COMBINATION THERAPY WITH THE ONCOLYTIC VIRUS CF33-CD19 AND BLINATUMOMAB FOR THE TREATMENT OF ADVANCED SOLID TUMORS

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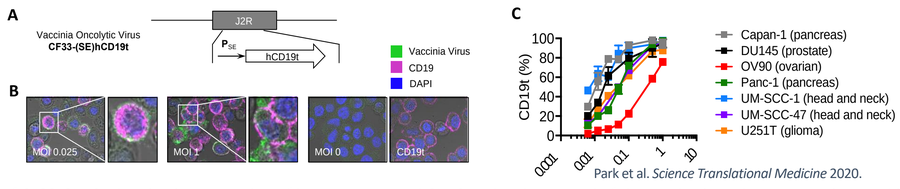
BACKGROUND

- This is a phase I, dose escalation and dose expansion, safety and tolerability study of onCARlytics (CF33-CD19), administered intravenously (IT) or intratumorally (IV) in combination with blinatumomab in adults with advanced or metastatic solid tumors (OASIS).
- CF33-CD19 is a novel chimeric oncolytic poxvirus, encoding a non-signaling and truncated human CD19 transgene. The transgene is inserted in place of the viral thymidine kinase gene at the J2R locus, resulting in attenuation of viral replication in normal cells. After infecting tumor cells with CF33-CD19, cell surface expression of CD19 occurs prior to virus-mediated tumor lysis, allowing for combination therapy with CD19 targeting therapies such as CD19 CAR Ts or bispecific T cell engagers (BiTEs) such as blinatumomab.

CF33-CD19 DELIVERS TARGETS TO "TARGETLESS" SOLID TUMORS



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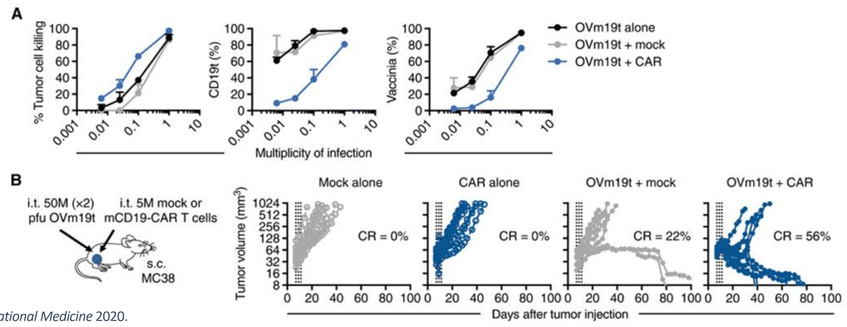
(A) Schematic of CF33-CD19, showing incorporation of human truncated CD19 under the control of the synthetic early promoter inserted into the J2R locus and replacing the thymidine kinase gene.
(B) Immunofluorescence microscopy of MDA-MB-468 cells infected for 24 hours with CF33-CD19 at multiplicity of infection (MOI) 0.025 or MOI 1, untransduced (MOI 0), or cells transduced with lentivirus to stably express CD19. Blue is DAPI, pink indicates CD19, and green indicates vaccinia/CF33.
(C) Quantification of CD19 positive cells in solid tumor cell lines after 24 hours at the indicated MOIs.

CF33-CD19 AND CD19-CAR T COMBINATION THERAPY ERADICATES TUMORS IN SYNGENEIC MODELS



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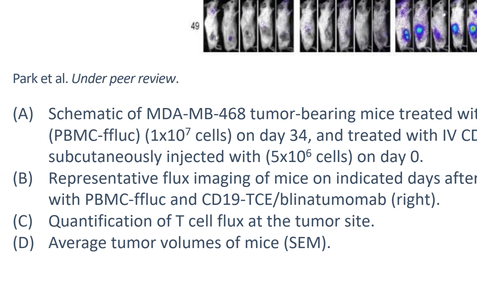
(A) Tumor killing of MC38 tumor cells treated with the indicated MOIs of CF33-CD19 (OVm19t) and cocultured with mCD19-CAR T cells or untransduced T cells (Mock) for 24 hours. Left: Tumor cell killing was assessed by flow cytometry. Middle: Quantification of percent tumor cells positive for CD19. Right: Quantification of percent cells positive for vaccinia/CF33.
(B) Left: Schematic of C57BL/6j mice with subcutaneous MC38 tumors treated with CF33-CD19 and mCD19-CAR T cells. Mice were subcutaneously (s.c.) injected with MC38 cells (5×10^5 cells) on day 0. On days 7 and 9, mice were intratumorally treated (i.t.) with 0 or two doses of 5×10^7 plaque forming units (PFU) CF33-CD19 per mouse. On day 11, mice were treated by intratumoral injection with either Mock or mCD19-CAR T cells (5×10^6 cells). Tumor volume was measured with calipers. Data for each mouse (n = 9 per group) is shown. Data are from one of two independent experiments. Percent of mice with complete response (curative response) is indicated.

