or pembrolizumab or cemiplimab or EGFR tyrosine kinase inhibitors or anti-PD-1 or anti-PD-L1 or checkpoint inhibitor* or check-point inhibitor*	14085
11	S9 or S10	19046
12	S5 and S8 and S11	265
13	limit S12 to English language	249

APPENDIX B: EXCLUDED PRIMARY STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type, 8=Outdated or ineligible systematic review (*not shown*), 9=Non-English language, 10=Unable to locate full text.

Citation	Exclude Reason
Pembrolizumab plus Chemotherapy Doubled Response Rate Over Chemotherapy Alone in NSCLC. *Personalized Medicine in Oncology.* 2016;5(9):384-384.	E1
Ahn HK, Choi YL, Han JH, et al. Epidermal growth factor receptor mutation and treatment outcome of mediastinoscopic N2 positive non-small cell lung cancer patients treated with neoadjuvant chemoradiotherapy followed by surgery. *Lung Cancer.* 2013;79(3):300-306.	E2
Andreano A, Bergamaschi W, Russo AG. Immune checkpoint inhibitors at any treatment line in advanced NSCLC: Real-world overall survival in a large Italian cohort. *Lung Cancer.* 2021;159:145-152.	E2
Anonymous. Atezolizumab Extends DFS after NSCLC Relapse. *Cancer Discovery.* 2021;11(11):OF3.	E7
Anonymous. Neoadjuvant ICI Response, Microbiome Probed in NSCLC. *Cancer Discovery.* 2021;11(5):OF1.	E10
Aokage K, Miyoshi T, Wakabayashi M, et al. Prognostic influence of epidermal growth factor receptor mutation and radiological ground glass appearance in patients with early-stage lung adenocarcinoma. *Lung Cancer.* 2021;160:8-16.	E2
Bai H, Wang Z, Chen K, et al. Influence of chemotherapy on EGFR mutation status among patients with non-small-cell lung cancer. *Journal of Clinical Oncology.* 2012;30(25):3077-3083.	E2
Bar J, Urban D, Redinsky I, et al. OA11.01 Neoadjuvant Pembrolizumab for Early Stage Non-Small Cell Lung Cancer. *Journal of Thoracic Oncology.* 2021;16(10):S865-S866.	E6
Beattie R, Furrer K, Dolan DP, et al. Two centres experience of lung cancer resection in patients with advanced non-small cell lung cancer upon treatment with immune checkpoint inhibitors: safety and clinical outcomes. *European Journal of Cardio-Thoracic Surgery.* 2021;60(6):1297-1305.	E6
Besse B, Adam J, Cozic N, et al. 1215O-SC Neoadjuvant atezolizumab (A) for resectable non-small cell lung cancer (NSCLC): Results from the phase II PRINCEPS trial. *Annals of Oncology.* 2020;31:S794-S795.	E6
Besse B, Mazieres J, Ribassin-Majed L, et al. Pazopanib or placebo in completely resected stage I NSCLC patients: results of the phase II IFCT-0703 trial. *Annals of Oncology.* 2017;28(5):1078-1083.	E2
Bott MJ, Yang SC, Park BJ, et al. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. *Journal of Thoracic & Cardiovascular Surgery.* 2019;158(1):269-276.	E6
Bryant AK, Sankar K, Strohbehn GW, et al. Prognostic and Predictive Role of PD-L1 Expression in Stage III Non-small Cell Lung Cancer Treated With Definitive Chemoradiation and Adjuvant Durvalumab. *International Journal of Radiation Oncology, Biology, Physics.* 2022;113(4):752-758.	E1

Citation	Exclude Reason
Bryant AK, Sankar K, Strohbehn GW, et al. Timing of Adjuvant Durvalumab Initiation Is Not Associated With Outcomes in Stage III Non-small Cell Lung Cancer. *International Journal of Radiation Oncology, Biology, Physics.* 2022;113(1):60-65.	E1
Bryant AK, Sankar K, Zhao L, et al. De-escalating adjuvant durvalumab treatment duration in stage III non-small cell lung cancer. *European Journal of Cancer.* 2022;171:55-63.	E1
Carbone D, Lee J, Kris M, et al. OA06. 06 Clinical/biomarker data for neoadjuvant atezolizumab in resectable stage IB-IIIB NSCLC: primary analysis in the LCMC3 study. *Journal of Thoracic Oncology.* 2021;16(3):S115-S116.	E6
Cascone T, William WN, Jr., Weissferdt A, et al. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial. *Nature Medicine.* 2021;27(3):504-514.	E2
Chaft JE, Hellmann MD, Velez MJ, Travis WD, Rusch VW. Initial Experience With Lung Cancer Resection After Treatment With T-Cell Checkpoint Inhibitors. *Annals of Thoracic Surgery.* 2017;104(3):e217-e218.	E6
Chang AY. The role of gefitinib in the management of Asian patients with non-small cell lung cancer. *Expert Opinion on Investigational Drugs.* 2008;17(3):401-411.	E2
Chen T, Ning J, Campisi A, et al. Neoadjuvant PD-1 Inhibitors and Chemotherapy for Locally Advanced NSCLC: A Retrospective Study. *Annals of Thoracic Surgery.* 2022;113(3):993-999.	E6
Chen Y, Yan B, Xu F, et al. Neoadjuvant chemoimmunotherapy in resectable stage IIIA/IIIB non-small cell lung cancer. *Transl Lung Cancer Res.* 2021;10(5):2193-2204.	E6
Chuang JC, Neal JW, Niu XM, Wakelee HA. Adjuvant therapy for EGFR mutant and ALK positive NSCLC: Current data and future prospects. *Lung Cancer.* 2015;90(1):1-7.	E7
Chung KP, Shih JY, Yu CJ. Favorable response to gefitinib treatment of lung adenocarcinoma with coexisting germline and somatic epidermal growth factor receptor mutations. *Journal of Clinical Oncology.* 2010;28(34):e701-703.	E6
Costa DB, Kobayashi S, Tenen DG, Huberman MS. Pooled analysis of the prospective trials of gefitinib monotherapy for EGFR-mutant non-small cell lung cancers. *Lung Cancer.* 2007;58(1):95-103.	E2
D'Angelo SP, Janjigian YY, Ahye N, et al. Distinct clinical course of EGFR-mutant resected lung cancers: results of testing of 1118 surgical specimens and effects of adjuvant gefitinib and erlotinib. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2012;7(12):1815-1822.	E6
Darrason M, Chatelain E, Ranchon F, Gervaise C, Duruisseaux M, Couraud S. Do systemic treatments delivered after Nivolumab result in better outcomes? A bicentric case-control study. *Respiratory Medical Research.* 2020;77:100-105.	E1
Dickhoff C, Senan S, Schneiders FL, et al. Ipilimumab plus nivolumab and chemoradiotherapy followed by surgery in patients with resectable and borderline resectable T3-4N0-1 non-small cell lung cancer: the INCREASE trial. *BMC Cancer.* 2020;20(1):764.	E7
Duan H, Wang T, Luo Z, et al. Neoadjuvant programmed cell death protein 1 inhibitors combined with chemotherapy in resectable non-small cell lung cancer:	E6

