 doi:10.20944/preprints202005.0478.v1

Multiple chemotherapy-based combination therapy strategies for advanced lung cancer patients: a systematic review and network meta-analysis

Xiong Lecai[1]MD, Bai Yuquan[1]MD, Zhou Xuefeng[1]PhD, Xu Ming[1]PhD, Pan Gaofeng[1]PhD, Zhao Jinping[1]PhD, Tang Hexiao[1] *PhD

[1] Department of Thoracic Surgery, Zhongnan Hospital of Wuhan University, Wuhan 430071, China

***Correspondence to**:

Tang Hexiao, MD, Ph. D, the Department of Thoracic Surgery, Zhongnan Hospital of Wuhan University, Wuhan 430071, China. Telephone number: +86-15102723563. E-mail: xuking0322@sina.com.

Running head: Chemotherapy Combined with the PD-1 Inhibitor.

Abbreviations:

OS: overall survival

PFS: progression-free survival

ORR: objective response rate

CT: Chemotherapy/Chemotherapy plus placebo

CT+T: chemotherapy plus one targeted therapy drug

CT+T+T: chemotherapy plus two targeted therapy drugs

CT+I: chemotherapy combined with immunotherapy

CT+B: chemotherapy combined with biotherapy

 doi:10.20944/preprints202005.0478.v1

NMA: network meta-analysis

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

HR: hazard ratio

CI: confidence interval

SE: standard error

IPD: individual patient data

OR: odds ratios

NSCLC: non-small cell lung cancer

SCLC: small cell lung cancer

MCMC: Markov Chain Monte Carlo

 doi:10.20944/preprints202005.0478.v1

Abstract:

Background: At present, the treatments for patients with advanced lung cancer focus on chemotherapy, targeted therapy, immunotherapy, or a combination of multiple treatments.

Purpose: The main purpose of this study is to compare the various chemotherapy-based combination therapies and find the best one for patients with advanced lung cancer.

Methods: Based on database (PubMed, EMBASE and Medline) for randomized controlled trials of advanced lung cancer with combination therapy from 2008 to 2020, we searched literatures with overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and adverse as outcome indicators and established a Bayesian mesh meta-analysis for multiple treatment strategies. Then, we combined the results of four outcome indicators to find out the best chemotherapy-based combination therapy strategy for patients with advanced lung cancer, further, we tried to screen out the best drugs of which were commonly used now.

Results: It contained a total of 51 studies, including five combination therapies: Chemotherapy/Chemotherapy plus placebo (CT), chemotherapy plus one targeted therapy drug (CT+T), chemotherapy plus two targeted therapy drugs (CT+T+T), chemotherapy combined with immunotherapy (CT+I) or chemotherapy combined with biotherapy (CT+B). In terms of four outcome indicators, CT+I showed the best therapeutic benefits. In the comparison of immunotherapy drugs, pembrolizumab showed the best effect.

Conclusion: Our results showed that, among the multiple chemotherapy-based

 doi:10.20944/preprints202005.0478.v1

combination therapy strategies, chemotherapy combined with immunotherapy is the best choice for patients with advanced lung cancer, and pembrolizumab combined with chemotherapy has the best effect.

Keywords: advanced lung cancer, network-meta analysis, combination therapy, chemotherapy

 doi:10.20944/preprints202005.0478.v1

Introduction:

Lung cancer is the most common type of malignancy worldwide and is also the leading cause of cancer-related deaths (18.4% of the total number of cancer deaths) [1]. More than 50% of patients diagnosed at a distant metastasis, for which the median overall survival (OS) is less than 1 year and the 5-year survival rate is only 4% [2].

For decades, platinum-based chemotherapy has been the main treatment for most patients with advanced lung cancer. But with the emergence and development of targeted therapy and immunotherapy in recent years, patients have more choices. More and more clinical trials have confirmed that both targeted therapy [3, 4] and immunotherapy [5-7] can bring survival benefits to patients in advanced stage. Therefore, the current status of coexistence of three treatment methods (chemotherapy, targeted therapy and immunotherapy) for patients with advanced lung cancer has been formed. However, the current status of treatment for patients with advanced lung cancer is still not optimistic. Targeted therapy only works well in patients with specific mutants [8], and even in the presence of mutants, most patients will experience various degrees of resistance in the coming months after using targeted therapy [9]. In addition, studies have shown that immunotherapy works only in a small number of patients, and many patients who initially responded quickly showed disease progression [10]. Therefore, it is imperative to find a more universal and effective treatment for patients with advanced lung cancer. In the clinical treatment of advanced lung cancer, combination therapy is an important way to avoid various drawbacks of using single drug. Some studies have shown that targeted therapy [11] [12] or immunotherapy [13] combined with

 doi:10.20944/preprints202005.0478.v1

chemotherapy can achieve better prognosis, but there is still controversy [14]. Therefore, this study compared the efficacy of several combination treatments (targeted therapy, immunotherapy or other treatments combined with chemotherapy).

Because this article involves multiple treatments and there is a lack of head-to-head research between some treatment strategies, traditional meta-analysis is not feasible. Bayesian network meta-analysis (NMA) is proper to be used, which allows direct and indirect comparison of multiple treatment modalities [15]. And this method can combine all the data into a single analysis, which can avoid the selection bias and information loss that may exist when analyzing individual statistics separately [16]. In search of the best combination therapy, we performed a random-effect network meta-analysis of five treatments, chemotherapy or chemotherapy plus placebo (CT), chemotherapy plus one targeted drug (CT+T), chemotherapy plus two targeted drugs (CT+T+T), chemotherapy combined with immunotherapy (CT+I), and chemotherapy combined with biological therapy (CT+B, oncolytic virus or pseudomonas aeruginosa preparation).

