Companies: Telik, Inc. (TELK)
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We recently identified Telik Inc. for review as a short thesis, based on its 1) relatively high market capitalization predicated on 2) excessive optimism in anticipation of clinical trial results from the company's first product.

Telik closed on October 14 at $22.80, giving it a market capitalization of $819 million based on 35.9 million shares outstanding (33.3 million float). With increasing daily volume (335,000 in last ten days versus 293,000 in last 90 days) and a decreasing short position (from 2.72 million in August to 2.22 million in September), the short ratio sits at ≈ 8.5 days (6.7 percent of float). At June 30, Telik reported $67.1 million of cash and equivalents ($1.87/share) and de minimis revenues of $1.29 million in the last twelve months.

Conclusion: Telik provides a strong short opportunity, but not for at least six months, with June 2004 (ASCO) providing a useful target date before which a follow-up review is warranted. Signals to look for will include a capital raise, increased announcements of early-stage clinical trials and "positive" clinical progress based on preliminary/interim analyses. Telik has embarked on two very high-risk, fundamentally experimental Phase 3 trials of its most advanced drug candidate, Telcyta. Targeting third-line ovarian cancer (no treatments exist) and third-line NSCL cancer (only AstraZeneca's Iressa is approved), the Company has conducted only small, single-arm, open-label Phase 2 trials of mixed (2nd and 3rd line) patient populations. Further, the scientific rational for Telcyta's tumor specificity appears flawed.

Introduction:

Founded in October 1988 as Terrapin Diagnostics (then Terrapin Technologies), the Company struggled for almost ten years, first in developing diagnostics, then pursuing rational drug design with an approach it called molecular mimicry. During that time, Telik also developed a screen for small molecules based on their binding affinity for a panel of 18 clinically relevant proteins. This became Telik's *TRAP* technology, for which it has booked several partnership agreements. These are uniformly insignificant, economically. The Company also had an active chemistry group synthesizing inhibitors of various clinically important enzymes.

Still, it wasn't until the biotechnology bubble in mid-2000 that Terrapin, now renamed Telik with all new management, was able to come public. That August, attempting to raise $50 million at $160 million pre-money (5.0 million shares at $9.00 to $11.00), Telik was only able to raise $35 million at $113 million pre-money (5.0 million at $7.00). Through March 2000, the Company had raised roughly $61 million through 11 rounds (Series K) of venture financing.

In January 2000, Telik initiated its first clinical trial, testing TLK286 ('286, now called Telcyta) in 36, no-option patients suffering from late-stage Non-Hodgkins lymphoma or other undisclosed solid tumors. The first patent application describing this molecule was filed, and later abandoned, in April 1991. The absence of better molecules and the long delay before entering the clinic suggest Telcyta may simply be the best Telik could come up with. And, that it may not be very good at all. This report focuses on Telcyta's clinical development, since that will be the key driver of Telik's stock over the next 15 months.

Telcyta

When a cell encounters a foreign, potentially noxious molecule, including a drug, several mechanisms exist to remove it. The liver's *cytochrome P450* enzyme system does just this, often by inactivating the molecule. Similarly, so-called *heat-shock proteins* (also called stress proteins) are produced in response to physical or chemical stresses. A third detoxification mechanism is enzymatic modification of the molecule to one which is more readily excreted by the kidneys. *Glucuronidation* and *glutathionylation* are two such systems. The last involves an enzyme, glutathione-S-transferase (GST), which, as the name implies, transfers a glutathione molecule to any number of target molecules, facilitating their excretion. Many chemotherapeutics used to treat cancer, especially halogenated (containing halogen atoms such as fluorine, chlorine, bromine) aromatics (water-insoluble), are detoxified by tumor cells over-expressing GST. Thus, chemotherapeutics such as Xeloda, Carmustine and Gemzar become less effective over time as tumor cells foster their removal. Agents designed to block GST, therefore, are called chemosensitizers.

In the early '90s, Telik was designing chemosensitizers to block GST. While this effort was not fruitful, it gave rise to an alternative strategy, that of using a glutathione-based pro-drug to target GST over-expressing tumor cells. Telik chose as a payload for the pro-drug a member from the oldest class of chemotherapeutics, a so-called nitrogen mustard. The first FDA approved oncology drug, cleared March 15, 1949, was Merck's Mustargen (meclorethamine), for NSCL. Telcyta (FKA TLK286, TER286) is a nitrogen mustard pro-drug being tested in ovarian and NSCL cancers. Both Phase 3 trials (NSCL begins Q4/03) are called *ASSIST-1* (ovarian) and *ASSIST-2* (NSCL). ASSIST is Assessment of Survival in Solid Tumors. Finally, a Phase 2 trial in CR cancer did not support further clinical development for that indication. Telcyta is dosed IV at 1,000 mg/m² every three weeks.

Each trial will be conducted under a Special Protocol Assessment (SPA). This means that the FDA and Telik have agreed, in writing, to the trial's design. It also mandates, barring unforeseen adverse clinical events, that FDA is committed to approve the drug if all criteria are met. Finally, a single pivotal trial will be adequate for FDA review.

