



KLL Tedavisinde Yeni Yolaklar

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10. ULUSAL AFEREZ KONGRESİ
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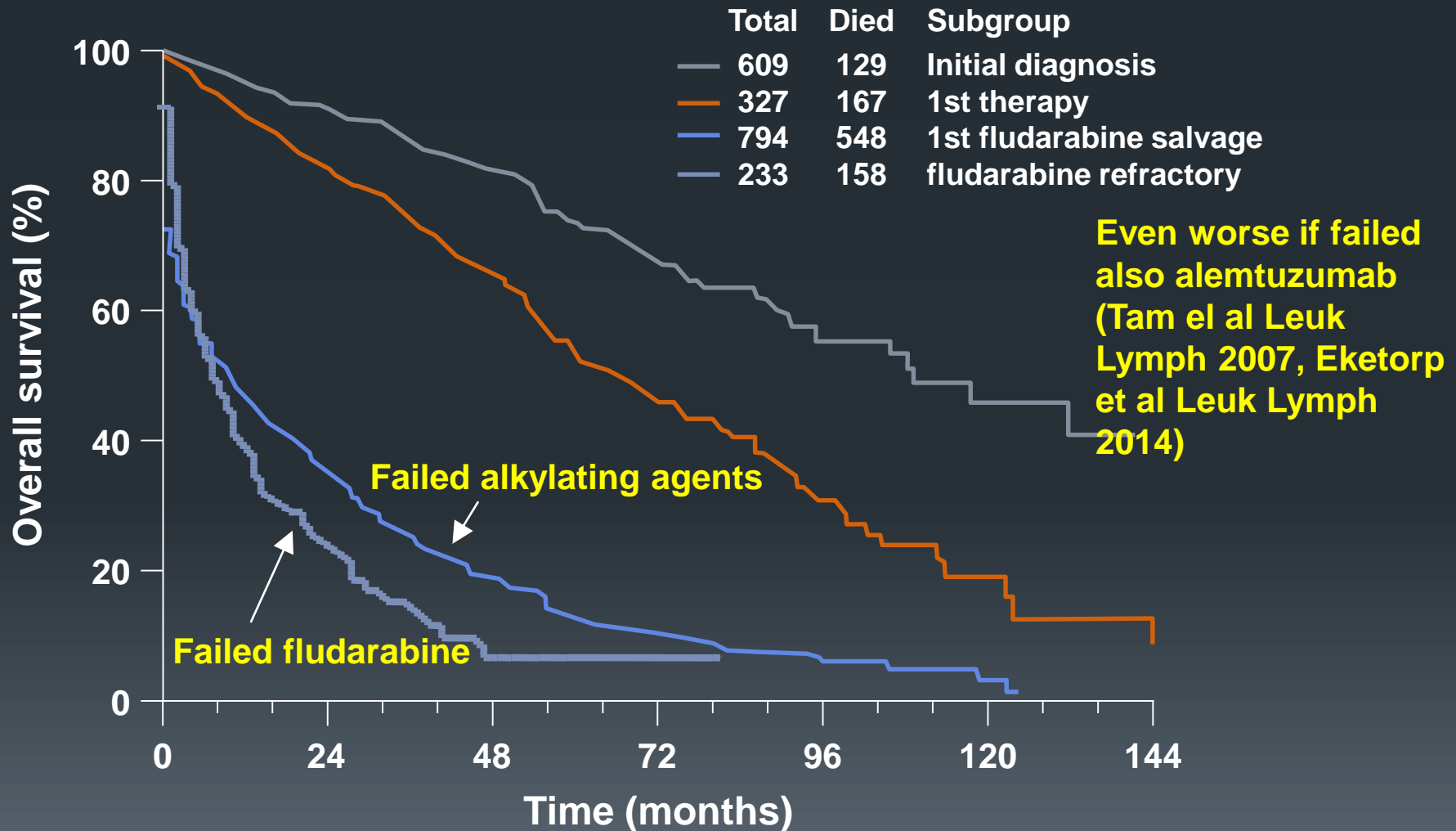
KLL

- CD19/20 + hücrelerde CD5 ve CD23 ekspresyonu
- PK >5000 lenfosit (olgun görünümde)
- Lenf nodu Bx: SLL
- Medyan yaş: 72

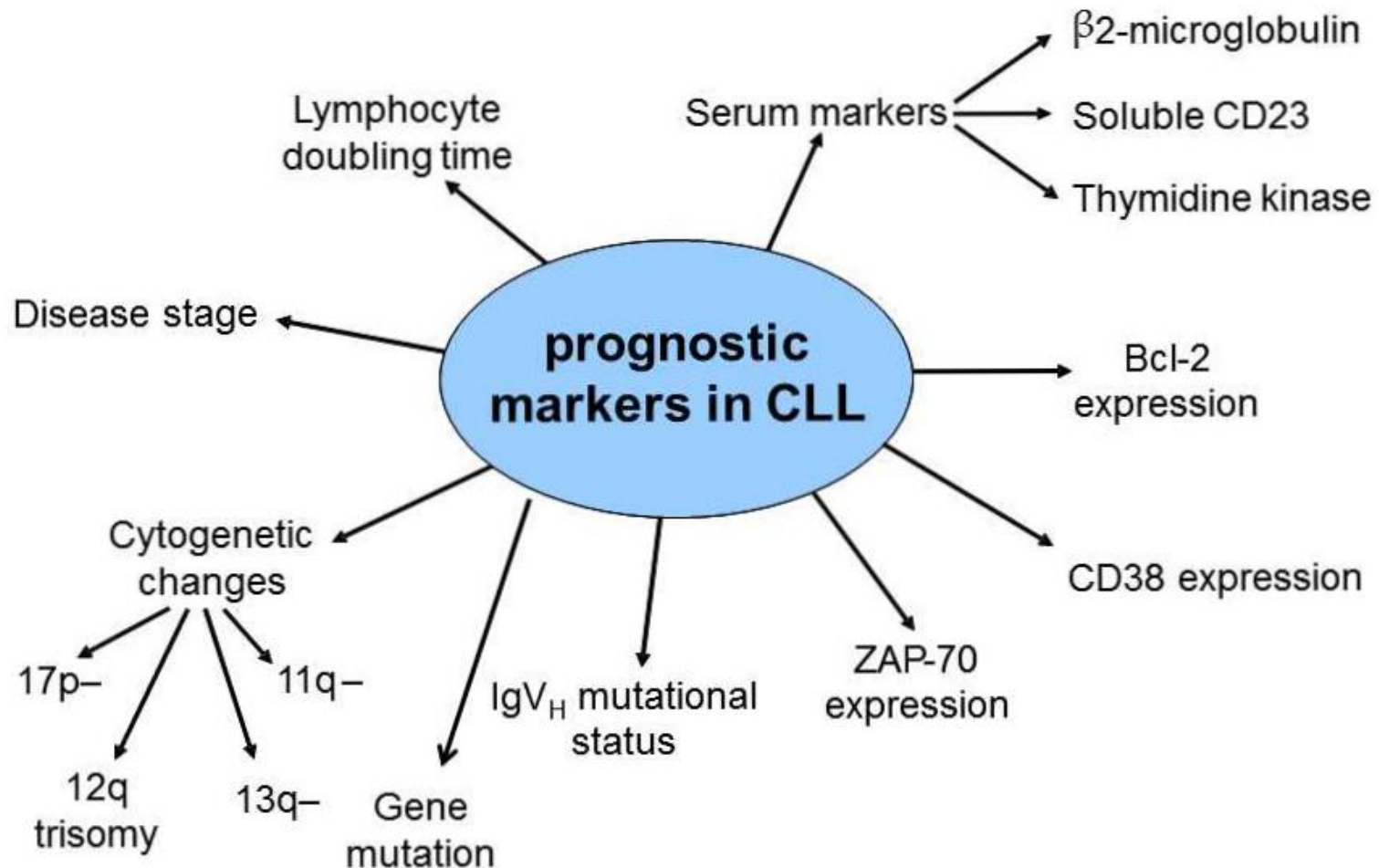
KLL Tedavisinde Sorular

- Ko- morbidite: ≥ 2 , sağkalımda azalma doğru orantılı
- < 70 / FORMDA HASTA :FCR UYGUN TEDAVİ Mİ?
- R-Benda: >70 formda hastalar
- >70 YAŞ/FORMDA OLMAYAN HASTAda TEDAVİ?
- Relaps Hastalıkta prognoz: 2. sıra etkin tedavi var mı?

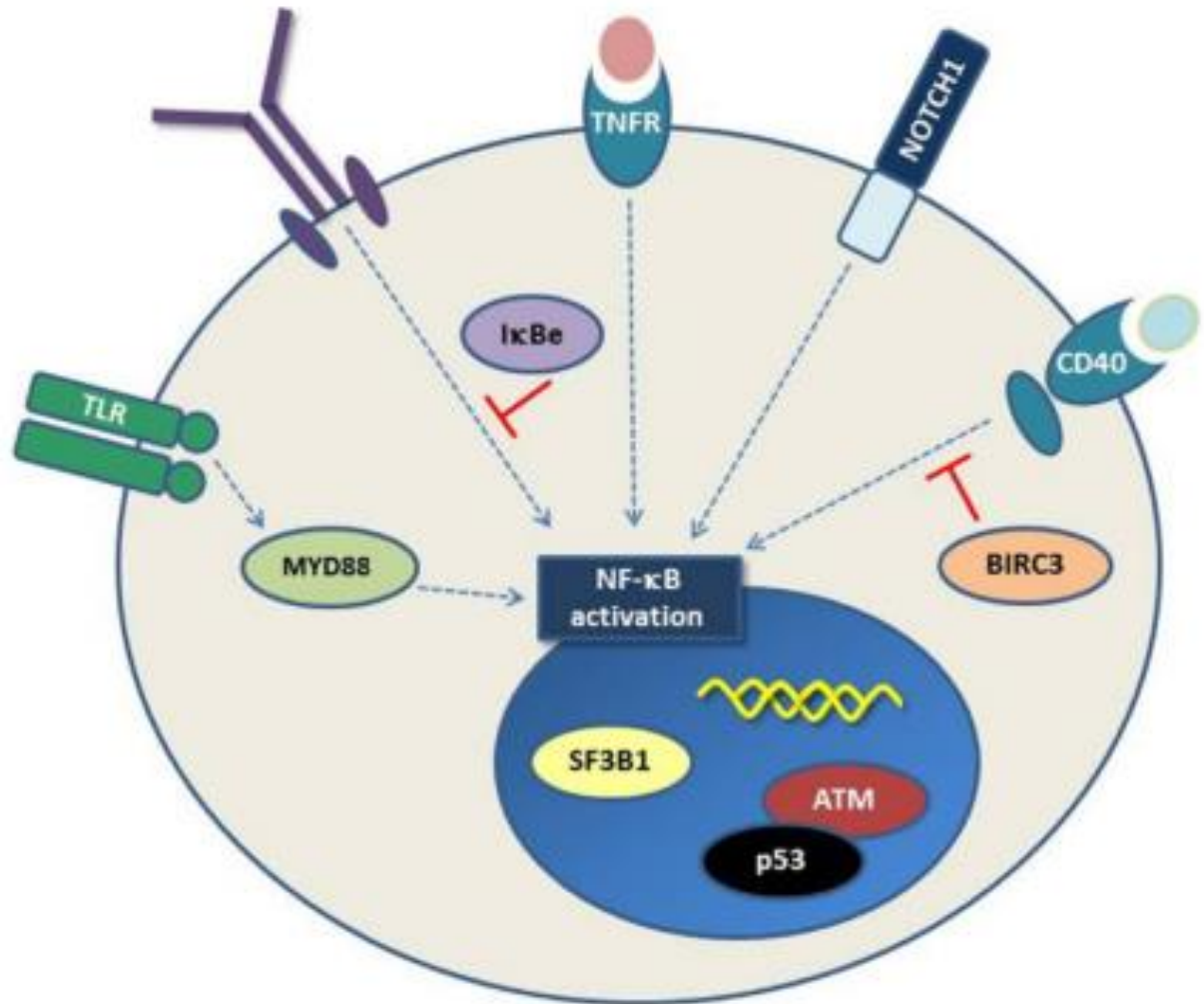
Konvansiyonel Tedaviye Refrakter KLL'de Prognoz



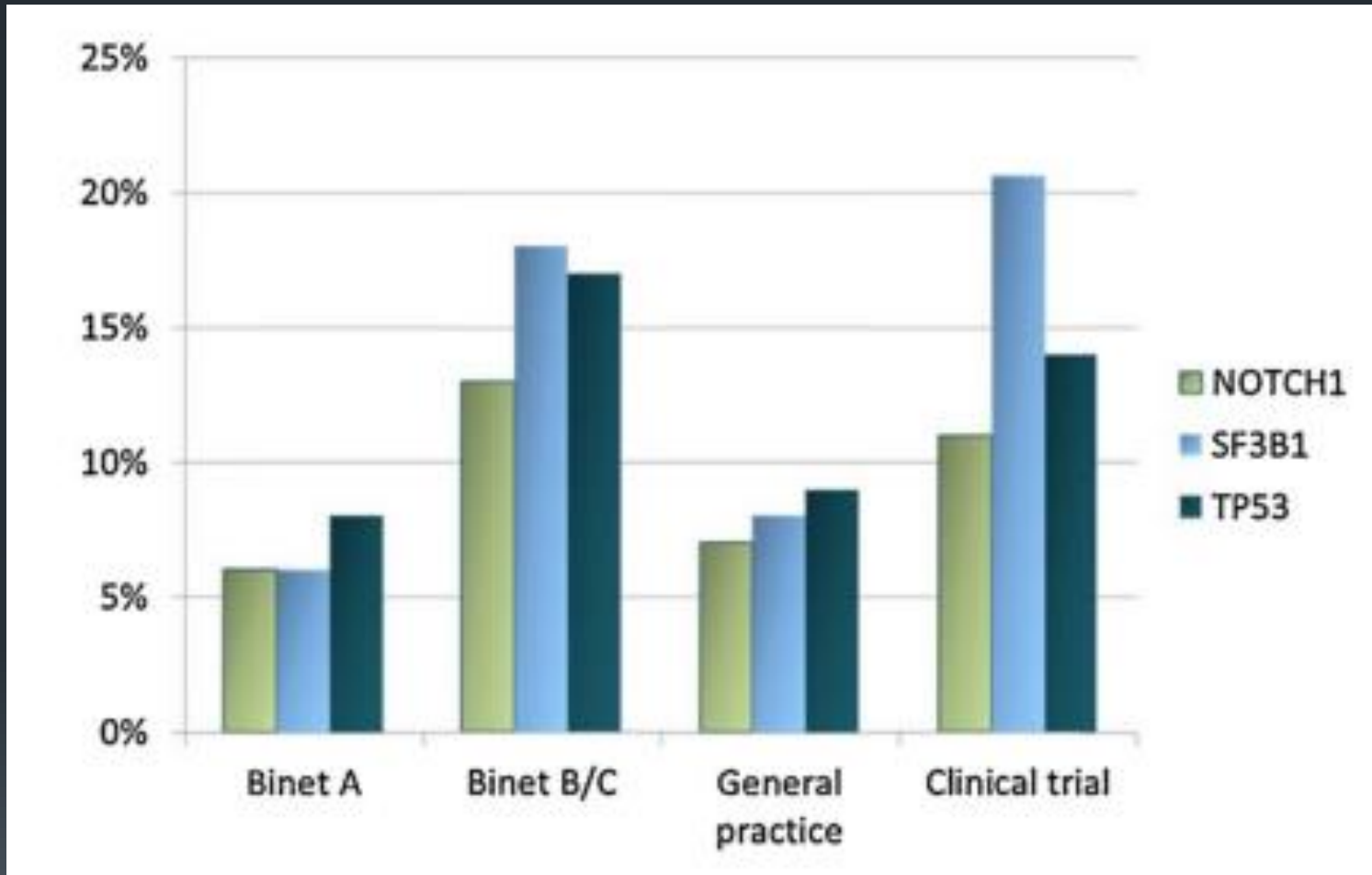
KLL: Prognostik Faktoren



KLL patogenezinde rol oynayan genetik bozukluklar



Rekürren mutasyonların sıklığı



- Baliakas P et al. Leukemia 2015



YÜKSEK RİSK KLL TANIMI

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

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 \(NHODG-D\)](#)

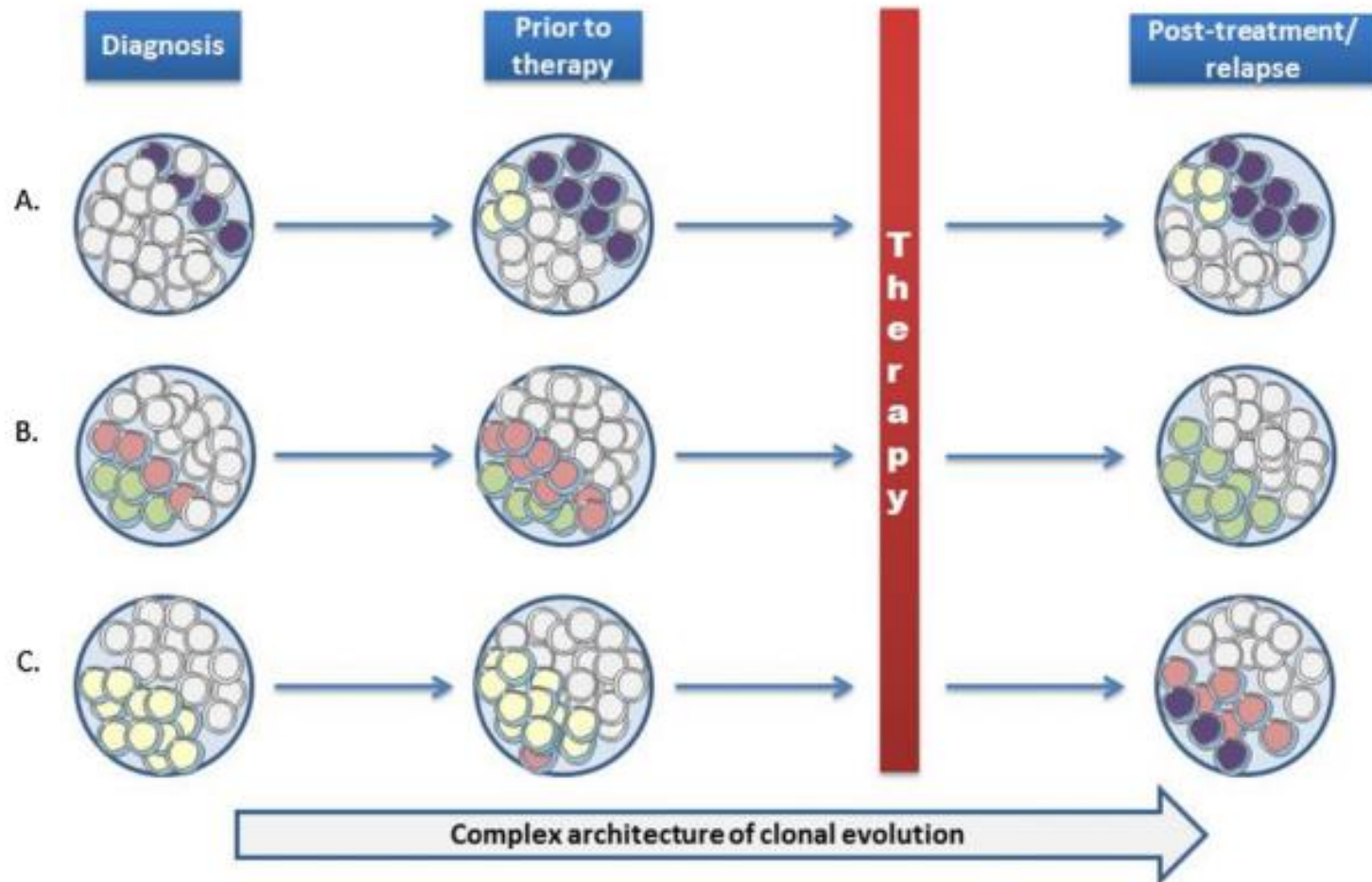
[See Suggested Regimens for
CLL with del \(17p\) \(2 of 4\)](#)

[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.

