



Original Article

The updated network meta-analysis of the therapeutic efficacies of lung cancer: A systematic review and meta-analysis

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ABSTRACT

Objectives: Lung cancer is one of the most common malignancies worldwide. We aim to investigate the most effective treatments for advanced/nonadvanced stages of lung cancer patients. **Materials and Methods:** We searched electronic databases to investigate the treatment efficacies of lung cancer. The network meta-analysis was used to identify the top five most effective therapeutic strategies. A total of 157 studies were collected with a cumulative total of 164,678 participants. **Results:** The results showed that the best top five treatments: (1) for advanced lung cancer in response rate, were Chemo + Chemotherapy + Targeted Therapy, Cell therapy + Immunotherapy, Targeted Therapy + Radiotherapy, Chemoradiotherapy + Immunotherapy, and Chemotherapy + Chemoradiotherapy with cumulative probabilities 50.5, 49.6, 47.7, 46.0, and 45.6%; (2) for advanced lung cancer in progression-free survival (PFS) rate, were Targeted + Radiotherapy, Targeted + Others Therapy, Targeted + Targeted Therapy, Immu + Immu + Chemo Therapy, and Chemoradiotherapy with cumulative probabilities 99.5, 82.8, 44.9, 36.5, and 33.6%; (3) for nonadvanced lung cancer in response rate, were Chemoradiotherapy + Immu, Chemoradiotherapy + Targeted therapy, Chemoradiotherapy + Others, Chemotherapy + Surgery, and Radiotherapy + Others with cumulative probabilities 79.1, 74.9, 66.9, 60.4, and 54.2%; (4) for non-advanced lung cancer in PFS rate, were Chemo + Surgery, Chemoradiotherapy + Targeted, Surgery, Surgery + Radiotherapy, and Chemoradiotherapy + Others with cumulative probabilities 88.3, 86.1, 78.3, 73.1, and 50.8%. **Conclusion:** We present the latest and most effective therapeutic strategies for patients with advanced or nonadvanced stages of lung cancer.

KEYWORDS: Lung cancer, Network meta-analysis, Therapeutic efficacy

INTRODUCTION

Lung cancer is one of the most common malignancies worldwide and a leading cause of cancer-related death. Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer-related deaths worldwide; there were an estimated 2.2 million new cases and 1.8 million deaths due to lung cancer [1]. Approximately 80%–85% of all lung cancer cases are classified as nonsmall-cell lung cancer (NSCLC) [2], and around 30% of patients receive a diagnosis of locally advanced NSCLC [3]. The previous report shows that the survival rate for patients diagnosed with lung cancer is low in most countries, with only 10%–20% of patients surviving at the 5-year mark after diagnosis [4]. This highlights the urgent need for effective prevention and treatment strategies to combat this deadly disease. Our previous study reported the top three best treatments for

patients with advanced (stage IIIB, IV) or nonadvanced lung cancer [5]. However, new and effective therapeutic strategies for lung cancer, such as cell therapy and new radiotherapy/target therapy, have been developed since then. Therefore, this updated study analyzes these new therapeutic strategies and identifies the top five best treatments for both advanced and nonadvanced lung cancer patients.

Recently, several new therapeutic strategies have emerged. Among those analyzed in this study are radiotherapy, including stereotactic body radiation therapy (SBRT) derived from intracranial stereotactic radiosurgery established in the early 2000s, which has shown efficacy as upfront

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treatment for lung cancer [6,7]; target therapies, such as third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) developed for advanced EGFR mutation-positive NSCLC [8,9] or multi-targeted TKIs approved as a therapy for NSCLC [10] as well as small-cell lung cancer (SCLC) [11] with positive outcomes [12], or HER3 targeted therapy, which is implicated in resistance to chemo-or targeted therapy [13]; and cell therapy, such as SNK01, autologous *ex-vivo* expanded NK cell treatment, combined with immunotherapy, which has significantly improved outcomes for NSCLC patients [14,15].

We have incorporated the latest information on therapeutic strategies for lung cancer and combined it with our previous findings. By using network meta-analysis, we identified the updated top five most effective treatment strategies (in terms of response rate/progression-free survival [PFS] rate) for patients with advanced and nonadvanced lung cancer, respectively.

MATERIALS AND METHODS

This study was conducted in this systematic review following the PRISMA-2020 guidelines and the PRISMA extension statement for network meta-analysis (PRISMA-NMA) [16,17]. The systematic review was not registered on PROSPERO; as it was an extension of the Ministry of Science and Technology of Taiwan project (grant number MOST 107-2118-M-032-004). And, a part of the data was published in our previous published paper: "Comparing the Therapeutic Efficacies of Lung Cancer: Network Meta-analysis Approaches" [5].

Literature search strategy

The literature search was performed for the related research articles from the following electronic databases: PubMed, Cochrane Library, Google Scholar, and Airiti Library. The updated search keywords we used were: ("Lung cancer" OR "Small cell lung cancer" OR "SCLC" OR "Non-small cell lung cancer" OR "Non-small-cell lung cancer" OR "NSCLC") AND (Chemotherapy OR Radiotherapy OR EGFR* OR

EGFR-TKI OR "Tyrosine Kinase Inhibitor" OR Surgery OR Platinum* OR "anaplastic lymphoma kinase" OR "ALK inhibitor" OR Crizotinib OR Ceritinib OR Carboplatin OR Erlotinib OR Gemcitabine OR Pemetrexed OR Bevacizumab OR Nivolumab OR Docetaxel OR Atezolizumab OR Gemcitabine OR Paclitaxel OR Thermotherapy OR "Shenqi Fuzheng Injection" OR "stereotactic body radiotherapy" OR "SBRT" OR "third-generation EGFR-TKI" OR "Befotertinib" OR "D-0316" OR "multi-targeted TKI" OR "Entrectinib" OR "crizotinib" OR "HER3" OR "targeted therapy" OR "patritumab deruxtecan" OR "cell therapy" OR "SNK01") AND ("Quality of Life" OR QOL OR "Functional Assessment of Cancer Therapy-Lung" OR "FACT-L" OR "Lung Cancer Symptom Scale" OR "Progression-free Survival" OR PFS OR "Overall Survival" OR "Tumor Response" OR "Performance status" OR WBC OR Platelet OR PLT OR Hemoglobin OR HB OR Nausea OR Vomiting) AND ("Clinical Trial" OR "Clinical Study"). In addition, we also first searched for those meta-analyses or systematic review articles with the theme of lung cancer efficacy, and then, found all the articles used in these articles. The final papers we included in this study satisfied the following inclusion and exclusion criteria. We included the remaining 157 articles to evaluate the reporting standard guidelines of network meta-analysis for evaluating the efficacies of the therapeutic strategies, the search flow chart presented in Figure 1.

Inclusion and exclusion criteria

Studies were included if they met the following inclusion criteria: (1) the participants have been diagnosed as lung cancer; (2) the study provided at least one efficacy indicator (e.g., tumor response, PFS rate); (3) the study provided sufficient information to evaluate the (Hedges' g) effect size [18], or the authors responded to our mail and willing to provide additional information; and (4) clinical trials that compare the treatment efficacies of two or more effective treatment strategies.

Studies met the following criteria were excluded: (1) the study did not provide sufficient information to evaluate the

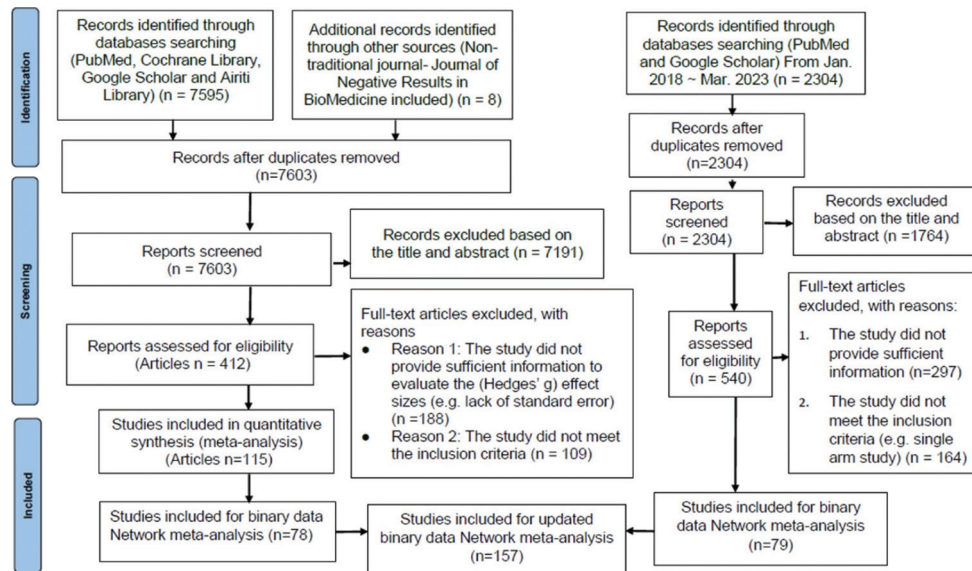


Figure 1: The PRISMA-NMA checklist diagram

response/PFS rate, or the authors did not respond to our mail or were not willing to provide additional information; (2) the study was case reports or cross-sectional study; (3) single arm or two arms with placebo control study; and (4) the study did not meet the above inclusion criteria.

Data extraction

The relevant information about the efficacy and its possible influencing factors we extracted from the collected articles were as follows: pretreated (yes vs. no), the severity of the disease (advanced vs. nonadvanced stage), and the treatment strategies. For binary category variables, such as tumor response (OS, PFS, and distance control survival), we extracted the number of events and nonevents for each indicator in each group. If there were missing data caused by unrepresented in the collected articles, we contacted the authors to inquire about relevant information. If the authors did not respond to our mail or were not willing to provide additional information, the article will be excluded for further data analysis.

The analysis procedure of the statistical software, named STATA, is related to the names of treatments' alphabetical order. Accordingly, it is necessary to recode the names of the treatments before doing the network meta-analysis. We recorded the treatment strategies as following: (1) A_Surgery; (2) A1_Surgery + Radio (Surgery + Radiotherapy); (3) B_Radio (Radiotherapy); (4) C_Chem (Chemo + Chemotherapy); (5) C1_Chem+Surg; (6) C2_ChemRadio (Chemoradiotherapy); (7) C3_C_ChemRadio; (8) Chemo (Chemotherapy); (9) D_Target (Targeted Therapy); (10) D2_Target + Radio; (11) D3_Chem + Target; (12) D4_Target + Target; (13) DC1_C_Chem + Target; (14) DC2_ChemRadio + Target; (15) DC3_Chem + Target + Target; (16) E_ImmuT (Immunotherapy); (17) E3_Chem + Immu; (18) E4_C_Chem + Immu; (19) EC2_ChemRadio + Immu; (20) EC3_ChemRadio + Immu + Immu; (21) F2_Radio + Others (Radio + Others Therapy); (22) F3_Chem + Others; (23) F4_Target + Others; (24) FC2_ChemRadio + Others; (25) FI_Immu + Immu; (26) F5_Immu + Chemo + Target; (27) F6_Immu + Immu + Chemo; (28) G1_Cell + Chemo (Cell therapy + Chemotherapy); (29) G2_Cell + Chemo + Cytokine; (30) G3_Cell + Immu. Here, the other therapies, such as Shenqi Fuzheng Injection, Recombinant human endostatin (rh-endostatin, Endostar (YH-16)), Apatinib (antiangiogenic therapy), anlotinib (AL3818, Anlotinib Hydrochloride), are those drugs that could not be clearly classified even after consulting with oncology doctors.

Outcomes

The primary outcomes of this study were the treatment-related response rate and the PFS rate. Accordingly, the principal summary measure we used is the log odds ratio.

Geometry of the network

The spectrum of comparisons among different treatment strategies for lung cancer patients was examined in terms of response rate and PFS rate within the network of published studies. The geometry of the networks for each outcome was appraised separately, and network graphs were provided.

The connection between treatment strategies was assessed, specifically focusing on direct comparisons made in the selected studies as well as indirect connections through other common comparators. The amount of evidence informing each comparison was also considered.

Quality assessment

The risk of bias and quality of the included studies were individually assessed by both authors. For nonrandomized studies, the Newcastle–Ottawa scale was used on a scale of 0–9 [19], where scores from 0 to 4 indicated poor quality and scores from 5 to 9 indicated high quality. For randomized controlled trials (RCTs), the Jadad scale was used [20]. It is a three-point questionnaire with a scale of 0–5, comprising 2 points for “Randomization,” 2 points for “Blinding/Masking,” and 1 point for “Withdrawals.” Disagreements regarding study quality were resolved through discussion.

Statistical analysis

STATA/SE version V14.0 for Windows (Stata Corporation, College Station, TX, USA) was used for all statistical analyses. The primary outcomes in this updated analysis were binary outcomes, specifically the response rate and the PFS rate. In the STATA system, the network suite uses three data formats, named augmented, standard, and pairs formats. To handle multi-arm studies, for simplicity and consistency, the data format we used is the standard format. The “network meta consistency” was used to assess the between studies' consistency and estimate the variance–covariance matrix. We also used “network sidesplit all” to assess the agreement of direct and indirect evidence in the treatment network (s) studied (a $P < 0.05$ means inconsistent). The network meta-analyses can be used to address the following question: “Ignoring the effects of other possible influencing factors, what are the top five most effective treatment strategies for response rate and PFS rate, respectively?”. Therefore, we utilized network meta-analyses to address the primary study purpose that raises concerns for both oncology doctors and lung cancer patients: identifying the top five most effective treatments after confirming the severity of lung cancer.

RESULTS

This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

Advanced stage

There were 23 out of 30 treatment strategies involved in the comparisons of the treatment efficacies in terms of response/PFS rate of advantaged-stage lung cancer. More specifically, they were C2_ChemRadio, C3_C_ChemRadio, C_Chem, Chemo, D2_Target + Radio, D3_Chem + Target, D4_Target + Target, DC1_C_Chem + Target, DC3_Chem + Target + Target, D_Target, E3_Chem + Immu, E4_C_Chem + Immu, EC2_ChemRadio + Immu, EC3_ChemRadio + Immu + Immu, E_ImmuT, F3_Chem + Others, F4_Target + Others, F5_Immu + Chemo + Target, F6_Immu + Immu + Chemo, FI_Immu + Immu, G1_Cell + Chemo, G2_Cell + Chemo + Cytokine, and G3_Cell + Immu. The network

meta-analysis was used to directly compare the 23 treatment types. The results of the network map are shown in Figure 2. The output shows that much of the data compares among treatments Chemo, E_ImmuT, D_Target, D4_Target + Target, D3_Chem + Target, C_Chemo, and F3_Chem + Others.