Citation	Exclude Reason
an open-label, multicenter, single-arm study. *Translational Lung Cancer Research.* 2021;10(2):1020-1028.	
Eichhorn F, Klotz LV, Kriegsmann M, et al. Neoadjuvant anti-programmed death-1 immunotherapy by pembrolizumab in resectable non-small cell lung cancer: First clinical experience. *Lung Cancer.* 2021;153:150-157.	E6
Eide IJZ, Nilssen Y, Lund-Iversen M, Brustugun OT. Factors affecting outcome in resected EGFR-mutated lung cancer. *Acta Oncologica.* 2022;61(6):749-756.	E2
El Husseini K, Piton N, De Marchi M, et al. Lung Cancer Surgery after Treatment with Anti-PD1/PD-L1 Immunotherapy for Non-Small-Cell Lung Cancer: A Case—Cohort Study. Cancers. 2021;13(19):4915.	E6
Faehling M, Witte H, Sebastian M, et al. Real-world multicentre analysis of neoadjuvant immunotherapy and chemotherapy in localized or oligometastatic non-small cell lung cancer (KOMPASSneoOP). *Therapeutic Advances in Medical Oncology.* 2022;14:17588359221085333.	E6
Feng Y, Sun W, Zhang J, et al. Neoadjuvant PD-1 inhibitor combines with chemotherapy versus neoadjuvant chemotherapy in resectable squamous cell carcinoma of the lung. Thoracic Cancer. 2022;13(3):442-452.	E6
Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. *New England Journal of Medicine.* 2018;378(21):1976-1986.	E6
Forde PM, Reiss KA, Zeidan AM, Brahmer JR. What lies within: novel strategies in immunotherapy for non-small cell lung cancer. *Oncologist.* 2013;18(11):1203-1213.	E7
Fuerst ML. Higher Doses of Second-Line Nivolumab Safe & Effective for Advanced NSCLC. *Oncology Times.* 2019;41(8):30-30.	E7
Gao S, Li N, Gao S, et al. Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer.* 2020;15(5):816-826.	E6
Ghisoni E, Wicky A, Bouchaab H, et al. Late-onset and long-lasting immune-related adverse events from immune checkpoint-inhibitors: An overlooked aspect in immunotherapy. *European Journal of Cancer.* 2021;149:153-164.	E1
Goodwin PM. Early Lung Cancer Responds to Neoadjuvant Nivolumab. *Oncology Times.* 2016;38(25):32-32.	E7
Gupta R, Zaid S, Sayed A, et al. Atezolizumab Induced Myocarditis on a Background of Cardiac Amyloidosis. *American Journal of Therapeutics.* 2019;26(6):e795-e797.	E6
Haratani K, Hayashi H, Chiba Y, et al. Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung Cancer. *JAMA Oncology.* 2018;4(3):374-378.	E1
He Q, Liu J, Cai X, et al. Comparison of first-generation EGFR-TKIs (gefitinib, erlotinib, and icotinib) as adjuvant therapy in resected NSCLC patients with sensitive EGFR mutations. Translational Lung Cancer Research. 2021;10(11):4120-4129.	E6
Hill A, Gong J, Wilczynski S, Mirza R, Erhunmwunsee L, Salgia R. Complete Pathologic Response When Adding Pembrolizumab to Neoadjuvant Chemotherapy in Stage IIIA Non-Small-Cell Lung Cancer. *Journal of oncology practice/American Society of Clinical Oncology.* 2018;14(9):569-571.	E6

Citation	Exclude Reason
Hong MH, Ahn B, Kim HR, et al. FP03.02 Interim Analysis of Neoadjuvant Chemoradiotherapy and Durvalumab for Potentially Resectable Stage III Non-Small Cell Lung Cancer (NSCLC). *Journal of Thoracic Oncology.* 2021;16(3):S194-S195.	E6
Hu Y, Ren S, Yang L, et al. Osimertinib as Neoadjuvant Therapy for Resectable Non-Small Cell Lung Cancer: A Case Series. Frontiers in Pharmacology. 2022;13:912153.	E6
Issa M, Tang J, Guo Y, et al. Risk factors and predictors of immune-related adverse events: implications for patients with non-small cell lung cancer. *Expert Review of Anticancer Therapy.* 2022;22(8):861-874.	E7
Janjigian YY, Park BJ, Zakowski MF, et al. Impact on disease-free survival of adjuvant erlotinib or gefitinib in patients with resected lung adenocarcinomas that harbor EGFR mutations. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2011;6(3):569-575.	E6
Joshi K, Muhith A, Obeid M, et al. Safety monitoring of two and four-weekly adjuvant durvalumab for patients with stage III NSCLC: implications for the COVID-19 pandemic and beyond. *Lung Cancer.* 2021;156:147-150.	E1
Kappers I, Klomp HM, Burgers JA, Van Zandwijk N, Haas RL, van Pel R. Neoadjuvant (induction) erlotinib response in stage IIIA non-small-cell lung cancer. *Journal of Clinical Oncology.* 2008;26(25):4205-4207.	E7
Kashiwabara K, Fujii S, Tsumura S, Sakamoto K, Semba H. Additional bevacizumab in EGFR-mutant lung adenocarcinoma patients who had oligo-progression after the failure of EGFR-TKI: A single-institute retrospective study. *Cancer Treatment And Research Communications.* 2020;22:100163.	E1
Kim Y, Saraf A, Iii DMM, et al. Quantitative Evaluation of Normal Lung Density Changes in Non-Small Cell Lung Cancer Patients Treated With Radiotherapy and PD-1 Immune Checkpoint Inhibitors. *International Journal of Radiation Oncology, Biology, Physics.* 2021;111(3):e131-e131.	E1
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APPENDIX C: QUALITY ASSESSMENT OF INCLUDED STUDIES

