# IMMUNOTHERAPY FOR PEDIATRIC CANCERS: A REVIEW OF PROGRESS TO DATE & A LOOK AHEAD

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## DISCLOSURES

- I have consulted for Advanced Microbubbles, AI Therapeutics, Bayer, Cellectis, Deciphera, GentiBio, Jazz Pharmaceuticals, Jumo Health, MassiveBio, Novartis, Pyramid Biosciences, and Y-mAbs Therapeutics

- I will discuss investigational use of CAR T-cells

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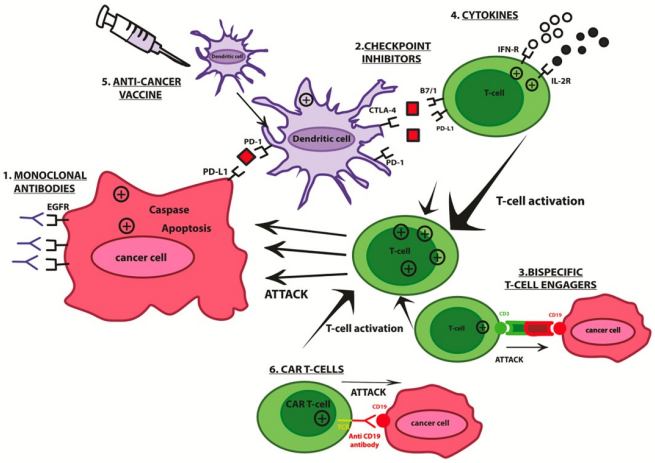
# OUTLINE

- Types of immunotherapy
- Immunotherapy successes
  - B-ALL
  - Neuroblastoma
- Challenges / a look ahead
  - Relapse after CD19 CAR
  - Solid tumors
  - Brain tumors
  - AML
  - T-ALL




Lobenwein IJ Cardiology. 2022.

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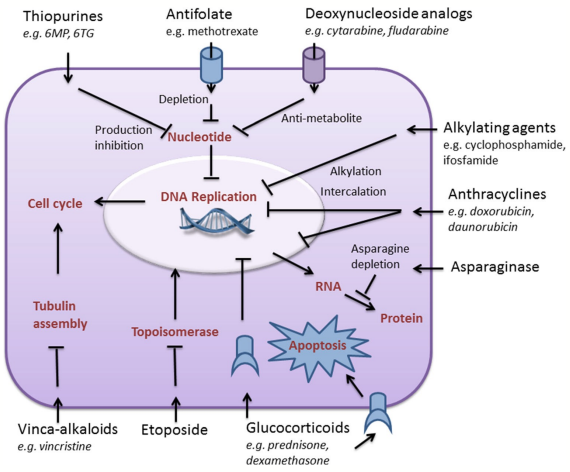
# TRADITIONAL CYTOTOXIC CHEMOTHERAPY




Most drugs used to treat cancer work by interfering with DNA replication which inhibits cell division.

Generally toxic to fast growing cells -> common side effects of chemotherapy.

Kloos. Cancer Metastasis Rev. 2017.

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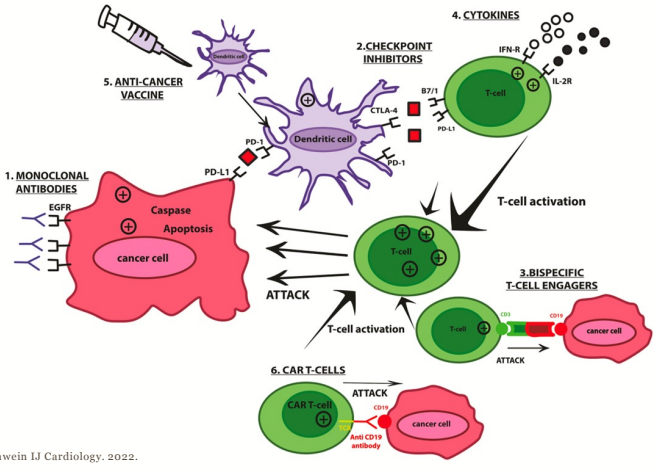
# IMMUNOTHERAPY FOR CANCER

Our immune systems are continuously surveilling and eliminating pre-cancerous cells. A diagnosis of cancer requires escape from immune surveillance.




Non-specific
- Cytokines
- Checkpoint inhibitors

Specific
- Antibodies
- Antibody drug conjugates
- Bispecific T-cell engagers
- CAR T-cells

Lobenwein IJ Cardiology. 2022.

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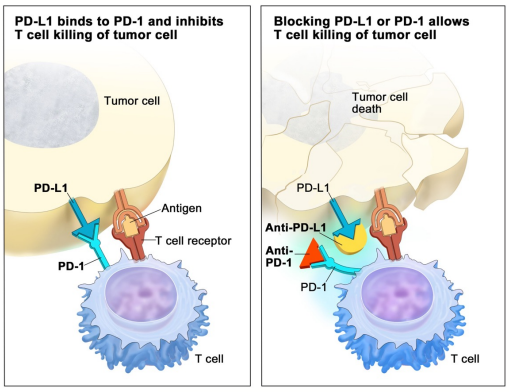
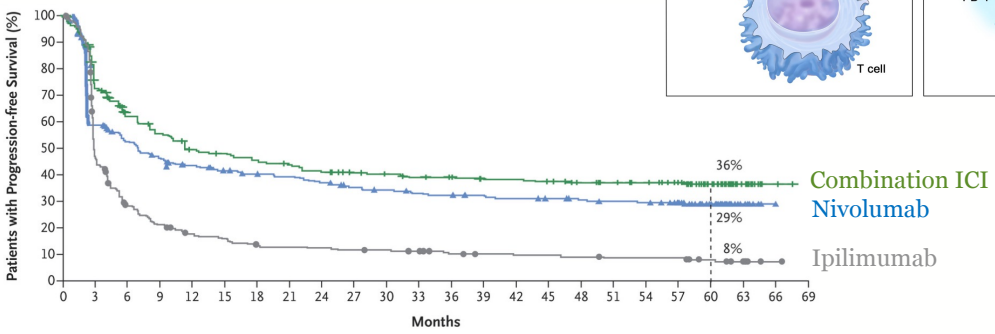
# CHECKPOINT INHIBITORS

Block inhibitory pathways to non-specifically activate the immune system.




Durable remissions ("Cures") in metastatic melanoma




National Cancer Institute. Larkin. NEJM. 2019.

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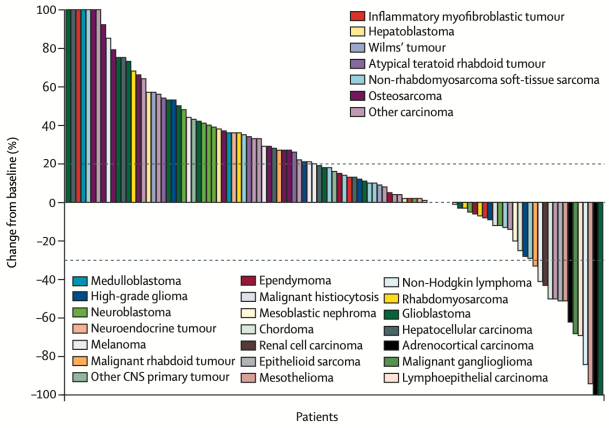
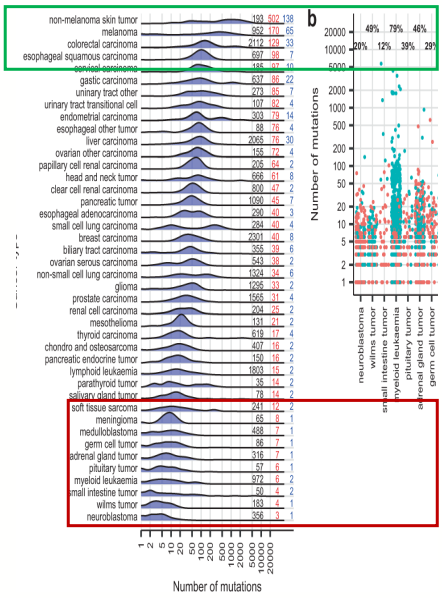
# ICI IN PEDIATRIC CANCER

Little Activity Across Pediatric Cancers Except Hodgkin's Lymphoma




Geoerger. Lancet Oncology. 2020. Martinez-Perez. NPJ Precision Oncology. 2021.

