ORIGINAL ARTICLE

Clinical Trial and Real-World Outcomes of Patients With Metastatic NSCLC in the Post-Platinum–Based Chemotherapy Failure Setting

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ABSTRACT

Introduction: A literature review was undertaken to identify clinical trials and real-world studies of patients with stage IV NSCLC who had progressed on or after treatment with platinum-based chemotherapy.

Methods: The EMBASE and MEDLINE databases were used to search for English-language studies published between September 28, 2017, and September 28, 2021. Studies were included in the review if they (1) were clinical trials or real-world analyses of one or more treatment regimens for patients with stage IV NSCLC who had progressed on or after treatment with platinum-based chemotherapy, (2) contained an end point including efficacy, effectiveness, or safety, and (3) included 45 or more patients.

Results: In total, there were 15 publications (nine unique trials and three real-world studies) included. Sample size ranged from 49 to 1253 patients. At least one treatment arm in eight of the nine clinical trials reported an overall response rate of ≥15%. Median progression-free survival (PFS) and overall survival ranged from 1.9 to 5.2 months and 5.4 to 15.4 months in clinical trials and 4.4 to 6.8 months and 8.3 to 18.0 months in real-world studies, respectively. Within studies reporting median PFS, a median PFS of more than or equal to 3 months was reported in eight of 11 clinical trials and both real-world studies. Discontinuation due to adverse events ranged from 1.9% to 18% across all included studies.

Conclusions: Patients with stage IV NSCLC had limited response and a high burden of adverse events during treatment after progression on platinum-containing chemotherapy. There remains a pressing unmet need for additional, effective, and tolerable treatment options in this setting.

Keywords: NSCLC; Literature review; Response; Real-world evidence

Introduction

NSCLC is the most common type of lung cancer making up approximately 85% of all lung cancer cases.[1] Within NSCLC, there are three major histologic subtypes including adenocarcinoma (approximately 40%), squamous cell carcinoma (approximately 25%–30%), and large cell carcinoma (approximately 5%–10%).[1] Incidence rates

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of lung cancer have generally been falling in developed countries but remain substantial with an estimated 228,820 new cases in the United States in 2020 (12.7% of all cancer cases).[2] In the People's Republic of China, the incidence rate of lung cancer has been rising sharply,[3] and the estimated number of cases in 2015 was approximately 787,000.[4]

Patients often present with advanced disease at diagnosis, which has a poor prognosis.[5] In the United States, it is estimated that 55% of patients have distant metastases at diagnosis.[6] Delayed diagnosis is common due to the common symptoms of lung cancer often mirroring chronic respiratory conditions.[7] These symptoms include fatigue, loss of appetite, respiratory problems, cough, pain, and blood in sputum. Common sites of metastases are the bone, lung, brain, adrenal gland, liver, and extrathoracic lymph node.[8] Five-year relative survival rates for metastatic NSCLC (mNSCLC) are only 8%.[9]

Treatment for mNSCLC includes chemotherapy, targeted therapy, and immunotherapy.[10] Platinum-based chemotherapy had long been the standard first-line treatment for patients with mNSCLC,[10] although the treatment paradigm has shifted to targeted agents and immunotherapies for patients with and without driver mutations,[11] respectively. Platinum-based chemotherapy alone has moved to later lines of use in patients with actionable oncogenic drivers and those without contraindications for immunotherapy.[12] Nevertheless, platinum-based chemotherapy can be used in combination with immunotherapy or targeted therapy in patients without actionable mutations regardless of their programmed death-ligand 1 (PD-L1) status, or those with actionable mutations, respectively.[12]

The objective of this review was to identify all clinical trials and real-world evaluations of therapeutic regimens for the treatment of patients with stage IV NSCLC after failure of a platinum-based chemotherapy regimen regardless of its positioning in the treatment paradigm and across all patient types. The results of this review can be used to better understand the unmet needs of patients with stage IV NSCLC after failure of platinum-based chemotherapy and contextualize the results of future treatments.

Methods

Search Strategy

A literature review was conducted using the MEDLINE (PubMed) and EMBASE databases to identify clinical trials and real-world studies of interventions specifically in patients with stage IV NSCLC regardless of oncogenic drivers, who have previously progressed on or after treatment with a platinum-containing chemotherapy regimen at any line of treatment. The search covered September 28, 2017, to September 28, 2021. Studies were excluded if they were not in English or did not include an abstract. Conference abstracts were included in this review.

Study Selection

After the searches were executed, duplicate publications were removed, and the remaining set of unique studies was screened in two phases. The first phase was a screening of the titles and abstracts to identify studies that were not clinical trials or real-world evaluations of interventions or were in a different patient population than the one of interest. Studies in this phase were screened by a single reviewer. Studies passing the title and abstract screen were then included in the full-text review. The full text of each study was evaluated by two independent reviewers to determine whether it met the criteria for inclusion in this review. A third independent reviewer served as the tiebreaker for any studies with a disagreement between the two primary reviewers.

Studies must have been either a clinical trial or real-world evaluation of one or more interventions in patients with stage IV (metastatic) NSCLC who had progressed on or after platinum-based chemotherapy. Studies with mixed populations of stage IIIa or IIIb and stage IV patients were not included unless results were available for a subgroup of stage IV patients only. There were no restrictions placed on the presence or absence of biomarkers, the number of prior treatment lines, or the type of previous treatment outside of patients having to have received and progressed on or after platinum-based chemotherapy. Patients may have previously received both platinum-based chemotherapy and targeted therapies. Studies with a sample size of less than 45 patients were excluded.

Studies must have also included at least one result for efficacy or effectiveness (response, progression-free survival [PFS], or overall survival [OS]) or safety (adverse events [AEs] grade $\geq$3). Response included objective response rate (ORR), disease control rate (DCR), complete response (CR), partial response (PR), stable disease (SDi), and progressed disease (PD).

Data Extraction

Studies included in the review had their contents extracted by a reviewer according to a data extraction sheet in Microsoft Excel. Key data extracted included the study type, country or setting, data source, number of patients, time period, patient population description, interventions, outcome measures, and results. In the case of clinical trials, the trial phase and National Clinical Trial (NCT) number were extracted when available.

