Crizotinib in *MET* deregulated or *ROS1* rearranged pretreated non-small-cell lung cancer (METROS): a phase II, prospective, multicentre, two-arms trial

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Statement of translational relevance

Treatment of patients with *MET* deregulated Non-Small Cell Lung Cancer (NSCLC) represents an urgent need because of lack of effective targeted therapies and unfavourable prognosis. The METROS trial is a prospective study evaluating the efficacy of crizotinib in two cohorts of patients: individuals with *MET* exon 14 mutations or amplification or individuals with *ROS1* rearrangements. In the *MET* deregulated cohort, although response rate was 27%, a remarkable result for a pretreated NSCLC population, median PFS and most importantly, median OS were disappointing with all patients rapidly progressing and dying. Interestingly, no difference for any clinical end-point was observed between *MET* amplified and exon 14 mutated patients. Overall, our data highlight the urgent need for more effective strategies in patients with *MET* mutations or amplification.

Abstract

Introduction

MET deregulated NSCLC represents an urgent clinical need because of unfavorable prognosis and lack of specific therapies. Although recent studies have suggested a potential role for crizotinib in patients harboring *MET* amplification or exon 14 mutations, no conclusive data are currently available. The present study aimed at investigating activity of crizotinib in patients harboring *MET* or *ROS1* alterations.

Methods

Patients with pretreated advanced NSCLC and evidence of *ROS1* rearrangements (Cohort A) or *MET* deregulation (amplification, ratio MET/CEP7 >2.2 or *MET* exon 14 mutations, Cohort B) were treated with crizotinib 250 mg BID orally. The co-primary end-point was objective response rate in the two cohorts.

Results

From December 2014 to March 2017, 505 patients were screened and a total of 52 patients (26 patients per cohort) were enrolled onto the study. At data cut-off of September 2017, in cohort A objective response rate was 65%, median progression free survival and overall survival were 22.8 months (95% CI 15.2 – 30.3) and not reached. In cohort B, objective response rate was 27%, median progression free survival was 4.4 months (95% CI 3.0- 5.8) and overall survival was 5.4 months (95% CI 15.2 – 30.3). No difference in any clinical end-point was observed between *MET* amplified and exon14 mutated patients. No response was observed among the 5 patients with co-occurrence of a second gene alteration. No unexpected toxicity was observed in both cohorts.

Conclusions

Crizotinib induces response in a fraction of *MET* deregulated NSCLC. Additional studies and innovative therapies are urgently needed.

Introduction

During the last ten years several molecular events, including gene mutations, gene copy number alterations and gene rearrangements have been discovered in small fractions of lung adenocarcinomas, dramatically improving patient treatment (1). This is the case of NSCLCs carrying epidermal growth factor receptor (*EGFR*) activating mutations or anaplastic lymphoma kinase (*ALK*) rearrangement, where targeted therapies have changed the natural history of the disease (2–5). Beyond *EGFR* mutations and *ALK* rearrangement, additional actionable alterations have been identified, with *ROS1* rearrangement and *MET* amplification or *MET* exon 14 mutations being the most appealing (5–8).

Crizotinib has been the first ALK inhibitor entered in clinical development within the PROFILE program and then approved worldwide for front line treatment of *ALK* positive NSCLC (3). Moreover, crizotinib has high specificity for ROS1 and MET kinase domains and it potently inhibits tumor growth and invasion in cell models of *MET* or *ROS1* addicted NSCLC (9). In the phase I PROFILE 1001, enrolling 50 *ROS1*-positive NSCLC patients, objective response rate (ORR) was 72% and median progression-free survival (PFS) exceeded 19 months (10). These results mirror those observed in *ALK* positive NSCLC and are comparable to what reported in subsequent retrospective and prospective trials (11–15). At present, crizotinib has a well established role in *ROS1* positive NSCLC and is worldwide available. Conversely, its role in *MET* addicted NSCLC is not demonstrated. Initial observations in solid tumors with MET overexpression or *MET* amplification showed potential efficacy only in *de novo MET*-amplified tumors (16–18). In NSCLC, crizotinib produced an ORR of approximately 40%, with evidence of activity only against tumors with intermediate or high levels of *MET* amplification, defined as a ratio *MET*/centromere 7 (MET/CEP7) of > 2.2 - < 5 or $\geq$ 5, respectively (19). Interestingly, preliminary results of the phase II AcSé trial, evaluating crizotinib in *MET* amplified NSCLC, showed an ORR of only

