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<b>New Rec: ImClone Systems (IMCL-\$36.88)</b>	<b>Nov. 21, 1999</b>
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**Position: Sell                      Target: \$12                      Timing: 2 (1=aggressive; 5=cautious)**

000\$	3Q99a	4Q99e	1Q00e	2Q00e	1999e	2000e
<b>Revs</b>	<b>138</b>	<b>600</b>	<b>625</b>	<b>150</b>	<b>1,621</b>	<b>1,175</b>
<b>EPS</b>	<b>(0.44)</b>	<b>(0.41)</b>	<b>(0.39)</b>	<b>(0.41)</b>	<b>(1.43)</b>	<b>(1.65)</b>
<b>Growth</b>						n/a
<b>PE</b>						n/a
<b>PSR</b>						n/a
<b>Consens</b>		<b>(0.13)</b>			<b>(0.36)</b>	<b>(1.36)</b>

**Shares Out: 28.4 M**

**Mkt. Cap: \$1.05 B**

**FYE: Dec.**

Summary: Shares of ImClone Systems have appreciated over 230% since March, fueled largely by the success of Genentech's Herceptin and IDEC's Rituxan (products seen as similar to ImClone's lead product C225), positive clinical trial data, the advancement of C225 into late stage development, and the hope for an

accelerated BLA filing in mid-2000. Encouraged by the company's public statements, bulls hope that ImClone will launch C225 by the end of 2000.

Nevertheless, in our opinion, ImClone has not convincingly demonstrated efficacy for C225, and has exaggerated its results to date. Trials have been small and of questionable design. Ongoing trials also have design problems, in our view.

ImClone has a European partner for C225, Merck KGaA, which owns 400,000 preferred IMCL shares. However, the deal is weak, and Merck's actions indicate that it, too, may have concerns about C225. ImClone is carrying \$14 M of Merck payments as "potentially refundable" on its books, and Merck is holding back on extending a \$30 M line of credit to ImClone for construction of a production facility for C225. The risk to ImClone is high. According to the agreement, Merck may cancel the deal whenever it chooses, and would receive a full refund on payments made to date.

Even if C225 were to be approved, we estimate the true revenue potential to ImClone for the current indication is only about \$37 M. "Street" analysts who arrive at a much greater market potential than we assume in our projections are including additional indications beyond head and neck cancers. They may be engaged in wishful thinking. C225 has failed to show efficacy in several important indications beyond head and neck cancer (kidney, prostate, and breast cancers), yet these analysts include those patients in the potential market numbers.

Moreover, there is significant competition not far behind C225 that employs a monoclonal antibody that should be safer and much more effective than C225. Abgenix' monoclonal antibody has the distinct advantage that it is not "chimerized" -- that is, unlike C225, which contains mouse fragments, it contains only human fragments. This should make it safer and significantly more potent.

Investors are hoping for fast track approval for C225, but we doubt this will happen. Clinical trials to date do not appear to be strong enough to warrant such an approval. The company has not received fast track designation from the FDA. The first trigger to a decline in IMCL's share price could be a delay in the filing of a BLA past mid 2000, which is the hoped for date. A second trigger could be that the BLA might be rejected as insufficient for approval, given the trial designs.

Other triggers to a decline could be that Merck registers its IMCL shares for sale, or even cancels its deal to extend credit to ImClone. Merck has its own similar compound in development. If Merck's compound progresses to Phase III, Merck could lose interest in C225.

ImClone has a colorful history. This is not the first time the stock has run up on misplaced hopes for a successful product. It was also the subject of a Barron's article in 1993 that was critical of the brothers who run the company. Its CFO is a former D. Blech employee.

The company completed a secondary offering of its shares on November 19 at \$32 per share. We think the best case for ImClone would be an approval of C225 in 2002 for a limited indication in head and neck cancer worth about \$37 M per year. After just one or two years on the market, however, the product will likely be replaced by superior competitors. With this limited potential revenue, and nothing else of near term value in the pipeline, in our opinion, we think the shares are fairly valued at about \$12 per share.

#### Background:

The company's lead product is C225, a chimerized monoclonal antibody being developed for the treatment of head and neck cancer and colorectal cancer. Chimerized antibodies are made up of fragments from more than one type of animal. In the case of C225, most of C225's fragments are human, but about a third are from mice. C225 binds to epidermal growth factor receptors (EGFr), which are over-expressed by a number of different solid tumor types. By binding to the receptors, C225 inhibits the stimulation of growth factors needed for the replication of certain cancer cells. This product and others like it are referred to as anti-EGFr antibodies.

Investors are excited about C225 mainly for three reasons. First, the company has reported dramatic positive results in Phase I/II trials. Second, the company has told investors that it hopes to file a BLA in mid-2000 based on the results of one or two Phase II trials currently underway in patients with refractory or metastatic head and neck and colorectal cancer. If given fast track designation, bulls say, this product could be on the market by the end of 2000. Finally, bulls estimate the product's market potential at \$500 million-\$1 billion. Beyond head and neck and colorectal cancers, they see applications in many other cancers, with a potential target population of 700,000 patients per year.

Careful review of the company's development efforts and the target market indicates these hopes may be unfounded. We think the Phase I/II results provide little comfort regarding the future of C225. As we describe below, ImClone's clinical development results to date actually tell us little about the drug's safety or efficacy. Therefore, the Phase II trials will be a more accurate test of the product's efficacy. Poor results from several other Phase II studies in different types of tumors lead us to think that C225 will fail in a more rigorous testing environment.

Moreover, as we detail below, even if the studies show some efficacy for C225, we think their design will fail the FDA's standards for accelerated approval.

