Clinical Outcomes of Second-Line and Beyond (2L+) Treatments in Locally Advanced or Metastatic Non–Small Cell Lung Cancer (aNSCLC): A Systematic Literature Review (SLR)

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Conclusions

- **The current systematic literature review (SLR) was comprehensive in terms of the included interventions. In most studies, improved response outcomes were reported in the immuno-oncology (IO) arm versus platinum-based chemotherapy (CT). IO demonstrated an improved or similar safety profile versus CT. Studies of other intervention combinations (IO vs. IO; and IO plus anti-angiogenic therapy [AT] vs. CT or AT) reported mixed results**
- **Most studies comparing IO versus CT as second-line (2L) and second-line and beyond (2L+) treatment demonstrated statistically significant improvements in median overall survival (mOS) in the IO arm versus CT, except the SUNRISE trial (bavituximab) and JAVELIN Lung 200 trial (avelumab). Most 2L studies reported statistically significant improvements in median progression-free survival (mPFS) for the IO arm versus CT, except the SUNRISE trial (bavituximab) and CheckMate 057 (nivolumab)**
- **In 2L+, KEYNOTE-033 (pembrolizumab) and RATIONALE-303 (tislelizumab) demonstrated significantly improved mPFS in the IO arm versus CT**

Background

- Non–small cell lung cancer (NSCLC) is the predominant subtype of lung cancer, accounting for 85% of all lung cancer cases
- NSCLC accounts for 14% of all cancer-related deaths and is the leading cause of cancer death among men and women, with a high incidence in developing nations where cigarette smoking is prevalent
- The current treatment landscape for NSCLC is complex, with treatment choices influenced by the presence of various prognostic factors and prior treatment status
- Current treatment options include CT, IO as monotherapy or in combination, or AT

Objective

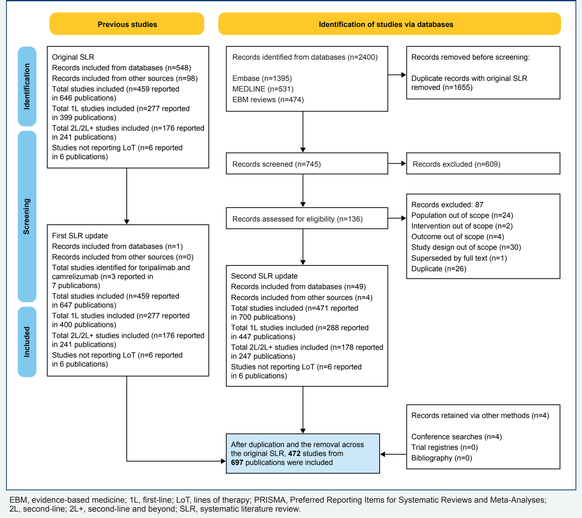
- This SLR was conducted to identify and summarize the evidence from randomized controlled trials (RCTs) with respect to efficacy, health-related quality of life (HRQoL), and safety and tolerability outcomes of CT, IO (as monotherapy or as combination therapy), and AT in 2L/2L+ locally advanced or metastatic NSCLC (aNSCLC)

Methods

- The SLR followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Publications (2001–2023 covering the original and 2 rounds of SLR update) were searched in Embase®, MEDLINE®, Cochrane library and evidence-based medicine databases. Non-indexed conferences and specific trial registries were also searched (2020–2023)
- English-language RCT publications including patients aged ≥18 years with unresectable or metastatic 2L/2L+ aNSCLC (Stage III or IV) were eligible for inclusion
- Two independent reviewers screened titles, abstracts, and full texts of relevant records against pre-defined inclusion/exclusion criteria
- Population demographics were extracted with reported measures of mOS, mPFS, and other outcomes of interest

Results

Figure 1. PRISMA Flow Diagram



EBM, evidence-based medicine; 1L, first-line; LoT, lines of therapy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; 2L, second-line; 2L+, second-line and beyond; SLR, systematic literature review.

- There were 472 studies (697 publications) from the original SLR (first and second updates) evaluating CT, IO, and AT regimens (**Figure 1**)
- Studies meeting the following criteria were prioritized:
  - Immunotherapy as an intervention
  - Both arms featured treatment regimens as per the Population, Interventions, Comparators, Outcomes and Study Design criteria
  - Sample size ≥100 patients
- There were 14 unique studies reported in 50 publications:
  - Eleven studies compared IO versus CT
  - One study compared IO versus IO
  - Two studies compared IO ± AT versus CT ± AT
- Most trials recruited patients with non-oncogenic aNSCLC; for trials including patients with genomic alterations, wild-type results were used
- Most studies were phase 3, open-label studies. The demographic and baseline characteristics were similar across trials
- Smoking status was available in 13 trials:
  - 5.0%–33.5% of patients had never smoked
  - 66.5%–94.0% were current or former smokers
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) was reported in all 14 studies, with most patients scoring 0 (13.0%–46.9%) or 1 (51.3%–88.3%); ECOG PS ≥2 ranged from 0.6%–23.0%
- Most studies included patients with mixed histology (9), followed by non-squamous only (3), and squamous only (2)
- Five studies reported subgroup results based on programmed death-ligand 1 (PD-L1) ≥50% expression

