The efficacy and safety of selumetinib as secondary therapy for late-stage and metastatic non-small cell lung cancer: results from a systematic review and meta-analysis

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Background: Non-small cell lung cancer (NSCLC) is the most common subtype of all lung cancers, and KRAS is the most common mutation in this population. Unfortunately, this subgroup remains "undruggable" with the lack of an approved targeted therapy. Selumetinib has been investigated as a secondary therapy in several trials and compared to various drug regimens. Therefore, we conducted this systematic review and network meta-analysis to determine the comparative effectiveness of this drug as compared to others in patients with late-stage and malignant NSCLC.

Methods: Up to July 1, 2020, 9 databases (PubMed, Scopus, Web of Science, mRCT, ICTRP, clinicaltrials.gov, VHL, SIGLE, and Google Scholar) were searched for studies following the PICOS framework: randomized trials reporting the efficacy (rate of disease progression/lack of response) of selumetinib compared to other therapies in patients with late-stage/metastatic NSCLC. The quality of retrieved studies were assessed with the revised Cochrane risk-of-bias tool. Frequentist network meta-analysis was conducted to estimate the efficacy of selumetinib as compared to other therapies and/or placebo.

Results: Out of the 163 articles yielded from the primary search, 9 studies (1,195 patients) were finally included in our systematic review. The majority of clinical cases had a performance status (PS) of 0–2, and the mean age was 62 years. The overall efficacy of selumetinib was 71.77% (95% CI: 63.24–81.45%), with selumetinib administered alone having better efficacy compared to combined therapy (65.20% *vs.* 74.08%). In the network analysis, selumetinib had higher efficacy compared to chemo- or immune therapy, but not significantly so. The overall SAE rate of selumetinib was 42.96% (95% CI: 34.74–53.13%), with selumetinib having a significantly better safety profile compared to combined therapy (10.49% *vs.* 47.38%). In the network analysis, the placebo had the best safety profile followed by selumetinib and chemo- and immune therapy. Five studies had high risk of bias, 2 had some concerns, and 2 had low risk of bias.

Discussion: The efficacy of selumetinib is not superior compared to combined therapy for treating NSCLC but does have a better safety profile. Current evidence is still limited, and more robust trials are still required.

Keywords: Non-small cell lung cancer (NSCLC); selumetinib; efficacy; safety

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Introduction

After non-melanocytic skin cancer, lung cancer currently is the most common tumor and accounts for the majority of tumor-associated deaths (1). In 2012, lung cancer was estimated to have an incidence rate of 1.2 million cases worldwide, being the most frequently diagnosed cancer in males (2). Among lung cancer, non-small cell lung cancer (NSCLC) is the predominant type, constituting 80% to 90% of lung cancer incidences (3).

Traditional cytotoxicity-based therapies for NSCLC provide a reported a median-survival of 52 weeks, even though improvements have been noted in patients who are eligible for immunotherapy (4,5). Despite these benefits, novel therapeutic strategies remain a critical need. It has been reported that a wide range of signals can activate the *RAS*/*RAF*/*MEK*/extracellular-signal-regulated kinase (*ERK*) pathway and subsequently affect tumor proliferation, survival, migration, angiogenesis, and even resistance to administered interventions (6,7). Therefore, these pathways have been targeted by the modern therapeutics of translational medicine. Considerable benefits for patients with NCSLC have been gained from targeting upstream epidermal growth factor receptor (*EGFR*) within clinical cases having identifiable *EGFR* mutations (8). In contrast, despite the fact that Kristen rat sarcoma virus (*KRAS*) mutations have been observed across nearly 30% of NSCLC clinical cases (9), *RAS*-specific interventions have not as of yet conferred any clinical benefit (10).

The increased knowledge regarding cancer biology has led the way in further developing targeted agents (TAs) for the key oncogenic molecules implicated in cancer. The therapeutic use of *EGFR*, together with anaplastic large-cell lymphoma kinase (ALK) inhibitors, has been validated for NSCLC, with response rates ranging from 45% to 65%, and *EGFR* targeted treatment is currently considered the standard therapeutic approach for individuals carrying *EGFR*-*ALK*-mutated tumors (8,11). Meanwhile, *KRAS* is one of the most commonly mutated oncogenes in NSCLC cases, with prevalence rates of approximately 30% across all patients (12). That being said, this patient population subgroup so far remains "undruggable", and treatment algorithms have not been proposed by the European Society for Medical Oncology (EMSO) or the National Comprehensive Cancer Network (NCCN) guidelines (13,14).

Selumetinib, AZD6244 or ARRY-142866, is known for its powerful and precise inhibition of *MEK-1/2* (15). Recently, a randomized phase II clinical trial examining 87 patients with NSCLC and the *KRAS* mutation has demonstrated promising therapeutic effects with selumetinib in combination with docetaxel (10). Although, no major variations were observed across the cohorts regarding overall survival (OS), selumetinib provided significant benefits in terms of progression-free survival (PFS) and objective response rate (ORR). Combination therapies currently represent the potential alternative solution to overcoming the complex *KRAS* pathway (through directly suppressing KRAS protein and regulators, altering KRAM membrane localization, or inhibiting the effector molecules downstream of KRAS pathway) while potentiating the activity of other agents and simultaneously suppressing this nexus (16). Several randomized trials have investigated the efficacy of selumetinib as compared to other therapeutic regimens in patients with late-stage NSCLC. However, these studies report conflicting findings, where some of them report no significant difference in efficacy when compared with chemotherapy (17) and others report improvement in efficacy and survival in patients with previously treated KRAS-mutant NSCLC (10,18).

Based on this discrepancy, and based on the differences in the comparator groups to selumetinib, a network meta-analysis was deemed of great importance in estimating the comparative effectiveness of selumetinib (either as monotherapy or adjuvant therapy) to other therapies and/or placebo among patients with late-stage *KRAS*-mutant or *KRAS*-wild type NSCLC. We present the following article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1849/rc).