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# TARGETED IMMUNOTHERAPEUTICS: SUCCESS IN PEDIATRIC CANCER

- Teaching the immune system to recognize a specific target on the patients' cancer
- Key challenge - identifying the right target(s):
  - Highly expressed and important for cancer cell survival
  - Low/no expression on critical normal tissues
- Other important factors:
  - Access to the tumor (microenvironment)
  - Understanding which immunotherapy is best
  - When/where/how to integrate with traditional therapy

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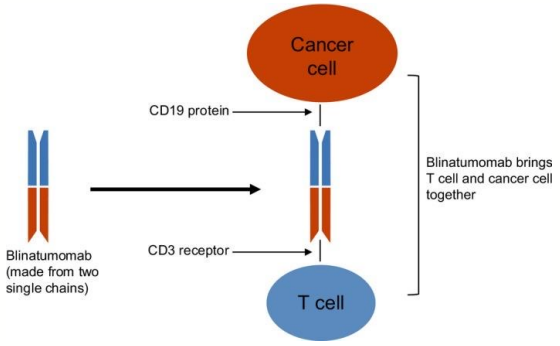
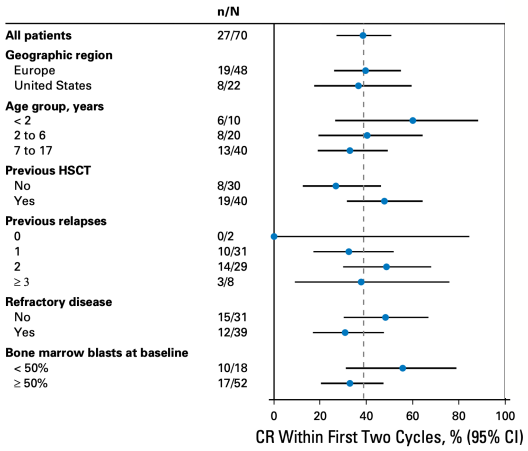
# KEY SUCCESS: B-ALL BLINATUMOMAB




Von Stackelberg. JCO. 2016.

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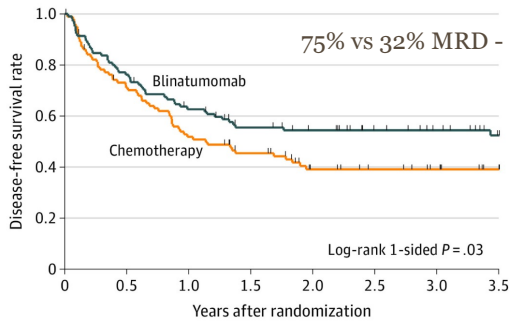
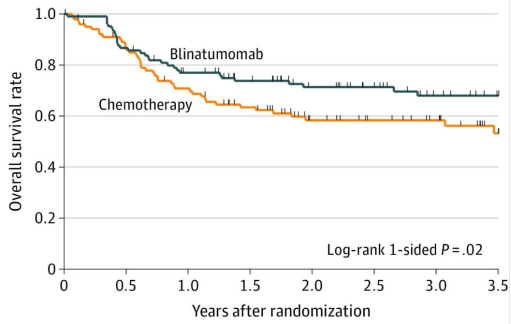
# KEY SUCCESS: B-ALL BLINATUMOMAB

AALL1331 found blinatumomab resulted in improved disease free and overall survival vs chemotherapy in first relapse of B-ALL.

Disease-free survival




Overall survival




Goal was stem cell transplant. Not considered curative alone.

Brown. JAMA. 2021.

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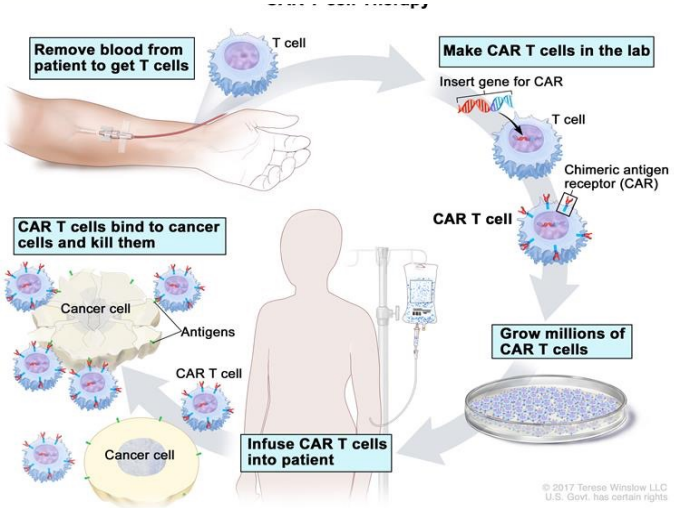
# CAR T-CELLS




Can make CAR T-cells to target essentially any antigen on the cell surface.

Most successful:
CD19 targeting for B-ALL

CD19 is a cell surface protein on both normal and malignant B-cells

https://www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy

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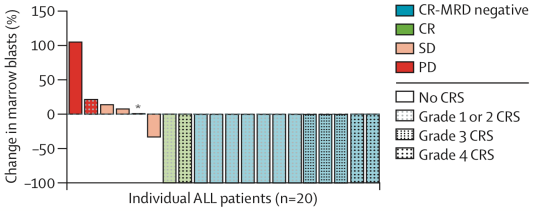
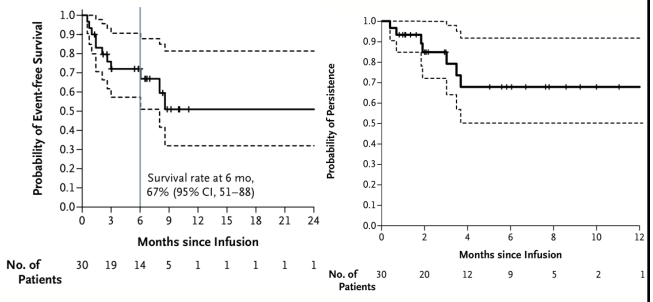
# KEY SUCCESS: CAR T-CELLS FOR B-ALL

NCI




CHOP




CAR T-cells result in remission in most patients (>70-80%), and some CAR T-cells (4-1BB) can persist and maintain remission

Lee. Lancet. 2015. Maude. NEJM. 2014.

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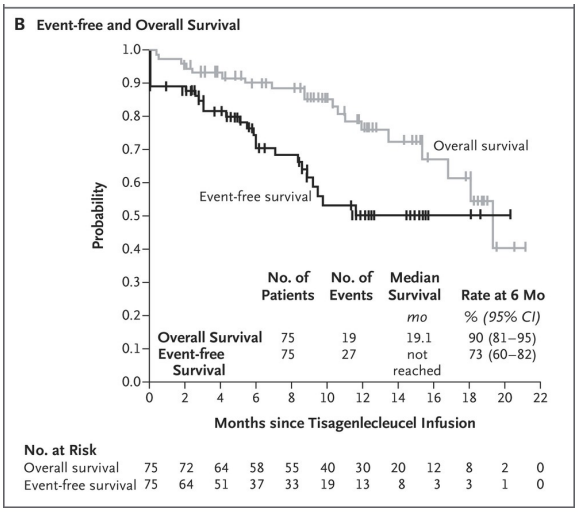
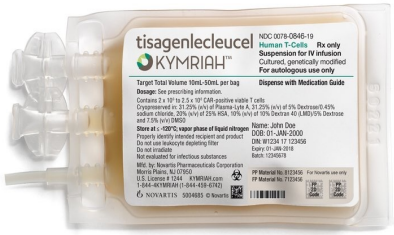
# FDA APPROVAL OF TISAGENLECLEUCEL FOR B-ALL




**CR/CRi** = 61/75 (81%)

RFS: 66% at 18 mos
OS: 70% at 18 mos
8 underwent HSCT

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13 S Maude. *N Engl J Med.* 2018.