Median Overall Survival

- All 14 included studies of 2L/2L+ reported mOS (**Figure 2**)

2L, IO versus CT

- Six studies compared IO versus CT, with mOS 9.2–12.2 months for IO versus 6.0–11.0 months for CT
- All IO demonstrated statistically significant improvements in mOS versus CT, except bavituximab, which showed similar results to CT
- The mOS was not reached in RATIONALE-303 (tislelizumab); however, tislelizumab demonstrated statistically significant improvements in mOS versus CT (hazard ratio [HR]: 0.64 [95% CI, 0.53–0.77])

2L, IO versus IO

- One study reported numerically improved mOS for the bavituximab + CT combination arm versus bavituximab-placebo (11.7 vs. 7.3 months, HR: 0.66 [95% CI, 0.40-1.10]; *P*=0.11)

2L+, IO versus CT

- Five studies compared IO versus CT, with mOS 10.6–17.8 months for IO versus 9.6–11.9 months for CT (including 3L; IO vs. CT result of RATIONALE-303 trial)
- All IO demonstrated significantly improved mOS versus CT, except the JAVELIN Lung 200 trial, which reported similar mOS in the 2 arms

2L+, IO ± AT versus CT ± AT

- Two studies reported mOS for IO ± AT versus CT ± AT. Both trials reported statistically significant improvement in the intervention arm versus standard of care (ARCTIC study A: durvalumab vs. erlotinib/gemcitabine/vinorelbine; Lung-MAP S1800A: ramucirumab-pembrolizumab vs. docetaxel/ramucirumab, docetaxel, gemcitabine, and pemetrexed)

Median Progression-Free Survival

- All 14 included studies of 2L/2L+ reported mPFS (**Figure 3**)

2L, IO versus CT

- Five studies compared IO versus CT, with mPFS 2.3–4.3 months for IO versus 2.6–4.4 months for CT. Of these, 2 studies reported statistically significant improvement in mPFS for IO versus CT (CheckMate 017- nivolumab vs. CT: 3.5 vs. 2.6 months; *P*<0.001 and ORIENT-3- sintilimab vs. CT: 4.3 vs. 2.8 months; *P*<0.00001)
- CheckMate 078 (nivolumab vs. CT) and KEYNOTE-010 (pembrolizumab vs. CT) reported similar mPFS between the arms; however, the HR favored the IO arm

2L, IO versus IO

- Bavituximab + CT combination did not show a significant improvement in mPFS versus bavituximab-placebo (4.5 vs. 3.3 months; *P*=0.24)

2L+, IO versus CT

- Five studies compared IO versus CT, with mPFS 2.7–4.2 months for IO versus 2.6–4.2 months for CT
- Two studies reported significantly improved mPFS for IO versus CT (KEYNOTE-033: pembrolizumab vs. CT: 3.4 vs. 3.2 months and RATIONALE-303: tislelizumab vs. CT: 4.2 vs. 2.6 months; *P*<0.0001)
- KEYNOTE-010 (pembrolizumab vs. CT) reported similar mPFS in the treatment arms; however, the HR favored the IO arm

2L+, IO ± AT versus CT ± AT

- Two studies reported mPFS for IO ± AT and CT ± AT. Both reported similar results between arms

Response rate

2L

- Six studies comparing IO versus CT reported response data (objective response rate [ORR; 6 studies], disease control rate [DCR; 1 study], and duration of response [DoR; 5 studies])
- ORR ranged from 14.0%–25.5% for IO versus 2.2%–12.4% for the CT arms
- Across all studies, IO resulted in improved response outcomes (odds ratios [ORs] or *P* values not reported [NR])

