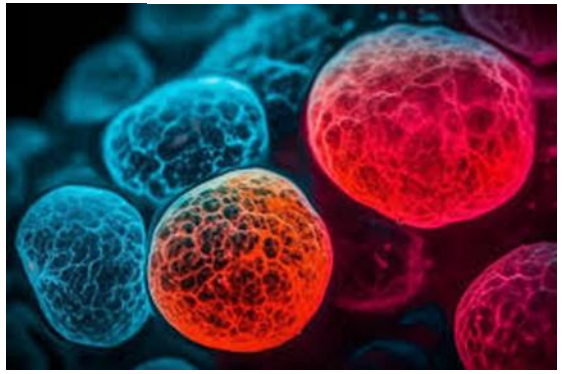
AOU Sassari

1° CORSO DI AGGIORNAMENTO

L'EVOLUZIONE DELLA CURA IN ONCOLOGIA TRA COMPLESSITÀ E CONTINUITÀ

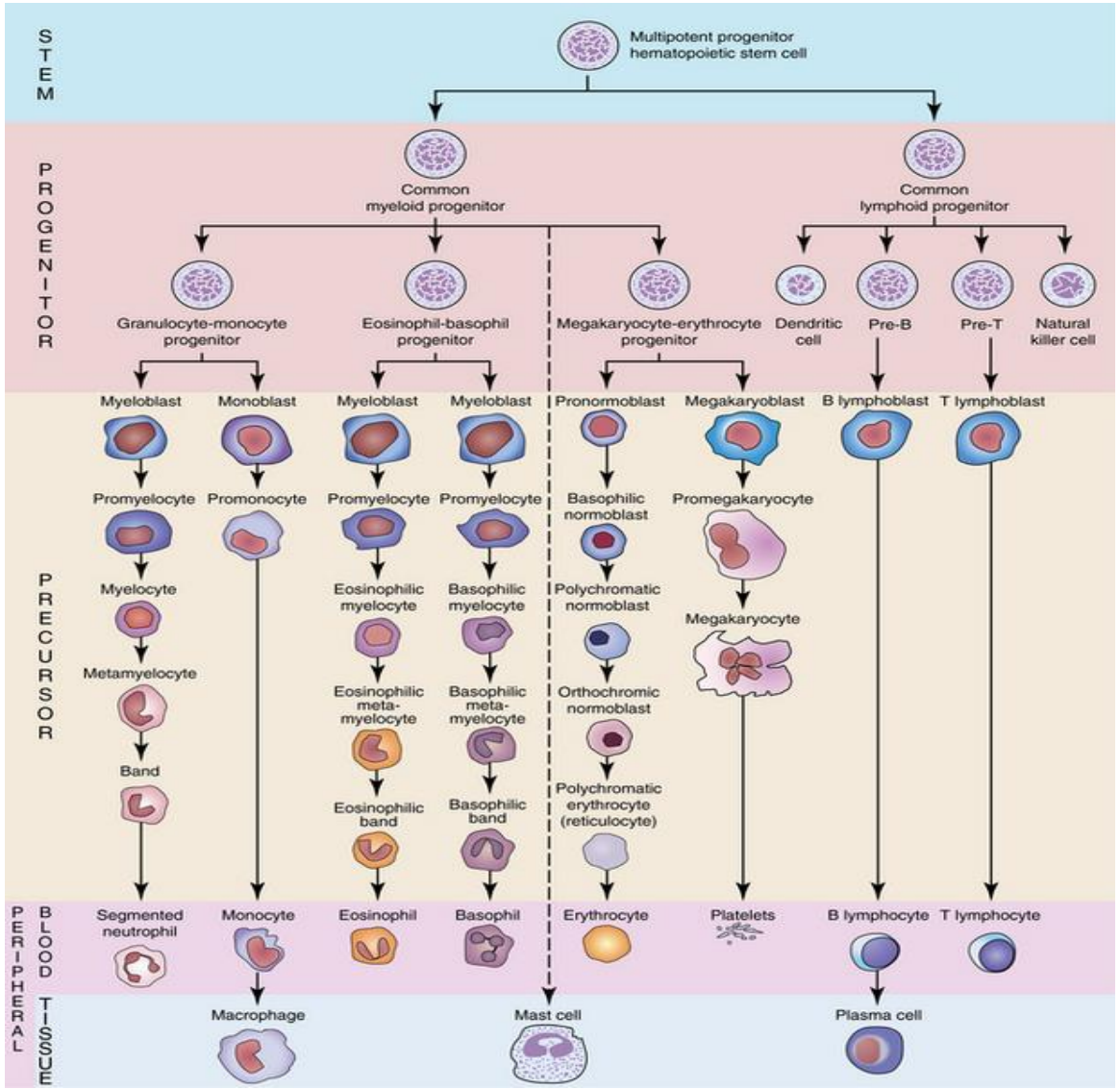
Nuove Strategie nel trattamento delle malattie emato-oncologiche

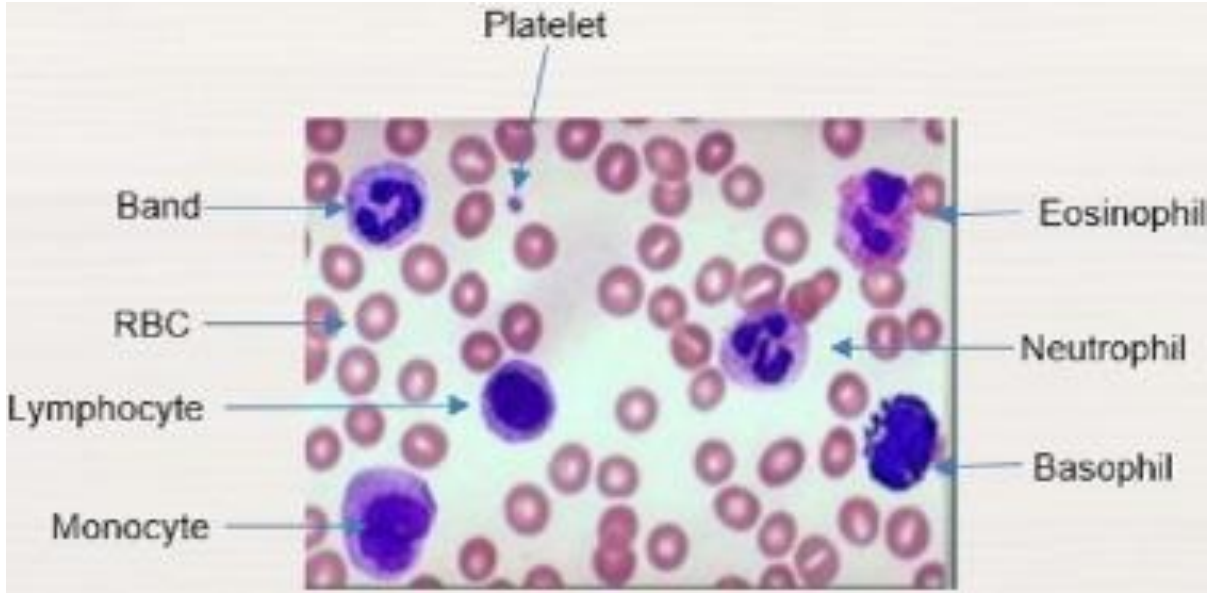


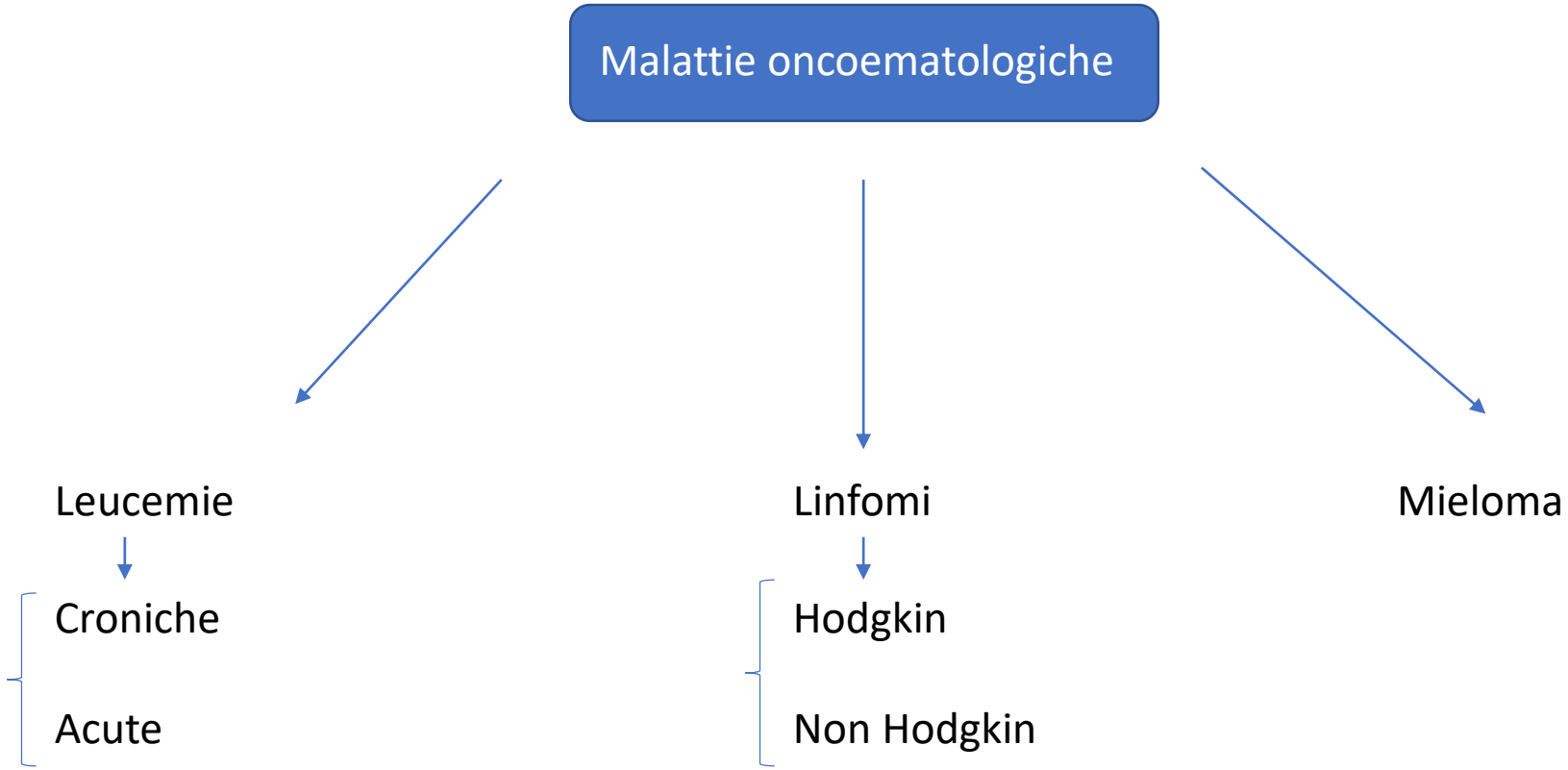
Sassari 12/10/2024

Luigi Podda
Ematologia AOU Sassari

Ematopoiesi






Malattie oncoematologiche
Leucemie
Croniche
Acute
Linfomi
Hodgkin
Non Hodgkin
Mieloma

Lymphoma

NHL

B-Cell

Precursor

Precursor B-lymphoblastic leukemia/ lymphoma

Peripheral

CLL/prolymphocytic leukemia/ small lymphocytic lymphoma

Lymphoplasmacytoid lymphoma/immunocytoma

Mantle cell lymphoma
Follicle center lymphoma
Marginal zone B-cell lymphoma
Splenic marginal zone lymphoma
Hairy cell leukemia
Plasmacytoma/plasma cell myeloma
Diffuse large B-cell lymphoma
Burkitt's lymphoma
High grade B cell lymphoma, Burkitt-like

T-cell and natural killer

Precursor

T-cell lymphoblastic lymphoma
T-cell lymphoblastic leukemia

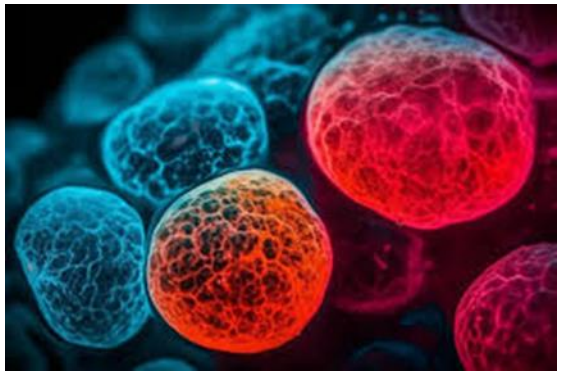
Peripheral & NK Cell

T-cell chronic lymphocytic leukemia/prolymphocytic leukemia
Large granular lymphocyte leukemia
Mycosis fungoides/Sezary syndrome
Peripheral T-cell lymphomas, NOS
Angioimmunoblastic T-cell lymphoma
Angiocentric lymphoma
Intestinal T-cell lymphoma
Anaplastic large cell lymphoma
Anaplastic large-cell lymphoma, Hodgkin's like

