

# Transgene

## Near-term data to define long-term strategy

Transgene develops virus-based product candidates for use in oncology and infectious diseases, its five clinical products are currently in 11 clinical trials across a variety of indications, its most advanced is Phase III trial with Pexa-Vec in first-line Hepatocellular Carcinoma with data anticipated in 2019. Its strategy remains to develop its candidates in combination with approved treatments, notably immune checkpoint inhibitors (ICIs). It anticipates eight clinical readouts across its five clinical candidates by year end, notably TG4010 in combination with Opdivo and chemo in first-line NSCLC. We value Transgene at €4.65/share vs €3.80/share previously.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (€)	Yield (%)
12/16	10.3	(23.1)	(0.43)	0.0	N/A	N/A
12/17	8.1	(35.0)	(0.52)	0.0	N/A	N/A
12/18e	7.2	(36.8)	(0.51)	0.0	N/A	N/A
12/19e	7.9	(34.0)	(0.55)	0.0	N/A	N/A

Note: \*PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

## All five product candidates to readout by year end

By year end Transgene forecast ICI combination readouts for TG4010 in first and second line NSCLC, TG4001 in head and neck cancer, in addition to Pexa-Vec in both first line hepatocellular carcinoma and solid tumours. This breath of data will give initial indications of whether Transgene's ICI combination strategy is valid; future funding and development opportunities will be significantly influenced by these readouts. Outside of ICI combination data, readouts for TG1050 in hepatitis B, TG6002 in glioblastoma and Pexa-Vec in breast cancer are anticipated in H218.

## ASCO data hint at Pexa-Vec IO potential

In collaboration with the University of Leeds, Transgene presented data at ASCO 2018, which monitored the effect a single dose of Pexa-Vec before surgery on nine patients with either colorectal cancer liver metastases (CRLM) (n=6) or metastatic melanoma (MM) (n=3). Of the four evaluable CRLM patient tumours, one patient's tumour was completely necrotic while another was partially necrotic.

## Financial: Funded into 2019

Transgene reported cash, cash equivalents and financial assets of €35.6m as of 31 March 2018 (compared to €41.4m as of 31 December 2017). Transgene's cash burn was €28.1m in 2017, driven in core by multiple trial initiations; the company anticipates its cash burn in 2018 to be comparable with that of 2017 as its clinical programmes progress. Our model predicts a current cash reach until mid-2019.

## Valuation: €289m (€4.65 per share)

We value Transgene at €289m (€4.65/share) vs €236m (€3.80/share) previously based on a risk-adjusted NPV model of TG4010, TG4001, TG1050, Pexa-Vec and TG6002. We have extended some of our forecasts to better represent full product sales cycles and pushed back Pexa-Vec launch in the EU to 2021 (from 2020). Additionally, we have rolled forward our model and updated for cash and fx.

## Pipeline readouts in H218

### Pharma & biotech

16 July 2018

**Price** €3.15  
**Market cap** €196m

Gross cash and short-term investments (€m) as of 31 March	35.6
Shares in issue	62.1m
Free float	38%
Code	TNG
Primary exchange	Euronext Paris
Secondary exchange	N/A

### Share price performance



%	1m	3m	12m
Abs	(2.8)	7.0	(0.5)
Rel (local)	(2.2)	4.7	(4.4)
52-week high/low	€3.58	€2.48	

### Business description

Transgene is a French drug discovery and development company focused on the treatment of cancer and infectious diseases with immunotherapies. Its products are Pexa-Vec, TG4010, TG4001, TG1050 and TG6002.

### Next events

Pexa-Vec + ipilimumab data solid tumours	H218
TG4010 + nivolumab in second-line NSCLC	H218
Pexa-Vec+ nivolumab data in first-line HCC	H218

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## Investment summary

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### Company description: Immunotherapy platform

Transgene is a drug discovery and development company that develops viral vector-based immunotherapies for the treatment of cancers and infections. It has two platforms: therapeutic vaccines and oncolytic viruses. Its two lead clinical-stage programmes are Pexa-Vec and TG4010. Pexa-Vec is an oncolytic virus partnered with SillaJen, its most advanced trial is a pivotal Phase III study in hepatocellular carcinoma (HCC). Therapeutic vaccine TG4010 is being trialled in combination with PD-L1 ICIs in first- and second-line non-squamous non-small cell lung cancer (NSCLC). Transgene's three other clinical candidates are TG4001 in head and neck cancer, TG1050 in hepatitis B and TG6002 in glioblastoma. Transgene is based near Strasbourg, France and was founded in 1979. It was listed on the Nouveau Marché (now Euronext) in 1998. Transgene is 57% owned by Institut Mérieux.

### Valuation: Updated rNPV of €289m

We value Transgene at €289m (€4.65/share) vs €236m (€3.80/share) previously. Our valuation is based on a risk-adjusted NPV model of TG4010, TG4001, TG1050, Pexa-Vec and TG6002. We have rolled forward our model and updated for both current cash and currency exchange rates. We have extended some of our forecasts to better represent full product sales cycles and pushed back our launch of Pexa-Vec in the EU to 2021 (from 2020 previously). Our valuation includes the prospects for TG4010 in NSCLC in the US and Europe (combined peak potential sales of €2.5bn); Pexa-Vec for HCC in Europe (€518m peak sales); and TG1050 for hepatitis B in the US and Europe (peak potential sales of €2.1bn in both regions, unchanged). For TG4010, we assume a classical development timeline, starting with the Phase I/II studies planned in combination ICIs. For Pexa-Vec, the Phase III PHOCUS study being conducted by SillaJen will potentially be sufficient to file for approval in Europe, assuming a positive study result. For TG1050, we assume Transgene develops it and a partner conducts Phase III trials, registration and marketing. We forecast both TG4001 in head and neck cancer and TG6002 in glioblastoma are partnered after Phase II trials.

