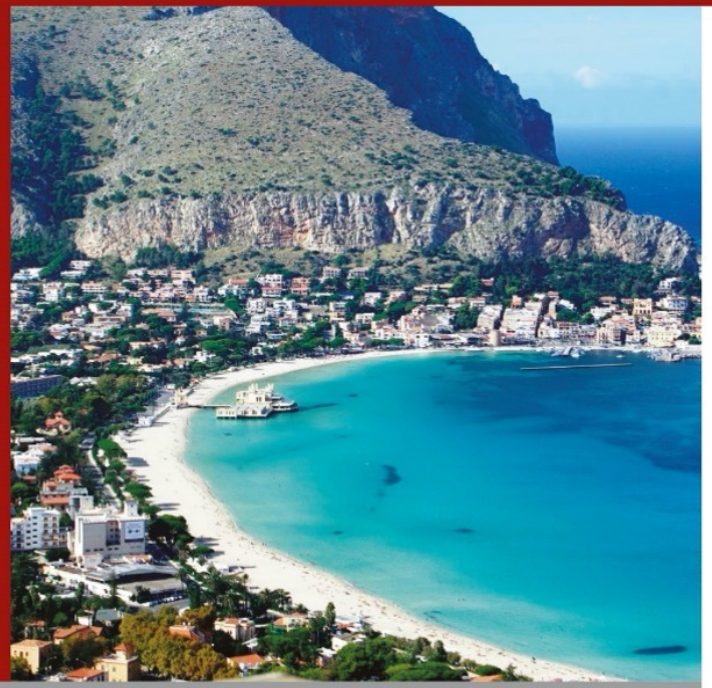
International Palermo Workshop on: Innovative Therapies for Lymphoid Malignancies



Palermo March 18, 2023
Hotel Federico II Central Palace

Current challenges and emerging opportunities after CAR- T therapies

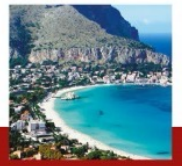
Giuseppe Gritti

ASST Papa Giovanni XXIII

Bergamo

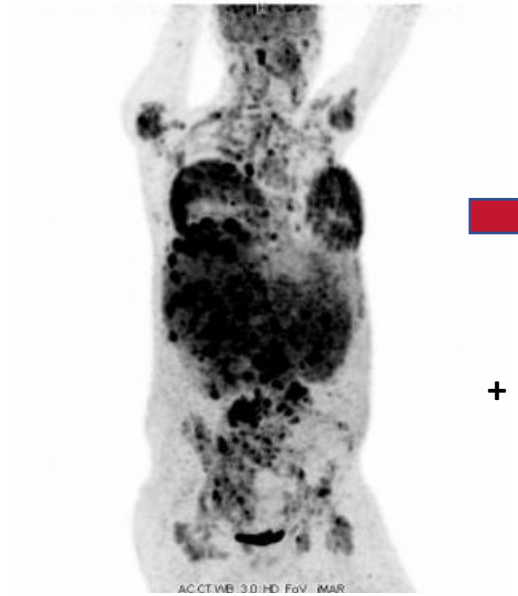
Disclosures of Giuseppe Gritti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche						X	
Takeda						X	
Kite-Gilead						X	
Ideogen					X	X	
Genmab						X	
Clinigen					X		
Beigene					X		X
Incyte					X		
Novartis					X		
Janssen							X
Sandoz							X



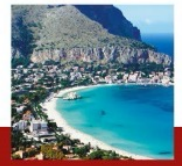
Clinical Case: 29 y/o Woman with Refractory DLBCL/HGBCL

DLBCL NOS, GCB with residual FL
Stage IVBE (breast, bone, liver)
IPI high, CNS IPI high



6 R-CHOP
+ IT MTX
+ IV R-MTX/ARAC

FISH: BCL2/BCL6 rearranged; MYC not rearranged but present in 3 copies



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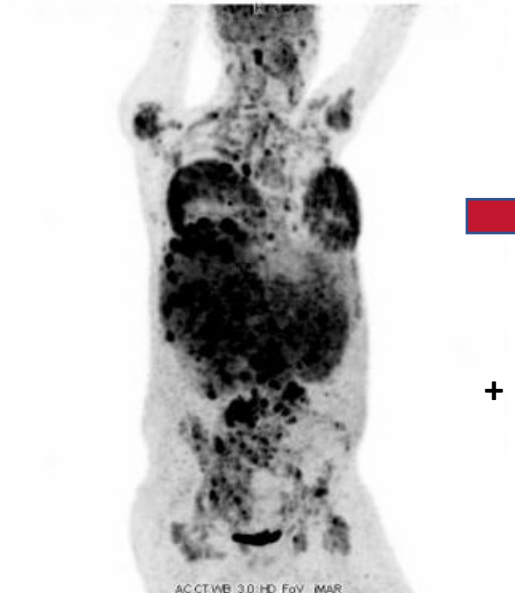

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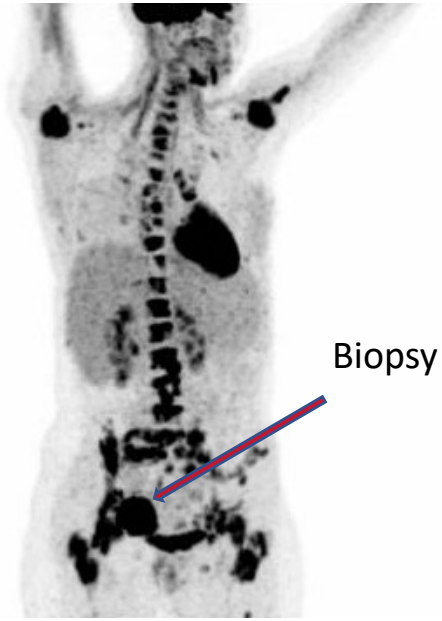
HGBCL Triple Hit
IVBE (ovary, bone)
IPI high, CNS IPI high



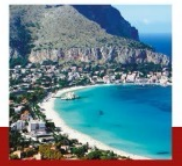
Biopsy

FISH: BCL2/BCL6/MYC rearranged

Further treatments:

- Glofitamab+Polatuzumab
- R-ICE
- CAR-T cell (Yescarta)

Initial response and subsequent progression



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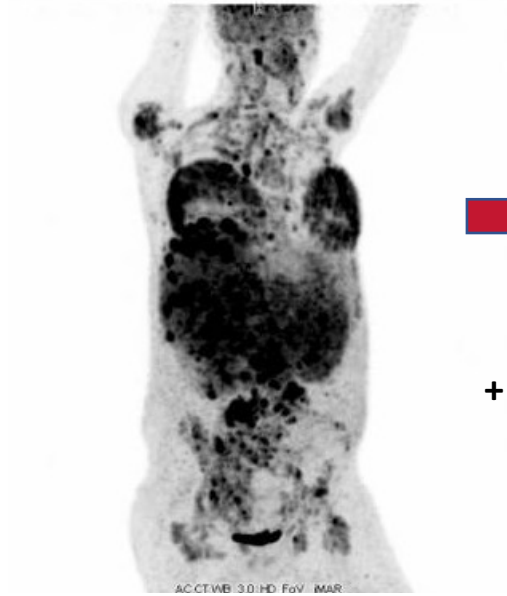

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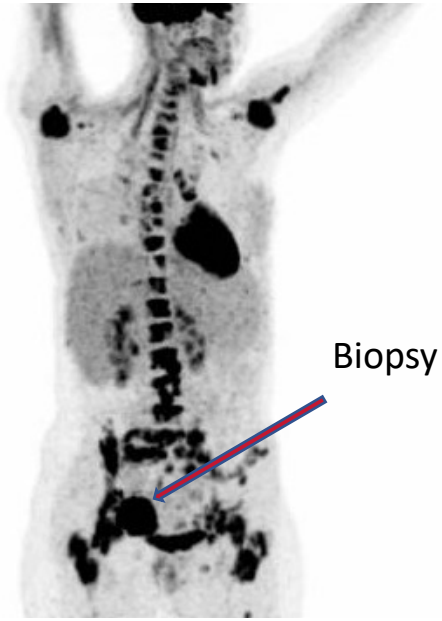

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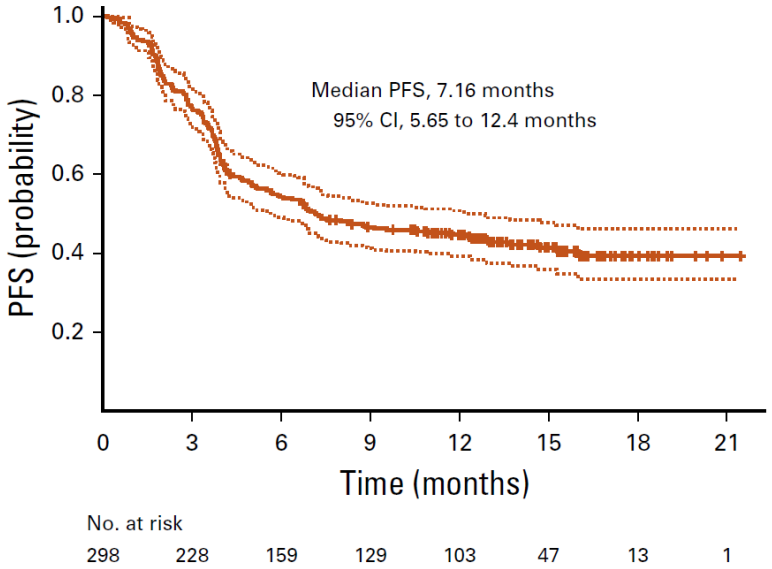
Initial response and subsequent progression

