Pooled Safety Analysis of Modified Vaccinia Virus Ankara-based Therapeutic Vaccine Alone or in Combination in Cancer and Cervical Intraepithelial Neoplasia (CIN) Clinical Trials.

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BACKGROUND

Transgene has developed therapeutic vaccines, based on Modified Vaccinia Virus Ankara (MVA) viral vector. TG MVA-based products (TG) were used as single agent or combined with chemotherapy (CT) and/or immune checkpoint inhibitor (ICI) in phases I-II cancer trials in several indications and in Cervical Intraepithelial Neoplasia (CIN) and Vulvar Intraepithelial Neoplasia (VIN) clinical trials.

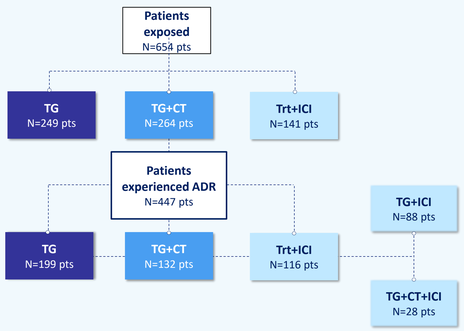
METHODS

The analysis provides an overall safety profile of TG alone or in combination. The analysis focused on all adverse drug reactions (ADRs) across Transgene clinical trials.

All studies were recoded using the same MedDRA version 27.1 in order to harmonize SOCs and PTs and support this pooled analysis.

The risk ratio (RR) measures how the probability of an event differs between groups (RR = 1 indicates no difference, RR > 1 higher risk, RR < 1 lower risk).

Predictive modeling with machine learning algorithms (ML) using XGboost was applied to predict the occurrence of the adverse events based on patients (pts) who experienced ADRs and the most influential factors through Shapley Additive exPlanations score (SHAP) value analysis.



RESULTS

7 phase I (n=56), 1 phase Ib/II (n=94) and 11 phase II trials (n=504) were reviewed. 654 patients (pts) were exposed, 447 (68.3%) experienced 1845 ADRs. Out of these 447 pts, 199 pts had received TG alone, 132 were exposed to combination with platinum-based CT, 88 pts had an ICI (aPD(L)-1) combination and 28 pts a combination of TG+ICI+CT. Local reactions at the injection site were the most frequently observed: 1023 events were reported in 342 pts, all being grade 1 or 2 and estimated with an occurrence of 76.4% using XGboost algorithm for pt who experienced an ADR. Other frequent ADRs were fatigue (111 events in 73 pts all grade 1/2 except 2 episodes in 2 pts) and pyrexia (94 events in 63 pts, all grade 1/2) and estimated respectively to 16.3% and 14% with the prediction algorithm.
A total of 36 grade 3/4 ADRs were experienced by 22 pts with hematological disorders (9 pts), fatigue, asthenia and gastrointestinal disorders (2 pts) being the most frequent. Out of these 36 events, only 1 occurred in TG arm. 10 serious ADRs were reported in 5 pts: no particular pattern could be observed. 2 pts experienced grade 5 ADRs (renal failure, left ventricular failure), both as well evaluated by the investigator as related to underlying disease.

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DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

label	All treated Patients (N=654) TG (N=249)	TG+CT (N=264)	Trt+ICI (N=141)	Overall (N=654)
Age (years)				
N	249	264	141	654
Mean (SD)	51.2 (14.43)	60.4 (9.36)	57.6 (11.27)	56.3 (12.60)
Median	54.0	61.0	58.0	58.0
Min - Max	21.0 - 82.0	34.0 - 81.0	28.0 - 80.0	21.0 - 82.0
Q1 - Q3	39.0 - 61.0	54.0 - 67.0	51.0 - 66.0	49.8 - 65.0
Gender				
N	249 (38.1%)	264 (40.4%)	141 (21.6%)	654 (100.0%)
Female	174 (69.9%)	83 (31.4%)	95 (67.4%)	352 (53.8%)
Male	75 (30.1%)	181 (68.6%)	46 (32.6%)	302 (46.2%)
Product				
N	249 (38.1%)	264 (40.4%)	141 (21.6%)	654 (100.0%)
TG4001	111 (44.6%)	0 (0.0%)	94 (66.7%)	205 (31.3%)
TG4010	116 (46.6%)	264 (100.0%)	44 (31.2%)	424 (64.8%)
TG4050	22 (8.8%)	0 (0.0%)	3 (2.1%)	25 (3.8%)
Route				
N	249 (38.1%)	264 (40.4%)	141 (21.6%)	654 (100.0%)
IM	31 (12.4%)	0 (0.0%)	0 (0.0%)	31 (4.7%)
SC	218 (87.6%)	264 (100.0%)	141 (100.0%)	623 (95.3%)

