Original Research

Long-term efficacy update of crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumour from EORTC trial 90101 CREATE

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KEYWORDS
Inflammatory myofibroblastic tumour (IMT); Tyrosine kinase inhibitor; Crizotinib; Anaplastic lymphoma kinase (ALK) rearrangements; Locally advanced or metastatic; ALK-positive; ALK-negative

Abstract Purpose: European Organisation for Research and Treatment of Cancer (EORTC) 90101 (CREATE) was a prospective, multicentric, non-randomised, open-label phase II basket trial to assess the efficacy and safety of crizotinib in patients with different types of cancers, including advanced inflammatory myofibroblastic tumour (IMT) with or without anaplastic lymphoma kinase (ALK) rearrangements. Here, we report updated results with long-term follow-up.

Patients/methods: After central reference pathology, eligible ALK-positive and ALK-negative patients with advanced/metastatic IMT deemed incurable with surgery, radiotherapy or systemic therapy received oral crizotinib 250 mg twice daily. The ALK status was assessed centrally using immunohistochemistry and fluorescence in situ hybridisation. The primary endpoint was the proportion of patients who achieved an objective response (i.e. complete or partial response). If ≥6 ALK-positive patients achieved a confirmed response, the trial would be deemed successful.

Results: At data cut-off on 28th January 2021, we performed the final analysis of this trial. Of the 20 eligible and treated patients (19 of whom were evaluable for efficacy), with a median follow-up of 50 months, five were still on crizotinib treatment (4/12 ALK-positive and 1/8 ALK-negative patients). The updated objective response rate (ORR) was 66.7% (95% confidence interval [CI] 34.9–90.1%) in ALK-positive patients and 14.3% (95% CI 0.0–57.9%) in ALK-negative patients. In the ALK-positive and ALK-negative patients, the median progression-free survival was 18.0 months (95% CI 4.0–NE) and 14.3 months (95% CI 1.2–31.1), respectively; 3-year overall survival rates were 83.3% (95% CI 48.2–95.6) and 34.3% (95% CI 4.8–68.5). Safety results were consistent with previously reported data.

Conclusion: These updated results confirm previous findings that crizotinib is effective, with durable responses, in patients with locally advanced or metastatic ALK-positive IMT. With further follow-up after the original primary analysis, the ORR increased, as patients derived long-term benefit and some responses converted from stable disease to partial responses.

Clinical trial number: EORTC 90101, NCT01524926.

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1. Introduction

Inflammatory myofibroblastic tumours (IMTs), which occur mainly in children and adolescents, are extremely rare mesenchymal neoplasms [1,2]. The treatment of IMTs is challenging; although surgery is the mainstay of treatment, the proximity of IMTs to vital structures may preclude complete resection, and there is a tendency for local recurrence [1–5]. The sensitivity of this rare malignancy to systemic chemotherapy is only reported retrospectively [6,7]. Thus, there is a need for effective treatments for IMTs and a prospective evaluation of treatment options in clinical trials.

Alterations in the anaplastic lymphoma kinase (ALK) gene are the predominant molecular feature underlying IMTs, with aberrant ALK signalling occurring in most IMTs [2–4,8,9]. Ligand-independent autophosphorylation of the ALK receptor tyrosine kinase activates the downstream signalling pathways which result in prolonged tumour cell survival, increased proliferation and enhanced cell migration [2–4,8–15]. The inhibition of ALK is therefore a suggestive target for the treatment of IMT.

Crizotinib is a small molecule tyrosine kinase inhibitor targeting ALK, MET, ROS proto-oncogene 1 receptor tyrosine kinase (ROS1) and Recepteur d’Origine Nantais (RON) [2,9,16–19]. Crizotinib is approved for adult patients with metastatic non-small-cell lung cancer (NSCLC) whose tumours are either ALK- or ROS1-positive, in paediatric patients ≥1 year and in young adults with refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive, and the recommended oral dose is 250 mg twice daily for metastatic NSCLC and 280 mg/m² twice daily for ALCL [17]. Crizotinib competitively inhibits adenosine triphosphate from binding to the ALK receptor, thereby blocking the downstream cascade of events, resulting in the inhibition of the growth and survival of ALK-dependent cells [9,16,17,20,21].

