Safety, efficacy, and biomarker analysis of crizotinib in MET-mutated non-small cell lung cancer-results from the drug rediscovery protocol

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Safety, Efficacy, and Biomarker Analysis of Crizotinib in MET-Mutated Non–Small Cell Lung Cancer—Results from the Drug Rediscovery Protocol

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ABSTRACT

Purpose: To provide patients with *MET*-mutated advanced non–small cell lung cancer (*MET*mut aNSCLC) access to crizotinib, further substantiate evidence of its efficacy and safety in this setting, and find potential biomarkers for nonresponse.

Patients and Methods: In the Drug Rediscovery Protocol (NCT0295234), patients with an actionable molecular profile are treated with off-label registered drugs. Both treated and untreated patients with aNSCLC harboring *MET* exon 14 skipping or other *MET* mutations received crizotinib 250 mg BID until disease progression or intolerable toxicity. Primary endpoints were clinical benefit [CB: RECIST v1.1 confirmed partial response, complete response (CR), or stable disease ≥16 weeks] and safety. Patients were enrolled using a Simon-like two-stage design, with eight patients in stage I and if ≥1/8 patients had CB, 24 patients in stage II. Whole-genome sequencing and RNA sequencing were performed on baseline biopsies.

Results: Between September 2018 and October 2022, 30 patients started treatment, and 24 were response-evaluable after completing ≥1 full treatment cycle. Two patients (8.3%) achieved CR, 13 (54.2%) partial response, and two (8.3%) stable disease. The CB rate was 70.8% [95% confidence interval (CI), 48.9–87.4], and the objective response rate was 62.5% (95% CI, 40.6–81.2). After 21.2-month median follow-up, median duration of response, progression-free survival, and overall survival were 9.3 (95% CI, 6.5–not available), 10.2 (95% CI, 6.0–20.1), and 13.0 months (95% CI, 9.0–not available), respectively. Twenty-three treatment-related grade ≥ 3 adverse events occurred in 12/30 patients (40%), causing treatment discontinuation in three (10%). One patient (achieving CR) had a tyrosine kinase domain mutation (p.H1094Y), and all other patients had *MET* exon 14 skipping mutations.

Conclusions: Crizotinib is a valuable treatment option in *MET*mut aNSCLC.

Introduction

With 1.80 million deaths estimated annually, lung cancer is the leading cause of cancer-related mortality worldwide (1). The disease is histologically and molecularly heterogeneous, with non–small cell lung cancer (NSCLC) being the major histologic subtype, comprising approximately 85% of lung cancers (2). Molecularly, approximately 60% of advanced NSCLCs (aNSCLC) in a Western population harbor an actionable oncogenic driver, including *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *ERBB2*, and *MET* (3). For many patients with these oncogene-driven aNSCLCs, the advent of molecularly targeted therapies has transformed outcomes and resulted in major improvements in survival (4).

MET emerges as an oncogenic driver in 3% to 4% of aNSCLCs (2, 5–8). The *MET* gene encodes the hepatocyte growth factor receptor (c-MET), which—upon binding of hepatocyte growth factor—induces downstream signaling to the RAS–RAF and PI3K pathways (7–9). Although controlled c-MET signaling is vital for e.g., embryonic development, tissue regeneration, and wound healing, pathologic c-MET activation promotes tumor

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Translational Relevance

MET mutations, present in 3% to 4% of advanced non–small cell lung cancer cases, correlate with poor survival. Despite known sensitivity to c-MET inhibition, no approved therapies existed for this indication until 2022. To provide patients' access to this promising treatment, a cohort to treat *MET*-mutated advanced non–small cell lung cancer with crizotinib was established in the Drug Rediscovery Protocol (NCT02925234). This cohort aimed to substantiate evidence of crizotinib's efficacy and safety and identify potential biomarkers for nonresponse. With an objective response rate of 62.5% and median duration of response of 9.3 months, crizotinib proved highly effective in this population. Numerically, crizotinib performed comparably to the newer generation c-MET inhibitors (i.e., tepotinib and capmatinib), with a toxicity profile including less severe edema but more hepatobiliary adverse events. No genomic or transcriptomic biomarkers to refine patient selection could be discovered, but *MET* tyrosine kinase domain mutations were confirmed as a rare but valuable target for c-MET inhibition.

proliferation, invasive growth, and angiogenesis (6). Oncogenic c-MET signaling can be caused by *MET* exon 14 skipping (*MET*ex14) mutations, *MET* mutations (*MET*muts) in the tyrosine kinase domain (TKD), *MET* gene amplification, and/or c-MET protein overexpression. *MET*ex14 mutations are the most commonly reported oncogenic *MET*muts and refer to any event causing fusion of exon 13 and exon 15 in mature mRNA, including alterations in the intronic regions surrounding exon 14, alteration within exon 14 itself, or complete genomic deletion of exon 14 (6). *MET* exon 14 encodes the protein's intracellular juxta membrane domain, which contains negative regulatory mechanisms essential for its degeneration (6, 9). Therefore, lack of exon 14 leads to enriched c-MET signaling and oncogenic potential (9).

