A Systematic Literature Review of the Clinical Efficacy and Safety Evidence Associated With Treatments for Patients With Metastatic Non-Small Cell Lung Cancer That Progressed on Prior Therapies

#CO114

Scan for more information

Nandita Kachru[1], Alex Pashley[2], Emily Kaiser[3], Charlotte Marris[4] and Matthew Radford[1]

[1]Gilead Sciences, Inc, Foster City, CA, USA; [2]Costello Medical, Cambridge, UK; [3]Costello Medical, Boston, Massachusetts, USA; [4]Costello Medical, Manchester, UK.

Conclusions

Outcomes with current treatments after progression on PBC and anti-PD-1/PD-L1 inhibitors remain poor, with few studies reporting median OS or PFS values greater than 1L PBC + ICI combination treatment.[1] These data highlight an unmet medical need in the metastatic NSCLC 1L and above population.

Background

Non-small cell lung cancer (NSCLC), which accounts for 85% of all lung cancers, is often diagnosed at an advanced stage.[2,3] Treatment options for those lacking actionable mutations, who progress on platinum-based chemotherapy (PBC) and programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) treatment (given either sequentially or in combination), are limited to docetaxel or best-supportive care. Clinical trials have shown that in patients with previously treated advanced NSCLC, treatment with docetaxel yields low response rates and is associated with high rates of Grade ≥3 adverse events (AEs).[4-6]

Objective

To report evidence on the efficacy and safety of treatments for patients with NSCLC who progressed after PBC and anti–PD-1/PD-L1 antibodies received in combination or sequentially.

Methods

MEDLINE, Embase, Cochrane and Database of Abstracts of Reviews of Effects databases were searched for relevant publications in June 2023. Grey literature searches of ClinicalTrials.gov and five congresses (occurring from 2021 to 2023) were undertaken, as well as systematic literature review bibliography hand-searches.

Inclusion criteria denoted adult patients with locally advanced (stage IIIB/C) or metastatic (stage IV) NSCLC who had progressed on prior treatment, specifically PBC and anti–PD-1/PD-L1 antibodies, received either in combination or sequentially in any order. Randomised controlled trials (RCTs), non-RCTs and observational studies which reported efficacy, safety, health-related quality of life (HRQoL) or patient-reported outcomes (PROs) were included. The quality of extracted studies was assessed using the University of York's Centre for Reviews and Dissemination or Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool.

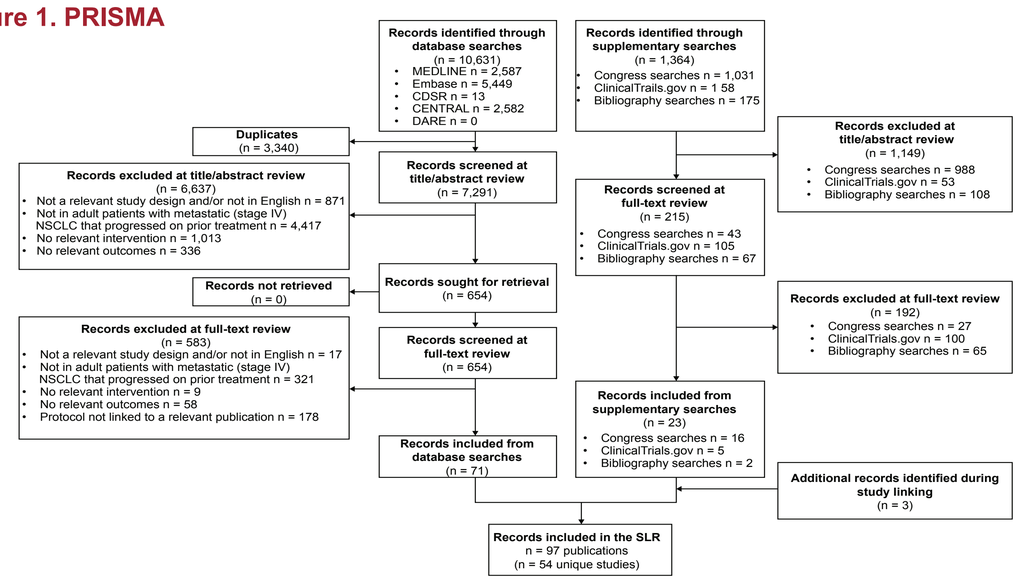
Extracted data included study and patient characteristics at baseline and efficacy outcomes such as overall survival (OS), progression-free survival (PFS) and objective response rate (ORR). Safety outcomes, including discontinuation rates and AEs, were also extracted, in addition to PROs and HRQoL data.

