MultipleMyelomaHub

General MM

Siltuximab for high-risk smoldering multiple myeloma

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This month, the Multiple Myeloma (MM) Hub are focussing on the educational theme of smoldering multiple myeloma (SMM). Here, the MM Hub report the results of a study by Timothy A. Brighton, Prince of Wales Hospital, New South Wales, AU, and colleagues, which investigated the use of siltuximab in patients with high-risk SMM. The results were originally published in *Clinical Cancer Research*.[1]

Background[1]

The current standard-of-care for SMM is observation and monitoring, with no treatment currently recommended for early intervention. However, several studies have recently shown that early intervention can be beneficial, specifically in high-risk patients. These studies include the EA306 study, presented at the American Society of Clinical Oncology (ASCO) meeting 2019, and the GEM-CESAR study, presented at the European Hematology Association (EHA) meeting 2019.[2,3]

This randomized, double-blind, placebo-controlled, multicenter study investigated the use of siltuximab, a monoclonal antibody that directly targets interleukin 6 (IL6), in patients with high-risk SMM. IL6 is a critical growth factor for MM cells; therefore, the study investigators hypothesized that siltuximab would block IL6 and prevent progression of SMM to active disease.

Study design[1]

Given as siltuximab versus placebo unless otherwise stated

- Patients had high-risk SMM for less than four years and an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 with:
  - Bone marrow plasma cells (BMPC) ≥10% and serum monoclonal (M)-protein >3 g/dL or abnormal free light chain (FLC) ratio <0.126 or >8 or serum M protein ≥1–3 g/dL
- Patients were randomized to receive either:
  - Siltuximab (n = 43): 15 mg/kg, one hour intravenous infusion every four weeks
    - Given until disease progression to symptomatic MM, unacceptable toxicity, withdrawal of consent or study end
  - Placebo (n = 42)
- Patient characteristics:
  - High-risk cytogenetics: 65% *vs* 82%
  - Ultra-high risk SMM by International Myeloma Working Group 2014 (IMWG) criteria[4] (>60% plasma cells or high risk FLC ratio [≤01 or ≥100] at baseline): 23% *vs* 41%

- Primary endpoint: 1-year progression-free survival (PFS) as per 2014 IMWG criteria[4]
- Secondary endpoints: progressive disease indicator rate, progression-free survival (PFS) and safety
    - Median age: 62 (21-84)
    - ECOG score of 0: 87%
    - Male patients: 57%
    - White patients: 85%
    - Median follow-up: 29.2 months

Efficacy[1]

Table 1: Efficacy of siltuximab *versus* placebo

	Siltuximab (n= 43)	Placebo (n= 42)
1-year PFS (95% CI)	84.5% 68.6–92.8	74.4% 57.3–85.5
PFS events at median follow-up 29.2 months	32.6%	42.9%
Median PFS (95% CI)	Not reached (NR)	23.5 months
Median overall survival (OS)	NR	NR
Post-hoc analysis		
Median PFS* (95% CI)	NR	40.5 months

* 10 patients in placebo and 17 in siltuximab groups reclassified and removed from analysis based on biomarkers

Siltuximab led to an absolute improvement in 1-year PFS rate of 10.1% meaning the study did not meet the hypothesized improvement of 14%. With regards to median PFS, the hazard ratio (HR) was 0.50 (0.24–10.4) with a *p* value of 0.0597.

The median PFS from the *post-hoc* analysis is shown in **Table 1,** with a HR of 0.610 (0.212–1.753) and a *p* value of 0.354. This data indicates siltuximab may prolong progression of SMM to active MM.

Safety[1]

Adverse events (AEs) reported within both arms of the study are shown in **Table 2.** The most common serious AEs (SAEs) were:

- Infections/infestations: 12% (n = 5) *vs* 14% (n = 6)
- Renal/urinary disorders: 2% (n = 1) *vs* 7% (n = 3)

Table 2: AEs and SAEs in the siltuximab and placebo arm

	Siltuximab (%, [n])	Placebo (%, [n])
≥1 AE	100% (43)	100% (42)
Grade ≥3 AEs	47% (20)	33% (14)
AE leading to dose delay	35% (15)	14% (6)
AE leading to discontinuation	21% (9)	7% (3)
SAE	30% (13)	31% (13)
Mortality*	2% (1)	5% (2)

*Seven patients in total died during the study. Deaths shown in this table occurred within 30 days of last dose.

Overall, siltuximab was well-tolerated with a comparable safety profile to placebo.

Conclusion[1]

The study did not meet the prespecified protocol hypothesis criteria that administration of siltuximab would increase 1-year PFS by 14% in patients with high-risk SMM.

The authors believe siltuximab may delay progression from SMM to active MM disease, though as monotherapy, siltuximab is unlikely to be investigated further. This is due to changing definitions of ultra-high-risk disease, and other more effective agents being available.

References

1. Brighton T.A. *et al*., Randomized, double-blind, placebo-controlled, multicenter study of siltuximab in high-risk smoldering multiple myeloma. 2019 March 19. Clin Canc Res. DOI: 10.1158/1078-0432.CCR-18-3470
2. Lonial S. *et al*., E3A06: Randomized phase III trial of lenalidomide versus observation alone in patients with asymptomatic high-risk smoldering multiple myeloma. 2019 Jun 02. Abstract #8001.American Society of Clinical Oncology meeting, Chicago, US.
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