

3rd Cuneo City ImmunoTherapy Conference (CCITC)

Immunotherapy in Hematological Malignancies **2023**

CUNEO
May 18-20, 2023
Spazio incontri Fondazione CRC

Mechanisms of Resistance to CAR T cells

Federico SIMONETTA MD, PhD



UNIVERSITÉ
DE GENÈVE

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

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(Target antigen related) Mechanisms of Resistance to CAR T cells

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DICHIARAZIONE

Relatore: Federico SIMONETTA

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(Kite/Gilead, Incyte)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(Kite/Gilead, Novartis, BMS/Celgene)**
- Partecipazione ad Advisory Board **(Kite/Gilead, Incyte)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro: sostegno viaggi **(Kite/Gilead, Novartis, AstraZeneca, Neovii, Janssen)**

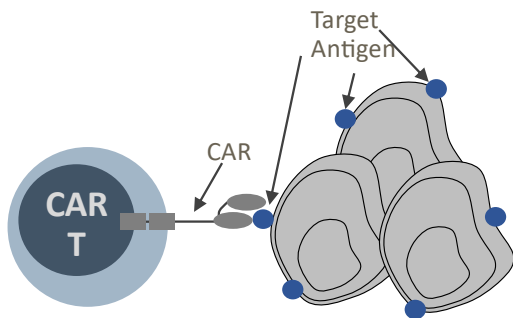
CD19 targeting agents in r/r DLBCL

CD19 CAR T cells

Axicabtagene Ciloleucel

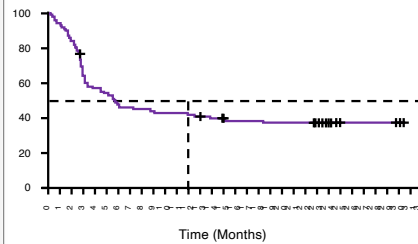
Tisagenlecleucel

Lisocabtagene Maraleucel



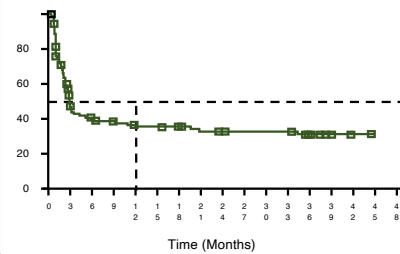
Axicabtagene
Ciloleucel

ZUMA-1



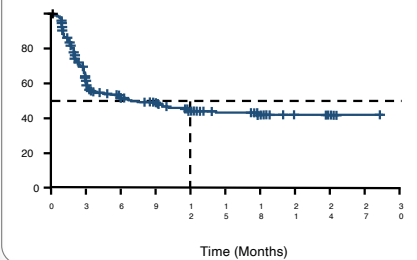
Tisagenlecleucel

JULIET



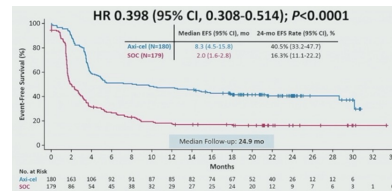
Lisocabtagene
Maraleucel

TRANSCEND NHL 001

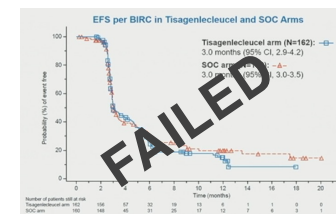


3rd line

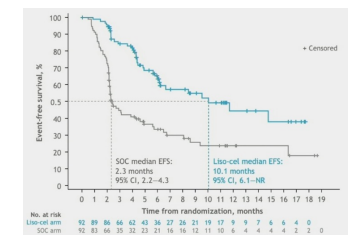
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BELINDA



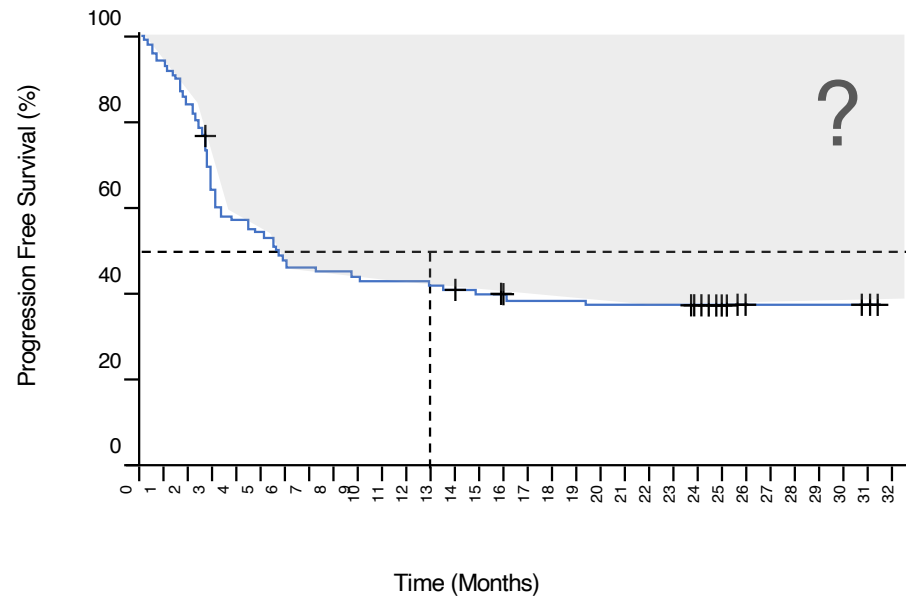
TRANSFORM



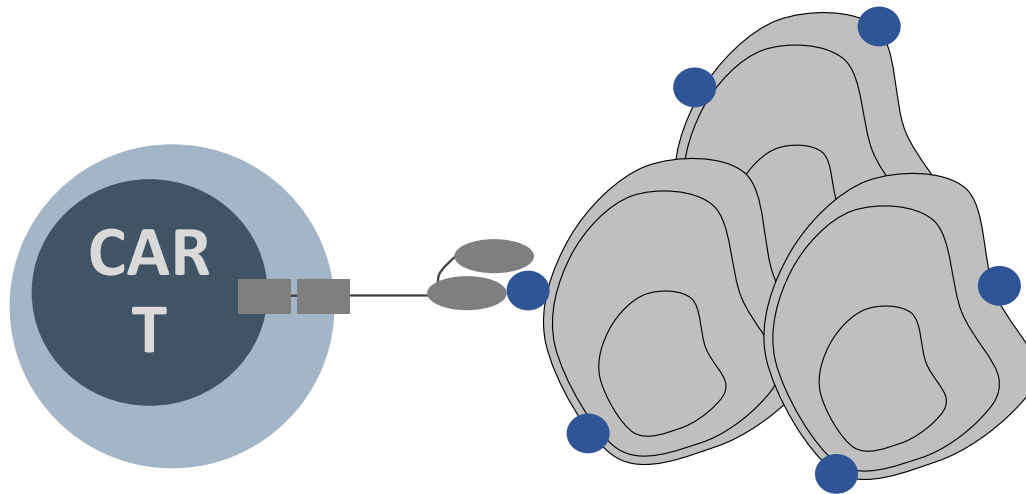
2nd line

FDA, EMA, Swissmedic approved

Why CAR T cells fail in most patients?

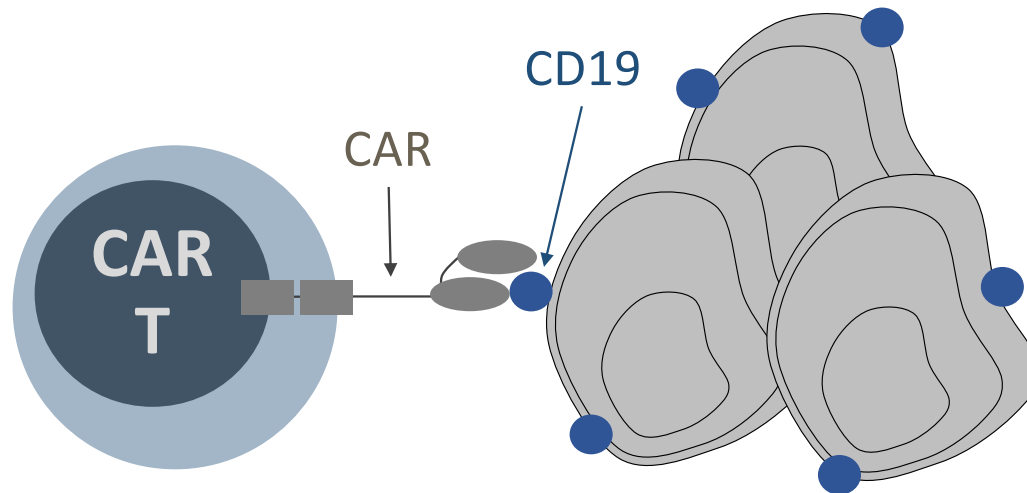


Mechanisms of Resistance to CAR T cell therapy

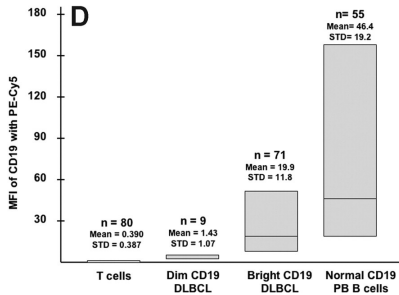
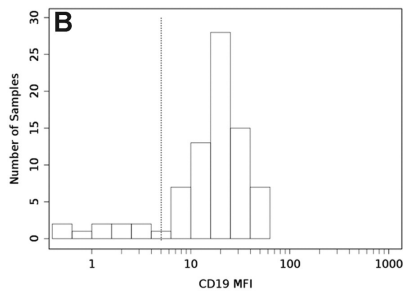


Mechanisms of Resistance to CAR T cell therapy

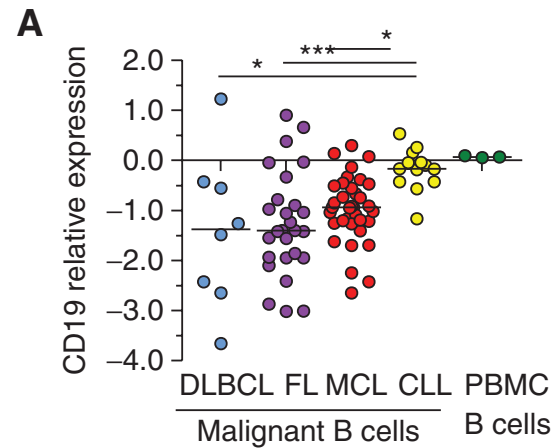
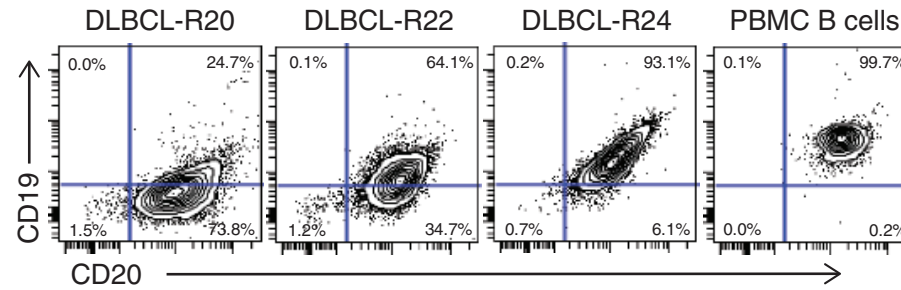
Target antigen expression