32% (20). Nevertheless, the criteria adopted for defining *MET* amplification were different than in the PROFILE 1001 study, providing a possible explication for the lower drug efficacy. Moreover, AcSé data suggested that levels of *MET* amplification could be relevant for defining patients with the highest sensitivity to the drug. In addition to *MET* amplification, a recent study showed that anti-MET agents such as crizotinib or cabozantinib induced tumor shrinkage in patients harboring *MET* exon 14 mutations, a phenomenon occurring in approximately 3% of NSCLC (7,8,21,22). In the phase 1 PROFILE 1001 study, ORR with crizotinib in *MET* exon 14 mutated patients was 44%, suggesting that the drug is effective against this alteration (23). Based on these premises and considering the urgent need of effective strategies for *MET* deregulated NSCLC, we designed this study aiming at investigating crizotinib efficacy in *MET* amplified or exon 14 mutated NSCLC. Because at the time of study design, few data were available in *ROS1* rearranged patients and no therapy was available in Italian clinical practice, a ROS1 rearranged cohort was also included.

Methods

Patients selection

Eligible patients had histologically confirmed diagnosis of locally advanced or metastatic NSCLC and availability of archival tissue for biomarkers analyses. A local pre-screening was allowed. For patients with *MET exon 14* mutations central confirmation was not required for trial inclusion, whereas central confirmation was mandatory for those patients who resulted positive for *ROS1* rearrangements or *MET* amplification at local labs. *ROS1* rearrangement and *MET* amplification were tested centrally by fluorescent in-situ hybridization (FISH), using the specific probes (Abbott Molecular, Des Plaines, IL, USA). Briefly, criteria for FISH positivity were 1) presence of ROS1-fusion patterns in ≥ 15% of tumor cells (24) or 2) a MET/CEP7 ratio > 2.2 according to Camidge Criteria (19) . *MET*

mutational status was assessed locally using direct sequencing or other high sensitive methods. Even if central confirmation was not required for trial inclusion, at the end of the study, all *MET* exon 14 mutant cases were centrally verified using Sanger direct sequencing (Applied Biosystem - ThermoFisher Scientific, San Francisco, CA, USA). Other inclusion criteria included: an Eastern Cooperative Oncology Group performance status (ECOG PS) $\leq$ 2, at least one previous chemotherapy line, at least one measurable tumor lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (25), adequate bone marrow and organ functions. Patients with known *EGFR* or *KRAS* mutations or previously treated with ROS1 or MET inhibitors or with symptomatic brain metastases were excluded. The study was done in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. Each center received the approval of the local ethics committee, and all patients provided written informed consent before participation. The final version of the protocol including full list of study criteria is reported in the Supplemental data.

Treatment

Patients were treated with crizotinib 250 mg twice daily in continuous 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, or death. Dose modifications or interruptions were considered in case of intolerable grade 2 or worse adverse events (AEs). Radiological assessment by CT scans was done at baseline and then every 8 weeks until disease progression; responses had to be confirmed by repeating assessment 4–8 weeks after initial response. All patients who discontinued study drug were followed up for subsequent treatments and survival every 12 weeks, until death or study completion. Patients were assessed for safety every 4 weeks. AEs, laboratory tests, and vital signs were graded according to the Common Terminology Criteria for Adverse Events version 4.0. The cutoff date for safety and efficacy data was September 30, 2017, which was the date of database lock.

Outcomes

The primary endpoint was investigator-assessed overall response, defined as the percentage of patients who achieved a confirmed complete response (CR) or partial response (PR) per RECIST version 1.1 (25). Secondary endpoints included PFS based on investigator-assessed disease response OS, safety and correlation between response and percentage of *ROS1* FISH positivity or levels of *MET* amplification (intermediate levels, [MET/CEP7 ratio $\geq$ 2.2 - <5] versus high levels, [MET/CEP7 ratio > 5]).

