

**Activity and safety of crizotinib in patients with alveolar soft part sarcoma with rearrangement of *TFE3*. European Organization for Research and Treatment of Cancer (EORTC) phase 2 trial 90101 "CREATE"**

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**Background:** Alveolar soft part sarcoma(ASPS) is an orphan malignancy associated with a rearrangement of transcription factor E3(*TFE3*), leading to abnormal *MET* gene expression. We prospectively assessed the efficacy and safety of the tyrosine kinase inhibitor(TKI) crizotinib in patients with advanced or metastatic ASPS.

**Patients and methods:** Eligible patients with reference pathology-confirmed ASPS received oral crizotinib 250 mg twice daily. By assessing the presence or absence of a *TFE3* rearrangement, patients were attributed to *MET*<sup>+</sup> and *MET*<sup>-</sup> sub-cohorts. The primary endpoint was the objective response rate(ORR) according to local investigator. Secondary endpoints included duration of response(DOR), disease control rate(DCR), progression-free survival(PFS), progression-free rate(PFR), overall survival(OS) and safety.

**Results:** Among 53 consenting patients, all had a centrally confirmed ASPS and 48 were treated. A total of 45 were eligible, treated and evaluable. Among 40 *MET*<sup>+</sup> patients, 1 achieved a confirmed PR that lasted 215 days and 35 had stable disease(SD) as best response(ORR:2.5%, 95%CI:0.6-80.6%). Further efficacy endpoints in *MET*<sup>+</sup> cases were DCR:90.0%(95%CI:76.3-97.2%), 1-year PFS rate: 37.5%(95%CI:22.9-52.1%) and 1-year OS rate:97.4%(95%CI:82.8-99.6%). Among 4 *MET*<sup>-</sup> patients, 1 achieved a PR that lasted 801 days and 3 had SD(ORR:25.0%,95%CI:0.6-80.6%) for a DCR of 100% (95%CI:39.8-100.0%). The 1 year PFS rate in *MET*<sup>-</sup> cases was 50%(95%CI:5.8-84.5%) and the 1-year OS rate was 75%(95%CI:12.8-96.1%). One patient with unknown *MET* status due to technical failure achieved SD but stopped treatment due to progression after 17 cycles. The most common crizotinib-related adverse events were nausea(34/48[70.8%]), vomiting (22/48[45.8%]), blurred vision(22/48[45.8%]), diarrhoea(20/48[41.7%]) and fatigue(19/48[39.6%]).

**Conclusion:** According to EORTC efficacy criteria for soft tissue sarcoma, our study demonstrated that crizotinib has activity in *TFE3* rearranged ASPS *MET*<sup>+</sup> patients.

**Clinical trial number:** EORTC 90101, NCT01524926

**Keywords:** Alveolar soft part sarcoma, ASPS, transcription factor E3 (*TFE3*) gene rearrangement, *MET* expression, MET tyrosine kinase inhibitor, crizotinib

**Prior presentations:** None

**Key message:** ASPS is a rare sarcoma with early metastatic spread. Objective responses to the crizotinib are uncommon, but a considerable proportion of patients achieve objective shrinkage of RECIST 1.1 target lesions and long term disease control. According to STS efficacy criteria established by EORTC, crizotinib is an active compound for ASPS, given the DCR and PFR observed in this histotype-specific trial.

## Introduction

Alveolar soft part sarcoma (ASPS) is a rare soft tissue sarcoma (STS) with high metastatic potential, accounting for 0.5-1% of all STS.<sup>1-7</sup> Typical metastatic sites include brain, lungs, lymph nodes and bone.<sup>2,4,5</sup> According to the literature, the 5-year survival is only 20% in patients with metastases vs 71% in patients with localised disease.<sup>6</sup>

Complete excision of the primary tumour can cure ASPS, but due to late diagnosis and early metastatic spread it is not an option for all patients.<sup>2</sup> Patients with advanced, inoperable and/or metastatic disease qualify for systemic treatment, but conventional chemotherapy has little efficacy.<sup>2,4</sup> A number of targeted agents are currently being tested in ASPS.

ASPS is characterised by the presence of a somatic translocation between chromosomes 17 and X (Supplementary Figure S1, S2), resulting in the *ASPSCR1-TFE3* fusion gene (Supplementary Introduction and Figure S3).<sup>5,8,9</sup> The *ASPSCR1-TFE3* fusion gene plays a critical role in the development of ASPS as it encodes a chimeric transcription factor, inducing an overexpression of the *MET* gene, encoding the MET receptor tyrosine kinase (Supplementary Figure S4).<sup>2,3,5,7,8</sup>

In normal cells the hepatocyte growth factor (HGF) activates the MET receptor resulting in a downstream cascade of events that regulate cell proliferation and differentiation.<sup>10</sup> In a variety of cancers, MET gets abnormally activated leading to abnormal cell division and survival, invasion, and metastases, resulting in a poor prognosis.<sup>4,7,10,11</sup>

The presence of MET activation and overexpression in ASPS provides a rationale to therapeutically target MET in this disease. Crizotinib (Xalkori<sup>®</sup>, Pfizer Inc.) is a small molecule targeting: MET, anaplastic lymphoma kinase (ALK), and ROS proto-oncogene 1 receptor tyrosine kinase (ROS1).<sup>12-15</sup> Crizotinib interferes with the MET pathway by competitively inhibiting adenosine triphosphate (ATP) from binding to the receptor, therefore abrogates its phosphorylation.<sup>12-15</sup> This blocks the downstream cascade of events, thereby inhibiting the growth and survival of MET dependent cells.<sup>12-15</sup> Crizotinib is indicated in adult patients for ALK-positive non-small cell lung cancer (NSCLC), and ROS1-positive advanced NSCLC,<sup>15</sup> and the recommended oral dose in adults is 250 mg twice daily.