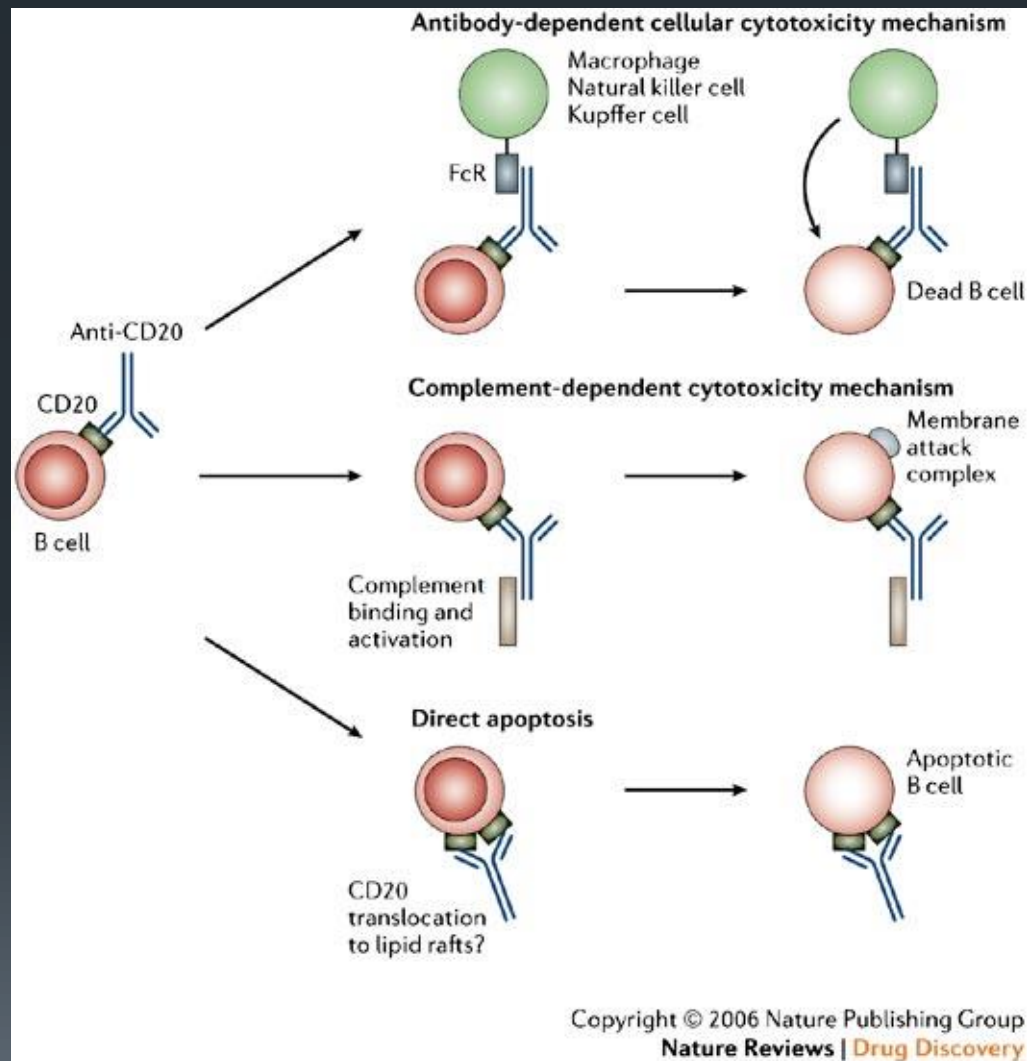
KLL'de kompleks klonal yapıya yol açan mekanizmalar



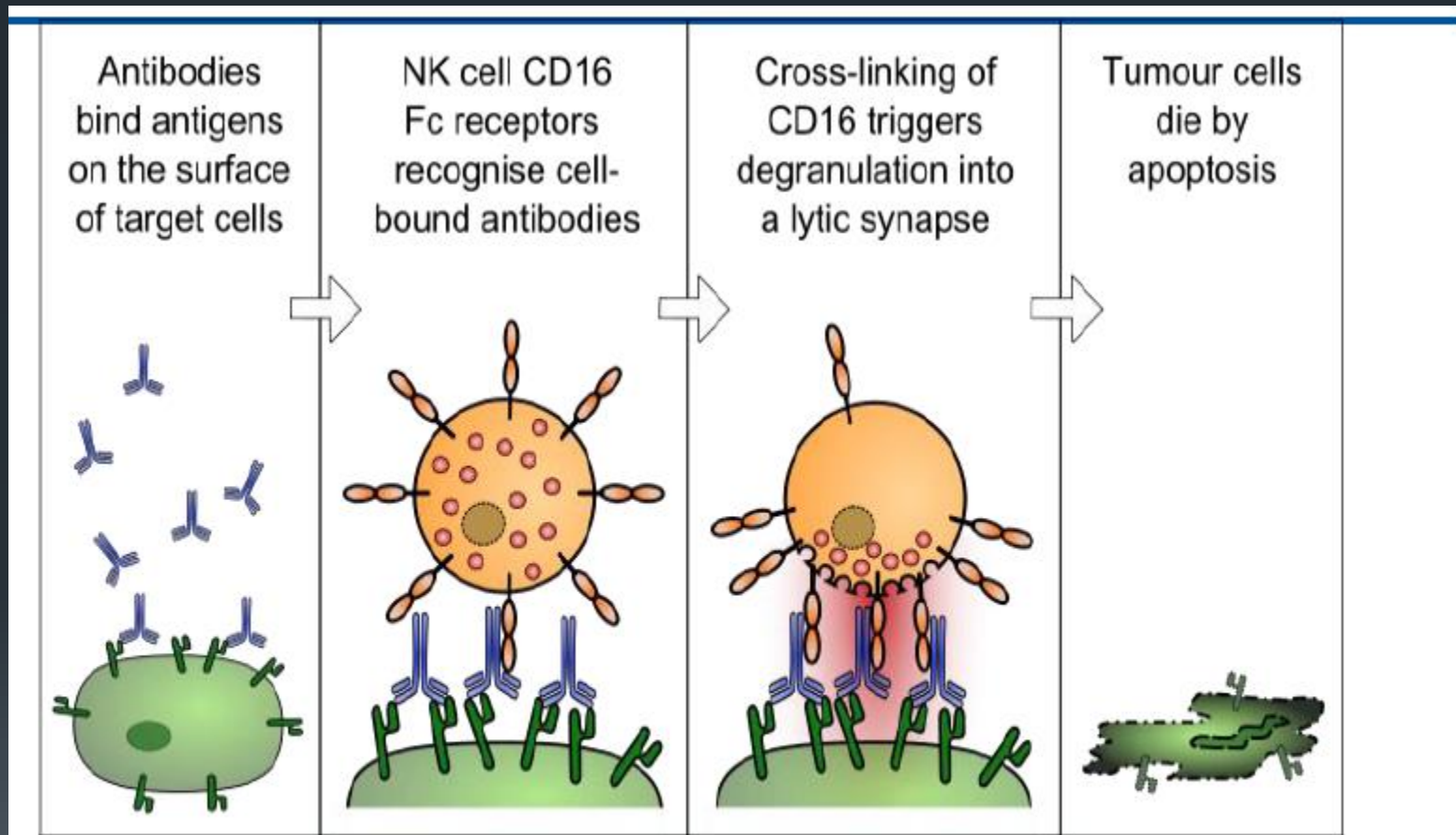


YENİ AJANLAR

Anti-CD20 (Rituximab)



ADCC-Antibody dependent cell mediated cytotoxicity



ADCC is triggered through interaction of target-bound antibodies of IgG or IgA or IgE classes with Fc receptors (FcRs), glycoproteins on the effector cell surface that bind the Fc region of Ig

Obinutuzumab/GA101

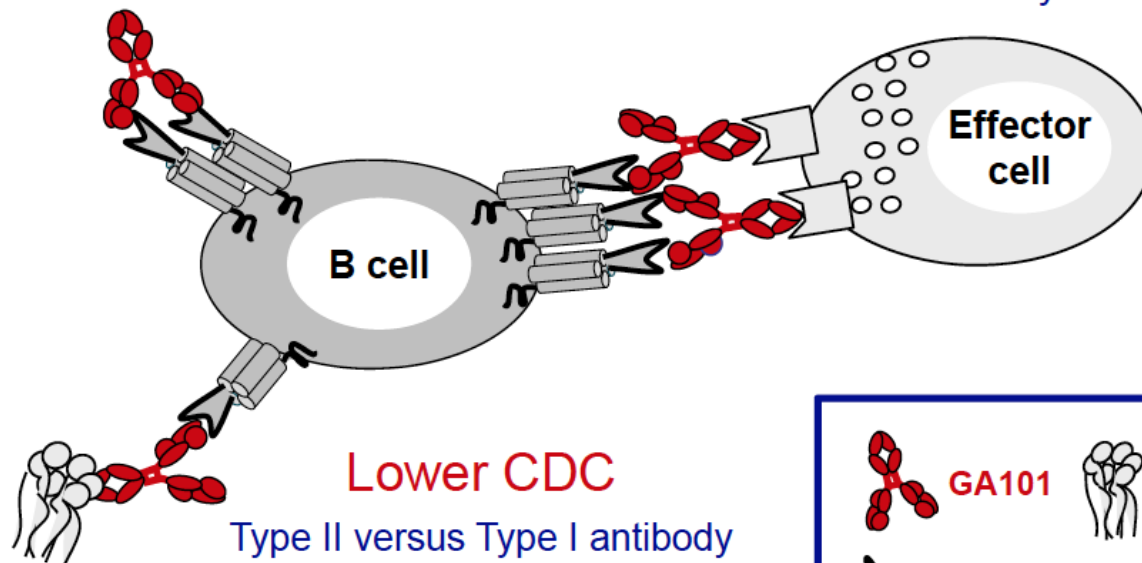
GA101: Mechanisms of action

Increased Direct Cell Death

Type II versus Type I antibody

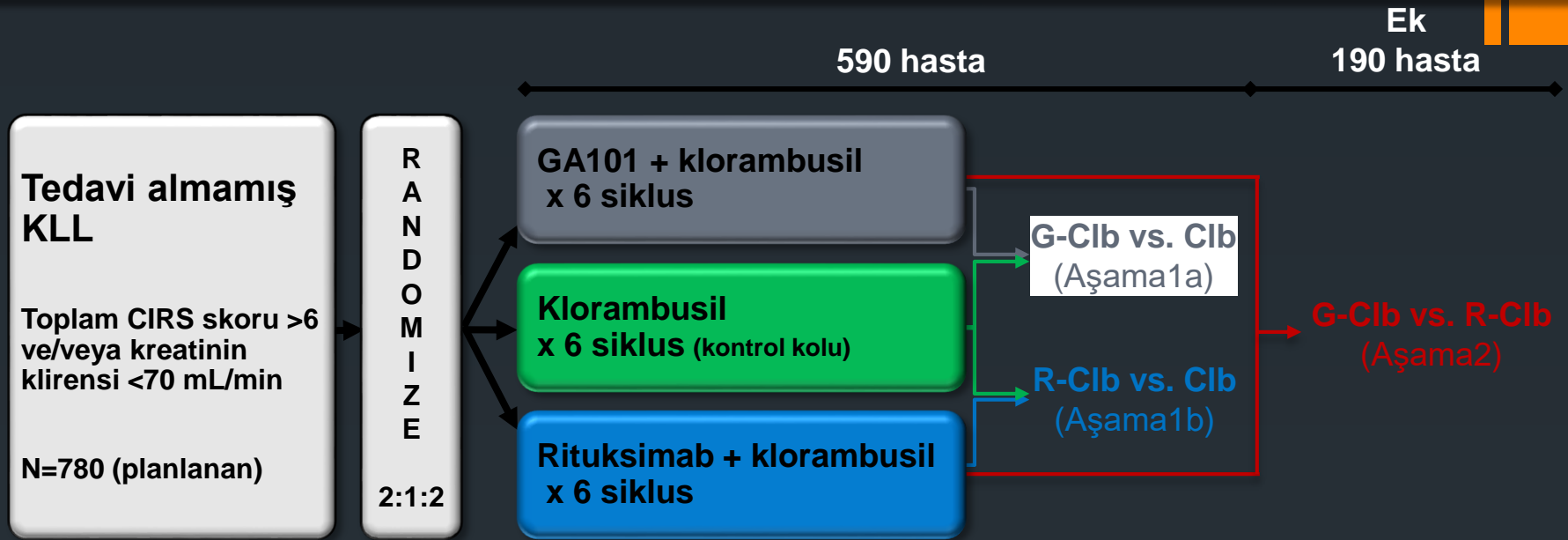
Enhanced ADCC

Glycoengineering for increased affinity to FcγRIIIa



ADCC, antibody-dependent cell-mediated cytotoxicity
CDC, complement-dependent cytotoxicity
Mössner E, *et al. Blood* 2010; 115:4393–4402

CLL11: Çalışma dizaynı



Dozlama şeması

- **GA101:** 1000 mg 1. siklusun 1., 8., and 15. günleri; 2-6. siklusun 1. günü, 28 günlük sikluslar
- **Rituksimab:** 375 mg/m² 1. siklusun 1. günü, 500 mg/m² 2-6. siklusun 1. günü, 28 günlük sikluslar
- **Klorambusil:** 0.5 mg/kg gün 1-6 siklusun 1. ve 15. günleri, 28 günlük sikluslar
- Clb kolunda progresif hastalığı olan hastaların G+Clb koluna geçişine izin verildi

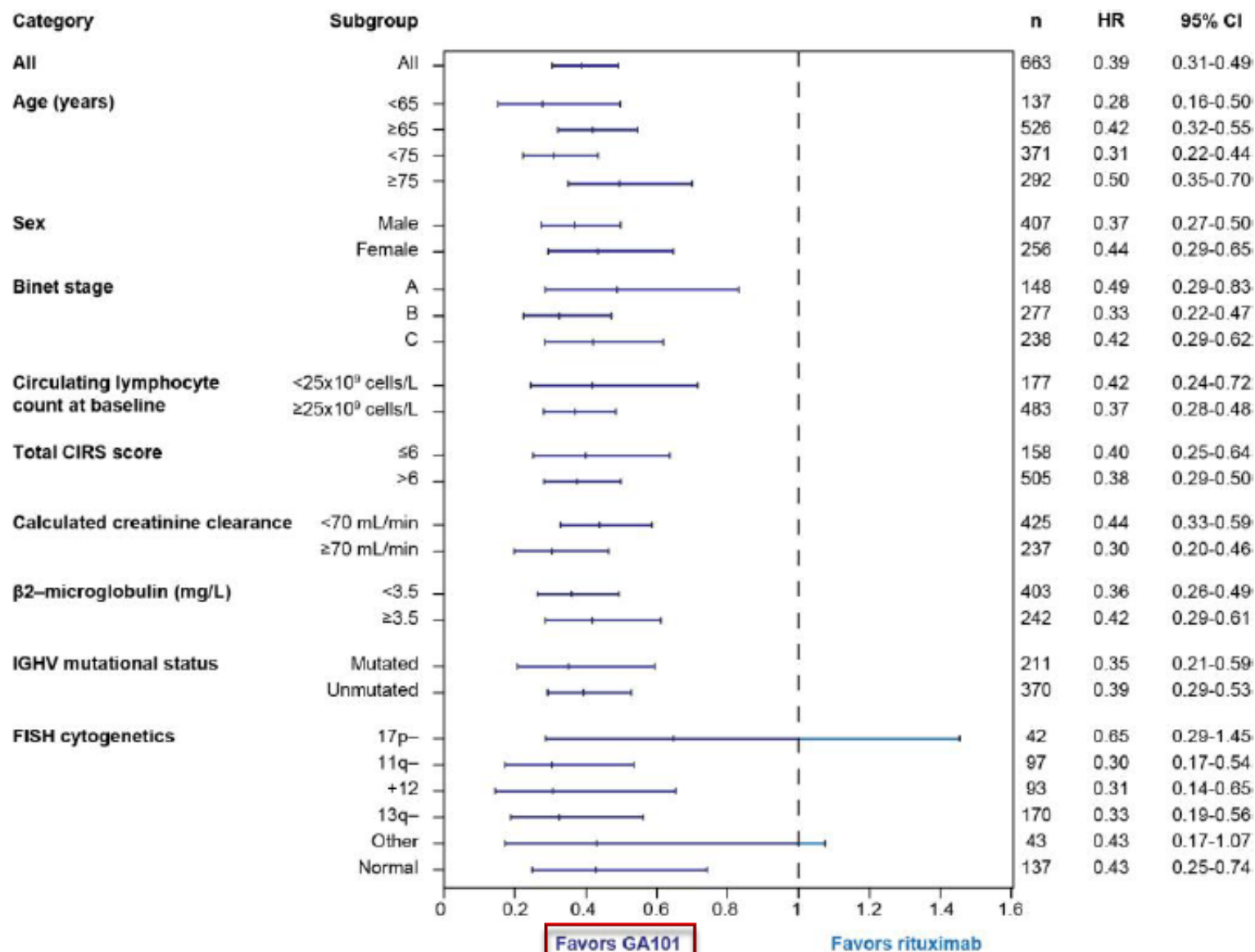
Sonlanım noktaları

- Primer sonlanım noktası
 - Araştırmacı değerlendirmeli PFS
- Önemli sekonder sonlanım noktaları:
 - IRC tarafından değerlendirilen PFS
 - Yanıt ve MRD negatifliği oranları
 - EFS, TTT
 - Genel sağkalım
 - Güvenlilik

CIRS; cumulative illness rating scale; G-Clb, GA101 plus chlorambucil; IRC, independent review committee; MRD, minimal residual disease; PFS, progression-free survival; R-Clb, rituximab plus chlorambucil

CLL11:

Alt gruplara göre PFS



CLL11: Sonuçlar

G-C1b
Vs
C1b

- **OS** (p:0.0014) Δ %53
- **PFS farkı** Δ 18.8 ay
- **TTNT farkı** Δ 27.6 ay
- **ORR, CR (yanıt oranları), MRD negatifliği, EFS ve yanıt süresi anlamlı üstün**

