**SUPPLEMENTARY DOCUMENTS**

**Appendix Table 1： Literature search strategies**

|  |  |  |
| --- | --- | --- |
|  | **Search string** | **Hits** |
| **PUBMED** |  |  |
| #1 | non-small-cell lung cancer[Title/Abstract] OR non-small-cell lung carcinoma[Title/Abstract] OR NSCLC[Title/Abstract] OR nsqNSCLC[Title/Abstract] | 66860 |
| #2 | nonsquamous OR non-squamous[All Fields] | 2200 |
| #3 | pembrolizumab[Title/Abstract] OR nivolumab[Title/Abstract] OR atezolizumab[Title/Abstract] OR Sintilimab[Title/Abstract] OR camrelizumab[Title/Abstract] OR tislelizumab[Title/Abstract] | 7719 |
| #4 | randomized[Title/Abstract]) OR (randomized controlled trial[Publication Type] | 784612 |
| #5 | #1 AND #2 AND #3 AND #4 | 46 |
| **COCHRANE** |  |  |
| #1 | non-small-cell lung cancer OR non-small-cell lung carcinoma OR NSCLC OR nsqNSCLC:ti,ab,kw | 13545 |
| #2 | nonsquamous OR non-squamous | 1605 |
| #3 | pembrolizumab OR nivolumab OR atezolizumab OR Sintilimab OR camrelizumab OR tislelizumab:ti,ab,kw | 312 |
| #4 | with Publication Year from 2008 to 2020 | 312 |
| #5 | in Trials | 312 |

**Appendix Table 2: PICOS criteria to assess studies for the SLR**

|  |  |
| --- | --- |
| **PICOS elements** | |
| **Population:** | Previously untreated Stage IIIB/C ineligible for surgery or local therapy and IV nsqNSCLC without activating EGFR mutations or ALK translocations |
| **Intervention-Treatment:** | PD-1s or PD-L1s approved or have clinical data for first-line nsqNSCLC treatment in combination therapy of platinum-based doublet chemotherapy |
| **Intervention-Comparison:** | PD-1s or PD-L1 approved or have clinical data for first-line non-squamous NSCLC treatment in combination therapy of pemetrexed/platinum: |
| **Outcomes:** | Hazard ratio of PFS and OS  Objective response rate (ORR)  Complete response rate (CR)  Partial response rate (PR)  Disease control rate(DCR)  Time to response (TTR)  Safety profile |
| **Study design:** | Randomized controlled trials (Phase II-III) |

## Appendix Table 3: Baseline characteristics and main outcomes of included trials

**Table 3.1 Baseline characteristics of included trials**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **N** | **Treatment** | **Age** | | **Sex (%)** | **ECOG SCORE (%)** | | | **Disease stage (%)** | | |
| **Median** | **range** | **Male** | **0** | **1** | **2** | **ⅢB** | **ⅢC** | **Ⅳ** |
| Yang 2020 | 266 | Sintilimab-combination | 61 | 30-75 | 76.7% | 28.6% | 71.4% | - | 5.3% | 2.6% | 92.1% |
|  | 131 | PT-DC | 61 | 35-75 | 75.6% | 26% | 74% | - | 4.6% | 6.9% | 88.5% |
| West 2019 | 451 | Atezolizumab-combination | 64 | 18-86 | 59.0% | 42.0% | 58.0% | - | - | - | 100.0% |
|  | 228 | carboplatin + nab-paclitaxel | 65 | 38-85 | 59.0% | 40.0% | 60.0% | <1% | - | - | 100.0% |
| Gandhi 2018 | 410 | Pembrolizumab-combination | 65.0 | 34-84 | 62.00% | 45.40% | 53.90% | 0.20% | - | - | 100% |
|  | 206 | PT-DC | 63.5 | 34-84 | 52.90% | 38.80% | 60.70% | 0.00% | - | - | 100% |
| Gadgeel 2020 | 410 | Pembrolizumab-combination | 65.0 | 34-84 | 62.00% | 45.40% | 53.70% | 0.20% | - | - | 100% |
|  | 206 | PT-DC | 63.5 | 34-84 | 52.90% | 38.80% | 60.70% | 0.00% | - | - | 100% |
| Zhou 2020 | 205 | Camrelizumab-combination | 59 | - | 71% | 23% | 77% | - | 15% | | 85% |
|  | 207 | PT-DC | 61 | - | 72% | 17% | 83% | - | 20% | | 80% |
| Lu 2020 | 223 | Tislelizumab-combination | 60 | 27-75 | 75.30% | 24.2% | 75.8% | - | 17.9% |  | 82.1% |
|  | 111 | PT-DC | 61 | 25-74 | 71.20% | 21.6% | 78.4% | - | 18.9% | - | 81.1% |
| Paz-Ares 2019 | 270 | Nivolumab-combination | - | - | - | - | - | - | - | - | - |
|  | 273 | PT-DC | - | - | - | - | - | - | - | - | - |
| Papadimitrakopoulou 2018 | 292 | Atezolizumab-combination | 64 | 31-85 | 65.80% | 43.20% | - | - | - | - | 100% |
|  | 286 | PT-DC | 63 | 33-83 | 67.1% | 40.10% | - | - | - | - | 100% |
| Nishio 2020 | 292 | Atezolizumab-combination | 64 | 31-85 | 65.80% | 43.20% | - | - | - | - | 100% |
|  | 286 | PT-DC | 63 | 33-83 | 67.1% | 40.10% | - | - | - | - | 100% |

