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Activity and safety of crizotinib in patients with advanced clear cell sarcoma with *MET* alterations. European Organization for Research and Treatment of Cancer phase 2 trial 90101 "CREATE"

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Summary

Background: Clear cell sarcoma (CCSA) is an orphan malignancy, characterised by a specific t(12;22) translocation, leading to rearrangement of the *EWSR1* gene and overexpression of MET. We prospectively investigated the efficacy and safety of the tyrosine kinase inhibitor (TKI) crizotinib in patients with advanced or metastatic CCSA.

Patients and methods: Patients with CCSA received oral crizotinib 250 mg twice daily. Primary endpoint was objective response rate (ORR), secondary endpoints included duration of response, disease control rate (DCR), progression-free survival (PFS), progression-free rate (PFR), overall survival (OS), overall survival rate (OSR) and safety. The study design focused on *MET*+ disease with documented rearrangement of the *EWSR1* gene by fluorescence *in situ* hybridization (FISH).

Results: Among 43 consenting patients with the local diagnosis of CCSA, 36 had centrally confirmed CCSA, 28 of whom were eligible, treated and evaluable. 26/28 patients had *MET*+ disease, of whom one achieved a confirmed partial response and 17 had stable disease (SD) (ORR 3.8%, 95% confidence interval:0.1-19.6). Further efficacy endpoints in *MET*+ CCSA were DCR:69.2% (48.2-85.7%), median PFS:131 days (49-235), median OS:277 days (232-442). The 3, 6, 12 and 24 month PFR was 53.8% (34.6-73.0), 26.9% (9.8-43.9), 7.7% (1.3-21.7) and 7.7% (1.3-21.7), respectively. Among two evaluable *MET*- patients, one had SD and one had progression. The most common treatment-related adverse events were nausea (18/34[52.9%]), fatigue (17/34[50.0%]), vomiting (12/34[35.3%]), diarrhea (11/34[32.4%]), constipation (9/34[26.5%]) and blurred vision (7/34[20.6%]).

Conclusions: The PFR with crizotinib in *MET*+ CCSA is similar to results achieved first-line in metastatic soft tissue sarcomas with single-agent doxorubicin. In further lines, the PFS is similar to pazopanib in previously treated sarcoma patients.

Clinical trial number: EORTC 90101, EudraCT number 2011-001988-52, NCT01524926

Key words: Clear cell sarcoma, *MET* gene, *EWSR1* gene rearrangement, tyrosine kinase inhibitor, crizotinib

Prior presentations Early data have been reported at the American Society for Clinical Oncology Annual Meeting in Chicago (IL) on Sunday, May 31, 2015 (abstract number: 10547).

Key message:

CCSA is a rare chemotherapy-resistant, translocation-related sarcoma. Our phase 2 trial demonstrated that crizotinib provided clinical benefit, with 69.2% (18/26, 95% CI:48.2-85.7) of CCSA cases with documented *EWSR1* gene rearrangement achieving disease control for a median of 131 days. We recommend using time-related endpoints for early studies of novel agents in STS.

Introduction

Clear cell sarcoma (CCSA) is a rare aggressive tumour that primarily affects adolescents and young adults, typically involves deep soft tissue of the lower extremities and tends to occur near tendons, fascias and aponeuroses.¹⁻⁵ CCSA is associated with a high rate of local recurrence, distant metastasis and lymph node involvement, which is uncommon in other types of soft tissue sarcoma (STS).³⁻⁵ The five-year OS is around 50-67%, but this decreases to 20% in patients with metastatic disease.^{3,6,7} CCSA tends to be resistant to conventional chemotherapy and to radiation therapy.^{3,6}