### Financials: Funded through initial trial readouts

Transgene reported cash, cash equivalents and financial assets of €35.6m as of 31 March 2018 (compared to €41.4m as of 31 December 2017). Transgene's cash burn was €28.1m in 2017, driven by multiple trial initiations; the company anticipates its cash burn in 2018 to be comparable with that of 2017 as its clinical programmes progress. We forecast gross cash will fund Transgene into mid-2019. In 2019, we assume €20m in illustrative debt to continue to fund Transgene. We forecast 2018 R&D and G&A expenses to be largely in line with 2017 as Transgene's clinical trials continue.

### Sensitivities: ICI combinations may not prove definitive

Transgene is subject to the usual risks associated with drug development, including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, and financing and commercial risks. The key sensitivities relate to the results of the ICI combination studies of TG4010, Pexa-Vec and TG4001. The outcome of the TG4010 combination studies in particular will have an impact on its partnership and/or the financing prospects for the programme. First results from these trials will be available later this year. The clinical performance of Pexa-Vec in the Phase III trial (data in 2019) is another key sensitivity. We note that the ICI combination trials are small, open label and non-controlled; therefore, it is not possible to ascertain the magnitude of the effect of each product separately and assess the actual synergistic effect.

## Combination strategy faces its first major tests

Transgene's strategy involves developing its immunotherapies for the treatment of cancer and viral indications in combination with other products, predominantly ICIs. By year end we expect data to be announced for all five product candidates, with a total of eight data readouts across Transgene's pipeline. Primary focus will be on the expected data readout for the Phase II trial testing TG4010 in combination with both nivolumab (Opdivo: Bristol Myers Squibb) and chemotherapy in first-line patients with non-squamous NSCLC ([NCT03353675](#)). A Phase II trial in second-line non-squamous NSCLC patients, which is testing the combination of TG4010 and nivolumab ([NCT02823990](#)), will also prove informative in determining the success or failure of Transgene's combination strategy for TG4010. The aim of both studies is to determine whether the addition of TG4010 to existing regimens improves response rates and survival in non-squamous NSCLC patients, particularly those with low or undetectable PD-L1 status.

PD-(L)1 or programmed death-ligand 1 is a transmembrane protein that is believed to play a key role in immune regulation. The binding of receptor PD-1 to its ligand PD-L1 activates suppressive signals that limit immune activation, an effect which cancerous cells exploit to limit the response against them. PD-(L)1 inhibitors have been developed to try and prevent this immune suppression and have proven successful across a range of cancers. PD-(L)1 ICIs, alone or in combination, have quickly become standard of care for many patients with NSCLC, however, the best responses generally remain confined to high PD-(L)1-expressing patients. Across oncology indications companies are now looking to test ICIs in combination with other treatments to broaden the therapeutic window of these drugs.

In addition to the ICI combination readouts from TG4010, Transgene forecasts ICI combination readouts for TG4001 in head and neck cancer in addition to Pexa-Vec in both first-line HCC and solid tumours by year end. We note that Transgene has no clinical data to indicate that its products will be successful in combination with ICIs. Outside of ICI combination data, Transgene forecasts readouts for TG1050 in hepatitis B, TG6002 in glioblastoma and Pexa-Vec in breast cancer by year end. The current cash runway into 2019 will enable these data readouts, while future financing and strategy will be influenced heavily by the results of the expected data packages. Exhibit 1 details Transgene's pipeline.

**Exhibit 1: Transgene's clinical pipeline**

Compound	Combination compound	Indication	Phase	Collaborators	Trial start	Data read-out
TG4010	Opdivo and chemo	First-line NSCLC	II	N/A	<a href="#">Ongoing</a>	H218
TG4010	Opdivo (nivolumab)	Second-line NSCLC	II	University of California Davis Medical Centre	<a href="#">Ongoing</a>	H218
TG4010	N/A	Neoadjuvant NSCLC	Translational	University of Strasbourg (PI Pr Quoix)	2018	N/A
Pexa-Vec	Sorafenib	First-line HCC	III	Conducted by partner SillaJen	<a href="#">Ongoing</a>	2019
Pexa-Vec	Yervoy (ipilimumab)	Solid tumours	II	Centre Léon Bérard	<a href="#">Ongoing</a>	H218
Pexa-Vec	Opdivo (nivolumab)	First-line HCC	II	Nancy, France.	<a href="#">Ongoing</a>	H218
Pexa-Vec	Cyclophosphamide	Sarcoma and breast	II	Institut Bergonié	<a href="#">Ongoing</a>	H218
Pexa-Vec	N/A	Solid tumours	Translational	University of Leeds	<a href="#">Ongoing</a>	N/A
TG4001	Avelumab	HPV+ (Human papilloma virus) head and neck squamous cell carcinoma (HNSCC)	II	Institut Curie (PI Pr Christopher Le Tourneau)	<a href="#">Ongoing</a>	H218
TG1050	Standard of care antiviral	Chronic hepatitis B	I/Ib	N/A	<a href="#">Ongoing</a>	H218
TG6002	N/A	Glioblastoma	I	Assist. Publ Hôpitaux, Paris (PI Pr Delattre); French NCI	<a href="#">Ongoing</a>	H218

Source: Edison Investment Research, Transgene

## TG4010: An evolving standard of care in NSCLC

Since the commercial launch of Keytruda (Merck) and Opdivo (Bristol Myers Squib) in melanoma in 2014, PD-(L)1 ICIs have become the standard of care in many cancers (FY17 sales of Opdivo and Keytruda were \$4.95bn and \$3.81bn respectively). At the forefront of developments has been NSCLC, where PD-(L)1 ICIs have become a mainstay in many treatment regimens. However, in general, patients that respond effectively to PD-(L)1 ICIs remain a small percentage of the total NSCLC patient population. For example, Keytruda's approved label ([Keynote-024](#)) demonstrated it had a 45% overall response rate as a monotherapy in first-line patients whose tumour proportion score (TPS) for PD-L1 expression was above 50%. In lower PD-L1 expressing patients, response rates are significantly less (Exhibit 2). As such, attempts to find synergistic combinations that improve the response rates for other patients are ongoing throughout the industry. For an overview of significant PD-(L)1 ICI data in non-squamous NSCLC see Exhibit 2.