CF33-CD19 INFECTION TAGS TUMOR CELLS FOR CYTOTOXIC KILLING OF BLINATUMOMAB ACTIVATED NON-TARGETED T-CELLS



Representative phase-contract microscopic images of MDA-MB-468 tumor cell killing. Tumor cells were co-cultured with non-targeting T cells at a ratio of 1:1 with increasing MOI of CF33-CD19 and increasing amounts of blinatumomab. Top row: negative control, 0 ng/mL blinatumomab. Bottom row: positive control, with CD19-CAR T cells. Right column: control, MDA-MB-468 cells stably expressing CD19 via lentiviral transduction.

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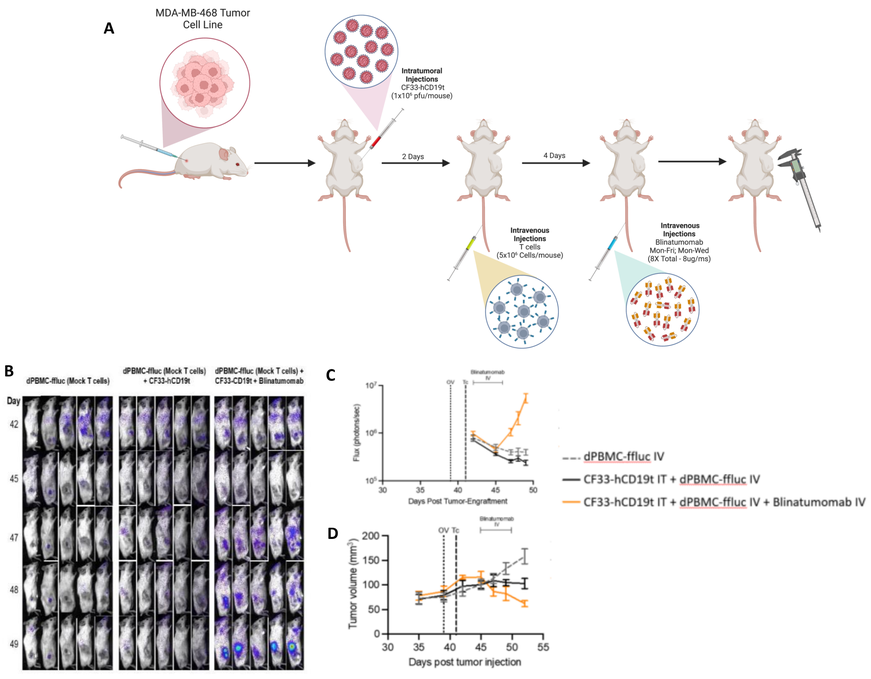
BLINATUMOMAB CAN ACTIVATE AND EXPAND NON-TARGETING T CELLS WHEN COMBINED WITH CF33-CD19 IN NSG MICE



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(A) Schematic of MDA-MB-468 tumor-bearing mice treated with IT CF33-CD19 ($1x10^7$ pfu) on day 32, engrafted with IV PBMC expressing firefly luciferase (PBMC-ffluc) ($1x10^7$ cells) on day 34, and treated with IV CD19-TCE/blinatumomab (100 ug/dose, 8 times) on days 38-42 and 45-47. NSG mice were subcutaneously injected with ($5x10^6$ cells) on day 0.
(B) Representative flux imaging of mice on indicated days after engraftment with PBMC-ffluc only (left), OV19t with PBMC-ffluc (middle), and CF33-CD19 with PBMC-ffluc and CD19-TCE/blinatumomab (right).
(C) Quantification of T cell flux at the tumor site.
(D) Average tumor volumes of mice (SEM).

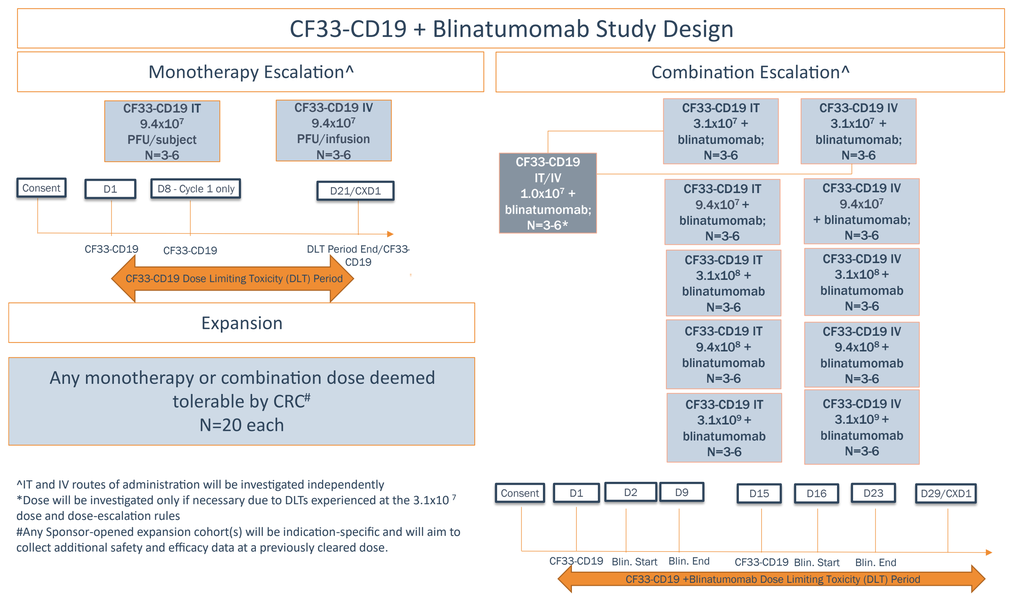
METHODS

STUDY DESIGN AND DOSING SCHEMA

This is an open-label, dose escalation and dose expansion, multi-center phase I study evaluating the safety and tolerability of CF33-CD19 administered IV and IT as monotherapy and in combination with blinatumomab in adult subjects with advanced or metastatic solid tumors.

