Updated clinical results of BT-001, an oncolytic virus expressing an anti-CTLA4 mAb, administered in combination with pembrolizumab in patients with advanced solid tumors

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BACKGROUND

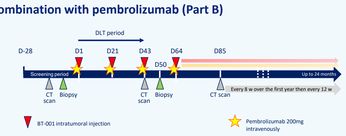
- **BT-001 is an oncolytic vaccinia virus (VV) genetically engineered to selectively replicate in tumor cells and express GM-CSF and a novel full-length anti-CTLA-4 hIgG1 mAb**.
- We previously reported (ESMO 2024, Abstract #3190, Poster #1024P) interim results of BT-001.01, a first-in-human dose-escalation trial evaluating intratumoral (IT) injections of BT-001 alone and in combination with intravenous (IV) MSD's (Merck & Co., Inc., Rahway, NJ, USA) anti-PD-1 therapy, KEYTRUDA® (pembrolizumab)** in patients (pts) with advanced/metastatic solid tumors. A total of 18 pts received BT-001 as monotherapy at doses ranging from 10^6 to 10^8 pfu/mL (Part A) and 6 pts received BT-001 at the dose of 10^7 pfu/mL in combination with IV pembrolizumab (Part B). In Part B, 2 pts had radiological partial responses (PR), one pt with PD-(L)1 resistant melanoma and one pt with heavily pre-treated leiomyosarcoma. Translational analyses showed that the virus replicated and expressed its anti-CTLA-4 payload in tumor biopsies with rare shedding in biological fluid or excreta. Anti-VV neutralizing antibodies were induced in all patients.
- Herein, we report the updated data of the Part B with the 6 previously reported pts, and 7 additional pts treated with BT-001 at the dose of 10^8 pfu/mL and focus on the overall results of this combination part.

METHODS

- In Part B, a total of 13 patients received IT injections of BT-001 every 3 weeks at doses of 10^7 pfu/mL (cohort 1, n=6) or 10^8 pfu/mL (cohort 2, n=7) combined to 200 mg of IV pembrolizumab.
- Treatment was to be 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.
- 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 over the first year and every 12 weeks thereafter.
- Translational analyses consisted of:
  - Measurement of serum levels of a panel of 19 cytokines related to viral infections and inflammation by MesoScaleDiscovery (MSD) multiplexed panels on Days 1, 5, 8, 22 and 36.
  - Analysis of immune cell infiltrates on tumor biopsies at baseline and on Day 50 using the Ultivue FlexVue 12-plex multiplex immunostaining kit (CD3, CD4, CD8, FoxP3, granzyme B, CD68, panCK/Sox10, PD-1, CD20, CD56, Ki67, MHCII and DAPI) on Oncore ProX (Biocare Medical) fully automated immunostainer.

TRIAL SCHEDULE

BT-001 combination with pembrolizumab (Part B)



IT injection
(Direct or ultrasound-guided injection)

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

Maximum volume of 4 mL if several lesions are injected on the same cycle

KEY ELIGIBILITY CRITERIA

- Age ≥ 18 years.
- Advanced/metastatic melanoma, sarcoma, Merkel cell carcinoma (MCC), triple negative breast cancer (TNBC), or non-small-cell lung carcinoma (NSCLC), with cutaneous or palpable subcutaneous lesions, or easily injectable lymph nodes.
- Failure and/or intolerance to standard therapeutic options.
- At least one injectable and measurable cutaneous, subcutaneous or nodal lesion.
- Longest diameter of the injected lesions ≤ 50 mm.
- ECOG performance status 0 or 1.

PATIENT AND DISEASE CHARACTERISTICS

A total of 13 pts from 3 sites in France were enrolled, mostly with melanoma (n=9) and soft tissue sarcoma (n=3).

They received a median number of 3 prior lines of antineoplastic therapy and, for patients with melanoma, 2 prior lines of immune checkpoint inhibitors (ICI).

Characteristics of all Part B patients	Cohort 10^7 PFU/mL (N=6)	Cohort 10^8 PFU/mL (N=7)	Overall Part B (N=13)
Male/Female	3/3	2/5	5/8
Age, years, median (min-max)	51 (28 - 62)	63 (49 - 76)	54 (28 - 76)
ECOG PS 0/1	5/1	6/1	11/2
BMI, Kg/m², median	31.6	27.1	31.1
Type of cancer			
- Melanoma	5	4	9
- Soft tissue sarcoma	1	2	3
- TNBC	0	1	1
Smallpox vaccinated	3	6	9
Disease stage IV at baseline	6	7	13
Time in months from diagnosis to enrollment, median (min-max)	34 (14-75)	93 (30-252)	71 (14-252)
Number of prior lines of antineoplastic therapy, median (min-max)	3.5 (2.0 - 5.0)	3.0 (3.0 - 5.0)	3.0 (2.0 - 5.0)
Prior exposure to ICIs	5	5	10*

