Loncastuximab tesirine with rituximab induces robust and durable complete metabolic responses in high-risk relapsed/refractory follicular lymphoma

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Background

- **Frontline therapy in follicular lymphoma (FL) is well-defined; however, there is no standard approach for patients with relapsed/refractory (R/R) disease**
  - Those experiencing disease progression within 24 months (POD24) after immunochemotherapy demonstrated worse outcomes
  - GELF criteria is used to categorize patients in need of immediate therapy, becoming a common eligibility requirement across FL studies
- **Loncastuximab tesirine (loncastuximab) is an antibody-drug conjugate comprising a humanized antiCD19 antibody conjugated to a PBD dimer cytotoxin currently approved in R/R DLBCL after ≥2 lines of therapy**
  - In the phase I study, loncastuximab demonstrated an overall response rate (ORR) of 78.6% with a complete response (CR) rate of 64.3% and not reached time-to-event endpoints in 14 patients with R/R FL
- **Here, we report the primary study endpoint of a clinical trial evaluating fixed-duration loncastuximab with rituximab in R/R FL (NCT04998669)**

Study Design

Phase II single arm and single center investigator-initiated study

Study design

- Simon's minimax two-stage design
- Sample size of 39 patients
- Clinically meaningful CR rate ≥50% (≤30% (H0))
- Type I error alpha 5% and power 80%

A total of ≥17 CRs among study cohort are required to reject the H0

Study endpoints

Primary endpoint:

- CR at week 12 by Lugano response criteria

Secondary endpoints:

- Overall response rate
- Safety and tolerability
- 2-year progression-free survival and overall survival

Key inclusion criteria

- R/R FL grade 1, 2 or 3A
- Previously treated with ≥1 line of systemic therapy
- Need for treatment based on GELF criteria, POD24, or second relapse
- ECOG PS 0 to 2
- Measurable disease by Lugano classification
- Adequate organ function

Safety analysis: ≥1 dose of loncastuximab
Efficacy analysis ≥3 doses of loncastuximab

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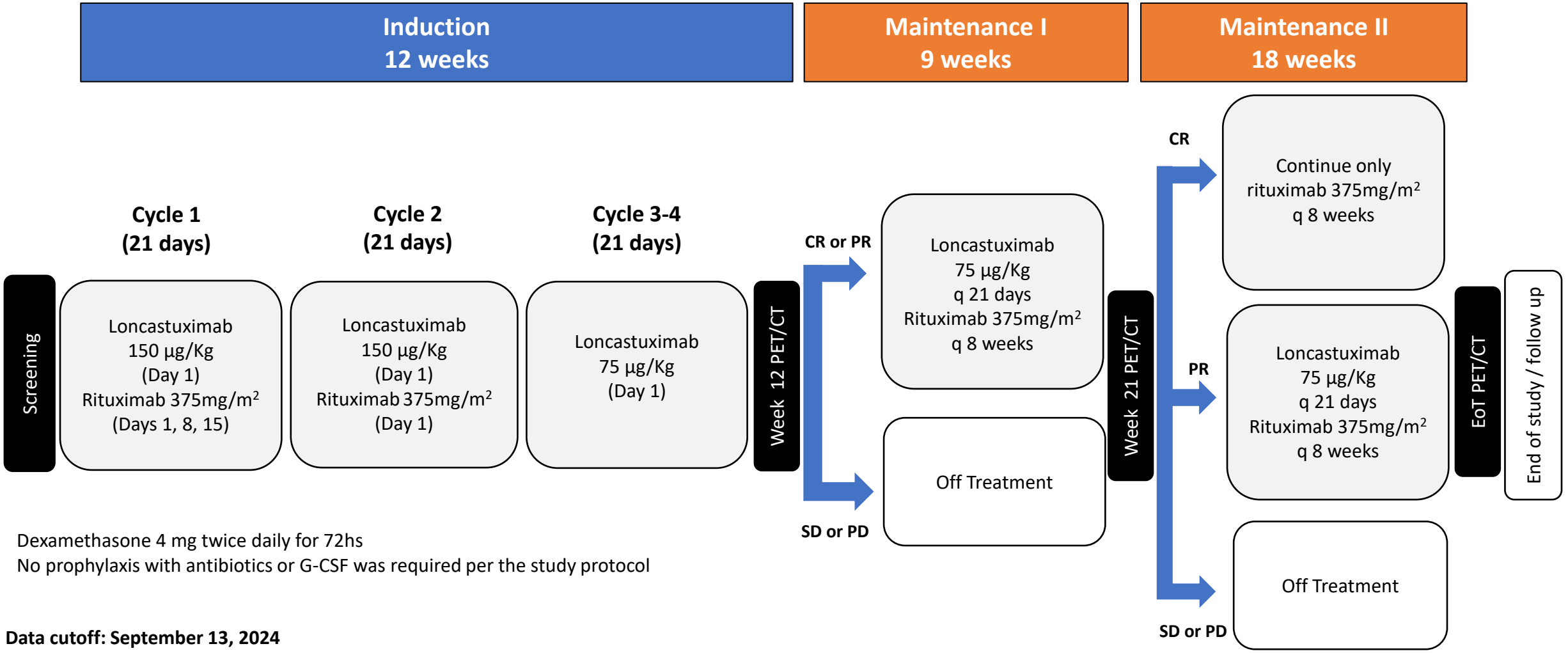
Study Schema



