Received: 15 June 2019 | Revised: 23 July 2019 | Accepted: 30 July 2019

DOI: 10.1002/hon.2662

ORIGINAL RESEARCH ARTICLE

WILEY

A phase II study to assess the safety and efficacy of the dual mTORC1/2 inhibitor vistusertib in relapsed, refractory DLBCL

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Funding information
CRUK Experimental Cancer Medicines Centre (ECMC); National Institute for Health Research (NIHR); Julian Starmer-Smith Lymphoma Fund; Bloodwise, Grant/Award Number: 14029

Peer Review
The peer review history for this article is available at publons.com/publon/10.1002/hon.2662

Abstract

Patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are unfit for or relapsed postautologous stem-cell transplantation have poor outcomes. Historically, mTORC1 inhibitors have produced responses in approximately 30% of patients in this setting. mTORC1 inhibitor efficacy may be limited by resistance mechanisms including AKT activation by mTORC2. To date, dual mTORC1/2 inhibitors targeting both the TORC1 and TORC2 complexes have not been investigated in DLBCL. This phase II trial investigated the oral dual mTORC1/2 inhibitor vistusertib in an intermittent dosing schedule of 125 mg b.d. for 2 days per week. Thirty patients received vistusertib and six received vistusertib-rituximab for up to six cycles (28-day cycles). Two partial responses were achieved on monotherapy. Durations of response were 57 and 62 days, respectively, for these patients. 19% had stable disease within six cycles. In the monotherapy arm, the median progression-free survival was1.69 (95% confidence

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interval [CI] 1.61-2.14) months and median overall survival was 6.58 (95% CI 3.81-not reached) months, respectively. The median duration of response or stable disease across the trial duration was 153 days (95% CI 112-not reached). Tumour responses according to positron emission tomography/computed tomography versus computed tomography were concordant. There were no differences noted in tumour volume response according to cell of origin by either gene expression profiling or immunohistochemistry. Vistusertib ± rituximab was well tolerated; across 36 patients 86% of adverse events were grade (G) 1-2. Common vistusertib-related adverse events were similar to those described with mTORC1 inhibitors: nausea (47% G1-2), diarrhoea (27% G1-2, 6% G3), fatigue (30% G1-2, 3% G3), mucositis (25% G1-2, 6% G3), vomiting (17% G1-2), and dyspepsia (14% G1-2). Dual mTORC1/2 inhibitors do not clearly confer an advantage over mTORC1 inhibitors in relapsed or refractory DLBCL. Potential resistance mechanisms are discussed within.

KEYWORDS
AZD2014, DLBCL, mTORC1, mTORC2, Vistusertib

1 | INTRODUCTION

Patients with diffuse large B-cell lymphoma (DLBCL) undergoing first-line treatment with curative intent have a 60 to 70% long-term progression-free survival (PFS). 30 to 40% are primary refractory or relapse (R/R) and typically have a poor prognosis. 30 to 40% respond to salvage chemotherapy and may undergo autologous stem-cell transplantation (ASCT) consolidation[1] although 50% of these DLBCL cases will relapse. Primary refractory DLBCL or relapsed DLBCL in patients <12-month post-ASCT have a median overall survival (OS) of 6.3 months.[2] There remains no widely applicable standard of care in this setting.

PI3K/AKT/mTOR is an evolutionarily conserved pathway that adjusts protein synthesis to regulate cell proliferation by integrating signals from growth factors, hormones, nutrients, and energy metabolism. It is a commonly deregulated pathway in B-cell malignancies with aberrant activation associated with poor prognosis.[3] Mechanisms of aberrant activation include activating PI3K and AKT mutations; inactivation of the negative pathway regulator, PTEN, in germinal centre B-cell (GCB)-type DLBCL, and upregulation of downstream effector molecules in activated B-cell (ABC) DLBCL.[4]

mTOR comprises two distinct multiprotein complexes, mTORC1 and mTORC2, which contain different proteins, Raptor and Rictor, respectively, and localize to different subcellular compartments. mTORC1 regulates cell proliferation, angiogenesis, and metabolism by phosphorylation of its downstream S6K1 and 4E-BP1, which promote mRNA translation of oncogenic proteins. AKT activates mTORC1 directly by phosphorylation of PRAS40, a component of mTORC1, and indirectly by inhibiting TSC2 mediated repression of Rheb, a selective activator of mTORC1. mTORC2 function is less understood but is likely involved in cell proliferation, survival, and nutrient uptake, partially through its ability to stimulate AKT, which is itself a critical survival kinase.[5]

