Real-world insights into patients with advanced NSCLC and MET alterations

Marisa Bittoni, James Chih-Hsin Yang, Jin-Yuan Shih, Nir Peled, Egbert F. Smit, D. Ross Camidge, Rajeswara Rao Arasada, Dina Oksen, Emmanuelle Boutmy, Christopher Stroh, Andreas Johne, David P. Carbone, Paul K. Paik

aJames Comprehensive Cancer Center, The Ohio State University, Columbus, OH, USA
bDepartment of Medical Oncology, National Taiwan University Cancer Center, Taiwan
cDepartment of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
dOncology Department, Shaare Zedek Medical Center, Jerusalem, Israel

This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

CRediT authorship contribution statement

Marisa Bittoni: Data curation, Investigation, Supervision, Validation, Writing - review & editing. James Chih-Hsin Yang: Data curation, Investigation, Supervision, Validation, Writing - review & editing. Jin-Yuan Shih: Data curation, Investigation, Supervision, Validation, Writing - review & editing. Nir Peled: Data curation, Investigation, Supervision, Validation, Writing - review & editing. Egbert F. Smit: Data curation, Investigation, Supervision, Validation, Writing - review & editing. Ross D. Camidge: Data curation, Investigation, Supervision, Validation, Writing - review & editing. Rajeswara Rao Arasada: Data curation, Investigation, Supervision, Validation, Writing - review & editing. Dina Oksen: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing - review & editing. Emmanuelle Boutmy: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing - review & editing. Christopher Stroh: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing - review & editing. Andreas Johne: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing - review & editing. David P. Carbone: Data curation, Investigation, Supervision, Validation, Writing - review & editing. Paul K. Paik: Data curation, Investigation, Supervision, Validation, Writing - review & editing.

Declaration of Competing Interest

Marisa Bittoni - Nothing to declare. Ross Camidge - advisory/consultancy: Anchiarno (SAB), Amgen, Takeda, Roche, EMD Serono, Sanofi, Pfizer, CBT Pharmaceuticals, Daichi-Sankyo (Interstitial Lung Disease adjudication committee), GI Therapeutics (data safety monitoring board), Bio-Thera (data safety monitoring board), Blueprint, Abbvie, Achilles, BeyondSpring, Apollomics (standing Scientific Review Committee), 14ner/Elevation (standing Scientific Review Committee), Archer, Helsinn, Bristol-Myers Squibb, Eli Lilly, Medtronic, Ribon, AstraZeneca, Takeda, Aryls/Kyn, Regeneron, Hengrui, Hansoh (Scientific Review Committee), Bio-Thera (data safety monitoring board), Roche/Genentech, Invivata; research funding: Takeda; principle investigator for company sponsored trials (institution): Abbvie, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Hansoh, Inhibrx, Lycera, Medimmune, Merck, Pfizer, Phosphati, Psoixus, Rain, Roche/Genentech, Seattle Genetics, Symphogen, Takeda, Tolero. David P. Carbone - honoraria: AstraZeneca, Nexus Oncology; consulting or advisory role: Abbvie, AstraZeneca, Bayer, Biothera, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis Oncology, Genentech/Roche, Helsinn Therapeutics, Incyte, Invivata, Loxo Oncology, Merck; Novartis, Peregrine Pharmaceuticals, Pfizer, Synta; research funding: Bristol-Myers Squibb, Paul Paik - advisor: Abbvie, Bristol-Myers Squibb, Calithera, Celgene, Lilly, Takeda; research expenses: EMD Serono; research institution has received research expenses from: Celgene, EMD Serono, Nir Peled - advisor & honorarium from & research with: AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Foundation Medicine, Gaurdant360, Merck, MSD, Novartis, NovellusDx, Pfizer, Roche, Takeda. Jin-Yuan Shih - research funding: Roche; advisor & honorarium: AstraZeneca, Roche, Boehringer Ingelheim, Eli Lilly, Pfizer, Novartis, Merck Sharp & Dohme, Ono Pharmaceutical, Chugai Takeda and Bristol-Myers Squibb. Egbert Smit - advisory/consultancy (institution): Lilly, AstraZeneca, Boehringer Ingelheim, Roche/Genentech, Bristol-Myers Squibb, Merck Healthcare KGaA, Darmstadt, Germany, MSD Oncology, Takeda, Bayer, Regeneron, Novartis, Daichi Sankyo, Seattle Genetics; research funding (institution): Boehringer Ingelheim, Bayer, Roche/Genentech, AstraZeneca, Bristol-Myers Squibb. James Chih-Hsin Yang - received personal fees: Boehringer Ingelheim, Eli Lilly, Bayer, Roche/Genentech, Chugai Pharmaceutical, MSD, Pfizer, Novartis, BMS, Ono Pharmaceuticals, AstraZeneca, ACT Genomics, Merck Serono, Celgene, Yuhan Pharmaceuticals, Daichi Sankyo, Hansoh Pharmaceuticals, Takeda Pharmaceuticals, Blueprint Medicine, Amgen, Dina Oksen, Emmanuelle Boutmy, Andreas Johne; employees of Merck Healthcare KGaA, Darmstadt, Germany.
Abstract

Objectives: To describe characteristics, treatment and outcomes of non-small cell lung cancer (NSCLC) patients with MET alterations (MET exon 14 [METex14] skipping or MET amplification [METamp]) in real-world clinical care.

Methods: This non-interventional cohort study used real-world data extracted from electronic medical records from academic oncology sites in Israel, The Netherlands, Taiwan, and the USA. Patients had confirmed diagnosis of advanced (Stage IIIB–IV) NSCLC harboring MET alterations (date of diagnosis = index date) between 1 Jan 2010 and 30 Sept 2018. Medical history was assessed prior to and at the index date (baseline period), and outcomes from first date of treatment to death, loss to follow-up, or end of study period.

Results: A total of 117 patients were included (METex14 n = 70; METamp n = 47); testing methods were heterogeneous. Concomitant oncogenic mutations were more common in the METamp cohort than METex14. Patients in the METex14 cohort were older than those in METamp, and a larger proportion were never smokers. Anticancer first-line therapies received by patients (METex14: METamp) included chemotherapy only (44%; 41%), MET inhibitors (33%; 29%), immune checkpoint inhibitor (ICI) mono-(12%; 15%) and combination-therapy (8%; 3%). Second-line therapies included chemotherapy (35%; 30%) and MET inhibitors (30%; 39%). In the METex14 cohort, objective response rate (ORR) was generally low (first-line 28%; second-line 30%); no patients who received ICIs had a response. In the METamp cohort, ORR was 36% in first-line and 22% in second-line. Median (95% confidence interval) overall survival from start of first-line therapy was 12.0 months (6.8, 19.2) in the METex14 cohort and 22.0 months (9.8, 31.2) in METamp.

Conclusions: Heterogeneous treatments reflect the changing landscape and availability of new treatments, as well as the high unmet medical need in older, METex14 patients who had more advanced disease at diagnosis. MET-targeted therapies could be beneficial in patients with these rare MET alterations.

Keywords
Advanced NSCLC; MET exon 14; MET amplification; Treatment patterns; Real-world data; Outcomes; Biomarkers

Classifications:
Systemic treatments
1. Introduction

The receptor for hepatocyte growth factor (HGF), a tyrosine kinase that is encoded by the mesenchymal epithelial transition factor (MET) oncogene, has a crucial role in cancer growth, invasion and metastasis. Oncogenic MET alterations can act as a primary driver of tumorigenesis, with tumor dependence on MET signaling for cancer initiation and progression, a phenomenon that is called ‘oncogene addiction’. MET exon 14 (METex14) skipping alterations and MET amplification have been identified as alterations that can convert MET into a primary oncogenic driver [1].

METex14 skipping alterations and MET amplification occur in a subset of treatment-naïve patients with non-small cell lung cancer (NSCLC) [1-3]. MET alterations are generally observed across different NSCLC histology subtypes [1,4].

NSCLC harboring METex14 skipping alterations in about 8–15% also harbor concomitant MET amplifications [4]; however, MET amplification as a primary driver also occurs as a distinct oncogenic event in the absence of METex14 skipping. Targeted therapies are being developed to target NSCLC harboring METex14 skipping alterations or MET amplification, and available information indicates that both MET alterations are predictive markers in NSCLC, conferring sensitivity to MET inhibition [1,2,5]. The level of amplification potentially has an impact on the efficacy of targeted treatment options, with patients with highly amplified tumors showing an expectedly better response to systemic treatment [6]. Among patients with advanced NSCLC, both oncogenic MET activation as well as MET overexpression were shown to predict shorter survival [1,7].

