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Original Research

Phase II trial of the glycoprotein non-metastatic B-targeted antibody–drug conjugate, glembatumumab vedotin (CDX-011), in recurrent osteosarcoma AOST1521: A report from the Children's Oncology Group

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Abstract ***Background:*** The prognosis is poor for children and adolescents with recurrent osteosarcoma (OS). Glycoprotein non-metastatic B (gpNMB) is a glycoprotein highly expressed in OS cells. We conducted a phase II study of glembatumumab vedotin (GV), a fully human IgG2 monoclonal antibody (CR011) against gpNMB conjugated to the microtubule inhibitor, monomethyl auristatin E.

Patients and methods: Patients aged ≥12 years and <50 years with relapsed or refractory OS were eligible. GV 1.9 mg/kg/dose was administered on day 1 of each 21 day cycle. Pharmacokinetics were mandatory in patients aged <15 years. gpNMB expression was measured by immunohistochemistry. The primary end-point was disease control at 4 months and Response Evaluation Criteria in Solid Tumours response. A 2-stage design was used to determine efficacy.

Results: Twenty-two patients were enrolled, and all were evaluable for response. Antibody–drug conjugate levels were detectable in patients, although small numbers limit comparison to adult data. The toxicities observed were similar to the previous studies with GV. The most common grade III adverse event was rash. One death from end organ failure occurred possibly related to GV. Of the 22 patients, one patient had a partial response, and two had stable disease. There was no correlation between gpNMB expression and response to GV.

Conclusions: GV was well tolerated in this population. Although there was some antitumour activity, the extent of disease control in stage I did not meet the level required to proceed to stage II.

Trial registration numbers: NCT02487979.

1. Introduction

The 5-year overall survival of patients with newly diagnosed, localised osteosarcoma (OS) is 70% with multiagent chemotherapy [1]. However, prognosis remains poor for patients with metastases or recurrent disease [2,3]. The 4-month event-free survival for patients with recurrent OS with measurable disease enrolled on previous phase II studies from the Children's Oncology Group (COG) is 12% (95% confidence interval [CI] 6–19%) [4] indicating novel treatment strategies are needed.

Glycoprotein non-metastatic B (gpNMB) is a type I transmembrane glycoprotein normally expressed in a variety of cell types contributing to tissue repair, cellular adhesion and regulation of cell growth [5]. Overexpression has been demonstrated in multiple cancers including melanoma, breast cancer and OS [5–8]. Glembatumumab vedotin (GV) is an antibody–drug conjugate (ADC) directed against gpNMB. Consisting of a fully human IgG2 monoclonal antibody (CR011) against gpNMB conjugated to the microtubule inhibitor, monomethyl auristatin E (MMAE) [5]. Three clinical trials of GV in patients with breast cancer and melanoma have been completed, and antitumour activity has been observed [9–11]. In pre-clinical testing, gpNMB was expressed in 92.5% of OS samples. GV induced cytotoxic effects in 74% of OS cell lines, and gpNMB protein levels correlated with GV *in vitro* cytotoxicity [6]. To evaluate the clinical activity of GV in OS, we conducted a single-arm phase II trial, AOST1521, in patients with recurrent or refractory OS.

2. Material and methods

2.1. Eligibility

Eligible patients with recurrent or refractory OS included those ≥12 and < 50 years with measurable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 [12]. Other eligibility criteria included normal renal, cardiac and liver function along with adequate bone marrow function. Performance status corresponding to Eastern Cooperative Oncology Group scores of 0, 1 or 2 and life expectancy ≥8 weeks was required. Patients were excluded for prior use of GV or other MMAE-containing products, peripheral neuropathy > grade II using Common Terminology for Classifying Adverse Events (CTCAE), version 4.0, major surgery within 2 weeks of enrolment, were pregnant or breast feeding, or had brain metastasis. Archival tumour specimen from any previous biopsy/resection was required for evaluation of gpNMB expression measured by immunohistochemistry (IHC); however, documented expression was not required for enrolment. Based on accrual rates of patients with OS from three prior COG studies, ADVL0421, ADVL0524 and ADVL0525 [13–15], approximately 18 patients were expected to enrol annually. This trial was approved by the National Cancer Institute (NCI) Paediatric Central Institutional Review Board (CIRB) and by local

regulatory boards at all sites not utilising NCI Paediatric CIRB. Informed consent documentation was signed by all patients or their parent/legal guardian, and assent was obtained according to local institutional guidelines prior to enrolment.