Cancer/Pre-cancer Indications	All treated Patients (N=654) TG (N=249)	TG+CT (N=264)	Trt+ICI (N=141)	Overall (N=654)
N	249 (38.1%)	264 (40.4%)	141 (21.6%)	654 (100.0%)
Cancer	180 (72.3%)	264 (100%)	141 (100%)	595 (89.4%)
NSCLC	11 (4.4%)	241 (91.3%)	44 (31.2%)	296 (45.3%)
Cervical	42 (16.9%)	0 (0.0%)	37 (26.2%)	79 (12.1%)
Breast	44 (17.7%)	0 (0.0%)	0 (0.0%)	44 (6.7%)
Prostate	40 (16.1%)	0 (0.0%)	0 (0.0%)	40 (6.1%)
Renal Cell Carcinoma	18 (7.2%)	23 (8.7%)	0 (0.0%)	41 (6.3%)
Anal	0 (0.0%)	0 (0.0%)	35 (24.8%)	35 (5.4%)
Head and neck	17 (6.8%)	0 (0.0%)	13 (9.2%)	30 (4.6%)
Genital	0 (0.0%)	0 (0.0%)	12 (8.5%)	12 (1.8%)
Ovarian	6 (2.4%)	0 (0.0%)	0 (0.0%)	6 (0.9%)
Other*	2 (0.8%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
Pre-cancer	69 (27.7%)	0 (0.0%)	0 (0.0%)	69 (10.6%)
CIN2/3	58 (23.3%)	0 (0.0%)	0 (0.0%)	58 (8.9%)
VIN3	11 (4.4%)	0 (0.0%)	0 (0.0%)	11 (1.7%)

Most of the pts (95.3%) received treatment by SC route, mainly TG4010 (64.8%) then TG4001 (31.3%), in overall there is no important difference in term of gender: 53.8% of female and 46.2% of male pts were included in this analysis, even though in each arm there is an imbalance between female and male pts. Overall, the mean of age was 56.3 years. In cancer group: NSCLC (45.3%), cervical cancer (12.1%) were the most frequent type of cancer treated, and CIN2/3 (8.9%) in pre-cancer group.

TG = Transgene product. CT=Chemotherapy, Trt+ICI=TG+CT+ICI or TG+ICI, ICIs = (aPD(L)-1), TG4010=MVA-MUC1-IL2, TG4001=MVA-HPV-IL2, TG4050=MVA-TSAs, TSA= Tumor Specific Antigens.
* Other : One patient with mesothelioma, and one patient with gastric cancer



Figure: Tree map of type of cancer by arm

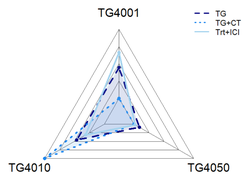


Figure: Radar plot on Product by arm

DURATION OF ADVERSE REACTION BY ARM

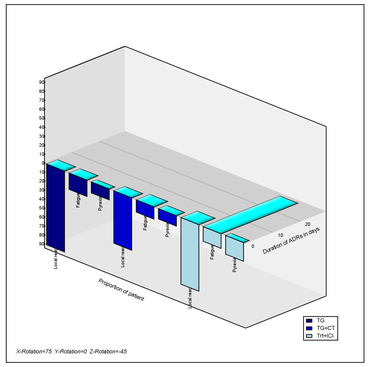
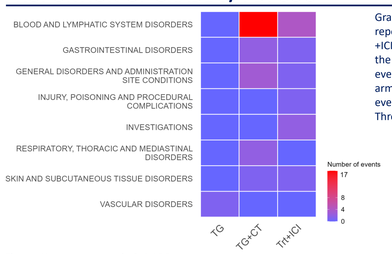


Figure: Proportion/ Duration of frequent ADRs by arm is presented in pts who experienced at least one ADR

Local reaction, fatigue and pyrexia were the most frequently reported adverse reactions for patients who experienced at least one ADR. For all arms, local reaction was more frequent specially in TG monotherapy (89.9%) and Trt+ICI (74.1%) arms compared to TG+CT (58.3%). The **median** duration was similar for local reaction and pyrexia between study group (2 to 6 days). The duration of fatigue was longer in Trt+ICI with 28 days compared to 2 days for the other groups.

