Limited Duration Loncastuximab Tesirine with Rituximab Induces High Complete Response Rate in High-Risk Relapsed/Refractory Follicular Lymphoma – a Phase 2 Study

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Background

- **There is no standard approach in the treatment of patients with relapsed/refractory (R/R) follicular lymphoma (FL)**
  - Those experiencing disease progression within 24 months (POD24) after immunochemotherapy demonstrated worse outcomes (5-year overall survival 73.5% vs. 95.4%)
  - GELF criteria is used to categorize patients in need of immediate therapy, becoming a common eligibility requirement in 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 systemic 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
- **Preclinical data revealed synergistic activity between rituximab-induced cytotoxicity and loncastuximab, providing the rationale for this combination**
- **Here, we report the initial results of a clinical trial evaluating this combination for the first time in R/R FL**

Casulo C et al. Blood 2022
Maddocks K et al. J Natl Cancer Inst 2016
Hamadani M et al. Blood 2021

Study Design

- **Phase II single-arm and single-center investigator-initiated study**

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 or POD24
- ECOG PS 0 to 2
- Measurable disease by PET/CT
- Adequate organ function

Study endpoints

Primary endpoint:

- CMR at week 12 by Lugano response criteria

Secondary endpoints:

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

Exploratory endpoints:

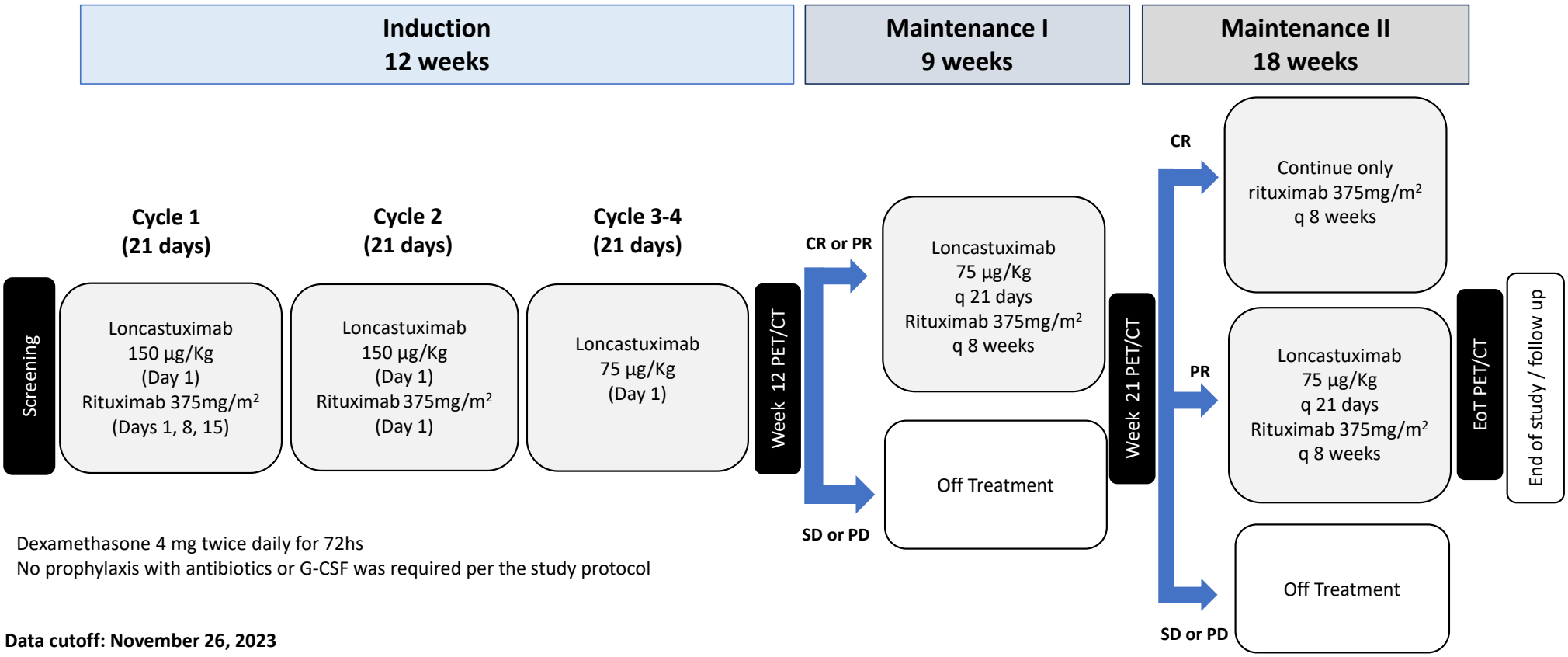
- Metabolic tumor volume and radiomics analyses obtained from the screening PET/CT
- Circulatory biomarkers
- Health-related quality of life assessment