2.2. Treatment and response assessment

NCI was the investigational new drug sponsor and supplied GV (Bethesda, MD). GV (1.9 mg/kg/dose) was administered as a 90-min intravenous infusion on day 1 of each 21-day cycle until disease progression or intolerance. Cycles were repeated for a maximum of 14 months or 18 cycles.

Toxicity was evaluated using CTCAE, version 4.0. Myeloid growth factor support for subsequent cycles was allowed for patients with grade IV neutropenia. Patients with continued grade IV neutropenia, grade IV thrombocytopenia or grade ≥III non-haematologic toxicity received dose reduction to 1.3 mg/kg/dose of GV in subsequent cycles. If toxicity did not resolve before the cycle following dose reduction, patients were removed from therapy.

Patients were evaluated for response following cycles 2, 4 and 6 and following every 3rd cycle thereafter using RECIST 1.1 [12].

To assess GV tolerability and toxicity in children, accrual of patients <18 years was suspended after the sixth patient was enrolled until all completed cycle 1. If < 1/3 of toxicity evaluable patients experienced dose limiting toxicity (DLT) during the first cycle of GV, subsequent enrolled patients would be treated at the same dose. All patients were monitored for DLT occurrence across all cycles considered evaluable for efficacy assessment. DLTs are defined in the protocol (supplementary materials).

2.3. Pharmacokinetics

Serum samples to assess pharmacokinetics (PKs) were required for the first six evaluable patients < 15 years. Samples were obtained before treatment; at the end of infusion; at 1, 2, 4, 8 and 24 h post-infusion on day 1 and 4, 7 and 21 days post-infusion. GV was quantitated in total antibody (TA) and AD using enzyme-linked immunosorbent assays. Free MMAE was quantified using liquid chromatography/mass spectrometry. All assays were described previously by Ott *et al.* [10].

Non-compartmental analysis was performed with WinNonlin 7.0 (Certara USA, Inc.) using nominal dosing for ADC and TA (1.9 mg/kg), and total MMAE per dose was based on molar coupling ratio in drug product and respective molecular weights of GV (150 kD) and auristatin E (718 Da). Infusion models were used for TA and ADC, and an extravascular model was used for free MMAE. Exposure (C_{max}, $AUC_{0\text{-}3w}$) was determined for ADC and TA by linear trapezoidal approximation. Terminal elimination half-life was determined by least squares fitting of experimental concentrations in the terminal phase for TA and ADC analytes, as well as for free MMAE.

2.4. gpNMB immunohistochemistry

Retrospective analysis of gpNMB expression in archived tumour specimens was conducted at a central laboratory (Mosaic Laboratories, Lake Forest, CA). gpNMB expression was assessed by IHC using a biotinylated CR011 monoclonal antibody. Stained slides were manually reviewed by a Mosaic pathologist using a standard bright field microscope. Maximum intensity of staining was graded on the following scale:1+ (weak), 2+ (moderate) and 3+(strong).

2.5. Statistical considerations

Primary end-point included two outcomes: (1) RECIST response according to RECIST v 1.1 [12] and (2) 4-month disease control. Eligible patients who received at least one dose of GV were considered evaluable for response, unless the patient received non-protocol therapy after first demonstrating complete response (CR) or partial response (PR) but before the confirmatory evaluation. Any evaluable patient who demonstrated a RECIST-defined CR or PR before the end of the sixth cycle of therapy was considered a RECIST responder. Disease control evaluable patients who did not demonstrate RECIST-defined disease progression through six cycles of protocol therapy or 4 months after study enrolment if GV therapy was stopped prior to the sixth cycle for any reason were considered a disease control success. Otherwise, the patient was considered a disease control failure. Four-month disease control was selected based on Lagmay *et al.* [4].

Patients not evaluable for RECIST response or disease control could be replaced for the application of the statistical rule. Patients evaluable for response but not disease control were considered not to have experienced disease control. The definitions above did not provide for a patient to be evaluable for disease control but not RECIST-response.

The study had two stages. Nineteen outcome evaluable patients would be enrolled. If four or fewer disease control successes and one or fewer RECIST responses were observed, the study would be stopped, concluding GV was not associated with sufficient activity for further evaluation. Otherwise, an additional 10 outcome evaluable patients would be enrolled (AOST1521 protocol found in supplementary materials).