HL

Histologic classification

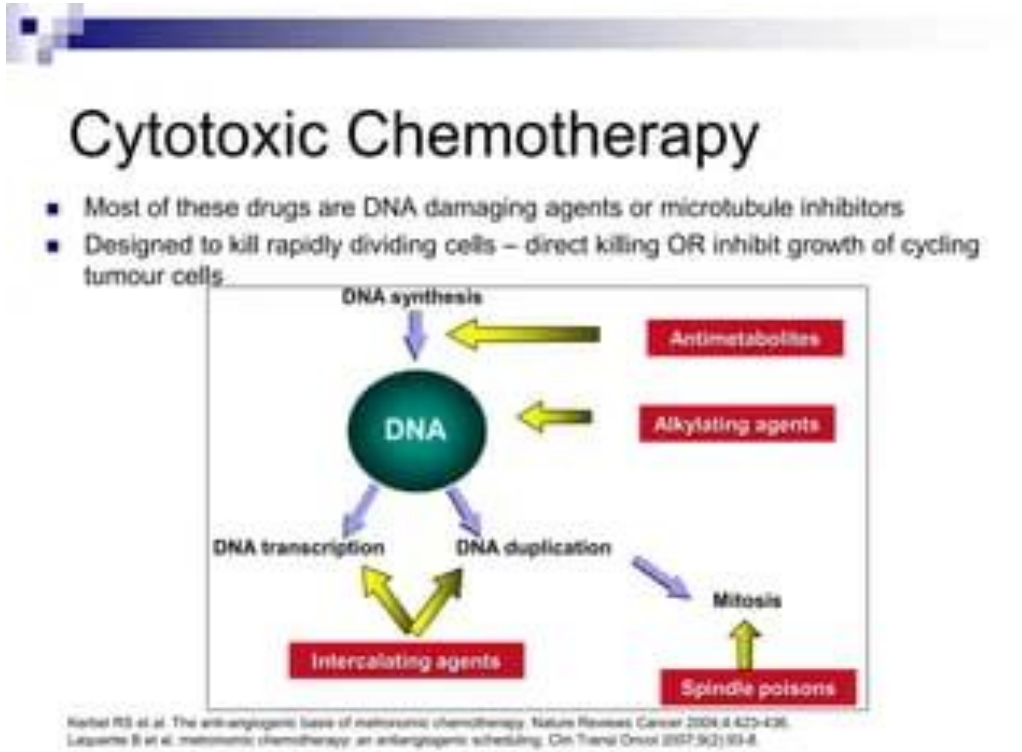
Lymphocyte predominance
Nodular sclerosis
Mixed cellularity
Lymphocyte depletion
Lymphocyte rich classical

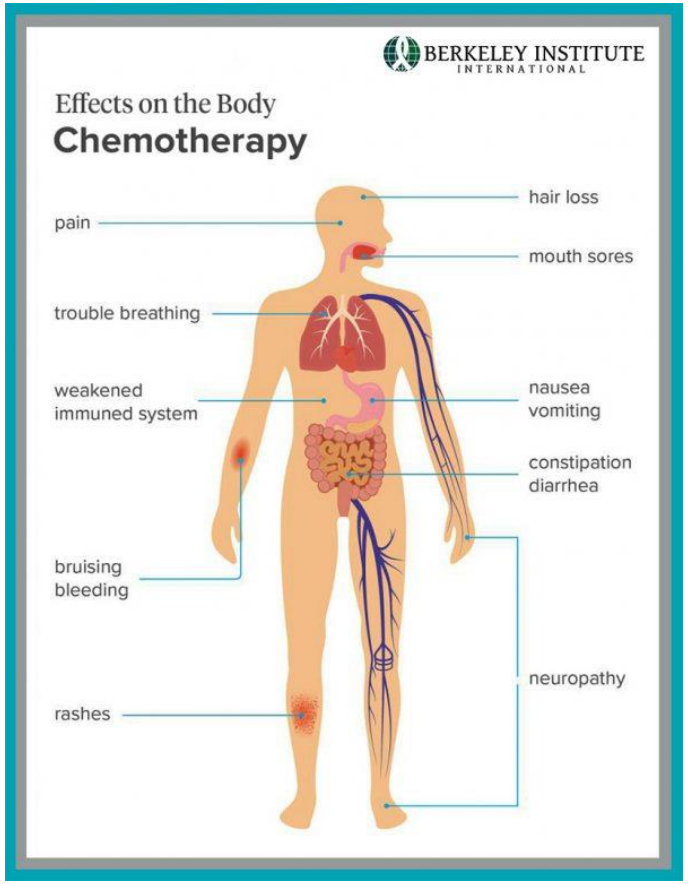


Chemioterapia

Il primo agente alchilante approvato dalla Food and Drug Administration (FDA) è stata la clormetina (mecloretamina), chiamata anche mostarda di azoto (1946)

Nel 1948, Farber riportò l'uso dell'aminopterina, che era il derivato 4-amminico dell'acido folico, per trattare la leucemia acuta nei bambini





Conventional Chemotherapy

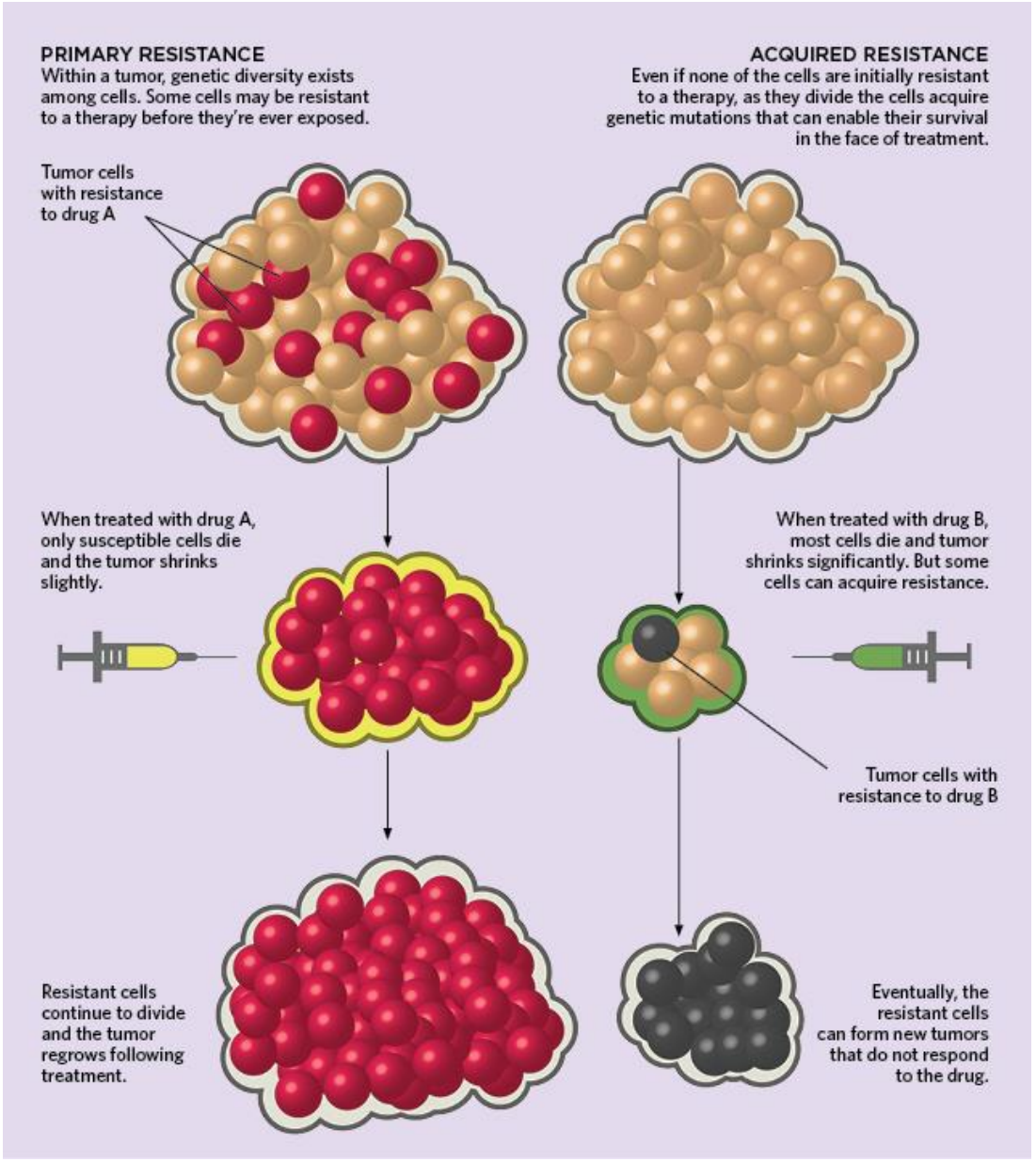
MTD Goal:

To obtain total eradication of cancer cells

Require prolonged breaks during successive cycles of therapy (generally 2-3 weeks)

- Allow for recovery of normal tissues
- To balance toxicity and efficacy

RESISTENZA CHEMIOTERAPICI



Ogni malato è unico.

Le Terapie mirate “Targeted therapy” tra cui l’Immunoterapia, nascono per l’esigenza di adattare la cura migliore ad ogni singolo malato ed alla sua malattia (“**Unmet needs**”)

A differenza della chemioterapia tradizionale le terapie mirate si focalizzano su specifiche molecole o mutazioni che sono importanti per la crescita del tumore e sulla capacità del Sistema immune di eliminare il “non-self” , e non sul blocco aspecifico della sintesi di DNA

Chiamata anche “Medicina di precisione" o “Medicina personalizzata”

Targeted therapy

-Attivazione sistema immune
“marcatura” delle cellule tumorali rendendo più facile per il sistema immunitario identificarle e distruggerle. Potenziamento delle funzioni e capacità del sistema immunitario di combattere il cancro.

-Blocco dei segnali di proliferazione
Blocco e trasformazione dei segnali che dicono alle cellule tumorali di crescere e dividersi.

-Blocco della neoformazione di vasi sanguigni (angiogenesi)
Le cellule tumorali richiedono un apporto costante di nutrienti e ossigeno per crescere e dividersi. Terapie mirate come gli inibitori dell’angiogenesi interferiscono con questo processo di crescita prevenendo la formazione di nuovi vasi sanguigni.

-Trasporto del chemioterapico direttamente alle cellule tumorali
Anticorpi monoclonali si attaccano a bersagli specifici sulla superficie delle cellule tumorali e le distruggono. Le cellule che non hanno il bersaglio non verranno danneggiate.

Targeted/Tailored Theraphy

- ✓Espresso dalla neoplasia
- ✓Fase specifico
- ✓Paziente-specifico

Maggiore efficacia

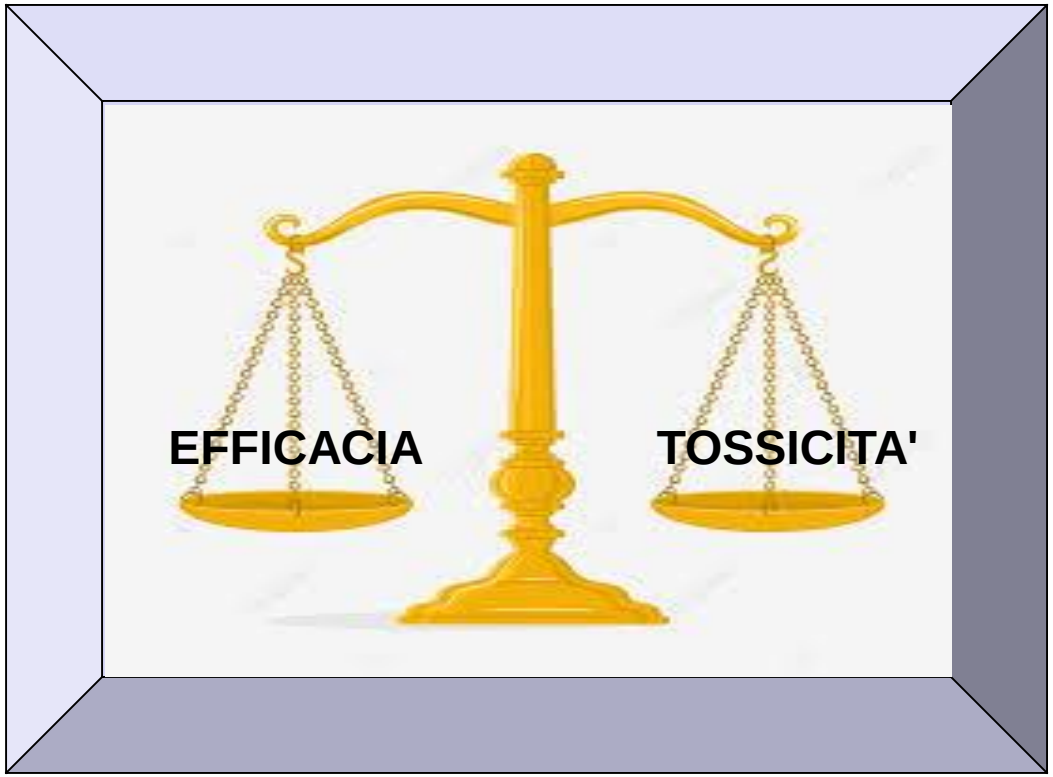
Minore tossicita'

Difference between Chemotherapy, Targeted Therapy and Immunotherapy

Centre for Clinical Haematology

	Chemotherapy	Targeted Therapy	Immunotherapy
How does it work?	Targets rapidly dividing cells (mostly cancer cells)	Targets Proteins required for cancer growth	Uses our immune system against cancer
Side Effects	Hair loss, intestinal damage, nausea	Liver problems, diarrhea, skin rash	Autoimmune effects
Limitations	Cancer cells develop resistance to chemotherapy, not specific	Cancer cells develop resistance	Tailored and expensive

Scelte Terapeutiche



Ogni volta che decidi perdi qualcosa.
Qualunque cosa tu decida.
E' sempre questione di capire cos'è
che non sei disposto a perdere

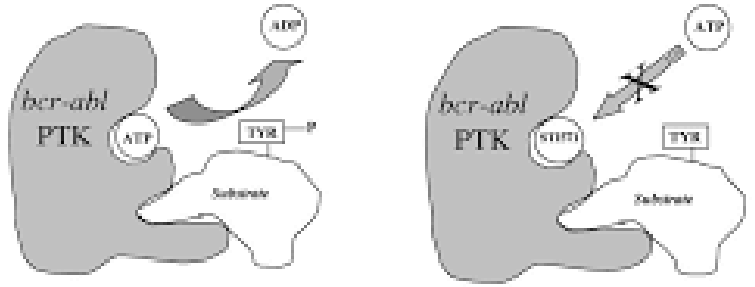
F. Stork

Inibitori tirosin chinasi

Leucemia mieloide cronica

Imatinib emblema delle cosiddette “terapie a bersaglio molecolare” o targeted therapies, le quali mirano a bloccare in maniera selettiva l’evento molecolare responsabile della proliferazione tumorale, in modo che le cellule tumorali siano uccise e che siano le uniche ad essere colpite.