Methods:

1. Search strategy and selection criteria

We conducted a systematic literature search based on the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [17]. All clinical studies involving multiple treatments for lung cancer from January 2008 to May 2020 were searched through PubMed, EMBASE, and Medline databases. Then we

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2020 doi:10.20944/preprints202005.0478.v1

reviewed all manuscripts and filtered them according to the following inclusion and exclusion criteria. Inclusion criteria: 1) Randomized controlled trial (RCT); 2) A multi-arm study involving two or more of the above five treatment strategies (CT, CT+T, CT+T+T, CT+I, CT+B); 3) Subject for advanced lung cancer. Exclusion criteria: 1) Non-RCT; 2) One-arm study; 3) Non-chemotherapy-based combination therapy; 4) Comparison between the same treatment strategies; 5) Non-advanced lung cancer.

2. Data extraction and assessment for risk of bias

Two evaluators (Lecai Xiong, Yuquan Bai) independently screened the literatures, extracted the data, and cross-checked. If the results were not uniform, we consulted with the third evaluator (Hexiao Tang). And then disagreements were discussed and resolved with the consensus of all evaluators. We conducted a risk assessment of the final included studies through the Cochrane bias risk assessment methodology, and summarized all the treatment strategies included in the study into five categories: CT, CT+T, CT+T+T, CT+I, CT+B (one is chemotherapy combined with oncolytic virus [18] and another is chemotherapy combined with pseudomonas aeruginosa preparation [19], we collectively refer them as chemotherapy combined with biological therapy). The basic information was extracted, such as research authors, publication time, and treatment strategies in the trials. The median overall survival (OS) and progression-free survival (PFS) were included as primary outcome measures, treatment objective response rate (ORR) and adverse were used as secondary outcome measures. We only focused on grade 3–4 adverse because grade 12 had lesser clinical significance and was not consistently reported in the included trials.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2020 doi:10.20944/preprints202005.0478.v1

3. Statistical process

OS, PFS, ORR and grade 3–4 adverse were used as the outcome measures. In order to balance the heterogeneity in different trials, we constructed a random effects model for meta-analysis. The network meta-analysis of OS and PFS used HRs and 95% CI data reported in the primary publications. When HRs were not reported, we estimated them from summary statistics with the method described by Tierney and colleagues [20]. We further calculated LnHR and its standard error (SE) according to the Cochrane handbook, then we corrected the LnHR and its SE in multi-arm trials [16]. In addition, there are comparisons between two or more of the same treatment strategies in some multi-arm trials [21-24]. The survival curve from the original manuscript was extracted and quantified by Engauge Digitizer 10.8 software, and then the individual patient data (IPD) was obtained through the "MASS", "splines", and "survival" R packages. By merging IPDs of the same treatment strategy, the new survival curves, HRs and its SE [25] were obtained. For the trails involving the same treatment strategy that cannot be combined, we randomly select one of the cohorts for analysis [26] [27] [28]. Finally, LnHR and its SE were used as initial data for network meta-analysis. For ORR and adverse, we calculated odds ratios (ORs) based on the number of total patients and the number of patients who responded or had an adverse reaction in each trial for meta-analysis, and merged data by direct superposition.

Bayesian network meta-analysis was done with “gemtc” package in R-3.4.3 [29-31]. We used non-informative uniform and normal prior distributions and three different sets of starting values to fit the model [15], yielding 20000 iterations (5000 per chain)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2020 doi:10.20944/preprints202005.0478.v1

to obtain the posterior distributions of model parameters [32]. In the OS and PFS groups, "cloglog" was used as the connection function, and in the ORR and the reverse group was "log".

Results

1. Search results and assessment for the risk of bias

The literature search identified a total of 3673 articles, among which we removed 3481 articles according to the title and abstract. We reviewed the full texts of 192 studies. Of these, studies of assessing two identical treatment strategies (n=37), non-chemotherapy-based combination therapy (n=34), no corresponding outcome indicator (n=22), non-RCT (n=14), assessing non-advanced lung cancer (n=12), assessing other treatments (n=12), one-arm study (n=10) were excluded. Finally, the remaining 51 studies were included in the analysis (Supplemental materials, Table A1). A flow chart of study selection is showed in Figure 1. We conducted a risk assessment of the included studies based on the Cochrane bias risk assessment methodology (Supplemental materials, Figure A1).

2. Characteristics of eligible studies

The including trials were all randomized controlled trials of Phase II/Phase III, a total of 23491 patients, all of them were patients with stage III-IV non-small cell lung cancer (NSCLC) or patients with extensive-stage small cell lung cancer (SCLC), and 42 trials were done in patients with NSCLC, 9 trials were done in patients with SCLC. Of the included trails, 50 trials connected to OS, 47 trials connected to PFS, 19 trials

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2020 doi:10.20944/preprints202005.0478.v1

for ORR, and 20 trials for adverse were analyzed respectively (Table A1).

3. Data collection and calculation

The values of OS and PFS related LnHR and its SE were obtained as described in the method, merged IPDs and made correction in multi-arm trials (Table 1). The ORR and adverse data were extracted from the included trials and summarized as Table A2.

4. Data analysis results

4.1 **Building networks**

Figure 2 is a network plot we built with stata/MP 13.1, it showed that among the 23491 patients included in the network meta-analysis, 10254 received sample chemotherapy or chemotherapy plus placebo (CT), 9621 patients received chemotherapy plus one targeted drug (CT+T), 1086 patients received chemotherapy plus two targeted drugs (CT+T+T), 2417 received chemotherapy combined with immunotherapy (CT+I), and 113 patients received chemotherapy combined with biological therapy (CT+B). We can see that the most frequently compared in the four analyses are CT and CT+T. CT+T, CT+T+T, CT+I and CT+B are directly compared with CT, and the numbers of cohorts in each group directly compared with CT are 35, 1, 10 and 2 respectively. There are also five comparisons between CT+T and CT+T+T, and one comparison between CT+T and CT+I.

