KRONİK LENFOSİTİK LÖSEMİ : GÜNCEL GELİŞMELER VE YENİ TEDAVİLER

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“Hematolojide Yeni Tedaviler: Nereye Doğru Gidiyoruz?”

- 1990’ların başında FDA’in yeni ilaç onaylarının sadece %5’i hedefe yönelik ilaçlardan oluşuyordu. 20 yıl sonra bu sayı yeni onaylananların %25’ine ulaştı. 2013’de ise yeni onaylı ilaçların %45’i hedefe yönelik ilaçlardı.

- FDA’nın önemli buluş (breakthrough) sınıfına aldığı yeni bileşiklerin %80’i hedefe yönelik ilaçlardır

.

Hedefe Yönelik Tedavi

Karsinogenezden sorumlu spesifik moleküler lezyonlara yönelik tedavi

Örnekler:

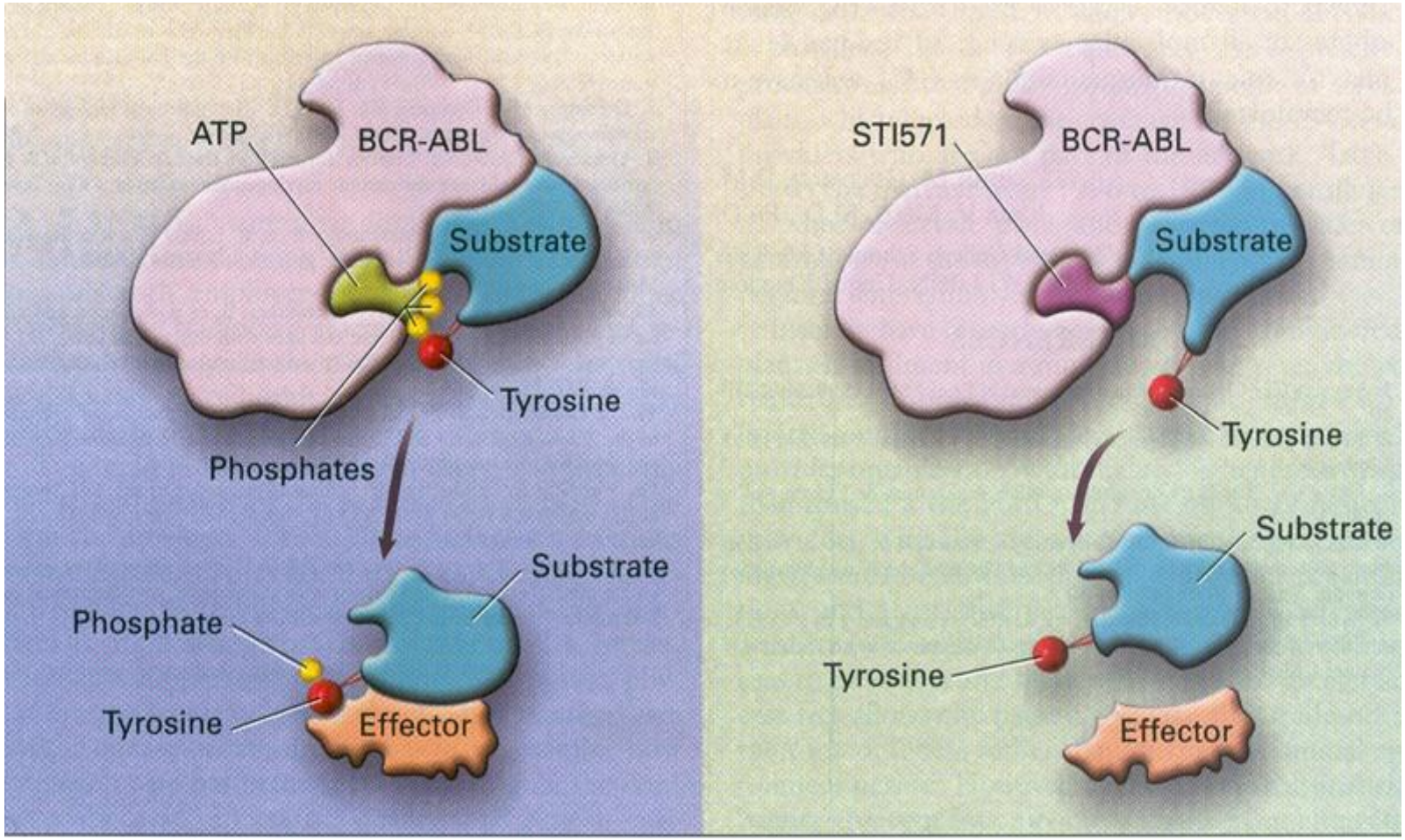
- Tirozin kinaz yolu (bcr-abl, PDGF, BTK)
- Proteozomal yolaklar
- Yaşam sinyal yolakları (MCL1, BCL2)
- Heat shock proteinleri
- İmmunolojik aktivasyon/tolerans (anti –PD1)

Imatinib Mesylate

Bcr/abl TK

PDGF

C-kit



Goldman JM, Melo JV. N Engl J Med. 344:1084-1086.

T cell activation can be augmented by targeting immune checkpoints

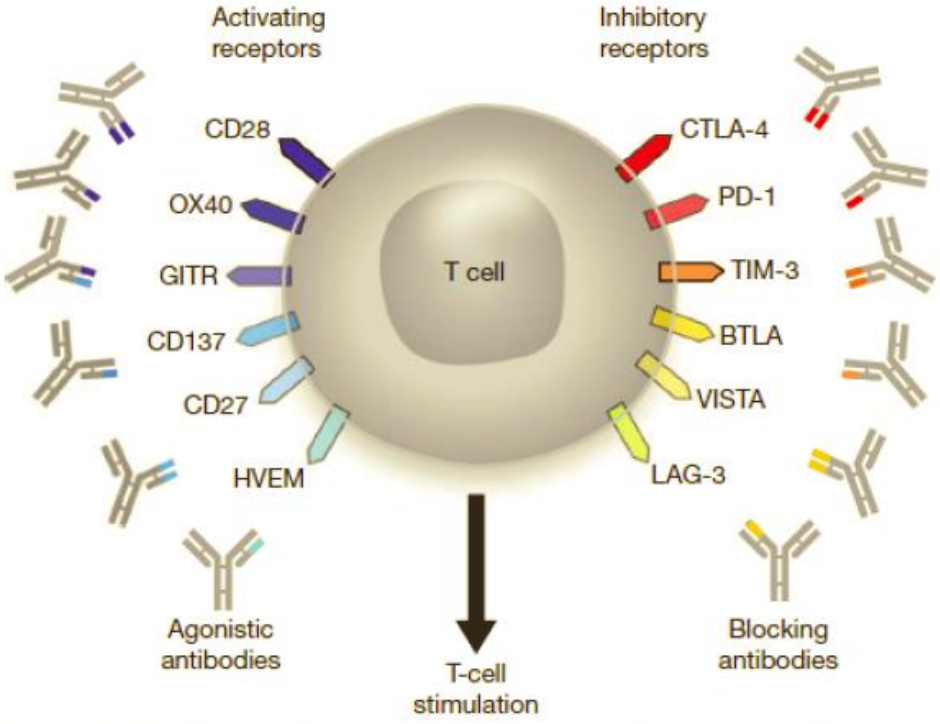


Figure 3 | T cell targets for immunoregulatory antibody therapy. In addition to specific antigen recognition through the TCR, T-cell activation is regulated through a balance of positive and negative signals provided by co-stimulatory receptors. These surface proteins are typically members of either the TNF receptor or B7 superfamilies. Agonistic antibodies directed against activating co-stimulatory molecules and blocking antibodies against negative co-stimulatory molecules may enhance T-cell stimulation to promote tumour destruction.

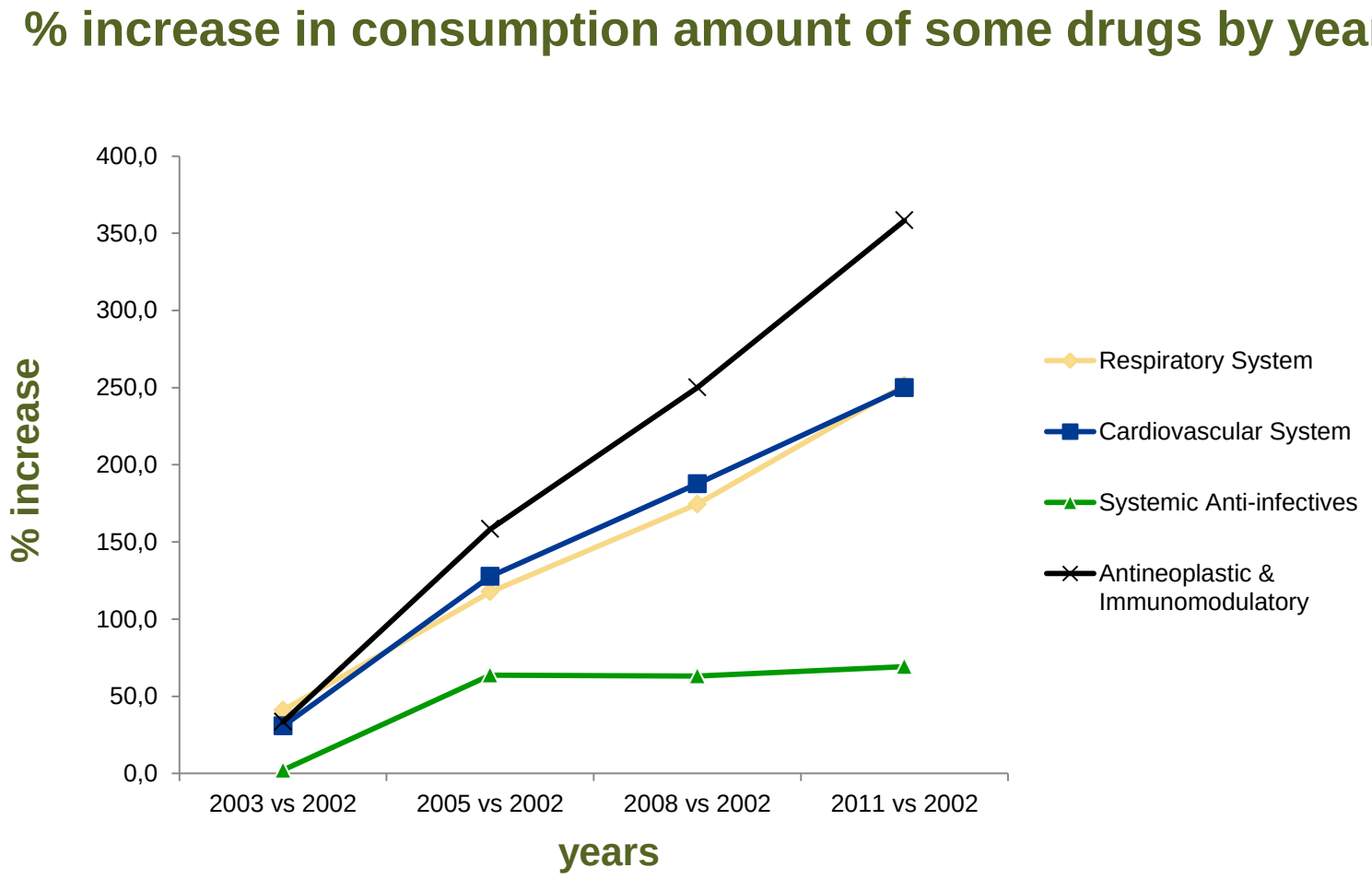
- Blocking an inhibitory receptor with an antagonist antibody has a net result of enhanced T cell activation
- Activating a costimulatory receptor with an agonist antibody has a net result of enhanced T cell activation

Cancer immunotherapy comes of age

Ira Mellman[1], George Coukos[2] & Glenn Dranoff[3]

480 | NATURE | VOL 480 | 22/29 DECEMBER 2011

Yıllar içinde ilaç tüketiminde değişiklik



Ref: Adapted from Turkish MoH-Health Statistics Yearbook 2011

KLL

CD19/20 + hücrelerde CD5 ve CD23 ekspresyonu

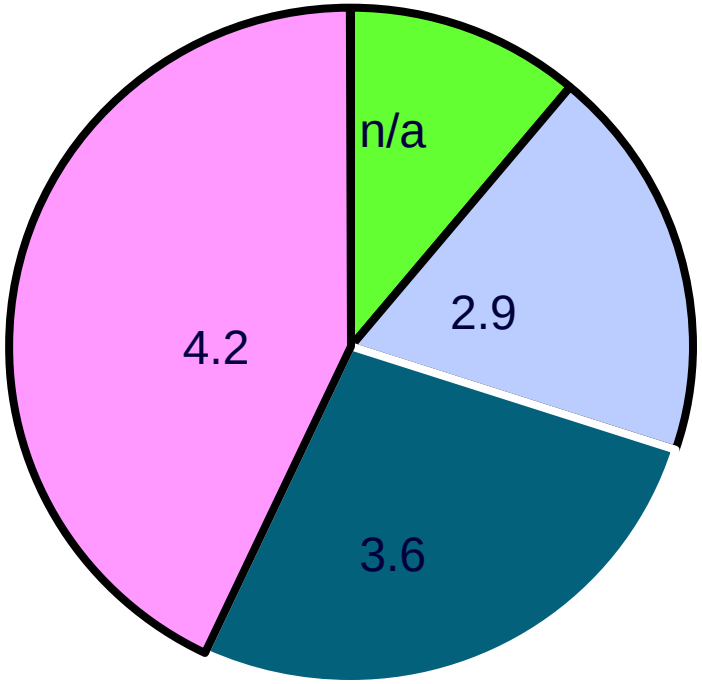
PK >5000 lenfosit (olgun görünümde)

