Clinical Trial Brief Report

Clinical Cancer Research

Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Siltuximab in High-Risk Smoldering Multiple Myeloma

Timothy A. Brighton[1], Amit Khot[2], Simon J. Harrison[2,3], David Ghez[4], Brendan M. Weiss[5], Andres Kirsch[6], Hila Magen[7], Mercedes Gironella[8], Albert Oriol[9], Matthew Streetly[10], Britte Kranenburg[11], Xiang Qin[12], Rajesh Bandekar[12], Peter Hu[13], Mary Guilfoyle[13], Ming Qi[12], Sepideh Nemat[14], and Hartmut Goldschmidt[15]

Abstract

Purpose: IL6 is important for the growth and survival of myeloma cells. This study evaluated blocking IL6 with siltuximab to delay the transition from high-risk smoldering multiple myeloma (SMM) to multiple myeloma.

Patients and Methods: In a randomized, double-blind, placebo-controlled, multicenter study, 85 patients with high-risk SMM were randomized to 15 mg/kg siltuximab (43 patients) or placebo (42 patients). The primary endpoint was 1-year progression-free survival (PFS) rate, based on IMWG CRAB criteria. Secondary endpoints included progressive disease indicator rate, PFS, and safety.

Results: Median age was 62 years (range: 21–84); 57% were male and 87% had a baseline Eastern Cooperative Oncology Group score of 0. The 1-year PFS rate was 84.5% (siltuximab) and 74.4% (placebo). After a median follow-up of 29.2 months, 32.6% of PFS events occurred with siltuximab and 42.9% with placebo. Median PFS was not reached with siltuximab but was 23.5 months with placebo [HR 0.50 (95% confidence interval, 0.24–1.04); $P = 0.0597$]. The safety profile of siltuximab was comparable with placebo. Most adverse events in the siltuximab group were grade 2/3; the most common serious adverse events were infections/infestations, and renal/urinary disorders. Mortality was low in both groups (3 deaths in the siltuximab group and 4 in the placebo group).

Conclusions: Although this study did not meet the prespecified protocol hypothesis criteria, data suggest that siltuximab may delay the progression of high-risk SMM.

[1]Prince of Wales Hospital, Randwick, New South Wales, Australia. [2]Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia. [3]Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia. [4]Service d'Hématologie, Département de Médecine, Gustave Roussy Cancer Campus, Villejuif, France. [5]Division of Hematology-Oncology, Department of Medicine, Abramson Cancer Center and Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. [6]Medizinisches Versorgungszentrum Onkologischer Schwerpunkt am Oskar-Helene-Heim, Berlin, Germany. [7]Institute of Hematology, Davidoff Cancer Center, Beilinson Hospital, Rabin Medical Center, Petah-Tikva, Israel, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel. [8]Haematology Department, Hospital Universitario Vall d'Hebron, Barcelona, Spain. [9]Institut Català d'Oncologia, Institut Josep Carreras, Hospital Germans Trias i Pujol, Barcelona, Spain. [10]Clinical Haematology, Guys Hospital, Guys and St. Thomas' NHS Foundation Trust, London, United Kingdom. [11]Janssen Biologics BV, Leiden, Netherlands. [12]Janssen Research & Development, LLC, Spring House, Pennsylvania. [13]Janssen Research & Development, LLC, Raritan, New Jersey. [14]Janssen-Cilag Ltd, High Wycombe, United Kingdom. [15]University Hospital, Internal Medicine V and National Center for Tumor Diseases Heidelberg, Heidelberg, Germany.

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Corresponding Author: Hartmut Goldschmidt, University of Heidelberg, Im Neuenheimer Feld 410, Heidelberg 69120, Germany. Phone: 4962-2156-8003; Fax: 4962-2156-5647; E-mail: Hartmut.Goldschmidt@med.uni-heidelberg.de

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Introduction

Smoldering multiple myeloma (SMM) is an asymptomatic clonal plasma cell disorder (1), which is distinct from multiple myeloma because of the absence of end-organ damage. The overall risk of progression to symptomatic multiple myeloma is 10% per year for the first 5 years, 3% per year for the next 5 years, and only 1% per year beyond 10 years of follow-up (2).

