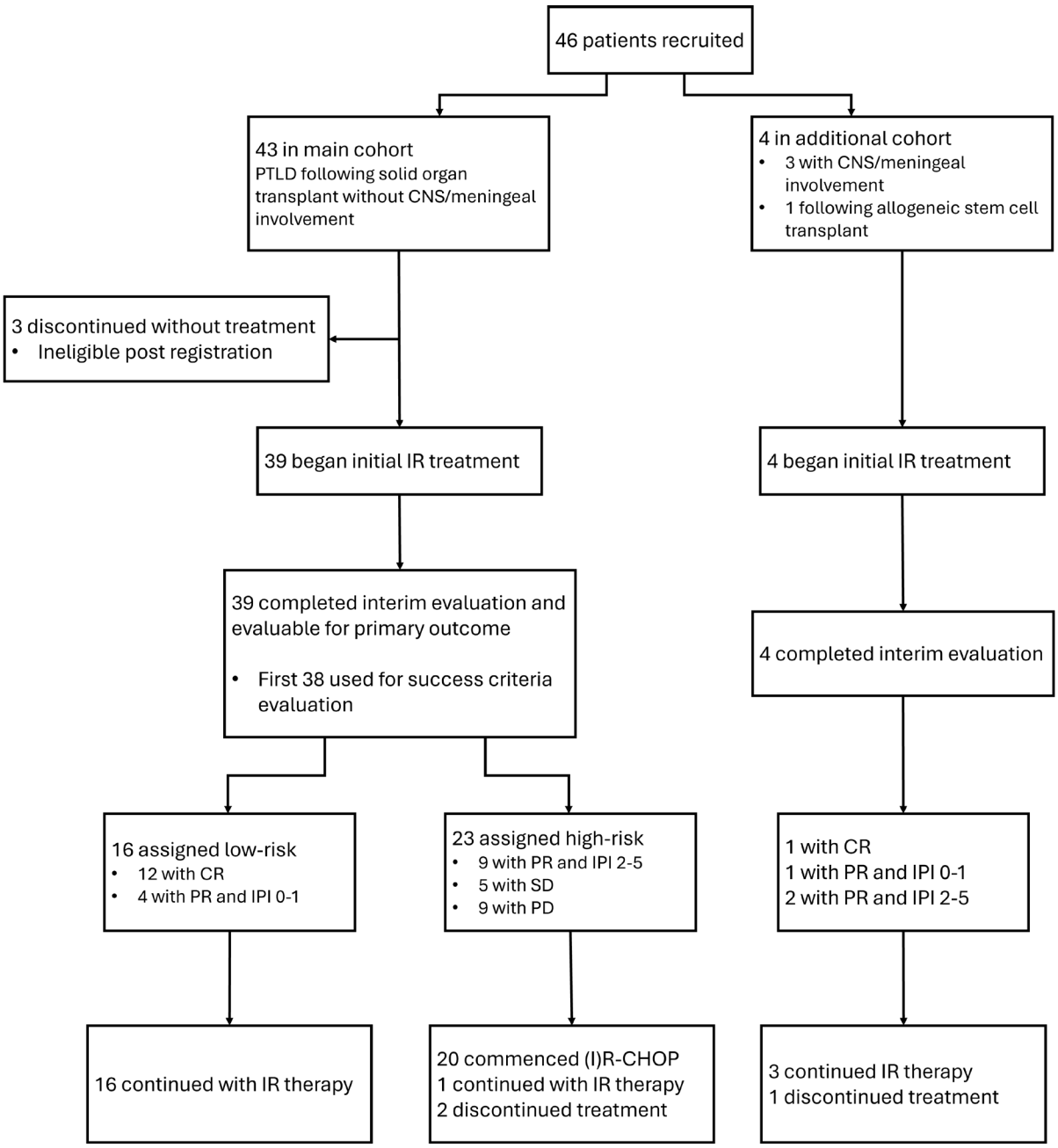
TIDaL Basic Results Summary

Patient Flow



Baseline Characteristics

Characteristic	Main Cohort (n = 42)	Additional Cohort (n = 4)	Overall (n = 46)
Age (years)			
Median (Range)	58 (22, 75)	51 (42, 65)	57 (22, 75)
Sex, n(%)			
Female	19 (45%)	1 (25%)	20 (43%)
Male	23 (55%)	3 (75%)	26 (57%)
Transplant, n(%)			
Allogeneic stem cell	0	1 (25%)	1 (2%)
Heart	4 (10%)	0	4 (9%)
Heart & Liver	1 (2%)	0	1 (2%)
Kidney	21 (50%)	2 (50%)	23 (50%)
Kidney & Pancreas	1 (2%)	1 (25%)	2 (4%)
Liver	13 (31%)	0	13 (28%)
Lung	2 (5%)	0	2 (4%)
Years from transplant to PTLD diagnosis			
Median (Range)	8.0 (0.5, 30.6)	7.5 (1.7, 21.7)	8.0 (0.5, 30.6)
Unknown	1	0	1
ECOG, n(%)			
0	24 (57%)	3 (75%)	27 (59%)
1	13 (31%)	0	13 (28%)
2	3 (7%)	1 (25%)	4 (9%)
Unknown	2 (5%)	0	2 (4%)
Ann Arbor stage, n(%)			
Stage I	6 (14%)	2 (50%)	8 (17%)
Stage II	9 (21%)	0	9 (20%)
Stage III	5 (12%)	0	5 (11%)
Stage IV	21 (50%)	2 (50%)	23 (50%)
Unknown	1 (2%)	0	1 (2%)
International prognostic index, n(%)			
0 - 1	17 (40%)	1 (25%)	18 (39%)
2 - 5	23 (55%)	3 (75%)	26 (57%)
Unknown	2 (5%)	0	2 (4%)
Epstein-Barr Virus association in tissue biopsy, n(%)			
Positive	14 (33%)	3 (75%)	17 (37%)
Negative	19 (45%)	1 (25%)	20 (43%)
Unknown	9 (21%)	0	9 (20%)
Locally assessed histology, n(%)			
Burkitt lymphoma	2 (5%)	0	2 (4%)
Classical Hodgkin lymphoma-type PTLD	1 (2%)	0	1 (2%)
Diffuse large B-cell lymphoma	33 (79%)	3 (75%)	36 (78%)
Plasmacytic hyperplasia, Polymorphic PTLD, Other B-cell neoplasms	1 (2%)	0	1 (2%)
Polymorphic PTLD	1 (2%)	0	1 (2%)
Polymorphic PTLD & Classical Hodgkin lymphoma-type PTLD	0	1 (25%)	1 (2%)
