Nieuwe behandelingen voor non-Hodgkin lymfomen

Focus op immuuntherapie

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Leuven, 26 oktober 2019

Lymfkdierkanker Vereniging Vlaanderen vzw

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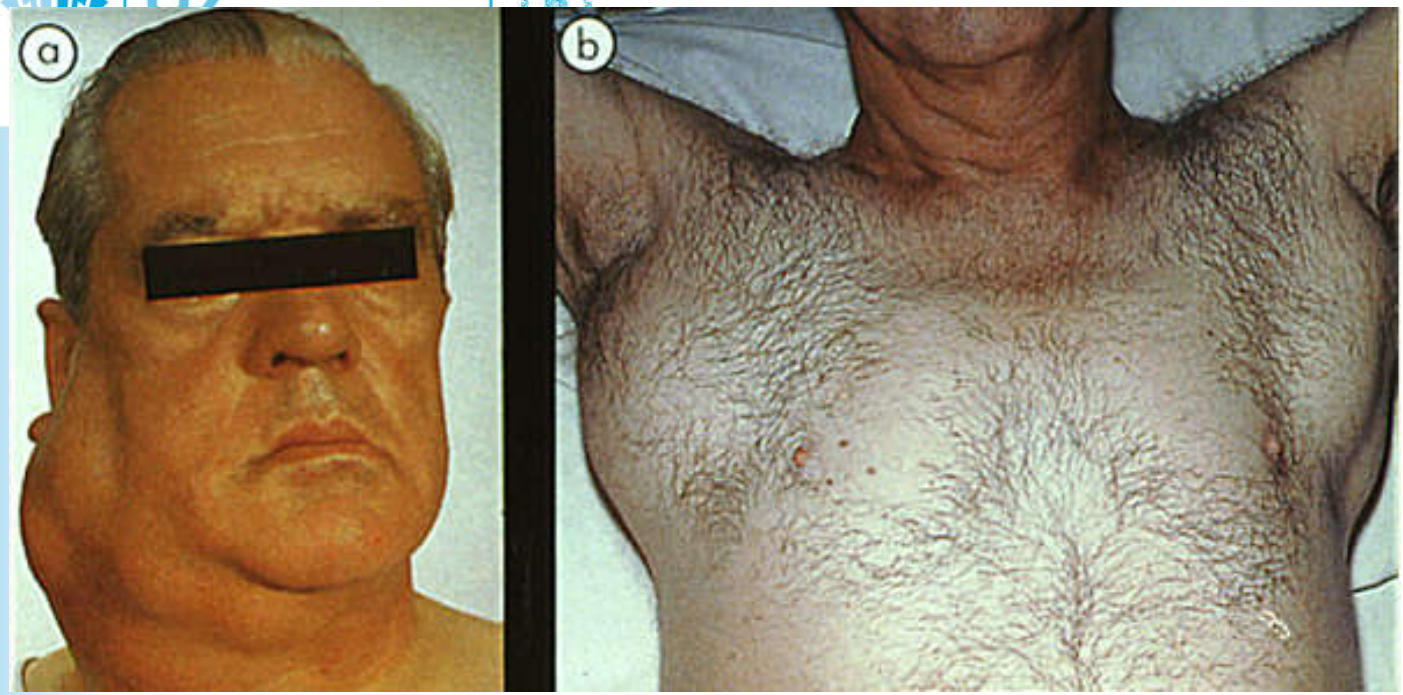
UNIVERSITY HOSPITALS LEUVEN

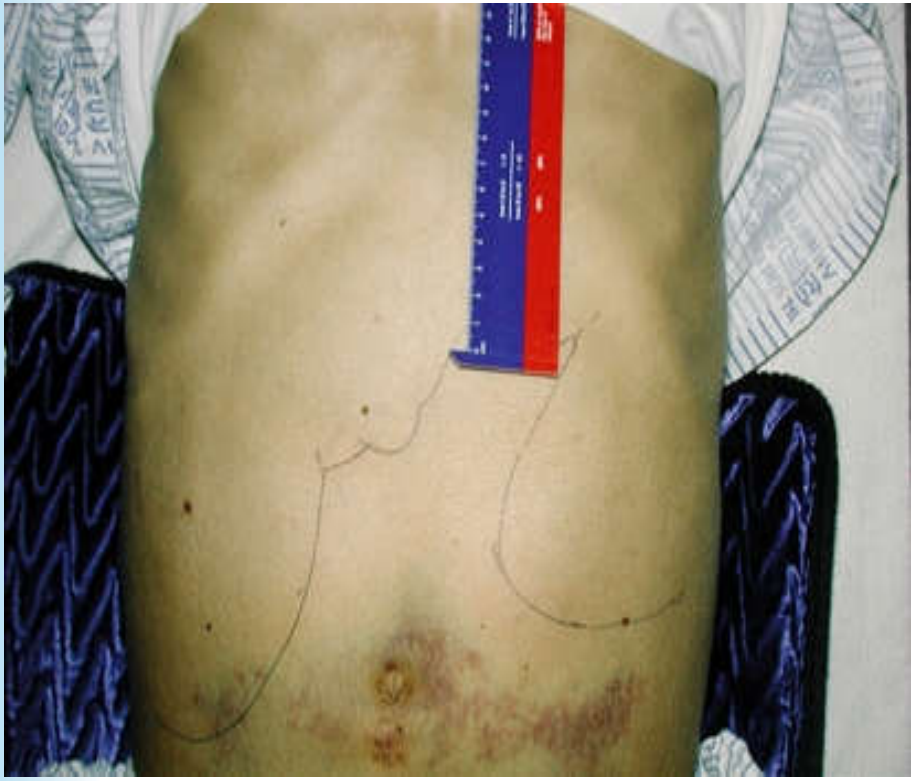
Klinische presentatie

- Pijnloze klierzwellingen (nodale aantasting)
- Extranodale aantasting
  - Alle organen
- B-symptomen
  - *Koorts (onverklaard, > 38°C)*
  - *Nachtzweten*
  - *Gewichtsverlies (niet-intentioneel, > 10% lichaamsgewicht in laatste 6 maand)*
- Vermoeidheid

Armitage JO, et al. Lancet 2017;390:298-310

Presentatie



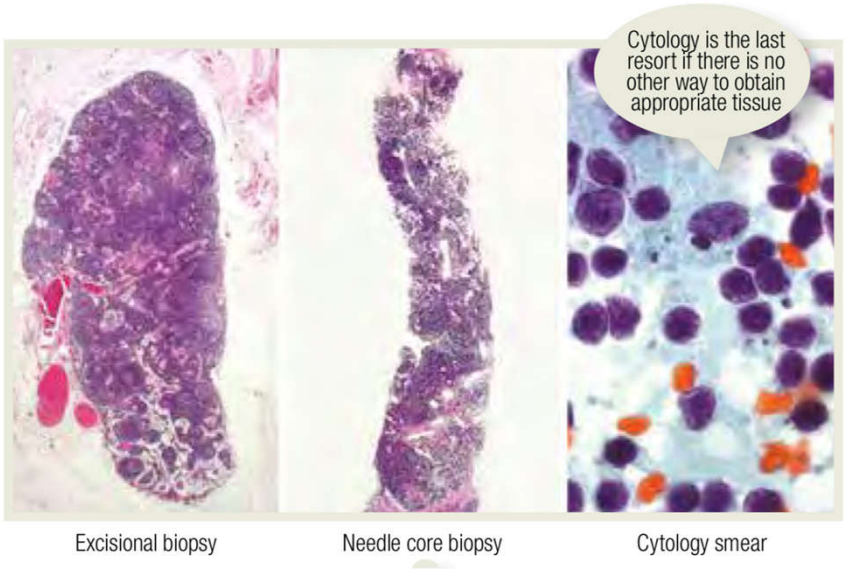


Biochemische presentatie

- CRP
- LDH
- Lymfocytose
- Cytopenie
- Immuun-gemedieerde complicaties
  - ITP
  - AIHA
- Spontane tumor lysis (zeer agressieve lymfomen)

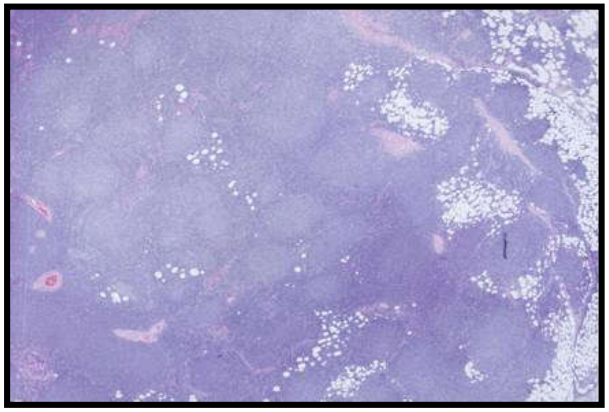
Diagnose

- Diagnose: excisiebiopsie



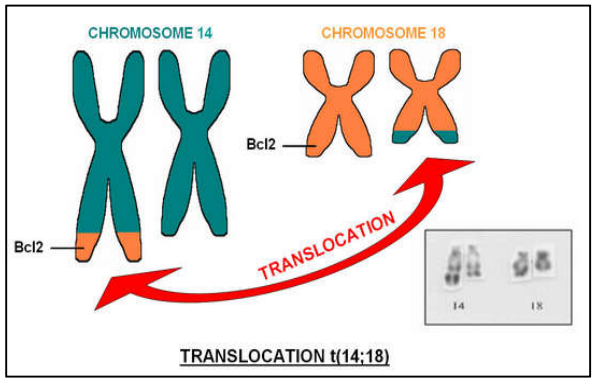
Diagnose

- Pathologie:
  - Morfologie



  - Immunohistochemie

  - Moleculaire/genetische analyses



Staging

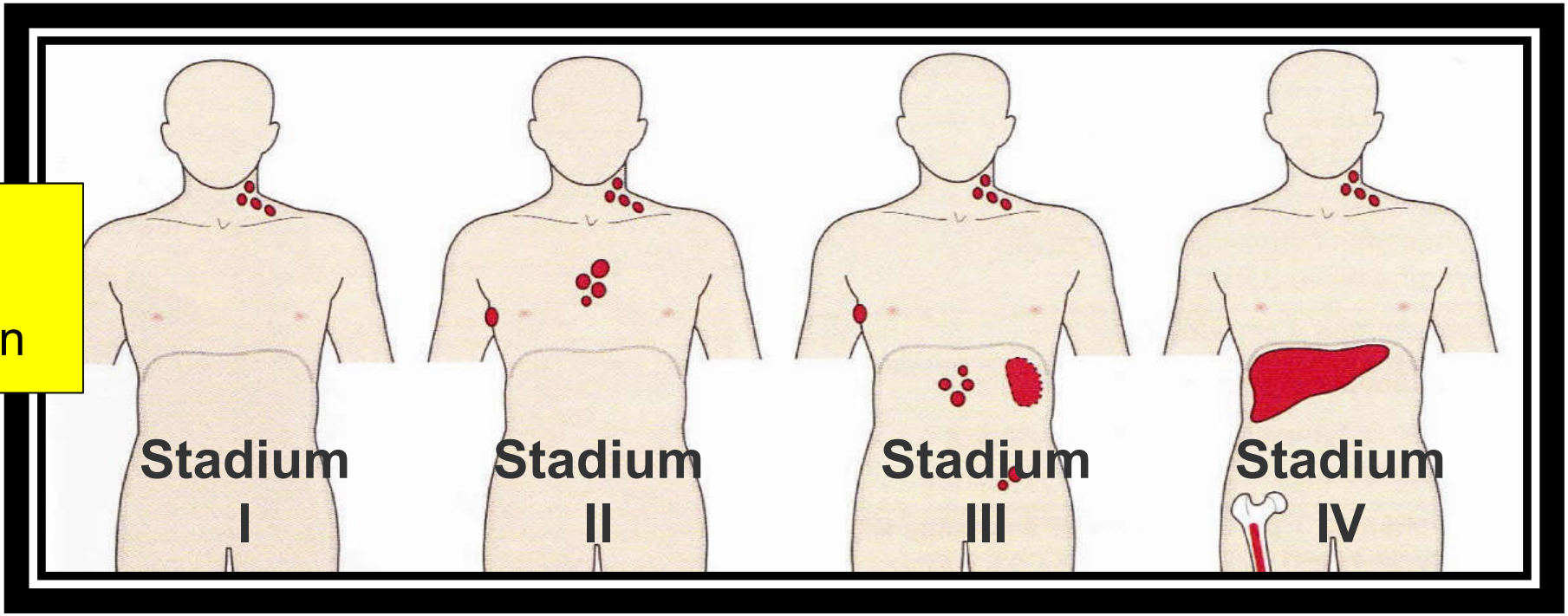
- Staging:
  - Beeldvorming
    - CT scan
    - PET/CT scan
  - Beenmergonderzoek
  - CZS evaluatie (MRI, lumbaalvocht)