The European Organization for Research and Treatment of Cancer (EORTC) initiated a multinational, multi-tumour, prospective phase 2 clinical trial (EORTC 90101 "CREATE") to evaluate the efficacy and safety of crizotinib in patients with advanced tumours driven by MET and/or ALK alterations. CREATE included 6 disease-specific groups, and we report here the results of the independent ASPS cohort.

## Methods

### *Study design*

This was a multicentre, biomarker-driven, single agent, non-randomized, open-label, two-stage phase 2 trial, assessing crizotinib in patients with locally advanced/metastatic ASPS. The patient population was divided by protocol into *MET* altered (*MET*+) and *MET* non-altered (*MET*-) sub-cohorts, assessed by the presence of *TFE3* rearrangement. Both cohorts were analysed separately.

Ethics approval was obtained for this study (ClinicalTrials.gov identifier NCT01524926), which was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation-Good Clinical Practice, and participating country and institution regulations.

### *Patient enrolment*

Patient enrolment was based on a multi-step registration procedure. Step 1 prerequisites for registration were a local diagnosis of advanced and/or metastatic ASPS deemed incurable by conventional surgery, radiotherapy or systemic therapy, the availability of a formalin-fixed paraffin embedded (FFPE) tumour-containing tissue block from primary tumour and/or metastatic site, and written informed consent of the patient for central collection of tissue and all other trial-specific procedures.

Criteria for step 2 included receipt of the tissue by a central biorepository (BioRep, Milan, Italy) with presence of tumour in the shipped material and confirmation of the correct diagnosis of ASPS by central reference pathology.

Screened patients were treated after completion of both steps, provided all other eligibility criteria were met. Details on patient selection and prior treatments are described in the study protocol (<http://www.eortc.be/services/doc/protocols/90101v10.0.pdf>).

Documentation of the presence of *TFE3* rearrangement was not required for a patient to enter the treatment phase (step 3). FISH analysis was done while patients were already receiving therapy, to avoid delaying start of treatment for patients in need for an experimental treatment.

### *Treatment, safety and efficacy assessment*

Eligible patients with centrally confirmed ASPS were treated with oral crizotinib at a starting dose of 250mg twice daily. One treatment cycle was defined as 21 days. Treatment, dose and schedule modifications were defined in the protocol.

Tumour assessments were done based on RECIST 1.1 using computer tomography or magnetic resonance imaging of chest, abdomen and pelvis. Baseline scans were not older than 28 days at study entry. The radiological assessment was done locally every 6 weeks and repeated to confirm objective responses at least 4 weeks after the initial documentation of a response. Objective responses were reviewed centrally.

Safety information was collected using the Common Terminology Criteria for Adverse Events (CTCAE) version: 4.0.

### *Assessment of TFE3 rearrangement*

Patients were attributed to *MET*<sup>+</sup> or *MET*<sup>-</sup> sub-cohorts on the basis of the presence or absence of a *TFE3* gene rearrangement, assessed by fluorescence *in situ* hybridization (FISH) on interphase nuclei of paraffin-embedded 4 µm tumour tissue sections, using custom bacterial artificial chromosomes (BAC) RP11-344N17 and RP11-552J9 probes that flank the *TFE3*/Xp11.2 gene. The BAC clones were obtained from the BACPAC Resource Center (CHORI; Oakland, CA). DNA isolation, probe labeling and hybridization were performed as previously described.<sup>16</sup> Slides were scored by two independent investigators and considered positive if >15% of at least 100 cells showed split signals.

### *Outcomes*

The main objective was to study the activity of crizotinib in ASPS patients with *TFE3* gene rearrangement (*MET*<sup>+</sup>). The primary endpoint was the ORR per RECIST 1.1 with response confirmation, assessed by the local investigator. This endpoint was chosen based on the response pattern seen with crizotinib in the labelled indication of NSCLC and due to the absence of reliable reference data on PFS or PFR in ASPS when the protocol was written. Secondary endpoints included: DOR, DCR, PFS, PFR, OS, overall survival rate (OSR), safety, and correlative/translational research endpoints. DCR was defined as the percentage of patients achieving a complete (CR), or partial response (PR), or stable disease (SD).

### *Statistical analysis*

A Simon's optimal two-stage design was implemented separately for the ASPS *MET*<sup>+</sup> and *MET*<sup>-</sup> sub-cohorts. The type I error and power were set at 10%. The study was conceptually focused on *MET*<sup>+</sup> disease, while *MET*<sup>-</sup> patients served as a non-randomized, treated internal control. The entry of "all comers" independent of their *MET* status allowed centres to avoid delaying treatment for patients in need of an active intervention and to provide reference data for both subsets for future clinical trials. The entry of *MET*<sup>-</sup> cases was considered ethical due to the lack of validated treatment alternatives.

