

Transgene expands Phase II clinical trial of therapeutic vaccine TG4001 in combination with avelumab versus avelumab monotherapy in patients with HPV16-positive anogenital cancers

- *Enrollment of the first patient is expected in Q2 2021*
- *Trial will focus on patients without liver metastases, based on encouraging data in Phase Ib/II study*
- *Trial targets indications where clinical outcomes can be improved versus standard therapeutic options and immune checkpoint inhibitors (“ICIs”)*
- *Continued clinical collaboration with Merck KGaA, Darmstadt, Germany, and Pfizer to conduct the expanded Phase II study*

Strasbourg, France, March 10, 2021, 5:45 pm CET – Transgene (Euronext Paris: TNG), a biotech company that designs and develops virus-based immunotherapeutics against cancer, today announces the expansion of a randomized, controlled study with TG4001 in combination with avelumab versus avelumab monotherapy in patients with HPV16-positive anogenital tumors ([NCT: 03260023](https://clinicaltrials.gov/ct2/show/study/NCT03260023)).

Transgene has amended the initial Phase Ib/II trial protocol to enable a more rapid start of this important Phase II study based on encouraging Phase Ib/II trial data. This randomized Phase II trial will be supported by a continuing collaboration with the alliance of Merck KGaA, Darmstadt, Germany, and Pfizer, which is supplying avelumab. Transgene retains all rights to TG4001.

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

The initial Phase Ib/II trial conducted in Europe (France and Spain) has been amended to include a randomized comparison of the combination of TG4001 with avelumab versus avelumab monotherapy in anogenital cancers. The submission of the amended protocol has been initiated in Europe. In addition, Transgene received US FDA clearance of the protocol under TG4001 IND. Patient enrollment is expected to start in Q2 2021.

The trial will focus on patients with recurrent or metastatic HPV16-positive anogenital cancer without liver metastases, including cervical, vulvar, vaginal, penile, and anal cancer. This population was shown in the Phase Ib/II study to derive improved clinical benefit from the combination regimen ^[1,2].

Patients will be randomized to either receive the combination regimen of the therapeutic vaccine TG4001 and avelumab or avelumab alone.

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.

The Phase II trial will be supported by the extension of the collaboration with the alliance of Merck KGaA, Darmstadt, Germany, and Pfizer, which is supplying avelumab for this trial. Transgene retains all rights to TG4001.

An interim analysis will be performed after the enrollment of nearly 50 patients. Transgene expects to communicate the interim analysis data around the end of 2022. This timeline is based on patient enrollment starting in Q2 2021 and there being no major impact on recruitment from the Covid-19 pandemic.

Commenting on this novel investigational immunotherapy regimen, **Prof. Christophe Le Tourneau, MD, Head of the Department of Drug Development and Innovation (D3i) at the Curie Institute and Principal Investigator of the trial**, added: *“I am very pleased that we are now moving ahead with a new part of this Phase II study. The promising data that we generated in the Phase Ib/II part of this study, in patients without liver metastases, gives me confidence that the amended study can generate the additional data needed to confirm the treatment benefits of the combination of TG4001 and avelumab in this patient population with very limited therapeutic options.”*

RECURRENT AND METASTATIC HPV16-POSITIVE ANOGENITAL CANCERS NEED BETTER TREATMENT OPTIONS

The Phase II trial focuses on indications where standard therapeutic options and immune checkpoint inhibitors have limited efficacy. These indications represent areas of important medical need; they include cervical, vulvar, vaginal, penile, and anal cancer. The trial will enroll patients who have received a maximum of one line of chemotherapy for the treatment of their recurrent or metastatic disease or who are not eligible for chemotherapy.

Transgene estimates the number of people diagnosed annually with these cancers to be around 25,000 patients per year (US, Europe 27, UK) ^[3-9]. In spite of recent progress, patients with these severe and heterogeneous malignancies need better treatment options, particularly after the recurrence of the disease: median overall survival is less than 11 months ^[10-13] and median progression-free survival is around 2 months ^[10-13].

Dr. Maud Brandely, MD, PhD, Chief Medical Officer of Transgene, concludes about this study: *“I am pleased we have been able to use a methodologically sound trial design to move ahead with this randomized Phase II study quickly. The results from the initial Phase Ib/II study demonstrated the potential of the combination of TG4001 with an immune checkpoint inhibitor in this advanced disease setting. We observed encouraging clinical outcomes with a response rate reaching 34.8% and median progression-free survival of 5.6 months in patients without liver metastases. The observed median progression-free survival shows that this combination can induce a sustained and durable benefit, which may be based on the induction of a specific immune response. This study is expected to provide us with the data required to discuss the registration path of TG4001.”*

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 advanced, recurrent and/or metastatic HPV16-positive anogenital cancers who have disease progression after a maximum of one line of systemic treatment, 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 5×10^7 pfu, 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, 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 up to 136 patients until the final analysis.

Patients with liver metastases will be followed in an ancillary arm and will be randomized to receive one of the treatment regimens; these patients will not be included in endpoint analyses.

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, 14, 15]. Its mechanism of action and good safety profile make TG4001 an excellent candidate for combinations with other therapies in HPV-mediated solid tumors.

About HPV-Positive Cancers

HPV-positive cancers comprise a variety of malignancies, including anogenital cancers^[3]. HPV-positive cancers include cervical^[4], vaginal^[5], vulvar^[6], anal^[7] and penile^[8] cancers, i.e., approximately 25,000 cancers at metastatic stage eligible for a first-line treatment and in second line for a locoregional disease^[9] (USA, EU 27, UK).

Current treatments mostly include chemoradiotherapy. However, better options are needed for advanced and metastatic HPV-positive cancers. It is thought that a therapeutic vaccine combined with other immunotherapeutic agents such as immune checkpoint inhibitors (ICIs) could provide a promising potential treatment option that would address this strong medical need^[16,17]. With immune checkpoint inhibitors, median overall survival remains less than 11 months^[10-13] and median progression-free survival is between 2 and 4 months^[10-13].

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](https://twitter.com/TransgeneSA)

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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

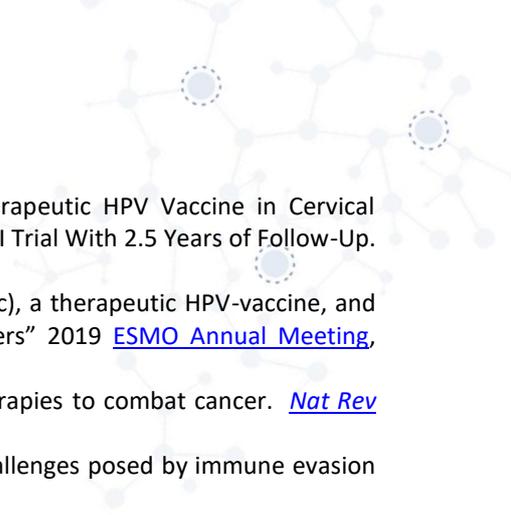
The warnings and precautions for avelumab (BAVENCIO®) include immune-mediated adverse reactions (such as pneumonitis and hepatitis [including fatal cases], colitis, endocrinopathies, nephritis, and other immune-mediated adverse reactions as a single agent or in combination with axitinib [which can be 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>.

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