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Developing Cancer Immunotherapies

ASX: IMU

ONCARLYTICS:
A first-in-class CD19-expressing OV for use in solid tumors

Grey Wilkinson, PhD
Senior Director, Translational Science

December 13, 2023

CELL THERAPY AND ONCOLYTIC VIRUS PLATFORMS DELIVER INNOVATIVE AND POTENT THERAPIES TO PATIENTS

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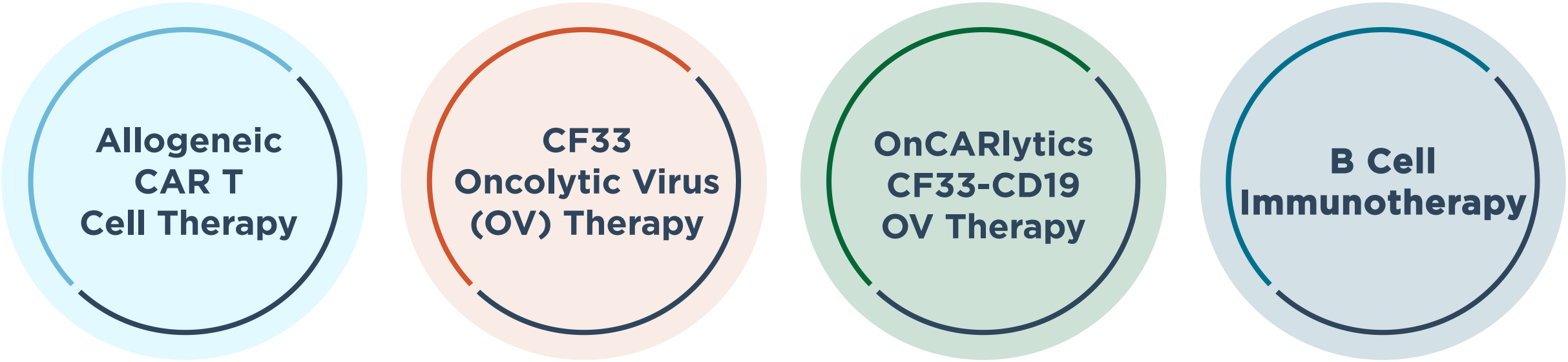

azer-cel

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onCARlytics

HER-Vaxx & PD1-Vaxx

onCARIytics
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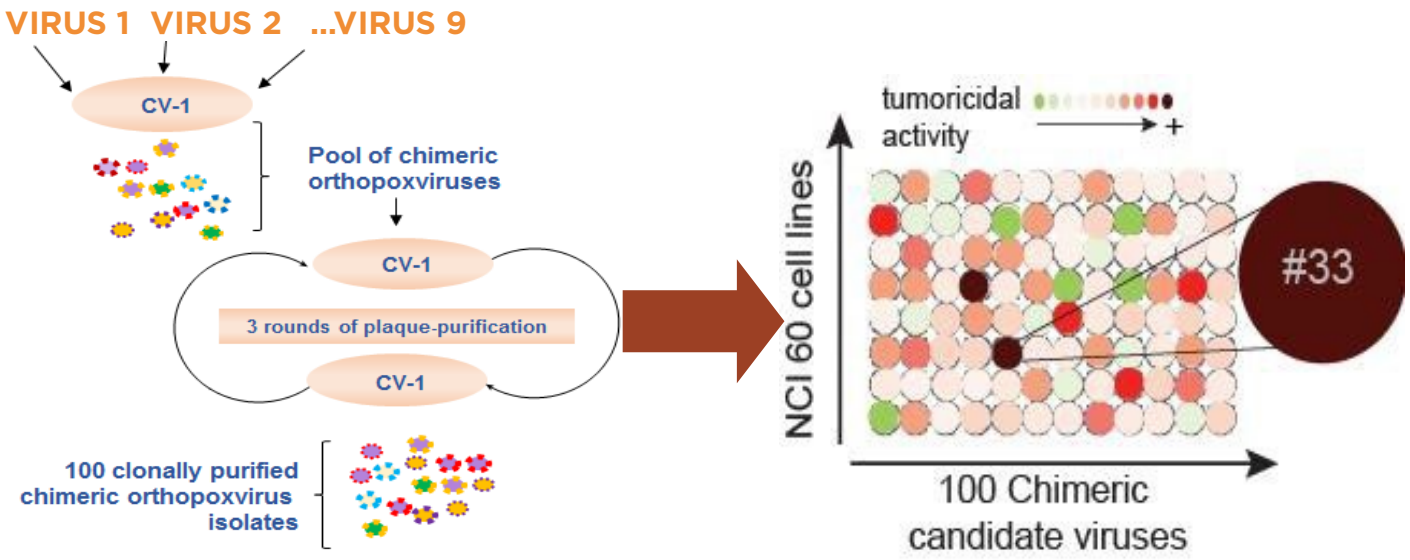
RATIONALE FOR COMBINATION THERAPY WITH CF33-CD19 + BLINATUMOMAB

CF33 GENERATION & EVALUATION OF NOVEL CHIMERIC POXVIRUSES



- Infection by 9 different pox vaccinia vaccine strains trading genetic material isolating over 100 different clones (new species)
- Placed in the State-of-the-art high throughput screening for efficacy against the NCI 60 cell lines.
- The 33rd virus was chosen for its eradication of all cancer cell lines in the NCI 60, CF33

STRATEGY

Engineer Novel Chimeric Viruses

High Through-put Screening for Efficacy Against NCI60

Safe in Animals

Arming with Additional Payloads

Hope Oncolytic Viruses (HOV)