13

# TISAGENLECLEUCEL: ADVERSE EVENTS OF SPECIAL INTEREST WITHIN 8 WEEKS

| Type of Event | Any Grade (N = 75) | Grade 3 (N = 75) | Grade 4 (N = 75) |
|---|---|---|---|
| | *number of patients (percent)* | | |
| Any adverse event of special interest | 67 (89) | 26 (35) | 30 (40) |
| Cytokine release syndrome | 58 (77) | 16 (21) | 19 (25) |
| Neurologic event | 30 (40) | 10 (13) | 0 |
| Infection | 32 (43) | 16 (21) | 2 (3) |
| Febrile neutropenia | 26 (35) | 24 (32) | 2 (3) |
| Cytopenia not resolved by day 28 | 28 (37) | 12 (16) | 12 (16) |
| Tumor lysis syndrome | 3 (4) | 3 (4) | 0 |

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14 S Maude. *N Engl J Med.* 2018.

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# KEY QUESTIONS

- How durable are these remissions? Are there "cures"?
- Do real world results match those from the clinical trials?
- Which patients are most/least likely to benefit?
- How do we prevent and treat relapse after CAR?



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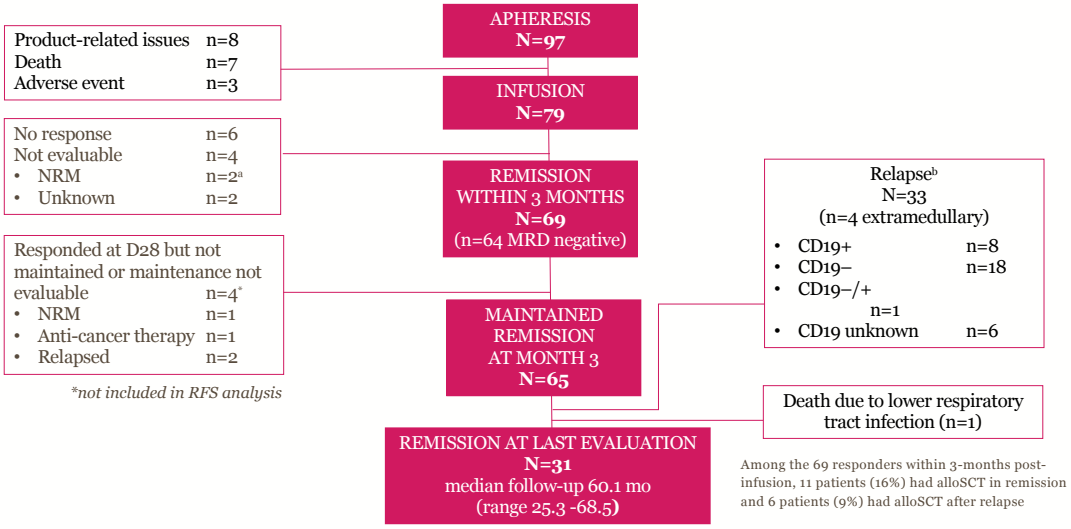
# 5-YEAR OUTCOME DATA FROM ELIANA



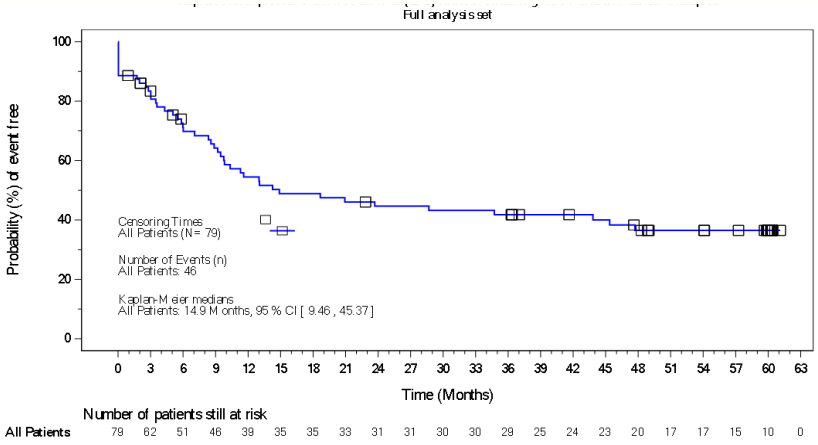



S Rives. EHA. 2022.

# MOST RELAPSES OCCUR WITHIN FIRST 12-18 MONTHS

**EFS Without Censoring for alloSCT and Other Antineoplastic Therapies**

5-year EFS: 43.7% (95% CI, 31%-56%)




No difference in EFS between pediatric (<18 y; n=65) and young adult (≥18 y; n=14) patients

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[17] S Rives. EHA. 2022.

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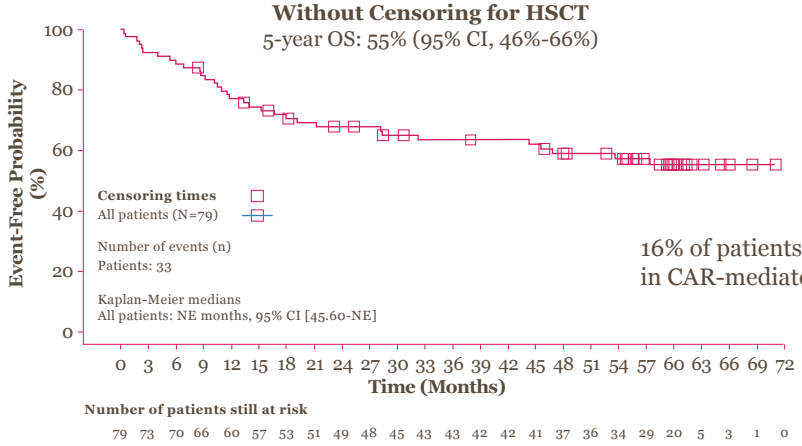
# 55% OF PATIENTS ARE LONG TERM SURVIVORS

**Overall Survival Without Censoring for HSCT**

5-year OS: 55% (95% CI, 46%-66%)




16% of patients underwent SCT in CAR-mediated remission

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[18] S Rives. EHA. 2022.

18

# SERIOUS SIDE EFFECTS ARE RARE, MOST COMMONLY CYTOPENIAS

| | Patients Who Achieved Remission Any Time During the Study N=70 | |
|---|---|---|
| **AESI occurring >1 y post infusion** | **Any Grade, n (%)** | **Grade ≥3, n (%)** |
| Number of patients with at least one event | 27 (39) | 15 (21) |
| Hemophagocytic lymphohistiocytosis | 1 (1) | 1 (1) |
| Infection | 23 (33) | 14 (20) |
| Hematological disorders, including cytopenias | 7 (10) | 4 (6) |
| Serious neurological events | 2 (3) | 1 (1) |
| Secondary malignancy | 1 (1) | 1 (1) |

[19]

- Ten (14%) patients in remission experienced long-term cytopenias persisting for >1 year; however, none of these patients experienced cytopenias persisting for >5 years (median, 2 y; range, 1.1-5y)
- Eighty-two percent of patients received IVIG at any time post-infusion; 33% >1 year and 16% >2 years post-infusion
  - 88% of patients in remission received IVIG during persistent B-cell aplasia

[19] S Rives. EHA. 2022.

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# 1ST PATIENT IN REMISSION >10 YEARS


[20]

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# DO REAL WORLD RESULTS MATCH CLINICAL TRIALS?

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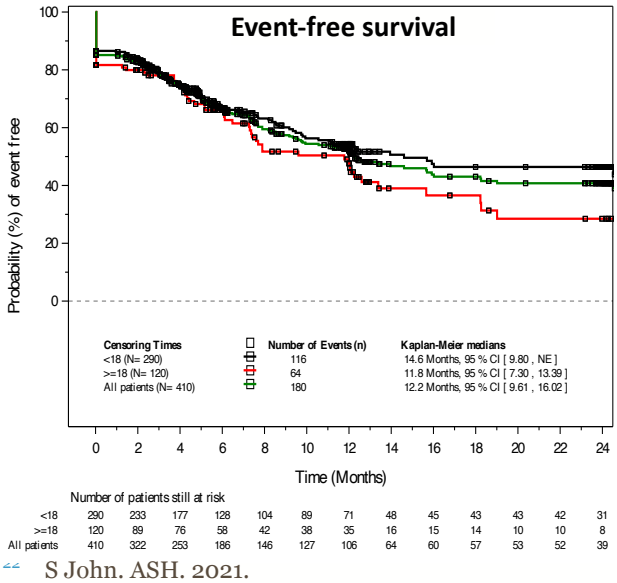
# REAL WORLD DATA: CIBMTR




S John. ASH. 2021.