RANDOMIZED CONTROLLED TRIALS (ROB-2)

Trial Name or Author, Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (Low, Some Concerns, High)
IMpower010[45-47]	Low Patients were randomly assigned (1:1) by a permuted-block method with a block size of four to either the atezolizumab arm or best supportive care arm with an interactive voice-web response system. Randomisation was stratified by sex (female vs male), tumour histology (squamous vs non-squamous), extent of disease (stage IB vs stage II vs stage IIIA), and PD-L1 expression status. Baseline balance.	Low Used open-label (unblinded) design. Only patients without disease recurrence after CT were enrolled.	Some concerns (DFS); Low (OS) Substantial differential discontinuation due to adverse events. Similar proportions of patients received non-protocol treatment at recurrence.	Low Explicit criteria for censoring.	Some concerns (DFS); Low (OS) Investigators assessing outcomes were aware of treatment assignment. Subgroup analysis of PD-L1 > 1%.	Low Protocol available. No changes to primary endpoints reported.	Some concerns (DFS); Low (OS)
Feng 2015[48]	Some concerns Does not appear to use stratified randomization. Baseline balance.	Some concerns Blinding not described.	Some concerns Blinding not described. Limited deviations.	Low	Some concerns Investigators assessing outcomes may have been aware of treatment assignment.	Some concerns Protocol not registered until after enrollment began. Funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.	Some concerns
CheckMate 816[64]	Low Stratified randomization by gender at birth and disease stage. Baseline balance.	Low Used open-label (unblinded) design but probably limited deviations due to context.	Low Used open-label (unblinded) design but limited deviations. Most patients in both groups completed treatment, but	Low Explicit criteria for censoring.	Low Assessment of primary endpoint was blinded. Subgroup analysis by PD-L1 expression level.	Low Protocol-specified primary outcome (MPR) changed to secondary outcome due to health authority feedback. Rationale provided in	Low

Trial Name or Author, Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (Low, Some Concerns, High)
			subsequent treatments were more frequent in CT only group (not considered a risk of bias because progression event counted toward EFS then was subsequently censored).			supplement, and MPR reported in supplement.	
EVIDENCE[50]	Low Randomization stratified by EGFR mutation subtype, clinical stage, and resection method. Baseline balance.	Some concerns Used open-label (unblinded) design. Substantially greater number of pts. in control group did not receive assigned treatment.	Some concerns Used open-label (unblinded) design	Some concerns Substantially greater number of pts. in control group missing crucial assessments.	Some concerns Investigators assessing outcomes were aware of treatment assignment. DFS and OS curves exhibit nonproportionality.	Some concerns Protocol not available.	Some concerns
Huang 2021[65]	Some concerns Randomization method not described, and randomization does not appear to be stratified. Groups did not differ significantly in baseline characteristics but were substantially imbalanced in size.	Some concerns Blinding not described.	Some concerns Blinding not described. Deviations not permitted by design.	Low	High Outcomes were retrospectively collected, suggesting that patients with missingness were not included in the study; investigators assessing outcomes may have been aware of treatment assignment. Did not examine subgroups by PD-L1 expression.	Some concerns No protocol/registration available.	High
RADIANT[51,52]	Some concerns Baseline balance in main groups; in EGFRm+ subgroup more patients in the erlotinib arm having stage IB	Low	Some concerns (DFS); Low (OS) Many more patients discontinued treatment because of adverse events	Low	Some concerns Investigators assessing outcomes may have been aware of treatment assignment.	Low	Some concerns

Trial Name or Author, Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (Low, Some Concerns, High)
	and more patients in the placebo arm having stage IIIA disease. A smaller proportion of patients receiving erlotinib had lobectomies and received adjuvant chemotherapy. Randomization stratified according to stage, histology, previous adjuvant chemotherapy, smoking status, EGFR status, and country.		in treatment arm (not considered an eligible outcome event.)		Violation of proportional hazards for EGFRm+ subgroup.		
Li 2014[49]	Some concerns Randomization method not described. Randomization was stratified according to gender (male vs female) and smoking history (current or former vs never) only. Baseline balance.	Some concerns Used open-label (unblinded) design.	Some concerns Used open-label (unblinded) design.	Low	Some concerns Investigators assessing outcomes may have been aware of treatment assignment.	Some concerns No protocol/registration available.	Some concerns
PEARLS/ KEYNOTE-091[43,44]	Low Triple-blinded design. Randomization was stratified by disease stage (IB vs II vs IIIA), receipt of adjuvant chemotherapy (yes vs no), PD-L1 tumor proportion score (TPS; percentage of tumor cells with membranous PD-L1 staining; <1% vs 1–49% vs ≥50%), and geographical region (Asia vs eastern Europe vs western Europe vs the rest of the world). Baseline balance.	Low Triple-blinded design.	Some concerns Triple-blinded design. Median duration and number of treatments were similar in both groups. Substantial differential discontinuation due to adverse events. Unclear whether there was balance in nonprotocol treatment of recurrences.	Low	Low Subgroup analyses by EGFR mutation status and PD-L1 expression.	Some concerns. No changes to primary endpoints apparent. Reporting of subgroup analysis by prior adjuvant therapy at risk of confounding by disease stage.	Some concerns

