Deep responses following treatment with loncastuximab tesirine in patients with relapsed/refractory including those with high-risk, TP53-altered Waldenström macroglobulinemia

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Introduction

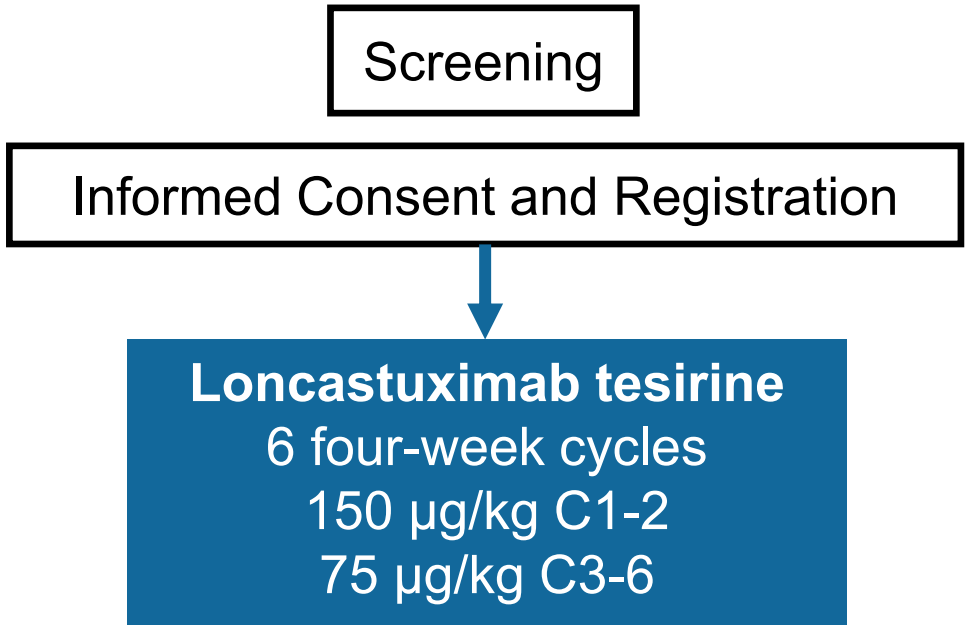
- There are multiple effective therapies for the treatment of Waldenström macroglobulinemia (WM)
- Disease response can be impacted by the mutational status of *MYD88*, *CXCR4*, *BTK*, and *TP53*
- *TP53* altered WM represents a high-risk disease group
- Loncastuximab tesirine, a CD19 antibody drug conjugate, is FDA approved for treatment of relapsed or refractory large B cell lymphoma

Methods

- Ongoing, single-arm, open label multi-center phase II trial
- Statistical assumptions: VGPR of ≥40% (H1), VGPR of ≤10% (H0), double-sided alpha of 0.037, and power of 87% for a sample size of 20 participants. The null hypothesis would be rejected if at least 6 participants achieve a VGPR.
- Data cut-off: August 1, 2025 (14 evaluable patients)

First trial of the Waldenstrom macroglobulinemia clinical trial network (WM-NET1)

Schema



www.clinicaltrials.gov: NCT05190705

Key Inclusion Criteria

- Clinicopathologic diagnosis of WM
- Symptomatic disease meeting criteria for treatment
- At least 2 prior therapies, including both an anti-CD20 mAb and BTK-inhibitor

Key Exclusion Criteria

- Prior CD19 directed therapy
- Clinically significant 3rd space fluid accumulation
- Significant cardiovascular or liver disease
- Recent significant infection

Baseline characteristics (n=14)

	N (range or %)
Median age, y	71 (53-81)
Male sex	9 (64%)
Median hemoglobin, g/dL	9.5 (8.5-12.6)
Median serum IgM, mg/dL	2146 (723-5955)
Median bone marrow involvement, %	53 (4-90)
Median number of prior therapies	4 (2-10)
MYD88 mutated	14 (100%)
CXCR4 mutated (n=13)	8 (62%)
TP53 altered	8 (57%)
BTK mutation (n=11)	4 (36%)
Splenomegaly ≥15 cm	1 (7%)
Lymphadenopathy ≥1.5 cm or EMD	3 (21%)