Lenf nodu Bx: SLL

KLL medyan yaş: 72

Ko-morbidite oranı yaşla birlikte artar

Mean no. of co-morbidities

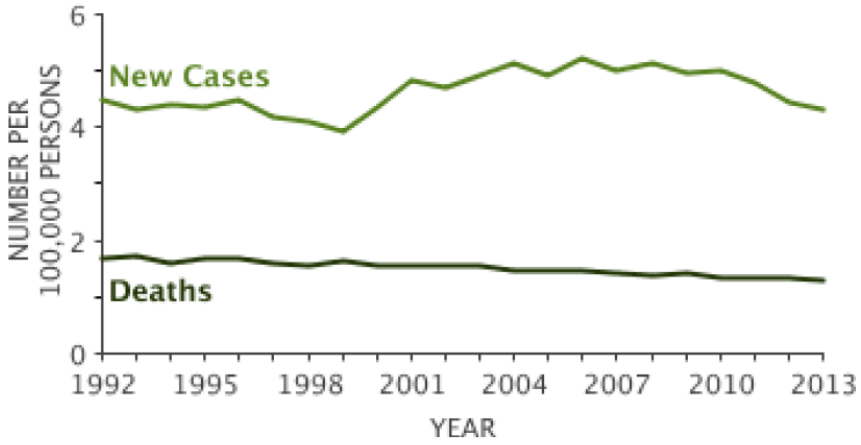


Age at CLL diagnosis (years)	Patients[1] (%)	Mean co-morbidities[2] (all cancer types, n)
≤ 54	11	n/a
55–64	19	2.9
65–74	27	3.6
75+	43	4.2

1. Ries LAG, *et al.* SEER Cancer Statistics Review, 1975–2005
Available at: http://seer.cancer.gov/csr/1975_2005/ accessed February 2009
2. Yancik R, *Cancer* 1997; 80:1273–1283

CLL-SEER data

Estimated New Cases in 2016	18,960
% of All New Cancer Cases	1.1%
Estimated Deaths in 2016	4,660
% of All Cancer Deaths	0.8%



Percent Surviving 5 Years
82.6%
2006–2012

cancer incidence and survival data from population-based cancer registries covering approximately 28 percent of the U.S. population

BINET SINIFLAMASI

Stage A. Hb $\geq$ 10 g/dL and platelets $\geq 100 \times 10^9$/L and up to two of the above involved.

Stage B. Hb $\geq$ 10 g/dL and platelets $\geq 100 \times 10^9$/L and organomegaly greater than that defined for stage A (i.e. three or more areas of nodal or organ enlargement).

Stage C. All patients who have Hb of less than 10 g/dL and/or a platelet count of less than 100×10^9/L, irrespective of organomegaly.

TEDAVİ ENDİKASYONLARI

- evidence of progressive marrow failure (anemia and/or thrombocytopenia);
- massive (i.e., ≥ 6 cm below the left costal margin) or progressive or symptomatic splenomegaly;
- massive nodes (i.e., ≥ 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy;
- progressive lymphocytosis with an increase of >50% over a 2-month period;
- lymphocyte doubling time (LDT) of less than 6 months;
- autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy;
- disease-related symptoms such as unintentional weight loss ≥ 10% within the previous 6 months, significant fatigue, fevers of greater than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection; or night sweats for more than 1 month without evidence of infection.

SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)

CLL without del (17p)

- Frail patient, significant co-morbidity (not able to tolerate purine analogs)
  - Chlorambucil ± prednisone
  - Rituximab (single)
  - Pulse corticosteroids

First line therapy[b]

- Age ≥ 70 y
  - Chlorambucil ± prednisone
  - Alkylating agent-based chemotherapy
    - CVP (cyclophosphamide + vincristine + prednisone)
  - Alemtuzumab[c]
  - Bendamustine[d,e]
  - Rituximab
  - Fludarabine[f] ± rituximab
- Age < 70 y or older with good co-morbidity index
  - Chemoimmunotherapy[d] (preferred)
    - FCR (fludarabine[f], cyclophosphamide[g], rituximab)
    - FR (fludarabine[f], rituximab)
    - PCR (pentostatin, cyclophosphamide[g], rituximab)
  - Purine-analogue therapy[g]
    - FC (fludarabine[f], cyclophosphamide[g])
  - Monotherapy
    - Chlorambucil ± prednisone
    - Fludarabine[f]
    - Alemtuzumab[c]
    - Bendamustine[d,e]

Relapsed/Refractory therapy

- Long response > 3 y
  - Retreat as in first line therapy until short response
- Short response < 2 y for age ≥ 70 y
  - Purine-analogue therapy[d]
    - Single agent (fludarabine[f] or pentostatin)
    - FC[f,g]
  - Chemoimmunotherapy[d]
    - Reduced-dose PCR[g]
    - Reduced-dose FCR[f,g]
    - Reduced-dose FR[f]
    - Bendamustine[d,e] ± rituximab
  - Ofatumumab
  - Dose-dense rituximab
- Short response < 2 y for age < 70 y or older with good co-morbidity index
  - Chemoimmunotherapy[d]
    - FCR[f,g]
    - PCR[f,g]
    - Bendamustine[d,e] ± rituximab
    - Fludarabine[f] + alemtuzumab
    - CHOP + R (cyclophosphamide[g], doxorubicin, vincristine, prednisone + rituximab)
    - HyperCVAD + R (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with rituximab plus high-dose methotrexate and cytarabine)
    - EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin+ rituximab)
    - OFAR (oxaliplatin, fludarabine[f], cytarabine and rituximab)
  - Ofatumumab
  - Alemtuzumab + rituximab
  - HDMP + R (high-dose methylprednisone + rituximab)

See Rituximab and Viral Reactivation (NHODG-D)

See Suggested Regimens for CLL with del (17p) (2 of 4)

See Footnotes for CLL with del (17p) on CSLL-D (2 of 4)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Complete Remission in CLL (NCI criteria)

Requires all of the following to be present for two or more months:

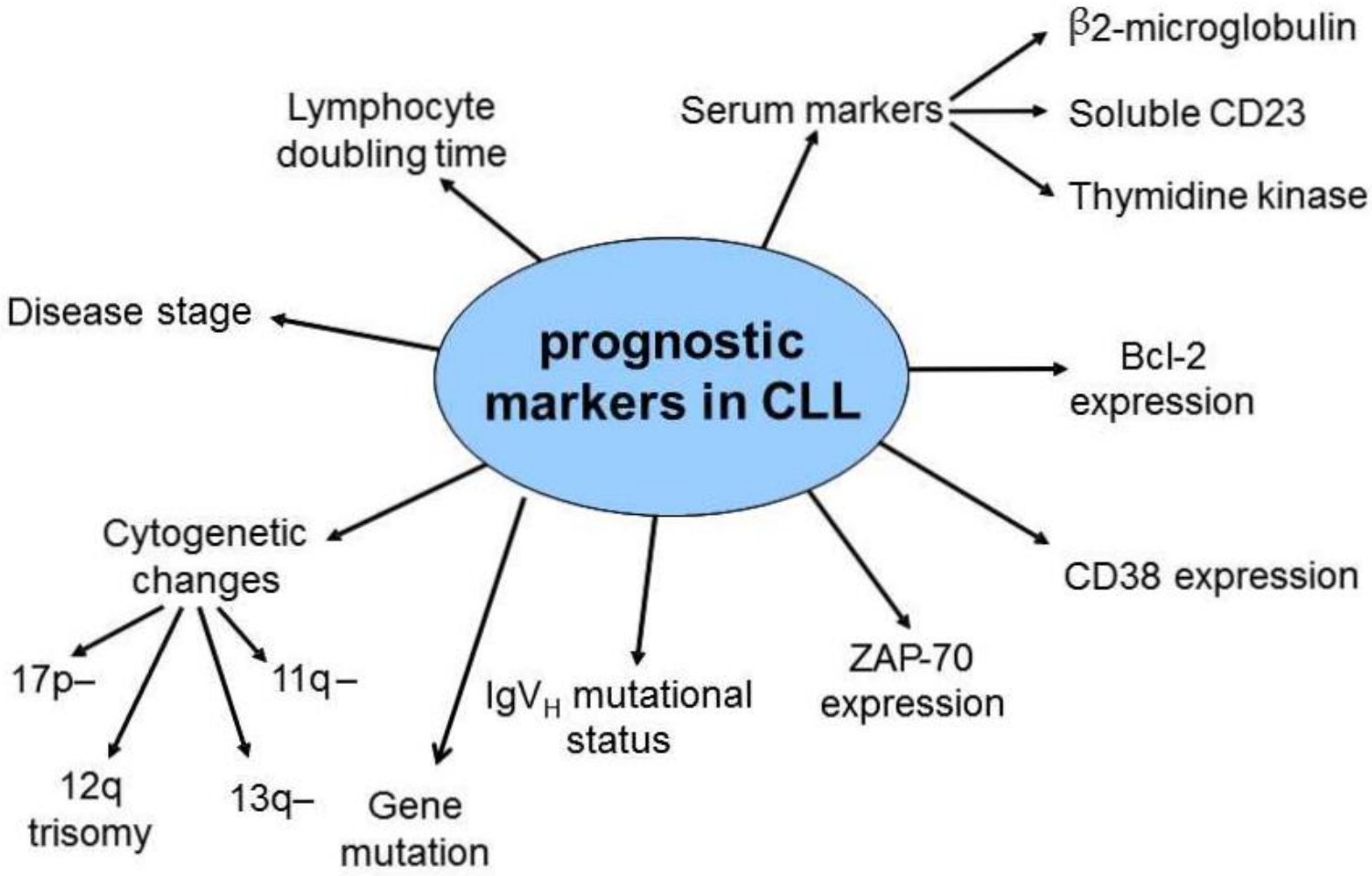
- Absence of symptoms attributable to CLL
- Normal findings on physical examination
- Absolute lymphocyte count <4000/microL
- Absolute neutrophil count >1500/microL
- Platelet count >100,000/microL
- Hemoglobin concentration >11 g/dL (untransfused)
- Bone marrow lymphocytosis <30 percent
- No nodules (lymphoid aggregates) on bone marrow biopsy

Cheson BD et al . Blood 1996; 87:4990

- CR, definition in general practice:
  - blood lymphocytes < 4000/µl
  - BM lymphoid cells ≤ 30%
- Definition in clinical trials with CR as an endpoint:
  - CT negative
  - MRD assessment
  - BM biopsy with immunohistochemistry or flow cytometry (according to MRD definition)

Figure 1. Definition of response in CLL, as proposed by the iwCLL 2008 guidelines [26]. MRD, minimal residual disease. CR, complete remission. PR, partial remission.

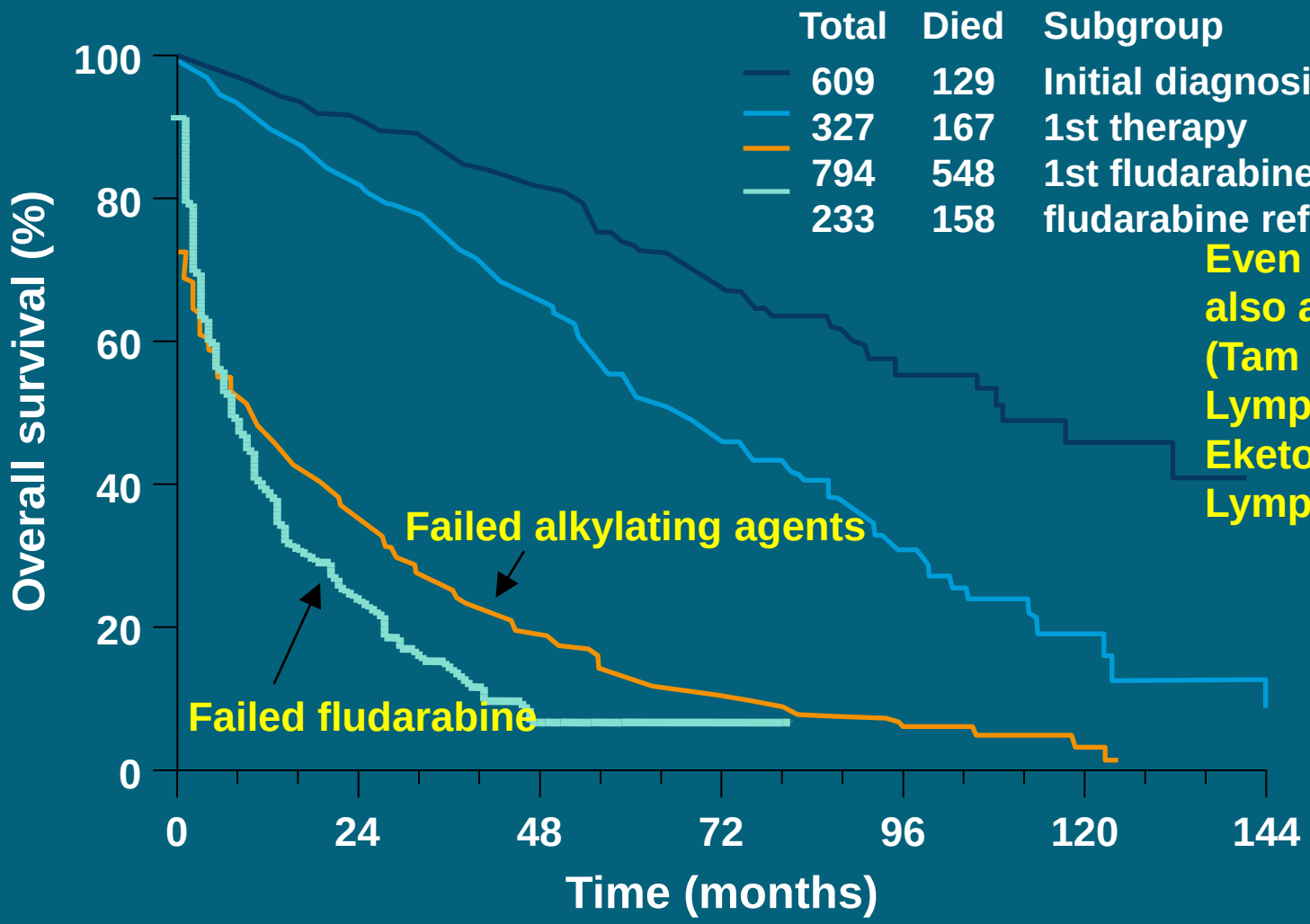
KLL: Prognostik faktörler



KLL: Prognostik faktörler

Marker	Low risk	High risk
Genomic aberrations	None, 13q–	11q–, 17p–
IgV_H	Mutated	Unmutated
CD38	≤ 30%	> 30%
ZAP-70	< 20%	≥ 20%
β2-microglobulin	< 4 mg/l)	≥ 4 mg/l