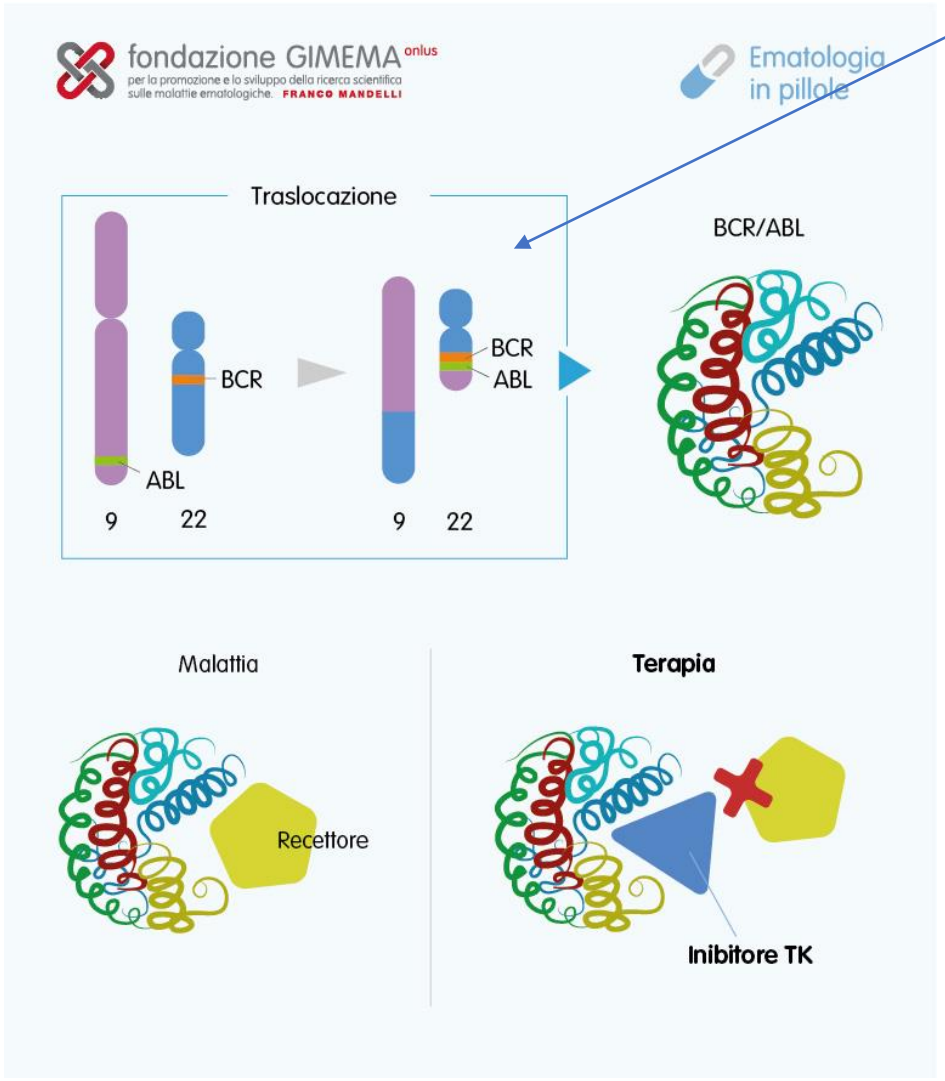
Meccanismo semplificato dell’azione del glivec (STI571) nella leucemia mieloide cronica



L’inibizione è di tipo allosterico con formazione di legami idrogeno tra il Glivec ed il sito attivo della bcr-abl PTK

LMC & Inibitori delle tirosin-Kinasi

Cromosoma Philadelphia t9;22



Con inibitori della tirosin-chinasi (TKI), la sopravvivenza è attualmente > 90% a 5 anni dopo la diagnosi della fase cronica della leucemia mieloide cronica. Prima che si utilizzassero gli inibitori della tirosin-chinasi (TKI), anche con il trattamento, il 5-10% dei pazienti decedeva entro 2 anni dalla diagnosi; il 10-15% decedeva ogni successivo anno. La sopravvivenza mediana era di 4-7 anni. La maggior parte (90%) dei decessi fa seguito a una fase blastica o a una fase accelerata della malattia. La sopravvivenza mediana dopo una crisi blastica era di circa 3-6 mesi o più lunga se la remissione era raggiunta.

Sic Transit Gloria Mundi

2001

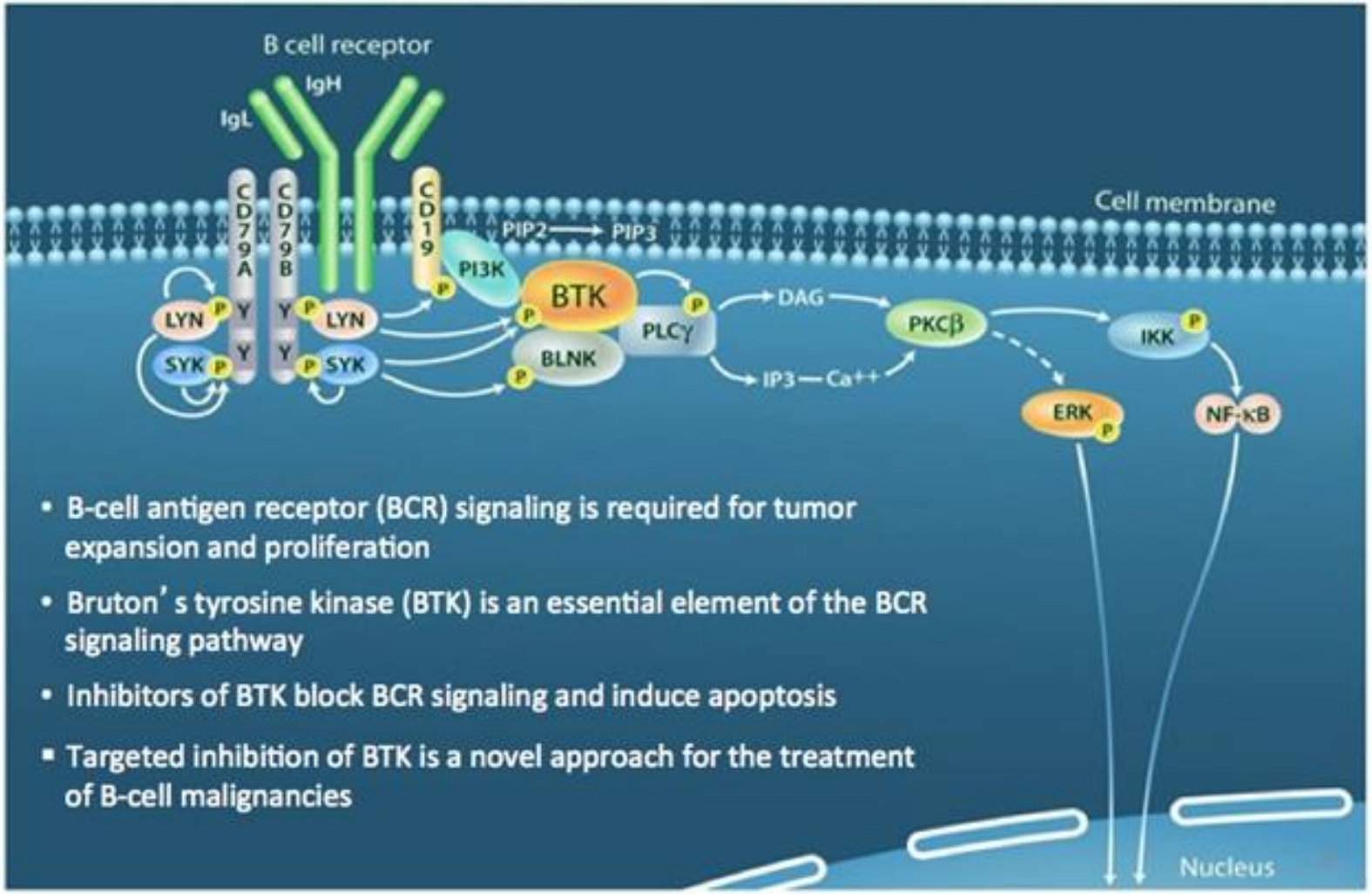
2024 ritiro dal commercio

LLC-LNH & BTK

Ibrutinib, Acalabrutinib
Zanubrutinib…….

Bruton's Tyrosine Kinase (BTK)

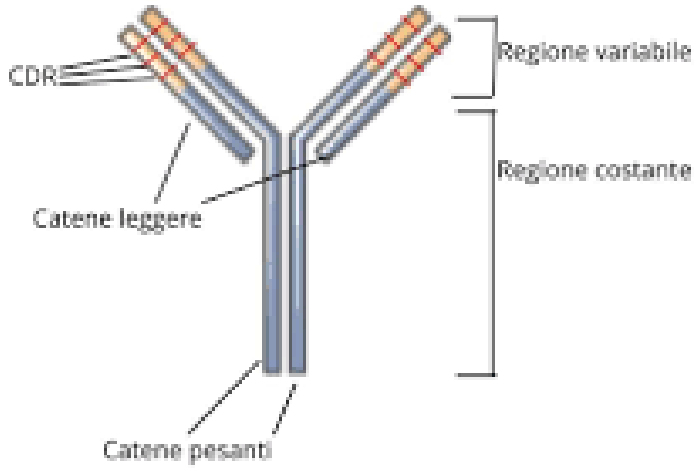
A critical kinase for lymphoma cell survival and proliferation



- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation
- Bruton's tyrosine kinase (BTK) is an essential element of the BCR signaling pathway
- Inhibitors of BTK block BCR signaling and induce apoptosis
- Targeted inhibition of BTK is a novel approach for the treatment of B-cell malignancies

Anticorpi monoclonali

Risposta immunitaria e anticorpi monoclonali



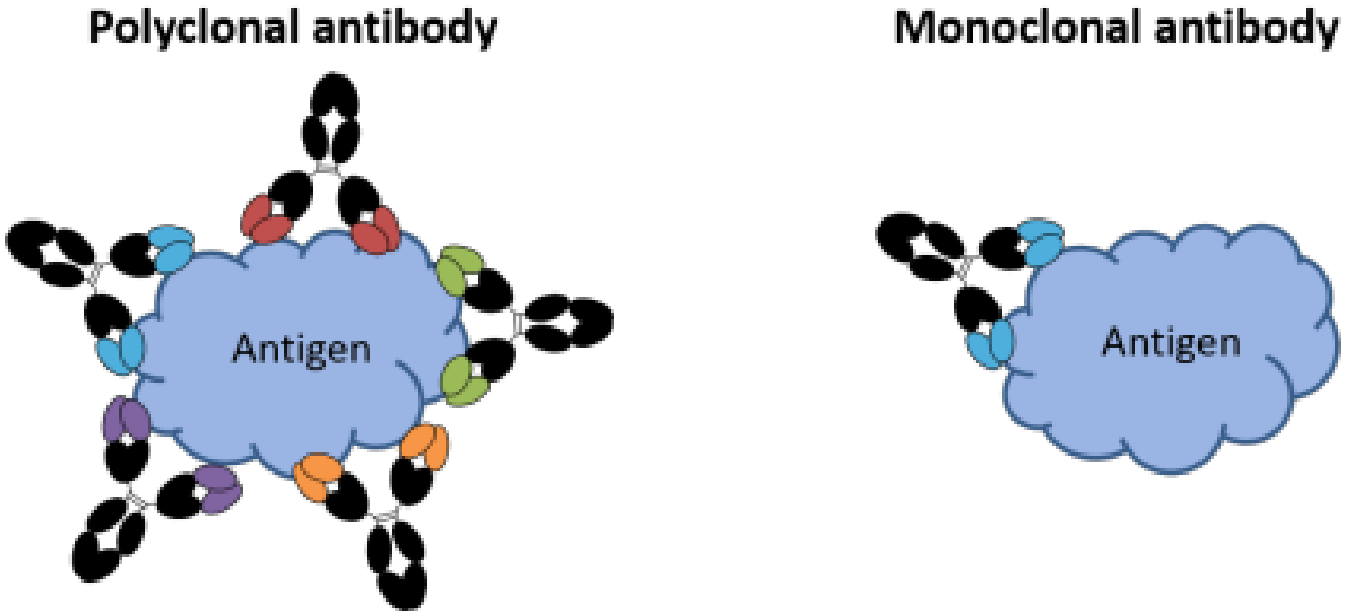
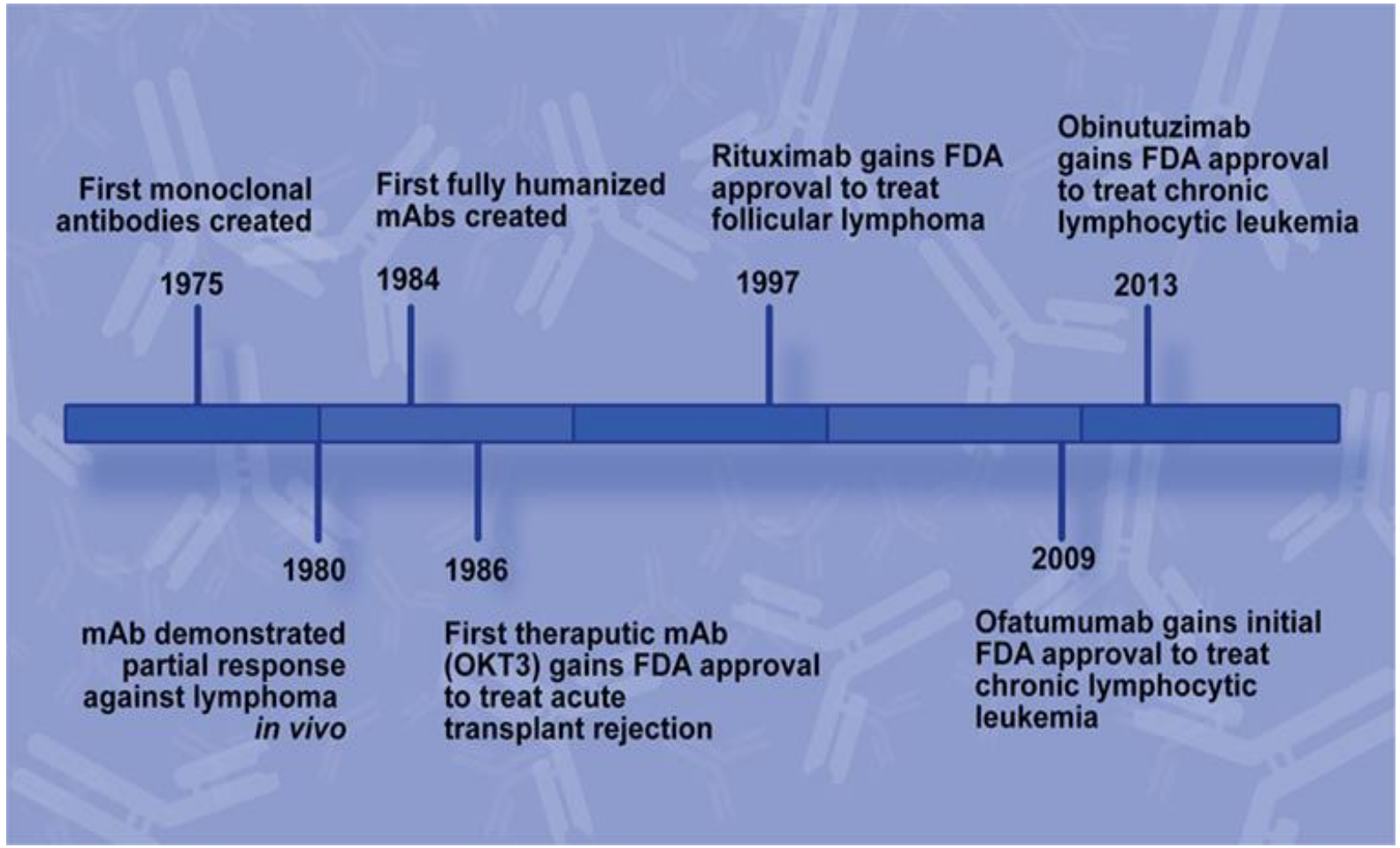
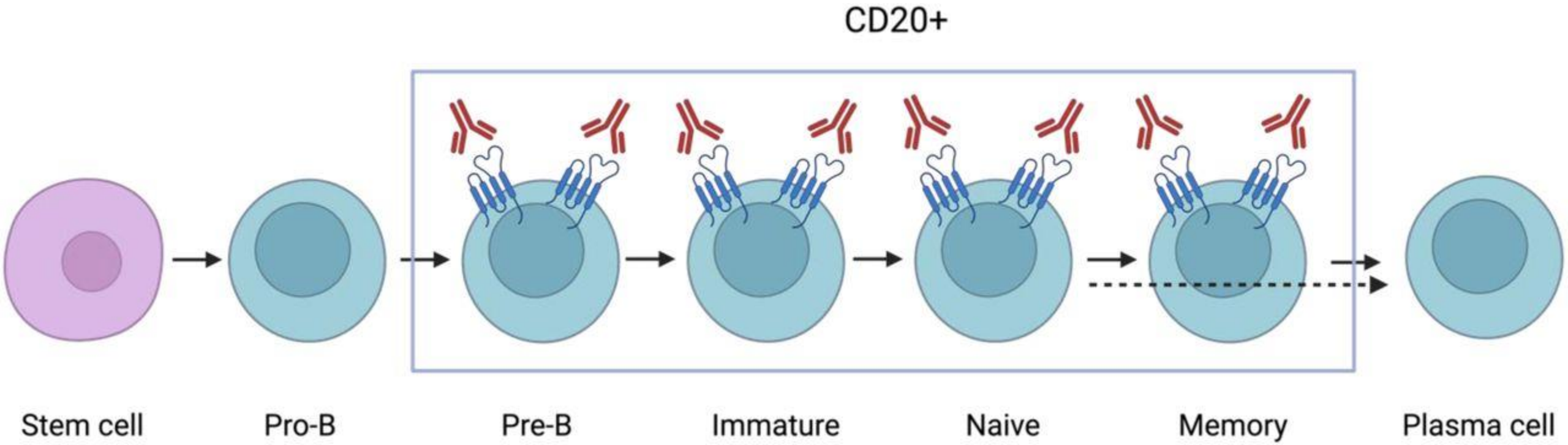