Trial Name or Author, Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (Low, Some Concerns, High)
IMPACT[53]	Low Randomization stratified/balanced by institution, stage (II vs III), sex (male vs female), and age. Baseline balance.	Low.	Some concerns Used open-label (unblinded) design.	Some concerns	Low Assessment of primary endpoint was blinded.	Low	Some concerns
ADAURA[54,55,71,72]	Low Randomization was according to disease stage (IB, II, or IIIA), EGFR mutational status (Ex19del or L858R), and race (Asian or non-Asian). Baseline balance.	Low	Low Double-blinded.	Low	Low Some concerns for DFS curves for with adjuvant chemotherapy (all stages) and without CT (stage IIIA) due to nonproportionality.	Low	Low
EVAN[57,58]	Low Randomization was stratified by EGFR mutation type (exon 19 vs 21), histology, and smoking status (smoker vs non-smoker). Baseline balance.	Some concerns Used open-label (unblinded) design.	Some concerns Used open-label (unblinded) design.	Low	Some concerns Investigators assessing outcomes may have been aware of treatment assignment. OS curve exhibits nonproportionality.	Low	Some concerns
ADJUVANT[59-61]	Low Randomization stratified by lymph node status (N stage [N1 vs N2]) and EGFR mutation subtype (exon 19 deletion vs exon 21 Leu858Arg). Baseline balance.	Low Used open-label (unblinded) design but probably limited deviations due to context.	Some concerns Used open-label (unblinded) design. Substantially more control group participants did not receive treatment as allocated.	Low	Some concerns Individuals with a direct role in the conduct and analysis of the trial did not have access to the randomisation schedule and were masked to treatment assignment until the database was locked. DFS curve exhibits nonproportionality and converge at 48 months.	Low	Some concerns

Trial Name or Author, Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (Low, Some Concerns, High)
EMERGING-CTONG 1103[69]	Low Randomization was stratified according to lymph node status (single-station N2 vs multiple station N2), histology, smoking status (never vs former vs current), and sex (male vs female). Baseline balance.	Some concerns Used open-label (unblinded) design.	Some concerns Used open-label (unblinded) design.	Low	Some concerns Investigators assessing outcomes may have been aware of treatment assignment.	Low	Some concerns

Abbreviations. CT=chemotherapy; EGFR=epidermal growth factor receptor; EGFRm+=EGFR mutation positive; PDL=programmed cell death ligand; TKI=tyrosine kinase inhibitor.

NONRANDOMIZED COMPARISON STUDIES (ROBINS-I)

Author Year	Bias Due to confounding	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures from Intended Interventions	Bias Due to Measurement of Outcomes	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Bias (Low, Moderate, Serious, Critical, No Information)
Xiong 2020[66]	Moderate Study is unrandomized and provides unadjusted comparisons, but most relevant baseline characteristics appear to be balanced.	No information Unclear how patients were selected (by investigators, consecutively, *etc*).	Moderate Specific edibility criteria provided, but method for determining EGFRm status not described.	Moderate Appears that all patients completed neoadjuvant treatment as allocated. Groups differed in proportion receiving resection as planned. CT offered to both groups after surgery.	Moderate Assessors likely unblinded to group status.	Serious Survival reporting only for those receiving resection (12/15 in treatment, 8/16 in control).	Moderate No protocol available, but no indication of selective reporting.	Serious
Zhao 2021[67]	Serious Study is unrandomized and provides unadjusted comparisons between 2 groups of patients from different sources (a single group trial for tx group and a database for ctrl group). Groups significantly differ in CEA at baseline.	Serious Selection of patients from database is not described (*ie*, presumably more than 15 database pts met eligibility criteria, so how was the subset of 15 selected?).	Low Specific edibility criteria and method for determining EGFRm status described.	Low Appears that all patients completed neoadjuvant treatment as allocated. CT offered to both groups after surgery. All pts underwent resection.	Serious Assessors likely unblinded to group status. Unclear if outcome assessment differed for trial (tx) and database (ctrl) pts.	Low Appears that most or all data were available.	Moderate Protocol available only for tx group pts, but no indication of selective reporting.	Serious
Zhong 2015[68]	Moderate Study is unrandomized and provides unadjusted comparisons, but most relevant baseline characteristics appear to be balanced (with the exception of nonsignificant differences in smoking duration and daily cigarette consumption).	No information Unclear how patients were selected (by investigators, consecutively, *etc*).	Moderate Specific edibility criteria provided, but method for determining EGFRm status not described.	Moderate Appears that all patients completed neoadjuvant treatment as allocated. Groups differed in proportion receiving resection as planned.	Moderate Assessors likely unblinded to group status.	Low Appears that most or all data were available.	Low Protocol available and no indication of selective reporting.	Moderate

Abbreviations. CEA=carcinoembryonic antigen; CT=chemotherapy; ctrl=control; EGFRm=epidermal growth factor receptor mutation; tx=treatment.

APPENDIX D: PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	—
2	2	Yes	—
3	3	Yes	—
4	4	No - The authors should start with the relevant clinical questions and then develop the evidence. It reads like the process was inverted	It is unclear what it is meant by this feedback.
5	5	Yes	—
6	6	Yes	—
Is there any indication of bias in our synthesis of the evidence?			
7	1	No	—
8	2	No	—
9	3	No	—
10	4	No	—
11	5	Yes - Significant tendency to ascribe lack of evidence for adjuvant therapy but in same paragraph say confidently that administering therapy at relapse may be just as good as in adjuvant setting (without evidence to support this statement).	Thank you, we have addressed this comment as discussed in further detail below.
12	6	No	—
Are there any published or unpublished studies that we may have overlooked?			
13	1	No	—
14	2	No	—
15	3	No	—
16	4	No	—
17	5	Yes - Mentioned several in the attachment.	We added a discussion of NADIM II findings, however we did not formally include the trial in strength of evidence ratings because findings