CIBMTR analysis: 410 patients (290 children, 145 adults)

- **CR rate**: 86.8%
  - 98% MRD-negative
- 12- mos EFS: 52.6%
  - Median follow-up: 27 mos

- Safety / Toxicity
  - Grade ≥3 CRS: n=52 (10.5%)
  - Grade ≥3 neurotox: n=25 (5.1%)
    - 8 patients with cerebral edema

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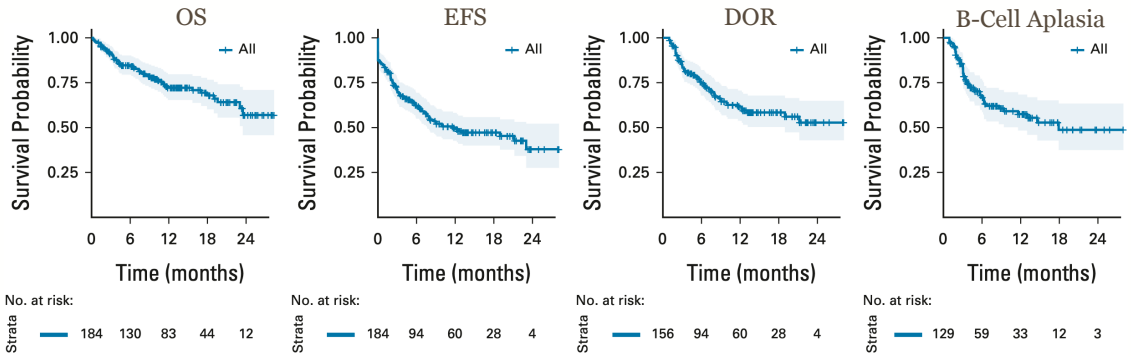
# PWRCC: OUTCOMES




| Outcome | 6-Month OS | 1-Year OS | 6-Month EFS | 1-Year EFS | 6-Month DOR | 1-Year DOR | 6-Month DBA | 1-Year DBA |
|---|---|---|---|---|---|---|---|---|
| *All patients* | 0.85 | 0.72 | 0.62 | 0.5 | 0.75 | 0.62 | 0.68 | 0.57 |

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[23] L Schultz. JCO. 2021.

23

# PWRCC: ADVERSE EVENTS

| Toxicity | | |
|---|---|---|
| ***CRS (N=183)*** | | |
| | None | 67 (37%) |
| | Any; Grade 1, 2, 3, 4, 5 | 116 (63%); 45, 32, 19, 19, 1 |
| ***Neurotoxicity (N=179)*** | | |
| | None | 141 (79%) |
| | Any; Grade 1, 2, 3, 4, 5 | 38 (21%); 19 , 7, 8, 3, 1 |
| | Cerebral Edema | 1 (0.6%) |
| | Cerebral Hemorrhage | 1 (0.6%) |
| ***Grade 4 Neutropenia persistent >day 28 (Analysis limited to patients with CR and evaluable counts; N=147))*** | | |
| | Yes | 23 (16%) |
| | No | 124 (84%) |
| ***Infections*** | | |
| | Patients<br>Infections/patient; Median (range) | 73 (40%)<br>1 (1-5) |
| ***PICU stay*** | | |
| | Yes, Duration (days); Median (range) | 57 (31%), 6 (1-33) |
| | No | 125 (68%) |

Abbreviations: CRS; Cytokine release syndrome, HLH; Hemophagocytic lymphohistiocytosis, PICU; Pediatric intensive care unit

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[24] L Schultz. JCO. 2021.

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# WHICH PATIENTS ARE MOST LIKELY TO BENEFIT?

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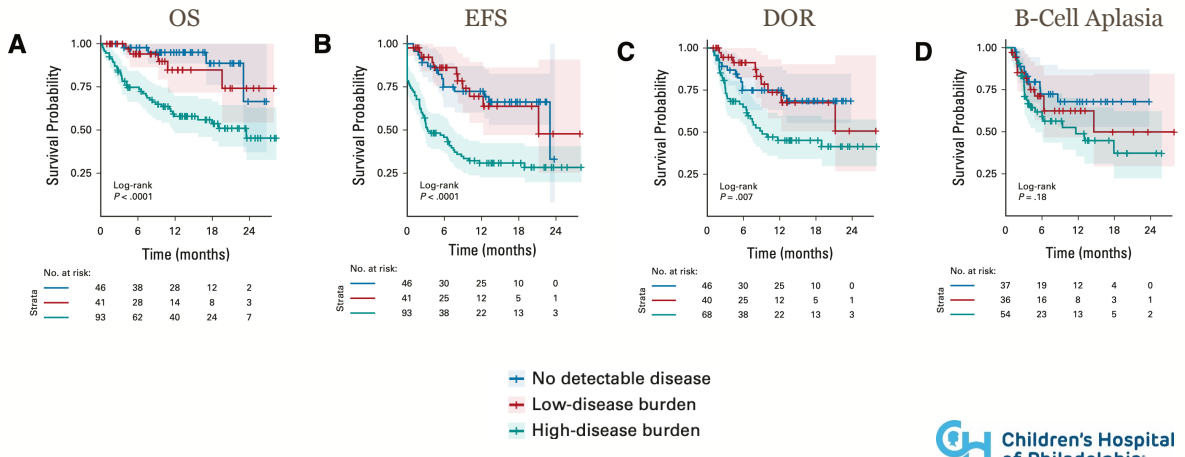
# PWRCC: HIGH DISEASE BURDEN ASSOCIATED WITH WORSE OUTCOMES




[26] L Schultz. JCO. 2021.

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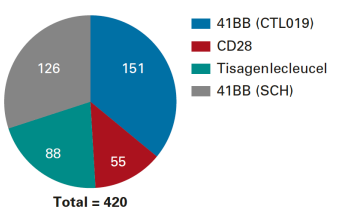
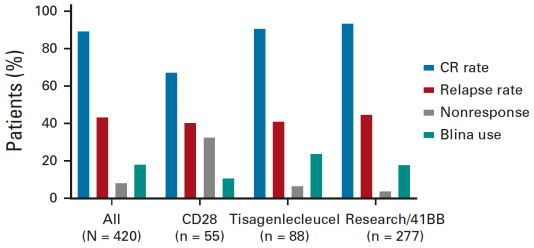
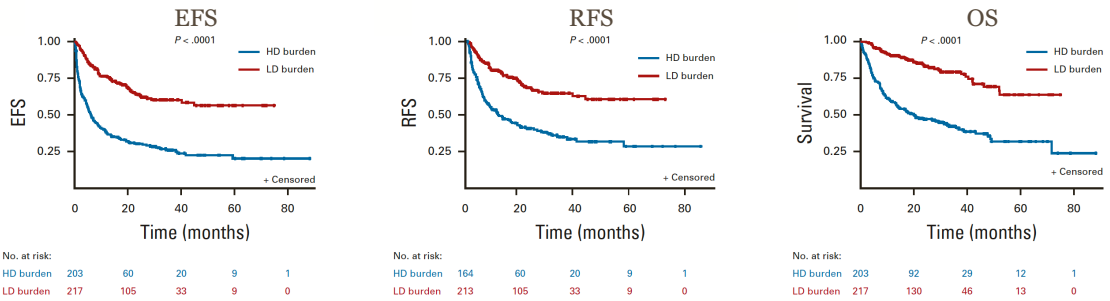
# CARNATION CONSORTIUM: DISEASE BURDEN




27 R Myers. JCO. 2021.

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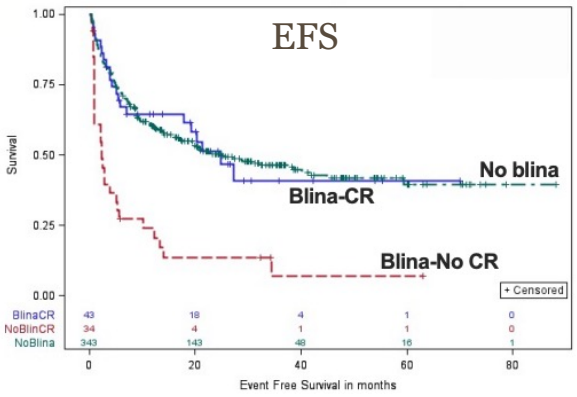
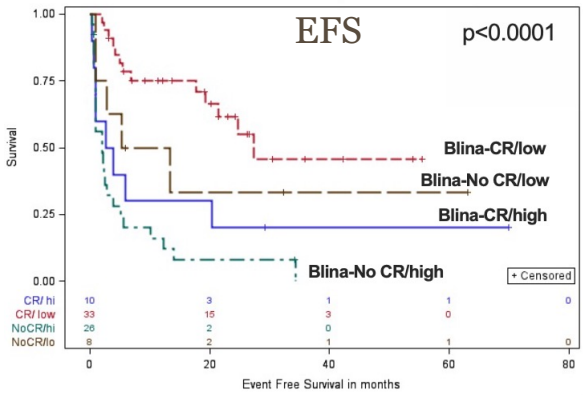
# CARNATION: BLINATUMOMAB NON-RESPONSE IS ASSOCIATED WITH WORSE OUTCOMES

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28 R Myers. JCO. 2021.