Before the widespread adaptation of c-MET inhibitors, *MET* alterations were associated with poor prognosis in patients with aNSCLC (10–12). The standard of care was platinum-based combination chemotherapy with or without immune checkpoint blockade (ICB) or solely ICB in case of ≥50% PD-L1 expression on tumor cells (2, 13). However, in line with other types of oncogene-driven aNSCLC, the outcomes of ICB in patients with *MET*ex14 aNSCLC are disappointing (11, 14–16). Sabari and colleagues (14) observed an objective response rate (ORR) of 17% [95% confidence interval (95% CI), 3–39] in 24 patients with *MET*ex14 aNSCLC treated with ICB, with a median progression-free survival (PFS) of 1.9 months (95% CI, 1.7–2.7). Responses were not enriched in patients with high PD-L1 expression ($N = 2/11$, 18%) or high tumor mutational burden ($N = 0/8$, 0%; ref. 14).

Targeted therapy is usually recommended over ICB in oncogene-driven aNSCLC, regardless of PD-L1 status (17). Yet, prior to the registration of capmatinib and tepotinib in 2020 and 2021, there were no FDA- or European Medicines Agency–approved therapies for *MET*-driven aNSCLC (13). In 2007, the oral tyrosine kinase inhibitor (TKI) crizotinib showed *in vitro* cytoreductive activity against *MET*-altered cell lines across different tumor types (18). Crizotinib is currently approved for *ALK*-positive and *ROS1*-positive aNSCLC (19, 20). When its off-label use expanded, evidence of crizotinib's clinical efficacy in patients with *MET*-altered aNSCLC rapidly accumulated (21–25).

To provide patients' access to this promising treatment, further substantiate evidence of its efficacy and safety, and find potential biomarkers for nonresponse, a cohort for patients with *MET* mutated (*MET*mut) aNSCLC was established in the Drug Rediscovery Protocol (DRUP; NCT02925234). Here, we present the results of this cohort.

Patients and Methods

Study design

The DRUP is an ongoing, prospective, multicenter, non-randomized basket and umbrella trial in which patients with advanced solid tumors are treated with approved targeted therapies or immunotherapy matched to their molecular profile, but outside their registered indication (26). The design allows for an unlimited number of parallel cohorts, each defined by a molecular target, a matched study drug, and a histologic tumor type (although several histology agnostic cohorts exist). DRUP was approved by the Medical Ethical Committee at the Netherlands Cancer Institute in Amsterdam, the Netherlands, and by the institutional review boards of every participating hospital. The study is conducted in accordance with the International Conference of Harmonization of Good Clinical Practice and the Declaration of Helsinki.

Patient population

Adult patients with aNSCLC harboring *MET*ex14 or other pathogenic *MET*muts (determined by consensus between two experienced clinical molecular biologists in pathology), detected in routine molecular diagnostics, were eligible for enrollment. For this cohort in DRUP, the general DRUP inclusion and exclusion criteria applied (26). Additional, drug-specific exclusion criteria included (i) eligibility for on-label treatment with crizotinib or for ongoing phase II/III trials, (ii) hypersensitivity to the drug or any of the excipients, (ii) significant cardiac comorbidity within the last 3 months prior to start of study treatment, (iv) ongoing cardiac dysrhythmias, (v) history of interstitial fibrosis/interstitial lung disease, and (vi) use of drugs or foods that are known CYP3A4 inhibitors or substrates. Patients with known active progressive brain metastases were excluded, except for those who received previous treatment and were stable and off-treatment for at least 1 month prior to registration. Given the aforementioned limited efficacy of standard of care in *MET*mut aNSCLC (11, 14–16), previous systemic treatment was not obligatory to be eligible for this cohort.

Study procedures

Patients provided written informed consent upon enrollment. If all inclusion and exclusion criteria were met, a new fresh-frozen tumor biopsy and a 10-mL blood sample were obtained by the participating hospital and subsequently sent to Hartwig Medical Foundation (Hartwig), Amsterdam, the Netherlands. Patients then received crizotinib tablets 250 mg twice daily in 28-day cycles until disease progression or intolerable toxicity. Dose reductions were allowed up to a minimum dose of 250 mg once daily, adhering to the summary of product characteristics. Tumor assessments were performed at baseline and after every second treatment cycle. Central nervous system imaging was mandatory only for patients with previously known brain metastasis or those who experienced symptoms indicative of brain metastasis. If patients were on

treatment for more than 6 months, tumor assessments were performed after every three cycles.

Study endpoints

The primary endpoints of the study are clinical benefit (CB)—defined as confirmed partial or complete response (PR; CR) or stable disease (SD) for at least 16 weeks according to RECIST v1.1 (27)—and safety. For the latter, serious and treatment-related Common Terminology Criteria for Adverse Events version 4.03 grade ≥ 3 adverse events (TRAE) from registration until 1 month after the last dose of study drug were assessed. Safety within the trial is monitored by an independent data monitoring committee, which is blinded for response rates during accrual. Secondary endpoints include ORR (defined as CR or PR), duration of response (DoR), PFS, and overall survival (OS). Exploratory endpoints include extensive *post hoc* biomarker analysis. All patients who started treatment were included in the safety analysis. Per protocol, patients who completed less than one full cycle of crizotinib (<28 days) were replaced for the efficacy and biomarker analyses.