The common standard of care in first-line therapy for NSCLC, without oncogenic drivers, involves use of platinum-based chemotherapy or immune checkpoint inhibitors (ICIs) either as single components or in combination, depending on the level of expression of programmed death-ligand 1 (PD-L1) or potential contraindications such as poor performance status, often found in patients of advanced age [8-12]. For patients advancing to second-line therapy, monotherapy with ICIs should be considered, if not previously given. Patients with oncogenic-driven NSCLC should receive targeted therapy where available [9,13], as the efficacy of standard therapies might be impaired in oncogene-addicted disease [14,15]. Reduced effectiveness of ICI monotherapy, chemotherapy or combinations has also been reported in patients with METex14 NSCLC [16-21]. Due to the importance of identifying these oncogenic drivers in patients with NSCLC, clinical guidelines advocate to perform molecular testing prior to the selection of NSCLC therapy [9,22].

Published literature on advanced NSCLC bearing selected MET alterations in real-world settings is sparse, as there is a lack of data to characterize patients due to the recent recognition of METex14 skipping alterations as an oncogenic driver mutation. Knowledge of the natural history of the disease and the clinical course of these patients is, therefore, currently limited. This study aims to comprehensively describe the biomarkers, demographics and clinical characteristics of these patients, as well as their treatment patterns and outcomes in real-world clinical care.
2. Materials and methods

2.1. Study design

This non-interventional retrospective cohort study extracted electronic medical record (EMR) data from academic oncology sites across Israel, The Netherlands, Taiwan, and the United States of America (USA). Informed consent was obtained for each participating site where required. Study-eligible patients were aged minimum 18 years old with advanced or metastatic NSCLC (Stage IIIB/IV) that was diagnosed between 1 January 2010 and 31 March 2019, and had a confirmed presence of METex14 skipping alterations/MET amplification at any time. The study was approved by the relevant Ethics Committees, Institutional Review Board, and/or local regulations of each site.

Two distinctive patient cohorts were studied: a METex14 cohort composed of patients harboring METex14 skipping alterations with or without concomitant MET amplification, and a MET-amplification cohort that was defined based on the presence of MET amplification (at any reported level) without METex14 skipping alterations.

The index date was defined as the recorded date of diagnosis of advanced NSCLC. Patients were described at baseline prior to and at their index date, and were followed up after treatment exposure until death, end of the study period, or loss to follow-up to describe effectiveness outcomes.

2.2. Data collection and outcomes assessment

Data were extracted from the EMR of each study-eligible patient. MET biomarker data were extracted at any time at or after diagnosis of NSCLC, including test type (liquid or tissue biopsy), test method, laboratory information, test results for the MET alteration (including the specific METex14 alteration, if available), the level of amplification given either by gene copy number (GCN), or the level of amplification indicated in the electronic case report form as positive, strongly positive or very strongly positive. Additionally, any available results for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), Kirsten Rat Sarcoma virus (KRAS), B-Raf proto-oncogene (BRAF), reactive oxygen species 1(ROS1), cell division protein kinase 6 (CDK6) and PD-L1 tests, were extracted. Baseline demographics and clinical characteristics, description of treatment patterns and disease outcomes were also extracted. The performance status of the patients was extracted as Eastern Cooperative Oncology Group Performance Status (ECOG PS), Karnofsky scores (converted into ECOG PS), or from the physician notes stating that the performance status was not impaired.

Each patient’s line of therapy in the advanced setting was determined by two clinical experts independently, then consolidated and compared with lines of therapy assigned by study sites. The line of therapy assessment was based on type of regimen, category of medication, start and end date of drug, treatment length, treatment overlaps, gap in days after treatment end and treatment start, ‘ongoing’ treatment status noted by site during data collection, date of diagnosis of advanced disease, tumor response, date of progressive disease (PD), death, date of death and cause of death for each individual patient.
Patients with a confirmed line of therapy were eligible for treatment pattern analysis and effectiveness outcomes. Similarly, only patients with non-missing information on tumor response or death were included in the outcome analyses. Treatment exposure was categorized into the following: all anticancer therapies, MET inhibitors, chemotherapy only, ICI as monotherapy, ICI as combination therapy, and other therapies.

Best overall response (BOR) was extracted for each patient per line of therapy and classified according to the following Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1-like categories [23]: complete response (CR), partial response (PR), stable disease (SD), PD, and not evaluable. If an extracted response was RECIST-like, it was classified as loosened RECIST in the categories ‘favorable’ or ‘unfavorable’, and undocumented responses were also recorded.

2.3. Statistical analysis

The statistical evaluation was performed using the software package Statistical Analysis System v14 or later. Statistical methods included standard descriptive statistics for patient characteristics and biomarker information. Treatment patterns were described in terms of sequence of treatments, number and percentages of anticancer treatment regimens received, by line of therapy from advanced diagnosis through the end of the medical record. Sankey diagrams were used to present treatment patterns over time by line of therapy.

The overall response rate (ORR) to a line of therapy was calculated as the sum of CR + PR for patients under the estimated RECIST v1.1 classification out of all patients with a recorded BOR and displayed with 95% Clopper Pearson confidence intervals (CI). In addition, in a sensitivity analysis the ORR was calculated including loosened RECIST responses (favorable or unfavorable response), and undocumented responses (unknown or not applicable) under the assumption that tumor response evaluations generally are expected to occur every three treatment cycles in clinical practice. Thus, the numerator counted the OR (BOR of CR, PR) as per RECIST v1.1 and patients with favorable response and the denominator counted all patients with a known response (CR, PR, SD, PD, not estimable (NE), other favorable, other unfavorable, and reclassified NE). Remaining undocumented (unknown or not applicable [NA]) responses did not count in the denominator [24]. For the MET-amplified cohort, outcome analyses were planned on patients with either mean GCN ≥ 10 or highly amplified by liquid biopsy, or mean GCN ≥ 8 or highly amplified by liquid biopsy.

Overall survival (OS) was reported from the start of a line of therapy after advanced diagnosis, through to the end of the medical record, irrespective of therapy received across different lines of therapies. Due to missing data for progression dates, duration of response (DoR) and progression-free survival (PFS) could not be assessed. Time to next treatment or death (TNTD), used as a proxy of PFS [25,26], was defined as the time from initiation of a therapy to either end of the line of therapy, any next systemic therapy or death as event. TNTD and OS were described using Kaplan–Meier curves and were presented with a summary of associated statistics with 95% CIs.
3. Results

3.1. Patient characteristics

A total of 117 patients were included in the study from six oncology sites, of which three were located in the USA (Israel n = 18; The Netherlands n = 13, Taiwan, n = 23, USA n = 63). Thirteen patients had information on treatment exposure recorded after the end of the study period (01 January 2010 up until 31 March 2019) but were nevertheless included. The last available date for these patients was on 30 December 2019. In total, 70 patients were in the METex14 cohort and 47 patients were in the MET-amplification cohort.

Patient demographics and clinical characteristics for these patients are presented in Table 1. Patients with METex14 skipping were, on average, older (median age 74.2 years, Q1-Q3: 66.8; 78.8) than patients with MET-amplified NSCLC (median age 63.1 years, Q1-Q3: 55.8; 70.5); there were fewer males (51.4% versus 65.1%) and less white ethnicity (58.6% versus 85.1%). In the METex14 cohort, nearly half the patients were never smokers (47.1%), whereas 14.9% were never smokers in the MET-amplification cohort. The median duration since stopping smoking was 30 years for patients with METex14 skipping and 6 years for patients with MET amplification.

The majority of patients in both cohorts were diagnosed with advanced stage at their initial diagnosis of NSCLC, with adenocarcinoma as the most frequent histology (METex14: 84.1%, MET-amplified: 82.2%). Sarcomatoid carcinoma was only observed in the METex14 cohort (5.8%). At index date (advanced diagnosis) most patients had Stage IV NSCLC. ECOG PS, Karnofsky score and impaired status were often missing. Almost half of patients had at least one comorbid condition present at the time of initial diagnosis. The most frequently observed comorbidities were uncomplicated diabetes, chronic obstructive pulmonary disease, and peripheral vascular disease. Brain metastases were seen in 19% of patients with METex14 skipping and 25% of patients with MET amplification.

3.2. Biomarkers

Biomarker information for both cohorts are presented in Table 2. Determination of METex14 status (81.4%) and MET amplification (76.6%) was mainly performed in tissue biopsy samples. For patients with METex14 skipping, the most common testing method was next-generation sequencing (NGS) (60.0%), and 8.6% patients had concomitant MET amplification. MET amplification was detected through fluorescence in situ hybridization (FISH) (55.3%) and NGS (44.7%) in the MET amplification cohort. The median time from initial diagnosis of NSCLC until a positive MET alteration result was 5.6 months (n = 67) in the METex14 skipping cohort, and <1 month in the MET amplification cohort (n = 42).

