חידושים באבחון וטיפול מחלות המטו-אונקולוגיות

דר אנטולי נמץ נמץ

יום עיון לחולים המטולוגיים

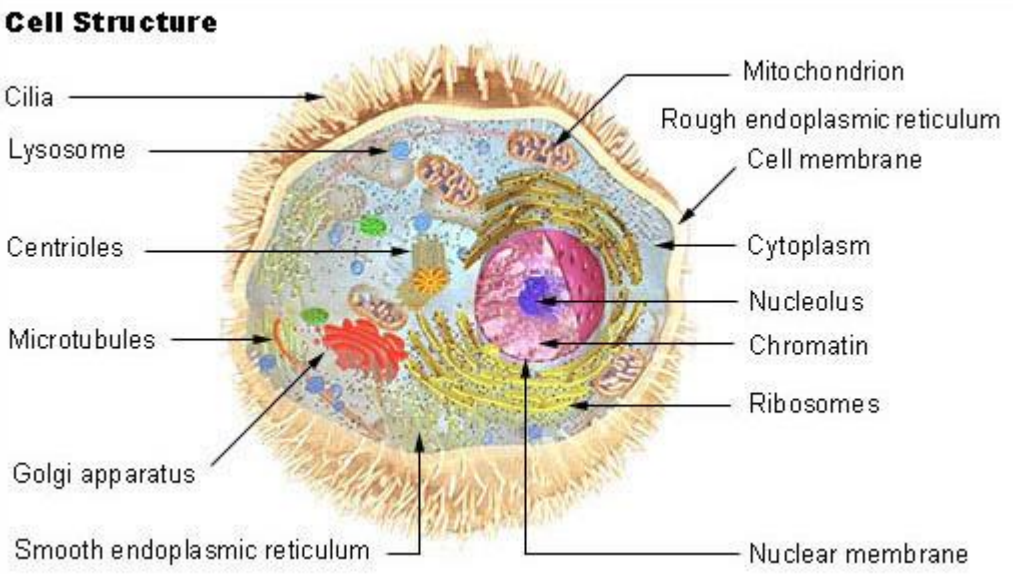
23/09/2019

Agenda

- Diagnostic tools-present and future
  - NGS
  - Liquid biopsy

- New treatment strategies
  - Monoclonal antibodies
  - Small molecules
  - CAR T

New diagnostic tools


Cell Structure
Cilia
Lysosome
Centrioles
Microtubules
Golgi apparatus
Smooth endoplasmic reticulum
Mitochondrion
Rough endoplasmic reticulum
Cell membrane
Cytoplasm
Nucleolus
Chromatin
Ribosomes
Nuclear membrane

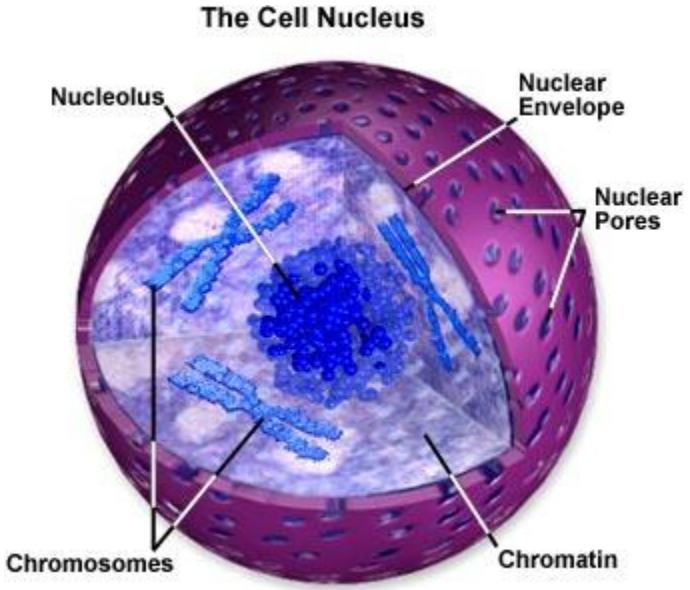
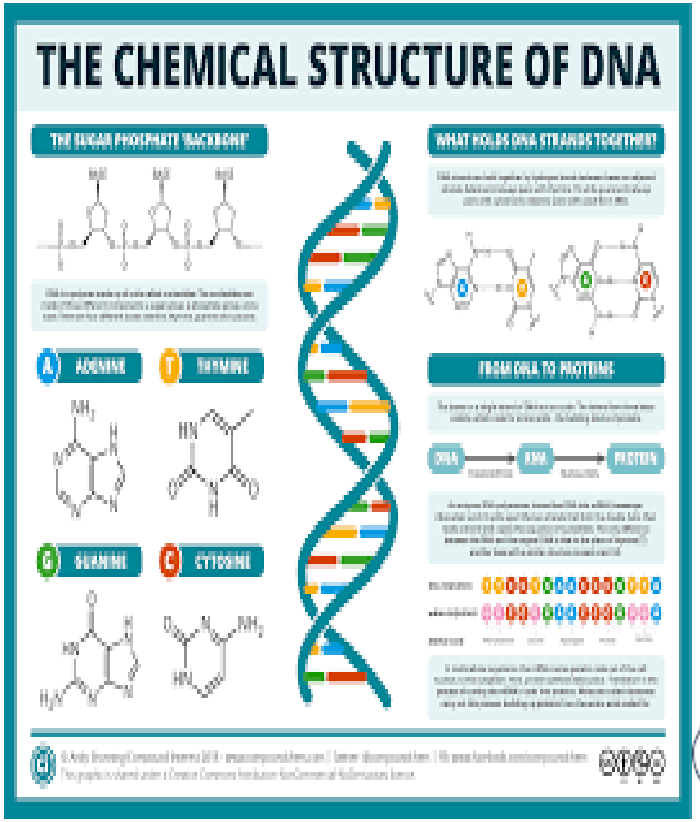
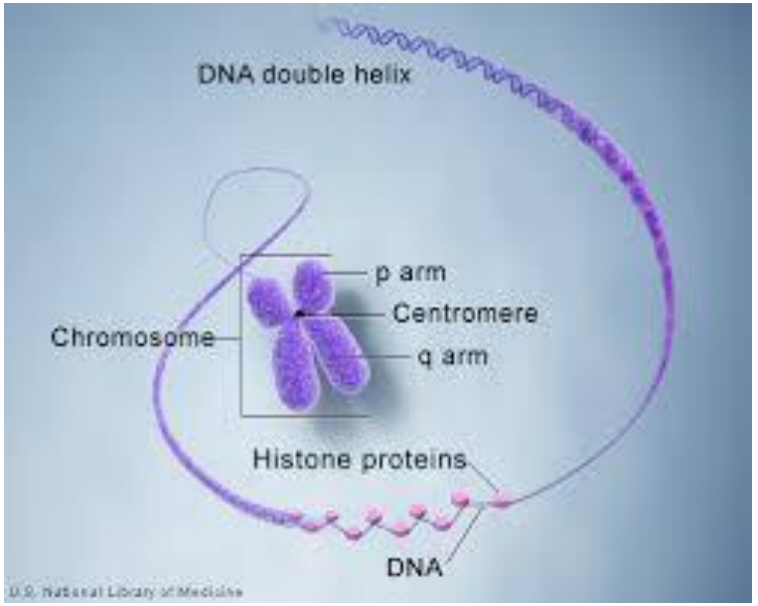
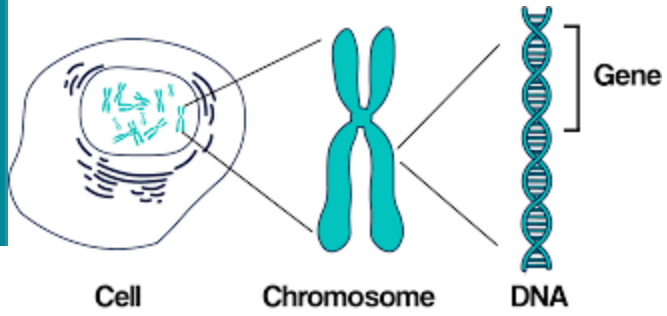

The Cell Nucleus
Nucleolus
Nuclear Envelope
Nuclear Pores
Chromosomes
Chromatin

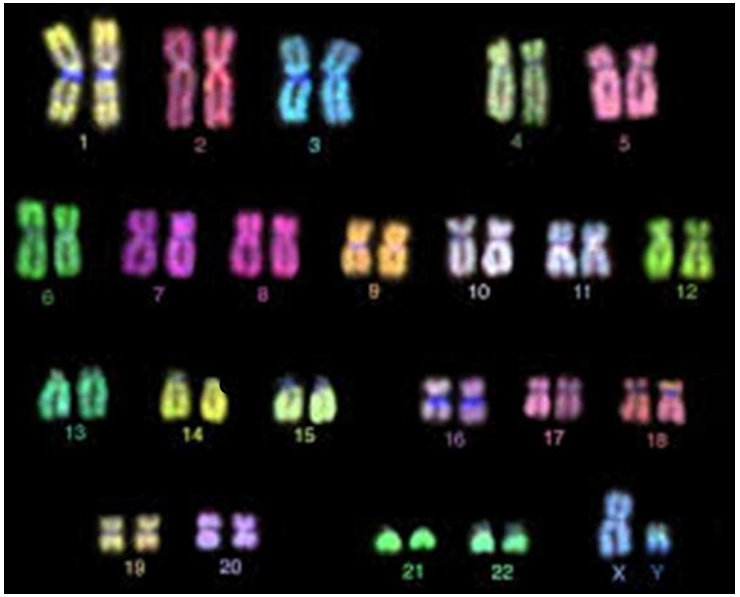
Figure 1


THE CHEMICAL STRUCTURE OF DNA
THE SUGAR PHOSPHATE 'BACKBONE'
WHAT HOLDS DNA STRANDS TOGETHER?
A ADENINE
T THYMINE
G GUANINE
C CYTOSINE
FROM DNA TO PROTEINS
DNA
RNA
PROTEIN

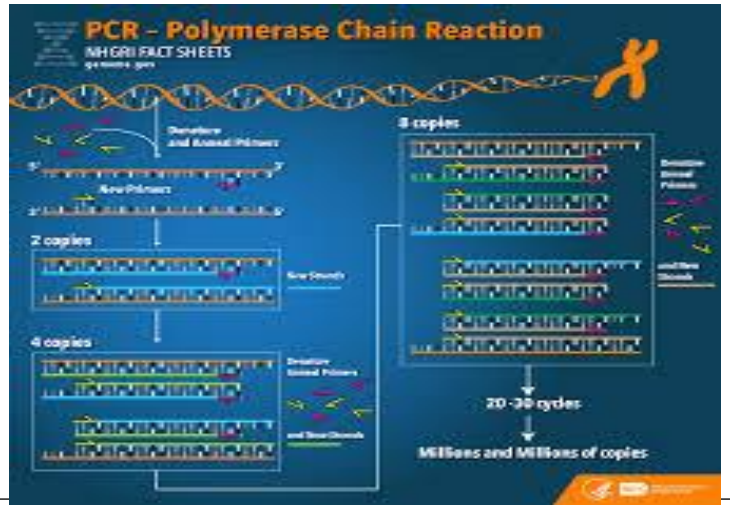

DNA double helix
p arm
Centromere
Chromosome
q arm
Histone proteins
DNA
U.S. National Library of Medicine

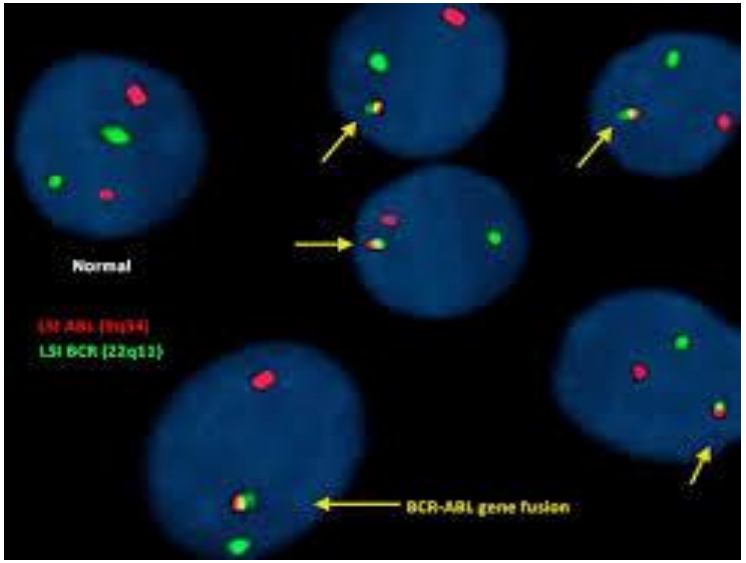

Gene
Cell
Chromosome
DNA

“Old” technologies

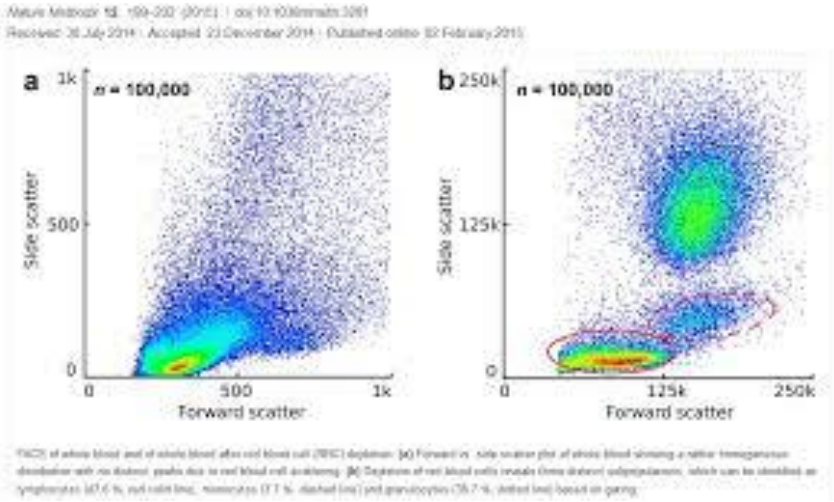


Classical cytogenetics



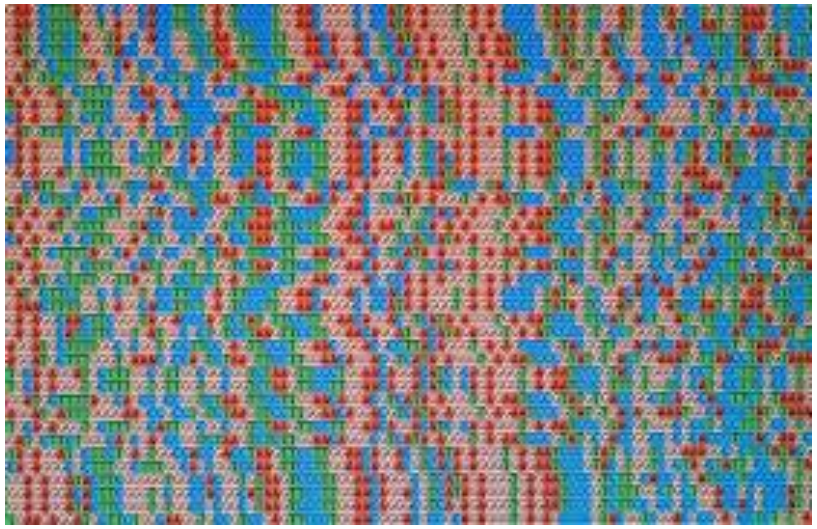


fluorescent in situ hybridization (FISH)