CD19 expression in DLBCL

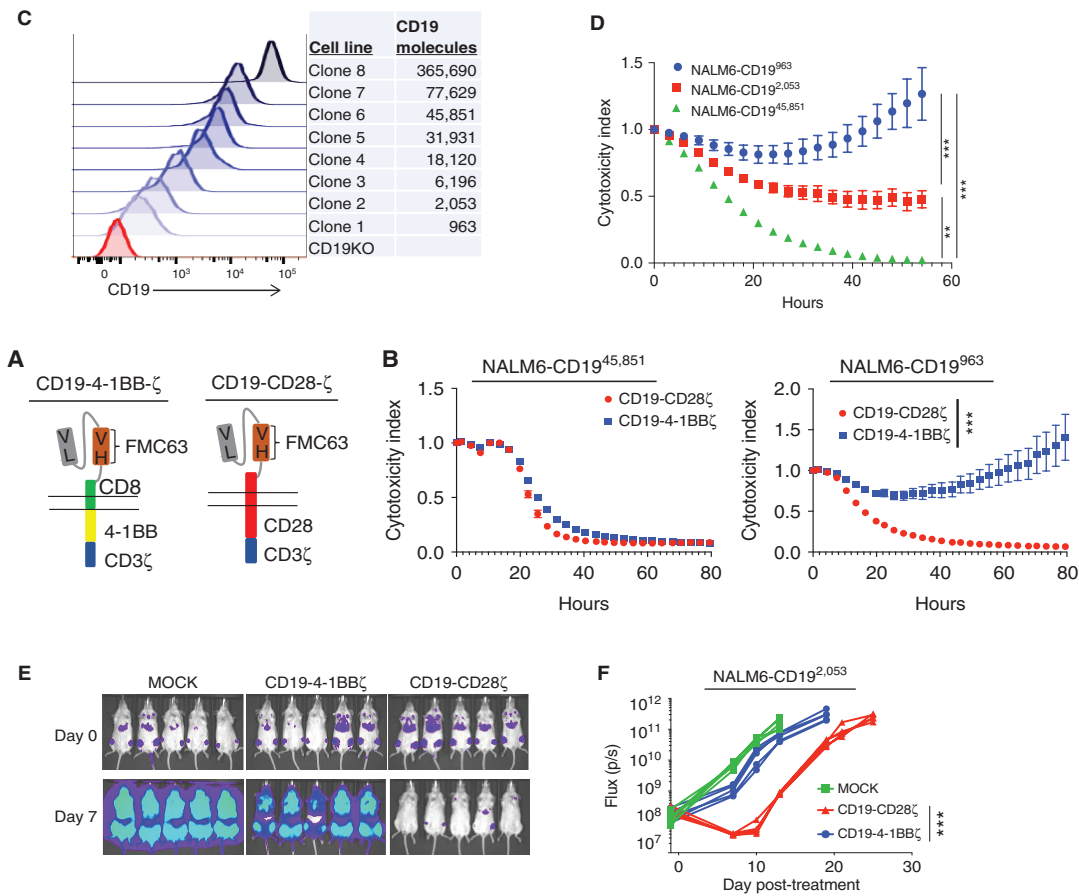


Johnson et al., Blood, 2009

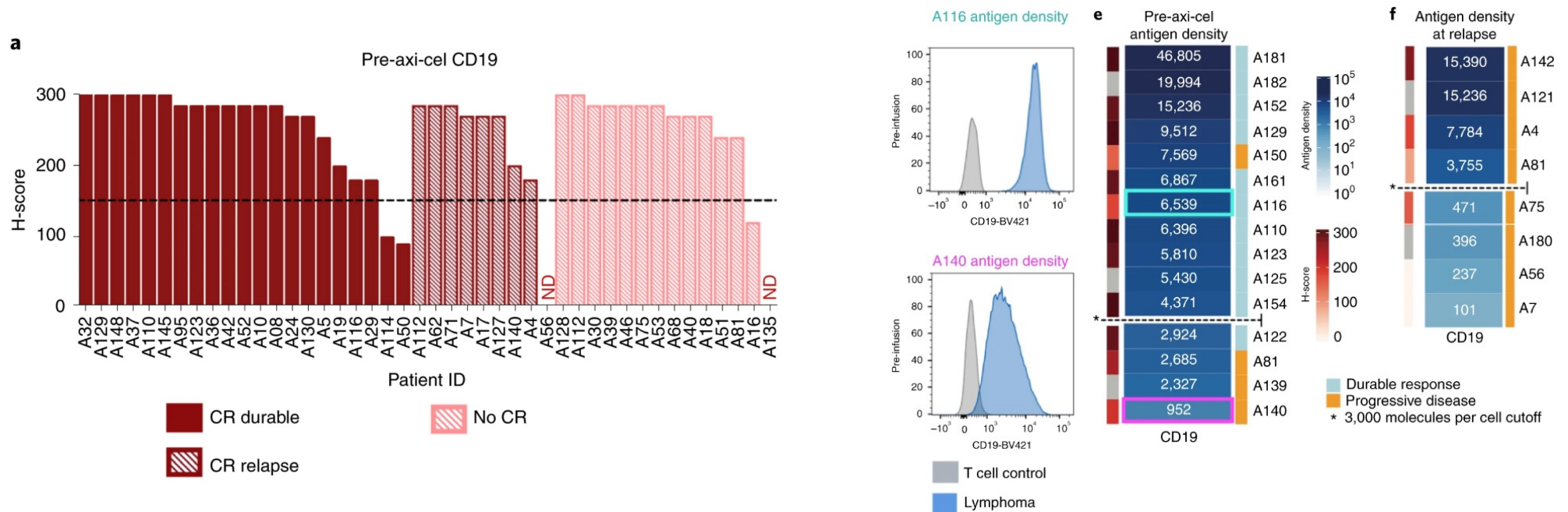


Majzner et al., Cancer Disc 2020

CD19 expression and CAR T cell response

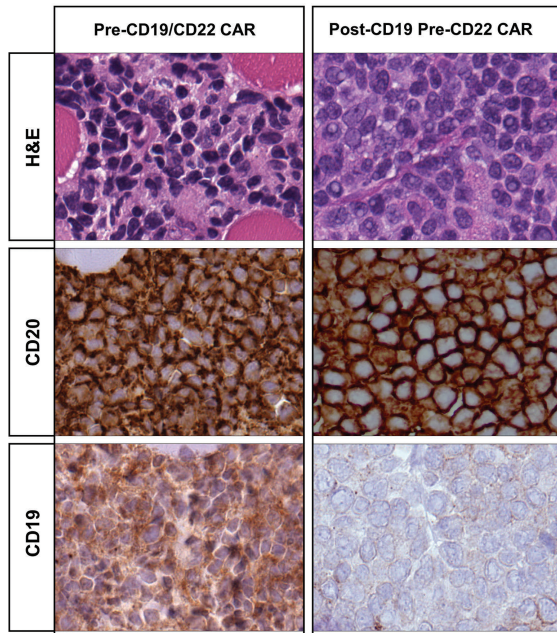


Heterogeneous CD19 antigen density in DLBCL – Potential impact on outcome after CAR T cells?

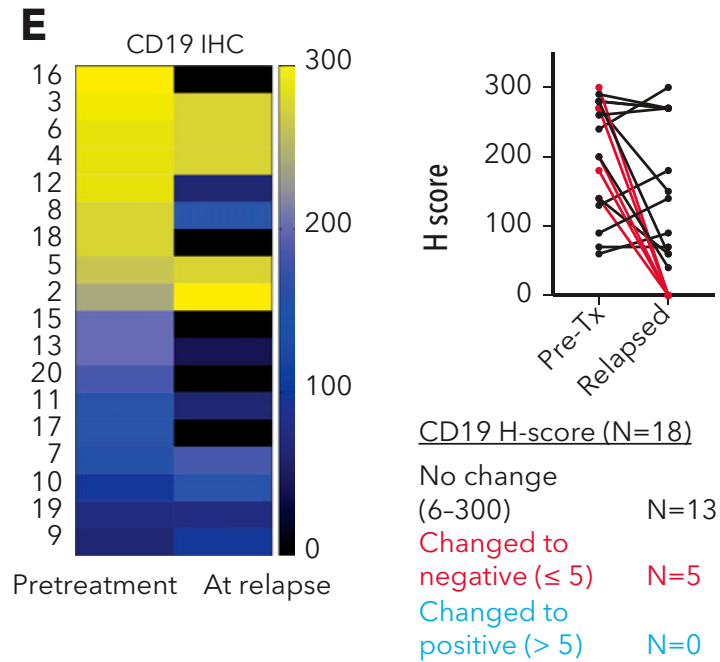


Spiegel et al., Nat Med 2021

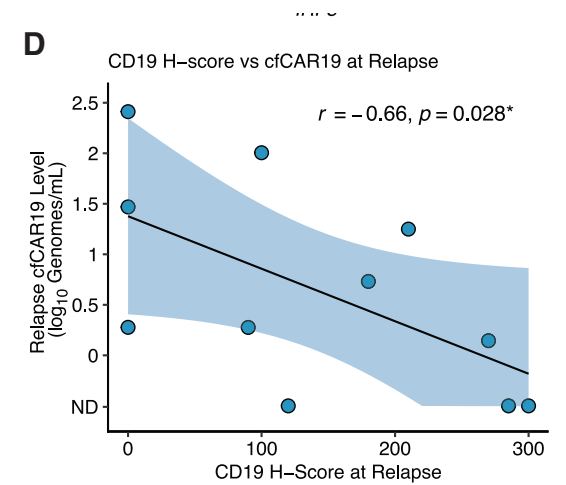
CD19 negative relapse after CAR T cell treatment in DLBCL