To evaluate the efficacy and safety of crizotinib in patients with advanced tumours characterised by ALK and/or MET alterations, the European Organisation for Research and Treatment of Cancer (EORTC) initiated a multinational, multitumour, prospective phase II clinical trial (EORTC 90101 CREATE). This trial included multiple independent cohorts of ALK- or MET-driven...
tumour types. We have previously presented the primary results of the IMT cohort with 28 months of median follow-up [9], and in the ALK-positive subcohort the objective response rate (ORR) was 50.0% (95% confidence interval [CI] 21.1–78.9%), the 12-month progression-free survival (PFS) was 73.3% (95% CI 37.9–90.6%) and the 12-month overall survival (OS) was 81.8% (95% CI 44.7–95.1%) [9]. Here, we provide updated results with a median follow-up of 50 months.

2. Materials and methods

2.1. Study design

The design and primary analyses have already been published (NCT01524926) [9]. EORTC 90101 CREATE was a multicentre, biomarker-driven, single-agent, non-randomised, open-label, two-stage phase II trial assessing the efficacy and safety of crizotinib in patients with locally advanced or metastatic IMT after central reference pathology confirmation of the diagnosis. The IMT patient population was divided by the protocol into ALK-positive and ALK-negative subcohorts. ALK positivity was defined as at least 15% of tumour cells with gene rearrangement using the Vysis LSI ALK dual colour break apart rearrangement probe (Abbott Molecular, Des Plaines, IL, USA) using fluorescence in situ hybridisation (FISH) or positivity on immunohistochemistry, or both, using the ALK monoclonal antibody clone CD246 (DAKO).

Ethics approval was obtained for this trial at all participating sites, and the study was conducted in accordance with participating country and institution regulations. The protocol is available online (http://www.eortc.be/services/doc/protocols/90101v10.0.pdf).

2.2. Patients

Patients were enrolled on a multistep procedure. Step 1 (pre-screening/registration) included a local diagnosis of advanced and/or metastatic IMT (deemed incurable by conventional surgery, radiotherapy or systemic therapy), the availability of a formalin-fixed paraffin embedded tumour-containing tissue block (from primary tumour or metastatic site) and written informed consent of the patient. Step 2 (central processing) of the procedure included receipt of the tissue from a central biorepository for confirmation of the correct diagnosis of IMT by central reference pathology [14]. Step 3 (clinical screening and treatment) occurred on confirmation of diagnosis by the central laboratory and included laboratory screening, baseline tumour assessment and enrolment on confirmation of eligibility. Documentation of the presence of a specific ALK alteration was not required for a patient to enter step 3; central analysis was performed while patients were already receiving therapy.

The key eligibility criteria included the following: age at least 15 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; adequate haematological, renal and liver function and measurable disease as per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. There was no limitation in terms of previous systemic or local treatment for IMT; only prior exposure to crizotinib or other ALK-inhibiting agents was not allowed. Further details are described in the online study protocol.

2.3. Treatment and procedures

Eligible patients with centrally confirmed diagnosis of IMT were treated with oral crizotinib at a starting dose of 250 mg twice daily, with one treatment cycle defined as 21 days in duration. Treatment was continued until documented disease progression, unacceptable toxicity or patient refusal. Further details on treatment dose and schedule modifications are described in the online study protocol. Safety data were assessed using Common Terminology Criteria for Adverse Events, version 4.0, and collected at the baseline, at day 15 of cycle 1 and 2 and at the end of every cycle. Tumour assessments were performed every other cycle by the local investigator or his/her radiologist as per RECIST 1.1.