Transgene believes its therapeutic vaccine TG4010, a modified vaccinia Ankara virus that expresses MUC1 antigen and IL-2, could prove beneficial in combination with PD-(L)1 ICIs. TG4010 is believed to induce a specific T-cell response to target MUC1-expressing cancer cells which when used in combination with a PD-(L)1 ICI that removes inhibitory effects on the T-cell. Along with the MUC1 T-cell stimulation, IL-2 enables the differentiation of T-cells into effector and memory T-cells, which could further enhance the response against the MUC1-expressing cancer cells.

Transgene has two ongoing clinical trials in non-squamous NSCLC with a third anticipated to enrol its first patient shortly. A Phase II ([NCT03353675](#)) in first-line patients testing a triple combination of TG4010, Opdivo (nivolumab, Bristol Myers Squib) and chemotherapy is expected to readout initial data by year end. The trial is a single-arm EU/US study and is anticipated to enrol 39 patients (without EGFR mutations or ALK rearrangements) who express low or undetectable levels of PD-L1. The primary endpoint is an objective response rate and Transgene is funding the study with Bristol Myers Squib supplying Opdivo. For patients without a driver mutation (EGFR, MEK etc) the standard of care has quickly become chemotherapy plus Keytruda, irrespective of PD-L1 status (Exhibit 2). We note the first-line setting could be a significant opportunity for Transgene if TG4010 in combination with a PD-(L)1 ICI is proven to be more effective than PD-(L)1 ICI monotherapy treatment in low PD-L1 expressing patients. This Phase II trial is single arm as there will be no direct comparator arm; however, we note Keytruda plus chemotherapy is approved in the first line setting (Exhibit 2: Keynote-021G and 189).

Also expected later this year are data from the Phase II study ([NCT02823990](#)) in second-line patients testing TG4010 in combination with nivolumab (Opdivo: Bristol Myers Squib). The study is being run in collaboration with University of California, Davis Medical Center, which will conduct the trial; Transgene will fund it and Bristol Myers Squib will supply Opdivo. Patient recruitment is ongoing, with a total of 33 patients expected to be enrolled. Patients must have not been previously treated with immunotherapies but can be treated with one line of a tyrosine kinase inhibitor. We note that as the first line treatment with a PD-(L)1 ICI becomes the standard of care in many countries, the number of immunotherapy-naïve second-line patients will shrink. There will be an interim analysis when 15 evaluable patients meet the pre-defined response criteria (anticipated before year end). If the criteria are met, enrolment will advance to 29 evaluable patients; if not, the trial will be stopped for futility. The primary endpoint is an objective response rate. While Transgene's Phase II trial does not include a comparative arm, comparisons will be made to Merck's Keytruda label (Keynote-010) and Bristol Myers Squib's Opdivo (Checkmate 057) label where they are the standard of care in many second-line NSCLC patients (Exhibit 2).

We note significant financial opportunity remains for companies that demonstrate its product can improve response rates when utilised in combination with a PD-L(1) ICI. Data were presented at

ASCO on Nektar Therapeutics' product candidate, NKTR-214. In the [PIVOT study](#) patients with melanoma, renal cell carcinoma and NSCLC were treated. Latest data from [ASCO 2018](#) demonstrated that in PD-L1-naïve first- and second-line NSCLC patients, the overall response rate was 60% (n=3/5) and DCR (disease control rate) was 80% (4/5). One patient had a complete response (CR) while another patient had an unconfirmed CR. While data remain early and patient numbers are limited, Bristol Myers Squibb [announced a joint development and commercialisation partnership](#) worth over \$3.6bn with Nektar Therapeutics for NKTR-214.

TG4010 has previously been tested in combination with chemotherapy. [Data](#) from the Phase IIb TIME trial compared chemotherapy plus TG4010 to chemotherapy plus placebo in patients with advanced NSCLC (n=222). For the total population (squamous and non-squamous NSCLC), patients receiving TG4010 benefited compared to the placebo arm (overall response rate, ORR: 39.6% vs 28.8%; Duration of response: 30.1 vs 18.7 weeks). In non-squamous NSCLC patients ORR was 40% (n=98) in the experimental arm compared with 28% in the control arm, with median duration of response of 41 and 18 weeks respectively. Median PFS in non-squamous NSCLC patients was 5.8 months (95% CI: 5.5 -7.2) vs 5.0 months (95% CI: 4.2 -5.8) for the control. While median OS in non-squamous NSCLC patients was 14.6 months (95% CI: 11.1 -20.4) vs 10.8 months (95% CI: 9.5 -14.5) for the control. In a post-hoc analysis of all non-squamous NSCLC patients there was a similar level of PFS and OS benefit in the 97 patients with low levels of PD-(L)1 expression (<5%) to that observed with all non-squamous NSCLC patients.