4.2 **Markov Chain Monte Carlo (MCMC)**

We plotted trace plots, density plots, and Brooks-Gelman-Rubin diagnosis plots in R to assess the convergence and stability of the model. Each group of trace plots showed that each MCMC chain overlaps, and the visual perception does not recognize any one

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2020 doi:10.20944/preprints202005.0478.v1

chain. All density plots showed a normal distribution and the bandwidth values approach zero. All above results prove that the model is very satisfactory [33]. In the Brooks-Gelman-Rubin diagnosis plots, the median value and the 97.5% value of the shrink factor both approached 1.0 and fit each other after 20,000 iterations, further showing that the model has good convergence [34]. The results can be found in supplemental materials (Figure A2).

4.3 **Differences in efficacy among five combination therapy strategies**

We summarized the results of pairwise comparisons in the NMA as shown in Table 2. As shown in the table, in the OS analyses, the hazard ratios of CT+T, CT+T+T, CT+I, CT+B comparing with CT were 0.91(95% confidence interval, 95% CI, 0.86, 0.96), 0.89(95% CI, 0.75, 1.1), 0.78(95% CI, 0.70, 0.85), 1.1(95% CI, 0.77, 1.40) respectively, which means all therapy strategies except CT+B were significantly superior to CT in the subgroup of OS. And the HRs of CT+T+T, CT+I comparing with CT+T were 0.98(95% CI, 0.84, 1.2), 0.85(95% CI, 0.76, 0.95) respectively, indicating that the CT+T+T and CT+I group had longer survival than the CT+T group. Finally, comparing with CT+T+T, CT+I had longer survival (HR 0.87, 95% CI, 0.71, 1.1). Based on the above results, it is not difficult to find that the patients in CT+I group have the longest survival time among the five treatment strategies, followed by CT+T+T. Similarly, we found that the four combination therapy strategies are superior to the CT, and the best treatment strategies are still CT+T+T and CT+I in PFS subgroup analyses. But unlike the OS analysis, the progression-free survival of CT+T+T was better than CT+I, followed by CT+T and CT. In the analysis of secondary outcome indicators (ORR and

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2020 doi:10.20944/preprints202005.0478.v1

adverse), the response rates from high to low were CT+I, CT+T+T, CT+T, CT+B, CT, and the incidence of 3-4 grade adverse reactions from high to low were CT+T+T, CT+B, CT+T, CT and CT+I respectively. In the Figure 3, we showed the forest plot of the OS analyses. The forest plot of PFS analyses presented in Figure A3.

4.4 **Ranking of different treatment strategies**

In Figure 4, the rankings of the five competing treatment strategies were summarized in terms of OS, PFS, ORR and adverse—with details provided in the supplemental materials, Table A3. CT+I and CT+T+T had similar ranking and was most likely to be ranked as the best or the second best in terms of OS, PFS, ORR. However, the incidence of adverse reaction in the CT+T+T group was significantly higher than in the CT+I group.

The two statistical analyses reached consistent results, both results indicated that CT+I was the best treatment strategy for chemotherapy-based combination therapy for advanced lung cancer.

4.5 **Comparison of different immunotherapeutic drugs**

To further explore the differences between the different drugs in the best combination therapy strategy (CT+I), we used OS and PFS as outcome indicators to compare them indirectly. There are 10 trails for chemotherapy combined with immunotherapy in this study, including 5662 patients. Three of them were chemotherapy plus pembrolizumab, four were chemotherapy plus ipilimumab, and one for each chemotherapy combined with TG4010, atezolizumab, durvalumab. There is no direct comparison between the drugs combined with chemotherapy. We connected them

 doi:10.20944/preprints202005.0478.v1

by chemotherapy alone or chemotherapy plus placebo and made indirect comparisons. Figure 5 and Figure A4 showed the forest plots for pairwise comparisons in the network of OS and PFS, and we summarized the results as Table 3. According to the results in the table, the effect of five immunotherapy drugs combined with chemotherapy are all better than chemotherapy or chemotherapy plus placebo, and chemotherapy combined with pembrolizumab is the best one (Compared with CT+ pembrolizumab, the HRs of OS of CT+ ipilimumab, CT+TG4010, CT+atezolizumab, CT+durvalumab are 1.6(95% CI, 1.1, 2.1), 1.3(95% CI, 0.80, 2.2), 1.2(95% CI, 0.74, 1.9), 1.3(95% CI, 0.79, 1.9) respectively).

Discussion

Before 2003, the treatment for patients with advanced lung cancer mainly relied on systemic chemotherapy. Although chemotherapy had a certain effect on the survival and quality of life for patients, the median survival time of patients after chemotherapy was still only 8-10 months [35]. With the development of targeted drugs, it brings a new hope to patients with advanced lung cancer. Currently, the most widely used targeted therapy is for patients with epidermal growth factor receptor (EGFR) gene mutations. Studies have shown that patients with tumors carrying EGFR mutants have a median survival time of more than 2 years after using EGFR inhibitors [9], better survival benefits to patients than chemotherapy alone. In recent years, another milestone in cancer treatment is the immunotherapy. Currently, there are two major immunotherapeutic agents, one is for the PD-1/PD-L1 pathway [36] and another is for

 doi:10.20944/preprints202005.0478.v1

the CTLA4 (Cytotoxic T-lymphocyte antigen 4) molecule [37]. Many studies have also shown that immunotherapy has many advantages over than traditional chemotherapy [6, 23, 38].

However, in-depth research on targeted therapy and immunotherapy also reveals the limitations of both. Firstly, it is the drug resistance of targeted therapy, due to long-term exposure to one targeted drug, patients will have various degrees of resistance [9]. In addition, targeted therapy is only effective in the patients with mutated genes, but such patients account for only a small fraction (about 25%) [8]. For immunotherapy, the obvious defect is the selectivity of the treatment population. Studies showed that only about 20% of patients benefit from monotherapy with immunosuppressive agents [39].