Dexamethasone 4 mg twice daily for 72hs
No prophylaxis with antibiotics or G-CSF was required per the study protocol

Data cutoff: September 13, 2024
Median follow-up: 18 (95% CI 12-19.3) months

Baseline Patient & Disease Characteristics

39 patients enrolled between January 2022 to June 2024

		n = 39	%
Median age, years (range)		68 (47-89)	
Male		21	53.8
Hispanic		22	56.4
Prior transformed FL		11	28.2
FL grade 3A		11	28.2
Bone marrow involvement		13	33.3
ECOG performance status	0 / 1	29 / 10	74.3 / 25.7
Elevated β2-microglobulin		27	69.2
Ann-Arbor stage	II / III-IV	7 / 32	17.9 / 79.1
FLIPI risk score	0-1 / 2 / 3-5	9 / 6 / 24	23 / 15.4 / 61.6
Progression of disease within 24 months		20	51.5
High-tumor burden by GELF criteria		36	92
Bulky disease (>7cm)		9	23

Prior Treatment Characteristics

	n = 39	%
Refractory to last therapy	20	51
Relapsed FL	19	49
Median no, of prior lines, n (range)	1 (1-6)	
≥3 lines of therapy	11	28
Prior frontline regimens		
• **R-CHOP**	22	56
• **Bendamustine with rituximab**	10	26
• **Rituximab**	6	15
• **Fludarabine, mitoxantrone, dexamethasone with rituximab**	1	3

TEAEs

Most Common (≥10% Overall) Treatment-Emergent Adverse Events								
Adverse event	**Grade 1-2, n**	**%**	**Grade 3, n**	**%**	**Grade 4, n**	**%**	**Any grade, n**	**%**
Neutropenia	10	25.6	4	10.3	1	2.6	15	38.5
Anemia	14	35.9					14	35.9
Lymphopenia	5	12.8	5	12.8	3	7.7	13	33.3
Thrombocytopenia	9	23.1					9	23.1
Hyperglycemia	16	41	1	2.6			17	43.6
Increased ALP	16	41					16	41
Increased ALT	14	35.9	1	2.6			15	38.5
Fatigue	15	38.5	1	3.1			15	38.5
Increased AST	15	38.5					15	38.5
Rash maculo-papular	14	35.9					14	35.9
Localized edema	5	12.8	1	2.6			6	15.4
Photosensitivity	6	15.4					6	15.4
Generalized edema	5	12.8	1	2.6			6	15.4
Diarrhea	6	15.4					6	15.4
Pleural effusion	5	12.8					5	12.8
Dyspnea	4	10.3	1	2.6			5	12.8

Hematological TEAEs

Non-hematological TEAEs

	Grade 1-2, n	%	Grade 3, n	%	Grade 4, n	Any grade n	%
Upper respiratory infection	4	10.3	1	2.6		5	12.6
Infections – Other*	5	12.6				5	12.6
UTI	4	10.3				4	10.3
Skin infection	2	5.1	1	2.6		3	7.7
Includes 3 cases of covid-19 infection							

- **Disease progression (n=2) was the most common cause of treatment discontinuation**

- **Four (10.2%) patients experienced serious adverse events (related)**
- Cellulitis after loncastuximab extravasation
- Febrile neutropenia
- Dyspnea secondary to pleural effusion
- Generalized edema

