workshop breve sulle neoplasie ematologiche

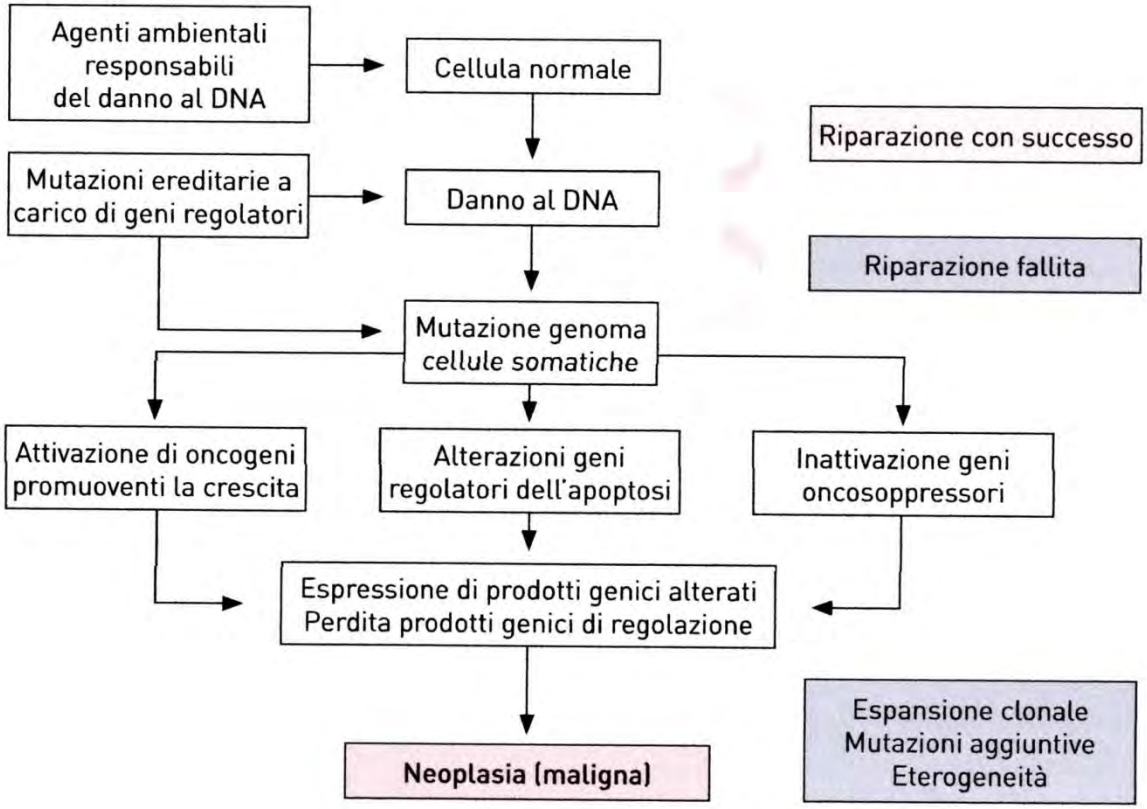
Civitanova Marche 25 gennaio 2020

L’evento cancro perché si possa realizzare richiede più di una mutazione a carico di diverse classi di geni.

La perdita del controllo della proliferazione ha luogo solo in seguito a mutazioni nei geni che controllano la divisione cellulare, la morte cellulare e i processi di riparazione del DNA.

Il nostro organismo è in grado attraverso processi di riparazione e attivazione del sistema immunitario di contrastare i processi di trasformazione ma quando questa capacità viene meno la cellula si trasforma, attraverso varie tappe, in cellula tumorale.

E’ quindi necessario sia l’attivazione dei geni che promuovono la crescita (ONCOGENI) sia l’inattivazione dei geni che inibiscono la crescita (ONCOSOPPRESSORI)


Agenti ambientali responsabili del danno al DNA
Cellula normale
Riparazione con successo
Mutazioni ereditarie a carico di geni regolatori
Danno al DNA
Riparazione fallita
Mutazione genoma cellule somatiche
Attivazione di oncogeni promuoventi la crescita
Alterazioni geni regolatori dell'apoptosi
Inattivazione geni oncosoppressori
Espressione di prodotti genici alterati
Perdita prodotti genici di regolazione
Espansione clonale
Mutazioni aggiuntive
Eterogeneità
Neoplasia (maligna)

	Sufficiente evidenza nell'uomo	Limitata evidenza nell'uomo
Agenti chimici e composti		
Formaldeide	Leucemie, nasofaringe	Cavità nasali e seni paranasali
Benzene	Leucemie	
Agenti occupazionali		
Alluminio	Polmone, vie urinarie	
Alcol isopropilico	Cavità nasali e seni paranasali	
Metalli		
Cromo	Polmone	Cavità nasali e seni paranasali
Nichel	Polmone, cavità nasali e seni paranasali	
Polveri e fibre		
Asbesto	Laringe, polmone, mesotelioma, ovaio	Colon-retto, faringe, stomaco
Polveri di cuoio e di legno	Cavità nasali e seni paranasali	
Radiazioni		
Radon 222	Polmone	Leucemia
Radio 226 e radio 228	Osso, processo mastoide, seni paranasali	
Agenti biologici		
Virus Epstein-Barr	Linfomi, nasofaringe	Carcinoma linfoepiteliale, stomaco
Virus epatite B, C	Carcinoma epatocellulare	Colangiocarcinoma
HV8	Sarcoma di Kaposi e linfoma non-Hodgkin	
Papilloma virus 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Cervice	
Helicobacter pylori	Linfoma, stomaco	
HIV-1	Ano, cervice, occhio (congiuntiva), linfoma di Hodgkin, sarcoma di Kaposi, linfoma non-Hodgkin	Fegato, pene, pelle (non melanoma), vagina, vulva
Abitudini personali		
Alcol	Mammella, colon-retto, laringe, fegato, esofago, cavità orale, faringe	Pancreas
Fumo di tabacco	Leucemia mieloide, cervice, colon-retto, rene, laringe, fegato, polmone, cavità nasali e seni paranasali, esofago, cavo orale, ovaio, pancreas, faringe, stomaco, uretere, vescica; in figli di fumatori: epatoblastoma	Mammella; in figli di fumatori: leucemia
Farmaci		
Ciclosporine	Linfomi non-Hodgkin, cute, altre sedi	
Estrogeni in menopausa	Endometrio, ovaio	Mammella
Contraccettivi con estrogeni e progesterone	Mammella, cervice, fegato	
Estrogeni e progesterone in menopausa	Mammella, endometrio	

TABELLA 2. Agenti cancerogeni per l'uomo e relativi tumori associati. IARC, 2011

(modificata da: Cogliano VJ, Baan R, Straif K, et al. Preventable exposures associated with human cancers. J Natl Cancer Inst 2011; 103 (24):1827-39. doi: 10.1093/jnci/djr483. Epub 2011 Dec 12).

Fattore di rischio	Quota di tumori attribuibili a vari fattori di rischio	
	USA, 2012*	Regno Unito, 2010**
	%	%
Tabacco	33	19
Dieta	5	19
Sovrappeso, obesità	20	5
Inattività fisica	5	1
Abuso di bevande alcoliche	3	4
Fattori occupazionali	5	4
Infezioni	8	3
Radiazioni ionizzanti e esposizione a raggi UV	2	5
Inquinamento ambientale	2	–

TABELLA 1. Quota di tumori attribuibili a vari fattori di rischio

*American Association for Cancer Research, 2013.

** Parkin DM. The fraction of cancer attributable to lifestyle and environmental factors in UK in 2010. Br J Cancer, 2011.

INFEZIONI E CANCRO

- Papillomavirus 16-18 per cancro della cervice
- Virus Epstein-Barr per linfoma e neoplasie del cavo orale
- Herpes Virus 8 per sarcoma di Kaposi e linfomi
- Helycobacter p. per linfomi gastrici e cancro gastrico
- Virus epatite B e C per carcinoma epatocellulare e linfomi MALT
- Infezioni da trematodi per colangiocarcinoma
- Infezioni da schistosoma per tumori della vescica

EREDITARIETA' E CANCRO

- Geni **BRCA 1 e 2** per cancro mammella e ovaio

- Sindrome di Lynch – Questa sindrome, detta anche carcinoma del colon retto non poliposico ereditario (HNPCC), porta anche ad un alto rischio di cancro all'endometrio, tumore alle ovaie, allo stomaco, intestino tenue, pancreas, rene, cervello, uretere e del dotto biliare. In questo caso, la causa può essere una mutazione in uno qualsiasi dei vari geni di riparazione mismatch (MMR): **MLH1, MSH2, MSH6, PMS1 e PMS2**. Questi geni sono normalmente coinvolti nella riparazione del DNA danneggiato; quando uno non funziona, le cellule possono sviluppare errori nel loro DNA che potrebbero portare ad altre mutazioni genetiche

- Sindrome di Li-Fraumeni – La sindrome di Li-Fraumeni può portare, invece, allo sviluppo di numerosi tumori, tra cui il sarcoma, la leucemia, i tumori cerebrali, il cancro della corteccia surrenale e cancro al seno. Le persone affette da questa sindrome possono, addirittura, presentare più tumori nel corso della propria vita. La causa principale sono le mutazioni ereditarie del **gene TP53, un oncosoppressore**. Normalmente, questo gene produce una proteina che impedisce la crescita di cellule anormali: se il gene è mutato, le cellule neoplastiche possono proliferare.

Sede	Maschi	Femmine
Vie aerodigestive superiori*	7.000	2.300
Esofago	1.500	500
Stomaco	8.400	5.900
Colon_Retto**	27.000	22.000
Fegato	8.000	4.600
Colecisti vie biliari	2.400	3.000
Pancreas	6.800	6.700
Polmone	29.500	13.000
Osso	550	500
Melanomi	6.700	5.600
Mesotelioma	1.300	500
Kaposi	700	400
Tessuti_molli	1.400	1.000
Mammella	500	53.000
Ovaio	-	5.300
Utero_cervice	-	2.700
Utero_corpo	-	8.700
Prostata	37.000	-
Testicolo	2.200	-
Rene, vie urinarie***	8.100	4.500
Vescica	24.000	5.700
SNC	3.100	3.200
Tiroide	3.200	9.000
LH	1.300	1.000
LNH	7.200	5.200
Mieloma	3.000	2.700
Leucemie	5.000	3.600
Totale	**196.000**	**175.000**

TABELLA 5. Numero di nuovi casi tumorali, totale e per alcune delle principali sedi, stimati per il 2019 (popolazione italiana residente da previsioni ISTAT – www.demo.istat.it)

*Comprende lingua, bocca, orofaringe, rinofaringe, ipofaringe, faringe NAS, laringe.

**Comprende colon e retto

***Comprende parenchima e pelvi e vie urinarie

LH	1.300	1.000
LNH	7.200	5.200
Mieloma	3.000	2.700
Leucemie	5.000	3.600

Rango	Maschi	Femmine	Tutta la popolazione
1°	Prostata (19%)	Mammella (30%)	Mammella (14%)
2°	Polmone (15%)	Colon-retto (12%)	Colon-retto (13%)
3°	Colon-retto (14%)	Polmone (12%)	Polmone (11%)
4°	Vescica* (12%)	Tiroide (5%)	Prostata (10%)
5°	Stomaco (4%)	Utero corpo (5%)	Vescica* (8%)

TABELLA 6. Primi cinque tumori più frequentemente diagnosticati e proporzione sul totale dei tumori (esclusi i carcinomi della cute) per sesso. Stime per l'Italia 2019

Rango	Maschi			Femmine		
	Età			Età		
	0-49	50-69	70+	0-49	50-69	70+
Totale casi incidenti	100% n=13.297	100% n=80.905	100% n=111.565	100% n=22.430	100% n=64.236	100% n=79.815
1°	Testicolo 12%	Prostata 22%	Prostata 19%	Mammella 40%	Mammella 35%	Mammella 22%
2°	Cute (melanomi) 9%	Polmone 14%	Polmone 17%	Tiroide 16%	Colon-retto 11%	Colon-retto 16%
3°	Tiroide 8%	Colon-retto 12%	Colon-retto 14%	Cute (melanomi) 7%	Utero corpo 7%	Polmone 7%
4°	LNH 8%	Vescica* 11%	Vescica* 12%	Colon-retto 4%	Polmone 7%	Pancreas 6%
5°	Colon-retto 7%	Vie aerodigestive superiori 5%	Stomaco 5%	Utero cervice 4%	Tiroide 5%	Stomaco 5%

TABELLA 7. Primi cinque tumori in termini di frequenza e proporzione sul totale dei tumori incidenti (esclusi i carcinomi della cute) per sesso e fascia di età. Pool AIRTUM 2010-2015 (i dati presentati non sono frutto di stime ma casi reali forniti dai registri per le annate indicate)

* Comprende sia tumori infiltranti sia non infiltranti.

Linfoma di hodgkin

Linfomi non hodgkin

leucemia linfatica cronica

Leucemia mieloide cronica

Leucemie acute

Mieloma multiplo

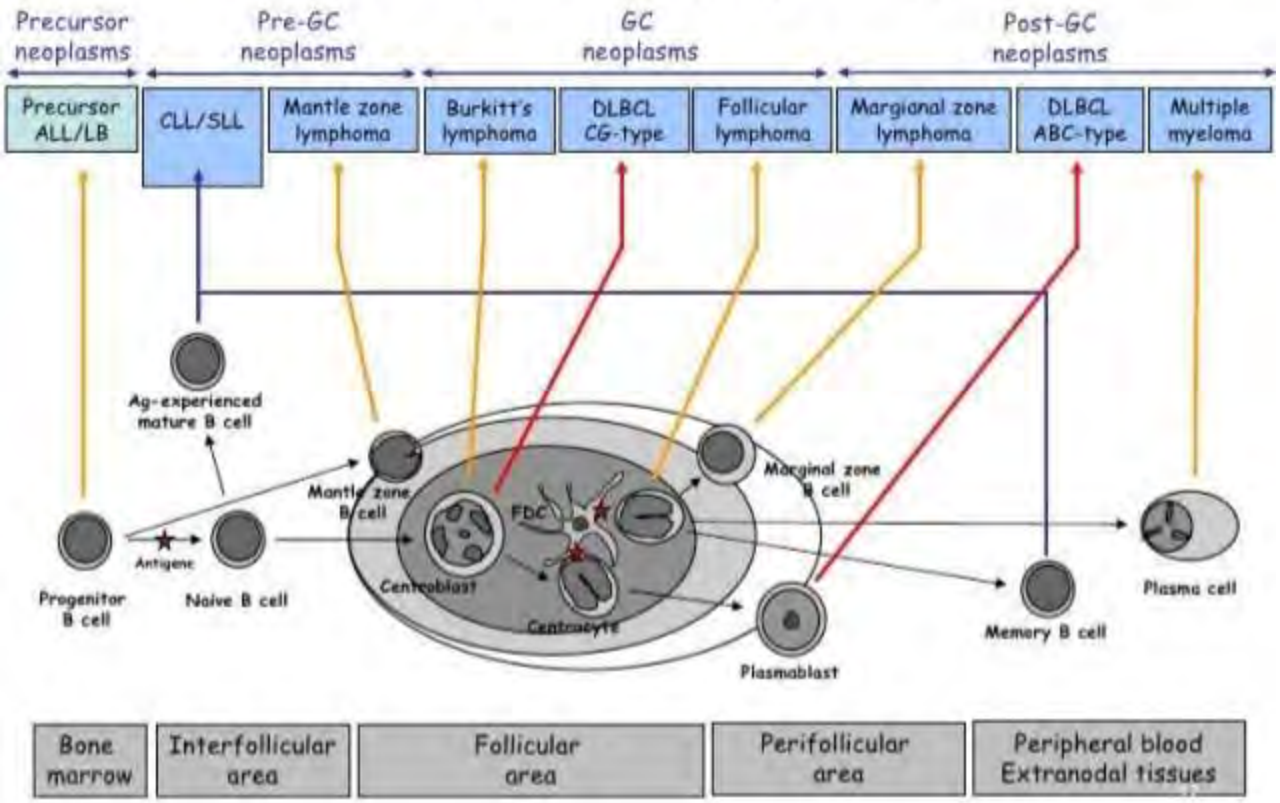
Mielodisplasie

LINFOMA

Definition of Lymphoma

- Heterogeneous group of lymphoproliferative malignancies
  - Results from clonal expansion of tumor cells derived from B, T, or NK cells
  - 85%-90% in the US are derived from B cells
- Variable clinical presentations
  - Range from asymptomatic pick up on routine blood work to painless adenopathy to an emergent medical problem
    - Pain, failure to thrive, organ failure
- Characterized by variable natural histories and therapeutic responses

B-cell ontogeny and lymphomagenesis



WHO Classification of Lymphoma

non Hodgkin lymphoma

Mature B cell neoplasms

- Chronic lymphocytic leukemia/Small lymphocy
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma (such as Wald
- Splenic marginal zone lymphoma
- Plasma cell neoplasms:
  - Plasma cell myeloma
  - Plasmacytoma
  - Monoclonal immunoglobulin deposition diseases
  - Heavy chain diseases
- Extranodal marginal zone B cell lymphoma, also called MALT lymphoma
- Nodal marginal zone B cell lymphoma (NMZL)

Mature T cell and natural killer (NK) cell neoplasms

- T cell prolymphocytic leukemia
- T cell large granular lymphocytic leukemia
- Aggressive NK cell leukemia
- Adult T cell leukemia/lymphoma
- Extranodal NK/T cell lymphoma, nasal type
- Enteropathy-type T cell lymphoma
- Hepatosplenic T cell lymphoma
- Blastic NK cell lymphoma
- Mycosis fungoides / Sezary syndrome
- Primary cutaneous CD30-positive T cell lymphoproliferative disorders
  - Primary cutaneous anaplastic large cell lymphoma
  - Lymphomatoid papulosis
- Angioimmunoblastic T cell lymphoma
- Peripheral T cell lymphoma, unspecified
- Anaplastic large cell lymphoma

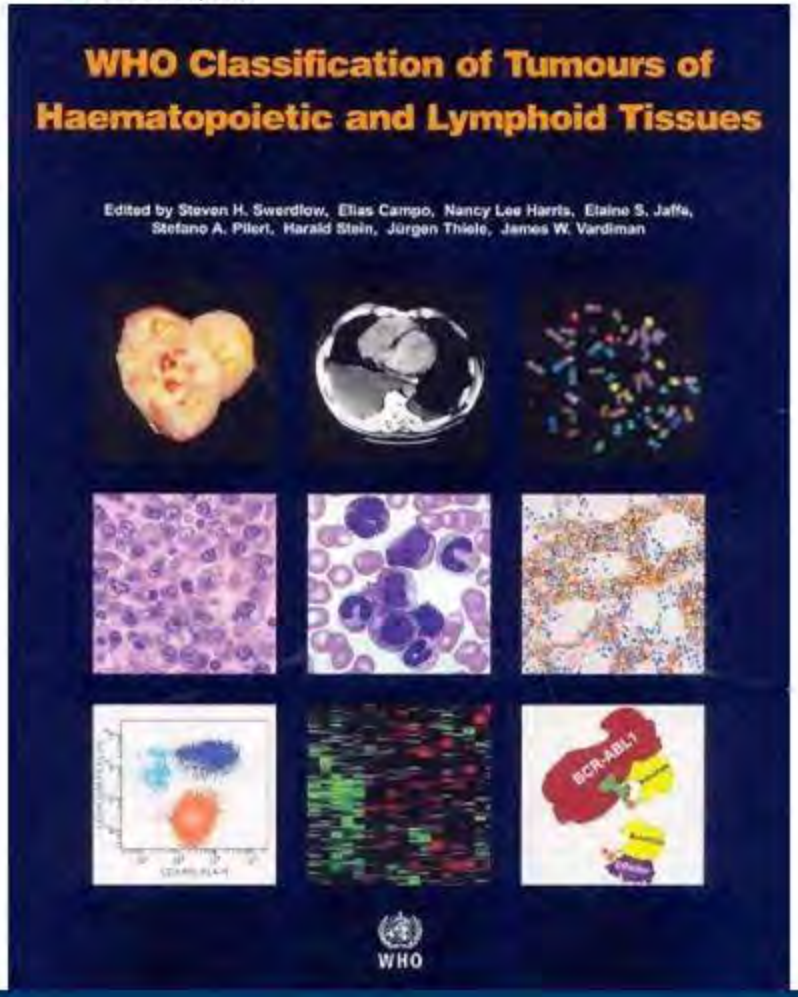
Hodgkin lymphoma

Main article: Hodgkin lymphoma

- Classical Hodgkin lymphomas:
  - Nodular sclerosis
  - Mixed cellularity
  - Lymphocyte-rich
  - Lymphocyte depletec
- Nodular lymphocyte-pre

Immunodeficiency-associated lymphoproliferative disorders

- Associated with a primary immune disorder
- Associated with the Human Immunodeficiency Virus (HIV)
- Post-transplant