Table 1. Summary of Study Details and Patient Characteristics

Study	Study Type	Study Location(s)	Study Start	Sample Size	Current Treatment Line	Prior Immunotherapy Use	Median Age	Brain Metastasis	Adenocarcinoma	Baseline Biomarker Testing	EGFR-mut	ALK+	PD-L1	KRAS	Experimental	Comparator
Disease progression after first-line platinum-based chemotherapy																
Kim et al.[13]	Trial (phase 2) - NCT01498562	Korea	Dec. 2011	160	2L	———	63	18.80%	66%	EGFR	19%	N/R	N/R	4%	Nimotuzumab + gefitinib	Gefitinib
Garon et al.[14]	Trial (phase 3) - NCT01168973	Multinational	Dec. 2010	1253	2L	———	62/61	N/R	N/R	N/R	3%	N/R	N/R	N/R	Docetaxel + ramucirumab	Docetaxel + placebo
Park et al.[15]					2L	———	62/57.5/ 62/61	N/R	N/R	N/R	3%	N/R	N/R	N/R		
Ramalingam et al. 2017[27]					2L	———	62	N/R	N/R	N/R	3%	N/R	N/R	N/R		
Reck et al.[16]				360	2L	———	63/60	N/R	59%	N/R	N/R	N/R	N/R	N/R		
Shih et al.[17]	Trial (phase 2) - NCT01168973/ NCT01703091	Multinational	Dec. 2010/ Dec. 2012	246	2L	———	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	Docetaxel + ramucirumab	Docetaxel + placebo
Garassino et al.[18]	Trial (phase 3) - NCT00637910	Italy	Oct. 2007	222	2L	———	67/66	N/R	69%	EGFR and KRAS	0%	N/R	N/R	N/R	Docetaxel	Erlotinib
Disease progression after second or subsequent-line platinum-based chemotherapy																
Brueckl et al.[19]	Real world (retrospective)	Germany	N/R	67	3L	100%	61.7	N/R	58%	Nonsquamous patients tested for EGFR and ALK	N/R	N/R	Negative: 22% N/R: 40% 1%-49%: 25% ≥50%: 12%	N/R	Ramucirumab + docetaxel	None
Disease progression after first or subsequent-line platinum-based chemotherapy																
Heist et al.[20]	Trial (phase 1/2) - NCT01631552	United States	Dec. 2013	54	2L: 9%; 3L: 32%; 4L: 28%; >5: 32%	33%	64	6%	N/R	N/R	17%	N/R	N/R	17%	Sacituzumab govitecan	None
Moezi et al.[21]	Real world (prospective, observational)	United States	N/R	383	2L and 3L	N/R	66 (mean)	N/R	N/R	N/R	N/R	N/R	N/R	N/R	Nivolumab	Chemotherapy
Katakami et al.[22]	Trial (phase 3) - NCT01454934	Multinational	Sept. 2011	540	2L: 3%; 3L: 42%; 4L: 30%; 5L: 18%; 6L+: 8%	N/R	62.0/62.0	N/R	N/R	N/R	15%	N/R	N/R	N/R	Eribulin	Physician's choice
Disease progression after platinum-based chemotherapy (lines of treatment not reported)																
Wills et al.[23]	Real-world (prospective, observational)	Colombia	Mar. 2011	49	Unknown	N/R	60	N/R	N/R	EGFR, KRAS, and TIMP1	29%	N/R	N/R	2%	Irinotecan + bevacizumab	None
Gerber et al. 2019[26]	Trial (phase 2) - NCT01778803	United States	Sept. 2013	55	Unknown	N/R	62 (mean)	N/R	N/R	KRAS, CDKN2A and TP53	N/R	N/R	N/R	100%	Defactinib	None
Goldman et al.[24]	Trial (phase 3) - NCT02152631	Multinational	Dec. 2014	453	Unknown	16.8%	62/63	N/R	90%	KRAS	N/R	N/R	N/R	100%	Abemaciclib	Erlotinib
Scagliotti et al.[25]	Trial (phase 2) - NCT02450539	Multinational	Aug. 2015	159	Unknown	N/R	64	N/R	N/R	N/R	N/R	N/R	N/R	N/R	Abemaciclib	Docetaxel

2L, second line; 3L, third line; 4L, fourth line; 5L, fifth line; 6L, sixth line; Aug., August; Dec., December; EGFR-mut, EGFR mutant; Mar., March; N/R, not reported; Oct., October; PD-L1, programmed death-ligand 1; Sept., September.

Results

Summary of Studies

There were a total of 15 publications identified, which covered nine unique clinical trials (12 publications) and three real-world studies (Table 1).[13–27] Within the clinical trials, there was one phase 1/2 study,[20] four phase 2 studies,[17,25,26,28] and four phase 3 studies.[14–16,18,22,24,27] The sample size of the trials ranged from 54 patients to 1253 patients. Five of the studies were large multinational trials[14–17,22,24,25,27] and four were conducted in single countries, which included the United States,[20,26] Korea,[13] and Italy.[18] All patients evaluated in the trials had stage IV disease and had progressed on or after platinum-based chemotherapy regimen. Across the nine clinical trials, there were 10 unique treatment arms evaluated. The most frequently evaluated regimens were docetaxel plus or minus placebo (n = 4), docetaxel plus ramucirumab (n = 2), abemaciclib (n = 2), and erlotinib (n = 2).

