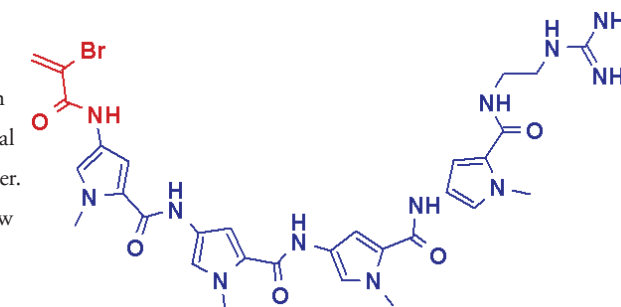




# Brostallicin

**B**rostallicin (bräst-al-iss-in) is a small molecule chemotherapeutic agent with a unique mechanism of action. Data in more than 230 patients treated in phase I/II clinical trials reveal evidence of activity in patients with refractory cancer. Brostallicin also has demonstrated synergy with new targeted agents as well as established treatments for common tumor types in preclinical trials.



### Brostallicin Highlights

- Unique minor groove binder without cumulative bone marrow toxicity
- Unique mechanism of action may be exploitable with genomic and clinical selection
- Strong candidate to demonstrate proof-of-principle for context of vulnerability approach
- Safety and anti-tumor activity have been assessed in more than 230 patients in phase I and early phase II clinical trials
- Strong worldwide patent rights for composition-of-matter, uses, biomarkers
- Exclusive worldwide rights

Brostallicin is a new class of cancer drug — a synthetic DNA minor groove binding agent. Most cytotoxic agents bind DNA's major groove, have little sequence-specificity, and are severely toxic to normal tissues (including topoisomerase inhibitors, such as camptothecins and anthracyclines).

DNA minor groove binders such as brostallicin possess high affinity and selectivity for interaction with either GC- or AT-rich regions of DNA. All minor groove binders bind to the same DNA structure. However, brostallicin has a unique and very interesting mechanism of action.

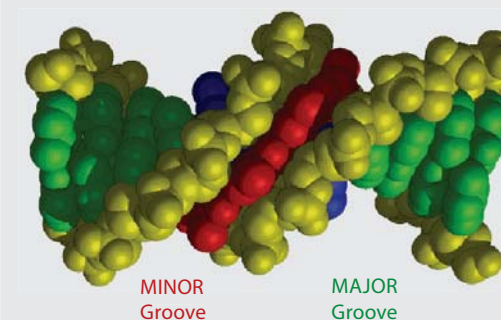
Brostallicin binds to DNA only in the presence of glutathione (GSH) and glutathione S-transferase (GST), which are produced to a greater extent in cancer cells, but not typically in normal cells. This gives brostallicin a novel and highly

selective mechanism of action that is superior to other minor groove binding agents (such as ET743/Yondelis™).

By binding to the minor groove, brostallicin provides a new target to interfere with cell division and lead to tumor cell death. Brostallicin is potently synergistic (in preclinical studies) in combination with standard cytotoxic agents as well as newer targeted therapies.

Brostallicin has a unique ability to retain activity in tumors that are resistant to other cancer drugs. Additionally, its anti-tumor activity remains high in the presence of a number of critical cancer-causing genetic abnormalities that cause resistance to standard anti-cancer agents. This activity profile makes it of extreme interest in designing trials to test its activity in targeted patients with certain genetic abnormalities, such as mismatch-repair mutations in inherited breast, ovarian, and colorectal cancers that are generally resistant to treatment.

### DNA Structure



Proteins that interact with DNA often make contact with the edges of the base pairs that protrude into the major groove. Chemical groups on the edges of GC and AT base pairs are available for interaction in the major and minor grooves.

Examples of MAJOR GROOVE binding agents include: anthracyclines, camptothecins

Examples of MINOR GROOVE binding agents include: brostallicin, trabectedin (ET-743)

### References

1. "Genomic Profiling of Cancer: What Next?" Workman P, Johnston P. *J Clin Oncol*. 2005 Oct 10;23(29):7342-9.

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## Brostallicin's History

Brostallicin was discovered at Pharmacia. Following a merger between Pfizer and Pharmacia, the rights to brostallicin were assigned to Nerviano Medical Sciences (NMS). NMS is one of the largest oncology-focused, integrated discovery and development companies in Europe.

NMS continued brostallicin's development and ultimately licensed exclusive worldwide rights to Systems Medicine, Inc. (SMi).

CTI acquired brostallicin in its acquisition of SMi (now known as Systems Medicine LLC) in July 2007.

## PRECLINICAL RESEARCH

Brostallicin has shown anti-tumor activity in human tumors both *in vitro* and *in vivo*.

Brostallicin induces apoptosis (programmed cell death) in cancer cells, including cancer cells with mismatch-repair deficiency common in inherited breast and colon cancers that are generally treatment resistant. It also has shown activity in cancer cells resistant to alkylating agents, topoisomerase I inhibitors, and platinum derivatives.

Brostallicin is synergistic or additive with widely used anti-tumor drugs such as cisplatin, gemcitabine, and irinotecan, with newer molecular targeted agents such as Iressa<sup>®</sup> (gefitinib) and Gleevec<sup>®</sup> (imatinib), and with monoclonal antibodies that target growth-factor receptors and their signaling pathways, such as Avastin<sup>®</sup> (bevacizumab).