CCSA is characterised by the t(12;22)(q13;q12) translocation resulting in the Ewing sarcoma breakpoint region 1 / activating transcription factor-1 (*EWSRI/ATF1*) fusion gene, presenting in >90% of cases (Supplementary Material/Introduction and Supplementary Figures S1,S2 provides details on the *EWSRI/ATF1* fusion gene and the MET signaling pathway).^{3,8,9} FISH is used to detect these fusions and to establish the diagnosis of CCSA (Supplementary Figure S3). Davies et al. confirmed MET expression requires EWS-ATF1 expression, and the viability and motility of CCSA is dependent on the HGF/MET axis signaling.³ MET inhibition may offer an indirect target for the treatment of CCSA.³ In studies using specific inhibitors of MET signalling, MET activity was found to be essential for proliferation and survival of CCSA cell lines and xenograft models.^{3,10,11}

Based on MET involvement in CCSA and the absence of a standard treatment for patients with advanced disease, strong rationale exists to explore therapies that target the MET tyrosine kinase receptor, such as crizotinib (Xalkori®, PF-02341066, Pfizer Inc.).^{8,11} MET engagement results in the activation of multiple downstream signaling pathways, including phosphatidylinositol 3 kinase (PI3K)/AKT, RAS/MAPK pathways, etc.^{3,10,12} While several active targets in CCSA exist for future investigations, our study focused on the MET receptor as a target for crizotinib inhibition. Crizotinib, a small molecule TKI, inhibits MET, anaplastic lymphoma kinase (ALK) and ROS proto-oncogene 1 receptor tyrosine kinase (ROS1).¹³⁻¹⁷ It interferes with pathways by competitively inhibiting adenosine triphosphate from binding to the receptor, thereby preventing phosphorylation.¹³⁻¹⁷ This blocks the downstream cascade of events, inhibiting the growth and survival of MET dependent cells.¹³⁻¹⁷ Crizotinib is approved for first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours are either ALK- or ROS1-positive, 250 mg twice daily is the recommended oral adult dose.¹⁸

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 characterized by *MET* and/or *ALK* alterations. CREATE included ALK or MET driven tumour types in 6 disease-specific cohorts. We present the independent CCSA cohort results here.

Methods

Study design

This was a multicentre, biomarker-driven, single agent, non-randomized, open-label, two-stage phase 2 trial, assessing the activity and safety of crizotinib in patients with locally

advanced or metastatic CCSA (EORTC 90101, ClinicalTrials.gov:NCT01524926). The patient population was divided into *MET* positive (*MET*⁺; presence of *EWSR1* gene rearrangement) and *MET* negative (*MET*⁻; absence of *EWSR1* gene rearrangement) sub-cohorts, which were analysed separately. Investigators were blinded to the centrally assessed *MET* status.

Ethics approval was obtained by competent committee(s) and according to national legislation. The study was conducted in accordance with: the Declaration of Helsinki; laws and regulations of each participating country/institution; and the International Conference on Harmonisation-Good Clinical Practice.

Patient enrolment

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

The requisite criteria for step 2 included receipt of the tissue block by a central biorepository (BioRep, Milan, Italy) with presence of tumour in the shipped material and confirmation of the correct diagnosis of CCSA by central pathology.

Screened patients were treated after completion of step 1 and 2, provided all eligibility criteria were met. There were no limitations in terms of previous systemic or local treatments for CCSA only prior exposure to crizotinib or other specific *MET*-inhibiting agents was not allowed. Details on the patient selection are described in the study protocol (<http://www.eortc.be/services/doc/protocols/90101v10.0.pdf>).

Treatment, safety and efficacy assessment

Eligible patients with centrally confirmed diagnosis of CCSA were treated with oral crizotinib at a starting dose of 250 mg twice daily. One treatment cycle was defined as 21 days in duration. Treatment continued until progression, unacceptable toxicity, or patient refusal. Dosing instructions were in line with the standard use of crizotinib in the labelled NSCLC indication. Dose and schedule modifications were defined in the protocol.

Safety information was collected at baseline, day 15 of cycle 1 and 2, and at the end of every cycle applying the Common Terminology Criteria for Adverse Events [CTCAE] version 4.0. Tumour assessments were performed every other cycle by the local investigator according to RECIST 1.1 on the basis of computer tomography or magnetic resonance imaging. Digital images were collected and objective responses were centrally reviewed.