Additionally, the potential market for C225, should it ever actually be approved, would most likely be much smaller than hoped. The number of head and neck cancer patients appropriate for C225 is much smaller than the company contends. Also, in earlier Phase II studies, C225 failed to show efficacy in other indications, including kidney, breast and prostate cancer. Moreover, competition from other potentially superior anti-EGFr antibodies and small molecules currently in development is likely to take away C225's market.

Significant patent and manufacturing issues further complicate the eventual commercialization of the product. Finally, the behavior of Merck KGaA, the company's European development partner, leads us to think that it, too, has serious reservations about the product.

ImClone's other products do not hold much promise for investors in the near term. They include BEC2, a cancer vaccine in Phase III trials. Despite the product's late stage of development, ImClone has received only \$3 M of a potential \$22.5 M in milestones from Merck KGaA, its worldwide development partner for the product. ImClone will also bear a significant portion of the product's worldwide development costs, including nearly 40% of Phase III costs, and building a manufacturing facility for the product. Moreover, the product will not be filed for approval until 2002 at the earliest. ImClone also plans to file an IND for c-p1C11, a chimerized monoclonal antibody that blocks vascular endothelial growth factor (VEGF) and inhibits angiogenesis (new blood vessel growth) in solid tumors. At this early stage of development, the compound contributes little to ImClone's market value. The IND filing for this product was expected in early 1999, but now is scheduled for 4Q99.

Triggers to a disappointment could be close for ImClone on both the clinical and business fronts. As we detail below, FDA approval based on a BLA filing for C225 using the Phase II studies seems unlikely. We think investors will have to wait for the Phase III data, pushing approval back to at least 2002. Such a delay would significantly narrow C225's lead over potentially superior products from several companies, including Abgenix, AstraZeneca, and Pfizer. Moreover, relations with its European partner, Merck KGaA, appear to be tenuous. Merck is holding back on issuing a \$30 M line of credit, for reasons that may include doubts about C225's potential. As a result, at least \$14 M in payments made by its European partner are recorded as liabilities deemed "potentially refundable". Merck may be waiting to cancel its deal until it can register and sell some of its preferred shares in mid-

February. Should ImClone's story on the clinical or business fronts fall apart, support for the company would rapidly deteriorate.

Discussion:

I. Phase I/II Trials: ImClone has not been able to demonstrate efficacy for C225 as a single agent in humans, despite encouraging results in animal studies. As a result, the company is pursuing development of C225 only in combination with either chemotherapy or radiation. It thinks that C225 will enhance the efficacy of these approaches because the drugs will work synergistically. Chemotherapy agents and radiation are cytotoxic (kill cells by damaging DNA), but cancer cells can upregulate their repair mechanisms and divide their way out of damage. C225 is cytostatic (inhibits cell replication and repair), and so may complement the action of the cytotoxic agents.

ImClone has completed two Phase I/II trials of C225 in head and neck cancer, one in combination with cisplatin, a chemotherapy agent, and one in combination with radiation. Both of these studies were very small, with 12 and 16 treated patients, respectively. The studies suffer from significant design and conduct flaws that lead us to question the strength of the results. We think the company has oversold the results of these studies to investors, creating a false sense of security about the prospects for C225 in Phase II studies and beyond. Despite the confidence exuded by the company and its supporters, these studies provide little comfort regarding the efficacy of C225.

A. Phase I/II Trial with Cisplatin: The chemotherapy combination trial in patients with advanced head and neck cancer was completed in June 1999. ImClone has trumpeted these results, and has used them to justify moving forward with an aggressive Phase II program that it hopes will result in a mid-2000 BLA filing. The results are actually less impressive than many think, and leave open the question of C225's efficacy and safety.

The 12 patients treated in this study had recurrent squamous cell head and neck cancer. Most had received previous treatment, and had either not responded to therapy, or had relapsed. In the study, patients received cisplatin chemotherapy plus seven weekly doses of C225. The method of response evaluation has not been disclosed, nor was the duration of the response disclosed.

Nine patients completed therapy and were evaluable. Three patients dropped out of the study due to severe neuropathy, allergic reactions, and death. Six of the nine patients responded to therapy (67% overall response rate). Two of the nine evaluable patients (22%) had a complete response (tumor became undetectable),

while four (44%) had a partial response (greater than 50% reduction in tumor size). The company has disclosed that three of the six responders had previously failed cisplatin therapy. According to the company, this response demonstrates that C225 works to enhance the efficacy of cisplatin, since it is unusual for patients who fail one course of cisplatin to later respond. The Phase II trial in head and neck cancer now underway focuses on this patient population, and includes only patients who have failed previous cisplatin therapy.

At first glance, these results may seem impressive. Head and neck patients who have failed chemotherapy currently have no viable next step in therapy. C225 would likely be approved if it can work with other agents to shrink tumors in these patients. But by reporting a 67% response rate in the evaluable patient population, the company has glossed over several critical points. First, this is not the response rate in the relevant patient population. While three of the six responders had previously failed cisplatin therapy, three had not previously been treated with cisplatin. Thus, it is impossible to know if these cisplatin-naïve patients were responding to the cisplatin or to the cisplatin + C225. Second, the company has not disclosed how many of the non-responders had failed previous cisplatin therapy. If any of them did, this would argue against a synergistic effect for C225 in patients who had failed cisplatin. Third, if we consider that 12 patients were treated in the study, and only three had a response we can directly attribute to C225, then the response rate is only 25%, not the 67% reported. The hopes and dreams of investors in IMCL, it seems, are pinned on study results in just these three patients.