Currently, it mainly combats resistance by using drugs against secondary mutations or combination different kind of therapies [40]. Similarly, immunotherapy combined with other treatments had also shown better efficacy [41]. Combination therapy not only overcomes drug resistance, but also reduces the dose of both drugs, thereby minimizing the side effects and enhancing the therapeutic effect of a single strategy [42]. This research mainly analyzes the therapeutic effects of multiple treatments combined with chemotherapy. The efficacy among different combination treatments is still controversial [14]. Some studies have shown that low-dose erlotinib combined with cisplatin has synergistic effects in some cell lines [43]. However, more trials have shown that the combination of targeted therapy and chemotherapy not only has no survival benefits, but also aggravates adverse reactions [44, 45]. Our study showed that

 doi:10.20944/preprints202005.0478.v1

chemotherapy combined with targeted therapy was superior to chemotherapy alone in terms of OS, PFS or ORR, but the incidence of adverse reactions did increase (Figure 4). At present, the mechanism of combination therapy is still unclear and more research is needed to explore its effectiveness. Combination therapy with multiple targeted drugs aims at circumventing drug resistance through a so-called bypass signaling mechanism by targeting horizontal pathways, or vertical pathways, or both [46]. And some studies have confirmed that the combination of two targeted drugs can restore the sensitivity of tumor cells to drugs [47, 48]. This study had the same conclusion as the previous researches, among the various combination therapies, the treatment effect of CT+T+T was second to CT+I in OS analyses (Table 2. HR 0.87(95% CI, 0.71, 1.1), even better than CT+I in controlling disease progression (Table 2. HR 1.1, 95% CI, 0.84, 1.5). However, the incidence of adverse reactions was the highest. Some studies have shown that chemotherapeutic drugs are likely to synergize or superimpose with immunological checkpoint inhibitors by boosting the immunosuppressive environment within tumor microenvironment [39]. The results of this study showed that CT+I was superior to other treatment strategies in terms of OS and ORR, and PFS was second only to CT+T+T. It is worth mentioning that the incidence of adverse reaction rate of CT+I was the lowest of the five treatment strategies in this study.

The efficacy of immunotherapy has been confirmed in many clinical trials, and some immunotherapeutic drugs have been incorporated in the treatment strategy of advanced non-small cell lung cancer in first- and second-line setting improving the prognosis of these patients [49]. There are many types of drugs for immunotherapy, and

 doi:10.20944/preprints202005.0478.v1

this study contained five of them (pembrolizumab, ipilimumab, TG4010, atezolizumab, durvalumab). Due to the lack of head-to-head research, we conducted an indirect comparison with them through network analysis. The results showed that among the five immunotherapy drugs, pembrolizumab combined with chemotherapy had the best therapeutic effect (Table 3). Even not directly, but this is the first time to compare the efficacy of various immunotherapy drugs combined with chemotherapy in clinical trials, and it's very important for patients with advanced lung cancer to choose in the future treatment and for our understanding with immunotherapy.

Conclusion:

According to the results of this study, chemotherapy combined with immunotherapy is the best combination of multiple chemotherapy-based combination therapy strategies for patients with advanced lung cancer, and it is superior to other treatment strategies in terms of long-term survival and adverse reactions. Moreover, we found that pembrolizumab combined with chemotherapy has the best effect by comparing various immune drugs.

Due to the lack of direct comparative trials between different immunotherapy drugs combined with chemotherapy, we can only construct indirect comparisons for them. There are many other combinations of combination therapy for advanced lung cancer, but this study is only based on chemotherapy-based combination therapies. Next, we will further explore the efficacy of other combination therapy strategies in patients with advanced lung cancer.

Acknowledgements: Thanks for the funding of the Program of Excellent Doctoral (Postdoctoral) of Zhongnan Hospital of Wuhan University.

Conflict of interest: The authors declare no potential conflicts of interest.

Funding: This work was supported by the Program of Excellent Doctoral (Postdoctoral) of Zhongnan Hospital of Wuhan University (Grant No. ZNYB2019002).

Role of the Funding Source: The grantee is the corresponding author of this article.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68:394-424.

[2] Bazan JG, Duan F, Snyder BS, Horng D, Graves EE, Siegel BA, et al. Metabolic tumor volume predicts overall survival and local control in patients with stage III non-small cell lung cancer treated in ACRIN 6668/RTOG 0235. Eur J Nucl Med Mol Imaging. 2017;44:17-24.

[3] Ahn JS, Ahn YC, Kim JH, Lee CG, Cho EK, Lee KC, et al. Multinational Randomized Phase III Trial With or Without Consolidation Chemotherapy Using Docetaxel and Cisplatin After Concurrent Chemoradiation in Inoperable Stage III Non-Small-Cell Lung Cancer: KCSG-LU05-04. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33:2660-6.

[4] Costa DB, Shaw AT, Ou SHI, Solomon BJ, Riely GJ, Ahn MJ, et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. Journal of Clinical Oncology. 2015;33:1881-8.

[5] Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. The New England journal of medicine. 2015;373:123-35.

[6] Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): A multicentre, open-label, phase 2 randomised controlled trial. The Lancet. 2016;387:1837-46.

[7] Reck M, Luft A, Szczesna A, Havel L, Kim SW, Akerley W, et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34:3740-8.

[8] Kohno T, Nakaoku T, Tsuta K, Tsuchihara K, Matsumoto S, Yoh K, et al. Beyond ALK-RET, ROS1 and other oncogene fusions in lung cancer. Translational lung cancer research. 2015;4:156-64.

[9] Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. Nature reviews Cancer. 2010;10:760-74.

[10] Liang H, Liu X, Wang M. Immunotherapy combined with epidermal growth factor receptor-tyrosine kinase inhibitors in non-small-cell lung cancer treatment. OncoTargets and therapy. 2018;11:6189-96.

[11] Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment

 doi:10.20944/preprints202005.0478.v1

of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial. The Lancet. 2014;384:665-73.