Ovarian Cancer - SOC

No drug has formal approval for third line use in ovarian cancer. In the US, the SOC for first line ovarian cancer, post ovariotomy, is Taxol (paclitaxel) plus a platinum-based agent such as cisplatin or carboplatin (e.g., Bristol Myers' Platinol or Paraplatin, respectively). Salvage (second line) therapy typically employs Hycamtin (topotecan) or Doxil (PEGylated liposome-encapsulated doxorubicin). A summary of the clinical results for each salvage regimen is below:

5/28/96: FDA clears Hycamtin (topotecan), IV topoisomerase I inhibitor (semi-synthetic camptothecin derivative), for 2nd line ovarian (and 2nd line SCLC);
Ovarian: Ph 3 in platinum-refractory; Hycamtin (N=112; ORR 21% (6 CR + 18 PR) vs Taxol (paclitaxel; N=114; ORR 14% (3 CR + 13 PR) (p=0.20); Median survival was Hycamtin (63.0 weeks) vs Taxol (53.0 weeks), (p=0.87); 2nd Ph 3: Open label in 111 pt.s, ORR 14%, median survival 67.9 weeks.

6/28/99: FDA expands Alza's sNDA for Doxil (liposomal doxorubicin) for paclitaxel and platinum refractory ovarian; Based on 3 (2 US, 1 OUS), open-label, single arm studies; Of 176 women, 145 refractory to paclitaxel and platinum (i.e., progressed either on regimen or w/in 6 months); Combined OR (CR, PR not broken out) was 20/145 (13.8%) as US-1 (6/27) + US-2 (14/82) + OUS (0/36); No data on survival; At least 1 CR was observed.

On the next page, Telik's Phase 2 designs and results are compared with the planned Phase 3 trial design for both ovarian and NSCL.

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TLK286 for Ovarian Cancer

Phase 2 Results

Begun in May 2001, '286 as monotherapy was tested as *second line* therapy in 16 ovarian cancer patients refractory to (1st line) SOC chemotherapy of cisplatinum and Taxol. An additional 20 patients had received one-to-three salvage therapies including Doxil (N=12), Hycamtin (N=10), Gemzar (N=4) or Taxotere (N=1). These 20 patients received '286 monotherapy as *third line* therapy. The study was *single arm and open-label*. Telik's May 19, 2002 press release updated Abstract #831 from ASCO, reporting that for 31 evaluable patients, there was a 13 percent overall response rate (1 CR, 3 PR). Telik's November 20, 2002 PR updated the data, with 34 evaluable patients. The ORR was 15 percent (1 CR, 4 PR) and the median survival was greater than 16 months. The single CR was cancer-free and off chemotherapy at June 2003.

Phase 3 Design

In late March 2003, Telik initiated testing of '286 monotherapy in 440 women as *3rd line therapy* (failed cisplatinum/Taxol, then failed Doxil or Hycamtin). Women will be randomized to '286 (N=220) versus J&J's Doxil or Glaxo's Hycamtin (N=220), whichever had not been used previously. The PCE is improved survival versus the control arm.

Telik has reported the expected median survival for 2nd line ovarian patients is nine months and for 3rd line patients, six months. However, the Package Insert for Hycamtin, approved as 2nd line therapy (after failing a "platinum-containing regimen") noted that all patients receiving either Hycamtin or Taxol had median survival times of more than a year (53 to 68 weeks). The Package Insert for Doxil had no survival information, since only single-arm studies were conducted. Telik has not disclosed if the single CR received Telcyta as second- or third-line therapy.

Finally, in December 2002, Telik initiated two additional Phase 2 trials of Telcyta in ovarian cancer. Both trials are single-arm, combination therapy (Telcyta plus Doxil or carboplatin) as second line treatment (failed platinum-based chemotherapy). Further details (number of patients, trial duration, PCE) were not disclosed.

Added 2/7/05 (no other changes):

2/7/05: **FDA** *full approval* (sNDA filed 3/04) for Doxil (*doxorubicin;* PEGylated liposomal) for 2nd line ovarian; No better than GSK's Hycamtin (*topotecan*); Open-label Ph 3 of 474 Pt.s as Doxil (N=239; 50mg/m² q28d) vs Hycamtin (N=235; 1.5mg/M²/day for 5dCOT, q21d);
PCE was TTP (*4.1* vs *4.2 months*; p=0.617), median survival (*14.4* vs *13.7 months*; p=0.05, unadjusted for multiple comparisons), OR (*19.7%* vs *17.0%*;) Package Insert (paper, *DB*);

NSCL Cancer - SOC

In general, the SOC for NSCL is surgical resection followed by chemotherapy. In the absence of chemotherapy, median survival is roughly four months. With any of four combination drug regimens tested, cisplatin+paclitaxel, cisplatin+gemcitabine, cisplatin+docetaxel or carboplatin+paclitaxel) the median survival increases to 8 to 10 months.