Note: PT-DC: platinum-based doublet chemotherapy; ECOG: Eastern Cooperative Oncology Group

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **N** | **Treatment** | **Smoking status (%)** | | | **Histologic features (%)** | | | |
| **Never** | **Current** | **Former** | **Adenocarcinoma** | **Large-cell carcinoma** | **NSCLC (*not otherwise specified*)** | **Other** |
| Yang 2020 | 266 | Sintilimab-combination | 35.7% | 18.4% | 45.9% | 95.1% | 0.8% | 1.5% | 2.6% |
|  | 131 | PT-DC | 33.6% | 17.6% | 48.9% | 93.9% | 2.3% | 2.3% | 1.5% |
| West 2019 | 451 | Atezolizumab-combination | 11.0% | 20.0% | 69.0% | 96.0% | 1.0% | - | 3% |
|  | 228 | carboplatin + nab-paclitaxel | 7.0% | 22.0% | 70.0% | 96.0% | 1.0% | - | 3% |
| Gandhi 2018 | 410 | Pembrolizumab-combination | 11.70% | 88.30% | | 96.10% | - | 2.40% | 1.50% |
|  | 206 | PT-DC | 12.10% | 87.90% | | 96.10% | - | 1.90% | 1.90% |
| Gadgeel 2020 | 410 | Pembrolizumab-combination | 11.70% | 88.30% | | 96.10% | - | 2.40% | 1.50% |
|  | 206 | PT-DC | 12.10% | 87.90% | | 96.10% | - | 1.90% | 1.90% |
| Zhou 2020 | 205 | Camrelizumab-combination | - | - | - | 99% | 1% | - | - |
|  | 207 | PT-DC | - | - | - | 99% | - | - | 1% |
| Lu 2020 | 223 | Tislelizumab- combination | 34.1% | 14.3% | 51.6% | - | - | - | - |
|  | 111 | PT-DC | 40.5% | 11.7% | 47.7% | - | - | - | - |
| Paz-Ares 2019 | 270 | Nivolumab-combination | - | - | - | - | - | - | - |
|  | 273 | PT-DC | - | - | - | - | - | - | - |
| Papadimitrakopoulou 2018 | 292 | Atezolizumab-combination | 12.70% | 87.30% | | - | - | - | - |
|  | 286 | PT-DC | 10.50% | 89.50% | | - | - | - | - |
| Nishio 2020 | 292 | Atezolizumab-combination | 12.70% | 87.30% | | - | - | - | - |
|  | 286 | PT-DC | 10.50% | 89.50% | | - | - | - | - |

