Polatuzumab vedotin with dose-adjusted etoposide, cyclophosphamide, doxorubicin, and rituximab (Pola-DA-EPCH-R) for upfront treatment of aggressive B-cell non-Hodgkin lymphomas.

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Background

- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) has been the standard regimen for untreated large B-cell lymphomas for nearly two decades.
- The phase 3 POLARIX trial demonstrated the superiority of polatuzumab vedotin (Pola) over vincristine in the R-CHOP regimen for large B-cell lymphomas[1]. Only 6.7% of enrolled patients here HGBCL with MYC and BCL2 and/or BCL6.
- However, it is unknown if Pola can be safely incorporated into intensified regimens typically utilized for the highest risk histologies[2].
- To address this question, we conducted a prospective trial (NCT04231877) evaluating Pola with 6 cycles of dose adjusted etoposide, cyclophosphamide, doxorubicin, and rituximab (Pola-DA-EPCH-R).
- *Herein we present the final results of our study*

Methods

Single center, open label, investigator-initiated clinical trial of 6 cycles of Pola-DA-EPCH-R. Planned enrollment of 18 patients.

Key Inclusion Criteria

- Would have received DA-EPOCH-R as standard of care (eg. High grade B-cell lymphoma, Primary mediastinal B-cell lymphoma, DLBCL-NOS with high risk features)
- Measurable FDG-avid disease by PET
- ECOG 0-2
- Adequate liver, kidney, and bone marrow function
- HIV with undectectable viral load allowed

Key Exclusion Criteria

- Transformation from CLL (transformation from other indolent histologies allowed provided there has been no prior systemic therapy for indolent component
- Burkitt lymphoma
- Pre-phase prednisone > 100 mg daily, or 30-100 mg for greater than 7 days.

Assessments

- Optional interim scan after 2 cycles
- EOT PET/CT 4-6 weeks after cycle 6
- Response defined by Lugano 2014
- CTCAE version 5.0

Objectives

- The primary objective is to estimate the safety of Pola-DA-EPCH-R as measured by the rate of dose-limiting toxicities (DLTs) in the first 2 cycles with pre-specified suspension rules if the lower limit of an 80% confidence interval cannot exclude a DLT rate of > 20% (requires sample size of 18 patients, to excludes > 6/18 patients with DLT)
- Secondary and exploratory objectives include efficacy, EFS, OS, dose intensity of polatuzumab vedotin, proportion of patients treated at each dose level, and correlation with response assessments with ctDNA levels collected at baseline, post C1, post C2 and EOT.

ctDNA Analysis

- ctDNA analysis was performed by Foresight Diagnostics Inc. using using PhasED-Seq[3] to track phased variants (PVs).
- PhasED-Seq lowers the error profile of mutation detection in sequencing data by requiring the concordant detection of two separate mutations in an individual cfDNA molecule.

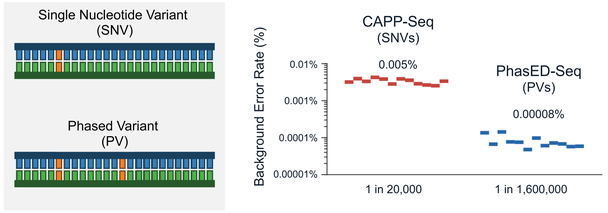


Table 1: Dosing

Dose Level	Polatuzumab vedotin
Starting dose	1.8 mg/kg per cycle
First dose reduction	1.4 mg/kg per cycle
Second dose reduction	1.0 mg/kg per cycle
Third dose reduction	Discontinue drug

Rituximab, etoposide, prednisone, cyclophosphamide, and doxorubicin dosing including escalation was administered as outlined in prior publications except for omission of vincristine[2]. Growth factor use was mandated. No intra-patient escalation of Pola was allowed.

