



MET Exon 14 Skipping in NSCLC: A Systematic Literature Review of Epidemiology, Clinical Characteristics, and Outcomes

Julien Mazieres,¹ Helene Vioix,² Boris M. Pfeiffer,² Rhiannon I. Campden,³ Zhiyuan Chen,³ Bart Heeg,³ Alexis B. Cortot⁴

Abstract

Introduction: *MET* exon 14 (*MET*ex14) skipping is a rare oncogenic driver in non-small-cell lung cancer (NSCLC) for which targeted therapy with *MET* tyrosine kinase inhibitors (TKIs) was recently approved. Given the heterogeneity in published data of *MET*ex14 skipping NSCLC, we conducted a systematic literature review to evaluate its frequency, patient characteristics, and outcomes. **Methods:** On June 13, 2022 we conducted a systematic literature review of publications and conference abstracts reporting frequency, patient characteristics, or outcomes of patients with *MET*ex14 skipping NSCLC. **Results:** We included 139 studies reporting frequency or patient characteristics (350,997 patients), and 39 studies reporting clinical outcomes (3989 patients). Median *MET*ex14 skipping frequency was 2.0% in unselected patients with NSCLC, with minimal geographic variation. Median frequency was 2.4% in adenocarcinoma or nonsquamous subgroups, 12.0% in sarcomatoid, and 1.3% in squamous histology. Patients with *MET*ex14 skipping NSCLC were more likely to be elderly, have adenocarcinoma histology; there was no marked sex or smoking status distribution. In first line of treatment, median objective response rate ranged from 50.7% to 68.8% with targeted therapies (both values correspond to *MET* TKIs), was 33.3% with immunotherapy, and ranged from 23.1% to 27.0% with chemotherapy. **Conclusions:** Patients with *MET*ex14 skipping are more likely to have certain characteristics, but no patient subgroup can be ruled out; thus, it is crucial to test all patients with NSCLC to identify suitable candidates for *MET* inhibitor therapy. *MET* TKIs appeared to result in higher efficacy outcomes, although no direct comparison with chemotherapy or immunotherapy regimens was found.

Clinical Lung Cancer, Vol. 24, No. 6, 483–497 © 2023 Published by Elsevier Inc.

Keywords: Tyrosine kinase inhibitor, Tepotinib, Capmatinib

Abbreviations: ALK, Anaplastic lymphoma kinase; ASCO, American Society of Clinical Oncology; *BRAF*, V-raf murine sarcoma viral oncogene homolog B; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CGP, Comprehensive genomic profiling; DARE, Database of Abstracts of Reviews of Effectiveness; DOR, Duration of response; *EGFR*, Epidermal growth factor receptor; EMA, European Medicines Agency; ESMO, European Society of Medical Oncology; FDA, US Food and Drug Administration; HTA, Health Technology Assessment; IHC, Immunohistochemistry; IO, Immunotherapy; ISPOR, Professional Society for Health Economics and Outcomes Research; IQR, Interquartile range; JBI, Joanna Briggs Institute; *KRAS*, Kirsten rat sarcoma viral oncogene homologue; *MET/CEP7*, Mean *MET* per cell and chromosome 7 centromere ratio; *MET*ex14, *MET* exon 14; NE, Not estimable; NGS, Next-generation sequencing; NICE, National Institute for Health and Care Excellence; NR, Not reached; NSCLC, Non-small-cell lung cancer; *NTRK*, Neurotrophic receptor tyrosine kinase; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; PD-L1, Programmed death-ligand 1; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; *RET*, Rearranged during transfection; SLR, Systematic literature review; TKI, Tyrosine kinase inhibitor; TPS, Tumor proportion score; TTP, Time to progression; US, United States; WCLC, World Conference on Lung Cancer.

¹CHU de Toulouse, Université Paul Sabatier, Toulouse, France

²The Healthcare Business of Merck KGaA, Darmstadt, Germany

³Ingress Health, A Cytel Company, Rotterdam, The Netherlands

⁴Université Lille, Centre Hospitalier Universitaire de Lille, Centre national de la recherche scientifique, Inserm, Institut Pasteur de Lille, Lille, France

Submitted: Feb 15, 2023; Revised: May 30, 2023; Accepted: Jun 12, 2023; Epub: 18 June 2023

Introduction

Lung cancer remains the leading cause of cancer death, globally.¹ The most common type of lung cancer is non-small-cell lung cancer (NSCLC), which accounts for over 80% of all diagnosed lung cancers.² NSCLC oncogenic drivers that have been successfully targeted by tyrosine kinase inhibitors (TKIs) include mutations in the epidermal growth factor receptor (*EGFR*) and V-raf murine sarcoma viral oncogene homolog B (*BRAF*) genes, and fusions and rearrangements in the anaplastic lymphoma kinase (*ALK*), *ROS1*, neurotrophic receptor tyrosine kinase (*NTRK*) and rearranged during transfection (*RET*) genes.² The activation of the *MET* proto-oncogene by exon 14 skipping (*MET*ex14) and its role as a targetable oncogenic driver in NSCLC has been established in the past few years.^{2–4} Studies evaluating large samples of patients with NSCLC have reported 2% have *MET*ex14 skipping,^{5,6} which is mutually exclusive with other oncogenic drivers⁷ that also

Address for correspondence: Julien Mazieres, MD, CHU de Toulouse, Université Paul Sabatier, Hôpital Larrey, Chemin de Pouvoirville, 31059 Toulouse, France
E-mail contact: mazieres.j@chu-toulouse.fr

represent a low proportion of NSCLC, such as *BRAF* mutations (5%-8%) and *ALK* (2%-7%) or *ROS1* rearrangements (1%-2%).⁸ Some oncogene-defined subgroups have been associated with certain clinical characteristics: never smoker young Asian women (*EGFR* mutations),⁸ never smoker younger women (*ROS1* fusions/translocations),^{8,9} and never smoker patients with adenocarcinoma histology (*ALK* fusions/translocations).^{8,10} *MET*ex14 skipping occurs mostly in older patients, including those with a history of smoking, and has been associated with a poor prognosis.¹¹⁻¹³ The general characteristics of patients with *MET*ex14 skipping NSCLC, however, are not well defined.

Treatment of patients with *MET*ex14 skipping NSCLC changed in recent years with the approval of several MET TKIs. The first MET TKI to gain approval was tepotinib, in Japan in 2020;¹⁴ tepotinib was later approved by the US Food and Drug Administration (FDA) in 2021 in any treatment line¹⁵ and by the European Medicines Agency (EMA) in 2022 as a second-line treatment.¹⁶ Capmatinib is another MET TKI approved by the FDA and EMA (in 2020 and 2022, respectively) in the same treatment lines as tepotinib;^{17,18} savolitinib is currently approved only in China (2021, for patients who have progressed after platinum-based chemotherapy or do not tolerate it),¹⁹ and other MET TKIs are under study.⁷

Due to the rarity of *MET*ex14 skipping and older age of patients, it is challenging to recruit sufficient patients for large phase III studies evaluating targeted treatments, and the largest clinical data sets derive from noncomparative phase II studies.²⁰⁻²² Additionally, given that *MET*ex14 skipping was only relatively recently recognized as an oncogenic driver,²³ and, thus, not routinely tested, there are limited clinical outcomes data on nontargeted treatments routinely used in patients with *MET*ex14 skipping NSCLC to compare with data for targeted agents. There is a need for a better understanding of the characteristics and outcomes of this population that may help guide clinical trial designs and highlight the need for *MET*ex14 skipping testing. We conducted a systematic literature review (SLR) to assess epidemiology, prognosis, clinical outcomes, economic burden, and quality of life of *MET*ex14 skipping NSCLC. Here, we report the epidemiology and clinical outcomes of patients with *MET*ex14 skipping NSCLC treated with targeted and nontargeted therapies to assess the potential benefits of targeted therapies for these patients.

Methods

Review Design

An SLR was performed on June 13, 2022 according to National Institute for Health and Care Excellence (NICE) preferred methodological principles,²⁴ as detailed in the University of York Centre for Reviews and Dissemination guidance for undertaking systematic reviews in health care.²⁵ Literature searches were conducted in key biomedical electronic databases including EMBASE, MEDLINE, EconLit, and the Cochrane Library—specifically, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effectiveness (DARE), the Health Technology Assessment (HTA) database, and the National Health System Economic Evaluation Database. In addition, the following congress websites

were searched on June 13, 2022 for relevant abstracts, posters and/or presentations with no time restrictions: American Society of Clinical Oncology (ASCO), World Conference on Lung Cancer (WCLC), Society for Health Economics and Outcomes Research (ISPOR), and the European Society of Medical Oncology (ESMO). The bibliographies of systematic reviews and meta-analyses identified after an initial review of the search results were then reviewed for potential references of interest regarding other studies.

Search syntax for publications included non-small-cell lung cancer, non-small-cell, (lung or pulmon or bronchioloalveolar), (cancer or tumor or carcino or adenocarcino or neoplas), NSCLC, MET exon14, *MET*ex14, *MET*ex 14, or MET exon 14, and subsequent combinations thereof. Search syntax for congress proceedings included MET EXON 14 OR METEX 14 OR "METEX14", MET exon 14, and MET mutation (the latter, broader term, was used only for ISPOR).

All publications in English language which fulfilled the following inclusion criteria were included in this review. In the case of epidemiology studies, real-world studies reporting incidence or frequency data for adult patients with NSCLC with *MET*ex14 skipping (or with majority *MET*ex14 skipping NSCLC). The term "incidence" was included to ensure that any studies that mistakenly reported frequency (ie, frequency in a specific population at a specific time or time period) as "incidence" (ie, rate of new cases in a population over a specific time period) were captured. In the case of clinical outcome studies, criteria were inclusion of adult patients with advanced or metastatic NSCLC with *MET*ex14 skipping; use of any line of therapy, any pharmacologic treatment, any study design; and reporting of clinical outcomes (overall survival [OS], progression-free survival [PFS], time to progression [TTP], response rates, safety, and tolerability).

The references identified from the electronic searches were first assessed against the eligibility criteria by 2 independent reviewers based on the title and/or abstract. Full-text copies of publications potentially meeting the eligibility criteria were then obtained and reviewed in more detail. At both stages, any disagreements between the reviewers were resolved by discussion until a consensus was reached, with a third reviewer making the final decision if necessary. The reviewers independently extracted data from all the included publications and generated 2 separate data extraction sheets that were then compared, and 1 uniform data extraction sheet was generated. Information extracted included publication information, study characteristics, patient characteristics, and frequency.

Publications that included overlapping patient populations (eg, patients from 1 study also contributing to a larger study) were considered as separate individual studies if they reported different outcomes. Where conference abstracts were subsequently reported as full-text publications and both were found in the literature review, only data from the full-text publication were gathered, as they contained the most evidence. The line of therapy associated with clinical outcome data reported in this SLR is the line described in the selected publication (eg, first line and beyond, second line).