Few concomitant oncogenic alterations were found in the test results for patients with METex14 skipping, except for one patient with activating EGFR kinase domain mutations (L858R) and two patients with activating KRAS mutations in codon 12.

There were four patients with MET amplification with a GCN ≥ 10 and five patients with MET amplification with a GCN ≥ 8. Patients with MET amplification more frequently had biomarker tests for other oncogenic drivers: EGFR (91.5%), ALK (87.2%), KRAS,
(80.9%), ROS1 (76.6%), BRAF (59.6%), and CDK6 (29.8%). Compared with patients with METex14, concomitant alterations were more frequently observed, including five patients with EGFR mutations and one patient with ALK fusion.

### 3.3. Treatment patterns

Anticancer therapy provided as first-, second- and third-line therapy is displayed by Sankey plots in Fig. 1 (METex14 cohort) and Fig. 2 (MET-amplification cohort) for patients with TNTD data (n = 52 with METex14 skipping and n = 34 with MET-amplification). For both cohorts, the most frequent therapy within first-line therapy was chemotherapy alone (METex14 cohort 44% [n = 23/52 platinum-based]; MET-amplification cohort 41% [n = 14/34 platinum-based]), followed by MET inhibitors (33% [n = 17]; 29% [n = 10]), ICI monotherapy (12% [n = 6]; 15% [n = 5]), and ICI combination therapy (2% [n = 1]; 3% [n = 1]). For patients with METex14 skipping, chemotherapy remained the most frequent treatment option within second- (35%; n = 1/10 including a taxane) and third-line (42%) therapy, followed by treatment with MET inhibitors (second-line 30%; third-line 25%). MET inhibitors were seen across all lines of therapy for these patients and were primarily given as a monotherapy. In the METex14 cohort, MET inhibitors comprised crizotinib (n = 17) in first-line; crizotinib (n = 5), capmatinib and cabozantinib (each n = 1) in second-line; and crizotinib (n = 5) and cabozantinib (n = 1) in later-line therapy. For patients with MET amplification, treatment with MET inhibitors was most commonly reported in second-line therapy (39%), followed by chemotherapy (30%; n = 2/7 including a taxane). The most frequent third-line therapy was chemotherapy. In the MET amplification cohort, MET inhibitors comprised crizotinib (n = 9) and capmatinib (n = 1) in first-line; crizotinib (n = 8) and cabozantinib (n = 1) in second-line; and capmatinib (n = 1) in later-line therapy. Overall, 13/86 patients in first-line, 11/46 patients in second-line and 7/22 patients in third-line received ICI, as monotherapy or in combination.

### 3.4. Effectiveness outcomes

In the METex14 cohort, 18 patients (first line), 10 patients (second line) and 8 patients (third line) had responses assessed according to RECIST v1.1-like criteria.

The ORR for the first and second line of therapy among patients with METex14 skipping alterations is presented in Fig. 3a. For first-line therapy, among patients with response assessed according to RECIST criteria, the ORR was 27.8% (95% CI: 9.7, 53.5), including 40.0% (n = 2/5) in patients who received MET inhibitors and 23.1% (n = 3/13) without MET inhibitors. No responses were observed in patients who received ICI mono or combination therapy (n = 3). For second-line therapy, the ORR by RECIST was 30.0% (95% CI: 6.7, 65.2), including 25.0% (n = 1/4) with MET inhibitors and 33.3% (n = 2/6) without. Again, there were no responses in patients receiving ICI mono or combination therapy (n = 2). In third-line therapy, there were 2/2 responses with MET inhibitors and 0/6 responses without MET inhibitors.

In the METex14 cohort, the median TNTD was 6.3 months (95% CI: 4.8, 10.9) for first-line therapy (n = 52), and 7.8 months (95% CI: 3.9, 11.3) for second-line therapy (n = 23) (Fig. 4). For patients who received MET inhibitors and those who did not, median TNTD was
10.92 months (95% CI: 3.2, 19.2) and 6.05 months (95% CI: 3.5, 7.2) in first-line, and 10.0 months (95% CI: 2.0, 18.0) and 6.3 months (95% CI: 3.0, 11.3) in second-line, respectively. In the METex14 cohort, the median OS was 12.0 months (95% CI: 6.8, 19.2) from start of first-line therapy (n = 52), and 11.7 months (95% CI: 6.0, 32.9) from start of second-line therapy (n = 21) (Fig. 5a).

In the MET-amplified cohort, 25 patients (first line), 18 patients (second line) and 6 patients (third line) had responses assessed according to RECIST v1.1-like criteria. For first-line therapy, the ORR was 36.0% (95% CI: 18.0, 57.5), including 33.3% (n = 3/9) with MET inhibitors and 37.5% (n = 6/16) without MET inhibitors. There was one CR and one PR among the five patients who received ICI monotherapy or combination therapy (ORR 40%). For second-line therapy, the ORR was 22.2% (95% CI: 6.4, 47.6) (Fig. 3b), including 42.9% in patients who received MET inhibitors (n = 3/7) and 9.1% in those who did not (n = 1/11). One patient received ICI monotherapy and did not respond. No patients received MET inhibitors in third-line therapy; there were 4/6 responses in patients who did not receive MET inhibitors, including 2/2 responses with ICI. There were insufficient patients numbers (≥ 10 patients) with information on the level of amplification to perform outcome analyses per level of MET amplification. Median TNTD overall was 9.0 months (95% CI: 6.1, 11.7) for first-line therapy (n = 34) and 5.13 months (95% CI: 3.3, 12.8) for second-line therapy (n = 23). For patients who received MET inhibitors and those who did not, median TNTD was 6.88 months (95% CI: 1.4, 11.6) and 9.36 months (95% CI: 4.4, 12.5) in first-line, and 3.09 months (95% CI: 1.1, 20.3) and 8.5 months (95% CI: 4.7, 19.4) in second-line, respectively. In the MET-amplified cohort, the median OS was 22.0 months (95% CI: 9.8, 31.2) from start of first-line therapy (n = 34), and 19.0 months (95% CI: 5.5, 20.3) from start of second-line therapy (n = 23) (Fig. 5b).

4. Discussion

Our findings present evidence on how the characteristics of patients with METex14 skipping and MET-amplified NSCLC differ, and how the treatment patterns of these patients in the real-world setting are heterogeneous, with non-targeted treatments being commonly used. Adenocarcinoma was the most frequent histology for both cohorts of patients, as has been previously reported, especially for patients harboring METex14 skipping alterations [4,16,19,27]. However, this finding may have been influenced by changes in clinical practice as, until recently, patients with squamous cell carcinoma histology were not screened for activating mutations. Patients with METex14 were characterized by a balanced sex ratio (51.4% male) and older age (median 75 years). Advanced age of patients with METex14 skipping compared to patients with NSCLC, on average, has also been observed in other studies [4,15,16,19,27,28]. This is in contrast to other driver oncogenes in NSCLC, such as EGFR and ALK, that are known to define a distinct patient population that is typically younger, with a strong female pre-dominance [29-34]. Patients from the MET-amplification cohort however, were younger than the typical patient with NSCLC. Similar results were shown in a US retrospective analysis of 99 patients with lung adenocarcinoma, and MET amplification (mean MET ≥ 5), with a median age of 61 years at diagnosis; 66% were current or former smokers [12]. Similarly, in the MET-amplification cohort in the current study, most patients were either current or former smokers and had, on average, only
recently stopped smoking. Contrary to this, in the METex14 cohort, nearly half the patients were never smokers. Over 30% of patients in the METex14 cohort were Asian, compared with <5% in the MET amplification group. While EGFR or ALK oncogenic alterations are more often reported in Asian patients with NSCLC [35], MET alterations such as METex14 generally appear to be less prevalent in Asian versus Caucasian patients [4,36,37]. The ability of this study to provide additional information on differences in the frequency of oncogenic drivers with different ethnicities is limited. However, while differences in the prevalence of individual oncogenic drivers are observed between populations, the functional impact of oncogenic drivers on NSCLC, i.e. their clinical manifestation and predictability for targeted therapies, is important across populations irrespective of ethnicity. The slightly higher number of Asian patients included in this study provides valuable information on an otherwise under-reported patient population; 23/117 patients in this study were enrolled from a Taiwanese site. In terms of treatment selection, ethnicity is not cited as a relevant factor in the treatment of oncogenic-driven NSCLC in the current Pan-Asian adapted ESMO Clinical Practice Guidelines [11].

