Repeat dosing of oncolytic adenovirus ONCOS-102 is associated with enhanced and persistent immune responses and improved systemic activity in anti-PD-1 resistant melanoma

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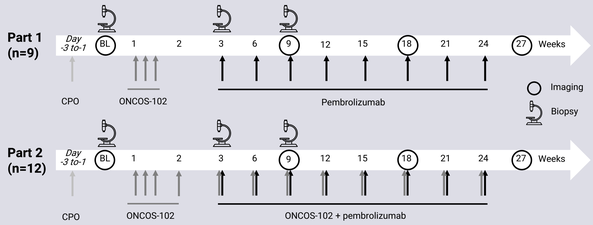
Background and aims

Defining the optimal dosing-schedule is critical for the development of novel immunotherapeutic combinations. We recently completed a phase 1/2 testing of ONCOS-102, a GM-CSF-encoding oncolytic adenovirus (Ad5/3-D24-GMCSF) in two different dosing schedules in combination with pembrolizumab (pem) in patients (pts) with unresectable, stage III-IV, anti-PD-1 resistant melanoma (NCT03003676). Here, we report safety, tumor viral exposure, T-cell infiltrate, comparative longitudinal gene expression analysis, and detailed analysis of local and systemic effects on tumor lesions according to dosing schedule.

Open-label, multicentre phase I/II study

Part 1: patients received 3 intra-tumoral priming doses of ONCOS-102 only, followed by up to 8 sequential doses of pembrolizumab every 3 weeks (Q3W)
Part 2: patients received 4 intra-tumoral priming doses of ONCOS-102, followed by up to 8 intra-tumoral booster doses concomitantly with Q3W pembrolizumab



Baseline characteristics

Part 2 patients showed higher tumor burden and more advance disease at baseline. Otherwise, the two cohorts have similar demographics.

	Part 1 (N=9)	Part 2 (N=12)	Total (N=21)
Median age, years (range)	73 (40–87)	72 (43–83)	73 (40–87)
Melanoma subtype, n (%)			
Cutaneous	8 (89)	6 (50)	14 (67)
Acral	1 (11)	1 (8)	2 (10)
Mucosal	0	2 (17)	2 (10)
Unknown Primary	0	3 (25)	3 (14)
AJCC stage, n (%)			
III (any stage)	6 (67)	5 (42)	11 (52)
IV			
iVM1a	2 (22)	2 (17)	4 (19)
iVM1b	0	2 (17)	2 (10)
iVM1c	1 (11)	3 (25)	4 (19)
Tumor burden at baseline			
Median number of lesions (range)	3 (1–10)	8.5 (3–17)	7 (1–17)
Prior cancer therapy, n (%)			
Surgery	9 (100)	11 (92)	20 (95)
Radiotherapy	2 (22)	4 (33)	6 (29)
Chemotherapy	1 (11)	6 (50)	7 (33)
Anti-PD-1 agent	9 (100)	12 (100)	21 (100)
Anti-CTLA-4 agent	4 (45)	8 (67)	12 (57)
BRAF and/or MEK inhibitor	2 (22)	1 (8)	3 (14)
Intralesional therapy	4 (45)	2 (17)	6 (29)

Safety

Overall, a similar safety profile of TEAEs for the two dosing schedules was observed, except injection site reaction / pain mainly observed in Part 2 patients

Preferred term n (%)	AEs related to ONCOS-102, only			AEs related to ONCOS-102 and pembrolizumab		
	Part 1 (N=9)	Part 2 (N=12)	Total (N=21)	Part 1 (N=9)	Part 2 (N=12)	Total (N=21)
All treatment-related AEs	8 (89)	9 (75)	17 (81)	3 (34)	6 (50)	9 (43)
Pyrexia	3 (33)	6 (50)	9 (43)	1 (11)	2 (17)	3 (14)
Chills	5 (56)	4 (33)	9 (43)	0	0	0
Nausea	3 (33)	3 (25)	6 (29)	0	1 (8)	1 (5)
Injection site pain	1 (11)	3 (25)	4 (19)	0	0	0
Vomiting	2 (22)	2 (17)	4 (19)	0	0	0
Injection site reaction	0	3 (25)	3 (14)	0	0	0
Myalgia	3 (33)	0	3 (14)	0	0	0
Fatigue	2 (22)	1 (8)	3 (14)	0	0	0
Diarrhea	2 (22)	0	2 (10)	0	0	0
Pruritus	1 (11)	1 (8)	2 (10)	0	0	0
Rash maculo-papular	1 (11)	1 (8)	2 (10)	0	0	0
Hypotension	0	2 (17)	2 (10)	0	0	0
ALT increased	1 (11)	0	1 (5)	0	1 (8)	1 (5)
AST increased	0	0	0	1 (11)	1 (8)	2 (10)

Conclusions

Intra-tumoral repeat dosing of ONCOS-102 concomitantly with Q3W pembrolizumab demonstrated:

- Good tolerability and no safety concerns
- Prolonged viral exposure in the tumor
- Stronger and more persistent immune activation
- Enhanced systemic activity, including two examples of complete regression of non-injected lesions

The results support further development of the ONCOS-102 repeat-dosing regimen in anti-PD-1 resistant melanoma

A multi-cohort phase 2 study is planned to validate these encouraging early findings in a larger patient cohort

Efficacy

In this study, 35% (7 of 20) of evaluable patients achieved RECIST v1.1 objective response. ORR was similar in the two cohorts: 38% (3 of 8 patients) in Part 1 and 33% (4 of 12 patients) in Part 2 (Fig. 1A), despite more stage IV disease and higher disease burden in Part 2. Fifty-two individual target lesions were assessed for response; 25% of injected target lesions completely regressed (Fig. 1B). In non-injected target lesions, ≥ 30% shrinkage was observed in 1 of 8 (12.5%) in Part 1 vs 7 of 28 (25%) in Part 2 (Fig. 1B).