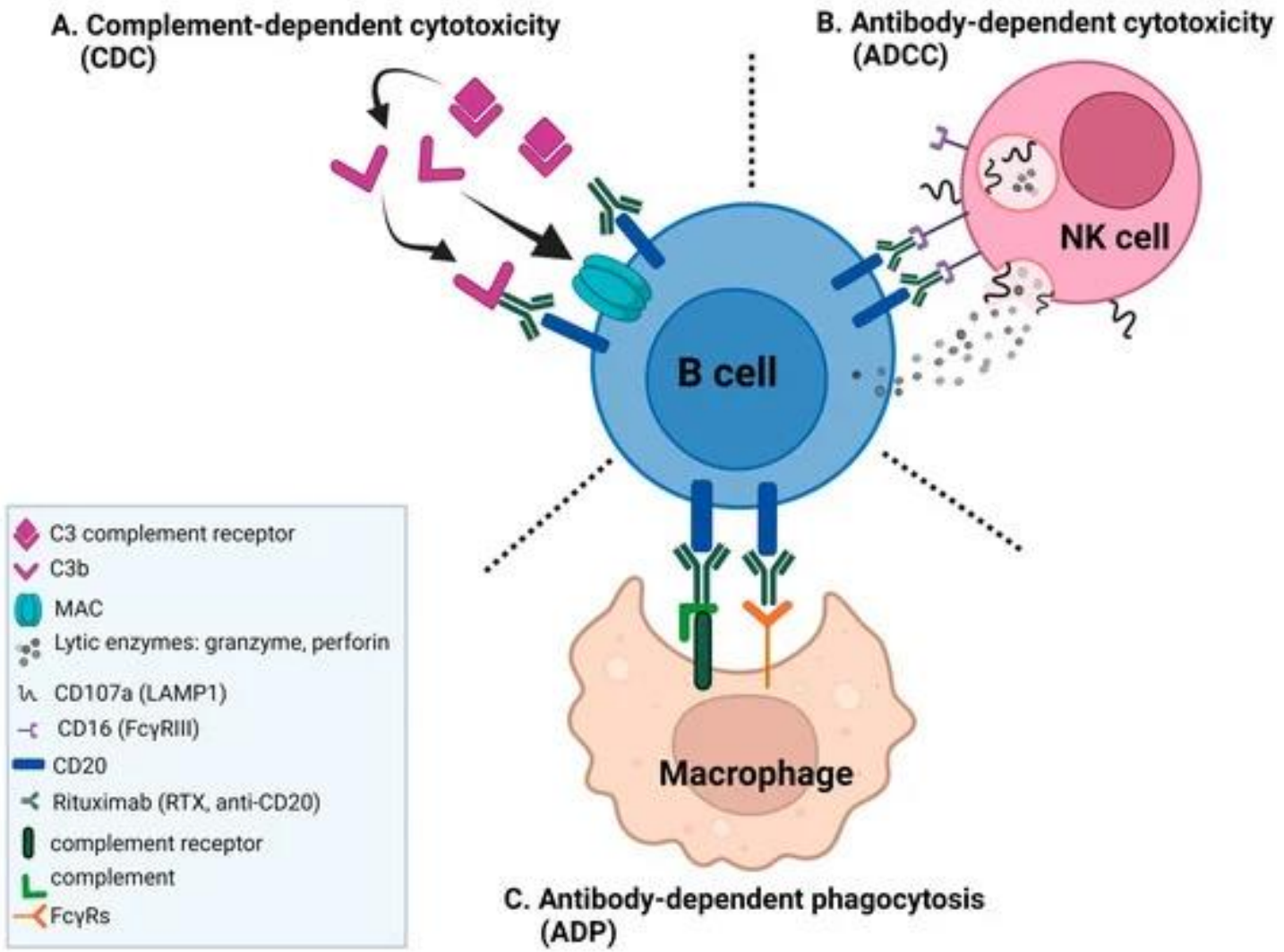
Fig 1. Monoclonal and Polyclonal Antibodies. The polyclonal antibody can bind to a single antigen, but can bind to different forms of it. The monoclonal antibody can only bind to a specific type of antigen.


First monoclonal antibodies created
1975
First fully humanized mAbs created
1984
Rituximab gains FDA approval to treat follicular lymphoma
1997
Obinutuzimab gains FDA approval to treat chronic lymphocytic leukemia
2013
1980
mAb demonstrated partial response against lymphoma *in vivo*
1986
First theraputic mAb (OKT3) gains FDA approval to treat acute transplant rejection
2009
Ofatumumab gains initial FDA approval to treat chronic lymphocytic leukemia

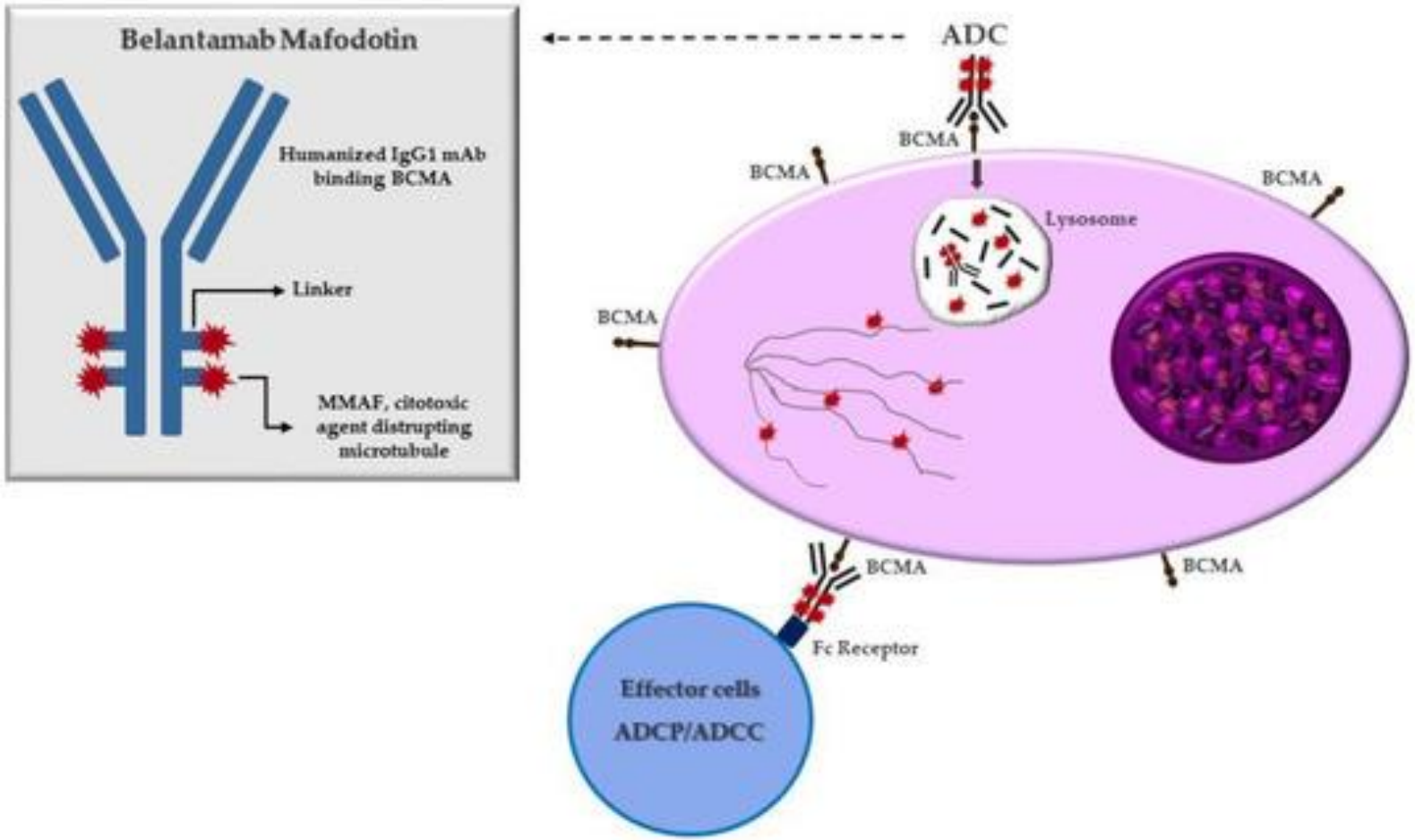
Rituximab (anti CD-20)



Meccanismo azione Rituximab



ADC (Antibody Drug Conjugate)



BiTe: Bispecific T-engaging

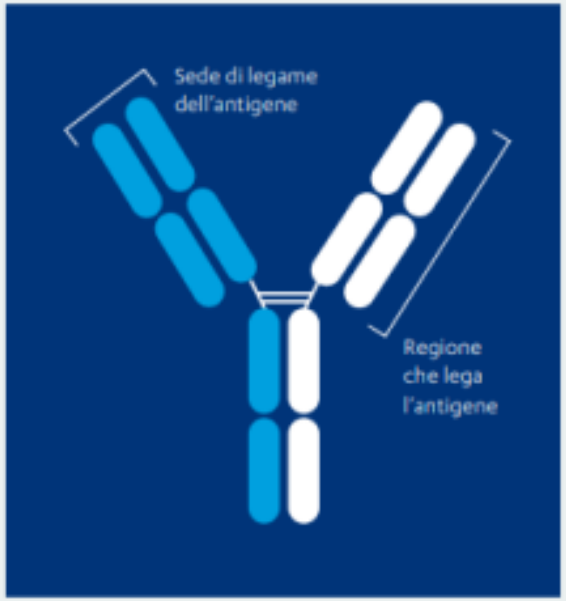
La struttura degli anticorpi bispecifici