* Corresponds to the 9 pts with melanoma and the pt with TNBC

Characteristics of melanoma patients (n=9)	Cohort 10^7 PFU/mL (N=5)	Cohort 10^8 PFU/mL (N=4)	Overall Part B (N=9)
Number of prior lines of ICI therapy, median (min-max)	2 (1-4)	3 (2-5)	2 (1-5)
Time in months from last ICI administration to D1, median (min-max)	2.1 (1.1-10.1)	2.3 (1.1-5.5)	2.1 (1.1-10.1)

ACKNOWLEDGMENT

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SAFETY DATA

Exposure

- Patients received a median number of 6 cycles of pembrolizumab + BT-001.
- Median number of injected lesions per pt was 1, ranging from 1 to 3.
- Median volume of BT-001 per injection was 1.8 mL, ranging from 0.7 to 2.0 mL.
- Pembrolizumab was fully administered at each infusion.

Adverse reactions

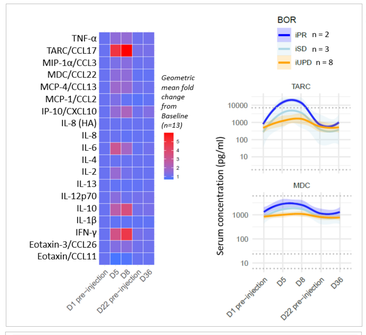
- Dose-limiting toxicity was observed in a single patient and consisted of 2 episodes of grade 3 fever.
- Injection or biopsy site AEs were reported in 10 pts, mainly grade 1-2 pain, induration and inflammation. One case of grade 1 pustule at the injection site with permeation nodule was observed.
- Immune-related AEs were reported in 6 pts, mainly pyrexia, pruritus and chills, with no case affecting an organ system.
- A single case of treatment-related SAE was reported and consisted of a grade 2 fever.

	Cohort 10^7 pfu/mL (N=6)		Cohort 10^8 pfu/mL (N=7)		Overall Part B (N=13)	
	N (%)	Ev	N (%)	Ev	N (%)	Ev
Treatment-related AE*	6 (100%)	26	7 (100%)	50	13 (100%)	76
Dose Limiting Toxicity AE	0 (0.0%)	0	1 (14.3%)	2	1 (7.7%)	2
Injection/biopsy site AE	4 (66.7%)	9	6 (85.7%)	11	10 (76.9%)	20
Immune-related AE	3 (50.0%)	5	3 (42.9%)	14	6 (46.2%)	19
SAE	2 (33.3%)	4	2 (28.6%)	2	4 (30.8%)	6
Treatment-related SAE*	0 (0.0%)	0	1 (14.3%)	1	1 (7.7%)	1
Grade 3/4 AE	4 (66.7%)	7	3 (42.9%)	5	7 (53.8%)	12
Treatment-related grade 3/4 AE*	0 (0.0%)	0	2 (28.6%)	3	2 (15.4%)	3

*related to BT-001 and/or pembrolizumab; Ev = event

- Most common treatment-related AEs were pyrexia in 9 pts (69.2%), pruritus in 4 pts (30.8%), chills in 4 pts (30.8%), erythema in 3 pts (23.1%), nausea in 3 pts (23.1%), and eosinophilia in 3 pts (23.1%).
- Grade 3 treatment-related AEs were reported in 2 pts, 1 pt with 2 episodes of fever and 1 pt with lymphopenia.
- No grade >3 AEs were reported.

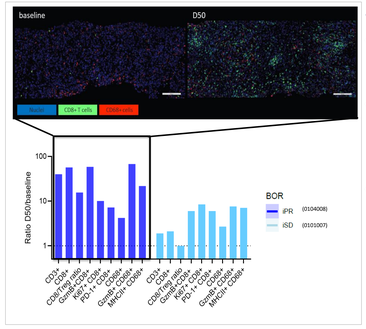
TRANSLATIONAL ANALYSES



Serum cytokines

- Transient upregulation of cytokines associated with viral infections, such as IFN-γ, IL-10, IL-6, IP-10, MDC, TARC, on D5 and D8 after the first dose.
- No association between the dose level (10^7 or 10^8 pfu/mL) and the profile or magnitude or the cytokine response.
- Trend for upregulation of TARC/CCL17 and MDC/CCL22 in clinical responders. Both are CCR4 ligands and production in the tumor was shown to attract activated T cells in animal models[1].

