



A phase I clinical trial of autologous HER2 CMV bispecific CAR T cells for progressive Glioblastoma

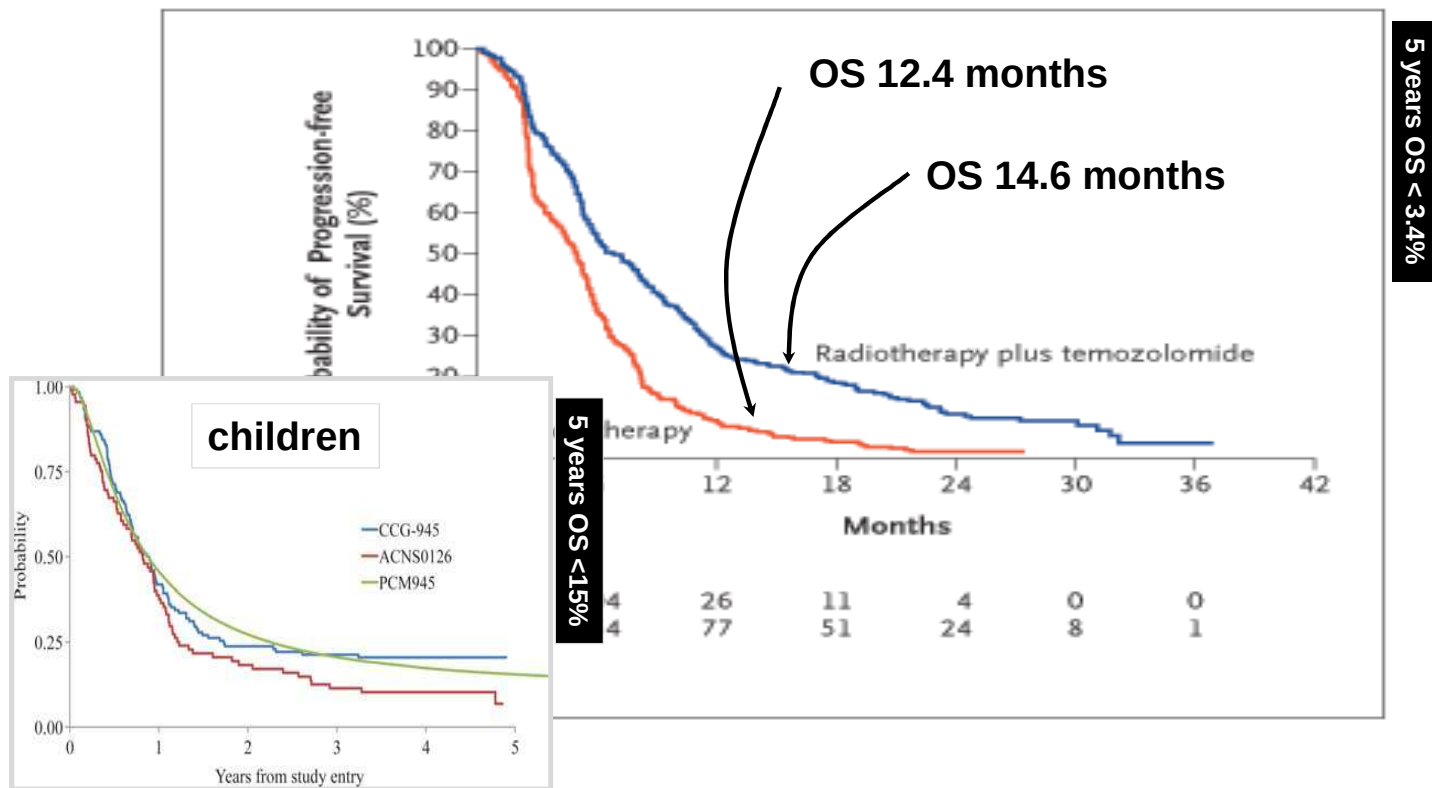
Nabil Ahmed, Vita Brawley, Oumar Diouf, Amada Corder, Aidin Ashoori, Alexia Ghazi, Claudia Gerken, Joanna Yi, Hao Liu, Cliona Rooney, Gianpietro Dotti, Adrian Gee, Robert Grossman, Yvonne Kew, David Baskin, Jonathan Zhang, Pamela New, John Hicks, Suzanne Z Powell, Winfried Wels, Malcolm Brenner, Helen Heslop and Stephen Gottschalk

Disclosure

Collaborative research agreement with [Aurora Biopharma](#) for developing HER2 CAR studies managed by Baylor College of Medicine



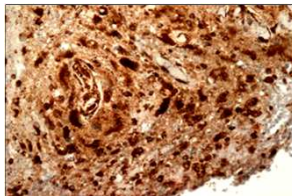
Glioblastoma



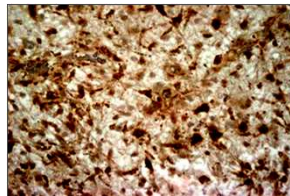
Stupp et al. *NEJM* 2005.

Targeting HER2 in GBM

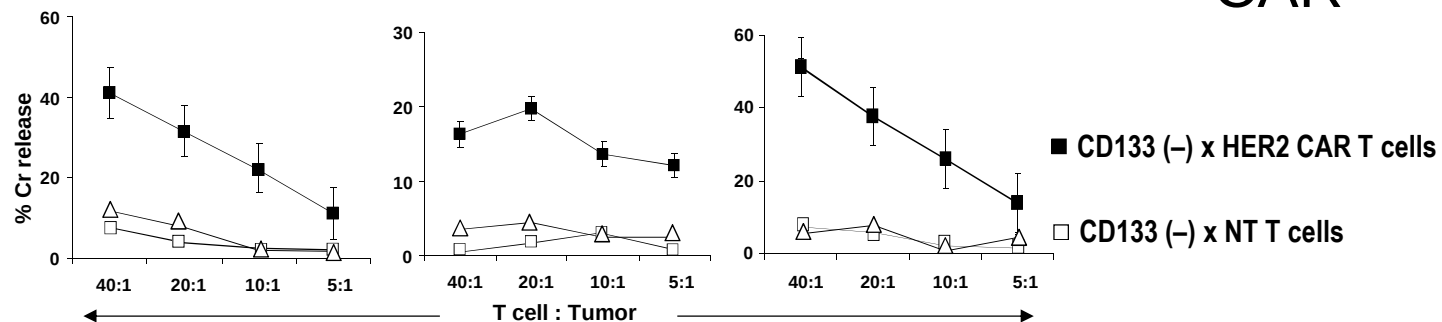
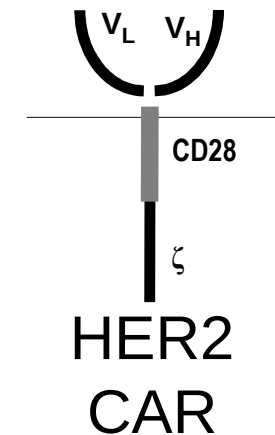
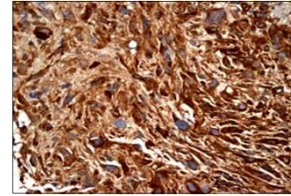
Patient 1