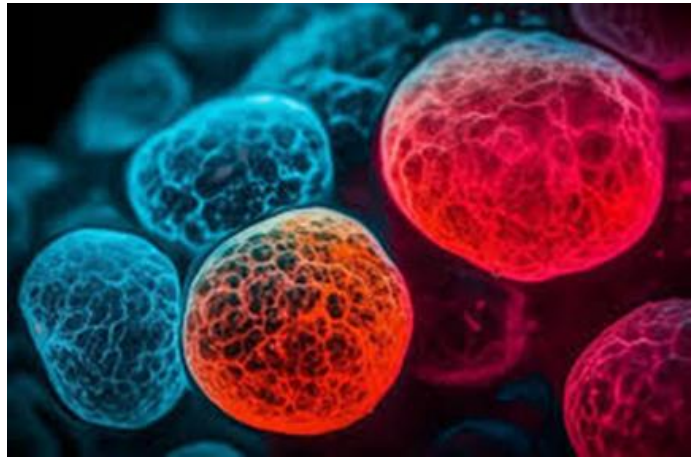
Gli anticorpi presenti in natura, ovvero le **immunoglobuline**, sono prodotti dal nostro sistema immunitario.[3]

Queste sono proteine a forma di Y con **due regioni leganti l'antigene identiche**, in grado quindi di riconoscere e legare lo stesso bersaglio cellulare.[3]

Gli anticorpi bispecifici **hanno due regioni che legano due antigeni** o due epitopi diversi di un antigene.[3]

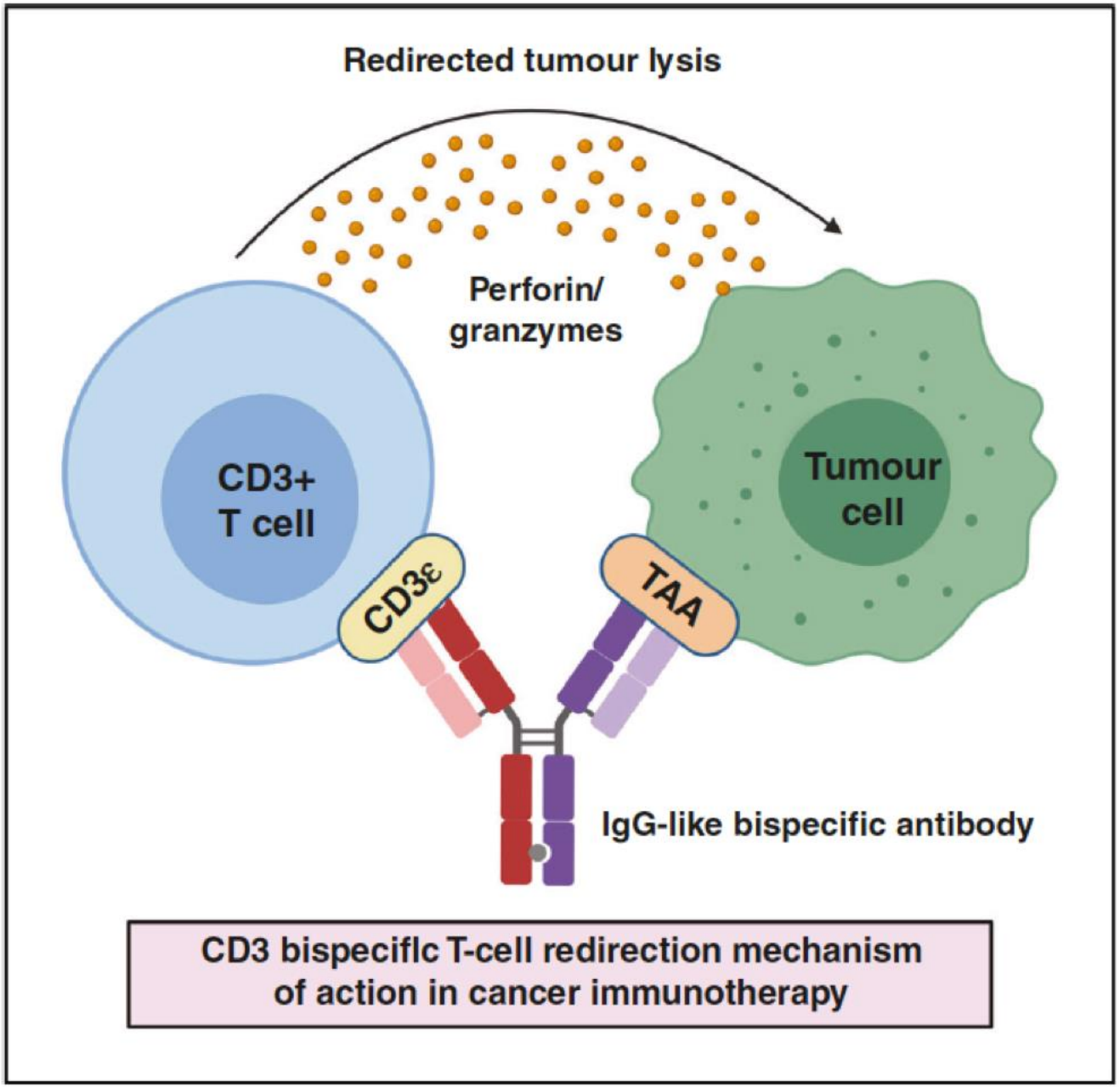
Legandosi a due cellule, i bispecifici possono portare tipi differenti di cellule in **stretta vicinanza**.[3]





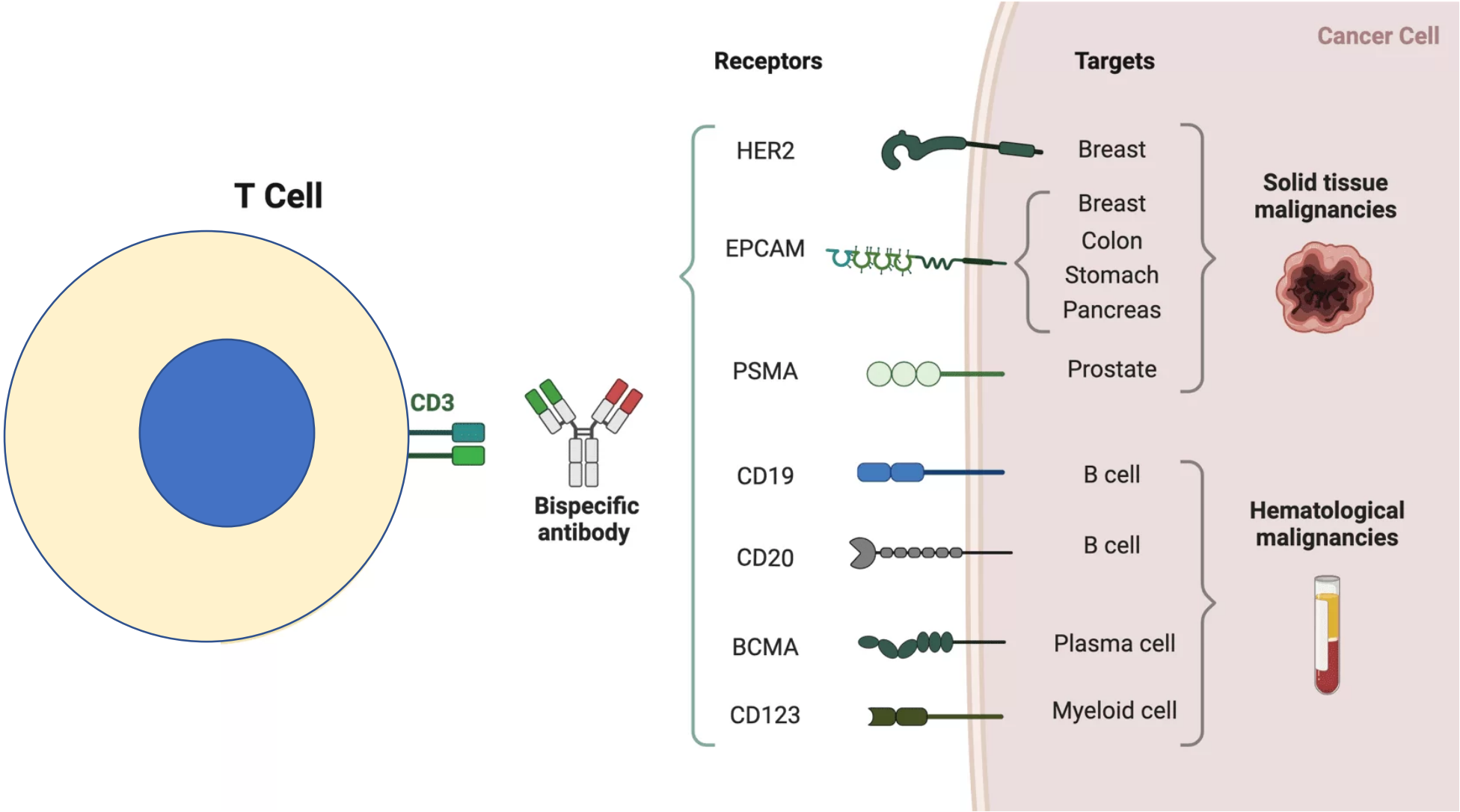
Bispecific T-Cell Engaging (BiTE)