[1]Kanagawa et al, CC-chemokine ligand 17 gene therapy induces tumor regression through augmentation of tumor-infiltrating immune cells in a murine model of preexisting CT26 colon carcinoma, International Journal of Cancer, 121-9, 2007



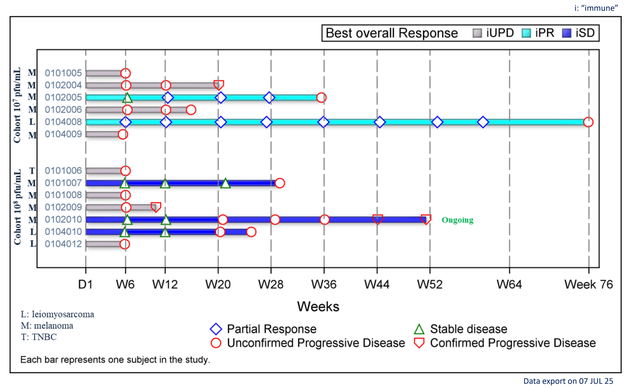
Tumor immune cell infiltration

- Infiltration of immune cells was assessed at baseline and D50 in paired biopsies of injected lesions for one iPR and one iSD patients.
- Infiltration of activated CD8 T cells (GzmB+, Ki67+ and PD-1+) and activated macrophages (MHCII+) in the tumor was increased after treatment in both patients.
- Higher increase in immune cell infiltration was observed in the patient with iPR (leiomyosarcoma) compared to the one with iSD (acral melanoma), consistent with the model that BT-001 in combination with pembrolizumab turns "cold" tumors into "hot", which supports immune-mediated tumor shrinkage.

EFFICACY DATA

Overall response

- Best overall response was partial response (iPR) in 2/13 pts, stable disease (iSD) in 3/13 pts and unconfirmed progressive disease (iUPD) in 8/13 pts.
- PR was observed in one patient (01.02.005) with anti-PD-1/anti-CTLA-4 resistant melanoma and one patient (01.04.008) with leiomyosarcoma treated with 5 prior lines of therapies and absence of TLS (tertiary lymphoid structure), and lasted 6 and 16 months, respectively.

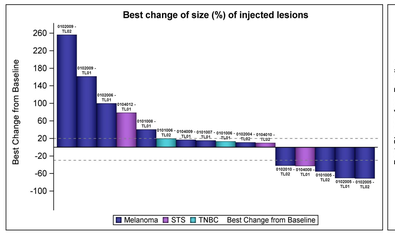


Data export on 07 JUL 25

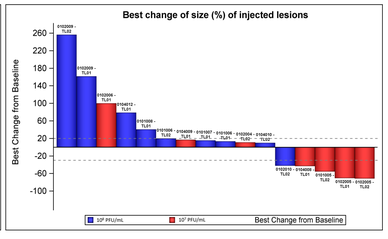
Best change of size of injected lesions

- Significant tumor shrinkage (≥30% decrease in longest diameter) was observed in 5 of a total of 16 injected lesions, in 3 pts with melanoma and 1 pt with sarcoma, with no apparent dose-response relationship.

By disease



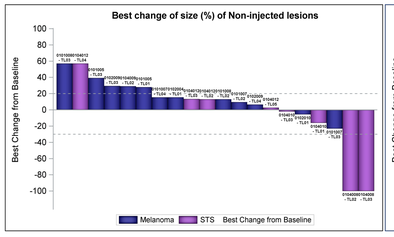
By dose



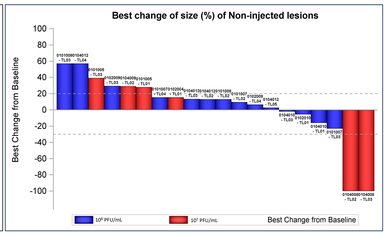
Best change of size of non-injected lesions

- A total of 4 pts had tumor shrinkage of non-injected lesions, 2 pts with melanoma, and 2 pts with sarcoma, including the complete disappearance of 2 lung nodules in one patient with sarcoma.

By disease



By dose



CONCLUSIONS

IT BT-001 in combination with IV pembrolizumab was well tolerated and showed local and abscopal antitumoral activity.

Durable PRs were observed in a pt with melanoma resistant to anti-PD-1/anti-CTLA-4 combination and a heavily pre-treated, PD-L1 negative leiomyosarcoma pt with a cold tumor microenvironment that turned hot after therapy***.

Translational analyses revealed increased concentrations of T cell chemoattractants in the blood and infiltration of activated CD8 T cells and macrophages in the tumor.

These data encourage further development of BT-001 in a variety of tumors to improve response to cancer immunotherapies.

***For detailed case reports, refer to the ESMO 2024 Abstract #3190, Poster #1024P

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