Patient 2

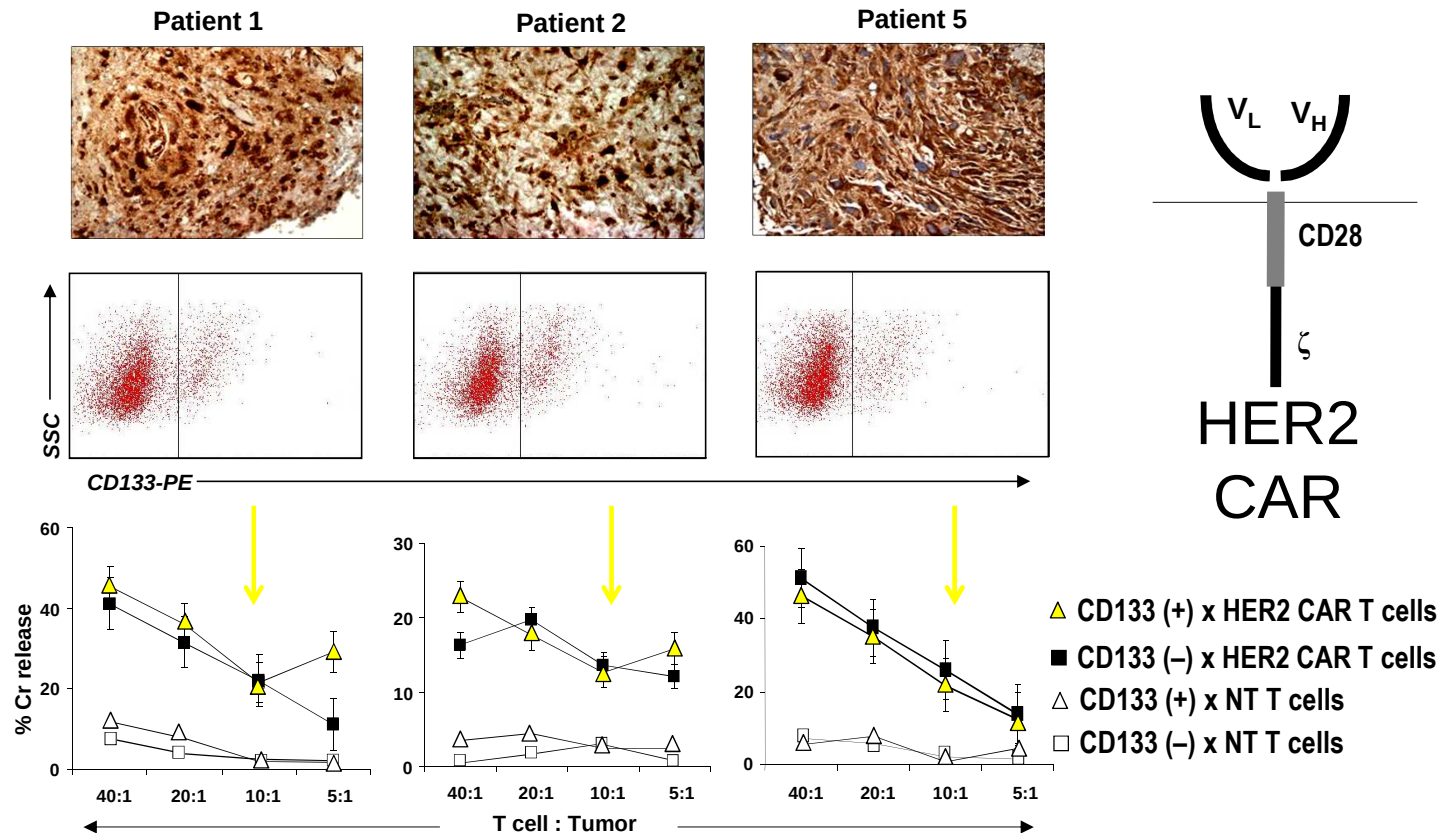


Patient 5



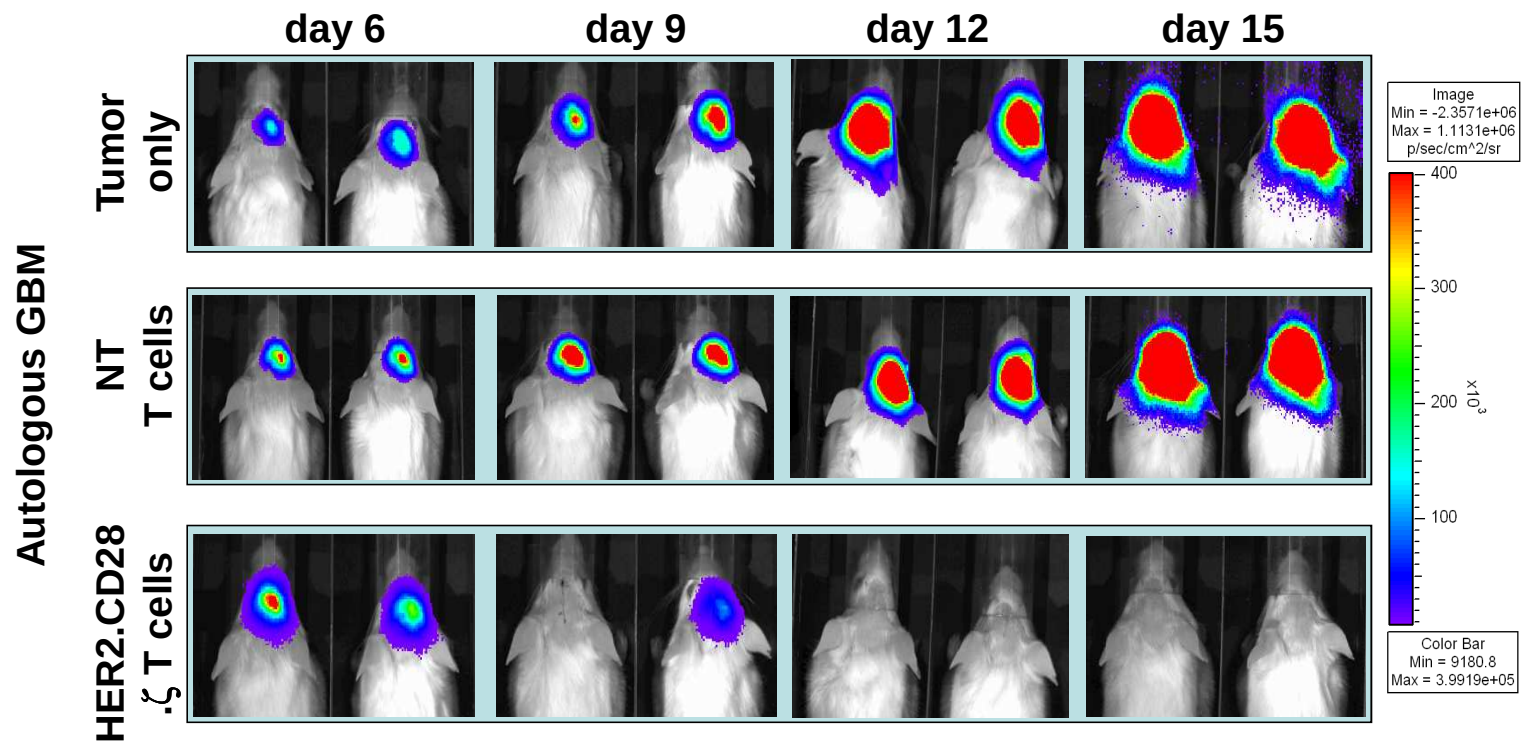
Wels et al. *Biotech* '92; Ahmed and Salsman et al. *Clin Can Res* 2009