Rapamycin analogues (mTORC1 inhibitors (i)), everolimus and temsirolimus, display an overall response rate (ORR) of 28 to 30% with a short median PFS (2.6 months) in R/R DLBCL.[6] The addition of rituximab results in a modest improvement in ORR (38%).[7] mTORC1 inhibitor efficacy may be limited by resistance mechanisms including AKT activation by mTORC2,[8] incomplete mTORC1 activation of its downstream effector 4E-BP1, activation of feedback loops, and activation of parallel signalling pathways.[5]

Dual mTORC1/2 selective ATP competitive inhibitors block phosphorylation of all downstream targets of both mTORC complexes without affecting other kinases. Preclinical data suggests that dual mTORC1/2 inhibition overcomes resistance to mTORC1 inhibition and have superior antiproliferative and proapoptotic effects.[5] AZD2014 (vistusertib) is a potent, specific dual mTORC1/2 inhibitor with superior pharmacokinetics compared with previously developed dual mTORC1/2 inhibitors.[9] Using continuous or intermittent schedules, it was well tolerated in a phase I trial in solid tumours.[10] An intermittent schedule of two consecutive days per week (four-weekly cycle) starting at 125 mg b.d. was recommended based on pharmacokinetics, pharmacodynamics, and potentially improved tolerability rather than 50 mg b.d. daily. We performed a phase II, single-arm, multicentre open-label trial to determine the activity and tolerability of vistusertib in R/R DLBCL, delivered as monotherapy or in combination with rituximab.

2 | METHODOLOGY

2.1 | Eligibility

To be eligible for the trial, patients 18 years or over with an ECOG performance status of 0 to 2 with histologically proven relapsed or refractory DLBCL and must have received at least one therapeutic line of potentially curative immunochemotherapy containing an anti-CD20 monoclonal antibody. Patients with high grade transformation from an underlying indolent lymphoma or chronic lymphocytic leukaemia were permitted if they had also failed one potentially curative line of therapy. Patients must have relapsed following salvage chemotherapy ± ASCT or be considered not suitable for ASCT for any reason. Patient must have measurable disease with a single lesion having a long axis diameter of ≥1.5cm or splenomegaly ≥14cm in craniocaudal length attributable to relapsed lymphoma. Eligible patients were HIV negative, hepatitis C negative, and hepatitis B surface antigen negative.

Key exclusion criteria included are listed as follows: (a) anticancer therapy (radiotherapy, endocrine, investigational, or immunotherapy) within 21 days (not including palliative radiotherapy at focal sites). Corticosteroids were permitted within 21 days of registration as long as the maximum dose was 10 mg (equivalent) of prednisolone on cycle one; day one (b) unresolved toxicity from prior therapy > grade two (CTCAE v 4.03); (c) previous exposure to mTORC1 or mTORC1/2 inhibitors; (d) requiring potent and moderate inhibitors and inducers of CYP3A4/5; (e) proven DLBCL central nervous system involvement; (f) clinically significant and uncontrolled major medical condition(s) including but not limited to infection, bleeding diathesis, symptomatic cardiac failure, cardiac arrhythmia, or psychiatric illness, which would limit protocol compliance; (g) left ventricular ejection fraction <50%; (h) major surgery < 4 weeks; (i) type I or uncontrolled type II diabetes (HbA1c >7 mmol/L); and (j) refractory nausea and vomiting, chronic gastrointestinal diseases, or bowel resection precluding adequate oral medication. All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and received ethical approval (REC number: 10/H0604/85).

The primary endpoint was the best ORR achieved during cycles one to six assessed by standard cross-sectional CT imaging. Secondary endpoints included PFS, OS, duration of response (DOR), change in tumour volume, and tolerability. OS was defined as the time from registration to date of death. Progression free survival (PFS) was defined as time from registration to date of progression or death from any cause. For both OS and PFS, patients without an event were censored at their latest assessment. DOR was the time from first documented response to time of death or progression. Time to event outcomes were assessed using Kaplan Meier survival plots. Maximum percentage decrease in the radiological sum of the products of the diameter (SPD) during the first six cycles was assessed using the Revised Response Criteria for Malignant Lymphoma.[11] Specific timing of positron emission tomography and computed tomography (PET-CT) scan on the days of reassessment during the six cycles was not mandated. In light of the unknown effect of dual mTORC inhibition on FDG-activity in DLBCL, the PET-based assessment was considered exploratory.