Polymorphic PTLD & Diffuse large B-cell lymphoma	1 (2%)	0	1 (2%)
Polymorphic PTLD, Diffuse large B-cell lymphoma & Classical Hodgkin lymphoma-type PTLD	1 (2%)	0	1 (2%)
Unknown	2 (5%)	0	2 (4%)

Outcome Measures – Main Cohort

Primary Outcome Measure

Complete remission (CR) rate after 7 weeks of initial IR. CR was assessed by CT scan between days 42 - 49.

Out of 39 patients who began treatment, 12 (31%, 95% CI: 17-48%) achieved complete remission at the interim response assessment.

Disease Response at Interim Assessment	**n (%)**
Complete remission	12 (31%)
Partial remission	13 (33%)
Stable disease	5 (13%)
Progressive disease	9 (23%)
Overall	39 (100%)

The trial was designed using a Simon's 2-stage design with an unacceptable response rate of 25% and a desirable response rate of 40%, using an alpha of 0.2 and power of 0.85. Under this design seven out of 24 CRs needed to be observed in order to proceed to the second stage; 12/38 CRs needed to be observed to warrant further investigations in a phase III trial.

Disease Response at Interim Assessment	**Stage 1**	**Stage 2**
Complete remission	7	11
Partial remission	9	13
Stable disease	2	5
Progressive disease	6	9
Overall	24	38

During stage 1, 24 patients were recruited, of these patients 7 (29%, 95% CI: 13-51%) achieved a CR meaning that the success criteria was met to proceed to stage 2. Using the first 38 patients who have a disease response available at 7 weeks, 11 CRs have been observed, this gives a proportion of 29% (95% CI: 15-46%). This does not meet the success criteria to warrant further investigations in a phase III trial.

