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CAR-T-cell therapies in pediatric solid cancers

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Discussant: **Dr Paula Perez Albert**, Young SIOPE Educational Group member, Sant Joan de Deu Hospital, Barcelona, Spain

Discussant: **Dr Roelof van Ewijk**, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

CAR-T-cell therapies in pediatric solid cancers

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DISCLOSURES

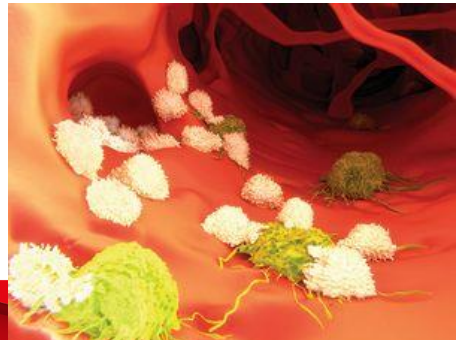
Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Miltenyi					X		
Bellicum	X				X	X	
Amgen					X	X	
Medac					X		
Neovii					X	X	
Novartis						X	
Sanofi						X	
Gilead					X		
BluebirdBio					X		

Advantages of immunotherapy

- Activated immune cells recognize and target remote areas of cancer cells that traditional surgery cannot access
- Stimulated immune system cells will not necessarily target only cells that rapidly divide
- Stimulated cells target cancerous growths and tissues more specifically while leaving healthy surrounding tissue intact and healthy
- Fewer or less devastating side effects than traditional therapies
- Memory cells can prevent cancer from returning after its initial treatment

Immunotherapy strategies

- **Checkpoint inhibitors (Nivolumab, Ipilimumab…)**
  - → Releasing the brake on T-cells
- **Antigen-specific antibodies (Blinatumomab…)**
  - → Making the tumor cells visible by the T cells
- **Gene-modified T-cells (CAR-T cells)**
  - → Redirecting and activating the T cells toward the tumor cell
- **Oncolytic viruses**
  - → Activating host immune response against infected cells
- **And much more… (cancer vaccines…)**



Main toxicities: CT vs CAR-T

CHEMOTHERAPY

SHORT-TERM
- Mucositis
- Cytopenia
- Infections
- Nephrotoxicity
- Hepatotoxicity
- Cardiac toxicity

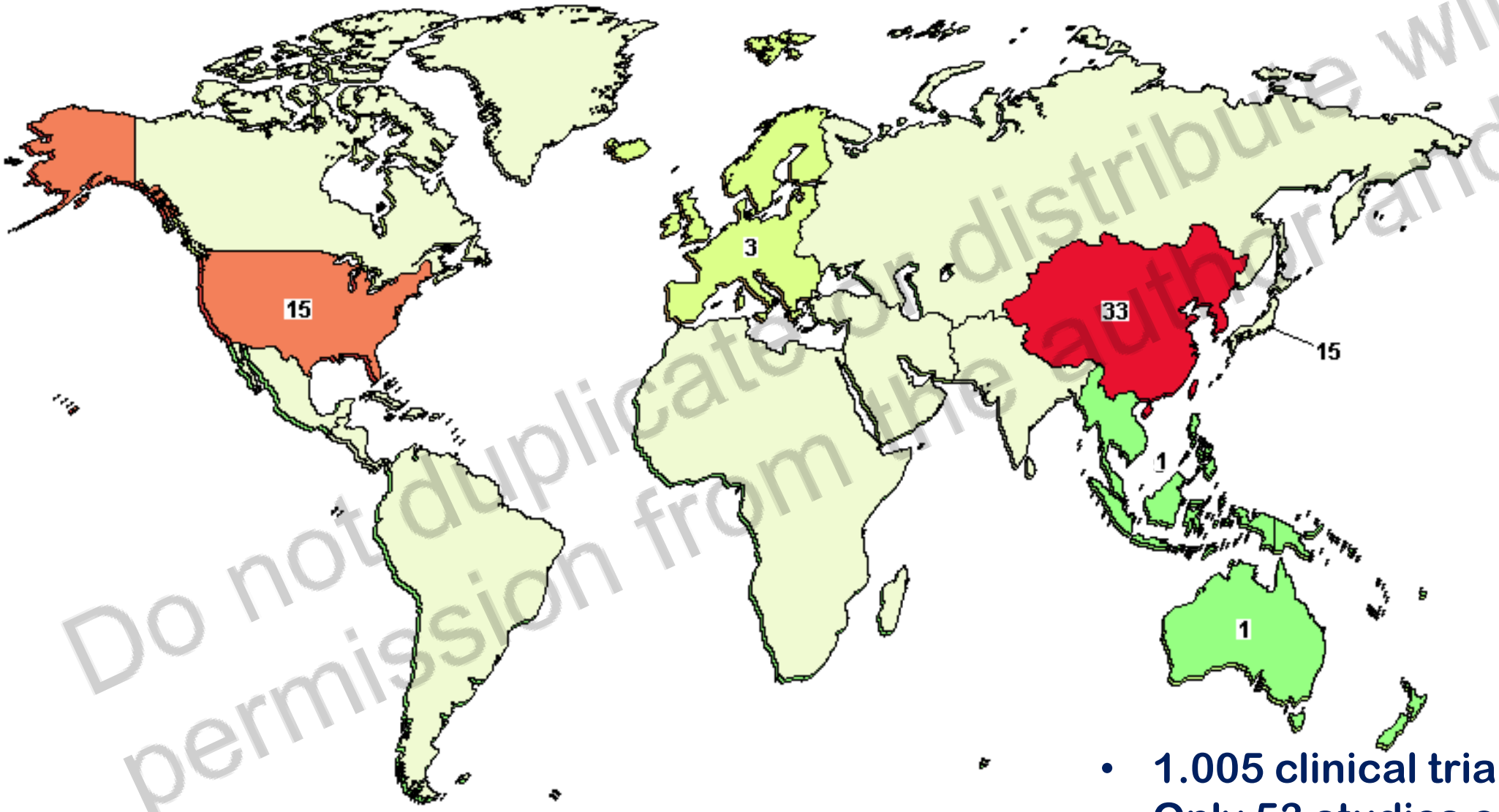
LONG-TERM
- Cardiac toxicity
- Endocrinopathy
- Obesity
- Respiratory
- Fertility issues
- Neurocognitive deficits
- Seizures
- Hearing/vision loss

CAR-T

SHORT TERM
- Cytokine release syndrome (day 1-10)
  - Fever
  - Malaise and fatigue
  - Hypotension
  - Nausea/vomiting, diarrhea
  - Cardiovascular failure
  - Respiratory Failure
- Cytopenia, sometimes prolonged
- Neurotoxicity (day 7-14)
- Pain

LONG TERM
- ?