CF33-CD19 (ONCARLYTICS) SELECTIVELY INFECTS AND DRIVES TUMOR-SPECIFIC EXPRESSION OF CD19

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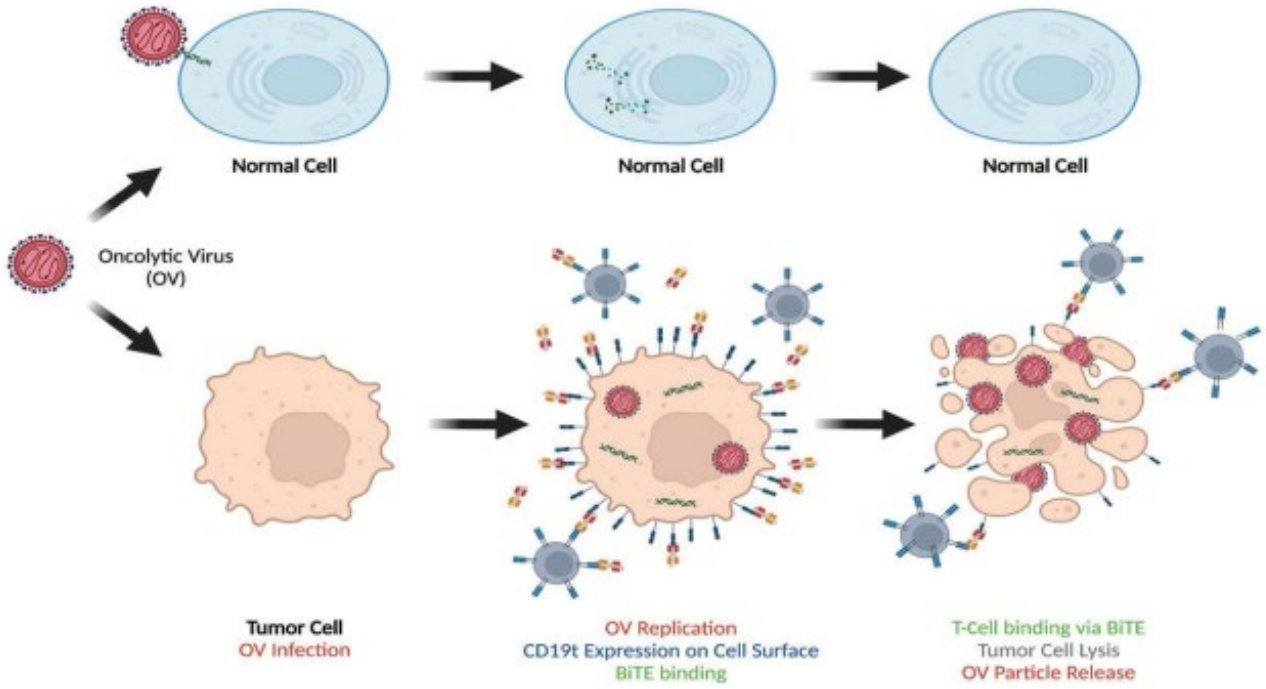
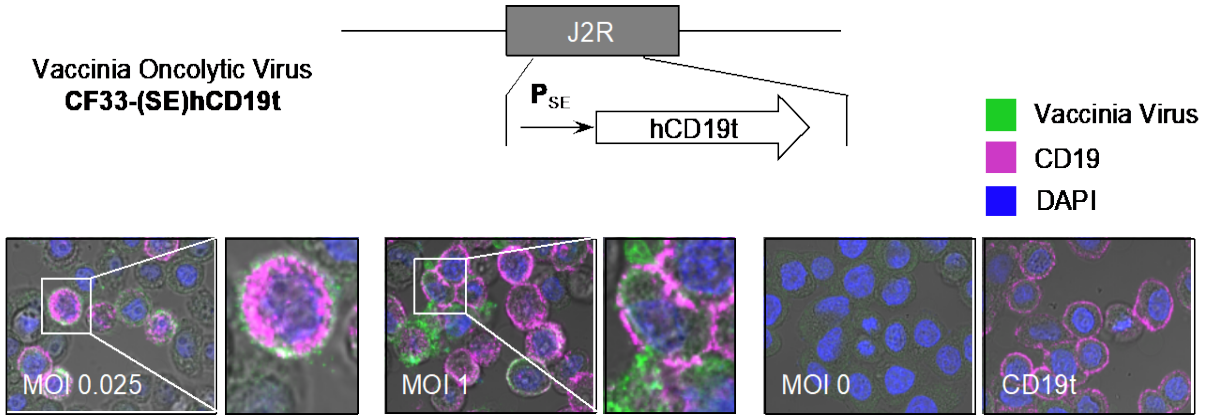
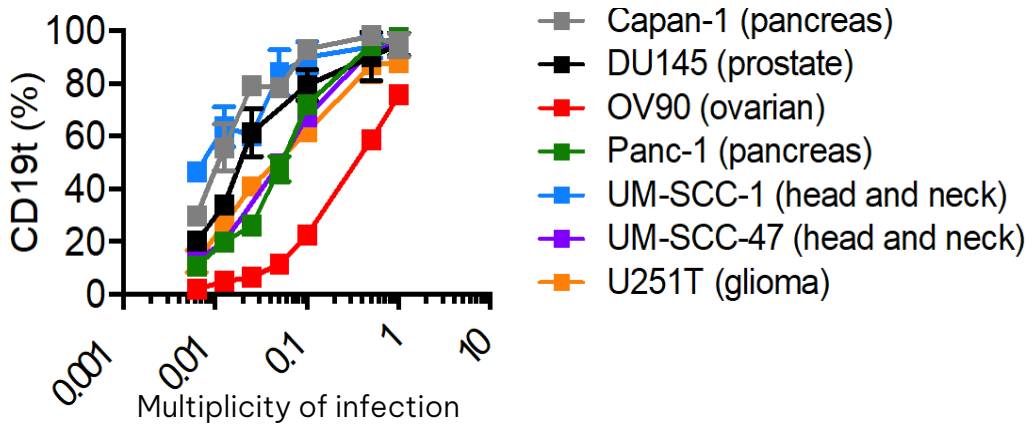
- CD19 is commonly expressed in blood cancers and is used with targeted therapies like CARTs to identify and kill tumor cells in a homogeneous manner
- Solid tumor cells don't have a common, abundant, or tumor-specific protein on their surface for targeting
- onCARlytics allows for CD19 to be expressed on solid tumor cells
- Ability to use any CD19 targeting agent to kill CD19 expressing solid tumors
- Large, unmet medical need for patients with solid tumors