**Exhibit 2: Non-squamous NSCLC PD-1 treatment paradigm**

Trial/ Treatment	Histology	Enrolment PD-L1 status	Key data
<b>First line</b>			
<a href="#">Keynote-021G:</a> Keytruda + pemetrexed + carboplatin (Approved, on label)	All non- squamous	Irrespective of PD-L1 36% had PD-L1 TPS <1%	On label: In the TPS <1% subgroup, the ORR was 57% in the KEYTRUDA-containing arm and 13.0% in the chemotherapy arm. In the TPS ≥1% subgroup, the ORR was 54% in the KEYTRUDA-containing arm and 38% in the chemotherapy arm.  Latest data from <a href="#">ESMO 2017</a> : HR for OS was 0.59 (95% CI, 0.34-1.05; p = 0.0344). Median (95% CI) OS has not been reached (95% CI: 22.8 - NR) for Keytruda + chemotherapy and was 20.9 (95% CI: 14.9- NR) months in the chemotherapy arm.
<a href="#">Keynote-189:</a> Keytruda+ carboplatin + pemetrexed	All non- squamous	Irrespective of PD-L1. 63% had TPS >1%	Phase III of Keynote-021G, latest data <a href="#">AACR 2018</a> : HR for OS of 0.49; 95% CI 0.38-0.64; p<.00001. Median OS not reached in Keytruda arm and was 11.3 months in control arm. OS HR for PD-L1 TPS <1% was 0.59 (95% CI: 0.38-0.92), 0.55 (0.34-0.90) for 1-49%, and 0.42 (0.26-0.68) for ≥50%.
<a href="#">Keynote-024:</a> Keytruda monotherapy (Approved, on label)	82% of patients treated across arms were non- squamous	>50% tumour proportion score (TPS) of PD-L1	Latest data at <a href="#">WCLC 2017</a> : Median (95% CI) OS was 30.0 (18.3; not reached) months in the Keytruda arm vs 14.2 (9.8–19.0) months in the chemotherapy arm. Hazard ratio for OS was 0.63 (95% CI, 0.47–0.86; nominal p=0.002)
<a href="#">Keynote-042:</a> Keytruda monotherapy	Approximately 60% of patients across arms were non- squamous	>1% tumour proportion score (TPS) of PD-L1	<a href="#">Latest data</a> : 36% of patients were TPS 1-19%, 17% were TPS 20-49% and 47% had a TPS equal to or above 50%. Median OS of patients with TPS > 50% was 20.0 months (95% CI 15.4-24.9) in the Keytruda arm vs 12.2 months (95% CI 10.4-14.2) in the chemo arm. Median OS of patients with TPS > 20% was 17.7 months (95% CI 15.3-22.1) in the Keytruda arm vs 13.0 months (95% CI 11.6-15.3) in the chemo arm. Median OS of patients with TPS >1% was 16.7 months (95% CI 13.9-19.7) in the Keytruda arm vs 12.1 months (95% CI 11.3-13.3) in the chemo arm.
<a href="#">IMpower150:</a> Tecentriq + carboplatin, paclitaxel, avastin	All non- squamous	Irrespective of PD-L1	<a href="#">IMpower150</a> : 1,202 patients into three arms. 402 patients were enrolled into Tecentriq + chemo (arm A), 400 into Tecentriq + Avastin + chemotherapy (arm B) and 400 into Avastin + chemo (arm C). OS was compared between Arms B and C in the intent to treat population with a HR of 0.76 (95% CI: 0.63-0.93). Median OS of arm B was 19.8 months (95% CI: 17.4-24.2) compared with 14.9 months (95% CI: 13.4-17.1) for arm C. ORR increased with increasing PD-L1 expression. In PD-L1 high (TC3 or IC3) patients, ORR was 62%, 69% and 49% for arms A, B and C respectively with median duration of responses (DOR) of 12.3, 22.1 and 7.0 months for the arms. In PD-L1 low (TC0 or IC0) patients, ORR was 31%, 51% and 36% for arms A, B and C respectively with median DOR of 7.6, 8.2 and 5.5 months for the arms.
<b>Second line</b>			
<a href="#">Checkmate-057:</a> Irrespective of PD-L1 / Opdivo (Approved, on label).	All non- squamous	Irrespective of PD-L1. 22% had non quantifiable PD-L1 status, patients who could be quantified were split into 46% PD-L1 negative and 54% positive	<a href="#">Checkmate-057</a> : In the total patient population, median OS in the Opdivo group was 12.2 months (95% CI: 9.7-15.0), compared with 9.4 months (95% CI: 8.0-10.7) in the docetaxel group. Subgroup analysis demonstrated correlations between OS and PD-L1 expression levels. Median OS for patients below 1% PD-L1 (defined as PD-L1 negative) was 10.4 months on Opdivo vs 10.1 for patients on docetaxel. Patients with PD-L1 above 1% demonstrated a median OS of 17.1 months on Opdivo vs 9.0 months on Docetaxel.
<a href="#">Keynote-010:</a> Keytruda monotherapy (Approved, on label).	70% of patients were non- squamous	Irrespective of PD-L1. 43% has high PD-L1 tumour expression (TPS > 50%)	<a href="#">Keynote-010</a> : In the total patient population, median OS in the 2mg/kg group was 10.4 months (95% CI: 9.4-11.9), in the 10mg/kg group it was 12.7 months (95% CI: 10.0-17.3), in the docetaxel arm it was 8.5 months (95% CI: 7.5-9.8). In the TPS > 50% population, median OS in the 2mg/kg group was 14.9 months (95% CI: 10.4 -NR), in the 10mg/kg group it was 17.3 months (95% CI: 11.8 -NR), in the docetaxel arm it was 8.2 months (95% CI: 6.4-10.7).
Source: Keytruda, Opdivo and Tecentriq prescribing information, ASCO 2018, WCLC 2017 and AACR 2018			

## Pexa-Vec: ICI combinations a new potential

Transgene's oncolytic virus product candidates use viral vector technology with the aim of killing infected or cancerous cells (directly or indirectly). Its lead asset is Pexa-Vec, an oncolytic virus that targets fast-dividing cells with an active EGFR/Ras signalling pathway, causing those cells to lyse and stimulate a T-cell immune response against nearby cells. Pexa-Vec demonstrated efficacy as monotherapy, however, Transgene has decided to advance it in combination with approved therapies, particularly ICIs, where it believes it can act synergistically to improve responses. Its rationale is that the tumour microenvironment may be dampening the response of its oncolytic viruses. By using ICIs to inhibit this tumour-generated immune dampening ('releasing the brakes' of the immune system), Transgene hopes that Pexa-Vec could have an improved effect in patients.

Pexa-Vec is in five ongoing clinical trials, with the lead study a Phase III trial ([PHOCUS](#)) in first-line HCC run by partner SillaJen; data are anticipated in 2019. Phase II trials are ongoing with Pexa-Vec in combination with Opdivo in HCC, Yervoy in solid tumours and chemotherapy in breast cancer. Data from all three are anticipated by year end. Additionally, Transgene (in collaboration with the University of Leeds) recently presented data at [ASCO 2018](#) on Pexa-Vec as a neoadjuvant (treatment of a cancer before the main treatment, usually as a form of shrinking a tumour before surgically resecting it).