Shalabi et al., *Haematologica* 2018



Prinks et al., *Blood* 2021



Sworder et al., *Cancer Cell* 2023

CD19 expression after CAR T cell treatment in DLBCL

Leukemia

















www.nature.com/leu

ARTICLE

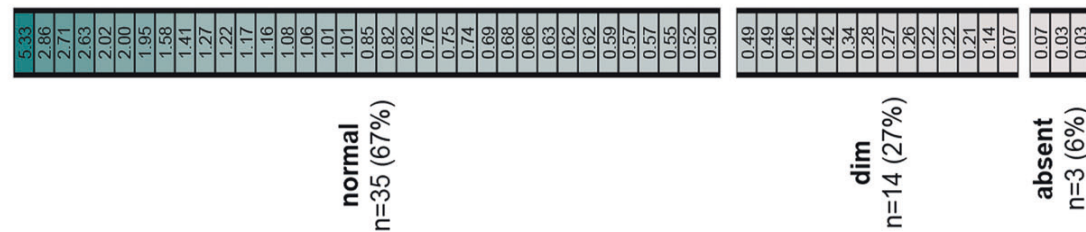
 Check for updates

LYMPHOMA

Outcomes of first therapy after CD19-CAR-T treatment failure in large B-cell lymphoma

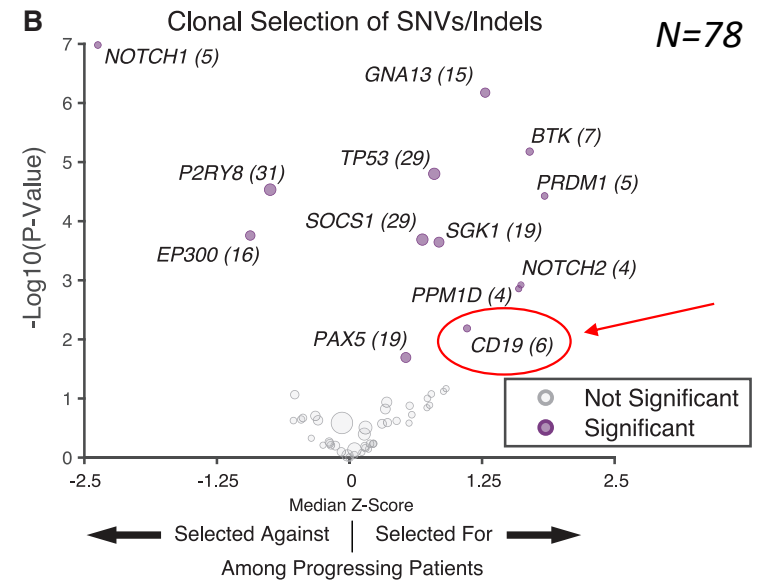
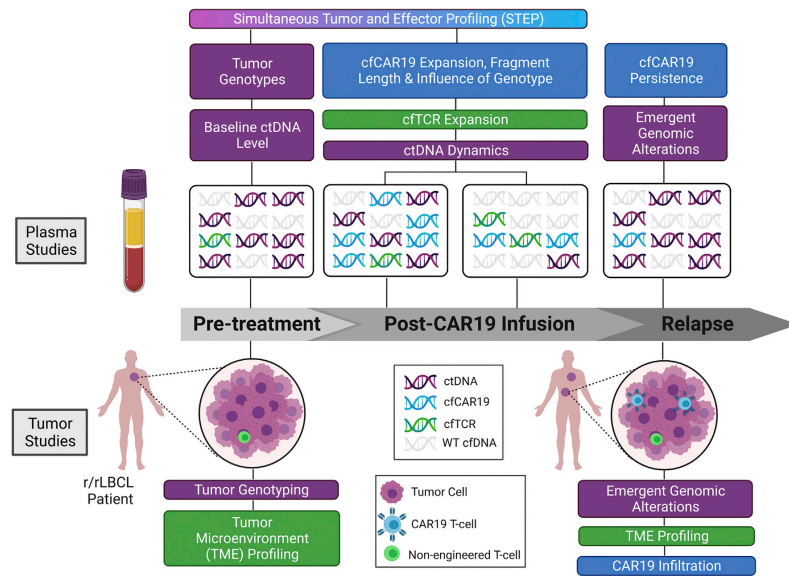
Ana Alarcon Tomas ^{1,2,12,17}, Joshua A. Fein ^{3,17}, Shalev Fried ^{4,5}, Jessica R. Flynn⁶, Sean M. Devlin⁶, Warren B. Fingrut¹, Theodora Anagnostou^{1,13}, Anna Alperovich^{1,14}, Nishi Shah¹, Ellen Frint ^{1,15}, Richard J. Lin ^{1,7}, Michael Scordo^{1,7}, Connie Lee Batlevi ⁸, Michal J. Besser^{5,9,16}, Parastoo B. Dahi ^{1,7}, Ivetta Danylesko^{4,5}, Sergio Giralt ^{1,7}, Brandon S. Imber¹⁰, Elad Jacoby ^{4,5}, Meirav Kedmi^{4,5}, Arnon Nagler^{4,5}, M. Lia Palomba ^{7,8}, Mikhail Roshal¹¹, Gilles A. Salles^{7,8}, Craig Sauter^{1,7}, Noga Shem-Tov^{4,5}, Avichai Shimoni ^{4,5}, Joachim Yahalom^{7,8}, Ronit Yerushalmi^{4,5}, Gunjan L. Shah ^{1,7}, Abraham Avigdor^{4,5,18}, Miguel-Angel Perales ^{1,7,18} ¹⁸ and Roni Shouval ^{1,4,7,18} ¹⁸

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Alarcon Tomas et al., *Leukemia* 2023

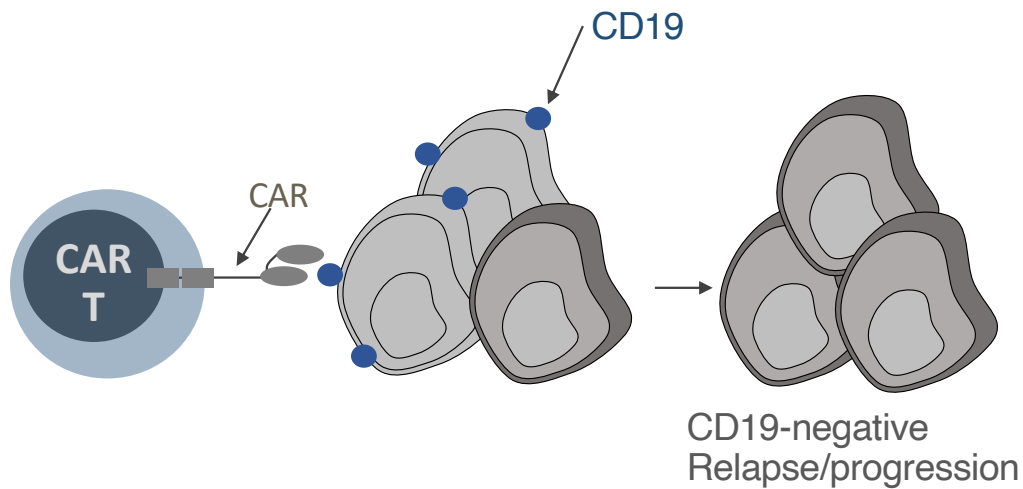
CD19-mutations after CAR T cell treatment