G-C1b
Vs
R-C1b

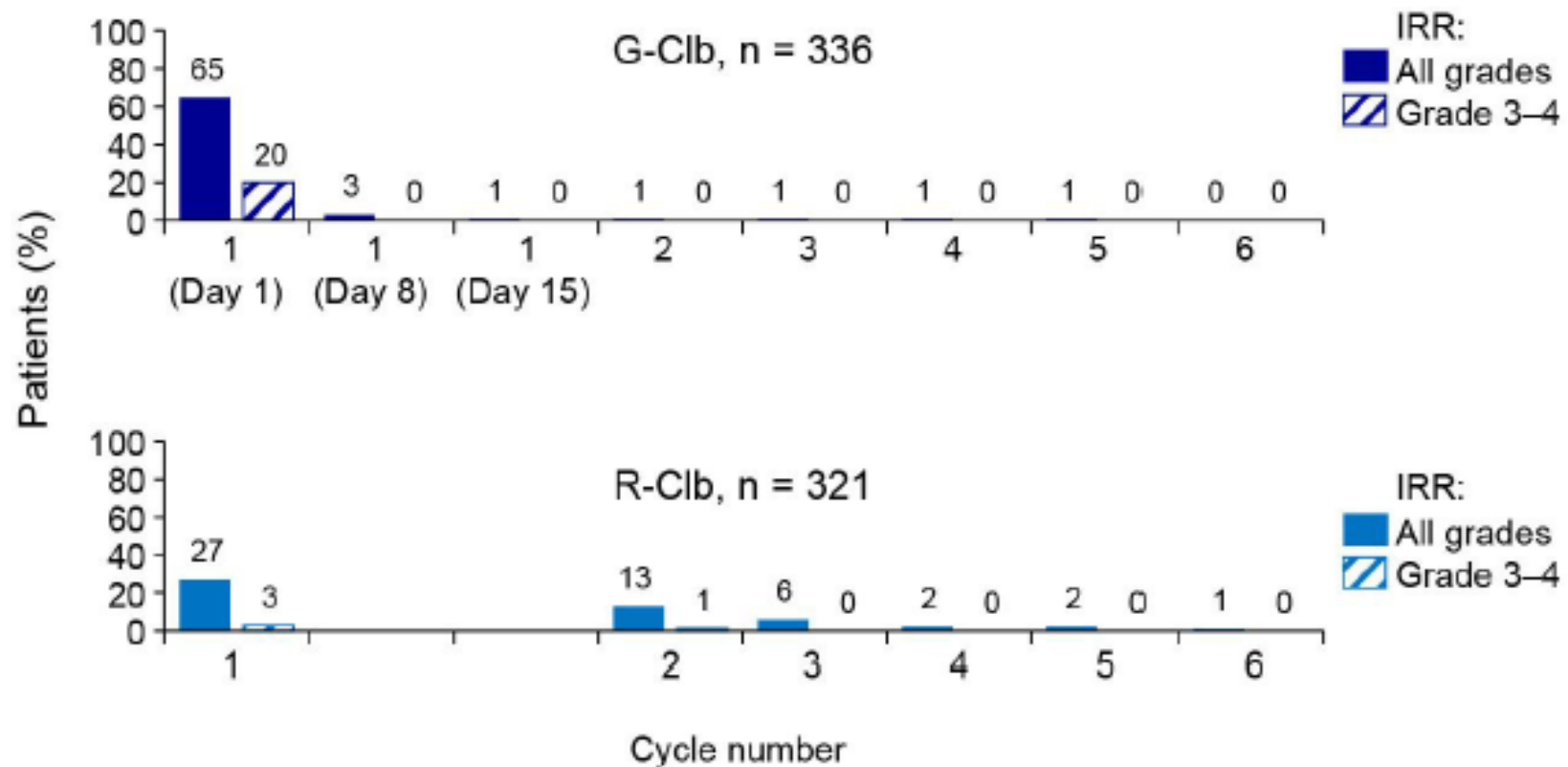
- OS (p:0.0632) henüz matür değil
- **PFS farkı** Δ 13.8 ay
- **TTNT farkı** Δ 10 ay
- **ORR, CR (yanıt oranları), MRD negatifliği, EFS ve yanıt süresi anlamlı üstün**

R-C1b
Vs
C1b


- OS (p:0.0242) Δ %40
- **PFS farkı** Δ 5.2 ay
- **TTNT farkı** Δ 17.6 ay
- **ORR, CR (yanıt oranları), MRD negatifliği, EFS ve yanıt süresi anlamlı üstün**

CLL11: IRR

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

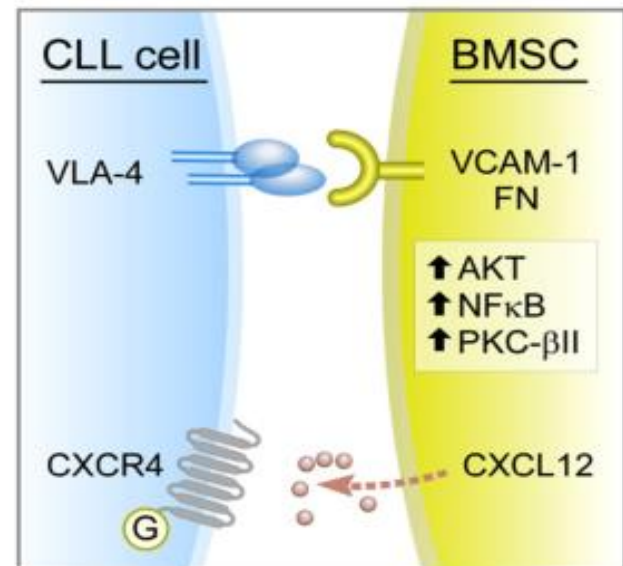
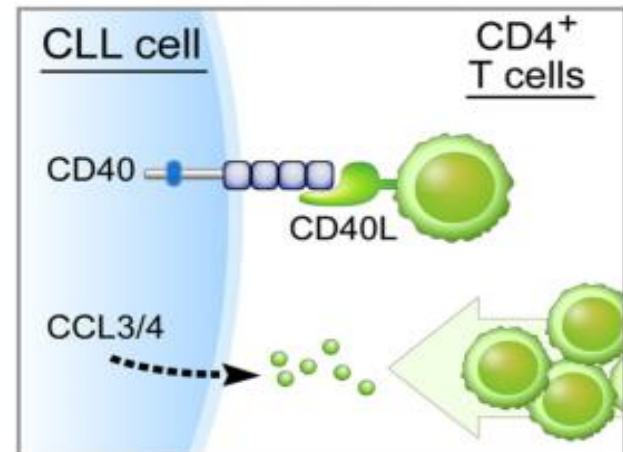
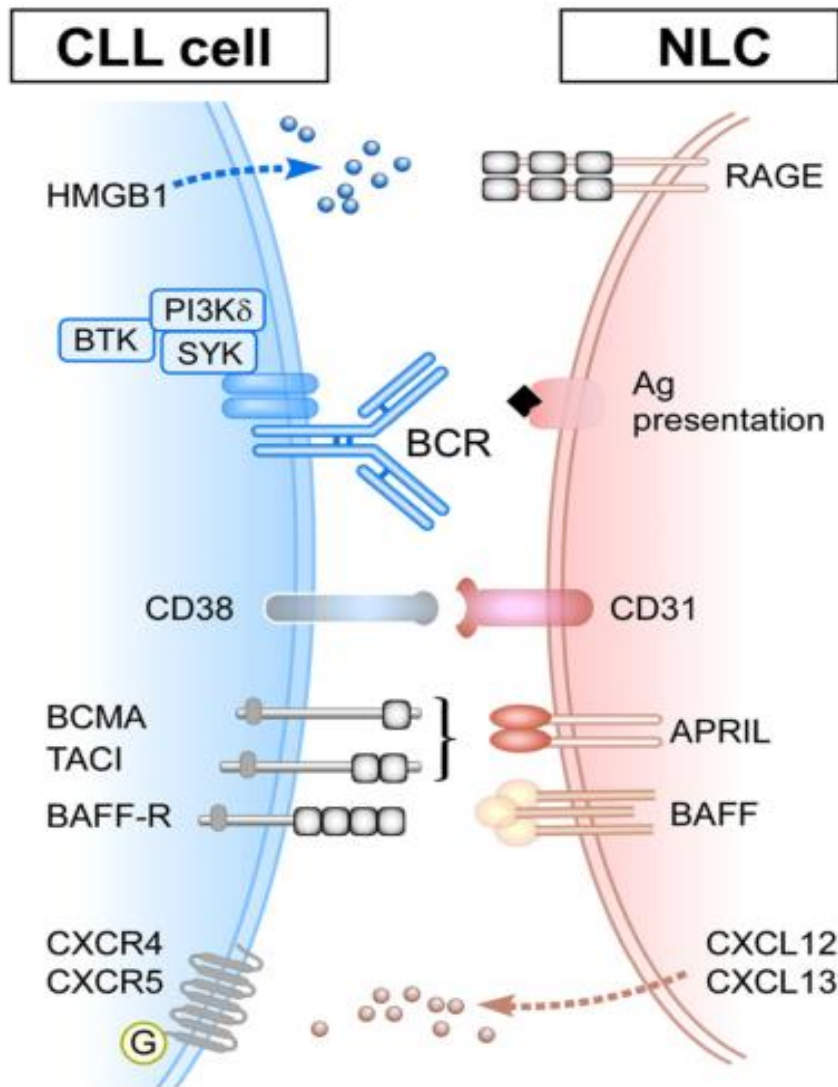


*There were no grade 5 IRR.

- 
- KLL mikroçevresi
 - B hücre reseptör yolağı

Mikroçevre

- Nurse like hücreler (NLCs): in vitro olarak KLL hastalarının periferik kan mononükleer hücrelerinin monosit fraksiyonundan meydana gelirler ve sekonder lenfoid organlarda bulunurlar
- NLCs, KLL hücrelerinde BCR sinyal yolağını aktive ederler ve CXCL12 ve CXCL13 kemokinlerini sekrete ederek KLL hücrelerini doku mikroçevresine çekerler

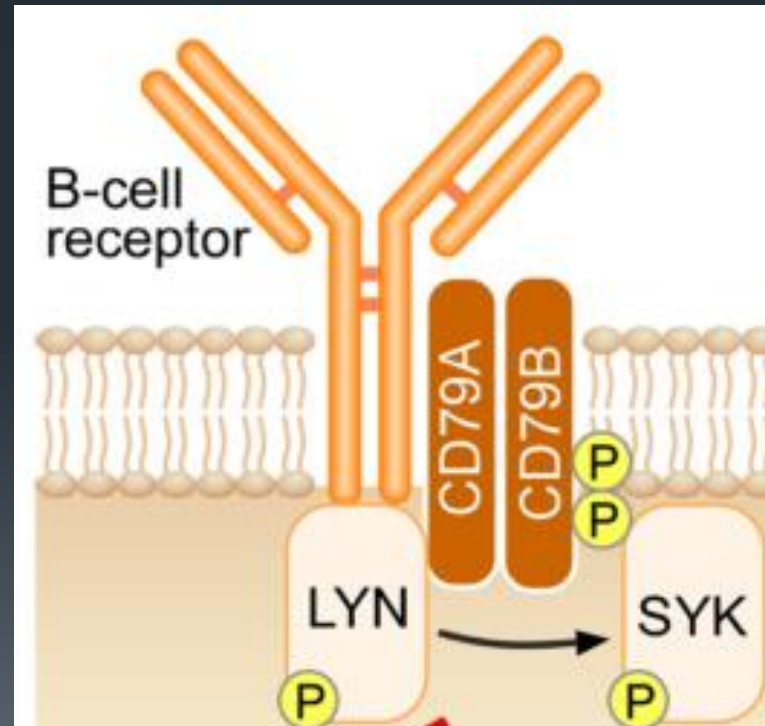


B hücre reseptörü ve sinyal yollarının önemi

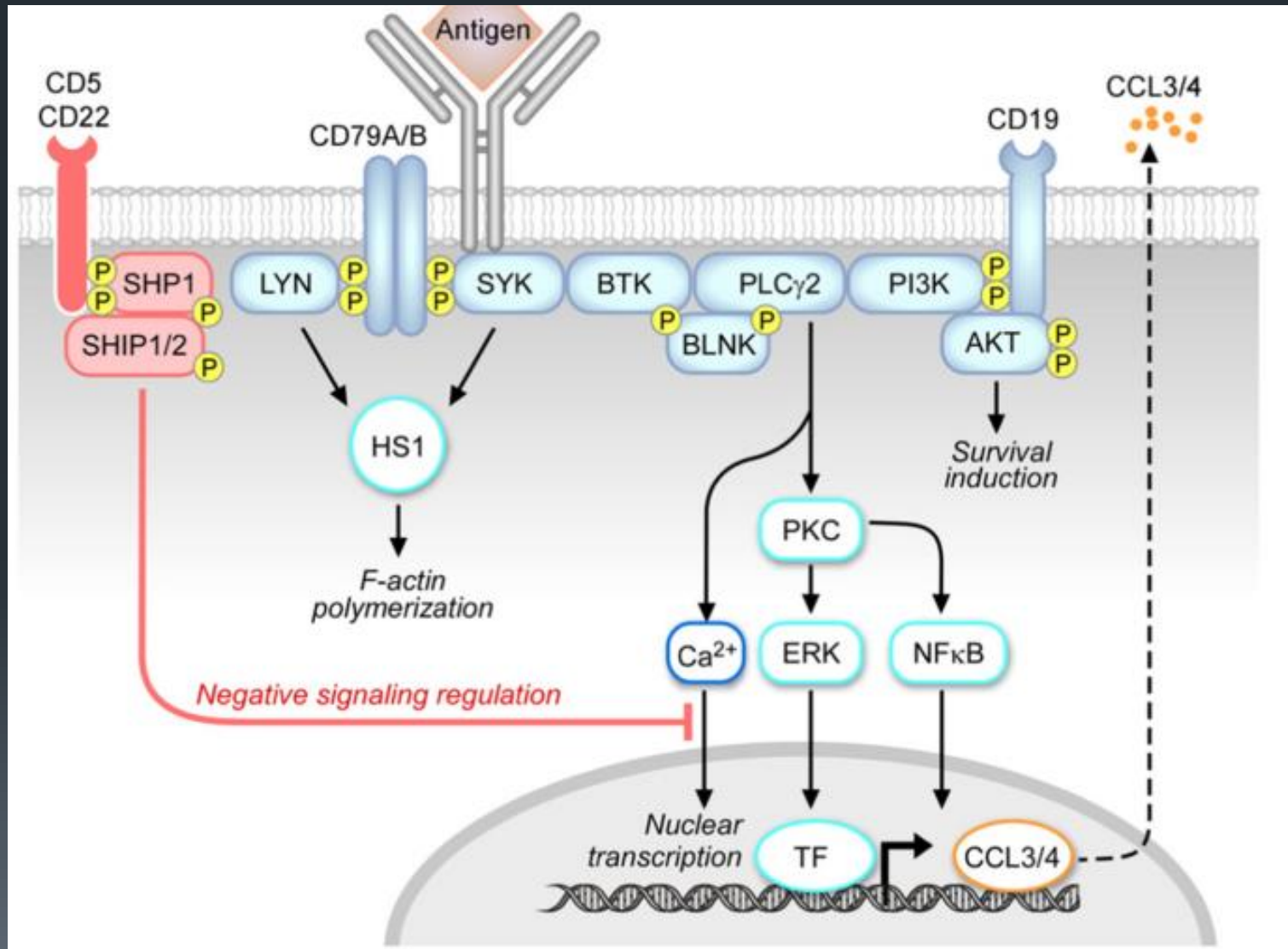
- B hücre reseptörü (B-cell receptor /BCR) tüm B hücrelerinde bulunur ve 2 ana fonksiyonu vardır:
 - Yabancı antijenleri tanımak
 - B hücrelerinin matürasyonu, sağkalımı, proliferasyonu ve immün yanıtta katılımı için klonal seleksiyonda sinyalizasyon yollarını başlatmak
- ***BCR sinyalizasyonu, PI3K δ , BTK, Syk, Lyn, and ZAP70 gibi proteinler aracılığı ile iletilir***

B hücre reseptörü

- Antijen-specific surface immunoglobulin (slg) ve the Ig- α /Ig- β hetero-dimerlerden (CD79A, CD79B) oluşan multimerik bir komplekstir

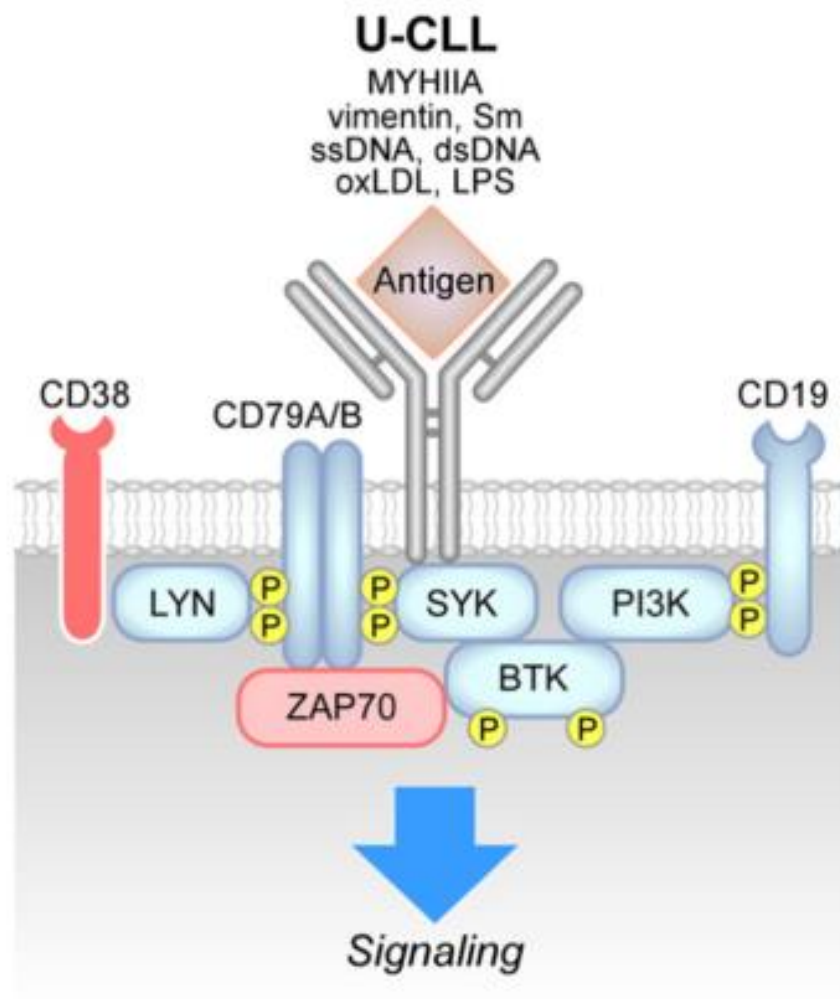
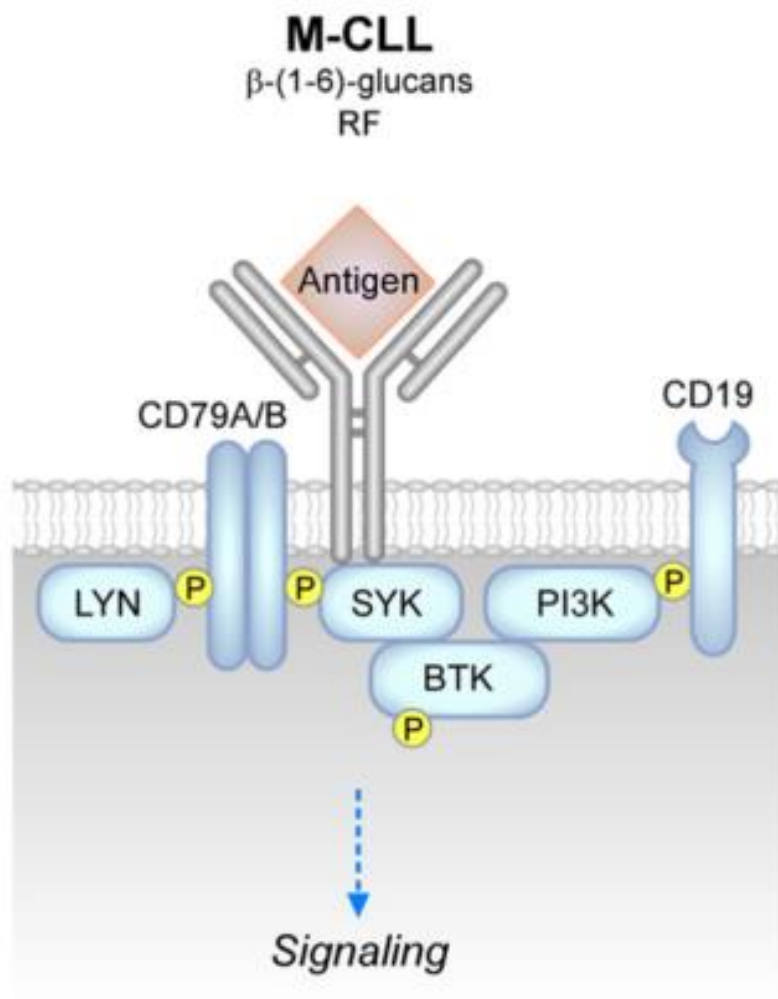