*Assessment of *MET* alterations*

Patients were attributed to the *MET*⁺ sub-cohort based on the presence of the *EWSR1* gene rearrangement. This was assessed by FISH with the commercially available dual colour break-apart rearrangement probe Vysis[®] LSI[®] *EWSR1*(22q12)(Abbott Molecular). At least 15% of tumour cells had to show a rearrangement for a case to be considered *MET*⁺. This threshold was established by validation of the specific FISH probe in the specific indication in

the laboratory performing the evaluation, as well as running this test in clinical routine. *EWSR1* rearrangement is a molecular hallmark of CCSA, so a very low rate of *MET*- cases were expected.

Outcomes

The main objective was to study the activity of crizotinib in *MET*+ CCSA patients. The primary endpoint was 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 in the absence of reliable reference data on PFS or PFR in CCSA. Secondary endpoints included: duration of response, DCR, PFS, PFR, OS, OSR, safety, and correlative/translational research endpoints. The DCR was defined as the percentage of patients achieving either a complete (CR) or partial response (PR) or SD.

Statistical analysis

The statistical design was conceptually focused on centrally documented *EWSR1* fusion (*MET*+ sub-cohort) cases. It was decided that showing an ORR > 10% (null hypothesis) in CCSA *MET*+ patients, a rare population, resistant to chemotherapy and radiotherapy, would be promising for future research. Therefore a Simon's optimal two-stage design¹⁹ was implemented with the aim of excluding an ORR ≤10% under the alternative assumption that 30% ORR can be achieved with crizotinib. The type I error and power were set at 10%. In stage 1, if at least two out of the first 12 eligible and evaluable CCSA *MET*+ patients achieved a confirmed RECIST PR or CR, a maximum of 35 patients were to be enrolled. In stage 2, if less than 6 out of 35 eligible and evaluable patients responded, the treatment was declared ineffective. If at least 6 out of the 35 patients responded, further study of crizotinib in CCSA was warranted.

MET- patients served as a non-randomized, non-historical, treated internal control. The entry of “all comers” independent of their *MET* status was allowed, to avoid delay of treatment for patients in need of an active intervention and to provide reference data for both subsets. The entry of *MET*- cases was considered ethical due to the lack of validated treatment alternatives for this disease.

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

Results

Patient disposition, reference pathology, clinical screening and enrolment

Between January 28, 2013 and December 1, 2014, 16 sites in 8 European countries recruited 43 patients with local diagnosis of CCSA. Only 36/43 (84%) patients had a confirmed CCSA according to reference pathology; were eligible for screening and potential treatment.

The 7 non-confirmed, non-eligible cases included two cases of melanoma, three non-specified malignancies, and one case with insufficient material for reference pathology. One patient withdrew from study before central review. These patients were not treated.

A total of 34 of the 36 patients with centrally confirmed CCSA were enrolled in the study (step 3) and started treatment with crizotinib. The two remaining patients withdrew consent. A total of 28 eligible patients (26 *MET*⁺ and 2 *MET*⁻) with confirmed CCSA who started treatment with crizotinib were evaluable for the primary endpoint (Supplementary Figure S4 provides the CONSORT-like patient disposition).

As expected, the number of patients with *MET*⁻ disease was very low (two patients eligible and evaluable). As the trial was conceptually focused on *EWSR1* rearranged cases, and due to the low sample size of *MET*⁻ disease, only some key results obtained in the latter cases will be presented. Supplementary Figure S4 depicts the trial profile.

Genetic analysis and molecular epidemiology

FISH testing was completed according to protocol by the academic laboratory within a median time of 4 days (range:1-15) after receipt of technically useful, unstained slides from the central biorepository.

Among 36 patients with centrally confirmed CCSA diagnosis, 32(88.9%) had documented *EWSR1* rearrangement (*MET*⁺ cases). Only 3 patients (8.3 %) had no detectable *EWSR1*. FISH testing could not be performed in the remaining patient due to technical failure. Supplementary Table S1 shows an overview of the molecular characteristics.