Targeting HER2 in GBM



Wels et al. *Biotech* '92; Ahmed and Salsman et al. *Clin Can Res* 2009

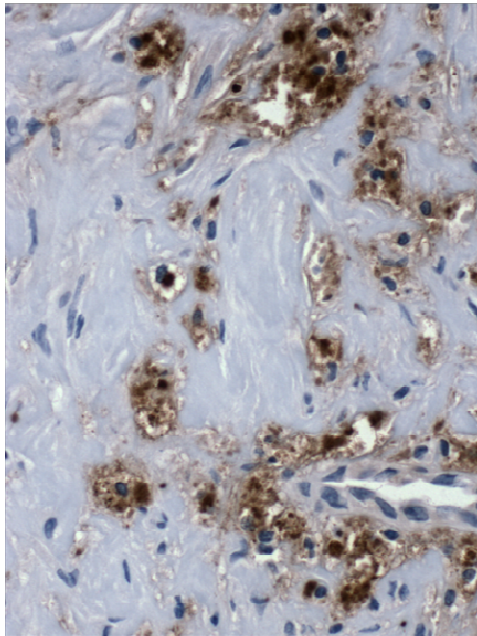
Regression of Autologous GBM



CMV and GBM

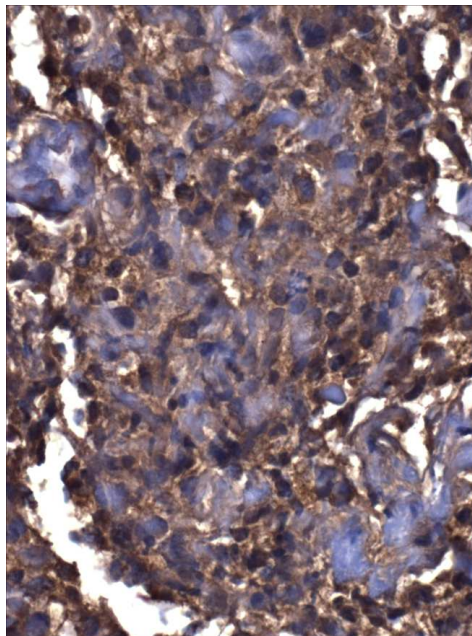
An Evolving Relationship

CMV_{pp65}

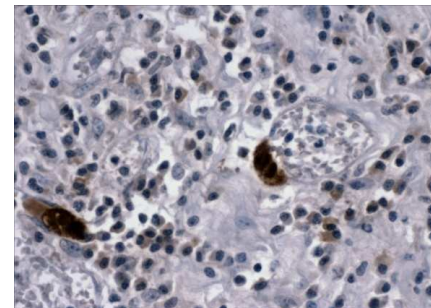


11/22 (50%)

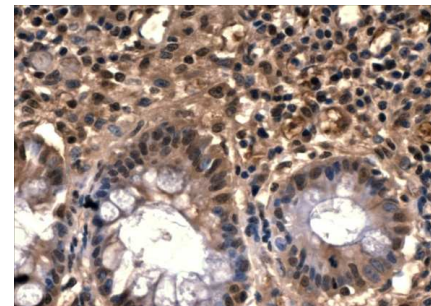
CMV_{IE1-72}



19/22 (86%)



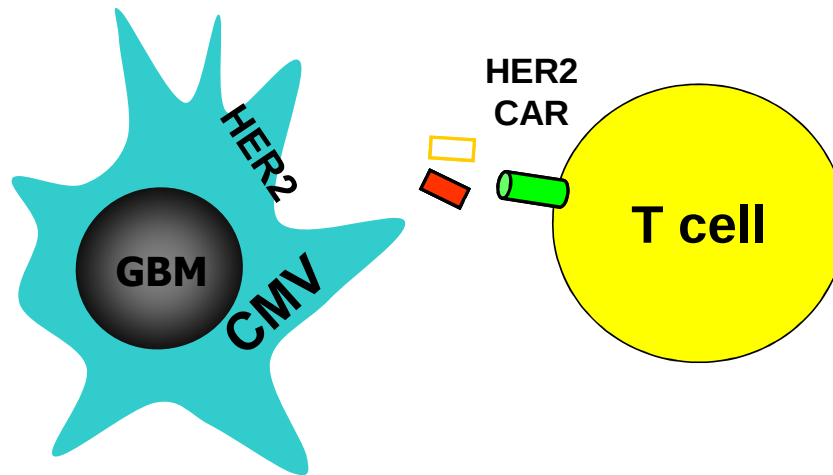
+ CMV_{pp65}



+ CMV_{IE1-72}

Scheurer. Act Neuropath '08; **Cobbs.** Can Res '03; **Mitchelle.** Neoronc '08
Ghazi. J ImmRx 2012; Pediatric data by **Corder** et al (in review)