Blastic plasmacytoid dendritic cell neoplasm	9727/3
Acute leukaemias of ambiguous lineage	
Acute undifferentiated leukaemia	9801/3
Mixed-phenotype acute leukaemia with t(9;22)(q34.1;q11.2); *BCR-ABL1*	9806/3
Mixed-phenotype acute leukaemia with t(v;11q23.3); *KMT2A*-rearranged	9807/3
Mixed-phenotype acute leukaemia, B/myeloid, NOS	9808/3
Mixed-phenotype acute leukaemia, T/myeloid, NOS	9809/3
Mixed-phenotype acute leukaemia, NOS, rare types	
Acute leukaemias of ambiguous lineage, NOS	
Precursor lymphoid neoplasms	
B-lymphoblastic leukaemia/lymphoma, NOS	9811/3
B-lymphoblastic leukaemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*	9812/3
B-lymphoblastic leukaemia/lymphoma with t(v;11q23.3); *KMT2A*-rearranged	9813/3
B-lymphoblastic leukaemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*	9814/3
B-lymphoblastic leukaemia/lymphoma with hyperdiploidy	9815/3
B-lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)	9816/3
B-lymphoblastic leukaemia/lymphoma with t(5;14)(q31.1;q32.1); IGH/*IL3*	9817/3
B-lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*	9818/3
B-lymphoblastic leukaemia/lymphoma, *BCR-ABL1*–like	9819/3*
B-lymphoblastic leukaemia/lymphoma with iAMP21	9811/3
T-lymphoblastic leukaemia/lymphoma	9837/3
Early T-cell precursor lymphoblastic leukaemia	9837/3
NK-lymphoblastic leukaemia/lymphoma	
Mature B-cell neoplasms	
Chronic lymphocytic leukaemia (CLL)/ small lymphocytic lymphoma	9823/3
Monoclonal B-cell lymphocytosis, CLL-type	9823/1*
Monoclonal B-cell lymphocytosis, non-CLL-type	9591/1*
B-cell prolymphocytic leukaemia	9833/3
Splenic marginal zone lymphoma	9689/3
Hairy cell leukaemia	9940/3
Splenic B-cell lymphoma/leukaemia, unclassifiable	9591/3
Splenic diffuse red pulp small B-cell lymphoma	9591/3
Hairy cell leukaemia variant	9591/3
Lymphoplasmacytic lymphoma	9671/3
Waldenström macroglobulinemia	9761/3
IgM monoclonal gammopathy of undetermined significance	9761/1*
Heavy chain diseases	
Mu heavy chain disease	9762/3
Gamma heavy chain disease	9762/3
Alpha heavy chain disease	9762/3
Plasma cell neoplasms	
Non-IgM monoclonal gammopathy of undetermined significance	9765/1
Plasma cell myeloma	9732/3
Solitary plasmacytoma of bone	9731/3
Extraosseous plasmacytoma	9734/3
Monoclonal immunoglobulin deposition diseases	
Primary amyloidosis	9769/1
Light chain and heavy chain deposition diseases	9769/1
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3
Nodal marginal zone lymphoma	9699/3
Paediatric nodal marginal zone lymphoma	9699/3
Follicular lymphoma	9690/3
In situ follicular neoplasia	9695/1*
Duodenal-type follicular lymphoma	9695/3
Testicular follicular lymphoma	9690/3
Paediatric-type follicular lymphoma	9690/3
Large B-cell lymphoma with IRF4 rearrangement	9698/3
Primary cutaneous follicle centre lymphoma	9597/3
Mantle cell lymphoma	9673/3
In situ mantle cell neoplasia	9673/1*
Diffuse large B-cell lymphoma (DLBCL), NOS	9680/3
Germinal centre B-cell subtype	9680/3
Activated B-cell subtype	9680/3
T-cell/histiocyte-rich large B-cell lymphoma	9688/3
Primary DLBCL of the CNS	9680/3
Primary cutaneous DLBCL, leg type	9680/3
EBV-positive DLBCL, NOS	9680/3
EBV-positive mucocutaneous ulcer	9680/1*
DLBCL associated with chronic inflammation	9680/3
Fibrin-associated diffuse large B-cell lymphoma	
Lymphomatoid granulomatosis, grade 1, 2	9766/1
Lymphomatoid granulomatosis, grade 3	9766/3*
Primary mediastinal (thymic) large B-cell lymphoma	9679/3
Intravascular large B-cell lymphoma	9712/3
ALK-positive large B-cell lymphoma	9737/3
Plasmablastic lymphoma	9735/3
Primary effusion lymphoma	9678/3
Multicentric Castleman disease	
HHV8-positive DLBCL, NOS	9738/3
HHV8-positive germinotropic lymphoproliferative disorder	9738/1*
Burkitt lymphoma	9687/3
Burkitt-like lymphoma with 11q aberration	9687/3*
High-grade B-cell lymphoma	
High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements	9680/3
High-grade B-cell lymphoma, NOS	9680/3
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma	9596/3

Mature T- and NK-cell neoplasms

T-cell prolymphocytic leukaemia	9834/3
T-cell large granular lymphocytic leukaemia	9831/3
Chronic lymphoproliferative disorder of NK cells	9831/3
Aggressive NK-cell leukaemia	9948/3
Systemic EBV-positive T-cell lymphoma of childhood	9724/3
Chronic active EBV infection of T- and NK-cell type, systemic form	
Hydroa vacciniforme–like lymphoproliferative disorder	9725/1*
Severe mosquito bite allergy	
Adult T-cell leukaemia/lymphoma	9827/3
Extranodal NK/T-cell lymphoma, nasal type	9719/3
Enteropathy-associated T-cell lymphoma	9717/3
Monomorphic epitheliotropic intestinal T-cell lymphoma	9717/3
Intestinal T-cell lymphoma, NOS	9717/3
Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract	9702/1*
Hepatosplenic T-cell lymphoma	9716/3
Subcutaneous panniculitis-like T-cell lymphoma	9708/3
Mycosis fungoides	9700/3
Sézary syndrome	9701/3
Primary cutaneous CD30-positive T-cell lymphoproliferative disorders	
Lymphomatoid papulosis	9718/1*
Primary cutaneous anaplastic large cell lymphoma	9718/3
Primary cutaneous gamma delta T-cell lymphoma	9726/3
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma	9709/3
Primary cutaneous acral CD8-positive T-cell lymphoma	9709/3*
Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder	9709/1
Peripheral T-cell lymphoma, NOS	9702/3
Angioimmunoblastic T-cell lymphoma	9705/3
Follicular T-cell lymphoma	9702/3
Nodal peripheral T-cell lymphoma with T follicular helper phenotype	9702/3
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9715/3*
Breast implant–associated anaplastic large cell lymphoma	9715/3*

Hodgkin lymphomas

Nodular lymphocyte predominant Hodgkin lymphoma	9
Classic Hodgkin lymphoma	9
Nodular sclerosis classic Hodgkin lymphoma	9
Lymphocyte-rich classic Hodgkin lymphoma	9
Mixed cellularity classic Hodgkin lymphoma	9
Lymphocyte-depleted classic Hodgkin lymphoma	9

Immunodeficiency-associated lymphoproliferative disorders

Post-transplant lymphoproliferative disorders (PTLD)	
Non-destructive PTLD	
Plasmacytic hyperplasia PTLD	
Infectious mononucleosis PTLD	
Florid follicular hyperplasia	
Polymorphic PTLD	9
Monomorphic PTLD	**
Classic Hodgkin Lymphoma PTLD	9
Other iatrogenic immunodeficiency-associated lymphoproliferative disorders	

Histiocytic and dendritic cell neoplasms

Histiocytic sarcoma	9
Langerhans cell histiocytosis, NOS	9
Langerhans cell histiocytosis, monostotic	9
Langerhans cell histiocytosis, polystotic	9
Langerhans cell histiocytosis, disseminated	9
Langerhans cell sarcoma	9
Indeterminate dendritic cell tumour	9
Interdigitating dendritic cell sarcoma	9
Follicular dendritic cell sarcoma	9
Fibroblastic reticular cell tumour	9
Disseminated juvenile xanthogranuloma	
Erdheim–Chester disease	9

The morphology codes are from the International Classification of Dis for Oncology (ICD-O) (1257A). Behaviour is coded /0 for benign tumo /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinom situ and grade III intraepithelial neoplasia; and /3 for malignant tumou The classification is modified from the previous WHO classification, ta into account changes in our understanding of these lesions.

* These new codes were approved by the IARC/WHO Committee for ICD-O.

** These lesions are classified according to the lymphoma to which th correspond, and are assigned the respective ICD-O code.

Italics: Provisional tumour entities.

STADIAZIONE LINFOMI

Esame obiettivo

Ecografia linfonodi (?)

Ecografia addome

TAC

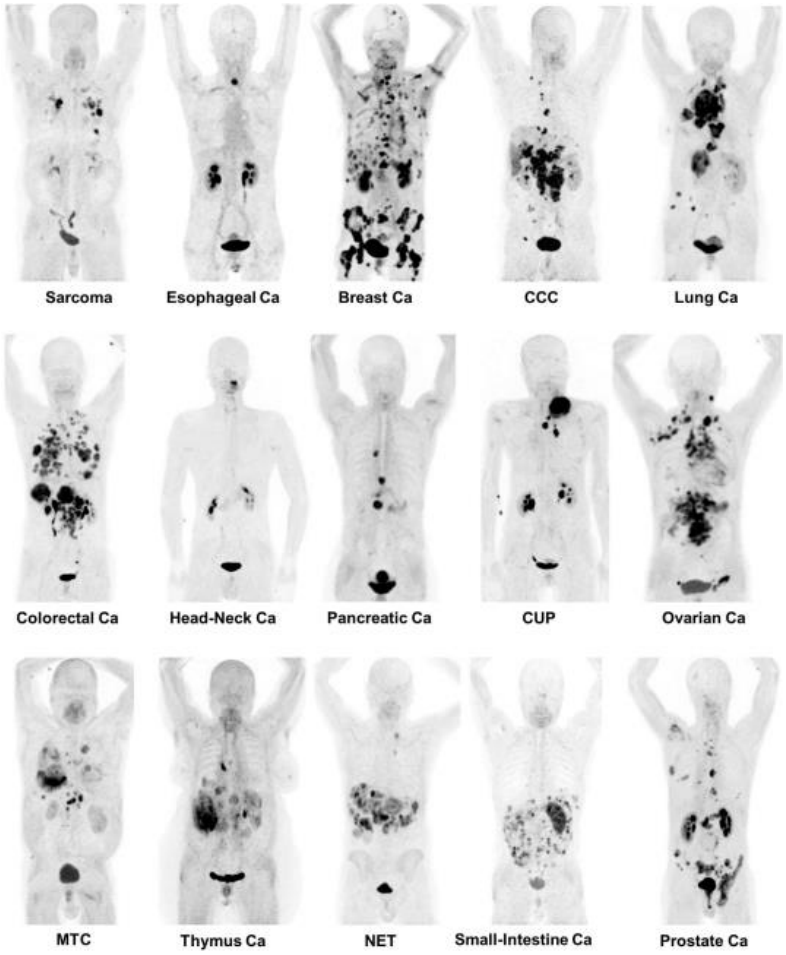
RMN

PET

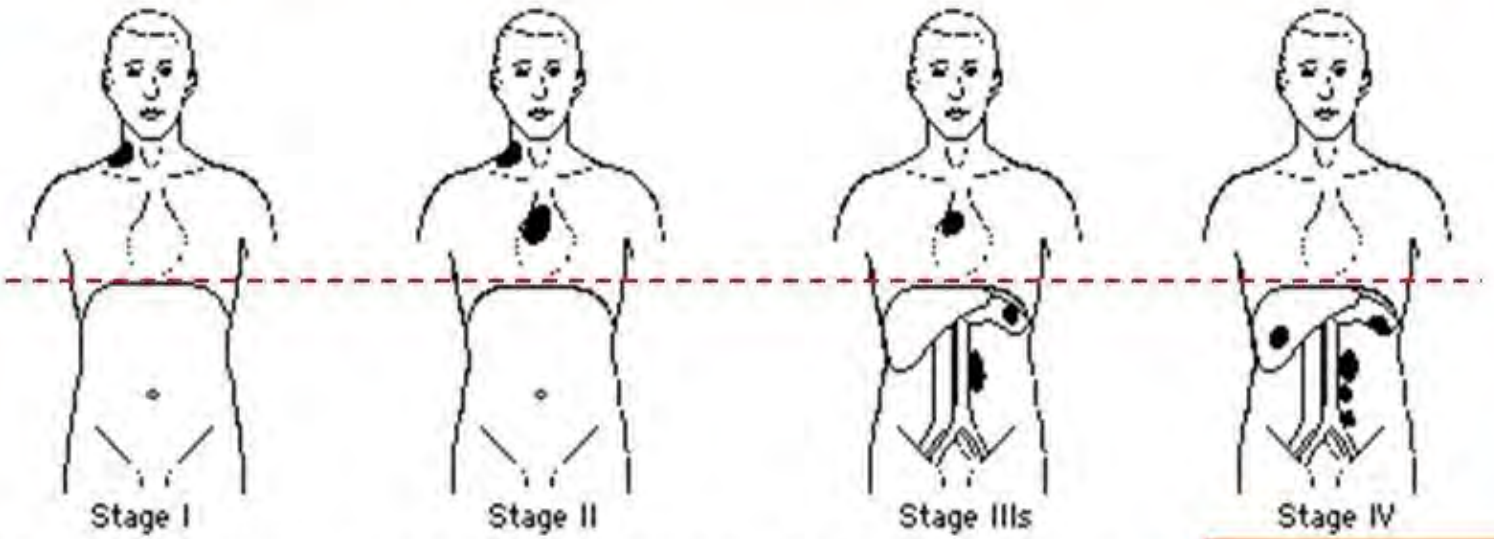
Biopsia ossea

PET

- Sfrutta il decadimento di radionuclidi emettitori di positroni legati a specifiche molecole di trasporto (Glucosio marcato con Fluoro 18-FDG fluorodeossiglucosio)
- Tempo di dimezzamento inferiore a due ore
- Possibilità di associare una macchina TAC (esame TAC-PET)
- Costo esame PET-TAC: circa € 1100
- Altri MDC
  - Colina per K prostata
  - LDOPA per morbo di Parkinson


Sarcoma
Esophageal Ca
Breast Ca
CCC
Lung Ca
Colorectal Ca
Head-Neck Ca
Pancreatic Ca
CUP
Ovarian Ca
MTC
Thymus Ca
NET
Small-Intestine Ca
Prostate Ca

Ann Arbor staging classification for Hodgkin's and NHL



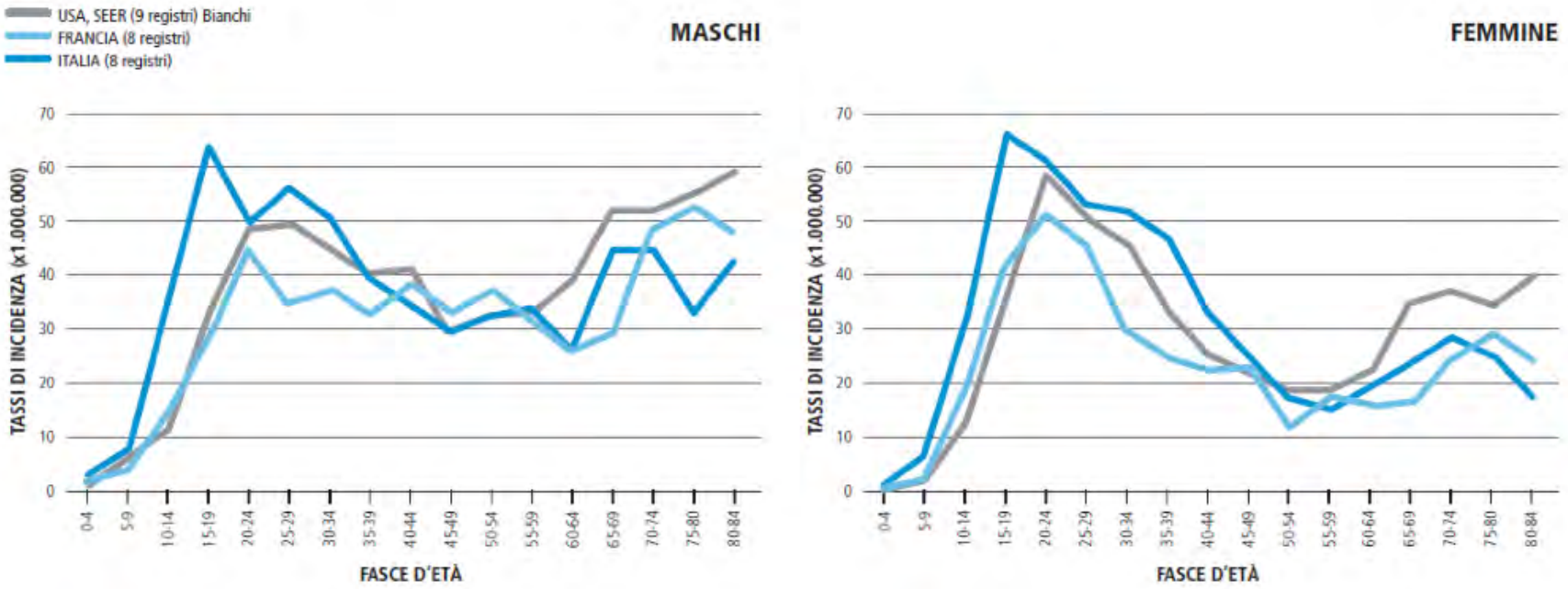
Stage I	Stage II	Stage IIIs	Stage IV
single lymph node region or single extralymphatic site (Ie)	two or more sites, same side of diaphragm or c contiguous extralymphatic site (IIe)	both sides of diaphram or c spleen (IIIs) or contiguous extralymphatic site (IIIe)	diffuse involvement of extralymphatic sites ± nodal disease

Stage subdivision: A-asymptomatic B-unexplained weight loss>10% in 6m and/or fever and/or night sweats

Extralymphatic = tissue other than lymph nodes, thymus, spleen, Waldeyer's ring, appendix & Peyer's patches

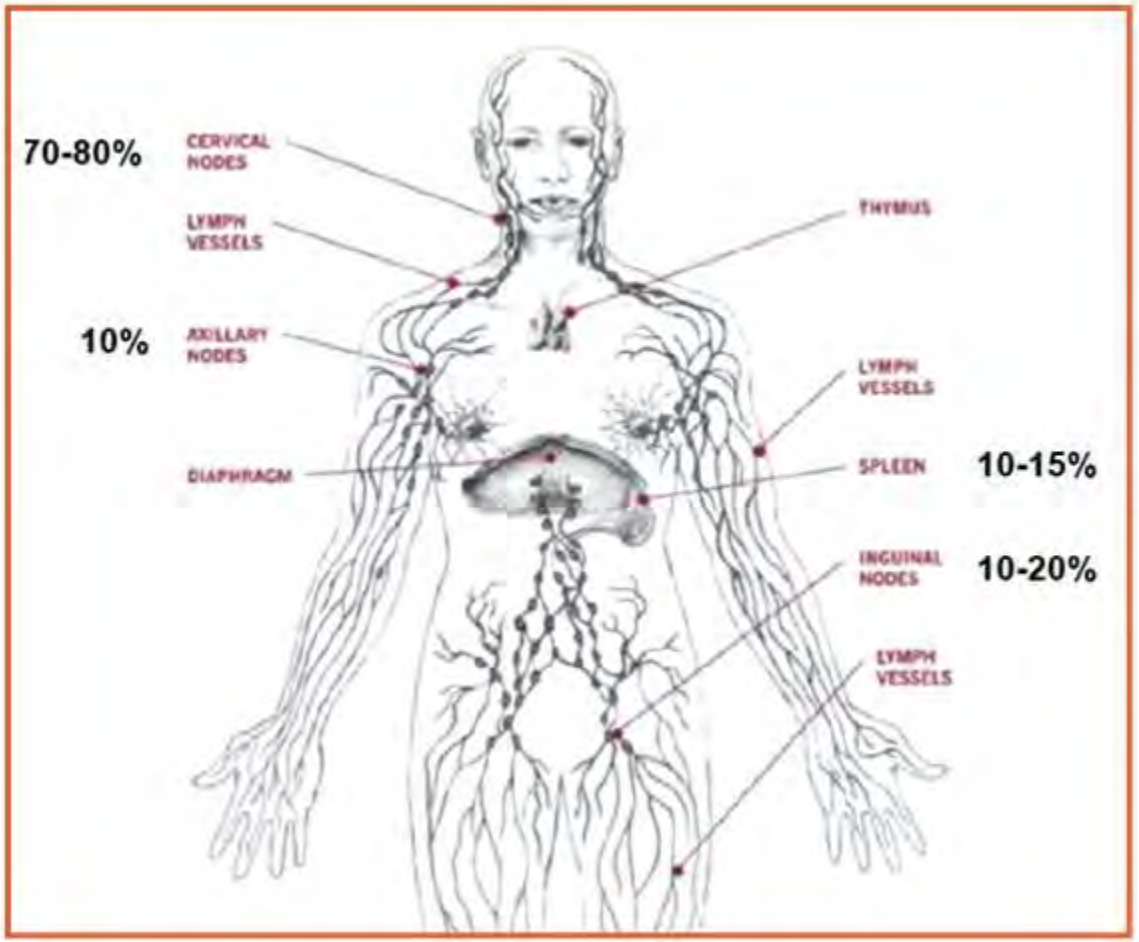
LINFOMA DI HODGKIN

LINFOMA DI HODGKIN: TASSI DI INCIDENZA SPECIFICI PER ETÀ (x1.000.000). MASCHI E FEMMINE (1998-2007). ITALIA, STATI UNITI E FRANCIA
Fonte: Cancer Incidence in Five Continents[3]



- linfoma di Hodgkin a predominanza linfocitaria nodulare (NLPLH) che rappresenta circa il 5% di tutti i LH

- linfoma di Hodgkin classico (cLH) che comprende 4 sottotipi morfologici:
- LH sclero-nodulare 75-80%
- LH a cellularità mista 20-25%
- LH ricco in linfociti 5%
- LH a deplezione linfocitaria <1%


70-80%
CERVICAL NODES
LYMPH VESSELS
10%
AXILLARY NODES
DIAPHRAGM
THYMUS
LYMPH VESSELS
SPLEEN
10-15%
INGUINAL NODES
10-20%
LYMPH VESSELS

Linfomi di Hodgkin - clinica

- Massa linfonodale non dolente con tendenza a riunirsi in pacchetti, ipomobile, con cute sovrastante normale.
  - Frequenza delle loclaizzazioni iniziali
    - superificiale laterocervicale o sporaclaveare (70-80%; sinistra 90%)
    - mediastinica 75%
    - ascellare 25-30%
    - para-aortica 30%
    - iliaci 20%
    - inguinali 15%
    - Milza 10%
    - Fegato 5%
    - Midollo osseo <5%
- Diffusione per via linfatica > per continuità > per via ematica
- Sintomi B (febbre, sudorazioni profuse, calo ponderale)
- prurito “sine materia”

LINFOMA DI HODGKIN

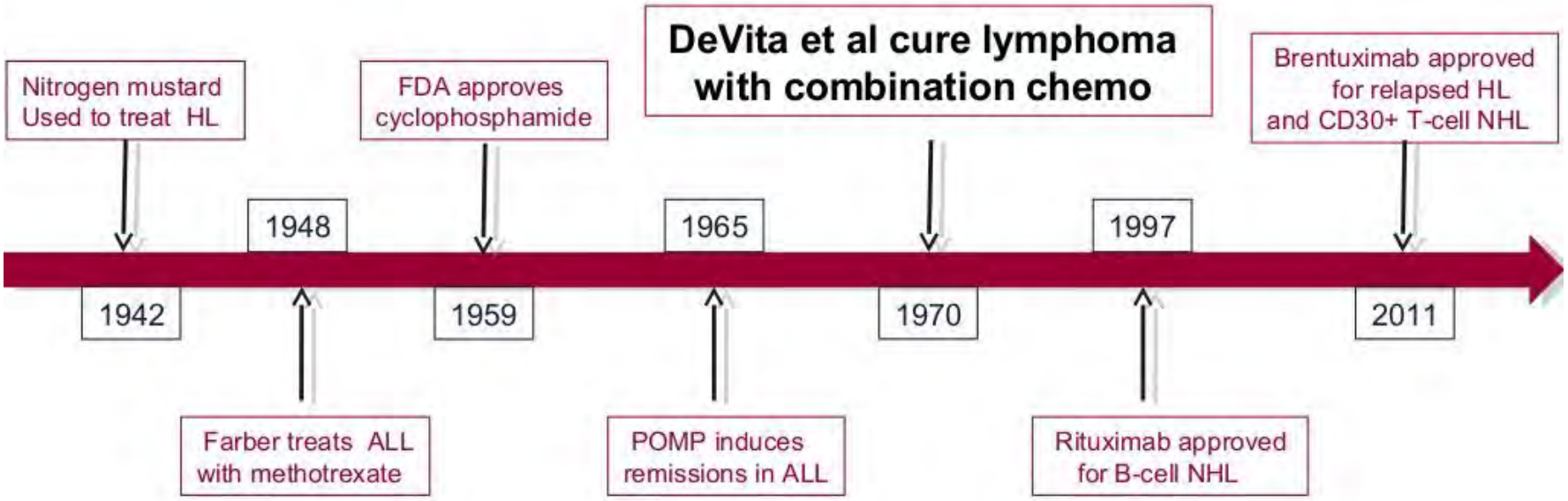
Terapia

- Stadio IA e IIA limitato*: Chemioterapia / Radioterapia
- Stadio IB e IIB limitato*: Chemioterapia / Radioterapia
- Stadio IE e IIE (A e B): Chemioterapia e Radioter. Limitata
- Stadio IIA avanzato*: Chemioterapia e Radioter. Limitata
- Stadio III e IV: Chemioterapia e Radioter. su bulky

*Limitato: coinvolgimento di non più di due sedi contigue

Università di Padova

History of lymphoma chemotherapy



MOPP for lymphoma

Nature Reviews | Cancer

Canellos and DeVita - MOPP which cured patients with Hodgkin and non-Hodgkin lymphoma

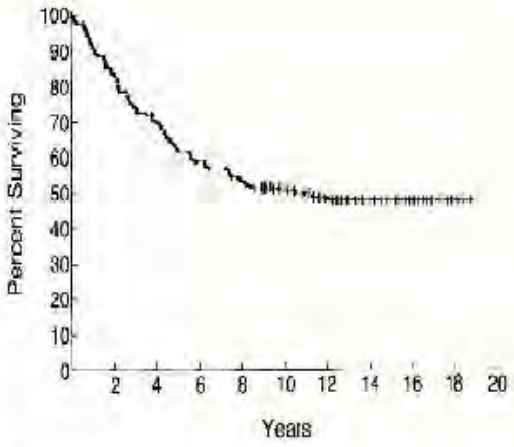
MOPP

- Devised by Devita and Longo in 1970s
- Doses:
  - Nitrogen Mustard 6 mg/m² I/V D1 and D8
  - Vincristine (Oncovine) 1.4 mg/m² IV D1 and D8
  - Procarbazine 100 mg/m² D1 to D14
  - Prednisone 40 mg/m² D1 to D 14
- Cycles repeated every 28 days for 6 such cycles
- Main features:
  - 1st CCT regimen to be started with a CURATIVE intent
  - 6 month treatment program
  - Sliding dosage scale devised to combat bone marrow toxicity.
  - All drugs had non overlapping toxicities and mechanisms of action.

