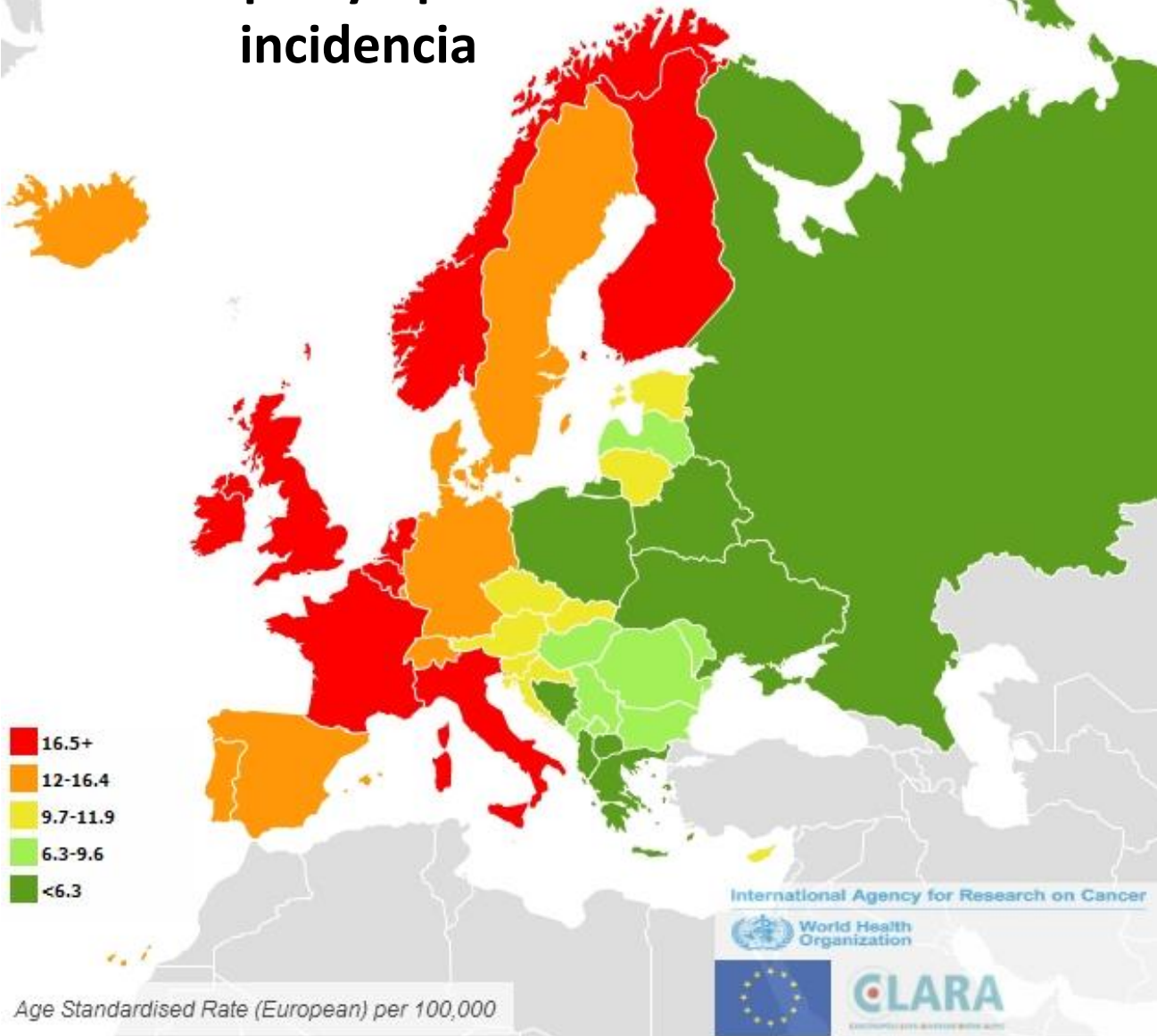


Újdonságok lymphomák diagnosztikájában, kezelésében

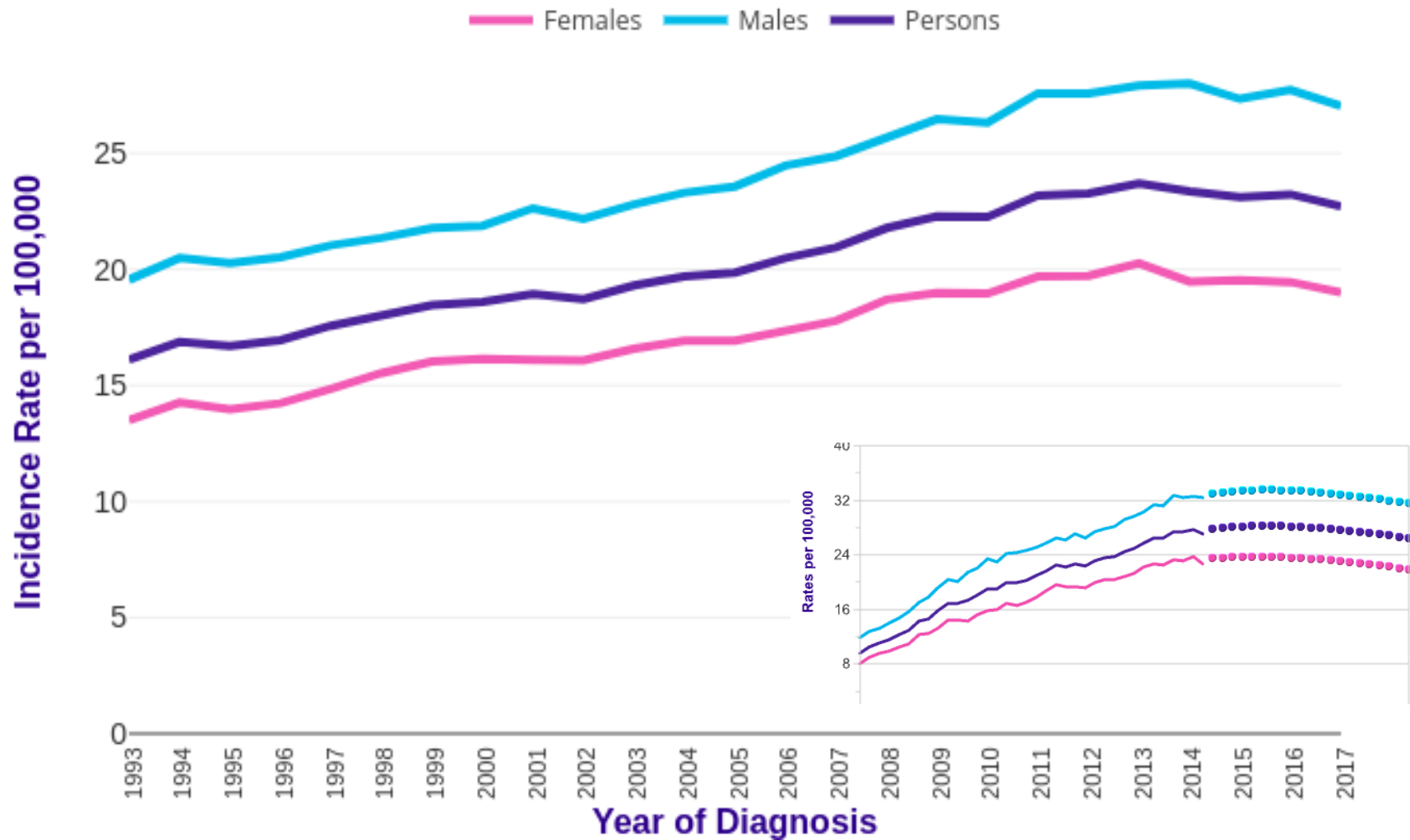
Dr. Szomor Árpád
PTE KK I. Belklinika

Belgyógyászati Szakvizsga Előkészítő Tanfolyam
Pécs, 2021.06.03.

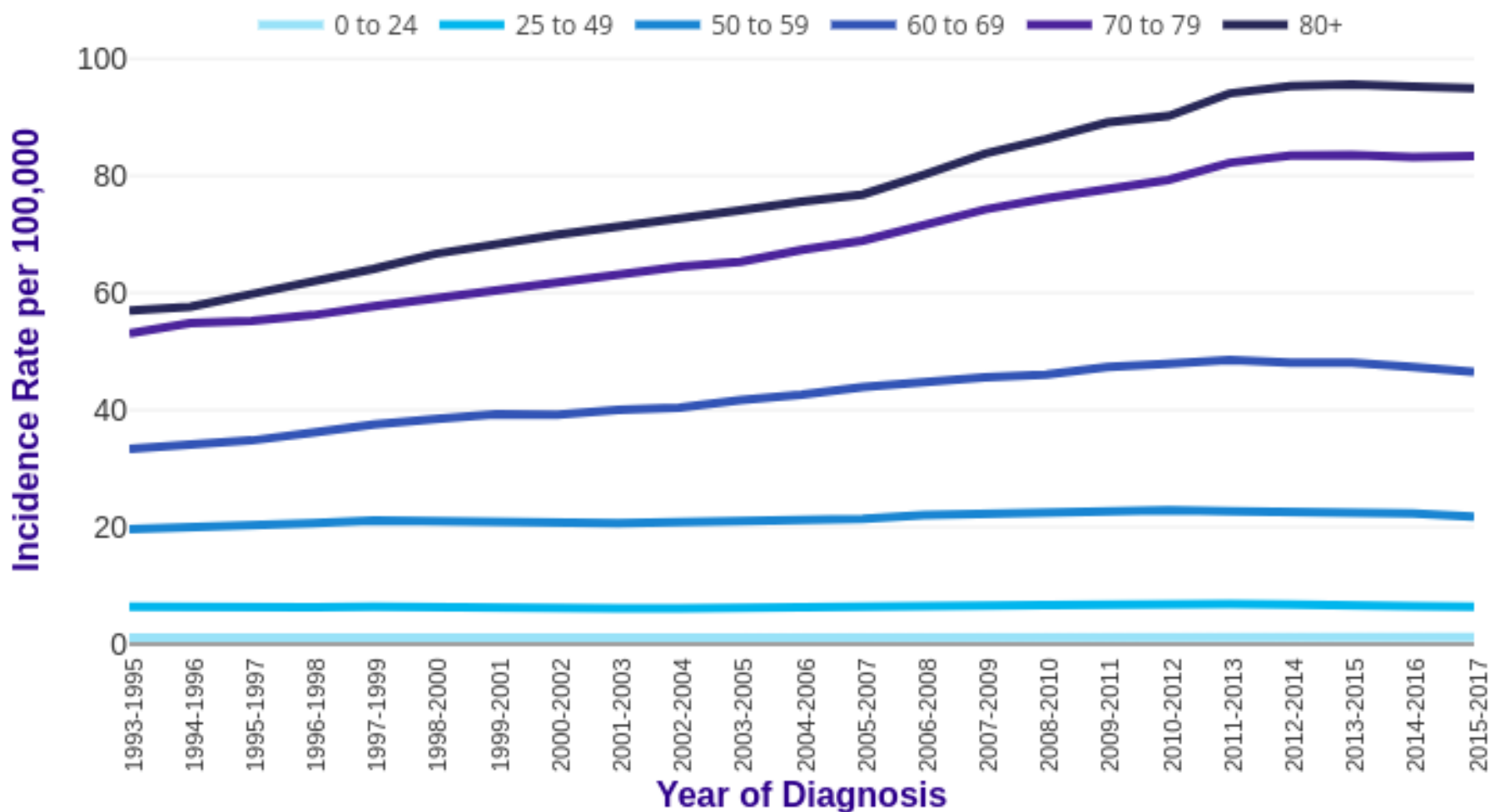
Európai lymphoma incidencia

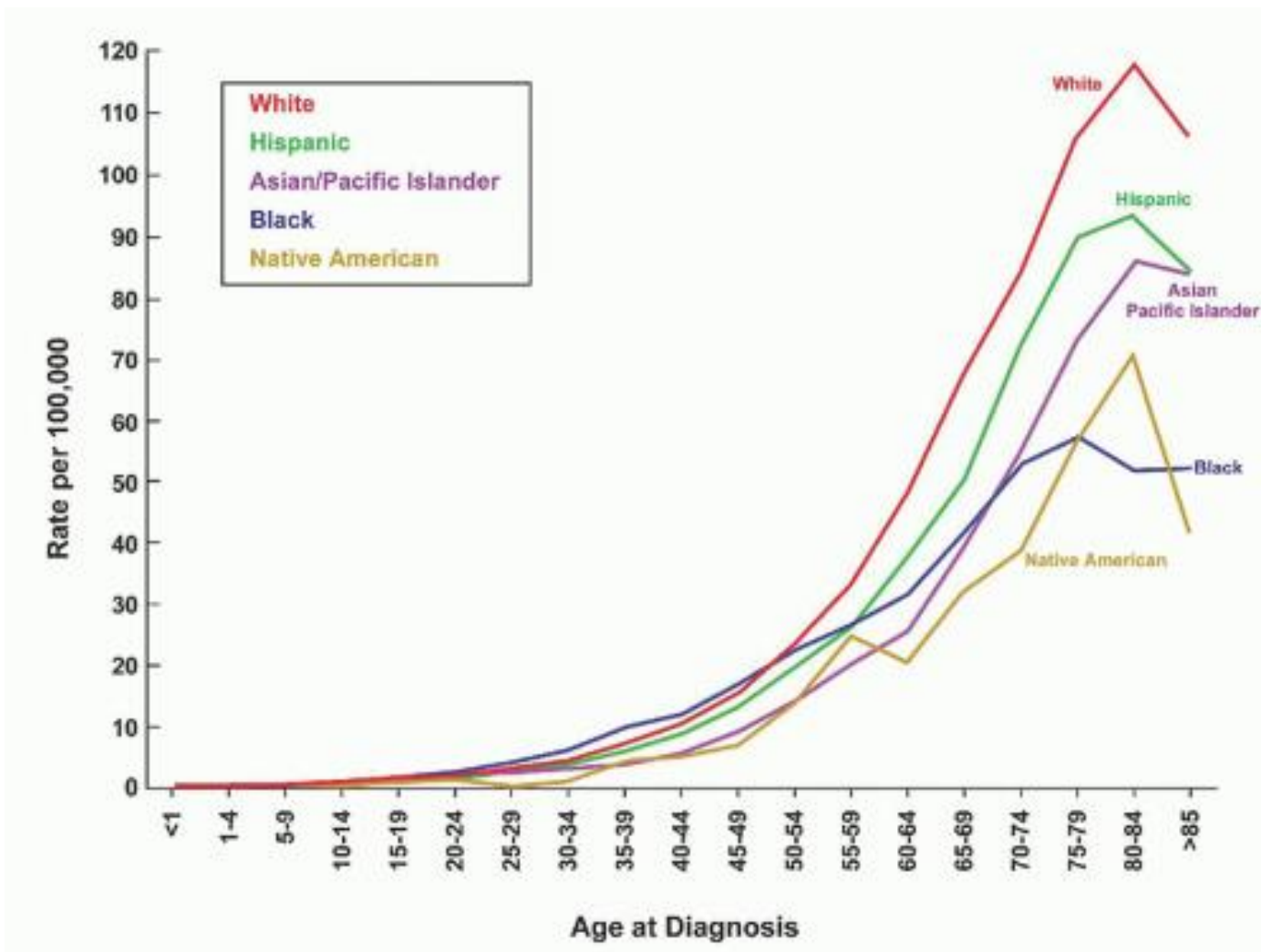


Non Hodgkin Lymphoma incidencia



NHL incidencia korcsoport szerint





Age-specific incidence rates of NHL according to race (SEER data, 1979 to 2009).

Lymphoma epidemiológia

Bármilyen életkorban előfordulhat

Incidencia, és a szubtypusok incidenciája változik földrajzi elhelyezkedéstől:

- Burkitt lymphoma trópusi Afrika

- IPSID (immunproliferative small intestine disease) Közel-Kelet

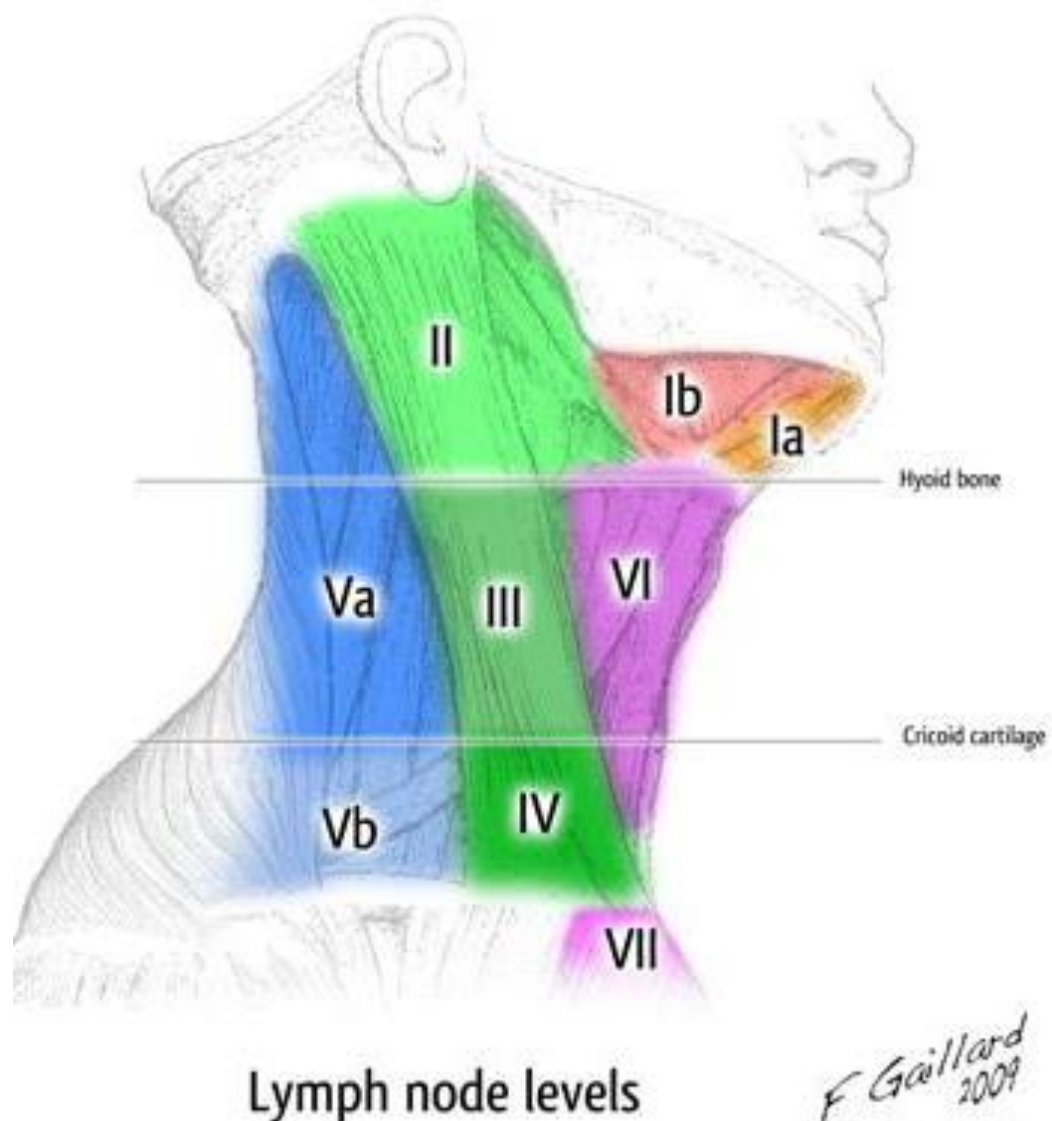
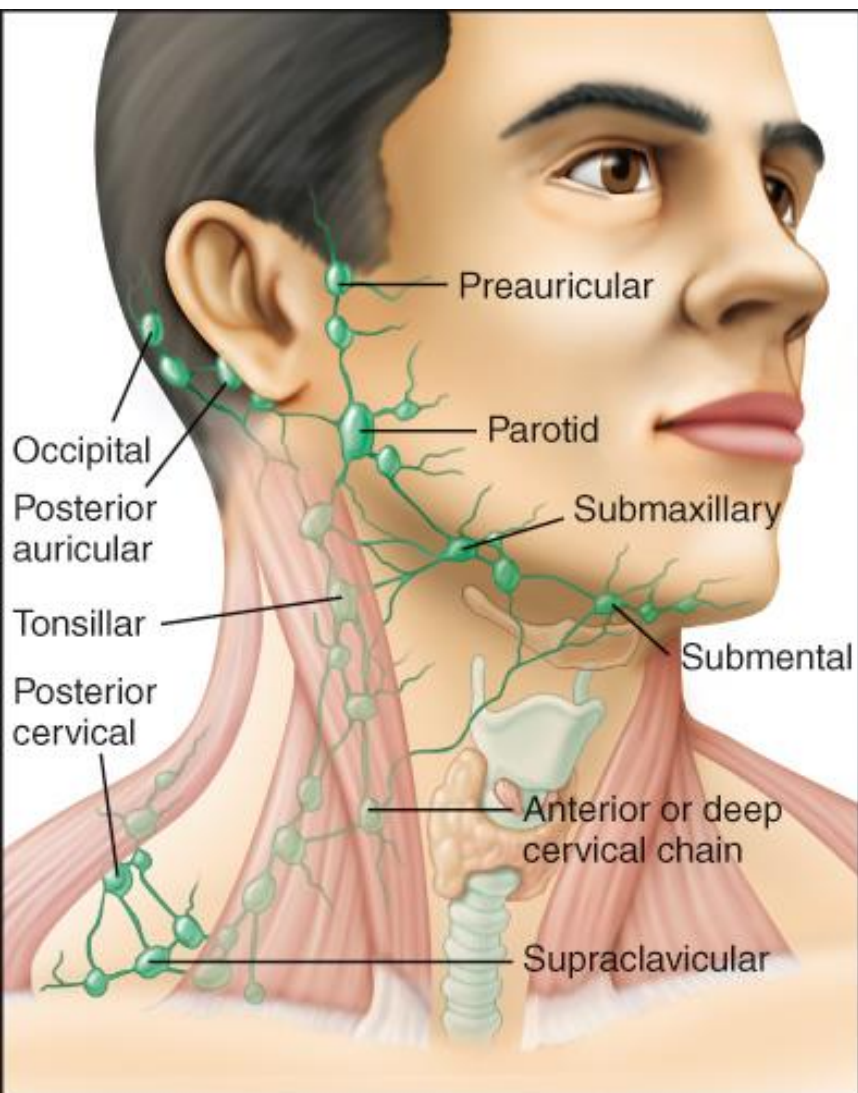
- Felnőtt T-sejtes leukémia-lymphoma Japán és Karibi térség

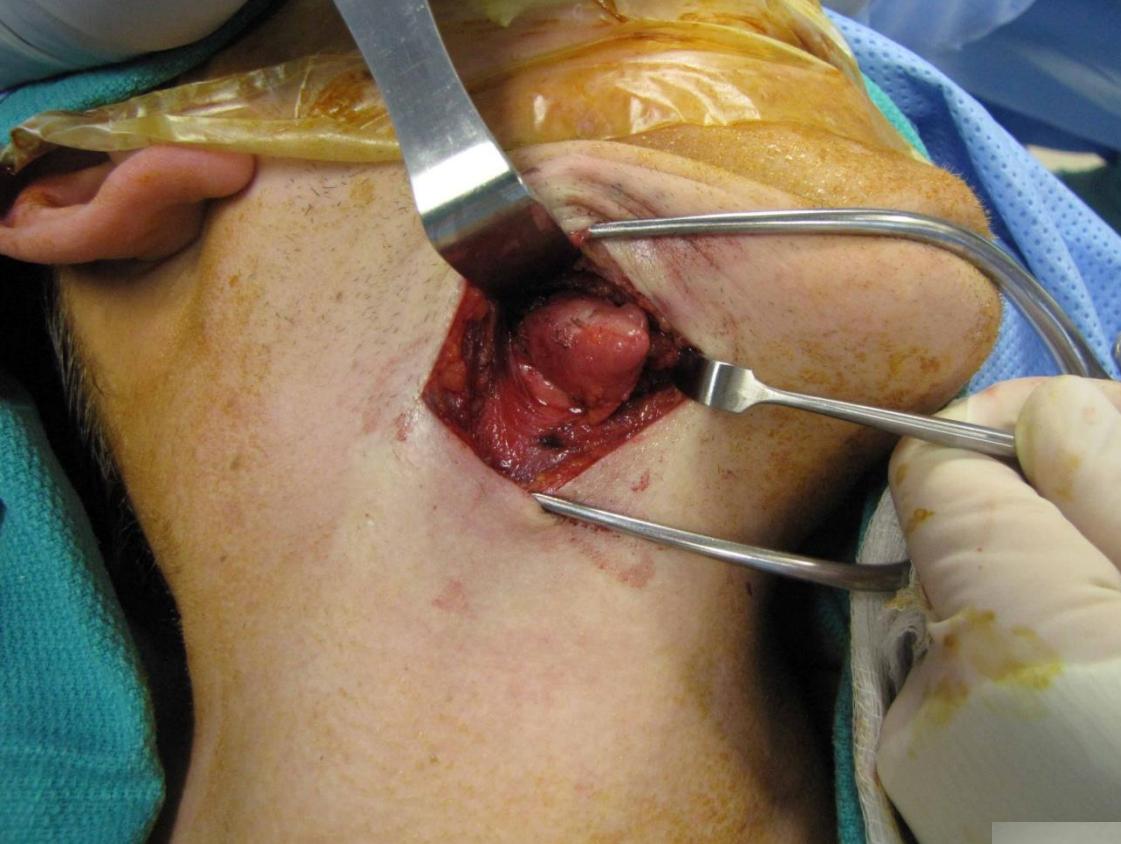
Indolens lymphomák fiatal korban ritkábbak, korral nő az incidencia.

Nagy-sejtes lymphoma (DLCL) kevésbé korfüggő, egyik leggyakoribb fiataalkori daganattípus.

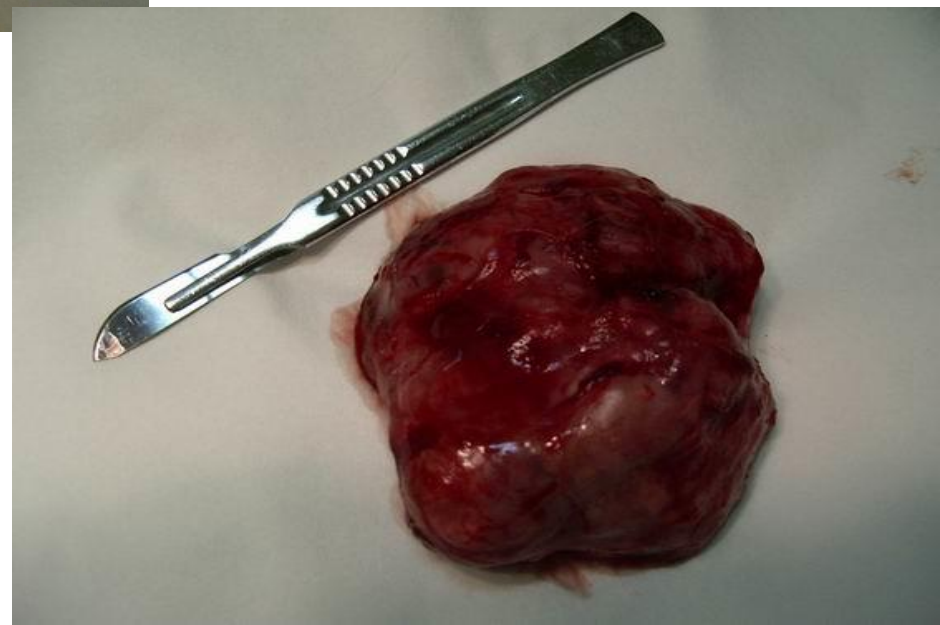
Burkitt és lymphoblastos lymphoma, ALK+ ALCL adolescens korban a leggyakoribb.

AIDS-es betegeknél agresszív, nagy malignitású lymphomák.





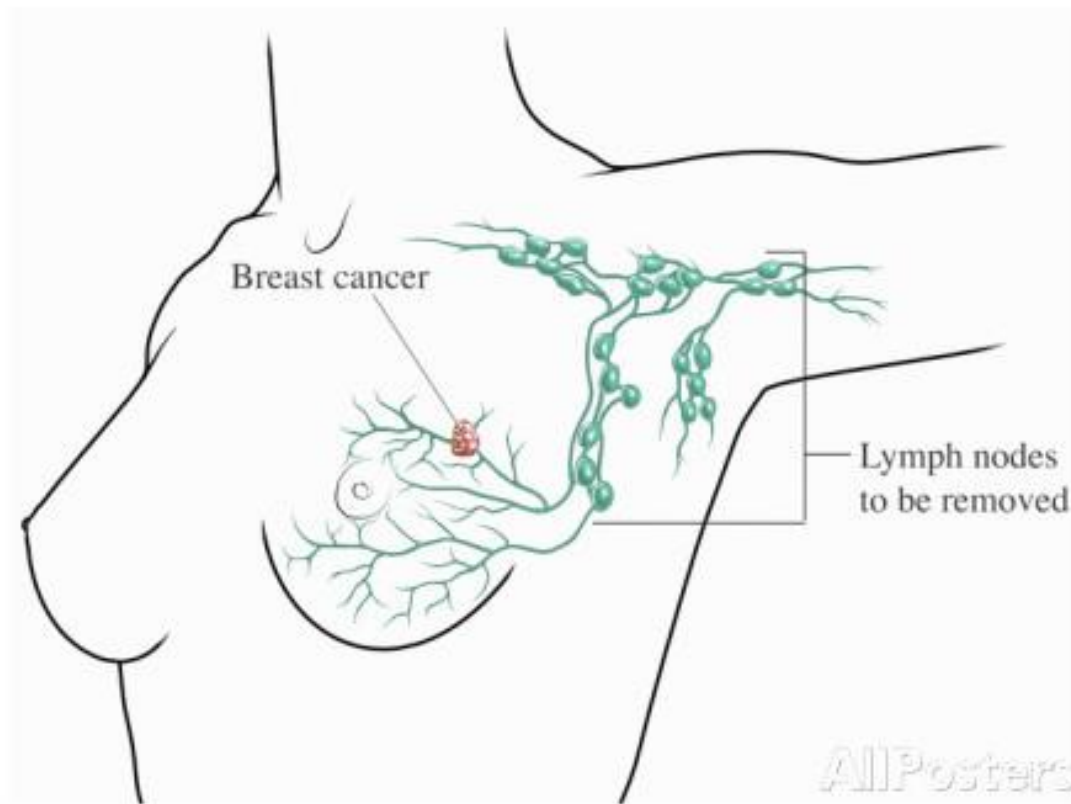
Nyirokcsomó excízió

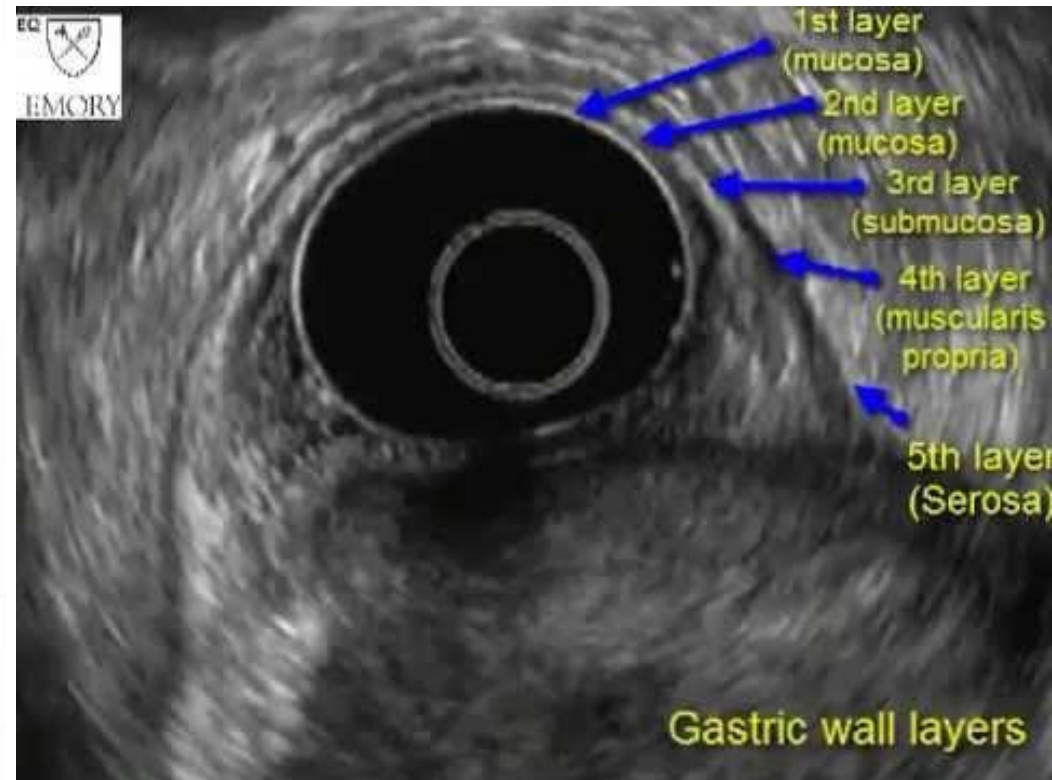
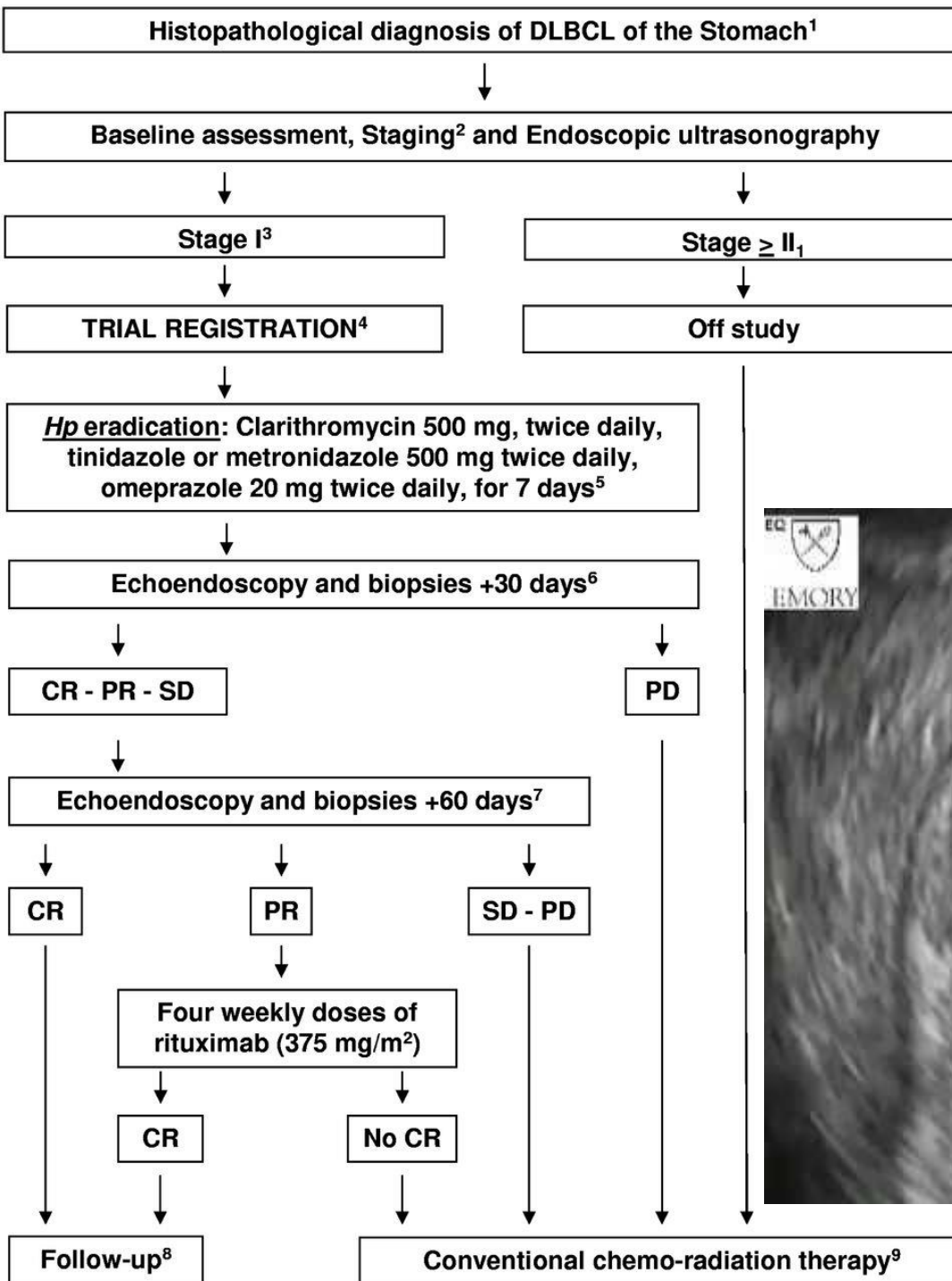


Virchow nyirokcsomó



Axillaris nyirokcsomó megnagyobbodás emlődaganat miatt





Kivizsgálás, staging

Vérkép, kémia, vizelet analízis
Nyak, mellkas, has és medence CT

PETCT

Csontvelőbiopszia és aspiráció
(Lumbálpunkció)

AIDS lymphoma

T-sejtes lymphoblastos lymphoma

Nagy malignitású lymphoma csv. érintettséggel

Burkitt lymphoma

Staging laparotomia és lymphangiográfia már
nem indikált non-Hodgkin lymphomában.