Patients were divided into ALK-positive and -negative subcohorts using FISH and immunohistochemistry. The molecular and immunohistochemical testing was carried out at the University Hospitals Leuven (Belgium).

2.4. Outcomes

The primary end-point was the ORR (defined as complete response [CR] or partial response [PR] at any time during treatment) as per RECIST, version 1.1, with response confirmation assessed by the local investigator. The secondary end-points included duration of response (DOR), disease control rate (DCR, defined as a CR + PR + stable disease [SD]), PFS (defined from the first day of treatment administration until progression or death), PFS rate, OS (defined from the first day of treatment administration until death), safety and correlative or translational research end-points. Censoring was applied as the last follow-up visit.

2.5. Statistical analysis

Simon’s optimal two-stage design was implemented for each of the IMT ALK-positive and ALK-negative
The treatment was considered ineffective if the ORR was \( \leq 10\% \); the alternative assumption was that crizotinib could achieve an ORR of at least 30\%. The type I and type II errors were set at 10\%. While the study was conceptually focused on ALK-positive disease, ALK-negative patients served as a non-randomised, treated internal control as there is no established standard of care for these patients.

In stage I, if at least two of the first 12 eligible and evaluable IMT ALK-positive patients achieved a confirmed RECIST PR or CR, a maximum of 35 patients were to be enrolled. In stage II, if fewer than 6 of the 35 eligible and evaluable patients responded, the treatment was declared ineffective. If at least 6 of the 35 patients responded, further study of crizotinib in IMT was warranted. Further details on defined stopping rules are described in the study protocol and in the primary publication [9].

Activity end-points were analysed in the per-protocol population (i.e. all eligible patients with centrally confirmed diagnosis of IMT who started crizotinib, with imaging assessment at the baseline and at least another imaging assessment after two or more cycles of crizotinib), and safety was analysed in all patients who started treatment. PFS and OS were estimated using the 

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- ORR, overall response rate
- ALK, anaplastic lymphoma kinase
- EORTC, European Organisation for Research and Treatment of Cancer
- PR, partial response
- CR, complete response
- RECIST, Response Evaluation Criteria in Solid Tumors
- PFS, progression-free survival
- OS, overall survival
- IMT, inflammatory myofibroblastic tumour
- ECOG, Eastern Cooperative Oncology Group
- PS, performance status

### Table 1

**Key baseline patient characteristics.**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>ALK-positive (n = 12)</th>
<th>ALK-negative (n = 8)</th>
<th>Total (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>35.5</td>
<td>59.5</td>
<td>45.5</td>
</tr>
<tr>
<td>Range</td>
<td>21.0–69.0</td>
<td>15.0–78.0</td>
<td>15.0–78.0</td>
</tr>
<tr>
<td>ECOG PS:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (58.3)</td>
<td>4 (50.0)</td>
<td>11 (55.0)</td>
</tr>
<tr>
<td>1</td>
<td>5 (41.7)</td>
<td>3 (37.5)</td>
<td>8 (40.0)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0.0)</td>
<td>1 (12.5)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (50.0)</td>
<td>5 (62.5)</td>
<td>11 (55.0)</td>
</tr>
<tr>
<td>Any previous major surgery</td>
<td>7 (58.3)</td>
<td>3 (37.5)</td>
<td>10 (50.0)</td>
</tr>
<tr>
<td>Any prior systemic anticancer therapy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>5 (41.7)</td>
<td>2 (25.0)</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>Other anticancer therapy</td>
<td>2 (16.7)</td>
<td>1 (12.5)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Previous systemic treatments:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>1 (8.3)</td>
<td>0 (0.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Palliative:</td>
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<td></td>
</tr>
<tr>
<td>1 line</td>
<td>5 (41.7)</td>
<td>2 (25.0)</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>2 lines</td>
<td>2 (16.7)</td>
<td>2 (25.0)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>3 lines</td>
<td>1 (8.3)</td>
<td>0 (0.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>4 lines</td>
<td>1 (8.3)</td>
<td>0 (0.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>5 lines</td>
<td>1 (8.3)</td>
<td>0 (0.0)</td>
<td>1 (5.0)</td>
</tr>
</tbody>
</table>