- **No treatment-related deaths occurred during the study course**

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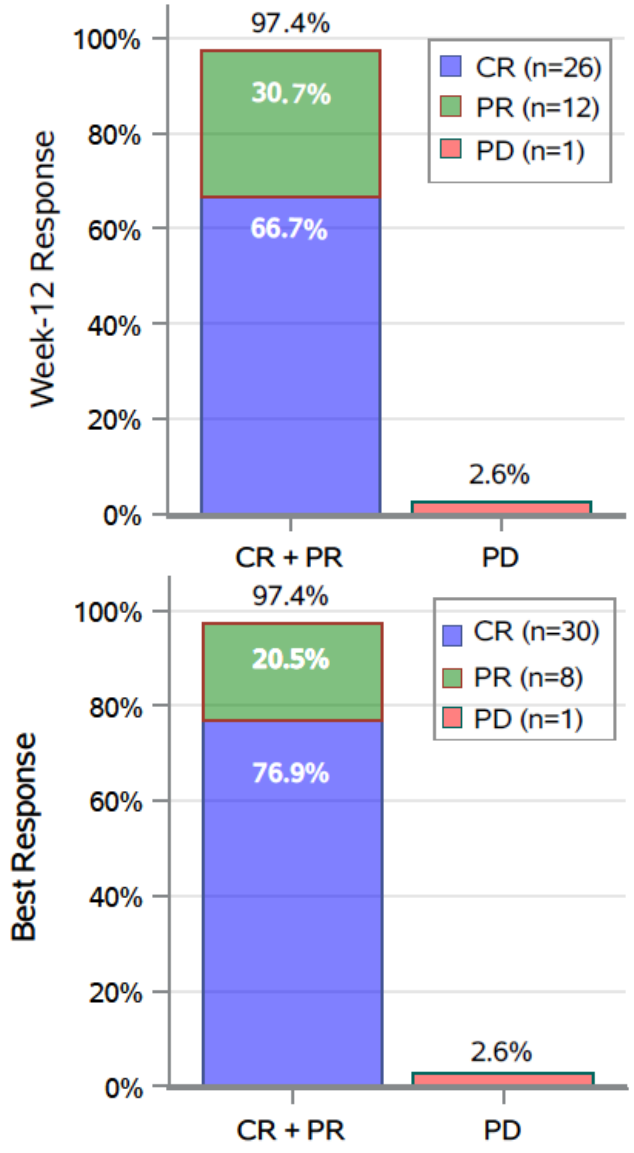
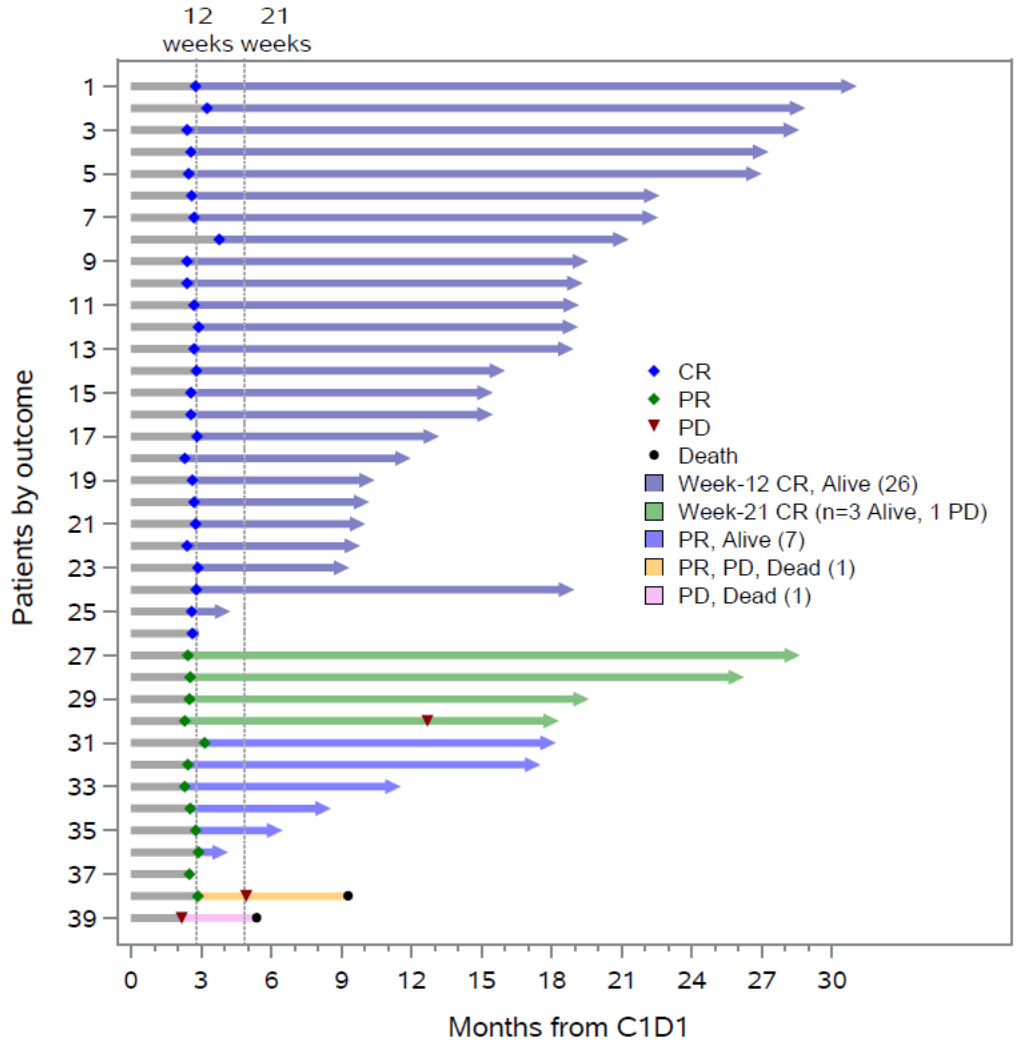
Efficacy





