The Activity of Crizotinib in Chemo-Refractory MET-Amplified Esophageal and Gastric Adenocarcinomas: Results from the AcSé-Crizotinib Program

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The Activity of Crizotinib in Chemo-Refractory MET-Amplified Esophageal and Gastric Adenocarcinomas: Results from the AcSé-Crizotinib Program

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Abstract

Background The AcSé-crizotinib program provides extensive screening of crizotinib-targeted genomic alteration in several malignancies. We here report the results in patients with esogastric MET-amplified adenocarcinomas.

Objective The objective of the study was to evaluate the efficacy and tolerability of crizotinib in patients with pretreated esogastric MET-amplified adenocarcinoma who have no alternative treatment options.

Patients and Methods MET expression was evaluated by fluorescence in situ hybridization in tumor samples with immunochemistry scores ≥ 2+. Patients with chemo-refractory tumors showing ≥ 6 MET copies were eligible for crizotinib 250 mg twice daily. The primary efficacy outcome was the objective response rate after two cycles of crizotinib.

Results MET was prospectively analyzed in 570 esogastric adenocarcinomas. Amplifications were found in 35/570 adenocarcinomas (29/523 gastric and 6/47 esophageal). Nine patients were treated with crizotinib. The objective response rate after two cycles was 33.3% (95% CI 7.5–70), the best overall response rate was 55.6% (95% CI 21.2–86.3), with median progression-free survival of 3.2 months (95% CI 1.0–5.4), and overall survival of 8.1 months (95% CI 1.7–24.6). Safety was consistent with that previously reported for crizotinib.

Conclusions Large-scale screening for MET-amplified esogastric adenocarcinomas is feasible. MET amplification was observed in 5.5% of gastric and 12.8% of esophageal adenocarcinomas. Crizotinib shows encouraging results in selected patients. Thus, c-MET inhibition for MET-amplified tumors deserves further evaluation.

Trial Registration Number NCT02034981.

Date of Registration 14 January 2014.

Key Points

MET-amplification, ≥ 6 copies, was detected in 6.1% of advanced esogastric adenocarcinomas.

The best overall response rate observed in the nine patients with MET-amplified tumors treated with crizotinib was 55.6%.

No new safety concerns were reported related to crizotinib in patients with esogastric adenocarcinoma.

1 Introduction

Molecular tumor profiling is increasingly being used to identify targetable alterations and to tailor treatment options. The drug registration process is slow and lengthy. Consequently, off-label use of new drugs is a growing concern. The AcSé program was initiated by the French National Cancer Institute (INCa) in 2013. Our objective was to give patients access to approved targeted therapies, even though the therapy had not been approved in a specific tumor indication [1]. However, the tumor needed to harbor the targeted molecular alteration. The program aimed to evaluate the efficacy and safety of targeted therapies in patients who had no alternative approved treatment options. Crizotinib is a selective small-molecule oral inhibitor of the anaplastic...
lymphoma kinase (ALK), c-MET/hepatocyte growth factor receptor (HGFR), and ROS receptor tyrosine kinases. MET amplification was reported in 5–6% of esogastric adenocarcinomas and is an oncogenic driver and therapeutic target [2]. Targeting c-MET receptor with monoclonal antibodies has been disappointing [3–5]. Nevertheless, a previous study reported tumor shrinkage in two patients with MET-amplified esogastric adenocarcinoma treated with crizotinib [6].

When the AcSé program started, crizotinib was approved as monotherapy for treating non-small-cell lung cancers with ALK gene rearrangement. We hypothesized that crizotinib could be active in esogastric adenocarcinoma with MET amplification. The AcSé crizotinib program comprised two parts: a biomarker testing study to identify patients with a malignancy showing genomic molecular alterations targeted by crizotinib (ALK, c-MET, or ROS-1) and a phase II clinical trial (with several disease cohorts) providing adults, adolescents, and children with biomarker-positive cancers and for whom all available and validated therapies have failed, access to crizotinib monotherapy. In this paper, we present the results of the esogastric cohort that enrolled adult patients with tumors having ≥ 6 copies of MET.