Comment #	Reviewer #	Comment	Author Response
			have not yet been released in a peer-reviewed publication. We have added ALCHEMIST to the listing of underway studies.
18	6	Yes - ALCHEMIST (EGFR cohort closed to accrual, awaiting future analysis)	We have added ALCHEMIST to the listing of underway studies.
Additional suggestions or comments can be provided below.			
19	1	Excellent review.	—
20	2	This is a well-conducted, evidence synthesis and summary of results of clinical trials testing anti-PD1 immune checkpoint blockade, and EGFR tyrosine kinase inhibition, as peri-operative treatment for specific subgroups of patients with stage I-III non-small cell lung cancer treated with surgery. One of the goals of this evidence synthesis and data summary is to develop clinical policies for the VA system which are independent of F.D.A. drug labels. As such, the words/language used in the Key Findings of the executive summary, and elsewhere in the text of the document (especially Discussion and Conclusions), are important, and worth careful consideration so as to avoid inaccurate value assignments based on words/language. Just looking at the words used in the Executive Summary and Conclusions of the document, one could conclude that the magnitude of disease free survival benefit afforded by either immunotherapy, or anti-PD1 checkpoint blockade, is similar. This is not accurate. The magnitude of disease free survival benefit afforded by osimertinib is much higher than atezolizumab or pembrolizumab. The biggest judgment in the language summary (one with which I happen to agree) is to limit consideration of adjuvant anti-PD1 to patients with PDL1 >= 1% (which is a reasonable departure from the F.D.A. label for pembrolizumab). This deserves, perhaps, a sentence in the text of the document to summarize the justification for this departure. Just looking at the words of the Discussion, one could conclude that the benefit of neoadjuvant nivolumab (added to chemotherapy) is clearer than the benefit of adjuvant atezolizumab or pembrolizumab. This is not accurate. The magnitude of disease free survival benefit is similar with	Thank you, we have addressed these points throughout. With respect to diagnostic testing, based on the inconsistent nature of reporting and pre-specification of subgroup analyses by potential diagnostic criteria (as discussed by several other reviewers), as well as other methodological limitations we note, we felt we could not conclude that testing for the features you described is essential (though we agree that there is the strong suggestion of this). We have added some content on diagnostic implications in the discussion.

Comment #	Reviewer #	Comment	Author Response
		either approach. I agree that the availability of pathologic response for risk assessment is unique, and the shorter treatment duration may reduce cost which is worth mentioning, but those distinctions should not result in language that might suggest superior efficacy, or clearer evidentiary support. The main impact of the clinical studies considered in this review, in terms of patient care and management, is a fundamental change in diagnostic testing for early stage lung cancers. Based on ADAURA, it is now essential to test resected lung adenocarcinomas for EGFR exon 19 deletion and L858R to allow for consideration of adjuvant EGFR TKI. Based on CHECKMATE 816, it is now essential to test patients being considered for neoadjuvant chemotherapy plus nivolumab for activating/sensitizing EGFR mutations and ALK fusions. Based on the results of IMPOWER-010 and PEARLS it is now essential to test resected lung cancers being considered for adjuvant ICI to be tested for PDL1 expression by IHC (note different, but equally valid methods for measuring PDL1 in the 2 studies). These new diagnostic standards of care should be highlighted as Key Findings.	
21	2	Suggest adding language about new diagnostic (molecular pathology) standards as a Key Finding	See response to previous comment.
22	2	Suggest not using identical language to summarize/describe the disease free survival benefit of adjuvant ICPI vs EGFR TKI. Perhaps summarize a range of hazard ratios to reflect these, or drop the use of "likely" when describing the effect of EGFR TKIs to distinguish this difference in magnitude.	We have added information on magnitude where possible.
23	2	Add a sentence at the end of the ICI evidence brief summarizing why it is reasonable to limit consideration of adjuvant ICI to PDL1 >= 1%, which is a "rule out" determination of a PEARLS subgroup based on consideration of both IMPOWER-010 and PEARLS.	See response to first comment.
24	2	Page 5, Line 32: I disagree that lung cancers with EGFR activating/sensitizing mutation have a worse prognosis. In fact, they may be more likely to be found in stage IA tumors, and may have a better prognosis (D'Angelo, J Thorac Oncol. 2012 Dec;7(12):1815-1822; among others)	This language has been removed.
25	2	Page 37, Line 46: I disagree that there is clearer support for neoadjuivant therapy with ICIs. There are some clear advantages including lower cost, and availability of pathologic response for risk assessment, but adding risk	We have revised our conclusion with these points in mind.

Comment #	Reviewer #	Comment	Author Response
		prior to surgery (the neoadjuvant approach in general) is particularly risky because it may interfere with surgery. We need longer follow-up to demonstrate the clear advantage to this approach, which is theoretically due to generating a more powerful immune response with cancer antigens still present.	
26	2	Page 40, Line 30-35: I disagree with this statement, and you need to be careful with this sort of language. This statement reads as if the currently available evidence suggests the superiority of conventional adjuvant chemotherapy for most patients, and to not give ICI or EGFR TKI. This is not accurate, so the language must be chosen more carefully. As ICI and EGFR TKI are clearly additional therapies, i.e. given in addition to traditional chemotherapy, perhaps the best rhetorical approach is to state that the standard of care remains to offer conventional adjuvant chemotherapy to stage II-III patients. Then, additional therapy may be considered for selected patients. This, at least, allows the reader a better appreciation for these major advances, even though these advances have not yet demonstrated overall survival benefit	Thank you, this statement has been removed.
27	3	It is unclear to me why treatments that have been shown in trials to have a statistically significant probability of being true based on randomized phase III evidence is only designated as "likely" true. If you characterize the benefit in DFS from adjuvant osimertinib as merely "likely", with a hazard ratio for DFS of 0.20, it suggests a bias such as characterizing gravity or evolution as a mere theory. I would say that there is no reasonable question that adjuvant osimertinib dramatically improves DFS, even if it does not improve OS.	“Likely” corresponds to strength of evidence ratings, as described in the Methods section. However, we have added additional information about effect magnitude and refined the wording of conclusions so as not to minimize substantial disease-free survival benefit where it is apparent.
28	3	One way it seems that uncertainty is introduced is by including a great deal of discussion of older data with inferior agents and smaller trials. I would argue in favor of temporal discounting, so that the most recent data from larger trials are far more heavily weighted in conclusions than negative results with inferior agents. There is no question that gefitinib and erlotinib are inferior to osimertinib, so pooling a lot of older results with far more recent results just dilutes the more appropriate conclusions to draw from more recent work. At the very least, it should be well noted that more recent data with osimertinib are more definitive than older and more equivocal work with unquestionably inferior EGFR TKIs.	Thank you, we have more explicitly accounted for drug generation in our synthesis and conclusions.
29	3	At the bottom of page 1 (line 57), note is made comparing the toxicity of immunotherapy compared to adjuvant chemotherapy. In fact, this is a false dichotomy that presumes an "either/or" approach when a "both/and"	We have revised the introduction to avoid this suggestion.

