Title Page

Results of a multicentre UK-wide compassionate use programme evaluating the efficacy of idelalisib monotherapy in relapsed, refractory follicular lymphoma

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Running title: idelalisib monotherapy in relapsed, refractory follicular lymphoma

Key Words follicular lymphoma; idelalisib; PI3K. **Conflicts of Interest** – GC, TE have received speaker fees, honorarium and travel grants from Gilead Sciences. None of the other authors have any conflicts of interest to declare. **Role of funding source**: Nil specific for the paper. **Ethical approval**: Not required

Follicular lymphoma (FL) is an indolent B-cell malignancy with a variable clinical course. Standard immuno-chemotherapy typically incorporate alkylator and anti-CD20 monoclonal antibody as first line (Rummel *et al,* 2013) commonly followed by 24 months rituximab maintenance (Salles *et al*, 2008). Combinations of anthracyclines, purine analogues, and alkylators are used at relapse and younger patients may have remissions consolidated with autologous or allogeneic stem-cell transplantation (alloSCT) (Kothari *et al*, 2014). Over time, responses to immuno-chemotherapy and length of remissions diminish. Relapsed or refractory (R/R) FL in patients unfit for transplantation or post-transplantation is incurable, and remains an unmet clinical need.

Idelalisib is a potent, small-molecule inhibitor of the phosphatidylinositol 3-kinase δ-isoform (PI3Kδ). The δ-isoform is critical for normal B-cell function, signal transduction and important cytokines, chemokines, and integrins (Durand *et al,* 2009). PI3Kδ pathways are constitutively activated in B-cell malignancies (Lannutti *et al,* 2011).

A phase II (DELTA) trial was performed in double-refractory indolent non-Hodgkin lymphoma (iNHL) (Gopal *et al* 2014). 125 patients (72 FL) received idelalisib 150mg b.d. until progressive disease (PD), unacceptable toxicity, or death. 90% were refractory to their prior regimen. All received alkylator and rituximab and a median of 4 regimens. The overall response rate (ORR) was 57% (FL 54%). The median duration of response was 12·5 months, median progression-free survival (PFS) 11·0 months and overall survival (OS) 20·3 months. Responses were superior to the prior therapy line.

Idelalisib was subsequently FDA and EMA approved but not NICE approved. Idelalisib was available in the UK and Ireland via the expanded access programme (2015-2016) for double-refractory FL. No data are published following DELTA. We investigated the efficacy of idelalisib in a retrospective, multicentre population of R/R FL. 51 centres were approached (Fig S1), with data collected from 46 sites (01/2015-08/2016). Baseline characteristics were collected at commencing idelalisib. Details on prior therapy were collected.

Refractory disease was defined as stable disease (SD) or PD to the prior treatment, or relapse <6 months following a previous partial/complete response (PR/CR) according to DELTA. Relapsed disease followed a remission >6 months. Adverse events (AEs) were collected although grading AEs was non-routine. Follow-up was censored at the most recent visit or death. The data were locked in 08/2016.

Patients received idelalisib 150mg b.d. until PD, toxicity or death. PFS and OS were calculated in standard fashion. Cox regression determined univariate predictors of PFS. Analyses were performed in Stata 14.1 (StataCorp, College Station, TX).

The median age was 64 years with an equal gender distribution (Table 1). Our cohort included a larger proportion of high FLIPI scores although more patients within DELTA had true refractory disease. Most received R-CHOP or R-CVP induction (Table 1S). Second line therapy was typically anthracycline-based or bendamustine.

24 patients received treatment post-idelalisib. This included 4 biopsy-confirmed or clinically suspected HGT (pixantrone (n=2), CHOP-R (n=1), dose-adjusted EPOCH-R (n=1). The remaining 55 either died without further therapy because of PD (n=17) or toxicity (n=1; toxic epidermal necrolysis (TEN)), remained on idelalisib without progression (n=35) or stopped due to toxicity without progression (n=2; recurrent grade (G)4 pneumonitis, G3 diarrhoea). Eight patients received an alloSCT and 2 were planned.

