LEUKEMIA2022

Rome, Hotel NH Collection - Vittorio Veneto

May 5-6, 2022

AIL President: G. Toro
Coordinators: A.M. Carella, S. Amadori

AIL
ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

UNDER THE AUSPICES OF:

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

GITMO

SIES

SIE - Società Italiana di Ematologia

IMMUNOTHERAPY IN ONCO-HEMATOLOGY:

STATE OF THE ART

Andrés J. M. Ferreri

Head of the Lymphoma Unit, IRCCS San Raffaele Scientific Institute, Milano
President of the Fondazione Italiana Linfomi

Disclosures

Speaker fees from Gilead, Adienne and Roche;

Member of advisory boards of Gilead, Juno, Novartis, PletixaPharm, and Roche;

Research grants from ADC Therapeutics, Bayer HealthCare Pharmaceuticals, Beigene, Bristol Myers Squibb, Genmab, Gilead, Hutchison Medipharma, Incyte, Janssen Research & Development, MEI Pharma, Novartis, PletixaPharm, Pharmacyclics, Protherics, Roche, and Takeda;

Patents on NGR-hTNF-α in brain tumours and NGR-hTNF/R-CHOP in relapsed or refractory PCNSL and SNGR-hTNF in brain tumors.

Immunotherapy: Definition and Goals

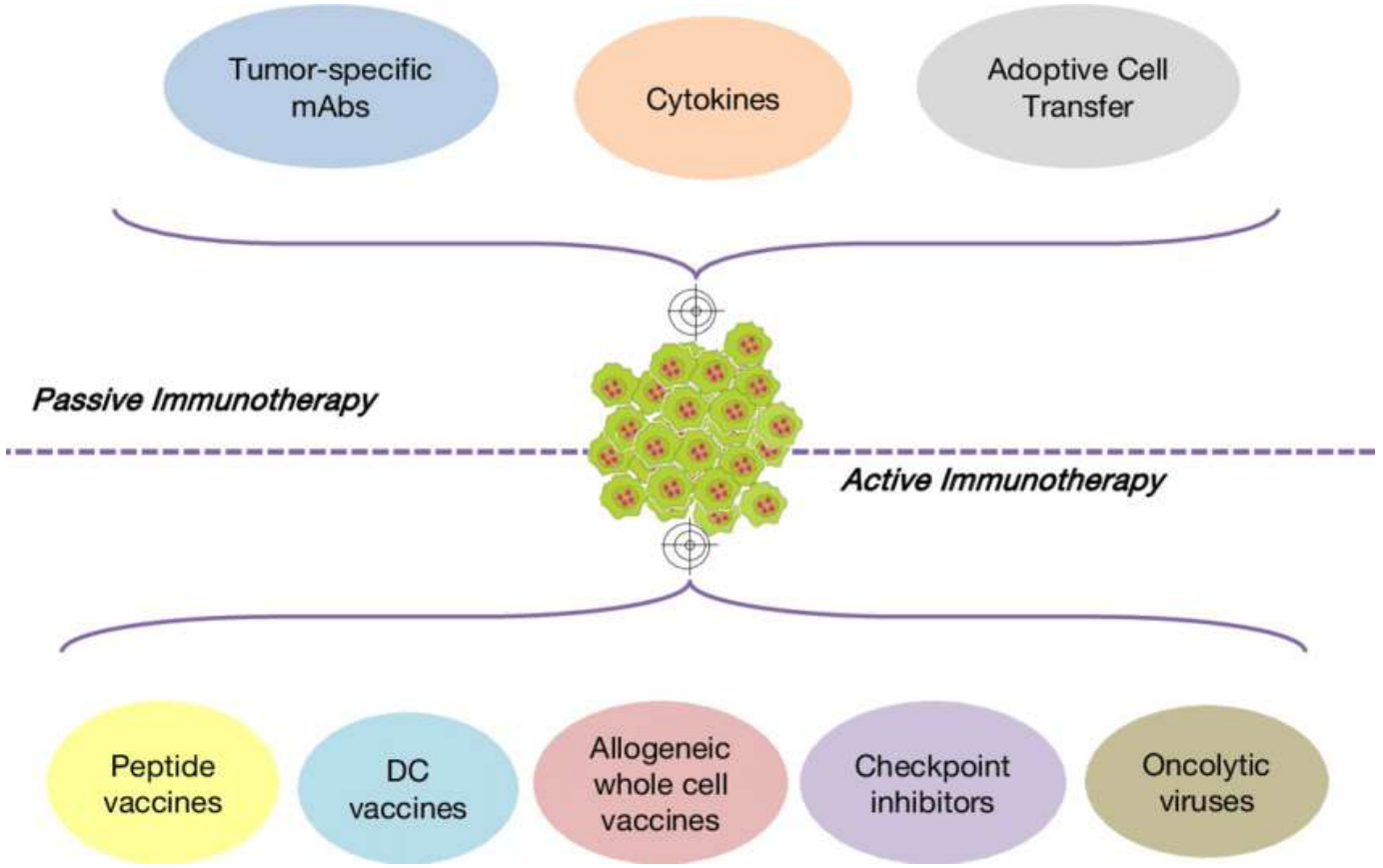
- It is a form of biological therapy that uses certain parts of the immune system to fight diseases, such as cancer, autoimmune disorders, degenerative diseases, and other pathological conditions.

- It includes a wide variety of treatments that:

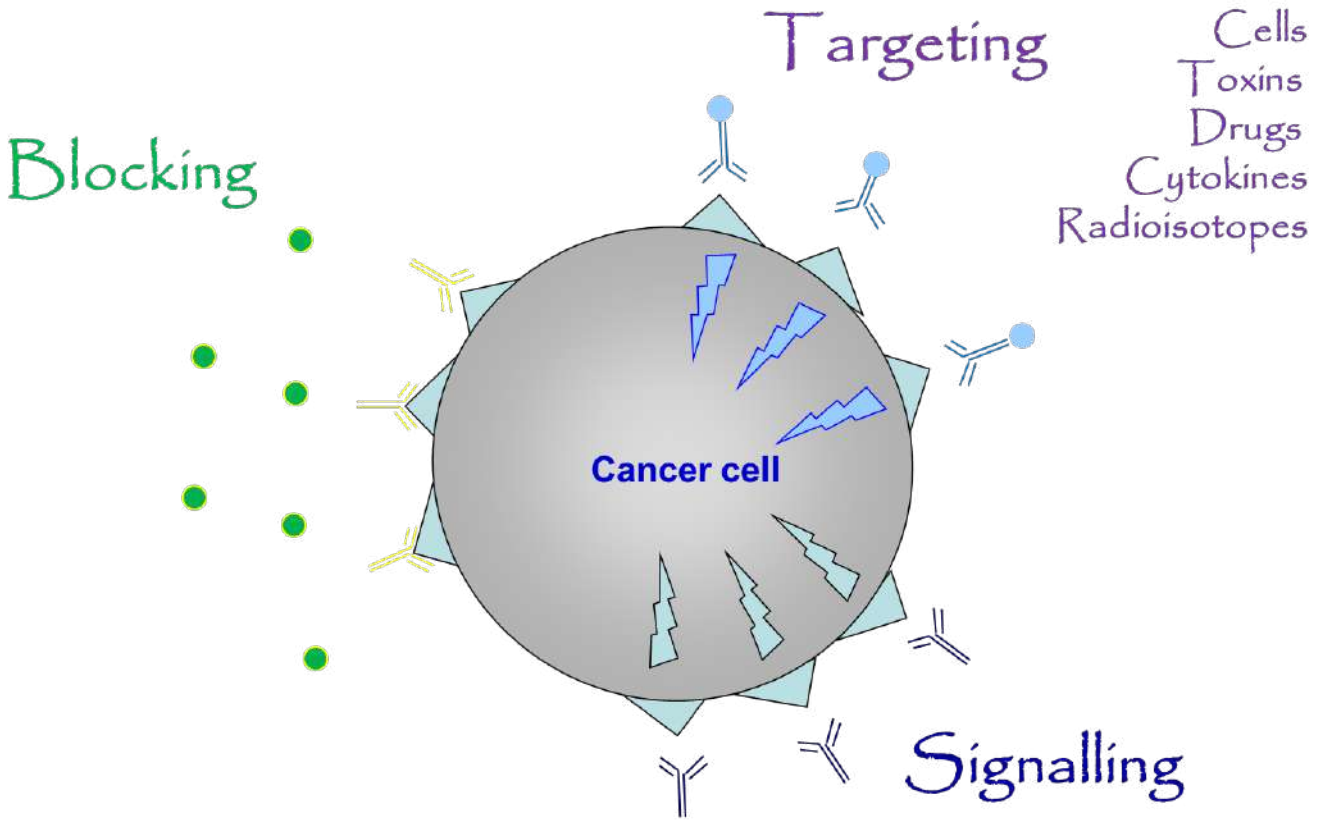
  - boost the immune system in a general way
  - train immune system to attack cancer cells specifically
  - use man-made (transfected, engineered, etc) immune components

- Promise: to treat cancer without serious side effects of chemotherapy, radiotherapy and surgery and with an effect longer than those of other biologics (cure?)

