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 1/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.

Conclusions
Intra-tumor 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).

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

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.

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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Tumor immune infiltration
Tumor infiltration of CD8+ and CD16+ 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 (DOR: 4/12 vs 0/10), 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 VPSs 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).

Efficacy
Overall, the ONCOS-102 repeat-dosing regimen is associated with enhanced tumor activity, including two examples of complete regression of non-injected lesions.

Fig 1: Change in tumor burden (efficacy population). A) Waterfall plot for best overall response (ORR) in 20 evaluable patients. 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 3: T-cell infiltration in injected lesions. A) Qualitative expression of ONCOS-102 encoded transgene [GMCSF, Adv_GMCSF] and viral particles [VPS, Adv+VPS] expression was detected as early as Week 3 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 4: RNAseq on tumor biopsies. A) Waterfall plot for best overall response (ORR) in 20 evaluable patients. 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).