

Title Page

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

Running head: dual mTORC1/2 inhibition in relapsed, refractory DLBCL

Authors: Toby A. Eyre 1*, Catherine Hildyard 1*, Angela Hamblin 1, Ayesha S. Ali 2, Aimee Houlton 2, Louise Hopkins 2, Daniel Royston 3, Kim M. Linton 4, Andrew Pettitt 5, Simon Rule 6, Kate Cwynarski 7, Sally F. Barrington 8, Victoria Warbey 8, David Wrench 9, Sharon Barrans 10, Caroline S. Hirst 11, Anesh Panchal 2, Martine P. Roudier 11, Elizabeth A. Harrington 11, Andrew Davies 12, Graham P. Collins 1.

1. Department of Haematology, Oxford University Hospitals NHS Foundation Trust, Churchill Hospital, Oxford, OX3 7EJ, UK.

2. Cancer Research UK Clinical Trials Unit, University of Birmingham.

3. Department of Cellular Pathology, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, OX3 9DU, UK.

4. Department of Medical Oncology, The Christie Hospital NHS Trust, Wimslow Road, Manchester, M20 4BX, UK.

5. Royal Liverpool and Broadgreen University Hospitals NHS Trust, Prescot Street, Liverpool, Merseyside L7 8XP, UK.

6. University of Plymouth Medical School, Derriford Road, Plymouth, PL6 8DH, UK.

7. Department of Haematology, University College London Hospitals 235 Euston Road, London, NW1 2BU.

8. Clinical PET Centre, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH.

9. Department of Haematology, Guy's and St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH.

10. St James' University Hospital, Leeds, United Kingdom

11. Translational Medicine, AstraZeneca Oncology R&D I Research & Early Development, Cambridge, United Kingdom

12. Cancer Research UK Centre, Cancer Sciences Unit, University of Southampton, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD.

*Joint first authors. Corresponding author and author responsible for reprint requests: Toby A. Eyre
toby.eyre@ouh.nhs.uk Telephone 01865 235886 Fax 01865 235260

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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, 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, MR developed the experimental design for pharmacodynamic biomarker analysis and assay optimization. All authors reviewed the final manuscript.

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Keywords AZD2014, Vistusertib, DLBCL, mTORC1, mTORC2

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ABSTRACT SUMMARY (290 words)

Patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) who are unfit for or relapsed post autologous 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 inhibitors vistusertib in an intermittent dosing schedule of 125 mg b.d. for two 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. Duration 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 was 1.69 (95% confidence interval 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% confidence interval 112-not reached). Tumour responses according to PET/CT versus CT 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.

ORIGINAL ARTICLE: MAIN TEXT

Introduction

Patients with diffuse large B-cell lymphoma (DLBCL) undergoing first-line treatment with curative intent have a 60-70% long-term progression-free survival (PFS). 30-40% are primary refractory or relapse (R/R) and typically have a poor prognosis. 30-40% 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 months 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 multi-protein complexes, mTORC1 and mTORC2, which contain different proteins, Raptor and Rictor, respectively and localise 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 28-30% 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. Pre-clinical data suggests dual mTORC1/2 inhibition overcomes resistance to mTORC1 inhibition, and have superior anti-proliferative and pro-apoptotic 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.

Methodology

Eligibility

To be eligible for the trial, patients 18 years or over with an ECOG performance status of 0-2 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 (CLL) 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 ≥ 1.5 cm or splenomegaly ≥ 14 cm in cranio-caudal 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: (i) anti-cancer 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 (ii) unresolved toxicity from prior therapy > grade two (CTCAE v 4.03) (iii) previous exposure to mTORC1 or mTORC1/2 inhibitors (iv) requiring potent and moderate inhibitors and inducers of CYP3A4/5 (v) proven DLBCL central nervous system involvement (vi) 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 (vii) left ventricular ejection fraction <50% (viii) major surgery < four weeks (ix) type I or

uncontrolled type II diabetes (HbA1c >7 mmol/L) (x) 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. Overall survival (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. Duration of response 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 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.

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 2-stage design for the monotherapy treatment cohort. The investigators needed to observe at least 10 'tolerable' outcomes i.e. at most 5 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/m² 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 (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 normalised. Neutropenic fever was managed according to local practice. Primary anti-viral, anti-fungal and anti-pneumocystis 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.

Immunohistochemistry (IHC) for Cell of Origin (COO)

IHC was performed on formalin-fixed paraffin embedded biopsy sections (4µm) 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 3µg/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 was 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 0.54µg/mL in TBS-Tween 0.05%. pAKT [Ser473] was used at final concentration of 8µg/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)]. Cell of origin (COO) was reported by immunohistochemistry according to the published Hans algorithm 12. Unblinded results were analysed using GraphPad (Prism v7.04) and graphs were generated comparing pre and post treatment biomarker changes.

Gene Expression Profiling (GEP) for Cell of Origin (COO)

Where sufficient tissue was remaining, additional sections were taken for Gene expression profiling 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 5µm 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 three hours. Digested samples were transferred to the HTG EdgeSeq processor for automated quantitative nuclease protection assay (qNPA) 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.

Results

Thirty-six patients were recruited (10/2015 to 04/2017). 30 received vistusertib and six vistusertib-rituximab. The median age was 68 years (range 33-82). Median prior lines was 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 I). 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 patients progressed at first response assessment. 13 patients discontinued treatment prior to first response assessment (at cycle 2) (reasons: disease progression (n=10), 15% 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 (Figure 1B-C). Of the two responses during treatment, DOR was 57 and 62 days. The median duration of response or stable disease 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 1S (Supplementary)).

Vistusertib+/-rituximab was well tolerated with most AEs occurring in early treatment cycles (Table 2; Table 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 pre- and on-treatment tumour biopsies from three patients using IHC (Figure S1-4 Supplementary). AKT phosphorylation was lower in post-treatment than pre-treatment 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 sub-optimally reduced in a further patient. Biomarker analysis of mTORC1 signalling also indicated sub-optimal pathway suppression: pS6 was reduced following vistusertib in tumour biopsies in two of three patients.

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 non-durable. 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 sub-optimal 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 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 pre-treated patients, suggesting 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 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 inhibitor 5. Combination studies with novel agents with non-overlapping 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 de-phosphorylation 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.

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.

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Table 1 Baseline Characteristics

Characteristic	Percentage and number
Gender	
Male	42% (15/36)
Female	58% (21/36)
Age (years; median, range)	68 years (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 (IPI)	
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)	
GCB	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

Table 2 – Common vistusertib related (possibly, probably or definitely) adverse events (AEs) and serious adverse events (SAEs)

Toxicity and Category	Overall	Grade 1	Grade 2	Grade 3	Grade 4	SAE
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%)	
Diarrhea	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%)	

Abbreviations: SAE: serious adverse event

Table 3 - Adverse events (AEs) by cycle

Cycle Number	Frequency and absolute % per patient (n = 36)			
	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%)

Figure legends

Figure 1: Tumour responses and patient survival

Figure 1A - Best Percentage Tumour Volume Response: waterfall plot. x = patient with 720% increase in tumour size. White circle denotes patient on vistusertib-rituximab combination.

Figure 1B: Progression-free survival (n = 36)

Figure 1C: Overall Survival (n = 36)

Figure S1: pATK, pS6 and pPRAS40 H scores pre-treatment and at D15.

Figure S2: pATK expression at pre-treatment at D15 on treatment

Figure S3: pS6 expression at pre-treatment at D15 on treatment

Figure S4: pPRAS40 expression at pre-treatment at D15 on treatment