ANTICORPI BI-SPECIFICI

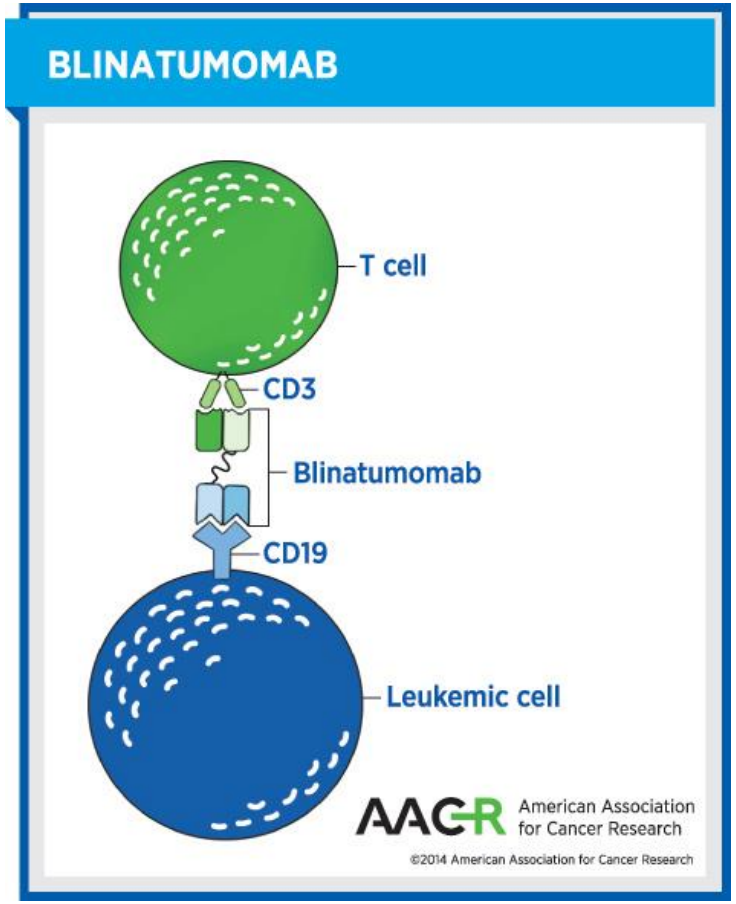


CD3 bispecifIc T-cell redirection mechanism of action in cancer immunotherapy

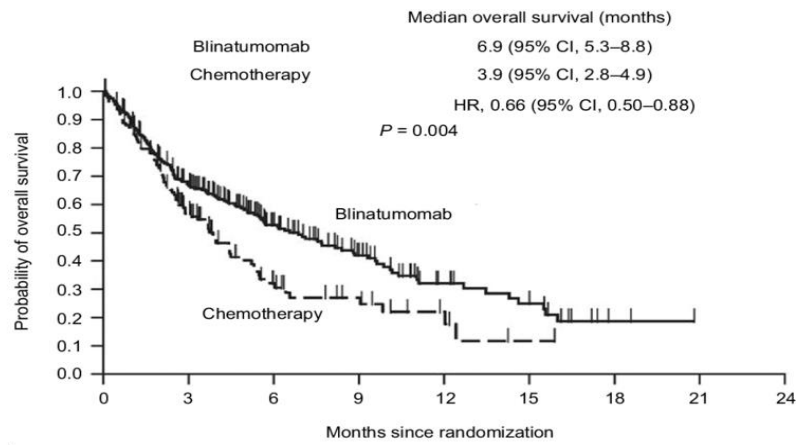
BiTe: Bispecific T-engaging



Leucemia Linfoblastica acuta refrattaria

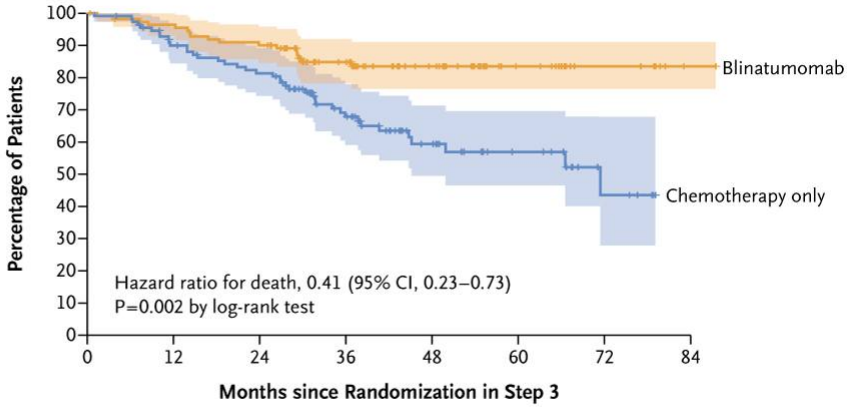


Overall survival censored at the time of stem cell transplantation



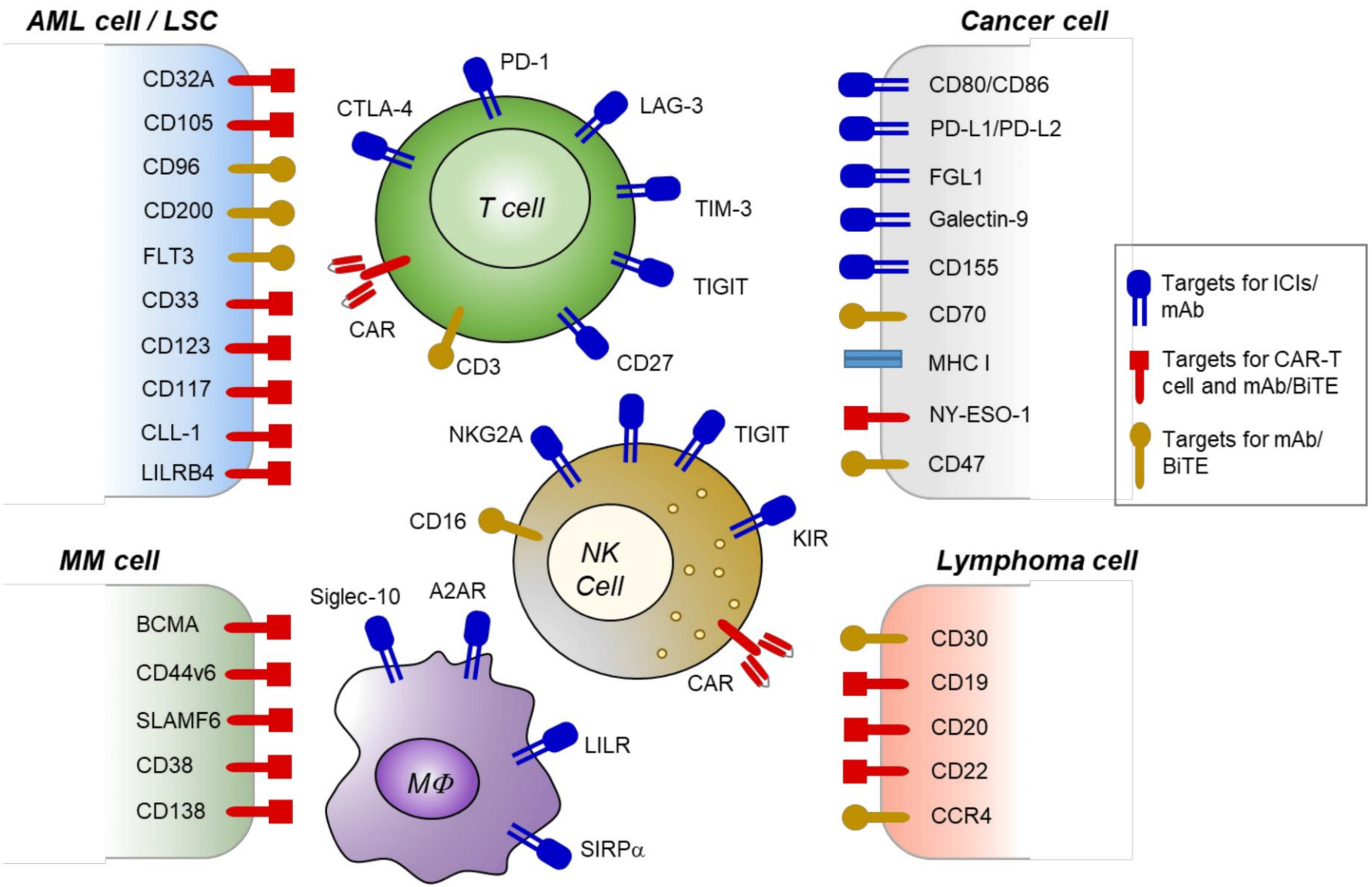
Number at risk									
Blinatumomab	271	163	80	44	21	13	2	0	0
Chemotherapy	134	56	21	12	5	1	0	0	0

Overall Survival among Patients with MRD-Negative Status



No. at Risk								
Blinatumomab	112	106	99	65	41	19	8	1
Chemotherapy only	112	96	85	53	28	15	5	0

Emerging immunotherapies with new targets for hematologic malignancies



https://doi.org/10.3390/ijms21218000

Types of hematologic malignancies and immunotherapies that received FDA approval

Leukemia

Characteristics & Types

Abnormal growth of myeloid or lymphoid white blood cells in BM and blood

- AML, CML, ALL, CLL
- MPN : PV
- BPDCN

Immunotherapies

- Gemtuzumab ozogamicin : ADC for AML
- Inotuzumab ozogamicin : ADC for B-ALL
- Blinatumomab : BiTE for B-ALL
- Ropeginterferon alfa-2b : Cytokine for PV (MPN) in Europe
- Tisagenlecleucel : CAR-T cell for B-ALL
- Tagraxofusp : ADC for BPDCN

Myeloma

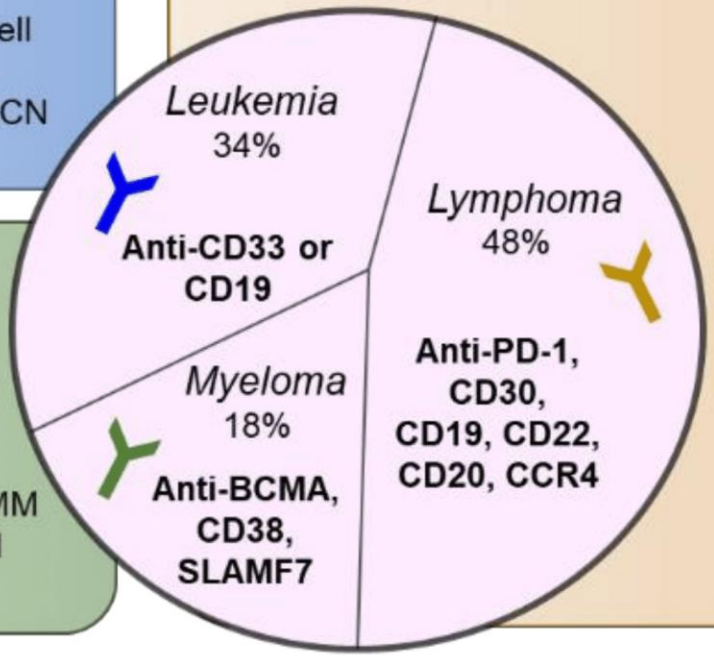
Characteristics & Types

Abnormal growth of plasma cells in BM and produce abnormal antibodies

- MM, Plasmacytoma

Immunotherapies

- Belantamab mafodotin : ADC for MM
- Daratumumab : mAb for MM
- Elotuzumab : mAb for MM
- Isatuximab : mAb for MM



Lymphoma

Characteristics & Types

Abnormal growth of lymphocytic cancer cells in lymph node or other tissue

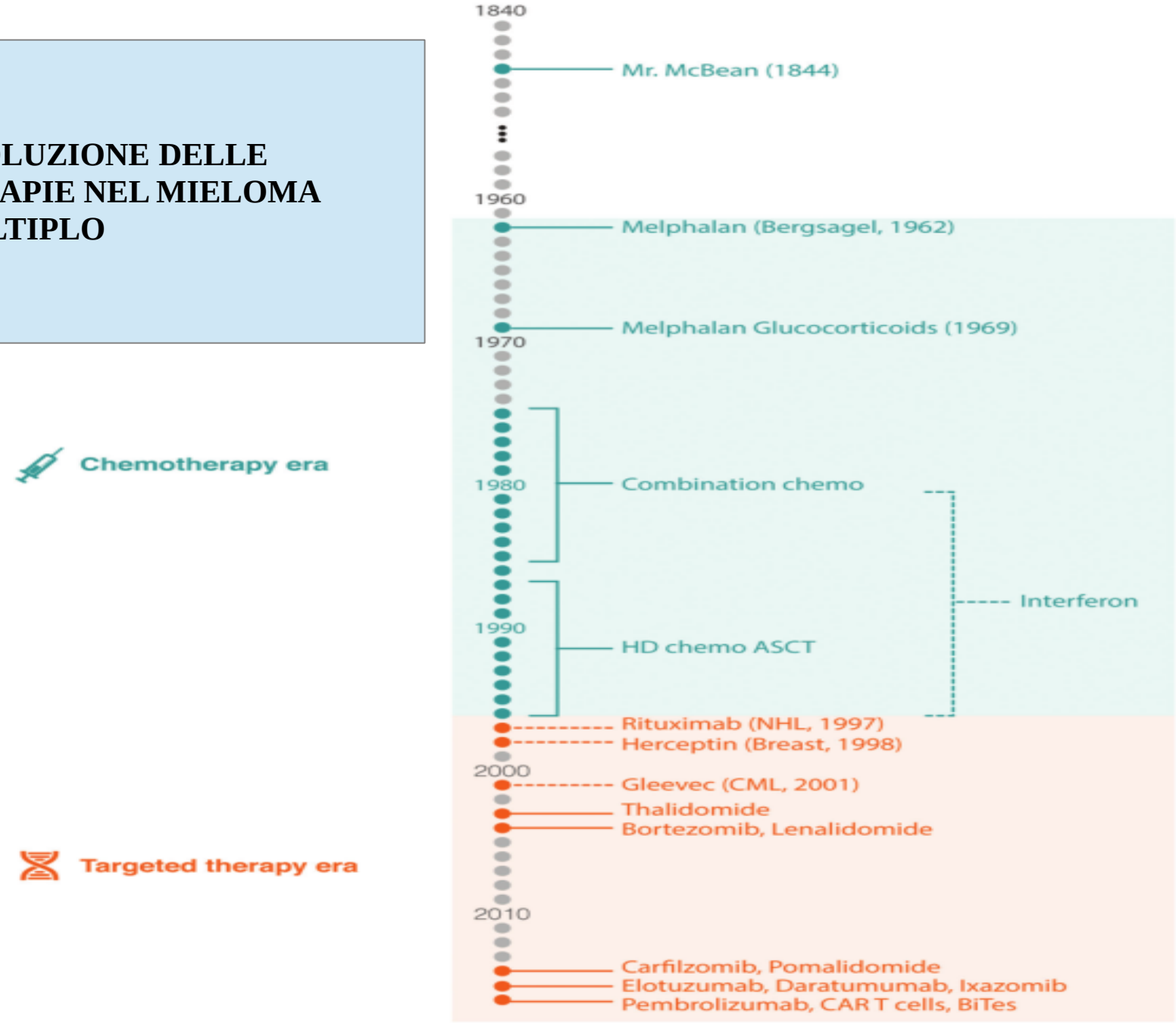
- HL
- NHL : DLBCL, FL, CLL, MCL, ALCL, ATCLL, CTCL

Immunotherapies

- Nivolumab / Pembrolizumab : ICIs for HL
- Brentuximab vedotin : ADC for HL, ALCL
- Rituximab : mAb for NHL
- Polatuzumab vedotin : ADC for DLBCL
- Recombinant interferon alpha-2b : Cytokine for hairy cell leukemia, FL
- Moxetumomab Pasudotox : ADC for hairy cell leukemia
- Tisagenlecleucel / Axicabtagene ciloleucel : CAR-T cells for DLBCL
- Brexucabtagene autoleucel : CAR-T cell for MCL
- Ibritumomab tiuxetan : mAb for NHL
- Mogamulizumab : mAb for ATCLL, CTCL
- Tafasitamab : mAb in combination with lenalidomide for DLBCL
- Obinutuzumab : mAb for CLL, FL

https://doi.org/10.3390/ijms21218000

EVOLUZIONE DELLE TERAPIE NEL MIELOMA MULTIPLO

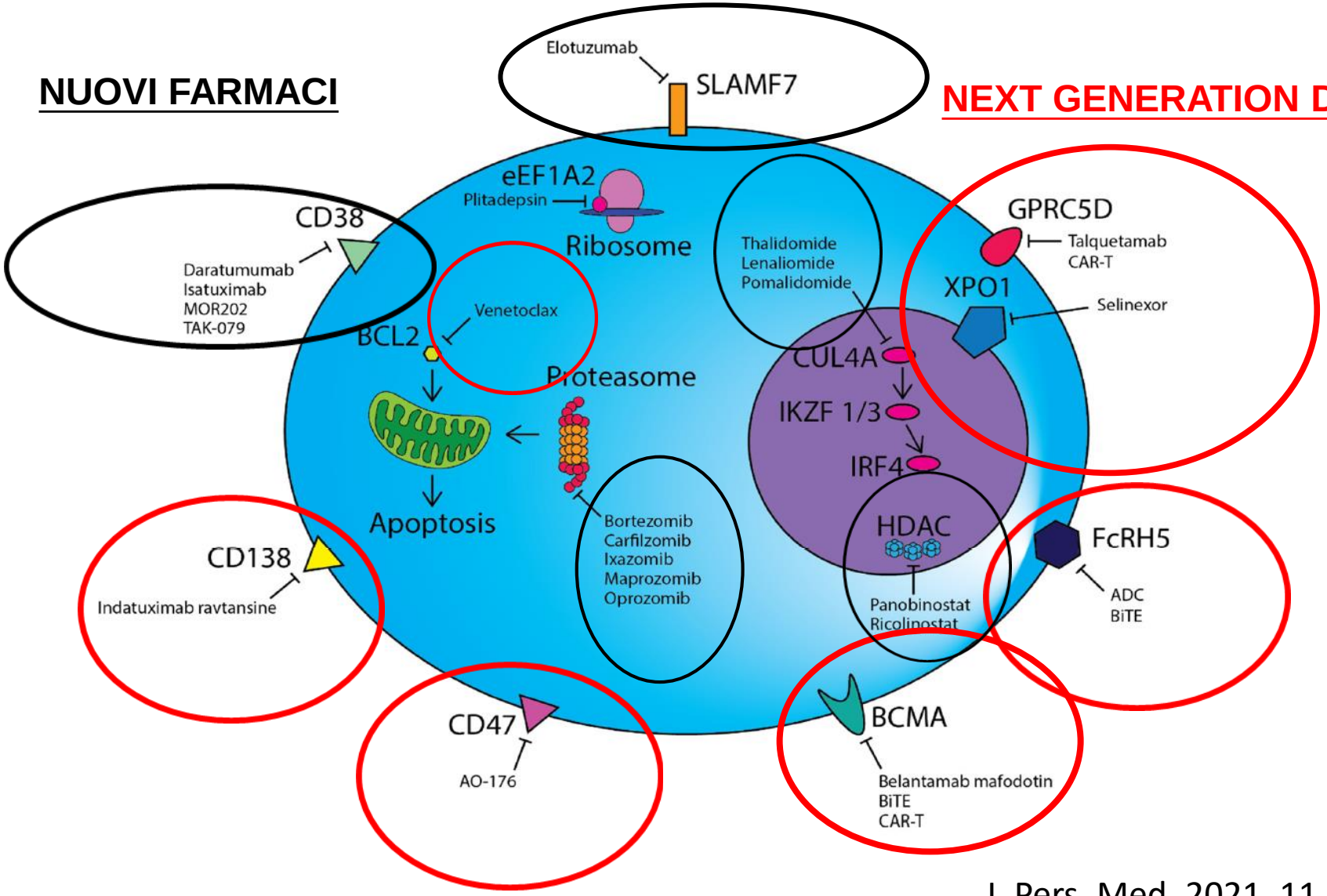


Haematologica | 2017; 102(3)

