Company: Imclone Systems, Inc. (IMCL)
Publication Date: November 30, 2001
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Around November 15, we began work on a (short) investment thesis in Imclone Systems, Inc. (IMCL). The rational for this project included (1) the Company's October 31 BLA submission to FDA for its first potential therapeutic product, Erbitux (AKA C225 or cetuximab) to treat colorectal cancer, based on a single, non-randomized, 120-patient Phase 2 clinical trial, (2) an ODAC Panel review in early December of the Saltz dosing regimen (on which IMCL's patients' cancers had progressed before entering the C225 trial) causing elevated mortality, (3) an ODAC panel review likely in late February of IMCL's Phase 2 data and (4) IMCL's breath-taking market capitalization of ≈ $4.5 billion (72.1 million shares at $62).

Conclusion: *There is insufficient concrete data to support, unequivocally, a decision about FDA Panel acceptance or rejection of C225; however, several high risk attributes surrounding IMCL's clinical study coupled with one minor and two major, potentially adverse catalytic events support building a short position in this stock.*

Based on several conversations with practicing GI oncologists, there is pervasive doubt as to whether the modest efficacy observed for C225 (22.5 percent overall tumor response) is genuine or due to systematic errors in the patient enrollment criteria. Another risk is attributed to patient concentration at a few, potentially biased, clinical investigation sites and too rapid patient accrual possibly leading to discrepancies between patients' raw medical charts ("source data") versus the Company's submitted case report forms. Such discrepancies might result in a conclusion of lower or no efficacy for C225 and Panel rejection. Finally, no oncology biological has ever been approved based on data obtained from combination therapy with standard chemotherapeutics and, C225 has yet to demonstrate efficacy when given alone (as monotherapy). Technical, secular attributes (e.g., stocks go to Panel perfectly priced, leaving only downside) further support this recommendation.

On the other hand, the prognosis for patients with CPT-11-refractory CR cancer is so grim (eight percent survive five years), C225's relatively modest toxicity profile (74 percent get acne-like rash) and oncologists' willingness to adopt new regimens (pure empiricism) based on even weak perceptions of benefit may be enough for Panel approval.

Background: Founded in 1984 to develop immunodiagnostics (the two with FDA approval are licensed to Chiron) and a gonorrhea vaccine (since abandoned), IMCL decided to enter the therapeutic domain in the early 1990s. IMCL licensed a monoclonal antibody specific for the EGF receptor, which is overexpressed in many tumors. The original "all mouse" antibody was chimerized (30 percent murine as F_{ab} plus 70 percent human as F_c) to reduce its being immunologically rejected. Since 1994, C225 has been tested in over 900 patients in 22 clinical trials (head and neck, pancreatic, colorectal, non-small cell lung cancers) based on preclinical (animal model) studies.

Clinical Trials: Patients Treated Too Soon? Data from two clinical trials (C225 as monotherapy in 57 patients or used with CPT-11 in 120 patients) will be used to support the Company's BLA submission to use C225 with CPT-11 (Pharmacia's Camptosar, AKA irinotecan) in patients with colorectal cancer refractory to CPT-11. Refractory means that, despite drug therapy, the patient's tumor mass increased in size ("progressed") by at least 25 percent as quantified by CT scans which were read by independent radiologists; however, GI oncologists with whom we have spoken have strongly suggested that some patients may not have been CPT-11 refractory, as rigorously defined. Specifically, one CPT-11 course-of-therapy (COT) entails four weeks on drug then two weeks "rest." Most oncologists believe a patient is refractory to a drug if there is 25 percent tumor progression *after* two full COTs (12 weeks (84 days) for CPT-11). The median time from "CPT-11 failure" to initiation of C225 treatment in the 120-patient trial was 30 days (mean of 54 days) according to an abstract submitted by Leonard Saltz et al. (Principal Investigator, based at Memorial Sloan-Kettering) in December 2000 and presented at ASCO in May 2001. If these patients were not truly CPT-11-refractory (i.e., enrolled in the trial too soon), then the benefit ascribed (by IMCL) to C225 may in fact have been due to continued treatment with CPT-11.

Intrinsic Efficacy? It is also significant that the 120-patient, combination therapy clinical trial began in October 1999 and that the 58-patient monotherapy trial began in March 2001, possibly at the behest of the FDA. This may suggest some FDA skepticism towards C225's intrinsic efficacy. In February 2001, FDA granted C225 a "fast track" designation, allowing IMCL to begin submitting the three modules of the BLA, including earlier clinical data. These data would have included the Company's C225 monotherapy trial in patients with metastatic renal cell carcinoma begun in December 1997. Results

reported in May 1999 from the 53-patient trial were disappointing. There was only one partial response (PR), meaning the tumor had shrunk by at least 50 percent. Imclone dropped further studies in renal cell carcinoma and conducted no other monotherapy trials of C225 until the 57-patient trial noted above.

Systematic Error? Finally, the geographical distribution of patients at the 20 clinical trial sites has not been disclosed, but some investigators believe that a disproportionate number of patients were enrolled at Memorial Sloan-Kettering (where the Saltz regimen was developed) and M.D. Anderson (home to C225's inventor, Dr. John Mendelsohn). If true, the potential for systematic (though unintentional) error or bias in patient enrollment exists.

