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,

respectively). 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 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 [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, Kaïdre 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 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.

***

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

Participant telephone numbers:
France: +33 (0) 1 7037 7166
United Kingdom: +44 (0) 20 3003 2666
United States: +1 212 999 6659

Confirmation code: Transgene

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

Contacts

Transgene:
Lucie Larguier
Director Corporate Communications & IR
+33 (0)3 88 27 91 04
investorrelations@transgene.fr

Media: Citigate Dewe Rogerson
David Dible/Sylvie Berrebi
+ 44 (0)20 7638 9571
transgene@citigatedewerogerson.com

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.

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

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

[1] Cohen et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet*. 2019;393:156–67

[2] Ferris et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med*. 2016;375:1856-1867

[3] Guigay et al. Avelumab (anti–PD-L1) in patients with platinum refractory/ ineligible recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): results from a phase 1b cohort, 2020 ESMO Annual Meeting, 19-21 September 2020, Poster presentation

[4] Morris et al. Nivolumab for Previously Treated Unresectable Metastatic Anal Cancer (NCI9673): A Multicentre, Single-Arm, Phase 2 Study. *Lancet Oncol.* 2017;18(4):446-453

[5] Marabelle et al. Pembrolizumab for previously treated advanced anal squamous cell carcinoma: Pooled results from the KEYNOTE-028 and KEYNOTE-158 studies. *J Clin Oncol* 38: 2020 (suppl; abstr 4020)

[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)

[7] Chung et al. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol*. 2019;10;37(17):1470-1478

[8] Le Tourneau 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

[9] Bilen et al. Sites of metastasis and association with clinical outcome in advanced stage cancer patients treated with immunotherapy. *BMC Cancer*. 2019;19: 857

[10] Tumeh et al. Liver Metastasis and Treatment Outcome with Anti-PD-1 Monoclonal Antibody in Patients with Melanoma and NSCLC. *Cancer Immunol Res* 2017; 5: 417 -424

[11] Sridhar et al. Prognostic Significance of Liver Metastasis in Durvalumab-Treated Lung Cancer Patients. *Clin Lung Cancer* 2019; e601 – e608

[12] Reck et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open label phase 3 trial. *Lancet Respir Med* 2019; 7: 387 - 401

[13] ICO/IARC – HPV Information Center> Prevention at a glance – accessed July 2020

[14] Kreimer et al., Human Papillomavirus Types in Head and Neck Squamous Cell Carcinomas Worldwide: A Systematic Review. *Cancer Epidemiol Biomarkers Prev*. 2005;14(2):467-75

[15] HPV-positive oropharynx cancer: Company estimates based on: Globocan/IARC 2018 Cancer Fact Sheets: oropharynx (C09-10) – accessed July 2020; ICO/IARC – HPV Information Center 2018 Statistics – accessed July 2020; Kreimer et al., Human Papillomavirus Types in Head and Neck Squamous Cell Carcinomas Worldwide: A Systematic Review. *Cancer Epidemiol Biomarkers Prev*. 2005;14(2):467-75

[16] HPV-positive cervical cancer: Globocan/IARC 2018 Cancer Fact Sheets: cervix uteri (C53) – accessed July 2020; ICO/IARC – HPV Information Center 2018 Statistics – accessed July 2020

[17] HPV-positive vaginal cancer: Globocan/IARC 2018 Cancer Fact Sheets: vagina (C52) – accessed July 2020; ICO/IARC – HPV Information Center 2018 Statistics – accessed July 2020; Kreimer et al., Human Papillomavirus Types in Head and Neck Squamous Cell Carcinomas Worldwide: A Systematic Review. *Cancer Epidemiol Biomarkers Prev*. 2005;14(2):467-75

[18] HPV-positive vulvar cancer: Globocan/IARC 2018 Cancer Fact Sheets: vulva (C51) – accessed July 2020; ICO/IARC – HPV Information Center 2018 Statistics – accessed July 2020; CDC United States Cancer Statistics: Data Visualizations – accessed July 2020; SEER Cancer stat facts: vulvar cancer – accessed July 2020

[19] HPV-positive anal cancer: Globocan/IARC 2018 Cancer Fact Sheets: anus (C21) – accessed July 2020; ICO/IARC – HPV Information Center 2018 Statistics – accessed July 2020; CDC>Cancer Home>HPV and Cancer>Statistics>Rates by Race and Ethnicity>HPV-Associated Anal Cancer Rates by Race and Ethnicity– accessed July 2020; American Cancer Society: Anal Cancer – accessed July 2020

[20] HPV-positive penile cancer: Globocan/IARC 2018 Cancer Fact Sheets: penis (C60) – accessed July 2020; ICO/IARC – HPV Information Center 2018 Statistics – accessed July 2020; CDC>Cancer Home>HPV and Cancer>Statistics>Rates by Race and Ethnicity>HPV-Associated Cancers Rates by Race and Ethnicity – accessed July 2020; Kreimer et al., Human Papillomavirus Types in Head and Neck Squamous Cell Carcinomas Worldwide: A Systematic Review. *Cancer Epidemiol Biomarkers Prev*. 2005;14(2):467-75

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

[22] Melero et al. Evolving synergistic combinations of targeted immunotherapies to combat cancer. *Nat Rev Cancer*. 2015;15(8): 457-472.

[23] Van der Burg et al. Vaccines for established cancer: overcoming the challenges posed by immune evasion *Nat Rev Cancer*. 2016;16(4):219-233
[24] Harper et al. The Efficacy and Safety of Tipapkinogen Sovacivec Therapeutic HPV Vaccine in Cervical Intraepithelial Neoplasia Grades 2 and 3: Randomized Controlled Phase II Trial With 2.5 Years of Follow-Up. *Gynecologic Oncology*. 2019; 153(3):521-529

Disclaimer

This press release contains forward-looking statements, which are subject to numerous risks and uncertainties, which could cause actual results to differ materially from those anticipated. The occurrence of any of these risks could have a significant negative outcome for the Company's activities, perspectives, financial situation, results, regulatory authorities' agreement with development phases, and development. The Company's ability to commercialize its products depends on but is not limited to the following factors: positive pre-clinical data may not be predictive of human clinical results, the success of clinical studies, the ability to obtain financing and/or partnerships for product manufacturing, development and commercialization, and marketing approval by government regulatory authorities. For a discussion of risks and uncertainties which could cause the Company's actual results, financial condition, performance or achievements to differ from those contained in the forward-looking statements, please refer to the Risk Factors ("Facteurs de Risque") section of the Universal Registration Document, available on the AMF website (http://www.amf-france.org) or on Transgene's website (www.transgene.fr). Forward-looking statements speak only as of the date on which they are made and Transgene undertakes no obligation to update these forward-looking statements, even if new information becomes available in the future.