Pexa-Vec has historically been involved in more than 10 clinical trials with contrasting results. It has been shown to be more effective in first-line than second-line treatment potentially as a result of lower tumour burden. A [Phase II dose-finding study](#) in HCC patients (sorafenib-naïve) (n=30; 80% first-line) found that those receiving high-dose Pexa-Vec (intratumoral delivery) had a median overall survival (OS) of 14.1 months compared to 6.7 months for those on a low dose (HR: 0.39; p=0.02;). However, the subsequent Phase IIb [TRAVERSE](#) study in second-line HCC (patients who have previously failed Sorafenib treatment through either disease progression or intolerance to treatment) was terminated early in 2013 as data from the first 80 events showed no evidence of OS benefit associated with Pexa-Vec.

The decision to continue development of Pexa-Vec was based on analysis of TRAVERSE and the prior Phase I/II trials with data from over 300 patients in total. Analysis determined that Pexa-Vec was more likely to demonstrate survival benefits in first line rather than second-line HCC. As such, the Phase III trial is in patients with first-line HCC ([PHOCUS](#)).

## PHOCUS Phase III study readout in 2019

The PHOCUS study is an international randomised (1:1), open-label study comparing Pexa-Vec followed by Bayer's sorafenib (anti-BRAF/VEGFR/PDGFR tyrosine kinase inhibitor) and versus sorafenib alone in patients with advanced HCC who have not received prior systemic therapy (n=600). Pexa-Vec will be administered as three bi-weekly intratumoral injections at day one and weeks two and four, followed by sorafenib at week six; the comparator arm will receive sorafenib 400mg twice daily starting on day one. The primary end point is OS; secondary end points include time to progression, progression-free survival, ORR and disease control rate. Initial OS data are expected in 2019. SillaJen has responsibility for conducting and funding the study and retains rights outside of Europe, China and South Korea. Transgene retains development and commercialisation rights in Europe, Lee Pharma retains China rights and Green Cross Pharma has South Korea rights.

## Pexa-Vec: ICI combination readouts by year end

Pexa-Vec is being tested in a variety of combinations that aim to synergistically enhance its efficacy. Phase I/II trials are ongoing with Pexa-Vec in combination with Opdivo in HCC, Yervoy in solid tumours and chemotherapy in breast cancer.

Patient enrolment is ongoing for the [Phase I/IIa trial](#) of Pexa-Vec in combination with Opdivo in first-line HCC patients. In the Phase I part, the safety of the combination will be assessed, in particular dose-limiting toxicities. In the Phase IIa part, the primary outcome will be efficacy with reference to the ORR. Secondary endpoints will include OS and DCR. Initial data from the Phase I component are forecast for year end.

An open-label, investigator-sponsored [Phase I/II trial](#) of Pexa-Vec in combination with Yervoy in up to 60 patients with solid tumours is ongoing at the Léon Bérard Cancer Centre. In Part A of the trial, primary outcomes will be the measurement of dose limiting toxicities (DLTs), while in Part B the ORR will be monitored. Initial data are forecast by year end.

In April 2017, Transgene started the Phase II part of the [METROmaJX trial](#). This Phase I/II study evaluates the combination of Pexa-Vec with metronomic cyclophosphamide (repetitive, low doses; shown to potentiate the activity of other immunotherapies) in patients with advanced soft tissue sarcoma and HER2-negative breast cancer and it will measure the maximum tolerated dose of the first cycle of the combination and anti-tumour activity. The trial is sponsored by the Bergonié Institute. The primary completion date is target for September 2018.

## First readout of the year presented at ASCO 2018

Transgene in collaboration with the University of Leeds presented data at [ASCO 2018](#), which monitored the effect a single dose of Pexa-Vec before surgery had on nine patients with either CRLM (n=6) or MM (n=3). Patients were treated with a single dose of Pexa-Vec ( $1 \times 10^9$ ) 14 ( $\pm$  4 days) days before surgery. Of the five evaluable CRLM patients, four had evaluable tumours of which one patient's tumour was completely necrotic while another was partially necrotic. Analysis of PD-L1 and CD69 (an early activation marker) expression demonstrated it increased in some patients across NK, CD4+ T cells, CD8+ T-cells.

## Broad asset pipeline gives multiple inflection points

While focus remains on Pexa-Vec and TG4010, Transgene has a range of other product candidates in the clinic with multiple readouts anticipated in the short term. Transgene forecasts readouts for TG4001 in head and neck cancer (in combination with PD-L1 inhibitor avelumab), TG1050 in hepatitis B and TG6002 by year end.

### TG4001: Potential in HPV-positive HNSCC

TG4001 is a therapeutic vaccine based on an MVA vector engineered to express HPV 16 antigens E6 and E7 with adjuvant interleukin-2 (IL-2). [Clinical data](#) from 206 female patients with CIN2/3 Intraepithelial Cervical Neoplasia showed a 38% (20/52) clearance rate in HPV 16 mono-infected patients compared with 9% for placebo (2/23) ( $p = 0.009$ ) with a favourable safety profile.

In collaboration with Pfizer and Merck, Transgene is running a [Phase Ib/II study](#) in second-line HPV-positive HNSCC combining TG4001 and the anti-PD-L1 antibody avelumab. Initial data are expected by year end. The trial is funded by Transgene, while Pfizer and Merck will provide avelumab. Pfizer and Merck do not have exclusive rights to the data or TG4001, both of which remain Transgene's. Patient enrolment is ongoing with 52 patients expected to be treated. The study is split into two parts, in the Phase Ib component, under a 3+3 design, consecutive cohorts of three to six patients will be tested at increasing doses of TG4001 in combination with a fixed dose of avelumab. These patients will have HPV16-positive recurrent or metastatic malignancies. In the expansion cohort (Phase II), patients with oropharyngeal squamous cell carcinoma of the head and neck will be enrolled into a single-arm cohort. The primary outcome of the Phase II part will be efficacy as measured by ORR. Details on the financial terms, IP rights or other aspects of the agreement between the three parties have not been disclosed. Initial data are expected by year end.

### TG1050: Potential outside of oncology to be tested in Hep B

TG1050 is a therapeutic vaccine for the treatment of chronic hepatitis B that expresses three antigens of the hepatitis B virus (HBV). In November 2016, the first patient was randomised in the multiple dose cohort of the ongoing [Phase I/Ib trial](#) of TG1050 with standard of care in patients with chronic hepatitis B infection. The clinical trial is an international, randomised, double-blind, placebo-controlled safety and dose-finding study evaluating single and multiple doses of TG1050 in patients who are being treated for chronic HBV infection with standard-of-care antiviral therapy (n=48).