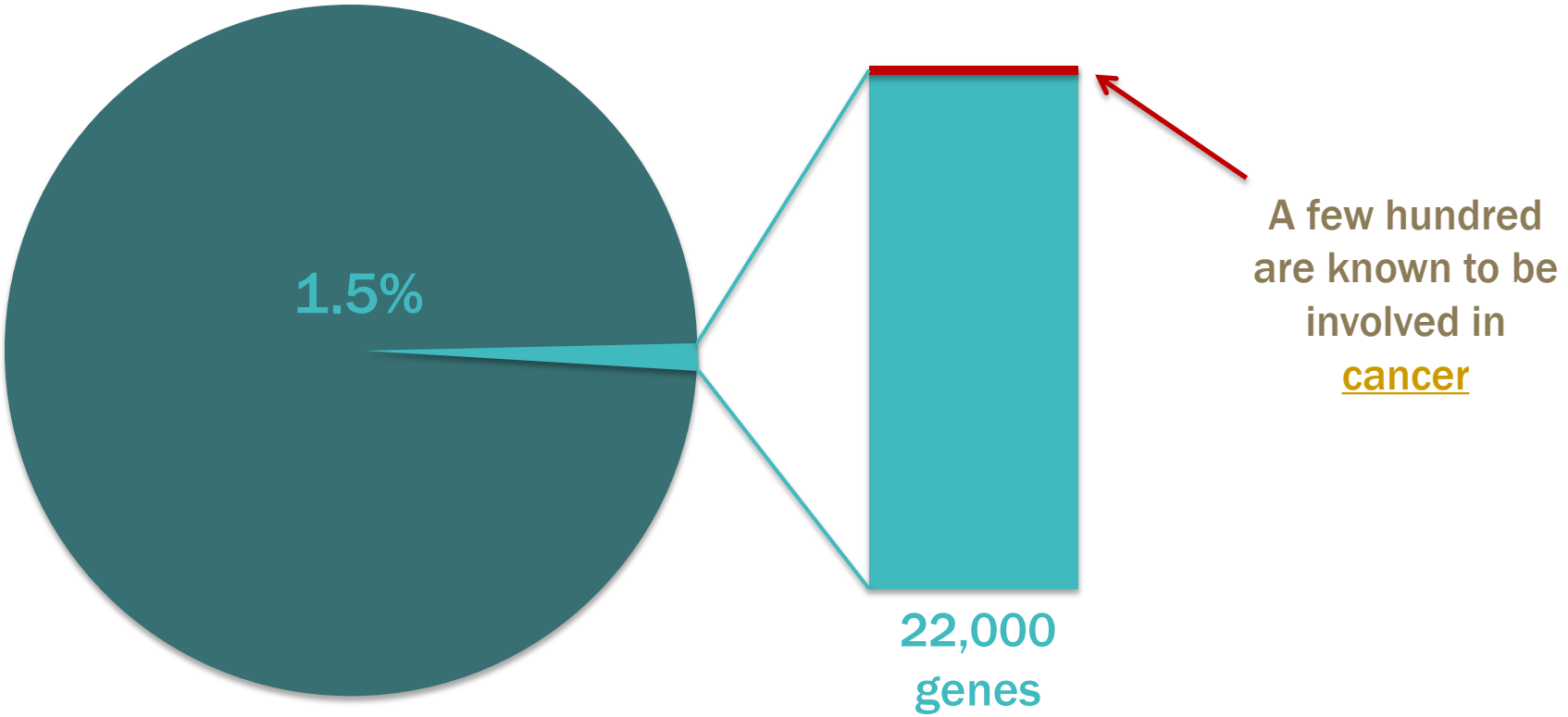


FACS

Human genome

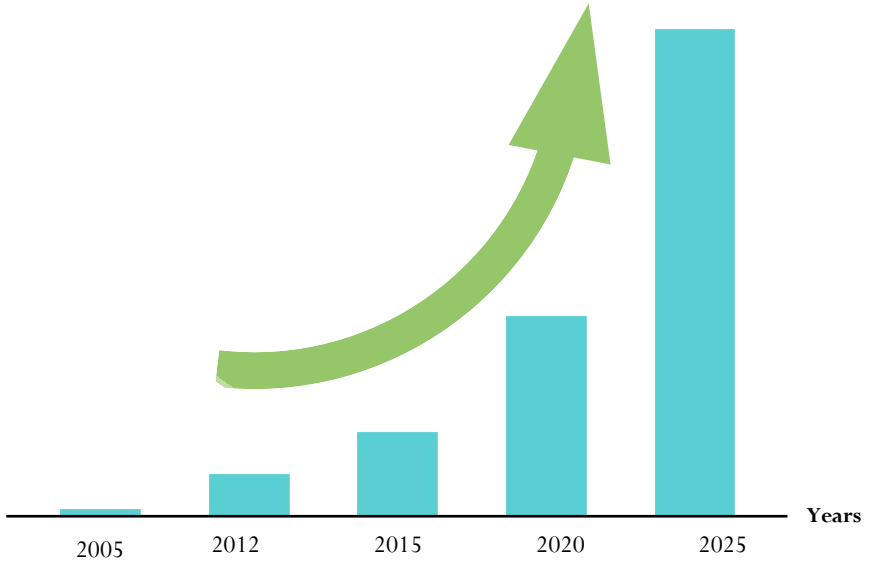


Only a subset of genes are relevant in cancer



The human genome

Number of targeted therapeutics is rising - Knowing which tests to use is becoming challenging

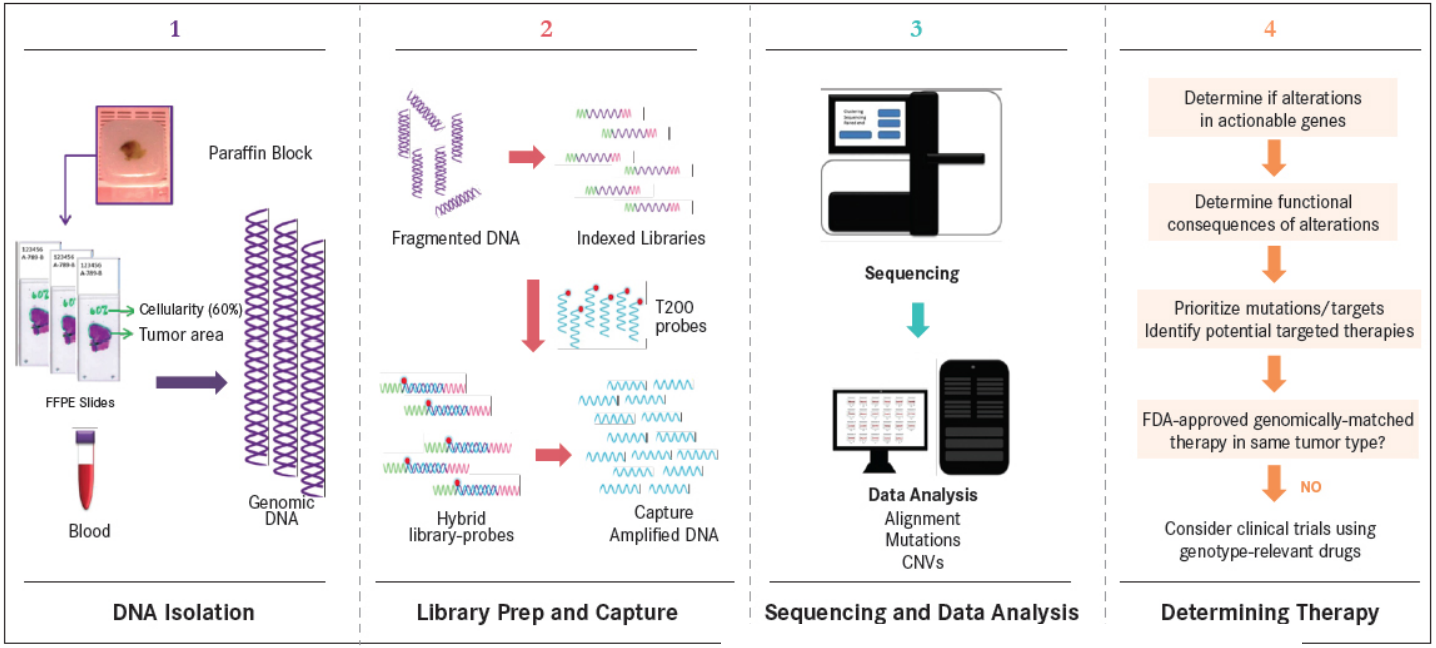


Coming soon

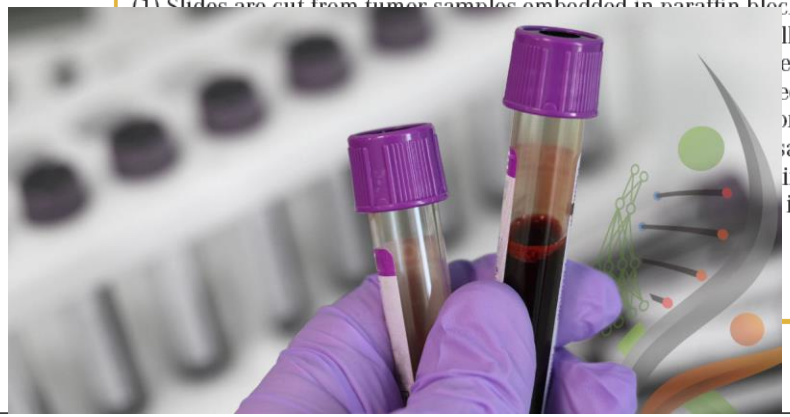
~700 compounds hitting ~150 targets in development

NGS- Next Generation Sequencing

FIGURE 1. Overview of a Potential Next-Generation Sequencing Work Flow

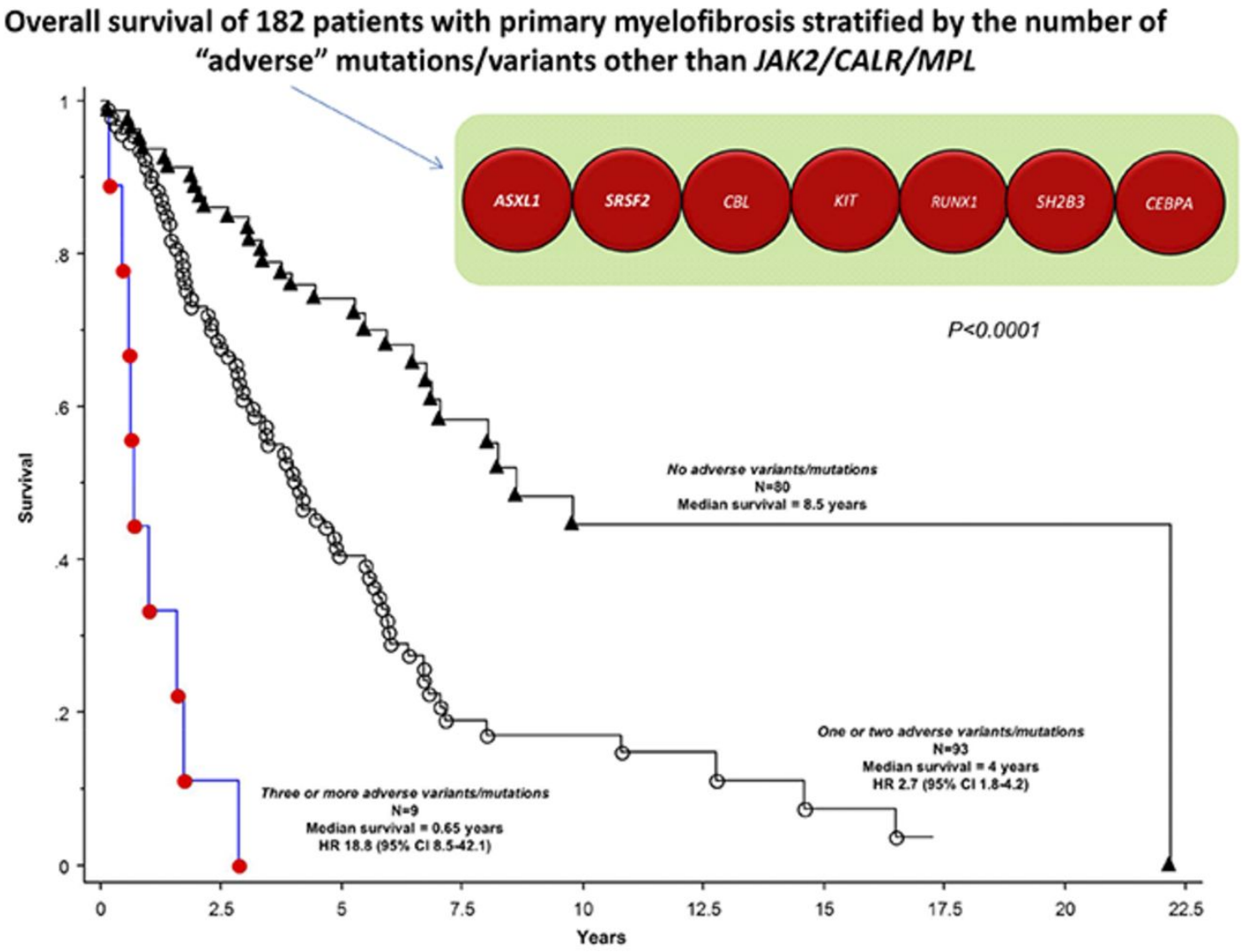


(1) Slides are cut from tumor samples embedded in paraffin blocks. Fo … erformed … llected … formalin- … esh tis … s saliva, … ed and … Libraries) … rmed; … d to DNA … ample … omitted … ification … ns in … in acti … known