Methods

Search strategy

In July, 1, 2020, 9 electronic repositories were scrutinized for clinical trials that reported our study's primary outcome of selumetinib efficacy for patients with NSCLC. This search was updated on May 3rd, 2022, and no more relevant studies were found. These databases included Google Scholar, System for Information on Grey Literature in Europe (SIGLE), Scopus, Web of Science (ISI), PubMed, Virtual Health Library (VHL), Clinical trials.gov, metaRegister of Controlled Trials (mRCT), and the WHO International Clinical Trials Registry Platform (ICTRP) repositories and were searched using keywords and medical

subject (MeSH) terms with different combinations suitable to each database. The main terms used were ("Selumetinib") AND ("lung cancer") AND ("trial" OR "RCT" OR "random" OR "randomized").

Selection criteria

Our selection criteria were based on participants, intervention, comparison, and outcomes (PICO). Criteria for eligible trials were the following: trial participants were clinical cases of advanced or metastatic NSCLC, intervention employed selumetinib (either as a monotherapy or as adjuvant to chemotherapy), the comparison included either placebo or other therapeutic agents (such as chemotherapies) as a control group, and the efficacy or safety profile was the outcome of interest. Efficacy was indicated by the rate of disease progression or absence of response, while safety was indicated by the serious adverse events (SAEs), as these are the most important factors in clinical decision-making.

We included only randomized clinical trials (RCTs) with no restrictions regarding language, age, or geographical region. Screened studies were removed whenever the exclusion criteria were present: (I) non-RCTs and other observational studies; (II) full-text of articles unavailable; (III) non-original studies such as reviews, editorials, commentaries, or letters; and (IV) *in vivo* and *in vitro* studies. Of note, review articles were screened at first to retrieve any potentially missing eligible trials that met our criteria. Retrieved studies from the initial database search were transferred to Endnote X9 (Thompson Reuters, USA) through which duplicated trial articles were discarded before screening processing. This screening was carried out by 2 independent reviewers, and any differences in opinions were solved through consultation with a senior author.

Data collection

Data collection was completed by 2 independent reviewers. The data extraction was performed using a Microsoft Excel sheet that was modified to fit all of our outcomes/endpoints through a pilot extraction phase. Any differences between reviewers were resolved by a third reviewer who checked the extracted data for accuracy. The extraction sheet included the following sections: study characteristics, outcomes of interest, and quality assessment. The first part of the sheet included baseline characteristics of each study, such as the last name of the first author; title; year of publication; journal's name; country and participant population size, age, and gender; study design; type of lung cancer; KRAS status; inclusion and exclusion criteria; treatment arms; and follow-up duration. The second part of the extraction sheet included the efficacy and safety endpoints for selumetinib, as reported within individual trials. The third part included the risk-of-bias evaluation for selected trial articles.

Risk-of-bias evaluation

Standards adopted for selected trials were evaluated by 3 reviewers, and differences or disagreements were resolved through discussion. The revised Cochrane quality assessment tool was used to assess the standards of included randomized controlled trials (Cochrane Methods, 2016). This quality assessment tool assessed the risk of bias across seven domains: randomization, deviation from intended interventions, missing outcome data, measurement of outcome, and selection of reported results. Each domain is given a final decision of either low, some concerns, or high risk of bias.

Statistical analysis

All evaluations were conducted through R v. 4.0.2 (The R Foundation of Statically Computing) (19). Frequentist network meta-analysis was performed through "netmeta" package to compare the efficacy and safety of selumetinib against other treatments or placebo (20). This approach was taken because of the variability in the reported interventions in the individual studies (different comparator groups), which deem the use of a simple meta-analysis unsuitable due to the different head-to-head comparisons. In order to account for this discrepancy and to included non-direct comparisons, a network analysis was deemed suitable. A fixed-effects model network meta-analysis was conducted due to the absence of heterogeneity, and evaluation was completed through I^2 Q-statistics with I^2>50% and P value <0.05 being considered significant (21). Therapeutic ranking depended on the P value being the frequentist form of the surface under the cumulative ranking (SUCRA) (22). In the assessment of the risk-of-bias and small-investigation influences, comparison-adjusted funnel plots could not be used due to the reduced size of the selected investigations (<10 studies) (23,24).

Employing "meta" package, we compared the safety and efficacy outcomes, and different treatment groups/placebo were evaluated for computing the pooled odds ratio (OR) (25).

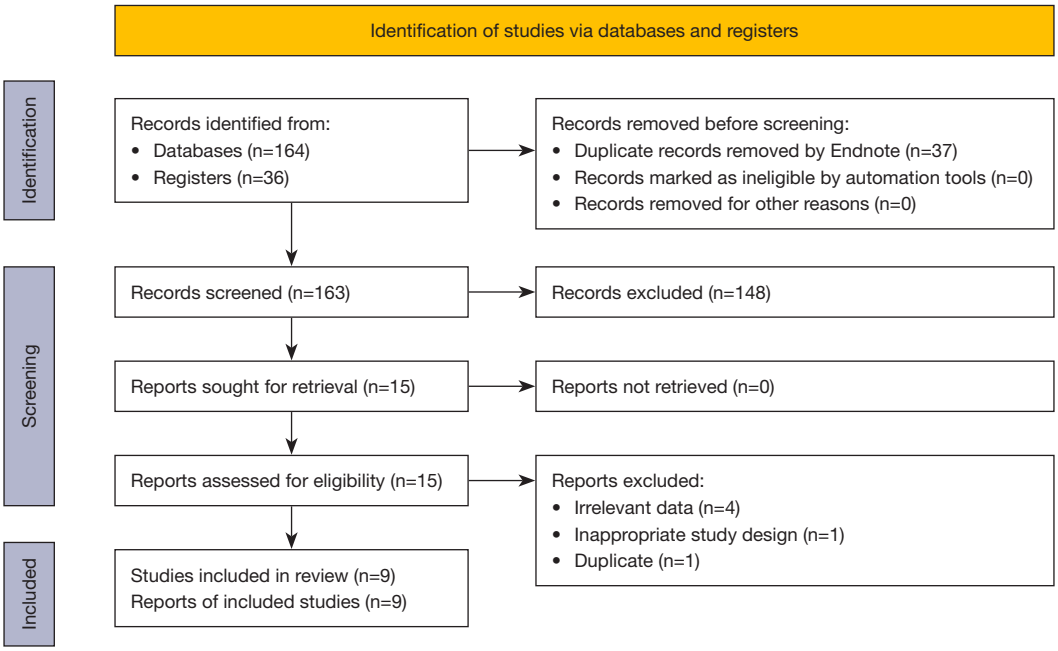

Figure 1 A PRISMA flowchart of the steps in our systematic review.