Minor groove binders such as brostallicin are reported to be highly active in myxoid liposarcomas, a subset of soft tissue sarcomas that have a unique genetic signature, the t(12;16) chromosomal translocation.

## CLINICAL RESEARCH

Phase I and phase II clinical trials have been conducted with brostallicin in both Europe and the US involving more than 230 patients in single agent and combination trials.

Brostallicin has been generally well tolerated with mild to moderate, reversible myelosuppression being the primary adverse event. It has had predictable and predominantly hematologic toxicities, which rarely required growth factor support.

At the recommended dose, responses, including tumor shrinkage and stable disease, have been reported in approximately 50 percent of sarcoma patients. Responses have also been reported in non-small cell lung cancer and in head and neck cancer.

The European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group completed a phase II trial of brostallicin, concluding that brostallicin met their criteria for continued development (47 percent of patients were progression-free at three months).

## Clinical Development

### Context of Vulnerability

A systems biology approach to drug development has been applied, combining pharmacogenomics and bioinformatics

with preclinical, clinical, and regulatory expertise to find and exploit a specific cancer's context of vulnerability.

The context of vulnerability is defined as the molecular and genetic alterations, or context, that cause cancer cells to be particularly sensitive (vulnerable) to a drug or combination of drugs. The relative vulnerability of cancer to a specific cancer drug depends on a cell's molecular context as determined by the state of the:

- direct drug target
- 'target associated' gene
- genes unrelated to the target

This approach is based on the translational application of powerful pharmacogenomic tools to the molecular profiling of cancer and the validity of this approach was described in an October 2005 editorial by Drs. Workman and Johnston published in the *Journal of Clinical Oncology*: "The next generation of clinical studies must be designed in a manner that allows the incorporation of genomic technologies alongside clinical drug development."<sup>1</sup>

## Clinical Trials

### Triple-Negative Breast Cancer (Ongoing)

In 2010, the North Central Cancer Treatment Group started a phase II study of brostallicin in combination with cisplatin in patients with triple-negative metastatic breast cancer patients in first, second, third or fourth line therapy. Enrollment is expected to be complete in early 2012. In addition to standard clinical efficacy measures, biological endpoints also will be evaluated to assist in understanding brostallicin's activity in this disease.

## Toxicity Profile

### Single-Agent Brostallicin

Dose limiting toxicity is primarily neutropenia, followed by other less frequent bone marrow toxicity parameters. These occur at doses of 7.5 and 10mg/m<sup>2</sup> every three weeks. Grade 3/4 neutropenia occurred in 22 and 47 percent respectively; febrile neutropenia occurred in 13 and 1.6 percent; thrombocytopenia occurred in 11 and 7.9 percent. Of the non-hematologic grade 3/4 toxicities that occurred, fatigue 23.8 and 1.6 percent; allergy 0 and 6.3 percent; emesis 9.5 and 0 percent; dyspnea 9.6 and 3.2 percent. Doublet regimens with various agents are currently being evaluated.

## Context of Vulnerability

Using a defined subset of patients uniquely responsive to selected products or combinations of products results in less expensive development, higher probability of success, and potential for faster approval.

We plan to use the context of vulnerability approach to transform brostallicin into a molecularly targeted drug, indicated for the patients who will respond to this agent.

## Completed Brostallicin Clinical Trials

SMI-BRS-101 Phase I	Study to determine maximum tolerated dose (MTD), dose-limiting toxicities (DLT) in combination with irinotecan or bevacizumab in patients with advanced solid tumors	Manageable toxicity shown at doses reached in cohort 2; 19 patients enrolled
SMI-BRS-202 Phase II	Myxoid liposarcoma with t(12;16) gene translocations	Need info
196-ONC-0100-003 Phase II EORTC trial	Second-line, single-agent in patients with locally advanced or metastatic soft tissue sarcoma who have failed one prior chemotherapy	23 partial response or stable disease in 42 patients
196-ONC-0100-004 Phase II	Second-line, single-agent in patients with recurrent/refractory or metastatic squamous cell carcinoma of the head and neck	12 partial response or stable disease in 27 chemotherapy-naïve patients
196-ONC-0100-005 Phase II	Second-line, single-agent in patients with refractory or platinum-resistant advanced non-small cell lung cancer	10 partial response or stable disease in 24 patients
196-ONC-0100-012 Phase II with dose escalation phase	Single arm, open label, two-stage dose escalation study to define MTD and DLT in combination with cisplatin for patients with recurrent/metastatic solid tumors usually treated with cisplatin	Dose level 2 recommended for future studies; 21 patients treated; main toxicity was hematologic
196-ONC-0100-014 Phase II	Third/fourth-line, single-agent treatment in patients with advanced/metastatic colorectal cancer	No CR or PR; stable disease seen as best response in 8 of 19 evaluable patients
196-ONC-0100-016 Phase II	Single-agent, second/third-line, two-stage study of patients with advanced/metastatic platinum resistant/refractory ovarian cancer	Study report under development
EORTC 62061 Phase II	Single-agent, first-line study, of patients with newly diagnosed advanced/metastatic soft tissue sarcoma	Study report under development