2.2 | Statistical analysis

Response rate (and therefore sample size) was determined for the monotherapy cohort using a single-stage A'hern design, and tolerability was assessed in both treatment cohorts using a Simon 2-stage design. The sample size for activity of vistusertib was based on an A'hern's single arm design (n=30). We would have 90% power for further investigation with a 40% ORR, if nine or more responses were observed. A further six patients received vistusertib-R, although this assessment was not statistically powered, it was planned from the outset of the trial. Tolerability of vistusertib was assessed using a Simon two-stage design for the monotherapy treatment cohort. The investigators needed to observe at least 10 “tolerable” outcomes, ie, at most five toxicities leading to delays or dose modifications during cycle one to two from the first 15 patients to have passed the interim assessment. If 21 or more “tolerable” outcomes from the 30 monotherapy patients were observed by the study investigators, we would conclude with 90.4% power that vistusertib dosing was tolerable. All analysis has been conducted on the intention to treat population.

In the monotherapy cohort, 30 patients initially received up to six cycles of orally administered vistusertib. For the combination cohort (n=6), rituximab 375 mg/m^2 was administered on day one of each cycle for six cycles alongside vistusertib. The safety of this combination was assessed after the recruitment to the monotherapy cohort. Vistusertib was continued until progression, toxicity, or patient choice. Rituximab was given until progression, toxicity, or patient choice for a maximum of six 28-day cycles. Patients with stable disease (SD), partial response (PR), or complete response (CR) remained on study; patients with radiological or clinical progressive disease (PD) were withdrawn.

Adverse events (AEs) were evaluated according to CTCAE version 4.03. G-CSF was permitted for grade (G) four neutropenia and was continued until neutrophil count normalized. Neutropenic fever was managed according to local practice. Primary antiviral, antifungal, and antipneumocystis prophylaxis was not mandated.

Exploratory outcomes included assessment of response by cell-of-origin (COO) (immunohistochemistry [IHC] and gene expression profiling [GEP] using the HTG EdgeSeq DLBCL COO assay) and pharmacodynamic immunohistochemical assessment of the mTOR pathway.

2.3 | IHC for COO

IHC was performed on formalin-fixed paraffin embedded biopsy sections (4 μm) using either pS6 [Ser235/6] (CST#4857), pAKT [Ser473] (DAKO M3628) or pPRAS40 (Thr264) (CST# 2997) primary antibodies. pPRAS40 (Thr264) was performed on the Leica Bond Rx at final concentration of 3ug/mL diluted in Antibody Diluent with Background Reducing Agents (DAKO S3022). The Polymer Refine Detection kit (Leica DS9880), Serum Free Protein Block

(DAKO X0909), Epitope Retrieval Buffer ER2, and F Standard protocol were used. For pS6 [Ser235/6] and pAKT [Ser473], sections were dewaxed, rehydrated, then antigen retrieved using a Milestone RHS-1 microwave in pH8 and pH9 retrieval buffer, respectively. Staining for pS6 [Ser235/6] and pAKT [Ser473] (DAKO M3628) was performed on Lab Vision™ Autostainer 720-2D (Thermo Scientific™) using the Rabbit EnVision™+System-HRP labelled polymer and Liquid DAB+ Substrate Chromogen System (DAKO). pS6 [Ser235/6] was used at final concentration of 0.54ug/mL in TBS-Tween 0.05%. pAKT [Ser473] was used at final concentration of 8ug/mL in Antibody Diluent (DAKO). Carazzi's haematoxylin was used to counterstain the nuclei. Slides were scanned at x20 using the Aperio AT2 scanner. The cytoplasmic staining of each antibody in the samples was evaluated blinded by a pathologist and the percentage of tumour cells with strong (3+), moderate (2+), weak (1+), or negative staining was captured. H-Scores were calculated as [(%1+ cells) + (%2+ cells*2) + (%3+ cells*3)]. COO was reported by IHC according to the published Hans algorithm.[12] Unblinded results were analysed using GraphPad (Prism v7.04), and graphs were generated comparing pretreatment and posttreatment biomarker changes.