In stage 1, if at least two out of the first 12 eligible and evaluable *MET*<sup>+</sup> ASPS patients achieved a confirmed RECIST PR or CR, a maximum of 35 patients were to be enrolled. In stage 2, if <6 out of the 35 eligible and evaluable patients responded, the treatment was declared ineffective. If ≥6 out of the 35 patients (17%) responded, further study of crizotinib was warranted. Treatment activity was declared if response rate was >10%.

Stopping rules and activity endpoints details are provided in [Supplementary Methodology](#). Analyses were performed using the SAS version 9.4 (SAS Institute, Cary, United States).

## **Results**

### *Patient disposition, reference pathology, clinical screening and enrolment*

Between 17 June 2013 and 29 June 2015, 19 sites in 10 European countries recruited 53 patients with the local diagnosis of ASPS. All patients had a centrally confirmed ASPS, which is likely a reflection of the routine use of FISH testing in this sarcoma subtype.

Forty-eight patients were enrolled in the study and started treatment with crizotinib (safety population: 43 *MET*<sup>+</sup>, 4 *MET*<sup>-</sup>, 1 *MET*<sup>?</sup>). Reasons for not entering the treatment phase in the 5 remaining patients are shown in the trial profile (Supplementary Figure S5). Out of 48 patients who started treatment, 45 were eligible and evaluable for the primary and secondary endpoints (40 *MET*<sup>+</sup>, 4 *MET*<sup>-</sup>, 1 *MET*<sup>?</sup>). Two were found ineligible due to the use of specific concomitant medication or residual toxicity from prior therapy, one patient had surgery after one treatment cycle without further imaging.

Recruitment to both the *MET*<sup>+</sup> and *MET*<sup>-</sup> sub-cohorts was suspended on 26 June 2015, with endorsement by the trial steering committee according to protocol.

### *Molecular analysis*

FISH analysis was completed within a median time of 5 days after receipt of technically useful, unstained slides from the central biorepository.

Among the 53 patients with centrally confirmed diagnosis, 48 (90.6%) had *TFE3* gene rearrangement and were defined as *MET*<sup>+</sup>, and 4 (7.5%) had no rearrangement detected by FISH. In one remaining patient, FISH analysis could not be performed due to insufficient quality of the available biological material. This patient was defined as *MET*<sup>?</sup>. [Supplementary Table S1](#) shows an overview of the cytogenetic findings.

### *Patient characteristics*

Characteristics of the 48 treated patients are shown in [table 1A](#). Their median age was 30 years, 75.0% (36/48) had an ECOG PS of 1, the majority (64.6% [31/48]) had undergone prior surgery, and 47.9% (23/48) had received systemic therapy.

Among the total group with confirmed diagnosis of ASPS, 43/48 *MET*<sup>+</sup> patients, 4/4 *MET*<sup>-</sup> patients, and the one *MET*<sup>?</sup> patient received crizotinib ([Supplementary Figure S5](#)).

### *Crizotinib study treatment*

As of 19 May 2017, with a median follow-up of 833 days (range: 85-1279), 2/45 treated patients were still receiving active treatment ([Supplementary Figure S5](#) and [table 1B](#)). The median relative dose intensity was 98.2%, with 27/45 treated patients requiring dose reductions or dose modifications. The treatment duration with crizotinib ranged from 2.4-156.1 weeks ([table 1B](#)). Reasons for treatment discontinuation are shown in [table 1B](#).

### *Activity of crizotinib*



Objective responses were observed in 1/40 *MET*<sup>+</sup> patients(2.5%ORR; 95% confidence interval[CI]:0-13.2%) and in 1/4 *MET*<sup>-</sup> patients(25.0%;95%CI:0.6-80.6%).Key efficacy data are summarized in [table 1C](#).The DOR was 215 days in the responding *MET*<sup>+</sup> patient and 801 days in the *MET*<sup>-</sup> patient.The responding patients progressed after 52 and 14 treatment cycles, respectively,and both are alive at the data cut-off. SD was observed in 87.5%(35/40) *MET*<sup>+</sup> patients, in 75.0%(3/4) *MET*<sup>-</sup> patients,and in the one *MET*<sup>?</sup> patient. The remainder of patients had progression. The DCR was 90%(36/40) in *MET*<sup>+</sup> patients(95%CI:76.3-97.2%),and 100% in *MET*<sup>-</sup>(95%CI:39.8-100.0%) and the one *MET*<sup>?</sup> patient.

The PFR at 1 year was 37.5%(95%CI:22.9-52.1%), 50.0%(95%CI:5.8-84.5%) and 0% in *MET*<sup>+</sup>, *MET*<sup>-</sup>, and *MET*<sup>?</sup> patients,respectively. The 3 and 6 months cumulative PFR in *MET*<sup>+</sup> patients were 85%(CI:73.9-96.1%) and 55.0%(39.6-70.4%),and in *MET*<sup>-</sup> 75.0% (95%CI:32.6-100%) and 50.0%(1.0-99.0),respectively. Two-years PFR are shown in [figure 1A](#) and [table 1C](#).

