Coxsackievirus A21 (CAVATAK, CVA21) is a bio-selected oncolytic immunotherapeutic virus. Following intravenous (i.v.) injection, CVA21 infects ICAM-1 expressing tumor cells, resulting in tumor cell lysis and a potential immunomodulatory effect. Previous studies showed that CVA21 treatment of murine tumors leads to elevated immune activity following administration in both immunocompetent and immunodepressed mice [2,22]. Administration of CVA21 alone in advanced cancer patients displayed signs of anti-tumor activity in these studies [23]. Blockade of programmed cell death protein 1 (PD-1) and/or cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) in advanced cancer patients has resulted in substantial tumor responses via a mechanism involving reversal of tumor induced T cell suppression [24]. We investigated the anti-tumor activity of a combination of intravenous delivered CVA21 and anti-PD-1 or -CTLA-4 blockade in a murine model that mimics human cancer (B16-H2AG7) and Non-Small Cell Lung Cancer (NSCLC). In addition, we assessed the capacity of immune checkpoint blockade to restrain the host "immunological handbrake" with respect to anti-tumor immune responses and subsequent impact on the anti-tumor activity of CVA21.

Introduction

Study Design: Melanoma

Study Design: Non-Small Cell Lung Cancer

Assessment of combination of intravenous CVA21 and immune checkpoint antibody blockade (anti-CTLA-4 and anti-PD-1) in an immunocompetent C57BL mouse model (B16-H2AG7) model.

Incidence of palpable secondary B16 tumor regrowth following combination of intravenous CVA21 and immune checkpoint antibody blockade (anti-CTLA-4 and/or anti-PD-1) in B16-H2AG7 melanoma model.

Kinetics of primary, metastatic, and immunological responses following combination of intravenous CVA21 and immune checkpoint antibody blockade (anti-CTLA-4 and/or anti-PD-1).

Conclusions

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Elevated immune activity following an anticancer combination therapy of a novel oncolytic immunotherapeutic agent, CAVATAK and immune checkpoint blockade

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• The significant antitumor activity mediated by the combination of CVA21 and checkpoint inhibitor antibodies (anti-PD-1 and anti-CTLA-4) observed in the presented murine melanoma and non-small cell lung cancer models supports clinical evaluation of such an immunotherapeutic combination treatment.

• Enhanced antitumor immune responses following immune checkpoint blockade confirms the loosening of the host "immunological handbrake" and a general heightening of systemic immune responses.

• The no reduction in the levels of anticancer activity generated from the combination treatment were observed in the presence of enhanced anti-CVA21 immune responses.

• Clinical evaluation of the activity of intravenous CVA21 in combination with systemic administration of pembrolizumab in patients with nonsmall cell lung cancer and metastatic lung cancer is currently underway [25]. ClinicalTrial.gov Identifier NCT03092066.

• Clinical evaluation of the antitumor efficacy of CVA21 in combination with systemic administration of pembrolizumab (Phase 1b NCT02577504 study). See Poster (CT021) and pembrolizumab (Phase 1c CALGB study) in patients with unresectable melanoma is currently underway.