2.4 | GEP for COO

Where sufficient tissue was remaining, additional sections were taken for GEP using the HTG EdgeSeq DLBCL Cell of Origin Assay, according to manufacturer's protocol. Briefly, a representative area of tumour was marked on a corresponding H/E by an expert haematopathologist and this area was measured and scraped from a 5 μm unstained section into a sterile microfuge tube using a sterile, disposable scalpel blade. An appropriate volume of lysis buffer was added, and sections heated to 95°C to melt the wax. After cooling, sections were digested with Proteinase K at 50°C for 3 hours. Digested samples were transferred to the HTG EdgeSeq processor for automated quantitative nuclease protection assay target capture of the 92 probes in the DLBCL COO assay. Following EdgeSeq processing, the targeted probes are PCR amplified and barcoded for primer sequencing and enumeration. Libraries were quantified, and pooling was adjusted and balanced to ensure appropriate cluster generation for sequencing on an Illumina MiSeq using standard protocols. FastQ files were imported back into the EdgeSeq for Parsing, and a COO classification was reported through the HTG Edge host system software.

As PI3K/AKT/mTOR promotes glucose uptake in response to insulin, inhibition may disproportionately switch-off the FDG uptake mechanism in DLBCL.[13] Therefore, the effect of mTORC1/2 inhibition on the sensitivity of FDG-avidity was also assessed by PET.

The "TORCH" trial (NCT02752204) was conducted through the Trials Acceleration Programme in affiliation with the University of Birmingham and funded by Bloodwise. AstraZeneca provided free drug and funding for exploratory studies.

3 | RESULTS

Thirty-six patients were recruited (10/2015 to 04/2017). Thirty received vistusertib and six vistusertib-rituximab. The median age was 68 years (range 33-82). Median prior lines were three (range 1-9). 47% (17/36) had primary refractory DLBCL. 17% (6/36) had undergone prior ASCT. By IHC, 71% (22/31) were GCB and 29% (9/31) non-GCB subtype. Of 20 samples yielding a result, 60% (12/20) were GCB and 40% (8/20) were ABC by GEP (Table 1). GEP and IHC COO correlated in 14/19 cases where both were available.

Across all 36 patients treated, the ORR was 6% (2/36). Two patients (6%) achieved PR, with no CRs. Seven patients (19%) had SD within six cycles. Both PRs occurred on monotherapy. Fourteen

TABLE 1 Baseline characteristics

Characteristic	Percentage and Number
Gender	
Male	42% (15/36)
Female	58% (21/36)
Age (years; median, range)	68 y (range 33-82).
ECOG performance status	
0	22% (8/36)
1	72% (26/36)
2	6% (2/36)
Prior lines of therapy (median, range)	3 (1-9)
Ann Arbor Staging	
1-2	14% (5/36)
3-4	86% (31/36)
First line therapy response	
Relapsed	53% (19/36)
Refractory	47% (17/36)
International prognostic index	
Low 0-1	11% (4/36)
Low/Intermediate 2	36% (13/36)
High/Intermediate 3	31% (11/36)
High 4-5	22% (8/36)
Prior autologous stem cell transplantation	
Yes	17% (6/36)
No	83% (30/36)
Cell of origin (immunohistochemistry) (n = 31)	
DGCB	71% (22/31)
Non-GCB	29% (9/31)
Cell of origin (gene expression profiling) (n = 21)	
GCB	60% (12/20)
ABC	40% (8/20)
Unclassifiable	n=1

Abbreviations: ABC: activated B cell; GCB: germinal centre B cell.

patients progressed at first response assessment. Thirteen patients discontinued treatment prior to first response assessment (at cycle 2) (reasons: disease progression [n=10], death [n=2], and toxicity [n=1]). A mean of 2.5 cycles of monotherapy were completed (range 1-9), and two cycles of combination treatment were completed (range 1-6). 40% (8/20) of those evaluable obtained tumour volume reduction (Figure 1A). In the monotherapy arm, the median PFS was 1.69 (95% CI 1.61-2.14) months and median OS was 6.58 (95% CI 3.81-NR) months (Figures 1B and 1C). Of the two responses during treatment, DOR was 57 and 62 days. The median DOR or SD across the trial duration was 153 days (95% CI 112-NR). Tumour responses according to PET/CT versus CT were concordant. There were no differences noted in tumour volume response according to COO by GEP and IHC (Table S1 in the supporting information).