Sworder et al., Cancer Cell 2023

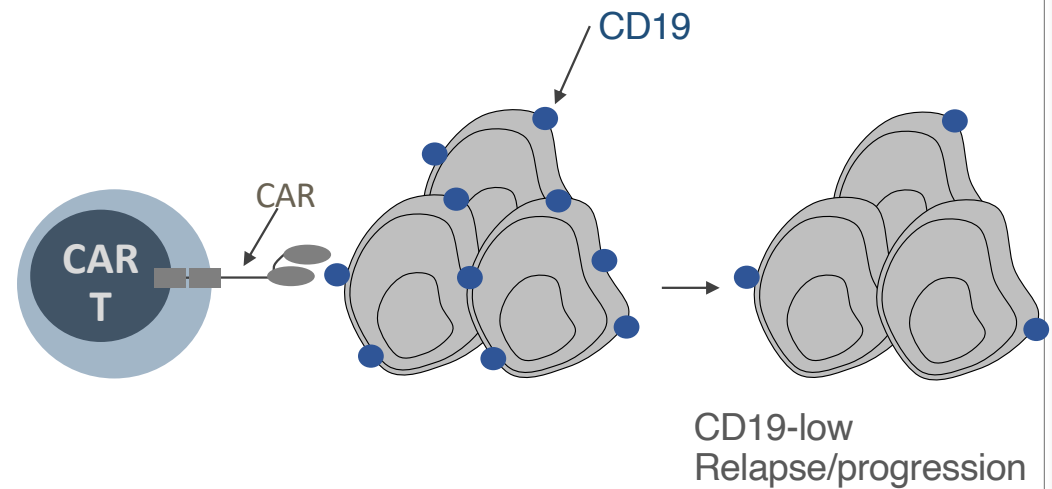
Mechanisms of CD19-mediated resistance

CD19 genomic loss



Rare

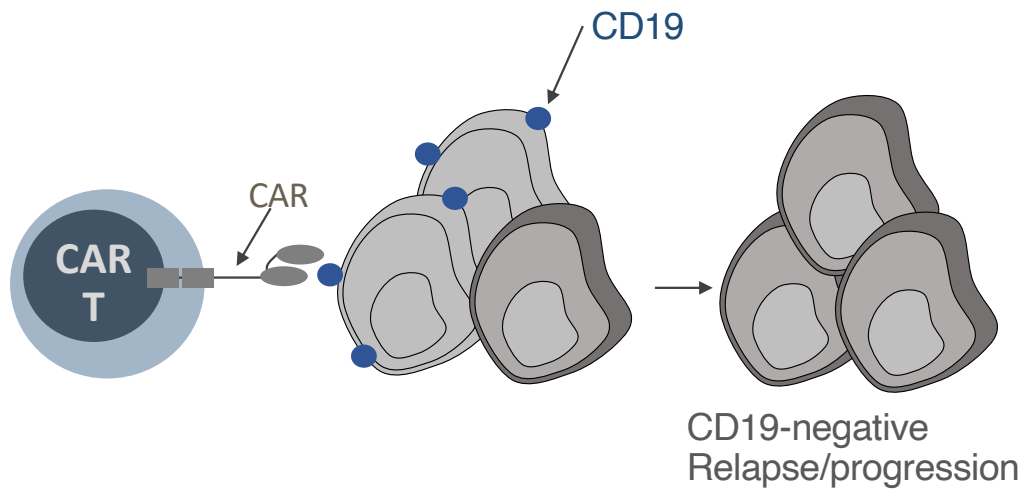
CD19 downregulation



Frequent

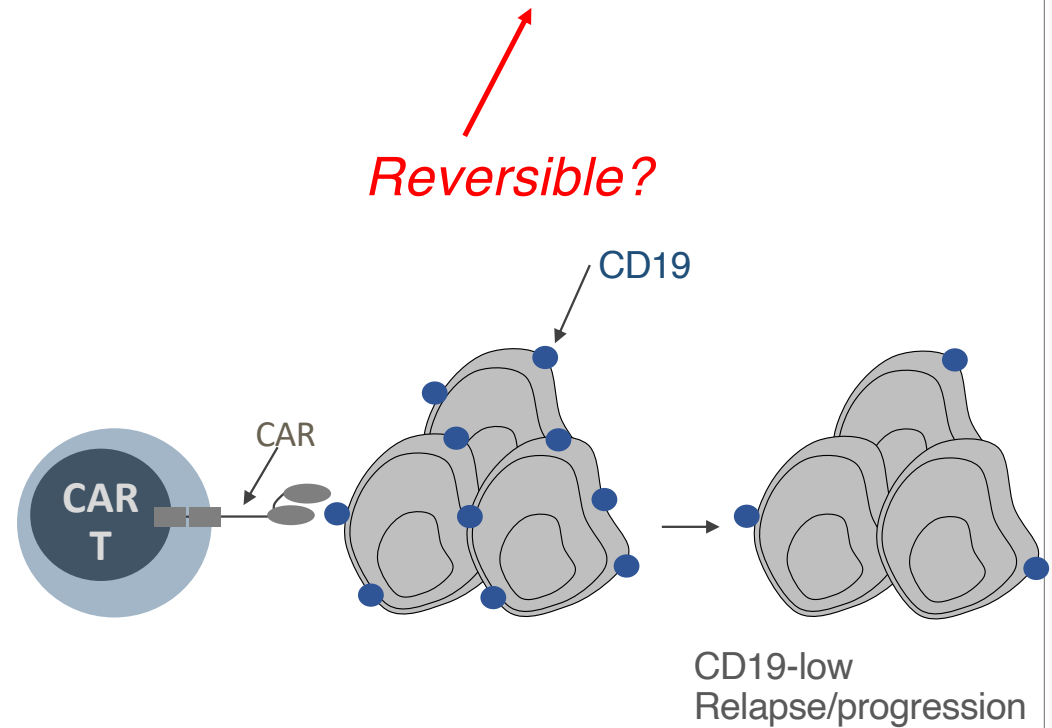
Mechanisms of CD19-mediated resistance

CD19 genomic loss



Rare

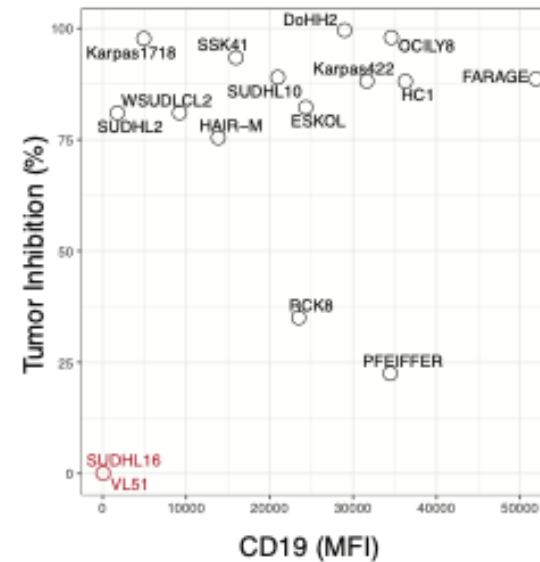
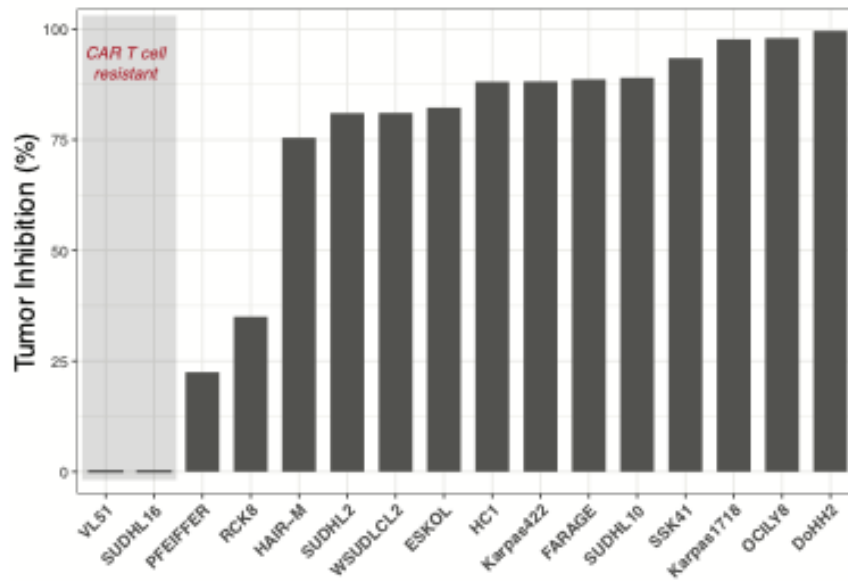
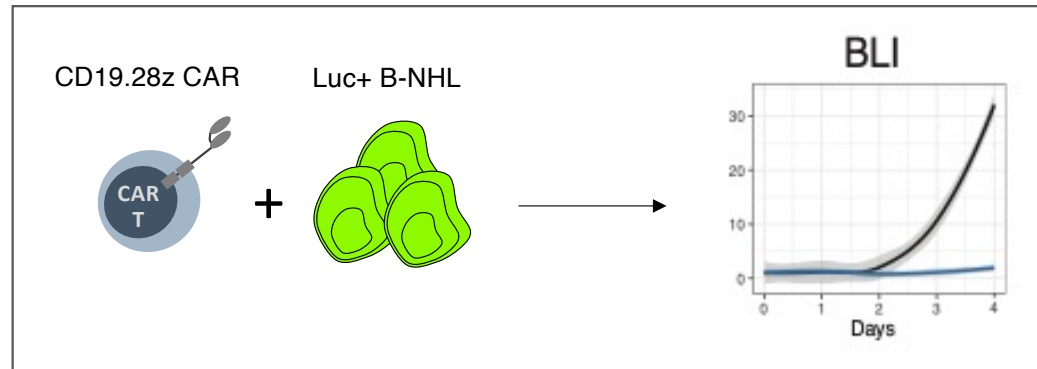
CD19 downregulation



Reversible?

Frequent

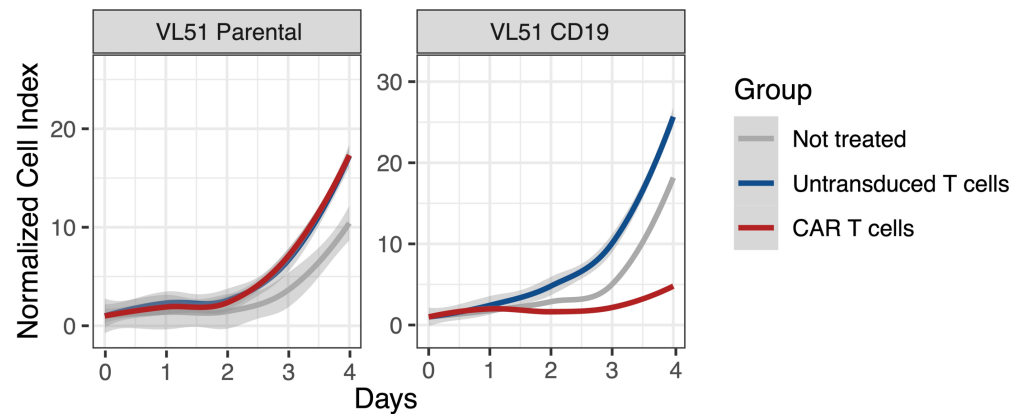
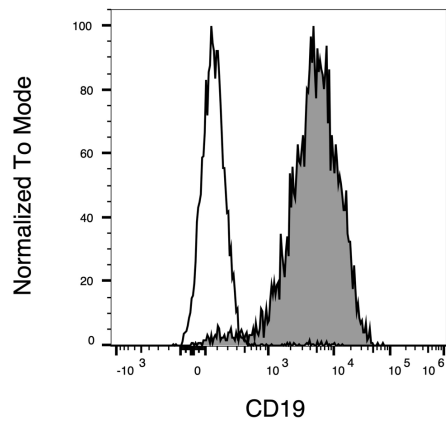
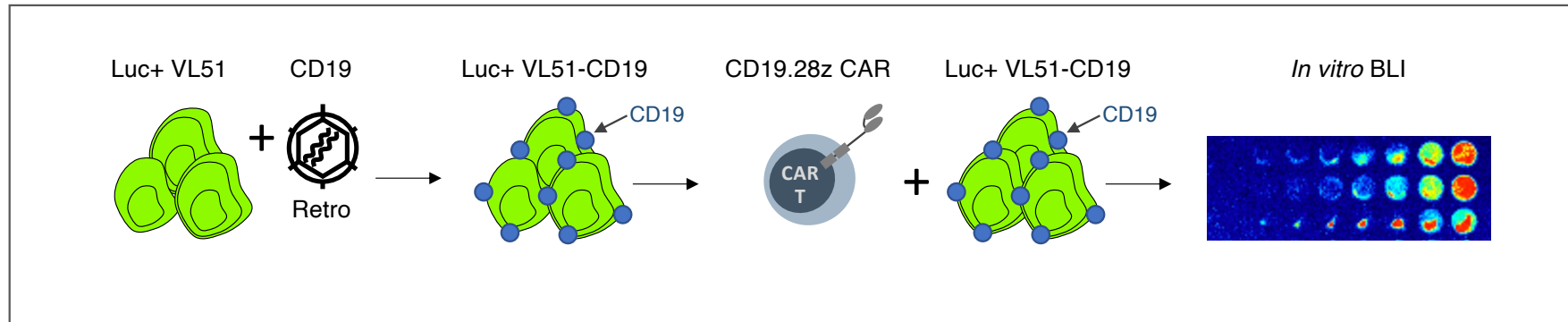
Preclinical models of CD19-mediated resistance