Additionally, 95% confidence intervals (CIs) of pooled effect size were determined through random effects from heterogeneity. The latter was evaluated through Q statistics or I^2 test, where I^2 value >50% or P value <0.05 (26) was considered to indicate significance. Publication bias was not conducted by Egger's regression test due the low number of eligible studies (<10 studies) (23,24).

Results

Search results

In all, 37 articles were excluded by EndNote X9 software following a duplicate check. Afterward, a total of 163 studies were imported into a Microsoft Excel sheet for title and abstract screening which identified 15 studies eligible for full-text screening. Six studies were excluded for the following reasons: irrelevant data (N=4), non-randomized trial (N=1), and duplicated record (N=4). Finally, 9 studies were identified for review and meta-analysis. Manual searching yielded no further articles (*Figure 1*).

Investigation profiles and quality of selected studies

The 9 RCTs included in the study totaled a sample-size of 1,195 individuals, with sample totals ranging from 39 to 510 in the individual studies. The average age for included cases was 62 years old, and the range was 59–66 years. The medical monitoring time frame ranged from 1–3 years. Selumetinib was employed as secondary therapy across all included studies (*Table 1*).

Risk of bias assessment

The overall risk of bias was high in about 50% of all domains. Regions having a peak risk of bias were those driven by a skew away from planned therapies, end point measurement, and selective reporting of results (*Figure 2A*). On the individual study level, 5 studies had an elevated risk of bias, 2 studies were concerning, while the remaining 2 articles demonstrated a reduced risk of bias (*Figure 2B*).

Efficacy of selumetinib

The efficacy of selumetinib whether alone (n=87) or in combination with other treatments (n=597) was evaluated in 684 patients (9 studies). The overall prevalence rate of disease progression or nonresponse events was 71.77% (95% CI: 63.24–81.45%). Using selumetinib alone yielded slightly better results with less disease progression and nonresponse events (65.20%; 95% CI: 39.15–100%) compared to selumetinib in combination with other treatments (74.08%;