Risk of Bias

Risk of bias was determined according to the NICE criteria for full-text publications;²⁶ frequency studies were assessed with the

Joanna Briggs Institute (JBI) checklist,²⁷ and a modified Downs and Black adapted checklist was used for clinical outcome studies.²⁸ Conference abstracts were excluded from the risk of bias assessment, given the limited information they provide.

Adequate sample size to determine frequency of *METex14* skipping in NSCLC was calculated according to the formula²⁹:

$$n = \frac{Z^2 P(1 - P)}{d^2}$$

Where *Z* corresponds to confidence level, *P* is the expected frequency, and *d* corresponds to effect size. For this calculation, the assumed frequency was 1%, and the precision (corresponding effect size) was set at 0.005 (one-fifth of the amount of precision in the case of a small *P* value³⁰).

Due to varying sample sizes, the clinical outcomes analyzed in this report are restricted to study arms with ≥ 10 patients. However, the details for all the studies (including study arms with < 10 patients) are included in the [Supplemental Tables](#). For endpoint analyses, we used the most recently reported data cut for individual studies. Studies reporting aggregated clinical outcomes for several types of therapy and studies not reporting the specific type of therapy used were categorized as “unspecified.”

Statistics

Frequency data were calculated as a percentage of the number of participants with NSCLC sampled and the total number of participants diagnosed with *METex14* skipping. Data for clinical characteristics are presented as range, median and interquartile range (IQR) as reported in the individual studies.

Results

Publications

Of the 1501 publications identified in the literature review, 324 were screened for eligibility, with 126 publications excluded. An additional 46 were included from manual checks of references in studies, resulting in 244 publications selected overall for all topics considered in the SLR, 230 corresponding to the topics reported here ([Figure 1](#)). Selected epidemiology reports consisted of 150 publications (60 full-text publications and 90 abstracts or posters) for 139 unique studies ([Supplemental Table 1](#)). Of these studies, 127 concerned NSCLC in particular and were conducted in Asia (*n* = 44, 35%), North America (*n* = 42, 33%), Europe (*n* = 32, 25%), South America (*n* = 2, 2%), and Eurasia (Turkey; *n* = 100, 1%). Five studies (4%) did not report the study location, and 1 study (1%) was conducted globally. Patient sample sizes ranged 13 to 11,306 in Asia,^{31,32} 36 to 60,244 in North America,^{5,33} 20 to 2369 in Europe,^{34,35} and 63 to 3784 in studies not specifying location;^{36,37} the global study had a sample size of 40,824.⁶ Frequency of *METex14* skipping in NSCLC was reported by 127 publications (*n* = 256,395 patients with NSCLC); clinical characteristics of patients were reported by 79 publications (*n* = 63,652). Publications reporting frequency or clinical characteristics of patients with *METex14* skipping NSCLC were more frequent in recent years. There were no studies using the term “incidence” for *METex14* skipping NSCLC in our literature search results.

Regarding clinical outcomes, 92 publications (34 full-text and 58 abstracts) from 39 unique studies were selected, 11 were nonrandomized interventional studies and 28 were real-world studies; there were no randomized controlled trials (RCTs) ([Supplemental Table 2](#)). The selected studies used targeted therapies/*MET* TKIs, chemotherapy, immunotherapy (IO) regimens, or unspecified treatments. The number of publications and unique studies reporting clinical outcomes in these patients increased from 2019 to 2022 ([Supplemental Figure 1A and B](#)).

Testing Methods for Detecting *METex14* Skipping in NSCLC

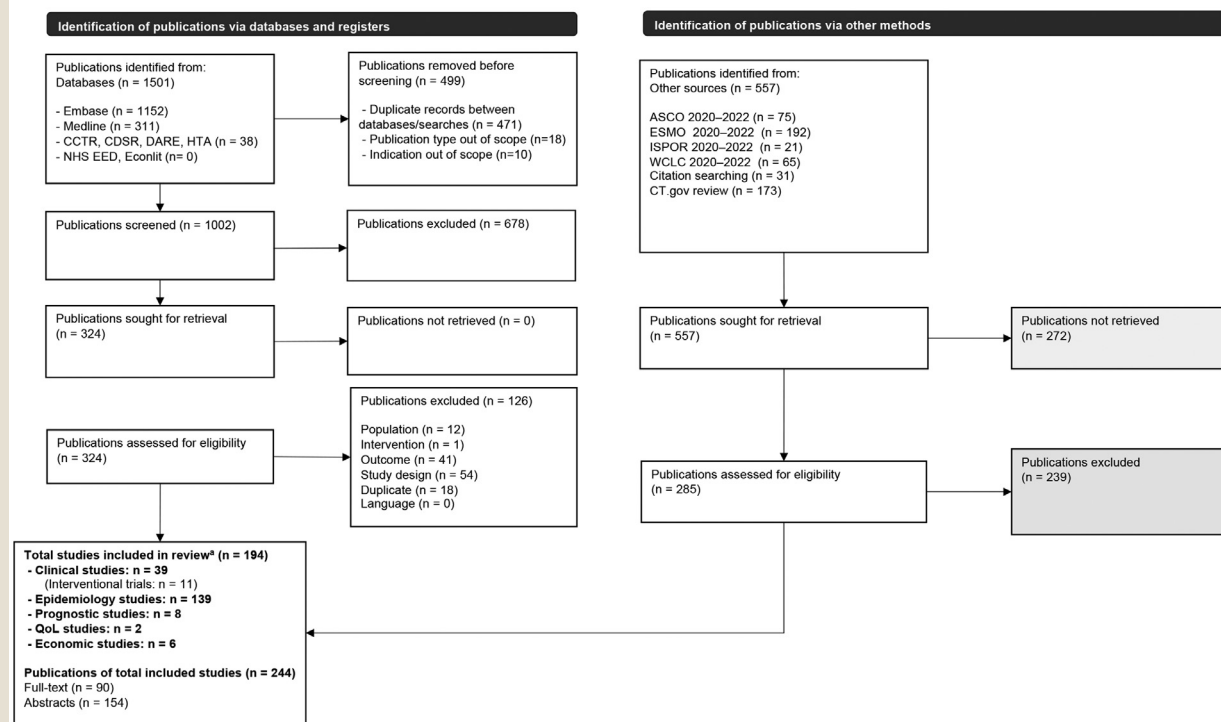
The type of biopsy used and the method of detection of *METex14* skipping in NSCLC varied across studies ([Figure 2](#)). Tissue alone was the most frequent type of biopsy used to detect *METex14* skipping (61.2% of studies), followed by tissue and liquid (7.9%); some studies reported either tissue or liquid was used (3.6%), and testing on liquid alone was conducted in 2.9% of studies. The type of biopsy used for testing was not reported in 24.5% of studies. Out of the 127 studies that reported on *METex14* skipping frequency in NSCLC, most studies (*n* = 98) used next-generation sequencing (NGS) (including comprehensive genomic profiling [CGP]) either as the only detection method or to confirm findings. Other testing methods included polymerase chain reaction (PCR)-based assays (*n* = 25) and Sanger sequencing (*n* = 13). NGS/CGP were used more frequently in studies published in recent years ([Supplemental Figure 2A](#)). Of the studies using solely NGS/CGP (*n* = 98) to detect all alterations in actionable genes, the most frequent sequencing substrate was DNA only (*n* = 42; including circulating tumor and circulating free DNA), followed by DNA/RNA (*n* = 20), or RNA only (*n* = 7); 29 studies did not report the substrate used. The use of NGS substrate over time is presented in [Supplemental Figure 2B](#).

Epidemiology of *METex14* Skipping in NSCLC

Frequency of METex14 Skipping in Advanced NSCLC not Selected by Histology, Smoking History, or Programmed Death-Ligand 1 (PD-L1) Expression. The frequency of *METex14* skipping in advanced NSCLC populations, without restricting inclusion criteria to specific histologies or highly selected subgroups, was reported by 59 publications ([Supplemental Table 3](#), [Supplemental Figure 3](#)). Median frequency was 2.0% overall (range 0.5%-6.8%), 2.5% in North America (0.6%-5.1%),^{38,39} 2.0% in Europe (0.5%-3.3%),^{40,41} 1.7% in Asia (0.5%-6.8% in Asia),^{42,43} and 1.7% in other locations (0.5%-3.0%).^{44,45}

Frequency of METex14 Skipping in NSCLC in Selected Patient Subgroups. A summary of frequency by region and patient subgroup can be found in [Figure 3](#). Forty-four studies reported frequency according to histological subtype, with a median of 2.4% (IQR 1.9-3.7) in adenocarcinoma or nonsquamous subgroups, 12.0% (IQR 8.0-16.9) in sarcomatoid, and 1.3% (IQR 0-2.3) in squamous histology. Thirty-one studies reported *METex14* skipping in adenocarcinoma, adenocarcinoma/adenosquamous, or nonsquamous subgroups ([Supplemental Table 4](#)), with frequency in the range of 1.2% to 9.0% in Asia,^{46,47} 0.5% to 5.3% in

Figure 1 PRISMA diagram of systematic literature searches conducted in June 2022. ASCO = American Society of Clinical Oncology; CCTR = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstracts of Reviews of Effectiveness; ESMO = European Society of Medical Oncology; HTA = Health Technology Assessment; ISPOR = the Professional Society for Health Economics and Outcomes Research; n = number of publications; NHS EED = National Health Service Economic Evaluation Database; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QoL = quality of life; WCLC = World Conference on Lung Cancer. ^aStudies with more than 1 outcome category were counted multiple times.



Europe,^{48,49} 0.8% to 4.7% in North America,^{50,51} and 1.5% in other locations.⁵² Three studies reported *MET*Ex14 skipping in patients with squamous carcinoma (Supplemental Table 5), with frequency reported as 0.0% in Asia,⁵³ 2.3% in North America,⁵⁴ and 1.3% in other regions.⁵⁵ Thirteen studies reported *MET*Ex14 skipping in patients with NSCLC and sarcomatoid histology (Supplemental Table 6), with frequency in the range of 6.1% to 25.0% in Asia,^{53,56} 6.2% to 10.0% in Europe,^{35,57} and 7.7% to 22.2% in North America.^{33,58,59}

Data from 10 studies showed that median frequency of *MET*Ex14 skipping in never smokers was 12% compared with 2% in ever smokers. Three studies^{53,60–62} reported *MET*Ex14 skipping frequency in never smokers (Supplemental Table 7), ranging from 1.5% in a study in China⁵³ (never smokers) to 18.5% in a study in the US⁶⁰ (never smokers wild-type for *EGFR*, *KRAS*, *BRAF*, or *ERBB2* mutations, or *ALK* or *ROS1* rearrangements).

