

# Siltuximab (CNTO 328): a promising option for human malignancies

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**Abstract:** Siltuximab (CNTO 328) is a promising antibody-drug conjugate targeting cytokine interleukin-6 (IL-6). It is highly binding to IL-6 and thus neutralizing IL-6 bioactivity and promoting death of tumor cell. In this review, we mainly focus on the mechanisms, clinical studies, and adverse effect of siltuximab in the treatment of human malignancies. We also provide our recommendations for siltuximab treatment in the future.

**Keywords:** interleukin-6, Castleman's disease, clinical trials

## Introduction

Siltuximab (CNTO 328) is an anti-interleukin-6 (IL-6) chimeric monoclonal antibody approved for the treatment of patients with human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative multicentric Castleman's disease (MCD) by the US Food and Drug Administration in 2014 with the dose of 11 mg/kg over 1 hour intravenous infusion every 3 weeks.<sup>1-3</sup> Siltuximab has been confirmed to neutralize the IL-6 effect in a number of human malignancies, such as MCD, multiple myeloma (MM), myelodysplastic syndrome (MDS), prostate cancer, ovarian cancer, and lung cancer, and it also can reduce cancer-related anorexia and cachexia.<sup>1,4-9</sup> In this review, we mainly focus on addressing the mechanisms of siltuximab. We also summarize clinical studies with siltuximab and provide our recommendations for critical strategies of siltuximab treatment in the future.

## Mechanisms

The main mechanism of siltuximab is verified highly binding to cytokine IL-6 and thus neutralizing IL-6 bioactivity.<sup>10</sup> IL-6 has various functions, including its critical role in B cell development, neuronal cell differentiation, myeloid lineage maturation, immune response, hepatic function, and bone resorption,<sup>10</sup> and it also plays a pivotal role in the progression, differentiation, survival, and angiogenesis of malignant cells.<sup>11</sup> Growing evidence suggests that blocking IL-6 may be an effective strategy in diseases with IL-6 dysregulation.<sup>6,10,12</sup>

IL-6 plays an important role in Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway according to the research.<sup>13</sup> The STAT family of transcription factors are potential targets for the treatment and prevention of cancers.<sup>14</sup> Siltuximab could inhibit STAT3 tyrosine phosphorylation in a cell-dependent manner and thus inhibiting tumor growth.<sup>8,15</sup> Siltuximab can also decrease p44/p42 mitogen-activated protein kinases (MAPK) and phosphoinositide 3-kinase (PI3K)/Akt pathway in cancer cells.<sup>16-18</sup> IL-6 can promote the angiogenesis within the tumor microenvironment by co-regulating tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1

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(IL-1), chemokine (C-C motif) ligand 2 (CCL2), C-X-C motif chemokine 12 (CXCL12), and vascular endothelial growth factor (VEGF), and siltuximab therapy has already been confirmed to increase in cytochrome P450 activity and prolong periods of disease stabilization with a significant decline in levels of TNF- $\alpha$ , IL-1, CCL2, CXCL12, and VEGF.<sup>19,20</sup>

Other mechanisms of siltuximab, such as reduction of VEGF, have also been reported.<sup>17</sup>

## Clinical studies

### Castleman's disease

Castleman's disease is a rare lymphoproliferative disorder with germinal center hyperplasia, accumulation of immunoblasts and plasma cells, and increased vascularity, and it is classified by unicentric Castleman's disease (UCD) and MCD.<sup>5,12</sup> UCD is localized and carries a very good prognosis, whereas MCD is a systemic disease with considerable morbidity and mortality, and the therapeutic landscape for its management continues to evolve. Surgical resection remains the standard therapy for UCD, while systemic therapies are required for the management of MCD.<sup>21</sup>

In a Phase I study conducted by van Rhee et al<sup>22</sup> 18 of 23 patients (78%) had complete response, and 12 patients (52%) demonstrated objective tumor response. All eleven patients treated with the highest dose of 12 mg/kg achieved complete response, and eight patients (73%) achieved objective tumor response. The results indicated that siltuximab is an effective treatment with favorable safety for the management of Castleman's disease.<sup>22</sup> In a Phase II study, van Rhee et al<sup>23</sup> enrolled HIV-negative and HHV-8-seronegative patients with symptomatic MCD, and 140 patients were screened, durable tumor and symptomatic responses occurred in 18 of 53 patients (34%) in the siltuximab group and none of 26 in the placebo group. All the above studies showed positive results of siltuximab for Castleman's disease.