Table 1 Characteristics of the included investigations

Author/year/country	Study design	Type of lung cancer	KRAS status	Line of treatment	Sample size	Baseline data	Inclusion criteria	Exclusion criteria	Previous anticancer treatment	Intervention arm	Control arm	Primary outcomes	Secondary outcomes	Follow-up
Melosky *et al.* /2019/ Canada (18)	A phase II multicenter RCT	Advanced or metastatic KRAS wildtype or unknown nonsquamous NSCLC	Mutation =44%, wild type =44%	Second-line	62	Age =66 [42–85]*; Male =30 (48%); Brain metastasis =5 (8.1%); WHO/ECOG performance status =0–1 (85% score 1)	≥18 years with KRAS confirmed histologically or cytologically as wild type or unknown nonsquamous NSCLC that was stage IIIB or IV	Patients with significant cardiac disease, active infection, active bleeding diatheses, or renal transplant, including any patient known to have hepatitis B, hepatitis C, or human immunodeficiency virus, neuropathy, significant gastrointestinal disease, those on potent inhibitors or inducers of CYP3A4/5, CYP2C19, and CYP1A2, those with current or past history of central serous retinopathy or retinal vein occlusion, high intraocular pressure (IOP), or uncontrolled glaucoma (irrespective of IOP level)	Surgery =8.1%, radiotherapy =50%, prior systemic drugs =21%	Arm A: intermittent selumetinib given on days 2–19; Arm B: continuous selumetinib given on days 1–21. All were combined with pemetrexed/ platinum chemotherapy	Arm C: pemetrexed/ platinum chemotherapy alone	ORR: 35%, 62%, and 24% in study arms A, B, and C, respectively. CR was 0% in all groups	PFS: 7.5, 6.7, 4.0 months in arms A, B, and C, respectively. OS: 10.0, 10.1, and 10.5 months in groups A, B, and C, respectively. AEs: venous thromboembolism (45%, 38%, 24% in groups A, B, C, respectively)	3 years#
Jänne *et al.* /2017/USA (17)	A multicenter RCT	KRAS-mutated advanced NSCLC	Mutation =100%	Second-line	510	Age =61.4 (8.3); Male =303 (59%); Brain metastasis =0%; WHO/ECOG performance status =0–1 (59% score 1)	≥18 years with histologically or cytologically confirmed locally advanced or metastatic NSCLC (stage IIIB–IV)	Mixed small cell lung cancer and NSCLC histology and presence of brain metastases or spinal cord compression (unless asymptomatic, treated, stable, and off steroids and anticonvulsants for ≥4 weeks prior to screening). Patients were also excluded if they had received more than 1 prior anticancer drug regimen for advanced or metastatic NSCLC, or prior treatment with an MEK inhibitor or any docetaxel-containing regimen	NCS	Oral selumetinib (75 mg) twice daily on a continuous schedule in combination with 75 mg/m^2 of docetaxel IV on day 1 of every 21-day cycle	Placebo plus docetaxel (same schedule)	PFS =3.9 *vs.* 2.8 months (intervention *vs.* control)	OS =8.7 *vs.* 7.9 months (intervention *vs.* placebo). ORR =20.1% *vs.* 13.7%. AE = overall AEs: 67% *vs.* 45%.	3 years#
Jänne *et al.* /2013/USA (10)	A multicenter, phase II, randomized placebo-controlled trial	KRAS-mutated advanced NSCLC	Mutation =100%	Second-line	87	Age =59.25; Male =41 (47%); Brain metastasis = NCS; WHO/ECOG performance status =0–1 (52% score 1)	≥18 years with histologically or cytologically confirmed stage IIIB–IV KRAS-mutant NSCLC	Patients were ineligible if they had received more than 1 chemotherapy, any previous treatment with an MEK inhibitor or docetaxel-containing regimen, or had mixed small cell and NSCLC histology	Surgery =26%, radiotherapy =40%, chemotherapy =100%	Oral selumetinib (75 mg twice daily in a 21-day cycle) plus IV docetaxel (75 mg/m² on day 1 of a 21-day cycle)	Placebo plus docetaxel (same schedule)	OS =9.4 *vs.* 5.2 months (INT *vs.* PL)	PFS =5.3 *vs.* 2.1 months (INT *vs.* PL). ORR =37% *vs.* 0% (INT *vs.* PL). AEs (grade III or higher) =82% *vs.* 67% (INT *vs.* PL)	1 year#
Jänne *et al.* /2015/USA (27)	Retrospective analysis from RCT	Advanced or metastatic NSCLC	Mutation =100%	Second-line	83	Age =59.25; Male =41 (47%); Brain metastasis = NCS; WHO/ECOG performance status =0–1 (52% score 1)	≥18 years with histologically or cytologically confirmed stage IIIB–IV KRAS-mutant NSCLC	Patients were ineligible if they had received more than 1 chemotherapy, had any previous treatment with an MEK inhibitor or docetaxel-containing regimen, or had mixed small cell lung cancer and NSCLC histology	Surgery =26%, radiotherapy =40%, chemotherapy =100%	Oral selumetinib (75 mg twice daily in a 21-day cycle) plus IV docetaxel (75 mg/m² on day 1 of a 21-day cycle)	Placebo plus docetaxel (same schedule)	In patients receiving selumetinib þ docetaxel and harboring KRAS G12C or G12V mutations there were trends toward greater improvement in OS, PFS, and ORR compared with other KRAS mutations	NCS	1 year#
Carter *et al.* /2016/USA (28)	A randomized, multicenter, phase II clinical trial	Advanced NSCLC	Mutation =41%, wild type =38%	Second-line	41	Age =65 [50–83]*; Male =18 (44%); Brain metastasis = NCS; WHO/ ECOG performance status = 0–2 (46% score 1 and 44% score 2)	≥18 years histologically proven advanced NSCLC, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, adequate organ function, and treated with or refused treatment with a platinum-containing doublet chemotherapy regimen	Uncontrolled disease unrelated to the primary malignancy, more than 2 prior systemic treatments and a history of prior EGFR TKI (erlotinib) or an MEK inhibitor	NCS	Combined therapy: selumetinib (150 mg twice daily) plus erlotinib (100 mg daily)	Single-agent: selumetinib (75 mg twice daily) alone	ORR =10% *vs.* 0% (combined *vs.* monotherapy); OS =21.8 *vs.* 10.5 months; PFS =2.3 *vs.* 4.0 months	NCS	NR
Goffin *et al.* /2019/ Canada (29)	A phase Ib clinical trial	Untreated advanced or metastatic NSCLC	Mutation =18%	Second-line	39	Age =62 [50–79]*; Male =16 (41%); Brain metastasis =0%; WHO/ ECOG performance status =0–1 (67% score 1)	Adults with pathologically confirmed NSCLC who were not candidates for curative therapy and who had received any prior systemic treatment for their incurable disease.	Patients were also excluded if they had brain metastasis, other malignancies treated within 2 years, a current or past history of significant heart disease, central serous retinopathy, retinal vein occlusion, high intraocular pressure, or uncontrolled glaucoma	NCS	Selumetinib [50 mg BID days 2–19 (dose level 1); 75 mg BID days 2–19 (dose level 2); 75 mg BID continuously] plus carboplatin (AUC 6) and paclitaxel (200 mg/m^2).	Selumetinib plus pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2)	Optimum dose (No OS, PFS, ORR, or time to response data)	AE	9 months
Hainsworth *et al.* /2010/ USA (30)	A phase II, open-label, multicenter, randomized clinical trial	Advanced NSCLC	NCS	Second or Third-line	84	Age =60.95; Male =53 (64%); Brain metastasis = NR; WHO/ECOG performance status =0–1	Patients aged ≥18 years with histologically or cytologically confirmed NSCLC who had previously received 1 or 2 chemotherapeutic regimens, had a World Health Organization performance status of 0 to 2, and had a life expectancy >12 weeks	Previous therapy with an MEK inhibitor or pemetrexed	Radiotherapy =37%, platinum therapy =94%, taxane therapy =46%	Selumetinib 100 mg oral, twice daily	Pemetrexed 500 mg/m^2 IV once every 3 weeks	Disease progression =70% *vs.* 59%	Most commonly reported AEs were dermatitis (43%) and diarrhea (30%) in the INT group, and fatigue (37%) and anemia (29%) in the CON group.	NR
Soria *et al.* /2017/UK (31)	A multicenter, phase II RCT	Advanced or metastatic NSCLC	Mutation =21%, wild type =68%	Second-line	212	Age =61.8 (8.8); Male =151 (71%); Brain metastasis = NR; WHO/ECOG performance status =0–1 (51% score 1)	Patients ≥18 years, with a WHO performance status (PS) 0/1, who had disease progression after first-line treatment of locally advanced or metastatic NSCLC due to progression of disease while on first-line therapy or relapse of disease following remission from first-line therapy	Patients were excluded if they had mixed small cell cancer and NSCLC histology, had received >1 prior anticancer drug regimen for advanced or metastatic NSCLC (platinum-based doublet chemotherapy, other single agent anticancer therapy, or combination regimen), or had received prior treatment with an MEK inhibitor or any docetaxel-containing regimen	NCS	Selumetinib 75 mg BID plus docetaxel 60 mg/m^2 (IV on day 1 of every 21-day cycle) OR selumetinib 75 mg BID plus docetaxel 75 mg/m^2	Placebo plus docetaxel (same schedule)	PFS =3.0, 4.2, and 4.3 months (SEL + DOC 60 mg *vs.* SEL + DOC 75 mg *vs.* PL + DOC)	ORR =33% *vs.* 14% (INT *vs.* PL)	NR
Oxnard *et al.*/2020/ USA (32)	A phase Ib clinical trial	Advanced EGFR-mutant NSCLC	NR	Second-line	77	Age =60.1; Male =30 (38.96%); Brain metastasis = NCS; WHO/ECOG performance status =0–1 (77.9% score 1)	Eligible patients 18 years (Japan: 20 years) who had WHO performance status 0–1 and advanced EGFR-mutant NSCLC with progression on prior therapy with any EGFR-TKI; intervening therapy was permitted	Patients were excluded if they had (I) previous EGFR-TKI treatment; (II) had any cytotoxic chemotherapy, investigational agents, or other anti-cancer drugs; (III) were receiving warfarin sodium; (IV) had evidence of severe or uncontrolled systemic diseases; and (V) had inadequate bone marrow reserve or organ function	NCS	Three arms: (I) osimertinib 80 mg orally once a day with selumetinib (oral 25–75 mg twice a day; continuous or intermittent), (II) savolitinib (oral 600–800 mg once a day), or (III) durvalumab (3–10 mg/kg intravenous every 2 weeks)	None	ORR in the selumetinib arm =42%	AE in the selumetinib arm: diarrhea (75%), rash (58%), and nausea (47%)	NR