Five studies reported *MET*Ex14 skipping frequency in patients with *MET* overexpression or *MET* amplification. Definitions of *MET* amplification varied between the included studies; however, gene copy number or *MET/CEP7* (mean *MET* per cell and chromo-

some 7 centromere ratio) ratio were most commonly reported. *MET* overexpression was defined as immunohistochemistry (IHC) of 2+ or 3+ by the selected studies. A Chinese study⁵³ reported increasing frequency of *MET*Ex14 skipping with higher *MET* IHC score (from 0% for IHC 0 to 6.1% for IHC 3+); a North American study reported 9.5% frequency;⁶³ 3 European studies reported a frequency of *MET*Ex14 skipping ranging from 0.0% to 2.7%.^{64–66} (Supplemental Table 8).

A retrospective registry study assessed the frequency of *MET*Ex14 skipping in patients with NSCLC and high PD-L1 expression (tumor proportion score [TPS] $\geq 90\%$; n = 133) versus absent PD-L1 expression (TPS $< 1\%$; n = 288) (Supplemental Table 9).⁶⁷ There was no difference in age or histology found between patients with NSCLC overall, split by PD-L1 status. Patients with a PD-L1 TPS $\geq 90\%$ were more likely to be smokers than those with a PD-L1 TPS $< 1\%$ (86.5% vs. 76.4%; $P = .02$).⁶⁷ Tumors in the PD-L1 TPS $\geq 90\%$ group were more likely to have *MET*Ex14 skipping than those in the PD-L1 TPS $< 1\%$ group (9.6% vs. 2.1%; $P = .003$).⁶⁷ A second study reported similar results in patients with NSCLC, with a *MET*Ex14 skipping frequency of 11.7% in the high

Figure 2 Testing methods used to detect *MET*ex14 skipping in NSCLC samples. DNA = deoxyribonucleic acid; *MET*ex14 = *MET* exon 14; NGS = next-generation sequencing; NR = not reported; NSCLC = non-small-cell lung cancer; PCR = polymerase chain reaction; RNA = ribonucleic acid; RT-PCR = reverse-transcriptase polymerase chain reaction. Values beside each testing method indicate number of studies and percentage that each testing method represents over all methods. Studies may have used more than 1 method.

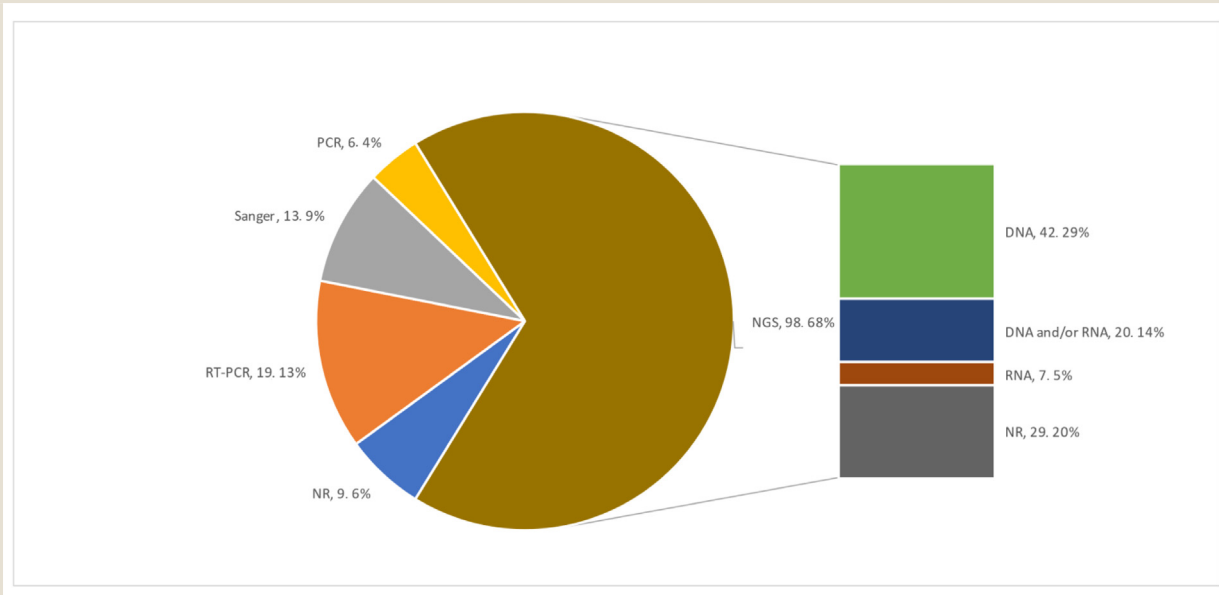


Figure 3 Frequency of *MET*ex14 skipping in NSCLC in patient subgroups and overall, by world region. *MET*ex14 = *MET* exon 14; NSCLC = non-small-cell lung cancer; PD-L1 = programmed death-ligand 1. Gray font indicates frequency of *MET*ex14 skipping in all patients with NSCLC not selected for histology, smoking history, or PD-L1 expression, by world region; values are median (range) (number of publications). All other values represent the frequency of *MET*ex14 skipping NSCLC in each world region, by subgroup; values indicate range (number of publications).

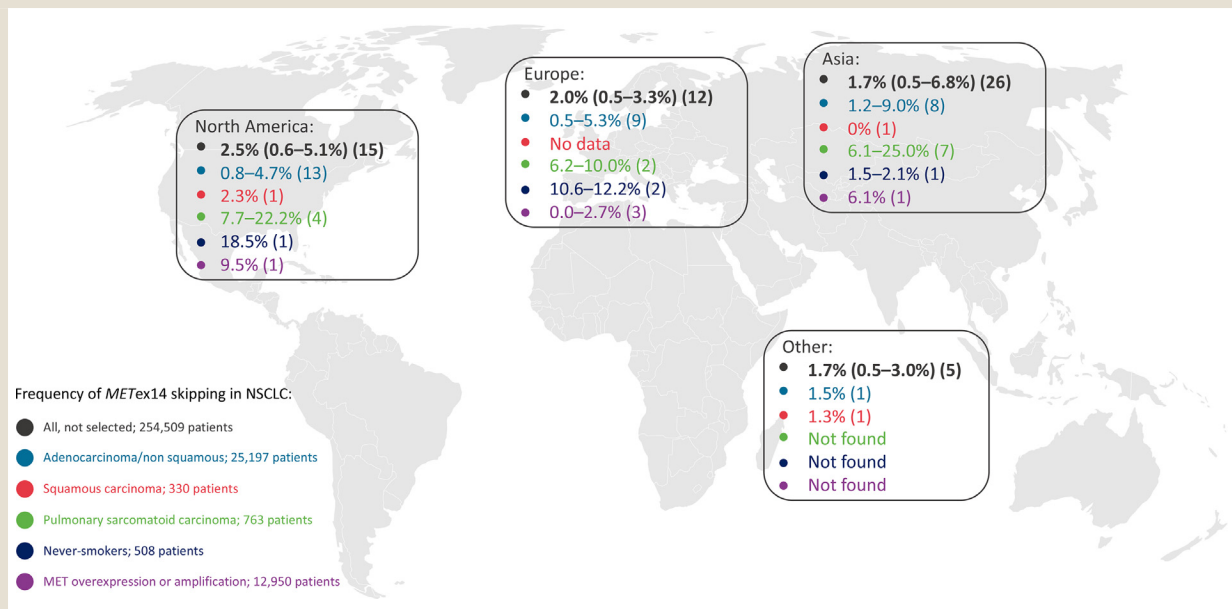
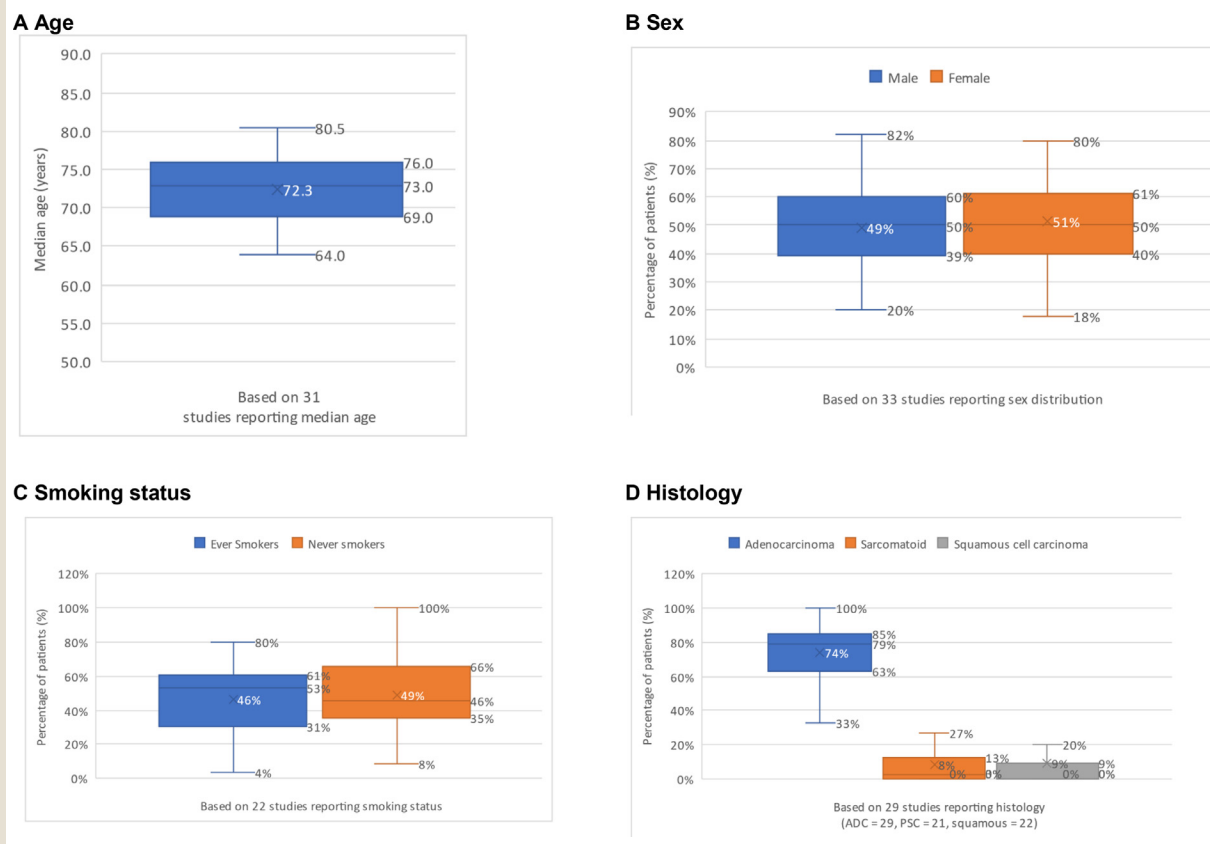


Figure 4 Clinical characteristics of patients with *MET*ex14 skipping NSCLC. Charts display the median and upper and lower quartiles (boxes), the range (whiskers), and mean (crosses). ADC = adenocarcinoma; *MET*ex14 = *MET* exon 14; NSCLC = non-small-cell lung cancer; PSC = pulmonary sarcomatoid carcinoma.