Relapse 4 months after CART

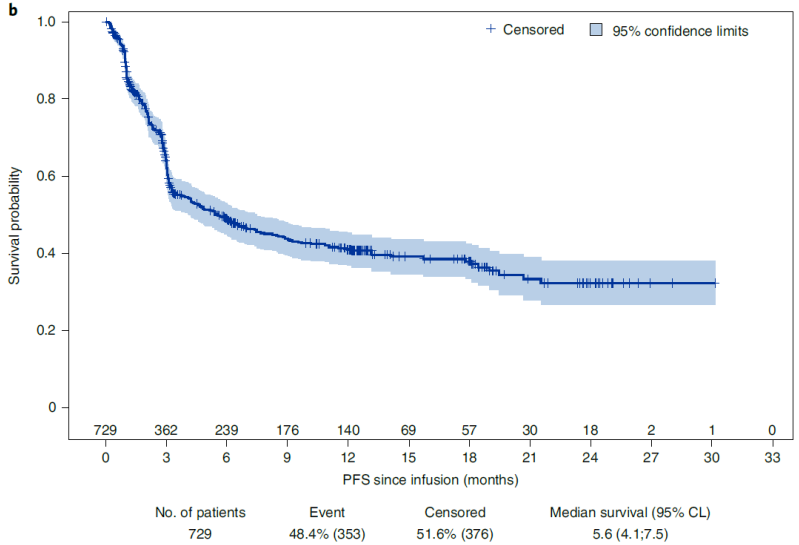
Biopsy: DLBCL NOS, CD20-, CD19+
Pending FISH

Outcomes of patients with aggressive B-cell lymphoma after anti-CD19 CAR T-cell therapy: Real World Evidence

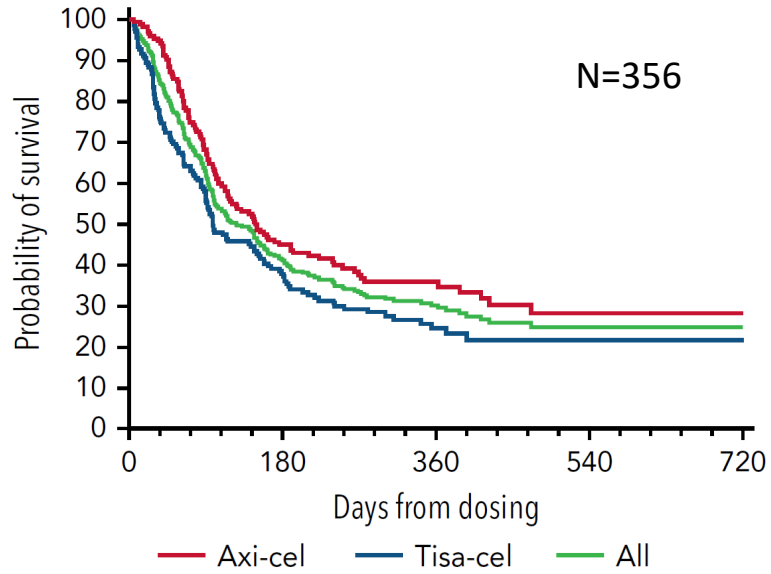
US Lymphoma CART Consortium Real-Life



DESCAR-T Real-Life



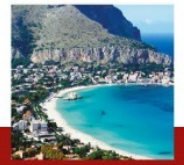
GLA/DRST Real-Life



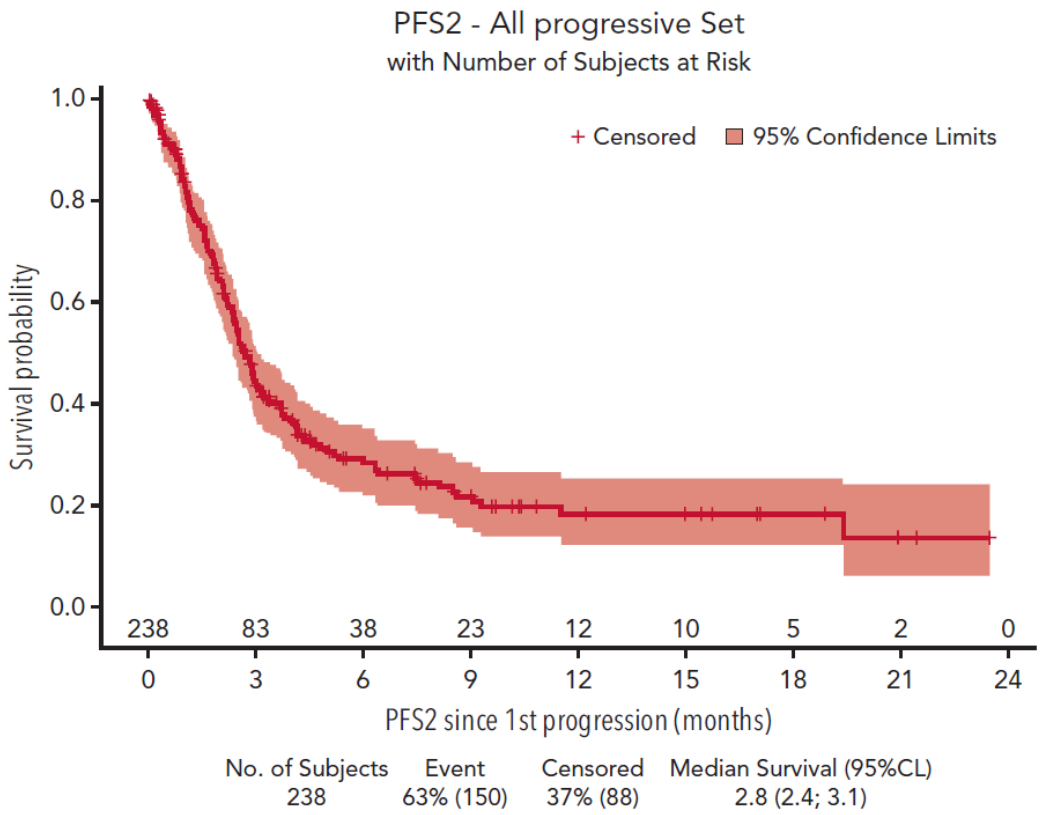
1-year PFS: 30-47%

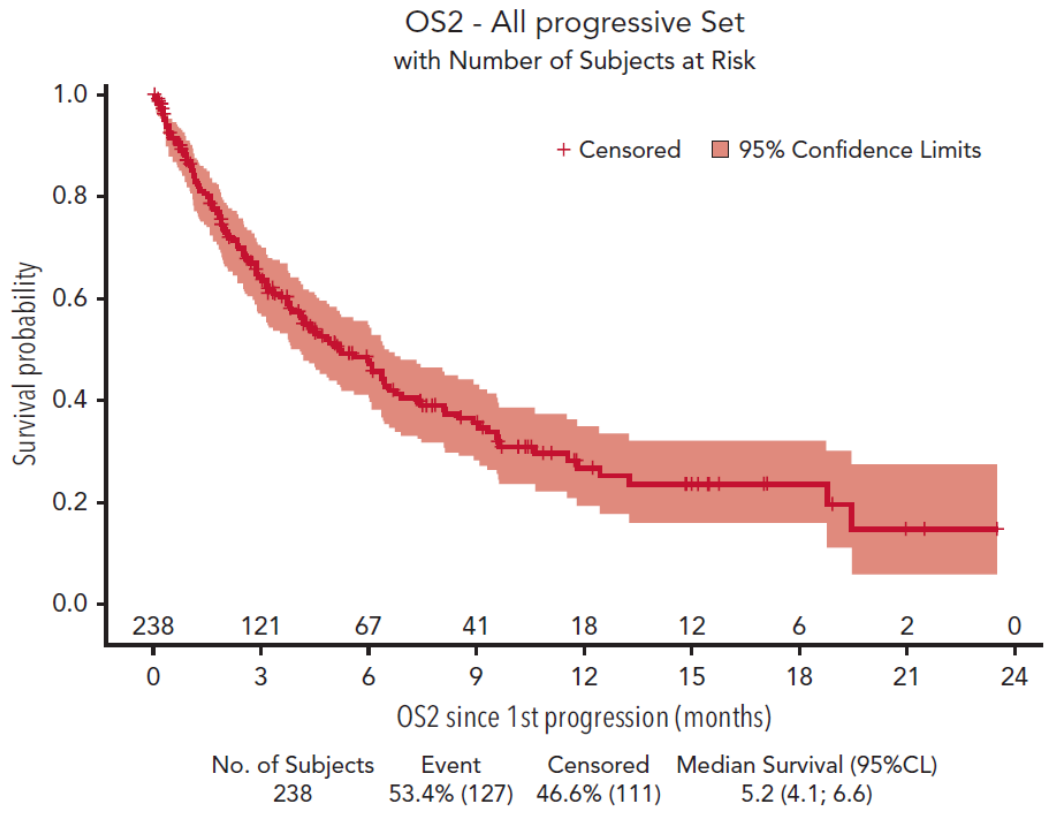
53-70% of the patients fails CART

Nastoupil, et al., JCO 2020
Bachy et al., Nat Med 2022
Bethge et al., Blood 2022



Outcomes of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell therapy: a DESCAR-T analysis