ORR was 57% (CR/CRu 15%; PR 42%) in 65 assessable. Three developed toxicities and were never radiologically assessed, and 11 were awaiting their first radiological assessment (typically cycle 2-4) at censoring. Fig 1(A-E) provides the survival outcomes. The median follow-up was 6.1 months (range: 0.1-18.8 months). The median PFS was 7·1 months (95% CI 5·0-9·1 months) (A) and median OS was not-reached (NR) (95% CI 13·7 months-

NR) (B). Patients with lower FLIPI have a non-statistically significant trend towards an improved outcome (C; median PFS: 9·3 months (95% CI 6·0 months-NR) vs. 6·6 months (95% CI 3·5-8·4 months), p=0·09). Responders had a durable median PFS of 14·1 months (D; 95% CI 8·1 months-NR). There was no difference between the PFS of the prior treatment and idelalisib (E; p=0·82).

Nineteen died from PD, 1 following cytomegalovirus (CMV) pneumonitis, 1 from TEN, 1 of a myocardial infarction whilst on pixantrone for HGT, and 1 from ischaemic bowel with otherwise SD.

There were no predictors of PFS (Table IIS). The best-fitting multivariate model showed a trend towards increased PD or death in patients with higher FLIPI (0-2 vs. 3-5, HR 2·09 (95% CI 0·98-4·45, p=0·055) and prior rituximab maintenance (HR 1·91, (95% CI 0·96-3·79, p=0·065).

Idelalisib was generally well tolerated, with no AEs reported in 52 (66%) patients (Table IIIS). This may represent some under-reporting of non-clinically significant G1-2 AEs. Commonly reported AEs were non-neutropenic infection and bronchial infection. G3-4 diarrhoea/colitis was noted in 5 patients and G3-4 pneumonitis in 4 patients post 2 cycles (n=3) and 6 cycles (n=1). One was associated with CMV reactivation. Idelalisib was stopped permanently in 7 patients due to toxicity (TEN (n=1), G3 diarrhoea (n=2) occurring at 8 months in both, G3 colitis/bronchial infection (n=1), recurrent G4 pneumonitis (n=1), G3 pneumonitis (n=1), G4 hepatitis (n=1)), two of whom had not progressed. All other G3-4 AEs were managed with supportive care, temporary withholding idelalisib and dose attenuation.

This is the only real-world series outlining the efficacy and survival of idelalisib-treated R/R FL. Our series (n=79) is larger than the trial arm (n=72). The ORR of 57% and PFS of 7·1 months highlights the efficacy of idelalisib in R/R FL, with similar responses to DELTA. Responders had durable remissions (median 14·1 months). A small number proceeded to alloSCT. The median PFS was inferior to DELTA (11 months), highlighting the well-described difficulty of extrapolation of trial data into the real world. The PFS curve for idelalisib almost overlaps that of the prior therapy and demonstrates the incremental value of idelalisib over historical options.

Recently, Gilead closed three international trials (GS-US-312-0123, GS-US-313-0124, GS-US-313-0125) following an increased death and infection rate in the idelalisib arms, with increased PCP and CMV infection.

The EMA recently confirmed a positive benefit: risk profile for idelalisib monotherapy in R/R FL and retained its licence. We report a rate of CMV reactivation, diarrhoea/colitis and pneumonitis consistent with the safety data from DELTA. We did not collect data on PCP prophylaxis and CMV monitoring as these recommendations post-dated our data collection.

The weaknesses of our study include the lack of centralised pathology review, formalised radiological reporting, prospective AEs reporting, and possible underreporting of G1-2 AEs. However standard UK practice mandates clinico-pathological review by a multi-disciplinary team prior to new therapy.

Ibrutinib (ORR 30%) (Bartlett *et al,* 2014) and venetoclax (ORR 27%) (Seymour *et al,* 2014) show limited monotherapy activity. As such, idelalisib remains the only licensed small-molecule inhibitor in R/R FL. Obinutuzumab-bendamustine with obinutuzumab maintenance is recently licenced in rituximab-refractory FL following the GADOLIN trial (Sehn *et al,* 2016) and will become increasingly available.

