Initial clinical results of BT-001, an oncolytic virus expressing an anti-CTLA4 mAb, administered as single agent and in combination with pembrolizumab in patients with advanced solid tumors

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ESMO 2024 #1024P

BACKGROUND

- Intra-tumoral (IT) administration of an oncolytic virus has been shown to induce local and systemic antitumor effects through direct tumor cell killing and adaptive cytotoxic T cell response.
- BT-001 is an oncolytic vaccinia virus with enhanced replication selectivity in tumor cells and genetically engineered to express GM-CSF and a novel full-length anti-CTLA-4 hIgG1 mAb.
- BT-001 showed strong antitumoral activity in various murine tumor models, including immunologically "cold" tumors, with enhanced activity when combined with an anti-PD-1 agent.
- BT-001.01 is a first-in-human dose-escalation trial, to evaluate safety, tolerability, and antitumor activity of IT injections of BT-001 alone and in combination with intravenous pembrolizumab in patients with advanced/metastatic solid tumors.

METHODS

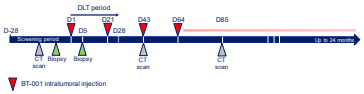
- A total of 24 patients received IT injections of BT-001 every 3 weeks as monotherapy (Part A) at doses of 10^6 pfu/mL (cohort 1, n=6), 10^7 pfu/mL (cohort 2, n=6) or 10^8 pfu/mL (cohort 3, n=6), or combined to 200 mg of IV pembrolizumab (Part B) at the dose of 10^7 pfu/mL (n=6).
- Treatment was administered until disappearance of all injectable lesions (for BT-001), confirmed disease progression per iRECIST, or unacceptable toxicity (for BT-001 and pembrolizumab), for a maximum of 24 months.
- Translational analyses were performed in part A, and consisted of

- Virus detection by qPCR in (1) tumor biopsies at baseline and on Day 5 or 50, (2) blood at baseline and from Day 1 to 64, (3) skin swabs (4) saliva (5) urine and (6) feces on Days 2, 8, 15, 43 and 64.
- Measures of (1) GM-CSF by Luminex assay in serum at baseline, on Days 5, 8, 15, 29 and 36, (2) anti-CTLA-4 mAb by ELISA concomitantly to virus detection in blood and, in tumor biopsies at baseline and on Days 5 or 50, and (3) anti-vaccinia virus antibodies in serum (parts A and B).

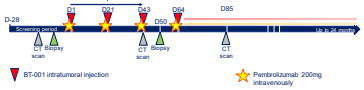
- Tumor response was assessed by the investigator using iRECIST and RECIST v1.1 on Days 43 (week 6), 85 (week 12), then every 8 weeks the first year and every 12 weeks thereafter.

TRIAL SCHEDULE

BT-001 monotherapy (Part A)



BT-001 combination with pembrolizumab (Part B)



Longest diameter (mm)	Volume mL
25 to 50	Up to 2.0
15 to 24	Up to 1.0
5 to 14	Up to 0.5
<5	No injection

Volume of BT-001 per injection according tumor size

KEY ELIGIBILITY CRITERIA

- Age ≥18 years
- Advanced/metastatic solid tumors having failed and/or intolerant to standard therapeutic options
- At least one injectable and measurable cutaneous, subcutaneous or nodal lesion
- Longest diameter of the injected lesions ≤ 50 mm (except in part A, cohort 1)
- ECOG performance status 0 or 1

PATIENT AND DISEASE CHARACTERISTICS

24 patients from 5 sites in France and Belgium were enrolled in this trial, mostly with melanoma (n=13) and soft tissue sarcoma (n=5).