14 patients completed therapy

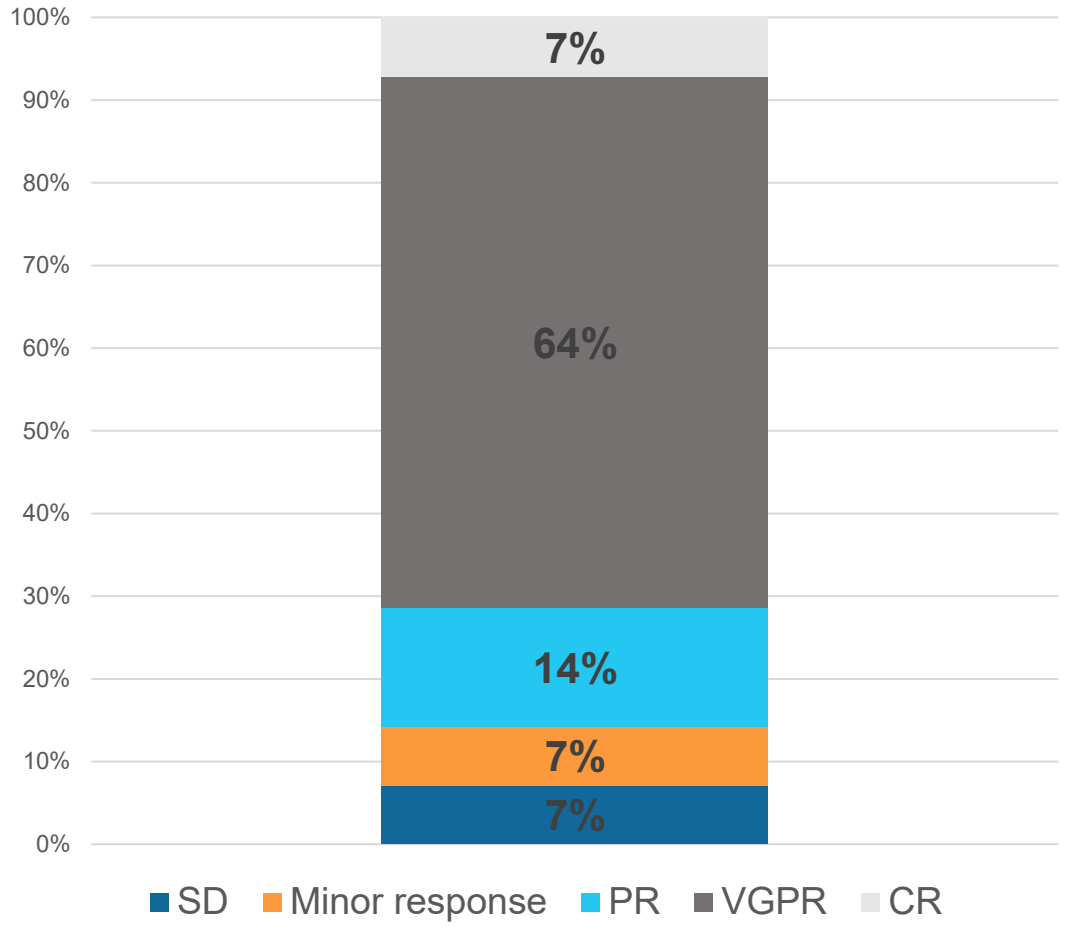
Loncastuximab tesirine
6 four-week cycles
150 µg/kg C1-2
75 µg/kg C3-6

- 5 of 14 patients required a dose reduction (for 1 cycle each)
- 9 patients were able to complete all 6 cycles
- 5 patients stopped treatment early
  - 1 patient stopped due to disease progression
  - 1 patient stopped due to patient choice
  - 1 patient stopped due to skin toxicity
  - 2 patients stopped due to GGT elevation