Idelalisib monotherapy is relatively safe and effective in R/R FL. ORR was similar to DELTA, and responses were durable. No new safety signals were raised and 10% received a subsequent alloSCT following remission.

Contributions: Conception and design: TE and GC made substantial contributions to conception and design. Collection and assembly of data: TE co-ordinated the collection of national data. WO, EGE, KA, SK, GS, DC, AA, PS, KB, YYP, AB, EV all managed patients in the study and were involved in collection and assembly of data. Data analysis and interpretation: TE, GC were involved in data analysis and interpretation. DE performed the statistical analysis. Manuscript writing: TE wrote the manuscript, which all authors critically reviewed. Final approval of manuscript: All authors were involved in research design, or the acquisition, analysis or interpretation of data, critically revising the manuscript and the final approval. TE is funded by the Julian Starmer-Smith lymphoma fund. GC acknowledges support by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Programme. KA is supported by the UCL/UCLH Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the funding bodies. The authors would like to the following health care professionals from across the United Kingdom for their kind and expert assistance in data collection: Wendy Osborne (The Newcastle Upon Tyne NHS Foundation Trust), Eve Gallop-Evans (Velindre Cancer Centre, Cardiff), Shalal Sadullah (James Paget University Hospitals NHS Foundation Trust), Jennifer Foreman (Clinical Research Nurse Ulster Hospital), Sarah Wexler (Royal United

Hospital, Bath), Jamie Maddox (South Tees NHS Foundation Trust), Simon Rule, David Lewis and David Tucker (Plymouth Hospitals NHS Trust), Brian Bird (Bon Secours Health System Ltd Cork), Donald McDonald (Imperial College Healthcare NHS Trust), Anne Fortune (Mater Misericordiae University Hospital, Dublin), Claire Hughes and Mamatha Karanth (West Suffolk Hospital), Mohammad Islam (Southend University Hospital NHS Trust), Arvind Arumainathan (Royal Liverpool University Hospital), Corinne De Lord (Princess Royal University Hospital Farnborough), Farooq Wandroo (Sandwell & West Birmingham Hospitals NHS Trust), Kris Bowles (Norfolk and Norwich University Hospital), Mark Bishton & Andrew McMillan (Nottingham University Hospitals NHS Trust), Kirit Ardeshna and Raakhee Shah (University College London Hospitals NHS Foundation Trust), Jorge Cartier-Gomez (Newham Healthcare NHS Trust), Chris Pocock (Kent and Canterbury Hospital NHS Trust), Paneesha Shankara and Iman Qureshi (Department of Haematology & Stem Cell Transplantation, Birmingham Heartlands Hospital), Gamal Sidra (Lincoln County Hospital), Pam McKay (Beatson West of Scotland Cancer Centre, Glasgow), Joel Newman (Eastbourne District General Hospital), Adrian Bloor (The Christie, Manchester), Ying Ying Peng (St George's Hospital, London), Oonagh Sheehy (Belfast City Hospital), Peter Cumber (Glangwili General Hospital, Wales), Andres Virchis (Barnet and Chase Farm Hospitals NHS Trust), Dominic Culligan (Aberdeen Royal Infirmary), Shalal Sadullah (James Paget University Hospitals NHS Foundation Trust), Shireen Kassam (King's College Hospital NHS Trust), Anna Morris (Dorset County Hospital), Stephen Jenkins (Dudley Hospital), Mac Macheta (Blackpool Hospital Trust), Sajir Mohamedbhai (North Middlesex NHS Trust), Mohsen Mahmoud (Darlington Memorial Hospital)

