PRESS RELEASE

First patient enrolled in expanded Phase II clinical trial of TG4001 + avelumab vs avelumab alone in patients with HPV16-positive anogenital cancers

Strasbourg, France, June 24, 2021, 5:45 pm CET – **Transgene (Euronext Paris: TNG), a biotech company that designs and develops virus-based immunotherapeutics against cancer, today announces that a first patient has been enrolled in a randomized, controlled Phase II study evaluating the combination of TG4001 with avelumab versus avelumab monotherapy in patients with HPV16-positive anogenital tumors** (NCT: 03260023)**.**

TG4001 IS AN INVESTIGATIONAL THERAPEUTIC VACCINE TARGETING HPV-POSITIVE TUMORS,

including cervical, anal, and other anogenital cancers. It is based on a Vaccinia vector (MVA), which is engineered to express HPV16 E6 and E7 antigens and interleukin 2 (IL-2). TG4001 is designed to alert the immune system specifically to cells presenting these HPV antigens (that can be found on HPV-related tumors) and to induce a specific cellular immune response against these cancer cells.

Based on promising data obtained in the Phase Ib/II part of the trial, Transgene is progressing the development of TG4001 in combination with avelumab, through a randomized Phase II trial and an extended collaboration with the alliance of Merck KGaA, Darmstadt, Germany, and Pfizer, which is supplying avelumab.

PHASE II TRIAL AIMS TO SHOW THE SUPERIORITY OF TG4001 + AVELUMAB OVER AVELUMAB MONOTHERAPY

The randomized Phase II trial is focusing on patients with recurrent or metastatic HPV16-positive anogenital cancer, including cervical, vulvar, vaginal, penile, and anal cancer, without liver metastases. In the Phase Ib/II part of the study, very encouraging clinical outcome was observed in patients without liver metastases [1,2].

Patients will be randomized to either receive the combination regimen of the therapeutic vaccine TG4001 and avelumab or avelumab alone. The trial will be enrolling patients in the USA and in Europe (France and Spain).

The primary endpoint of the trial is progression-free survival (PFS) according to RECIST 1.1. Secondary endpoints include objective response rate (ORR), disease control rate (DCR), overall survival (OS) and a series of immunological parameters.

An interim analysis will be performed after the enrollment of approximately 50 patients. **Transgene expects to communicate interim analysis data around the end of 2022.**

Dr. Maud Brandely, MD, PhD, Chief Medical Officer of Transgene, added: *"We are confident that the combination regimen of TG4001 and avelumab has the potential to deliver improved progression-free survival for patients with advanced/recurrent HPV16-positive anogenital cancer without liver metastases. This confidence is based on the very encouraging results from the initial Phase Ib/II study, which showed important clinical benefits in this patient population in terms of response rate and progression-free survival. This earlier study part also showed that patients had vaccine-induced reactive T cells against E6, E7 or both. This randomized trial has been designed to further demonstrate that the addition of TG4001 to an immune checkpoint inhibitor can improve the clinical outcome for patients with HPV16-positive anogenital cancer without liver metastases. We are looking forward to announcing the interim results from this expanded study which could be a key milestone in bringing TG4001 to patients in need of improved treatment options."*

About the trial

The multi-center, open label, randomized Phase II trial (NCT03260023) is designed to compare the efficacy of the combination of TG4001 and avelumab versus avelumab alone in patients with HPV16-positive anogenital cancers who have disease progression after a maximum of one line of systemic treatment for recurrent/metastatic disease, or who are not eligible for first-line chemotherapy.

Prof. Christophe Le Tourneau, M.D., PhD, Head of the Department of Drug Development and Innovation (D3i) at the Curie Institute, is the Principal Investigator of the study. The trial is being conducted in collaboration with Merck KGaA, Darmstadt, Germany, and Pfizer Inc. (NYSE: PFE), which are providing avelumab for the trial. Avelumab is co-developed and co-commercialized by Merck KGaA, Darmstadt, Germany and Pfizer Inc. Transgene will continue to be the sponsor of the trial and conduct the trial.

Patients will receive TG4001 at the dose of $5x10^7$ plaque-forming units (pfu), subcutaneously (SC), weekly for 6 weeks, every 2 weeks up to six months, and every 12 weeks thereafter, in combination with avelumab or avelumab alone at 800 mg, intravenously (IV) every two weeks, until disease progression. The primary endpoint of the trial is progression-free survival (PFS) according to RECIST 1.1. Secondary endpoints include objective response rate (ORR), disease control rate (DCR), overall survival (OS) and other immunological parameters. The trial could enroll approximately 150 patients until the final analysis.

Patients with liver metastases will be followed in an ancillary arm and will not be included in the primary analyses.