The null hypothesis was rejected (one-sided p<0.0001)

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Post-hoc Efficacy Analyses

	n	Best ORR	Best CR rate
POD24	20	100%	85%
High risk FLIPI score	24	96%	67%
Prior transformed FL	11	100%	73%
Rituximab with an alkylating agent	32	100%	75%

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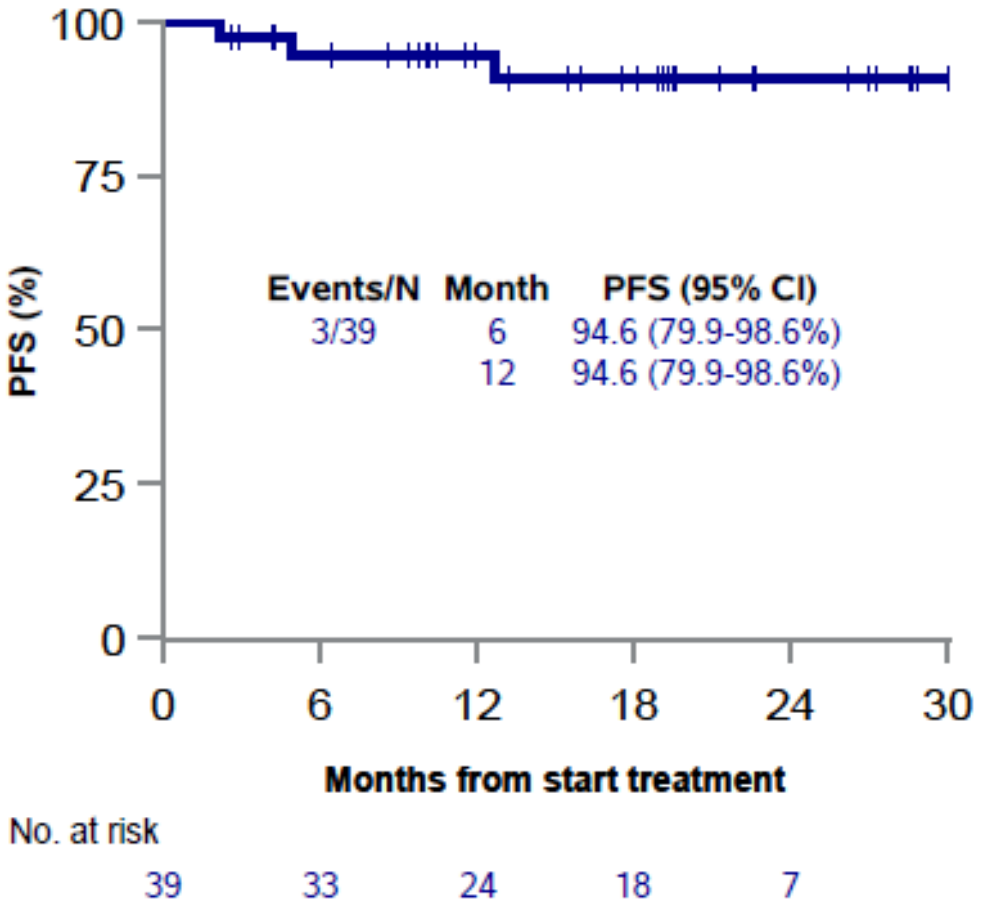
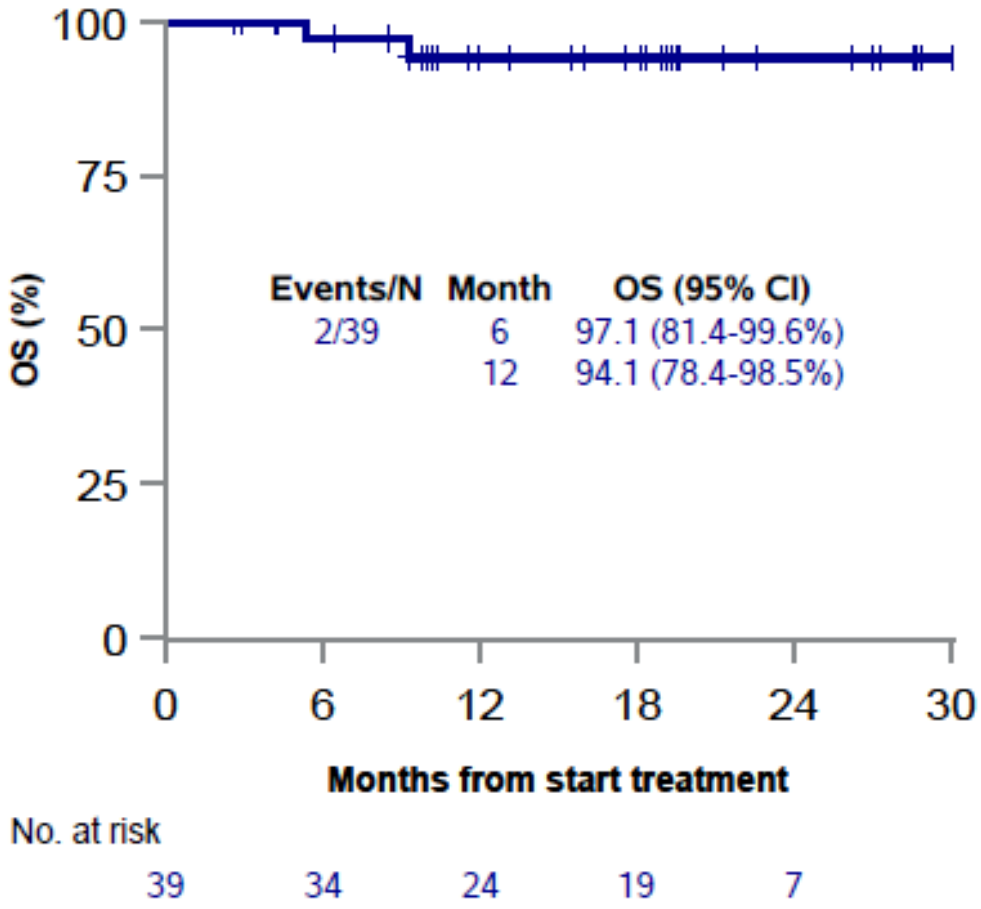
Time-to-Event Endpoints