Statistical analysis

The METROS was a phase II, two arms, non-comparative trial in which arms were determined by the presence of *ROS1* rearrangement or *MET* deregulation. The study was designed to test the hypothesis of an ORR ≥ 50% versus ORR ≤ 10% in each arm at a significance level of 5% (one sided) with a power of 98%. The study was originally designed to include only *MET* amplified NSCLCs. However, clinical data published in 2015 suggested *MET* exon 14 mutated NSCLCs as an additional population potentially benefiting to crizotinib (8,21). For such reason the trial was amended to include also patients with such aberration without modification in the statistical plan. Patients and disease characteristics were analyzed using descriptive statistics and expressed as relative frequency (percentage) for discrete variables or median and interquartile range (IQR) for continuous variables. Associations among factors were evaluated with the chi-square test while differences in distribution of quantitative variables were measured with the Mann-Whitney test. Confidence interval (95%) for ORR was calculated according to the exact method. PFS and OS were calculated from the date of starting therapy to the date of first evidence of either disease progression or death of the patient in the absence of documented disease progression (PFS), or death for any cause (OS). Patients without an event were censored at the date of last follow-up. Survival times were estimated using Kaplan–Meier analysis and expressed as medians with corresponding two-sided 95%

confidence intervals (CIs). Differences between curves were evaluated using the log-rank test. This trial is registered with ClinicalTrials.gov, number NCT 02499614.

Results

Patients

From December 2014 to March 2017, 505 patients were screened (Fig. 1). Four hundred and thirty-three (86%) patients had tumor tissue evaluable for *ROS1* and *MET* FISH analyses. Thirty-three individuals (7.6%) resulted *ROS1* positive and 37 *MET* deregulated (8.5%). Among them, 18 patients were not included due to death (3 *ROS1* and 4 *MET* patients), screening failure (4 *ROS1* and 4 *MET* patients) or unknown reason (3 *MET* patients). Twenty-six patients per cohort (cohort A, *ROS1* positive; cohort B, *MET* positive) accounted for the final population of the trial. Demographic and disease characteristics are reported in table 1. Briefly, cohort A included mainly females, never smokers and with median age of 68 years, whereas cohort B included mainly males, current or past smokers with median age of 56 years. In both cohorts, most patients had an ECOG PS of 0-1, presented with two or more metastatic sites, and received crizotinib as second line treatment. Fifty-four percent of patients in the MET cohort had PD as best response to last therapy compared to less than 30% in ROS1 cohort. A platinum-doublet regimen was the latest treatment before crizotinib in 69% and 81% of ROS1 and MET deregulated patients, respectively (Supplemental Table S1). Among individuals included in the *MET* cohort, 16 patients had *MET* amplification (intermediate levels, 14 patients; high levels, 2 patients), 9 patients had exon 14 mutation (c.2962C>T, 1 case; c.3029C>T, 5 cases; c.3082G>T, 1 case; c.3082+1G>A, 1 case; c.3082+3A>T, 1 case), and one patient had co-occurrence of *MET* amplification (intermediate levels) and *MET* mutation (c.2942-19_2961delinsC). At the end of the study, *MET* mutational status was centrally re-tested in all exon 14 mutant cases, with confirmation of local reports. Only one case resulted uncorfirmed due to

inadequate tumor sample for direct sequencing (data not shown). This patient had stable disease as best response to study drug.

Median number of crizotinib cycles and median duration of treatment were 15 (range 0.3 - 34.4; IQR 5.4-24.9) and 15.2 months (95% CI 4.7-25.2) in cohort A, and 3 (range 0.4-28.6; IQR 2.0 – 5.6) and 4.0 months (95% CI 2.0-5.5) in cohort B. At data cutoff, 9 patients in cohort A and 6 patients in cohort B were still receiving treatment.

Efficacy

Summary of efficacy measures is reported in table 2. In Cohort A, ORR was 65% (CI 44 – 82), including one (4%) CR and 16 (61%) PR. Six patients (23%) obtained SD, resulting in an overall disease control rate (DCR) of 85%. With a median follow-up of 21 months (95% CI 19.0 – 24.5), median PFS was 22.8 months (95% CI 15.2 – 30.3), whereas median OS was not reached (Fig. 2,3). Median time to response (TTR) and median duration of response (DOR) were 7.9 weeks (IQR, 7.4-10.3) and 21.4 months (95% CI 12.7-30.1). Depth of response, defined as the median percentage of reduction in target lesions from baseline, was -51.7% (IQR, -77.5% - -42.7%). In responding patients, median percentage of *ROS1* FISH positivity was significantly higher than in non-responders (50% versus 22%, Mann-Whitney test p=0.005, Supplemental Table S2).