[12] Reck M, Kaiser R, Mellemgaard A, Douillard JY, Orlov S, Krzakowski M, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): A phase 3, double-blind, randomised controlled trial. The Lancet Oncology. 2014;15:143-55.

[13] Kanda S, Goto K, Shiraishi H, Kubo E, Tanaka A, Utsumi H, et al. Safety and efficacy of nivolumab and standard chemotherapy drug combination in patients with advanced non-small-cell lung cancer: a four arms phase Ib study. Annals of oncology : official journal of the European Society for Medical Oncology. 2016;27:2242-50.

[14] Yang Z, Tam KY. Combination Strategies Using EGFR-TKi in NSCLC Therapy: Learning from the Gap between Pre-Clinical Results and Clinical Outcomes. International journal of biological sciences. 2018;14:204-16.

[15] Sutton A, Ades AE, Cooper N, Abrams K. Use of indirect and mixed treatment comparisons for technology assessment. PharmacoEconomics. 2008;26:753-67.

[16] Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. BMC medical research methodology. 2010;10:54.

[17] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed). 2009;339:b2535.

 doi:10.20944/preprints202005.0478.v1

[18] Bradbury PA, Morris DG, Nicholas G, Tu D, Tehfe M, Goffin JR, et al. Canadian Cancer Trials Group (CCTG) IND211: A randomized trial of pelareorep (Reolysin) in patients with previously treated advanced or metastatic non-small cell lung cancer receiving standard salvage therapy. Lung Cancer. 2018;120:142-8.

[19] Chang J, Liu Y, Han B, Zhou C, Bai C, Li J. Pseudomonas aeruginosa preparation plus chemotherapy for advanced non-small-cell lung cancer: a randomized, multicenter, double-blind phase III study. Medical Oncology. 2015;32.

[20] Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.

[21] Reck M, Von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. Journal of Clinical Oncology. 2009;27:1227-34.

[22] Reck M, Krzakowski M, Chmielowska E, Sebastian M, Hadler D, Fox T, et al. A randomized, double-blind, placebo-controlled phase 2 study of tigatuzumab (CS-1008) in combination with carboplatin/paclitaxel in patients with chemotherapy-naive metastatic/unresectable non-small cell lung cancer. Lung Cancer. 2013;82:441-8.

[23] Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: Results from a randomized, double-blind, multicenter phase II study. Journal of Clinical Oncology. 2012;30:2046-54.

[24] Belani CP, Yamamoto N, Bondarenko IM, Poltoratskiy A, Novello S, Tang J, et

 doi:10.20944/preprints202005.0478.v1

al. Randomized phase II study of pemetrexed/cisplatin with or without axitinib for non-squamous non-small-cell lung cancer. BMC Cancer. 2014;14.

[25] Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC medical research methodology. 2012;12:9.

[26] Boutsikou E, Kontakiotis T, Zarogoulidis P, Darwiche K, Eleptheriadou E, Porpodis K, et al. Docetaxel-carboplatin in combination with erlotinib and/or bevacizumab in patients with non-small cell lung cancer. OncoTargets and Therapy. 2013;6:125-34.

[27] Park K, Kim JH, Cho EK, Kang JH, Shih JY, Zimmermann AH, et al. East Asian subgroup analysis of a randomized, double-blind, phase 3 study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small cell lung cancer following disease progression after one prior platinum-based therapy (REVEL). Cancer Research and Treatment. 2016;48:1177-86.

[28] Wakelee H, Zvirbule Z, De Braud F, Kingsley CD, Mekhail T, Lowe T, et al. Efficacy and Safety of Onartuzumab in Combination With First-Line Bevacizumab- or Pemetrexed-Based Chemotherapy Regimens in Advanced Non-Squamous Non-Small-Cell Lung Cancer. Clinical lung cancer. 2017;18:50-9.

[29] Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. International journal of epidemiology. 2012;41:818-27.

 doi:10.20944/preprints202005.0478.v1

[30] Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Statistics in medicine. 2010;29:932-44.

[31] Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33:607-17.

[32] Agostinho NB, Machado KS, Werhli AV. Inference of regulatory networks with a convergence improved MCMC sampler. BMC bioinformatics. 2015;16:306.

[33] Herbei R, Paul R, Berliner LM. Applying diffusion-based Markov chain Monte Carlo. PLoS One. 2017;12:e0173453.

[34] Brooks SP, Gelman A. General Methods for Monitoring Convergence of Iterative Simulations. Journal of Computational and Graphical Statistics. 1998;7:434-55.

[35] Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. The New England journal of medicine. 2002;346:92-8.

[36] Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. The New England journal of medicine. 2012;366:2443-54.

[37] Egen JG, Kuhns MS, Allison JP. CTLA-4: new insights into its biological function and use in tumor immunotherapy. Nature immunology. 2002;3:611-8.

[38] Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung

 doi:10.20944/preprints202005.0478.v1

Cancer. The New England journal of medicine. 2015;373:123-35.

[39] Li XT, Yang JJ, Wu YL, Hou J. Toward innovative combinational immunotherapy: A systems biology perspective. Cancer treatment reviews. 2018;68:1-8.

[40] Pakkala S, Ramalingam SS. Personalized therapy for lung cancer: Striking a moving target. JCI insight. 2018;3.

[41] Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. The Lancet Oncology. 2016;17:1497-508.

[42] Yazdi MH, Faramarzi MA, Nikfar S, Abdollahi M. A Comprehensive Review of Clinical Trials on EGFR Inhibitors Such as Cetuximab and Panitumumab as Monotherapy and in Combination for Treatment of Metastatic Colorectal Cancer. Avicenna journal of medical biotechnology. 2015;7:134-44.

[43] Lee JG, Wu R. Erlotinib-cisplatin combination inhibits growth and angiogenesis through c-MYC and HIF-1alpha in EGFR-mutated lung cancer in vitro and in vivo. Neoplasia (New York, NY). 2015;17:190-200.