Among the three real-world studies, one study each was conducted using data from Colombia,[23] Germany,[19] and the United States.[21] The study sample size ranged from 49 patients to 383. Two of the studies evaluated one treatment regimen (docetaxel + ramucirumab and irinotecan + bevacizumab),[19,23] and the other study compared nivolumab with chemotherapy.[21]

Clinical Trials

Brief descriptions of the trials and a summary of the patients included are reported in Table 1.[13–27] The mean or median reported age in all clinical trials was above 60 years of age. Two studies reported the prevalence of brain metastases in patients, which ranged from 6% to 18.8%.[13,20]

There were seven clinical trial publications (four unique trials) evaluating outcomes exclusively in the second-line setting,[13–18,27] two in a mix of second- and third-line and above,[20,22] and the remaining three trials did not report the exact treatment line(s).[24–26]

Clinical outcomes for the included trials are detailed in Table 2.[13–27] Response rates including ORR, DCR, CR, PR, SDi, or PD were reported in nine publications,[14–16,18,22,24,25,27,28] PFS in 11,[14–16,18,20,22,24–28] and OS in 11.[14–18,20,22,24,25,27,28] An ORR of ≥15% for any treatment arm was observed in eight of the nine studies reporting ORR. ORR varied between 2.7% (erlotinib) and 25.6% (docetaxel + ramucirumab).[24,28] The 2.7% ORR for erlotinib was observed in a phase 3 trial of 453 patients receiving either abemaciclib (ORR = 8.9%) or erlotinib.[24] All patients in this trial had stage IV NSCLC with KRAS-mutated (KRAS-mut) tumors. Erlotinib was also studied in Garassino et al., which reported a similar ORR of 3%.[18]

Docetaxel plus ramucirumab was compared with docetaxel plus placebo in the REVEL trial,[14] subgroup analyses,[15,16,27] and pooled analysis.[17] Subgroup analyses included demographics (East Asian versus non-East Asian patients[15] and age[27]) and NSCLC type (adenocarcinoma versus all patients[16]). Reported ORRs were relatively consistent across the primary REVEL analysis, subgroup analyses, and pooled analysis for docetaxel plus ramucirumab (range: 20%–25.6%) and docetaxel plus placebo (range: 8.7%–15%).[14–17,27] Docetaxel was also evaluated as a monotherapy in two additional trials, which reported a similar (15.5%[18]) and slightly higher (20.8%[25]) ORR compared with the REVEL trial and subgroup analyses.

Median PFS was reported in 11 of the 12 publications, and eight of the 11 publications reported a median PFS of three or more months in one or more treatment arms. Median PFS in the 14 studies with data ranged from 1.9 months (defactinib)[26] to 5.2 months (sacituzumab govitecan).[20] Median PFS was the only outcome of interest reported for defactinib in the phase 2 trial of 55 patients with EGFR wild-type (EGFR-wt), KRAS-mut, and stage IV NSCLC and ranged from 41 to 47 days depending on TP53 and CDKN2A alterations.[26] Other instances of median PFS of two months or less were reported for erlotinib in the phase 2 study of EGFR-wt patients[29] and nimotuzumab plus gefitinib.[13] Docetaxel plus ramucirumab consistently reported median PFS of more than 4 months in the REVEL analyses.[14–17,27] Docetaxel monotherapy reported a median PFS of 4.1 months in a REVEL subgroup analysis of patients 70 years and older[27] and a broader trial of patients with stage IV squamous NSCLC.[25] One study reported the 6-month PFS rate, which was 16.5% for erlotinib.[18]

Median OS was reported in 11 publications and ranged from 5.4 months (erlotinib)[18] to 15.4 months (docetaxel + ramucirumab)[17] (Fig. 1). All trials reported at least one regimen with a median OS of 6 or more months. The lowest median OS was observed for erlotinib in a phase 3 study of EGFR-wt patients with a median OS of 5.4 months. Nevertheless, another phase 3 study of KRAS-mut patients reported a slightly improved median OS of 7.8 months for erlotinib.[24] Median OS of docetaxel plus ramucirumab and docetaxel plus placebo in various analyses of the REVEL trial ranged from 8.3 months to 15.44 months and 6.2 months to 12.88 months, respectively.[14–17,27] Outside of the REVEL analyses, docetaxel had a median OS of 8.2 months[18] in EGFR-wt NSCLC and 12.4 months in squamous NSCLC.[25] One-year OS rate was reported in one trial with rates of 39.6% for docetaxel and 31.8% for erlotinib.[18]

The incidence of grade ≥3 AEs was relatively high for all studies with reporting data. AE (grade ≥3) rates were noticeably higher in patients receiving docetaxel-based

Table 2. Summary of Outcomes in Clinical Trials and Real-World Studies in Stage IV NSCLC After Platinum-Based Chemotherapy

						Outcomes							
							Progression-Free Survival		Overall Survival				
Study	Study Type	Sample (n)	Treatment Line	Subgroup(s)	Regimen	Response	Median	6-mo (%)	Median (mo)	12-mo (%)	Grade ≥3 AEs	Most Frequent Grade 3+ AEs	Discontinuation due to AE
Disease progression after first-line platinum-based chemotherapy													
Garon et al.[14]	Clinical trial	1253	2L	———	Docetaxel + ramucirumab	ORR: 23%	4.5 mo	———	10.5	———	79%	Neutropenia, febrile neutropenia, fatigue	15.00%
					Docetaxel + placebo	ORR: 14%	3 mo	———	9.1	———	71%	Neutropenia, leucopenia, fatigue	8.90%
Kim et al.[13]	Clinical trial	160	2L	———	Nimotuzumab + gefitinib	ORR: 16.7% CR: 0% PR: 16.7% SDi: 37.2% DCR: 53.9%	2.0 mo	———	14.0	———	———	Acneiform rash, diarrhea, anorexia, AST elevation, and ALT elevation	———
					Gefitinib	ORR: 22.1% CR: 0% PR: 22.1% SDi: 42.9% DCR: 64.9%	2.8 mo	———	13.5	———	———	Anorexia, ALT elevation, AST elevation, and nausea	———
Park et al.[15]	Clinical trial	1253	2L	East Asian patients	Docetaxel + ramucirumab	ORR: 25.6%	4.9 mo	———	15.4	———	75 mg/m^2 docetaxel: 96.9% 60 mg/m^2 docetaxel: 54.5%	Neutropenia, febrile neutropenia, anemia	———
					Docetaxel + placebo	ORR: 8.7%	2.8 mo	———	10.2	———	75 mg/m^2 docetaxel: 78.8% 60 mg/m^2 Docetaxel: 53.8%	Neutropenia, febrile neutropenia, anemia	———
				Non-East Asian patients	Docetaxel + ramucirumab	ORR: 22.7%	4.5 mo	———	10.3	———	75 mg/m^2 Docetaxel: 78.4%	Neutropenia, febrile neutropenia, fatigue	———
					Docetaxel + placebo	ORR: 14%	3.0 mo	———	9.1	———	75 mg/m^2 docetaxel: 71.9%	Neutropenia, fatigue, febrile neutropenia	———
Ramalingam et al.[27]	Clinical trial	1253	2L	<65 y	Docetaxel + ramucirumab	ORR: 24.3%	4.8 mo	———	10.9[a]	———	75.60%	Neutropenia, febrile neutropenia, leukopenia	8.50%
					Docetaxel + placebo	ORR: 13.5%	2.8 mo	———	9.1[b]	———	68.80%	Neutropenia, leukopenia, febrile neutropenia, fatigue	4.70%
				≥65 y	Docetaxel + ramucirumab	ORR: 20.7%	4.4 mo	———	8.8[a]	———	84.40%	Neutropenia, febrile neutropenia, fatigue	10.50%
					Docetaxel + placebo	ORR: 13.8%	4.1 mo	———	9.0[b]	———	77.60%	Neutropenia, febrile neutropenia, fatigue	6.10%