Due to rapid accrual of patients, a delay in reporting clinical efficacy results to EORTC, and in the light of the lack of treatment alternatives for this highly resistant malignancy, we overrecruited the CCSA cohort of EORTC 90101. We recruited more than the 12 *MET*⁺ CCSA patients required to complete stage 1, but less than 35 eligible and evaluable patients for completing stage 2 according to protocol. Recruitment to both the *MET*⁺ and *MET*⁻ CCSA sub-cohorts was suspended on February 5, 2015, after having analyzed the ORR in the first 12 eligible and evaluable *MET*⁺ cases.

Patient characteristics

Among the total group with confirmed diagnosis of CCSA, 31 patients with *MET*⁺ disease were treated, two patients with *MET*⁻ CCSA entered the treatment phase and one patient with *MET*[?] received crizotinib.

Table.1A shows the characteristics of these 34 treated patients. Their median age was 44 years, 35.3%(12/34) had an ECOG PS of 1 and the majority (91.2%[31/34]) had undergone prior surgery. Only 26.5%(9/34) had received prior systemic therapy, illustrating the lack of treatment options outside of clinical trials for such patients.

Crizotinib treatment

As of March 2 2017, with a median follow-up of 281 days (range:43-933), 2.9 %(1/34) of patients were still receiving treatment. Only 38.2%(13/34) of treated patients required dose reductions or dose modifications (Table.1B). The total treatment duration with crizotinib ranged from 3 to 849+ days. Reasons for treatment discontinuation are shown in table.1B.

*Activity of crizotinib in *MET*⁺ CCSA*

The primary endpoint was the ORR as assessed by the local investigator, with response confirmation. An objective PR was observed in 1/26 *MET*+ patients (3.8% ORR;95% confidence interval [CI]:0.1-19.6%). The primary endpoint of the trial was not met. The duration of response in the responding patient was 851+ days; the patient is still on active treatment at the data cut-off, having received 40+ cycles of treatment. RECIST SD was observed in 17/26 *MET*+ patients (65.4%). Disease progression was seen in 8 patients (30.8%). Disease control was achieved in 18/26 *MET*+ patients (DCR;69.2%,95% CI:48.2-85.7). The median PFS was 131 days (95% CI:49-235; ([Supplementary Figure S5](#))). The 3, 6, 12 and 24 month PFR was 53.8%(34.6-73.0), 26.9%(9.8-43.9), 7.7%(1.3-21.7) and 7.7%(1.3-21.7), respectively. The median OS was 277 days (95% CI:232-442), and the OSR was 36.1%(95% CI:18.2-54.3%) at 1 year and 9.4%(95% CI:1.7-25.3%) at 2 years ([Supplementary Figure S6](#)). [Figure.1A](#) illustrates the maximum shrinkage of target lesions during treatment. Half of the *MET*+ CCSA cases had crizotinib measurable reduction of target lesions. [Figure.1B](#) summarizes the clinical course of all treated patients.

Activity of crizotinib in MET-/MET+ CCSA

None of the *MET*- patients had a response: one had SD followed PD at day 143 and one had PD at day 66. Key efficacy data for the total study population are summarized in [table.1C](#).

Safety and toxicity

No new or unexpected safety signals were detected. The most common treatment-related adverse events occurring in $\geq 10\%$ of the 34 patients who started crizotinib were nausea (52.9% of patients), fatigue (50.0%), vomiting (35.3%), diarrhoea (32.4%), constipation (26.5%), and blurred vision (20.6%). The reported treatment-related grade 3/4 adverse events were nausea (two patients), fatigue (two), gastritis (one), Qt prolongation (one) and anorexia (one). [Supplementary Tables S2](#) and [S3](#) show adverse events occurring in $\geq 10\%$ of treated patients.

Three deaths occurred on treatment or within 4 weeks of treatment-discontinuation, all deemed unrelated to crizotinib treatment. There was one possibly treatment-related death. This patient developed pneumonia, pulmonary embolism and pneumonitis during cycle 12 of treatment.

