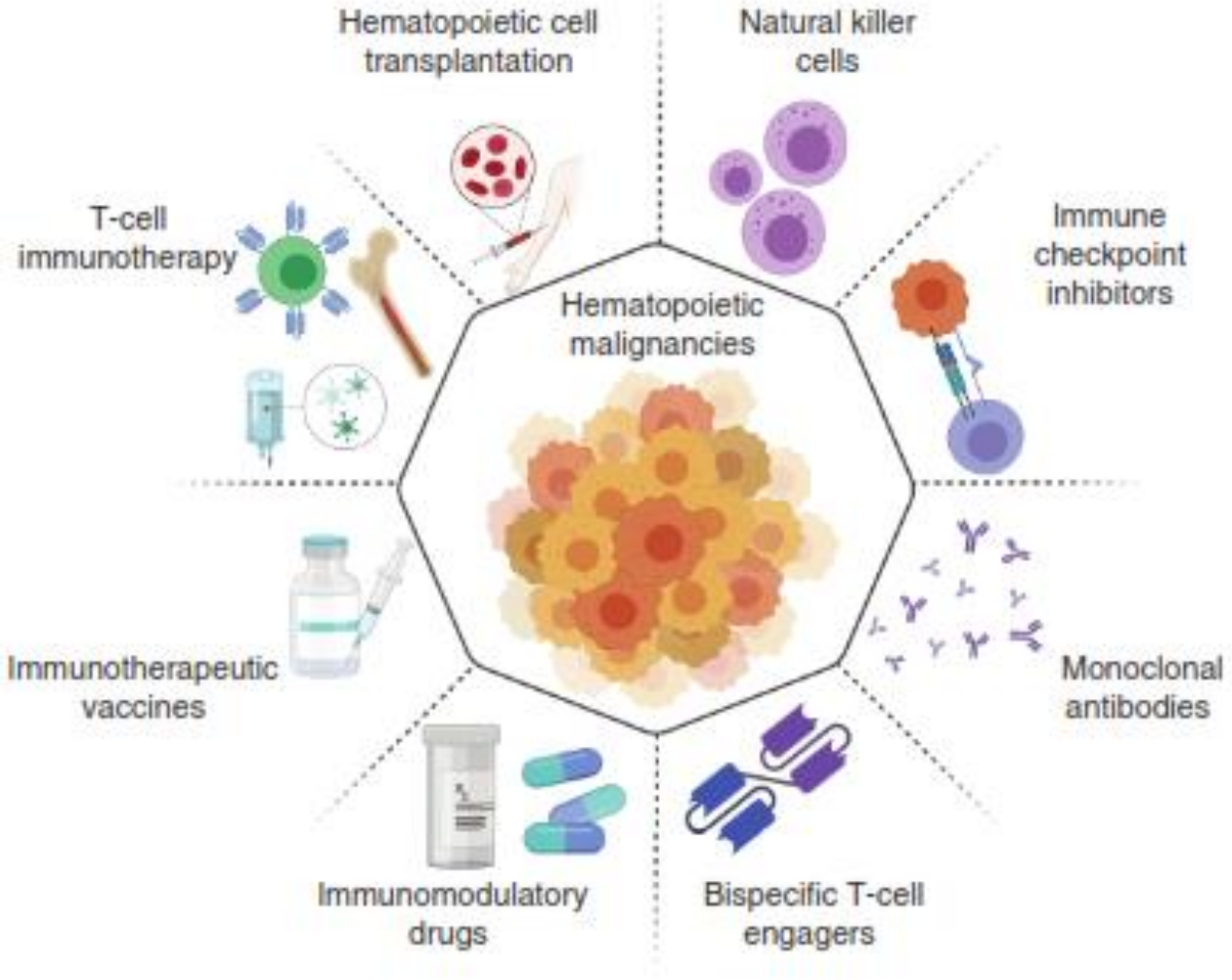
Bone marrow malignancies - immunotherapy

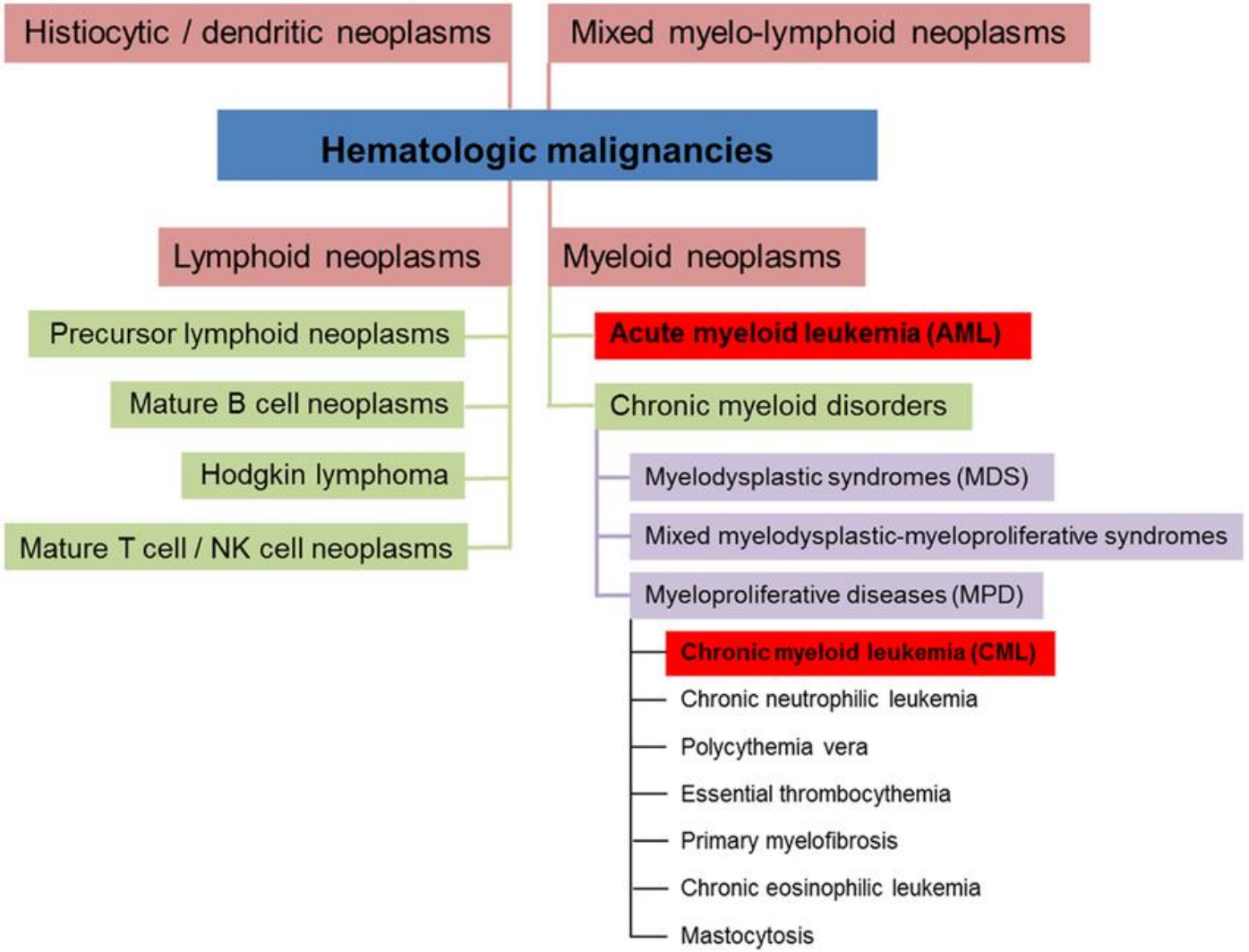
Χαράλαμπος Ποντίκογλου

Ιατρική Σχολή Πανεπιστημίου Κρήτης

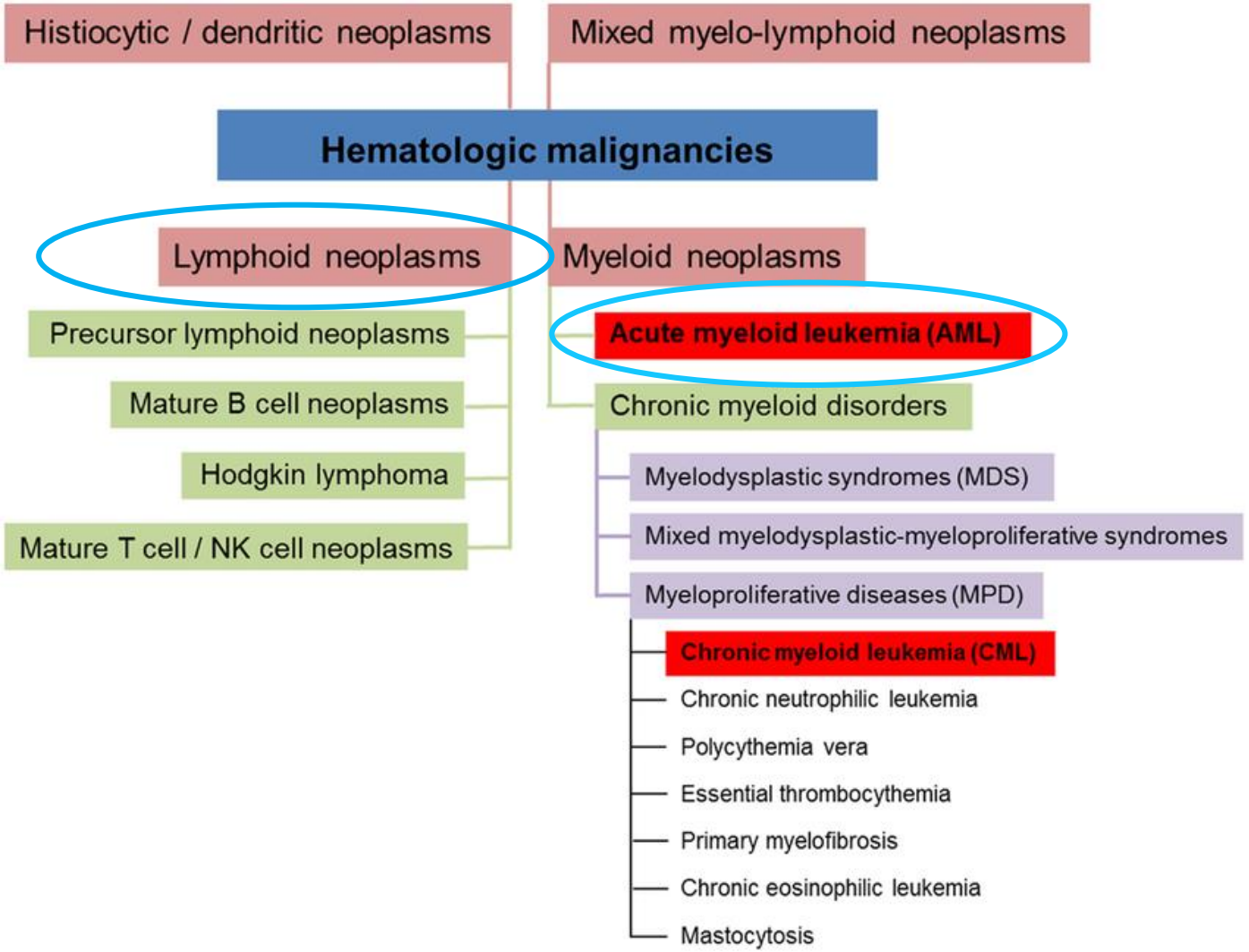
Immunotherapy in hematological malignancies



Hematologic Malignancies



Hematologic Malignancies



Hodgkin's Lymphoma (HL)

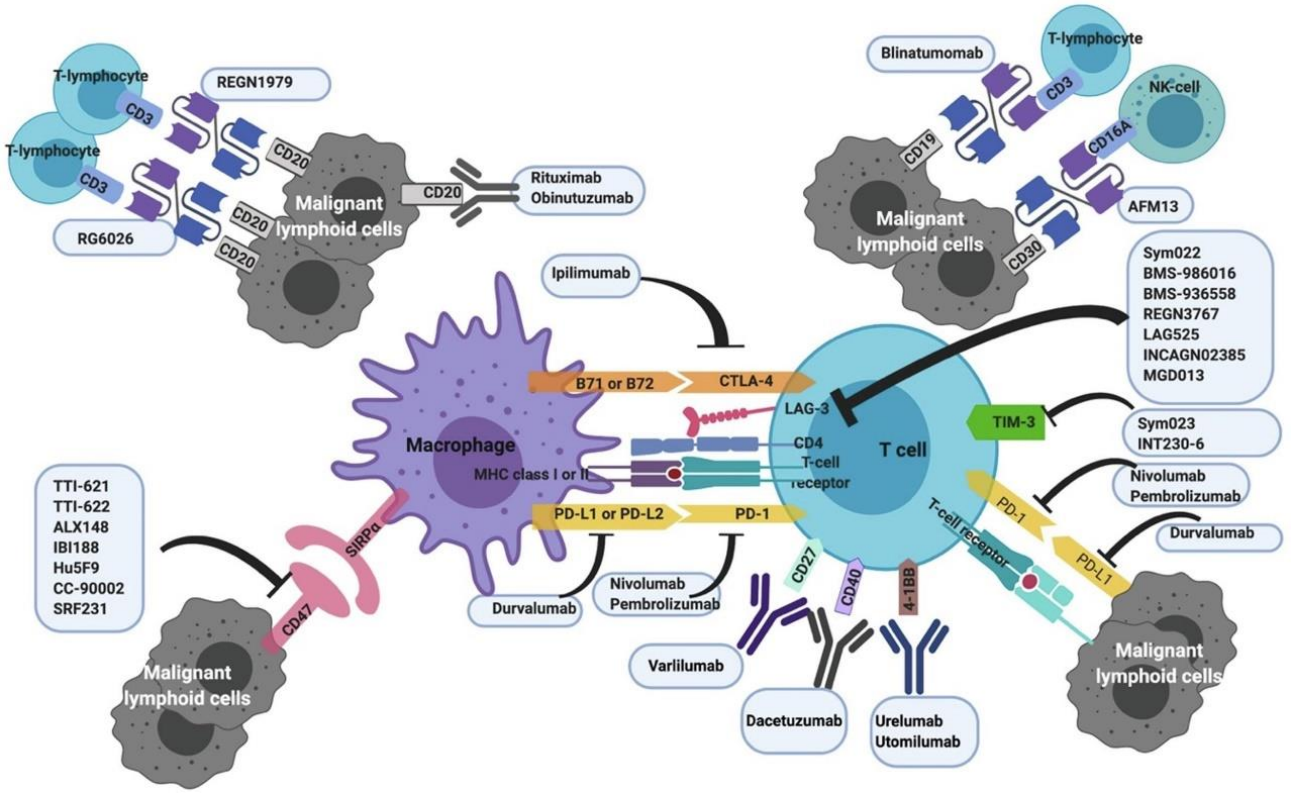
- Hodgkin lymphoma (HL) accounts for about 10% of lymphoma patients
- It has a bimodal distribution where most of the affected patients are between ages 20 to 40 years, and there is another peak from age 55 years and older. It affects males more than females
- Although classical Hodgkin lymphoma (cHL) is usually curable, 20–30% of the patients experience treatment failure and most of them are typically treated with salvage chemotherapy and autologous stem cell transplantation (autoSCT).
- However, 45–55% of that subset further relapse or progress despite intensive treatment.
- At the advanced stage of the disease course, recently developed immunotherapeutic approaches have provided very promising results with prolonged remissions or disease stabilization in many patients.

Non Hodgkin's λεμφώματα

- Ευρύ φάσμα νοσολογικών οντοτήτων
- Προέρχονται από Β, Τ ή ΝΚ λεμφοκύτταρα
- Νοσήματα καθ΄υπεροχήν της μέσης και προχωρημένης ηλικίας
- Συνήθης εμφάνιση: επιπολής ψηλαφητή λεμφαδενοπάθεια με ή χωρίς σπληνομεγαλία ή ηπατομεγαλία
- Συχνές αμιγώς εξωλεμφαδενικές εντοπίσεις με ανάλογη εικόνα
- Χαμηλής κακοήθειας λεμφώματα συνήθως ανίατα, αλλά με μακρά κλινική πορεία και επιβίωση
- Επιθετικά λεμφώματα: συνήθως με ταχεία εξέλιξη, αλλά ιάσιμα σε αναλογία 40-80% των ασθενών

Tumor- immune cell interactions in lymphomas

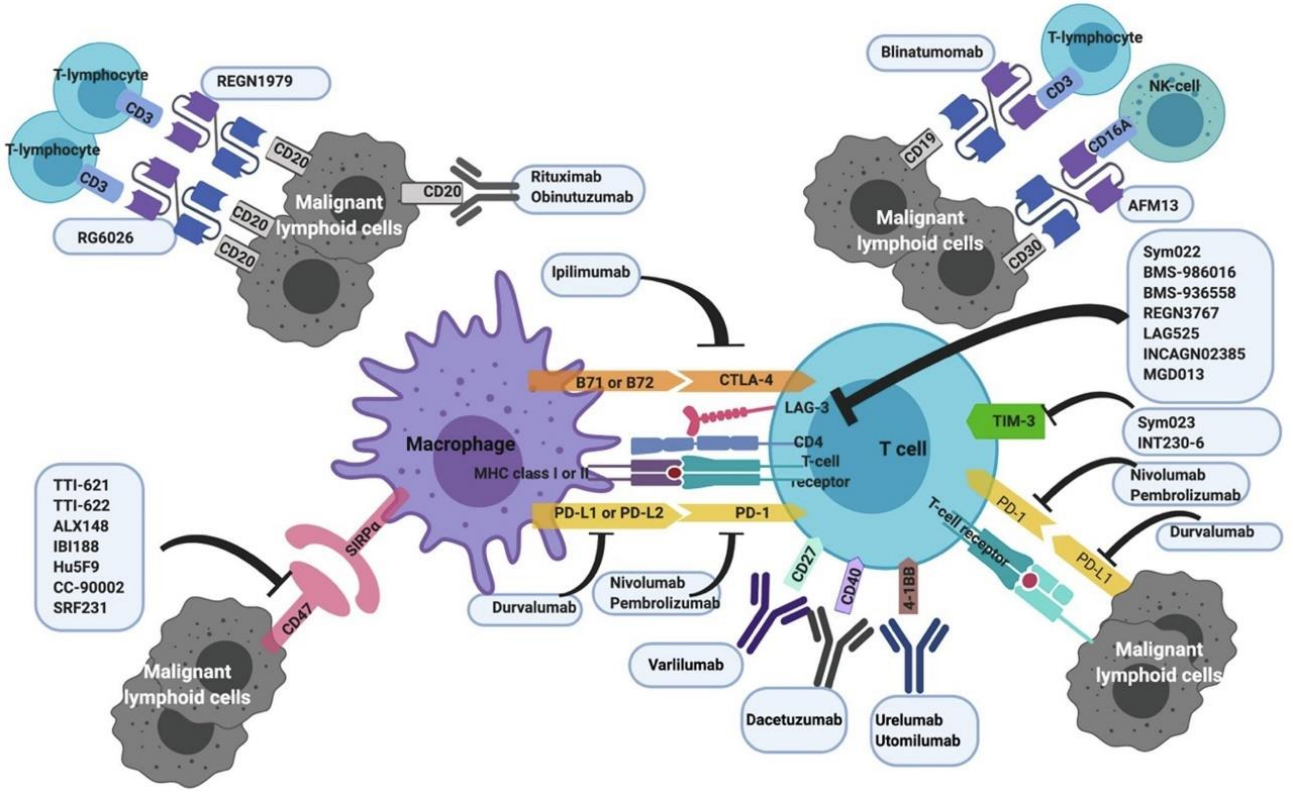
- Most tumor antigens are poorly immunogenic and commonly produce immunologic tolerance
- MHC class I and II expression ↓/- resulting in inadequate presentation of tumor antigens to immune cells
- Lymphocyte-activation gene 3 (LAG-3), compromises antigen presentation by binding to peptide-MHC class II with higher affinity than CD4 and suppressing the immune presentation
- Malignant cells express high levels of CD47 that sends a “don’t-eat-me” signal by interacting with signal regulatory protein alpha (SIRP) on monocytes, dendritic cells, and granulocytes, thereby inhibiting their function and enabling lymphoma cells to evade phagocytosis