Adoptive CAR-T cell therapies

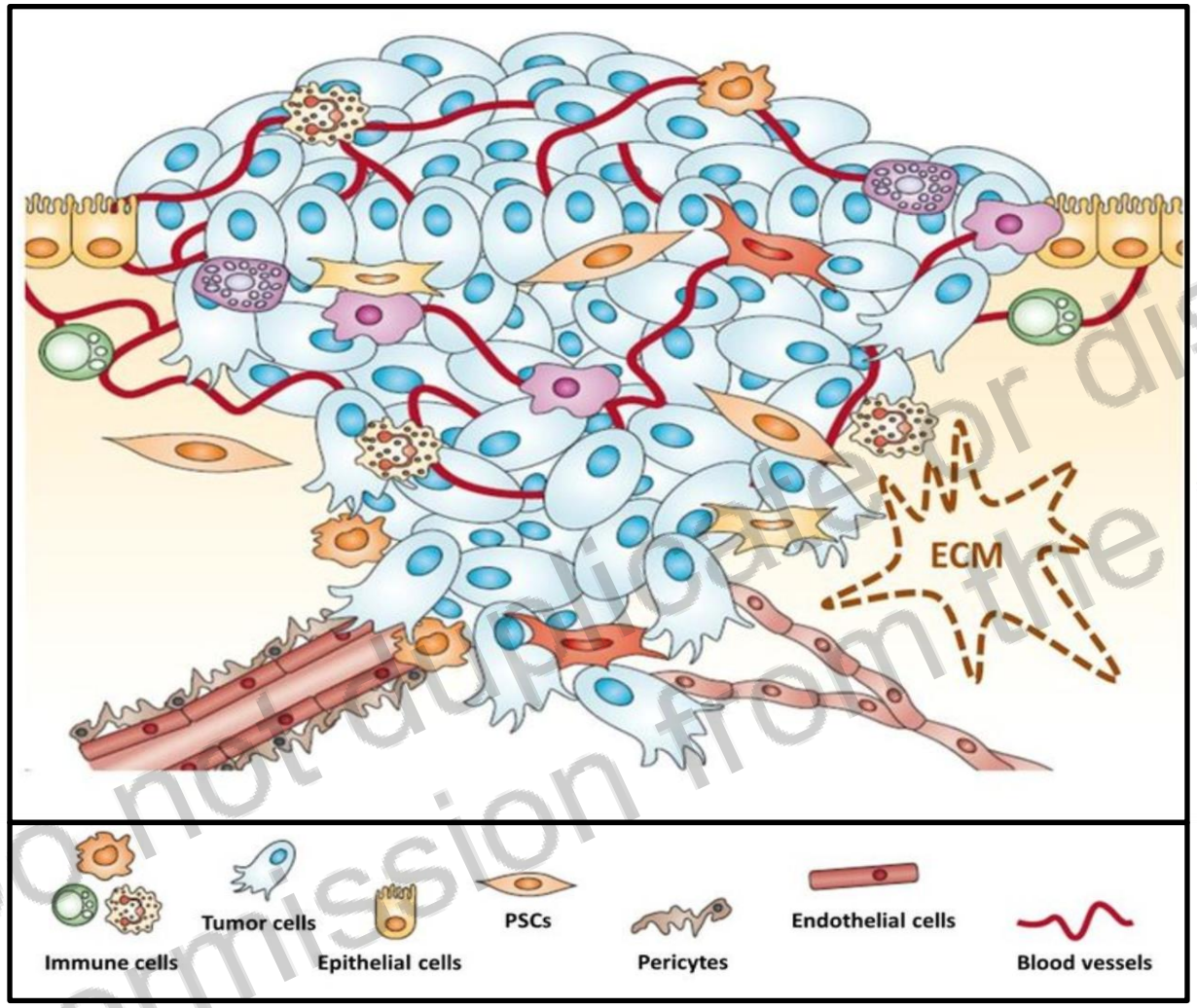


- 1.005 clinical trials in the World
- Only 53 studies on solid tumors…

Active Clinical TRIALS on CAR T cells in pediatric setting

	Indication	Route of administration	Distinctive features	Center
CD171	Neuroblastoma	Systemic	tEGFR	Seattle Children's Hospital
EGFRvIII	Recurrent Glioblastoma/-sarcoma	Intracerebral	radiolabeling (111In) of CAR T	Duke
	Glioblastoma/-sarcoma	Systemic	radiolabeling (111In) of CAR T	Duke
	Glioblastoma/-sarcoma, Brain Cancer	Systemic	IL-2 administration	NCI
GD2	(r/r) Neuroblastoma/bone sarcoma	Systemic	iCas9	**Bambino Gesù Hospital, Rome**
	Neuroblastoma	Systemic	NK T cells, IL-15 administration	Texas Children's Hospital
	r/r Neuroblastoma	Systemic		UCL, Great Ormond Street Hospital for Children
	Diffuse Intrinsic Pontine Gliomas(DIPG) & Spinal Diffuse Midline Glioma(DMG)	Systemic		LPCH Stanford
	(r/r) Neuroblastoma or Osteosarcoma	Systemic	IL15 in CAR vector	University of North Carolina
	GD2-expressing Brain Tumors Neuroblastoma	Systemic	Costitutive IL7R	Texas Children's Hospital
GPC3	Pediatric Solid Tumors	Systemic		Texas Children's Hospital
HER2(ErbB2)	r/r Pediatric CNS Tumors	Intracerebral	tEGFR	Seattle Children's Hospital
	r/r Glioblastoma	Intracerebral	tCD19	City of Hope Medical Center
	r/r Glioblastoma	Intracerebral		Houston Methodist Hospital
	Sarcoma	Systemic		Houston Methodist Hospital
IL13Rα2	Glioblastoma, r/r Brain Neoplasm	Intracerebral	tCD19	City of Hope Medical Center

The next great challenge



1) Identification of suitable target antigens, selectively or preferentially expressed by tumor cells

2) Escape from the immune depotentiating activity of tumor microenvironment

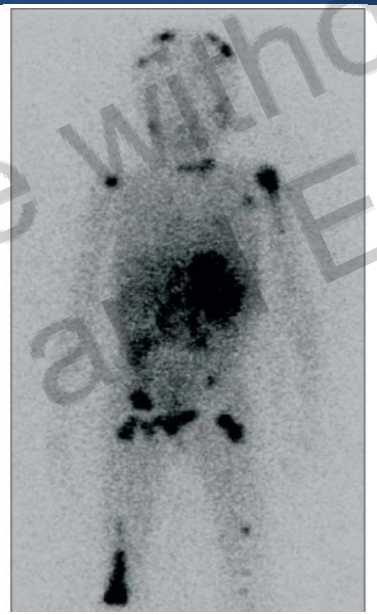
3) Penetration of CAR T cells in the tumor mass

4) Survival into the hypoxic tumor environment

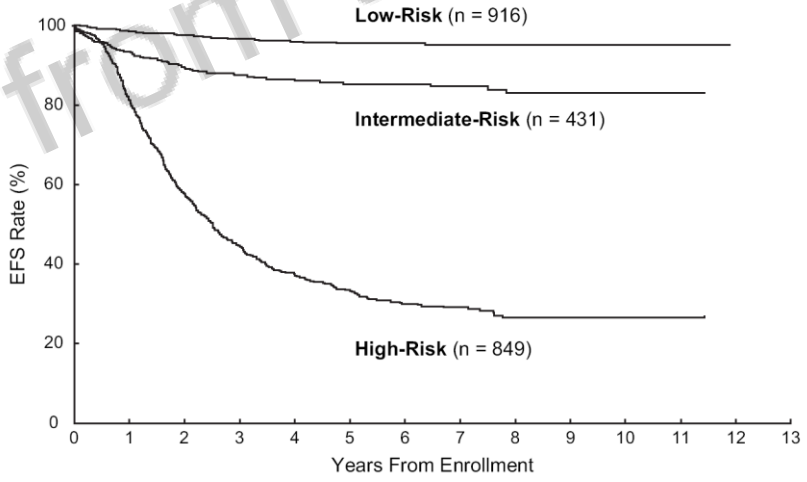
5) Long-term persistence of CAR T cells

Neuroblastoma (NB)

1. **The most common malignant extracranical solid tumor of childhood**
2. **Derived from the sympathetic nervous system**
3. **Present as an abdominal mass originating from the adrenal gland but the neck, chest and pelvis are other common sites of origin**
4. **Metastatic evolution is frequently observed**



The prognosis of High-Risk Neuroblastoma remains poor



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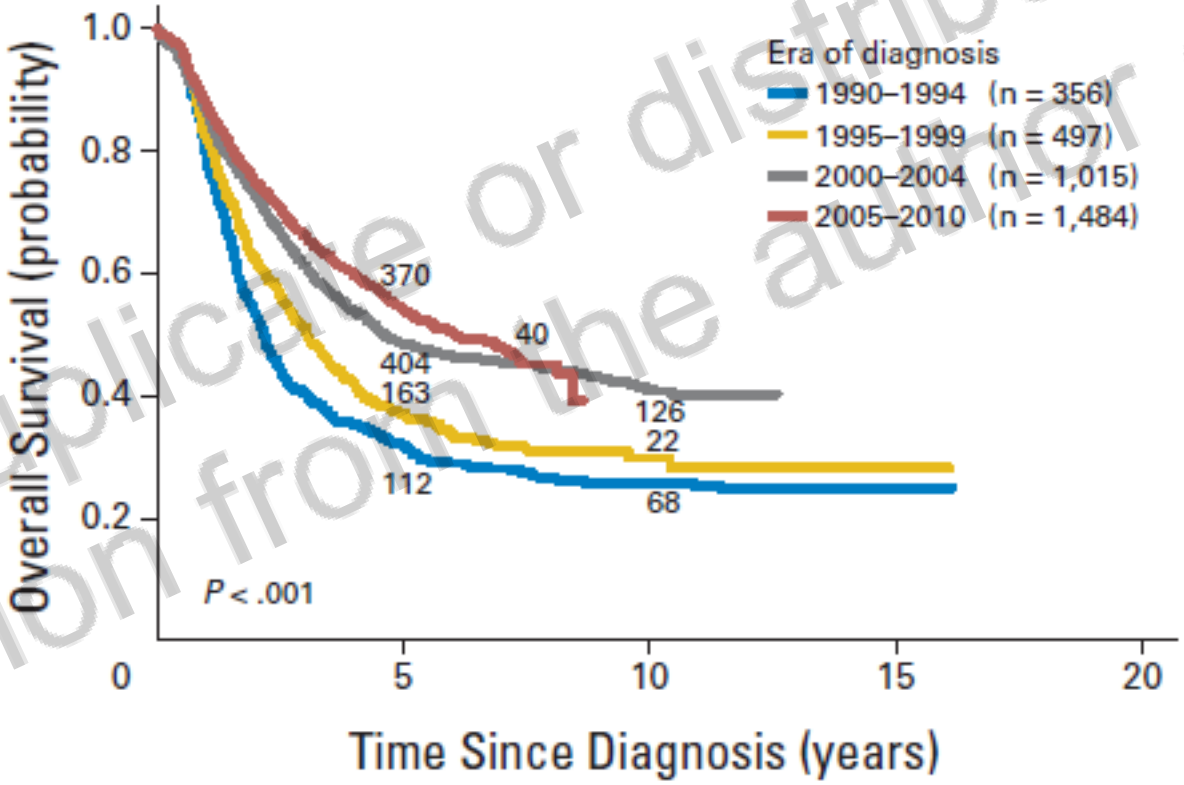
High-Risk Neuroblastoma: need for innovative therapeutic approaches



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Pinto NR et al. JCO 2015

GD2-CAR T cells and Neuroblastoma

GD2-CAR Construct	Cell platform	Outcome	Ref
1st generation	Autologous EBV CTLs + ATLs	- Minimal CAR T expansion - 3 CR - No neurotoxicity	Pule MA, Nat Med 2008 Louis CU, Blood 2011
3rd generation (CD28.OX40)	Autologous ATLs	- CAR T expansion - No objective response - No toxicity	Heczey A, Mol Ther 2017
2nd generation (CD28)	Autologous ATLs	- CAR T expansion - 3 reduction of soft tissue and bone disease - No toxicity	Straathof K, Sci Transl Med 2020
2nd generation (CD28) + IL15	Autologous NKT	- CAR NKT expansion - 2 SD, 1 PR - No toxicity	Heczey A, Nat Med 2020

