



cti®

# Tosedostat

**T**OSEDOSTAT (formerly CHR-2797) is a first in class aminopeptidase inhibitor that is administered chronically as a once daily capsule. It has clinically demonstrated anti-tumor activity as a single agent in both solid tumors and hematological malignancies. Tosedostat is a prodrug that is converted intracellularly into a pharmacologically active product, CHR-7988 (Figure 1). Tosedostat is the only aminopeptidase

## Proposed Target Profile

- Efficacy as both a single-agent and in synergy with other agents to treat AML.
- Ease of administration - Tosedostat is an oral therapy.

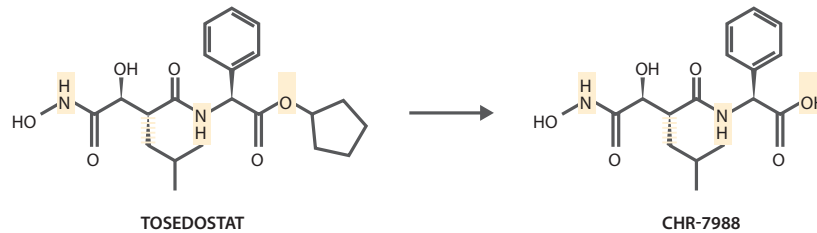


Figure 1. Structure of tosedostat and its active metabolite

inhibitor in advanced clinical development. Under a March 2011 agreement with Chroma Therapeutics, Ltd. (Oxford, UK), CTI obtained both development and commercialization rights for tosedostat in the Americas.

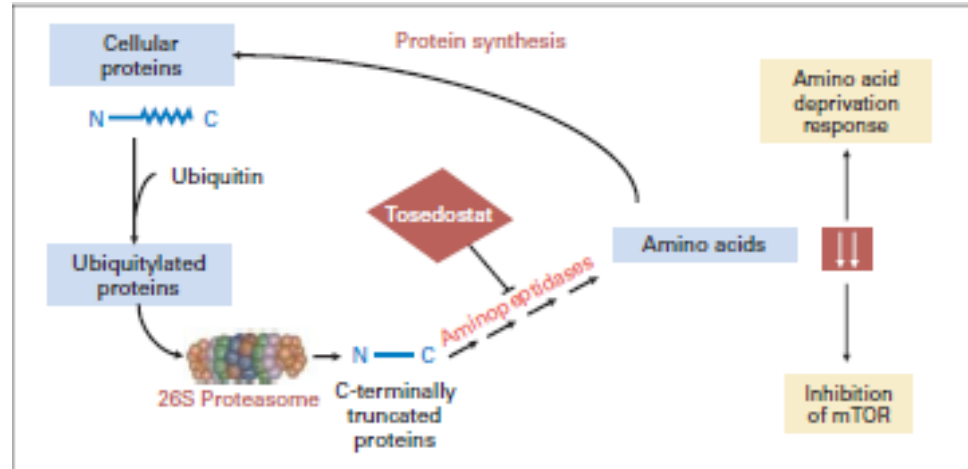


Figure 2. Tosedostat mechanism of action

## References

- [1] Krige et al. Cancer Res. 2008;68:6669-79.
- [2] Jenkins et al. Leuk Res. 2011;35:677-81.
- [3] Lowenberg et al. J Clin Oncol. 2010; 28:4333-8.

## Mechanism of Action

Tosedostat offers tumor selective targeted therapy that interferes with cellular pathways necessary for tumor survival and induces apoptotic death in sensitive cells. The active metabolite of tosedostat targets intracellular members of the M1/17 family of aminopeptidases at low nanomolar concentrations. Tosedostat shows selectivity for neoplastic over normal cells, both in vitro and in vivo. Inhibition of aminopeptidases in tumor cells results in a transcriptional response culminating in amino acid depletion. This Amino Acid Deprivation Response (AADR) leads to up-regulation of pro-apoptotic signaling genes such as CHOP and NOXA, and ultimately results in apoptosis in malignant cells of multiple origins (Figure 2).

## AML Information

Acute Myeloid Leukemia is one of the most common types of leukemia in adults. AML is a cancer of the myeloid line of blood cells, characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells. AML is the most common acute leukemia affecting adults, and its incidence increases with age.