Targeted Therapies for Multiple Myeloma

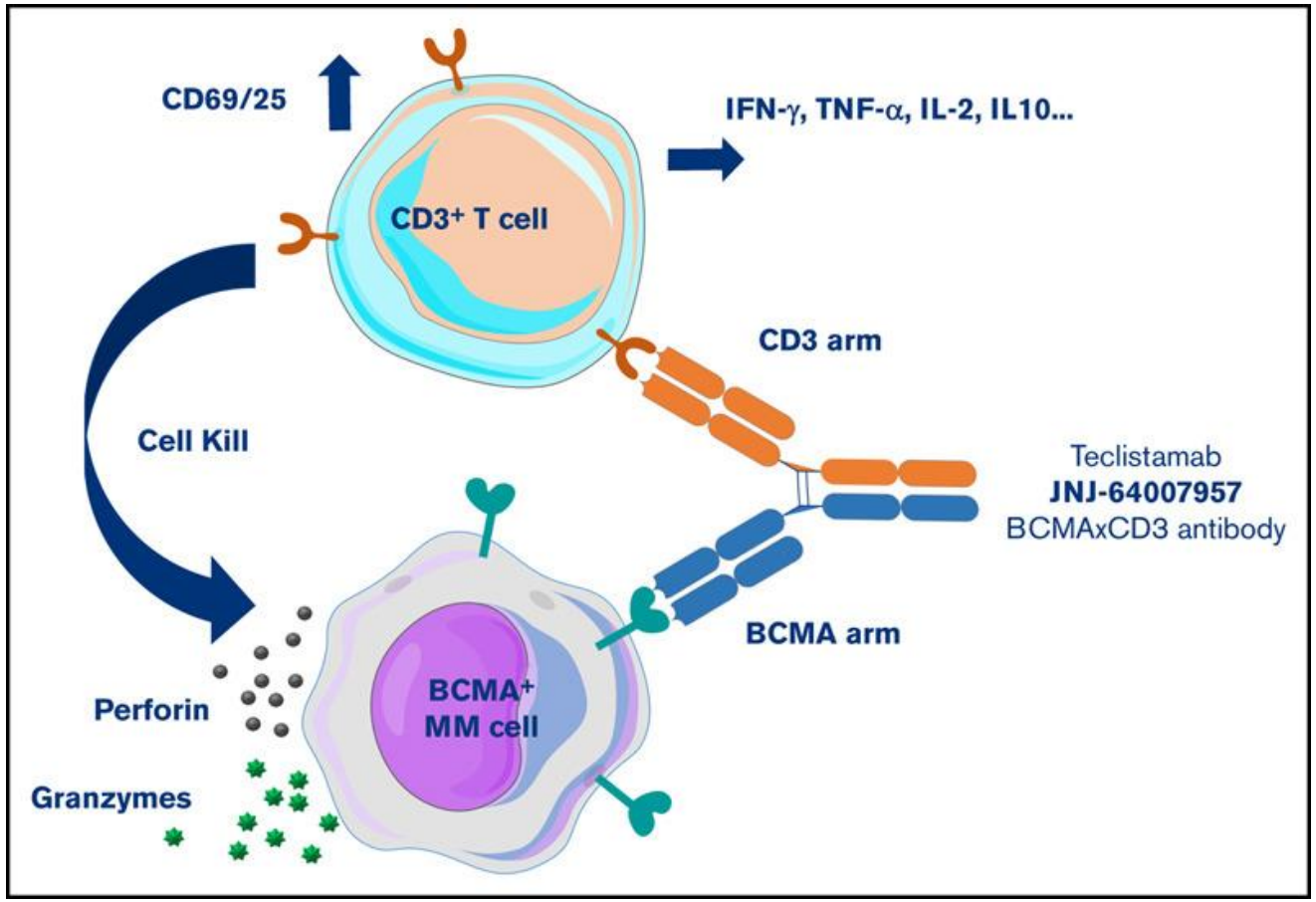
NUOVI FARMACI

NEXT GENERATION DRUGS

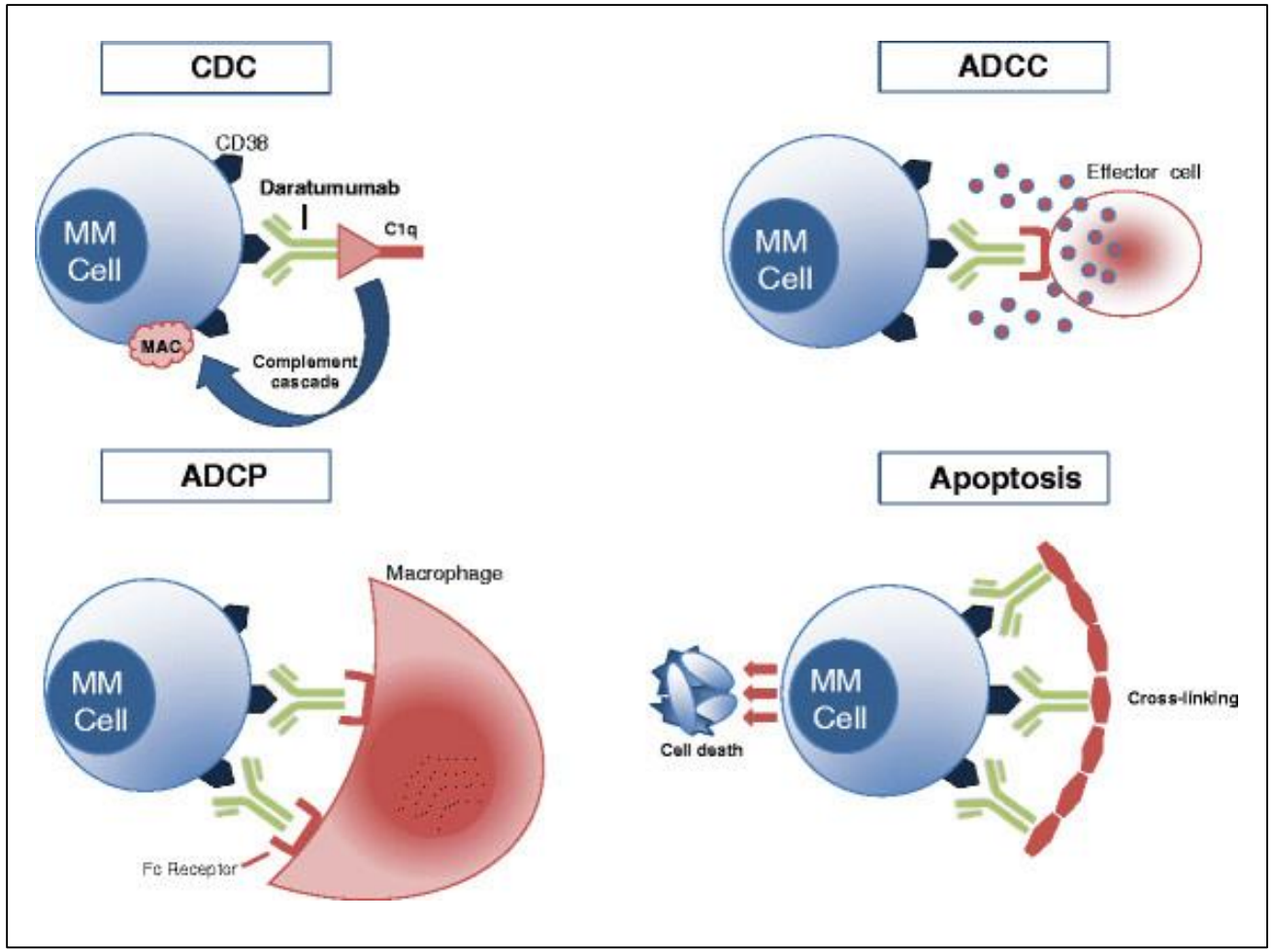


J. Pers. Med. 2021, 11, 334

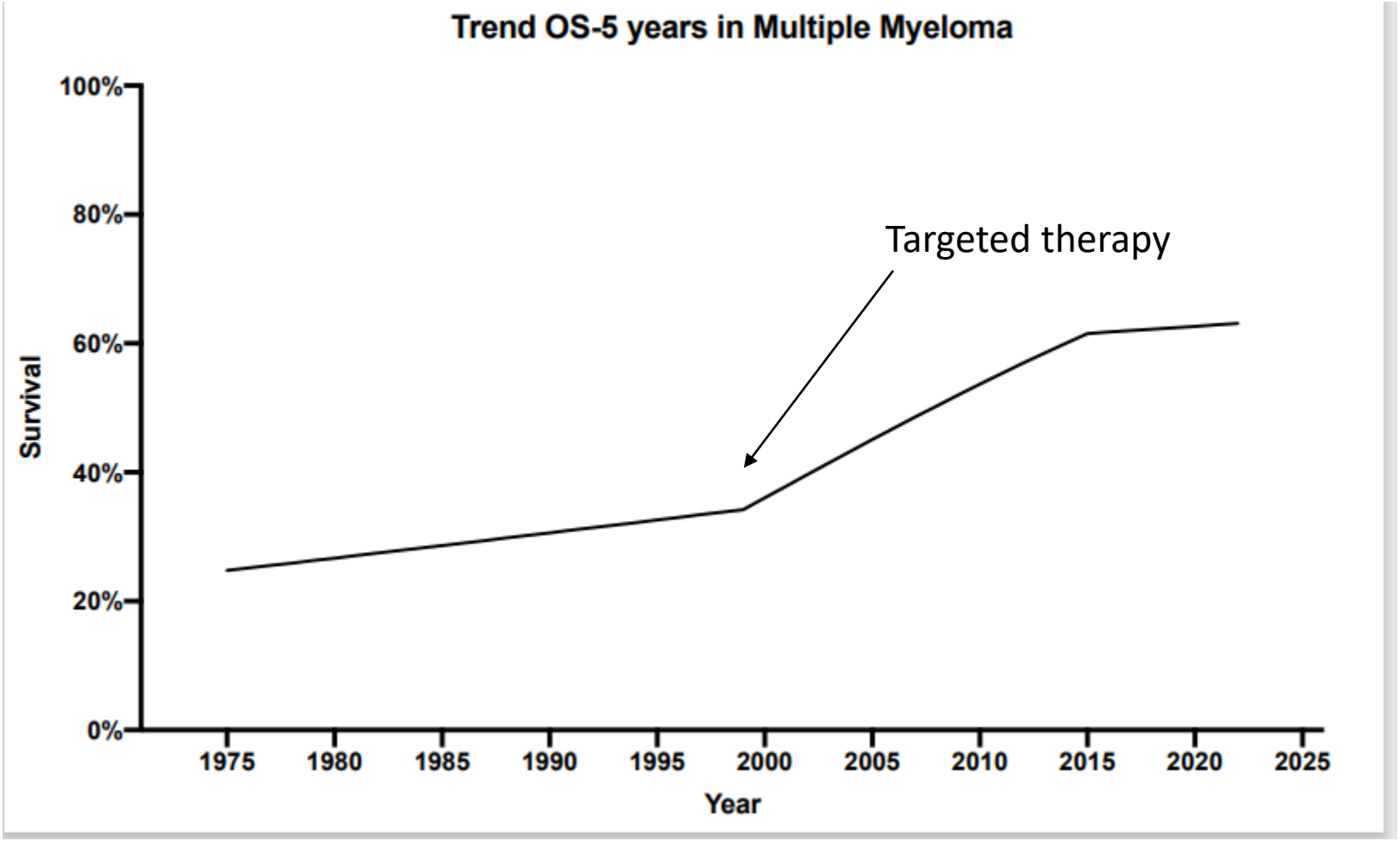
Teclistamab



Daratumumab



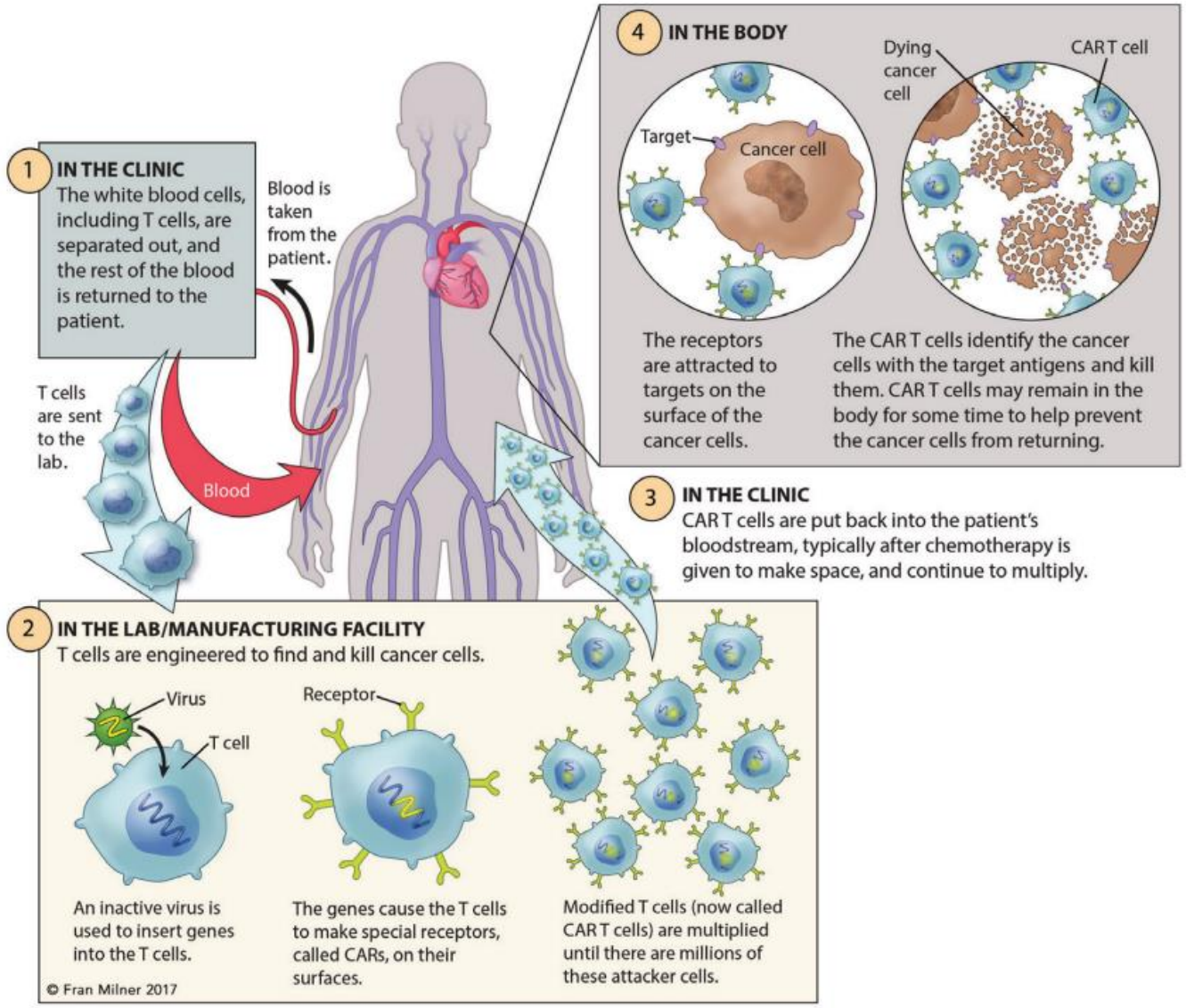
Mieloma & Sopravvivenza



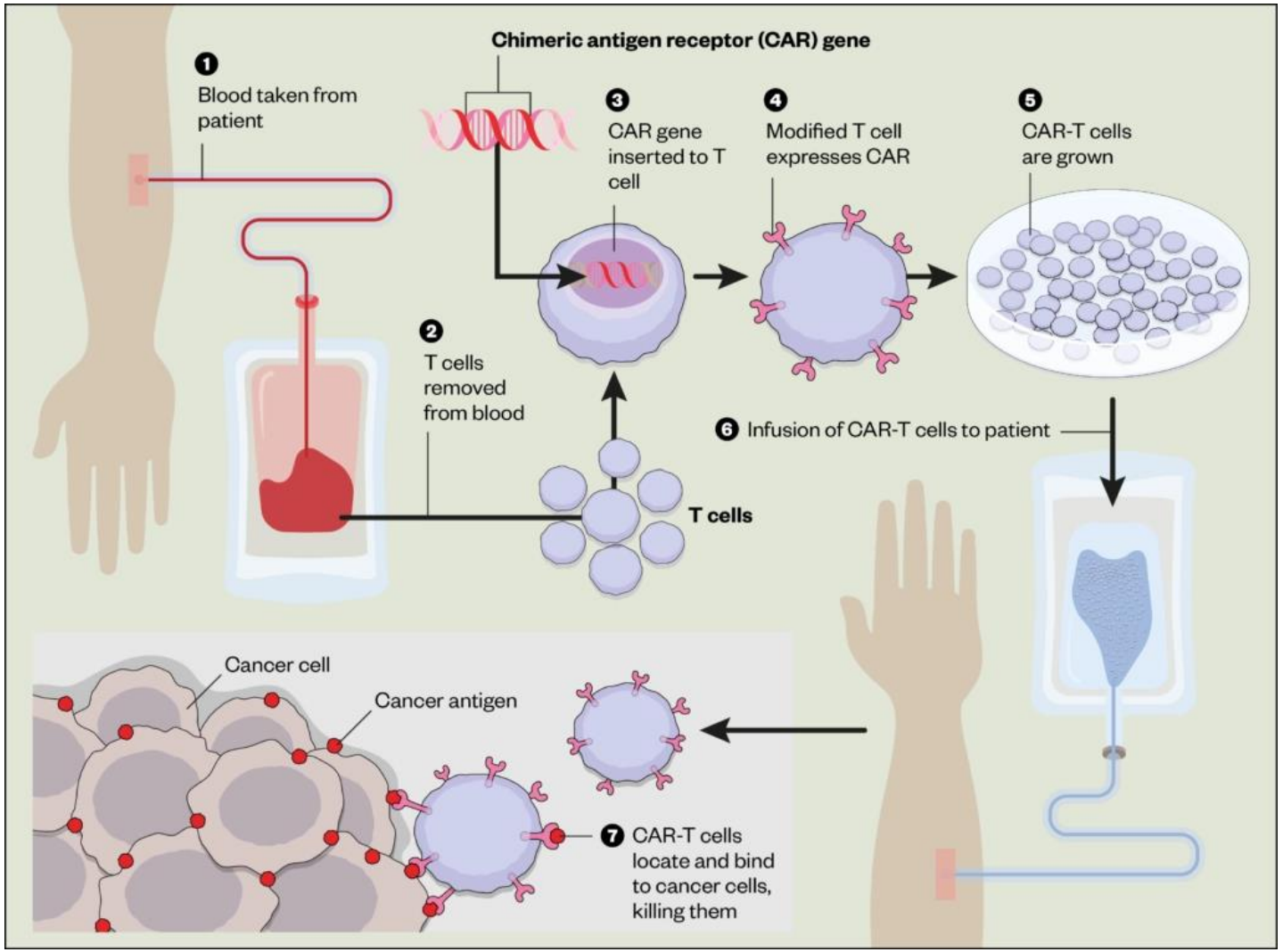
American Cancer Registry 2024

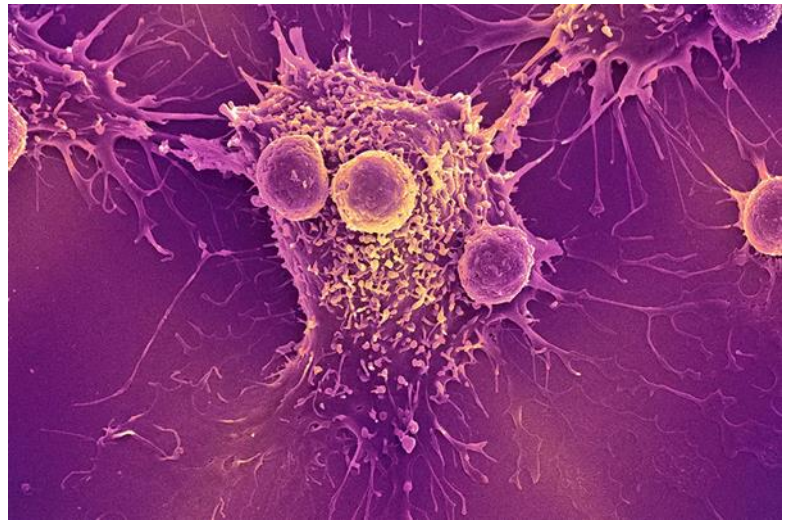
CAR-T

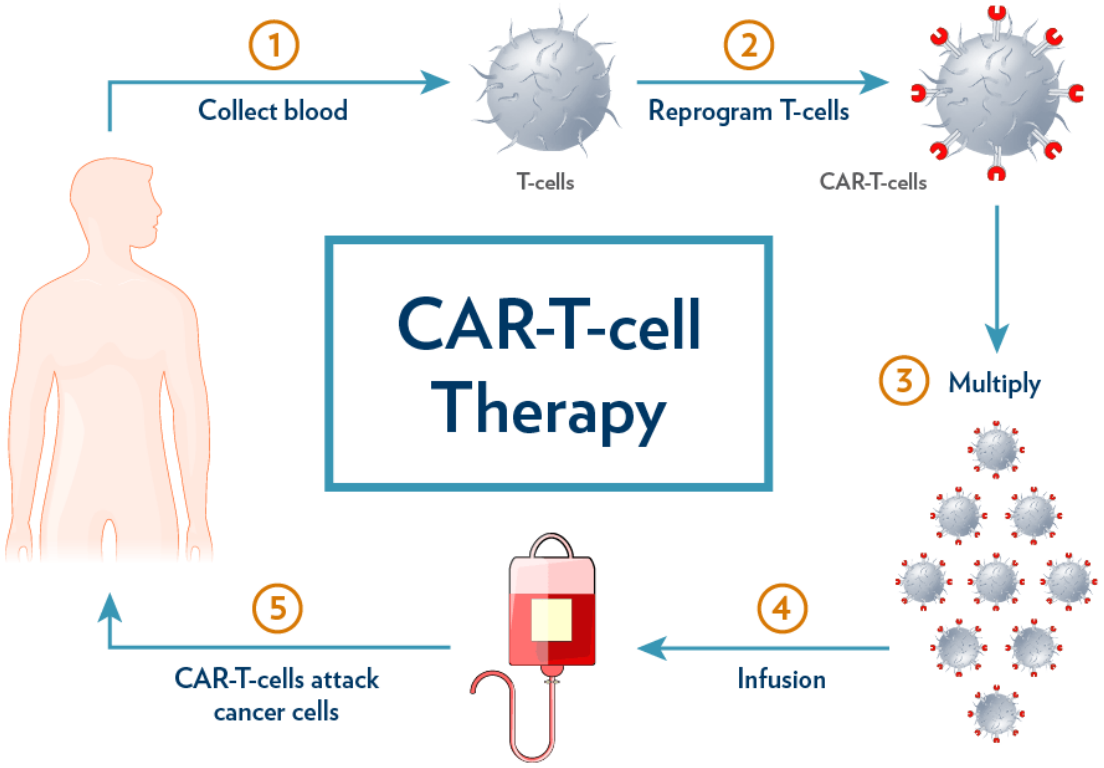
CAR-T therapy



CAR-T THERAPY