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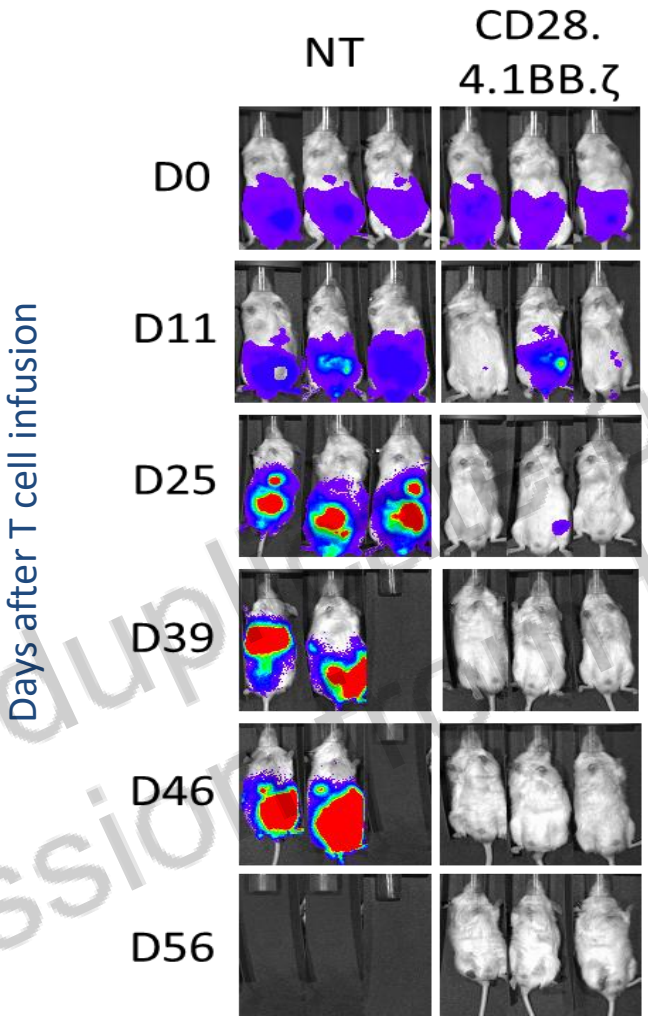
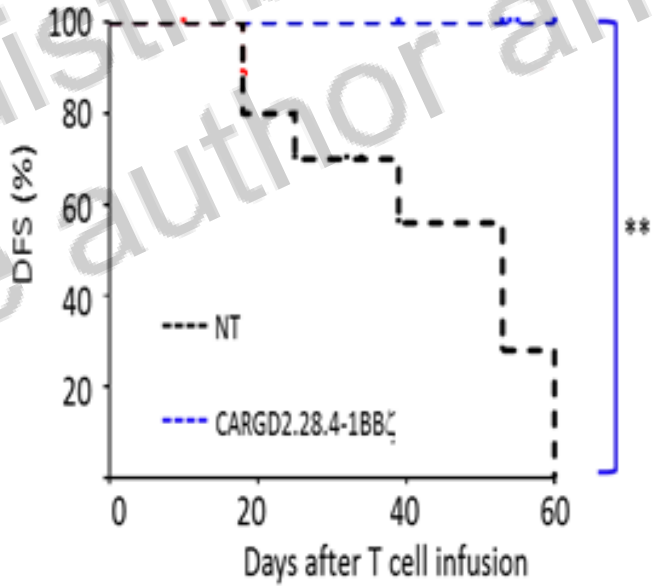
IN VIVO ACTIVITY OF IIICAR.GD2 T CELLS





Quintarelli C, et al. Oncoimmmunology 2018

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Inclusion criteria for treatment

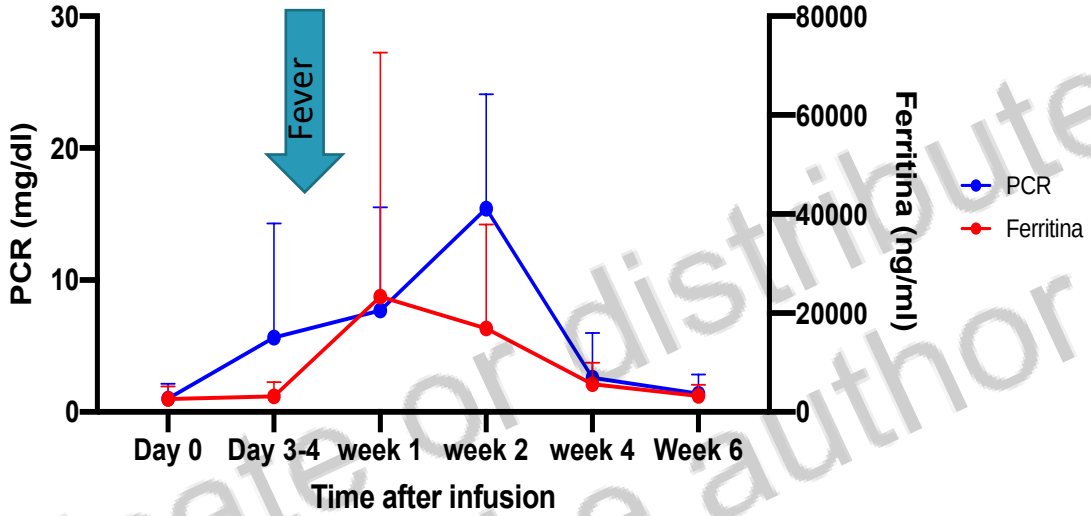
- Diagnosis of High-Risk NBL that have been treated with frontline therapy and is judged to be incurable (phase I and II)

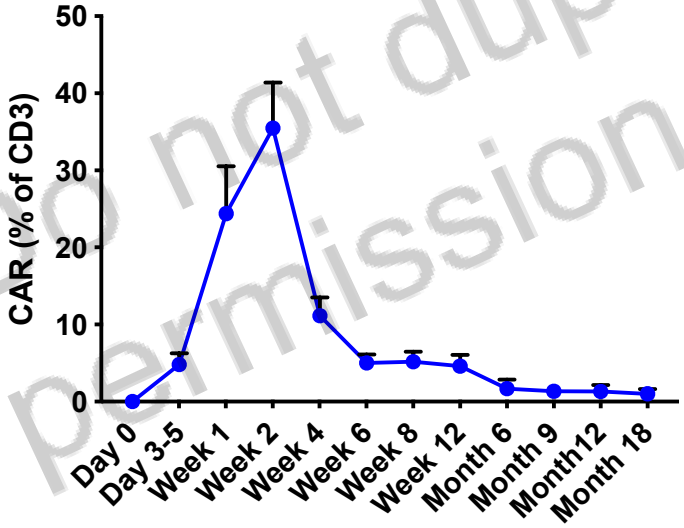
OR

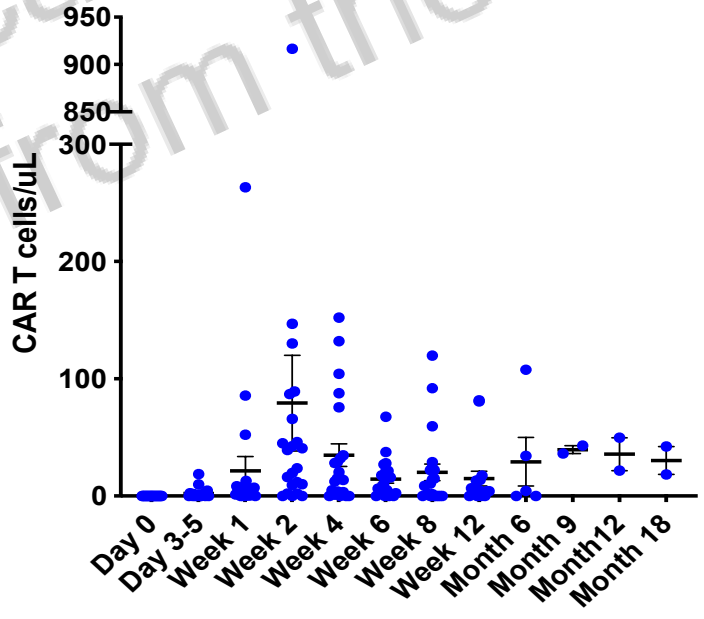
- Diagnosis of High Risk NBL at extremely high risk of relapse, even if NED at the end of the first-line treatment according to the Standard of Care (Phase II ONLY)

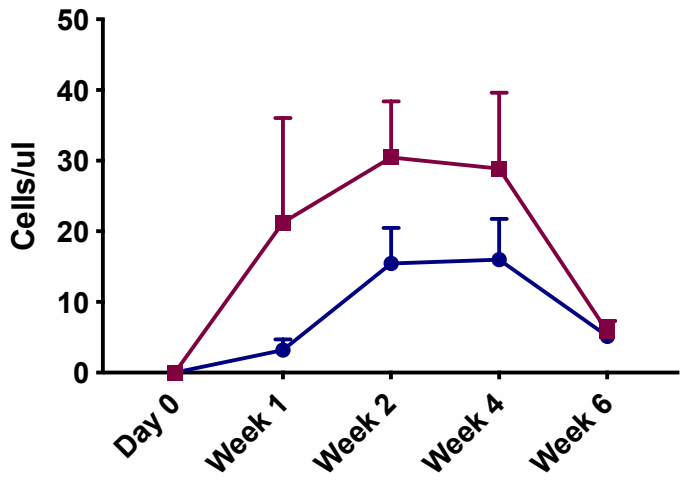
- Patients with relapsed/refractory disease must have measurable or evaluable disease at the time of treatment enrolment
- Age: 12 months – 25 years
- Voluntary informed consent is given
- Clinical performance status: ≥ 60% (Karnofsky or Lansky)