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About the data presented at SITC 2020 and ESMO IO 2020 [1,2]

The results from the Phase Ib/II parts of the trial combining TG4001 with avelumab in HPV16-positive recurrent and/or metastatic malignancies were presented at SITC 2020 [1] and ESMO IO 2020[2].
The combination of TG4001 and avelumab demonstrated anti-tumor activity (23.5% ORR) in patients with previously treated recurrent and/or metastatic HPV-related cancers (including patients with oropharyngeal cancers and anogenital cancers). **Presence of liver metastases had a profound impact on the outcome in terms of ORR and PFS**. **In patients without liver metastases, an ORR of 34.8% and a median PFS of 5.6 months were achieved.** The treatment induced HPV-specific T-cell responses and was associated with increased levels of immune cell infiltration in the tumors and expression of genes associated with activation of the immune system.

About TG4001

TG4001 is an investigational therapeutic vaccine based on a non-propagative, highly attenuated Vaccinia vector (MVA), which is engineered to express HPV16 antigens (E6 & E7) and an adjuvant (IL-2). TG4001 is designed to have a two-pronged antiviral approach: to alert the immune system specifically to cells presenting the HPV16 E6 and E7 antigens, that can be found in HPV16-related tumors, and to further stimulate the infection-clearing activity of the immune system through interleukin 2 (IL-2). TG4001 has been administered to more than 300 individuals, demonstrating good safety and promising efficacy results [1, 2]. Its mechanism of action and good safety profile make TG4001 an excellent candidate for combinations with other therapies in HPV-mediated solid tumors.

About Transgene

Transgene (Euronext: TNG) is a biotechnology company focused on designing and developing targeted immunotherapies for the treatment of cancer. Transgene's programs utilize viral vector technology with the goal of indirectly or directly killing cancer cells.

The Company's clinical-stage programs consist of two therapeutic vaccines (TG4001 for the treatment of HPV-positive cancers, and TG4050, the first individualized therapeutic vaccine based on the *myvac*® platform) as well as two oncolytic viruses (TG6002 for the treatment of solid tumors, and BT-001, the first oncolytic virus based on the Invir.IO™ platform).

With Transgene's *myvac*® platform, therapeutic vaccination enters the field of precision medicine with a novel immunotherapy that is fully tailored to each individual. The *myvac*® approach allows the generation of a virus-based immunotherapy that encodes patient-specific mutations identified and selected by Artificial Intelligence capabilities provided by its partner NEC.

With its proprietary platform Invir.IO™, Transgene is building on its viral vector engineering expertise to design a new generation of multifunctional oncolytic viruses. Transgene has an ongoing Invir.IO™ collaboration with AstraZeneca.

Additional information about Transgene is available at: www.transgene.fr.// Follow us on Twitter: @TransgeneSA

Avelumab Approved Indications

Avelumab (BAVENCIO®) is indicated in the US for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy. BAVENCIO is also indicated for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy, or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Avelumab in combination with axitinib is approved in the US for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

In the US, the FDA granted accelerated approval for BAVENCIO for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC). This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

Avelumab Important Safety Information from the US FDA-Approved Label

The warnings and precautions for avelumab (BAVENCIO®) include immune-mediated adverse reactions (such as pneumonitis and hepatitis [including fatal cases], colitis, endocrinopathies, nephritis, and other immune-mediated adverse reactions as a single agent or in combination with axitinib [which can be severe and have included fatal cases]), infusion-related reactions, hepatotoxicity in combination with axitinib, major adverse cardiovascular events (MACE) in combination with axitinib [which can be severe and have included fatal cases], and embryo-fetal toxicity.

Common adverse reactions (reported in at least 20% of patients) in patients treated with BAVENCIO® monotherapy include fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction peripheral edema, decreased appetite, urinary tract infection and rash. Common adverse reactions (reported in at least 20% of patients) in patients receiving BAVENCIO® in combination with axitinib include diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, cough, dyspnea, abdominal pain and headache. Grade 3-4 hematology laboratory value abnormalities reported in at least 10% of patients with Merkel cell carcinoma treated with BAVENCIO® monotherapy include lymphopenia; in patients receiving BAVENCIO® in combination with axitinib, grade 3-4 clinical chemistry abnormalities include blood triglyceride increased and lipase increased.

For full US Prescribing Information and Medication Guide for BAVENCIO®, please see http://www.BAVENCIO.com.

References

[1] Le Tourneau et al. "TG4001 (Tipapkinogene sovacivec) and avelumab for recurrent/metastatic (R/M) Human Papilloma Virus (HPV)-16+ cancers: clinical efficacy and immunogenicity." 2020 SITC Annual Meeting, 9-11 November 2020, Poster presentation

[2] Le Tourneau et al. "TG4001 therapeutic vaccination combined with PD-L1 blocker avelumab remodels the tumor microenvironment (TME) and drives antitumor responses in Human PapillomaVirus (HPV)+ malignancies."2020 ESMO IO meeting, 12 December 2020, mini-oral presentation