Companies: Genta Incorporated (GNTA)
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Within the past week, we began work on a (short) investment thesis in Genta, Inc. (GNTA). The rational for this project included (1) the Company's 14-year history in the difficult area of antisense drug therapy without producing a single product, 2) coupled to its market capitalization of ≈ $875 million ($13.26 with 65.7 million shares on January 18), 3) the expected release, in April (at AACR) of data from up to three Phase 3 trials of the same drug in melanoma, multiple myeloma and chronic lymphocytic leukemia, with each trial predicated on small, single-site Phase 2 studies and 4) a checkered past, more recently dominated by several rounds of agency/principal financing from Paramount Capital/Aries Funds.

Conclusion: *There is compelling data to support a short position in Genta. The company's aggressive, "spray-and-pray" clinical development program for Genasense™, an oligonucleotide designed to block Bcl-2 translation, is built upon insufficient data to justify any of its late-stage trials in three different cancers. While all three trials are appropriately designed as SOC ± Genasense, each is based on one, open-label, single arm study performed on 10 to 20 patients at a single investigative site. The risk of prior systematic error and the essentially experimental trial design carry a high likelihood of failure in all three studies.*

Risk to this short thesis obtains from just one of the clinical trials "working," possibly enabling an NDA submission to FDA.

Background: Founded in 1988 in San Diego, Genta came public during the 1991 biotech bubble. The company was built around "antisense" technology, i.e., the use of short DNA-based oligonucleotides to bind to mRNA and therefore block protein translation. This drug class from Genta and its competitors (Isis Pharmaceuticals, Hybridon, AVI Biopharma) faced the same issues of enzymatic breakdown and inefficient delivery to the cell interior. The development of several so-called 2nd and 3rd generation chemical variants (methylphosphonates, phosphorothioates) helped address these problems. Genta's first clinical trial of its only drug, Genasense (aka '3139), began in late 1995 in the U.K. and was tested in patients with non-Hodgkins lymphoma (NHL).

In the early '90s, the company completed two imprudent acquisitions (JBL Scientific, a chemical reagents supplier and Virna Pharmaceuticals, dermatological drug delivery) and formed a 50/50 JV with Jagotec AG (oral, controlled release drug delivery). By the summer of 1996, Genta was low on cash and saw little chance for survival. Paramount Capital helped restructure and recapitalize the firm and moved the company first to Massachusetts and then to its present location in New Jersey. At September 30, 2001, Genta reported $34.2 million of cash and liquid securities, 63.2 million shares outstanding, an accumulated deficit of $181 million and was ≈ 42 percent owned by Paramount/Aries, both entities wholly owned by Lindsey Rosenwald, MD. In late November, Genta completed a PIPE, raising $32.7 million from the sale of 2.5 million shares at $13.10, 16 percent off the prior day's close of $15.40. The two major investors were Franklin Templeton and SF Capital Partners (a part of Stark Investments, an arbitrage fund).

The short position in Genta has risen in each of the past four months from 4.9 million shares in October to 9.3 million in January. The company's 32 employees are led by Raymond Warrell, M.D., MBA, Chairman, President and CEO, his wife, Loretta Itri, M.D., VP Clinical and Chief Medical Officer and Alfred Fernandez, Chief Financial Officer, who joined in July.

Clinical Trial History: Genta has tested Genasense in several cancer indications. The most relevant for an NDA submission are summarized below:

Melanoma: At the AACR in April 2000, Genta reported results from a trial of Genasense + dacarbazine (aka DTIC) for stage IV melanoma conducted in 14 patients. Dosing information is scant as are other details, but the company reported one CR, durable tumor regression in six patients and median survival of more than one year. In March 2001, Genta updated the median survival time from this study to 17 months. In March 2000, Genta announced initiating its Phase 3 trial in 270 patients in the US, Canada and Europe who will receive dacarbazine ± Genasense (trial design uncertain) with an 18mFU. Dosing (uncertain) of Genasense will be at 7 mg/Kg/day, IV for five days. In March 2001, the company indicated likely trial completion by H2/01.

Multiple myeloma: On February 13, 2001, Genta announced initiating its Phase 3 trial at 65 sites in the US, Canada and the U.K. in 200 patients (post-surgery relapse) who will receive dexamethasone ± Genasense. Dosing (uncertain) will be at 3-4 mg/Kg/day. The PCEs (uncertain) are response rate, duration and QOL. The trial's duration is uncertain. It is not clear that Genta completed any clinical trials in this disease previously.

Chronic lymphocytic leukemia (CLL): On January 19, 2001, Genta announced initiating a Phase 2 trial (1st line drug refractory) using Genasense as monotherapy. No information regarding trial size, site locations, duration or dosing was disclosed; however, on December 12, 2001 at ASH, Genta announced results from the Phase 1/2 monotherapy trial noted above. Fourteen patients with refractory CLL were treated in what appears to be a dose-ranging study of 3-7 mg/Kg/day for 5-7 days. Clinical outcomes were not disclosed, but the 3mg dosing regimen was described as best due to toxicity at the higher doses. On February 28, 2001, Genta announced initiating its Phase 3 trial in 200 patients (1st line drug refractory) at 60 sites in the US, Canada and Europe. Patients will be receiving standard second line therapy of fludarabine and cyclophosphamide ± Genasense, dosed at 3 mg/Kg/day. PCEs are response rate, duration and QOL.

Genta has indicated that it plans to file an NDA in Q3/02 for that indication with the best data, and to file sNDAs upon approval, for additional indications.

Events: There are two events relevant to GNTA.

4/6/02: AACR begins. The company has presented clinical results at this conference in the past.

5/18/02: ASCO begins. The company has presented clinical results at this conference in the past.