GD2-CAR T cells expand robustly and show long term persistence in the peripheral blood

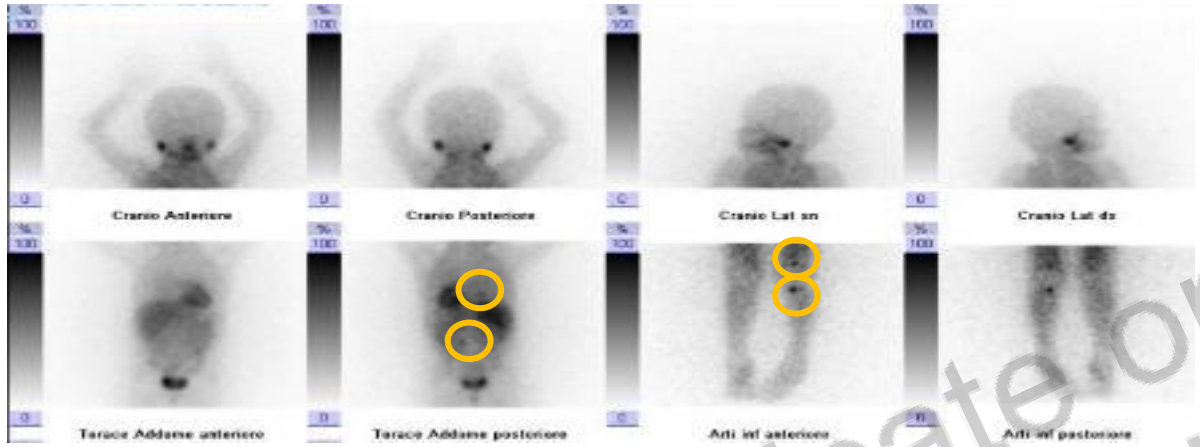






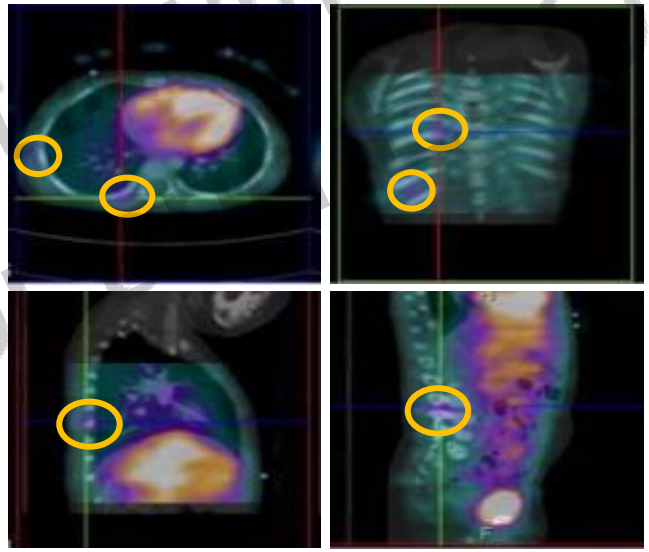


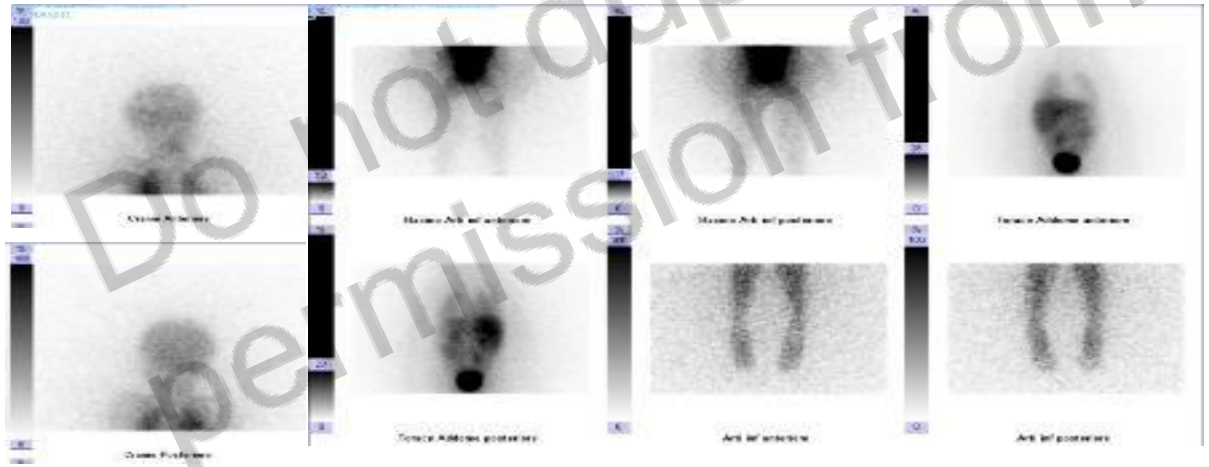
GD2-OPBG-007: disease evaluation MIBG-scintigraphy Neuroblastoma patient



Pre-CAR

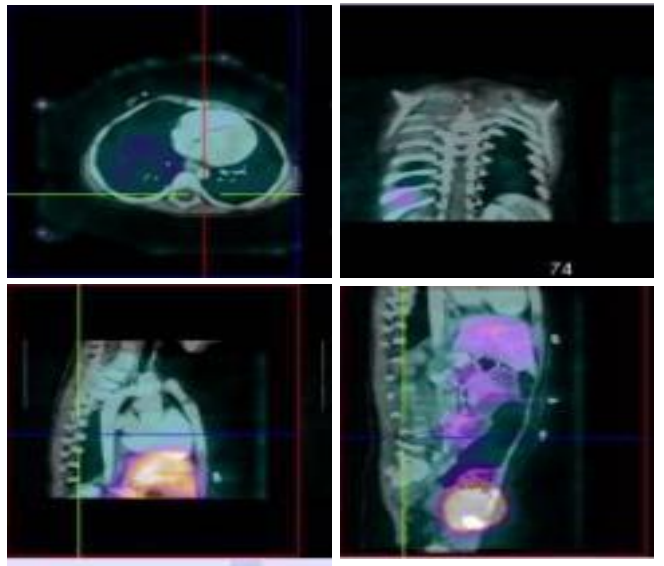
(multiple bone lesions)





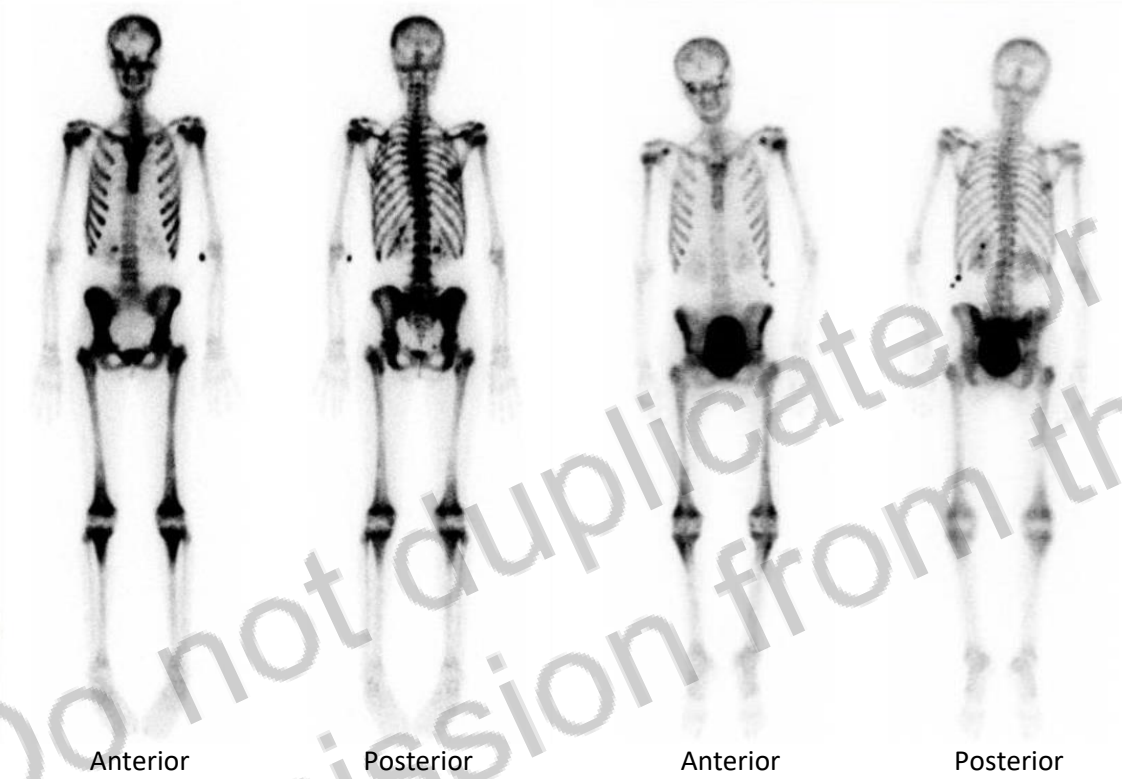
Week +6

(CR)