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Figure 1 A to E Panel

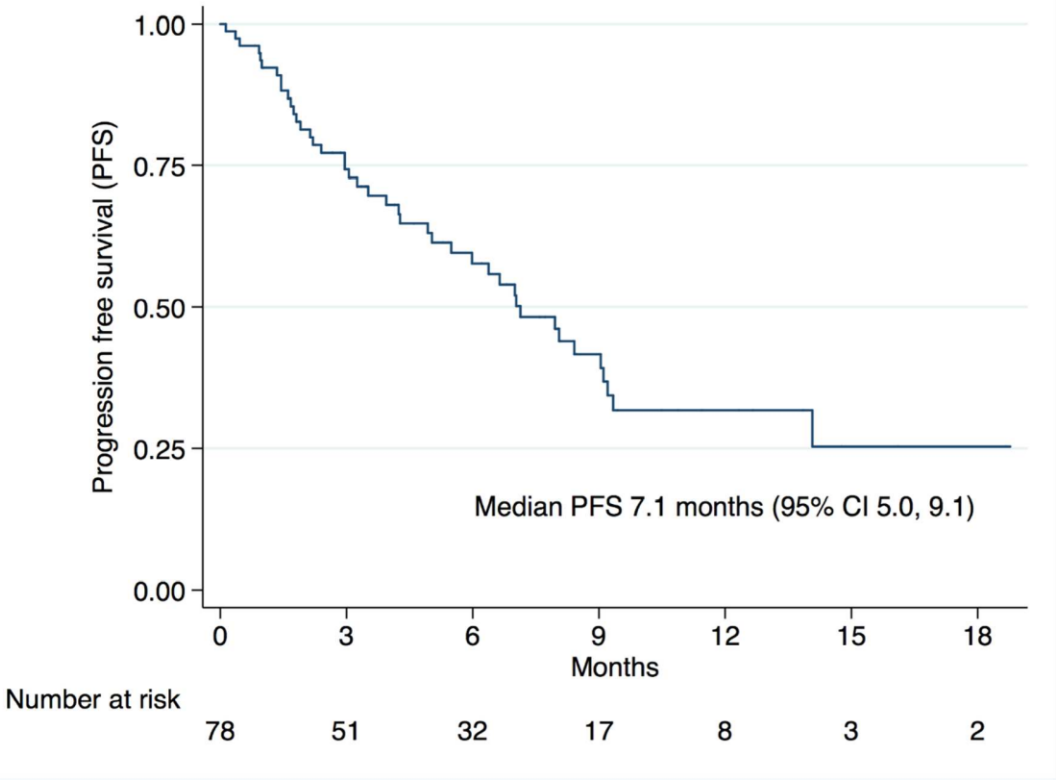

Figure A Progression Free Survival

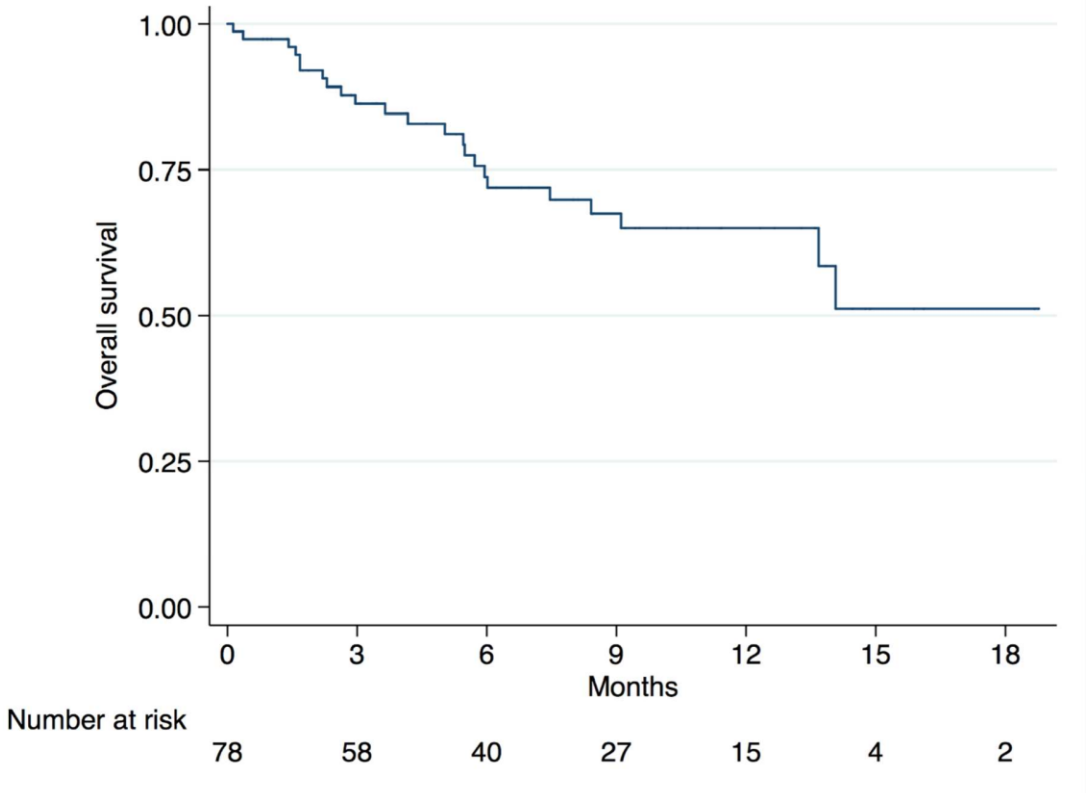

Figure B Overall Survival

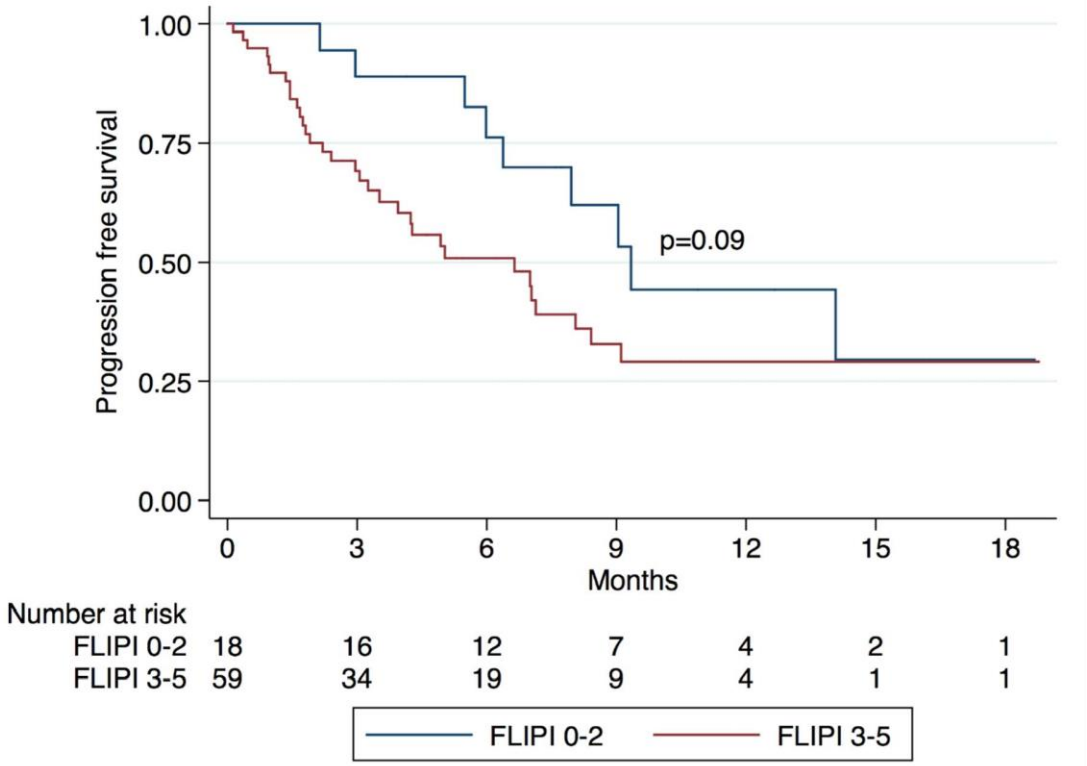

Figure C Progression free survival according to FLIPI

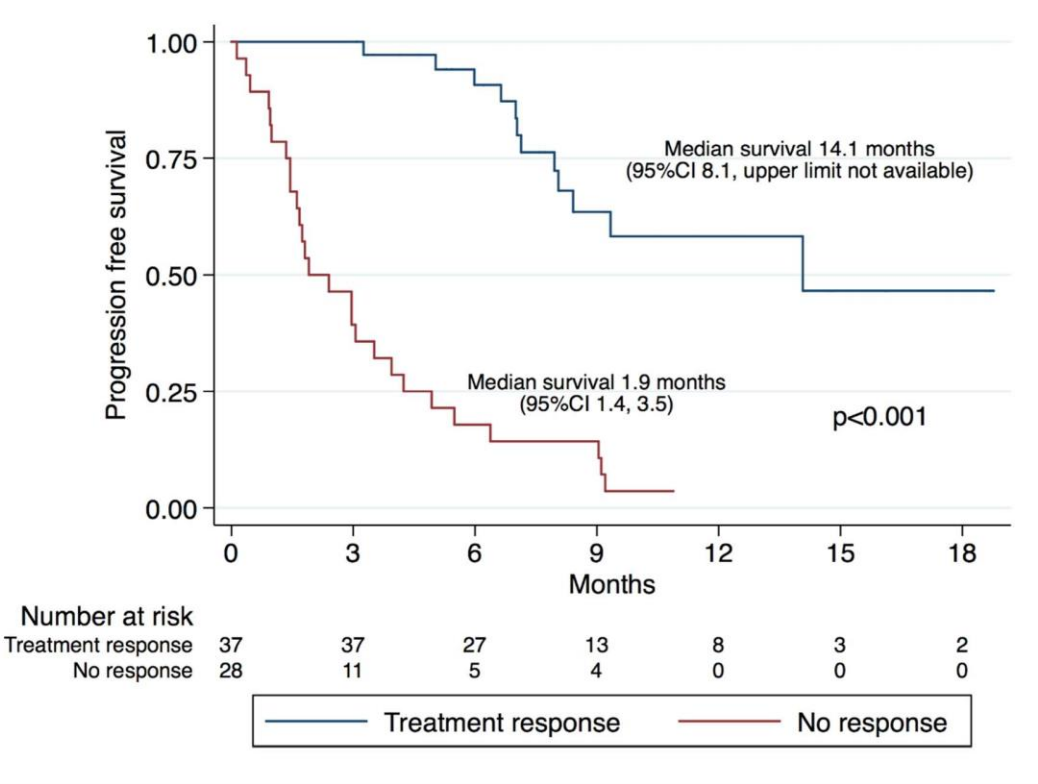

Figure D PFS according to response

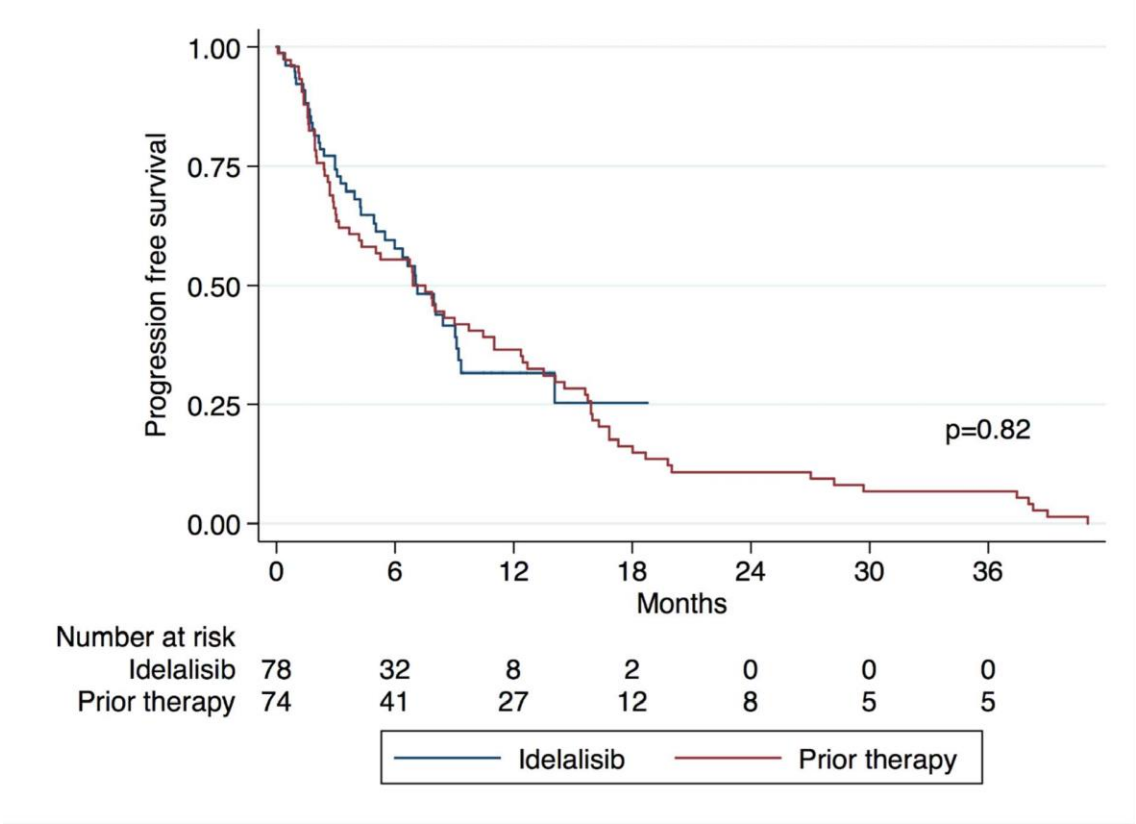

Figure E Progression free survival compared to prior line of therapy

Table I: Baseline Characteristics