Moreover, there are some aspects of the study's design that might make C225 appear to be more efficacious than it actually is. First, we do not know how tumor response was evaluated in the trial. If, like other studies conducted by the company, response was evaluated by physical exam instead of CT scan, then the results are questionable. Physical exams are much less sensitive than CT scans, and their use results in higher reported response rates. Moreover, without a permanent visual record, blinded evaluators cannot corroborate the results. Second, the duration of response is not reported. We understand from other literature sources that a response of as little as four weeks is considered a reportable result. Other products approved on an accelerated approval basis (e.g., Camptosar, described below) have demonstrated an average six month duration of response.

The objectivity of the results is further compromised, in our opinion, by the conflicted position of the study's lead author. We note that this individual is well respected within the cancer research community, and now serves as president of the M.D. Anderson Cancer Center, where he led this study. However, he is also intimately involved with ImClone and C225 on a number of levels. Not only is he an inventor on the composition of matter patent covering C225, he also sits on the

company's board of directors and scientific advisory board, holds options on 183,476 shares of common stock, and has received consulting payments from the company for the past three years.

B: In our view, this trial provides little basis for moving into Phase II trials on an accelerated basis. We suspect the decision to pursue this strategy was based more on business than on scientific realities. In March 1999, when the company announced this accelerated strategy, its stock was languishing at \$11 per share, and it had about one year of cash in the bank. Faced with accelerating development and manufacturing costs, the company needed a new cash infusion. Since the company announced the potential for a mid-2000 BLA filing on March 10, the stock has appreciated more than 200%, and ImClone completed a very lucrative secondary offering at \$32 per share.

C: Phase I/II Trial with Radiation: The radiation combination trial, completed in January 1999, has also generated excitement among investors. It showed an amazing 100% overall response rate and 87% complete response rate among the 15 evaluable patients in the study. According to the company's most recent S-3, this compares to "historical response rates of approximately 40% in similar patients treated with radiation alone."

The 16 patients enrolled had advanced local squamous cell head and neck cancer that had not been previously treated. In addition to radiation therapy, the patients received eight weekly doses of C225. At the completion of the study, 13 of these patients had a complete response, while two had a partial response based on physical and endoscopic examination. One patient in the study suffered from a serious anaphylactic reaction three minutes into the first C225 infusion, requiring removal from the study. While company press releases state that the median duration of response was greater than 12 months, the duration is not noted in the scientific abstract of the study or in the company's recently filed S-3.

There are several reasons why the study results do not justify the excitement they have generated. First, the company is comparing these results to an historical control, e.g., the historical response rate of 40% treated with radiation alone. Such historical comparisons are dangerous, since they do not match treatment protocols, the types of patients included in the trial, or the methods used to assess response rates. The ImClone study investigator may have chosen younger, healthier patients with smaller tumors that would be more likely to respond to treatment. The historical result would be lower because it would include patients with more difficult disease states. Moreover, response in the ImClone study was measured by physical exam, not by CT scan as in historical comparisons. As discussed above, physical exams result in higher response rates and less objective assessment. Finally, these

results should be compared to the current standard of care for patients with previously untreated local advanced head and neck cancer. This is not radiation alone, but radiation plus chemotherapy. In controlled trials of patients with local advanced disease who have not received prior therapy, the overall response rate to radiation plus chemotherapy is 85%-90%. Complete response rates in this group are around 50%.

Our review of the literature and discussions with experts clearly suggests that patients with advanced local head and neck cancer should receive a combination of chemotherapy and radiation. Perhaps the investigators chose patients for this study who were highly likely to respond to radiation alone, e.g., healthier patients with smaller tumors. If this is the case, then radiation alone could have generated the results seen, making it possible that C225 added no additional therapeutic value at all.

D. Safety in Phase I/II Trials: Little information is available regarding the safety of C225. Company filings indicate that only 3 of the 200 patients given C225 have suffered from serious anaphylactic reactions. Rashes and nail bed changes have been noted in each of the clinical trials. The available information leads us to think that the compound is relatively safe, especially in the context of the serious cancer being treated. However, very few patients to date have received the higher dose (500 mg/m<sup>2</sup> loading dose, 250 mg/m<sup>2</sup> weekly dose) that will likely be used in the Phase II and III studies. In fact, by our count, only 10 patients have been dosed at this level. We are concerned about a higher rate of side effects when larger numbers of patients are given a higher dose.

II. Phase II Trials: ImClone has moved into an aggressive Phase II program based on the study results discussed above. Its goal in these studies is to demonstrate tumor shrinkage in patients who have failed all other forms of therapy. In this group of patients, C225 may serve an unmet medical need, and could therefore be approved under an FDA policy that allows for accelerated approval of cancer therapeutics “based upon a verified and recognized demonstration of objective tumor shrinkage” with effectiveness that outweighs toxicities. (“Reinventing the Regulation of Cancer Drugs,” FDA, March 1996).

ImClone bulls point to the accelerated approval in 1996 of Pharmacia & Upjohn’s Camptosar (CPT-11) as evidence that the hurdle for an approval is low enough for ImClone to jump. Camptosar was tested as a single agent in patients with metastatic colorectal cancer who had failed previous 5-FU therapy. Bulls point out correctly that Camptosar was approved based on open label single arm Phase II studies. ImClone will use open label studies to support its accelerated approval. They further note that the overall response rate in the Camptosar studies was low

(12.5%) compared to the responses seen in ImClone's Phase I/II studies (66% in the C225 plus cisplatin study).

The clinical trials for Camptosar provided much stronger proof of efficacy than what is likely to be generated by the ImClone studies. Camptosar showed consistent results in three separate Phase II studies with a total of 304 colorectal cancer patients. Data from a total of 503 colorectal cancer patients (Phase I and II) who had failed 5-FU were submitted for the accelerated approval. Results were assessed by CT scan, and confirmed by an independent review panel. The duration of response averaged six months.