Enrolment involved two groups. Stratum 1 included patients who had not received eribulin before enrolment, and stratum 2 included patients who had received eribulin before enrolment, thus minimising potential cross-resistance that could develop from prior microtubule

inhibitor exposure e.g. eribulin. The efficacy of GV would be evaluated according to the design stated above for patients enrolled in stratum 1. Stratum 2 enrolment would be stopped when the evaluation of stratum 1 was complete or when sufficient data were obtained to fully evaluate GV in stratum 2, whichever occurred first. If the adult dose of GV was considered tolerable in patients <18 years, those patients were included in the stratum indicated by the patient's history of eribulin treatment before enrolment.

By study design, the relationship between gpNMB expression measured by IHC and the probability of 4-month disease control was assessed only in patients without prior exposure to eribulin. The hypothesis of no association between strength of IHC expression and probability of disease control was assessed by the exact conditional test of proportions. The hypothesis of a linear trend was assessed using logistic regression with IHC reading taken as a continuous variable [16].

3. Results

3.1. Patient characteristics

Twenty-two adolescents and young adults (AYA) were enrolled (3 with prior eribulin therapy) at 17 centres throughout the United States and Canada between February 2016 to August 2016. As all patients had completed therapy, data current to June 2017 were used in this analysis. Enrolment occurred more rapidly than anticipated; Stage I completed within 6 months. Seven patients <18 years were enrolled instead of the planned six because of a data entry error in a patient's date of birth. The patient was allowed to remain on study. Median age of enrolment was 20 years. All patients were evaluable for response, and the median number of RECIST lesions was two (range 1–5). Lung and bone were the most common sites of disease (Table 1 and Supplementary Table 1).

Table 1
Patient characteristics of 22 patients enrolled on AOST1521.

Characteristic		
Age in years at study enrolment	Mean	20 years
	Median	20 years
	Range	12 years −31 years
	Number ≥18 Years	15
Patient Sex	Number male	15
	Number female	7
Race	Number white	20
	Number African-American	2
	Number American Indian, Aleutian or Eskimo	0
Ethnicity	Number Hispanic	3
	Number Not Hispanic	19
Number of lesions measured for RECIST evaluation	Mean	2.5
	Median	2
	Range	1 −5
Tumour burden of largest lesion in millimetres	Mean	35.1
	Median	33
	Range	10 −146
Sites of measurable disease	Lung	10
	Bone	3
	Lung + Bone	2
	Lung + Other	6
	Lung + Bone + Other	1

RECIST, Response Evaluation Criteria in Solid Tumours.

3.2. Treatment tolerability

GV was well tolerated. The most common grade III adverse events included rash and hypokalaemia (Table 2). One of the seven patients <18 years had a DLT, grade III anaphylaxis, during the first cycle. GV administered at 1.9 mg/kg was considered tolerable in younger patients. DLTs occurred in six of the 61 cycles in six patients, indicating no excessive rate of DLT (Supplementary Table 2). One patient death occurred during cycle 1 at day 16 following therapy.

3.3. Pharmacokinetics

GV PK were studied in four patients aged 12–14 years (Table 3). TA and ADC were detectable through 4–7 days, while free MMAE was detectable 7–21 days following infusion. The half-life of TA ranged from 28.6 to 41.1 h, and ADC half-life ranged from 17.3 to 36.8 h. Maximum free unconjugated MMAE levels occurred 4 days after dosing, ranging from 2.4 to 8.0 ng/mL (Fig. 1).

3.4. Disease control and response rate

Nineteen patients were considered in the analysis of disease control and response rate. One patient demonstrated both 4-month disease control and a RECIST PR. Two patients achieved the primary outcome measure of 4-month disease control without RECIST response. The activity level was inadequate to proceed to stage II based on our trial design.

3.5. gpNMB expression

Tumour samples were submitted for 21 of 22 patients for gpNMB expression. IHC analysis was completed on all specimens with H-scores ranging from 0 to 3+. Fifteen (68%) specimens expressed a score of 3 + indicating strong gpNMB expression. The patient with a RECIST PR and one of the two patients with 4-month disease control response both had score of 3+. The other patient with 4-month disease control had an score

Table 2
Adverse event (AE) count during the 61 cycles of chemotherapy administered to 22 patients on AOST1521.