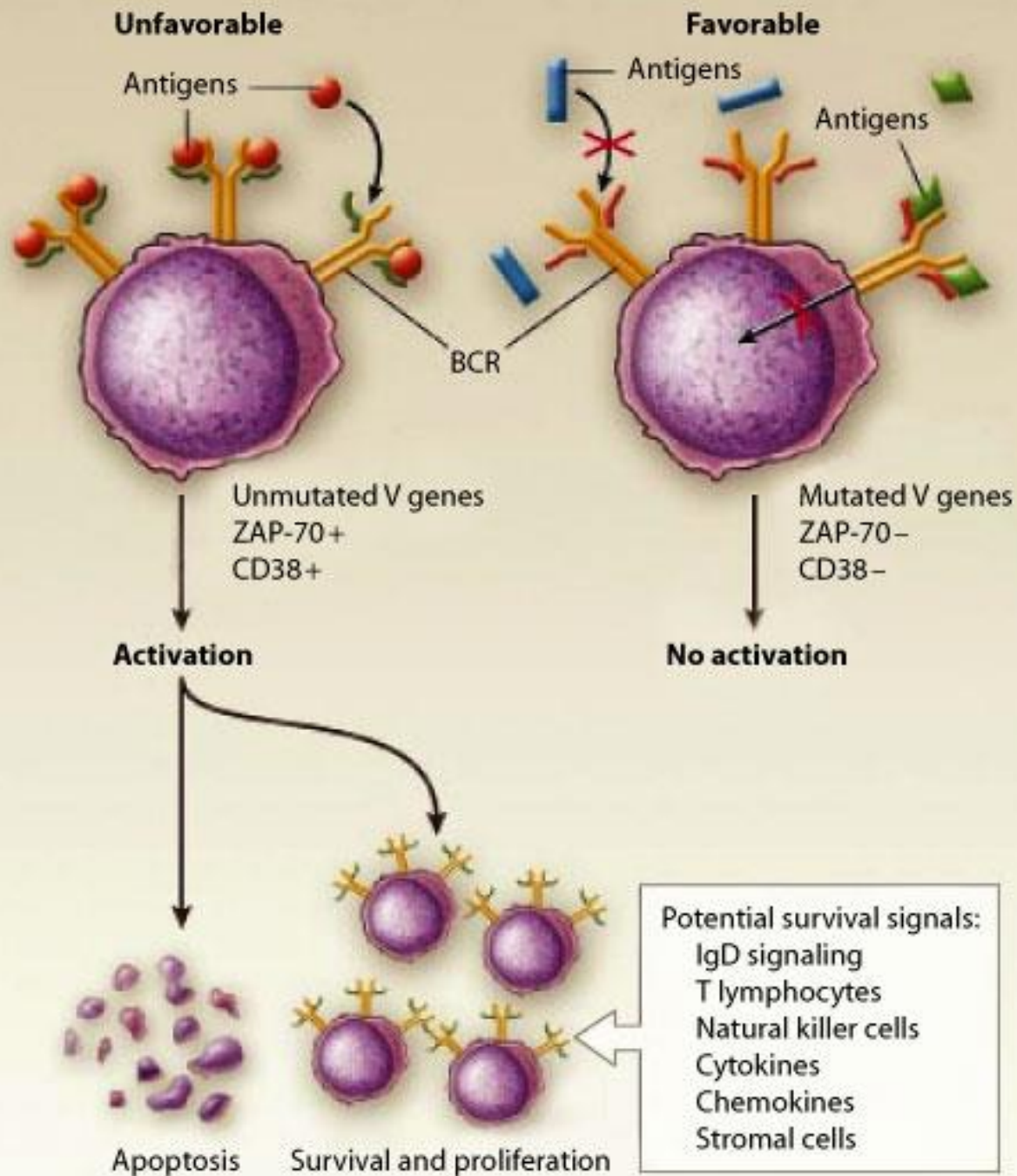
BCR SİNYAL YOLAĞI



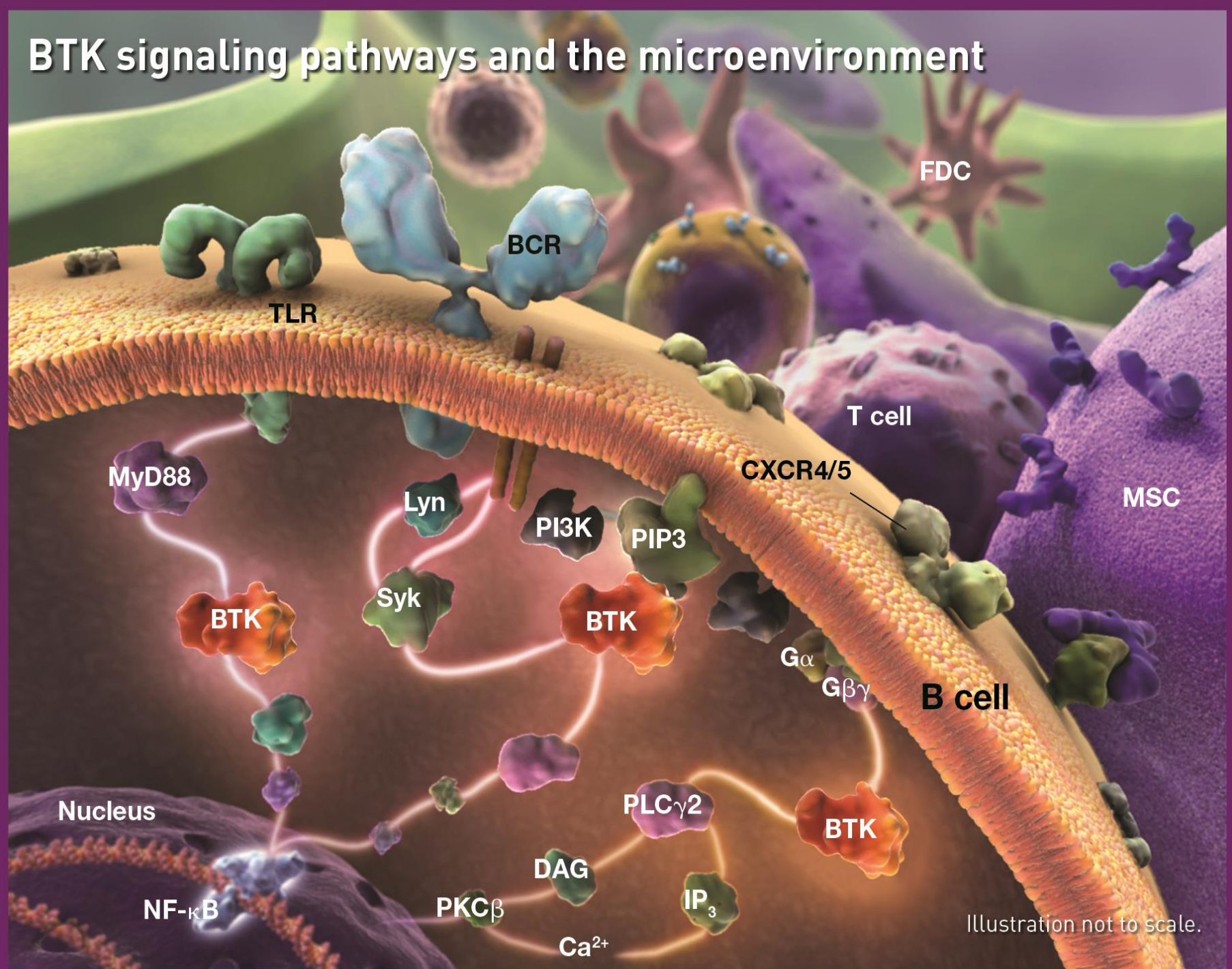


- B hücre reseptör (BHR) sinyal yolağı mikro çevre etkileşimi ile KLL patogeneğinde önemli rol oynamaktadır
- BHR'ünün IgVH (immün globülin ağır zincir değişken bölge geni) mutasyonlarının prognostik değeri tanımlanmış
- Bu yolağın kendi kendine aktivitesinin sebepleri? antijenik uyarım teorisi? yolağı aktive eden evrensel bir antijen, patojen veya süperantijen tespit edilememiştir





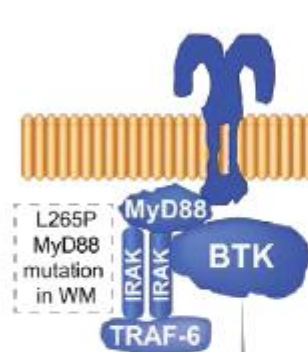
BTK signaling pathways and the microenvironment



BTK: An Essential Effector of Multiple B-cell Processes

Toll-like Receptor

TLR^{1,2}

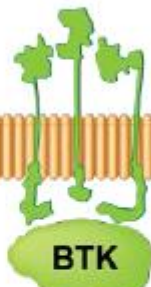


NF- κ B

Proliferation/
survival

B-cell Receptor

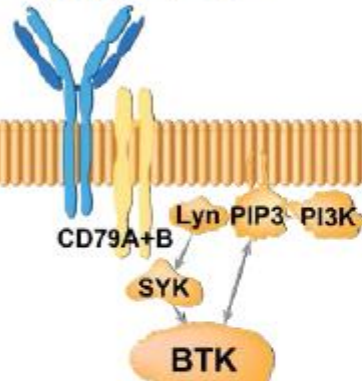
BAFF-R³



NF- κ B

Proliferation/
survival

BCR^{1,4,5,6,7}



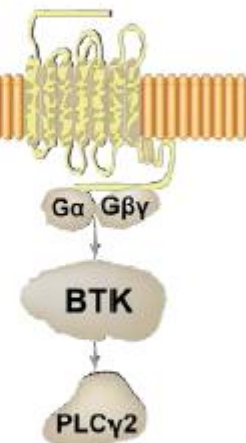
NF- κ B
NFAT

Proliferation/
survival

Actin
remodeling

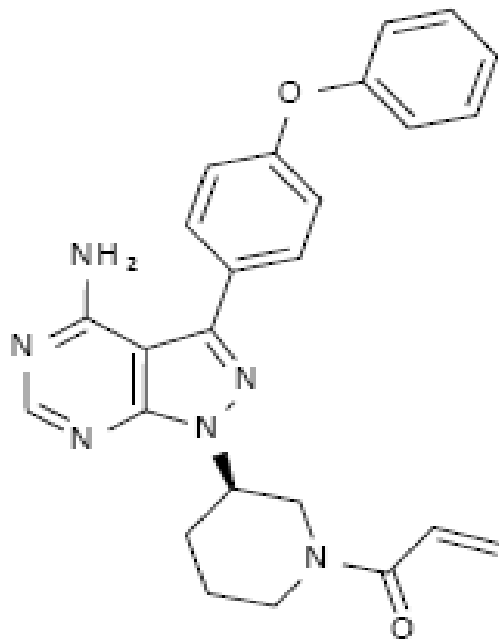
Chemokines

CXCR4/5⁸



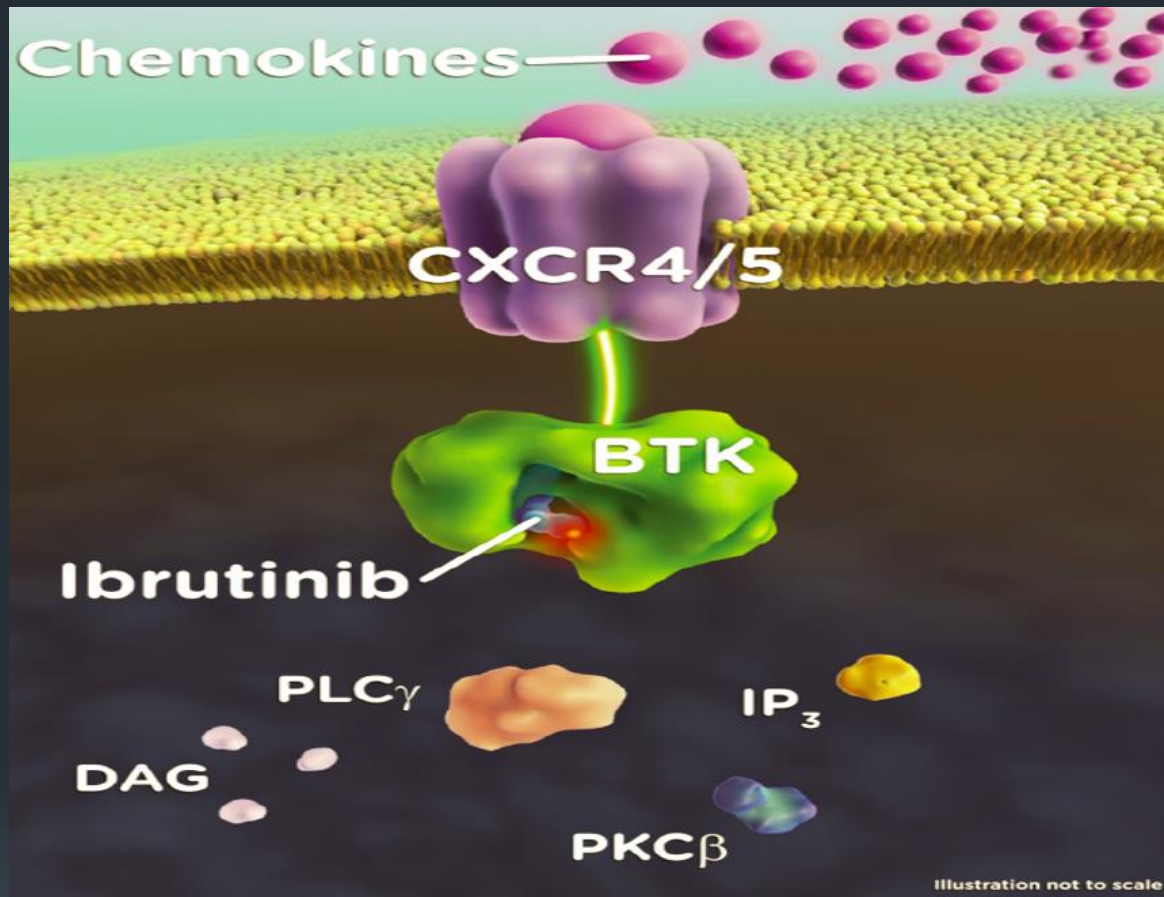
Chemokine-controlled
B-cell migration/
adhesion + homing

İbrutinib: Bruton Tirozin Kinaz (BTK) İnhibitörü

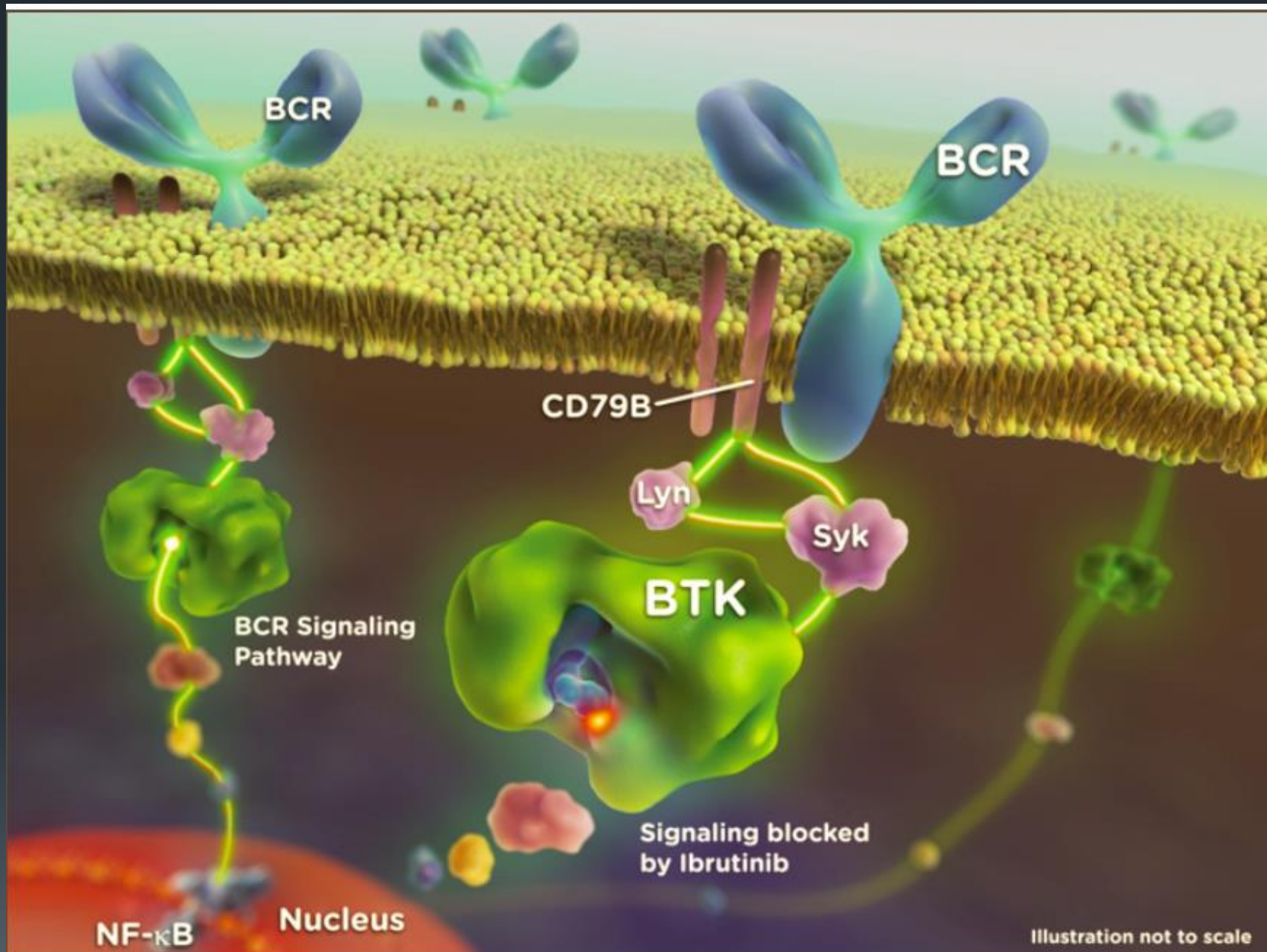


PCI-32765

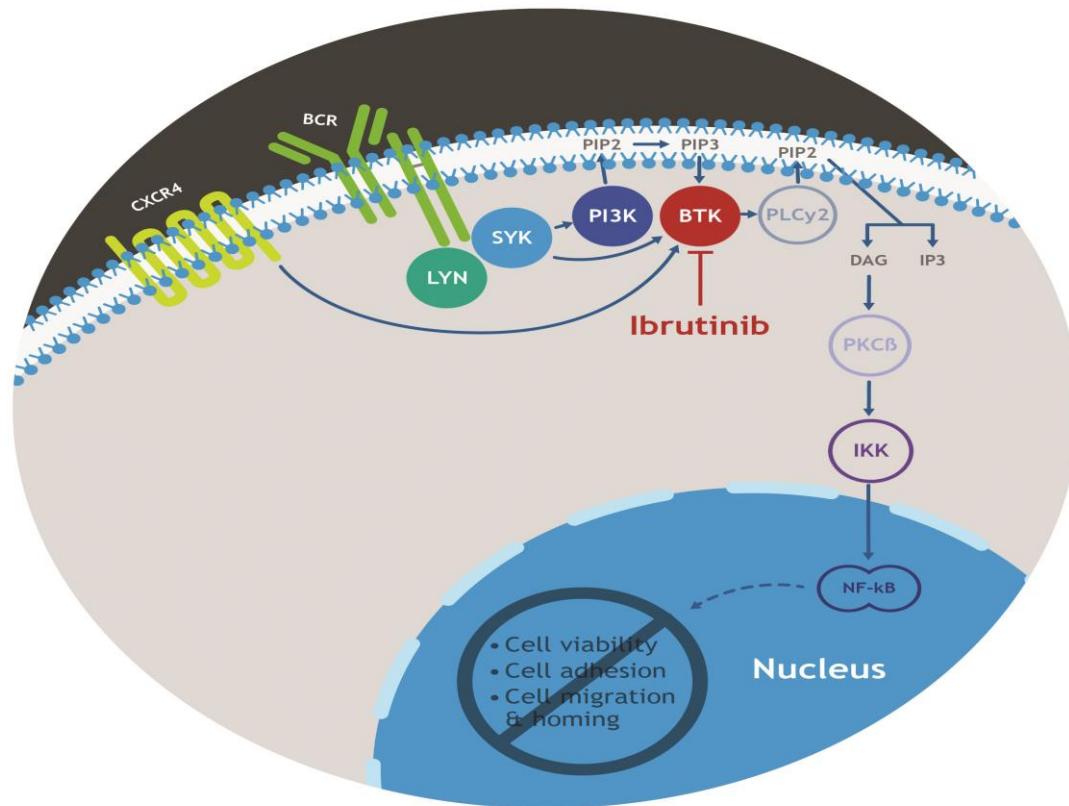
- Bruton Tirozin Kinaz (BTK) inhibitörüdür ve oral olarak uygulanır
- Oldukça güçlü BTK inhibisyonu (sistein 481 kovalent) yapar
- Malign B hücrelerinde:
 - Proliferasyonu, adhezyonu, yerleşmeyi inhibe eder,
 - Apoptozu indükler.
- T veya NK hücreleri üzerinde sitotoksik etkisi yoktur



