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



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. PRIS	6MA Flo	w Diagram

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• 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 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

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)

Study name	Intervention	mOS outcomes (months)
IMpower130 ²	Atezo + CT	HR: 0.8 (0.65–0.99) 18.1
	СТ	13.9
IPSOS ⁹	Atezo	HR: 0.78 (0.63–0.97) 10.3
	СТ	9.2
CameL ²⁵	Camre + CT	HR: 0.72 (0.57–0.92) 27.1
	СТ	19.8
CameL-Sq ²⁶	Camre + CT	HR: 0.57 (0.44–0.71) 27.4
·	СТ	15.5
EMPOWER-Lung 1 ¹⁸	Cemip	HR: 0.634 (0.524–0.768) 23.4
	СТ	
EMPOWER-Lung 3 (Part 1) ³⁴		HR: 0.615 (0.441–0.857) 20.1
(Fart T)		
EMPOWER-Lung 3 (Part 2) ³³		FIR: 0.65 (0.51–0.82) 21.1
(F all 2)		
		$\begin{array}{c} \text{HR: } 0.75 (0.63 - 0.66) \\ \text{HR: } 0.94 (0.74 - 0.00) \\ \text{HR: } 42.2 \end{array}$
POSEIDON ^{20,39}		Reference arm 44.7
		Reference arm 11.7 HP: 0.77 (0.66, 0.91) 17.1
Cneckwate 227 (Part1a: PD-L1 ≥1%) ³⁷		
ChackMate 227	Nivo + ini	HP: 0.65 (0.52–0.81) 17 /
(Part1b: PD-L1 <1%) ¹²		12.2
	Nivo + ini	HR: 0 74 (0 62–0 87) 15 8
CheckMate 9LA ³⁸	СТ	
	Pembro	HR: 0.62 (0.48–0.81) 26.3
KEYNOTE-024 ²²	CT	13.4
	Pembro	HR: 0.79 (0.7–0.89) 16.4
KEYNOTE-042 ²³	СТ	12.1
KEYNOTE-042	Pembro	HR: 0.66 (0.51–0.87) 20.2
China ³⁹	СТ	13.5
	Pembro + CT	HR: 0.6 (0.5-0–72) 22
<u>reinuie-189'*</u>	СТ	10.6
KEYNOTE-407	Pembro + CT	HR: 0.71 (0.59–0.85) 17.2
Global ⁴⁰	СТ	11.6
KEYNOTE-407	Pembro + CT	HR: 0.41 (0.27–0.63) 29.6
China extension ⁴¹	СТ	12.7
AK105-3027	Penpu + CT	Not Reached HR: 0.55 (0.4–0.75)
	СТ	19.8
ORIENT-11 ²⁴	Sinti + CT	HR: 0.65 (0.5–0.85) 24.2
	СТ	16.8
ORIENT-12 ⁶	Sinti + CT	Not Reached HR: 0.567 (0.353–0.909)
	СТ	Not Reached
GEMSTONE-30242	Sugema + CT	HR: 0.65 (0.5–0.84) 25.4
	СТ	16.9
RATIONALE-30743	TIS + carbo + pacli	HR: 0.69 (0.5–0.95) 26.1
	СТ	19.4
CHOICE-01 ²⁷	Tori + CT	Not Estimated HR: 0.69 (0.53–0.92)
	СТ	17.1

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.

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• 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

