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A first-in-human trial of the novel multi-action therapy tinostamustine (EDO-S101) in patients with relapsed/refractory (R/R) Hodgkin lymphoma (HL)

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Introduction and objectives

- Although 70–80% of patients with advanced Hodgkin lymphoma (HL) are cured by first-line therapy, the management of primary refractory disease and post-transplant recurrence remains an area of high unmet need, even in the era of brentuximab vedotin (BV) and immune checkpoint inhibitors (CPI).[1]
- Tinostamustine (EDO-S101), an alkylating deacetylase inhibiting molecule, is a novel multi-action drug, which has been shown in preclinical studies to improve drug access to the DNA strands within cancer cells, break them and counteract damage repair.[2–5]
- The aim of this study is to investigate the safety and pharmacokinetics of tinostamustine in patients with haematological malignancies who have progressed despite one or more previous lines of treatment.
- Here we report findings from the dose-escalation stage of this open-label Phase I study in a subgroup of patients with a confirmed diagnosis of HL (NCT02576496).

Methods

- The safety, tolerability, pharmacokinetics (PK), maximum tolerated dose (MTD), and recommended Phase II dose (RP2D) of tinostamustine in patients with R/R HL was determined during the dose-escalation stage of this Phase I, first-in-human, multicentre, open-label study.
- Dose-limiting toxicities (DLTs), based on Cycle 1 events, were defined as: any Grade 3 or 4 non-haematological toxicity (excluding alopecia and easily correctable electrolyte abnormalities); nausea, vomiting or diarrhoea ≥10 days despite aggressive symptomatic treatment; Grade 4 neutropenia or thrombocytopenia for ≥7 days; any Grade 2 or more toxicity for >3 weeks; any toxicity resulting in a delay of the next dose administration (Cycle 2 Day 1 ≥14).
- Patients were recruited using a standard 3+3 design, with the first cohort receiving 40mg/m^2 tinostamustine administered IV over 60 minutes, with five ascending cohorts to a maximum dose of 120mg/m^2; further dose cohorts were administered over 45 minutes (80mg/m^2) and 30 minutes (60mg/m^2, 80mg/m^2).
- MTD and the maximum administered dose (MAD) was determined by evaluating toxicities during dose escalation.
- Blood samples for PK analysis were collected 0.5 hours pre-dose, 15, 30, 45 minutes, and 1, 1.25, 1.5, 2, 3, 8, 24, 48 and 72 hours from the start of infusion and analysed for tinostamustine and metabolites (M2-EDO-S101 and M8-EDO-S101).

Results

Patients

- A total of ten heavily pre-treated HL patients were enrolled into the dose-escalation stage of the study and formed the safety population (**Table 1**).
  - All ten patients received at least one dose of tinostamustine.
- The majority of patients (n=6) had primary refractory disease.
- All patients were heavily pretreated, having received three (n=2), four (n=3), five (n=1), six (n=3) and seven (n=1) previous lines of therapy.

Table 1. Patient demographics (safety population)

	Tinostamustine
Number of patients, N	10
Mean age ± SD, years	50.22 ± 17.85
Male, n (%)	3 (30)
Race	
White, n (%)	10 (100)
Black or African American, n (%)	0
Diagnosis, n (%)	
HL	10 (100)
Primary refractory disease, n (%)	6 (60)
Patients with relapsed disease, n (%)	4 (40)
Number of previous relapses, n (%)	
1	2 (20)
2	1 (10)
3	0
4	1 (10)
B symptoms, n (%)	
Weight loss	0
Night sweats	1 (10)
Unexplained fever	1 (10)

SD, standard deviation

Safety

- All 10 patients in the safety population experienced at least one treatment-emergent adverse event (TEAE) that was related to study treatment (**Table 2**).
  - No dose-modifying events (DMEs) were reported.
  - No renal or liver toxicity was observed at the studied doses.
  - Observed gastrointestinal toxicity was mild in intensity.
- In total 10 patients (100%) experienced 89 TEAEs.
- One patient (10%) experienced at least one serious TEAE of febrile neutropenia.
- Two DLTs occurred in the 120mg/m^2 over 60 minutes cohort: Grade 4 thrombocytopenia ≥7 days (1 patient), and prolonged thrombocytopenia/toxicity resulting in the delay of the next dose (1 patient).
- Three patients (30%) experienced TEAEs leading to permanent study withdrawal: thrombocytopenia (2 events in 2 patients); febrile neutropenia (1 event in 1 patient); neutropenia (1 event in 1 patient).

Table 2. Number (%) of patients with TEAEs

	Patients N=10
TEAEs*, n (%)	10 (100)
At least 1 related TEAE*, n (%)	10 (100)
Grade 3 TEAE, n (%)	6 (60)
Grade 4 TEAE, n (%)	2 (20)
At least 1 serious TEAE, n (%)	2 (20)
Permanent withdrawals due to TEAEs, n (%)	3 (30)
TEAEs with outcome of death, n (%)	0

*TEAEs included AEs that were recorded as Relationship Possible, Probable, or Definite.
TEAE, treatment-emergent adverse event

- One patient died of disease-related causes during the dose-escalation stage.
  - There were no deaths related to study treatment.

Dosing and pharmacokinetic profile

- The MTD was 100mg/m^2 tinostamustine with an infusion time of 60 minutes.
- The tinostamustine RP2D for HL depended on platelet count at treatment initiation: 100mg/m^2 intravenous over 60 minutes (≥200 x 10^9/L platelets) 80mg/m^2 intravenous over 60 minutes (<200 x 10^9/L, >100 x 10^9/L platelets), and 50mg/m^2 intravenous over 60 minutes (≤100 x 10^9/L platelets).
- PK studies showed that peak serum concentrations (C_{max}) reached therapeutic levels in the RP2D cohorts.

Efficacy

- Signals of efficacy were observed for patients with HL who received tinostamustine. These included:
  - 1 complete response
  - 5 partial responses
  - 2 patients with stable disease
  - and only 2 out of the 10 patients experienced disease progression (PD).
- Notably, a patient with primary refractory disease who had never achieved a response despite previous chemoradiotherapy, BV and CPIs, and had never been auto-transplanted due to PD, obtained a complete response with a duration of 8 months.
  - This patient was consolidated by haplo-transplant, is graft versus host disease (GvHD)-free >20 months after last tinostamustine dose and remained in complete response as of March 2019.

Conclusions

- In patients with HL and limited treatment options, tinostamustine was generally well tolerated, and preliminary signs of efficacy were observed.
- Baseline platelet levels were the main predictor of thrombocytopenia and therefore RP2D depends on baseline platelet level.
- The RP2D will be further investigated in the dose-expansion stage of this Phase I study with a larger cohort (maximum of 70 patients) recruited into one of five R/R haematological malignancy cohorts (Hodgkin lymphoma, peripheral T-cell lymphoma, cutaneous T-cell lymphoma, T-cell prolymphocytic leukaemia and multiple myeloma).

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NOVEL TREATMENTS

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