Selinexor-based regimens for the treatment of myeloma refractory to chimeric antigen receptor T cell therapy

Recent reports indicate that chimeric antigen receptor T cell (CAR-T) therapy can induce deep and durable responses for many patients with heavily-pretreated multiple myeloma (MM), with median progression-free or event-free survival ranging between 7 and 12 months (Zhao *et al.*, 2018; Cho *et al.*, 2018; Raje *et al.*, 2019; Xu *et al.*, 2019). Relapse post CAR-T, however, is common, and treatment options for these patients are limited. Currently, there is minimal published data and no consensus on subsequent therapies after progression on CAR-T. Most strategies, including CAR-T retreatment, have proven largely ineffective, establishing a major unmet medical need for this patient population.

Selinexor is an oral, small-molecule inhibitor of the nuclear export protein exportin 1 (XPO1) that induces accumulation of tumour suppressor proteins in the nucleus, reductions in oncoproteins, cell cycle arrest and apoptosis of cancer cells (Abdul Razak *et al.*, 2016; Chen *et al.*, 2017; Vogl *et al.*, 2018). XPO1 is overexpressed in many cancers, including MM, and elevated levels are correlated with poor prognosis, increased bone lytic lesions and resistance to therapy (Tai *et al.*, 2014). In patients with penta-exposed, triple-class refractory MM, selinexor plus low-dose dexamethasone (Sd) produced an overall response rate of 26·2% and clinical benefit rate (≥ minimal response) of 39·3%, which translated into a survival benefit for responding patients (Chari *et al.*, 2019). The activity of selinexor was preserved regardless of prior therapy, as expected from a drug with a novel mechanism of action; however, the efficacy after CAR-T therapy has not been specifically described. Here, we report on observations of the activity of Sd alone or administered as a triplet in combination with bortezomib (SVd) or carfilzomib (SKd) in patients with MM whose disease has progressed after CAR-T therapy.

We identified seven patients across selinexor trials who received lymphodepleting conditioning with fludarabine and/or cyclophosphamide followed by an effective dose of CAR-T cell therapy [$>10^8$ CAR-positive cells targeting B-cell maturation antigen (BCMA)] for their MM prior to being enrolled in a trial using a selinexor-containing regimen. One patient was treated on the STORM study (NCT02336815) with selinexor (80 mg twice-weekly, days 1 and 3) plus dexamethasone (20 mg twice-weekly, days 1 and 3); one patient was treated with selinexor (100 mg once-weekly) plus bortezomib (1·3 mg/m^2 once-weekly for 4 of 5 weeks) and dexamethasone (40 mg once-weekly) in the compassionate use program; and five patients were treated with selinexor (100 mg once-weekly) plus carfilzomib (20/56 or 20/70 mg/m^2) and dexamethasone (40 mg once-weekly or 20 mg twice-weekly) in the NCT02199665 trial. Response was assessed by the treating physician per International Myeloma Working Group (IMWG) criteria.

Baseline characteristics for the seven patients are summarized in Table I. All patients were heavily pretreated (median 10 prior therapeutic regimens; range: 5–15) and had high-risk cytogenetics; six patients had rapidly progressing disease as evidenced by the percent increase in paraprotein from screening to cycle 1, day 1 (C1D1) (range: 17–91%). Four patients had MM that was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab in a prior regimen (penta-refractory), and all patients had progressed after autologous stem cell transplantation, alkylating agents, as well as CAR-T therapy. The median time to progression on CAR-T therapy was 4 months (1–7 months). All patients received a selinexor combination immediately after progression on CAR-T (with the exception of one patient who received two additional lines of therapy prior to receiving Sd). As of the date of data cutoff, the median time on a selinexor-based regimen was 6·0 months (range: 3·7–8·3 months); four patients' disease had progressed, one patient had withdrawn consent, and two patients were still responding and on therapy.

Response assessments for each patient are outlined in Fig. 1A,B, and included one stringent complete response, three very good partial responses, two partial responses and one minimal response. Responses (≥ partial response) occurred within the first cycle of treatment for four patients; a noteworthy observation, given the rapidly progressing paraprotein levels at baseline. Interestingly, despite meeting IMWG criteria for having disease progression (>25% increase from nadir) after 6·5 months, Patient 1 continued treatment with Sd for an additional 1·5 months and derived clinical benefit before ending study with paraprotein levels nearly 50% below C1D1.