Until recently, testing for MET alterations has not been routine, in part due to the lack of approved treatment options. Accordingly, testing patterns for MET alterations were heterogeneous with several testing methods used. NGS was the most frequently used method for METex14 patients. FISH was most often used to detect MET amplification (55.3%) followed by NGS (44.7%). Despite being invasive and possibly inadequate to represent the whole malignancy, tumor tissue biopsy appears to remain the gold standard to investigate potentially actionable biomarkers. Median time to identification for both MET alteration types was <6 months from initial diagnosis. In line with other alterations, such as EGFR or ALK, MET alterations are considered to appear early in NSCLC carcinogenesis and do not seem to be affected by other anticancer treatments. Therefore, the time of determination in the clinical course of patients may not be relevant for the effectiveness of MET-directed therapies, although, of course, earlier identification of oncogenic drivers allows for the earlier use of targeted drugs.

The presence of 8.6% concomitant MET amplification in the METex14 cohort is in agreement with previous research; reporting Stage IV METex14-mutated NSCLC being likely to have some concurrent MET amplification [38]. METex14 skipping is reported to be mutually exclusive with other targetable oncogenic drivers (very few concomitant alterations), whereas the situation is less clear for patients with MET amplification where it may depend on the actual copy number increase and focality [39]. In both our study cohorts, patients who were tested seemed to not commonly harbor other oncogenic driver mutations. Interestingly, results from the French Immunotarget study, on 34 patients with NSCLC, showed that PD-L1 was co-expressed with the METex14 alterations and not with MET amplification [40]. Our data suggest that PD-L1 expression occurred at a similar rate in both cohorts.

In both patient cohorts, the treatment landscape was heterogeneous and treatment changes frequent. In the METex14 cohort, the most common treatment regimen was chemotherapy with or without a vascular endothelial growth factor inhibitor, and MET/HGF inhibitors in both first- and second-line therapy. Similarly, in the MET-amplification cohort, the most common types of anticancer therapies were platinum-based chemotherapy regimens and MET/HGF inhibitors. Results reflect changes in the treatment landscape with multiple,
recently approved (such as ICIs) and available therapies for patients with NSCLC during the period studied (01 January 2010 up until 30 December 2019).

For patients with *MET*ex14 skipping, the observed ORR assessed according to RECIST v1.1 criteria overall was about 30% for both the first and second lines of therapy. When using loosened tumor response criteria in the first line, results were moderately impacted; however, in the second line, it reduced the observed ORR to about 20%. These results are lower than the ORRs observed in recent trials, investigating the diverse anti-MET tyrosine kinase inhibitors within this specific population (range 32–46%) [41-44], and for patients with *MET*ex14 skipping in line with effectiveness outcome results from a recently similar non-interventional study on a cohort of patients with advanced NSCLC *MET*ex14 [45].

Patients in this study received both standard therapies, such as chemotherapy, and emerging care, such as MET/HGF inhibitors, ICI monotherapy and ICI combination therapy. There is limited published evidence on tumor response across different lines of anticancer therapy in the advanced setting. Sabari and colleagues (2018) reported an ORR of 17% (95% CI: 6.0, 36.0) in an analysis of 24 patients with NSCLC and *MET*ex14 skipping alterations that had received immunotherapy [16]. In first-line therapy, our data showed higher ORR with MET inhibitors (40%) than non-MET inhibitor regimens (23.1%) in patients with *MET*ex14 skipping NSCLC, with the opposite trend in second-line (25% and 33.3%, respectively). In both first- and second-line, median TNTD was approximately 10 months with MET inhibitors and approximately 6 months with non-MET inhibitor regimens. For patients with *MET* amplification, ORR to first-line therapy was similar for MET inhibitors and non-MET inhibitor regimens (33.3% and 37.5%, respectively), and higher for MET inhibitors in second-line (42.9% and 9.1%, respectively) than for regimens without MET inhibitors. However, responses appeared to be less durable with MET inhibitor regimens in first- and second-line (median TNTD 6.9 and 3.1 months, respectively) than for regimens not including MET inhibitors (median TNTD 9.4 and 8.5 months, respectively). These data are, therefore, broadly supportive of MET inhibitor-based therapy versus non-MET inhibitor regimens in patients with *MET*-aberrant NSCLC, although they should be interpreted with caution due to the small sample sizes involved and heterogeneity of the data.

In our study, there were no responses seen in first- or second-line therapy with ICI inhibitors in patients with *MET*ex14 skipping NSCLC, except for one loosened RECIST response observed in the first line. Although these response rates should be interpreted with caution due to small study sample size, they concur with previously observed poor tumor response to ICI among patients with NSCLC with *MET* alterations [40,45,46]. It should also be noted that as the first ICI approval for lung cancer (nivolumab) did not occur until 2014 [47], and our cohort included patients diagnosed between 2010 and 2019, it may be expected that ICI therapy would be, to some extent, under-represented in this analysis compared with the current use of ICIs in NSCLC.

The results from our study are similar compared to the published literature. One study in Korea examining 20 patients with NSCLC and *MET*ex14 skipping, who were observed for first-line therapy, showed a median OS of 9.5 months and a PFS of 4.0 months [21]. Wolf and colleagues (2018) presented results from a multinational, multicenter, retrospective,
non-interventional chart review study, and reported on 87 patients with advanced NSCLC with METex14 mutations; a median survival of 10.9 months (95% CI: 7.4, 16.9) was observed for those who did not receive a MET inhibitor (n = 51), and 25.3 months (95% CI: 18.8, 40.9) for those who did (n = 36) [18]. Similarly, Awad and colleagues (2019) reported on patients with metastatic NSCLC with METex14 skipping alterations; a median survival of 8.1 months was shown for those who did not receive a MET inhibitor (n = 34), and 24.6 months for those who did (95% CI: 12.1, NA) (n = 27) [19]. The majority of our patients who received a MET inhibitor received crizotinib as either first- or second-line therapy, and the ORRs from our study (27.8% in first-line and 30.0% in second-line) are comparable with the ORR of 32% reported by Drilon et al. [43] in their cohort of 65 response-evaluable patients with METex14 NSCLC.

In the MET-amplification cohort, the median OS in this study is higher than has previously been reported for patients with advanced NSCLC with MET amplification. Wolf and colleagues (2018) analyzed patient-level data obtained from a multinational, multicenter, retrospective, non-interventional chart review study on 44 patients with advanced NSCLC with MET amplification, and reported a median OS of 17.8 months (95% CI: 7.2, 85.2) in patients who received MET inhibitors (n = 5) and 6.1 months (95% CI: 4.2, 7.9) in those who did not (n = 39). The survival patterns for these patients were, on average, higher than expected considering that the majority of patients were Stage IV at index, and compared to the published literature (although limited). In one recent US cohort study on patients with Stage IV NSCLC, 6,455 patients (66.8%) received first-line therapy, 2,966 (30.7%) received second-line therapy, and 1,204 (12.5%) received third-line therapy. Median OS was 11.1 months (95% CI: 10.8, 11.5) from the index date, 11.7 months (95% CI: 11.3, 12.0) from the initial date of NSCLC diagnosis, and 10.1 months (95% CI: 9.7, 10.4) from the start of first-line therapy. Median OS was longer with first-line immunotherapy (17.5 months [95% CI: 16.9, 18.8]; 60.6% data maturity) versus chemotherapy (15.0 months [95% CI: 14.0, 15.9]; 75.6% data maturity; p < 0.05) and chemotherapy/non-immunotherapy monotherapy (6.8 months [95% CI: 6.6, 7.1]; 77.3% data maturity; p < 0.05). Median OS was 17.5 months (95% CI: 16.8, 18.7; 60.8% data maturity) with first-line chemotherapy and second-line immunotherapy, and was longer compared with first- and second-line chemotherapy (14.2 months [95% CI: 13.6, 14.8]; 76.1% data maturity; p < 0.05) [48].

Censoring assumptions in survival analysis with Kaplan–Meier methods should be ‘non-informative’ – that is, participants who drop out of the study should do so due to reasons unrelated to the study. But, due to the nature of assessments of tumor response in real-world patients, resulting in missing tumor response assessment, we used loosened RECIST criteria as a sensitivity analysis. Certainly, some patients might have missing data or be lost to follow-up for reasons related to the study outcomes. Thus, we think that the missing data, censored in the Kaplan–Meier survival analysis, might be partly informative. Patients who come off study before progression, are likely to have progressed shortly thereafter or died, which reflects not only an increased risk for the censored patients, but a direct dependence on the censoring and progression times. However, the reclassification of patient responses, based on evaluation of treatment patterns and physicians’ assessments, should have minimized the informative censoring.
As this study was based on secondary use of data extracted from patient charts at each participating study site, data entry errors (information bias), while minimized with a standardized data collection process (electronic case report forms and monitoring), at the point of care might still happen but could not be corrected for during analyses. The availability of additional information, such as PD-L1 expression levels and exact timing of diagnostic procedures, could also not be addressed.