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Multicenter Study

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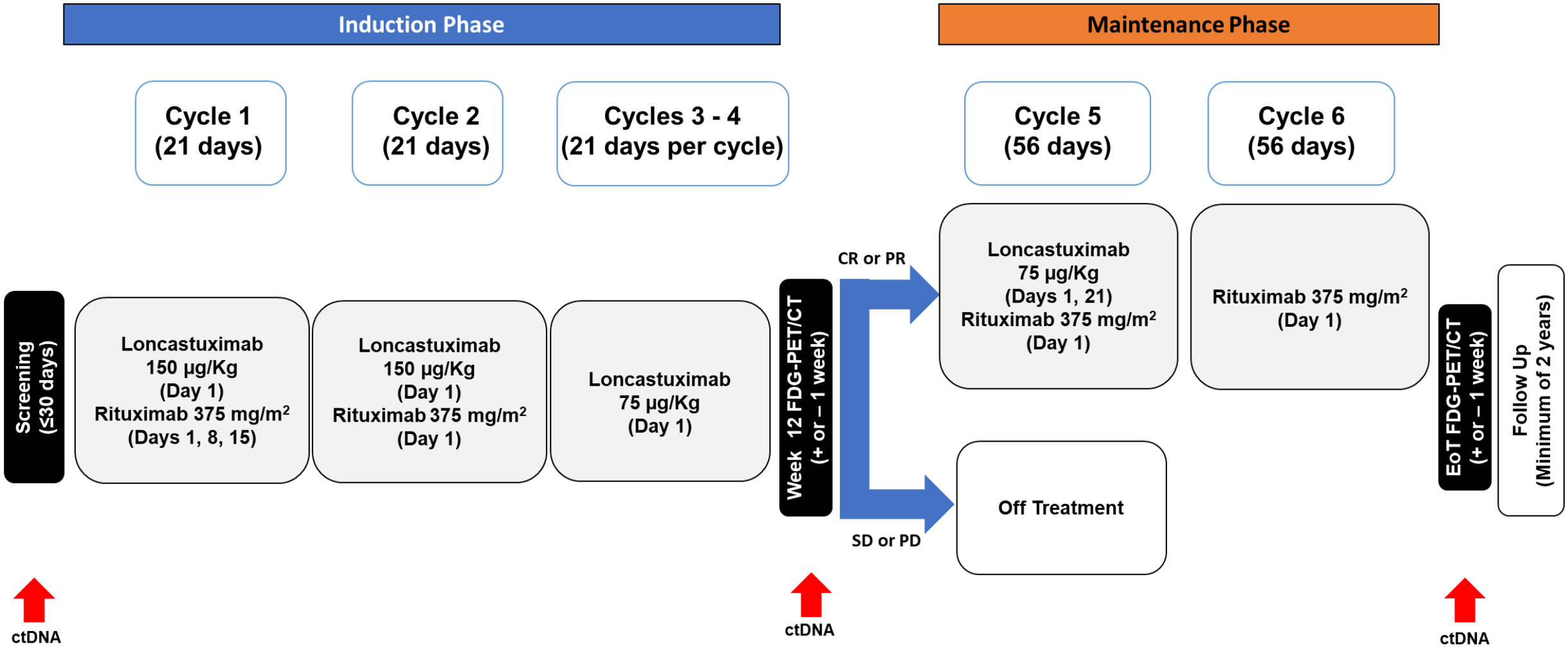
UNIVERSITY OF MICHIGAN HEALTH

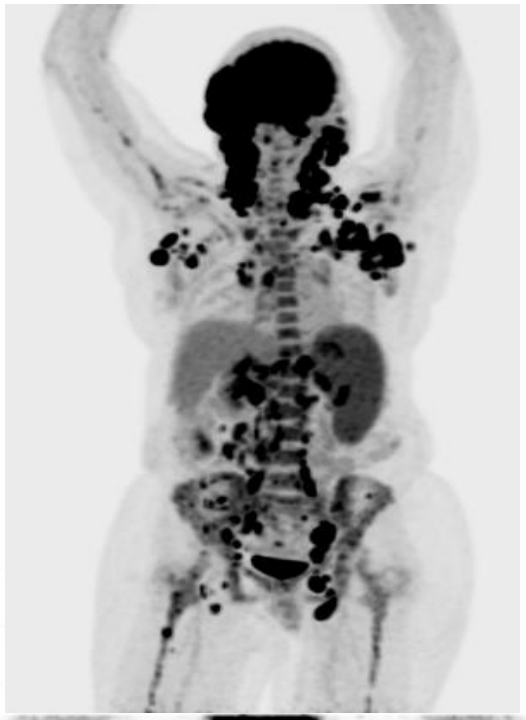
RUTGERS HEALTH
Rutgers Cancer Institute

FLORIDA CANCER SPECIALISTS & Research Institute

Research at Allegheny Health Network



Screening MTV



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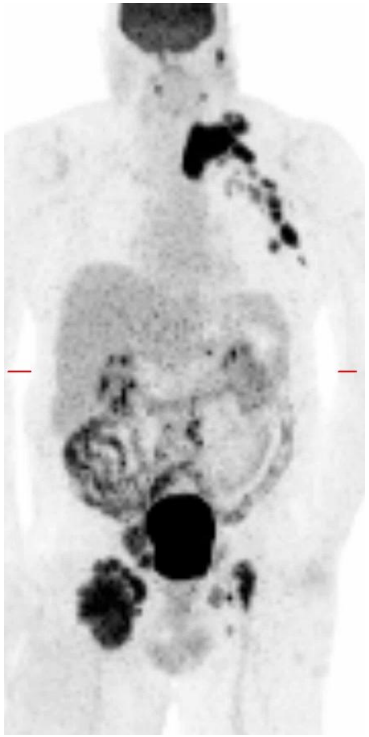