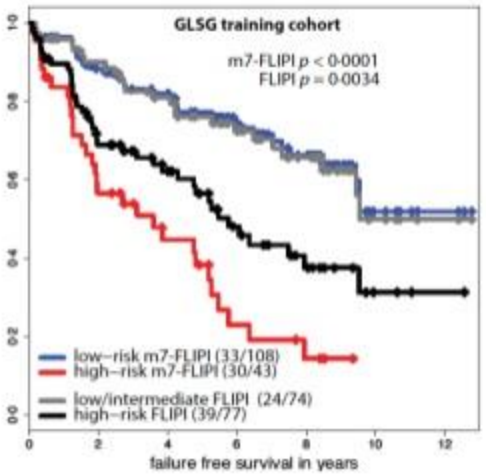
GENOMIC TESTING COOPERATIVE

7 “bad” genes in myelofibrosis



7 “bad” genes in Follicular Lymphoma

M7-FLIPI Improves Prognostication of FL Patients Receiving Chemoimmunotherapy



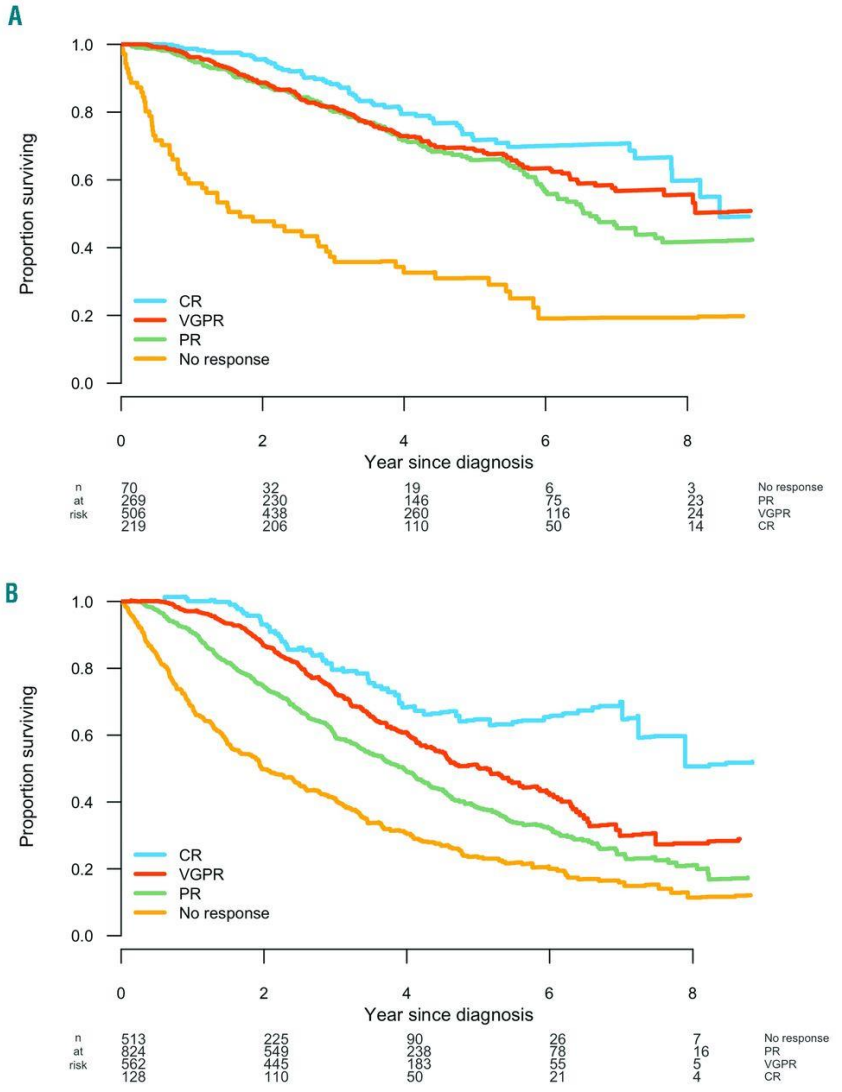
- FLIPI
- ECOG PS
- EZH2, ARID1A, MEF2B, EP300, FOX01, CREBBP, and CARD11

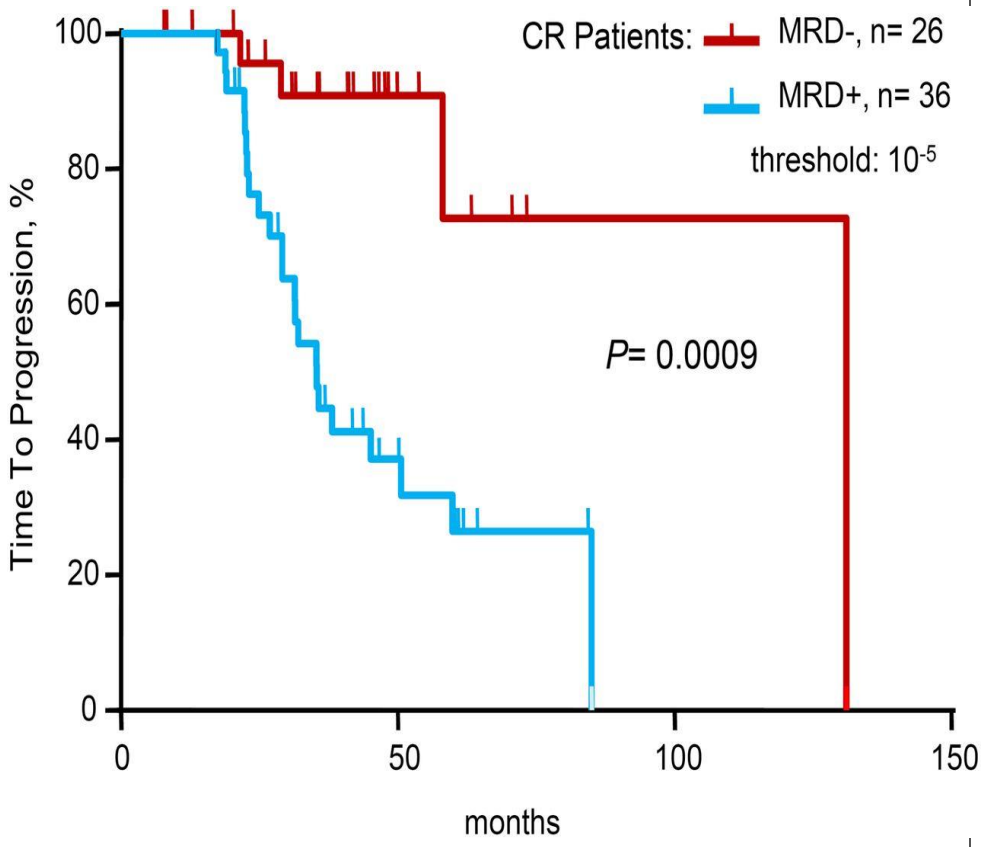
	5-year FFS (%)	5-year OS
FLIPI low/int	76	91
FLIPI high	57	75
M7-FLIPI low	77	90
M7-FLIPI high	38	65

GLSG = German Low-Grade Lymphoma Study Group; FFS = failure-free survival.
Pastore et al, 2015.

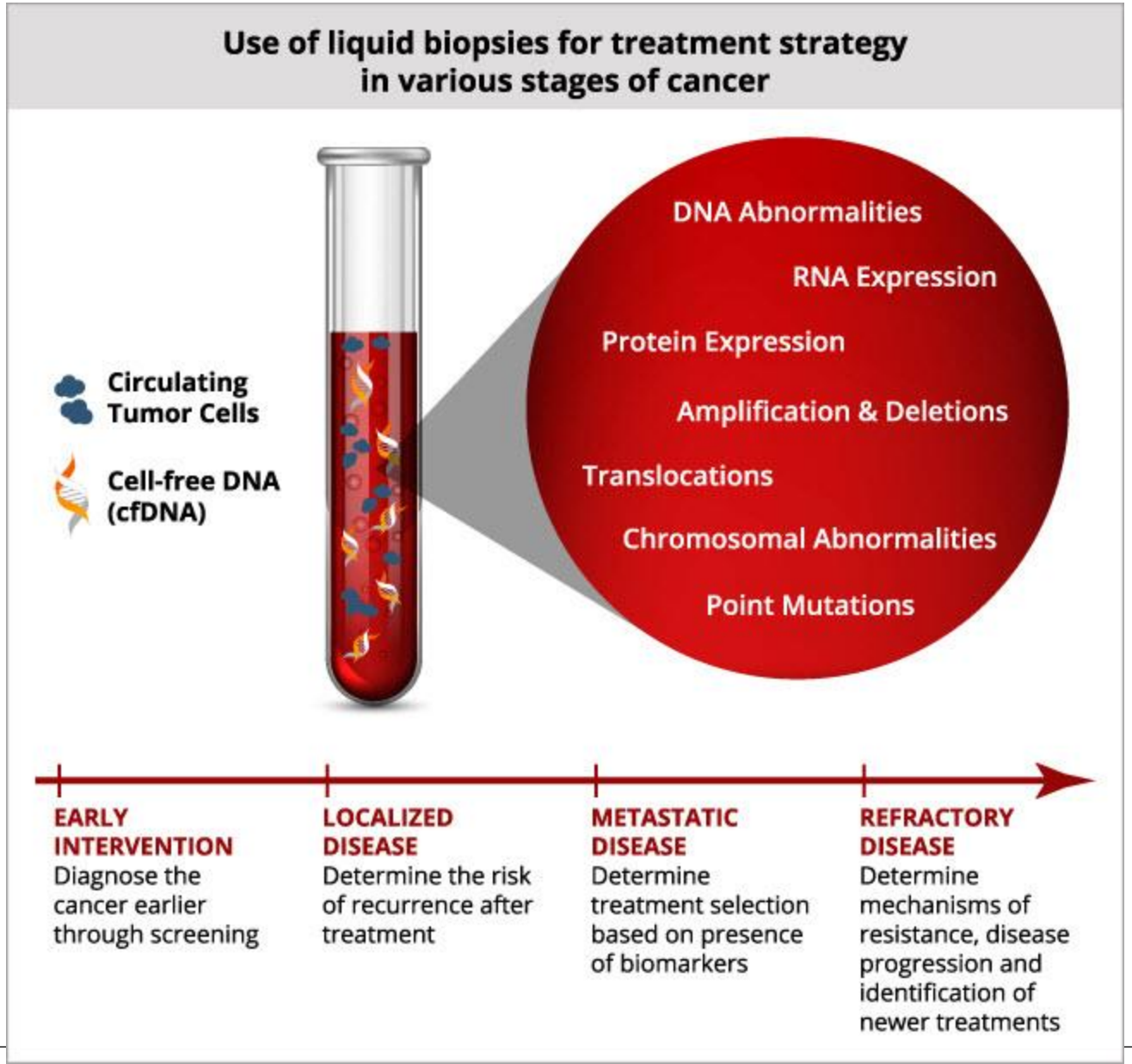
i3Health
Education on Point™

MRD (minimal residual disease) in Myeloma pts



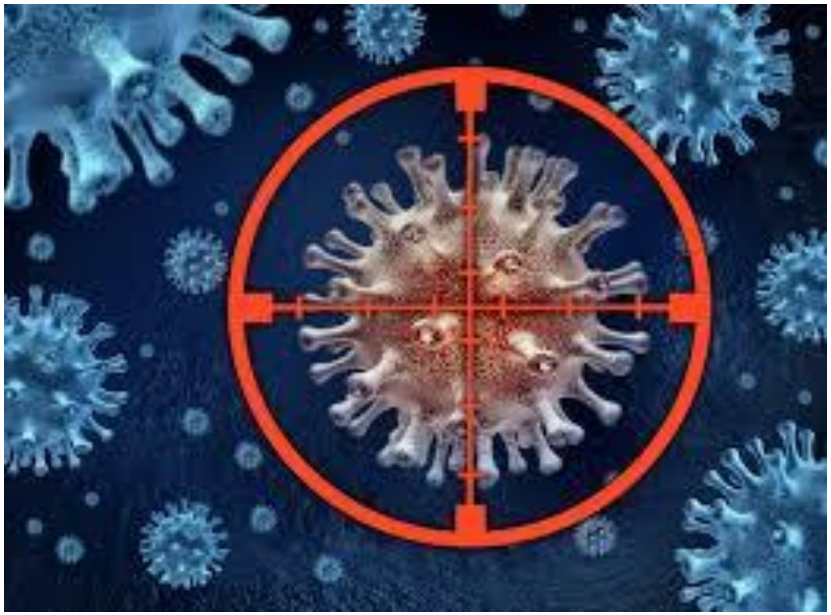


Liquid biopsy

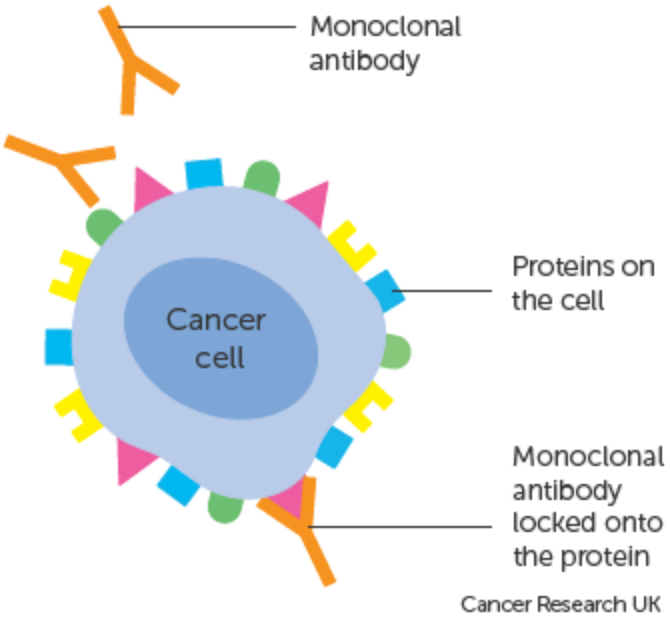


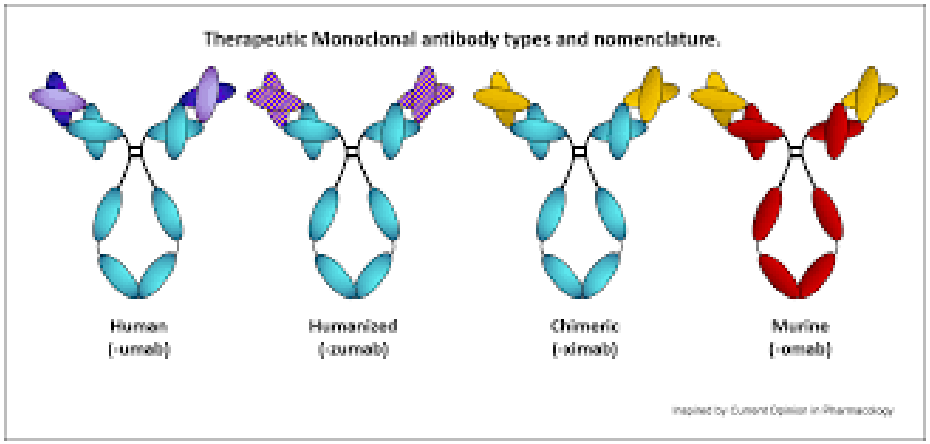
New treatment strategies

Target therapy



Monoclonal Antibodies





Rituximab : Chimeric anti-CD20 monoclonal antibody

Mabthera

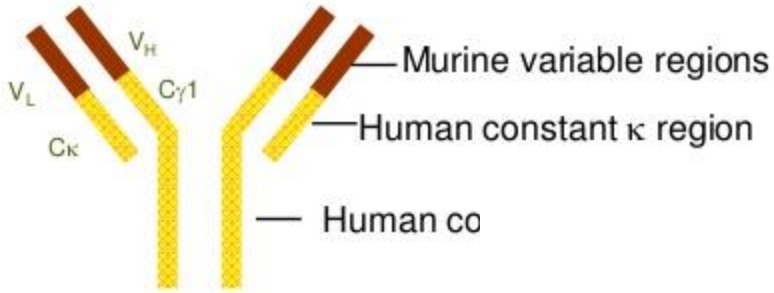
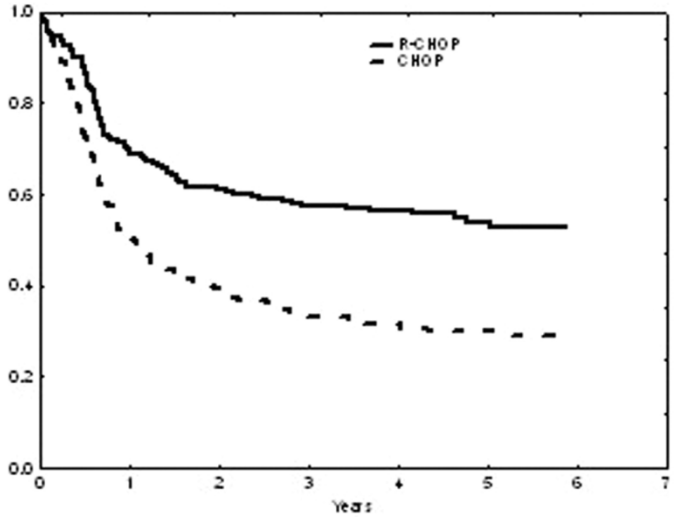