In cohort B, ORR was 27% (CI 11 – 47), including only PR. Eleven patients (42%) had SD, for an overall DCR of 69%. With a median follow-up of 21 months (95% CI 19.0 – 24.5), median PFS and median OS were 4.4 months (95% CI 3.0 – 5.8) and 5.4 months (95% CI 4.2– 6.5), respectively (Fig. 2,3). Median TTR and DOR were 7.4 weeks (IQR 6.4-9.3) and 3.7 months (95% CI 1.1-6.3). Depth of response was -47.9% (-56.5%- -35.6%). According to *MET* deregulation, responses occurred in 5 patients with *MET* amplification (intermediate levels only), in 1 patient with *MET* mutation and in the co-altered *MET* amplified and mutant case (Supplemental Table S3). Further, we separately analyzed outcome in *MET* amplified and in *MET* exon 14 mutated groups. In both groups ORR,

289 median DOR, PFS, and OS were similar to the whole *MET* deregulated cohort
290 (Supplemental Table S4).
291 Further, to better characterize the study population, we retrospectively performed a
292 Sequenom analysis in 48 out of 52 tissue specimens collected at baseline. A second
293 driver was found in 7 (14%) cases, including two cases with concomitant *MET*
294 amplification (intermediate levels), three cases with *MET exon 14* mutation and two cases
295 with *ROS1* rearrangement. Details are reported in supplemental Tables S2-S3. Among the
296 4 evaluable patients with *MET/KRAS* and *ROS1/KRAS* co-altered tumors, 1 achieved PR,
297 2 had SD, and 1 progressed. The double *MET* amplified/*BRAF* mutant subject progressed,
298 whereas the *ROS1/MET* positive patient voluntary discontinued crizotinib after only 1 cycle
299 without any tumor assessment.
300 Finally, as illustrated in Table 3, we evaluated the intracranial efficacy of the drug in the
301 eleven patients with brain metastases at baseline (six in Cohort A and five in Cohort B)
302 and responses were observed only in ROS1 positive patients.
303
304 *Toxicity*
305 Safety profile of crizotinib was consistent with literature data and no new safety alert was
306 reported in both cohorts (Supplemental Table S5). Treatment related adverse events
307 (TRAEs), most of which were of grade 1 or 2, occurred in 26 (100%) patients in Cohort A
308 and in 21 (81%) patients of cohort B. In both cohorts, the most common TRAEs of any
309 grade were fatigue (58% in cohort A and 31% in cohort B), peripheral edema (50% in
310 cohort A and 31% in cohort B), nausea (46% in cohort A and 31% in cohort B), pain (30%
311 in cohort A and 19% in cohort B), transaminases elevation (27% in both cohort A and
312 cohort B), respiratory symptoms including dyspnea and cough (42% in cohort A and 46%
313 in cohort B), and visual disorders (23% in cohort A and 27% in cohort B). In cohort A,
314 TRAEs of grade 3/4 were peripheral edema, neutropenia and respiratory symptoms each

occurring in one patient (4%), and nausea and fatigue each occurring in two (8%) patients. In cohort B, TRAEs of grade 3/4 were nausea, neutropenia, anemia, and respiratory symptoms each occurring in one patient (4%), nausea and transaminases elevation occurring in two patients (8%). Overall, TRAEs leading to dose reduction, temporary or permanent of discontinuation of the drug were reported in 8 (15%), 13 (25%), and 3 (6%) patients. Among 13 serious AEs (SAEs) reported, only two were judged as related to study drug (Supplemental Table S6). Finally, we analyzed the incidence and clinical correlates of venous thromboembolism occurring prior or during crizotinib treatment in patients enrolled in the trial; the results of this analysis are the object of a separate publication (26).

Discussion

Treatment of patients with *MET* deregulated NSCLC represents an urgent clinical need because of lack of effective targeted therapies and unfavorable prognosis (7,27). The METROS is a prospective study evaluating the efficacy of crizotinib in patients with *MET* exon 14 mutations or amplification. Although response rate was remarkable for a pretreated NSCLC population, median PFS and, most importantly, median OS were disappointing, with all patients rapidly progressing and dying.