Di Blasi et al., Blood 2022

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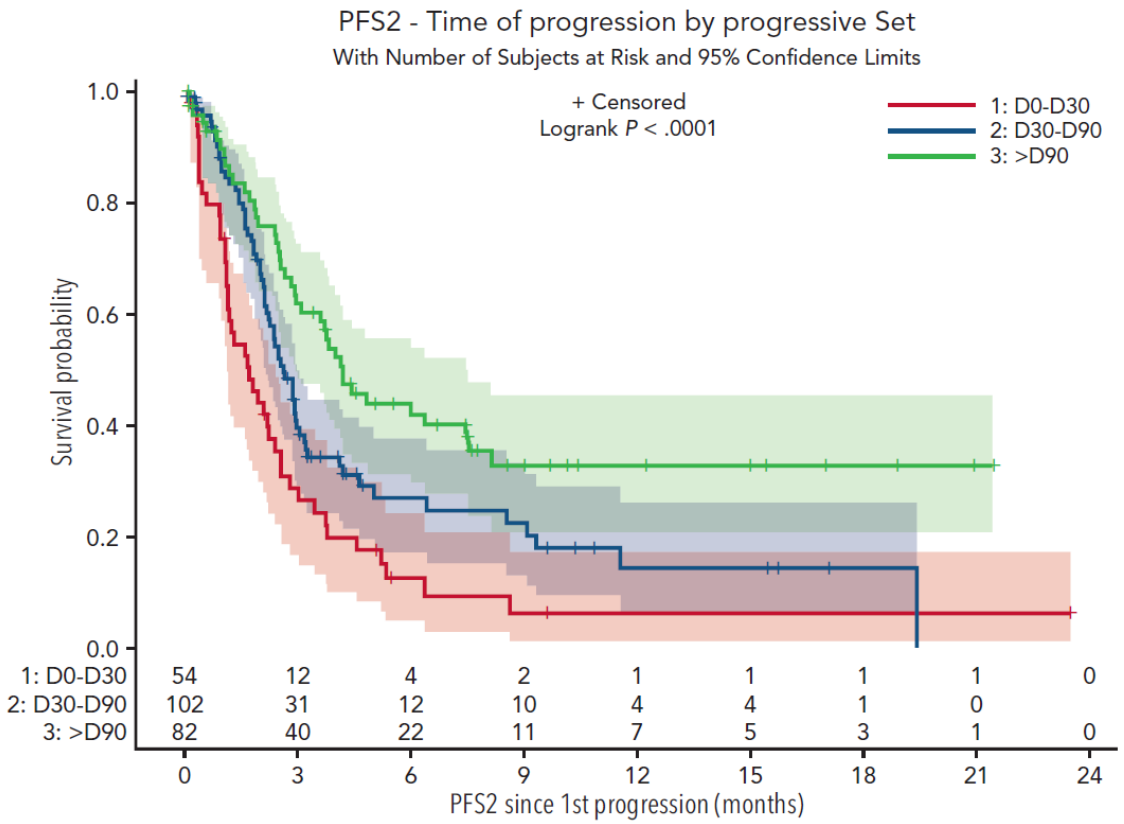
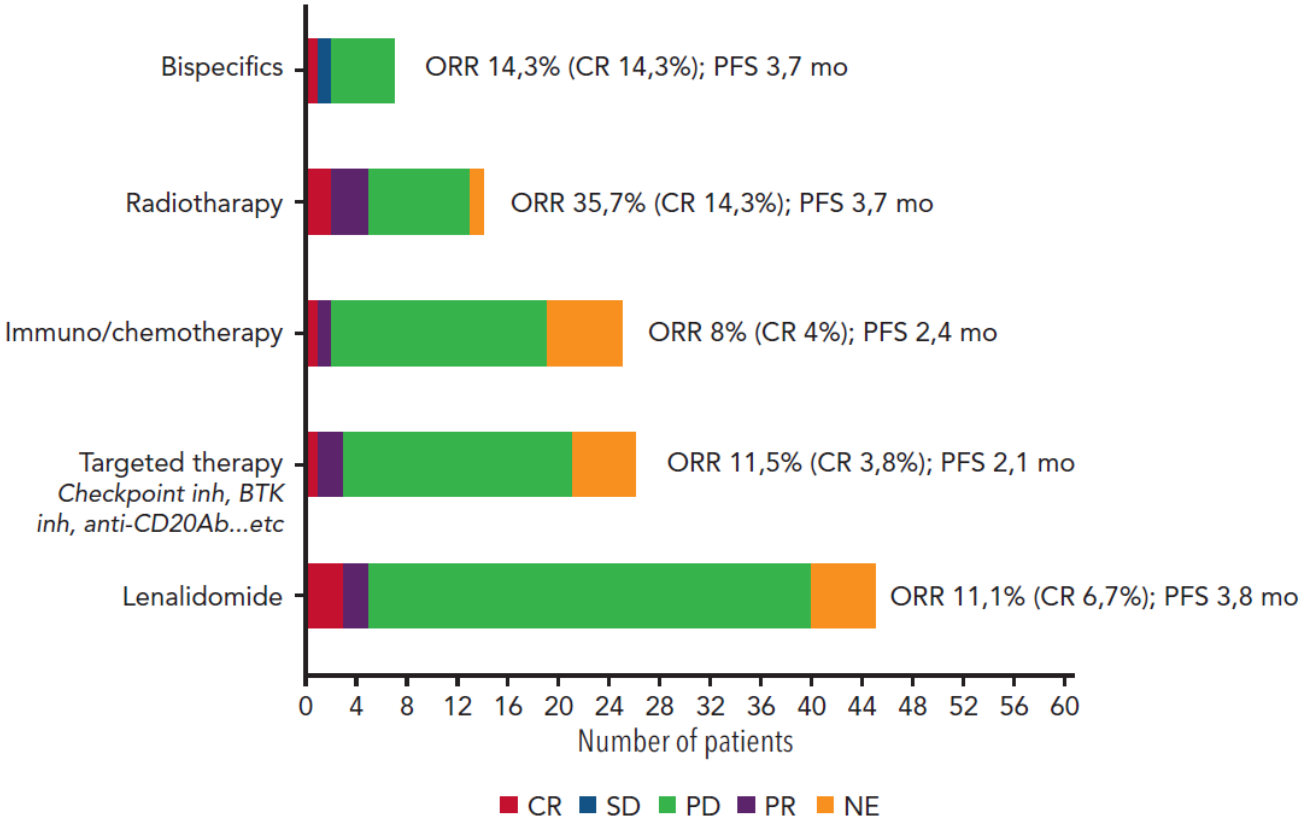




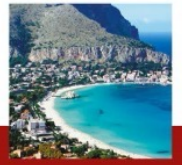
Di Blasi et al., Blood 2022

Therapeutic Options after CART-cell failure

- Bispecific antibodies
- Targeted therapy
- Immune-modulators
- Immuno-chemotherapy
- Radiotherapy

- Role of allogeneic stem-cell transplant?

Di Blasi et al., Blood 2022



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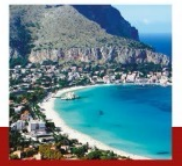


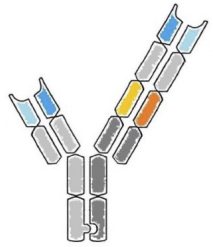
T-cell Redirecting Bispecific Antibodies in Clinical Development for B-cell NHL

BiTE CD19xCD3

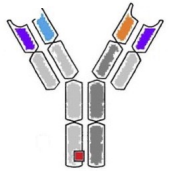
Blinatumomab

IgG CD20xCD3

Mosunetuzumab



Glofitamab

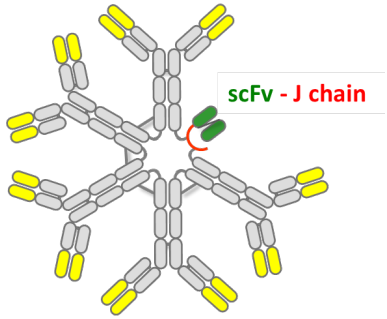


Odronextamab

Epcoritamab

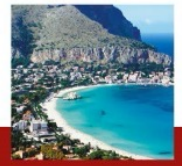
Plamotamab

IgM CD20xCD3



Imvotamab

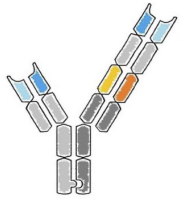
Lussana, Gritti, Rambaldi, JCO 2021

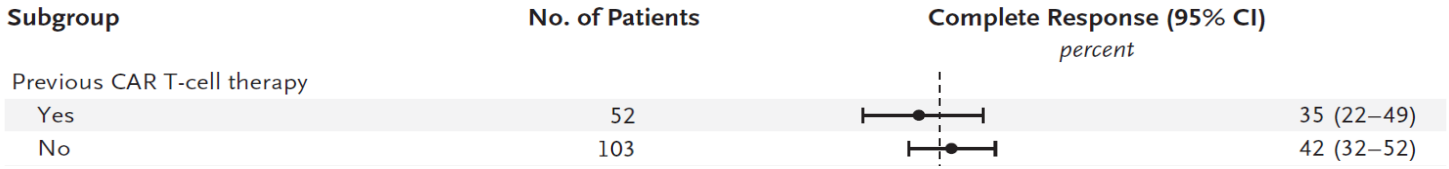


Bispecific Antibodies after CART-cell Failure in DLBCL: Data from Published Phase I/II Studies

Glofitamab (N=52)

CR 35%

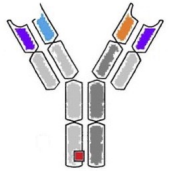




Epcoritamab (N=61)

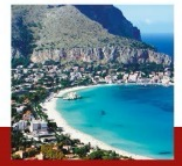
ORR 54.1%
CR 34.4%
DOR 9,7 (95% CI, 5.4 to not reached)

Odronextamab (N=33)