Vistusertib±rituximab was well tolerated with most AEs occurring in early treatment cycles (Tables 2 and 3). Common vistusertib-related AEs were nausea (47% G1-2), diarrhoea (27% G1-2, 6% G3), fatigue (30% G1-2, 3% G3), mucositis (25% G1-2, 6% G3), vomiting (17% G1-2), and dyspepsia (14% G1-2). 86% of all AEs were G1-2 and were manageable. One patient developed reversible G4 thrombocytopenia managed by temporary vistusertib cessation and dose reduction. Two patients developed G4 neutropenia, managed with G-CSF, temporary vistusertib cessation, and dose reduction. The trial passed the interim toxicity assessment.

To assess pharmacodynamic activity of vistusertib, biomarkers of mTORC1/2 signalling were assessed in pretreatment and on-treatment tumour biopsies from three patients using IHC (Figures S1-S4 in the supporting information). AKT phosphorylation was lower in posttreatment than pretreatment biopsies in all patients, indicating inhibition of mTORC2. However, AKT phosphorylation was not completely reduced by vistusertib. Phosphorylation of another biomarker of mTORC2 activity, PRAS40, was only reduced completely in one of three patients and was suboptimally reduced in a further patient. Biomarker analysis of mTORC1 signalling also indicated suboptimal pathway suppression: pS6 was reduced following vistusertib in tumour biopsies in two of three patients.

4 | DISCUSSION

We demonstrated very modest activity of dual mTORC1/2 inhibition in a poor risk R/R DLBCL population. Vistusertib demonstrated biological activity according to tumour volume responses; however, ORR was low and nondurable. As a comparison, SCHOLAR-1 demonstrated a 26% ORR to a "subsequent therapeutic line" in a similar cohort, showing inferior responses in primary refractory patients compared with those relapsing post-ASCT or after response to prior line(s) (ORR: 20% versus 34% and 26%, respectively).[2]

We could not demonstrate that dual mTORC1/2 inhibition conferred an advantage over mTORC1 inhibition. This may have been due to suboptimal mTORC1/2 inhibition. It is possible that mechanisms other than mTORC2 escape that confer resistance to mTORC1 inhibition or that mTORC2 resistance may occur to dual mTORC1/2