The 1 year OSR were 97.4 %(95%CI:82.8-99.6%) in *MET*<sup>+</sup> patients and 75.0%(95%CI:12.8-96.1%) in *MET*<sup>-</sup> patients. The OS at 2 years was 81.3%(95%CI:64.7-90.6%) in *MET*<sup>+</sup> patients and unchanged in *MET*<sup>-</sup> patients(75.0%[95%CI:12.8-96.1%])([figure 1B](#) and [table 1C](#)).The long follow-up of this trial allows us to provide important information on the clinical course of advanced/metastatic ASPS,and serves as a useful resource for future research in this rare cancer.

[Figure 1C](#) illustrates the maximum target lesion shrinkage,[figure 1D](#) summarizes the clinical course of the treated patients.

### *Safety and toxicity*

No new, unexpected safety signals were detected in ASPS patients. The most common(overall, grade  $\geq$ 1) crizotinib-related adverse events were nausea(34/48[70.8%]), vomiting (22/48[45.8%]),blurred vision(22/48[45.8%]),diarrhoea(20/48[41.7%]),and fatigue (19/48[39.6%]).

Treatment-related grade 3/4 events were fatigue(two patients),hypotension grade 4 combined with bradycardia grade 4,blurred vision,diarrhoea and febrile neutropenia(one patient each).Adverse events details are shown in [Supplementary Table S2](#) and [S3](#). The [Supplementary Results](#) summarises serious adverse events.

No deaths occurred on treatment or within 4 weeks of treatment discontinuation.

## **Discussion**

Information from prospective clinical trials on the efficacy of systemic treatments for ASPS is limited. EORTC 90101 CREATE is one of the first ASPS-specific prospective studies. The main objective of this phase 2 study was to assess the activity of crizotinib in ASPS,a very

rare and chemotherapy-resistant, translocation-related sarcoma. The primary endpoint of the trial was not met, as we did not observe at least two objective and radiologically confirmed RECIST 1.1 responses among the first 12 eligible and evaluable *MET*<sup>+</sup> cases.

Multiple factors led to over recruitment of patients. The rapid accrual of ASPS cases, with more than half of the patients previously untreated, reflected the high unmet medical need for this orphan and hard to treat malignancy. Investigators observed a relevant proportion of patients achieving early disease stabilization with crizotinib, and all these cases could theoretically still convert, upon further exposure, to an objective response. Furthermore, all responses had to be confirmed by a second scan, to be in line with RECIST 1.1. This led to a delay in reporting efficacy data for trial participants, as investigators had to wait until their patients either came off study or had reached a confirmed PR. By that time we had exceeded the originally planned maximum sample size to assess the futility of crizotinib in *MET*<sup>+</sup> ASPS. In the light of the lack of validated treatment alternatives for this malignancy we accepted this over recruitment.

The majority of our trial participants had a centrally confirmed *TFE3* gene rearrangement, and none of the study ASPS patients were misclassified according to central pathology review. This is likely a reflection of the increasing local use of molecular testing in many institutions in translocation-related STS.

Of note, 4 patients had no detectable rearrangement of the *TFE3* gene by FISH (classified as *MET*<sup>-</sup>). It is possible that these were false negative cases due to cryptic gene rearrangements that are under microscopic visibility. This could explain also the challenging observation that some of these *MET*<sup>-</sup> patients seemed to benefit from the treatment with crizotinib. Confirmation of *ASPSCR1/TFE3* fusion by RT-PCR or other molecular techniques in these cases would be required to prove this notion.

Even though *TFE3* rearrangement, potentially leading to altered MET expression, was present in the majority of our patients, crizotinib's inhibition of MET translated in only sporadic, but durable objective responses. It is unclear why two of our patients (one *MET*<sup>+</sup>, one *MET*<sup>-</sup>) had exceptional responses, but we hope that further tissue-based analysis will provide an explanation. We cannot exclude that the presence of the *ASPSCR1-TFE3* fusion led to different level of altered MET expression/abnormal activation. On the other hand these responses might be induced by effects other than MET inhibition, as crizotinib affects more than one target.

Interestingly, 90% of our patients with *TFE3* gene rearrangement achieved disease control and the duration of therapy was long (median number of 12.5 treatment cycles in *MET*<sup>+</sup> patients), suggesting that PFS or PFR would have been better primary endpoints. The response pattern of MET-driven malignancies to crizotinib is clearly different than the impressive volumetric responses seen in ALK or ROS1 driven NSCLC.

Based on a retrospective statistical analysis of multiple EORTC sarcoma trials, Van Glabbeke et al. proposed reference values for potentially active agents in STS.<sup>17</sup> For first line therapy, she recommended a 6 month PFR of  $\geq 30$ -56% and for second line therapy a 3 month PFR of

$\geq 40\%$  as an indicator of promising activity, while a 6 month PFR of  $\leq 20\%$  would suggest inactivity of a novel compound. In our ASPS *MET*+ group, the 3 and 6 months cumulative PFR were 85% (CI: 73.9-96.1%) and 55.0% (39.6-70.4%). In an exploratory analysis of our study, in pretreated *versus* non-pretreated *MET*+ patients, the first-line subset had a 3 and 6 month PFR of 52.6% (30.2-75.1) and 42.1% (19.9-64.3%). The second-line subset had a 3 and 6 month PFR of 57.1% (20.5-93.8%) and 14.3% (0.0-40.2%). This *post hoc* analysis suggests that crizotinib is active in this setting following Van Glabbeke's criteria.