CF33-CD19 DELIVERS TARGETS TO "TARGETLESS" SOLID TUMORS

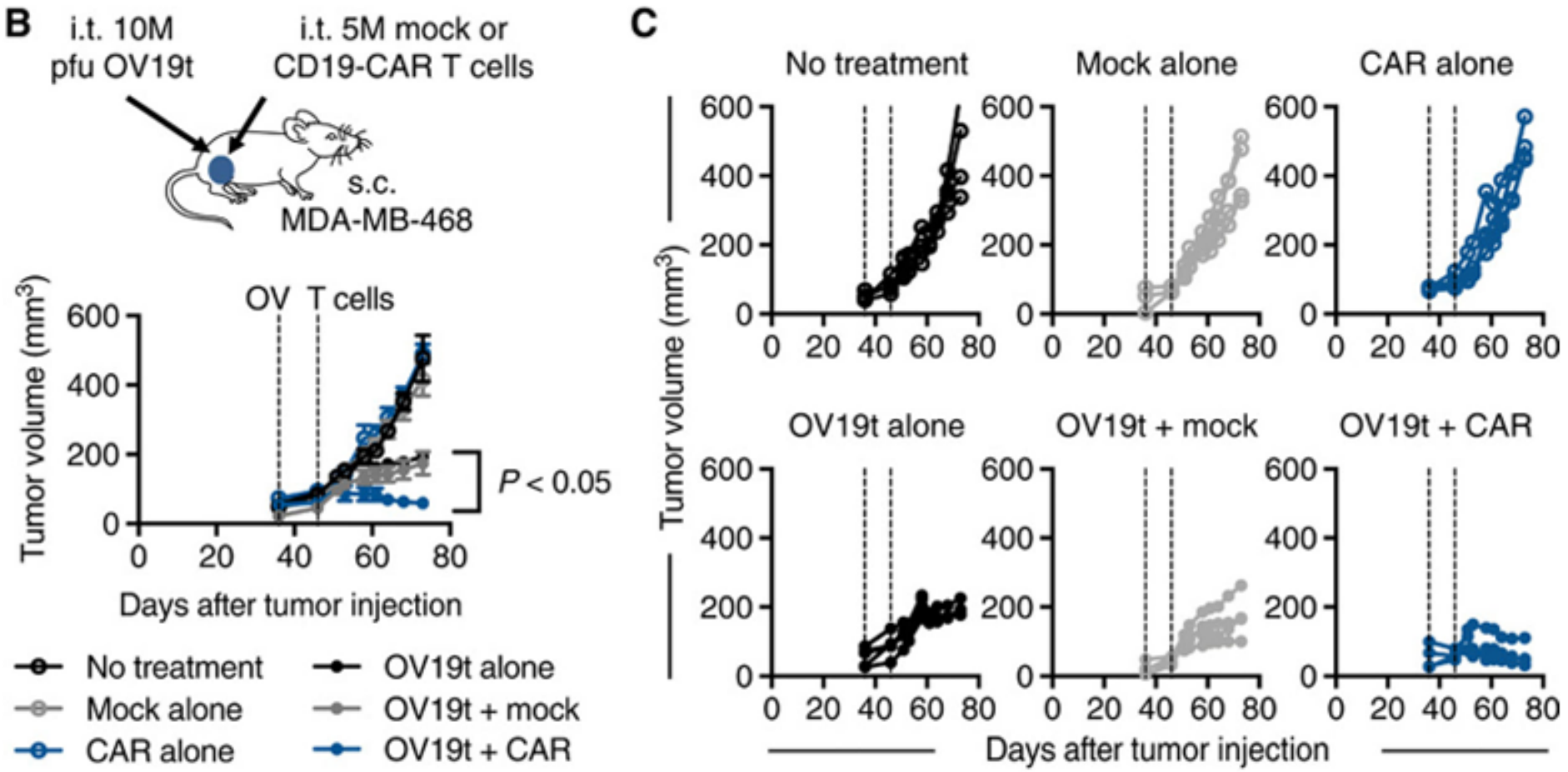


onCARlytics (CF33-CD19) infects a wide array of solid Tumor cell lines, with dose-dependent CD19 cell surface expression



Park et al. *Science Translational Medicine* 2020

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



Park et al. *Science Translational Medicine* 2020

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

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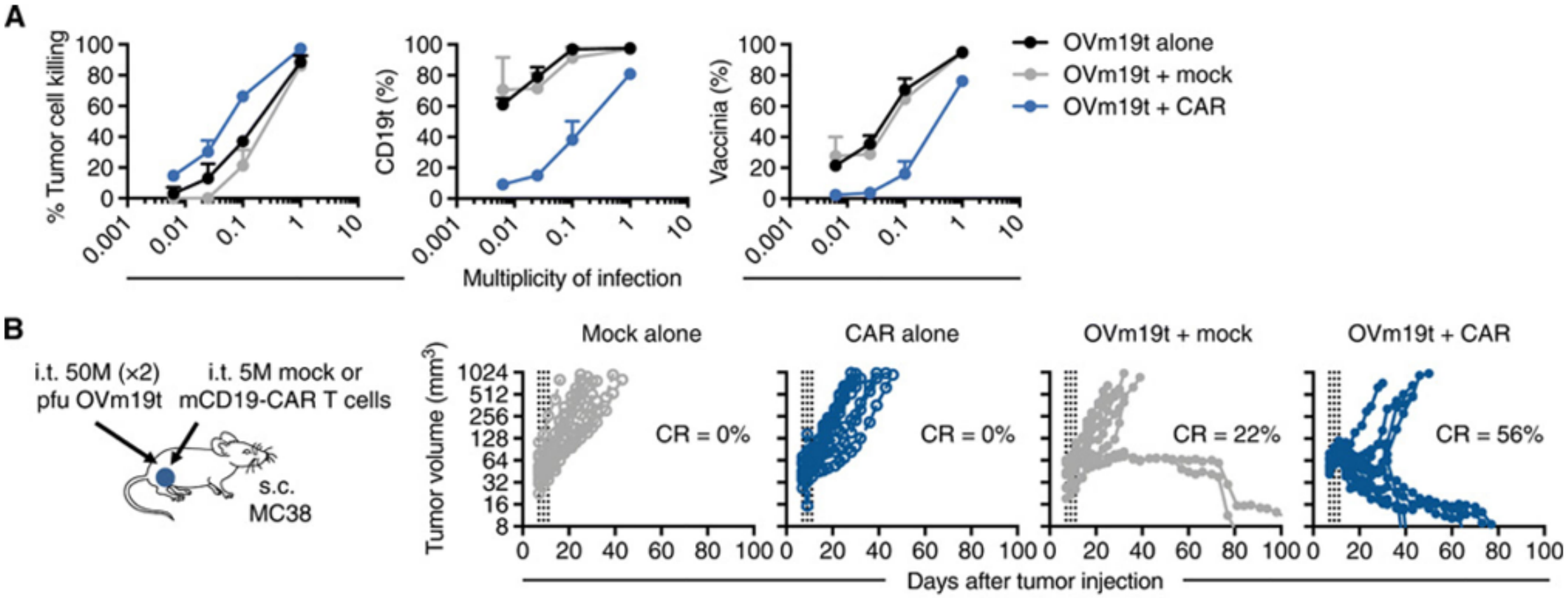

Park et al. *Science Translational Medicine* 2020

BLINATUMOMAB (BLINCYTO®) IS A BITE IMMUNOTHERAPY THAT BINDS CD3 AND CD19

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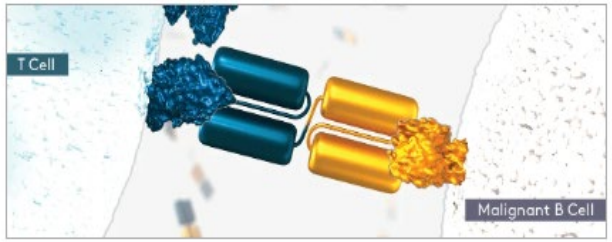
Blinatumomab is Approved for the treatment of adult and pediatric patients with B-cell precursor acute lymphoblastic leukemia