Characteristics	BT-001 monotherapy (n=18)	BT-001 in combination with pembrolizumab (n=6)	Overall (n=24)
Age, years, med. (range)	59 (31-77)	51 (28-62)	57 (28-77)
Male (No)/**Female** (No)	9/9	3/3	12/12
Type of cancer, No (%)			
Melanoma	8 (44.4)	5 (83.3)	13 (54.2)
Soft tissue sarcoma	4 (22.2)	1 (16.7)	5 (20.8)
Other: 2 breast cancers, 1 Merkel cell carcinoma, 1 anal SSC, 1 ovarian cancer, 1 larynx SSC	6 (33.3)	0 (0.0)	6 (25.0)
Overall stage at baseline, No (%)			
IIIB-C/IV	2 (11.1)/16 (88.9)	0 (0.0)/6 (100.0)	2 (8.3)/22 (91.7)
Number of prior lines of antineoplastic therapy	3 (1-7)	2.5 (2-6)	3 (1-7)
Number of patients with prior exposure to ICIs, No (%)	11 (61.1)	5 (83.3)	16 (66.7)
Time from diagnosis to enrollment, months, med. (range)	60.7 (10.8-145.6)	34.2 (13.8-75.4)	56.7 (10.8-145.6)
Smallpox vaccinated, No (%)	10 (55.6)	3 (50.0)	13 (54.2)

ACKNOWLEDGMENT

The authors wish to thank all patients, families, caregivers and technical staff involved in the project.

SAFETY DATA

Exposure

- Patients received a median number of 4 BT-001 injections (range, 2-19).
- Median size of injected lesions was 27 mm (range, 15-65)
- Median volume of BT-001 per administration was 2.0 mL (range, 1.0-4.0).
- In the combination part, median number of pembrolizumab infusions was 7.5 (range, 2-11).

Safety

- No dose-limiting toxicity was observed.
- No AEs led to BT-001 and/or pembrolizumab discontinuation
- Most common BT-001-related AEs are reported in the table below.

BT-001-related AEs occurring in more than 2 patients	BT-001 monotherapy (10^6 to 10^8 pfu/mL) N=18		BT-001 in combination with pembrolizumab (10^7 pfu/mL) N=6		Overall N=24	
Event	N	%	N	%	N	%
Pyrexia	7	38.9	3	50.0	10	41.7
Chills	3	16.7	1	16.7	4	16.7
Skin ulcer	4	22.2	0	00.0	4	16.7
Injection site inflammation	1	5.6	2	33.3	3	12.5
Injection site ulcer	3	16.7	0	00.0	3	12.5
Eosinophilia	1	5.6	2	33.3	3	12.5

- A total of 18 episodes of BT-001 related pyrexia (15 of grade 1, 3 of grade 2) were observed in 10 patients.
- Injection or biopsy site AEs were reported in 15 patients, including all 6 patients of cohort 1 in the monotherapy part, and mainly consisted of grade 1-2 skin ulcer, and injection site inflammation, pain and ulcer. The trial Safety Review Committee considered that some of them were rather due to disease progression.
- A total of 2 grade ≥3 BT-001-related AEs were observed: one grade 3 skin ulcer located at the injection/biopsy site, and one grade 3 transient lymphocyte count decrease.
- Five of the 6 patients treated with BT-001 in combination with pembrolizumab presented a total 13 AEs related to pembrolizumab, none of them being grade ≥ 3. Most common AEs were pyrexia (n=3), pruritus (n=2), and eosinophilia (n=2).

EFFICACY DATA

A. Best Overall Response according to iRECIST

Part	N	iPR n (%)	iSD n (%)	iUPD n (%)	iCPD n (%)
BT-001 monotherapy	18	0 (0.0)	4 (22.2)	8 (44.4)	6 (33.3)
BT-001 in combination with pembrolizumab (10^7 pfu/mL)	6	**2 (33.3)**	0 (0.0)	3 (50.0)	1 (16.7)

2 of the 6 patients treated with BT-001 in combination with pembrolizumab exhibited PR

iUPD: Unconfirmed Progressive Disease
iCPD: Confirmed Progressive Disease
iPR: Partial Response
iSD: Stable Disease

B. BT-001 in combination with pembrolizumab: swimming plot (iRECIST)

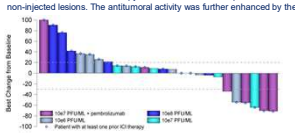
PR was observed in:
- one patient (01.02.005) with PD(L)-1 resistant melanoma
- one patient (01.04.008) with leiomyosarcoma treated with 5 prior lines of therapies.

Both showed a sustained PR.