Whole-genome sequencing

Sequencing of pretreatment biopsies, together with a matched blood sample to correct for germline variants, was performed by Hartwig as previously described (28). In brief, DNA was isolated according to the supplier's protocols (QIAGEN) using the DSP DNA Midi kit and QIAsymphony DSP DNA Mini kit for blood and tissue, respectively. Sequencing was performed on the Illumina NovaSeq (2 × 151 bp) platform with a median average depth of 106× (tumor) and 38× (blood). Samples that demonstrated a tumor cell percentage of <20% were excluded. Sequenced reads were mapped to the GRCh37 reference genome and subsequently processed using the Hartwig's in-house tools for somatic variant calling (SAGE), structural variant calling (GRIDSS), purity and ploidy estimations and driver calling (PURPLE) and copy number analysis (LINX). The optimized pipeline is publicly available (https://github.com/hartwigmedical/pipeline5; refs. 28, 29).

RNA sequencing

Total RNA was extracted using the QIAGEN QIAsymphony RNA kit. Samples with approximately 100 ng total RNA were prepared with KAPA RNA Hyper + RiboErase HMR, and RNA libraries were paired-end sequenced on the Illumina NextSeq550 platform (2 × 75 bp) or Illumina NovaSeq6000 platform (2 × 150 bp). Reads were first subjected to adapter removal and read length trimming using Cutadapt and subsequently mapped using STAR (v2.7.10a, RRID: SCR_004463) against the GRCh38 (GENCODE v35) human reference genome. Gene counts were then computed using featureCounts (v2.0.1, RRID: SCR_012919). Differential expression analysis was performed using R packages EdgeR (v3.40.2, RRID: SCR_012802; ref. 30) and Limma including Voom (v3.54.2, RRID: SCR_010943; ref. 31). After filtering raw read counts for lowly expressed genes, EdgeR was used to calculate normalization factors. Subsequently, Voom was used to calculate residuals and fit a smoothened curve to the $\sqrt{}$(residual standard deviation) by average gene expression. Lastly, differential expression of genes was calculated using a linear Limma model with empirical Bayes smoothing of SEs.

Statistical analysis

Within the DRUP, a Simon-like two-stage "admissible" monitoring plan is used to identify cohorts with evidence of clinical activity (32). Initially, eight patients are included. If at least one of them exhibits CB, an additional 16 patients are included. For these 24 patient stage II cohorts, four or fewer patients with CB would suggest lack of (clinically meaningful) activity, whereas at least five patients with CB would suggest that further investigation may be warranted in a confirmatory expansion cohort [stage III within the DRUP (33)]. The null hypothesis and alternative hypotheses to be tested in stage II are defined as CB rate (CBR) of 10% versus ≥30%. This monitoring rule has 85% power to reject the null hypothesis of 10% when the true CBR is 30%, with a one-sided alpha error rate of 7.8%.

Patient characteristics, tumor responses, and AEs were summarized using descriptive statistics. Exact 95% CIs of the CBR and ORR were calculated using the Clopper–Pearson method. Associations between OR and baseline characteristics or genomic markers were calculated with the Fisher's exact test (categorical variables), Wilcoxon's test (continuous variables), and linear by linear association test (ordinal variables). P values < 0.05 were considered statistically significant. The Kaplan–Meier method was used to estimate time on treatment, DoR, PFS, and OS. The reverse Kaplan–Meier method was used to estimate the duration of follow-up. All analyses were performed on R version 4.2.0. For RNA sequencing, FDRs were calculated using Benjamini–Hochberg correction of the obtained P values.

Data availability

The data described in this study are available for academic use upon request. Whole-genome sequencing (WGS) data can be obtained through the Netherlands Cancer Institute and Hartwig Medical Foundation. Procedures and requested forms can be found at https://www.hartwigmedicalfoundation.nl/en. An independent data access board will evaluate whether the intended use of the data is compatible with the consent given by the patients and whether there would be any applicable ethical or legal constraints. Clinical data can be obtained at a per-patient level by emailing the Institutional Review Board of the Netherlands Cancer Institute (IRB@nki.nl).

Results

Patients

Between September 28, 2018 and October 17, 2022, 44 cases of patients with *MET*mut aNSCLC were submitted to the central study team for review. Of these, 30 patients were eligible and started study treatment. Six patients completed less than one full cycle (28 days) of crizotinib. Per protocol, these patients were replaced for the efficacy and biomarker analyses but included in the safety analysis. At data cut-off (February 2024), crizotinib treatment was discontinued in 26/30 patients (86.7%). A full overview of accrual and follow-up is provided in Supplementary Fig. S1. Baseline characteristics of the included patients are summarized in **Table 1**. The median age in this cohort was 74.5 (70.3–78.0), the majority of the patients were male (N = 19, 63.3%), former smokers (N = 20, 66.7%), had adenocarcinoma (N = 23, 76.7%), and approximately two-third of the tumors were PD-L1 positive >50% (N = 20, 69.0%).

Efficacy

Among the 24 patients included in the efficacy analysis, the median duration of treatment was 8.0 months (95% CI, 6.3–21.2, **Fig. 1**). Two patients (8.3%) achieved a CR, 13 patients (54.2%) achieved a PR, and two patients (8.3%) had SD for ≥16 weeks. This

Table 1. Baseline characteristics.

