
3rd Cuneo City ImmunoTherapy Conference (CCITC)
Penn Medicine
Center for Cellular Immunotherapies
Immunotherapy in Hematological Malignancies 2023
CUNEO
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Spazio incontri Fondazione CRC
Modulation of apoptosis to enhance CAR-T immunotherapy
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Scientific Director Lymphoma Program
Organized by Prof. Massimo Massaia, SC Ematologia AO S.Croce e Carle, Cuneo, Italy
and Centro Interdipartimentale di Ricerca in Biologia Molecolare (CIRBM), Torino, Italy

Disclosures of Marco Ruella:

- ***Inventor:*** CART technologies, Univ. of Pennsylvania, partly licensed to Novartis, Tmunity, and viTToria biotherapeutics
- ***Research Funding:*** AbClon, Beckman-Coulter, ONI, Lumicks, Gemini Bio, viTToria bio
- ***DSMB****:* PeproMene
- ***Consultancy/Honoraria:*** nanoString, GLG
- ***Advisory Board:*** AbClon, BMS, Sana, GSK, Bayer, viTToria bio
- ***Scientific Founder:*** viTToria biotherapeutics

Exciting years for CART immunotherapy for r/r CD19+ and BCMA+ malignancies

August 2017: **Ped. and AYA B-ALL**
May 2018: **LBCL;** ***May 2022:*** **FL**

July 2020: **MCL**
Oct 2021: **adult B-ALL**

March 2021: **MM**

October 2017: **LBCL + 2nd line**
March 2021: **FL**

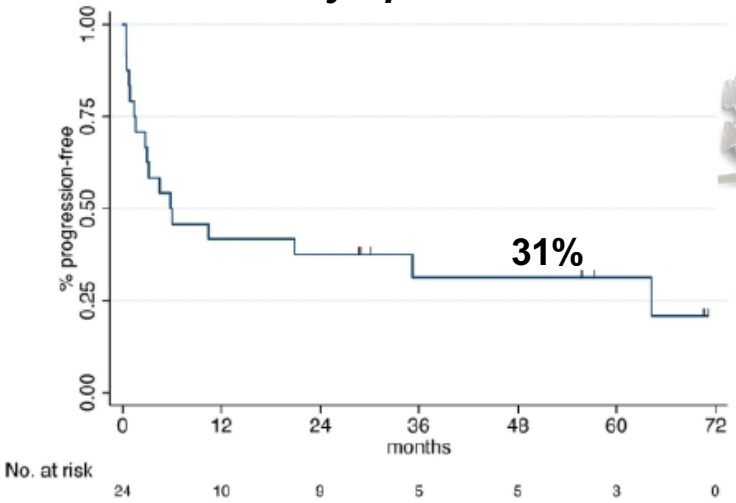
February 2021: **LBCL + 2nd line**

March 2022: **MM**

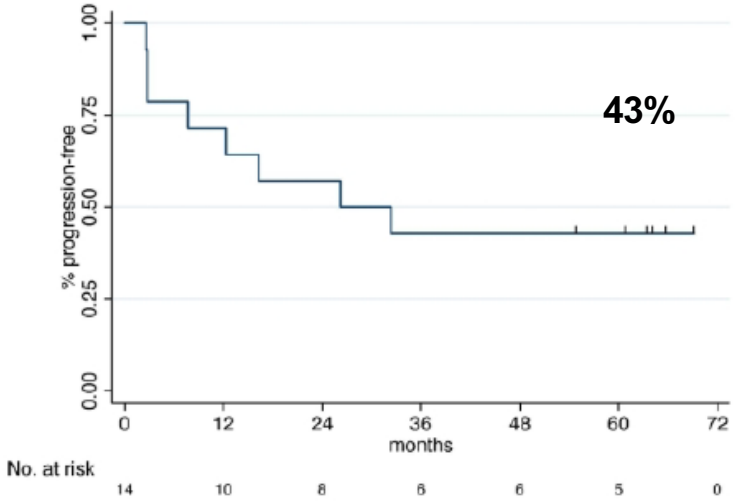
Long-term (5yrs) results of CART19 for non-Hodgkin lymphoma

