Siltuximab is associated with improved progression-free survival in iMCD

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Supplementary Material

Supplementary Methods

Overall survival was defined as the time from randomization until death by any cause.

Tumour response was scored according to modified Cheson criteria, where tumor complete response (CR) was defined as complete disappearance of all measurable and evaluable disease. Tumor partial response (PR) was defined as a ≥50% decrease in the sum of the product of the diameters (SPD) of index lesion(s), with at least stable disease (SD) in all other evaluable disease. Tumor SD was defined as failure to attain CR or PR without evidence of progressive disease (PD). Tumor PD was defined by a ≥50% increase in SPD of index lesion(s) compared with nadir, or at least 1 new lesion that had been confirmed and measured >1.5 cm in longest dimension. Malignant transformation in a previously defined mass was also considered PD.

Lymph node response was defined as the time from baseline to a reduction of 50% or greater in SPD. Patients not achieving SPD normalization were censored at the time of last assessment for SPD, with death prior to SPD normalization considered as a competing risk.

Symptomatic response was calculated based on the 34 multicentric Castleman disease (MCD)-related signs and symptoms according to the NCI-CTCAE v4.0 (US National Cancer Institute, Common Terminology Criteria for Adverse Events v.4.0). A symptomatic response (PR and CR) was defined as a ≥50% reduction in the overall MCD-related symptom score.

A durable symptomatic response (PR and CR) was defined as a 50% reduction in the baseline MCD-related overall symptom score that was maintained for a minimum of 18 months.

Time to symptomatic response was defined as the time from randomization to the first evidence of symptomatic response. Time to complete symptomatic response was defined as the time from randomization to the first evidence of complete symptomatic response. The duration of symptomatic response was defined as the time from randomization to the first documented evidence of symptom progression prior to treatment failure. Patients not achieving the 34-point score normalization were censored at the time of last assessment for the 34-point score, with death prior to the score.

Durable tumor and symptomatic response was assessed by radiologic imaging and disease assessments, and was defined by either CR or PR, maintained for a minimum of 18 months.

Time to treatment failure for patients treated with siltuximab and placebo in the phase 2 study has been reported previously.[1] Here, we describe treatment failures in more detail and compare 6-month estimates for time to treatment failure between the two groups. A notable difference within this analysis compared with the primary analysis of the phase 2 study is the use of the cumulative incidence competing risk methodology to estimate the distribution of time to treatment failure, modeling death prior to treatment failure as a competing risk.[2]

Treatment failure was defined as a sustained increase in grade ≥2 disease-related symptoms persisting ≥3 weeks; new disease-related grade ≥3 symptoms; sustained >1-point increase in Eastern Cooperative Oncology Group performance status persisting for ≥3 weeks; or radiological progression by modified Cheson criteria or initiation of another treatment for iMCD.

References

1. van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 2014;15:966-974.
2. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496-509.

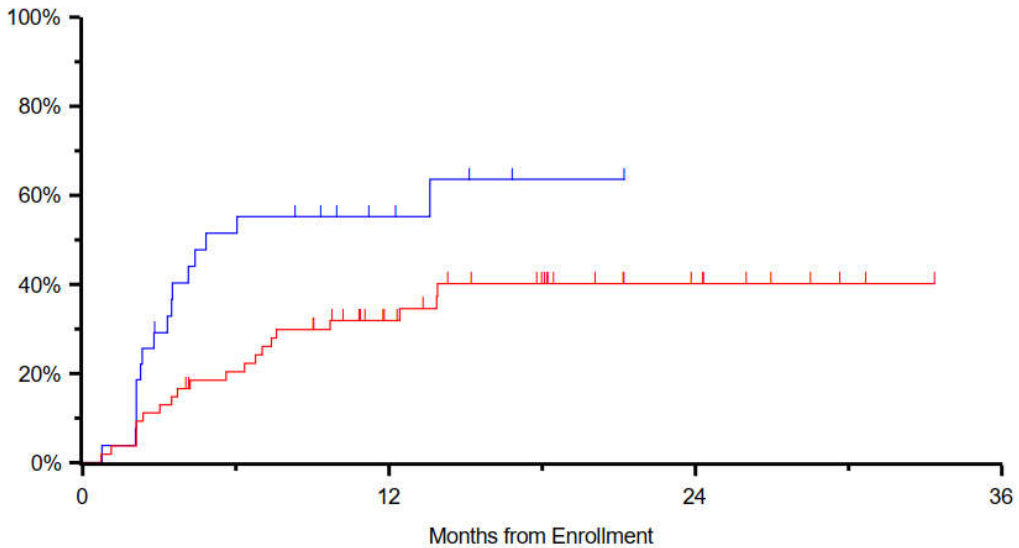
Supplementary Tables and Figures

Supplementary Table 1. Reasons for treatment failure in patients treated with siltuximab or placebo

Reason for treatment failure	Siltuximab arm (n = 53)	Placebo arm (n = 26)	Total (N = 79)
Radiologic progression	1	6	7
Initiation of therapy for MCD	5	0	5
Sustained increase in MCD symptom	11	8	19
Onset of any new disease-related ≥3 symptom	2	1	3
Sustained increase in MCD symptom/onset of any new disease-related ≥3 symptom	1	0	1
Sustained increase in MCD symptom/onset of any new disease-related ≥3 symptom/increase of more than 1 in ECOG score from baseline	0	1	1
Total treatment failures	**20**	**16**	**36**

MCD, multicentric Castleman disease; ECOG, Eastern Cooperative Oncology Group.

Supplementary Figure 1. Cumulative incidence curve for time to treatment failure in patients treated with siltuximab or placebo



Supplementary Figure 2. Sequence of normalization of laboratory, clinical, and lymph node responses in siltuximab responders (those achieving a durable tumor [radiologic] and symptomatic response; n=18)