Study design

- Simon's minimax two-stage design with a total sample size of 39 patients based upon a projected CMR rate ≥50% vs ≤30% (H0)
- Type I error alpha 5% and power 80%
- **Stage I:** ≥7 CMRs among 19 patients required to proceed with stage II
- **Stage II**: 20 additional patients will be enrolled

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

Study Schema



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

Data cutoff: November 26, 2023
Median follow-up: 9.7 (3.6 to 21.5) months

Baseline Patient & Disease Characteristics

		n = 33	%
Median age, years (range)		68 (47-89)	
Age ≥65		20	61
Male		18	54.5
Hispanic		17	51.5
Prior transformed FL		7	21.2
FL grade 3A		10	30.3
Bone marrow involvement		10	30.3
ECOG performance status	0 / 1	25 / 8	75.8 / 24.2
Elevated β2-microglobulin		21	63.3
Ann-Arbor stage	II / III-IV	7 / 26	21.2 / 78.8
FLIPI risk score	0-1 / 2 / 3-5	9 / 6 / 18	27.3 / 18.2 / 54.5
Progression of disease within 24 months		18	54.5
High-tumor burden by GELF criteria		28	84.8

Prior Treatment Characteristics

	n = 33	%
Refractory to last therapy	17	51.5
Relapsed FL	16	48.5
Median no, of prior lines, n (range)	1 (1-6)	
≥3 lines of therapy	8	24.2
Prior frontline regimens		
• **R-CHOP**	18	54.5
• **Bendamustine with rituximab**	8	24.2
• **Rituximab**	6	18.2
• **Fludarabine, mitoxantrone, dexamethasone with rituximab**	1	3.1

Safety Profile

Most common TEAEs (≥10% for all grades in 32 evaluable patients for toxicity)

	Adverse event	Grade 1, n	%	Grade 2, n	%	Grade 3, n	%	Grade 4, n	%	Any grade, n	%
Hematological TEAEs	Neutropenia	5	15.6	4	12.5	2	6.2	1	3.1	12	37.5
	Anemia	6	18.7	3	9.3					9	28.1
	Thrombocytopenia	7	21.8							7	21.8
Non-hematological TEAEs	Increased ALP	13	40.6	4	12.5					17	53.1
	Hyperglycemia	13	40.6	1	3.1	1	3.1			15	46.8
	Increased ALT	12	37.5	1	3.1	1	3.1			14	43.7
	Fatigue	11	34.3	2	6.2	1	3.1			14	43.7
	Rash maculo-papular	12	37.5	1	3.1					13	40.6
	Increased AST	11	34.3	1	3.1					12	37.5
	Pedal edema	7	21.8	1	3.1					8	25
	Photosensitivity	7	21.8	1	3.1					8	25
	Anasarca	5	15.6	2	6.2					7	21.8
	Diarrhea	3	9.3	2	6.2					5	15.6
	Face edema	4	12.5							4	12.5
	Pleural effusion	1	3.1	3	9.3					4	12.5
	Dyspnea	3	9.3			1	3.1			4	12.5