PROPORTION OF GRADE 3/4 BY SOC



Grade 3-4 ADRs were most commonly reported in the arm TG + CT and Trt +ICI. The most frequent ADR was in the SOC blood and lymphatic (17 events). It was only reported in the arm TG+CT and includes Anaemia (5 events), Neutropenia (5 events), Thrombocytopenia (4 events)

Figure: Heatmap on grade 3-4 ADRs

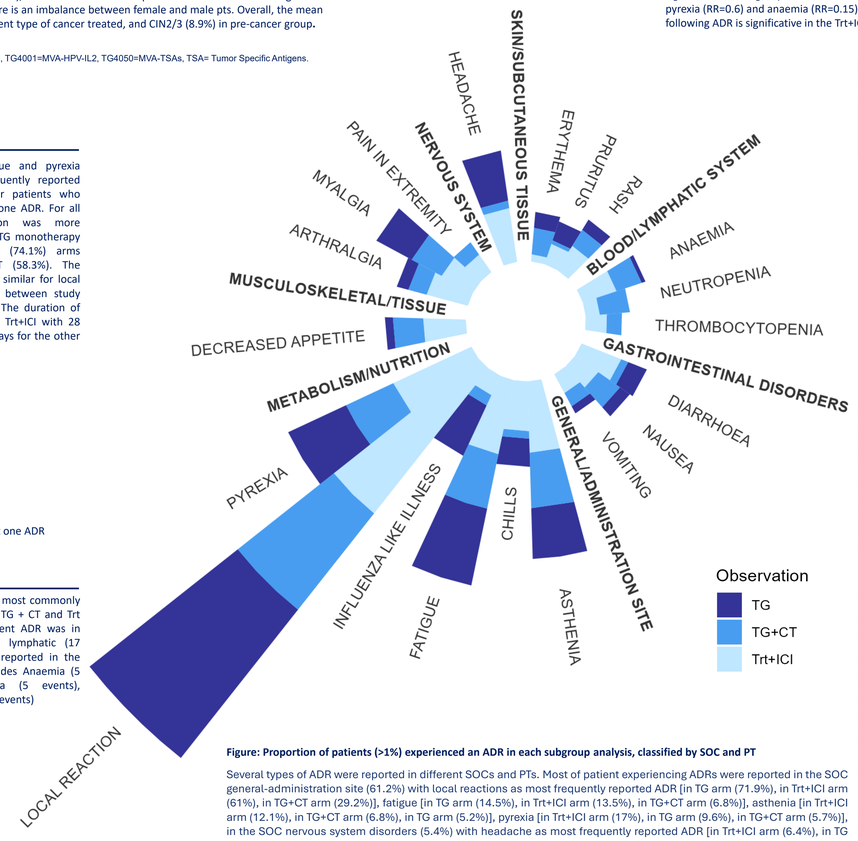
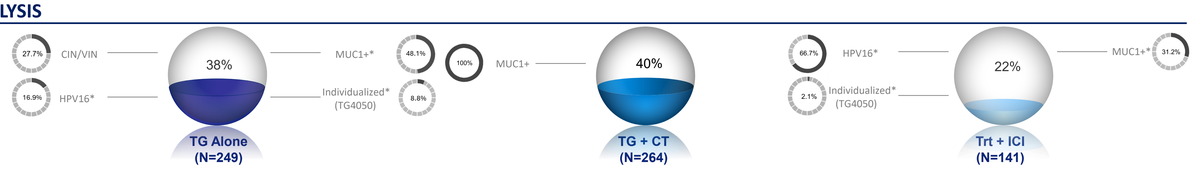


Figure: Proportion of patients (>1%) experienced an ADR in each subgroup analysis, classified by SOC and PT