Staging

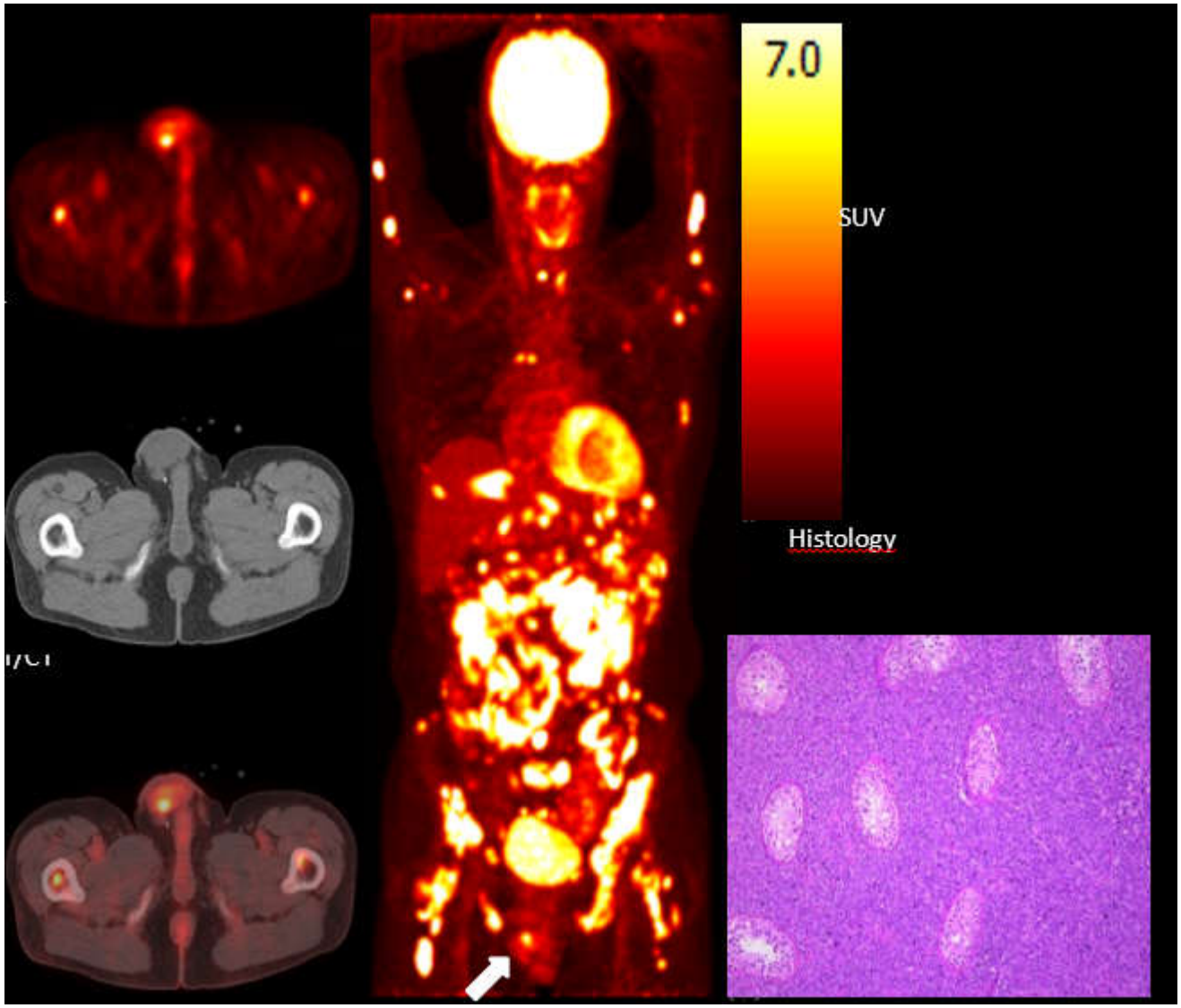
Ann Arbor staging

Stage I	**Involvement of one lymph node station or one lymphocytic structure (spleen, thymus or Waldeyer's ring,**
Stage II	**Involvement of at least two lymph node stations at one side of the diaphragm.**
Stage III	**Involvement of lymph nodes at both sides of the diaphragm.**
Stage IV	**Visceral involvement (bone, liver, …) or bone marrow invasion.**

A: geen B-symptomen
B: B-symptomen



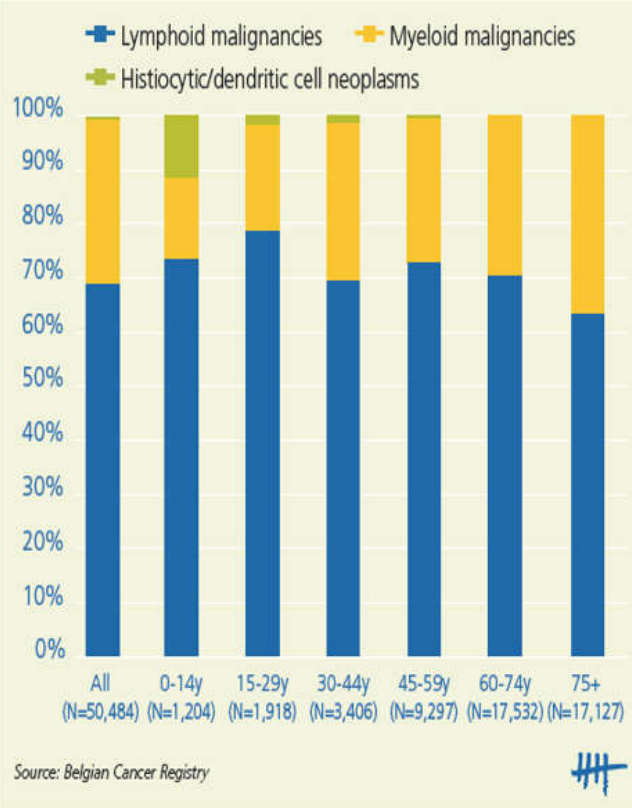
Staging



Classificatie

Hodgkin lymphoma (HL)	Non-Hodgkin lymphoma (NHL)
10%	
Classical HL	B-cell NHL 80%
Non-classical HL	T-cell NHL 10%
(B-cell origin)	NK-cell NHL

FIGURE 8 HAEMATOLOGICAL MALIGNANCIES: INCIDENCE BY CELL LINEAGE AND AGE GROUP, BELGIUM 2004-2012

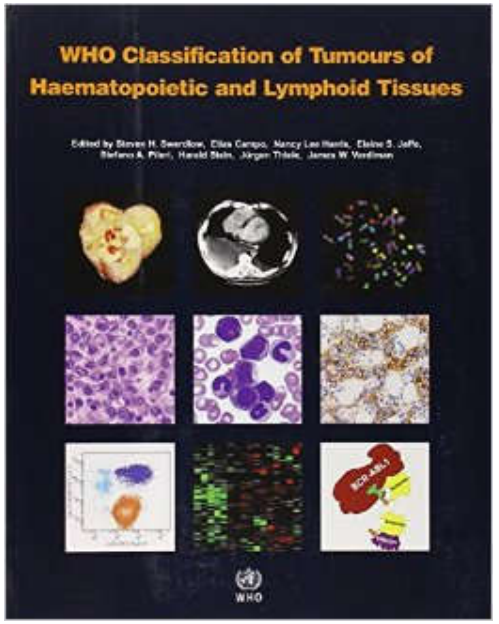


Classificatie

Table 1.
Brief history of the classification of lymphomas

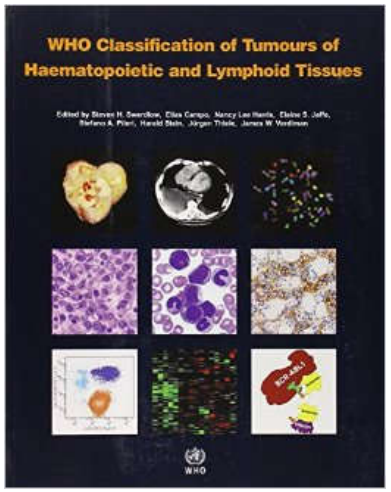
Year	Classification of lymphoma
1832	Hodgkin describes what will be known as 'Hodgkin disease'
1845	Virchow describes 'lymphosarcoma'
1850	WHO Classification of Diseases
1893	Kundrant distinguishes 'lymphosarcoma' from 'Hodgkin disease'
1914	Ewing describes 'reticulosarcoma' of bone and lymphoid organs
1916	Gohn and Roman
1934	Callendar, American Registry of Pathology
1938	Rob-Smith, Oxford University (UK)
1942	Gall and Mallory, Massachusetts General Hospital (US)
1939	Jackson and Parker, Boston City Hospital (US)
1956	Rappaport's morphological classification
1966	Lukes and Butler propose the modern classification of Hodgkin lymphoma
1973	Formation of European Lymphoma Club
1973	British National Lymphoma Investigation
1974	Kiel's classification; high- vs low-grade, then separated into B- or T-cells
1974	Lukes/Collins immunologically based classification
1974	Dorfman classification
1976	WHO International Histological Classification of Tumours
1982	Working Formulation, NCI (US)
1994	REAL classification, International Lymphoma Study Group
2001	WHO Classification: Tumours of Haematopoietic and Lymphoid Tissues, 3rd Edition
2008	WHO Classification: Tumours of Haematopoietic and Lymphoid Tissues, 4th Edition

2017



Gifford GK, et al. Pathology 2016;48:5-16
Swerdlow SH, et al. IARC Press: Lyon 2017

Classificatie



Mature B-cell neoplasms

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis*
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- *Splenic B-cell lymphoma/leukemia, unclassifiable*
  - *Splenic diffuse red pulp small B-cell lymphoma*
  - *Hairy cell leukemia-variant*
- Lymphoplasmacytic lymphoma
  - Waldenström macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS), IgM*
- μ heavy-chain disease
- γ heavy-chain disease
- α heavy-chain disease
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Monoclonal immunoglobulin deposition diseases*
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
  - *Pediatric nodal marginal zone lymphoma*
- Follicular lymphoma
  - In situ follicular neoplasia*
  - Duodenal-type follicular lymphoma*
- Pediatric-type follicular lymphoma*
- *Large B-cell lymphoma with IRF4 rearrangement**
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
  - In situ mantle cell neoplasia*
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - Germinal center B-cell type*
  - Activated B-cell type*
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- Primary cutaneous DLBCL, leg type
- EBV⁺ DLBCL, NOS*
- *EBV⁺ mucocutaneous ulcer**
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK⁺ large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- *HHV8⁺ DLBCL, NOS**
- Burkitt lymphoma
- *Burkitt-like lymphoma with 11q aberration**
- High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
- High-grade B-cell lymphoma, NOS*
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Mature T and NK neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK cells*
- Aggressive NK-cell leukemia
- Systemic EBV⁺ T-cell lymphoma of childhood*
- Hydroa vacciniforme–like lymphoproliferative disorder*
- Adult T-cell leukemia/lymphoma
- Extranodal NK-/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*
- *Indolent T-cell lymphoproliferative disorder of the GI tract**
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30⁺ T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- *Primary cutaneous CD8⁺ aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous acral CD8⁺ T-cell lymphoma**
- *Primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- *Follicular T-cell lymphoma**
- *Nodal peripheral T-cell lymphoma with TFH phenotype**
- Anaplastic large-cell lymphoma, ALK⁺
- Anaplastic large-cell lymphoma, ALK⁻*
- *Breast implant–associated anaplastic large-cell lymphoma**

Hodgkin lymphoma

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Lymphocyte-depleted classical Hodgkin lymphoma

Posttransplant lymphoproliferative disorders (PTLD)

- Plasmacytic hyperplasia PTLD
- Infectious mononucleosis PTLD
- Florid follicular hyperplasia PTLD*
- Polymorphic PTLD
- Monomorphic PTLD (B- and T-/NK-cell types)
- Classical Hodgkin lymphoma PTLD

Histiocytic and dendritic cell neoplasms

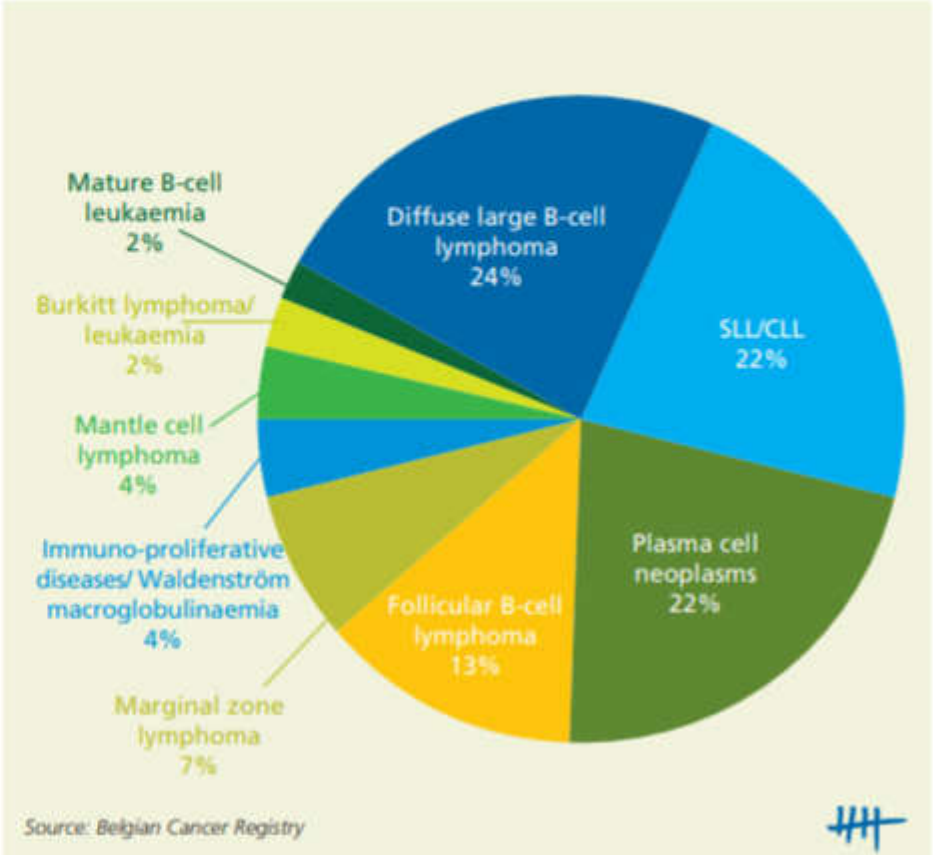
- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Indeterminate dendritic cell tumor
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Disseminated juvenile xanthogranuloma
- Erdheim-Chester disease*

