

Transgene announces detailed results from clinical study of TG4001 in combination with avelumab in advanced HPV-positive cancers

- *Combination of TG4001 and avelumab demonstrates anti-tumor activity (23.5% overall response rate (ORR)) in patients with previously treated recurrent and/or metastatic HPV-related cancers.*
- *In patients without liver metastases, an ORR of 34.8% and a median progression-free survival (PFS) of 5.6 months were achieved.*

Strasbourg, France, October 27, 2020, 07:30 a.m. CET – Transgene (Euronext Paris: TNG), a biotech company that designs and develops virus-based immunotherapeutics against cancer, today announced the detailed results from the Phase 1b/2 trial combining TG4001, a HPV16-targeted therapeutic vaccine, with avelumab (BAVENCIO®), a human anti-PD-L1 antibody, in HPV16-positive recurrent and/or metastatic malignancies.

Following the unauthorized download of all abstracts on the SITC website, Transgene is communicating the content of the late-breaking poster abstract that will be presented at the SITC 35th Anniversary Annual Meeting (SITC 2020), to be held virtually November 9-14, 2020.

The purpose of this exploratory Phase 1b/2 trial was to evaluate the safety and efficacy of the combination of TG4001 and an immune checkpoint inhibitor in a heterogeneous group of patients with aggressive, recurrent and/or metastatic HPV16-positive cancers.

Key findings of the trial:

- **The combination of TG4001 and avelumab demonstrates anti-tumor activity (23.5% ORR)** in patients with previously treated recurrent and/or metastatic HPV-related cancers.
- **Presence of liver metastases has a profound impact on 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.
- These results warrant further confirmation in a larger controlled randomized study.

An overall response rate of 23.5% was observed in the 34 evaluable patients. 8 patients achieved confirmed response, including 1 complete response and 7 partial responses (according to RECIST 1.1). Responses were observed in all primary tumor types and across all lines of prior therapy. These results compare favorably to current standards of care and single-agent immune checkpoint inhibitors ^[1-7].

In patients without liver metastases (n=23), the response rate is 34.8% and median progression free survival (PFS) reaches 5.6 months versus 0% and a PFS of 1.4 month in patients with liver metastases (n=11). The presence of liver metastases is generally associated with very poor prognosis ^[9] even when patients are treated with an anti-PD-1/PD-L1 ^[10-12].

“The results we have announced today demonstrate the potential of the combination of TG4001 with an immune checkpoint inhibitor in this particularly severe disease setting. We observed very encouraging

responses rates, as high as 34.8 % in patients who did not have liver metastases. In addition, the observed median PFS shows that the regimen can induce a sustained and durable response, which is also shown consistently by the induction of a specific immune response. Based on these promising findings, Transgene intends to continue the clinical development of TG4001 in a larger, controlled confirmatory study as we look to provide a better treatment option for this patient population,” added **Dr. Maud Brandely, MD, PhD, Chief Medical Officer of Transgene.**

Commenting on this novel 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: “We have seen very encouraging efficacy results in this hard-to-treat patient population, as well as a satisfying safety profile. I believe this combination regimen has the opportunity to provide real hope for patients with HPV-16 related cancers.”

The trial is conducted in collaboration with Merck KGaA, Darmstadt, Germany, and Pfizer.

Philippe Archinard, Chairman and CEO of Transgene, and Dr. Maud Brandely, MD, PhD, Chief Medical Officer of Transgene, will provide some further background to the data after the publication of the e-poster during a conference call and webcast scheduled on November 12, at 6:00 pm CET.

Number and title of the late-breaking poster abstract: (793) TG4001 (Tipapkinogene sovacivec) and avelumab for recurrent/metastatic (R/M) Human Papilloma Virus (HPV)-16+ cancers: clinical efficacy and immunogenicity.

Authors: Christophe Le Tourneau, Philippe Cassier, Frédéric Rolland, Sébastien Salas, Jean-Marc Limacher, Olivier Capitain, Olivier Lantz, Ana Lalanne, Christina Ekwegbara, Annette Tavernaro, Hakim Makhloufi, Kaïdre Bendjama, Jean-Pierre Delord.

Session & Q&As: The e-poster will be displayed in the Virtual Poster Hall from November 11 to November 14, 2020, 9:00 a.m.-5:00 p.m. ET (3:00-11:00 p.m. CET). The first author will be available for questions on November 11 from 5:15–5:45 p.m. ET (11:15-11:45 p.m. CET) and November 13 from 4:40-5:10 p.m. ET (10:40-11:10 p.m. CET).