Although approximately 60% of patients will eventually progress to multiple myeloma (3), the current standard-of-care for SMM is close patient monitoring with no specific treatment. At the time of study protocol development, high-risk SMM was defined as patients having both serum monoclonal M-protein $\geq$3 g/dL and bone marrow plasma cells (BMPC) $\geq$10% (4). For those patients in high-risk categories, the median time-to-progression is approximately 2 years and the risk of progression to multiple myeloma is approximately 70% in 5 years (4). Therefore, patients with high-risk SMM may achieve significant benefit from early treatment (5). We sought to evaluate the benefit of inhibiting IL6, a known critical growth factor for multiple myeloma, with siltuximab, a mAb that directly targets IL6.

Translational Relevance

IL6 is important for the growth and survival of myeloma cells. This randomized, double-blind, placebo-controlled, multicenter study of siltuximab in high-risk smoldering multiple myeloma (SMM) evaluated blockage of IL6 with siltuximab to delay the transition from high-risk SMM to multiple myeloma. The primary endpoint was 1-year progression-free survival (PFS) based on IMWG CRAB criteria. A total of 85 patients with high-risk SMM were randomly assigned to 15 mg/kg siltuximab (43 patients) or placebo (42 patients). After a median follow-up of 29.2 months, 32.6% of PFS events occurred with siltuximab and 42.9% with placebo. Median PFS was not reached with siltuximab but was 23.5 months with placebo [HR, 0.50 (95% confidence interval, 0.24–1.04); $P = 0.0597$]. The safety profile of siltuximab was similar to that of placebo. Although this study did not meet the prespecified protocol hypothesis criteria, data suggest that siltuximab may delay the progression of high-risk SMM.

Patients and Methods

In a randomized, double-blind, placebo-controlled, multicenter study, approximately 74 patients (37 per group) with high-risk SMM were planned to be randomized in a 1:1 ratio to 15 mg/kg of siltuximab or placebo administered as a 1-hour intravenous infusion every 4 weeks until progression to symptomatic multiple myeloma, unacceptable toxicity, withdrawal of consent, or the end of the study. Randomization stratification was based on the number of risk factors present for progression to symptomatic multiple myeloma (<2 risk factors vs. ≥2 risk factors) using the criteria from Bladé and colleagues (2) and Dispenzieri and colleagues (6).

Patients enrolled were at least 18 years of age with a diagnosis of high-risk SMM for <4 years (defined as BMPC ≥10% and either serum M-protein ≥3 g/dL, or abnormal free light chain ratio [<0.126 or >8] and serum M-protein ≥1 <3g/dL) and an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1. The primary endpoint was 1-year progression-free survival (PFS) rate (progression to symptomatic multiple myeloma as defined by CRAB-IMWG criteria; ref. 7). Secondary endpoints included progressive disease indicator rate and PFS.

Review boards at all participating institutions approved the study, which was conducted in accordance with the Declaration of Helsinki. Prior to any study-related procedures, all patients provided written informed consent.

Safety evaluations

Safety assessment was based on reported adverse events (AE), clinical laboratory tests, vital sign measurements, physical examinations, chest X-ray, and electrocardiogram findings.

Statistical analyses

Thirty-seven patients per treatment group would provide at least 87% probability to demonstrate that the 1-year PFS rate of siltuximab is higher than that of placebo if a 1-year PFS rate of 0.70 for placebo and 0.84 for siltuximab was observed. All efficacy analyses were based on intent-to-treat population. Time-to-progression to symptomatic multiple myeloma and overall survival were estimated using Kaplan–Meier methods, and significance was determined with a two-sided log-rank test. Safety analyses were restricted to patients who received at least one administration of study treatment.

Results/Discussion

Baseline characteristics/demographics

The original protocol projected enrollment of 100 patients but was amended and a total of 85 patients were enrolled. The two groups were similar except the placebo group had more patients with high-risk cytogenetic abnormalities [defined as: t(4;14), t(14;16), 17p deletion by FISH; t(4;14), 17p deletion by karyotype; siltuximab: 65%; placebo: 82%], and ultra-high-risk SMM by IMWG 2014 criteria [≥60% plasma cells or high-risk FLC ratio (≤0.01 or ≥100) at baseline; siltuximab: 23%; placebo: 41%].