Collaboration with F. Bertoni, IOR

Wang, Unpublished

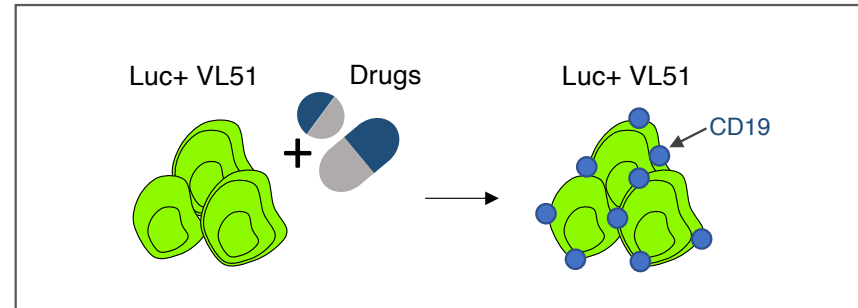
CD19-mediated resistance – VL51 model



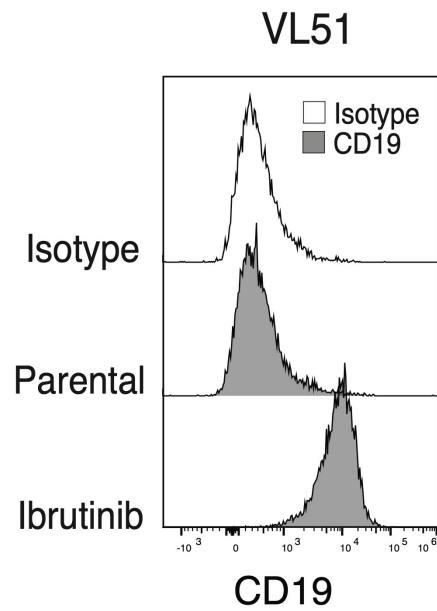
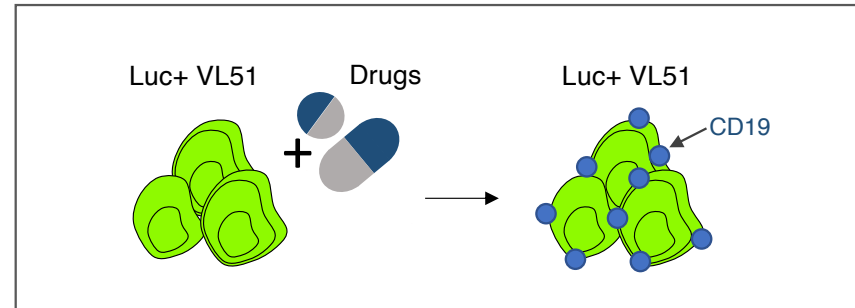
Collaboration with F. Bertoni, IOR

Wang, Unpublished

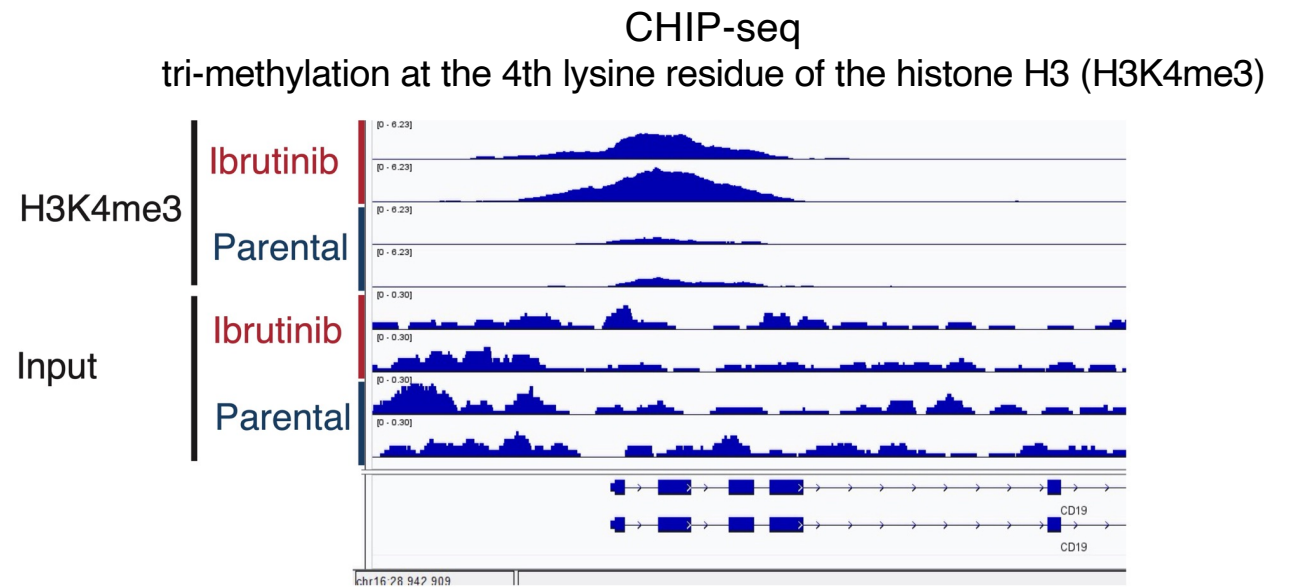
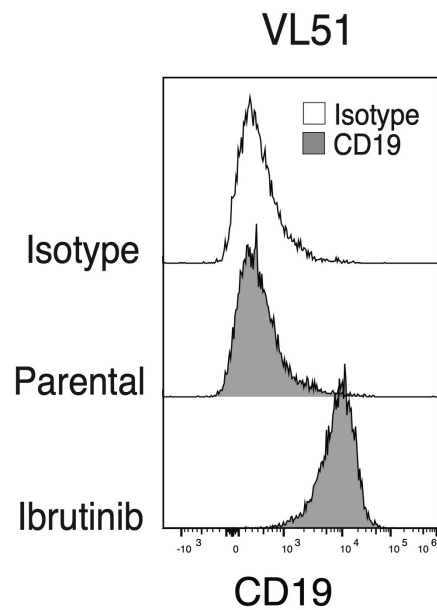
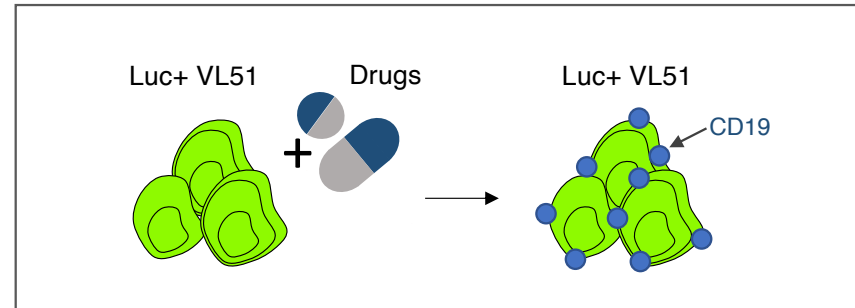
Pharmacological modulation of CD19



Pharmacological modulation of CD19

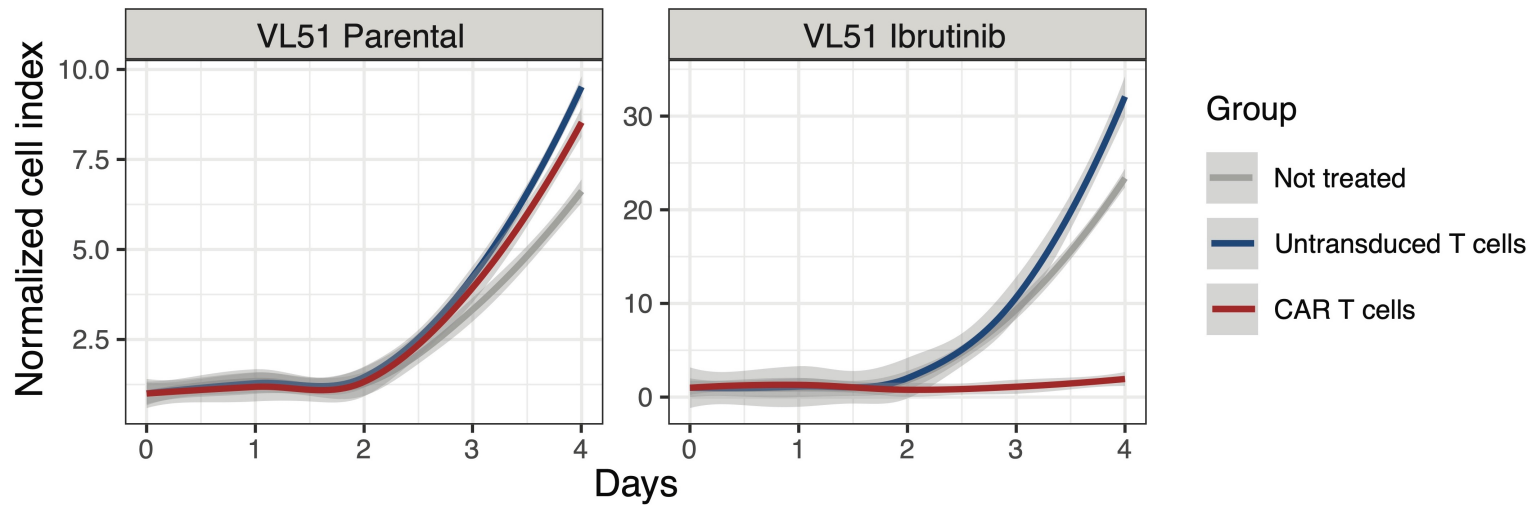
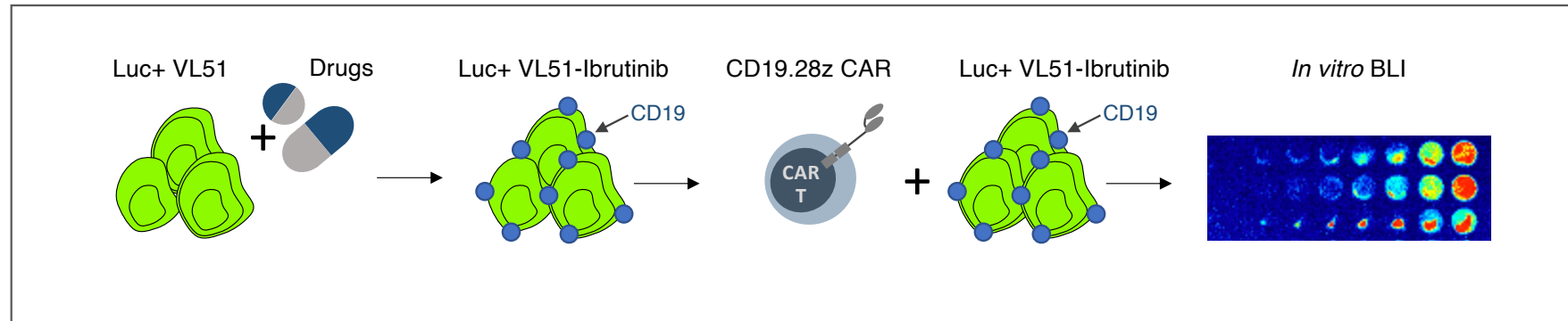


