Transgene (TNG.PA)

Transgene’s Asset Portfolio Provides Potential Synergies with Immune Checkpoint Inhibitors Across Various Cancer Indications.

On February 13, Transgene (Paris: TNG.PA) announced that it has dosed the first patient in a Phase I trial evaluating the oncolytic virus Pexa-Vec plus Bristol-Myers Squibb’s (NYSE: BMY) anti-CTLA-4 mAb, Yervoy (ipilimumab), in the treatment of locally advanced and/or metastatic solid tumors. The Phase I, investigator-led, open-label trial is evaluating safety and efficacy of the combination in this setting. Interim results are expected at the end of 2017. In addition to this ongoing Phase I trial, Transgene is conducting three separate trials combining either their therapeutic vaccines or oncolytic viruses with immune checkpoint inhibitors, which we describe below.

- **Transgene is Developing Multiple Oncology Assets in Combination Trials.** In addition to the Phase I trial of Pexa-Vec plus Yervoy in solid tumors, Transgene has several ongoing trials evaluating its immune-targeted therapies with approved immune checkpoint inhibitors. Of note, the Company recently established a collaborative agreement with UC Davis to support an investigator-led trial to evaluate TG4010 in combination with the Bristol-Myers Squibb’s anti-PD1 therapy Opdivo (nivolumab) in non-small cell lung cancer (NSCLC) patients who have progressed after one line of platinum-based chemotherapy. The mechanism of action for Transgene’s assets, and their safety profile, make them ideal candidates for combination therapies. For example, the potential induction of immuno-surveillance by Pexa-Vec, and the potential upregulation of immunosuppressive factors in response to TG4010, make both of these promising candidates for combination with immunotherapies.

- **Transgene and Léon Bérard Cancer Center Announce Dosing of the First Patient in a Combination Trial for Solid Tumors.** Transgene and the Léon Bérard Cancer Center announced that the first patient in a Phase I trial to evaluate the safety and efficacy of the combination of Pexa-Vec and Yervoy in patients with locally advanced and/or metastatic solid tumors. Pexa-Vec is Transgene’s engineered oncolytic vaccinia virus in development for several cancer indications. Oncolytic viruses are intended to exploit multiple mechanisms to selectively kill tumor cells. The Pexa-Vec virus is engineered with a disruption of thymidine kinase (TK), a gene necessary for viral replication that is expressed primarily in rapidly dividing cells such as cancer cells due to its role in DNA synthesis. TK disruption minimizes replication of Pexa-Vec in healthy cells, which do not express sufficient levels of TK to support viral replication.

**Expected Upcoming Milestones**

- H1 2017 – Initiate Phase II trials with TG4010 + ICI in 1st line NSCLC.
- H2 2017 – Expected data from Phase I/IIb trial with TG4010 and Opdivo in 2nd line non-small cell lung cancer (NSCLC).
- 2017 – Initiate Phase I/II study for TG4001 + avolumab in head and neck cancer
- H1 2017 – Initiate Phase I study with TG6002 in glioblastoma
- 2017- Initiate Phase II study with Pexa-Vec + nivolumab in 1st line HCC
- H2 2017- Efficacy data for TG1050 in Chronic Hepatitis B.
Two transgenes have been inserted into the viral vector: granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate a robust immune response and β-galactosidase as a visual marker to assess replication. As depicted in Figure 1, inflammatory changes induced by oncolytic viruses result in induced cell death, enhanced antigen presentation, recruitment of effector T cell, and changes in the microenvironment that reduce immunosuppression. In addition to these effects, oncolytic viruses lead to the activation of antigen presenting cells (APCs), such as dendritic cells, with subsequent activation of effector T-cells.

Figure 1. Proposed Rational for OVs in Combination with Anti-CTLA-4 Therapy

Immune responses induced by oncolytic viruses could complement immunotherapies such as anti-CTLA-4 therapies, designed to boost immune surveillance, resulting in anti-tumor effects. Indeed, preclinical data in mouse models of melanoma, colorectal cancer, and renal cell cancer have shown synergistic effects when the two therapies are combined. This leaves open the possibility that combined therapies in context of solid tumors may result in complementary effects by concurrently activating dendritic cells and enhancing immune surveillance of tumors.

- **Phase I Trial with Pex-Vec plus Yervoy in Solid Tumors.** The Phase I trial is a 60-patient, open-label, dose escalation trial to evaluate the safety and initial efficacy of intratumoral (IT) Pexa-Vec plus Yervoy in locally advanced and/or metastatic solid tumors that can be accessed by injection. The trial is a 2-part study encompassing a dose escalation portion and a treatment segment, both outlined below:
  - Dose selection portion: This segment of the study will follow a 3+3 design, where 3 to 6 patients will be enrolled at each dose level in order to find the optimal dose for future trials. Specifically, 2.5 mg, 5 mg, 7.5 mg, and 10 mg doses of Yervoy. An escalation in dose will be dependent on toxicity.
  - Treatment of expansion cohorts: Patients in up to three cohorts will receive an IT boost injection of Pexa-Vec at 1x10⁹ pfu/injection at week 1, followed IT injections of Pexa-Vec plus Yervoy at day 1 of weeks 3, 5, and 9.