(continued)

Table 2. Continued

Study	Study Type	Sample (n)	Treatment Line	Subgroup(s)	Regimen	Outcomes							
						Response	Progression-Free Survival		Overall Survival		Grade ≥3 AEs	Most Frequent Grade 3+ AEs	Discontinuation due to AE
							Median	6-mo (%)	Median (mo)	12-mo (%)			
Reck et al.[16]	Clinical trial	360	2L	———	Docetaxel + ramucirumab	ORR: 23%	4.0 mo	———	8.3	———	74%	———	5%
					Docetaxel + placebo	ORR: 13%	2.5 mo	———	6.3	———	70%	———	4%AZ
				Adenocarcinoma	Docetaxel + ramucirumab	ORR: 20%	4.0 mo	———	8.5	———	74%	———	5%
					Docetaxel + placebo	ORR: 15%	2.6 mo	———	6.2	———	72%	———	4%
Shih et al.[17]	Clinical trial	246	2L	———	Docetaxel + ramucirumab	N/R	———	———	15.44	———	———	———	———
					Docetaxel + placebo	N/R	———	———	12.88	———	———	———	———
Disease progression after second or subsequent-line platinum-based chemotherapy													
Brueckl et al.[19]	Retrospective	67	3L only	———	Ramucirumab + docetaxel	ORR: 36%	6.8 mo	———	11	———	———	Neutropenia, diarrhea, stomatitis, and hematothorax	———
Disease progression after first or subsequent-line platinum-based chemotherapy													
Heist et al.[20]	Clinical trial	54	2L: 9%; 3L: 32%; 4L: 28%; >5: 32%	———	Sacituzumab govitecan	N/R	5.2 mo	———	9.5	———	———	Neutropenia, leukopenia, pneumonia	1.90%
				Prior immune checkpoint inhibitor therapy		N/R	5.2 mo	———	14.6	———	———		
Katakami et al.[22]	Clinical trial	540	2L: 3%; 3L: 42%; 4L: 30%; 5L: 18%; 6L+: 8%	———	Eribulin	ORR: 12%	3.0 mo	———	9.5	———	———	Neutropenia, leukopenia, asthenia	———
					TPC	ORR: 15%	2.8 mo	———	9.5	———	———	Neutropenia, leukopenia, dyspnea	———
Moezi et al.[21]	Prospective, observational	383	2L and 3L	———	Nivolumab	N/R	———	———	11.5	———	———	———	9%
					Chemotherapy	N/R	———	———	8.3	———	———	———	18%
Disease progression after platinum-based chemotherapy (lines of treatment not reported)													
Garassino et al.[18]	Clinical trial	222	Unknown	———	Docetaxel	CR: 5.2% PR: 10.3% OR: 15.5%	2.9 mo	27.3%	8.2	39.6%	———	Neutropenia, alopecia, neurologic	Docetaxel weekly: 5%
					Erlotinib	CR: 0% PR: 3.0% OR: 3.0%	2.4 mo	16.5%	5.4	31.8%	———	Dermatologic, asthenia, diarrhea	3%

(continued)

Table 2. Continued

Study	Study Type	Sample (n)	Treatment Line	Subgroup(s)	Regimen	Outcomes							
							Progression-Free Survival		Overall Survival				
						Response	Median	6-mo (%)	Median (mo)	12-mo (%)	Grade ≥3 AEs	Most Frequent Grade 3+ AEs	Discontinuation due to AE
Gerber et al. 2019[26]	Clinical trial	55	Unknown	Wild-type INK4a/ARF and wild-type TP53	Defactinib	N/R	41 d	———	———	———	27%	Nausea, vomiting, hyperbilirubinemia	9.3%
				INK4a/ARF alteration and wild-type TP53		N/R	47 d	———	———	———			
				Wild-type INK4a/ARF and TP53 mutation		N/R	47 d	———	———	———			
				INK4a/ARF alteration and TP53 mutation		N/R	47 d	———	———	———			
Goldman et al.[24]	Clinical trial	453	Unknown	———	Abemaciclib	ORR: 8.9% CR: 0% PR: 8.9% SDi: 45.6%	3.6 mo	———	7.4	———	Grade 3: 49.1% grade 4: 9.1%	Neutropenia, anemia, fatigue	———
					Erlotinib	ORR: 2.7% CR: 0% PR: 2.7% SDi: 29.0%	1.9 mo	———	7.8	———	Grade 3: 34.3% grade 4: 3.4%	Diarrhea, fatigue, dyspnea	———
Scagliotti et al.[25]	Clinical trial	159	Unknown	———	Abemaciclib	ORR: 2.8% DCR: 50.9%	2.5 mo	———	7.0	———	———	———	———
					Docetaxel	ORR: 20.8% DCR: 64.2%	4.2 mo	———	12.4	———	———	———	———
Wills et al.[23]	Prospective, observational	49	Unknown	———	Irinotecan + bevacizumab	ORR: 32%	4.4 mo	———	18.0	———	———	Hematological (neutropenia and thrombocytopenia)	———

[a]Includes patients aged <70 years.
[b]Includes patients aged >70 years.
2L, second line; 3L, third line; 4L, fourth line; 5L, fifth line; 6L, sixth line; AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; CR, complete response; DCR, disease control rate; N/R, not reported; OR, objective response; ORR, overall response rate; PR, partial response; SDi, stable disease; TPC, treatment of physician's choice.