Tun AM et al Cancer Treat Rev. 2020

Tumor- immune cell interactions in lymphomas

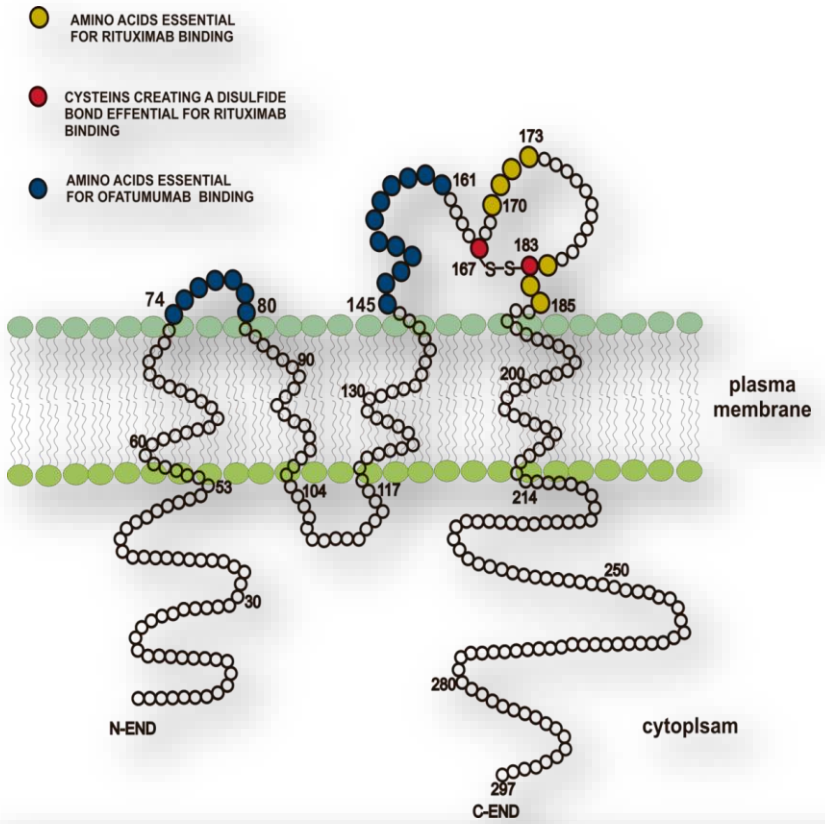
- Inadequate co-stimulatory signaling
- Inhibitory ligands are also commonly overexpressed in B-cell *ie* ↑ expression of programmed death-ligand 1 and 2 PD-L1 and PD-L2) , T- cell immunoglobulin and mucin domain 3 (TIM-3)
- ↑ signaling via cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- Upregulated Treg cell activity via
  - Myeloid derived suppressor cells
  - Malignant B cells and intertumoral T cells producing TGF-β
- Upregulated immunosuppressive factors ie IL-10

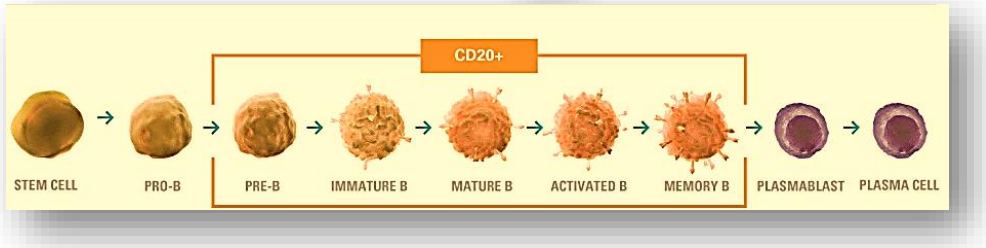


Tun AM et al Cancer Treat Rev. 2020

Characteristics of CD20

- 35 kDa integral membrane protein of the cell surface, spanning the plasma membrane 4 times
- Appears to play a role in Ca^{2+} transport
- Involved in B cell receptor activation and signaling
- Not shed from B cell surface
- Does not internalize after binding antibody

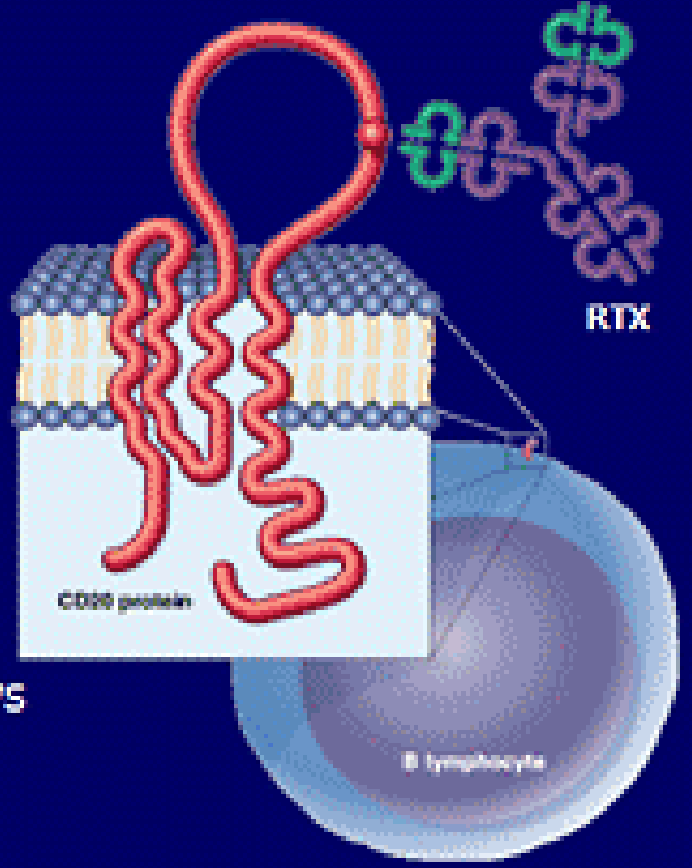




Casan JML et al. Hum Vaccin Immunother. 2018

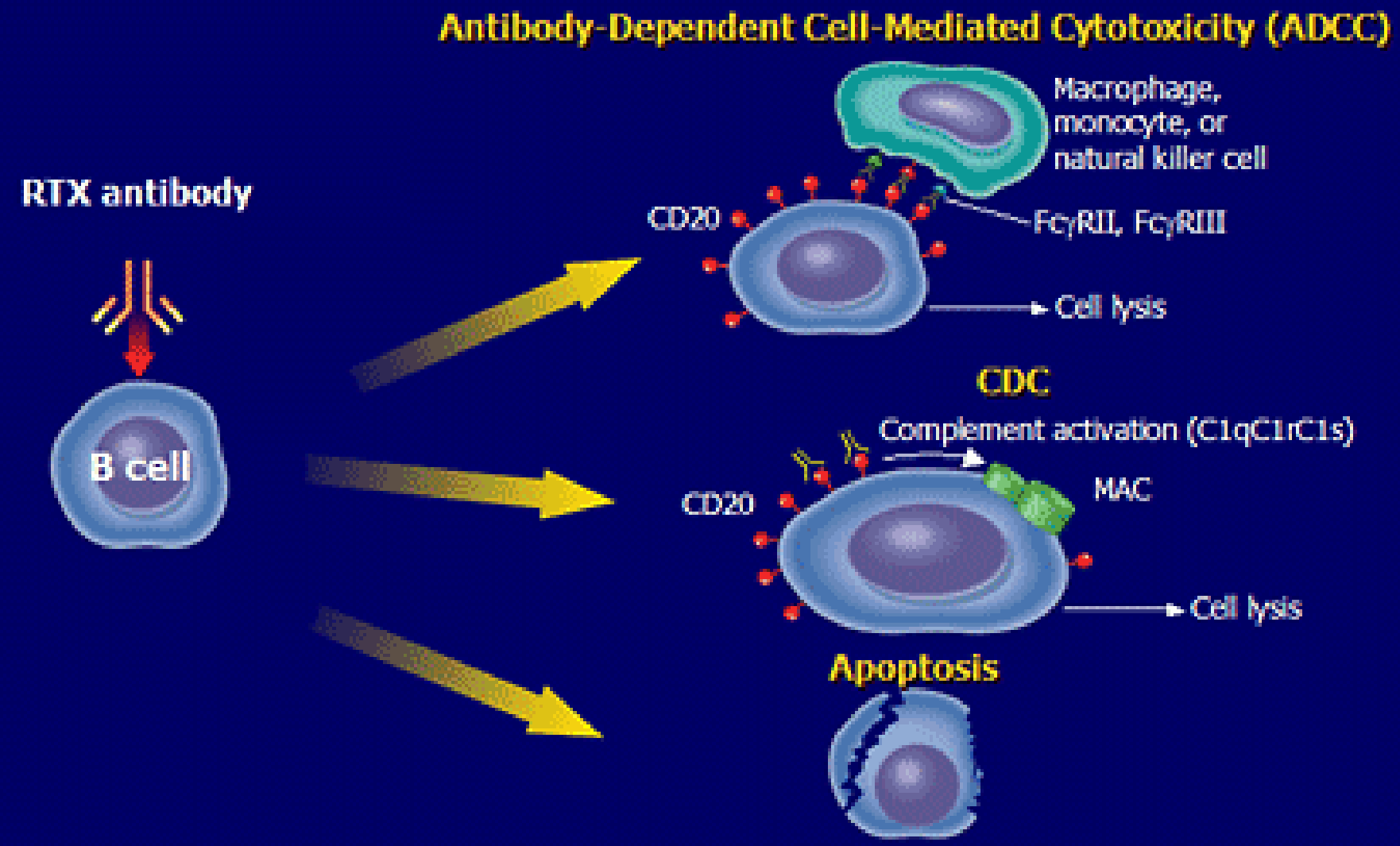
Rituximab Anti-CD20 Monoclonal Antibody

- Chimeric murine/human monoclonal antibody
  - Variable light and heavy chain regions from murine model
  - Human IgG1, kappa constant region
- Long serum half-life
  - RA (1000 mg)
    - After second infusion $t_{1/2}$ = 19–22 days



Berinstein NL et al. *Ann Oncol*. 1998;9:995-1001; Maloney DG et al. *J Clin Oncol*. 1997;15:3266-3274; Maloney DG et al. *Blood*. 1997;90:2188-2195; Davies B et al. European League Against Rheumatism (EULAR); June 9–12, 2004; Berlin, Germany.

Rituximab: Mechanism of Action



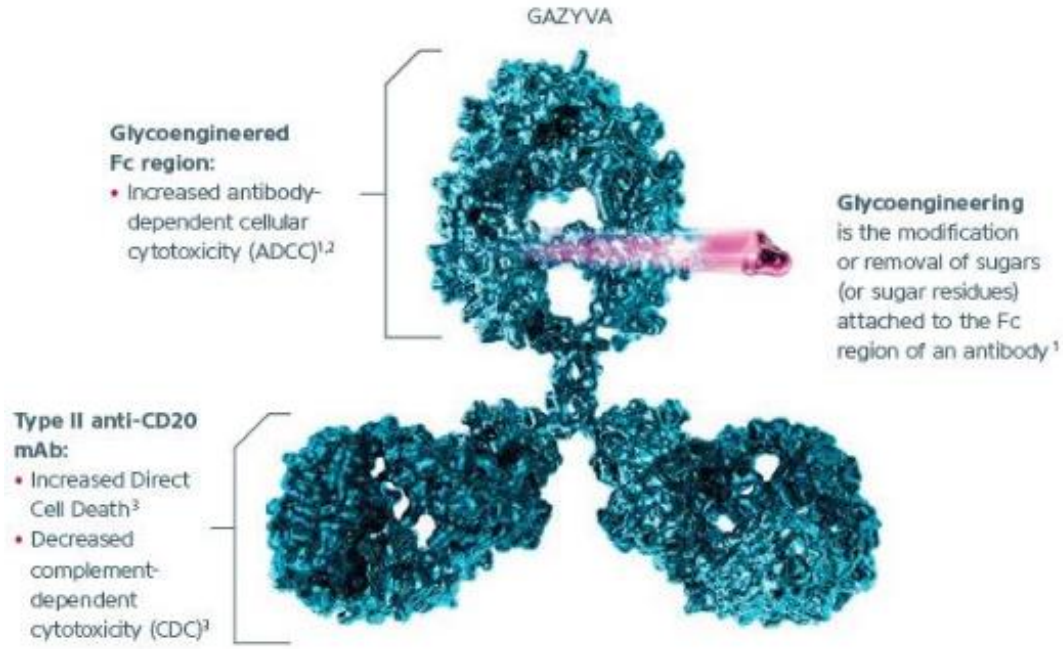
Anderson DR et al. *Biochem Soc Trans.* 1997;25:705-708; Golay J et al. *Blood.* 2000;95:3900-3908; Reff ME et al. *Blood.* 1994;83:435-445; Clynes RA et al. *Nat Med.* 2000;6:443-446; Shan D et al. *Cancer Immunol Immunother.* 2000;48:673-683; Silverman GJ et al. *Arthritis Rheum.* 2003;48:1484-1492.

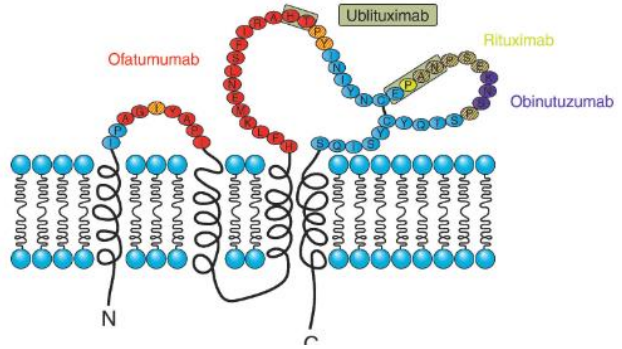
Rituximab: Therapeutic Indications

- Non-Hodgkin's lymphoma (NHL)
  - Rituximab is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.
  - Rituximab maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.
  - Rituximab monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.
  - Rituximab is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.
- Chronic lymphocytic leukaemia (CLL)
  - MabThera in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL.

Obinutuzumab

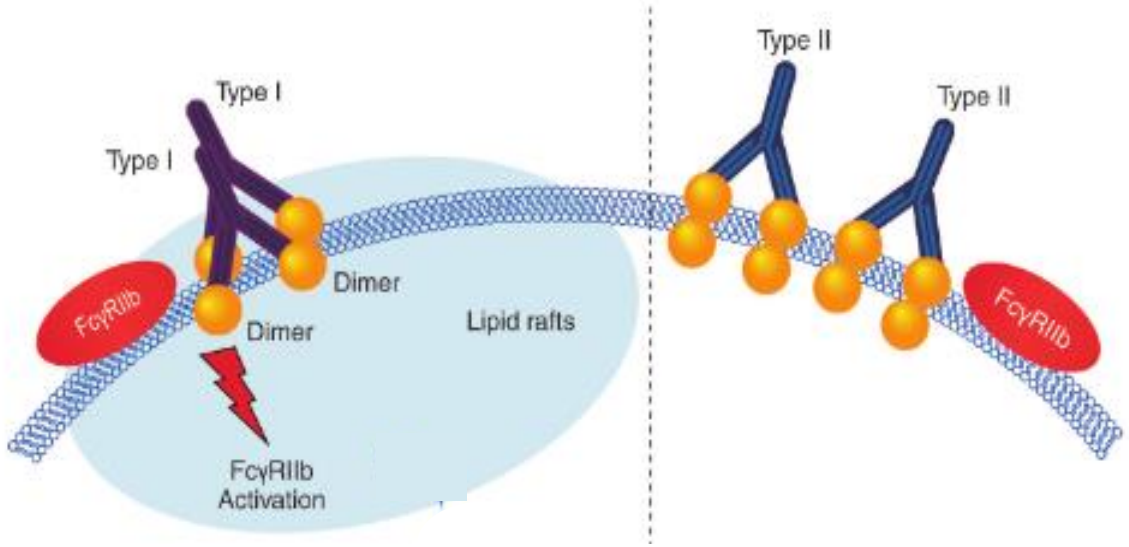
- Type II humanized anti-CD20 antibody with a glycoengineered Fc portion to enhance binding to the FcγRIII receptor on immune cells and a variable region that binds CD20





Casan JML et al. Hum Vaccin Immunother. 2018

Obinutuzumab



Antibody	Obinutuzumab	Rituximab
Trade name (EU)	Gazyvaro	MabThera
Manufacturer	Roche	Roche
Antibody type	II	I
IgG subclass	IgG1	IgG1
Structure	Humanized	Chimeric
Binding to CD20 epitope	Large loop	Large loop
Binding to lipid rafts	–	++
ADCC	++++	++
CDC	+	++
Direct cell death induction	++++	+

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; I Ig, immunoglobulin.

Casan JML et al. Hum Vaccin Immunother. 2018

Obinutuzumab: Therapeutic Indications

- In Europe, obinutuzumab is approved in combination with chlorambucil, venetoclax, or ibrutinib for previously untreated Chronic Lymphocytic Leukemia

- In combination with chemotherapy for previously untreated follicular lymphoma or with bendamustine in refractory Follicular Lymphoma

Casan JML et al. Hum Vaccin Immunother. 2018

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- However, 45–55% of that subset further relapse or progress despite intensive treatment.
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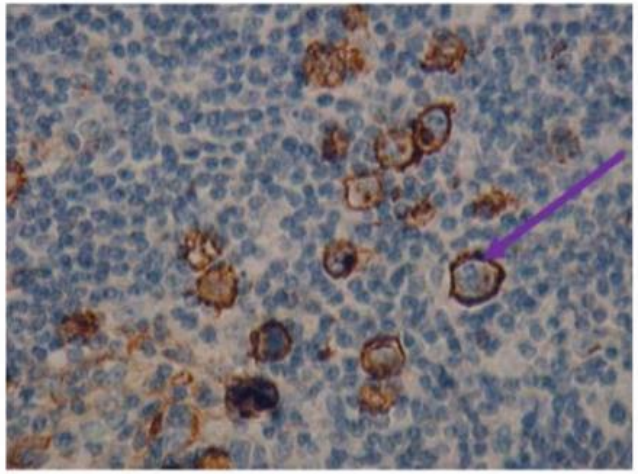
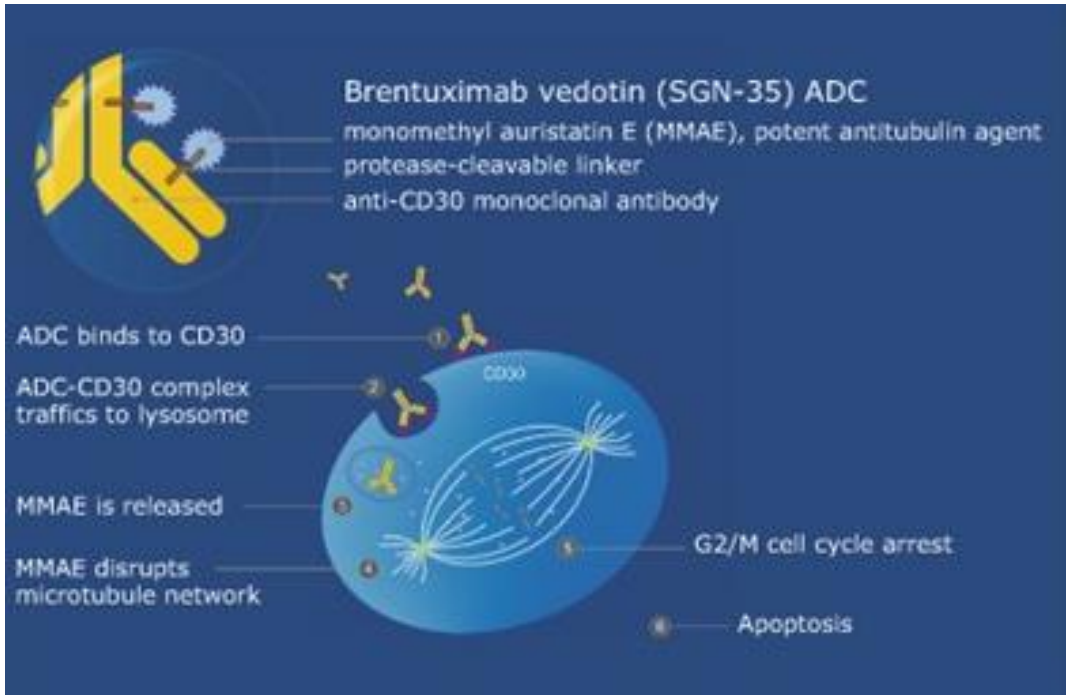
Hodgkin's Lymphoma: CD30 targeted therapy

- CD30 is a member of the TNF receptor superfamily
- It is highly expressed on HRS cells
- In healthy individuals, its expression is restricted to a small fraction of activated B-, T-lymphocytes, and eosinophils.



