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REPEAT DOSING OF ONCOLYTIC ADENOVIRUS ONCOS-102 IS ASSOCIATED WITH ENHANCED AND PERSISTENT IMMUNE RESPONSES AND IMPROVED SYSTEMIC ACTIVITY IN ANTI-PD-1 RESISTANT/REFRACTORY (R/R) MELANOMA

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Background Defining the optimal dosing-schedule is critical for the development of novel immunotherapeutic combinations. We recently completed 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/refractory melanoma (NCT03003676). Here, we report tumor viral exposure, comparative, longitudinal gene expression analysis of tumor samples, safety, and detailed analysis of local and systemic effects on tumor lesions according to dosing schedule.

Methods In study Part 1, pts (n=9) received sequential treatment comprising three priming injections of ONCOS-102 (3x1011 VP/injection, intra-tumoral) at every 3 days during the first week of treatment followed by i.v. pem administration (10 mg/kg) every 3 weeks from day 22 for 6 months. In study part 2, pts (n=12) received concomitant treatment with three priming injections of ONCOS-102 during the first week and at day 15 and then ONCOS-102+pem every 3 weeks from day 22. Injected and non-injected target lesion response was assessed, and tumor biopsies were collected at baseline, day 22 and 64. Total RNA sequencing with differential gene expression analysis was conducted on samples from 17 pts. AEs were assessed according to CTCAE.

Results 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, despite evidence of more advanced disease in Part 2. Fifty-two individual target lesions (TL) were assessed for response; 16 injected (I)-TL and 36 non-injected (NI)-TL. In I-TL, 25% completely regressed. In NI-TL, $\geq 30\%$ shrinkage was observed in 1 of 8 (12.5%) in Part 1 vs 7 of 28 (25%) in Part 2.

Greater persistence of ONCOS-102 DNA in the tumor through day 64 was observed in Part 2. This correlated with an increased expression of immune-related genes particularly at day 64.

The most frequently reported TEAEs were pyrexia (48%), chills (43%), hypertension (43%), nausea (33%), and alanine aminotransferase increase (33%) with similar incidence, and severity in both parts.

Conclusions Repeat dosing concomitantly with pembrolizumab demonstrated greater viral persistence in the tumor and a trend for upregulation of immune-related genes at Day 64, with no added toxicity concerns beyond pyrexia and local injection site events. Persisting immune activation and substantial tumor shrinkage in non-injected lesions supports the extended (Part 2) dosing regimen for further clinical development.

Trial Registration NCT03003676

Ethics Approval The study obtained ethics approval in the US by:

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Protocol # 16-1107
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All participants gave informed consent before taking part.

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