Immunotherapy: 1, 100, 1.000

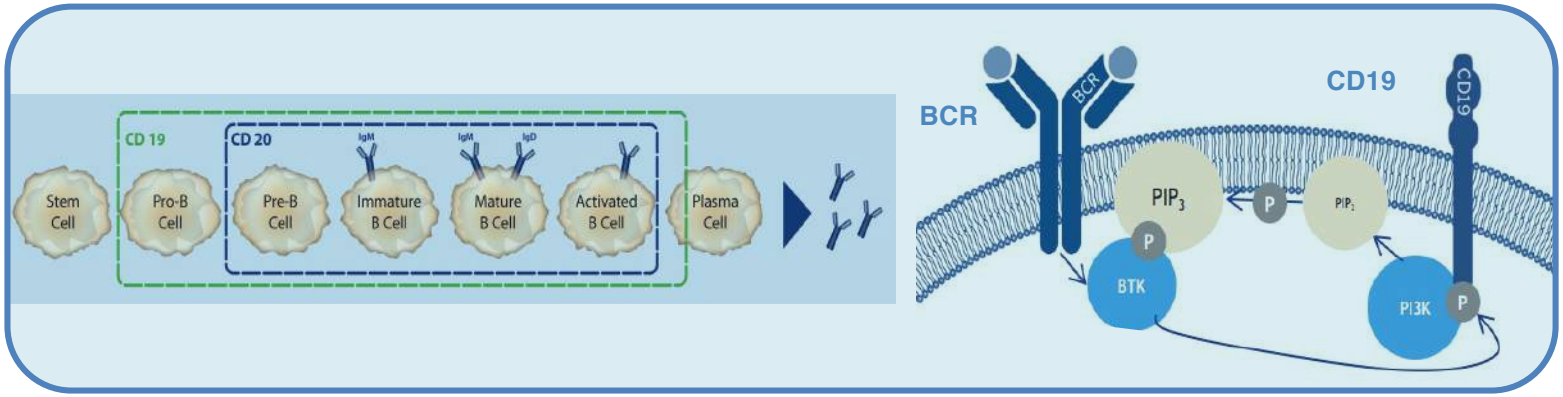


Monoclonal Antibodies



CD19: from marker to target

- **CD19 is broadly and homogeneously expressed across different B-cell malignancies**
- **CD19 enhances tumor cell survival and proliferation via B-cell receptor (BCR) survival signaling**
- **CD19 expression is thought to be preserved during treatment of B-cell malignancies**



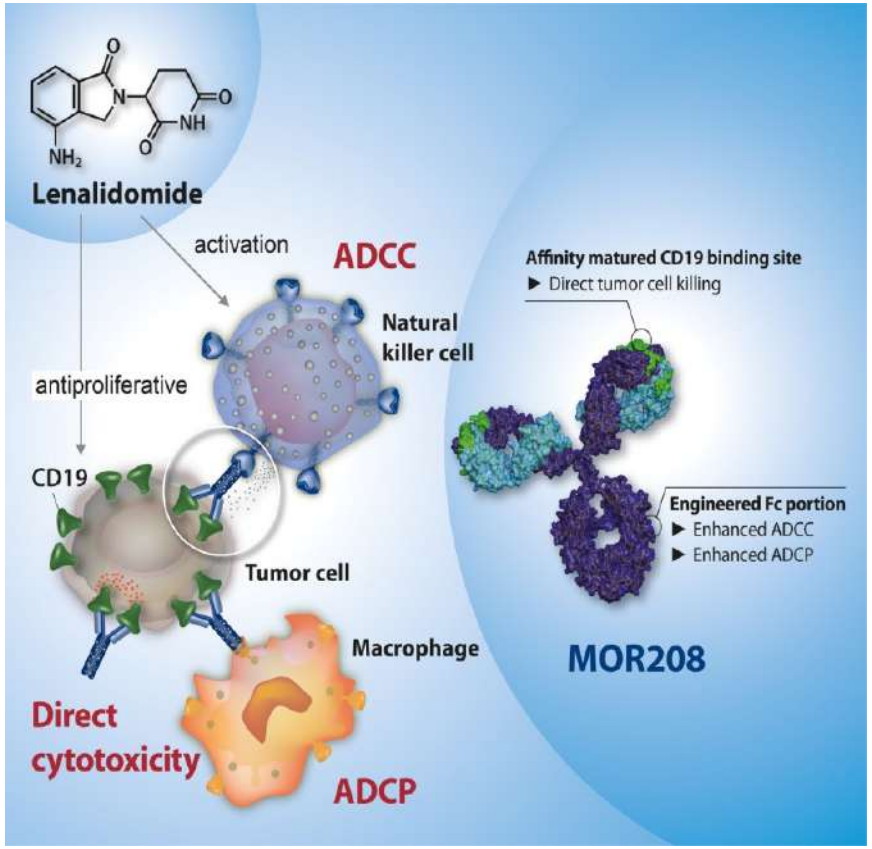
➔ **Therefore, CD19 may be an ideal target antigen in B-cell malignancies**

Olejniczak et al., 2006; Fujimoto et al., 1998; Fujimoto et al., 2000; Carter et al. 1991; Poe et al. 2012; Kamburova et al. 2013; Hiraga et al., 2009; Lapalombella et al. 2011, Bojarczuk et al. 2014, Maude et al. 2014.

CLL, chronic lymphocytic leukemia

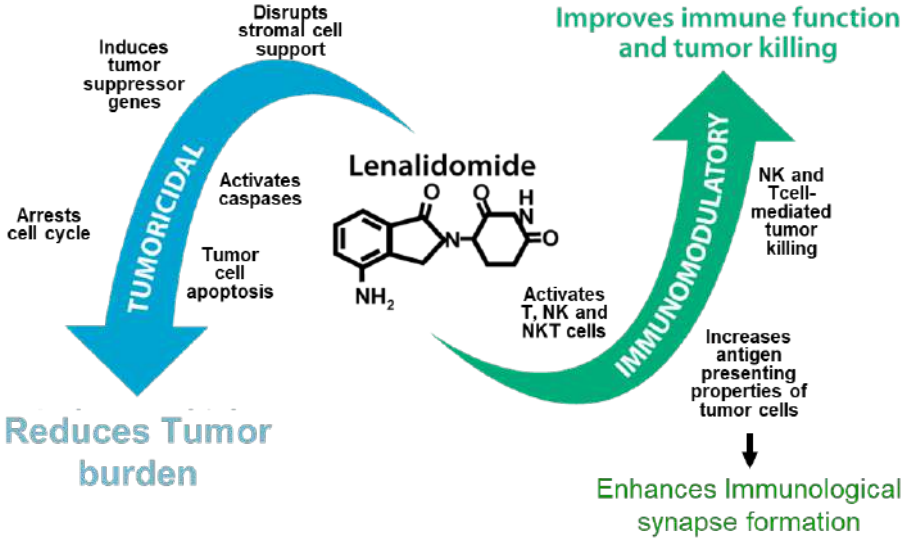
Tafasitamab (MOR208) & Lenalidomide (L-MIND)

Fc-enhanced, anti-CD19 mAb

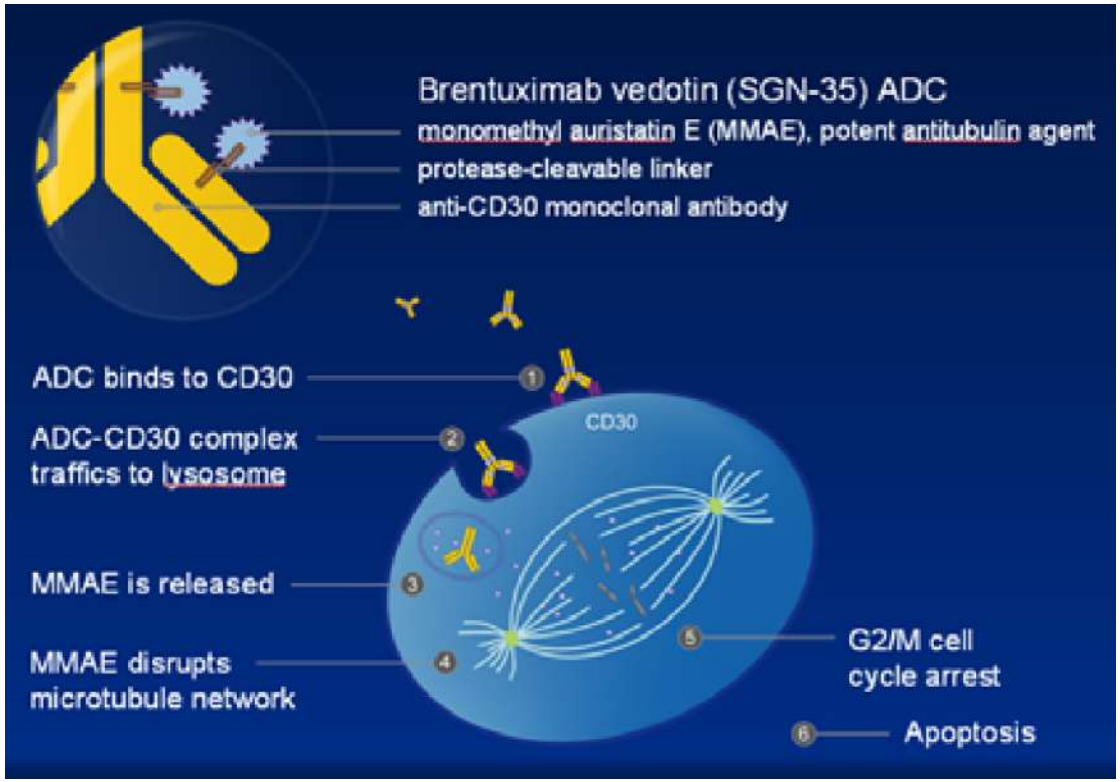


+

Lenalidomide



ADC: Brenduximab Vedotin



58 relapsed or refractory ALCL

- ORR 86%
- CR 53%
- median DoR 13 mos

102 post-auto transplant HL

- ORR 75%
- CR 34%
- 7 mos (20 mos in CRs)