Figure: Progression-free survival



Anti- CD20 mAb

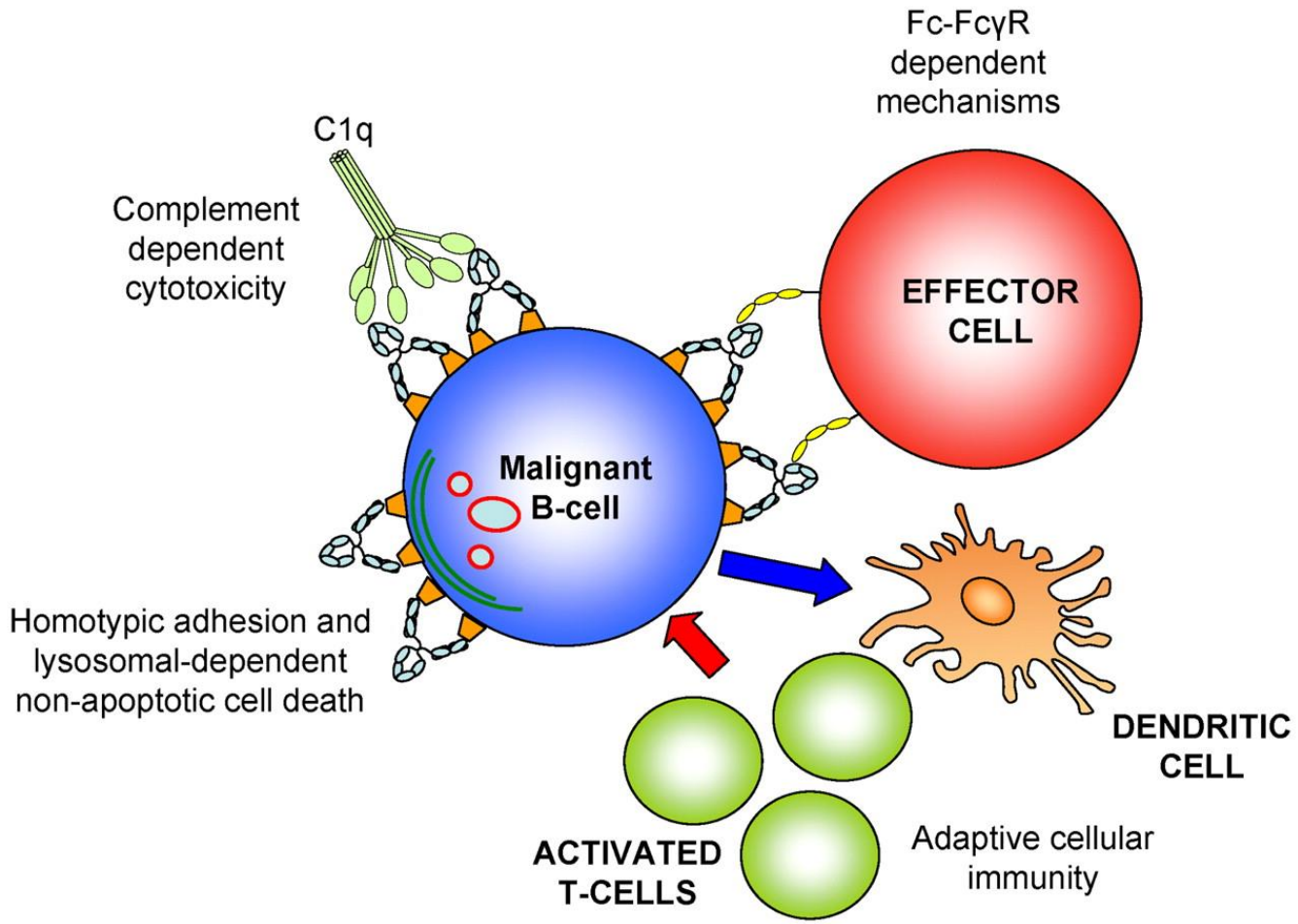
1997

first FDA-approved monoclonal antibody (mAb)

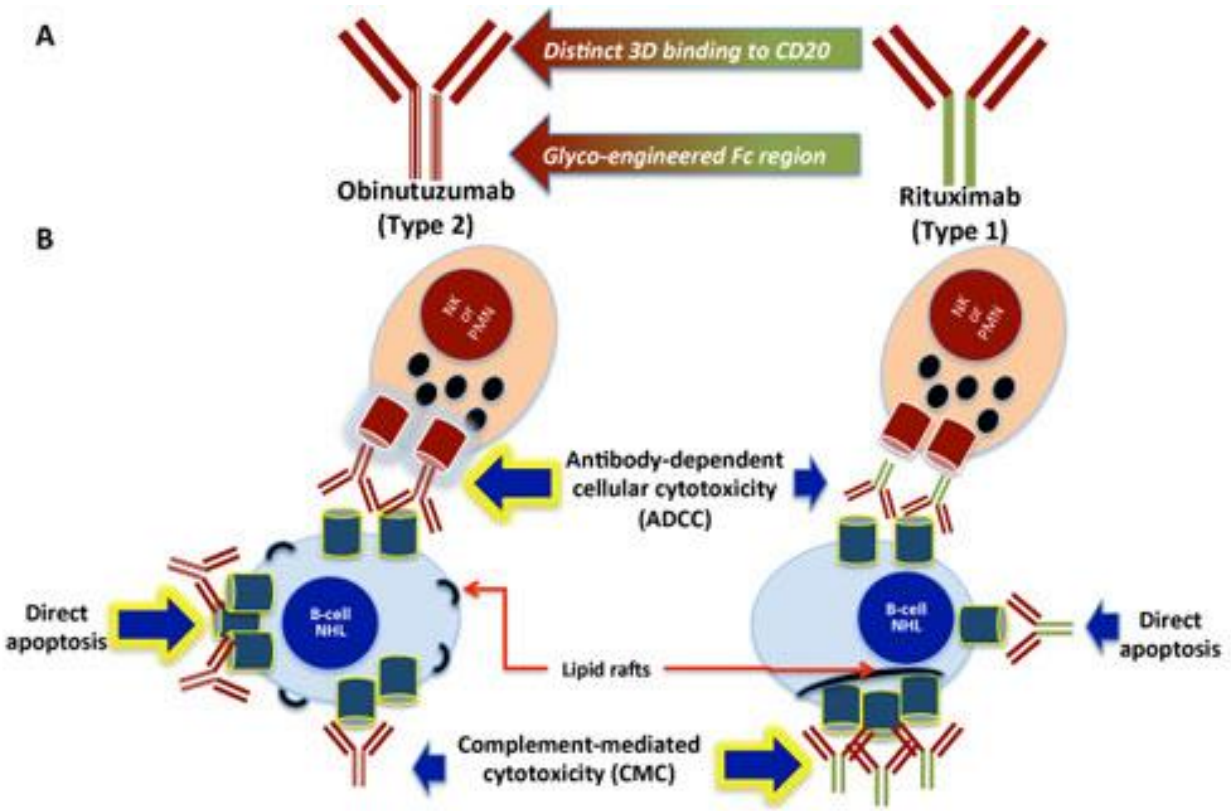
Rituximab (chimeric anti-CD20 mAb) for the treatment of B-NHL cells

Subsequently, over 20 approved mAbs have been in use clinically for the treatment of various cancers and several non-cancer related diseases.

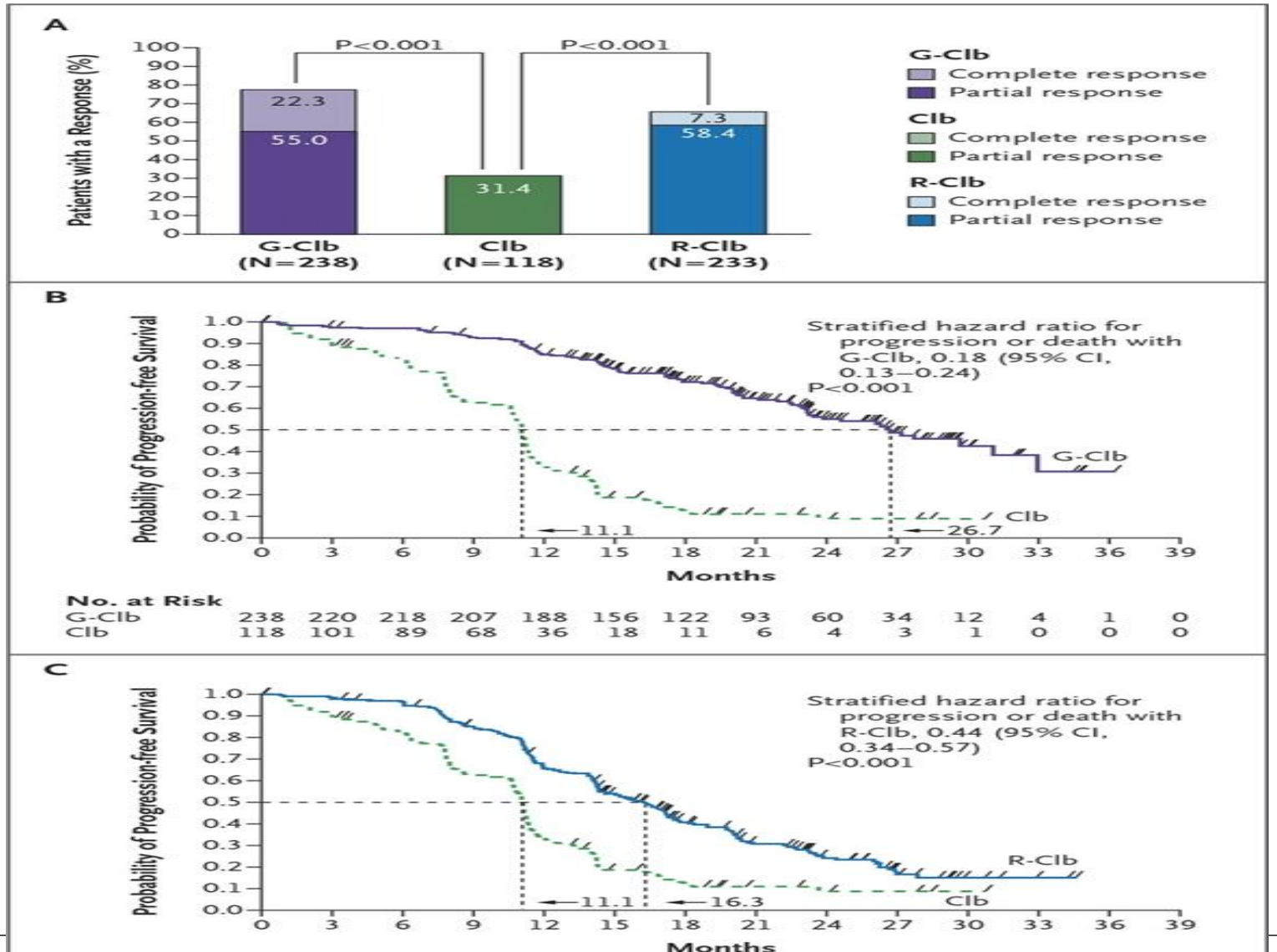
Mechanism of action



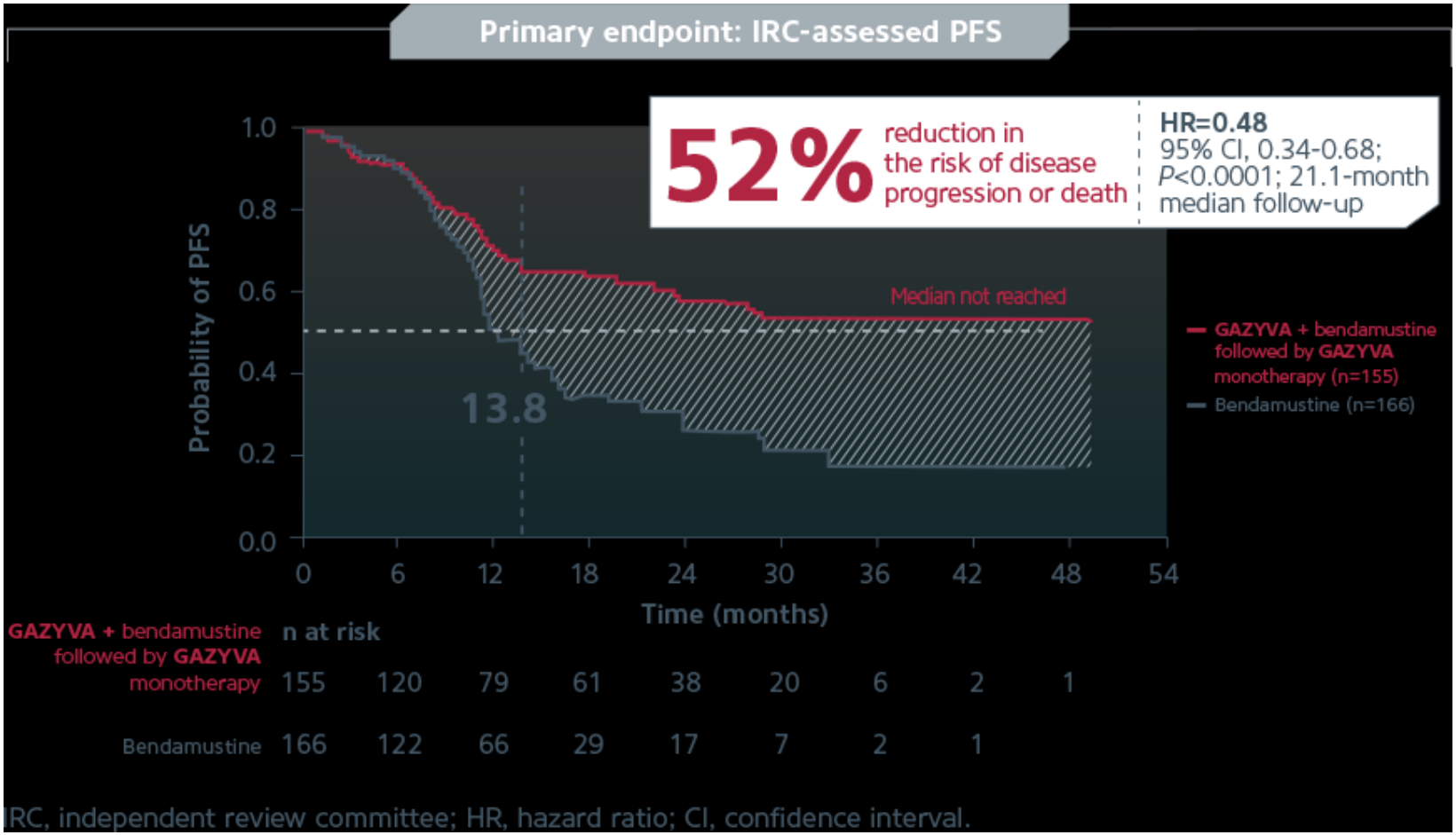
Gazyva


A
Distinct 3D binding to CD20
Glyco-engineered Fc region
Obinutuzumab
(Type 2)
Rituximab
(Type 1)
B
NK or PMN
Antibody-dependent
cellular cytotoxicity
(ADCC)
Direct
apoptosis
B-cell
NHL
Lipid rafts
Direct
apoptosis
Complement-mediated
cytotoxicity (CMC)

Gazyva+Leukeran in CLL

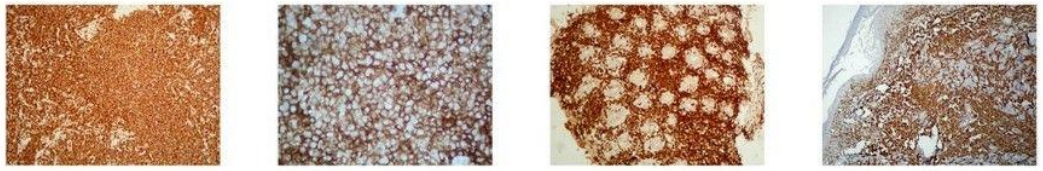


Gazyva + chemo in FL



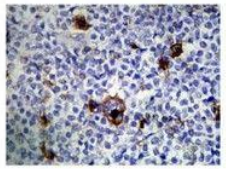
Anti CD30-Brentuximab Vedotin ADCETRIX

Expression of CD30 in neoplasms

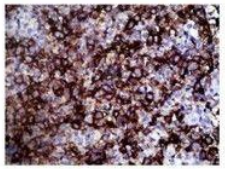


A. Case of ALCL involving lymph node and colon, both. The first two images show diffuse and strong membranous expression of CD30 in the tumor cells. The third image shows infiltrate of CD30 positive cells in the lamina.

B. Case of cutaneous lymphomatoid papu--losis. CD30+ tumor

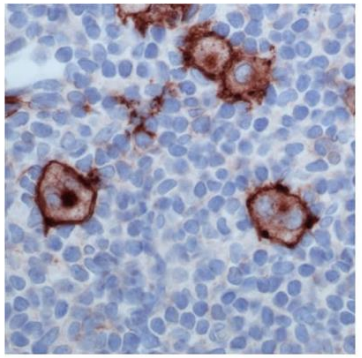


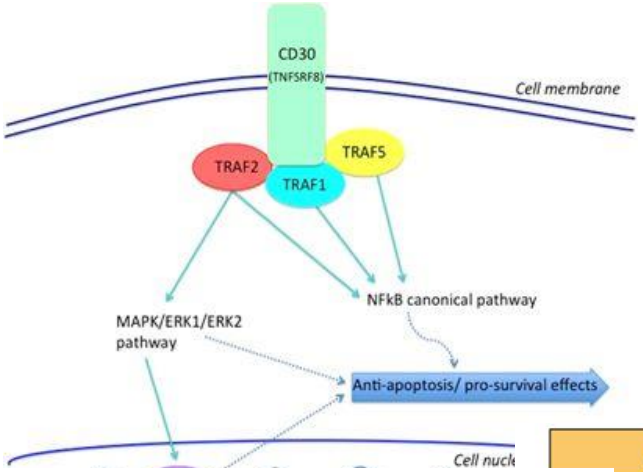
C. CHL, expressing CD30 in membranous pattern with golgi region accentuation.



