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R&D INSIGHT REPORT

Siltuximab: First Global Approval

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Abstract The anti-interleukin-6 (IL-6) chimeric monoclonal antibody siltuximab is the first drug to be approved for the treatment of multicentric Castleman's disease (MCD) in the US and European union (EU), having gained approval under the FDA priority review program in the US and from an accelerated assessment and recommendation by the Committee for Medicinal Products for Human Use (CHMP) in the EU. Development of the drug is continuing in smoldering multiple myeloma. This article summarizes the milestones in the development of siltuximab leading to this first approval for MCD.

1 Introduction

Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disorder with high morbidity that is caused by dysregulated interleukin-6 (IL-6) production. Although not a malignancy, the multicentric form of this disease has similarities to lymphoma, and patients can progress to non-Hodgkin's lymphoma. While human herpesvirus-8 (HHV-8) is now well established as the cause of MCD in HIV-positive and some HIV-negative patients, there is a group of HIV- and HHV-8-negative MCD patients. The aetiology of MCD in these patients is unknown, but several possible processes have been proposed including viral, inflammatory and neoplastic. It has been proposed that this form of MCD be called idiopathic MCD. Current treatment options for MCD include cytotoxic chemotherapy, antiviral agents, interferon-α, corticosteroids, and targeted immunotherapy [1–3]. The humanised anti-IL-6 receptor monoclonal antibody tocilizumab is approved in Japan for the treatment of unspecified Castleman's disease [4].

Siltuximab is an IL-6 chimeric monoclonal antibody developed by Janssen Research and Development (formerly Centocor) for the treatment of MCD and various other disorders where overproduction of IL-6 is believed to have a role. Siltuximab is the first approved treatment in the US for MCD, and this is the first global approval for the drug [5]. It was reviewed under the FDA priority review program, which provides an expedited review for drugs that have the potential to provide a significant improvement in safety or effectiveness in the treatment of a serious condition. The drug was also granted orphan product designation [6]. Siltuximab is approved for the treatment of patients with MCD who are HIV and HHV-8 negative. It was not studied in MCD patients who are HIV or HHV-8 positive because it did not bind to virally produced IL-6 in a nonclinical study. The recommended dosing regimen for siltuximab is 11 mg/kg given over 1 h by intravenous (IV) infusion every 3 weeks [7]. The drug was subsequently approved for the same indication in the EU, following an accelerated assessment and recommendation from Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency [8, 9]. Siltuximab is also the first agent to be approved in the EU for the treatment of patients with MCD.

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Features and properties of siltuximab

Alternative names	Sylvant™, CNTO 328
Class	Monoclonal-antibodies
Mechanism of action	Interleukin 6 inhibitor
Route of administration	Intravenous infusion
Pharmacodynamics	Interleukin-6 inhibitor. Associated with sustained reductions in IL-6 levels and various other cytokines/markers
Pharmacokinetics	Mean C_{max} at steady state 332 μg/ml (42 % coefficient of variation), mean serum pre-dose trough value 84 μg/ml (78 % coefficient of variation) [7]
Adverse events	
Most frequent	Pruritus, weight gain, skin rash, hyperuricaemia, and upper respiratory tract infection oedema [7]
Occasional	Thrombocytopenia, lower respiratory tract infection, constipation, hypertrygliceridaemia, oropharyngeal pain, renal impairment, headache, skin hyperpigmentation, eczema, psoriasis, dry skin, hypercholesterolemia, headache, hypotension [7]
ATC codes	
WHO ATC code	L01X-C (monoclonal antibodies)
EphMRA ATC code	L1X3 (antineoplastic monoclonal antibodies)
Chemical name	Immunoglobulin G1, anti-(human interleukin 6) (human-mouse monoclonal CNTO 328 heavy chain), disulfide with human-mouse monoclonal CNTO 328 κ-chain, dimer

Development of siltuximab as a treatment for smoldering multiple myeloma is ongoing; however, development of the drug as a treatment for advanced multiple myeloma, myelodysplastic syndrome, hormone-refractory prostate cancer and ovarian cancer has been discontinued. Clinical trials of siltuximab have also been conducted in patients with non-Hodgkin's lymphoma and renal cancer but development in these indications also appears to be discontinued.

2 Scientific Summary

2.1 Pharmacodynamics

2.1.1 Preclinical Trials

In in vitro studies siltuximab has been shown to inhibit IL-6-induced Stat3 activation, nuclear translocation and downstream gene expression in ovarian cancer cells [10], and induced apoptosis in a model of advanced prostate cancer [11]. The drug was cytotoxic alone—and markedly enhanced the cytotoxicity of dexamethasone and melphalan—in human myeloma cell lines [12, 13].