[44] Janne PA, Wang X, Socinski MA, Crawford J, Stinchcombe TE, Gu L, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30:2063-9.

 doi:10.20944/preprints202005.0478.v1

[45] Michael M, White SC, Abdi E, Nott L, Clingan P, Zimet A, et al. Multicenter randomized, open-label phase II trial of sequential erlotinib and gemcitabine compared with gemcitabine monotherapy as first-line therapy in elderly or ECOG PS two patients with advanced NSCLC. Asia-Pacific journal of clinical oncology. 2015;11:4-14.

[46] Tong CWS, Wu WKK, Loong HHF, Cho WCS, To KKW. Drug combination approach to overcome resistance to EGFR tyrosine kinase inhibitors in lung cancer. Cancer letters. 2017;405:100-10.

[47] Sano T, Takeuchi S, Nakagawa T, Ishikawa D, Nanjo S, Yamada T, et al. The novel phosphoinositide 3-kinase-mammalian target of rapamycin inhibitor, BEZ235, circumvents erlotinib resistance of epidermal growth factor receptor mutant lung cancer cells triggered by hepatocyte growth factor. International journal of cancer. 2013;133:505-13.

[48] Deng QF, Su BO, Zhao YM, Tang L, Zhang J, Zhou CC. Integrin beta1-mediated acquired gefitinib resistance in non-small cell lung cancer cells occurs via the phosphoinositide 3-kinase-dependent pathway. Oncology letters. 2016;11:535-42.

[49] Remon J, Hendriks LE, Cabrera C, Reguart N, Besse B. Immunotherapy for oncogenic-driven advanced non-small cell lung cancers: Is the time ripe for a change? Cancer treatment reviews. 2018;71:47-58.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2020 doi:10.20944/preprints202005.0478.v1

Figure Legends

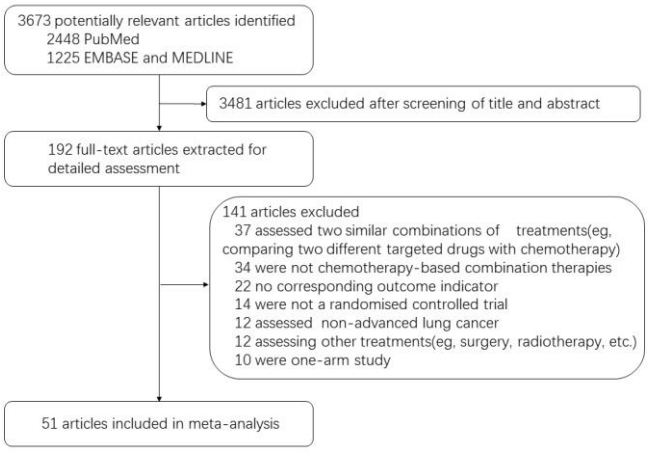

Figure 1. Literature search and selection

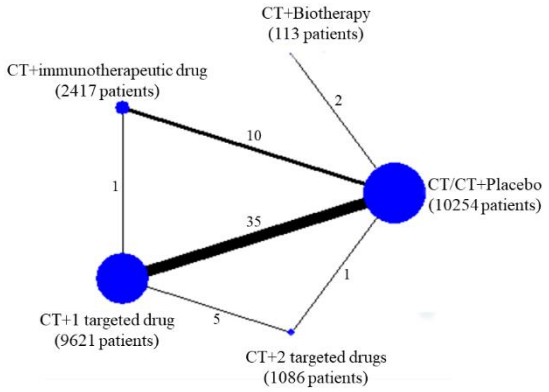

Figure 2. Network of the comparisons for the Bayesian network meta-analysis. The size of the nodes is proportional to the number of patients, randomized to receive the treatment. The width of the lines is proportional to the number of trials comparing the connected treatments.

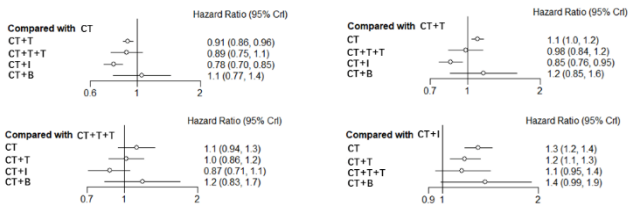

Figure 3. Forest plots for pairwise comparisons in the network of OS under comparison of different combined treatment strategies. CrI: confidence interval.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2020 doi:10.20944/preprints202005.0478.v1

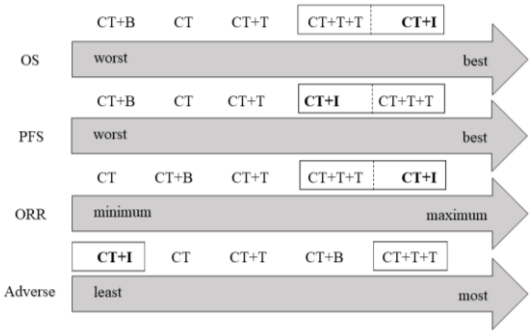

Figure 4. Ranking of treatments in terms of OS, PFS, ORR and adverse. The first and second arrows indicate that an increase in overall survival and progression-free survival from left to right. The third and fourth arrows indicate that the left to right treatment response rate and the 3-4 grade adverse reaction rate increase in turn.

