Non-Hodgkin Lenfomalarda Yenilikler

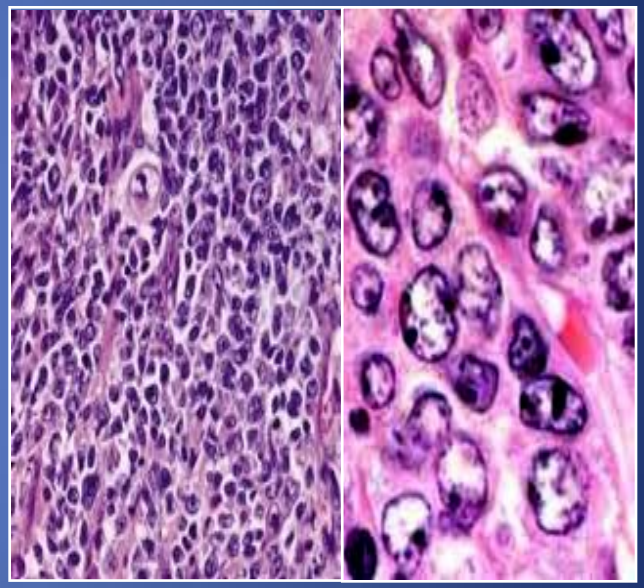
Dr. Mustafa Benekli

Genel Bakış

- Diffüz büyük B-hücreli lenfoma
- Folliküler lenfoma
- Mantle hücreli lenfoma

Diffüz Büyük B-Hücreli Lenfoma

- En sık görülen NHL
- İnsidans: 60'lı yaşlarda en sık
- Lenf nodu folliküler yapısını silen diffüz büyük hücre infiltrasyonu
- Ekstranodal hastalık sıktır (mide, SSS, testis, cilt)
- Hastaların >50% 'sinde küratif
- Tedavisiz sağkalım haftalar-aylar

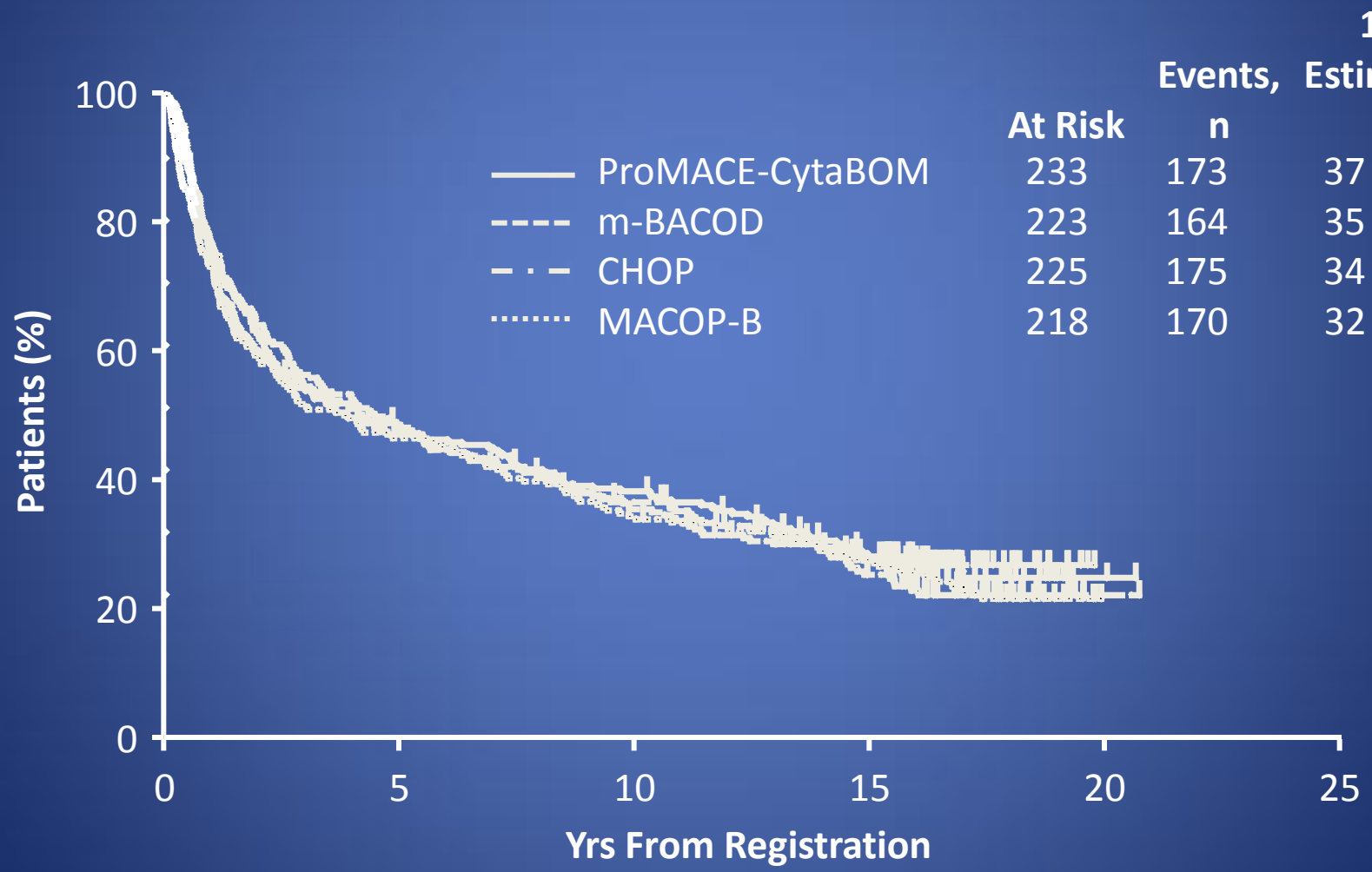


Comparison of a Standard Regimen (CHOP) With 3 Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma

Results of the National High Priority Lymphoma Study

Fisher RI, Gaynor ER, Dahlberg S, et al.
N Engl J Med. 1993;328:1002-1006.

Genel Sağkalım, S8516



Fisher RI, et al. N Engl J Med. 1993;328:1002-1006.

International Prognostic Index

- Kötü risk faktörleri
  - > 60 yaş
  - Evre III - IV
  - > 2 ekstranodal bölge
  - Performans skoru > 2
  - LDH > normal
- Risk kategorisi
  - Düşük
  - Düşük orta
  - Yüksek orta
  - Yüksek
- Risk faktörleri
  - 0, 1
  - 2
  - 3
  - 4, 5

N Engl J Med. 1993;329:987-994.

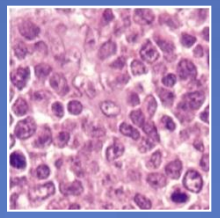
IPI (Bütün hastalar)

Risk Group*	Risk Factors, n	Distribution of Cases, %	CR Rate, %	Survival Rate, %	
				2 Yrs	5 Yrs
Low	0, 1	35	87	84	73
Low Intermediate	2	27	67	66	51
High Intermediate	3	22	55	54	43
High	4, 5	16	44	34	26

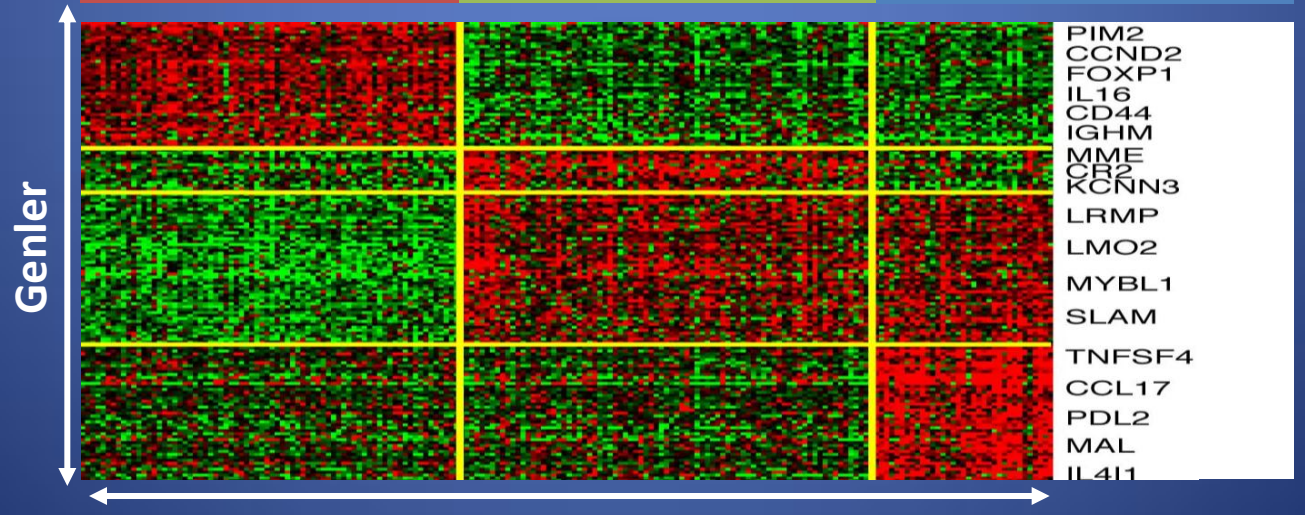
N Engl J Med. 1993;329:987-994.

Agresif Lenfomaların 3 Kategorisi

Diffüz Büyük B Hücreli Lenfoma

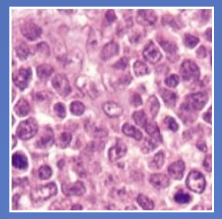


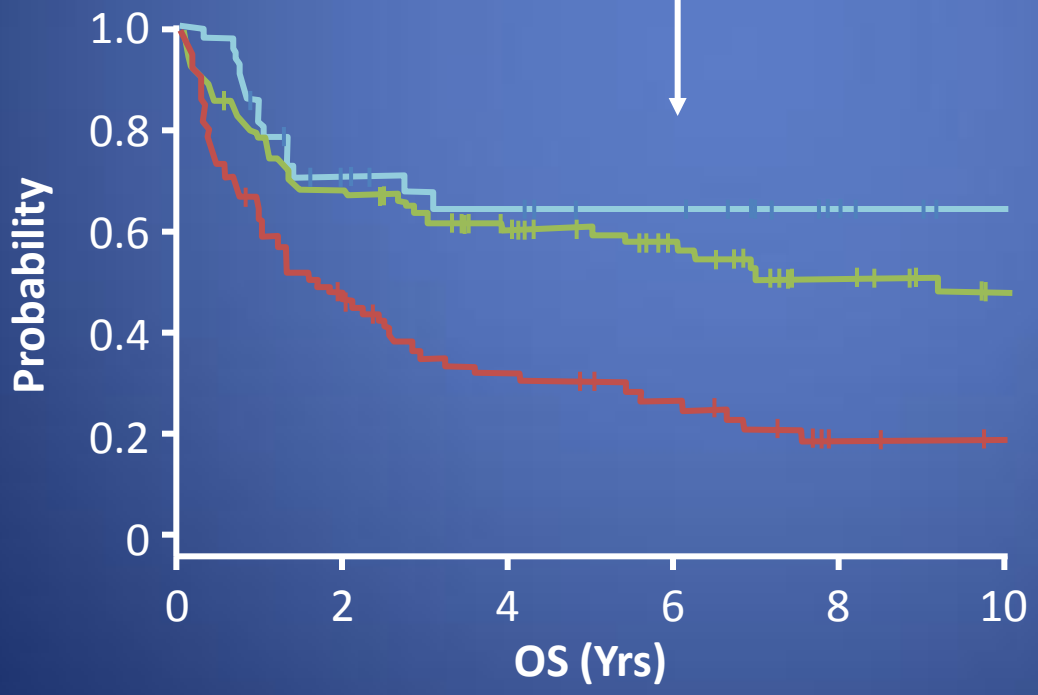
Activated B-cell–like diffuse large B-cell lymphoma	Germinal center B-cell–like diffuse large B-cell lymphoma	Primary mediastinal B-cell lymphoma



Farklı Genetik Gruplarda Sağkalım Oranları

Diffüz Büyük B Hücreli Lenfoma



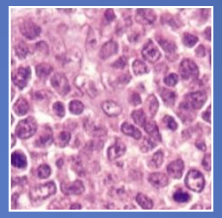


5-Yıl Sağkalım

PMBL	64%
GCB DLBCL	59%
ABC DLBCL	30%

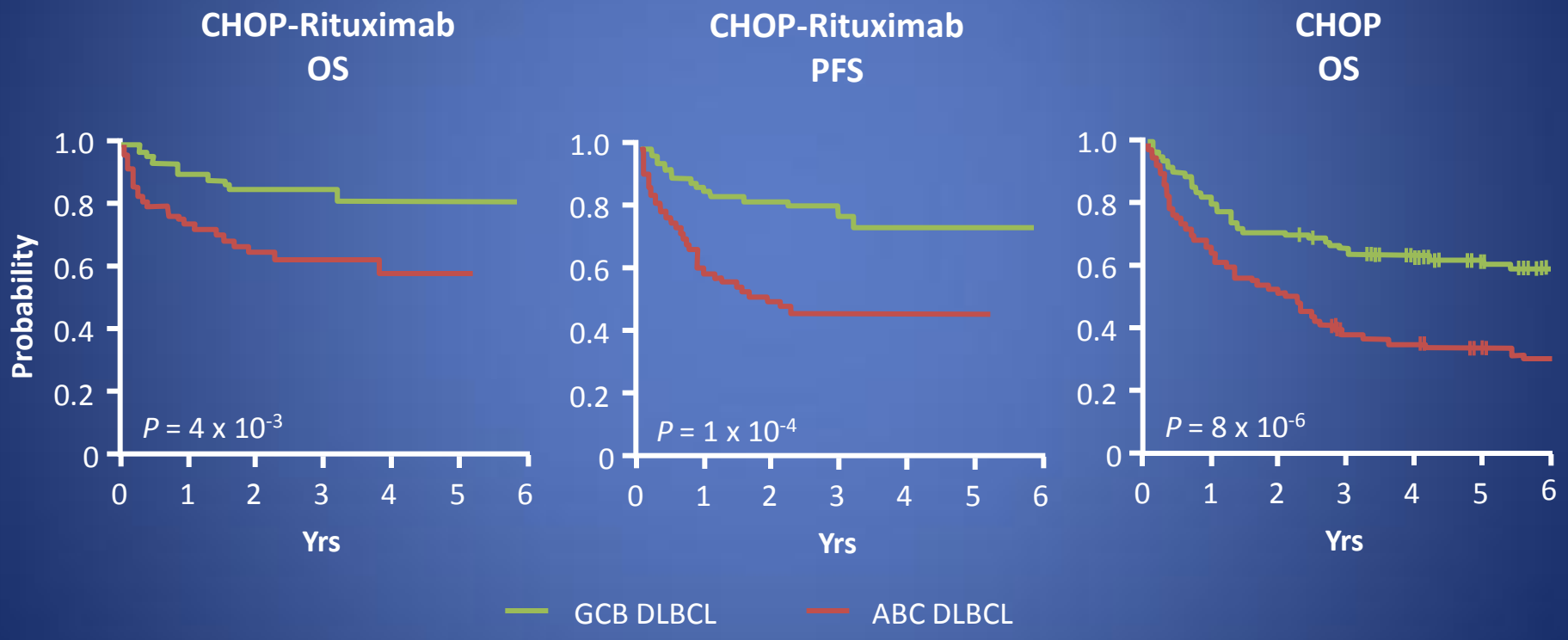
Moleküler ve Klinik Farklı Altgruplar

Diffüz Büyük B Hücreli Lenfoma



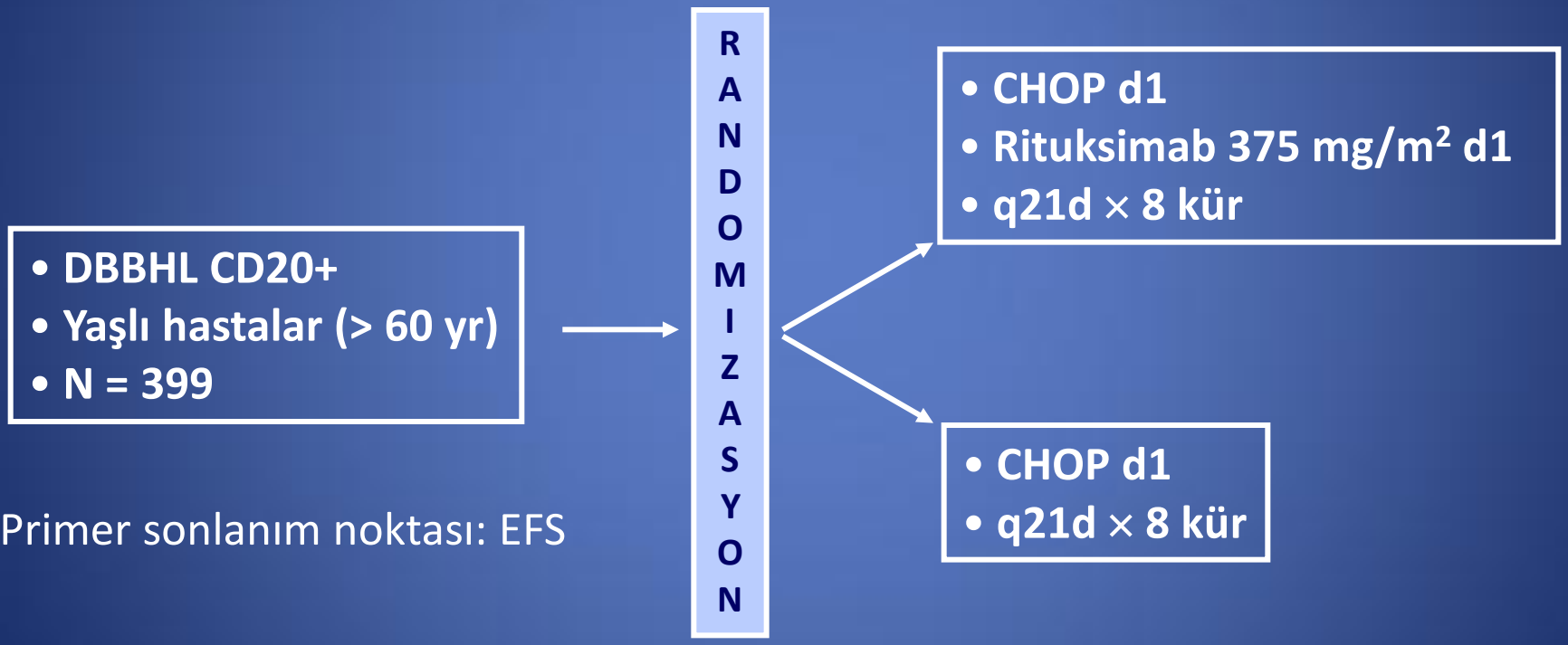
	GCB DLBCL	ABC DLBCL	PMBL
c-rel Amplifikasyonu	16%	0	25%
BCL-2 Translokasyonu	45%	0	18%
Kromozom 3q kazanımı	0	24%	5%
Kazanım/amp kromozom 9p24	0	6%	43%
Sürekli NF-κB Aktivasyonu	-	+	+

DBBHL GCB ve ABC Alttipleri Arasındaki Farklar



Lenz G, et al. N Engl J Med. 2008;359:2313-2323.