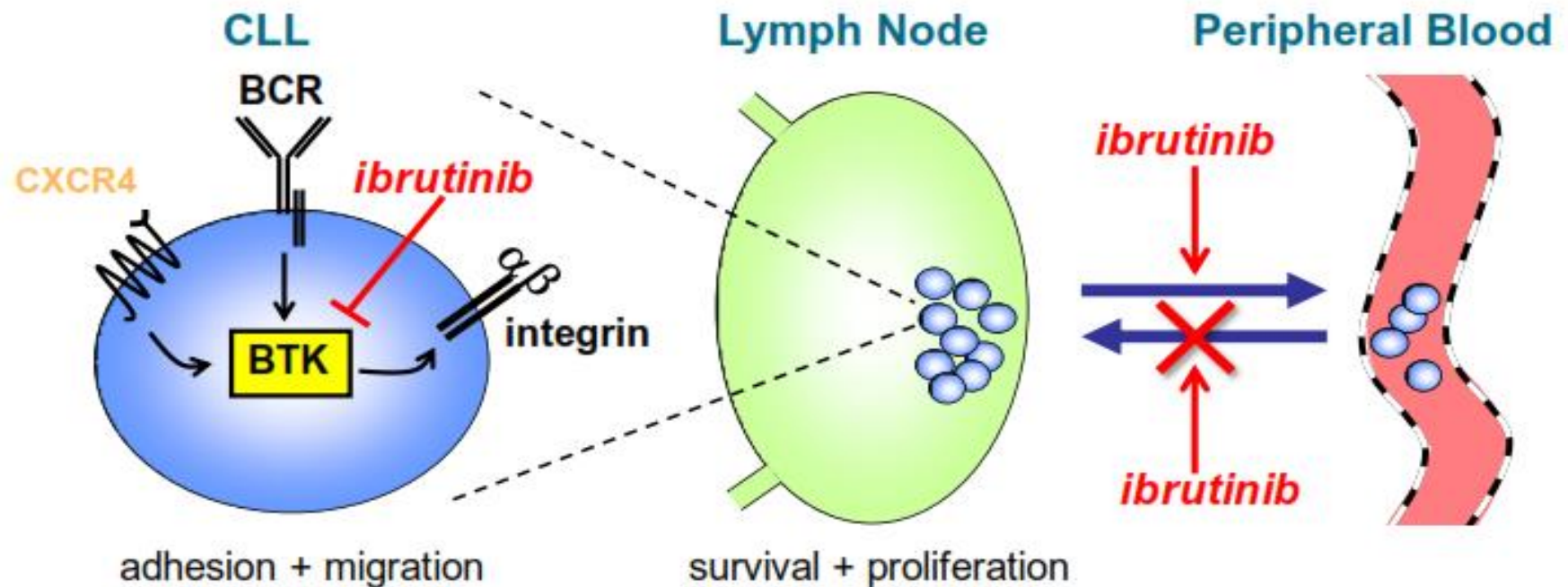
The binding of Ibrutinib to Bruton's tyrosine kinase (BTK) can block chemokine signaling in the malignant B cell



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



Mechanism of Action of Ibrutinib in CLL



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

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

- 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

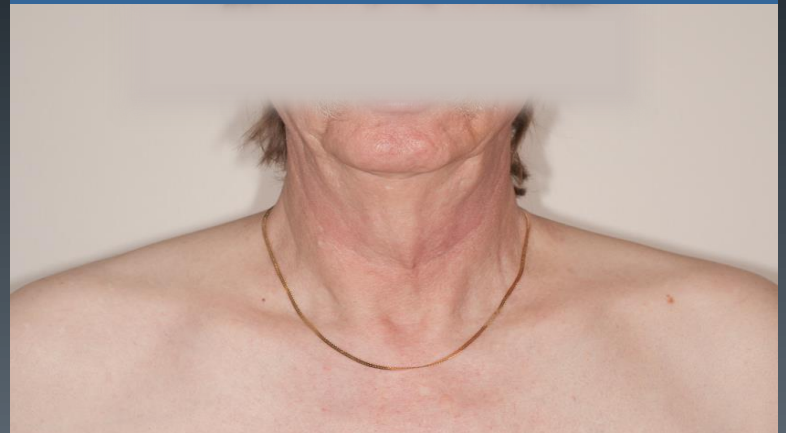
Lenfositoz

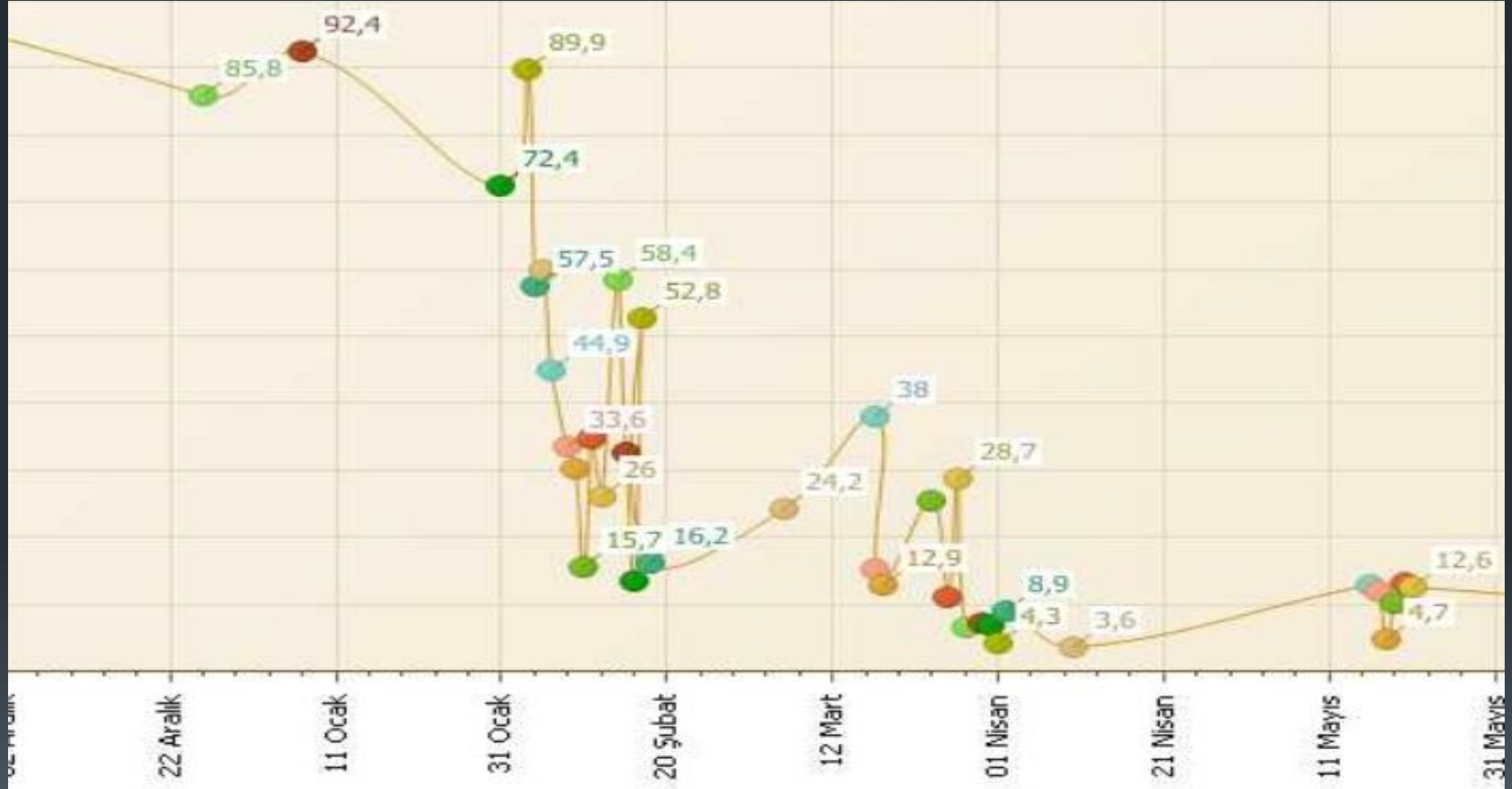
- İbrutinib tedavisiyle, çoğunlukla lenfadenopati azalmasıyla paralel olan lenfosit sayısında geri dönüşümlü artış gözlenmiştir (başlangıca göre \geq %50 ve 5000/mcL mutlak sayı üzerinde artış)
- CLL/SLL: çoğu hastada gözlenmiştir (%75.2)
- MCL: bazı hastalarda gözlenmiştir (%33)
- Lenfositoz tipik olarak 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

Before



4 Wks





RESONATE (PCYC-1112) Study Design

N=391

Enrolled June 2012 → April 2013: 391 pts in 10 mo!

- Phase 3, open-label, randomized, multicenter study
- Patients with previously treated CLL or SLL; not appropriate for purine analogue treatment

R
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1:1

Oral ibrutinib
420 mg once daily*
n = 195

*until PD or
unacceptable toxicity

Crossover* to
ibrutinib 420 mg
with IRC confirmed PD
(n = 57)

IV ofatumumab
12 doses **over 24 wks***
n = 196

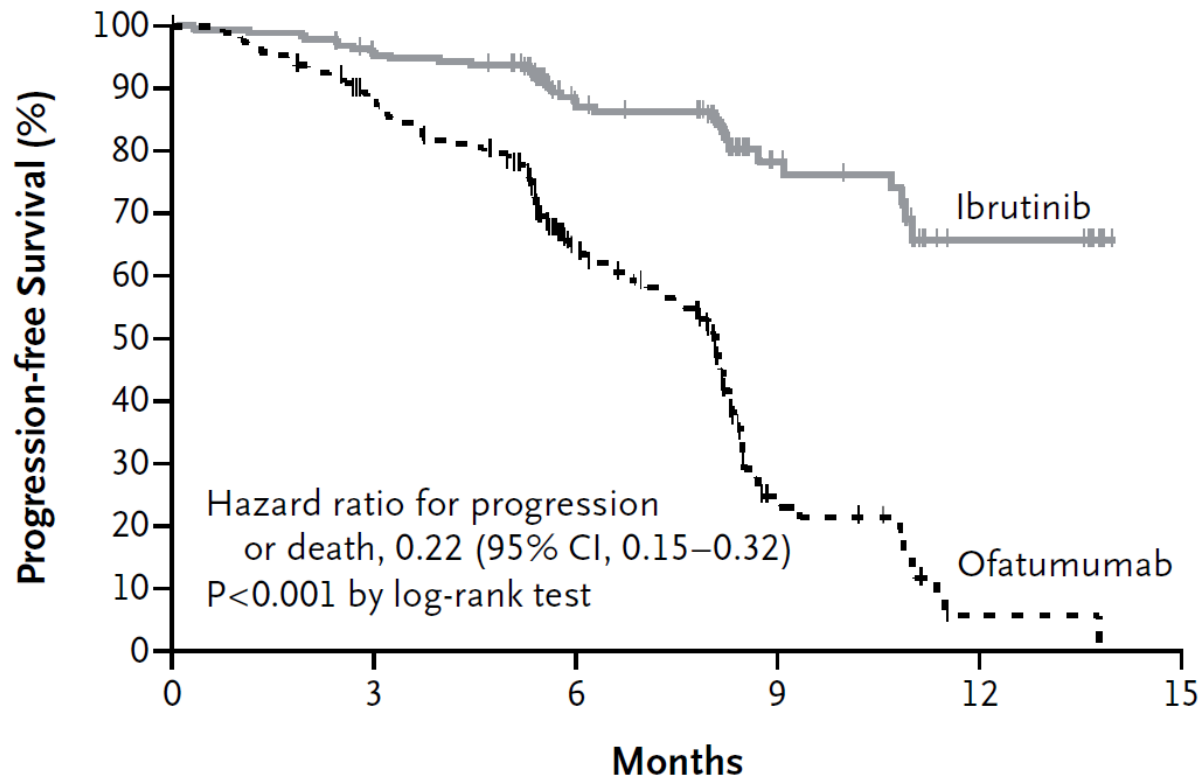
*initial dose of 300 mg followed
by 2000 mg weekly for 7 weeks
and then every
4 weeks for 16 weeks

IRC, independent review committee;
IV, intravenous; PD, progressive disease.

- Stratification according to:
 - Disease refractory to purine analog chemoimmunotherapy (no response or relapsed within 12 months)
 - Presence or absence of the 17p13.1 deletion (del17p)
- At time of analysis, median time on study was 9.4 months

***A protocol amendment was released approximately 4 months after the last patient randomized allowing patients randomized to ofatumumab with IRC-confirmed PD to receive ibrutinib (n=57 out of 196 ofa-treated).**

Primary End Point: IRC-Evaluated PFS



No. at Risk

Ibrutinib	195	183	116	38	7	
Ofatumumab	196	161	83	15	1	0

Median PFS not reached
PFS rate: 88% at 6 mo)

Median PFS of 8.1 mo
PFS rate: 65% at 6 mo)

Richter's transformation was confirmed in 2 patients on each arm. An additional patient on the ibrutinib arm experienced disease transformation to prolymphocytic leukemia

Safety Overview

Adverse Event, (%)	Ibrutinib (N = 195)	Ofatumumab (N = 191)
Subjects reporting ≥ 1 SAE [§]	42	30
Reporting ≥ 1 AE grade ≥ 3	57	47
Any infection grade ≥ 3	24	22
Grade ≥ 3 AE atrial fibrillation	3	0
Major hemorrhage ^a	1	2

[§]Exposure adjusted analysis did not demonstrate an increase in SAE rate, any Grade ≥ 3 AE for ibrutinib compared to ofatumumab.

^aEither intracranial haemorrhage, any hemorrhagic event \geq Grade 3 or resulting in transfusion of red cells or hospitalization.

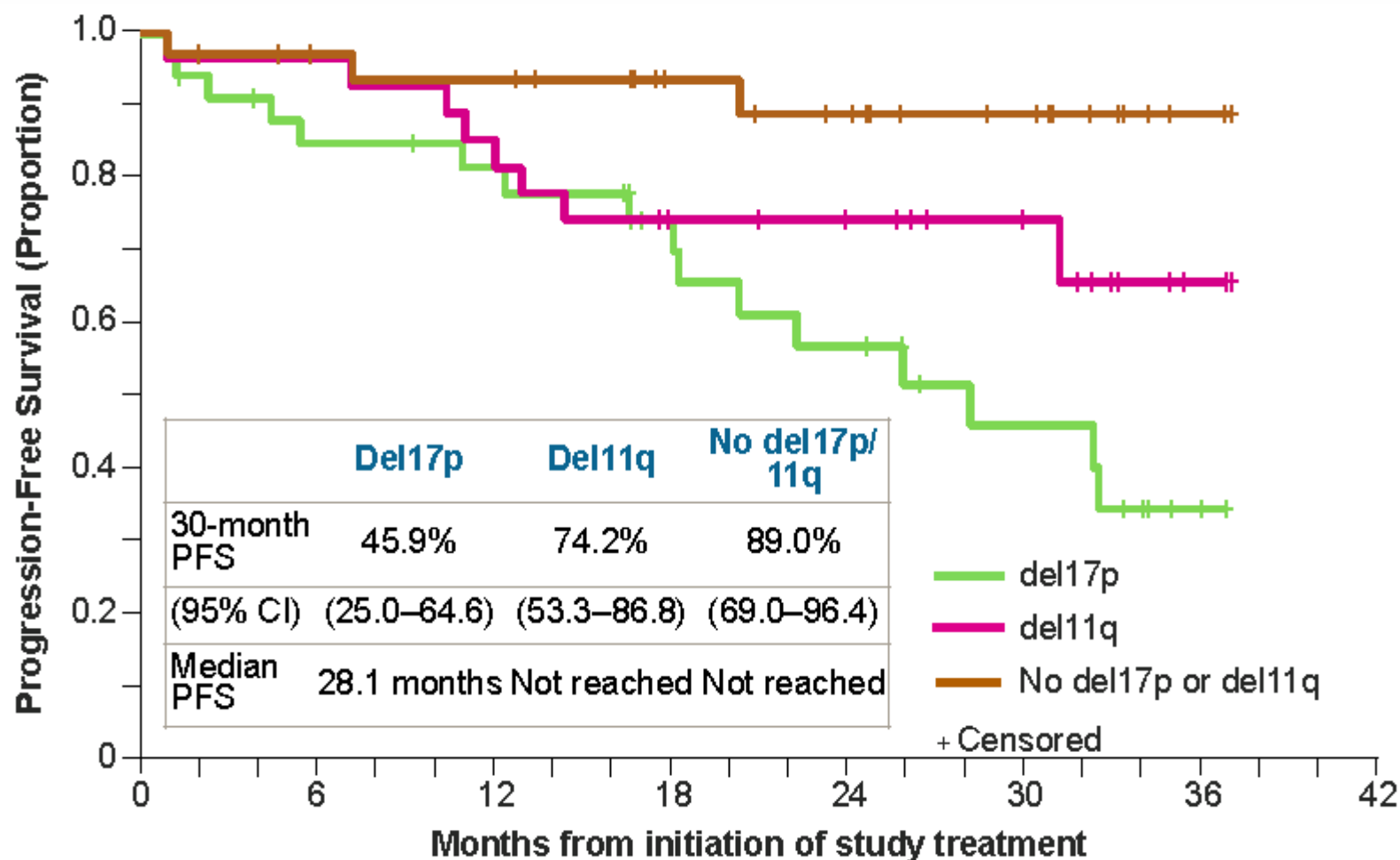
- Exposure adjusted analysis showed no difference in any grade infection and a 40% relative reduction in grade 3 or 4 infections comparing ibrutinib to ofatumumab
- Any-grade infusion reactions (28% vs. 0%), peripheral sensory neuropathy (13% vs. 4%), urticaria (6% vs. 1%), night sweats (13% vs. 5%) and pruritus (9% vs. 4%) were more common with ofatumumab
- Basal and squamous cell carcinomas were reported in 5% of patients in the ibrutinib arm and 2% in the ofatumumab arm; non-skin cancers were seen in 3% and 1% respectively.