The anti-myeloma activity seen in patients with disease that was refractory to bortezomib, carfilzomib and/or dexamethasone in a prior line of therapy validates reported data showing that selinexor overcomes resistance to proteasome inhibitors (PIs). Preclinical studies have demonstrated that selinexor synergizes with PIs and glucocorticoids through enhanced suppression of the NF-κB signaling pathway and potentiation of glucocorticoid receptor transcriptional activity in the presence of dexamethasone, respectively (Kashyap *et al.*, 2016; Argueta *et al.*, 2018). These results are supported with clinical findings from the STOMP (NCT02343042) and NCT02199665 trials, which have demonstrated efficacy of Sd

Table I. Baseline demographics.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age	66	70	62	35	62	67	64
Sex	F	F	M	M	M	F	F
Ethnic origin	White	White	White	White	White	White	White
ECOG performance status	1	0	1	1	1	1	1
ISS staging at diagnosis	III	II	I	II	I	II	Unknown
Time from initial diagnosis (years)	6·3	15·9	9·8	8·9	10·0	4·8	8·0
Cytogenetics	t(14;16)	Gain (1q21), trisomy 3, 7, 9 plus IGH translocation	t(4; 14)	Hyperdiploidy with + 1q and trisomy 9, 11, 15	t(4;14)	+1q, t(4;14), del 13	Complex hyperdiploid karyotype with del 1p
Extramedullary plasmacytomas ≥1	No	Yes (2 sites)	No	Yes (2 sites)	Yes (2 sites)	Yes (3 sites)	Yes (1 site)
LDH at Baseline (U/l)	202	161	176	186	205	245	225
Prior therapeutic regimens (N)	10	15	7	5	11	6	12
Bortezomib exposed/ refractory	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/No	Yes/No	Yes/Yes
Carfilzomib exposed/ refractory	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes
Lenalidomide exposed/ refractory	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/No
Pomalidomide exposed/ refractory	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/No	Yes/Yes	Yes/No
Daratumumab exposed/ refractory	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/No	Yes/Yes	Yes/Yes
Elotuzumab exposed/ refractory	Yes/Yes	Yes/Yes	No/No	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes
Panobinostat exposed/ refractory	No/No	No/No	No/No	No/No	Yes/Yes	No/No	No/No
Anti-PD1/anti-PDL1 exposed/refractory	Yes/Yes	No/No	Yes/Yes	No/No	No/No	No/No	No/No
Prior ASCT (#)	Yes (2X)	Yes (2X)	Yes (2X)	Yes (2X)	Yes (2X)	Yes (1x)	Yes (3x)
CAR-T best response and time to progression (months)	VGPR (4)	SD (4)	PR (7)	VGPR (5)	PR (3)	SD (2)	SD (1)
Selinexor Regimen	Sd	SKd	SKd	SKd	SKd	SKd	SVd
% Increase in MM marker from screening to C1D1	23% (8 days)	91% (22 days)	48% (18 days)	51% (7 days)	17% (18 days)	0% (14 days)	21% (14 days)

ECOG, Eastern cooperative oncology group; ISS, international staging system; LDH, lactate dehydrogenase; ASCT, allogeneic stem cell transplant; CAR-T, chimeric antigen receptor T cell therapy; Sd, selinexor and dexamethasone; SKd, selinexor, carfilzomib, and dexamethasone; SVd, Selinexor, bortezomib, and dexamethasone. Refractory is defined as <25% decrease in M-protein while on therapy, or progression within 60 days of completing therapy. Time to progression is defined as the day the patient received CAR-T therapy until the day of documented disease progression.

in combination with bortezomib or carfilzomib in patients with MM refractory to PIs (Bahlis *et al.*, 2018; Jakubowiak *et al.*, 2019).

