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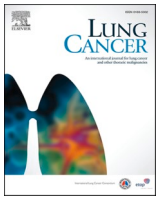

Research Paper

Efficacy and safety of crizotinib in the treatment of advanced non-small cell lung cancer with *ROS1* gene fusion: a systematic literature review and meta-analysis of real-world evidence

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ABSTRACT

Background: Crizotinib was approved to treat patients with advanced non-small cell lung cancer (aNSCLC) with *ROS proto-oncogene 1 (ROS1)* gene fusion in 2016. We conducted a systematic literature review to identify real-world evidence (RWE) studies and estimated the efficacy and safety of crizotinib using meta–analyses (MA) for objective response rate (ORR), real-world progression-free survival (PFS), and overall survival (OS).

Methods: We searched MEDLINE®, Embase, and Cochrane CENTRAL from January 2016 to March 2023 using Ovid® for published single-arm or comparative RWE studies evaluating patients (N ≥ 20) receiving crizotinib monotherapy for aNSCLC with *ROS1* gene fusion. Pooled estimates for ORR and grade 3/4 adverse events (AEs) were derived using the *metafor* package in R while pooled estimates for median real-world PFS (rwPFS) and OS were derived using reconstructed individual patient data from published Kaplan-Meier curves. The primary analysis included all studies regardless of crizotinib line of therapy; a subgroup analysis (SA) was conducted using studies evaluating patients receiving first-line crizotinib.

Results: Fourteen studies met the eligibility criteria and were considered feasible for MA. For the primary analysis, the pooled ORR (N = 9 studies) was 70.6 % (95 % confidence interval [CI]: 57.0, 81.3), median rwPFS was 14.5 months (N = 11 studies), and OS was 40.2 months (N = 9 studies). In the SA, the pooled ORR (N = 4 studies) was 81.1 % (95 % CI: 76.1, 85.2) and the median rwPFS (N = 4 studies) and OS (N = 2 studies) were 18.1 and 60 months, respectively. All MAs were associated with significant heterogeneity ($I^2 > 25$ %). Grade 3/4 AEs occurred in 18.7 % of patients (pooled estimate).

Conclusion: The results from this study are consistent with clinical trial data and, taken collectively, supports crizotinib as a safe and effective treatment across different lines of therapy in patients with *ROS1* aNSCLC in the real-world setting.

1. Introduction

Lung cancer (LC) is one of the most incident malignancies and the leading cause of cancer death worldwide [1]. According to the International Agency for Research on Cancer, an estimated 2.2 million new LC cases and 1.8 million LC-related deaths occurred in 2020 [1]. Non-small cell lung cancer (NSCLC) accounts for 85 % of LC cases [2] and include the most common histological subtypes such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [3].

With the emergence of genomic techniques, tumor genotyping has led to the identification of actionable driver alterations in NSCLC. The *ROS1* gene encodes a tyrosine kinase receptor that plays an important role in the activation of several signaling pathways associated with cellular differentiation, proliferation, growth, and survival [2,4]. *ROS1* gene rearrangement is rare and is detected as an oncogenic driver in 0.9

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% to 2.6 % of NSCLC [5]. Improved deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) sequencing techniques have enabled the identification of numerous *ROS1* rearrangements [2]. Although break-apart fluorescence in-situ hybridization (FISH) is currently regarded as the gold standard for the detection of *ROS1* rearrangement, a myriad of other detection methods may also be employed [6].

Treatment of NSCLC largely depends on the stage of disease at diagnosis and the therapies available to target specific tumor genetic alterations [2,3,7]. Clinical practice guidelines recommend a variety of treatment options for *ROS1*-rearranged advanced or metastatic NSCLC (aNSCLC), including crizotinib, entrectinib, ceritinib, lorlatinib, and repotrectinib [8–10].

Crizotinib is a first-in-class ATP-competitive small-molecule inhibitor of the receptor tyrosine kinases (RTK) c-Met, anaplastic lymphoma kinase (ALK), and *ROS1* [11]. Crizotinib was first approved for *ROS1* aNSCLC in the United States (US) in 2016 and has received regulatory approval for the frontline treatment of patients with aNSCLC with *ROS1* gene rearrangement in many countries worldwide [12–17].

Multiple clinical trials have demonstrated consistent efficacy and safety of crizotinib in patients with *ROS1*–rearranged and ALK-rearranged aNSCLC [18–23]. One such trial, PROFILE 1001, showed a median overall survival (OS) of 51.4 months, median progression-free survival (PFS) of 19.3 months, objective response rate (ORR) of 72 %, and median duration of response (DOR) of 24.7 months with a median follow-up of 62.6 months [18]. Over 50 % of patients in the PROFILE 1001 study remain alive four years following treatment with crizotinib [18]. In addition, several real-world studies in *ROS1* aNSCLC patients across the US, the European Union (EU), and East and South Asia have further established the effectiveness and safety of crizotinib for the treatment of *ROS1*–rearranged aNSCLC [24–37].

While clinical trial data has been instrumental in understanding the efficacy and safety of crizotinib in patients with *ROS1*-rearranged aNSCLC, real-world evidence (RWE) studies offer insight into the effectiveness and safety in the real-world setting. As the first tyrosine kinase inhibitor (TKI) available for patients with aNSCLC *ROS1* rearrangement, there exists more RWE for crizotinib compared to other TKIs used to treat patients with this rare genetic alteration. To our knowledge, there are no published systematic literature reviews (SLRs) and *meta*-analyses (MA) evaluating the effectiveness and safety of crizotinib in the treatment of patients with *ROS1*-rearranged aNSCLC strictly in an RWE setting. Therefore, the aim of this SLR and MA is to identify and quantitatively synthesize the real-world effectiveness and safety of crizotinib for patients with *ROS1*-rearranged aNSCLC.

2. Methods

2.1. Literature search

The literature review was performed and reported in alignment with the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) statement [38,39] to identify all RWE studies assessing the effectiveness and safety of crizotinib for the treatment of patients with aNSCLC across all lines of therapy (LOTs). Additional details pertaining to the search strategy are available in the **Supplementary Information**.