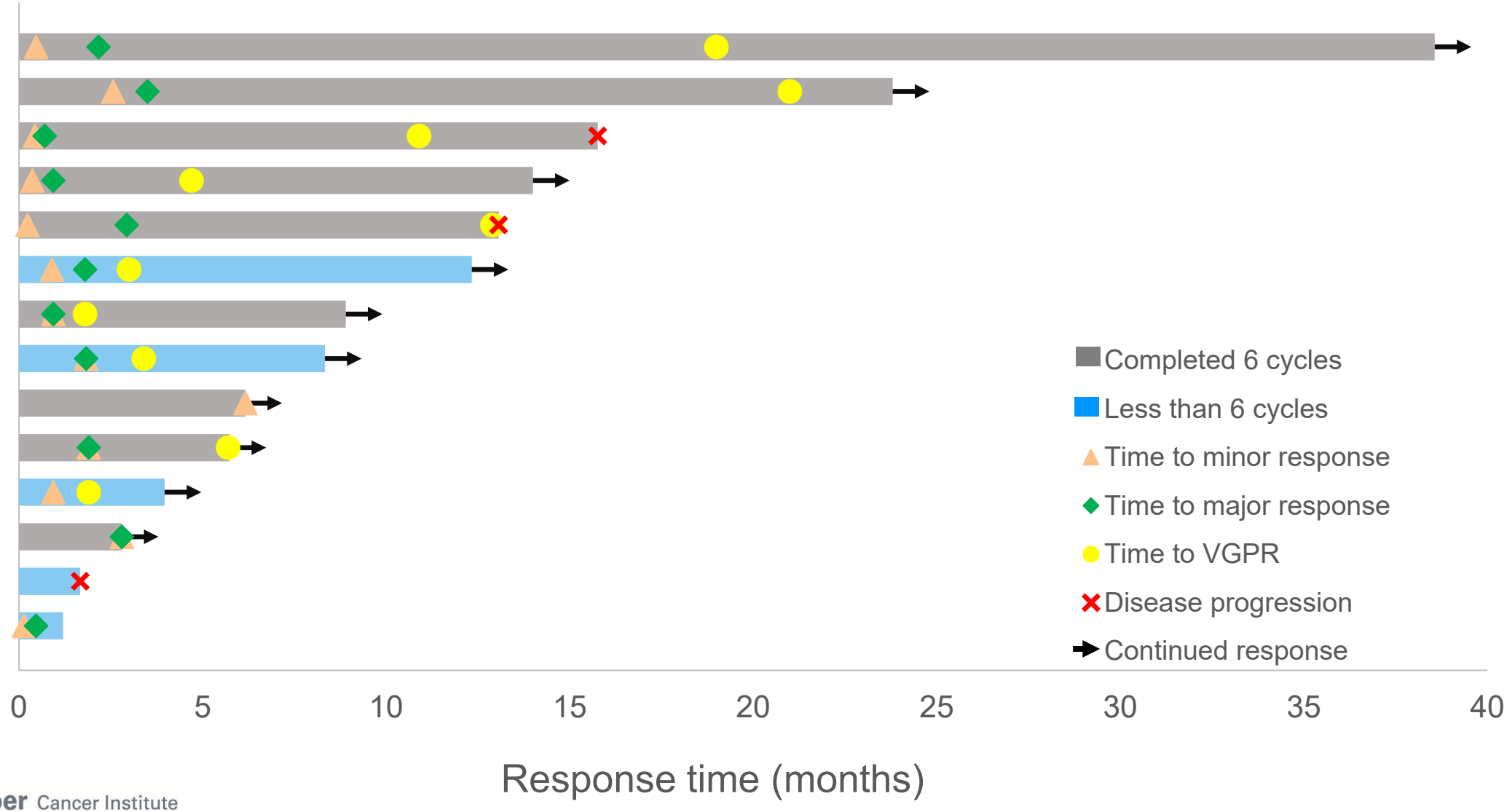
→ Skin and liver toxicity were transient

Best hematologic response (n=14)