2.1.2 Clinical Trials

Up to 3 doses of siltuximab 6 mg/kg were associated with higher levels of markers of proliferation and apoptosis compared with no treatment in patients with prostate cancer. Decreased phosphorylation of Stat3 and p44/p42 mitogen-activated protein kinases, and down-regulation of genes immediately downstream of the IL-6 signalling pathway were also observed [14].

Siltuximab produced a rapid and sustained reduction in endogenous IL-6 production in nine patients with multiple myeloma who participated in a phase I trial. IL-6 production declined from a median 60 μg/day at baseline to below 3 μg/day immediately after commencement of treatment, and remained suppressed during the 100 day study period [15]. In a phase II study of siltuximab in 18 patients with advanced platinum-resistant ovarian cancer, plasma levels of tumour necrosis factor (TNF)-α, IL-8 and vascular endothelial growth factor declined markedly in one patient who had a partial response. TNF-α and IL-8 were significantly lower in the patient who responded and in 7 who had stable disease, compared to patients who did not respond [16].

An analysis of data from several trials reported that siltuximab reduced C-reactive protein levels—which are directly correlated to IL-6 levels—generally to below detectable limits [17]. Marked sustained reductions in serum C-reactive protein and amyloid A have also been observed in patients with metastatic renal cell carcinoma during treatment with siltuximab [18]. Modelling based on data from a phase I study of siltuximab in patients with non-Hodgkin's lymphoma, multiple myeloma or Castleman's disease predicted the drug at a dose of 11 mg/kg every 3 weeks would reduce serum C-reactive protein levels to below the lower level of quantification, but that less intensive schedules, such as 5.5 mg/kg every 2 weeks would not [19]. Patients with Castleman's disease treated

with siltuximab 12 mg/kg every 3 weeks had a 77 % median reduction in C-reactive protein levels after 3 cycles of treatment compared with a 52 % median reduction in those given the drug at a dosage of 9 mg/kg every 3 weeks [20]. Because of a difference in the absorptivity constant used for calculating the dose of study drug administered (≈9% difference), the dose that was intended to be administered (12 mg/kg) was actually 11 mg/kg.

2.2 Pharmacokinetics

The pharmacokinetic parameters of siltuximab have been examined in a phase I study in patients with Castleman's disease, non-Hodgkin's lymphoma or multiple myeloma; pharmacokinetic data were reported for 37 of 67 enrolled patients. Six cohorts of patients received IV infusions of siltuximab at a dose of 3–12 mg/kg once every 1–3 weeks for 43 days. Siltuximab serum concentrations declined in a bi-exponential manner; mean t½ and clearance were 17.73–20.64 days and 4.03–4.59 ml/day/kg, respectively, after the first dose. Maximum plasma concentrations and AUC_{0-t} increased in an approximately dose proportional manner after both the first and repeated doses. Accumulation after repeated doses to steady-state was consistent with t½. There was no apparent variation in the pharmacokinetics of the drug when values in patients with Castleman's disease, non-Hodgkin's lymphoma and multiple myeloma were compared [20]. Similar pharmacokinetic parameters were observed in a Phase I/II, two-part, open-label, multiple-dose, dose-escalation study of siltuximab in patients with solid tumours [21].

2.3 Therapeutic Trials

2.3.1 Multicentric Castleman's Disease

The efficacy of siltuximab as treatment for MCD has been evaluated in a phase II randomised, double-blind, placebo-controlled study (MCD2001). 79 patients with newly diagnosed or previously treated idiopathic MCD were randomised 2–1 to treatment with IV siltuximab 11 mg/kg every 3 weeks. Treatment was given until treatment failure, at which point patients in the placebo group could cross over to unblinded siltuximab. The primary analysis of efficacy was conducted at 48 weeks. 34 % of 56 siltuximab recipients experienced durable tumour response (1 complete and 17 partial responses) and improvement in symptoms compared with none in the placebo group ($p = 0.0012$). The median duration of tumour response and improvement in symptoms was 340 days, suggesting prolonged disease control. The tumour response rate—as measured by central radiology review—was 38 % in patients treated with siltuximab compared with 4 % in the placebo group ($p = 0.0022$). No treatment failures were observed during the study in patients treated with siltuximab compared to a median time to treatment failure of 134 days in the placebo group ($p = 0.0013$). The durable symptomatic response rate was 57 versus 19 % ($p = 0.0018$) with complete symptom resolution seen in 25 % of siltuximab versus no placebo recipients. Haemoglobin levels improved by ≥15 g/l by week 13 in 61 % of anaemic patients treated with siltuximab compared with none in the placebo group ($p = 0.0002$). Siltuximab therapy was also associated with sustained reductions in C-reactive protein and fibrinogen levels, and increased albumin levels. 13 of 26 patients randomised to placebo were crossed over to siltuximab [22].

