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TARGETING BRAIN METASTASES FROM HER2-POSITIVE BREAST CANCER WITH INTRAVENTRICULARLY ADMINISTERED CAR T CELLS

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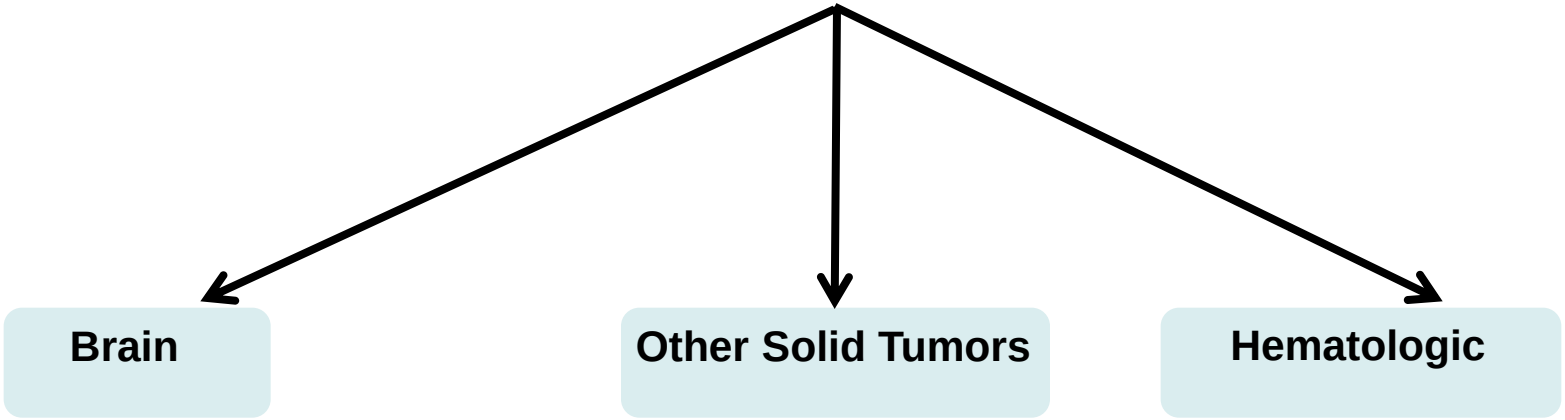
Disclosures

- I do not have anything to disclose

T Cell Therapy Program at COH
"Beyond CD19-CARs"



- Glioma
- **Brain Metastasis**

- Prostate
- Breast
- Pancreatic
- Ovarian

- Leukemia – AML, ALL
- Lymphoma
- Multiple Myeloma

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CAR T Cells for the Treatment of Solid Tumors

- CAR T cells targeting different tumor-associated antigens (eg.,CEA, mesothelin, IL13Ra2, EGFRvIII, HER-2) have been studied in many solid tumors:

sarcoma	colon cancer
ovarian cancer	glioblastoma
neuroblastoma	kidney cancer
pancreatic cancer	mesothelioma

- So far, the results with CAR T cells in solid tumors have been disappointing compared to those seen with the hematologic malignancies.

- Possible reasons
  - Antigen escape
  - CAR T cells need to track through stromal elements associated with many solid tumors
  - The immunosuppressed microenvironment of solid tumors.

Landscape of HER2-CAR T Cell Therapies

- NIH phase I clinical trial of HER2-CAR T cells in patients with HER2+ metastatic cancer. for a metastatic colon cancer

(case report, Morgan RA *Mol Ther* 2010)

39 y.o. woman with HER2+ metastatic colon cancer involving her liver and lungs.

3rd generation CAR (HER2-28/BBz), 10e10 cells IV after lymphodepletion with Flu-Cy, supplemental IL-2

Within 15 min of completing the CAR T cell infusion, she developed respiratory distress; died 5 days later of multi-organ failure.

Death due to the HER2-CAR T cells recognizing low expression of HER2 on normal lung epithelium, triggering severe CRS.