Discussion

The treatment of advanced, inoperable CCSA remains a challenge due to the lack of an established systemic treatment standard. Information from prospective clinical trials on the efficacy of systemic treatments for CCSA is limited. EORTC 90101 CREATE is likely the first, well powered study in this setting. The main objective of this phase 2 study was to assess the activity of crizotinib in this rare and chemotherapy-resistant, translocation-related sarcoma. The ORR was 3.8%(1/26 PR,95% CI:0.1-19.6%) and the primary endpoint of the trial was not met, as we did not observe at least two objective and radiologically confirmed responses among the first 12 eligible and evaluable *MET*+ cases.

Multiple factors led to overrecruitment of patients beyond stage 1 of Simon's optimal two-stage design. We saw rapid accrual of CCSA cases, with the majority of patients previously

untreated, reflecting the high unmet medical need in this orphan malignancy. Investigators observed a large proportion of patients achieving early SD under treatment 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 to EORTC, as investigators had to wait until their patients came off study or had reached a confirmed PR. By that time we had exceeded the minimum sample size to assess the futility of crizotinib, without having reached the stage 2 sample size according to trial design. Due to the lack of treatment alternatives we accepted this overrecruitment and this also provided an opportunity to gain deeper insight into the natural course of this cancer.

Even though we found alterations leading to MET expression in 88.9% of our cases, which is in line with the literature, the inhibition of MET by crizotinib only translated in one, however durable response. It is unclear why this patient had such exceptional response, but we hope that further tissue-based analysis will provide an explanation. We cannot exclude that this response was induced by effects other than MET inhibition, as crizotinib inhibits more than one target. Interestingly, 18/26(69.2%,95% CI:48.2-85.7) of our cases achieved disease control for a median of 131 days. This suggests that PFS or PFR would have been better endpoints for assessing the efficacy of crizotinib in this disease. The response pattern of MET-driven malignancies to TKI might be different from the volumetric responses seen in ALK-driven NSCLC.

Although it was shown that the presence of EWSR1-ATF1 fusion protein, characteristic of CCSA, was required for MET expression and that MET inhibition significantly reduced CCSA cell growth *in vitro*³ it is not yet known if MET expression and/or activation is present at the same level in all CCSA cases. It is possible that other factors (e.g. level of HGF expression) contributes to the role of MET in oncogenesis and therefore variable elements may influence the response to MET inhibitors. This hypothesis, along with the influence of MET-related pathways status, is currently being tested.

Based on a retrospective statistical analysis of multiple EORTC sarcoma trials, Van Glabbeke et al.² proposed reference values for potentially active agents in STS. 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. In our CCSA *MET*⁺ group, the 3 and 6 month PFR was 53.8%(34.6-73.0) and 26.9%(9.8-43.9). In an exploratory analysis we looked at the outcome achieved with crizotinib in pretreated ($N=7/26$) versus non-pretreated ($N=19/26$) patients with EWSR1 rearrangement. 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 approval and routine use of most drugs for the treatment of STS has been based on trials pooling various types of sarcoma together, which limits the interpretation of the efficacy of such agents in a given histological subtype. Our phase 2 trial was highly histotype-specific, involved reference pathology and genetic characterization of CCSA as one of the rarest and most treatment-resistant members of the STS family. In this context it is noteworthy that the PFS seen with crizotinib in *MET*⁺ CCSA was similar to 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),²⁰ or with the oral angiogenesis inhibitor pazopanib in previously treated

patients (4.6 months, 95% CI:3.7-4.8).² In our smaller, more exploratory study, crizotinib achieved a median PFS in CCSA with MET alterations of 4.4 months (95% CI:1.6-7.8).

Statistically we focused on cases with *EWSR1* positive CCSA as assessed by FISH, while allowing “all comers” to enter the study, provided they had a centrally confirmed diagnosis. This served multiple strategic purposes: to avoid delay during study entry after consent; to give the laboratory sufficient time for FISH testing; to offer an experimental treatment to patients with an unmet medical need; to collect data on the molecular epidemiology of advanced CCSA; and to provide a reference for future trials in this rare cancer. The expected small sample size of the *MET*- subcohort of our trial population however precludes drawing definitive conclusions for this group.