Several types of ADR were reported in different SOCs and PTs. Most of patient experiencing ADRs were reported in the SOC general-administration site (61.2%) with local reactions as most frequently reported ADR [in TG arm (71.9%), in Trt+ICI arm (61%), in TG+CT arm (29.2%)], fatigue [in TG arm (14.5%), in Trt+ICI arm (13.5%), in TG+CT arm (6.8%)], asthenia [in Trt+ICI arm (12.1%), in TG+CT arm (6.8%), in TG arm (5.2%)], pyrexia [in Trt+ICI arm (17%), in TG arm (9.6%), in TG+CT arm (5.7%)], in the SOC nervous system disorders (5.4%) with headache as most frequently reported ADR [in Trt+ICI arm (6.4%), in TG arm (5.2%), in TG+CT arm (0.8%)], and in the SOC musculoskeletal and connective tissue disorders (7.5%) with myalgia as most frequently reported ADR [in TG arm (4%), in Trt+ICI arm (3.5%), in TG+CT arm (3.4%)].

SUBGROUP ANALYSIS



* Type for advanced cancer

Number of patients with:	TG4001: CIN/VIN (N=69) Pt (%) Ev	TG4001: HPV16 (N=42) Pt (%) Ev	TG4010: MUC1+ (N=116) Pt (%) Ev	TG4050: Ovarian / H&N (N=22) Pt (%) Ev	Plot overview
ADR	55 (79.7%) 195	27 (64.3%) 53	95 (81.9%) 515	22 (100.0%) 145	79,9%
SAR	0 (0.0%) 0	1 (2.4%) 1	0 (0.0%) 0	0 (0.0%) 0	0,4%
Grade ≥3 ADR	0 (0.0%) 0	1 (2.4%) 1	1 (0.9%) 1	0 (0.0%) 0	0,8%

Number of patients with:	TG4010: MUC1+ NSCLC (N=241) Pt (%) Ev	TG4010: MUC1+ Renal Carcinoma (N=23) Pt (%) Ev	Plot overview
ADR	112 (46.5%) 373	20 (87.0%) 94	50%
SAR	3 (1.2%) 8	0 (0.0%) 0	1,1%
Grade ≥3 ADR	12 (5.0%) 25	1 (4.3%) 1	4,9%

Number of patients with:	TG4001: HPV16 (N=94) Pt (%) Ev	TG4010: MUC1+ (N=44) Pt (%) Ev	TG4050: Ovarian / H&N (N=3)	Plot overview
ADR	87 (92.6%) 399	27 (61.4%) 66	2 (66.7%) 5	82,3%
SAR	0 (0.0%) 0	1 (2.3%) 1	0 (0.0%) 0	8,7%
Grade ≥3 ADR	1 (1.1%) 2	7 (15.9%) 8	0 (0.0%) 0	6,4%

RISK RATIO ON PREFERRED TERM BY STUDY GROUP

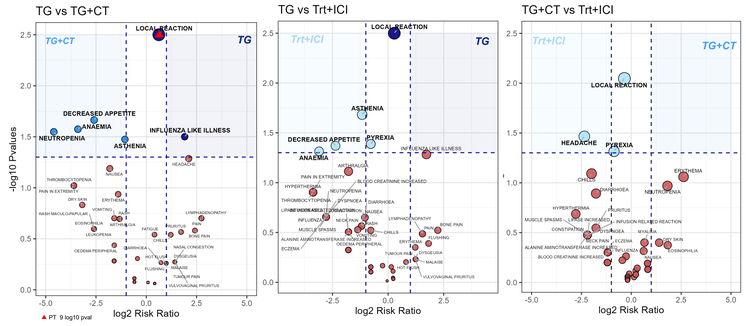


Figure 1: : Volcano Plot based on Risk ratio on Preferred term

The risk ratio (RR) compares the probability of an event between arms; using log2(RR) in a volcano plot provides a clear view of both risk differences and their significance. Each plot presents the log2(RR) between two arms, comparing the frequency of PTs among pts who experienced at least one ADR.
By comparing TG vs TG+CT the risk of developing ADR is significative for Influenzae like illness (RR=3.7) and local reaction (RR=1.5) tend to be present more in the group TG. The risk of experiencing neutropenia (RR<0.1) , anemia (RR=0.1), decreased appetite (RR=0.16) and asthenia (RR=0.4) are significative in the group of TG+CT. The comparison of TG vs Trt + ICI showed that the risk of presenting asthenia (RR= 0.6), decreased appetite (RR=0.2), pyrexia (RR=0.6) and anaemia (RR=0.15) are significative in the Trt+ICI group. The comparison of TG+CT vs Trt+ICI revealed that the risk of developing the following ADR is significative in the Trt+ICI group: local reaction, headache and pyrexia.