Note: PT-DC: platinum-based doublet chemotherapy

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **N** | **Treatment** | **PD-L1 TPS, %, (%)** | | | | **Platinum choice (%)** | | **Brain metastases (%)** |
| **<1** | **≥1** | **≥1 to <49** | **≥50** | **Cisplatin** | **Carboplatin** |
| Yang 2020 | 266 | Sintilimab-combination | 32.0% | 68.0% | 27.8% | 40.2% | 26.7% | 73.3% | 13.5% |
|  | 131 | PT-DC | 33.6% | 66.4% | 19.8% | 46.6% | 25.2% | 74.8% | 16.8% |
| West 2019 | 451 | Atezolizumab-combination | 52% | - | 28% | 20% | - | - | 28% |
|  | 228 | carboplatin + nab-paclitaxel | 53% | - | 29% | 18% | - | - | 28% |
| Gandhi 2018 | 410 | Pembrolizumab-combination | 31.00% | 63.40% | 31.20% | 32.20% | 27.60% | 72.40% | 17.80% |
|  | 206 | PT-DC | 30.60% | 62.10% | 28.20% | 34.00% | 28.20% | 71.80% | 17.00% |
| Gadgeel 2020 | 410 | Pembrolizumab-combination | 31.00% |  | 31.20% | 32.20% | 27.60% | 72.40% | 17.80% |
|  | 206 | PT-DC | 30.60% |  | 28.20% | 34.00% | 28.20% | 71.80% | 17.00% |
| Zhou 2020 | 205 | Camrelizumab-combination | 24% | 67% | 53% | 15% | - | - | 5% |
|  | 207 | PT-DC | 33% | 57% | 47% | 10% | - | - | 2% |
| Lu 2020 | 223 | Tislelizumab-combination | 43.00% | - | 23.80% | 33.20% | - | - | 4.90% |
|  | 111 | PT-DC | 43.20% | - | 24.30% | 32.40% | - | - | 6.30% |
| Paz-Ares 2019 | 270 | Nivolumab-combination | - | - | - | - | - | - | - |
|  | 273 | PT-DC | - | - | - | - | - | - | - |
| Papadimitrakopoulou 2018 | 292 | Atezolizumab-combination | 50.00% | - | 35.80% | 14.20% | - | 60.60% | - |
|  | 286 | PT-DC | 44.60% | - | 43.50% | 11.90% | - | 61.10% | - |
| Nishio 2020 | 292 | Atezolizumab-combination | 50.00% | - | 35.80% | 14.20% | - | 60.60% | - |
|  | 286 | PT-DC | 44.60% | - | 43.50% | 11.90% | - | 61.10% | - |

Note: PT-DC: platinum-based doublet chemotherapy; TPS: Tumor Proportion Score

## Appendix Table 3: Baseline characteristics and main outcomes of included trials

**Table 3.2 Main outcomes of included trials**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **Sintilimab**  ***Interim*** | **Atezolizumab**  ***Final*** | **Pembrolizumab *Interim*** | **Pembrolizumab**  ***Final*** | **Tislelizumab**  ***Interim*** | **Camrelizumab**  ***Interim*** | **Nivolumab**  ***Final*** | **Atezolizumab**  ***Interim*** | **Atezolizumab**  ***Final*** |
| Author year | **Yang 2020** | **West 2019** | **Gandhi 2018** | **Gadgeel 2020** | **Lu 2020** | **Zhou 2020** | **Paz-Ares 2019** | **Papadimitrakopoulou 2018** | **Nishio 2020** |
| Publication | **Full article** | **Full article** | **Full article** | **Full article** | **Abstract** | **Full article** | **Abstract** | **Abstract** | **Abstract** |
| Trial | ORIENT-11 | IMPOWER-130 | KEYNOTE-189 | KEYNOTE-189 | RATIONALE-304 | SHR-  1210 | CHECKMATE-227 | IMPOWER-132 | IMPOWER-132 |
| N | 397 | 679 | 616 | 616 | 334 | 412 | 543 | 578 | 578 |
| Follow-up time | 8.9 | 18.5 | 10.5 | 23.1 | 9.8 | 11.9 | 19.5 | 14.8 | 28.4 |
| Time to response (months) | 1.5 (1.2-7.0) | - | 2.2(1.1-11.1) | - | - | 1.5(1.2-5.7) | - | - | - |
| Objective response rate | 51.9%  (45.7-58.0) | 49.2%  (44.5-54.0) | 47.6%  (42.6-52.5) | 48.0 %  (43.1 to 53.0) | 57.4%  (50.6-64.0） | 60.5%  (53.4-67.2) | 48.10% | 47% | - |
| Complete response rate | 1.1% | 2% | 0.5% | 1% | 3.10% | - | - | 2% | - |
| Partial response  rate | 50.8% | 47% | 47.1% | 47.1% | 54.30% | - | - | 45% | - |
| Disease control rate | 86.8% | - | 84.60% | - | 89.2% | 87.8% | - | - | - |
| Progression free survival | 8.9  (7.1-11.3) | 7.0  (6.2-7.3) | 8.8  (7.6-9.2) | 9.0  (8.1-9.9) | 9.7  (7.7-11.5) | 11.3  (9.6-15.4) | 8.7 | 7.6  (6.6-8.5) | 7.7 |
| Progression free survival, HR | 0.482  (0.363-0.643) | 0.64  (0.54-0.77) | 0.52  (0.43-0.64) | 0.48  (0.40-0.58) | 0.645  (0.462, 0.902) | 0.60  (0.45-0.79) | 0.67  (0.55-0.82) | 0.59  (0.494-0.719) | 0.56  (0.47-0.67) |
| Overall survival | NR | 18.6  (16.0-21.2) | NR | 22.0  (19.5-25.2) | - | NR (16.6-NR) | 18.8 | 18.1(13.0-NR) | 17.5  （13.2-19.6) |
| Overall survival, HR | 0.609  (0.400-0.926) | 0.79  (0.64-0.98) | 0.49  (0.38-0.64) | 0.56  (0.45-0.7) | - | 0.73(0.53-1.02) | 0.86  (0.69-1.08) | 0.813  (0.644-1.025) | 0.86  (0.71-1.06) |