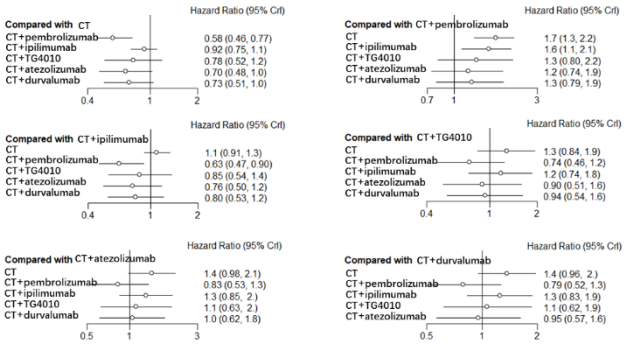

Figure 5. Forest plots for pairwise comparisons in the network of OS under comparison of different immunotherapeutic drugs. CrI: confidence interval.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2020 doi:10.20944/preprints202005.0478.v1

Tables

Author	Arms	Sample	LnHR(MOS)	SE	LnHR(PFS)	SE
Baggstrom, M. Q 2017	CT+T	100	-0.020202707	0.1491678	-0.4780358	0.1419826
	CT	100				
Belani, C. P 2014#	CT+T	113	0.202124184	0.2092955	-0.0403013	0.2117957
	CT	57				
Boutsikou, E 2013*	CT+T+T	60	-0.423120043	0.4374486	NA	NA
	CT+T	56	-0.263965546	0.3667315	NA	NA
	CT	61		0.359342	NA	NA
Dittrich, C 2014	CT+T	76	-0.385662481	0.1929403	-0.46203546	0.1825561
	CT	83				
Doebele, R. C 2015	CT+T	69	0.029558802	0.1987079	-0.28768207	0.1912792
	CT	71				
Ellis, P. M 2014	CT+T+T	480	0	0.0961607	-0.41551544	0.0923762
	CT+T	240				
Garon, E. B 2014	CT+T	628	-0.15082289	0.0682345	-0.27443685	0.0599081
	CT	625				
Garon, E. B 2016	CT+T+T	32	0.058268908	0.3331308	0.039220713	0.3129902
	CT+T	31				
Gerber, D. E 2018	CT+T	297	0.058268908	0.0975703	0	0.1013525
	CT	300				
Hanna, N. H 2016	CT+T	353	0.009950331	0.0900866	-0.18632958	0.0884246
	CT	360				
Herbst, R. S 2010	CT+T	694	-0.094310679	0.0705625	-0.23572233	0.0558477
	CT	697				
Hirsch, F. R 2008	CT+T	121	0.322083499	0.2024033	NA	NA
	CT	124				
Johnson, B. E 2013	CT+T+T	370	-0.083381609	0.1396161	-0.34249031	0.1004858
	CT+T	373				
Langer, C. J 2014	CT+T	342	0.165514438	0.0883986	0.09531018	0.0893374
	CT	339				
Lu, S 2015	CT+T	69	0	0.1944235	-0.22314355	0.1546265
	CT	69				
Lynch, T. J 2010	CT+T	338	-0.116533816	0.0847207	-0.10314076	0.0866953
	CT	338				
Niho, S 2012	CT+T	121	-0.010050336	0.2133286	-0.49429632	0.1915732
	CT	59				
Novello, S 2014	CT+T	182	-0.116533816	0.1162804	-0.16251893	0.1365161
	CT	178				
Ouyang, X 2018	CT+T	342	-0.061875404	0.1254402	-0.90782665	0.1212686
	CT	110				
Park, K 2016						

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2020 doi:10.20944/preprints202005.0478.v1

cohort1	CT+T	43	-0.271808723	0.2754248	-0.41855035	0.2435605
	CT	46				
cohort2	CT+T	585	-0.14618251	0.0700636	-0.26136476	0.0624824
	CT	579				
Paz-Ares, L 2015	CT+T	315	0.009950331	0.0931055	-0.04082199	0.0947866
	CT	318				
Pirker, R 2009	CT+T	557	-0.138113302	0.0683165	NA	NA
	CT	568				
Pujol, J. L 2015	CT+T	37	-0.223143551	0.2437529	0.09531018	0.2263529
	CT	37				
Reck, M 2014	CT+T	655	-0.287682072	0.1090418	-0.23572233	0.0771125
	CT	659				
Reck, M 2013	CT+T	49	-0.051293294	0.2600877	-0.04082199	0.2496705
	CT	48				
Reck, M 2009#	CT+T	696	NA	NA	-0.28688239	0.0856222
	CT	347				
Sanborn, R. E 2017	CT+T	34	-0.2269006	0.2998343	-0.01816397	0.3031992
	CT	33				
Soria, J. C 2015	CT+T	133	0.482426149	0.2233339	-0.15082289	0.1410716
	CT	132				
Spigel, D. R 2017	CT+T	110	-0.186329578	0.2593233	0	0.1768233
	CT	57				
Spigel, D. R 2011	CT+T	52	0.148420005	0.2878738	-0.63487827	0.2521968
	CT	50				
Takeda, K 2010	CT+T	300	-0.15082289	0.0913426	-0.38566248	0.0864733
	CT	298				
Thatcher, N 2015	CT+T	545	-0.174353387	0.0663987	-0.17435339	0.0603033
	CT	548				
Wakelee, H 2017						
cohort1	CT+T+T	69	0.292669614	0.313153	0.223143551	0.230499
	CT+T	70				
cohort2	CT+T	59	0.139761942	0.259378	0.207014169	0.2120764
	CT	61				
Zhou, C 2015	CT+T	138	-0.385662481	0.1583103	-0.91629073	0.1585939
	CT	138				
Argiris, A 2017	CT+T+T	75	-0.010050336	0.1823095	-0.08338161	0.1787781
	CT+T	78				
Fukuda, M 2019	CT+T	20	-0.235722334	0.4163362	-0.17435339	0.405143
	CT	20				
Owonikoko, T. K 2019	CT+T	64	-0.186329578	0.1311086	NA	NA
	CT	64				
Reck, M 2019	CT+I	399	-0.162518929	0.0949105	-0.21072103	0.2011371
	CT+T	394				
Watanabe, S 2019	CT+T	90	-0.415515444	0.1740949	-0.41551544	0.1740949

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2020 doi:10.20944/preprints202005.0478.v1