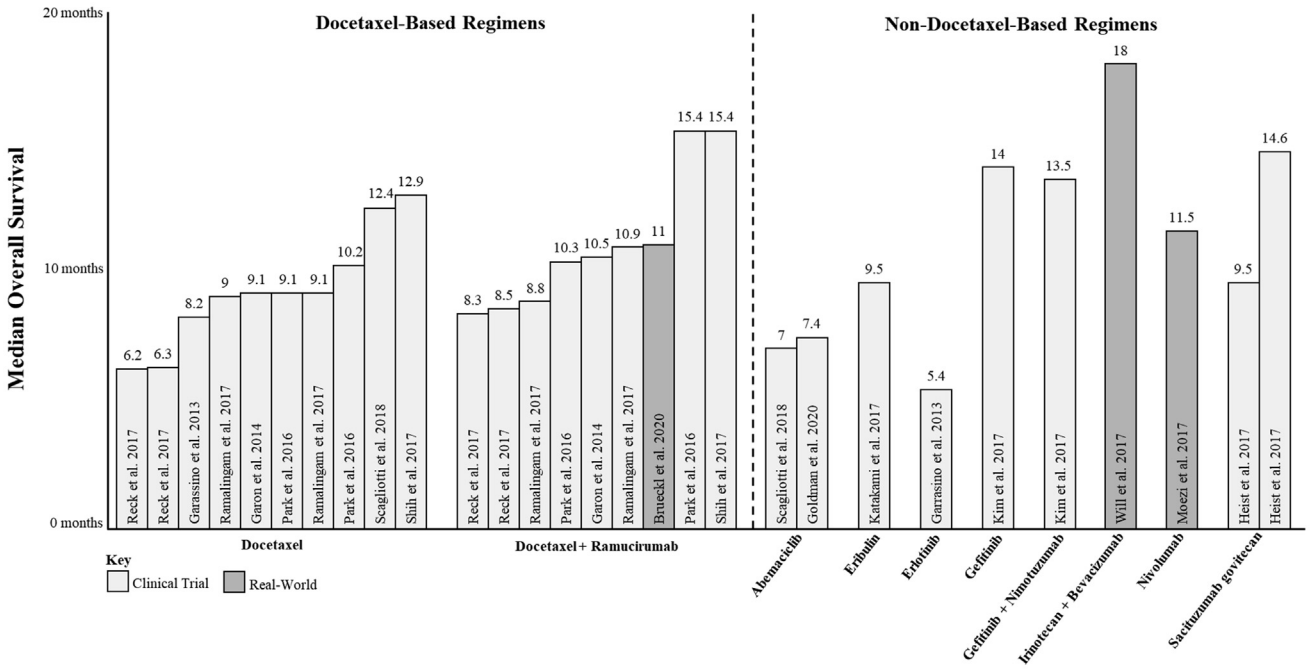

Figure 1. Overall survival results for clinical trials and real-world studies.

regimens including docetaxel monotherapy (53.8%–78.8%)[14–16,27] and docetaxel plus ramucirumab (54.5%–96.9%).[14–16,27] Common grade ≥3 AEs for docetaxel-based regimens included neutropenia, febrile neutropenia, anemia, fatigue, and leukopenia. Abemaciclib reported grade 3 and 4 AE rates of 49.1% and 9.1%,[24] which was slightly higher than erlotinib with 34.3% and 3.4%, respectively.[24]

Discontinuation due to an AE ranged from 3% to 8.9% in docetaxel monotherapy,[14,16,18,27] 5% to 15% in docetaxel plus ramucirumab,[14,16,27] 1.9% for sacituzumab govitecan,[21] 3% for erlotinib monotherapy,[18] and 9.3% for debactinib.[26]

Real-World Studies

A summary of the included real-world studies and the patient characteristics are reported in Table 1 [13–27] and reported outcomes in Table 2.[13–27] The age of patients included in the real-world studies was overall consistent with the clinical trials with the reported median or mean ages above 60 years in all three studies. The presence of brain metastases was not reported in any of the included studies. As with the patient population of the clinical trials, patients in the real-world study were heavily pretreated. The study of Brueckl et al.[19] only included patients receiving third-line therapy, and in Wills et al.,[23] most patients had received an average of three prior lines.

Response rates were reported in two of the three real-world studies, whereas OS and PFS were reported in two and three of the studies, respectively. Within the response rates, the ORR ranged from 32% (docetaxel + ramucirumab) to 36% (irinotecan + bevacizumab).[19,23] Median PFS was reported for the same two studies also reporting ORR and was 6.8 months for docetaxel plus ramucirumab and 4.4 months for irinotecan plus bevacizumab.[19,23]

Median OS ranged from 8.3 months (chemotherapy) to 18.0 months (irinotecan + bevacizumab) (Fig. 1).[21,23] A median OS of 11 months for docetaxel plus ramucirumab in the third line was reported for patients without treatable EGFR or ALK mutations.[19]

The most common real-world grade 3 to 4 AEs were neutropenia, diarrhea, stomatitis, and hematothorax as reported for docetaxel plus ramucirumab.[19] Discontinuation due to an AE was reported for nivolumab and chemotherapy in the real-world study by Moezi et al.[21] and was 9% and 18%, respectively.