Landscape of HER2-CAR T Cell Therapies

New approaches to try to increase safety of CAR T cells:

- Improvements in CAR design
- Starting with lower doses of CAR T cells in phase I clinical trials
- Local/regional delivery compared with systemic
- Adding suicide genes to enable elimination of CAR T cells if needed
- Improving the ability to predict and manage CRS

Landscape of HER2-CAR T Cell Therapies

Phase I HER2-CAR T cell study in sarcoma patients
(Ahmed et al., *J Clin Oncol* 2015)

Phase I HER2-CAR modified virus-specific T cells in glioblastoma pts
(Ahmed et al., *JAMA Oncol* 2017)

2nd generation CAR (HER2-28z), IV administration of up to 1x10^8 cells, no lymphodepletion

Well tolerated; no DLTs

Some clinical activity seen:

SD in 4/17 sarcoma pts, ranging from 3-14 months

PR for 9 months in 1 GBM pt, 7 GBM pts had SD for 8 weeks to 29 months

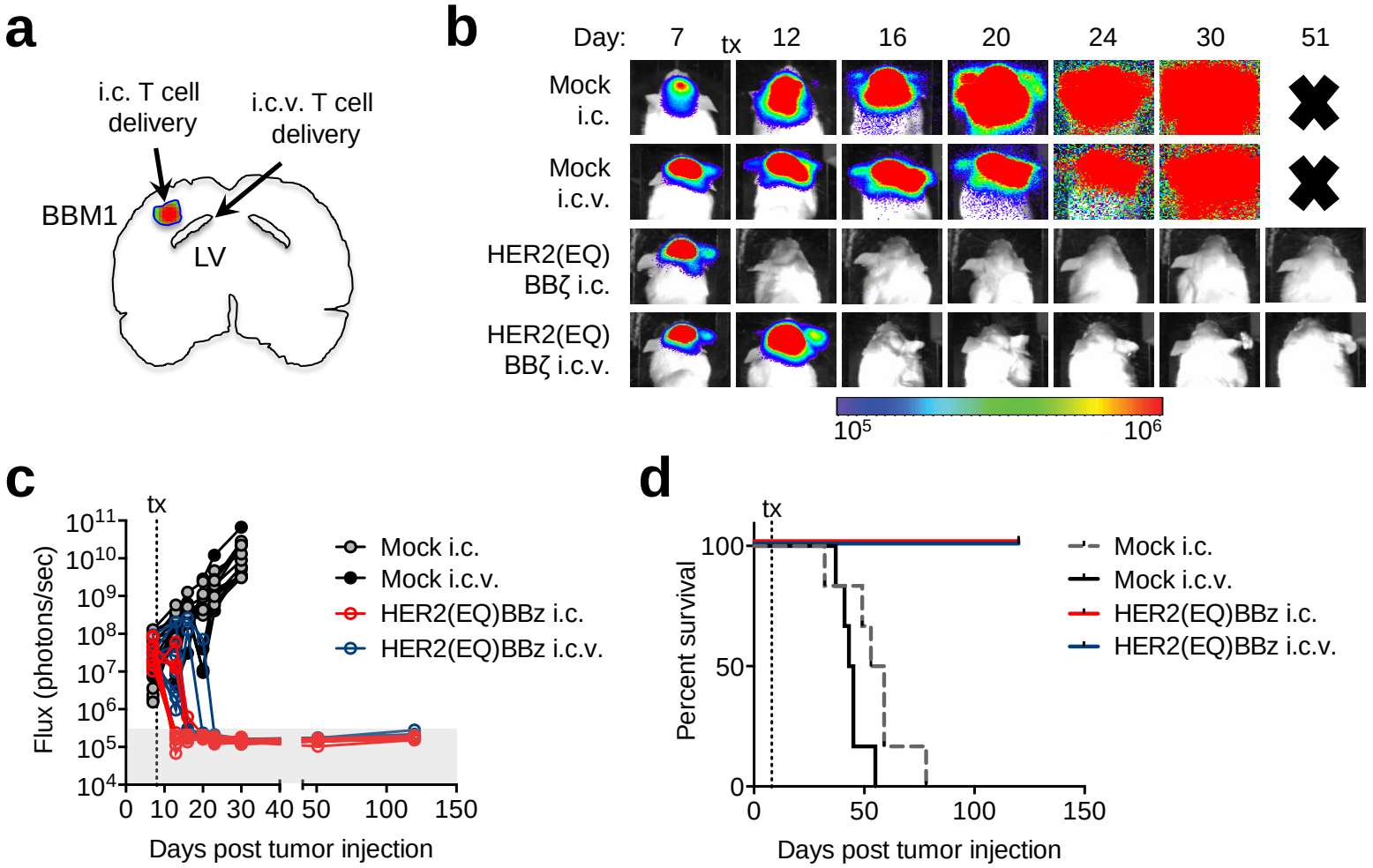
Targeting HER2+ Breast Cancer Brain Metastases with CAR T Cells