Hodgkin Reed-Sternberg (HRS) cell



Wang, Y. et al *J Hematol Oncol*, 2018

Brentuximab Vedotin

- EMA approved in classical HL:
  - Patients who failed ASCT or were not eligible for ASCT and who failed ≥ 2 regimens
  - Consolidation for patients with high risk of relapse/progression after ASCT
  - Patients with previously untreated stage III/IV disease in combination with chemotherapy (AVD)

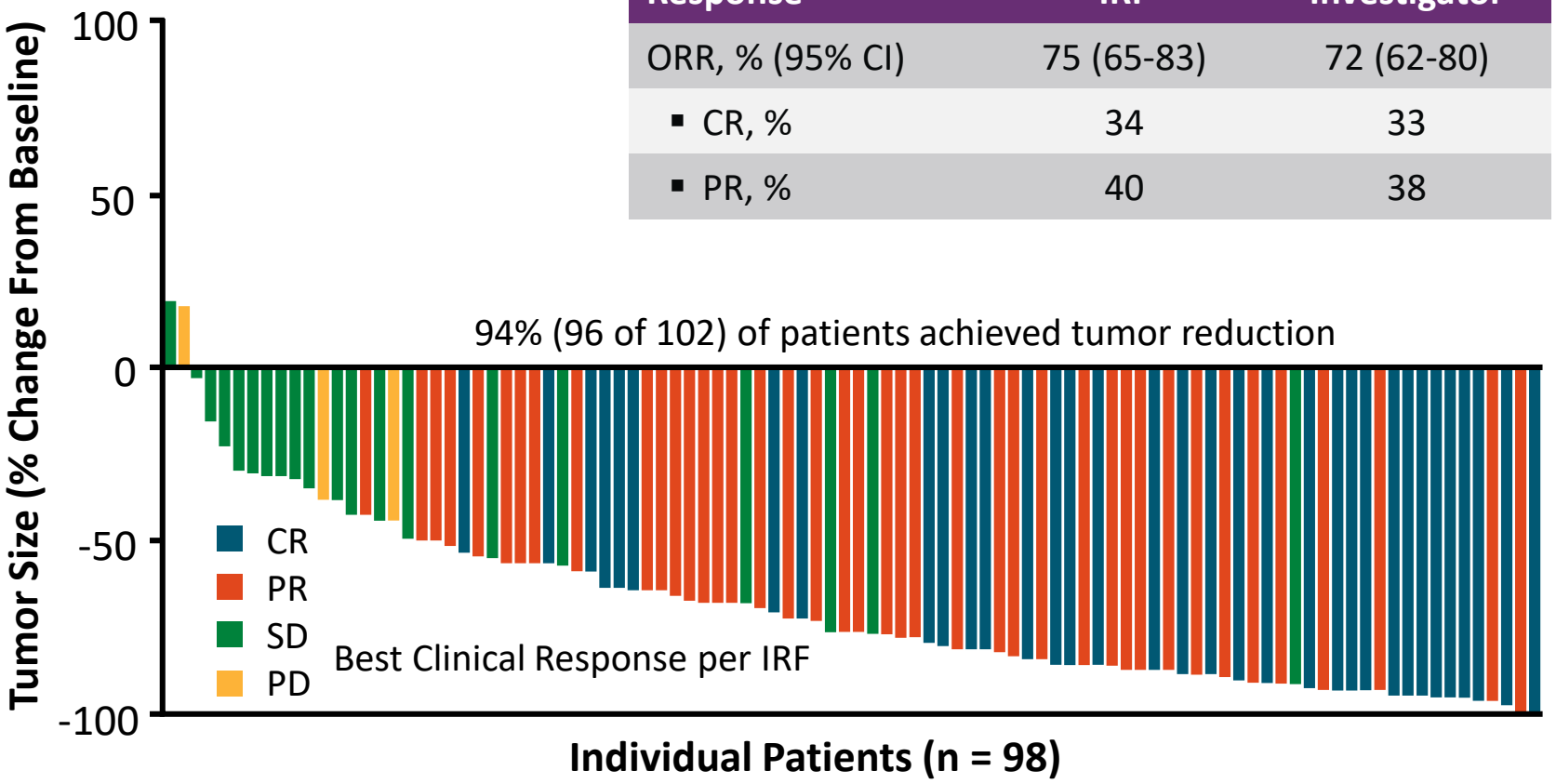
Brentuximab vedotin PI. 2018. Younes. NEJM. 2010;363:1812.

Slide credit: clinicaloptions.com

Brentuximab Vedotin Pivotal Trial in Relapsed/ Refractory HL After ASCT

- Pivotal phase II study of brentuximab vedotin for patients with relapsed/refractory HL after ASCT (N = 102)

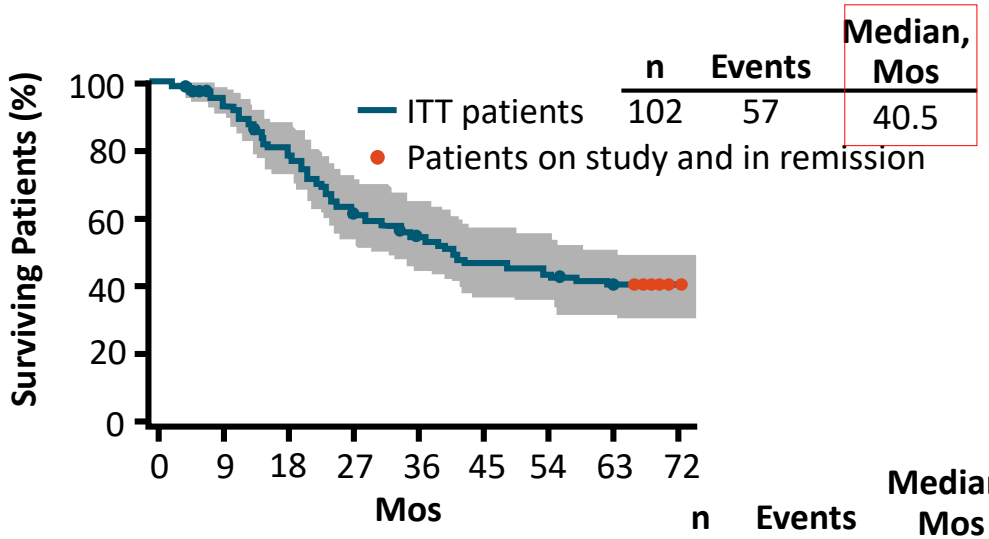
Response	IRF	Investigator
ORR, % (95% CI)	75 (65-83)	72 (62-80)
▪ CR, %	34	33
▪ PR, %	40	38

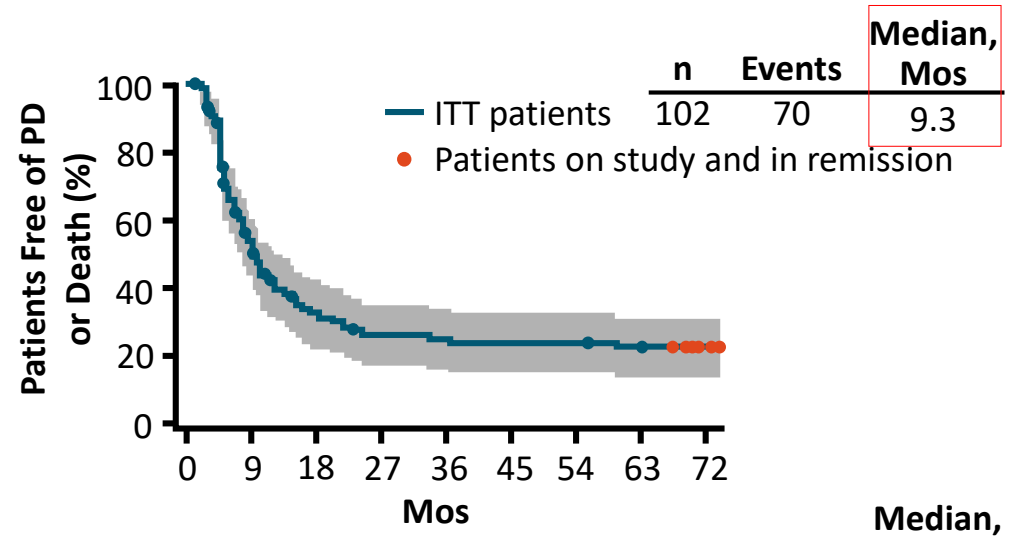


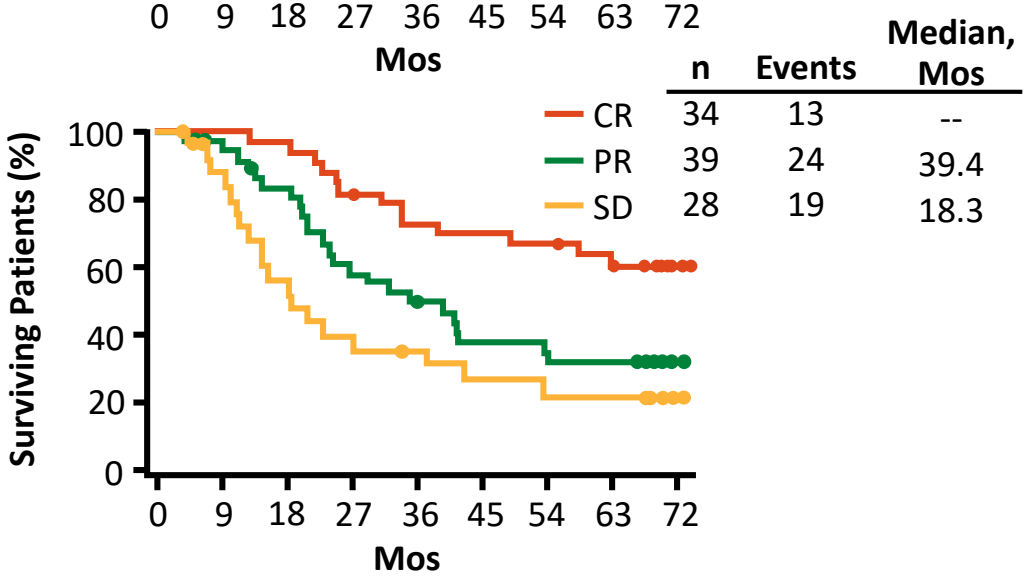
Younes A, et al. J Clin Oncol. 2012;30:2183-2189.

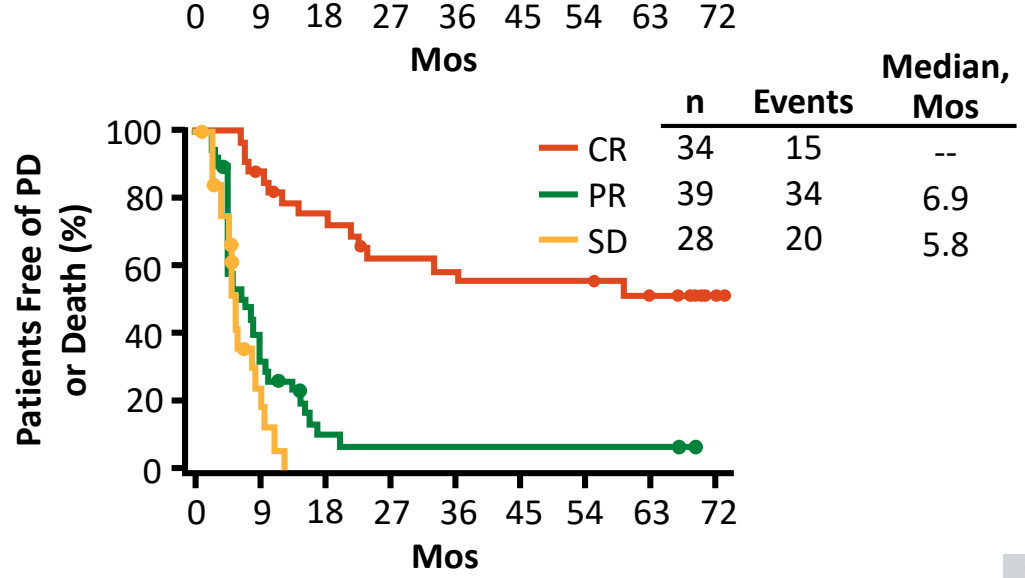
Slide credit: clinicaloptions.com

Brentuximab Vedotin in Relapsed/Refractory cHL After ASCT: 5-Yr Survival Outcomes









Chen. Blood. 2016;128:1562.

Slide credit: clinicaloptions.com

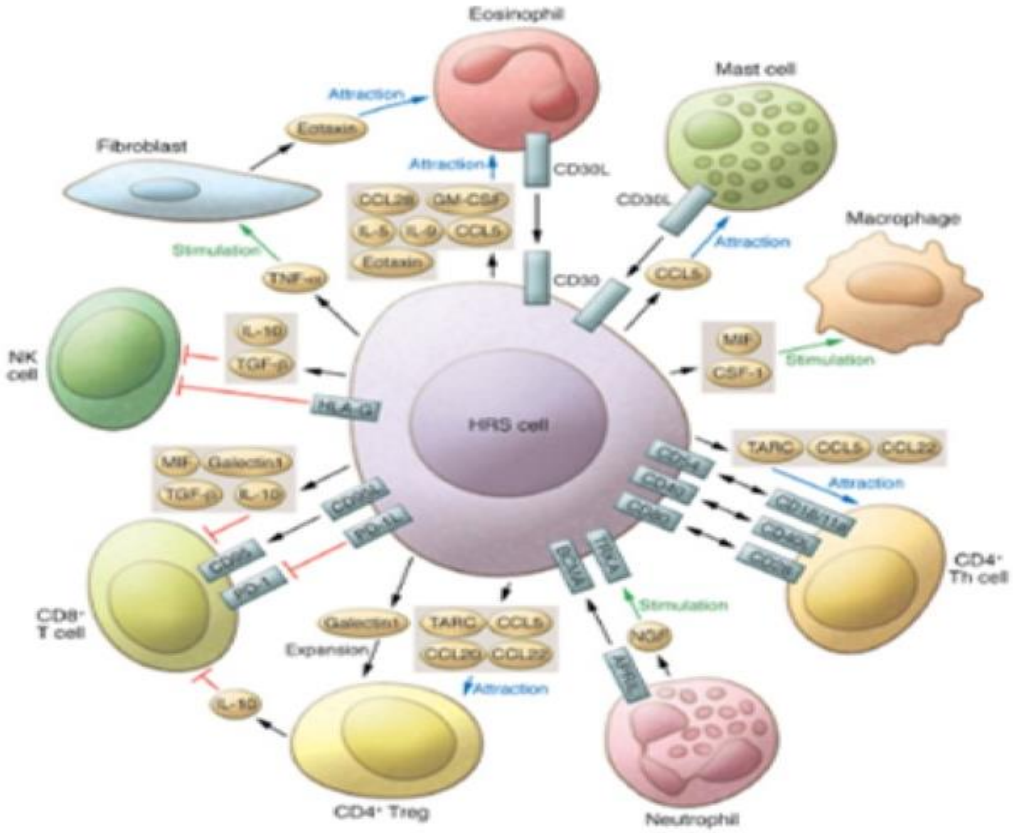
Targeting Immune Checkpoint Pathway in HL

- The outcome of patients who fail both autoSCT and BV is extremely poor.
- Conventional chemotherapy or experimental approaches based on small molecules provide disappointing PFS rates of only 3.5 months median duration and a median OS of ~2 years.
- AlloSCT can be curative in this setting, but several limitations make it applicable only in a minority of patients. Thus, novel approaches are urgently required.
- Restoring the immune response against the HRS cells rather than targeting them with cytotoxic agents appears to be the way to go.

Vassilakopoulos TP et al., Cells 2019

Pathophysiology of HL

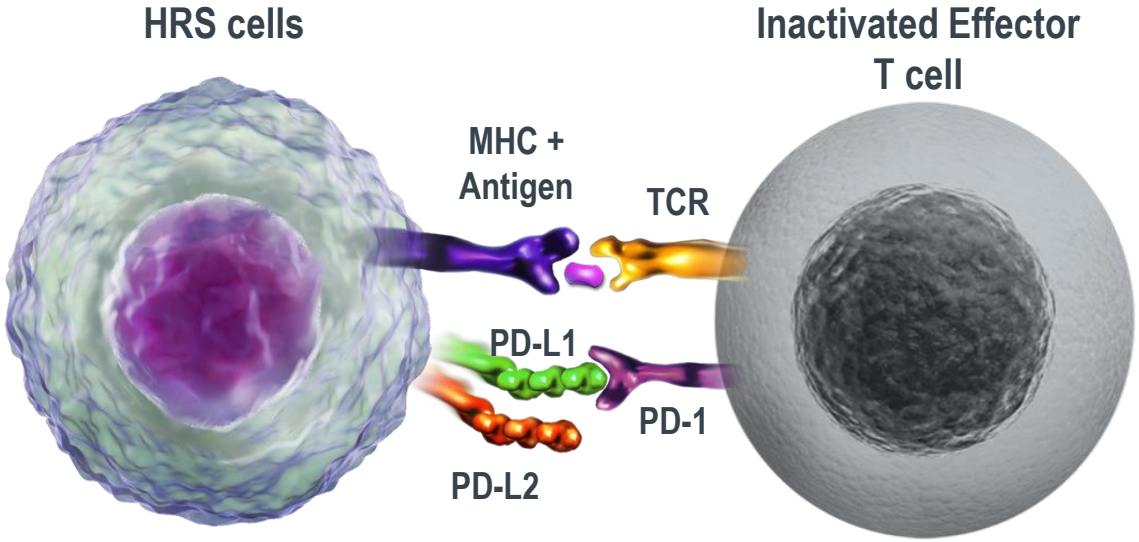
- The malignant lymphocyte in HL is called Reed-Sternberg (HRS) cell
- HRS ells comprise 0.1%-2% of total tumor bulk
- The remainder are cells of the patients' immune system that facilitate the HRS cells in evading immune detection:
  - Immunosuppressive T cells and TH2 cells are abundant within HL tumors and provide a hypo-proliferative tumor microenvironment (TME)
  - HPS cells lack proper antigen presentation via MHC class I and II molecules on their surface



Pezeshki PS et al Expert Rev Anticancer Ther 2021

Pathophysiology of HL

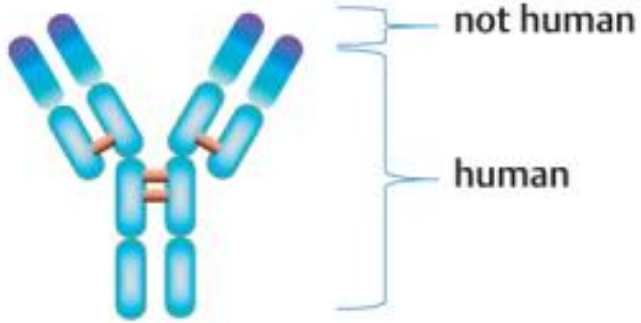
- Immune evasion may also result from:
  - Tumor infiltrating lymphocytes upregulating PD-1 expression
  - HRS cells up-regulating PD-L1 because of:
    - EBV infection
    - amplification of chromosome 9p24.1



Pezeshki PS et al Expert Rev Anticancer Ther 2021

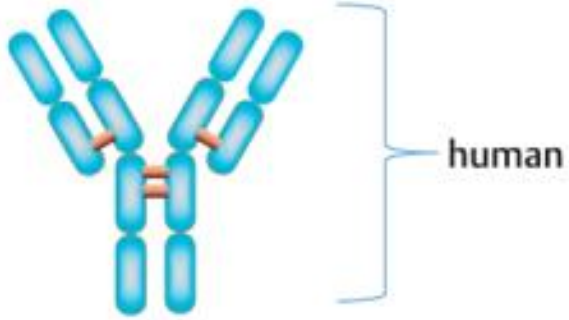
PD-1–blocking Monoclonal Antibodies

Humanized (-zumab)