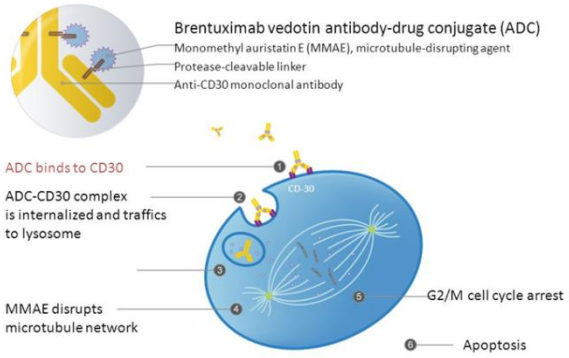
D. Mediastinal gray zone lymphoma. CD30+ tumor cells

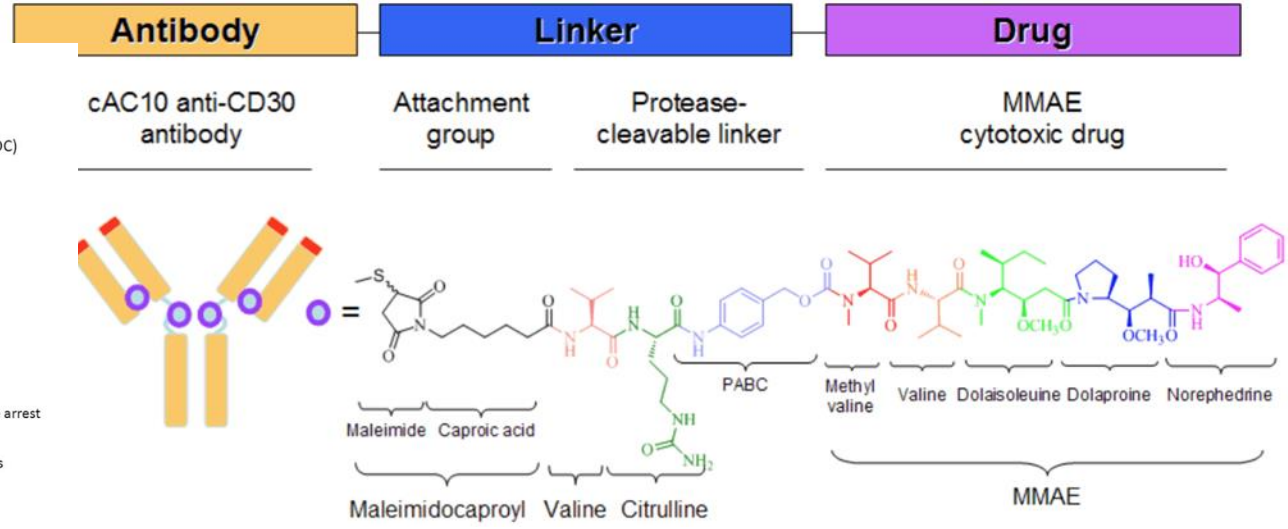
E. CHL, CD cells



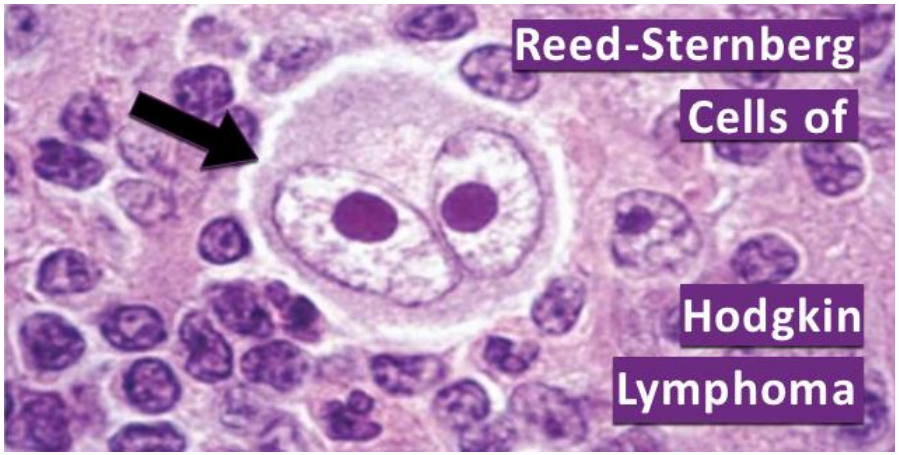


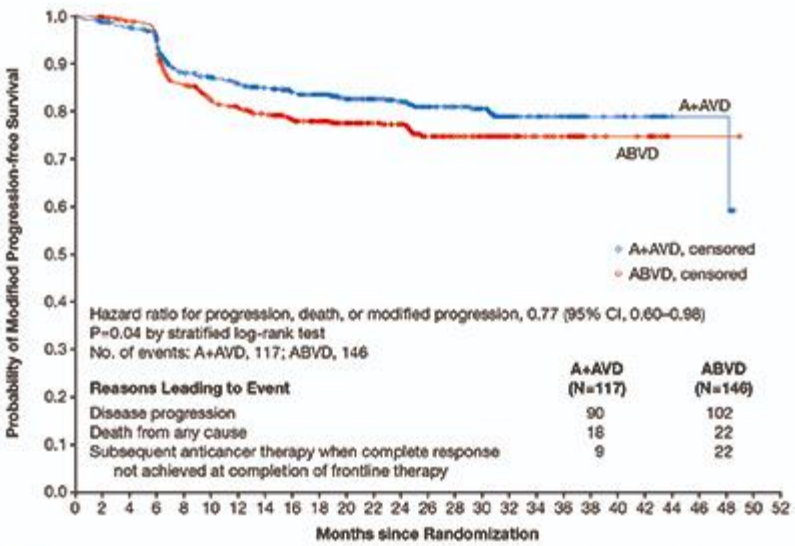
Brentuximab Vedotin

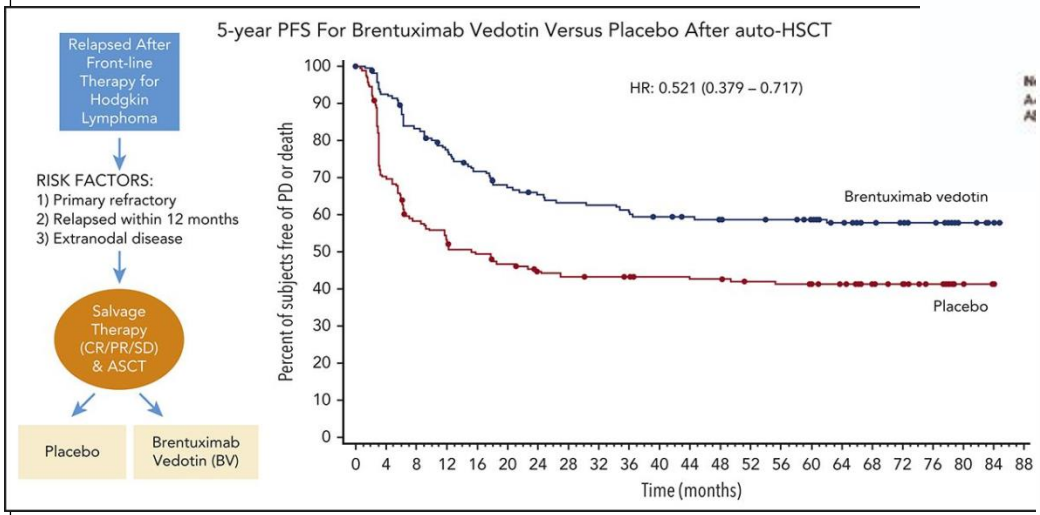




BV in Hodgkin's Lymphoma







Brentuximab Vedotin: Adverse Events

Most common adverse events (≥ 20%):

- Peripheral sensory neuropathy
- Neutropenia
- Fatigue
- Nausea
- Anemia
- Rash
- Upper respiratory tract infection
- Diarrhea
- Rash
- Pyrexia
- Thrombocytopenia
- Cough
- Vomiting

Brentuximab vedotin [package insert]. 2015.

Immunity and Cancer

Antibody

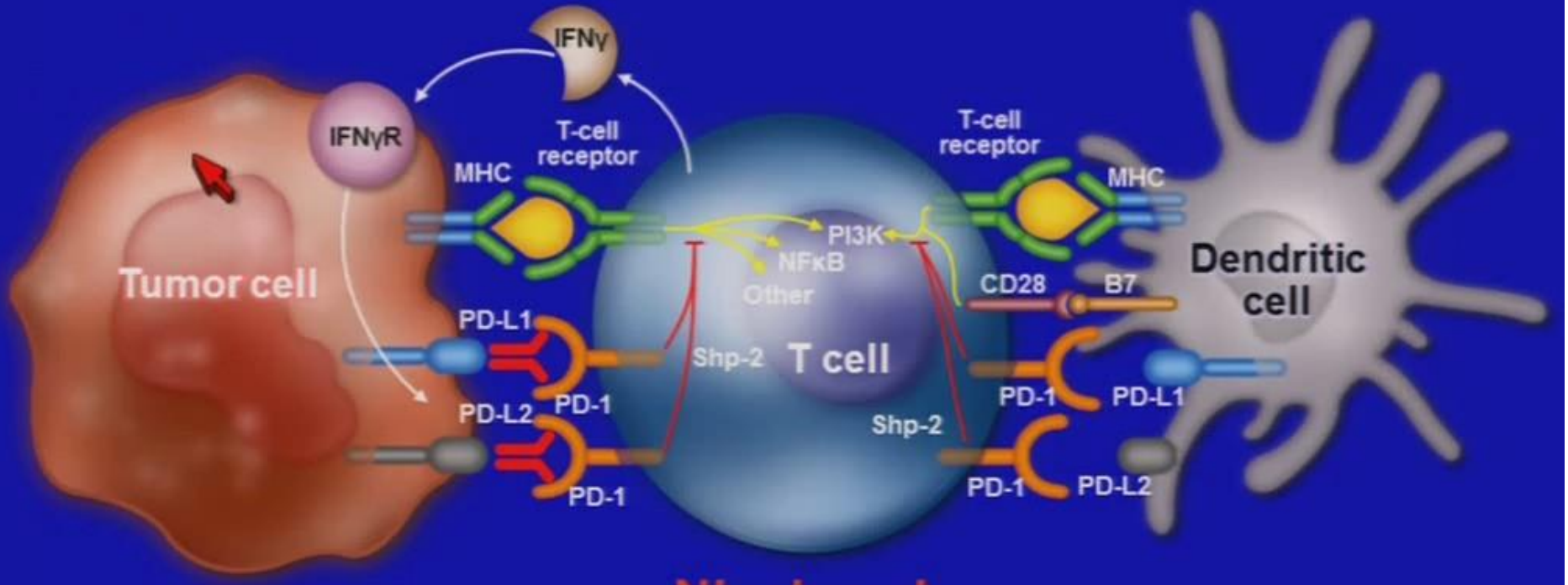
Artwork by Jeanne Kelly. ©2004

NATIONAL CANCER INSTITUTE

Role of PD-1 Pathway in Suppressing Anti-tumor Immunity

Recognition of tumor by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 up-regulation on tumor

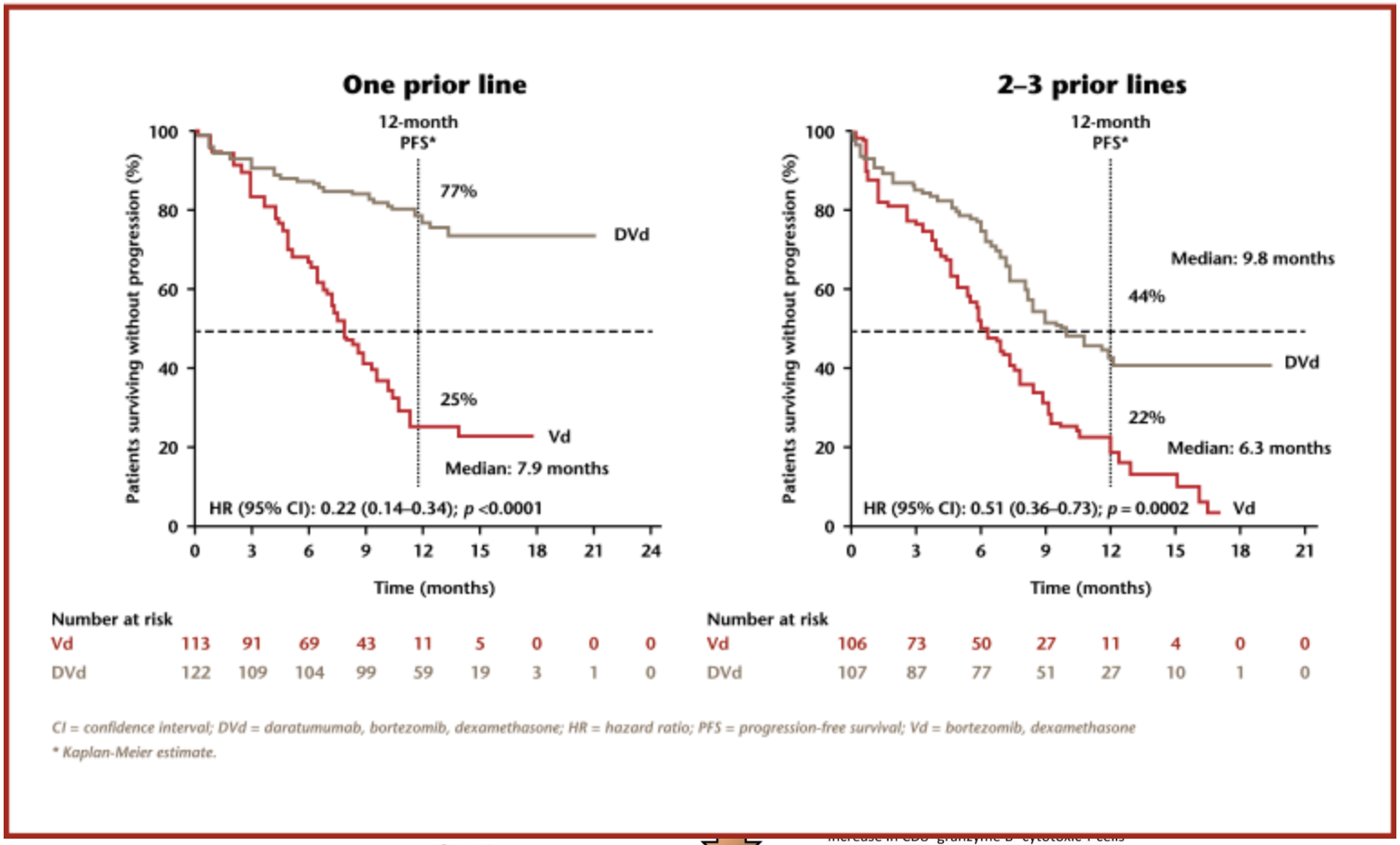
Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells



Nivolumab
PD-1 Receptor Blocking Ab

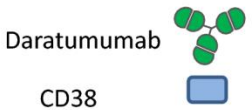
Anti CD 38 – Daratomumab Multiple Myeloma

Figure 2. PFS stratified by prior lines of treatment



CI = confidence interval; DVd = daratumumab, bortezomib, dexamethasone; HR = hazard ratio; PFS = progression-free survival; Vd = bortezomib, dexamethasone