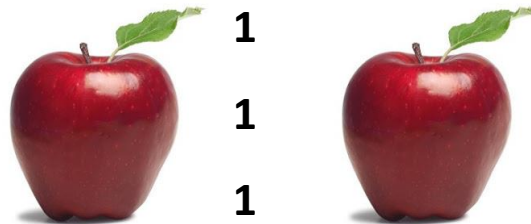
Ann Arbor stádium beosztás

- I. 1 nyics régió
- II. >1 nyics régió a rekesz ugyanazon oldalán
- III. A rekesz mindkét oldalán nyics.
- IV. Extranodális szervi érintettség primer “E”-n kívül

Alstádiumok: A, B, E, S, X

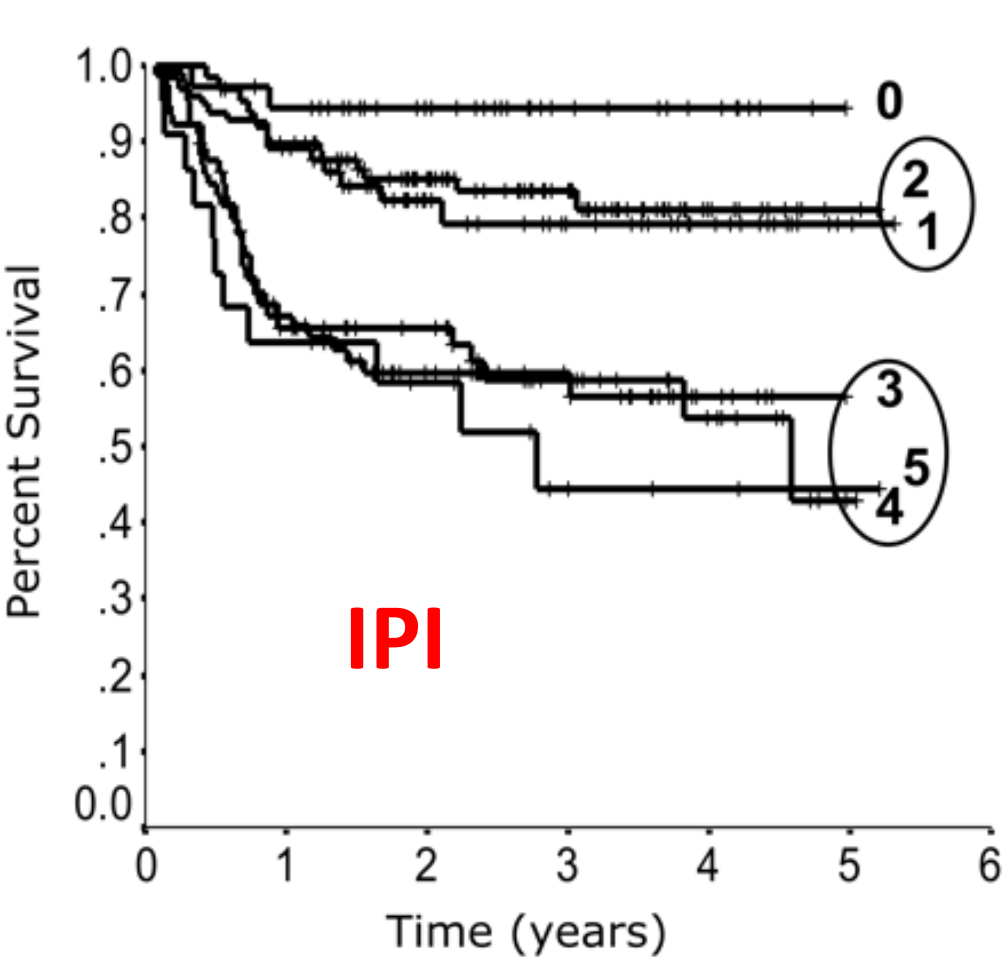
Nemzetközi prognosztikai index (IPI)

<u>Minden betegre</u>				
A	Kor: > 60 év	1	0-1:	kis rizikó
P	Performance st. > 2	1	2:	kis-közepes rizikó
L	LDH: > normál	1	3:	nagy-közepes rizikó
E	Extranodális >1	1	4-5:	nagy rizikó
S	Stádium: III-IV	1		

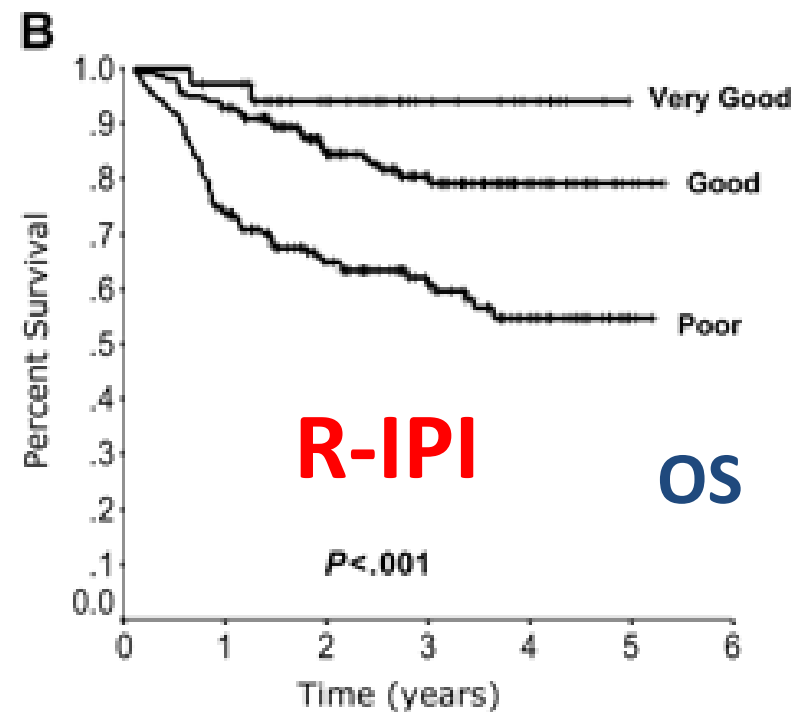
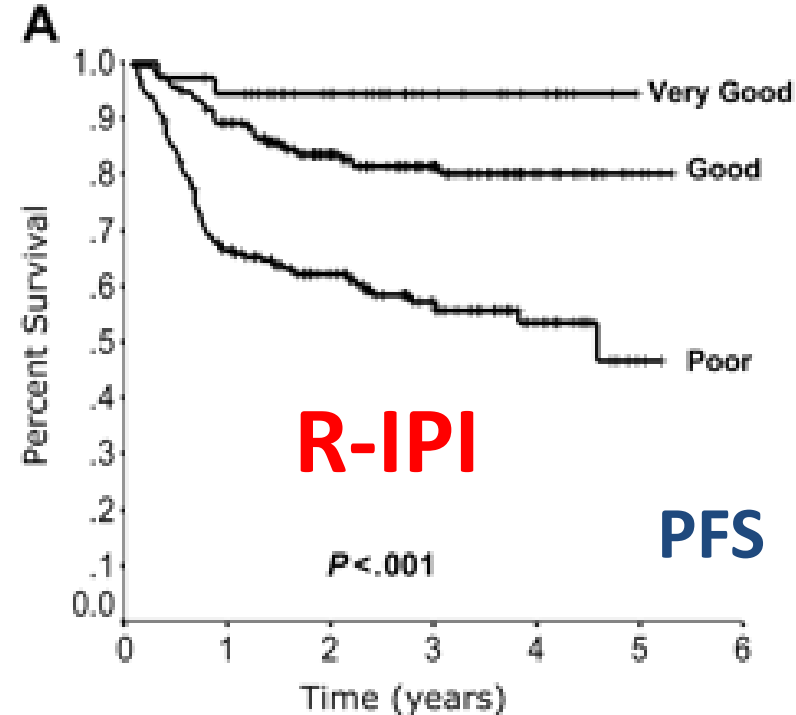


Age-adjusted international prognostic index (aaIPI) < 60 év

Stádium: III-IV	1	0: kis rizikó
Performance st. > 2	1	1: kis-közepes rizikó
LDH: > normál	1	2: nagy-közepes rizikó
		3: nagy rizikó



Sehn Lh. Blood 2007 109:1857-1861



NCCN-IPI

Clinical factors prognostic of overall survival from multivariate selection in the NCCN cohort

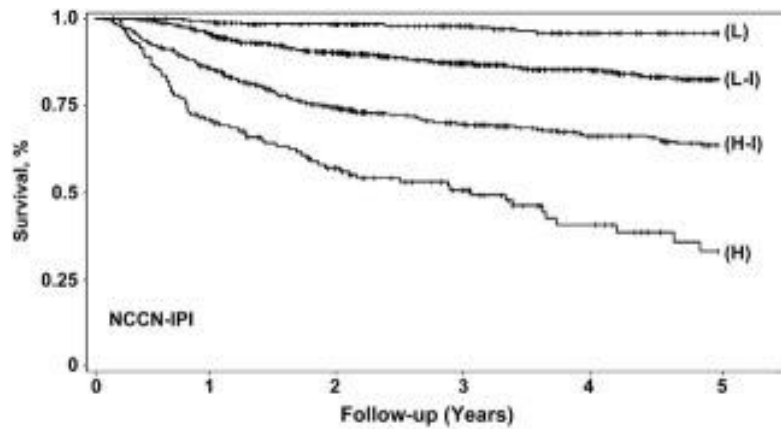
NCCN (n = 1650)	HR	95% CI	P value	Score
Age				
≤40 y	1.0			0
41-60 y	2.4	(1.4-4.2)	.0002	1
61-75 y)	3.2	(2.0-5.3)	<.0001	2
>75 y	6.1	(3.5-10.6)	<.0001	3
LDH-R ≤1	1.0			0
LDH-R (>1-3)	2.1	(1.6-2.7)	<.0001	1
LDH-R >3	3.3	(2.3-4.8)	<.0001	2
ECOG PS ≥2	1.9	(1.5-2.4)	<.0001	1
Ann Arbor stage, III-IV	1.5	(1.1-2.0)	.0062	1
Extranodal disease*	1.5	(1.2-1.9)	.0008	1

Zhou Z. Blood 2014;123:837-842.

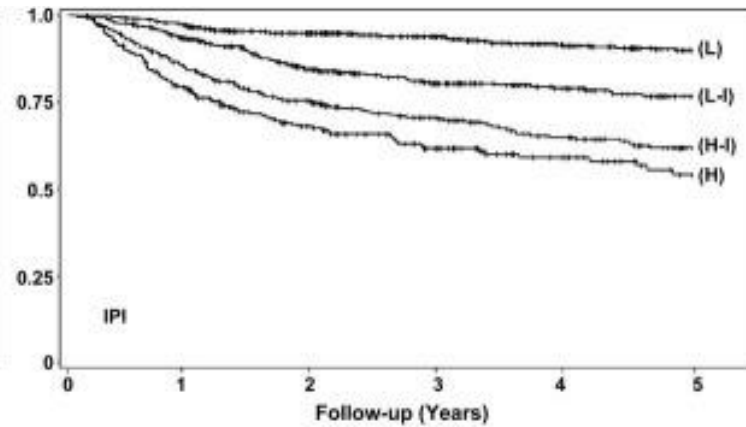
HR, hazard ratio; LDH-R, LDH ratio.

*Lymphomatous involvement in bone marrow, CNS, liver/GI tract, or lung.

NCCN-IPI

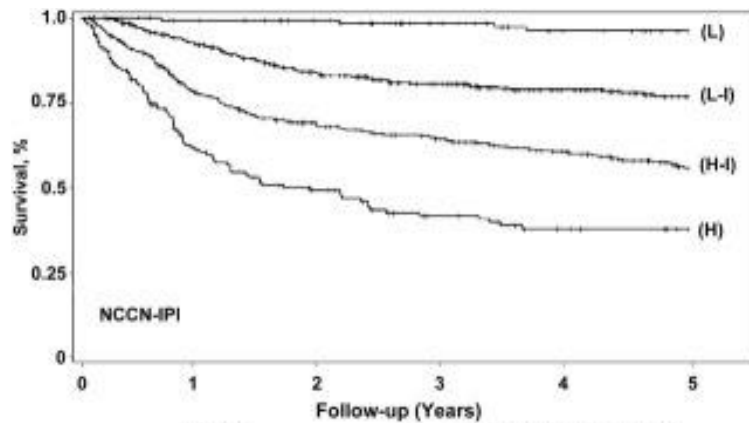


Low (L) High-Intermediate (H-I)
Low-Intermediate (L-I) High (H)

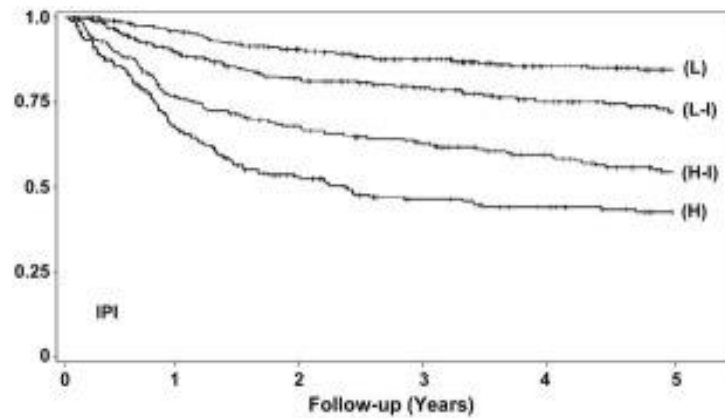


Low (L) High-Intermediate (H-I)
Low-Intermediate (L-I) High (H)

NCCN
1650
beteg



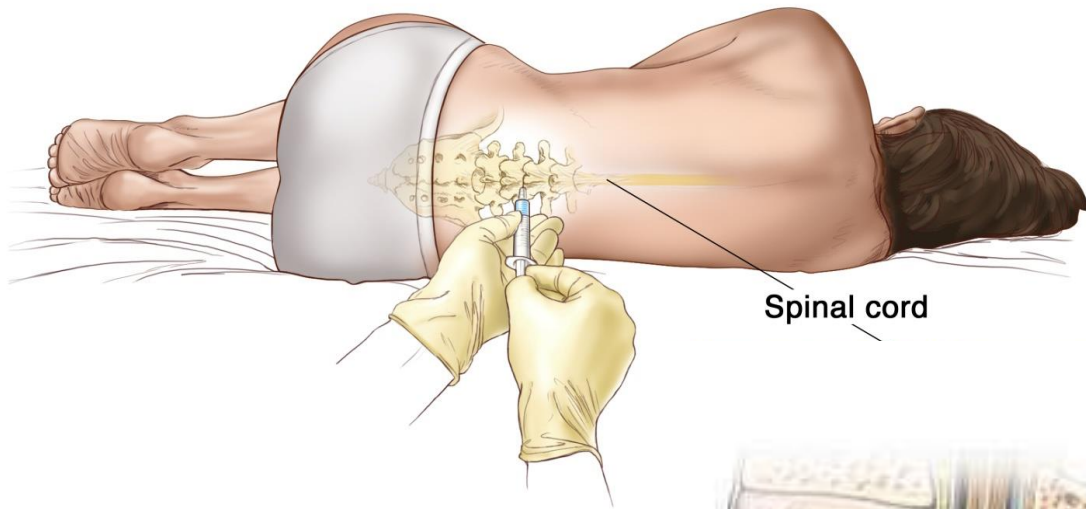
Low (L) High-Intermediate (H-I)
Low-Intermediate (L-I) High (H)



Low (L) High-Intermediate (H-I)
Low-Intermediate (L-I) High (H)

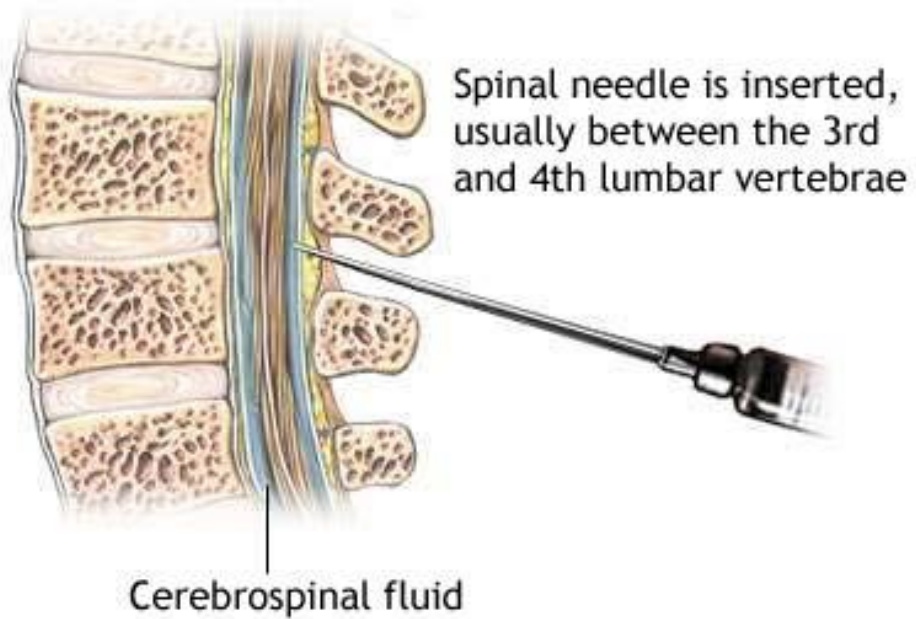
BCCA
1138
beteg

Agyvíz vétele



Cerebrospinal fluid

Spinal needle

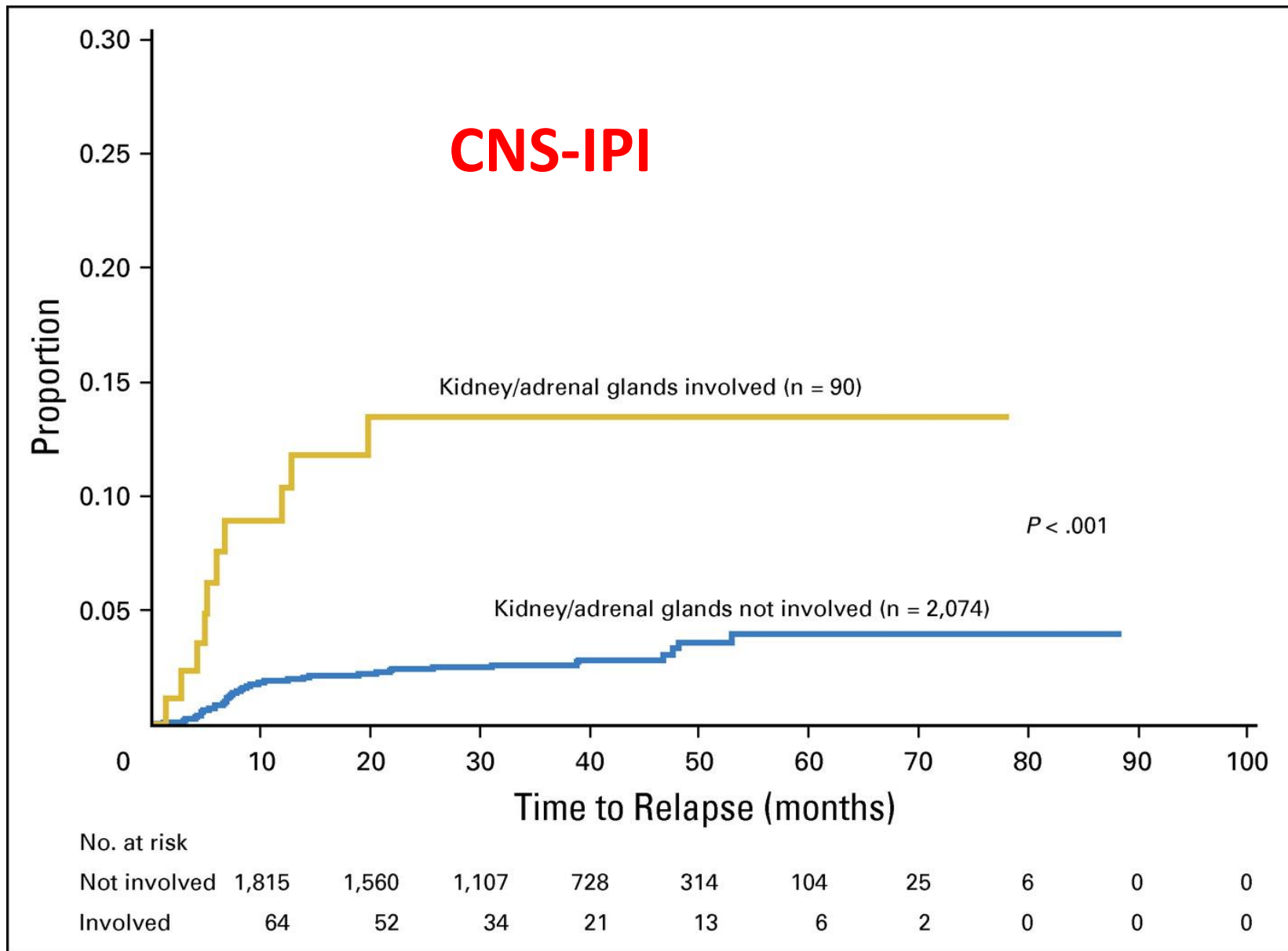


CNS-IPI

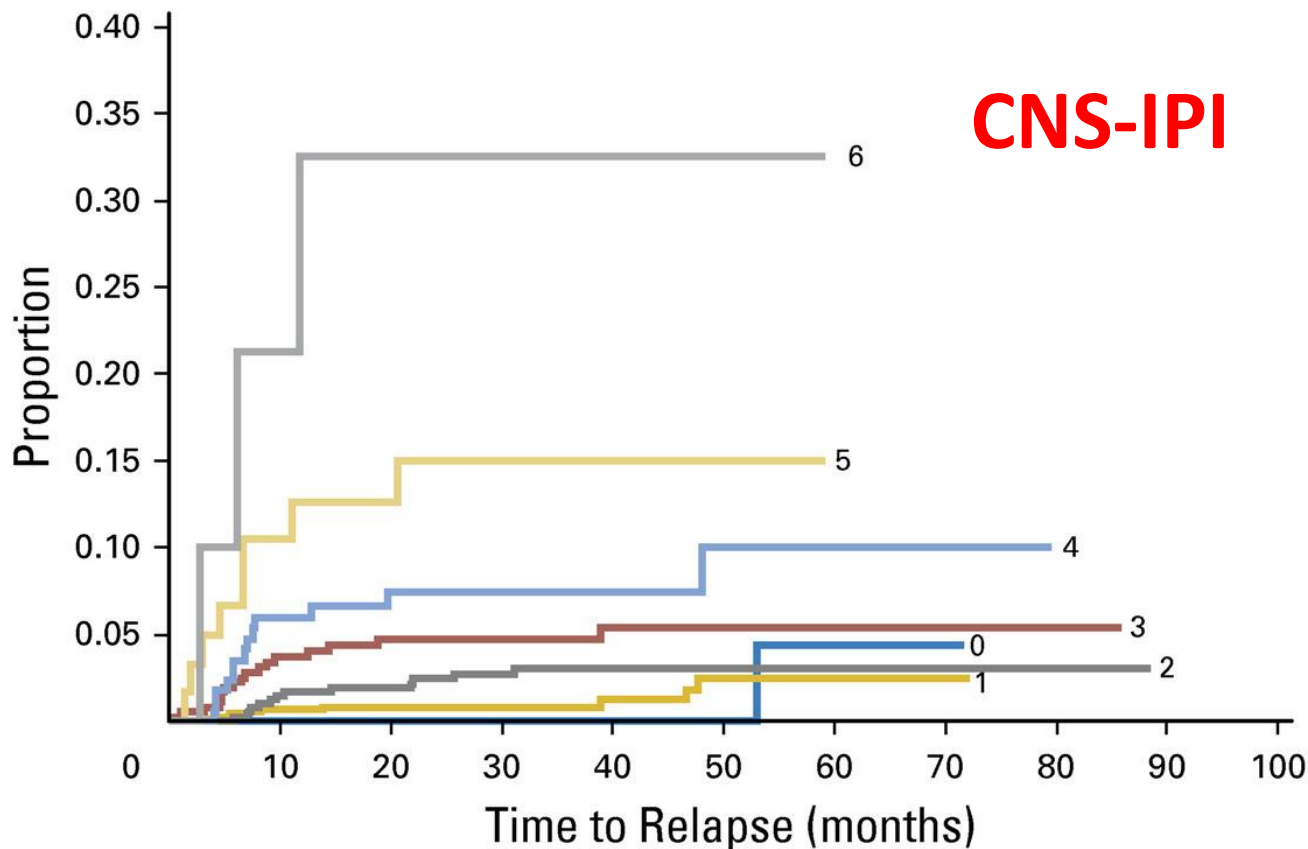
Table 2. Factors Defining the CNS International Prognostic Index: Results of Multivariable Analysis

Factor	Hazard Ratio	95% CI	<i>P</i>
Kidney and/or adrenal glands involved	2.8	1.3 to 5.8	.006
Age > 60 years	2.5	1.3 to 4.5	.001
LDH > normal	2.4	1.3 to 4.5	.005
ECOG PS > 1	2.2	1.3 to 3.9	.006
Stage III/IV disease	2.0	1.0 to 3.8	.039
Extranodal involvement > 1	1.0	0.5 to 1.8	.935

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.



Schmitz N. JCO. 2016;34: 3150-3156.



No. of factors	Singular year: 2-year rate
0 (n = 235)	0.0%
1 (n = 767)	0.8%
2 (n = 516)	2.4%
3 (n = 380)	4.7%
4 (n = 188)	7.4%
5 (n = 62)	15.0%
6 (n = 13)	32.5%

No. at risk

0	217	196	140	91	37	12	1	0	0	0
1	687	601	422	267	110	32	4	0	0	0
2	458	388	273	183	85	31	12	4	0	0
3	316	259	185	126	56	21	7	2	0	0
4	146	122	92	66	31	14	3	0	0	0
5	45	37	25	13	6	0	0	0	0	0
6	7	6	4	3	2	0	0	0	0	0

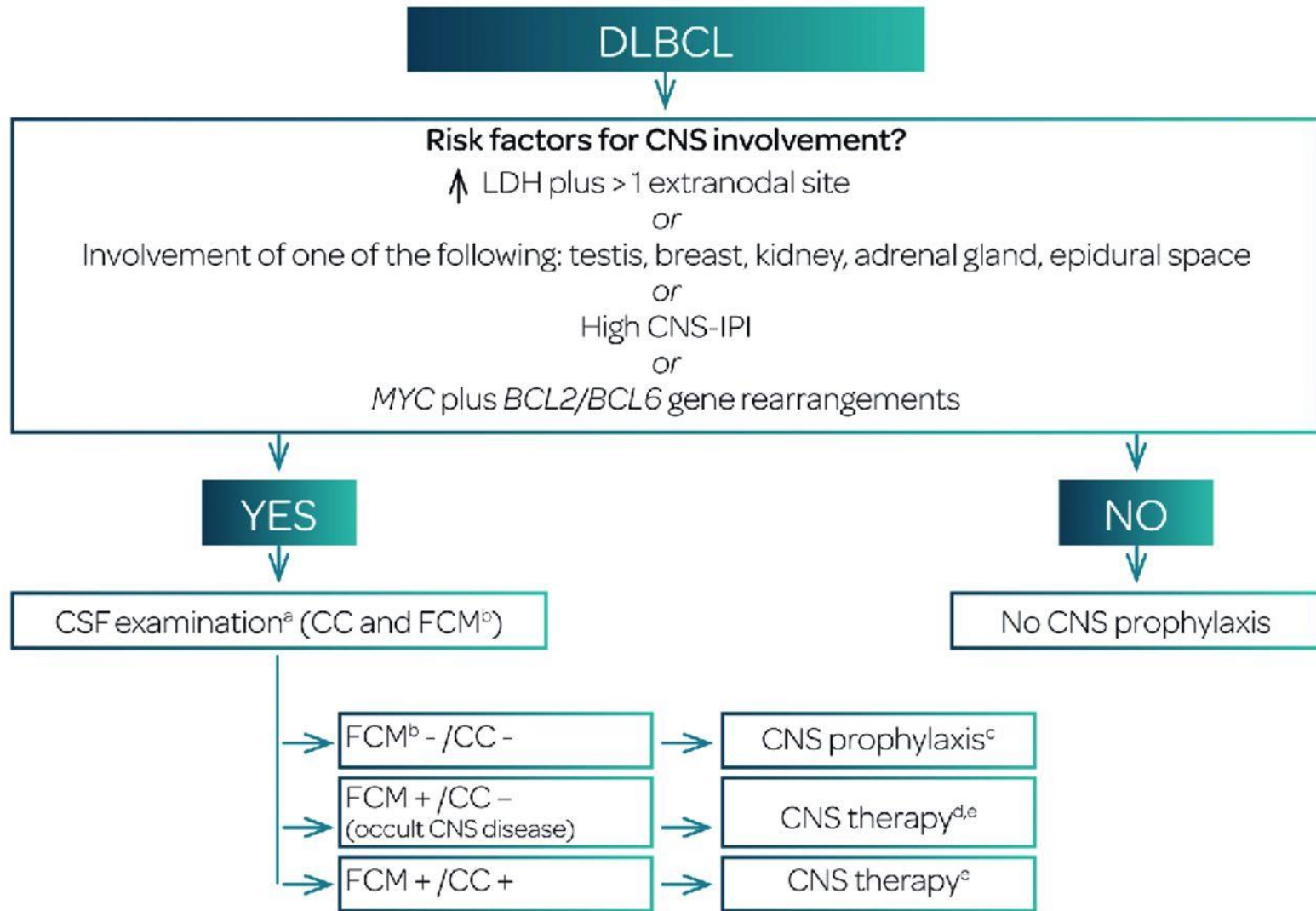
Kezelési lehetőség CNS lymphomában

Kemoterápia: nagy dózisú methotrexate alapú - $\geq 3\text{g/m}^2$ véragygáton átjutni. Nagy dózisú cytosine arabinoside is. (procarbazin, carmustin)

Intrathecalis kezelés, prophylaxis: methotrexate, cytosin arabinosid, steroid (hydrocortison vagy dexamethason), liposomal cytosin arabinosid