Clinical Trial Outcomes Versus Real-World Outcomes

Docetaxel plus ramucirumab was the only treatment regimen included in both the trials and real-world studies. It was evaluated in one real-world study[21] and two unique clinical trials, the results of which were included in five separate publications.[14–17,27]

Differences in patient populations and the number of patients being studied make cross-study comparisons difficult. Nonetheless, clinical outcomes were remarkably similar between real-world studies and clinical trials for docetaxel plus ramucirumab. The ORR was higher in the

real-world study of Brueckl et al.[19] (36%) compared with the clinical trials, which ranged between 20%[16] and 25.6%.[15] This difference may be attributed to the exclusion of nonsquamous patients with treatable EGFR/ALK mutations, although this patient population was heavily pretreated as all were on third-line therapy,[19] whereas the clinical trial outcomes were all in the second-line setting. Median OS in the real-world study was 11 months and fell within the reported range of 8.3 months and 15.44 months in the clinical trials. Grade 3 to 4 AE rates were not reported in the real-world study, but the most common grade 3 to 4 AEs included neutropenia, which was also consistently observed as a common AE in clinical trials.

Prior Immunotherapy Use

Within the studies included in this review, three studies reported the percentage of patients who had received immune checkpoint inhibitors before their inclusion into the study.[19,20,24] Two were trials[20,24] and the other was a real-world study.[18] Within the two trials, 33% of patients in Heist et al.[20] and 16.8% in Goldman et al.[24] had received prior therapy with an immune checkpoint inhibitor. All patients in the real-world study were previously treated with immune checkpoint inhibitors.[19]

The study of Heist et al.[20] of sacituzumab govitecan reported results for all patients (n = 47) and patients specifically with prior immune checkpoint inhibitor therapy (n = 14). The reported clinical benefit (PR + SDi for four or more months) was similar for both patient groups with 43% (n = 20) rate among all patients and 36% (n = 5) among patients with prior immune checkpoint inhibitor use. Median PFS was the same (5.2 mo) for both treatment groups. Nevertheless, median OS was 9.5 months for all patients and 14.6 months among patients with prior immune checkpoint inhibitor use.

The phase 3 trial of 453 patients evaluating abemaciclib versus erlotinib reported no significant differences in the hazard ratios between patients with and without prior immunotherapy use for OS ($p = 0.4827$) and PFS ($p = 0.5084$).[24]

Biomarkers

The reporting of the prevalence of biomarkers and the number of trials that included testing as part of enrollment were low considering the importance of biomarkers to the current treatment paradigm of mNSCLC. Four of the included trials included biomarker testing as a part of enrollment.[13,18,24,26] Kim et al.[13] included EGFR testing as did Garassino et al.,[18] which tested for EGFR and KRAS mutations to exclude EGFR-mut patients from the study population. The trials reported by Goldman et al.[24] and Gerber et al.[26] both tested for KRAS and only included KRAS+ patients. Gerber et al.[26] also tested for CDKN2A and TP53 mutations using central fluorescence in situ hybridization testing.

Within the real-world studies, Moezi et al.[21] did not report biomarker rates or exclusions on the basis of biomarkers but did exclude patients receiving TKIs for EGFR or ALK-mutated NSCLC. The study by Brueckl et al.[19] mandated EGFR and ALK testing for nonsquamous patients to exclude these patients with actionable mutations. This study also reported PD-L1 expression by immunohistochemistry, the only study (trial or real-world) to report such in our review. Last, Wills et al.[23] reported EGFR, KRAS, and TIMP1 mutation rates.

One real-world study evaluated the impact of EGFR mutation on clinical outcomes.[23] In the analysis of irinotecan plus bevacizumab, EGFR-mut patients had significantly improved PFS compared with EGFR-wt patients with no difference in OS.[23] In the same study, lower median expression of TIMP1 was found to be significantly associated with improved OS but not PFS.[23]

EGFR was evaluated in three clinical trials.[13,14,22] Patients with EGFR-mut had significantly longer PFS and OS in the study of gefitinib with and without nimotuzumab ($p < 0.001$ for PFS and $p = 0.001$ for OS).[13] The phase 3 trial of eribulin compared with physician's choice included patients with EGFR-mut (16.3%), EGFR-wt (61.9%), and EGFR unknown (21.9%) NSCLC.[22] Median OS was numerically higher for both eribulin (13.9 mo versus 8.9 mo) and physician's choice (13.0 mo versus 8.7 mo) in EGFR-mut patients compared with EGFR-wt patients. The REVEL trial evaluating ramucirumab plus docetaxel versus docetaxel plus placebo reported a consistent hazard ratio between the comparators in both OS and PFS for EGFR-wt and EGFR-mut patients.[14] Nevertheless, EGFR-mut patients were only 2% and 3% of the ramucirumab plus docetaxel and docetaxel plus placebo arms, respectively.

The phase 3 clinical trial of patients evaluating docetaxel versus erlotinib in patients with EGFR-wt mNSCLC reported no significant differences in the hazard ratios between the treatments according to KRAS mutation status for OS ($p = 0.82$) and PFS ($p = 0.32$).[18] A phase 2 study of defactinib did not find any association of TP53 or CDKN2A with survival in KRAS-mut patients.[26]

Discussion

Previous literature reviews and meta-analyses have either only focused on clinical trials, treatment in the second-line, or have been limited to only PFS and OS as

outcomes.[30,31] This is the first review of clinical trial and real-world treatment outcomes specifically for patients with stage IV NSCLC after failure on or after platinum-based chemotherapy across all patient types and treatment lines. As expected, overall treatment outcomes for these patients were relatively poor and in a tight range. Median PFS and OS ranged from 1.9 to 5.2 months and 5.4 to 15.4 months in clinical trials and 4.4 to 6.8 months and 8.3 to 18.0 months in real-world studies, respectively. The frequency of AEs, especially docetaxel-based regimens, was high, as was the rate of discontinuation due to AEs.