Reference pathology was an important component of the trial. Our pathology review was completed within a median of 3 days (range, 1-17) after receipt of unstained slides. It was based on a review of local pathology and FISH reports, central microscopy and additional stainings if required, and FISH testing in Leuven in all cases. Of note, only 36 of the 43 consenting patients had a centrally confirmed CCSA. This highlights once again the complexity of proper morphological characterization of rare malignancies, even in highly dedicated academic institutions, especially in tumour types that can mimick other diseases. The misclassification rate here was similar to that seen in other STS studies.

Another specific feature was the mandatory collection of a non-returnable, archived tissue block from all participating patients for research. Many investigators are hesitant to provide commercial trial sponsors with a tissue block for research, while EORTC as an academic non-for-profit organization has the capacity to function as a biobank and non-commercial facilitator of translational work. We were able to collect tissue from 42 consenting patients, including material from 36 individuals with centrally confirmed CCSA. This precious resource is now the basis for multiple ongoing and planned exploratory studies, which will lead to a better understanding of the CCSA biology and the identification of prognostic or predictive biomarkers and treatment strategies for this rare cancer.

Our study showed variable response in the *MET*+ cohort which suggests the presence of other factors in combination with *EWSR1* rearrangement which might predict crizotinib’s efficacy. We are currently performing correlative studies using whole exome sequencing to evaluate the mutational profile and 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 CCSA and individual cases’ sensitivity or resistance to crizotinib.

In our complex trial we demonstrated that EORTC can perform multi-tumour, precision-medicine phase 2 trials in rare cancers with collection of tissue blocks, real time reference pathology and molecular characterization. Given the inherent limitations of performing larger prospective trials in ultra-rare diseases, innovative trial methodology like the basket approach chosen in EORTC 90101, and new regulatory mechanisms are required to provide patients with orphan malignancies with potentially active drugs such as crizotinib.

The adverse events observed in this study were consistent with safety data for crizotinib in patients with NSCLC. No new adverse events were observed. Dose intensity was high and the incidence of dose modifications was relatively low.

This study illustrates once again the methodological limitations using response rate in early clinical trials in oncology. This endpoint had been chosen based on the impressive 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 this rare type of sarcoma. In general, EORTC is recommending using time-related endpoints such as PFR during the early exploration of novel agents in STS,¹ which provided the phase 2 rationale for at least two successful registration trials during the past 5 years.^{2,21}

We were able to demonstrate that crizotinib provided clinical benefit to patients with locally advanced or metastatic *MET*+ CCSA. This is noteworthy as this orphan malignancy is renowned for being profoundly resistant to conventional systemic agents. Response rate should not be the primary endpoint for future phase 2 trials with *MET* inhibiting agents for CCSA. DCR, PFS and/or PFR would be a more appropriate reflection of the therapeutic effects of treatments in this disease, where progression arrest might be more important than shrinkage of the tumour and its metastasis. Other *MET* inhibitors, such as small molecules (highly specific or multi-targeted) or monoclonal antibodies, either given as single agents or in combination with other drugs, could be studied in future CCSA trials.

Other local investigators

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Disclosure

PS: no competing interest

AW: no competing interest

PRutkowski: received honoraria from Pfizer outside the scope of this study

JYB: Research support and honoraria from Pfizer outside the scope of this study

LHL: received honoraria from Pfizer outside the scope of this study

SS: no competing interest

AA: no competing interest

FD: no competing interest

SR: no competing interest

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MGL: no competing interest

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

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WvdG: Research support from Novartis, honoraria from Bayer

RS: no competing interest

MDR: no competing interest

SM: no competing interest

ML: no competing interest

TR: no competing interest

LC: no competing interest

SB: received honoraria from Pfizer for consulting and CME activities

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Figure.1A. Maximum shrinkage of target lesions (per protocol) according to local investigator's assessment.

Figure.1B. Clinical course of patients in the CCSA *MET+* and *MET-* sub-cohorts.