GD2-CAR T cells in sarcomas of the bone

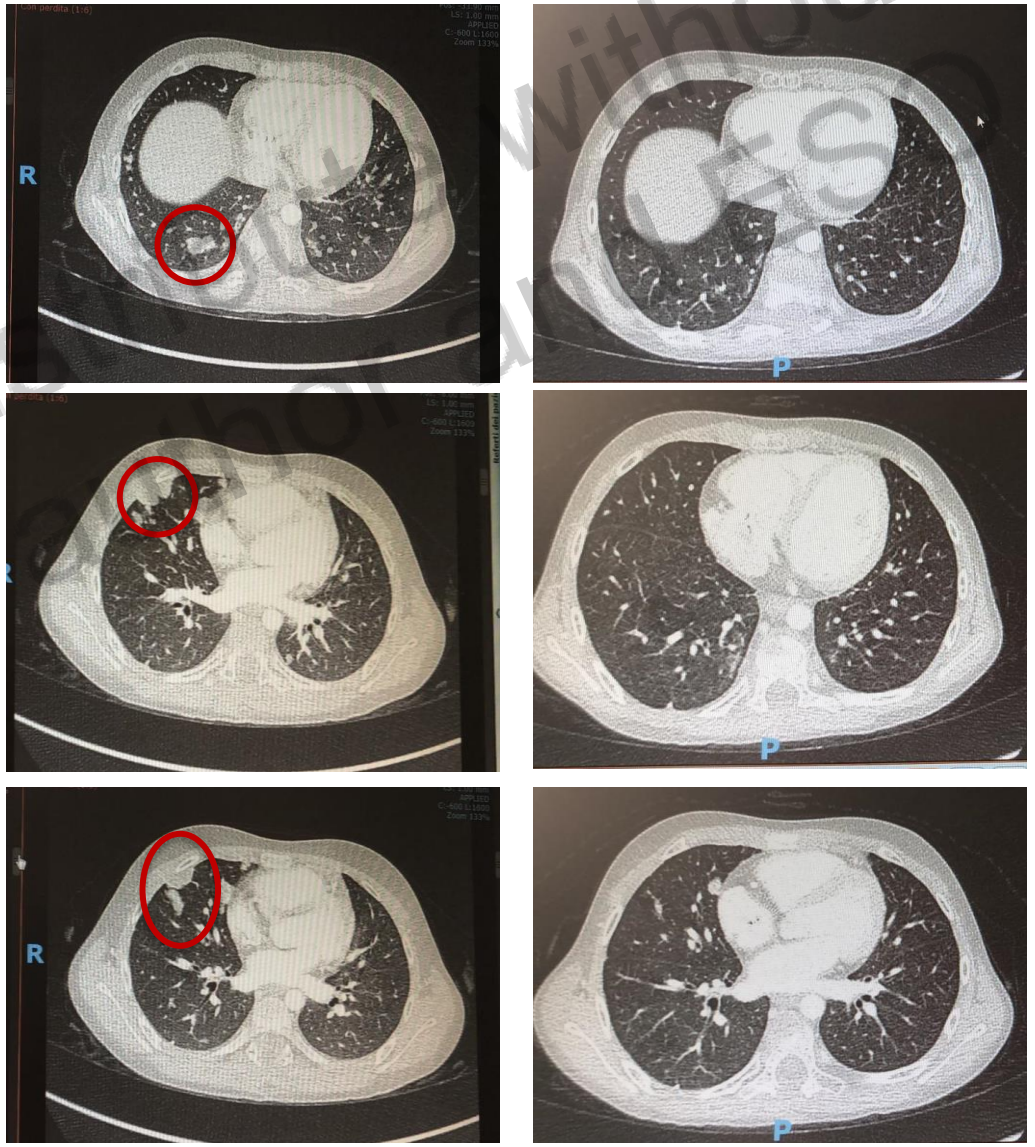
Pre-infusion **Post-infusion**



Anterior Posterior Anterior Posterior

EWING SARCOMA

Pre-infusion **Post-infusion**



OSTEOSARCOMA

In vivo anti-tumor activity of GD2-CAR T cells

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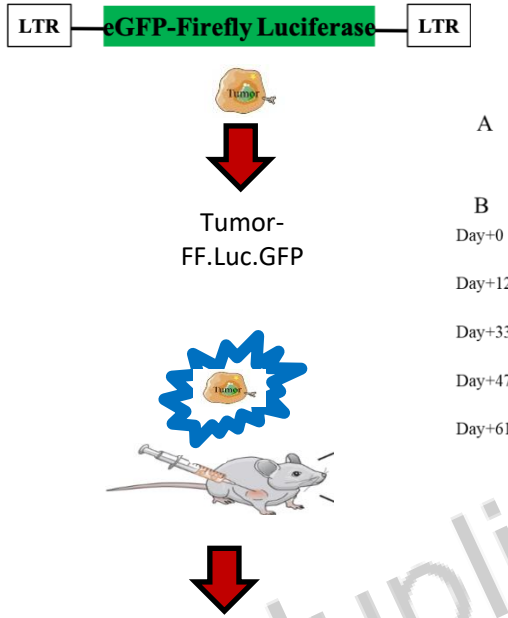
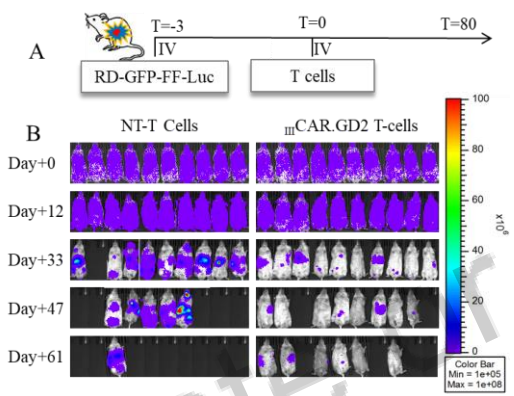
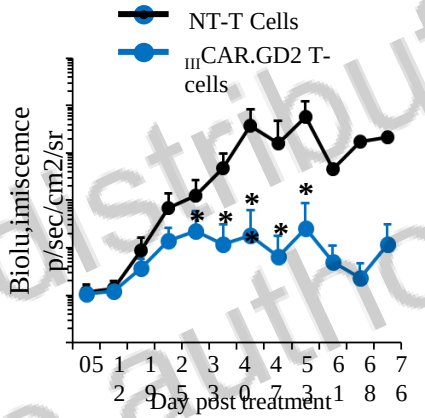
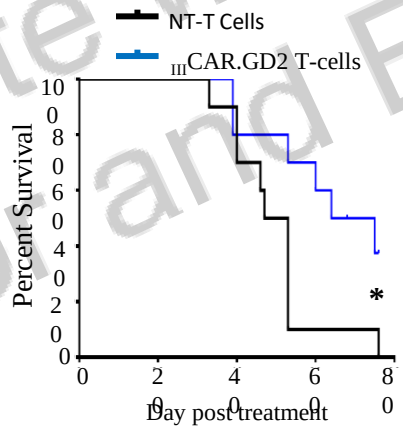
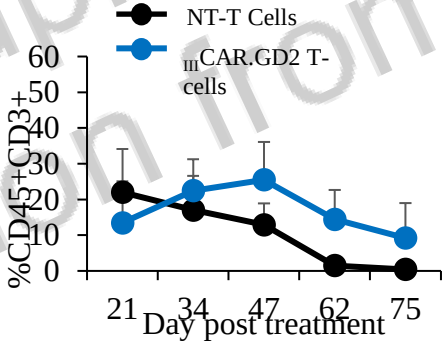


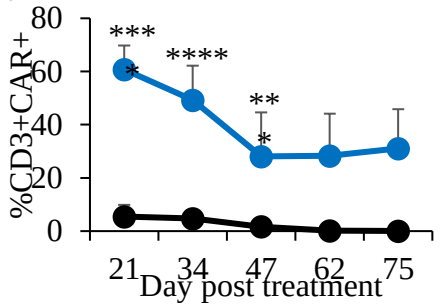
RD (ERMS)