Konvansiyonel Tedaviye Refrakter KLL'de Prognoz



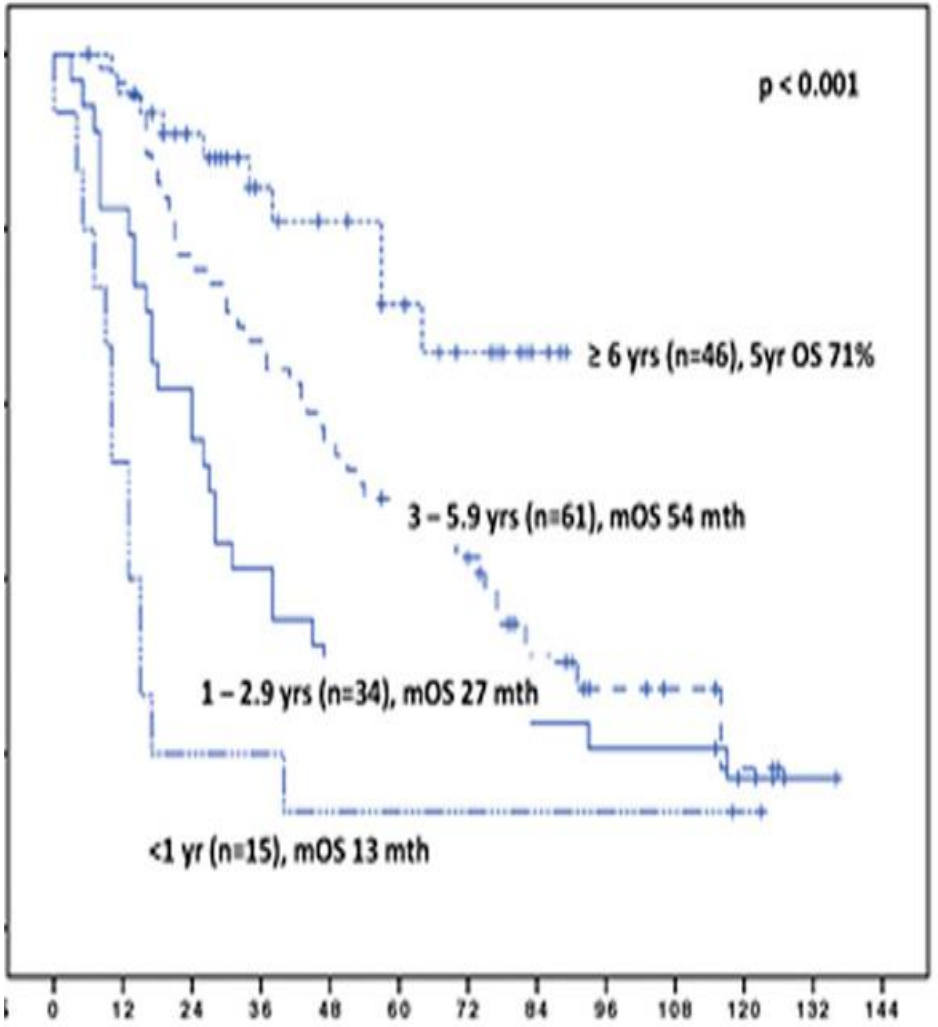
Even worse if failed also alemtuzumab (Tam el al Leuk Lymph 2007, Eketorp et al Leuk Lymph 2014)

Keating et al, Leuk Lymph 2002

FCR YANIT SÜRESİ ve PROGNOZ

- 2.sıra tedavi uygulanan hastalar için son yıllara kadar prognoz olumlu şekilde değişmemiştir.
- daha önce FCR almış ve ilk 3 yıl içinde nüks gösteren hastalar konvansiyonel rejimler ile tedavi edildiklerinde sağkalımları aldıkları rejimin ne olduğuna bakmaksızın kısa bir sağkalım periyoduna sahip olmaktadırlar

Tam CS et al Blood. 2014;124: 3059-3064.



YÜKSEK RİSK KLL TANIMI

- 17p-
- Pürin Analog Refrakter
- Doz yoğun tedaviden sonra iki yıl içinde nüks

FCR

- İmmünglobulin ağır zincir variable gen (IGHV) mutasyonu taşıyanlar dahil ve del 17p ve 11q taşıyanlar hariç olmak üzere düşük risk hastaların ortalama %60'ı, 10 yıllık takipte remisyonda kalacaktır.

- IGHV mutasyonlu ve MRD negatif hastalarda progresyonsuz sağ kalım 13 yılda % 80'dir

Thompson PA, Blood 2015

FCR toksisitesi olan bir rejimdir

	Chemotherapy (n=396)	Chemoimmunotherapy (n=404)	p value	<65 years (n=560)	≥65 years (n=240)	p value
Total number of patients with at least one grade 3 or 4 event	249 (63%)	309 (76%)	<0·0001	375 (67%)	183 (76%)	0·009
Haematological toxicity	157 (40%)	225 (56%)	<0·0001	254 (45%)	128 (53%)	0·04
Neutropenia	83 (21%)	136 (34%)	<0·0001	146 (26%)	73 (30%)	0·21
Leucocytopenia	48 (12%)	97 (24%)	<0·0001	106 (19%)	39 (16%)	0·37
Thrombocytopenia	44 (11%)	30 (7%)	0·07	50 (9%)	24 (10%)	0·63
Anaemia	27 (7%)	22 (5%)	0·42	35 (6%)	14 (6%)	0·82
Autoimmune haemolytic anaemia	4 (1%)	3 (<1%)	0·69	4 (<1%)	3 (1%)	0·46
Tumour lysis syndrome	2 (<1%)	1 (<1%)	0·55	3 (<1%)	0	0·26
Cytokine release syndrome	0	1 (<1%)	0·32	1 (<1%)	0	0·51
Infections, total	85 (21%)	103 (25%)	0·18	127 (23%)	61 (25%)	0·4
Infections, not specified	68 (17%)	83 (21%)	0·19	104 (19%)	46 (19%)	0·84
Bacterial infection	5 (1%)	11 (3%)	0·14	6 (1%)	10 (4%)	0·004
Viral infection	17 (4%)	17 (4%)	0·95	26 (5%)	8 (3%)	0·4
Fungal infection	1 (<1%)	3 (<1%)	0·33	3 (<1%)	1 (<1%)	0·83
Parasitic infection	0	1 (<1%)	0·32	0	1 (<1%)	0·13

Data are number (%), unless otherwise indicated. Chemotherapy=fludarabine and cyclophosphamide. Chemoimmunotherapy=fludarabine, cyclophosphamide, and rituximab.

Table 6: **Incidence of grade 3 and 4 adverse events**

Hallek MH, et al. Lancet 2010 Oct 2;376(9747):1164-7

FCR’a alternatif tedavi?

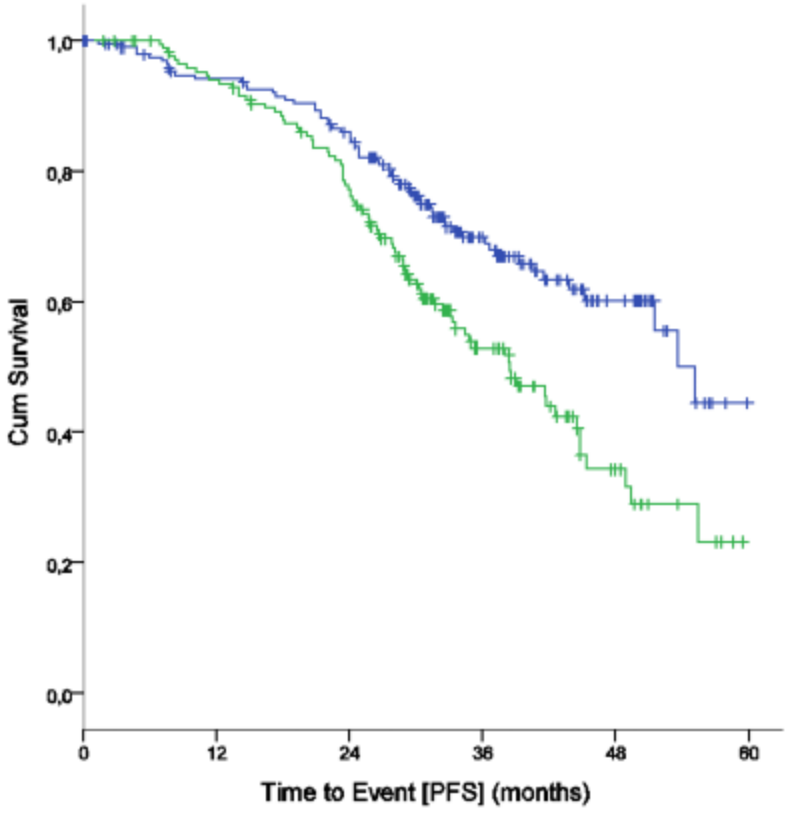
CLL10 STUDY: FCR VS BR IN FRONT-LINE

DEUTSCHE STUDIENGRUPPE

Progression-free survival by age group

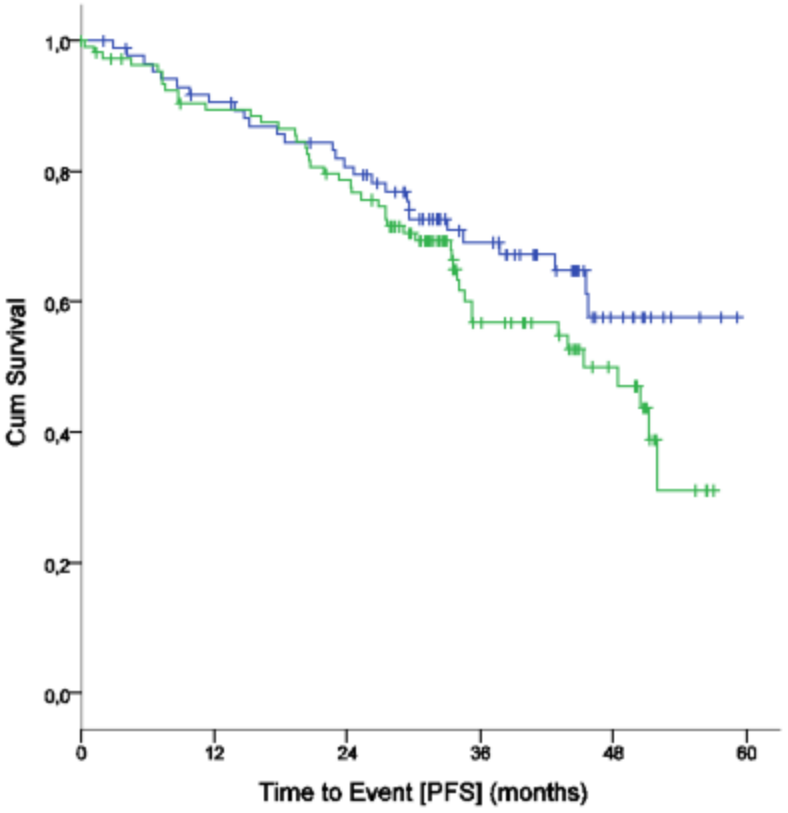
Patients ≤ 65 years: ***P < 0.001***

FCR 53.6 months BR 38.5 months



Patients > 65 years: ***P = 0.170***

FCR not reached BR 48.5 months



FCR VS BR (CLL10): Yan Etkiler

Adverse event	FCR (% of pt)	BR (% of pt)	p value
All Infections	**39.1**	**26.8**	**<0.001**
Infections during therapy only	22.6	17.3	0.1
Infections during first 5 months after therapy	11.8	3.6	<0.001
All infections in patients ≤ 65years	35.2	27.5	0.1
All infections in patients > 65years	47.7	20.6	<0.001

Eichhorst et al. ASH 2014: abstract 19 (oral presentation)
Eichhorst et al. Lancet Oncol 2016;S1470-

R-benda: >65 formda hastalar

R-FC: <65 yaş formda hastalar

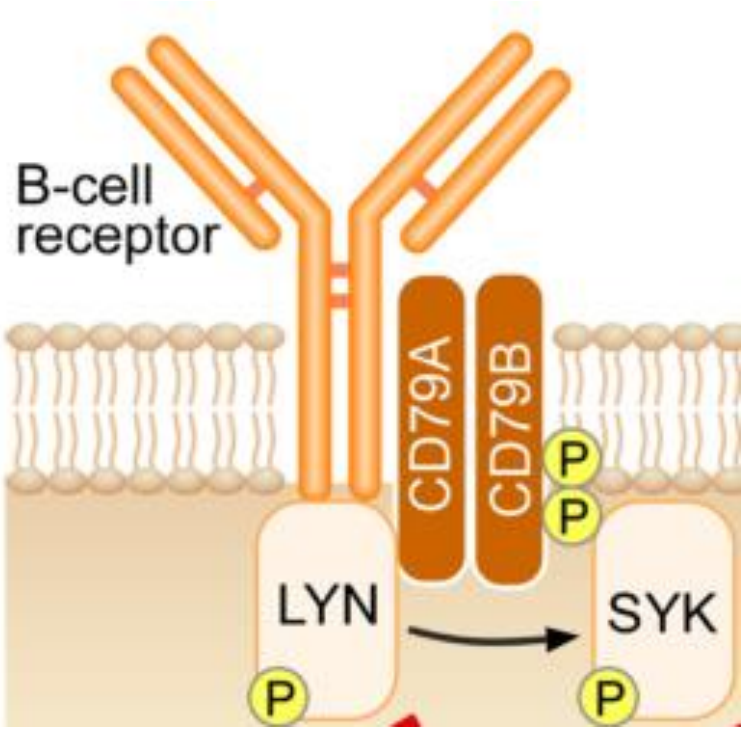
B hücre reseptörü ve sinyal yolaklarının önemi