Efficacy data are available for 37 patients with Castleman's disease who participated in a phase I open-label dose-finding study. Seven cohorts of patients received IV infusions of siltuximab at a dose of 3–12 mg/kg once every 1–3 weeks. In 6 cohorts the drug was given for 43 days with responders able to receive extended treatment at the investigators discretion; patients in the seventh cohort were treated until disease progression or the emergence of unacceptable or unmanageable treatment-related toxicity. Of 36 patients evaluable according to central radiological review the best response was complete response in one patient, partial response in 11, unconfirmed partial response in three, stable disease in 20 (median 6.2 months), and progressive disease in one. The one patient with complete response and 10 of 11 partial responders did not have progressive disease at the end of the study. All but 3 of the 12 responders received siltuximab at a dose of 12 mg/kg. All 37 patients were evaluable for clinical benefit response. Of these, 78 % improved in fatigue, 65 % in the size of the largest lymph node, 60 % in weight and 51 % in fever/night sweats. In addition, mean haemoglobin level increased 1–2 g/dl over time in all groups. Median follow-up was 2.4 years during which only 3 patients (8 %) died [20]. 19 patients enrolled in this study continued to receive siltuximab in a phase II extension study. At the start of the extension study one patient had complete response, 11 had partial response and 7 had stable disease. IV siltuximab was administered at a dose of 11 mg/kg every three weeks on an ongoing basis. At an interim analysis after a median follow-up of 5.1 years the overall survival rate was 100 %. All 19 patients have sustained disease control (stable disease or better) including eight who had their dosing interval increased to once every 6 weeks after achieving prolonged partial or complete response [23]. Analysis of computed tomography scans prospectively collected in this study indicated a >1 kg gain (mean 2.3 kg) in muscle mass in 38 % of patients, stable muscle mass, gain or loss <1 kg in 47 % and a loss of >1 kg (mean 3.1 kg) in 15 % [24].

Clinical trials of siltuximab

Drug regimen	Indication	Study phase	Status	Study location	Trial identifiers	Sponsor
Siltuximab (plus best supportive care)	MCD	II	Ongoing, not recruiting	Multinational	NCT01024036	Janssen Research & Development
Siltuximab	MCD	II (extension trial)	Ongoing, but not recruiting	Multinational	NCT01400503	Janssen Research & Development
Siltuximab	MCD, multiple myeloma and non-Hodgkin's lymphoma (monotherapy, second-line therapy or greater)	I	Completed	USA	NCT00412321	Centocor
Siltuximab	Smouldering multiple myeloma (first-line therapy, monotherapy)	II	Recruiting	Multinational	NCT01484275	Janssen Research & Development
Siltuximab (in combination with bortezomib and dexamethasone)	Multiple myeloma (combination therapy, second-line therapy or greater)	III	Withdrawn prior to enrolment	Multinational	NCT01266811	Centocor
Siltuximab (in combination with bortezomib)	Multiple myeloma (combination therapy, second-line therapy or greater)	II	Ongoing, not recruiting	Multinational	NCT00401843	Janssen Research & Development
Siltuximab (in combination with bortezomib, melphalan and prednisone)	Multiple myeloma (combination therapy, first-line therapy)	II	Completed	Multinational	NCT00911859	Janssen Research & Development
Siltuximab	Multiple myeloma (monotherapy, second-line therapy or greater)	II	Completed	USA and the Netherlands	NCT00402181	Centocor
Siltuximab (in combination with lenalidomide, bortezomib and dexamethasone)	Multiple myeloma (combination therapy, first-line therapy)	Ib/II	Ongoing, not recruiting	USA	NCT01531998	M.D Anderson Cancer center (in collaboration with Janssen Services)
Siltuximab (in combination with bortezomib and dexamethasone)	Multiple myeloma (combination therapy, second-line therapy or greater)	I	Terminated	Japan	NCT01309412	Janssen Pharmaceutical K.K.
Siltuximab (plus best supportive care)	Myelodysplastic syndrome	II	Terminated	Multinational	NCT01513317	Janssen Research & Development
Siltuximab (in combination with mitoxantrone and prednisone)	Prostate cancer (combination therapy, hormone refractory, metastatic disease)	II	Terminated	Multinational	NCT00385827	Centocor
Siltuximab	Prostate cancer (hormone refractory, metastatic disease)	II	Completed	USA	NCT00433446	Southwest Oncology Group (in collaboration with National Cancer Institute)
Siltuximab (in combination with docetaxel)	Prostate cancer (combination therapy, hormone refractory, metastatic disease)	I	Completed	USA	NCT00401765	Centocor
Siltuximab	Renal cancer (metastatic disease)	I/II	Completed	USA	NCT00256135	Centocor
Siltuximab	Renal cancer (metastatic disease, unresectable)	II	Withdrawn prior to enrolment	USA	NCT00311545	Southwest Oncology Group (in collaboration with National Cancer Institute)