Primary outcomes are to test the safety and tolerability of TG1050. Secondary objectives include the antiviral activity of, and immune responses to, TG1050. Data are expected in H218.

There are limited treatments for HBV. The cure rate from nucleotide analogues such as tenofovir (Viread) and entecavir (Baraclude) or pegylated interferon- $\alpha$  is only 3-5%, so patients normally need long-term antiviral therapy to control their infection. Around 240 million people have chronic HBV infection, according to the World Health Organization. Transgene will look to partner TG1050 once it has proof-of-concept data from this study.

We note Transgene is progressing a similar product to TG1050 through a joint venture (50:50) with Tasly Pharmaceuticals. At the start of 2018, it announced the first patient had been dosed in China in a Phase I trial of T101 for the treatment of chronic HBV infection. T101 is a viral vector that expresses the same suite of HBV antigens as TG1050. The trial is a randomised, double-blind, placebo-controlled study, which is expected to enrol up to 36 patients who are on antiviral therapy. While the primary endpoint is to validate the tolerability of T101, key secondary endpoints include studying how the drug acts (in comparison to TG1050) in a Chinese population with different characteristics to that of an EU and US population. Initial data are expected at the start of 2019; at this time, we anticipate safety and efficacy comparable with that of TG1050.

## Next-generation viral vector in TG6002

TG6002 is a viral vector derived from vaccinia virus expressing the FCU1 gene. The FCU1 gene encodes a protein that catalyses the transformation of the nontoxic pro-drug flucytosine, into 5-FU and 5-fluorouridine monophosphate, a widely used chemotherapy. Its expression is restricted to tumours, thereby reducing toxicity to normal tissues. The company has conducted numerous in vitro and in vivo [experiments](#) to establish its mechanism of action.

A Phase I trial in glioblastoma with Assistance Publique Hôpitaux de Paris (principal investigator Professor Delattre) and support from French National Cancer Institute is enrolling patients. Initial data are expected by year end.

## Invir.IO: Deals demonstrate value in next-gen platform

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In 2017, Transgene launched its Invir.IO technology platform. The technology aims to use the cancer cell-killing capability of oncolytic viruses in combination with the ability of the viruses to insert relevant genes into cancer cells to express other anti-cancer compounds. The technology is based around high-capacity vaccinia viruses, which are engineered to express a range of anti-cancer drugs such as ICIs, enzymes, ligands, chemokines and cytokines. Transgene is developing both its own internal proprietary product candidates and partnered candidates.

On the back of the launch of the platform, Transgene signed two partnership deals with BioInvent and Randox based on the Invir.IO technology. The partnership with Randox aims to develop multifunctional viruses for use in solid tumours, where it will look to vectorise Randox's single domain antibodies. Financially, both parties will share costs, with no further detailed financial terms disclosed. The BioInvent deal will look to vectorise BioInvent's anti-CTLA-4 antibodies for use in cancers. R&D costs, in addition to revenues and royalties from any candidates produced, will be shared 50:50. Transgene has 10 wholly owned preclinical candidates based on its Invir.IO platform and it anticipates the first product candidate will enter the clinic in 2019.

The flexibility and potential capability of multifunctional viral vectors have made the companies developing them attractive for partnerships or acquisition. In February Merck [announced the proposed acquisition](#) of Australian oncolytic immunotherapy company, Viralytics. The deal valued Viralytics at approximately A\$502m (US\$394m) and is predominately focused on CAVATAK, an

oncolytic virus (Coxsackievirus Type A21) that is believed to preferentially infect and kill cancer cells. CAVATAK is in multiple Phase I and II trials, including in combination with Merck's Keytruda.

More recently Janssen (J&J) announced the proposed [acquisition](#) of privately held BeneVir for \$140m upfront and up to \$900m in contingent payments. The deal is focused on BeneVir's T-stealth oncolytic virus platform. Janssen intends to advance pre-clinical candidates as standalone therapies and in combination with other immunotherapies for the treatment of solid tumours.

Transgene's R&D capabilities continue to be at the centre of its recent business development activities. Transgene and Servier have entered into a research collaboration for the application of Transgene's viral vectorisation technology for the production of allogenic CAR-T cell therapies. The final objective is to achieve an allogenic CAR-T preparation method with better transgene integration yields and fewer steps. The research collaboration could generate €30m in revenues for Transgene.

## Sensitivities

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Transgene is subject to the usual risks associated with drug development, including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, and financing and commercial risks. The key sensitivities relate to the results of the ICI combination studies of TG4010, Pexa-Vec and TG4001. The outcome of the TG4010 combination studies in particular will have an impact on its partnership and/or the financing prospects for the programme. First results from these trials will be available later this year. The clinical performance of Pexa-Vec in the Phase III trial (data in 2019) is another key sensitivity. We note that the ICI combination trials are small, open-label and non-controlled; therefore, it is not possible to ascertain the magnitude of the effect of each product separately and assess the actual synergistic effect.

## Financials

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Transgene reported cash, cash equivalents and financial assets of €35.6m as of 31 March 2018 (compared to €41.4m as of 31 December 2017)

Revenue in Q118 was €1.8m (Q117: €1.9m). In 2017 revenue was €8.1m (2016: €10.3m). In core, this was driven by government financing in the form of research grants and tax credits, which were €5.4m (2016: €6.4m) and less than €0.1m (2016: €0.1m), respectively.

R&D expenses in 2017 were €30.4m, an increase on 2016 expenditure of €26.4m, driven by the initiation of multiple trials in 2017. We forecast 2018 R&D will increase slightly to €31.2m as the clinical trials mature. The majority of R&D expenditure continues to be driven by payroll costs as R&D staff costs are accounted for in the R&D expenditure; these were €11.1m vs €10.8m in 2016. Of note, intellectual property costs increased substantially to €4.8m from €1.1m in the previous period, mainly as a result of a €3.8m milestone payment to SillaJen. This was triggered on the first European patient being enrolled in the Phase 3 Pexa-Vec trial (PHOCUS). We note a final payment of \$1.5m is expected in September 2018. External expenses for clinical projects remained flat at €7.0m (2016: €7.0m).

