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A phase 2, multicentre, single-arm, open-label study to evaluate the safety and efficacy of single-agent lenalidomide (Revlimid®) in subjects with relapsed or refractory peripheral T-cell non-Hodgkin lymphoma: The EXPECT trial

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Abstract ***Background:*** This multicentre, single-arm, open-label phase 2 trial investigated the efficacy and safety of lenalidomide monotherapy in patients with relapsed/refractory peripheral T-cell lymphoma (PTCL).
Methods: Patients received oral lenalidomide 25 mg once daily on days 1–21 of each 28-day cycle for a maximum of 24 months, until disease progression or development of unacceptable adverse events (AEs). The primary end-point was efficacy; safety was evaluated as a secondary end-point. This study was registered with ClinicalTrials.gov, number NCT00655668.
Findings: A total of 54 patients with PTCL were treated. The overall response rate was 22% (12 of 54), including complete response (CR) or unconfirmed CR (CRu) in 11% of patients; 31% of

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patients with angioimmunoblastic T-cell lymphoma (AITL) responded (CR/CRu in 15% of patients). The median progression-free survival and median response duration were 2.5 and 3.6 months, respectively, in the intent-to-treat population, and 4.6 and 3.5 months, respectively, in patients with AITL. Thrombocytopenia and neutropenia were the most common grade 3 or 4 haematological AEs, in 11 (20%) and 8 (15%) patients, respectively. Overall, 19 patients (35%) experienced at least 1 AE leading to study dose interruption or reduction (commonly neutropenia or thrombocytopenia). Serious AEs were observed in 54% of patients and 12 patients died during the study; lymphoma progression ($n = 6$); and acute respiratory distress syndrome, dyspnea, lung infiltration, neutropenic sepsis, pneumonia and cerebral ischaemia ($n = 1$ each).
Interpretation: Lenalidomide exhibited single-agent activity in heavily pretreated patients with PTCL, particularly in patients with AITL. Future development is warranted in specific histologies, such as AITL, and in combination with chemotherapy or other agents considered active in PTCL.
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1. Introduction

T-cell lymphomas account for approximately 15% of all cases of non-Hodgkin lymphoma (NHL) in the United States of America (USA). Over 20 subtypes of mature T-cell and natural killer (NK)-T-cell lymphomas are categorised in the World Health organisation classification of haematological malignancies.[24] The most common histologies include: peripheral T-cell lymphoma (PTCL) not otherwise specified (PTCL-NOS; approximately 30% of all PTCL); anaplastic large cell lymphoma (ALCL; approximately 15–20% of all PTCL); angioimmunoblastic T-cell lymphoma (AITL; approximately 15–20% of all PTCL) and cutaneous T-cell lymphoma (CTCL), with mycosis fungoides as the most common subtype.

Aggressive T-cell NHL has traditionally been treated with combination chemotherapy containing anthracyclines.[12,2] Activity has also been reported with nucleoside analogues given as single-agent chemotherapy. For example, pentostatin is a safe and active agent for T-cell lymphoma[5] and gemcitabine is active in patients with relapsed/refractory PTCL-NOS.[30] Several other single-agent treatments were recently approved by the US Food and Drug Administration for the treatment of T-cell lymphoma: pralatrexate for the treatment of relapsed/refractory PTCL based on the PROPEL study[14]; romidepsin for relapsed/refractory CTCL and PTCL[25,3]; denileukin diftitox for persistent or recurrent CTCL[16] and brentuximab vedotin (SGN-35) for relapsed/refractory systemic ALCL.[17] However, long-term outcomes for patients with aggressive T-cell NHL remain poor, and a great unmet need exists for new treatment options.

Lenalidomide could be an option because it is an immunomodulatory agent with anticancer properties, including tumour cytotoxicity, immunomodulatory effects,[22] antiangiogenic properties[8] and enhancement of NK- and T-cell function[27] via the enhanced formation of immunological synapses.[21] Lenalidomide has shown single-agent activity in a broad range of haematological malignancies including multiple myeloma (MM),[23] myelodysplastic syndrome[11] and relapsed/refractory T- and B-cell lymphoma.[9,26]

In this multicentre, single-arm, open-label phase 2 EXPECT trial we investigated the efficacy and safety of lenalidomide monotherapy in patients with relapsed/refractory PTCL.

2. Methods

2.1. Patients

The study population comprised patients with biopsy-proven PTCL of any subtype or CTCL of the subtype mycosis fungoides only, who had relapsed or were refractory to previous therapy for T-cell lymphoma. Eligibility criteria included measureable disease on cross-sectional imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) of at least 2 cm in the longest diameter, prior exposure to at least one combination chemotherapy regimen containing at least two cytotoxic agents, and an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1 or 2.

The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable local regulatory requirements and laws. Approval from the institutional review board or independent ethics committee at each participating centre was required. All patients provided written informed consent prior to study enrolment.

2.2. Study design and treatment

This was a phase 2, multicentre, single-arm, open-label study of oral lenalidomide 25 mg once daily on days 1–21 of each 28-day cycle for a maximum of 24 months, until disease progression or development of unacceptable adverse events (AEs) as classified using