The information collected for this study was limited to what was available in the medical records and collected, as part of routine clinical practice but not for research purposes. In that context, a non-interventional study can be used to accurately describe routine clinical practice, and detect associations but cannot establish causality in the same way as prospective, randomized studies unless advanced and robust statistical methods to deal with confounders are applied.

5. Conclusions

In patients with both METex14 skipping alterations and MET amplification, the presence of oncogenic drivers other than MET was low. The treatment landscape was diverse. Effectiveness outcomes for non-targeted therapies in this setting indicated that these rare patients have a high unmet medical need and may benefit from a targeted treatment with a MET inhibitor. Nevertheless, the sample size of the study was small, and results could be strengthened with further studies and updated as treatment patterns change in the advanced NSCLC setting.

Acknowledgements

Writing support was provided by Syneos Health, London, UK and funded by Merck Healthcare KGaA, Darmstadt, Germany. Intellectual and administrative assistance was provided by Doreen-Allen Kahangire, Merck Healthcare KGaA, Darmstadt, Germany.

Abbreviations:

- **ALK**: anaplastic lymphoma kinase
- **BMI**: body mass index
- **BOR**: best overall response
- **BRAF**: B-Raf proto-oncogene
- **CDK6**: cell division protein kinase 6
- **CI**: confidence interval
- **CR**: complete response
- **DoR**: duration of response
- **ECOG PS**: Eastern Cooperative Oncology Group Performance Status
- **EGFR**: epidermal growth factor receptor
EMR electronic medical record
FISH fluorescence in situ hybridization
GCN gene copy number
HGF hepatocyte growth factor
ICI immune checkpoint inhibitor
KRAS Kirsten Rat Sarcoma virus
MET mesenchymal epithelial transition factor
MET<sub>ex14</sub> MET exon 14
NA not available
NE not estimable
NGS next-generation sequencing
NSCLC non-small cell lung cancer
ORR overall response rate
OS overall survival
PD progressive disease
PD-L1 programmed death-ligand 1
PFS progression-free survival
PR partial response
RECIST Response Evaluation Criteria In Solid Tumors
ROS reactive oxygen species
SD stable disease
TNTD time to next treatment or death
USA United States of America

References
[1]. Salgia R, MET in lung cancer: Biomarker selection based on scientific rationale, Mol. Cancer Ther 16 (2017) 555–565, 10.1158/1535-7163.MCT-16-0472. [PubMed: 28373408]
[2]. Frampton GM, Ali SM, Rosenzweig M, Chmielecki J, Lu X, Bauer TM, Akimov M, Bufill JA, Lee C, Jentz D, Hoover R, Ou SH, Salgia R, Brennan T, Chalmers ZR, Jaeger S, Huang A, Elvin JA, Erlich R, Fichtenholtz A, Gowen KA, Greenbowe J, Johnson A, Khaira D, McMahon C, Sanford EM, Roels S, White J, Greshock J, Schlegel R, Lipson D, Yelensky R, Morosini D, Ross JS, Collisson E, Peters M, Stephens PJ, Miller VA. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to...
MET inhibitors, Cancer Discov. 5 (2015) 850–859, 10.1158/2159-8290.cd-15-0285. [PubMed: 25971938]

[3]. Awad MM, Lee JK, Madison R, Classon A, Kmak J, Frampton GM, Alexander BM, Venstrom J, Schrock AB, Characterization of 1,387 NSCLCs with MET exon 14 (METex14) skipping alterations (SA) and potential acquired resistance (AR) mechanisms, J. Clin. Oncol 38 (2020) 9511, 10.1200/jco.2020.38.15_suppl.9511.

[4]. Schrock AB, Frampton GM, Suh J, Chalmers ZR, Rosenzweig M, Erlich RL, Halmos B, Goldman J, Forde P, Leuenberger K, Peled N, Kalemkerian GP, Ross JS, Stephens PJ, Miller VA, Ali SM, Ou SHI, Characterization of 298 patients with lung cancer harboring MET exon 14 skipping alterations, J. Thorac. Oncol 11 (2016) 1493–1502, 10.1016/j.jtho.2016.06.004. [PubMed: 27343443]

[5]. Cortot AB, Kherrouche Z, Descarpentries C, Wislez M, Baldacci S, Furlan A, Tulasne D, Exon 14 deleted MET receptor as a new biomarker and target in cancers, J. Natl. Cancer Inst 109 (2017) djw262, 10.1093/jnci/djw262.

[6]. Schuler MH, Berardi R, Lim W-T, Van Geel R, De Jonge MJ, Bauer TM, Azaro A, Gottfried M, Han J-Y, Lee DH, Wollner M, Hong DS, Vogel A, Delmonte A, Krohn A, Zhang Y, Squires M, Giovannini M, Akimov M, Bang Y-J, Phase (Ph) 1 study of the safety and efficacy of the MET inhibitor capmatinib (INC280) in patients (pts) with advanced cMET+ non-small cell lung cancer (NSCLC), J. Clin. Oncol 34 (2016) 9067, 10.1200/jco.2016.34.15_suppl.9067.

[7]. Dimou A, Non L, Chae YK, Tester WJ, Syrigos KN, MET gene copy number predicts worse overall survival in patients with non-small cell lung cancer (NSCLC): A systematic review and meta-analysis, PLoS One. 9 (2014) e107677, 10.1371/journal.pone.0107677. [PubMed: 25232729]

[8]. Hanna NH, Robinson AG, Temin S, Baker S, Brahmer JR, Ellis PM, Gaspar LE, Haddad RY, Hesketh PJ, Jain D, Jaiyesimi I, Johnson DH, Leigh NB, Moffitt PR, Phillips T, Riely GJ, Rosell R, Schiller BJ, Schneider BJ, Singh N, Spigel DR, Tashbar J, Masters G, Temin S, Baker S, Brahmer JR, Ellis PM, Gaspar LE, Haddad RY, Hesketh PJ, Jain D, Jaiyesimi I, Johnson DH, Leigh NB, Phillips T, Riely GJ, Robinson AG, Rosell R, Schiller BJ, Singh N, Spigel DR, Stabler JO, Tashbar J, Masters G, Therapy for stage IV non–small-cell lung cancer without driver alterations: ASCO and OH (CCO) joint guideline update, J. Clin. Oncol 39 (2020) 1040–1091, 10.1200/JCO.19.03022.

[9]. National Comprehensive Cancer Network, Non-Small Cell Lung Cancer Version 4.2021, (2021). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed March 18, 2021).

[10]. Planchar D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, Mok TS, Reck M, Van Schil PE, Hellmann MD, ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up †, Ann. Oncol 192–237 (2018).

[11]. Wu YL, Planchar D, Lu S, Sun H, Yamamoto N, Kim DW, Tan DSW, Yang JCH, Azrif M, Mitsudomi T, Park K, Soo RA, Chang JWC, Alip A, Peters S, Douillard JY, Pan-asian adapted clinical practice guidelines for the management of patients with metastatic non-small-cell lung cancer: A CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS, Ann. Oncol 30 (2019) 171–210, 10.1093/annonc/mdy554. [PubMed: 30596843]

[12]. Le X, Heymach JV, New verse for a familiar song: Small molecule inhibitors for MET exon 14 skipping non-small cell lung cancer, Oncologist. 25 (2020) 822–825, 10.1634/theoncologist.2020-0760. [PubMed: 33400286]

[13]. Hanna N, Johnson D, Temin S, Baker S, Brahmer J, Ellis PM, Giaccone G, Hesketh PJ, Jaiyesimi I, Leigh NB, Riely GJ, Schiller JH, Schneider BJ, Smith TJ, Tashbar J, Biermann WA, Masters G, Systemic therapy for stage IV non–small-cell lung cancer: American Society of clinical oncology clinical practice guideline update, J. Clin. Oncol 35 (2017) 3484–3515, 10.1200/JCO.2017.74.6065. [PubMed: 28806116]

[14]. Gainor JF, Shaw AT, Sequist LV, Fu X, Azzoli CG, Piotrowska Z, Huynh TG, Zhao L, Fulton L, Schultz KR, Howe E, Farago AF, Sullivan RJ, Stone JR, Digumarthy S, Moran T, Hata AN, Yagi Y, Yeap BY, Engelman JA, Mino-Kenudson M, EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: A retrospective analysis, Clin. Cancer Res 22 (2016) 4585–4593, 10.1158/1078-0432.CCR-15-3101. [PubMed: 27225694]
[15]. Lee CK, Man J, Lord S, Links M, Gebski V, Mok T, Yang JCH, Checkpoint inhibitors in metastatic EGFR-mutated non-small cell lung cancer—a meta-analysis, J. Thorac. Oncol 12 (2017) 403–407. 10.1016/j.jtho.2016.10.007. [PubMed: 27765535]