In comparison, ImClone will submit Phase II results in just one study of 98 patients with refractory head and neck cancer, and one study of 98 patients with refractory colorectal cancer. With only one study in each patient group, there is no way to demonstrate consistent Phase II results across studies. Moreover, if the company is assessing responses with CT scans in the Phase II, it will have a difficult time matching the response rates seen with the less rigorous physical exam in Phase I/II. We also have no information regarding the duration of response seen in earlier trials, but we think that the company would have publicized the duration if it had been six months or more.

Companies developing products for accelerated approval typically consult closely with the FDA early in the development process, yet ImClone has not mentioned any FDA meetings regarding its Phase II plans. We note that the company has not hesitated to announce other positive interactions with the FDA, such as a "successful meeting" with the FDA prior to initiation of a Phase III trial. We think we would have heard about similar meetings surrounding the Phase II trials. If ImClone is proceeding without buy-in from the FDA, it could face significant problems down the line. Moreover, the company has not announced a fast track designation for C225, although it would be of great value to the company. To receive this designation, ImClone must establish for the FDA that C225 has the potential to fill a medical need not met by existing therapy. Perhaps it has not been able to establish this potential to the FDA's satisfaction.

ImClone has initiated two Phase II trials of C225 in combination with chemotherapy that it plans to use for a BLA submission in mid-2000. One is in patients with refractory head and neck cancer who have failed a regimen containing cisplatin, and one is in patients with recurrent colorectal cancer who have failed Camptosar. A review of the company's Phase II trials, coupled with the doubtful data generated by Phase I/II studies, suggest that a BLA filing based on this data is highly unlikely. Moreover, poor results from several other Phase II studies support our view that C225 will likely fail in a more rigorous testing environment.

A. Phase II Trial in Head and Neck Cancer: A Phase II study in head and neck cancer patients who have failed a regimen containing cisplatin began in June, with patients receiving treatment beginning in September. The company plans to enroll 175 patients at 40 or more sites, with 98 ultimately receiving C225 plus cisplatin. Forty-nine patients with progressing disease will comprise one treatment group, and 49 patients with stable disease will comprise the other. The study is open label and non-randomized. This means that all patients will receive C225 plus cisplatin, with the knowledge of both doctors and patients. The goal of the study is to demonstrate tumor reduction in advanced head and neck cancer patients who have failed cisplatin.

In our opinion, this study should fail to demonstrate the objective and verifiable efficacy required for an accelerated approval. First, this study is non-randomized. Therefore, no true statistical evaluation of efficacy is possible. FDA reviewers will have to compare the results of this study to historical results of other therapies in refractory patients to determine if the response seen can be attributed to C225. Second, the study is open label. Since the investigators know that the patients received the drug, they cannot be truly objective in their assessment of treatment response. These problems were overcome in the Camptosar trial by showing consistent results across three separate studies in a large number of patients, and by using CT scans for response assessment. “Street” analysts report that physical exams, rather than CT scans, will be used in this study to assess treatment response. If this is so, it clearly makes an objective, verifiable demonstration of tumor shrinkage difficult to obtain. Without CT scans, there will be no opportunity for blinded reads by multiple clinicians.

Further problems with the study are related to the efforts being made by ImClone to complete the study in time for a mid-2000 BLA filing. First, the study has a very high number of sites. This speeds enrollment, since more potential patients can be captured in a shorter period of time. With 40 or more sites and 98 treated patients, each site will have an average of just 2-3 patients each. Consistent efficacy within sites is hard to demonstrate with such a small number of patients. Second, the company is likely pressuring investigators to enroll patients quickly in the hope of filing a BLA by mid-2000. Under these time constraints, they may choose to enroll less desirable subjects (e.g., patients with larger tumors, poorer health, more concomitant conditions), which could result in poorer outcomes.

For these reasons, we think it is highly unlikely that this Phase II trial will support an approval for use of C225 with cisplatin in patients who have failed previous cisplatin therapy.

B. Phase II Trial in Colorectal Cancer: The Phase II study in colorectal cancer is not based on any Phase I/II results. Instead, the company chose to pursue this indication based on an observation in just one patient with colorectal cancer who responded to C225 plus Camptosar given under a compassionate use protocol. According to a recent presentation by the company, this patient had failed therapy with several chemotherapy agents, including 5-FU, oxaloplatin, and Camptosar. Therapy with C225 plus Camptosar resulted in a >50% reduction in liver metastases, and a reduction of CEA (a marker for colorectal cancer) from 1400 to 23. The duration of effect has been greater than six months to date.

A Phase II study in colorectal cancer in patients who have failed a regimen containing Camptosar began in July, and treatment commenced in October. The company plans to enroll 98 patients at 20 or more sites. The study is open label and non-randomized, meaning that all patients will receive C225 plus Camptosar. Patients will be prospectively stratified into two groups: those with progressing disease, and those with stable disease. The goal of the study is to demonstrate tumor reduction in advanced colorectal cancer patients who have failed Camptosar. No information on planned method of tumor assessment is disclosed.

This study suffers from many of the same problems as the Phase II head and neck cancer study. Again, it is non-randomized. Reviewers will have to assess response versus historical experience to determine if any response can be attributed to C225. If physical exams instead of CT scans are used to assess response, it will be difficult to determine the objectivity of the results. Finally, investigators will be under pressure to enroll patients quickly to meet company hopes for a mid-2000 filing based on the data. For these reasons, and because the product has previously shown efficacy in only one patient, we think it is highly unlikely that the data from this trial will support an early BLA approval.

C. Earlier Studies: As shown in the table below, the current Phase II trials are not ImClone's first attempt at moving C225 closer to approval. Details of these previous studies are mysteriously absent from the company's recent filings. We have gathered this information from company press releases, abstracts from scientific meetings, and "street" analyst reports.