Swerdlow SH, et al. IARC Press: Lyon 2017

Epidemiologie

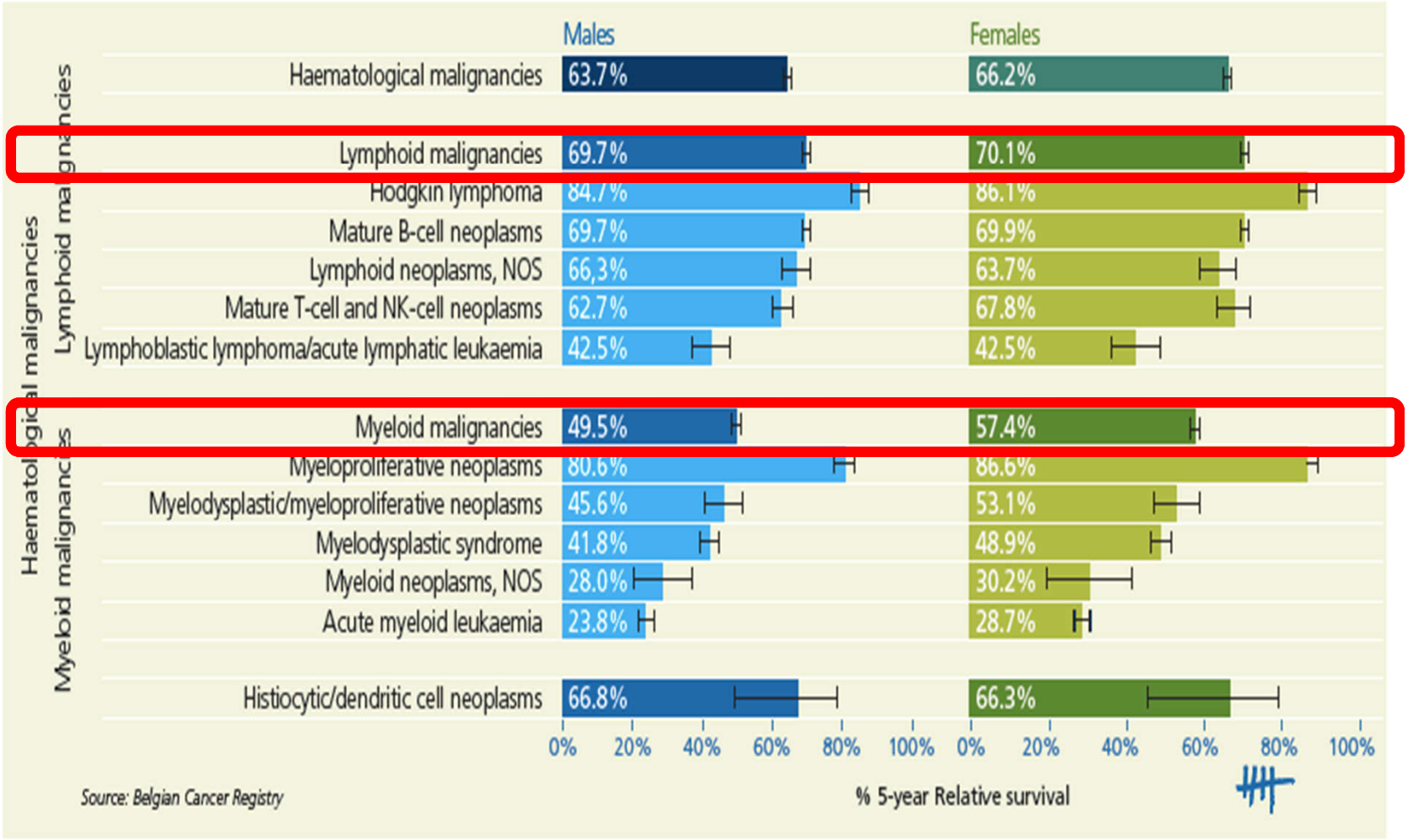
FIGURE 33 MATURE B-CELL NEOPLASMS: AGE-SPECIFIC INCIDENCE RATES (N/100,000) BY SEX, BELGIUM 2004-2012

FIGURE 34 MATURE B-CELL NEOPLASMS: INCIDENCE BY SUBTYPE, BELGIUM 2004-2012



Epidemiologie

FIGURE 14 HAEMATOLOGICAL MALIGNANCIES: 5-YEAR RELATIVE SURVIVAL BY SEX AND SUBTYPE, BELGIUM 2004-2012



Source: Belgian Cancer Registry

NHL

Heel agressief	Agressief	Indolent
Dagen-weken	Weken-maanden	Maanden-jaren
Intensive immunochemotherapie (bv, Rituximab + Hoelzerprotocol)	Immunochemotherapie (bv. R-CHOP)	Immunochemotherapie (bv. R-CVP of R-benda) Immunotherapie (bv. rituximab) Gerichte therapie (bv. ibrutinib)
Curatief (tot > 90%)	Curatief (tot 70%)	Niet-curatief
Burkitt NHL	DLBCL T-cel NHL Mantelcel lymfoom	CLL/SLL Folliculair lymfoom Ziekte vanWaldenström Marginale zone lymfoom Hairy cell leukemie

NHL

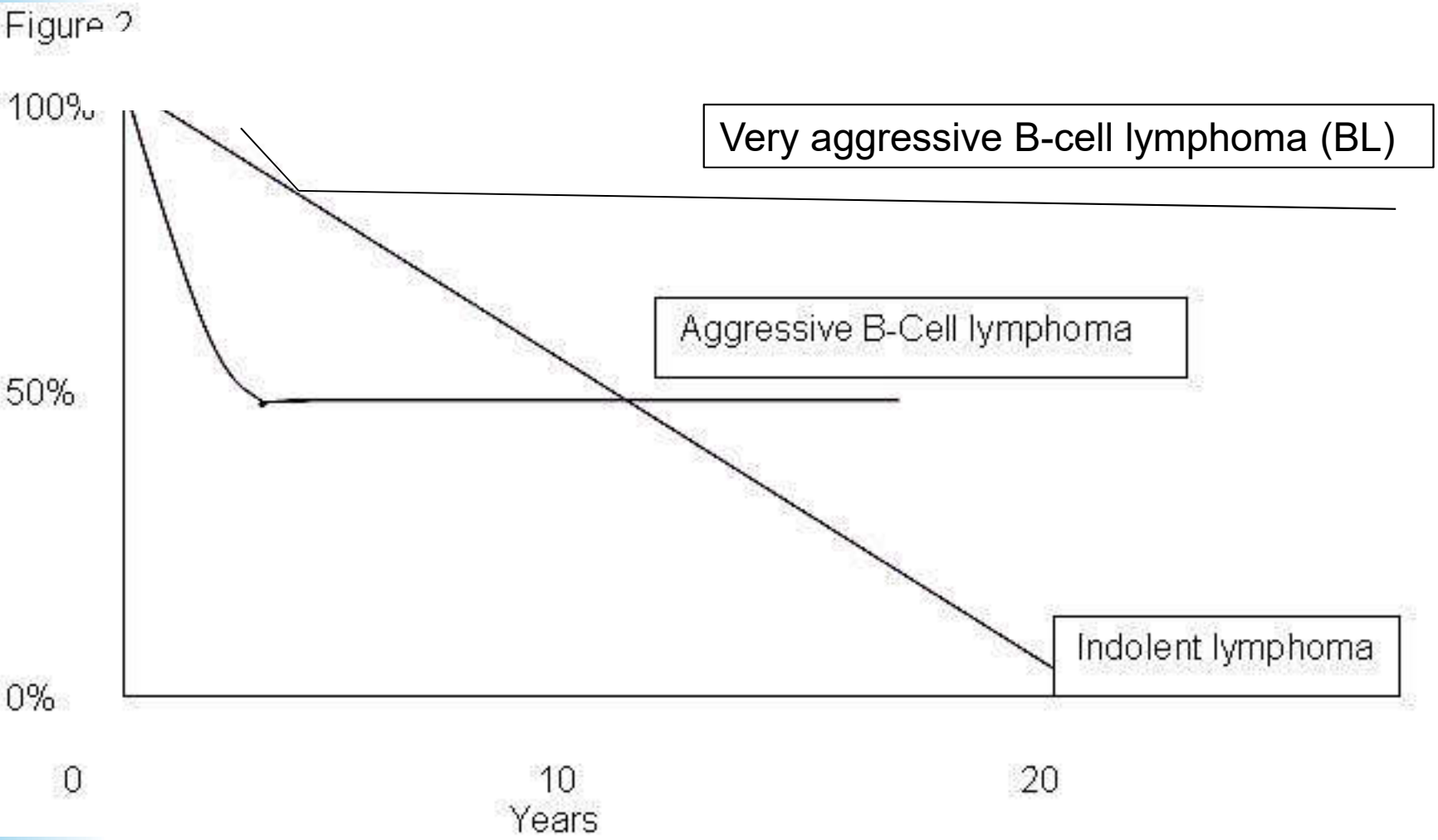


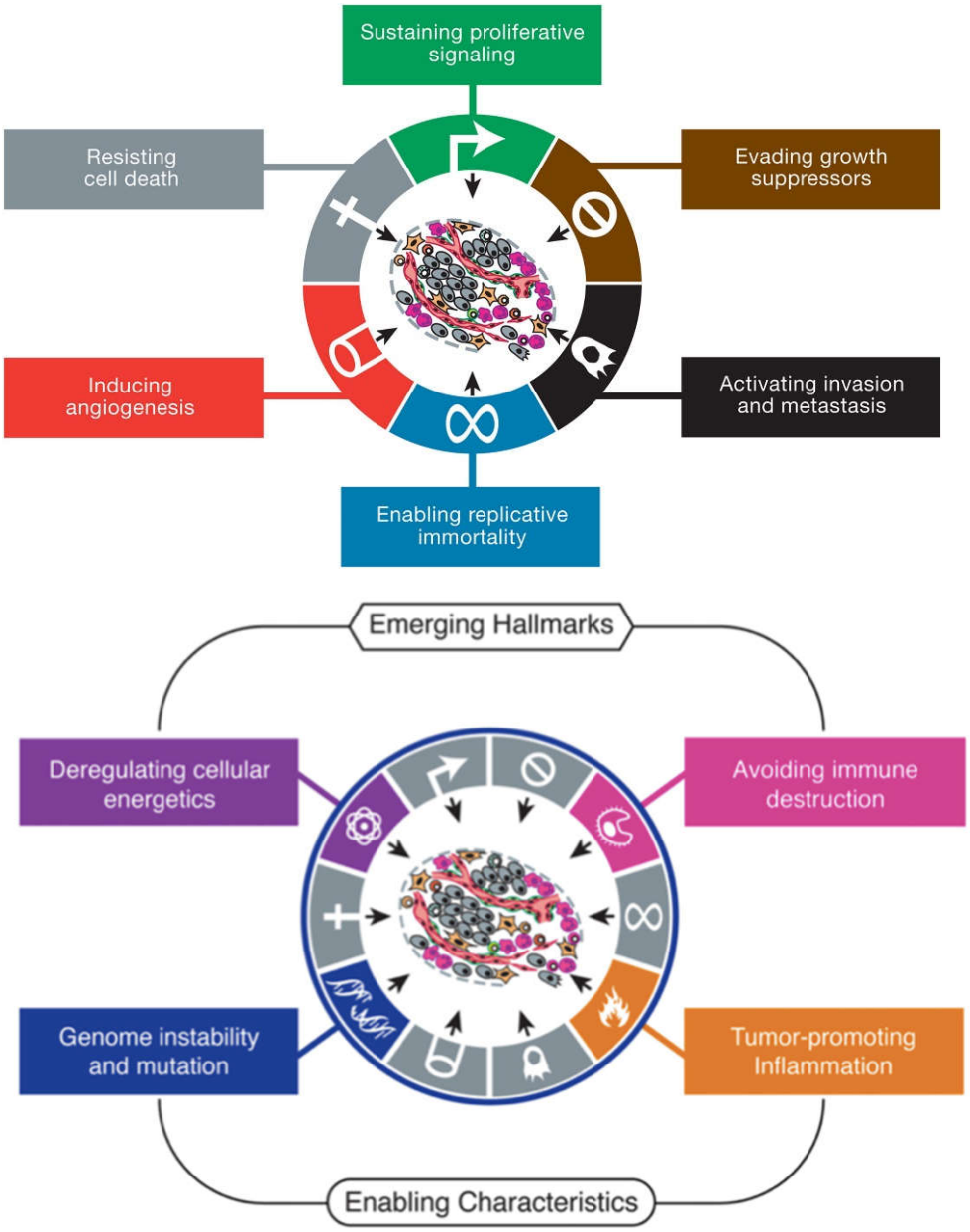
Figure 2
100%
50%
0%
0
10
20
Years
Very aggressive B-cell lymphoma (BL)
Aggressive B-Cell lymphoma
Indolent lymphoma

?

Ja

Ja

“Hallmarks of cancer”



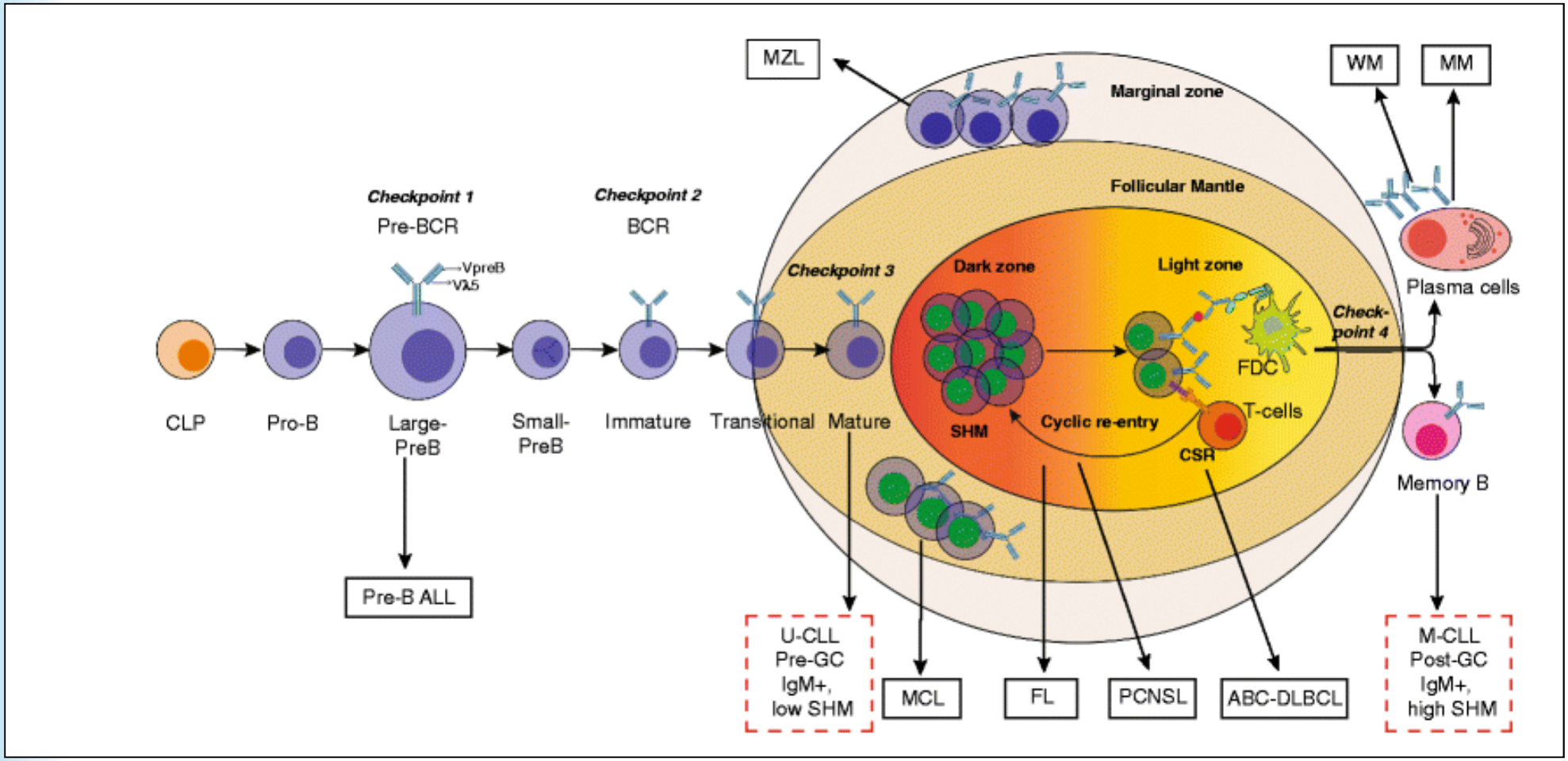
Hanahan D, Weinberg RA. Cell 2000;100:57-70