Comment #	Reviewer #	Comment	Author Response
		strategy that incorporates both chemotherapy and immunotherapy is very likely the most appropriate. I don't think the question should be framed as if immunotherapy should be considered as a replacement of standard chemotherapy.	
30	3	The opening sentence of the conclusions on page 4 of the report suggests that reactive treatment initiated as needed at the time of relapse, may result in a survival benefit compared to adjuvant EGFR TKI use "for most patients". While it is possible that treatment only as needed at the time of relapse could produce comparable, statistically non-inferior results as adjuvant EGFR TKI therapy for all, the premise that treating patients only at relapse, with some relapsing with brain metastases and rapidly declining performance status, would be superior in overall survival to proactive adjuvant therapy is barely theoretically feasible, and no experienced clinician in the field considers it remotely plausible that reactive treatment will be superior. To me, this conveys either inappropriate judgment or bias against the data presented in the ADAURA trial.	We have removed statements that could be taken to imply that reactive treatment is superior, and refined conclusions in general.
31	3	The last sentence in the second paragraph of page 6, starting at line 25, states that lack of an OS benefit in a trial in which there has been extensive crossover "is a more conclusive indicator that the therapy is ineffective". That is an incorrect conclusion. Seeing an absence of improvement in OS when there has been crossover demonstrates that the TIMING of a treatment is not critical, but there can still be a remarkably effective therapy given early or late that leads to comparable survival in the face of crossover.	Thank you, this paragraph has been revised.
32	3	As I noted in point 2 above, the data collection portrayed in the flowchart on page 11 does not factor in the exceptionally high probability that research with newer agents could be different from research with older agents. In my mind, this is a fundamental question. Reviews of the newest iPhone don't include an extensive discussion of the features and challenges of iPhones from the earliest years. We are far more interested in the latest, best iteration, not the cumulative record that includes inferior ones, especially not having them weighed equally.	We have more explicitly accounted for drug generation in our synthesis and conclusions.
33	3	The opening paragraph of page 13 of the report appropriately characterizes the lack of certainty whether identified improvements in DFS with adjuvant ICIs will translate into improvements in OS. That said, many clinicians, and I would even say most, feel it is appropriate to give patients	See response to first comment.

Comment #	Reviewer #	Comment	Author Response
		"the benefit of the doubt" while we await this information, particularly when the surrogate endpoints point in a favorable direction.	
34	3	The same issue of wanting to give patients "the benefit of the doubt" applies to adjuvant TKI (specifically osimertinib) in EGFR mutation-positive resected NSCLC; the concluding sentence at the bottom of page 18 of the report is true, but it is a particularly uncharitable and strict way of viewing the state of the field today that is out of step with how nearly all thoracic oncologists view the prospect of benefit vs. risk of overtreatment vs. undertreatment based on the results of ADAURA as we know them today.	Thank you, we have refined this section along the same lines as discussion of DFS benefits for TKIs.
35	3	The sentence starting at line 13 of page 24 of the report notes how certain trials address the question of whether EGFR TKI therapy can/should replace chemotherapy in the adjuvant setting, most US-based thoracic oncologists feel that this is not the optimal question to be asking, because the benefits may well be additive.	We have refined this section with this feedback in mind.
36	4	In regard to adjuvant ICI there are 2 trials which led to the approval and clinical availability of atezolizumab and pembrolizuamb. The atezolizumab trial used a hierarchical design and the DFS benefit has been established for patients with stage II and III with a PD-L1 ≥1%, and for pembrolizumab the benefit was observed in stage IB-III, regardless of PD-L1 status. The results demonstrate benefit in different patient populations according to stage and PD-L1 expression. In the summary statement there is a general statement of DFS for PD-L1 ≥1% and stage II and III patients for ICI. In order, to clarify I think there needs to be separate statements about each agent	We have incorporated this feedback.
37	4	In the summary statement I recommend clarify the overall survival benefit observed to date rather than “may improve overall survival.” For instance, “data on overall survival with adjuvant ICI is immature at this time” This clarifies for a clinician	We have incorporated this feedback.
38	4	The cut-off of PD-L1 ≥ 1% for pre-operative chemotherapy and ICI is unclear since the ITT analysis included all patients. Only 43% of patients had PD-L1 <1% (n=145) which is inadequately powered for a definitive analysis	We have revised discussion of the role of PD-L1 status.
39	4	A common clinical question is adjuvant EGFR TKI or ICI for patients with an EGFR mutation and who are eligible for ICI. The data that are available are small subset analyses, but given the clinical question a brief paragraph discussing the issue may be valuable.	Thank you for this suggestion, we have added this information for IMpower010 (PEARLS does not