Trial Design: Preliminary results of the 120-patient trial were reported by IMCL (as was preliminary data in an investigator's abstract submitted in December) in May 2001 at ASCO. The trial was originally designed to enroll 98 patients at 20 US sites. Patients could be enrolled if their disease was progressing after treatment with (1) the "Mayo" regimen of 5-FU and leucovorin, followed by CPT-11 or (2) the "Saltz" regimen of all three drugs simultaneously (the "primary group" or "registration arm"). Patients were also enrolled if they were on either of the two drug regimens, but their disease was stable ("secondary" group of "smoldering patients"). Of 138 patients enrolled in the study, 18 were stable upon enrollment. They were analyzed as a separate cohort and results were first presented in Paris (at Cowen) on November 29. Imclone reported one CR and eight PRs from that cohort, which, while encouraging, is subject to the same risks noted earlier. As a secondary cohort, it could not support Panel approval.

CPT-11 dosing was kept identical to that on which patients had progressed upon entering the trial and most (90 percent) were on the 4-week on/2-week rest protocol. C225 treatment entailed an intravenous infusion every week on an out-patient basis. After six weeks, patients were evaluated for tumor size. If they had continued progressing, they were dropped from the trial (84 were) and if they were stable or responding, they continued on another six-week COT. Partial responses had to be sustained over at least 12 weeks.

Trial Results: Of the 120 patients treated with C225 plus CPT-11, 27 (22.5 percent) had a PR which lasted for a median duration of 186 days. An additional nine patients (7.5 percent) had stable disease for at least 12 weeks. There were no complete responses (CR; 100 percent tumor reduction) observed. The overall response (OR) rate is the sum of PR plus CR. While there is no firm threshold for OR rate in cancer, Panel oncologists might reasonably be expected to hold IMCL to a 15 percent response rate in this patient cohort. Again, inadequate adherence to enrollment criteria as well as discrepancies between raw data and submitted case report forms (fairly common) may put the observed response rate at risk. The Company has not disclosed results from its 57 patient C225 monotherapy trial (open-label, uncontrolled) but has guided analysts that it is seeing a 10-15 percent (six to eight patients) response rate. Our conversations with clinicians support this guidance.

Corporate Partner: In September, Bristol-Myers Squibb (BMY), a dominant if weakening player in oncology, signed a $2 billion biobuck deal with IMCL for North American rights to C225 and a 50 percent split of revenues in Japan. Bristol took two Board seats (total 12, post). This investment comprised a tender offer for 19.9 percent (14.4 million shares with a 3-year lockup and a 5-year standstill) of IMCL shares at $70.00 per share, a 40 percent premium to the $50.01 prior close plus $200 million up-front. There is another $300 million milestone conditioned on FDA declaring the BLA fileable (by December 30, 2001) and a further $500 million upon FDA approval. Also, Imclone has had a long relationship with Merck KGaA, since late 1990 for BEC2 (a potential cancer vaccine) and, since late 1998, assigning Merck European rights to C225. Merck has paid in roughly $35 million total for both projects.

According to Sam Waksal, IMCL's President and CEO, Bristol had its own radiologists review IMCL's registration arm data. However, some viewed the investment as Bristol's only chance to participate in the EGF-receptor antagonist approach. Further, Bristol's oncology franchise has weakened due in part to valuable drugs (taxol in cancer, metformin in diabetes) having lost patent protection. Finally, the company had recently stumbled at FDA with the June rejection of Zelnorm for inflammatory bowel disease. Bristol's announcements to sell Clairol in May, acquire DuPont Pharmaceuticals in June and spin-off Zimmer in August clearly reflect a company in flux.

Competition: At least two other companies are pursuing EGF-receptor antagonists in oncology. The furthest along is AstraZeneca, which in May, had fully enrolled two phase 3 trials for its small molecule inhibitor called Iressa. Iressa is being

tested in non-small cell lung (NSCL) cancer either with gemcitabine/cisplatin at two doses in over 1,000 patients or with paclitaxel/carboplatin in the same format. Iressa monotherapy trials also in progress for NSCL. Due to GI side-effects similar to Camptosar, IMCL does not foresee Iressa entering colorectal cancer trials.

Further behind AstraZeneca is OSI Pharmaceuticals' Tarceva, which has been partnered with Roche and Genentech. This year, Tarceva has been entered into four phase 3 trials to treat either NSCL (two different combination regimens and another as monotherapy) or metastatic pancreatic cancer.

Events: There are three events relevant to IMCL.

December 6: ODAC will review the "Saltz" regimen (as originally approved April 2000) due to a DSMB suspension of two NCI-sponsored colorectal cancer trials in April. Mortality on regimen appeared to be higher than expected. In July, the trials were re-opened, generally with lower doses of CPT-11. A publication in JCO in September confirmed the higher mortality due to the Saltz regimen versus Mayo and suggested more careful patient monitoring. Many patients enrolled in IMCL's trial were refractory on Saltz regimen, but there were no deaths among the 120 patients. Some people believe that an especially adverse review of the Saltz regimen will complicate IMCL's BLA status. We think analysts with a "sell" will jump on the event putting pressure on the stock. "Buy" analysts will jump to the rescue. Transient stock drop opportunity.

December 30: Imclone completed the submission of its BLA (Biological License Application) on October 31. FDA is required to accept or reject the submission for filing in 60 days. A rejection (unlikely) would be catastrophic and the stock would be expected to lose at least half its value.

February 27/28: Assuming IMCL receives a fileable notice in December, we expect the Company to also receive "accelerated approval" allowing for provisional clearance conditioned upon further clinical trials. In addition, IMCL expects to receive "priority review" which expedites FDA's process (from 10 months down to six months). These FDA procedures could lead to an ODAC Panel review in late February. FDA considers, but is not obligated to follow, the recommendations of its outside experts. We believe IMCL's BLA is at risk of rejection.