G&A costs decreased to €5.7m in 2017 from €6.2m in 2016. This was driven in core by a reduction in payroll costs, which were reported at €3.0m for the period (2016: €3.8m), offset slightly by increases in share-based payments, admin fees and other fixed costs. We note interest on the EIB loan (€10m) that was drawn down in June 2016 is not repayable until 2019 with the capital repayable in 2021.

Net loss for 2017 was €32.3m, compared with €25.2m in 2016. We forecast net loss to remain relatively stable over 2018 and 2019 at €31.5m and €34.1m, respectively.

In 2017, Transgene's cash burn was €28.1m in 2017 vs €30.6m in 2016 excluding capital increases and EIB loan; the company anticipates its cash burn in 2018 to be comparable with that of 2017. Our model predicts a current cash reach until mid-2019, which will incorporate multiple trial readouts later this year.

## **Valuation: €289m (€4.65/share)**

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We value Transgene at €289m (€4.65/share) vs €236m (€3.80/share) previously. Our valuation is based on a risk-adjusted NPV model of TG4010, TG4001, TG1050, Pexa-Vec and TG6002. We have rolled forward our model and updated for both current cash and currency exchange rates. We have extended some of our forecasts to better represent full product sales cycles and pushed back our launch of Pexa-Vec in the EU to 2021 (from 2020 previously). Our valuation includes the prospects for TG4010 in NSCLC in the US and Europe (combined peak potential sales of €2.5bn); Pexa-Vec for HCC in Europe (€518m peak sales); and TG1050 for hepatitis B in the US and Europe (peak potential sales of €2.1bn in both regions, unchanged). For TG4010, we assume a classical clinical development timeline, starting with the Phase I/II studies planned in combination ICIs. For Pexa-Vec, the Phase III PHOCUS study being conducted by SillaJen will potentially be sufficient to file for approval in Europe, assuming a positive study result. For TG1050, we assume Transgene develops it and a partner conducts Phase III trials, registration and marketing. We forecast both TG4001 in head and neck cancer and TG6002 in glioblastoma are partnered after Phase II trials.

Our key assumptions on TG4010, Pexa-Vec, TG1050, TG6002 and TG4001 are the following:

- TG4010: we model a classical clinical development timeline for the project, starting with the Phase I/II studies planned in combination ICIs, and use NSCLC as a proxy for this opportunity. As such, there could be considerable upside should the company go for accelerated filing, and/or development is expanded into other cancer indications.
- Pexa-Vec: we have assumed that the Phase III PHOCUS study, which plans to include EU trial sites, will be sufficient to file for approval in Europe, assuming a positive study result. Under the deal with SillaJen, Transgene will be responsible for funding, compiling and submitting the regulatory application in Europe.
- TG1050: our valuation includes the EU and US market and we have assumed that TG1050 will be out-licensed on completion of a successful Phase II proof-of-concept study. We forecast that a partner will fund Phase III trials, registration and commercial launch.
- TG6002: our valuation is based on recurrent glioblastoma patients in the EU and US. We expect a higher penetration and price for TG6002 than typical; as if successful in clinical development it would address a significant unmet need.
- TG4001: our valuation is based on HPV-positive oesophageal patients in the EU and US who have failed standard therapy.

We have rolled forward our model, updated for current exchange rates and full-year results. Our operational and product assumptions remain unchanged (Exhibit 3).

**Exhibit 3: Transgene valuation model and key assumptions**

Product	Status	Market launch	NPV (€m)	Peak sales (€m)	Probability of success	Royalty estimate	rNPV (€m)	rNPV/ share (€)	Key assumptions
TG4010 – NSCLC (EU)	Phase I/II	2025	179.4	1,062	40%	17.5%	76.2	1.23	Approximately 313k annual EU-28 incidence of lung cancer; 85% NSCLC; 75% MUC1 +ve; 66% normal NK cells; 20% peak penetration; €30k treatment price; €30m upfront on Phase IIb completion.
TG4010 – NSCLC (US)	Phase I/II	2025	150.5	1,429	40%	17.5%	60.2	0.97	Approximately 222k annual US incidence of lung cancer; 85% NSCLC; 75% MUC1 +ve; 66% normal NK cells; 20% peak penetration; \$50k treatment price.
Pexa-Vec – HCC (EU)	Phase III	2021	146.0	518	50%	25.0%	71.2	1.15	Approximately 66k annual EU incidence of liver cancer; 80% HCC; 25% peak penetration; €30k treatment price.
TG1050 – HepB (EU + US)	Phase Ib	2025	361.6	2,054	15%	20.0%	44.5	0.72	Approximately 5.4m chronic hep B prevalence in EU + US; 66% diagnosis rate; 33% require treatment; 5% peak penetration; €35k treatment price.
TG4001 – Oesophageal cancer (EU + US)	Phase Ib/II	2026	40.0	198	15%	20.0%	4.0	0.06	Approximately 42k annual incidence of oesophageal cancer in EU5 + US; 70% with HPV; 75% fail; 25% peak penetration; 20% peak royalty rate; €35k treatment price.
TG6002 – Glioblastoma (EU + US)	Phase I/IIa	2026	61.7	240	15%	25.0%	7.3	0.12	Approximately 36k annual incidence of brain/central nervous system cancer in EU5 + US; 30% are glioblastoma, 85% will be recurrent, 50% peak penetration, 25% peak royalty rate, €50k treatment price.
Net cash (30 March 2018)							25.3	0.41	
Total							288.8	4.65	

Source: Edison Investment Research. Note: Peak sales represent the largest one-year sales that occur over the projected product lifespan. Spot rate \$1.23/€.