1) Terapia «one shot»
2) Costi
3) Effetti collaterali

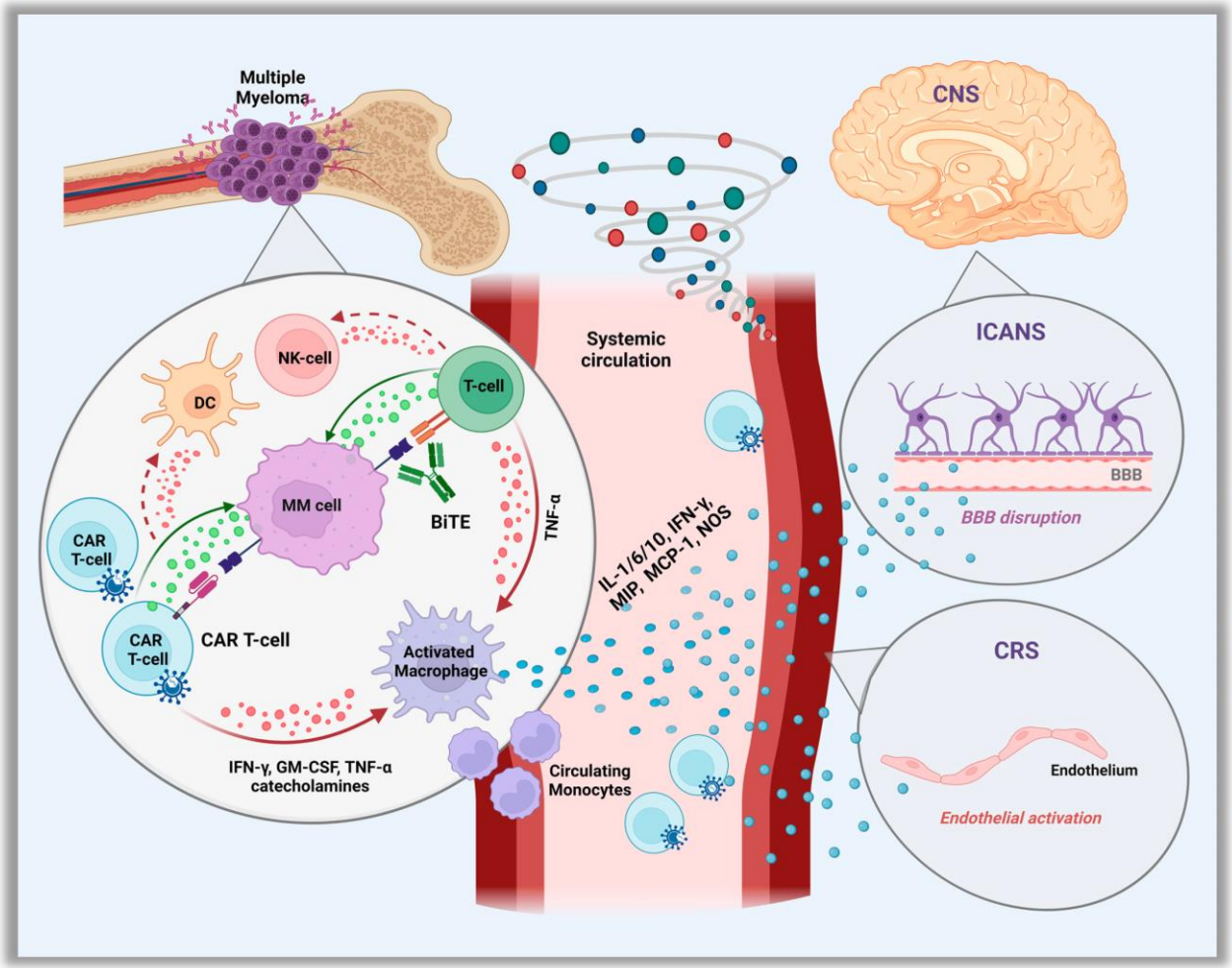
In Italia approvate per:
LNH: lisocabtagene maraleucel (liso-cel) terza linea

Mieloma 4 linea: Abecma (idecabtagene vicleucel liso-cel)

Effetti avversi BiTe/CAR-T

CRS: Cytokine Release Syndrome

ICANS: Immune Cell Associated Neurological Syndrome



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Considerazioni

- Ricerca scientifica
- Terapia «sartorializzata»
- Nuovi farmaci=Nuove tossicità
- Tossicità finanziaria