**ALK**, anaplastic lymphoma kinase; **ECOG**, Eastern Cooperative Oncology Group; **PS**, performance status.

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**Fig. 1**. The trial profile of the EORTC 90101 CREATE study for the inflammatory myofibroblastic tumour (IMT) cohort. 10 patients’ IMTs were not confirmed, and tissue samples were not available for 2 patients; 2 patients died, 1 patient withdrew consent and 1 patient started another treatment; 1 patient had no suitable lesion for response evaluation—treatment still ongoing; 3 patients had disease progression, 2 patients stopped because of patients’ decision, 1 patient stopped because of surgery and 2 patients stopped because of symptomatic progression without radiological evidence of progressive disease/relapse; 5 patients had disease progression, 1 patient stopped because of toxicity (elevated transaminases) and 1 patient stopped because of symptomatic progression without radiological evidence of progressive disease/relapse. **ALK**, anaplastic lymphoma kinase.
Table 2
Crizotinib treatment exposure and treatment modifications.a

<table>
<thead>
<tr>
<th>Treatment details</th>
<th>ALK-positive (n = 12)</th>
<th>ALK-negative (n = 8)</th>
<th>Total (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of treatment (months)</td>
<td>18.8</td>
<td>4.5</td>
<td>10.4</td>
</tr>
<tr>
<td>Range</td>
<td>3.4–77.5</td>
<td>1.3–103.7</td>
<td>1.3–103.7</td>
</tr>
<tr>
<td>Median number of cycles of treatment</td>
<td>27.5</td>
<td>7.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Range</td>
<td>5.0–72.0</td>
<td>2.0–86.0</td>
<td>2.0–86.0</td>
</tr>
<tr>
<td>Median relative dose intensity (%)</td>
<td>100.0</td>
<td>95.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Range</td>
<td>80.9–100.0</td>
<td>52.4–100.0</td>
<td>52.4–100.0</td>
</tr>
</tbody>
</table>

Treatment modifications, n (%):
- Number of patients with at least 1 treatment modification: 3 (25.0) 4 (50.0) 7 (35.0)
- Dose level reduction to 200 mg twice daily: 2 (16.7) 3 (37.5) 5 (25.0)
- Dose level reduction to 250 mg once daily: 0 (0.0) 2 (25.0) 2 (10.0)
- Interruption of treatment: 1 (8.3) 4 (50.0) 5 (25.0)

ALK, anaplastic lymphoma kinase.

a Patients for whom the treatment is still ongoing were censored at the last treatment information received, and exposure was based on available information at the time of the database lock. Five patients were still on crizotinib treatment at the time of final analysis.

Kaplan-Meier method, and 95% CIs are reported. Analyses were performed with SAS software, version 9.4 (SAS Institute).

3. Results

Between 3rd October 2012 and 12th April 2017, 13 study sites in eight European countries recruited 35 patients with the local diagnosis of IMT, of whom only 24 patients had a centrally confirmed IMT diagnosis. Twenty of these 24 patients were enrolled in the study and started treatment with crizotinib (Fig. 1). The remaining four patients did not enter the treatment phase because of death (n = 2), withdrawal of consent (n = 1) or starting of another treatment (n = 1). Of the 20 eligible patients with centrally confirmed IMTs who started treatment with crizotinib, 19 were evaluable for the primary and secondary end-points, with the remaining one patient having no suitable lesion for response evaluation.

On 30th June 2017, recruitment to both IMT subcohorts was suspended without having reached the
computed from the first day of treatment administration.