Phase	Description	No. of Pts.	Results
Phase I	Single infusion in patients with EGFr positive tumors	13	Not reported
Phase I/II	Multiple infusion in patients with EGFr positive tumors	17	Interim results: 7 patients demonstrate stable disease after four weeks

Phase I/II	Head/neck and lung cancer with cisplatin	22	Of 9 evaluable patients at higher doses, 6 showed stable disease, 2 achieved partial responses
Phase I/II	Head/neck as adjunct to surgery (initiated in 1997)	4	Not reported
Phase II	Prostate cancer with doxorubicin (initiated 1/96)	36	Interim results: PSA* declined in 1 patient, stable in 4 patients, elevations in 14 patients. All responders had not had previous chemotherapy.
Phase II	Breast cancer with paclitaxel (initiated 5/96)	12	Not reported
Phase II	Kidney cancer as single agent (initiated 12/97)	54	Interim results: 1 partial, 2 minor responses; >25% have stable disease for min. 6 months

\*PSA (prostate specific antigen) is a marker for prostate cancer. Declines are indicative of tumor shrinkage.

The results of ImClone's efforts, when viewed in their totality, are much less encouraging than the results of Phase I/II trials reviewed above. We therefore remain very doubtful of C225's efficacy, and its ability to ever receive FDA approval.

**III. Phase III Studies:** ImClone is conducting two Phase III studies concurrently with the Phase II studies discussed above. These studies are designed to expand the indication for C225 to first line use with chemotherapy or radiation. Results of these studies will not be available until 2001, and approval for any expanded indication would not come until 2002 at the earliest.

**A. Phase III Trial with Radiation:** A Phase III study of C225 in combination with radiation as first line therapy in patients with head and neck cancer that has not metastasized was initiated in February 1999, with patient treatment beginning in April. The company plans to enroll 416 patients at 50 or more sites, with half of patients receiving radiation plus C225, and half receiving radiation only. The study is open label (it is difficult to blind administration of radiation) and randomized. The goal of the study is to demonstrate better local regional disease control at one year than seen with radiation alone. Direct exam and CT scan will be used to assess response. The company expects enrollment to take 1-1.5 years, and follow-up will take one year from the last enrolled patient. On this timeline, the earliest the final patient would exit the study is February 2001.

This study is meant to support the Phase II studies above by demonstrating the efficacy of C225 in a large controlled, randomized study. Moreover, it seeks to define a role for C225 as first line therapy in local/regional disease, a much larger potential market than the refractory patients being studied in Phase II. However,

experts tell us that in head and neck cancer, there are two patient types appropriate for radiation therapy: early stage patients who do very well with radiation alone, and later stage patients without metastases who should receive radiation in combination with chemotherapy. Note that patients with metastases typically receive chemotherapy as their primary treatment.

While the company has not disclosed specifics about the patients who will be enrolled in the study, neither early nor later stage patients without metastases seem appropriate for the success of this study. Patients with localized, early stage disease are usually treated with radiation and/or surgery. The cure rate in these patients is 90%. If this is the population in the study, how will C225 demonstrate a statistically significant improvement over radiation alone? Patients with more advanced but non-metastasized disease now typically receive concurrent chemotherapy and radiation. How can the study investigators ethically include these patients in a study using radiation and an unproven agent?

B. Phase III Trial with Cisplatin: A Phase III study of C225 in combination with cisplatin as first line therapy (e.g., cisplatin-naive patients) in patients with recurrent or metastasized head and neck cancer was initiated in June 1999. Patient treatment had not yet begun as of the company's most recent filing, but is supposed to begin in November. The company plans to enroll 114 patients at 50 or more sites, with half of patients receiving cisplatin plus C225, and half receiving cisplatin plus a placebo. The study is double-blinded and randomized. The goal of the study is to demonstrate better progression-free survival than seen with cisplatin alone. The company expects the study to take 1.5 years to complete.

Of all the studies underway at ImClone, this design is the most likely to establish whether or not C225 actually works to make cisplatin more efficacious. By looking only at cisplatin-naive patients, and comparing cisplatin only to cisplatin plus C225 in a controlled manner, we may finally get an objective measure of the product's efficacy. Unfortunately, we have data in only three patients in a poorly controlled Phase I/II study to suggest the result will be positive. While the company calls this a Phase III study, it is actually the first study in this patient population.

This study is small, just 114 patients, with 57 in each arm. The study with radiation has almost four times as many patients. A drop out rate of 25% (as seen in the Phase I/II with cisplatin) could reduce the number to 43 per arm. If C225 does not dramatically increase the response of these patients to cisplatin, there may not be enough power in the study to detect the improvement. With 50 sites, there will only be about two patients per site. It will therefore be difficult to demonstrate consistent results within sites. Moreover, with only one controlled study in this patient population, it will be difficult to demonstrate consistent results across

studies.

IV. Potential Market: ImClone claims that the potential market for C225 in head and neck cancer is comprised of 61,000 Americans who are diagnosed with this cancer each year. A review of the National Cancer Institute's incidence data and the success rate of currently available treatment modalities suggests that this may be a gross overstatement.

According to data from National Cancer Institute, in 1999 about 40,400 Americans will be diagnosed with cancers of the head and neck. We do not know the reason for the discrepancy with ImClone's estimates, but we suspect that ImClone might be including 18,100 thyroid cancer cases in its count. Thyroid cancer should not be included because it does not over-express EGFr, and so is not a target for C225 therapy. The various sites of head and neck cancer occurrence and their incidence are shown on the table below.

U.S. Estimated New Cancer Cases by Site, 1999

Tongue	6,600
Mouth	10,800
Pharynx	8,300
Other oral cavity	4,100
Larynx	10,600
Total	40,400

Source: NCI Surveillance, Epidemiology, and End Results Program, 1998.