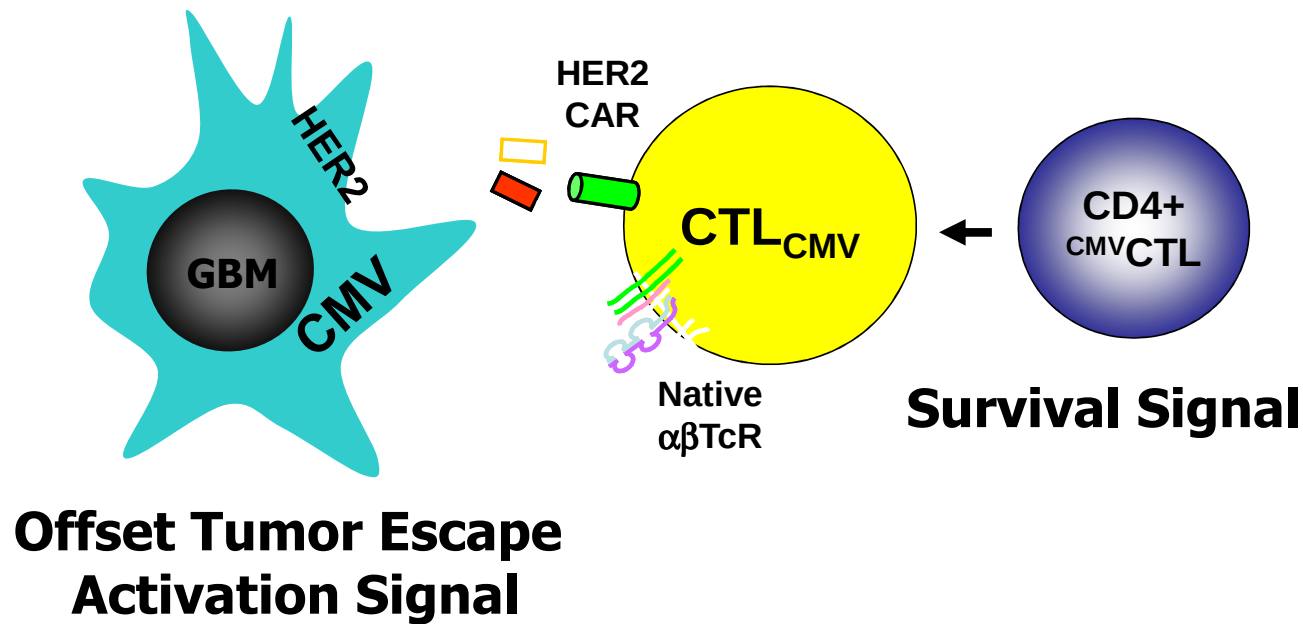
Rationale



Rossig et al. *Blood* 2002; Savoldo et al. *Blood* 2007; Pule et al. *Nat Med* 2008

HERT-GBM

HER2 CAR CMV T cells in GBM patients



HERT-GBM: NCT01109095

HERT-GBM: *objectives*

Primary

Safety

Secondary

Persistence of infused T cells

Anti-tumor activity of T cells

HERT-GBM: *eligibility*

Subject

Progressive GBM
CMV seropositive
KPS/LPS ≥ 50

Tumor

HER2 +

T cells

$\geq 15\%$ HER2 CAR
 $\geq 20\%$ killing

No therapy

≥ 4 wk before

≥ 6 wk after

Organ functions

Birth Control

Consent

Excluded

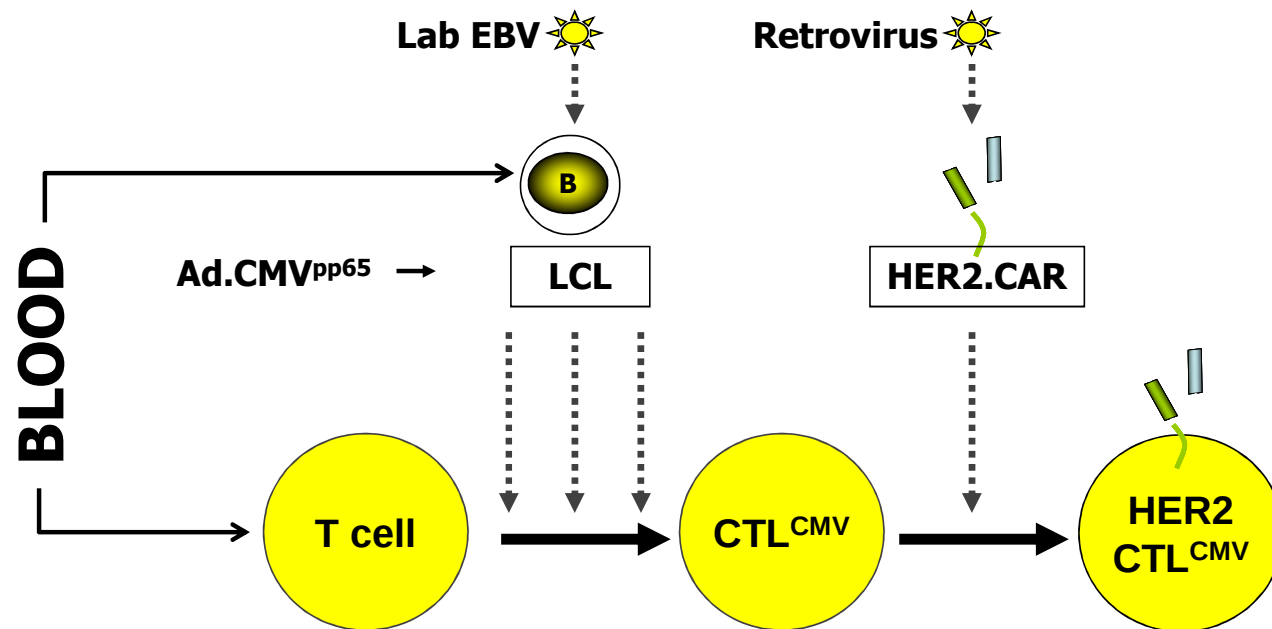
- HIV
- Infection
- Pregnancy
- Lactation
- Murine Allergy

Subjects

UPN	Age	Sex	Surgery	XRT	+TMZ	Salvage Therapies	Investigational
1	45	F	3	+x 5	+	5	2
2	60	M	1	+	+	1	0
3	30	M	1	+x3	+	2	1
4	18	M	NO	+	+	0	0
5	64	M	2	+	+	2	0
6	61	F	2	+	+	4	2
7	63	F	1	+	+	1	1
8	11	M	1	+	NO	0	0
9	65	M	2	+	+	0	1
10	51	F	1	+	+	1	0
11	64	M	1	+	+	0	0
12	14	M	2	+	+	1	0
13	71	F	1	+	+	0	0
14	16	M	1	+	+	0	0
15	15	F	2	+	NO	2	1
16	11	F	4	+	NO	0	0
17	17	F	2	+	+	1	0