Target

BLINCYTO® targets malignant and benign B cells via the CD19 cell surface antigen while simultaneously engaging the patient's own T cells through the CD3 antigen.[2]

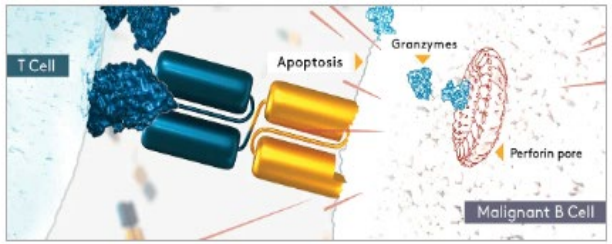
Activate

BLINCYTO® activates the T cell, resulting in the formation of a synapse between the T cell and malignant B cell.[1]



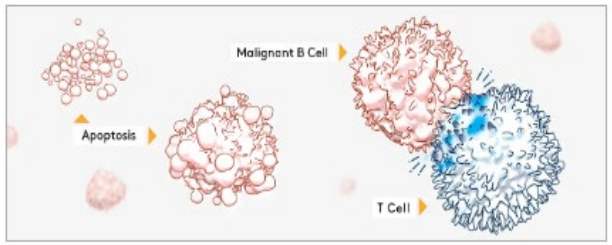
Fight

The activated T cell then fights the malignant B cell by releasing perforin and granzymes through the perforin pore to induce apoptosis.[3]



Persist

The activated T cells persist in the blood stream, allowing for serial lysis of multiple target cells. Sustained activation of T cells results in local proliferation and enhanced polyclonal expansion of memory T cells, helping to fight cancer cells.[4]



www.blincytohcp.com/mechanism-of-action

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

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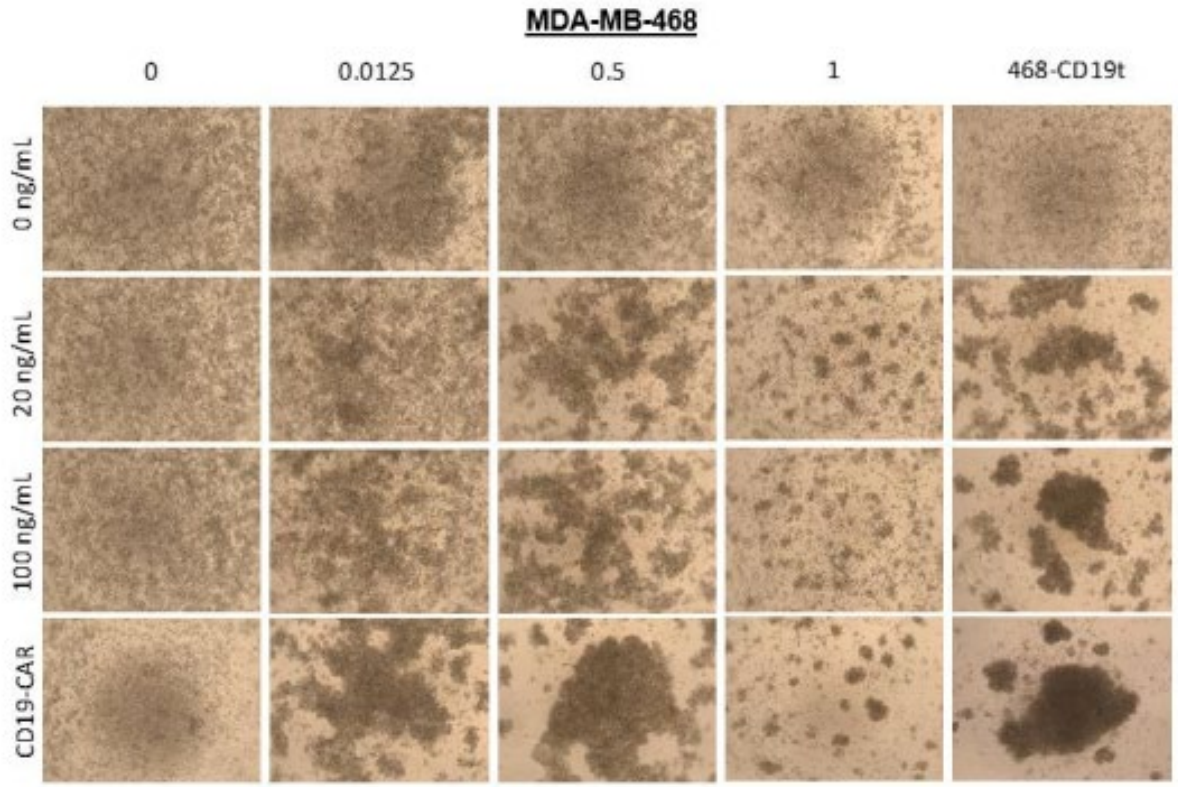
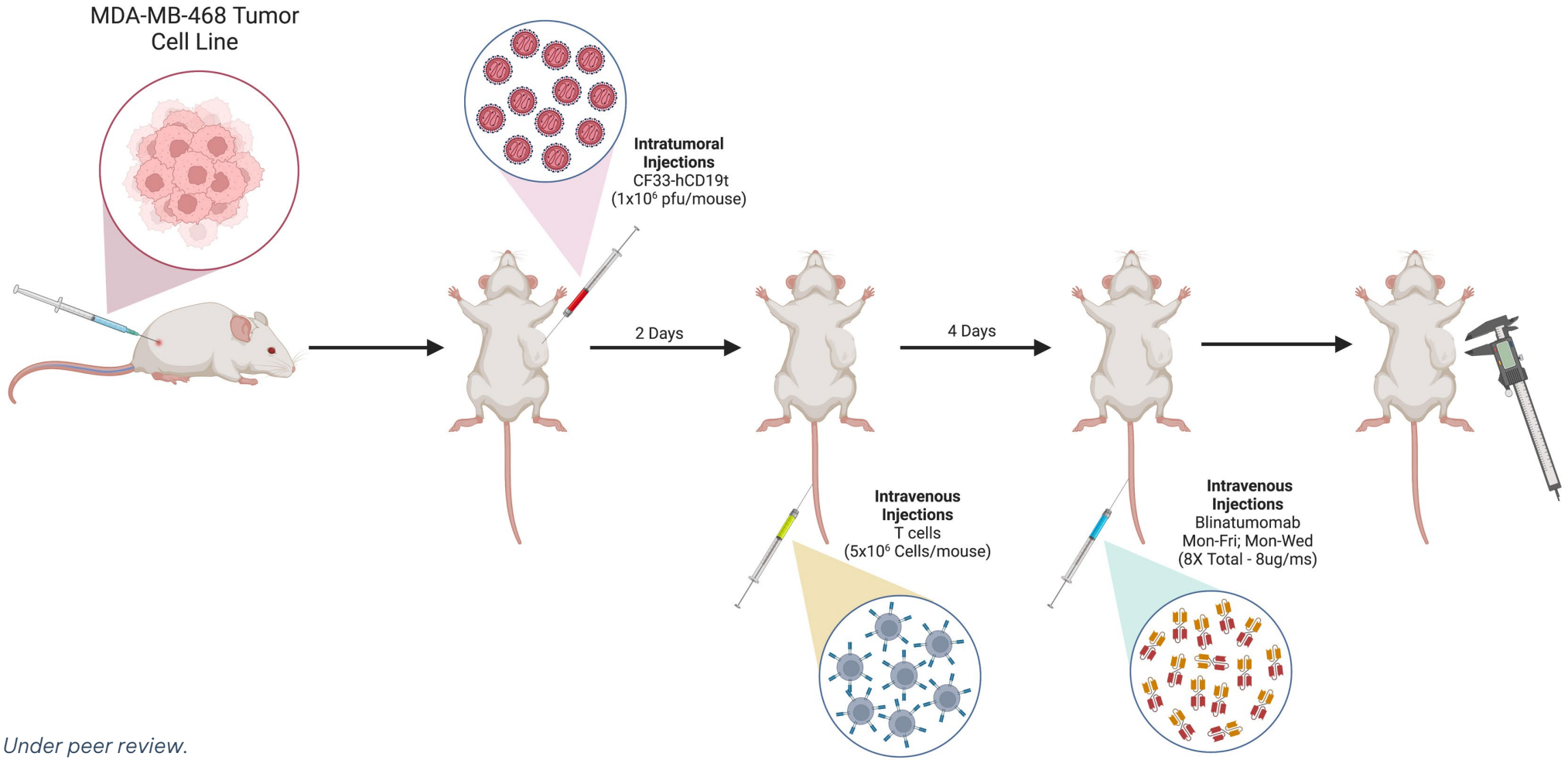


