Clinical Outcomes of First-line (1L) 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) comprehensively captured first-line (1L) treatments for advanced non–small cell lung cancer (aNSCLC). In most studies, improved response outcomes were reported in the immuno-oncology (IO) therapy ± chemotherapy (CT) (IO ± CT) arm compared with CT. Most studies comparing IO ± CT versus CT reported similar rates of all-cause adverse events (AEs) and treatment-emergent AEs (TEAEs), while mixed results were reported for treatment-related AEs (TRAEs). Other treatment combinations (IO ± CT vs. IO and IO ± anti-angiogenic therapy [AT] + CT vs. AT + CT) reported mixed results**
- **Most studies comparing IO ± CT versus CT as 1L treatment showed significant improvement in median overall survival (mOS) in the IO arm. Such results were reported for both the intention-to-treat (ITT) population and the subgroup of patients with programmed death-ligand 1 (PD-L1) ≥50%. Studies reported mixed results for median progression-free survival (mPFS), with a mix of statistically significant and numerical improvement reported in the IO ± CT arms compared with the CT arm**
- **Combinations of IO and CT ± AT demonstrated improved mOS and mPFS in the PD-L1 ≥50% subgroup**

Background

- Non–small cell lung cancer (NSCLC) is the predominant subtype of lung cancer, responsible for approximately 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 more 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 platinum-based CT, IO as monotherapy or in combination therapy, or AT in patients with oncogenic alterations

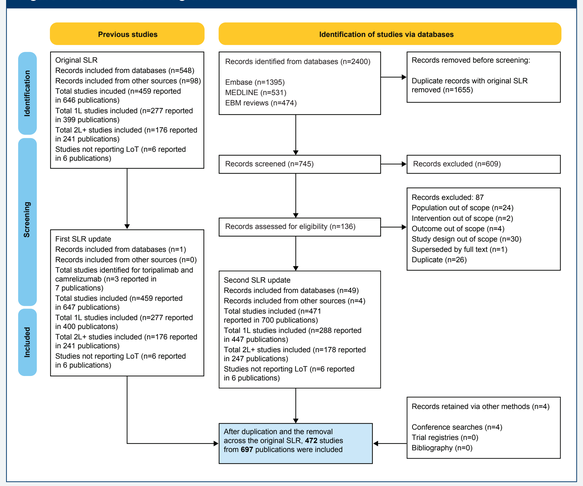
Objective

- This SLR was conducted to identify and summarize evidence from randomized control trials (RCTs) concerning efficacy, health-related quality of life, safety and tolerability outcomes of CT, IO (as monotherapy or as combination therapy), and AT in 1L aNSCLC

Methods

- The SLR followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Publications (2010–2023 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 searched in addition (2020–2023). The SLR was performed based on an existing SLR published in 2015, Pilkington et al 2015,[1] whose search covered publications between 2001 and 2009
- RCTs published in English and including patients ≥18 years of age with unresectable or metastatic 1L 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 (e.g., response and safety outcomes)

Figure 1. PRISMA Flow Diagram

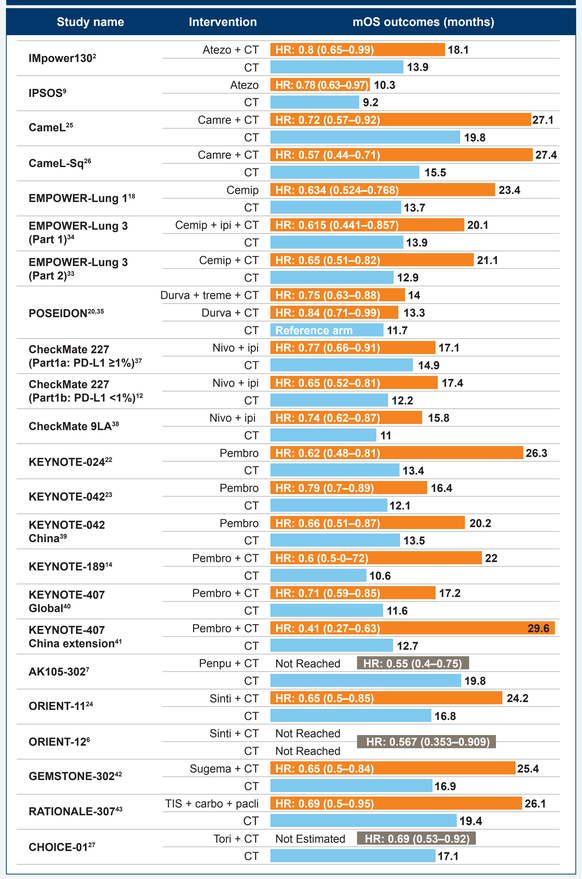


EBM, evidence-based medicine; 1L, first-line; LoT, lines of therapy; PRISMA; Preferred Reporting Items for Systematic Reviews and Meta-Analyses; 2L+, second-line and beyond; SLR, systematic literature review.