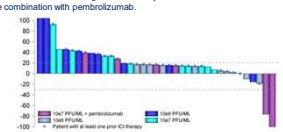
C. Best change of size of injected lesions (%)

D. Best change of size of non-injected lesions (%)

Overall, BT-001 as monotherapy or in combination with pembrolizumab induced tumor shrinkage in 9 of 26 injected lesions and in 5 of 37 non-injected lesions. The antitumoral activity was further enhanced by the combination with pembrolizumab.



BT-001 injections were administered in skin lesions (n=5), subcutaneous nodules (n=7), lymph nodes (n=7) and other soft tissue lesions (n=7)
A significant tumor shrinkage (≥30% decrease in longest diameter) was observed in 2 of 20 injected lesions after BT-001 monotherapy and 4 of 6 injected lesions after the combination of BT-001 with pembrolizumab.



BT-001 in combination with pembrolizumab induced a significant tumor shrinkage in 2 of 6 non-injected lesions.

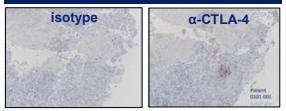
TRANSLATIONAL ANALYSES

A. Tumor biopsy analyses (part A)

Patient	Dose (pfu/mL)	Tumor	Injected lesion/size mm	Biopsy collection	qPCR (copie/µg DNA)	RT-qPCR (ΔCt-GTLA 4)
01.03.001	10^6	Anal squamous cell carcinoma	Perineal skin/20	D5	Not detected	10.2515
01.03.002	10^6	Breast cancer	Breast nodule/30	D5	8.06E+02	Not evaluable
01.01.001	10^6	Melanoma	Axillary lymph node/39	D5	1.31E+06	1.833
01.03.003	10^6	Larynx carcinoma	Subcutaneous sternal node/25	D5	1.68E+07	3.212
01.01.002	10^6	Melanoma	Inguinal lymph node/59	D5	1.15E+03	Not done
01.02.001	10^6	Melanoma	Skin lesion/65	D5	7.64E+03	-0.1625
01.03.011	10^8	Leiomyosarcoma	Muscular lesion (trapezius)/25	D50	4.65E+02	Not detected

(A) (B) Virus backbone and/or α-CTLA-4 payload were found in all tumor biopsies.

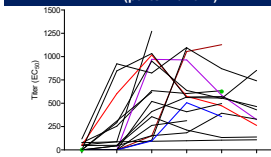
B. IHC Intratumoral detection of α-CTLA-4



C. Biological fluids analyses (part A)

	Analyses	Number of tested samples	Number of positive samples
Detection in blood	Virus detection	198	4
	GM-CSF	96	0
	α-CTLA-4 monoclonal antibody	350	0
Shedding	Skin swab	53	4
	Saliva	54	2
	Urine	53	0
	Feces	40	0

D. Anti-vaccinia virus neutralizing antibodies (parts A and B)



(C) BT-001 oncolytic virus replicated within the tumor with rare and sporadic shedding in biological fluids or excreta.
(D) Anti-vector neutralizing antibodies were induced in all patients including those who had PR (01.02.005, and 01.04.008) and those with significant decrease (≥30%) in size of injected lesions (01.01.001, 01.01.005, and 01.03.004).

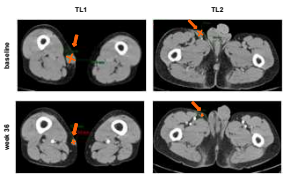
PATIENTS WITH PARTIAL RESPONSE

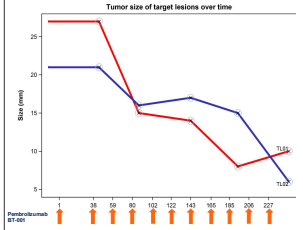
PD(L)-1 resistant melanoma

48-year-old male
Stage IV melanoma diagnosed in 2020
Three prior lines of antineoplastic therapy (nivolumab-ipilimumab x2 and durvalumab-ceralasertib).

BT-001 was injected at the dose of 10^7 pfu/mL in 2 right thigh subcutaneous lesions in combination with IV pembrolizumab. Longest diameter of target lesions (TL) progressively decreased over time. PR was observed from week 6 to 28.