Progression-free survival

Diffuse large B-cell lymphoma



Follicular Lymphoma

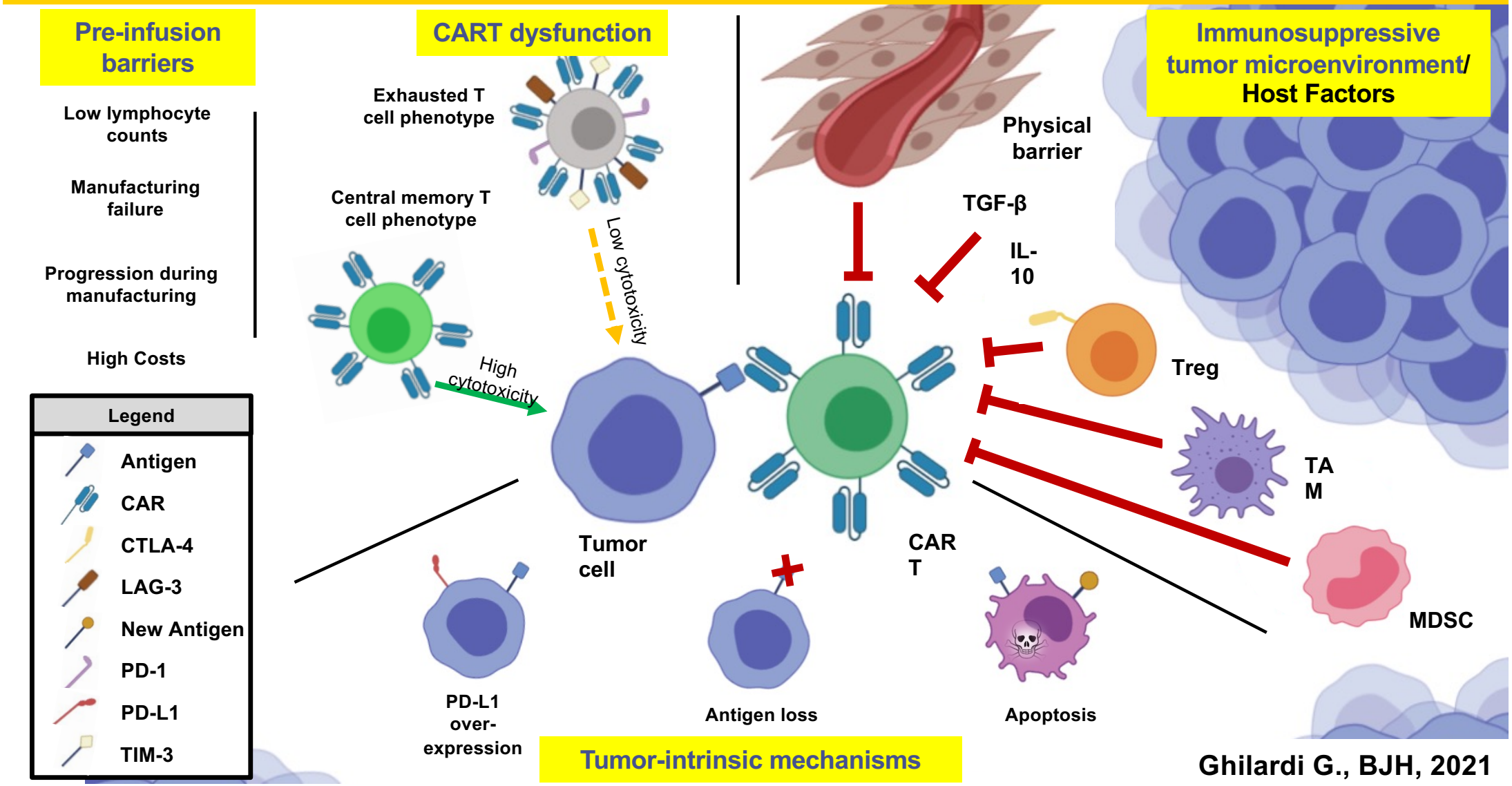


Resistance Mechanisms → **Novel Effective Approaches**

Chong E., Ruella M., Schuster S.J., NEJM, 20

The NEW ENGLAND JOURNAL of MEDICINE

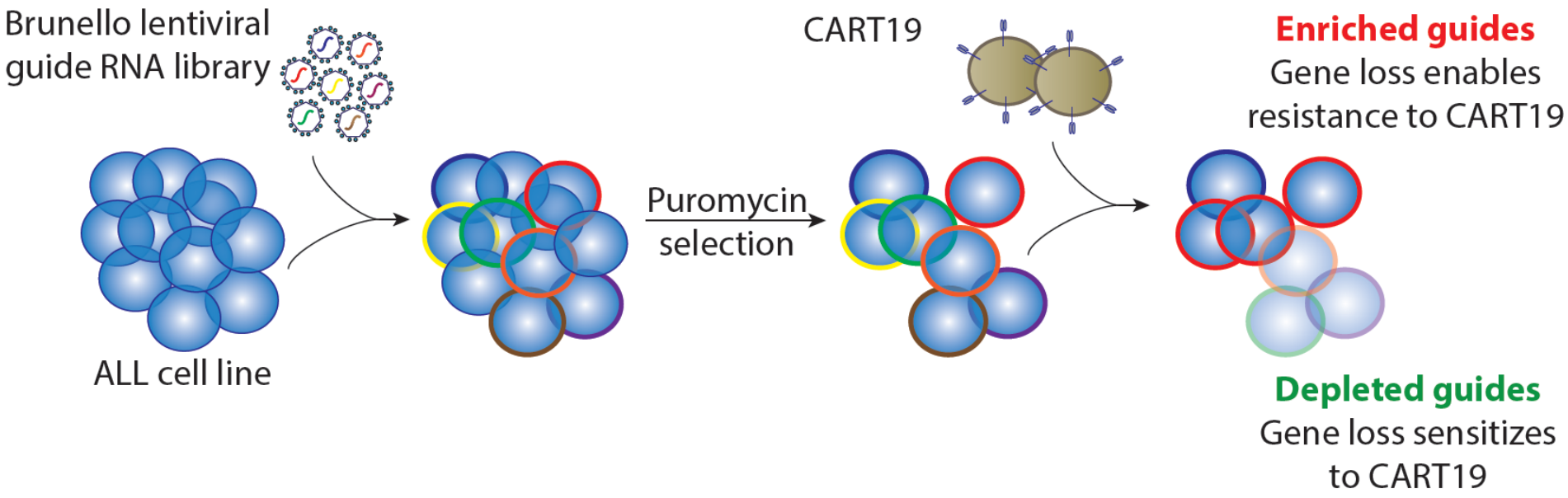
Causes of Failure of CART19 Immunotherapy



Ghilardi G., BJH, 2021

Interrogating CD19+ relapses with Functional Genomics

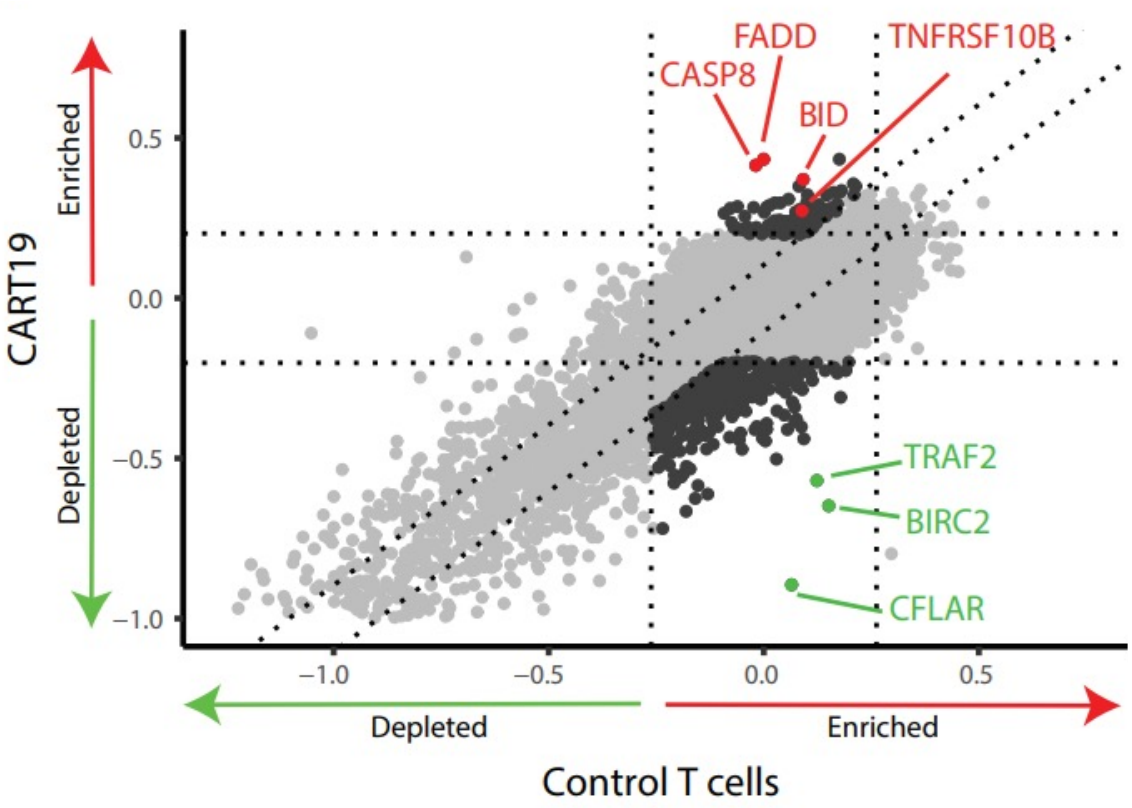
Genome-wide CRISPR-Cas9 Knock-out Screening to Identify Resistance to CART19