- B hücre reseptörü (B-cell receptor /BCR) tüm B hücrelerinde bulunur ve 2 ana fonksiyonu vardır:
  - Yabancı antijenleri tanımak
  - B hücrelerinin matürasyonu, sağkalımı, proliferasyonu ve immün yanıta katılımı için klonal seleksiyonda sinyalizasyon yolaklarını başlatmak

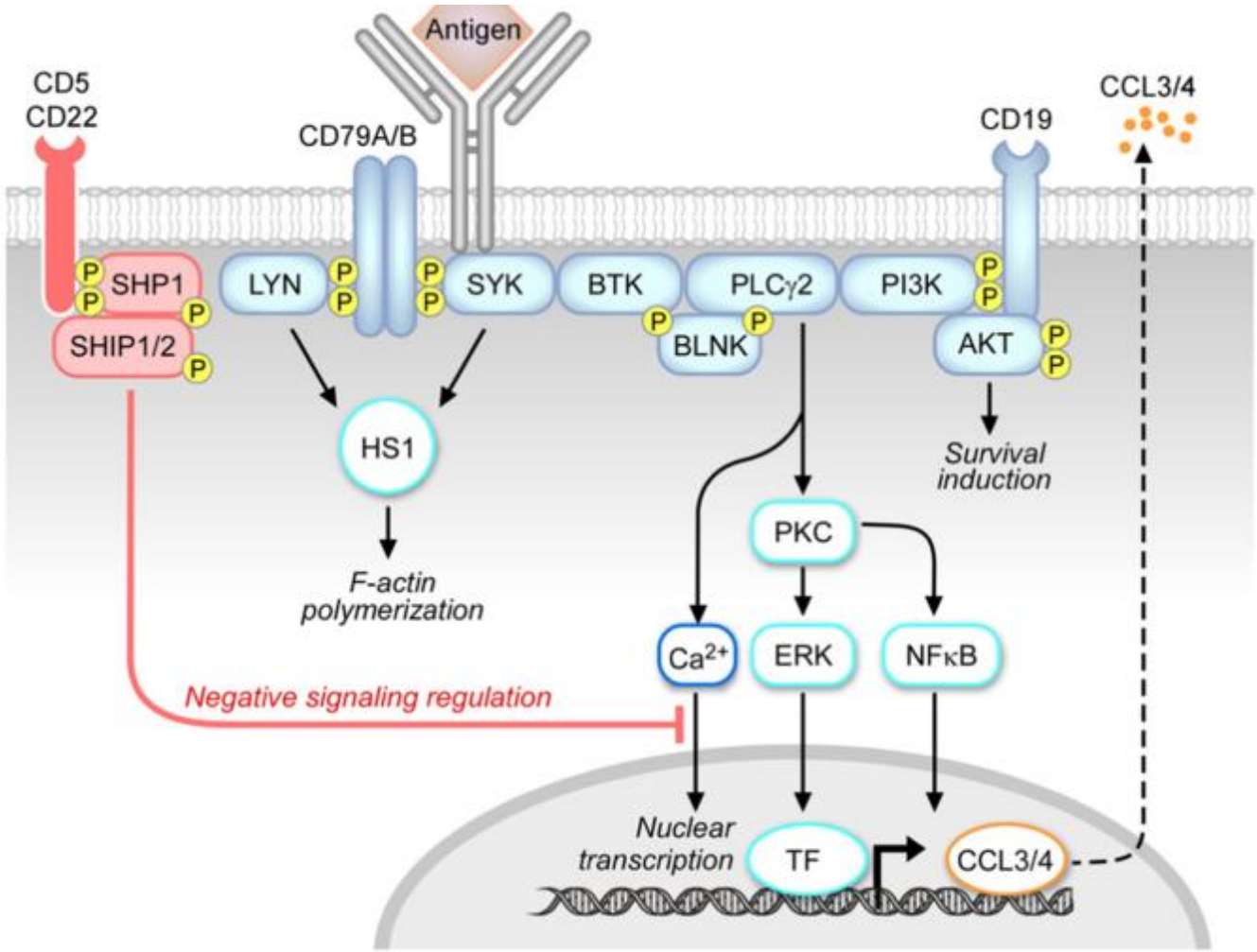
- ***BCR sinyalizasyonu, PI3Kδ, BTK, Syk, Lyn, and ZAP70 gibi proteinler aracılığı ile iletilir***

B hücre reseptörü

- antijen-specific surface immunoglobulin (sIg) ve the Ig-α/Ig-ß hetero-dimerlerden (CD79A, CD79B) oluşan multimerik bir komplekstir



BCR SİNYAL YOLAĞI

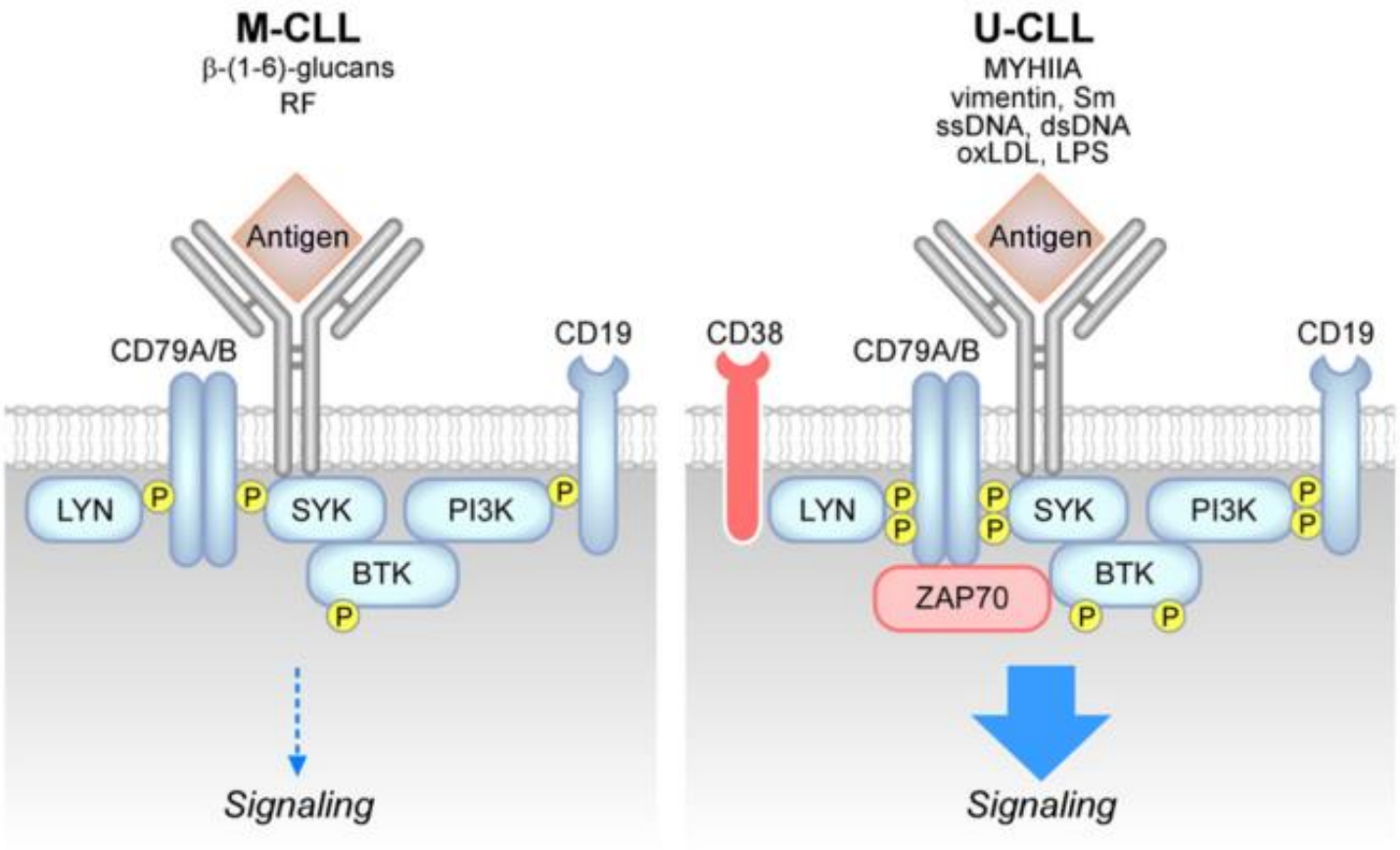


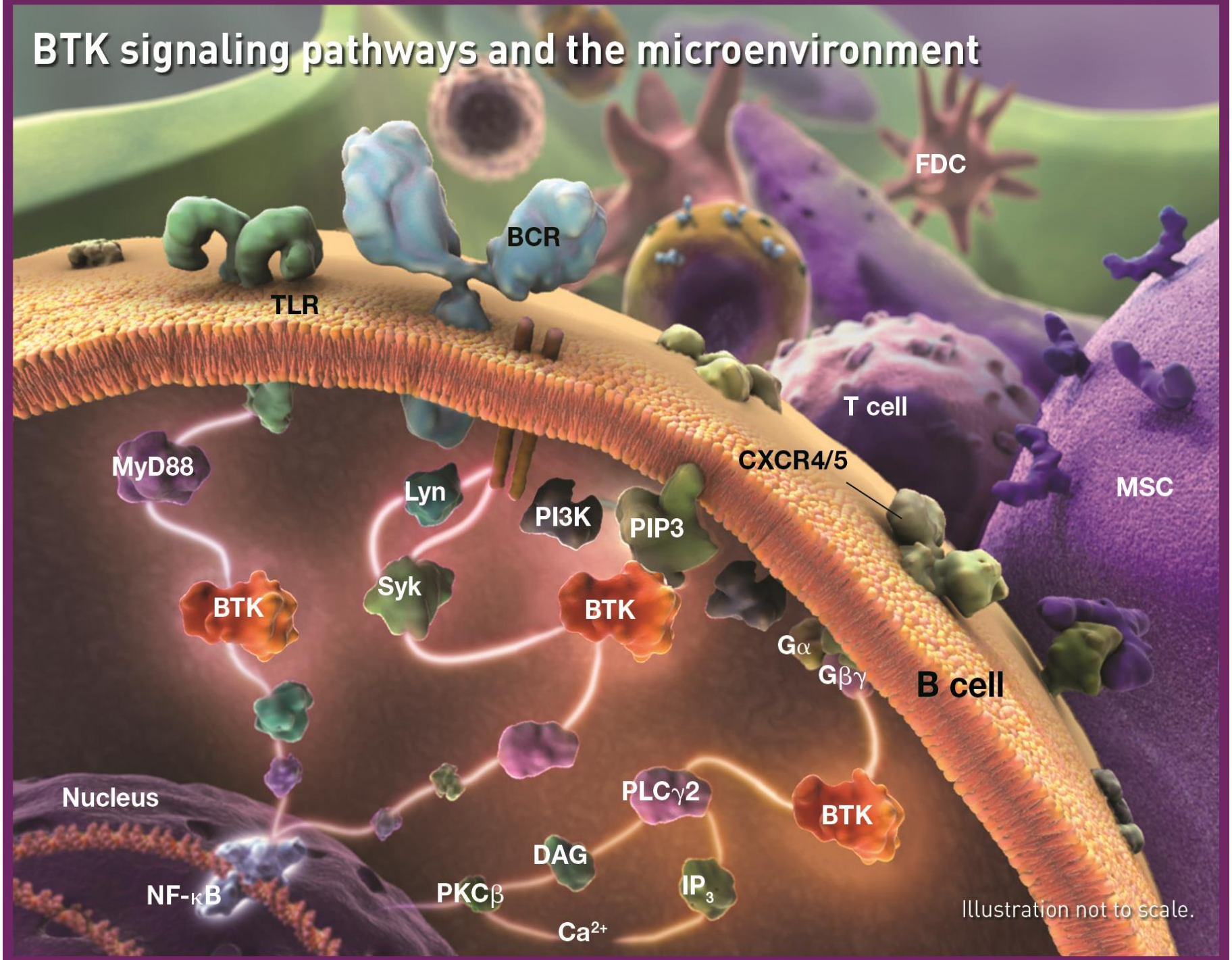
- B hücre reseptör (BHR) sinyal yolağı mikro çevre etkileşimi ile KLL patogenezinde önemli rol oynamaktadır

- BHR'ünün IgVH (immün globülin ağır zincir değişken bölge geni) mutasyonlarının prognostik değeri tanımlanmış