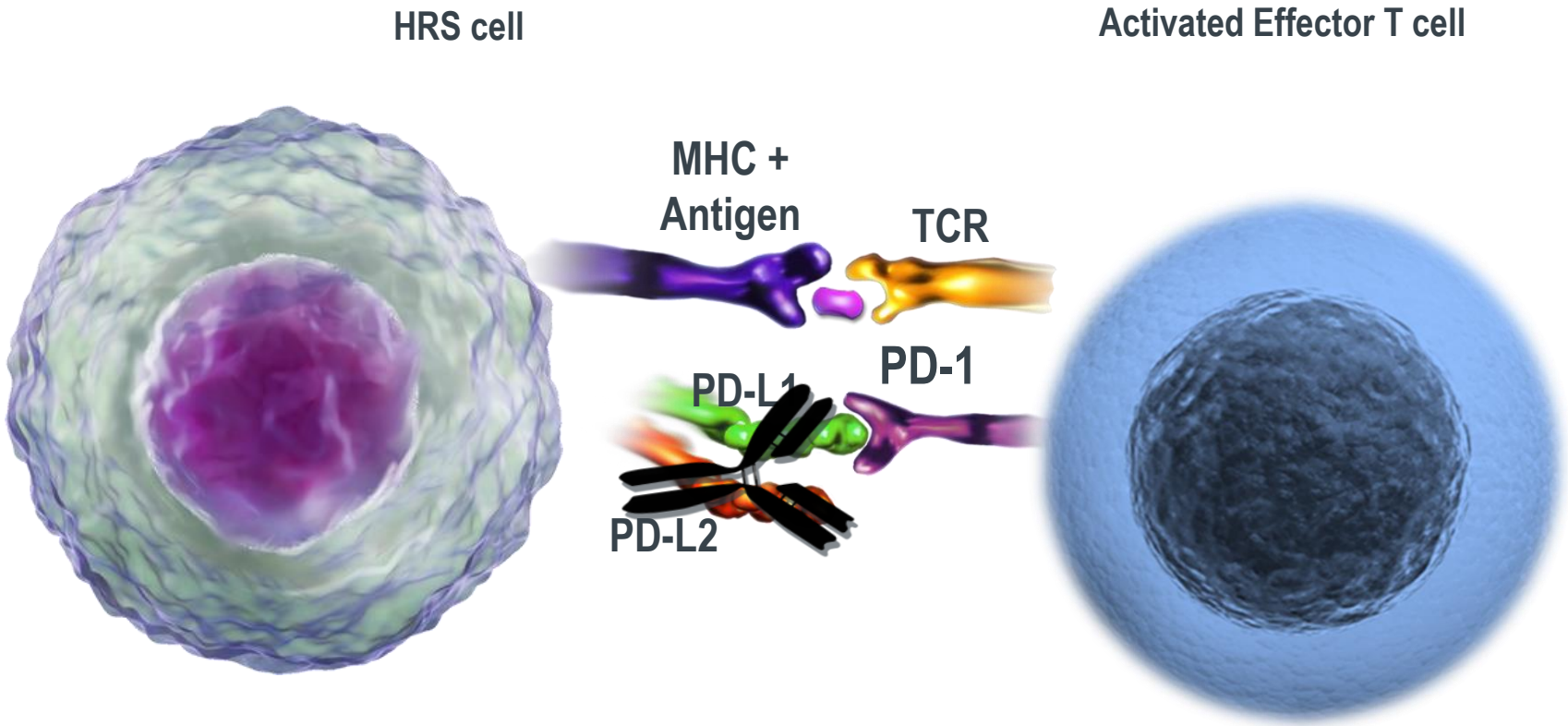


e.g. Pembrolizumab, Trastuzumab

Human (-umab)



e.g. Nivolumab, Ipilimumab



Du Rusquec P, et al. *Cancer Manag Res*. 2019;11:4297–4312.

Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial

- Phase II clinical trial investigated the efficacy of nivolumab monotherapy (3 mg/kg, q2wk) on patients with relapse after ASCT following the failure of BV therapy
- More than 70% of patients that did not respond to their latest round of BV therapy showed at least a partial response to nivolumab
- This trial showed an ORR of 66.3% and a CRR of 8.8%
- Grade 3 or 4 AEs were observed in 40% of the patients

Younes A et al Lancet Oncol 2016

KEYNOTE-087: Pembrolizumab in Patients With Relapsed/Refractory Classical Hodgkin Lymphoma

Study Design

Key Eligibility Criteria

Participants (N=210)

- RRcHL
- Measurable disease
- Provide evaluable core or excisional lymph node biopsy for biomarker analysis
- ECOG PS 0 or 1

Cohort 1 (n=69):

- Progressed after auto-SCT and subsequent BV therapy

Cohort 2 (n=81):

- Failed salvage chemotherapy and BV therapy and were ineligible for auto-SCT

Cohort 3 (n=60):

- Progressed after auto-SCT but not treated with BV post-transplantation

Pembrolizumab
200 mg Q3W

Survival Follow-up

- CT scan repeated Q12W
- PET scan repeated at weeks 12 and 24 to confirm CR or PD and as clinically indicated

Additional Criteria

- Initial data cutoff: September 25, 2016
- 2-year Follow-up data cutoff: March 21, 2018
- 3-year Follow-up data cutoff: March 21, 2019
- Median (range) follow-up: 39.5 (1.0–44.8) months

Primary Outcome Measures

- ORR by BICR according to RRC
- Safety

Secondary Outcome Measures

- ORR by investigator review according to RRC
- CRR by BICR and investigator assessment according to RRC
- PFS and DOR by BICR and investigator assessment according to RRC
- OS

Chen R, et al. *J Clin Oncol*. 2017;35:2125-2132

KEYNOTE-087: Overall Response Rate

Response, n (%)	Cohort 1 Assessed by BICR (n = 69)	Cohort 2 Assessed by BICR (n = 81)	Cohort 3 Assessed by BICR (n = 60)	All Pts Assessed by BICR (N = 210)	All Pts Assessed by Investigators (N = 210)
ORR	51 (73.9)	52 (64.2)	42 (70.0)	145 (69.0)	143 (68.1)
▪ CR*	15 (21.7)	20 (24.7)	12 (20.0)	47 (22.4)	63 (30.0)
▪ PR	36 (52.2)	32 (39.5)	30 (50.0)	98 (46.7)	80 (38.1)
SD	11 (15.9)	10 (12.3)	10 (16.7)	31 (14.8)	40 (19.0)
PD	5 (7.2)	17 (21.0)	8 (13.3)	30 (14.3)	23 (11.0)
Undetermined	2 (2.9)	2 (2.5)	0	4 (1.9)	4 (1.9)

*In pts negative on PET, residual mass was permitted.

At 2 –year follow up the ORR was 73% and the CRR was 27.6%

Moskowitz CH, et al. ASH 2016. Abstract 1107.

KEYNOTE-087: Treatment-Related AEs

Any-Grade AEs in ≥ 5% of Pts, n (%)	All Pts (N = 210)
Hypothyroidism	26 (12.4)
Pyrexia	22 (10.5)
Fatigue	19 (9.0)
Rash	16 (7.6)
Diarrhea	15 (7.1)
Headache	13 (6.2)
Nausea	12 (5.7)
Cough	12 (5.7)
Neutropenia	11 (5.2)

AEs, n (%)	All Pts (N = 210)
Any-grade grade 3/4 AE	23 (11)
Grade 3 AEs in ≥ 2 pts	
▪ Neutropenia	5 (2.4)
▪ Diarrhea	2 (1.0)
▪ Dyspnea	2 (1.0)
AEs of interest in ≥ 2 pts	
▪ Grade 1/2 infusion-related reactions	10 (4.8)
▪ Grade 2 pneumonitis	6 (2.9)
▪ Grade 1/2 hyperthyroidism	6 (2.9)
▪ Grade 2/3 colitis	2 (1.0)
▪ Grade 2/3 myositis	2 (1.0)

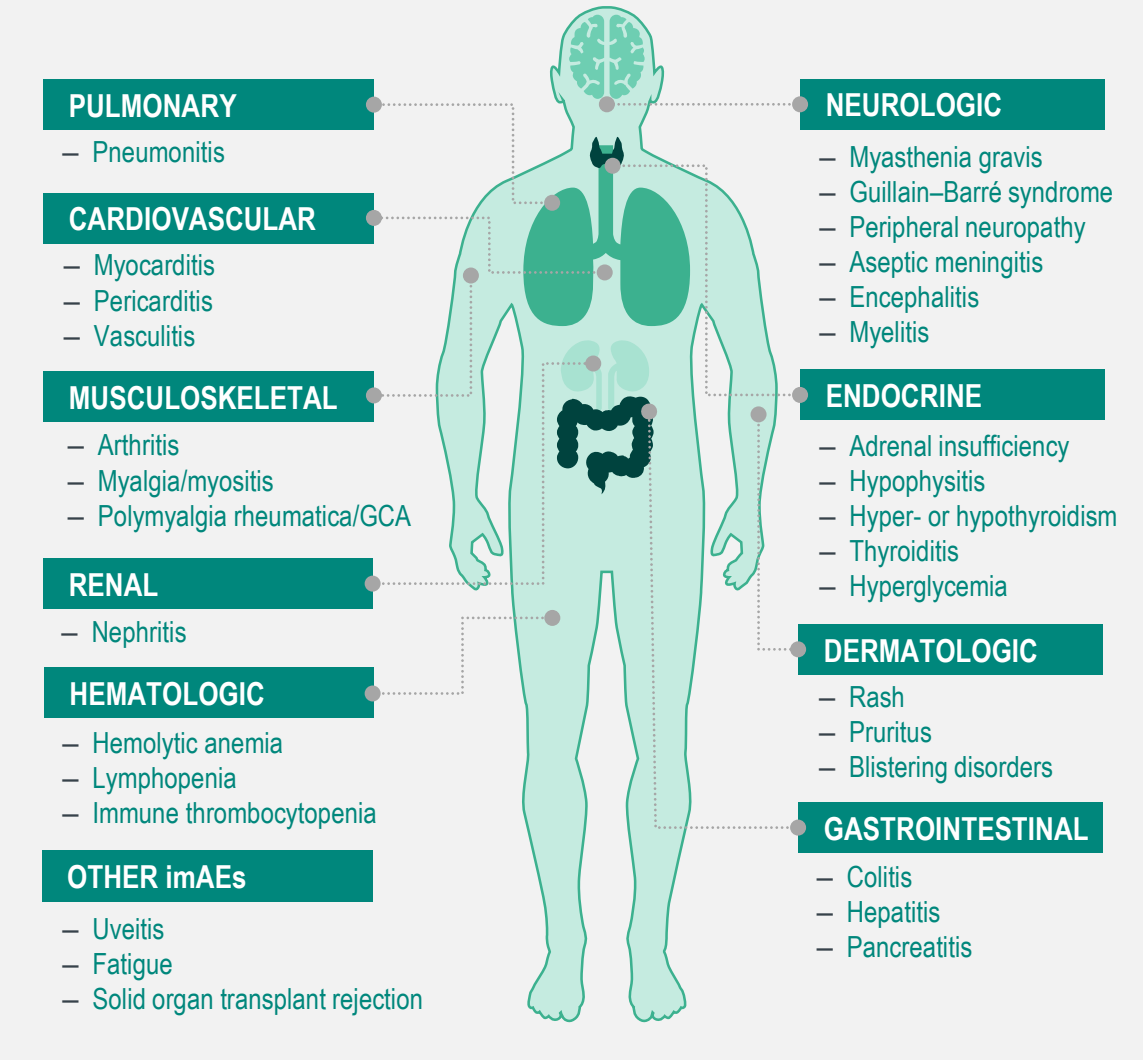
- 9 pts discontinued because of treatment-related AEs
- No treatment-related deaths (2 deaths on study)

Moskowitz CH, et al. ASH 2016. Abstract 1107.

Slide credit: clinicaloptions.com

imAEs Are a Unique Spectrum of Adverse Effects Associated With Immune Checkpoint Blockade

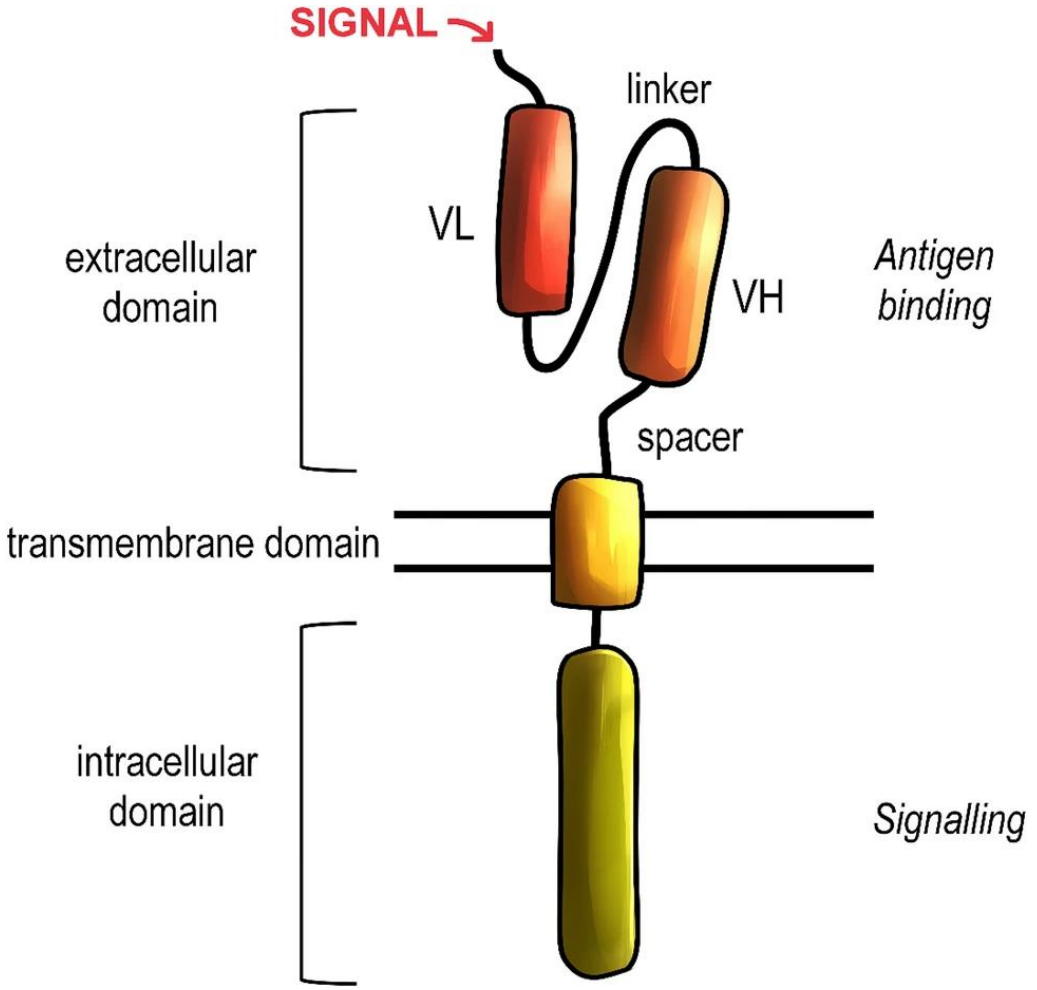
- imAEs may result when the immune system is activated, leading to an excess immune response to normal organs and tissues.[1,2]
- imAEs can affect virtually any organ system.[3,4]
  - imAEs are mechanistically and clinically distinct from AEs associated with chemotherapy.[1,5]
  - Overall, imAEs affecting the skin, endocrine system, GI tract, and lungs are most commonly encountered.[6]
  - More rarely, neurologic, ocular, cardiovascular, hematologic, and renal imAEs can occur.[6]
- Clinical practice guidelines are available for the monitoring, diagnosis, and treatment of imAEs for appropriate patient management.[7–10]



1. Ramos-Casals M et al. *Nat Rev Dis Primers*. 2020;6(1):38. **2.** Martins F et al. *Nat Rev Clin Oncol*. 2019;16(9):563–580. **3.** Postow MA et al. *N Engl J Med*. 2018;378(2):158–168. **4.** Palmieri DJ, Carlino MS. *Curr Oncol Rep*. 2018;20(9):72. **5.** Nagai H, Muto M. *Int J Clin Oncol*. 2018;23(3):410–420. **6.** Daniels GA et al. *Emerg Med J*. 2019;36(6):369–377. **7.** Brahmer JR et al. *J Clin Oncol*. 2018;36(17):1714–1768. **8.** Haanen JBAG et al. *Ann Oncol*. 2017;28(suppl 4):iv119–iv142. **9.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Management of Immunotherapy-related Toxicities V3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed 25 May 2021. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the guideline, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data become available. **10.** Puzanov I et al. *J Immunother Cancer*. 2017;5(1):95.

Chimeric antigen receptor (CAR)-T cells

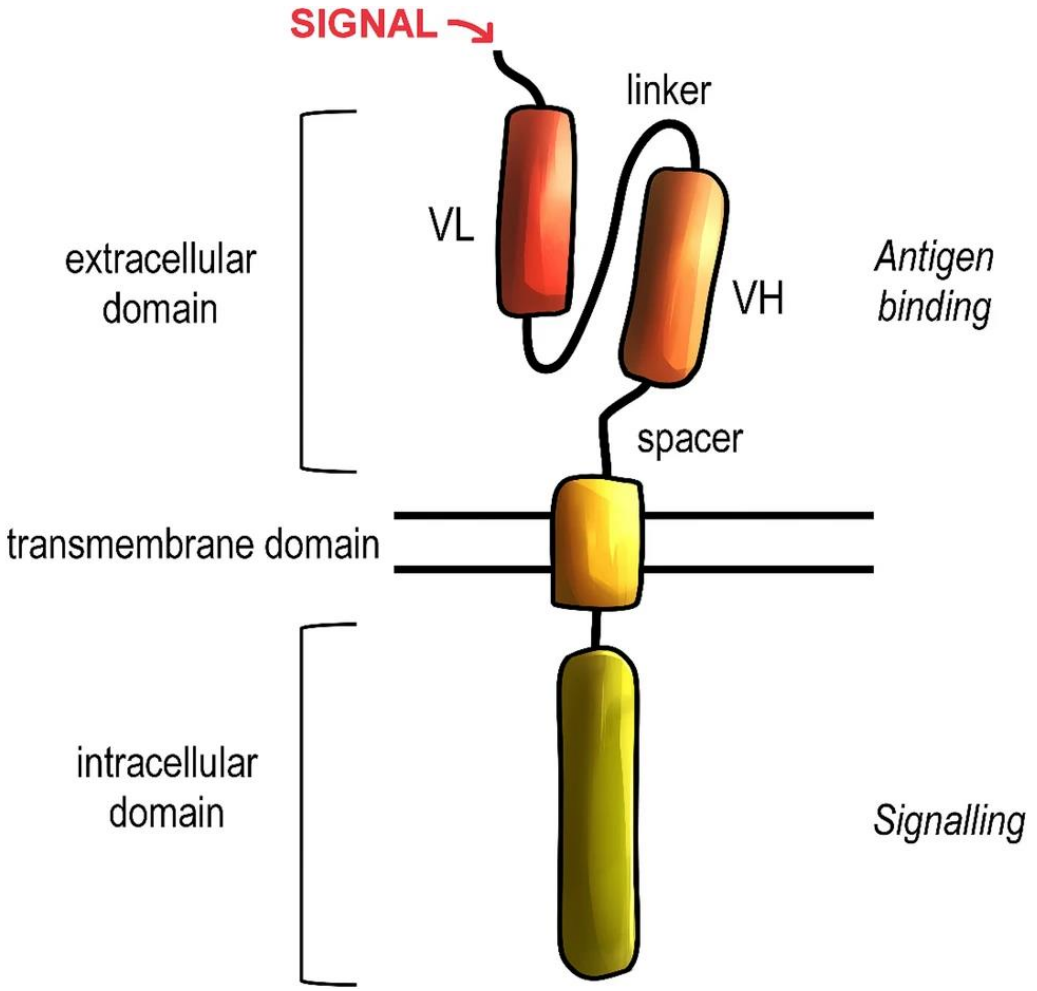
- CAR comprises of an antigen-binding domain isolated from the antibody and an activating domain derived from the TCR.
- The main concept behind the making of this synthetic T-cell construct was to combine the Ab specificity properties with regular T-cell functions, such as proliferation, cytokine production, and elimination of targeted cells
- CAR consists of the extracellular domain, which specifies a CART target, the spacer domain followed by the transmembrane domain, and then the intracellular domain The intracellular part of the receptor is formed by multiple signaling domains.