TLC	Platelet (lacs)	Dose adjustment
> 4000	> 1.3	100% all drugs
≥ 3000	≥ 1	100% VCR & PRED 50% HN_2 & PROC
≥ 2000	≥ 0.8	100% PRED 50% VCR 25% HN_2 & PROC
≥ 1500	≥ 0.5	100% PRED 25% VCR
< 1500	< 0.5	100% PRED

MOPP : Results

- CR of 81% documented
- Long term disease free survival rates (10 yrs) in the range of 56% (47% by actuarial analysis)
- 19% of patients attaining CR died of intercurrent illnesses unrelated to HD.
- National mortality figures for Hodgkin lymphoma decreased by more than 60% in the decade that followed the introduction of MOPP chemotherapy.
- Thus, MOPP chemotherapy became the gold standard of care for patients with Stage III / IV Hodgkin's Disease.



Actuarial survival analysis of HD patients treated with MOPP regimen

Toxicity of MOPP

- A highly toxic regimen
- Special precautions indicated while handling nitrogen mustard – can cause vesication on contact with skin or mucosa.
- Main dose limiting toxicity is myelopsuppresssion and it may appear as early as 24 hrs after drug administration.
- Prior to availability of effective anti emetic agents nausea and vomiting were severe enough to merit indoor admission in all patients prior to chemotherapy.
- Additional late toxicity also substantial:
  - 2nd malignancies : Hematological
  - Infertility and premature menopause
  - Neurotoxicity : Due to vincristine

ABVD

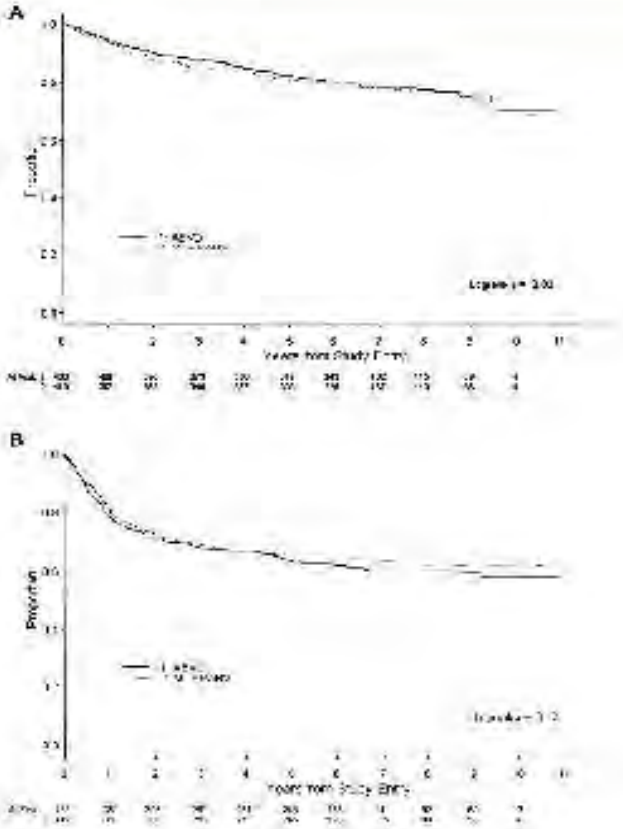
- The four-drug combination of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine (ABVD) was developed by Bonadonna et al at the Istituto Nazionale Tumori in Milan.
- The authors selected these agents because of:
  - Each of the new drugs potentially non cross resistant with MOPP
  - Doxorubicin and Bleomycin has independent efficacy in HD
  - Vinblastine is effective in patients failed on Vincristine
  - Therapeutic efficacy of DTIC in previously treated HD had been demonstrated by Frei et al in 1972.
  - In addition DTIC has little myelotoxicity so can be combined with adriamycin or bleomycin with little synergistic **toxicity**.

ABVD Schedule

- Dosage and Frequency:
  - Adriamycin 25 mg/m^2 IV D1 and D14
  - Bleomycin 10 U/m^2 IV D1 and D14
  - Vinblastine 6 mg/m^2 IV D1 and D14
  - Dacarbazine 375 mg/m^2 D1 and D14
- The authors suggested a D1 and D15 schedule for a minimum of 6 cycles every 28 days.
- Initial 3 patients treated with D1 and D8 schedule had consistent leucopenia at D 8 and so a D1 and D14 schedule was adopted.
- Also the original schedule had DTIC administered in the doses of 150 mg/m^2 D1 to D5 which was later changed to the present schedule.

ABVD alone: Results

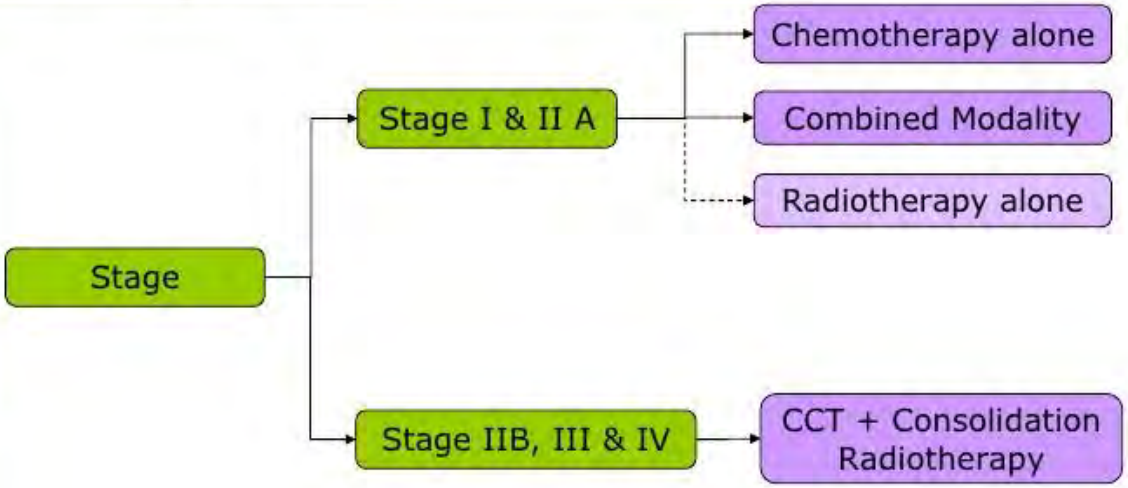
- Trials by Canellos et and Anderson et al had already demonstrated that ABVD alone was better than MOPP alone in terms of CR , FFS and OS.
- Duggan et al compared ABVD alone vs MOPP-ABV hybrid in an intergroup trial randomizing 875 patients.
  - CR: 71% with ABVD (73% for MOPP-ABV), P = NS
  - FFS: 65% with ABVD (67% for MOPP-ABV), P = NS
  - OS: 85% with ABVD (87% for MOPP-ABV), P = NS



Evolution of Rx

1. Clinical Staging equal to Surgical staging
2. Extended field radiotherapy equivalent to IFRT in terms of overall survival.
3. Use of combined modality therapy reduced the risk of failure but failed to improve the overall survival.
4. ABVD showed to be better than MOPP alone and equivalent to MOPP-ABV hybrid regimens.

Management Outline



Limited stage disease

- Definition:
  - Nonbulky Stage IA
  - Nonbulky Stage IIA
- Important features:
  - Almost 90-95% cure rates expected.
  - Disease is radiosensitive and radiocurable
  - Also chemosensitive and chemocurable
  - Relapses rare and easily salvaged
- Optimization of treatment needed:
  - Reduce long term side effects
  - Maintain cure rates
  - Deliver Rx in the most cost effective manner.

Conclusions

- Combined modality approach reduces the number of recurrences but the overall survival remains same when compared to RT alone.
- Extended field radiotherapy is equivalent to involved field radiotherapy in this group.
- 2 - 4 cycles of ABVD with RT are enough to:
  - Eliminate occult HL in the abdomen
  - Prevent recurrence of HL in apparently uninvolved sites adjacent to known HL
- Questions that remain to be answered are:
  - Is the added benefit in terms of freedom from relapse worthwhile in terms of the added toxicity of the additional CCT
  - Are failures after CCT + IFRT more difficult to treat than failures after RT alone.
  - Was CCT alone better than combined modality approach

Unfavorable Early disease

- The 3 factors consistently identified to be associated with a poor prognosis in HD are:
  - Bulky Mediastinal Disease
  - Presence of B symptoms
  - Older age
- Approximately 20% patient relapse when treated with EFRT alone.
- So CCT identified as a modality to treat these patients.

Advanced Disease

- The role of Chemotherapy in advanced disease has already been shown.
- ABVD alone results in good results in advanced disease.
- The standard number of cycles is 6-8 cycles (originally 2 more cycles after attaining CR as recommended by Bonadonna et al)
- A recent CALGB (Canellos et al) trial found 6 - 8 cycles and 12 cycles to be comparable.
- The question is whether RT needs to be added to CCT in advanced HD

More "Intense" regimens

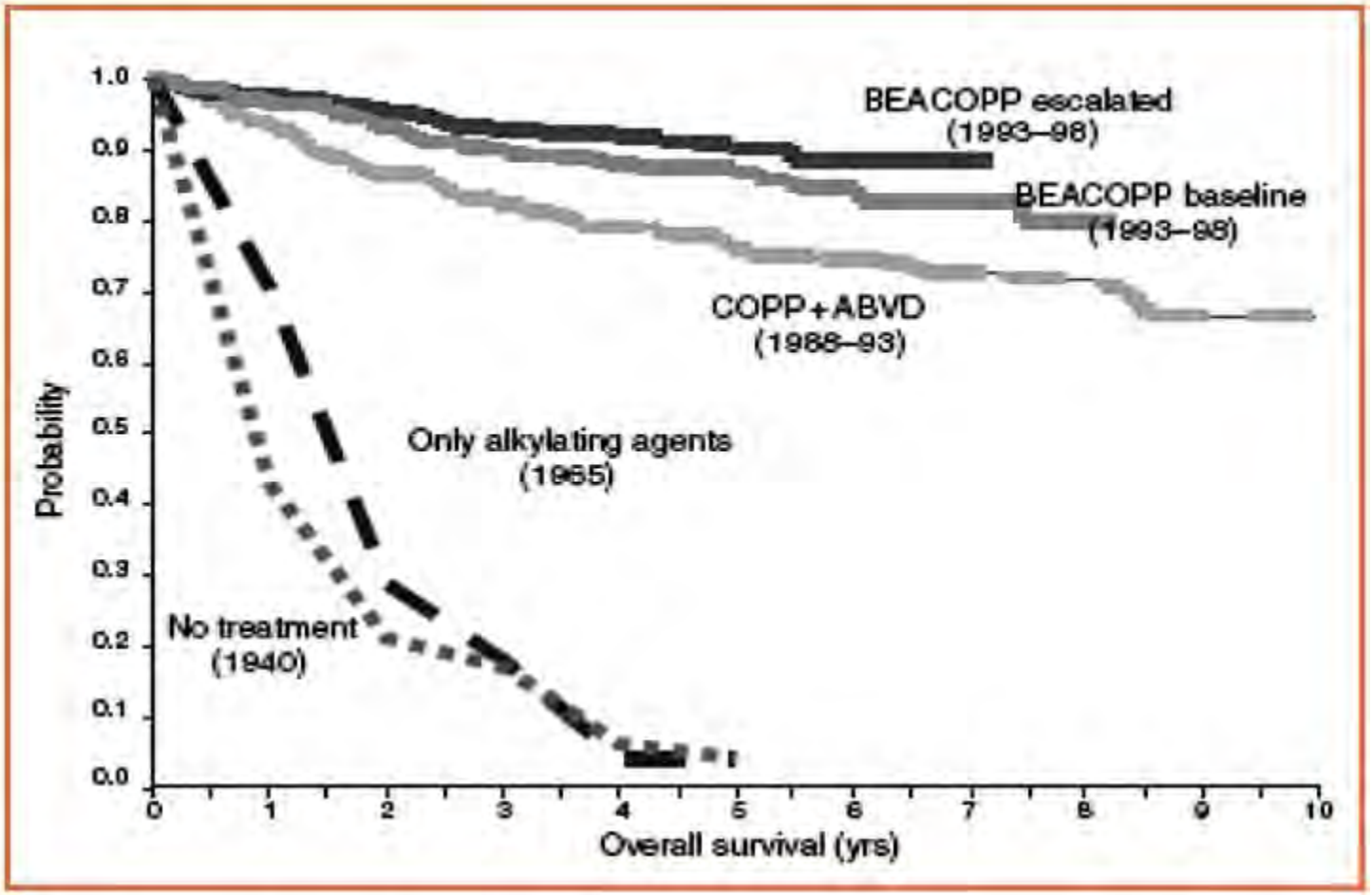
- In an effort to improve the results seen with ABVD attempts were made to:
  - Increase the number of drugs given simultaneously
  - Shorten the period of administration so that greater dose could be given in a shorter period of time.
  - One particular concern was bleomycin induced long term pulmonary toxicity in children when combined with radiation which could be circumvented by use of etoposide.
  - Etoposide also had a 20-60% RR in refractory HL and hence was used in all these regimens
- Dose Intensity: Increasing the dose or the frequency of administration of CCT
- Dose Density: Increasing both the frequency and dose together.

BEACOPP and variants

Drug	Dose	Days	Drug	Dose	Days
BEACOPP		**21**	**BEACOPP Increased Dose**		**22**
Bleomycin	**10**	**8**	Bleomycin	**10**	**8**
Etoposide	**100**	**1–3**	Etoposide	**200**	**1-3**
Adriamycin	**25**	**1**	Adriamycin	**35**	**1**
Cyclophosphamide	**650**	**1**	Cyclophosphamide	**1250**	**1**
Oncovin (vincristine)	**1.4**	**8**	Oncovin	**1.4**	**8**
Procarbazine	**100**	**1–7**	Procarbazine	**100**	**1-7**
Prednisone	**40**	**1–14**	Prednisone	**40**	**1-14**
			G-CSF	—	

Results BEACOPP

- The HD 9 trial evaluated BEACOPP vs COPP-ABVD and escalated BEACOPP.
- Complete response rates were comparable:
  - 83% for COPP-ABVD,
  - 88% for BEACOPP
  - 96% for escalated BEACOPP
- Freedom from failure at 5yrs is **improved** with escalated BEACOPP at 2 yrs p = 0.0001 as compared to COPP-ABVD (85% vs 67%).
- Toxicity:
  - Treatment related deaths were approximately 3%.
  - 16 of the 454 BEACOPP patients, including 11 who received escalated-dose therapy, have developed myelodysplasia or acute leukemia.
  - 100% infertility in men
  - 100% infertility plus premature menopause in most women over the age of 25 years


BEACOPP escalated
(1993–98)
BEACOPP baseline
(1993–98)
COPP+ABVD
(1988–93)
Only alkylating agents
(1965)
No treatment
(1940)
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
6
7
8
9
10
Overall survival (yrs)

Gallamini et al. Haematologica 2006; 91(4)

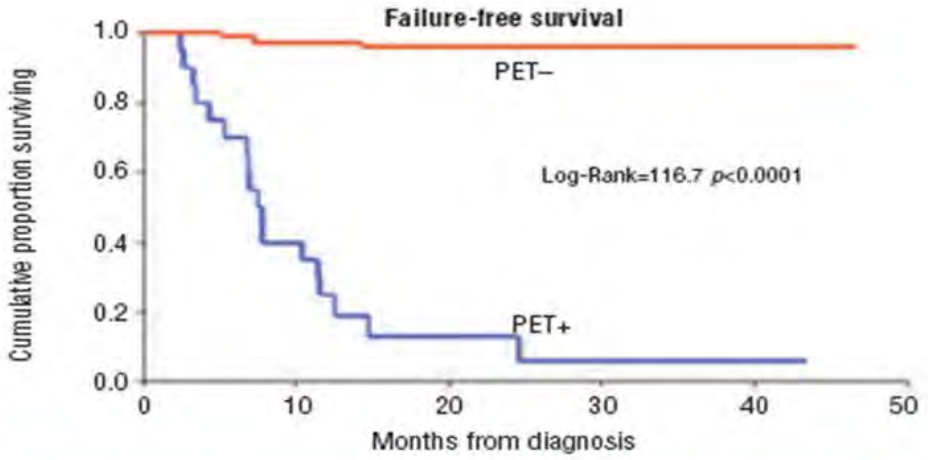
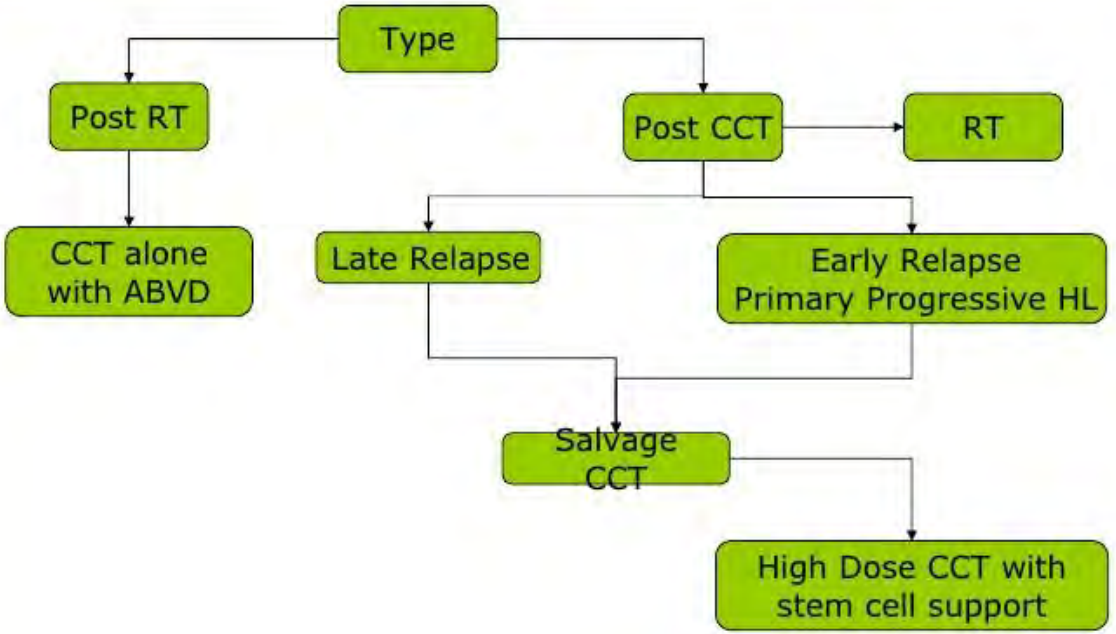


Figure 3. Probability of failure-free survival according to PET-2 results.

Salvage Chemotherapy

- Most frequent ~ 2-5 yrs.
- 3 types of failures known:
  - Primary Progressive HL : ~ 10% of all diagnosed
  - Early relapse (< 12 months): 15% patients
  - Late relapse: 15% patients
- Early recurrence usually implies resistance to the original regimen.
- By proxy it also implies a very poor survival and prognosis.