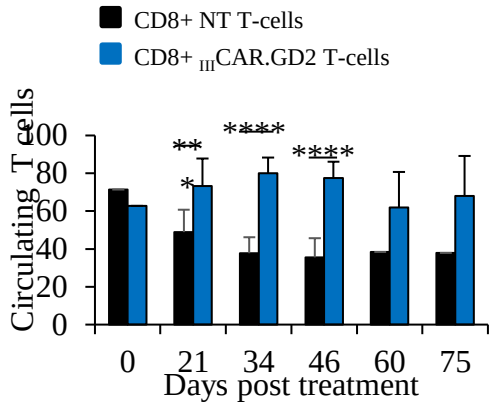












Future applications of GD2-CAR

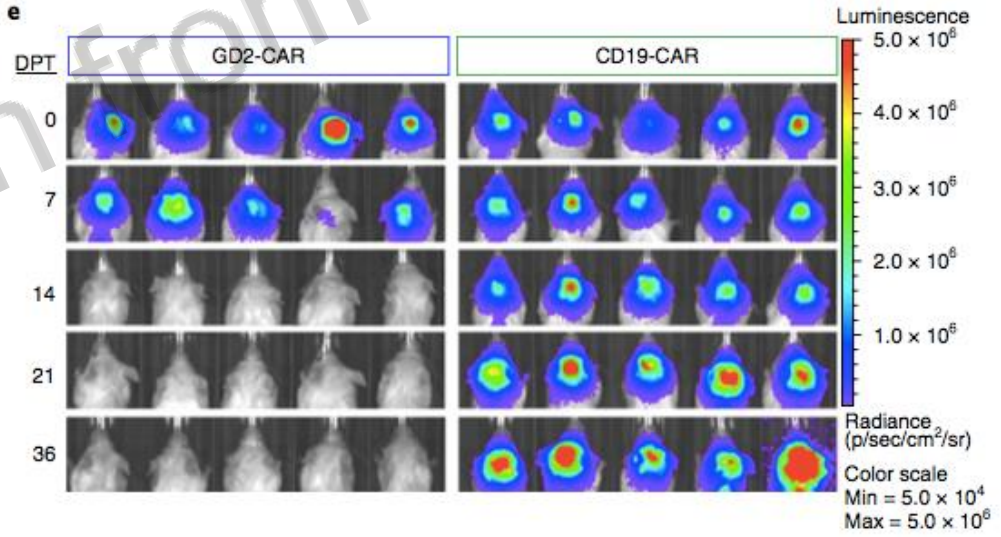
nature medicine

LETTERS

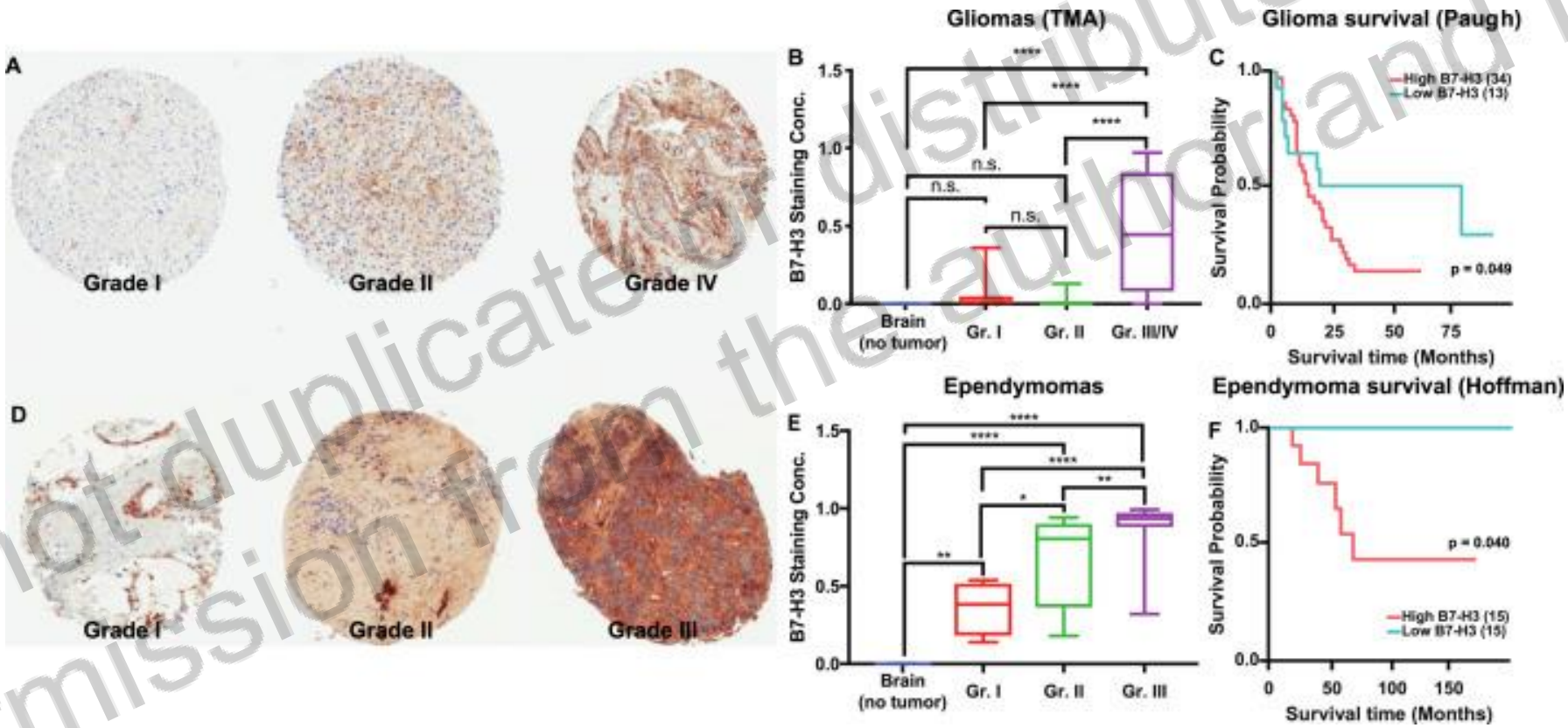
https://doi.org/10.1038/s41591-018-0006-x

Potent antitumor efficacy of anti-GD2 CAR T cells in H3-K27M+ diffuse midline gliomas

Christopher W. Mount[1,2,3,12], Robbie G. Majzner[4,12], Shree Sundaresh[1], Evan P. Arnold[1], Meena Kadapakkam[4], Samuel Haile[4], Louai Labanieh[4,5], Esther Hulleman[6], Pamelyn J. Woo[1], Skyler P. Rietberg[4], Hannes Vogel[1,4,7,8], Michelle Monje[1,4,7,8,9,10]* and Crystal L. Mackall[4,9,11]*

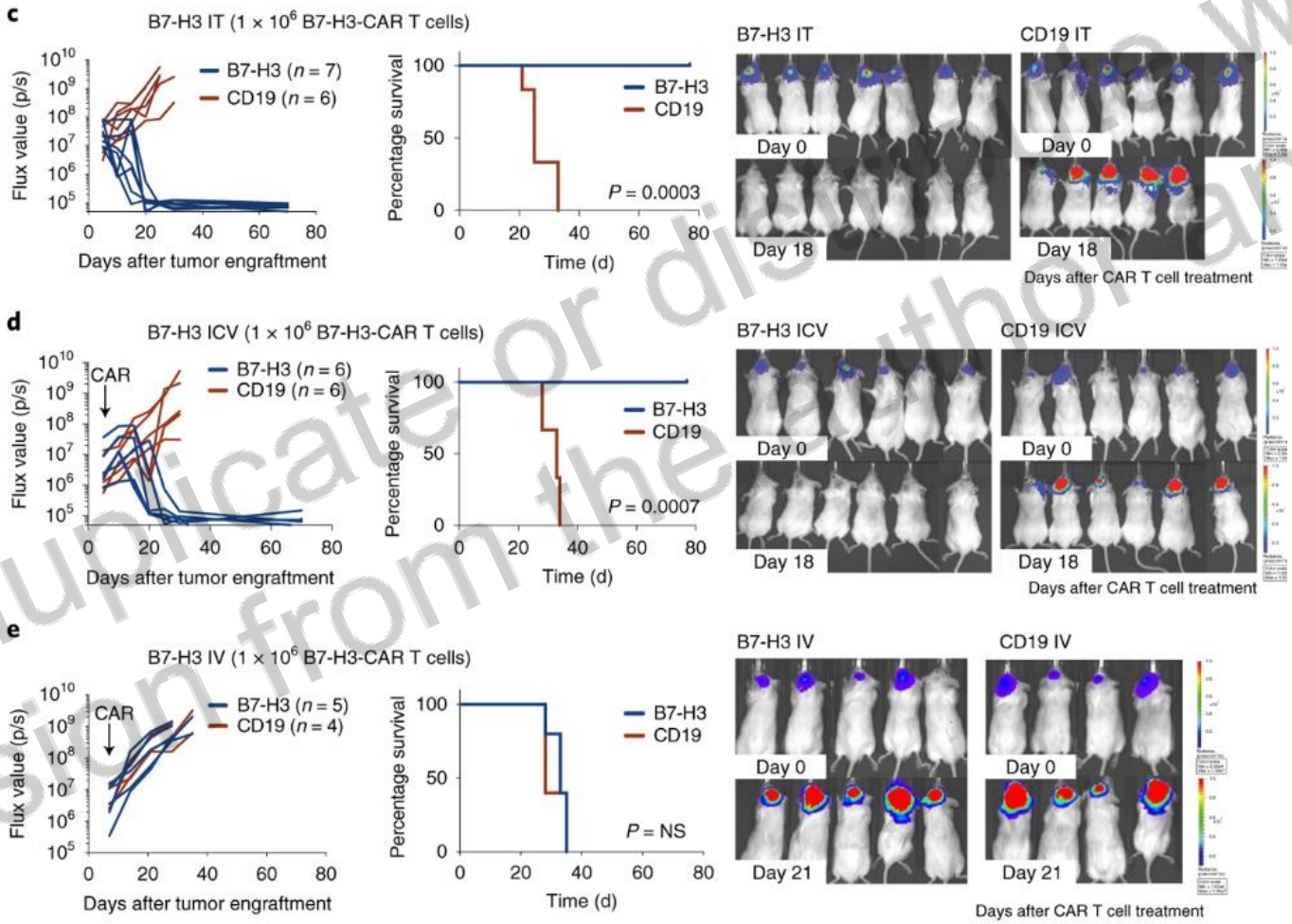


CD276 and its high expression in Brain Tumors



Oncoimmunology, 2019 Nov 4;9(1):1684127.