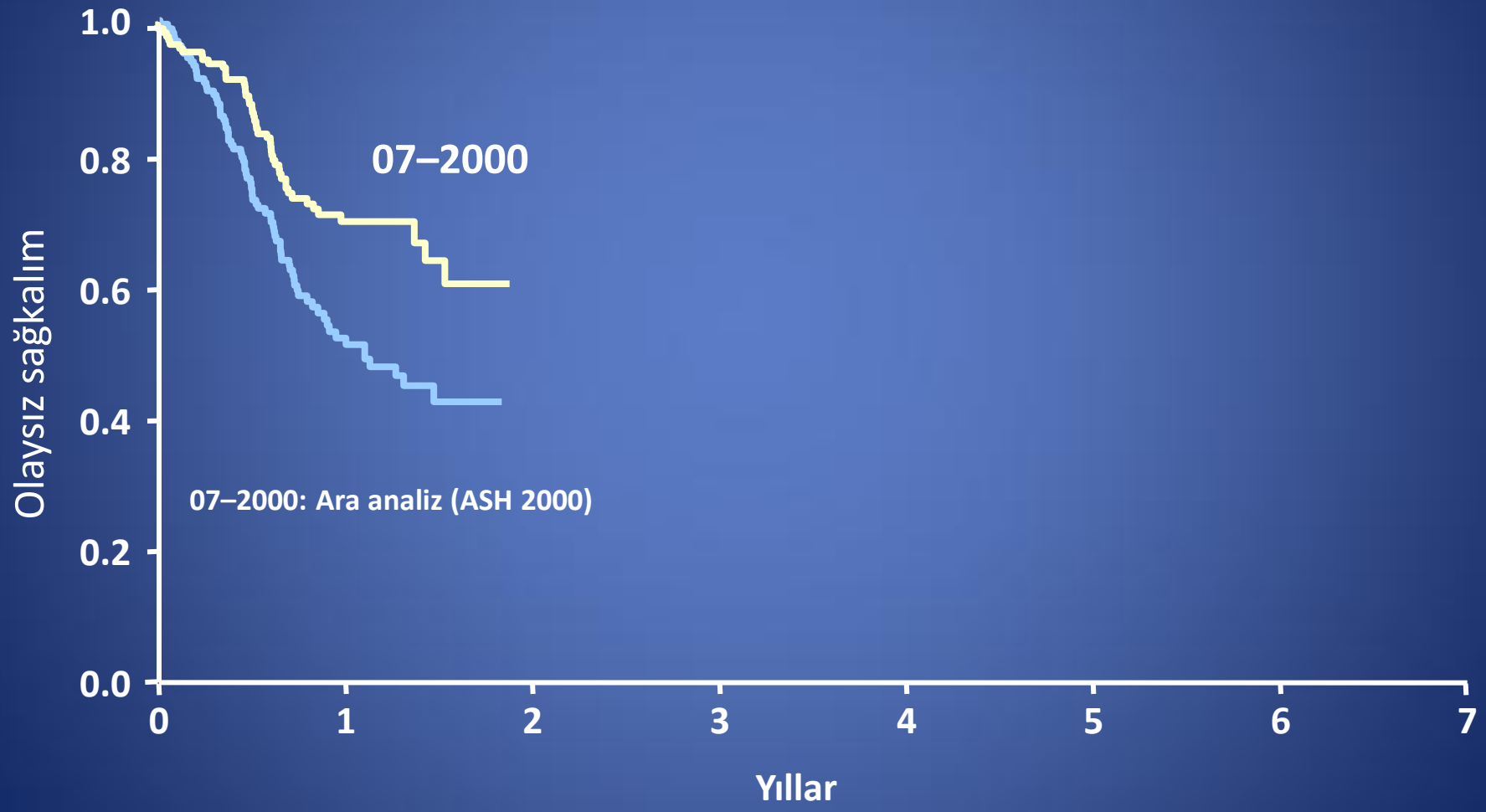
Faz III Çalışma: Yaşlı DBBHL: CHOP ± Rituksimab