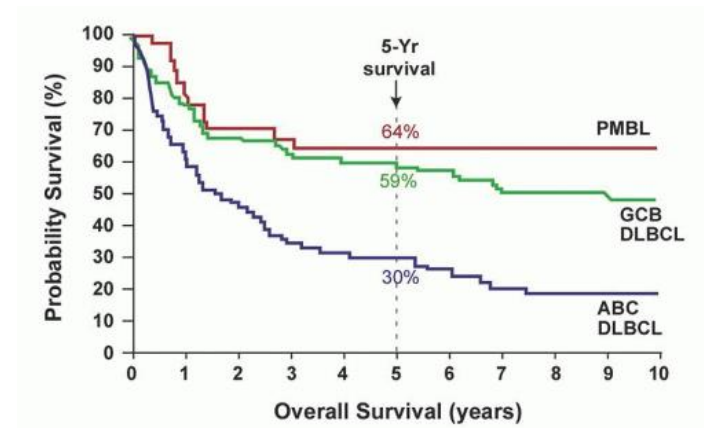
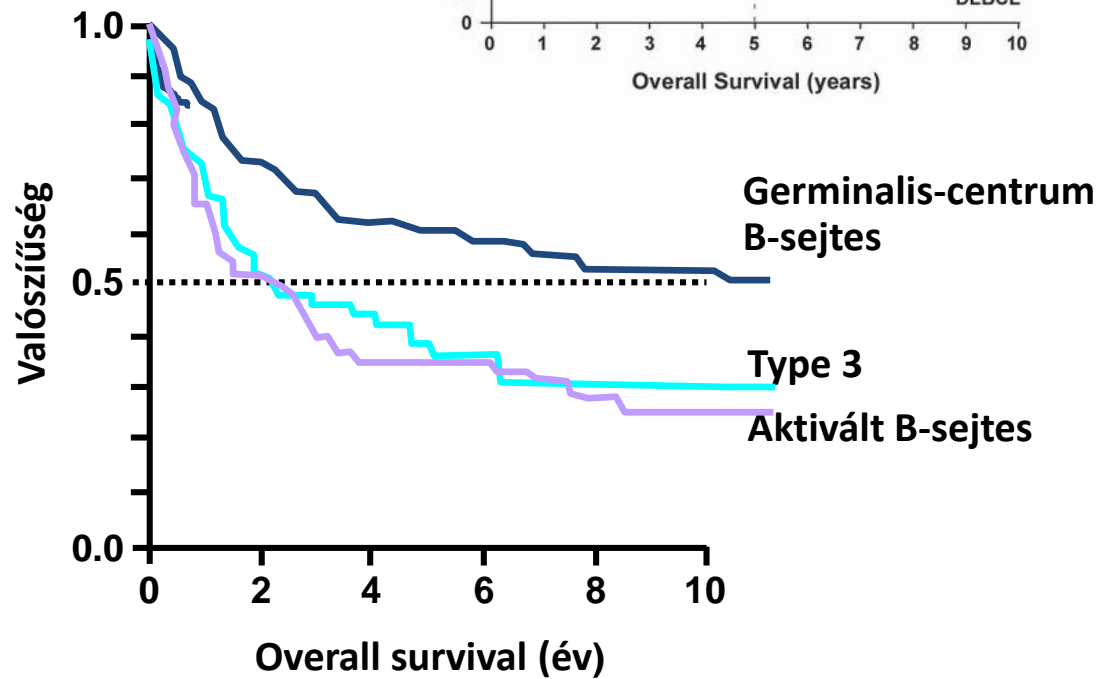
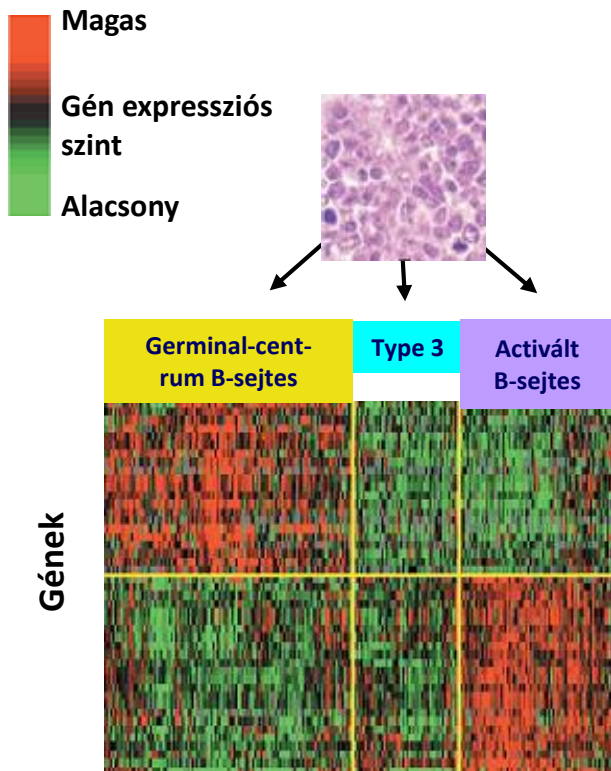
Koponya irradiáció (WBRT) – teljes agy irradiáció

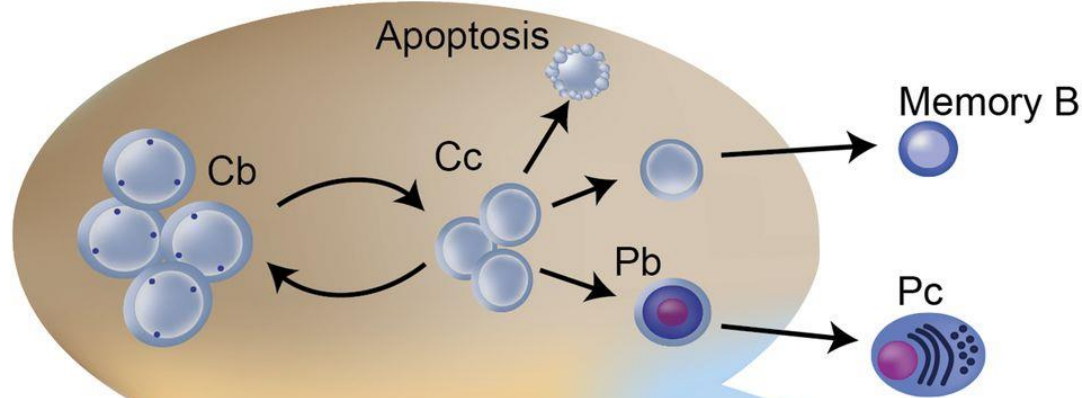
Őssejt transzplantáció



Prognosztikus alcsoportok *de novo* DLCL-ben

DNS microarray analízis megjósolja a
kemoterápiát követő túlélést





GCB

Histone modification

- EZH2* mutations
- MLL2* mutations
- CREBBP* mutations
- EP300* mutations

Blocks to terminal differentiation

- BCL6* expression, *EZH2* mutations

Cell cycle activation +\- blocks to apoptosis

- MYC* and *BCL2* translocations (DHIT) and protein over-expression

MTOR pathway activation

Signaling cascades

- PTEN* del/loss (PI3K and AKT activation)

ABC

BCR/NF- κ B signaling

- CD79A/B*, *CARD11*, *MYD88* mutations, *TNFAIP3* (A20) deletions

Histone modification

- MLL2* mutations
- CREBBP* mutations
- EP300* mutations

Blocks to terminal differentiation

- BCL6* translocations, *PRDM1* loss/ mutations

Cell cycle activation +\- blocks to apoptosis

- MYC* translocations, *MYC* and *BCL2* protein over-expression

MTOR pathway activation

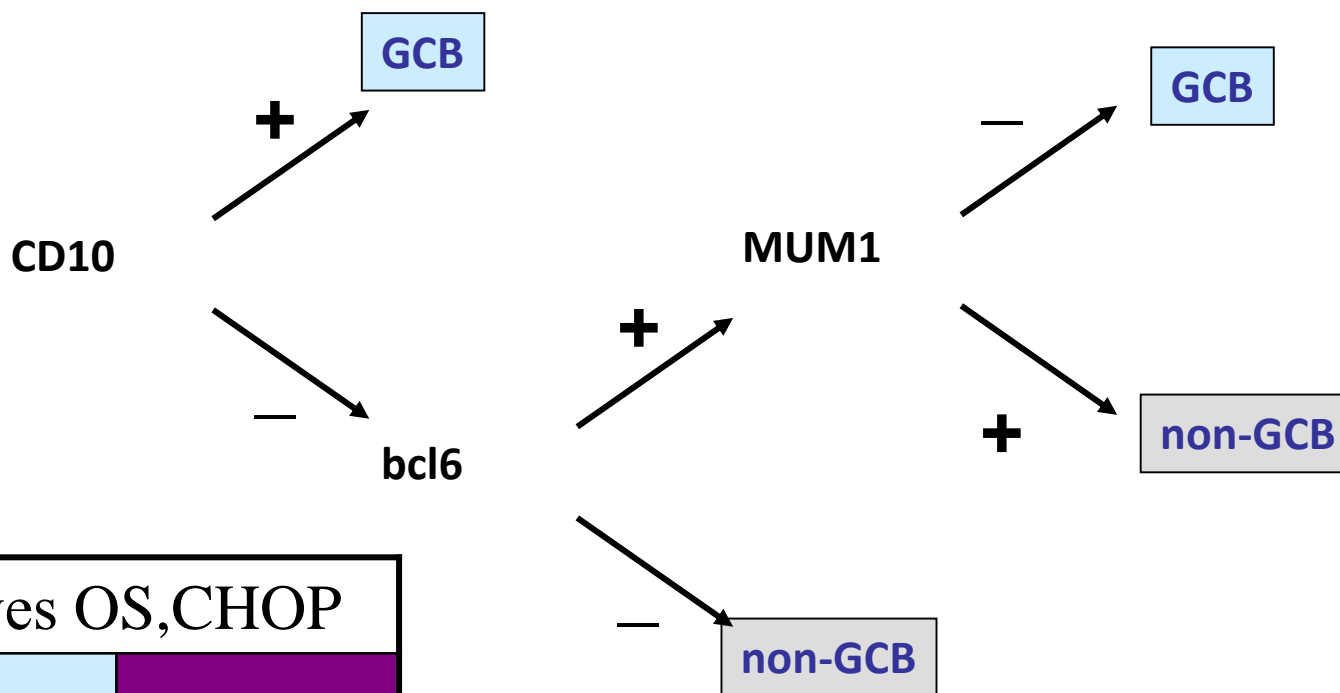
Signaling cascades

- PI3K and AKT activation

Cytokine signaling/JAK-STAT pathway activation

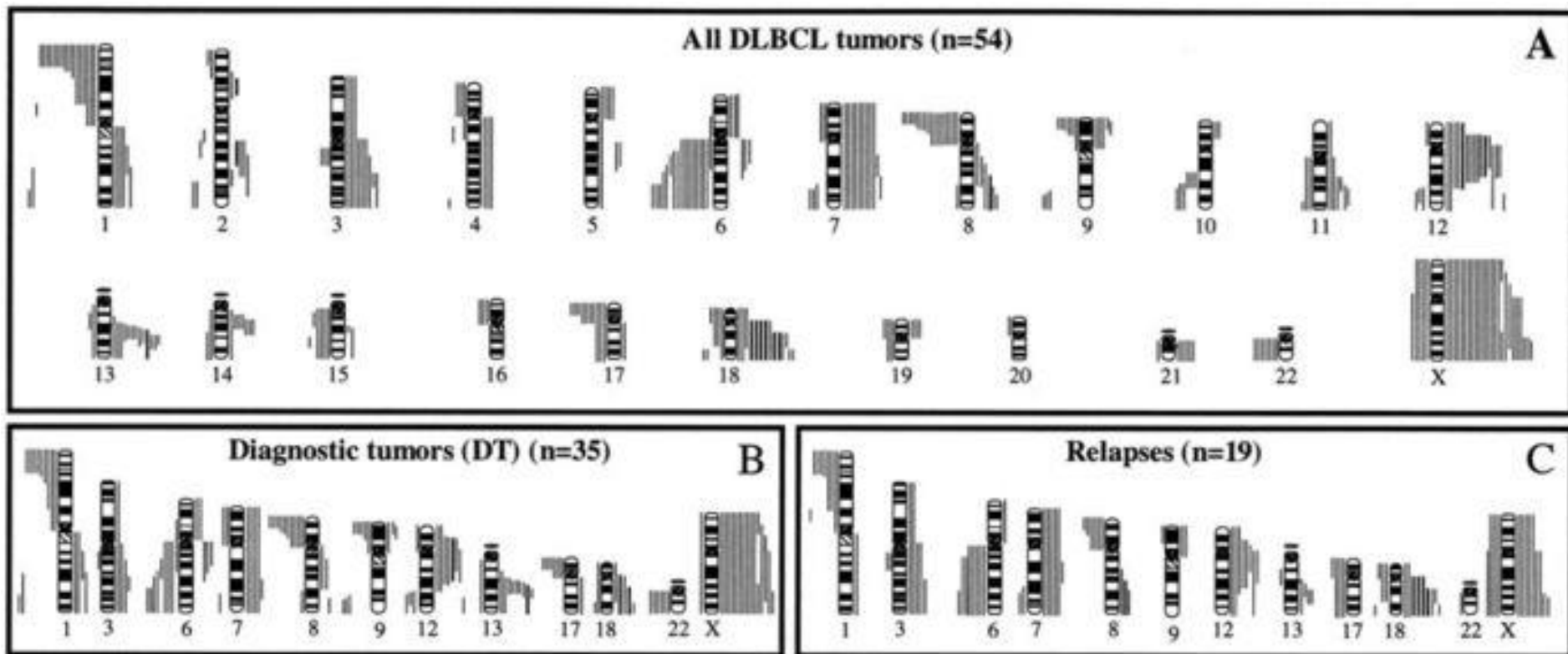
Sehn LH. Blood
2015;125:22-32

de novo DLCL szubklasszifikáció



5-éves OS,CHOP	
GCB	non-GCB
76%	34%

Kromoszómális egyensúlyhiány DLBCL-ben



kromoszóma vesztes bal oldal; nyeres jobb oldal

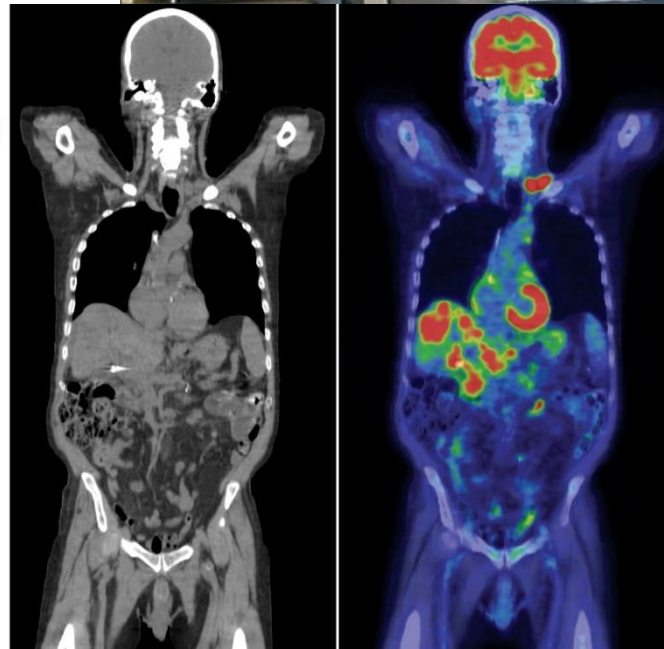
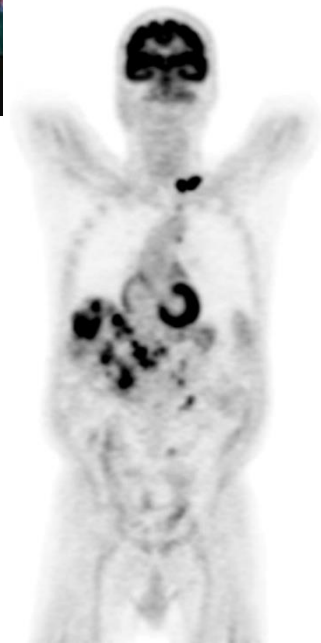
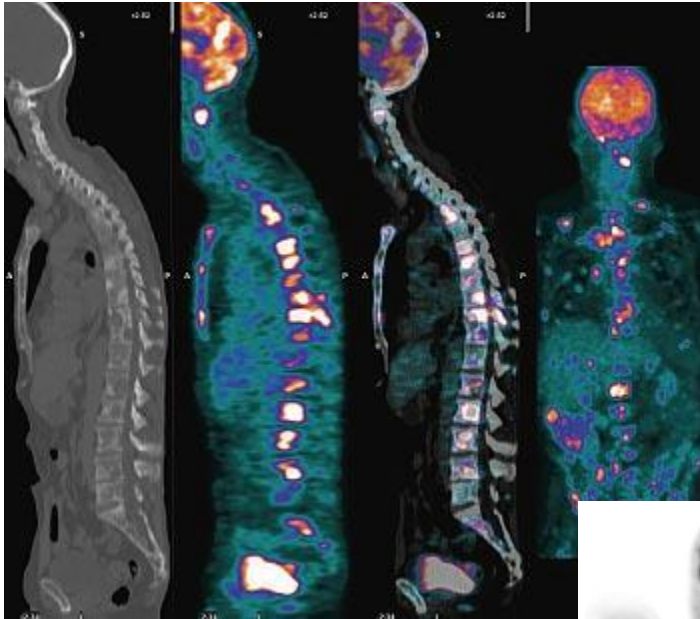
Berlung M. Modern Pathology 2002;15:807–816

Prognosztika

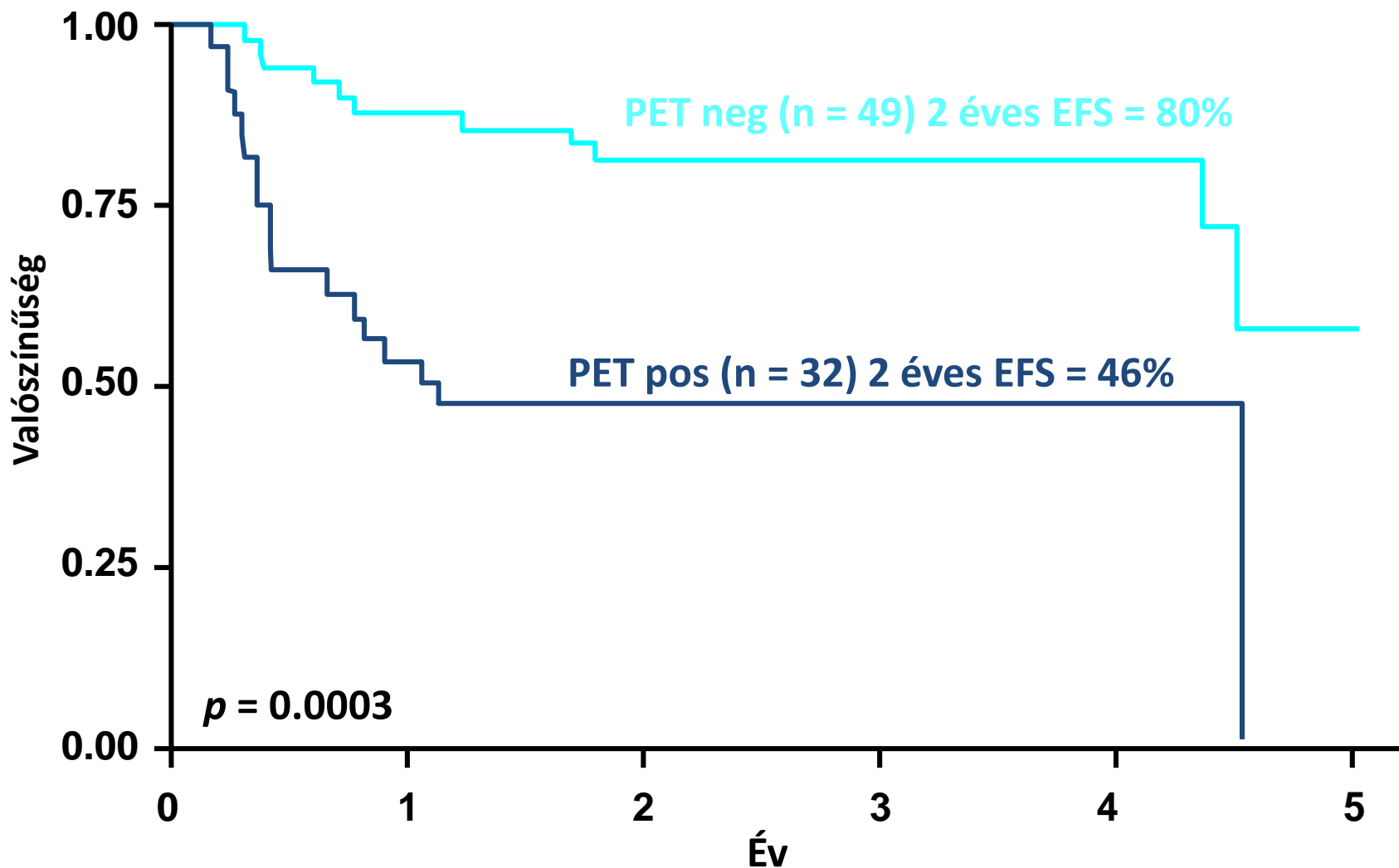
- IPI, aaIPI – klinikai jelentőség
- Betegség kiterjedtsége (stádium, bulky betegség)
- Beteg (kísérő betegségek)
- Therapiára adott válasz (korai PET-CT)
- -----

Finomabb prognosztika: pathológiai altípus, bcl-2, p53, DNS-CHIP, stb

PET/CT

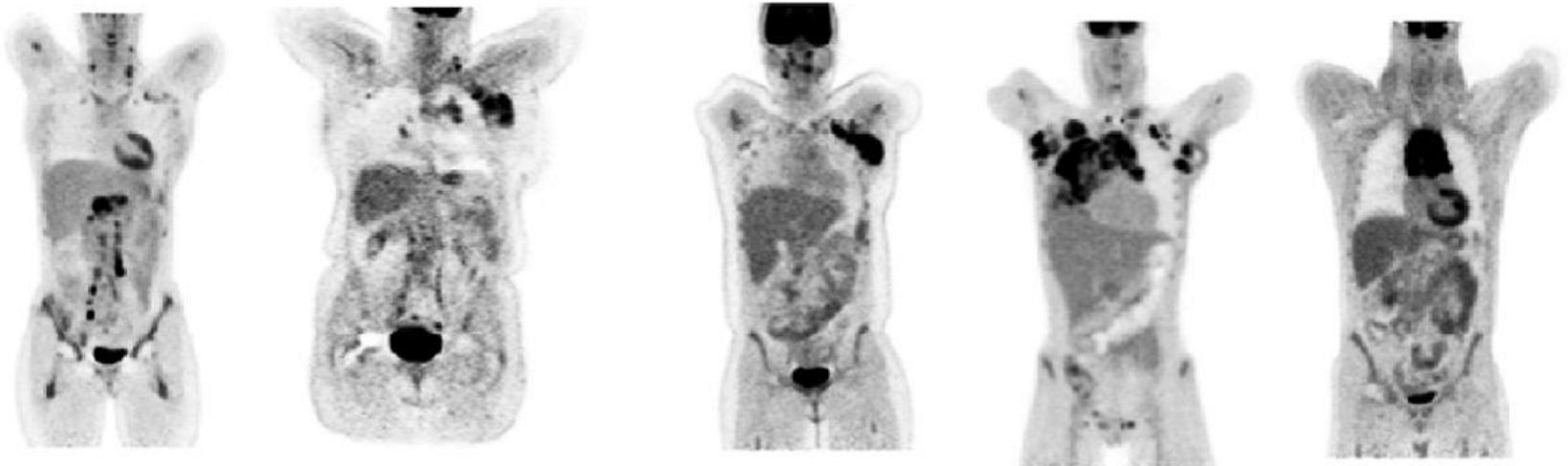


Eseménymentes túlélés (EFS) alakulása a 4 ciklus kezelés utáni PET státusz alapján

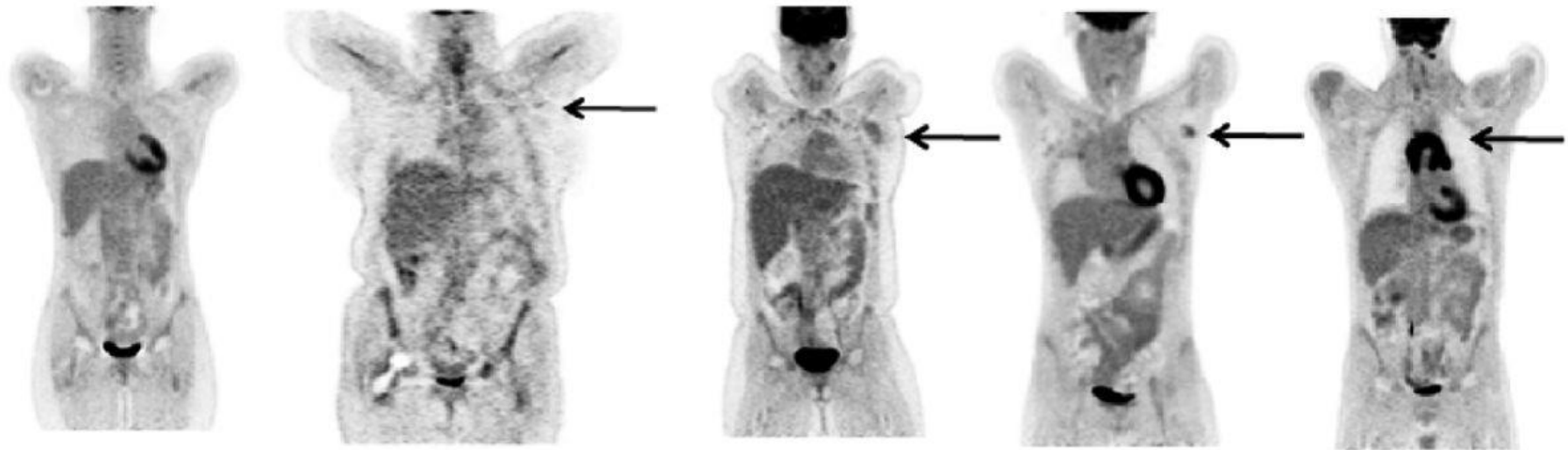


PETCT válaszok fokozatai

Staging



Response



1

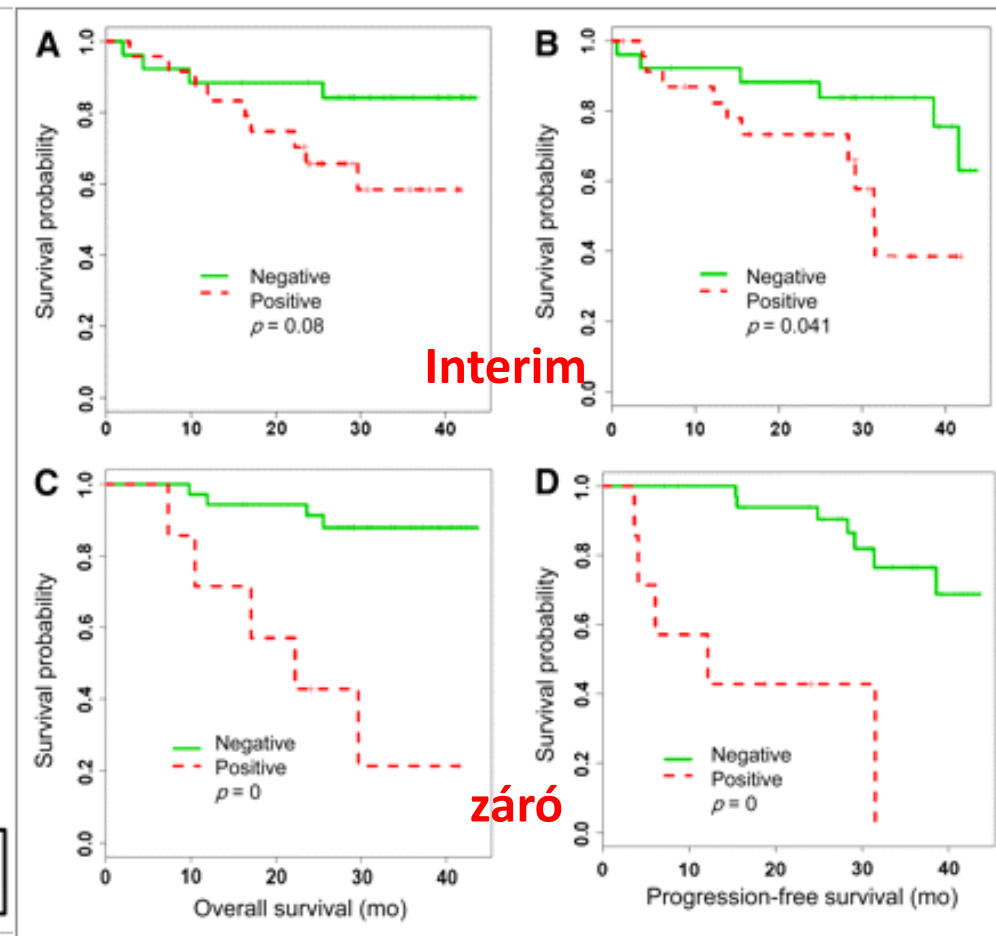
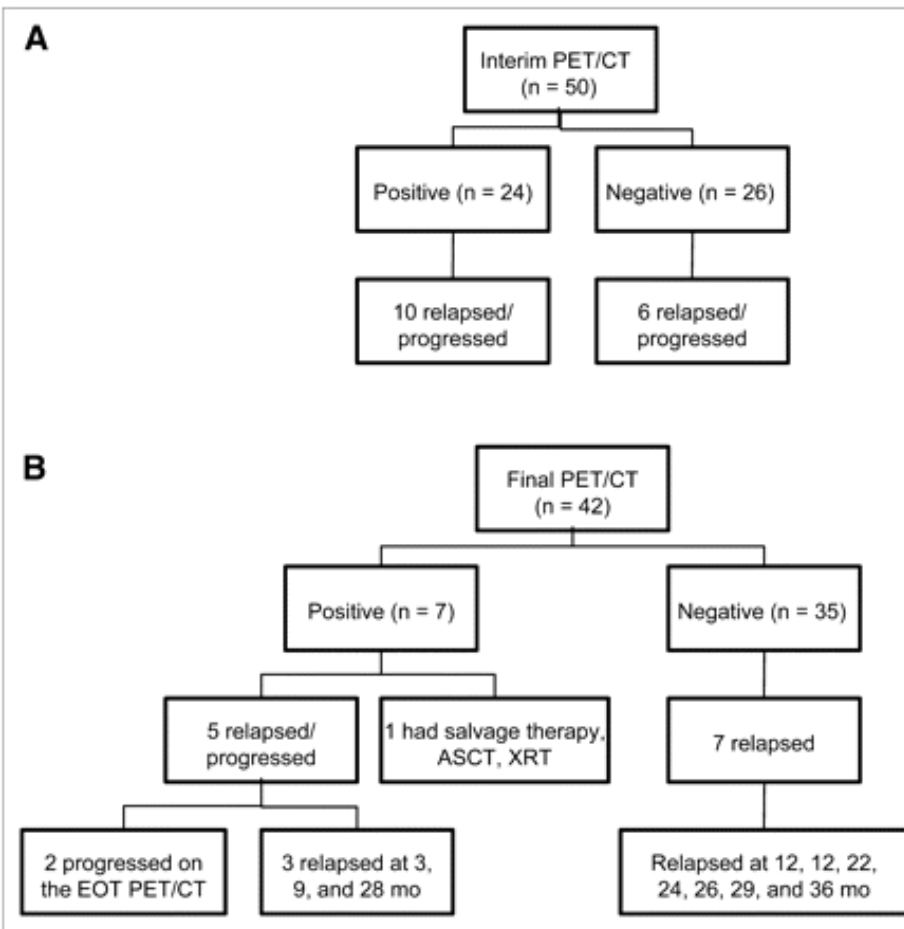
2

3

4

5

No uptake FDG < MBP FDG > MBP ≤ liver FDG > liver FDG >> liver



Az interim PETCT szenzitivitása és specificitása nem meggyőző.

A tumorok 2 ciklus után még nem válnak PET negatívvá.