Results

- There were 472 unique studies, reported in 697 publications, identified from the SLR (**Figure 1**)
- Studies meeting the following criteria were prioritized:
  - IO as an intervention
  - Both arms featured treatment regimens as per the Population, Interventions, Comparators, Outcomes and Study Design criteria
  - Sample size ≥100
- There were 36 unique prioritized studies based on the aforementioned criteria, reported in 141 publications:
  - Thirty-two studies compared IO ± CT versus CT
  - Two studies compared IO ± CT versus IO
  - Two studies compared IO ± AT + CT versus AT + CT
- 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 trials. The demographic and baseline characteristics of the trial cohorts were largely similar across the studies

Figure 2. mOS of IO ± CT Versus CT (Trials Reporting Statistically Significant Differences)



Atezo, atezolizumab; Camre, camrelizumab; Carbo, carboplatin; Cemip, cemiplimab; CT, chemotherapy; Durva, durvalumab; HR, hazard ratio; IO, immuno-oncology; Ipi, ipilumab; mOS, median overall survival; Nivo, nivolumab; Pacli, paclitaxel; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; Penpu, penpulimab; Sinti, sintilimab; Sugema, sugemalimab; TIS, tislelizumab; Tori, toripalimab; Treme, tremelimumab.

- Smoking status was available in 34 studies:
  - 3.2%–40.5% of patients had never smoked
  - 59.4%–100% were current or former smokers
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) was reported in 35 studies, with most patients scoring 0 (11%–46.9%) or 1 (37.4%–87.6%); ECOG PS ≥2 ranged from <1%–76.8%
- Most studies included patients with mixed histology (21), followed by non-squamous only (8) and squamous only (5)
- Twenty-two studies reported subgroup results for patients with PD-L1 ≥50% expression

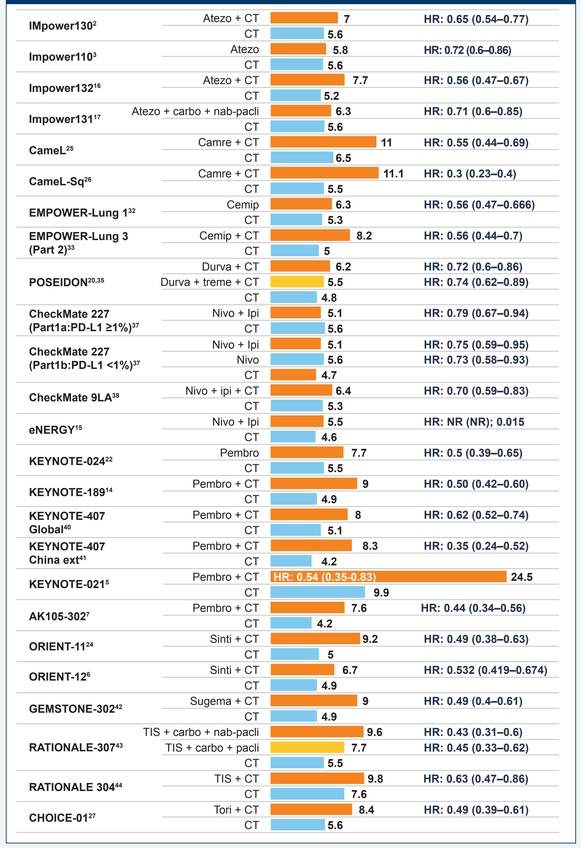
Median Overall Survival

- All 36 studies included reported mOS

IO ± CT versus CT

- There were 32 studies that compared IO ± CT versus CT, with mOS between 5.0–34.5 months for IO ± CT versus 6.0–21.1 months for CT. Of these, 21 studies comparing IO ± CT versus CT reported statistically improved mOS in the IO ± CT arm (studies reporting significantly different mOS are presented in **Figure 2**)
- At the time of publishing the studies, mOS was not reached in ORIENT-12 (sintilimab), AK105-302 (penpulimab) and not estimated in CHOICE-01 (toripalimab), although all 3 studies reported significant benefit in OS for IO ± CT versus CT

Figure 3. mPFS of IO ± CT Versus CT (Trials Reporting Statistically Significant Differences)



Atezo, atezolizumab; Camre, camrelizumab; Carbo, carboplatin; Cemip, cemiplimab; CT, chemotherapy; Durva, durvalumab; HR, hazard ratio; IO, immuno-oncology; Ipi, ipilumab; mPFS, median progression-free survival; nab-pacli, nab-paclitaxel; Nivo, nivolumab; Pacli, paclitaxel; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; Penpu, penpulimab; Sinti, sintilimab; Sugema, sugemalimab; TIS, tislelizumab; Tori, toripalimab; Treme, tremelimumab.

- Results from both the ITT population and the PD-L1 ≥50% subgroup suggested survival benefit in terms of mOS for IO monotherapy or IO combination therapy versus CT (**Table 1**)

Table 1. Interstudy Ranges of mOS for IO Monotherapy or in Combination Versus CT

	IO monotherapy	CT	IO combination*	CT
mOS- ITT (range, months)	10.3–26.3	9.2–14.9	5.0–34.5	6.0–21.1
mOS- PD-L1 ≥50% (range, months)	11.0–26.1	12.2–14.7	15.2–36.6	10.1–15.8

*IO combination includes combinations of different IO therapies and IO + CT.
CT, chemotherapy; IO, immuno-oncology; ITT, intention-to-treat; mOS, median overall survival; PD-L1, programmed death-ligand 1.