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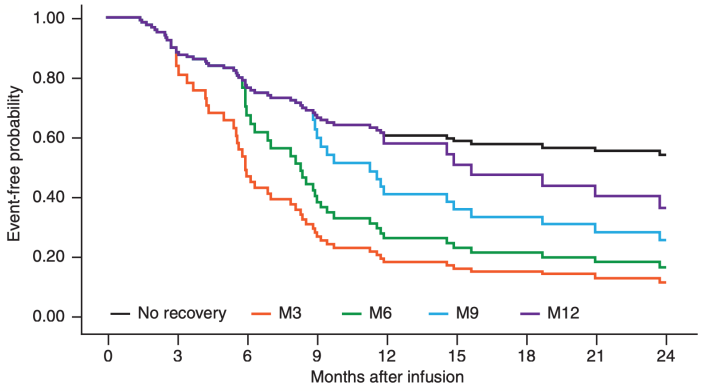
# EARLY B-CELL RECOVERY




Post-hoc analysis of ELIANA/ENSIGN (N=143):

- B-cell recovery w/in 1 year: HR 4.5, $p$ <0.001

Adjusted EFS curves for patients with B-cell recovery by month 3, 6, 9, and 12

- 2-year EFS for BCR by M3 = 9%

Seattle's PLAT-02 trial:

- B-cell recovery: HR for relapse = 3.5, $p$ = 0.04

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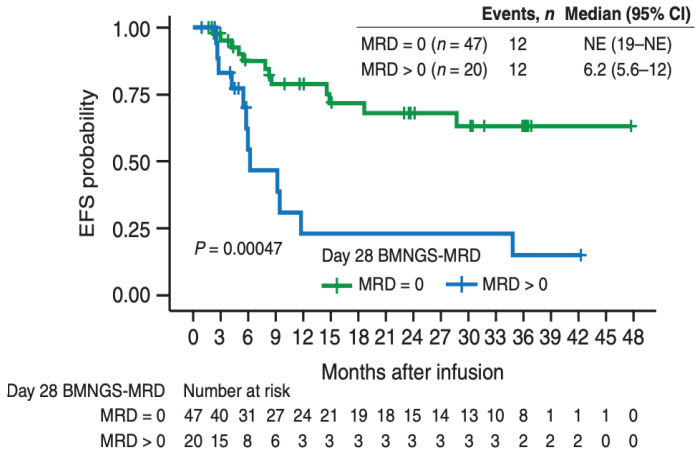
29 M.A. Pulsipher et al, *Blood Cancer Discovery* 2021. R.M. Gardner et al, *Blood* 2017

29

# NEXT GENERATION SEQUENCING MRD

- Day 28: HR 4.87, p<0.001
- Month 3: HR 12, p<0.001

- 26 patients with consecutive NGS-MRD >0 tests:
  - 19 relapsed
  - 6 were censored for subsequent therapy
  - 1 was lost to follow-up

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30 M.A. Pulsipher et al, *Blood Cancer Discovery* 2021.

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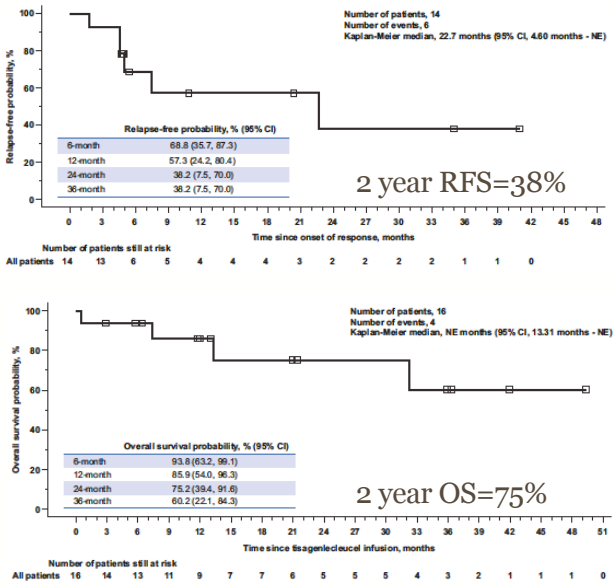
# DOWN SYNDROME: CLINICAL TRIAL OUTCOMES

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[31] T. Laetsch. Leukemia. 2022.

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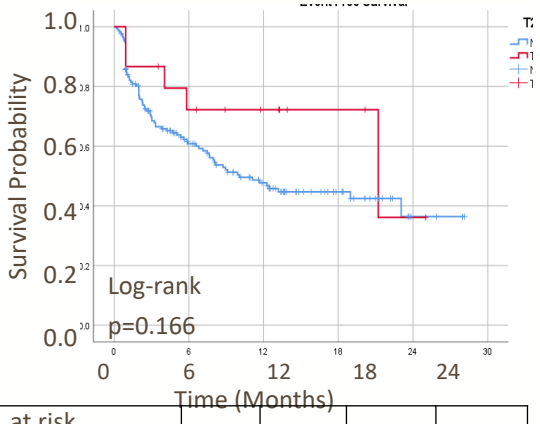
# DOWN SYNDROME: PRWCC OUTCOMES

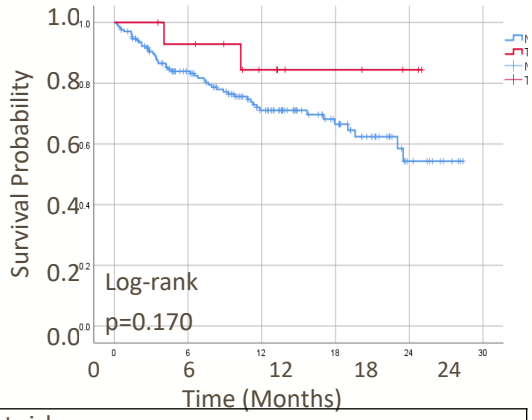
DS-ALL
NDS-ALL

EFS




| No. at risk | | | | | |
|---|---|---|---|---|---|
| DS-ALL | 15 | 10 | 7 | 3 | 1 |
| NDS-ALL | 170 | 80 | 50 | 23 | 3 |

OS




| No. at risk | | | | | |
|---|---|---|---|---|---|
| DS-ALL | 15 | 13 | 8 | 4 | 2 |
| NDS-ALL | 170 | 117 | 75 | 40 | 10 |

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[32] H Pacenta. SIOP. 2021.

32

## TOXICITY FOLLOWING TISAGENLECLEUCEL

| | | DS-ALL | NDS-ALL | p-value |
|---|---|---|---|---|
| Toxicity | CRS<br>Any grade | 80% (12/15) | 62% (104/168) | 0.175 |
| | ≥ Grade 3 | 20% (3/15) | 21% (36/168) | 0.897 |
| | ICANS | 13% (2/15) | 22% (37/166) | 0.530 |
| | Infection any grade | 21% (3/14) | 42% (70/168) | 0.151 |
| Toxicity Management | Received tocilizumab | 27% (4/15) | 27% (43/159) | 0.999 |
| | Received steroids | 20% (2/15) | 16% (24/155) | 0.999 |

- 2 patients with DS-ALL died after tisagenlecleucel infusion
  - 1 Non-responder died of disease
  - 1 Responder died of infection while in remission 123 days after tisagenlecleucel.

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33 H Pacenta. SIOP. 2021.