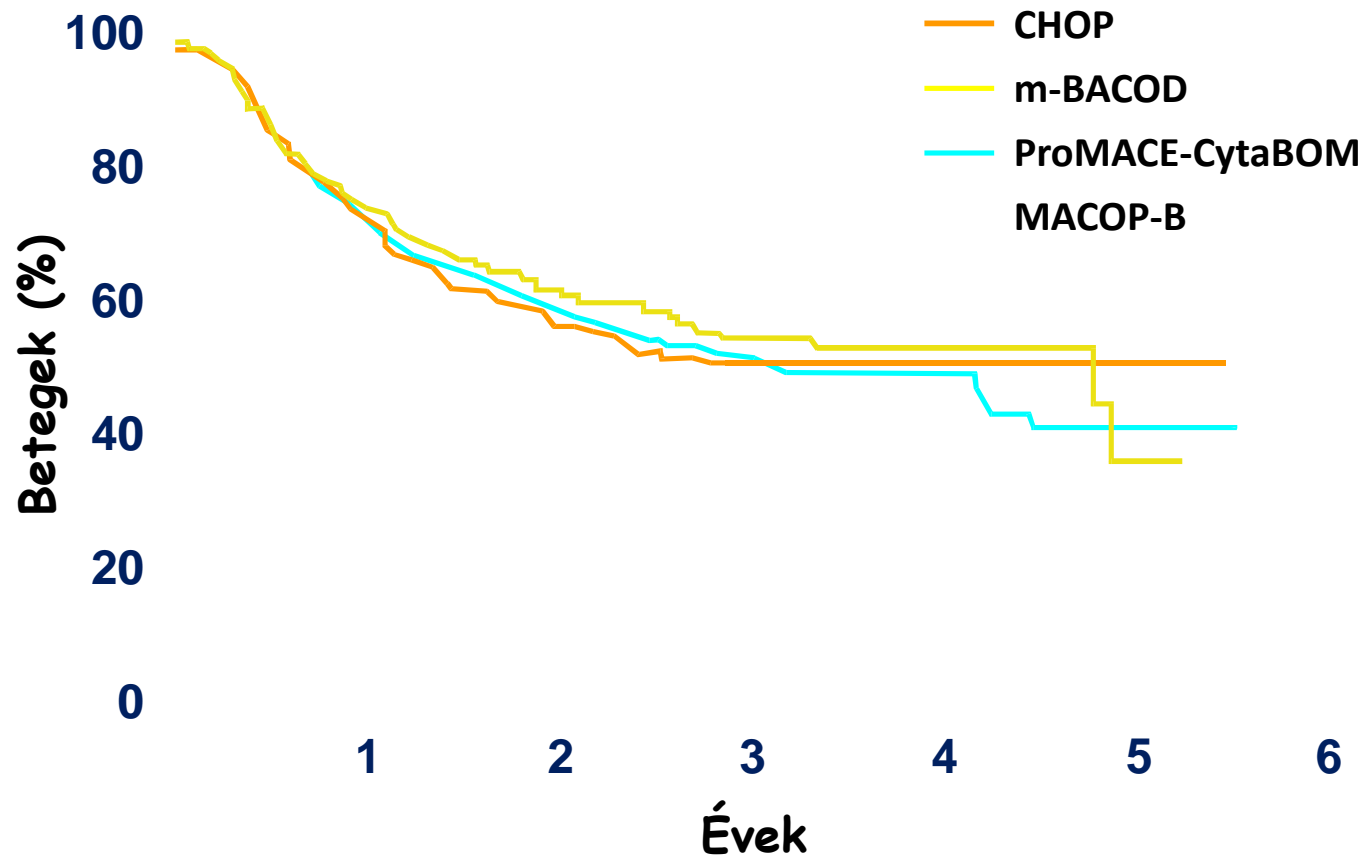
Kezelést lezáró PETCT már szenzitívebb, specifikusabb

Cashen AS. J Nucl Med 2011;52:386-392

CHOP kemoterápia

- **C**yclophosphamide (Cytosan)
- **H**ydroxydaunorubicin
(Adriamycin)
- **O**ncovin (Vincristine)
- **P**rednisone

Agresszív NHL túlélés összehasonlítása

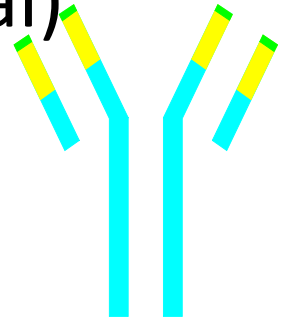


CD20, mint terápiás célpont előnyei

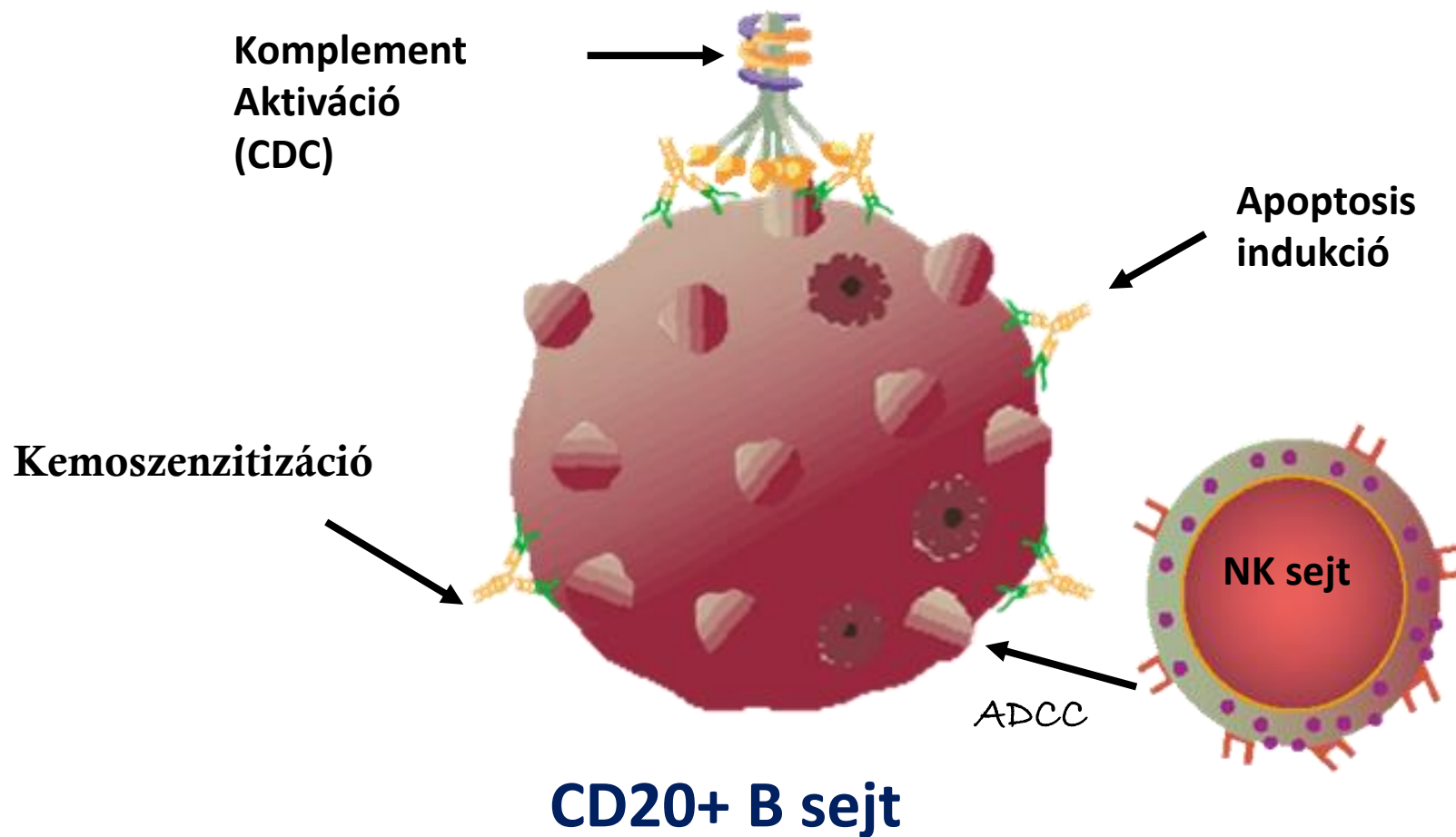
- Nem tumorspecifikus, de **B sejt specifikus**
- A B-NHL több mint **95%**-án jelen van
- **Minden** tumorsejten jelen van, **magas** kópia számban
(50.000-200.000/tumorsejt)
- A membránban **stabil**, nincs Ag variáns
- Biológiai funkciója van (Ca^{++} csatorna)
- Nincs jelen a B sejt prekursor őssejten

Rituximab

- **Felfedezése:** 1990 (Maloney és mtsai)
- **Terápiás alkalmazás:** 1995 óta
- **Ajánlott dózis:**
 - 375 mg/m² , ambulanter adható
- **Mellékhatások:**
 - „First dose” reakció (tumor lysis, citokin release)
 - B sejt deplécio
 - Ritkán késői agranulocytosis, immunszövődmények



Hatásmechanizmus

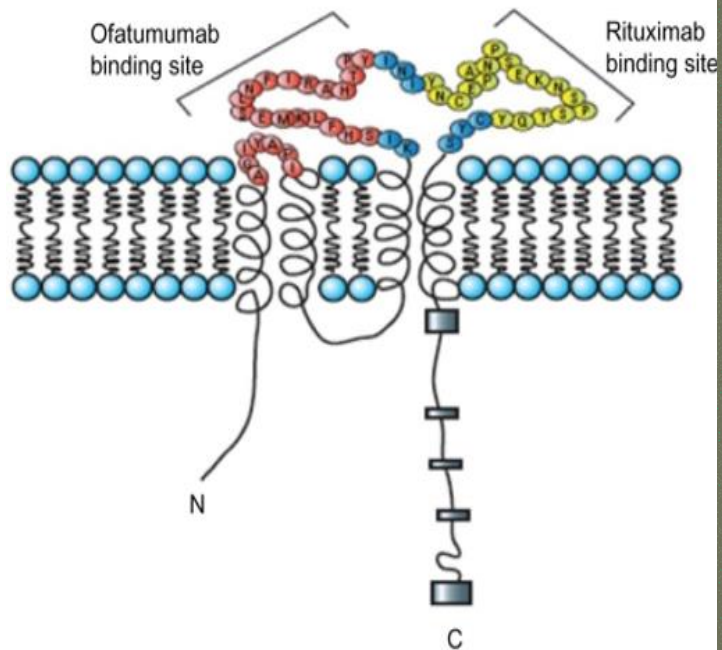


Rituximab alkalmazása DLCL-ben

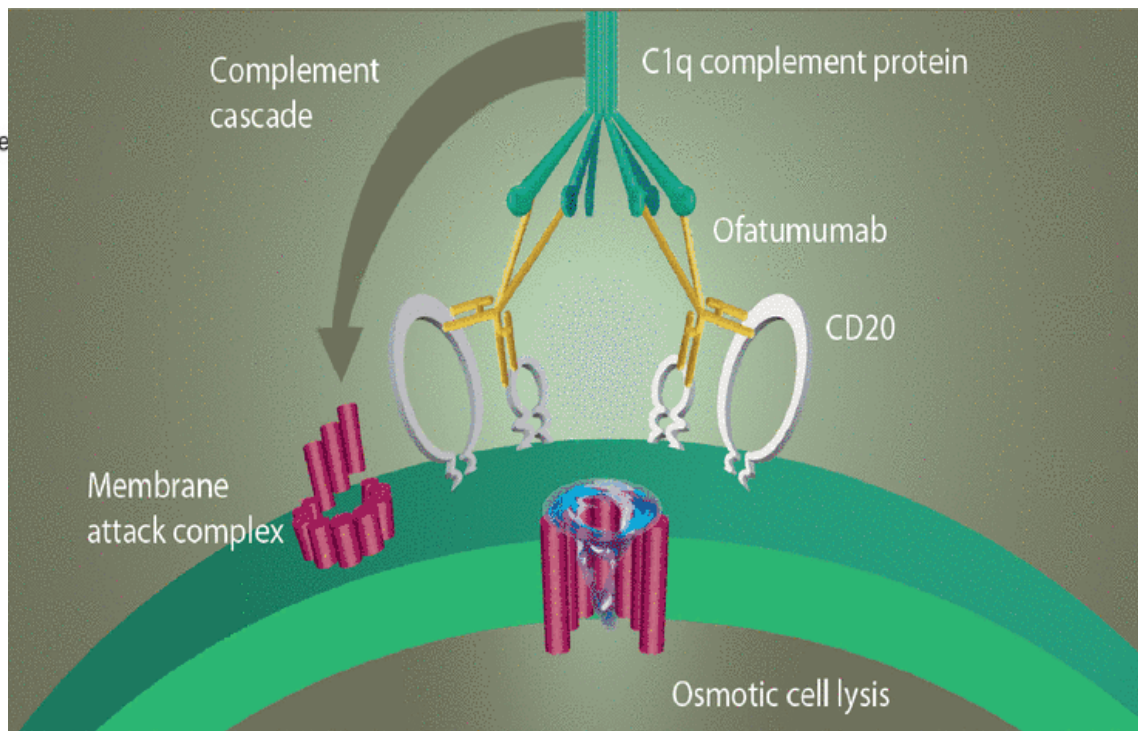
- Alapkezelésként **immuno-kemoterapia (R-CHOP alapú)** kor, IPI és prognózishoz igazítva
- R-CHOP alapú kemoterapia **intenzitása** (21, 14, dose-dense, optimális kombinációk)
- Mabthera **konzolidáció és fenntartó kezelés** (1. és 2. remisszióban)
- Mabthera és **transzplantáció** (őssejt mobilizáció; transzplantációt követő fenntartó kezelés)
- Mabthera **relapszusban**

Ofatumumab vs. Rituximab

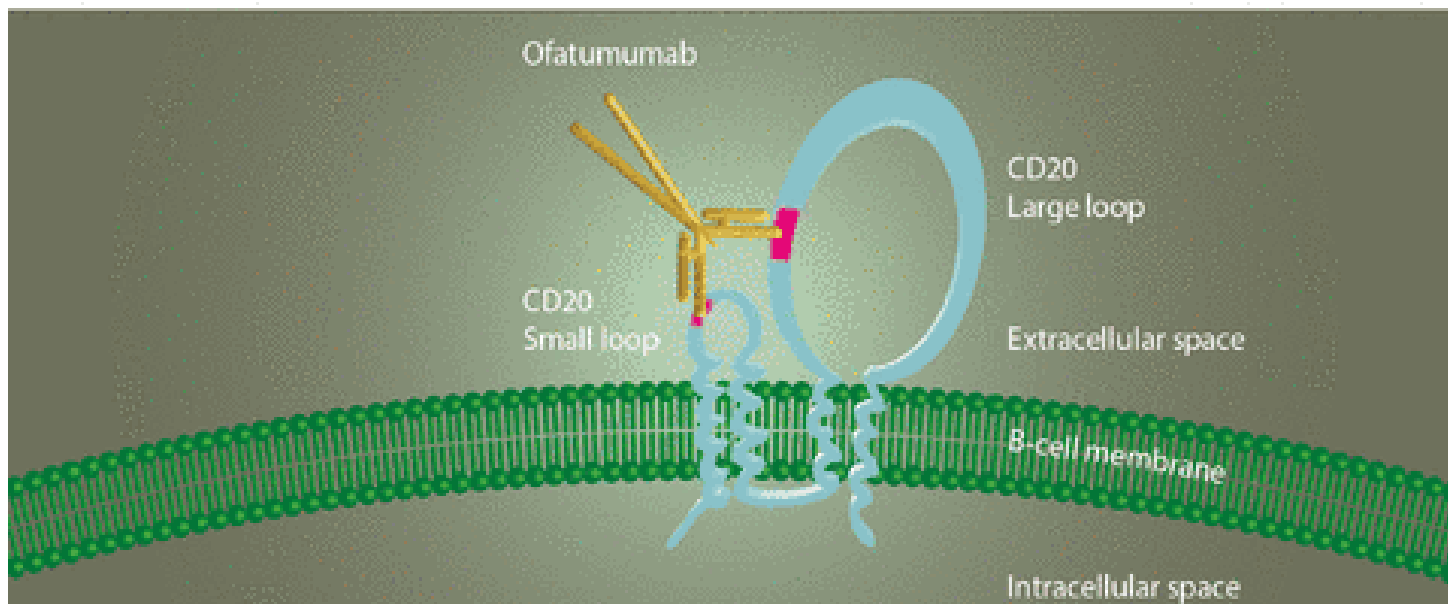
CD20



J Clin Oncol. 2010;28:3525.



Ofatumumab



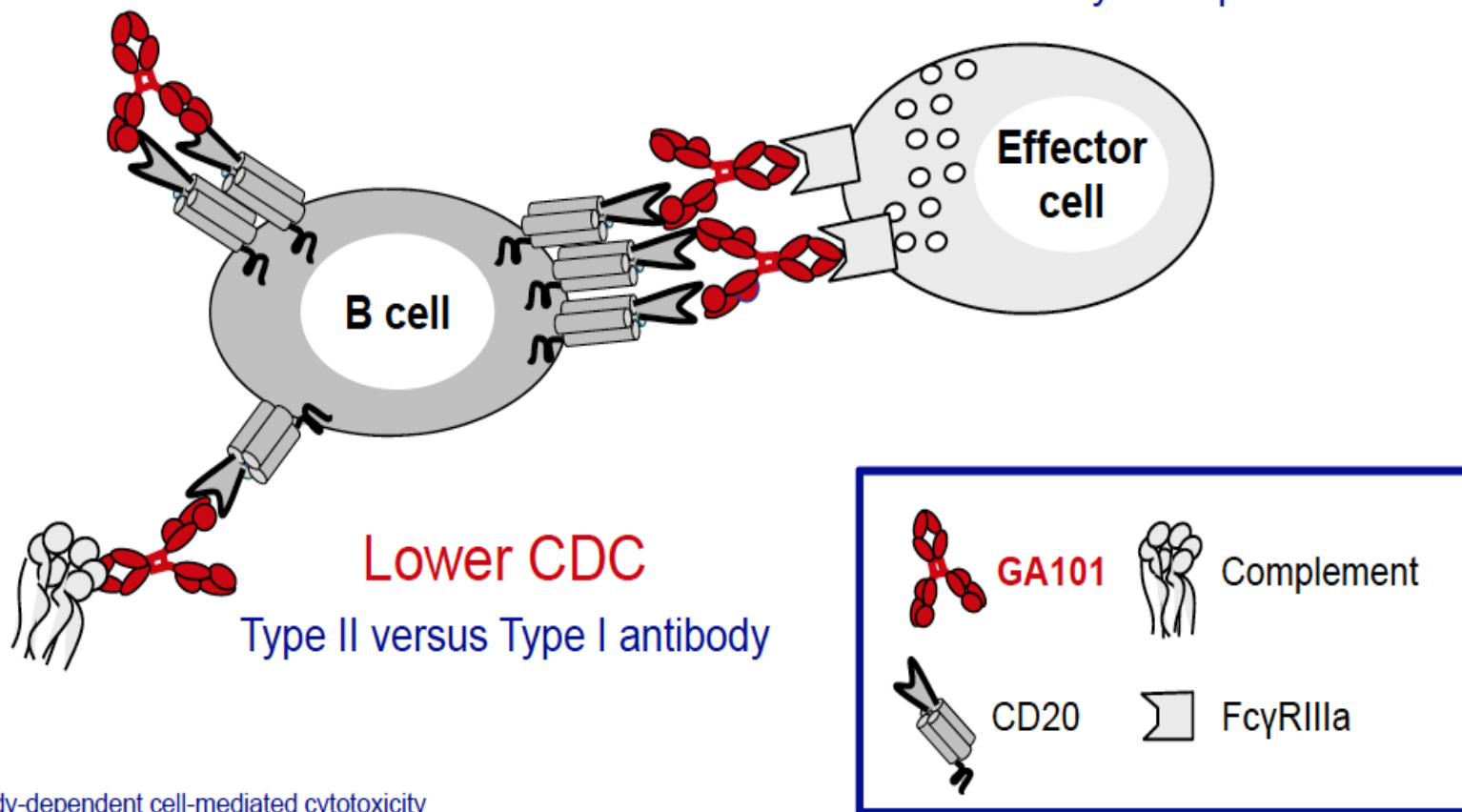
Obinutuzumab

Increased Direct Cell Death

Type II versus Type I antibody

Enhanced ADCC

Glycoengineering for increased affinity to FcγRIIIa



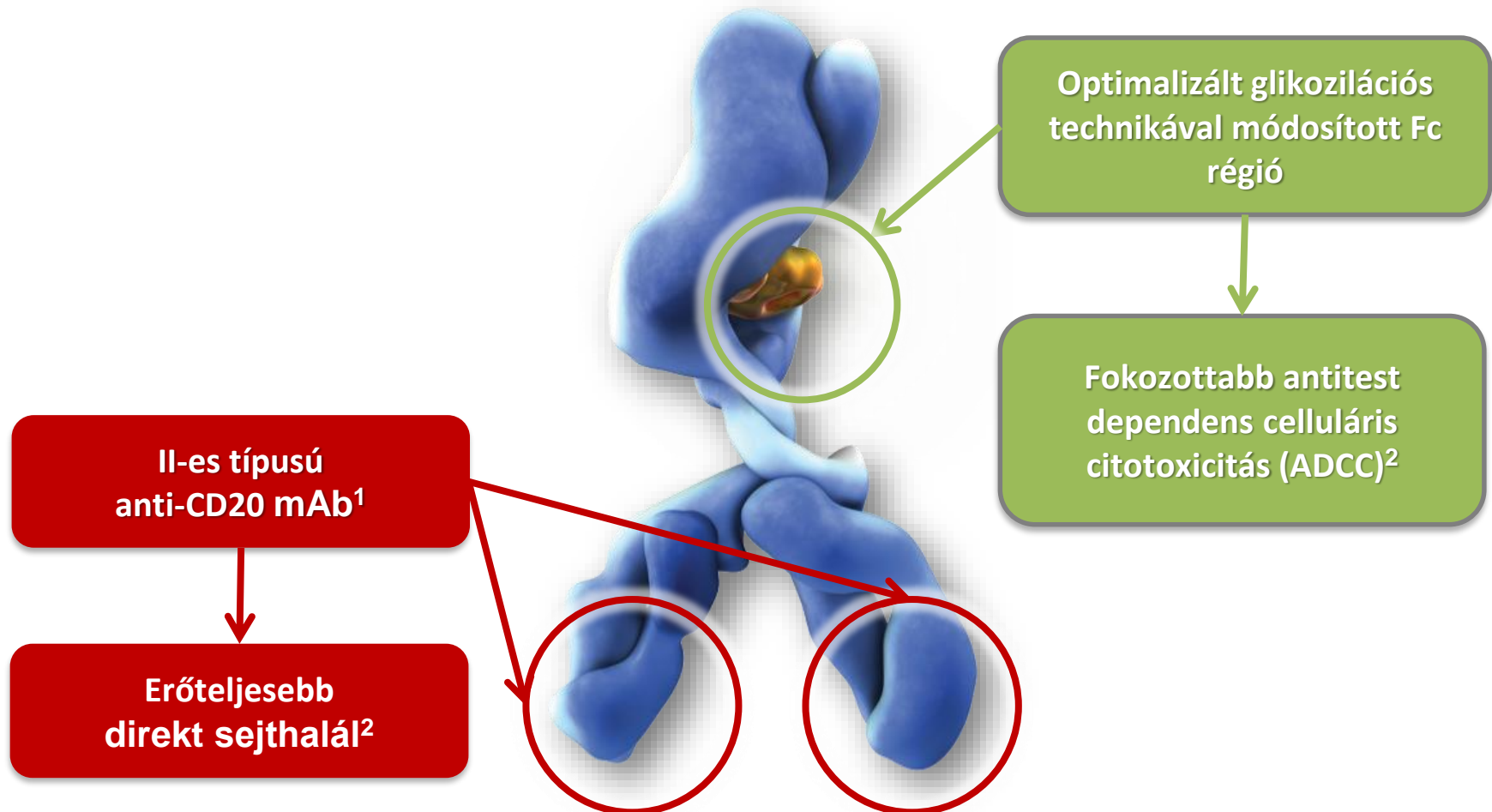
ADCC, antibody-dependent cell-mediated cytotoxicity

CDC, complement-dependent cytotoxicity

Mössner F. *et al. Blood* 2010; 115:4393–4402

GAZYVARO (obinutuzumab)

ARRA TERVEZTÉK, HOGY KIFEJEZETTEBB HATÁSSAL RENDELKEZZEN A KÓROS B-SEJTEKSEL
SZEMBEN

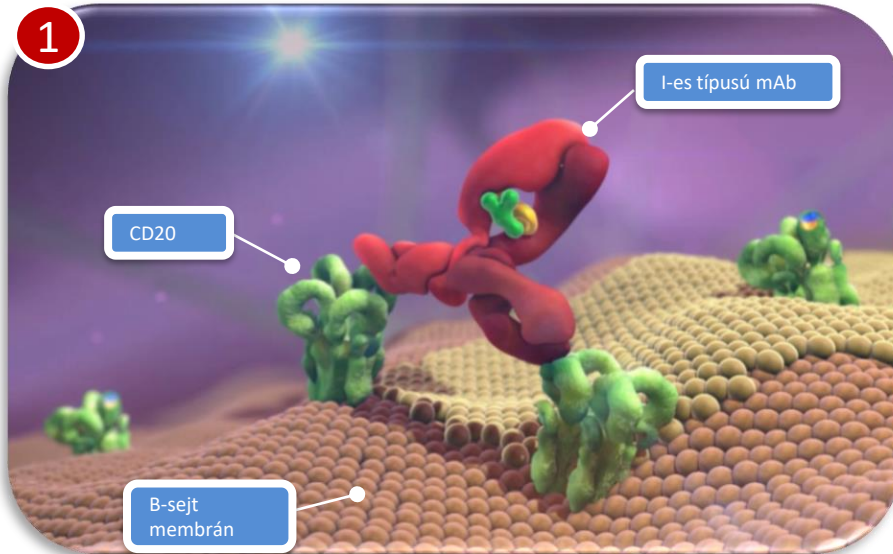


I-ES ÉS II-ES TÍPUSÚ MONOKLONÁLIS ANTITESTEK

ELTÉRŐ KÖTŐDÉS A CD20 MOLEKULÁHOZ

I-es típus:
rituximab

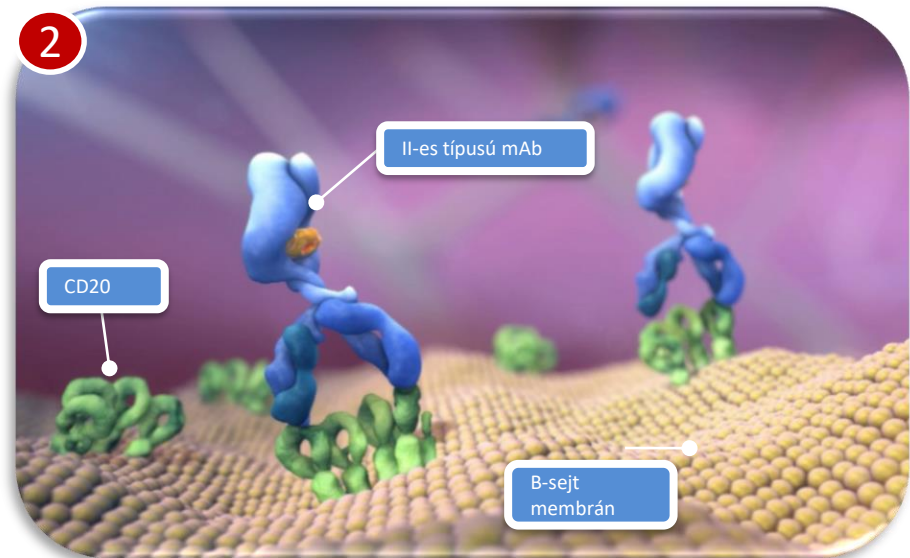
Intertetramerikus kötődés



Az I-es típusú monoklonális antitestek, mint a MabThera, a CD20 tetramereknek egymástól távolabb levő térbeli alakzatával képesek csak kapcsolódni.¹

II-es típus:
obinutuzumab

Intratetramerikus kötődés



A II-es típusú monoklonális antitest, mint a Gazyvaro, a CD20 tetramerekkel teljesen más térbeli alakzatot vesz fel, mint az I-es típusúak.^{1,2}

I-ES ÉS II-ES TÍPUSÚ MONOKLONÁLIS ANTITESTEK

ELTÉRŐ MŰKÖDÉS

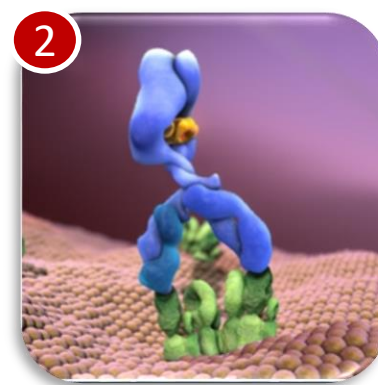
I-es típus: rituximab



Apoptózis

- Az I-es típusú antitestek **klasszikus apoptózist** indukálnak.^{1,2}

II-es típus: obinutuzumab

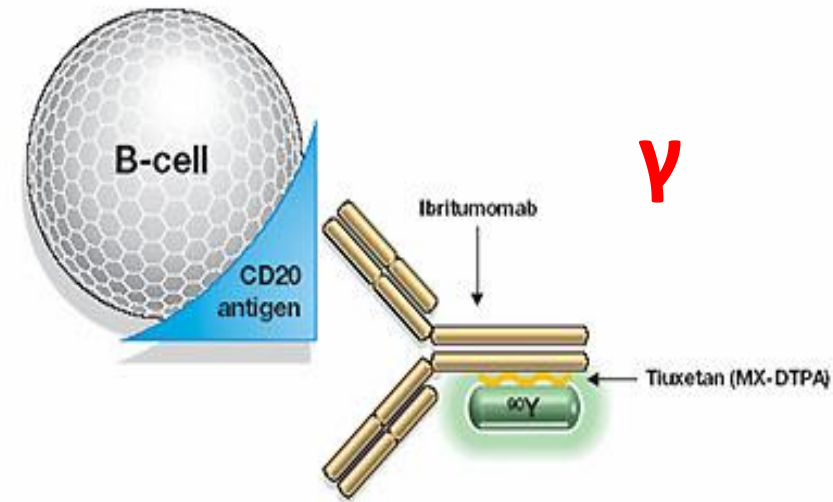


Direkt sejthalál (DCD)

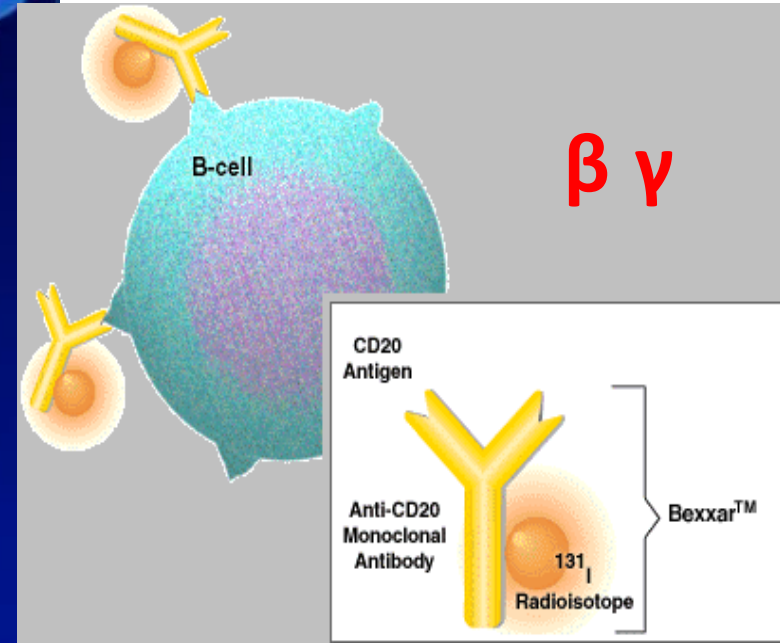
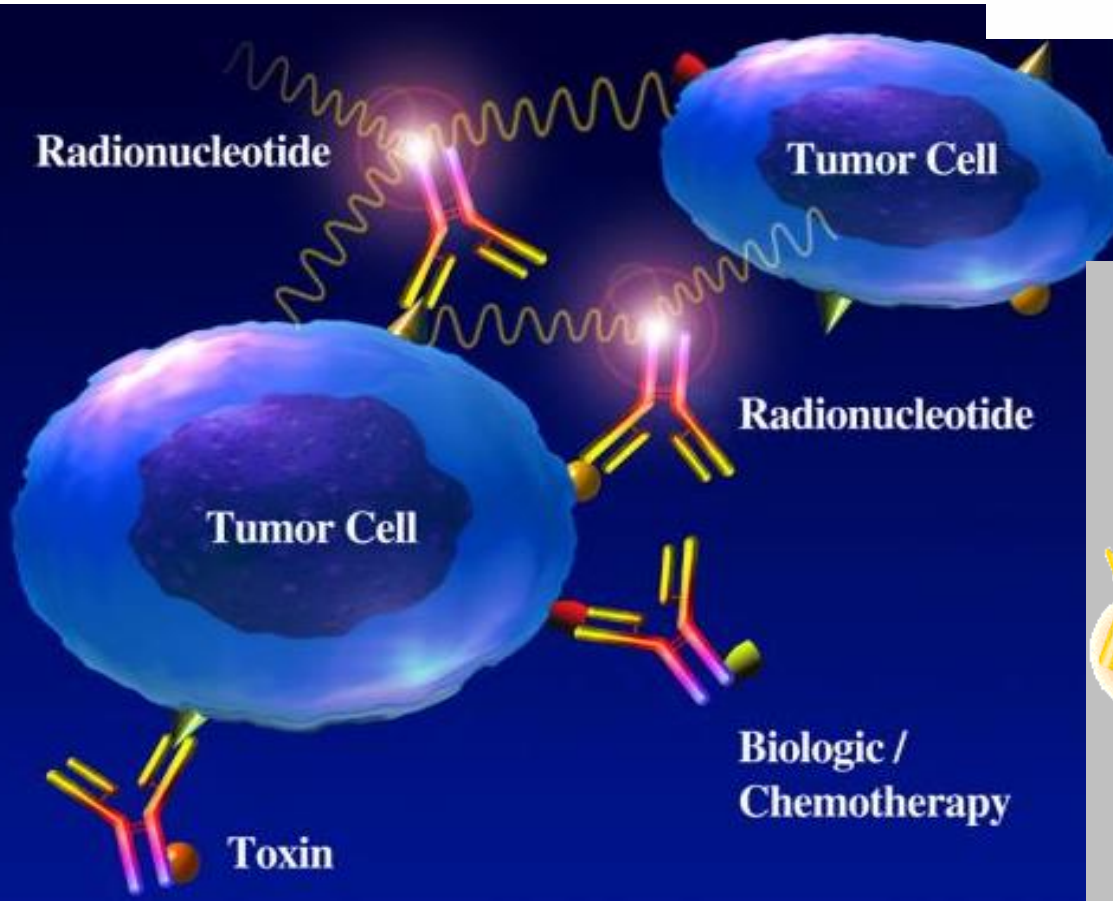
- Az obinutuzumab II-es típusú monoklonális antitest, ami nem a klasszikus apoptózis révén vezet direkt sejthalálhoz, hanem **az intracelluláris kaszkádrendszert** aktiválja.^{3,4}