IO ± CT versus IO

- Two studies including IO in both arms (durvalumab-tremelimumab-CT versus durvalumab-tremelimumab, and pembrolizumab-ipilumab versus pembrolizumab) reported similar results between arms
- Similar results were also observed for the PD-L1 ≥50% subgroup of CCTG BR34 trial

IO ± AT + CT versus AT + CT

- Two studies comparing IO ± AT + CT versus AT + CT reported statistically improved mOS in the IO + AT + CT arm (atezolizumab-bevacizumab-CT vs. bevacizumab-CT and nivolumab-bevacizumab-CT vs. bevacizumab-CT)
- mOS was similar between IO + CT versus AT + CT arm (atezolizumab-CT vs. bevacizumab-CT)
- One trial assessed the PD-L1 ≥50% subgroup and demonstrated numerically improved mOS upon addition of nivolumab to bevacizumab-CT

Median Progression-Free Survival

- All included studies reported mPFS

IO ± CT versus CT

- Thirty-two studies compared IO ± CT versus CT and reported results for mPFS, ranging between 2.9–24.5 months for IO ± CT versus 4.0–9.9 months for CT (studies reporting significantly different mPFS are presented in **Figure 3**)
- Of these, 24 studies reported statistically significant improvement in mPFS for IO ± CT versus CT
- Six studies reported numerically improved mPFS for CT versus IO ± CT (including the nivolumab monotherapy arm of the 3-arm CheckMate 227 Part 1a study)
- Four studies reported similar results between arms (including Part 1 of the EMPOWER-Lung 3 study)
- Results from the ITT population showed a mixed picture regarding the benefit of IO (monotherapy or in combination with CT) in terms of mPFS. However, for the PD-L1 ≥50% subgroup, the reported mPFS tended to show benefit for IO monotherapy or IO combination therapy compared to CT (**Table 2**)

Table 2. Interstudy Ranges of mPFS for IO Monotherapy or in Combination Versus CT

	IO monotherapy	CT	IO combination*	CT
mPFS – ITT (range, months)	4.2–7.7	4.0–6.8	2.9–24.5	4.0–9.9
mPFS – PD-L1 ≥50% (range, months)	5.4–8.3	2.8–6.6	6.8–14.6	4.5–5.7

*IO combination includes IO + CT.
CT, chemotherapy; IO, immuno-oncology; ITT, intention-to-treat; mPFS, median progression-free survival; PD-L1, programmed death-ligand 1.

- In the PD-L1 ≥50% subgroup, most IO combinations reported mPFS hazard ratios <1 and statistically significantly longer PFS versus CT

IO ± CT versus IO

- Two studies including IO in both arms reported mixed results for mPFS
- In a PD-L1 ≥50% population, KEYNOTE-598 compared 2 different IOs (pembrolizumab-ipilumab versus pembrolizumab-placebo) and reported similar results between the arms
- The CCTG BR34 trial of all comers, reported that the addition of chemotherapy to durvalumab-tremelimumab resulted in significantly improved mPFS versus durvalumab-tremelimumab
- While in the PD-L1 ≥50% subgroup (durvalumab-tremelimumab-CT vs. durvalumab-tremelimumab), the addition of CT to IO numerically improved mPFS

IO ± AT + CT versus AT + CT

- Two studies comparing IO ± AT + CT versus AT + CT reported significantly improved mPFS in the IO ± AT + CT arm. mPFS was not reported for the IO + CT arm (atezolizumab-CT arm)
- One trial assessed the PD-L1 ≥50% subgroup and demonstrated numerically improved mPFS with addition of atezolizumab to bevacizumab-CT

Response Rate

- Twenty-seven studies comparing IO ± CT versus CT reported response data (objective response rate [ORR; 27 studies], disease control rate [DCR; 6 studies], and duration of response [27 studies])
- ORR ranged from 16.9%–75.0% for IO ± CT versus 7.9%–50.0% for CT arms
- Higher ORR in the IO ± CT arm was reported in 23 studies versus CT; DCR ranged from IO ± CT (57.3%–91.2%) versus CT (56.3%–91.0%)
- The studies including IO in both arms and comparing IO ± AT + CT versus AT + CT also reported improved response outcomes in the intervention arms

Safety Outcomes

- Thirty-two studies investigated the safety profile of IO ± CT versus CT
- The rates of all-cause any grade AEs and TEAEs were similar between IO ± CT versus CT in most studies
- The rate of TRAEs showed mixed results with small numerical differences, where some studies favored the IO ± CT arm versus CT, and others reported similar results between arms
- Two studies comparing IO ± CT versus IO reported similar rates of all-cause any grade AEs and higher rates of TRAEs in the intervention arm
- Two studies comparing IO ± AT + CT versus AT + CT reported mixed results for TRAEs rates

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Presenter disclosures

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