	Patient cycles (N = 61)
Haematologic (AE grade IV or greater)	N (%)
Neutrophil count decreased	2 (3.3)
Platelet count decreased	1 (1.6)
White blood cell decreased	1 (1.6)
Non-haematologic (AE grade III or greater)	N (%)
Abdominal pain	2 (3.3)
Anaphylaxis	1 (1.6)
Anorexia	1 (1.6)
Back pain	2 (3.3)
Constipation	1 (1.6)
Febrile neutropenia	1 (1.6)
Headache	1 (1.6)
Hypertension	1 (1.6)
Hypocalcaemia	1 (1.6)
Hypokalaemia	4 (6.6)
Hypophosphataemia	2 (3.3)
Hypotension	1 (1.6)
Infections and infestations–other, specify: *UTI*	1 (1.6)
Mucositis oral	2 (3.3)
Myalgia	1 (1.6)
Nausea	1 (1.6)
Neoplasms benign, malignant and unspecified[a]	1 (1.6)
Pain	2 (3.3)
Pain in extremity	1 (1.6)
Peripheral sensory neuropathy	1 (1.6)
Pneumothorax	1 (1.6)
Rash acneiform	1 (1.6)
Rash maculo-papular	6 (9.8)
Respiratory failure	1 (1.6)
Somnolence	1 (1.6)

[a] The term neoplasm is describing progressive osteosarcoma.

of 1+. There was no correlation between gpNMB expression and disease control at 4 months ($P = 0.68$). The odds ratio for disease control success for non-eribulin patients with at most 2 + staining compared with 3 + staining was 0.91(95% CI, 0.66–13) (Supplementary Table 3).

4. Discussion

Our study was conducted in refractory or relapsed heavily pre-treated adolescents and young adults with OS reflecting current US Food and Drug Administration draft guidance that adolescents 12–17 years be eligible for enrolment in adult oncology clinical trials at all stages of drug development when the histology and biologic behaviour of the cancer under investigation is the same in, or the molecular target of the drug is relevant to cancers in both adult and adolescent patients [17]. While some antitumour activity was observed in stage I, it did not meet criteria to initiate stage II. However, one patient had a RECIST response. In contrast, five previous COG phase II trials enrolling patients with recurrent OS with a primary end-point of RECIST response had no observable RECIST responses [4], and the recently completed COG clinical trial AOST1322 utilising eribulin in patients with relapsed OS exhibited zero responses to therapy [18]. Additionally, one patient in the current study had prolonged stable disease receiving all 18 cycles of GV. This indicates GV has activity in some patients with OS, and further study of GV could be considered if a biomarker predicting benefit were identified.

In pre-clinical experiments using patient-derived xenograft (PDX) models of OS, IHC testing showed expression of gpNMB (1 + to 3+) in six out of seven samples. These six PDX models received GV, and three maintained a CR and had IHC 2 + to 3 + for gpNMB expression [8]. Despite 15 of our patient samples expressing high levels (IHC 3+) of gpNMB, only two met the disease-control end-point. Further, one patient with prolonged stable disease had IHC 1+, suggesting IHC expression of gpNMB did not predict response.

There are multiple possible explanations for discrepancy between pre-clinical evidence and our trial results. Microtubule inhibitors may not be as active in OS. There may be differential competition for GV between non-tumour GPNMB in PDX models versus humans as a result of different affinities for human versus mouse GPNMB. This may be inferred from the longer half-life observed in PDX models versus those observed in clinical trials [10,19]. PDX models may not represent the high likelihood of tumour heterogeneity in patients that have already received multiple forms of systemic therapy, and gpNMB expression in archival tissue may be not a reliable predictor of OS tumour response. Recent research has identified alternatives to difficult to obtain biospecimens for biomarker studies such as serum microRNAs, long non-coding RNAs, circulating tumour cells and circulating tumour DNA [20–22]. In future OS clinical trials, it would be ideal to evaluate blood-based assays for their ability to serve as biomarkers to facilitate patient selection.

Toxicities with GV were as expected and similar to previous GV studies [9–11]. Our patients <18 years tolerated GV well, and if stage II had proceeded, enrolment would have been opened again to younger patients. The patient who died had advanced metastatic disease before enrolment including lung involvement and a disease-related pericardial effusion. The patient received colchicine for pericardial effusion treatment before starting protocol therapy and developed neutropenic fever, mucositis and acute kidney injury following GV. Cause of death was end organ failure, and GV was considered to be a contributing factor. As both colchicine and GV are microtubule inhibitors, there may have been an interaction between the two drugs.