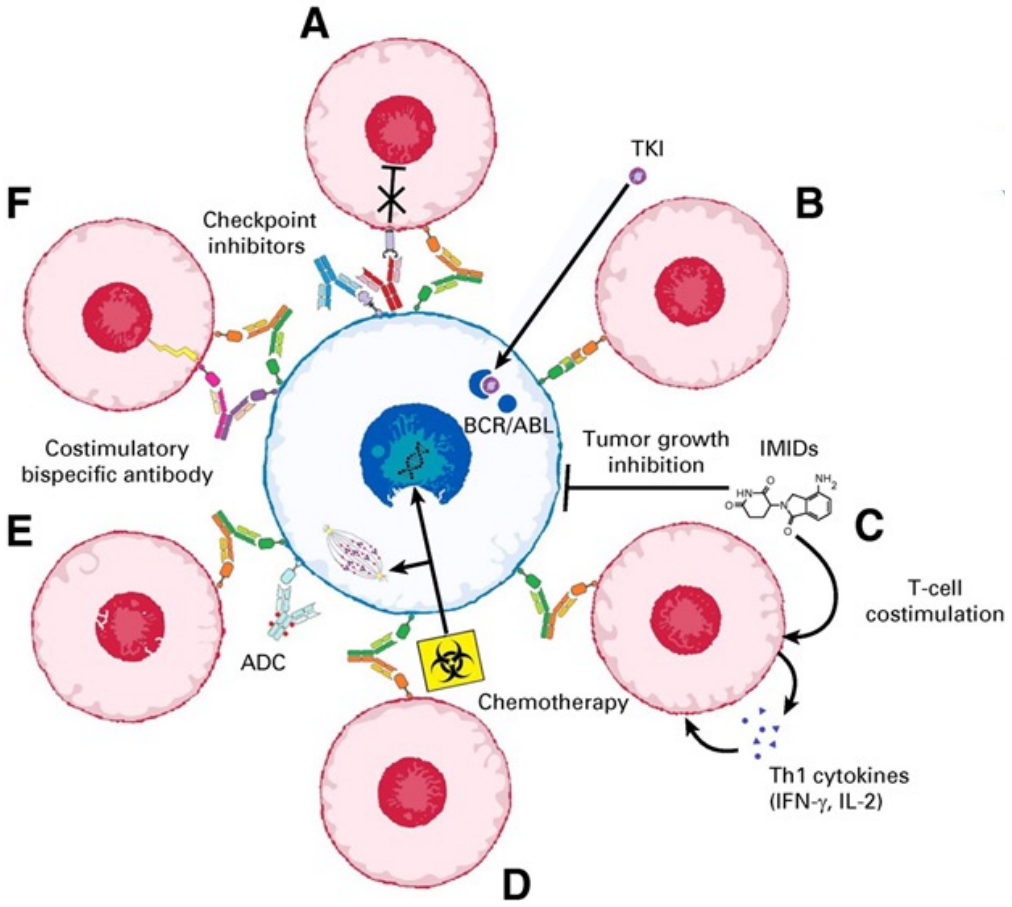


ORR 33%
CR 24%
DOR Not Reached (95% CI 1·6–NE)

Dickinson et al., NEJM 2022; Thieblemont et al., JCO 2022; Bannerji et al., Lancet Haem 2022



Combination of T-cell Redirecting Bispecific Antibodies in Clinical Trials



A - Checkpoint inhibitors

~~B - TKI (B-ALL)~~

C - IMIDs

D - Chemotherapy

E - ADCs

F - Costimulatory bispecific antibodies

Lussana, Gritti, Rambaldi, JCO 2021

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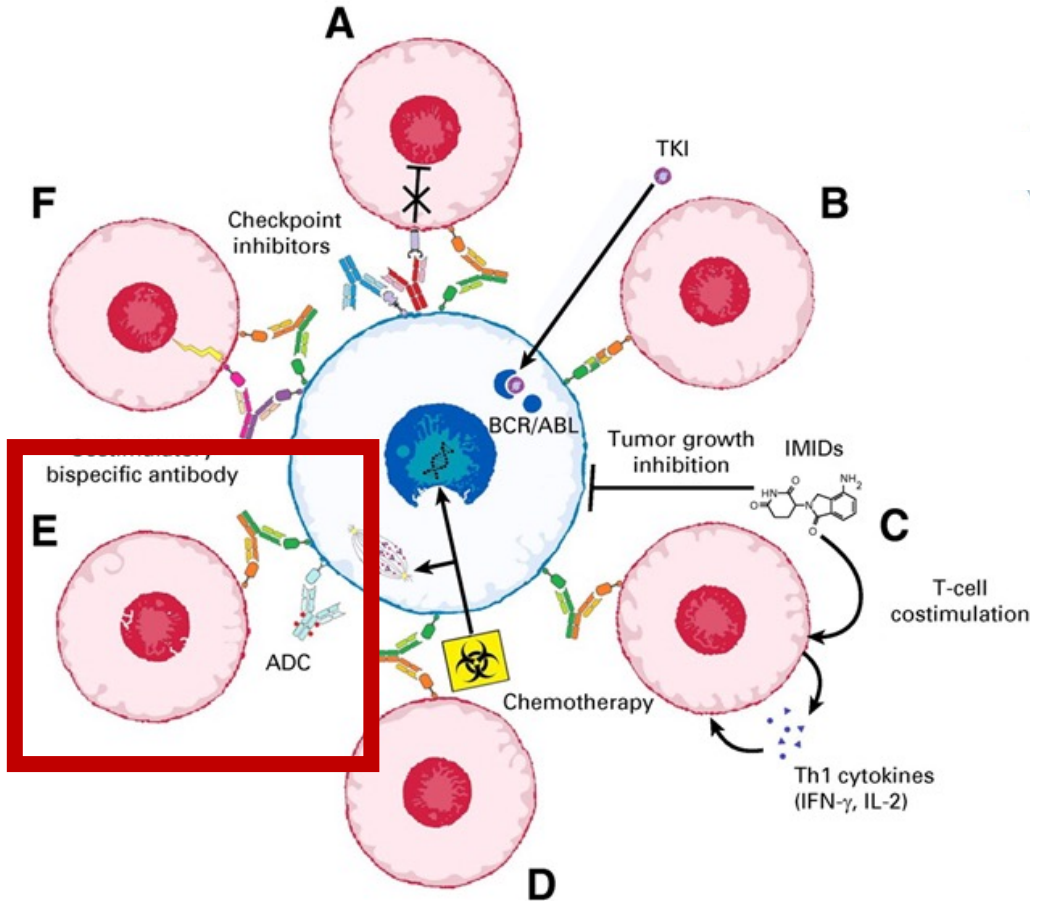

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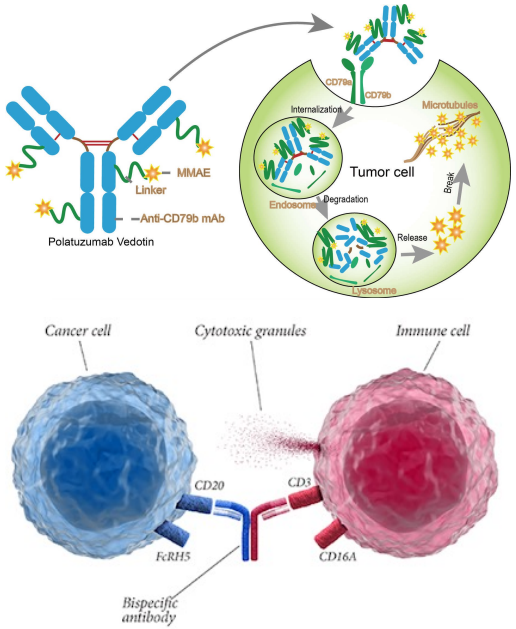
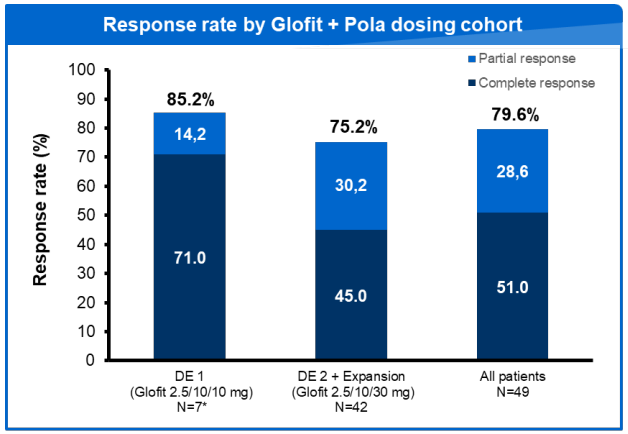
Glofitamab plus Polatuzumab in R/R DLBCL/HGBCL

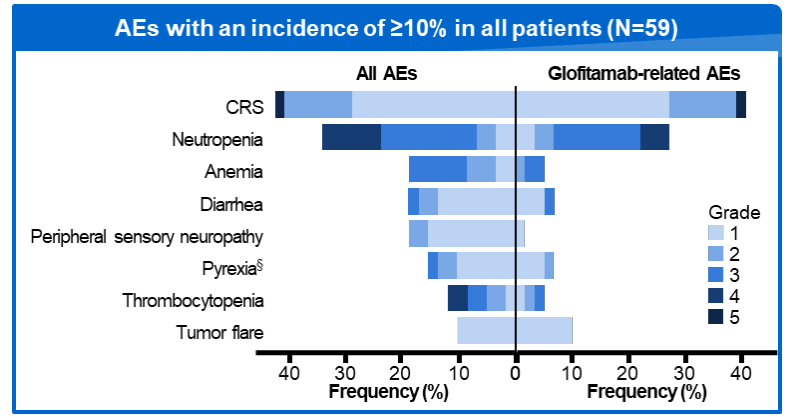
Glofit + Pola combines two non-overlapping MoA



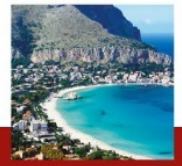
High response rates



Safety profile consistent with that of the individual drugs



Hutchings et al., ASH 2021



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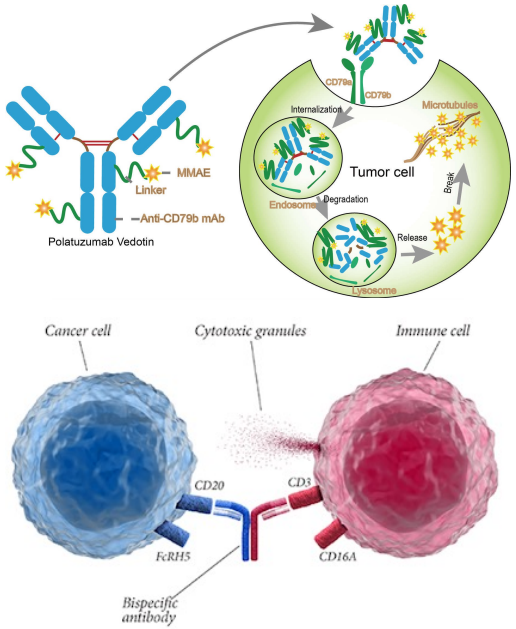