Results

Study and Patient Characteristics

Of 11,995 records retrieved, 54 unique studies were included (**Figure 1**). The majority of studies were international, Phase 2 and non-RCTs (**Table 1**).

Figure 1. PRISMA



CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; MEDLINE, Medical Literature Analysis and Retrieval System Online; NSCLC, non-small cell lung cancer; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; SLR, systematic literature review.

Table 1. Study and Patient Characteristics

Study/Patient Characteristics	Total Studies (N = 54)
Study design, number of studies	
RCT	9
Non-RCT	24
National registry/database	6
Prospective/retrospective cohort	15
Phase of interventional studies, number of studies	
Phase I	2
Phase II	17
Phase III	6
Region/geography, number of studies	
France	2
Germany	3
Italy	1
United States	20
International	23
Other[a]	4
Age, number of studies (range)	48 (23–94)
Sex, number of studies	48
Female, % of patients	0–80.9
Male, % of patients	19–100
Disease stage, number of studies	27
Stage IV, % of patients	86.1–100
Recurrent disease, % of patients[b]	18.1
Disease histology, number of studies	42
Non-squamous, % of patients	70.4–100
Squamous cell, % of patients	0–100
Adenocarcinoma, % of patients	43.3–100
Large cell, % of patients	1–14
Others and NOS, % of patients	0–20
PD-L1 status, number of studies	24
PD-L1 positive, % of patients	25.3–54.4
PD-L1 negative, % of patients	10–49.5
PD-L1 <50%, % of patients	2.1–100
PD-L1 ≥50%, % of patients	4–42
Treatment line, number of studies	33
2nd Line, % of patients	5.9–100
3rd Line, % of patients	21.4–100
4th Line, % of patients	28–32.1
5th Line and above, % of patients[b]	32

Percentages are presented as maximum and minimum percentage reported for outcome across all studies. Reported characteristics included only.
[a]The 'Other' category includes China (n = 1), Croatia (n = 1), Lebanon (n = 1) and Japan (n = 1). [b]Only reported in one study.
NOS, not otherwise specified; PD-L1, programmed death-ligand 1; RCT, randomized controlled trial.

Results Continued

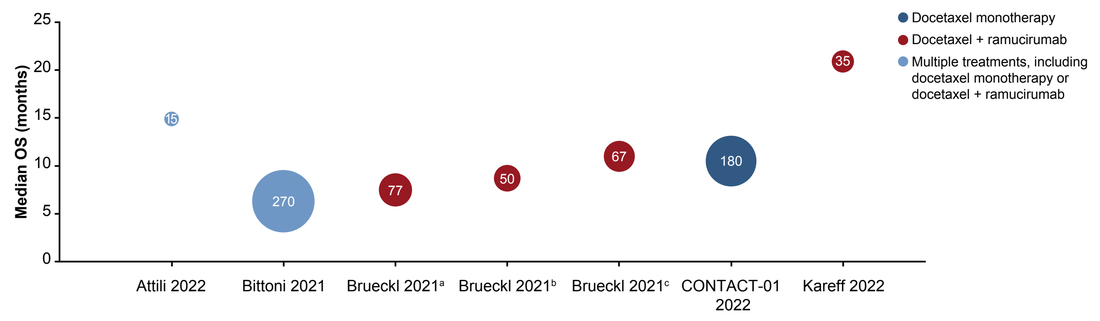
Efficacy Outcomes

Median OS (n = 37) ranged from 3.4 (any third-line [3L] treatment following docetaxel + ramucirumab) to 22.8 months (durvalumab + ceralasertib); it was not estimable in five studies. For patients with stage IV NSCLC treated with docetaxel, median OS was reported in five studies (**Figure 2**). For these patients treated with docetaxel + ramucirumab, the highest reported median OS was 20.9 months (**Figure 2**). In most studies, statistical analyses for OS were not reported (n = 34) or were not significant (n = 4). Only three studies reported significant differences ($p < .05$) in OS between treatments, including pembrolizumab + ramucirumab versus standard of care.