Overall, treatment outcomes between clinical trials and real-world studies were relatively consistent. One key difference between clinical trials and real-world studies was the type of included interventions. Clinical trials most often included chemotherapies and targeted therapies. There were no trials evaluating immune checkpoint inhibitors fitting the inclusion criteria of this review. Nivolumab was included in one real-world study.[21] Nevertheless, three additional real-world studies of nivolumab were excluded from this review due to the sample size restriction.[32–34]

An interesting finding of this review was the relatively low testing, reporting of prevalence, and analysis of key biomarkers for mNSCLC. Given the patient population of interest and the time frame of most of the included studies, it is possible that these patients may not have been tested given the lack of targeted therapies available at the time and their initiation of platinum-based chemotherapy or due to lack of access to testing. Nevertheless, biomarker testing has risen significantly in recent years with approximately two-thirds of patients with newly diagnosed mNSCLC receiving guideline-recommended biomarker testing for the five major biomarkers (BRAF, ROS1, EGFR, ALK, and PD-L1).[35] Adherence to biomarker testing guidelines has also been found to improve patient outcomes.[36] In this analysis, only six studies evaluated the impact of one or more biomarkers including EGFR, KRAS, TP53, TIMP, and CDKN2A on outcomes.[13,14,18,22,23,26] Furthermore, only EGFR was found to significantly affect outcomes.[13,23] These findings can perhaps be due to the low sample size in most of the studies which limit the ability to conduct statistical comparisons and the relatively low survival rates overall.

Cross-study comparison is limited due to large variations in the patient populations owing to locations of metastases, prior therapies, mutation status, and other clinical characteristics. Furthermore, the methodologies used in the assessment and quantification of clinical and safety outcomes can vary between studies and may have significant differences between clinical trials and real-world studies. This also includes the time used to measure outcomes as clinical trials often start measurement at study entry or randomization whereas a retrospective study may index patients on their first dose of the treatment regimen. The frequency of monitoring and examination may also lead to differences in outcomes between clinical trials and real-world studies as patients in clinical trials are often subject to more frequent interactions with the health system. For example, the monitoring of AEs in the real world may not be as frequent or stringent as a clinical trial.[37]

Within the study, comparisons of treatment regimens were limited as there was only one real-world comparative study, which compared nivolumab with chemotherapy.[21] Comparative studies were more common in clinical trials, with 10 of 12 publications including more than one treatment arm. The average incremental PFS gain was only 1.3 months (range: 0.2–2.1 mo) across the nine studies reporting median PFS and more than one treatment arm.[13–16,18,22,24,25,27] In the real-world study, the median OS was numerically 3.2 months higher for nivolumab compared with chemotherapy.[21] In the clinical trials, the average incremental gain in median OS between treatment arms was 2.0 months (range: 0–5.4 mo). These incremental gains in median OS and PFS between treatment arms are heavily influenced by the choice of comparators, which make it difficult for crosstrial comparison. Given the extremely small increases of median OS and PFS between the treatment arms within the studies, a large unmet need exists for new and innovative therapies that can significantly extend life in this population.

This study has several limitations. First, as with any review of the literature, this study is subject to the sensitivity of the searches, databases used, and the human judgment in the selection of appropriate articles. Some relevant publications could have been missed due to the limitations of the search, which include only English-language publications and publication within the searched databases. Second, this review only included studies of patients with stage IV NSCLC. Studies with a mixed population of patients with other stages in addition to stage IV, including stage IIIa or IIIb NSCLC, were excluded. Third, comparison across trials, real-world studies, and between trials and real-world studies is problematic due to large differences in the patient populations, regimens, monitoring, assessment of outcomes, and other confounding factors. Last, the relevance and impact to clinical practice are limited as this review includes interventions that may not be approved by regulatory authorities for the treatment of stage IV NSCLC or those that are being studied in patient populations that differ from their approved population.

In conclusion, few clinical trials and real-world studies focus specifically on patients with stage IV NSCLC with progression on or after platinum-based therapy. Overall treatment outcomes in clinical trials and real-world analyses were similar with both revealing limited PFS and OS duration along with a high burden of AEs. Additional research and investment are needed in this indication to identify life-extending interventions.

CRediT Authorship Contribution Statement

Yu Yang Soon: Methodology, Writing—review and editing.

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References

1. Zappa C, Mousa SA. Non-small cell lung cancer: current treatment and future advances. *Transl Lung Cancer Res*. 2016;5:288.
2. American Cancer Society. Cancer facts & figures 2020. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html. Accessed April 1, 2022.
3. Cao M, Chen W. Epidemiology of lung cancer in China. *Thorac Cancer*. 2019;10:3–7.
4. Gao S, Li N, Wang S, et al. Lung cancer in People's Republic of China. *J Thorac Oncol*. 2020;15:1567–1576.
5. Birring S, Peake M. Symptoms and the early diagnosis of lung cancer. *BMJ*. 2005:268–269.
6. Noone A, Howlader N, Krapcho M. SEER Cancer Statistics Review (CSR) 1975–2015. National Institutes of Health, National Cancer Institute, Surveillance, Epidemiology, and End Results. https://seer.cancer.gov/csr/1975_2015/. Accessed April 1, 2022.
7. Ellis PM, Vandermeer R. Delays in the diagnosis of lung cancer. *J Thorac Dis*. 2011;3:183.
8. Tamura T, Kurishima K, Nakazawa K, et al. Specific organ metastases and survival in metastatic non-small-cell lung cancer. *Mol Clin Oncol*. 2015;3:217–221.
9. American Cancer Society. Lung cancer survival rates. https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/survival-rates.html. Accessed April 1, 2022.
10. Simeone JC, Nordstrom BL, Patel K, Klein AB. Treatment patterns and overall survival in metastatic non-small-cell lung cancer in a real-world, US setting. *Future Oncol*. 2019;15:3491–3502.
11. Hanna NH, Robinson AG, Temin S, et al. Therapy for stage IV non-small-cell lung cancer without driver alterations: ASCO and OH (CCO) joint guideline update. *J Clin Oncol*. 2021;39:1040–1091.
12. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(suppl 4):iv192–iv237.
13. Kim HR, Jang JS, Sun JM, et al. A randomized, phase II study of gefitinib alone versus nimotuzumab plus gefitinib after platinum-based chemotherapy in advanced non-small cell lung cancer (KCSG LU12-01). *Oncotarget*. 2017;8:15943.
14. Garon EB, Ciuleanu T, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384:665–673.
15. Park K, Kim JH, Cho EK, et al. East Asian subgroup analysis of a randomized, double-blind, phase 3 study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small cell lung cancer following disease progression after one prior platinum-based therapy (REVEL). *Cancer Res Treat*. 2016;48:1177–1186.
16. Reck M, Paz-Ares L, Pérol M, et al. Subgroup analysis of patients (Pts) refractory to first-line (1L) chemotherapy from REVEL, a randomized phase 3 study of docetaxel (DOC) with ramucirumab (RAM) or placebo (PBO) for second-line (2L) treatment of stage IV non-small-cell lung cancer (NSCLC). *Ann Oncol*. 2017;28:vi54–vi55.
17. Shih J, Yoh K, Hosomi Y, et al. Ramucirumab in East Asian patients with stage IV non-small cell lung cancer after disease progression on platinum-based therapy: a pooled analysis of two randomized double-blind studies. *Ann Oncol*. 2017;28:x122.
18. Garassino MC, Martelli O, Broggini M, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. *Lancet Oncol*. 2013;14:981–988.
19. Brueckl WM, Reck M, Rittmeyer A, et al. Efficacy of docetaxel plus ramucirumab as palliative third-line therapy following second-line immune-checkpoint-inhibitor treatment in patients with non-small-cell lung cancer stage IV. *Clin Med Insights Oncol*. 2020;14:1179554920951358.
20. Heist RS, Guarino MJ, Masters G, et al. Therapy of advanced non-small-cell lung cancer with an SN-38-Anti-Trop-2 drug conjugate, sacituzumab govitecan. *J Clin Oncol*. 2017;35:2790–2797.