Singh N., Lee YG, Cancer Discov, 2020

Modeling Resistance Primary Resistance

gRNA NGS after 24-hour co-culture

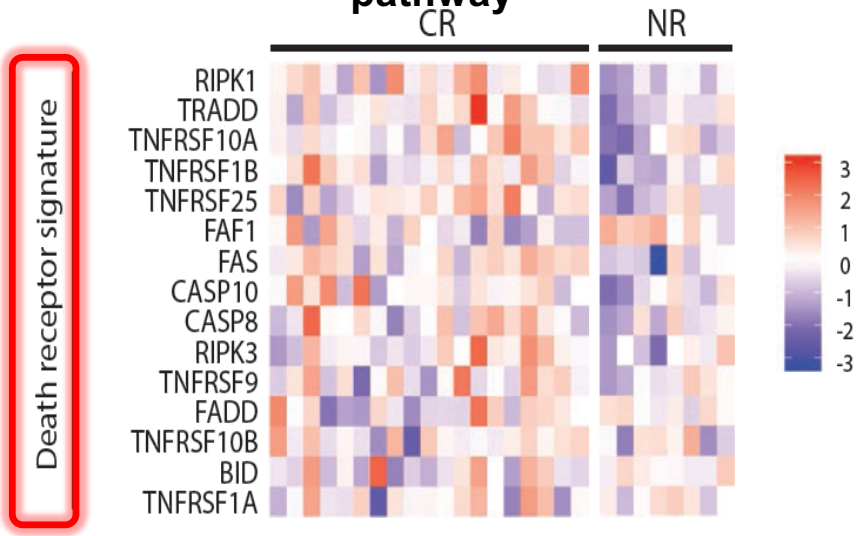


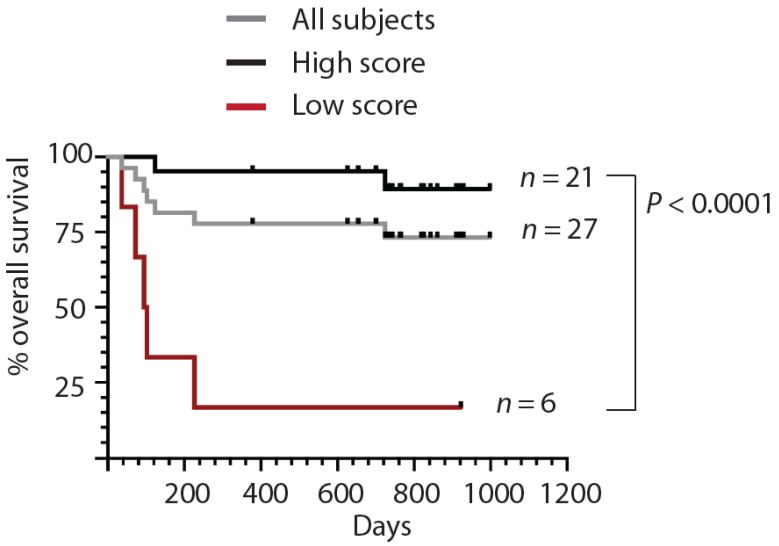
Singh N., Lee YG, Cancer Discov, 2020

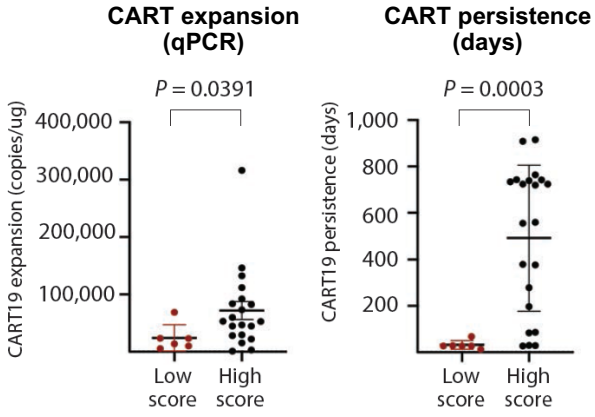
Extrinsic apoptosis and CART outcomes in ALL

Pediatric B-ALL trial (ELIANA)