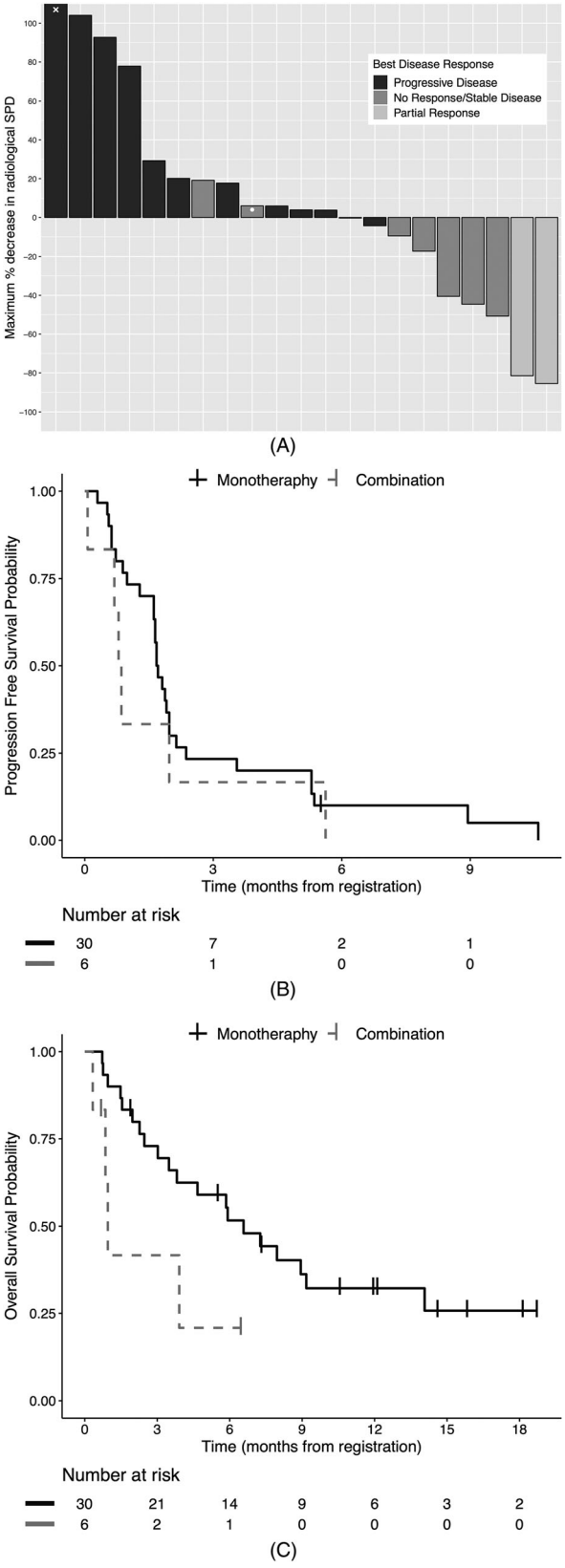

FIGURE 1 Tumour responses and patient survival. A, Best percentage tumour volume response: waterfall plot. *x* = patient with 720% increase in tumour size. The white circle denotes patient on vistusertib-rituximab combination. B, Progression-free survival (n = 36). C, Overall Survival (n = 36)

TABLE 2 Common vistusertib related (possibly, probably or definitely) adverse events and serious adverse events

	Overall	Grade 1	Grade 2	Grade 3	Grade 4	SAE
Toxicity and Category	**Frequency and absolute % per patient (n = 36)**					
Gastrointestinal						
Nausea	17 (47%)	10 (28%)	7 (19%)	0 (0%)	0 (0%)	
Fatigue	12 (33%)	7 (19%)	4 (11%)	1 (3%)	0 (0%)	
Diarrhoea	12 (33%)	7 (19%)	3 (8%)	2 (6%)	0 (0%)	1
Mucositis oral	11 (31%)	8 (22%)	1 (3%)	2 (6%)	0 (0%)	1
Vomiting	6 (17%)	3 (8%)	3 (8%)	0 (0%)	0 (0%)	
Other	5 (14%)	4 (11%)	1 (3%)	0 (0%)	0 (0%)	
Abdominal pain	3 (8%)	1 (3%)	2 (6%)	0 (0%)	0 (0%)	1
General disorders and administration site conditions						
Fever	3 (8%)	2 (6%)	1 (3%)	0 (0%)	0 (0%)	1
Investigations						
Electrocardiogram QT corrected interval prolonged	3 (8%)	3 (8%)	0 (0%)	0 (0%)	0 (0%)	
Platelet count decreased	4 (11%)	1 (3%)	1 (3%)	1 (3%)	1 (3%)	
Metabolism and nutrition disorders						
Anorexia	4 (11%)	3 (8%)	1 (3%)	0 (0%)	0 (0%)	
Dyspepsia	5 (14%)	2 (6%)	3 (8%)	0 (0%)	0 (0%)	
Musculoskeletal and connective tissue disorder						
Other	4 (11%)	3 (8%)	1 (3%)	0 (0%)	0 (0%)	
Skin and subcutaneous tissue disorders						
Rash maculo-papular	4 (11%)	3 (8%)	1 (3%)	0 (0%)	0 (0%)	
Other	3 (8%)	2 (6%)	1 (3%)	0 (0%)	0 (0%)	

Abbreviation: SAE: serious adverse event.

TABLE 3 Adverse events by cycle

	Frequency and Absolute % per Patient (n = 36)			
Cycle Number	**Overall**	**Yes**	**No**	**Missing**
1	36 (100%)	33 (92%)	3 (8%)	0 (0%)
2	25 (69%)	22 (61%)	1 (3%)	2 (6%)
3	11 (31%)	7 (19%)	2 (6%)	2 (6%)
4	10 (28%)	5 (14%)	0 (0%)	5 (14%)
5	7 (19%)	5 (14%)	0 (0%)	2 (6%)
6	6 (17%)	5 (14%)	0 (0%)	1 (3%)

inhibitor. In our study, we observed that complete inhibition of mTORC1/2 signalling was not achieved. In contrast, everolimus has resulted in near complete pS6 inhibition in a phase I study of advanced solid tumours patients.[14]