Konjugált monoklonális antitestek

Yttrium-90 labelled Zevalin®

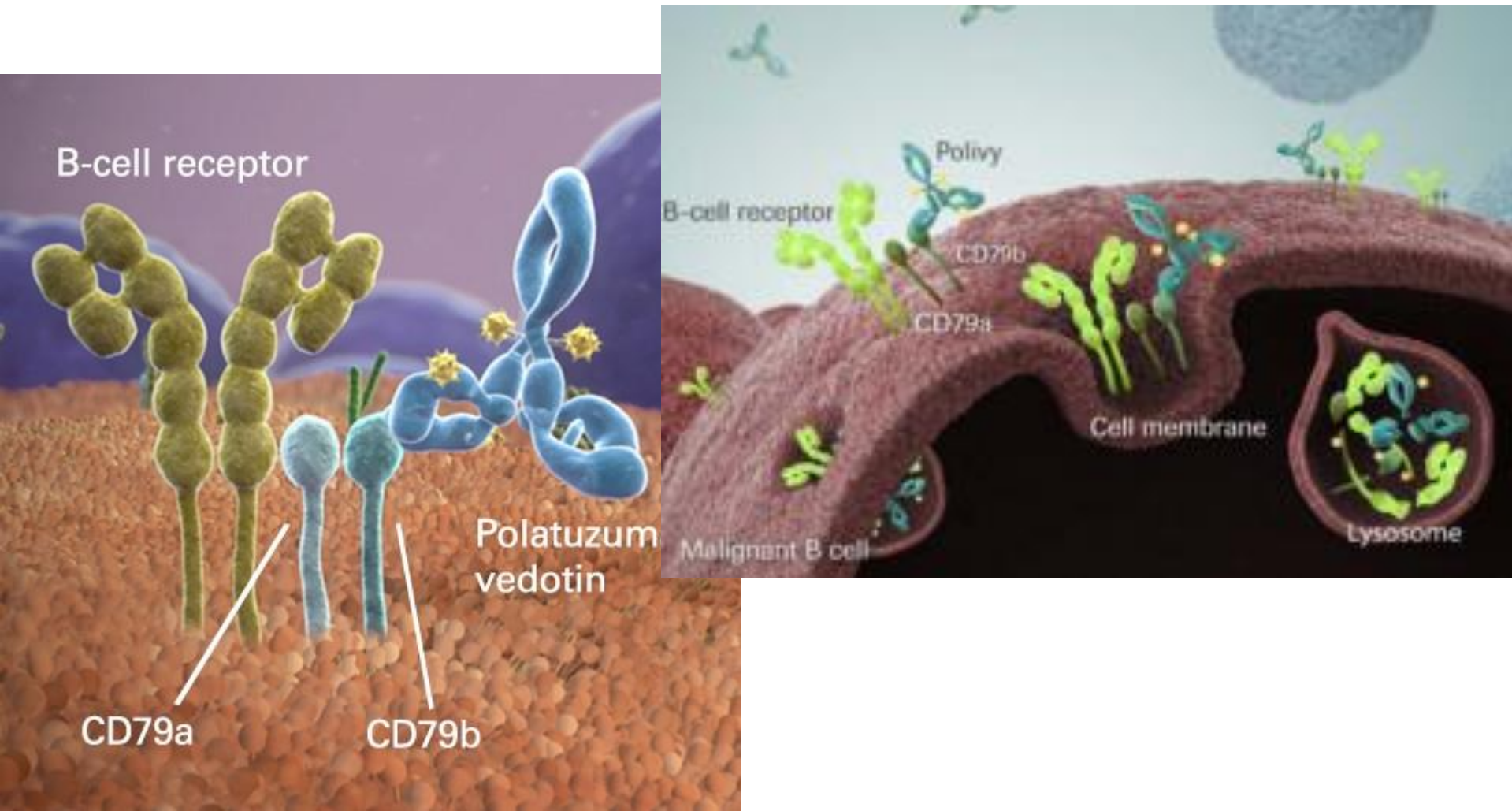


γ

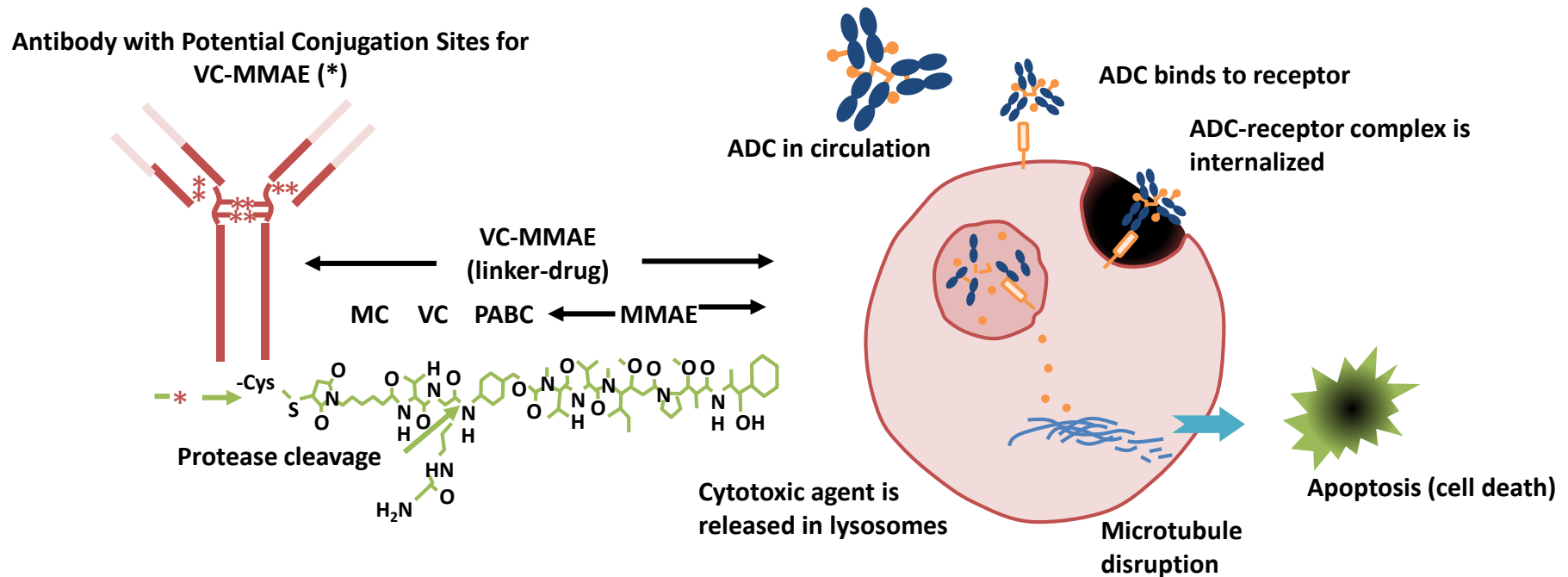


$\beta \gamma$

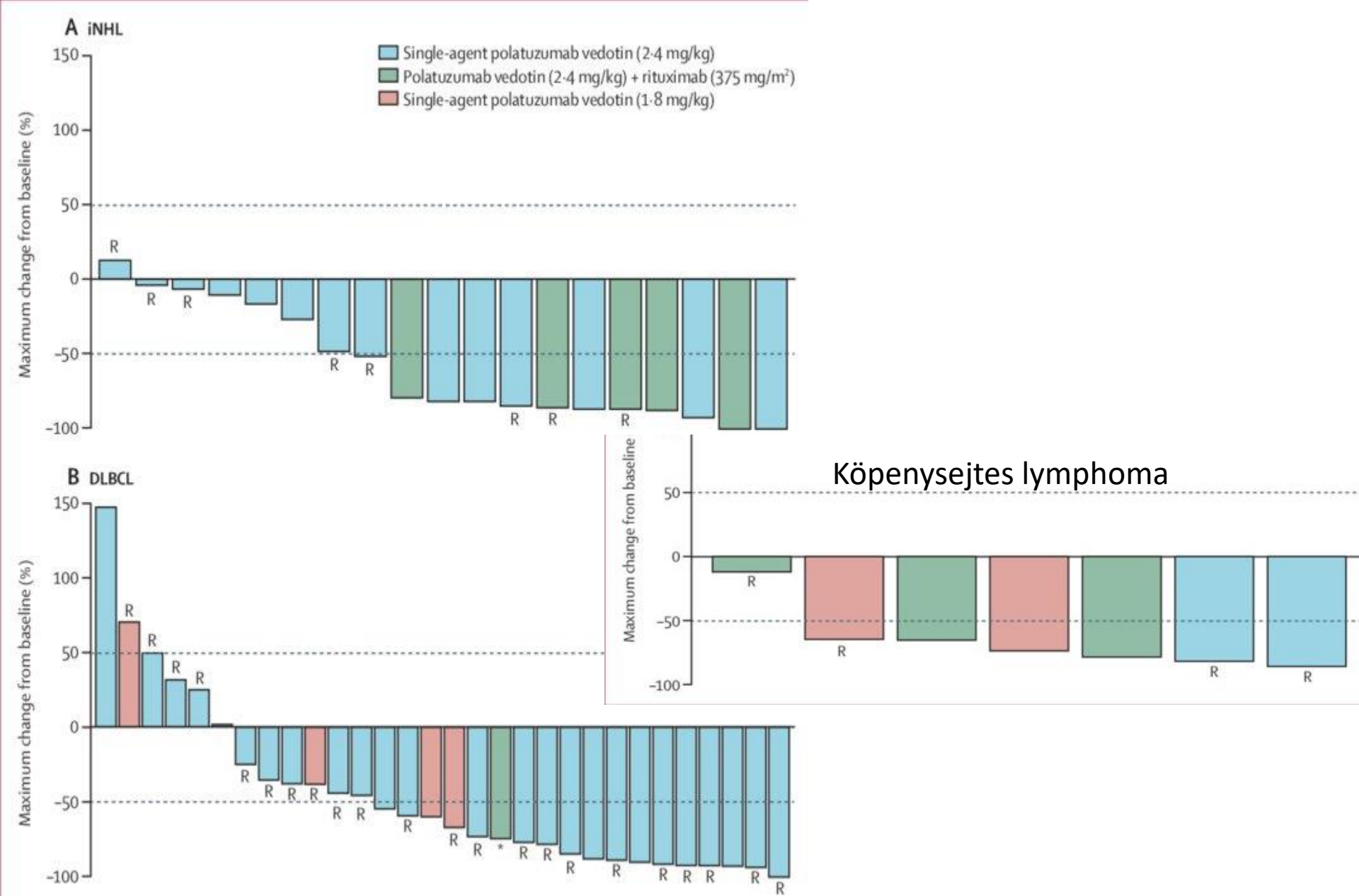
Polatuzumab vedotin



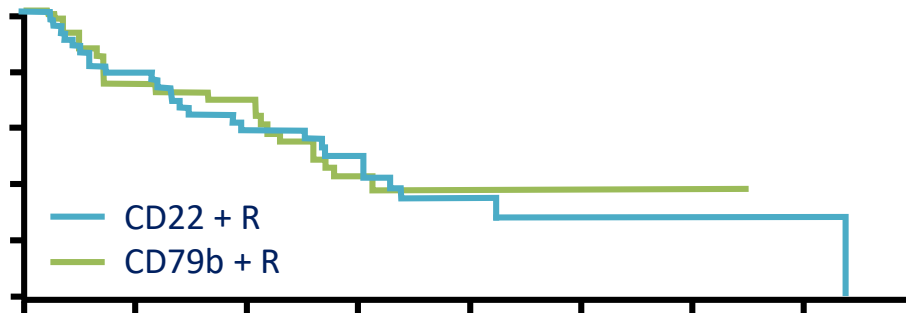
Polatuzumab Vedotin és Pinatuzumab Vedotin aktivitása Rel/Ref NHL-ban



- Antibody–drug conjugates made up of a potent microtubule inhibitor called monomethyl auristatin E which is connected to monoclonal antibodies anti-CD22 and CD79b (expressed by many B-cell malignancies) by a protease-cleavable peptide linker
- Both polatuzumab and pinatuzumab have shown activity in phase I trials

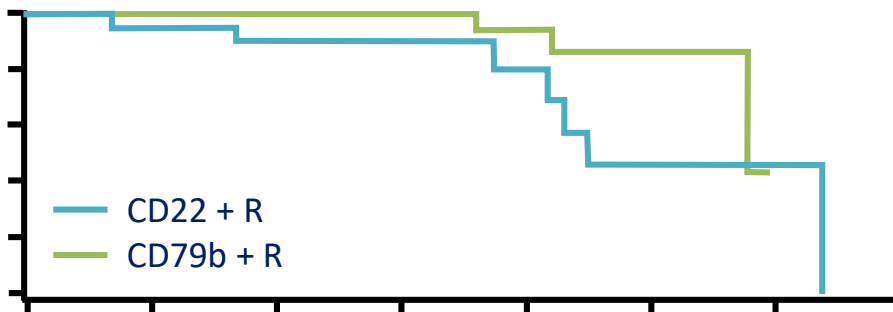


Polatuzumab (CD79b) + R vs Pinatuzumab (CD22) + R: PFS



Median PFS, Mos (95% CI)

R + CD22 ADC (N = 42)	R + CD79b ADC (N = 39)
5.4 (2.8-8.4)	5.2 (4.1-NR)



Median PFS for FL not reported due to insufficient duration of follow-up

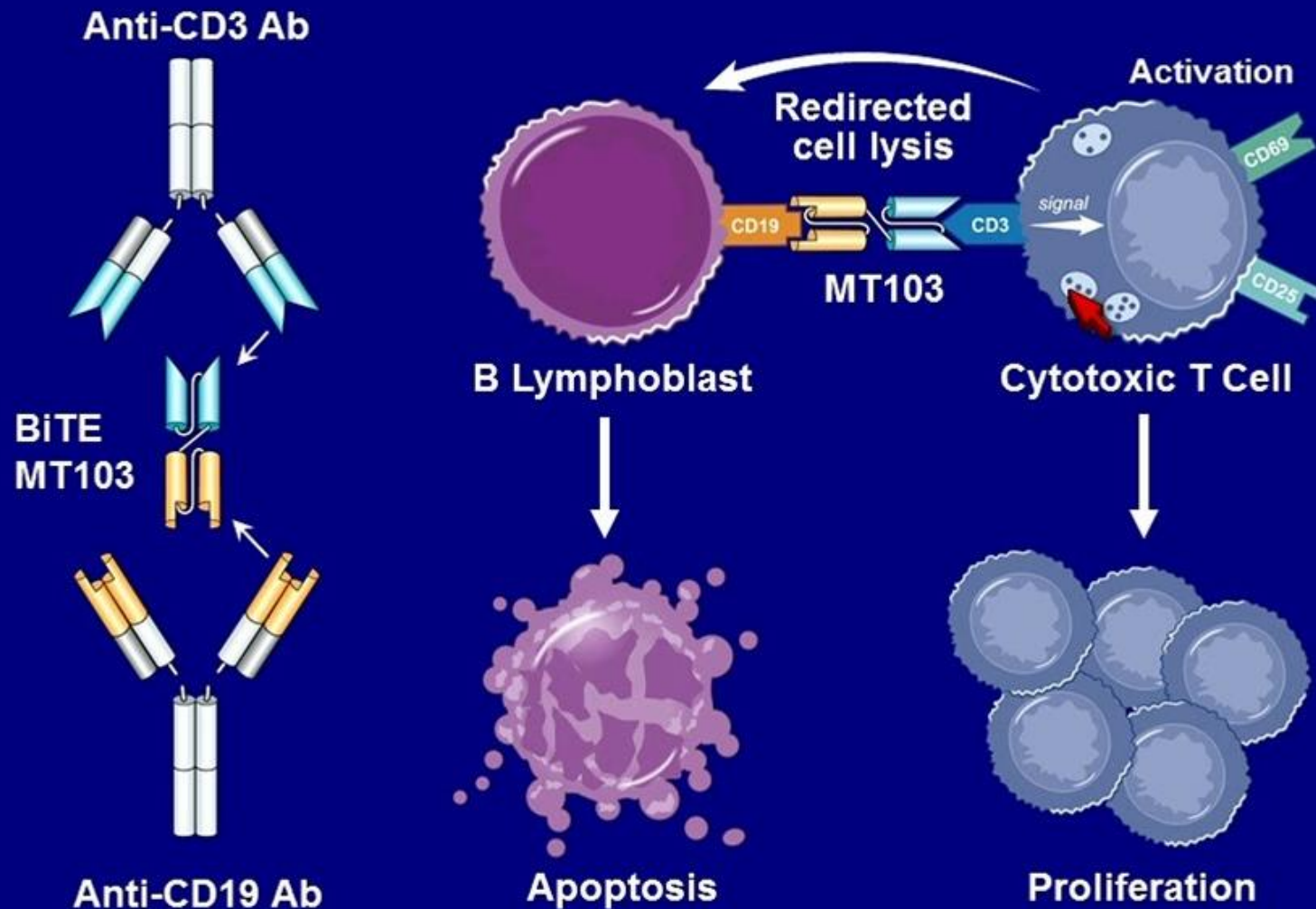
Relapszusos, refrakter diffúz nagy B-sejtes lymphomában

Polatuzumab 1,8 mg/m²

rituximab 375 mg/m²

bendamustin 2x90 mg/m²

Blinatumomab (MT103)[®] A T Cell-Engaging BiTE Antibody

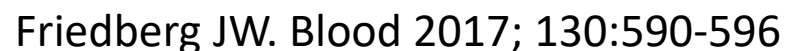
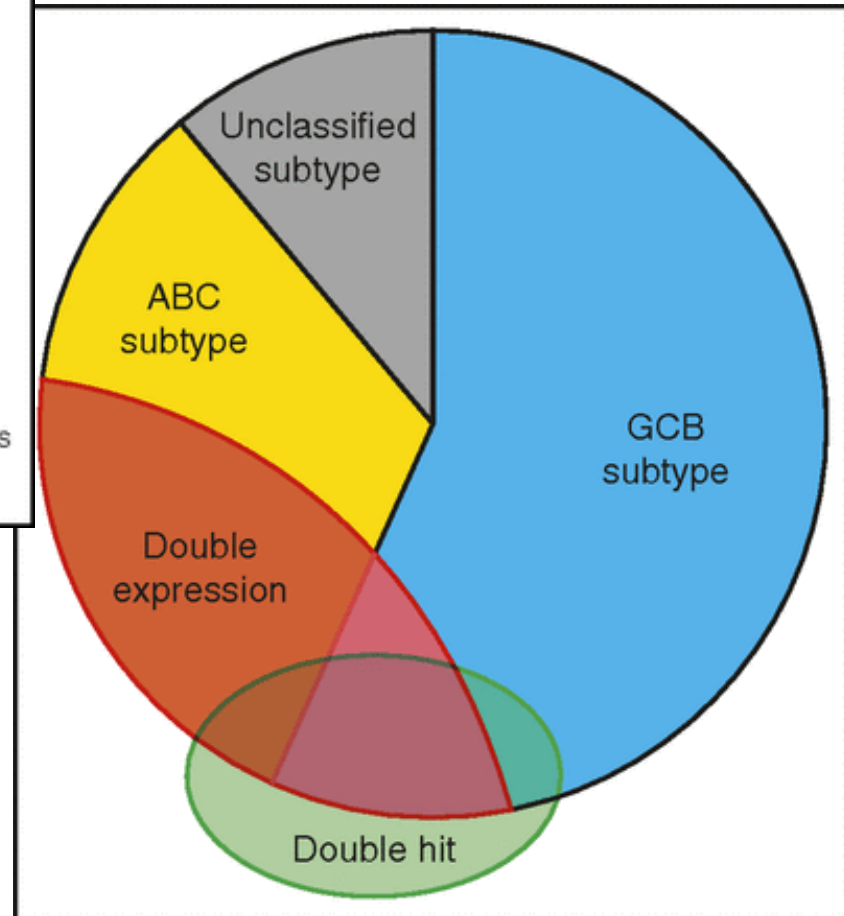


Adapted from: Nagorsen D et al; Blood 2009; 114: 2723

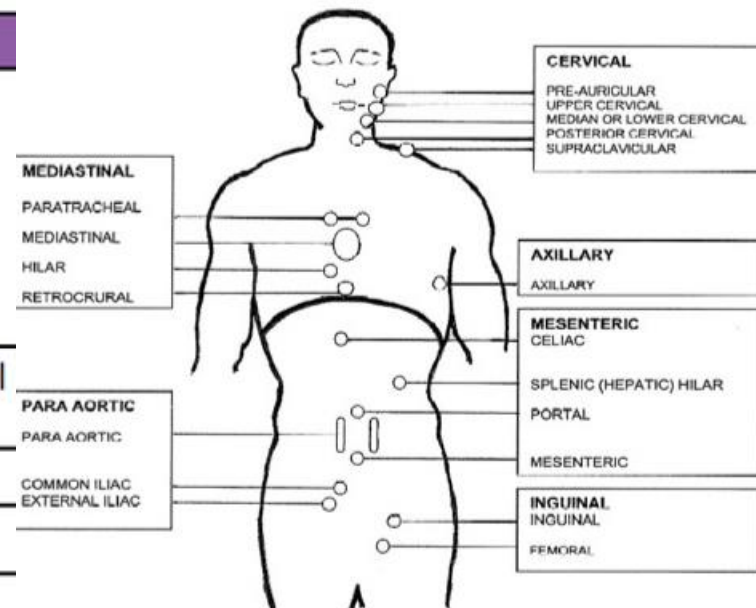
Bispecifikus antitest (CD20 és CD3) mosunetuzumab



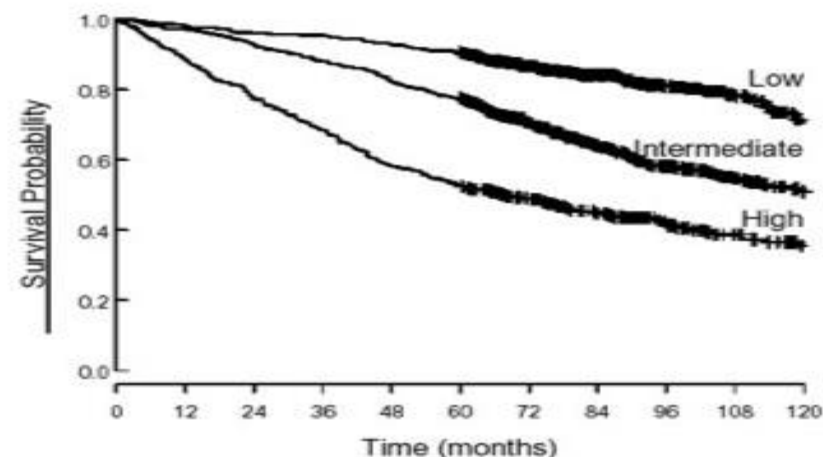
High-grade B-cell lymphoma with translocations involving *myc* and *bcl-2* or *bcl-6*.



FLIPI (Follicular Lymphoma)		IPI (Large Cell Lymphoma)	
Age >60 yr Ann Arbor stage (III or IV) Hemoglobin level <12 g/dL (120 g/L) Number of nodal* areas >4 Serum LDH level above normal		Age >60 yr Stage I or II Performance status 0 or 1 Extranodal involvement >1 site Serum LDH level >1x normal	
Risk Categories (Factors)	5-/10-yr Overall Survival (%)	Risk Categories (Factors)	5-yr Overall Survival
Low (0-1)	90/70	Low (0-1)	73
Intermediate (2)	77/50	Low Intermediate (2)	51
High (>3)	52/35	High Intermediate (3)	43
		High (4-5)	26
FLIPI = Follicular Lymphoma International Prognostic Index; IPI = International Prognostic Index; LDH = lactate dehydrogenase *The nodal categories are cervical, mediastinal, axillary, mesenteric, para-aortic, inguinal, epitrochlear, and poplit			



FLIPI



Philippe Solal-Céligny et al.
 Blood 2004;104: 1258-1265

FLIPI2

Follicular Lymphoma International Prognostic Index 2 (FLIPI2) Calculator

Prognostic score for untreated follicular lymphoma

Applies at the time of first treatment.

	Value	Points
Age (years)		0
Serum beta 2 microglobulin	-Please Select ▼	0
Bone marrow involvement	-Please Select ▼	0
Longest diameter of largest involved node (cm)		0
Hemoglobin (g/dL)		0
Sum of score		0
Risk category		LOW

1. Sum the number of risk factors to calculate FLIPI-2 score

Age:	< 60 years	60 years or older
Serum beta 2 microglobulin:	Normal	Raised
Bone marrow involvement:	Absent	Present
Longest diameter of largest involved node:	Less than 6 cm	6 cm or more
Hemoglobin:	12 g/dL or greater	< 12 g/dL

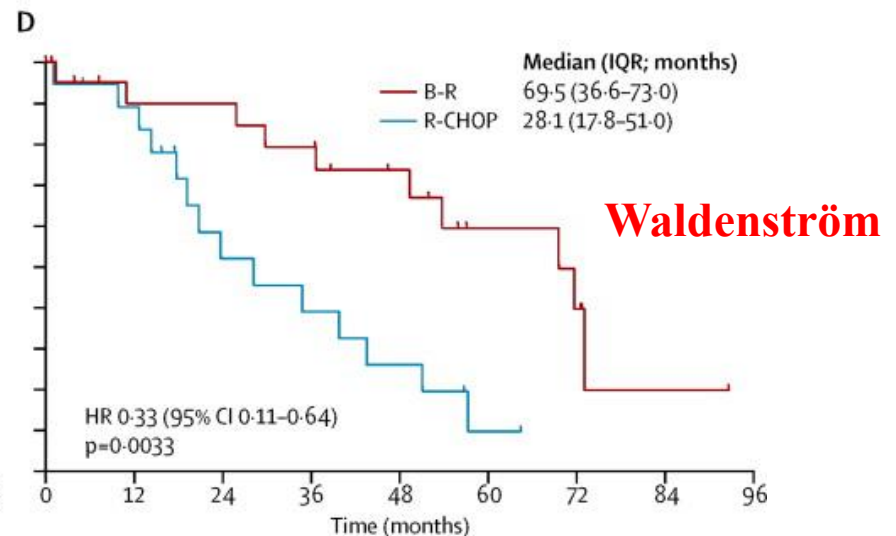
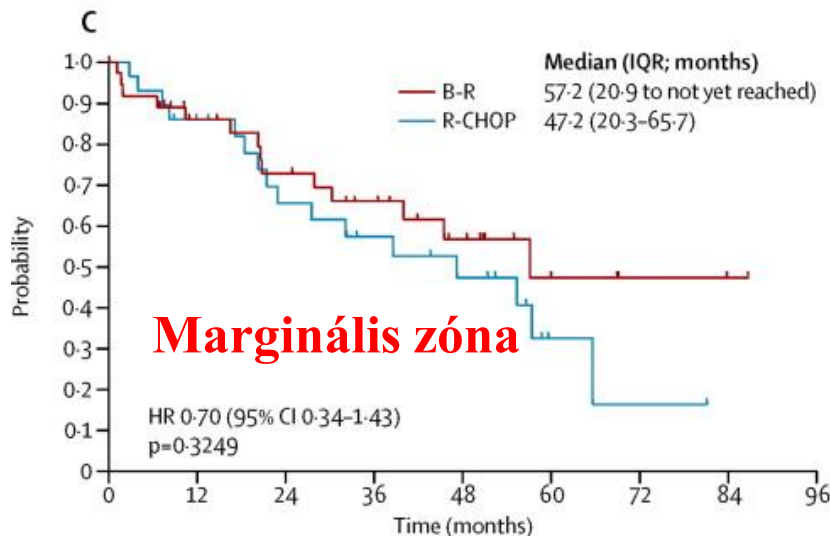
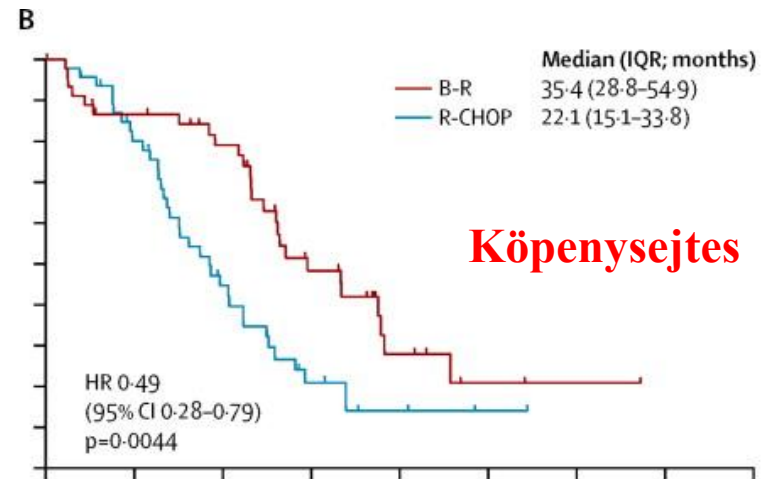
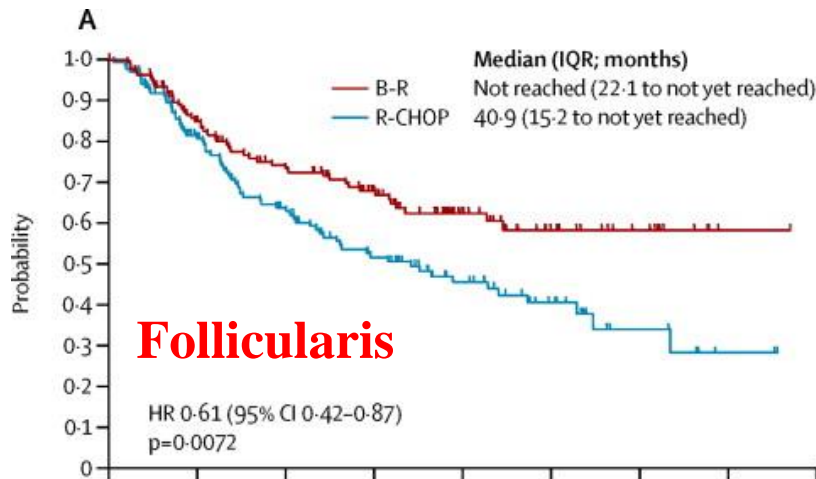
2. Determine risk category and prognosis

FLIPI-2 score	FLIPI-2 risk category	5 year PFS (%) ¹	5 year PFS (%)
0	Low risk	80	76
1 - 2	Intermediate risk	51	49
3 - 5	High risk	19	37

References

[Federico M, Bellei M, Marcheselli L, Luminari S, Lopez-Guillermo A, Vitolo U et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor p](#)

Rituximab-bendamustin vs rituximab-CHOP kis malignitású lymphomákban





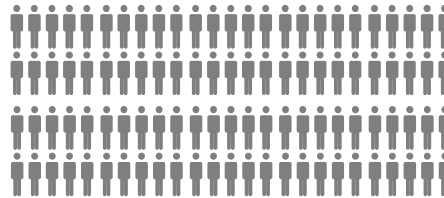
**COVID-19 idején ajánlás:
 bendamustinnal óvatosság!**

MJ Rummel Lancet 2013;381:1203-1210.