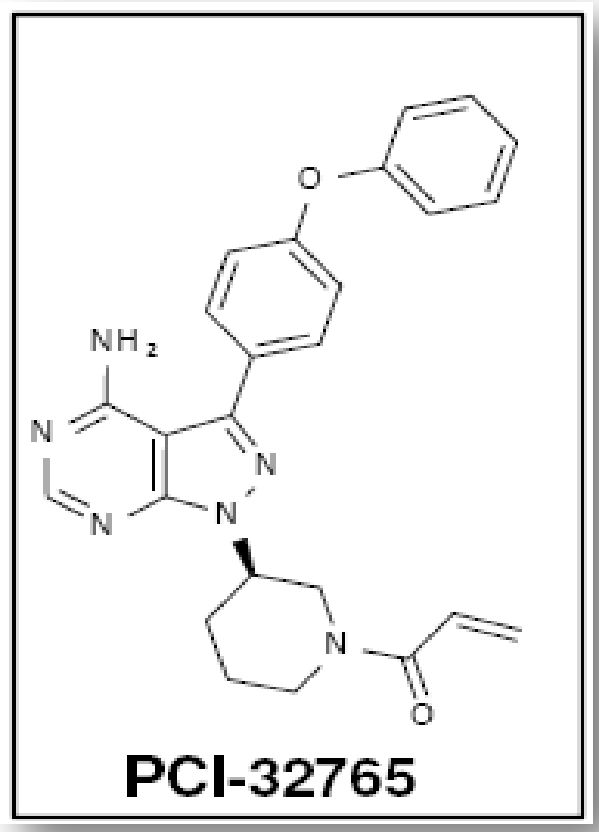
- Bu yolağın kendi kendine aktivitesinin sebepleri? antijenik uyarım teorisi? yolağı aktive eden evrensel bir antijen, patojen veya süperantijen tespit edilememiştir

Mutasyonlu ve mutasyonsuz IgVH

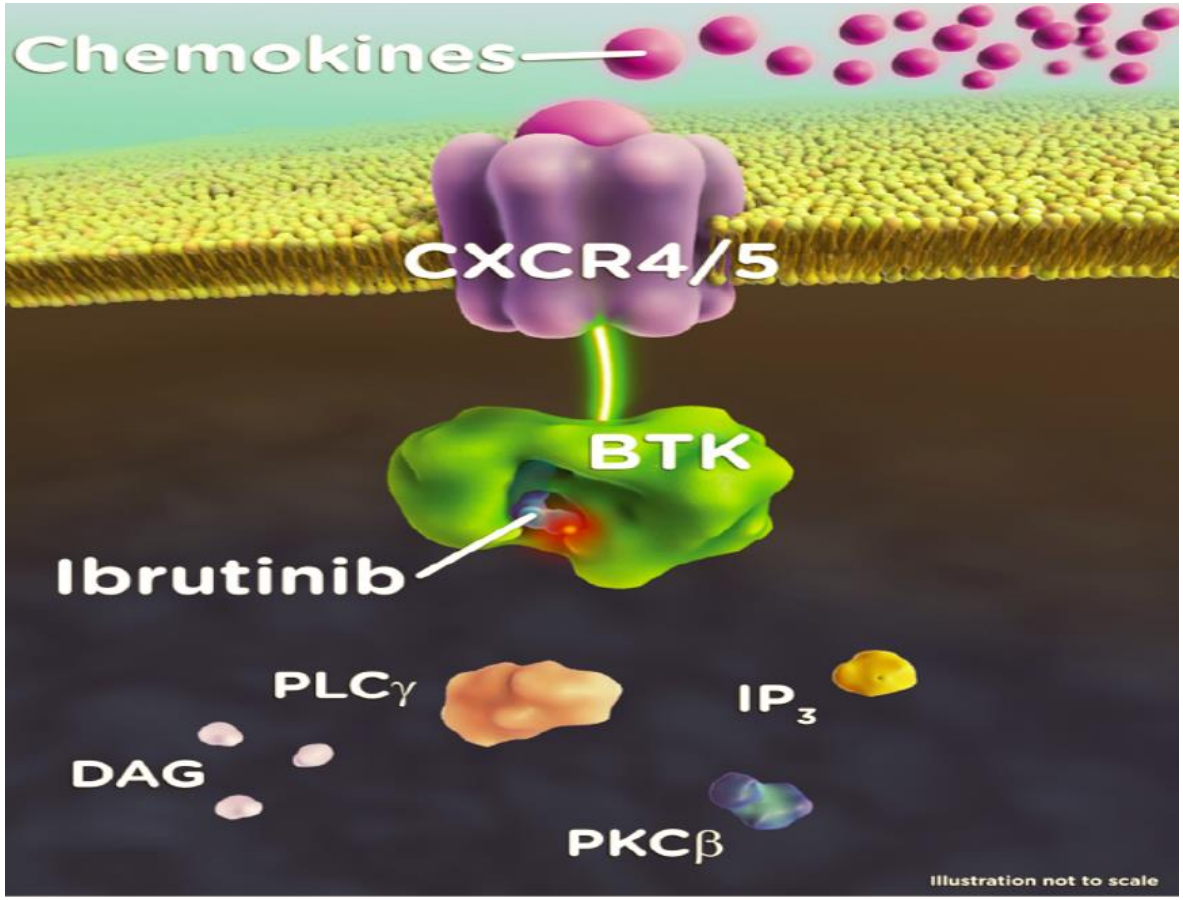



BTK signaling pathways and the microenvironment
FDC
BCR
TLR
T cell
CXCR4/5
MSC
MyD88
Lyn
PI3K
PIP3
Syk
BTK
BTK
Gα
Gβγ
B cell
Nucleus
PLCγ2
BTK
DAG
NF-κB
PKCβ
IP3
Ca2+
Illustration not to scale.

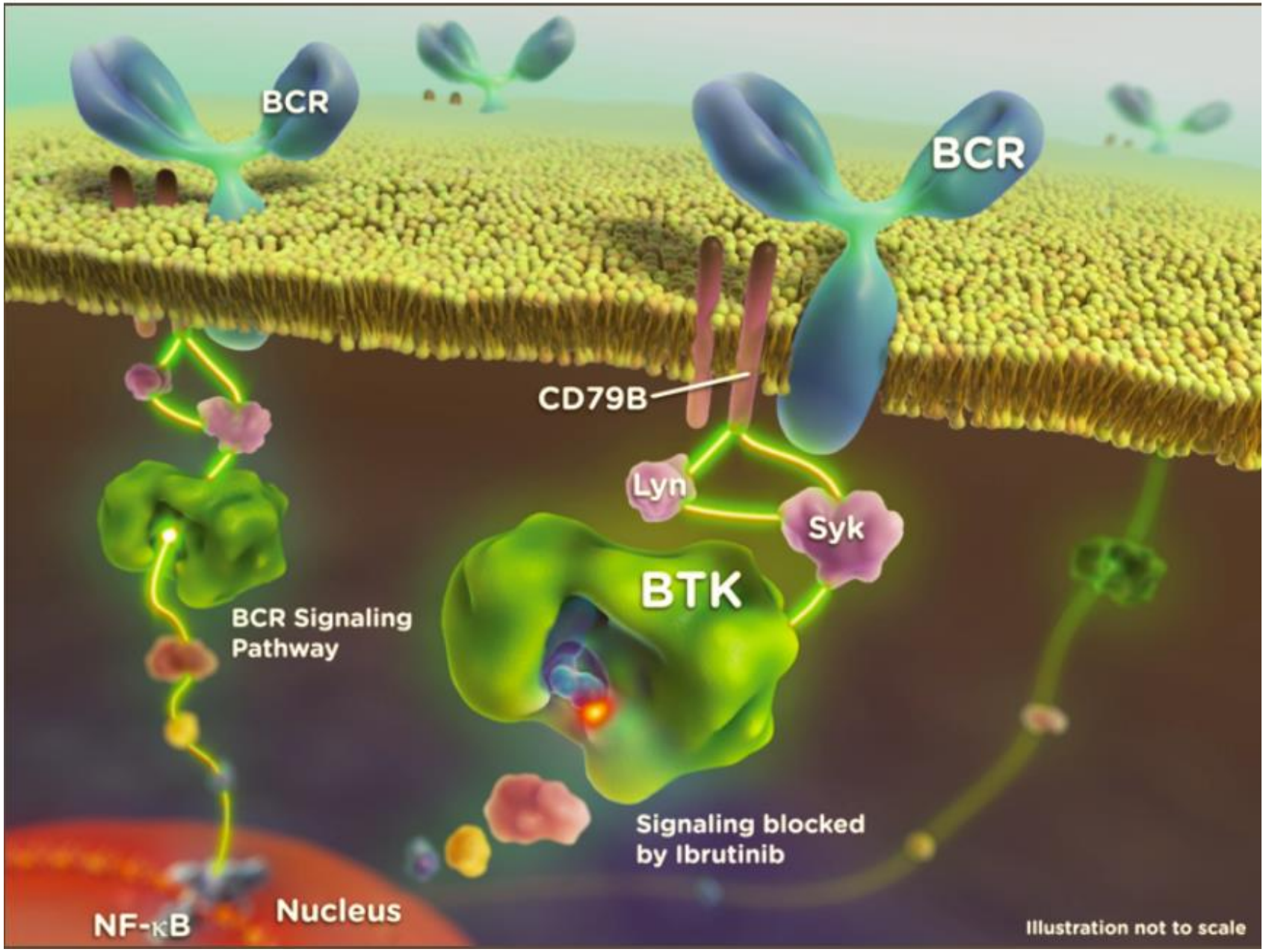
İbrutinib: Bruton Tirozin Kinaz (BTK) İnhibitörü



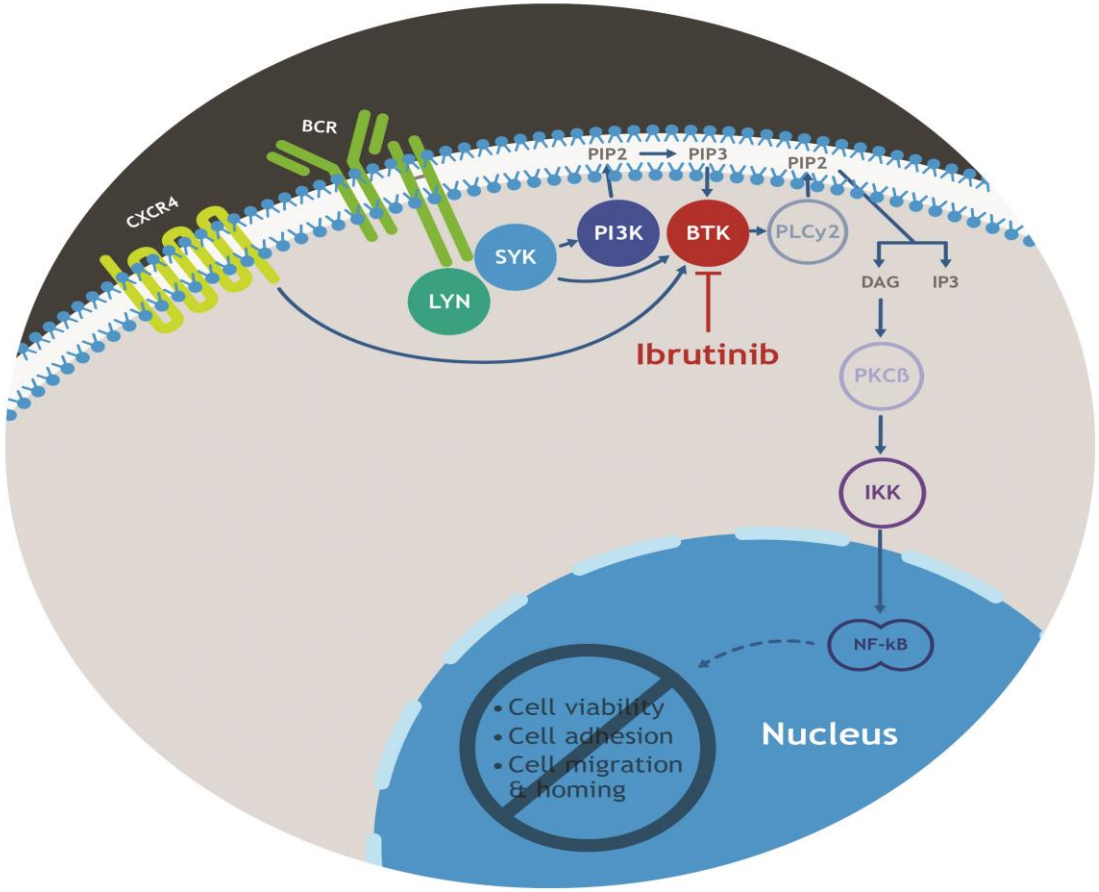
- Bruton Tirozin Kinaz (BTK) inhibitörüdür ve oral olarak uygulanır
- Oldukça güçlü BTK inhibisyonu (sistein 481 kovalent) yapar
- Malign B hücrelerinde:
  - **Proliferasyonu, adhezyonu, yerleşmeyi inhibe eder,**
  - **Apoptozu indükler.**
- T veya NK hücreleri üzerinde sitotoksik etkisi yoktur