Brentuximab in cHL at Risk of Progression After ASCT

AETHERA

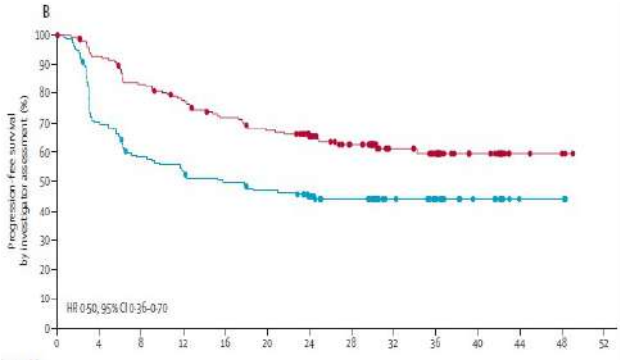
Key eligibility:

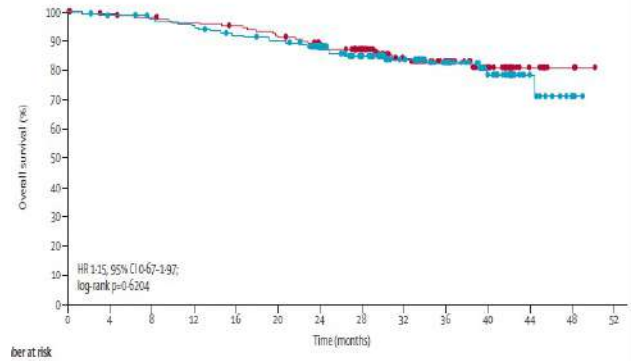
- Pts with HL and a CR, PR, or SD to salvage therapy prior to ASCT
  - Refractory to frontline therapy
  - Relapse <12 months
  - Relapse ≥12 months after frontline therapy with extranodal disease

(N = 329)

Brentuximab vedotin 1.8 mg/kg IV
outpatient every 3 wks
For up to 16 cycles (approx. 12 mos)
+
Best Supportive Care
(n = 165)

Placebo
+
Best Supportive Care
For up to 16 cycles (approx. 12 mos)
(n = 164)



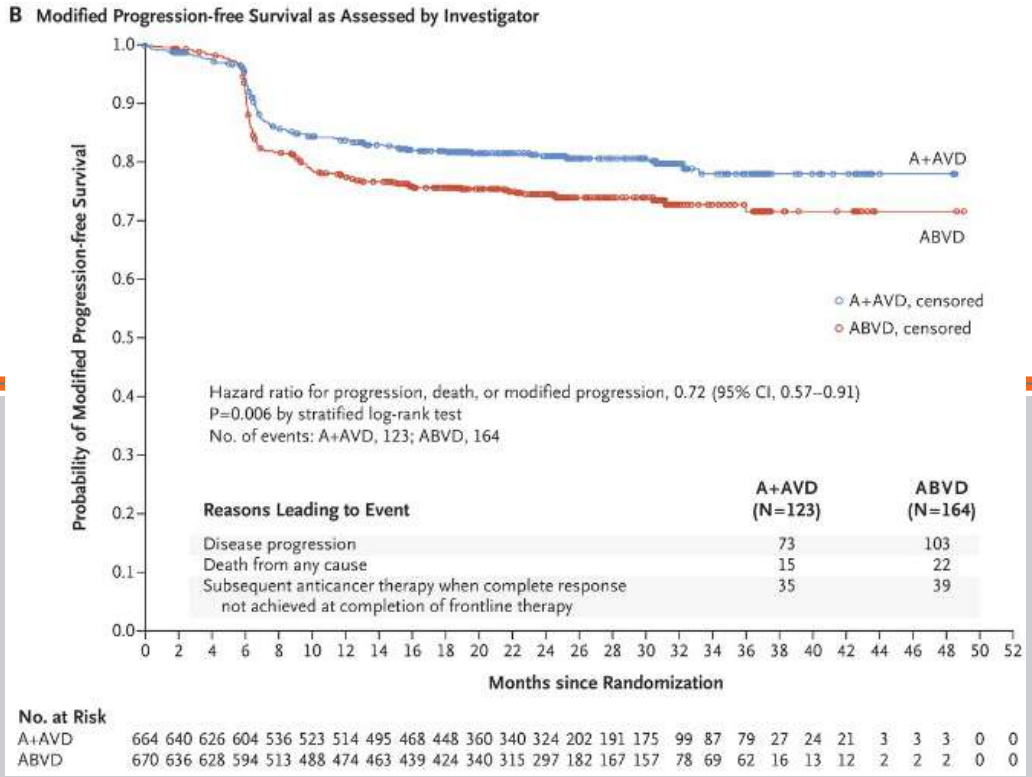


Moskowitz CH, et al. Lancet Oncol 2014

Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma

Joseph M. Connors, M.D., Wojciech Jurczak, M.D., Ph.D., David J. Straus, M.D., Stephen M. Ansell, M.D., Ph.D., Won S. Kim, M.D., Ph.D., Andrea Gallamini, M.D., Anas Younes, M.D., Sergey Alekseev, M.D., Árpád Illés, M.D., D.Sci., Marco Picardi, M.D., Ewa Lech-Maranda, M.D., Ph.D., Yasuhiro Oki, M.D., et al., for the ECHELON-1 Study Group*

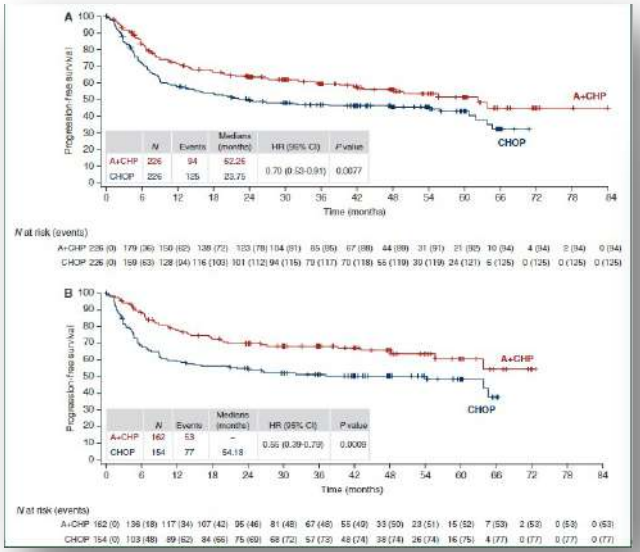
ECHELON-1

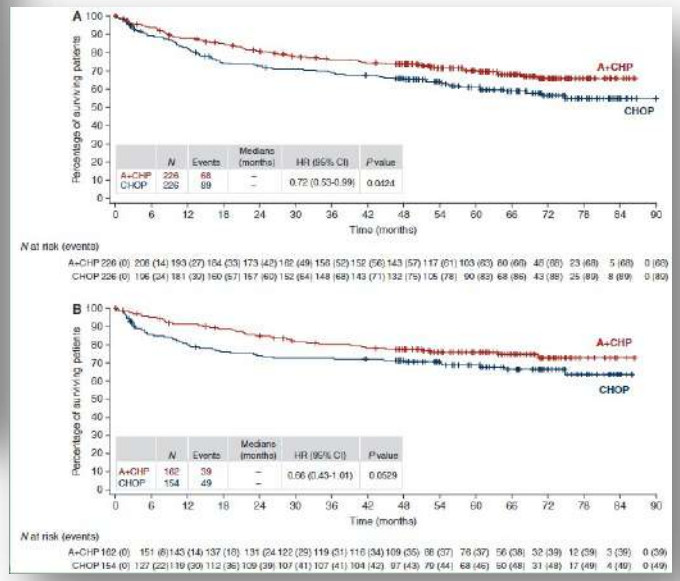


Waiting EHA/ASCO to know OS benefit

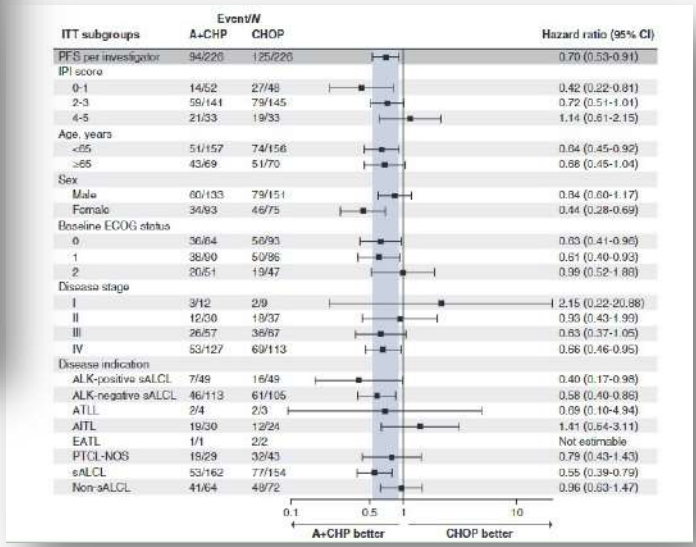
….