[16]. Sabari JK, Leonardi GC, Shu CA, Umeton R, Montecalvo J, Ni A, Chen R, Dienstag J, Mrad C, Bergagnini I, Lai VW, Offin M, Arbour KC, Ploedkowski AJ, Halpenny DF, Paik PK, Li BT, Riely GJ, Kris MG, Rudin CM, Sholl LM, Nishino M, Hellmann MD, Rekhtman N, Awad MM, Drilon A, PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers, Ann. Oncol 29 (2018) 2085–2091, 10.1093/annonc/mdy334. [PubMed: 30163571]

[17]. Pruis MA, Geurts-Giele WRR, van der TJH, Meijssen IC, Dijnuts WNM, V Aerts JGJ, Dingemans AMC, Lolkema MP, Paats MS, Dubbink HJ, Highly accurate DNA-based detection and treatment results of MET exon 14 skipping mutations in lung cancer, Lung Cancer. 140 (2020) 46–54. Doi: 10.1016/j.lungcan.2019.11.010. [PubMed: 31862577]

[18]. Wolf J, Baik C, Heist RS, Neal JW, Mansfield AS, Buettner R, Davis KL, Giovanni M, Mutebi A, Awad MM, Natural history, treatment (tx) patterns, and outcomes in MET dysregulated non-small cell lung cancer (NSCLC) patients (pts), in: EORTC/ACCR/NCI Symp., Dublin, 2018: p. PB–066.

[19]. Awad MM, Leonardi GC, Kravets S, Dahlberg SE, Drilon A, Noonan SA, Camidge DR, Ou SHI, Costa DB, Gadgeel SM, Steuer CE, Forde PM, Zhu VW, Fukuda Y, Clark JW, Janne PA, Mok T, Sholl LM, Heist RS, Impact of MET inhibitors on survival among patients with non-small cell lung cancer harboring MET exon 14 mutations: a retrospective analysis, Lung Cancer. 133 (2019) 96–102. 10.1016/j.lungcan.2019.05.011. [PubMed: 31200835]

[20]. Landi L, Chiari R, Tiseo M, D’Inca F, Dazzi C, Chella A, Delmonte A, Bonanno L, Giannarelli D, Cortinovis DL, de Marinis F, Borra G, Morabito A, Gridelli C, Galetta D, Barbieri F, Grossi F, Capelletti E, Minuti G, Mazzoni F, Verusio C, Bria E, Al G, Bruno R, Piogett A, Fontanini G, Crino L, Cappuzzo F, Crizotinib in MET-deregulated or ROS1-rearranged pretreated non–small cell lung cancer (METROS): A phase II, prospective, multicenter, two-arms trial, Clin. Cancer Res 25 (2019) 7312–7319, 10.1158/1078-0432.CCR-19-0994. [PubMed: 31416808]

[21]. Hur JY, Ku BM, Shim JH, Jung HA, Sun J-MM, Lee S-HH, Ahn JS, Park K, Ahn M-JJ, Characteristics and clinical outcomes of non-small cell lung cancer patients in Korea with MET exon 14 skipping, In. Vivo 34 (2020) 1399–1406, 10.21873/invivo.11920. [PubMed: 32354937]

[22]. Kalemkerian GP, Narula N, Kennedy EB, Biermann WA, Donington J, Leighl NB, Lew M, Pantelas J, Ramalingam SS, Reck M, Saqi A, Simoff M, Singh N, Sundaram B, Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American society of clinical oncology endorsement of the college of American pathologists/international association for the study of lung cancer/association for molecular pathology clinical practice guideline update, J. Clin. Oncol 36 (2018) 911–919, 10.1200/JCO.2017.76.7293. [PubMed: 29401004]

[23]. Schwartz LH, Litière S, De Vries E, Ford R, Gwyther S, Mandrekar S, Shankar L, Bogaerts J, Chen A, Dancey J, Hayes W, Hodi FS, Hoekstra OS, Huang EP, Lin N, Liu Y, Therasse P, Wolchok JD, Seymour L, RECIST 1.1 - Update and clarification: From the RECIST committee, Eur. J. Cancer 62 (2016) 132–137. Doi: 10.1016/j.ejca.2016.03.081. [PubMed: 27189322]

[24]. Song P, Zhang J, Shang C, Zhang L, Real-world evidence and clinical observations of the treatment of advanced non-small cell lung cancer with PD-1/PD-L1 inhibitors, Sci. Rep 9 (2019) 4728, 10.1038/s41598-019-04748-7. [PubMed: 30894612]

[25]. Blumenthal GM, Gong Y, Kehl K, Mishra-Kalyani P, Goldberg KB, Khozin S, Kluzt PG, Oxnard GR, Pazdur R, Analysis of time-to-treatment discontinuation of targeted therapy, immunotherapy, and chemotherapy in clinical trials of patients with non-small-cell lung cancer, Ann. Oncol 30 (2019) 830–838, 10.1093/annonc/mdz060. [PubMed: 30796424]

[26]. Gong Y, Kehl KL, Oxnard GR, Khozin S, Mishra-Kalyani PS, Blumenthal GM, Time to treatment discontinuation (TTD) as a pragmatic endpoint in metastatic non-small cell lung cancer (mNSCLC): A pooled analysis of 8 trials, J. Clin. Oncol 36 (2018) 9064, 10.1200/jco.2018.36.15_suppl.9064.
[27]. Digumarthy SR, Mendoza DP, Zhang EW, Lennerz JK, Heist RS, Clinicopathologic and imaging features of non-small-cell lung cancer with MET exon 14 skipping mutations, Cancers (Basel). 11 (2019) 1–11, 10.3390/cancers11202033.

[28]. Camidge DR, Kim HR, Ahn MJ, Yang JCH, Han JY, Lee JS, Hochmair MJ, Li JYC, Chang GC, Lee KH, Gridelli C, Delmonte A, Garcia-Campelo R, Kim DW, Bearz A, Griesinger F, Morabito A, Felip E, Califano R, Ghosh S, Spira A, Gettinger SN, Tiseo M, Gupta N, Haney J, Kerstein D, Popat S, Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer, N. Engl. J. Med 379 (2018) 2027–2039. Doi: 10.1056/NEJMoa1810171. [PubMed: 30280657]

[29]. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez P, Pallares C, Sanchez JM, Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial, Lancet Oncol. 13 (2012) 239–246, 10.1016/S1470-2045(11)70393-X. [PubMed: 22285168]

[30]. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez P, Pallares C, Sanchez JM, Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial, Lancet Oncol. 13 (2012) 239–246, 10.1016/S1470-2045(11)70393-X. [PubMed: 22285168]

[31]. Mok TS, Wu Y-L, Thongprasert S, Yang C-H, Chu D-T, Saijo N, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins C, Armour AA, Fukuoka M, Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma, N. Engl. J. Med 361 (2009) 947–957, 10.1056/NEJMoa0810699. [PubMed: 19692680]

[32]. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nagomi N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchar D, Su WC, Gray JE, Lee SM, Hodge R, Marotti M, Rukazenkov Y, Ramalingam SS, Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer, N. Engl. J. Med 378 (2018) 113–125, 10.1056/NEJMoa1713137. [PubMed: 29151359]

[33]. Shaw AT, Gandhi L, Gadgeel S, Riely GJ, Cetnar J, West H, Camidge DR, Socinski MA, Chiappori A, Mekhail T, Chao BH, Borghaei H, Gold KA, Zeaeter A, Bordogna W, Balas B, Puig O, Henschel V, Ou S-H, Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial, Lancet Oncol. 17 (2016) 234–242, 10.1016/S1470-2045(15)00488-X. [PubMed: 26708155]

[34]. Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, Seto T, Takiguchi Y, Nishio M, Yoshioka H, Imamura F, Hotta K, Watanabe S, Goto K, Satouchi M, Shimizu H, Nakagawa K, Matsudomi T, Yamamoto N, Asakura T, Asabe R, Tanaka T, Tamura T, Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial, Lancet. 390 (2017) 29–39, 10.1016/S0140-6736(17)30565-2. [PubMed: 28501140]

[35]. Meng H, Guo X, Sun D, Liang Y, Lang J, Han Y, Lu Q, Zhang Y, An Y, Tian G, Yuan D, Xu S, Geng J. Genomic profiling of driver gene mutations in Chinese patients with non-small cell lung cancer, Front. Genet 10 (2019) 1008, 10.3389/fgene.2019.01008. [PubMed: 31749831]

[36]. Cheng Y, He Y, Li W, Zhang H, Zhou Q, Wang B, Liu C, Walding A, Saggese M, Huang X, Fan M, Wang J, Ramalingam SS, Osimertinib versus comparator EGFR TKI as first-line treatment for EGFR-mutated advanced NSCLC: FLAURA China, a randomized study, Target. Oncol (2021) 165–176, 10.1007/s11523-021-00794-6. [PubMed: 33544337]