In addition, these 40,400 patients are not all candidates for C225 therapy. About one third of patients are diagnosed with early stage, local disease. These patients have high cure rates with surgery and/or radiation, and so are unlikely to need C225. This leaves about 26,700 potential patients. However, about 30% of these patients are cured with a regimen of chemotherapy and radiation. This leaves 18,700 patients as potential candidates for C225, less than a third of ImClone's estimate. If therapy costs \$10,000 per year, then the maximum potential market for C225 in head and neck cancer is \$187 M. With generous penetration rates of 20% in the first two years C225 could be a \$37M product in this indication. We doubt that it could grow much beyond \$37M. Further growth would be inhibited by competing products, such as the Abgenix product.

Of course, investors are looking beyond the initial head and neck cancer indication for further revenue from C225. One "street" analyst puts the number of potential C225 patients at 700,000, and the potential sales for C225 at \$500 million - \$1 billion. ImClone has suggested that breast, prostate, lung, and kidney cancers would be candidates for C225 therapy. However, we know that C225 has already shown mediocre results in previous Phase II trials in breast, prostate, and kidney

cancer. Therefore, we think success in these cancers is even more unlikely than in head and neck.

V. Partnership with Merck KGaA: In December 1998, ImClone signed a development and commercialization agreement for C225 with Merck KGaA, a German pharmaceutical company. The deal gives Merck an exclusive right to market C225 outside of the U.S. and Canada, and to co-market the product with ImClone in Japan. Merck is to pay \$30 M in cash up front payments and milestones, and an additional \$30 M in payments for common stock priced at varying premiums to the market upon the achievement of additional milestones. Merck is also to guaranty a \$30 M credit line for the construction of a manufacturing facility for commercial production of C225.

While ImClone has pointed to this deal as validation of the potential of C225, Merck has not yet made any actual financial commitment to C225. Merck has paid ImClone \$14 M in up front and milestone payments, but these payments are currently booked as “potentially refundable.” An additional \$6 M in milestones has been earned but not yet paid, and will also likely be booked as potentially refundable. The two circumstances under which these funds must be repaid point to the tenuous nature of Merck’s commitment to C225.

First, Merck can terminate the deal if ImClone fails to obtain certain collateral licenses to patents that would be infringed by marketing of C225. ImClone has one year from the time these patents are deemed valid and not subject to opposition or appeal to secure these licenses. If it fails, ImClone must return all milestone payments to Merck, and pay \$500,000 in damages. We are not sure what patents are at issue here, but it is likely that Genentech’s chimerization and combination therapy patents (discussed in more detail in the patent section below) are involved. We think Genentech will drive a hard bargain for these licenses, demanding a significant payment and royalty on sales. Moreover, it could be years before these licenses are obtained, leaving Merck’s payments in doubt for some time. Note that ImClone must pay half of any royalties owed on these licenses for sales in Merck’s territory.

Second, if Merck chooses not to guaranty the \$30 M line of credit, then either party can terminate the deal, and ImClone must return all milestone payments to Merck (see Section 4.9 of the Merck agreement, included in ImClone S-3/A filed 1/11/99). According to the agreement, the line of credit was to be guaranteed once Merck and ImClone agreed on a production concept for the facility. The companies reached such an agreement in April 1999, but the credit line has still not been guaranteed. As result, Merck can cancel the deal and get back its \$14 M. According to the company’s most recent filing, ImClone and Merck are “currently working

toward securing” the guaranty.

We wonder why Merck is holding back the credit. Perhaps it is because if Merck cancels the agreement now, it loses nothing. Once it guarantees the credit line, however, its potential loss increases to \$32 M, since failure of C225 would make it very difficult for ImClone to repay the credit. If it has doubts about C225’s future, then waiting seems wise.

Some potentially important licenses granted to Merck under the agreement survive its termination, and may be the real reason that Merck did the deal in the first place. Merck now has an exclusive license in its territory (the world excluding the U.S., Canada, and Japan) to certain patents and patent applications controlled by ImClone that cover the use of anti-EGFr antibodies in combination with chemotherapy and radiation. If C225 fails in the U.S. and Canada, then Merck’s license becomes a world-wide license.

A license to these patents and patent applications might prove especially valuable to Merck since it has two other development programs that would benefit. Merck has its own humanized anti-EGFr antibody, called MAb 425, in Phase II development in Germany. With the license, it will be able to market its product in its territory in combination with chemotherapy and radiation without infringing ImClone. Merck is developing another anti-EGFr antibody, MDX-477, with Medarex. That compound is in Phase II development. Again, the ImClone patents could be important for marketing the product in combination with chemotherapy or radiation.

Merck certainly seems to be spreading out its bets by committing to three anti-EGFr antibody programs. It has committed nothing thus far to ImClone’s C225, and \$5.85 M to Medarex (\$4.35 M in equity). With its own program in Phase II, its spending is beginning to ramp up. Now that C225 has reached Phase III in the U.S., and its other two programs are nearing expensive Phase III trials, it is likely Merck will narrow down its efforts. With no further financial backing for C225 yet evident, we think Merck’s interest in the program may be flagging.

It should be noted, however, that Merck has made a significant investment in ImClone to date. In connection with the BEC2 program described below, in December 1997, Merck purchased 400,000 shares of preferred stock for \$40 M, on which it receives an annual dividend of \$6 per share. At present, 100,000 preferred shares are convertible into 800,000 shares of common stock at \$12.50 per share. On January 1, 2000, an additional 100,000 shares are convertible. Given the company’s current stock price, Merck has a significant incentive to keep ImClone’s stock price high long enough for it to recoup its \$40 M investment. Merck can register these

shares 90 days after the prospectus date, which will be approximately mid-February.