2.2. Study selection

All studies retrieved from the database searches were imported into EndNote (version 20.5, Clarivate EndNote, Chandler, AZ, USA) for the deduplication process and subsequently imported into DistillerSR (version 2.35, DistillerSR Inc. 2021, Ottawa, Canada) for screening. Two reviewers independently reviewed the titles and abstracts of all articles based on the prespecified population, intervention, comparator, outcome, and study design (PICOS) criteria (**Supplementary Table 1**). Any differences between the reviewers were resolved by consensus; a third reviewer was consulted to resolve discrepancies as required. Bibliographies of relevant reviews identified during study selection were reviewed to validate findings from the database searches. Additional details regarding study selection are available in the **Supplementary Information**.

2.3. Data extraction & quality assessment

For studies meeting the eligibility criteria, data were extracted into a Microsoft® Excel-based data extraction form by a single reviewer; a second reviewer validated the accuracy of extracted values. Study and patient characteristics, patient eligibility criteria, outcome measures such as effectiveness and safety outcomes, and effectiveness outcome definitions were extracted (as available). The quality/risk of bias of each publication was assessed using the Newcastle-Ottawa scale (NOS) for non-randomized cohort studies [40]. Study quality assessment was conducted by a single reviewer and a second reviewer validated consistency and integrity of the assessments.

2.4. Feasibility assessment

To ensure sensible and robust comparisons in the MA, the similarity of included studies was qualitatively assessed. Included studies that reported common outcomes were compared to assess their clinical and methodological similarities. Consistency across studies was evaluated by comparing effectiveness and safety outcome definitions. A rigorous qualitative between-study heterogeneity evaluation for the following elements were conducted: study design and region, median follow-up length, baseline patient characteristics, LOT at which crizotinib was received, and prior treatment(s) received.

2.5. Meta-Analysis

A conventional frequentist MA was conducted for response-based outcomes (i.e., ORR) by deriving pooled estimates using the metafor package in R (version 4.2.3) [41,42]. As recommended in the Cochrane Handbook for Systematic Reviews of Interventions, [43] pooled estimates for continuous outcomes (i.e., PFS and OS) were derived by digitizing published Kaplan-Meier (KM) curves using DigitizeIt software (Braunschweig, Germany) and generating pseudo individual patient data (pIPD). For the primary analysis (which included all studies reporting the outcome of interest, regardless of crizotinib LOT), pooled estimates and their corresponding 95 % confidence intervals (CIs) were calculated using a random-effects model. A random effects model was chosen for the primary analyses as the cross-study heterogeneity observed in our dataset (which was suspected to result from the differing LOTs across studies) necessitated the assumption that the effect of interest differs amongst studies. The random effects model can account for this by incorporating both the within and between-study variance into the analysis [44,45]. Meta-regression, another valid approach for high-heterogeneity outcomes, was not feasible to use in this instance due to the low number of studies included in the analysis that reported the outcome(s) of interest [43]. For the subgroup analysis (which included studies involving patients treated with crizotinib strictly in the first–line [1L] setting), pooled estimates and their 95 % CIs were calculated using a fixed-effects model. Scenario analyses were conducted using landmark real-world PFS and OS outcomes at 1-, 2-, and 3-years for all studies reporting the outcome (either explicitly or via KM curves). For the scenario analyses, pooled estimates and their 95 % CIs were calculated using a random-effects model. An additional analysis of safety outcomes (i.e., grade 3/4 adverse events [AEs]) was performed on all studies that reported this outcome; pooled estimates and their 95 % CIs were calculated using a fixed-effects model. Heterogeneity among the included studies was tested using the I^2 statistic, representing the percentage of the total variation between studies that cannot be attributed to chance. Heterogeneity was classified as low if $I^2 < 40$ %, moderate if

30 % < I^2 < 60 %, substantial if 50 % < I^2 < 90 % and high if I^2 > 75 % [43]. Publication bias was analyzed using funnel plots and a p-value ≤ 0.05 was considered to be statistically significant publication bias.

3. Results

3.1. Literature search

The database searches yielded 374 records; after removal of duplicates, 301 were screened at the title and abstract phase, of which 282 were excluded. Of the remaining 19 records considered at the full-text screening phase, 14 fulfilled the eligibility criteria and were deemed suitable for inclusion (**Supplementary** Fig. 1).

Reviewing the bibliographies of relevant SLRs [24,27,46,47] yielded 18 records that were further assessed in their full-text form for inclusion. All 18 records were excluded after full-text review as they either did not meet the PICOS criteria or were already captured during screening of the database records (**Supplementary** Fig. 1).

3.2. Study characteristics

Of the 14 included studies, 13 were retrospective, observational studies and 1 was a non-interventional study with secondary use of observational and clinical trial data [26]. Nine of the included studies were single-arm studies; the remaining five studies were comparative. Of the included studies, nine were conducted in China [29,30,34,48–53], three in the US [25,26,36], one in Canada [54], and one in Turkey [55]. The sample size of studies ranged from 21 [55] to 258 [49] patients. A summary of study characteristics is presented in Table 1. Study quality scores using the NOS ranged from four to nine points out of a maximum of nine (**Supplementary Table 2**).

3.3. Patient characteristics

Patient baseline characteristics are presented in Table 2**.** The median age of patients ranged from 48 to 63 years across all studies [25,26,29,30,34,36,48–55]. Less than 50 % of the patients were male in 11 studies [25,26,30,34,36,48–50,52–54]. Variability was noted in the proportion of patients with smoking history: in three studies [25,26,55], more than 50 % of patients were current or former smokers while in 11 studies, more than 60 % of patients had no smoking history [29,30,34,36,48–54].

Across all studies, most patients were diagnosed with aNSCLC with tumors histologically classified as adenocarcinomas and had an ECOG performance status between 0 and 1 [25,26,29,30,34,36,48–55]. The method of detection for *ROS1* fusion was noted to vary across included studies (Table 2) and the proportion of patients with baseline brain metastases ranged from 16 % to 30 % across studies reporting this variable [25,26,29,30,34,36,48–55].