Median PFS (n = 35) ranged from 1.4 (durvalumab + olaparib; durvalumab + oleclumab) to 12.3 months (docetaxel + ramucirumab); it was not estimable in one study (PBC/non-PBC). Median PFS was reported in five studies for patients with stage IV NSCLC treated with docetaxel; in this group, the highest median PFS was 6.8 months in patients treated with 3L docetaxel + ramucirumab (**Figure 3**).

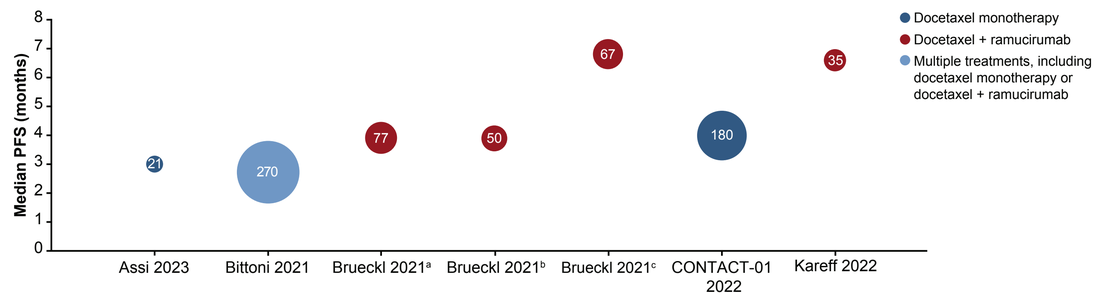
Overall, ORR (n = 31) ranged from 0% (multiple treatments including durvalumab + danvatirsen) to 100% (3L single-agent chemotherapy). Only two studies reported ORR for patients with stage IV NSCLC treated with docetaxel, with the highest reported ORR of 36% in patients (n = 67) treated with 3L docetaxel + ramucirumab (**Figure 4**). In the same study, second-line (2L) docetaxel + ramucirumab following first-line (1L) PBC + PD-1/PD-L1 and docetaxel + ramucirumab following 1L PBC + pemetrexed + pembrolizumab were similar at 33% (n = 77) and 34% (n = 50), respectively. A separate study of docetaxel monotherapy reported a markedly poorer ORR of 13% (n = 180).

Figure 2. Median OS in Patients With Stage IV NSCLC Treated With Docetaxel



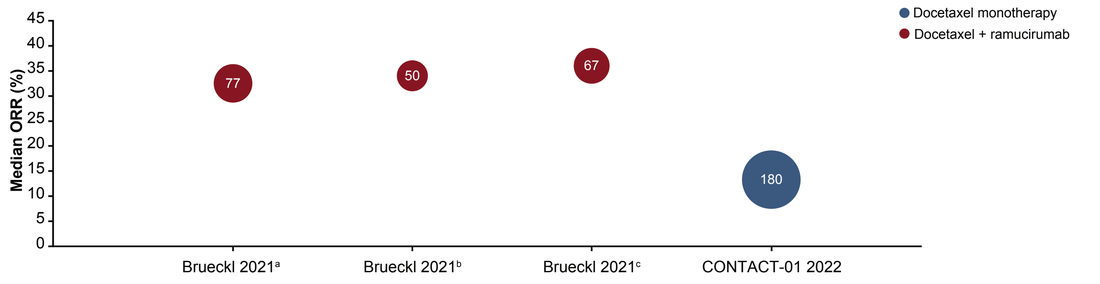
Data values indicate sample size.
[a]2L docetaxel + ramucirumab following 1L platinum chemotherapy + ICI. [b]2L docetaxel + ramucirumab following 1L platinum chemotherapy + pemetrexed + pembrolizumab. [c]3L docetaxel + ramucirumab.
1L, first-line; 2L, second-line; 3L, third-line; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival.