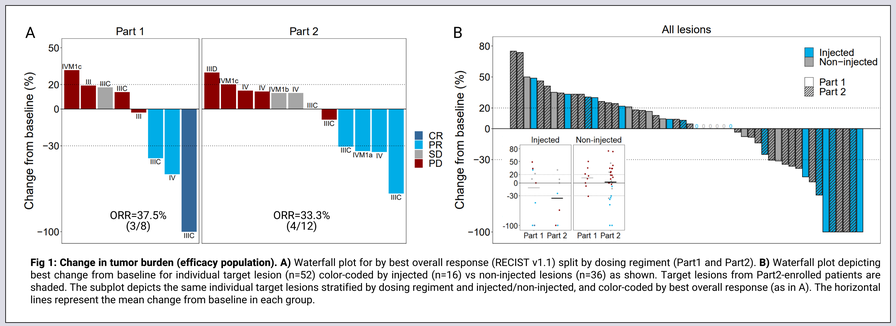


Fig 1: Change in tumor burden (efficacy population). A) Waterfall plot for by best overall response (RECIST v1.1) split by dosing regiment (Part1 and Part2). **B)** Waterfall plot depicting best change from baseline for individual target lesion (n=52) color-coded by injected (n=16) vs non-injected lesions (n=36) as shown. Target lesions from Part2-enrolled patients are shaded. The subplot depicts the same individual target lesions stratified by dosing regiment and injected/non-injected, and color-coded by best overall response (as in A). The horizontal lines represent the mean change from baseline in each group.

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Tumor immune infiltration

Tumor infiltration of CD8+, CD4+ and CD8+ GrzB+ T-cells (Fig. 2A-C) in injected lesions differed significantly between patients with disease control vs. PD. At baseline, higher T-cell infiltration was observed in patients with subsequent disease control (CR+PR+SD, n=11) compared to PD (n=10). T-cell tumor infiltration increased strongly at Week 3 (after ONCOS-102 priming and prior to pembrolizumab), but only persisted at Week 9 in patients with DC. This outcome was consistent with higher persistence of viral particles (VPs, Fig. 3A) and transgene expression (AdV_GMCSF, Fig. 3B) in tumors from patients with DC. Notably, ONCOS-102 VPs remained robustly detectable in tumors over at least 6 injections and up to 3 weeks after the last injection in patients on the Part 2 regimen (Fig. 3C). Finally, transcriptome analysis of differential gene expression over time revealed numerous significant changes in immunological pathways between the Part 1 and Part 2 dosing regimens (Fig. 4A-B).

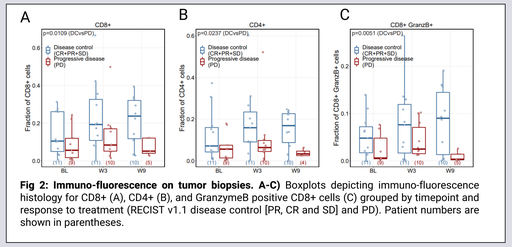

Fig 2: Immuno-fluorescence on tumor biopsies. A-C) Boxplots depicting immuno-fluorescence histology for CD8+ (A), CD4+ (B), and GranzymeB positive CD8+ cells (C) grouped by timepoint and response to treatment (RECIST v1.1 disease control [PR, CR and SD] and PD). Patient numbers are shown in parentheses.

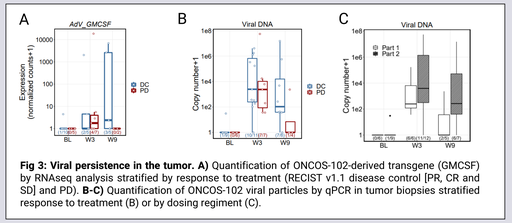

Fig 3: Viral persistence in the tumor. A) Quantification of ONCOS-102-derived transgene (GMCSF) by RNAseq analysis stratified by response to treatment (RECIST v1.1 disease control [PR, CR and SD] and PD). **B-C)** Quantification of ONCOS-102 viral particles by qPCR in tumor biopsies stratified response to treatment (B) or by dosing regiment (C).

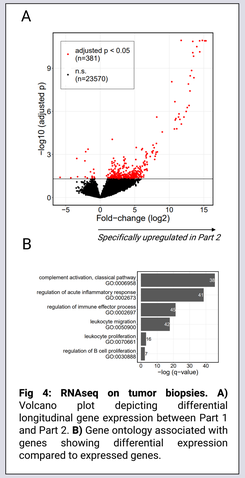

Fig 4: RNAseq on tumor biopsies. A) Volcano plot depicting differential longitudinal gene expression between Part 1 and Part 2. **B)** Gene ontology associated with genes showing differential expression compared to expressed genes.

Future directions

In an upcoming phase 2 study (NCT05561491), the ONCOS-102 repeat dosing regimen will be evaluated in combination with both anti-PD-1 and anti-CTLA-4 checkpoint blockade in PD-1 resistant melanoma patients. The aims include further evaluation of safety and tolerability, determining the recommended phase 2 dose (RP2D), evaluating monotherapy activity and validating clinical efficacy of ONCOS-102 in a larger patient cohort.

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