The PFS seen with crizotinib in *MET*+ ASPS is better than results achieved in non-selected patients with advanced STS treated with single-agent doxorubicin in first line (4.6 months, 95% CI: 2.9-5.6),<sup>18</sup> or with the oral angiogenesis inhibitor pazopanib in previously treated STS patients (4.6 months, 95% CI: 3.7-4.8).<sup>19</sup> However, the biological behaviour of ASPS is so different from the majority of sarcomas, that the value of comparing the results of this study with all-comer STS studies is relatively limited. In a retrospective database review evaluating the efficacy of pazopanib and/or trabectedin in advanced ASPS patients, the median PFS for pazopanib (*N*=29) was 13.6 months (range: 1.6-32.2+) at 19-month median follow-up, the median PFS for trabectedin (*N*=23) was 3.7 months (range: 0.7-109) at 27-months.<sup>20</sup> In our trial, in ASPS with *TFE3* gene rearrangement (with about half of the patients previously treated), crizotinib (*N*=40) was associated a median PFS of 8.0 months (95% CI: 4.1-12.8) and the median OS was not reached after a median 833 days (range: 85-1279).

The tissue blocks collected from 53 ASPS patients are now the basis for multiple ongoing exploratory studies, to improve our understanding of the biology and the identification of new prognostic/predictive biomarkers and treatment strategies for this rare cancer.

Our study showed variable responses, which suggests the presence of other factors in combination with *TFE3* rearrangement which might predict efficacy of crizotinib. As the level of *MET* expression and/or activation may vary in different ASPS tumours, even with ASPSCR1-*TFE3* fusion present, it should be thoroughly evaluated using immunohistochemistry for both total and activated forms of the signalling pathway components. Furthermore, the level of *MET* gene expression could be assessed utilising *in situ* hybridisation or quantitative polymerase chain reaction. This translational part of the project is on-going, using leftover material. In addition, we are currently performing correlative studies using whole exome sequencing to evaluate the mutational profile and perform low-coverage whole genome sequencing to study copy number changes, which will be supplemented by research using tissue microarrays constructed from the tissue blocks, to better understand the molecular background of ASPS and the sensitivity or resistance of individual cases to crizotinib.

The range of adverse events observed in this study was consistent with safety data for crizotinib in NSCLC patients. No new types of adverse events were observed in ASPS. Dose intensity was high and the incidence of dose modifications due to toxicity was moderate.

This study illustrates some of the methodological limitations using response rate in early clinical trials in oncology. Our study's primary endpoint was chosen based on the volumetric responses seen with crizotinib in the labelled indication of *ALK*+ NSCLC and due to the

absence of reliable reference data on PFS or PFR in ASPS. In general, EORTC is recommending the use of time-related endpoints such as PFR during the early exploration of novel agents in STS,<sup>17</sup> which provided the phase 2 rationale for at least two successful registration trials in STS in the past years.<sup>19,21</sup>

We currently see more trial activity in ASPS than in the past. Most trials focus on angiogenesis inhibitors, which can induce a clinically relevant reduction in tumour burden in individual patients. NCT01337401 (CASPS), evaluating the efficacy and safety of cediranib vs placebo (with crossover to cediranib), used a somewhat artificial primary endpoint measuring the percentage change in the sum of target marker lesion diameters from baseline to week 24 (or progression if sooner). The study met its primary endpoint. PR was observed with cediranib in 6/28 ASPS patients vs 0/16 patients on placebo, SD occurred in 19/28 (68%) of patients on cediranib and 12/16 (75%) on placebo. The median PFS was 10.8 months for cediranib vs 3.7 months for placebo (Hazard Ratio: 0.54 [90% CI: 0.30-0.97,  $p=0.041$ ]).<sup>22</sup> Cediranib is also being tested in two other studies (NCT00942877 and NCT01391962). Other antiangiogenic agents under evaluation in ASPS are pazopanib (NCT02113826) and sunitinib (NCT01391962).

In this study in patients with advanced or metastatic ASPS with central determination of rearrangement of *TFE3*, we were able to demonstrate that crizotinib is an active compound for ASPS, given the DCR and PFR observed in this histotype-specific trial. We would recommend for future early clinical trials involving novel targeted therapies for ASPS that endpoints such as DCR, PFS and/or PFR should be considered.

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The lead investigator had access to all data in the study, was responsible for providing regular information to the relevant committees monitoring this trial and had final responsibility for the decision to submit for publication. All authors were responsible for data interpretation and final approval of the manuscript for submission.

## **Disclosures**

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P Reichardt: received grants and personal fees from Novartis, received personal fees from Pfizer, Bayer, PharmaMar, Amgen, AstraZeneca, Clinigen, Lilly, Deciphera, outside the submitted work

JS: Honoraria from Roche, Novartis, Swedish Orphan, Merck

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MDR: no competing interest

RS: no competing interest

TVC: no competing interest

SM: no competing interest

TR: no competing interest

SC: no competing interest

SS: no competing interest

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**Figure 1A.** Kaplan-Meier estimates for progression-free survival for the *MET*<sup>+</sup> and *MET*<sup>-</sup> sub-cohorts per protocol.