Consistent with other studies testing Sd, SVd or SKd in heavily pretreated patients with MM, the most common adverse events among the patients described here were nausea, fatigue, thrombocytopenia, neutropenia and anaemia (Chen *et al.*, 2017; Bahlis *et al.*, 2018; Vogl *et al.*, 2018; Jakubowiak *et al.*, 2019). Most patients required a dose interruption or reduction in selinexor during the course of treatment. The seven patients presented here were managed for nausea with prophylactic 5-HT3 antagonists, and additional supportive care agents including rolapitant, omeprazole, lorazepam or olanzapine. In addition, thrombocytopenia was managed and reversible with dose reductions or interruptions combined with weekly doses of romiplostim, a thrombopoietin agonist (typically starting at 1 ug/kg and increasing, if needed, to 10 ug/kg), to stimulate platelet production.

(A) Table of Best Response

	Treatment Regimen	Best Response on Selinexor Regimen	Time to Response (≥ PR) (months)	Time on Study (months)	Duration of Response (≥ PR) (months)	Off Study Reason	Therapy After Selinexor Regimen
Patient 1	Sd	PR	0.9	8.0	5.6	Progressive Disease	TAK573
Patient 2	SKd	PR	2.7	4.1	1.4	Progressive Disease	Not Started
Patient 3	SKd	sCR	0.9	8.3+	7.4+	Ongoing	-
Patient 4	SKd	VGPR	1.0	6.0	5.0	Progressive Disease	CC220 + Carfilzomib
Patient 5	SKd	MR	-	5.0	-	Progressive Disease	DCEP
Patient 6	SKd	VGPR	0.3	3.7	3.4	WC	BET inhibitor
Patient 7	SVd	VGPR	1.4	6.0+	4.6+	Ongoing	-

(B)

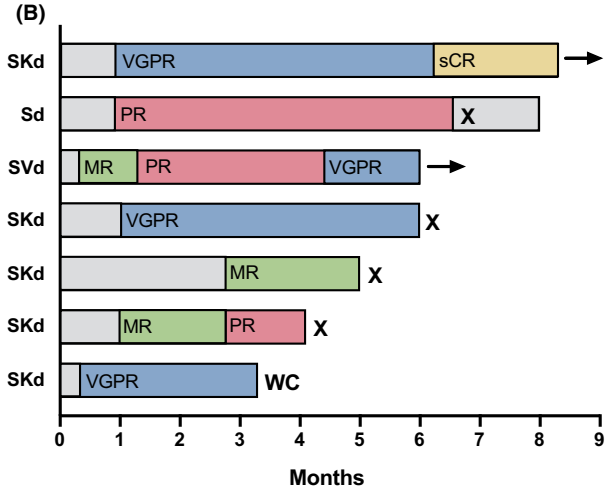

Fig 1. Efficacy of selinexor-containing regimens post CAR-T therapy. (A) Table of best response. sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; WC, withdrawal of consent due to decreased quality of life; DCEP, Dexamethasone, Cyclophosphamide, Etoposide, Cisplatin; + indicates the patient is continuing therapy. (B) Swim lane plot of time on study. Grey indicates time on study without a known response per IMWG criteria. X, disease progression; arrow indicates patient in continuing on therapy.

This is the first data set demonstrating anti-myeloma activity of selinexor-based rfegimens in patients who have progressed after CAR-T therapy. The activity was observed regardless of prior treatment history, with no cross resistance. Though the findings reported here are based on a small group of patients, the responses are intriguing and warrant further investigation. Currently, the available therapeutic options for patients described here include intensive multi-agent chemotherapy, recycling various combinations or entry onto an investigational trial. As CAR-T therapy moves into earlier lines of MM treatment and more patients develop resitance to this approach, selinexor-based regimens may offer important therapeutic benefit, underpinned by a novel mechanism of action which is key in the setting of relapsed and refractory disease, and should be considered (Richardson & Blade, 2014).

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Author contributions

A.C., D.T.V., S.J., J.J. and A.J.: enrolled patients, analysed and interpreted data, wrote and reviewed the manuscript. T.J.U. and A.D.: collected, analysed and interpreted the data; wrote and reviewed the manuscript. J.S., M.K. and S.S.: contributed to the design of the study, analysed and interpreted the data, wrote and reviewed the manuscript.