Characteristics	**FL patients in the phase II trial (n = 72)**	**Retrospective cohort (n = 79)**
Median age (years) >60 years	62 (33-84) *Not available*	64 (29-86) 51/79 (65%)
Gender Male Female	 39 (54%) 33 (46%)	 40 (51%) 39 (49%)
ECOG 0-1 2-4	 66 (92%) 6 (8%)	 59 (75%) 20 (25%)
Median NHL Duration (years, range)	4·7 (0·8–18·4)	4·5 (0·4-24·6)
Baseline tumour assessment Refractory Relapsed	 62 (86%) 10 (14%)	 41 (54%) 35 (46%) 3 unclassifiable
Histology - DLBCL at any time point Yes No	 0 (0%) 72 (100%)	 7 (9%) 72 (91%)
Ann Arbor staging 1-2 3-4	 12 (17%) 60 (83%)	 12 (15%) 67 (85%)
FLIPI score 0-2	 33 (46%)	 19 (25%)

3-5	39 (54%)	59 (75%) 1 unclassifiable
Response to most recent chemotherapy CR/CRu PR SD PD	*Not available*	 19 29 16 13 2 unavailable
Median time from last chemotherapy to idelalisib (months, range)	*Not available*	8·6 (0·9-99·2)
Median number of previous chemotherapy regimens (number, range)	4 (2-12)	3 (1-13)
Prior rituximab Prior rituximab maintenance Prior alkylator	72 (100%) *Not available* 72 (100%)	78 (99%) 51 (65%) 79 (100%)
Previously received stem-cell transplantation Yes No	 12 (17%; all autologous) 60 (83%)	 21 (27%; 4 allogenic, 16 autologous, 1 both) 58 (73%)
Idelalisib treatment duration (months, range)	Treatment duration median 6–5 (0–6–31–0)	Treatment duration median 4·3 (0·1–18·8)

Abbreviations: ECOG; *Eastern Cooperative Oncology Group, DLBCL; diffuse large B cell lymphoma, iNHL; indolent non-Hodgkin lymphoma, PR;* Partial response, CR/CRu; complete response / unconfirmed complete response, SD; stable disease, PD; progressive disease, ULN; upper limit of normal, CI; confidence interval, FLIPI; follicular lymphoma international prognostic index, N/S: non-significant.