Secondary Outcome Measures

Overall response after 7 weeks of initial ibrutinib and rituximab and at end of treatment; entry to low-risk arm; progression-free survival; progression-free survival post initial IR therapy; event-free survival; overall survival; treatment-related mortality; dose modifications; treatment tolerability; grade 3 or higher leucocytopenia and infections.

Overall Response

At the 7-week interim response assessment 25 of 39 patients (64%, 95% CI: 47-79%) achieved complete or partial remission.

At the end of treatment assessment 26 of 39 patients (67%, 95% CI: 50-81%) achieved complete or partial remission.

Disease Response at End of Treatment Assessment	**n (%)**
Complete remission	22 (56%)
Partial remission	4 (10%)
Stable disease	1 (3%)
Progressive disease	6 (15%)
Unable to classify	1 (3%)
Discontinued after interim assessment	2 (5%)
Died before assessment	3 (8%)
Overall	39 (100%)

Entry into low-risk arm

After the interim assessment patients were assigned low risk if they achieved complete remission or if they achieved partial remission and had a baseline international prognostic index of 0-1, all other patients were assigned high risk.

Of the 39 patients who began treatment, 16 (41%, 95% CI: 26-58%) were assigned low risk and 23 (59%) were assigned high risk.

Progression-free survival

Progression-free survival defined as time from trial entry to progression or death from any cause. Disease progression during the initial 7 weeks of IR therapy was counted as an event. Patients who had not progressed or died were censored at their date last seen.

Population	**N**	**Events**	**6-month estimate**	**1-year estimate**	**2-year estimate**
Intention-to-treat	42	19	69% (95% CI: 56-84%)	64% (95% CI: 50-80%)	58% (95% CI: 45-76%).
Per protocol	39	18	69% (95% CI: 56-85%)	63% (95% CI: 50-81%)	58% (95% CI: 44-76%)

Progression-free survival post initial IR therapy

Progression-free survival post-IR is defined as time from trial entry to progression or death from any cause. Disease progression during the initial 7 weeks of IR therapy does NOT count as an event. Patients who had not progressed or died were censored at their date last seen.

Population	N	Events	6-month estimate	1-year estimate	2-year estimate
Intention-to-treat	42	16	83% (95% CI: 72-95%)	70% (95% CI: 58-86%)	65% (95% CI: 52-82%)
Per protocol	39	15	84% (95% CI: 73-97%)	71% (95% CI: 57-87%)	65% (95% CI: 52-82%)

Event-free survival

Event-free survival is defined as time from date of registration to the first of:

- Treatment discontinuation due to toxicity
- Disease progression (including progression during the initial IR therapy)
- Death from any cause

Patients who had not experienced an event were censored at their date last seen.

Population	N	Events	6-month estimate	1-year estimate	2-year estimate
Intention-to-treat	42	20	66% (95% CI: 53-82%)	61% (95% CI: 48-78%)	56% (95% CI: 42-74%)
Per protocol	39	19	66% (95% CI: 53-83%)	61% (95% CI: 47-78%)	55% (95% CI: 41-74%)

Overall survival

Overall survival is defined as time from trial entry to death from any cause. Patients who have not died were censored at their date last seen.

Population	N	Events	6-month estimate	1-year estimate	2-year estimate
Intention-to-treat	42	11	90% (95% CI: 82-100%)	80% (95% CI: 69-94%)	75% (95% CI: 63-90%).
Per protocol	39	10	92% (95% CI: 84-100%)	81% (95% CI: 70-95%)	76% (95% CI: 63-91%)

Of the ten deaths that occurred in patients who received treatment, five were classed as disease related, three as other non-cancer and two as trial treatment related.

Treatment related mortality

Treatment related mortality is defined as time from registration to death in patients who have experienced an ibrutinib related toxicity. Death in patients who have not experienced an ibrutinib related toxicity will be treated as a competing event. An ibrutinib related toxicity is defined as an AE or SAE deemed to be definitely, probably or possibly related to ibrutinib. Patients who have not died were censored at their date last seen.

Population	N	Events	6-month estimate	1-year estimate	2-year estimate
Per protocol	39	9	8% (95% CI: 0-16%)	16% (95% CI: 4-28%)	21% (95% CI: 8-35%)

Dose modifications

Dose modifications are defined as dose interruptions, dose reduction or treatment discontinuations. Dose modifications are ranked in the following order:

- Discontinuation
- Reduction
- Interruption

(e.g. if a patient has their dose interrupted, reduced and discontinued, they will be classed as a discontinuation as this outranks interruption and reduction).