The median age was similar across both treatment groups; 62 years (range, 21–84 years). More patients were men (48 patients; 57%), and white (72 patients; 85%) and had a baseline ECOG score of 0 (74 patients; 87%).

Efficacy

The primary efficacy endpoint, 1-year PFS rate, was assessed by prespecified CRAB criteria, and based on the ITT population. The 1-year PFS rate was 84.5% [95% confidence interval (CI), 68.6–92.8] in the siltuximab group and 74.4% (95% CI, 57.3–85.5) in the placebo group (Table 1). An absolute improvement of 10.1% was observed, which indicated that the study did not meet the prespecified hypothesis that siltuximab would increase the 1-year PFS rate by at least 14%. After a median follow-up of 29.2 months, 32.6% of PFS events occurred with siltuximab and 42.9% with placebo (Fig. 1). Median PFS was not reached with siltuximab but was 23.5 months with placebo. The HR of PFS (siltuximab vs. placebo) was 0.50 (95% CI, 0.24–1.04; $P = 0.0597$). Median overall survival was not reached in either group by the end of the study.

While the study was ongoing, there were major advances in the diagnosis, prognosis, and management of SMM including a revised disease definition (8), identification of several new prognostic factors, a classification based on underlying cytogenetic changes, and new treatment options. Importantly, a subset of patients previously considered SMM were reclassified as multiple myeloma based on biomarkers. In a *post hoc* analysis, removing these reclassified patients (10, siltuximab; 17, placebo), 33 (76.7%) remained in the siltuximab group and 25 (59.5%) remained in the placebo group. Median PFS was not reached with siltuximab but was 40.5 months (95% CI, 21.1–40.5) for the placebo group (Table 1), HR 0.610 (95% CI, 0.212–1.753; $P = 0.354$). These results are consistent with the overall PFS analysis, which indicated that siltuximab may delay the progression of patients with SMM.

Safety

All patients reported 1 or more AE (Table 1), and the incidence of grade 3 or higher AEs was higher in the siltuximab group compared with placebo (47% vs. 33%); however, <5% of the patients in siltuximab group had grade 4 AEs. Adverse events leading to dose delay and discontinuation of study treatment were higher in the siltuximab group (35% and 21%) compared with placebo group (14% and 7%),

Table 1. Summary of PFS; ITT population and ultra-high-risk population. Overview of treatment-emergent adverse events and number of patients with 1 or more treatment-emergent adverse events with frequency of at least 10%