Hanahan D , Weinberg RA. Cell 2011;144:646-74

Nieuwe therapieën werken in op deze “hallmarks”

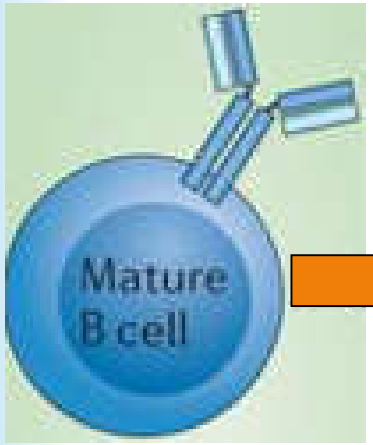
- Ibrutinib
- Venetoclax
- Immuuntherapie

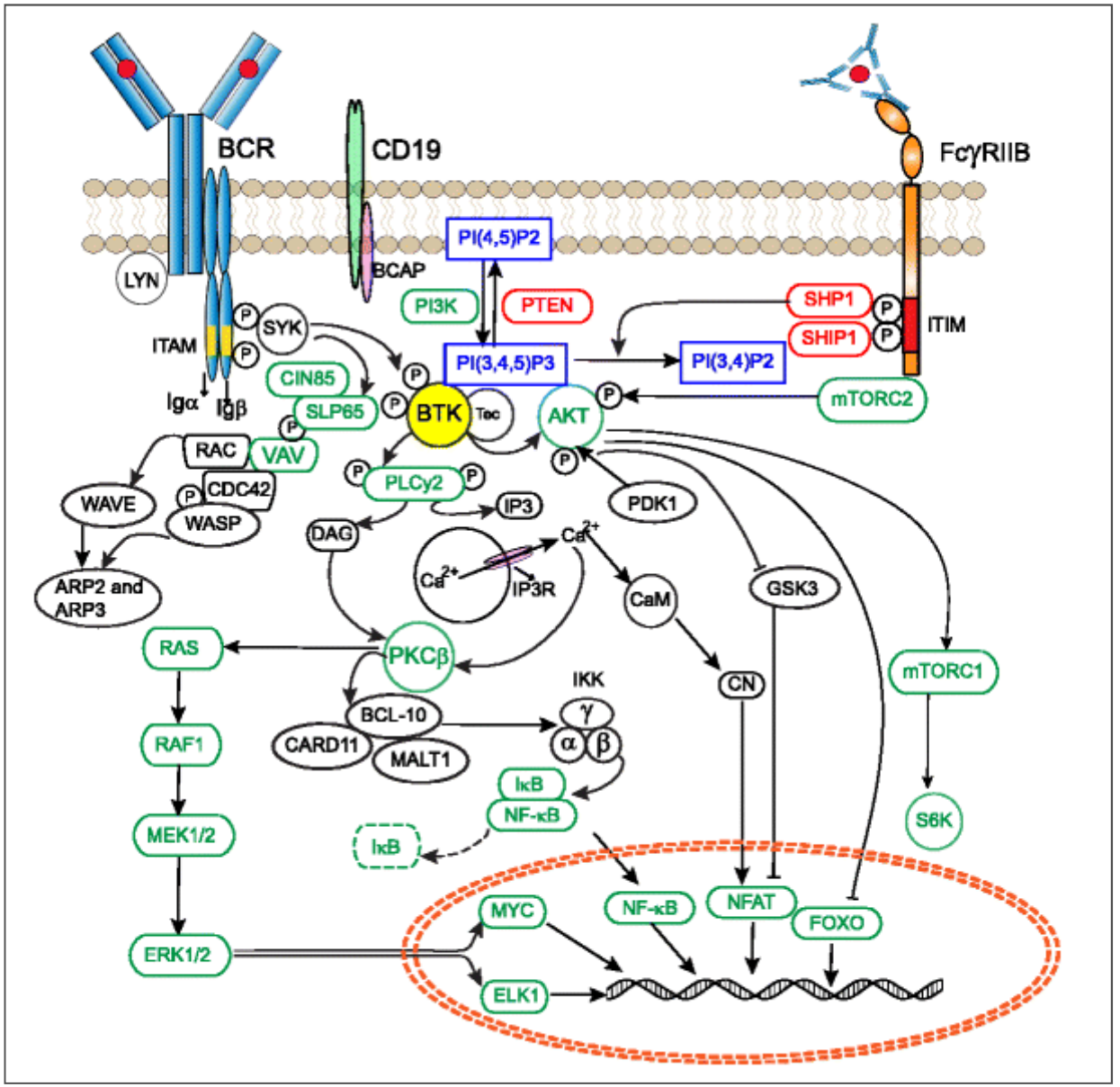
Ibrutinib



Pal Singh S, et al. Mol Cancer 2018:17:57

Ibrutinib

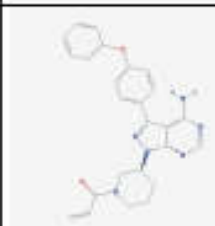
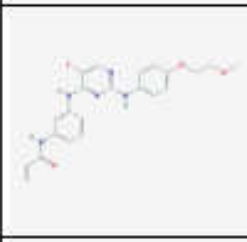
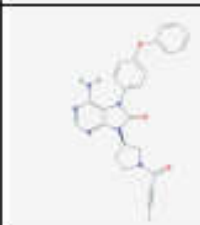
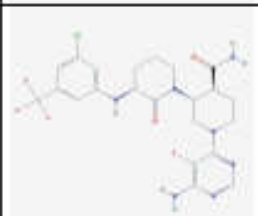




Rickert RC. Nat Rev Immunol 2013;13:578-91
Pal Singh S, et al. Mol Cancer 2018:17:57

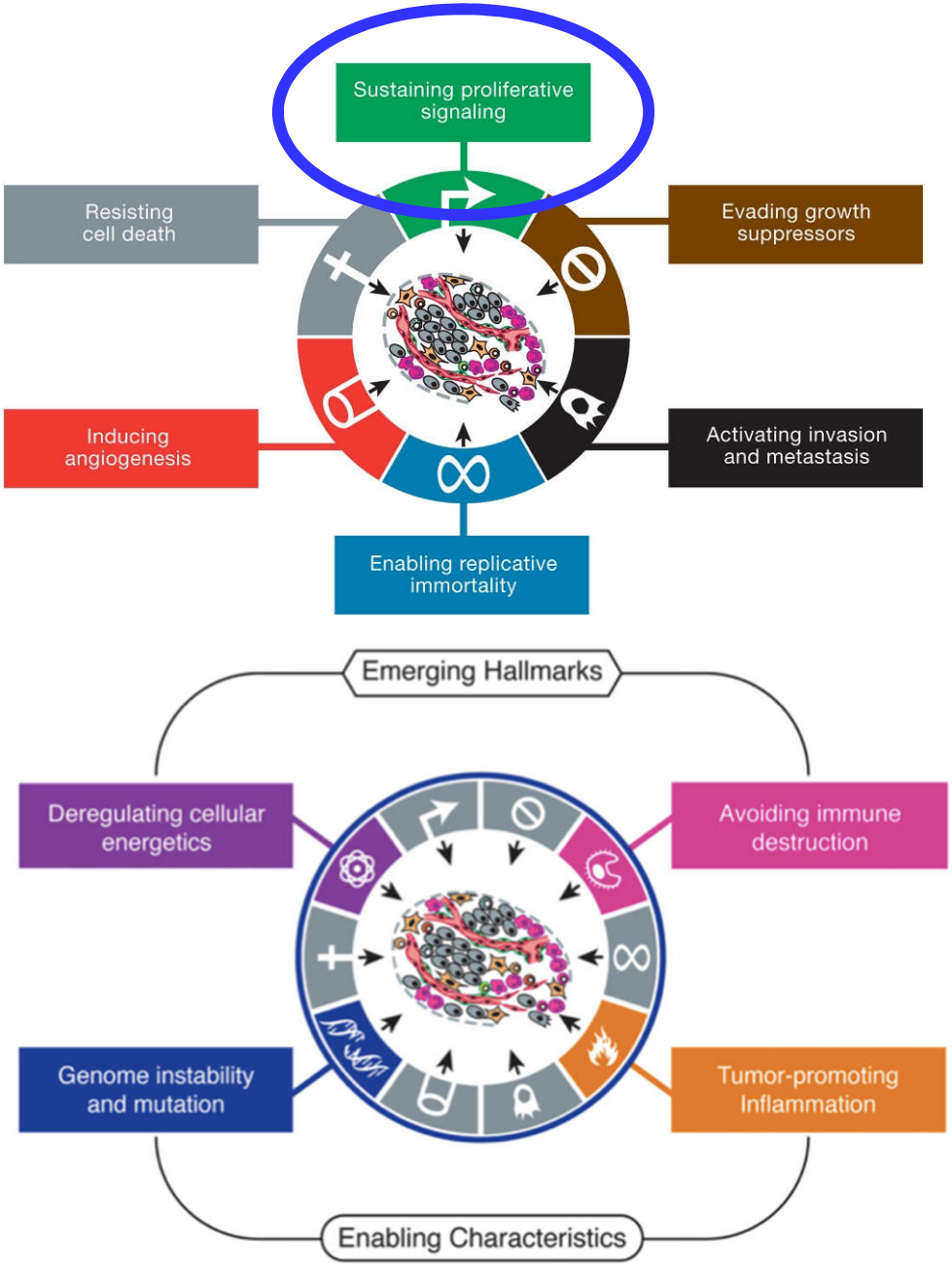
Ibrutinib

Patient population	Therapeutic regimen	Phase	Efficacy
R/R CLL	Ibrutinib	Ib/II	ORR (71%), PR(20%)
R/R CLL	Ibrutinib	III	ORR (63%)
TN CLL	Ibrutinib	Ib/II	ORR (85%), CR(26%)
TN CLL	Ibrutinib	III	ORR (86%), CR(4%)
R/R MCL	Ibrutinib	II	ORR (68%), CR(21%)
R/R MCL	Ibrutinib	III	ORR (72%), CR(19%)
R/R WM	Ibrutinib	II	ORR(91%), Major response (73%)
R/R ABC-DLBCL	Ibrutinib	II	ORR (37%)
R/R CLL	Ibrutinib-Rituximab	II	ORR (95%), CR(8%)
R/R CLL	Ibrutinib-bendamustine-rituximab	III	ORR (83%), CR(10%)
R/R MCL	Ibrutinib-Rituximab	II	ORR (88%), CR(44%), PR(44%)
R/R CLL	Acalabrutinib	I/II	ORR(95%)
R/R	Acalabrutinib	II	ORR (81%), CR (40%), PR(41%)
R/R CLL	ONO/GS-4059	I	ORR(96%)
R/R MCL	ONO/GS-4059	I	ORR(92%)
R/R non-GCB DLBCL	ONO/GS-4059	I	ORR(92%)
R/R CLL	BGB-3111	I	ORR(90%)
R/R MCL	BGB-3111	I	ORR(80%)
R/R MZL	Ibrutinib	II	ORR(51%)
R/R FL	Ibrutinib	I	ORR(38%)

Drug	Molecular structure	Mechanism of action
Acalabrutinib		Irreversible binding
Ibrutinib		Irreversible binding
Spebrutinib		Irreversible binding
Tirabrutinib		Reversible binding
Vecabrutinib		Reversible, function against C418S

Pal Singh S, et al. Mol Cancer 2018:17:57
Da Cunha-Bang C, Niemann CU. Drugs 2018;78:1653-63