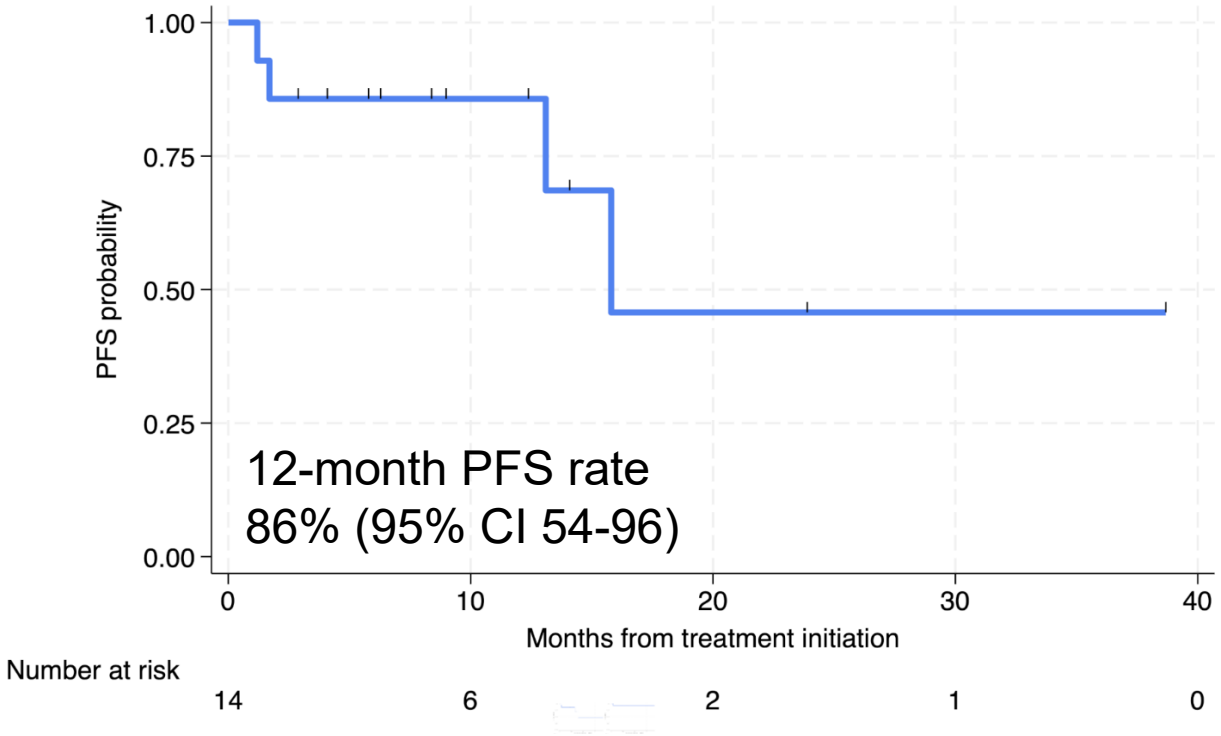
- Median follow-up of 12.3 months (95% CI 5.7-20.8)
- Overall response rate 93% (n=13)
- Major response rate 86% (n=12)
- VGPR/CR rate 71% (n=10),
  including 1 CR