Note: NR: Not report

## Appendix Table 4: PRISMA checklist

**Table 4: PRISMA checklist**

| **Section and Topic** | **Item #** | **Checklist item** | **Location where item is reported** |
| --- | --- | --- | --- |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review. | <Title page>Page 1/Line 1-2 |
| **ABSTRACT** | | |  |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | <Main manuscript>Page 1/Line 2-20 |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | <Main manuscript>Page 2-3/Line 26-55 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | <Main manuscript>Page 3/Line 57-62 |
| **METHODS** | | |  |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | <Main manuscript>Page 4/Line 77-82 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | <Main manuscript>Page 4/Line 70-75 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | <Main manuscript>Page 4/Line 70-75 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | <Main manuscript>Page 4/Line 85-90 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | <Main manuscript>Page 4/Line 85-90 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | <Main manuscript>Page 5/Line 93-113 |
| 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | <Main manuscript>Page 5/Line 93-113 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | <Main manuscript>Page 4/Line 89-90 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | <Main manuscript>Page 5/Line 93-113 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | <Main manuscript>Page 5/Line 93-113 |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | <Main manuscript>Page 5/Line 93-113 |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | <Main manuscript>Page 5/Line 93-113 |
| 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | <Main manuscript>Page 5/Line 106-113 |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | <Main manuscript>Page 7/Line 142-154 |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | <Main manuscript>Page 5/Line 101-104 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | <Main manuscript>Page 4/Line 89-90 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | <Main manuscript>Page 5/Line 106-113 |
| **RESULTS** | | |  |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Appendix Table 1 and Appendix Figure 1 |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | <Main manuscript>Page 6/Line 117-119 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Appendix Table 3 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Appendix Figure 2 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Appendix Table 3 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | <Main manuscript>Page 8-10/Line 146-195 |
| 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | <Main manuscript>Page 8-10/Line 146-195 |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | <Main manuscript>Page 8-10/Line 146-195 |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | <Main manuscript>Page 10/Line 193-195 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | <Main manuscript>Page 7/Line 143-145 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | <Main manuscript>Page 8-10/Line 146-195 |
| **DISCUSSION** | | |  |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | <Main manuscript>Page 10-11/Line 215-219 |
| 23b | Discuss any limitations of the evidence included in the review. | <Main manuscript>Page 12/Line 251-257 |
| 23c | Discuss any limitations of the review processes used. | <Main manuscript>Page 12/Line 251-257 |
| 23d | Discuss implications of the results for practice, policy, and future research. | <Main manuscript>Page 10-12/Line 204-249 |
| **OTHER INFORMATION** | | |  |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | <Main manuscript>Page 3/Line 67 |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | <Main manuscript>Page 3/Line 67 |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. | <Main manuscript>Page 3/Line 67 |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | <Title page>Page 1/Line 23-25 |
| Competing interests | 26 | Declare any competing interests of review authors. | <Title page>Page 1/Line 28-30 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | The report has stated any availability of data, code and other materials |