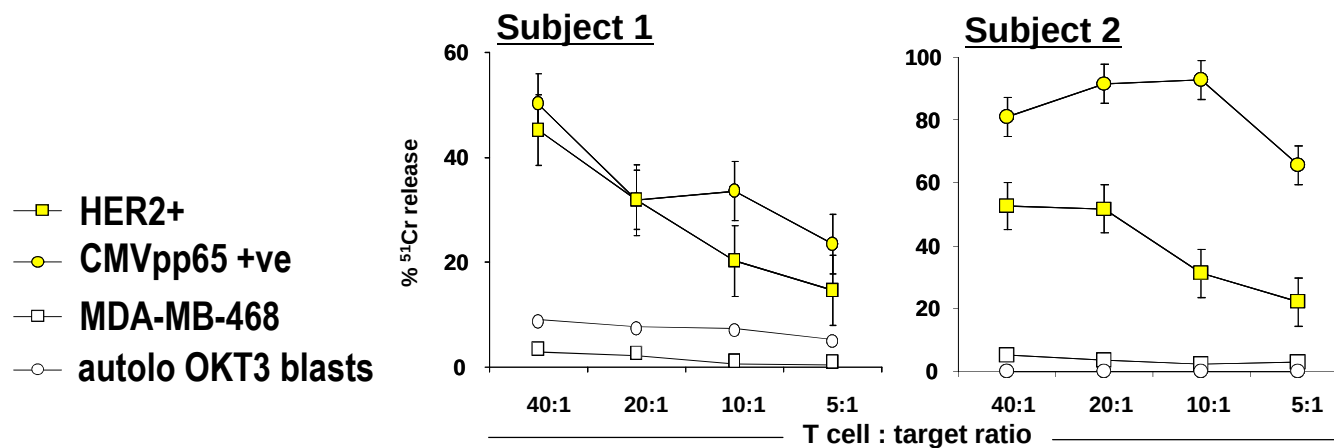
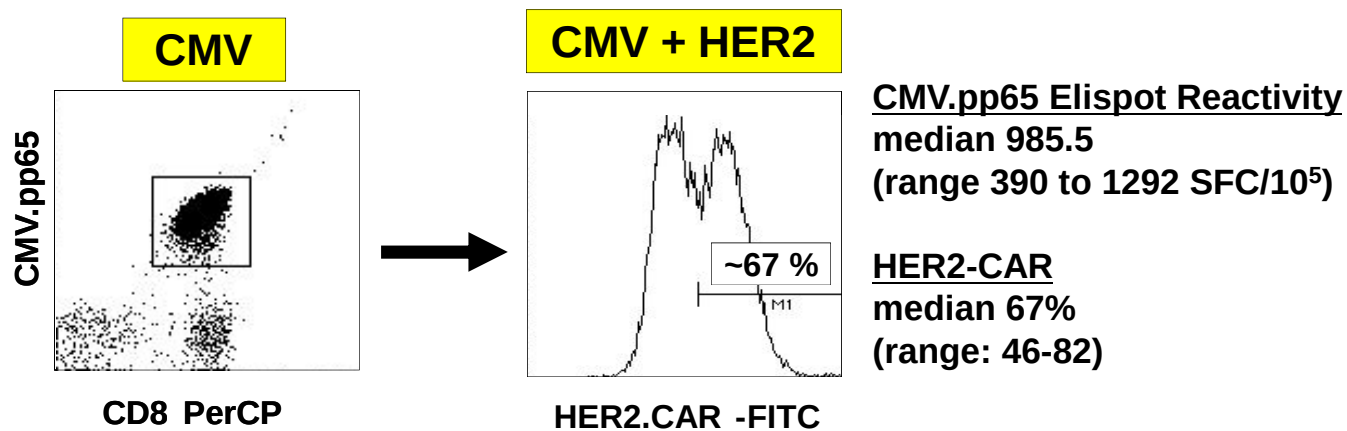
57/14

HERT-GBM: *product generation*



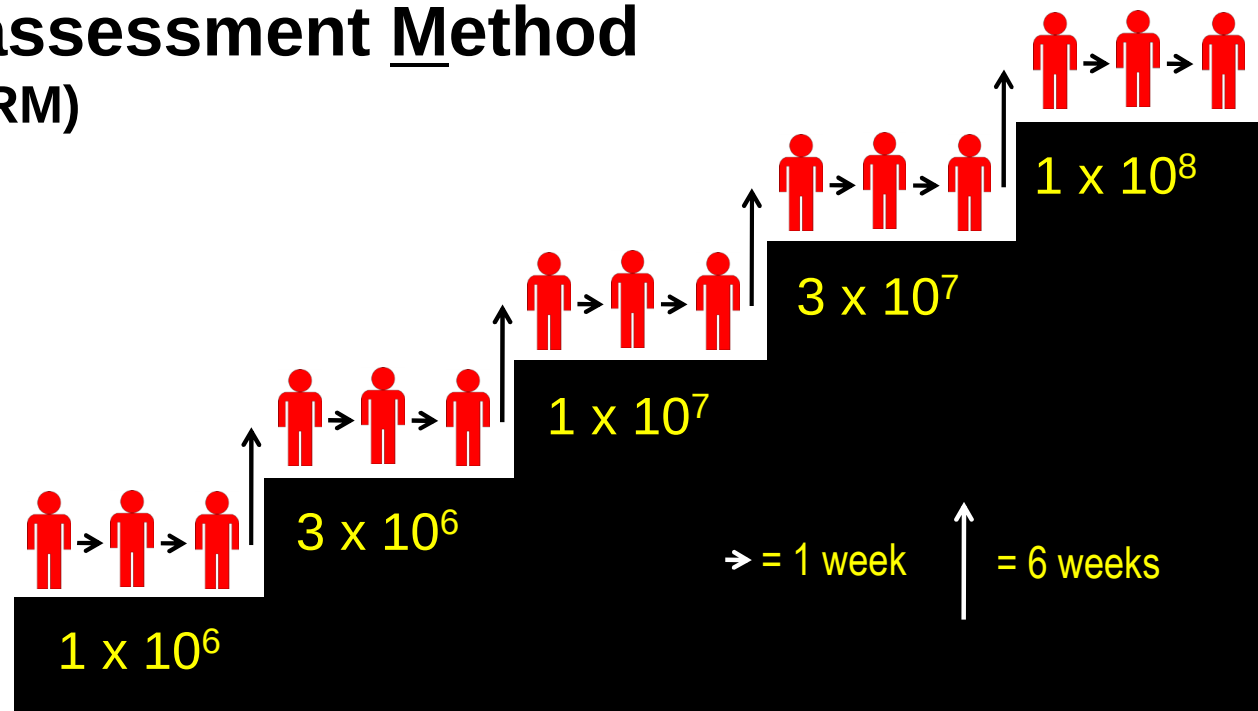
Rooney et al. *The Lancet* 1995; Pule et al. *Nat Med* 2009; Ghazi et al. *J ImmunoRx* '12