Four studies examined crizotinib exclusively as a 1L therapy [34,50–52], while two studies had > 50 % of patients receiving 1L crizotinib [25,54] and six studies reported the majority of patients (>50 %) received crizotinib as second-line (or later) therapy [29,30,36,48,49,53]. Two studies did not report the LOT at which crizotinib was received [26,55]. Notably, data reported in two studies [29,50] were sourced from the same institution with overlapping timeframes. Despite the potential for data overlap, both studies were included in the analyses since one study [50] included patients treated with crizotinib strictly in the 1L setting while the other [29] included patients treated with crizotinib in any LOT [29,50]. Treatments received prior to crizotinib mainly included chemotherapy and radiation [26,30,36,48,49,54,55] as well as anti-cancer biological agents [30,54].

3.4. Effectiveness outcomes

Effectiveness outcomes reported across the 14 included studies are shown in Table 3. Median real-world PFS (rwPFS) and median OS were the most reported effectiveness outcomes (13 and 9 studies, respectively). Median rwPFS ranged from 7.7 months [26] to 26.1 months [55] and median OS ranged from 16.7 months [48] to 60.0 months [52]. ORR ranged from 29 % [54] to 87 % [50]. Only one study [54] reported DOR and duration of treatment (DOT) (Table 3**)**.

Table 1
Study characteristics of included real-world evidence studies.

Reference	Study Design	Comparator (if any)	Country/Region(s)	Sample Size (N)	LOT
Cui, 2020 [49]	Retrospective	N/A	China	Total Patients: 258 Exposed to Crizotinib: 68 Crizotinib patients with PFS data available: 43	All
Doebele, 2021 [26]	Non-interventional study with secondary use of observational and clinical trial data	Entrectinib	United States	65	NR
Dogan, 2022 [55]	Retrospective	N/A	Turkey	21	NR
Gainor, 2017 [36]	Retrospective	N/A	United States	30	1L and 2L
Gibson, 2022 [54]	Retrospective	Platinum-Pemetrexed (+/- maintenance pemetrexed therapy), lorlatinib, immune checkpoint inhibitors	Canada, United States, Germany	21	All
He, 2019 [48]	Retrospective	N/A	China	38	All
Li, 2018 [29]	Retrospective	N/A	China	36	All
Liu, 2019 [30]	Retrospective	N/A	China	35	All
Shen, 2020 [50]	Retrospective	Platinum-pemetrexed chemotherapy	China	30	1L
Waterhouse, 2022 [25]	Retrospective	N/A	United States	38	All
Xu, 2020 [34]	Retrospective	Platinum-based chemotherapy	China	56	1L
Zhang, 2021 [51]	Retrospective	1L Chemotherapy	China (Hunan, Hubei, Guangdong and Zhejiang provinces)	168	1L
Zheng, 2020 [52]	Retrospective	N/A	China	56	1L
Zhu, 2019 [53]	Retrospective	N/A	China	23	All

Abbreviations: 1L = first-line; LOT = line of therapy; N/A = not applicable; NR = not reported; PFS = progression-free survival.

Table 2
Patient characteristics of included real-world evidence studies.

Author, Year	Sample Size (N)	Age (years, median [range])	Sex (% male)	Smoking History	ECOG performance status at baseline	Histological classification	Stage at diagnosis	Method of ROS1 Detection	Metastases sites at baseline	Prior systemic therapy received[a]	LOT at which crizotinib monotherapy was received
Cui, 2020 [49]	43*	Total Patients: 54 (26–96)	32.5 %*	NR	NR	Lung adenocarcinoma: 93 %* Lung squamous cell carcinoma: 2.3 %* Mixed: 2.3 %* N/A: 2.3 %*	II: 2.3 %* III: 11.6 %* IV: 81.4 %* NA: 4.7 %*	NGS	NR	Chemotherapy: 47 %* Brigatinib: 4.7 %* Lorlatinib:16 %* Carbozatinib:4.7 %* Ceritinib: 4.7 %*	1L: 32.4 % 2L+: 67.6 %
Doebele, 2021 [26]	65	65 (55–73)	43 %	Smoker: 57 % Never smoker: 43 %	0: 29 % 1: 17 % 2: 11 % Missing: 43 %	Non-squamous cell carcinoma: 94 % Squamous cell carcinoma: 3 % Not otherwise specified: 3 %	NR; only patients with stage IIIB/IV included	NGS; FISH	Brain: 26 %	Prior targeted therapy (any line): 14 % Prior chemotherapy (any line): 31 %	NR
Dogan, 2022 [55]	21	56 (23–79)	52.40 %	Yes: 57.2 % No: 23.8 % Unknown: 19 %	NR	NR	Stage 1: 4.8 % Stage 2: 9.5 % Stage 3: 23.8 % Stage 4: 61.9 %	FISH	Lung: 85.7 % Brain: 28.6 % Liver: 19 % Adrenal gland: 14.3 % Bone: 9.5 % Other: 14.3 %	Palliative chemotherapy: 33.3 %	NR
Gainor, 2017 [36]	30	48 (23–76)	43 %	Never: 77 % Light (≤10 pack-years): 13 % Heavy (>10 pack-years): 10 %	0–1: 97 % 2: 3 %	Adenocarcinoma: 100 % Squamous: 0 % Other: 0 %	IV: 83 % Other: 17 %	FISH; NGS; real-time PCR	Pulmonary Nodules: 82.1 % Pleural Disease: 51.3 % Pericardial Disease: 5.1 % Intrathoracic Lymph Nodes: 82.1 % Liver: 20.5 % Adrenal: 5.1 % Bone: 33.3 % Brain: 19.4 % Extrathoracic Lymph Nodes: 41 % Other Metastatic Sites:7.7 % Any Extrathoracic Site: 59.0 %	Platinum-Pemetrexed: 11 (36.7 %) Platinum-Paclitaxel: 5 (16.7 %) Other Platinum-Doublet: 1 (3.3 %) Pemetrexed: 1 (3.3 %) Erlotinib: 1 (3.3 %) Clinical Trial Agent: 2 (6.7 %)	1L: 40 % 2L: 60 %
Gibson, 2022 [54]	21	51.6 (43.9–59.7)	33.30 %	Never Smoker: 85.7 % Ever Smoker: 14.3 %	At Crizotinib Initiation: 0 or 1: 66.7 % 2 or 3: 28.6 %	ADC: 100 %	NR	FISH	Brain: 28.6 %	Previous Systematic Therapy Exposure: Curative-intent (adjuvant cytotoxic chemotherapy): 9.5 % Palliative-intent (cytotoxic chemotherapy or	1L: 52.4 % 2L: 38.1 % 3L: 0