Of the 19 patients who began treatment 28 (72%) experienced a dose modification.

Treatment tolerability

Treatment tolerability is defined as the absence of any ibrutinib related toxicities. An ibrutinib related toxicity is defined as an AE or SAE deemed to be definitely related, probably related or possibly related to ibrutinib.

Of the 39 patients who began treatment, 7 (18%, 95% CI: 8-34%) did not experience an ibrutinib related toxicity, and so tolerated treatment. Of the 16 low risk patients 3 (19%) tolerated treatment, while of the 23 high risk patients 4 (17%) tolerated treatment.

Grade 3 or higher leucocytopenia and infections

There have been no reported incidences of leucocytopenia.

There have been 15 grade 3 or higher infections reported, affecting 10/39 (26%, 95% CI: 13-42%) patients. Nine of these infections had been reported as an SAE. Thirteen of these infections occurred during IR-CHOP therapy with the remaining 2 occurring during initial IR therapy.

Adverse Events

There have been 596 adverse events reported in total, experienced by all 39 patients (100%, 95% CI: 91-100%). Of these, 89 were grade 3 or higher, experienced by 23 patients (59%, 95% CI: 42-74%).

One AE has not been graded, an incidence of COVID-19.

Of the 596 adverse events, 238 (40%) occurred during the initial IR therapy, 89 (15%) occurred during subsequent IR therapy and 268 (45%) occurred during IR-CHOP therapy. 1 adverse event does not have a start date and so could not be classified.

Category	Adverse Event	Initial IR	Subsequent IR	IR-CHOP
Blood and lymphatic system disorders	Anemia	2 (2)	0 (0)	6 (4)
	Febrile neutropenia	0 (0)	1 (1)	8 (6)
Cardiac disorders	Pericardial effusion	0 (0)	1 (1)	0 (0)
Gastrointestinal disorders	Abdominal distension	1 (1)	0 (0)	1 (1)
	Abdominal pain	4 (4)	1 (1)	2 (2)
	Diarrhea	1 (1)	0 (0)	2 (2)
	Dysphagia	0 (0)	0 (0)	1 (1)
	Nausea	1 (1)	0 (0)	0 (0)
	Other, proximal jejunitis	0 (0)	0 (0)	1 (1)
	Vomiting	1 (1)	0 (0)	0 (0)
General disorders and administration site conditions	Chills	1 (1)	0 (0)	0 (0)
	Fever	1 (1)	0 (0)	0 (0)
	Other, facial swelling	1 (1)	0 (0)	0 (0)
Infections and infestations	Catheter related infection	1 (1)	0 (0)	0 (0)
	Device related infection	0 (0)	0 (0)	1 (1)
	Lung infection	0 (0)	0 (0)	1 (1)
	Nail infection	0 (0)	0 (0)	1 (1)
	Other, chest infection	1 (1)	0 (0)	
	Other, neutropenic sepsis	0 (0)	0 (0)	1 (1)
	Other, pneumocystis carinii pneumonia	0 (0)	0 (0)	1 (1)
	Other, shingles	0 (0)	0 (0)	1 (1)
	Sepsis	0 (0)	0 (0)	5 (3)
	Upper respiratory infection	0 (0)	0 (0)	1 (1)
	Urinary tract infection	0 (0)	0 (0)	1 (1)
Injury, poisoning and procedural complications	Hip fracture	0 (0)	1 (1)	0 (0)
Investigations	Neutrophil count decreased	0 (0)	3 (2)	7 (5)
	Other, neutropenic sepsis	0 (0)	0 (0)	1 (1)
	Other, raised amylase	1 (1)	0 (0)	0 (0)
Metabolism and nutrition disorders	Acidosis	0 (0)	0 (0)	1 (1)
	Hyperglycemia	1 (1)	0 (0)	0 (0)
	Hypokalemia	0 (0)	1 (1)	0 (0)
	Hypomagnesemia	0 (0)	0 (0)	1 (1)
	Hypophosphatemia	0 (0)	0 (0)	2 (1)
	Tumor lysis syndrome	0 (0)	0 (0)	1 (1)