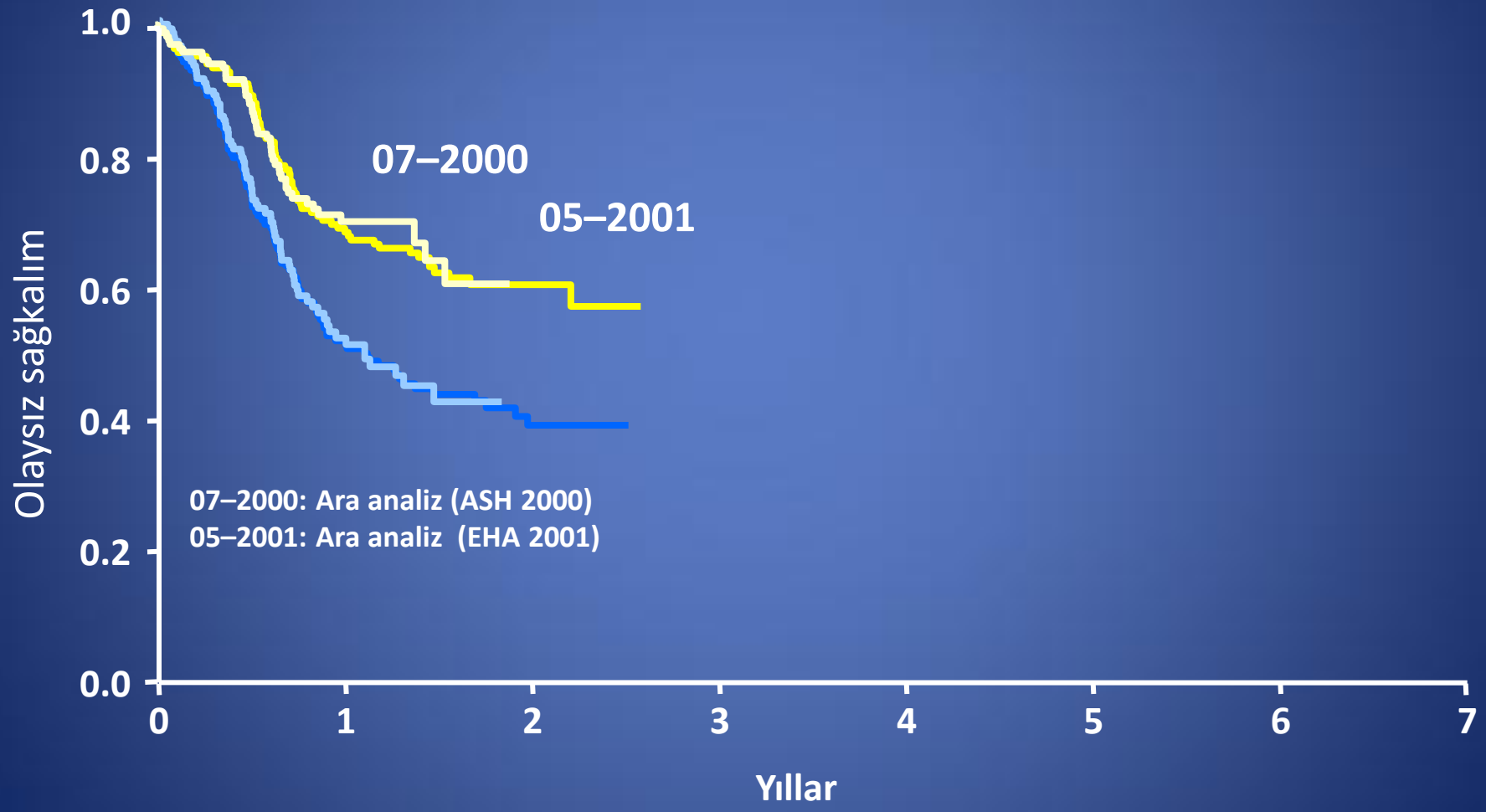
Primer sonlanım noktası: EFS

Coiffier B, et al. N Engl J Med 2002;346:235–43

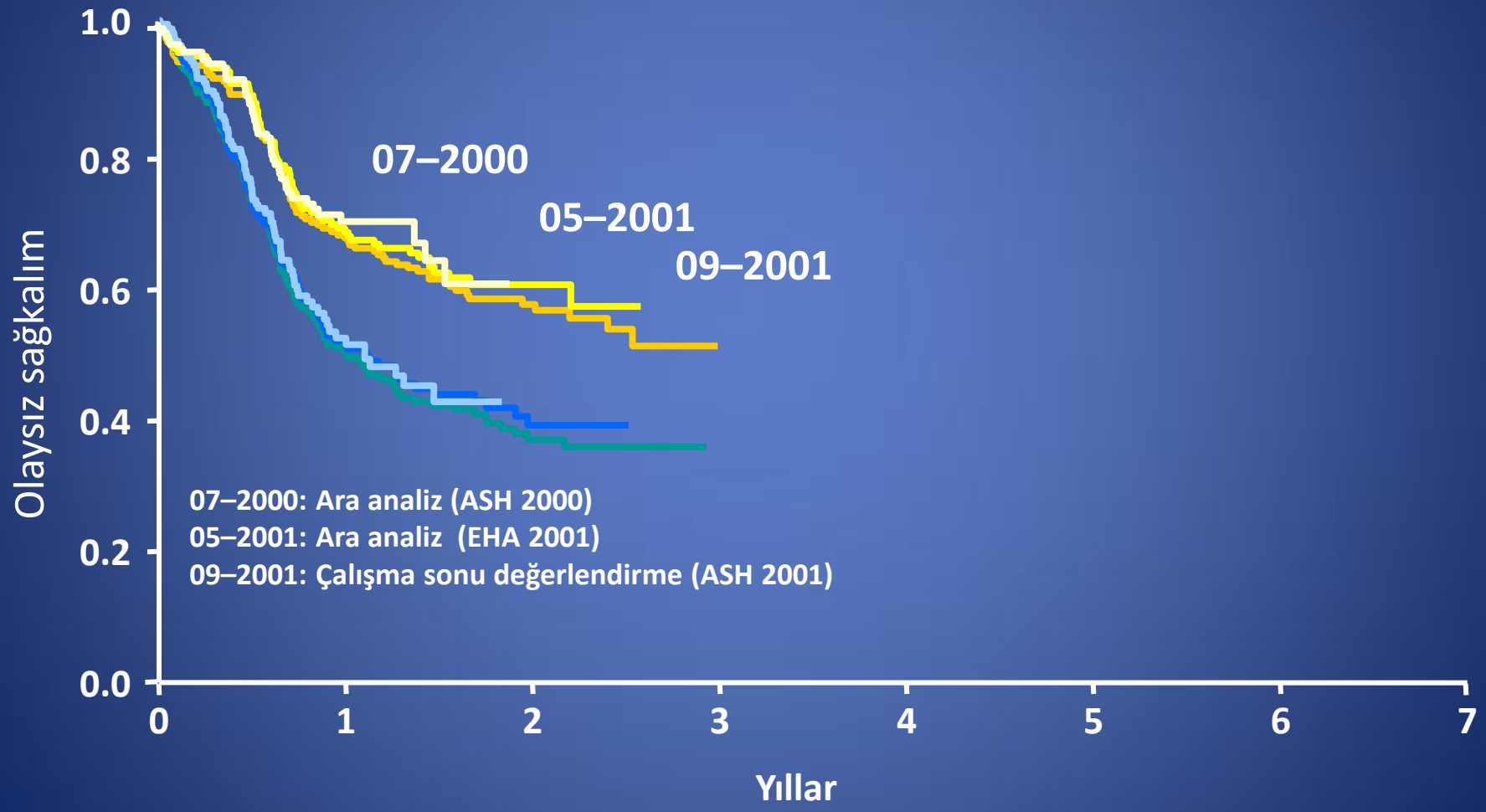
LNH-98.5: Olaysız Sağkalım



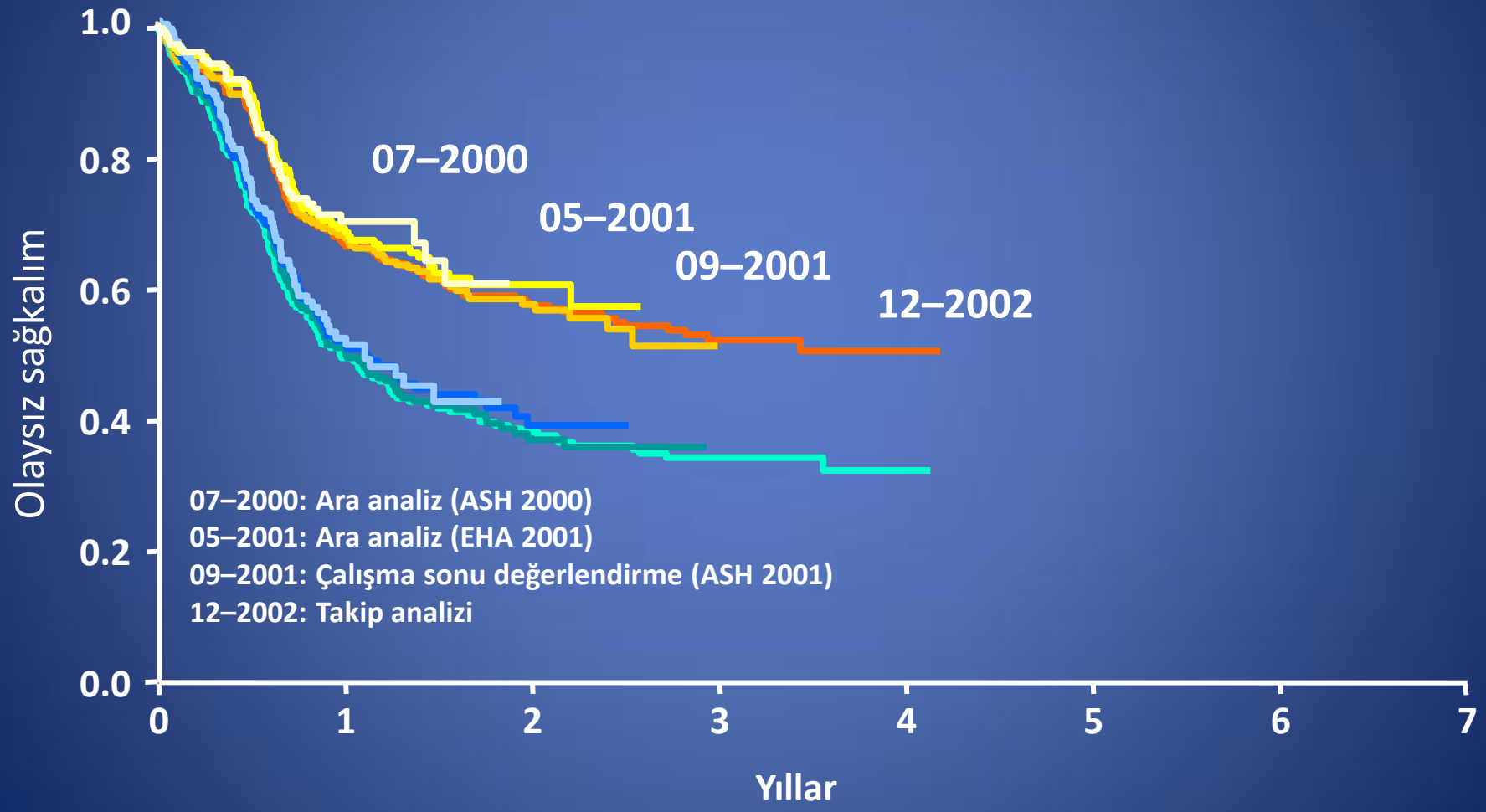
LNH-98.5: Olaysız Sağkalım



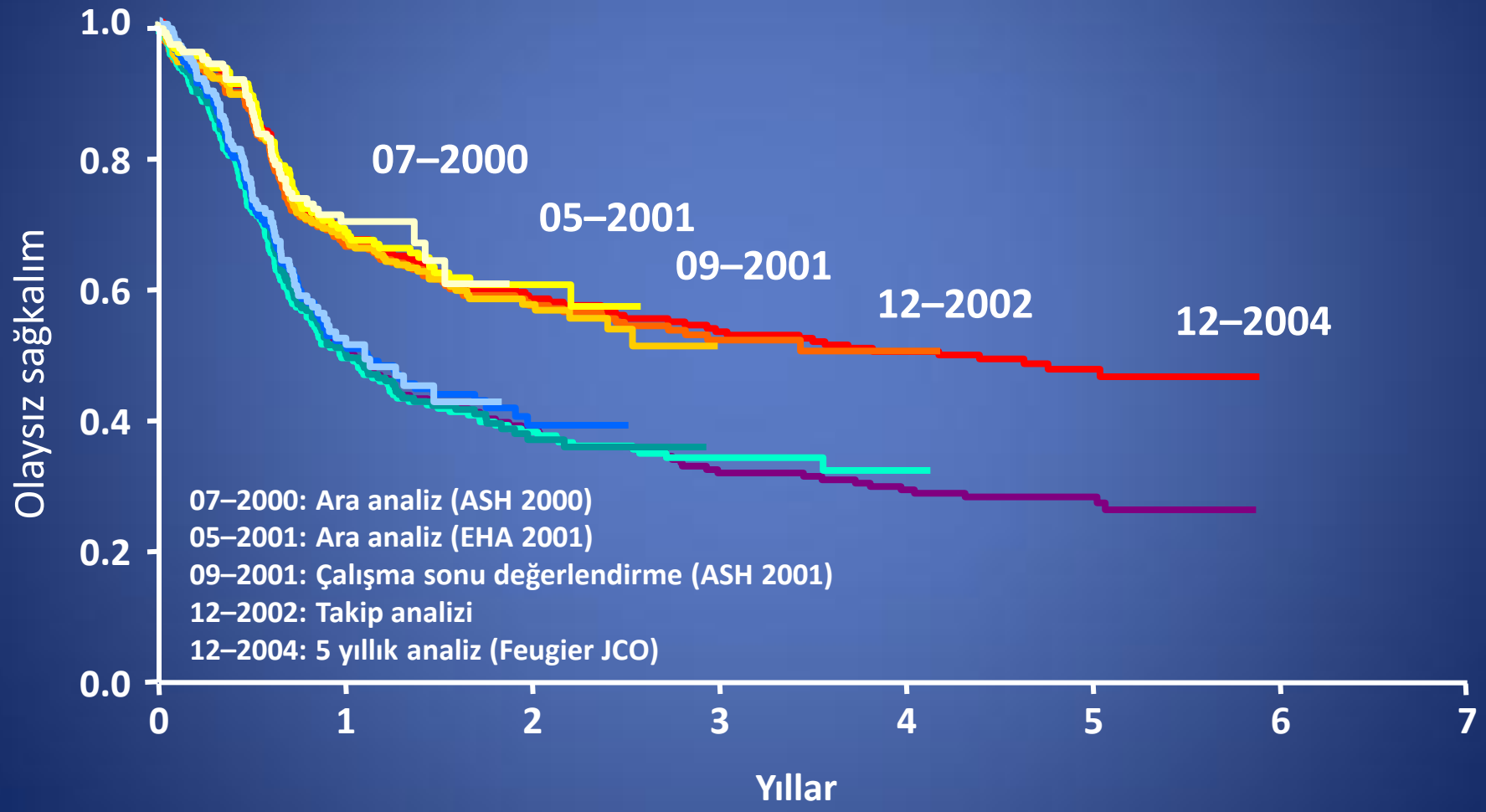
LNH-98.5: Olaysız Sağkalım



LNH-98.5: Olaysız Sağkalım

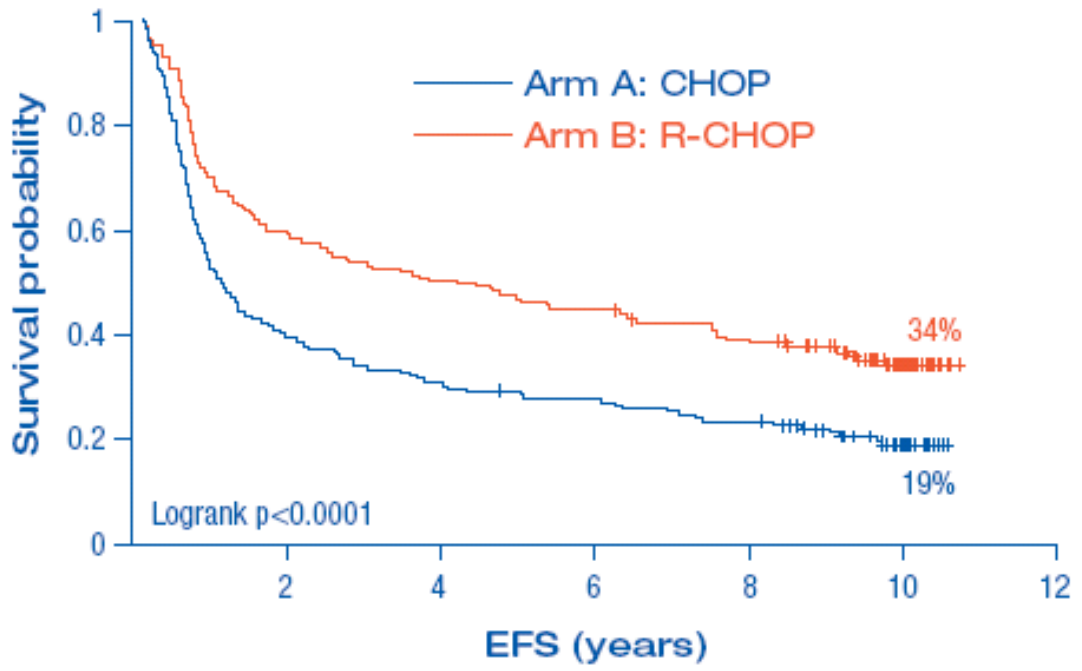


LNH-98.5: Olaysız Sağkalım



10 yıllık Olaysız Sağkalım

Olaysız Sağkalım



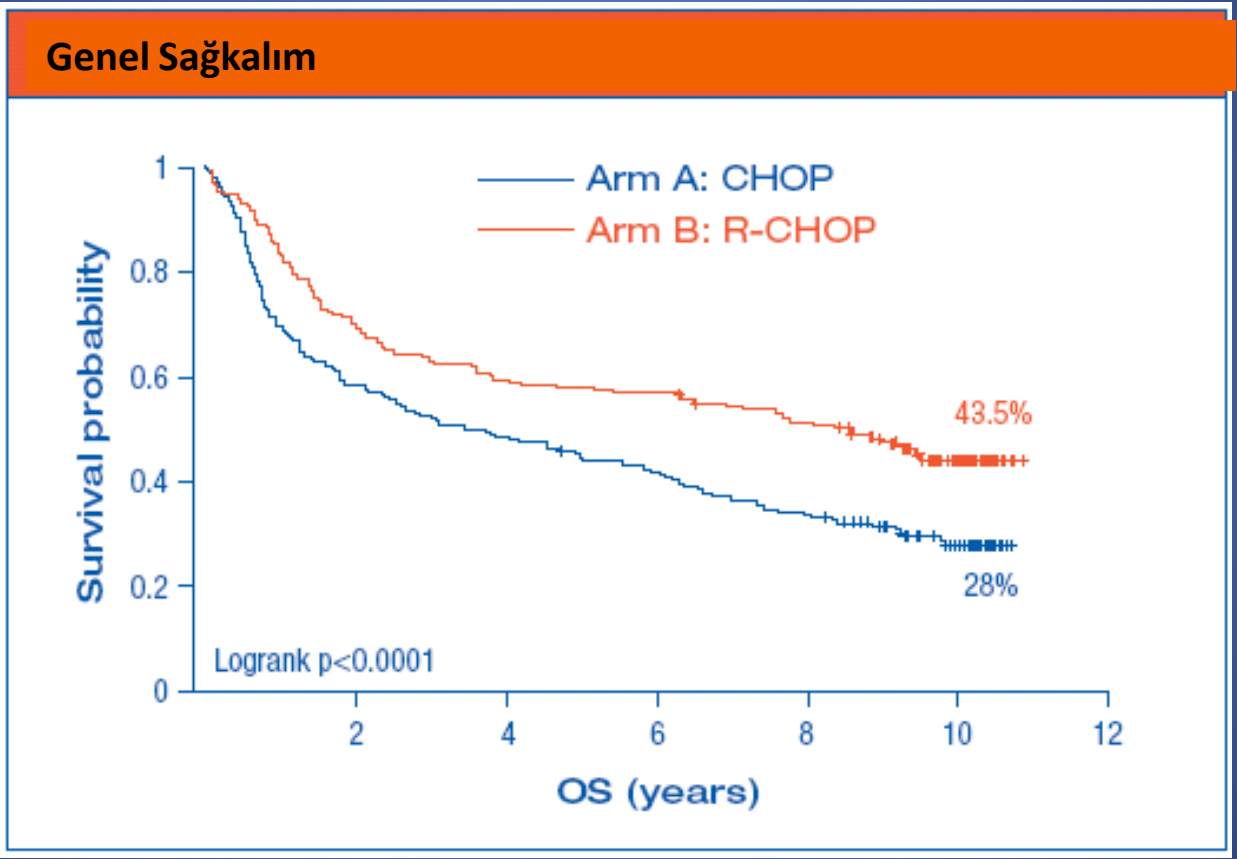
<u>7 yıllık gözlemde: olaysız sağkalım</u>

CHOP kolunda %25

R-CHOP kolunda %42

Coiffier et al. ASH 2009 Abst.3741

10 yıllık Genel Sağkalım



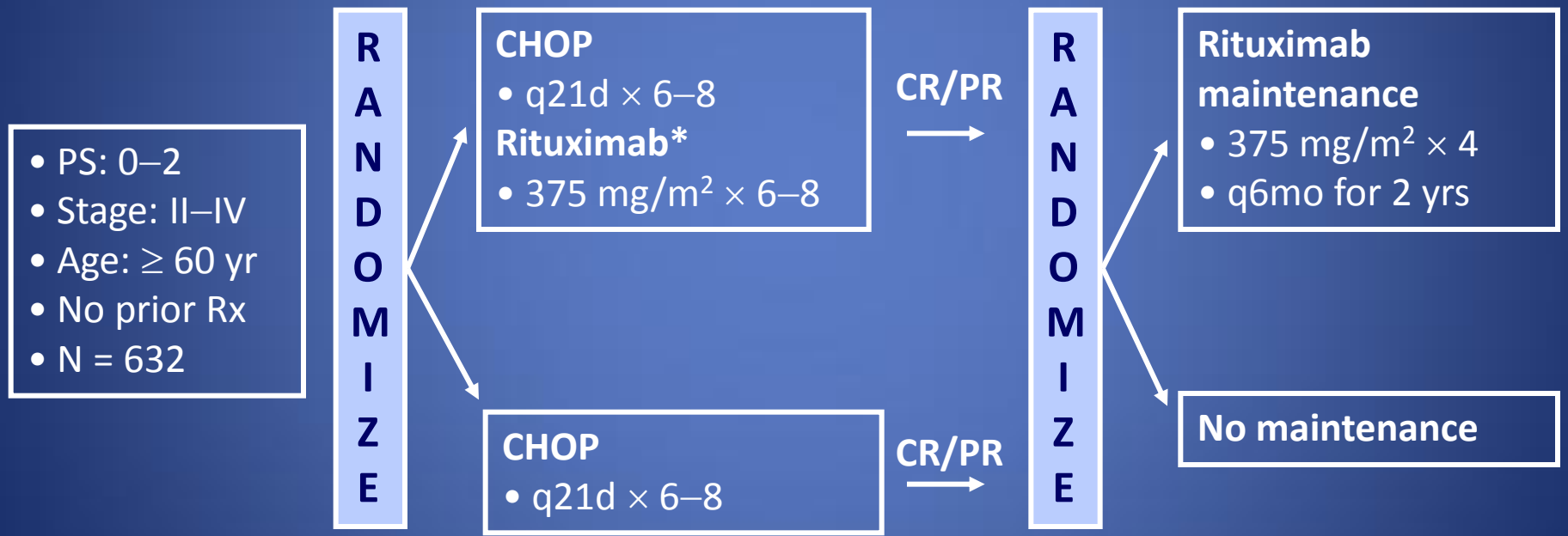
Medyan genel sağkalım

CHOP kolunda 37 ay

R-CHOP kolunda 7 yıl 9 ay

Coiffier et al. ASH 2009 Abst.3741

Rituksimab + CHOP: DBBHL birinci basamak tedavisinde Intergroup çalışması



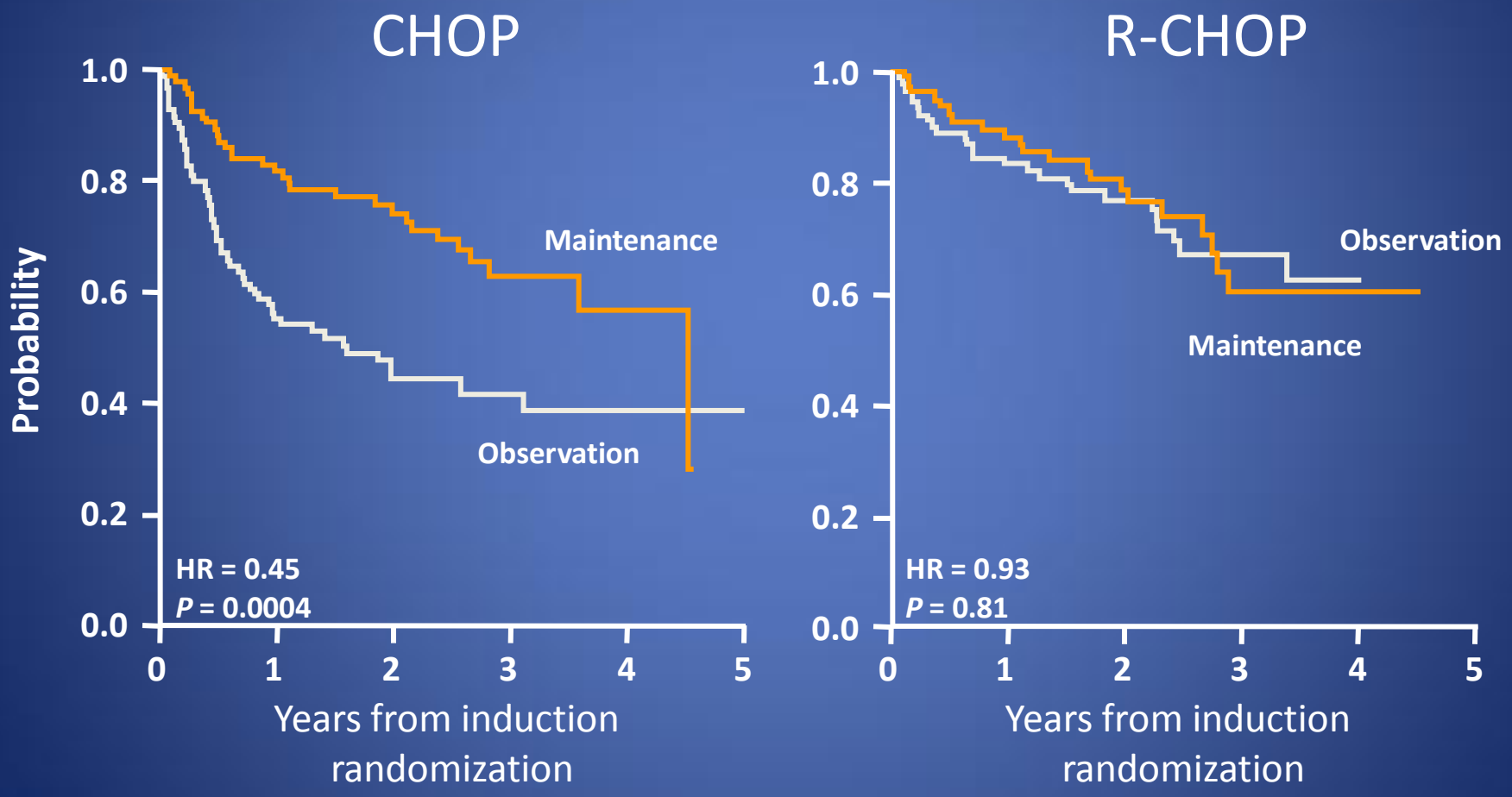
Habermann TM, *et al. JCO 2006;24:3121-3127.*

Maintenance Rituximab vs Observation After R-CHOP or CHOP in Older DLBCL Patients