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Table 2 (*continued*)

Author, Year	Sample Size (N)	Age (years, median [range])	Sex (% male)	Smoking History	ECOG performance status at baseline	Histological classification	Stage at diagnosis	Method of ROS1 Detection	Metastases sites at baseline	Prior systemic therapy received[a]	LOT at which crizotinib monotherapy was received
										immune checkpoint inhibitors): 47.6 %	
					Unknown: 4.8 %						4L: 9.5 %
He, 2019 [48]	38	55 (26–79)	39.47 %	Nonsmoker predominance) – % Not reported	NR	ADC: 92.11 % Squamous cell carcinoma: 2.63 % Adenosquamous carcinoma: 5.26 %	IIIB: 13.16 % ≥IV: 86.84 %	NGS	Brain: 21.05 % Others not reported	Pemetrexed-based chemotherapy: 55.3 %	1L: 17 (44.7 %) 2L+: 21 (55.3 %)
Li, 2018 [29]	36	50.8 (32–78)	50 %	Yes: 5 (13.9) No: 31 (86.1)	0–1: 34 (94.4) 2: 2 (5.6)	ADC: 100 %	IV: 30 (83.3) Postoperative recurrent: 6 (16.7)	Reverse-transcriptase-PCR	Brain: 16.7 % Others not reported	NR	1L: 14 (38.9 %) 2L: 15 (41.7 %)
											3L+: 7 (19.5 %)
Liu, 2019 [30]	35	51.0 (26–82)	34.30 %	Never: 80.0 %	0: 2.8 %	ADC: 100 %	IIIA: 5.7 %	FISH; Reverse-transcriptase PCR; NGS	Lung: 22.9 %	Pemetrexed, pemetrexed-platinum chemotherapy: 15 (42.9 %)	1L: 48.6 %
				Former/current: 17.1 %	1: 88.6 %		IIIB: 8.6 %		Brain: 22.9 %	Bevacizumab: 2 (5.7 %)	2L: 31.4 %
				Unknown: 2.9 %	2: 8.6 %		IV: 85.7 %		Bone: 40.0 %	Non-pemetrexed-platinum chemotherapy: 3 (8.6 %)	3L+: 20.0 %
							–IVM1a: 28.6 %		Liver: 8.6 %	Chemotherapy included docetaxel, paclitaxel, pemetrexed monotherapy,	
							–IVM1b: 2.9 %		Adrenal gland: 5.7 %	or regimens used in clinical trials.	
							–IVM1c: 54.3 %		Supraclavicular lymph node: 28.6 %		
									Pleural: 34.3 %		
									Others: 22.9 %		
Shen, 2020 [50]	30	51.5 (29–78)	30.00 %	Never: 83.3 % Ever/current: 16.7 %	NR (Patients recruited had to have an ECOG score of 0–1)	ADC: 100 % Non-adenocarcinoma: 0 %	IIIB-IIIC: 10.0 % IVA-IVB: 90.0 %	Real-time PCR	Brain: 30.0 %	N/A – first-line treatment	1L: 100 %
Waterhouse, 2022 [25]	38	68 (60.0–73.0)	34.20 %	Current/Previous smoker: 55.9 %	0: 15.8 %	Non-squamous cell carcinoma: 76.3 %	Stage I-III: 32.4 %	NR	Bone: 23.7 %	Anticancer treatment: 34.2 %	1L: 76.3 %
					1: 44.7 %	Other/not documented: 23.7 %	Stage IV: 67.6 %		Lung: 26.3 %		2L+: 23.7 %
					2 18.4 %				Other: 36.8 %		
				Never smoker: 44.10 %	Not documented: 21.1 %						
Xu, 2020 [34]	56	≥60: 19 (33.9 %) <60: 37 (66.1 %) (median of 52 years reported in text refers to entire patient	26.80 %	Yes: 14.3 % No: 85.7 %	0–1: 89.3 % 2: 10.7 %	ADC: 98.2 % Non-ADC: 1.8 %	IIIb: 8.9 % IV: 91.1 % Recurrence: 13.7 %	FISH; NGS	Brain: 19.6 %	N/A	1L: 100 %

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Table 2 (*continued*)

Author, Year	Sample Size (N)	Age (years, median [range])	Sex (% male)	Smoking History	ECOG performance status at baseline	Histological classification	Stage at diagnosis	Method of ROS1 Detection	Metastases sites at baseline	Prior systemic therapy received[a]	LOT at which crizotinib monotherapy was received
		population [chemo and crizotinib])									
Zhang, 2021 [51]	168	52 (27–79)	62 %	Smoker or former smoker: 19 % Nonsmoker: 81 %	0–1: 96 % ≥2: 4 %	ADC: 99 % Squamous cell carcinoma: 1 %	III: 6 % IIIa: 0 IIIb: 1 % IIIc: 5 % IV: 94 %	NGS	Site of progression: Brain 43 %; Non-brain: 57 %	N/A – Treatment-naïve population	1L: 100 %
Zheng, 2020 [52]	56	53 (24–72)	44.60 %	Never: 66.1 % Smoker: 33.9 %	0: 21.4 % 1 or 2: 78.6 %	ADC: 91.1 % Adenosquamous carcinoma: 8.9 %	IIIB: 17.9 % IV or relapsed: 82.1 %	ARMS; FISH; NGS	Bone: 32.1 % Contralateral pulmonary: 26.8 % Intracranial: 19.6 % Pleural: 16.1 % Liver: 7.1 % Adrenal glands: 5.4 % Other organs: 7.1 %	Previous 1L treatment with crizotinib: 5.4 %	1L: 100 %
Zhu, 2019 [53]	23	64 (3579)	34.8 % (n = 8)	Yes: 2 (8.7 %) No: 21 (91.3 %)	0–1: 21 (91.3 %) 2: 2 (8.7 %)	ADC: 100 % Non-adenocarcinoma: 0 %	IIIbIV: 100 %	Reverse-transcriptase-PCR; FISH; NGS	NR	NR	1L: 4 (17.4 %) 2L: 5 (21.7 %) 3L+: 14 (60.9 %)

[a]All instances of prior surgery and radiotherapy have been removed for simplicity.