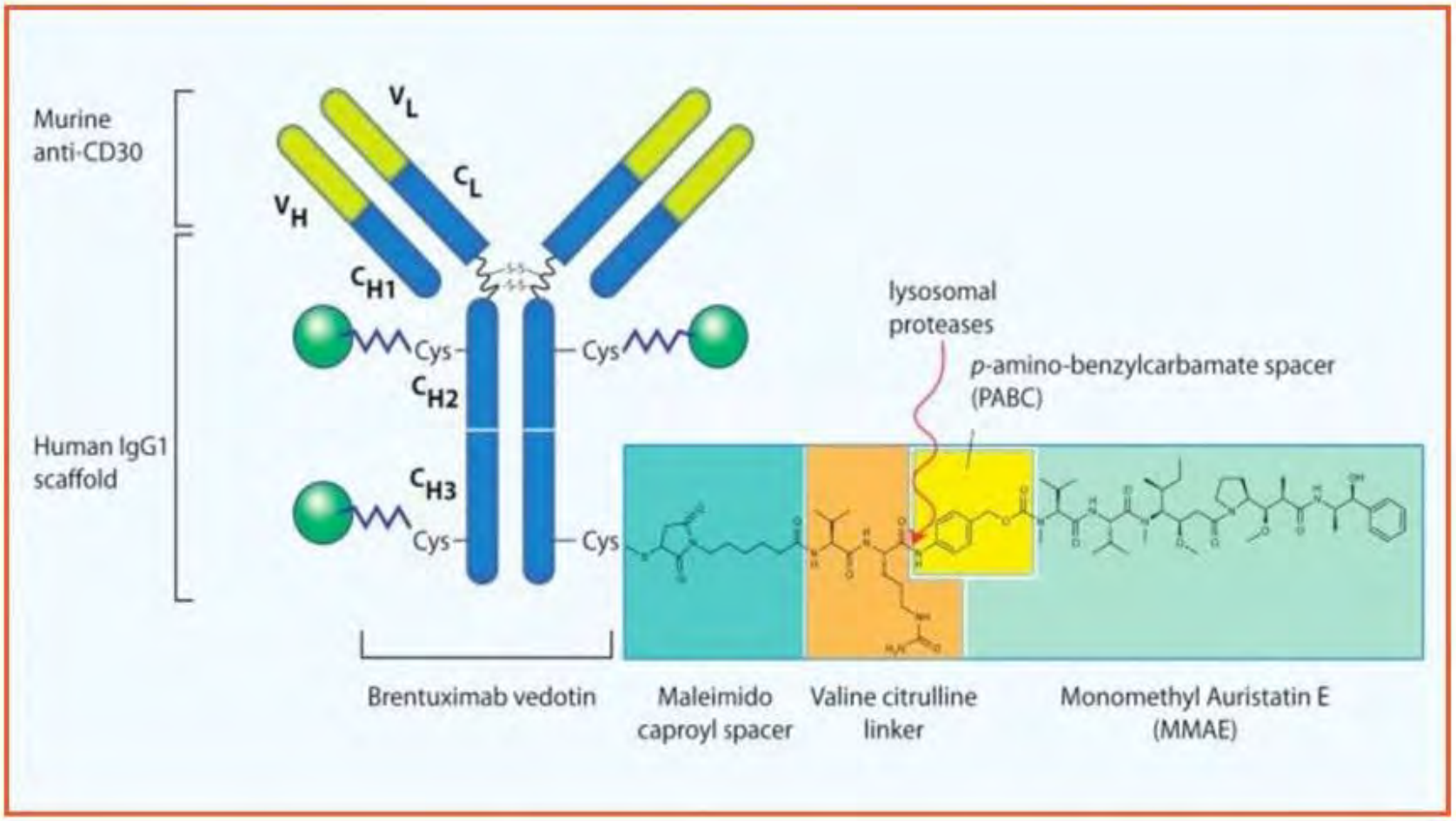
Treatment of recurrence



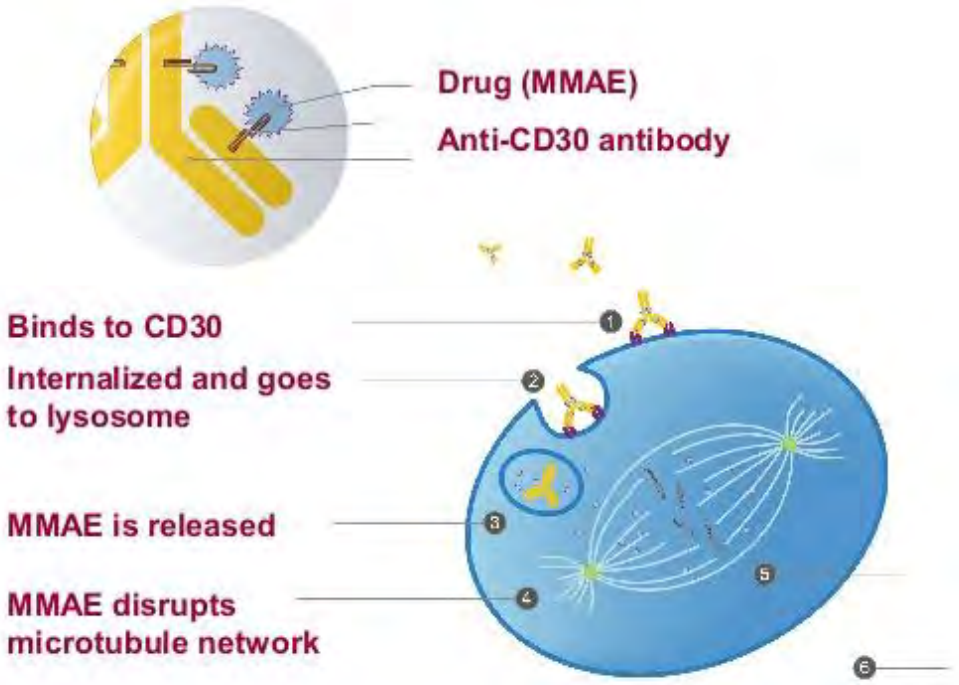
High Dose Chemotherapy

- Given along with stem cell support.
- Usually limited to primary progressive HL and early relapse after salvage CCT failure
- Regimens used:
  - CBV regimen (Cyclophosphamide, BCNU, Etoposide)
  - BEAM (BCNU, Etoposide, Ara-C, Melphalan)
- No diff if TBI or CCT based preparative regimens are used.
- While diff exist in RFS these don't translate into survival differences
- Complications:
  - Treatment related mortality : 14% -5%
  - Infections: Early and delayed
  - MDS / AML risk : 4% -15% within 5yrs.
  - Cardiac and Pulmonary complications
  - Sterility : Universal

BRENTUXIMAB-VEDOTIN è un anticorpo coniugato a farmaco composto da un anticorpo monoclonale anti-CD30 (immunoglobulina chimerica ricombinante G1 [IgG1], prodotto mediante tecnologia del DNA ricombinante in cellule ovariche di criceto cinese), legato in modo covalente all'agente antimicrotubulare monometilauristatina E (MMAE).


Murine
anti-CD30
Human IgG1
scaffold
V_L
C_L
V_H
C_{H1}
C_{H2}
C_{H3}
Cys
Cys
Cys
Cys
lysosomal
proteases
p-amino-benzylcarbamate spacer
(PABC)
Brentuximab vedotin
Maleimido
caproyl spacer
Valine citrulline
linker
Monomethyl Auristatin E
(MMAE)

Brentuximab Vedotin

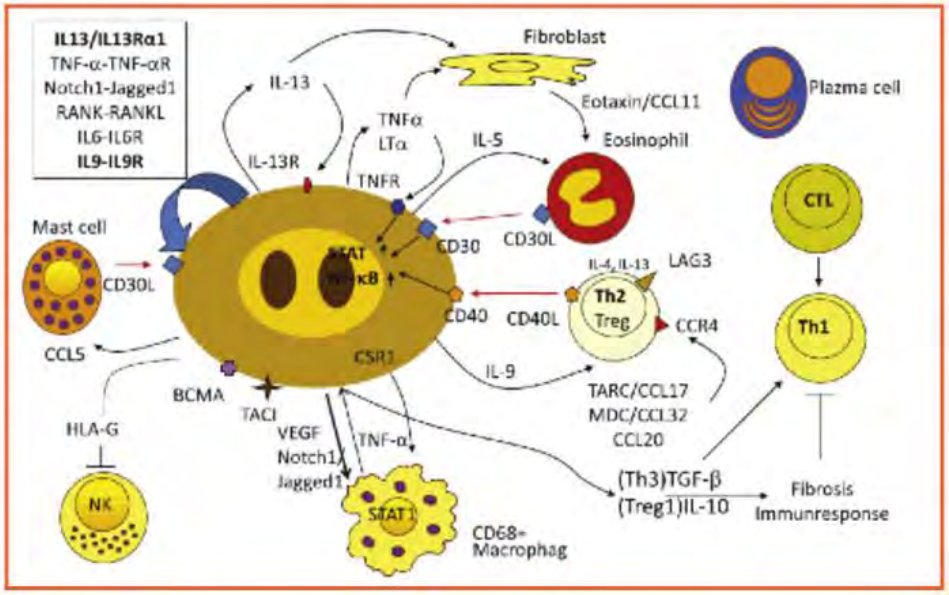


Author	Year	Treatment	Study type	N (pts)	PR	CR	ORR %	Ref
Younes et al.	2010	BV q3wk (dose escalation); MTD 1.8 mgjkg	Phase I	45 (42 HL, 2 ALCL, 1 CD30+ AITL)	7	10	17 (40%)	[49**]
Fanale et al.	2012	BV qlwk (dose escalation); MTD 1.2 mgjkg	Phase I	35 (38 HL, 5 ALCL, 1 PTCL-NOS)	10	14	24 (59 %)	[40]
Younes et al.	2012	BV 1.8 mgfkg q3wk (max 16 cycles)	Phase II	102 (HL relapsed after auto-SCT)	42	34	76 (75 %)	[51]
Pro et al.	2012	BV 1.8 mgfkg q3wk (max 16 cycles)	Phase II	58 (ALCL)	17	33	50 (86 %)	[52]
Gopal et al.	2012	BV 1.2 or 1.8 mgfkg q3wk (max 16 cycles)	Pilot	25 (H L after allo-SCT)	9	3	12 (50 %)	[55]
Younes et al.	2013	BV + ABVO or AVO q2 wk (dose escalation)	Phase I	51 (newly diagnosed HL stage IIB-IV)	45	0	45 (88 %)	[54]

ORR overall response rate; CR, complete response; PR partial response; HL Hodgkin lymphoma; ALCL anaplastic large cell lymphoma; AITL angioimmunoblastic T-cell lymphoma; PTCL-NOS peripheral T-cell lymphoma. not otherwise specified

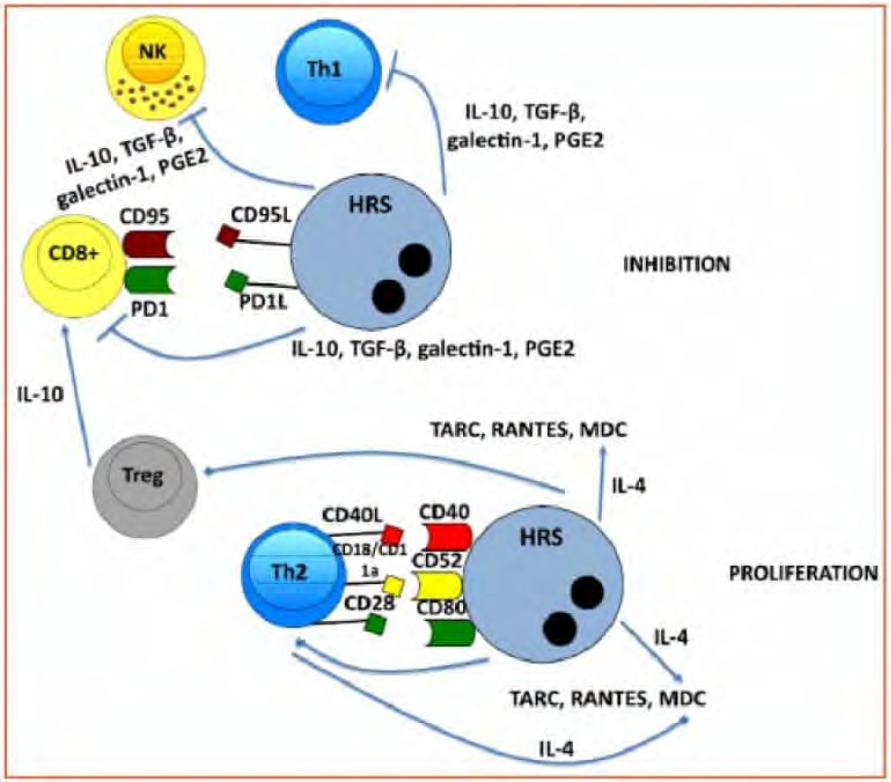
Inibitori dei checkpoint immunitari dell'asse PD1-PDL1-2

INTERAZIONE FRA CELLULA DI REED-STEMBERG E MICROAMBIENTE TUMORALE



La cellula di RS intesse una complessa rete di rapporti con le differenti componenti (cellulari ed extra-cellulari) del microambiente circostante, attraverso interazioni e meccanismi non ancora del tutto chiariti. La cellula neoplastica produce un'ampia serie di citochine e chemochine che attraggono gli elementi non neoplastici
CCL5 (RANTES), CCL17 (TARC), CCL20 e CCL22 attraggono i linfociti Th2
IL-5, IL-9, RANTES, CCL-11, CCL28 e GM-CSF attraggono gli eosinofili
RANTES e IL-9 attraggono i mastociti
IL-8 attrae i neutrofili
IL-6 e CCL28 attraggono le plasmacellule.

Le cellule RS sono infine in grado di modulare la risposta T cellulare attraverso l'inibizione della risposta Th1 mediata a favore di quella Th2 mediata (Jona, 2013)



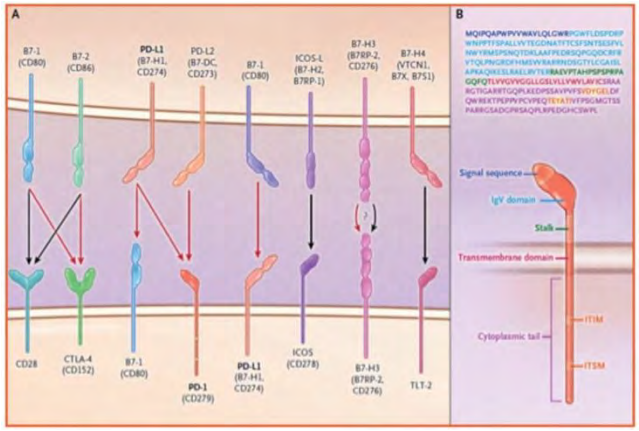
Le cellule RS sono inoltre in grado di evadere la risposta T immune attraverso vari meccanismi:

– ridotta espressione dei complessi MHC di classe I e II

– induzione di meccanismi di inibizione della cellula T attraverso molecole come CTLA-4, LAG-3 e l'asse PD-L1/2-PD-1.

PD-1 (programmed cell death 1 o CD279) è una molecola trasmembrana di 288 aminoacidi appartenente alla superfamiglia delle immunoglobuline. Identificata per la prima volta nelle cellule apoptotiche, è in realtà coinvolta nella modulazione della risposta immune, in particolare quella T-mediata. E' espressa, in misura variabile e soggetta a modulazione, sulle cellule T mature attivate ma anche su altre cellule immunitarie come i linfociti CD4-/CD8- timici, le cellule NK, i linfociti B, i monociti e le cellule di Langerhans immature. Di notevole rilievo è la scoperta della sua **espressione nel melanoma, tumore del polmone, LH.**

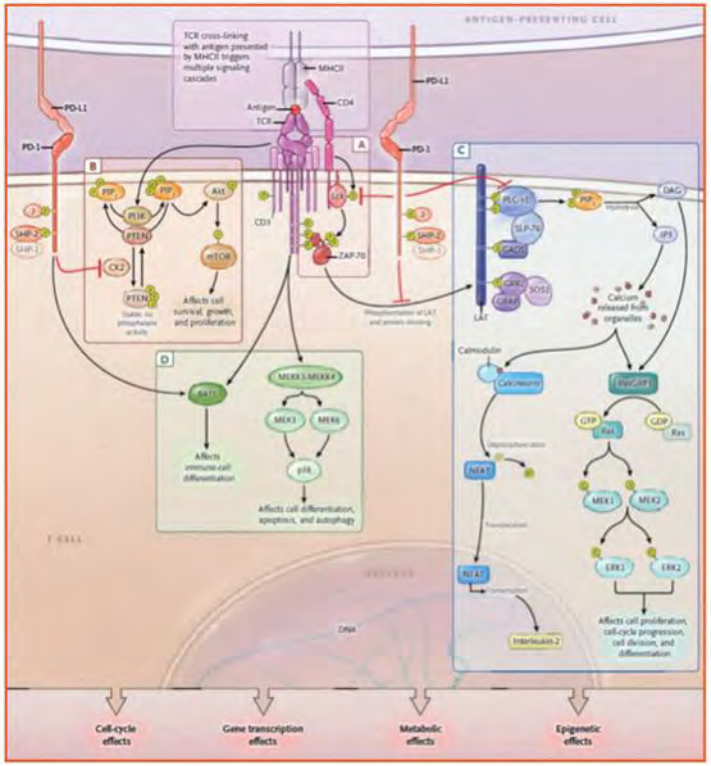
PD-L1 (PD ligand 1) è espressa fisiologicamente a bassi livelli sulle cellule APC (professioniste e non) e su altre cellule non emopoietiche come quelle endoteliali vascolari, pancreatiche e sulle cellule di santuari immunologici come l'occhio, la placenta e il testicolo.



In un contesto fisiologico il legame tra PD-L1/2 e PD-1 svolge un'azione inibitoria sulle cellule T attivate, limitando l'espansione della risposta immune e facilitando quindi la risoluzione del processo infiammatorio.

I meccanismi attraverso cui PD-1 inibisce l'attivazione della cellula T sono molteplici come illustrato nella Figura IV:

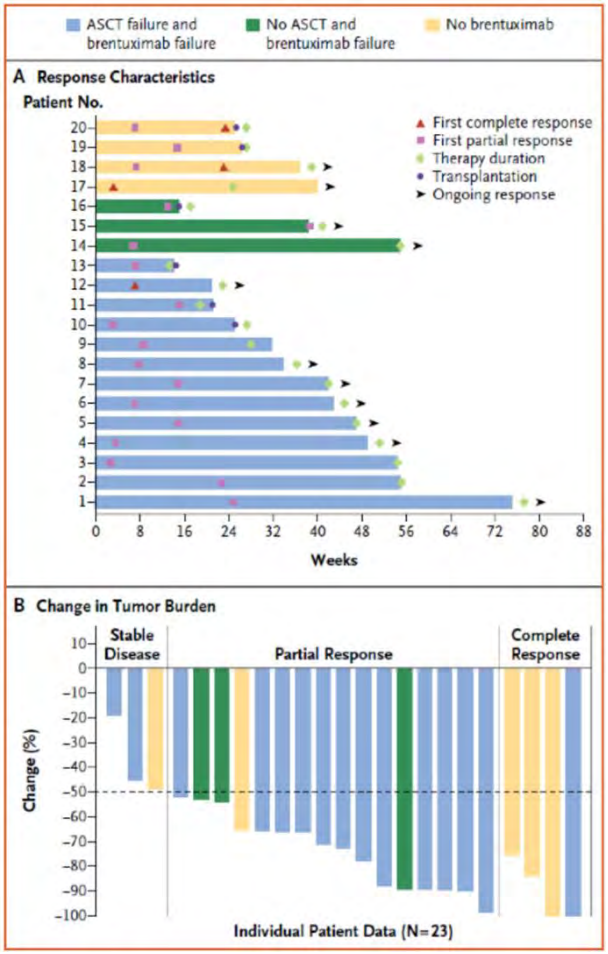
1) riduzione della fosforilazione Lck-mediata di ZAP-70 e delle vie di segnale da esso mediata;
2) inibizione della via PI3K-Akt attraverso la destabilizzazione di PTEN;
3) inibizione dell'attivazione di Ras e PLC-γ1 e delle chinasi a valle MEK-ERK e MILe vie che portano all'iper-espressione di PD-L1/2 sulla cellula di RS sono molteplici:



Nel LH c’è una iper-espressione di PD-L1/2 sulla cellula di RS

nivolumab

RC: 4 (17%)
RP: 16 (70%)
SD: 3 (13%)
Prog: 0



PEMBRULIZUMAB

Table 2. Best Overall Response by Blinded Independent Central Review

Response	Cohort 1 (n = 69) After ASCT/BV		Cohort 2 (n = 81) Ineligible for ASCT and Experienced Treatment Failure With BV		Cohort 3 (n = 60) No BV After ASCT		All Patients (N = 210)	
	No. (%)	95% CI†	No. (%)	95% CI†	No. (%)	95% CI†	No. (%)	95% CI†
Overall response rate	51 (73.9)	61.9 to 83.7	52 (64.2)	52.8 to 74.6	42 (70.0)	56.8 to 81.2	145 (69.0)	62.3 to 75.2
Complete remission*	15 (21.7)	12.7 to 33.3	20 (24.7)	15.8 to 35.5	12 (20.0)	10.8 to 32.3	47 (22.4)	16.9 to 28.6
Partial remission	36 (52.2)	39.8 to 64.4	32 (39.5)	28.8 to 51.0	30 (50.0)	36.8 to 63.2	98 (46.7)	39.8 to 53.7
Stable disease	11 (15.9)	8.2 to 26.7	10 (12.3)	6.1 to 21.5	10 (16.7)	8.3 to 28.5	31 (14.8)	10.3 to 20.3
Progressive disease	5 (7.2)	2.4 to 16.1	17 (21.0)	12.7 to 31.5	8 (13.3)	5.9 to 24.6	30 (14.3)	9.9 to 19.8
Unable to determine	2 (2.9)	0.4 to 10.1	2 (2.5)	0.3 to 8.6	0 (0)	—	4 (1.9)	0.5 to 4.8

Abbreviations: ASCT, autologous stem cell transplantation; BV, brentuximab vedotin.
*For complete remission, a residual mass was permitted for patients who had negative positron emission tomography scan results.
†On the basis of binomial exact CI method.