Table 3
Summary of glembatumumab vedotin pharmacokinetics in patients aged 12–14 years.

	n	Cmax (μg/mL)	Tmax (hr)	$T_{1/2}$ (hr)	$AUC_{0\text{-}3w}$ (hr-μg/mL)	Vz (mL/kg)	Cl (mL/hr/kg)
TA	4	48.8 ± 10.0	1.8 ± 0.5	35.2 ± 6.4	2319 ± 334	42.5 ± 11.7	0.8 ± 0.1
ADC	4	59.8 ± 16.3	3.3 ± 1.7	29.1 ± 8.4	2260 ± 750	37.9 ± 16.3	0.9 ± 0.3
MMAE	4	0.006 ± 0.003	96 ± 0.0	62.6 ± 14.6	1.28 ± 0.88	42,802 ± 28,786	533 ± 468

TA = total antibody; ADC = antibody–drug conjugate; MMAE = monomethyl auristatin E; n = number; Cmax = maximum concentration; $T_{1/2}$ = half-life; AUC = area under the curve; Vz = volume of distribution; Cl = clearance.

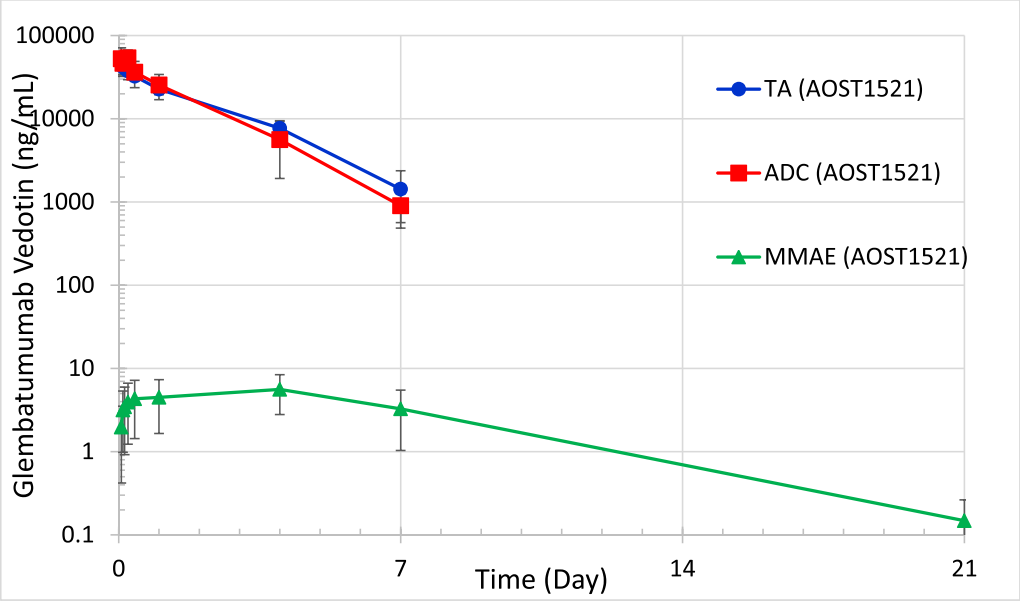

Fig. 1. Glembatumumab vedotin exposure among paediatric osteosarcoma patients (n = 4) enrolled in AOST1521. TA = total antibody; ADC = Antibody–Drug Conjugate; MMAE = monomethyl auristatin E. Serum Concentrations are represented as arithmetic mean (n=4) with y-axis in log-base-10 scale. Error bars represent ± standard deviation.

PK data were minimal, and comparison of concentration versus time profiles against historical data from the EMERGE trial in breast cancer [9] indicates similar exposure of components (Supplementary Fig. 1); however, the small population size makes direct comparisons difficult.

Along with signs of early activity, another positive outcome of this study was a more rapid than predicted patient accrual. Additionally, the median age of enrolment was 20 years, demonstrating our success in enrolling AYA patients ≥18 years to a trial led by the COG. This is encouraging as traditionally AYAs have poor representation on clinical trials [23,24].

5. Conclusions

Although our trial did not meet sufficient disease control in stage I to proceed to stage II, some patients had meaningful responses, indicating there may be a role for GV in OS. To determine which patients with OS will benefit, further exploration of predictive biomarkers would need to be done.

Conflict of interest statement

L.M.K. is an employee of the contract research organisation Covance. M.K. is a consultant for Merck. K.A.J. has received travel reimbursement from Loxo oncology. R.G. has received laboratory research funding from Eisai. T.H. and E.C. are employees of Celldex.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.08.015.

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