An Intergroup E4494/C9793 Update

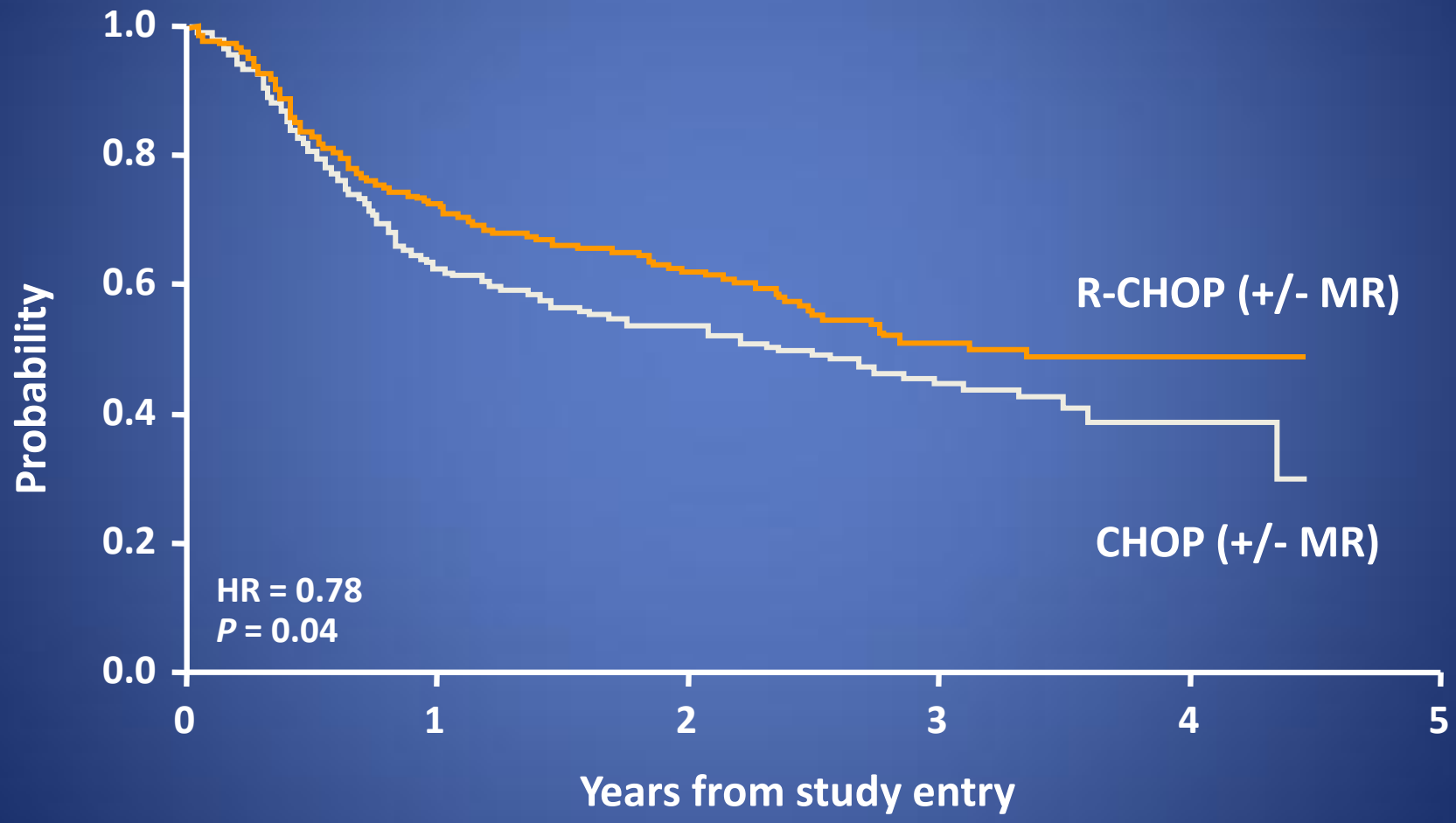
Morrison VA, Weller EA, Habermann TM, et al.
ASCO 2007. Abstract 8011.

Dört kollu analiz: TTF
Değerlendirilebilen CR/PR hastaları (n = 352)



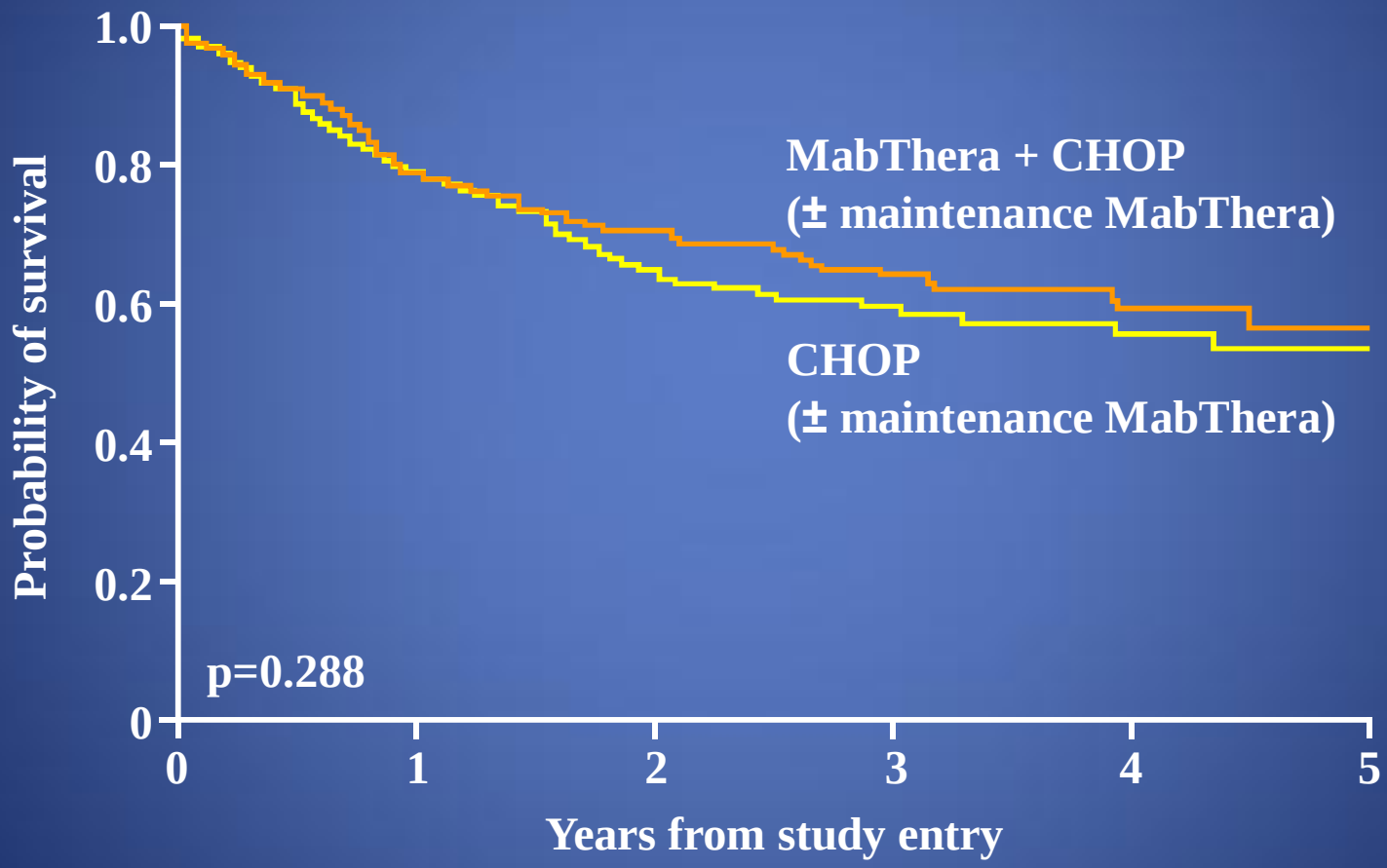
Morrison VA, et al. Proc ASCO 2007; 25: 8011

Indüksiyon tedavisi: TTF
Değerlendirilebilen hastalar (n = 546)



Morrison VA, et al. Proc ASCO 2007; 25: 8011

Agresif NHL'da CHOP ± R:
genel sağkalım (indüksiyon tedavisi)



Morrison VA, et al. Proc ASCO 2007; 25: 8011

The MabThera International Trial

Düşük Riskli DBBHL Genç Hastalarda R-Kemoterapi

The MabThera International Trial (MInT)

CD20+ DLBCL
18–60 yaş
IPI 0 = 43%
IPI 1 = 57%
Evre II–IV
Bulky evre I
N = 823

RANDOMİZASYON

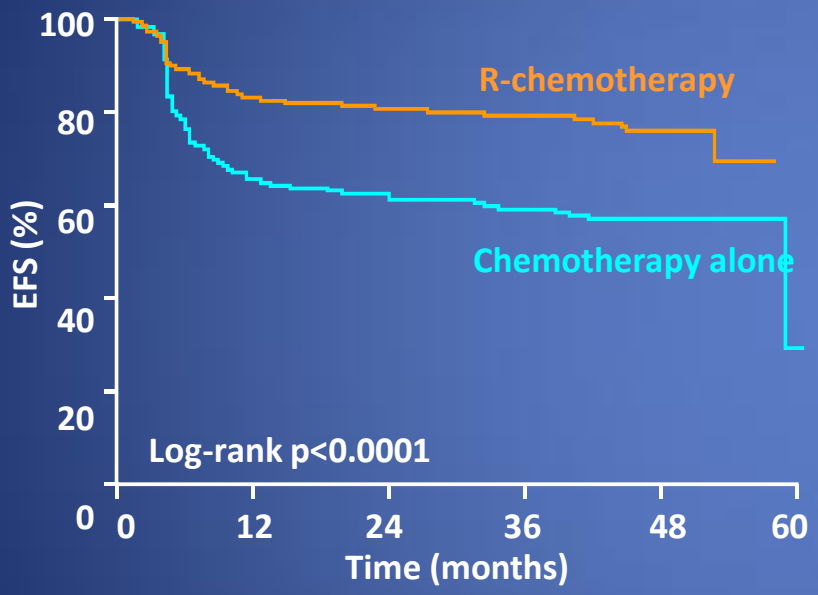
**6 × CHOP-benzeri*
+ 30–40 Gy (bulk, E)**

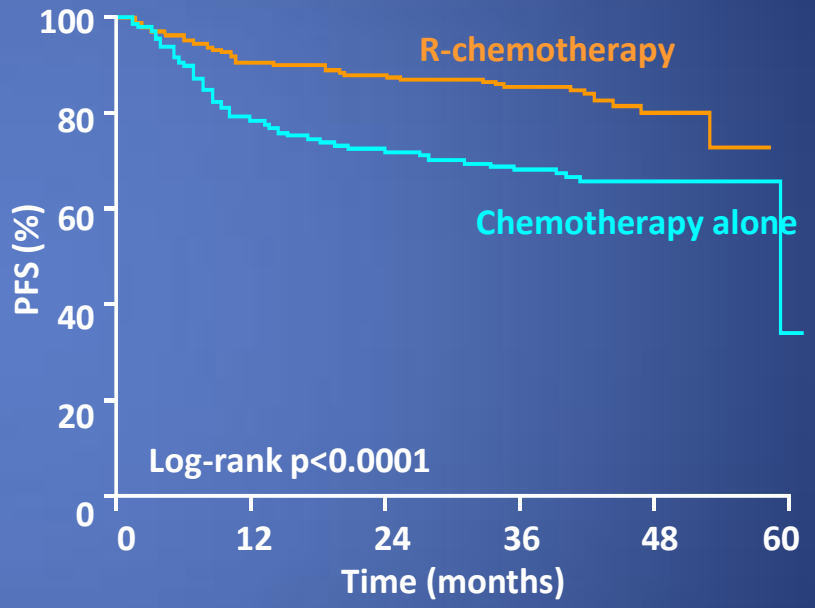
**6 × rituksimab
+ CHOP-benzeri*
+ 30–40 Gy (bulk, E)**

CHOP benzeri kemoterapi: CHOP (%48), CHOEP (%44)

Pfreundschuh M, et al. Lancet Oncology 2006;7:379–91

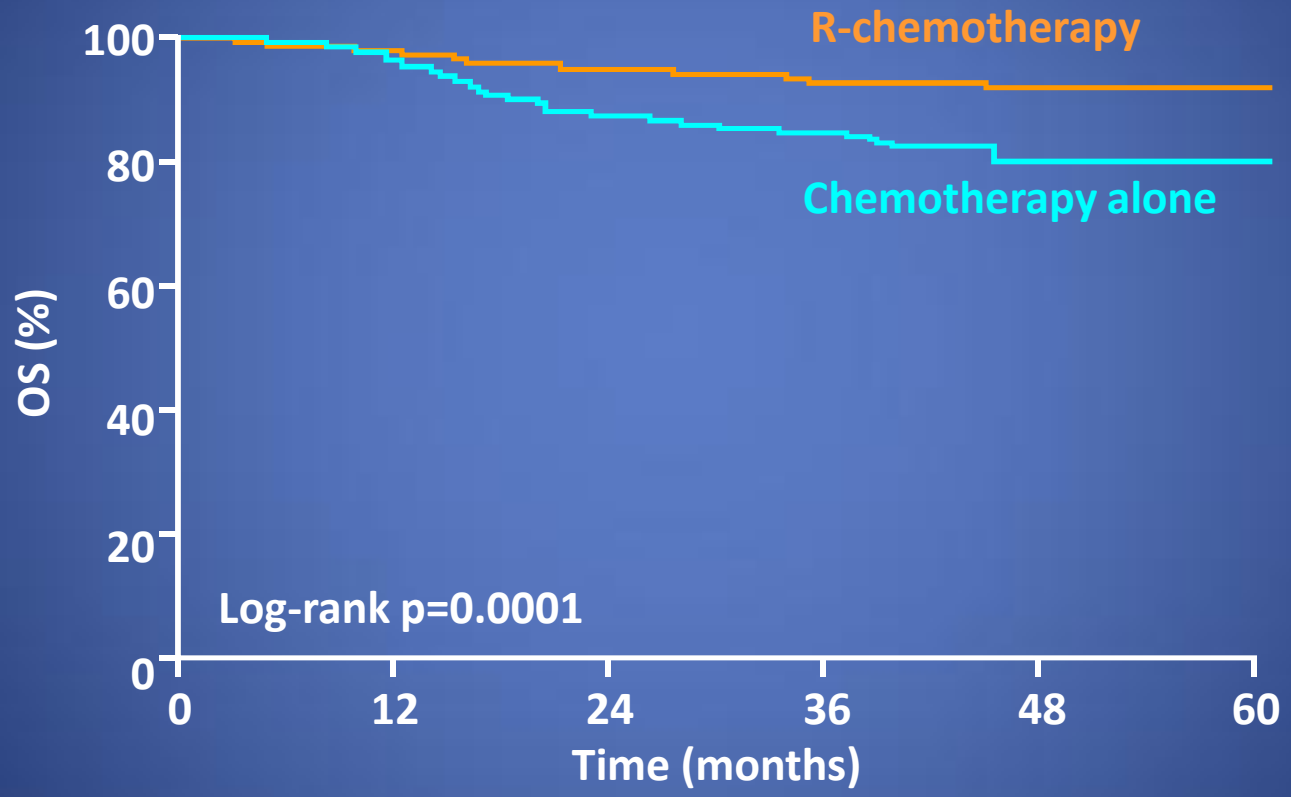
MInT: EFS ve PFS





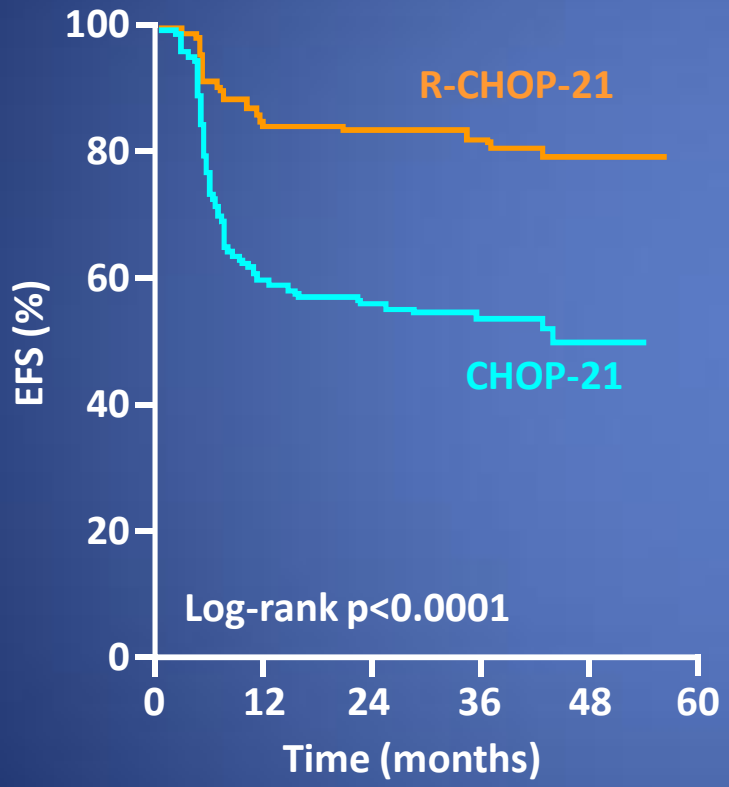
Pfreundschuh M, et al. Lancet Oncology 2006;7:379–91