In oncogene addicted NSCLCs, such as *EGFR* or *ALK* addicted NSCLC, targeted therapies are extending survival with medians ranging between 3-5 years.(1–5) Similar outcome has been observed in *ROS1* addicted patients and the results of our study, including also a *ROS1* cohort, confirmed that crizotinib is highly effective in such patients. The primary end-point of ORR was met in *ROS1* cohort, where durable responses were observed in 65% of patients, median PFS exceeded 22 months and median OS was not reached, with approximately 80% of patients alive at 1 year. These data favorable compare with other trials, reinforcing the role of this agent in the treatment of *ROS1* driven lung cancers (10–14). Interestingly, we observed a significant association between

percentage of *ROS1* FISH positivity and response to crizotinib, a phenomenon previously described only in *ALK* positive NSCLC, deserving further investigations (28).

Different results were obtained in *MET* deregulated patients. This cohort included both *MET* amplified or exon 14 mutated. Although recent data suggest that these are different patient population (19,23), this concept was not emerged yet at the time of trial design and statistical hypothesis has been formulated considering *MET* deregulated as a homogeneous group. However, even with such limitation, outcome was similar in *MET* amplified or exon 14 mutated subgroups, with limited responses and with only one month elapsing from time of tumor progression and patient death. These data are in agreement with other studies, such as the AcSé and the PROFILE 1001 (29, 30). Final results of the AcSé *MET* FISH positive cohort, showed an ORR of 32% and a median PFS of only 3.4 months, comparable to what observed in our experience, even if criteria for *MET* positivity differed (29). In the last update of the PROFILE 1001, including a total of 37 *MET* amplified patients, ORR was 27%, similar to the 31% observed in METROS. Importantly, among the 20 patients with high levels of amplification ORR was 40%, including 2 cases with CR (30). In our study, only one patient had high levels of amplification, precluding the possibility to explore the impact of the drug in presence of such characteristic. Nevertheless, high levels of *MET* amplification rarely occur in patients with NSCLC. In a previous study conducted in surgically resected NSCLC, among 435-screened patients only three (0.6%) had high levels of amplification (27). METROS trial screened more than 430 advanced NSCLCs and only 0.4% displayed high levels of *MET* amplification, confirming the relative rarity of the event.

METROS study also included patients with *MET* exon 14 mutations, accounting for less than 3% of the screened population, as expected according to literature data (7,8). In *MET* exon 14 mutated patients the benefit produced by crizotinib in terms of ORR, PFS and OS was limited. Although our findings seem inferior to what recently reported by Drillon et al.

in PROFILE 1001, in which PFS exceed 7 months and OS is approximately 20 months, differences in patients selection limit comparison between the two studies (30). Exon 14 mutations include a wide range of abnormalities, such as insertion, deletion or point mutation that generally lead the loss or attenuation of ubiquitin-mediated receptor degradation, for instance by disrupting the splice acceptor site of intron 13 or affecting the splice donor site of intron 14 (8,27,32). How different mutations could affect sensitivity to MET inhibitors, especially crizotinib, remains an unanswered question. In our cohort among the 4 patients with splicing mutations only one responded.

METROS study also confirms the very unfavorable prognosis of *MET* deregulated NSCLC. In 2009 our group first demonstrated that *MET* gene copy number was a negative prognostic factor in NSCLC (27). Additional studies confirmed that MET deregulation, including overexpression, gene copy number gain or mutation, confers an aggressive phenotype (33). In addition to an aggressive behavior, also reinforced by the scarce sensitivity to prior chemotherapy, MET deregulated NSCLC demonstrated modest and transient responsiveness to crizotinib, suggesting that other factors could modulate sensitivity to MET-inhibition, such as co-occurrence of driver events or expression of the MET protein as recently reported (33–36). Particularly, in a context of *MET* amplification Tong et al. demonstrated that low levels of amplification may occur in a background of *KRAS* mutation, while high levels of *MET* amplification were mutually exclusive with major oncogene drivers (33). In addition, it is not possible to exclude that other approaches or new drugs might be more effective. On this perspective, we are now conducting a phase II trial evaluating cabozantinib in both *MET* amplified or mutated lung cancer untreated with MET-inhibitor or refractory to crizotinib (CABinMET trial, EudraCT 2017-004157-16).

In conclusion, results of METROS trial indicate that even if crizotinib induces a tumor shrinkage in a fraction of *MET* deregulated NSCLC, the drug minimally impacts the clinical course of the disease, at least in pretreated *MET* mutated or *MET* with intermediate levels

of amplification, whereas the efficacy of the drug in presence of high levels of amplification remains investigational. Additional studies and innovative therapies are urgently needed against this aggressive disease.