refers to the median and not the mean of the follow-up period; *, randomized clinical trials. RCT, randomized controlled trial; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; AE, adverse event; SEL, selumetinib; PL, placebo; INT, intervention; ORR, objective response rate; WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group; KRAS, Kristen rat sarcoma virus; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NCS, not clearly specified; NR, not reported; USA, United States of America; UK, United Kingdom.

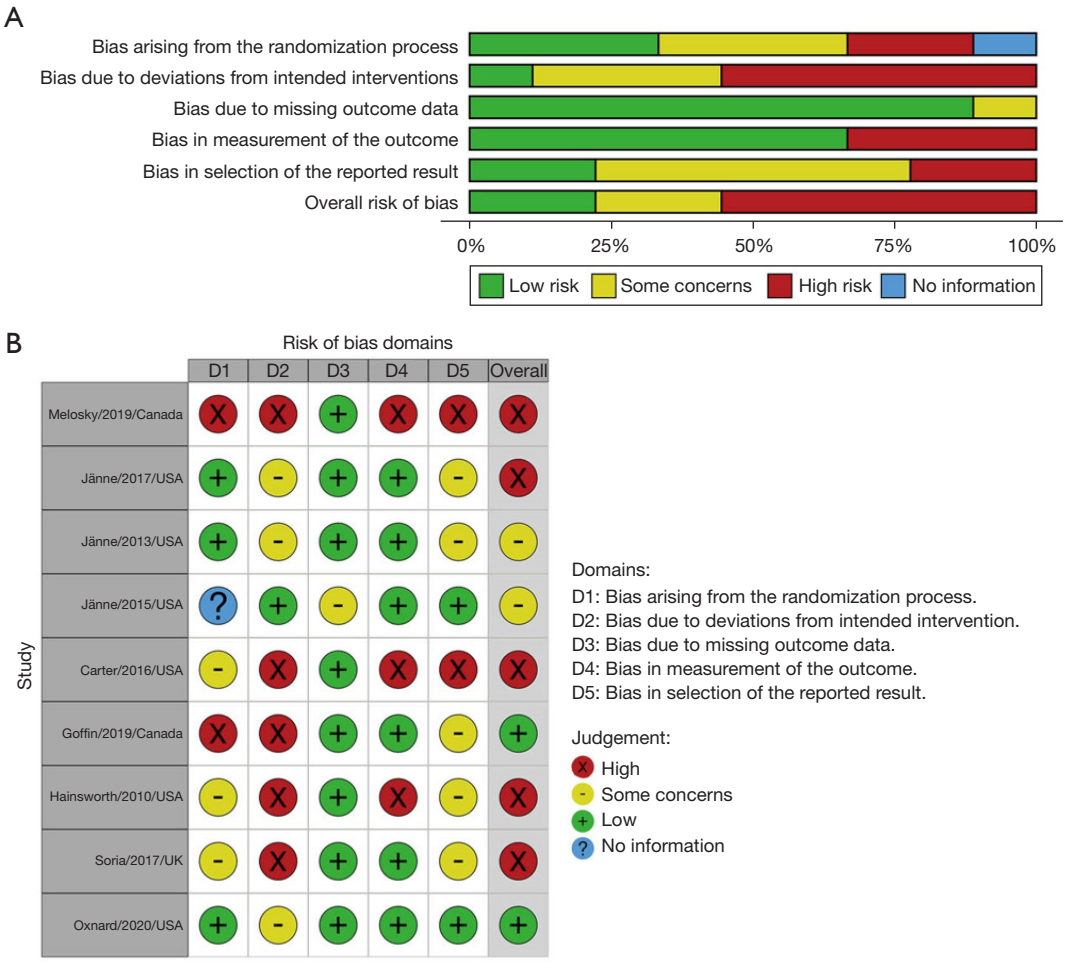

Figure 2 Risk-of-bias assessment of included investigations. (A) Quality assessment of different domains of the Cochrane tool; (B) overall quality.

95% CI: 64.65–84.89%). Major heterogeneity was seen across the selected trials (I^2=89%; P value <0.001; *Figure 3*).

A further 7 investigations comprising 1,026 cases were selected to analyze the efficacy of selumetinib in comparison to other therapies. The arms of pairwise comparisons contained 4 and 3 investigations, which were used to create a symmetrical networking plot (*Figure 4A*). Compared to placebo (P=0.12), selumetinib treatment was found to have superior efficacy with less disease progression or nonresponse events (P=0.82), which was followed by chemotherapy or immunotherapy treatments (P=0.56; *Figure 4B*). However, no major differences were observed in comparisons of selumetinib and chemotherapy/immunotherapy [odds ratio (OR) =0.87; 95% CI: 0.47–1.62], selumetinib and placebo (OR =0.62; 95% CI: 0.37–1.04), or chemotherapy/immunotherapy and placebo (OR =0.71; 95% CI: 0.32–1.59; *Figure 5*). Furthermore, no major heterogeneity or inconsistency was observed (τ^2=0.05; I^2=17%; P=0.304).

Safety profile of selumetinib

Overall, 622 patients (7 studies) received selumetinib both alone (n=76) or in combination with other treatments (n=546) and were assessed for its safety. The overall prevalence rate of SAEs was 42.96% (95% CI: 34.74–53.13%). Using selumetinib alone was associated with significantly fewer SAEs (10.49%; 95% CI: 0.93–100%) as compared to selumetinib in combination with other treatments (47.38%; 95% CI: 39.73–56.51%). There was significant heterogeneity across studies (I^2=74%; P<0.001; *Figure 6*).