(TPS ≥ 50) versus 1.2% in the low (TPS < 50 %) PD-L1 expression group.⁵³

Clinical Characteristics of Patients With *MET*ex14 Skipping NSCLC

Patient Characteristics From Epidemiology Studies. Only studies that described patient clinical characteristics for the total population that was sampled are reported. Details of the 36 publications reporting clinical characteristics for patients with *MET*ex14 skipping NSCLC are shown in Supplemental Table 10, and the distribution of key characteristics are shown in Figure 4. Median age of patients was 73.0 years (31 studies; $n = 1712$ patients), and 50.0% of patients were women (33 studies; $n = 1750$). There was no marked distribution between ever smokers (median 53.0% in 22 studies; $n = 1046$) and never smokers (median 46.0% in 22 studies; $n = 1046$).

The most commonly reported histologies in patients with *MET*ex14 skipping NSCLC were adenocarcinoma (median 79.0% in 29 studies; $n = 1594$), sarcomatoid (median 6.0% in 21 studies; $n = 1411$), and squamous cell carcinoma (median 4.0% in 22 studies; $n = 1492$).

Clinical Efficacy Outcomes

Efficacy endpoints by type and line of treatment for the patients in study arms with ≥ 10 patients with *MET*ex14 skipping NSCLC are shown in Table 1. Baseline demographics and disease characteristics of 3989 patients with clinical outcome data are summarized in Supplemental Table 11 (full study details are available in Supplemental Table 12). The median age of patients was 72.0 years (range, 63.0-77.7), 44.0% (range, 27.0-70.0) were male, the most common tumor histology was adenocarcinoma (81.0% [range, 16.0-94.0]), and there was a similar proportion of ever smokers (58.0% [range, 31.0-78.0]) and never smokers (45.5% [range, 23.5-79.0]).

Objective Response Rate. In total, 27 publications of 24 studies with patients with *MET*ex14 NSCLC reported an objective response rate (ORR) with targeted therapies/MET TKIs (21 publications of 18 studies), chemotherapy (5 publications of 4 studies), IO regimens (7 publications of 6 studies), and unspecified treatments (2 publications from 2 studies). ORR was assessed by independent review committee and/or investigator assessment, mostly according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; some studies did not report how ORR was assessed.

Table 1 Overview of Efficacy Endpoints (ORR, DOR, PFS, and OS) in Studies With ≥ 10 Patients With METex14 Skipping NSCLC in Study Arms

	ORR		Median PFS, Mo		Median OS, Mo		Median DOR, Mo	
	Lowest Reported ORR	Highest Reported ORR	Lowest Reported PFS (95% CI)	Highest Reported PFS (95% CI)	Lowest Reported OS (95% CI)	Highest Reported OS (95% CI)	Lowest Reported DOR (95% CI)	Highest Reported DOR (95% CI)
All targeted therapies (1L)	IRC: 50.7% n = 69	IRC: 68.8% n = 32	INV: 8.5 (NA) n = 44	IRC: 12.5 (6.9-20.5) n = 32	10.9 (7.5-14.0) n = 13	21.1 (12.7-NR) n = 95	IRC: 12.6 (5.6-NE) n = 28	IRC: 46.4 (13.8-NE) n = 164
MET TKIs:	IRC: 50.7% n = 69	IRC: 68.8% n = 32	INV: 8.5 (NA) n = 44	IRC: 12.5 (6.9-20.5) n = 32	10.9 (7.5-14.0) n = 13	21.1 (12.7-NR) n = 95	IRC: 12.6 (5.6-NE) n = 28	IRC: 46.4 (13.8-NE) n = 164
• Capmatinib	IRC: 68.8% n = NR	IRC: 68.8% n = 32	IRC: 10.6 (5.5-15.7) n = NR	IRC: 12.5 (6.9-20.5) n = 32	NE (10.9-NE) n = 32	20.8 (12.4-NE) n = 28	IRC: 12.6 (5.6-NE) n = 28	16.6 (8.3-NE) n = 28
• Crizotinib	NA	NA	INV: 8.5 (NA) n = 44		11.3 (NA) n = 44		NA	NA
• Savolitinib	NA	NA	NA	NA	10.9 (7.5-14.0) n = 13		NA	NA
• Tepotinib	IRC: 50.7% n = 69	60% n = 95	10.3 (8-15.3) n = 69	15.9 (10.4-NR) n = 95	19.1 (13.7-23.7) n = 164	21.1 (12.7-NR) n = 95	IRC: 46.4 (7.2-NE) n = 69	IRC: 46.4 (13.8-NE) n = 164
All targeted therapies (1L+)	INV: 21.1% n = 19	INV: 58.0% n = 18	INV: 2.6 (1.2-8.9) n = 21	13.8 (9.5-13.8) n = 161	9.5 (4.1-13.4) n = 25	41 (10.4-71.6) n = 21	IRC: 6.9 (4.9-12.5) n = 70	IRC: 20.8 (12.6-NE) n = 161
MET TKIs:	INV: 31.0% n = 54	58% n = 19	INV: 2.6 (1.2-8.9) n = 21	13.8 (9.5-13.8) n = 161	9.5 (4.1-13.4) n = 25	41 (10.4-71.6) n = 21	IRC: 6.9 (4.9-12.5) n = 70	IRC: 20.8 (12.6-NE) n = 161
• Capmatinib	58% n = 19		9.5 (4.7-14.3) n = 81		18.2 (13.2-23.1) n = 81		NA	NA
• Crizotinib	INV: 31.0% n = 54	INV: 40.0% n = 25	INV: 3.6 (1.6-7.0) n = 25	INV: 7.9 (5.8-10.4) n = 21	9.5 (4.1-13.4) n = 25	41 (10.4-71.6) n = 21	INV: 9.1 (6.4-12.7) n = 69	
• Savolitinib	IRC: 40.0% n = 25	INV: 47.1% n = 70	IRC: 5.5 (2.8-9.6) n = 25	IRC: 9.7 (4.3-NR) n = 45	12.5 (10.5-21.4) n = 70		IRC: 6.9 (4.9-12.5) n = 70	IRC: 9.6 (4.2-NR) n = 45
• Tepotinib	IRC: 50.8% n = 313	INV: 54.7% n = 161	11.2 (9.5-13.8) n = 313	13.8 (9.5-13.8) n = 161	19.3 (15.8-22.3) n = 313		IRC: 18.0 (12.4-NE) n = 313	IRC: 20.8 (12.6-NE) n = 161
All targeted therapies (2L)	IRC: 44.3% n = 88	IRC: 51.6% n = 31	INV: 2.6 (2.2-3.0) n = 10	8.9 (6.9-13.7) n = 88	NE (13.5-NE) n = 31		IRC: 8.4 (4.2-NE) n = 31	12.4 (8.3-NE) n = 88
MET TKIs:	IRC: 44.3% n = 88	IRC: 51.6% n = 31	INV: 2.6 (2.2-3.0) n = 10	8.9 (6.9-13.7) n = 88	NE (13.5-NE) n = 31		IRC: 8.4 (4.2-NE) n = 31	12.4 (8.3-NE) n = 88
• Capmatinib	IRC: 51.6% n = 31		IRC: 6.9 (4.2-13.3) n = 31		NE (13.5-NE) n = 31		IRC: 8.4 (4.2-NE) n = 31	

(continued on next page)

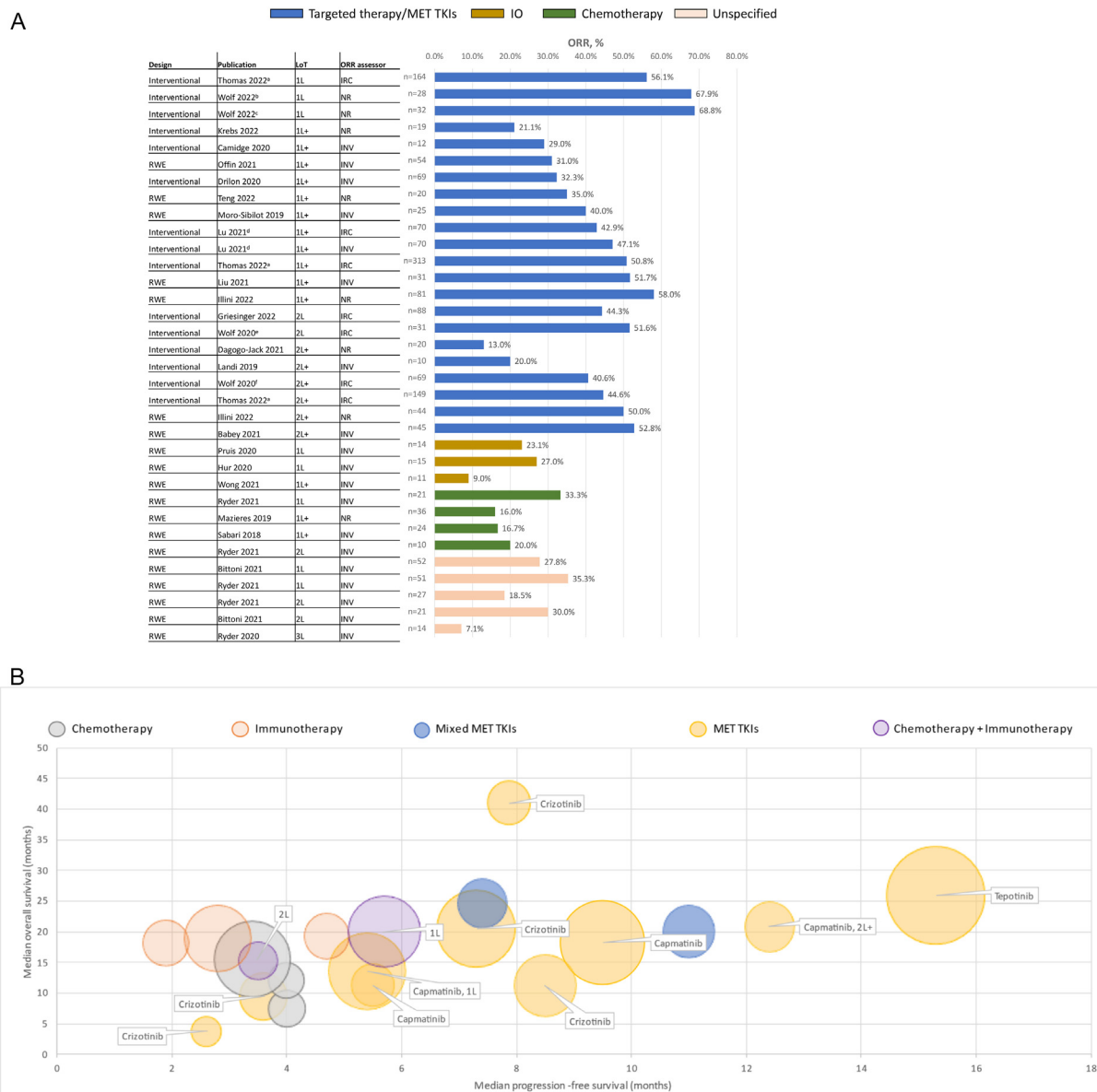
Table 1 (continued)