33

## HOW DO WE TREAT AND PREVENT RELAPSE AFTER CAR?

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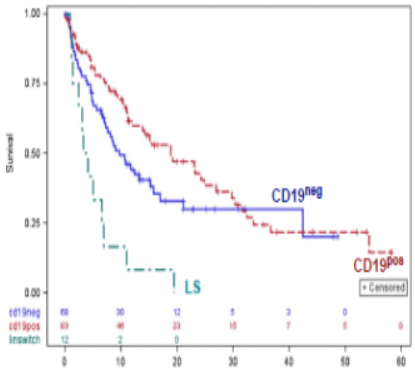
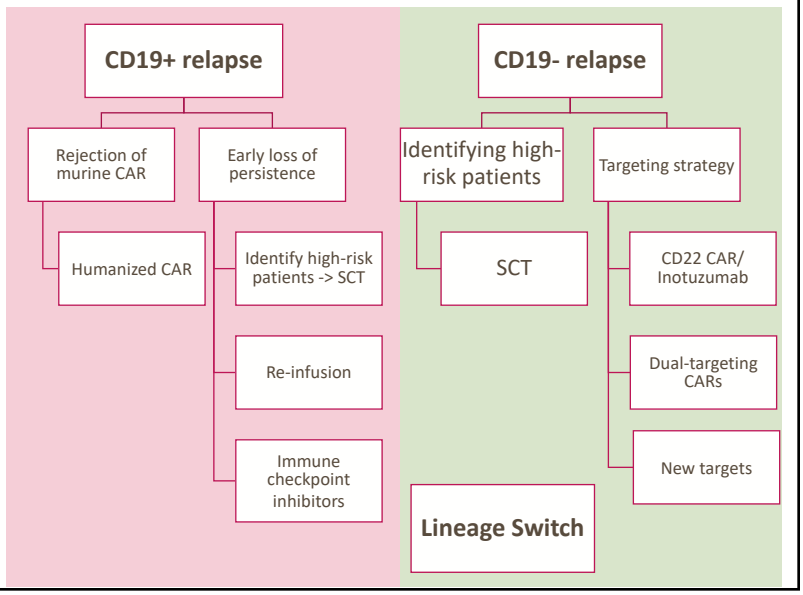
# APPROXIMATELY 50% OF PEDIATRIC PATIENTS ULTIMATELY RELAPSE

Outcome post CART relapse is poor




A. Lamble. ASH 2021.

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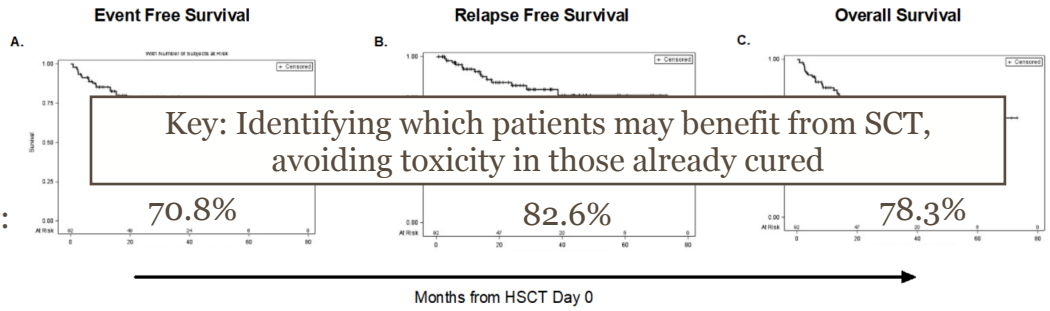
# SCT FOLLOWING CAR T-CELLS: CARNATION DATA

- 92 patients underwent consolidative HSCT within first year after CD19 CAR
  - Planned CAR as bridge to HSCT (n=52, many CD28 CARs, median 93 days)
  - B-cell recovery (n=39, median 146 days)
  - Bone marrow aplasia (n=1)




[36] R Myers. JCO. 2021.

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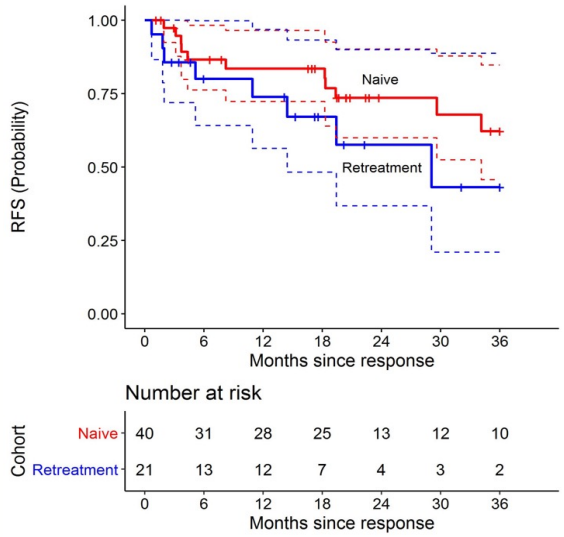
# HUMANIZED CAR T-CELLS




CAR-naïve cohort: 40/41 CR (98%) but 26 were MRD-neg at infusion

Retreatment cohort: 26/33 CR (79%) but 15 were MRD-neg at infusion
CR with B cell aplasia 21/33 (64%)

6-month probability of B cell recovery: 15% v 29% on CTL019, p=0.15

Similar safety profile: decreased severe CRS, but small proportion of patients with high-tumor burden

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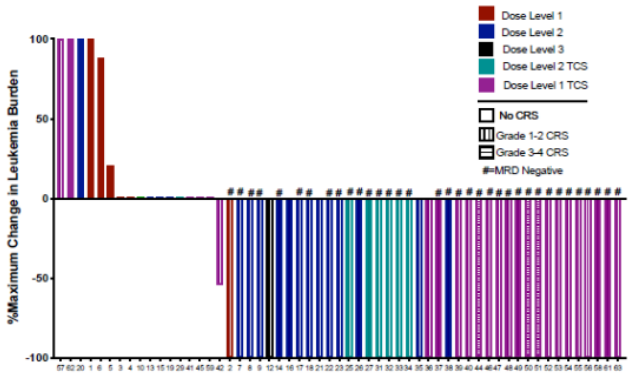
[37] R Myers. JCO. 2021.

37

# ALTERNATIVE CAR TARGETS FOR CD19-LOSS

- CD22 (NIH/CHOP)
  - 70% CR rate (40/58), 88% MRD neg
  - Consolidative transplant
  - CRS 10%, little neurotoxicity

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[38] N. Shah et al. J. Clin Oncology 2020

38

# IMMUNOTHERAPY FOR NEUROBLASTOMA

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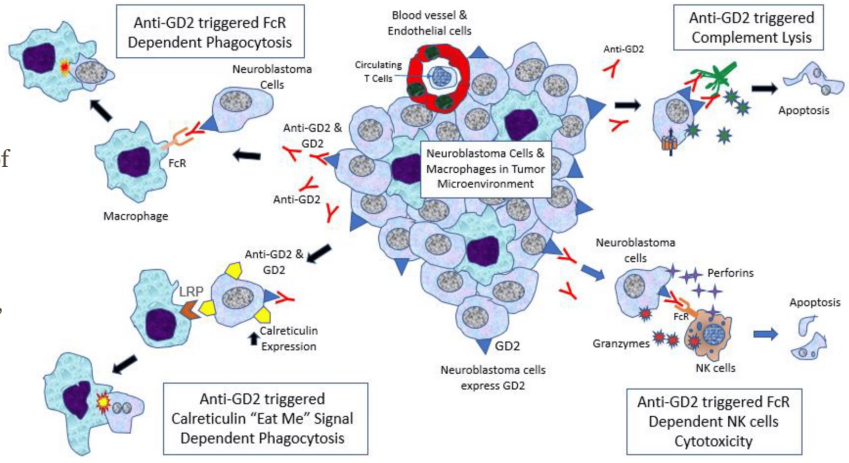
# DINUTUXIMAB

Antibody against GD2
- Expressed on surface of most neuroblastoma cells
- Normal neuron expression
- Main side effects: pain, allergic reactions