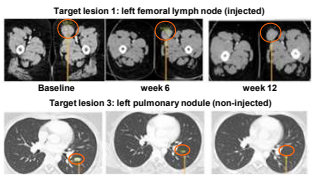
At week 36, a new metastatic pancreatic lesion was observed.

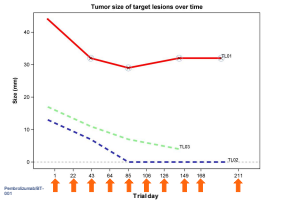




Multiresistant leiomyosarcoma

28-year-old female
Stage IV intraosseous dorsolumbar junction leiomyosarcoma diagnosed in 2021
Radiation therapy, then 5 lines of antineoplastic therapy (Cisplatin-ifosfamide-adriamycin/pazopanib/trabectedin/ dacarbazine/olaparib) and radiotherapy of a pulmonary cardiophrenic angle lesion one month before inclusion
BT-001 was injected at the dose of 10^7 pfu/mL in a left femoral adenopathy in combination IV pembrolizumab.
Longest diameter of TL progressively decreased over time. PR was observed from week 6 to 28+ with a clear reduction in the size of multiple and bilateral non-injected pulmonary lesions.

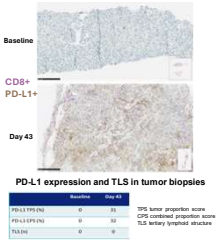




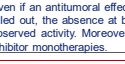
Tumor immune-profiling was performed by multiplex IHC at baseline and on Day 43 on tumor biopsies of the injected lesion (**Gustave Roussy Unlock program**, analysis performed by **Veracyte, Inc.**).

At baseline, tumor cells were PD-L1 negative and immune profile was cold with a low T cell infiltrate, a dominant M2 macrophage infiltrate, and lack of tertiary lymphoid structure (TLS).

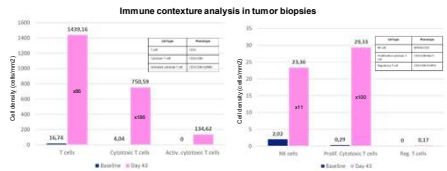
CD8+/PD-L1 IHC in tumor biopsies (Immunoscore® CD8 PD-L1)



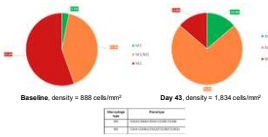
PD-L1 expression and TLS in tumor biopsies



Immune contexture analysis in tumor biopsies



Macrophage subsets representation in tumor biopsies



On Day 43, tumor cells switched to PD-L1 positive and immune profile significantly warmed up with a high T cell infiltrate and a switch to dominant M1 macrophage infiltrate.

Even if an antitumoral effect of pembrolizumab alone, or to a lesser extent of an abscopal effect of the radiation therapy, cannot be ruled out, the absence at baseline of T cell infiltrate or TLS, and the tumor PD-L1 negative status suggest a key role of BT-001 in observed activity. Moreover, leiomyosarcomas, particularly in the absence of TLS are not likely to respond to immune checkpoint inhibitor monotherapies.

CONCLUSIONS

IT BT-001 alone or in combination with IV pembrolizumab was well tolerated and showed antitumoral activity, including in a PD-(L)1 resistant tumor. BT-001 replicated in the tumor and expressed its GM-CSF and anti-CTLA-4 transgenes. The combination of BT-001 at the dose of 10^7 PFU/mL with pembrolizumab showed first signs of efficacy with documented radiological responses in 2/6 patients. The trial is still ongoing to further evaluate BT-001 at the dose of 10^8 pfu/mL combined with pembrolizumab (cohort 2). In a patient with a heavily pre-treated sarcoma, BT-001 treatment in combination with pembrolizumab turned cold to hot the tumor microenvironment with a high T cell infiltrate, a higher M1/M2 ratio, and a shift to PD-L1 positivity.

Trial sponsored by TRANSGENE, 400 Boulevard Gonthier d'Andernach - Parc d'Innovation - CS80166 67405 Illkirch Graffenstaden Cedex – France. This trial is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

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