*Value for patients treated with crizotinib with median rwPFS data available.

Abbreviations: 1L = first-line; 2L = second-line; 2L+ = second-line and beyond; 3L = third-line; 3L+ = third-line and beyond; 4L = fourth-line; ADC = adenocarcinoma; ARMS = amplification-refractory mutation system; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in-situ hybridization; LOT = line of therapy; N/A = not applicable; NGS = next generation sequencing; NR = not reported; PCR = polymerase chain reaction; PFS = progression-free survival; rwPFS = real-world progression-free survival; TKI = tyrosine kinase inhibitor.

Table 3
Effectiveness outcomes reported in the included real-world evidence studies.

Author, Year	Median follow-up (Months)	Median Real-World PFS (months; 95 % CI)	Median OS (months; 95 % CI)	ORR (%; 95 % CI)	CR Rate (%; 95 % CI)	PR Rate (%; 95 % CI)	Median DOR (months; 95 % CI)	Median DOT
Cui, 2020 [49]	NR	10.1 (progressed on crizotinib population n/N: 43/68)	NR	NR	NR	NR	NR	NR[c]
Doebele, 2021 [26]	14.1	7.7 (5.4–10.0)[§] (n/N: 54/65)	19.9 (14.4-NE)[§] (n/N: 35/65)	NR	NR	NR	NR	NR
Dogan, 2022 [55]	17[a]	26.1 (8.1–44.1)	35.2 (13.5–56.9)	47.6 %	0	47.6 %	NR	NR
Gainor, 2017 [36]	38.4[b]	11.0 months	30 (12-NR)[d]	NR	NR	NR	NR	NR
Gibson, 2022 [54]	NR	10.6	33.1	29 %	0	28.6 %	5.0 (0.3–10.8)	6.9 cycles (IQR: 1.3–17.1) 4.8 months (range 0–34.2 months)
He, 2019 [48]	NR	12 months (258 days for patients with SDC4-ROS1; 357 days for patients with other fusion partners)[§]	16.7 months (501 days for patients with SDC4-ROS1, 516 days for patients with other fusion partners)[§]	NR	NR	NR	NR	NR
Li, 2018 [29]	31.9	12.63 months (IQR: 7.67–19.30)	32.70 (IQR ¼ 18.77–not reached)	83.3 %	NR	83.3 %	NR	NR
Liu, 2019 [30]	NR	11.0 (7.8–14.2)	41.0 (22.5–59.5)	71.4 % (56.2–86.6)	0	71.4 %	NR	NR
Shen, 2020 [50]	28.1 (95 % CI: 19.2–39.0)	18.4 (6.4–30.3)	Not reached*	86.7 % (73.3–96.7)	3.3 %	83.3 %	NR	NR
Waterhouse, 2022 [25]	15.3	NR	36.2 (15.9-NR)	NR	NR	NR	NR	NR
Xu, 2020 [34]	24.9	14.9 (10.9–18.7)	Not reached	83.9 %	0	83.9 %	NR	NR
Zhang, 2021 [51]	28	18.0	NR	85.7 %	NR	NR	NR	NR
Zheng, 2020 [52]	29.0	23.0 (12.4–33.6) (n/N: 51/56)	60.0 (40.7–79.3) (n/N: 51/56)	64.7 %	2 %	62.7 %	NR	NR
Zhu, 2019 [53]	NR	14.5 (95 % CI 9.5–19.5)	NR	56.52 %	0	56.52 %	NR	NR

[§]Values used in MA differ from those reported in table since data used in MA were derived from digitized KM curves. *Median OS values were not explicitly reported in the article text, pooled estimates were derived by digitizing KM curves and generating pIPD (see Methods section) [34,50,51].
[a]Value represents mean, not median, follow-up time as reported in the article [55].
[b]Converted to months, article originally reports median follow up time as 3.2 years [36].
[c]Article reported DOT values for individual patients but does not report pooled DOT value [49].
[d]Converted to months; originally reported as OS of 2.5 years [36].
Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; DOT = duration of treatment; IQR = interquartile range; NE = not estimable; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; pIPD = pseudo individual patient data.

3.5. Safety outcomes

Of the 14 studies included in this review, only 5 reported grade 3/4 AEs (**Supplementary Table 3**) [30,50,53–55]. Little overlap was observed in the composition of the grade 3/4 AEs reported across included studies; the percentage of patients with reported grade 3/4 AEs ranged from 5 % [55] to 26 % [53].

3.6. Feasibility assessment

A qualitative comparison of study and patient characteristics and outcome definitions (**Supplementary Table 4**) was conducted to assess consistency across the 14 included RWE studies and overall feasibility of conducting a MA. Most studies (13 out of 14) were retrospective, observational studies and the remaining study was a non-interventional study with secondary use of observational data and clinical trial data [55]. Heterogeneity was observed across the studies with respect to both median follow-up time (Table 3) and the LOT at which patients received crizotinib (Table 2). Heterogeneity was also observed with the *ROS1* rearrangement detection method, both within and between studies (Table 2). The median age of patients, male/female sex distribution, stage of disease at diagnosis, and proportion of patients with brain metastases were similar across all studies (Table 2).

Although there were some differences in methodology and patient populations and minor differences noted in the stated definitions of rwPFS and OS in selected studies, overall, the identified RWE studies were deemed sufficiently similar to derive valid pooled estimates of effectiveness. Meta-analyses were deemed feasible for median rwPFS, OS, ORR, CR, PR, and grade 3/4 AEs; however, a lack of reported data precluded MA for DOR and DOT. Meta-analysis for ORR was conducted to collectively analyze response–based outcomes, while individual MA for CR rate and PR rate were not performed due to implicit differences in response assessment frequency and methodology inherent to real-world studies. As such, MA were conducted for median rwPFS, OS, ORR, and grade 3/4 AEs and the results of these analyses are detailed in the ensuing sections.