The results of response rate

We utilized “network rank max” to determine the top five most effective treatments among these 23 treatment strategies while ignoring the effects of other potential influencing factors. The results of the estimated probabilities (in percentage, %) of each treatment being the best (and other ranks) in response rate (Advanced stage) are shown in Supplementary Table 1. Accordingly, the estimated cumulative probabilities (in percentage, %) of the top five most effective treatment strategies in response rate (Advanced stage) are shown in Table 1. More specifically, the top five best treatments for advanced lung cancer in response rate were as follows: (1) the chances of being the best treatment in the response rate of advanced lung cancer for Cell therapy + Immunotherapy (G3_Cell + Immu), Targeted Therapy + Radiotherapy (D2_Target + Radio), Chemo + Chemotherapy + Targeted Therapy (DC1_C_Chemo+Target), Chemo+chemoradiotherapy(C3_C_ChemoRadio), and Targeted Therapy + Others (F4_Target + Others) were, respectively, 28.1, 20.3, 14.2, 12.5, and 9.5; (2) the chances of being one of the best two treatments in the response rate of advanced lung cancer for G3_Cell + Immu,

DC1_C_Chemo + Target, D2_Target + Radio, EC2_ChemoRadio + Immu, and C3_C_ChemoRadio were 38.3, 31.1, 28.8, 22.9, and 22.8, respectively; (3) the chances of being one of the best three treatments in the response rate of advanced lung cancer for G3_Cell + Immu, DC1_C_Chemo + Target, D2_Target + Radio, EC2_ChemoRadio + Immu, and F4_Target + Others were 43.5, 39.6, 35.1, 33.6, and 29.9, respectively; (4) the chances of being one of the best four treatments in the response rate of advanced lung cancer for G3_Cell + Immu, DC1_C_Chemo + Target, EC2_ChemoRadio + Immu, D2_Target + Radio, and C2_ChemoRadio were 46.9, 44.9, 41.5, 40.9, and 39.6, respectively; (5) the chances of being one of the top five treatments in the response rate of advanced lung cancer for DC1_C_Chemo + Target, G3_Cell + Immu, D2_Target + Radio, EC2_ChemoRadio + Immu, and C3_C_ChemoRadio were 50.5, 49.6, 47.7, 46.0, and 45.6, respectively [Table 2]. The corresponding Rankogram (Cumulative Probability Curve) for the advanced lung cancer in response rate is shown in Figure 3a.

The results of progression-free survival rate

The results of the network map were identical to those of the response rate [Figure 2]. The “network rank max” command in STATA was used to determine the top five most effective treatments, in terms of PFS rate, among these 23 treatment strategies. The estimated probabilities and

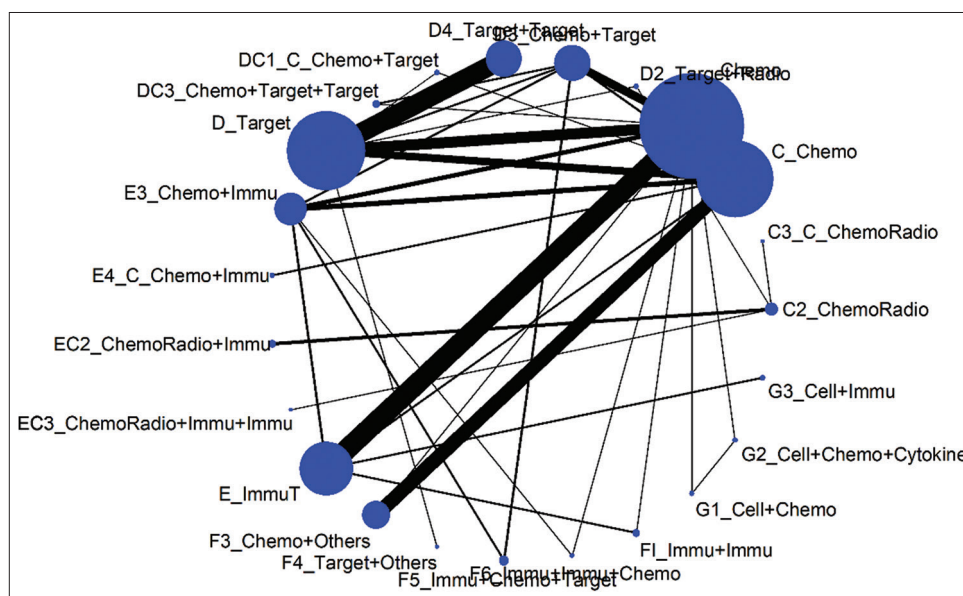


Figure 2: Network map of response/progression-free survival rate (advanced stage)

Table 1: Estimated cumulative probabilities (%) of the top 5 most effective treatment strategies in response rate (advanced stage)

Rank	1	2	3	4	5
Best	G3_Cell+Immu_28.1	D2_Target+Radio_20.3	DC1_C_Chemo+Target_14.2	C3_C_ChemoRadio_12.5	F4_Target+Others_9.5
2 nd	G3_Cell+Immu_38.3	DC1_C_Chemo+Target_31.1	D2_Target+Radio_28.8	C3_C_ChemoRadio_22.9	EC2_ChemoRadio+Immu_22.8
3 rd	G3_Cell+Immu_43.5	DC1_C_Chemo+Target_39.6	D2_Target+Radio_35.1	EC2_ChemoRadio+Immu_33.6	F4_Target+Others_29.9
4 th	G3_Cell+Immu_46.9	DC1_C_Chemo+Target_44.9	EC2_ChemoRadio+Immu_41.5	D2_Target+Radio_40.9	C2_ChemoRadio_39.6
5 th	DC1_C_Chemo+Target_50.5	G3_Cell+Immu_49.6	D2_Target+Radio_47.7	EC2_ChemoRadio+Immu_46.0	C3_C_ChemoRadio_45.6

Table 2: Estimated cumulative probabilities (%) of the top 5 most effective treatment strategies in progression-free survival rate (advanced stage)

Rank	1	2	3	4	5
Best	D2_Target+Radio_67.3	F4_Target+Others_24.9	C3_C_ChemoRadio_2.5		
2 nd	D2_Target+Radio_92.3	F4_Target+Others_60.9	C3_C_ChemoRadio_10.0	EC3_ChemoRadio+Immu+Immu_7.7	F6_Immu+Immu+Chemo_7.0
3 rd	D2_Target+Radio_97.6	F4_Target+Others_72.1	C3_C_ChemoRadio_20.5	F6_Immu+Immu+Chemo_18.3	G3_Cell+Immu_14.8
4 th	D2_Target+Radio_99.1	F4_Target+Others_78.3	D4_Target+Target_31.5	F6_Immu+Immu+Chemo_28.2	C3_C_ChemoRadio_25.0
5 th	D2_Target+Radio_99.5	F4_Target+Others_82.8	D4_Target+Target_44.9	F6_Immu+Immu+Chemo_36.5	C2_ChemoRadio_33.6

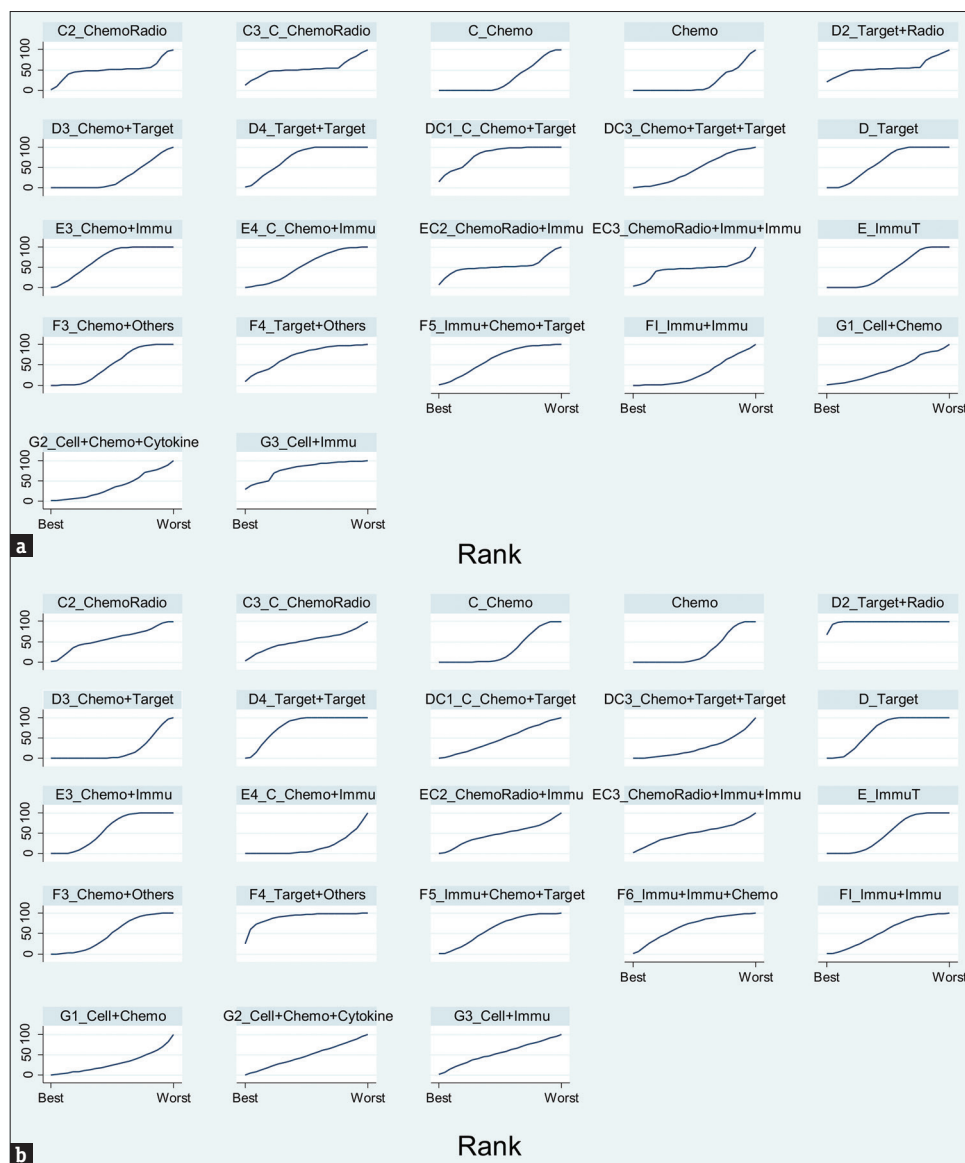


Figure 3: Rankogram for the advanced lung cancer in response rate (a) and Rankogram for the advanced lung cancer in progression-free survival rate (b)

cumulative probabilities of each treatment being the best (and other ranks) in PFS rate (Advanced stage) are shown in Supplementary Table 2 and Table 2, respectively. As shown in Table 2, the top five best treatments for advanced lung cancer in PFS rates were as follows: (1) the chances of being the best treatment in the PFS rate of advanced lung cancer for D2_Target + Radio, F4_Target + Others, and C3_C_ChemoRadio were 67.3, 24.9, and 2.5, respectively; (2) the chances of being one of the best two treatments in the PFS rate of advanced

lung cancer for D2_Target + Radio, F4_Target + Others, C3_C_ChemoRadio, EC3_ChemoRadio + Immu + Immu, and F6_Immu + Immu + Chemo were 92.3, 60.9, 10.0, 7.7, and 7.0, respectively; (3) the chances of being one of the best three treatments in the PFS rate of advanced lung cancer for D2_Target + Radio, F4_Target + Others, C3_C_ChemoRadio, F6_Immu + Immu + Chemo, and G3_Cell + Immu were 97.6, 72.1, 20.5, 18.3, and 14.8, respectively; (4) the chances of being one of the best four treatments in the PFS rate of advanced

lung cancer for D2_Target + Radio, F4_Target + Others, D4_Target + Target, F6_Immu + Immu + Chemo, and C3_C_ChemoRadio were 99.1, 78.3, 31.5, 28.2, and 25.0, respectively; (5) the chances of being one of the best five treatments in the PFS rate of advanced lung cancer for D2_Target + Radio, F4_Target + Others, D4_Target + Target, F6_Immu + Immu + Chemo, and C2_ChemoRadio were 99.5, 82.8, 44.9, 36.5, and 33.6, respectively. The corresponding Rankogram (Cumulative Probability Curve) for the advanced lung cancer in PFS rate is shown in Figure 3b.

Nonadvanced stage

There were 15 out of 30 treatment types involved in the comparisons of the treatment efficacies for nonadvanced stage lung cancer patients in response/PFS rate. More specifically, they were A1_Surgery + Radio, A_Surgery, B_Radio, C1_Chemo + Surg, C2_ChemoRadio, C_Chemo, Chemo, D3_Chemo + Target, DC2_ChemoRadio + Target, D_Target, E3_Chemo + Immu, EC2_ChemoRadio + Immu, E_ImmuT, F2_Radio + Others, and FC2_ChemoRadio + Others. The network meta-analysis was used to directly compare the 15 treatment types. The results of the network map are shown in Figure S1.