Locoregional administration of B7-H3 CAR T cells results in a effective therapy for ATRT (xenografts model)

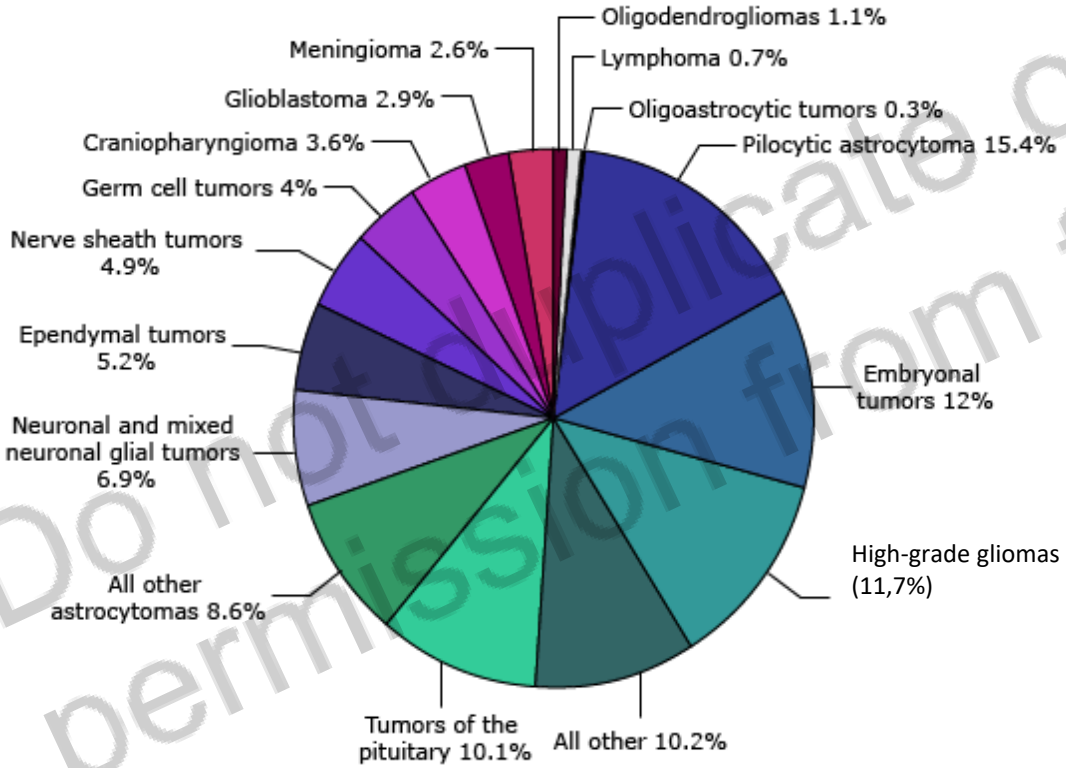


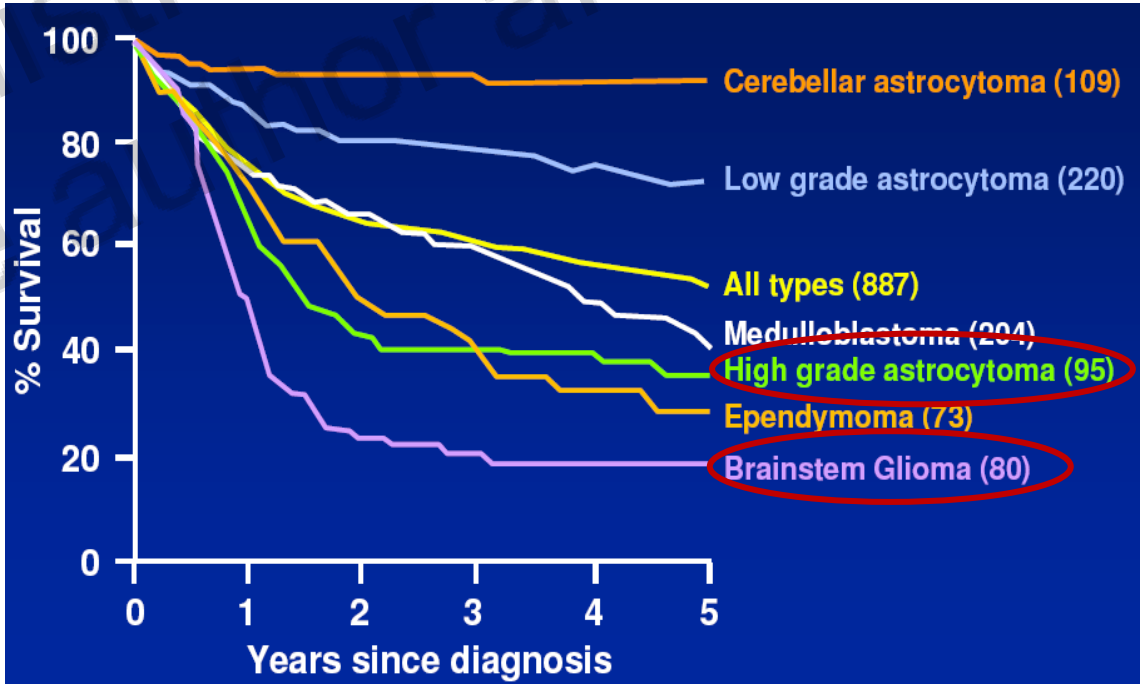
Nat Med. 2020 May; 26(5): 712–719.

Childhood HGG: a highly unmet medical need

Neuro-Oncology 2016; **0**, 1–9, doi:10.1093/neuonc/now101

Pediatric high-grade glioma: biologically and clinically in need of new thinking





CBTRUS, Neuro-Oncology 2014
Binda et al. Cancer Cell 2012
Wykosky et al. Clin Cancer Res 2008

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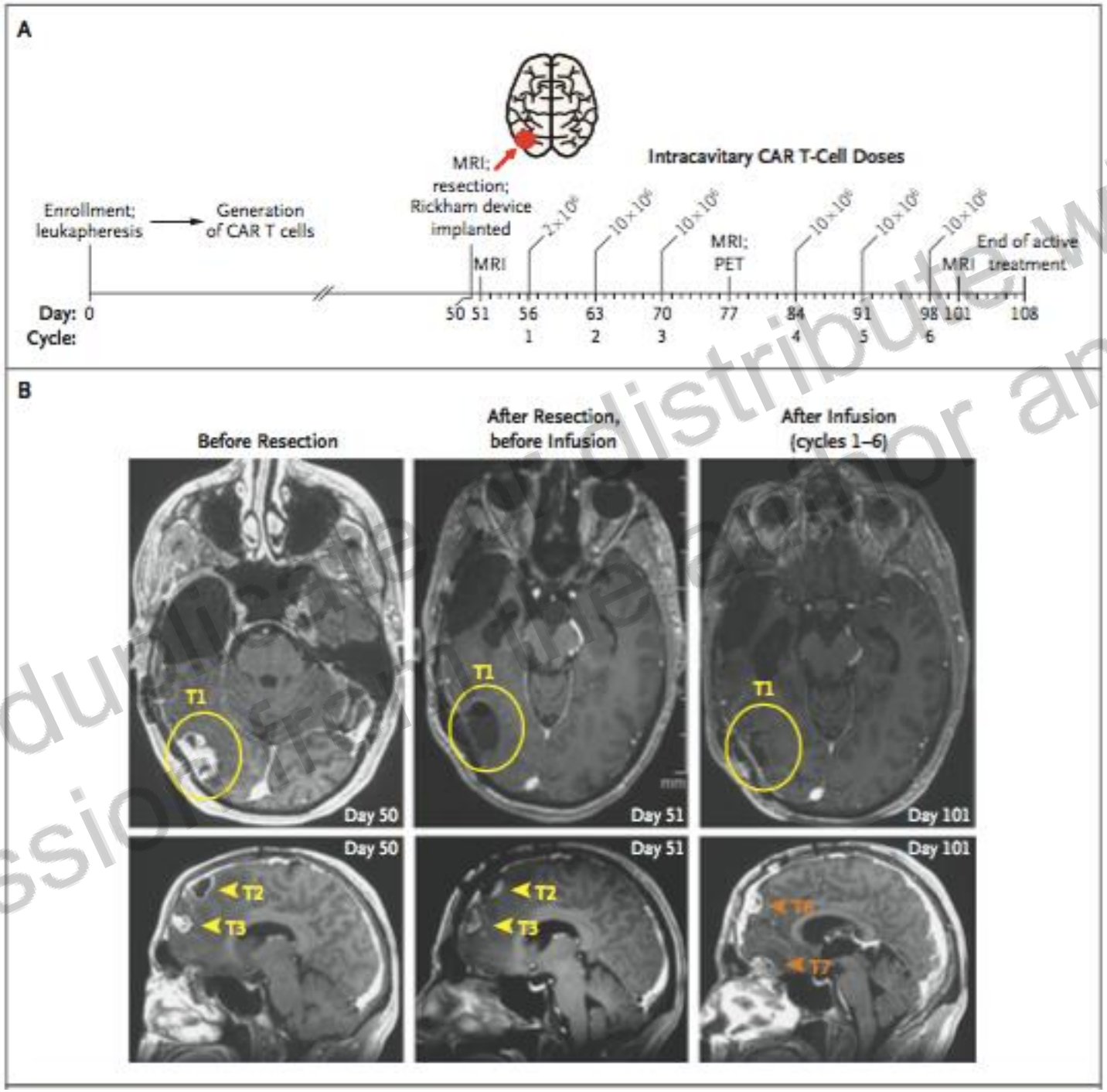
BRIEF REPORT