2 Patients and Methods

2.1 Patients and Molecular Testing

The trial screened patients with inoperable, histologically confirmed locally advanced or metastatic esogastric adenocarcinomas, without an available approved treatment option. Patients needed a measurable lesion by computed tomography (CT)-scan (using response criteria in solid tumors [RECIST] v1.1) and an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. The trial protocol is available in the Online Supplementary Material. The study was approved by the Ethics Committee (CPP IDF VII, Hôpital de Bicêtre n°13-016 in May 13, 2013) and registered in EudraCT with the number 2013-000885-13. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki. A consent was obtained from all patients to participate in the study after detailed information.

Patients were included in the esogastric cohort if their tumors were MET amplified (MET ≥ 6 copies). A tissue sample of the primary or metastatic lesion was analyzed in one of the 28 certified regional genetics centers in the French network. Patients were initially screened by immunohistochemistry (IHC) to assess c-MET expression. For patients with diffuse or focal c-MET expression of 2+ or 3+ by IHC, MET amplification was assessed by fluorescence in situ hybridization (FISH). The numbers of MET gene copies were read in ≥ 100 nuclei. The MET amplification threshold for study enrollment was set at ≥ 6 copies. The numbers of MET gene copies were also classified by the MET copies per centromere ratio: high polysomy (< 1.8 MET/centromere), low (≥ 1.8 to ≤ 2.2), intermediate (> 2.2 to < 5.0), and high amplifications (≥ 5.0).

2.2 Treatment

Patients were treated with oral crizotinib, 250 mg twice daily, until disease progression, patient decision, or for any reason in the interest of the patient. Treatment was divided into 28-day cycles for reporting purposes.

2.3 Study Objectives and Outcomes

The primary objective was to assess the efficacy of crizotinib, using the confirmed objective response rate (ORR) after two cycles of crizotinib. An objective response was defined as a complete response (CR) or partial response (PR) by RECIST v1.1. Tumor response was assessed by CT scan and/or magnetic resonance imaging (MRI) at baseline, then every 8 weeks. In addition, a confirmation CT scan and/or MRI were required when disease progressions were suspected or to confirm a PR or CR (minimum delay of 4 weeks). An independent central review was performed for each patient with PR or CR. Patients with clinical progression, without RECIST assessment, were considered as having progressive disease.

The secondary objectives were best overall response rate (BOR), disease control rate at two cycles, progression-free survival (PFS), and overall survival (OS). Disease control rate was defined as the percentage of patients with a CR, PR, or SD according to RECIST and was assessed after cycle 2 and 4. Best response over the whole treatment duration was described using all RECIST evaluations. Best response, according to RECIST, was centrally reviewed for patients with CR and PR. If a patient had no centrally reviewed response, the best response was based on the RECIST evaluation performed by the investigator at the center. PFS was defined as the time interval between the date of first intake of crizotinib and the date of the first documented sign of disease progression or date of death, whichever occurred first. OS was defined as the time interval between the date of first intake of crizotinib and date of death, whatever the cause. Response duration was defined as the time interval between the date of the first recorded CR or PR and the date of documented disease recurrence or progression, or death, whichever occurred first.

Crizotinib tolerance was also assessed, graded by the common terminology criteria for adverse events (CTCAE) v4.0. Adverse events were recorded as worst grade for each category, patient, and cycle. The investigator assessed
whether the reported events were related or not to crizotinib. We only report adverse events considered at least possibly related to crizotinib. For adverse events considered related to crizotinib, the maximum grade observed during treatment by patient and type of toxicities were also recorded.

2.4 Study Design and Statistical Methods

The AcSé crizotinib cohorts were based on a two-stage Simon design. In the esogastric cohort, crizotinib was deemed worthy of further evaluation if the objective confirmed response rate at two cycles was ≥ 30% (P1) and ineffective if the response rate was ≤ 10% (P0) (alpha = 10%, beta = 10%). During the first stage, if no tumor response was observed in the first 11 patients, accrual would be stopped. Otherwise, further patients would be enrolled in the second stage. In the final analysis of 25 evaluable patients, crizotinib would be considered as not sufficiently efficient if ≤ 4 responses were observed or as deserving further development if ≥ 5 responses were observed. PFS, OS, and duration of response were analyzed using the Kaplan-Meier method.

Patients who received at least one dose of crizotinib were included in the efficacy and safety analyses. The analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC, USA).

