Single intravenous preoperative administration of the oncolytic vaccinia virus Pexa-Vec to prime anti-tumor immunity

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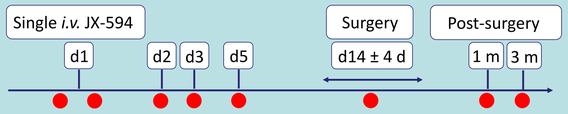
Background

- Oncolytic viruses (OVs) constitute a promising modality of cancer therapy.
- Pexa-Vec (a thymidine kinase-deactivated vaccinia virus expressing GM-CSF and β-galactosidase) has been shown previously to successfully target tumor tissue after intravenous (*i.v.*) administration (1).
- However, to date, the modulating effects of OVs on patients' immune systems *in situ* has not been elucidated.
- In this study, we investigate the immunostimulatory effect of Pexa-Vec in patients with either colorectal cancer liver metastases (CRLM) or metastatic melanoma.

Trial summary

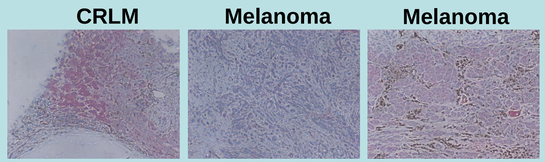
- A single dose of 1x10^9 plaque forming units (pfu) of Pexa-Vec was administered by *i.v.* infusion to 9 patients (3 with metastatic melanoma, 6 with CRLM) prior to planned surgical resection.



Results: Tumor histology

IHC for β-galactosidase (red) is used to examine the presence of Pexa-Vec in tumor

- Pexa-Vec transgene expressionis detected in virus-treated patient tumors (Patient 2 & 4) 15 days after administration.



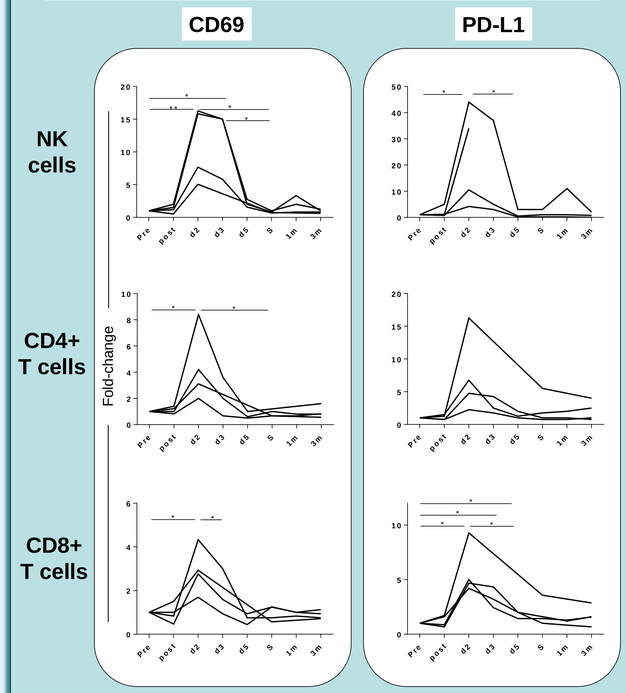
- Pathological examination of tumor tissue from CRLM patients showed signs of inflammation & fibrosis. Of the four evaluable CRLM patient tumors following Pexa-Vec treatment, one was partially necrotic and one was completely necrotic (no viable tumor cells).

1. Breitbach *et al.* Nature. **2011** 477(7362):99-102.

Results: Immune cell activation

Peripheral blood was collected at baseline & throughout treatment to assess the immune response to Pexa-Vec.

Immunophenotyping of peripheral blood mononuclear cells (PBMCs) was performed using an extensive panel of immune cell markers (data are presented for four representative patients).