Brentuximab Vedotin as 1L for CD30+ Peripheral T-Cell Lymphomas



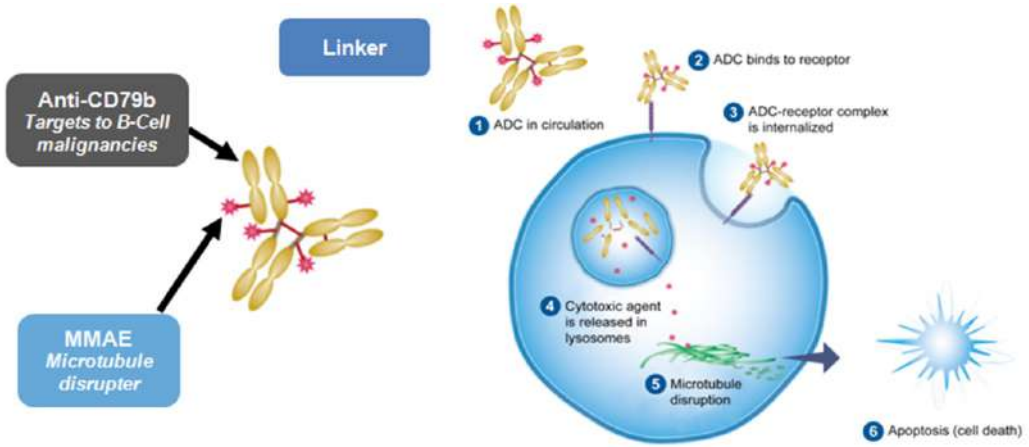


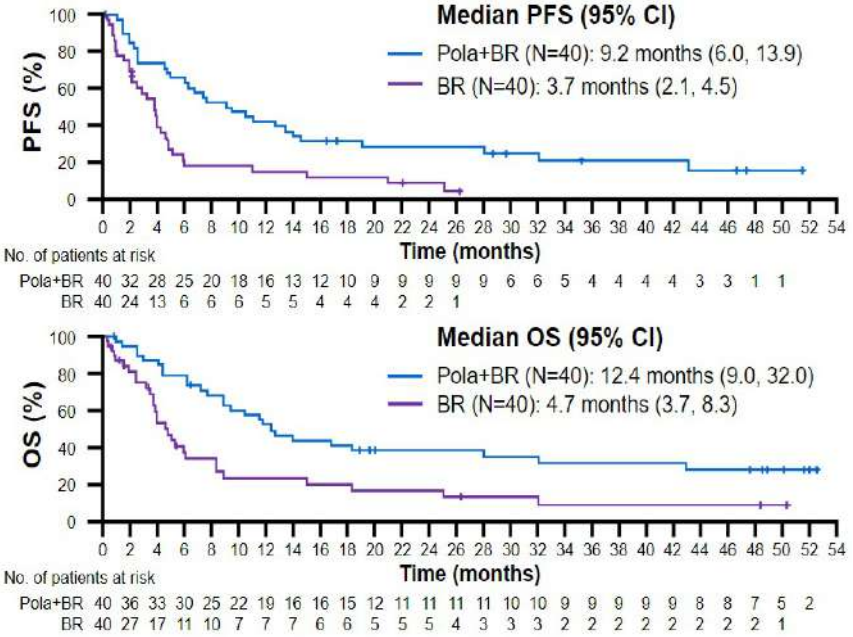
ECHELON-2

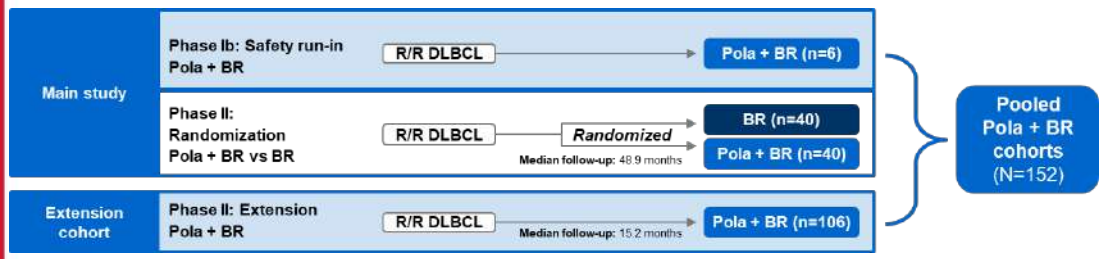


Horwitz S, et al. Ann Oncol 2022

Polatuzumab Vedotin: an anti-CD79b ADC for RR-DLBCL

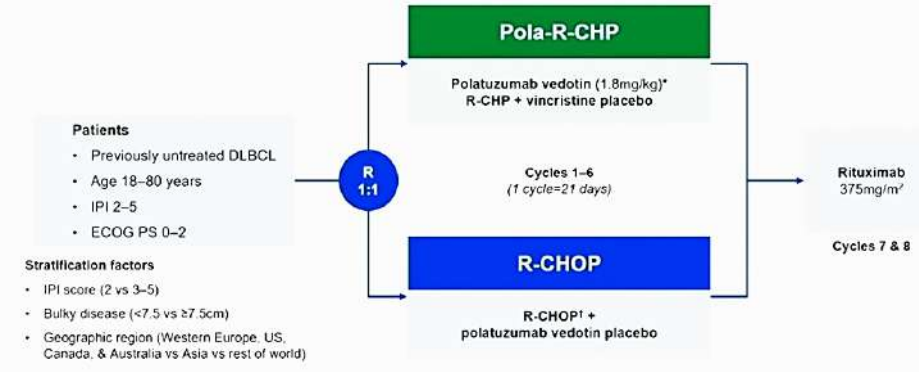


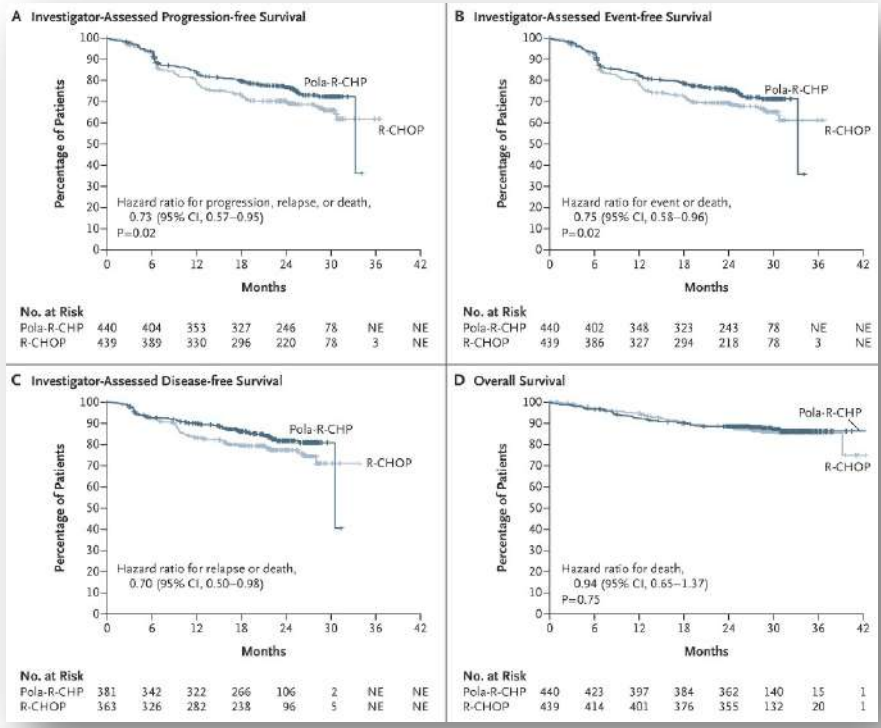


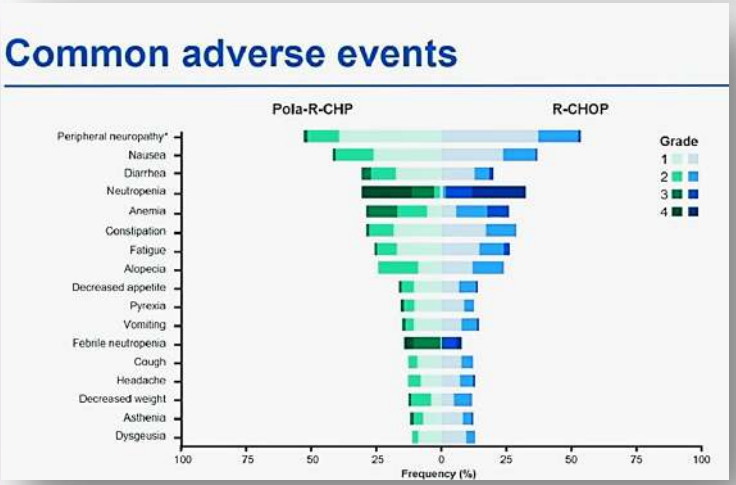


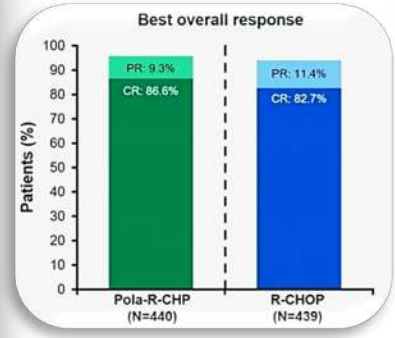
Sehn L, JCO 2020, Blood Adv 2021

Polatuzumab Vedotin: an anti-CD79b ADC as 1L for DLBCL



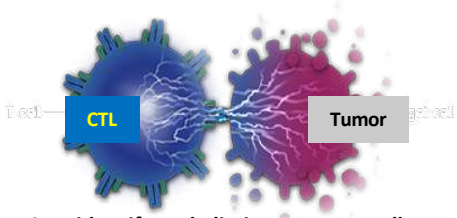






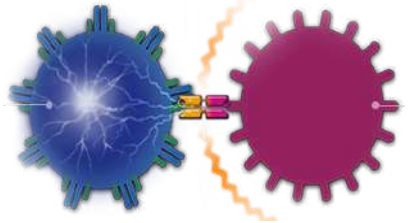
Tilly H, et al. NEJM 2021

Triggering T lymphocytes against tumor cells

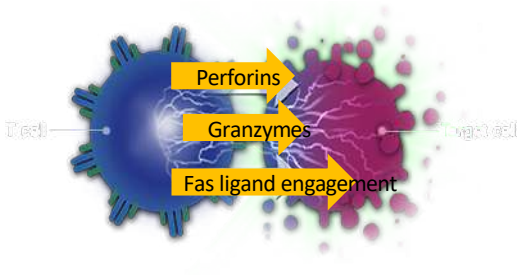


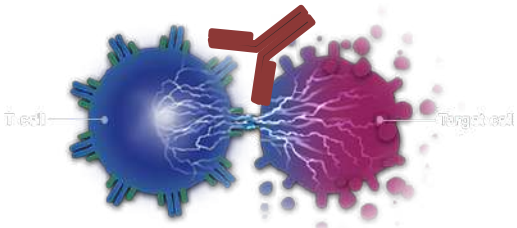
CTLs identify and eliminate cancer cells.