- HER2 is an oncogenic protein overexpressed in 25-30% of all breast cancers.
- At least 1/3 of women with $HER2^{+}$ breast cancer develop brain metastasis.
- Anti-HER2 monoclonal antibodies do not sufficiently cross the blood-brain barrier; small molecule TKIs do not durably control breast cancer brain metastases.

Targeting HER2+ Breast Cancer Brain Metastases with CAR T Cells

- Multifocal disease requires more broad distribution of therapies.
- Our preclinical studies demonstrate a lack of T cell trafficking through the blood-brain-barrier, therefore local/regional therapy is preferred.
- Intraventricular therapy may target multiple tumor lesions in the brain.
- *HER2-CAR T cells regionally administered to patients with HER2+ Brain Metastases.*

Intraventricular Delivery of HER2-BBz CAR T Cells for Brain Metastasis



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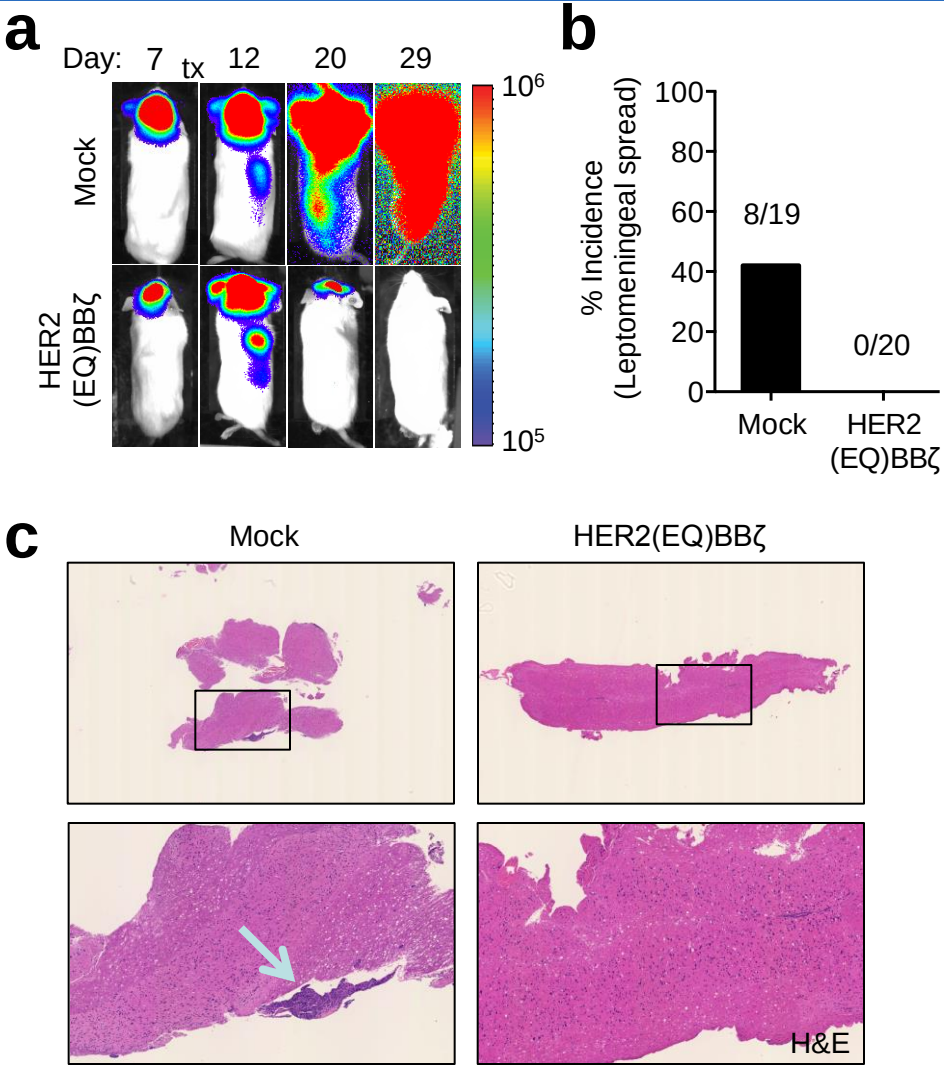
Priceman, et al. *Clin Cancer Res 2018*