The study is composed of two parts:

- Safety Run-In Phase – Three subjects will be treated with monotherapy CF33-CD19 (IV; $9.4x10^7$ PFU) and three subjects will be treated with CF33-CD19 (IT; 9.4x107 PFU). The subjects in each cohort (IV and IT) will be dosed on Days 1 and 8 of Cycle 1 and on Day 1 of each subsequent cycle (21-day cycles). Each subject will be assessed for safety during Cycle 1.
- Dose Escalation Combination Phase – This phase of the study will follow a traditional 3+3 dose escalation scheme for each route of CF33-CD19 administration (IV and IT). CF33-CD19 (IV or IT) will begin at dose level -1: $3.1x10^7$. Both CF33-CD19 and blinatumomab will be administered on a 28-day cycle with CF33-CD19 on Days 1 and 15. Blinatumomab will be given on Days 2 to 9 and 16 to 23, via continuous infusion (7 days on, 7 days off). Blinatumomab will be administered continuously using infusion pumps which provide 24-hour, 48-hour, or 7-day infusion durations.



^IT and IV routes of administration will be investigated independently
*Dose will be investigated only if necessary due to DLTs experienced at the $3.1x10^7$ dose and dose-escalation rules
#Any Sponsor-opened expansion cohort(s) will be indication-specific and will aim to collect additional safety and efficacy data at a previously cleared dose.

In Cycle 1, subjects are required to be hospitalized for three days following the first blinatumomab infusion, Cycle 1, Days 2 to 5. Subjects are again required to be hospitalized for two days following the second blinatumomab infusion, Cycle 1, Days 16 to 18

KEY INCLUSION AND EXCLUSION CRITERIA

INCLUSION

- >18 years of age
- Life expectancy of at least 3 months. With ECOG status of 0 or 1
- Any histologically or cytologically confirmed advanced or metastatic solid tumor
- Eligible subjects must have received at least two prior lines of approved therapies
- At least one measurable lesion as defined by RECIST v1.1 criteria
- Adequate renal, hepatic, and hematological function

EXCLUSION

- Prior treatment with an oncolytic virus or a bispecific CD19-directed CD3 T-cell engager
- Prior systemic anti-cancer treatment including investigational agents within 4 weeks of the first dose of study treatment
- Continuous systemic treatment with either corticosteroids or other immunosuppressive medications
- Any radiation within 2 weeks of start of study treatment
- Active autoimmune disease
- Prior allogeneic tissue/organ transplant or other medical conditions requiring ongoing treatment with immunosuppressive drugs
- History or presence of brain or other central nervous system (CNS) metastases

OBJECTIVES

PRIMARY OBJECTIVES:

- To evaluate safety and tolerability of IV and IT CF33-CD19 monotherapy
- To determine the recommended Phase 2 dose (RP2D) dose to apply to the Dose Escalation Combination Phase
- To evaluate safety and tolerability of IV and IT CF33-CD19 in combination with blinatumomab

SECONDARY OBJECTIVES:

- To evaluate the preliminary anti-tumor activity of IV and IT CF33-CD19 monotherapy using RECIST v1.1 and iRECIST v1.0
- To determine the RP2D for CF33-CD19 (IV and IT) in combination with blinatumomab

EXPLORATORY OBJECTIVES:

- To assess CD19 expression on tumor tissue following CF33-CD19 treatment (IV and IT)
- To evaluate antitumor and antiviral immune activation (IV and IT)
- To evaluate the pharmacokinetics (PK) of CF33-CD19 following IV treatment
- To assess viral shedding (IV and IT)

STUDY INFORMATION

NUMBER OF PATIENTS:

- During the Safety Run-In and Dose Escalation Combination Phases, up to 6 evaluable subjects will be treated in each cohort (IV and IT) with 3 subjects evaluated initially. If one of those 3 subjects has a DLT, 3 additional subjects will be evaluated.
- The total number of patients enrolled in the escalation cohorts will be between 36 and 66 patients.
- Once a monotherapy or combination dose has been deemed tolerable, indication-specific expansion cohorts treating up to 20 patients each at that dose may be opened to obtain additional safety and efficacy information

STATUS / ENROLLMENT: Enrollment into the monotherapy safety run-in phase in complete. Recruitment into the combination therapy cohorts is ongoing.

CLINICALTRIALS.GOV ID: NCT06063317

NUMBER OF SITES: Approximately 10 participating sites in the United States.