**Figure 1B.** Kaplan-Meier estimates for overall survival for the *MET*<sup>+</sup> and *MET*<sup>-</sup> sub-cohorts per protocol.

**Figure 1C.** Maximum shrinkage of RECIST 1.1 target lesions (per protocol) in the *MET*<sup>+</sup>, *MET*<sup>-</sup>, and *MET*<sup>?</sup> sub-cohorts, according to local investigator's assessment.

**Figure 1D.** Clinical course of patients in the ASPS *MET*<sup>+</sup>, *MET*<sup>-</sup> and *MET*<sup>?</sup> sub-cohorts

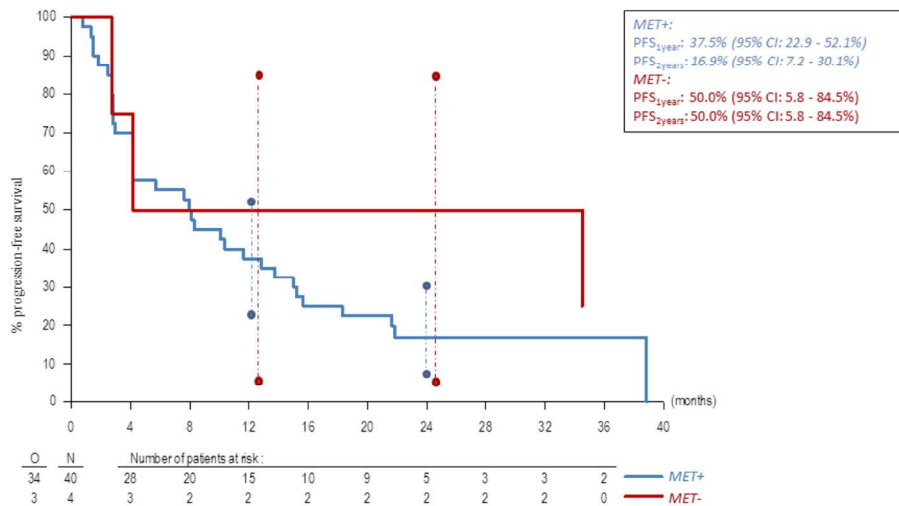


Figure 1A. Kaplan-Meier estimates for progression-free survival for the *MET+* and *MET-* sub-cohorts per protocol. † Legend: The vertical bars represent the 95% confidence intervals for the 1- and 2-year progression-free survival (PFS) rates. The median PFS in *MET+* patients was 8.0 months (95% CI: 4.1-12.8).

254x190mm (150 x 150 DPI)

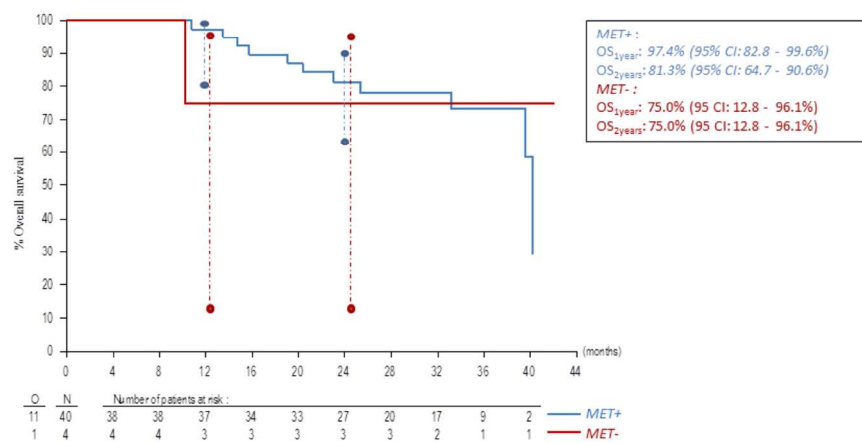


Figure 1B. Kaplan-Meier estimates for overall survival for the *MET+* and *MET-* sub-cohorts per protocol.!! † Legend: The vertical bars represent the 95% confidence intervals for the 1- and 2-year overall survival (OS) rates. The median OS has not been reached.

254x190mm (150 x 150 DPI)

