Transgene presents e-poster outlining detailed results from the Phase 1b/2 trial of TG4001 in combination with avelumab in advanced HPV-positive cancers at SITC 2020

- **Combination of TG4001 and avelumab demonstrated a clinically relevant anti-tumor activity with an overall response rate (ORR) of 23.5%**

- **Presence of liver metastases had a notable impact on outcomes: in patients without liver metastases, an ORR of 34.8% and a median progression-free survival (PFS) of 5.6 months were achieved**

- **Treatment associated with changes in the tumor microenvironment characterized by a significant and sustainable immune response and activity against the tumor**

Conference call to take place on November 12, at 6:00 p.m. CET (in English). See details below.

Strasbourg, France, November 9, 2020, 05:45 p.m. CET – Transgene (Euronext Paris: TNG), a biotech company that designs and develops virus-based immunotherapeutics against cancer, today announced the presentation of 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 (NCT03260023).

The late-breaking e-poster is available and will be presented at the Society for Immunotherapy of Cancer 35th Anniversary Annual Meeting (SITC 2020), held virtually November 11 to 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, previously treated HPV16-positive cancers.

Key findings of the trial:
- The combination of TG4001 and avelumab demonstrated a clinically relevant anti-tumor activity (23.5% ORR) in patients with previously treated recurrent and/or metastatic HPV-related cancers.
- Presence of liver metastases has a notable 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. Eight patients achieved confirmed response, including 1 complete response (CR) 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 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 metastasis was consequently identified as having a significant negative impact on clinical outcomes (the p-values were 0.012 and 0.001 regarding the ORR and the PFS,
The presence of liver metastases is generally associated with very poor prognosis \cite{9} even when patients are treated with an anti-PD-1/PD-L1 \cite{10-12}.

The disease control rate (DCR) at 12 weeks was 56.6% in patients without liver metastasis, against 9.1% in patients with liver metastasis. 60% of the patients without liver metastasis did not see their disease progress at month 4 versus 0% for patients with liver metastasis. At month 6 this rate was still 40% for patients without liver metastasis.

The treatment was able to modulate the tumor microenvironment and induced a switch toward a “hot tumor” phenotype. Seven over 11 evaluable patients had vaccine-induced reactive T cells against E6, E7 or both. With 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 day 43 and was sustained at 6 months after initiation of therapy, consistent with the durable disease-control. CD3+ and CD8+ T-cell infiltrates, and expression of PD-L1 were increased in most patients after 43 days of TG4001 and avelumab treatment. In the overall patient population, all three parameters were higher after treatment. Furthermore, the analysis of the gene expression profile in tumor demonstrated that immune related genes were significantly overexpressed at day 43 compare to the baseline. Those genes are related to immune activities such as the antigen processing, the T-cell effector functions, and the T-cell cytotoxic activity.

Consistent with Phase 1b data \cite{8}, the combination of TG4001 and avelumab had a manageable safety profile. The most frequently reported treatment-related adverse events (TRAEs) were related to general disorders (fever) and administration site conditions (skin redness). 9.5% of the patients reported TRAEs of grade 3/4/5.

Dr. Maud Brandely, MD, PhD, Chief Medical Officer of Transgene, concludes about this study: “These promising results reinforce what we had previously reported. They clearly suggest that the immunotherapeutic combination of TG4001 and avelumab can benefit patients with previously treated advanced HPV-16-positive cancers, and support further clinical development in a controlled and randomized setting and in a larger cohort of patients including patients with earlier disease. We are currently discussing the final design of this follow-up study with clinicians and external experts and will keep you informed on the progress of our promising therapeutic vaccine candidate TG4001.”

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

**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, Kaidre Bendjama, Jean-Pierre Delord.

**Poster availability:** The e-poster is displayed in the Virtual Poster Hall of the SITC 35th Anniversary Annual Meeting (SITC 2020) from today to December 31,2020. The e-poster is also available online on the Transgene website (transgene.fr).

**Sessions & Q&As:** The e-poster is displayed in the Virtual Poster Hall from today November 9 to December 31, 2020. The poster will be presented on Wednesday, November 11, from 5:15-5:45 p.m. EST (11:15-11:45 p.m. CET) and Friday, November 13, from 4:40-5:10 p.m. EST (10:40-11:10 p.m. CET). The first author will be available for questions during these poster presentation sessions.
**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). Thirty-four patients received TG4001 at the dose of 5x10^7 pfu, SC, weekly for 6 weeks, every 2 weeks up to 6 months, and every 12 weeks thereafter, in combination with avelumab at 10 mg/kg, IV every 2 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](https://clinicaltrials.gov).

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A conference call in English is scheduled November 12, 2020, at 12:00 p.m. ET (6:00 p.m. CET).

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.

**Webcast link to English language conference call:**

[https://channel.royalcast.com/transgene/#!/transgene/20201112_1](https://channel.royalcast.com/transgene/#!/transgene/20201112_1)

**Participant telephone numbers:**

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Confirmation code: Transgene

A replay of the call will be available on the Transgene website ([www.transgene.fr](http://www.transgene.fr)) following the live event.

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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 heterogenous 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.


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 // Follow us on Twitter: @TransgeneSA
References


[6] Lonardi et al. Randomized phase II trial of avelumab alone or with cetuximab for unresectable, locally advanced or metastatic squamous cell anal carcinoma progressed to at least one line of treatment: The CARACAS study. *J Clin Oncol*. 38:2020 (suppl; abstr 4051)


[8] Le Tournéau et al. “Phase Ib/II trial of TG4001 (Tipapkinogene sovacivec), a therapeutic HPV-vaccine, and Avelumab in patients with recurrent/metastatic HPV16 positive cancers” 2019 ESMO Annual Meeting, 30 September 2019, Poster presentation


[21] Company estimates based on notes 16, 17, 18, 19, 20


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