CTLs are activated when TCRs bind tumor Ags.

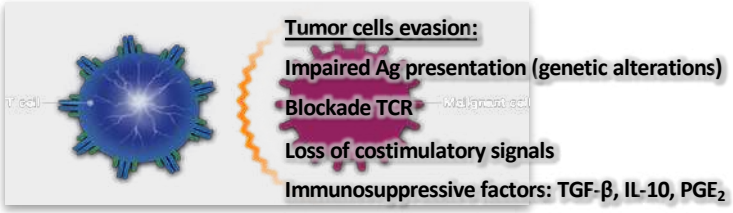


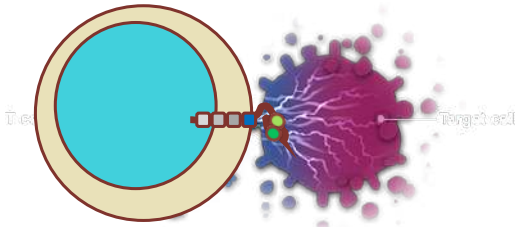
Bispecific T-cell Engager





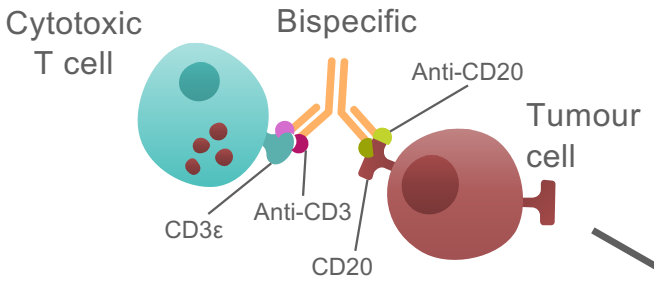
Immune Checkpoint Blockade





Chimeric Antigen Receptors (CAR-T)

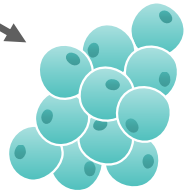
Mode of action of anti-CD20/CD3 bispecific antibodies



1. Local secretion of chemokines leading to the recruitment of T cells from the periphery

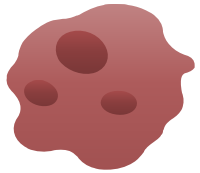
Anti-CD20/CD3 bispecifics redirect endogenous non-specific T cells to engage and eliminate malignant B cells in NHL[1–3]

2. T cells undergo proliferation and expansion at the tumour site



3. T-cell activation occurs via downstream signalling events leading to the secretion of cytotoxic granules

5. Apoptosis

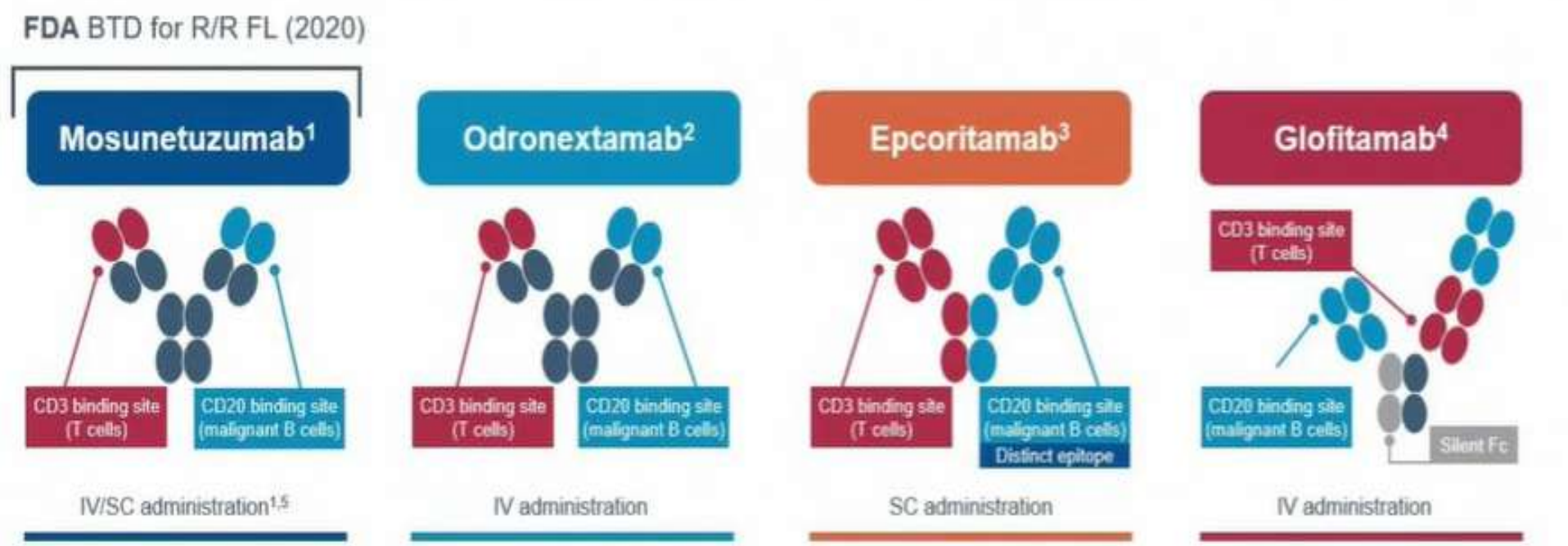


4. Potent lysis of tumour cells

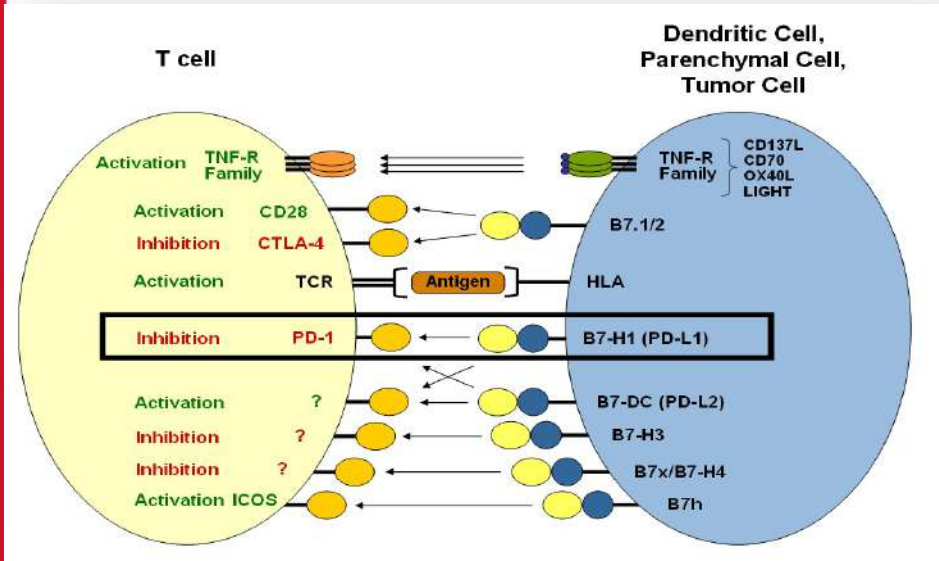
6. T cell–mediated tumour killing

1. Sun LL, et al. Sci Transl Med 2015;7:287ra70; 2. Dieckmann NM, et al. J Cell Science 2016;129:2:2881–6
3. Bacac M, et al. Clin Cancer Res 2018;24:4785–97
Adapted from Aldoss I, et al. Leukemia 2017;31:777–87

Anti-CD20 / anti-CD3 Bispecific Antibodies

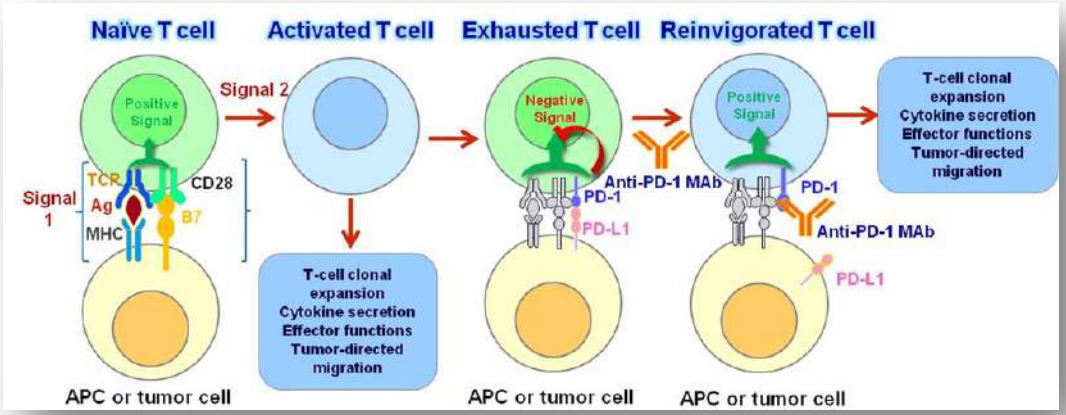


PD-1/PD-L: Role in T-Cell Activation



What is PD-1?