## VI. Other Issues

A. Patents: ImClone's patent position on C225 is weak in several respects. First, it does not have a composition of matter patent on C225. It has licensed a U.S. patent covering the murine (mouse) form of C225 (Patent 4,943,533), and will rely on the doctrine of equivalents to protect its position. Under this doctrine, no one else could market another version of C225 (chimeric or otherwise) because it would do substantially the same thing in substantially the same way to achieve the same result. Should another company try to market another version of C225, ImClone would have to sue for infringement and possibly face a jury trial. The outcome of such a trial is far from certain. Moreover, the licensed murine patent was not filed outside of the U.S., so protection in Europe and Japan against other versions of C225 is non-existent.

With insufficient protection of C225's composition of matter, the company must instead rely on filed method of use patent applications covering the use of anti-EGFr antibodies in combination with radiation and chemotherapy. The Canadian patent for use with chemotherapy has issued (Canadian patent 1,340,417), but the U.S. and European patents have not. The company has disclosed that a Genentech patent (U.S. Patent 5,770,195) has issued with similar claims. ImClone has so far pushed aside concerns about infringement, saying its patent counsel and a special patent counsel have written non-infringement opinions. We think the claims are very similar, and that this will be a problem for ImClone for years to come.

The Genentech and ImClone patents both claim the use of anti-EGFr antibodies and chemotherapeutic agents in combination. The key difference pointed out by ImClone's attorneys is that the Genentech patent claims the antibody "sensitizes" the tumor cells to the chemotherapeutic, while ImClone patent claims the antibody and the chemotherapeutic both work to inhibit the growth of tumor cells. We think the matter is too close to call. Without a patent on combination use, however, ImClone has very weak protection for the use of C225. We suspect Genentech will recognize ImClone's difficult position, and will make ImClone pay dearly for a license or else take them to court.

Finally, the method of making C225 likely infringes another Genentech patent covering the chimerization process (Patent 4,816,567). This patent is known as the "Cabilly" patent, and is recognized as a key patent teaching the method of making antibodies comprised of fragments from two different species. Genentech sued Centocor in 1994 for infringing the same patent, and now receives royalties on sales of Reopro in settlement of the suit. Without a license to this patent, C225 would

infringe Cabilly, and ImClone would be subject to treble damages.

**B. Manufacturing:** ImClone has responsibility for manufacturing world-wide clinical and commercial supplies of both C225 and BEC2. Monoclonal antibody production is quite an undertaking for any company, let alone one with resources as limited as ImClone's. Industry sources tell us that Genentech invested \$250 M in its manufacturing facility for Herceptin. ImClone's soon-to-be constructed facility for C225 is estimated to cost \$40 M. We think significant further investment will be required to make C225.

**C. Competition:** ImClone faces significant competition from other companies targeting the EGFr receptor with antibodies and small molecules. While these companies are behind in development, their products may be superior to C225. Should C225 ever reach the market, one or more of the following products may quickly replace it.

Perhaps the most important potential competitor for C225 is Abgenix' anti-EGFr antibody, ABX-EGF. While C225 is chimerized (part human, part mouse), ABX-EGF is fully human. Thus, it has no mouse fragments that could elicit an immune response leading to the anaphylactic reactions seen with C225. Moreover, experts feel that because it is fully human it will be more potent than C225. Recent data suggests that ABX-EGF may be 5-10 times more potent than C225. It is being developed as monotherapy (as opposed to C225's combination therapy with chemotherapeutics), which should make demonstrating efficacy much more straightforward. While only in Phase I testing at present, strong results could propel it forward rapidly.

Product	Developer	Description	Development Stage
ABX-EGF	Abgenix	Human anti-EGFr antibody	Phase I
Mab 425	Merck KGaA	Humanized anti-EGFr antibody	Phase IIa
MDX-477	Medarx/Merck KGaA	Humanized anti-EGFr antibody	Phase II
Iressa (ZD 1839)	AstraZeneca	Tyrosine kinase inhibitor, inhibits EGFr (small molecule)	Phase III (initiate early 2000)
CP358,774	Pfizer	Tyrosine kinase inhibitor, inhibits EGFr (small molecule)	Phase II

## VII: Other ImClone Drugs and Collaborations:

BEC2 is a monoclonal antibody being developed by ImClone as a cancer

vaccine to be given to patients after an initial response to other cancer therapy. It is intended to boost a patient's immune response to cancer cells, and therefore reduce cancer recurrence or slow its progression.

BEC2 has been in development at ImClone at least since the company went public in November 1991. At that time, the compound was called MelVax, and was being developed for malignant melanoma. The company heavily touted the pilot study results, but the product never moved forward in development for this indication. It was later reincarnated as a vaccine for small cell lung cancer.

Information on the efficacy of BEC2 is very limited. The company and its partner, again Merck KGaA, have moved into a 570 patient Phase III trials based on the results from one 15 patient Phase I trial. This trial for small cell lung cancer was supposed to have been initiated in May 1998, with enrollment taking two years. Now the company estimates enrollment will be complete in 2001, with a possible BLA filing in 2002.

Merck KGaA licensed BEC2 worldwide in April 1990. ImClone retained the right to co-promote the product in the U.S. Since 1990, Merck has paid ImClone just \$4.7 M in research support payments and \$3 M in milestones. Merck is to pay another \$19.5 M upon the achievement of product development milestones. ImClone will also receive single digit royalties on sales of BEC2 outside of the U.S., although a portion of the milestones will be credited against royalties.

ImClone tells investors that Merck is responsible for the cost and conduct of the BEC2 Phase III trial. However, if these costs exceed \$9 M, then ImClone must pay 40% of the excess expenses. This level has not yet been reached, despite supposed initiation of the trial. Clinical material alone would likely push spending toward the \$9 M level. Note that in the C225 program, ImClone's spending on contract manufacturing alone will exceed \$6.4 M. Moreover, nowhere in the ImClone filings do we find mention of BEC2 manufacturing, although it is ImClone's responsibility. We suspect, therefore, that the Phase III trial, while perhaps technically "initiated", has not yet begun treating patients. As with the C225 program, Merck seems to be cautious about moving forward.