Pharmacological modulation of CD19



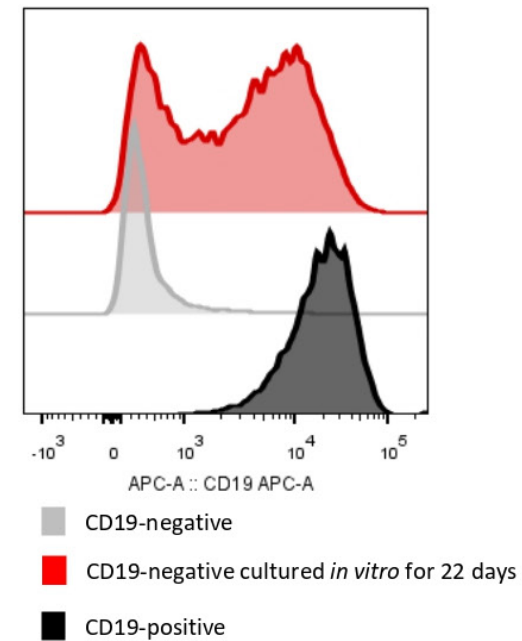
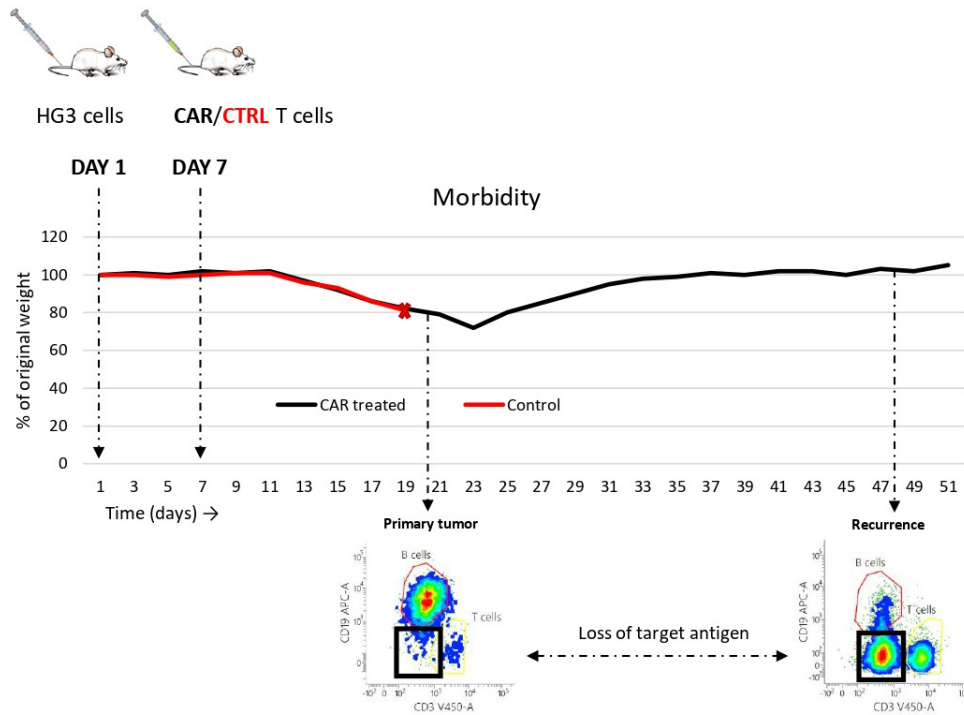
Collaboration with F. Bertoni, IOR

Pharmacological modulation of CD19 induces sensitivity to CAR T cell killing



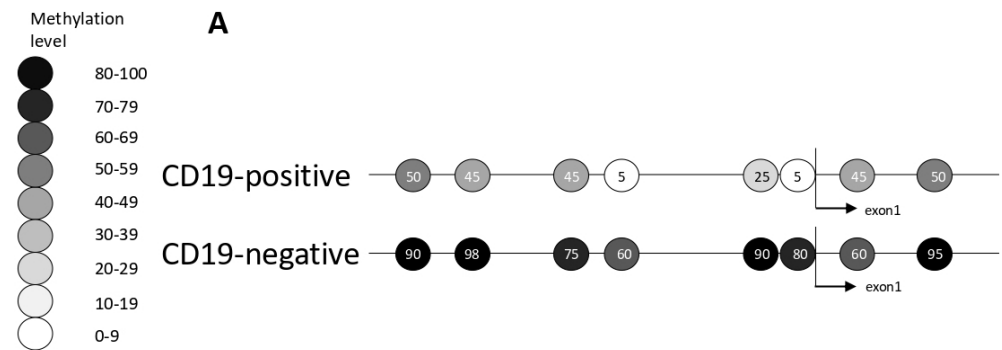
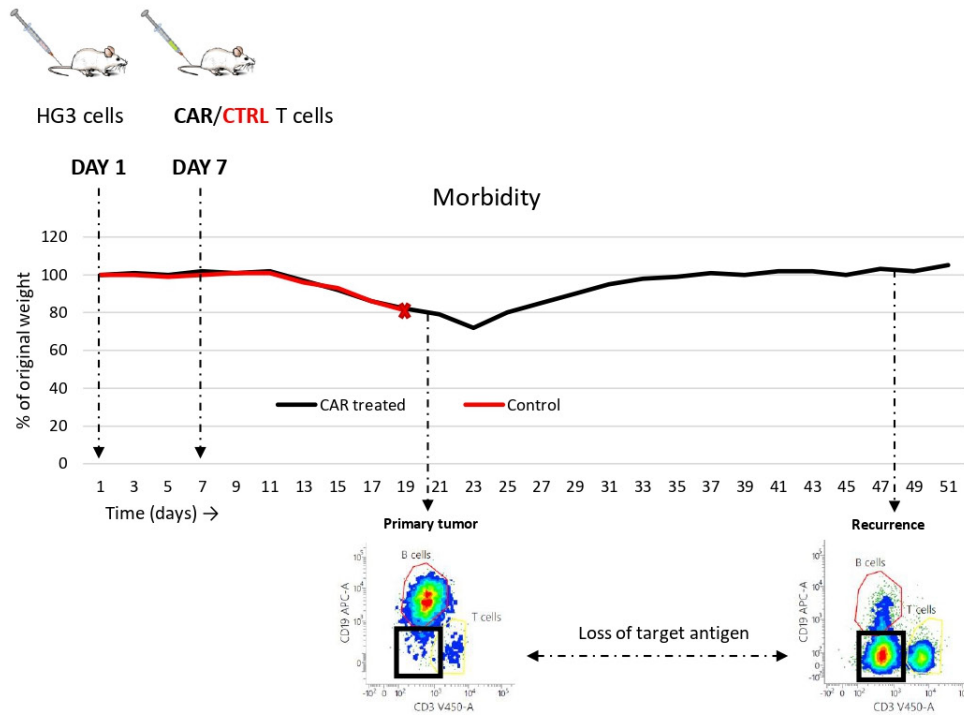
Wang*, Arribas* et al., ASH Meeting 2022

Hypermethylation of CD19 promoter enables antigen-negative escape to CAR T cells in a CLL model



Ledererova A, et al. *J Immunother Cancer* 2021

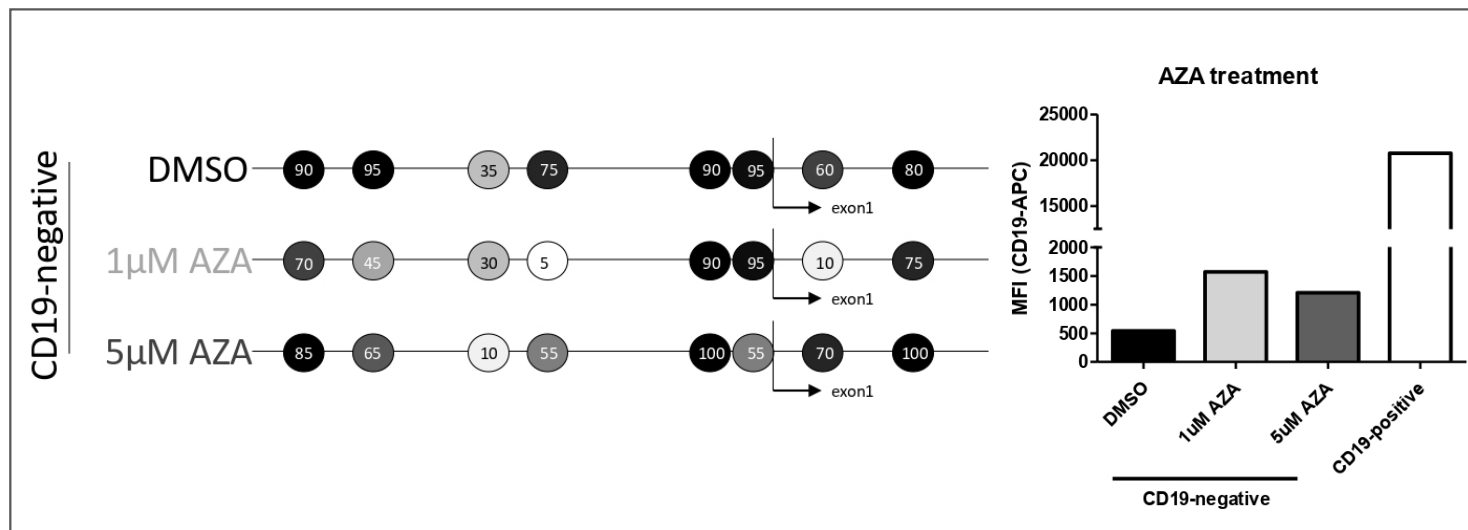
Hypermethylation of CD19 promoter enables antigen-negative escape to CAR T cells in a CLL model



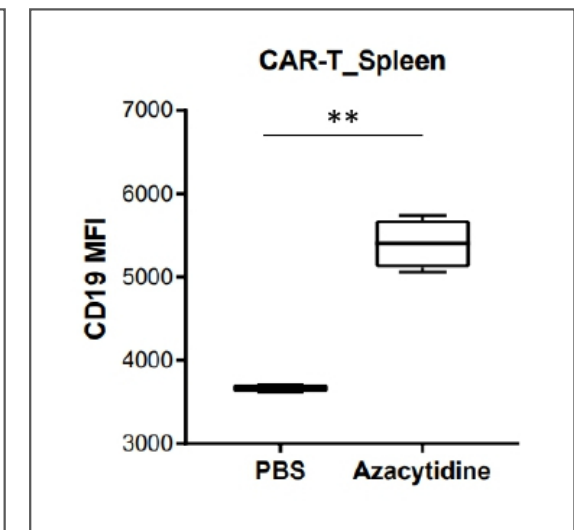
Ledererova A, et al. *J Immunother Cancer* 2021