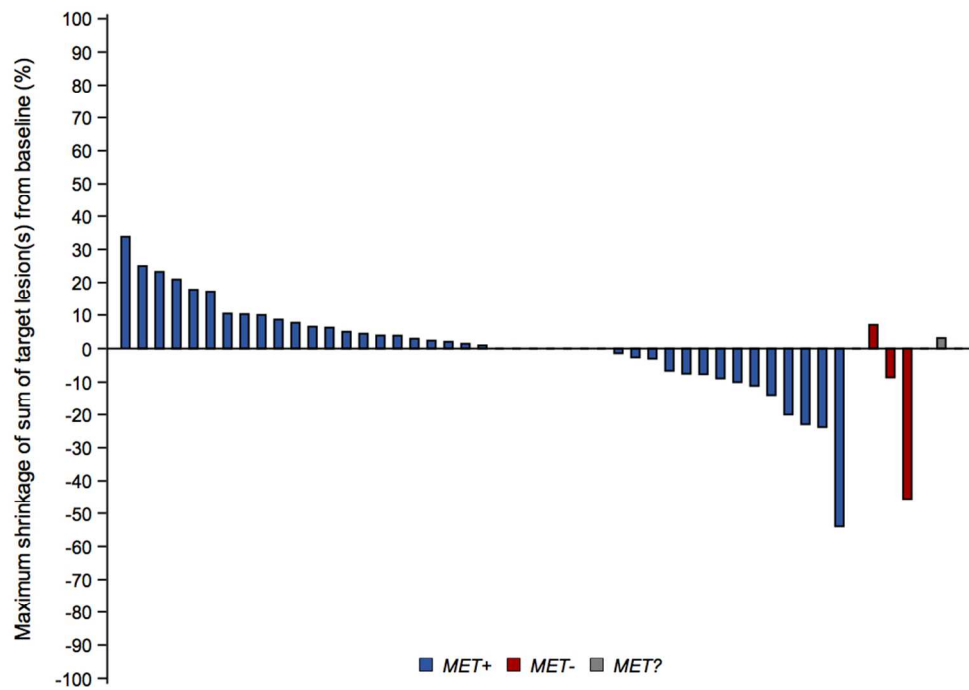


Figure 1C. Maximum shrinkage of RECIST 1.1 target lesions (per protocol) in the *MET+*, *MET-*, and *MET?* sub-cohorts, according to local investigator's assessment.

185x132mm (150 x 150 DPI)

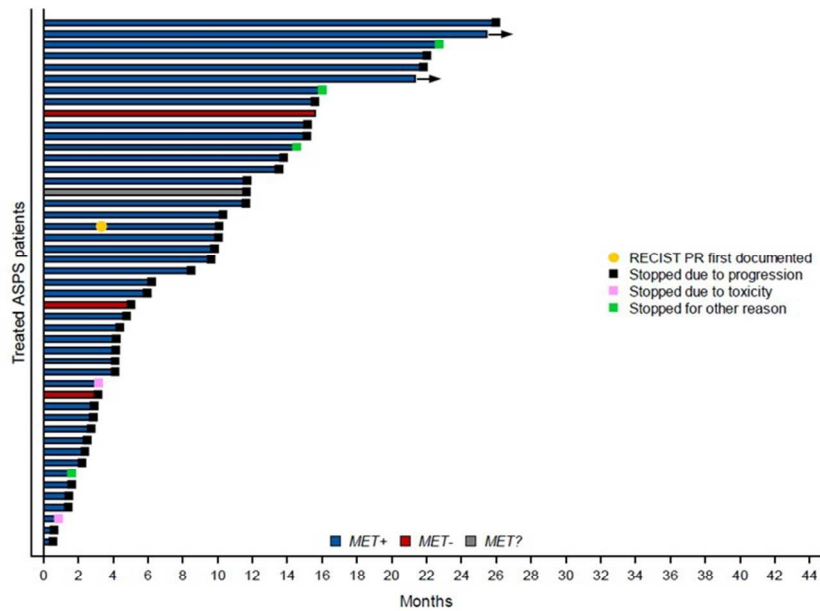


Figure 1D. Clinical course of patients in the ASPS *MET+*, *MET-* and *MET?* sub-cohorts.

254x190mm (96 x 96 DPI)

**Table 1.** Patient characteristics, study treatment, and response assessment and efficacy summary.

**Table 1A.** Key patient characteristics.

	<i>MET</i> status			Total (N=48) N (%)
	<i>MET</i> + (N=43) N (%)	<i>MET</i> - (N=4) N (%)	<i>MET</i> ? (N=1) N (%)	
Age (years)				
Median	30	41	35	30
Range	16 - 54	22 - 69	n/a	16 - 69
Eastern Cooperative Oncology Group performance status				
0	33 (76.7)	2 (50.0)	1 (100.0)	36 (75.0)
1	9 (20.9)	2 (50.0)	0 (0.0)	11 (22.9)
2	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.1)
Sex				
Male	22 (51.2)	3 (75.0)	1 (100.0)	26 (54.2)
Female	22 (51.2)	3 (75.0)	1 (100.0)	26 (54.2)
Any previous major surgery	28 (65.1)	2 (50.0)	1 (100.0)	31 (64.6)
Any previous systemic anticancer therapy	21 (48.8)	1 (25.0)	1 (100.0)	23 (47.9)
Chemotherapy	10 (23.3)	0 (0.0)	1 (100.0)	11 (22.9)
Tyrosine kinase inhibitor	13 (30.2)	1 (25.0)	n/a	14 (29.2)
Mammalian target of rapamycin inhibitor	2 (4.6)	n/a	n/a	2 (4.2)
Autologous stem cell reinfusion for ASPS	1 (2.3)	n/a	n/a	1 (2.1)

Legend: Patients were attributed to *MET* sub-cohorts on the basis of the presence or absence of a *TFE3* gene rearrangement assessed by fluorescence *in situ* hybridization (FISH). *MET*+, *MET* altered (>15% of at least 100 cells showed split signals); *MET*-, *MET* non-altered; *MET*?, FISH analysis could not be performed due to insufficient quality of the available biological material; n/a, not applicable.