PCYC-1103: 3-year follow-up of the first ibrutinib trial

- 132 treatment-naïve and relapsed/refractory patients were included:¹
 - 31 patients were treatment-naïve and elderly (age ≥65 years)
 - 101 patients were relapsed/refractory, including patients with high-risk CLL/SLL
- Median age: 71 years in treatment-naïve group and 64 years in relapsed/refractory group¹
- Median of 4 prior therapies¹
 - Most patients had received prior anti-CD20-based therapy¹
- Cytogenetics:¹
 - 6% of patients in the treatment naïve group and 34% in the relapsed/refractory group had the del(17p) mutation
 - 3% of patients in the treatment naïve group and 35% of patients in the relapsed/refractory group had the del(11q) mutation
- 60% of patients remained on ibrutinib therapy¹
 - 81% of treatment-naïve patients and 53% of relapsed/refractory patients
- Median time on trial: 30 months in treatment-naïve group and 23 months in relapsed/refractory group¹
- Disease progression occurred in 1% of patients in treatment-naïve group and 21% of patients in relapsed/refractory group¹

1. Byrd *et al*, Blood 2015 125(16): 2497-2506.

Evaluation of ibrutinib efficacy 3 years post-initiation of monotherapy including in del17p CLL

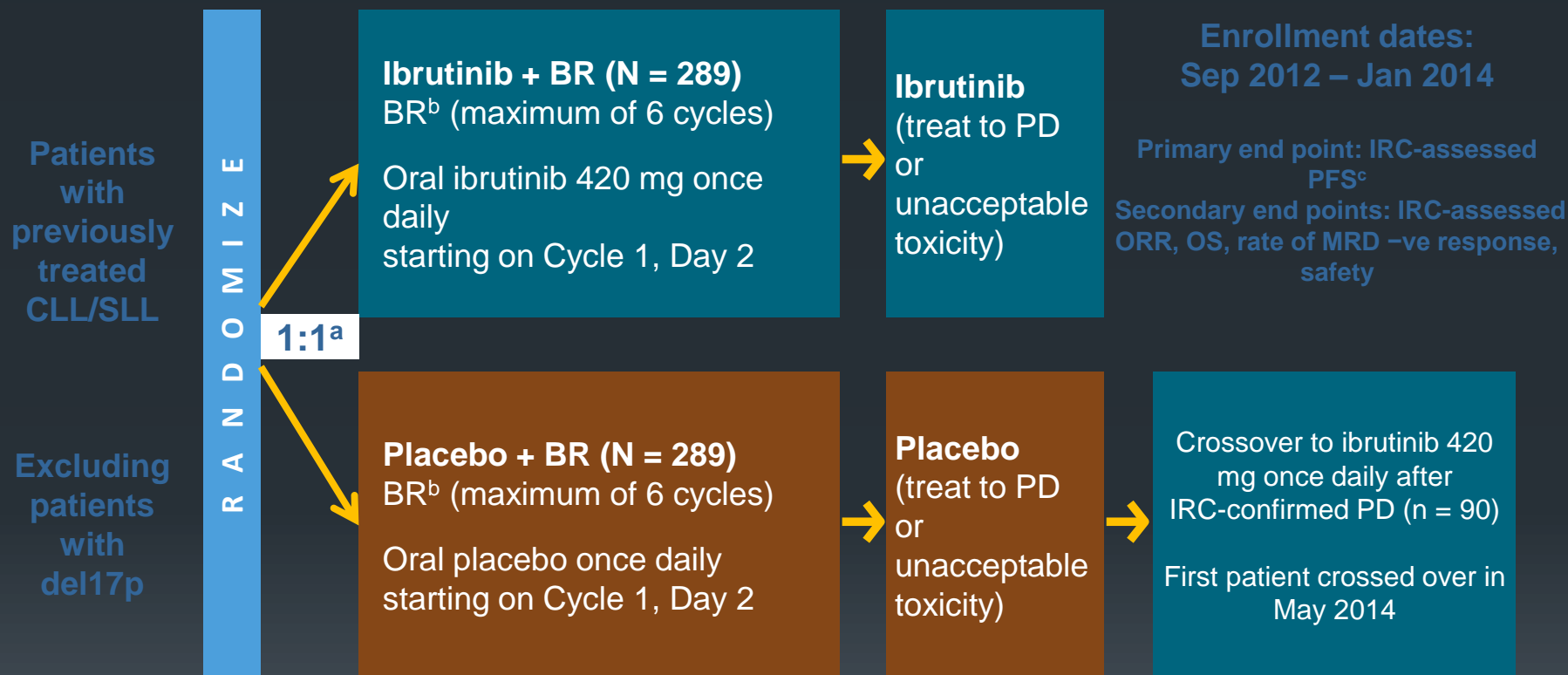


Ibrutinib Combined With Bendamustine and Rituximab in Previously Treated CLL/SLL: First Results From a Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study

Asher Chanan-Khan,¹ Paula Cramer,² Fatih Demirkan,³ Graeme Fraser,⁴ Rodrigo Santucci Silva,⁵ Halyna Pylypenko,⁶ Sebastian Grosicki,⁷ Ann Janssens,⁸ Aleksander Pristupa,⁹ Jiri Mayer,¹⁰ Marie-Sarah Dilhuydy,¹¹ Javier Loscertales,¹² Nancy Bartlett,¹³ Abraham Avigdor,¹⁴ Simon Rule,¹⁵ Steven Sun,¹⁶ Michelle Mahler,¹⁶ Masha Salman,¹⁶ Angela Howes,¹⁷ and Michael Hallek¹⁸

¹Mayo Clinic Cancer Center, Mayo Clinic, Jacksonville, Florida, USA; ²Department I of Internal Medicine and German CLL Study Group, University of Cologne, Germany; ³Division of Hematology, Dokuz Eylül University, Izmir, Turkey; ⁴Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; ⁵IEP SÃO LUCAS / Hemoméd Oncologia e Hematologia, São Paulo, Brazil; ⁶Department of Hematology, Cherkassy Regional Oncological Center, Cherkassy, Ukraine; ⁷Department of Cancer Prevention, Faculty of Public Health, Silesian Medical University, Katowice, Poland; ⁸Universitaire Ziekenhuizen Leuven, Leuven, Belgium; ⁹Regional Clinical Hospital, Ryazan, Russia; ¹⁰Department of Internal Medicine, Hematology and Oncology, University Hospital Brno, Jihlavska, Brno, Czech Republic; ¹¹Hopital Haut Leveque, Bordeaux, Pessac, France; ¹²Hematology Department, Hospital Universitario La Princesa, IIS-IP, Madrid, Spain; ¹³Washington University School of Medicine, Siteman Cancer Center, St. Louis, MO, USA; ¹⁴Division of Hematology and Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel-Hashomer and Sackler School of Medicine, University of Tel-Aviv, Tel-Aviv, Israel; ¹⁵Department of Haematology, Derriford Hospital, Plymouth, UK; ¹⁶Janssen Research & Development, LLC, Raritan, NJ, USA; ¹⁷Janssen Research & Development, High Wycombe, UK; ¹⁸Department I of Internal Medicine and Center of Integrated Oncology, University of Cologne, Cologne, Germany

HELIOS: Phase 3 Study Design



IRC, independent review committee; MRD - ve, minimal residual disease negative; PD, progressive disease.

^aStratified by purine analogue refractory status (failure to respond or relapse in ≤ 12 months) and by number of prior lines of therapy (1 line vs > 1 line).

^bSimilar dosing to Fischer K, et al. *J Clin Oncol*. 2011;29:3559-3566.

^cAccording to 2008 iwCLL criteria (Hallek M, et al. *Blood*. 2008;111:5446-5456).

Baseline Characteristics

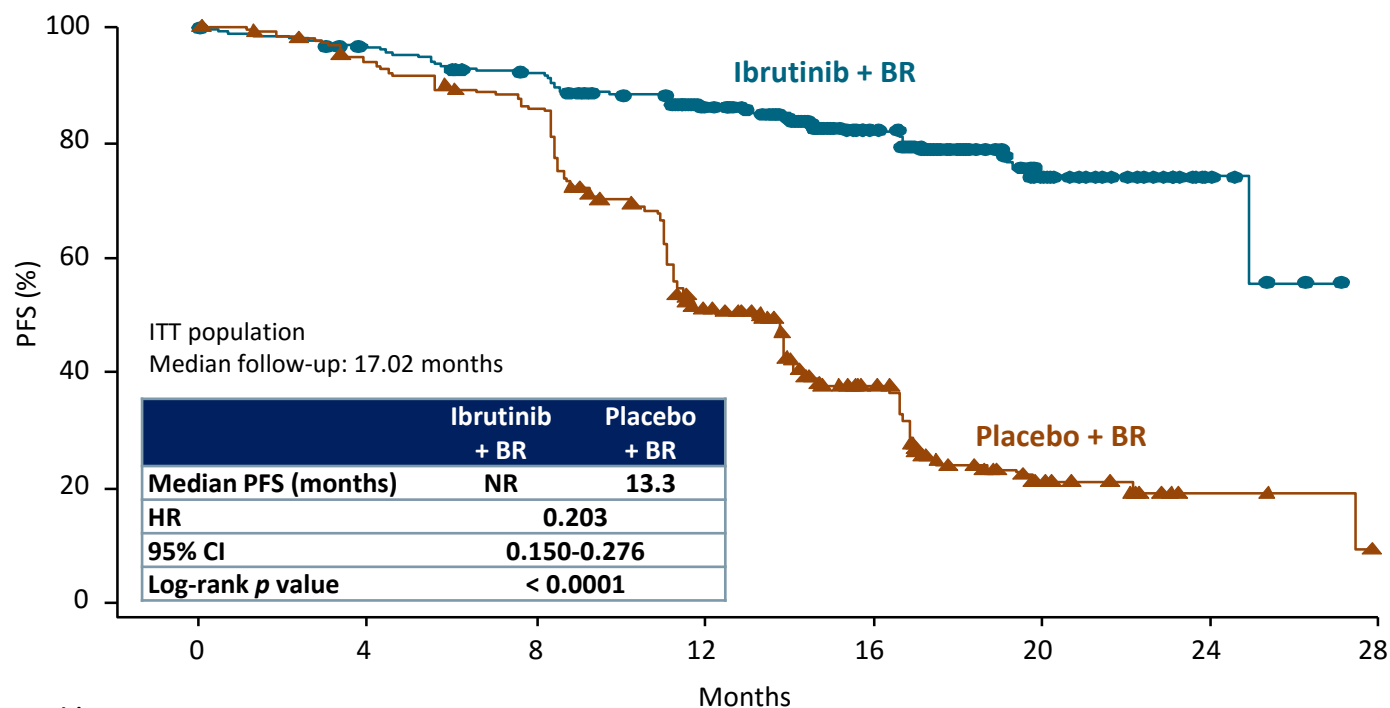
ITT Population	Ibrutinib + BR (N = 289)	Placebo + BR (N = 289)
Median age (range), years	64 (31-86)	63 (36-83)
Male, n (%)	193 (66.8)	189 (65.4)
CLL, n (%)	257 (88.9)	257 (88.9)
SLL, n (%)	32 (11.1)	32 (11.1)
ECOG PS, n (%)		
0	125 (43.3)	126 (43.6)
1	164 (56.7)	163 (56.4)
Rai stage,* n (%)		
0-II	157 (61.3)	139 (53.9)
III-IV	99 (38.7)	119 (46.1)
Bulky disease ≥ 5 cm, n (%)	168 (58.1)	156 (54.0)
Del11q, n (%)	87 (30.1)	65 (22.5)
IgVH status, [†] n (%)		
Mutated	49 (18.9)	52 (20.0)
Unmutated	210 (81.1)	208 (80.0)

*Ibrutinib + BR (n = 256)/placebo + BR (n = 258). [†]Ibrutinib + BR (n = 259)/placebo + BR (n = 260).

Baseline Characteristics (Cont.)

ITT Population	Ibrutinib + BR (N = 289)	Placebo + BR (N = 289)
Purine analog refractory, n (%)	75 (26.0)	74 (25.6)
Median (range) prior therapies	2.0 (1-11)	2.0 (1-9)
1 prior line, n (%)	140 (48.4)	139 (47.9)
2 prior lines, n (%)	72 (24.9)	78 (27.1)
≥ 3 prior lines, n (%)	77 (26.6)	72 (25.0)
Prior therapy, n (%)		
Purine analogue	206 (71.3)	209 (72.3)
Alkylating agents	275 (95.2)	275 (95.2)
Bendamustine	10 (3.5)	7 (2.4)
Anti-CD20	203 (70.2)	200 (69.2)
Median time from progression/relapse since last line of treatment to randomization (range), months	2.9 (0-48)	2.6 (0-73)

Primary End Point: IRC-Assessed PFS



Patients at risk:

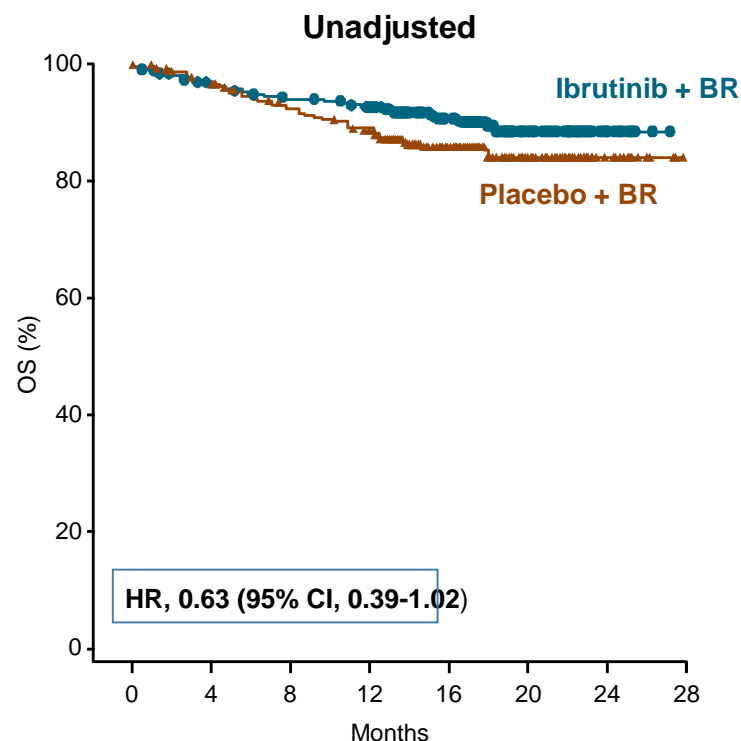
Ibrutinib + BR	289	264	247	200	127	52	5	0
Placebo + BR	289	259	234	117	59	17	3	0

CI, confidence interval; HR, hazard ratio.

Investigator-assessed HR for ibrutinib + BR vs placebo + BR was 0.201 (95% CI, 0.145-0.278).

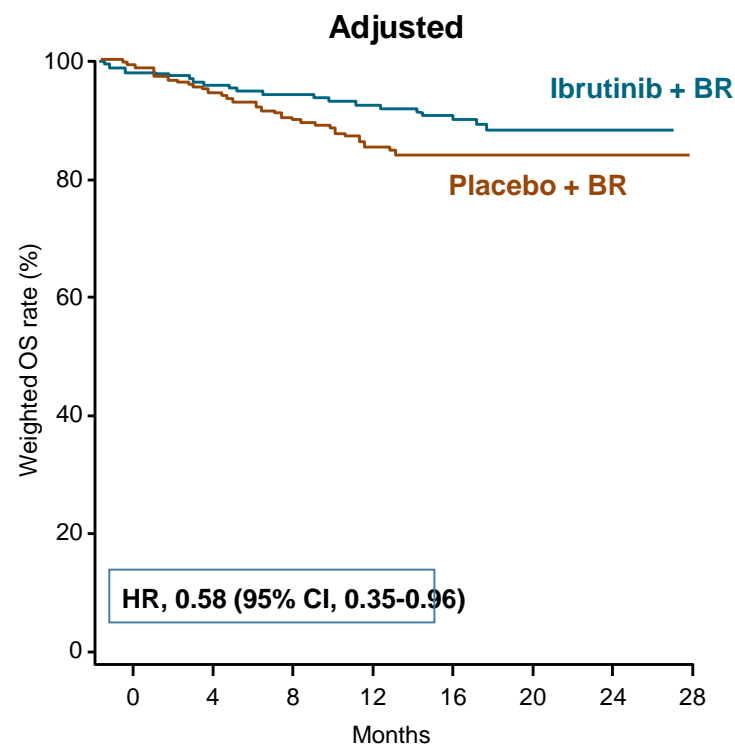
No Richter's transformations were observed in the ibrutinib arm and 3 in the placebo arm.

Overall Survival (OS): Unadjusted and Adjusted^a for Crossover



Patients at risk:

	0	4	8	12	16	20	24	28
Ibrutinib + BR	289	273	261	250	147	73	8	0
Placebo + BR	289	273	255	237	138	70	16	0



Patients at risk:

	0	4	8	12	16	20	24	28
Ibrutinib + BR	289	273	261	250	147	73	8	0
Placebo + BR	289	273	254	213	101	43	8	0

- OS results are confounded by crossover to receive single-agent ibrutinib
- 90 patients (31%) in the placebo + BR arm crossed over to receive ibrutinib
- Overall, ibrutinib reduced the risk of death by 37% without adjustment, and by 42% with adjustment for crossover

^aOS was adjusted for crossover using an inverse probability of censoring weighting method

Group/Subgroup	Parameter		N	HR (95% CI)
All Patients			578	0.20 (0.15, 0.28)
Age (years)	< 65		305	0.17 (0.11, 0.26)
	≥ 65		273	0.27 (0.18, 0.42)
Sex	Male		382	0.20 (0.14, 0.28)
	Female		196	0.23 (0.13, 0.39)
Diagnosis	CLL		514	0.19 (0.14, 0.27)
	SLL		64	0.40 (0.19, 0.85)
Rai stage at screening	Stage 0-II		296	0.13 (0.08, 0.21)
	Stage III-IV		218	0.30 (0.19, 0.48)
Refractory to purine analog therapy	Yes		149	0.24 (0.14, 0.39)
	No		429	0.19 (0.13, 0.28)
Prior lines of therapy	1		281	0.19 (0.12, 0.31)
	> 1		297	0.22 (0.15, 0.33)
Baseline ECOG	0		251	0.16 (0.09, 0.26)
	1		327	0.26 (0.18, 0.38)
Bulky disease	No (< 5 cm)		254	0.22 (0.13, 0.37)
	Yes (≥ 5 cm)		324	0.19 (0.13, 0.27)
Del11q	Yes		152	0.08 (0.04, 0.16)
	No		426	0.27 (0.19, 0.39)
IgVH	Mutated		101	0.42 (0.19, 0.97)
	Unmutated		418	0.16 (0.11, 0.23)

HELIOS- Sonuçlar

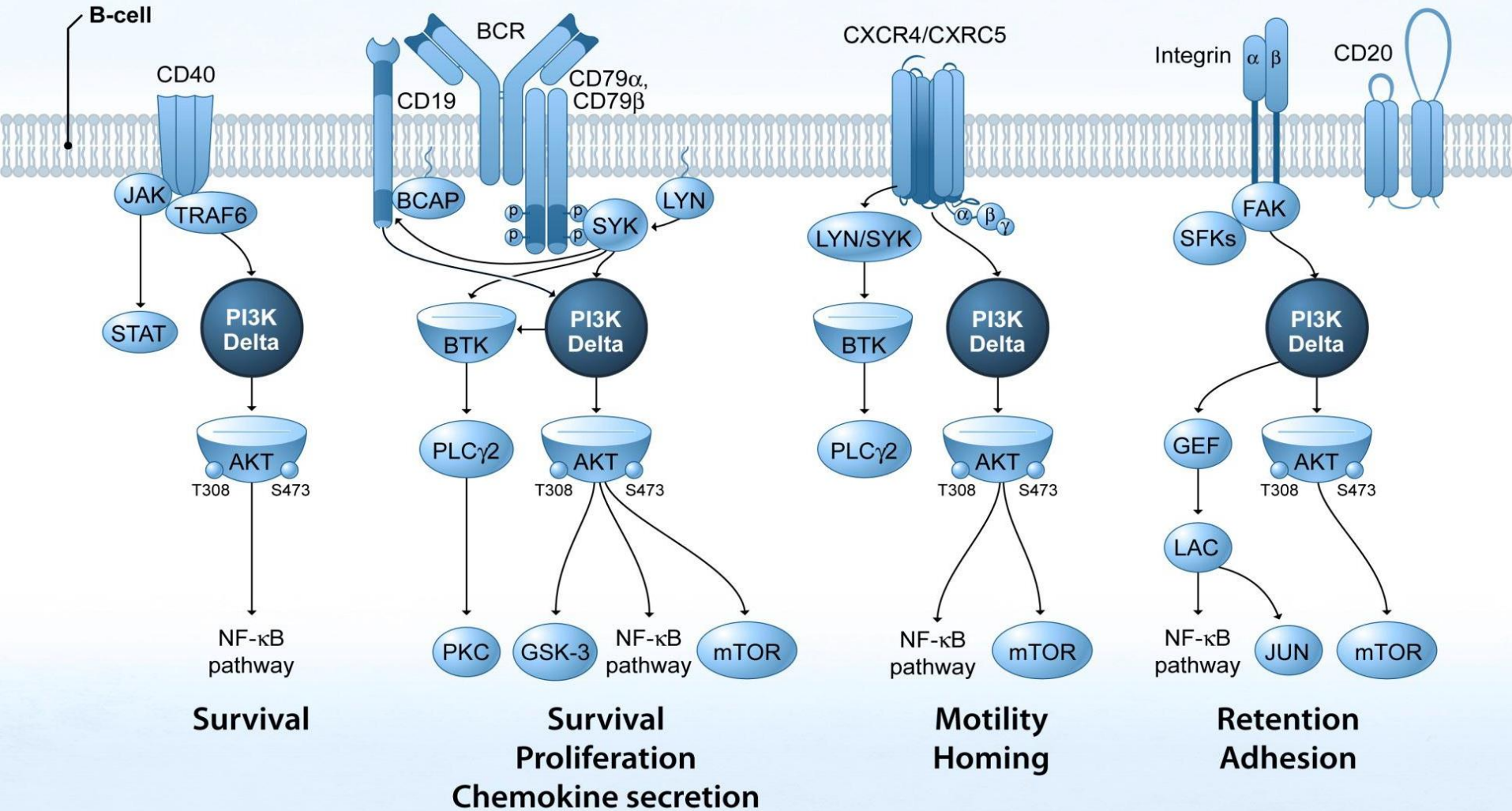
- İbrutinib + BR ile hastalık progresyonu veya ölüm riskinde % 80 azalma ($p < 0.0001$)
- İbrutinib + BR, placebo + BR kolundan çapraz geçiş yapan hastalar için ayarlama yapıldıktan sonra placebo+BR koluna göre ölüm riskini % 42 azaltıyor
- Daha önce tedavi görmüş görmüş KLL/SLL hastalarında ibrutinib temelli kemo-immünoterapi, standard kemo-immünoterapiye (BR) üstün