Hypomethylating agents restore/prevent CD19 downregulation in a CLL model

In vitro – AZA 48h

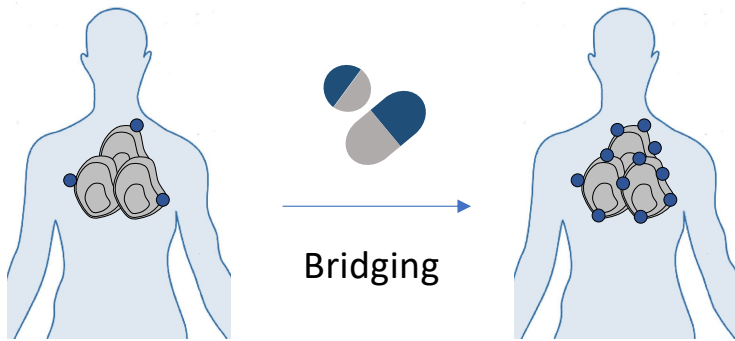


In vivo – CAR T +/- AZA

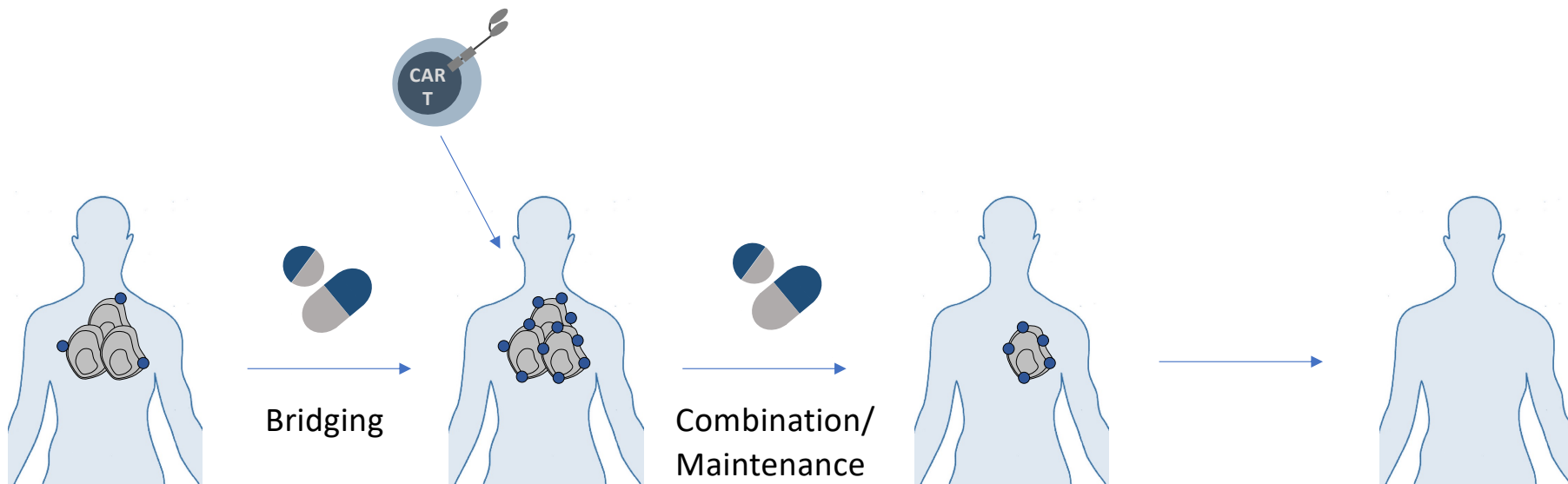


Ledererova A, et al. *J Immunother Cancer* 2021

Pharmacological modulation of CD19 expression to improve responses to CAR T cells?

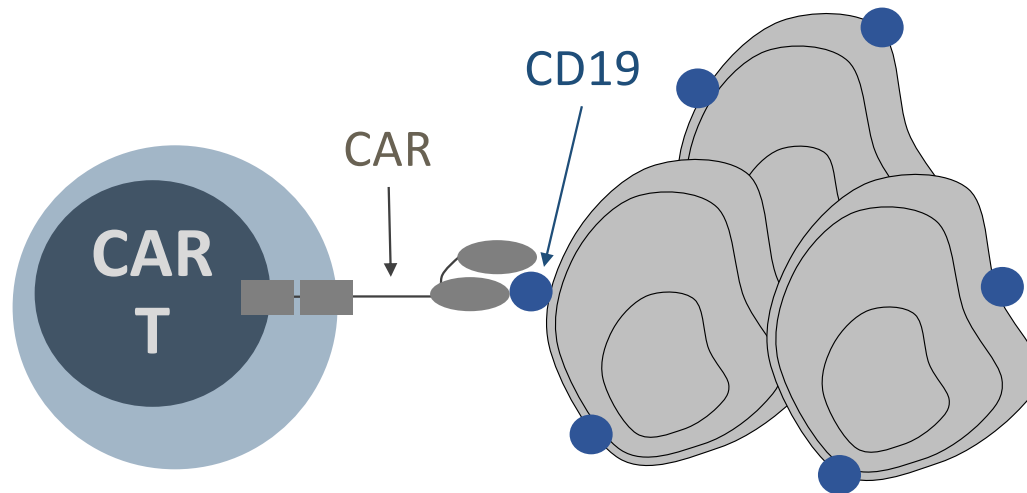


Pharmacological modulation of CD19 expression to improve responses to CAR T cells?