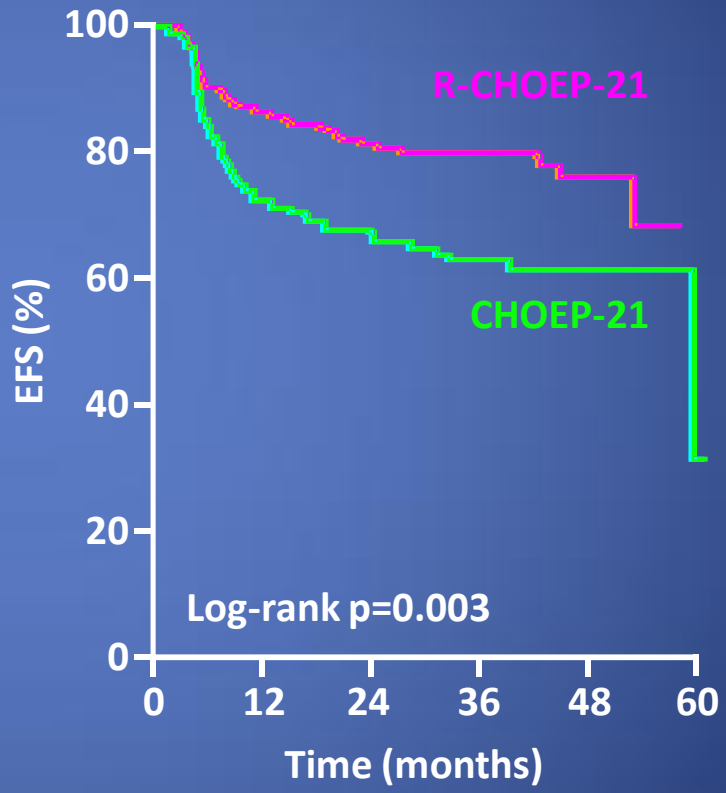
MInT: OS



Pfreundschuh M, et al. Lancet Oncology 2006;7:379–91

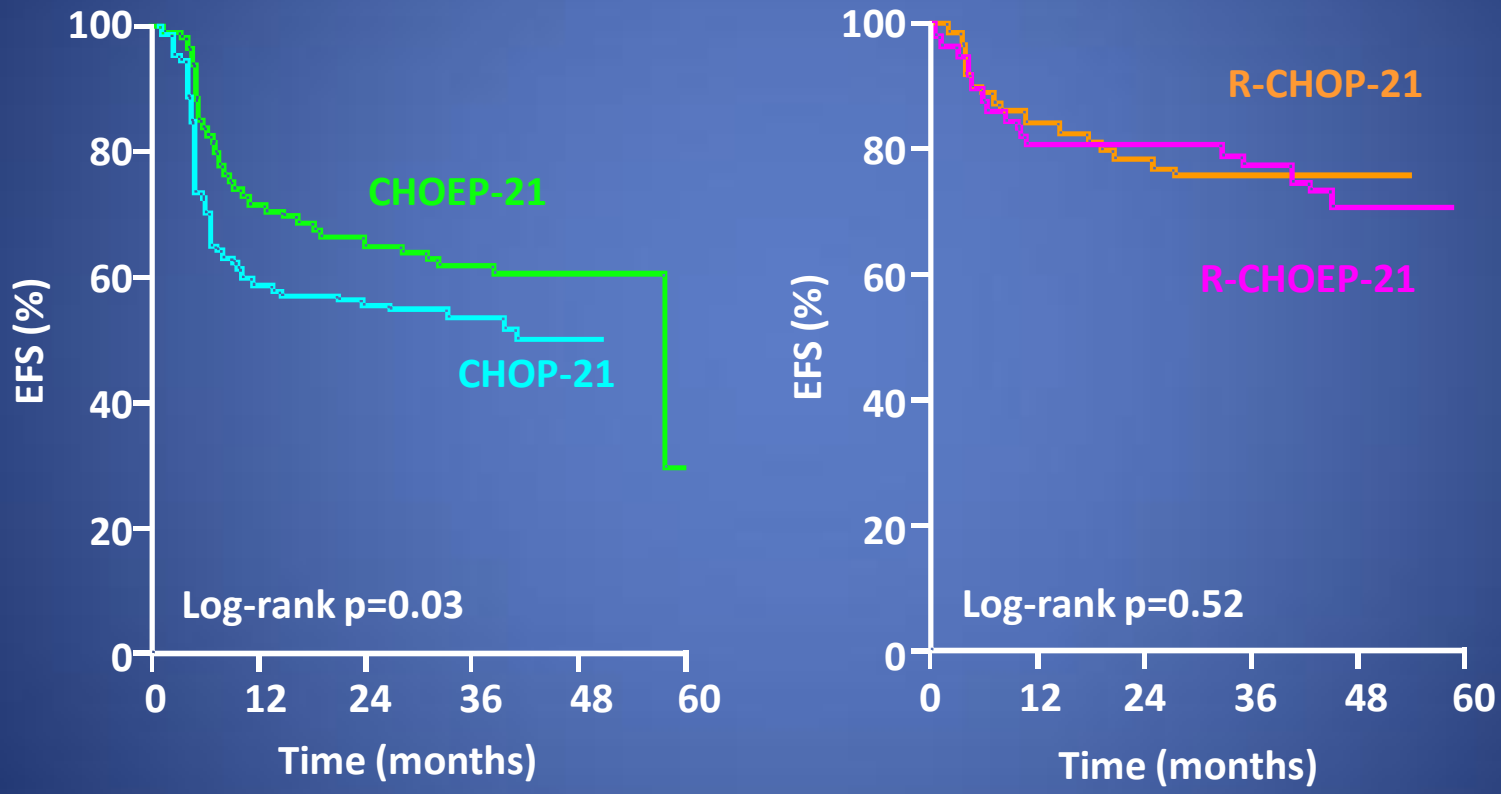
R-CHOP vs CHOP & R-CHOEP vs CHOEP: EFS





Pfreundschuh M, et al. Lancet Oncology 2006;7:379–91

CHOP vs CHOEP & R-CHOP vs R-CHOEP: EFS

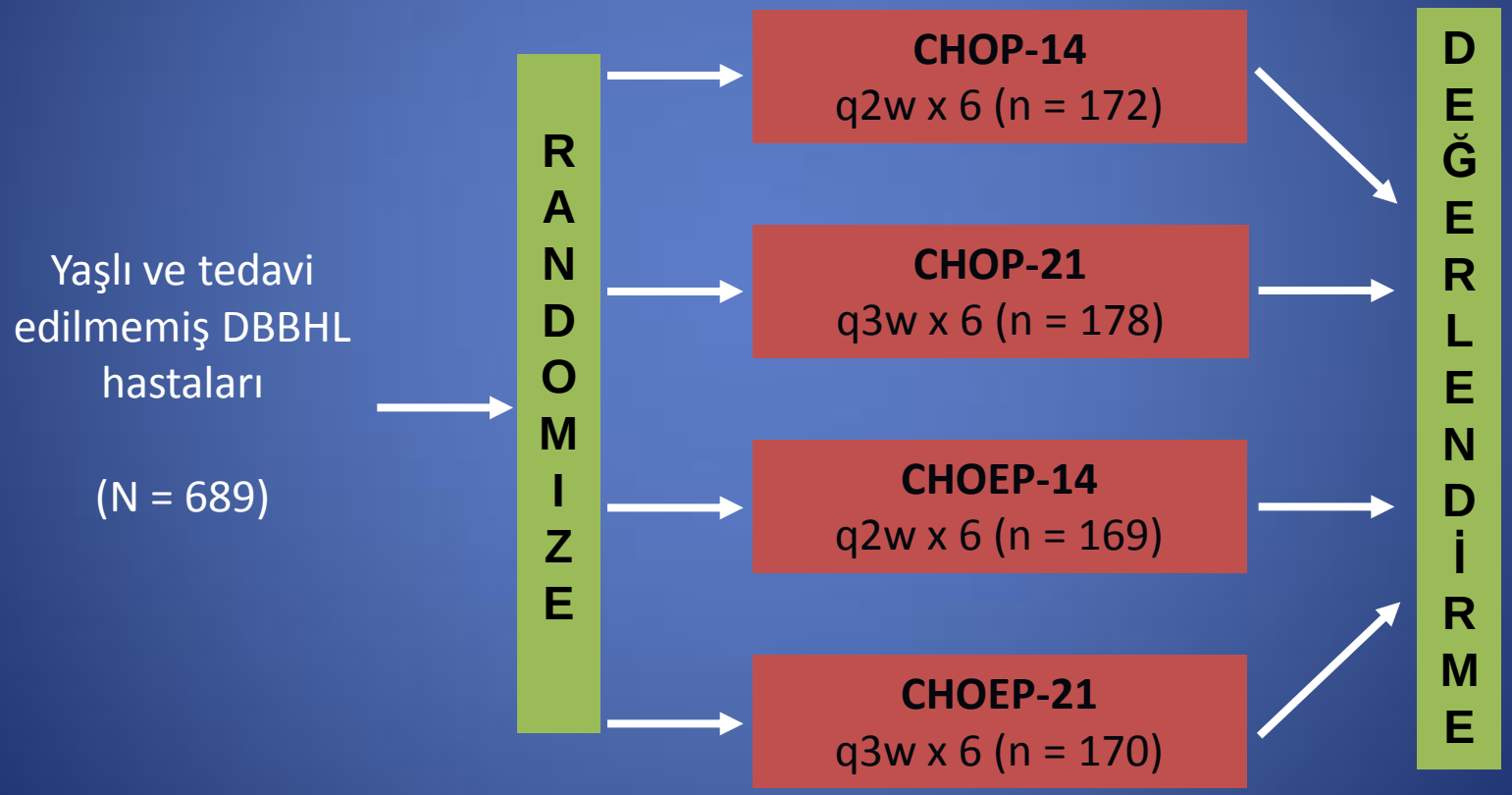


Pfreundschuh M, et al. Lancet Oncology 2006;7:379–91

CHOP-Rituksimab İleri Evre Diffüz Büyük B Hücreli Lenfomalı Bütün Hastaların Tedavisinde Standart Tedavidir

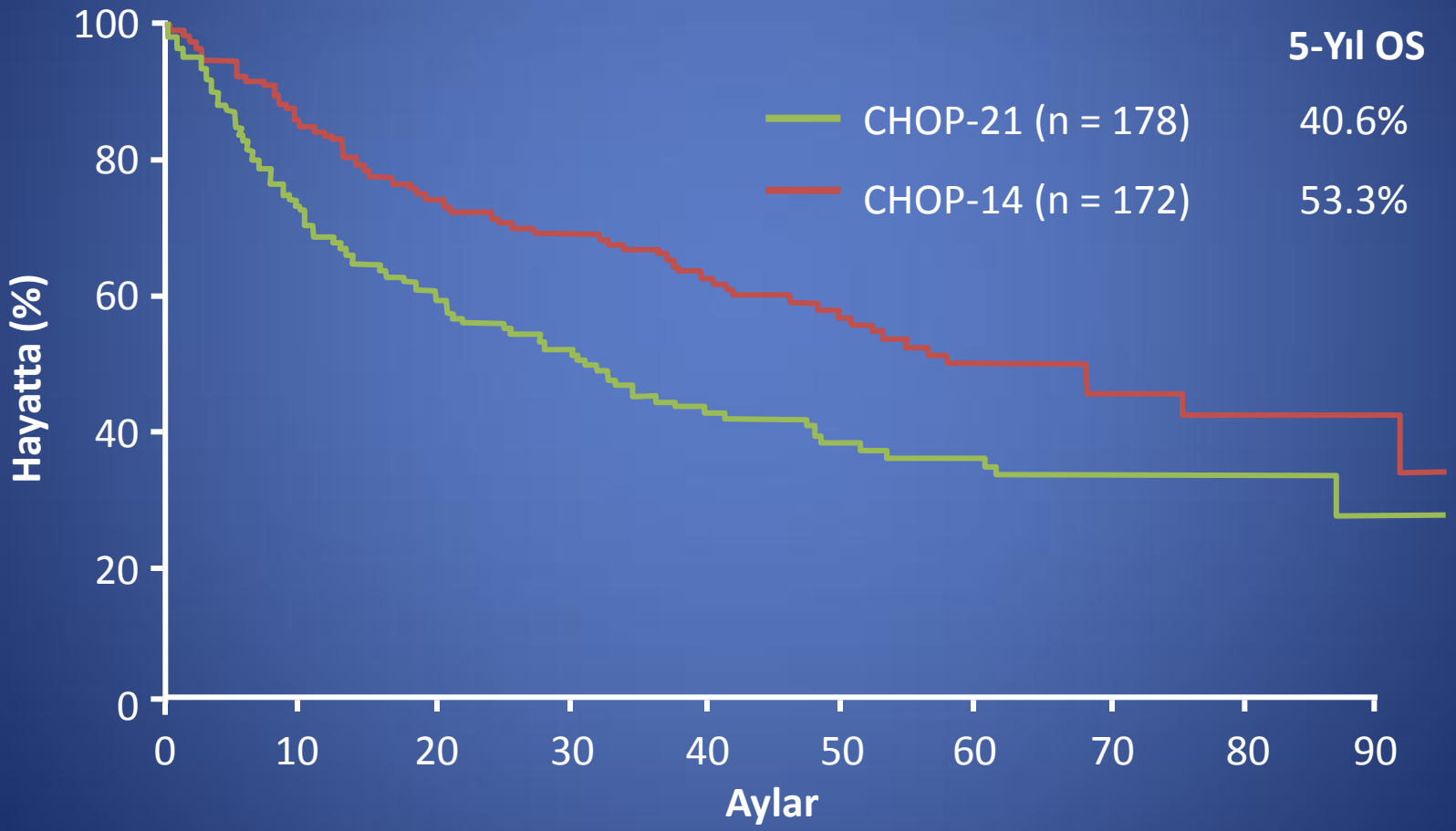
DBBHL'da Doz İntensifikasyonunun Rolü Var Mıdır?

Yaşlı DBBHL Hastalarında kemoterapi (Alman Çalışması)



Pfreundschuh M, et al. Blood. 2004;104:634-641.

Yaşlı DBBHL Hastalarında kemoterapi (Alman Çalışması): Genel Sağkalım



Pfreundschuh M, et al. Blood. 2004;104:634-641

RICOVER 60

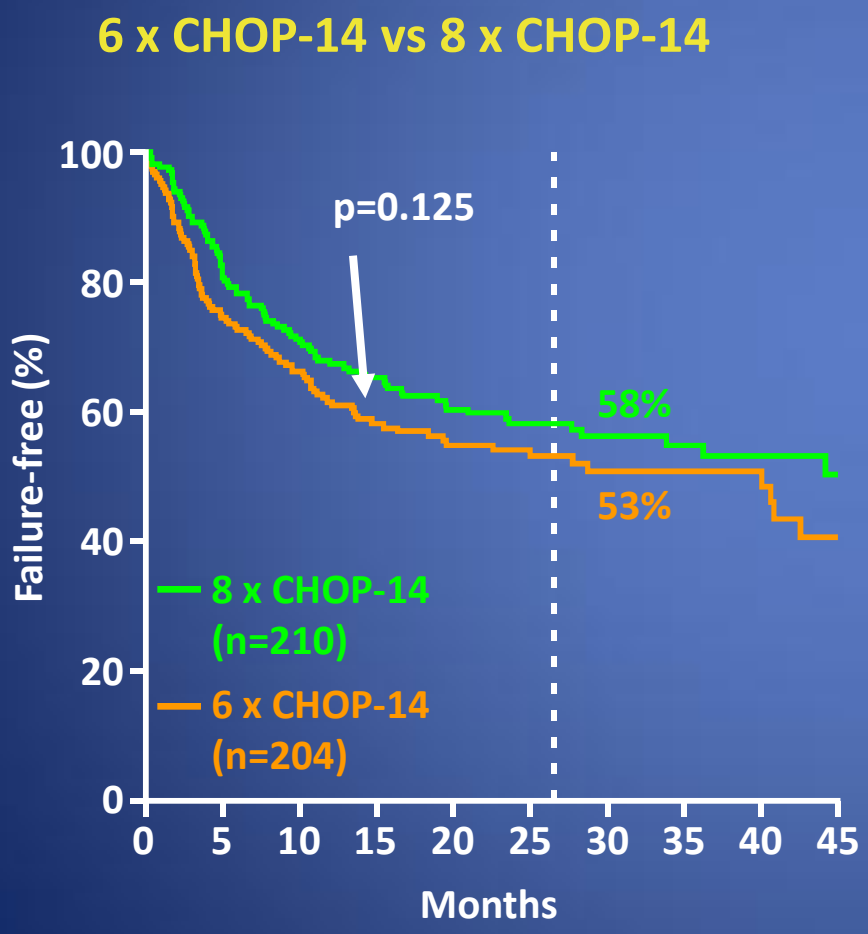
Yaşlı DBBHL Hastalarında R ± CHOP-14

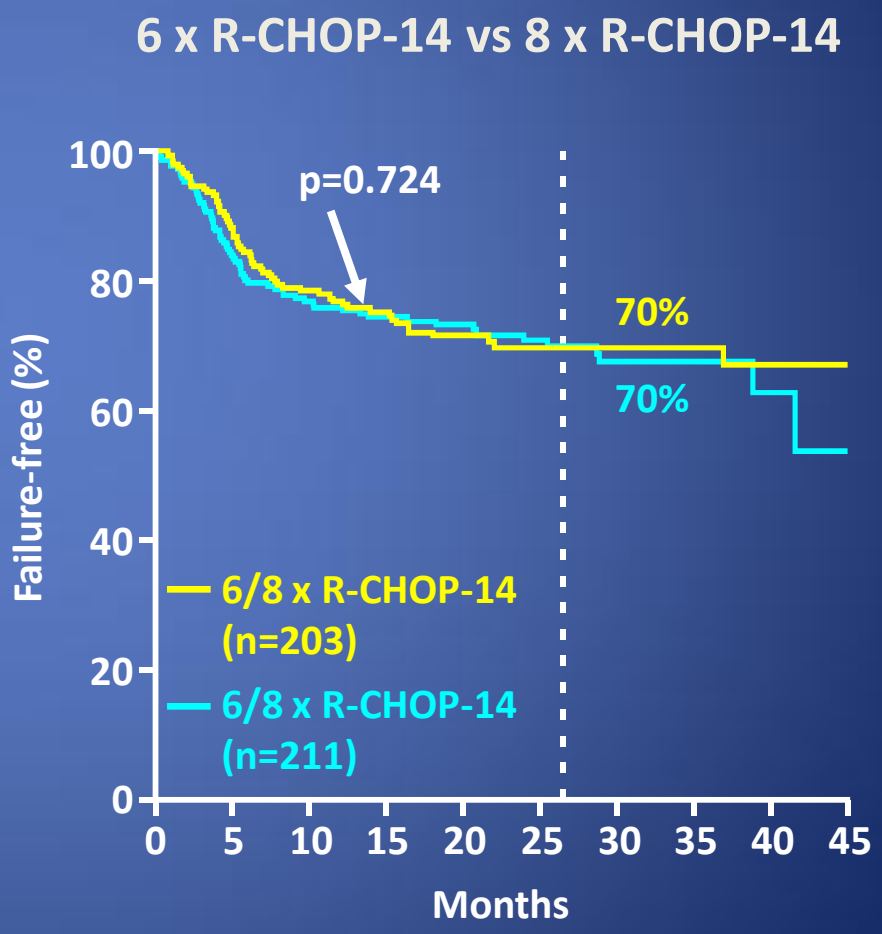
Pfreundschuh M, et al. Lancet Oncol 2008