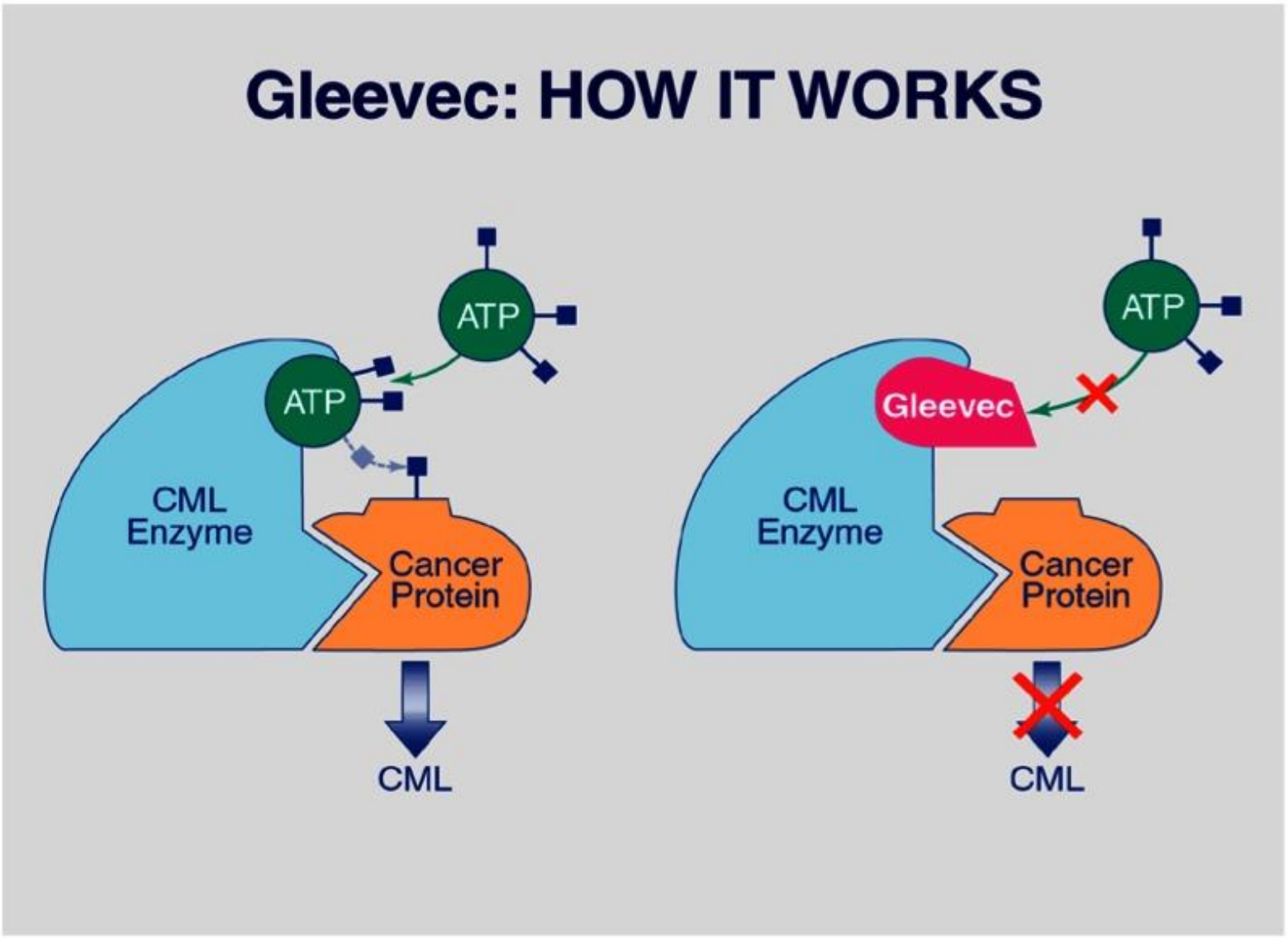
** Kaplan-Meier estimate.*



Myeloma cell death

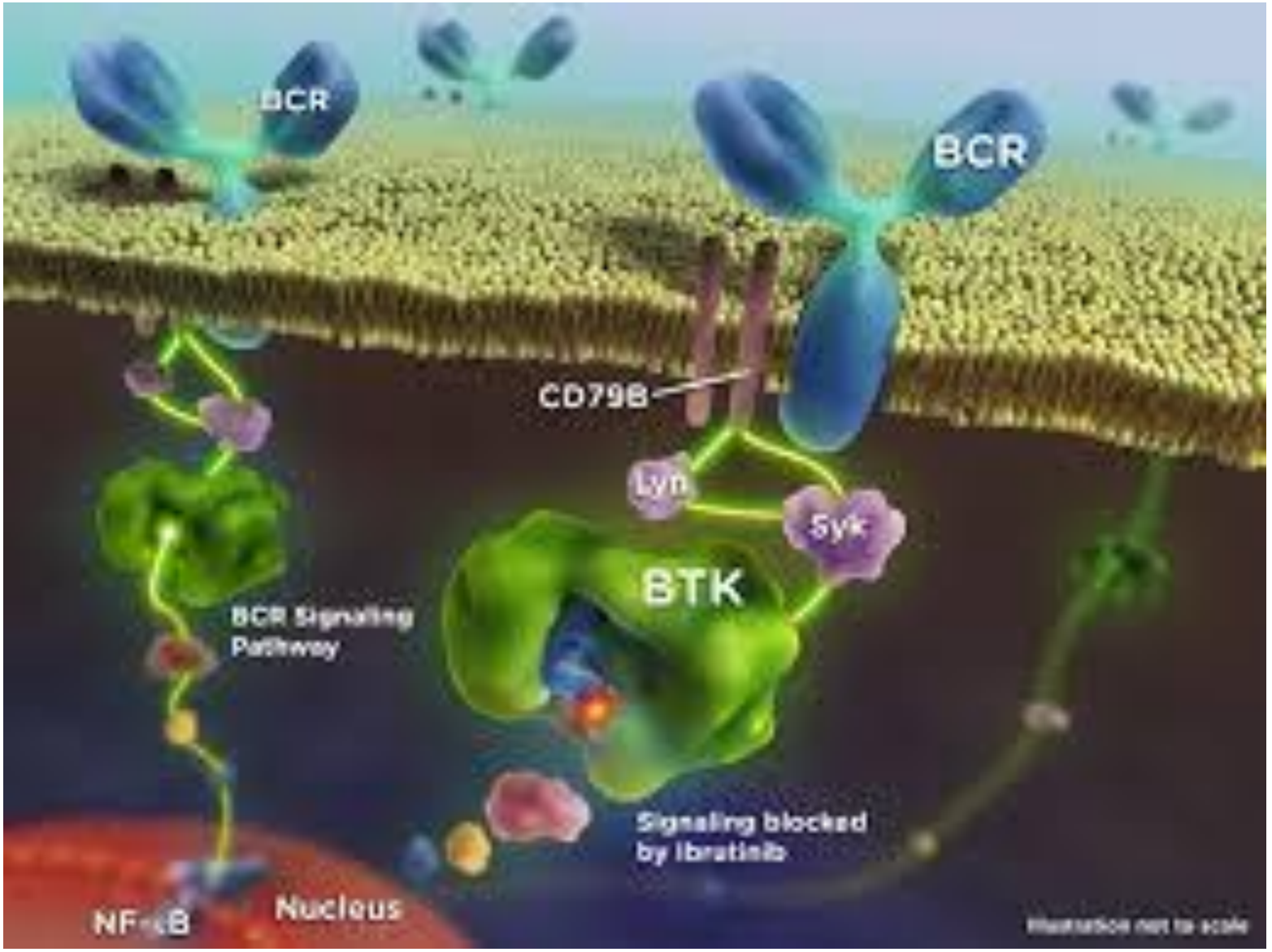
and CD4+ helper T cells

Small molecules



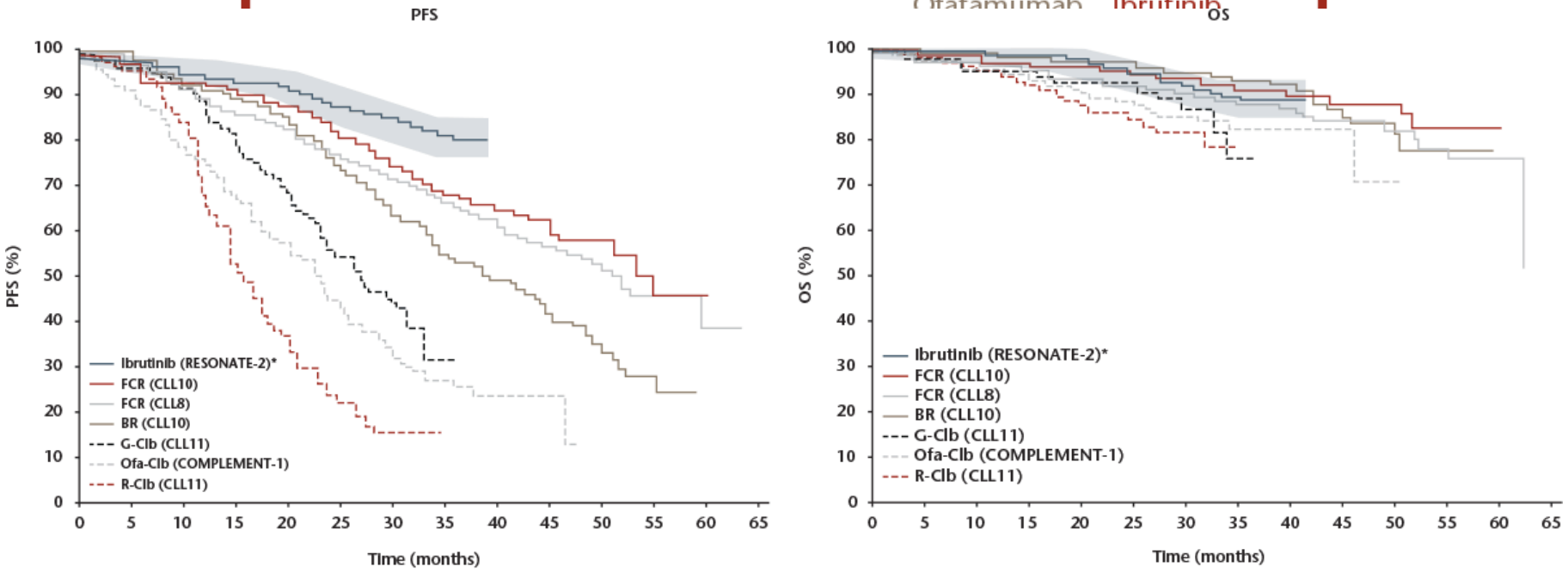
March 15, 2001

TKI in CLL


BCR
BCR
CD79B
Lyn
Syk
BTK
BCR Signaling Pathway
Signaling blocked by Ibrutinib
NF-κB
Nucleus

Ibrutinib in CLL

Figure 1. Progression-free survival

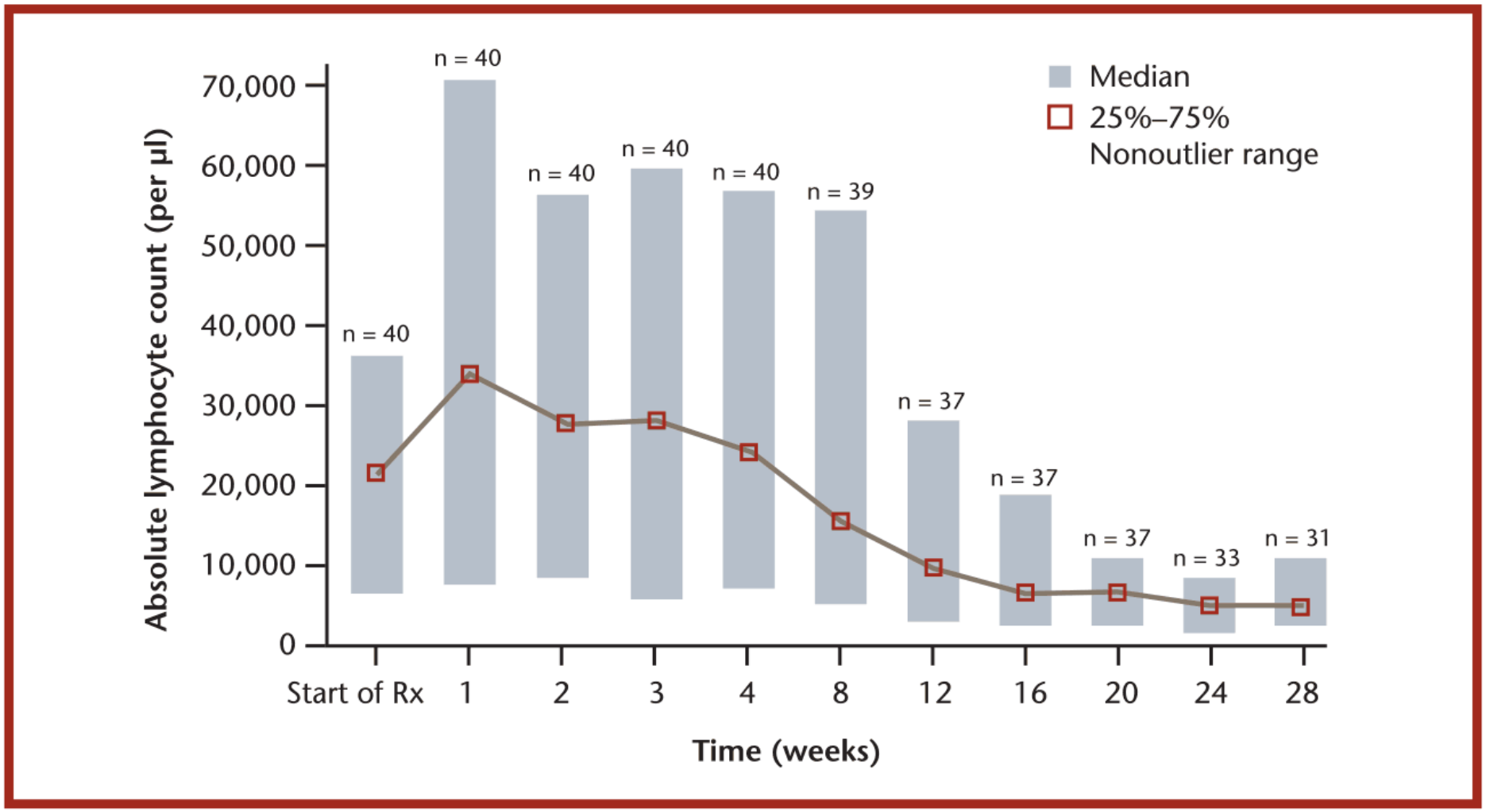


BR = bendamustine, rituximab; FCR = fludarabine, cyclophosphamide, rituximab; G-Clb = obinutuzumab, chlorambucil; Ofa-Clb = ofatumumab, chlorambucil; OS = overall survival; PFS = progression-free survival; R-Clb = rituximab, chlorambucil

** Shaded area represents 95% confidence band with ibrutinib.*

CI = confidence interval; NR = not reached

Figure 1: Transient Lymphocytosis on iR



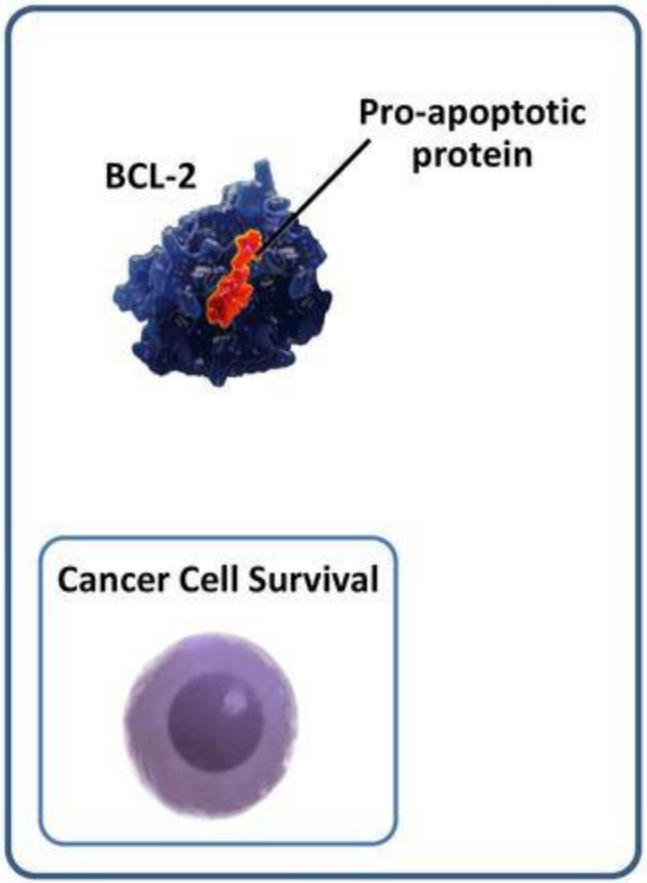
תופעות לוואי של IRBESARTAN

	Previously untreated [33, 62]	Previously treated [8, 9, 11, 20, 34, 65, 92]
Total (number)	165	730
Diarrhea, any grade	42-68	29-82
Grade ≥3	4-13	0-7
Fatigue, any grade	30-32	21-98
Grade ≥3	1-3	2-4
Arthralgia, any grade	16-23	17
Grade ≥3	0	0-1
Bleeding, any grade	NR	10-50
Grade ≥3 *	4	6-8
AF, any grade	6	4-14
Grade ≥3	1	2-12
Neutropenia, any grade	16	16-48
Grade ≥3	10-17	0-11
Anemia, any grade	16-19	16-48
Grade ≥3	0-6	0-16
Thrombocytopenia, any grade	13	17-52
Grade ≥3	2-3	4-13
Infection, any grade	NR	70-78
Grade ≥3	10	24-28
Febrile neutropenia, any grade	2	3
Pneumonia, any grade	NR	10-20
URTI, any grade	17-26	16-28
Cataract, any grade	NR	3