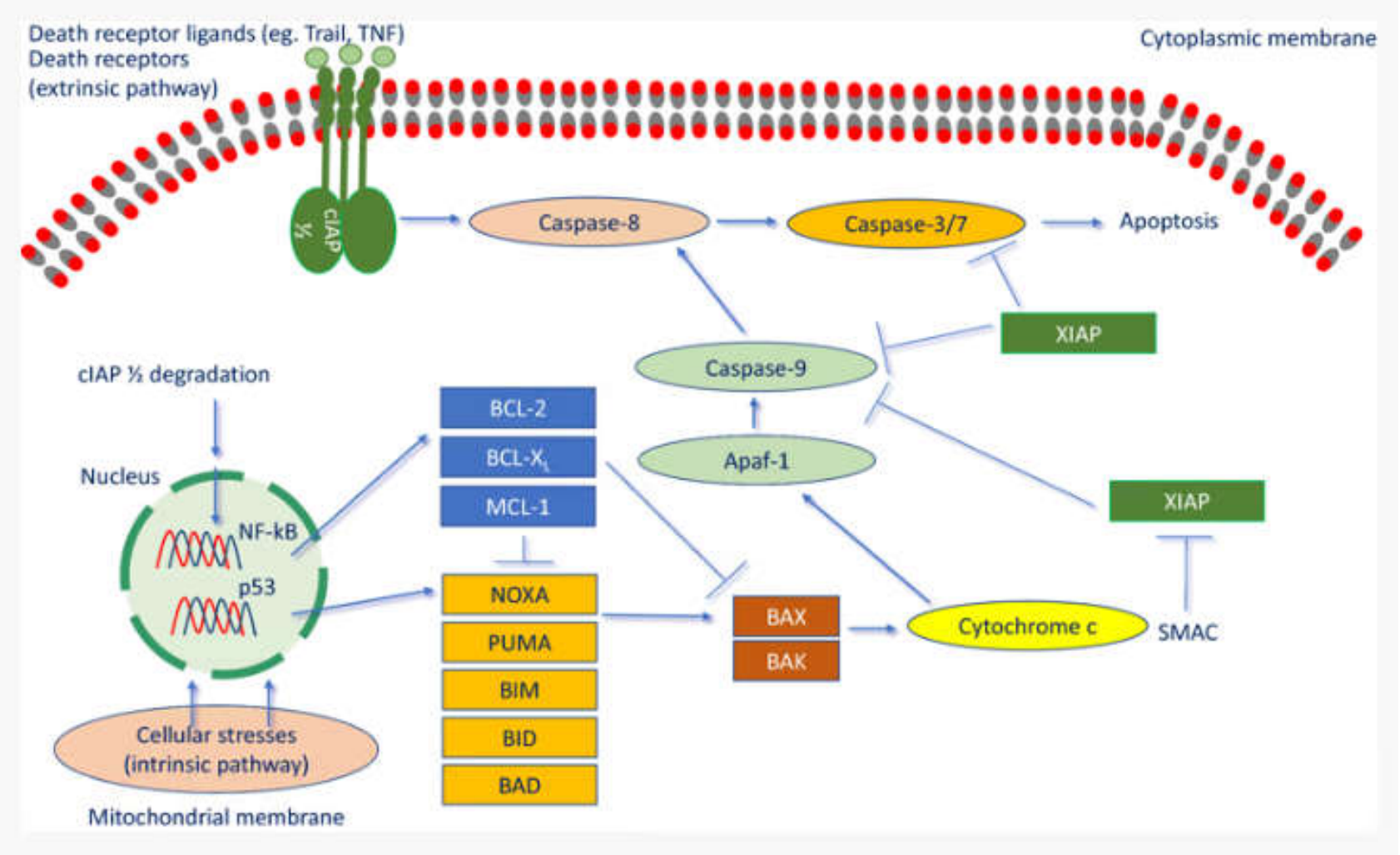
“Hallmarks of cancer”



Hanahan D, Weinberg RA. Cell 2000;100:57-70

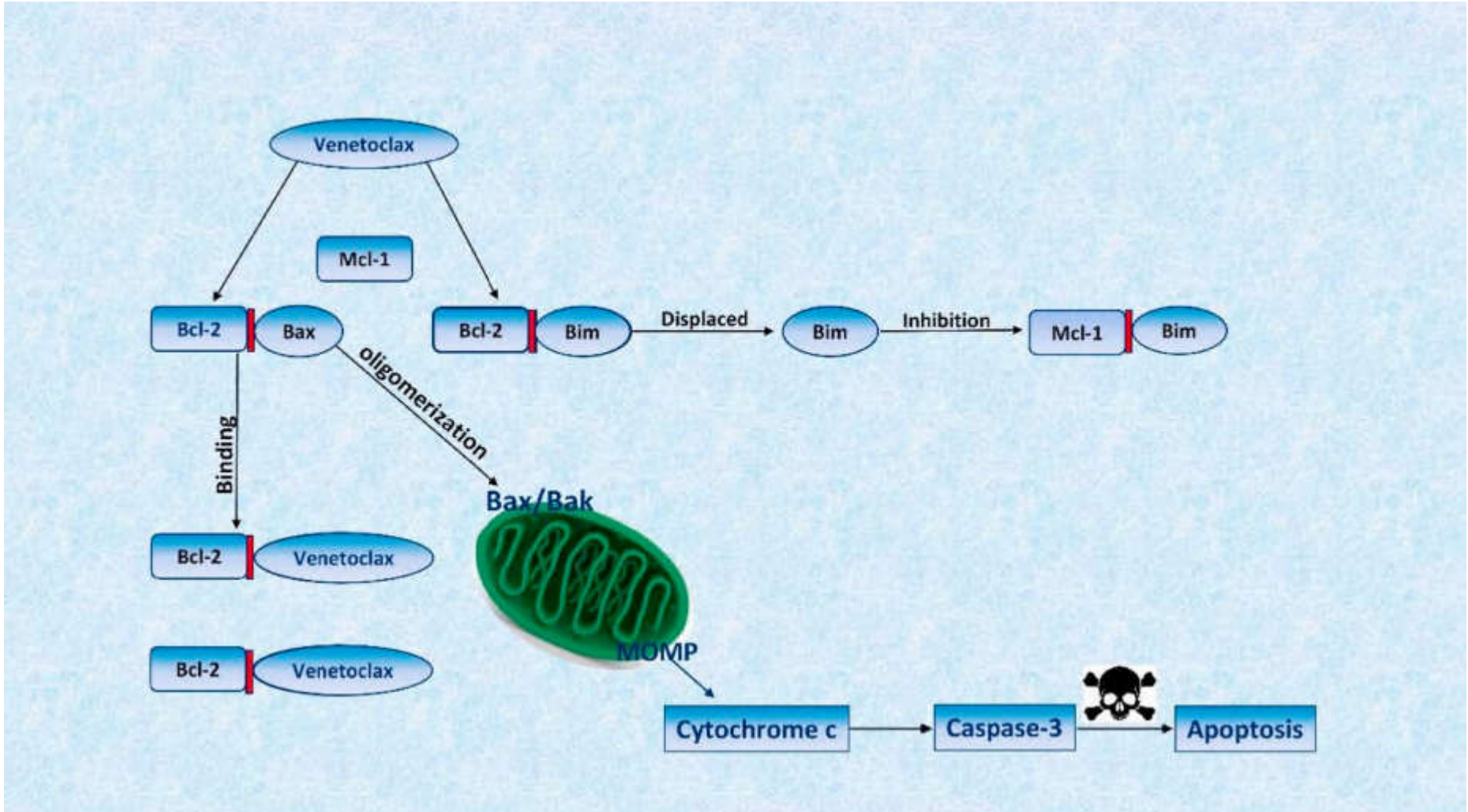
Hanahan D, Weinberg RA. Cell 2011;144:646-74

Venetoclax



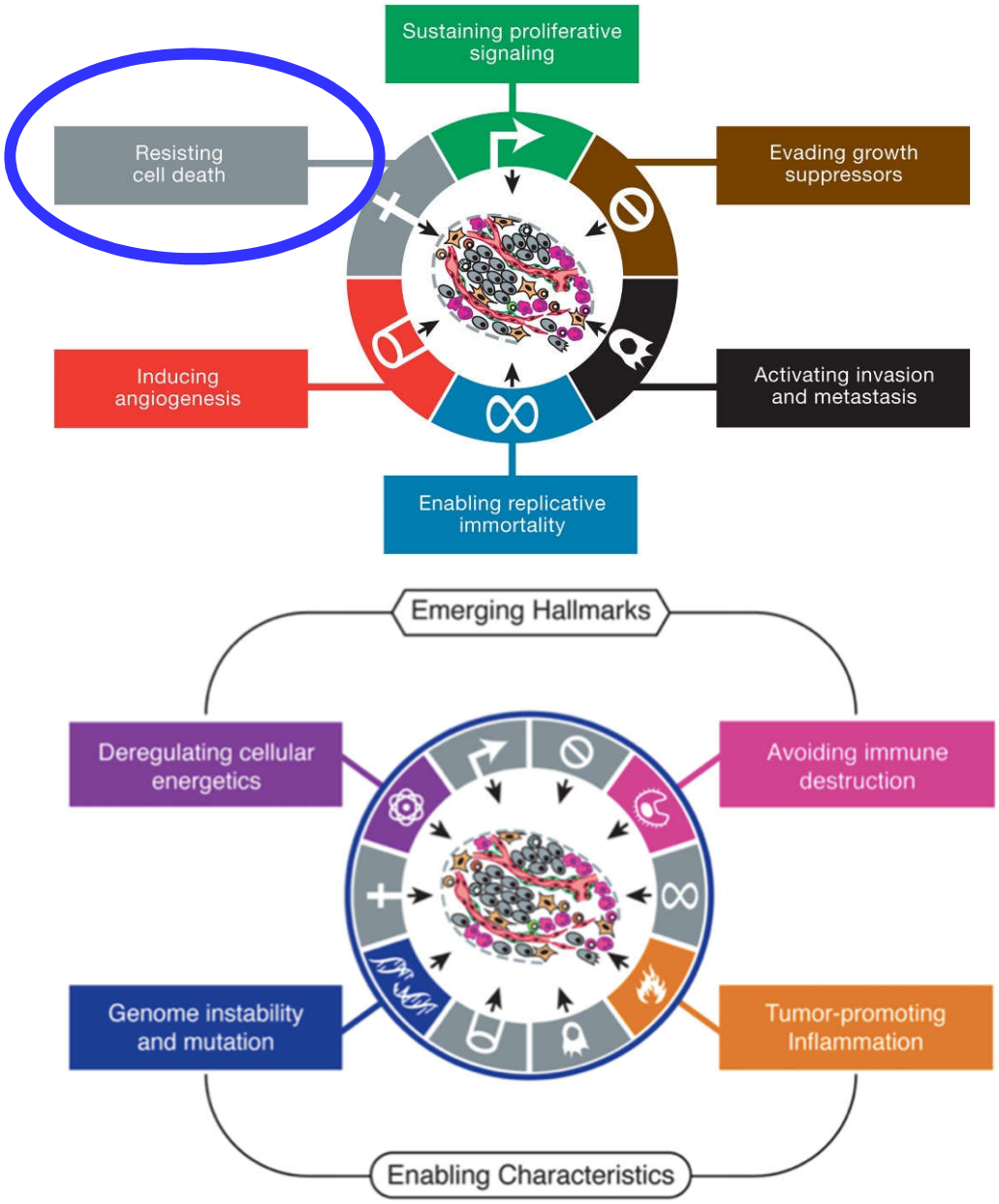
Yalniz FF, Wierda WG. Drugs 2019;79:1297-304

Venetoclax



Suvarna V, et al. Eur J Pharmacol 2019;862:172655

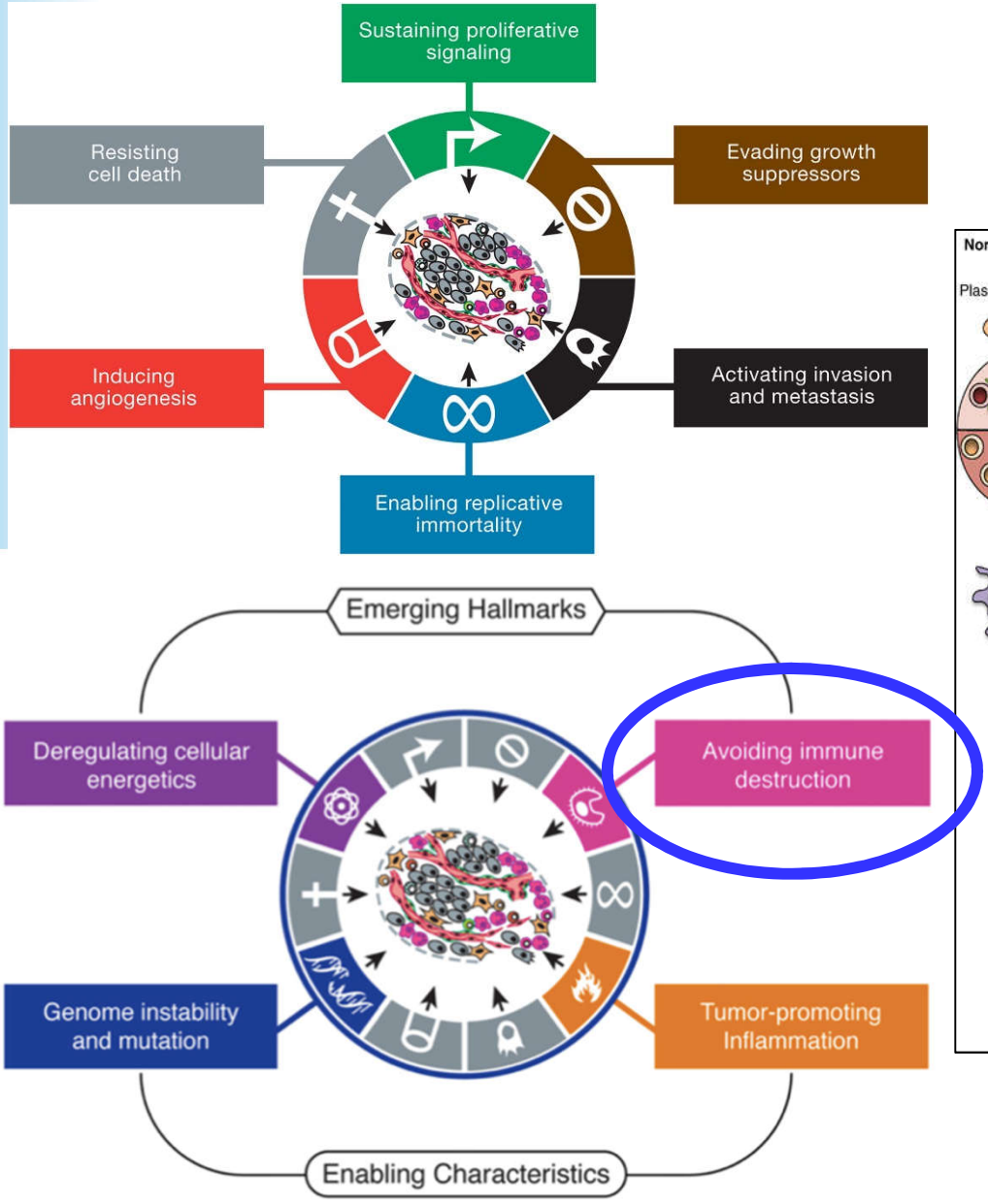
“Hallmarks of cancer”