Mechanisms of dual mTORC1/2 inhibitor resistance include activating mutations in the mTOR kinase domain rather than drug-binding site mutations, as seen in mTORC1 inhibitor resistance. Such mutations are identified in drug-naïve and pretreated patients, suggesting that some patients may have intrinsic mTORC inhibitor resistance. Third-generation mTORC inhibitors in development simultaneously overcome acquired binding sites mutations and activating point mutations in the mTOR kinase domain, achieved through bivalent binding to both mTORC1 and mTORC2 binding sites. Negative feedback loops may also contribute to resistance. For example, mTORC1 inhibition suppresses the downstream effector S6K1, which normally degrades insulin receptor substrate (IRS-1). Inhibition leads to an enhanced growth signal from intact IRS-1. S6K1 suppression may also enhance signalling via PDGFR and MAP/ERK pathways.[15]

Intermittent dosing may have negatively impacted response as vistusertib has a short half-life and response is dose-dependent.[9] The schedule was chosen to improve tolerability and to limit reactivation of upstream pathways due to loss of negative feedback. In vivo cell line models suggested evidence of enhanced cell death using an intermittent dosing.

Despite limited efficacy, we demonstrate that this specific mTORC1/2 inhibitor at the dosing schedule described was well tolerated in patients with a good performance status (ECOG 0-1 94%) and can be safely combined with rituximab. Common AEs were similar to the phase 1 trial[10] and other mTORC1/2 inhibitors.[5] Combination studies with novel agents with nonoverlapping toxicities may augment responses. For example, mTORC1/2 inhibitor resistance has been associated with BCL2 overexpression, and combination with BCL2 inhibition has shown synergy in mouse models.[16] As demonstrated in Burkitt cell lines, HDAC inhibition may overcome resistance through negative feedback pathways by causing dephosphorylation of AKT

and synergy.[17] Ibrutinib and vistusertib are synergistic in ABC DLBCL cell lines and in a xenograft model, possibly through cooperative inhibition of oncogene translation and abolition of crosstalk signalling between mTOR and NFkB-STAT3 pathways[4] and a BTK inhibitor plus mTORC1/2 inhibitor combination is currently being evaluated.

5 | CONCLUSION

Targeting the mTORC1 and mTORC2 complexes with the dual mTORC1/2 inhibitor vistusertib did not clearly improve on outcomes documented with mTORC1 inhibitors in patients with relapsed or refractory DLBCL.

Disclaimers

Nil

ROLE OF FUNDING SOURCE

This trial is funded by Bloodwise under the Trials Acceleration Programme (TAP). AstraZeneca provided free of charge Vistusertib under the terms of partnership agreements between AstraZeneca and the University of Birmingham as Sponsor. An unrestricted educational grant was provided to support the trial and adjunctive science by AstraZeneca.

ETHICAL APPROVAL

REC number: 10/H0604/85

CONTRIBUTIONS

TE and GC designed the trial. SB and VW centrally reviewed and interpreted the PET-CT studies. TE wrote the manuscript. GC, TE, CH, KL, KC, SR, AP, AD, and DW recruited patients and managed them whilst on study. ASA, AP, AH, and LH provided expert data management, administrative, and statistical input. EH designed the PD biomarker strategy, selection of mTORC1 and mTORC2 markers, and experimental planning. CH and MR developed the experimental design for pharmacodynamic biomarker analysis and assay optimization. All authors reviewed the final manuscript.

ACKNOWLEDGEMENTS

The team would like to thank all the patients involved in the study and their families. T. E. acknowledges support from the Julian Starmer-Smith Lymphoma Fund. G. C. acknowledges support from the Haematology and Stem cells theme of the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Programme and the CRUK Experimental Cancer Medicines Centre (ECMC). The views expressed are those of the authors and not necessarily those of the funding bodies. The trial was supported by the Trials Acceleration Programme (TAP) in affiliation with Bloodwise. An unrestricted educational grant was provided to support the trial and adjunctive science by AstraZeneca. AZD2014 (Vistusertib) was provided free of charge by AstraZeneca.

CONFLICT OF INTEREST

C. H., M. R., and E. H. are employees of AstraZeneca. None of the other authors have relevant conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Eyre TA, Hildyard C, Hamblin A, et al. A phase II study to assess the safety and efficacy of the dual mTORC1/2 inhibitor vistusertib in relapsed, refractory DLBCL. *Hematological Oncology*. 2019;37:352–359. https://doi.org/10.1002/hon.2662