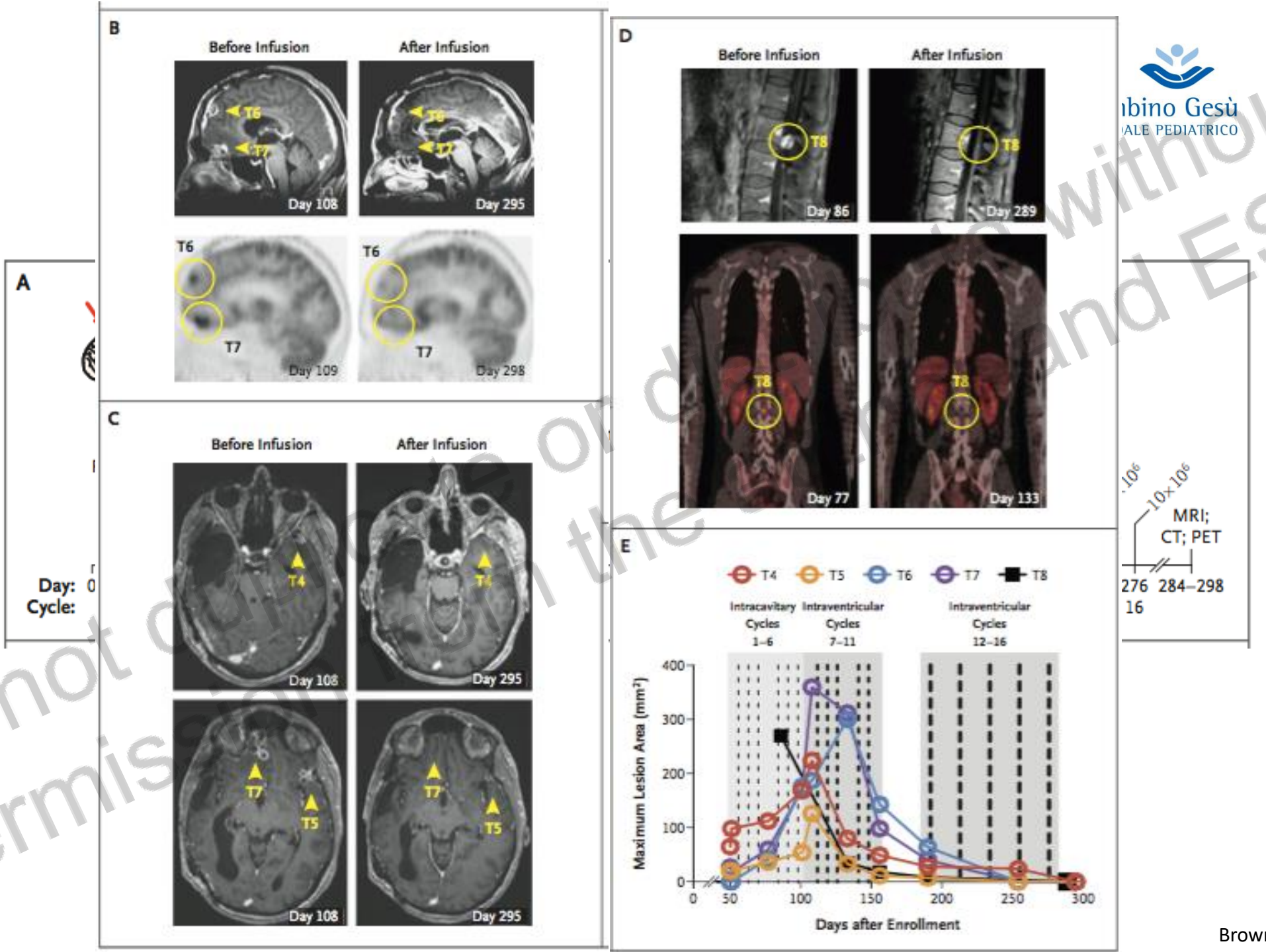
Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy

Christine E. Brown, Ph.D., Darya Alizadeh, Ph.D., Renate Starr, M.S., Lihong Weng, M.D., Jamie R. Wagner, B.A., Araceli Naranjo, B.A., Julie R. Ostberg, Ph.D., M. Suzette Blanchard, Ph.D., Julie Kilpatrick, M.S.N., Jennifer Simpson, B.A., Anita Kurien, M.B.S., Saul J. Priceman, Ph.D., Xiuli Wang, M.D., Ph.D., Todd L. Harshbarger, M.D., Massimo D'Apuzzo, M.D., Julie A. Ressler, M.D., Michael C. Jensen, M.D., Michael E. Barish, Ph.D., Mike Chen, M.D., Ph.D., Jana Portnow, M.D., Stephen J. Forman, M.D., and Behnam Badie, M.D.

Brown CE, et al. NEJM 2016



Brown CE, et al. NEJM 2016



Brown CE, et al. NEJM 2016

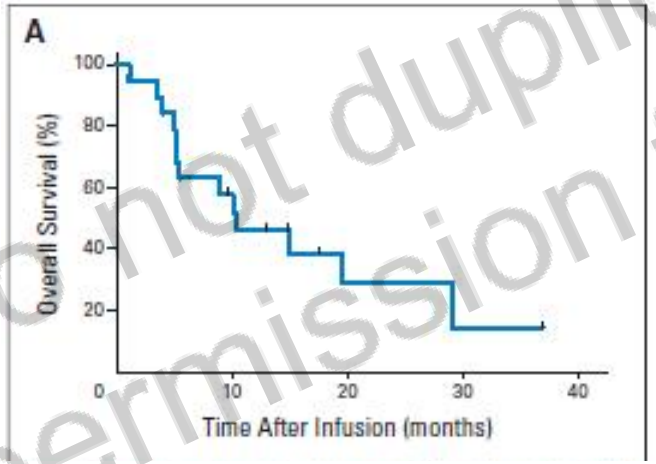
Clinical activity of CAR T in childhood sarcoma

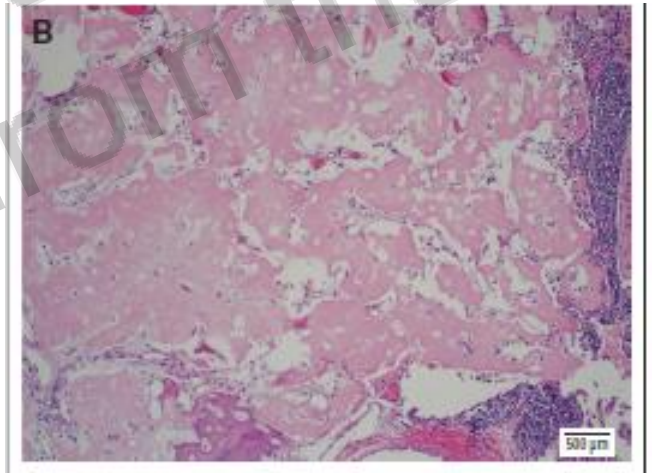
VOLUME 33 · NUMBER 15 · MAY 20 2015

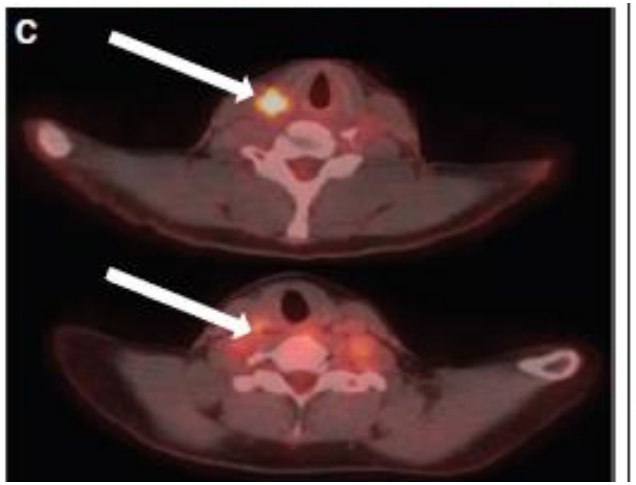
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Human Epidermal Growth Factor Receptor 2 (HER2) –Specific Chimeric Antigen Receptor–Modified T Cells for the Immunotherapy of HER2-Positive Sarcoma

Nabil Ahmed, Vita S. Brawley, Meenakshi Hegde, Catherine Robertson, Alexia Ghazi, Claudia Gerken, Enli Liu, Olga Dakhova, Aidin Ashoori, Amanda Corder, Tara Gray, Meng-Fen Wu, Hao Liu, John Hicks, Nino Rainusso, Gianpietro Dotti, Zhuyong Mei, Bambi Grilley, Adrian Gee, Cliona M. Rooney, Malcolm K. Brenner, Helen E. Heslop, Winfried S. Wels, Lisa L. Wang, Peter Anderson, and Stephen Gottschalk







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Department of Immunology

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GMP Facility

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All Team!

Cell Manipulation Unit

Giuseppina Li Pira

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Simona Sivori

Simona Carlomagno