Personalized immunotherapeutic platform with evidence of clinical activity in glioblastoma (IGV-001) protects mice against other lethal solid tumor challenges

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Background

IGV-001 is a novel immunotherapy that combines irradiated patient-derived glioblastoma tumor cells and an antisense oligonucleotide against insulin-like growth factor type 1 receptor (IMV-001) in biodiffusion chambers (BDC). We recently reported [1] IGV-001-treated newly diagnosed glioblastoma patients had a median progression free survival of 17.1 months compared with 6.5 months in historical standard-of-care-treated patients (p=0.0025) at the highest exposure of the combination product. We have now found activity with the equivalent murine approach in multiple cancer models, highlighting the transformative potential of this immunotherapeutic platform beyond glioblastoma.

Methodology

We utilized several murine models including the ID8-luciferase (-Luc) intraperitoneal ovarian cancer, the Hepa1-6-Luc hepatocellular carcinoma orthotopic model and the PAN02 pancreatic cancer orthotopic model. BDC containing saline or 1x10^6 IMV-001-treated tumor cells (hereon IOV-001, IHV-001, and IPV-001 respectively) were implanted in flanks of C57BL/6 mice and explanted 48 h later, as per glioblastoma clinical protocol. Primary tumor challenge for all models was conducted 28 days after chamber implantation. Mice were monitored for survival and for tumor growth, as determined by bioluminescence intensity. At Day 102, IHV-001-treated surviving mice were rechallenged with intra-mammary Hepa1-6 cells compared to naïve comparably-aged control mice. Cytokine assays and immunophenotyping were conducted to determine immune-correlates associated with survival and lower tumor burden.

Fig. 1: IOV-001 immunotherapy significantly improves the survival of C57Bl/6 mice challenged intraperitoneally with ID8 cells. (a) Survival. (b) Tumor burden.

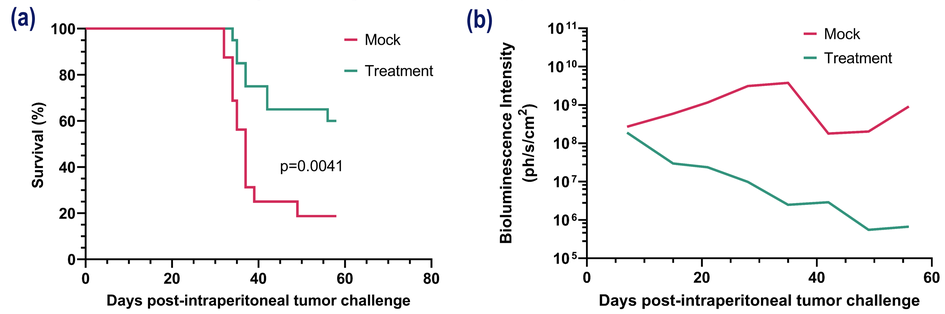


Fig. 2: IHV-001 immunotherapy significantly improves the survival and reduces tumor burden of C57Bl/6 mice challenged with Hepa1-6 cells. (a) Survival plot. (b) Individual tumor burden in orthotopically challenged mice. (c) Tumor size of intramammary re-challenged and control naïve mice.