	Started treatment *N* = 30	Included in efficacy analysis *N* = 24
Sex, *N* (%)		
Male	19 (63.3)	15 (62.5)
Female	11 (36.7)	9 (37.5)
Age, median (IQR)	74.5 (70.3–78.0)	74.5 (68.5–78.3)
ECOG performance status, *N* (%)		
0	7 (23.3)	6 (25.0)
1	16 (53.3)	12 (50.0)
2	7 (23.3)	6 (25.0)
Intracranial metastases, *N* (%)		
Brain	3 (10.0)	3 (12.5)
Leptomeningeal	2 (6.7)	2 (8.3)
None	25 (83.3)	19 (79.2)
Previous systemic treatment lines, *N* (%)		
0	23 (76.7)	19 (79.2)
1	5 (16.7)	3 (12.5)
3	2 (6.7)	2 (8.3)
Smoking status, *N* (%)		
Current	1 (3.3)	1 (4.2)
Former	20 (66.7)	14 (58.3)
Never	9 (30.0)	9 (37.5)
Histology, *N* (%)		
Adenocarcinoma	23 (76.7)	17 (70.8)
Squamous cell carcinoma	4 (13.3)	4 (16.7)
Other[a]	3 (10.0)	3 (12.5)
PD-L1 status, *N* (%)[b]		
<1%	4 (13.8)	3 (13.0)
1%–50%	5 (17.2)	4 (17.4)
>50%	20 (69.0)	16 (69.6)
Local *MET* testing, *N* (%)		
DNA and RNA based	9 (30.0)	7 (29.2)
DNA based	15 (50.0)	12 (50.0)
RNA based	6 (20.0)	5 (20.8)

Baseline characteristics of all patients who started treatment (and are included in the safety analysis) and all patients who completed at least one full cycle of 28 days of crizotinib treatment and are therefore included in the efficacy analysis.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

[a]Two patients with NSCLC not otherwise specified and one patient with undifferentiated NSCLC.

[b]Missing for one patient.

resulted in an ORR of 62.5% (95% CI, 40.6–81.2) and a CBR of 70.8% (95% CI, 48.9–87.4). Among the seven patients who did not have CB, one (4.2%) had progressive disease upon first response evaluation, two (8.3%) had an unconfirmed PR, and three (12.5%) had SD < 16 weeks. The last patient was not evaluable after SD measured at 9 weeks because the target lesions could no longer be measured reliably due to increased pleural effusion; the patient was on study without confirmed progression for 5.3 months. A decrease in the sum of the target lesions was observed in all but one patient (**Fig. 2**). The clinical characteristics did not differ significantly between patients who achieved an objective response and those that did not (Supplementary Table S1). None of the baseline intracranial metastases qualified as target lesions. During treatment, no intracranial lesions disappeared, and for two patients, they were the site of first progression (Supplementary Table S2). The time on treatment of the five patients with baseline intracranial metastasis ranged from 1.7 to 23.9 months. The median DoR was 9.3 months [95% CI, 6.5–not reached (NR)] in confirmed responders and 8.0 months (95% CI, 5.0–NR) in all responders. After a median follow-up of 21.2 months, the median PFS and OS were 10.2 months (95% CI, 6.0–20.1) and 13.0 months (95% CI, 9.0–NR), respectively (**Fig. 3**).

Although per protocol patients who completed less than one full treatment cycle (28 days) of crizotinib were replaced for the efficacy analysis, in order to increase comparability with other studies, we also performed an analysis of all patients who started crizotinib treatment ($N = 30$). Here, the resulting ORR is 50.0% ($N = 15/30$, 95% CI, 31.3–68.7), CBR is 56.7% ($N = 17/30$, 95% CI, 37.4–74.5), and median PFS and OS are 8.3 (95% CI, 5.7–17.9) and 10.2 months (95% CI, 7.4–NR), respectively.

Safety

The overall safety profile of crizotinib in all 30 patients who started treatment was comparable to what was expected based on the summary of product characteristics. A total of 23 unique TRAEs were reported in 12 patients (40%). These are listed in **Table 2**. Most TRAEs were hepatobiliary (i.e., elevated enzymes, autoimmune hepatitis) or concerned edema. There was one grade 5 TRAE, which was also reported as a suspected unsuspected serious adverse reaction. This involved a depressed level of consciousness due to an opioid intoxication following CYP3A4 inhibition caused by crizotinib. Three patients (10%) discontinued study treatment due to an AE, two of which included elevated liver transaminases and one nonviral hepatitis.

Biomarkers

WGS was available for 11 out of the 24 patients (46%) included in the efficacy analysis. For four (17%) other patients, no tissue was available and in nine patients (38%), the sequencing failed due to a low tumor cell percentage in the biopsy. For 10 patients with WGS (91%), additional RNA sequencing was available.

Five patients (17%) were included based on an insertion/deletion at the splice acceptor site of exon 14, 19 patients (63%) had a base substitution at the splice donor site, one patient (3.3%) had a mutation inside exon 14 (c.2935_2939del, p.H979fs*2), which led to exon 14 skipping on the RNA level, one patient (3.3%) was included based on a *MET* TKD mutation (c.3280C>T, p.H1094Y), and for four patients (13%), their exact *MET* alteration was unknown because they were included based on exon 14 skipping on RNA level, and they did not have WGS available (**Fig. 4A**; Supplementary Table S3). There was no apparent correlation between type of *MET* alteration and response. However, notably, the only patient who was included based on a TKD mutation achieved a CR. The concurrent genomic alterations revealed by WGS are shown in **Fig. 4B**. The most common non–*MET*-associated genomic alterations in the tumor involved *TP53* ($N = 5$, 45%), *CDK4*, *CDKN2A*, *MDM2*, *MUC16*, *MUC5B*, and *PIK3CA* (all $N = 4$, 36%). No significant association between any specific alteration and response was found. Furthermore, no correlation could be identified between response and *MET* copy number, sample purity adjusted variant allele frequency of the *MET* alteration, tumor mutational burden, and number of concurrent molecular drivers (likelihood ≥ 0.8) as determined by Hartwig's pipeline (**Fig. 4C–F**).