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Table 1. Baseline Characteristics

	Cohort A *ROS1^{FISH+}*		*Cohort B* *MET ^{Ex14}* or *MET $^{FISH+}$*		*p**
	26	**100%**	**26**	**100%**	
Age, median (range)	**68 (28-86)**		**56 (39-78)**		**0.07**
M/F	**10/16**	**38/62**	**17/9**	**65/35**	**0.05**
ECOG PS 0/1/2	**18/7/1**	**69/27/4**	**11/13/2**	**42/50/8**	**0.05**
Never Smoker/Past Smoker/Current smoker	**14/9/3**	**54/35/11**	**6/12/8**	**23/46/31**	**0.05**
Adenocarcinoma/Other histology**	**26/0**	**100/0**	**23/3**	**89/11**	**n.a.**
Type of MET deregulation					
• **Amplification**	**n.a.**		**16**	**61**	
• **Mutation**	**n.a**		**9**	**35**	
• **Concorrent amplification and mutation**	**n.a**		**1**	**4**	
Metastatic sites, 1/2/>2	**5/11/10**	**19/42/39**	**4/11/11**	**15/42/42**	**0.92**
Disease sites					
• **Lung**	**22**	**85**	**22**	**85**	**0.99**
• **Lymph Node**	**16**	**61**	**12**	**46**	**0.40**
• **Liver**	**3**	**11**	**6**	**23**	**0.46**
• **Bone**	**9**	**35**	**5**	**19**	**0.35**
• **Brain**	**6**	**23**	**5**	**19**	**0.73**
• **Pleura**	**3**	**11**	**6**	**23**	**0.46**
• **Adrenal gland**	**2**	**7**	**6**	**23**	**0.25**
Prior line of therapy, 1/2/>2	**20/3/3**	**76/12/12**	**21/3/2**	**81/11/8**	**0.63**
Time from end of last treatment to Crizotinib start (months, median)	**12 (3-43)**		**3 (2-8)**		**0.02**
Best response to prior therapy					
• **Complete Response + Partial Response**	**10**	**38**	**4¶**	**15**	**0.12**
• **Stable Disease**	**7**	**27**	**6**	**23**	
• **Progressive Disease**	**7**	**27**	**14**	**54**	
• **Unknown**	**2**	**8**	**2**	**8**	

Data are median (IQR) or n (%). * Chi-square test and Mann-Whitney were used for categorical items and for continuous variables, respectively. ECOG PS=Eastern Cooperative Oncology Group performance status.**Other histologies includes two patients with NSCLC not otherwise specified (NOS) and one patient with pleomorphic carcinoma. All histology was determined by local pathological report.n.a.= not applicable; ¶ only partial responses.

Table 2. Efficacy endpoints in cohort A (ROS1 positive) and Cohort B (MET deregulated)

	Cohort A – ROS1 (N=26)	Cohort B– MET (N=26)
Best overall response		
Complete response	1 (4%)	0
Partial response	16 (61%)	7 (27%)
Stable disease	6 (23%)	11 (42%)
Progressive disease	1 (4%)	6 (23%)
Not evaluable or not assessed	2 (8%)	2 (8%)
Progression free survival (PFS)		
Number of events	14 (54%)	18 (69%)
PFS (months)	22.8 (15.2 – 30.3)	4.4 (3.0- 5.8)
6 months PFS rate	80.6%	30.9%
12 months PFS rate	71.9%	20.6%
Overall survival (OS)		
Number of events	10 (39%)	16 (61%)
OS (months)	NR	5.4 (4.2 – 6.5)
6 months OS rate	96.2%	43.9%
12 months OS rate	79.2%	26.3%

Data are n (%) or median (95% CI), unless otherwise stated. NR, not reached.

Table 3. Intracranial disease characteristics, intracranial response and pattern of failure in patients with brain metastases at baseline