The results of progression-free survival rate

We used the “network rank max” command in STATA to determine the top five most effective treatments in response rate for these 15 treatment strategies, without taking into account the effects of other potential influencing factors. The results of the estimated probabilities (%) of each treatment being the best (and other ranks) in response rate of nonadvanced stage lung cancer patients are shown in Supplementary Table 3. The corresponding estimated cumulative probabilities (%) of the top five most effective treatment strategies for nonadvanced stage lung cancer patients in response rate are shown in Supplementary Table 4, as indicated. More specifically, as shown in Supplementary Table 4, the top five best treatments for nonadvanced stage lung cancer in response rate were as follows: (1) the chances of being the best treatment in the response rate of non-advanced lung cancer for A1_Surgery + Radio, DC2_ChemoRadio + Targe, FC2_ChemoRadio + Other, F2_Radio + Others, and E3_Chemo + Immu were 39.8, 16.1, 13.8, 10.5, and 7.6, respectively; (2) the chances of being one of the best two treatments in the response rate of non-advanced lung cancer for A1_Surgery + Radio, DC2_ChemoRadio + Targe, FC2_ChemoRadio + Other, F2_Radio + Others, and EC2_ChemoRadio + Immu were 41.7, 38.3, 32.8, 23.6, and 22.2, respectively; (3) the chances of being one of the best three treatments in the response rate of nonadvanced lung cancer for DC2_ChemoRadio + Targe, FC2_ChemoRadio + Other, EC2_ChemoRadio + Immu, A1_Surgery + Radio, and F2_Radio + Others were 53.5, 46.6, 43.4, 43.2 and 35.4, respectively; (4) the chances of being one of the best four treatments in the response rate of nonadvanced lung cancer for DC2_ChemoRadio + Targe, FC2_ChemoRadio + Other, EC2_ChemoRadio + Immu, F2_Radio + Others, and A1_Surgery + Radio were 65.4, 63.0, 57.7, 46.1, and 44.1, respectively; (5) the chances of being one of the best five treatments in the response rate of nonadvanced lung cancer for EC2_ChemoRadio + Immu,

DC2_ChemoRadio + Targe, FC2_ChemoRadio + Other, C1_Chemo + Surg, and F2_Radio + Others were 79.1, 74.9, 66.9, 60.4, and 54.2, respectively. The corresponding Rankogram (Cumulative Probability Curve) for the nonadvanced lung cancer in response rate is shown in Figure S2.

The results of progression-free survival rate

We used the “network rank max” command in STATA to determine the top five most effective treatments, in terms of PFS rate, among these 15 treatment strategies. The estimated probabilities and cumulative probabilities of each treatment being the best (and other ranks) in PFS rate are shown in Supplementary Tables 5 and 6, respectively. As shown in Supplementary Table 6, the top five best treatments for nonadvanced lung cancer in PFS rates were as follows: (1) the chances of being the best treatment in the PFS rate of nonadvanced lung cancer for DC2_ChemoRadio + Targe, F2_Radio + Others, C1_Chemo + Surg, A1_Surgery + Radio, and FC2_ChemoRadio + Other were 32.3, 19.0, 14.9, 14.6, and 13.8, respectively; (2) the chances of being one of the best two treatments in the PFS rate of nonadvanced lung cancer for DC2_ChemoRadio + Targe, C1_Chemo + Surg, A1_Surgery + Radio, F2_Radio + Others, and FC2_ChemoRadio + Other were 52.2, 40.9, 31.0, 28.5, and 26.5, respectively; (3) the chances of being one of the best three treatments in the PFS rate of nonadvanced lung cancer for DC2_ChemoRadio + Targe, C1_Chemo + Surg, A1_Surgery + Radio, F2_Radio + Others, and FC2_ChemoRadio + Other were 66.7, 62.8, 45.1, 35.3, and 34.6, respectively; (4) the chances of being one of the best four treatments in the PFS rate of nonadvanced lung cancer for C1_Chemo + Surg, DC2_ChemoRadio + Targe, A1_Surgery + Radio, A_Surgery, and F2_Radio + Others were 80.1, 76.9, 59.8, 57.4, and 42.5, respectively; (5) the chances of being one of the best five treatments in the PFS rate of nonadvanced lung cancer for C1_Chemo + Surg, DC2_ChemoRadio + Targe, A_Surgery, A1_Surgery + Radio, and FC2_ChemoRadio + Other were 88.3, 86.1, 78.3, 73.1, and 50.8, respectively. The corresponding Rankogram (Cumulative Probability Curve) for the nonadvanced lung cancer in PFS rate is shown in Figure S3.

In summary, the top five treatments: (1) for advanced lung cancer in response rate, were Chemo + Chemotherapy + Targeted Therapy (DC1_C_Chemo + Target), Cell therapy + Immunotherapy (G3_Cell + Immu), Targeted Therapy + Radiotherapy (D2_Target + Radio), Chemoradiotherapy + Immunotherapy (EC2_ChemoRadio + Immu), and Chemotherapy + Chemoradiotherapy (C3_C_ChemoRadio) with cumulative probabilities 50.5, 49.6, 47.7, 46.0, and 45.6%, respectively; (2) for advanced lung cancer in PFS rate, were D2_Target + Radio, Targeted Therapy + Others Therapy (F4_Target + Others), D4_Target + Target, F6_Immu + Immu + Chemo, and C2_ChemoRadio with cumulative probabilities 99.5, 82.8, 44.9, 36.5, and 33.6%, respectively; (3) for nonadvanced lung cancer in response rate, were EC2_ChemoRadio + Immu, DC2_ChemoRadio + Targe, FC2_ChemoRadio + Other, Chemotherapy + Surgery (C1_Chemo + Surg), and F2_Radio + Others with cumulative

probabilities 79.1, 74.9, 66.9, 60.4, and 54.2%, respectively; (4) for nonadvanced lung cancer in PFS rate, were C1_Chemo + Surg, DC2_ChemoRadio + Targe, A_Surgery, A1_Surgery + Radio, and FC2_ChemoRadio + Other with cumulative probabilities 88.3, 86.1, 78.3, 73.1, and 50.8%, respectively.

In Tables 1, 2 and Supplementary Tables 4, 6, we used text-shadow to highlight the treatment strategies that appeared in our previous study as the top three best treatments. For non-advanced stages in response and/or PFS rates [Supplementary Tables 4 and 6], these top three treatments were included among the top five best treatments. However, in Table 2, only one treatment named “F4_Target + Others” appeared in the fifth positions of the best and third rank. Furthermore, the probability of being one of the best three treatments in the response rate of advanced lung cancer was 29.9%. That is, there were four other treatment strategies with higher probabilities of being one of the best three treatments in the response rate of advanced lung cancer than “F4_Target + Others.” These strategies were labeled “G3_Cell + Immu” (43.5%), “DC1_C_Chemo + Target” (39.6%), “D2_Target + Radio” (35.1%), and “EC2_ChemoRadio + Immu” (33.6%) in the 3rd row of Table 1.

Furthermore, as shown in the Supplementary Table 7, 131 out of 157 studies were RCT (Randomized Control Trial). That is, more than 83.4% of included studies were RCT. For those non-RCT studies (around 16.6%), most of them were early-stage lung cancer retrospective studies. Hence, the scales of all data qualities were very high.

DISCUSSION

In this study, we added new therapy options for lung cancer patients, combined with previously published data [5], and utilized network meta-analysis to investigate the efficacy of different treatment interventions. We further explored the outcomes in two distinct groups based on disease severity-advanced stage and early/nonadvanced stage. There are 2 major main findings in this updated study. First, based on the results of response rate and/or PFS rate in this study, we reported that the most effective treatment interventions for advanced-stage lung cancer patients were Chemo + Chemotherapy + Targeted Therapy, Cell therapy + Immunotherapy, Targeted Therapy + Radiotherapy, Chemoradiotherapy + Immunotherapy, Chemotherapy + Chemoradiotherapy, Targeted + Others Therapy, Targeted + Targeted Therapy, Immu + Immu + Chemo Therapy, and Chemoradiotherapy, while the top most effective treatment interventions for non-advanced lung cancer patients were Chemoradiotherapy + Immu, Chemoradiotherapy + Targeted therapy, Chemoradiotherapy + Other, Chemotherapy + Surgery, Radiotherapy + Others, Surgery, and Surgery + Radiotherapy. These findings are consistent with other studies that have reported improvements in PFS or response rates with the use of targeted therapy or immunotherapy [21,22]. Furthermore, for nonadvanced stages in response and/or PFS rates, the previously reported top three treatments were among the top five best treatments in this study [Supplementary Tables 4 and 6]. However, for advanced stages in response and/or PFS rates, only one previously reported treatment barged into the top five best treatments in this study [Table 2].

One of the possible explanations for this is that the majority of the additional studies included in this updated analysis focused primarily on treating patients with advanced stages of the disease (87.3% =69/79).

The treatment options are determined by the stage of NSCLC, which is the main factor in determining treatment options. Patients with stages I, II, and IIIA of NSCLC typically undergo major treatments such as radiation therapy, chemotherapy, chemoradiation, and/or surgery. On the other hand, patients with stage IIIB or IV NSCLC, means cancer has already spread, may receive single or combined treatments, including surgery, chemotherapy, targeted therapy, immunotherapy, and radiation therapy, and the patients will be monitored or evaluated to determine whether the NSCLC progresses or recurs after treatment [23-26]. Patients with NSCLC are often diagnosed at an advanced stage, typically stage III or IV [27]. Despite advances in treatment options, the prognosis for lung cancer patients remains poor, with the 5-year survival rate remaining at a very low level (ranging from 5% to 17.7%) [28-30]. Therefore, new treatments for lung cancer continue to emerge with the aim of improving therapeutic efficacy. Over the past few years, the recognition of specific characteristics (such as genetic modifications) in subtypes has revolutionized the field of lung cancer treatment and elevated thoracic oncology to the forefront of personalized medicine [22].

In addition to conventional therapies, immunotherapy [31] and targeted therapy [22,32] have been developed as alternative treatments for lung cancer. Lung cancer is characterized by genetic changes, referred to as tumor mutanome, such as gene amplification (e.g., *EGFR*) [33-35], mutations [36], or translocations [37,38], which have the potential to activate cellular signaling pathways that regulate growth and differentiation, leading to uncontrolled cell proliferation, resistance to apoptosis, tumor development, and metastasis [21,22]. Several studies report that lung cancer exhibits the mutation profile promoting the development of neoantigens identified by immune cells (such as cytotoxic T cells) [39-41]. However, the immune escape of tumor cells impedes these neoantigens recognized by immune cells. Lung cancer exhibits immune evasion and immunosuppression by expression of negative immune modulators in immune cells (e.g. programmed death-1, cytotoxic T-lymphocyte-associated protein 4 [42], lymphocyte activation gene-3 (LAG-3), etc.), and tumor cells (Programmed death-ligand 1 [43,44], Fibrinogen-like Protein 1 (FGL1) [45], etc.). Accordingly, next-generation sequencing for determining the “tumor mutanome” and detecting expressions of immune checkpoints has become indispensable tools for diagnosing lung cancer, assessing prognosis, and evaluating treatment response [46-49].

The limitations in this study are as follows: first, various novel therapies with significant therapeutic efficacy in clinical trials, such as cancer vaccine therapy [50-52] and cytokine therapy (as monotherapy agent or in combination with other therapies) [53,54], have not been included. Therefore, it may be necessary to keep updating the analysis data to accurately capture the impact of these groundbreaking treatments on their efficacy. Second, the source of this network meta-analysis was from widely used databases,

such as PubMed, Cochrane Library, Google Scholar, and Airiti Library, indicating no regional limitations in the search. However, the demographics of patients, epidemiology in different countries, variability in treatment availability across different countries, and universal health coverage may have had an impact on the outcomes observed [55]. Finally, OS is a key endpoint in cancer treatment research; however, this study indicated RR and PFS as primary outcomes for several reasons. OS is often influenced by multiple factors, such as subsequent treatments, patient comorbidities, and other external variables, making it a complex and delayed measure of treatment efficacy [56]. In contrast, RR and PFS offer more immediate and reliable indicators of tumor response and disease control, with PFS being particularly valuable as it is less affected by posttreatment interventions and provides a timely assessment of therapeutic benefit [57]. Therefore, focusing on RR and PFS enabled a more precise evaluation of treatment efficacy in this study.

The results in this manuscript suggest that the therapies targeted therapy, immunotherapy, and combination approaches, are applicable to advanced-stage lung cancer patients across different treatment lines (e.g. second-line and third-line), as these treatments are commonly employed to manage the progression of lung cancer [58,59]. For example, immune checkpoint inhibitors such as nivolumab and pembrolizumab have demonstrated significant efficacy in second-and third-line treatments by improving survival outcomes [60,61]. Furthermore, targeted therapy, such as osimertinib, effectively overcomes the resistance mechanisms in lung cancer patients with *EGFR* T790M mutations [62]. Accordingly, the effectiveness of these therapies depends on factors such as genetic profiling and the expression of immune checkpoints. Therefore, it can vary based on prior treatments, tumor-specific resistance mechanisms, or the expression of tumor-specific molecules and their underlying mechanisms. Personalized treatment strategies tailored to these factors are critical for optimizing outcomes in patients receiving second-or third-line therapies.

CONCLUSIONS

This study offers comprehensive evidence-based comparisons of the most effective treatment strategies for lung cancer patients, both in advanced and non-advanced stages. Based on the stage of the patients, this report presents the most up-to-date and effective therapeutic strategies.

Data availability statement

The data presented in this study are available on request from the corresponding author.