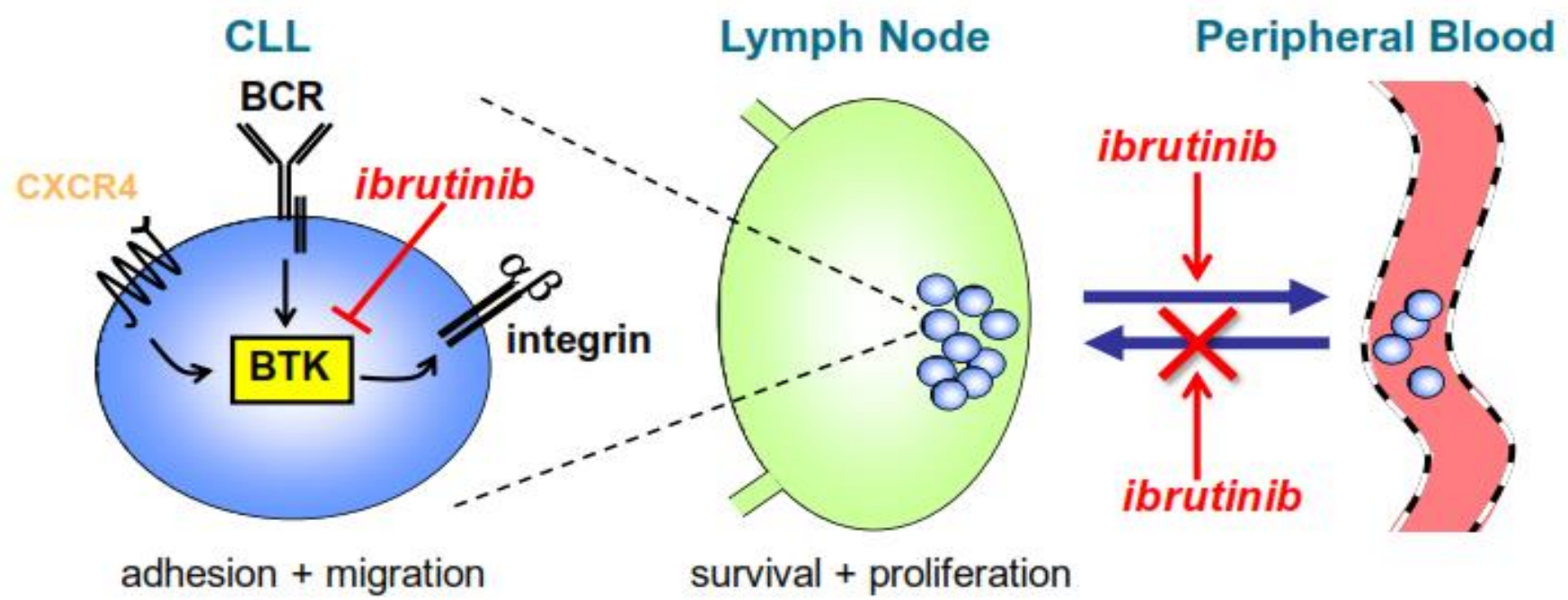
The binding of Ibrutinib to Bruton's tyrosine kinase (BTK) can block chemokine signaling in the malignant B cell


BCR
BCR
CD79B
Lyn
Syk
BTK
BCR Signaling Pathway
Signaling blocked by Ibrutinib
NF-κB
Nucleus
Illustration not to scale

Ibrutinib, Bcr sinyal yolağında Btk inhibisyonu ile anti neoplastik etkisini gösterir



Mechanism of Action of Ibrutinib in CLL



- Ibrutinib, a first-in-class, oral, covalent inhibitor of Bruton's tyrosine kinase (BTK)
  - promotes apoptosis
  - inhibits B-cell proliferation
  - inhibits cell adhesion and migration

de Rooij MF, et al. *Blood*. 2012; 119:2590-2594.

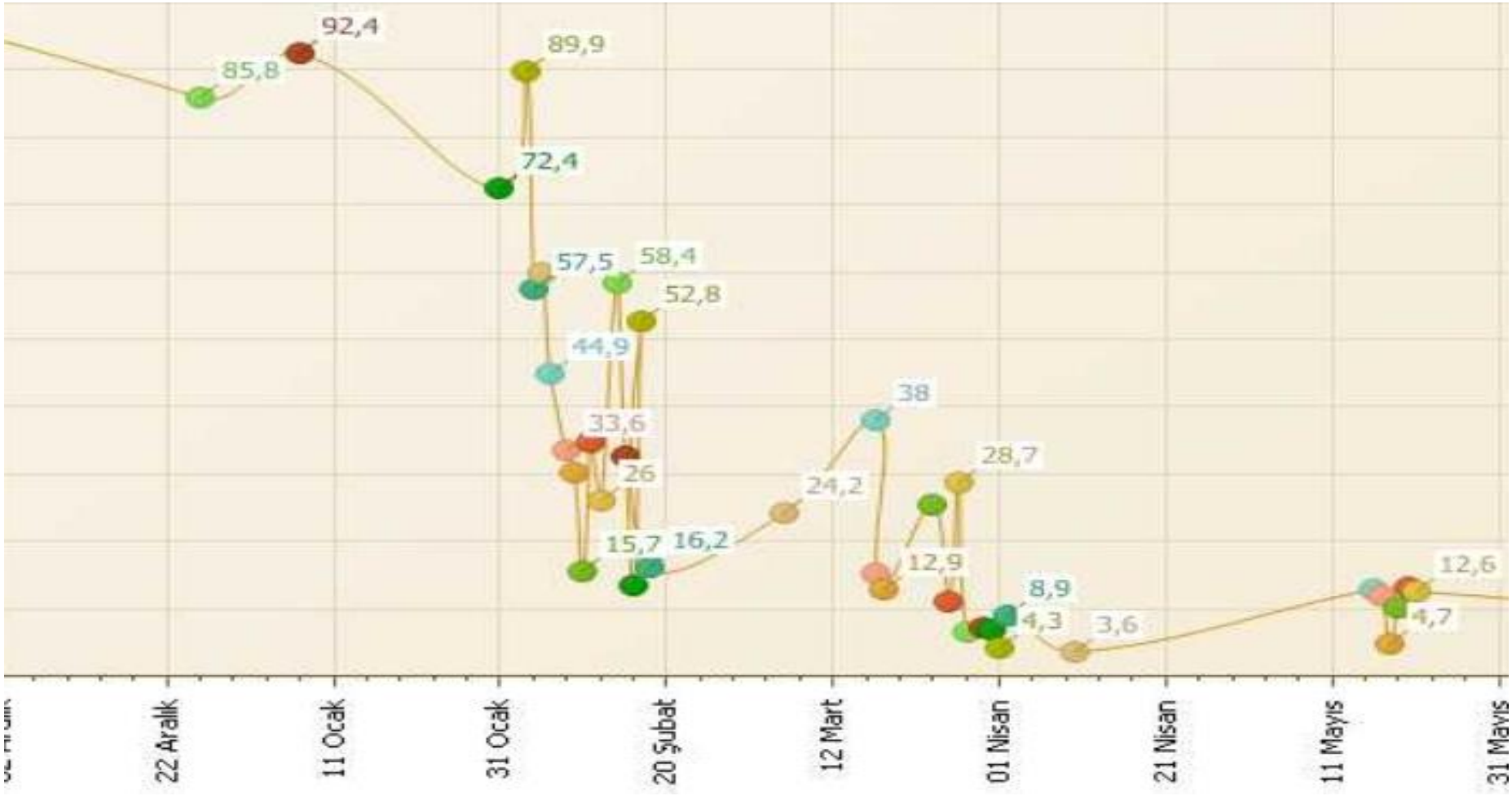
American Society of Clinical Oncology 2014, PCYC 1102/1103, O'Brien et al.

Lenfositoz

- İbrutinib tedavisiyle, çoğunlukla lenfadenopati azalmasıyla parelel olan lenfosit sayısında geri dönüşümlü artış gözlenmiştir (başlangıca göre ≥ %50 ve 5000/mcL mutlak sayı üzerinde artış)
- CLL/SLL: çoğu hastada gözlenmiştir (%75.2)
- Lenfositoz tipik olarak ibrutinib tedavisinin ilk birkaç haftasında meydana gelir (medyan süre 1.1 hafta) ve tipik olarak medyan iyileşme süresi MCL hastalarında 8.0 hafta ve CLL/SLL hastalarında 18.7 haftadır

Images provided by Susan M. O'Brien, MD.

İbrutinib-lenfositoz ilişkisi



Endikasyon

- Ibrutinib, Monoterapi 420 mg/gün (140mgx3kapsül)
- KLL'de FDA[1] onayını 12 Şubat 2014, EC onayını[2] da, 17 Ekim 2014 tarihinde almıştır.

1.http://www.fda.gov/
2.http://ir.pharmacyclics.com/releasedetail.cfm?releaseid=876757

Ibrutinib Endikasyon Bilgisi

			
CLL	**Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) & CLL/SLL with 17p deletion**.	IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukaemia **(CLL) who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation** in patients unsuitable for chemo-immunotherapy.	IMBRUVICA, **70 yaş üzeri olup CIRS* > 6** olması nedeniyle kemo-immünterapiye uygun olmayan **del 17p/TP53 mutasyonu pozitif** olan kronik lenfositik lösemi (KLL) olgularının **ilk basamak tedavisinde**, **70 yaş ve üzeri veya CIRS > 6 o**lması nedeniyle kemoterapiye uygun olmayan ve ilk basamak tedaviye yanıtsız/nüks KLL hastalarında **ikinci basamak tedavide, CIRS ≤ 6 olup** kemo-immünterapiye uygun olan ve **del 17p/TP53 pozitif KLL** olgularında ilk basamak tedavi sonrası yanıtsızlık/nüks durumunda **ikinci basamak tedavide endikedir**. **CIRS < 6 olup** kemo-immünterapiye uygun olan **KLL hastalarında** iki seri tedaviye rağmen yanıtsızlık/nüks durumunda **üçüncü basamak tedavide endikedir**.
MCL	IMBRUVICA is indicated for treatment of **Mantle cell lymphoma (MCL) who have received at least one**	IMBRUVICA is indicated for the treatment of adult patients with **relapsed or refractory mantle**	IMBRUVICA, en az 3 kür rituksimab ve alkilleyici ajan kombinasyonu sonrası nüks eden veya dirençli olan veya otolog kök hücre nakli sonrası **nüks eden mantle hücreli lenfomada (MHL) endikedir.**

KLL' de Imbruvica'nın onaylı endikasyonları

Imbruvica KLL endikasyonlar	Koşullar
1.Sıra tedavide (Del 17p/TP53 mutasyonlu)	≥70 yaş olup CIRS >6 olan
2.Sıra tedavide (ilk basamak tedavi sonucu RR KLL hastaları)	CIRS ≤ 6 olan del17p /TP53 mutasyonlu
	≥70 yaş **veya** CIRS >6 olan
≥ 3 Sıra tedavide (2 seri tedavi sonucu RR KLL)	RR KLL hastaları

*CIRS: Cumulative Illness Rating Scale; RR KLL: Relaps Refrakter Kronik Lenfositik Lösemi

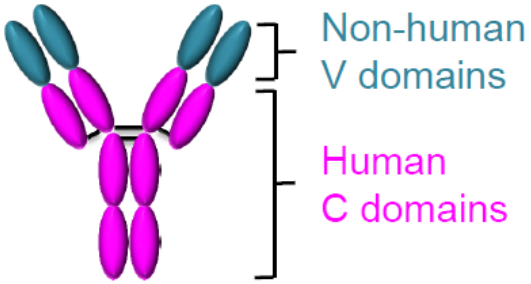
Imbruvica Kısa ürün bilgisi, 9.9.2016

Monoklonal Antikorlar için Uluslararası Tescilli olmayan İlaç İsimleri (Non proprietary drug names -INNs)

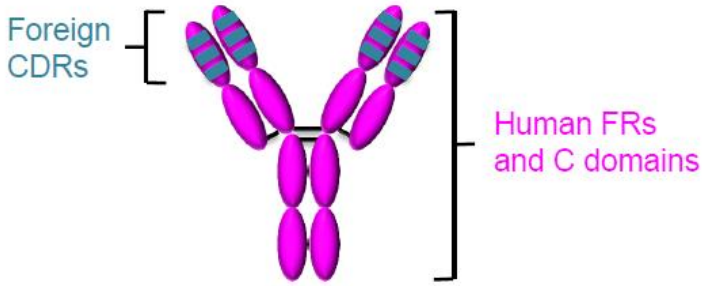
1990'da «mab» eki monoklonal antikorlar için kök olarak kabul edilmiştir

1997'de antikor kaynağını belirtmek için sub kökler geliştirilmiştir

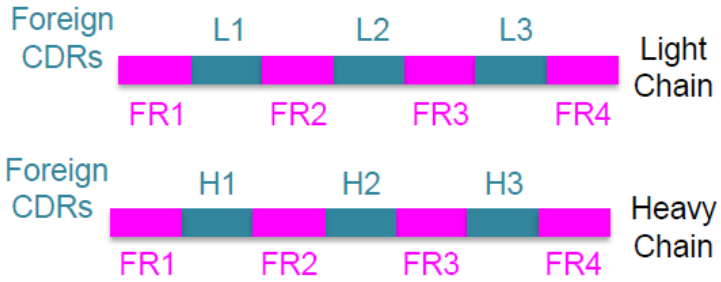
Common Antibody Origin	INN Substem	Representative Examples
Chimeric	-xi-	Abciximab, Rituximab, Infliximab, Cetuximab
Humanized	-zu-	Palivizumab, Trastuzumab, Bevacizumab, Natalizumab
Human	-u-	Adalimumab, Panitumumab Golimumab, Ipilimumab