Pt ID	Biomarker	Characteristics of CNS disease	Method for CNS Assessment	Prior RT	Date of RT	Date of start crizotinib	Intracranial response	Pattern of failure
MT-006-118	*ROS1*	Multiple lesions, non-target	Brain MRI	No	NA	01 Dec 2015	CR	Extra- and intracranial
MT-001-013	*ROS1*	Single lesion, non-target	Brain CT scan	No	NA	31 Mar 2015	SD	Intracranial only
MT-001-001	*ROS1*	Single lesion, non-target	Brain CT scan	Yes	Jun 2012	27 Feb 2015	CR	Extra- and intracranial
MT-012-087	*ROS1*	Single lesion, non-target	Brain CT scan	No	NA	27 Jan 2016	SD	Extracranial only
MT-001-011	*ROS1*	Single lesion, non-target	Brain CT Scan	No	NA	20 Feb 2015	SD	Intracranial only
MT-019-238	*ROS1*	Multiple lesions, non-target	Brain MRI	Yes	NR	25 Jul 2016	SD	Intracranial only
MT-006-079	*MET* $^{FISH+}$	Single lesion, non- target	Brain MRI	Yes	Aug 2015	10 Aug 2015	PD	Extra- and intracranial
MT-012-182	*MET* $^{FISH+}$	Multiple lesions, target (1 lesion)	Brain CT scan	Yes	Apr 2016	26 Jul 2016	SD	Extracranial only
MT-004-286	*MET* ^{Ex14}	Multiple lesions, non-target	Brain MRI	Yes	Jun 2016	14 Sep 2016	SD	NA§
MT-012-129	*MET* ^{Ex14}	Multiple lesions, target (1 lesion)	Brain CT scan	No	NA	22 Sep 2016	PD	Extra- and intracranial
MT-020-441	*MET* ^{Ex14}	Single lesion, non-target	Brain CT scan	Yes	Jun 2017	05 Jul 2017	SD	Extracranial only

MET $^{FISH+}$, MET amplified (intermediate level only, MET/CEP7 ratio 3.4 and 2.6 for MT-006-079 and MT-012-182, respectively); RT, radiotherapy; NR, not reported; NA, not applicable; § PT ID MT-004-286 permanently discontinued crizotinib due to SAE

Figure legend

Figure 1. Study profile.

Figure 2. Tumor responses in *MET* deregulated and *ROS1* rearranged NSCLC.

Maximum percentage reduction from baseline sum of lesion diameters by best investigator-assessed confirmed response in 52 patients receiving crizotinib as second-line or later treatment.

Figure 3. Kaplan-Meier curve of investigator-assessed progression-free survival (A) and overall survival (B) in *ROS1* positive (red line) and *MET* deregulated (blue line) non-small cell lung cancer receiving crizotinib.

