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Original Research

The tyrosine kinase inhibitor crizotinib does not have clinically meaningful activity in heavily pre-treated patients with advanced alveolar rhabdomyosarcoma with *FOXO* rearrangement: European Organisation for Research and Treatment of Cancer phase 2 trial 90101 'CREATE'

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KEYWORDS
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Crizotinib

Abstract ***Background:*** Alveolar rhabdomyosarcomas (ARMSs) can harbour MET and anaplastic lymphoma kinase (ALK) alterations. We prospectively assessed crizotinib in patients with advanced/metastatic ARMS.
Methods: Eligible patients with a central diagnosis of ARMS received oral crizotinib 250 mg twice daily. Patients were attributed to *MET*/*ALK*+ or *MET*/*ALK*− subcohorts by assessing the presence or absence of the forkhead box O1 (*FOXO1*; a marker of MET upregulation) and/or *ALK* gene rearrangement. The primary end-point was the objective response rate (ORR). Secondary end-points included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), progression-free rate (PFR), overall survival (OS) and safety.
Findings: Nineteen of 20 consenting patients had centrally confirmed ARMS. Molecular assessment revealed rearrangement of *FOXO1* in 17 tumours and *ALK* in none. Thirteen eligible patients were treated, but only eight were evaluable for the primary end-point because of the observed aggressiveness of the disease. Among seven evaluable *MET*+/*ALK*− patients, only one achieved a confirmed partial response (ORR: 14.3%; 95% confidence interval [CI]: 0.3−57.8) with a DOR of 52 d. Further *MET*+/*ALK*− efficacy end-points were DCR: 14.3% (95% CI: 0.3−57.8), median PFS: 1.3 months (95% CI: 0.5−1.5) and median OS: 5.6 months (95% CI: 0.7−7.0). The remaining *MET*+/*ALK*− and *MET*−/*ALK*− patients had early progression as best response. Common treatment-related adverse events were fatigue (5/13 [38.5%]), nausea (4/13 [30.8%]), anorexia (4/13 [30.8%]), vomiting (2/13 [15.4%]) and constipation (2/13 [15.4%]). All 13 treated patients died early because of progressive disease.
Interpretation: Crizotinib is well tolerated but lacks clinically meaningful activity as a single agent in patients with advanced metastatic ARMS. Assessing single agents in aggressive, chemotherapy-refractory ARMS is challenging, and future trials should explore established chemotherapy ± investigational compounds in earlier lines of treatment.
Clinical Trial Number: EORTC 90101, ClinicalTrials.gov NCT01524926.
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1. Introduction

Rhabdomyosarcoma (RMS) is a rare malignancy; however, it is the most common sarcoma in children and adolescents, with an incidence of approximately 50% of all soft-tissue sarcomas in these age groups [1,2]. In adult patients, RMS is an orphan disease, accounting for only 3% of all soft tissue sarcomas [1−3]. There are different subtypes of RMS: pleomorphic, embryonal, alveolar RMS (ARMS) and the botryoid and spindle cell variants [1,2,4]. Microscopically, ARMS consists of small densely packed round cells that resemble pulmonary alveoli, although a more solid variant has also been identified [1,2,5].

In ARMS, specific chromosomal translocations occur in 70−80% of patients [2,6]. The disease is typically characterised by a fusion of the paired box 3 (*PAX3*) or *PAX7* gene with forkhead box O1 (*FOXO1*) [1,7]. In approximately 60% of ARMS, translocation t(2; 13)(q35; q14) occurs, while in about 20%, translocation t(1; 13)(p36; q14) is found [1,2]. The t(2; 13)(q35; q14) translocation results in the expression of its chimeric transcription factor *PAX3-FOXO1*, while the t(1; 13)(p36; q14) translocation leads to the expression of *PAX7-FOXO1* [1,2]. Both fusion genes encode the subsequent chimeric proteins, which are more abundant and transcriptionally more potent than their wild-type counterparts [8−11]. Studies suggest that the presence of the PAX3-FOXO1 and PAX7-FOXO1 fusion proteins downstream contribute towards tumourigenesis [8,11]. PAX-FOXO1 stimulates tumour cell proliferation, angiogenesis, activates the myogenic program and inhibits apoptosis [2,12]. PAX3 is a main regulator of myogenesis, while PAX7 induces satellite cell specification [1,13,14].

PAX3 activates the transcription of a number of target genes involved in myogenic cell lineages, including *MET*, *MYOD* (myogenic differentiation 1) and *LBX1* (ladybird homeobox 1), and was shown to cause ligand-independent activation of MET in pre-clinical models [1,15−17]. *MET* encodes for the MET tyrosine kinase cell surface receptor, which is activated by its ligand hepatocyte growth factor (HGF), and MET phosphorylation in turn stimulates multiple signal pathways that play an important role in cell survival, proliferation, angiogenesis, migration, invasiveness and metastasis [19−21]. The ARMS-specific PAX3-FOXO1 fusion leads to MET overexpression, frequently observed in this entity [1]. Of note, Rees *et al.* assessed the role of a putative HGF−MET pathway in a panel of 68 clinical primary RMS samples and found MET was surprisingly a consistent feature of embryonal and not alveolar RMS [18].

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