Comment #	Reviewer #	Comment	Author Response
			report this analysis within the PD-L1-positive sample).
40	4	A lot of subset and exploratory analyses are included in the document. Many times these are insufficiently powered and susceptible to an imbalance of prognostic factors. I realize these are included to be "comprehensive" but the results can be misleading. I would restrict the reporting to primary and secondary analyses, unless there is a well-defined clinical question (please see above).	We have pared down discussion of post hoc/exploratory subgroup analyses and/or added cautionary notes about their interpretation.
41	4	I do not see the value of discussing trials of adjuvant EGFR TKI's that were performed in unselected patients (e.g. BR.19, RADIANT) since the use is restricted to patients with a confirmed EGFR mutation. The EGFR mutation positive patient population is the relevant patient population for clinicians	We have reduced discussion of the 2 trials that were terminated early and that used unselected patients (BR19, Tsuboi 2005). As already noted in the Results section, our discussion of RADIANT focused on the EGFRm+ subsample.
42	4	The manuscript would benefit a narrower focus on the clinically relevant studies and their merits and weaknesses to assist the clinician. The most relevant studies for clinical care and health system decision making are: adjuvant osimertinib (Wu et al NEJM 2020), the IMpower010 (Felip et al Lancet 2021), PEARLS/Keynote-091 (O'brien et al Lancet Oncology 2022), Checkmate 0816 (Forde et al NEJM 2022)	We have pared down discussion of studies using older-generation EGFR-TKIs.
43	4	On page 5, the prognostic implications of EGFR mutant and EGFR wild-type NSCLC are debated, especially in the surgically resectable patient population. I recommend removing the statement "in NSCLC, mutations to the EGFR are associated with poor prognosis" The cited references do not address this issue.	This statement has been removed.
44	4	The underway studies sections are hard to cover since there are numerous studies which have different treatment plans, stages and maturity. These paragraphs are not helpful	Thank you for this feedback; however, we feel it is important to highlight when additional evidence may become available.
45	4	When discussing the adjuvant EGFR TKI's trials I would include the differences in design in that ADUARA was an active therapy vs placebo, and the other trials were an investigational therapy (EGFR TKI) vs a standard therapy (platinum-based doublet). This context is important for interpreting the HR	Thank you for this feedback; this information is already discussed in the initial paragraphs of the adjuvant EGFR-TKI section and reflected in the structure of the section.

Comment #	Reviewer #	Comment	Author Response
46	4	I would include a statement that the OS data is immature for the EGFR TKI trials in the table as a footnote	We have incorporated maturity into the tables.
47	4	In the interval between developing the evidence synthesis and currently the ADURA update has been published in JCO	Thank you for bringing this to our attention; we have updated references accordingly.
48	4	I would include the duration of EGFR TKI therapy in table 2 since this may influence the report of the DFS at specific time points	Thanks, however we feel there is already a great deal of information presented in these tables. And, while planned treatment duration did differ somewhat across trials, overall there was similarity.
49	4	On page 28, I do not understand the discussion about patients discontinuing the placebo at a higher rate than the active therapy for disease progression as a concern. Patients on the control arms are expected to come off study therapy at the time of disease progression and this would suggest the active arm has greater efficacy	We have clarified this section.
50	4	On page 30, when discussing the role of neoadjuvant chemotherapy an important detail is the rate patients in each arm went to surgical resection and the rate of R0 surgical resection in each arm. Please include this in the text	This information has been added.
51	4	On page 31, I am uncertain why the single arm trial nivolumab or chemotherapy is included. This trial does not investigate chemotherapy with immunotherapy which is the goal of this section. I also do not understand why other trials that have not been analyzed or completed accrual are included in this section.	The trial mentioned was not single arm, though we have substantially reduced discussion of the trials referenced.
52	4	On page 40, please include the comparison for the ALINA trial	This information has been added.
53	5	Would strongly suggest having lung cancer content experts as co-authors, there are many within the VA system. While the authors have done a good job collating the evidence there are clear deficiencies in the interpretation of the nuances of the data and statements made that no practicing oncologist would consider accurate. For example the arbitrary selection of PD-L1 1%+ disease for neoadjuvant or adjuvant therapy without a nuanced discussion of the study results is not good. The biggest debate in this area of oncology is whether adjuvant atezolizumab should be offered to just 50%+ or 1%+ per the label but this is not explored. Similarly the nuances of the PEARLS trial (unusual results	We have refined discussion of the role of PD-L1 status throughout the report, particularly in the discussion.

Comment #	Reviewer #	Comment	Author Response
		for the co-primary endpoint in PD-L1 50%+) are not discussed in any detail.	
54	5	Key findings – adjuvant therapy with ICIs: the comparison is not with "no additional chemotherapy". Additional chemotherapy is not a standard here, the comparison is best supportive care (impower010) or placebo (PEARLS trial). Not sure about the use of "likely" here, what does it mean? Two phase 3 trials have shown improved DFS.	"Likely" corresponds to strength of evidence ratings, as described in the Methods section. However, we have added additional information about effect magnitude and refined the wording of conclusions so as not to minimize substantial disease-free survival benefit where it is apparent.
55	5	Key findings – adjuvant therapy with TKIs: Again, likely is an unusual term, particularly when the HR for DFS is so strong in this setting. The comparison in Adaura was not adjuvant chemotherapy alone. Patients were not required to receive adjuvant chemo in either arm, Please review the study design again. Again, this is being stated in a very unusual way, I would just state the actual study design rather than selecting out study subgroups like this.	See previous response.
56	5	Key findings – adjuvant therapies with ICIs or EGFR-TKIs: This is uncertain, at least as uncertain as the previous statements. DFS is an accepted surrogate in the adjuvant setting for lung cancer by FDA and most regulatory authorities worldwide. At the very least adjuvant atezolizumab is very likely to result in an OS benefit for pts with PD-L1 50% or greater lung cancer, see the presentation from ESMO 2022.	We have refined this statement.
57	5	Key findings – neoadjuvant therapy with ICIs: Would add in parenthesis that patients with non squamous tumors should be tested for EGFR and ALK alterations prior to treatment as such patients were excluded from CheckMate 816. I would not suggest selecting out the PD-L1 positive group, CheckMate 816 was a small trial (358 pts compared to 2-3 times that many in the adjuvant trials) in the context of phase 3 randomized studies for early stage cancer and the subgroups are very underpowered. For comparison the DFS benefit HR from adjuvant chemotherapy vs. no adjuvant chemotherapy (Pignon et al, LACE meta analyses 2008) has essentially the same HR as the HR for chemo nivo vs. chemo alone in CheckMate 816. And you have a strong recommendation for adjuvant chemo, this seems contradictory. The recent NICE assessment and approval of neoadjuvant chemo-nivolumab in the UK showed cost effectiveness for all comers irrespective of PD-L1.	Thank you, we have refined this statement.