As for RNA, differential expression analysis revealed no hits that survived multiple hypothesis testing correction (Supplementary Table S4).

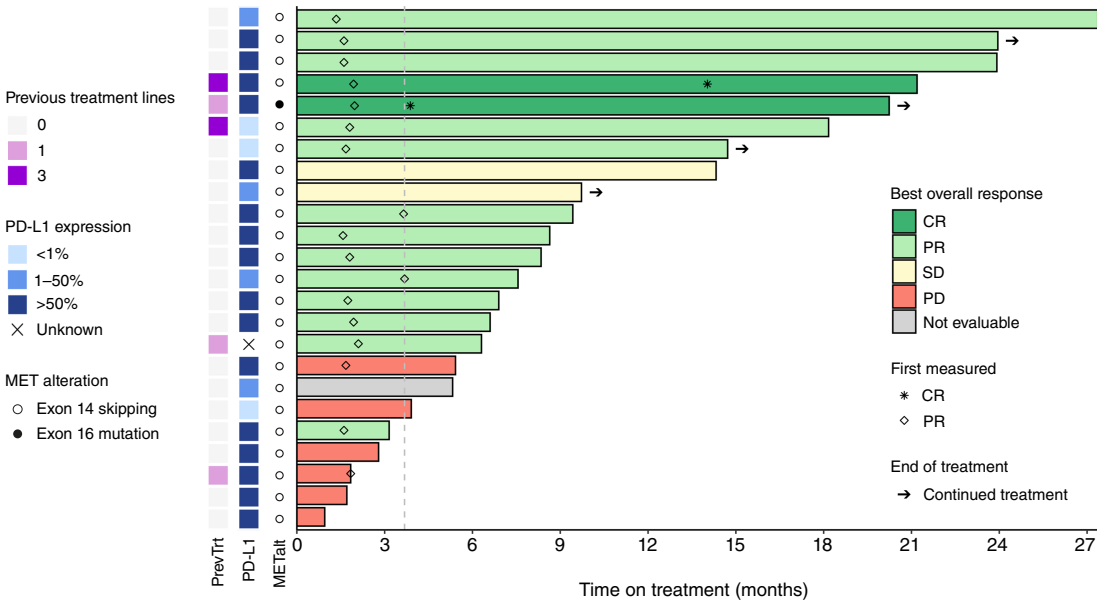


Figure 1.

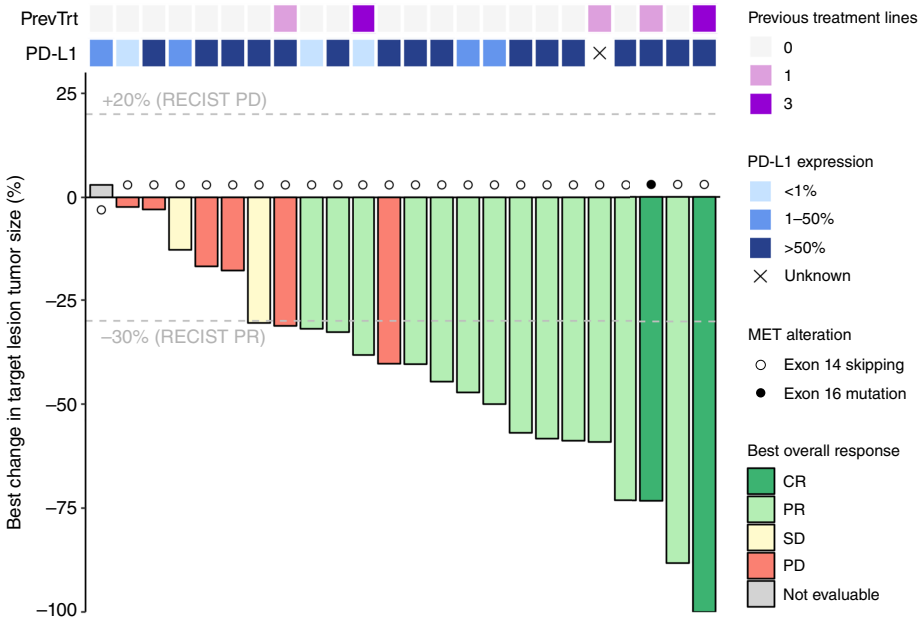
Swimmer plot showing the time on crizotinib treatment for all patients included in the efficacy analysis. Stars indicate the first measurements of CR and diamonds the first measurements of PR. Arrows indicate continued treatment after data cut-off. The dashed line indicates 16 weeks. The plot is annotated with the number of previous lines of systemic anticancer treatment the patients received, the PD-L1 expression, and the type of *MET* alteration that was found at baseline. PrevTrt, previous treatment lines; METalt, *MET* alteration; PD, progressive disease.