mRNA expression of positive regulators of the extrinsic apoptotic pathway





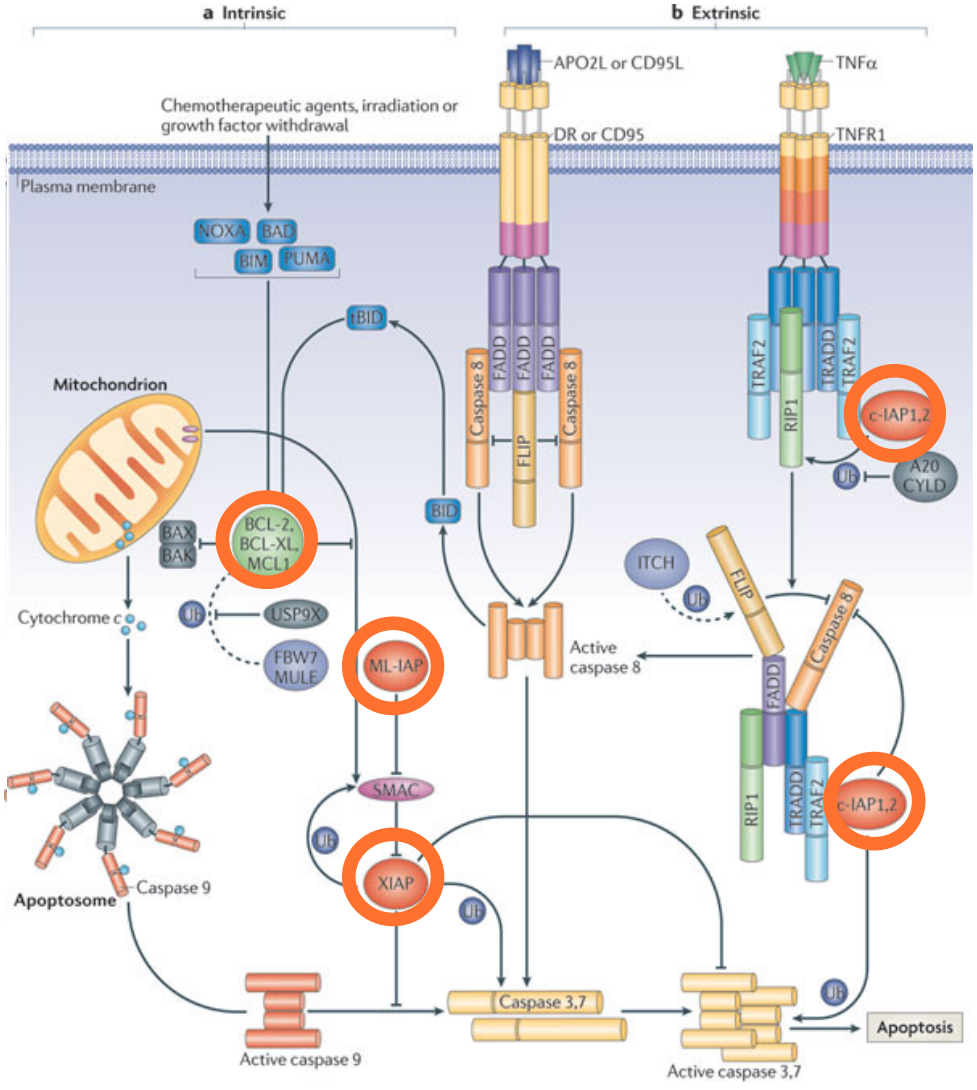


Singh N., Lee YG, Cancer Discov, 2020

Apoptosis as the key for cancer resistance

Genome-wide CRISPR-KO Screening (~80,000 gRNAs)

Singh N, Cancer Discov, 2020



Vucic *Nat Rev Mol Cell Biol*, 2011

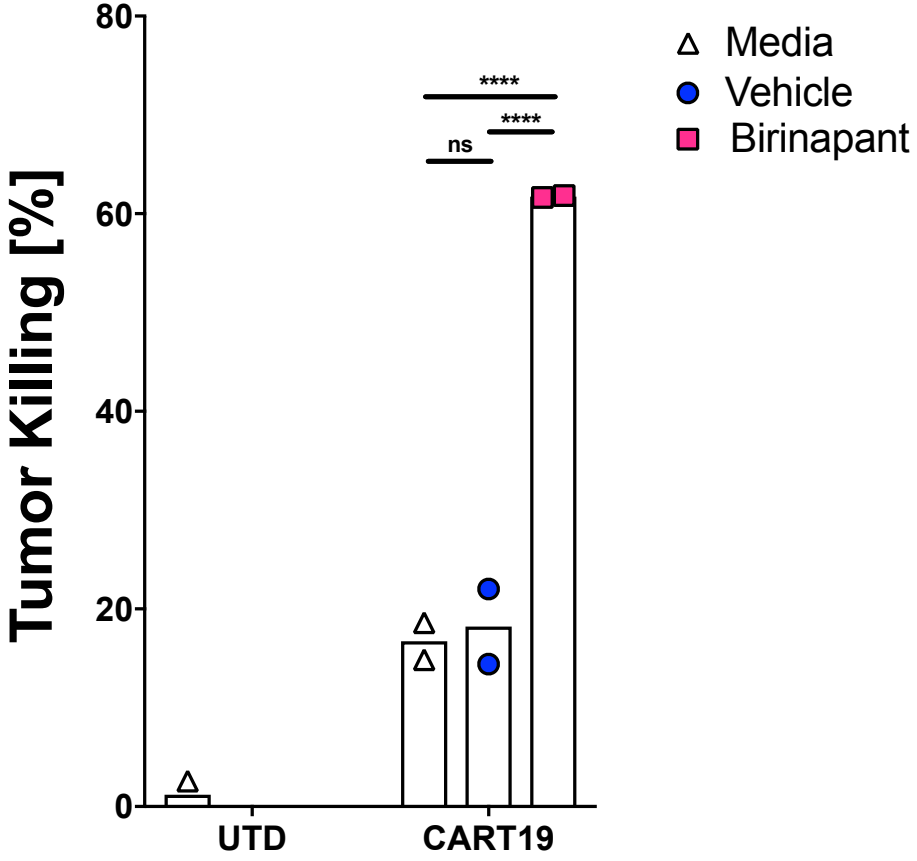
Small Molecule HTS (~3,000 molecules)

Lee YG, Cancer Discov, 2022

1. **SMAC mimetics (birinapant)**
2. **BCL-2 antagonists**

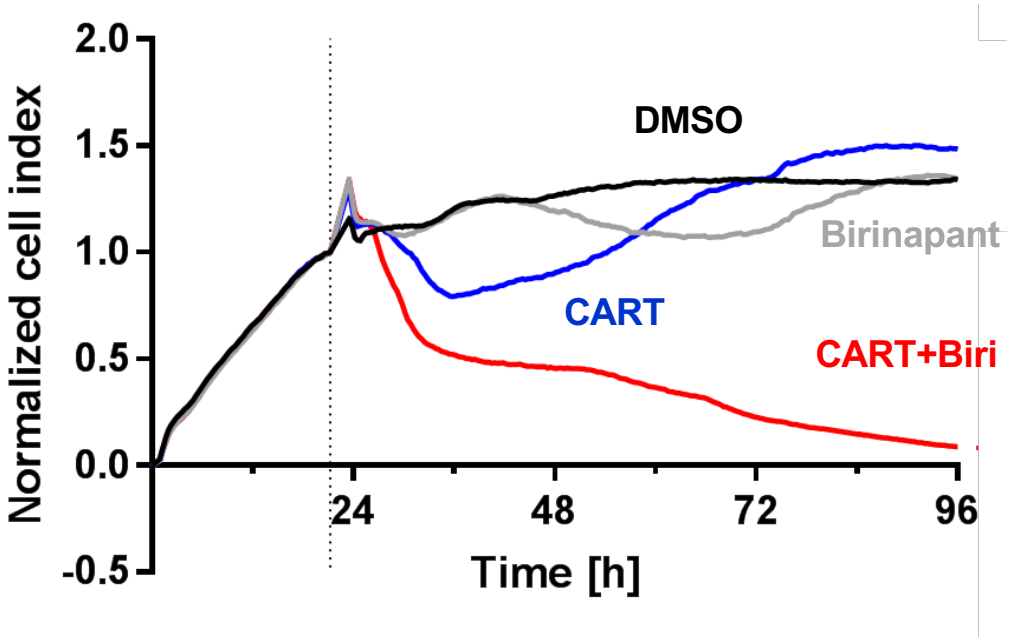
SMAC mimetics enhance CART killing – IN VITRO