	ORR		Median PFS, Mo		Median OS, Mo		Median DOR, Mo	
	Lowest Reported ORR	Highest Reported ORR	Lowest Reported PFS (95% CI)	Highest Reported PFS (95% CI)	Lowest Reported OS (95% CI)	Highest Reported OS (95% CI)	Lowest Reported DOR (95% CI)	Highest Reported DOR (95% CI)
• Crizotinib	NA	NA	INV: 2.6 (2.2-3.0) n = 10		NA	NA	NA	NA
• Savolitinib	NA	NA	NA	NA	NA	NA	NA	NA
• Tepotinib	IRC: 44.3% n = 88		8.9 (6.9-13.7) n = 88		NA	NA	12.4 (8.3-NE) n = 88	
Chemotherapy								
Chemotherapy (1L)	INV: 23.1% (NA) n = 14	INV: 27.0% (NA) n = 15	INV: 4.0 (0.3-16.9) n = 15	INV: 5.7 (4.6-7.1) n = 59	9.5 (6.5-23.1) n = 15	20 (10.9-24.6) n = 59	NA	NA
Chemotherapy (1L+)	INV: 9.0% (NA) n = 11		NA		NA		NA	NA
Chemotherapy (2L)	NA	NA	INV: 3.5 (1.9-11.1) n = 16		15.3 (4-41.1) n = 16		NA	NA
Immunotherapy								
Immunotherapy (1L)	INV: 33.3% n = 21		INV: 2.4 (1.4-3.2) n = 18	INV: 4.1 (1.5-8.1) n = 21	12.0 (NA) n = 13	48.3 n = 14	NA	NA
Immunotherapy (1L+)	INV: 16.0% n = 36	INV: 16.7% n = 24	INV: 1.9 (1.7-2.7) n = 24	INV: 6.0 (1.9-24.9) n = 16	10.0 (6.7-13.3) n = 20	18.4 (7.0-NR) n = 36	NA	NA
Immunotherapy (2L)	INV: 20.0% n = 10		INV: 2.8 (0.9-5.7) n = 10	INV: 4.7 (2.8-12.9) n = 23	19.3 (11.6-NE) n = 23		NA	NA
Unspecified								
Unspecified (1L)	INV: 27.8% n = 18	INV: 35.3% n = 51	INV: 3.1 (2.3-5.0) n = 51	INV: 6.2 (3.4-9.1) n = 29	10.4 (1.3-73.0) n = 52	20.0 (7.2-NR) n = 29	NA	NA
Unspecified (1L+)	NA	NA	INV: 5.7 (4.6-7.1) n = 41		10.0 (6.7-13.3) n = 20	24.4 (10.1-48.3) n = 32	NA	NA
Unspecified (2L)	INV: 18.5% n = 27	INV: 30.0% n = 10	INV: 4.6 (1.6-5.7) n = 27		11.2 (4.0-19.3) n = 27	11.7 (6.0-32.9) n = 21	NA	NA

Abbreviations: 1L = first line; 1L+ = first line and beyond; 2L = second line; 2L+ = second line and beyond; CI = confidence interval; DOR = duration of response; INV = investigator assessed; IO = immunotherapy; IRC = Independent Review Committee; METex14 = MET exon 14; METi = MET inhibitor; n = number of patients in study; NA = not available; NE = not evaluable; NR = not reached; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SLR = systematic literature search; TKI = tyrosine kinase inhibitor.

Complete ORR data are available in Supplemental Tables 13-16, PFS data in Supplemental Tables 18-21, OS data in Supplemental Tables 22-25, and DOR data in Supplemental Table 17.

Figure 5 Overview of efficacy outcomes in included study arms with ≥ 10 patients with METex14 skipping NSCLC (combined SLR results) for: (A) ORR in study arms by therapy type; and (B) OS and PFS by therapy type across all lines of therapy, where bubble size indicates n for each cohort. 1L = first line, 1L+ = first line or beyond; 2L = second line, 2L+ = second line or beyond; IRC = independent review committee; INV = investigator; IO = immunotherapy; LoT = line of therapy; ORR = objective response rate; NR = not reported; PSC = pulmonary sarcomatoid carcinoma; RWE = real-world evidence; TKI = tyrosine kinase inhibitor. ^aCohorts A + C; ^bCohort 5b; ^cCohort 7; ^dPulmonary sarcomatoid carcinoma and other histologies; ^eCohort 6; ^fCohort 4. Numbers in call-outs indicate line of therapy and/or type of MET TKI, if applicable/available. Most recent data cuts used where multiple available.



ORR for study arms by therapy type are shown in Figure 5A (not all studies reported independently reviewed data). Below, we report ORR of studies with ≥ 10 patients per study arm.

In patients with advanced or metastatic NSCLC harboring METex14 skipping, ORR with targeted therapies/MET TKIs

ranged 50.7% to 68.8% in first line and 44.3% to 51.6% in second line (Table 1, Supplemental Table 13).

The ORR of chemotherapy for patients with METex14 skipping NSCLC ranged 23.1% to 27.0% in first line (Table 1, Supplemental Table 14).

MET Exon 14 Skipping in NSCLC

The ORR of IO for patients with advanced or metastatic NSCLC harboring *MET*Ex14 skipping was 33.3% in first line and 20.0% in second line (Table 1, Supplemental Table 15).

Results from studies using unspecified treatments are available in Table 1 and Supplemental Table 16.

Duration of Response. No studies reported duration of response (DOR) in patients with *MET*Ex14 NSCLC receiving chemotherapy, IO, or unspecified treatments. However, 7 publications of 4 studies reported median DOR for patients receiving targeted therapies/*MET* TKIs. DOR in studies with ≥ 10 patients per study arm ranged from 12.6 months (95% CI, 5.6-not estimable [NE]) to 46.4 months (95% CI, 13.8-NE) in first line, and 8.4 months (95% CI, 4.2-NE) to 12.4 months (95% CI, 8.3-NE) in second line (Table 1, Supplemental Table 17).

Progression-Free Survival. In total, median PFS was reported in 28 publications of 25 studies with patients with *MET*Ex14 NSCLC treated with targeted therapies/*MET* TKIs (21 publications of 17 studies), chemotherapy (3 publications of 3 studies), IO regimens (9 publications of 8 studies), and unspecified treatments (4 publications of 3 studies). Below, we report PFS of studies with ≥ 10 patients per study arm.

In patients with *MET*Ex14 skipping NSCLC treated with targeted therapies/*MET* TKIs, median PFS ranged from 8.5 months (95% CI not reported) to 15.9 months (95% CI, 10.4-not reached [NR]) in first line, and 2.6 months (95% CI, 2.2-3.0) to 8.9 months (95% CI, 6.9-13.7) in second line (Table 1, Supplemental Table 18).

In patients with advanced or metastatic NSCLC harboring *MET*Ex14 skipping receiving chemotherapy, median PFS ranged from 4.0 months (95% CI, 0.3-16.9) to 5.7 months (95% CI, 4.6-7.1) in first line, and was 3.5 months (95% CI, 1.9-11.1) in second line (Table 1, Supplemental Table 19).

Median PFS when treating patients with advanced or metastatic NSCLC harboring *MET*Ex14 skipping with IO ranged from 2.4 months (95% CI, 1.4-3.2) to 4.1 months (95% CI, 1.5-8.1) in first line, and 2.8 months (95% CI, 0.9-5.7) to 4.7 months (95% CI, 2.8-12.9) in second line (Table 1, Supplemental Table 20).

Results from studies using unspecified treatments are available in Table 1 and Supplemental Table 21.

Median Overall Survival. Median OS was reported in 35 publications of 27 studies where patients with *MET*Ex14 NSCLC were treated with targeted therapies/*MET* TKIs (22 publications of 18 studies), chemotherapy (4 publications of 4 studies), IO regimens (9 publications of 7 studies), and unspecified treatments (11 publications of 7 studies). Below, we report OS of studies with ≥ 10 patients per study arm.

In patients with advanced or metastatic NSCLC harboring *MET*Ex14 skipping receiving targeted therapies/*MET* TKIs, median OS ranged from 10.9 months (95% CI, 7.5-14.0) to 21.1 months (95% CI, 12.7-NR) in first line, and was not evaluable in second line (95% CI, 13.5-NE) (Table 1, Supplemental Table 22).

In studies where patients with advanced or metastatic NSCLC harboring *MET*Ex14 skipping received chemotherapy, median OS ranged from 9.5 months (95% CI, 6.5-23.1) to 20 months (95%

CI, 10.9-24.6) in first line, and was 15.3 months (95% CI, 4-41.1) in second line (Table 1, Supplemental Table 23).

Studies treating patients with advanced or metastatic NSCLC harboring *MET*Ex14 skipping with IO reported median OS ranging from 12.0 months (95% CI NR) to 48.3 months (95% CI NR) in first line, and being 19.3 months (95% CI, 11.6-NE) in second line (Table 1, Supplemental Table 24).

Results from studies using unspecified treatments are available in Table 1 and Supplemental Table 25.

Figure 5B shows reported PFS and OS of studies with ≥ 10 patients per study arm. *MET* TKIs were associated with the highest median OS and PFS. *MET* TKIs were the most intensively studied therapies; comparatively few data were found for chemotherapy and IO.

Brain Metastases

Few publications ($n = 13$) reported on sites of metastasis in patients with *MET*Ex14 skipping advanced NSCLC. The median frequency of metastases at baseline was 15.0% for brain (range 3.6%-100%; 10 publications), 6.3% for bone (range 0.9%-41.7%; 6 publications), and 28.6% for pleura (range 9.1%-35.0%; 6 publications). Other less commonly reported sites included liver, lung, adrenal glands, peritoneum chest wall, lymph nodes, skin, and soft tissue.

Efficacy outcomes for patients with *MET*Ex14 skipping NSCLC with brain metastases were reported by 18 publications from 8 studies; publications with the most recent cut-offs are shown in Table 2. All of these studies used *MET* TKIs, and one of them also used IO as a comparator for *MET* TKIs.⁶⁸ Hur et al.⁶⁹ reported efficacy for only 1 patient with brain metastases (PFS of 9 days); data are not included in Table 2. In first line, intracranial ORR with *MET* TKIs was 87.3% (85.0% in radiation therapy-naïve patients);⁶⁸ 1 study reported an ORR of 20.0% but did not specify line of treatment.⁷⁰ Intracranial ORR with IO was 27.3% in first line (11.1% in radiation therapy-naïve patients).⁶⁸ PFS was 14.1 months with *MET* TKIs in first line; 5.1 months for IO.⁶⁸ Duration of response was only reported with *MET* TKIs in first line or beyond.