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Acquired haemophilia A treated with recombinant porcine factor VIII: a single centre UK experience

Recombinant porcine factor VIII (rpFVIII; Obizur, Susoctocog-alfa) was commissioned by NHS England in June 2018 as a first line treatment option for actively bleeding patients with acquired haemophilia A (AHA). Obizur has sufficient sequence homology to human (h) FVIII to be haemostatic in humans whilst lack of complete homology means it eludes autoantibody inhibition in many patients with AHA (cross-reactivity 5–10%) (Kruse-Jarres *et al.*, 2015).

Previous standard of care in actively bleeding patients with AHA was with bypassing agents (BPAs): activated prothrombin complex concentrate (aPCC) and activated recombinant FVII (rFVIIa). In contrast to BPAs, rpFVIII levels can be measured using a one-stage assay, allowing replacement based on assay levels, as well as clinical response. Furthermore, Obizur may result in less thrombotic risk than BPAs and therefore be more suitable for patients with cardiovascular comorbidities (Knoebl *et al.*, 2012; Kruse-Jarres *et al.*, 2015; Tarantino *et al.*, 2017). We present our single centre experience of the first five patients treated with Obizur between June 2018 and August 2019 with lower initial doses than previously published (50–80 u/kg Obizur compared to licensed dose of 200 u/kg).

Tables 1 and 2 summarise key patient information and treatment, which is supplemented by individual case descriptions.

Patient 1: This 86-year-old man initially presented with haematemesis whilst on rivaroxaban for atrial fibrillation, and rivaroxaban was stopped. At 2 months later, he developed a left proximal deep vein thrombosis (confirmed by Doppler ultrasonography), which was then treated with therapeutic enoxaparin. At 1 month later, whilst on enoxaparin, he presented with right leg swelling and computed tomography (CT) scan confirmed a thigh haematoma. The enoxaparin was stopped. Following minimal clinical improvement in thigh swelling, the local haematology team was contacted. On review his activated partial thromboplastin time (APTT) had been persistently elevated at about 55 s (reference range 20·0–30·0 s) since the haematemesis. The diagnosis of AHA was made and immunosuppression commenced. BPAs were not started as there was no active bleeding by that stage. On day 16 of steroids, he developed new spontaneous flank haematoma. Upon Obizur administration, haemostasis was achieved rapidly; further dosing was given to maintain trough of FVIII initially >0·5 iu/ml (as per guidelines for inherited haemophilia and supported by Obizur data) (Kruse-Jarres *et al.*, 2015; Srivastava *et al.*, 2013). Obizur was stopped after 9 days, but he subsequently developed *Staphylococcus aureus* septicaemia and died.

Patient 2: An 88-year-old man presented with haematoma causing compartment syndrome of the left leg, secondary to trauma. He had a background of myocardial infarction and stenting 2 years prior; and had undergone a transcatheter aortic valve implantation procedure 6 months previously, followed by clopidogrel and aspirin for 3 months. He was on aspirin alone at time of admission and this was stopped. APTT was raised at 35·2 s but further investigations were not sent. He had an urgent fasciotomy but bled postoperatively with re-accumulation of his haematoma requiring red cell transfusion. Fresh frozen plasma was given, and he returned to theatre for a repeat washout of his wound. When bleeding continued, haematology advice was sought on day 4 and a diagnosis of AHA was made. Bleeding promptly stopped upon Obizur administration and haematoma size remained static. Obizur was continued for 5 days. He subsequently developed pneumoperitoneum secondary to a perforated diverticulum whilst on steroids. He deteriorated rapidly developing multi-organ failure. Due to his multiple comorbidities surgery was considered very high risk and following discussion with the family and multidisciplinary team, a decision was made for palliation.

Patient 3: An 86-year-old man with ischaemic heart disease on aspirin presented with a 3-day history of widespread bruising, acute 60 g/l drop in haemoglobin and spontaneous iliopsoas bleed. Aspirin was stopped.

APTT was raised at 62·7 s. Haematology were contacted on day 3 of admission. Once AHA diagnosis was confirmed, Obizur was given. His haemoglobin stabilised with no new bleeds identified and improvement to existing bruising. Obizur was continued for 4 days. He responded to second-line immunosuppression and has not had further active bleeding.

Patient 4: An 84-year-old woman with hypertension and congestive cardiac failure presented with rectal bleeding and dysphasia. CT demonstrated intracranial haemorrhage and retroperitoneal haematoma. APTT was raised at 49 s.