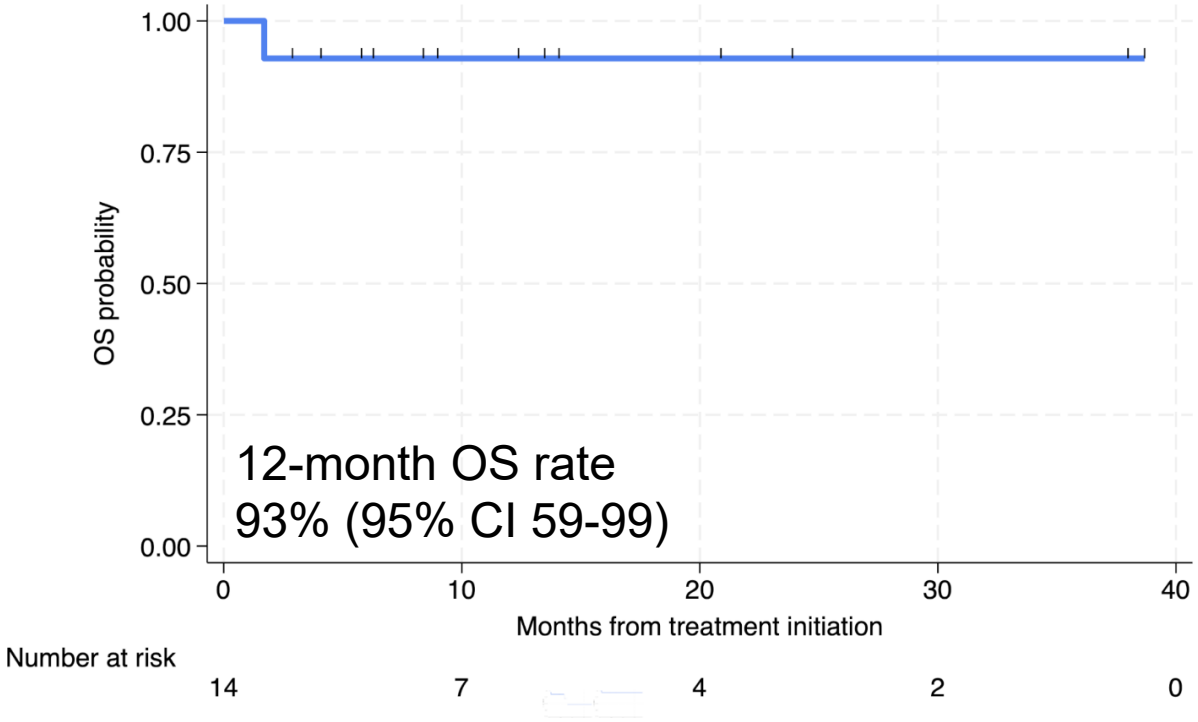


Hematologic responses (14 evaluable patients)



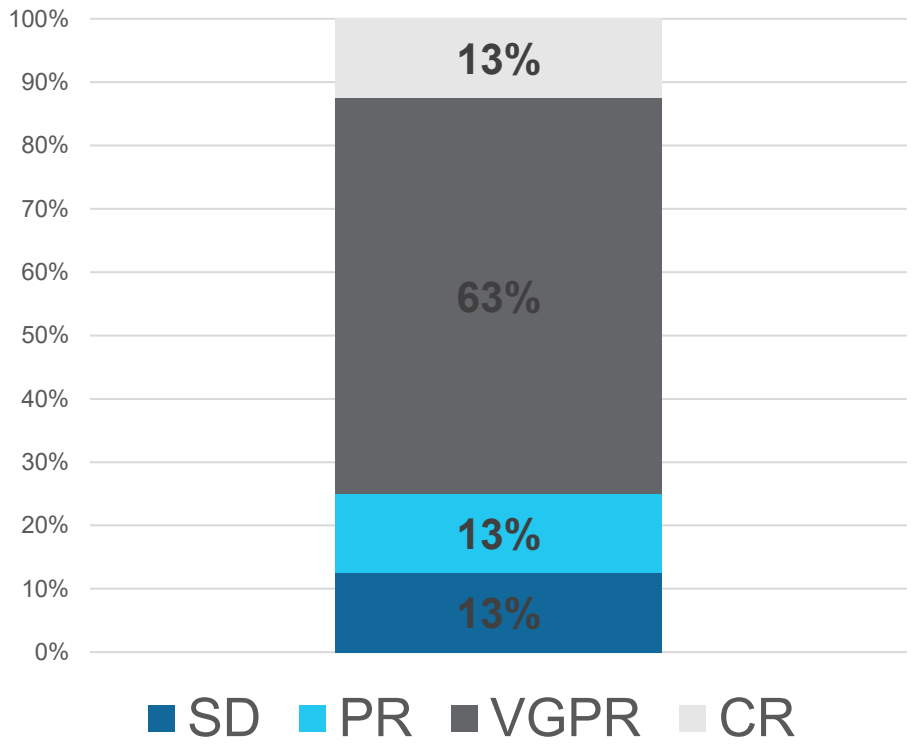
Median follow-up: 12.3 months (95% CI 5.7-20.8)