Risk of Bias

Forty full-text publications reporting frequency were assessed using the JBI checklist for frequency studies (Supplemental Table 26).²⁷ Positive responses ranged from 44% to 78%, with a median of 67%.

Detection of *MET*Ex14 skipping was unclear in 23 epidemiology publications (50%), for a variety of reasons including not stating the method(s) used, not describing the reason for missing data, and not specifying the same method for all tested patients. Only 6 studies reported an adequate sample size of ≥ 1522 based on the recommended calculation by Naing et al.²⁹

Thirty-three full-text publications reporting clinical outcomes were assessed using the Downs and Black adapted checklist, with an average score of 14.5 on the risk of bias assessment tool (Supplemental Table 27-29). As all of the studies were nonrandomized, hence a power calculation between treatment arms could not be conducted. The answer options for the modified questionnaire

Table 2 Efficacy Data of MET TKIs in Patients With Brain Metastases

Trial Name or Number	Author (Data Cut-Off)	Treatment Line	Study Arm	Sample Size	Median PFS, Mo (95% CI)	ORR % (95% CI)	PR, n	SD, n	Median DOR, Mo (95% CI)
NCT02864992 (VISION)	Griesinger et al. 2022 Cohorts A + C (Feb 1, 2021)	1L+	Tepotinib	51		52.9 (38.5-67.1) S			9.0 (5.6-NE)
	Thomas et al. 2022 Cohorts A+C (Feb 20, 2022)	1L+	Tepotinib	43	20.9 (5.7-NE)	-	-	-	-
			Tepotinib Patients with target lesions only	15	-	66.7 (38.4-88.2) IC	-	-	NE (0.9-NE)
	Le et al. 2022 Cohort A (Jul 1, 2020)	1L+	Tepotinib IRC	23	9.5 (5.7-11.2)	47.8 (26.8-69.4) S			9.5 (5.5-NE)
NCT02414139 (GEOMETRY mono-1)	Wolf et al. 2020 (Jan 6, 2020)	1L+	Capmatinib IRC	13	-	53.8 ^a IC	3	-	-
NCT02897479	Lu et al. 2021 (Aug 3, 2020)	1L+	Savolitinib IRC	15	6.9 (4.1-NE)	46.7 (21.3-73.4) ^b EC	3	-	-
NCT02499614	Landi et al. 2019 (Sep 30, 2017)	2L+	Crizotinib	3	-	0 IC	0	2	-
— (RWE)	Illini et al. 2022	1L+	Capmatinib	11	-	46 (17-77) IC	-	-	-
— (RWE)	Offin et al. 2020	-	Crizotinib	5	-	20	1	3	-
— (RWE)	Paik et al. 2022	1L	Capmatinib Radiation therapy-naïve ^c	20		85.0 (62.1-96.8) S; 85.0 (62.1-96.8) IC	-	-	-
		1L	IO-containing regimens Radiation therapy-naïve	9	-	66.7 (29.9-92.5) S; 11.1 (0.3-48.3) IC	-	-	-
		1L	Capmatinib Entire cohort ^c	55	14.1	87.3 IC	-	-	-
		1L	IO-containing regimens Entire cohort	11	5.1	27.3 IC	-	-	-

Abbreviations: 1L = first line; 1L+ = first line and beyond; 2L+ = second line and beyond; CI = confidence interval; DOR = duration of response; EC = extracranial; IC = intracranial; IO = immunotherapy; IRC = Independent Review Committee; n = number of patients in study; NE = not evaluable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RWE = real-world evidence; S = systemic; SD = stable disease; SLR = systematic literature search; TKI = tyrosine kinase inhibitor.

^a Seven of 13 patients had an intracranial response, including 4 who had a complete response.

^b The 3 patients with brain metastases selected as target lesions by investigators had intracranial partial responses.

^c Capmatinib was started after diagnosis of brain metastases.

MET Exon 14 Skipping in NSCLC

were limited to a) Unable to determine = 0; b) Yes = 1; and c) No = 0, as opposed to a) <n1; b) n1 to n2; c) n3 to n4; d) n5 to n6; e) n7 to n8; or f) n8+. As the study power was not reported for nonrandomized studies, 0 was selected for “unable to determine.” Publications with a score under 15 were mainly scored low due to the limited information they presented (eg, reporting) and possible selection bias due to study design (especially for the real-world studies).

Discussion

This SLR found the median frequency of *MET*Ex14 skipping NSCLC was 2.0% and MET-directed targeted therapies were associated with high efficacy outcomes in this patient population while other treatments had limited efficacy. These outcomes are in line with those from studies on oncogene-addicted NSCLC such as EGFR- or ALK-positive NSCLC, for which RCTs have demonstrated superiority of targeted therapies over chemotherapy, also in patients with brain metastases.^{71,72}

Our findings help to better characterize the demographic and clinical characteristics of patients with *MET*Ex14 skipping NSCLC. Patients with *MET*Ex14 skipping NSCLC were typically elderly (median age of 73.0 years), with adenocarcinoma histology, and they had an even distribution by sex and smoking status, contrasting with characteristics reported for patients with *EGFR* (more prevalent in women, never smokers),⁷³ or *BRAF* mutations (more prominent in women, never smokers),⁷⁴ and *ALK* (more prominent in younger patients, never smokers)⁷⁵ or *ROS1* (more prominent in women, never smokers)⁹ rearrangements. *MET*Ex14 skipping was found across histologies, but most commonly in sarcomatoid histology. Brain, bone, and pleura metastases were reported in *MET*Ex14 skipping advanced NSCLC, a pattern that is characteristic of NSCLC in general.⁷⁶ Patient characteristics obtained from clinical outcome studies were similar to those found in the larger set of epidemiology studies.

*MET*Ex14 skipping can be tested with several approaches. Historically, several methods were used to identify *MET*Ex14 skipping, including single-gene tests, which are now considered impractical.⁷⁷ Currently, NGS/CGP is the preferred technology;⁷⁷ accordingly, we found 68% of included NSCLC studies used NGS, and it use increased over time. The most common substrate used for NGS was DNA from solid tumors. There was no increased use of RNA over time, despite the fact that testing based on DNA may miss *MET*Ex14 skipping cases compared with RNA.^{78,79}

The rarity of *MET*Ex14 skipping NSCLC (and lack of data from large-scale RCTs) makes retrospective pooled data valuable in having a better understanding of this distinct group of patients, including its frequency. The frequency of *MET*Ex14 skipping in NSCLC varied greatly depending on the population screened, testing method, and the study sample size. The reported median frequency of *MET*Ex14 skipping in unselected NSCLC populations was 2.0% and values ranged 0.5% to 6.8%. There were no clear differences in frequency by world region. Of note, most studies reported frequency of *MET*Ex14 skipping in sampled patients, rather than in a population. The highest frequencies of *MET*Ex14 skipping NSCLC were reported in 4 studies that evaluated restricted populations: patients with sarcomatoid histology (22.0%)³³; patients wild-

type for *EGFR*, *KRAS*, *BRAF*, or *ERBB2* mutations, or *ALK* or *ROS1* rearrangements (18.5%),⁶⁰ which are mutually exclusive with *MET*Ex14 skipping^{60,7} or patients with *MET* alterations (20.5%⁸⁰ and 20.7%⁸¹). Interestingly, although *MET*Ex14 skipping is not typically reported alongside other oncogenic drivers, its frequency was greater in patients with high PD-L1 expression (9.6%-11.7%) than in those with lower PD-L1 expression (1.2%-2.1%), albeit these studies using different PD-L1 scoring.^{53,67} This observation suggests that dual targeting of PD-L1 and *MET* may warrant investigation in some patients. However, to date, the clinical efficacy of PD-L1 blockade in patients with *MET*Ex14 skipping NSCLC has been modest, possibly as a result of the low tumor mutation burden observed in such tumors.^{7,39}

Our SLR results show that publications reporting *MET*Ex14 skipping frequency in NSCLC or patient characteristics increased in recent years, coinciding with the approval of tepotinib and capmatinib. Since 2019, the number of publications reporting clinical outcomes for the treatment of advanced or metastatic NSCLC harboring *MET*Ex14 skipping has continued to increase—the SLR was conducted in June 2022, thus, growth during this year cannot be fully estimated. This increase in publications may reflect clinical research activities supporting the initial regulatory approvals of *MET* TKIs for the treatment of patients with *MET*Ex14 skipping NSCLC (tepotinib, capmatinib, and savolitinib).^{7,13,15-19} The inclusion of *MET* TKIs as a treatment option for *MET*Ex14 skipping NSCLC in treatment guidelines such as the National Comprehensive Cancer Network may have also played a role.²

Most publications in this SLR reporting clinical outcomes included treatment arms with small patient numbers (<50 patients). The largest study reporting outcomes for patients with *MET*Ex14 skipping NSCLC is VISION, treating 313 with tepotinib.⁸² Few studies used targeted therapies that were not *MET* TKIs (amivantamab, Sym015), and the outcomes achieved were surpassed by *MET* TKIs.⁸³⁻⁸⁵ In this review, none of the studies evaluating patients with *MET*Ex14 skipping used antibody-drug conjugates. Treatment outcomes in patients with *MET*Ex14 skipping may vary by histology; however, some histology types are underrepresented in studies, and subgroup analysis by histology may be limited by their small sample size.^{3,4,86,87} Given this variability in response and the lack of direct comparisons between treatment options for patients with *MET*Ex14 skipping, phase III comparative clinical trials should be conducted, enrolling patients with different histologies and evaluating their outcomes separately. In recent years, the treatment landscape for patients with NSCLC has dramatically changed with the improved understanding of disease biology and the approval of therapies that target oncogenic drivers.⁸⁸ Here, we have observed that, overall, targeted therapies/*MET* TKIs appeared to result in improved clinical outcomes in ORR, median PFS, and median OS compared with either chemotherapy- or IO-only regimens, with the caveat of this being an indirect comparison. In the first line of treatment, the highest ORR achieved with tepotinib was 60.0%; longest PFS, OS, and DOR were 15.9 months, 21.1 months, and 46.4 months, respectively. In the first line of treatment, the highest ORR achieved with capmatinib was 68.8%; longest PFS, OS, and DOR were 12.4 months, 20.8 months, and 16.6 months, respectively. A recent matching-adjusted indirect compari-

son predicted prolonged PFS and OS with tepotinib compared with capmatinib and crizotinib.⁸⁹ Outcomes of chemotherapy and IO regimens were all derived from real-world studies, and there was paucity of data for these therapies compared with those of targeted therapies. Studies generally did not specify the type of chemotherapy or IO regimen used, and DOR was not available for either of them.

In the SLR, only 8 studies reported treatment activity in brain metastases in patients with *MET*ex14 skipping NSCLC and all except for 1 study used MET TKIs alone. MET TKIs achieved an intracranial ORR of 87.3% in first line (85.0% in radiation therapy-naïve patients); IO achieved 27.3% in first line (11.1% in radiation therapy-naïve patients).⁶⁸ PFS was 14.1 months with MET TKIs in first line and was not reported for IO. Duration of response ranged from 9.0 to 9.5 months with MET TKIs in first line or beyond, and was not reported in other lines or treatments.