Discussion

In this study, crizotinib proved to be highly effective in patients with *MET*mut aNSCLC. We identified an ORR of 62.5% (95% CI, 40.6–81.2) with a median DoR, PFS, and OS of 9.3 (95% CI, 6.5–NR), 10.2 (95% CI, 6.0–20.1), and 13.0 months (95% CI, 9.0–NR), respectively. After this DRUP cohort was initiated, several other prospective studies of crizotinib in patients with *MET*mut aNSCLC were published, of which the characteristics and efficacy outcomes are summarized in Supplementary Table S5 (34–37). Remarkably, our ORR point estimate falls above the 95% CIs of these trials (range 11%–58.3%), as does our median PFS (range 1.6–9.2 months). This may partly be explained by the replacement of patients who did not complete one full treatment cycle in the efficacy analysis in DRUP, as opposed to most other studies. When including all patients who started treatment in the efficacy analysis, our ORR is 50.0% ($N = 15$/

Figure 2.

Waterfall plot showing the best change in the sum of target lesions for all patients included in the efficacy analysis. The plot is annotated with the number of previous lines of systemic anticancer treatment the patients received, the PD-L1 expression, and the type of *MET* alteration that was found at baseline. Of note, the complete responder that did not reach 100% reduction in their target lesion tumor size only had two lymph nodes as target lesions that were no longer pathologically enlarged. PrevTrt, previous treatment lines; PD, progressive disease.



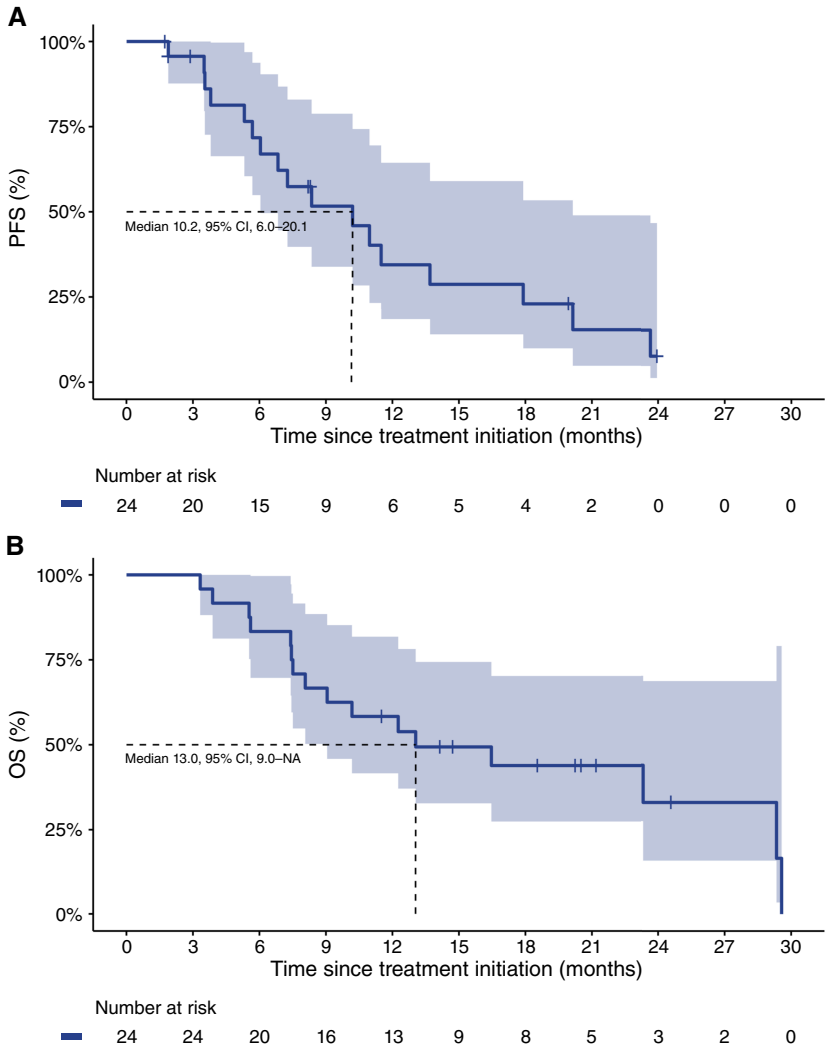


Figure 3.
Kaplan–Meier curves for PFS (**A**) and OS (**B**). The median PFS and OS times with 95% CIs are annotated in plots **A** and **B**, respectively. NA, not available.

30, 95% CI, 31.3–68.7) with a median PFS and OS of 8.3 (95% CI, 5.7–17.9) and 10.2 months (95% CI, 7.4–NR), respectively. These point estimates for both ORR and PFS still exceed the point estimates in the other studies. The median age, percentage of patients with brain metastasis, or ECOG performance statuses in our cohort were not more favorable than those in the previous studies. However, the

Table 2. Treatment-related CTCAE version 4.03 grade ≥ 3 AEs.

CTCAE term	Grade 3	Grade 4	Grade 5
Acute kidney injury	1		
Alanine aminotransferase increased	1	4	
Aspartate aminotransferase increased	1	3	
Blood bilirubin increased		1	
Depressed level of consciousness			1
Dyspnea	1		
Edema limbs	2		
Electrocardiogram QT corrected interval prolonged	1		
Gamma-glutamyltransferase increased	1		
Hepatitis (nonviral)	2		
Hyperkalemia	1		
Localized edema	1		
Neutrophil count decreased	1		
Sepsis	1		

Abbreviation: CTCAE, Common Terminology Criteria for AEs.