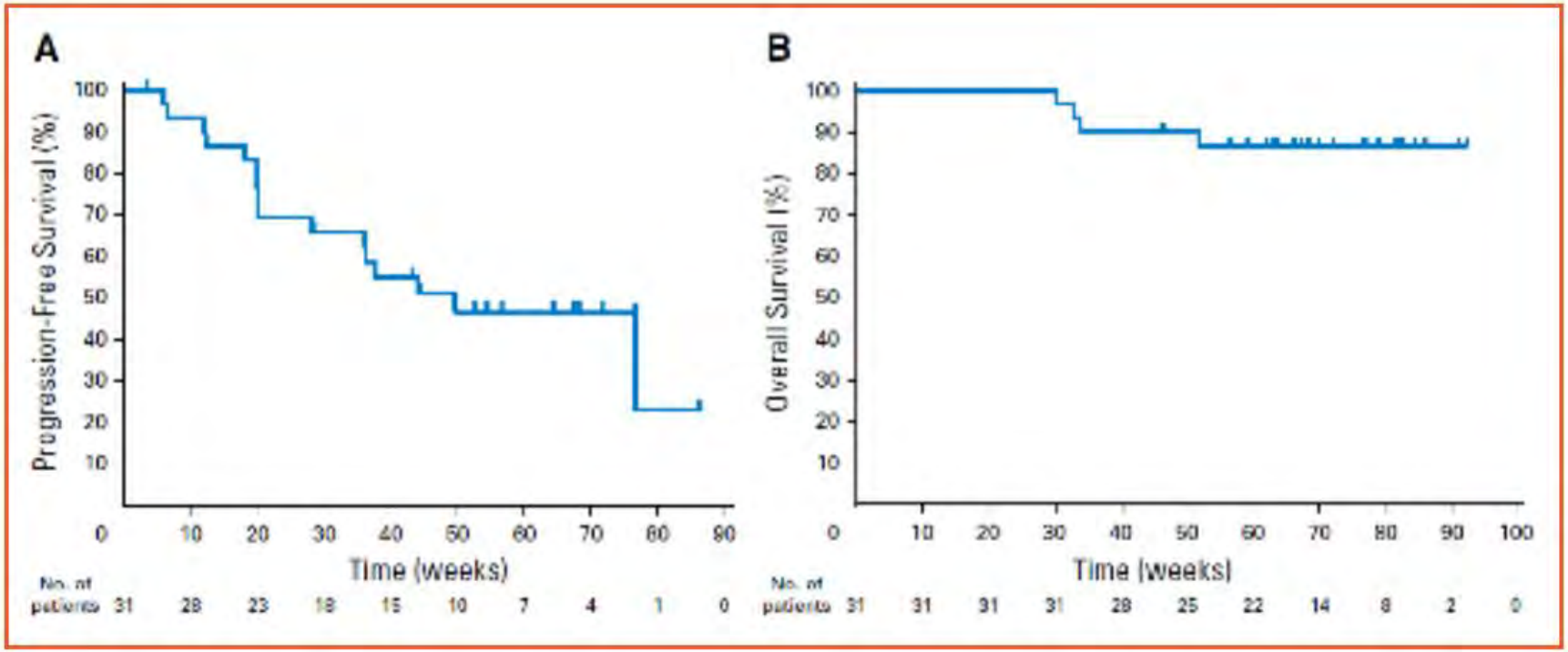
RC: 20% circa

RP: 40-50%

SD: 16 circa

Prog: 7-20%

PEMBROLIZUMAB

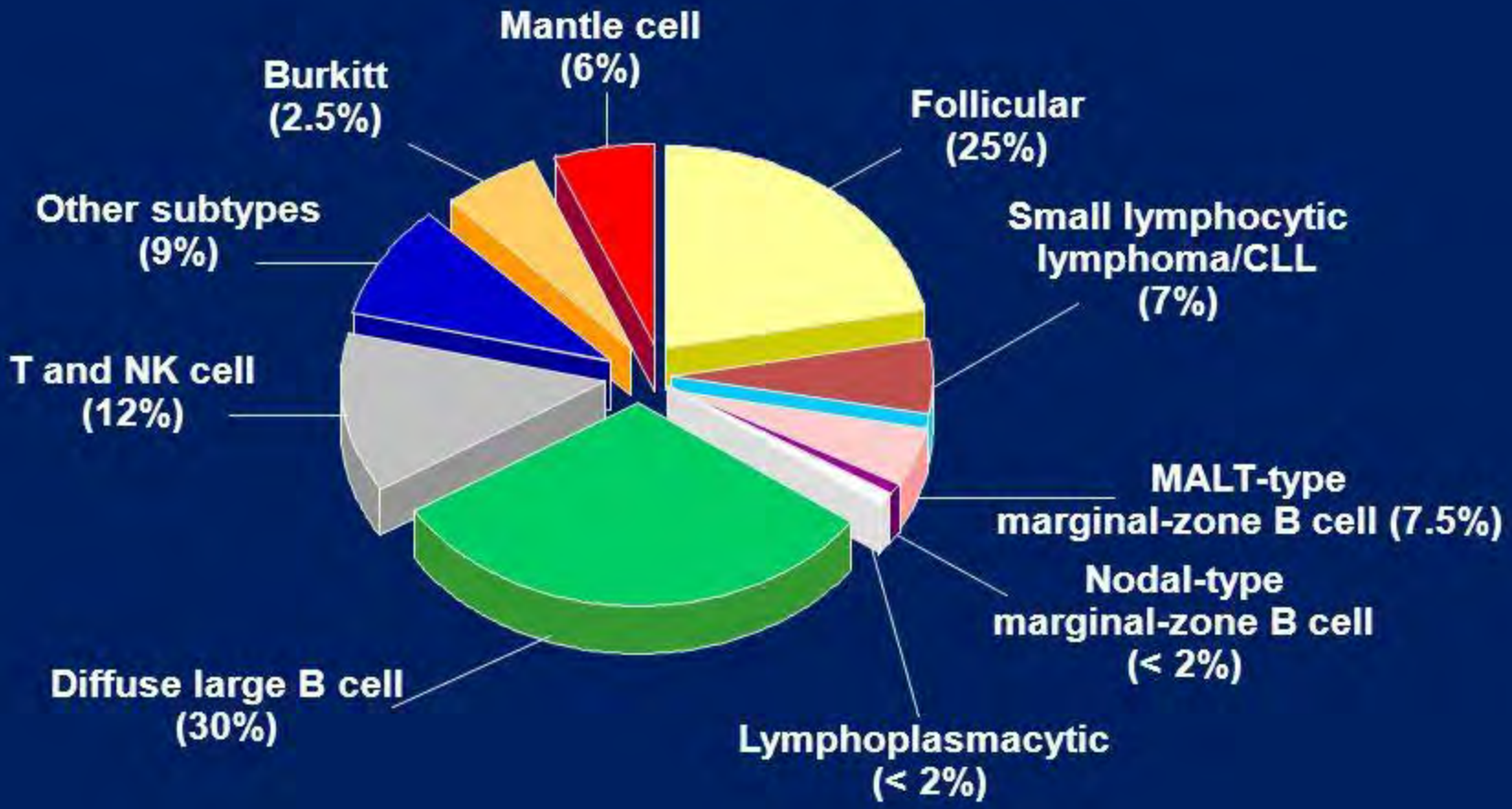


LINFOMI NON HODGKIN

LINFOMI NON HODGKIN

- Incidenza: 13-15/100.000
- Originano per l'80-85% dai linfociti B e per il 15-20% dai linfociti T; i linfomi di origine da cellule NK sono molto rari
- Rappresentano il 4-5% di tutte le neoplasie
- Sono la 9^ causa di morte per neoplasia nell'uomo e la 6^ nella donna

Subtypes of NHL



Lichtman MA. *Williams Hematology.* (7th Ed). New York, NY: McGraw Hill, 2006;1408.

Etiology – Non-Hodgkin Lymphoma

Infectious agents	• Epstein-Barr virus (EBV), Human T-cell leukemia virus type 1 (HTLV-1) , Hepatitis C virus (HCV), Kaposi sarcoma–associated herpesvirus (KSHV) , *Helicobacter pylori* infection.
Chromosomal translocations	• The t(14;18)(q32;q21) translocation is the most common chromosomal abnormality associated with NHL.
Environmental factors	• chemicals (eg, pesticides, herbicides, solvents, organic chemicals, wood preservatives, dusts, hair dye), chemotherapy, and radiation exposure.
Immunodeficiency states	• Congenital immunodeficiency states, AIDS, Celiac disease.
Chronic inflammation	• Sjögren syndrome and Hashimoto thyroiditis.

Source: http://emedicine.medscape.com/article/201886-overview#aw2aab6b2b3

Clinical features

- **Widely disseminated at presentation**
- **Nodal involvement**:
  Painless lymphadenopathy, often cervical region is the most common presentation
- Hepatospleenomegaly
- **Extranodal** *Intestinal lymphoma* (abdominal pain, anemia, dysphagia);
  CNS (headache, cranial nerve palsies, spinal cord compression) ;

  Skin, Testis; Thyroid; Lung
  Bone marrow (low grade): Pancytopenia

Clinical features contd

- **Systemic symptoms**
  - Sweating, weight loss, itching
  - *Metabolic complications:* hyperuricemia, hypercalcemia, renal failure
- Compression syndrome:
  - Gut obstruction
  - Ascites
  - SVC obstruction
  - S/C Compression

Oncologic emergencies

- — Potentially emergent complications of NHL may be present at the time of diagnosis and need to be considered during the initial workup and evaluation of a patient with suspected pediatric NHL..

  These can include:

  - Superior or inferior vena cava obstruction
  - Acute airway obstruction
  - Intestinal obstruction, intussusception
  - Spinal cord compression

- Pericardial tamponade
- Lymphomatous meningitis and/or CNS mass lesions
- Hyperuricemia and tumor lysis syndrome
- Ureteral obstruction, unilateral or bilateral hydronephrosis
- Venous thromboembolic disease

Characteristic Differences between Hodgkin and Non-Hodgkin Lymphomas

	Hodgkins Lymphoma	**NHL**
Age	Bimodal age distribution 1st peak - 15-to-34-years 2nd peak - over-50-years	Increases in incidence with advancing age
Presentation	Localized presentation, involving a single or a contiguous lymph node chain. Wide spread is seen only in later course.	Have a diffuse presentation or wide spread (early in course)
Spread of disease	Is in an orderly fashion (in a single or contiguous LN)	Randomly - In a less predictable fashion
Site	Essentially a **nodal disease** Extranodal sites - rarely involves	Essentially an **extranodal disease** (Head and neck –frequently)
	Restricted to one group of lymph nodes	Multiple group of nodes
Location	***Cervical lymphatic chain*** (frequently involved by HL) that give the patient a so-called **Bull-neck appearance** - Due to the presence of bulky unilateral or bilateral fused lymph node masses of the cervical lymphtic chain	***Mucosa of the hard and/or soft*** palate is the most common site > pharyngeal and lingual tonsils and the pharyngeal walls. Above locations are considered as the **Waldeyer's ring.**

classification	Indolent"good"	Aggressive"bad"	Highly aggressive "ugly"
Type	Follicular B CLL/SLL Lymphoplasmacytic	Mantle DLBCL PTCL	Burkitt LBL

Diffuse Large B-Cell Lymphoma

(DLBLC). DLBCL is the most common type of non-Hodgkins lymphoma, accounting for about 30% of all NHL cases. It is an aggressive, fast-growing lymphoma that usually affects adults but can also occur in children. DLBCL can occur in lymph nodes or in organs outside of the lymphatic system. DLBCL includes several subtypes such as mediastinal large B-cell lymphoma, intravascular large B-cell lymphoma, and primary effusion lymphoma.

Follicular Lymphoma (FLs).

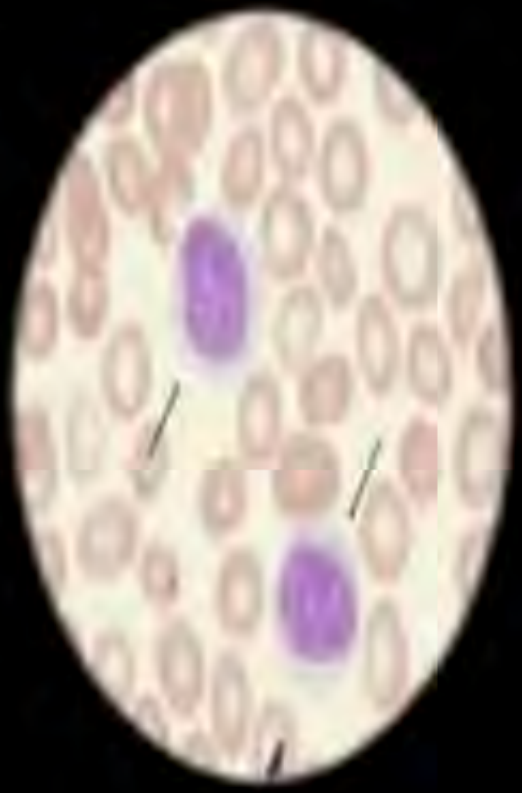
Follicular lymphoma is the second most common type lymphoma, accounting for about 20% of all NHL cases. It is usually indolent (slow growing) but about half of follicular lymphomas transform over time into the aggressive diffuse large B-cell lymphoma.

Mantle Cell Lymphoma.

Mantle cell lymphoma is an aggressive type of lymphoma that represent about 7% of NHL cases. It is a difficult type of lymphoma to treat and often does not respond to chemotherapy. It is found in lymph nodes, the spleen, bone marrow, and gastrointestinal system. Mantle cell lymphoma usually develops in men over age 60.

Small Lymphocytic Lymphoma (SLL). SLL is an indolent type of lymphoma that is closely related to B-cell chronic lymphocytic leukemia (CLL). It accounts for about 5% of NHL cases.

Marginal Zone Lymphomas (MZL). MZLs are categorized depending on where the lymphoma is located. Mucosa-associated lymphoid tissue lymphomas (MALT) usually involve the gastrointestinal tract, thyroid, lungs, saliva glands, or skin. MALT is often associated with a history of an autoimmune disorder (such as Sjogren syndrome in the salivary glands or Hashimoto's thyroiditis in the thyroid gland).

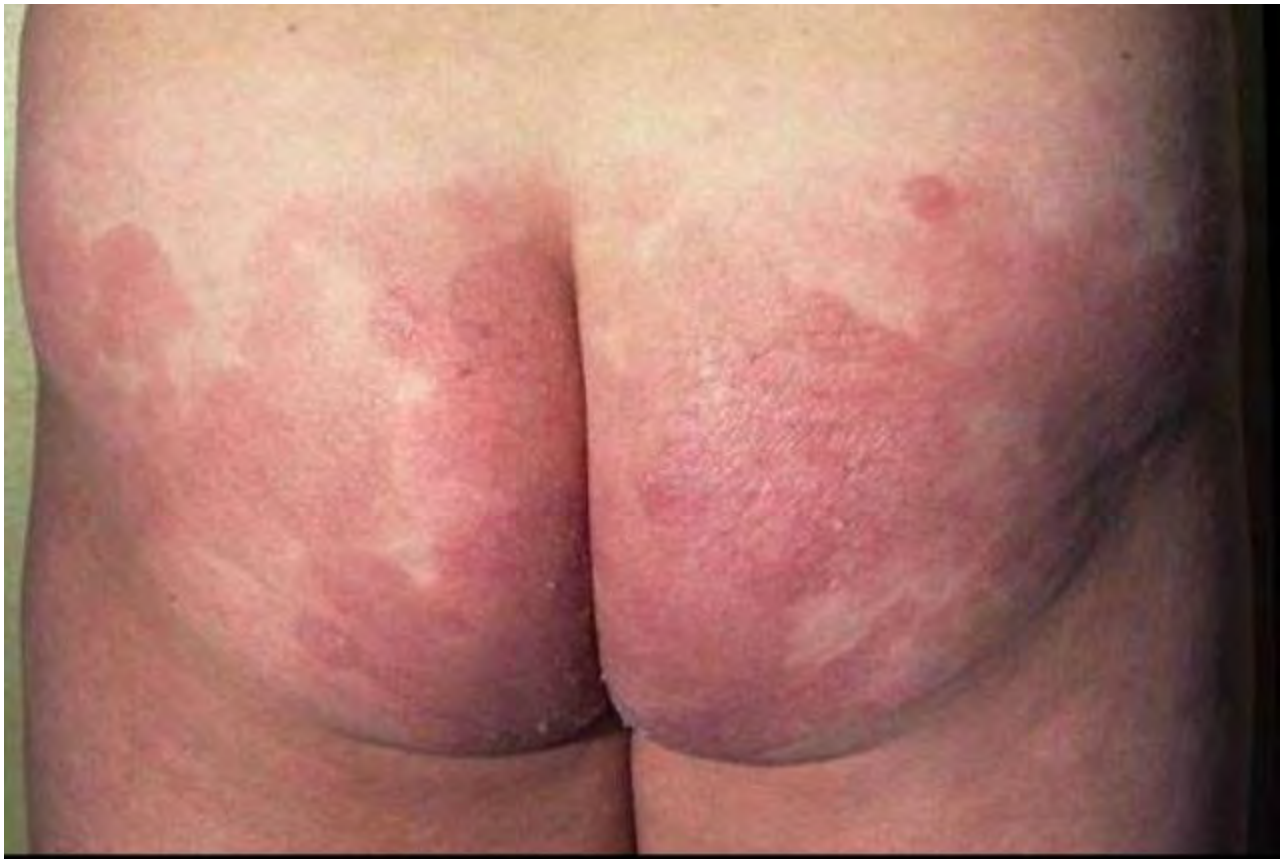


Primary Central Nervous System Lymphoma.

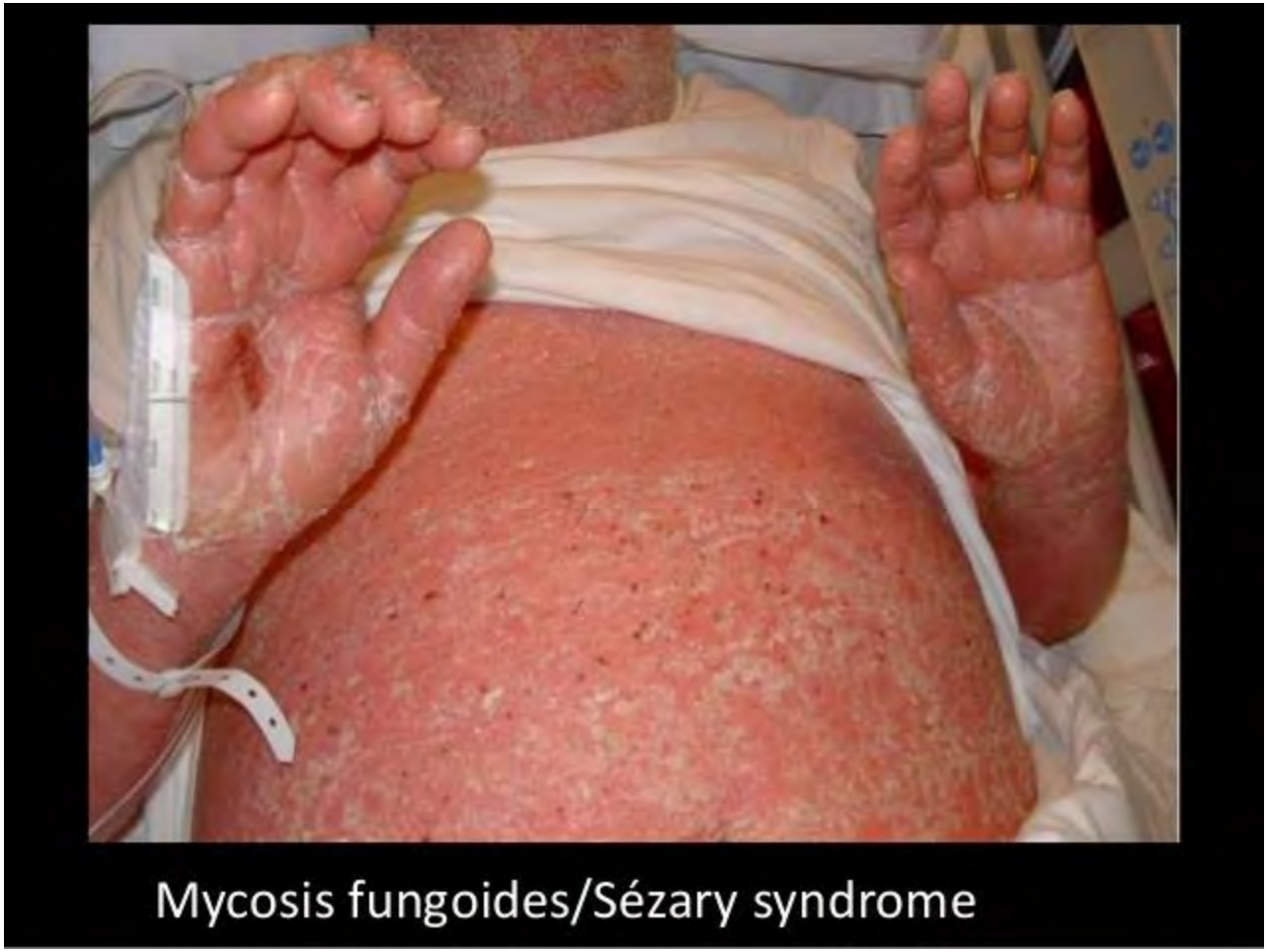
This lymphoma involves the brain and spinal cord. Although it is generally rare, it is common in people who have AIDS.

MYCOSIS FUNGOIDES/SEZARY SYNDROME

- Tumour of CD4+ cells,
- Predilection to involve skin,
- Infiltration of epidermis and upper dermis by T-cells with cerebriform nucleus,
- Spreads to lymphnodes and bone marrow,
- Indolent tumours – median 8 – 9 yrs;
- May transform to large T-cell lymphoma;



Mycosis fungoides/Sézary



Mycosis fungoides/Sézary syndrome

Imaging studies

- **Integrated positron emissions tomography (PET)/CT scanning** is more sensitive and specific than CT in certain histologic subtypes of NHL, including the most common subtypes seen in children
- Imaging of the bones with plain films, CT, and/or magnetic resonance imaging (MRI) is not routinely performed in NHL, but is indicated in the presence of **bone pain and/or suspicion of a pathologic fracture**.

- Chemotherapy is the use of cytotoxic (cell damaging) medicines to target and kill tumors. The drugs work by interrupting the DNA of fast-growing cells, preventing them from growing or reproducing.

- Immunotherapy uses the body's own immune system to attack and remove cancer cells.

- Radiation therapy

-uses high doses of X-rays, gamma rays, or other types of ionizing (damaging) radiation to kill cancer cells. It may be applied to the whole body or to a specific zone.