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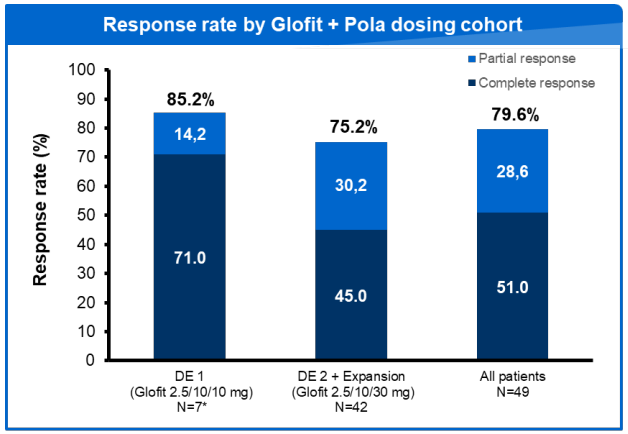

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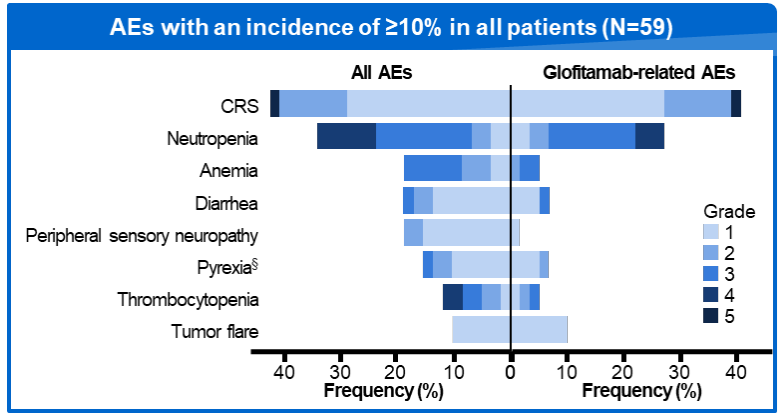
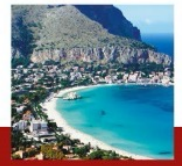
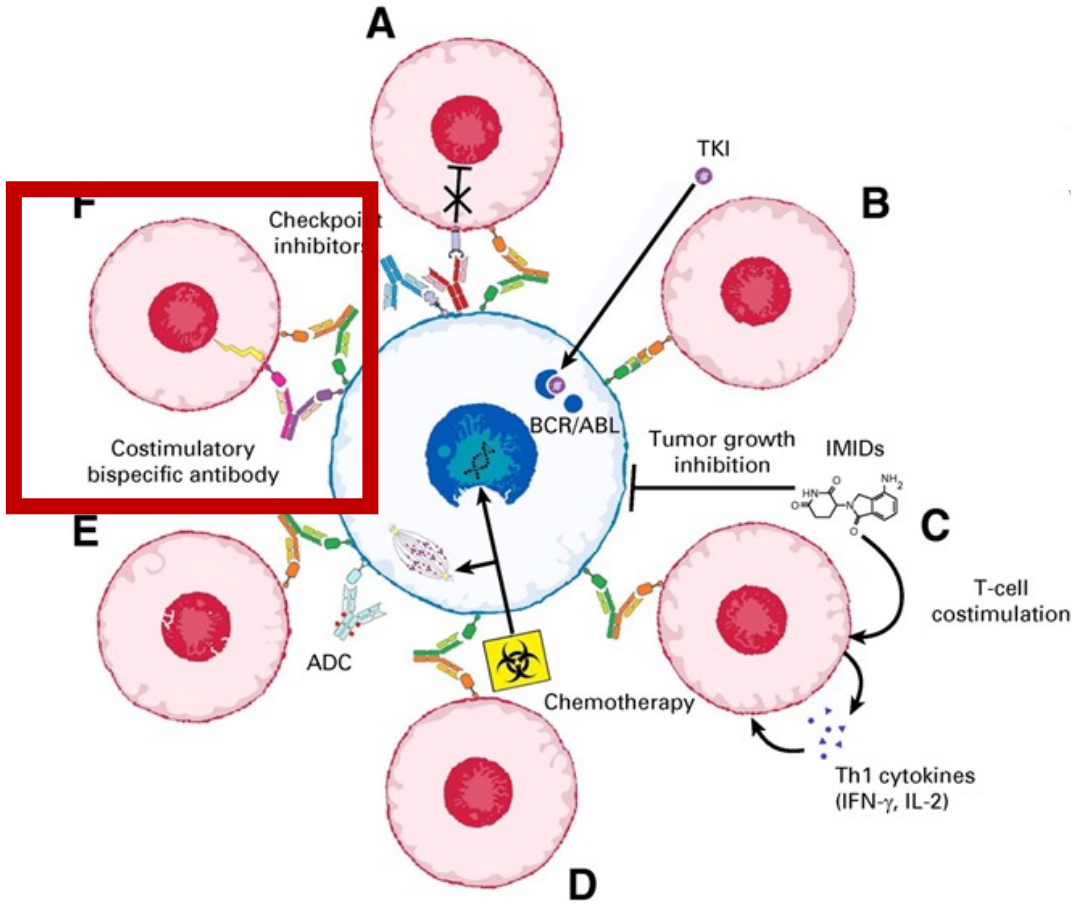


→ ICML 2022: data on 111 patients (25% prior CART)

Hutchings et al., ASH 2021



Combination of T-cell Redirecting Bispecific Antibodies in Clinical Trials



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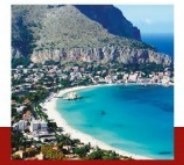
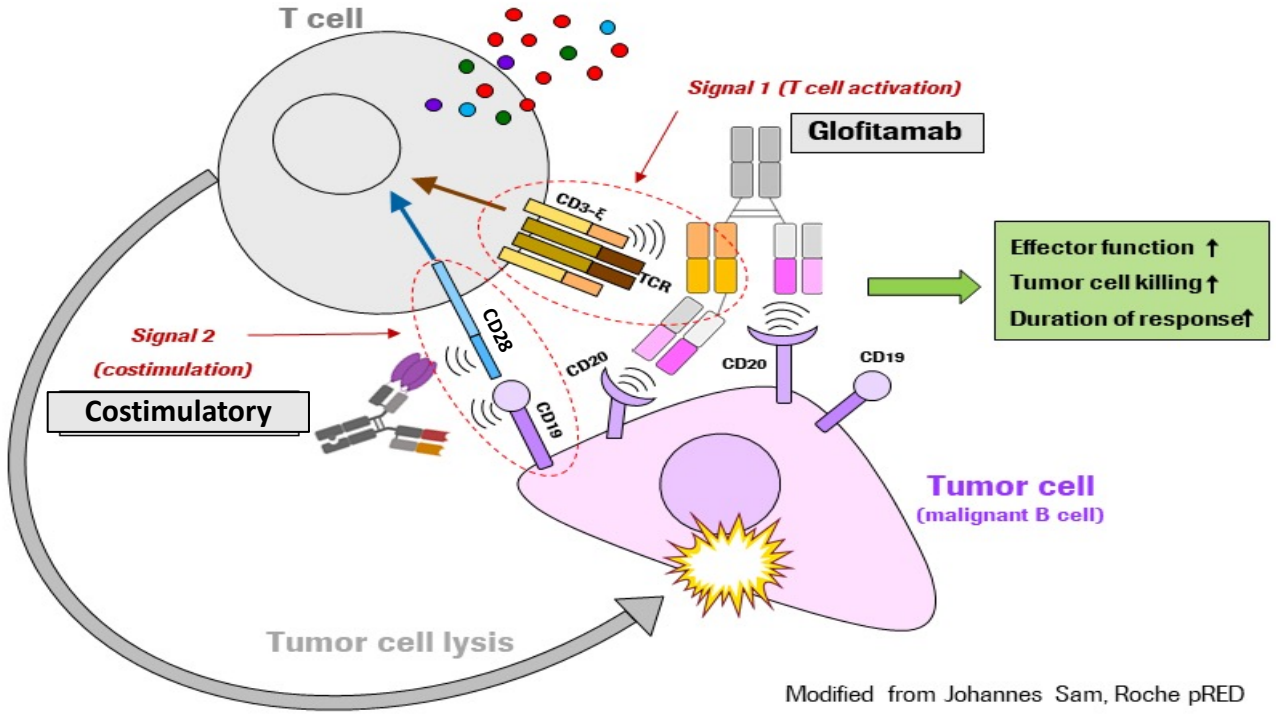
Lussana, Gritti, Rambaldi, JCO 2021