Treating Leptomeningeal Disease with HER2-BBz CAR T Cells



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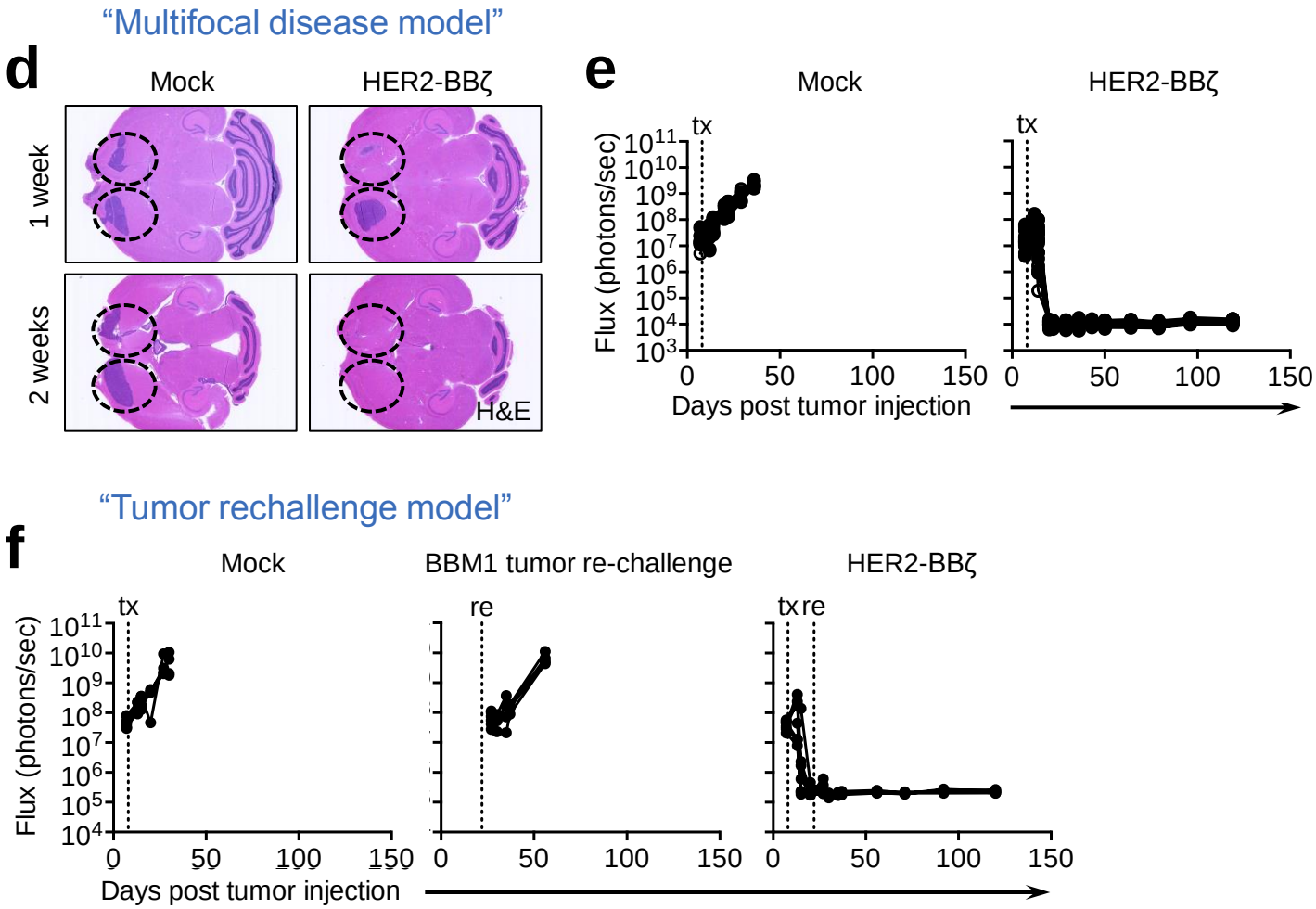
Priceman, et al. *Clin Cancer Res 2018*