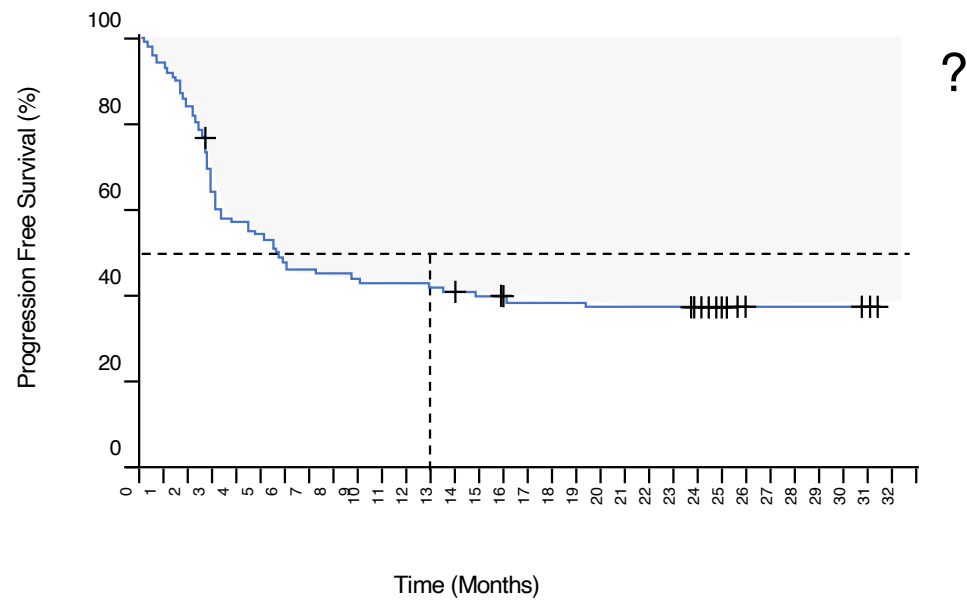


Mechanisms of Resistance to CAR T cell therapy

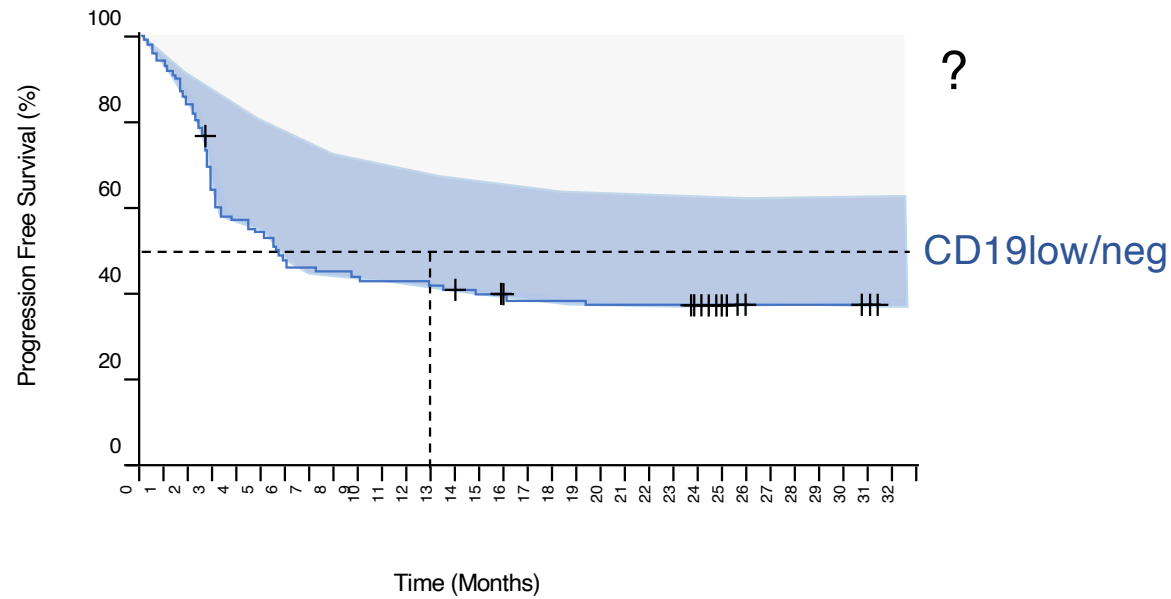
Target antigen expression



Some axes to improve CD19 CAR T Cells efficacy in r/r DLBCL

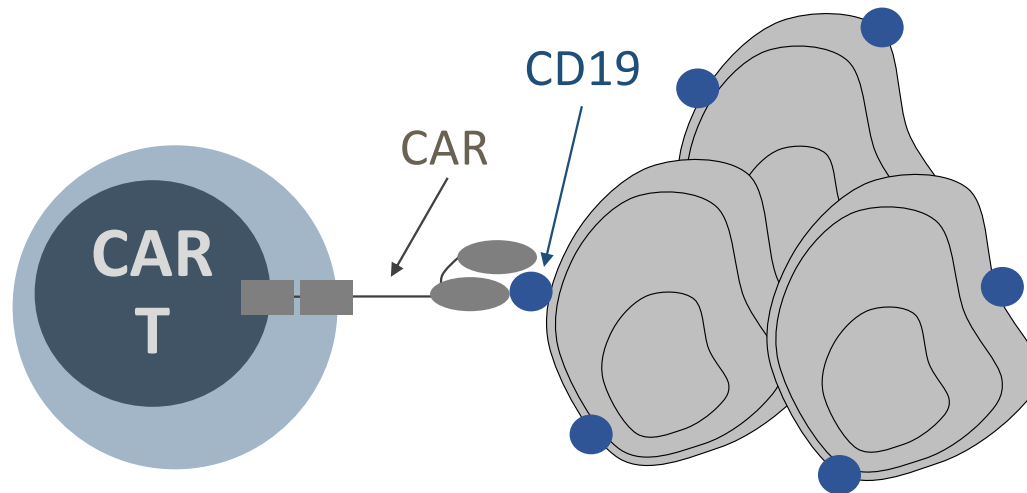


Some axes to improve CD19 CAR T Cells efficacy in r/r DLBCL

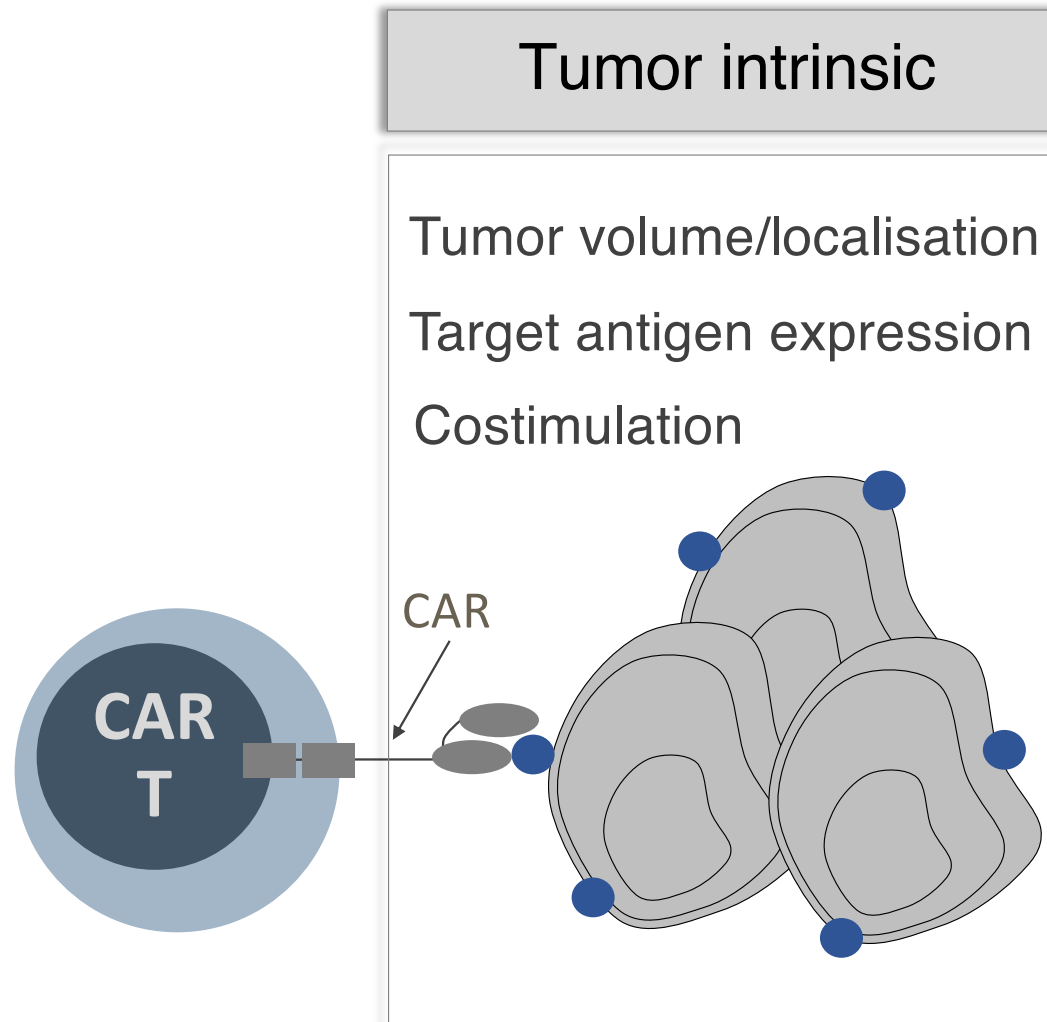


Mechanisms of Resistance to CAR T cell therapy

Target antigen expression



Mechanisms of Resistance to CAR T cell therapy



Mechanisms of Resistance to CAR T cell therapy

CAR T cell intrinsic

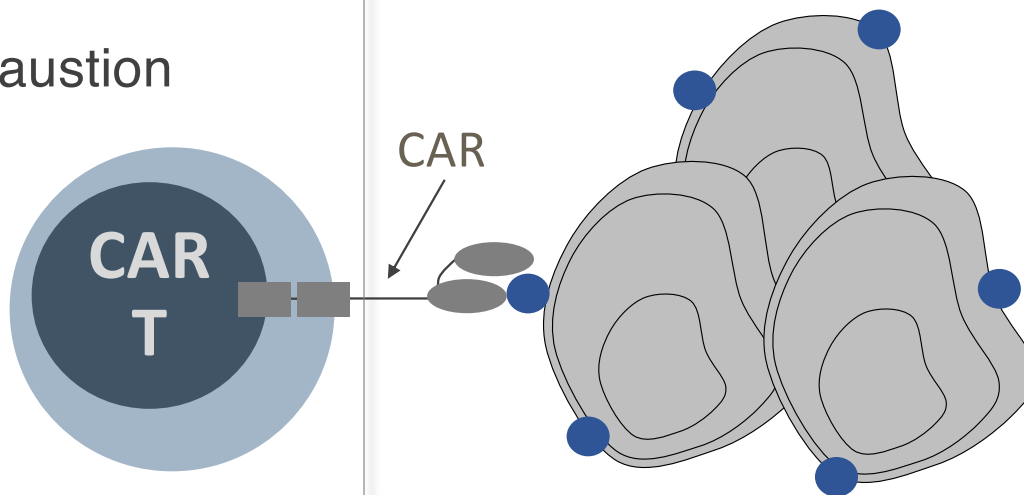
Expansion

Migration

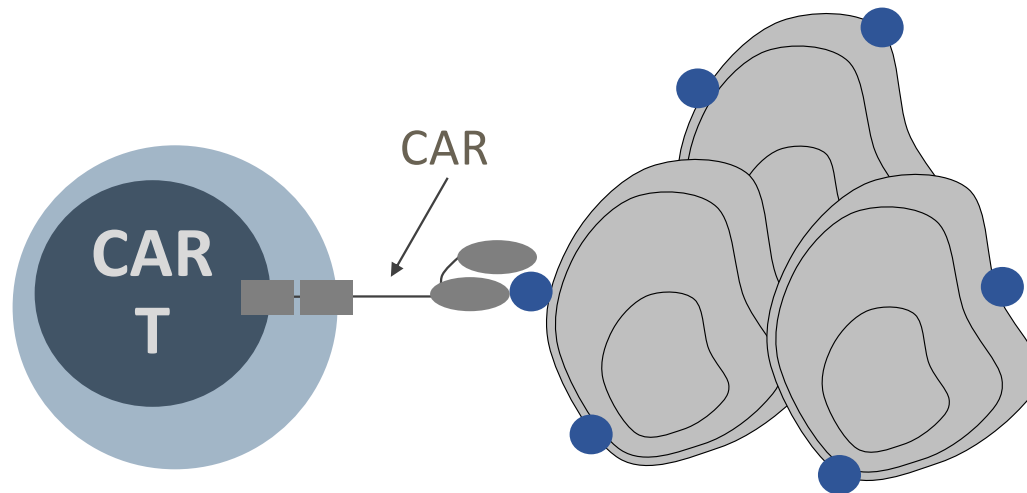
Persistence

Fitness/Exhaustion

Treg



Mechanisms of Resistance to CAR T cell therapy



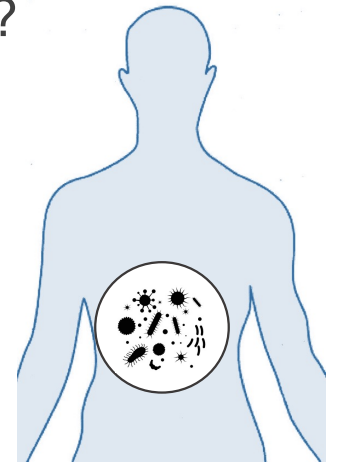
Extrinsic

Patient

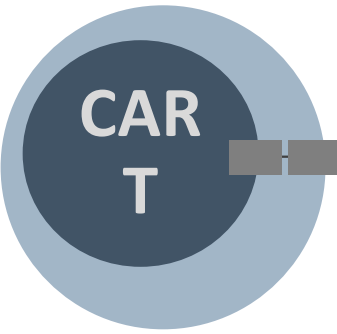
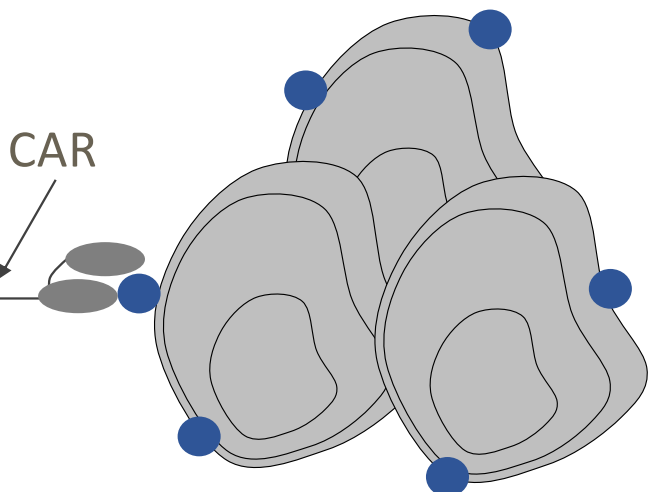
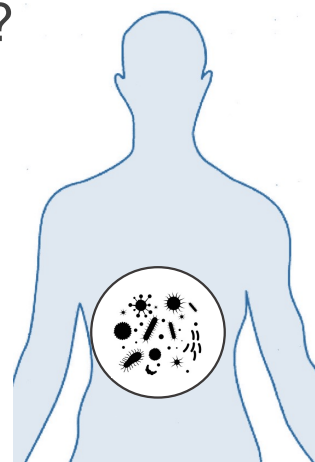
TME

Microbiome

Other...?



Mechanisms of Resistance to CAR T cell therapy

CAR T cell intrinsic	Tumor intrinsic	Extrinsic
<p>Expansion</p> <p>Migration</p> <p>Persistence</p> <p>Fitness/Exhaustion</p> <p>Treg</p>  <p>A circular diagram of a CAR T cell. The outer ring is light blue, and the inner circle is dark blue with the text 'CAR T' in white. A grey rectangular structure representing the CAR protein is shown extending from the cell surface.</p>	<p>Tumor volume/localisation</p> <p>Target antigen expression</p> <p>Costimulation</p>  <p>A diagram showing several grey, irregularly shaped tumor cells. Blue dots representing target antigens are scattered on their surfaces. Two CAR T cells, shown as grey ovals with blue dots, are interacting with the tumor cells. An arrow labeled 'CAR' points to one of these interacting cells.</p>	<p>Patient</p> <p>TME</p> <p>Microbiome</p> <p>Other...?</p>  <p>A light blue silhouette of a human torso. In the abdominal area, there is a circular inset containing various black icons representing different types of microorganisms, such as bacteria, viruses, and fungi.</p>

Acknowledgements



Amandine Pradier
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Caroline Stephane
Dominique Clerc-Renaud



Francesco Bertoni
Alberto Arribas
Chiara Tarantelli



Robert Negrin

Crystal Mackall
Rebecca Richards



Fondation
Henriette Meyer



Choose Life