Study name	Intervention	mOS outcomes (months)
Mpowor1202	Atezo + CT	7 HR: 0.65 (0.54–0.77)
	CT	5.6
	Atezo	5.8 HR: 0.72 (0.6–0.86)
mpower110 [°]	СТ	5.6
	Atezo + CT	7.7 HR: 0.56 (0.47–0.67)
mpower132 ¹⁶	СТ	5.2
Atez	ro + carbo + nab-pacli	6.3 HR: 0.71 (0.6–0.85)
mpower131 ¹⁷	CT	56
	Camre + CT	11 HR: 0.55 (0.44–0.69)
ameL ²⁵	CT	6.5
	Camre + CT	11 1 HR: 0 3 (0 23–0 4)
ameL-Sq ²⁶		5.5
	Cemin	6 3 HP: 0 56 (0 47_0 666)
EMPOWER-Lung 1 ³²		5.2 HK. 0.36 (0.47–0.000)
INIPOWER-LUNG 3 Part 2133		0.2 MK: U.56 (U.44–U./)
r ai i 2)**		
	Durva + CT	6.2 HR: 0.72 (0.6–0.86)
USEIDON ^{20,35}	Durva + treme + CT	5.5 HR: 0.74 (0.62–0.89)
	CT	4.8
CheckMate 227	Nivo + Ipi	5.1 HR: 0.79 (0.67–0.94)
Part1a:PD-L1 ≥1%) ³⁷	СТ	5.6
bockMate 227	Nivo + Ipi	5.1 HR: 0.75 (0.59–0.95)
Part1h:PD-I 1 <1%) 37	Nivo	5.6 HR: 0.73 (0.58–0.93)
	СТ	4.7
SheekMate OL A38	Nivo + ipi + CT	6.4 HR: 0.70 (0.59–0.83)
	CT	5.3
	Nivo + Ipi	5.5 HR: NR (NR); 0.015
NERGY ¹⁵	CT	4.6
	Pembro	7.7 HR: 0.5 (0.39–0.65)
KEYNOTE-024 ²²	СТ	5.5
	Pembro + CT	9 HR: 0.50 (0.42–0.60)
EYNOTE-189 ¹⁴		4.9
	Dombro + CT	4.5 8 HP: 0.62 (0.52_0.74)
$\frac{1}{2} \log \left(\frac{1}{2} \log \left(1$		5 1
		5.1
LEYNUIE-407		8.3 HR: 0.35 (0.24–0.52)
EYNOTE-021⁵	Pembro + CT	1R: 0.54 (0.35-0.83) 24.5
	CT	9.9
K105-302 ⁷	Pembro + CT	7.6 HR: 0.44 (0.34–0.56)
	CT	4.2
ORIENT-11 ²⁴	Sinti + CT	9.2 HR: 0.49 (0.38–0.63)
	CT	5
ORIENT-12 ⁶	Sinti + CT	6.7 HR: 0.532 (0.419–0.674)
	CT	4.9
	Sugema + CT	9 HR: 0.49 (0.4–0.61)
	CT	4.9
TIS RATIONALE-30743	S + carbo + nab-pacli	9.6 HR: 0.43 (0.31–0.6)
	TIS + carbo + pacli	7.7 HR: 0.45 (0.33–0.62)
	CT	5.5
	TIS + CT	9.8 HR: 0.63 (0.47–0.86)
ATIONALE 30444		76
	Tori + OT	

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; Sinti, sintilimab; Sugema, sugemalimab; TIS, tislelizumab; Tori, toripalimab; Treme, tremelimumab.

Table 1.

mOS- ITT

mOS- PD-L

- IO ± CT versus IO between arms
- $IO \pm AT + CT$ versus AT + CT

• All included studies reported mPFS

- IO ± CT versus CT

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

mPFS – IT mPFS – PD-

- *IO combination includes IO + CT.
- *IO* ± *CT* versus *IO*

Response Rate

Safety Outcomes

- studies

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• 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**)

terstudy Ranges of mOS for IO Monotherapy or in Combination Versus CT				
	IO monotherapy	СТ	IO combination*	СТ
ange, months)	10.3–26.3	9.2–14.9	5.0–34.5	6.0–21.1
≥50% (range, months)	11.0–26.1	12.2–14.7	15.2–36.6	10.1–15.8

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

• Two studies including IO in both arms (durvalumab-tremelimumab-CT versus durvalumabtremelimumab, and pembrolizumab-ipilumab versus pembrolizumab) reported similar results

• Similar results were also observed for the PD-L1 ≥50% subgroup of CCTG BR34 trial

• 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 nivolumabbevacizumab-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

• 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**)

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

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

• 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 durvalumabtremelimumab 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

$IO \pm AT + CT$ versus AT + CT

• Two studies comparing IO ± AT + CT versus AT + CT reported significantly improved mPFS in the $IO \pm AT + CT arm.$ 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

• 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 \pm AT + CT versus AT + CT also reported

improved response outcomes in the intervention arms

• 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 • 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 \pm AT + CT versus AT + CT reported mixed results for TRAEs rates

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