Kimerik Antikorlar
-ximab

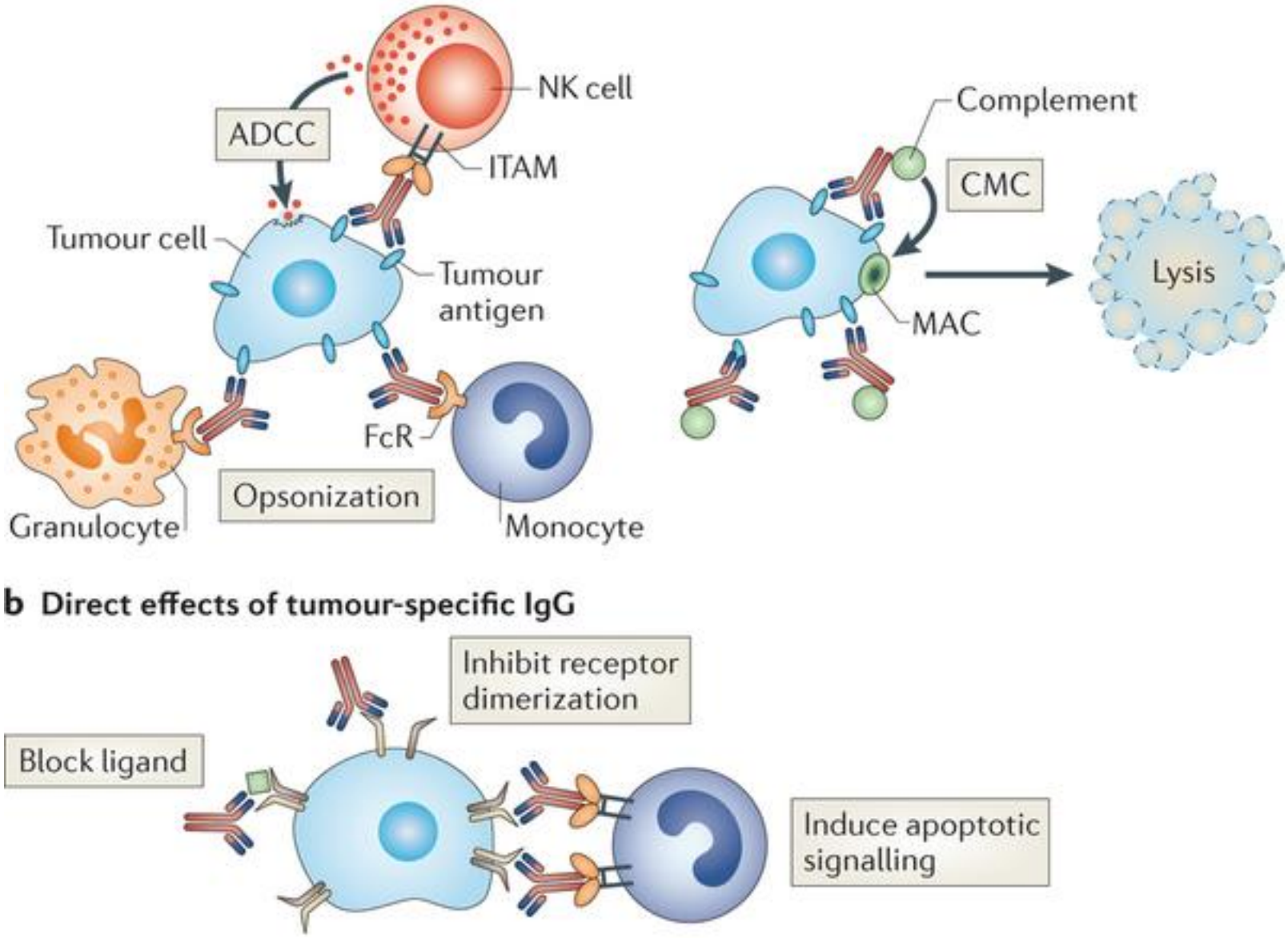


Humanize antikorlar
-zumab

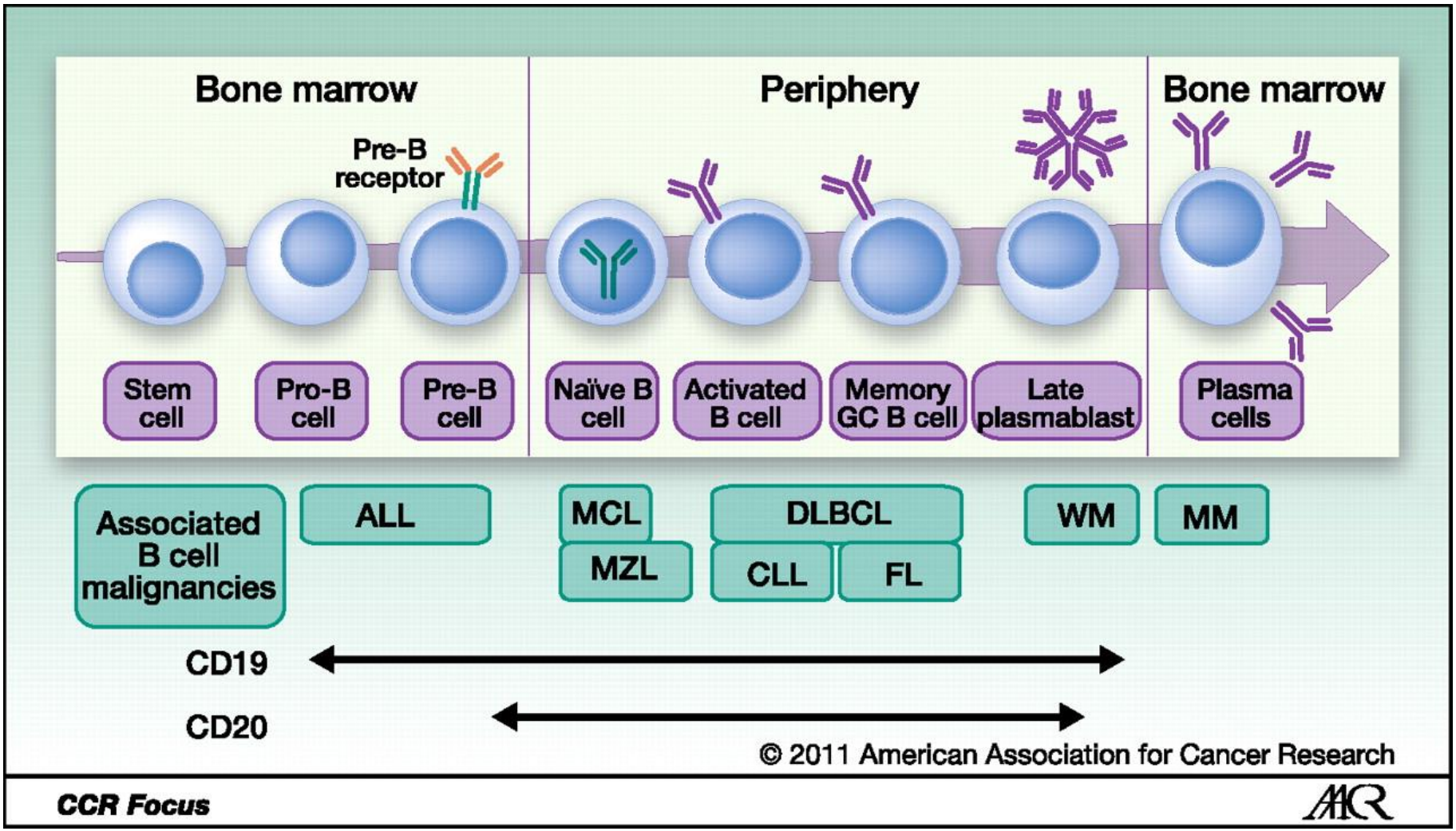


Complementarity determining regions (CDR)

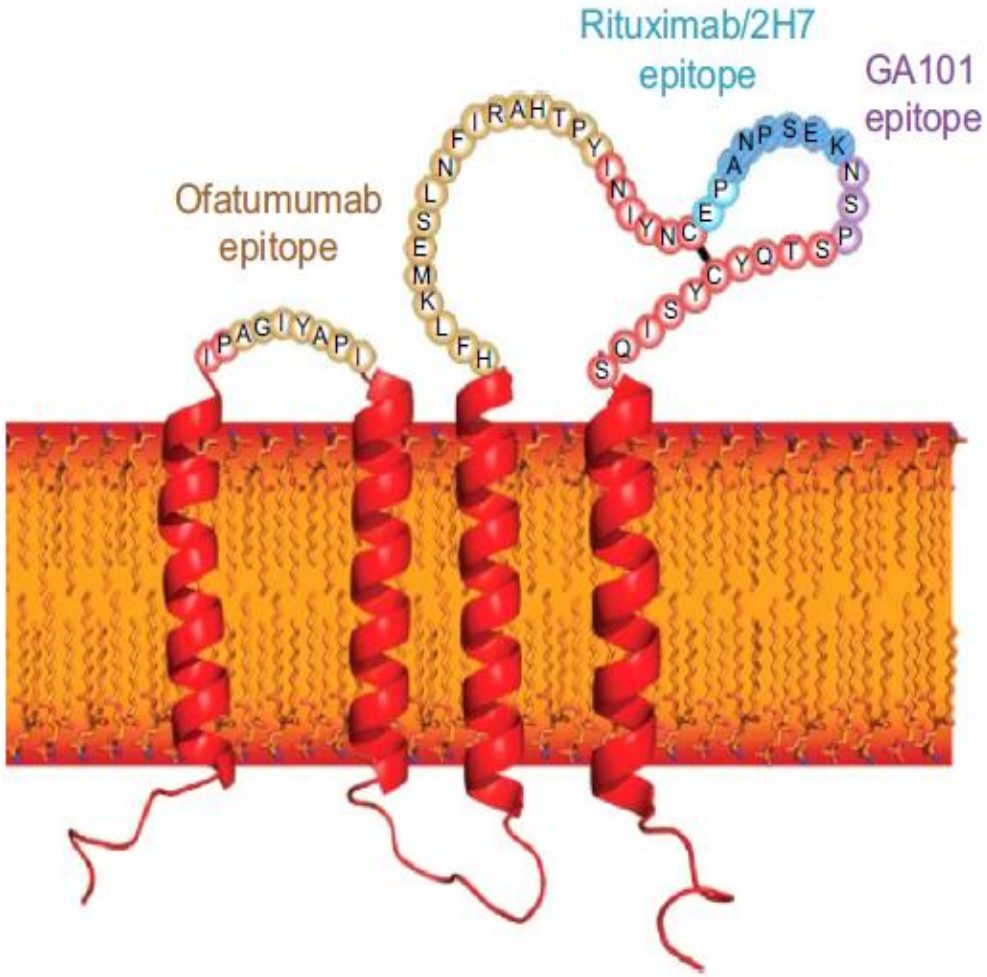
Variable bölgelerin sekans analizi: <%85 –ximab, ≥ %85 –zumab veya -umab


a Immune-mediated effects of tumour-specific IgG
NK cell
ADCC
ITAM
Tumour cell
Tumour antigen
FcR
Opsonization
Granulocyte
Monocyte
Complement
CMC
MAC
Lysis
b Direct effects of tumour-specific IgG
Inhibit receptor dimerization
Block ligand
Induce apoptotic signalling

CD 20 Ekspresyonu



CD20 yi hedefleyen antikorların epitop etkileşimleri

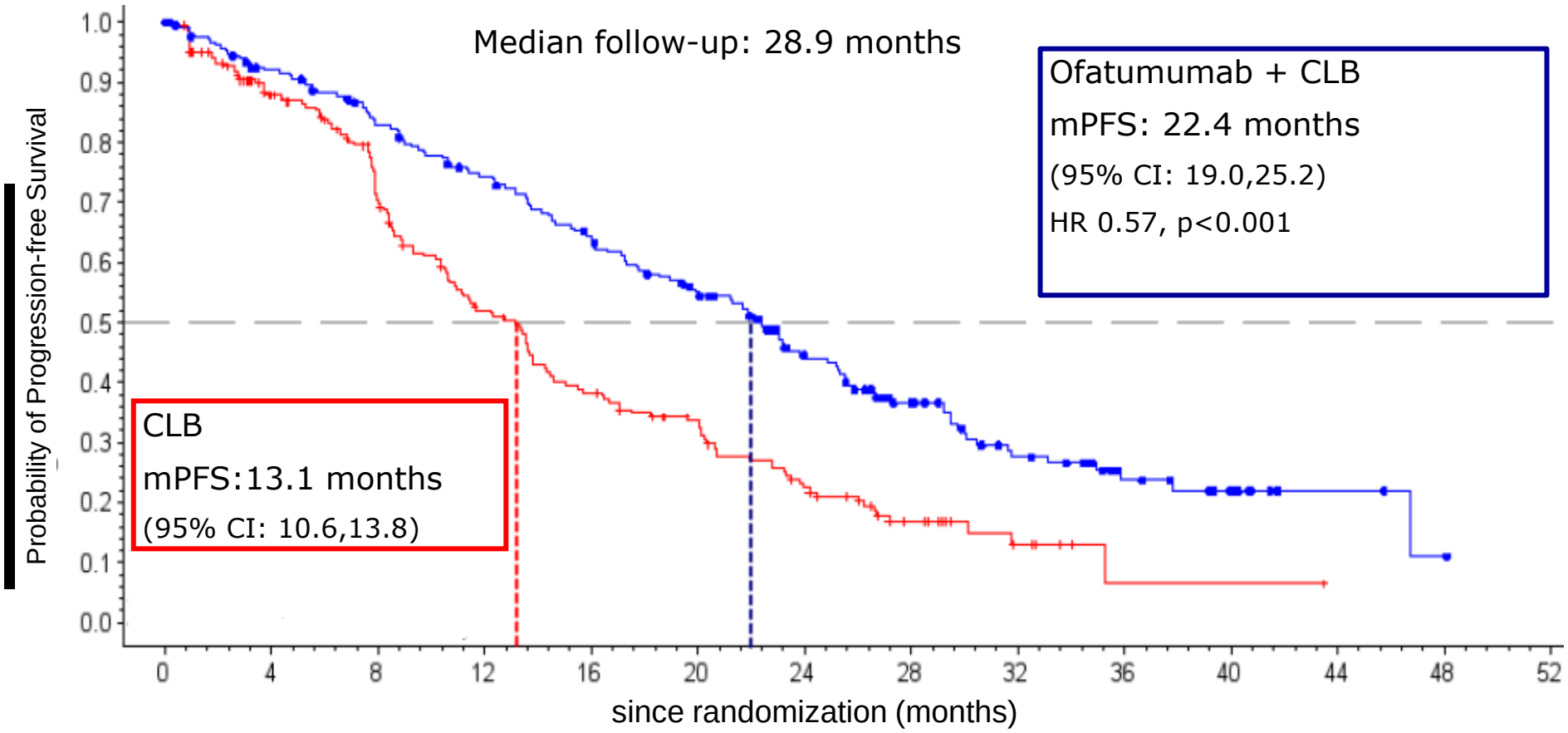


Anti-CD20 monoklonal antikorların etkileri

Table I Mechanisms of cell death by anti-CD20 monoclonal antibodies

	Rituximab	Ofatumumab	Obinutuzumab
Antibody type	Type I	Type I	Type II
Format	Chimeric	Humanized	Humanized
CD20 binding site	Large loop	Large and small loops, closer to cell membrane	Large loop
Localization to lipid rafts	Yes	Yes	No
Complement-dependent cytotoxicity	High	High	Low
Antibody-dependent cellular cytotoxicity	Low	Low	High
Direct cell death	Low	Low	High