Best hematologic response

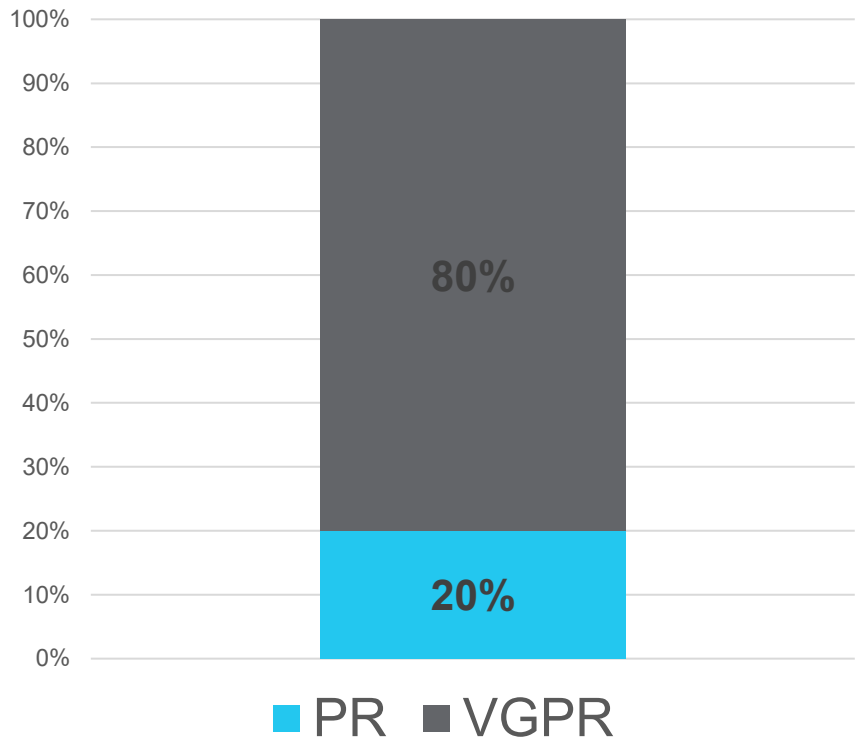
CXCR4 mutated (n=8)



Major response rate 89%

VGPR/CR rate 76%

CXCR4 wild-type (n=5)



Major response rate 100%

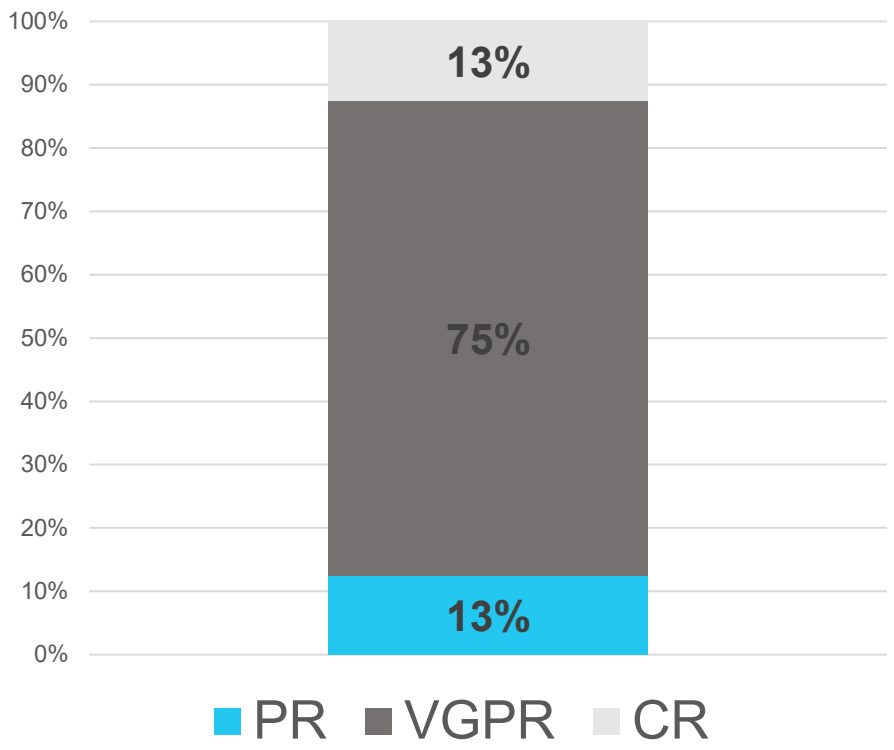
VGPR/CR rate 80%

Baseline characteristics of patients with TP53 altered disease (n=8)