	Placebo	Siltuximab
Patients in ITT population	42	43
PFS (days)[a]		
N	42	43
Median	715.0	NE
95% CI of median	(490–1,232)	(703–NE)
Observed	18 (42.9%)	14 (32.6%)
Censored	24 (57.1%)	29 (67.4%)
P[b]		0.0597
HR (95% CI)[c]		0.503 (0.243–1.042)
1-year PFS rate % (95% CI)	74.4 (57.3–85.5)	84.5 (68.6–92.8)
1-year PFS rate % (95% CI)		
Risk factor <2	100.0 (100.0–100.0)	89.3 (63.2–97.2)
Risk factor ≥2	48.1 (24.2–68.6)	79.8 (54.4–91.9)
Patient in ITT population: No ultra-high-risk pts	25	33
PFS (days)[a]		
N	25	33
Median	1,232	NE
95% CI of median	(641–1,232)	(898–NE)
Observed	7 (28.0%)	8 (24.2%)
Censored	18 (72.0%)	25 (75.8%)
P[b]		0.3540
HR (95% CI)[c]		0.610 (0.212–1.753)
Patients in safety-evaluable population	42	43
Total number of patients with AEs	42 (100.0%)	43 (100.0%)
At least one reasonably related to siltuximab/placebo	22 (52.4%)	25 (58.1%)
Maximum toxicity grade		
Grade 1	5 (11.9%)	2 (4.7%)
Grade 2	23 (54.8%)	21 (48.8%)
Grade 3	12 (28.6%)	17 (39.5%)
Grade 4	0	2 (4.7%)
Grade 5	2 (4.8%)	1 (2.3%)
Grade ≥3	14 (33.3%)	20 (46.5%)
Any SAE	13 (31.0%)	13 (30.2%)
AEs leading to siltuximab/placebo dose delay	6 (14.3%)	15 (34.9%)
AEs leading to discontinuation of siltuximab/placebo	3 (7.1%)	9 (20.9%)
Patients in safety-evaluable population	42	43
Back pain	12 (28.6%)	10 (23.3%)
Nasopharyngitis	15 (35.7%)	9 (20.9%)
Nausea	10 (23.8%)	9 (20.9%)
Asthenia	3 (7.1%)	8 (18.6%)
Cough	8 (19.0%)	8 (18.6%)
Neutropenia	1 (2.4%)	8 (18.6%)
Anemia	6 (14.3%)	6 (14.0%)
Diarrhea	7 (16.7%)	6 (14.0%)
Fatigue	14 (33.3%)	6 (14.0%)
Headache	9 (21.4%)	6 (14.0%)
Rash	0	6 (14.0%)
Arthralgia	11 (26.2%)	5 (11.6%)
Constipation	7 (16.7%)	5 (11.6%)
Musculoskeletal chest pain	9 (21.4%)	5 (11.6%)
Pain in extremity	8 (19.0%)	5 (11.6%)
Pneumonia	2 (4.8%)	5 (11.6%)
Thrombocytopenia	0	5 (11.6%)
Upper respiratory tract infection	10 (23.8%)	5 (11.6%)
Abdominal pain	6 (14.3%)	3 (7.0%)
Dizziness	6 (14.3%)	3 (7.0%)
Pyrexia	6 (14.3%)	3 (7.0%)
Oropharyngeal pain	10 (23.8%)	2 (4.7%)
Chest pain	5 (11.9%)	1 (2.3%)
Influenza-like illness	5 (11.9%)	1 (2.3%)
Epistaxis	5 (11.9%)	0
Muscle spasms	5 (11.9%)	0

(Continued on the following column)

Table 1. Summary of PFS; ITT population and ultra-high-risk population. Overview of treatment-emergent adverse events and number of patients with 1 or more treatment-emergent adverse events with frequency of at least 10% (Cont'd)

Abbreviations: Ultra-high-risk, ≥60% plasma cells or high-risk FLC ratio (≤0.01 or ≥100) at baseline; NE, not estimable

[a]Kaplan–Meier estimates (n = number of patients at risk).

[b]P value is based on the log-rank test adjusted for the stratification factors.

[c]HR and 95% CI from a Cox proportional hazards model adjusted for the stratification factor.

respectively. Grade 5 AEs were low in both groups (2% in the siltuximab group and 5% in the placebo group).

The incidence of serious AEs (SAE) was balanced between the treatment groups. At least 1 SAE occurred in 13 patients (30%) and 13 patients (31%) in the siltuximab and placebo groups, respectively. The most common SAEs, by system organ class, included infections and infestations [5 patients (12%) siltuximab; 6 patients (14%) placebo], and renal and urinary disorders [1 patient (2%) siltuximab; 3 patients (7%) placebo]. Three patients reported SAEs assessed as related to study drug.

Seven patients died during the study, including 3 patients in the siltuximab group and 4 patients in the placebo group. Three patients, one in the siltuximab group and two in the placebo group, died due to an AE within 30 days of last dose. The patient in the siltuximab group died due to pneumonia, assessed as possibly unrelated to treatment, while the patients in the placebo group died due to cardiac arrest and ischemia, both unrelated to study treatment. Two patients in the placebo group, died due to disease progression and septic shock, respectively, and 2 patients in the siltuximab group died of unknown cause, all occurring more than 30 days after last dose.

This study suggests that siltuximab may delay the disease progression in patients with high-risk SMM; however, the prespecified hypothesis that siltuximab would increase the 1-year PFS rate by at least 14% was not met. Siltuximab as single agent is unlikely to be investigated further due to other more effective agents and the changed definition of ultra-high-risk disease. Consistent with earlier studies, siltuximab was well tolerated and no additional safety concerns were identified.