The main strength of this study is the rigorous approach followed to ensure all relevant studies were retrieved during the literature search. This was achieved by using a broad search strategy in terms of keywords (concerning solely the tumor type and the alteration of interest, *MET*ex14 skipping) and sources (both peer-reviewed publications and conference abstracts were considered). This resulted in a larger number of publications that were then carefully reviewed. Because of the high heterogeneity in the selected studies, summarizing the data to give an overview of *MET*ex14 skipping in NSCLC presented certain challenges and may have introduced bias. A limitation of this study is the collection of data from studies that were heterogeneous in terms of data quality, location, study design, sample size, patient selection, detection methods and thresholds (these are also influenced by when the study was conducted), data reporting, and outcome evaluation approaches (in particular, the comparability of investigator-assessed and independently verified results). This approach can potentially introduce bias, and while most of the epidemiology studies included were deemed to have acceptable quality per JBI, clinical outcome studies received low scores on the Downs and Black checklist. Comparative data from head-to-head trials are required to determine the relative efficacy of targeted therapies compared with other therapeutic approaches; however, the feasibility of such studies may be difficult due to the rarity of the disease. Finally, a considerable amount of retrospective real-world studies included here were available in abstract format only. These abstracts have not undergone a formal peer review process—although they are reviewed by the conference committee—and the clinical information presented may be incomplete; as such, the reported results should be interpreted with caution.

Conclusions

*MET*ex14 skipping is an oncogenic driver that represents a distinct population in NSCLC. While patients are more likely to have certain characteristics (older age, adenocarcinoma histology), no characteristic has been identified to rule out *MET*ex14 skipping. These observations underscore the importance of *MET*ex14 skipping testing in all patients with NSCLC to identify candidates for MET inhibitor therapy; testing in patients with sarcomatoid histology is particularly important, given the higher frequency in

this subgroup. Targeted therapies/MET TKIs appear to result in better clinical outcomes (ORR, median PFS, and OS) than regimens with no targeted therapies. These data support the use of MET TKIs in patients with *MET*ex14 skipping NSCLC, in line with current treatment guidelines. All reported clinical outcomes in this SLR were derived from noncomparative interventional studies or real-world studies; given the lack of head-to-head comparisons, phase III clinical trials should be conducted.

Disclosure

Julien Mazieres has received grants or contracts from AstraZeneca, Roche and Pierre Fabre and honoraria from the healthcare business of Merck KGaA, Darmstadt, Germany, AstraZeneca, BMS, Merck & Co., Roche, Novartis, Daiichi and Pfizer.

Alexis Cortot has received grants or contracts from the healthcare business of Merck KGaA, Darmstadt, Germany and Novartis; consulting fees from AstraZeneca, BMS, Novartis, Pfizer, Takeda and Roche; honoraria from AstraZeneca, BMS, Merck & Co., Novartis, Pfizer, Takeda and Roche and meeting/travel support from AstraZeneca, Merck & Co., Novartis, Pfizer, Takeda and Roche.

Rhiannon I. Campden, Nora Zhiyuan Chen, and Bart Heeg are employed by Ingress Health, a Cytel company, contracted by the healthcare business of Merck KGaA, Darmstadt, Germany to support with this study.

Boris Pfeiffer and Helene Vioix are employees of the healthcare business of Merck KGaA, Darmstadt, Germany.

Author Contributions

Concept and design: Pfeiffer, Vioix; Acquisition of data: Heeg, Campden, Chen; Analysis and interpretation of data: Pfeiffer, Vioix, Heeg, Campden, Chen, Mazieres, Cortot; Drafting of the manuscript: Pfeiffer, Vioix, Heeg, Campden, Chen, Mazieres, Cortot; Critical revision of the paper for important intellectual content: Pfeiffer, Vioix, Heeg, Campden, Chen, Mazieres, Cortot; Statistical analysis: Pfeiffer, Vioix, Heeg, Campden, Chen; Provision of study materials or patients: NA; Obtaining funding: NA; Administrative, technical, or logistic support: Vioix; Supervision: NA.

Acknowledgments

This SLR was conducted by Ingress Health, a Cytel Company (Rotterdam, The Netherlands), and funded by the healthcare business of Merck KGaA, Darmstadt, Germany. The authors thank Andrea Garcia for contributions to the SLR searches and analysis.

Medical writing assistance was provided by Syneos Health, UK, and funded by the healthcare business of Merck KGaA, Darmstadt, Germany.

This work was supported by the healthcare business of Merck 635 KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.clcc.2023.06.008](https://doi.org/10.1016/j.clcc.2023.06.008).

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72:7–33.
2. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Version 5.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (2022).
3. Paik PK, et al. Tepotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. *N Engl J Med*. 2020;383:931–943.
4. Wolf J, et al. Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. *N Engl J Med*. 2020;383:944–957.
5. Lee JK, et al. Characterization of non-small-cell lung cancers with MET exon 14 skipping alterations detected in tissue or liquid: clinicogenomics and real-world treatment patterns. *JCO Precis Oncol*. 2021;5:PO.21.00122.
6. Le X, et al. Landscape and clonal dominance of co-occurring genomic alterations in non-small-cell lung cancer harboring MET Exon 14 skipping. *JCO Precis Oncol*. 2021;1802–1812. doi:10.1200/po.21.00135.
7. Santarpia M, et al. A narrative review of MET inhibitors in non-small cell lung cancer with MET exon 14 skipping mutations. *Transl Lung Cancer Res*. 2021;10:1536–1556.
8. Chevallier M, Borgeaud M, Addeo A, Friedlaender A. Oncogenic driver mutations in non-small cell lung cancer: past, present and future. *World J Clin Oncol*. 2021;12(4):217–237. doi:10.5306/wjco.v12.i4.217.
9. Bi H, et al. Clinical characteristics of patients with ROS1 gene rearrangement in non-small cell lung cancer: a meta-analysis. *Transl Cancer Res*. 2020;9:4383–4392.
10. Zhao F, et al. Clinicopathological characteristics of patients with non-small-cell lung cancer who harbor EML4-ALK fusion gene: a meta-analysis. *PLoS One*. 2015;10.
11. Awad MM, et al. MET exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and c-Met overexpression. *J Clin Oncol*. 2016;34:721–730.
12. Drilon A, Cappuzzo F, Ou S-HI, Camidge DR. Targeting MET in lung cancer: will expectations finally be met? *J Thorac Oncol*. 2017;12:15–26.
13. Reungwetwattana T, Liang Y, Zhu V, Ou S-HI. The race to target MET exon 14 skipping alterations in non-small cell lung cancer: the why, the how, the who, the unknown, and the inevitable. *Lung Cancer*. 2017;103:27–37.
14. Cortot A, et al. Safety of MET tyrosine kinase inhibitors in patients with MET exon 14 skipping non-small cell lung cancer: a clinical review. *Clin Lung Cancer*. 2022;23(3):195–207 In Press. doi:10.1016/j.clcc.2022.01.003.
15. US Food and Drug Administration. TEPMETKO (tepotinib) Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214096s000lbl.pdf (2021).
16. European Medicines Agency. TEPMETKO (Tepotinib) Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/tepmetko-epar-product-information_en.pdf (2022).
17. European Medicines Agency. TABRECTA (Capmatinib) Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/tabrecta-epar-product-information_en.pdf (2022).
18. US Food and Drug Administration. TABRECTA (Capmatinib) Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213591s000lbl.pdf (2020).
19. Markham A. Savitinib: first approval. *Drugs*. 2021;81:1665–1670.
20. ClinicalTrials.gov. Clinical study of oral cMET inhibitor INC280 in adult patients with EGFR wild-type advanced non-small cell lung cancer (geometry mono-1). Available at: <https://www.clinicaltrials.gov/ct2/show/NCT02414139>.
21. ClinicalTrials.gov. A phase II study of HMPL-504 in lung sarcomatoid carcinoma and other non-small cell lung cancer. Available at: <https://clinicaltrials.gov/ct2/show/NCT02897479>.
22. ClinicalTrials.gov. Tepotinib phase II in NSCLC harboring MET alterations (VISION). Available at: <https://www.clinicaltrials.gov/ct2/show/NCT02864992> (2016).
23. Cortot AB, et al. Exon 14 deleted MET receptor as a new biomarker and target in cancers. *J Natl Cancer Inst*. 2017;109:djw262.
24. Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU Technical Support Document 1: Introduction to Evidence Synthesis for Decision Making*. Sheffield, UK: University of Sheffield, Decision Support Unit; 2011:1–24.
25. Sataloff RT, Johns MM, Kost KM. *CRD's Guidance for Undertaking Reviews in Healthcare*. Centre for Reviews and Dissemination, York, UK; 2009.
26. National Institute for Health and Care Excellence. *Developing NICE Guidelines: The Manual*; 2015.
27. The Joanna Briggs Institute. Checklist for prevalence studies. Available at: https://jbi.global/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Prevalence_Studies2017_0.pdf (2017).
28. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52:377–384.
29. Naing L, Winn T, Rusli BN. Practical issues in calculating the sample size for prevalence studies. *Arch Orol Sci*. 2006;1:9–14.
30. Pourhoseingholi MA, Vahedi M, Rahimzadeh M. Sample size calculation in medical studies. *Gastroenterol Hepatol Bed Bench*. 2013;6:14–17.
31. Shen R, et al. *Molecular and Cellular Biology / Genetics*. Comprehensive genomic profiling in Chinese patients with pulmonary sarcomatoid carcinoma. American Association for Cancer Research. Annual Meeting, Atlanta, GA, USA; March 29 - April 3, 2019; Abstract 3400; 2019.
32. Yang H, et al. Characterization of MET exon 14 alteration and association with clinical outcomes of crizotinib in Chinese lung cancers. *Lung Cancer*. 2020;148:113–121.
33. Sharma J, et al. P2.01-056 Distinct PD-L1 expression in different components of pulmonary sarcomatoid carcinoma and its association with MET mutation. *J Thorac Oncol*. 2017;12:S819–S820.
34. Champagnac A, et al. Frequency of MET exon 14 skipping mutations in non-small cell lung cancer according to technical approach in routine diagnosis: results from a real-life cohort of 2,369 patients. *J Thorac Dis*. 2020;12:2172–2178.
35. Gray S, et al. P3.02-053 optimization and characterization of assays to identify met exon 14 skipping in FFPE embedded NSCLC samples. *J Thorac Oncol*. 2017;12:S2256–S2257.
36. Dziadziuszko R, et al. 1307P Blood-based genomic profiling of advanced non-small cell lung cancer (aNSCLC) patients (pts) from blood first assay screening trial (BFAST) and comparison with real-world data (RWD). *Ann Oncol*. 2020;31:S845–S846.
37. Denize T, et al. RNA targeted analysis for the detection of druggable fusions in lung adenocarcinoma: one year experience. *Mod Pathol*. 2020;33:1934–2024.
38. Vanderwalde AM, et al. Distribution and pathogenicity of nSNPs in receptor tyrosine kinases (RTKs) in non-small cell lung cancer (NSCLC) patients (pts). *J Clin Oncol*. 2017;35:e20618.
39. Sabari JK, et al. PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. *Ann Oncol*. 2018;29:2085–2091.
40. Schatz S, et al. Hybrid capture NGS reliably detects a spectrum of clinically significant genetic aberrations in both, primary diagnostics and the relapse scenario. *Ann Oncol*. 2018;29:viii517.
41. Katalinic D, Aleric I, Vcev A. MET exon 14 splicing mutation and its correlation with clinicopathological features in subjects with non-small cell lung cancer. *Ann Oncol*. 2018;29:viii54.
42. Hong Y, et al. Detection of multiple types of cancer driver mutations using targeted RNA sequencing in NSCLC. *J Clin Oncol*. 2022;40:e15043–e15043.
43. Zhuo M, Gu W, Chen R, Yuan M. 1269P Identification of rare gene fusions in non-small cell lung cancer with next-generation sequencing. *Ann Oncol*. 2021;32:S992.
44. Buyuksimsek M, et al. Results of liquid biopsy studies by next generation sequencing in patients with advanced stage non-small cell lung cancer: single center experience from Turkey. *Balkan J Med Genet*. 2019;22:17–24.
45. Arguello D, Voss A, Gatalica Z, Bender RO. 04: profiling of MET-amplified non-small cell lung cancer (NSCLC), correlation to cMET protein expression/MET exon 14 skipping. *J Thorac Oncol*. 2016;11:S170.
46. Detarom S, et al. P3.09-08 tumor heterogeneity and molecular profile of NSCLC in Thai population. *J Thorac Oncol*. 2018;13:S949–S950.
47. Motoi N, Sunami K, Ohe Y, Watanabe SI, Kohno T. Lung adenocarcinoma with MET exon 14 skipping mutation; clinicopathological characteristics and immunohistochemical MET expression. *Lab Invest*. 2018;98:742.
48. Karachaliou N, et al. Homology-directed repair (HDR)-defective lung adenocarcinomas (LUACs) in circulating tumor DNA (ctDNA). *Ann Oncol*. 2018;29:viii671.
49. Saffroy R, et al. MET exon 14 mutations as targets in routine molecular analysis of primary sarcomatoid carcinoma of the lung. *Oncotarget*. 2017;8:42428–42437.
50. Phung T, et al. Clinical utility of reflex ordered testing for molecular biomarkers in lung cancer. *Am J Clin Pathol*. 2018;150:S143.
51. Benayed R, et al. High yield of RNA sequencing for targetable kinase fusions in lung adenocarcinomas with no mitogenic driver alteration detected by DNA sequencing and low tumor mutation burden. *Clin Cancer Res*. 2019;25:4712–4722.
52. Ferreira CG, Zalis M, Reis M, Schluckebier L, Montella T. PUB070 rare actionable mutations in a lung adenocarcinoma cohort in Brazil. *J Thorac Oncol*. 2017;12:S2388–S2389.
53. Xu Z, et al. Incidence and PD-L1 expression of MET 14 skipping in Chinese population: a non-selective NSCLC cohort study using RNA-based sequencing. *Oncotargets Ther*. 2020;13:6245–6253.
54. Sands JM, et al. Next-generation sequencing informs diagnosis and identifies unexpected therapeutic targets in lung squamous cell carcinomas. *Lung Cancer*. 2020;140:35–41.
55. Lam VK, et al. Targeted tissue and cell-free tumor DNA sequencing of advanced lung squamous-cell carcinoma reveals clinically significant prevalence of actionable alterations. *Clin Lung Cancer*. 2019;20:30–36.
56. Chen X, et al. MET exon 14 splice site mutation, protein expression, and amplification in pulmonary sarcomatoid carcinoma: a multi-center study from China. *J Clin Oncol*. 2017;35:e20595.
57. Mignard X, et al. c-MET overexpression as a poor predictor of MET amplifications or exon 14 mutations in lung sarcomatoid carcinomas. *J Thorac Oncol*. 2018;13:1962–1967.
58. Halmos B, et al. Lung sarcomatoid carcinoma (LSC) harbors targetable genomic alterations and high mutational burden as observed by comprehensive genomic profiling (CGP). *Ann Oncol*. 2016;27:vi419.
59. Liu X, et al. Next-generation sequencing of pulmonary sarcomatoid carcinoma reveals high frequency of actionable MET gene mutations. *J Clin Oncol*. 2016;34:794–802.
60. Heist RS, et al. MET exon 14 skipping in non-small cell lung cancer. *Oncologist*. 2016;21:481–486.