	N (range or %)
Median age, y	70 (53-77)
Male sex	4 (50%)
Median hemoglobin, g/dL	9.2 (8.5-11.6)
Median serum IgM, mg/dL	1877 (723-5639)
Median bone marrow involvement, %	65 (20-90)
Median number of prior therapies	4 (2-10)
MYD88 mutated	8 (100%)
CXCR4 mutated	6 (75%)
TP53 altered	8 (100%)
BTK mutation (n=6)	3 (50%)
Splenomegaly ≥15 cm	1 (13%)
Lymphadenopathy ≥1.5 cm or EMD	1 (13%)

Best hematologic response

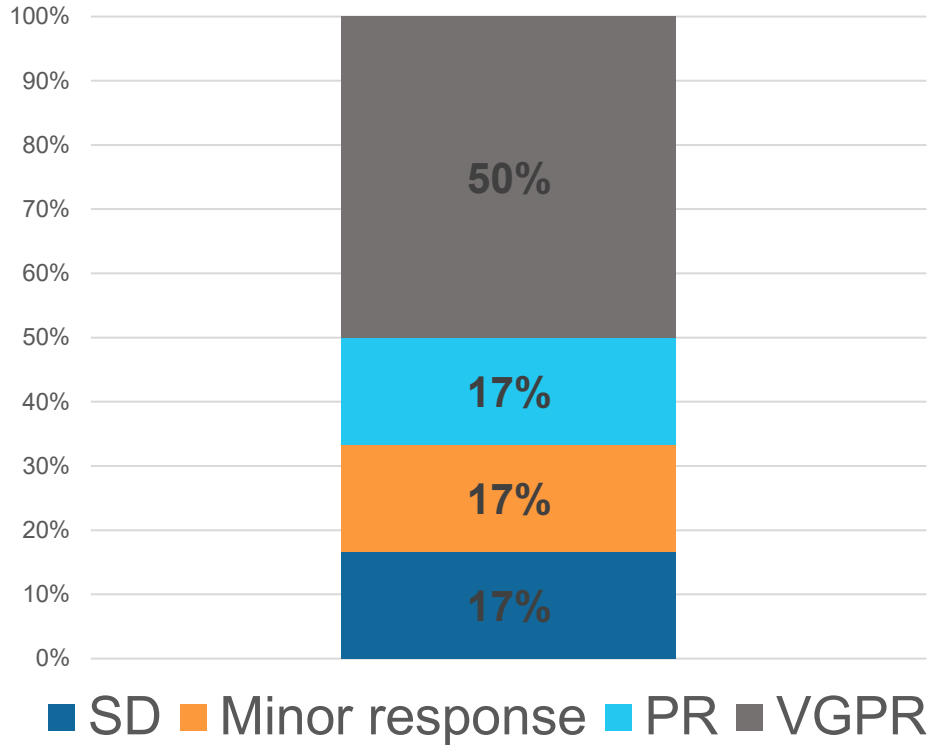
TP53 altered (n=8)



