PTI Therapeutics, Inc
Overview of Proprietary Advanced Technologies for Oncology Therapeutics
Combinatorial Local and Oral Targeted Therapy

Postsurgical Therapeutics, Inc. ("PTI") is a privately held development stage company based in Irvine, California. PTI is a virtual company drawing on functional experts as needed. PTI is developing advanced drug delivery technologies and products formulated with them primarily for the treatment of cancer but including other diseases.

Advances in Medical Treatment of Cancer

Medical treatment of cancer includes chemotherapy and targeted therapy. Chemotherapy generally kills both cancer cells and normal healthy cells causing serious side effects. By contrast, targeted therapy interferes with molecules (generally proteins) specific to cancer cells and eventually kills only cancer cells. The targeted therapy is more efficient and less toxic than chemotherapy, resulting in improved overall survival rates for cancer patients. Many different targeted drugs have been approved by the FDA for use in the treatment of cancer. These targeted drugs include hormone therapy drugs, signal transduction inhibitors, gene expression modulators, apoptosis inducers, angiogenesis inhibitors, immunotherapy drugs and toxin delivery molecules.

Although targeted therapy improves patient outcomes, resistance eventually develops to the targeted therapy and cancer progresses. The resistance is caused by genomic alterations in cancer cells that enable a tumor to progress by alternative pathways.

Biopharmaceutical companies and others are investigating the simultaneous use of two or more targeted drugs to overcome the resistance. The use of multiple targeted drugs may be successful in blocking all potential pathways that may enable cancer cells to survive. This approach has been successful for the treatment of some types of cancer. However, most targeted drugs are administered orally or intravenously (IV). As a result, serious systemic side effects may result from the cumulative side effects of multiple targeted drugs.

PTI's Technologies for Advanced Medical Treatment of Cancer

To avoid the side effects associated with systemic absorption of multiple targeted drugs, PTI is developing a novel delivery approach, a Combination of Local and Oral Targeted Therapy ("CLOTT") along with appropriate diagnostics. Although PTI prefers that all targeted drugs for treatment to be delivered locally (i.e. intratumorally), there are some targeted drug with relatively low potency that are not suitable for local administration. For example, a targeted drug requiring more than 100 mg daily oral or intravenous dose may require a dose that is too large for a long acting dose for local administration. The dosing interval may be shorter than is acceptable for general use. PTI targets one injection at interval of one to three months.

Local delivery by intratumoral injection is expected to virtually eliminate systemic exposure of the delivered drug while maintaining therapeutic levels in the tumor. The overall systemic side effects would be limited to the effects of the targeted drug administered orally or intravenously. The use of CLOTT is expected to avoid the serious side effects observed with systemic delivery of two or more targeted drugs.

PTI is also developing formulations of two or more potent (daily oral dose of less than 100 mg) targeted drugs by encapsulating them in formulations of Polylactic Glycolic Acid (PLGA) (microsphere or in situ gelling formulation) for sustained, controlled release over periods ranging from one to three months.

The formulations will be administered pre- or post-surgery. For pre-surgery treatment, the formulations can be delivered intratumorally by use of an ultrasound image-guided system for delivery to specific locations. As further described below, PTI is collaborating with a company based in Germany that developed a hand-held ultrasonic image-guided system. For treatment after surgery, the controlled release formulations can be applied to the resected area using a suitable hand-held sprayer before the surgical site is sutured.

PTI believes that these polymeric formulations can also be used for the treatment of metastatic cancer. Based on genetic differences between the primary and secondary tumors, one group of targeted drugs would be delivered to the primary cancer site and a different group of targeted drugs would be delivered to secondary cancer site(s) without causing the serious side effects resulting from systemic administration.