The study has two primary endpoints. The first primary endpoint is safety, defined as dose limiting toxicities, such as AEs and injection site reactions. The second primary endpoint for this study explores efficacy in the expansion cohort by assessing the objective response rate (ORR) after 3 months of treatment. In this setting, ORR is defined by the percentage of patients having a complete response or a partial response according to the immune-related response criteria (iRC). Notable secondary endpoints for this study include ORR after 3 months of treatment, defined by iRC and RECIST 1.1 criteria, best objective response rate after 12 months, duration of response, progression free survival, overall survival, and time to progression. Data from this study are expected in late 2017.

- **Transgene is Evaluating Multiple Assets in Combination with Checkpoint Inhibitors.** Although immune activation has been observed following the administration of viral-based and peptide vaccines therapies, tumor induced immune suppression may inhibit
their activity. Immune checkpoint inhibition as a way to preclude immunosuppression is receiving significant attention in the medical community. Several preclinical studies have shown success of checkpoint inhibitors in combination vaccine therapies, highlighting an opportunity to improve the prospects of success for viral-vector and peptide immunotherapies. In accordance with these findings, Transgene has developed three partnerships with players in the checkpoint inhibitor space to test enhanced efficacy in distinct cancer indications, highlighting the adaptability of these therapies. Clinical trials resulting from these partnerships are outlined here:

- **Pexa-Vec plus Opdivo** in hepatocellular carcinoma (HCC), partnered with SillaJen (private).
- **TG4001** in combination with avelumab in HPV-positive head and neck cancer, partnered with Merck KgaA (FRA: MRK.F) and Pfizer. TG4001 is a modified virus expressing two oncoproteins of the human papilloma virus (HPV).
- **TG4010 plus Opdivo** in non-small cell lung cancer (NSCLC) patients who have progressed after one line of platinum-based chemotherapy, partnered with Bristol-Meyers. TG4010 is an attenuated virus designed to trigger an immune response.

### Previous Data with TG4010 in Combination with Chemotherapy.

Transgene performed a randomized, open label, placebo controlled, **Phase II trial** comparing TG4010 as an adjuvant to first-line therapy in 148 patients with advanced NSCLC. A retrospective analysis in a subset of patients expressing the lowest levels of a particular biomarker called triple activated lymphocyte (TrPAL), found that TG4010 in combination with chemotherapy resulted in a median overall survival of 17.1 months compared to 11.3 months in chemotherapy treated patients. TrPAL lymphocytes are positive for CD16, CD56 and CD69, and are associated with activated natural killer (NK) cell phenotype. More recently, the randomized, double-blinded, placebo controlled **Phase Ib TIME trial** of 222 patients found that TG4010 plus chemotherapy treated patients with low TrPAL and non-squamous histology, experienced 6 months progression free survival (p=0.0033) compared to 4.9 months in the chemotherapy treated group. These patients also had an overall survival of 15.1 months (p=0.0072) in contrast to 10.3 months for those treated with chemotherapy. These results suggest the level of natural killer cell activation can act as a biomarker for TG4010 efficacy in this setting.

NK cells play a role in generating adaptive immunity by closely interacting with both dendritic an effector T cells, leading to their activation. However, if the level of activation becomes too high, there is a shift toward immunosuppression. NK cells are reactive the presence of tumor cells and viruses. As a result, the level of activation is critical. For example, high levels of NK cell activation may counteract the efficacy TG4010. The potential for immunosuppressive events as result of TG4010 therapy signal its use in combination with checkpoint inhibitors such as Opdivo, for the treatment of NSCLC.

### Phase II Clinical Trial with TG4010 in Combination with Opdivo in NSCLC.

In December 2016, Transgene announced a single-arm, open-label **Phase II trial** will evaluate the safety and efficacy of TG4010 in combination with Opdivo in stage IV, histologically confirmed non-squamous NSCLC patients who have previously failed on platinum-based chemotherapy. Patients will receive 1 to 3 courses of TG4010 subcutaneously once per week and every 2 weeks thereafter. In addition, patients will receive IV Opdivo over 30 minutes every 2 weeks. The outlined regimens will be administered every 2 weeks for up to 2 years barring any evidence of disease progression or toxicity. The primary endpoint of the study is overall response rate, measured as the proportion of patients whose best overall response is either a complete response or a partial response by RECIST 1.1 criteria. Secondary endpoints for this study include the safety and toxicity profile of the combination, PSF by RECIST 1.1, OS, duration of response and the occurrence of response over time, rate and duration of stable disease, and finally disease control rate. The first patient is expected to enroll during the first half of 2017 and a first readout is expected during the second half of 2017.

### Risk to Investment

We consider an investment in Transgene to be a high-risk investment. Transgene is a development stage company with no history of taking a treatment to market, and currently has no EMA or FDA approved drugs in its portfolio. Transgene’s lead programs have not yet completed pivotal Phase III trials and have limited data to date. Furthermore, early indications of efficacy do not necessarily translate into positive late-stage results. Ongoing clinical trials will result in significant additional expenses to the Company and may require additional rounds of dilutive financing. As with any company, Transgene may be unable to obtain sufficient capital to fund planned development programs. There are regulatory risks associated with the development of any drug and Transgene may not receive EMA or FDA approval.
for its candidates despite significant time and financial investments. Regulatory approval to market and sell a drug does not guarantee that the drug will penetrate the market, and sales may not meet expectations.
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