Safety Profile – Infectious AEs

	Grade 1, n	%	Grade 2, n	%	Grade 3, n	%	Grade 4, n	Any grade n	%
Skin infection	1	3.1	1	3.1	1	3.1		3	9.3
Covid-19	1	3.1	2	6.2				3	9.3
UTI			3	9.3				3	9.3
Conjunctivitis	2	6.2						2	6.2
Oral thrush			1	3.1				1	3.1
URI			1	3.1				1	3.1
Bronchoaspiration			1	3.1				1	3.1
Herpes-Zoster	1	3.1						1	3.1

- **Serious adverse events occurred in three patients**
- Cellulitis after loncastuximab extravasation
- Dyspnea secondary to pleural effusion
- Fatigue followed by a fall and bronchoaspiration

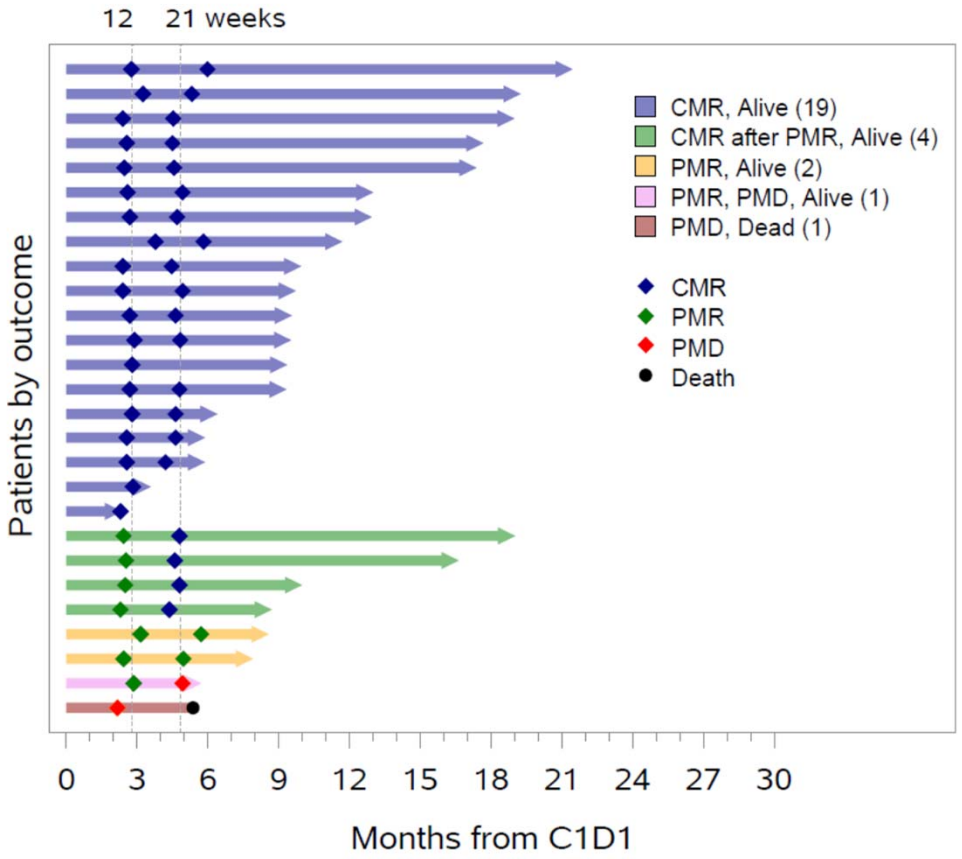
- **Four (12.5%) patients required loncastuximab dose reduction due to AEs**
- **All patients received planned doses of loncastuximab**