Representative phase-contract microscopic images of MDA-MB-468 tumor cell killing. Tumor cells were co-cultured with non-targeting T cells at a ratio of 1:1 with increasing MOI of CF33-CD19 and increasing amounts of blinatumomab. Top row: negative control, 0 ng/mL blinatumomab. Bottom row: positive control,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

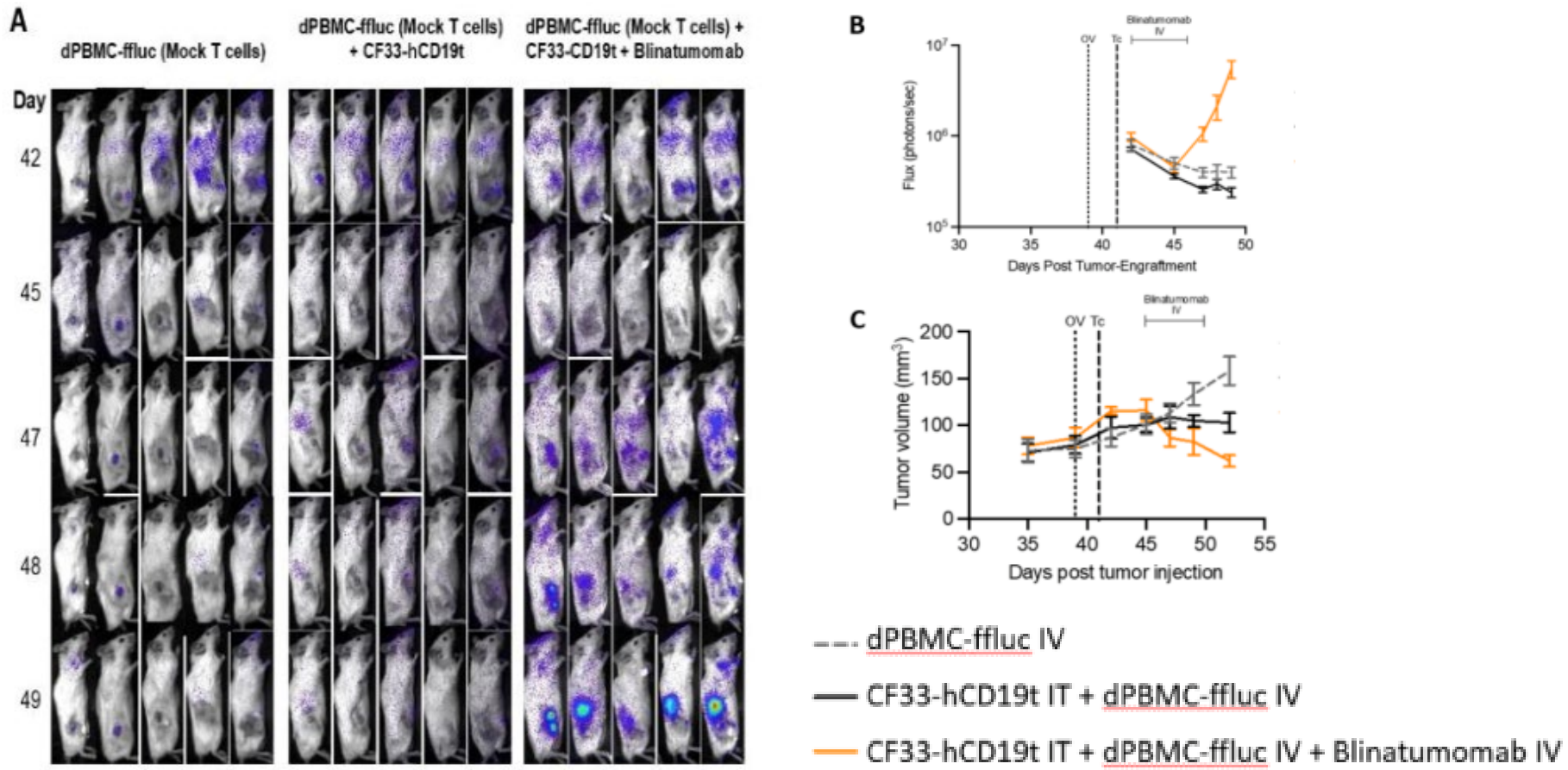
Park et al. Under peer review.

IN VIVO STUDY TESTING BLINATUMOMAB IN COMBINATION WITH CF33-CD19 IN NSG MICE



Park et al. Under peer review.