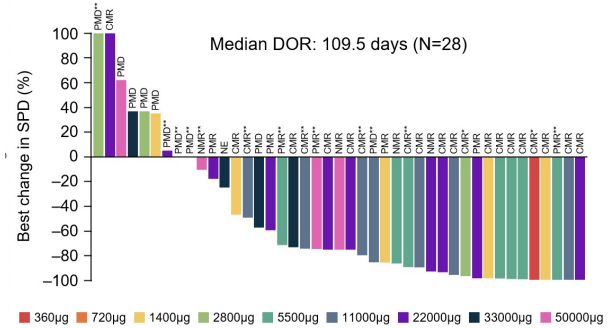


Combination of T-cell Redirecting with Costimulatory BSA

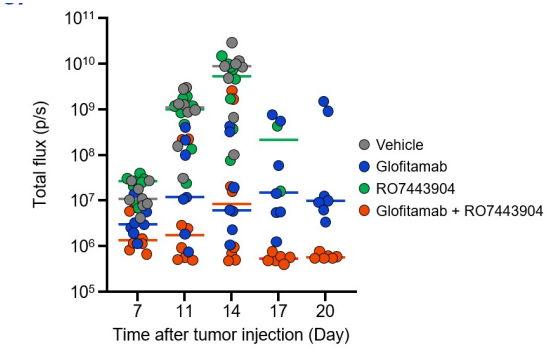


Modified from Johannes Sam, Roche pRED

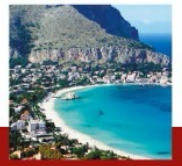
RO7227166: CD19x41BBL BSA



RO7443904: CD19xCD28 BSA



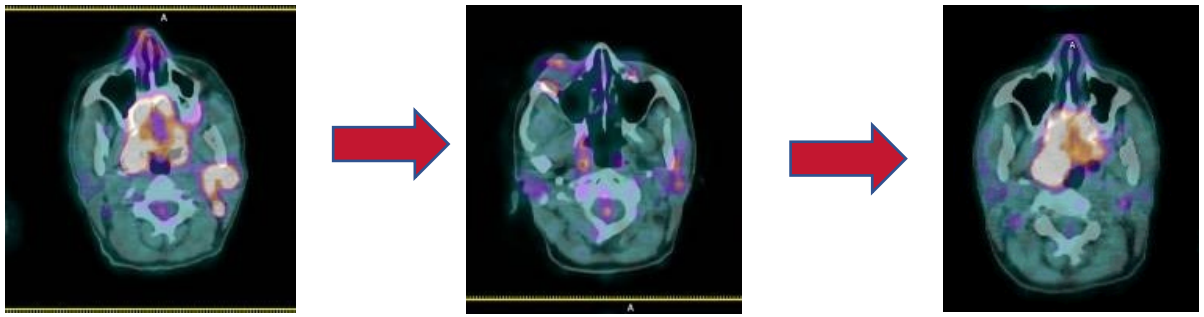
Hutchings et al., ASH 2022; Dickinson et al., ASH 2022



Combination of T-cell Redirecting with Costimulatory BSA

Clinical Case: 47 y/o Woman with Relapsed DLBCL

CD20xCD3 BSA



Baseline **PMR** **PD**

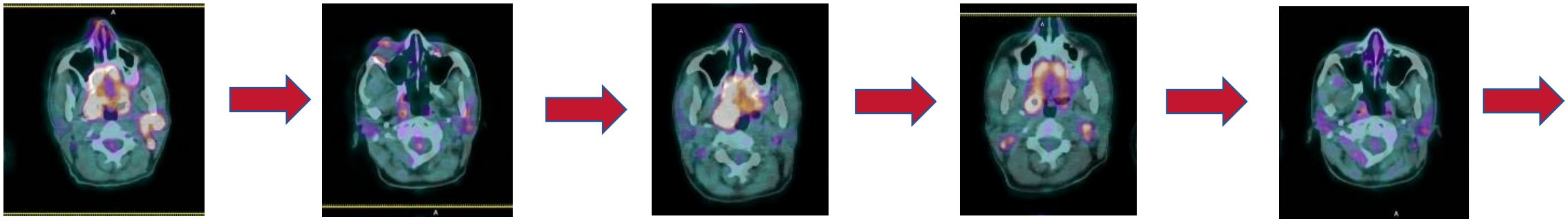
Biopsy: DLBCL NOS, non-GC
CD20+ and CD19+

Combination of T-cell Redirecting with Costimulatory BSA

Clinical Case: 47 y/o Woman with Relapsed DLBCL

CD20xCD3 BSA

CD20xCD3 BSA + Co-stimulatory BSA



Baseline

PMR

PD

Biopsy: DLBCL NOS, non-GC CD20+ and CD19+

PMR

Biopsy: T-cell infiltrate, absence of DLBCL or B-cells

CMR

Checkpoint inhibitors after CART-cell Failure in DLBCL

Background:

Single agent checkpoint inhibitor provides poor response in R/R DLBCL

- Nivolumab in Auto-SCT-failed: ORR 10%
- Nivolumab in Auto-SCT-ineligible: ORR 3%

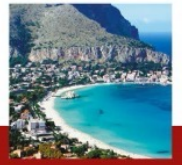
Rationale

CART-cell resistance is related to:

- T-cell exhaustion
- Immunosuppressive tumor microenvironment (with PDL1 expression)

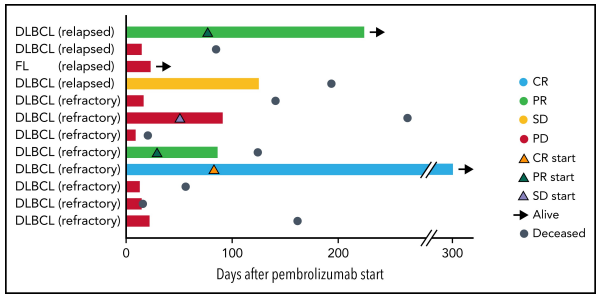
→ Can checkpoint blockade reverse T-cell exhaustion after CAR T-cell?

Ansell et al., JCO 2019; Neelapu et al., ASH 2017



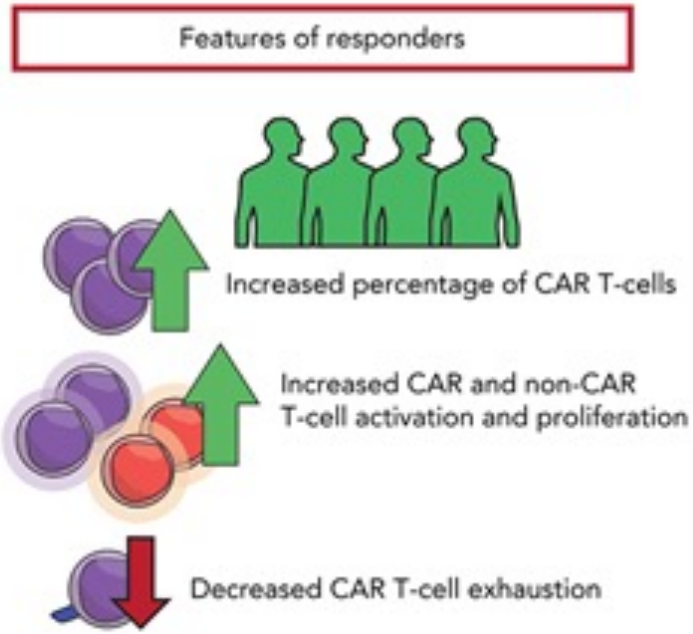
Pembrolizumab after CART-cell Failure

Overall response Rate: 20% (3/15)

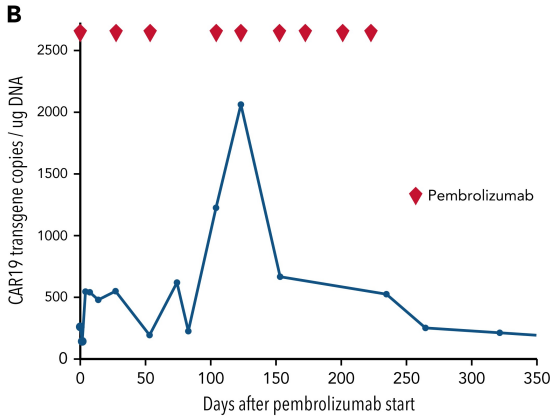


1 CR (7%)
2 PR (13%)

Low degree of T-cell exhaustion is improved by Pembro



Evidence of CART cell expansion after Pembro



Responders showed repeated expansion peak after Pembro infusions

Chong et al., Blood 2022

Pembrolizumab after CART-cell Failure

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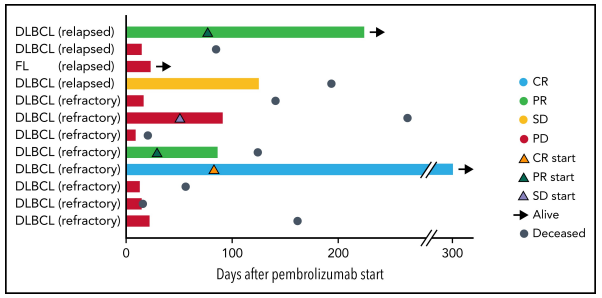

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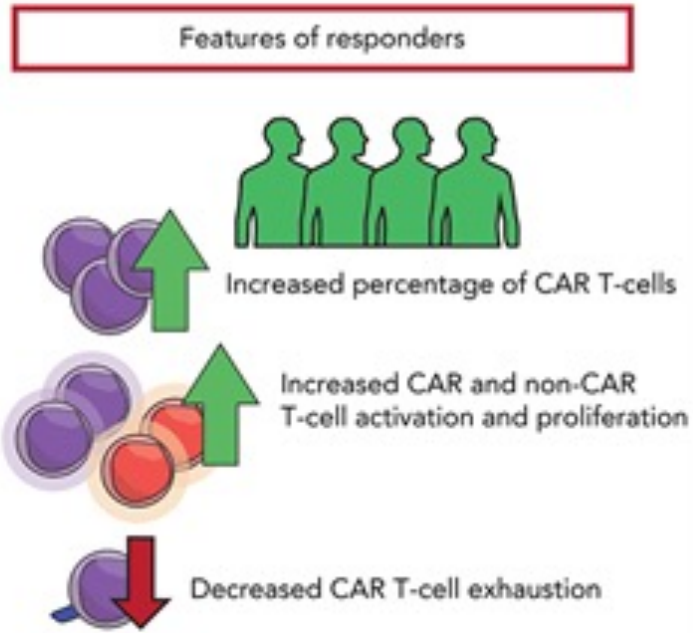