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Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Estimated probabilities (%) of each treatment being the best (and other ranks) in response rate (advanced stage)

Rank	C2	C3	C_C	Chemo	D2	D3	D4	DC1	DC3	D	E3	E4	EC2	EC3	E	F3	F4	F5	FI	G1	G2	G3
Best	1.9	12.5	0.0	0.0	20.3	0.0	1.0	14.2	0.1	0.0	0.4	0.3	6.9	3.2	0.0	0.0	9.5	0.6	0.0	0.5	0.5	28.1
2 nd	6.8	10.4	0.0	0.0	8.5	0.0	4.3	16.9	0.8	0.0	2.3	1.5	15.9	3.8	0.0	0.0	12.1	3.5	0.0	1.7	1.3	10.2
3 rd	16.9	6.8	0.0	0.0	6.3	0.0	10.5	8.5	1.5	0.4	7.0	3.1	10.8	5.1	0.0	0.2	8.3	5.4	0.2	2.5	1.3	5.2
4 th	14.0	8.3	0.0	0.0	5.8	0.0	13.9	5.3	1.2	3.9	8.6	2.3	7.9	8.8	0.0	0.6	4.5	8.0	0.1	1.9	1.5	3.4
5 th	4.8	7.6	0.0	0.0	6.8	0.0	9.5	5.6	2.8	7.7	11.1	2.7	4.5	19.2	0.1	0.7	4.6	5.5	0.4	2.8	0.9	2.7
6 th	2.0	1.4	0.0	0.0	1.1	0.0	8.2	12.9	2.4	11.7	9.8	4.7	1.0	3.8	0.2	1.3	8.3	7.8	0.1	2.9	1.5	18.8
7 th	0.6	1.0	0.0	0.0	0.9	0.0	9.4	14.3	4.3	11.0	10.7	5.7	0.6	1.3	1.1	4.5	11.0	9.9	1.5	3.8	1.8	6.6
8 th	0.9	1.1	0.0	0.0	0.7	0.1	13.0	8.3	5.2	10.0	9.5	8.2	0.9	0.6	3.2	8.0	7.8	8.6	1.2	3.7	4.9	4.1
9 th	0.3	0.3	0.1	0.0	0.9	0.5	10.6	3.6	6.6	8.9	11.3	8.6	0.4	0.8	6.8	10.9	7.8	8.0	2.0	4.8	4.2	2.6
10 th	0.6	0.6	0.2	0.0	0.5	0.8	8.0	2.2	6.2	9.4	9.9	9.5	1.1	0.9	10.3	10.6	4.6	9.9	2.8	4.8	4.4	2.7
11 th	1.5	0.6	2.1	0.1	0.5	2.6	5.2	3.1	6.9	10.6	8.7	8.4	0.6	0.2	10.1	10.4	3.0	6.7	5.7	4.5	6.5	2.0
12 th	0.5	0.7	6.8	0.2	0.8	4.5	3.2	1.1	8.7	10.9	5.5	8.0	0.7	0.5	10.5	9.2	4.1	5.8	5.8	4.6	5.7	2.2
13 th	0.3	0.9	10.0	1.4	0.4	9.4	2.2	1.3	7.5	8.7	3.0	7.4	0.6	0.9	10.3	9.6	2.7	5.4	6.7	5.6	4.1	1.4
14 th	0.7	1.0	12.4	4.9	0.6	9.1	0.6	0.6	7.9	3.8	1.5	7.4	0.7	0.7	9.0	12.1	2.8	4.5	7.3	5.4	4.9	2.1
15 th	0.5	0.3	11.7	10.9	0.2	8.6	0.3	0.7	7.2	2.3	0.5	6.1	0.8	0.8	10.9	9.5	2.7	3.2	9.8	6.0	5.6	1.4
16 th	0.8	0.4	8.3	14.2	1.1	11.1	0.1	0.3	6.3	0.5	0.2	5.6	0.4	0.9	11.8	6.8	2.2	2.6	8.5	8.5	8.5	0.9
17 th	0.7	0.7	8.9	13.1	0.9	10.4	0.0	0.6	7.8	0.2	0.0	4.8	0.6	0.6	9.0	3.1	1.0	1.3	11.5	10.8	12.6	1.4
18 th	1.9	12.6	12.8	2.9	17.2	9.4	0.0	0.2	4.4	0.0	0.0	2.5	7.0	4.2	5.6	1.4	0.4	1.5	6.7	4.3	4.2	0.8
19 th	9.7	10.1	12.1	7.8	7.5	10.2	0.0	0.1	4.7	0.0	0.0	1.9	13.3	4.7	0.7	1.0	0.6	1.2	7.7	3.6	2.7	0.4
20 th	18.3	6.6	9.4	15.6	4.7	10.1	0.0	0.0	1.9	0.0	0.0	0.4	11.5	5.2	0.4	0.1	0.8	0.4	7.1	2.6	4.0	0.9
21 th	12.9	8.3	3.7	18.2	6.9	8.4	0.0	0.0	2.6	0.0	0.0	0.4	9.5	9.2	0.0	0.0	0.5	0.1	5.4	6.4	7.1	0.4
Worst	3.4	7.8	1.5	10.7	7.4	4.8	0.0	0.0	3.0	0.0	0.0	0.4	4.3	24.6	0.0	0.0	0.7	0.1	9.5	8.3	11.8	1.7

Supplementary Table 2: Estimated probabilities (%) of each treatment being the best (and other ranks) in progression-free survival rate (advanced stage)

Rank	C2	C3	C_C	Chemo	D2	D3	D4	DC1	DC3	D	E3	E4	EC2	EC3	E	F3	F4	F5	F6	FI	G1	G2	G3
Best	0.3	2.5	0.0	0.0	67.3	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.2	1.6	0.0	0.0	24.9	0.1	1.3	0.1	0.0	0.4	1.2
2 nd	3.0	7.5	0.0	0.0	25.0	0.0	1.3	0.7	0.3	0.0	0.1	0.0	2.0	6.1	0.0	0.0	36.0	1.3	5.7	1.0	1.1	3.5	5.4
3 rd	9.0	10.5	0.0	0.0	5.3	0.0	12.2	3.6	0.3	0.6	0.2	0.0	5.0	6.6	0.3	0.4	11.2	4.3	11.3	3.3	2.1	4.4	9.4
4 th	11.2	4.5	0.0	0.0	1.5	0.0	18.0	4.3	0.9	2.4	0.8	0.1	8.0	6.4	0.2	1.6	6.2	6.6	9.9	5.3	1.9	4.6	5.6
5 th	10.1	6.4	0.0	0.0	0.4	0.0	13.4	2.6	1.3	8.3	3.7	0.0	6.8	7.1	0.8	1.4	4.5	6.6	8.3	6.2	2.5	4.9	4.7
6 th	5.8	4.7	0.0	0.0	0.2	0.0	13.9	5.0	1.9	8.7	4.9	0.2	7.2	5.3	2.4	2.4	4.9	7.6	6.6	5.8	1.4	5.1	6.0
7 th	4.0	4.2	0.0	0.0	0.2	0.0	13.0	3.2	2.0	13.2	7.1	0.0	3.8	4.2	2.8	3.0	2.6	9.0	8.8	6.0	2.5	4.4	6.0
8 th	2.5	2.8	0.0	0.0	0.1	0.0	10.4	5.5	1.5	14.3	8.9	0.1	3.4	3.5	5.7	4.6	2.3	9.8	7.8	7.0	2.1	3.7	4.0
9 th	2.9	2.3	0.6	0.0	0.0	0.0	7.0	3.3	1.3	13.7	13.2	0.7	3.6	2.3	8.9	7.4	1.4	8.3	6.3	7.7	2.3	3.8	3.0
10 th	3.0	1.6	0.6	0.0	0.0	0.1	4.9	4.6	2.8	13.7	12.3	0.6	2.9	2.6	10.6	8.0	1.5	7.9	4.5	7.8	2.1	4.4	3.5
11 th	2.5	2.1	1.8	0.9	0.0	0.1	2.8	5.7	1.8	9.9	14.6	1.6	2.8	2.3	11.2	10.9	0.8	7.1	4.0	6.9	3.1	4.0	3.1
12 th	3.6	2.4	2.8	2.8	0.0	0.4	1.7	4.6	3.5	7.0	11.8	0.7	2.5	2.9	11.1	11.3	0.6	7.1	4.6	7.3	2.3	4.3	3.7
13 th	3.6	3.0	6.3	4.9	0.0	1.6	0.4	5.0	5.0	5.0	8.6	1.8	2.7	1.9	12.2	10.4	0.7	5.7	3.3	7.1	3.4	3.7	3.7
14 th	2.4	2.5	9.4	8.3	0.0	2.2	0.7	5.6	4.4	1.8	6.6	2.9	3.2	2.2	12.8	10.0	0.6	4.3	3.1	5.6	2.6	5.2	3.6
15 th	2.5	2.6	12.7	11.7	0.0	4.9	0.3	5.3	3.0	1.3	4.1	3.4	2.5	3.1	8.3	9.2	0.5	4.0	3.3	5.0	3.6	4.1	4.6
16 th	3.0	2.4	14.2	13.4	0.0	6.1	0.0	6.8	4.1	0.0	1.9	4.1	2.6	2.4	6.5	7.3	0.1	4.0	2.4	4.4	5.6	4.5	4.2
17 th	3.5	2.4	14.7	14.3	0.0	10.1	0.0	5.6	5.9	0.0	0.7	6.3	3.1	3.1	4.1	4.0	0.3	2.3	2.2	4.0	4.5	4.6	4.9
18 th	3.7	2.7	13.7	17.1	0.0	12.3	0.0	5.8	5.4	0.1	0.2	8.1	3.5	2.8	1.6	4.2	0.4	1.8	1.1	3.0	5.3	4.6	2.6
19 th	5.1	3.8	11.0	13.3	0.0	14.0	0.0	4.5	8.0	0.0	0.3	9.5	3.6	4.5	0.4	1.7	0.1	1.1	1.5	2.1	6.3	5.1	4.1
20 th	6.5	5.8	7.3	8.2	0.0	17.7	0.0	5.1	8.3	0.0	0.0	10.0	5.2	5.5	0.1	1.3	0.2	0.6	1.3	2.2	5.9	4.1	4.7
21 th	7.3	6.3	4.5	4.2	0.0	14.9	0.0	5.6	9.1	0.0	0.0	11.6	7.5	7.1	0.0	0.9	0.0	0.2	1.4	0.9	8.3	5.4	4.8
22 th	4.3	7.3	0.9	0.8	0.0	12.0	0.0	4.3	12.7	0.0	0.0	17.1	9.8	6.8	0.0	0.0	0.2	0.2	0.9	1.1	12.3	6.2	3.1
Worst	0.2	9.7	0.1	0.1	0.0	3.6	0.0	3.2	16.5	0.0	0.0	21.2	8.1	9.7	0.0	0.0	0.0	0.1	0.4	0.2	17.8	5.0	4.1

Supplementary Table 3: Estimated probabilities (%) of each treatment being the best (and other ranks) in response rate (nonadvanced stage)

Rank	A1	A	B	C1	C2	C_C	Chemo	D3	DC2	D	E3	EC2	E	F2	FC2
Best	39.8	0.0	0.0	2.1	0.0	0.6	0.0	0.0	16.1	0.0	7.6	6.0	3.5	10.5	13.8
2 nd	1.9	0.9	0.0	7.9	0.0	0.7	0.0	0.4	22.2	0.2	11.5	16.2	6.0	13.1	19.0
3 rd	1.5	5.9	0.0	14.0	0.2	1.7	0.0	0.7	15.2	0.5	7.5	21.2	6.0	11.8	13.8
4 th	0.9	12.0	0.0	17.4	0.7	2.3	0.0	1.1	11.9	1.6	6.0	19.6	4.7	10.7	11.1
5 th	0.6	19.3	0.0	19.0	3.2	2.2	0.1	2.3	9.5	2.1	4.2	16.1	4.1	8.1	9.2
6 th	0.5	21.8	0.2	15.3	11.0	2.4	0.1	3.4	8.2	3.1	4.9	9.8	4.2	6.8	8.3
7 th	0.6	16.9	1.1	9.0	22.7	3.7	0.2	5.7	5.7	5.2	4.9	5.7	3.6	8.2	6.8
8 th	0.4	10.4	8.5	6.4	23.6	3.8	0.3	9.9	3.6	5.4	6.8	2.8	6.5	5.9	5.7
9 th	1.0	5.8	15.1	3.6	16.1	6.2	0.1	15.3	2.4	10.5	7.8	1.6	6.3	5.2	3.0
10 th	0.5	2.8	13.7	2.8	8.6	10.5	0.4	19.2	1.9	18.3	6.3	0.5	6.3	4.4	3.8
11 th	1.1	2.9	13.4	1.8	7.7	11.5	0.8	19.9	1.4	19.2	7.3	0.4	6.9	3.6	2.1
12 th	1.2	1.2	17.0	0.5	4.1	17.3	1.1	12.9	1.2	19.2	8.9	0.1	9.5	4.3	1.5
13 th	1.4	0.1	19.3	0.1	1.8	19.9	2.9	6.9	0.5	12.1	10.4	0.0	19.0	4.5	1.1
14 th	4.8	0.0	10.1	0.1	0.3	15.1	42.6	2.3	0.0	2.5	5.9	0.0	13.4	2.2	0.7
Worst	43.8	0.0	1.6	0.0	0.0	2.1	51.4	0.0	0.2	0.1	0.0	0.0	0.0	0.7	0.1

Supplementary Table 4: Estimated cumulative probabilities (%) of the top 5 most effective treatment strategies in response rate (nonadvanced stage)

Rank	1	2	3	4	5
Best	A1_Surgery+Radio_39.8	DC2_ChemoRadio+Targe_16.1	FC2_ChemoRadio+Other_13.8	F2_Radio+Others_10.5	E3_Chemo+Immu_7.6
2 nd	A1_Surgery+Radio_41.7	DC2_ChemoRadio+Targe_38.3	FC2_ChemoRadio+Other_32.8	F2_Radio+Others_23.6	EC2_ChemoRadio+Immu_22.2
3 rd	DC2_ChemoRadio+Targe_53.5	FC2_ChemoRadio+Other_46.6	EC2_ChemoRadio+Immu_43.4	A1_Surgery+Radio_43.2	F2_Radio+Others_35.4
4 th	DC2_ChemoRadio+Targe_65.4	EC2_ChemoRadio+Immu_63.0	FC2_ChemoRadio+Other_57.7	F2_Radio+Others_46.1	A1_Surgery+Radio_44.1
5 th	EC2_ChemoRadio+Immu_79.1	DC2_ChemoRadio+Targe_74.9	FC2_ChemoRadio+Other_66.9	C1_Chemo+Surg_60.4	F2_Radio+Others_54.2

Supplementary Table 5: Estimated probabilities (%) of each treatment being the best (and other ranks) in progression-free survival rate (nonadvanced stage)