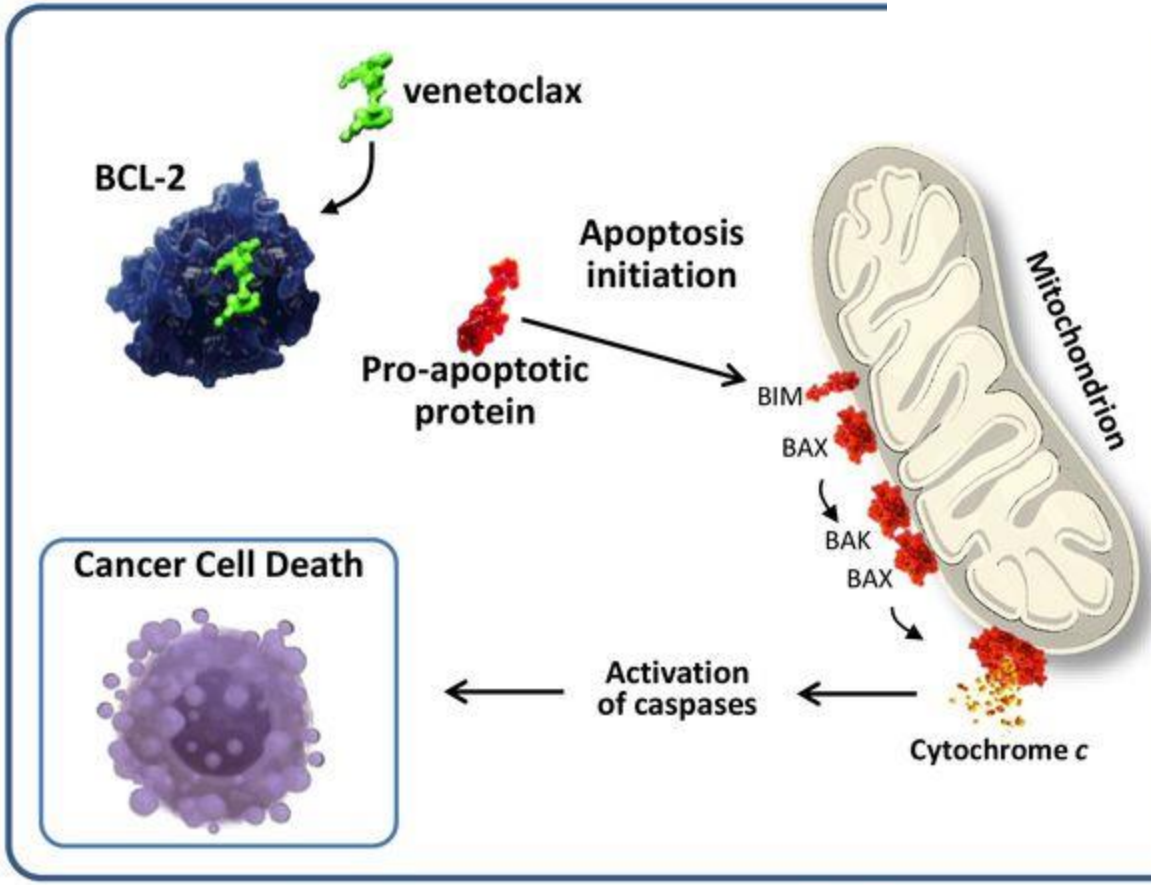
Values represent percentages of patients affected. AF: atrial fibrillation, URTI: upper respiratory tract infection, NR: not reported.

Venetoclax is a BCL-2 Selective Inhibitor

Promotes apoptosis through selective inhibition of BCL-2

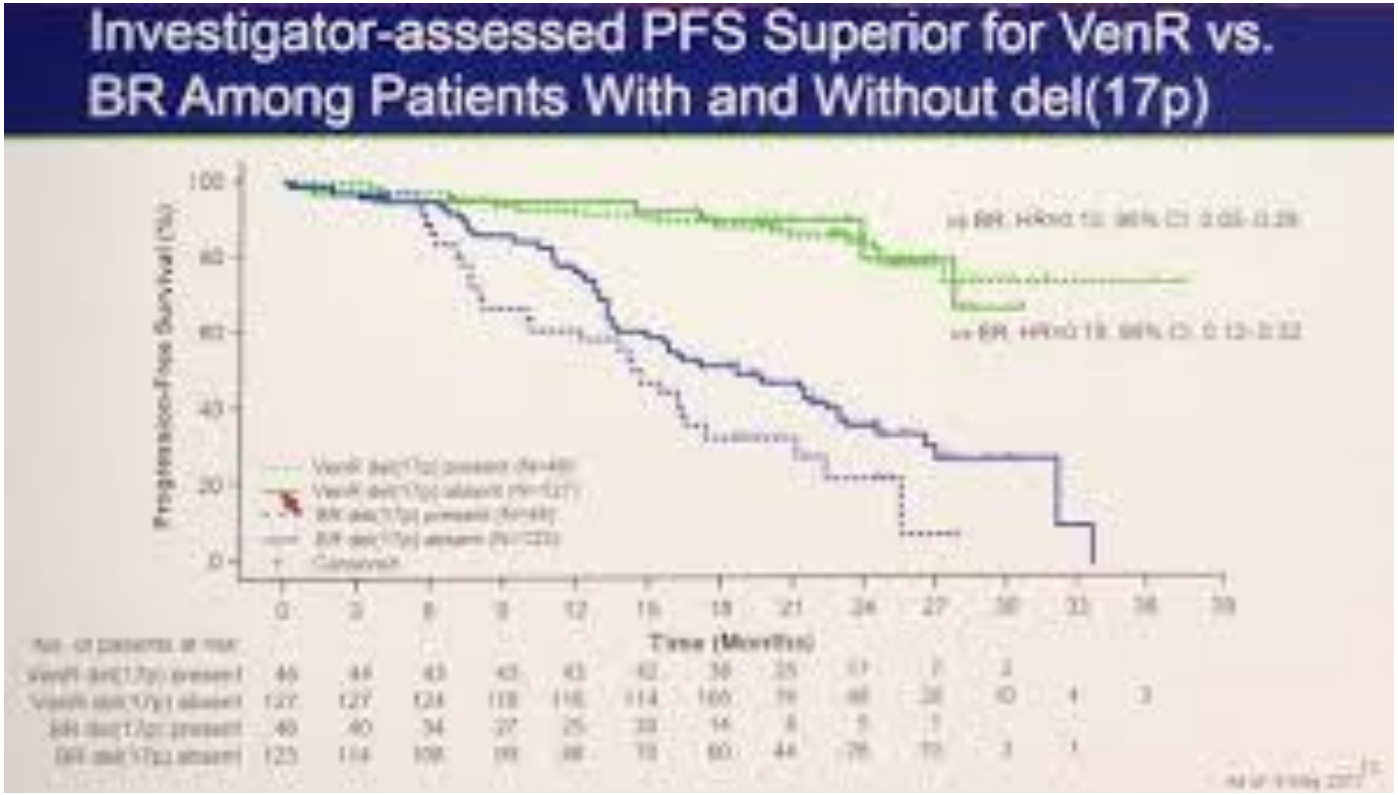


BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1-3]



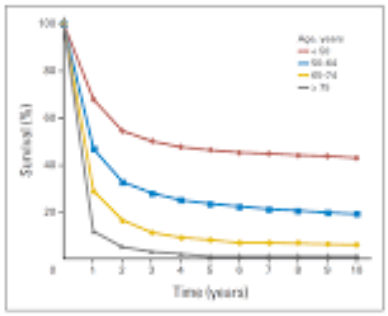
Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).[4-6]

Venetoclax in CLL



Venetoclax +Vidaza in AML

AML Survival by Age



FDA APPROVED

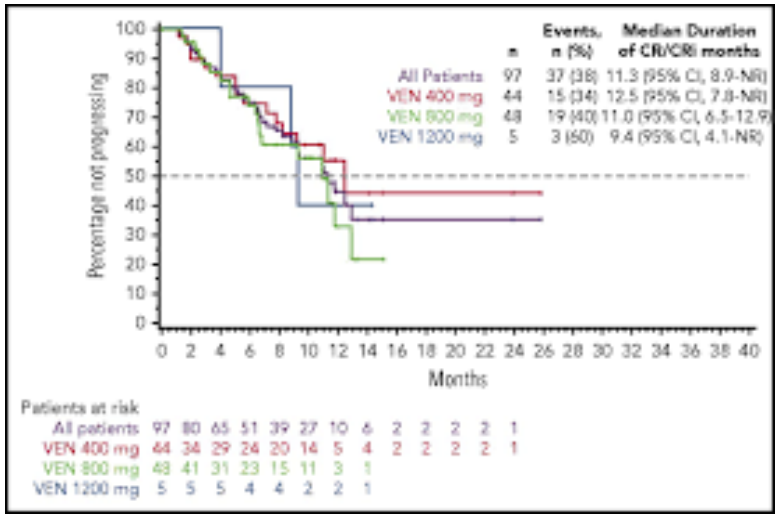
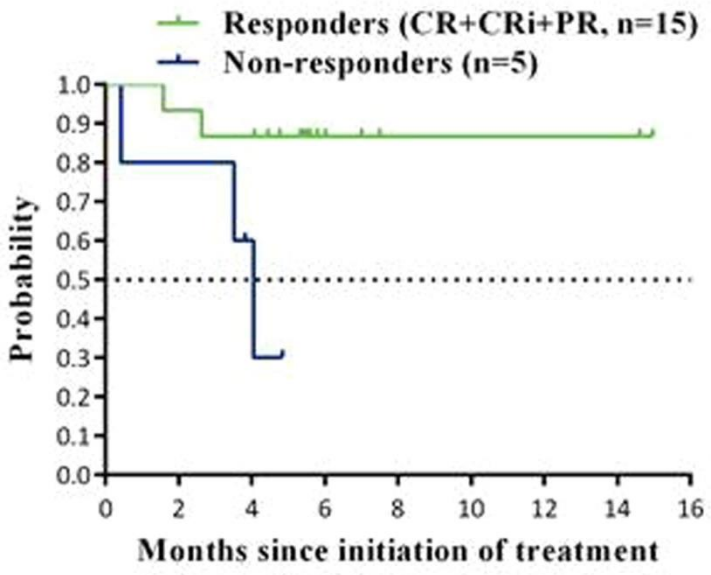
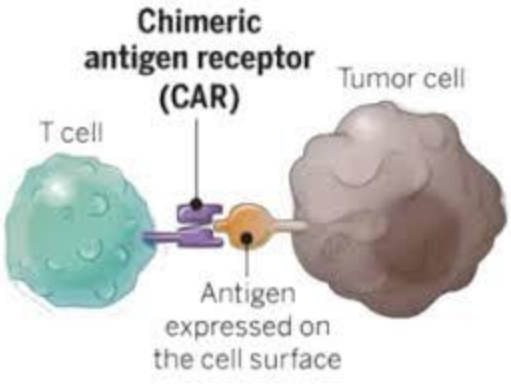


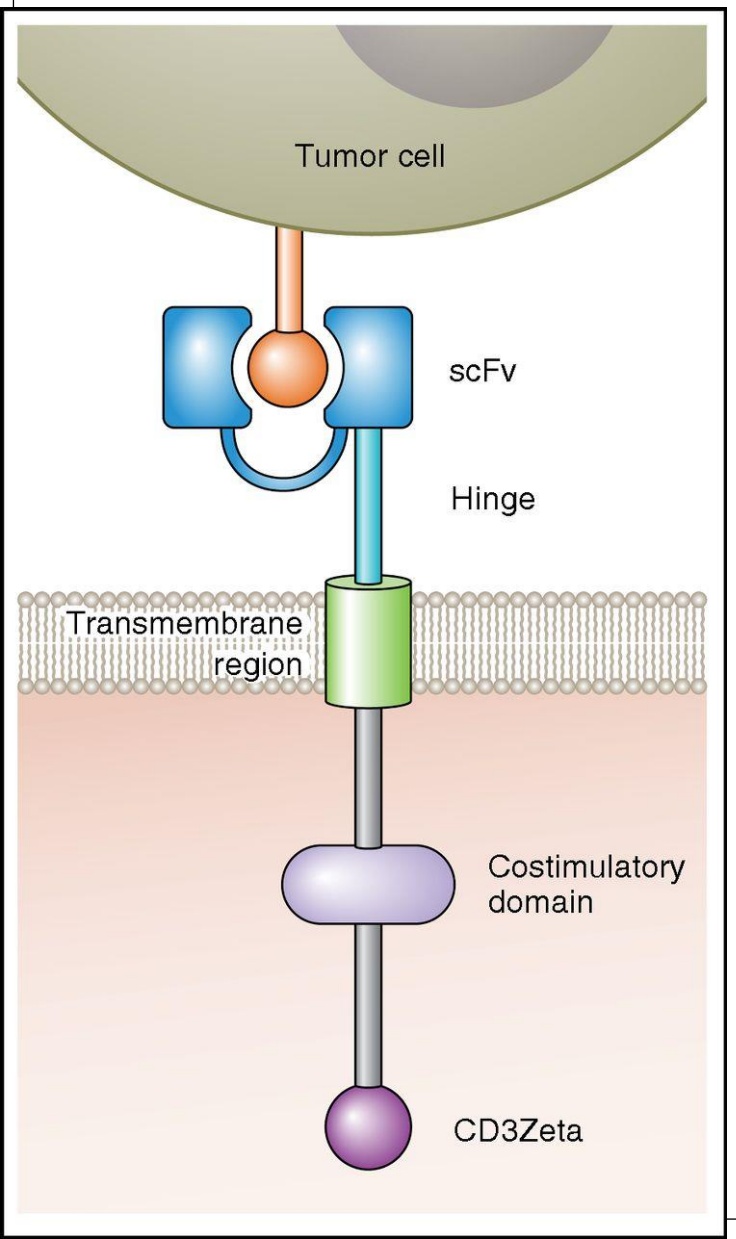
Figure 1. Overall survival in responders vs. non-responders