Chemoimmunotherapy improves outcomes in patients not fit for FCR



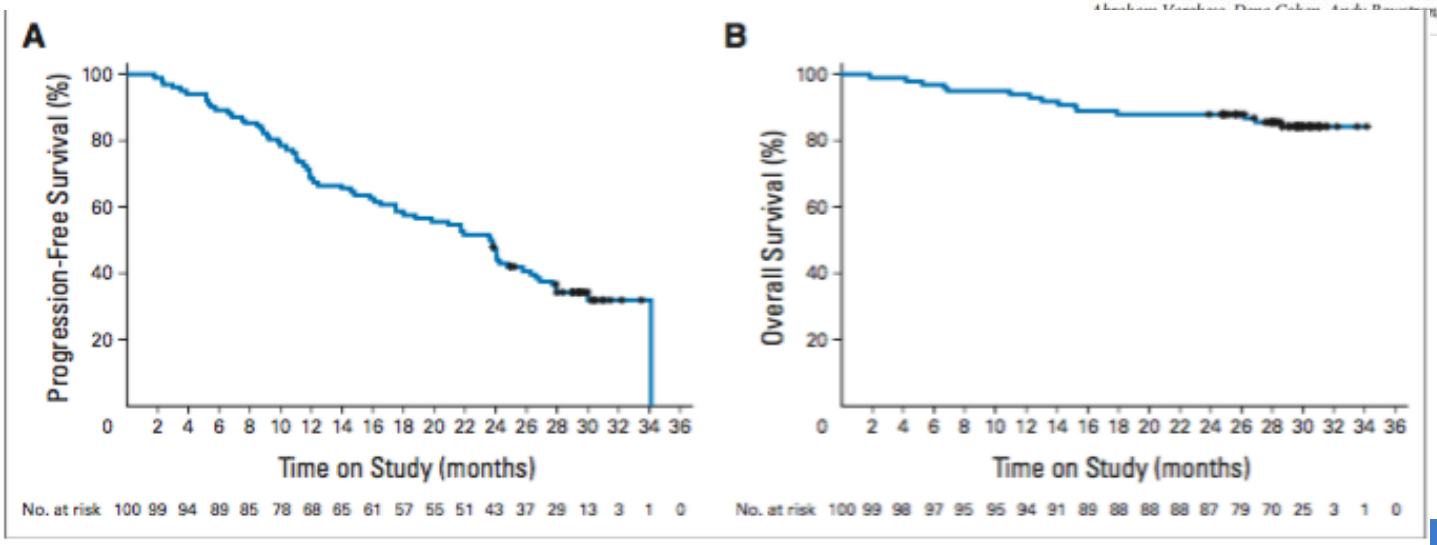
Hillmen et al. Lancet. 2015;385(9980):1873-83

R-KLORAMBUSİL

VOLUME 32 · NUMBER 12 · APRIL 20 2014
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Rituximab Plus Chlorambucil As First-Line Treatment for Chronic Lymphocytic Leukemia: Final Analysis of an Open-Label Phase II Study

Peter Hillmen, John G. Gribben, George A. Follows, Donald Milligan, Hazem A. Sayala, Paul Moreton, David G. Oscier, Claire E. Dearden, Daniel B. Kennedy, Andrew R. Pettitt, Amit Nathwani, Abraham Varghese, Dana Cohen, Andy Boyntun, Stephan Oertel, and Christopher F.E. Pocock



N= 100 , medyan yaş: 70, un-fit

ORR: %84, CR: %10 (IgVH mut olanlarda CR ve PR oranları yüksek)

Medyan 30 ay izlem sonunda:

PFS: 23.5 ay

OS: ulaşılamamış.

İYİ TOLERE EDİLEBİLEN ETKİN BİR TEDAVİ OLUP R-FC İÇİN UYGUN OLMAYAN UN-FIT OLGULARDA BİR SEÇENEK OLABİLİR

NDC 50242-070-01

Gazyva®
(obinutuzumab)
Injection

1000 mg/40 mL
(25 mg/mL)

For Intravenous Infusion After Dilution.
Single-Dose Vial. Discard Unused Portion.
No preservative.

℞ only

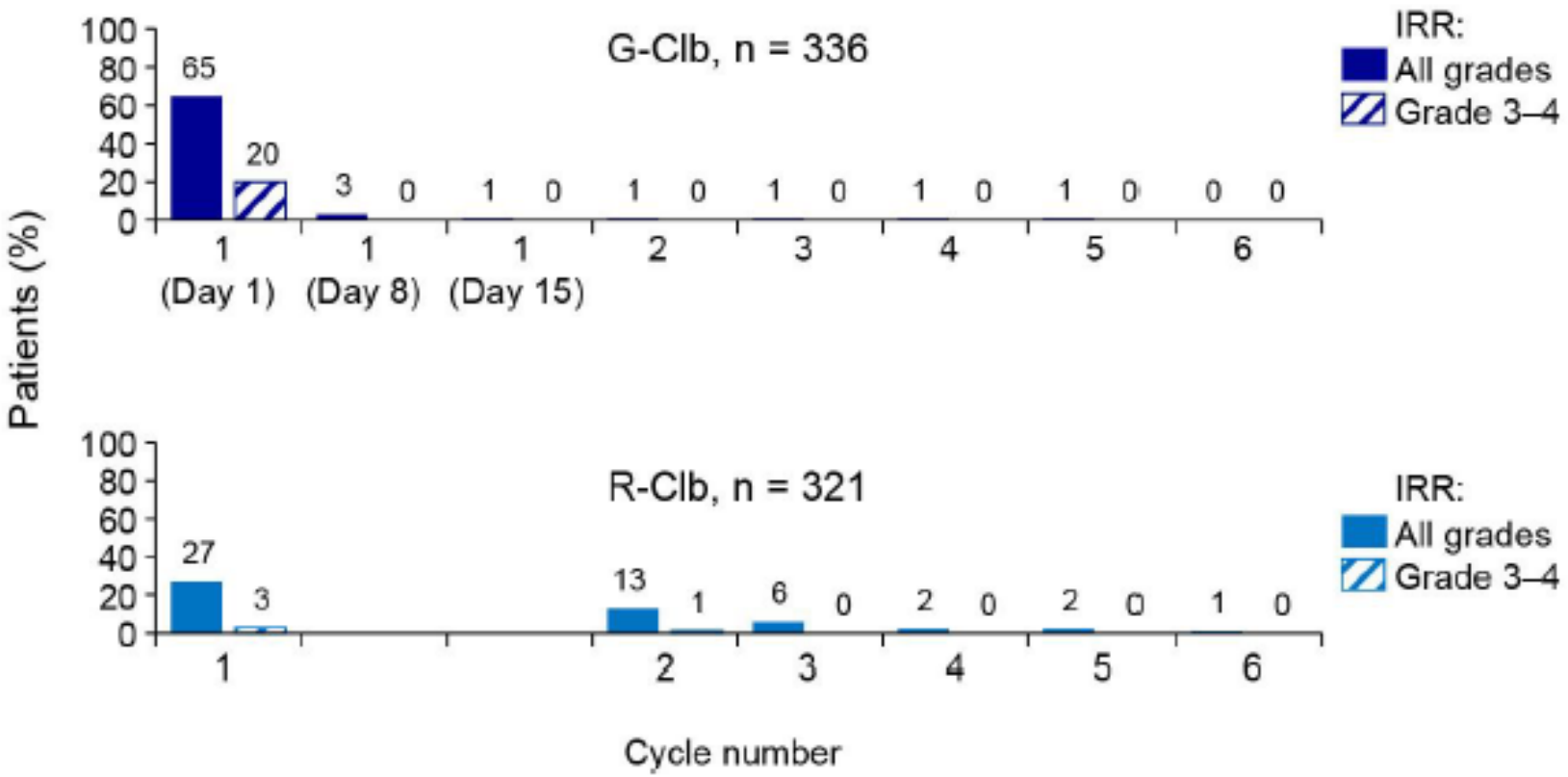
1 vial

Genentech

10173393

CLL11: IRR

Figure S2. All grade and grade 3–4* infusion-related reactions by day of infusion†



*There were no grade 5 IRR.

Goede V, et al. N Engl J Med. 2014 Mar 20;370(12):110

DOSING SCHEDULE

CYCLE 1

WEEK 1

WEEK 2

WEEK 3

WEEK 4

NO INFUSION GIVEN

FIRST 100 mg
Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate

REMAINING 900 mg
Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr

SUBSEQUENT INFUSIONS
If no infusion reaction occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr

CYCLES 2-6

WEEK 1

If no infusion reaction occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr

WEEKS 2-4

NO INFUSION GIVEN

Premedikasyon-prospektüs bilgisi

Ne zaman?

- Birinci siklus 1 ve 2. günlerde tam premedikasyon
- Bir önceki infüzyonda grade 2-3 infüzyon ilişkili reaksiyon olduysa veya bir sonraki tedaviden önce lenfosit sayımı ≥ 25.000/mm3 ise tam premedikasyon
- Diğer sikluslarda ve hastalarda sadece asetaminofen ve anti histaminik

Premedication	**Administration**
Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone*	Completed at least 1 hour prior to GAZYVA infusion.
650–1000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
anti-histamine (e.g., 50 mg diphenhydramine)	

YENİ JENERASYON BCL-2 İNHİBİTÖRLERİ: ABT-199 (Venatoclax)

BCL-2 sequesters the proteins BAX & BAK, allowing the CLL cell to evade death.

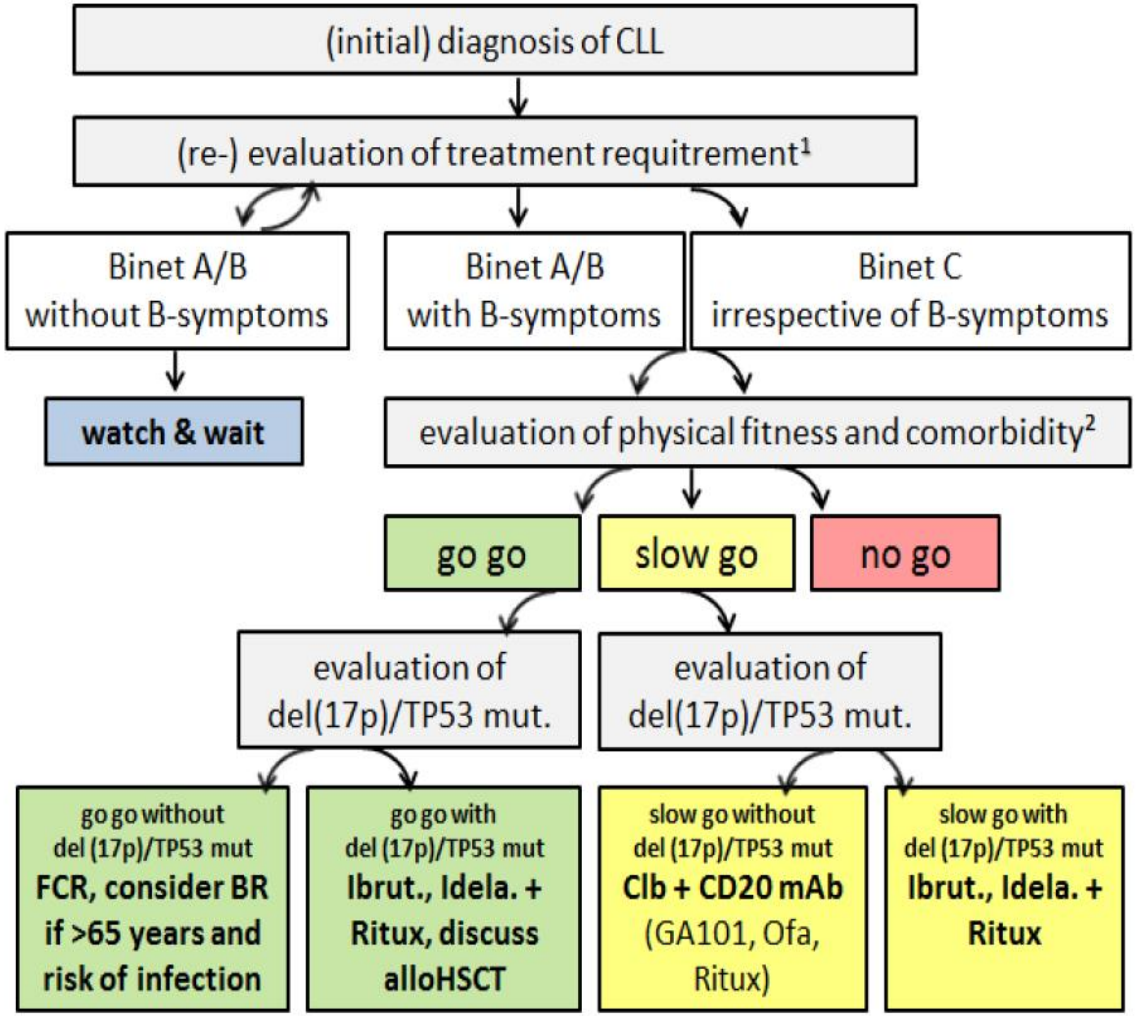
ABT199 blocks BCL-2, releasing BAX and BAK, which trigger cell death.

The Mechanism of Action of ABT-199: A. BCL-2 normally traps and inactivates the proteins (BAX and BAK) that would cause a CLL cell to die, tilting the balance towards signals from the proteins that promote cell growth and proliferation. ABT-199 inactivates BCL-2, releasing BAX and BAK, which trigger the death of the CLL cell.

Therapeutic algorithm of the GCLLSG

(April 2015)

DEUTSCHE STUDIENGRUPPE CLL



References: [1]) Hallek et al., Blood 2008
[2]) Gribben, Blood 2009