Phosphatidylinositol 3-kinase δ inhibitörleri

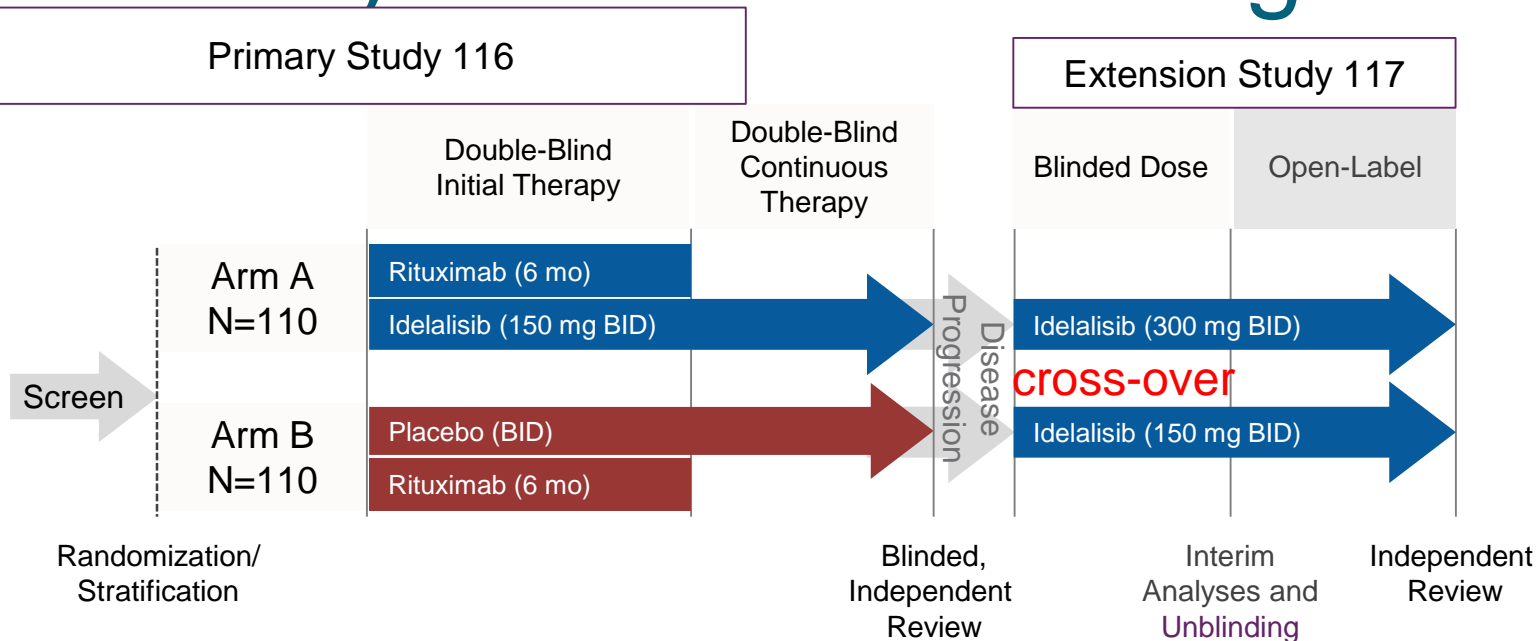
- PI3K δ primer olarak dolaşımdaki lenfositler, nötrofiller ve monositlerde ve dalak, lenf bezleri ve timüs gibi lenfoid dokularda eksprese edilir
- PI3K δ , BCR sinyal yolağında rol oynayan ve hematolojik malinitelerde aktive olan anahtar bir izoformdur
- İdelalisib PI3K δ 'nın reversible oral inhibitörüdür. Diğer class I PI3K izoformlarına göre δ izoformunu 110-450 misli daha fazla inhibe eder ve bu nedenle malin B hücrelerinde PI3K δ bağımlı yolakları hedefler.



PI3K δ



116 study Phase 3 Trial Design



- Primary Endpoint: PFS
- Secondary Endpoint: ORR, LNR, OS
- 1st interim analyses (IAs) planned at 50% of total events, DMC recommended early study stop after 1st IA (Furman *et al.*, NEJM 2014)
- 2nd IA conducted at end of the blinded-phase according to amendment (data cut-off 09 October 2013 with 63% of total PFS events)
- High risk subpopulations analyses performed using 1st IA data for PFS and ORR

116 study

Baseline Patient Characteristics

	Idelalisib + R n=110	Placebo + R n=110
Gender, male, %	69	62
Median age, y (range)	71 (48-90)	71 (47-92)
Rai stage 0 / I-II / III-IV, %	0 / 31 / 64	1 / 26 / 66
Prior therapies, median (range)	3 (1-12)	3 (1-10)
Cytopenia*, and Grade, Grade 3/4, %	85, 32	88, 39
Total CIRS score >6, %	88	82
Estimated CrCl <60 mL/min, %	44	36
High-risk parameter, %		
Del(17p) and/or <i>TP53</i> mutation	42	45
Del(11q)	34	30
Unmutated <i>IGHV</i>	83	85
ZAP70+	92	85
CD38+	57	46
β 2-microglobulin: >4 mg/L	85	78

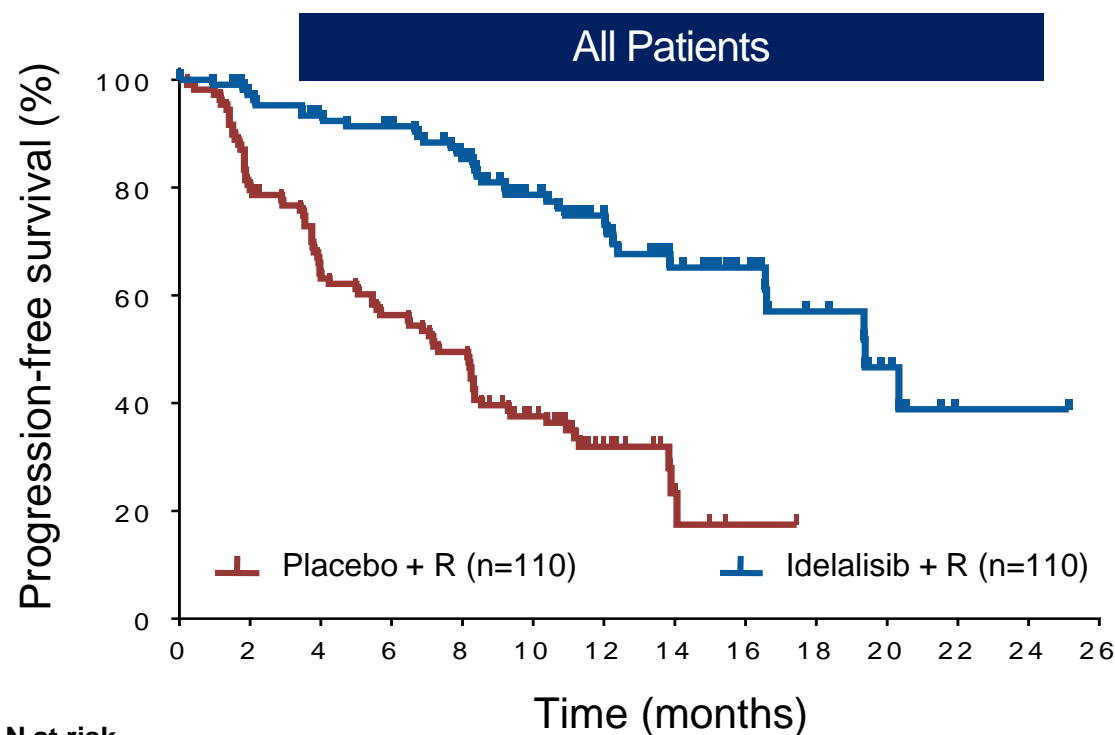
116 study

Baseline Patient Characteristics (cont')

	Idelalisib + R n=110	Placebo + R n=110
Time since diagnosis, median, years	7.9	8.6
Prior therapy, agent, %		
Rituximab (R)	92	89
Cyclophosphamide (C)	65	70
Fludarabine (F)	57	64
Bendamustine (B)	60	55
Chlorambucil (Chl)	31	23
Prior therapy, regimen, %		
BR	46	44
FCR	33	36
R	31	30
FR	16	18
Chl	18	15

116 study

PFS, 2nd Interim Analysis at Follow-Up, including Extension Study (117)*



*Placebo + R includes patients who received open-label idelalisib after unblinding without prior progression (n=42).

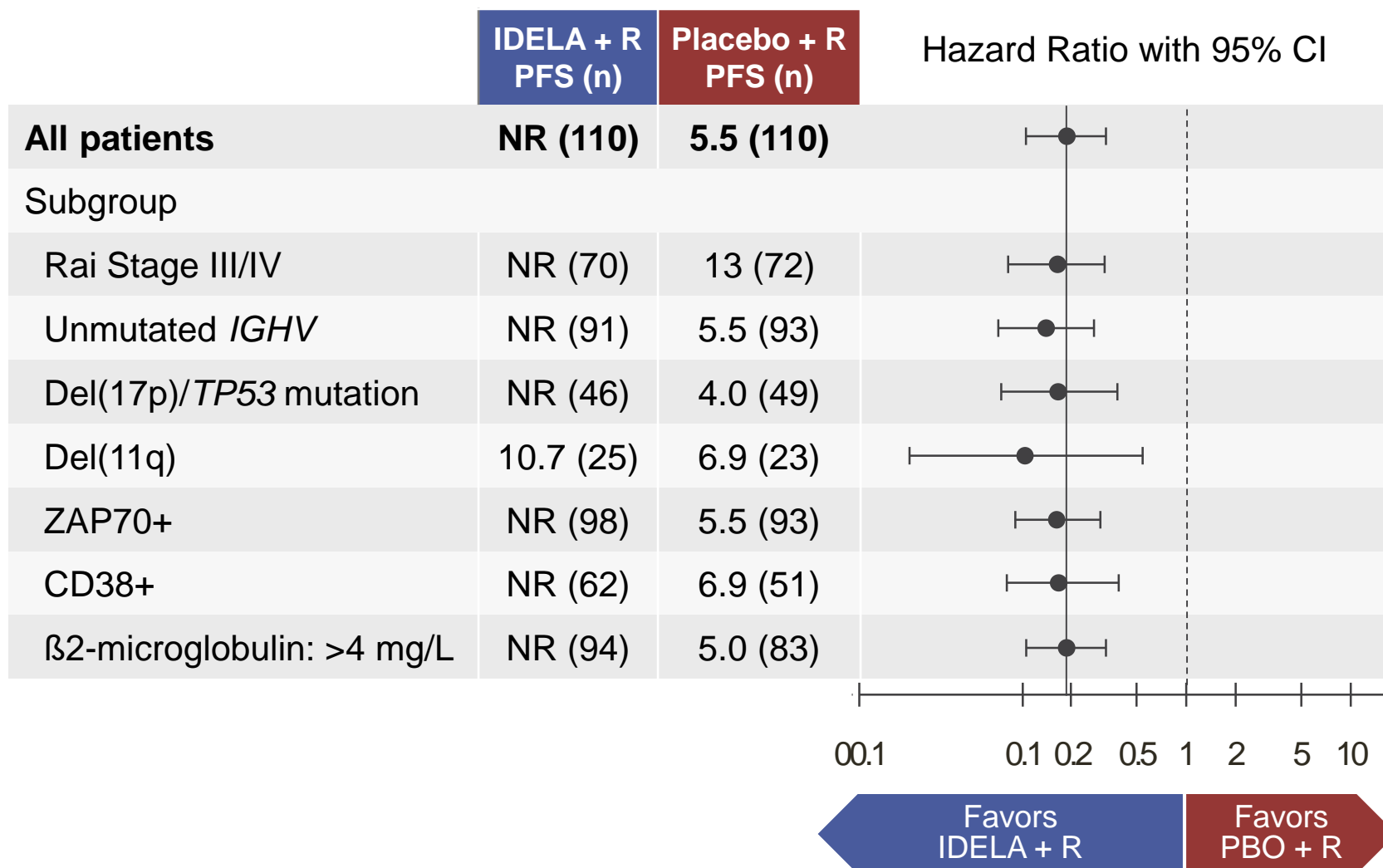
N at risk

Pbo + R	110	86	66	58	51	33	15	5	1	0	-	-	-	-
Idela + R	110	102	95	92	83	64	43	26	19	12	7	1	1	0

	Median PFS (95% CI)	HR (95% CI)	p-value
Pbo + R	7.3 mo (5.5, 8.5)	0.25 (0.16, 0.39)	<0.0001
Idela + R	19.4 mo (16.6, NR)		

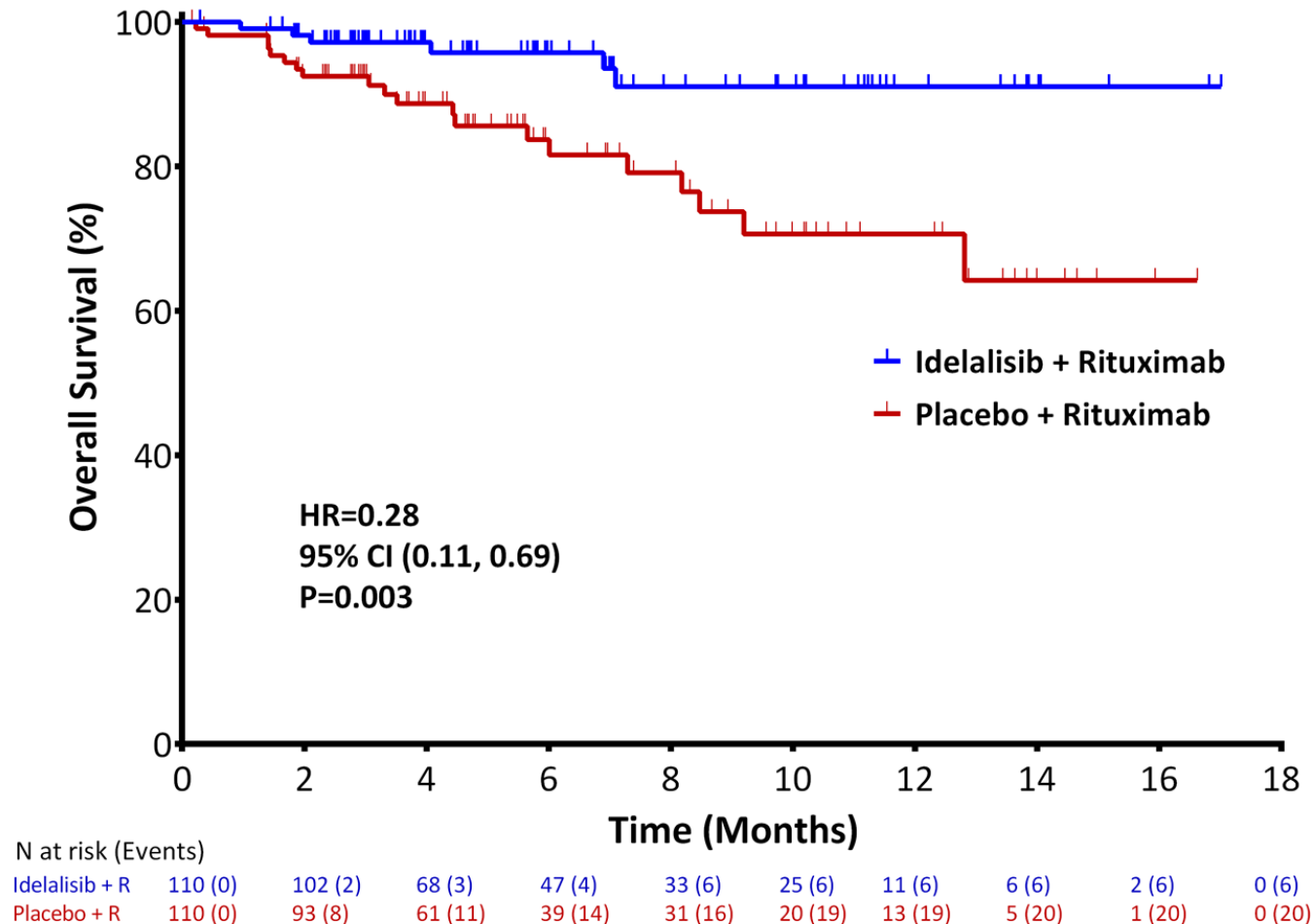
116 study

PFS, 2nd Interim Analysis by Risk Group



116 study

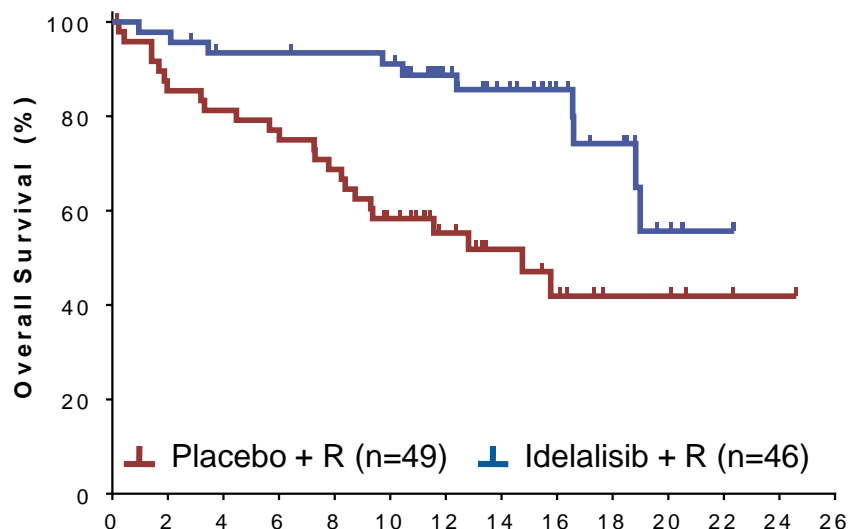
Overall Survival (OS). 2nd Interim Analysis



116 study

OS, 2nd Interim Analysis at Follow-Up, including Extension Study (117)*

Del17p/TP53 Mutation (Either)



N at risk

Pbo + R	49	41	39	37	33	25	17	11	8	4	4	2	1	0
Idela + R	46	45	41	41	40	39	30	23	16	12	5	2	0	0

Median OS (95% CI)

PBO + R 14.8 mo (8.4, NR)

IDELA + R NR (18.8, NR)

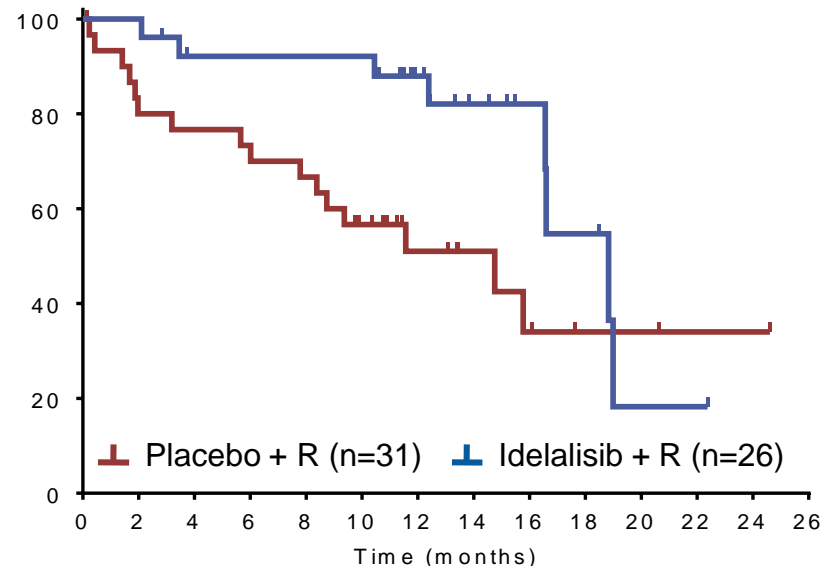
HR (95% CI)

0.31 (0.15, 0.65)

p-value

0.0011

Del17p Positive



Pbo + R	31	24	23	22	20	15	9	6	4	2	2	1	1	0
Idela + R	26	26	22	22	22	22	16	10	6	4	1	1	0	-

Median OS (95% CI)

14.8 mo (7.8, NR)

18.8 (16.6, NR)

HR (95% CI)

NA

p-value

0.04

*As randomized, including crossover study.