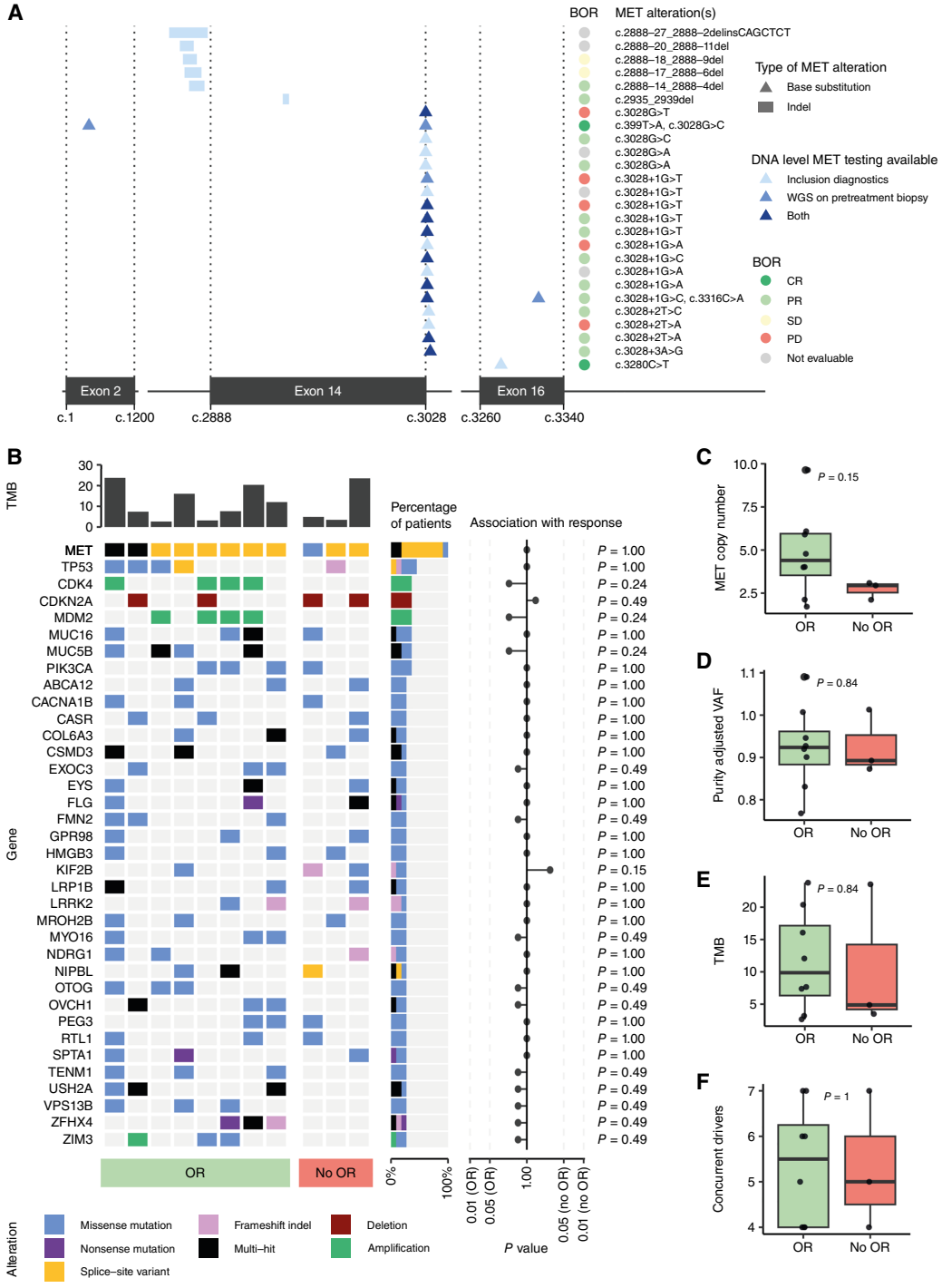


Figure 4.

Correlation between clinical outcome and type of *MET* alteration, concurrent genomic alterations, and other genomic markers. **A,** Baseline *MET* alterations found by either local testing, WGS, or both, correlated to BOR to crizotinib treatment. Variants annotated according to the NM_000245 (MANE transcript). Excluding four patients for whom WGS was not available and who were included solely based on RNA testing. **B,** Oncoplot showing genes that were altered in ≥3 patients, not filtered for driver likelihood. Colored tiles indicate the type of alteration. Bar plot on top indicated the TMB in mutations per megabase. Bar plot on the side indicates the percentage of patients who have a certain genomic alteration. Lollipop plot indicates the association between each genomic alteration and response, calculated using Fisher's exact test. Left side of the plot indicates potential associations with response and the right side with nonresponse. **C–F,** Boxplots showing the correlation between response and *MET* copy number (**C**), sample purity adjusted VAF of the *MET* alteration (**D**), TMB (**E**), and number of concurrent driver mutations with a high driver likelihood (>0.8) as determined by Hartwig's pipeline (**F**). *P* values are calculated using Wilcoxon's test. BOR, best overall response; OR, objective response; TMB, tumor mutational burden; VAF, variant allele frequency.

percentage of treatment-naïve patients in our cohort (76.7%) is substantially higher than that in the other studies (0%–38%). In more severely pretreated patients, evolution of resistant clones may occur under therapeutic pressure, which may explain the difference (6). Yet, within our cohort, we did not observe this signal, as the pretreated patients did not do worse than the treatment-naïve patients.