### Multiple myeloma

MM is a malignant plasma cell disorder that will result in highly disparate outcomes based on its heterogeneous biology. Over the past decade, the introduction of high-dose chemotherapy with peripheral blood stem cell transplantation and novel agents has substantially prolonged the survival of patients with the disease; however, most of the patients will still relapse and become refractory to therapy due to development of drug resistance.<sup>24–26</sup> It is verified by different studies that siltuximab is a promising agent in MM therapy, especially for those patient with MM who are relapsed or refractory.<sup>12</sup>

In a Phase I dose-escalating study of siltuximab conducted in Japan, nine patients were treated. Across both doses, 66% patients had complete or partial response, and 11.0 mg/kg once every 3 weeks is recommended.<sup>27</sup> In the Phase II randomized controlled clinical trial, the safety and efficacy of siltuximab plus bortezomib with placebo in patients with relapsed/refractory MM were assessed. Siltuximab was given by 6 mg/kg intravenous every 2 weeks, and after the study, it was found that the addition of siltuximab to bortezomib did not improve progression-free survival or overall survival despite a numerical increase in response rate in patients with relapsed or refractory MM.<sup>28</sup>

However, a Phase II study conducted by Voorhees et al<sup>29</sup> did not achieved objective response for patients with relapsed or refractory MM who had two prior lines of therapy, one of which had to be bortezomib based.

Combination of siltuximab with melphalan or bortezomib was proven to have synergistic effect and siltuximab could partially overcome melphalan or bortezomib resistance.<sup>17</sup> Based on the above results, siltuximab addition was considered for melphalan-based or bortezomib-based therapies.<sup>27</sup> However, in another study, the addition of siltuximab to the bortezomib–melphalan–prednisone regimen does not seem to improve complete response, progression-free survival, and overall survival, it only improves very good partial responses in patients who are transplant ineligible with newly diagnosed MM.<sup>4</sup>

### Myelodysplastic syndrome

MDS is a clonal disorder that is characterized by ineffective hematopoiesis and an increased risk of transformation into acute myeloid leukemia (AML),<sup>30</sup> and IL-6's role in the pathophysiology of MDS is not so clear. In a double-blind, placebo-controlled Phase II study, siltuximab was assessed in patients with low- and intermediate-1-risk MDS who require transfusions for MDS anemia, and the study demonstrated that siltuximab did not reduce red blood cell transfusions in transfusion-dependent patients with low- and intermediate-1-risk MDS compared to placebo.<sup>31</sup>

### Solid tumors

Several solid tumors like prostate cancer, ovarian cancer, and lung cancer have been investigated in several studies.

A Phase I/II study evaluated safety, efficacy, and pharmacokinetics of patients with advanced or refractory solid tumors, including Kirsten rat sarcoma-2-mutant tumors, ovarian, pancreatic, or anti-epidermal growth factor (EGF) receptor refractory/resistant non-small cell lung cancer,

colorectal, or head and neck cancer. However, siltuximab monotherapy appears to be well tolerated but no clinical activity was found in these solid tumors.<sup>32</sup>

## Prostate cancer

An open-label Phase II trial assessed mitoxantrone/prednisone with and without siltuximab in the treatment of patients with metastatic castration-resistant prostate cancer who received prior docetaxel-based chemotherapy, and the result showed that siltuximab plus mitoxantrone/prednisone was well tolerated, but improvement in outcomes was not demonstrated.<sup>33</sup> Dorff et al<sup>34</sup> conducted a multicenter Phase II study of siltuximab as second-line therapy for men with castration-resistant prostate cancer showed that siltuximab resulted in a prostate specific antigen response rate was 3.8% and the stable disease rate was 23%. In another study of siltuximab for prostate cancer patients after radical prostatectomy, no adverse events related with siltuximab were observed, and higher levels of proliferation and apoptosis markers were observed in patients treated with siltuximab.<sup>16</sup>

## Renal cancer

In a Phase I/II trial about metastatic renal cell cancer, siltuximab was confirmed to stabilize disease in more than 50% of progressive metastatic patients, and the patients were well tolerated with no immune response.<sup>35</sup>

## Adverse effect

Siltuximab is safe demonstrated by both basic and clinical studies though manageable adverse events happened in nearly all patients according to the reports.<sup>22,34,36</sup> The most common adverse reactions (above 10% compared with placebo) during siltuximab treatment were increased weight, rash, pruritus, hyperuricemia, and upper respiratory tract infection.<sup>37,38</sup>

## Conclusion and future directions

Siltuximab is a promising therapy for a group of human malignancies. In various basic and clinical studies, siltuximab showed its advantages with its favorable effect and less toxicities. Though siltuximab received its approval in 2014 in the US and European Union for the treatment of patients with HIV-negative and HHV-8 negative MCD, studies about other cancers are still ongoing and some results of the studies are not very satisfactory. Siltuximab should be further studied with larger sample of patients, the concrete mechanisms and efficacy about siltuximab combined with other chemotherapy agents or radiotherapy should also be evaluated more in-depth.

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## Disclosure

The authors report no conflicts of interest in this work.

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