HERT-GBM: *bispecificity*

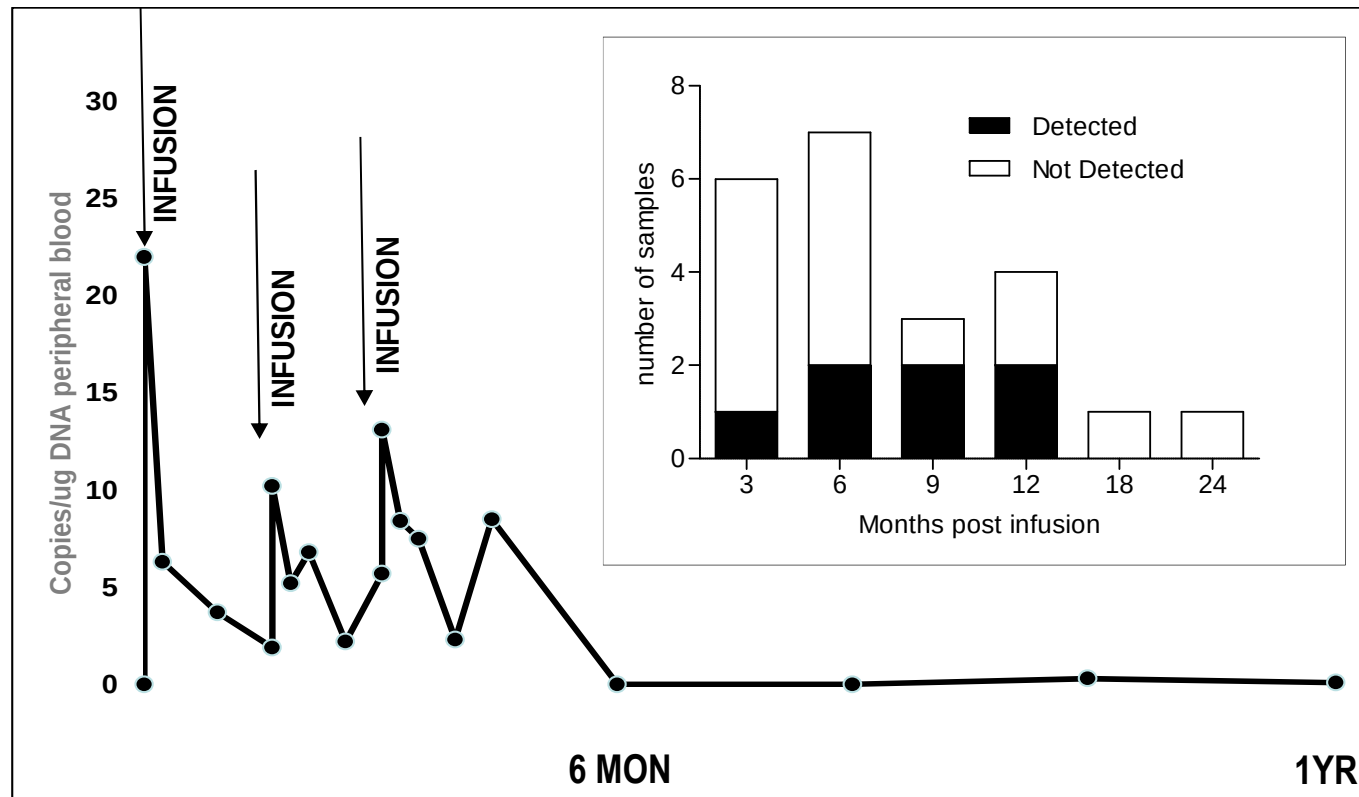


Escalation Design

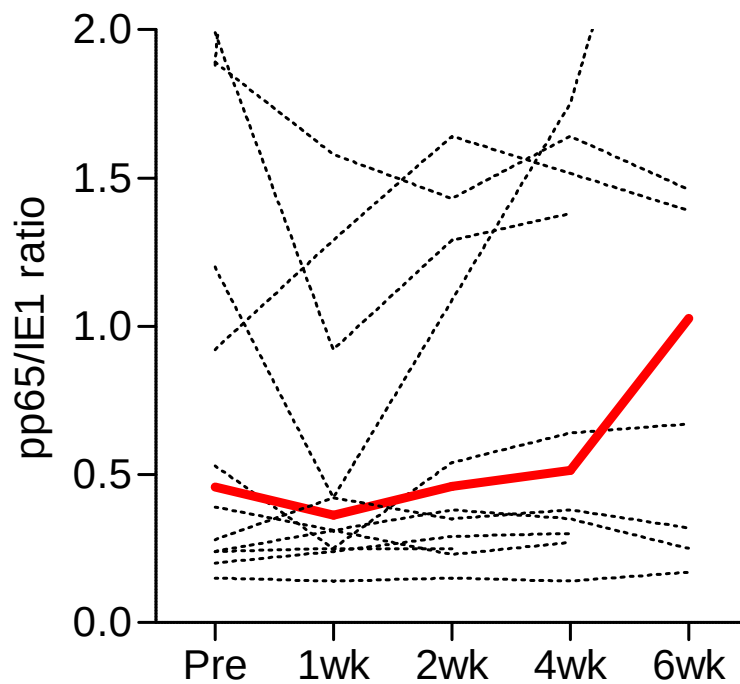
- Phase I dose escalation
- modified Continual Reassessment Method (mCRM)