Skorka, K *et al.*. *Arch. Immunol. Ther. Exp* 2020

Chimeric antigen receptor (CAR)-T cells

- The extracellular domain is responsible for antigen binding and it includes the single-chain variable fragment, derived from the antibody domains, precisely variable heavy (VH) and light (VL)
- CARs can recognize the antigen independently of MHC
- The domains are connected together via linker and anchored in the transmembrane domain by a spacer. The spacer is important for enabling and enhancing epitope binding in vivo
- The transmembrane domain is responsible for the stabilization of CAR
- The intracellular domains are derived from the T-cell receptor and are responsible for inducing the cell response after the antigen recognition

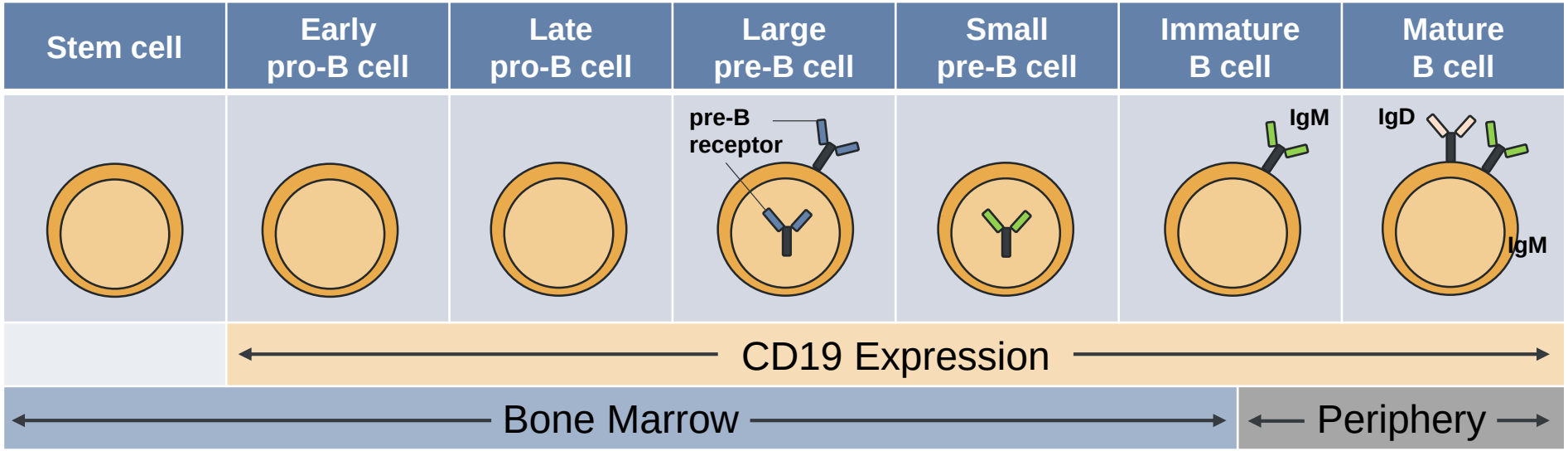


Skorka, K *et al.*. *Arch. Immunol. Ther. Exp* 2020

Why is CD19 the most common therapeutic target?

- CD19 is present throughout the most of the B cell maturation process

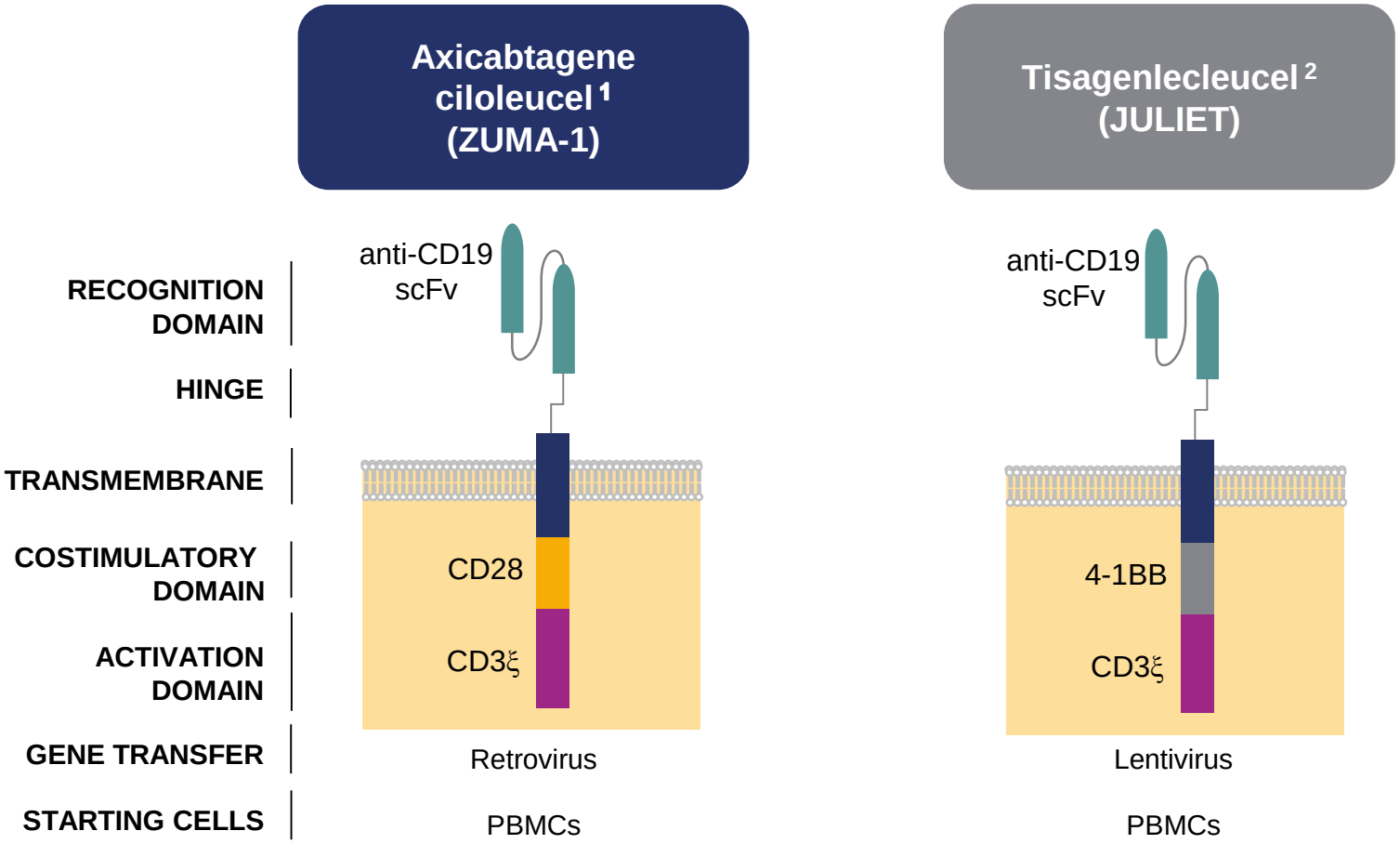
- CD19 is present in most B cell leukemias and lymphomas, but not in any normal tissue other than the B cell lineage



IgD, immunoglobulin D; IgM, immunoglobulin M.

Murphy KM, Weaver C, eds. *Janeway's Immunobiology*. 9th ed. Garland Science; 2017:1-36,295-344
Sadelain M, et al. Cancer Discov. 2013;3:388-398.

Approved CD19 Targeting CAR T-cell Therapies



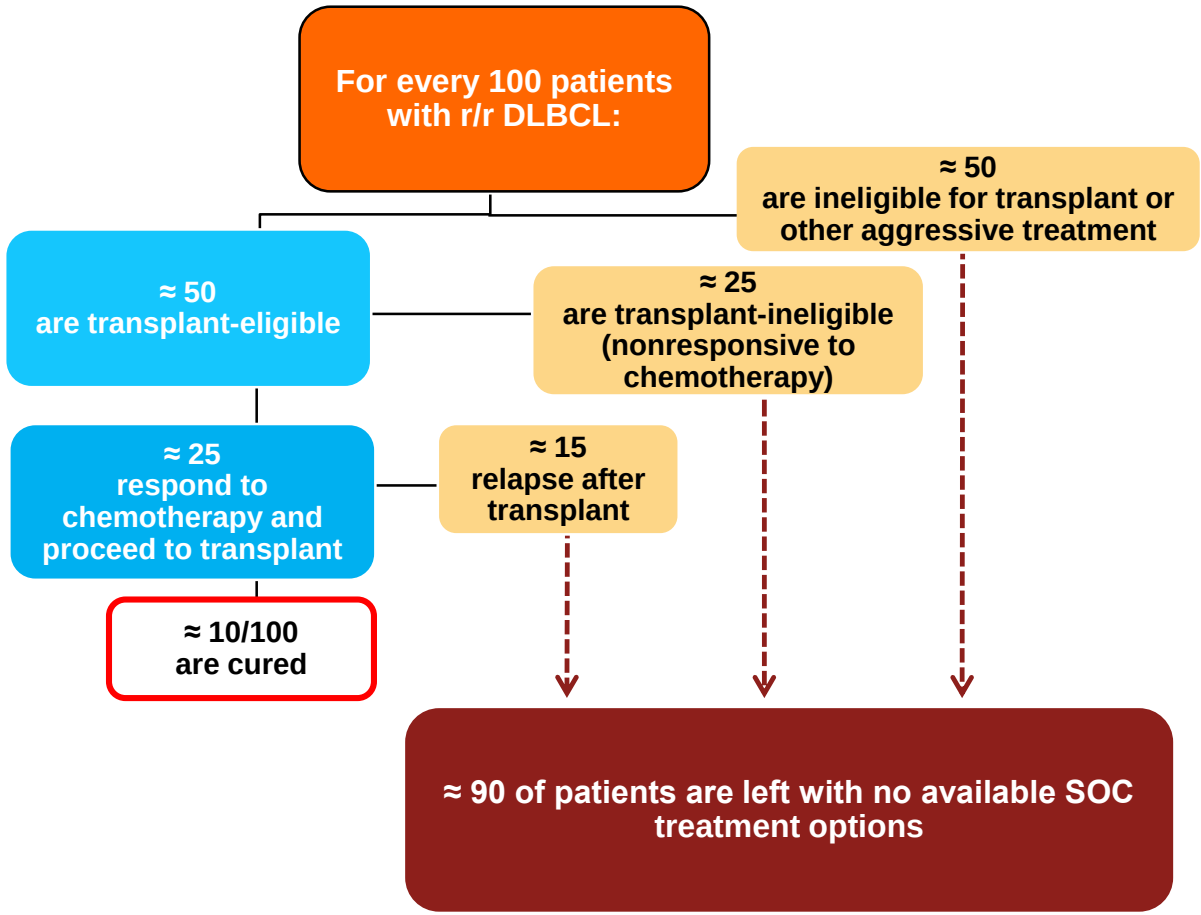
*BREYANZI® (lisocabtagene maraleucel) is prepared from the patient's T cells, which are obtained from the product of a standard leukapheresis procedure. The purified CD8-positive and CD4-positive T cells are separately activated and transduced with the replication-incompetent lentiviral vector containing the anti-CD19 CAR transgene.

CAR, chimeric antigen receptor; PBMC, peripheral blood mononuclear cells; scFv, single chain variable fragment.

1. YESCARTA® (axicabtagene ciloleucel) Prescribing information. Kite Pharma, Inc; 2021.
2. KYMRIAH® (tisagenlecleucel) Prescribing information. Novartis Pharmaceuticals Corporation; 2020.

Diffuse Large B cell Lymphoma

- Diffuse large B el lymphoma is the most common type of non-Hodgkin's lymphoma in adults and it makes up approximately 30–40% of all lymphoma cases worldwide
- The median age of DLBCL patients at the time of diagnosis is 70 years. Current 5-year OS for DLBCL is 60–70% after standard therapy
- Despite the fact that the majority of patients can respond well to the first-line chemotherapy, acquiring the primary refractory disease or relapsing is not rare



Rovira J et al. Ann Hematol 2015
Figure adapted from Friedberg JW. *Hematology Am Soc Hematol Educ Program*. 2011

Approved CD19-Directed CAR T-Cell Products for DLBCL

	Axicabtagene Ciloleucel[1]	Tisagenlecleucel[2]
Construct	Anti–CD19-**CD28**-CD3z	Anti–CD19-**41BB**-CD3z
Dose	2 x 10^6/kg (max 2 x 10^8)	0.6 to 6.0 x 10^8
Bridging therapy	None allowed in pivotal trial, often used in standard practice	92%
Lymphodepletion	Flu/Cy 500/30 x 3 days	Flu/Cy 250/25 x 3 days, or bendamustine x 2 days
EMA approval status	**DLBCL primary mediastinal B-cell lymphoma, after ≥ 2 lines of systemic therapy**	**Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.** **Adult patients with RR DLBCL after ≥ 2 lines of systemic therapy**

1. Axicabtagene ciloleucel , YESCARTA® PI. 2. Tisagenlecleucel PI.

CD19-CAR T-Cell Therapies Approved for DLBCL: Summary

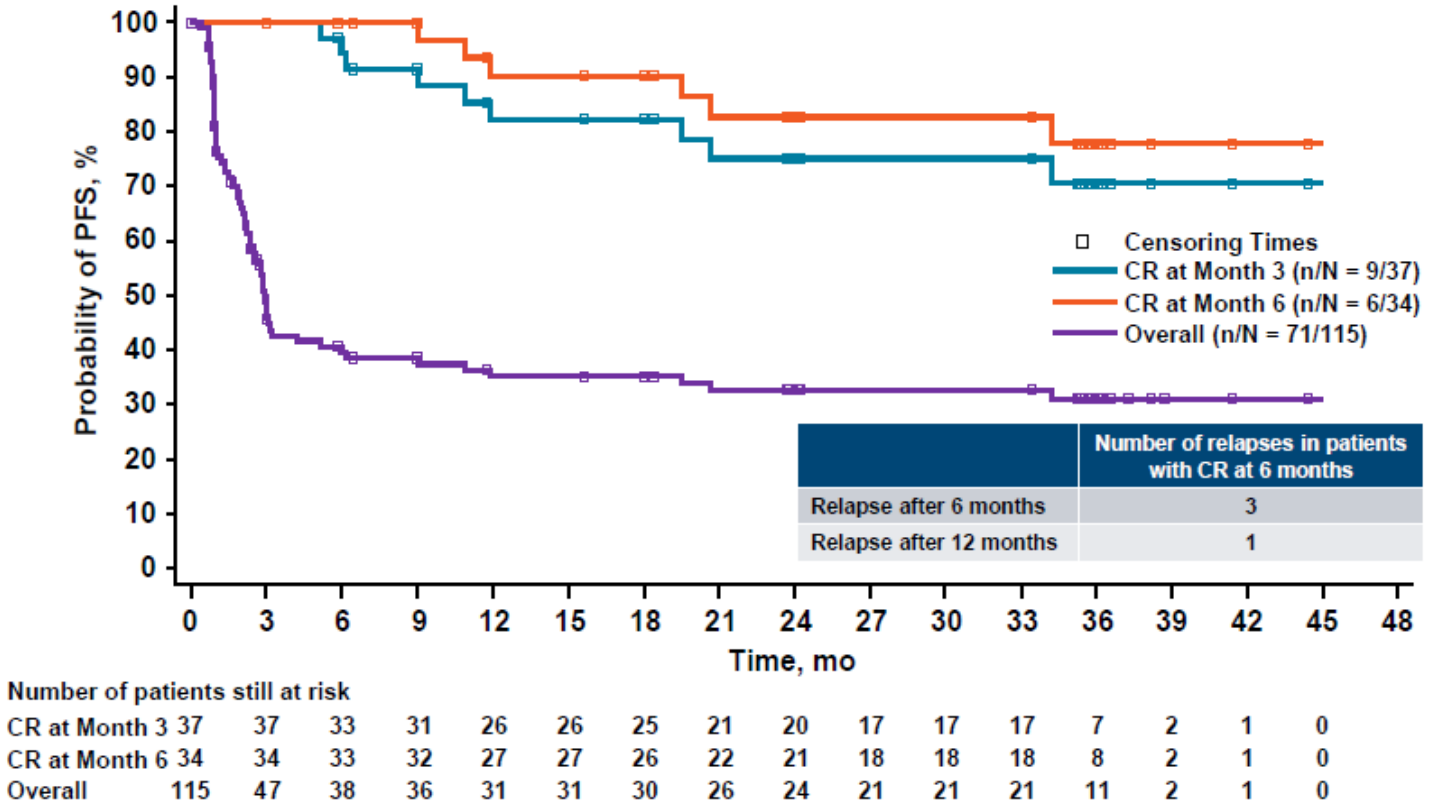
	Axicabtagene Ciloleucel[1,2]	Tisagenlecleucel[3,4]
Disease (response evaluable patients)	R/R DLBCL (n = 77) R/R tFL/PMBCL (n = 24)	R/R DLBCL (n = 89) R/R tFL (n = 22)
Median follow-up, mos	15.4	14
Efficacy		
n	101	93
ORR/CR, %	82/54 (best)	52/40 (best)
PFS for CR at 12 mos, %	79	78.5
DoR (CR + PR; median), mos	11.1 mos	Not reached
DoR (CR; median), mos	Not reached	Not reached

- Caveats in cross-trial comparisons: different eligibility criteria, phase of study, dose levels

1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31. 3. Schuster. NEJM. 2019;380:45. 4. Borchmann. EHA 2018. Abstr S799.

JULIET 40.3 months median follow-up: Progression-Free Survival

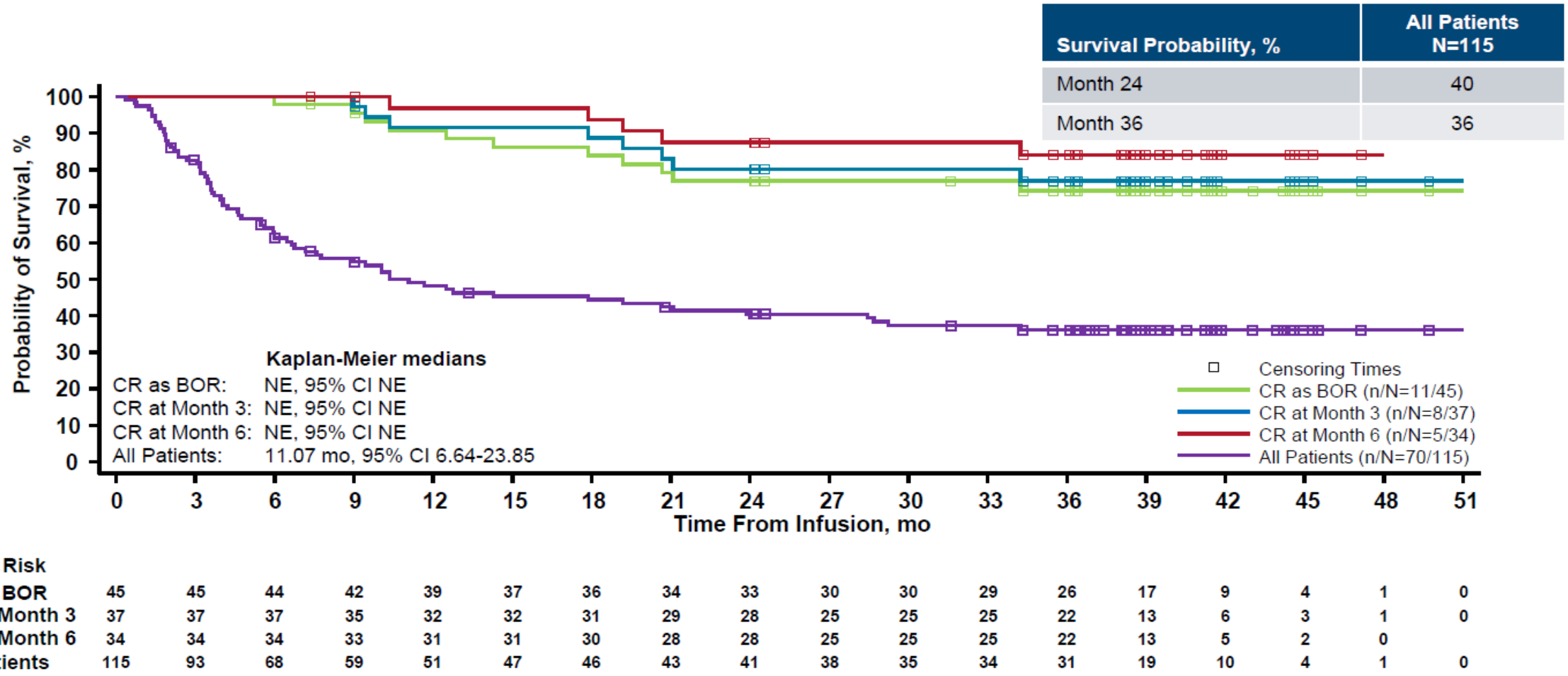
- The 24- and 36-month PFS were 33% and 31%, respectively
- Among all responders, 60% were estimated to maintain that response at 24 and 36 months
- With long-term follow-up, no new adverse events were detected



Note: Efficacy assessments were taken at Day 28, Month 3, 6, 9, 12, 18, 24, 36, 48, and 60 or as clinically indicated.
CR, complete response; DLBCL, diffuse large B-cell lymphoma; PFS, progression-free survival.
Data cutoff February 20, 2020

Jaeger U. et al. Presented at American Society of Hematology Annual Meeting & Exposition 2020 (poster, abstract #1194)

JULIET 40.3 months median follow-up: Overall Survival



BOR, best overall response; NE, not estimable.