3.7. Meta-Analysis

3.7.1. Progression-free survival

The primary MA included all studies reporting median rwPFS irrespective of the LOT at which crizotinib was administered. There were 11

RWE studies that reported this outcome and provided a KM curve which was used to derive pIPD for the MA [26,30,34,36,48,50–55]. Two additional RWE studies identified in the SLR reported median rwPFS results; however, these were not included in the primary MA as KM curves were unavailable [29,49]. Across the 11 RWE studies included in the primary MA, median rwPFS ranged from 8.2 months (based on weighted data from [26] for which a KM curve was available) to 23 months with a median follow-up of 28 months (range: 14.1 months to 38.4 months; Table 3). Median follow-up was only reported in 5 of the 11 RWE studies [34,50–53]. The pooled estimate for median rwPFS was 14.5 months (95 % CI: 13.2, 16.9 months).

A subgroup analysis was conducted that included four RWE studies [34,50–52] evaluating patients treated with crizotinib strictly in the 1L setting. The reported median rwPFS values ranged from 14.9 months to 23.0 months (Table 3) with a pooled median rwPFS estimate of 18.1 months (95 % CI: 15.9, 20.4 months). The median follow-up time was reported in all four studies and yielded an overall median follow-up time of 28 months for the subgroup analysis (range: 24.9 months to 29 months; Table 3).

A scenario analysis for median rwPFS at the 1-year landmark was performed for the 11 studies reporting this outcome (i.e., the same 11 studies analyzed in the primary analysis) [26,30,34,36,48,50–55]. The scenario analysis of median rwPFS at the 2-year landmark included data from 9 of the studies in the 1-year landmark analysis; the remaining 2 studies [53,55] were excluded due to paucity of data at this timepoint. In comparison to the studies informing the 2-year landmark median rwPFS analysis, two additional studies [30,48] were excluded at the 3-year timepoint due to lack of data. The forest plots for the scenario analyses of median rwPFS at the 1-, 2-, and 3-year landmarks are presented in **Supplementary Fig. 2**, with funnel plots for the corresponding analyses presented in **Supplementary Fig. 3**. The results demonstrated that, in a real-world setting, 56.3 %, 31.2 %, and 25.9 % of patients remained progression-free at the 1-, 2-, and 3-year landmarks, respectively (**Supplementary Fig. 3**).

3.7.2. Overall survival

The primary MA included all studies that reported OS irrespective of the LOT at which crizotinib was administered. Nine RWE studies reported this outcome and provided a KM curve which was used to derive pIPD for MA [25,26,30,36,48,50,52,54,55]. One additional RWE study reported OS but did not include a KM curve and was not included in the primary MA for this outcome [29]. Across the nine RWE studies included in the primary MA, median OS ranged from 18.5 months (based on weighted data from [26] for which a KM curve was available) to 60 months with a median follow-up of 28.1 months, derived from the three studies [25,36,52] which reported median follow-up times ranging from 15.3 months to 38.4 months (Table 3). The pooled estimate for median OS was 40.2 months (95 % CI: 29.5, 46.9 months).

A subgroup analysis was conducted that included two RWE studies [50,52] evaluating patients treated with crizotinib strictly in the 1L setting for which OS KM data were available. One of these studies [52] reported a median OS value of 60.0 months (95 % CI: 40.7, 79.3) and the median OS in the other study [50] was not reached. Therefore, using the range of reported median values to assess heterogeneity for OS in the subgroup analysis was not possible (Table 3). The median follow-up time was similar for both studies at 29 months [52] and 28.1 months [50]. The pooled estimate for median OS in patients receiving 1L crizotinib was 60 months (95 % CI: 46.9 months, not reached).

The scenario analyses for OS at 1- and 2-year landmarks were performed for the nine studies which reported this outcome (i.e., the same nine studies analyzed in the primary analysis) [25,26,30,36,48,50,52,54,55]. For the scenario analysis of OS at the 3-year landmark, one study was excluded due to paucity of data at this timepoint [48]. The forest plots for the scenario analyses at 1-, 2-, and 3-year landmarks are presented in **Supplementary Fig. 4**, with funnel plots for the corresponding analyses presented in **Supplementary Fig. 5**. The results demonstrated that OS rates for the 1-, 2-, and 3-year landmarks were 80.7 %, 60.5 %, and 54.4 %, respectively (**Supplementary Fig. 4**).

3.7.3. Objective response rate

The primary MA for ORR included nine RWE studies [29,30,34,50–55]. Of the nine RWE studies reporting both ORR and median follow-up time, the median follow-up was 28 months (range: 17 months to 31.9 months) [29,34,50–52]. The pooled ORR was 70.6 % (95 % CI: 57.0 %, 81.3 %). The forest and funnel plots for the primary ORR analysis are presented in **Fig. 1A** and **Supplementary Fig. 6**, respectively.

The subgroup analysis included four RWE studies evaluating crizotinib in the 1L setting [34,50–52] and the pooled ORR across these studies was 81.1 % (95 CI%: 76.1 %, 85.2 %). The forest and funnel plots for the this subgroup analysis are presented in **Fig. 1B** and **Supplementary Fig. 7**, respectively.

3.7.4. Grade 3/4 adverse events

The MA for grade 3/4 AEs was performed using data from five studies as shown in **Supplementary Table 3** [30,50,53–55]. The pooled results indicate that 18.7 % of patients experienced grade 3/4 AEs when treated with crizotinib. The forest and funnel plots for grade 3/4 AEs are presented in Fig. 2 and **Supplementary Fig. 8**, respectively. Only one of the five studies reporting grade 3/4 AEs focused strictly on crizotinib treatment in the 1L setting; as such, a subgroup analysis was not conducted [50].