[37]. Lung J, Hung MS, Lin YC, Lee KF, Jiang YY, Huang SL, Fang YH, Lu MS, Lin CK, Yang TM, Lin PY, Hsieh MJ, Tsai YH, MET exon 14 skipping mutations and gene amplification in a Taiwanese lung cancer population, PLoS One. 14 (2019), e0220670, 10.1371/journal.pone.0220670. [PubMed: 31369639]

[38]. Awad MM, Oxnard GR, Jackman DM, Savukoski DO, Hall D, Shviddasani P, Heng JC, Dahlberg SE, Janne PA, Verma S, Christensen J, Hammerman PS, Sholl LM, 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 34 (2016) 721–730, 10.1200/JCO.2015.63.4600. [PubMed: 26729443]
[39]. Noonan SA, Berry L, Lu X, Gao D, Barón AE, Chesnut P, Sheren J, Aisner DL, Merrick D, Doebele RC, Varella-Garcia M, Camidge DR, Identifying the appropriate FISH criteria for defining MET copy number-driven lung adenocarcinoma through oncogene overlap analysis, J. Thorac. Oncol 11 (2016) 1293–1304, 10.1016/j.jtho.2016.04.033. [PubMed: 27262212]

[40]. Mazieres J, Drilon A, Lusque A, Mhanna L, Cortot AB, Mezquita L, Thai AA, Mascaux C, Couraud S, Veillon R, Van den Heuvel M, Neal J, Peled N, Früh M, Ng TL, Gounant V, Popat S, Diebold J, Sabari J, Zhu VW, Rothchild SI, Bironzo P, Martinez-Marti A, Curioni-Fontecedro A, Rosell R, Lattuca-Truc M, Wiesweg M, Besse B, Solomon B, Barlesi F, Schouten RD, Wakelee H, Camidge DR, Zaleman G, Novello S, Ou SI, Milia J, Gautschi O. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: Results from the IMMUNOTARGET registry, Ann. Oncol 30 (2019) 1321–1328, 10.1093/annonc/mdz167. [PubMed: 31125062]

[41]. Paik P, Felip E, Veillon R, Sakai H, Cortot AB, Garassino MC, Mazieres J, Viteri S, Senellart H, Van Meerbeeck J, Raskin J, Reinmuth N, Conte P, Kowalski D, Cho BC, Patel JD, Horn L, Griesinger F, Han JY, Kim YC, Chang GC, Tsai CL, Yang JC, Chen YM, Smit EF, van der Wekken AJ, Kato T, Juraeva D, Stroh C, Bruns R, Straub J, Johne A, Scheele J, Heymach JV, Le X. Teptotitinib in non-small-cell lung cancer with MET exon 14 skipping mutations, N. Engl. J. Med 383 (2020) 931–943, 10.1056/NEJMoa2004407. [PubMed: 32469185]

[42]. Wolf J, Seto T, Han JY, Reguart N, Garon EB, Groen HJM, Tan DSW, Hida T, de Jonge M, Orlof SV, Smit EF, Souquet PJ, Vansteenkiste J, Hochmair M, Felip E, Nishio M, Thomas M, Ohashi K, Toyozawa R, Overbeck TR, de Marinis F, Kim TM, Laack E, Rrobeva A, Le Mouhaer S, Waldron-Lynch M, Sankaran B, Balbin OA, Cui X, Giovannini M, Akimov M, Heist RS, Capmatinitib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer, N. Engl. J. Med 383 (2020) 944–957, 10.1056/NEJMoa2002787. [PubMed: 32877583]

[43]. Drilon A, Clark JW, Weiss J, Ou SHI, Camidge DR, Solomon BJ, Otterson GA, Villaruz LC, Riely GJ, Heist RS, Awad MM, Shapiro GI, Satouchi M, Hida T, Hayashi H, Murphy DA, Wang SC, Li S, Usari T, Wilner KD, Paik PK, Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration, Nat. Med 26 (2020) 47–51, 10.1038/s41591-019-0716-8. [PubMed: 31932802]

[44]. Bylicki O, Paleiron N, Assié JB, Chouaid C. Targeting the MET-signaling pathway in non-small–cell lung cancer: Evidence to date, Onco. Targets. Ther 13 (2020) 5691–5706, 10.2147/OTT.S219959. [PubMed: 32606781]

[45]. Center for Drug Evaluation and Research, Novartis Multi-Country Chart Review Study, (2019). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213591Orig1s000AdminCorres.pdf (accessed January 7, 2021).

[46]. Guisier F, Dubos-Arvis C, Viñas F, Dohre H, Ricordel C, Ropert S, Janicot H, Bernardi M, Fournel P, Lamy R, Pérol M, Dauba J, Gonzales G, Falchero L, Decroissette C, Assouline P, Chouaid C, Bylicki O. Efficacy and safety of anti–PD-1 immunotherapy in patients with advanced NSCLC with BRAF, HER2, or MET mutations or RET translocation: GFPC 01-2018, J. Thorac. Oncol 15 (2020) 628–636, 10.1016/j.jtho.2019.12.129. [PubMed: 31945494]

[47]. Ono J, Chihara Y, Uchino J, Shimamoto T, Morimoto Y, Iwasaku M, Kaneko Y, Yamada T, Takayama K. Immune checkpoint inhibitors for lung cancer treatment: A review, J. Clin. Med 9 (2020) 1362, 10.3390/jcm9051362.

[48]. Simeone JC, Nordstrom BL, Patel K, Klein AB. Treatment patterns and overall survival in metastatic non-small-cell lung cancer in a real-world, US setting, Futur. Oncol 15 (2019) 3491–3502, 10.2217/fon-2019-0348.
Fig. 1.
Treatment patterns for the METex14 skipping cohort within first-, second- and third-line therapy. *N = 70 for patients with METex14 NSCLC. ICI, immune checkpoint inhibitor; METex14, MET exon 14; NSCLC, non-small cell lung cancer; TNTD, time to next treatment or death.
Fig. 2.
Treatment patterns for the MET-amplification cohort within first-, second- and third-line therapy. *N = 47 for patients with MET-amplified NSCLC. ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; TNTD, time to next treatment or death.
Fig. 3.
ORR for the first and second line of therapy among patients with METex14 skipping alterations (a) or MET amplification (b). Loosened = ORR was calculated including RECIST responses (favorable or unfavorable response). CI, confidence interval; METex14, MET exon 14; ORR, overall response rate; RECIST, Response Evaluation Criteria In Solid Tumors.

| (a)     | ORR criteria | Events/total | ORR (95% CI) |
|---------|--------------|--------------|--------------|
| **First-line treatment (any)** |              |              |              |
| Primary analysis | RECIST      | 5/18         | 27.8 (9.7, 53.5) |
| Sensitivity analysis | Loosened    | 11/37        | 29.7 (15.9, 47.0) |
| **Second-line treatment (any)** |              |              |              |
| Primary analysis | RECIST      | 3/10         | 30.0 (6.7, 65.2) |
| Sensitivity analysis | Loosened    | 3/17         | 17.6 (3.8, 43.4) |

| (b)     | ORR criteria | Events/total | ORR (95% CI) |
|---------|--------------|--------------|--------------|
| **First-line treatment (any)** |              |              |              |
| Primary analysis | RECIST      | 9/25         | 36.0 (18.0, 57.5) |
| Sensitivity analysis | Loosened    | 12/31        | 36.7 (21.8, 57.8) |
| **Second-line treatment (any)** |              |              |              |
| Primary analysis | RECIST      | 4/18         | 22.2 (6.6, 47.6) |
| Sensitivity analysis | Loosened    | 5/21         | 23.8 (8.2, 47.2) |

Lung Cancer. Author manuscript; available in PMC 2022 August 02.
**Fig. 4.**
Time to next treatment or death from start of the first or second line of therapy in patients with \( METex14 \) skipping alterations. \( METex14 \), \( MET \) exon 14.
Fig. 5.
Overall survival from start of first or second line of therapy in patients with METex14 skipping alterations (a) or MET amplification (b). METex14, MET exon 14.
Table 1
Demographics and clinical characteristics of patients with advanced NSCLC and MET alterations.