Objective response rate

<table>
<thead>
<tr>
<th>ALK-positive</th>
<th>ALK-negative</th>
<th>Total (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 12)</td>
<td>(n = 7)</td>
<td>n (%)</td>
</tr>
</tbody>
</table>

Best response by the local investigator:

- Complete response (CR)
  - (34.9, 0.0) 1 (14.3) 7 (36.8)
  - (90.1%, 57.9%) 71.1%

Disease control rate

<table>
<thead>
<tr>
<th>(ORR = CR + PR) (95% CI)</th>
<th>(73.5, 42.1) 1 (14.3) 10 (52.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(DCR = CR + PR + SD) (95% CI)</td>
<td>(100.0%, 99.6%) 99.8%</td>
</tr>
</tbody>
</table>

Best response by medical review:

- Confirmed CR/PR
  - (58.3, 20.2) 1 (14.3) 8 (42.1)

PFS rates, % at 1 year (95% CI)

<table>
<thead>
<tr>
<th>OS rates, % at 1 year (95% CI)</th>
<th>(83.3, 85.7) 1 (14.3) 10 (52.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS rates, % at 2 years (95% CI)</td>
<td>(83.3, 85.7) 1 (14.3) 10 (52.6)</td>
</tr>
<tr>
<td>OS rates, % at 3 years (95% CI)</td>
<td>(83.3, 85.7) 1 (14.3) 10 (52.6)</td>
</tr>
</tbody>
</table>

Overall survival (OS):

<table>
<thead>
<tr>
<th>Survival status</th>
<th>Alive</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 12)</td>
<td>9 (75.0) 1 (14.3) 10 (52.6)</td>
<td></td>
</tr>
<tr>
<td>(n = 7)</td>
<td>3 (25.0) 6 (85.7) 9 (47.4)</td>
<td></td>
</tr>
</tbody>
</table>

Reason of death

- Progression of IMT
  - (20.2) 1 (14.3) 2 (10.5)

- Cardiovascular disease
  - (14.3) 1 (14.3) 2 (10.5)

Median OS in months (95% CI)

<table>
<thead>
<tr>
<th>OS rates, % at 1 year (95% CI)</th>
<th>(83.3, 85.7) 1 (14.3) 10 (52.6)</th>
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</tr>
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</table>

Baseline patients and disease characteristics are summarised in Table 1. Of the 20 eligible patients, 12 were ALK-positive and 8 were ALK-negative. The median age was 35.5 and 59.5 years in the ALK-positive and ALK-negative subcohorts, respectively. At least half of the maximum of 35 ALK-positive patients because of slow patient entry (due to the low incidence of IMT) and because the trial had already met the success criteria in stage I and stage II of the study.

For the primary analysis, at the time of database lock on 9th November 2017, 7 patients were still on treatment, and these data have been presented previously [9]. For the final analysis, at the time of cut-off on 28th January 2021, five patients were still on treatment (Fig. 1), and these updated data with a longer follow-up are presented here.

3.1. Patient characteristics

Baseline patients and disease characteristics are summarised in Table 1. Of the 20 eligible patients, 12 were ALK-positive and 8 were ALK-negative. The median age was 35.5 and 59.5 years in the ALK-positive and ALK-negative subcohorts, respectively. At least half of the
patients in both subcohorts (58.3% [7/12] of ALK-positive patients and 50.0% [4/8] of ALK-negative patients) had an ECOG PS of 0, and 50.0% (6/12) of ALK-positive patients and 62.5% (5/8) of ALK-negative patients were male. Fifty percent (6/12) and 25.0% (2/8) of patients in the ALK-positive and ALK-negative subcohorts, respectively, had received prior systemic anticancer therapy.

3.2. Exposure to treatment

Exposures to crizotinib and treatment modifications are shown in Table 2. In total (n = 20), the median relative dose intensity was 100.0% (range 52.4–100.0%). At the data cut-off on 28th January 2021, for the 5 patients (4/12 ALK-positive and 1/8 ALK-negative patients) who were still on treatment, the relative dose intensity ranged from 80.2% to 100.0%, with two of these five patients having a dose reduction of crizotinib to 200 mg twice daily, one of whom also had treatment interruption. An additional patient out of these five patients also had treatment interruption.