3 Results

From 08/2013 to 03/2018, c-MET was prospectively analyzed in 570 esogastric adenocarcinoma. MET amplification was found in 35 tumors (6.1%). MET was amplified in 29/523 patients (5.5%) with gastric adenocarcinomas and 6/47 (12.8%) with esophageal adenocarcinomas. Among the 35 patients with MET amplified tumors, 11 patients (31%) were enrolled in the AcSé crizotinib esogastric cohort. Two patients died before starting treatment and were excluded from the analysis (Fig. 1). Due to slow accrual, recruitment was stopped before reaching the 11 evaluable patients needed for the first stage. In the nine patients treated, the median copy number of MET was 7 (range 6–11), the median MET rate of positive nuclei was 50% (range: 2–80%) and the median rate of positive cells was 90% (range 50–100%). Three patients (33%) had a low ratio of MET copies per centromere and six patients (66%) had an intermediate ratio of MET copies per centromere. We observed a tumor objective response in 2/3 patients (67%) with a low tumor MET-amplification and in 3/6 (50%) with an intermediate tumor MET-amplification.

The characteristics of the nine treated patients are presented in Table 1. The median follow-up was 8.1 months. At the cut-off date for analysis, no patient was still receiving crizotinib. Crizotinib discontinuation was due to disease progression, either radiological or clinical, in seven patients (77.8%) or due to adverse events in two patients (22.2%): increased alanine aminotransferase (ALT) and bilirubin in one patient, and pneumopathy in the other patient. The median number of cycles was five (range 2–12). The median treatment duration was 115 days (range 30–312).

The ORR after two cycles was 33.3% (95% CI 7.5–70). The BOR was 55.6% (95% CI 21.2–86.3) (Fig. 2a). One patient had a discordant tumor response with an objective response of the target lesion but with a new lesion. The disease control rate at two cycles was 55.6% (95% CI 21.2–86.3) and at four cycles was 44.4% (95% CI 13.7–78.8). The median duration of response in the five patients with a tumor response was 2.7 months (Fig. 2b). At the cut-off date for analysis, all patients had progressed and died. The median PFS was 3.2 months (95% CI 1.0–5.4) and the median OS was 8.1 months (95% CI 1.7–24.6) (Fig. 3).

The safety analysis revealed five patients with grade ≥ 3 treatment related adverse events: two patients with alkaline phosphate increases, one with ALT and aspartate aminotransferase (ASAT) increases, one with fatigue, one with gamma-glutamyltransferase (GGT) increase, and one with pneumonia. The most common adverse events (all grades) were ASAT increase in 67% of patients and visual disorders, nausea, edema, and ALT increase each occurring in 56% of patients (Fig. 4).

4 Discussion

The AcSé program provided patients with safe and secure access to innovative drugs, outside of their marketed indication. The esogastric cohort of the phase II AcSé crizotinib study assessed crizotinib in patients with esogastric adenocarcinomas having MET ≥ 6 copies. The incidence
of MET-amplified tumors was in line with that previously observed for gastric adenocarcinomas [2, 6]. However, to our knowledge, we are the first to report that the rate of MET amplified tumors for esophageal adenocarcinomas was twice that observed in gastric adenocarcinomas.

This study gave promising results with an ORR > 30% after two cycles of crizotinib in previously treated patients. Moreover, the ORR continued to increase after two cycles to reach a BOR of 56%. It is noteworthy that the patients enrolled in this study were heavily pre-treated: 66% having received at least three lines of treatment before the study. Thus, we suspect that the disease had become heterogeneous with several clonal populations: this may explain the limited effect of crizotinib observed.

Several other treatments have been evaluated in pre-treated patients with esogastric adenocarcinomas. In a randomized phase II trial in patients who had received one or two previous lines of treatment, regorafenib gave an ORR of 3.5%, a median PFS of 2.6 months, and OS of 5.8 months [7]. In addition, a randomized phase III trial evaluated trifluridine-tipiracil in patients who had received at least two previous chemotherapy regimens. This treatment gave an ORR of 4%, a median PFS of 2.0 months and OS of 5.7 months [8]. Finally, the immune checkpoint inhibitor, pembrolizumab, as second-line treatment gave an ORR of 16%, a median PFS of 1.5 months, and OS of 9.1 months [9]. Thus, our observed efficacy with crizotinib compares well with those previously observed in patients with chemoresistant tumor. Nevertheless, our results were obtained in the subgroup of patients with MET amplified tumors and cannot be extrapolated to all esogastric adenocarcinomas. Moreover, due to the few patients treated, a larger study is needed to confirm our results.