Besides studies with crizotinib—which is a type Ia nonselective c-MET inhibitor—several studies with selective type Ib c-MET inhibitors (tepotinib, capmatinib, and savolitinib) in *MET*mut aNSCLC have also been published (38–40). The summarized characteristics and efficacy outcomes of these studies are provided in Supplementary Table S6. Notably, in the predominantly first-line setting within this DRUP cohort, crizotinib did not significantly underperform compared with the newer generation c-MET inhibitors in terms of extracranial efficacy. Intracranially, however, type Ib c-MET inhibitors seem superior. Whereas the previous crizotinib studies either excluded patients with untreated brain metastasis (34) or did not observe/report any intracranial activity in *MET*ex14 patients (as in the current study; refs. 35, 36), tepotinib led to baseline brain metastasis shrinkage in 55% of patients (38), and capmatinib led to intracranial disease control or response in 92% and 54% of patients, respectively (39). Both tepotinib and capmatinib gained European Medicines Agency approval based on single-arm trials and are now recommended for treatment of *MET*ex14 aNSCLC following prior treatment with ICB and/or platinum-based chemotherapy according to European Society for Medical Oncology guidelines (13, 41). Yet, despite this second-line approval, for capmatinib a similar signal was observed as in our cohort compared with previous crizotinib studies: treatment-naïve patients seem to have improved outcomes (39). Therefore, one may argue that there is a rationale to administer c-MET inhibition in first-line, as is customary with TKIs in most other oncogene-driven aNSCLCs. In this setting, and in patients without intracranial involvement, crizotinib may also be a valuable treatment option. This is especially true when newer generation c-MET inhibitors are not (yet) available or reimbursed, such as in Canada where the Canadian Agency for Drugs and Technologies recommended tepotinib not to be reimbursed by public drug plans in 2022 due to insufficient evidence of its efficacy (42).

Considering safety, the toxicity profile of crizotinib we observed was largely comparable to previous studies (34–37). Drilon and colleagues (34) observed grade ≥ 3 TRAEs in 25% of patients with *MET*ex14 aNSCLC treated with crizotinib, most commonly involving elevated transaminases, and TRAEs leading to treatment discontinuation in 7%. These rates are slightly lower than the respective 40% and 10% we observed, potentially due to our population being frailer at baseline (23.3% vs. 1% of patients with ECOG 2). When comparing the safety profile of crizotinib to that of the newer generation c-MET inhibitors, grade ≥ 3 TRAEs and TRAEs leading to treatment discontinuation occurred in 28% and 11% for tepotinib and in 37.6% and 11% for capmatinib, respectively, and were most commonly related to peripheral edema. Therefore, the toxicity profile of the newer generation c-MET inhibitors seems different, but not superior to that of crizotinib.

Although the outcomes of c-MET inhibition in patients with *MET*ex14 aNSCLC clearly surpass ICB monotherapy treatment (ORR 17%, 95% CI, 3–39; median PFS 1.9 months, 95% CI, 1.7–2.7; ref. 14), they remain modest compared with the outcomes of TKIs for other oncogene-driven aNSCLCs (43). This may indicate the presence of resistance mechanisms, of which on-target *MET* TKD mutations or focal *MET* amplification and off-target *ERBB3*, *EGFR*, *KRAS*, or *BRAF* mutations or amplifications are known examples (44). Yet, previous research has failed to identify any baseline genomic biomarkers for nonresponse (34, 38, 39, 43). Also in our study, potentially due to the limited sample size, we were unable to add any genomic or transcriptomic biomarkers to refine patient selection in *MET*ex14 aNSCLC. Future research may need to focus on proteomic levels, as *MET*ex14 causes decreased degradation of c-MET rather than increased transcription. Guo and colleagues (43) previously discovered a correlation between c-MET expression on mass spectrometry and response [ORR 60% ($N = 6/10$)] in patients with detectable c-MET versus 0% ($N = 0/5$) in patients without, $P = 0.04$).

What we did find is additional evidence for a potential new target for c-MET inhibition: the only patient who was included based on a *MET* TKD mutation (c.3280C>T, p.H1094Y) achieved a CR. Yao and colleagues (45) previously identified *MET* TKD mutations in 0.06% ($N = 32/54{,}752$, including p.H1094Y in eight patients) of treatment-naïve patients with NSCLC, which were mutually exclusive with other known oncogenic driver alterations. Ai and colleagues (46) also described a patient with a p.H1094Y mutation that achieved a PR on crizotinib as third-line therapy. Based on these results, *MET* TKD mutations may present a rare, but valid target for c-MET inhibition in NSCLC. Moreover, Pecci and colleagues (47) recently reported *MET* TKD mutations as putative oncogenic drivers with a frequency of approximately 0.5% across more than 600,000 diverse cancers studied, potentially identifying a larger group of patients who may benefit from this treatment.

Limitations of our study include the lack of a control group. Additionally, pretreatment WGS and RNA sequencing data were unavailable for a large number of patients, which resulted in insufficient power for the biomarker analysis. Lastly, no longitudinal sampling was performed. Hence, we were unable to assess for any secondary resistance mechanisms.

In conclusion, crizotinib proved to be highly effective in patients with *MET*mut aNSCLC. Numerically, crizotinib seems as effective as the newer generation c-MET inhibitors, with a toxicity profile including less severe edema but more hepatobiliary AEs. No genomic or transcriptomic biomarkers to refine patient selection could be discovered, but a CR in the only patient included based on a *MET* TKD mutation confirmed this type of *MET*mut as a rare but valuable additional target for c-MET inhibition.

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Note

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