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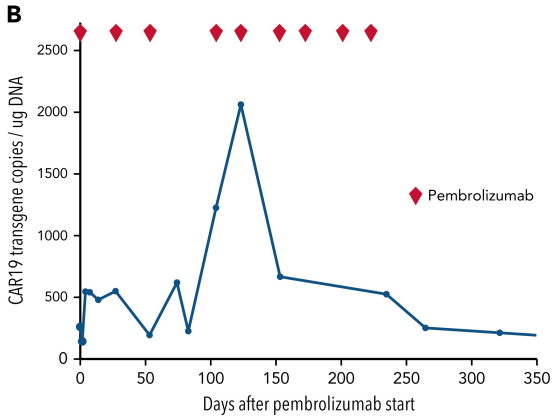


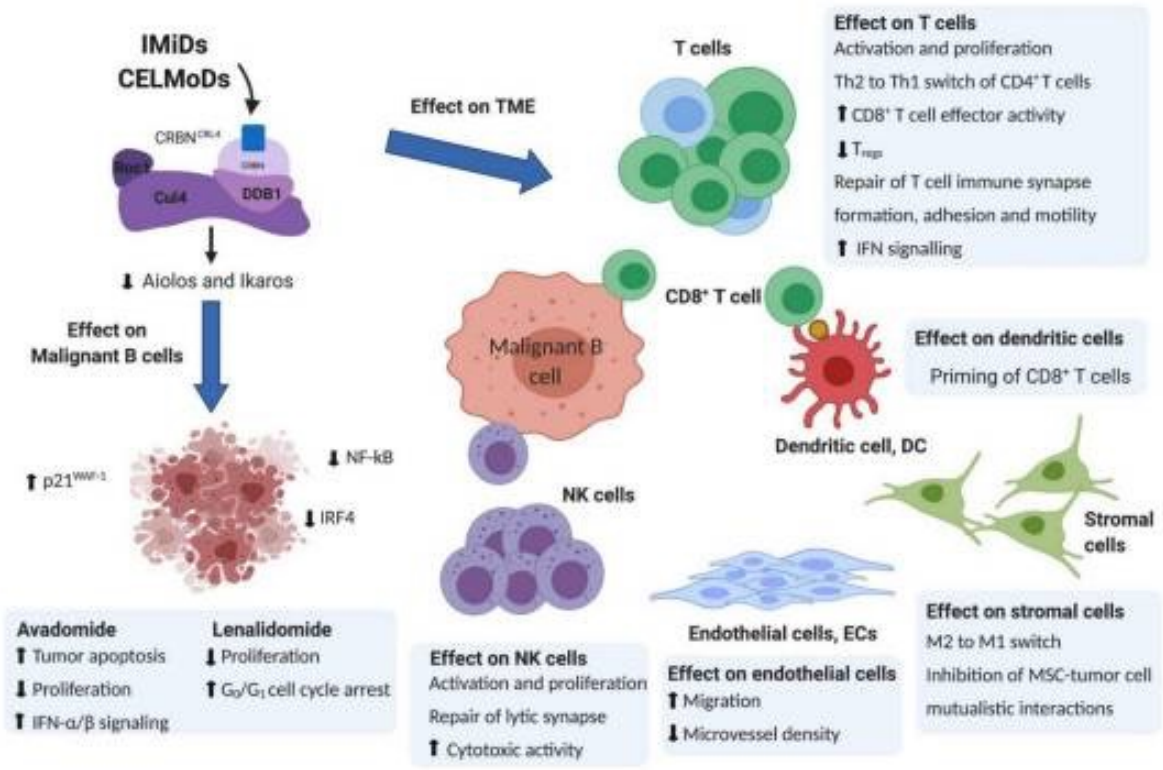
Responders showed repeated expansion peak after Pembro infusions

Who may benefit from Checkpoint Inhibitors?

Chong et al., Blood 2022

Immunomodulatory Drugs: IMiDs and CELMoDs

Pleiotropic effects of IMiDs and CELMoDs



Lenalidomide

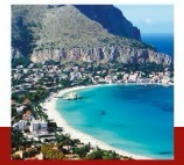
- 41 patients treated post CAR-T (70% with Rituximab)
- Improved outcome in patients with early start of Lenalidomide (< day 15): ORR 7/11, 63.6% (vs 9/48, 18.8%), CR 4/11, 36.4% (vs 5/48, 10.4%)

Avadomide (CC-122)

Iberdomide (CC-220)

Golcadomide (CC-99282)

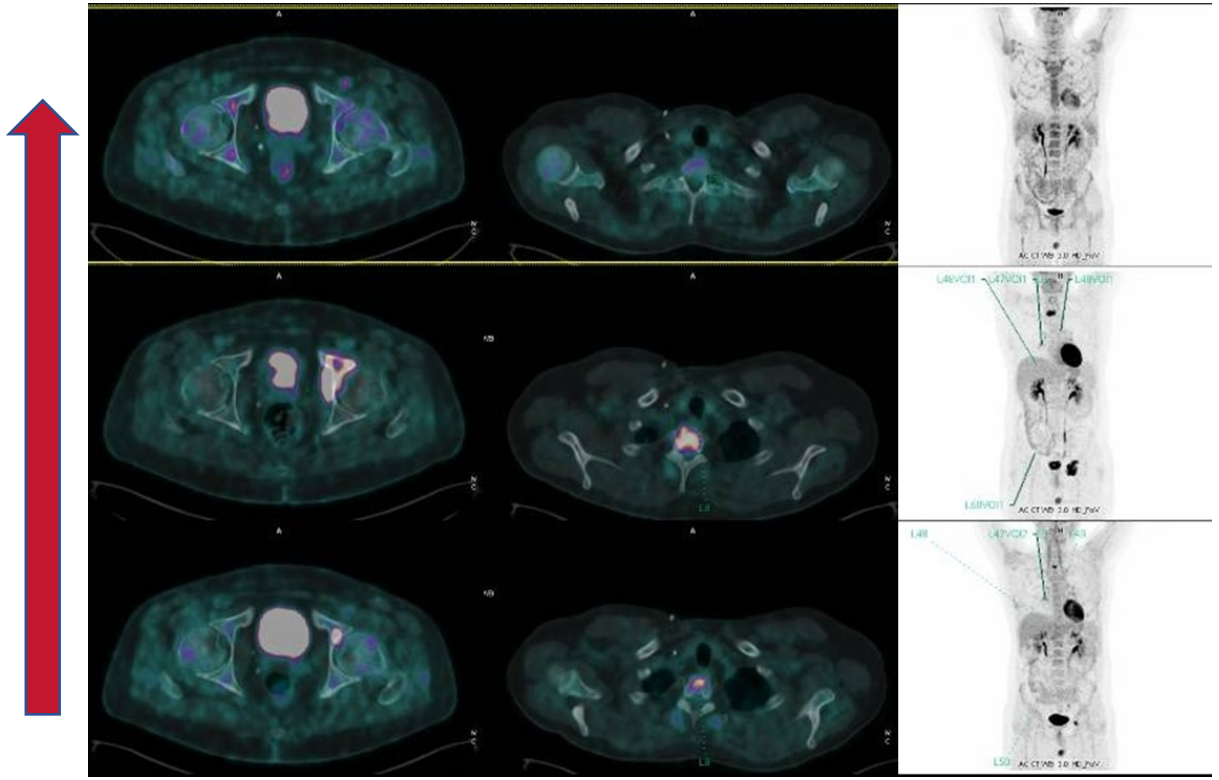
Ioannou, et al., Int J Mol Sci. 2021, Thieblemont et al., ASH 2020



Immunomodulatory Drugs: CELMoDs after CART-cell

Clinical Case:
56 y/o Man with R/R non-GC DLBCL

Previous treatments:
- R-CHOP
- R-DHAP + autologous SCT
- Lenalidomide
- R-Pola-Bendamustine
- Allogeneic SCT
- CART-cell



3-months Post-CelMod

3-months Post-CART Pre-CelMod

Pre-CART

Allogeneic SCT after CART-cell Failure

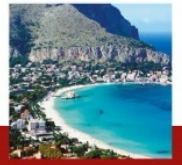
Requirements

- Disease control
  - CR is the goal
- Fittness
  - Age
  - Comorbidity
- Donor availability

"Even if AlloSCT for patients who relapse/progress after CAR-T seems reasonable, this population is very difficult to treat.