Results

Table 2: Characteristics (N = 18)

Age, median (range)	64 (41-74)
Male	10 (56%)
Stage IV	13 (72%)
IPI 3-5	13 (72%)
High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement	6 (33%)
DLBCL lymphoma, NOS	8 (44%)
Primary mediastinal B-cell lymphoma	4 (22%)
Elevated LDH	14 (78%)
MYC rearrangement (n=17)	9 (53%)
Bulk (> 10 cm)	7 (39%)
Pre-phase prednisone use	9 (50%)
Diagnosis to treatment interval, median (range)	24 (10-37)

Table 3: Toxicity

Grade 3-4 non-heme AEs in > 1 patient	N (%)
Oral Mucositis	4 (22%)
Thromboembolic events	4 (22%)
Hyperglycemia	3 (17%)
Febrile neutropenia	3 (17%)
Hypokalemia	2 (11%)
Abdominal pain	2 (11%)

- 5 SAEs (one death (sepsis), three febrile neutropenia, one colonic perforation/diverticulitis
- 3 DLTs (one death, two pulmonary emboli)
- One Pola dose reduction (G4 thrombocytopenia)
- One treatment delay (12 days due to G3 colon perforation)
- G1 Neuropathy (22%), No G2+ seen

Fig 1. Dose Level by Cycle

Histology, Age/Gender	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
HGBCL, 48F	1	2	3	4	5	5
PMBCL, 45F	1	2	3	4	4	5
DLBCL, 52M	1	2	3	4	4	4
DLBCL, 58F	1	2	3	4	4	4
HGBCL, 64M	1	2	3	4	4	3
DLBCL, 68M	1	1	2	3	3	3
DLBCL, 64M	1	1	2	3	2	3
DLBCL, 74M	1	1	2	3	3	3
DLBCL, 69M	1	1	2	3	3	2
HGBCL, 73F	1	2	2	2	2	2
HGBCL, 55M	1	2	2	2	2	2
HGBCL, 66M	1	1	2	2	2	2
DLBCL, 61F	1	2	2	2	2	2
PMBCL, 64M	1	2	2	2	2	2
PMBCL, 41M	1	1	2	2	2	2
PMBCL, 48F**	1	2	2	2	1	1
HGBCL, 71F*	1	1	1	-1	-1	-1
DLBCL, 64F***	1					

* G4 thrombocytopenia
** G3 colon perforation/diverticulitis, 12 day delay
***G5 sepsis in cycle 1

Fig 2. Overall Survival

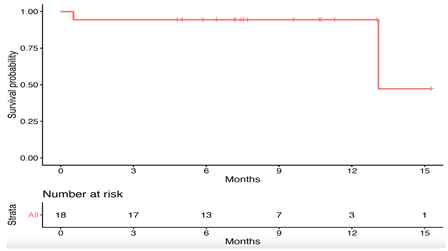


Fig 3. Event Free Survival

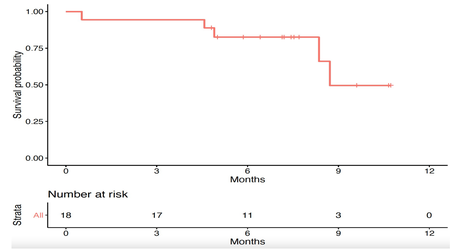


Fig 3. ctDNA kinetics during therapy reflect clinical outcomes

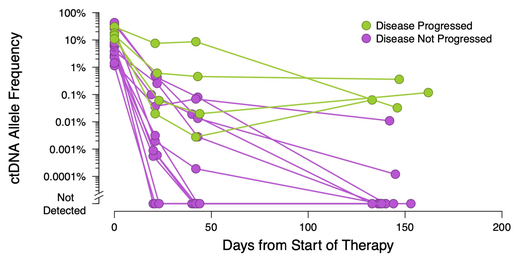
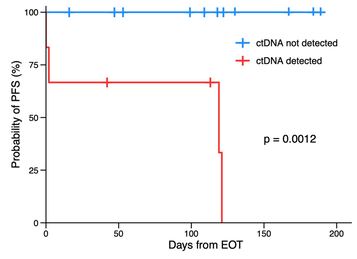


Fig 4. ctDNA detection at the end of therapy stratifies outcomes



Conclusions

- Pola 1.8 mg/kg in combo with DA-EPCH-R met its primary safety endpoint with only 3 DLTs observed
- 89% of patients were able to achieve DL2, and 50% achieved DL3.
- ctDNA kinetics during therapy, and at the end of therapy, strongly predicted clinical outcomes.
- No patients with undetectable ctDNA at the end of therapy have progressed to date.
- This regimen can be considered in patients who would receive DA-EPOCH-R.

Acknowledgements

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References

1. Tilly H, Morschhauser F, Sehn LH, et al: Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. N Engl J Med, 2021, **2.** Dunleavy K, Fanale MA, Abramson JS, et al:. Lancet Haematol 2018. **3.** Kurtz DM et al: Enhanced detection of minimal residual disease by targeted sequencing of phased variants in circulating tumor DNA. Nature Biotechnology 2021.