40 Chan. Biomolecules. 2022.

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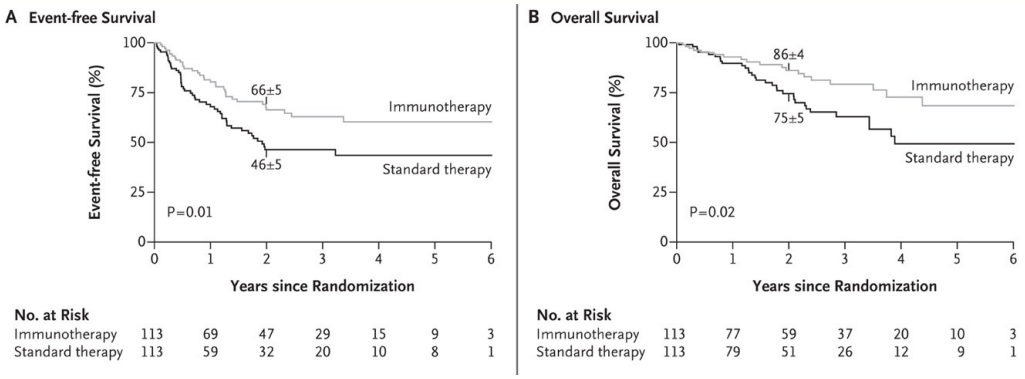
# DINUTUXIMAB IMPROVES SURVIVAL FOR CHILDREN WITH NEUROBLASTOMA

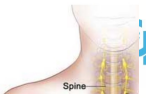



**FDA Approves First Therapy for High-Risk Neuroblastoma**

Subscribe

March 27, 2015, by NCI Staff

The Food and Drug Administration (FDA) has approved dinutuximab (Unituxin™) as part of first-line therapy for children with high-risk neuroblastoma—the first approval of a therapy specifically for patients with the high-risk form of this disease. The FDA approval covers the use of

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41 Yu. NEJM. 2010.

41

# INTO THE FUTURE: IMMUNOTHERAPY FOR SOLID TUMORS, BRAIN TUMORS

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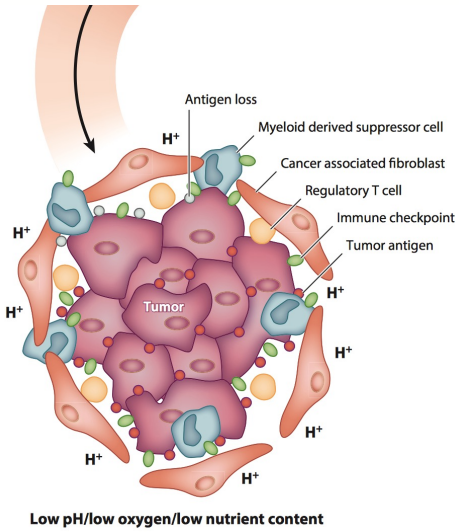
# BARRIERS TO IMMUNOTHERAPY IN SOLID TUMORS

- Immunosuppressive microenvironment
- Poor blood supply
- Lack of specific tumor associated antigens not present on normal cells
- Potential antigen loss if not critical for cancer cell survival




43 Newick et al Annu. Rev. Med. 2017

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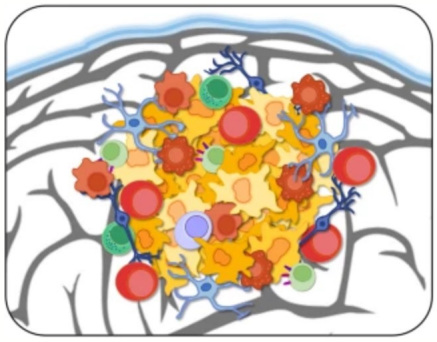
# BARRIERS OF IMMUNOTHERAPY IN CNS

- Blood-brain barrier and CSF-brain barrier
- Pediatric CNS tumors generally "cold"
- Potential for CNS toxicity
  - Inflammation
  - On-target/off-tumor effect



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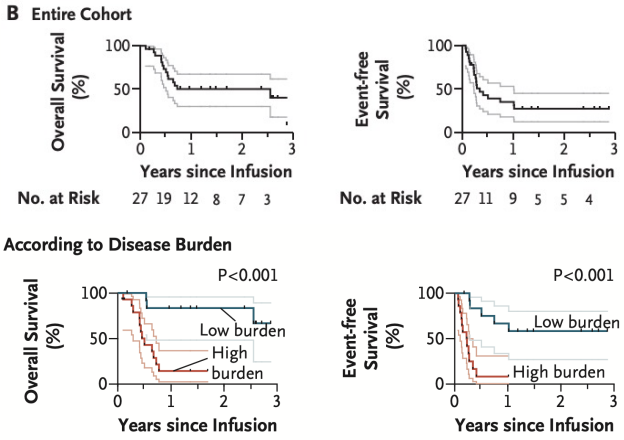
# GD2 CAR T-CELLS FOR NEUROBLASTOMA

- N=27
  - Overall response rate 63%
    - 9 CR, 8 PR
  - Patients on P2D: OS 60%, EFS 36%
- Toxicities:
  - CRS very frequent (74%) but usually mild (G1-2)
  - Hepatic toxicity
  - Brain hemorrhage in 1 patient




45 Del Bufalo et al. NEJM 2023

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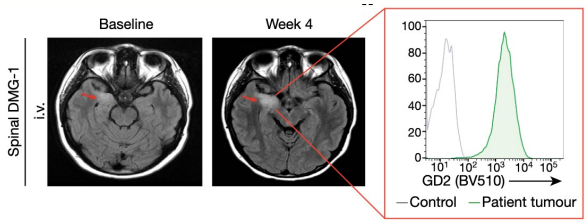
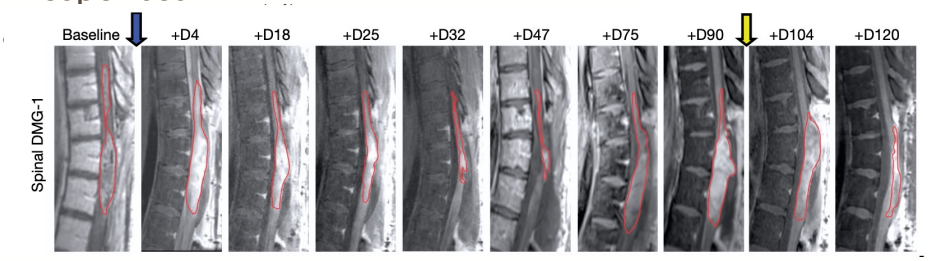
# CAR T CELLS–

- GD2-CAR given IV, subsequent doses ICV
- DIPG (n=3), spinal DMG (n=1)
- 3 of 4 patients with objective responses




Majzner et al. Nature 2022

46

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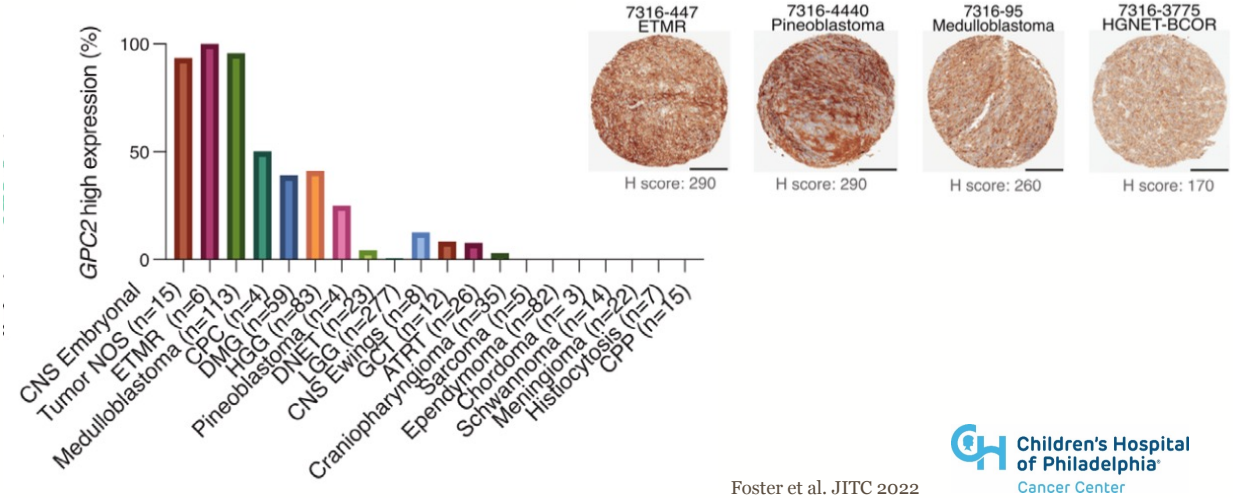
# GPC2 AS A NEW TARGET