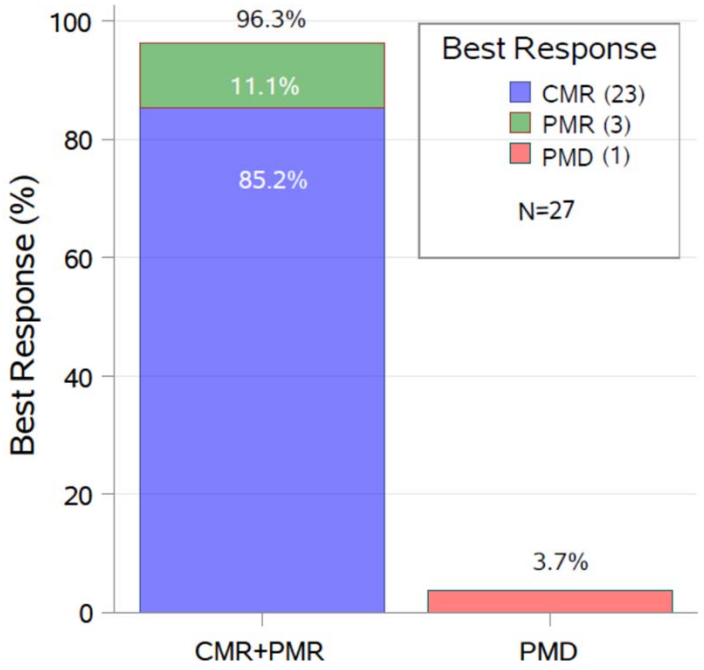
- **Three patients have been removed from the study**
- Cholangiocarcinoma currently in CR from both malignancies
- Transformation to large B-cell lymphoma in two patients

All lesions were present on screening PET/CTs but radiologically considered FL

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

Summary of Efficacy in 27 Evaluable Patients





- The median time to overall response was 11.9 weeks
- The median time to CMR was 11.7 weeks

Response by FLIPI score and POD24 status

		Overall Response Rate		CMR rate	
FLIPI risk group	**n**	**n**	**%**	**n**	**%**
• **Low**	8	8	100	7	87.5
• **Intermediate**	5	5	100	5	100
• **High**	14	13	92.9	11	78.6
POD24	16	16	100	14	87.5
No POD24	11	10	90.9	9	81.8

Interim Analysis

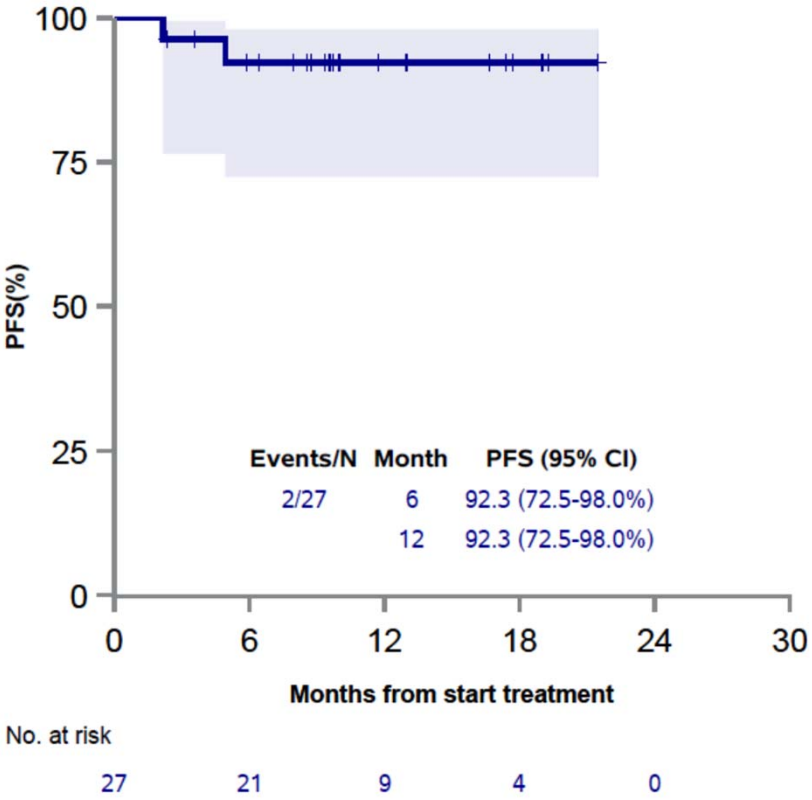
Stage 1 (futility analysis)		
Response at week 12	**n**	**%**
CMR	14	73.7
PMR	4	21
Disease progression	1	5.3