BLINATUMOMAB CAN ACTIVATE AND EXPAND NON-TARGETING T CELLS WHEN COMBINED WITH CF33-CD19T



A) Non-invasive bioluminescence imaging of mice engrafted with MDA-MB-468 tumor cells and treated with dPBMC-ffluc alone, dPBMC-ffluc with CF33-hCD19t or dPBMC-ffluc with CF33-hCD19t and Blinatumomab. **B)** Quantification of average flux at the tumor site. **C)** Average tumor volumes of mice.

Park et al. Under peer review.

CD19T TRANSGENE EXPRESSION IS LIMITED TO TUMOR TISSUE IN MURINE MODELS

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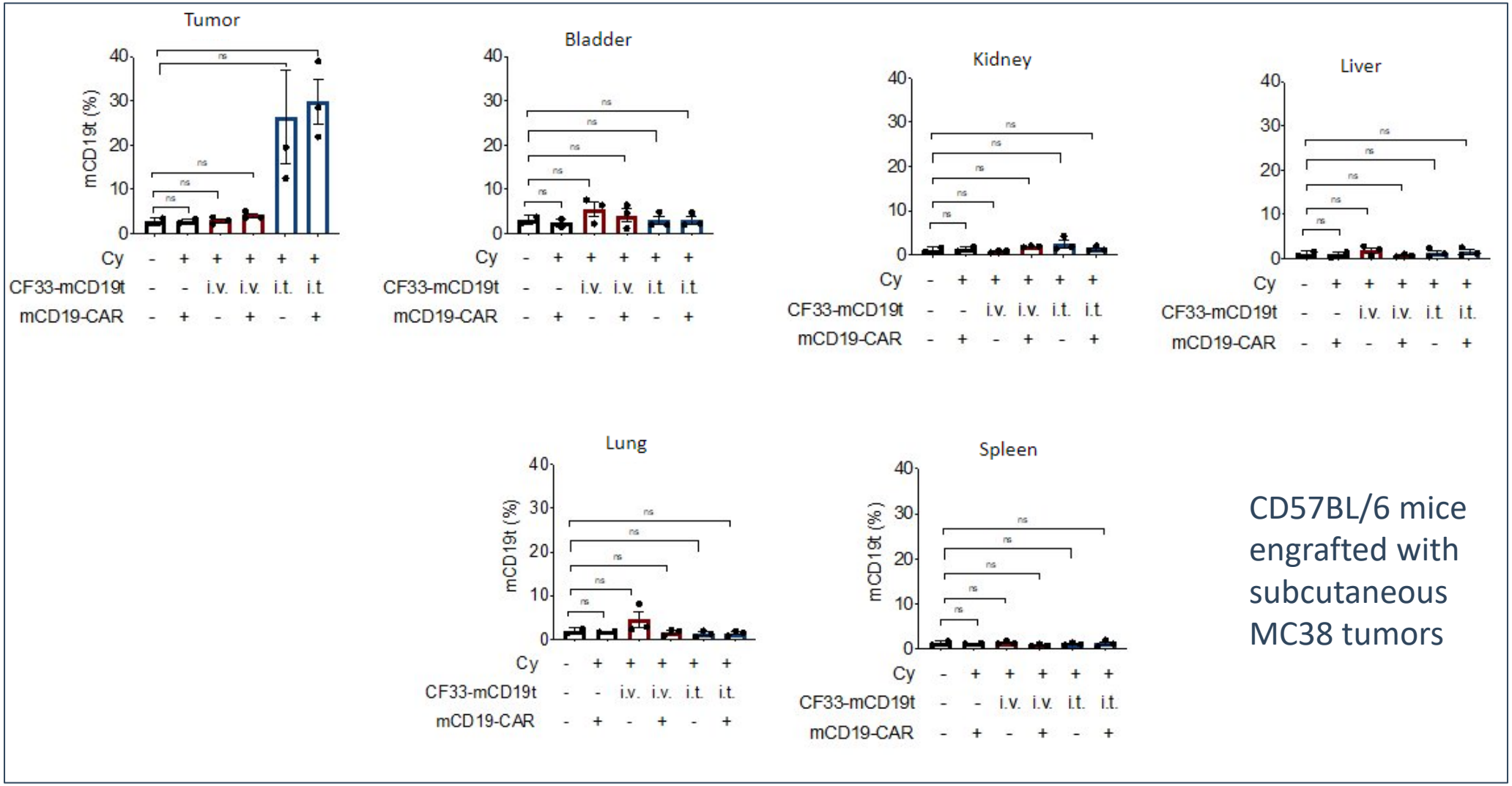

CD57BL/6 mice engrafted with subcutaneous MC38 tumors

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CLINICAL RATIONALE FOR CF33-CD19 + BLINATUMOMAB COMBINATION THERAPY

T CELLS OF BLINATUMOMAB-TREATED ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS SHOW SIGNS OF EXHAUSTION IN THE FIRST CYCLE

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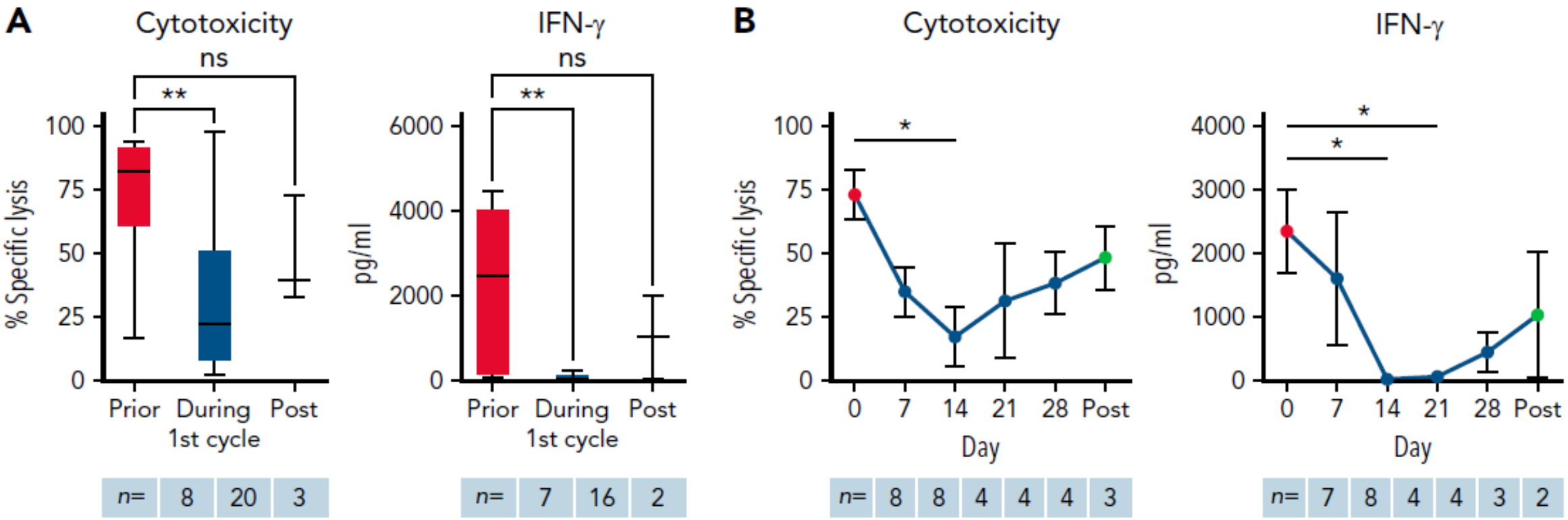