**Exhibit 4: Financial summary**

	€'000s	2015	2016	2017	2018e	2019e
Year end 31 December		IFRS	IFRS	IFRS	IFRS	IFRS
<b>PROFIT &amp; LOSS</b>						
Revenue		9,949	10,311	8,144	7,170	7,887
Cost of Sales		0	0	0	0	0
Gross Profit		9,949	10,311	8,144	7,170	7,887
R&D expenses		(32,138)	(26,419)	(30,359)	(31,175)	(34,292)
G&A expenses		(5,798)	(6,236)	(5,674)	(5,844)	(6,020)
EBITDA		(25,671)	(20,397)	(26,352)	(28,413)	(31,093)
Operating Profit (before amort. and except.)		(27,957)	(22,514)	(28,043)	(29,774)	(32,363)
Intangible Amortisation		(350)	(150)	0	(75)	(62)
Exceptionals (restructuring costs / discontinued operations)		(15,965)	(1,024)	0	0	0
Operating Profit		(44,272)	(23,688)	(28,043)	(29,849)	(32,425)
Other		0	0	0	0	0
Net Interest		(930)	(602)	(2,287)	(1,619)	(1,677)
Profit Before Tax (norm)		(28,887)	(23,116)	(35,048)	(36,786)	(34,040)
Profit Before Tax (IFRS)		(45,202)	(24,290)	(30,330)	(31,467)	(34,101)
Tax		0	0	0	0	0
Minority interest		(1,172)	(917)	(1,944)	0	0
Profit After Tax (norm)		(30,059)	(24,033)	(32,274)	(31,392)	(34,040)
Profit After Tax (IFRS)		(46,374)	(25,207)	(32,274)	(31,467)	(34,101)
Average Number of Shares Outstanding (m)		38.5	56.0	62.1	62.1	62.1
EPS - normalised (c)		(78.1)	(42.9)	(52.0)	(50.6)	(54.8)
EPS - IFRS (€)		(1.20)	(0.45)	(0.52)	(0.51)	(0.55)
Dividend per share (c)		0.0	0.0	0.0	0.0	0.0
<b>BALANCE SHEET</b>						
Fixed Assets		49,841	48,895	42,137	41,186	40,363
Intangible Assets		485	423	250	206	176
Tangible Assets		16,559	14,580	13,604	12,697	11,904
Other		32,797	33,892	28,283	28,283	28,283
Current Assets		51,028	74,055	58,736	31,672	23,844
Stocks		1,164	221	270	270	270
Debtors		1,784	2,385	2,564	2,750	3,025
Cash		31,650	56,207	41,405	14,155	6,052
Other		16,430	15,242	14,497	14,497	14,497
Current Liabilities		(26,725)	(19,919)	(16,866)	(15,255)	(13,785)
Creditors		(6,521)	(4,504)	(2,868)	(3,117)	(3,429)
Short term borrowings		0	0	0	0	0
Short term leases		(9,396)	(10,198)	(10,283)	(8,423)	(6,641)
Other		(10,808)	(5,217)	(3,715)	(3,715)	(3,715)
Long Term Liabilities		(47,597)	(56,528)	(55,918)	(55,174)	(74,461)
Long term borrowings		0	0	0	0	(20,000)
Long term leases		(44,401)	(52,803)	(51,717)	(50,973)	(50,260)
Other long term liabilities		(3,196)	(3,725)	(4,201)	(4,201)	(4,201)
Net Assets		26,547	46,503	28,089	2,429	(24,040)
<b>CASH FLOW</b>						
Operating Cash Flow		(46,082)	(34,187)	(37,657)	(29,520)	(32,271)
Net Interest		930	602	2,287	(1,860)	(1,782)
Tax		0	0	0	0	0
Capex		(1,527)	(47)	(462)	(485)	(508)
Acquisitions/disposals		0	0	0	0	0
Financing		477	45,080	13,272	0	0
Dividends		0	0	0	0	0
Other		12,975	4,561	8,935	5,358	7,170
Net Cash Flow		(33,227)	16,009	(13,625)	(26,506)	(27,390)
Opening net debt/(cash)		(13,744)	22,147	6,794	20,595	45,241
HP finance leases initiated		(2,646)	(427)	(120)	1,860	1,782
Other		(18)	(229)	(56)	(0)	0
Closing net debt/(cash)		22,147	6,794	20,595	45,241	70,850

Source: Company data, Edison Investment Research

Contact details	Revenue by geography
Boulevard Gonther d'Andernach Parc d'Innovation – CS80166 F-67405 Illkirch-Graffenstaden France +33 (0)3 88 27 91 00 <a href="http://www.transgene.fr">www.transgene.fr</a>	N/A
Management team	
<b>Chairman and CEO: Philippe Archinard</b> Philippe Archinard became CEO in 2004. From 2000 to 2004, he was CEO of Innogenetics; previously he was at bioMérieux, where he held various positions including CEO of its US operations. He has a PhD in biochemistry from Lyon University.	<b>EVP, research &amp; development: Eric Quéméneur</b> Eric Quéméneur joined Transgene in 2014. Prior to this, he spent over 20 years at the CEA (Atomic Energy Commission) where he was director of research programmes and industrial partnerships in the life science division. He has a PhD in biochemistry from the Claude Bernard University in Lyon.
<b>VP, finance: Jean-Philippe Del</b> Jean-Philippe Del became VP, finance at Transgene in 2014, previously serving as finance senior director. He has previously worked at Mazars and Kronenbourg Breweries. He has a post-graduate degree in accounting and finance and a master's degree from the University of Strasbourg.	<b>CMO: Dr Maud Brandely</b> Dr Maud Brandely joined Transgene in March 2016. She was previously director of clinical development at Pierre Fabre Oncologie until February 2016 where she was responsible for all clinical trials from Phase I to Phase III trials. She previously worked at Rhone-Poulenc (now Sanofi) and at Hoescht-Roussel-Uclaf (now Sanofi). Dr Brandely has an MD and PhD in immunology from the University of Paris VI.
Principal shareholders	(%)
Institut Merieux SACA	56.92
Dassault Belgique Aviation	4.68
OFI Asset Management SA	1.36
Companies named in this report	
BioInvent., Bristol Myers Squib (BMY), Merck (MRK), Randox, Servier, Sillajen (215600)	

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