CAR T cell Persistence

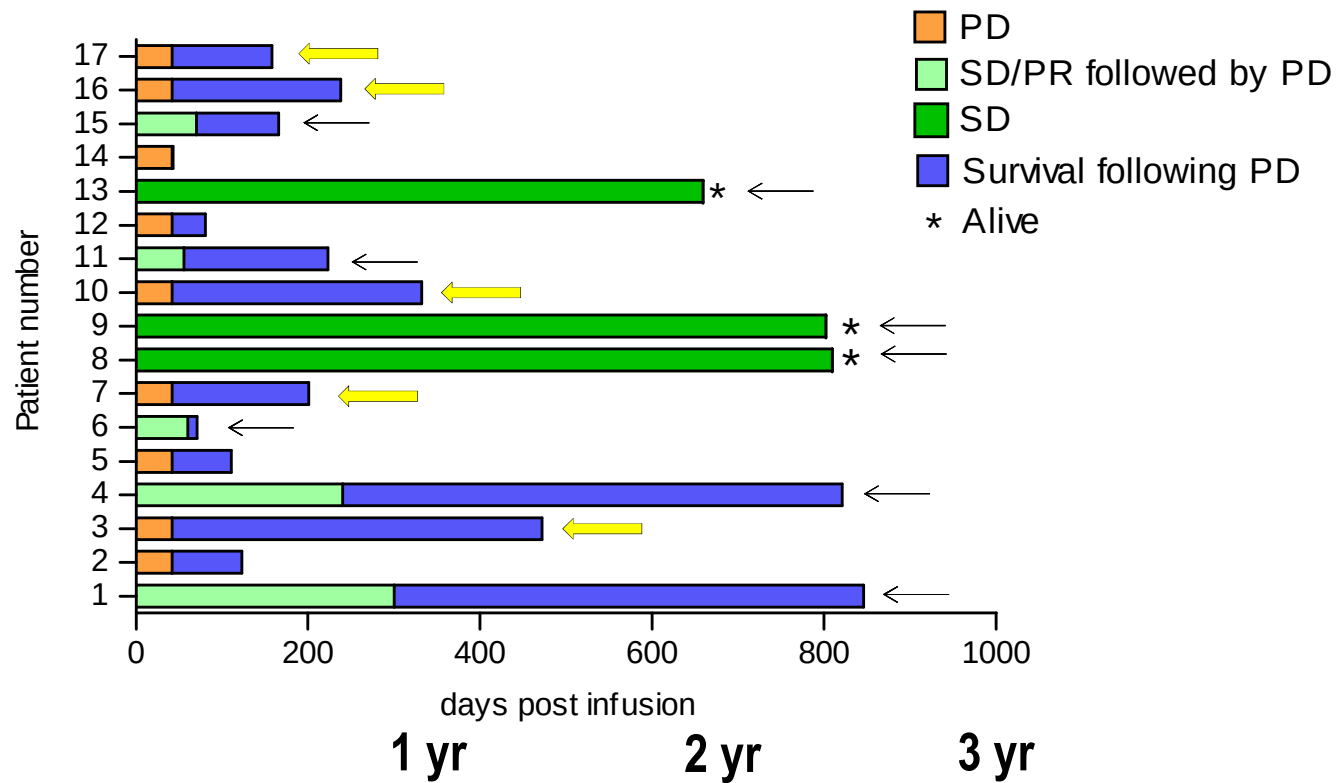


CMV Immune Reconstitution



→
**Data past 6 weeks
pending**

Outcomes

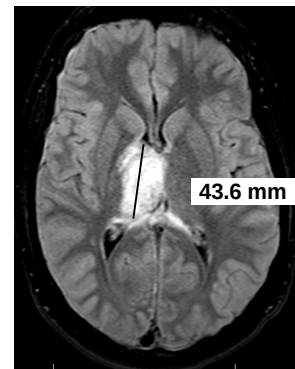


17 year old male

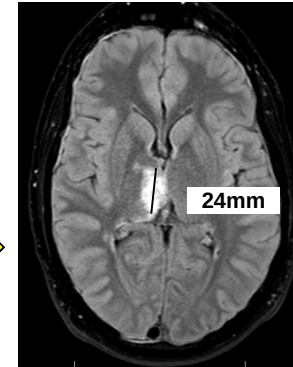
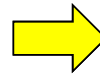
Thalamic tumor

Unresectable

Dose Level 2



DL2



MRI

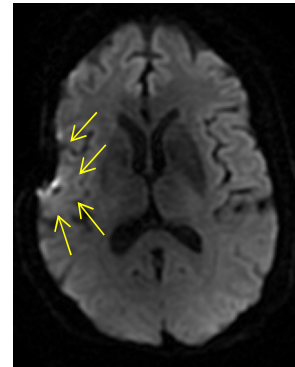
10 months

71 year old female

Parieto-temporal

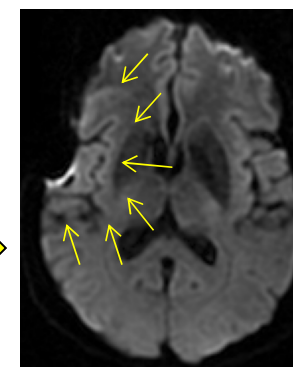
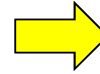
GTR → Progressed

Dose Level 4



DL4

x2



>24 months

15 year old female

Fronto-caudate

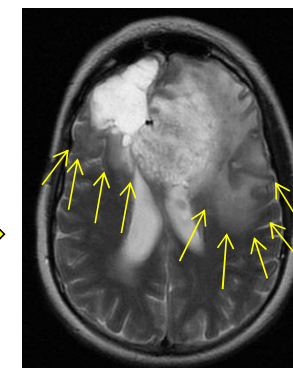
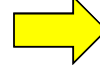
Debulk → Progressed