21. Moezi M, Chandler J, Waterhouse D, et al. Nivolumab versus chemotherapy as post-platinum therapy for advanced non-small cell lung cancer in a real-world setting. *J Thorac Oncol*. 2017;12(suppl 2):S1913–S1914.
22. Katakami N, Felip E, Spigel DR, et al. A randomized, open-label, multicenter, phase 3 study to compare the efficacy and safety of eribulin to treatment of physician's choice in patients with advanced non-small cell lung cancer. *Ann Oncol*. 2017;28:2241–2247.
23. Wills B, Cardona AF, Rojas L, et al. Survival outcomes according to TIMP1 and EGFR expression in heavily treated patients with advanced non-small cell lung cancer who received biweekly irinotecan plus bevacizumab. *Anticancer Res*. 2017;37:6429–6436.
24. Goldman JW, Mazieres J, Barlesi F, et al. A randomized phase III study of abemaciclib versus erlotinib in patients with stage IV non-small cell lung cancer with a detectable KRAS mutation who failed prior platinum-based therapy: JUNIPER. *Front Oncol*. 2020;10:578756.
25. Scagliotti GV, Bondarenko I, Ciuleanu T, et al. A randomized phase 2 study of abemaciclib versus docetaxel in patients with stage IV squamous non-small cell lung cancer (sqNSCLC) previously treated with platinumbased chemotherapy. *J Clin Oncol*. 2018;36.
26. Gerber DE, Camidge DR, Morgensztern D, et al. Phase 2 study of the focal adhesion kinase inhibitor defactinib (VS-6063) in previously treated advanced KRAS mutant non-small cell lung cancer. *Lung Cancer*. 2020;139:60–67.
27. Ramalingam SS, Pérol M, Reck M, et al. Efficacy and safety of ramucirumab with docetaxel versus placebo with docetaxel as second-line treatment of advanced non-small-cell lung cancer: a subgroup analysis according to patient age in the REVEL trial. *Clin Lung Cancer*. 2018;19:270–279.e3.
28. Kim EJ, Ko D, Ji W, et al. A randomized phase I/IIa study to evaluate the safety and efficacy of SNK01 (non-genetically modified autologous natural killer cells with enhanced cytotoxicity) plus pembrolizumab in patients with stage IV non-small cell lung cancer. *J Clin Oncol*. 2020;38(suppl 15):3037–3037.
29. Neal JW, Dahlberg SE, Wakelee HA, et al. Erlotinib, cabozantinib, or erlotinib plus cabozantinib as second-line or third-line treatment of patients with EGFR wild-type advanced non-small-cell lung cancer (ECOG-ACRIN 1512): a randomised, controlled, open-label, multicentre, phase 2 trial. *Lancet Oncol*. 2016;17:1661–1671.
30. Vickers AD, Winfree KB, Cuyun Carter G, et al. Relative efficacy of interventions in the treatment of second-line non-small cell lung cancer: a systematic review and network meta-analysis. *BMC Cancer*. 2019;19:1–16.
31. Cope S, Mojebi A, Popoff E, et al. PCN29 comparative efficacy of nivolumab versus relevant treatments in pretreated advanced non-small cell lung cancer (NSCLC): a systematic literature review and indirect treatment comparison of randomized controlled trials (RCTs). *Value Health*. 2019;22:S440.
32. Abbas W, Acharya RP, Pandit A, Gupta S, Rao RR. The real-world experience with nivolumab in previously treated patients with advanced non-small cell lung cancer from a cancer center in India. *S Asian J Cancer*. 2020;9:50–52.
33. Li J, Tong X, Li H. Efficacy and safety of apatinib monotherapy in elderly patients with advanced metastatic non-small cell lung cancer. *Indian J Cancer*. 2020;57:13–17.
34. Somani N, Agarwal P, Singhal H, et al. An observational single-center study of nivolumab in Indian patients with recurrent advanced non-small cell lung cancer. *Indian J Cancer*. 2019;56:315–319.
35. Pasmann AM, Nibley WE, Goldfarb SD, Shetty V, Apple JM, Shah A. BPI22-022: real world adherence to biomarker testing guidelines that inform first-line treatment decisions for patients newly diagnosed with metastatic non-small cell lung cancer in the community setting. *J Natl Compr Canc Netw*. 2022;20:BPI22-022–BPI22-022.
36. John A, Yang B, Shah R. Clinical impact of adherence to NCCN guidelines for biomarker testing and first-line treatment in advanced non-small cell lung cancer (aNSCLC) using real-world electronic health record data. *Adv Ther*. 2021;38:1552–1566.
37. Ewer MS, Herson J. Cardiovascular adverse events in oncology trials: understanding and appreciating the differences between clinical trial data and real-world reports. *Cardio Oncol*. 2022;8:1–7.