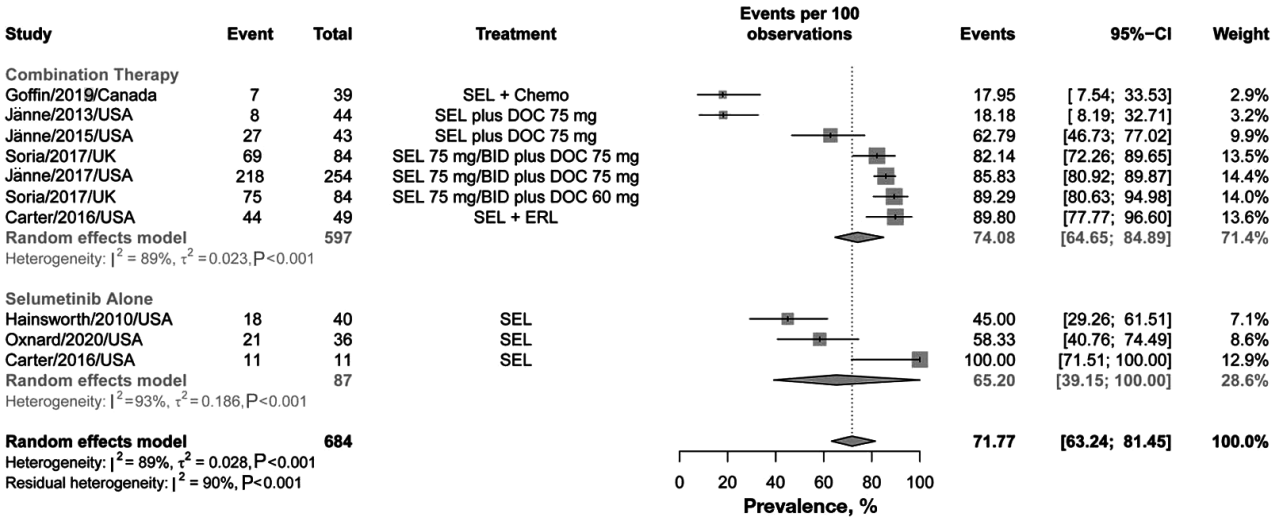

Figure 3 Meta-analysis of the efficacy (rate of disease progression or lack of response) of selumetinib alone or in combined therapy. SEL, selumetinib; Chemo, chemotherapy/immunotherapy; DOC, docetaxel; BID, twice a day; CI, confidence interval.

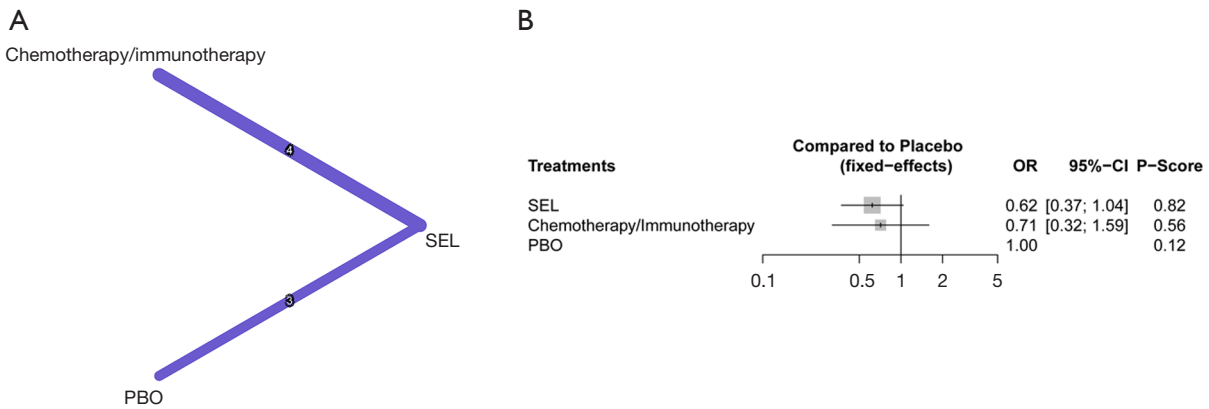

Figure 4 Network analysis of the efficacy (rate of disease progression or lack of response) of selumetinib, placebo, and chemotherapy/immunotherapy. SEL, selumetinib; PBO, placebo; OR, odds ratio; CI, confidence interval.

Selumetinib	**0.41 (0.17 to 0.97)**	**2.01 (1.48 to 2.73)**
0.87 (0.47 to 1.62)	**Chemotherapy/immunotherapy**	**4.92 (1.96 to 12.35)**
0.62 (0.37 to 1.04)	0.71 (0.32 to 1.59)	**Placebo**

Figure 5 Network meta-analysis of selumetinib efficacy (progression/no response; lower part) and safety (serious adverse events; upper part) rates*. *, treatments are reported in order of efficacy and safety profile according to P values. Comparisons should be read from left to right. Data are reported in the form of OR and their corresponding 95% CI. ORs below 1 favors the row-defining treatment. Significant results are in bold font. OR, odds ratio; 95% CI, 95% confidence interval.