Approach Considerations

The treatment of non-Hodgkin lymphoma (NHL) varies greatly, depending on the following factors:

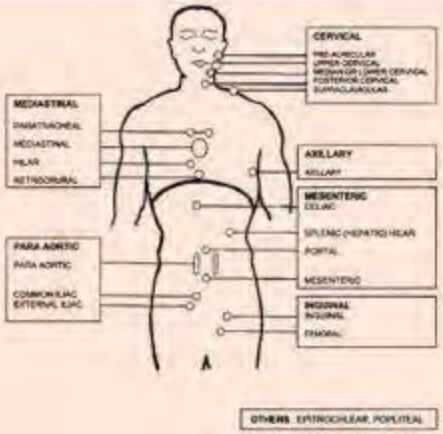
- Tumor stage
- Phenotype (B-cell, T-cell or natural killer [NK] cell/null-cell)
- Histology (ie, low-, intermediate-, or high-grade)
- Symptoms
- Performance status
- Patient age
- Comorbidities

LINFOMI INDOLENTI

Istotipo	% sul totale dei NHL B
Linfoma Follicolare	29%
Leucemia Linfatica Cronica/Linfoma Linfocitico	12%
Linfoma della Zona Marginale Extranodale MALT	9%
Linfoma della Zona Marginale Nodale	2%
Linfoma Linfoplasmocitico/Macroglobulinemia di Waldeström	1.4%
Linfoma della Zona Marginale Splenica	0.9%
Hairy Cell Leukemia	<1%

Modificato da: Swerdlow SH et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press Lyon 2008.

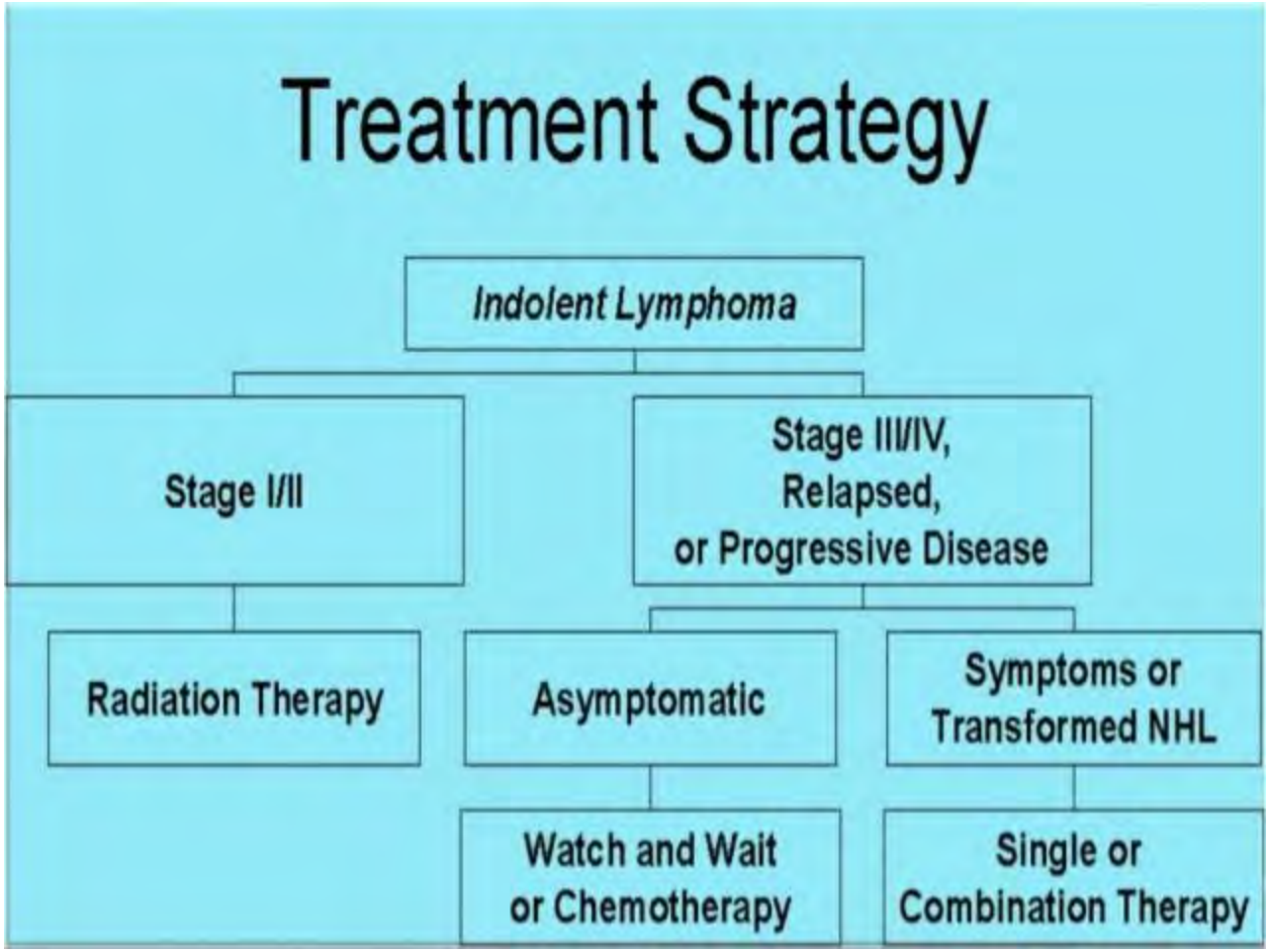
Parametro	Fattore prognostico negativo	
	FLIPI[a]	FLIPI2[b]
Età	≥ 60 anni	≥ 60 anni
Stadio sec. Ann Arbor	III-IV	
Livello di emoglobina	< 12 g/dL	< 12 g/dL
Livello di LDH	superiore alla norma	
N° di stazioni linfonodali	> 4	
Beta2-microglobulina		superiore alla norma
Coinvolgimento midollare		presente
Maggior diametro nodale		> 6 cm



	FLIPI			FLIPI2	
Rischio	**N° di fattori avversi**	**OS a 5 anni**	**OS a 10 anni**	**N° fattori avversi**	**OS a 5 anni**
Basso	0-1	90.6%	70.7%	0	79%
Intermedio	2	77.8%	50.9%	1-2	51%
Alto	3-4-5	52.5%	35.5%	3-4-5	20%

[a]Modificato da: Solal-Celigny P et al. Blood, 2004;104:1258-1265; [b]Fedenco M et al. J Clin Oncol, 2009; 27: 4555-4562.

Treatment Strategy



Management of Indolent NHL

- Indolent stage I and contiguous stage II NHL
- Standard management consists of radiotherapy alone.
- **Indolent noncontiguous stage II, III, and IV NHL**
- Frequently used combination regimens are

  -**(R- CHOP)** (Rituximab,cyclophosphamide, hydroxydaunomycin [Adriamycin], vincristine [Oncovin], and prednisone),

  -CVP (cyclophosphamide, vincristine, and prednisone), and fludarabine alone or in combination (eg, with cyclophosphamide or mitoxantrone).

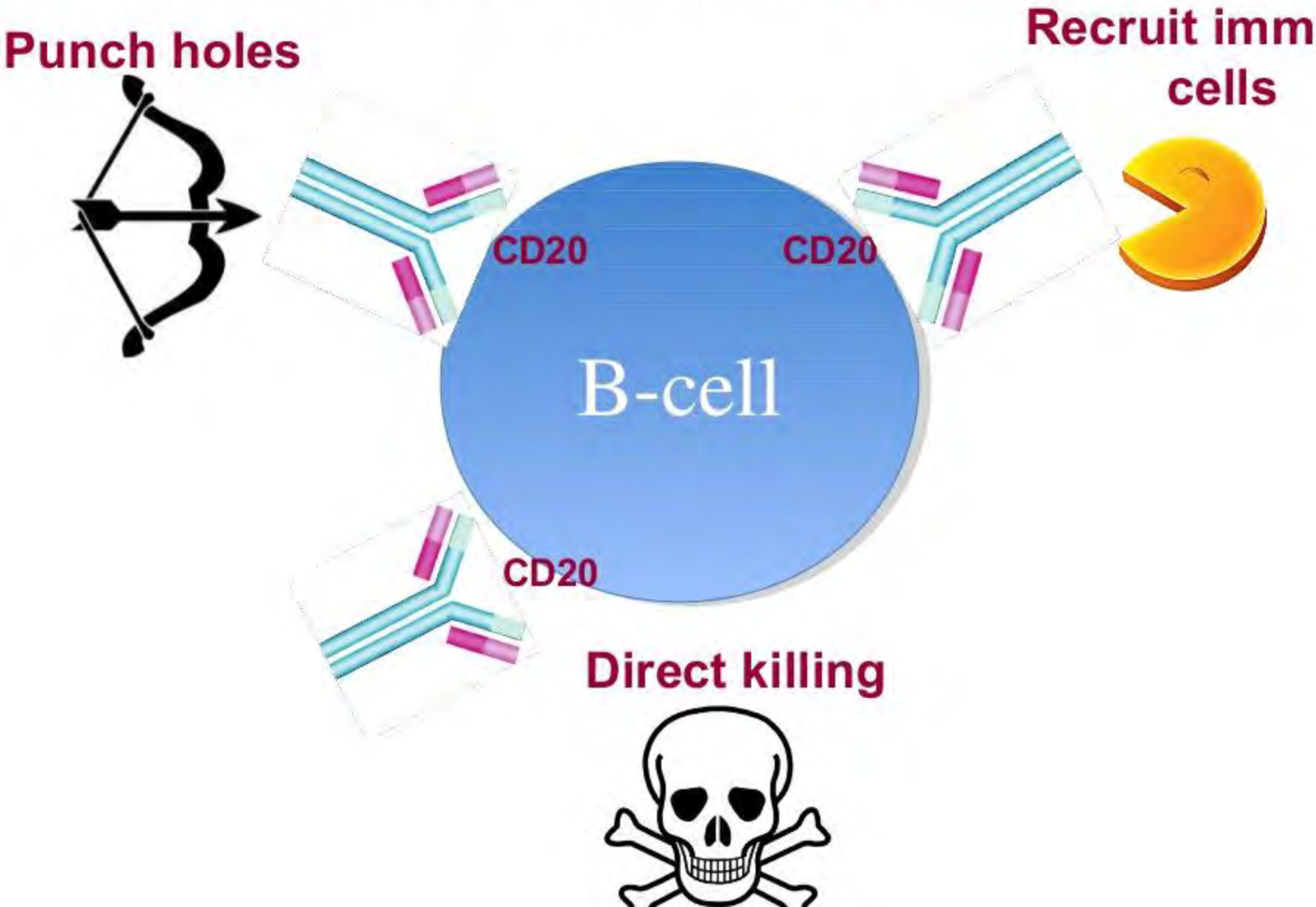
Management of Indolent NHL

- Bendamustine plus rituximab has demonstrated efficacy for the first-line treatment of advanced follicular, indolent, and mantle cell lymphomas.
- Current National Comprehensive Cancer Network guidelines give **bendamustine plus rituximab, RCHOP, and RCVP (rituximab, cyclophosphamide, vincristine, prednisone)** category 1 recommendations for first-line therapy of follicular lymphoma.

Immunotherapy

1. Perhaps the most promising new approach to the treatment of NHL has been the recent development of effective immunotherapy.
2. The malignant lymphomas express a variety of surface antigens, most notably the B-cell antigen CD20.
3. The ubiquitous presence of the CD20 antigen in many varieties of B-cell lymphomas led to the genetic engineering of a human chimeric anti-CD20 antibody rituximab.
4. In contrast to prior murine derived monoclonal antibodies, rituximab is quite well tolerated in humans. Rituximab was the first antibody of any type to receive U.S. Food and Drug Administration (FDA) approval (1997) for the treatment of any human malignancy.
5. There are few data on the treatment of high–tumor burden disease with single-agent rituximab. Among patients with low-burden disease, overall response rates have ranged from 47% to 74%.

How does rituximab work?



Rituximab maintenance also impacts progression-free survival among patients treated with chemotherapy alone and those receiving rituximab plus chemotherapy.

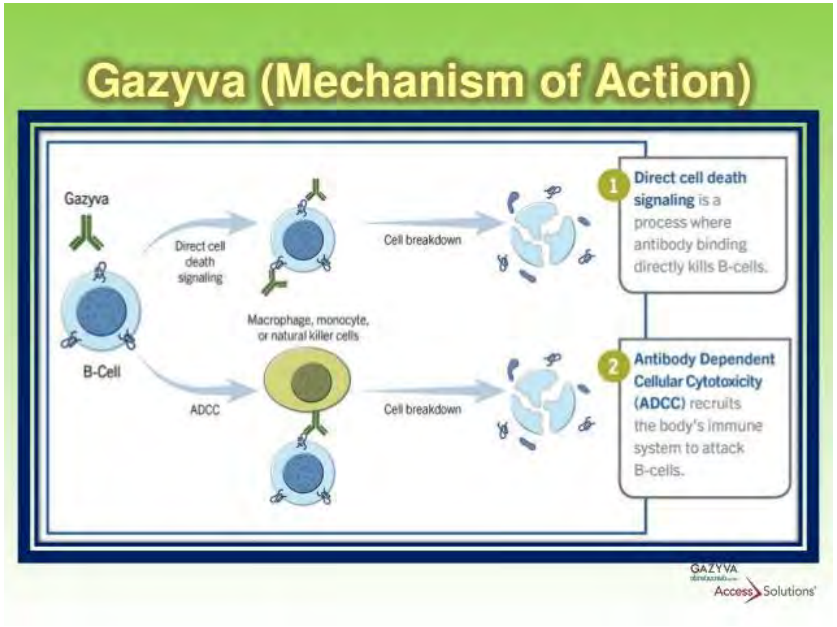
Among previously untreated patients with follicular lymphoma who responded to immunochemotherapy (R-CVP [rituximab, cyclophosphamide, vincristine, prednisone], R-CHOP, or R-FCM [rituximab, fludarabine, cyclophosphamide, mitoxantrone]), rituximab maintenance resulted in a significant improvement in progression-free survival over observation in the PRIMA phase III trial (6-year; 59% vs 43%; $P < .0001$), recently updated by Salles and colleagues

Chemotherapy with and without rituximab.
For patients with high–tumor burden disease and/or symptoms, the addition of rituximab to chemotherapy has resulted in major improvements in clinical outcome, including overall survival.

Four phase III trials comparing combinations of chemotherapy and rituximab with chemotherapy alone in previously untreated patients have all shown benefit for the combination, establishing chemoimmunotherapy as the standard of care for symptomatic patients or those with high–tumor burden disease.

Overall response rates and either median time to treatment failure or event-free survival were superior in the chemoimmunotherapy arm in every series. An overall survival benefit has been demonstrated in three of the four trials and in the high-risk subset of the fourth study.

OBINUTUZUMAB



Obinutuzumab è un anticorpo monoclonale anti-CD20 di tipo II umanizzato della sottoclasse IgG1,
derivato dalla umanizzazione dell'anticorpo murino parenterale B-Ly1 e prodotto dalla linea cellulare ovarica di hamster cinese mediante tecnologia del DNA ricombinante.

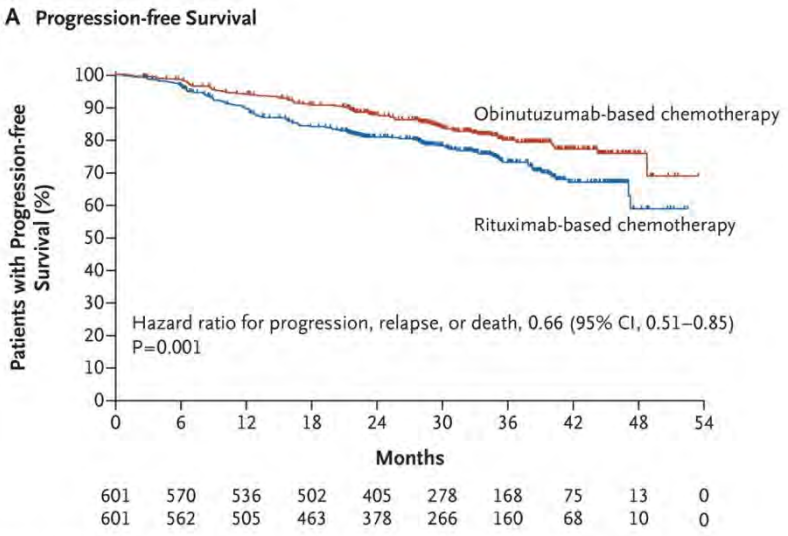
Leucemia linfatica cronica (LLC)
Gazyvaro in associazione a clorambucile è indicato nel trattamento di pazienti adulti affetti da
leucemia linfatica cronica (LLC) non pretrattata e con comorbilità che li rendono non idonei a una
terapia a base di fludarabina a dose piena (vedere paragrafo 5.1).

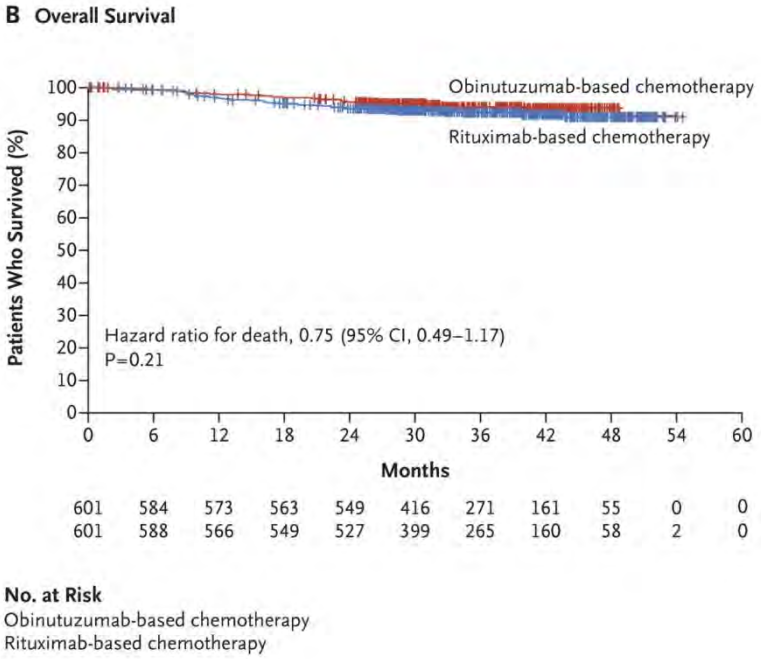
Linfoma follicolare (LF)
Gazyvaro in associazione a chemioterapia, seguito da Gazyvaro come terapia di mantenimento nei soggetti che ottengono una risposta, è indicato per il trattamento di pazienti con linfoma follicolare
avanzato non pretrattato (vedere sezione 5.1).

Gazyvaro in associazione a bendamustina, seguito da Gazyvaro in mantenimento è indicato nel trattamento di pazienti con linfoma follicolare (LF) che non rispondono o che hanno avuto
progressione di malattia durante o fino a 6 mesi dopo il trattamento con rituximab o un regime contenente rituximab.

LINFOMA FOLLICOLARE

Confronto fra rituximab e obinotuzumab





Aggressive NHL

- Diffuse large B-cell lymphoma is the most common type of NHL. Other distinct entities in this group include immunoblastic, anaplastic, lymphoblastic, large-cell, Burkitt, and Burkitt-like lymphomas (high-grade lymphomas).
- Mantle cell lymphomasalso behave aggressively

Istotipo	% sul totale dei NHL B
Linfoma B Diffuso a Grandi Cellule Linfoma B a Grandi Cellule T-Cell/Histiocyte rich Linfoma B a Grandi Cellule Primitivo del Sistema Nervoso Centrale Linfoma B a Grandi Cellule Primitivo Cutaneo, leg type	37%
Linfoma Mantellare	7%
Linfoma B Primitivo del Mediastino	3%
Linfoma di Burkitt	0.8%
Linfoma B Diffuso a Grandi Cellule associato a Flogosi Cronica	<1%
Granulomatosi Linfomatoide	<1%
Linfoma B a Grandi Cellule Intravascolare	<1%
Linfoma B a Grandi Cellule ALK-positivo	<1%
Linfoma Plasmoblastico	<1%
Linfoma B a Grandi Cellule associato alla malattia di Castleman	<1%
Primary Effusion Lymphoma	<1%

Modificato da: Swerdlow SH et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press Lyon 2008.

International Prognostic Index

- Age >60
- Serum LDH ↑
- ECOG performance status 2
- Ann Arbor clinical stage III or IV
- Number of involved extranodal disease sites >1

ECOG Performance Status

Performance Status	Definition
0	Fully active; no performance restrictions
1	Strenuos physical activity restricted; fully ambulatory and able to carry out light work
2	Capable of all selfcare but unable to carry out any work activities, Up and about 50 percent of waking hours
3	Capable of only limited selfcare; confined to bed or chair, less than50% of waking hours
4	Completely disabled; cannot carry out any selfcare; totally confined to bed or chair

5-yr OS and CR rates according to IPI score

Score	Risk group	5-yr OS (%)	CR rate (%)
0 to 1	Low risk	73	87
2	Low-intermediate risk	51	67
3	High-intermediate risk	43	55
4 to 5	High risk	26	44

Management of Aggressive NHL

- Aggressive stage I and contiguous stage II (nonbulky or < 10 cm) NHL
- combination chemotherapy (3 cycles of CHOP) plus involved-field radiation therapy.