3.3. Efficacy

In this updated analysis, the ORR was 66.7% (8/12, 95% CI 34.9–90.1%) in ALK-positive patients and 14.3% (1/7, 95% CI 0.0–57.9%) in ALK-negative patients (Table 3). The median DOR was 39.0 months in the ALK-positive responding patients (range: 1.4–76.3). In the responding ALK-negative patients, the DOR was 7.6 months. Disease control (SD, PR or CR as the best response) was achieved in 100.0% (12/12, 95% CI 73.5–100.0%) of ALK-positive patients and in 85.7% (6/7, 95% CI 42.1–99.6%) of ALK-negative patients (Table 3).

At a median follow-up of 50 months, the median PFS was 18.0 months (95% CI 4.0–NE) and 14.3 months (95% CI 1.2–31.1) in the ALK-positive and ALK-negative patients, respectively (Table 3, Fig. 2). At 1 year, the PFS rate was 58.3% (95% CI 27.0–80.1) and 57.1% (95% CI 17.2–83.7) in the ALK-positive and ALK-negative patients, respectively. At 3 years, the PFS rate was 41.7% (95% CI 15.2–66.5) and 14.3% (95% CI 0.7–46.5) in the ALK-positive and ALK-negative patients, respectively (Table 3).

At the time of this updated analysis with a median follow-up of 50 months, 10 patients were still alive, of which 9 patients were in the ALK-positive subcohort and 1 patient was in the ALK-negative subcohort. OS results are shown in Table 3 and Fig. 3. In total, in the per-protocol population (n = 19), the median OS was 46.9 months (95% CI 20.2–NE). The median OS was not reached for the ALK-positive patients, whereas the median OS was 26.6 months (95% CI 7.9–58.1) for ALK-negative patients. At 1 year, the OS rate was 83.3% (95% CI 48.2–95.6) and 85.7% (95% CI 33.4–97.9) in
the ALK-positive and ALK-negative patients, respectively. At 3 years, the OS rate remained 83.3% (95% CI 48.2–95.6) in the ALK-positive patients, whereas it was 34.3% (95% CI 4.8–68.5) in the ALK-negative patients. Fig. 4 shows the maximum target lesion shrinkage, and Fig. 5 summarises the clinical course of the treated patients with IMT.

3.4. Safety

Treatment-related, non-haematological adverse events occurring in >10% of patients are shown in Table 4, and the most common were nausea (55% [11/20]), blurred vision (45% [9/20]), fatigue (45% [9/20]), diarrhoea (35% [7/20]) and vomiting (35% [7/20]). There were four grade

### Table 4

<table>
<thead>
<tr>
<th>Haematological and biochemical adverse events</th>
<th>Grade I N (%)</th>
<th>Grade II N (%)</th>
<th>Grade III N (%)</th>
<th>Grade IV N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematology (emergent/worsening)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td></td>
<td>3 (15)</td>
<td></td>
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<tr>
<td>Neutropenia</td>
<td>2 (10)</td>
<td>2 (10)</td>
<td></td>
<td>4 (20)</td>
<td></td>
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<tr>
<td>Lymphopenia</td>
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<td>3 (15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemistry (emergent/worsening)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>9 (45)</td>
<td>3 (15)</td>
<td>2 (10)</td>
<td>12 (60)</td>
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<tr>
<td>Hypoalbuminaemia</td>
<td>2 (10)</td>
<td>6 (30)</td>
<td>2 (10)</td>
<td>10 (50)</td>
<td></td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>6 (30)</td>
<td>3 (15)</td>
<td>9 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia</td>
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<td>3 (15)</td>
<td>5 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>4 (20)</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>7 (35)</td>
<td></td>
</tr>
<tr>
<td>SGPT</td>
<td>9 (45)</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>13 (65)</td>
<td></td>
</tr>
<tr>
<td>SGOT</td>
<td>8 (40)</td>
<td>1 (5)</td>
<td>3 (15)</td>
<td>13 (65)</td>
<td></td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>7 (35)</td>
<td>1 (5)</td>
<td></td>
<td>8 (40)</td>
<td></td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>7 (35)</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>10 (50)</td>
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<tr>
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<td>3 (15)</td>
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<td></td>
<td>14 (70)</td>
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<tr>
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<td></td>
<td></td>
<td>3 (15)</td>
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</tbody>
</table>

SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.
 treatment-related, non-haematological adverse events in three patients, which included fatigue, hepatic failure, sepsis and weight gain.