| Characteristics                                      | METex14 cohort (n = 70) | METamp cohort (n = 47) |
|------------------------------------------------------|-------------------------|-----------------------|
| Age; n                                               |                         |                       |
| Median (Q1, Q3)                                      | 74.2 (66.8, 78.8)       | 63.1 (55.8, 70.5)     |
| BMI (kg/m²)                                          | n = 52                  | n = 29                |
| Median (Q1, Q3)                                      | 24.6 (21.7, 27.7)       | 23.7 (21.4, 28.9)     |
| Gender, n (%)                                        |                         |                       |
| Male                                                 | 36 (51.4)               | 32 (68.1)             |
| Female                                               | 34 (48.6)               | 15 (31.9)             |
| Race, n (%)                                          |                         |                       |
| White                                                | 41 (58.6)               | 40 (85.1)             |
| Asian                                                | 24 (34.3)               | 2 (4.3)               |
| Black or African American                            | 1 (1.4)                 | 3 (6.4)               |
| Not collected at site or unknown                     | 4 (5.7)                 | 2 (4.3)               |
| Tobacco smoking status, n (%)                        |                         |                       |
| Never smoker                                         | 33 (47.1)               | 7 (14.9)              |
| Former or current smoker                             | 34 (48.6)               | 37 (78.7)             |
| Unknown                                              | 3 (4.3)                 | 3 (6.4)               |
| Time from initial to advanced diagnosis, n (%)       | n = 65                  | n = 40                |
| Advanced stage at initial diagnosis or < 6 months    | 55 (84.6)               | 36 (90.0)             |
| 6 months – <1 year                                   | 1 (1.5)                 | 1 (2.5)               |
| ≥1 year                                              | 9 (13.9)                | 3 (7.5)               |
| Stage at initial diagnosis of NSCLC, n (%)           | n = 67                  | n = 45                |
| Stages I–IIIA                                        | 12 (18.0)               | 9 (20.0)              |
| Stages IIIB–IV                                       | 55 (82.0)               | 36 (80.0)             |
| Histology at initial diagnosis of NSCLC, n (%)       | n = 69                  | n = 45                |
| Adenocarcinoma                                       | 58 (84.1)               | 37 (82.2)             |
| Sarcomatoid carcinoma                                | 4 (5.8)                 | 1 (2.2)               |
| NSCLC NOS                                            | 4 (5.8)                 | 4 (8.9)               |
| Squamous cell carcinoma                              | 1 (1.4)                 | 1 (2.2)               |
| Other                                                | 2 (2.9)                 | 1 (2.2)               |
| Stage of disease of advanced or metastatic NSCLC (study index); n (%) | | |
| Stage IIIB                                           | 9 (12.9)                | 8 (17.0)              |
| Stage IV                                             | 61 (87.1)               | 39 (83.0)             |
| Brain metastases; n (%)                              | n = 52                  | n = 28                |
| Present                                              | 10 (19.0)               | 7 (25.0)              |
| Performance status; n (%)                            | n = 38                  | n = 36                |
| ECOG 0–1                                            | 30 (78.9)               | 31 (86.1)             |
| ECOG 2–3                                            | 8 (21.1)                | 3 (8.3)               |
| ECOG 4                                               | 0                       | 2 (5.6)               |

Lung Cancer. Author manuscript; available in PMC 2022 August 02.
| Characteristics                                  | METex14 cohort (n = 70) | METamp cohort (n = 47) |
|------------------------------------------------|-------------------------|-----------------------|
| **Number of comorbid conditions present at the time of initial diagnosis; n (%)** |                         |                       |
| None                                           | 31 (44.3)               | 25 (53.2)             |
| 1–3 comorbidities                              | 34 (48.6)               | 19 (40.4)             |
| >4 comorbidities                               | 5 (7.1)                 | 3 (6.4)               |
| **Most frequent comorbid conditions present at the time of initial diagnosis; n (%)** |                         |                       |
| Diabetes uncomplicated                         | 7 (10.0)                | 3 (6.4)               |
| Chronic obstructive pulmonary disease          | 6 (8.6)                 | 6 (12.8)              |
| Peripheral vascular disease                    | 6 (8.6)                 | 1 (2.1)               |
| **Past history of neoplasm other than NSCLC; n (%)** |                         |                       |
| Yes                                            | 6 (8.6)                 | 9 (19.1)              |

All values are n (%) unless otherwise stated. N numbers are given for where the sample size is less than the total due to missing data.

*ECOG PS 1 was based on Karnofsky assessment for seven METex14 patients and one MET amplified patient. BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; METamp, MET amplification; METex14, MET exon 14; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; Q, quartile.
Table 2

Biomarker details for the study cohorts.

| Characteristics                              | METex14 patients (n = 70) | METamp patients (n = 47) |
|----------------------------------------------|----------------------------|--------------------------|
| **Type of tumor biopsy test**, n (%)         |                            |                          |
| Tissue                                       | 57 (81.4)                  | 36 (76.6)                |
| Liquid                                       | 14 (20.0)                  | 12 (25.5)                |
| **Method of MET testing**, n (%)              |                            |                          |
| Next-generation sequencing                   | 42 (60.0)                  | 21 (44.7)                |
| Real-time polymerase chain reaction          | 25 (35.7)                  | 0                        |
| DNA sequencing                               | 2 (2.9)                    | 0                        |
| Polymerase chain reaction                    | 1 (1.4)                    | 0                        |
| Fluorescence in situ hybridization           |                            | 26 (55.3)                |
| **MET amplification (yes), n (%)**           | 47 (100)                   |                          |
| **Results of MET amplification test, n (%)** |                            |                          |
| Positive                                     | –                          | 16 (34.0)                |
| Strongly positive                            | –                          | 11 (23.4)                |
| Very strongly positive                       | –                          | 8 (17.0)                 |
| Unknown                                      | –                          | 12 (25.5)                |
| **MET amplification: gene copy number, n (%)** | 4 (5.7)                   | 47 (100)                 |
| Median (range)                               | 2.8 (0.7 to 5.3)           | –                        |
| 2–8                                         | –                          | 17 (36.2)                |
| 8–10                                        | –                          | 1 (2.1)                  |
| >10                                         | –                          | 4 (8.5)                  |
| Unknown                                     | 25 (53.2)                  |                          |
| **EGFR test (yes), n (%)**                   | 33 (47.1)†                | 43 (91.5)                |
| Identified alterations                       | 2 (6.1)                    | 5 (11.6)                 |
| L858R                                       | 1 (3.0)                    | –                        |
| I744F substitution                           | –                          | 1 (2.3)                  |
| T790 mutation                               | –                          | 3 (7.0)                  |
| c.2361G > A                                 | –                          | 1 (2.3)                  |
| EGFR amplification – equivocal               | 1 (3.0)                    |                          |
| **KRAS test (yes), n (%)**                   | 22 (31.4)                  | 38 (80.9)                |
| Identified alterations                       | 3 (13.6)                   | 5 (13.2)                 |
| D47H                                        | 1 (4.5)                    | –                        |
| G12D                                        | 1 (4.5)                    | 1 (2.6)                  |
| G12C                                        | 1 (4.5)                    | –                        |
| Q61H                                        | –                          | 1 (2.6)                  |
| Substitution                                | –                          | 1 (2.6)                  |
| Missense variant – GOF                      | –                          | 1 (2.6)                  |
| **ALK test (yes), n (%)**                    | 29 (41.4)                  | 41 (87.2)                |
| Characteristics                        | METex14 patients (n = 70) | METamp patients (n = 47) |
|---------------------------------------|--------------------------|-------------------------|
| Identified alterations                | 1 (3.4)                  | 3 (7.3)                 |
| EML4-ALK fusion                      | –                        | 2 (4.9)                 |
| ALK L1152V                            | –                        | 1 (2.4)                 |
| H976N                                 | 1 (3.4)                  | –                       |
| **ROS proto-oncogene 1 test (yes), n (%)** | 22 (31.4)               | 36 (76.6)               |
| Identified alterations                | –                        | 3 (8.3)                 |
| Chromosome 6q22                       | –                        | 2 (5.6)                 |
| **PD-L1 test (yes), n (%)**           | 15 (21.4)                | 19 (40.4)               |
| PD-L1 expression **<sup>**</sup>      | 11 (73.3)                | 8 (42.1)                |
| **CDK6 test (yes), n (%)**            | 5 (7.1)                  | 14 (29.8)               |
| Identified alterations                | 1 (20.0)                 | 4 (28.6)                |
| **BRAF test (yes), n (%)**            | 16 (22.9)                | 28 (59.6)               |
| Identified alterations                | 0                        | 4 (14.3)                |

* Results can be overlapping as patients could test positive by more than one method.

† EGFR mutations may also have been included in NGS testing.

** Level of PD-L1 expression: NA.

All values are n (%). N numbers are given for where the sample size is less than the total due to missing data. ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; CDK6, cell division protein kinase 6; EGFR, epidermal growth factor receptor; KRAS, Kirsten Rat Sarcoma virus; METamp, MET amplification; METex14, MET exon 14; NA, not available; PD-L1, programmed death-ligand 1; ROS, reactive oxygen species.