Furthermore, Allo-SCT can be complicated by the aggressiveness of disease, poor patient performance status and/or cytopenias, which can preclude the administration of induction therapy"

Castagna et al., Front Med 2022



Allogeneic SCT after CART-cell Failure

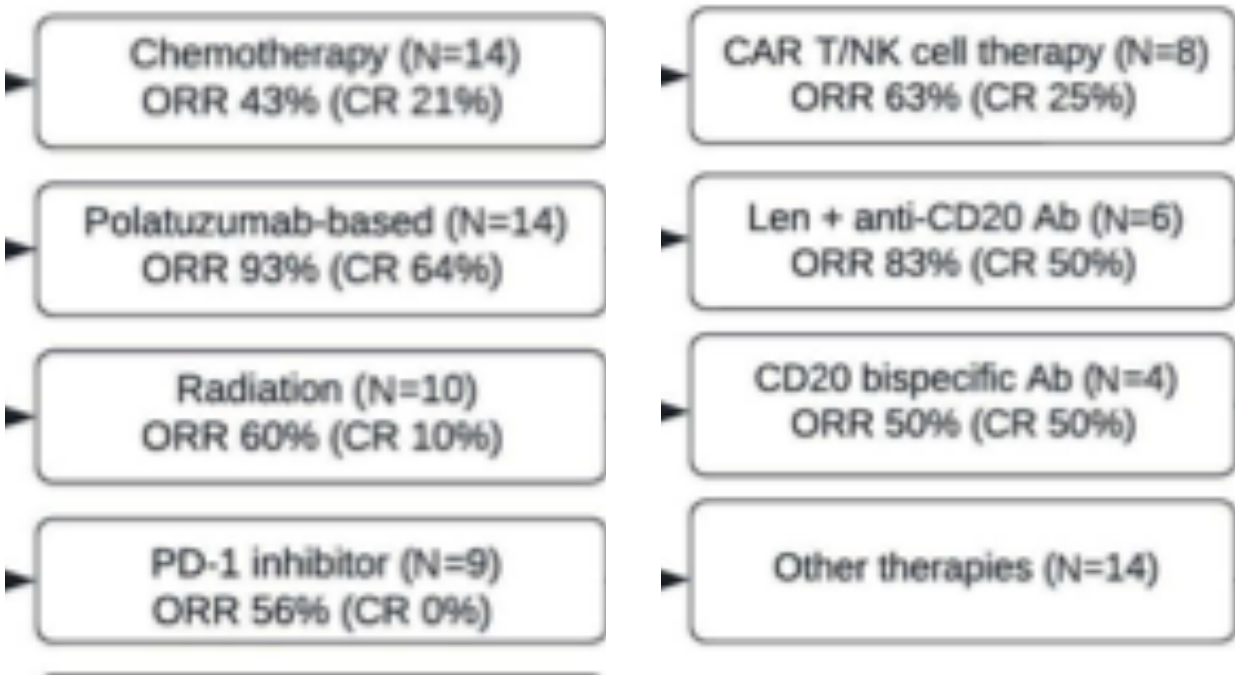
US multicenter retrospective study
88 R/R LBCL treated with CAR T therapy between 2013-2021 and subsequently receiving alloSCT

Median age 54 (19-72)

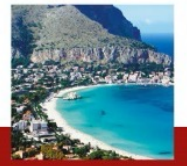
Treatment lines
- Pre CART: 3 (1-7)
- Post CART: 1 (0-7)

Low intensity conditioning in 77%

Treatments



Zurko et al., Hematologica 2023



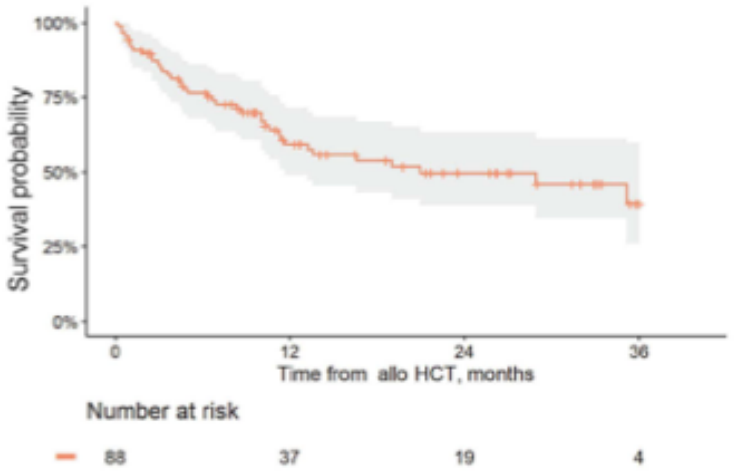
Allogeneic SCT after CART-cell Failure

US multicenter retrospective study

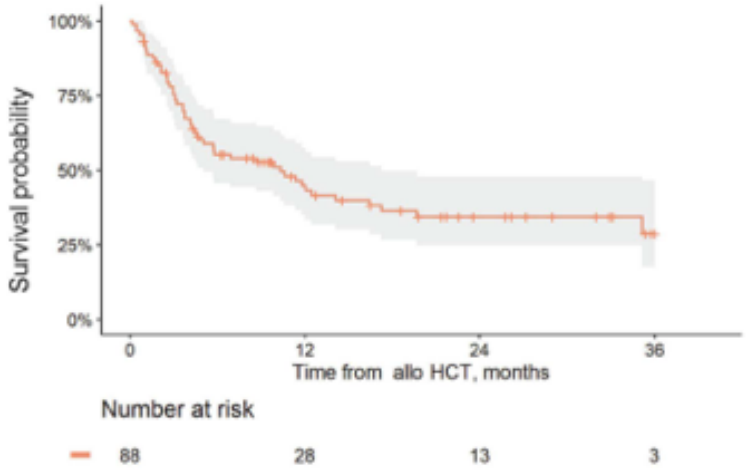
Outcome at 1 year:

- OS 59%,
- PFS: 45%,
- GVHD-free/DFS: 39%
- NRM: 22%
- Relapse: 33%

OS



PFS

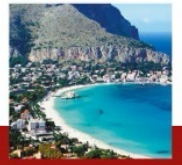


Zurko et al., Hematologica 2023

Early Phase Clinical Trials: Risky Business for End-Stage Patients or Opportunity?

- The improved understanding of the tumor biology and the emergence of innovative therapy expanded the aims of Phase I trials beyond assessment of toxicity and pharmacokinetic/RP2D

- Substantial response rates and long-term disease control achieved in early phase clinical trials

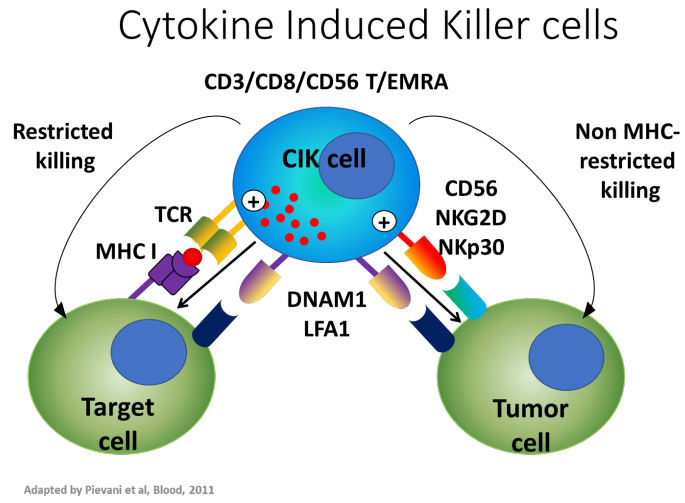


Allogeneic CD19-CARCIK in B-cell NHL and CLL

- After CD19-CART failure, antigen loss occurs in a minority of the cases
- Several patients are excluded from commercially available CART-cell (e.g. age, HIV)

Citokine Induced Killers (CIK)

- Non MHC-restricted NK-like cytotoxicity, negligible alloreactivity and minimal GVHD
- Intrinsic capability of reaching disease-infiltrated tissues
- Clinical experience with allogeneic CIK cells: feasible, safe and well tolerated

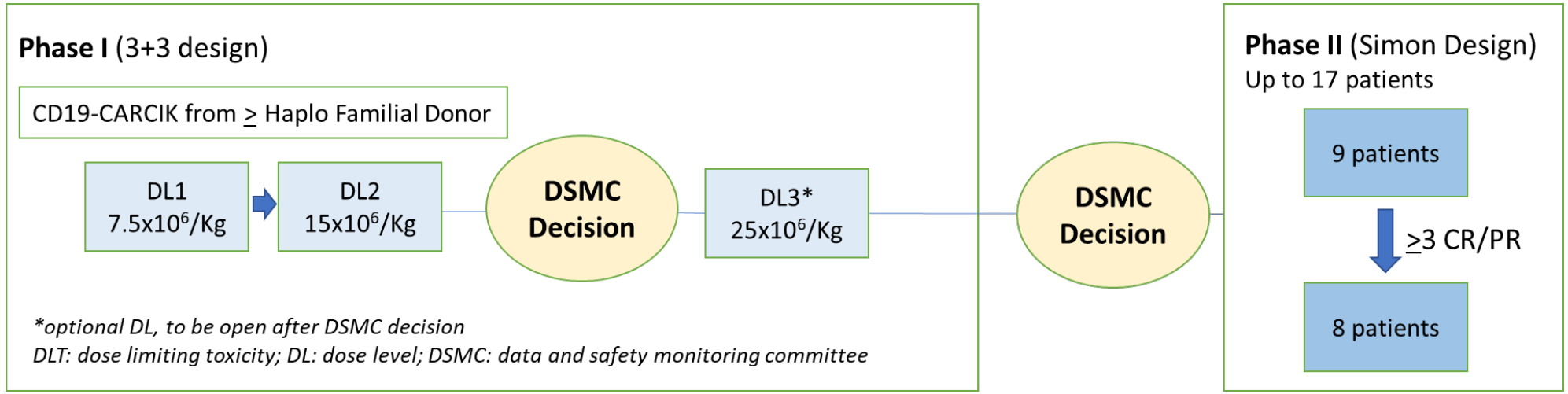


Pievani et al, Blood, 2011; Sangiolo et al. JC 2011; Introna et al, Haematol. 2007; Rambaldi et al., Leukemia 2015; Introna et al., BBMT 2017

Allogeneic CD19-CARCIK in B-cell NHL and CLL

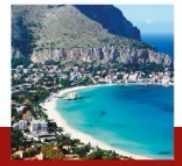
Can allogeneic CD19-CARCIK cells provide disease control?

Phase I/II Clinical Trial FT04CARCIK



Acknowledgments

ASST Papa Giovanni XXIII, Bergamo
Università degli Studi di Milano, Milan, Italy
Prof. Alessandro Rambaldi

Phase I Unit
Federico Lussana
Laura Paris
Monica Galli
Marco Frigeni
Marta Bellini
Anna Grassi
Anna Barbui
Silvia Ferrari
Silvia Mariani
Elena Bertuletti
Silvia Lanzani
Gaia Bonacina
Simone Castelli

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Olga Pedrini
Josee Golay
Silvia Zaninelli