- Member of CD28 family involved in T-cell regulation
- Expressed by activated T-cells, memory T-cells, and regulatory T-cells
- Down regulates T-cell activity upon binding to PD-L1/L2
- Tumor PD-L1 expression may correlate with negative prognosis→ potential mechanism of tumor self defense



Hamanishi et al. PNAS. 2007
Sznol et al. J Clin Oncol 2010
Nurieva et al. Immunol Rev 2011

Anti-PD-1/PD-L1 for Hodgkin and Non-Hodgkin Lymphomas

	Pts	ASCT	Anti-CD30	Median f-up	CRR	ORR	6-mo PFS
Nivolumab	**23**	**78%**	**78%**	**5,7 mo.**	**17%**	**87%**	**86%**

Ansell SM, et al. NEJM 2015

Nivolumab & Pembrolizumab are indicated in adults with R/R cHL after ASCT and Bv.

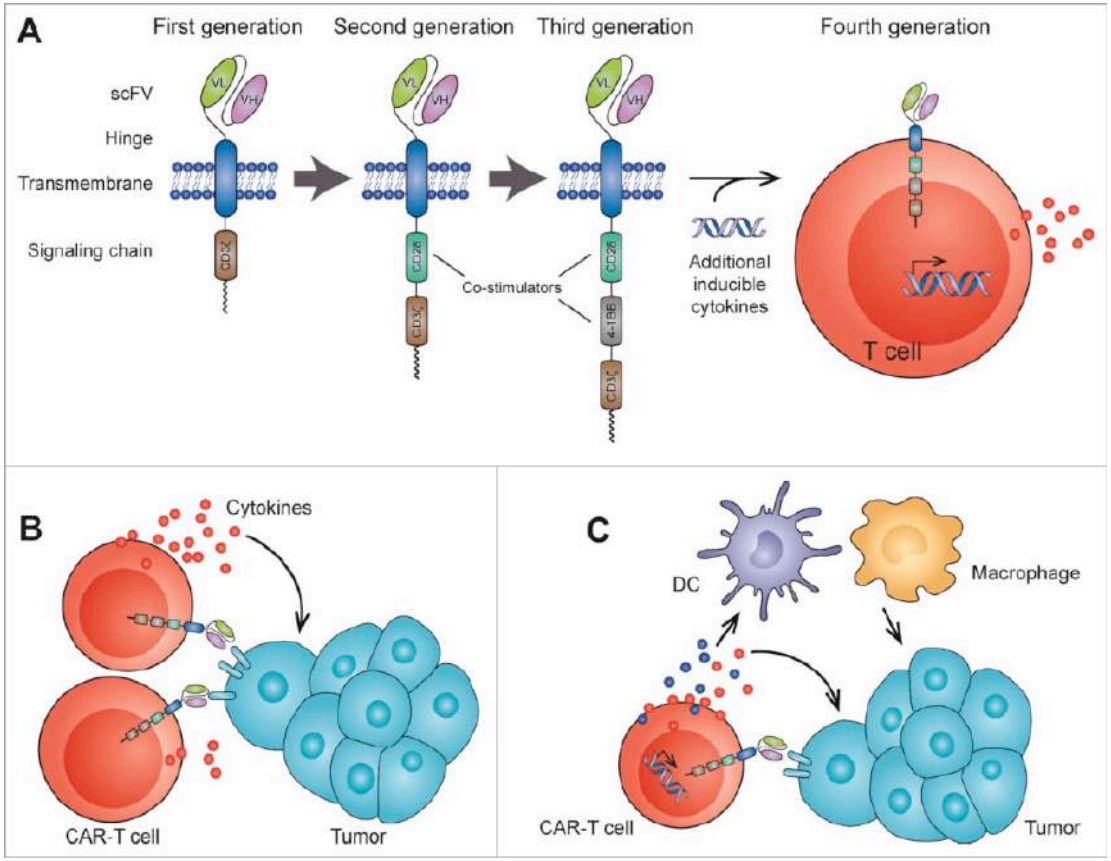
Combination with Bv is safe and active, even in elderly and unfit patients with newly diagnosed cHL.

Promising results in mediastinal large B-cell lymphoma.

Being explored in aggressive extranodal lymphomas with increased PD-1/PD-L1 expression (PCNSL & testicular DLBCL).

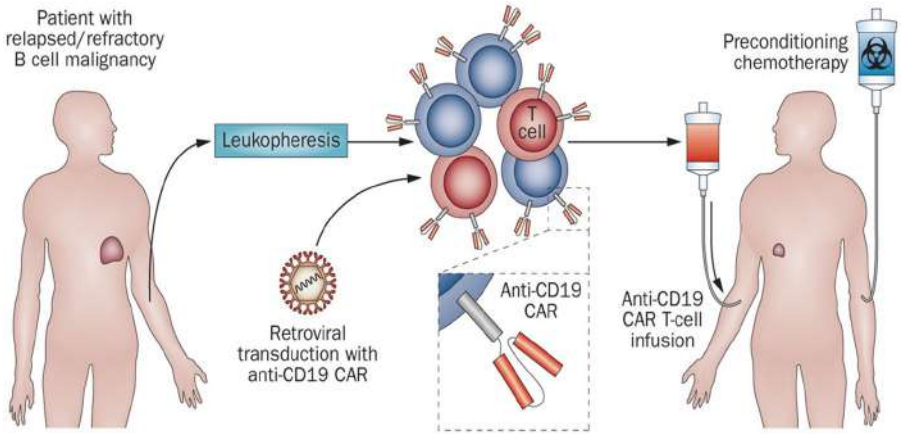
Initial favorale results in Extranodal NK/T-cell lymphoma.

Chimeric Antigen Receptor (CAR) T-cell Therapy



Advantages

Recognition is HLA-independent
Targeting of proteins, sugars, lipids
No need of repetitive administrations
Multiple, direct effector mechanisms
Optimal biodistribution
Platform for implementation of safety & efficacy factors



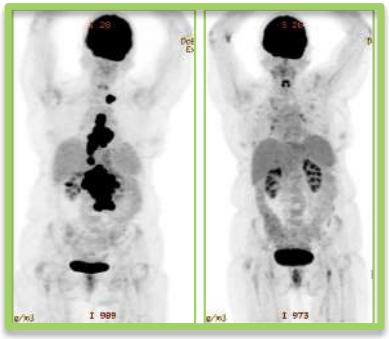
Zhang et al, *Oncoimmunology* 2016
Klebanoff, C. A. *et al. Nat. Rev. Clin. Oncol* 2014

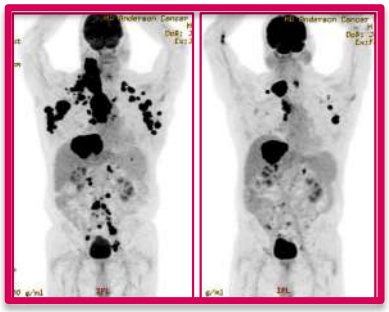
CAR T-cell Therapy for RR-DLBCL

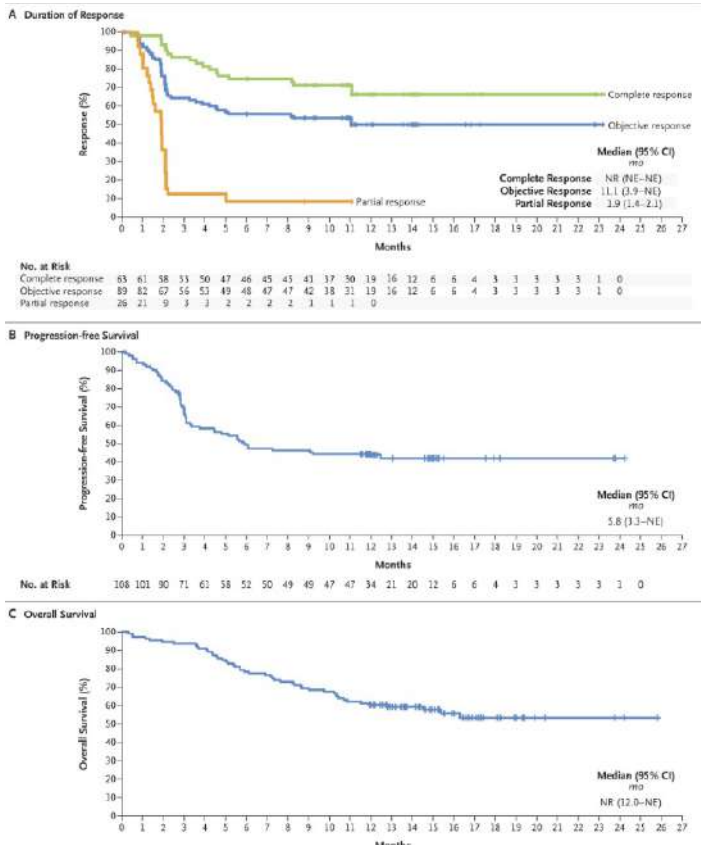
Pivotal trial	Histotypes	Bridging	Infused	Median turnround	Median follow-up	ORR	CRR	CRS g≥3	Neurotox g≥3	TRM
ZUMA-1 (n= 111)	DLBCL - HGT PMLBCL	No	91%	17 days	9 months	82%	54%	13%	28%	3%
JULIET (n=167)	DLBCL	Yes (89%)	60%	NR	40 months	53%	45%	26%	13%	0%
TRANSCEND (n=344)	DLBCL - HGT HGBCL - FL g3B PMLBCL - MCL	Yes (59%)	78%	NR	19 months	66%	53%	2%	10%	1%