4. Discussion

Crizotinib is one of the few treatment options available for patients with aNSCLC with *ROS1* gene rearrangement [11]. To our knowledge, this is the first study to focus strictly on RWE to identify and quantitatively synthesize data on the real-world effectiveness and safety of crizotinib for the treatment of adult patients with *ROS1*-rearranged aNSCLC. We identified 14 studies evaluating the real–world effectiveness of crizotinib in the 1L and subsequent LOTs for aNSCLC presenting with *ROS1* gene alteration. To ensure sensible and robust estimates in the MA, the similarity of included studies was assessed. Although there were some differences in methodology and patient populations, the identified RWE studies were deemed similar enough to derive reasonable estimates of effectiveness. When considering crizotinib administered at any LOT, the MA showed pooled values for median rwPFS and OS of 14.5 months and 40.2 months, respectively, and an ORR of 70.6 %. Notably, baseline brain metastases ranged from 16.7 %-30.0 %, 22.9 %-30.0 %, and 16.7 %-30.0 % in the primary analysis of median rwPFS, OS, and ORR, respectively.

The safety and effectiveness results from this study generally align with those observed in clinical trials; the results of the primary analysis for all outcomes assessed fall within the range of values reported across the six trials (**Supplementary Table 5**) [18–23,27]. Effectiveness results from the subgroup analysis for patients treated with crizotinib exclusively in the 1L setting were numerically higher than those reported across the crizotinib clinical trials. This result is not surprising due to differences in patient populations; whereas the subgroup analysis included only patients treated in the 1L setting, patients enrolled in the clinical trials spanned multiple LOTs.

An SLR and MA published in 2020 [27] included both clinical trial data and RWE for patients with *ROS1*–rearranged aNSCLC treated with crizotinib and reported pooled values for PFS, OS, and ORR (**Supplementary Table 5**). The effectiveness results of our study align closely with the data reported in the prior MA with the exception of OS. Since the SLR and MA conducted by Vuong et al. [27] included both randomized controlled trial (RCT) data and RWE, a median OS value higher than that reported in the current study may be expected since RCT data typically exceed outcomes reported in RWE studies [56]. However, the

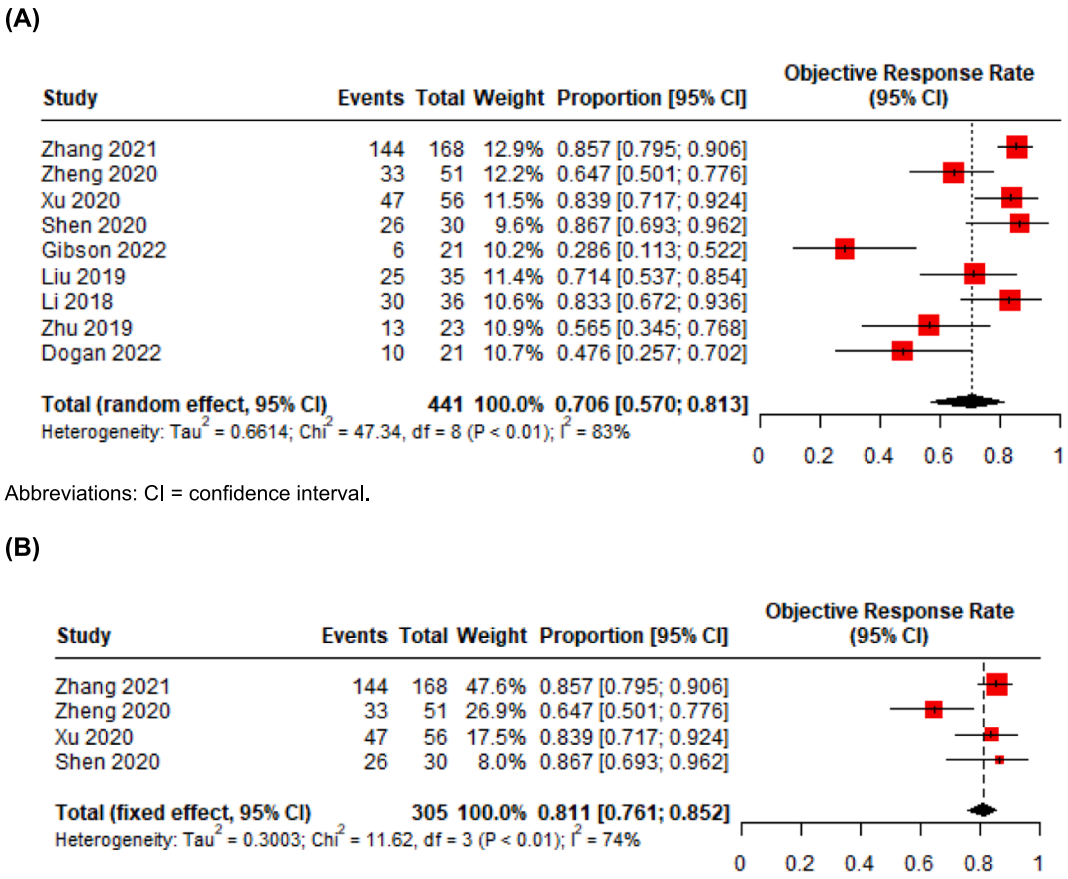

Fig. 1. Forest Plot for ORR in the Primary Analysis (A) and Subgroup Analysis (B). Abbreviations: CI = confidence interval. Abbreviations: CI = confidence interval.

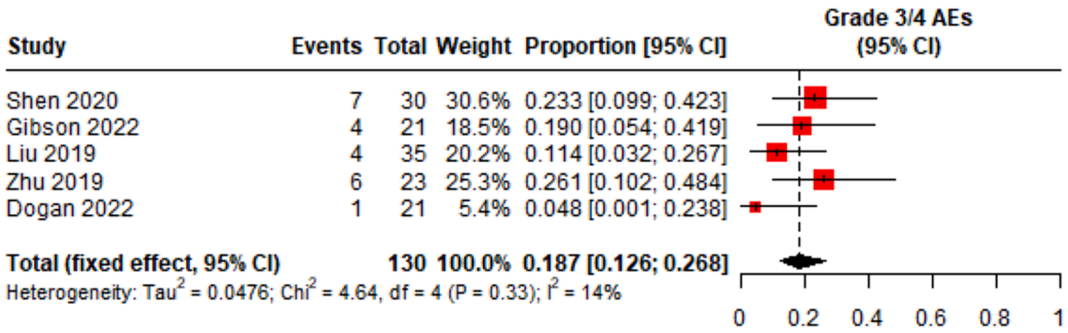

Fig. 2. Forest Plot for Grade 3/4 Adverse Events. Abbreviations: AE = adverse event; CI = confidence interval.

opposite was true in this circumstance owing to two articles [50,52] published (in 2020) after the search date in the Vuong study. In both articles [50,52], the median OS exceeded 50 months which accounts for the superior pooled median OS value reported in our MA versus that reported by Vuong and colleagues [27]. The longer OS values reported in the additional two articles [50,52] may result from differences in patient populations since patients in the two studies received crizotinib exclusively as a 1L treatment. In support of this, the MA results for OS in our subgroup analysis including only studies with patients receiving 1L crizotinib were higher than the MA of OS for studies with patients across varying LOTs.