Foster et al. JITC 2022

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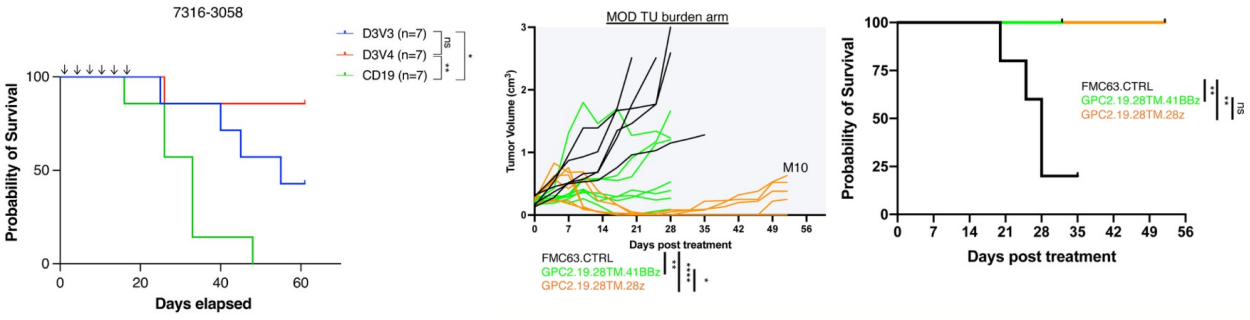
# GPC2 CAR T-CELLS EFFECTIVE IN PRECLINICAL STUDIES

Diffuse Midline Glioma

Neuroblastoma




48

Foster. JITC 2022. Heitzeneder. Cancer Cell. 2022

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## OTHER TARGETS IN CLINICAL TRIALS

- MAGE-A4 – sarcomas
- B7H3 – sarcomas, medulloblastoma
- Her2 – sarcomas
- CD33/123 – AML
- CD7 – T-ALL
- Many more…



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## OTHER IMMUNOTHERAPEUTIC STRATEGIES IN DEVELOPMENT

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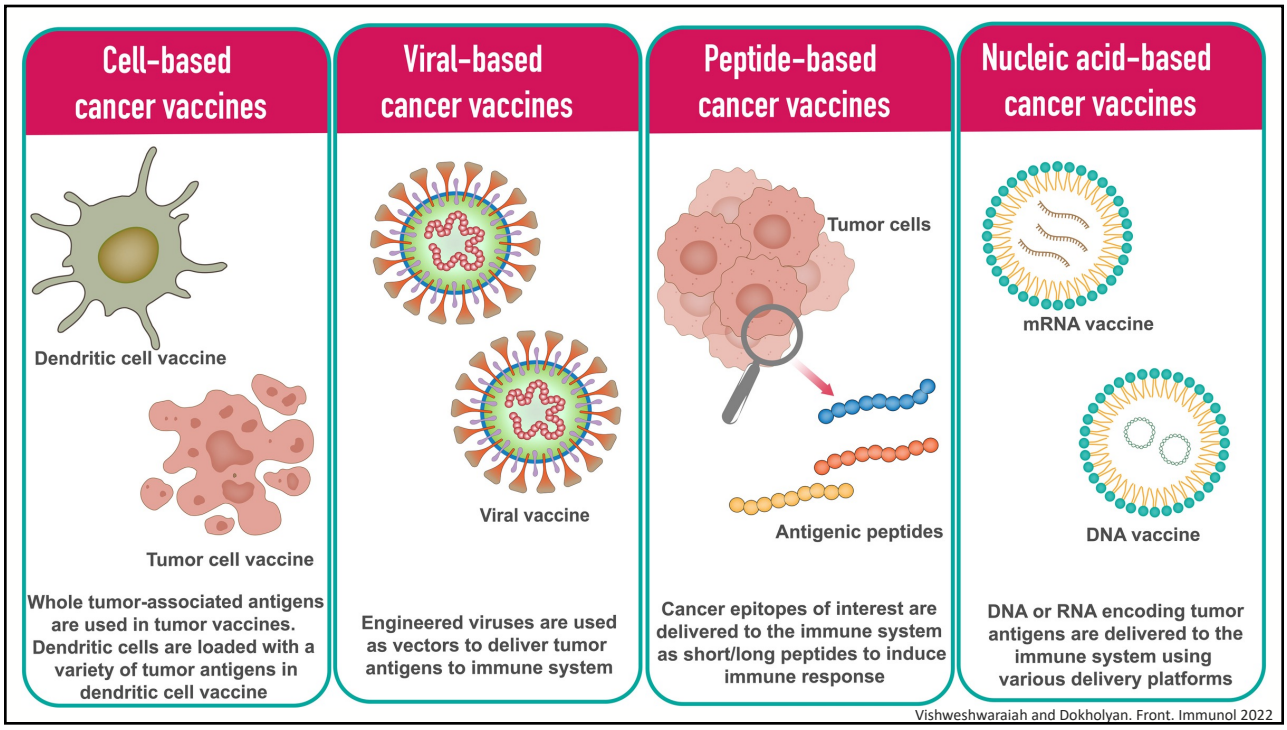
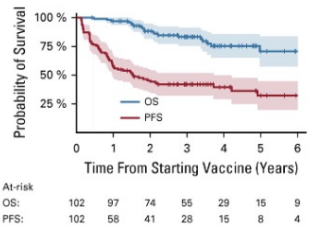


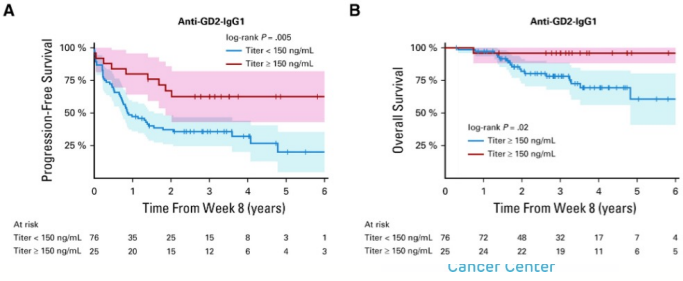

Vishweshwaraiah and Dokholyan. Front. Immunol 2022

51

## CARBOHYDRATE VACCINE – GD2/GD3

- 101 patients with relapsed HR neuroblastoma
  - 5 year PFS 32%, OS 71%
- Anti-GD2-IgG1 titer ≥ 150 ng/mL by week 8 was associated with favorable PFS and OS
- Prior episodes of PD and the time from last PD to vaccine were associated with PFS




52 Cheung et al. JCO 2021

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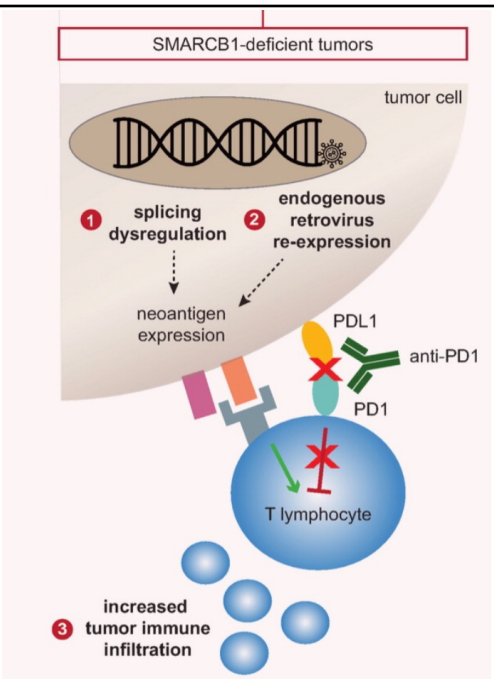
# ANOTHER LOOK AT CHECKPOINT INHIBITORS

- Replication repair deficient tumors
- Malignant rhabdoid
- Atypical teratoid/rhabdoid
- Undifferentiated chordoma
- Renal medullary carcinoma
- Epithelioid sarcoma




53

Long et al. Am Soc Clin Oncol Educ Book. 2022

53

# SUMMARY

- Immunotherapy has revolutionized the care of patients with B-ALL and neuroblastoma
  - Still significant unmet need in these diseases
- Many exciting areas of development for other pediatric tumors
  - Primary focus has been targeted immunotherapeutics against specific cell surface markers
  - Challenges exist in solid and brain tumors, but exciting preliminary results

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## QUESTIONS

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