116 study: Adverse Events* in $\geq 15\%$ of Patients at 2nd IA vs Follow-Up

AE by Preferred Term	IDEA + R (N=110)				PBO + R → IDEA (N=108)			
	Any Grade, %		Grade ≥ 3 , %		Any Grade, %		Grade ≥ 3 , %	
	2 nd IA	Update	2 nd IA	Update	2 nd IA	Update	2 nd IA	Update
Any AE	96	98	64	80	98	100	52	78
Pyrexia	35	44	3	6	17	32	1	3
Diarrhea/colitis	21	42	6	16	16	44	—	13
Fatigue	26	36	5	5	28	43	3	5
Cough	17	34	1	2	28	44	2	2
Nausea	26	31	—	2	21	36	—	1
Chills	21	26	2	2	16	22	—	—
Infusion reaction	19	20	—	—	30	32	4	4
Constipation	13	19	—	—	11	21	—	1
Decreased appetite	12	19	—	2	10	17	2	3
Pneumonia	10	18	8	13	13	31	9	20
Dyspnea	13	17	3	6	19	25	3	5
Rash	10	17	1	3	5	12	—	1
Vomiting	13	17	—	—	8	21	—	1
Upper respiratory infection	7	15	2	1	11	24	2	2
Edema, peripheral	10	15	—	—	9	19	2	3
Night sweats	11	14	—	2	10	20	—	—
Asthenia	7	12	1	—	9	19	4	6
Abdominal pain	7	10	1	2	9	19	1	2

YENİ JENERASYON BCL-2 İNHİBİTÖRLERİ: ABT-199

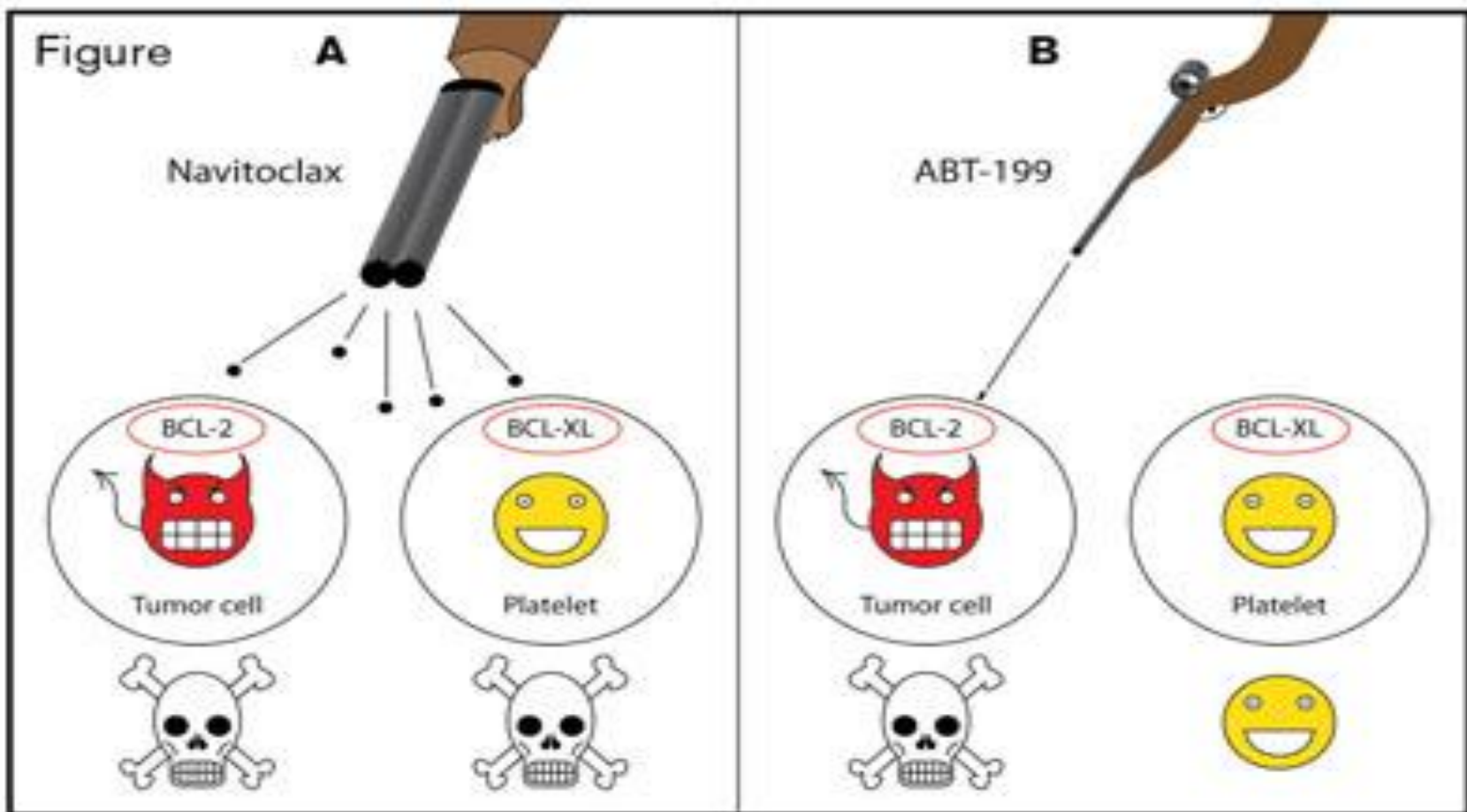
BCL-2 sequesters the proteins BAX & BAK, allowing the CLL cell to evade death.



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.



ABT-199 Selectively Kills BCL-2-Dependent Tumor Cells While Sparing Platelets. A) Navitoclax (ABT-263) binds to both BCL-2 and BCL-X_L. Platelets are dependent on the anti-apoptotic activity of BCL-X_L for survival. Consequently, thrombocytopenia is a dose-limiting adverse effect of treatment with navitoclax. B) ABT-199 is specific for BCL-2 and induces selective death of BCL-2-dependent tumor cells while sparing platelets.

Reprinted from Cancer Cell, 23, Davids MS and Letai A, Taking Dead Aim at BCL-2, page 140, 2013, with permission from Elsevier. Figure created by Richard Oakley.

Yeni jenerasyon Bcl-2 inhibitörleri

ABT-199 çok yüksek riskli ileri evre CLL de faz 1-2 sonuçları

- Lower affinity for Bcl-XL = **less thrombocytopenia**
- Dose-finding study in CLL (n=84) , relapsed/refractory, *high-risk* patients
- Starting dose 20 mg, then weekly increased up to 400 mg
- Tumor lysis syndrome in 8% (1 fatal), diarrhea 37 %, neutropenia 32%
- ORR : 17p- 78% (n=23). F-refr 79%.
- Response duration 20 months
- Safety cohort further expanded

Venetoclax (ABT-199/GDC-0199)

Venetoclax+ Rituximab Open-label, dose-escalation, multicenter, international phase Ib trial, 49 patients

- Venetoclax plus rituximab well tolerated, with potential activity in patients with relapsed/refractory chronic lymphocytic leukemia (CLL)
 - No new toxicities identified
 - Venetoclax 400 mg identified as recommended dose for future studies
 - ORR: 88%
 - CR/CR with incomplete blood count recovery (CRi): 31%
 - Minimal residual disease (MRD) negativity in bone marrow: 46%
 - MRD negative in 9 of 15 patients achieving CR/CRi
 - MRD negative in 8 of 22 patients achieving PR
 - No effect of rituximab on venetoclax exposure
- Phase III trial under way comparing venetoclax plus rituximab vs bendamustine plus rituximab in patients with previously treated CLL

Mikroçevreyi hedefliyen tedavi: Lenalidomid

- Lösemik hücrelerde ılımlı apoptoz oluşturur
- Lösemik hücre proliferasyonunu cereblon/p21 bağımlı mekanizmayla azaltır; ve NLC ve endotel ilişkili yaşam desteğini engeller
- KLL mikroçevresi üzerine pleotropik etkileri vardır:
 - CD4 T- hücre aracılıklı antijen prezentasyonu, proliferasyon ve aktivasyonunu artırır,
 - NK ve CD4 hücre aracılıklı anti tümör yanıtlarını artırır
 - T hücreleri ve KLL hücreleri arasındaki fonksiyonel sinapsı restore eder; PD-1/PD-L1 immunsupresif aksını baskılar

Lenalidomid ilk sıra tedavi

Response To 7 Cycles Of Lenalidomide + Rituximab *2-3 Months After Completion Of Therapy*

Final iwCLL Response to Therapy	Arm A (< 65 years old; n = 40)		Arm B (≥ 65 years old; n = 29)	
	No. of Patients	%	No. of Patients	%
Complete response	8	20	2	7
CRi	0		1	3
Nodular partial response	7	18	0	
Partial response	23	58	20	69
Stable disease	0		3	10
Progressive disease	0		1	3
Nonevaluable	2	5	2	7
Overall response rate	38	95	23	79
95% CI	85 to 99		63 to 91	
Complete response, including CRi	8	20	3	10
95% CI	10 to 33		3 to 25	

Abbreviations: CRi, complete response incomplete marrow recovery; iwCLL, International Workshop for Chronic Lymphocytic Leukemia.

SUGGESTED TREATMENT REGIMENS^a
(in order of preference)

CLL without del (11q) or del (17p)

Frail patient, significant comorbidity
(not able to tolerate purine analogs)

- **Obinutuzumab + chlorambucil** (category 1)
- Ofatumumab + chlorambucil
- Rituximab + chlorambucil
- Obinutuzumab (category 2B)
- Rituximab (category 2B)
- Chlorambucil (category 2B)
- Pulse corticosteroids (category 3)

See Supportive Care for Patients with CLL ([CSLL-C](#))

Consider prophylaxis for tumor lysis syndrome ([See NHODG-B](#))

See monoclonal antibody and viral reactivation ([NHODG-B](#))

First-line therapy^b

- Age ≥70 y and younger patients with significant comorbidities
 - **Obinutuzumab + chlorambucil** (category 1)
 - Ofatumumab + chlorambucil
 - Rituximab + chlorambucil
 - Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) ± rituximab
 - Obinutuzumab (category 2B)
 - Fludarabine^{c,d,e} ± rituximab (category 2B)
 - Chlorambucil (category 2B)
 - Rituximab (category 3)
 - Cladribine (category 3)^f
- Age <70 y without significant comorbidities
 - Chemoimmunotherapy
 - ◊ FCR^c (fludarabine, cyclophosphamide, rituximab) (category 1)^g
 - ◊ FR^c (fludarabine, rituximab)
 - ◊ PCR (pentostatin, cyclophosphamide, rituximab)
 - ◊ Bendamustine ± rituximab^g

Relapsed/Refractory therapy

[See Suggested Regimens for Relapsed/Refractory therapy for CLL without del \(11q\) or del \(17p\) \(2 of 7\)](#)

[See Suggested Regimens for CLL with del \(17p\) \(3 of 7\)](#)

[See Suggested Regimens for CLL with del \(11q\) \(4 of 7\)](#)

^a See references for regimens [CSLL-D 6 of 7](#) and [CSLL-D 7 of 7](#).

^b [See Supportive Care for Patients with CLL \(CSLL-C\)](#).

^c Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

^d In patients ≥70 y, fludarabine does not have a benefit for first-line therapy over other therapies including chlorambucil.

^e See Discussion for further information on oral fludarabine.

^f In rare circumstances of CNS disease, cladribine is potentially useful.

^g Data from the CLL10 study confirms the superiority of FCR over BR in younger patients. For patients >65 y, the outcome was similar for both regimens with less toxicity for BR. BR may be a reasonable alternative for older patients otherwise eligible for chemoimmunotherapy and is associated with fewer myelosuppressive toxicities.

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.



SUGGESTED TREATMENT REGIMENS^a
(in order of preference)

CLL without del (11q) or del (17p)

Relapsed/Refractory therapy^b

- Age ≥70 y and younger patients with significant comorbidities

- ▶ Ibrutinib^h (category 1)
- ▶ Idelalisib ± rituximab^{h,i}
- ▶ Chemoimmunotherapy
 - ◊ Reduced-dose FCR^{c,e}
 - ◊ Reduced-dose PCR
 - ◊ Bendamustine ± rituximab
 - ◊ High-dose methylprednisolone (HDMP) + rituximab
 - ◊ Rituximab + chlorambucil
- ▶ Ofatumumab
- ▶ Obinutuzumab
- ▶ Lenalidomide^j ± rituximab
- ▶ Alemtuzumab^k ± rituximab
- ▶ Dose-dense rituximab (category 2B)

- Age <70 y without significant comorbidities

- ▶ Ibrutinib^h (category 1)
- ▶ Idelalisib ± rituximab^{h,i}
- ▶ Chemoimmunotherapy
 - ◊ FCR^{c,e}
 - ◊ PCR
 - ◊ Bendamustine ± rituximab
 - ◊ Fludarabine^{c,e} + alemtuzumab
 - ◊ RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
 - ◊ OFAR^c (oxaliplatin, fludarabine,^e cytarabine, rituximab)
- ▶ Ofatumumab
- ▶ Obinutuzumab
- ▶ Lenalidomide^j ± rituximab
- ▶ Alemtuzumab^k ± rituximab
- ▶ HDMP + rituximab

See Supportive Care for
Patients with CLL (CSLL-C)

Consider prophylaxis for tumor
lysis syndrome (See NHODG-B)

See monoclonal antibody and
viral reactivation (NHODG-B)

See Suggested Regimens for CLL with del (17p) (3 of 7)

See Suggested Regimens for CLL with del (11q) (4 of 7)

^aSee references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.

^bSee Supportive Care for Patients with CLL (CSLL-C).

^cAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

^eSee Discussion for further information on oral fludarabine.

^hSee Special Considerations for Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib) (NHODG-E).

ⁱIndicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)

^jLenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al, Blood 2011;118:Abstract 980, Badoux XC, Keating MJ, Wen S, et al, Blood 2011;118:3489-3498, Chanan-Khan A, Miller KC, Musial L, et al, J Clin Oncol 2006;24:5343-5349.

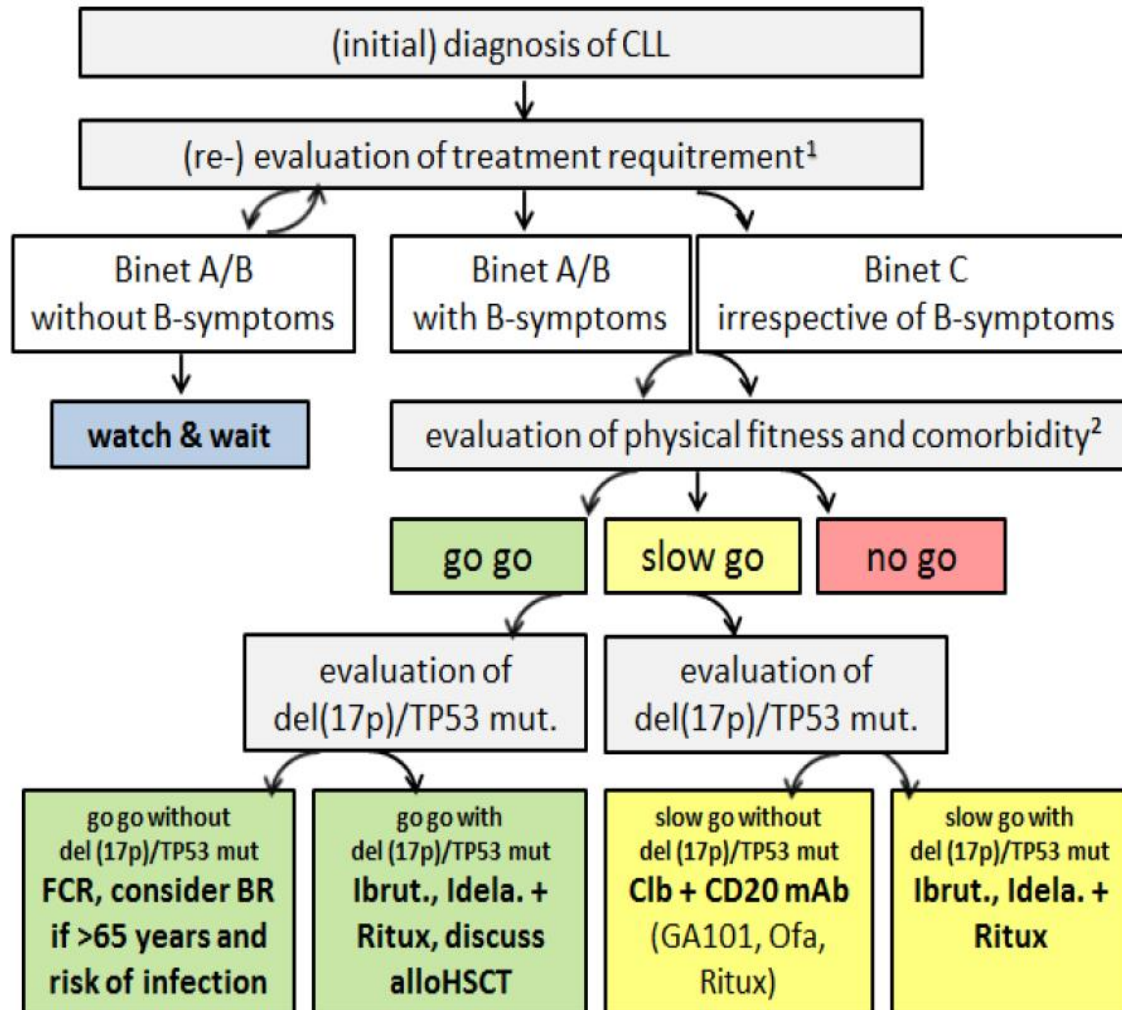
^kWhile alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use. Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

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.

Therapeutic algorithm of the GCLLSG

(April 2015)



References:

¹) Hallek et al., Blood 2008

²) Gribben, Blood 2009