Figure S1: Consort diagram summarising study recruitment across the UK and Ireland

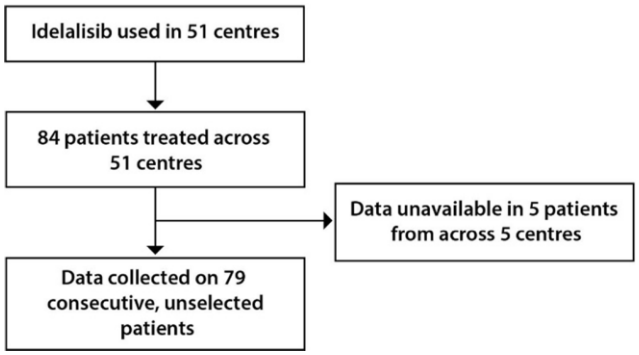

Table IS: Therapies used prior to and following idelalisib use

Therapies prior to Idelalisib use						Therapies post Idelalisib use	
First line (n = 79)	**Patient number**	**Second line (n = 67)**	**Patient number**	**Third Line (n = 47)**	**Patient number**	**Post idelalisib (n = 24)**	**Patient number**
CVP+/-R +/- MR	37	CHOP+/-R +/- MR	15	B+/-R+/- MR	12	Allogeneic SCT	8 (1 additional planned
CHOP+/-R +/- MR	25	B+/-R+/- MR	15	Local palliative RT	8	GEM-based +/-R	4
Chlorambucil +/- prednisolone +/- R	4	ESHAP +/-R	7	GEM-based +/-R	4	Lenalidomide	2
BR+/- MR	5	CVP+/-R +/- MR	5	CHOP+/-R +/- MR	7	Steroid based	2
Other	8	ICE +/-R	5	IVE+/-R	3	Pixantrone (DLBCL)	2
		IVE+/-R	5	Zevalin+/-R	3	Bendamustine	2
		DHAP+/-R	4	ESHAP +/-R	3	Local RT	4
		GEM-based +/-R	5			Clinical trial	2
		Other	14	Other	12	Other	3

Abbreviations: *CHOP+/-R; cyclophosphamide, doxorubicin, vincristine, prednisolone, rituximab, CVP+/-R; rituximab, cyclophosphamide, vincristine, prednisolone, ICE; ifosfamide, carboplatin, etoposide, GEM; gemcitabine, DHAP; dexamethasone, high dose cytarabine, cisplatin; ESHAP; etoposide, high dose cytarabine, methylprednisolone, cisplatin, IVE; ifosfamide, epirubicin, etoposide, RT; radiotherapy, B; bendamustine, MR; maintenance rituximab.*

Table IIS: Univariate predictors of progression or death

A: Univariate predictors of progression or death		
Predictor	**Hazard ratio (95% CI)**	**P**
FLIPI 0-2 v 3-5	1·88 (0·89 – 3·97)	0·097
Male gender	0·65 (0·35 - 1·20)	0·172
ECOG 0-1 vs 2-4	1·16 (0·83 - 1·61)	0·399
Prior DLBCL	0·39 (0·09 – 1·62)	0·195
Age > 60 years	0·99 (0·96 - 1·02)	0·420
LDH > ULN	1·74 (0·92 – 3·28)	0·087
Lymph node enlargement > 4 areas	1·14 (0·57 – 2·26)	0·360
Stage III	1·07 (0·36 – 3·14)	0·907

Stage IV	1·63 (0·63 – 4·27)	0·317
Haemoglobin <12 g/dL	0·99 (0·97 – 1·01)	0·296
Relapsed FL	0·62 (0·35 - 1·15)	0·133
Prior transplant	1·16 (0·58 - 2·30)	0·681
Prior lines of treatment	0·98 (0·82 - 1·18)	0·852
Prior Rituximab Maintenance	1·67 (0·86 – 3·22)	0·128

Table IIIS: Adverse Events

Adverse Events reported	Total number of events
Neutropenic Fever / Infection	0
Non-Neutropenic Fever / Infection Bronchial Infection	5 4
Haematological Neutropenia	 3
Gastroenterological Diarrhoea / Colitis Hepatitis Constipation	 5 (all grade 3-4) 2 (1 grade 1, 1 grade 4) 1 (grade 2)
Pneumonitis	4 (1 CMV-induced, and 3 related to idelalisib (grade 3 (n = 2), grade 4 (n =1))
Cytomegalovirus (CMV) reactivation Varicella Zoster virus (VZV) infection	2 (1 asymptomatic) 1
Rash Toxic Epidermal necrolysis	1 1
Pyrexia	2
Others	1