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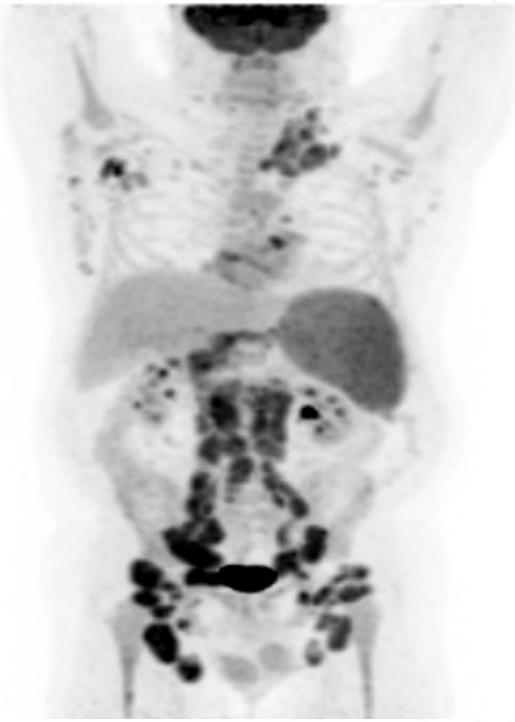

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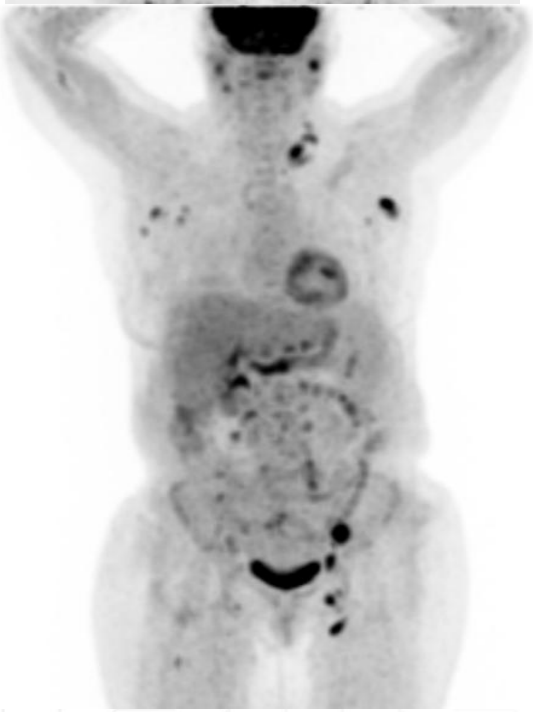
Week 12 MTV



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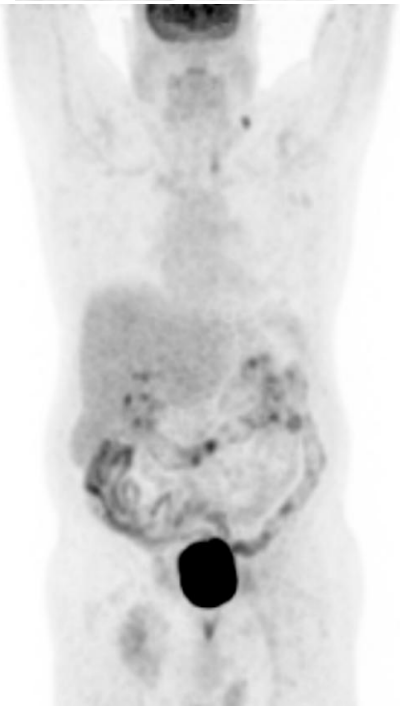