Leukemia (CART19 + NALM6)



*E:T=0.03:1, [Drug]=500nM, 48h

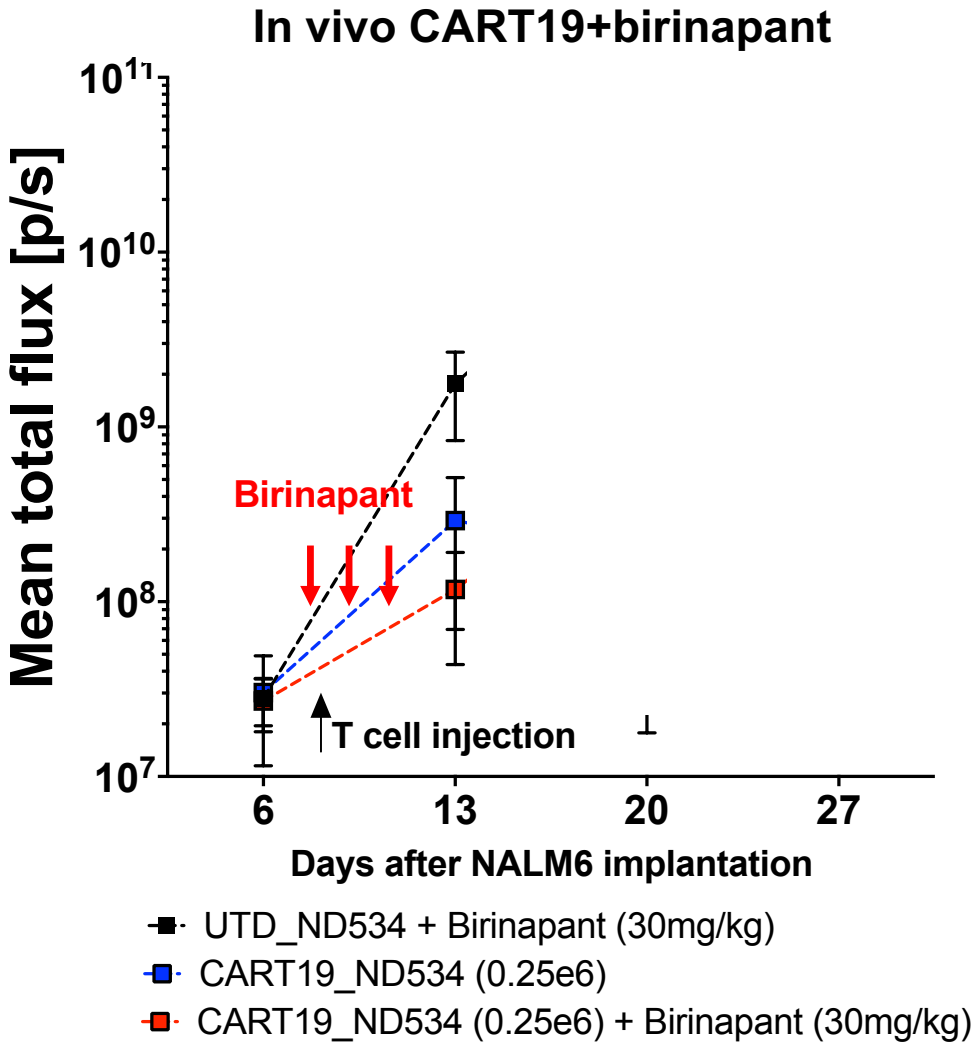
Solid Tumor ovarian cancer (HER2-CART, SKOV3)