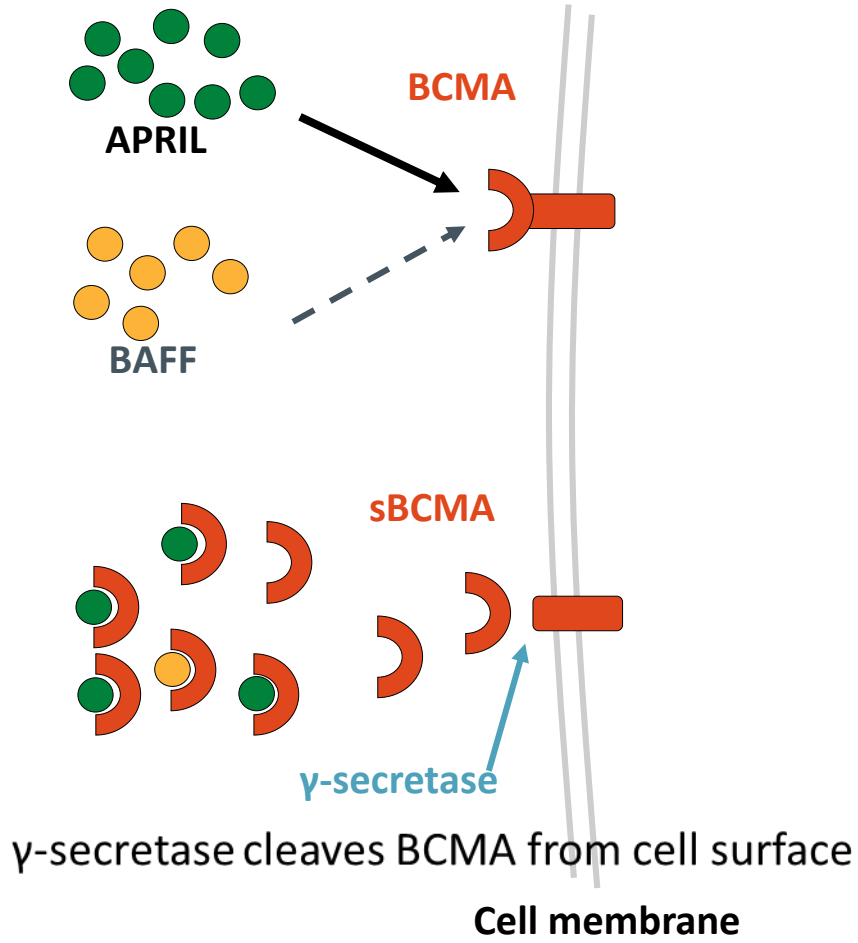
Jaeger U. et al. Presented at American Society of Hematology Annual Meeting & Exposition 2020 (poster, abstract #1194)

CAR-T cells in Multiple Myeloma

Multiple Myeloma

- It is characterized by a clonal expansion of aberrant plasma cells in the bone marrow, resulting in the production of an abnormal quantity of monoclonal immunoglobulins (Ig) called M protein.
- M proteins attack organs, such as kidney and bone, leading to end-organ damage.
- Since it remains an incurable malignancy many therapeutic regimens, particularly immunotherapies using mAbs and CAR-T cell therapies, are emerging.

BCMA as a Target in Myeloma Treatment



- BCMA: Antigen expressed specifically on plasma and myeloma cells
- Higher expression on myeloma cells than normal PCs
- Not expressed in other tissues
- In plasma cells, supports survival of long-lived PCs, antibody production, class switch of immunoglobulin
- Promotes myeloma cell growth, chemotherapy resistance, immunosuppression in bone marrow microenvironment
- Expression of BCMA increases with progression from MGUS to advanced myeloma
- Increased sBCMA level associated with poorer outcome

Cho. Front Immunol. 2018;9:1821.

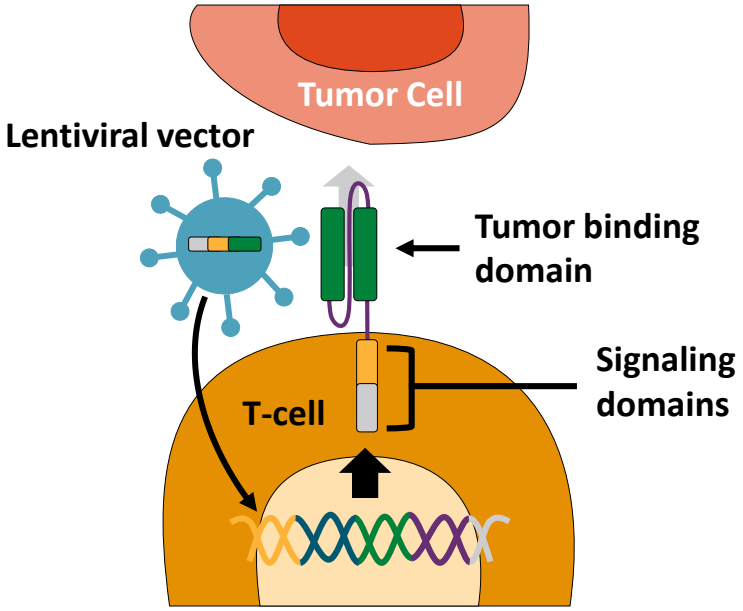
Slide credit: clinicaloptions.com

KarMMa: Background

- No standard of care and poor prognosis for patients with R/R MM after treatment and progression with IMiDs, PIs, and anti-CD38 mAbs
  - Median PFS: 3.4 mos; median OS: 9.3 mos[1]
- Idecabtagene vicleucel (bb2121), investigational BCMA-directed CAR T-cell therapy with activity in R/R MM in phase I study[2]
  - ORR: 85%; median PFS: 11.8 mos; median DoR: 10.9 mos
  - Grade 3 CRS occurred in 2/33 (6%), grade 4 neurotoxicity in 1/33 (3%)
- Current study assessed efficacy and safety of ide-cel in R/R MM in phase II setting[3]

1. Gandhi. Leukemia. 2019;33:2266. 2. Raje. NEJM. 2019;380:1726. 3. Munshi. ASCO 2020. Abstr 8503.

Idecabtagene Vicleucel (bb2121): Second-generation BCMA-Targeted CAR T-Cell



Idecabtagene CAR design

Extracellular domain

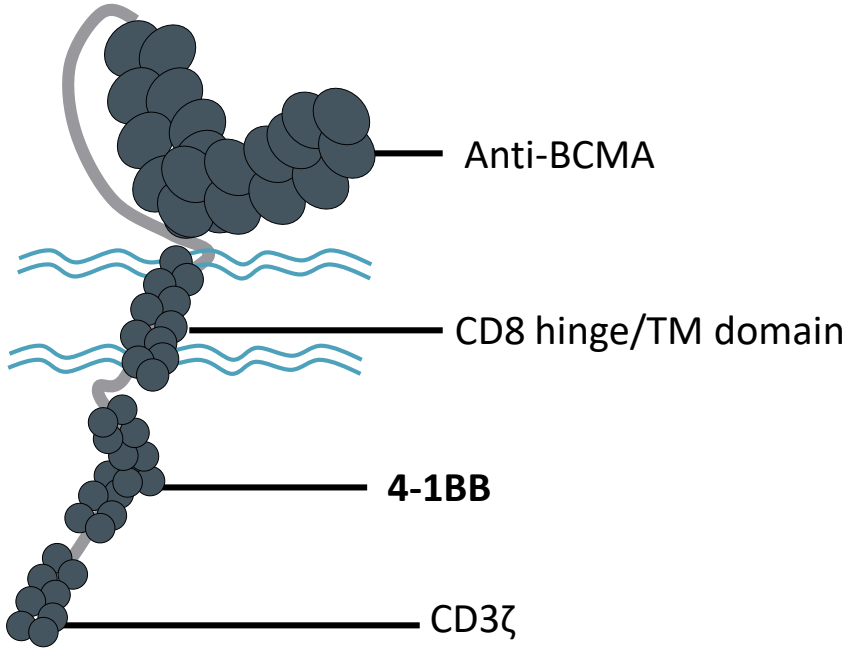
Targeting domain

Hinge/TM domain

Intracellular domain

Costimulatory domain

T-cell activation domain



Raje. ASCO 2018. Abstr 8007.

Slide credit: clinicaloptions.com

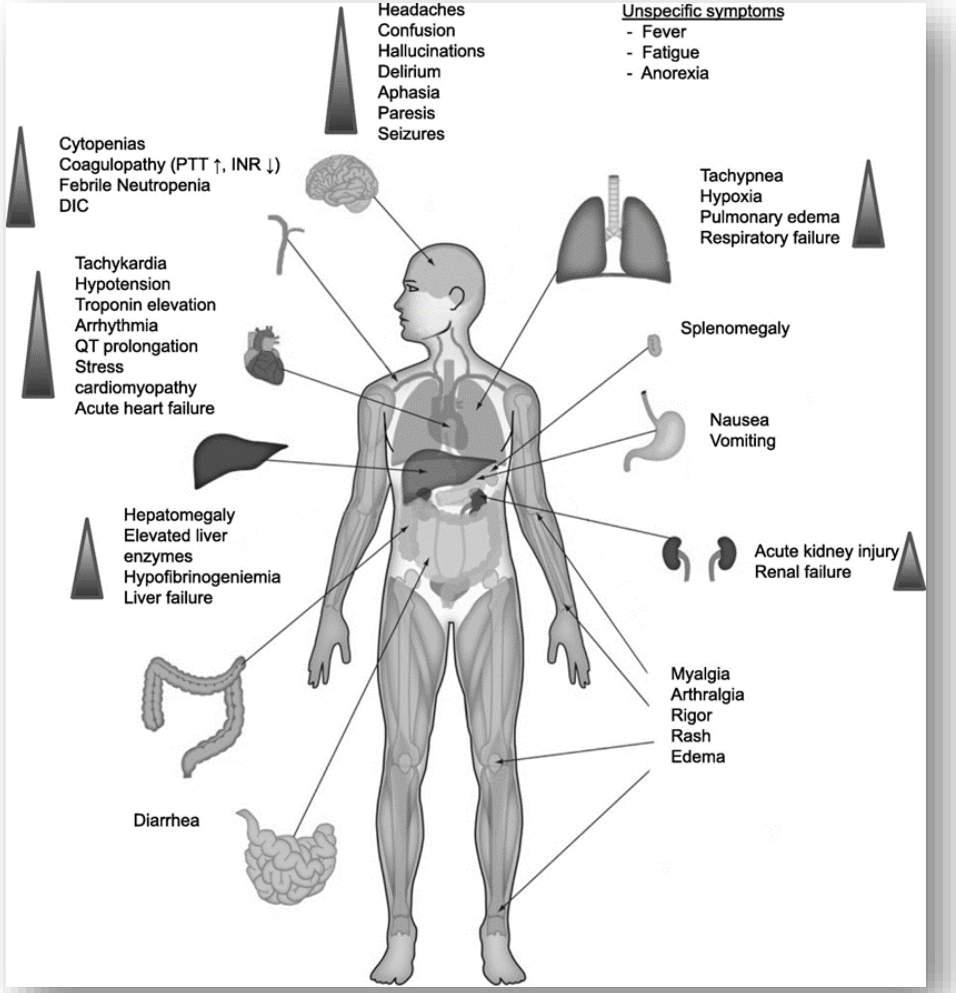
KarMMa: Conclusions

- In patients with R/R MM, use of idecabtagene vicleucel CAR T-cell therapy resulted in durable responses
  - ORR: 73%; CR: 33%
  - Median DoR: 10.7 mos; median PFS: 8.8 mos
    - Median DoR: 19.0 mos; median PFS: 20.2 mos in patients achieving CR/sCR
  - Median OS 19.4 mos
- Idecabtagene vicleucel was tolerable, with grade 3 CRS or neurotoxicity occurring in ≤ 6% of patients at target dose 450 x 10^6 CAR T-cells
- Authors conclude idecabtagene vicleucel appears promising in patients with heavily pretreated MM refractory to IMiDs, PIs, and anti-CD38 mAbs

Munshi. ASCO 2020. Abstr 8503.

Slide credit: clinicaloptions.com

Cytokine Release Syndrome (CRS)



Shimabukuro-Vornhagen A et al. J Immunother Cancer 2018

- CRS can present with a variety of symptoms
- Mild symptoms of CRS include fever, fatigue, headache, rash, arthralgia, and myalgia.
- More severe cases are characterized by hypotension & ↑ fever and can progress to an uncontrolled systemic inflammatory response with vasopressor-requiring circulatory shock, vascular leakage, DIC and multi-organ system failure.
- Laboratory abnormalities that are common in patients with CRS include cytopenias, ↑ creatinine and liver enzymes, deranged coagulation parameters, and ↑CRP
- The incidence of CRS in patients with hematological malignancies is approximately 55.3% and the incidence of severe CRS (sCRS) is approximately 18.5%

Cytokine Release Syndrome (CRS)

The mechanism of CRS:

A. Activated CAR-T cells release numerous cytokines

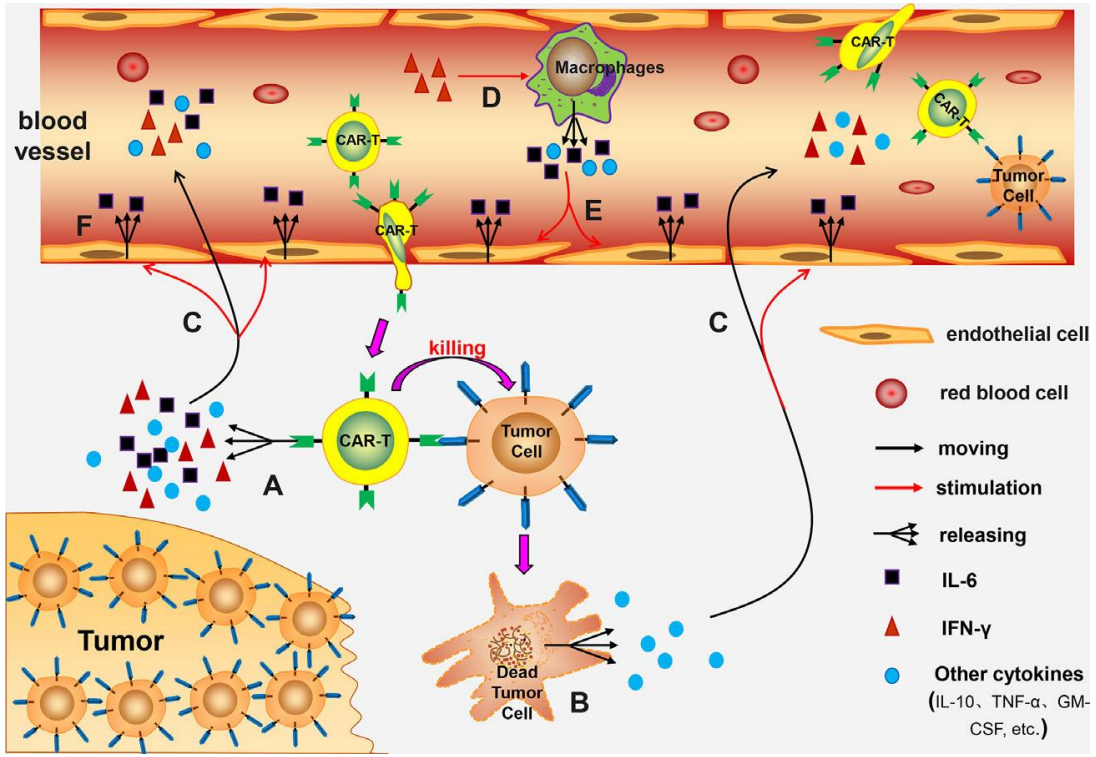
B. The lysed tumor cells release a large number of cytokines

C. These cytokines enter the blood circulation and activate endothelial cells

D. IFN-g further induces macrophages activation

E. The activated macrophages release many cytokines into the blood circulation which activate endothelial cells

F. The activated endothelial cells release large amounts of IL-6, forming a vicious circle.



Miao L et al. Front Immunol 2021

ASTCT Guidelines for Grading of CRS

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥38°C	Temp ≥38°C	Temp ≥38°C	Temp ≥38°C
with				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
and/or				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)
Treatment	Symptomatic	Symptomatic and supportive	Supportive treatment & immunosuppressants (Corticosteroids, Tocilizumab)	

Lee. Biol Blood Marrow Transplant. 2019

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

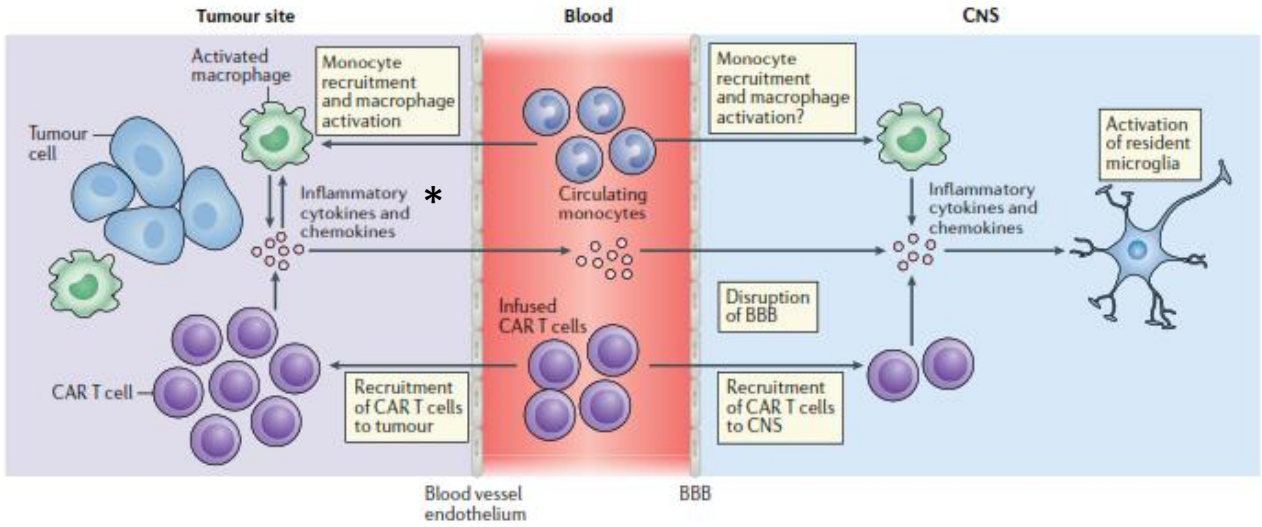
- Neurotoxicity, also referred to as immune effector cell-associated neurotoxicity syndrome (ICANS) occurs in up to 67% of patients with leukemia and 62% of patients with lymphoma .
- ICANS usually appears within one to 3 weeks after CART cell infusion, although there have been reports of delayed ICANS development.
- ICANS often accompanies and correlates with CRS, but it has also been occasionally reported to occur independently from CRS.
- Early manifestations of ICANS include expressive aphasia, tremor, dysgraphia, and lethargy; these symptoms can progress to global aphasia, seizures, obtundation, stupor, and coma

Miao L et al. Front Immunol 2021

CAR-T cell therapy: Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

- The pathophysiology of ICANS seems to start with the production of pro-inflammatory cytokines by CAR T cells and the activation of bystander immune cells in the tumor microenvironment.