Blinatumomab-mediated cytotoxicity and IFN-g secretion against REH cells

Pre-treatment
During cycle 1
Post cycle 1

Philipp et al. Blood. 8 Sept 2022. Vol 140, #10

A TREATMENT FREE INTERVAL WITH BITE REINVIGORATES T-CELL FUNCTION

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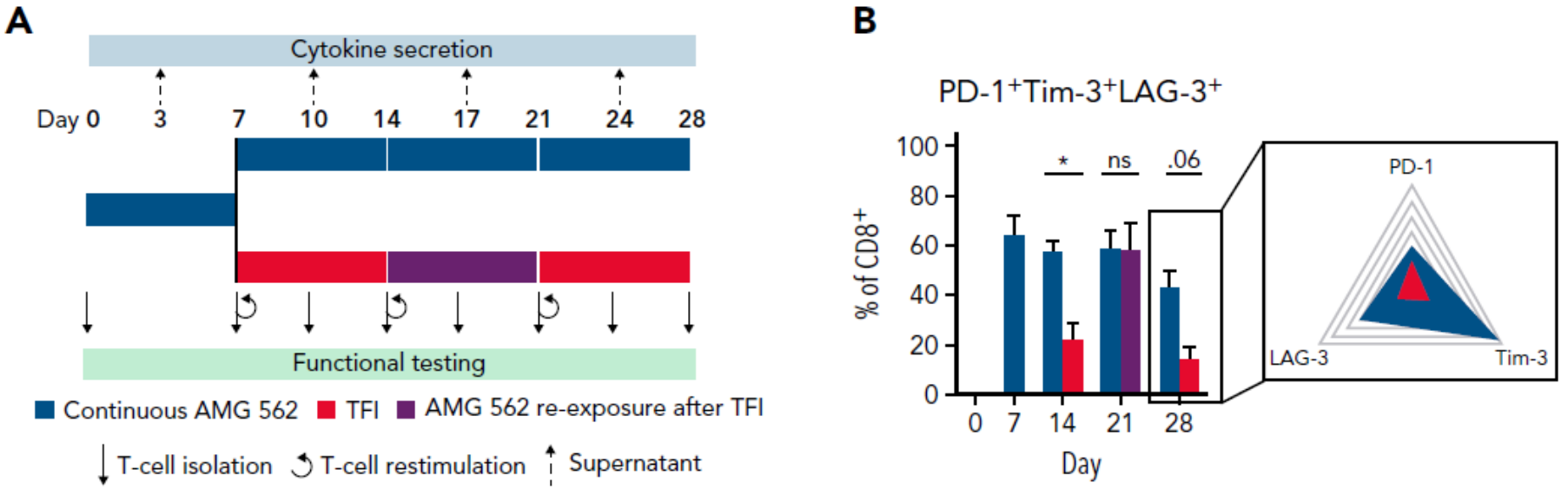

(A) Timeline of continuous vs TFI T-cell stimulation with AMG562 over 28days.
(B) Percentage of CD8 T cells co-expressing PD-1, Tim-3, and LAG-3.
(C) Cytokine levels determined by CBA in coculture supernatants on day 17

Philipp et al. Blood. 8 Sept 2022. Vol 140, #10

THE CURRENT BLINATUMOMAB TREATMENT REGIME MAY NOT BE SUITABLE FOR SOLID TUMOR PATIENTS

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Recommended Blinatumomab Dosage and Schedule for the Treatment of Relapsed or Refractory B-cell Precursor ALL																																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Blinatumomab																																									
Combination Therapy Treatment Schedule																																									
All cycles	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**														
CF33-CD19																																								
Blinatumomab																																								

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

ADVERSE EVENTS TO DATE IN PHASE 1 WITH SIMILAR ONCOLYTIC VIRUS CF33-HNIS ARE MOSTLY GRADE 1/2

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As of 31 Oct 2023, the following treatment related adverse events have been reported in the MAST study (CF33-hNIS +/- pembrolizumab).

AEs related to the investigational products in >10% of patients and all AEs > grade 3, n = 34	All, n (%)	Grade 1 /2, n (%)	Grade 3, n (%)
Any	26 (76)	26 (76)	1 (3)
FATIGUE	10 (29)	10 (29)	0
FEVER	8 (24)	8 (24)	0
CHILLS	5 (15)	5 (15)	0
LYMPHOCYTE COUNT DECREASED	1 (3)	0	1 (3)

- Treatment with CF33-hNIS is associated with mild 'flu-like' symptoms in ~30% of patients
- No evidence to date indicates that CF33-hNIS exacerbates immune related adverse events associated with checkpoint inhibitors

SIGNIFICANT OVERLAPPING TOXICITIES WITH CF33-CD19 AND BLINATUMOMAB ARE NOT EXPECTED

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Adverse Reactions Occurring at ≥ 10% Incidence for Any Grade or ≥ 5% Incidence for Grade 3 or Higher in BLINCYTO-Treated Patients with MRD-Positive B-cell Precursor ALL (N=137)

Adverse Reaction	Any Grade, n (%)	≥ Grade 3, n (%)
Neutropenia	21 (15)	21 (15)
Leukopenia	19 (14)	13 (9)
Thrombocytopenia	14 (10)	8 (6)
Arrhythmia	17 (12)	3 (2)
Pyrexia	125 (91)	9 (7)
Chills	39 (28)	0 (0)
Infections - pathogen unspecified	53 (39)	11 (8)
Infusion related reaction	105 (77)	7 (5)
Decreased immunoglobulins	25 (18)	7 (5)
Weight increased	14 (10)	1 (<1)
Hypertransaminasemia	13 (9)	9 (7)
Back pain	16 (12)	1 (<1)
Headache	54 (39)	5 (4)
Tremor	43 (31)	6 (4)
Aphasia	16 (12)	1 (<1)
Dizziness	14 (10)	1 (<1)
Encephalopathy	14 (10)	6 (4)
Insomnia	24 (18)	1 (<1)
Cough	18 (13)	0 (0)
Rash	22 (16)	1 (<1)
Hypotension	19 (14)	1 (<1)