Disclosure of Conflicts of Interest

A. Khot is a consultant/advisory board member for Janssen Oncology, Celgene, and Amgen. S.J. Harrison reports receiving commercial research grants and speakers bureau honoraria from and is a consultant/advisory board member for Janssen Cilag. B.M. Weiss is an employee of Janssen Research and Development. A. Oriol reports receiving speakers bureau honoraria from and is a consultant/advisory board member for Amgen, Celgene, and Janssen. P. Hu holds ownership interest (including patents) in the form of stock in Johnson & Johnson. S. Nemat holds ownership interest (including patents) in the form of stocks in Johnson & Johnson. H. Goldschmidt reports receiving speakers bureau honoraria from Celgene, Janssen, Novartis, Chugai, Bristol-Myers Squibb, and ArtTempi. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: R. Bandekar, M. Qi, H. Goldschmidt

Development of methodology: R. Bandekar, M. Guilfoyle, M. Qi, H. Goldschmidt

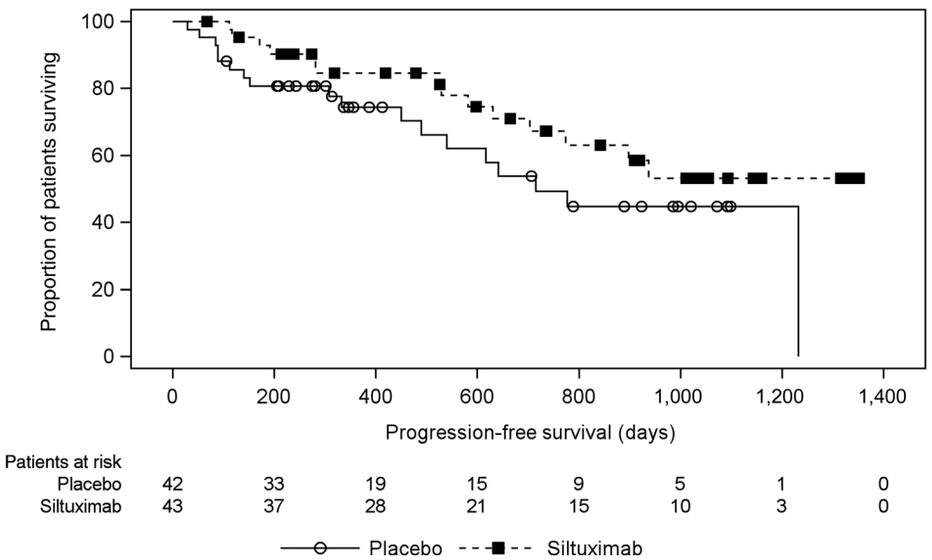

Figure 1.
Progression-free survival: Kaplan–Meier estimate; intention-to-treat population.

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T.A Brighton, A. Khot, S.J. Harrison, D. Ghez, B.M. Weiss, A. Kirsch, M. Gironella, A. Oriol, M. Qi

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T.A Brighton, A. Khot, B.M. Weiss, A. Oriol, X. Qin, R. Bandekar, P. Hu, M. Guilfoyle, M. Qi, H. Goldschmidt

Writing, review, and/or revision of the manuscript: T.A Brighton, A. Khot, S.J. Harrison, D. Ghez, B.M. Weiss, M. Gironella, A. Oriol, M. Streetly, B. Kranenburg, R. Bandekar, P. Hu, M. Guilfoyle, M. Qi, S. Nemat, H. Goldschmidt

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Qi

Study supervision: A. Oriol, M. Streetly, M. Guilfoyle, M. Qi, H. Goldschmidt

Other (patient recruitment): H. Magen

Other (medical review of clinical data): B. Kranenburg

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Investigators: Australia: T.A. Brighton, S.J. Harrison, A. Khot; Belgium: L. Noens, K. Wu; France: L. Benboubker, D. Ghez; Germany: H. Goldschmidt, A. Kirsch, H.J. Salwender; Israel: D. Ben-Yehuda, A. Braester, S. Bulvik, G. Lugassy, H. Magen; South Korea: D.Y. Jo, K. Kim, C.K. Min; Spain: J. De la Rubia, M. Gironella, J.A. Hernandez, M.V. Mateos, A. Oriol, L. Rosinol, A.I. Teruel; United Kingdom: J. Cavenagh, S. Kulkarni, M. Streetly; United States: J. Fay, P. Kuriakose, A. Lesokhin, C Rosenbaum, G. Spitzer, B.M. Weiss.

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