- Inflammatory cytokines and chemokines produced by CAR T cells and myeloid cells in the tumour microenvironment diffuse into the bloodstream and, eventually, result in disruption of the blood–brain barrier with accumulation of cytokines and CAR T cells in the CNS together with activation of resident microglial cells.



*IL-1β, IL-6, IL-10, CXCL8, CCL2, IFN-γ, GM-CSF, TNF-α

Morris EC et al. Nat Rev Immunol 2021

ASTCT Guidelines for Grading of ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 mins) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing triad

*An ICE score of 0 may be classified as grade 3 ICANS if patient is awake with global aphasia; otherwise classified as grade 4 ICANS if unarousable.

Treatment: Corticosteroids, Tocilizumab (?), Siltuximab, Anakinra

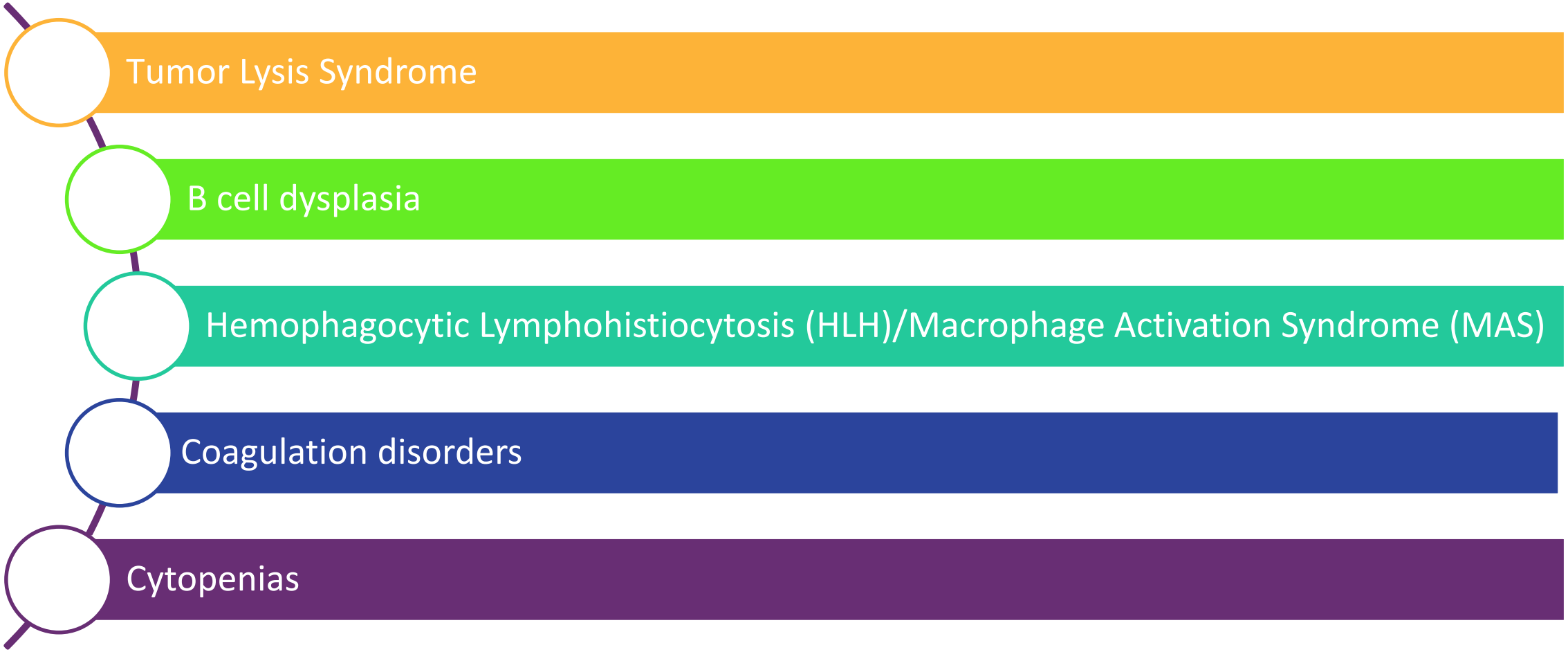
Lee. Biol Blood Marrow Transplant. 2019
Miao L et al. Front Immunol 2021

CAR-T cell therapy: Infections

- In the registration trials for tisagenlecleucel, axicabtagene ciloleucel and lisocabtagene maraleucel, infection occurred in 12–55% of patients within the first year, with 23–33% of these being severe
- Surprisingly, fatality due to infection was low (⩽3%) with most deaths occurring due to relapsed malignancy
- In cohort studies, incidence of all infection events within the first 30 days: 27% -36% of patients
- Microbiological diagnosis and confirmation are often difficult with pathogenic organisms only identified in 72% of infection episodes (60% bacterial, 92% viral, 50% fungal) in one study
- One third of bacterial infections occurred within 30 days
- Viral infections typically included respiratory syncytial virus, CMV, influenza and polyomaviruses; their incidence ranged from 9.2%-28%; they occurred mostly after 30 days
- The majority of fungal infection clusters within the first 30 days and typically occurs in the setting of neutropenia and/or CRS; invasive fungal infection has a reported incidence of between 1%-15%

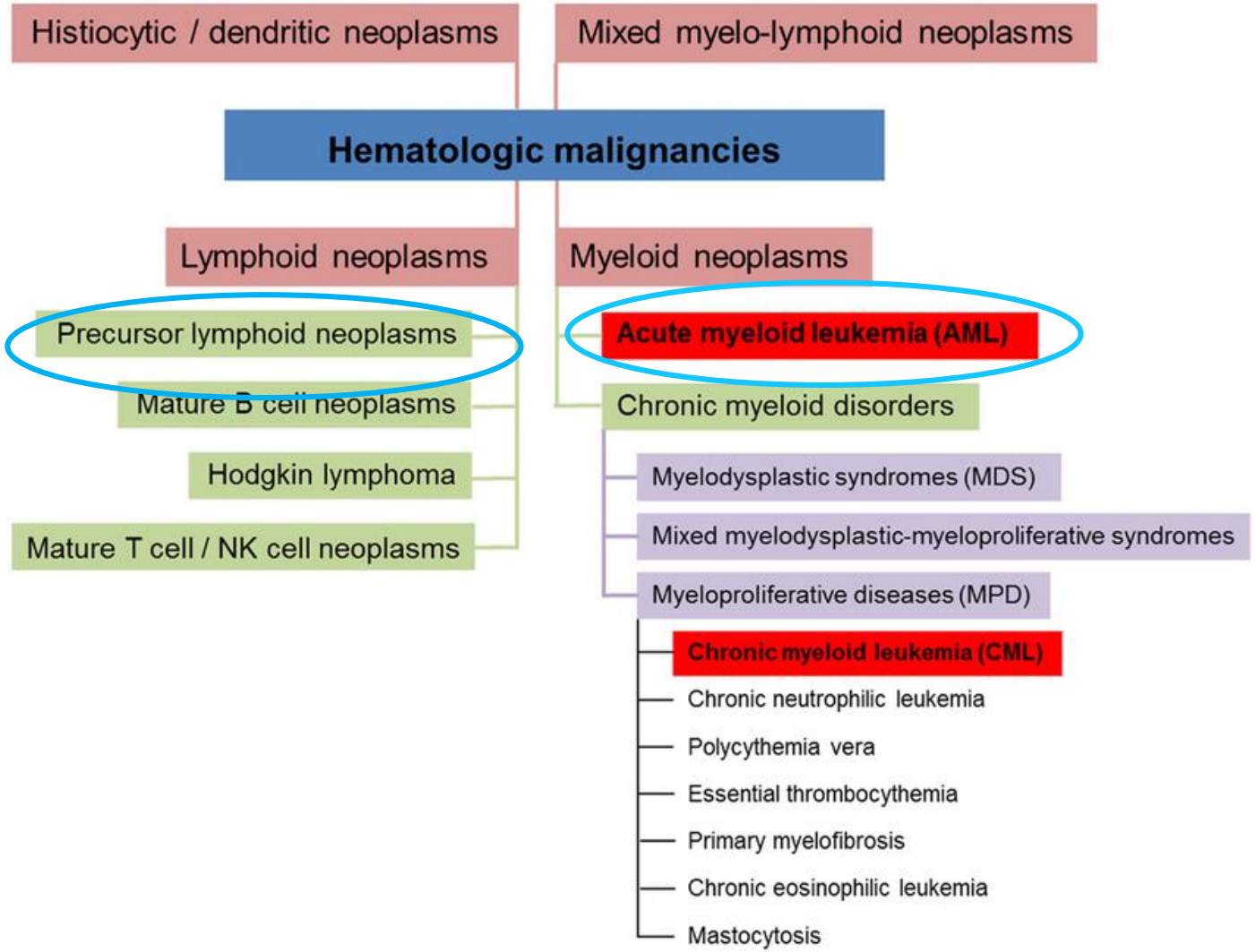
Stewart AG et al. Therapeutic Advances in Infectious Disease 2021
Hill JA Blood Rev 2019

CAR-T cell therapy: other toxicities



Miao L et al. Front Immunol 2021

Hematologic Malignancies



Οξεία Μυελογενής Λευχαιμία

- Ετερογενής ομάδα νεοπλασματικών νοσημάτων
- Επίπτωση που αυξάνει με την ηλικία
- Αναιμία, θρομβοπενία, λευκοκυττάρωση ή σπανιότερα λευκοπενία
- Η λευκοκυττάρωση οφείλεται στην παρουσία μεγάλου αριθμού βλαστικών κυττάρων στο αίμα
- Μυελός με αυξημένη κυτταροβρίθεια και παρουσία μεγάλου αριθμού βλαστικών κυττάρων με παράλληλη διαταραχή της ωρίμανσης
- Κυτταρογενετικές και μοριακές βλάβες που σχετίζονται με πρόγνωση
- Βελτίωση πρόγνωσης με την προσθήκη αλλογενούς μεταμόσχευσης μυελού

Οξεία Λεμφοβλαστική Λευχαιμία

- Ετερογενής ομάδα νεοπλασματικών νοσημάτων με προέλευση τα Β- ή Τ- πρόδρομα κύτταρα της λεμφικής σειράς
- Νόσος κυρίως της παιδικής ηλικίας
- Αναιμία, θρομβοπενία, παρουσία λεμφοβλαστών στο αίμα με ή χωρίς λευκοκυττάρωση
- Μυελός με αυξημένη κυτταροβρίθεια και παρουσία μεγάλου αριθμού λεμφοβλαστών με παράλληλη διαταραχή της ωρίμανσης
- Κυτταρογενετικές και μοριακές βλάβες που σχετίζονται με πρόγνωση
- Καλή πρόγνωση της νόσου της παιδικής ηλικίας
- Χειρίστη πρόγνωση επί ανεύρεσης χρωμοσώματος Philadelphia

Περιορισμένες θεραπευτικές επιλογές σε ασθενείς που υποτροπιάζουν μετά από μεταμόσχευση ή έχουν νόσο ανθεκτική στη χημειοθεραπεία

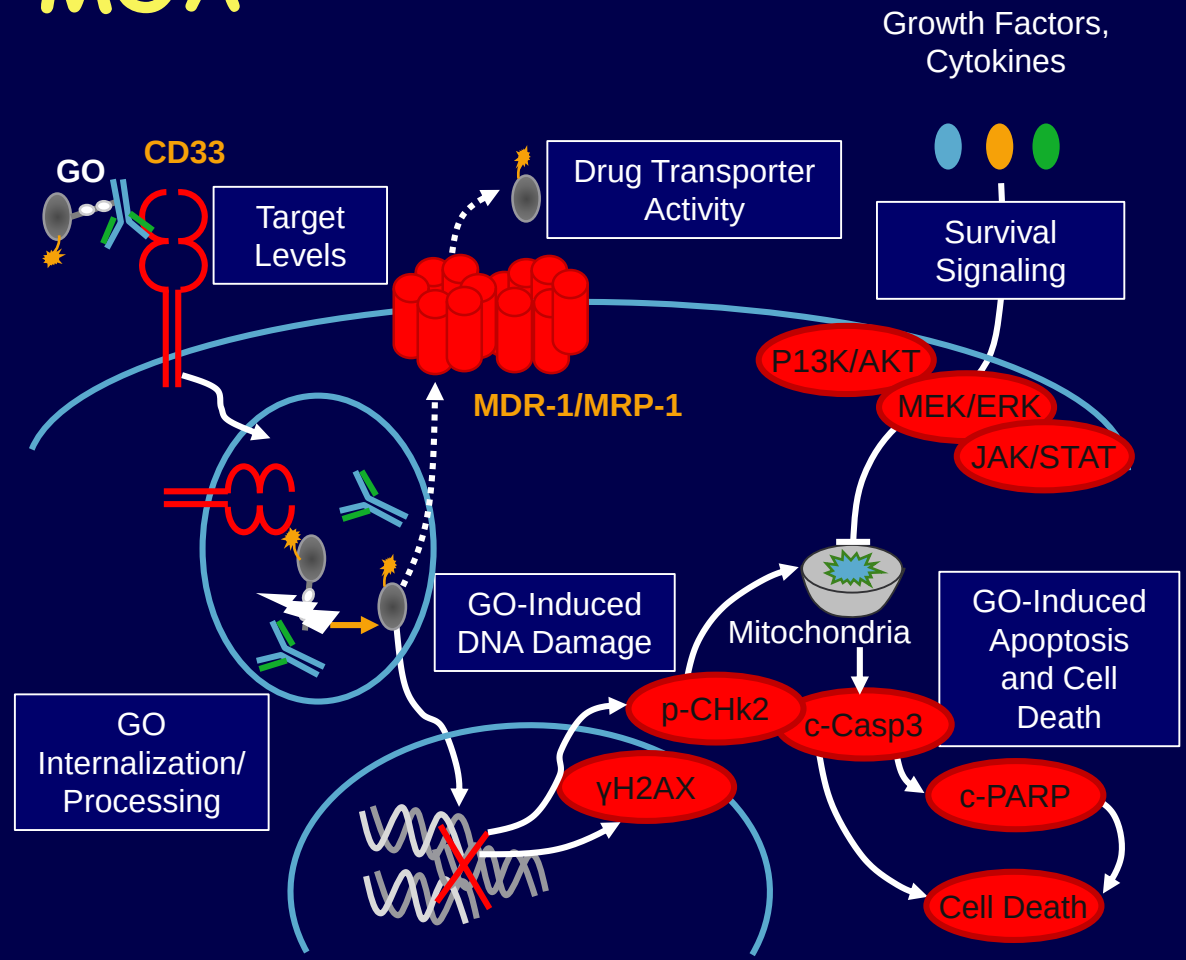
Rationale for CD33 as a Target in AML

- CD33 broadly expressed in AML: 87% to 98% of cases[1,2]
- Function of CD33 poorly understood
  - Implicated in cell adhesion and activation
  - May function as an inhibitory receptor dampening immune response[3]
- CD33 internalized upon binding[4]
- In some myeloid leukemias, CD33 thought to be expressed on LSCs[5]

1. Ehninger A, et al. Blood Cancer J. 2014;4:e218. 2. Andrews RG, et al. J Exp Med. 1989:169:1721-1731. 3. Crocker PR, et al. Ann N Y Acad Sci. 2012;1253:102-111. 4. Walter RB, et al. J Leukoc Biol. 2008;83:200-211. 5. Walter RB, et al. Blood. 2012;119:6198-6208. 6. Crocker PR, et al. Nat Rev Immunol. 2007;7:255-266.

Gemtuzumab Ozogamicin: MOA

- Monoclonal anti-CD33 antibody linked to calicheamicin-γ1[1]
- Internalized and cleaved in lysosomes to release free calicheamicin moiety[2]
- Calicheamicin moiety enters nucleus and interacts with DNA causing double-strand breaks initiating apoptosis[1-3]



Rosen DB, et al. PLoS One. 2013;8:e53518.

1. Zein N, et al. Science. 1988;240:1198-1201. 2. Naito K, et al. Leukemia. 2000; 14:1436-1443.
3. Elmroth K, et al. DNA Repair (Amst). 2003;2:363-374.

Slide credit: clinicaloptions.com

Gemtuzumab Ozogamicin in AML: Development Overview

- Approved for AML in 2000, withdrawn in 2010
  - Voluntarily withdrawn from the market after addition of gemtuzumab to frontline chemotherapy shown to increase mortality[1]
- Critics of the withdrawal noted increased mortality only slightly higher than normally seen in AML
- Subsequently, studies of gemtuzumab in AML have demonstrated survival benefits, particularly in pts younger than 60 yrs of age and favorable-risk pts

1. Petersdorf S, et al. Blood. ASH 2009. Abstract 790.

Gemtuzumab Ozogamicin in AML: clinical trials

Trial	Study design	Patient population	Enrolled patients	Primary endpoint	Results	Reference
ALFA-0701	Randomized phase III	Patients aged 50–70 years with de novo AML	280	EFS	GO arm, median 17.3 months vs control arm, median 9.5 months; p=0.0002	137 138
EORTC-GIMEMA AML-19	Randomized phase III	Patients aged 61 years or older with de novo AML unsuitable for intensive chemotherapy	237	OS	Median OS 4.9 months vs 3.6 months (HR, 0.69; 95% CI, 0.53 to 0.90; p=0.005)	139
Mylo-France 1	Single-arm, open label phase II	Patients aged 18 years or older with RR AML	57	CRR	CRR 26% and 7% CR with incomplete platelet recovery	140
AAML0531	Multicenter randomized phase III	Patients aged 0 to 29 years with newly diagnosed AML	1022	EFS,OS	GO+chemotherapy improved EFS (3 years: 53.1% v 46.9%, p=0.04) OS, 3 years: 69.4% v 65.4%,p=0.39 GO+chemotherapy versus chemotherapy alone	141

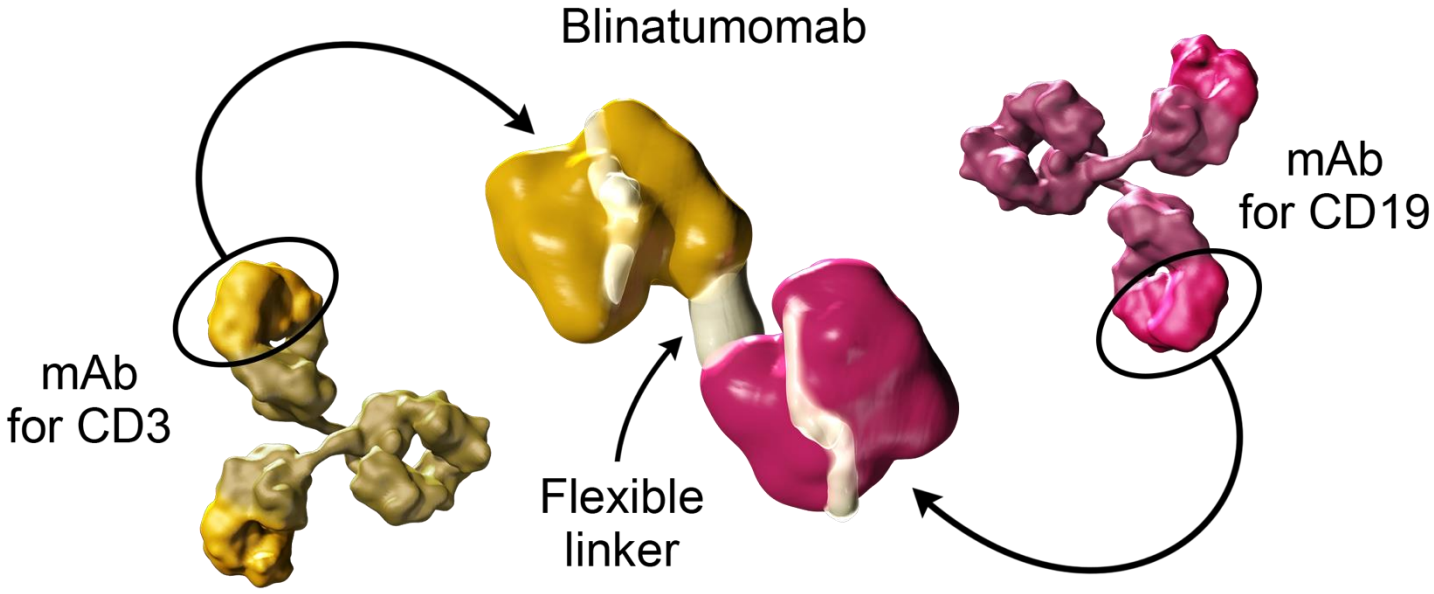
The addition of GO to induction/consolidation improved EFS and OS in newly diagnosed AML patients, with a safe toxicity profile