- "The most common adverse reactions (≥ 20%) were infections (bacterial and pathogen unspecified), pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia."
- Cytokine Release Syndrome (CRS) and Neurological toxicities often occur within the first cycle of treatment

BLINCYTO® (blinatumomab) – FDA label

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OASIS PROTOCOL OVERVIEW

A Phase I, Dose Escalation and Dose Expansion, Safety and Tolerability Study of onCARIytics (CF33-CD19), Administered Intravenously or Intratumorally in Combination with Blinatumomab in Adults with Advanced or Metastatic Solid Tumors (OASIS)

STUDY DESIGN AND DOSING SCHEMA

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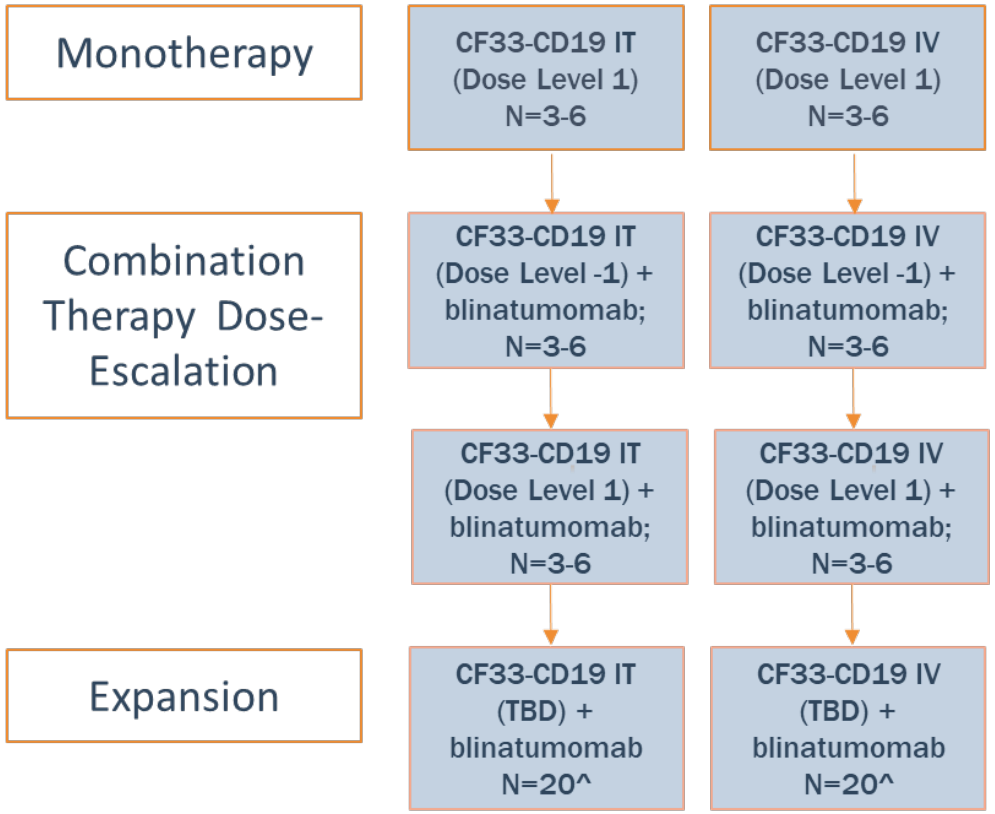
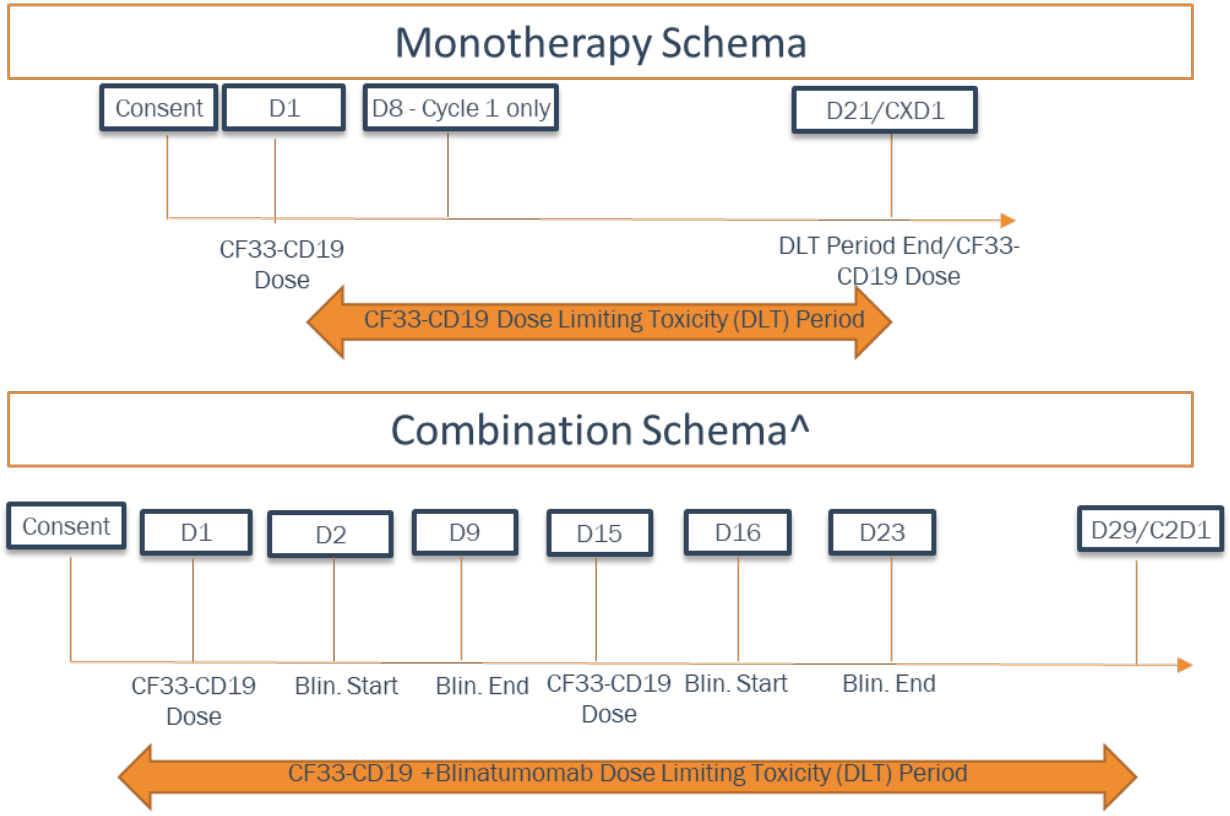
CF33-CD19 + Blinatumomab Study Design





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

PATIENT POPULATION

Key inclusion and exclusion criteria:

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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

STUDY OBJECTIVES

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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)

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