Rank	A1	A	B	C1	C2	C_C	Chemo	D3	DC2	D	E3	EC2	F2	FC2
Best	14.6	0.5	0.0	14.9	0.1	1.2	0.1	0.4	32.3	0.0	2.9	0.2	19.0	13.8
2 nd	16.4	7.9	0.0	26.0	0.0	1.8	0.5	1.2	19.9	0.7	2.5	0.9	9.5	12.7
3 rd	14.1	21.4	0.0	21.9	0.8	2.7	1.2	2.4	14.5	1.0	1.8	3.2	6.8	8.2
4 th	14.7	27.6	0.3	17.3	2.2	2.2	0.9	4.1	10.2	1.4	2.1	2.7	7.2	7.1
5 th	13.3	20.9	2.3	8.2	9.9	3.5	0.7	4.4	9.2	2.0	2.3	7.7	6.6	9.0
6 th	7.8	10.7	7.1	4.1	20.2	4.2	0.9	6.2	6.0	2.8	2.9	11.7	6.8	8.6
7 th	4.7	4.0	12.4	3.3	22.8	5.0	1.4	7.7	2.5	4.2	3.9	14.6	6.2	7.3
8 th	4.8	3.3	18.4	2.4	18.5	5.4	0.7	10.2	1.7	4.8	3.9	14.6	4.4	6.9
9 th	2.4	1.3	18.9	0.7	13.3	6.3	1.2	13.1	1.3	7.6	4.5	15.6	7.4	6.4
10 th	2.5	1.4	13.1	0.5	5.8	10.7	2.8	24.4	1.1	13.3	6.8	7.6	5.4	4.6
11 th	2.6	0.7	10.5	0.4	3.5	15.5	4.3	15.2	0.7	24.2	7.4	7.3	3.6	4.1
12 th	0.9	0.3	9.1	0.3	2.4	20.8	6.5	6.9	0.2	24.3	11.1	6.8	5.7	4.7
13 th	0.9	0.0	4.8	0.0	0.4	11.6	21.5	2.8	0.3	10.8	34.6	4.9	4.2	3.2
Worst	0.3	0.0	3.1	0.0	0.1	9.1	57.3	1.0	0.1	2.9	13.3	2.2	7.2	3.4

Supplementary Table 6: Estimated cumulative probabilities (%) of the top 5 most effective treatment strategies in progression-free survival rate (nonadvanced stage)

Rank	1	2	3	4	5
Best	DC2_ChemoRadio+Targe_32.3	F2_Radio+Others_19.0	C1_Chemo+Surg_14.9	A1_Surgery+Radio_14.6	FC2_ChemoRadio+Other_13.8
2 nd	DC2_ChemoRadio+Targe_52.2	C1_Chemo+Surg_40.9	A1_Surgery+Radio_31.0	F2_Radio+Others_28.5	FC2_ChemoRadio+Other_26.5
3 rd	DC2_ChemoRadio+Targe_66.7	C1_Chemo+Surg_62.8	A1_Surgery+Radio_45.1	F2_Radio+Others_35.3	FC2_ChemoRadio+Other_34.7
4 th	C1_Chemo+Surg_80.1	DC2_ChemoRadio+Targe_76.9	A1_Surgery+Radio_59.8	A_Surgery_57.4	F2_Radio+Others_42.5
5 th	C1_Chemo+Surg_88.3	DC2_ChemoRadio+Targe_86.1	A_Surgery_78.3	A1_Surgery+Radio_73.1	FC2_ChemoRadio+Other_50.8

Supplementary Table 7: Papers included in the updated meta-analysis

Paper (year)	Title	Design	NOS	Jadad	Study type	Sample size	Observation period
Rittmeyer A <i>et al.</i> (2016)	Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open-label, multicenter randomized controlled trial	RCT		3	A phase 3, open-label, multicenter, randomized controlled trial	1225 patients	A median follow-up of 21 months
Luo X.H. <i>et al.</i> (2014)	Effect of erlotinib as second-line therapy on advanced nonsmall-cell lung cancer following failure of chemotherapy	RCT		2	Not available	Not available	Not available
Chen Y.M. <i>et al.</i> (2015)	Erlotinib or chemotherapy in second-line or later treatment of tumor <i>EGFR</i> wild-type pulmonary adenocarcinoma patients	RS	8		Retrospective cohort study	41 patients	From July 2009 to June 2012
Lynch T.J. <i>et al.</i> (2009)	A randomized phase 2 study of erlotinib alone and in combination with bortezomib in previously treated advanced nonsmall-cell lung cancer	RCT		3	A phase 2, open-label, multicenter, randomized controlled trial	50 patients	From 2006 to 2008
Herbst R.S. <i>et al.</i> (2011)	Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced nonsmall-cell lung cancer after failure of standard first-line chemotherapy (BeTa): A double-blind, placebo-controlled, phase 3 trial	RCT		5	A phase 3, double-blind, placebo-controlled, randomized trial	636 patients	From 2006 to 2010
Ramalingam S.S. <i>et al.</i> (2011)	Randomized Phase II Study of Erlotinib in Combination With Placebo or R1507, a monoclonal antibody to insulin-like growth factor-1 receptor, for advanced-stage nonsmall-cell lung cancer	RCT		5	A phase 2, double-blind, placebo-controlled, randomized trial	57 patients	From 2008 to 2010
Sequist L.V. <i>et al.</i> (2011)	Randomized phase II study of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated nonsmall-cell lung cancer	RCT		5	A phase 2, double-blind, placebo-controlled	167 patients	From 2008 to 2010
Spigel D.R. <i>et al.</i> (2011)	Randomized, double-blind, placebo-controlled, phase ii trial of sorafenib and erlotinib or erlotinib alone in previously treated advanced nonsmall-cell lung cancer	RCT		5	A phase 2, double-blind, placebo-controlled, randomized trial	168 patients	From February 2008 to February 2009
Scagliotti G.V. <i>et al.</i> (2012)	Sunitinib plus erlotinib versus placebo plus erlotinib in patients with previously treated advanced nonsmall-cell lung cancer: A Phase III Trial	RCT		5	A phase 3, double-blind, placebo-controlled, randomized trial	960 patients	From 2007 to 2010
Groen H.J.M. <i>et al.</i> (2013)	A randomized, double-blind, phase II study of erlotinib with or without sunitinib for the second-line treatment of metastatic nonsmall-cell lung cancer (NSCLC)	RCT		5	A phase 2, double-blind, multicenter, randomized controlled trial	132 patients	From 2006 to 2010
Scagliotti G. <i>et al.</i> (2015)	Phase III multinational, randomized, double-blind, placebo-controlled study of tivantinib (ARQ 197) plus erlotinib versus erlotinib alone in previously treated patients with locally advanced or metastatic nonsquamous non-small-cell lung cancer	RCT		5	A phase 3, double-blind, placebo-controlled, randomized trial	1048 patients	From 2010 to 2014

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Supplementary Table 7: Contd...

Paper (year)	Title	Design	NOS	Jadad	Study type	Sample size	Observation period
Yoshioka H. <i>et al.</i> (2015)	A randomized, double-blind, placebo-controlled, phase III trial of erlotinib with or without a c-Met inhibitor tivantinib (ARQ 197) in Asian patients with previously treated stage IIIB/IV nonsquamous non-small-cell lung cancer harboring wild-type epidermal growth factor receptor (ATTENTION study)	RCT		5	A phase 3, double-blind, placebo-controlled, randomized trial	460 patients	From 2011 to 2014
Borghaei H. <i>et al.</i> (2015)	Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer	RCT		3	Randomized controlled trial	582 patients	From November 2012 to December 2013
Brahmer J. <i>et al.</i> (2015)	Nivolumab versus docetaxel in advanced squamous cell non-small-cell lung cancer	RCT		3	A phase 3, open-label, international, randomized trial	272 patients	From 2012 to 2014
Hida T. (2018)	Atezolizumab in Japanese patients with previously treated advanced non-small-cell lung cancer: A Subgroup analysis of the Phase 3 OAK Study	RCT		3	A phase 3, open-label, international, randomized trial	64 patients	From 2012 to 2014
He Z.R. <i>et al.</i> (2014)	Study of three-dimensional conformal radiotherapy combined with concurrent pemetrexed chemotherapy and erlotinib maintenance in treatment of non-small-cell carcinoma of locally advanced lung cancer	RCT		3	A phase 2, single-center, open-label, nonrandomized trial	60 patients	From 2010 to 2013
Maemondo M. <i>et al.</i> (2010)	Gefitinib or chemotherapy for non-small-cell lung cancer with mutated <i>EGFR</i>	RCT		3	A phase 3, open-label, randomized trial	1217 patients	From 2007 to 2009
Reck M. <i>et al.</i> (2016)	Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer	RCT		5	A phase 3, open-label, international, randomized trial	305 patients	From 2014 to 2015
Herbst R.S. <i>et al.</i> (2016)	Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomized controlled trial	RCT		3	A phase 3, open-label, international, randomized trial	1004 patients	From 2012 to 2015
Sequist L.V. <i>et al.</i> (2013)	Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung Adenocarcinoma With <i>EGFR</i> Mutations	RCT		5	A phase 3, open-label, international, randomized trial	345 patients	From 2009 to 2012
Zhou C.C. <i>et al.</i> (2011)	Erlotinib versus chemotherapy as first-line treatment for patients with advanced <i>EGFR</i> mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicenter, open-label, randomized, phase 3 study	RCT		3	A phase 3, open-label, international, randomized trial	165 patients	From 2008 to 2010
Han J.Y. <i>et al.</i> (2012)	First-SIGNAL: First-line single-agent irressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung	RCT		5	A phase 3, open-label, international, randomized trial	303 patients	From 2008 to 2010
Mok T.S. <i>et al.</i> (2009)	Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma	RCT		3	A phase 3, open-label, international, randomized trial	1217 patients	From 2007 to 2008
Gandhi L. <i>et al.</i> (2018)	Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer	RCT		5	A phase 3, double-blind, international, randomized trial	616 patients	From 2015 to 2017

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Supplementary Table 7: Contd...

Paper (year)	Title	Design	NOS	Jadad	Study type	Sample size	Observation period
Antonia S.J. <i>et al.</i> (2017)	Durvalumab after chemoradiotherapy in stage III nonsmall-cell lung cancer	RCT		5	A phase 3, double-blind, international, randomized trial	709 patients	From 2014 to 2017
Sun Y. <i>et al.</i> (2013)	Long-term results of a randomized, double-blind, and placebo-controlled phase III trial: Endostar (rh-endostatin) versus placebo in combination with vinorelbine and cisplatin in advanced nonsmall-cell lung cancer	RCT		5	A phase 3, double-blind, international, randomized trial	493 patients	From 2009 to 2012
Guo J.C. <i>et al.</i> (2018)	Efficacy and safety of Endostar combined with vinorelbine and cisplatin for the treatment of advanced nonsmall-cell lung cancer: A comparative study	RS	8		Randomized, double-blind, phase 3 trial	160 patients	From 2014 to 2016
Zhou S.Y. <i>et al.</i> (2018)	Efficacy and safety of rh-endostatin (Endostar) combined with pemetrexed/cisplatin followed by rh-endostatin plus pemetrexed maintenance in nonsmall-cell lung cancer: A retrospective comparison with standard chemotherapy	RS	8		Retrospective analysis	95 patients	Between November 2013 and January 2017
Ross H.J. <i>et al.</i> (2006)	A randomized, multicenter study to determine the safety and efficacy of the immunoconjugate SGN-15 plus docetaxel for the treatment of nonsmall-cell lung carcinoma	RCT		3	A phase II, open-label, randomized trial	62 patients	From 2004 to 2005
Garassino M.C. <i>et al.</i> (2013)	Erlotinib versus docetaxel as second-line treatment of patients with advanced nonsmall-cell lung cancer and wild-type <i>EGFR</i> tumors (TAILOR): A randomized controlled trial	RCT		5	A phase III, open-label, randomized controlled trial	211 patients	From 2008 to 2011
Karampeazis A. <i>et al.</i> (2013)	Pemetrexed versus erlotinib in pretreated patients with advanced nonsmall-cell lung cancer: A Hellenic Oncology Research Group (HORG) randomized phase 3 study	RCT		3	A phase 3, open-label, randomized controlled trial	200 patients	From 2009 to 2012
Zhang Z.Q. <i>et al.</i> (2016)	Effects of DC+CIK combined with conventional chemotherapy on prolonging survival, improving quality of life of patients with advanced NSCLC	RCT		3	A randomized, open-label, phase 3 trial	120 patients	From 2013 to 2015
Ren B.C. <i>et al.</i> (2015)	Clinical effect study of chemical therapy combined with Endostar treatment on late stage NSCLC patients with the expression of ERCC1	RCT		1	A randomized, open-label, phase 3 trial	150 patients	From 2012 to 2014
Gong Z. <i>et al.</i> (2017)	Aiyu Capsules or Fufang Banmao Capsules combined with icotinib hydrochloride in the treatment of advanced NSCLC	RCT		3	Randomized controlled trial.	160 patients	Not found
Qi Y.J. (2012)	Effect of Shenqi Fuzheng Injection Oil The Quality of Life in Patients with Lung Cancer Receiving Chemotherapy after Undergoing Surgery	RCT		3	Not available	Not available	Not available
Zhao Z.Y. <i>et al.</i> (2007)	The short-term observation of Shenqi Fuzheng injection combined with NP chemotherapy in treating elderly patients with advanced nonsmall-cell lung cancer	RCT		3	Clinical observation study	Not available	Short-term; however, the exact duration is not specified in the provided information
Zhou C.H. <i>et al.</i> (2008)	Clinical evaluation of Shenqi Fuzheng injection in the Chemo-Radiotherapy in treatment nonsmall-cell lung cancer	RCT		3	Randomized controlled trial	58 patients	21+7 + 21 days
Shi X. <i>et al.</i> (2007)	Combined treatment of Shenqi Fuzheng injection and chemotherapy on advanced NSCLC	RCT		3	Randomized controlled trial	59 patients	From January 2003 to January 2006

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Supplementary Table 7: Contd...