Major response rate 100%

VGPR/CR rate 88%

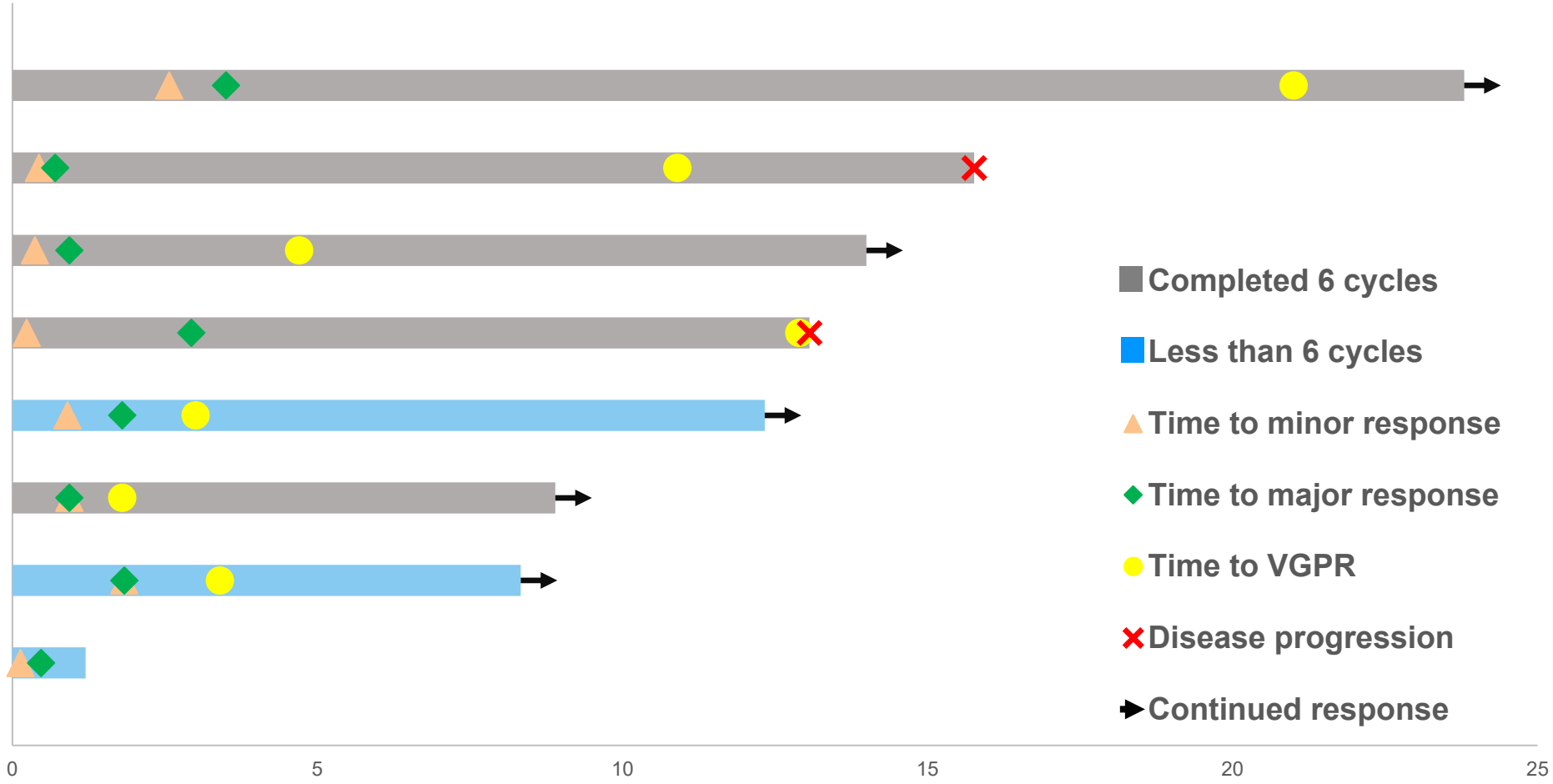
TP53 wild-type (n=6)



Major response rate 67%

VGPR/CR rate 50%

Hematologic responses in TP53 altered disease (n=8)



Grade ≥3 events in all patients

Adverse events	Grade 3 N (%)	Grade 4 N (%)
HEMATOLOGIC		
Anemia	5 (36)	2 (14)
Thrombocytopenia	1 (7)	5 (36)
Neutropenia	5 (36)	2 (14)
INFECTIOUS		
Febrile Neutropenia	2 (14)	
Pneumonia	2 (14)	
Pyelonephritis	1 (7)	

All skin toxicity was Grade 1-2

Adverse event	Grade 3 N (%)	Grade 4 N (%)
HEPATIC		
GGT elevation	1 (7)	2 (14)
ALT elevation	1 (7)	
AST elevation	1 (7)	
Alkaline phosphatase elevation	1 (7)	
CARDIAC		
Myocardial infarction	1 (7)	
Supraventricular tachycardia	1 (7)	
Hypotension	1 (7)	
Edema	1 (7)	
OTHER		
Syncope	1 (7)	
Hip pain	1 (7)	
Hyperglycemia	1 (7)	

Conclusions

- With 10 patients achieving a VGPR/CR this study has met its endpoint
- Loncastuximab tesirine is an effective, fixed-duration therapy for relapsed/refractory WM
- High response rates are achieved, even in patients with high-risk disease
- Additional follow-up is needed to assess duration of response and time to next treatment

Patients and their caregivers

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