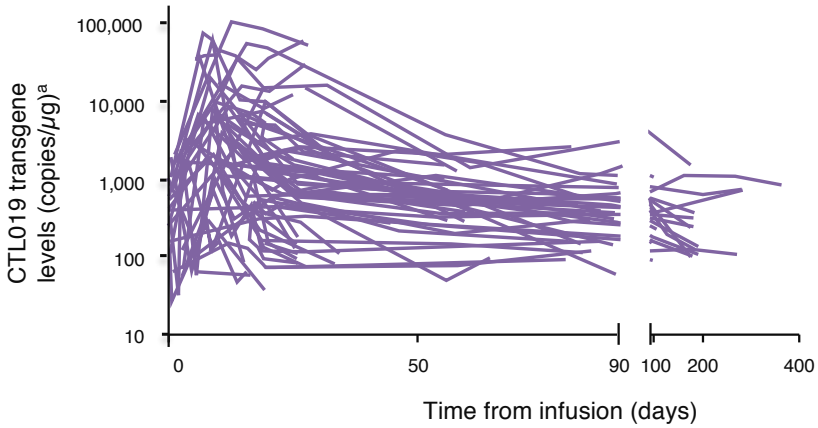
Neelapu SS, et al. NEJM 2017; Schuster SJ, et al. Lancet Oncol 2021: Abramson JS, et al. Lancet 2020

Efficacy of CAR T-cell Therapy in RR-DLBCL





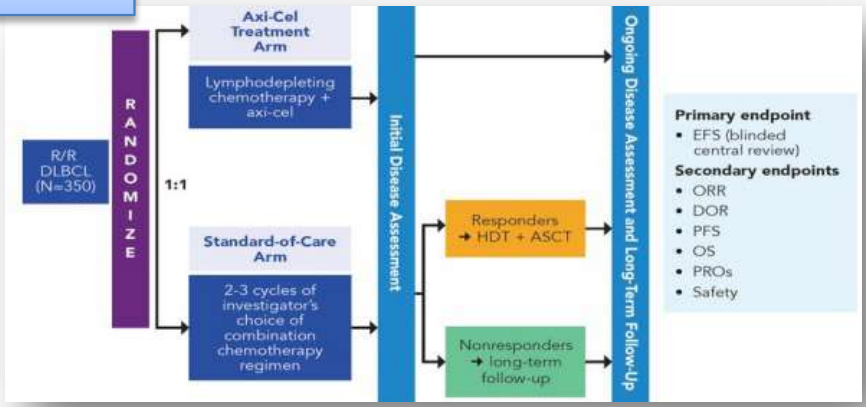


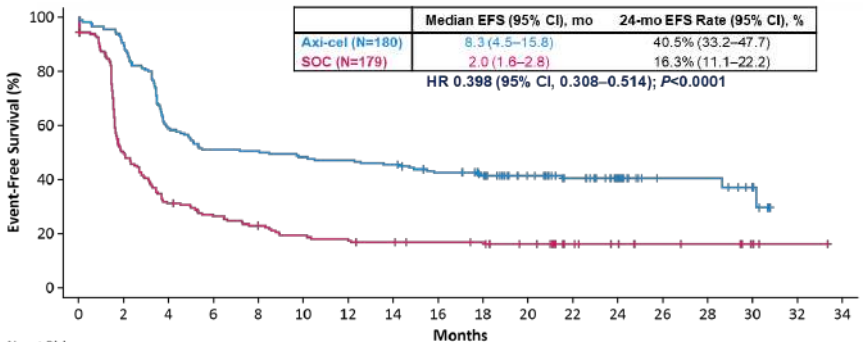


Neelapu SS, et al. NEJM 2017; Schuster SJ, et al. Lancet Oncol 2021: Abramson JS, et al. Lancet 2020

CAR T-cells vs. ASCT at First Relapse

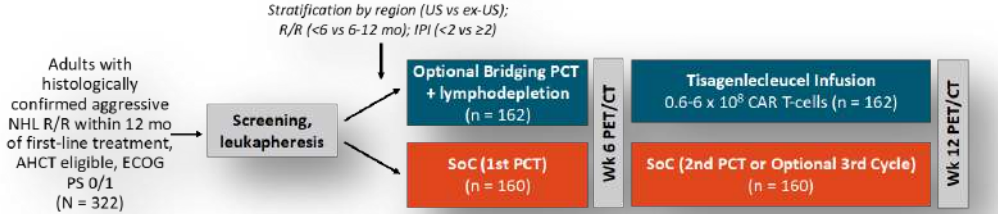
ZUMA-7



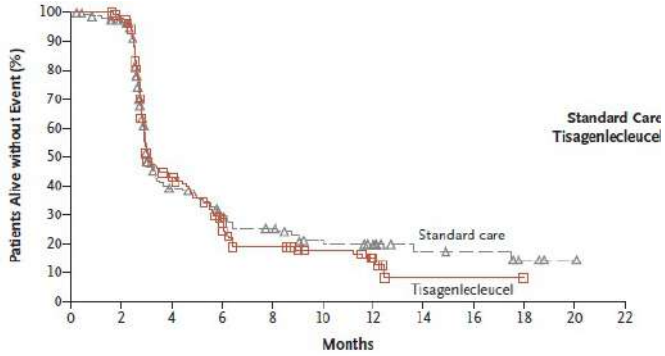


Locke FL, et al. NEJM 2022

BELINDA

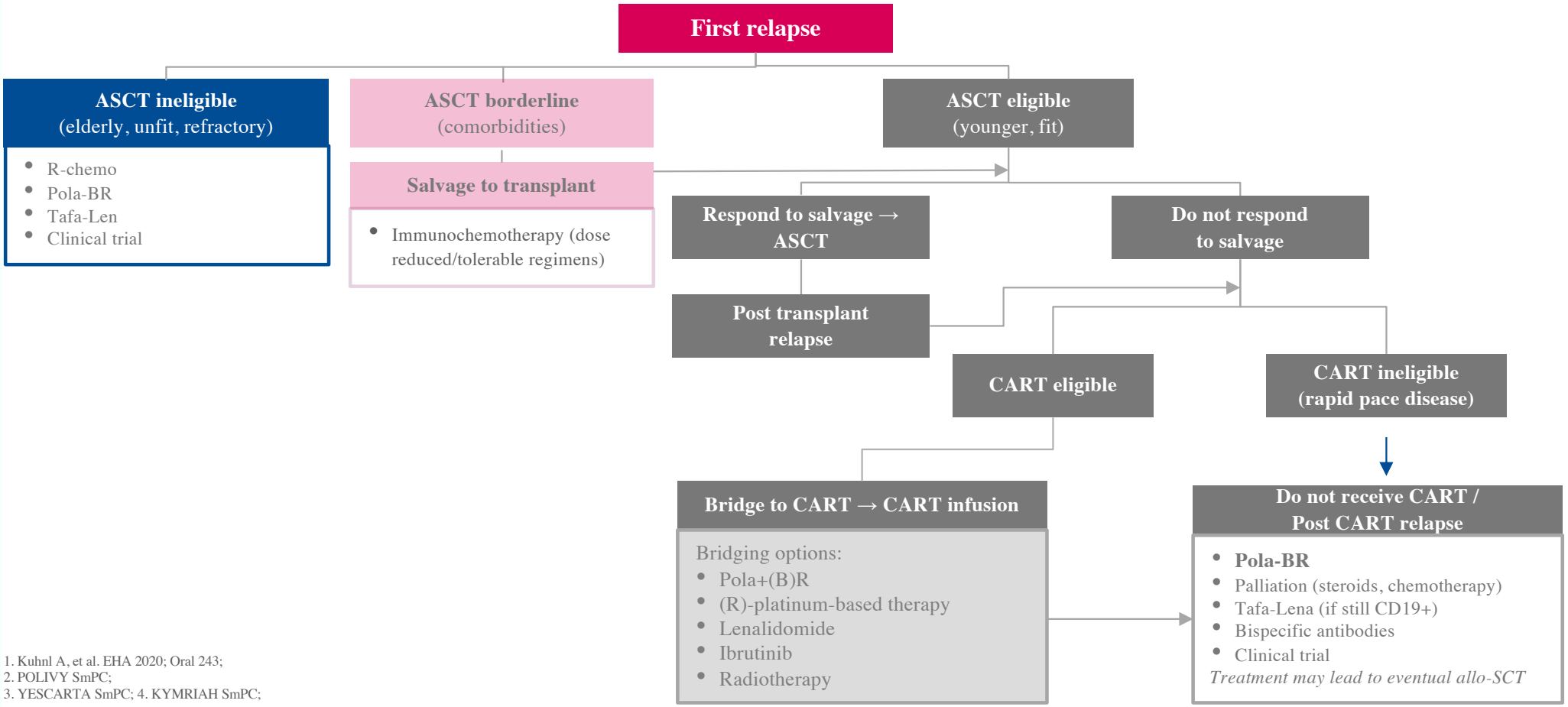


SoC arm received first PCT + AHCT for responders or second PCT for nonresponders, based on Wk 6 assessment. Crossover to tisagenlecleucel permitted for SoC at Wk 12 for nonresponders. Patients assessed at Wk 6 and 12, then 3-monthly to Mo 12, 6-monthly to Mo 24, and yearly to Mo 60.