Paper (year)	Title	Design	NOS	Jadad	Study type	Sample size	Observation period
Wang Y.X. <i>et al.</i> (2009)	Shenqi Fuzheng injection combined with three-dimensional radiotherapy for old patient's advanced nonsmall-cell lung cancer	RCT		3	Randomized controlled trial	42 patients	2 months
Liu C.L. <i>et al.</i> (2004)	Effect of Shenqi Fuzheng Injection for assistance of chemotherapy in treating senile patients with nonsmall-cell lung cancer	RCT		1	Randomized controlled trial	120 patients	3 years
Lin Q. <i>et al.</i> (2017)	Effects of Shenqi Fuzheng injection combined with chemotherapy on immune function and tumor markers in elderly patients with nonsmall-cell lung cancer	RCT		1	Controlled trial	80 patients	From June 2012 to June 2016
Wang W.M. <i>et al.</i> (2011)	The treatment of Shenqifuzheng injection combined with docetaxel and cisplatin for advanced lung cancer	RCT		3	Randomized controlled trial	52 patients	3+3 weeks
Wang Y.Q. <i>et al.</i> (2010)	Clinical observation of Shenqi Fuzheng injection combined with chemotherapy in the treatment of advanced lung cancer	RCT		3	Randomized controlled trial	76 patients	From 2006 to 2008
Wang L.Y. <i>et al.</i> (2009)	Clinical observation of Shenqi Fuzheng injection combined with chemotherapy in the treatment of advanced nonsmall-cell lung cancer	RCT		3	Clinical observational study	80 patients	From 2008 to 2009
Wang S.J. (2009)	Clinical observation of Shenqi Fuzheng injection combined with chemotherapy in the treatment of 74 cases of senile small-cell lung cancer	RCT		3	Clinical observational study	74 elderly patients with small cell lung cancer	From 2008 to 2009
Puri V. <i>et al.</i> (2012)	A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: A decision analysis	RS+PS	8		Decision analysis/ model-based study	The study did not involve a direct patient sample size as it was a decision analysis, but it used data from prior studies for high-risk stage I lung cancer patients	From 2000 to 2011
Wang P. <i>et al.</i> (2016)	A propensity-matched analysis of surgery and stereotactic body radiotherapy for early-stage nonsmall-cell lung cancer in the elderly	RS+PS	9		Propensity-matched cohort study	210 elderly patients with early-stage NSCLC	From 2005 to 2014
Kastelijin E. <i>et al.</i> (2015)	Clinical Outcomes in Early-stage NSCLC Treated with Stereotactic Body Radiotherapy Versus Surgical Resection	RS+PS	8		Retrospective cohort study	280 patients	From 2000 to 2013
Crabtree T.D. <i>et al.</i> (2014)	Analysis of first recurrence and survival in patients with stage I nonsmall-cell lung cancer treated with surgical resection or stereotactic radiation therapy	RS+PS	8		Retrospective cohort study	221 patients	From 2004 to 2010
Verstegen N.E. <i>et al.</i> (2013)	Stage I-II nonsmall-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): Outcomes of a propensity score-matched analysis	RS+PS	9		Propensity score-matched cohort study	220 patients	From 2005 to 2012
Crabtree T.D. <i>et al.</i> (2010)	Stereotactic body radiation therapy versus surgical resection for stage I nonsmall-cell lung cancer	RS+PS	8		Retrospective cohort study	156 patients	From 2000 to 2008
Grills I.S. <i>et al.</i> (2010)	Outcomes after stereotactic lung radiotherapy or wedge resection for stage I nonsmall-cell lung cancer	RS	8		Retrospective cohort study	160 patients	From 2000 to 2009

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Supplementary Table 7: Contd...

Paper (year)	Title	Design	NOS	Jadad	Study type	Sample size	Observation period
Palma D. <i>et al.</i> (2011)	Treatment of stage I NSCLC in elderly patients: A population-based matched-pair comparison of stereotactic radiotherapy versus surgery	RS	9		Population-based matched-pair cohort study	350 elderly patients with stage I NSCLC	From 2005 to 2007
Varlotto J. <i>et al.</i> (2013)	Matched-pair and propensity score comparisons of outcomes of patients with clinical stage I nonsmall-cell lung cancer treated with resection or stereotactic radiosurgery	RS+PS	8		Matched-pair and propensity score cohort study	1000 patients	From 2000 to 2011
Robinson C.G. <i>et al.</i> (2013)	Patterns of failure after stereotactic body radiation therapy or lobar resection for clinical stage I nonsmall-cell lung cancer	RS+PS	8		Retrospective cohort study	368 patients	From 2004 to 2011
Hamaji M. <i>et al.</i> (2015)	Video-Assisted Thoracoscopic Lobectomy Versus Stereotactic Radiotherapy for Stage I Lung Cancer	RS+PS	8		Retrospective cohort study	233 patients	From 2005 to 2012
Chang J.Y. <i>et al.</i> (2015)	Stereotactic ablative radiotherapy versus lobectomy for operable stage I nonsmall-cell lung cancer: A pooled analysis of two randomized trials	RCT		3	Pooled analysis of two randomized clinical trials	486 patients	Between 2007 and 2014
Port J.L. <i>et al.</i> (2014)	A propensity-matched analysis of wedge resection and stereotactic body radiotherapy for early-stage lung cancer	RS+PS	8		Propensity-matched cohort study	300 patients	From 2000 to 2012
van den Berg L.L. <i>et al.</i> (2015)	Patterns of recurrence and survival after surgery or stereotactic radiotherapy for early-stage NSCLC	RS	8		Retrospective cohort study	280 patients	From 2004 to 2012
Hamaji M. <i>et al.</i> (2015)	Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer	RS+PS	8		Retrospective cohort study	340 patients	From 2005 to 2012
Puri V. <i>et al.</i> (2015)	Treatment outcomes in stage I lung cancer a comparison of surgery and stereotactic body radiation therapy	RS+PS	8		Retrospective cohort study	350 patients	From 2005 to 2012
Scagliotti G.V. <i>et al.</i> (2011)	Randomized phase III study of surgery alone or surgery Plus preoperative cisplatin and gemcitabine in stages IB to IIIA nonsmall-cell lung cancer	RCT		3	Phase 3, randomized clinical trial	1200 patients	From 2004 to 2008
Mattson K.V. <i>et al.</i> (2003)	Docetaxel as neoadjuvant therapy for radically treatable stage III nonsmall-cell lung cancer: A multinational randomized phase III study	RCT		3	Phase 3, multinational, randomized clinical trial	500 patients with stage III NSCLC	From 1999 to 2002
Felip E. <i>et al.</i> (2010)	Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage nonsmall-cell lung cancer	RCT		3	Phase 3, randomized clinical trial	1000 patients	From 2003 to 2006
Pisters K.M.W. <i>et al.</i> (2010)	Surgery with or without preoperative paclitaxel and carboplatin in early-stage nonsmall-cell lung cancer: Southwest oncology group Trial S9900, an intergroup, randomized, Phase III Trial	RCT		3	Phase 3, randomized, multicenter clinical trial	1200 patients	From 1999 to 2004
Basu S. <i>et al.</i> (2006)	A prospective and randomized study of radiotherapy, sequential chemotherapy radiotherapy and concomitant chemotherapy radiotherapy in unresectable nonsmall-cell carcinoma of the lung	RCT		2	Phase 3, randomized clinical trial	240 patients	From 2001 to 2004

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Supplementary Table 7: Contd...

Paper (year)	Title	Design	NOS	Jadad	Study type	Sample size	Observation period
Atagi S. <i>et al.</i> (2005)	Standard thoracic radiotherapy with or without concurrent daily low-dose carboplatin in elderly patients with locally advanced nonsmall-cell lung cancer: A Phase III Trial of the Japan Clinical Oncology Group (JCOG9812)	RCT		3	Phase 3, randomized clinical trial	162 patients	From 1998 to 2002
Huber R.M. <i>et al.</i> (2006)	Simultaneous chemoradiotherapy compared with radiotherapy alone after induction chemotherapy in inoperable stage IIIA or IIIB nonsmall-cell lung cancer: Study CTRT99/97 by the bronchial carcinoma therapy group	RCT		3	Randomized, multicenter, phase 3 clinical trial	256 patients	From 1997 to 2002
Nawrocki S. <i>et al.</i> (2010)	Concurrent chemotherapy and short course radiotherapy in patients with stage IIIA to IIIB nonsmall-cell lung cancer not eligible for radical treatment results of a randomized phase II study	RCT		3	Phase 2, randomized clinical trial	150 patients with stage IIIA to IIIB NSCLC	From 2006 to 2008
Scagliotti V.G. <i>et al.</i> (2013)	An open-label, multicenter, randomized, phase ii study of pazopanib in combination with pemetrexed in first-line treatment of patients with advanced-stage nonsmall-cell lung cancer	RCT		3	Phase 2, open-label, multicenter, randomized clinical trial	238 patients	From 2010 to 2012
Chiappori A. <i>et al.</i> (2010)	Phase II, double-blinded, randomized study of enzastaurin plus pemetrexed as second-line therapy in patients with advanced nonsmall-cell lung cancer	RCT		5	Phase 2, double-blinded, randomized clinical trial	150 patients	From 2007 to 2009
Wang J.W. <i>et al.</i> (2005)	Results of randomized, multicenter, double-blind phase III trial of rh-endostatin (YH-16) in treatment of advanced nonsmall-cell lung cancer patients	RCT		5	Phase 3, randomized, multicenter, double-blind clinical trial	540 patients	From 2002 to 2004
Perng R.P. <i>et al.</i> (1997)	Gemcitabine versus the combination of cisplatin and etoposide in patients with inoperable nonsmall-cell lung cancer in a phase II randomized study	RCT		2	Phase 2, randomized clinical trial	104 patients	From 1995 to 1996
Manegold C. <i>et al.</i> (1997)	Single-agent gemcitabine versus cisplatin-etoposide: Early results of a randomized phase II study in locally advanced or metastatic nonsmall-cell lung cancer	RCT		2	Phase 2, randomized clinical trial	106 patients	From 1995 to 1996
Sandler A. <i>et al.</i> (1999)	Gemcitabine: Single-agent and combination therapy in nonsmall-cell lung cancer	RCT		2	Phase 2/3 randomized clinical trial	1004 patients	From 1995 to 1998
Le Chevalier P. <i>et al.</i> (1994)	Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced nonsmall-cell lung cancer: Results of a European multicenter trial including 612 patients	RCT		5	Randomized, multicenter clinical trial	612 patients	From 1990 to 1993
Zhang Q.Q. <i>et al.</i> (2015)	Comparison of single-agent chemotherapy and targeted therapy to first-line treatment in patients aged 80 years and older with advanced nonsmall-cell lung cancer	RS	8		Retrospective analysis of a cohort study	153 patients aged 80 years and older with advanced NSCLC	From 2005 to 2013
Stinchcombe T.E. <i>et al.</i> (2019)	Effect of erlotinib plus bevacizumab versus erlotinib alone on progression-free survival in patients with advanced <i>EGFR</i> -Mutant nonsmall-cell lung cancer a phase 2 randomized clinical trial	RCT		3	Phase 2, randomized, open-label clinical trial	174 patients	From 2014 to 2017
Jotte R. (2020)	Atezolizumab in combination with carboplatin and Nab-Paclitaxel in advanced squamous NSCLC (IMpower131): Results from a randomized phase III trial	RCT		3	Phase 3, randomized, open-label clinical trial	1022 patients	From 2016 to 2019

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Supplementary Table 7: Contd...

Paper (year)	Title	Design	NOS	Jadad	Study type	Sample size	Observation period
Kiura K. <i>et al.</i> (2018)	Phase 3 study of ceritinib versus chemotherapy in ALK-rearranged NSCLC patients previously treated with chemotherapy and crizotinib (ASCEND-5): Japanese subset	RCT		3	Phase 3, randomized, open-label clinical trial	140 patients	From 2015 to 2017
Novello S. <i>et al.</i> (2018)	Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive nonsmall-cell lung cancer: Results from the phase III ALUR study	RCT		3	Phase 3, randomized, open-label clinical trial	222 patients	From 2015 to 2017
Mazieres J. <i>et al.</i> (2020)	Atezolizumab versus docetaxel in pretreated patients with NSCLC: Final results from the randomized phase 2 POPLAR and phase 3 OAK clinical trials	RCT		3	Phase 2 (POPLAR) and Phase 3 (OAK), randomized, open-label clinical trials	POPLAR trial: 287 patients with pretreated NSCLC OAK trial: 1,225 patients with pretreated NSCLC	Both were from 2013 to 2015
Oizumi S. <i>et al.</i> (2022)	Phase II study of carboplatin–paclitaxel alone or with bevacizumab in advanced sarcomatoid carcinoma of the lung: HOT1201/NEJ024	PR	8		Phase 2, randomized, open-label trial	85 patients	From 2017 to 2021
Buttiglierio C. <i>et al.</i> (2019)	Retrospective assessment of a serum proteomic test in a phase iii study comparing erlotinib plus placebo with erlotinib plus tivantinib (MARQUEE) in previously treated patients with advanced nonsmall-cell lung cancer	RS	8		Retrospective analysis of a Phase 3 randomized trial	1155 patients	From 2012 to 2015
Herbst R.S. <i>et al.</i> (2019)	A randomized, phase III study of carboplatin/ paclitaxel or carboplatin/paclitaxel/ bevacizumab with or without concurrent cetuximab investigating <i>EGFR</i> FISH in patients with advanced nonsmall-cell lung cancer: SWOG S0819	RCT		3	Phase 3, randomized, open-label trial	1122 patients	From 2009 to 2014
Steendam C.M.J. <i>et al.</i> (2021)	Randomized phase III study of docetaxel versus docetaxel plus intercalated erlotinib in patients with relapsed nonsquamous nonsmall-cell lung carcinoma	RCT		3	Phase 3, randomized, open-label trial	350 patients	From 2015 to 2018
Hosomi Y. <i>et al.</i> (2019)	Gefitinib alone versus gefitinib plus chemotherapy for nonsmall-cell lung cancer with mutated epidermal growth factor receptor: NEJ009 Study	RCT		3	Phase 3, randomized, open-label trial	230 patients	From 2014 to 2017
Okamoto I. <i>et al.</i> (2020)	Comparison of carboplatin plus pemetrexed followed by maintenance pemetrexed with docetaxel monotherapy in elderly patients with advanced nonsquamous nonsmall-cell lung cancer a phase 3 randomized clinical trial	RCT		3	Phase 3, randomized, open-label clinical trial	403 elderly patients	From 2013 to 2016
Lu S. <i>et al.</i> (2020)	Nivolumab versus docetaxel in a predominantly Chinese patient population with previously treated advanced nonsmall-cell lung cancer: 2-year follow-up from a randomized, open-label, phase 3 study (CheckMate 078)	RCT		2	Phase 3, randomized, open-label trial	431 patients	From 2014 to 2017
Vokes E.E. <i>et al.</i> (2018)	Comparison of carboplatin plus pemetrexed followed by maintenance pemetrexed with docetaxel monotherapy in elderly patients with advanced nonsquamous nonsmall-cell lung cancer a phase 3 randomized clinical trial	RCT		3	Phase 3, randomized, open-label clinical trial	452 elderly patient	From 2013 to 2016

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Supplementary Table 7: Contd...