Aggressive noncontiguous stage II, III, and IV NHL

- any of the following regimens [35] :
- CHOP
- (ProMACE-CytaBOM) Prednisone, methotrexate, leucovorin, doxorubicin, cyclophosphamide, and etoposide—cyclophosphamide, etoposide, Adriamycin, cytarabine, bleomycin, Oncovin, methotrexate, leucovorin, and prednisone

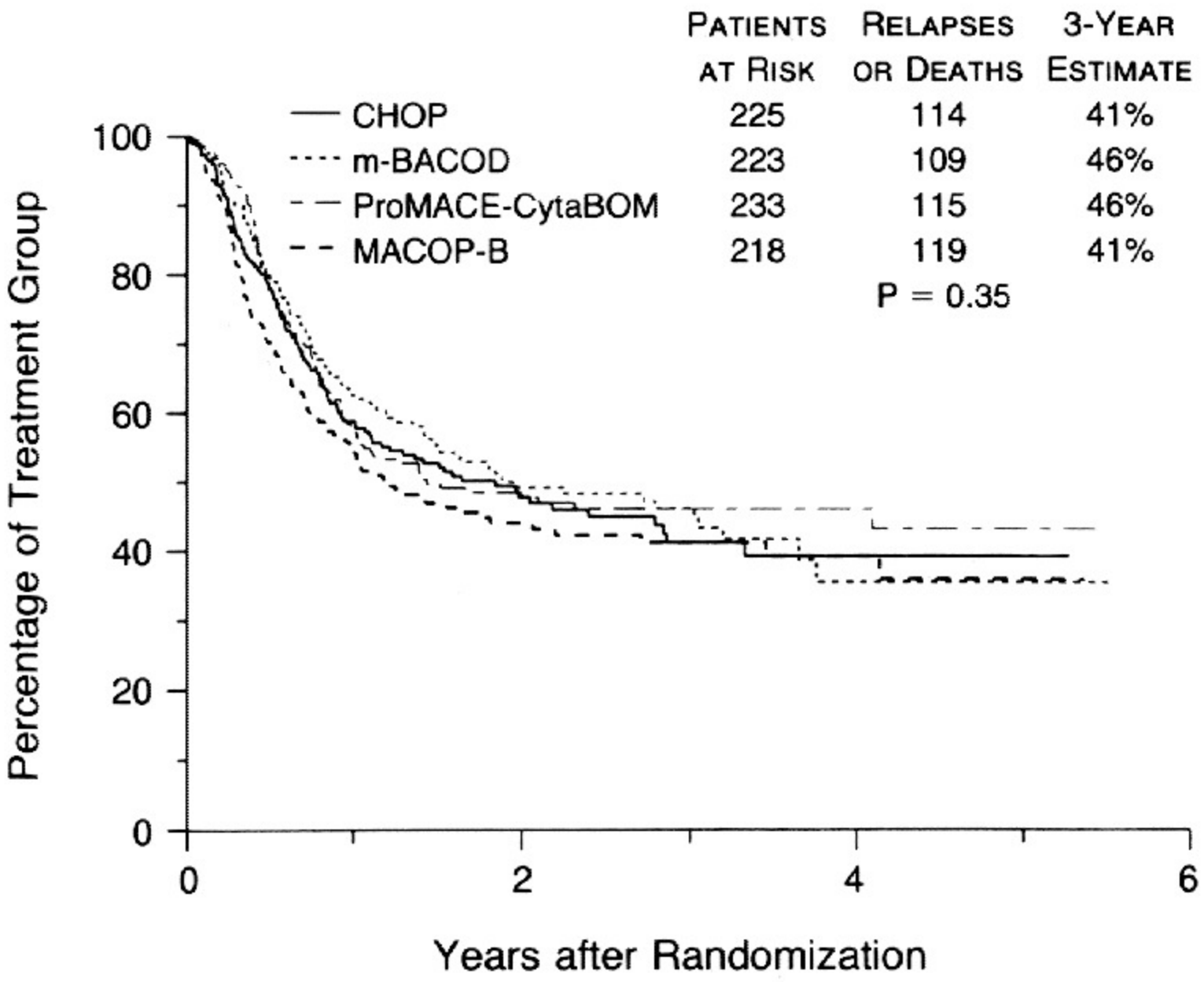
Aggressive noncontiguous stage II, III, and IV NHL

- (m-BACOD) –Methotrexate, bleomycin, doxorubicin (Adriamycin), cyclophosphamide, Oncovin, and dexamethasone
- (MACOP-B) –

  -Methotrexate-leucovorin, Adriamycin, cyclophosphamide, Oncovin, prednisone, and bleomycin

Aggressive noncontiguous stage II, III, and IV NHL

- **Hyper-CVAD** (cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with methotrexate and cytarabine) plus rituximab has been shown high rate of remission in patients with mantle cell lymphoma.
- Bendamustine and rituximab combination has been successfully used in patients with **mantle cell lymphoma in the first and second-line setting.**

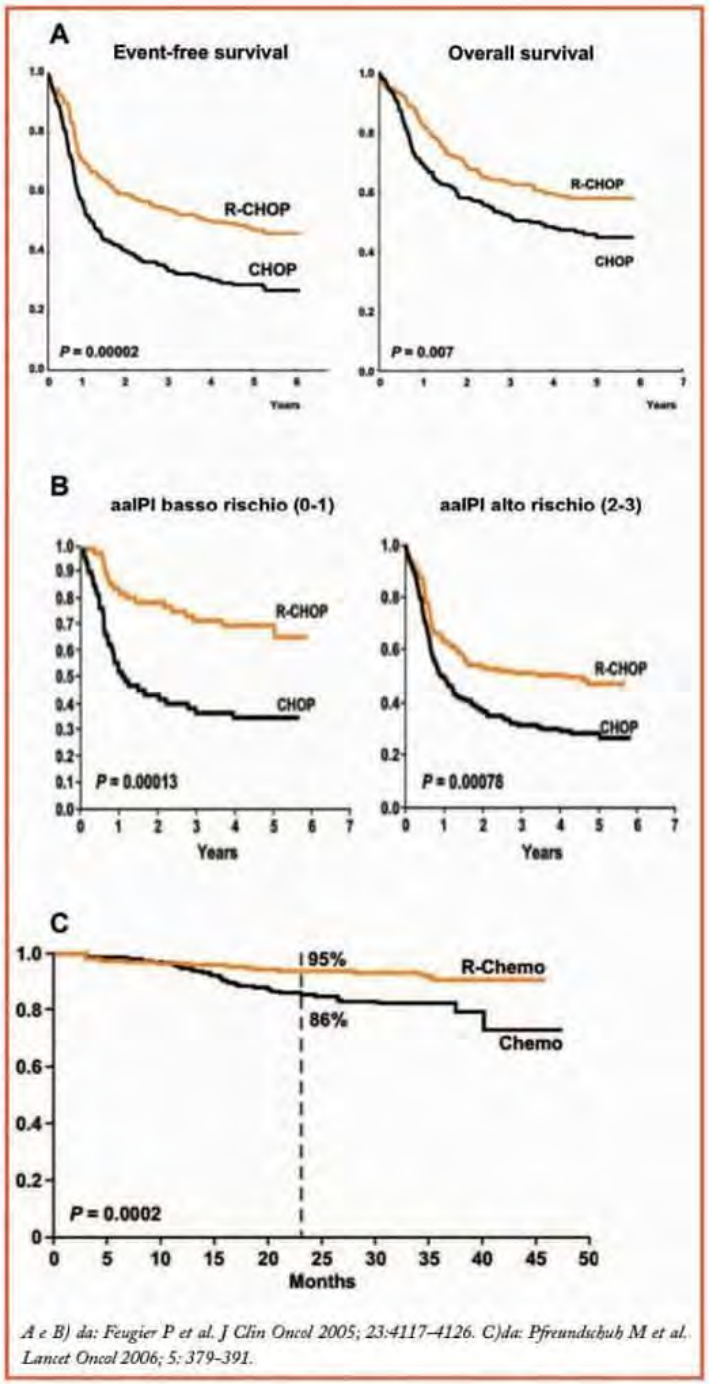

Patients at Risk
Relapses or Deaths
3-Year Estimate
CHOP 225 114 41%
m-BACOD 223 109 46%
ProMACE-CytaBOM 233 115 46%
MACOP-B 218 119 41%
P = 0.35
Percentage of Treatment Group
100
80
60
40
20
0
0
2
4
6
Years after Randomization

LINFOMA DIFFUSO A GRADI CELLULE: RUOLO DEL RITUXIMAB

A: studio GELA 1998

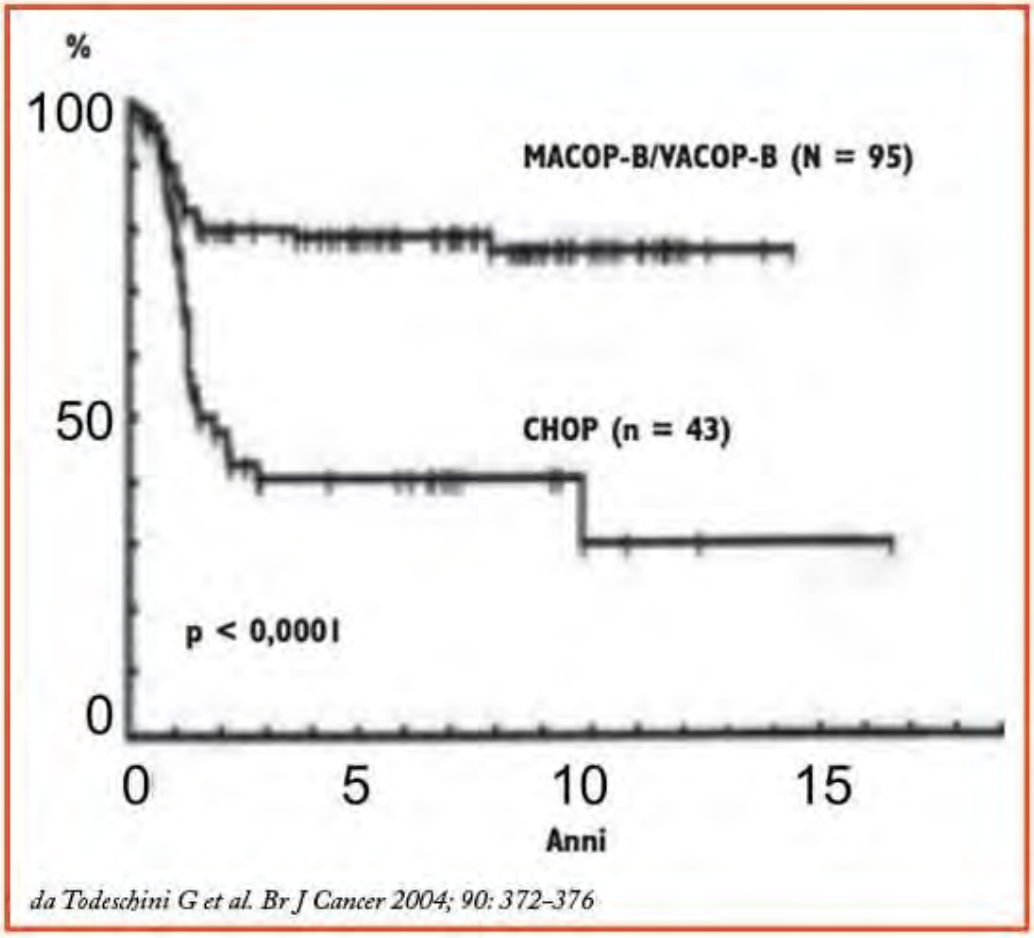
B: curve di sopravvivenza a seconda della classe di rischio

C: studio MINT: sopravvivenza a 23 mesi di pazienti di età<60a



A e B) da: Feugier P et al. J Clin Oncol 2005; 23:4117–4126. C)da: Pfreundschuh M et al. Lancet Oncol 2006; 5: 379–391.

LINFOMA PRIMITIVO DEL MEDIASTINO



da Todeschini G et al. Br J Cancer 2004; 90: 372–376

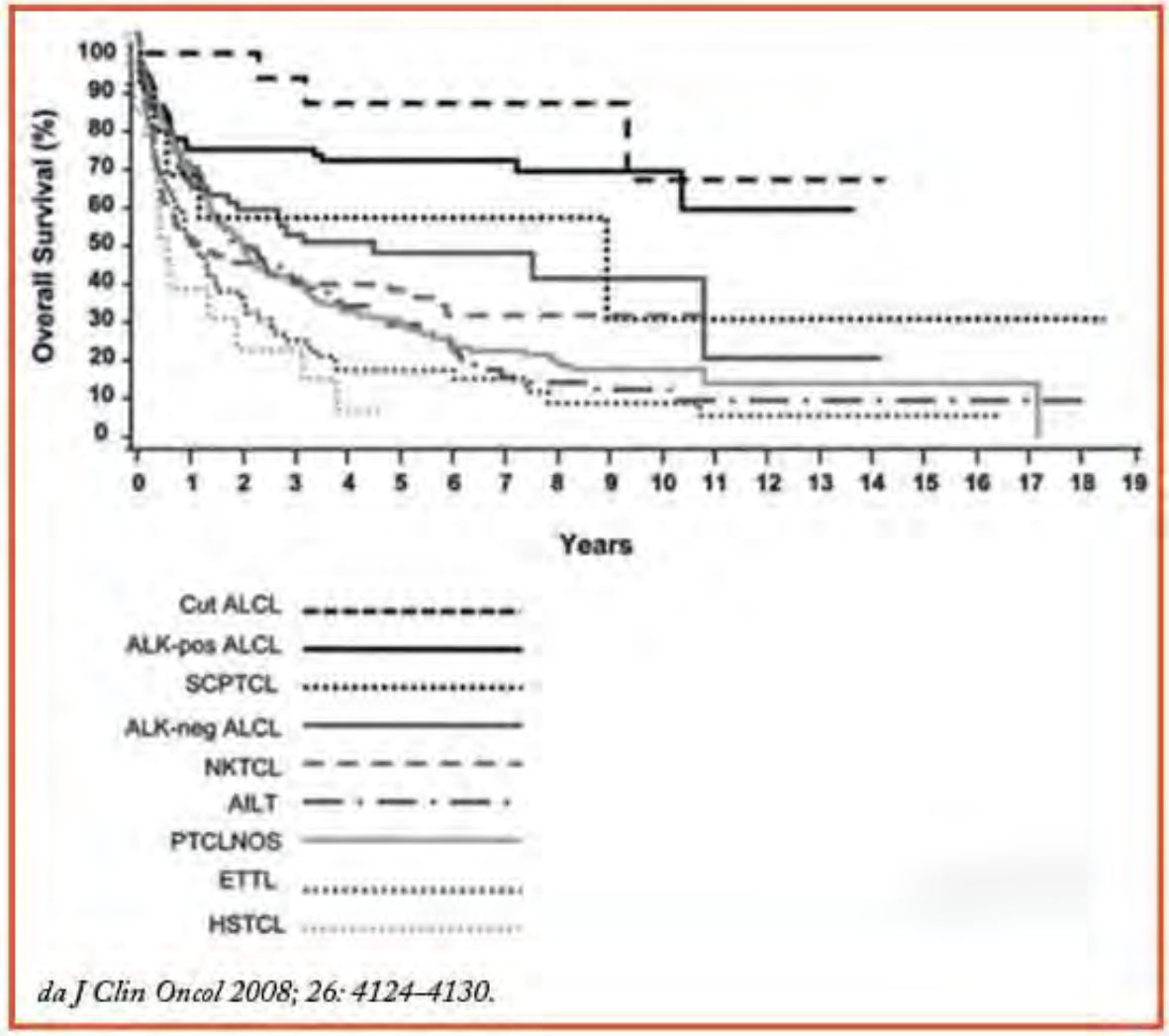
LINFOMI A CELLULE T

Istotipo	% sul totale dei NHL T/NK*
Linfoma T Periferico NAS	25.9%
Linfoma Angioimmunoblastico	18.5%
Linfoma a cellule T/NK Extranodale	10.4%
Leucemia/Linfoma a Cellule T dell'Adulto	9.6%
Linfoma Anaplastico a Grandi Cellule ALK+	6.6%
Linfoma Anaplastico a Grandi Cellule ALK-	5.5%
Linfoma T "enteropathy-type"	4.7%
Linfoma Anaplastico a Grandi Cellule Primitivo Cutaneo	1.7%
Linfoma T epatosplenico	1.4%
Linfoma Sottocutaneo Panniculitico	0.9%
Linfoma T Periferico non classificabile	2.5%
Altri istotipi di Linfoma T/NK	12.2%

Modificato da: Swerdlow SH et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press Lyon 2008.

**La frequenza dei vari istotipi varia significativamente a seconda delle aree geografiche.*

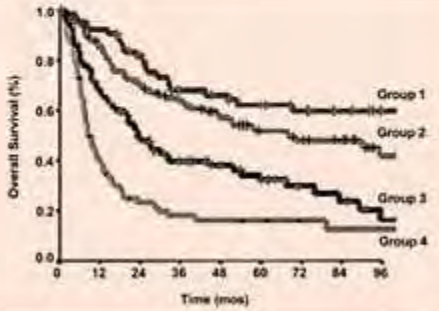
Curve di sopravvivenza di vari istotipi di linfomi non Hodgkin T/NK. Cut ALCL: linfoma anaplastico a grandi cellule CD30+ cutaneo. ALK-pos ALCL: linfoma anaplastico a grandi cellule CD30+ ALK-positivo. SCPTCL: linfoma sottocutaneo panniculitico. ALK-neg ALCL: linfoma anaplastico a grandi cellule CD30+ ALK-negativo. NKTCL: linfoma extranodale T/NK "nasal-type". AILT: linfoma angioimmunoblastico. PTCLNOS: linfoma T periferico non altrimenti specificato. ETTL: linfoma T "enterropathy-type". HSTCL: linfoma Tγδ epatosplenico.



da J Clin Oncol 2008; 26: 4124–4130.

Parametro	Fattore prognostico negativo
Età	> 60 anni
Performance Status secondo ECOG	≥ 2
Livello di LDH	superiore alla norma
Interessamento midollare	presente

Rischio	N° di fattori avversi
Gruppo 1	0
Gruppo 2	1
Gruppo 3	2
Gruppo 4	3-4



Modificato da: Gallamini A et al. Blood, 2004;103:2474-2479.

Stem Cell Transplantation and High-Dose Chemotherapy

- There has been a great interest in the application of HDC with stem cell rescue in the treatment of malignant lymphomas, both for relapsed disease following initial treatment and for those patients deemed to be at high risk for relapse at diagnosis.
- The underlying concept is that larger doses of conventional chemotherapy will result in greater tumor cell kill and increased cure rates.
- The doses involved are so large that they would be lethal because of hematopoietic toxicity without a rescue strategy.
- Accordingly, hematopoietic progenitor cells are harvested from the patient before the HDC, either from the bone marrow itself or more often mobilized from the patient's peripheral blood and then reinfused to re- establish marrow function (autologous stem cell transplantation [ASCT]).
- The high frequency of bone marrow involvement in certain types of NHL limits this strategy, as well as chemotherapy resistance.

- Alternatively, an allogeneic transplant may be carried out in individuals with a suitable matched donor in which the stem cells are harvested from the donor.
- In this procedure, it is hoped that the infused donor stem cells will additionally mount an immunologic attack on the tumor.
- Allogeneic transplantation may be preceded by full-dose (myeloablative) chemotherapy designed to have not only an antitumor effect, but also to condition the patient for the infusion of the donor cells, or it may be preceded by a nonmyeloablative or reduced intensity conditioning (RIC) program designed primarily to enable the recipient to accept the donor stem cells.
- In this latter situation the major antitumor effect is postulated to derive from the infused donor stem cells. RIC allogeneic transplants are associated with a much lower treatment-related mortality (10% to 20%) compared with myeloablative allogeneic transplants (40% to 50%). TBI is often a component of the conditioning program, with doses varying quite widely from 2 to 13.5 Gy

In general, ASCT has been investigated in three types of situations:

(a) patients who have been treated with conventional chemotherapy and then relapsed

(b) patients who fail conventional chemotherapy from the onset (so-called primary refractory disease)

(c) patients who have responded well to primary chemotherapy but are considered at high risk for relapse.

The most widely accepted use is for the treatment of patients with DLBCL who have relapsed following initial CHOP or R-CHOP chemotherapy.

- In a phase III trial from the Parma group, patients with DLBCL who had relapsed following initial CHOP chemotherapy and who were responsive to a salvage program (dexamethasone, cisplatin, cytarabine [DHAP]) were then randomly assigned to receive either four additional cycles of DHAP or a high-dose chemotherapy program.

- Those receiving the HDC program had a markedly improved FFS and OS compared with those getting conventional chemotherapy (46% FFS vs. 12%, 53% OS vs. 32%).

- Note that in both arms of this trial, IFRT to original bulky sites of disease (≥5 cm) was utilized, with a dose of 35 Gy in 20 fractions in the conventional chemotherapy arm and 26 Gy in 1.3 Gy fractions twice a day in the HDC arm.

- All patients in the Parma trial were <60 years of age. Patients with a favorable IPI score of 0 did not benefit. Those with a short remission after initial chemotherapy had a worse outcome

- The Parma trial and associated phase II studies have led to the adaptation of ASCT as standard of care for patients <60 years of age with DLBCL relapsing after initial chemotherapy, although the Parma trial is the only phase III investigation of relapsed DLBCL patients ever done.

- HDC and ASCT have generally not been successful in improving survival and curing patients with indolent disease (e.g., FL). These data have also been comprehensively reviewed recently.

- In brief, OS for indolent lymphomas does not appear to be improved with HDC/ASCT for relapsed disease. Late consequences, particularly the development of myelodysplasia or acute leukemia, are a real concern. The data on the use of allogeneic SCT are all from phase II trials, and, while promising, this procedure is still inhibited by the substantial treatment-related mortality, about 20% at 3 years for RIC transplants and 40% for myeloablative transplants. Thus, allogeneic SCT remains investigational.

NUOVI FARMACI

B-cell receptor signaling

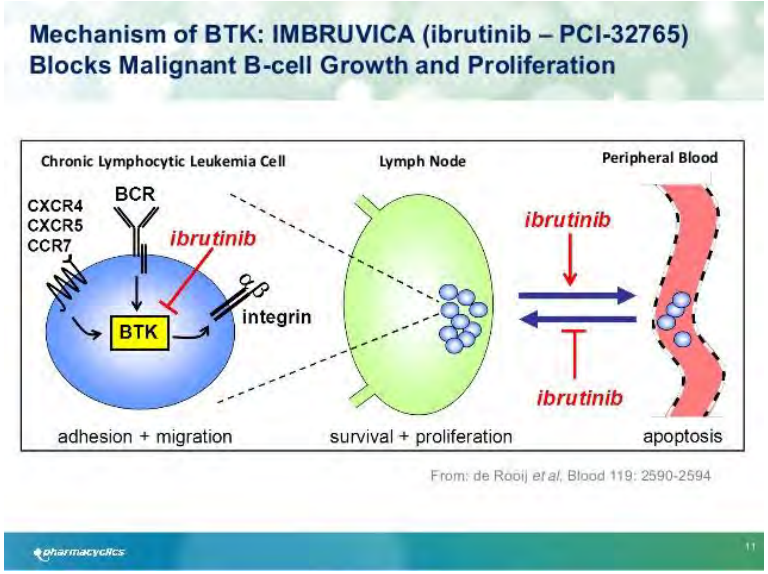
Bruton's tyrosine kinase (BTK)

- is a non-receptor kinase
- its function is essential to normal B cells
- is phosphorylated by SYK and then phosphorylates phospholipase Cγ2, leading to activation of protein kinase C beta and, in turn, CARD11

Phosphoinositide 3-kinase (PI3K)

- PI3K/AKT pathway is critical for essential cellular processes such as metabolism, growth, and proliferation
- The p110 delta and p110 gamma isoforms are expressed primarily in cells of hematopoietic origin

Ibrutinib, primo di una nuova classe di farmaci, è un inibitore selettivo dell'enzima BTK (tiron chinasi di Bruton) che interferisce con la via di segnale che promuove la proliferazione, la differenziazione e la sopravvivenza delle cellule neoplastiche. Il meccanismo della molecola provoca la morte della cellula B maligna e impedisce la sua migrazione e adesione nei linfonodi, favorendo il rilascio delle cellule maligne nel circolo ematico. Le cellule maligne trovandosi nel sangue e non nel linfonodo, che è il loro ambiente naturale, non riescono a sopravvivere e muoiono.