The symptoms of AML are caused by replacement of normal bone marrow with leukemic cells, which causes a drop in red blood cells, platelets, and normal white blood cells. These symptoms include fatigue, shortness of breath, easy bruising and bleeding, and increased risk of infection. Several risk factors and chromosomal abnormalities have been identified, but the specific cause is not clear. As an acute leukemia, AML progresses rapidly and is typically fatal within weeks or months if left untreated.

AML has several subtypes; treatment and prognosis varies among subtypes. AML is treated initially with chemotherapy aimed at inducing a remission; patients may go on to receive additional chemotherapy or a hematopoietic stem cell transplant.

## MDS Information

The myelodysplastic syndromes (MDS, formerly known as "preleukemia") are a diverse collection of hematological (blood-related) medical conditions that involve ineffective production (or dysplasia) of the myeloid class of blood cells.

Patients with MDS often develop severe anemia and require frequent blood transfusions. In most cases, the disease worsens and the patient develops cytopenias (low blood counts) due to progressive bone marrow failure. In about one third of patients with MDS, the disease transforms into acute myelogenous leukemia (AML), usually within months to a few years.

## Preclinical Data

Tosedostat has greatest anti-neoplastic activity in myeloid leukemia, myeloma and selected solid tumor cell lines in vitro [1]. Tosedostat is synergistic in vitro with cytarabine, demethylating agents, and proteasome inhibitors, as well as most standard cytotoxic agents. Importantly, the action of tosedostat does not appear to be affected by resistance to these agents [2].

## Clinical Data in Solid Tumors

In this Phase I clinical trial, 40 patients with treatment refractory metastatic cancer were treated with an ascending dose of tosedostat. In June 2007, Chroma announced results from this study showing that tosedostat could be administered safely for up to 10 months in doses up to 240 mg per day. Evidence for activity was demonstrated in renal cell cancer resistant to standard tyrosine kinase inhibitor therapy. A partial response (PR) was observed in 1 patient and stable disease (SD) was confirmed in 7 patients with breast cancer, non-small cell lung cancer, and hepatoma. The most common toxicities observed were fatigue, diarrhea, nausea, vomiting, and dizziness.

## Clinical Data in Acute Myeloid Leukemia

### CHR-2797-002

CHR-2797-002 was a Phase I / II study of once daily oral dosing of tosedostat as monotherapy in 57 previously treated elderly patients with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), or multiple myeloma (MM) who relapsed or exhibited refractory disease after first line or salvage treatment [3]. Tosedostat showed promising anti-leukemic effects in this difficult to treat patient population and was well tolerated, even with daily dosing for over 2 years. A 30% overall

response rate (ORR) was achieved. The most common toxicities observed were thrombocytopenia, fatigue, peripheral edema, and diarrhea.

### OPAL Study (CHR-2797-038)

OPAL was a Phase II study conducted in elderly patients with relapsed or refractory AML. Patients were randomized to one of two dose groups: 120 mg per day, or 240 mg per day for 56 days and 120 mg per day thereafter. The primary objective was to compare the proportion of patients in each dose group achieving ORR (bone marrow complete response [CR] or PR). In June 2011, CTI and Chroma announced interim data from this study.

The interim ORR at 3 months was 21% in the 120 mg arm and 20% in the 240 mg arm. In patients who had received prior therapy with hypomethylating agents, the ORR was 36%. Forty percent of responses occurred by study day 29, and the remaining occurred on or after day 57. The most common toxicities observed other than those associated with refractory leukemia were grade 1-2 diarrhea and edema. Final 6-month data from this study will be presented at an oral session at the American Society of Hematology annual meeting in December 2011.

### Future Studies

A Phase III study for potential US and EU approval is planned in patients with intermediate-2 to high risk MDS who have failed prior hypomethylating agent therapy. The FDA and the EMA have granted tosedostat orphan drug status for AML. Further studies in patients with AML are planned. In addition, a Phase I-II study with tosedostat in combination with bortezomib is being designed for patients with refractory MM as well as studies in patients with refractory solid tumors.



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**Additional Information**  
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