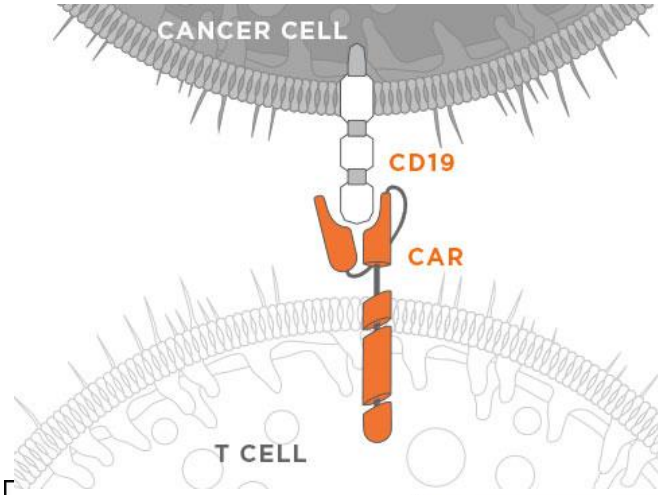


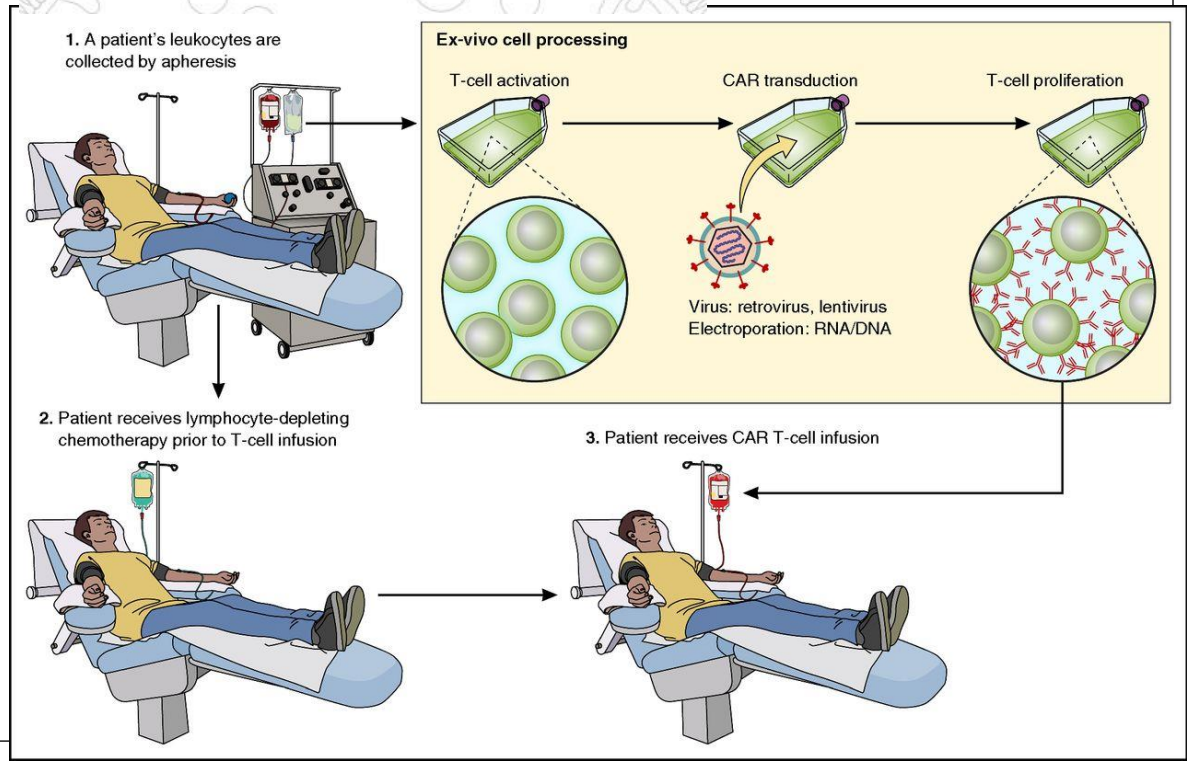
C A R –T cell


Chimeric
antigen receptor
(CAR)
Tumor cell
T cell
Antigen
expressed on
the cell surface

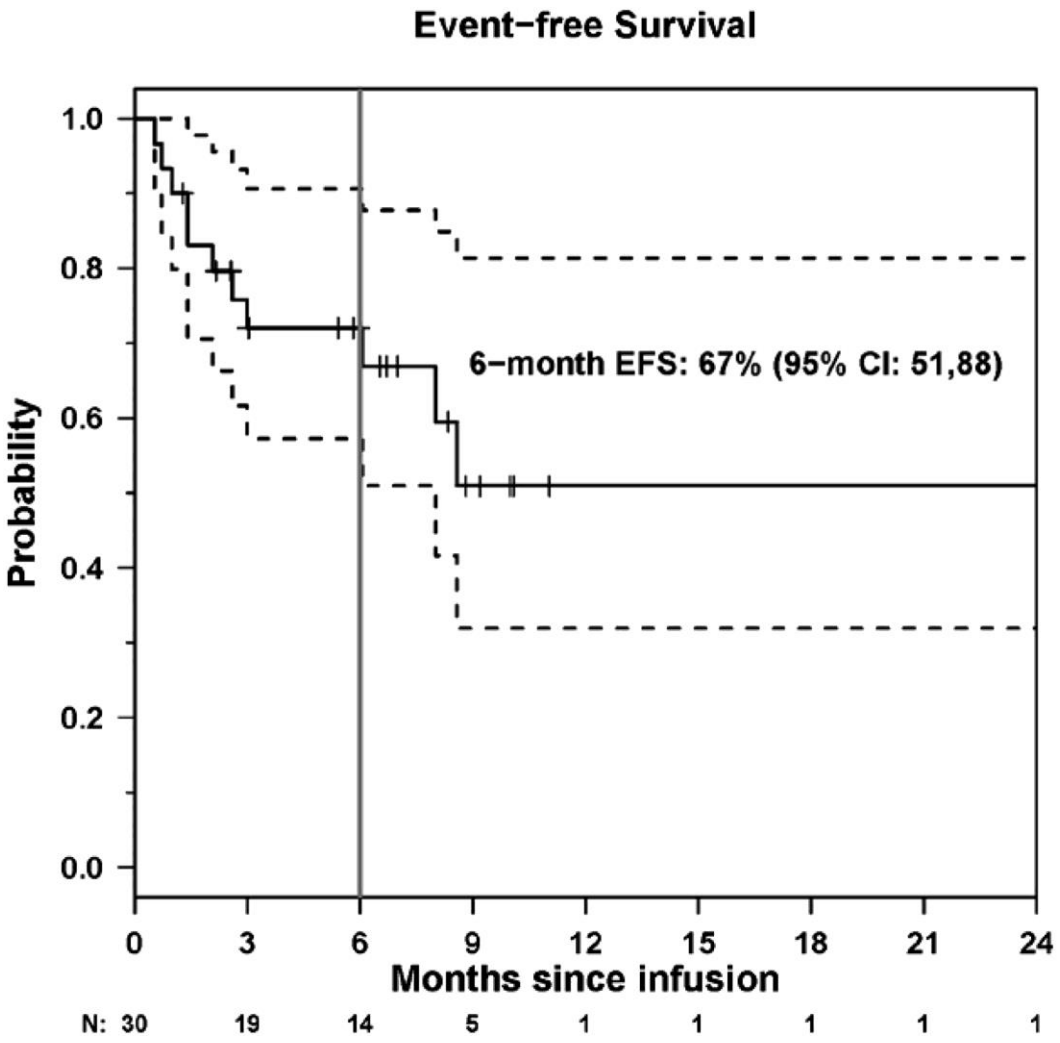
CAR-T Cells therapy







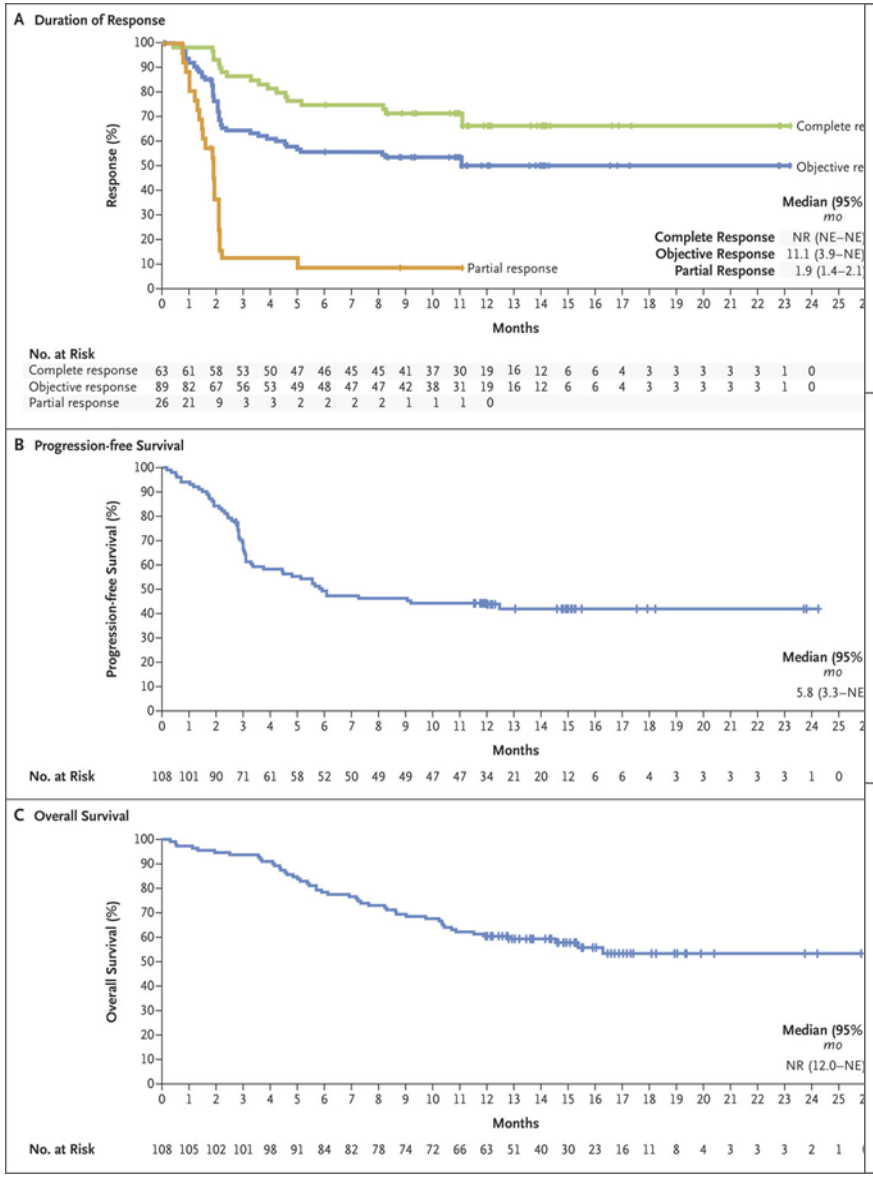
Event-free survival in 30 children and adults treated with CTL019 therapy.

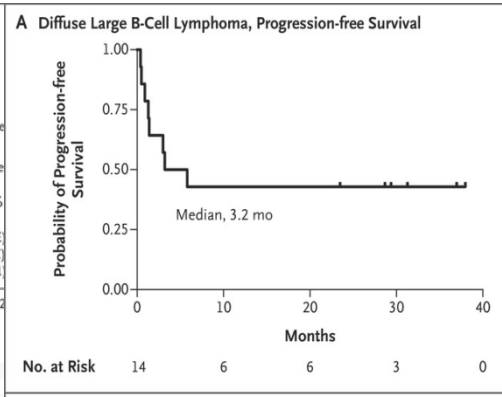


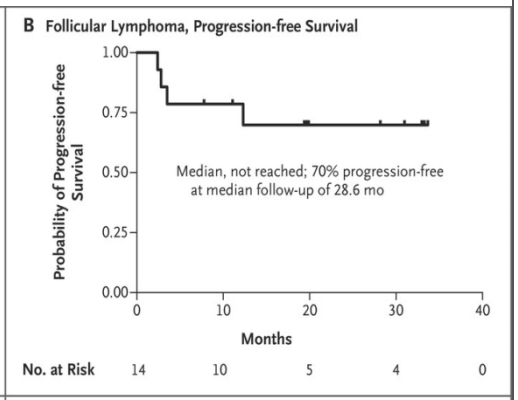
Shannon L. Maude et al. Blood 2015;125:4017-4023

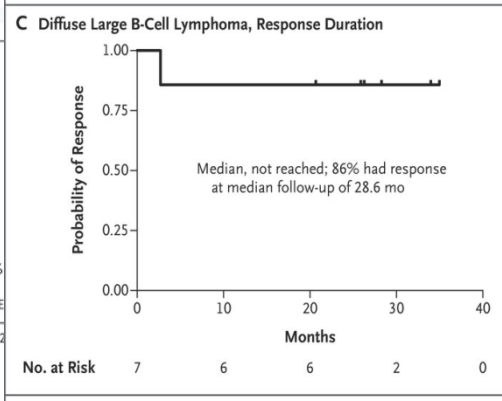
Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

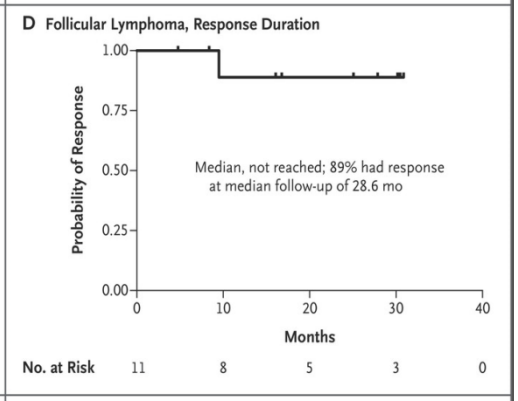
Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas

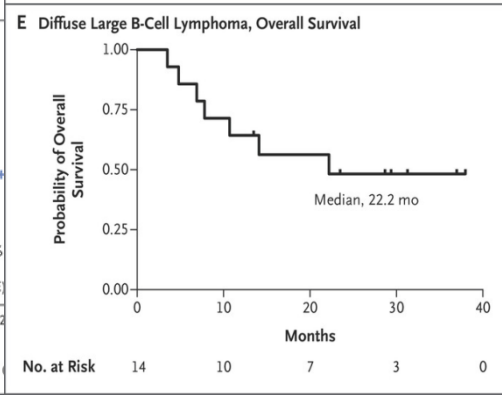


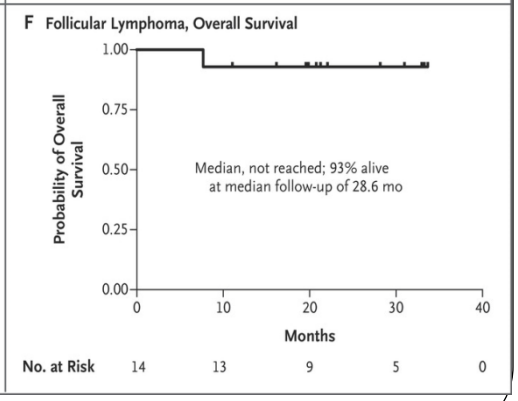












COMMON SIDE EFFECTS OF CAR T-CELL THERAPY AND THEIR TREATMENT

Side Effect	Symptoms	Treatment
Cytokine release syndrome	Fever, myalgia, headache, anorexia, nausea and vomiting, renal dysfunction, coagulopathy, hypotension, capillary leak, and pulmonary edema	Acetaminophen, narcotics, total parenteral nutrition, antiemetics, renal dosing of medications to dialysis, fresh frozen plasma, cryoprecipitate, platelets, vasoactives, tocilizumab, methylprednisone, oxygen support, and intubation
Graft-versus-host disease	Rash, diarrhea, and hyperbilirubinemia	Topical triamcinolone and possible systemic treatments with calcineurin inhibitors or steroids (only in discussion with CAR T-cell therapy team)
Neurologic symptoms	Confusion, B-cell aphasia, unresponsiveness, and seizures	Supportive care (e.g., reorientation, antiepileptics)
Tumor lysis syndrome	Hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia	Allopurinol and hydration

מסקנות

- טכנולוגיות אבחנתיות וטיפוליות בהמטולוגיה מתקדמות
- בקרוב תהיה אפשרות
  - לאבחון מוקדם יותר
  - סיווג יותר טוב לפי מאפיינים פרוגנוסטיים
  - בחירת טיפול אינדיבידואלי
  - קביעת עומק תגובה לטיפול (MRD)
  - גילוי מוקדם של הישנות המחלה

תודה על ההקשבה