Bishop MR, et al. NEJM 2022

Current treatment algorithm for RR-DLBCL



1. Kuhnl A, et al. EHA 2020; Oral 243;
2. POLIVY SmPC;
3. YESCARTA SmPC; 4. KYMRIAH SmPC;

CAR T-cell Therapy for RR-Mantle Cell Lymphoma

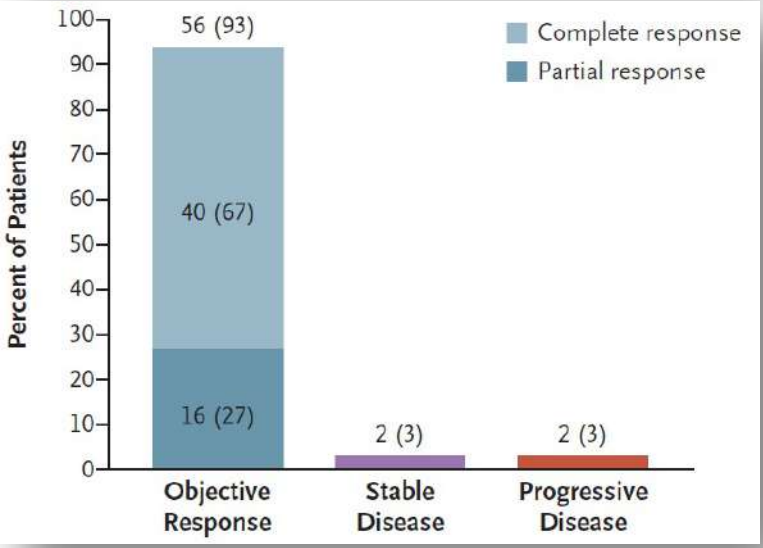
ZUMA-2

ORIGINAL ARTICLE

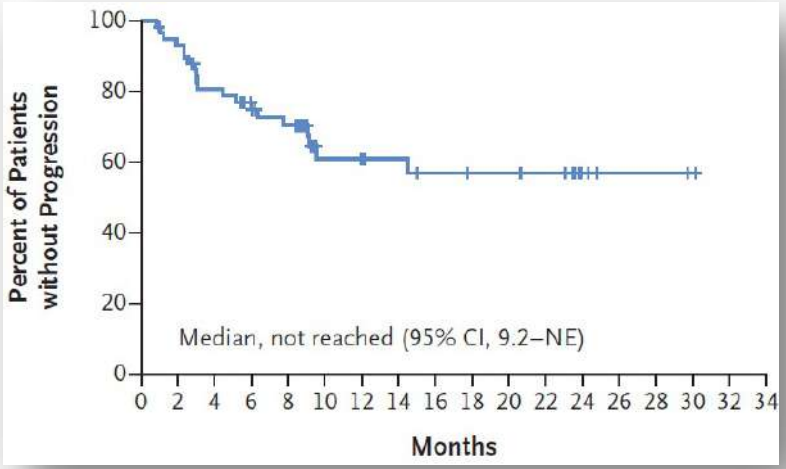
KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan

Adults (≥18 years of age) with RR-MCL (<5 lines) with either cyclin D1 overexpression or t(11;14).
Previous therapy must have included anthracycline- or bendamustine-containing chemo, an anti-CD20 MAb, and BTKi (every line).



median follow-up of 12.3 months



G≥3 CRS: 15%

G≥3 Neurotox: 31%

TRM: 3%

CAR T-cell Therapy for RR-Follicular Lymphoma

ELARA

nature medicine
ARTICLES
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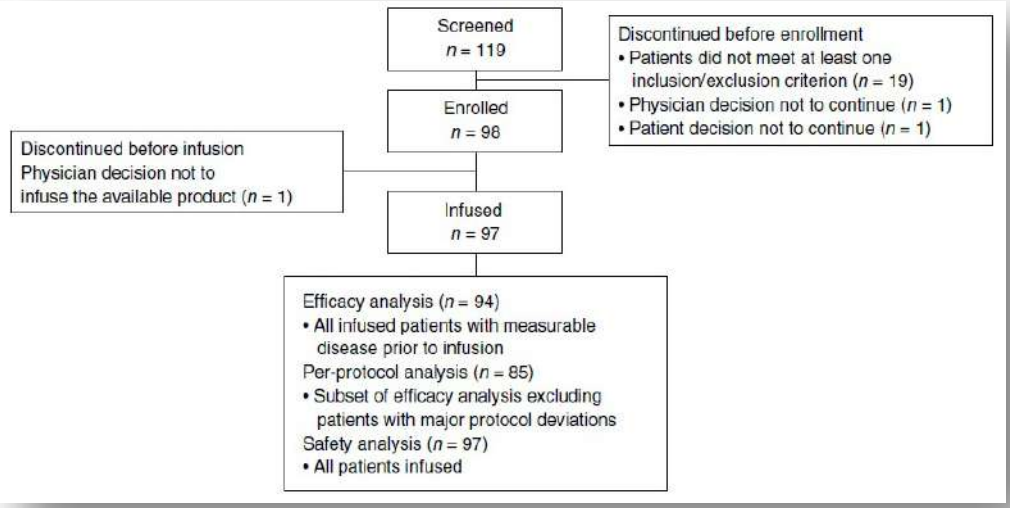
Check for updates

Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial

Nathan Hale Fowler[1,2], Michael Dickinson[3], Martin Dreyling[4], Joaquin Martinez-Lopez[5], Arne Kolstad[6], Jason Butler[7], Monalisa Ghosh[8], Leslie Popplewell[9], Julio C. Chavez[10], Emmanuel Bachy[11], Koji Kato[12], Hideo Harigae[13], Marie José Kersten[14], Charalambos Andreadis[15], Peter A. Riedell[16], P. Joy Ho[17], José Antonio Pérez-Simón[18], Andy I. Chen[19], Loretta J. Nastoupil[1], Bastian von Tresckow[20,21], Andrés José María Ferreri[22], Takanori Teshima[23], Piers E. M. Patten[24,25], Joseph P. McGuirk[26], Andreas L. Petzer[27], Fritz Offner[28], Andreas Viardot[29], Pier Luigi Zinzani[30,31], Ram Malladi[32], Aiesha Zia[33], Rakesh Awasthi[34], Aisha Masood[35], Oezlem Anak[33], Stephen J. Schuster[36,38] and Catherine Thieblemont[37,38]

≥18 yo; FL (grade 1, 2 or 3A)
(1) refractory to or early relapse ≥2 systemic therapy (anti-CD20 & alkylating agent);
(2) relapsed during/within 6 mo anti-CD20 maintenance (≥2 systemic lines)
(3) relapsed after autologous HSCT.



Median no. of previous therapies (range) 4 (2–13)
POD24: 61 (63%)

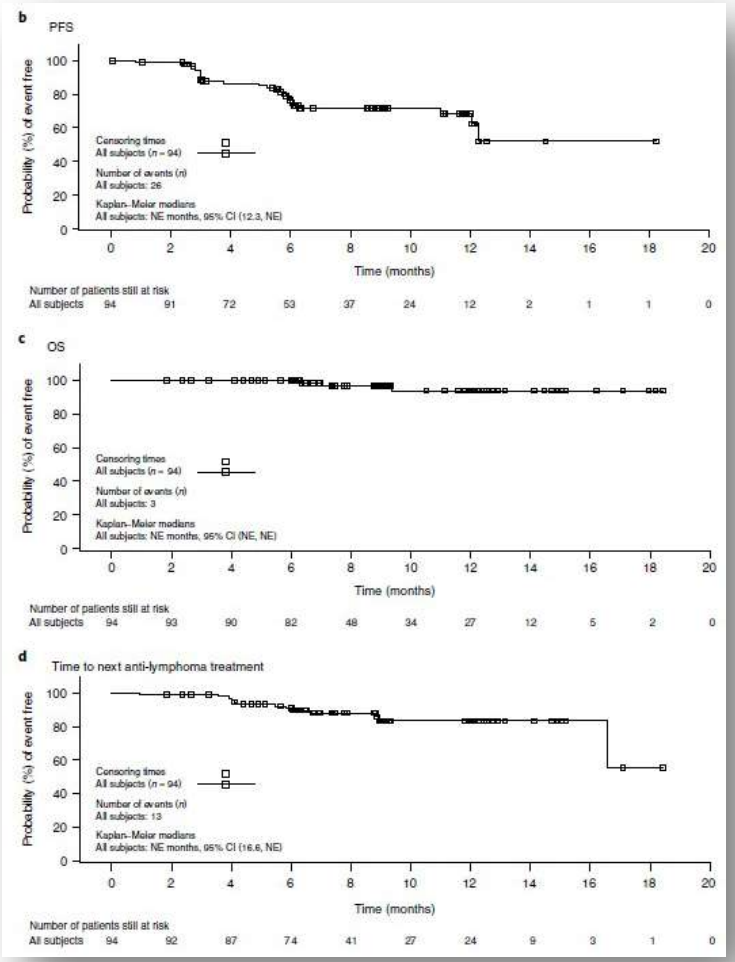
ELARA Trial

Parameter	Per-protocol set, $n=85$		EAS, $n=94$	
	Local assessment	IRC assessment	Local assessment	IRC assessment
Best overall response, *n* (%)				
CR	64 (75.3); 95% CI, 64.7–84.0	62 (72.9); 95% CI, 62.2–82.0	68 (72.3); 95% CI, 62.2–81.1	65 (69.1); 95% CI, 58.5–78.3
PR	14 (16.5)	12 (14.1)	17 (18.1)	16 (17.0)
SD	2 (2.4)	3 (3.5)	3 (3.2)	3 (3.2)
PD	5 (5.9)	8 (9.4)	6 (6.4)	9 (9.6)
UNK				1 (1.1)
Overall response rate (CR + PR), *n* (%)	78 (91.8); 95% CI, 83.8–96.6	74 (87.1); 95% CI, 78.0–93.4	85 (90.4); 95% CI, 82.6–95.5	81 (86.2); 95% CI, 77.5–92.4

G≥3 CRS: 0%

G≥3 Neurotox: 0%

TRM: 0%



Take Home Messages

- Passive and active immunotherapies play a central role in the treatment of lymphomas
- The best candidates and therapeutic sequences will be investigated
- Will it be more effective than chemotherapy as upfront treatment?
- Effective combinations with or without chemotherapy will be developed
- The very very very hard scenario of comparative trials
- Several experimental alternatives (allo-CART, bispecific IgM, anti-CD47, CIK cells)
- Dynamic acknowledge process