Dose Level 5



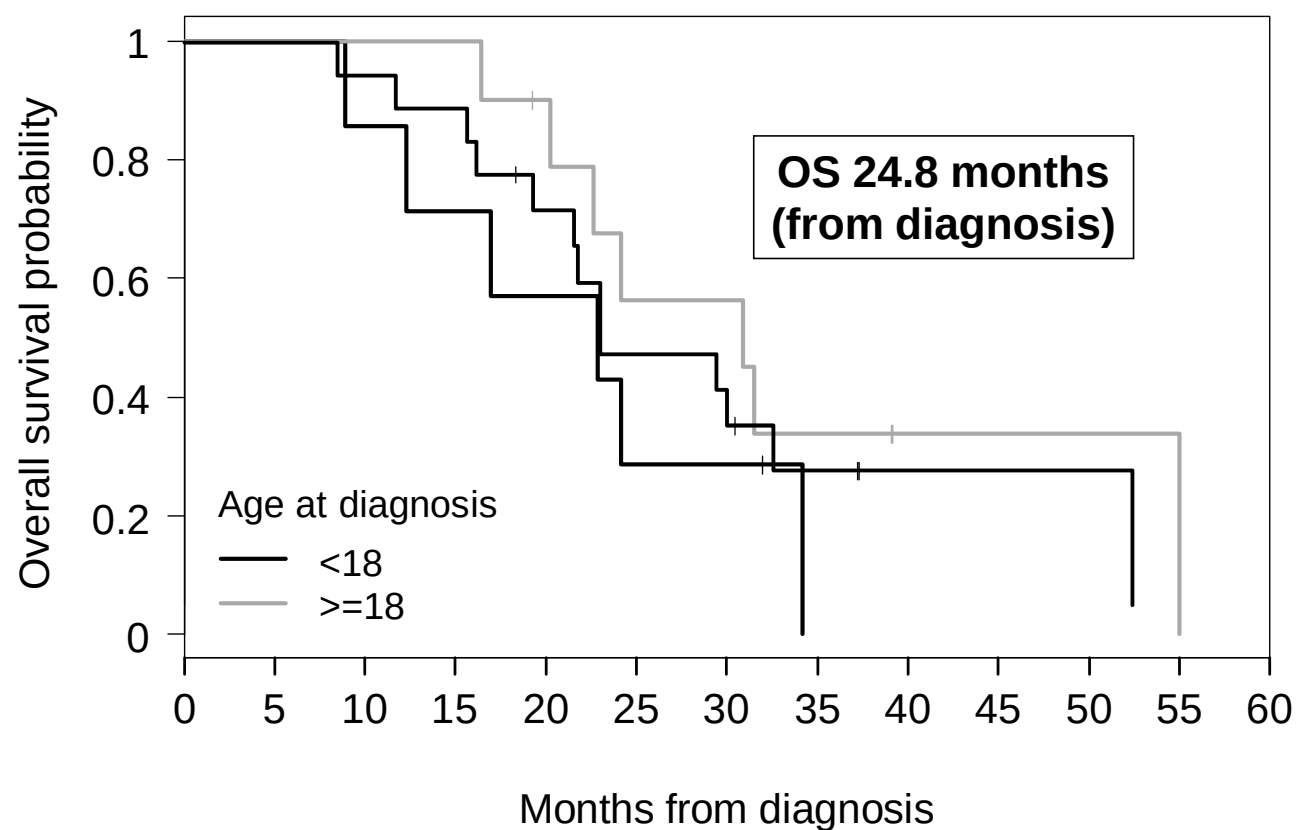
DL5

x2

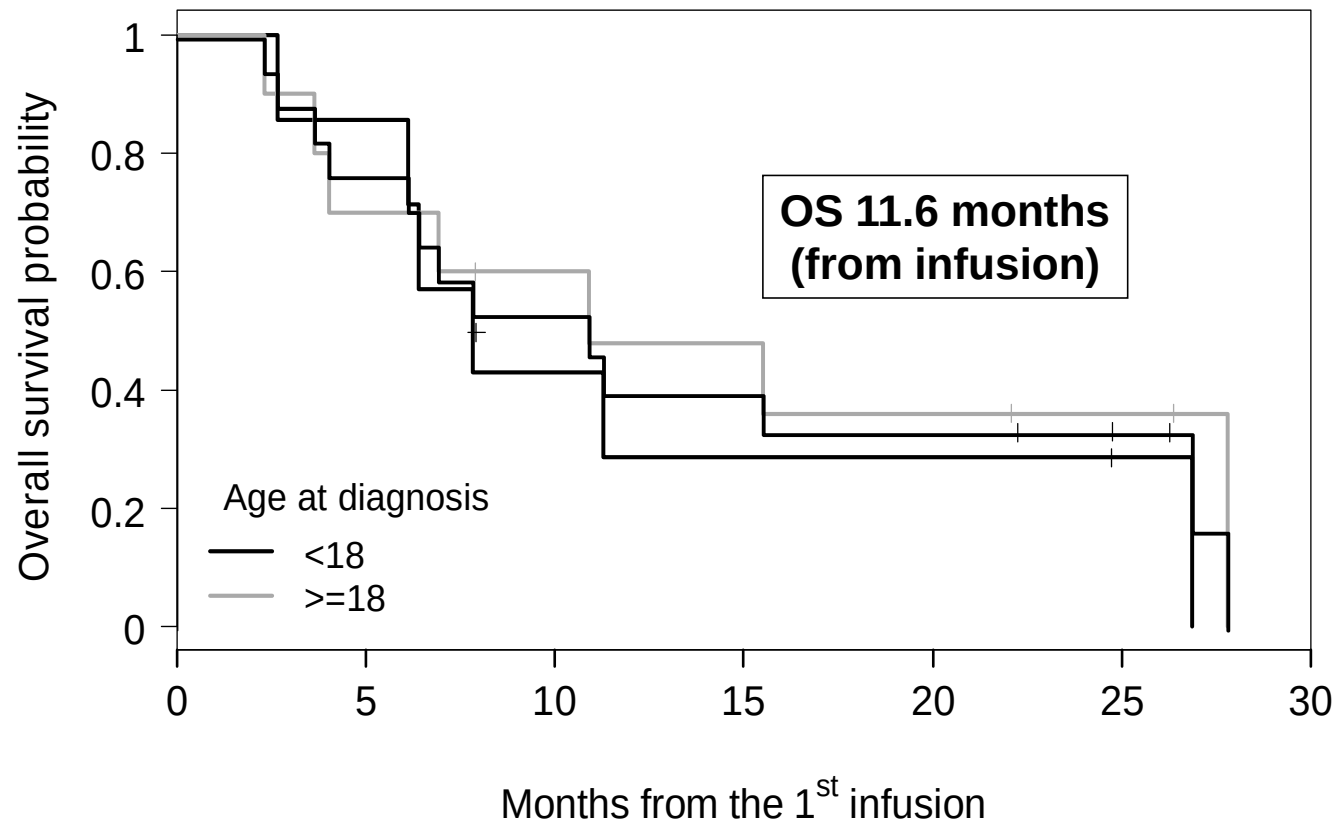


>5 months

Survival from Diagnosis



Survival from 1st Infusion



HERT-GBM: *summary*

Intent-to-treat: 20 lines; 17 subjects 5DL

- **Severe Adverse Events** *none*
- **Cytokine Release Syndrome** *none*

Efficacy

1/16 unevaluable

8/16 (50%) PD

8/16 (50%) SD (7/16) or PR (1/16)

3/16 (19%) LTS >30 months

Future

- **Optimizing T cell Expansion v2.0**
 - HDC Conditioning
 - CTX 30 mg/kg/day on day -7, -6
 - Flu 25 mg/m²/day day -5 to -1
- **Rapidly generated HER2 CAR^{CMV}CTLs**
 - pp65 and IE1 peptide pulsing (Ann Leen)
- **Intracranial Delivery (iCAR-GBM)**
primary HER2 CAR T cells [NCT 02442297](#)

Acknowledgments

THE PATIENTS

Stephen Gottschalk

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Houston Methodist Hospital

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Georg Speyer Haus (J Koch; W Wels)