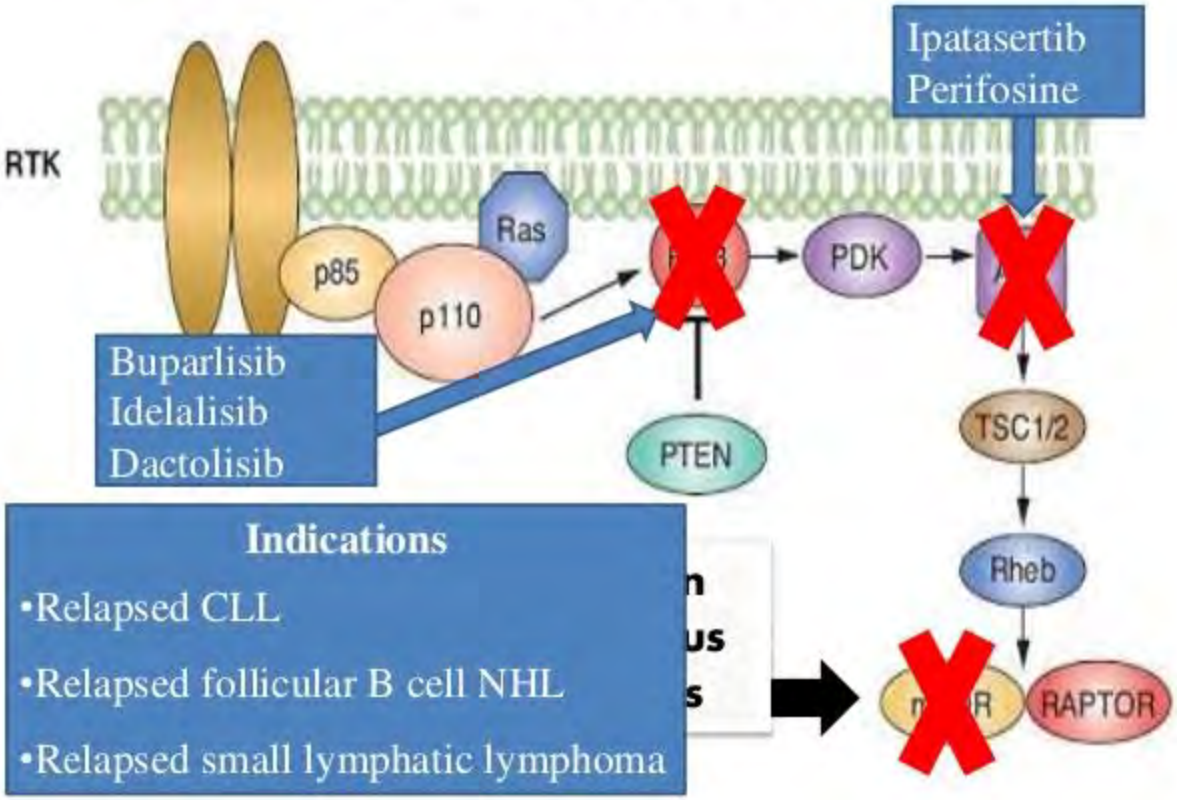
IMBRUVICA in monoterapia o in associazione a bendamustina e rituximab (BR) è indicato per il trattamento di pazienti adulti con CLL che hanno ricevuto almeno una precedente terapia.

IMBRUVICA in monoterapia è indicato per il trattamento di pazienti adulti con macroglobulinemia di Waldenström (WM) che hanno ricevuto almeno una precedente terapia, o in prima linea per i pazienti per i quali una chemio-immunoterapia non è appropriata.

IMBRUVICA in monoterapia è indicato per il trattamento di pazienti adulti con linfoma mantellare (MCL) recidivato o refrattario.

IMBRUVICA in monoterapia è indicato per il trattamento di pazienti adulti con leucemia linfocitica cronica (CLL) precedentemente non trattata (vedere paragrafo 5.1).

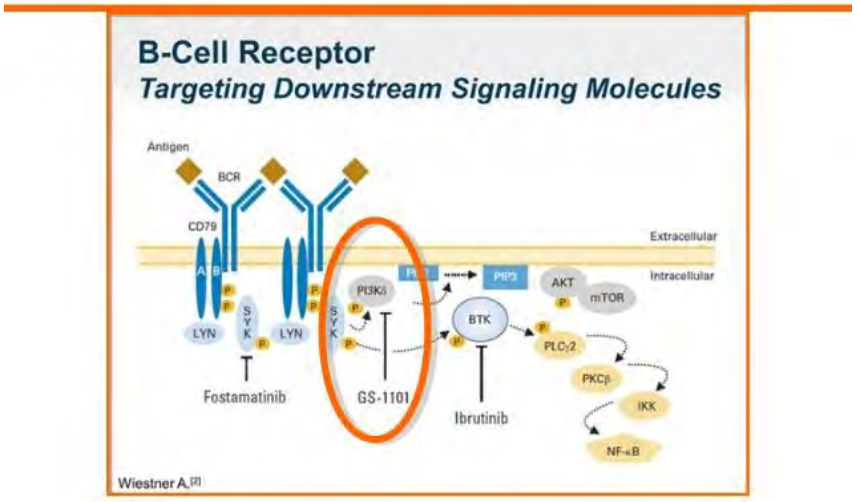
PI3K/PKB(Akt) /MTOR inhibitors



Indications

- Relapsed CLL
- Relapsed follicular B cell NHL
- Relapsed small lymphatic lymphoma

Idelalisib



Idelalisib inibisce la fosfatidilinositolo 3-chinasi p110δ (PI3Kδ), che è iperattiva nelle neoplasie delle cellule B e riveste un ruolo fondamentale nella proliferazione, sopravvivenza, migrazione e ritenzione delle cellule neoplastiche nei tessuti linfatici e nel midollo osseo.
Inoltre, si è visto che induce l'apoptosi e inibisce la proliferazione in linee cellulari derivate da cellule B neoplastiche e in cellule tumorali primarie.

Zydelig è indicato in associazione con rituximab per il trattamento di pazienti adulti affetti da

leucemia linfatica cronica (LLC):
• che hanno ricevuto almeno una terapia precedente, o
• come trattamento di prima linea in presenza di una delezione 17p o una mutazione TP53 in
pazienti non idonei alla chemioimmunoterapia.

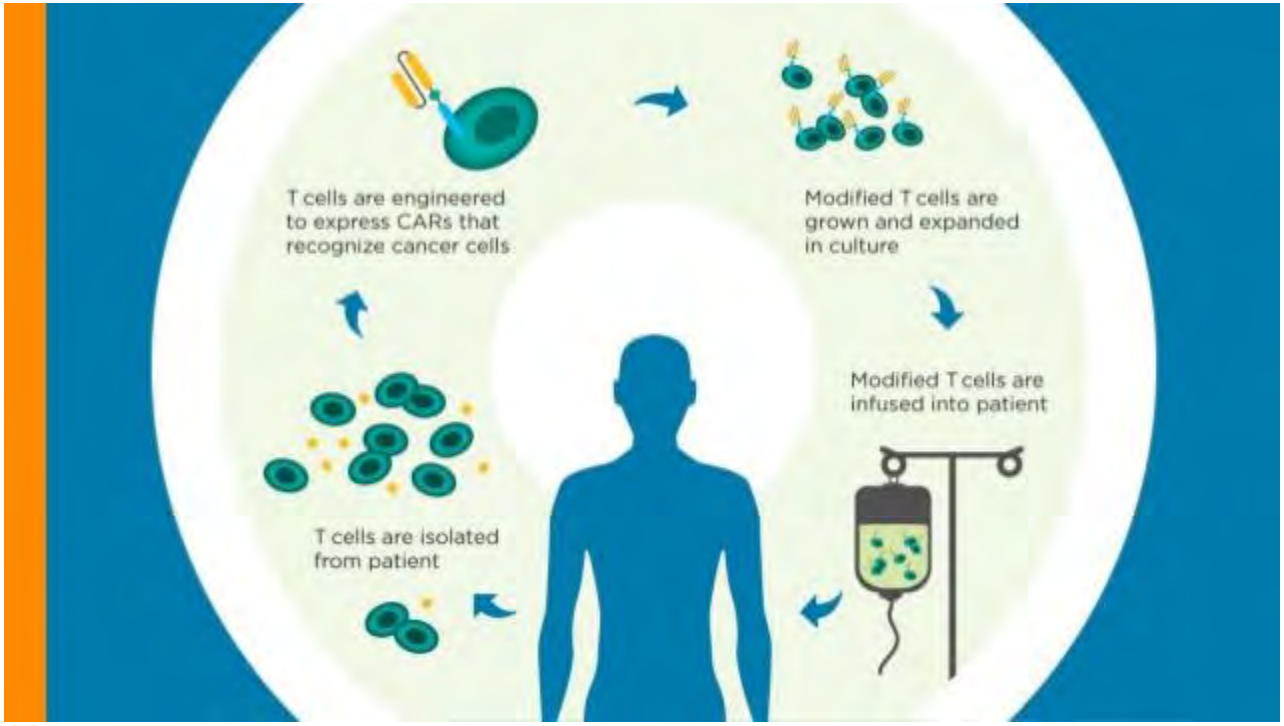
Zydelig è indicato in monoterapia per il trattamento di pazienti adulti affetti da linfoma follicolare (follicular lymphoma, FL) refrattario a due precedenti linee di trattamento.

CART-T

CAR-T

si tratta infatti di una immunoterapia cellulare autologa, prodotta a partire dai linfociti T del paziente, riprogrammati per identificare ed eliminare le cellule esprimenti CD19, in modo altamente personalizzato..

Con tecniche di ingegneria genetica si inserisce un gene nei linfociti T che così esprimeranno il recettore chimerico per l'antigene (CAR -Chimeric Antigen Receptor). Chimerico perché, come la chimera, la figura mitologica formato da parti del corpo di animali diversi, è costituito da porzioni di molecole diverse: un anticorpo che, come un radar, riconosce l'antigene da aggredire (il CD19) e porzioni co-stimolatorie (4-1BB) che attivano il linfocita contro quel bersaglio. Così il linfocita T diventa un’arma potentissima che intercetta le cellule tumorali distruggendole.

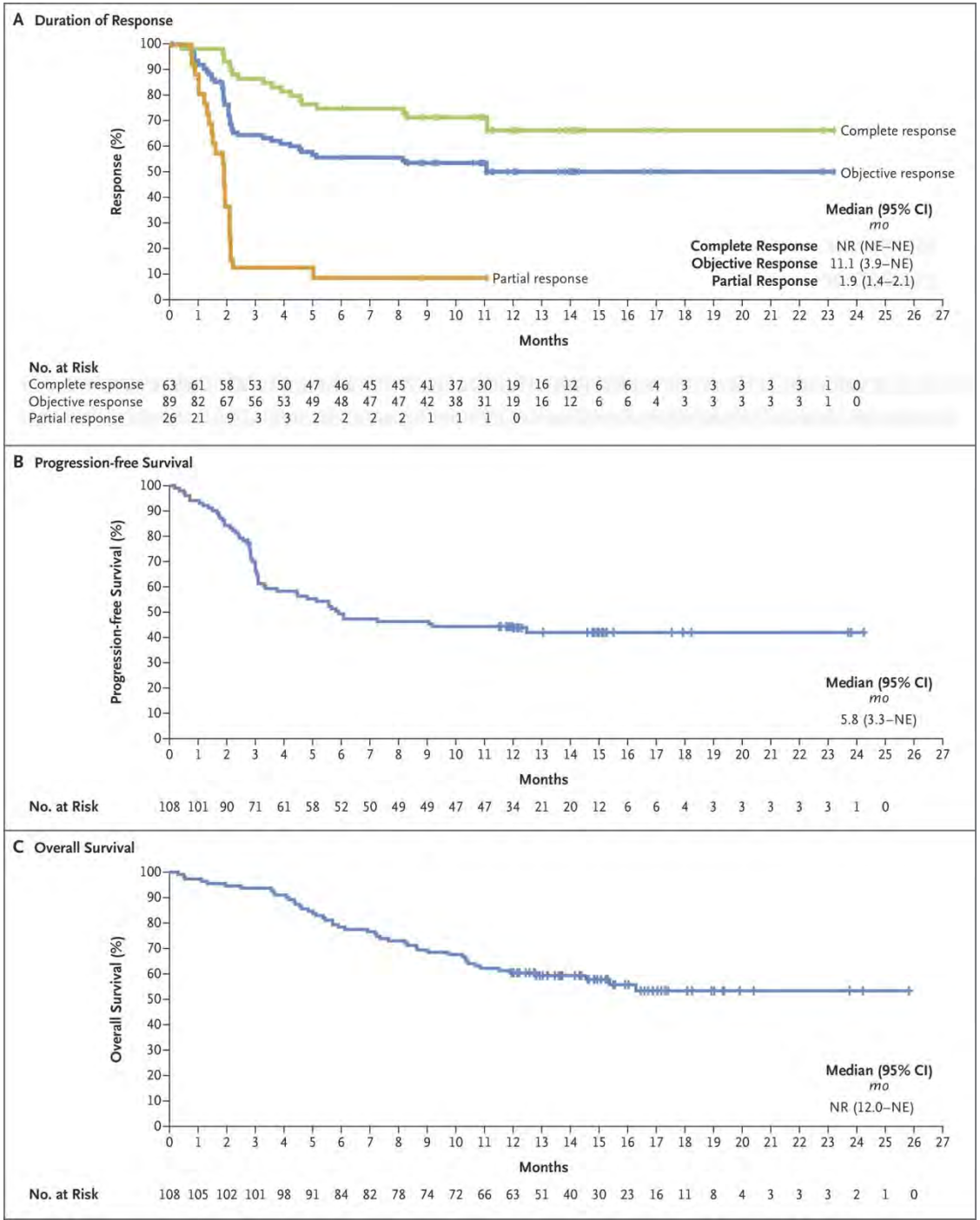

T cells are engineered to express CARs that recognize cancer cells
Modified T cells are grown and expanded in culture
Modified T cells are infused into patient
T cells are isolated from patient

HISTORY

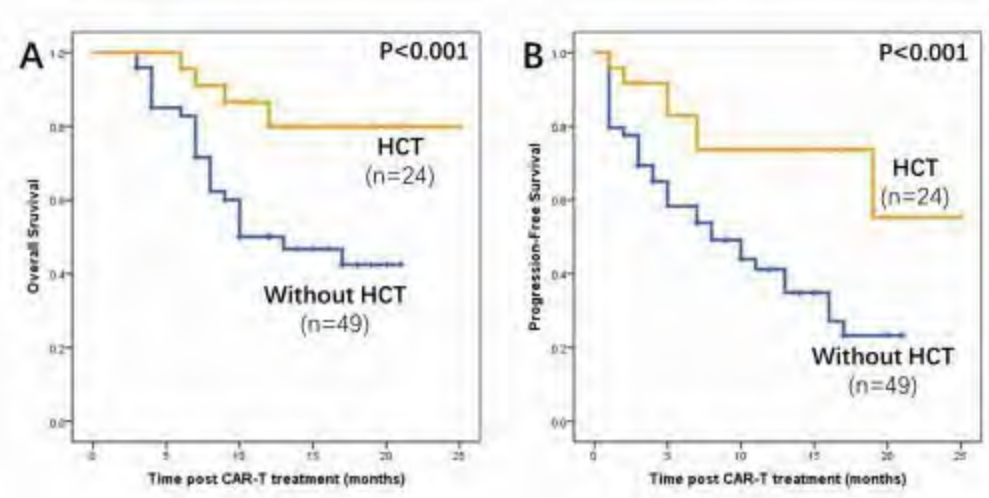
- In 1987, an Israeli immunologist, Zelig Eshhar, PhD, from The Weizmann Institute of Science, created the first "chimeric antigen receptor," an engineered receptor that does not exist in nature. The DNA encoding the receptor was implanted in the T cells so they could fight and kill cancer.
- In the year 2010 the first successful cancer treatment with CAR-T was for an advanced follicular lymphoma patient and was reported by the lab of Steven Rosenberg, M.D., Ph.D., chief of the SurgeryBranch in NCI's Center for Cancer Research.
- On August 30, 2017, tisagenlecleucel (Kymriah) was the first CAR T-cell immunotherapy approved by the FDA. It was approved for children and young adults aged 25 and under who relapsed or were not responding to therapy for acute lymphoblastic leukemia (ALL).

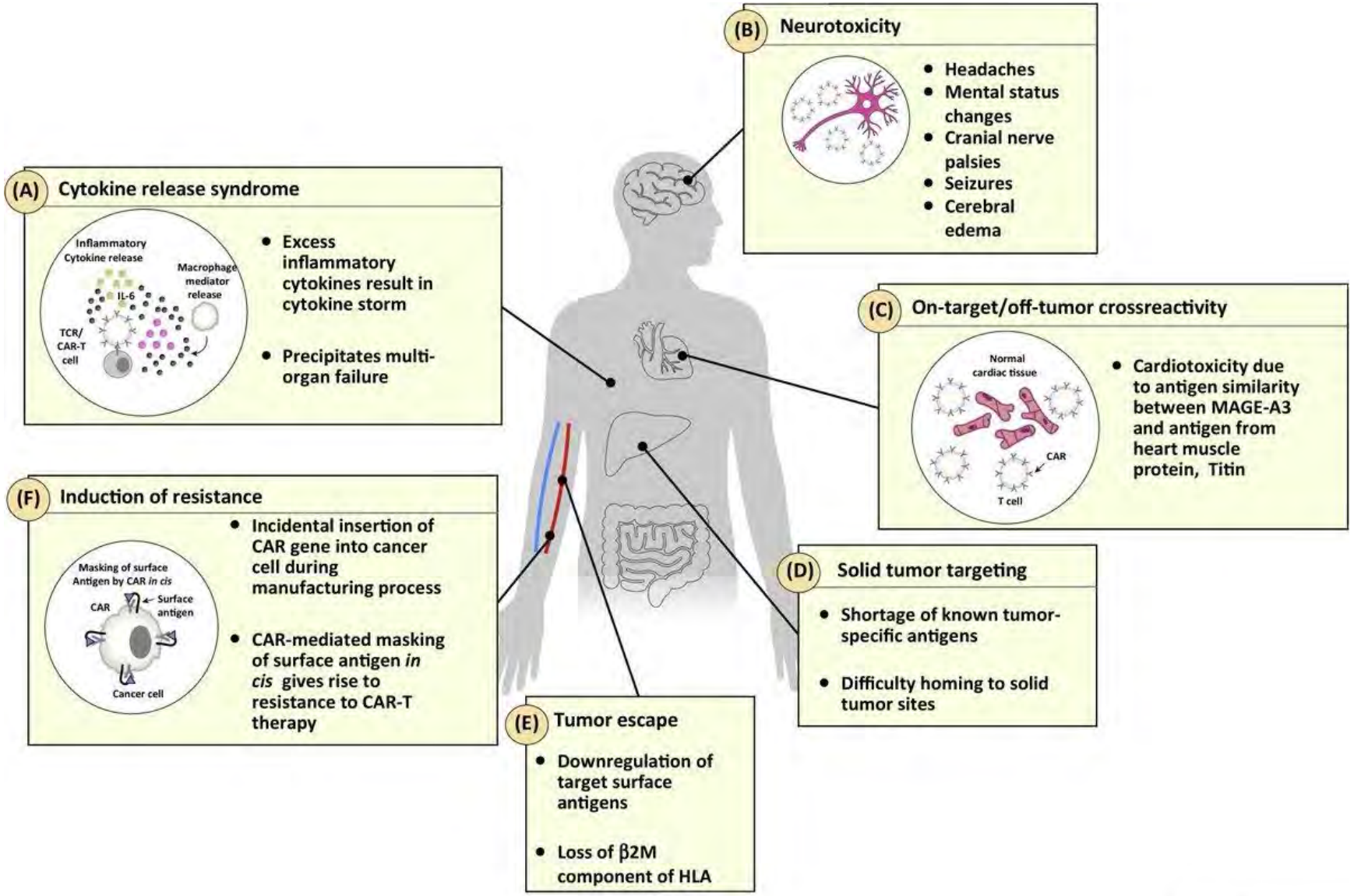
Axicabtagene ciloleucel (Yescarta) (Gilead)

tisagenlecleucel (Kymriah) (Novartis)


A Duration of Response
Response (%)
Complete response
Objective response
Partial response
Median (95% CI)
mo
Complete Response NR (NE–NE)
Objective Response 11.1 (3.9–NE)
Partial Response 1.9 (1.4–2.1)
Months
No. at Risk
Complete response 63 61 58 53 50 47 46 45 45 41 37 30 19 16 12 6 6 4 3 3 3 3 3 1 0
Objective response 89 82 67 56 53 49 48 47 47 42 38 31 19 16 12 6 6 4 3 3 3 3 3 1 0
Partial response 26 21 9 3 3 2 2 2 2 1 1 1 0
B Progression-free Survival
Progression-free Survival (%)
Median (95% CI)
mo
5.8 (3.3–NE)
Months
No. at Risk 108 101 90 71 61 58 52 50 49 49 47 47 34 21 20 12 6 6 4 3 3 3 3 3 1 0
C Overall Survival
Overall Survival (%)
Median (95% CI)
mo
NR (12.0–NE)
Months
No. at Risk 108 105 102 101 98 91 84 82 78 74 72 66 63 51 40 30 23 16 11 8 4 3 3 3 2 1 0

LEUCEMIA ACUTA LINFOIDE




(A) Cytokine release syndrome
Inflammatory Cytokine release
Macrophage mediator release
IL-6
TCR/ CAR-T cell
Excess inflammatory cytokines result in cytokine storm
Precipitates multi-organ failure
(B) Neurotoxicity
Headaches
Mental status changes
Cranial nerve palsies
Seizures
Cerebral edema
(C) On-target/off-tumor crossreactivity
Normal cardiac tissue
CAR
T cell
Cardiotoxicity due to antigen similarity between MAGE-A3 and antigen from heart muscle protein, Titin
(D) Solid tumor targeting
Shortage of known tumor-specific antigens
Difficulty homing to solid tumor sites
(E) Tumor escape
Downregulation of target surface antigens
Loss of β2M component of HLA
(F) Induction of resistance
Masking of surface Antigen by CAR in cis
CAR
Surface antigen
Cancer cell
Incidental insertion of CAR gene into cancer cell during manufacturing process
CAR-mediated masking of surface antigen in cis gives rise to resistance to CAR-T therapy