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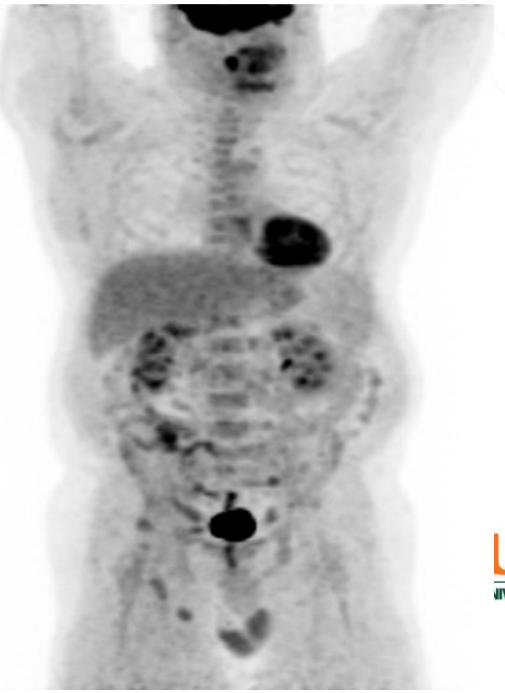

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Conclusions

- **Limited duration loncastuximab with rituximab drives significant CR rate in second-line and later FL with high-tumor burden and POD24**
- **This study met its primary endpoint with a week 12 CR rate of more than 50%**
- **CRs appear prolonged with a 12-month PFS of 94.6% and not reached median PFS at the current follow-up**
- **The safety profile in FL was consistent with prior studies in large B-cell lymphoma with no new safety signals**
  - Most AEs were grade 1-2, including hyperglycemia, increase in liver enzymes, fatigue, and rash
- **This study suggests that a fixed-duration program of loncastuximab with rituximab is a promising combination in second-line and later FL**

Loncastuximab tesirine with rituximab in patients with relapsed or refractory follicular lymphoma: a single-centre, single-arm, phase 2 trial

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Summary

Background Preliminary data suggest promising activity of loncastuximab tesirine in follicular lymphoma, and synergistic activity between rituximab-induced cytotoxicity and loncastuximab tesirine. In this study, we evaluated loncastuximab tesirine combined with rituximab for second-line and later treatment of follicular lymphoma.

Methods We did a single-arm, investigator-initiated, phase 2 trial at Sylvester Comprehensive Cancer Center in Miami, FL, USA. We recruited patients aged 18 years or older with histologically confirmed relapsed or refractory follicular lymphoma (grade 1–3A) treated with one or more lines of therapy and presenting with progression or relapse of disease within 24 months (POD24) after the first line of treatment, one or more Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, or second relapse, and with an Eastern Cooperative Oncology Group performance status of 0–2. Intravenous loncastuximab tesirine was administered on day 1 of a 21-day cycle, at 0·15 mg/kg for two cycles, then 0·075 mg/kg thereafter. Intravenous rituximab was administered on day 1 of cycle 1, at 375 mg/m² for four once-weekly doses, followed by one dose every 8 weeks on cycles 5, 6, and 7. At week 21, patients with a complete response discontinued loncastuximab tesirine and received two more doses of rituximab once every 8 weeks. Patients with a partial response at week 21 continued both agents for 18 more weeks. The primary endpoint was complete response rate at week 12 assessed by the Lugano 2014 classification in patients who had received at least three doses of loncastuximab tesirine. The safety analysis included all patients who received one or more doses of loncastuximab tesirine. The trial is registered with ClinicalTrials.gov, NCT04998669, and is ongoing (open to recruitment); the data cutoff for this analysis was Sept 13, 2024.

Findings Between Jan 28, 2022, and June 3, 2024, we enrolled 39 patients (median age 68 years [IQR 58–77]; 21 [54%] male patients and 18 [46%] female patients). All patients presented with one or more GELF criteria (n=36 [92%]) or POD24 after the first line of treatment (n=20 [51%]) at baseline. As of Sept 13, 2024, the median follow-up was 18·2 months (95% CI 12·0–19·3). Week 12 complete response rate was 67% (n=26 of 39). The most common grade 3 or worse treatment-emergent adverse events (TEAEs) were lymphopenia (eight [21%] of 39 patients) and neutropenia (five [13%] patients; one of whom had a serious grade 3 TEAE of febrile neutropenia that was considered to be related to study treatment). Generalised and peripheral oedema was predominantly grade 1–2 and all cases of oedema were treatable with diuretics. Serious TEAEs that were considered to be related to study drugs occurred in four (10%) of 39 patients. No fatal TEAEs occurred.

Interpretation Loncastuximab tesirine with rituximab showed clinically meaningful activity in relapsed or refractory follicular lymphoma, and had a manageable safety profile.

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