Figure 3. Median PFS in Patients With Stage IV NSCLC Treated With Docetaxel



Data values indicate sample size.
[a]2L docetaxel + ramucirumab following 1L platinum chemotherapy + ICI. [b]2L docetaxel + ramucirumab following 1L platinum chemotherapy + pemetrexed + pembrolizumab. [c]3L docetaxel + ramucirumab.
1L, first-line; 2L, second-line; 3L, third-line; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

Figure 4. Median ORR in Patients With Stage IV NSCLC Treated With Docetaxel



Data values indicate sample size.
[a]2L docetaxel + ramucirumab following 1L platinum chemotherapy + ICI. [b]2L docetaxel + ramucirumab following 1L platinum chemotherapy + pemetrexed + pembrolizumab. [c]3L docetaxel + ramucirumab.
1L, first-line; 2L, second-line; 3L, third-line; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; ORR, objective response rate.

Safety Outcomes

Discontinuations due to AEs (n = 14) ranged from 0% (atezolizumab) to 40% of patients (nintedanib + docetaxel) (**Table 2**). The most reported severe AEs were fatigue (n = 10) and anaemia (n = 9) (**Table 2**).

Table 2. Safety Outcomes and Severe AEs

Safety Outcome	Total Studies (N = 54)
Discontinuation overall, number of studies (% of patients)	9 (6.5–93.8)
Discontinuation due to AEs, number of studies (% of patients)	14 (0–40)
Overall AEs, number of studies (% of patients)	8 (91–100)
Severe or serious anaemia,[a] number of studies (% of patients)	9 (0–19.05)
Severe or serious fatigue,[a] number of studies (% of patients)	10 (0–16.67)

Percentages are presented as maximum and minimum percentage reported for outcome across all studies. [a]Severe or serious AEs correspond to Grade 3 or above.
AE, adverse event.

PRO/HRQoL Outcomes

PRO/HRQoL data were reported in two studies: CANOPY-2 and CodeBreak 200. Both studies reported European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) data, in addition to EQ-5D (CANOPY-2) and EORTC QLQ-LC13 (Codebreak).

References: **1.** Tanimura, K, et al. *Cancers*. 2023;15:4988. **2.** Goldstraw P, et al. *Lancet*. 2011;378:1727–40; **3.** Siegel RL, et al. *CA Cancer J Clin*. 2021;71:7–33; **4.** Borghaei H, et al. *NEJM*. 2015;373:1627–39. **5.** Brahmer J, et al. *NEJM*. 2015;373:123–35; **6.** Herbst RS, et al. *J Clin Oncol*. 2020.

Acknowledgments: The authors acknowledge Charlotte Marris, PhD, Costello Medical, Manchester, UK, for medical writing and editorial assistance. This study was funded by Gilead Sciences, Inc. All costs associated with development of this presentation were funded by Gilead Sciences, Inc.

Author contributions: Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: NK, AP, EK, CM and MR; Drafting of the publication, or revising it critically for important intellectual content: NK, AP, EK, CM and MR; Final approval of the publication: NK, AP, EK, CM and MR.

Correspondence: Nandita Kachru, nandita.kachru@gilead.com

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; AE, adverse event; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effect; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-C30; EORTC QLQ-LC13, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-LC13; EQ-5D, EuroQoL 5 dimensions; HRQoL, health-related quality of life; ICI, immune checkpoint inhibitor; MEDLINE, Medical Literature Analysis and Retrieval System Online; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression free survival; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; PRO, patient-reported outcomes; ROBINS-I, Risk Of Bias In Non-randomised Studies - of Interventions; RCT, randomised controlled trial; SLR, systematic literature review.

Disclosures: **NK** and **MR**: Employees and shareholders of Gilead Sciences, Inc; **AP, EK** and **CM**: Employees of Costello Medical.

ISPOR EU 2024, November 17–20, 2024, Barcelona, Spain