MCD Multicentric Castleman's Disease

2.3.2 *Multiple Myeloma*

2.3.2.1 Previously Untreated In a phase II trial the addition of siltuximab to standard bortezomib–melphalan–prednisone (VMP) therapy improved response rates in patients with newly diagnosed multiple myeloma who were not candidates for high-dose chemotherapy with autologous stem cell transplantation. Patients were randomised to receive siltuximab 11 mg/kg every 3 weeks plus VMP (n = 52) or VMP alone (n = 54) for up to 9 cycles (median treatment duration 12.5 months and 12.9 months, respectively). 21 patients with at least partial response in the siltuximab arm received maintenance siltuximab monotherapy for an additional 6.25 (median) months. After a median follow-up of 23.3 months, 27 % of patients in the siltuximab arm had complete response compared with 22 % in the VMP arm (median follow-up 21.9 months), with an overall response rate (complete or partial) of 88 % versus 80 %, respectively. At least very good partial response occurred in 71 % and 51 %, respectively (p = 0.0382). Median progression-free survival (17 months) and overall survival at one year (88 %) were the same in both groups [25].

2.3.2.2 Previously Treated/Advanced Addition of siltuximab to bortezomib as treatment for relapsed/refractory multiple myeloma has been evaluated in a double blind phase II study. Patients were randomised to bortezomib in combination with either siltuximab (n = 42) or placebo (n = 144) for 5.1 (median) months. Median progression-free survival was 8.1 and 7.6 months in the siltuximab and placebo groups, respectively. The overall response rate (complete plus partial) was 55 % and 47 % respectively. Overall survival was 30.8 and 36.9 months respectively after 24.5 months median follow up [26].

The efficacy of siltuximab alone and in combination with dexamethasone has been also evaluated in a phase II study in patients with previously treated (median 4 prior lines of therapy) relapsed or refractory multiple myeloma. An initial 14 patients received siltuximab alone; in 10 of these patients dexamethasone was later added because of suboptimal response, with 39 subsequently enrolled patients received siltuximab plus dexamethasone. No patients responded to siltuximab monotherapy, but combination therapy yielded a partial or minimal response rate of 23 %, with some responses seen in dexamethasone-refractory disease. Median overall survival on combination therapy was 20.4 months, with time to progression and progression-free survival of 4.4 and 3.7 months, respectively [27]. The development of siltuximab in advanced multiple myeloma has been terminated due to lack of efficacy.

2.4 Adverse Events

The most common adverse reactions in patients with MCD in the phase II trial MCD2001 were rash (28 % of siltuximab vs. 12 % of placebo recipients), pruritus (28 vs. 8 %), upper respiratory tract infection (26 vs. 15 %), increased weight (19 vs. 0 %) and hyperuricaemia (11 vs. 0 %). Other adverse events included thrombocytopenia (9 vs. 4 %), lower respiratory tract infections, oropharyngeal pain, constipation and headache (each 8 vs. 4 %), hypertriglyceridaemia and renal impairment (each 8 vs. 0 %), and eczema, dry skin, psoriasis, skin hyper-pigmentation, hypercholesterolaemia and hypotension (each 4 vs. 0 %) [7].

Long-term tolerability data are available for 19 patients with MCD who received siltuximab for 5.1 [median (range 3.4–7.2)] years in an extension of an initial dose-finding study. The most common adverse reactions were upper respiratory tract infection (63 %); diarrhoea (32 %); pain in extremities, arthralgia and fatigue (21 % each). No patient was removed from therapy for any reason. There were no deaths and no cumulative toxicities were identified [7].

Of the approximately 750 patients treated with siltuximab, one has experienced an anaphylactic reaction. Among 249 patients who have received siltuximab monotherapy, 4.8 % experienced infusion-related reactions such as back pain, chest pain or discomfort, nausea and vomiting, flushing, erythema and palpitations [7].

2.5 Ongoing Clinical Trials

Two trials investigating the use of siltuximab as treatment for MCD are currently underway, NCT01400503—an extension of a phase II study evaluating the efficacy and tolerability of long-term treatment—and NCT01024036, a phase II study comparing siltuximab and placebo in conjunction with best supportive care.

A study of siltuximab in patients with high-risk smoldering multiple myeloma (NCT01484275) is also ongoing.

3 Current Status

Siltuximab received its first global approval on the 23rd of April 2014 in the US, and its second approval on the 4th of June 2014 in the European Union, for the treatment of patients with MCD who are HIV negative and HHV-8 negative.

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