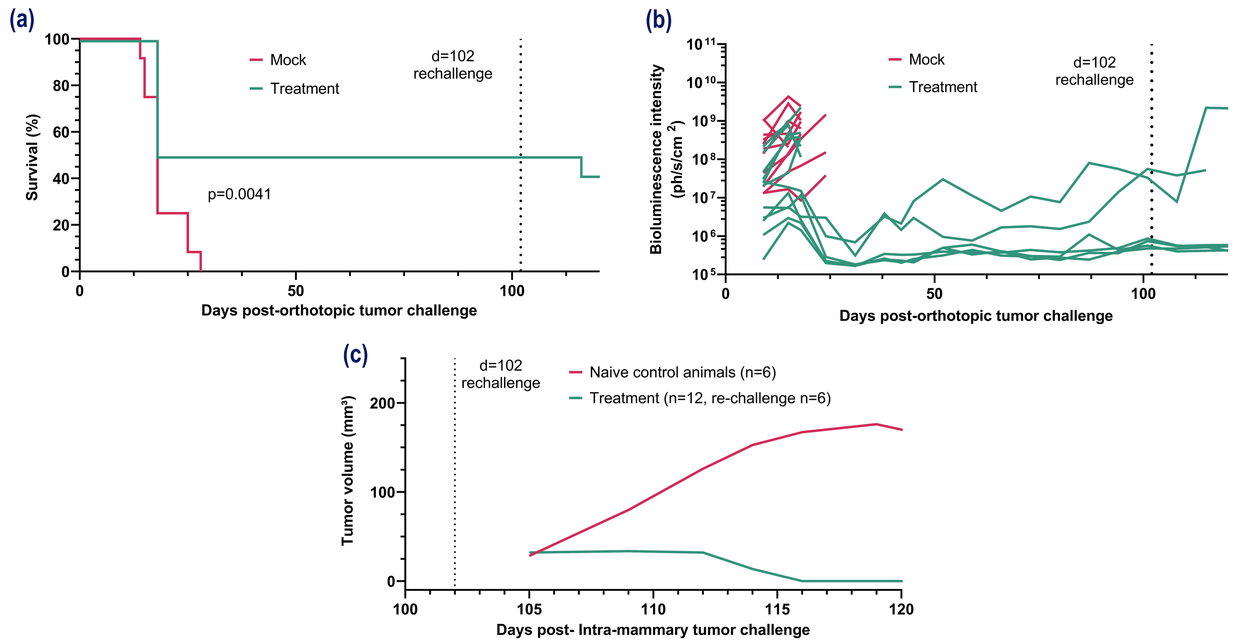


Fig. 3: IFNγ is upregulated in IOV-001 and IHV-001 treated mice. (a) Ovarian cancer model (in serum, d1) ***p<0.001. (b,c) HCC model (in CD4$^+$ and CD8$^+$ splenocytes, d0)

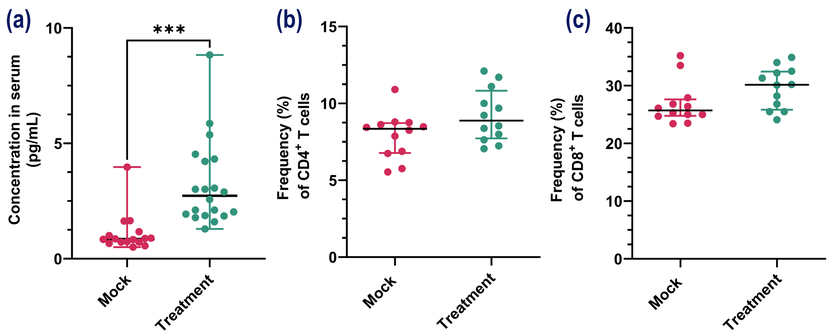


Fig. 4: Lower PD1 expression on d14 predicts long term survival of IHV-001 treated mice. ***p<0.001, **p=0.002

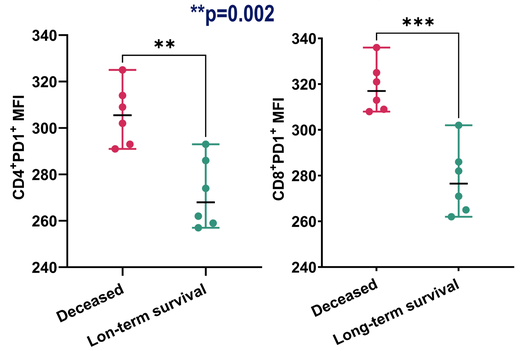
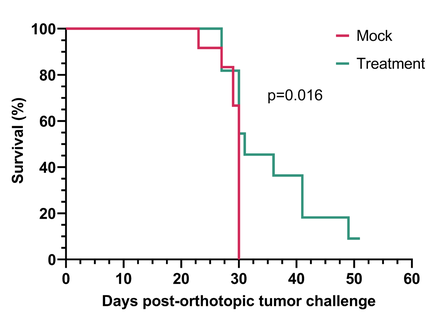


Fig. 5: IPV-001 immunotherapy improves the survival of C57Bl/6 mice challenged orthotopically with PAN02 cells



Results

- 60% of IOV-001-treated mice were alive on day 58 post–tumor challenge, compared to only 19% of mice in the saline group (Median survival time, MST=37d, p=0.004) (Fig. 1).
- In the Hepa1-6 model, 50% of IHV-001-treated mice were alive by day 100 post-tumor challenge (Fig. 2). In comparison, there were no survivors in the saline group beyond day 28 (MST=18d; p=0.004) (Fig. 2). Most of the long-term survivors had undetectable tumor; a fraction showed some level of tumor burden which rose and fell, in combination with the immune responses seen, demonstrating immune control (Fig. 2).
- Circulating IFNγ was significantly higher in IOV-001-treated mice compared to controls on day 1 post-tumor challenge (p<0.001) and trended higher in those receiving IHV-001 on day 14 after tumor challenge (Fig. 3). On day 14, PD1$^+$ expression in both CD4$^+$ and CD8$^+$ T cell subsets was significantly lower (p=0.002) in long-term surviving mice treated with IHV-001 (Fig. 4).
- Improved survival of IPV-001 treated mice was also observed in the Pan02 orthotopic pancreatic model (Fig. 5).

Conclusions

The data support the antitumor activity of the IxV-001 immunotherapeutic platform in multiple cancers, beyond glioblastoma [1]. Results provide evidence that efficacy is associated with a durable and systemic immunological response, resulting in generation of Th1 antitumor cytotoxic T cells. Lower PD1 expression was also associated with best outcomes in IHV-001 treated mice. Future studies are seeking to determine the factors triggering responses in treated mice versus controls and non-responders using phenotypic evaluation of T cell activation / exhaustion markers and Th1/Th2 cytokine production.

[1] Andrews, David W et al. “Phase Ib Clinical Trial of IGV-001 for Patients with Newly Diagnosed Glioblastoma.” *Clinical Cancer Research.* vol. 27,7 (2021): 1912-1922. doi:10.1158/1078-0432.CCR-20-3805l

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