PREDICTION OF ADR USING MACHINE LEARNING ALGORITHMS

Parameter	Pre cancer TG (N=55)	Cancer TG (N=144)	TG+CT (N=132)	TG+ICI (N=88)	TG+CT+ICI (N=28)
General-Administration site disorders	97.7%	92.9%	80.7%	95%	79.1%
Local reaction	96%	85.7%	60.9%	78.1%	59.0%
ISR	38.9%	44.8%	15.2%	17.6%	14.4%
ISE	25.9%	28.1%	22.2%	33.6%	20.6%
ISP	15.2%	16.4%	17.9%	19.1%	19.5%
Fatigue	22.7%	23.6%	17.0%	11.9%	18.2%
Pyrexia	12.6%	15.0%	9.7%	21.3%	*8.9%*
Blood - Lymphatic System	10.2%	4.7%	9.3%	9.0%	10.4%

Predictive modeling using machine learning algorithms (XGboost) was applied to predict the occurrence of the experienced ADRs and the most influential factors through Shapley Additive explanations (SHAP) score, including indication, product, sex, age, route.

Local reaction includes: ISR (injection site reaction, ISE (injection site erythema), ISP injection site pain)

The prediction of ADR using XgBoost algorithm showed local reactions were more frequent in that group pre-cancer (97.7%) compared to each Trt arm of the group of cancer (mostly advanced cancers). In the group of cancer, local reaction were reported in the TG arm (85.7%). This difference observed in these 2 groups about % of local reactions could be explained by reporting of other events considered as more relevant in the cancer group specially in the arms with CT.

For fatigue, in the group of cancer, pts with TG experienced more ADRs (23.6%), followed by TG+CT+ICI arm (18.2%), then TG+CT (17.0%), and TG+ICI arm (11.9%). These results showed that the addition of other Therapies to TG did not increase the % of local reactions and fatigue.
For pyrexia the group pre-cancer experienced less frequence of ADR (12.6%) compared to the pts treated with TG (15%) and TG+ICI (21.3%) in the group of cancer. In the group of cancer, pyrexia was more common in the pts treated with TG and TG+ICI versus pts treated with TG+CT and TG+CT+ICI. These results showed that the addition of CT to TG or TG+ICI did not increase pyrexia.

This prediction confirmed that the addition of ICI and/or CT to TG did not increase the % of common reported ADRs in Transgene trials.
Additionally, analysis was focused on the SOC Blood-Lymphatic system because : Grade 3-4 ADRs were most commonly reported in this SOC. The results of prediction showed that the % of ADR in this SOC was most frequently reported in the group pre-cancer (mild intensity), compared to TG alone in the cancer group. Only lymphadenopathy (5 pts) and Lymphadenitis (1 pt) were reported in the group pre-cancer, the median duration of these ADR was 4 days.
In the group cancer pts treated with combination TG+CT+ICI presented more ADR (10.4%) compared to TG+CT (9.7%), followed by TG+ICI (9%) and TG alone (4.7%). Anemia, neutropenia and thrombocytopenia were most commonly observed in the group cancer specially in the arms with CT, these events only reported in that group are consistent with the safety profile of most of the drugs used in chemotherapy.

KEY MESSAGES AND CONCLUSION

- **IN THIS POOLED SAFETY ANALYSIS THE MOST FREQUENT ADRs REPORTED WERE GRADE 1/2. ONLY FEW SEVERE ADRs AND SAR WERE REPORTED MOSTLY IN ARMS WITH CT.**
- **THE PREDICTION CONFIRMED THAT THE ADDITION OF CT AND/OR ICI DID NOT INCREASE THE RISK IN PTS.**
- **TG ALONE HAS FEW SIDE EFFECTS OTHER THAN LOCAL SITE REACTIONS. IN COMBINATION WITH OTHER AGENTS, THE SAFETY IS MANAGEABLE AND ALLOWS FURTHER DEVELOPMENT OF TG+ICI IN ONCOLOGY.**