Prefaz tedavi

- Prefaz tedavi zorunlu
  - Vinkristin -7. gün
  - Prednizon 100 mg -7 ile -1. günler arası
- G-CSF takvimine mutlaka uyulacak
- Doz azaltması yok (>7 günden fazla gecikme olmaksızın)

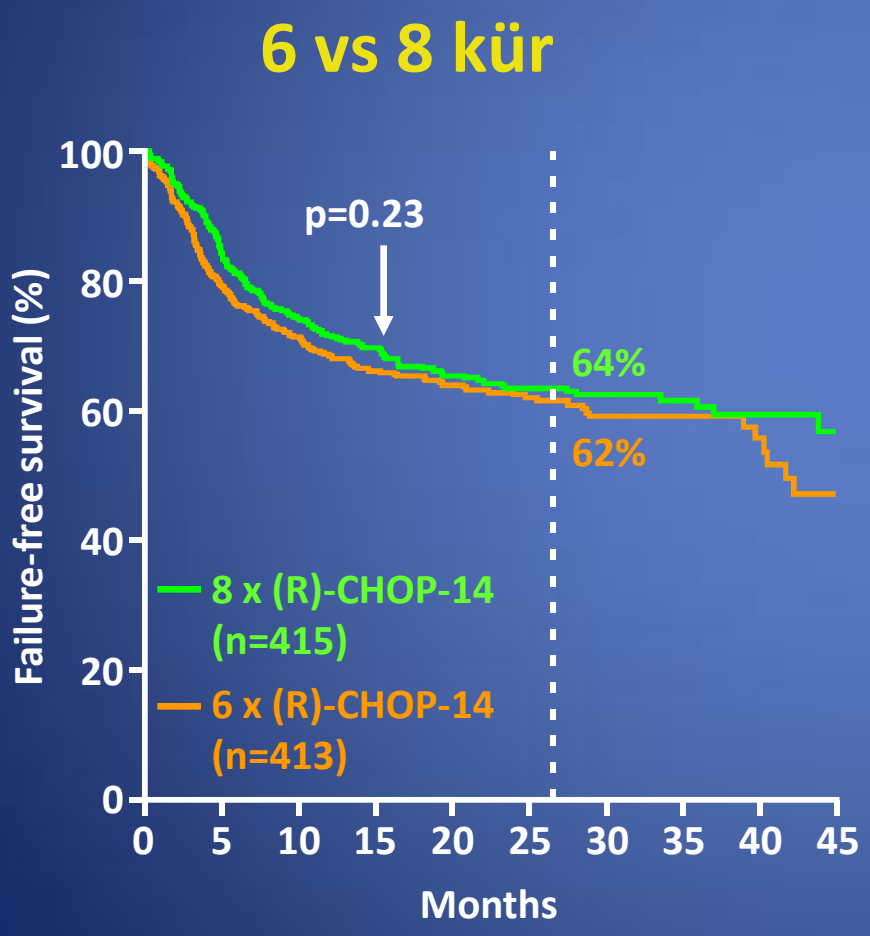
RICOVER 60: TTF

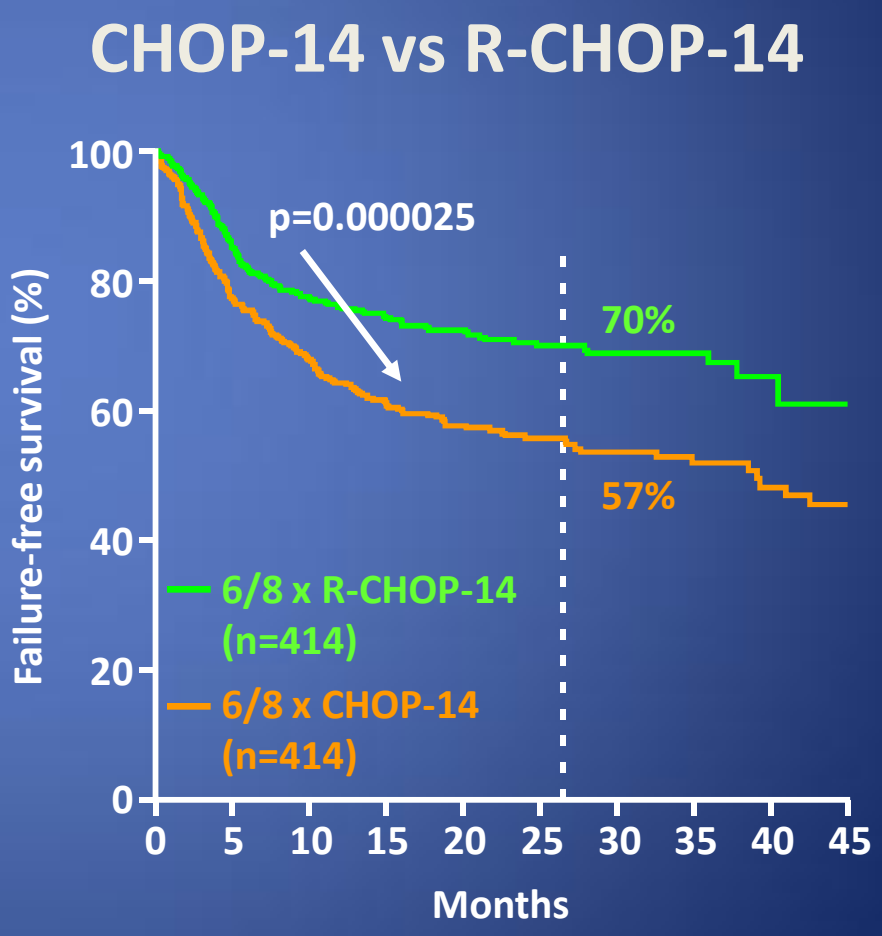




Pfreundschuh M, et al. Lancet Oncol 2008

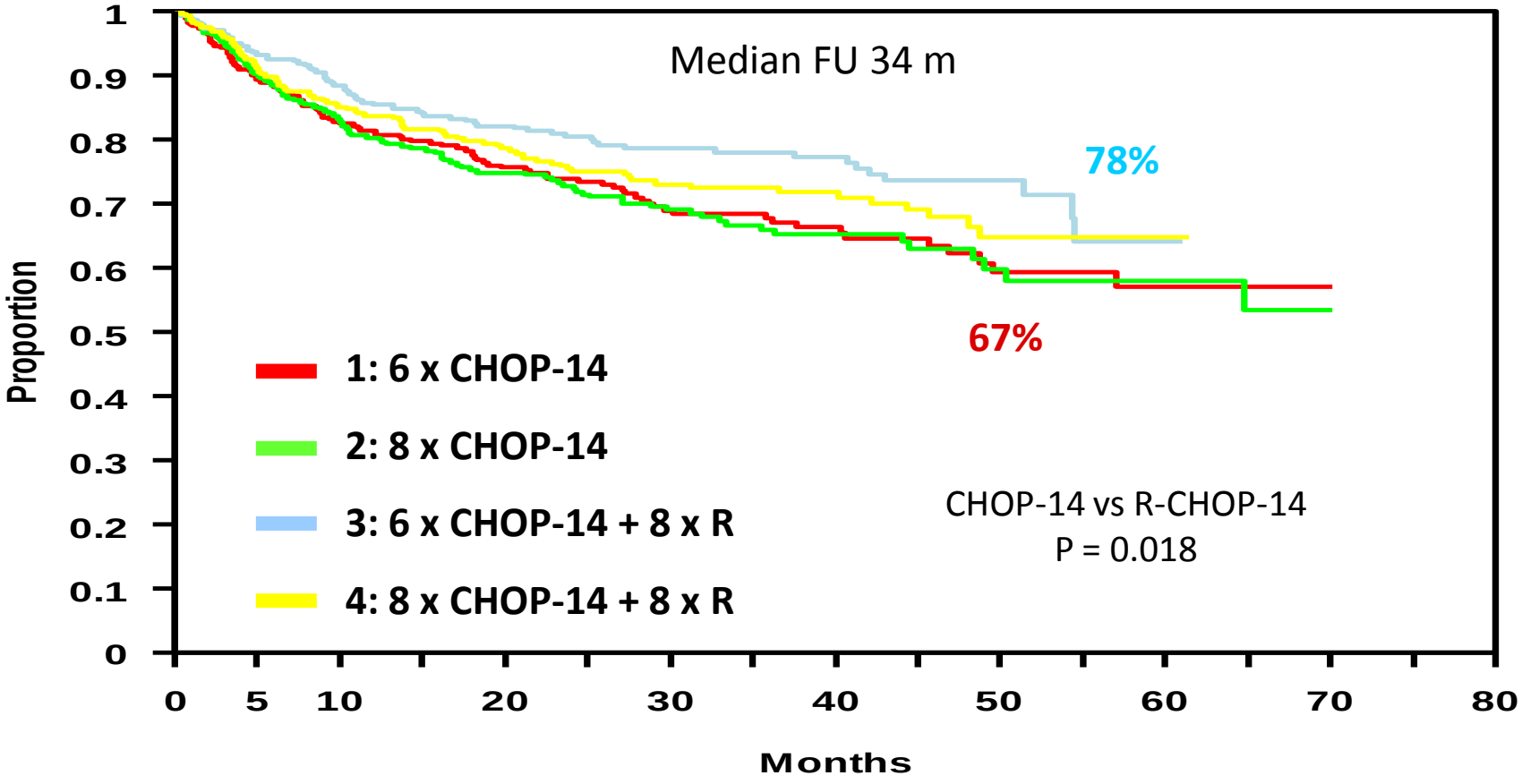
RICOVER 60: TTF





Pfreundschuh M, et al. Lancet Oncol 2008

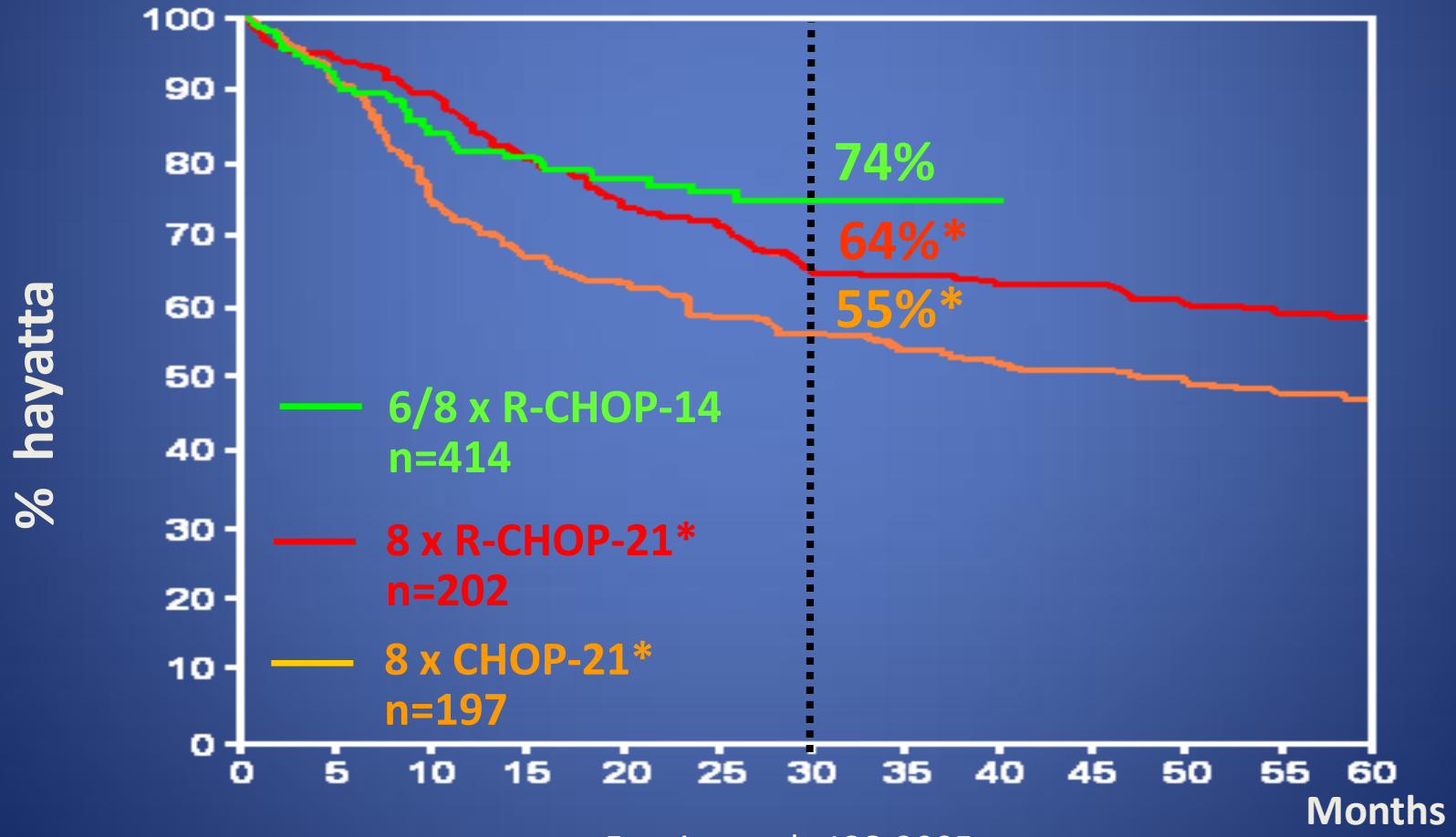
RICOVER 60: survival



R-CHOP-14 vs R-CHOP-21

Yaşlılarda DBBHL: Sağkalım

Historik Perspektif: Evre II-IV

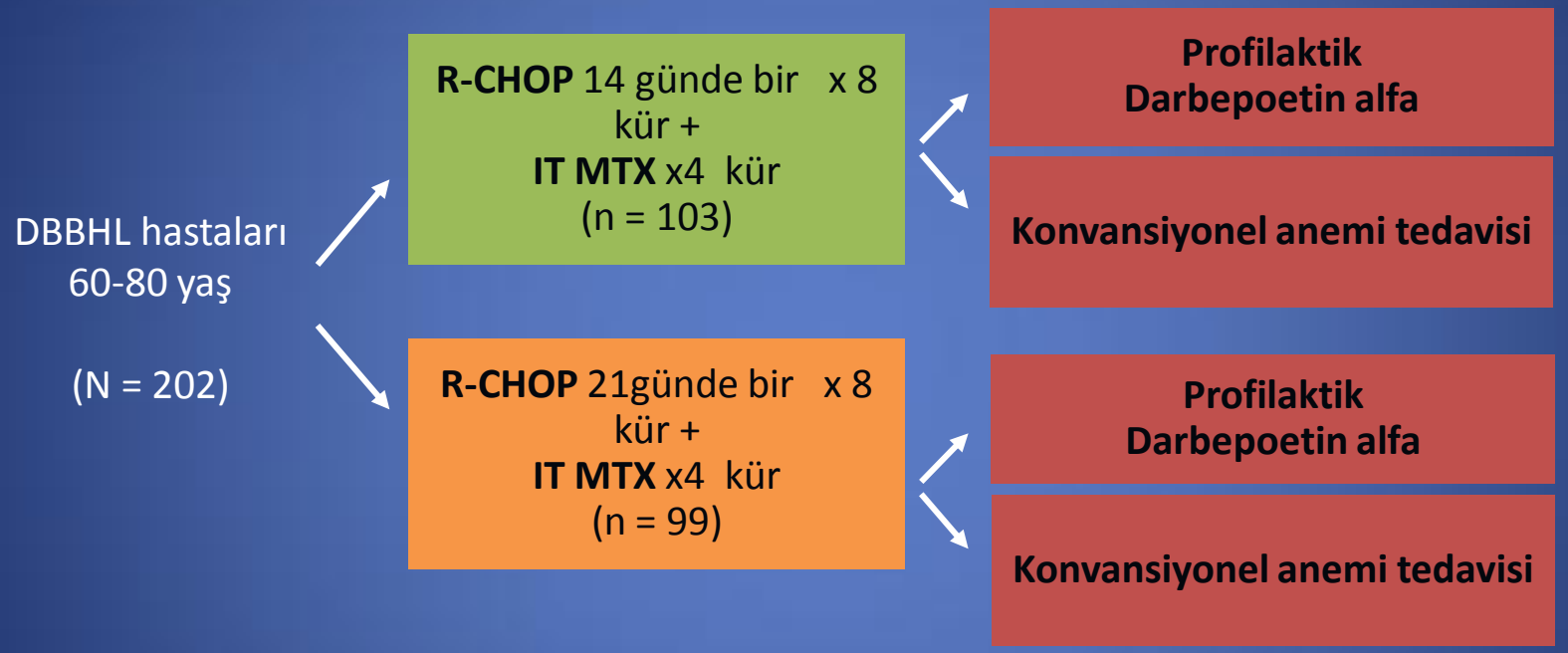


Feugier et al., JCO 2005

R-CHOP-14 Compared to R-CHOP-21 in Elderly Patients With Diffuse Large B-Cell Lymphoma: Results of the Interim Analysis of the LNH03-6B GELA Study

Delarue R, Tilly H, MD, Salles G, et al. ASH 2009. Abstract 406.