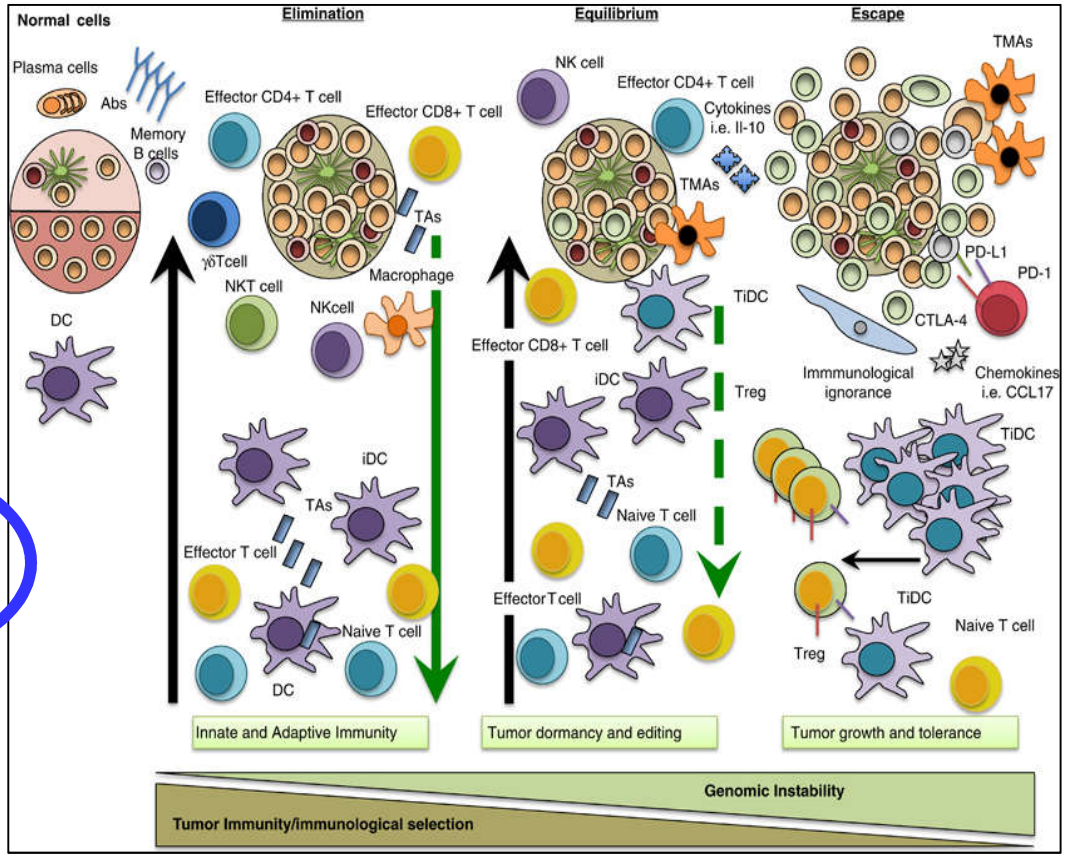


Hanahan D, Weinberg RA. Cell 2000;100:57-70

Hanahan D, Weinberg RA. Cell 2011;144:646-74

Immuuntherapie





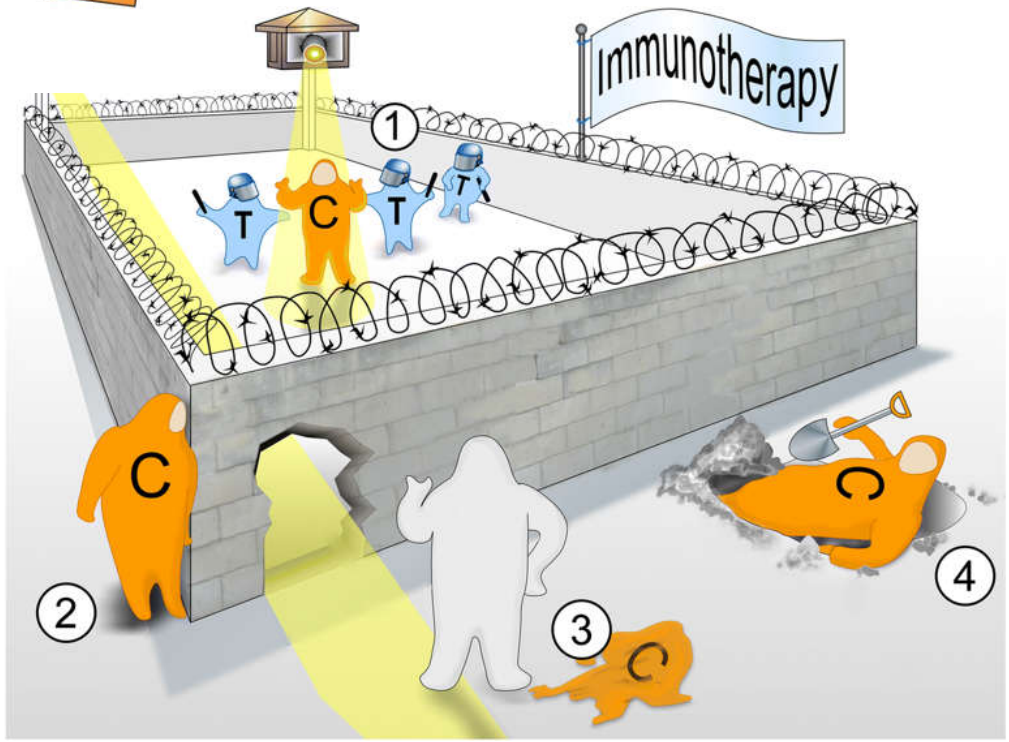
Hanahan D, Weinberg RA. Cell 2000;100:57-70

Hanahan D, Weinberg RA. Cell 2011;144:646-74

Pizzi M, et al. Leukemia 2016;30:1805-15

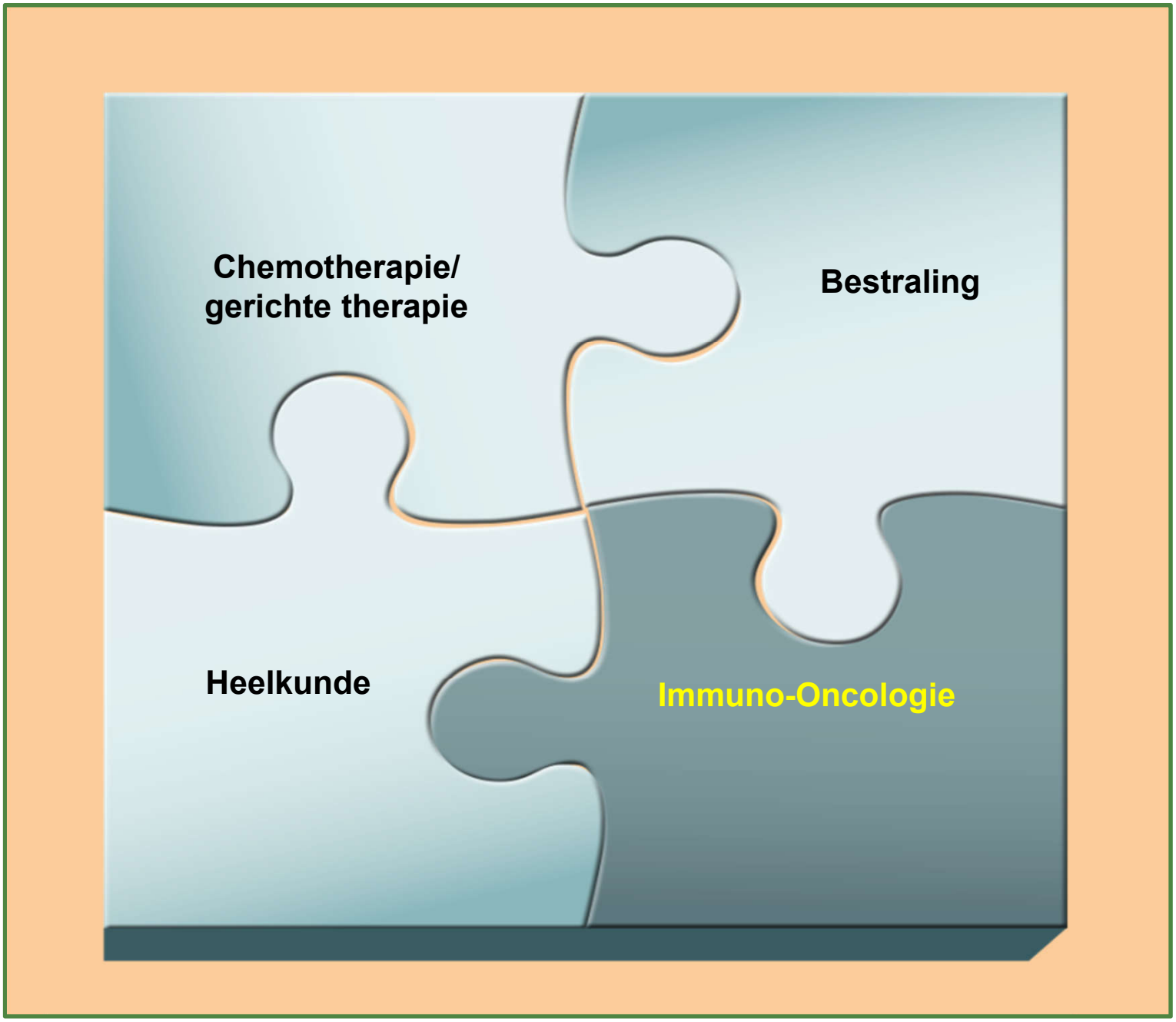
Immuuntherapie

Anti-tumor immunity		Intrtumoral immunosuppression	
CTLs	IFN-γ	TGF-β	Treg
Th1	THF-α	IL-10	Th2 cells
pTh17	IL-2	IDO	MDSCs
NK cells	GM-CSF	PGE2	TAMs (M2)
DCs	IL-12	CTLA-4	Some B cells
	Type I IFN	PD1/PD-L1	(e.g., Breg)
	Chemokines (e.g., CXCL9/10)	IL-4/IL-13	



Pitt JM, et al. Ann Oncol 2016;27:1482-92
Iorgulescu JB, et al. Genome Med 2018;10:87