Treating Multifocal Disease with HER2-BBz CAR T Cells



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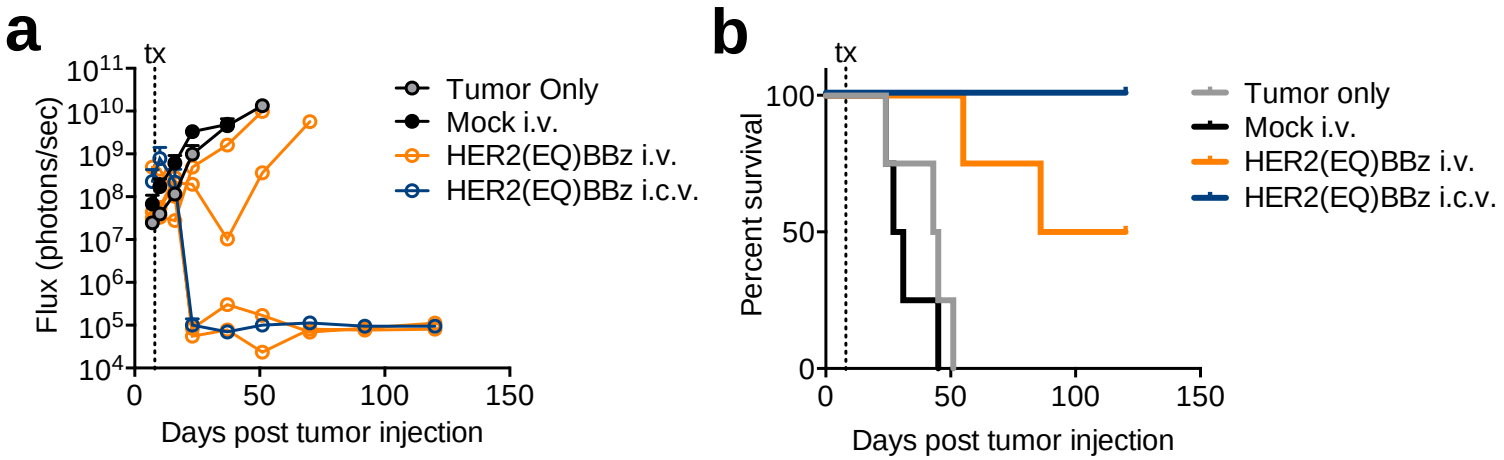
Priceman, et al. *Clin Cancer Res 2018*