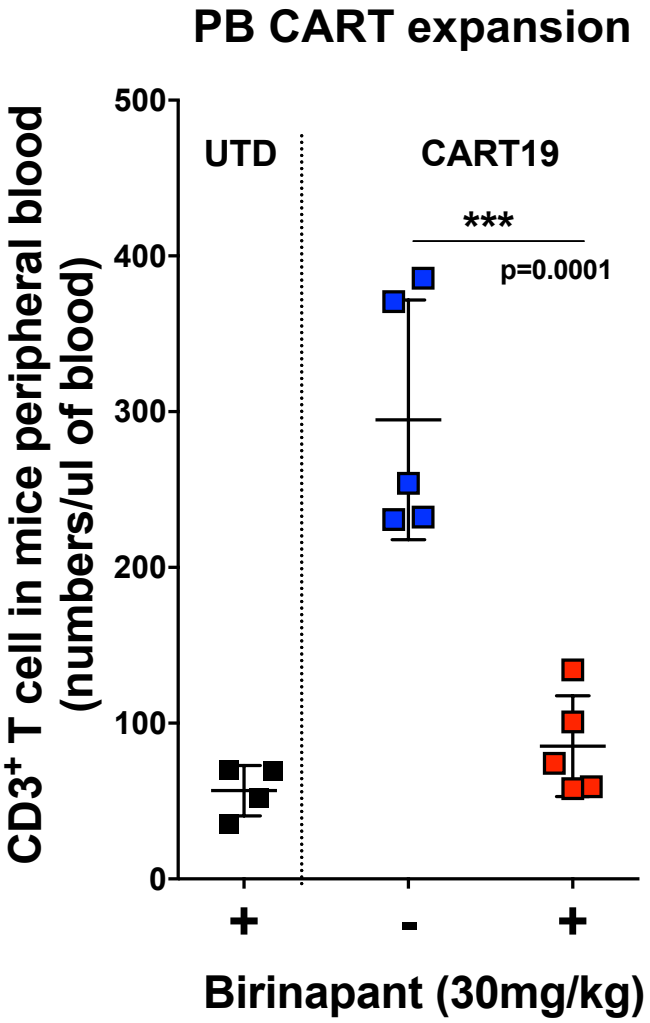


E:T=0.25:1

unpublished

SMAC mimetics are toxic to CART – IN VIVO

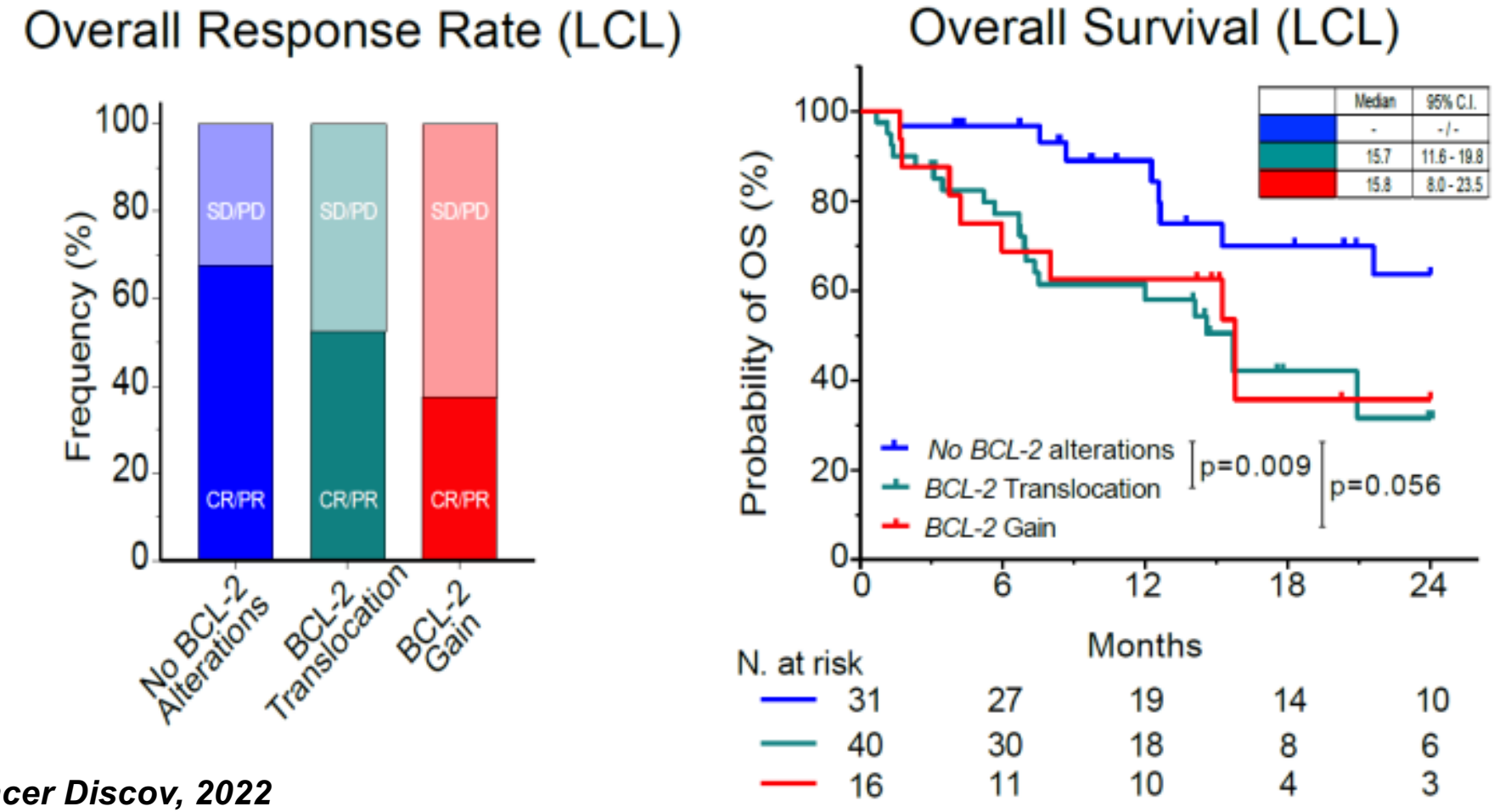




unpublished

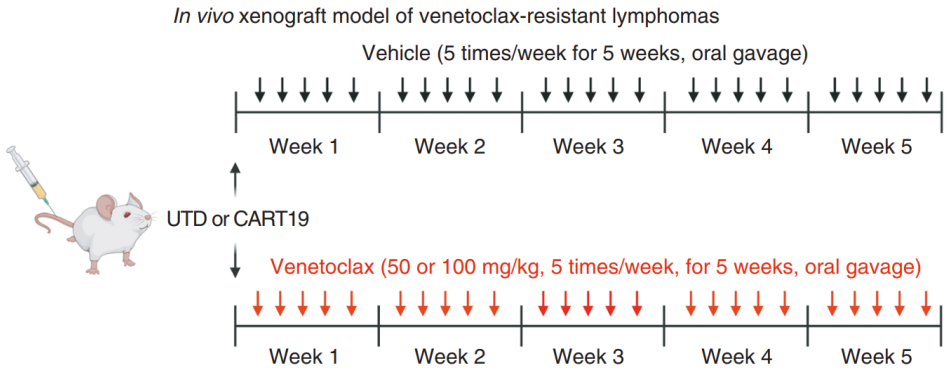
BCL-2 inhibition and CART in lymphoma

Large-cell lymphoma Patients treated with CART19



Lee YG, Cancer Discov, 2022

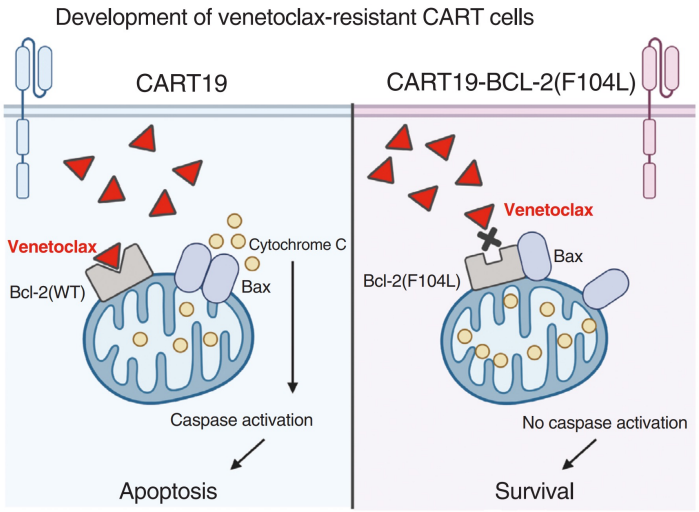