Az iNHL-s betegek egy része nem reagál a rituximab alapú kezelésre

For each 100 patients treated with R-chemotherapy in 1L

 1 relapse expected within 5 years
 >1 relapse expected within 5 years



10 refractory

45 progress within 5 years

45 have a response lasting >5 years



10 refractory to 1L treatment

22 refractory to 2L treatment

23 respond >2.5 years to 2L treatment

Most of these patients will eventually relapse

Treatment options for these patients are limited
Outcome following salvage treatment¹⁻³
 Median PFS <1 year
 Median OS <3 years

Median OS >5 years⁴

Can be retreated with R-chemotherapy
 Median OS >10 years

¹Kahl B, et al. Cancer 2010;116:106–14

²Horning SJ, et al. J Clin Oncol 2005;23:712–9

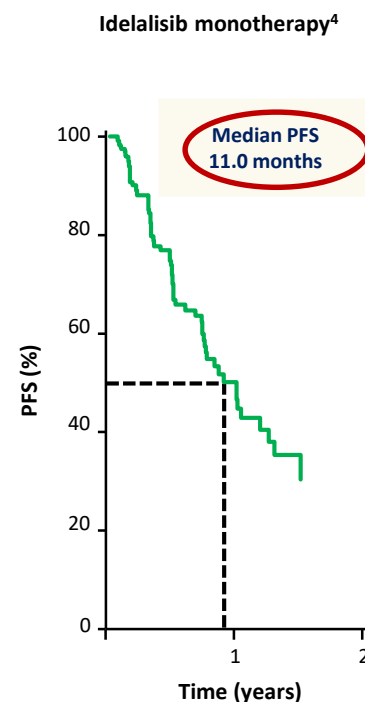
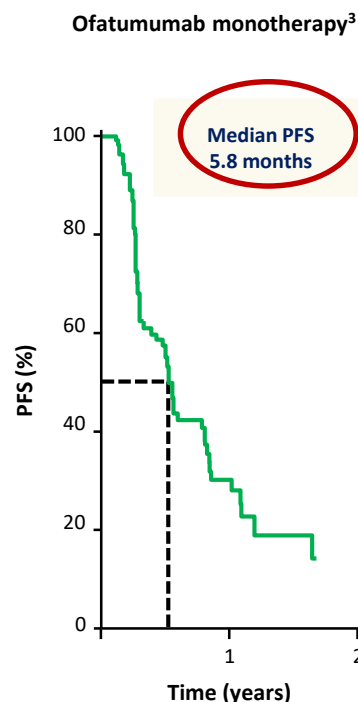
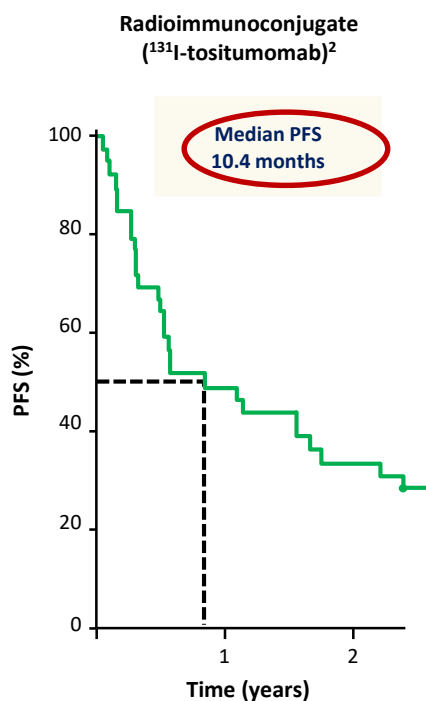
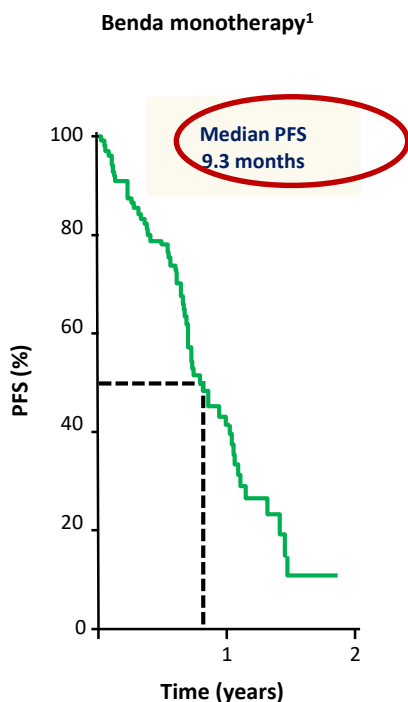
³Czuczman MS, et al. Blood 2012;119:3698–704

⁴Estimated from EORTC20981 trial: Van Oers MH, et al. J Clin Oncol 2010;28:2853–8

*Some of the patient numbers provided here have been estimated and extrapolated from multiple reference sources and may therefore not be wholly accurate
 1L, first-line; 2L, second-line; iNHL, indolent non-Hodgkin lymphoma;
 OS, overall survival; PFS, progression-free survival; R, MabThera

Jelenleg nincs meghatározott standard kezelés rituximab refrakter iNHL esetén

A refrakter betegek >50%-ánál a terápiás válasz <1 év



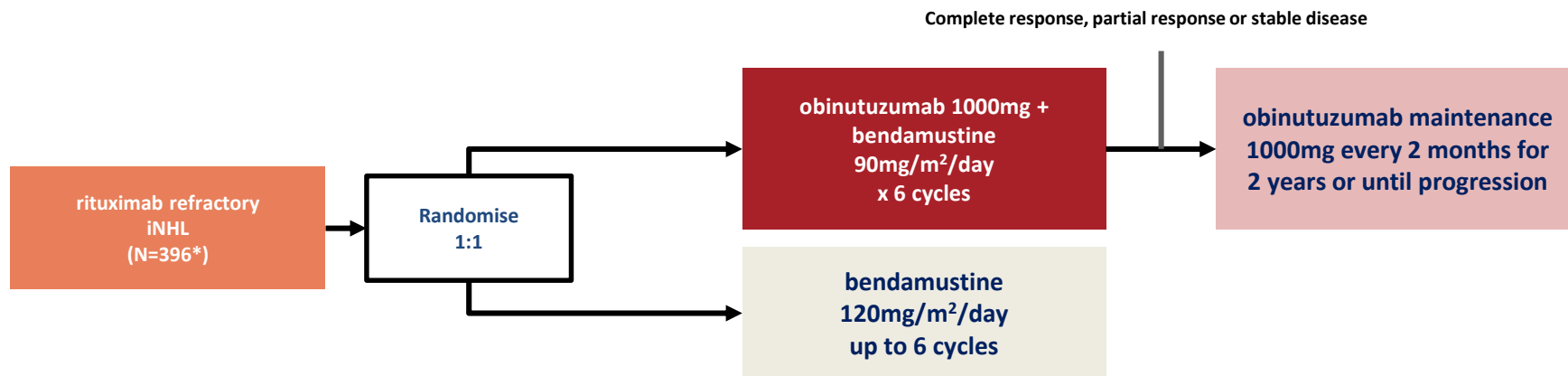
¹Kahl B, et al. Cancer 2010;116:106–14

²Horning SJ, et al. J Clin Oncol 2005;23:712–9

³Czuczman MS, et al. Blood 2012;119:3698–704

⁴Gopal AK, et al. N Engl J Med 2014;370:1008–18

GADOLIN: vizsgálati terv



Bendamustine: 120mg/m²/day or 90mg/m²/day on Days 1 and 2 of 6 x 28-day cycles
 GAZYVA: 1000mg on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycles 2–6 and every 2 months for up to 2 years

Primary endpoint	PFS as assessed by an IRC
Secondary endpoints	PFS as assessed by investigator, OS, BOR, ORR, CRR, DOR, EFS, DFS, safety, PK, pharmacoeconomics, PRO, MRD response (exploratory endpoint)
Safety plan	Early safety interim analysis conducted by a DSMB after 20 patients received Cycle 1 to evaluate for overt excess toxicity resulting in protocol modifications to be considered

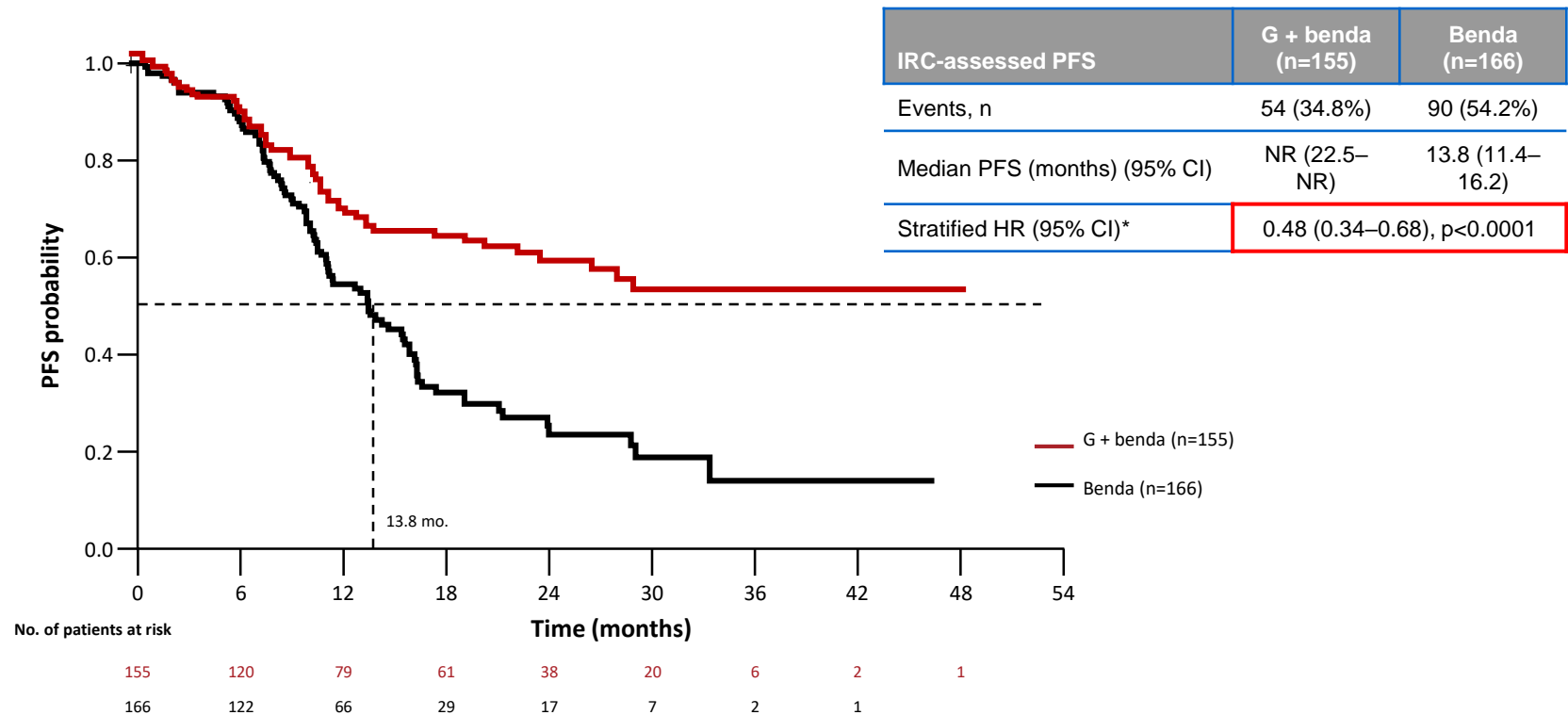
The bendamustine doses prescribed were as high as recommended for anti-CD20 combination therapy and monotherapy, respectively¹

¹Cheson B, et al. Clin Lymphoma Myeloma Leuk. 2010;10:21–7
 Sehn L, et al. Lancet Oncol. 2016;17(8):1081-93.
 Trněný M, et al. EHA June 2016. Oral presentation
 Sehn L, et al. ASCO May/June 2015. Oral presentation
 Sehn L, et al. EHA June 2015. Poster presentation
 Cheson B, et al. ICML June 2015. Oral presentation

*At the data analysis cut-off (1 September 2014) 396 patients were enrolled and randomised; 17 additional patients were enrolled after the cut-off and therefore were not included in the analysis
 BOR, best overall response; CRR, complete response rate; DFS, disease-free survival;
 DOR, duration of response; DSMB, data safety monitoring board; EFS, event-free survival;
 iNHL, indolent non-Hodgkin lymphoma; IRC, independent review committee;
 MRD, minimal residual disease; ORR, overall response rate; OS, overall survival;
 PFS, progression-free survival; PK, pharmacokinetic; PRO, patient-reported outcomes

52%-kal csökkent a progresszió kockázata G-benda kombinációval (FL)

Szignifikánsan javult a PFS G + benda kombinációval



*Stratification factors: refractory type (R vs R-chemo), prior therapies (≤2 vs >2)

Benda, bendamustine; CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio;

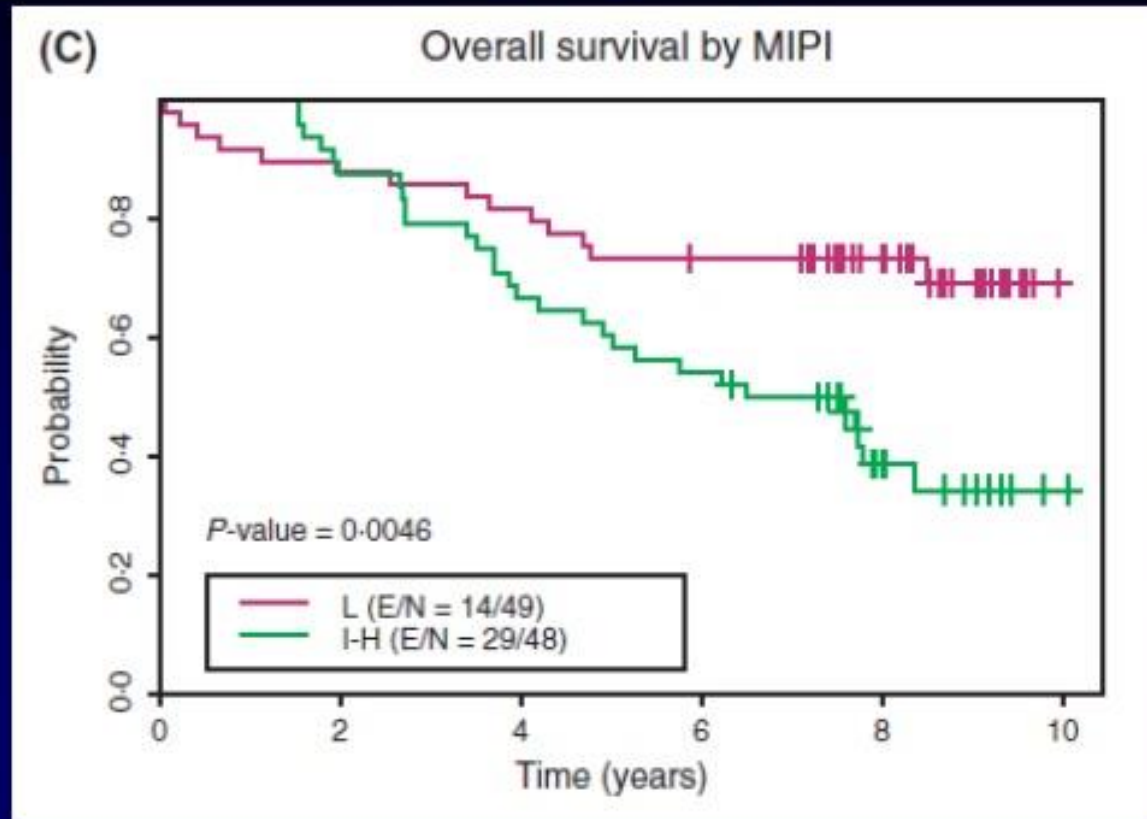
IRC, independent review committee; mo., months; NR, not reached; PFS, progression-free survival

Mantle cell international prognostic index (MIPI)

Pont	Kor (év)	PS	LDH	FVS (G/l)
0	<50	0-1	<0,67xnorm	<6,7
1	50-59		0,67-0,99xn	6,7-9,999
2	60-69	2-4	1-1,49xn	10-14
3	>70		>1,5xnorm	>15

Kis rizikó (0-3)	Átlag túlélés: „not yet reached”
Kp rizikó (4-5)	Átlag túlélés: 51 hó
Nagy rizikó (6-11)	Átlag túlélés: 29 hó

Overall Survival according to Mantle cell IPI (MIPI)



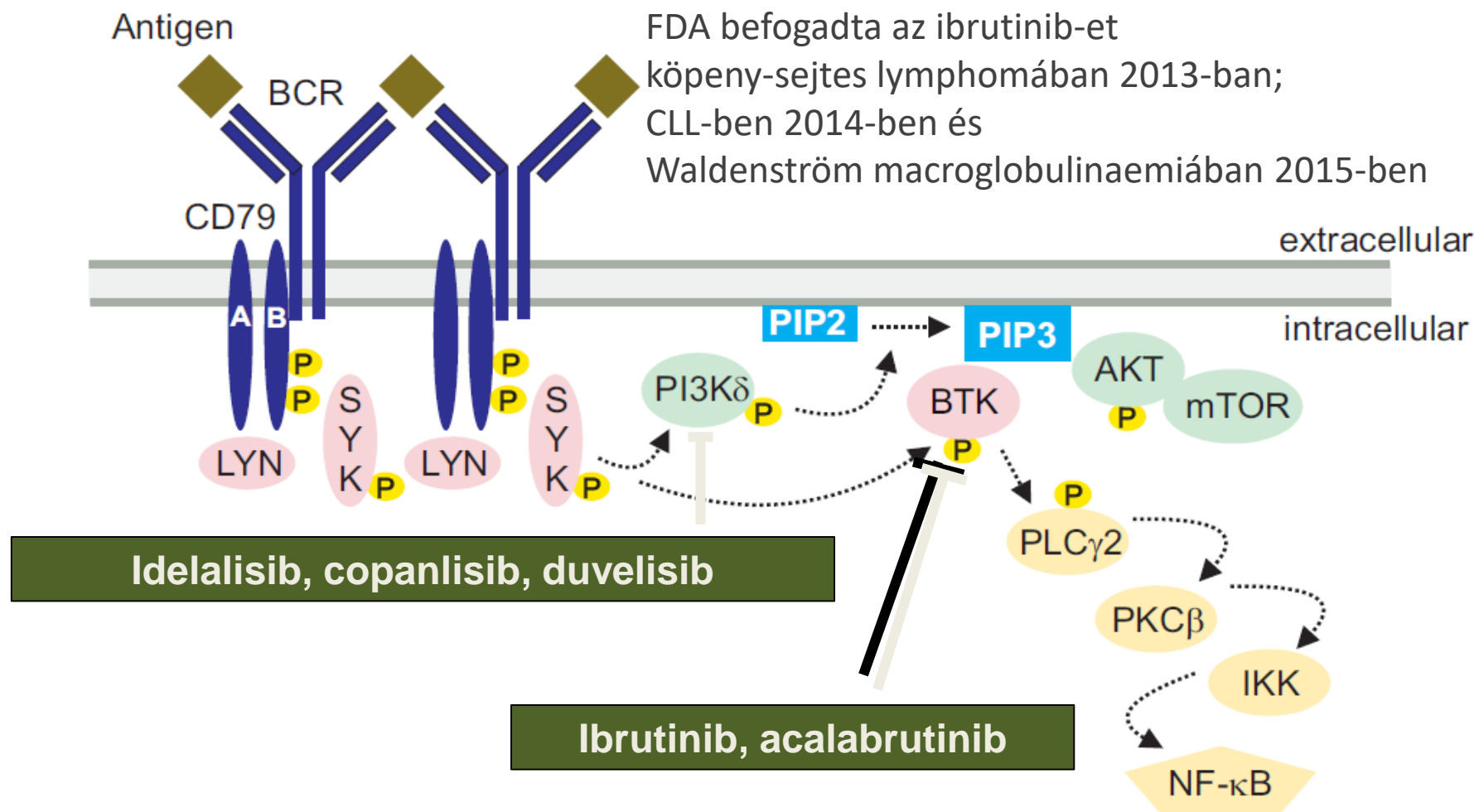
Romaguera et al, British J Heme, 2008

MCL
Kezelés:

Nordic MCL2 protocol: This consists of the administration of three cycles of rituximab-CHOP alternating with three cycles of high • doses of Ara-C, followed by ABMT with BEAM or BEAC .

Célzott Kináz gátlás BCR jelátvitelben

BCR: B-sejt receptor



Differenciáldiagnosztika B-sejtes kis malignitású lymphomában

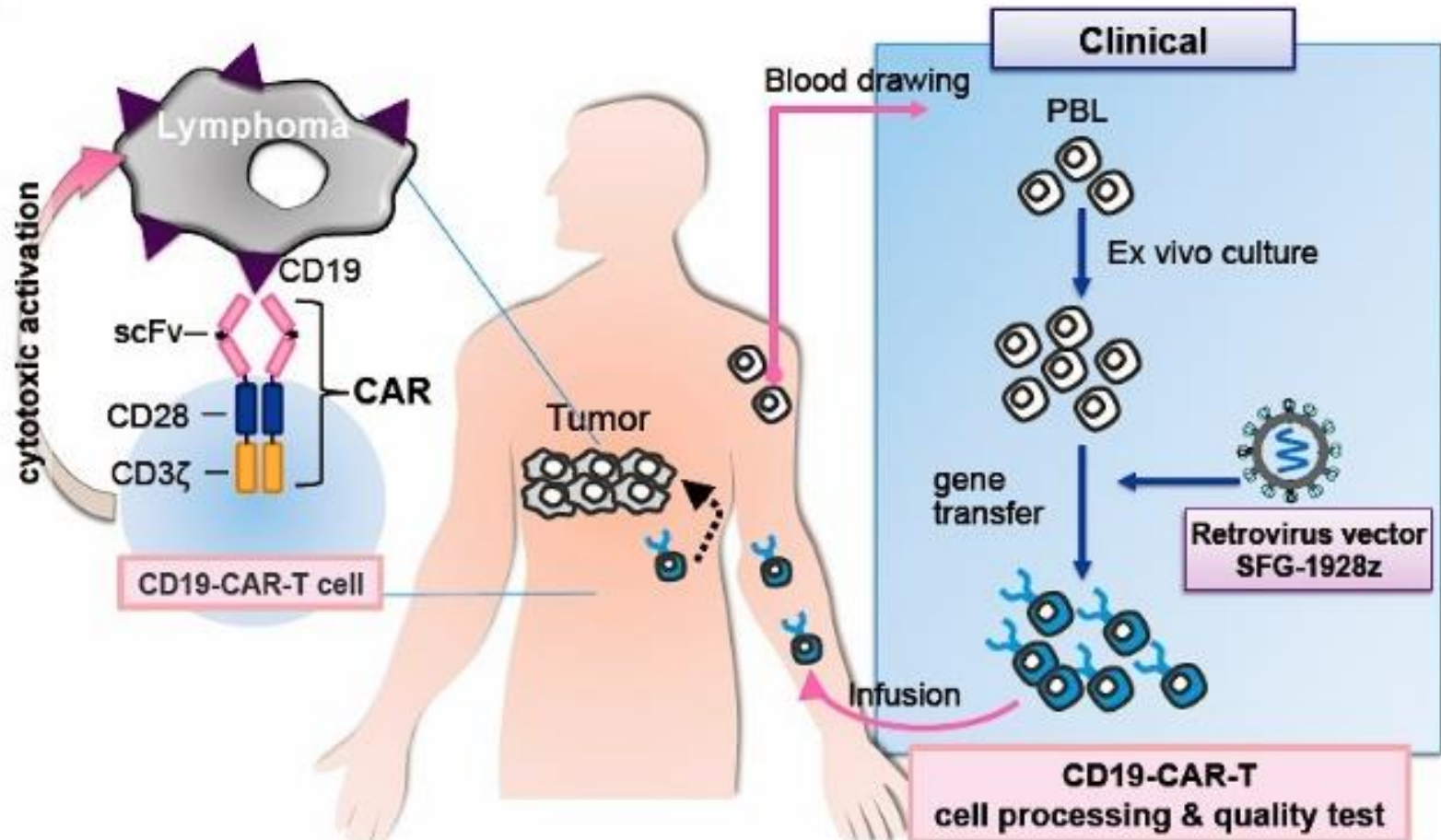
Immunophenotypic Fingerprint CD markers for Variety of B-cell Cancers

Cancer Type	Sig	CD5	CD19	CD20	CD10	CD11c	CD22	CD23	CD43	CD103	Cyclin D1
CLL/SLL	+	+	+	+	-	-	-	+	+	-	-
MCL	++	+	+	+	+/-	-	+	-	+	-	+
HCL	++	-	+	+	-	+	+	-	-	+	
LPL	++	-	+	+	-	-	+	-	-	-	-
SML	++	-	+	+	-	-	+	-	-	-	-
FCL	++	-	+	+	+	-	+	-	-	-	-

Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; MCL, mantle cell lymphoma; HCL, hairy cell leukemia; LPL, lymphoplasmacytic lymphoma; SML, splenic marginal zone lymphoma; FCL, follicular cell lymphoma.

<http://jco.ascopubs.org/cgi/reprint/26/8/1193>

Adoptive Immuno-Gene Therapy using CAR-T-cells for Refractory B Cell Non-Hodgkin Lymphoma



Chimera antigen receptor

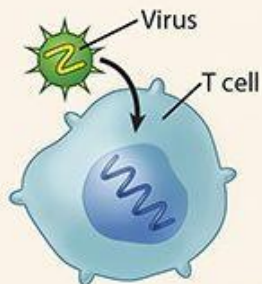
1 IN THE CLINIC
The white blood cells, including T cells, are separated out, and the rest of the blood is returned to the patient.

Blood is taken from the patient

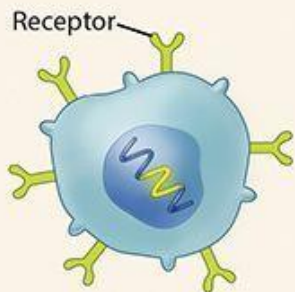
T cells are sent to the lab

Blood

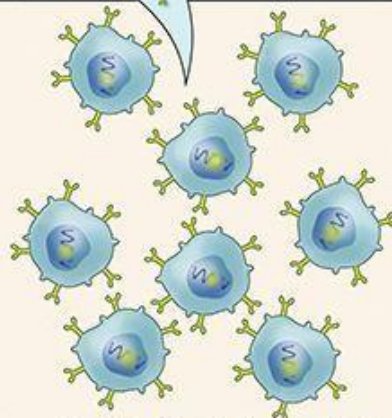
2 IN THE LAB/MANUFACTURING FACILITY
T cells are engineered to find and kill cancer cells.



An inactive virus is used to insert genes into the T cells.

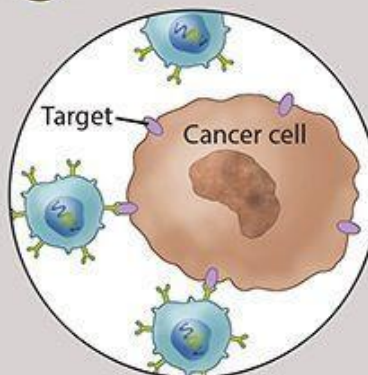


The genes cause the T cells to make special receptors, called CARs, on their surfaces.

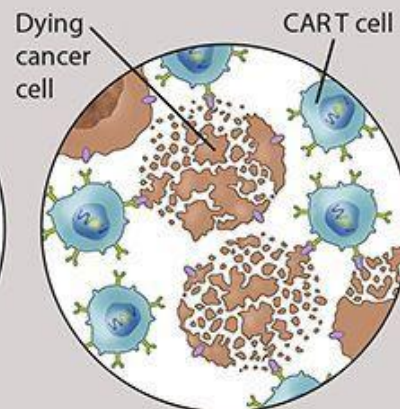


Modified T cells (now called CAR T cells) are multiplied until there are millions of these attacker cells.

4 IN THE BODY



The receptors are attracted to targets on the surface of the cancer cells.

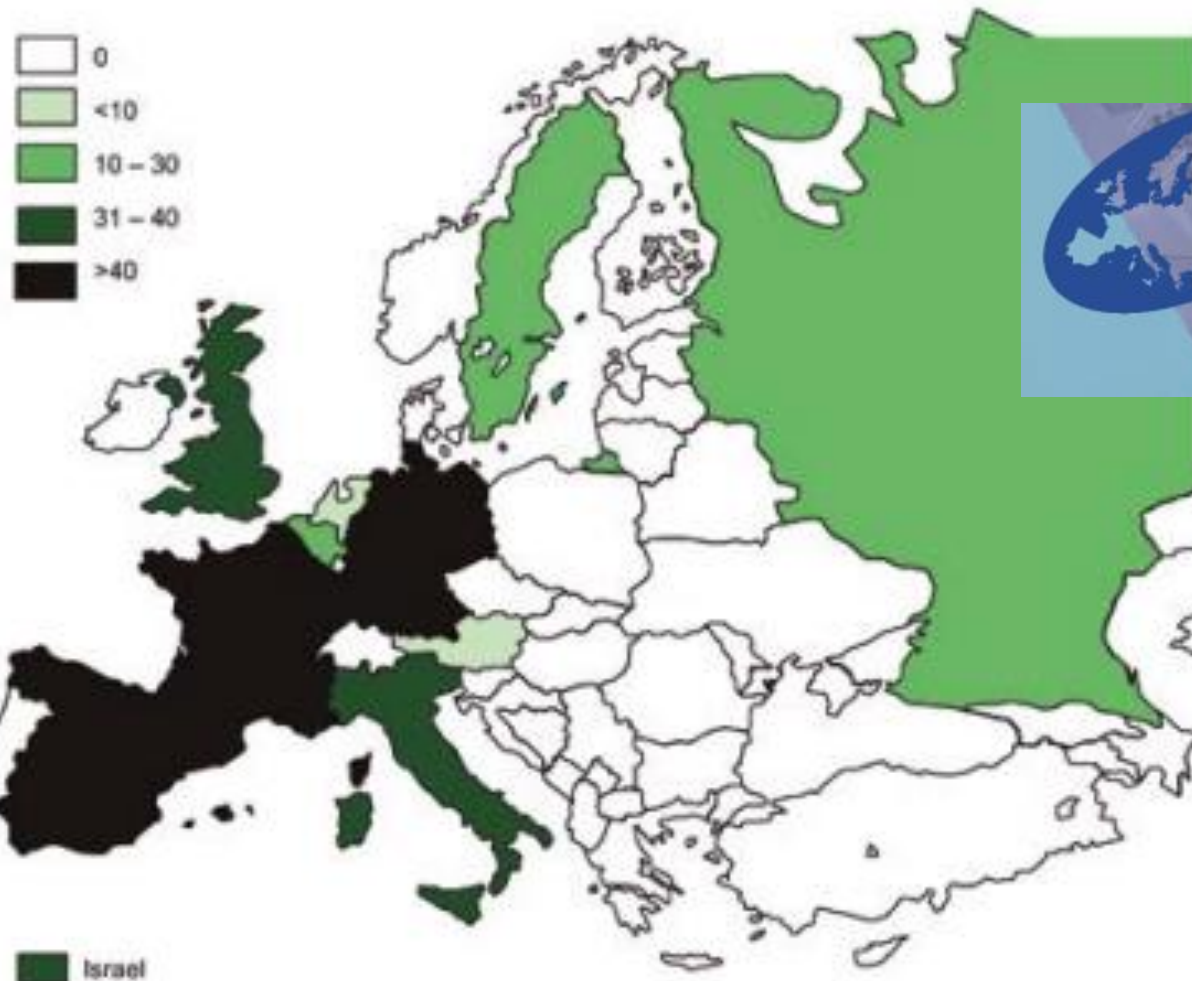
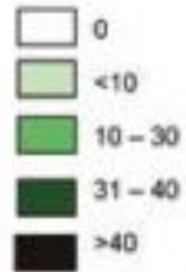


The CAR T cells identify the cancer cells with the target antigens, and kill them. CAR T cells may remain in the body for some time to help prevent the cancer cells from returning.

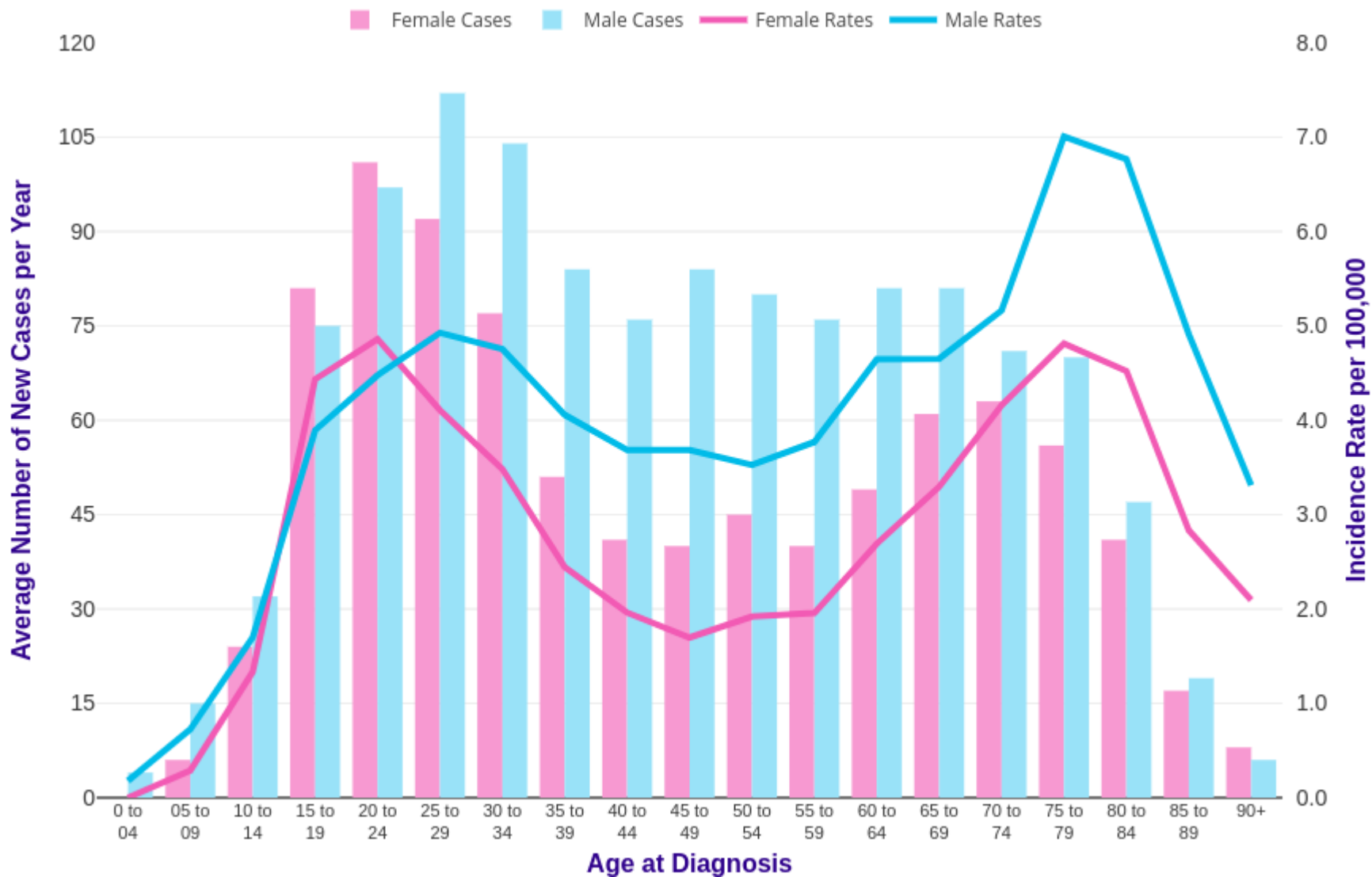
3 IN THE CLINIC
CAR T cells are put back into the patient's bloodstream, typically after chemotherapy is given to make space, and continue to multiply.