Body of the abstract:

Background	Specific immune cell responses against oncogenic antigens are major determinants to achieve long-term disease control for HPV-related malignancies. We developed TG4001, a viral based vaccine against the HPV E6 and E7 antigens. Following the demonstration of its safety in Phase 1b, we aimed to evaluate the antitumor activity and immune priming effects of TG4001 in combination with the PD-L1 inhibitor avelumab in HPV-related malignancies in phase II (NCT03260023).
Methods	Patients (pts) with previously treated R/M HPV-16+ cancers received TG4001 at 5×10^7 pfu SC weekly for 6 weeks, every 2 weeks up to M6, and every 12 weeks thereafter in combination with avelumab IV at 10mg/kg every 2 weeks. PBMC and tissue samples were collected longitudinally prior to and during the treatment period. Specific T cell response was assessed using ex-vivo IFNg-ELISPOT, and changes in the tumor microenvironment by phenotyping of immune infiltrate and transcriptomic analyses of immune related genes.
Results	34 pts with anal (15), oropharyngeal (8), cervical (6) or vulvar/vaginal (5) cancer, were enrolled. Median age was 61 years; the majority (88%) had received at least 1 prior line of chemotherapy (CT) with 32% having received ≥ 2 lines. 8 pts achieved confirmed response according to RECIST 1.1 (1 CR, 7 PR, ORR 23.5%). Responses were observed in all primary tumor types and across all lines of prior therapy. Liver metastases had a profound impact on outcome: ORR was 34.8% and PFS 5.6 months

	<p>in pts without liver metastases (n=23) versus 0% and PFS of 1.4 months in pts with liver metastases (n=11). Consistent with Phase 1b data, the combination had a favorable safety profile.</p> <p>11 pts were evaluable for T-cell response at day (D) 43. 7/11 patients had vaccine-induced reactive T cells against E6, E7 or both. In particular, in the patient with CR, lesions disappearance was accompanied by the development of a strong T-cell response against E6 and E7. This response developed as early as D43 and sustained at 6 months after initiation of therapy, consistent with the durable disease-control. Increased infiltrates, expression of immune related genes and higher PD-L1 protein expression were observed across all patients suggesting a remodeling of the tumor microenvironment consistent with a switch toward a “hot tumor” phenotype.</p>
Conclusions	Our study suggests that immunotherapeutic combination of TG4001 and avelumab shows valuable tumor activity in pts with previously treated advanced HPV-16+ cancers. These results warrant validation in a larger cohort of patients.
Trial Registration	NCT03260023

About the trial

This multi-center, open-label Phase 1b/2 trial is assessing the safety and efficacy of this immunotherapy combination regimen (TG4001 + avelumab) in patients with HPV16-positive cancers who have disease progression after at least one line of systemic treatment (NCT03260023). Prof. Christophe Le Tourneau, M.D., PhD, Head of the Department of Drug Development and Innovation (D3i) at the Curie Institute, and a world expert in drug development and head and neck cancers, is the Principal Investigator of the study. The trial is being conducted in collaboration with Merck KGaA, Darmstadt, Germany, a leading science and technology company, which in the US and Canada operates its biopharmaceutical business as EMD Serono, and Pfizer Inc. (NYSE: PFE).

34 patients received 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 at 10 mg/kg, IV every two weeks, until disease progression.

The primary endpoint of the Phase 2 part is the overall response rate (ORR, using RECIST 1.1).

Secondary endpoints include progression-free survival, overall survival, disease control rate and other immunological parameters.

More information on the trial is available on clinicaltrials.gov.

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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, significant HPV clearance rate and promising efficacy results^[8; 24]. 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 head and neck cancers and anogenital cancers [13]. Squamous cell carcinoma of the head and neck (SCCHN) is a heterogeneous group of cancers that can affect sites including the oral cavity, pharynx, and larynx [14]. The incidence of HPV16-related SCCHN has significantly increased in recent years [14]. HPV16 infection is associated with more than 85% of oropharynx squamous cell carcinomas [14], i.e. approximately 10,000 patients at metastatic stage and receiving a second line of treatment [15]. Other HPV16-positive cancers include cervical [16], vaginal [17], vulvar [18], anal [19] and penile [20] cancers, i.e. approximately 15,000 cancers at metastatic stage and eligible for a second line of treatment [21].

Current treatments include chemoradiotherapy, immune checkpoint inhibitors, or surgical resection with radiotherapy. However, better options are needed for advanced and metastatic HPV+ cancers. It is thought that this immunotherapy combined with other immunotherapeutic agents such as immune checkpoint inhibitors could provide a promising potential treatment option that would address this strong medical need [23,24]. With immune checkpoint inhibitors, median overall survival remains inferior to 11 months [1-7] and median progression-free survival is between 2 and 4 months [1-7]. In this heterogeneous group of malignancies, overall response rates are around 10–15% [1-7].

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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About Transgene

Transgene (Euronext: TNG) is a publicly traded French 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.

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