BCL-2 inhibition and CART lymphomas



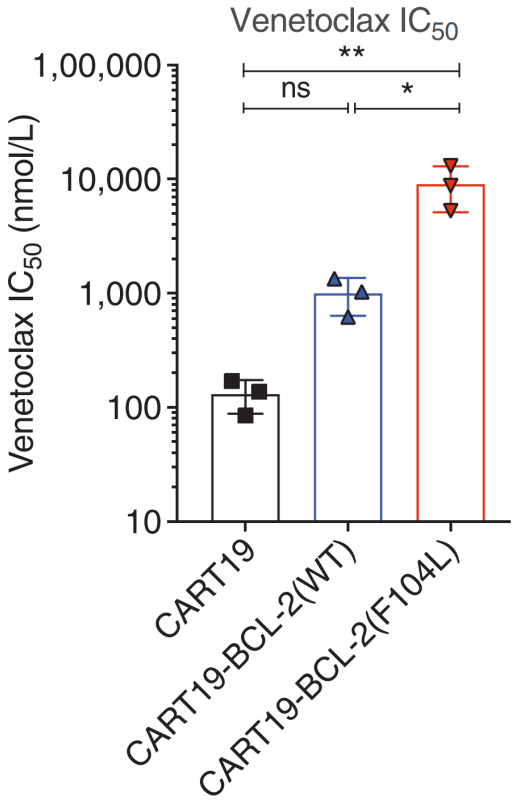
Lee YG, Cancer Discov, 2022

A strategy to increase the therapeutic window of ven-CART

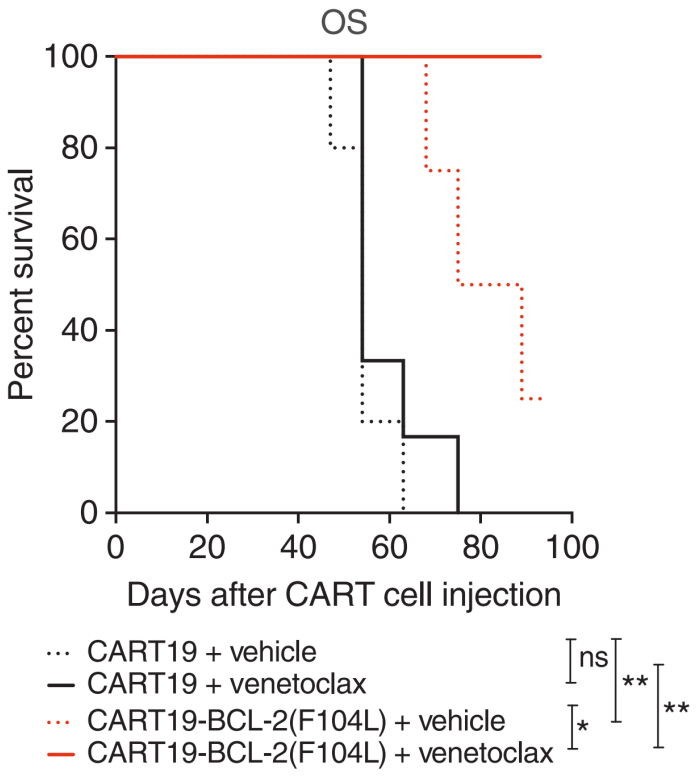
Hypothesis:



BCL-2(F104L) protects CART cells

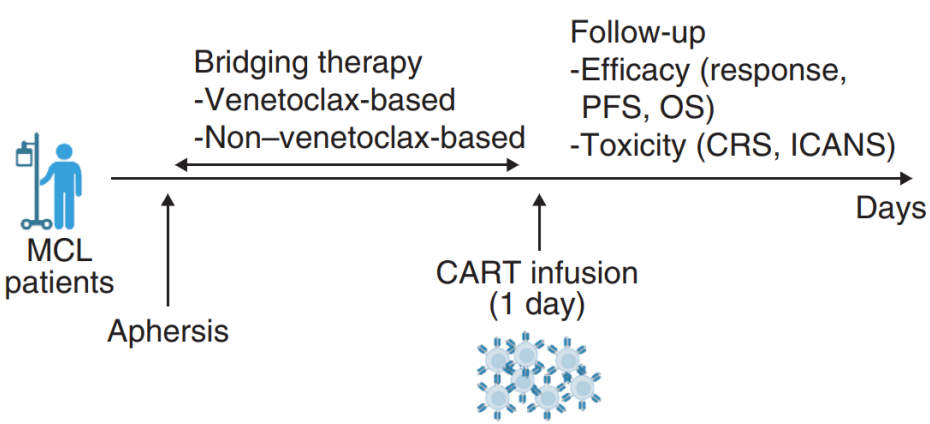


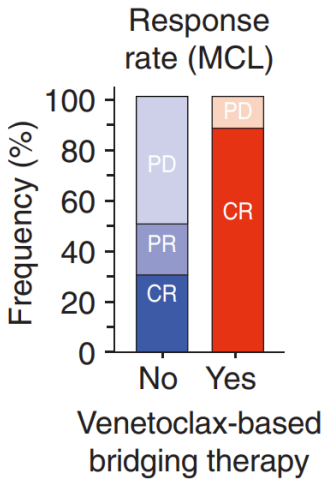
In vivo synergy of CART19-BCL-2(F104L) and venetoclax