Superior Anti-Tumor Activity of Intraventricular Delivery Compared with Systemic



i.c.v. dose: $0.5e^6$
i.v. dose: $5e^6$

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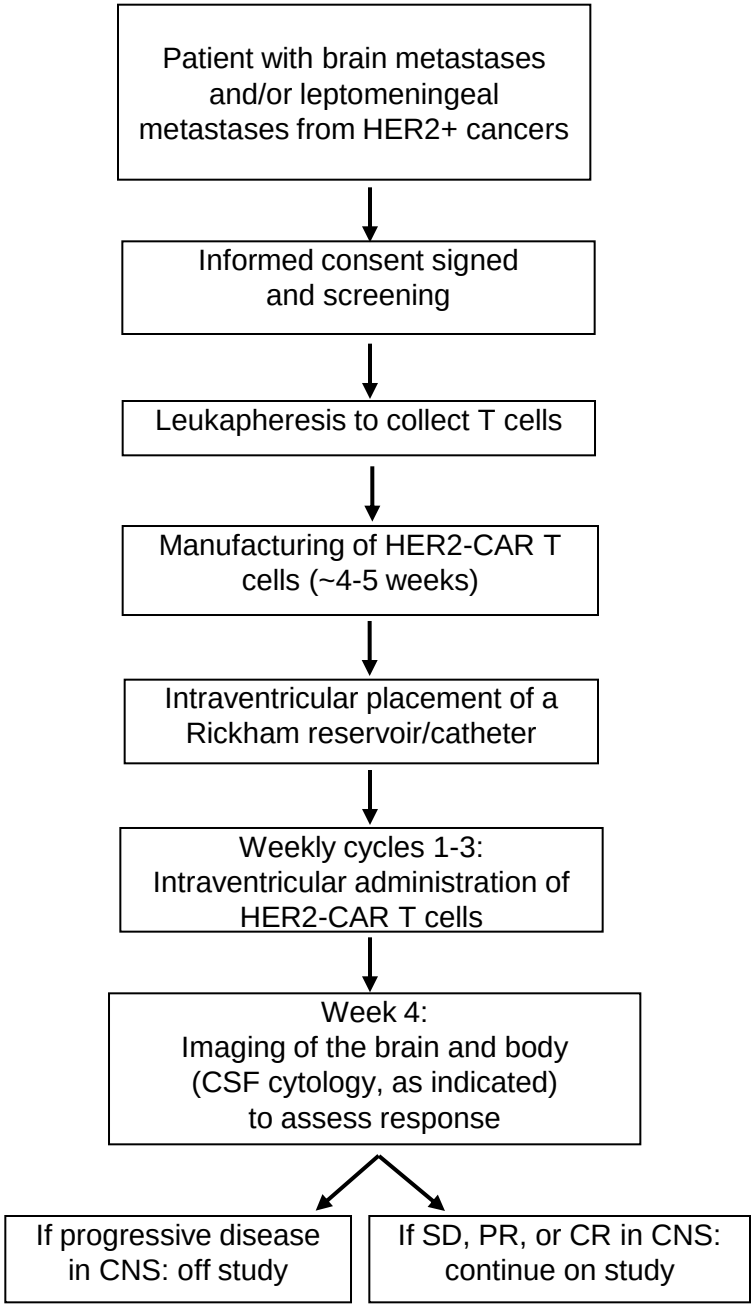
Priceman, et al. *Clin Cancer Res 2018*