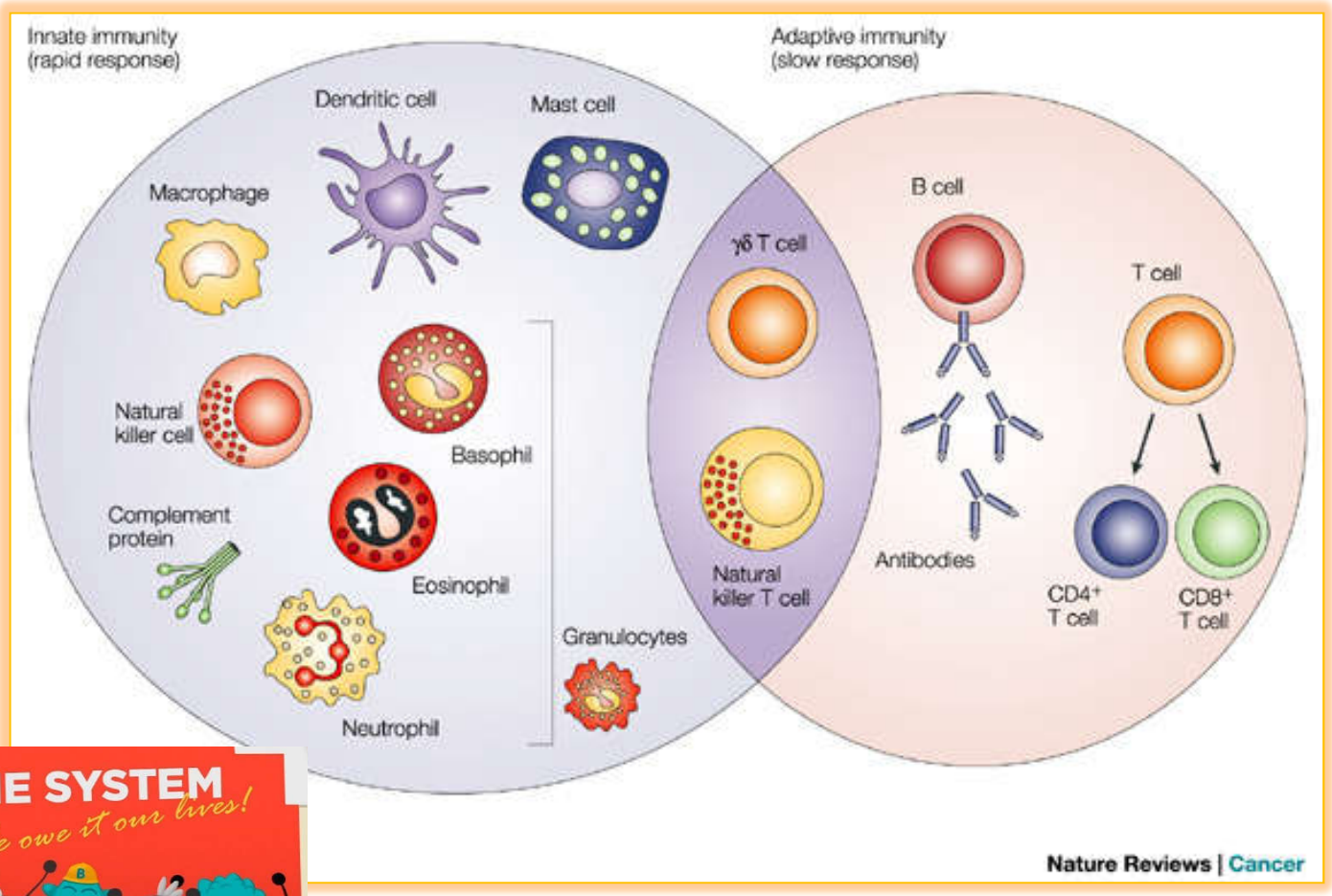
Behandeling kanker

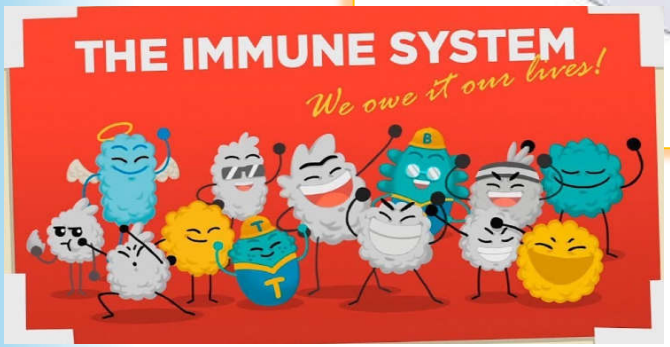


Het immuun systeem

Aspecifieke/natuurlijke/
aangeboren immuniteit

Specifieke/verworven/
adaptieve immuniteit



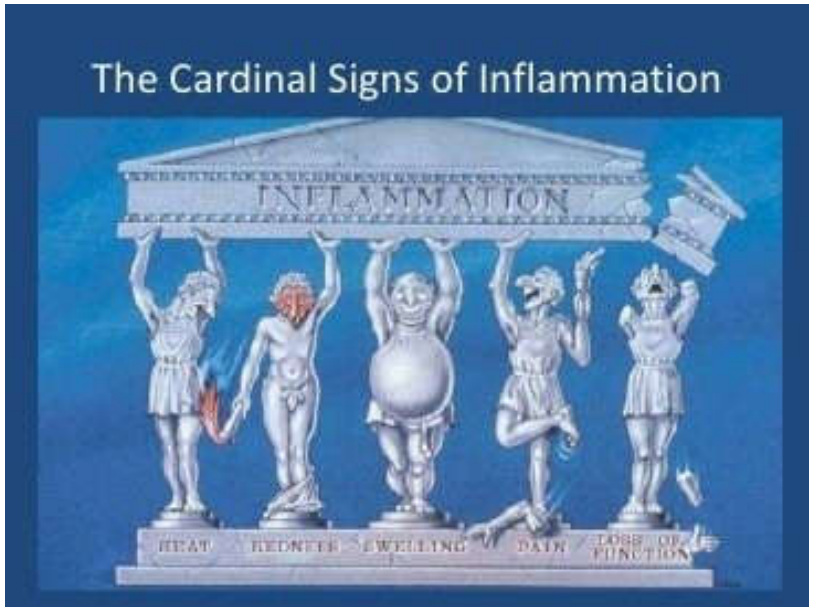


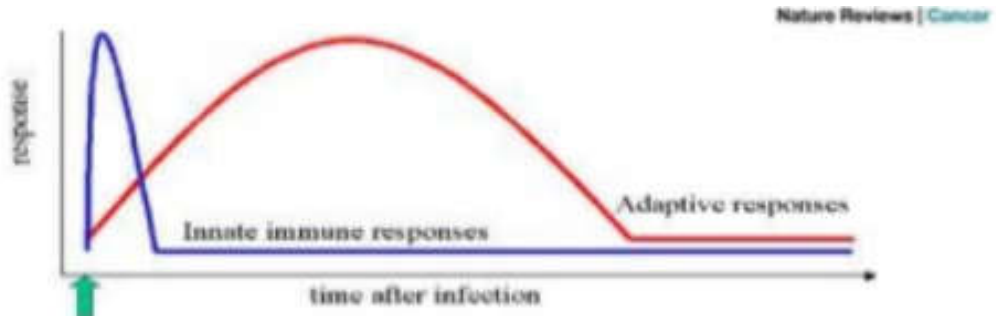
Dranoff G. Nat Rev Cancer 2004;4:11-22

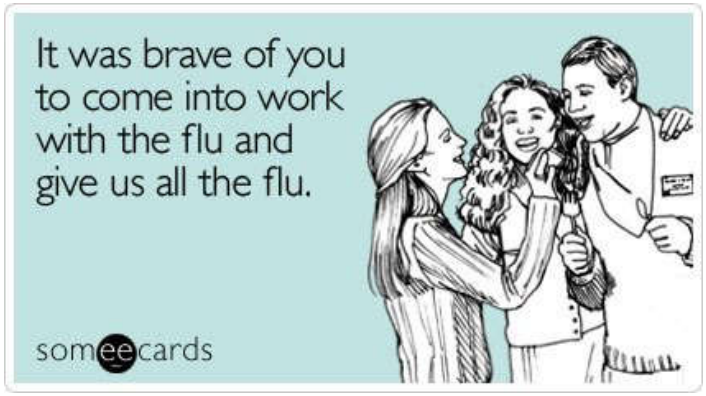
Het immuun systeem

Aspecifieke/natuurlijke/
aangeboren immuniteit

Specifieke/verworven/
adaptieve immuniteit







Het immuun systeem

verworven immuniteit

- Geheugen

- Humorale immuniteit:

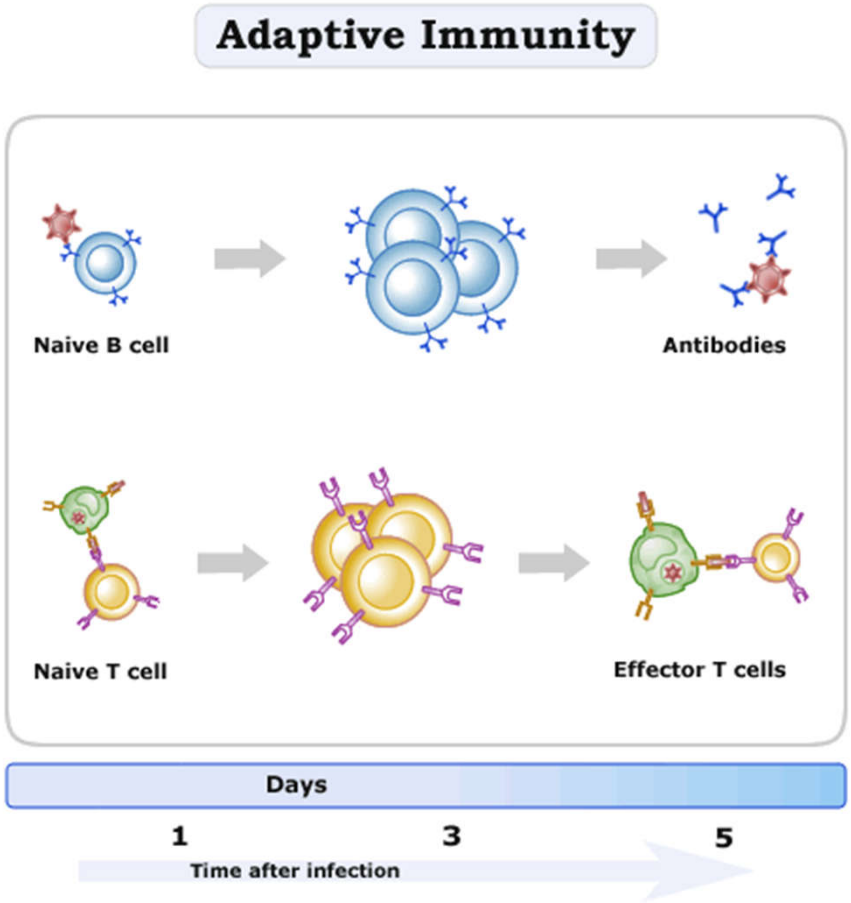
B-lymfocyten

Plasmacellen

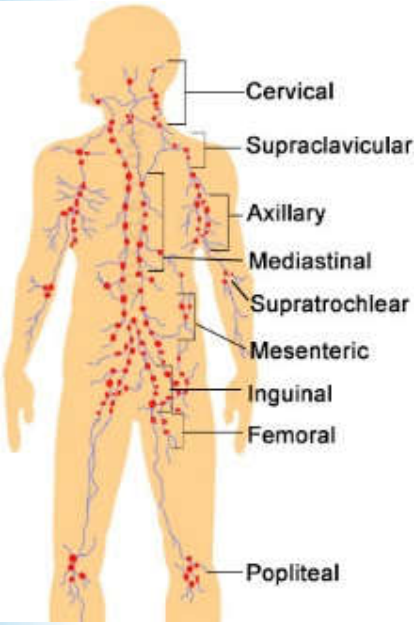
Antilichamen

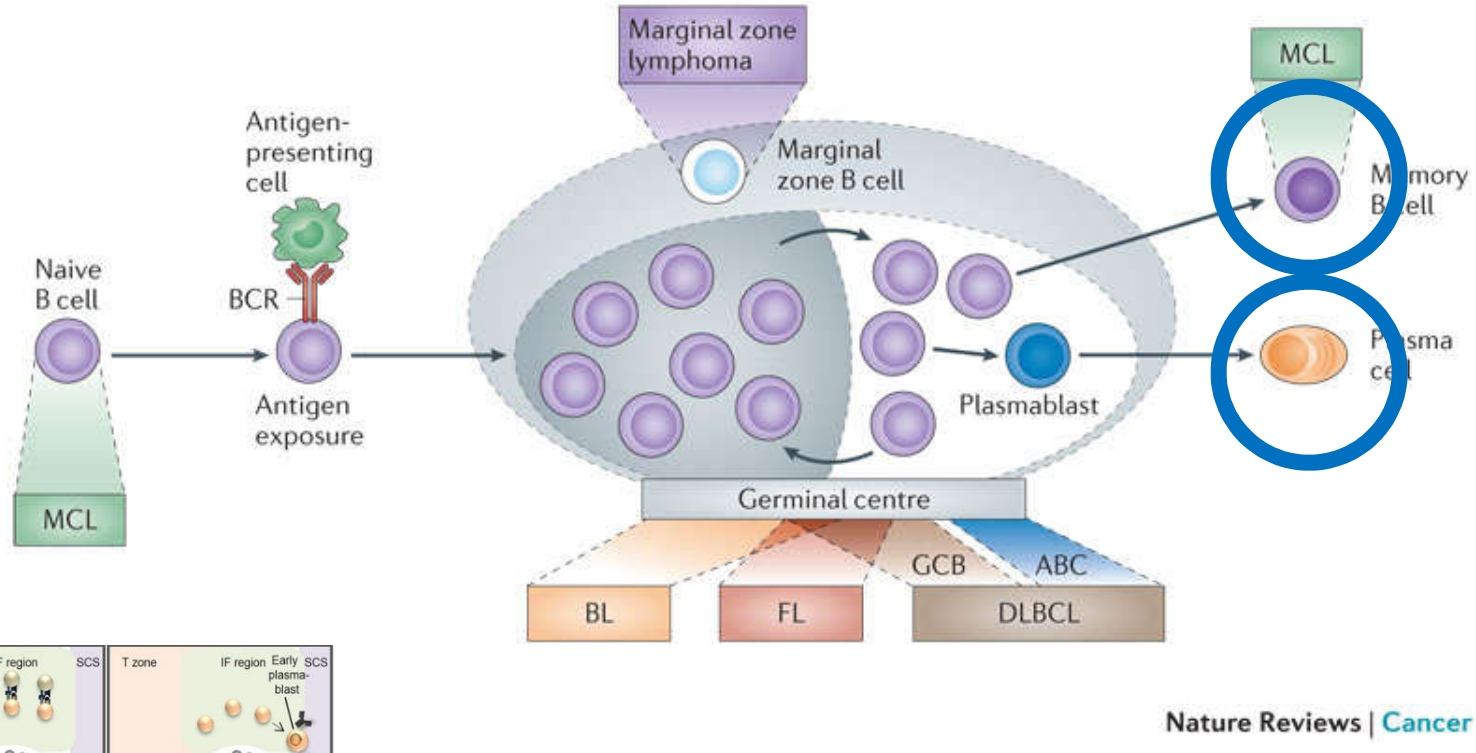
- Cellulaire immuniteit:

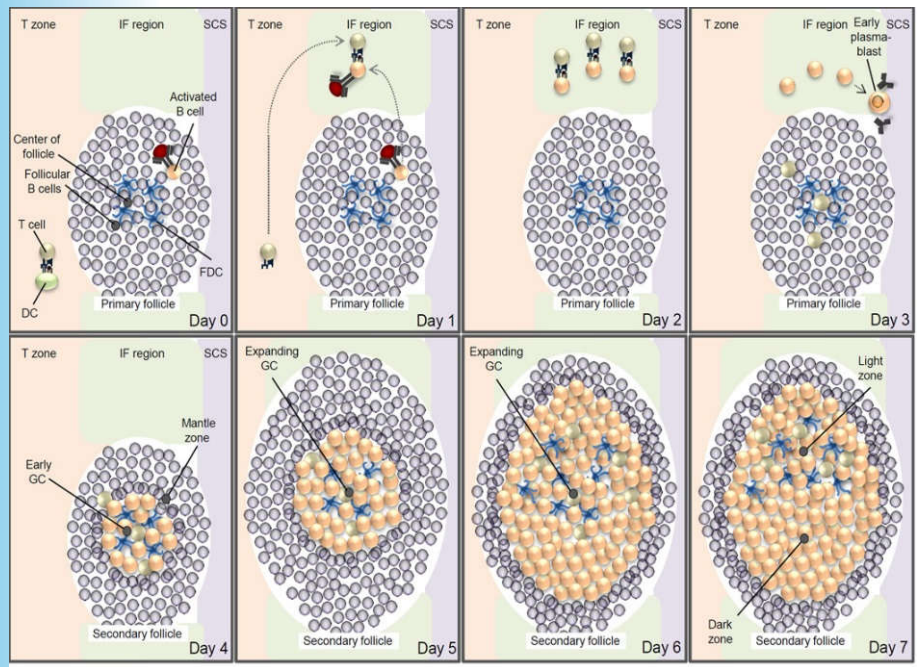
T-lymfocyten



B-lymfocyten







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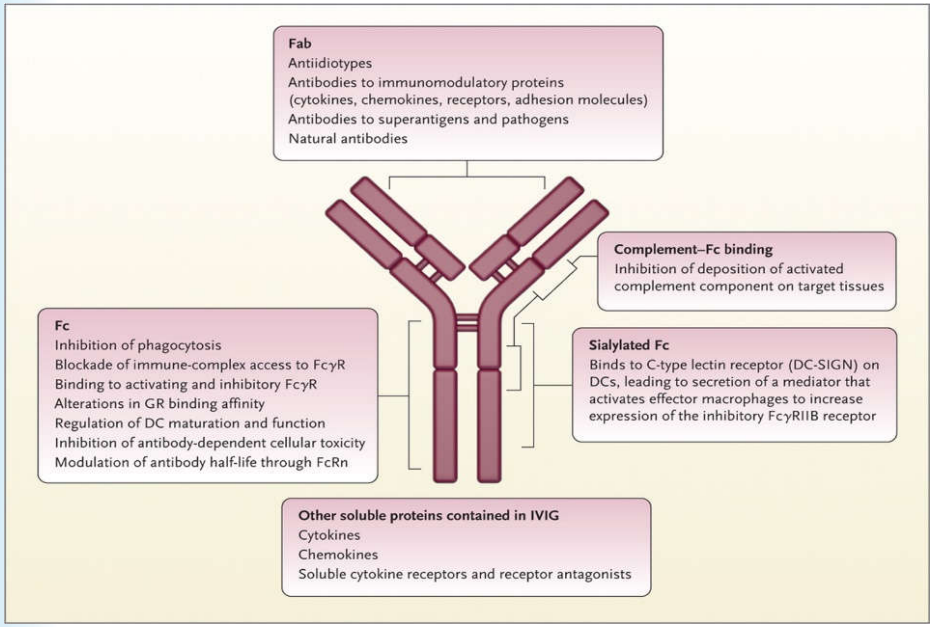
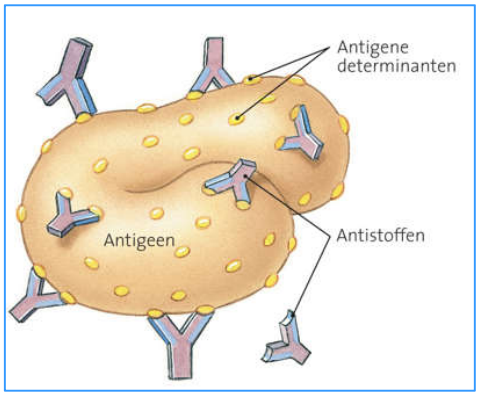
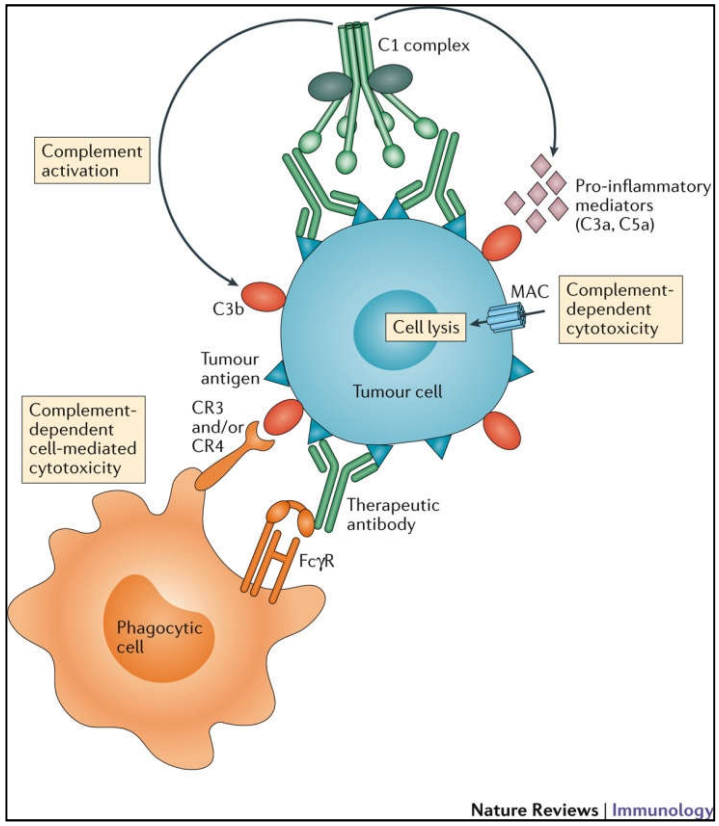
B-lymfocyten







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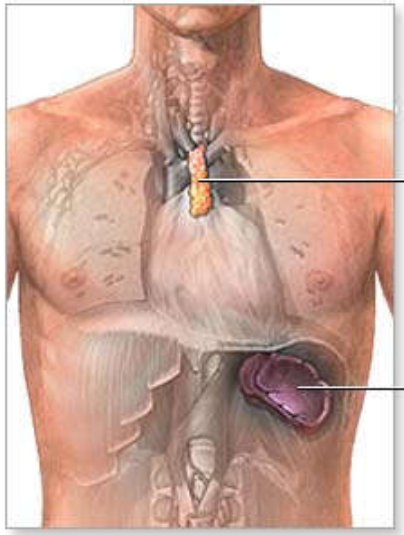
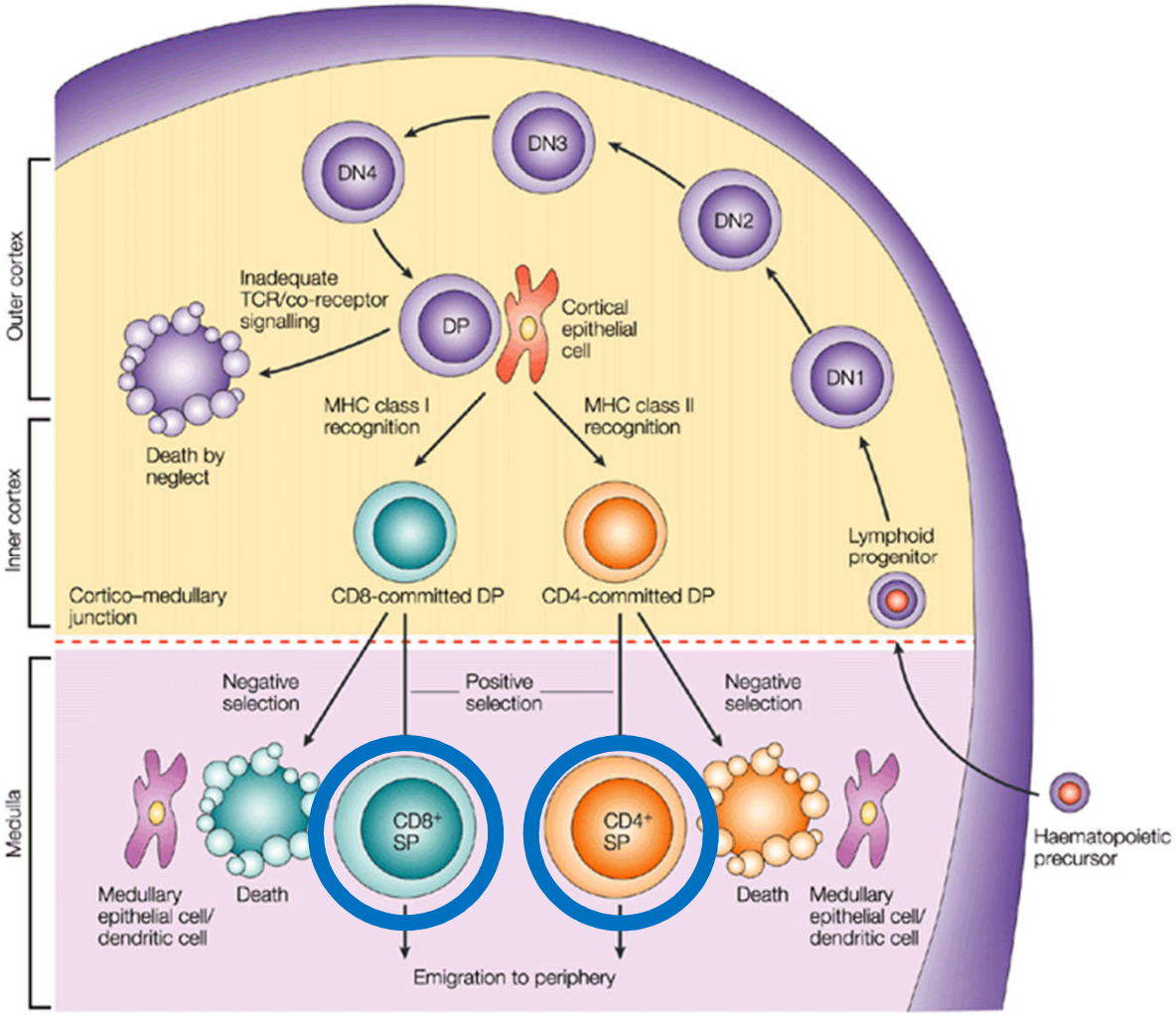
T-lymfocyten





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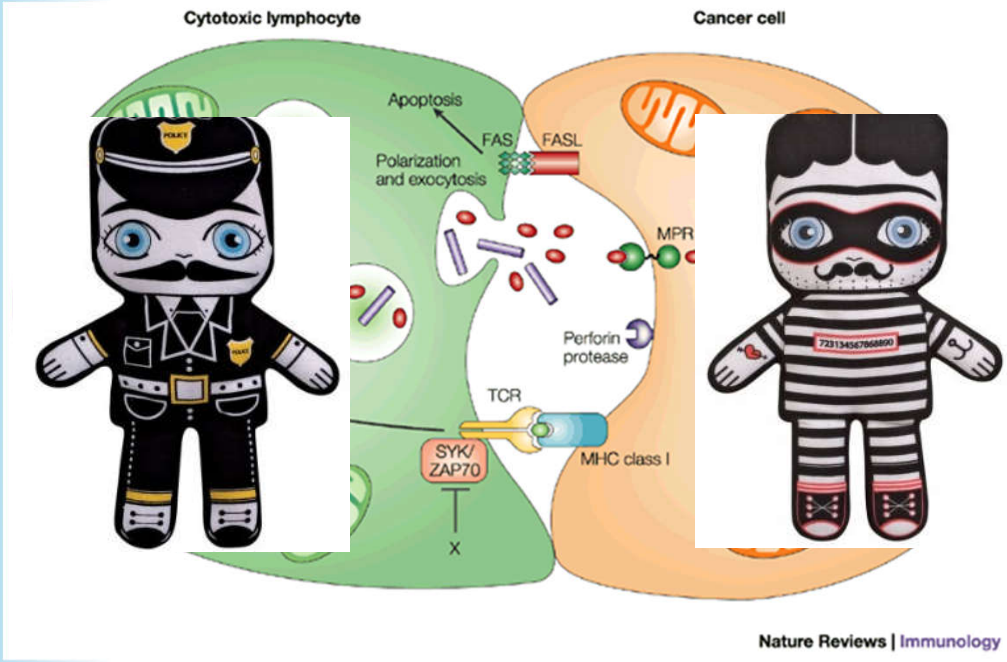
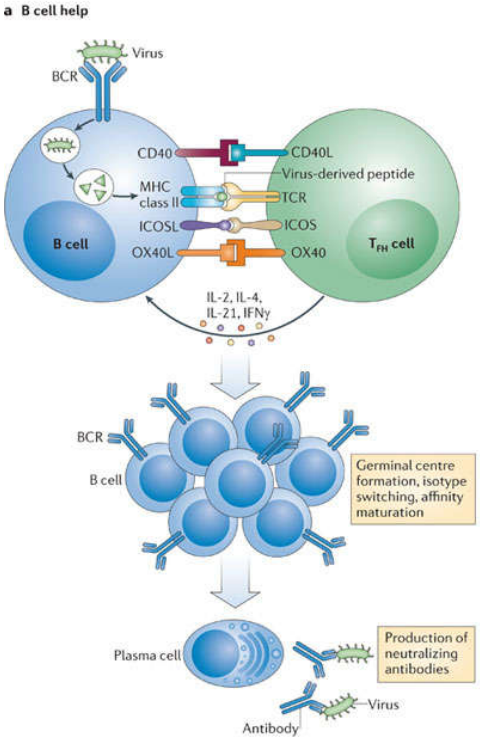
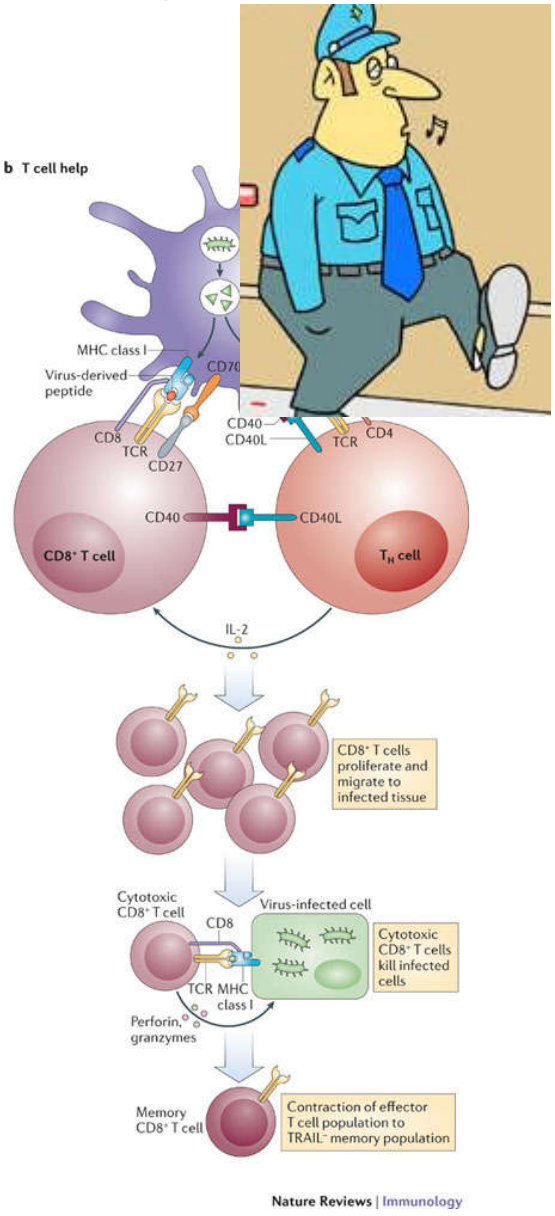
T-lymfocyten

CD8+ T_C

CD4+ T_H







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