Paper (year)	Title	Design	NOS	Jadad	Study type	Sample size	Observation period
Taniguchi Y. <i>et al.</i> (2022)	A Randomized Comparison of Nivolumab versus Nivolumab+Docetaxel for Previously Treated Advanced or Recurrent ICI-Naïve NonSmall-Cell Lung Cancer: TORG1630	RCT		3	Phase 2, randomized, open-label trial	210 patients	From 2018 to 2021
Hayashi H. <i>et al.</i> (2022)	A Randomized Phase II Study Comparing Nivolumab with Carboplatin–Pemetrexed for <i>EGFR</i> -Mutated NSCLC with Resistance to <i>EGFR</i> Tyrosine Kinase Inhibitors (WJOG8515L)	RCT		3	Phase 2, randomized, open-label trial	218 patients	From 2017 to 2020
Forde P.M. <i>et al.</i> (2022)	Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer	RCT		3	Phase 2, randomized, open-label trial	358 patients	From 2019 to 2021
Noronha V. <i>et al.</i> (2019)	Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in <i>EGFR</i> -mutated lung cancer	RCT		3	Phase 2, randomized, open-label trial	210 patients	From 2014 to 2017
Gettinger S.N. <i>et al.</i> (2022)	Nivolumab plus ipilimumab versus nivolumab for previously treated patients with stage IV Squamous cell lung cancer the lung-MAP S1400I Phase 3 randomized clinical trial	RCT		3	Phase 3, randomized, open-label clinical trial	714 patients	From 2015 to 2020
Paz-Ares L. <i>et al.</i> (2018)	Pembrolizumab plus chemotherapy for squamous nonsmall-cell lung cancer	RCT		5	Phase 3, randomized, double-blind trial	559 patients	From 2016 to 2017
Takamochi K. <i>et al.</i> (2021)	Randomized phase II trial of pemetrexed-cisplatin plus bevacizumab or thoracic radiotherapy followed by surgery for stage IIIA (N2) nonsquamous nonsmall-cell lung cancer	RCT		3	Phase 2, randomized, open-label trial	120 patients	From 2014 to 2018
Camidge D.R. <i>et al.</i> (2022)	A Randomized, Open-Label Phase II Study Evaluating Emibetuzumab Plus Erlotinib and Emibetuzumab Monotherapy in MET Immunohistochemistry Positive NSCLC Patients with Acquired Resistance to Erlotinib	RCT		3	Phase 2, randomized, open-label trial	240 patients	From 2017 to 2020
Nie K.K. <i>et al.</i> (2018)	Osimertinib compared docetaxel-bevacizumab as third-line treatment in <i>EGFR</i> T790M mutated nonsmall-cell lung cancer	RCT		3	Phase 3, randomized, open-label trial	419 patients	From 2015 to 2017
Xiong L.W. <i>et al.</i> (2019)	Efficacy of erlotinib as neoadjuvant regimen in <i>EGFR</i> -mutant locally advanced nonsmall-cell lung cancer patients	PR	8		Phase II, single-arm, open-label trial	47 patients	From 2016 to 2018
Yang J.C.H. <i>et al.</i> (2020)	Efficacy and safety of rociletinib versus chemotherapy in patients with <i>EGFR</i> -mutated NSCLC: The Results of TIGER-3, a phase 3 randomized study	RCT		3	Phase 3, randomized, open-label trial	435 patients	From 2015 to 2019
Zemanova M. <i>et al.</i> (2021)	Autologous dendritic cell-based immunotherapy (DCVAC/LuCa) and carboplatin/paclitaxel in advanced nonsmall-cell lung cancer: A randomized, open-label, phase I/II trial	RCT		3	Phase 1/2, randomized, open-label trial	107 patients	From 2016 to 2020.
Nishio M. <i>et al.</i> (2020)	Ramucirumab or placebo plus erlotinib in <i>EGFR</i> -mutated, metastatic nonsmall-cell lung cancer: East Asian subset of RELAY	RCT		5	Phase 3, randomized, double-blind, placebo-controlled trial	232 patients	From 2016 to 2019
Akamatsu H. <i>et al.</i> (2018)	Osimertinib in Japanese patients with <i>EGFR</i> T790M mutation-positive advanced nonsmall-cell lung cancer: AURA3 trial	RCT		3	Phase 3, multicenter, randomized, open-label trial	219 patients	From 2014 to 2017
Ramalingam S.S. <i>et al.</i> (2021)	Veliparib in combination with platinum-based chemotherapy for first-line treatment of advanced squamous cell lung cancer: A randomized, multicenter phase III study	RCT		5	A Randomized, Multicenter Phase III Study	1000 patients	From 2016 to 2020

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Paper (year)	Title	Design	NOS	Jadad	Study type	Sample size	Observation period
Byers L.A. <i>et al.</i> (2021)	Veliparib in combination with carboplatin and etoposide in patients with treatment-naïve extensive-stage small cell lung cancer: A phase 2 randomized study	RCT		5	A Phase 2 Randomized Study	181 patients	From 2016 to 2019
Argiris A. <i>et al.</i> (2021)	A dose-finding study followed by a phase II randomized, placebo-controlled trial of chemoradiotherapy with or without veliparib in stage III non-small-cell lung cancer: SWOG 1206 (8811)	RCT		3	Phase 2 randomized, placebo-controlled trial	640 participants	From 2012 to 2018
Shimokawa T. <i>et al.</i> (2020)	Randomized phase II trial of S-1 plus cisplatin or docetaxel plus cisplatin with concurrent thoracic radiotherapy for inoperable stage III non-small cell lung cancer	RCT		3	A Phase 2, multicenter, randomized, open-label clinical trial	120 patients	From December 2012 to January 2016.
Xing L.G. <i>et al.</i> (2021)	Erlotinib versus etoposide/cisplatin with radiation therapy in unresectable stage III epidermal growth factor receptor mutation-positive non-small-cell lung cancer: A multicenter, randomized, Open-Label, Phase 2 Trial	RCT		3	A Phase 2, multicenter, randomized, open-label clinical trial	120 patients	From December 2012 to January 2016
Zhong W.Z. <i>et al.</i> (2022)	Erlotinib versus gemcitabine plus cisplatin as neoadjuvant treatment of stage IIIA-N2 <i>EGFR</i> -mutant non-small-cell lung cancer: Final overall survival analysis of the EMERGINGCTONG 1103 randomized phase II trial	RCT		3	A Phase 2, open-label, randomized controlled trial	72 patients	From 2014 to 2018. The median follow-up duration for the study was 62.5 months
Kiura K. <i>et al.</i> (2018)	Phase 3 study of ceritinib versus chemotherapy in ALK-rearranged NSCLC patients previously treated with chemotherapy and crizotinib (ASCEND-5): Japanese subset	RCT		2	A Phase 3, open-label, randomized, multicenter clinical trial	29 patients	From 2013 to 2016, with a median follow-up duration of 16.6 months
Wang Z.J. <i>et al.</i> (2022)	Toripalimab Plus chemotherapy for patients with treatment-naïve advanced non-small-cell lung cancer: A multicenter randomized phase III trial (CHOICE-01)	RCT		3	A Phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial	465 patients	From April 2019 to August 2020
Lee Y.J. <i>et al.</i> (2022)	A randomized phase 2 study to compare erlotinib with or without bevacizumab in previously untreated patients with advanced non-small-cell lung cancer with <i>EGFR</i> mutation	RCT		3	A Phase 2, randomized, open-label clinical trial	108 patients	From September 2017 to September 2022, with a median follow-up duration of 15.3 months
Hou X. <i>et al.</i> (2023)	Gefitinib plus chemotherapy versus Gefitinib alone in untreated <i>EGFR</i> -mutant non-small-cell lung cancer in patients with brain metastases the GAP BRAIN open-label, randomized, multicenter, phase 3 study	RCT		3	A Phase 3, open-label, randomized, multicenter clinical trial	161 patients	From January 13, 2016, to August 27, 2021, with a median follow-up time of 21.1 months
Novello S. <i>et al.</i> (2022)	Pembrolizumab plus chemotherapy in squamous non-small-cell lung cancer: 5-year update of the phase III KEYNOTE-407 Study	RCT		5	A Phase 3, randomized, double-blind, placebo-controlled trial	559 patients	The median follow-up duration was 56.9 months; from 2016 to 2022

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Paper (year)	Title	Design	NOS	Jadad	Study type	Sample size	Observation period
Garassino M.C. <i>et al.</i> (2023)	Pembrolizumab plus pemetrexed and platinum in nonsquamous non-small-cell lung cancer: 5-year outcomes from the phase 3 KEYNOTE-189 study	RCT		5	A Phase 3, randomized, double-blind, placebo-controlled trial	616 patients	The median follow-up duration was 64.6 months
Kim E.J. <i>et al.</i> (2022)	A phase I/IIa randomized trial evaluating the safety and efficacy of SNK01 plus pembrolizumab in patients with stage IV non-small-cell lung cancer	RCT		3	A Phase 1/2a Randomized Trial	18 patients	From 2019 to 2021
Senan S. <i>et al.</i> (2022)	Outcomes with durvalumab after chemoradiotherapy in stage IIIA-N2 non-small-cell lung cancer: An exploratory analysis from the PACIFIC trial	RCT		5	The PACIFIC trial, a pivotal phase 3 study	713 patients	From 2014 to 2020
Peters S. <i>et al.</i> (2022)	Atezolizumab versus chemotherapy in advanced or metastatic NSCLC with high blood-based tumor mutational burden: Primary analysis of BFAST cohort C randomized phase 3 trial	RCT		3	A randomized, open-label, phase 3 clinical trial	471 patients	From 2017 to 2020
Leighl N.B. <i>et al.</i> (2022)	CCTG BR34: A randomized phase 2 trial of durvalumab and tremelimumab with or without platinum-based chemotherapy in patients with metastatic NSCLC	RCT		3	A randomized Phase 2 Trial	301 patients	From 2017 to 2020
Papadimitrakopoulou V.A. <i>et al.</i> (2020)	Osimertinib versus platinum-pemetrexed for patients with <i>EGFR</i> T790M advanced NSCLC and progression on a prior <i>EGFR</i> -tyrosine kinase inhibitor: AURA3 overall survival analysis	RCT		5	A randomized, open-label, phase 3 clinical trial	419 patients	From 2014 to 2019
Piccirillo M.C. <i>et al.</i> (2022)	Addition of bevacizumab to erlotinib as first-line treatment of patients with <i>EGFR</i> -mutated advanced non-squamous NSCLC: The BEVERLY Multicenter randomized phase 3 trial	RCT		5	A multicenter, randomized, open-label, phase 3 clinical trial	200 patients	From 2015 to 2019
de Castro G. <i>et al.</i> (2022)	NEPTUNE: Phase 3 Study of First-Line Durvalumab Plus Tremelimumab in Patients With Metastatic NSCLC	RCT		3	A phase 3, open-label, randomized controlled trial	823 patients	From 2019 to 2022
Otsubo K. <i>et al.</i> (2022)	Nintedanib plus chemotherapy for non-small-cell lung cancer with idiopathic pulmonary fibrosis: A randomized phase 3 trial	RCT		3	A randomized, open-label, phase 3 clinical trial	400 patients	From 2017 to 2021
Zhou C.C. <i>et al.</i> (2022)	Tislelizumab versus docetaxel in patients with previously treated advanced NSCLC (RATIONALE-303): A phase 3, open-label, randomized controlled trial	RCT		3	A randomized, open-label, phase 3 clinical trial	805 patients	From November 30, 2017, to July 15, 2021
Aix S.P. <i>et al.</i> (2023)	Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (ATLANTIS): A multicenter, randomized, open-label, phase 3 trial	RCT		3	A randomized, open-label, phase 3 clinical trial	600 patients	From 2019 to 2022
Zhong W.Z. <i>et al.</i> (2023)	Erlotinib versus gemcitabine plus cisplatin as neoadjuvant treatment of stage IIIA-N2 <i>EGFR</i> -mutant non-small-cell lung cancer: Final overall survival analysis of the EMERGINGCTONG 1103 randomized phase II trial	RCT		3	A randomized, controlled, open-label phase II clinical trial	54 patients	From 2014 to 2019
de Langen A.J. <i>et al.</i> (2023)	Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with <i>KRAS</i> G12C mutation: A randomized, open-label, phase 3 trial	RCT		3	A randomized, open-label, phase 3 clinical trial	354 patients	From 2019 to 2022

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Supplementary Table 7: Contd...

Paper (year)	Title	Design	NOS	Jadad	Study type	Sample size	Observation period
Dai F.Q. <i>et al.</i> (2022)	Neoadjuvant immunotherapy combined with chemotherapy significantly improved patients' overall survival when compared with neoadjuvant chemotherapy in nonsmall-cell lung cancer: A cohort study	RS+PS	8		A retrospective cohort analysis	180 patients	From 2011 to 2017
Miyauchi E. <i>et al.</i> (2022)	Updated analysis of NEJ009: Gefitinib-alone versus gefitinib plus chemotherapy for nonsmall-cell lung cancer with mutated <i>EGFR</i>	RCT		3	A randomized, controlled, open-label phase 3 clinical trial	230 patients	From 2011 to 2017
Gogishvili M. <i>et al.</i> (2022)	Cemiplimab plus chemotherapy versus chemotherapy alone in nonsmall-cell lung cancer: A randomized, controlled, double-blind phase 3 trial	RCT		5	A randomized, controlled, double-blind phase 3 clinical trial	466 patients	From August 2019 to December 2021
Huang Z. <i>et al.</i> (2022)	PD-1 inhibitor versus bevacizumab in combination with platinum-based chemotherapy for first-line treatment of advanced lung adenocarcinoma: A retrospective-real world study	RS	8		A retrospective-real world study	276 patients	From January 2018 to March 2021
Senan S. <i>et al.</i> (2022)	Outcomes with durvalumab after chemoradiotherapy in stage IIIA-N2 nonsmall-cell lung cancer: An exploratory analysis from the PACIFIC trial	RCT		5	<i>Post hoc</i> exploratory analysis of a randomized, double-blind, placebo-controlled phase 3 trial	713 patients	Between May 2014 and April 2016
Chen Y.B. <i>et al.</i> (2022)	Impact of brain metastases on treatment patterns and outcomes with first-line durvalumab plus platinum-etoposide in extensive-stage SCLC (CASPIAN): A brief report	RCT		3	<i>Post hoc</i> analysis of the phase 3 CASPIAN trial	805 patients	From March 14, 2017, to May 29, 2018
Shi Y.K. <i>et al.</i> (2022)	Sintilimab versus docetaxel as second-line treatment in advanced or metastatic squamous nonsmall-cell lung cancer: An open-label, randomized controlled phase 3 trial (ORIENT-3)	RCT		3	Open-label, randomized controlled phase 3 trial	290 patients	From August 25, 2017, to November 7, 2018
Lu S. <i>et al.</i> (2020)	Nivolumab versus docetaxel in a predominantly Chinese patient population with previously treated advanced nonsmall-cell lung cancer: 2-year follow-up from a randomized, open-label, phase 3 study (CheckMate 078)	RCT		3	Randomized, open-label, phase 3 clinical trial	504 patients	From November 2014 to August 2016
Sugawara S. <i>et al.</i> (2021)	Nivolumab with carboplatin, paclitaxel, and bevacizumab for first-line treatment of advanced nonsquamous nonsmall-cell lung cancer	RCT		5	Phase 2, open-label, single-arm, multicenter trial	40 patients	A median duration of 14.2 months; from June 2017 to March 2019
West H.J. <i>et al.</i> (2022)	Clinical efficacy of atezolizumab plus bevacizumab and chemotherapy in <i>KRAS</i> -mutated nonsmall-cell lung cancer with <i>STK11</i> , <i>KEAP1</i> , or <i>TP53</i> comutations: Subgroup results from the phase III IMpower150 trial	RCT		2	<i>Post hoc</i> analysis of the randomized, open-label, phase 3 IMpower150 trial	1202 patients	From February 2015 to December 2016
Zhou Q. <i>et al.</i> (2022)	Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III nonsmall-cell lung cancer in China (GEMSTONE-301): Interim results of a randomized, double-blind, multicentre, phase 3 trial	RCT		5	Randomized, double-blind, placebo-controlled, phase 3 trial	381 patients	August 30, 2018–December 30, 2020

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Supplementary Table 7: Contd...