Telcyta will be tested as third line therapy in NSCL cancer. Only AstraZeneca's Iressa has formal, albeit conditional, approval for third line use in this setting. In the US, the SOC for first line NSCL cancer is Taxol (paclitaxel) plus carboplatin. Salvage (second line) therapy typically employs Taxotere (docetaxel). A summary of the clinical results for taxotere as a salvage regimen follows.

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12/23/99: FDA expands Taxotere (docetaxel) to 2nd line NSCL (prior platinum, no taxane as 1st drug); *TAX'317*: Of 104 enrolled, docetaxel (N=55) vs BSC (N=49), PCE survival, ↑ from 4.6 to 7.5 months ($p \leq 0.05$), ORR 5.5%, TTP ↑ from 7.0 weeks to 12.3 weeks ($p \leq 0.05$) and 1y survival was 37% vs 12%; but, *TAX'320*: Of 373 enrolled (3 arms), docetaxel at 75mg/M²(N=125; 5.7 month median survival, TTP 8.3 weeks, 30% 1y survival) vs docetaxel at 100mg/M² (N=125; this arm dropped due to toxicity deaths) vs docetaxel+[vinorelbine or ifosfamide] (N=123; 5.6 month median survival, TTP 7.6 weeks, 20% 1y survival); No improvement in survival, TTP, ORR;

TLK286 for NSCL Cancer

Phase 2 Results

Begun in June 2001, '286 as monotherapy was tested in second line or higher, platinum resistant, NSCL. The PCE was survival at 12mFU. The study was *single arm and open-label*. In May 2002, ahead of the ASCO meeting, Telik reported preliminary results. Of 52 patients enrolled, 41 were evaluable and the median survival had not been reached at 39 weeks. Nine patients had failed only platinum; the others had also failed Taxol and 13 had failed second line Taxotere. In November, Telik provided final results for 51 patients (23 as second line, 28 as third line or greater), reporting a median survival of *nine months*.

Phase 3 Design

In October, Telik's Special Protocol Assessment was cleared with FDA for the ASSIST-2 trial of '286 monotherapy versus AstraZeneca's Iressa in 3rd line NSCL. The trial will randomize 500 patients and the PCE is improved survival.

Curiously, the median survival of nine months reported by Telik in its November 20, 2002 press release is at odds with that reported by its clinical investigators at the EORTC/AACR Conference. In that abstract (#106A), Papadimitrakopoulou et al. reported that median survival had not been reached and exceeded 10 months.

In October 2002, like with ovarian cancer, Telik initiated an additional Phase 2 trial of Telcyta in NSCL. The trial is a single-arm, combination therapy of Telcyta plus Taxotere as second line treatment (failed platinum-based chemotherapy). Further details (number of patients, trial duration, PCE) were not disclosed.

Risk Assessment

- *Experimental Phase 3 Trials* Both Phase 3 trials have improved survival as PCEs despite no rigorous evidence from the Phase 2 results of a survival benefit. Since both Phase 2 trials were single-arm studies, patients were not randomized into a comparator arm. Thus a survival benefit, or any benefit technically, is indiscernible. Comparing results to historical outcomes is unreliable. More than a few companies' pivotal clinical trials have failed due to unexpectedly robust results in the comparator arm.

  In addition, both Phase 2 studies tested mixed patient populations with respect to degree of prior-drug refractoriness. For example, the single CR in the ovarian Phase 2 trial may have originated in the second line cohort. Note that for both Hycamtin and Doxil, at least one CR was observed. Telcyta's survival benefit in ovarian cancer is dubious. Similarly, at nine months, the median survival result from the Phase 2 NSCL appears indistinguishable from past drug regimens. Although unethical, a clinical trial testing placebo in drug refractory NSCL patients might yield the same "benefit."

· *Questionable Drug Specificity* Telcyta has two chemically intriguing attributes. First, the payload is a nitrogen mustard. This is a class of toxic compounds (bifunctional DNA alkylators) that disrupt an actively growing cell. Thus, it is like many chemotherapeutics. Curiously, ovarian cancer is somewhat atypical in that it is *not* a fast-growing cancer which may explain why chemotherapeutics rarely, if ever, succeed in this inexorably fatal disease. Telcyta's "activity" in the ovarian cancer setting is enigmatic. Still, since the first oncology drug ever approved by the FDA was Merck's Mustargen, and that for NSCL, there is some reason for optimism in this second indication.

However, the second attribute of Telcyta is its pro-drug design. The embedded nitrogen mustard is inactive until released by glutathione-S-transferase, an enzyme which is overexpressed in various solid tumor types. Unfortunately, the apparent logic behind this design fails on two fronts. First, GSTs are abundant throughout the body and second, the enzymes lack substrate specificity. Like the cytochrome P450 system, detoxification enzymes *ought* to be able to attack multiple foreign agents. Thus, Telcyta's toxic payload should be deployed (in some sense diluted) in large organs like the liver and skin. The absence of reported toxicity for Telcyta more likely suggests sub-therapeutic dosing rather than inherent safety.