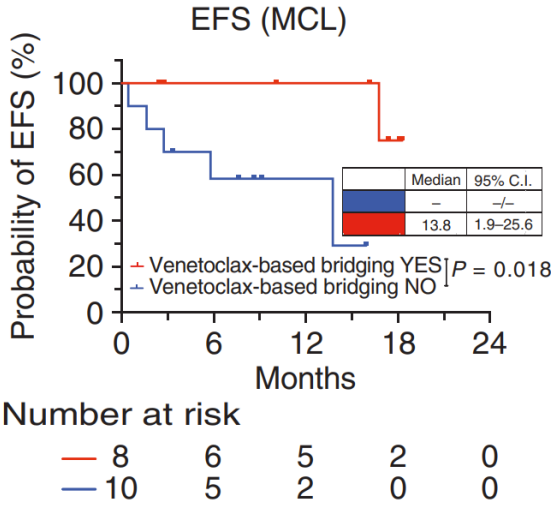


Lee YG, Cancer Discov, 2022

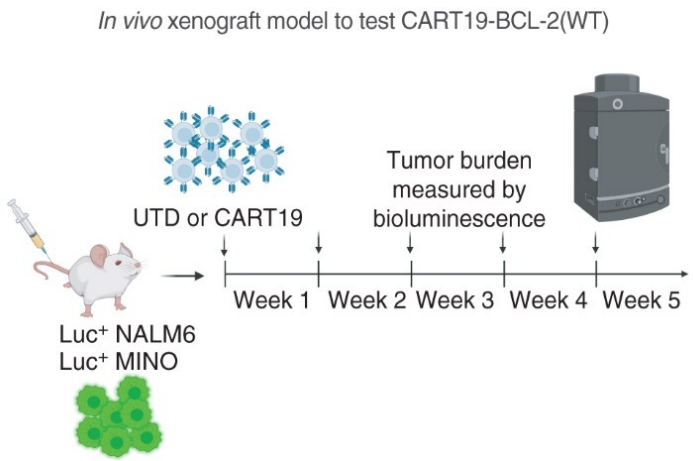
Ventoclax bridging before Tecartus

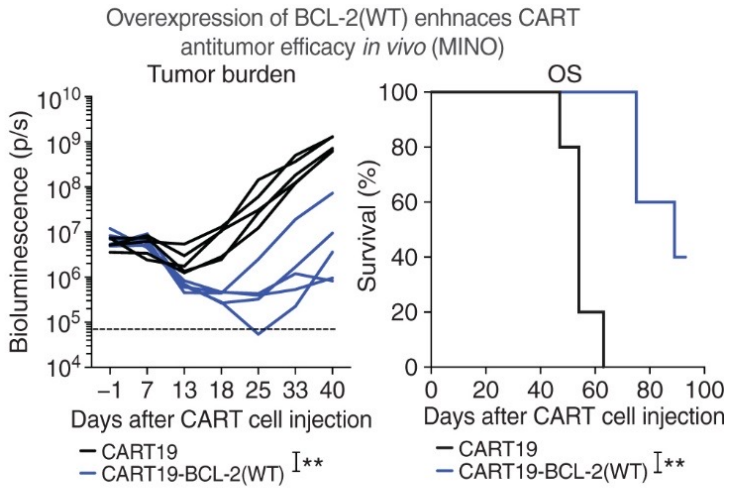


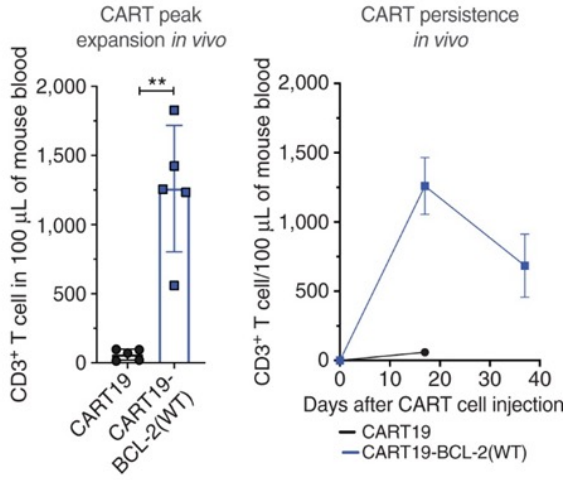


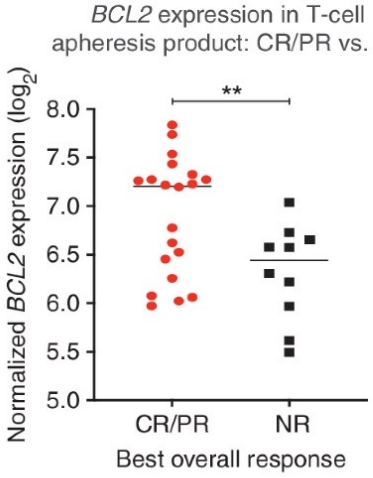


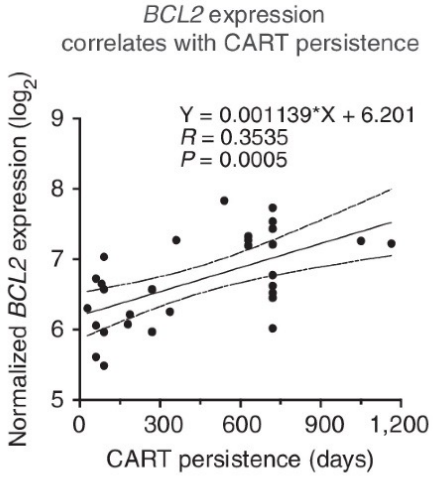
Wild type BCL-2 overexpression enhances CART immunotherapy

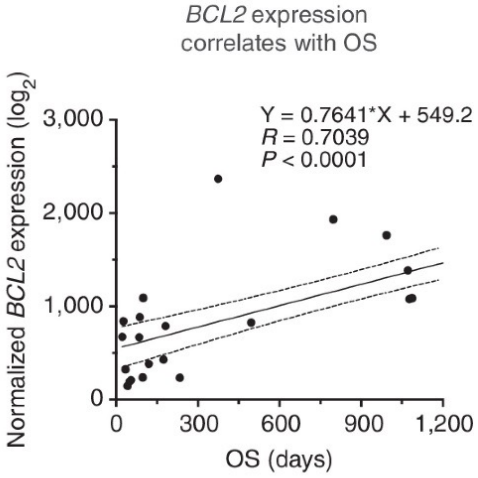












Summary and Perspectives

- CART immunotherapy is leading to ***remarkable results*** in lymphoid malignancies, in particular B-ALL and NHL
- Despites these successes the majority of patients will ***ultimately fail*** this treatment
- We described a new mechanism of resistance involving ***reduced pro-apoptotic factors*** in leukemic cells
- ***Small molecules*** against IAPs or BCL-2 lead to enhanced killing at short term but drive CAR T cell apoptosis over time
- We devised a strategy to make ***CART resistant to BCL-2 inhibition*** and lead to synergy when combined with venetoclax.

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