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Clinical Trial

Phase 1 study of dalotuzumab monotherapy and ridaforolimus–dalotuzumab combination therapy in paediatric patients with advanced solid tumours

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Abstract ***Aim:*** Dalotuzumab is a highly specific, humanised immunoglobulin G1 monoclonal antibody against insulin-like growth factor receptor 1. This multicenter phase 1 study (NCT01431547) explored the safety and pharmacokinetics of dalotuzumab monotherapy (part 1) and the combination of dalotuzumab with the mammalian target of rapamycin inhibitor ridaforolimus (part 2) in paediatric patients with advanced solid tumours.
Methods: Dalotuzumab was administered intravenously every 3 weeks starting at 900 mg/m^2 and escalating to 1200 and 1500 mg/m^2. Combination therapy included intravenous dalotuzumab at the defined single-agent recommended phase 2 dose (RP2D) and oral ridaforolimus

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28 mg/m^2 daily (days 1–5), repeated weekly. Pharmacokinetic studies were performed to evaluate the mean serum trough dalotuzumab concentration, which guided the RP2D.
Results: Twenty-four patients were enrolled (part 1, n = 20; part 2, n = 4). No dose-limiting toxicities were observed in patients receiving dalotuzumab alone. One patient experienced dose-limiting stomatitis in the combination arm. Pharmacokinetic data showed dose-dependent increases in exposure (area under the curve from zero to infinity [$AUC_{0-\infty}$]) (87,900, 164,000, and 186,000 h*mg/ml for the 900, 1200, and 1500 mg/m^2 dose levels, respectively), maximum serum concentration (C_{max}) (392, 643, and 870 mg/ml), and serum trough concentration (C_{trough}) (67.1, 71.6, and 101 mg/ml). The mean half-life was 265, 394, and 310 h, respectively. Dalotuzumab pharmacokinetics were not affected by coadministration with ridaforolimus. One of six patients with Ewing sarcoma had confirmed partial response to dalotuzumab monotherapy at 900 mg/m^2. Time to response was 41 d, and progression occurred at 126 d.
Conclusion: Dalotuzumab was well tolerated in paediatric patients with advanced solid malignancies. The RP2D of dalotuzumab is 900 mg/m^2 (ClinicalTrials.gov identifier: NCT01431547, Protocol PN062).

1. Introduction

Insulin-like growth factor (IGF) signalling plays an important role in several paediatric cancers [1], and activation of IGF-IGF receptor 1 (IGF-1R) signalling is a hallmark of Ewing sarcoma [2]. Monoclonal antibodies that target IGF-1R have demonstrated activity in pre-clinical models of Ewing sarcoma, neuroblastoma, rhabdomyosarcoma, and osteosarcoma [3–8]. Interesting clinical responses have also been observed, primarily in a limited number of patients with Ewing sarcoma [9–13] but also in patients with osteosarcoma, rhabdomyosarcoma, and alveolar soft part sarcoma [14].

Dalotuzumab (MK-0646) is a highly specific, humanised immunoglobulin G1 kappa IGF-1R monoclonal antibody that induces IGF-1R internalisation and degradation, inhibiting IGF-1R autophosphorylation and AKT phosphorylation, thereby inhibiting cell proliferation [15]. When combined with chemotherapeutic agents, dalotuzumab was well tolerated and demonstrated anti-tumour activity [16,17].

Ridaforolimus is an inhibitor of the mammalian target of rapamycin (mTOR) that showed promising anti-proliferative activity in pre-clinical studies [18,19]. It has been investigated in a range of cancer indications as monotherapy and in combination with other agents [20–24]. In paediatric patients with advanced solid tumours, intravenous ridaforolimus was well tolerated, with no dose-limiting toxicities (DLTs), and stable disease was achieved in 40% of patients treated at 8, 10, 13, or 16 mg/m^2 [25]. Combining IGF-1R inhibitors with agents such as mTOR inhibitors has demonstrated additive or synergistic anti-tumour activity in pre-clinical studies and clinical trials [26–31].

This study was designed to explore the safety, tolerability, recommended phase 2 dose (RP2D), and pharmacokinetics of dalotuzumab as monotherapy and in combination with oral ridaforolimus in paediatric patients with advanced solid tumours. The rationale for this combination is that dalotuzumab may abrogate the feedback activation of AKT induced by ridaforolimus, producing synergistic effects greater than either agent alone.

2. Methods

2.1. Study design

This was a 3-part, phase 1, multicenter, multinational, open-label, dose-escalation trial (ClinicalTrials.gov identifier: NCT01431547, Protocol PN062). Part 1 was a dose escalation of dalotuzumab monotherapy. Part 2 was a dose escalation of ridaforolimus plus dalotuzumab. Part 3 was a cohort expansion of the recommended combination dose from part 2. However, the study was terminated during part 2 because of shifting sponsor priorities, and as a result part 3 was not initiated.

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and local and federal regulatory laws. The protocol was approved by the Institutional Review Board at each site. Patients and their parents/guardians provided written informed consent and assent according to institutional requirements.

2.2. Patients

Part 1 enrolled patients aged 3–17 years, and part 2 included patients aged 6–17 years (due to the available tablet formulation of ridaforolimus). Patients were eligible if they had a histologically or cytologically confirmed advanced solid tumour, measurable or non-