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Depth of response from fixed-duration treatment is associated with superior survival in Waldenstrom Macroglobulinemia

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Abstract

Introduction: The treatment landscape for Waldenström macroglobulinemia (WM) continues to evolve with the introduction of new therapies, expanding our options for managing this disease. This evolution underscores the ongoing debate on whether achieving deeper response or merely controlling the disease should be the primary therapeutic goal. While deeper responses correlate with longer progression-free intervals (PFS), the impact of depth of response through fixed-duration therapy on overall survival (OS) in WM patients remains uncertain.

Methods: This international, multicenter study aimed to evaluate the prognostic significance of depth of response achieved with fixed-duration frontline treatment using landmark survival analysis. Major response (MaR) was defined as achieving partial response (PR), very good partial response (VGPR), or complete response (CR).

Results: The study included 440 patients with WM who underwent frontline fixed-duration regimens. Patient characteristics are shown in Table 1. Attaining MaR was associated with superior outcomes, including longer OS. Patients achieving a MaR at 6 months demonstrated a 5-year PFS rates of 50% compared to 32% for those who did not ($p < 0.001$). Similarly, the 5-year OS rates were 89% for patients achieving MaR at 6 months versus 70% for those who did not ($p < 0.001$), Figure 1. In multivariable analysis, achieving MaR at 6 months independently predicted superior PFS (HR 0.66, $p = 0.007$) and OS (HR 0.28, $p < 0.001$), Table 2. Similar findings were observed when considering deeper responses (CR + VGPR vs. PR).

Conclusion: This study demonstrates that depth of response at 6 months with fixed-duration frontline treatment is an important prognostic indicator in WM, independently predicting both PFS and OS. These results underscore its relevance as a suitable endpoint in clinical studies in WM.

Table 1. Baseline Patient Characteristics

	Count (%) or Median (Range)
Age at diagnosis	65.7 (36-94.5)
Sex, male	261 (59.3%)
Hemoglobin at diagnosis (g/dL)	10.5 (3.6-17.1)
Platelet count at diagnosis (10^9/L)	219 (5-580)
Serum ß2-microglobulin at diagnosis (mg/L)	3.1 (0-30)
Serum IgM at diagnosis (mg/dL)	3470 (80-63321)
Bone marrow involvement at diagnosis (%)	50 (10-100)
IPSSWM	
Low risk	67 (21%)
Intermediate Risk	88 (27.6%)
High Risk	164 (51.4%)
Missing	121
MYD88^{L265P} mutation status	
Positive	198 (88%)
Negative	25 (12%)
Missing	217
Treatment Regimen	
DRC	224 (51.5%)
BR	133 (30.6%)
BDR	78 (17.9%)
Missing	5

Table 2. Multivariate Cox proportional-hazard regression model for PFS at 6 months

	PFS		**OS**	
	6 months			
Characteristic	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age >65 years at treatment	1.30 (0.91-1.85)	0.14	7.52 (2.78-20.35)	**<0.001**
High IPSSWM	1.23 (0.87-1.74)	0.23	0.78 (0.38-1.64)	0.52
MaR at 6 months	0.66 (0.49-0.89)	**0.007**	0.28 (0.15-0.51)	**<0.001**

Figure 1: Time-to-event outcomes for patients attaining a MaR at 6 months after frontline fixed-duration therapy

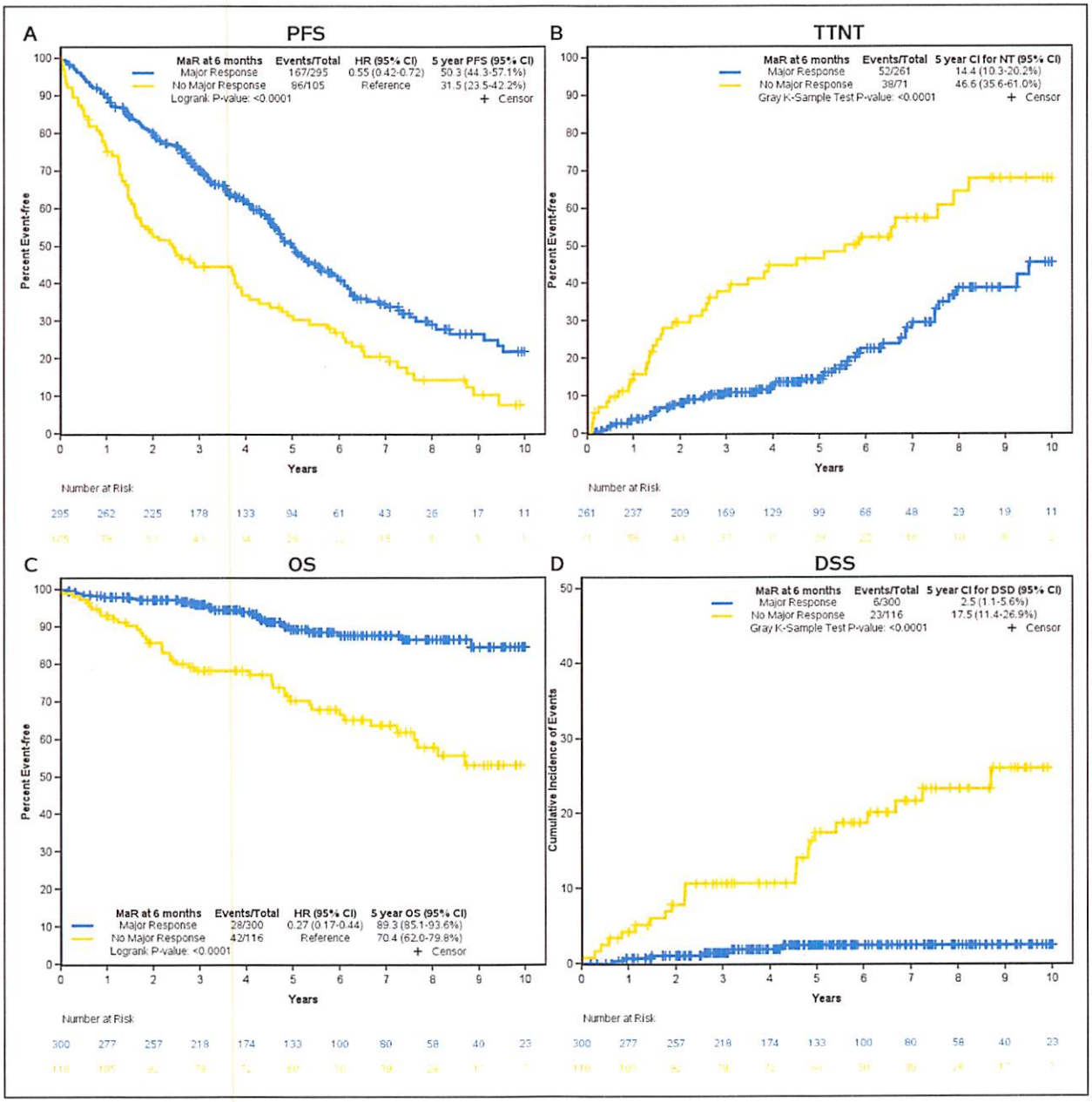

Figure 1. (A) Kaplan-Meier analysis of progression free survival (PFS) curve; (B) Cumulative incidence function analysis of Time-to-next-treatment (TTNT); (C) Kaplan-Meier analysis of Overall Survival (OS); (D) Cumulative incidence function analysis of Disease Specific Survival (DSS). All x-axes represent time since 6-month landmark.