IRB# 17237
Study Treatment Schema



HER2-CAR T Cell Dose Escalation

Planned Infusions	**Dose schedule 1de[a]**	**Dose schedule 1**	**Dose schedule 2de[a]**	**Dose schedule 2**	**Dose Schedule 3de[a]**	**Dose schedule 3**
Cycle 1	A: $2x10^6$	A: $2x10^6$	C: $10x10^6$	C: $10x10^6$	C:$10x10^6$	F: $20x10^6$
Cycle 2	B: $5x10^6$	C: $10x10^6$	D: $25x10^6$	E: $50x10^6$	G:$75x10^6$	H:$100x10^6$
Cycle 3	B: $5x10^6$	C: $10x10^6$	D: $25x10^6$	E: $50x10^6$	G:$75x10^6$	H:$100x10^6$
Total Dose	*$12\ x10^6$*	*$22\ x10^6$*	*$60\ x10^6$*	*$110\ x10^6$*	*$160\ x10^6$*	*$220\ x10^6$*
Evaluation/Restaging						
Cycle 4+[b]	$\leq 5x10^6$	$\leq 10x10^6$	$\leq 25x10^6$	$\leq 50x10^6$	$\leq 75x10^6$	$\leq 100x10^6$

[a]de = de-escalation schedule.
[b]After cycle 3, the dose for subsequent cycles of HER2-CAR T cells may be less than the dose specified in Table 1, depending on how much remaining T cell product the patient has.

Estimated sample size: 21 patients

Dose escalation will follow the toxicity equivalence range design of Blanchard and Longmate.

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Primary Objective

Determine the **safety and recommended phase 2 dosing** (RP2D) of intraventricularly (ICV) administered HER2-CAR T cells in patients with brain and/or leptomeningeal metastases from HER2+ cancers.

Secondary Objectives

- Assess for **persistence of HER2-CAR T cells** in CSF and peripheral blood and evidence of **activation of the endogenous immune system** during study treatment and afterwards.

- Describe **changes in cytokine levels** in the CSF and peripheral blood during the study period.

- **In study patients who undergo tumor resection or biopsy** during or after study treatment or when permission for an autopsy is given:
  - Evaluate **T cell persistence & changes in cytokine levels** in the tumor micro-environment
  - Evaluate **HER2 expression levels** pre- and post-treatment with HER2-CAR T cells

- Describe the **CNS clinical benefit & median CNS PFS and OS.**

Main Eligibility Criteria

- Patient has a **histologically confirmed cancer which is HER2+**, defined as 3+ by IHC or gene amplification by FISH.
- Patient has **recurrent brain metastases** after radiation.
- Patients has **recurrent leptomeningeal metastases** after intrathecal chemotherapy. (Concomitant brain metastases are allowed but not required.)
- Age **18 and 75 years old.**
- **KPS ≥ 70.**
- **Life expectancy of ≥ 8 weeks**.

Main Exclusion Criteria

- Patient must be taking **no more than 6 mg/day of dexamethasone** for at least one week prior to undergoing leukapheresis.

- Patient is **unwilling to stop systemic treatment** with chemotherapy or endocrine therapy during the first 3 cycles of HER2-CAR T cell treatment.

Administration of HER2-CAR T Cells

- **Day 1 of each weekly cycle**
  - Collect blood and CSF samples
  - Manually administer the HER2-CAR T and flush over 5 min.

- **Day 2 of each weekly cycle**
  - Assess for toxicity
  - Collect blood and CSF samples

Assessment of Response

- **After the first 3 weekly cycles (DLT period):**

  Brain MRI

  PET/CT scan of brain

  Imaging of systemic disease

- Patients who stay on study treatment, but whose systemic disease is progressing, may start a new chemotherapy or endocrine therapy or resume taking a prior one to control the systemic disease.

- Additional leukapheresis may be needed to manufacture more HER2-CAR T cells, depending on how long a patient remains on study.

Protocol Status

- **Open to accrual**

  1st patient has completed the DLT evaluation period

  2nd patient has started treatment

  Side effects: grade 1-2 fatigue, body aches, low grade fevers lasting for a couple days after CAR T cell administration

  Switching from Tcm to Tn/mem after this first cohort

  T n/mem cells have shown significant improved activity in COH leukemia patients treated with CD19-CARs

- **Future directions**

  Lymphodepletion

  IV + intraventricular administration