LNH03-6B GELA Çalışması: Şema



- Birincil sonlanım noktası: EFS
- İkincil sonlanım noktaları: CR veya CRu , ORR, PFS , DFS, OS, doz yoğunluğu, toksisite

Delarue R, et al. ASH 2009. Abstract 406.

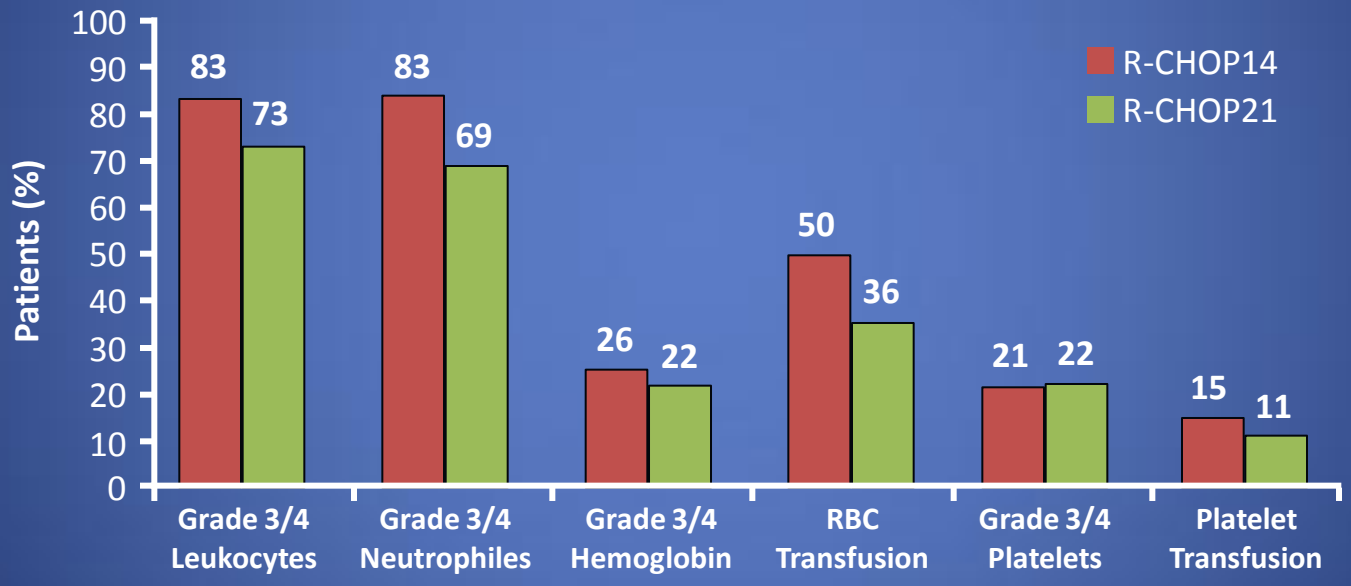
LNH03-6B GELA Çalışması: Sonuçlar

Sonuç	R-CHOP21 (n = 99)	R-CHOP14 (n = 103)	*P*
2-yıl EFS, %	61	48	.11
OrtancaEFS, mos	ulaşılamadı	22	--
2-yıl PFS, %	63	49	.12
Ortanca PFS, mos	ulaşılamadı	23	--
2-yıl DFS, %	70	57	.40
Ortanca 2-yr OS, %	70	67	.37
Tedavi sonu cevap oranları			
▪ CR + CRu	75	67	NS
▪ PR	9	14	NS
▪ ORR	84	81	NS

Delarue R, et al. ASH 2009. Abstract 406.

LNH03-6B GELA Çalışması: Toksisiteler

- Hematolojik toksisiteler R-CHOP14 kolunda daha fazla



- R-CHOP14 hastalarında daha sık febril nötropeni, hospitalizasyon ve toksik ölüm görüldü

Delarue R, et al. ASH 2009. Abstract 406.

LNH03-6B GELA Çalışması: Sonuçlar

- Ortanca takip süresi: 24 ay
- R-CHOP21 hastaları planlanan doz yoğunluğunu alabilmiş
  - ortanca siklofosfamid doz yoğunluğu
    - 96% (R-CHOP21) vs 84% (R-CHOP14)
  - ortanca doksorubisin doz yoğunluğu
    - 95% (R-CHOP21) vs 83% (R-CHOP14)
- G-CSF desteği
  - 90% (R-CHOP14) vs 68% (R-CHOP21)

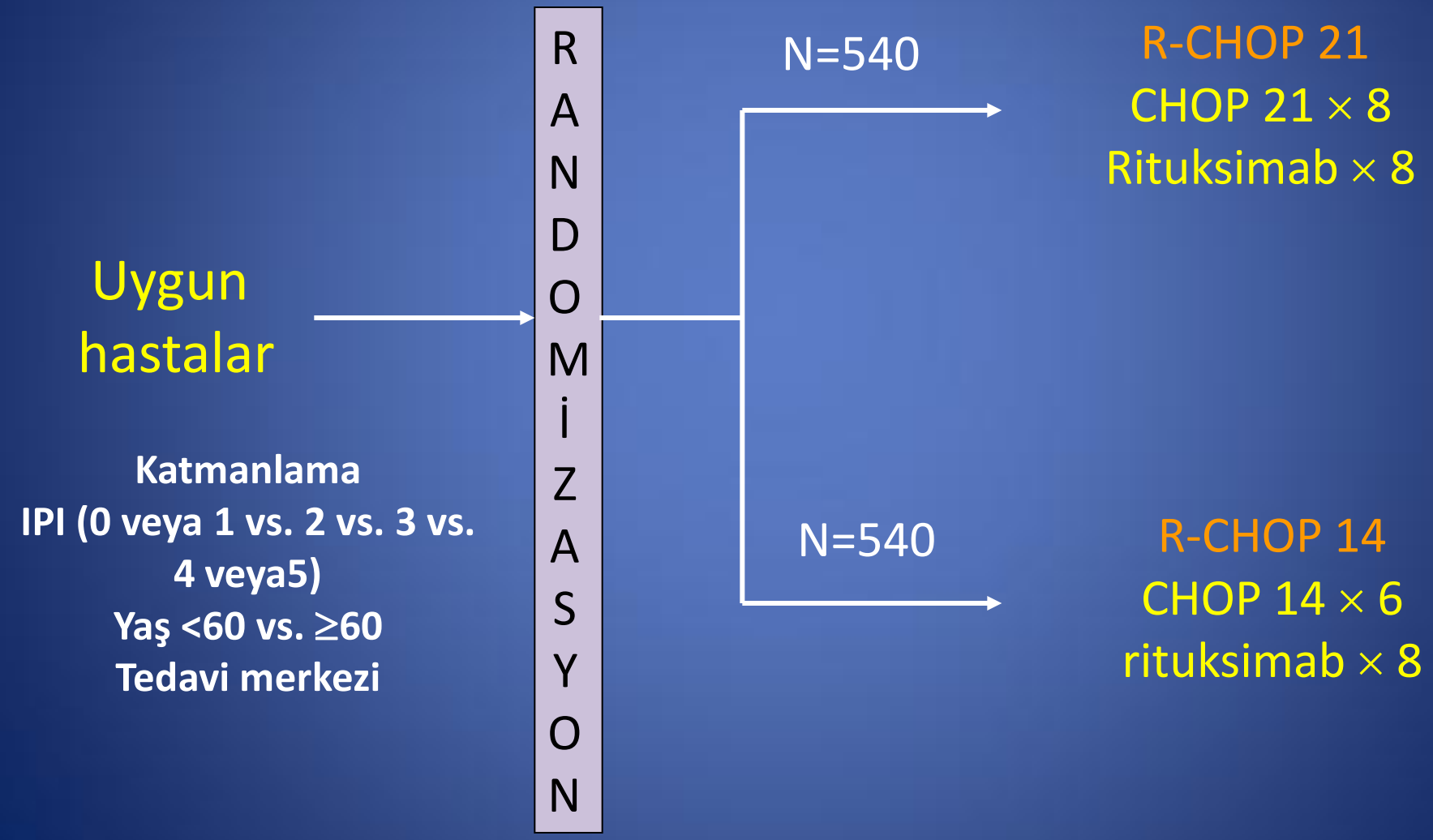
Delarue R, et al. ASH 2009. Abstract 406.

A Phase III Trial Comparing R-CHOP-14 and R-CHOP-21 for the Treatment of Newly Diagnosed DLBCL

Results from a UK NCRI Lymphoma Group Study

Cunningham D, Smith P, Mouncey P, et al. ASCO 2009. Abstract 8506.

NCRI trial: R-CHOP 14 vs 21



Genel Yanıt Oranları

Tedavi sonu değerlendirme (N = 831)	R-CHOP-21, % (n = 405)	R-CHO-14, % (n = 426)
CR	49	40
CRu	14	18
PR	24	32
SD	6	5
PD/relaps	6	4
CR/CRu (*P* = .183)	**63**	**58**
CR/CRu/PR (*P* = .139)	**88**	**91**

249 hasta değerlendirilemedi, data eksik

Cunningham D, et al. ASCO 2009. Abstract 8506.

Yaşlı DBBHL Hastalarına R-CHOP-14 Tedavisi Verilmeli Mi?

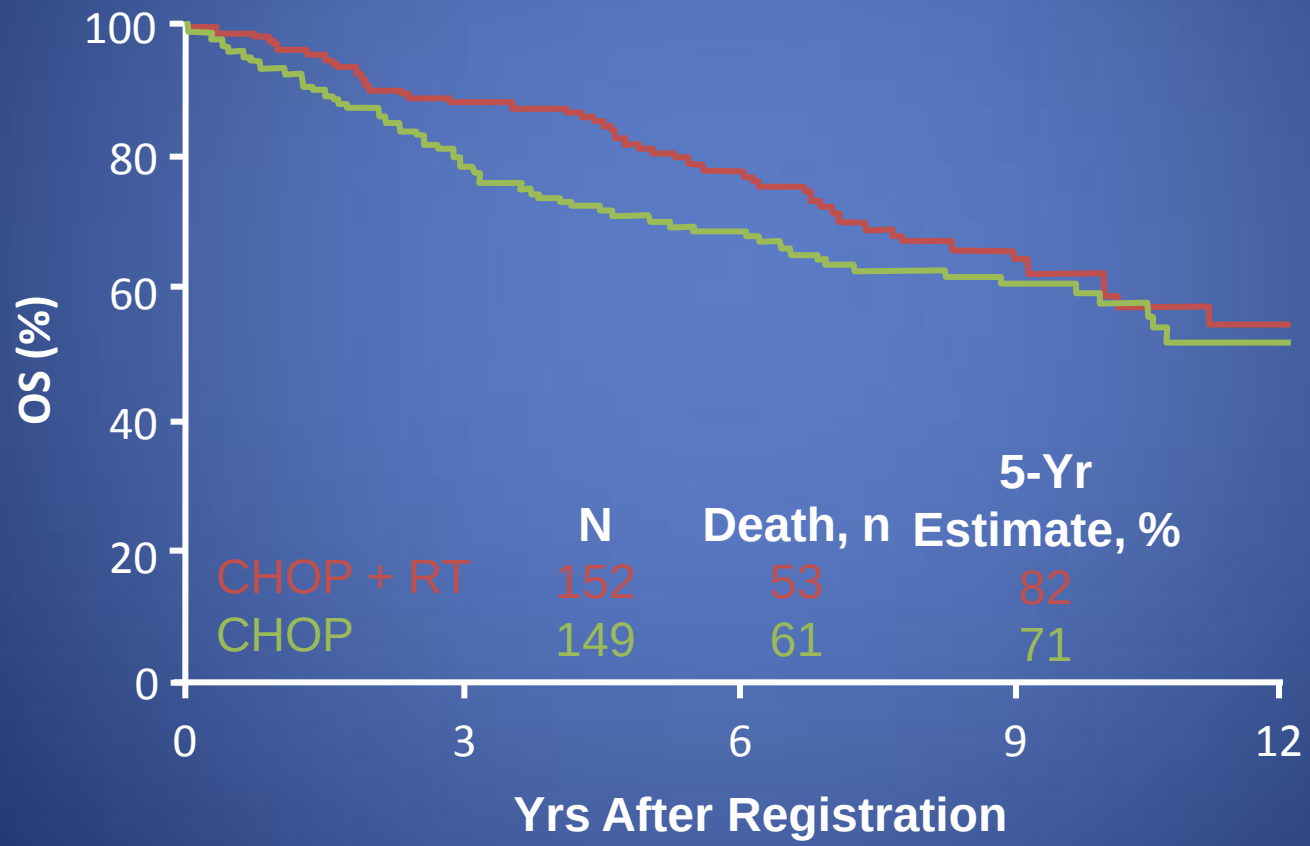
Cevap: şimdi değil

Erken Evre DBBHL Tedavisinde Birinci Sıra Tedavi nasıl Olmalıdır?

Chemotherapy Alone Compared With Chemotherapy Plus Radiotherapy for Localized Intermediate- and High-Grade Non-Hodgkin's Lymphoma (SWOG 8736 study)

Miller TP, Dahlberg S, Cassady R, et al. N Engl J Med. 1998;339:21-26.

S8736: OS for DLBCL



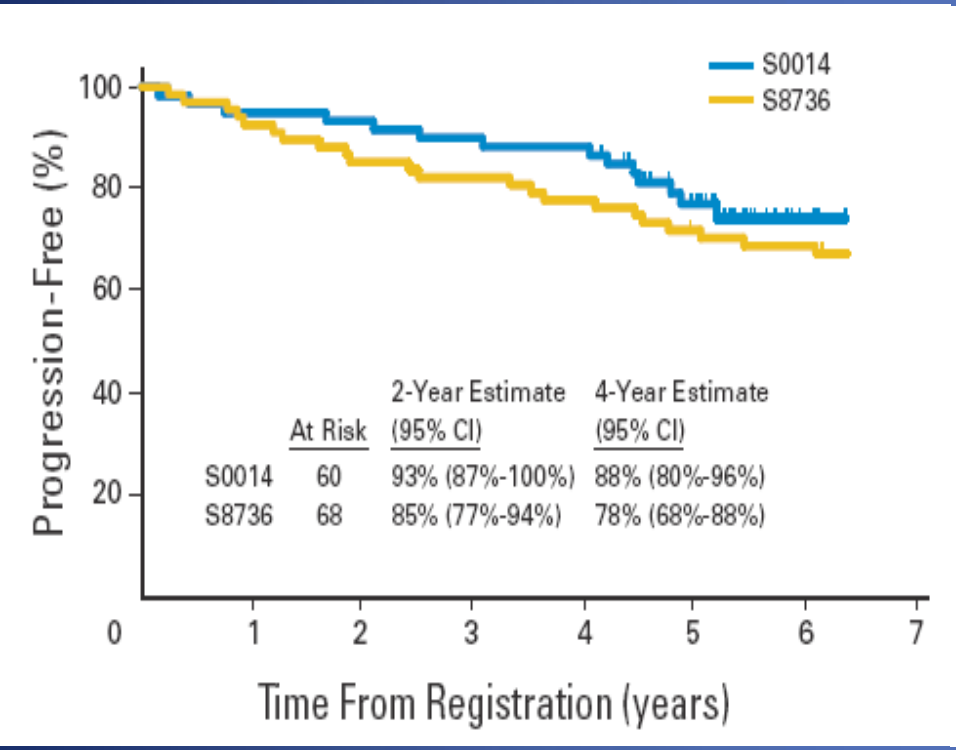
Miller TP, et al. N Engl J Med. 1998;339:21-26.