Gemtuzumab Ozogamicin in AML:

- MYLOTARG is indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia

Blinatumomab Is Generated From Two Single Chain Antibodies Joined by a Non-Immunogenic Linker[1-6]

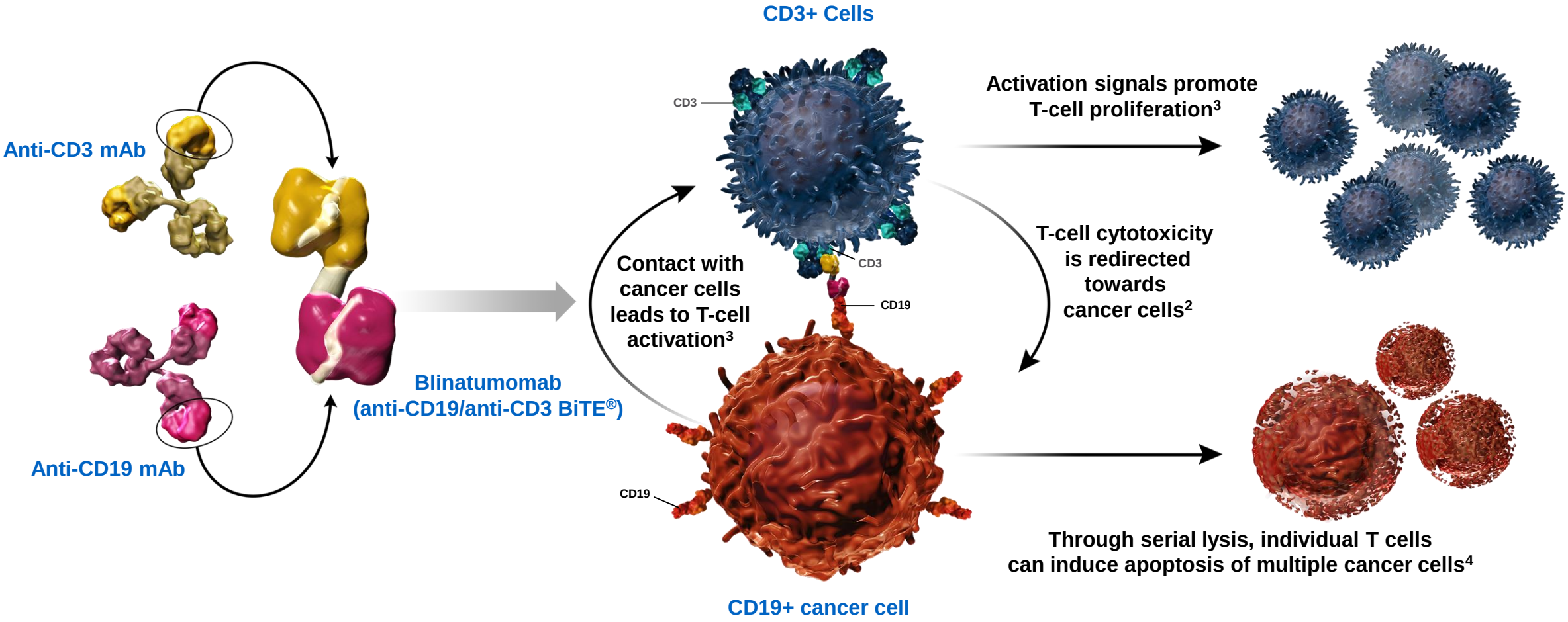
- Blinatumomab is formed by genetically linking the scFv of mAbs for CD3 on T cells and for CD19 on B cells[1-4]
- The two separate single chain peptides are fused together by a short, flexible non-immunogenic linker[5,6]



CD, cluster of differentiation; mAb, monoclonal antibody; scFv, single-chain fragment variable.

1. Baeuerle PA, et al. *Cancer Res*. 2009;69:4941-4944. 2. Hoffmann P, et al. *Int J Cancer*. 2005;115:98-104. 3. Nagorsen D, et al. *Exp Cell Res*. 2011;317:1255-1260. 4. Baeuerle PA, et al. *Curr Opin Mol Ther*. 2009;11:22-30. 5. Wolf E, et al. *Drug Discov Today*. 2005;10:1237-1244. 6. Portell CA, et al. *Clin Pharmacol*. 2013;5:5-11.

Blinatumomab MoA Summary: A BiTE® Designed to Bridge T Cells to CD19-Expressing Cancer Cells, Inducing Apoptotic Cell Death[1]



BiTE®, Bispecific T Cell Engager; CD, cluster of differentiation; mAb, monoclonal antibody; MoA, mechanism of action.

1. Baeuerle PA, et al. *Cancer Res.* 2009;69:4941-4944. 2. Bargou R, et al. *Science.* 2008;321:974-977.
3. Klinger M, et al. *Blood.* 2012;119:6226-6233. 4. Hoffmann P, et al. *Int J Cancer.* 2005;115:98-104.

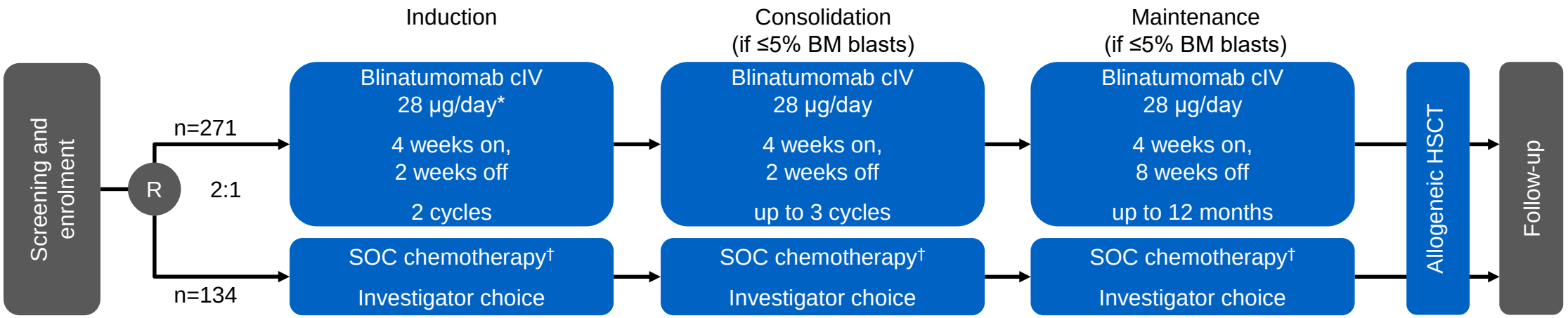
Blinatumomab therapeutic indication (EU)

- Blinatumomab is indicated as monotherapy for the treatment of adults with CD19-positive relapsed or refractory B-precursor ALL. Patients with Ph-positive B-precursor ALL should have failed treatment with at least 2 TKIs and have no alternative treatment options
- Blinatumomab is indicated as monotherapy for the treatment of adults with Ph-negative CD19-positive B-precursor ALL in first or second complete remission with MRD greater than or equal to 0.1%
- Blinatumomab is indicated as monotherapy in paediatric patients aged 1 year or older with Ph-negative CD19-positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic HSCT
- All other settings are investigational

Phase 3 randomised study of blinatumomab vs standard of care (SOC) chemotherapy in adult patients with R/R Ph-negative B-precursor ALL

Study 00103311 (TOWER)
NCT02013167

Study design



Primary endpoint	▪ Overall survival
Secondary endpoints	▪ Rate of CR/CRh/CRi in induction ▪ Event-free survival ▪ MRD response‡ ▪ Allogeneic HSCT realisation ▪ 100-day TRM after allogeneic HSCT ▪ Incidence and severity of AEs ▪ Global health status/quality of life

Inclusion criteria	▪ Age ≥18 years ▪ R/R Ph-negative B-precursor ALL – Refractory disease – Untreated 1st relapse (CR1 duration <12 months) – Untreated ≥2nd relapse – Any relapse after allogeneic HSCT ▪ >5% BM blasts ▪ ECOG PS ≤2 ▪ No clinically relevant CNS pathology ▪ No acute or active chronic GvHD

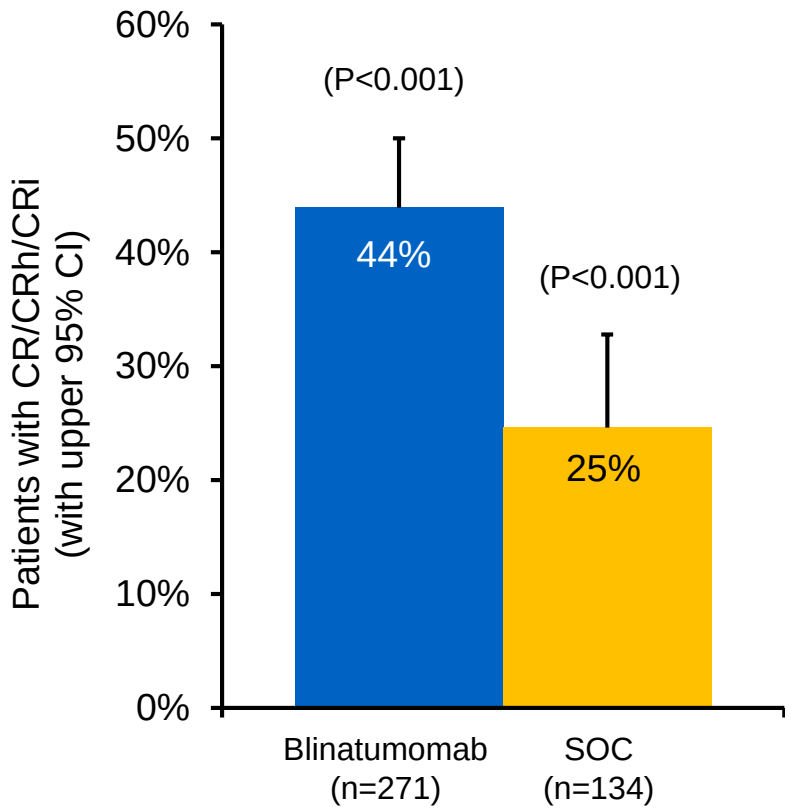
Patients with high tumour load were to receive pre-phase dexamethasone to prevent cytokine release syndrome. Patients were to receive pre-dose dexamethasone to prevent infusion reactions.

*9 µg/day on Days 1–7 of Cycle 1; †SOC chemotherapy: fludarabine, high-dose cytarabine and granulocyte colony-stimulating factor (FLAG), high-dose cytarabine (HiDAC), methotrexate-based or clofarabine based; ‡Defined as $<10^{-4}$ BM blasts in first 12 weeks by flow cytometry (USA) or PCR (other countries).
AE, adverse event; BM, bone marrow; CRi, CR with incomplete haematological recovery; GvHD, graft vs host disease; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, haematopoietic stem cell transplantation; TRM, treatment-related mortality.

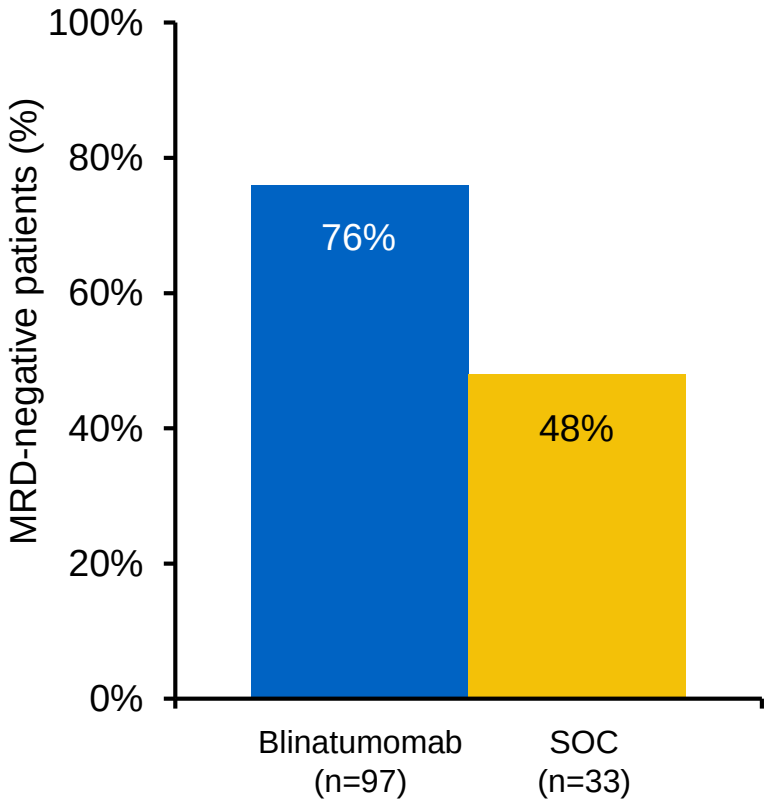
Kantarjian H, et al. N Engl J Med 2017;376:836–47;
https://clinicaltrials.gov/ct2/show/NCT02013167 (accessed February 2021).

Remission rate and MRD negativity

**Overall remission rate*
(patients with CR/CRh/CRi)**



**MRD negativity rate
(in responders)**



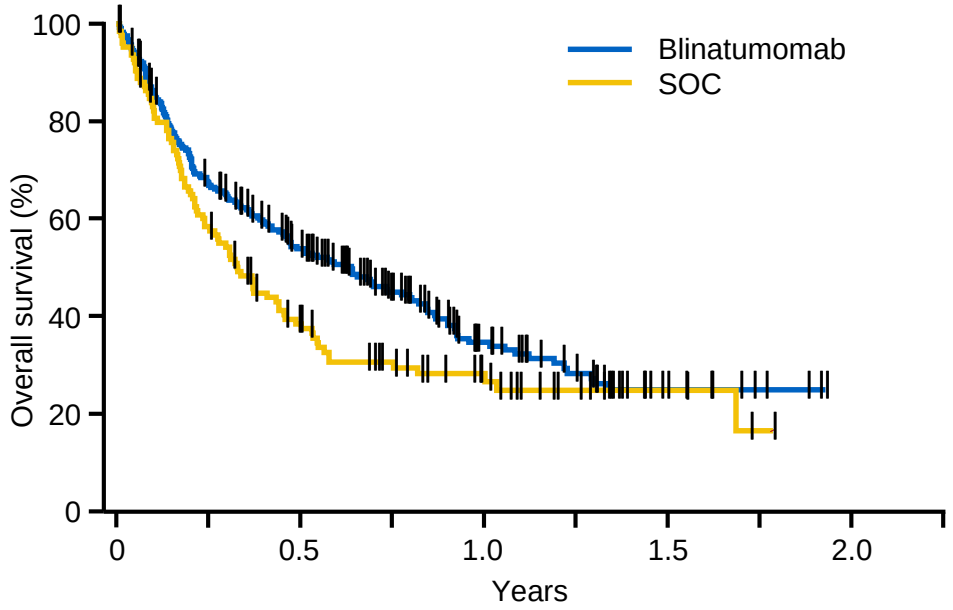
*Intent-to-treat analysis.
CI, confidence interval.

Kantarjian H, et al. N Engl J Med 2017;376:836–47;
Topp MS, et al. EHA 2016; Abstract S149 and oral presentation.

Overall survival

Intent-to-treat population

	Blinatumomab	SOC
Median OS, months (95% CI)	**7.7 (5.6–9.6)**	**4.0 (2.9–5.3)**
Median follow-up, months	11.7	11.8
HR for OS (95% CI)	0.71 (0.55–0.93); P=0.01*	

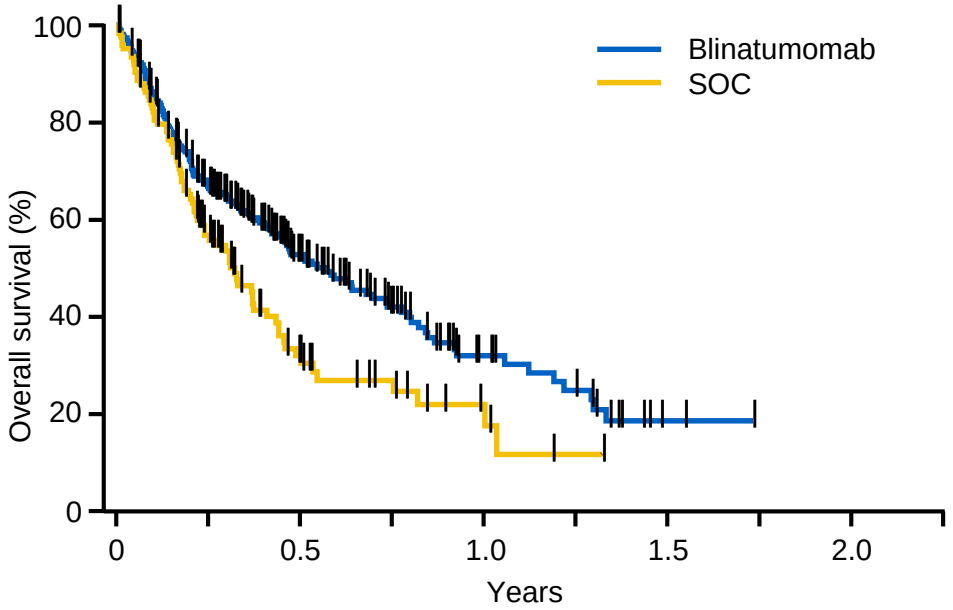


Number of patients at risk:

271	176	124	79	45	27	9	4	0	0
134	71	41	27	17	7	4	1	0	0

Censoring at time of allogeneic HSCT

	Blinatumomab	SOC
Median OS, months (95% CI)	**6.9 (5.3–8.8)**	**3.9 (2.8–4.9)**
HR for OS (95% CI)	0.66 (0.50–0.88); P=0.004*	



Number of patients at risk:

271	163	80	44	21	13	2	0	0	0
134	56	21	12	5	1	0	0	0	0

*Stratified log-rank P-value.
HR, hazard ratio; OS, overall survival.

Adapted from Kantarjian H, et al. N Engl J Med 2017;376:836–47.

Adverse events (regardless of causality)

Event, n (%)	Blinatumomab (n=267)		SOC chemotherapy (n=109)	
	n	%	n	%
Any	263	98.5	108	99.1
Leading to discontinuation of study treatment	33	12.4	9	8.3
Serious AE	165	61.8	49	45.0
Fatal AE	51	19.1	19	17.4
Any Grade ≥3 AE	231	86.5	100	91.7
Grade ≥3 AEs of interest categories*				
Neutropenia	101	37.8	63	57.8
Infection	91	34.1	57	52.3
Elevated liver enzymes	34	12.7	16	14.7
Neurological events	25	9.4	9	8.3
Cytokine release syndrome	13	4.9	0	0
Infusion reaction	9	3.4	1	0.9
Lymphopenia	4	1.5	4	3.7
Any decrease in platelets	17	6.4	13	11.9
Any decrease in WBC count	14	5.2	6	5.5

*Reported for ≥3% of patients in either group.
WBC, white blood cell.

Kantarjian H, et al. N Engl J Med 2017;376:836–47.

Conclusions

- Immunotherapeutic approaches in hematologic malignancies have been a great success in recent years.
- Several regimens of immunotherapy have been studied and approved by the FDA and EMA, while many are still in the late stages of clinical development.
- However, in spite of the enormous achievements of immunotherapy in hematological malignancies over the past years, managing their associated severe adverse effects is an unmet need to be solved and required further investigations.
- Combined the use of multiple immune therapeutics could offer a more effective therapeutic approach for hematological malignancies in the near future.
- Moreover, the precise identification of new molecular targets and new molecular pathways, to reduce the damage of normal cells, is still needed.
- Altogether, these future and supplemental studies will lead to the development of novel therapeutic approaches that will complement the existing treatment strategies and improve the overall longevity and lifestyle of cancer patients.