Musculoskeletal and connective tissue disorders	Other, proximal myopathy secondary to steroids	0 (0)	0 (0)	1 (1)
	Pain in extremity	0 (0)	1 (1)	0 (0)
Nervous system disorders	Ischemia cerebrovascular	0 (0)	0 (0)	1 (1)
	Peripheral sensory neuropathy	0 (0)	0 (0)	3 (3)
	Somnolence	0 (0)	0 (0)	1 (1)
	Syncope	1 (1)	0 (0)	0 (0)
Psychiatric disorders	Confusion	0 (0)	0 (0)	1 (1)
Renal and urinary disorders	Acute kidney injury	0 (0)	0 (0)	1 (1)
Respiratory, thoracic and mediastinal disorders	Dyspnea	1 (1)	0 (0)	1 (1)
Skin and subcutaneous tissue disorders	Other, erythematous rash	1 (1)	0 (0)	0 (0)
Vascular disorders	Hypotension	0 (0)	0 (0)	2 (2)

Data are # occurrences (# patients affected)

Serious Adverse Events

There have been 55 SAEs reported with 130 corresponding symptoms. These events were experienced by 23 (59%) of the 39 patients. Admitting symptoms which affected the most patients were abdominal pain (n=6), febrile neutropenia (n=5) and diarrhea (n=4).

Of the 55 SAEs, 16 (29%) occurred during the initial IR therapy, 5 (9%) occurred during subsequent IR therapy and 34 (62%) occurred during IR-CHOP therapy.

The table below summarises the number of occurrences and patients affected for each SAE. The event used is the admitting symptom, that is the symptom which prompted reporting as a serious adverse event.

Category	**Adverse Event**	**# occurrences (# patients affected)**
Blood and lymphatic system disorders	Anemia	1 (1)
	Febrile neutropenia	7 (5)
	Other, neutropenia	1 (1)
	Other, renal failure	1 (1)
Cardiac disorders	Chest pain - cardiac	1 (1)
Gastrointestinal disorders	Abdominal pain	7 (6)
	Diarrhea	7 (4)
	Nausea	1 (1)
	Vomiting	2 (2)
General disorders and administration site conditions	Fever	3 (3)
	Other, pyrexia	2 (1)
Infections and infestations	Catheter related infection	1 (1)
	Other, neutropenic sepsis	1 (1)
	Other, pneumocystis carinii pneumonia	1 (1)
	Other, shingles	1 (1)
	Sepsis	4 (2)
	Upper respiratory infection	1 (1)
Investigations	Neutrophil count decreased	2 (2)
	Other, neutropenia	1 (1)
Metabolism and nutrition disorders	Hyperglycemia	1 (1)
	Hyperkalemia	1 (1)
Nervous system disorders	Ischemia cerebrovascular	1 (1)
	Peripheral sensory neuropathy	1 (1)
Renal and urinary disorders	Acute kidney injury	2 (2)
Respiratory, thoracic and mediastinal disorders	Dyspnea	2 (2)
	Other, breathlessness	1 (1)
Surgical and medical procedures	Other, fractured neck of femur	1 (1)
Overall		55 (23)

Additional Cohort

All four patients started initial IR treatment and reached the interim assessment. One patient (25%) with meningeal or CNS involvement achieved complete remission while the remaining three achieved partial remission. One of the patients with meningeal or CNS involvement discontinued at this stage after withdrawing consent. However, the remaining three patients received all four subsequent cycles of ibrutinib and rituximab and achieved complete remission (n=2) or partial remission (n=1). None of the four patients have reported progression or death.

In the additional cohort, 22 adverse events were experienced in 3 of the 4 patients; the patient who underwent ASCT and two of the patients with CNS/meningeal involvement. All of these AEs were grade 1 or 2 and of those that had an outcome available, all were resolved with no sequelae. Of the 22 adverse events, 9 occurred during the initial 7 weeks of IR therapy with the remaining 13 occurring during subsequent IR therapy. Seven of the adverse events were not related to treatment, 9 were related to ibrutinib and rituximab, 5 only related to ibrutinib and 1 only related to rituximab.

No serious adverse events were reported in the additional cohort.