Haematological and biochemistry adverse events occurring in >10% of patients are shown in Table 5, and the most common were hypocalcaemia (70% [14/20]), increased serum glutamic oxaloacetic transaminase (65% [13/20]) and increased serum glutamic-pyruvic transaminase (65% [13/20]).

4. Discussion

EORTC 90101 was the first prospective phase II trial assessing the efficacy of an ALK inhibitor in patients with advanced IMT. The initial analysis of outcomes of this trial, performed after termination of further accrual of patients in this cohort of the multitumour study, resulted in an impressive ORR of 50.0% for patients with ALK-positive IMT [9]. Apart from the high response rate, another
striking finding of the original publication was the high rate of patients still receiving active treatment at the time of the initial data cut-off (9th November 2017) with a median follow-up of 28 months [9]. These patients were kept on active treatment in the context of this trial, as crizotinib was not available through other mechanisms. At a median follow-up of 50 months, we observed that the response status of some of the patients converted from SD to an objective response, which prompted us to prepare a final analysis of the efficacy of crizotinib in IMT.

In this updated analysis, the ORR achieved for ALK-positive patients with crizotinib (66.7%) is higher than previously reported (50.0%) [9]. This is due to the further reduction in tumour volume over time with long-term crizotinib treatment. For the ALK-negative subcohort, the ORR in this updated analysis remained constant to the previously reported data (i.e. an ORR of 14.3% for both the primary and updated analysis) [9].

The study met the primary end-point; crizotinib achieved an ORR of 66.7% in ALK-positive patients, which is above the alternative assumption that crizotinib would achieve an ORR of at least 30% in the original protocol. Even in patients with ALK-negative disease, the ORR of 14.3% was above the <10% limit for consideration of efficacy, and the total ORR with crizotinib in both subcohorts was 47.4%.

Compared with our previously reported data, during the follow-up period for this updated analysis, a further one ALK-positive patient and two ALK-negative patients died because of progression of IMT, highlighting the life-threatening character of this rare malignancy, and one ALK-negative patient died because of cardiovascular disease. In this updated analysis, 52.6% (10/19) of evaluable patients in both subcohorts are still alive, of which 9 of these patients are in the ALK-positive subcohort. The median DOR was 39.0 months in the ALK-positive responding patients, and the DOR was 7.6 months in the responding ALK-negative patient. The median PFS was 18.0 months and 14.3 months for the ALK-positive and ALK-negative patients, respectively, and the median OS of 26.6 months in ALK-negative patients has been reported here, whereas the median OS for the ALK-positive patients has still not been reached in this updated analysis, likely due to the high activity of the ALK inhibitor in this disease. With further follow-up, we have also been able to report 3-year OS here, with an impressive 83.3% rate in the ALK-positive subcohort.

These updated efficacy results with long-term follow-up, that are reported here, confirm previous findings that crizotinib is highly effective in patients with ALK-positive IMT and provides durable benefit, with five patients still receiving crizotinib treatment.

All patients with ALK-positive IMT benefited from crizotinib treatment (DCR: 100.0%). While only one ALK-negative patient had an objective response, DCR was observed in 85.7% (6/7) of the ALK-negative patients, suggesting potentially derived benefits from crizotinib treatment through other mechanisms. The ALK-negative patient who had the objective response had an ETV6-NTRK3 fusion in the tumour specimen which may have made the IMT sensitive to crizotinib, as reported in a recent publication on case studies [22].