Crizotinib has a broad spectrum of activity and inhibits several kinases. More selective agents, with better safety profiles, need to be evaluated. Indeed, crizotinib toxicity is concerning especially when compared to that of other agents, including immune checkpoint inhibitors. Other c-MET inhibitors have demonstrated efficacy in treating MET-amplified esogastric adenocarcinomas. Capmatinib, a type Ib inhibitor that is highly specific for c-MET, gave an ORR of 22% in a recent phase I study [10]. Another study reported an ORR of 18%, a PFS of 3.4 months, and an OS of 7.9 months in patients with MET-amplified esogastric adenocarcinomas treated with AMG 337 [11]. Finally, a study treated 20 patients with MET-amplified gastric adenocarcinoma with the c-MET inhibitor savolitinib and reported an ORR of 50%. Interestingly, patients with high MET copy numbers had high response rates [12].

The pre-screening method used to identify patients more likely to respond is crucial. Previously, when IHC was used to select patients with c-MET positive tumor, IHC failed to predict efficacy of monoclonal antibodies targeting c-MET [3, 4]. It has been shown that MET amplification of ≥ 5 or ≥ 6 copies is associated with a worse prognosis [6, 13]. The threshold of ≥ 6 copies was derived from HER2 guidelines established in breast cancer [14]. The relevance of the threshold of ≥ 6 copies was derived from HER2 guidelines established in breast cancer [14]. The relevance of the threshold of ≥ 6 copies was derived from HER2 guidelines established in breast cancer [14].

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not collected. Perhaps the performance status of these heavily pre-treated patients rapidly declined, preventing treatment with crizotinib in our trial. Thus, we suggest that screening be performed as early as possible during the first palliative line of treatment and be restricted to patients considered fit enough for treatment.

We conclude that large-scale screening for MET-amplified esogastric adenocarcinomas is feasible. Nevertheless, only routine screening may offer opportunity to enroll enough patients for a large trial. MET amplification was observed in 5.5% of gastric adenocarcinomas and in 12.8% of esophageal adenocarcinomas. Crizotinib treatment shows encouraging results in selected patients. Consequently, c-MET inhibition for MET-amplified tumors deserves further evaluation.

Fig. 2 a Waterfall plot for best overall response of target lesion from baseline. b Individual patient history

Fig. 3 Overall and progression-free survival
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Declarations

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Conflict of interest  T. Aparicio has received honorarium from Roche, Ipsen, Amgen, Servier, Sanofi, and Bioven. L. Mineur has received honorarium from Merck, Servier, and Pierre Fabre and has received research grants from Amgen and Sanofi. R. Guimbaud has received honorarium from AAA, AstraZeneca, Amgen, BMS, Pierre Fabre, Novartis, Roche, and Servier. E. Samalin has received honorarium from Roche, Servier, Sanofi, MSD, BMS, Amgen, and Pierre Fabre. T. Lecomte has received honorarium from Ipsen, Amgen, Merck, Sanofi, Servier, Bayer, and Novartis. CA. Gomez-Roca has received honorarium from BMS, Roche, Pierre Fabre, Eisai, and Foundation Medicine, and has received research grants from Roche and BMS. G. Vassal has received honorarium from Bayer, Boehringer-Ingelheim, BMS, Celgene, Exelixis, Incyte Biosciences, Lilly, Merck, Novartis, Pfizer, Roche/Genentech, Servier and Takeda. N. Cozic, C. De La Foucauld, E. Meriaux, J. Plaza, F. Mary, P.A. Haineaux, A. Gratet, J. Selves, Y. Menu, N. Colignon, L. Johnson, and F. Legrand declare that they have no conflicts of interest that might be relevant to the contents of this article.

Ethics approval  The study was approved by the ethics committee (13 May 2013 by CPP Ile De France VII Kremlin Bicêtre, protocol 2013-000885-13)

Availability of data  Data are available from the corresponding author upon reasonable request.

Author contributions  Study design: TA, NCoz, GV. Data acquisition: TA, CF, EM, JP, LM, RG, ES, FM, TL, CAGR, PAH, AG, JS, YM, NCol, FL. Statistical analysis: NCoz. Manuscript preparation: TA, NCoz, LI. Manuscript review: all authors.

Consent for publication  Not applicable.

Code availability  Not applicable.

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