Comment #	Reviewer #	Comment	Author Response
58	5	Page 1, line 54: Reword sentence, the benefit of ICIs alone has not been shown in PD-L1 negative advanced lung cancer.	This sentence has been reworded.
59	5	Page 2, line 7: Pembro is only approved after adjuvant chemo.	This sentence has been corrected.
60	5	Page 2, line 19: This concern has been almost exclusively applied to TKIs not ICIs	This sentence has been reworded.
61	5	Page 2, line 52: Need to reword, this is a misconception, the comparator is not additional or no additional chemo as nobody would give more chemo here.	This sentence has been reworded.
62	5	Page 2, line 55: A more nuanced discussion would be helpful here. If you want to take a very pragmatic approach then just offering adjuvant atezolizumab to PD-L1 50%+ would not be unreasonable, that is the approach many health systems outside US are taking. But the way this is worded currently really does not make sense when you look at the two trials.	We have refined this section.
63	5	Page 3, line 11: As mentioned this is an unusual way to look at the data. The applicable study for a US population is Adaura, trials such as CTONG really are not applicable to a US population both in terms of demographics and also treatment approach which is non standard.	We have refined this section.
64	5	Page 3, line 32: As mentioned above would not use underpowered subgroup here, even if you do the DFS benefit is the same as adjuvant chemo	We have refined this section.
65	5	Page 4, line 5: No data to support this statement	This statement has been removed.
66	6	Stage definitions changed between design and reporting of most clinical studies (AJCC edition 7) and current practice (AJCC edition 8). In particular, tumors 3-4 cm and tumors 4-5 cm without node involvement moved from stage group IA to IB and IB to IIA, respectively. Thus, in the current staging system, no RTCs include stage I (i.e., IB) by AJCC edition 8. The language throughout the manuscript should include a designation of the staging system used to describe the study.	We have added staging information for trials, when available.
67	6	Page 29, paragraph starting on line 20. ALCHEMIST study of adjuvant erlotinib was partially accrued prior to being closed. When ADAURA led to FDA approval of osimertinib. The primary endpoint is overall survival. https://clinicaltrials.gov/ct2/show/NCT02194738 .	This information has been added.

Comment #	Reviewer #	Comment	Author Response
68	6	Page 19, paragraph starting on line 35-36. The radiographic imaging studies performed to determine the stage of patients is not consistent between clinical trials and standard clinical practice in the US. That variation affects the true stage of the study population. For example, if PET scans are not performed, then some patients who are thought to have stage I-III may actually have stage IV. The ADAURA study did not require imaging studies that met US standards: neither PET scan nor brain MRI with contrast were required. This is a significant limitation in understanding how to apply the results of ADAURA since some patients may have actually had stage IV disease and contributed to the improvement in observed DFS.	We have noted this point alongside concerns already raised about understaging.
69	6	PD-L1 subgroup analyses should be discussed as PD-L1-high (50%-100%), PD-L1-low (1%-49%) and PD-L1-zero (0%). Studies that combine results from 2 groups obscure the clinically meaningful impact of the PD-L1 result. This is most frequently done by combining PD-L1-high and PD-L1-low. The result is that the combined group may have a significant outcome but that significance is driven by the PD-L1-high group while the PD-L1-low group is not significant. Clinicians may then apply the results of the study to those with PD-L1 >= 1% rather than PD-L1 >= 50%. Studies that do not separately report these 3 PD-L1 groups are obscuring the results. An example is IMPower010 survival results, page 10, paragraph starting on line 3.	We have expanded our discussion of the role of PD-L1 status and result reporting throughout the report.
70	6	IMPower010 statistical plan is one of hierarchical design with OS being the 4th of 4 analyses. Because the 3rd analysis (PFS in stage IB-IIIA) is not statistically significant (and is unlikely to be significant in the future), OS cannot be formally assessed for survival. Thus, the results discussed on page 10 have not been formally tested and must be indicated as “hypothesis generating” and for “descriptive purposes only”.	This information has been added.
71	6	Page 18, paragraph starting on line 22 (Underway Studies) should include a description of the primary endpoint (and whether there is hierarchical design) and whether overall survival is any endpoint. That is, whether overall survival be formally analyzed.	This information has been added.
72	6	Page 21, paragraph starting on line 11-12. What was the overall rate of drug discontinuation for toxicity in the two arms? This is the most important comparison. What fraction of patients in the osimertinib arm did not complete 3 years of drug for reasons other than disease progression?	This comparison is included in the current text: At the late-2022 update, 13% of patients receiving osimertinib and 3% of placebo patients had

Comment #	Reviewer #	Comment	Author Response
			discontinued treatment because of an adverse event.
73	6	Page 21, line 25 and following paragraphs. Would describe only the EGFR-mutant subsample of RADIANT. Otherwise, the comparisons to ADAURA are meaningless. The main cohort is not relevant and including it makes it difficult to focus on the EGFR-mutant subsample. If it must be included, describe it separately from the EGFR-mutant subsample.	As currently written, the discussion of RADIANT focuses on the EGFRm+ subsample.
74	6	Page 22, paragraph beginning on line 41. BR21 and the Tsubi (reference 68) trial participants were not selected by EGFR mutation and analyses were not done or were no informative by EGFR status. Thus, this paragraph is not helpful and should be reduced to a sentence, a footnote, or removed entirely.	Discussion of these trials has been substantially reduced.