Figure 1

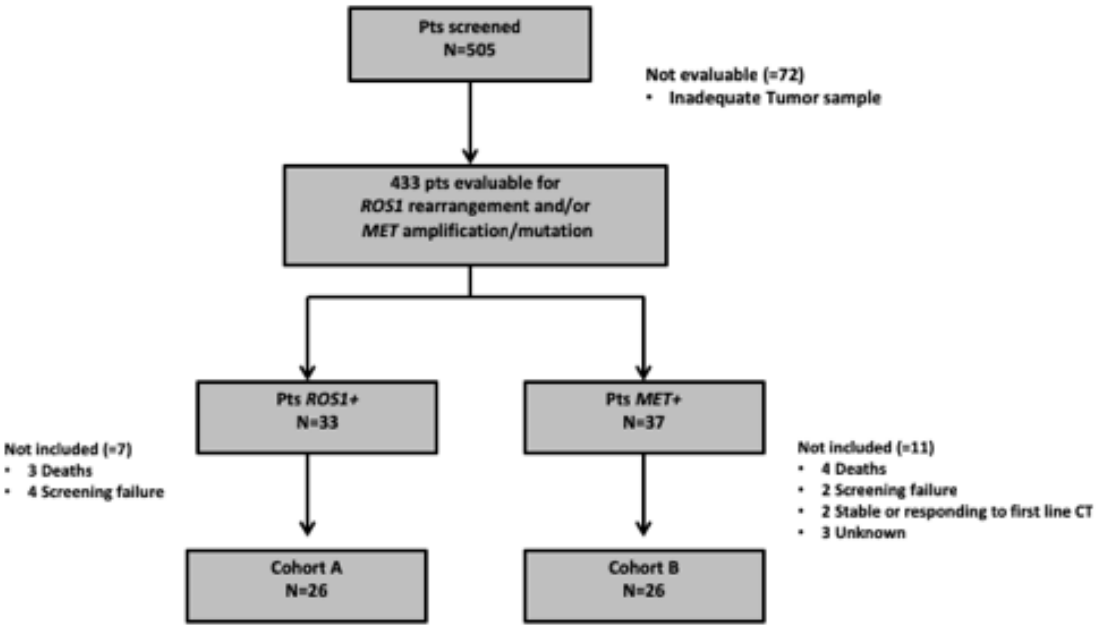


Figure 2

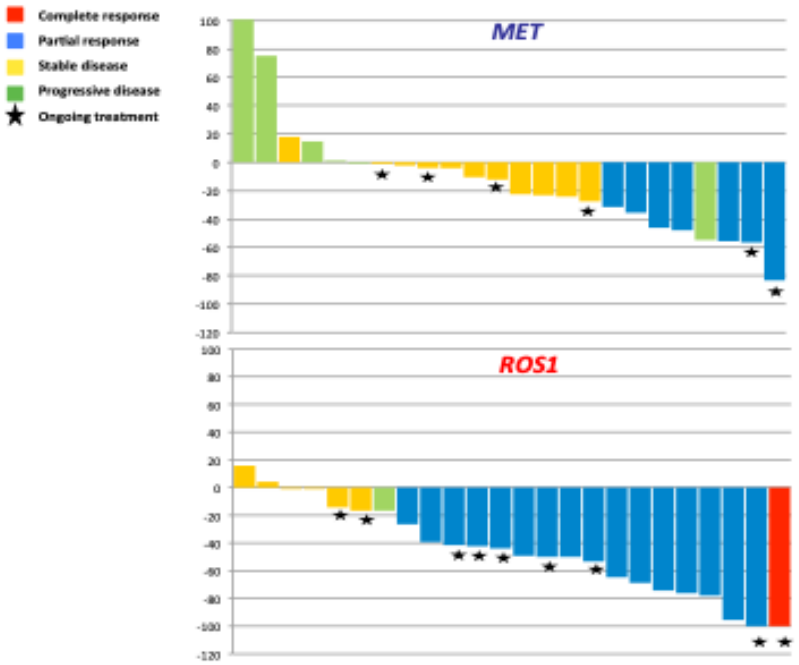
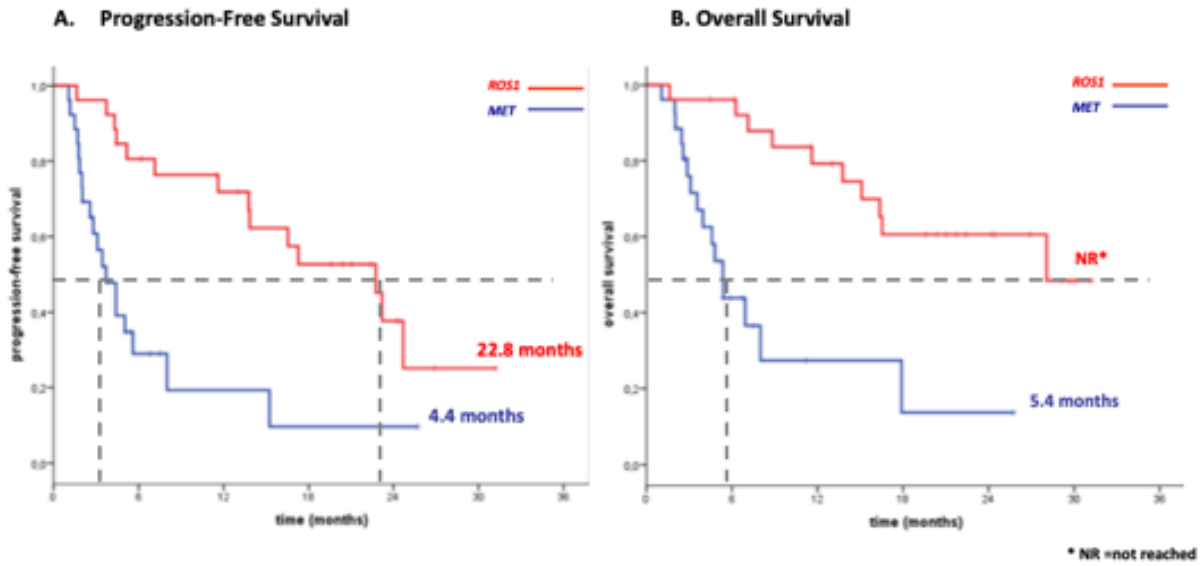


Figure 3



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Clinical Cancer Research

Crizotinib in *MET* deregulated or *ROS1* rearranged pretreated non-small-cell lung cancer (METROS): a phase II, prospective, multicentre, two-arms trial

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