PTI's Product Development

Recent reports have determined that 60 – 70% of all cancers are caused by mutated oncogenes involved in MAPK and PI3K pathways[1]. Among oncogenes in the MAPK pathways, KRAS mutations are present in approximately 25% of all cancers, making them one of the most common gene mutations linked to cancer. They are frequent drivers in lung, colorectal and pancreatic cancers. KRAS drives 32% of lung cancers, 40% of colorectal cancers, and 85% to 90% of pancreatic cancer cases.

The MAPK and PI3K pathways crosstalk and provide an escape route if one of two pathways is blocked by a specific inhibitor. There have been many clinical trials to block both pathways simultaneously by combining inhibitors for both pathways. However, cumulative systemic toxicity caused by combined inhibitors was difficult to overcome during Phase 1 clinical trials. In order to reduce the systemic toxicity, patients were treated with less than effective dose or intermittent dosing schedule, which is not an optimal treatment. For example, the results of a Phase 1 study investigating oral everolimus (mTOR inhibitor) combined with oral sorafenib (RAF

inhibitor) in patients with advanced hepatocellular carcinoma (HCC), the everolimus maximum tolerated dose (MTD) in combination with standard dose of sorafenib was only 2.5 mg once daily dose, which was lower than a therapeutically effective dose of 5 – 10 mg.[2] The results of that Phase 1 study did not establish a recommended Phase 2 dose. In another example, a Phase 1b study investigated the safety and MTD of oral trametinib (MEK inhibitor) in combination with oral everolimus (mTOR inhibitor) in 67 patients with advanced solid tumors. The results of that combination treatment study were frequent treatment-related adverse events and did not establish a recommended Phase 2 dose and schedule due to severe systemic toxicity[3]. In addition to these two examples, there are many additional failures of early clinical trials for combination therapies due to severe systemic side effects[4].

Using CLOTT platform, PTI is investigating two combinations of targeted therapies for blocking both PI3K and MAPK pathways:

Combination 1 = sorafenib + everolimus
Combination 2 = trametinib + everolimus

Preliminary Animal Studies for Combination 1

PTI's first study investigated tumor growth in mice following administration by intratumoral (IT) injection compared with oral administration.

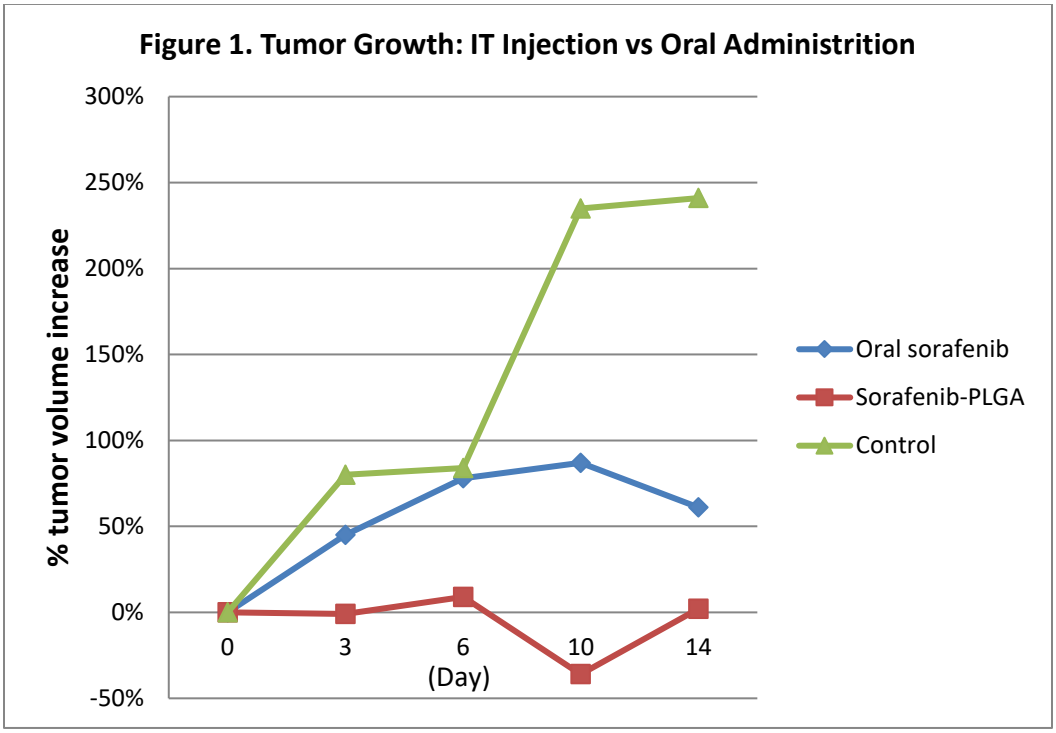
Using the C26 tumor bearing mouse model, Torok previously reported that sorafenib taken orally did not penetrate and distribute into tumor tissue and consequently tumor still grew although sorafenib was active in vitro against C26 cells[5].