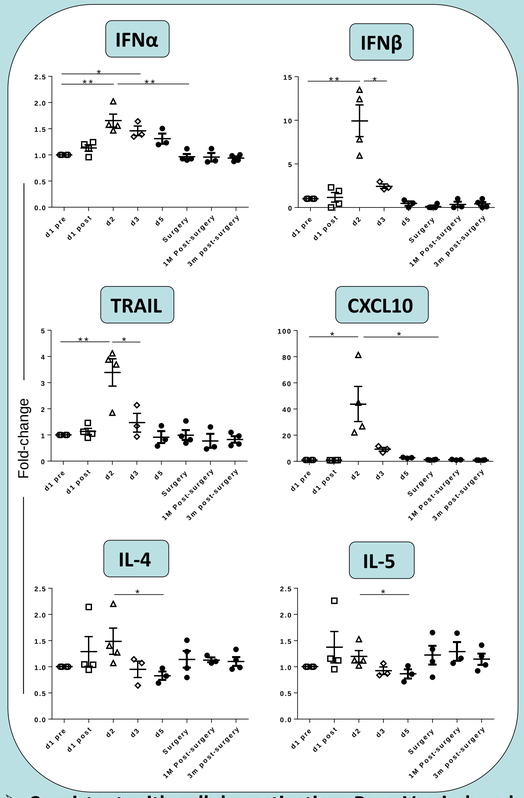


PBMCs exhibited robust activation *in vivo* by 24 hrs post-infusion of Pexa-Vec:

- Expression of CD69 (an early activation marker) was enhanced on effector cell populations, notably NK & T cells
- Expression of PD-L1 (an immune checkpoint ligand) was also increased on many cells

Results: Cytokine profile

The cytokine / chemokine profile within patient plasma, in response to Pexa-Vec infusion, was investigated using 21- and 27-plex Luminex assays (data are presented for four representative patients)



- Consistent with cellular activation, Pexa-Vec induced a cytokine/chemokine profile indicative of an inflammatory response in all patients
- Associated with this was a reduction in Th2-type cytokines, e.g. IL-4 & IL-5

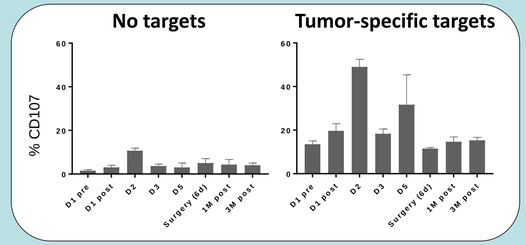
Conclusions

In summary, following i.v. infusion, Pexa-Vec selectively persists in tumor indicating a targeted oncolytic action, which translates into a complete pathological response in one CRLM patient. In addition, we demonstrate for the first time that Pexa-Vec can trigger a robust activation of tumor-specific innate & adaptive immunity and subsequent expression of immune checkpoint PD-L1. These data support a rationale for sequential Pexa-Vec and anti-PD-1 viro-immunotherapy.

Results: Functional assays

NK cell degranulation

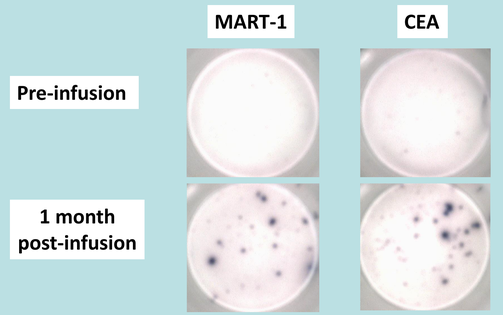
- PBMCs were cultured with/without tumor-specific target cells to assess the NK cell cytotoxic capacity following Pexa-Vec infusion
- CD107 surface expression represents NK cell degranulation & their potential to kill tumor cells



- Pexa-Vec administration leads to a stimulation of NK cytotoxicity towards cancer cells
- NK cytotoxicity is further enhanced when exposed to tumor-specific targets (SW620 for CRLM patients; Mel888 for melanoma patients)

T cell ELISpot

- PBMCs were cultured with/without tumor-associated antigen (TAA) peptides to assess the T cell functional response following Pexa-Vec infusion
- IFN-γ release was assessed by ELISpot



- A tumor-specific adaptive T cell response to MART-1 or CEA peptide is enhanced in melanoma & CRLM patients, respectively, following Pexa-Vec infusion (data is shown from one representative melanoma & CRLM patient)