	CT	91				
Gandhi, L 2018	CT+I	410	-0.713349888	0.1329839	-0.65392647	0.1014497
	CT	206				
Govindan, R 2017	CT+I	388	-0.094310679	0.0839345	-0.13926207	0.0759266
	CT	361				
Langer, C. J 2016	CT+I	60	-0.105360516	0.3863785	-0.63487827	0.2747123
	CT	63				
Lynch, T. J 2012#	CT+I	138	-0.110149744	0.1785956	-0.28754875	0.1707142
	CT	65				
Quoix, E 2016	CT+I	111	-0.248461359	0.1582622	-0.30110509	0.1473557
	CT	111				
Reck, M 2013#	CT+I	85	-0.150009267	0.2318266	-0.02460012	0.2184526
	CT	45				
Reck, M 2016	CT+I	478	-0.061875404	0.0757395	-0.16251893	0.0656181
	CT	476				
Horn, L 2018	CT+I	201	-0.356674944	0.1331315	-0.26136476	0.1115341
	CT	202				
Paz-Ares, L 2019	CT+I	268	-0.314710745	0.1105413	-0.24846136	0.0941091
	CT	269				
Paz-Ares, L 2018	CT+I	278	-0.446287103	0.1405181	-0.5798185	0.1127124
	CT	281				
Bradbury, P. A 2018	CT+B	77	-0.020202707	0.16075	-0.10536052	0.166818
	CT	75				
Chang, J 2015	CT+B	36	0.252533118	0.2889268	0.076961041	0.2911734
	CT	36				

MOS: Median overall survival in months; Sample: the number of patients; PFS: Progression-free survival in months; ORR: objective response rate; SE: standard error; HR: hazard ratio; NA: not available. * represents corrected data, #represents data after IPDs consolidation.

Table 1. Summary of OS and PFS data in randomized controlled trials of patients with advanced lung cancer undergone combined therapy. This table summarizes the basic information of the trials (authors, publication time, treatment strategy, number of samples), and also included the LnHR and its SE corresponding to each OS/PFS after data merging and correction.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2020 doi:10.20944/preprints202005.0478.v1

OS	CT				
	0.91(0.86, 0.96)	CT+T			
	0.89(0.75, 1.1)	0.98(0.84, 1.2)	CT+T+T		
	0.78(0.70, 0.85)	**0.85(0.76, 0.95)**	0.87(0.71, 1.1)	CT+I	
	1.1(0.77, 1.40)	1.2(0.85, 1.6)	1.2(0.83, 1.7)	1.4(0.99, 1.9)	CT+B
PFS	CT				
	0.78(0.72, 0.85)	CT+T			
	0.64(0.51, 0.83)	0.83(0.66, 1.0)	CT+T+T		
	0.72(0.62, 0.83)	0.92(0.78, 1.1)	1.1(0.84, 1.5)	CT+I	
	0.96(0.64, 1.4)	1.2(0.80, 1.9)	1.5(0.92, 2.4)	1.3(0.86, 2.1)	CT+B
ORR	CT				
	1.4(1.3, 1.5)	CT+T			
	1.7(1.4, 2.2)	**1.2(1.0, 1.5)**	CT+T+T		
	1.8(1.3, 2.7)	1.3(0.91, 2.0)	1.1(0.69, 1.7)	CT+I	
	1.6(0.81, 3.5)	1.2(0.59, 2.5)	0.94(0.45, 2.1)	0.89(0.40, 2.1)	CT+B
Adverse	CT				
	1.2(1.1, 1.2)	CT+T			
	1.5(1.2, 1.7)	**1.3(1.1, 1.5)**	CT+T+T		
	0.99(0.91, 1.1)	**0.85(0.77, 0.94)**	**0.68(0.56, 0.83)**	CT+I	
	1.4(1.1, 1.8)	1.2(0.98, 1.6)	0.97(0.73, 1.3)	**1.4(1.1, 1.8)**	CT+B

Table 2. Pooled hazard ratios for OS/PFS/ORR/adverse. Numbers outside the parentheses are the HRs of the column treatment compared with the row treatment (eg, the first number 0.92 is the HRs of CT+T compared with CT), numbers inside the parentheses are the 95% CI. Bold numbers represent statistical significance.

OS	CT					
	0.58(0.46, 0.77)	CT+pembrolizumab				
	0.92(0.75, 1.1)	**1.6(1.1, 2.1)**	CT+ipilimumab			
	0.78(0.52, 1.2)	1.3(0.80, 2.2)	0.85(0.54, 1.4)	CT+TG4010		
	0.70(0.48, 1.0)	1.2(0.74, 1.9)	0.76(0.50, 1.2)	0.90(0.51, 1.6)	CT+atezolizumab	
	0.73(0.51, 1.0)	1.3(0.79, 1.9)	0.80(0.53, 1.2)	0.94(0.54, 1.6)	1.0(0.62, 1.8)	CT+durvalumab
PFS	CT					
	0.54(0.45, 0.65)	CT+pembrolizumab				
	0.86(0.74, 0.99)	**1.6(1.3, 2.0)**	CT+ipilimumab			
	0.74(0.53, 1.0)	1.4(0.93, 2.0)	0.87(0.60, 1.3)	CT+TG4010		
	0.77(0.57, 1.0)	1.4(1.0, 2.0)	0.90(0.65, 1.2)	1.0(0.66, 1.6)	CT+atezolizumab	
	0.78(0.59, 1.0)	1.4(1.0, 2.0)	0.91(0.67, 1.2)	1.0(0.68, 1.6)	1.0(0.68, 1.5)	CT+durvalumab

Table 3. Pooled hazard ratios for OS/PFS in comparative analysis of different

 doi:10.20944/preprints202005.0478.v1

drugs for immunotherapy combined with chemotherapy. Numbers outside the parentheses are the HRs of the column treatment compared with the row treatment, numbers inside the parentheses are the 95% CI. Bold numbers represent statistical significance.