**CAR-T sejt
terápia**

ABSOLUTE NUMBERS OF PATIENTS RECEIVING CAR-T CELLULAR THERAPIES



Hodgkin lymphoma incidencia korcsoport szerint

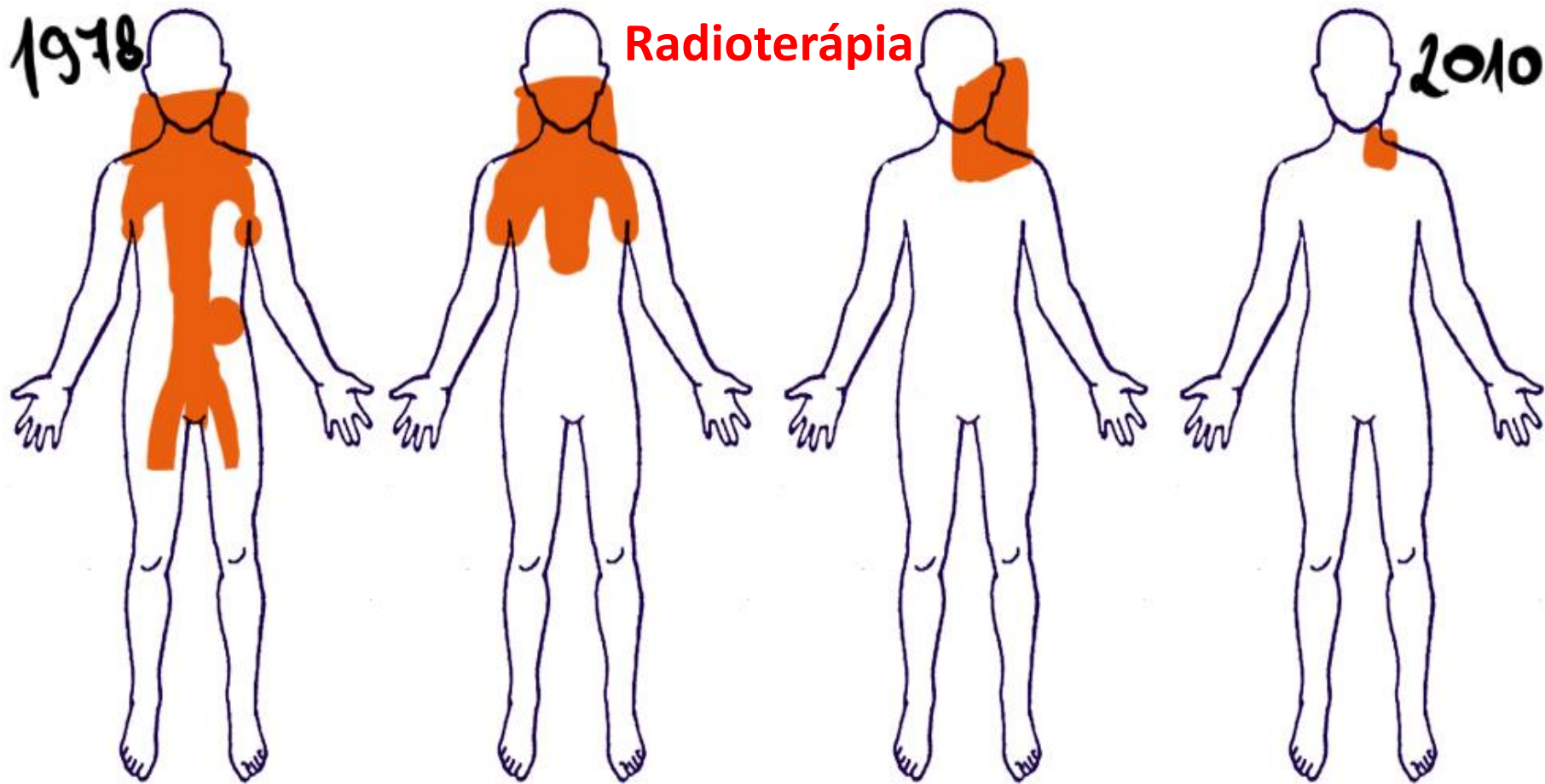


Kemoterápiás protokollok Hodgkin lymphomában

- MOPP, COPP, COPP-ABV hybrid
- **ABVD (leggyakrabban használt)**
 - **A**driamycin, **B**leomycin, **V**inblastine, **D**acarbazine
- BEACOPP
- Stanford V

Kezelési lehetőségek

- Kombinált kemoterápia és radioterápia bulky mediastinális masszára (kemot. majd érintett mezős irradiáció).
- Relapszus esetén salvage kemoterápia szükséges (DHAP).



Total nodal

Regional nodal

Involved field

Involved node

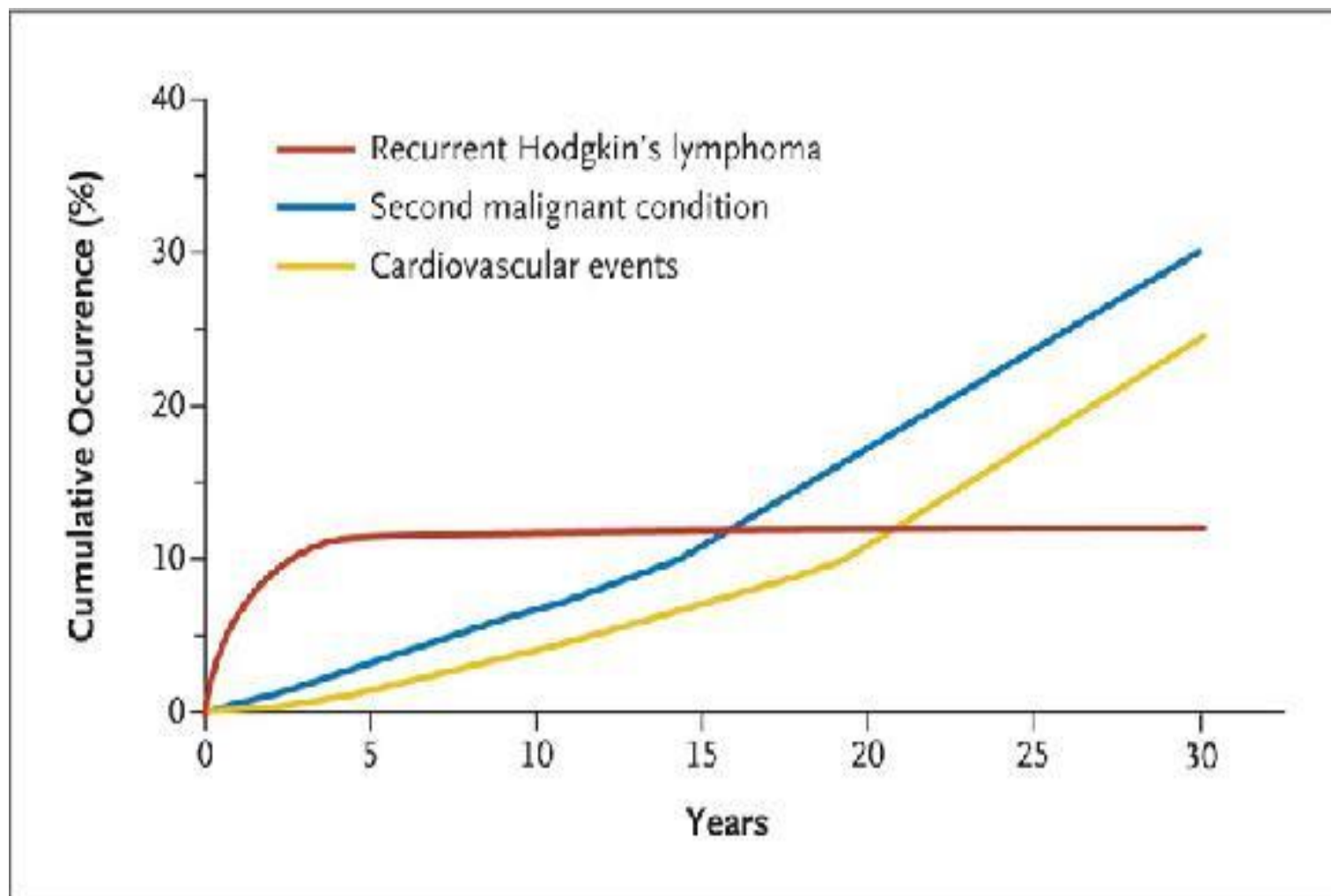
Dózis: 20-40 Gy



20 Gy \pm 10 Gy

Joachim Yahalom ábrája ASCO 2010

Késői szövődmények



NEJM 2010

Késői szövődmények Hodgkin lymphomában

- Magas incidencia második malignitásra
 - Első 10 évben leukémia, később solid tumorok.
- Leukémia, akik alkiláló szert vagy kombinált kemo/RT-t kaptak.
- Tüdő cc és emlő cc, akik mellkas besugárzást kaptak, főleg erős dohányosok.

További késői komplikációk

- Hypothyreoidismus nyak besugárzás után.
- Constrictive pericarditis mediastinum radioterápia után.
- Infertilitás alkiláló szerek után.
- Szívelégtelenség Adriamycin kezeléstől.

Új kezelések Hodgkin lymphomában

Monoklonális antitestek:

Anti-CD30: SGN30; MDX060; SGN35

Anti-CD30 + monomethyl auristatin E konjugátum

(szintetikus anti-microtubulus szer)

Anti-CD40: SGN-40 és HCD122

Anti-TRAIL-R1/R2 ± vorinostat, bortezomib

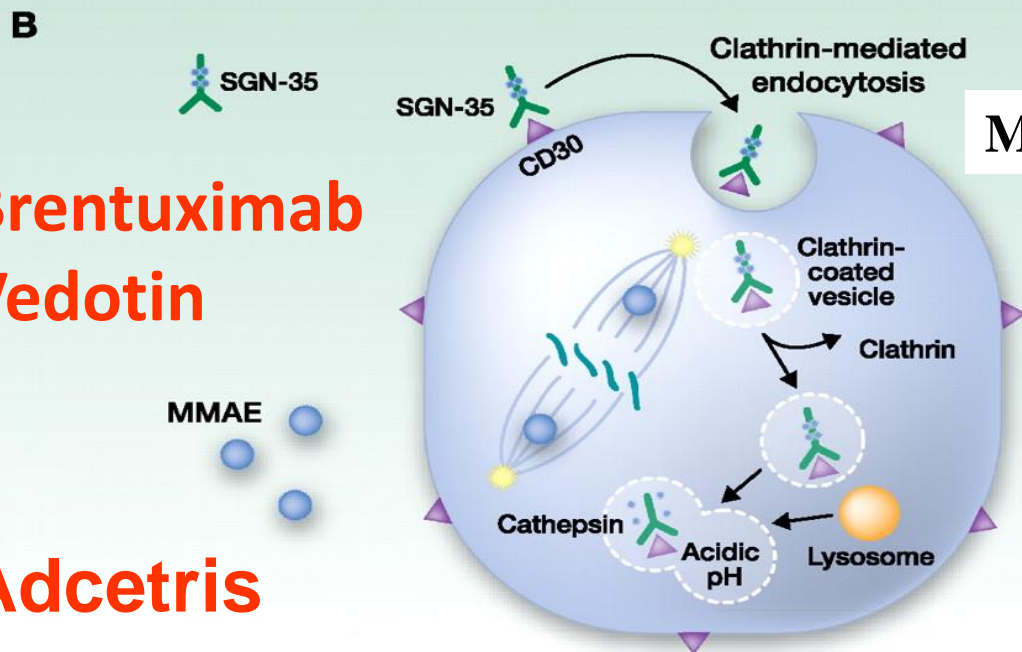
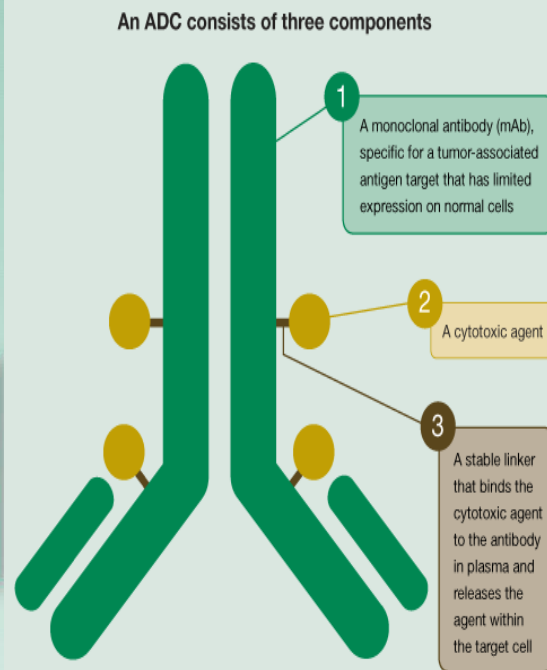
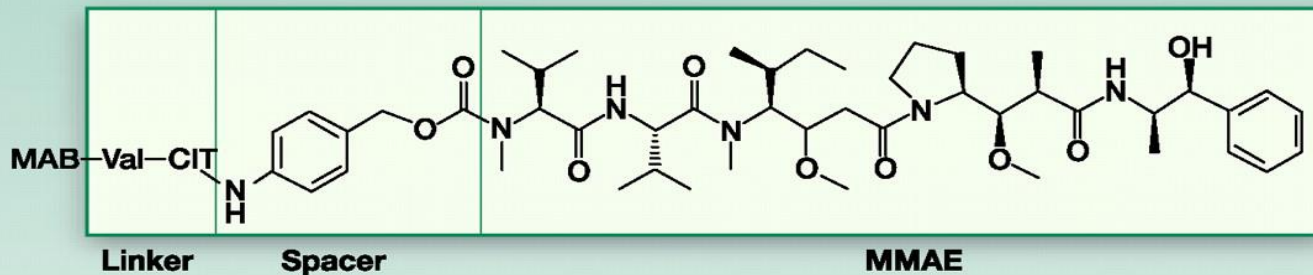
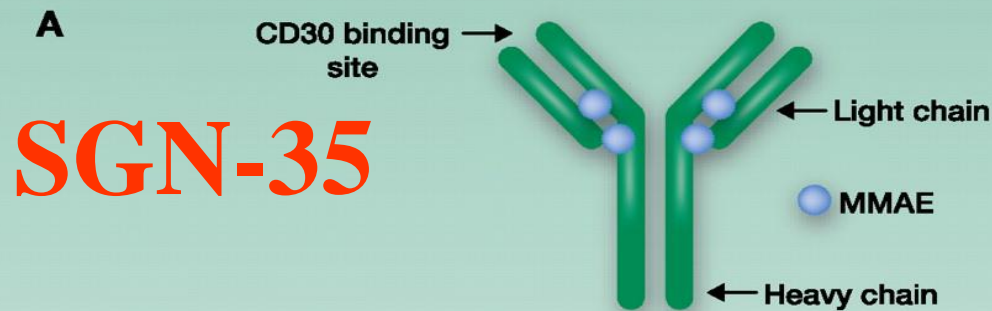
Anti-CD80 (galiximab)

Anti-IL-13 fully human monoclonalis antitest(TNX-650)

Histon deacetylase inhibitorok (I-IV. csoport): pan-deacetylase inhibitorok: Vorinostat, Belinostat, Romidepsine, Panobinostat, (MGCD-0103, Etenostat)

PI3K/Akt/mTOR NF-kappaB gátlás (bortezomib) Hő-sokk protein 90 Lenalinomid, Rituximab
(mikrokörnyezet gátlás)

Check-point gátlók



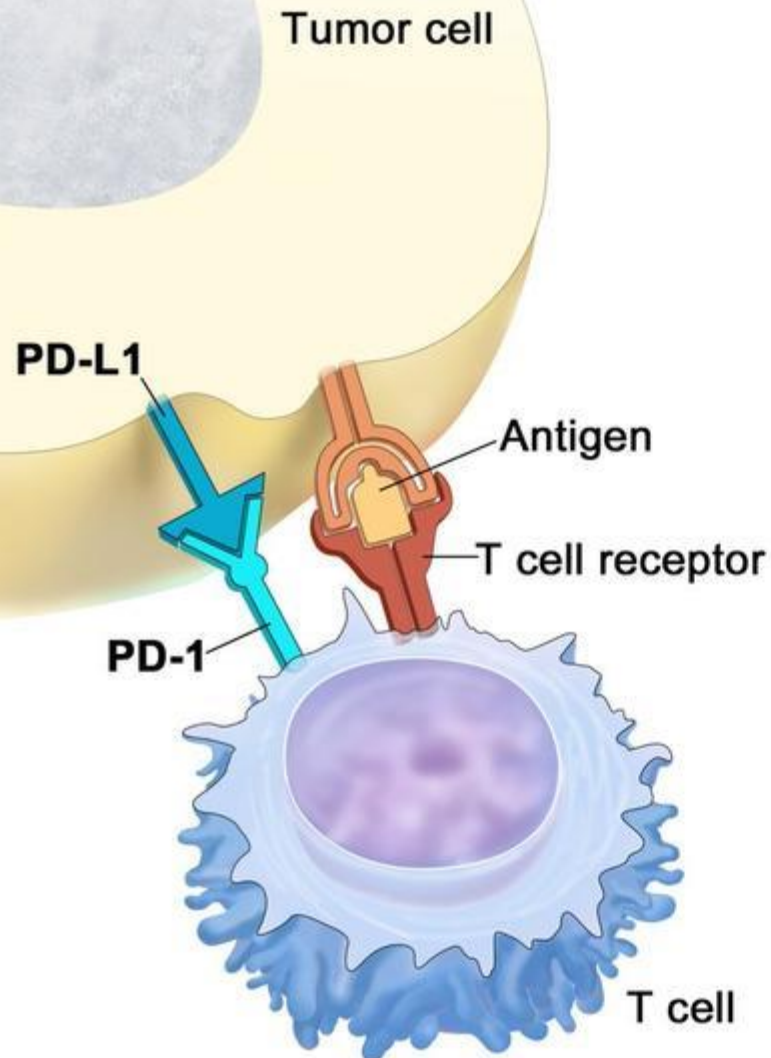
Monomethylauristatin E

Katz J et al. Clin Cancer Res 2011;17:6428-6436

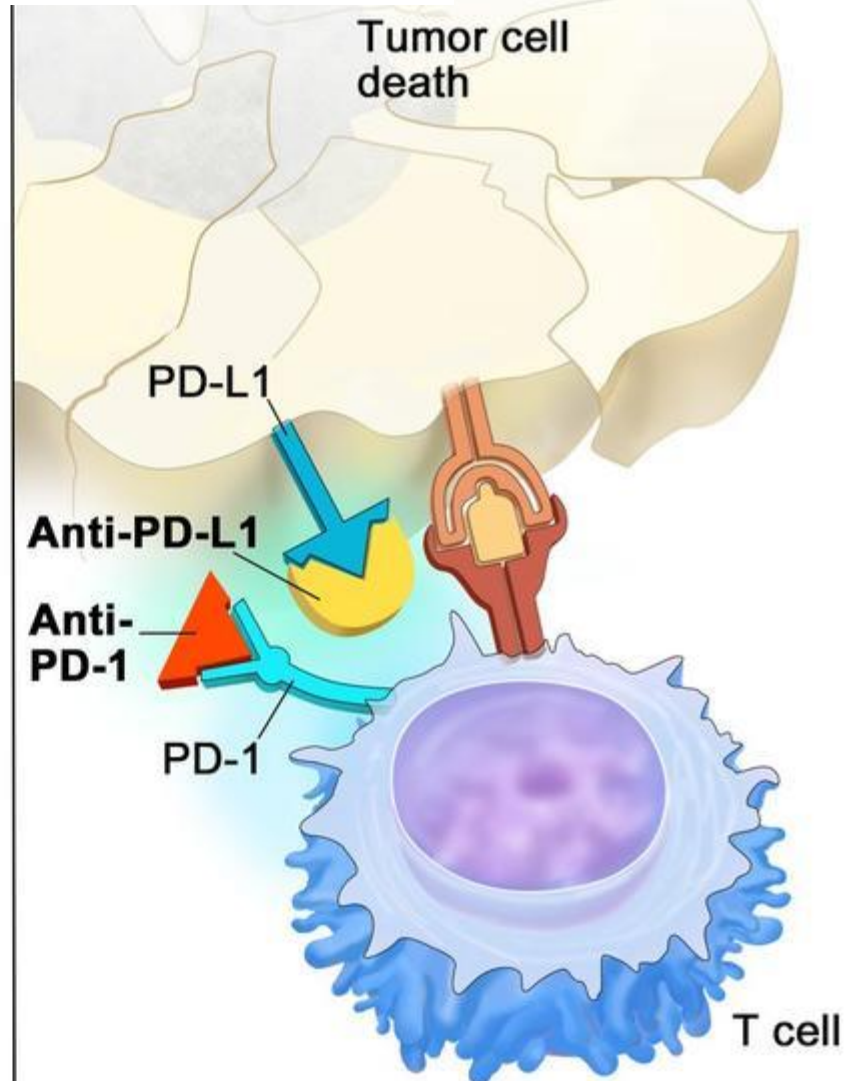
80-87 % ORR
ALCL-ben

PD-L1 binds to PD-1 and inhibits T cell killing of tumor cell

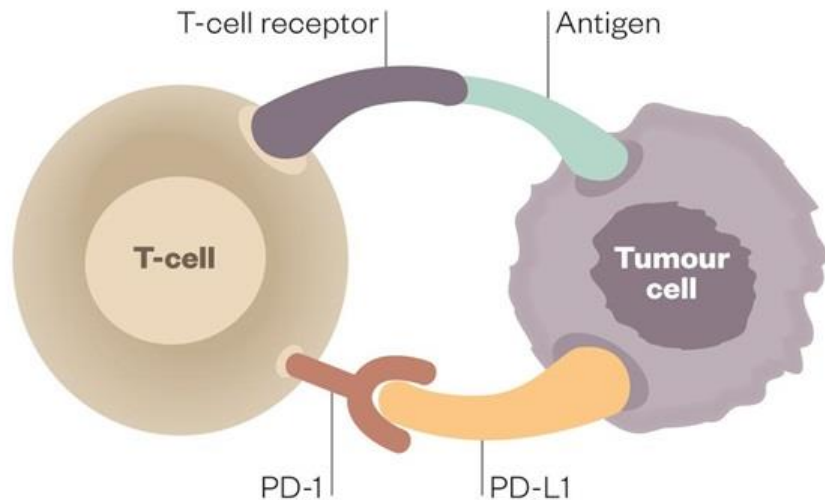
programmed-death receptor (PD-1)
programmed death-ligand 1 (PD-L1)



Blocking PD-L1 or PD-1 allows T cell killing of tumor cell



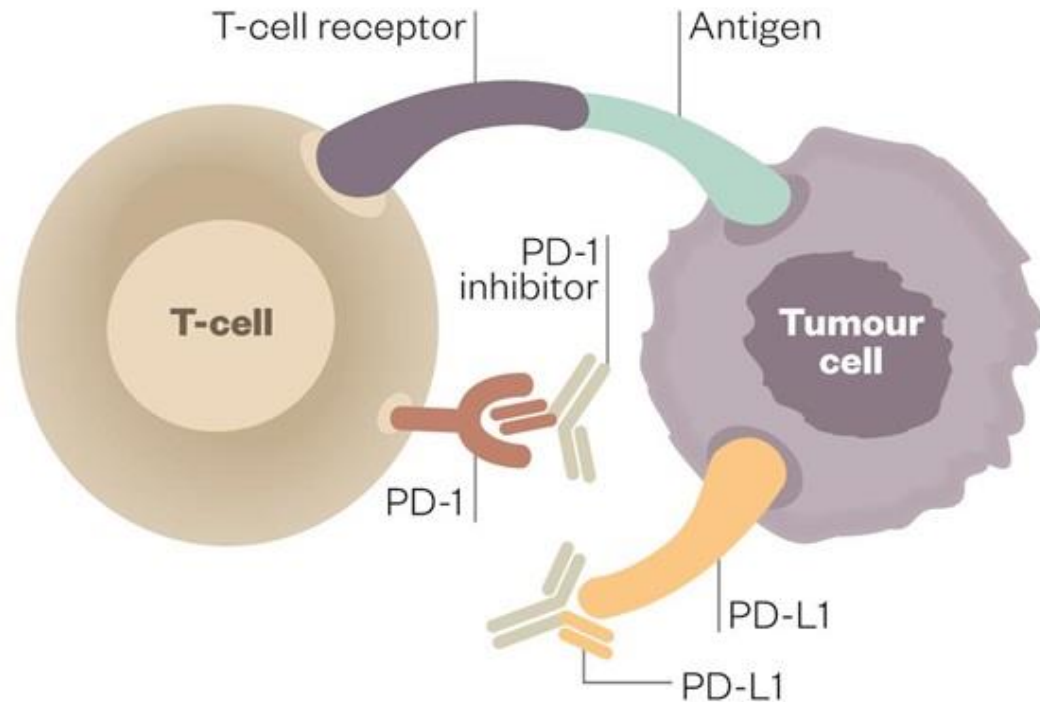
Checkpoint gátlók



Nivolumab, pembrolizumab

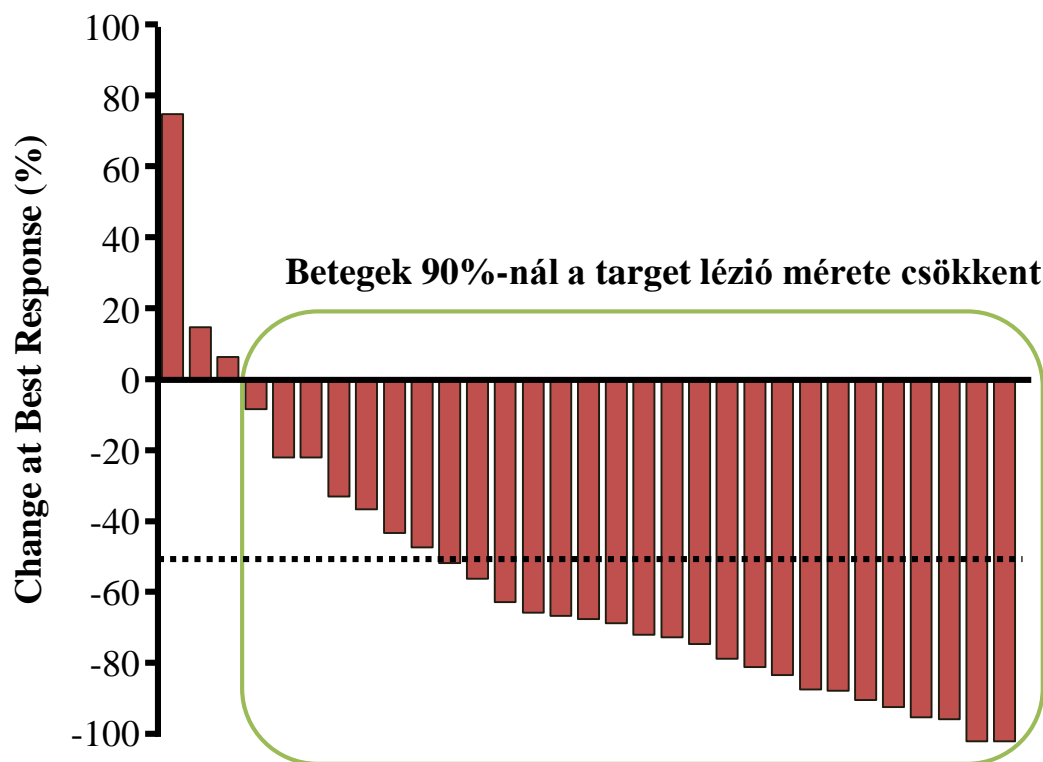
Guha M. The Pharmaceutical
Journal 2014;293: DOI:
10.1211/PJ.2014.20067127

programmed-death receptor
(PD-1) és programmed death-
ligand 1 (PD-L1)



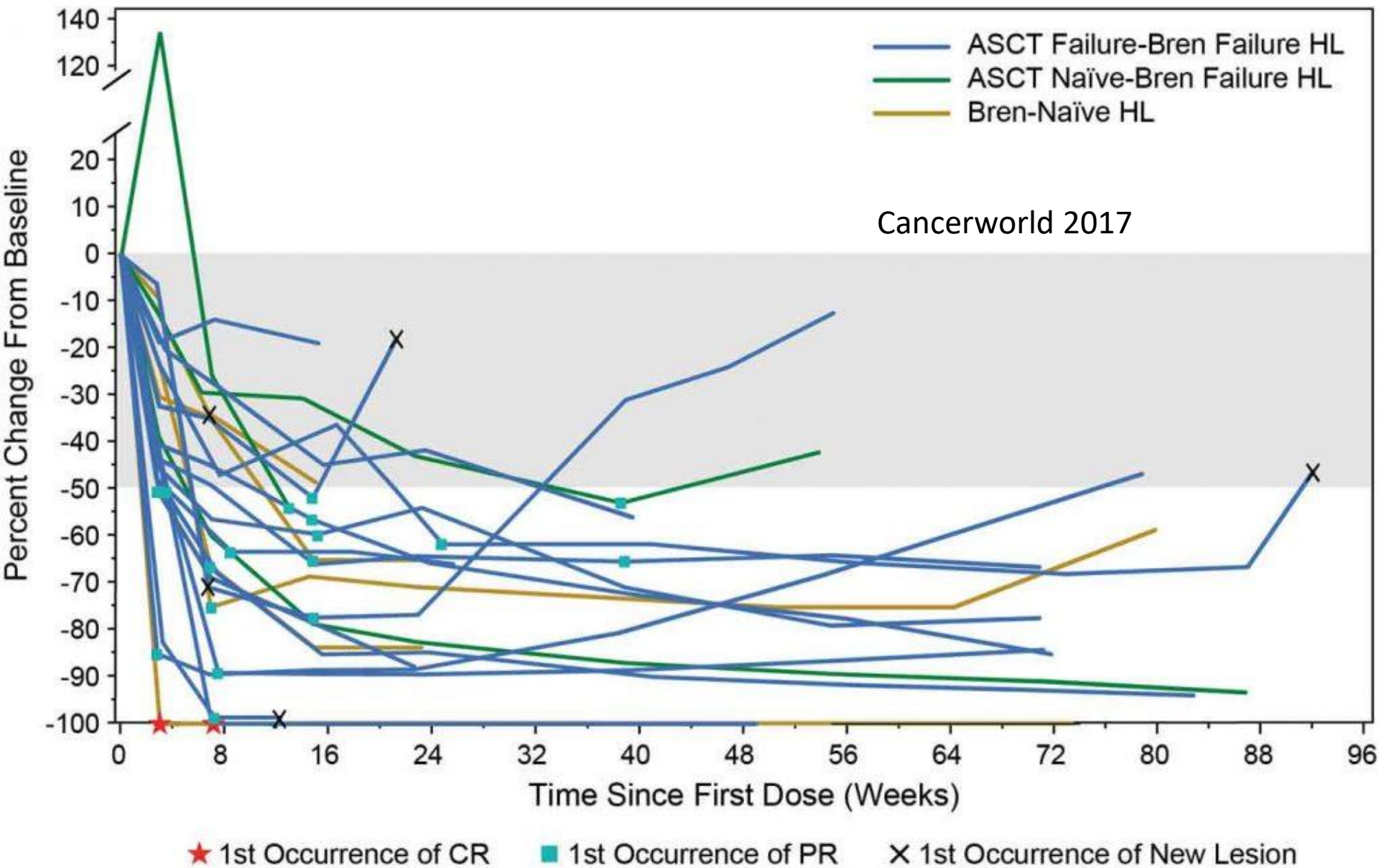
KEYNOTE-013 tanulmány: Válasz

Pemrolizumab 10 mg/kg heti 2x, ha brentuximab nem hatásos

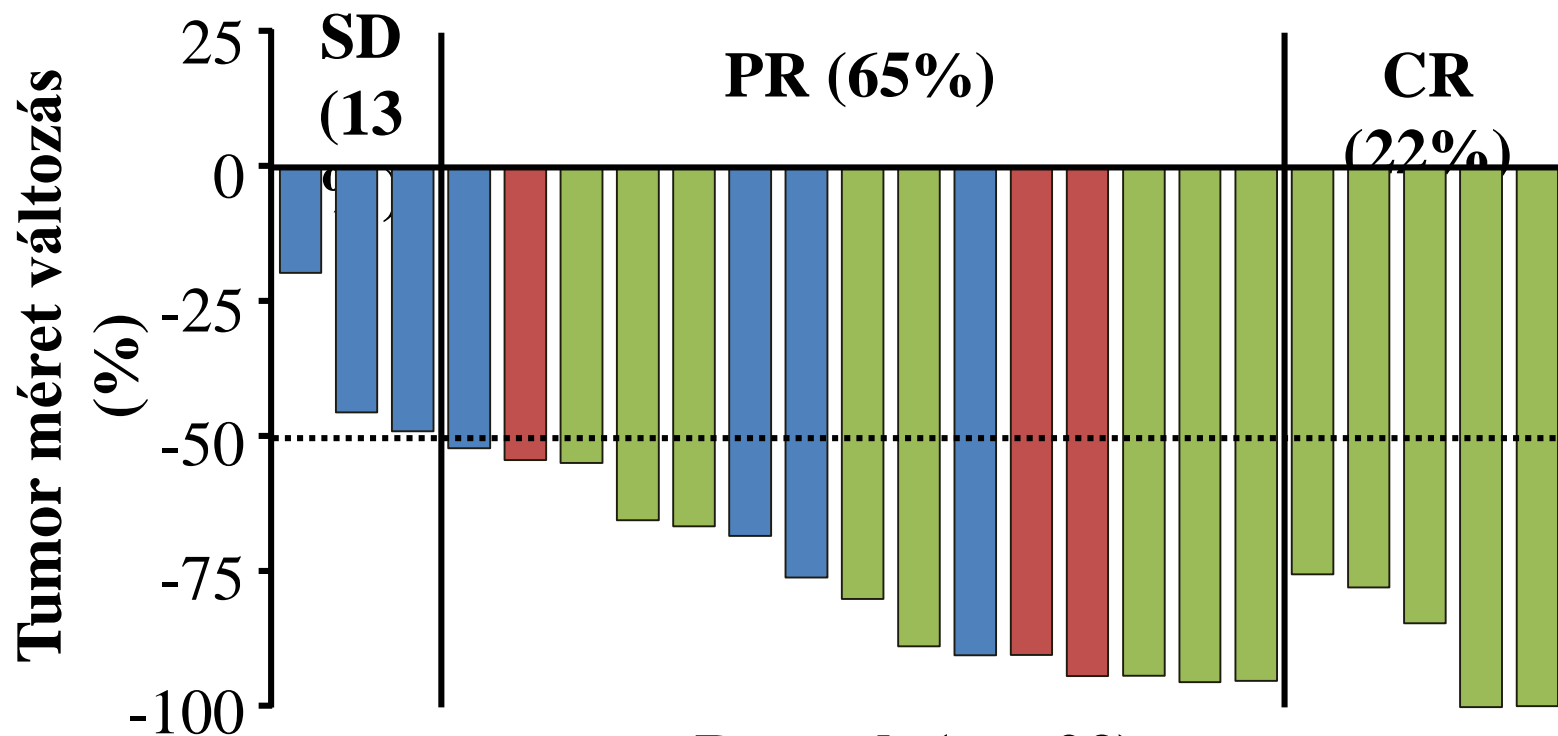


- ORR (n = 31): 65%
 - CR: 16%

Nivolumab hatásosság Hodgkin lymphomában



Nivolumab: refrakter, relabáló cHL: Legjobb válasz



- On treatment, ongoing response
- Off treatment without disease progression
- PD, following response or SD

Prognosztikus faktorok	5 éves túlélés	10 éves túlélés
I. Csoport 0 adverz faktor	62,3 %	54,9 %
II. Csoport 1 adverz faktor	52,9 %	38,8 %
III. Csoport 2 adverz faktor	32,9 %	18,0 %
IV. Csoport 3 v.4 adverz faktor	18,3 %	12,6 %