ImClone plans to file an IND for c-p1C11 in 4Q99. This chimerized antibody targets KDR, a principle receptor the VEGF (vascular endothelial growth factor). The agent is designed to block binding of VEGF to KDR, thereby inhibiting tumor growth. Little else about the agent is currently disclosed.

ImClone also has collaborations with Abbott, American Home Products, and Immunex. None of these are viewed as significant near or long term revenue

generators for the company, and so will be reviewed in a later update.

### VIII. Company History:

ImClone Systems is not a new name for seasoned investors. The company went public during the biotech glory days in 1991, at \$14 per share, and reached \$27 before the biotech market fell apart in early 1992. The stock languished for several years, dipping below \$1 per share in early 1995. In May 1996, it reached \$17 a share on the promise of C225 for breast cancer, and an expansion of Merck KGaA's deal for BEC2. Until March 1999, however, ImClone's shares remained below \$14 as investors waited for more positive clinical results. In March 1999, the company announced a potential mid-2000 filing for C225, again exciting investors. Since then the stock has performed well, reaching almost \$39.

Management at ImClone has a colorful past. The CEO and COO are brothers who founded the company in 1984 when they were 38 and 31 years old, respectively. The CEO left his position as the Director of Immunopathology at Mount Sinai School of Medicine to found ImClone. Rumors about the circumstances surrounding the CEO's departure appeared in a Barron's article published in 1993. Several former colleagues suggested that the financial condition of the department was under a cloud at the time. Moreover, some questions were raised about the ownership of some molecular modeling technology later pursued by ImClone. The COO was just finishing his residency in Pathology at the time ImClone was founded. Just two years before, however, he was found guilty of possession of cocaine with intent to distribute, and sentenced to nine years in prison. He appealed, and in 1993 the conviction was overturned based on an illegal seizure of the evidence. Since the ruling threw out the evidence in the case, it was not retried, and no time was served.

The company has also made significant loans to the CEO and COO. In earlier years, these loans were for amounts as high as \$374,000. Most recently, in January 1998 the company loaned the CEO \$131,000, at an interest rate of 8.5%. This loan is still outstanding. Note that the CEO earned \$900,000 in salary and bonus in 1998. In October 1998, the company loaned the COO \$100,000. This loan was paid in full in April 1999. The COO earned \$550,000 in salary and bonus in 1998.

We note also that the CFO hails from D. Blech & Co., where he served as Director of Research from June 1991 until June 1994, just three months before the firm failed so spectacularly. Finally, two board members are luminaries in the field of cancer research, and both lead institutions where ImClone clinical studies have been conducted. We are concerned that their involvement with the company may

lead to conflicts of interest in clinical trials.

IX. Financial projections: N.B. Our projections assume that over the next year ImClone does not receive the \$30 M line of credit from Merck KGaA, and does not acquire the necessary collateral licenses. It will therefore be unable to recognize previous or future milestones as revenue. Additionally, we assume that the BEC2 project does not move forward, and no further milestones are received.

\$000	1Q99	2Q99	3Q99	4Q99e	1999e
License Fees					
Milestones	-	-	-	500	500
BEC2	-	-	-	-	-
R & D Funding	-	-	-	-	-
BEC2	425	108	-	-	533
Infectious Disease	75	75	75	-	225
Royalty (Abbott)	124	71	63	100	358
Other	5	-	-	-	5
Total Revenue	629	254	138	600	1,621
R & D Expenses	6,354	7,151	8,626	10,000	32,131
General/Admin.	2,002	1,675	2,107	2,191	7,975
Total Expenses	8,356	8,826	10,733	12,191	40,106
Interest Expense	(123)	(123)	(150)	(151)	(547)
Interest Income	(228)	564	589	1,140	2,065
Preferred Dividends	(928)	(934)	(938)	(930)	(3,730)
Income Before Taxes	(9,006)	(9,065)	(11,094)	(11,532)	(40,697)
Income Taxes	-	-	-	-	-
Income After Taxes	(9,006)	(9,065)	(11,094)	(11,532)	(40,697)
EPS	(0.37)	(0.36)	(0.44)	(0.41)	(1.43)
Avg Sh	24,447	24,986	25,398	28,400	28,400

\$000	1Q00e	2Q00e	3Q00e	4Q00e	2000e
License Fees					
Milestones	500	-	-	-	500
BEC2	-	-	-	-	-
R & D Funding	-	-	-	-	-
BEC2	-	-	-	-	-
Infectious Disease	-	-	-	-	-
Royalty (Abbott)	125	150	200	200	675
Other	-	-	-	-	-
Total Revenue	625	150	200	200	1,175
R & D Expenses	10,000	10,000	10,000	10,000	40,000
General/Admin.	2,279	2,370	2,465	2,563	9,677
Total Expenses	12,279	12,370	12,465	12,563	49,677
Interest Expense	(151)	(151)	(151)	(151)	(604)
Interest Income	1,600	1,550	1,500	1,450	6,100
Preferred Dividends	(930)	(930)	(930)	(930)	(3,720)
Income Before Taxes	(11,135)	(11,751)	(11,846)	(11,994)	(46,726)
Income Taxes	-	-	-	-	-
Income After Taxes	(11,135)	(11,751)	(11,846)	(11,994)	(46,726)
EPS	(0.39)	(0.41)	(0.42)	(0.42)	(1.65)
Avg Sh	28,400	28,400	28,400	28,400	28,400