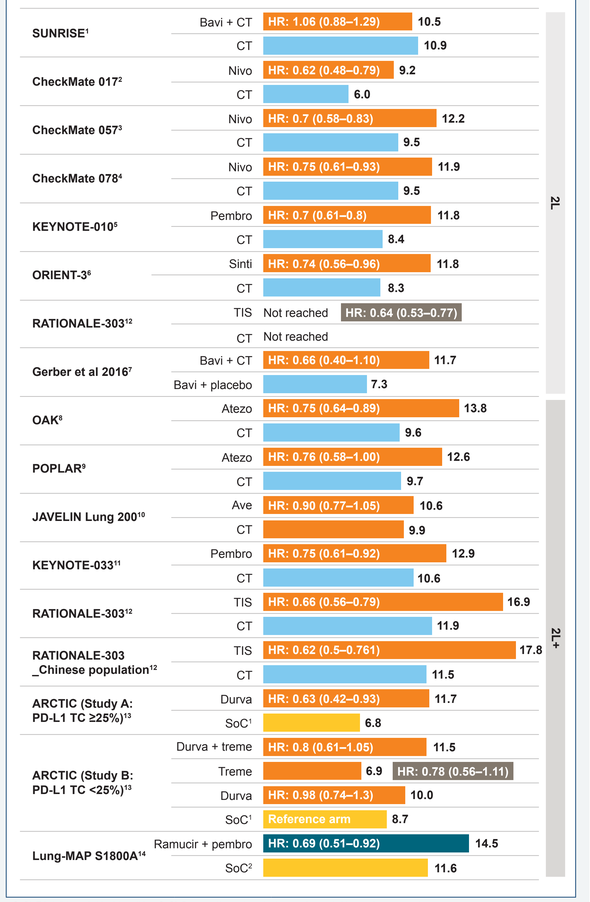
2L+

- Five studies comparing IO versus CT reported response data (ORR [5 studies], DCR [1 study], and DoR [4 studies])
- ORR ranged from 13.9%–22.6% for IO versus 5.5%–14.7% for the CT arms
- Across all studies, IO resulted in improved response outcomes (ORs or *P* values NR)
- DoR ranged from 13.5–23.9 months for IO and 4.2–6.3 months for CT

Safety

- Five IO versus CT 2L studies reported treatment-related adverse events (TRAEs). Four studies reported lower incidence of TRAEs in the IO arm versus CT. The ORIENT-3 trial reported similar incidences of TRAEs in the treatment arms
- The incidence of grade ≥3 TRAEs was lower in the IO arms of all the studies versus CT
- An IO versus IO study reported a similar incidence of TRAEs between arms

Figure 2. mOS of the Included Trials



SoC[1]: Erlotinib/gemcitabine/vinorelbine; SoC[2]: Docetaxel/ramucirumab, docetaxel, gemcitabine, and pemetrexed.
Atezo, atezolizumab; Ave, avelumab; Bavi, bavituximab; CT, chemotherapy; Durva, durvalumab; HR, hazard ratio; mOS, median overall survival; Nivo, nivolumab; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; Ramucir, ramucirumab; 2L, second-line; 2L+, second-line and beyond; Sinti, sintilimab; SoC, standard of care; TC, tumor cell; TIS, tislelizumab; Treme, tremelimumab.

- Five IO versus CT 2L+ studies reported TRAEs. Of these, 4 studies showed lower incidence of TRAEs in the IO arm (atezolizumab, avelumab, and tislelizumab) versus the CT arm. KEYNOTE-033 reported similar results between the arms
- Two studies of IO ± AT versus CT ± AT reported mixed results

HRQoL

- Three 2L nivolumab studies and one 2L pembrolizumab study versus CT reported European Quality of Life 5-Dimension Questionnaire (EQ-5D) mean scores. All reported improvement in the IO arm; CheckMate 017 reported an improvement in EQ-5D mean scores in the 2L nivolumab arm from weeks 12–66 versus CT
- Patients receiving 2L+ IO treatments reported improvement in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ)-Core30 scores (OAK trial: atezolizumab; RATIONALE-303 trial: tislelizumab) versus CT with better least squares mean differences between the treatment arms in global health status/quality of life, physical function, and role function domains
- RATIONALE-303 also reported improved QLQ-Lung Cancer-13 scores in the tislelizumab arm versus CT

Figure 3. mPFS of the Included Trials

SoC[1]: Erlotinib/gemcitabine/vinorelbine; SoC[2]: Docetaxel/ramucirumab, docetaxel, gemcitabine, and pemetrexed.
Atezo, atezolizumab; Ave, avelumab; Bavi, bavituximab; CT, chemotherapy; Durva, durvalumab; HR, hazard ratio; mPFS, median progression-free survival; Nivo, nivolumab; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; Ramucir, ramucirumab; 2L, second-line; 2L+, second-line and beyond; Sinti, sintilimab; SoC, standard of care; TC, tumor cell; TIS, tislelizumab; Treme, tremelimumab.

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Presenter disclosures

Lin Zhan is an employee of BeiGene and may hold stock or other ownership.

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