Paper (year)	Title	Design	NOS	Jadad	Study type	Sample size	Observation period
Zhou C.C. <i>et al.</i> (2022)	Sugemalimab versus placebo, in combination with platinum-based chemotherapy, as first-line treatment of metastatic nonsmall-cell lung cancer (GEMSTONE-302): Interim and final analyses of a double-blind, randomized, phase 3 clinical trial	RCT		5	Double-blind, randomized, Phase 3 trial	479 patients	Median follow-up of 8.6 months; from 2018 to 2021
Wolf J. <i>et al.</i> (2022)	Final efficacy and safety data, and exploratory molecular profiling from the phase III ALUR study of alectinib versus chemotherapy in crizotinib-pretreated ALK-positive non-small-cell lung cancer	RCT		3	Open-label, randomized, Phase 3 trial	119 patients	From 2016 to 2018
Gadgeel S. <i>et al.</i>	Comparison of SP142 and 22C3 Immunohistochemistry PD-L1 assays for clinical efficacy of atezolizumab in nonsmall-cell lung cancer: Results from the randomized OAK Trial	RCT		2	Randomized, open-label, Phase 3 trial	1225 patients	From 2013 to 2016; Median follow-up of 14.1 months
Peters S. <i>et al.</i> (2021)	Consolidation nivolumab and ipilimumab versus observation in limited disease small-cell lung cancer after chemo-radiotherapy e results from the randomized phase II ETOP/IFCT 4-12 STIMULI trial	RCT		3	Open-label, randomized, Phase 2 trial	100 patients	From 2012 to 2018
Pechoux C.L. <i>et al.</i> (2022)	Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected nonsmall-cell lung cancer and proven mediastinal N2 involvement (Lung ART, IFCT 0503): An open-label, randomized, phase 3 trial	RCT		3	Open-label, randomized, Phase 3 trial	501 patients	From 2005 to 2018
Tada H. <i>et al.</i> (2021)	Randomized phase III study of gefitinib versus cisplatin plus vinorelbine for patients with resected stage II-IIIa nonsmall-cell lung cancer with <i>EGFR</i> mutation (IMPACT)	RCT		3	Randomized, open-label, Phase 3 trial	234 patients	Median follow-up of 35.9 months. From 2014 to 2018
Wang X.S. <i>et al.</i> (2022)	Randomized trial of first-line tyrosine kinase inhibitor with or without radiotherapy for synchronous oligometastatic <i>EGFR</i> -mutated nonsmall-cell lung cancer	RCT		3	Multicenter, randomized Phase 2 trial	133 patients	The median follow-up was 23.6 months From 2018 to 2021
Soo R.A. <i>et al.</i> (2021)	A randomised phase II study of osimertinib and bevacizumab versus osimertinib alone as second-line targeted treatment in advanced NSCLC with confirmed <i>EGFR</i> and acquired T790M mutations: The European Thoracic Oncology Platform (ETOP 10-16) BOOSTER trial	RCT		3	Open-label, randomized Phase 2 trial	155 patients	The median follow-up duration was 33.8 months
Bylicki O. <i>et al.</i> (2023)	Atezolizumab with or without bevacizumab and platinum-pemetrexed in patients with stage IIIB/IV nonsquamous nonsmall-cell lung cancer with <i>EGFR</i> mutation, ALK rearrangement or ROS1 fusion progressing after targeted therapies: A multicentre phase II open-label nonrandomized study GFPC 06-2018	PR	9		Multicenter, Phase 2, open-label, nonrandomized study	40 patients	From 2018 to 2021; The median follow-up duration was 12.5 months

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Paper (year)	Title	Design	NOS	Jadad	Study type	Sample size	Observation period
Mazieres J. <i>et al.</i> (2020)	Atezolizumab versus docetaxel in pretreated patients with NSCLC: Final results from the randomized phase 2 POPLAR and phase 3 OAK clinical trials	RCT		3	POPLAR Study: This Phase 2 trial randomized OAK Study: This Phase 3 trial randomized	POPLAR Study: 287 patients OAK Study: between 1225 patients	POPLAR Study: between 2014 and 2015 OAK Study: between 2014 and 2016
Han Y. <i>et al.</i> (2021)	Autologous cytokine-induced killer (CIK) cells enhance the clinical response to PD-1 blocking antibodies in patients with advanced non-small-cell lung cancer: A preliminary study	RS	8		Preliminary, single-center, open-label study	18 patients	From 2017 to 2019
Hart L.L. <i>et al.</i> (2021)	Myelopreservation with trilaciclib in patients receiving topotecan for small-cell lung cancer: Results from a randomized, double-blind, placebo-controlled phase II study	RCT		5	Phase 2, randomized, double-blind, placebo-controlled trial	61 patients	From 2018 to 2019
Spigel D.R. <i>et al.</i> (2020)	Nanoparticle albumin-bound paclitaxel plus carboplatin induction followed by nanoparticle albumin-bound paclitaxel maintenance in squamous non-small-cell lung cancer (ABOUND.sqm): A phase III randomized clinical trial	RCT		3	Phase 3, randomized clinical trial	420 patients	The median follow-up duration was 24.2 months
Aix S.P. <i>et al.</i> (2021)	RELAY, ramucirumab plus erlotinib versus placebo plus erlotinib in patients with untreated, <i>EGFR</i> -mutated, metastatic non-small-cell lung cancer: Europe/United States subset analysis	RCT		5	Phase 3, double-blind, placebo-controlled trial	449 patients	The median follow-up duration was 20.7 months
Goldman J.W. <i>et al.</i> (2021)	Durvalumab, with or without tremelimumab, plus platinum–etoposide versus platinum–etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): Updated results from a randomized, controlled, open-label, phase 3 trial	RCT		3	Phase 3, open-label, randomized trial	805 patients	As of March 22, 2021, the median follow-up duration was 39.4 months
Yamamoto N. <i>et al.</i> (2021)	Erlotinib plus bevacizumab versus erlotinib monotherapy as first-line treatment for advanced <i>EGFR</i> mutation-positive non-squamous non-small-cell lung cancer: Survival follow-up results of the randomized JO25567 study	RCT		3	Randomized phase 2 trial	152 patients	The median follow-up duration was 34.7 months
Park K. <i>et al.</i> (2021)	Avelumab versus Docetaxel in patients with platinum-treated advanced NSCLC: 2-year follow-up from the JAVELIN lung 200 phase 3 trial	RCT		3	Phase 3, open-label, randomized trial	792 patients	From 2015 to 2021
Spigel D.R. <i>et al.</i> (2020)	Randomized phase 2 studies of checkpoint inhibitors alone or in combination with Pegiloddecakin in patients with metastatic NSCLC (CYPRESS 1 and CYPRESS 2)	RCT		5	Both are randomized phase 2 study	CYPRESS 1: Enrolled 101 patients CYPRESS 2: Enrolled 52 patients	CYPRESS 1: Median follow-up of 10.0 months CYPRESS 2: Median follow-up of 11.6 months

RCT: Randomized controlled trial, PR: Prospective study, RS: Retrospective study, PS: Propensity score, NOS: Newcastle–Ottawa Scale, NSCLC: Nonsmall-cell lung cancer

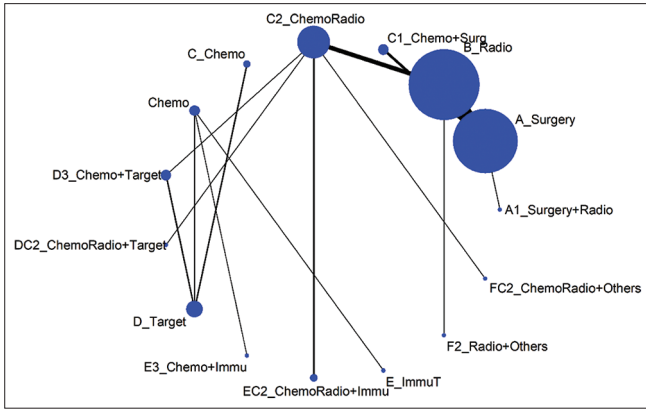


Figure S1: Network map of response/progression-free survival rate (nonadvanced stage)

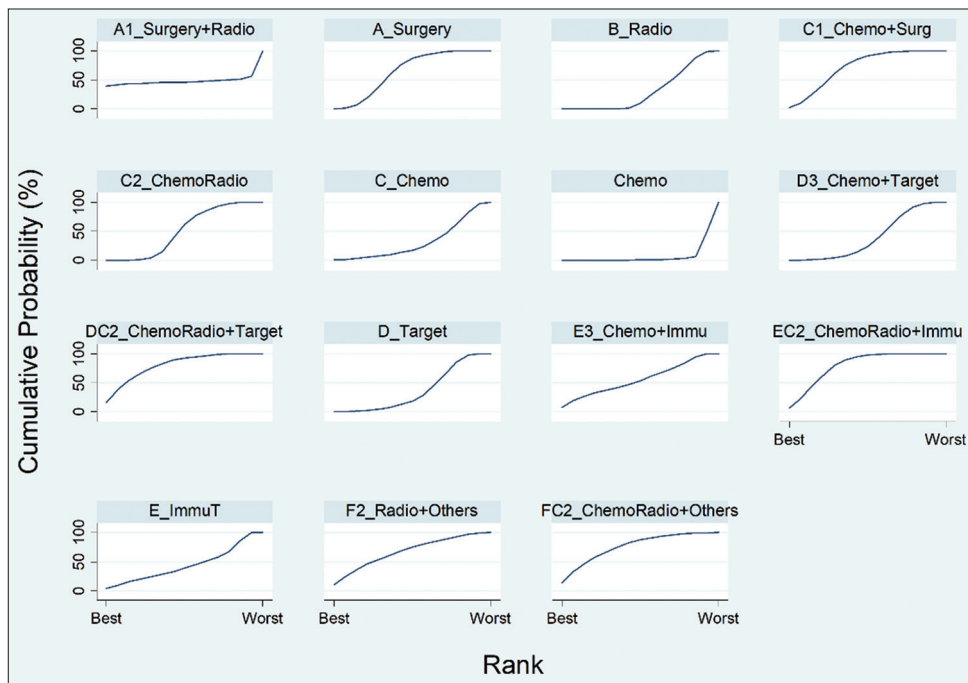


Figure S2: Rankogram for the nonadvanced lung cancer in response rate

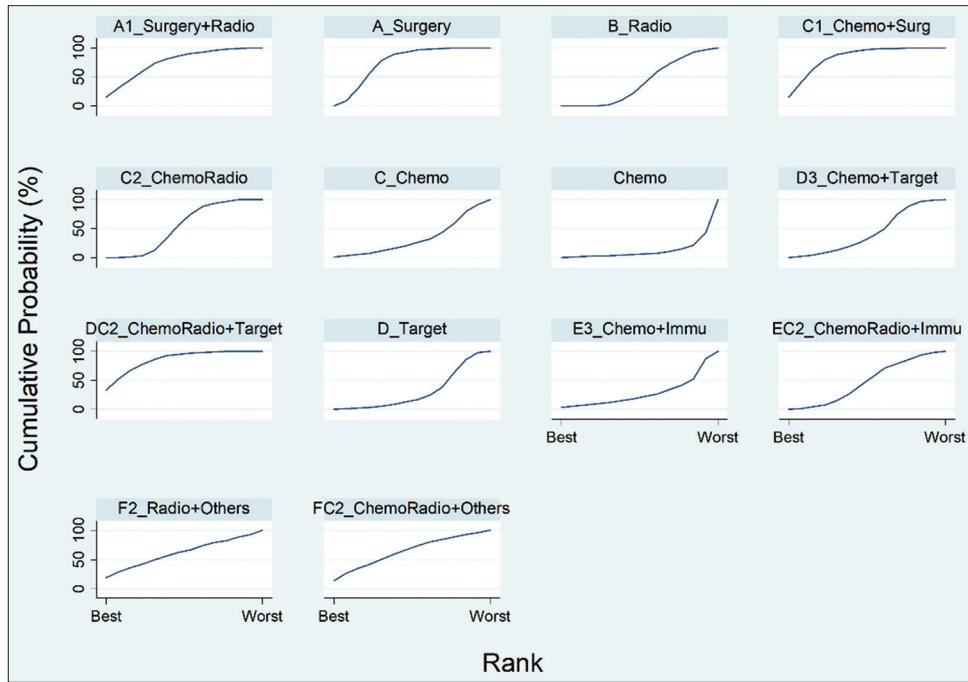


Figure S3: Rankogram for the nonadvanced lung cancer in progression-free survival rate