**Table 1B.** Treatment, dose intensity and dose adjustments.

	<i>MET</i> status			Total
	<i>MET</i> + ( <i>N</i> =40) <i>N</i> (%)	<i>MET</i> - ( <i>N</i> =4) <i>N</i> (%)	<i>MET</i> ? ( <i>N</i> =1) <i>N</i> (%)	( <i>N</i> =45) <i>N</i> (%)
Treatment, dose intensity and dose adjustments:				
Relative dose intensity (%)				
Median	98.1	98.3	98.3	98.2
Range	57.8 - 101.1	95.8 - 100.3	98.3 - 98.3	57.8 - 101.1
Number of patients with at least one treatment modification				
Reduction to dose level -1 (200 mg twice daily)	9 (22.5)	0 (0.0)	0 (0.0)	9 (20.0)
Reduction to dose level -2 (250 mg once daily)	3 (7.5)	0 (0.0)	0 (0.0)	3 (6.7)
Other dose level modification	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Interruption of treatment	16 (40.0)	1 (25.0)	1 (100.0)	18 (40.0)
<b><u>Treatment duration:</u></b>				
Duration of treatment (weeks)				
Median	39.5	45.0	50.9	42.0
Range	2.4 - 113.3	13.7 - 156.1	50.9 - 50.9	2.4 - 156.1
Number of cycles				
Median	12.5	15.5	17.0	13.0
Range	1.0 - 38.0	5.0 - 52.0	17.0 - 17.0	1.0 - 52.0
<b><u>Reasons for treatment discontinuation:</u></b>				
Treatment status				
Ongoing	2 (5.0)	0 (0.0)	0 (0.0)	2 (4.4)
Stopped	38 (95.0)	4 (100.0)	1 (100.0)	43 (95.6)
Major reason for protocol treatment discontinuation				
Progression of ASPS	32 (84.2)	3 (75.0)	1 (100.0)	36 (83.7)
Toxicity	2 (5.3)	0 (0.0)	0 (0.0)	2 (4.7)
Hepatic toxicity	1			
Multiple adverse events (diarrhea, vomiting, dizziness, headache, blurred vision, rash, nausea)	1			
Patient decision	3 (7.9)	0 (0.0)	0 (0.0)	3 (7.0)
Symptomatic deterioration without radiological evidence of PD/relapse	0 (0.0)	1 (25.0)	0 (0.0)	1 (2.3)
Other	1 (2.6)	0 (0.0)	0 (0.0)	1 (2.3)
Discontinuation for resection of target lesions	1			

**Table 1C.** Response assessment and efficacy summary, according to investigator assessment.

	MET status			Total (N=45) N (%)
	MET+ (N=40) N (%)	MET- (N=4) N (%)	MET? (N=1) N (%)	
<b>Best RECIST 1.1 response</b>				
Complete response	-	-	-	-
Partial response	1 (2.5)	1 (25.0)	0 (0.0)	2 (4.4)
Stable disease	35 (87.5)	3 (75.0)	1 (100.0)	39 (86.7)
Progressive disease	4 (10.0)	0 (0.0)	0 (0.0)	4 (8.9)
Objective response rate (95% CI)	2.5% (0-13.2%)	25.0% (0.6-80.6%)	0% (0-97.5%)	4.4% (0-15%)
Disease control rate (95% CI)	90.0% (76.3-97.2)%	100.0% (39.8-100.0%)	100.0% (2.5-100.0)%	91.1% (78.8-97.5)%
<b>Progression-free survival</b>				
Alive with no evidence of disease	6 (15.0)	1 (25.0)	0 (0.0)	7 (15.6)
Progression of ASPS or died	34 (85.0)	3 (75.0)	1 (100.0)	38 (84.4)
1-year progression-free survival rate (95% CI)	37.5 % (22.9-52.1%)	50.0 % (5.8-84.5%)	0.0 % -	37.8 % (23.9, 51.6%)
2-year progression-free survival rate (95% CI)	16.9 % (7.2-30.1%)	50.0 % (5.8-84.5%)	0.0 % -	19.6 % (9.5-32.3%)
Median (months) (95%CI)	8.0 (4.1-12.8)	19.3 (2.8-infinity)	-	8.1 (4.2-12.8)
<b>Survival status</b>				
Alive	29 (72.5)	3 (75.0)	0 (0.0)	32 (71.1)
Dead	11 (27.5)	1 (25.0)	1 (100.0)	13 (28.9)
Reason of death :				
Progression of ASPS	9 (22.5)	1 (25.0)	1 (100.0)	11 (24.4) *
Unspecified (information received via a registry)	2 (5.0)			
1-year survival rate (95% CI)	97.4% (82.8-99.6%)	75.0% (12.8-96.1%)	-	95.4% (82.7-98.8%)
2-year survival rate (95% CI)	81.3% (64.7-90.6%)	75.0% (12.8-96.1%)	-	81.2% (65.9-90.1%)
Median (months) (95%CI)	not reached	-	-	not reached

Legend: CI, confidence interval