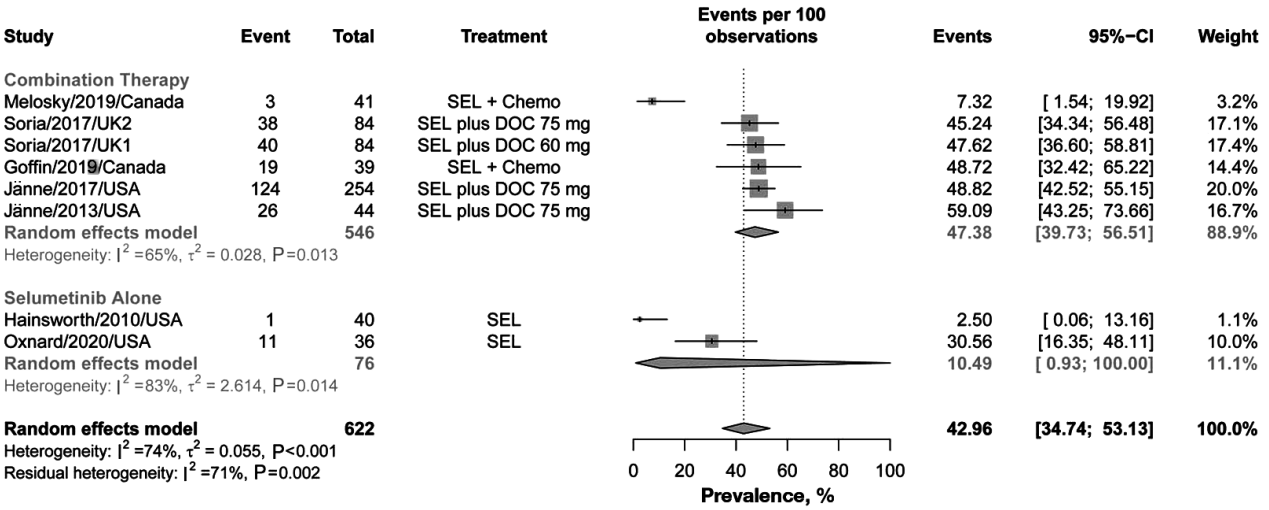

Figure 6 Meta-analysis of the safety (frequency of SAEs) of selumetinib alone and combined therapy. SEL, selumetinib; Chemo, chemotherapy/immunotherapy; DOC, docetaxel; CI, confidence interval; SAEs, serious adverse events.

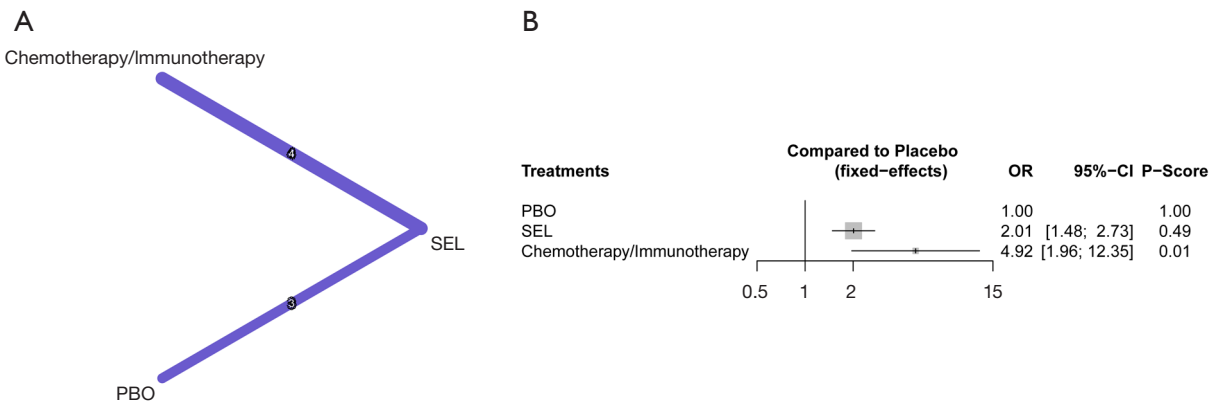

Figure 7 Network analysis of the safety (frequency of SAEs) of selumetinib, placebo, and chemotherapy or immunotherapy. SEL, selumetinib; PBO, placebo; OR, odds ratio; CI, confidence interval; SAEs, serious adverse events.

A further 5 studies comprising 884 cases were selected to analyze the safety of selumetinib. The arms of pairwise comparisons consisted of 4 and 3 investigations which constituted the symmetrical networking plot (*Figure 7A*). Compared to placebo (P=1), selumetinib treatment was found to have the best safety, having a minimal number of SAEs (P=0.49), and was followed by chemotherapy or immunotherapy treatments (P=0.01; *Figure 7B*). In addition, selumetinib has shown better safety profile when compared with chemotherapy/immunotherapy (OR =0.41; 95% CI: 0.17–0.97), however, it was associated with worse safety when compared to placebo (OR =2.01; 95% CI: 1.48–2.73). Similarly, chemotherapy/immunotherapy was associated with worse safety when compared to placebo (OR =4.92; 95% CI: 1.96–12.35; *Figure 5*). There was no significant heterogeneity or inconsistency observed across studies (τ^2<0.01; I^2=0%; and P value =0.570).

Discussion

Despite the growing evidence supporting combination therapy as an approach that can reduce or overcome chemoresistance within EGFR-mutated NSCLC (33-35), there are, to date, no globally adopted *EGFR*-based

combination therapies in NSCLC. Moreover, interventions for cases with acquired chemoresistance for *EGFR* tyrosine kinase inhibitors (TKIs) remain notably scarce. *KRAS* mutations, occurring within approximately 20% of patients with NSCLC (36), have been found to be linked to intrinsic chemoresistance against TKIs (37). Consequently, various targeted therapies have been deployed against *RAS/RAF/MEK/ERK* pathways and have been shown to be effective across numerous malignancies. Selumetinib is a *MEK1/2* inhibitor that has demonstrated promising therapeutic value as a second-line treatment either alone or combined with other chemotherapies/immunotherapies for managing clinical cases of late-stage or metastatic NSCLC (25,29,38-41). In this systematic review, we included 9 phase I, II, and III trials (1,195 patients) that investigated the efficacy of selumetinib either as a stand-alone therapy or combined with other agents for the treatment of NSCLC.