Safety results were consistent with the known safety profile of crizotinib, with nausea, blurred vision, fatigue, diarrhoea and vomiting being common events. No new safety concerns were reported in this update.

The limitations of this study include it being a single-arm, non-comparative study with small patient numbers compared with the larger phase III trial often seen with other tumour types. These limitations are typical of those of rare diseases, such as IMT [2], where because of the limited number of patients, it is not possible to conduct a large, randomised phase III trial. Patient recruitment was slow. Furthermore, among the 35 patients recruited with a local diagnosis of IMT, diagnosis was not confirmed in 9 patients by central reference pathology as IMT, which emphasises the complexity of proper morphological classification of such tumours.

The remarkable efficacy we observed with crizotinib in patients with ALK-positive IMT supports the targeting of the inhibition of the genetically altered ALK pathway. In our previous report, we proposed crizotinib as the potential standard of care for patients with locally advanced or metastatic, ALK-positive IMT who do not qualify for curative surgery, based on the unprecedented activity and good safety profile of crizotinib and the unmet medical need in IMT [9]. After this updated analysis, we continue to support this statement. Recent publications also provide further support on the targeting of IMT by ALK inhibitors [23–25]. The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (Version 2.2021) and ESMO guidelines for soft tissue sarcoma now recommend the use of ALK inhibitors, such as crizotinib, in IMT with ALK translocation [26].

5. Conclusions

This updated analysis reinforces previous findings, with landmark analyses showing that crizotinib provides a high ORR, which is sustainable, with long PFS and OS in patients with ALK-positive IMT. Crizotinib should clearly be considered a standard of care for inoperable patients with locally advanced or metastatic ALK-positive IMT who do not qualify for curative surgery. EORTC 90101 CREATE provides the highest level of scientific evidence for meeting an unmet medical need in this ultra-rare disease, where conventional regulatory standards (such as the use of a large, randomised, confirmatory clinical trial) cannot be achieved.
Author contribution

P.S. had the original idea for this trial, proposed it to EORTC and Pfizer, developed and designed the study and searched the published works. Protocol writing was a collaboration effort between P.S., EORTC Headquarters staff and A.W. A.W. coordinated the molecular analysis. R.S. was responsible for reference pathology, and M.D-R. did the FISH analysis. P.S., J-Y.B., S.J.S., Si.S., P.R., V.B., M.G.L., A.I., N.I., F.M.S. and B.K. contributed to data collection and patient accrual. A.N. maintained the trial database. An.N. did the data analysis, and P.S. oversaw the management of the clinical trial and data collection. A.W. and P.S. coordinated reference pathology, FISH testing and the central review of radiological responses and reported results to EORTC. All authors contributed to the interpretation of the data, were involved in the preparation of the manuscript, contributed to revisions of the manuscript and approved the final version of the manuscript. The corresponding author had full access to the data and was responsible for providing regular information to the relevant committees monitoring this trial and had final responsibility for the decision to submit for publication. This article was reviewed and approved by all authors.

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Role of funding source

This work was an investigator-initiated trial. EORTC was the legal sponsor. Pfizer Inc. provided the investigational agent and funding, but had no role in the study design, data collection, analysis, interpretation, writing of the report or decision to publish this report. The database is held by EORTC, and EORTC statisticians performed and updated the analysis.

Conflict of interest statement

P.S. reports no competing interest related to crizotinib, Pfizer or EORTC, received research support to the institution outside of the scope of this study and reports an advisory or consulting role outside the scope of this study. P.R. received honoraria from Pfizer outside the scope of this study. V.B., M.G.L., A.I., N.I., M.D-R., R.S., F.S., Ax.N. and An.N. report no competing interest. B.K. reports no competing interest related to crizotinib, Pfizer or EORTC, received research support to the institution outside of the scope of this study and reports an advisory or consulting role outside of the scope of this study. M.K., T.S. and A.W. report no competing interest.

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