PTI developed PLGA microsphere formulations of an MAPK pathway inhibitor (sorafenib, a RAF inhibitor) and a PI3K pathway inhibitor (everolimus, mTOR inhibitor) and completed a preliminary animal study to test the hypothesis that IT injection can overcome the problem of insufficient penetration and distribution of some orally-administered targeted drugs into tumor tissue.

The results of PTI's study were that direct IT injection of sorafenib encapsulated in PLGA microspheres released sorafenib slowly into tumor tissue and stopped the growth of tumor (Figure 1). For this study the back of mouse was inoculated with C26 cells. When the tumor grew to about 200 mm^3, the mice were randomized into three treatment groups:

Group1: Sorafenib-PLGA microspheres were injected once using syringe with 21-gauge needle (30 mg of sorafenib-PLGA microspheres containing 4.5 mg of sorafenib)
Group 2: Oral sorafenib (API) was given 5 times a week for two weeks (100 mg/kg dose)
Group 3: Solution of sorafenib used to make PLGA microspheres was injected as a control.

After treatments, tumor growth of the three groups was monitored for 14 days.



The results indicate that there may be differences between the control and sorafenib-PLGA and between oral sorafenib and sorafenib-PLGA.

Additional *in vitro* and *in vivo* studies for Combination 2

To complement the initial Preliminary Study, PTI developed an 'in situ gelling' formulation of trametinib-PLGA and everolimus-PLGA. The combination is being tested in *in vitro* and *in vivo* studies.

PTI is testing the combination against cancer cell lines and mouse models associated with several subtype mutations of KRAS:

- AGS cell line: Stomach cancer with G12D subtype mutation
- Mia Paca-2 cell line: Pancreatic cancer with G12C subtype mutation
- NCI H441 cell line: Lung cancer with G12V subtype mutation
- SW 403 cell line: Colon cancer with G12V subtype mutation

These studies are scheduled for completion by November, 2023; relevant reports will then be prepared.

Enabling Technologies

Ultrasound Image-Guided Delivery System & Multiport Needles for Injection

To enable IT delivery of the formulations to the tumor(s), PTI is collaborating with EZONO, based in Jena, Germany. EZONO has developed and commercialized its eZGuide system which utilizes real time ultrasound images to guide the needle to deliver the formulations to the desired location within the tumor. The companies recognize that delivering formulations at multiple locations in tumor tissue will be more effective than to a single location. In addition, PTI is developing a 19 – 21 gauge needle with multiple pores along its length to deliver formulations to wider areas within the tumor(s).

Intellectual Property

PTI filed a provisional patent application in April, 2020 (#63/008,554). The provisional patent application was converted into a non-provisional patent application in the United States and was also filed in Europe in April, 2021. PTI is preparing a CIP to strengthen the original application and plans to file it in November, 2023.

Commercialization Strategy

PTI intends to continue development of the technology and resulting products through collaborations with corporate partners and others. The corporate partners will complete the development, obtain regulatory approvals and commercialize the approved products worldwide.

REFERENCES

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