Most studies identified in this review were single-arm, retrospective, observational studies. Generally, such studies are considered lower quality evidence compared to RCTs [57]; however, due to the rarity of *ROS1* rearrangement in aNSCLC, large RCTs are not feasible. Notably, study quality assessment resulted in an average score of ~ 6/9, indicating relatively high-quality studies despite an inherent bias in NOS scoring for comparative studies [58]. Although the quality of the included studies was deemed high, significant heterogeneity was observed in the primary MA of effectiveness outcomes and heterogeneity was also noted in the reported ranges across studies for both median rwPFS and OS. This result was expected since RWE studies typically have less stringent inclusion criteria compared to RCTs, including patients with complex care needs, multiple comorbidities, and concomitant medications; all of which may contribute to inherent heterogeneity of the patient population [56,57].

Another notable factor differentiating RCTs and RWE studies pertains to study design and the lack of standardization across molecular testing methods, tumor assessment, and clinical management, more specifically in relation to irregularly scheduled clinician visits and/or data being collected at irregular intervals [57]. As a result, RWE may have implicit differences in response assessment frequency and

methodology. In an attempt to mitigate heterogeneity resulting from these implicit differences, we conducted a MA collectively for ORR as opposed to individual MA for CR and PR rates.

When considering heterogeneity across the studies included in this SLR, some differences were noted in relation to the LOT at which crizotinib was received, median follow-up time, detection method of *ROS1* rearrangement, and outcome (i.e., OS and PFS) definitions. To mitigate the heterogeneity observed in the primary analysis, a subgroup analysis was conducted including studies with patients treated with crizotinib strictly in the 1L setting. As expected, the heterogeneity observed according to the range of reported median rwPFS was reduced in the subgroup analysis compared with the primary analysis. Similarly, heterogeneity was reduced in the subgroup analysis for ORR ($I^2 = 74$ %) compared to the primary analysis ($I^2 = 83$ %).

The strengths of this study pertain to the robust search strategy, steps taken to mitigate heterogeneity, and the MA methodology. Attempts to reduce heterogeneity included limiting this SLR strictly to RWE studies (rather than including a mix of RWE studies and RCTs) and performing a subgroup analysis involving only studies of patients receiving 1L crizotinib. Finally, the methodology employed in conducting the MA for survival outcomes (i.e., rwPFS and OS) aligned with recommendations in the Cochrane Handbook for Systematic Reviews of Interventions by (a) using pIPD generated by digitizing KM curves and (b) using a random effects model for the primary *meta*-analysis [43]. A random effects model was the most appropriate method by which to conduct the primary analysis since the cross-study heterogeneity observed in our dataset necessitated the assumption that the effect of interest differs amongst studies. Using digitized KM curves to generate pIPD was employed since traditional MA techniques for continuous outcomes (i.e., rwPFS and OS) require the assumption that the median is equal to the mean. As survival data are typically skewed, using traditional MA methods to summarize continuous outcomes and assuming the median was equivalent to the mean was not appropriate.

This study has some notable limitations. The included studies were subject to inherent selection bias due to their retrospective design and some differences were observed across studies in relation to reporting of patient baseline characteristics, LOT at which crizotinib was received, and outcome definitions (**Supplementary Table 4**). Furthermore, the *ROS1*-rearrangement detection method differed both across and within studies, potentially contributing to the heterogeneity of the study results. The exact impact of differing methods of *ROS1* fusion detection is unclear and should be investigated in future studies. Lastly, despite our best efforts to mitigate heterogeneity, residual cross-trial difference may still persist and, due to the low number of studies included in the analysis that reported the outcome(s) of interest, a *meta*-regression was not feasible due to an insufficient number of studies per adjustment variable required to have adequate statistical power [43].

5. Conclusion

The results of this SLR and MA of RWE demonstrates the effectiveness and safety of crizotinib in *ROS1*–rearranged aNSCLC in first- and any LOT. The results are consistent with previously reported clinical trial data evaluating the efficacy of crizotinib. The findings of the RWE as demonstrated in the current study ensures the totality of evidence of crizotinib as a standard of care in the treatment of *ROS1*-rearranged aNSCLC.

6. Ethical disclosure

NA.

7. Data sharing statement

NA.

CRediT authorship contribution statement

Ernest Nadal: Writing – review & editing, Conceptualization. **Nada Rifi:** Writing – review & editing, Conceptualization. **Sarah Kane:** Writing – review & editing, Writing – original draft, Conceptualization. **Sokhna Mbacke:** Writing – review & editing, Writing – original draft, Conceptualization. **Lindsey Starkman:** Writing – review & editing, Writing – original draft, Conceptualization. **Beatrice Suero:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Hannah Le:** Writing – review & editing, Conceptualization. **Imtiaz A. Samjoo:** Writing – review & editing, Data curation, Conceptualization.

Declaration of competing interest

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Author Contributions

All authors participated in the conception and design of the study. EN, IAS, NR, SK, SM, LS, BS, and HL contributed to the literature review, data collection, analysis, and interpretation of the data. BS participated in the conduct of the quantitative analyses. All authors contributed to the interpretation of the data and critically reviewed for importance of intellectual content for the work. All authors were responsible for drafting or reviewing the manuscript and for providing final approval. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

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Appendix A. Supplementary data

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