61. Salomonsson A, et al. FP16.04 a nationwide population-based mapping of mutations and gene fusions in lung cancer among never-smokers. *J Thorac Oncol.* 2021;16:S974.
62. Salomonsson A, et al. P1.14-37 lung cancer in never-smokers: a nationwide population based mapping of targetable alterations. *J Thorac Oncol.* 2019;14(suppl 10):S568–S569.
63. Schrock A, et al. MA16.05 MET kinase domain rearrangements (KDRE) in non-small cell lung cancer (NSCLC) identified through comprehensive genomic profiling (CGP). *J Thorac Oncol.* 2018;13:S412.
64. Overbeck TR, et al. Top-level MET gene copy number gain defines a subtype of poorly differentiated pulmonary adenocarcinomas with poor prognosis. *Transl Lung Cancer Res.* 2020;9:603–616.
65. Bubendorf L, et al. Prevalence and clinical association of MET gene overexpression and amplification in patients with NSCLC: results from the European Thoracic Oncology Platform (ETOP) Lungscape project. *Lung Cancer.* 2017;111:143–149.
66. Baldacci S, et al. High MET overexpression does not predict the presence of MET exon 14 splice mutations in NSCLC: results from the IFCT PREDICT.amm study. *J Thorac Oncol.* 2020;15:120–124.
67. Lamberti G, et al. P2.04-32 comparison of clinicopathological and genomic characteristics between NSCLCs with a PD-L1 tumor proportion score of $\geq 90\%$ vs $< 1\%$. *J Thorac Oncol.* 2019;14:S720–S721.
68. Paik PK, et al. Real-world assessment of clinical outcomes in NSCLC patients with MET exon 14 skipping mutation and brain metastases (BM) treated with capmatinib. *J Thorac Oncol.* 2022;40:e21171–e21171.
69. Hur JY, et al. Characteristics and clinical outcomes of non-small cell lung cancer patients in Korea with MET exon 14 skipping. *In Vivo (Brooklyn).* 2020;34:1399–1406.
70. Offin M, et al. CNS metastases in patients with MET exon 14–altered lung cancers and outcomes with crizotinib. *JCO Precis Oncol.* 2020;4:871–876.
71. Taslimi S, et al. Comparative efficacy of systemic agents for brain metastases from non-small-cell lung cancer with an EGFR mutation/ALK rearrangement: a systematic review and network meta-analysis. *Front Oncol.* 2021;11 Preprint at. doi:10.3389/fonc.2021.739765.
72. Ferrara MG, et al. Oncogene-addicted non-small-cell lung cancer: treatment opportunities and future perspectives. *Cancers.* 2020;12.
73. Zhang YL, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget.* 2016;7:78985–78993.
74. Cui G, et al. A meta-analysis of the association between BRAF mutation and nonsmall cell lung cancer. *Medicine (Baltimore).* 2017;96(14):e6552. doi:10.1097/MD.00000000000006552.
75. Fan L, Feng Y, Wan H, Shi G, Niu W. Clinicopathological and demographical characteristics of non-small cell lung cancer patients with ALK rearrangements: a systematic review and meta-analysis. *PLoS One.* 2014;9.
76. Niu F-Y, et al. Distribution and prognosis of uncommon metastases from non-small cell lung cancer. *BMC Cancer.* 2016;16:149.
77. Socinski MA, Pennell NA, Davies KD. MET exon 14 skipping mutations in non-small-cell lung cancer: an overview of biology, clinical outcomes, and testing considerations. *JCO Precis Oncol.* 2021;653–663. doi:10.1200/po.20.00516.
78. Davies KD, et al. DNA-Based versus RNA-Based Detection of MET Exon 14 skipping events in lung cancer. *J Thorac Oncol.* 2019;14:737–741.
79. Jurkiewicz M, et al. Efficacy of DNA versus RNA NGS-based Methods in MET Exon 14 skipping mutation detection. *J Clin Oncol.* 2020;38:9036–9036.
80. Huang G, et al. Analysis of MET genetic aberrations in Chinese solid tumor patients. *J Clin Oncol.* 2022;40:e15031–e15031.
81. Ai X, et al. Comprehensive analysis of MET mutations in NSCLC patients in a real-world setting. *Ther Adv Med Oncol.* 2022;14.
82. Thomas M, et al. OA03.05 tepotinib in patients with MET exon 14 (METex14) skipping NSCLC: primary analysis of the confirmatory VISION Cohort C. *J Thorac Oncol.* 2022;17:S9–S10.
83. Spira A, et al. OA15.03 amivantamab in non-small cell lung cancer (NSCLC) with MET exon 14 skipping (METex14) mutation: initial results from CHRYSALIS. *J Thorac Oncol.* 2021;16:S874–S875. doi:10.1016/j.jtho.2021.08.084.
84. Krebs M, et al. Amivantamab in patients with NSCLC with MET exon 14 skipping mutation: updated results from the CHRYSALIS study. *J Clin Oncol.* 2022;40:9008–9008.
85. Camidge DR, et al. Safety and preliminary clinical activity of the MET antibody mixture, Sym015 in advanced non-small cell lung cancer (NSCLC) patients with MET amplification/exon 14 deletion (MET Amp/Ex14Δ). *J Clin Oncol.* 2020;38:9510.
86. Lu S, et al. Once-daily savolitinib in Chinese patients with pulmonary sarcomatoid carcinomas and other non-small-cell lung cancers harbouring MET exon 14 skipping alterations: a multicentre, single-arm, open-label, phase 2 study. *Lancet Respir Med.* 2021;9:1154–1164.
87. Le X, et al. Tepotinib efficacy and safety in patients with MET exon 14 skipping NSCLC: outcomes in patient subgroups from the VISION study with relevance for clinical practice. *Clin Cancer Res.* 2022;28:1117–1126.
88. Tan AC, Tan DSW. Targeted therapies for lung cancer patients with oncogenic driver molecular alterations. *J Clin Oncol.* 2022;40:611–625.
89. Paik PK, Pfeiffer BM, Vioix H, Garcia A, Postma MJ. Matching-adjusted indirect comparison (MAIC) of tepotinib with other MET inhibitors for the treatment of advanced NSCLC with MET exon 14 skipping mutations. *Adv Ther.* 2022;39:3159–3179.