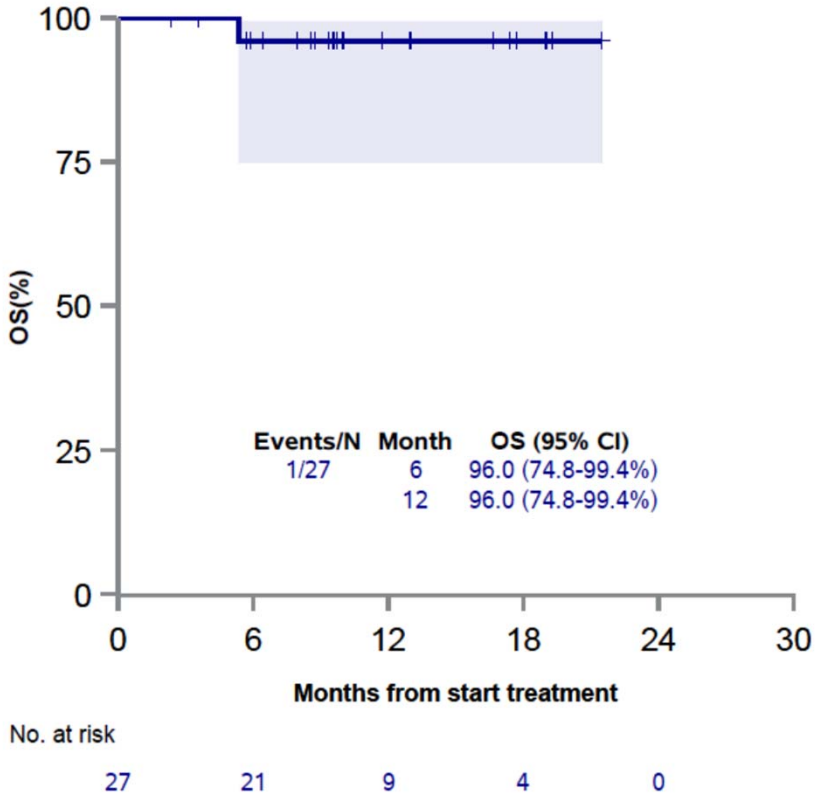
The study met the prespecified criteria of ≥7 CMRs among 19 to proceed to stage 2

Stage 2		
Response at week 12	**n**	**%**
CMR	5	62.5
PMR	3	37.5
Disease progression	0	0

At the current follow-up, we observed 19 CMRs, aligning with the ≥17 needed to reject the H0 (CMR: 30%)

Progression-Free Survival & Overall Survival





Conclusions

- **Limited duration loncastuximab with rituximab drives significant CMR rate in R/R FL with high-tumor burden and POD24**
  - Best ORR of 96.3% and CMR of 85.2%, with a significant number achieving early responses
- **We already observed the prespecified week 12 CMRs needed to reject the H0, and the median PFS was not reached at the current follow-up**
  - CMRs appear robust, similar to prior observations from the phase I study
- **The safety profile in patients with FL was consistent with prior studies in large B-cell lymphoma with no new safety signals**
  - Majority of AEs were grade 1, including rash, increase in liver enzymes, and fatigue
- **Loncastuximab with rituximab demonstrated clinically meaningful benefit in patients with R/R FL, supporting this combination as a new treatment option**
- **A multicenter clinical trial aiming to expand the current cohort and decrease the length of therapy to six cycles is planned to be launched during the first quarter of 2024**

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Thank you!

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