# 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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# 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<sup>®</sup>, MEDLINE<sup>®</sup>, 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

Previous studies	Identification of studies via databases				
Original SLR Records included from databases (n=548)	Records identified from databases (n=2400)	Records removed before screening:			
Records included from other sources (n=98) Total studies included (n=459 reported in 646 publications) Total 1L studies included (n=277 reported in 399 publications)	Embase (n=1395) MEDLINE (n=531) EBM reviews (n=474)	Duplicate records with original SLR removed (n=1655)			
Total 2L/2L+ studies included (n=176 reported in 241 publications) Studies not reporting LoT (n=6 reported					
in 6 publications)	Records screened (n=745)	Records excluded (n=609)			
First SLR update Records included from databases (n=1) Records included from other sources (n=0) Total studies identified for toripalimab and camrelizumab (n=3 reported in 7 publications) Total studies included (n=459 reported in 647 publications) Total 1L studies included (n=277 reported in 400 publications) Total 2L/2L+ studies included (n=176 reported in 241 publications) Studies not reporting LoT (n=6 reported in 6 publications)	Records assessed for eligibility (n=136) Second SLR update Records included from databases (n=49) Records included from other sources (n=4) Total studies included (n=471 reported in 700 publications) Total 1L studies included (n=288 reported in 447 publications) Total 2L/2L+ studies included (n=178 reported in 247 publications) Studies not reporting LoT (n=6 reported in 6 publications)	Records excluded: 87 Population out of scope (n=24) Intervention out of scope (n=2) Outcome out of scope (n=4) Study design out of scope (n=30) Superseded by full text (n=1) Duplicate (n=26)			
	After duplication and the removal across the original SLR, <b>472</b> studies from <b>697</b> publications were included	Records retained via other methods (r Conference searches (n=4) Trial registries (n=0) Bibliography (n=0)			

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**)

#### References

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• 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 (2L) and second-line (2L) and second-line (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

2L+

#### • 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  $\pm$  AT versus CT  $\pm$  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 versus 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
- $2L+, IO \pm AT$  versus  $CT \pm AT$

• Two studies reported mPFS for IO  $\pm$  AT and CT  $\pm$  AT. Both reported similar results between arms **Response rate** 

- 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])

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• 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

Study name	Intervention		mOS o	outcome	es (months			Figure
	Bavi + CT	HR: 1.06 (0.88–1.29) 10.5				Stud		
SUNRISE <sup>1</sup>	СТ	CT 10.9						
CheckMate 017 <sup>2</sup>	Nivo	HR: 0.62 (0.	48–0.79)	9.2				
	СТ		6.0					SUN
CheckMate 057 <sup>3</sup>	Nivo	HR: 0.7 (0.5	8–0.83)		12.2			Che
	СТ			9.5				Che
CheckMate 078⁴	Nivo	HR: 0.75 (0.	61–0.93)		11.9			Che
	СТ			9.5			N	
KEYNOTE-010⁵	Pembro	HR: 0.7 (0.6	1–0.8)		11.8	22	ř	Che
	СТ		1	8.4				
ORIENT-36	Sinti	HR: 0.74 (0.	56–0.96)		11.8			KEY
	СТ		ŧ	8.3				
RATIONALE-303 <sup>12</sup>	TIS	Not reached	HR: 0.64	4 (0.53–	0.77)			ORI
	СТ	Not reached						
Gerber et al 2016 <sup>7</sup>	Bavi + CT	HR: 0.66 (0.	40–1.10)		11.7			Ger
	Bavi + placebo		7.3					
OAK <sup>8</sup>	Atezo	HR: 0.75 (0.	64–0.89)		13.8			OAI
	СТ			9.6				
POPLAR <sup>9</sup>	Atezo	HR: 0.76 (0.	58–1.00)		12.6			POI
	CT			9.7	7			
JAVELIN Lung 200 <sup>10</sup>	Ave	HR: 0.90 (0.	77–1.05)	10	.6			JAV
	СТ			9.9				
KEYNOTE-033 <sup>11</sup>	Pembro	HR: 0.75 (0.	61–0.92)		12.9			KE
	СТ			10	10.6			
RATIONALE-303 <sup>12</sup>	TIS	HR: 0.66 (0.	56–0.79)			16.9		RAT
	CT				11.9		2L	
RATIONALE-303 _Chinese population <sup>12</sup>	TIS	HR: 0.62 (0.	5–0.761)			17.8	+	RAT
	2 CT				11.5			Ch
ARCTIC (Study A: PD-L1 TC ≥25%) <sup>13</sup>	Durva	HR: 0.63 (0.	42–0.93)		11.7			AR
	SoC <sup>1</sup>		6.8					PD-
ARCTIC (Study B: PD-L1 TC <25%) <sup>13</sup>	Durva + treme	HR: 0.8 (0.6	1–1.05)		11.5			
	Treme		6.9	HR: 0.	78 (0.56–1.	11)		AR
	Durva	HR: 0.98 (0.	74–1.3)	10.0				PD
	SoC <sup>1</sup>	Reference a		8.7				
Ra Lung-MAP S1800A <sup>14</sup>	Ramucir + pembro	HR: 0.69 (0.	51–0.92)		14.	5		Lun
	SoC <sup>2</sup>				11.6			

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.

Presenter disclosures

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

• 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  $\pm$  AT versus CT  $\pm$  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

mPFS of the Included Trials mPFS outcomes (months) Intervention Bavi + CT Not reported HR: 1.00 (0.82–1.22) ISE<sup>1</sup> CT Not reported Nivo HR: 0.61 (0.47–0.8) 3.5 kMate 017<sup>2</sup> СТ 2.6 Nivo HR: 0.9 (0.75–1.08) 2.3 kMate 057<sup>3</sup> СТ 4.4 Nivo HR: 0.78 (0.64–0.96) 2.8 kMate 0784 СТ 2.8 IR: 0.84 (0.73–0.96) Pembro 4.0 **IOTE-010**<sup>5</sup> СТ 4.1 IR: 0.52 (0.39–0.68) 4.3 Sinti NT-3<sup>6</sup> CT 2.8 Bavi + CT HR: 0.74 (0.45–1.21) 4.5 er et al 2016<sup>7</sup> 3.3 Bavi + placebo Atezo HR: 0.96 (0.85–1.08) 2.7 СТ 3.8 Atezo HR: 0.94 (0.72–1.23) 2.7 AR 3.0 СТ Ave HR: 1.16 (0.97–1.40) 2.8 LIN Lung 200<sup>10</sup> СТ 4.2 HR: 0.79 (0.63–0.99) Pembro 3.4 **NOTE-033**<sup>11</sup> СТ 3.2 TIS HR: 0.63 (0.53–0.75) 4.2 **DNALE-303**<sup>12</sup> СТ 2.6 TIS HR: 0.61 (0.501–0.741) 4.1 DNALE-303 ese population<sup>12</sup> 2.3 СТ Durva 3.8 R: 0.71 (0.49–1.04) ΓIC (Study A: l TC ≥25%)<sup>13</sup> 2.2 SoC<sup>1</sup> IR: 0.77 (0.59–1.01) 3.5 Durva + treme 2.1 HR: 0.67 (0.49–0.92) Treme IC (Study B: I TC <25%)<sup>13</sup> Durva HR: 0.87 (0.68–1.12) 3.1 3.5 SoC<sup>1</sup> HR: 0.86 (0.66–1.14) 4.5 Ramucir + pembro MAP S1800A<sup>1</sup> 5.2 SoC<sup>2</sup>

/gemcitabine/vinorelbine; SoC<sup>2</sup>: 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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