Overall, 9 studies (684 NSCLC cases) were selected for our efficacy meta-analysis (the rate of disease progression or absence of response). In all, 87 patients were given selumetinib alone, while 597 patients were given selumetinib in combination with other therapies. The overall rate of disease progression in our study was 71.77% (95% CI: 63.24–81.45%). However, upon conducting a meta-analysis on combined selumetinib therapy versus selumetinib alone, we found that selumetinib alone had slightly higher efficacy compared to combination therapies, with efficacy rates of 65.2% *vs*. 74.08%, respectively. However, this result must be cautiously interpreted, as the resultant 95% CI: was wide, and the efficacy rate of selumetinib alone was 65.2% (95% CI: 39.15–100%), and the efficacy of combined therapy was 74.08% (95% CI: 64.65–84.89%). Such a wide range of the reported 95% CI reflects a significant degree of uncertainty regarding the definitive value of the rate of disease progression or lack of response (42). Moreover, our analysis revealed a significant degree of heterogeneity. This should also be taken into account, given the fact that analyzed populations of included investigations were heterogeneous at baseline. For instance, the performance status (PS) of the majority of included populations ranging from 0 to 1, with rates of PS 1 ranging from 46% to 85%. Also, the phase II clinical investigation by Carter and colleagues (28) included cases having PS 0–2, and almost half of their population had a PS of 2 (44%). Another point to consider is the variability in treatment protocols among included investigations along with the varying doses of selumetinib in each trial. As a part of their treatment protocols, some investigations administered selumetinib as a continuous course (10,32,34,38,39), while other investigations used an intermittent course (25,32); in 1 trial (25), it was reported that the continuous selumetinib course had superior efficacy over the intermittent course. Moreover, some populations had worse prognosis at baseline compared to other populations. For example, the multicenter phase II clinical trial of Melosky *et al.* (18) recruited NSCLC patients with brain metastasis (8.1%), while other investigations did not recruit brain metastasis cases. Importantly, most selected trials were conducted when immunotherapies were still under development, and thus, the majority of included populations underwent primary platinum-based chemotherapeutic measures (10,26-28,31). With the continuous changes in therapeutic strategies, the advent of immunotherapy could be a limiting factor in the aforementioned trials since both the efficacy and safety profile of selumetinib within NSCLC either alone or combined with other therapies were not investigated in patients who had undergone first-line immunotherapy.

Consequently, a network meta-analysis was conducted for determining the comparative efficacy in placebo, selumetinib alone, and other chemotherapies or immunotherapies. We found that selumetinib was superior to other interventions in terms of fewer rates of disease progression or lack of response and was followed by selumetinib and placebo. Although selumetinib showed superior efficacy over the reported chemotherapies and immunotherapies, the difference did not reach statistical significance even when compared to placebo. However, we noted no significant heterogeneity in this network analysis.

According to preclinical evidence indicating selumetinib has peak efficacy within *KRAS*-mutated NSCLC, the prospective randomized phase II clinical trial by Jänne *et al.* (10) investigated the efficacy and safety-profile of selumetinib combined with docetaxel as secondary treatment within *KRAS*-mutated NSCLC. Cases were allocated into two groups: intervention (combined therapy, 44 patients) and control (placebo plus docetaxel, 43 patients). Despite both arms being comparable regarding OS, the intervention arm was associated with major enhancements within PFS, ORR, and patient-reported outcomes. Meanwhile, the frequency of AEs leading to death was comparable in both arms (9% for the intervention cohort *vs.* 7% for the control cohort). In another study (25), despite no visible correlation for *KRAS*-status and selumetinib efficacy being noted, the authors reported that cases having elevated signature values had enhanced PFS. However, due to the small sample size of this study, the interpretation for this finding is limited. Since

certain *KRAS*-mutation subtypes have been hypothesized, based on previous trial (27), to have the greatest response to selumetinib, Jänne *et al.* (17) conducted the largest trial (SELECT-1 trial) on 510 centrally confirmed KRAS-mutated patients. Clinical cases were designated as either undergoing selumetinib + docetaxel or solely docetaxel. The authors conducted a subset analysis of 2 cohorts based on the type of *KRAS* mutation: a *KRAS G12C* or *KRAS G12V* cohort and an other-*KRAS*-mutations cohort; their findings did not confirm the observations of the previous trial or other reports in the literature. The absence of concrete evidence within this type of clinical case subgroup analysis is represented in the lack of definite ESMO and NCCN recommendations, and no therapeutic algorithms have been thus far proposed by either body (13,14). There still exists a greater need for developing efficacious interventions in clinical cases with *KRAS* mutations, with the aforementioned trials further highlighting this point.

Out of 7 trials (622 patients) included in our meta-analysis, the overall frequency of reported SAEs was 42.96%, with selumetinib alone having a better safety profile compared to combination therapies (10.44% *vs.* 47.38%). However, as previously mentioned, due to the wide range of the reported 95% CI: in this analysis, the absolute value of the frequency of SAEs in NSCLC patients who were given selumetinib alone could be any value from 0.93% to 100%, and therefore, this finding should be interpreted with caution. Moreover, significant heterogeneity was noted within this analysis. In the network analysis of 5 studies (884 patients), we found that placebo was superior in terms of the safety profile (SAEs) followed by selumetinib and chemotherapy/immunotherapy. Notably, selumetinib carried an enhanced safety profile in comparison with chemotherapy or immunotherapy, with significantly fewer SAE events (OR =0.41). In addition, based on the network comparisons, both selumetinib and chemotherapy/immunotherapy showed worse safety when compared to placebo, but when compared to one another, selumetinib showed better safety.

Limitations

Our study had several limitations, the most important of which was the low number of selected trials, together with the small sample size of each individual trial (sample sizes ranged from 39 to 510), and thus, the risk of publication bias was not evaluated. Second, the majority of selected investigations carried an elevated risk of bias (5 studies), with only 2 studies being concerning and 2 showing a reduced risk of bias. Third, most trials were conducted during the development of immunotherapy, and therefore assessing selumetinib efficacy as secondary treatment following immunotherapy-based therapy was not possible. Fourth, significant heterogeneity was noted in most of the subset in our analysis. More importantly, the reported 95% CI in our safety and efficacy analysis of selumetinib was wide, and this reflects a significant degree of uncertainty regarding the true value. Based on these limitations, there may be a considerable degree of uncertainty in our findings, and thus the efficacy and safety of selumetinib either alone or combined with other therapies as secondary therapy for advanced or metastatic NSCLC (*KRAS* mutant or wild type) are not yet supported. More reliable randomized controlled trials are needed to obtain a more definite conclusion.

Conclusions

Within clinical cases of previously treated advanced or metastatic NSCLC (*KRAS* mutant or wild type), selumetinib alone failed to demonstrate superior efficacy (rate of disease progression or lack of response) over combination therapies, chemotherapy, or immunotherapy. However, selumetinib has a better safety profile with fewer SAEs compared to chemotherapy and immunotherapy. Based on the current limitations in the literature, trials with a greater degree of reliability and larger sample sizes are needed to concretely determine whether selumetinib has superior efficacy in certain *KRAS* subtypes of NCSLC.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1849/coif). The authors have no conflicts of interest to declare.

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