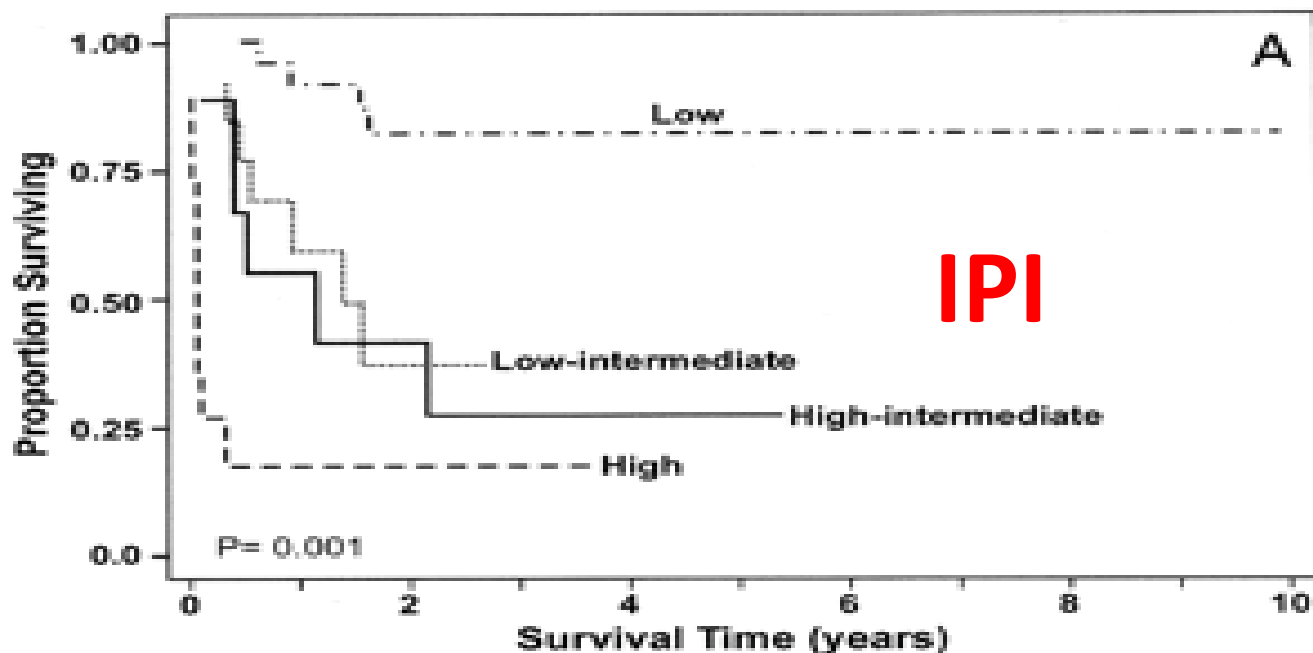
Kedvezőtlen faktorok:

385 beteg alapján **T-sejtes
lymphoma**

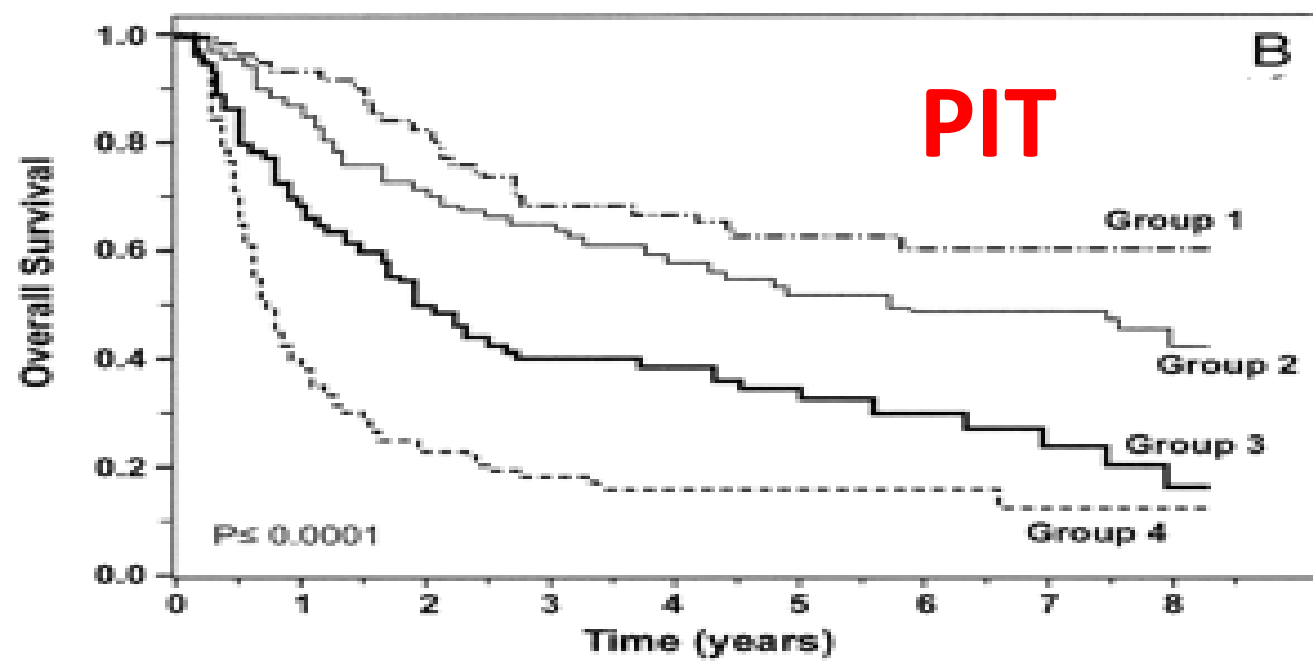
kor > 60 év; PS ≥2; LDH>normális; csontvelő érintettség.

PIT

Gallamini A. Blood 2004; 103: 2474-2479.

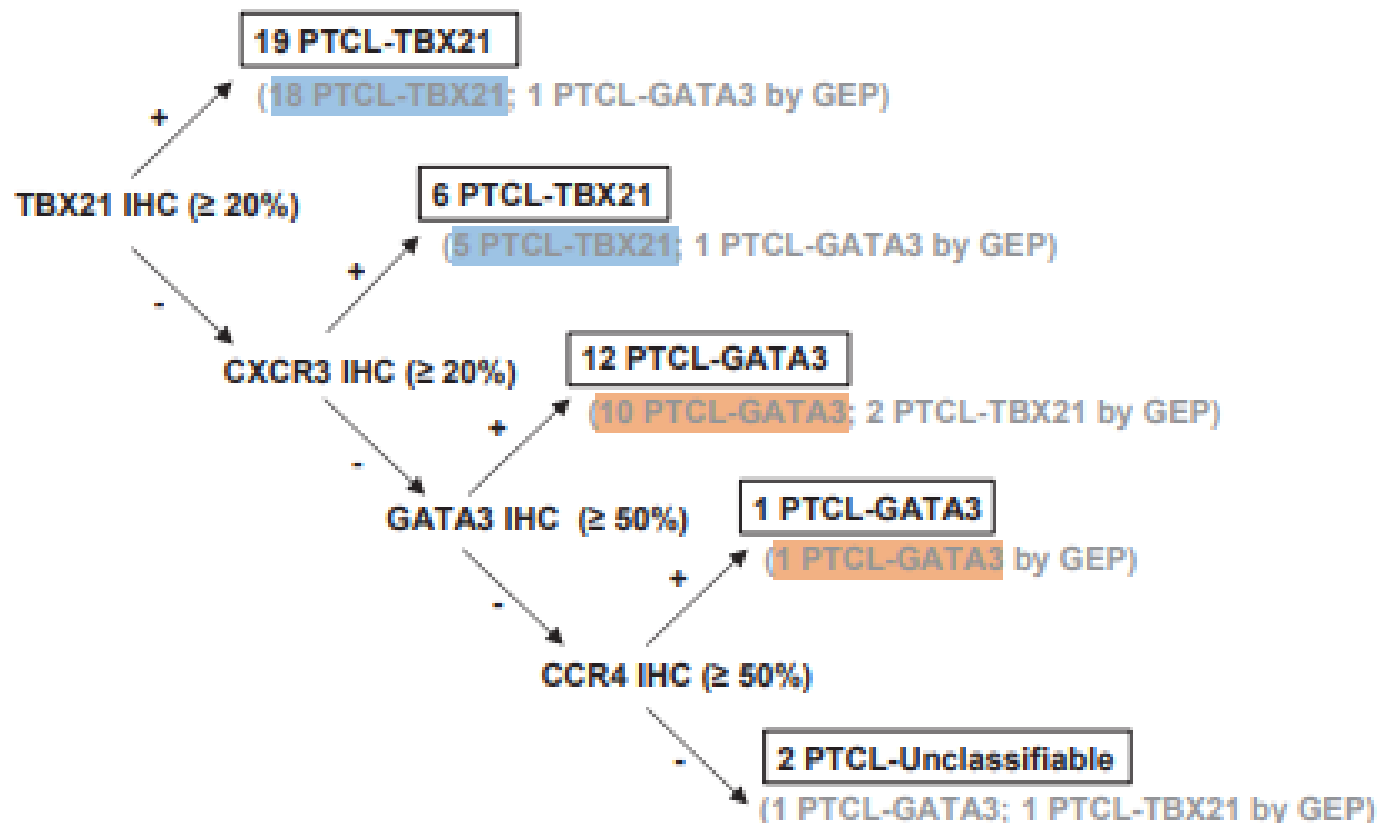


**Összesített
túlélés
PTCL-ben**



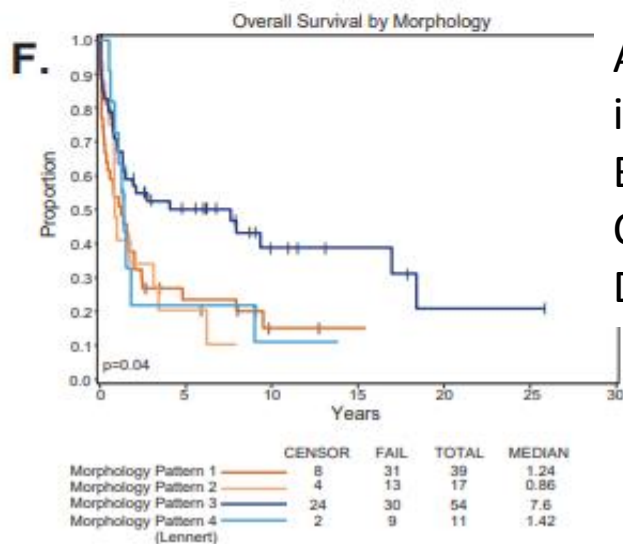
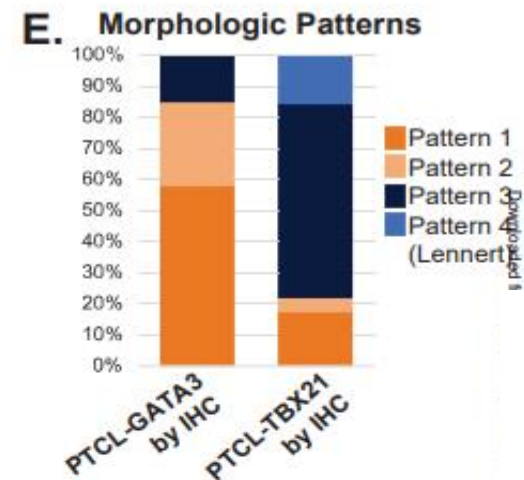
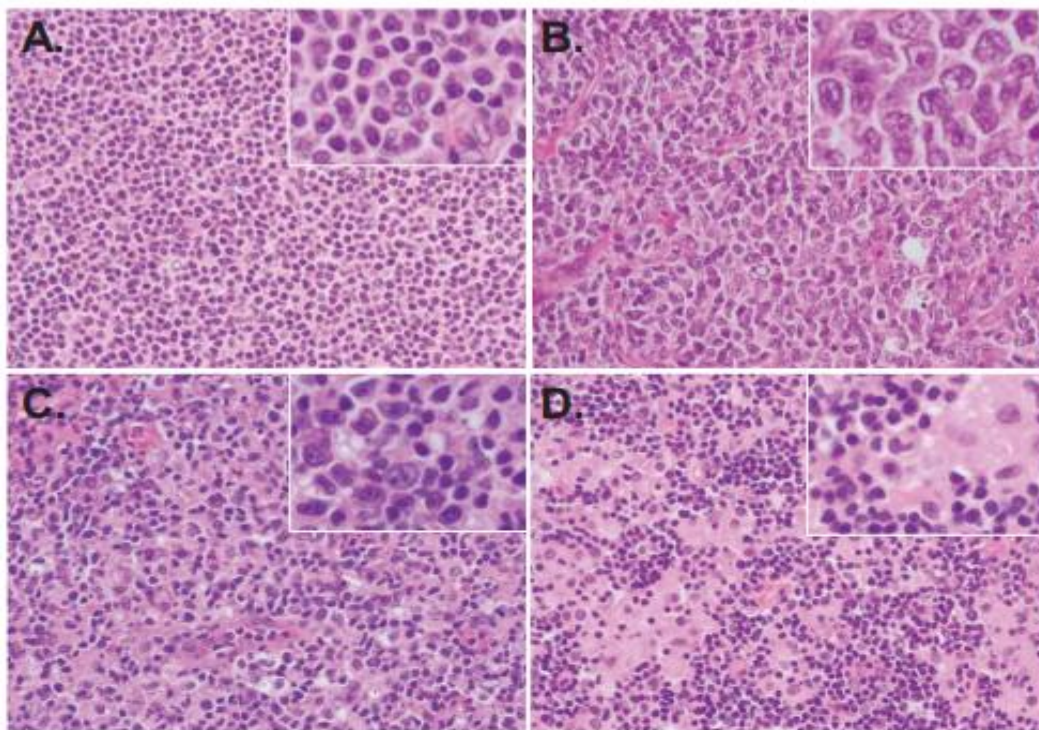
Gallamini A. Blood.
2004;103:2474–2479

IHC algoritmus PTCL-NOS-ban



[Amador C. Blood](#). 2019. szept. 27. pii: blood.2019000779. doi: 10.1182/blood.2019000779.

	PTCL-TBX21 by GEP (n=26)	PTCL-GATA3 by GEP (n=14)	PTCL-UNC by GEP (n=9)
PTCL-TBX21 by IHC	23 (88%)	2 (14%)	6 (67%)
PTCL-GATA3 by IHC	2 (8%)	11 (79%)	2 (22%)
Unclassified by IHC	1 (4%)	1 (7%)	1 (11%)



A: monomorf, tumorsejt gazdag GATA3, minimális inflammatórikus háttér

B: csoportosan nagy sejtek – pattern 2

C: polymorph, kevert inflammatórikus háttér pattern 3

D: lymphohistiocytás (Lennert) – pattern 4

[Amador C. Blood](#). 2019.szept. 27. pii:
blood.2019000779. doi:
10.1182/blood.2019000779.

Való-világ adatok anthracyclin bázisú kezelést követő túlélésről perifériás T-sejtes lymphomában

Subgroup	ITLP ^a		Swedish ^b	
	5-y PFS	5-y OS	5-y PFS	5-y OS
ALK-positive ALCL	60%	70%	63%	79%
ALK-negative ALCL	36%	49%	31%	38%
PTCL-NOS	20%	32%	21%	28%
AITL	18%	32%	20%	31%

a. Vose J, et al. *J Clin Oncol*. 2008;26:4124-4130.^[3]

b. Ellin F, et al. *Blood*. 2014;1570-1577.^[7]

Ajánlások PTCL primer kezelésére

NCCN (2015)^a

ALK+ ALCL	CHOP21
	CHOEP21 ←
ALK- ALCL	CHOEP21 ←
PTCL-NOS	CHOP14
AITL	CHOP21
	DA-EPOCH
	HyperCVAD

Consider consolidative HDC/SCT
(exception ALK+ or IPI 0 or 1)

ESMO (2013)^b

ALCL	}	CHOP21
PTCL-NOS		CHOEP21 ←
AITL		'CHOP-like'

Consider consolidative HDC/ASCT if IPI/PIT = 2 or higher and if PR or CR after induction

SIE-SIES-GITMO (2014)^c

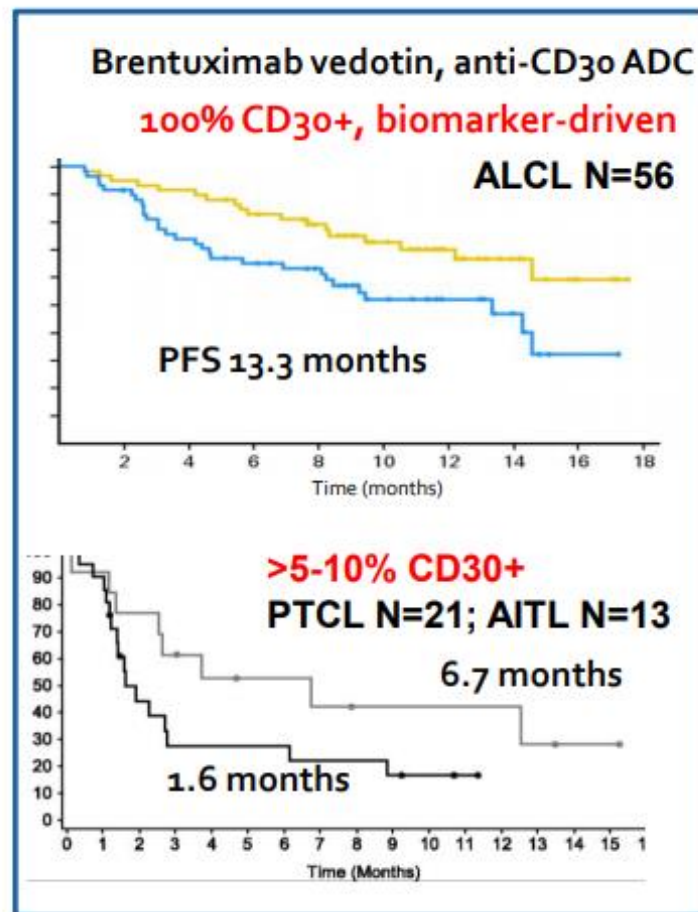
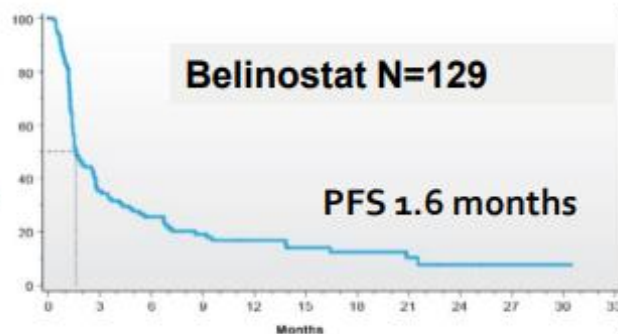
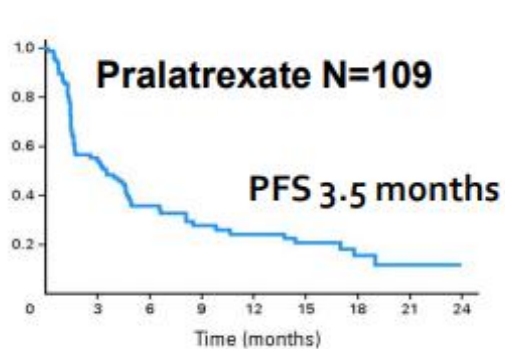
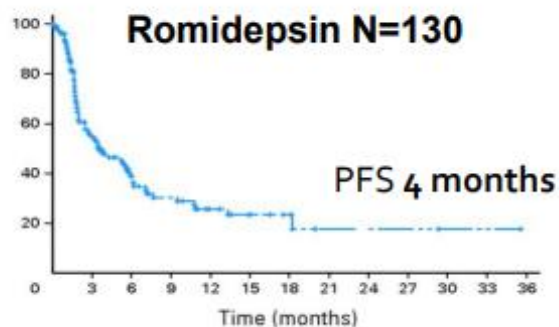
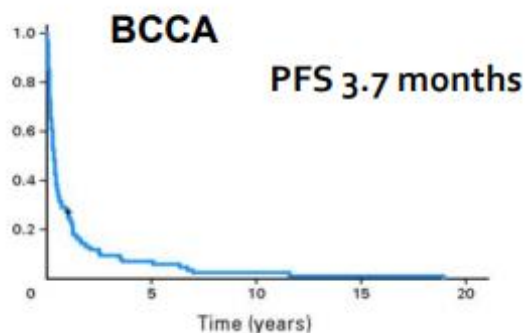
ALK+ ALCL IPI 0-2	CHOP/CHOEP	
≤ 65 y	} Gruppo Italiano Trapianto di Midollo Osseo	
ALCL		CHOP21
PTCL-NOS		CHOEP21 ←
AITL		

Recommend consolidative ASCT for all
(include ALK+ IPI = 3 or higher)

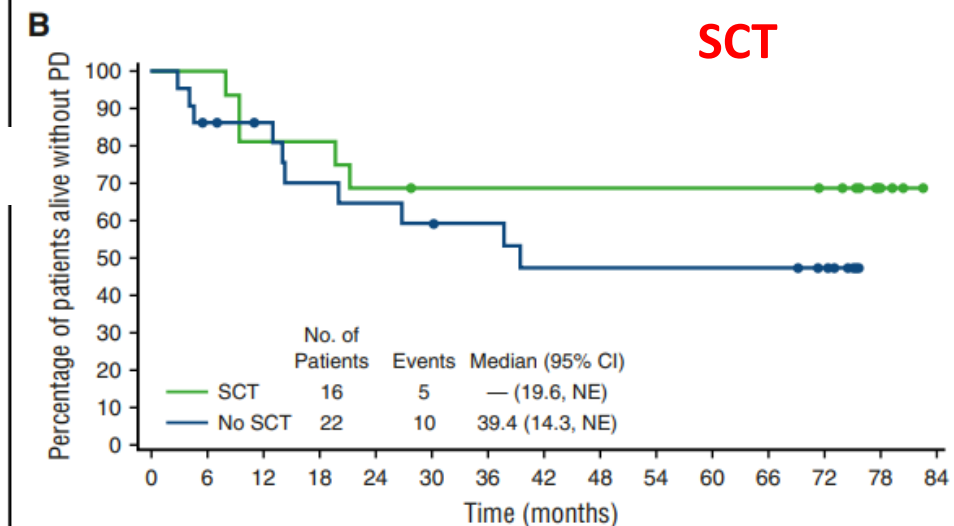
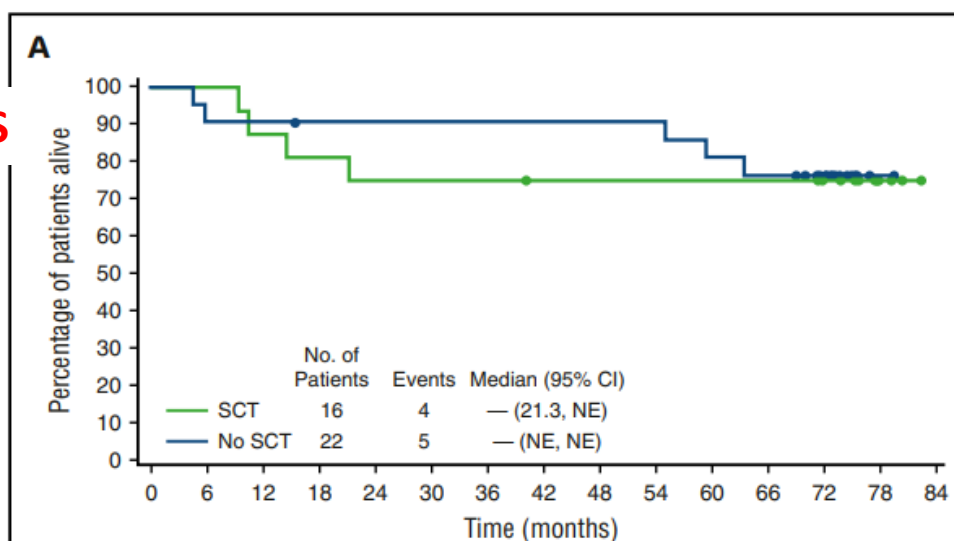
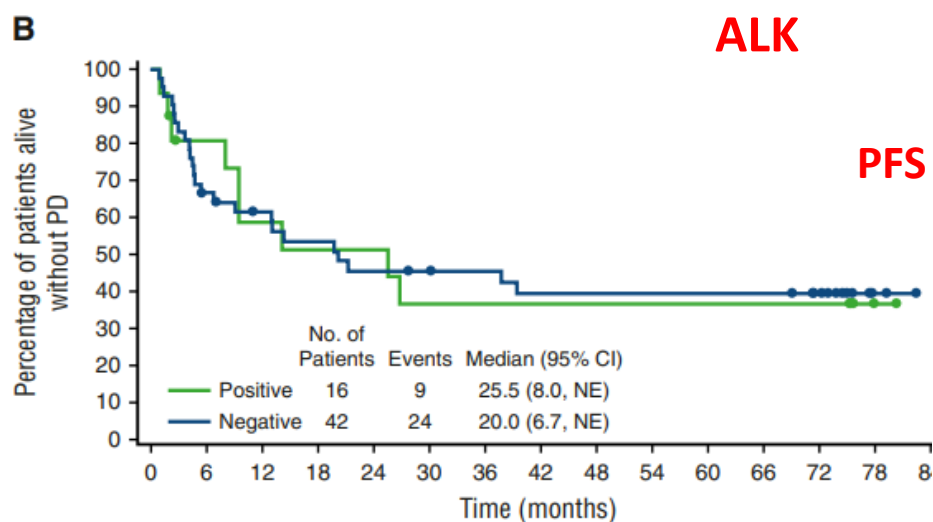
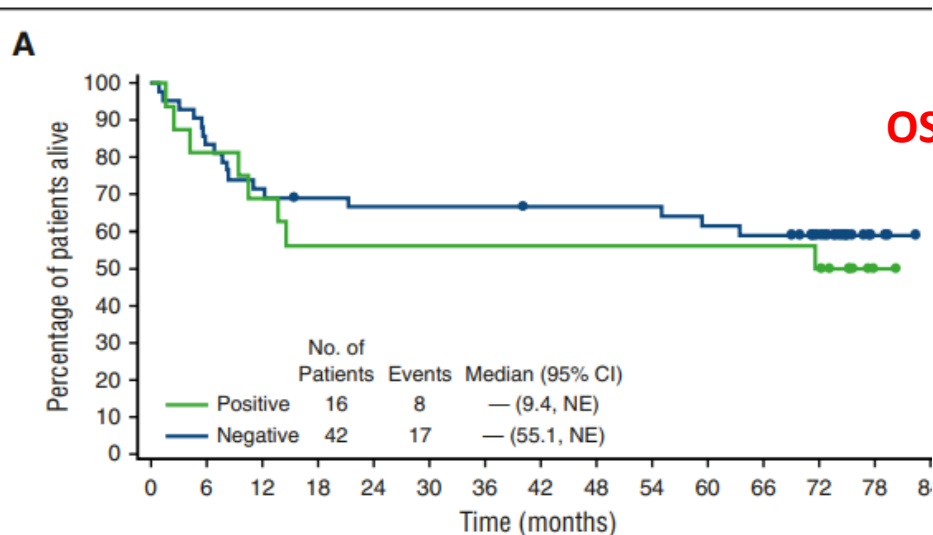


a. NCCN guidelines. Non-Hodgkin's lymphoma. Version 2.2015^[8]; b. Dreyling M, et al. *Ann Oncol.* 2013;857-877^[9]; c. Corradini P, et al. *Ann Oncol.* 2014;25:2339-2350.^[10]

Túlélési adatok refrakter/relapszusos T-sejtes lymphomában

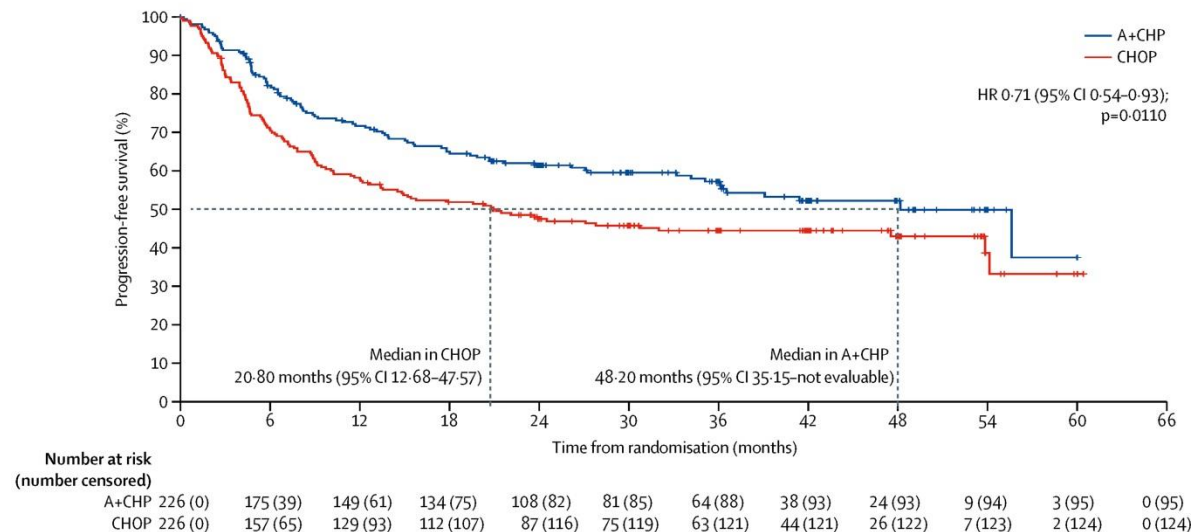


Refrakter/relapszusos ALCL kezelése brentuximab vedotinnal

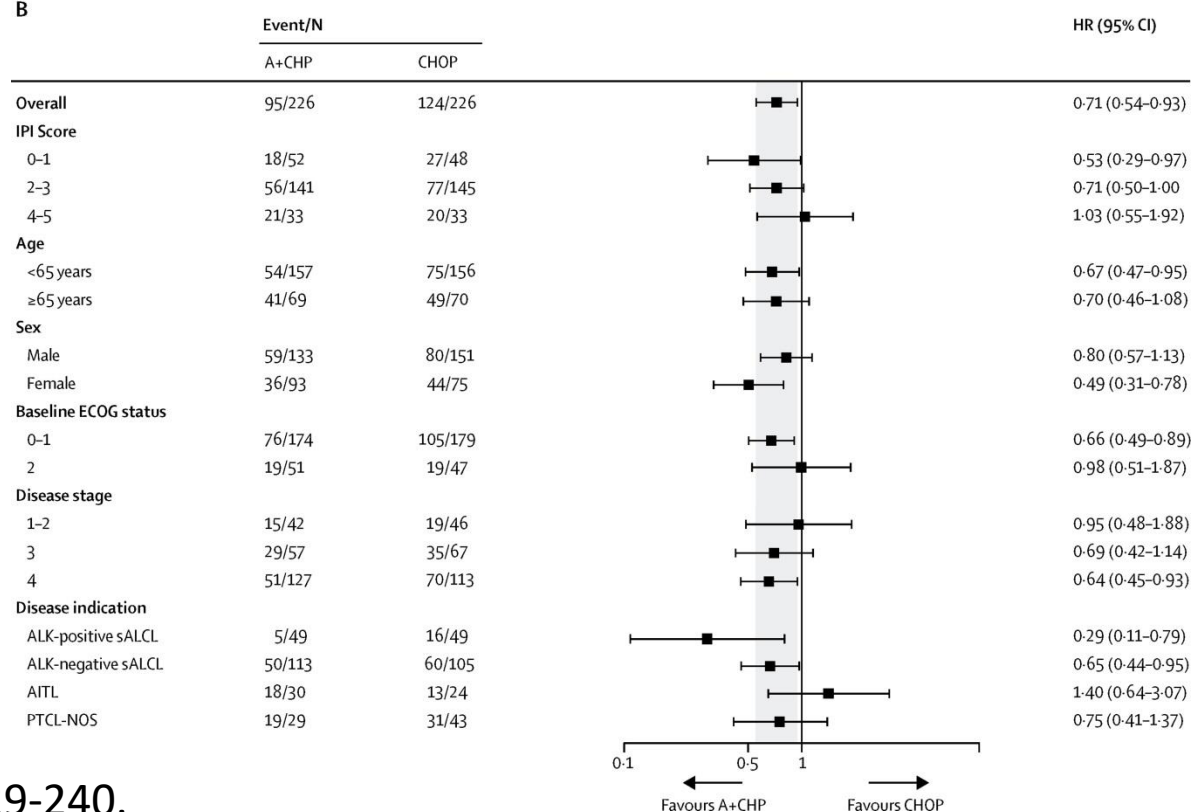


CHOP versus brentuximab-CHP CD30+ PTCL-ben

A



B



UpToDate 2019 indukció: CD30+ (>10%-a a tumorsejtnek): A-CHP
CD30-: kor< 60 év: CHOEP; kor>60: CHOP
konszolidáció: ASCT



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NCCN Guidelines Version 2.2019 Peripheral T-Cell Lymphomas

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SUGGESTED TREATMENT REGIMENS^a

First-line Therapy:

- Clinical trial^b
- ALCL^c
 - ▶ Preferred regimen
 - ◊ Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)^d (category 1)
 - ▶ Other recommended regimens
 - ◊ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
 - ◊ CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
 - ◊ Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
- Other histologies:^{e,f}
 - ▶ Preferred regimens (in alphabetical order)
 - ◊ Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)^d for CD30+ histologies
 - ◊ CHOEP
 - ◊ CHOP
 - ◊ Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
 - ▶ Other recommended regimens (in alphabetical order)
 - ◊ CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with intermediate-dose methotrexate [Newcastle Regimen] [studied only in patients with EATL]^g
 - ◊ HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine (category 3)

First-line Consolidation:

- Consider consolidation with high-dose therapy and stem cell rescue.

See Second-line and Subsequent Therapy:

- PTCL-NOS; EATL; MEITL; nodal PTCL, TFH; FTCL ([TCCL-B 2 of 5](#))
- AITL ([TCCL-B 3 of 5](#))









Cutan DLBCL