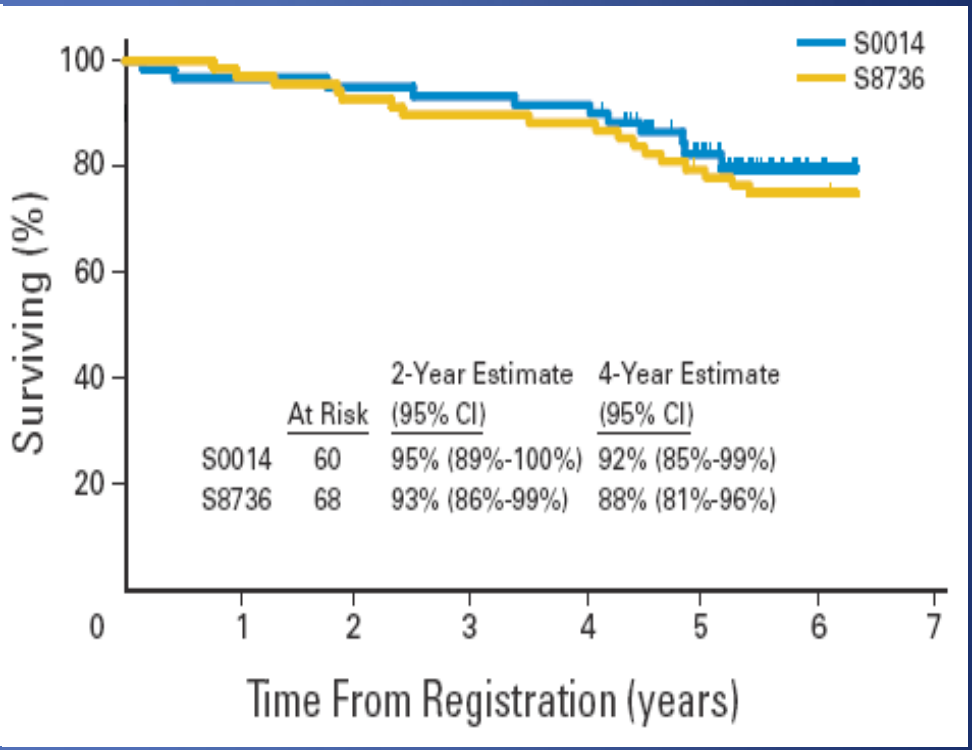
Effect of Adding Rituximab to Three Cycles of CHOP, Plus Involved-Field Radiotherapy for Limited-Stage Aggressive Diffuse B-Cell Lymphoma

Southwest Oncology Group Study 0014

Persky DO, Unger J, Spier CM, et al. J Clin Oncol. 2008;26:2258-2263.

SWOG 0014 ve SWOG 8736 karşılaştırması





Persky D, et al. J Clin Oncol. 2008;26:2258-2263.

R-CHOP x3 + IF-XRT: Sonuçlar

- Çalışmaların karşılaştırılmasında kötü-risk hastalarda R eklenmesinin PFS ve OS faydası var
- Prospektif randomize çalışma olmamasına rağmen, R-CHOP bu hastalarda standart olmuştur.

Persky D, et al. J Clin Oncol. 2008;26:2258-2263.

DBBHL Tedavisinde Yeni Ajanlar

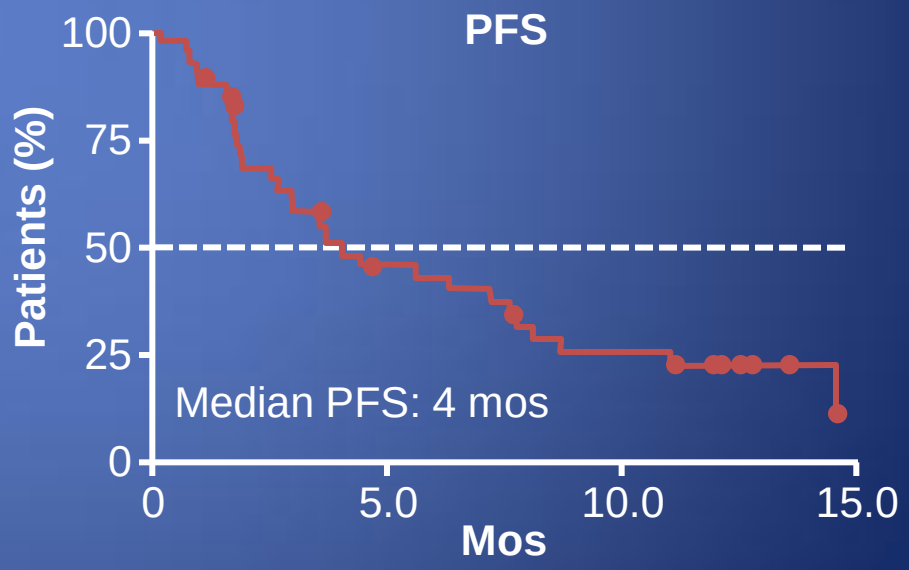
- Proteosome inhibitörleri
  - Bortezomib
  - Carfilzomib
- IMiDs
  - Lenalidomide
  - Pomalidomide
- Antikorlar
  - RO5072759— humanized anti CD20
  - Blinatumomab—anti-CD19
  - Inotuzumab ozogamicin—anti-CD2 + calicheamicin
  - Milatuzumab—anti-CD74
  - Galiximab—anti-CD80
  - Dacetuzumab—anti-CD40

DBBHL Tedavisinde Yeni Ajanlar

- Histone deacetylase inhibitörleri
  - Vorinostat
  - LBH589
  - MS-275
  - Romidespin
- Apoptosis protein inhibitörleri
  - YM155—survivin protein inhibitor
- Küçük molekül inhibitörleri
  - BI2536— Polo-like kinase-1
  - PS1145—kappaB kinase inhibitörü
  - PX478— HIF1a inhibitörü
  - TW-37—Bcl-2 inhibitörü
- Heat shock protein inhibitörleri
  - IPI-504

Lenalidomide

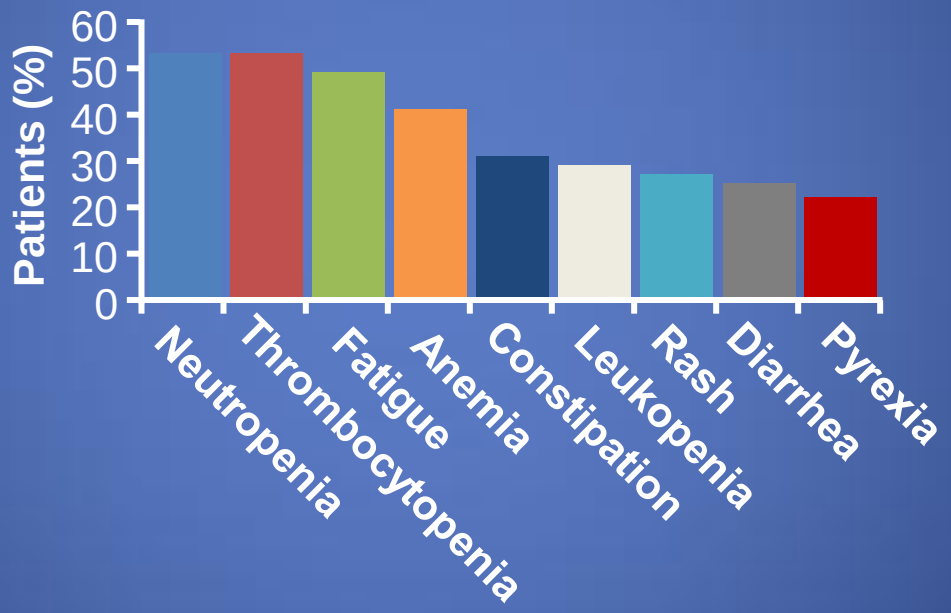
- Lenalidomide: oral immunomodulatuar ajan
  - Antiangiogenic, thalidomid'in daha az toksik türevi
  - NCCN kılavuzuna girdi[1]
- Relaps/refrakter agresif NHL'da Faz II çalışma (N = 49)[2]
  - ORR: %35 (%12 CR/Cru)
  - DBBHL, MCL ve FL'da cevap var
  - Primer grade 3/4 toksisite: myelosupresyon



1. NCCN practice guidelines in oncology: non-Hodgkin's lymphomas. V.1.2010.
2. Wiernik PH, et al. J Clin Oncol. 2008;26:4952-4957.

Lenalidomide: Toksisiteler

Relaps/refrakter agresif NHL'da Faz II Çalışma: Lenalidomide



%32 hastada toksisite nedeniyle doz azaltılması gerekti

Wiernik PH, et al. J Clin Oncol. 2008;26:4952-4957.

Erken ^{18}Fluorodeoxyglucose PET: Prognostik belirteç

- R-KT tedavisi verilen hastalarda PET prognostik değerini araştıran prospektif çalışma
- 112 yeni hasta R-antrasiklin KT tedavisi
  - R-CHOP14 (n = 24)
  - R-CHOP21 (n = 57)
  - R-ACVBP (n = 31)
- 2 kür R-KT sonrası erken PET bulguları görsel olarak pozitif-negatif olarak yorumlanmış

Safar V, et al. ASH 2009. Abstract 98.

Erken ^{18}Fluorodeoxyglucose PET: Sonuçlar

- Ortanca takip: 38 ay

Parametre	PET Negatif (n = 70)	PET Pozitif (n = 42)
Progresyon, n (%)	10 (14)	22 (52)
5-yıl PFS, %*	81	47
5-yıl OS, %	88	62
Ölümler, n (%)	9 (13)	42 (36)

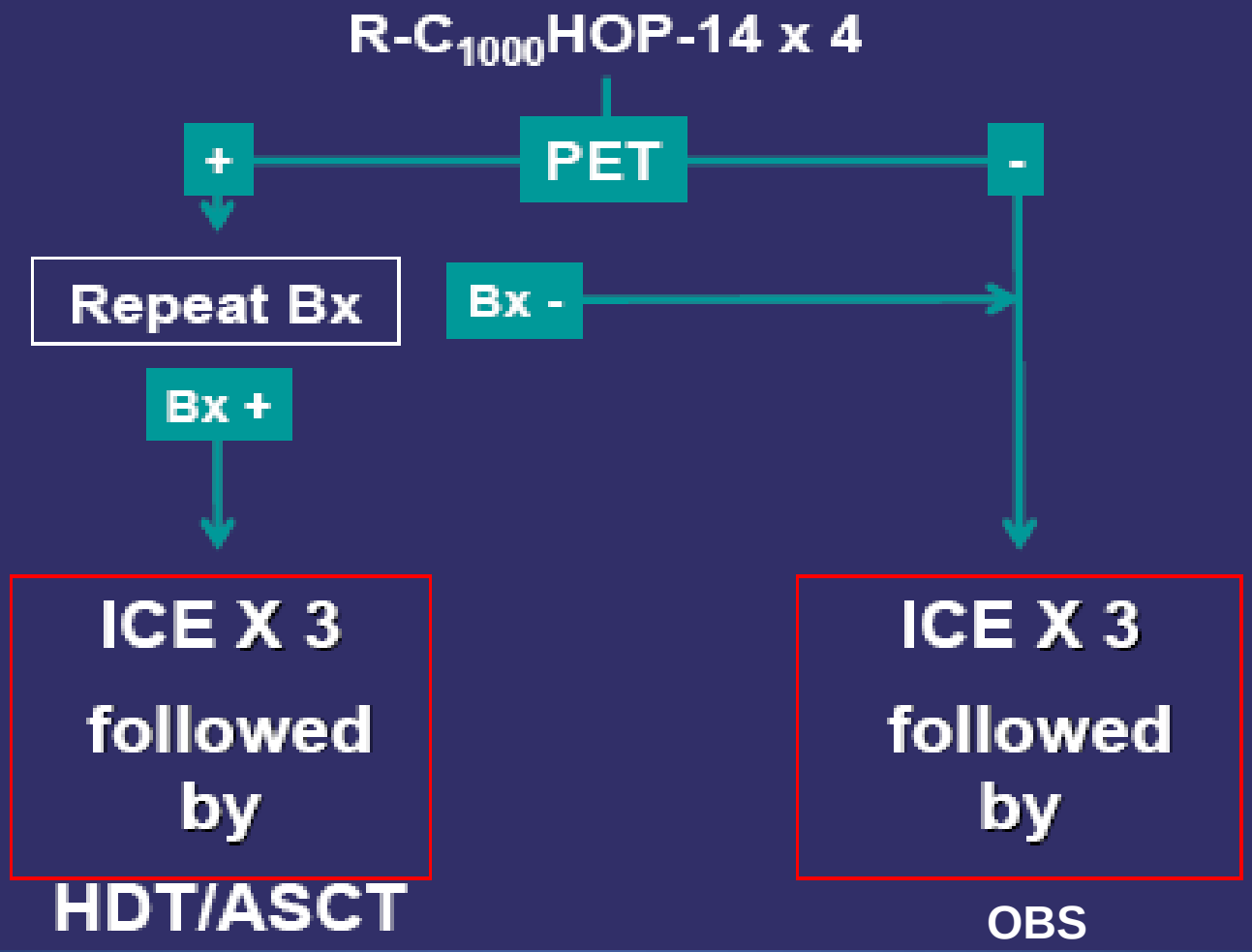
*Log rank test, $P < .0001$

- Erken PET'in PFS için dose-dense KT ($P = .0056$) veya R-CHOP21 ($P = .0006$) verilen hastalarda prognostik değeri var
- Erken PET'in OS için R-CHOP21 ($P = .0225$) verilen hastalarda prognostik değeri var

Safar V, et al. ASH 2009. Abstract 98.

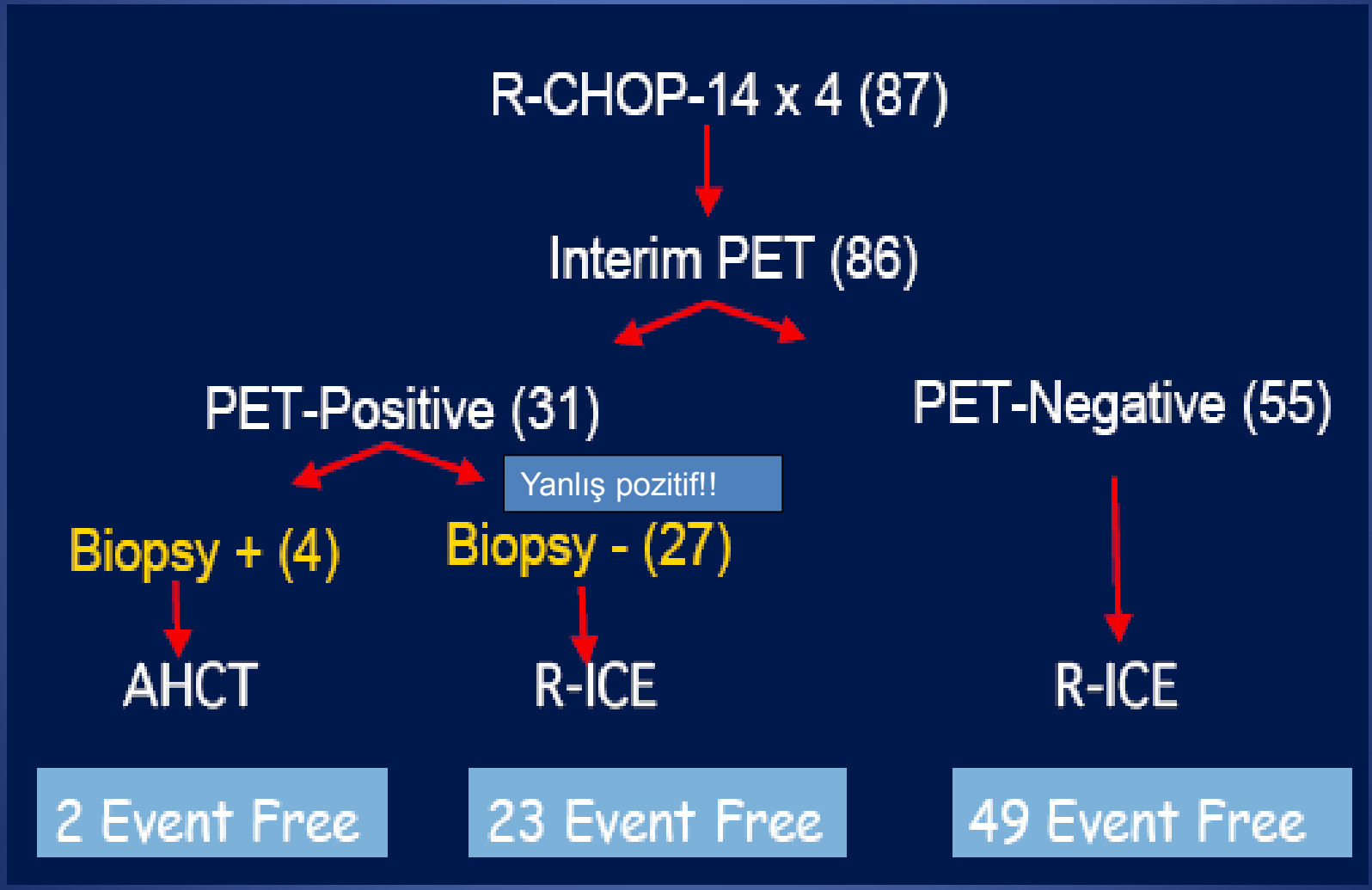
DLBCL: Risk Adapted Therapy

MSKCC 01-142 aaIPI 1-3 factors



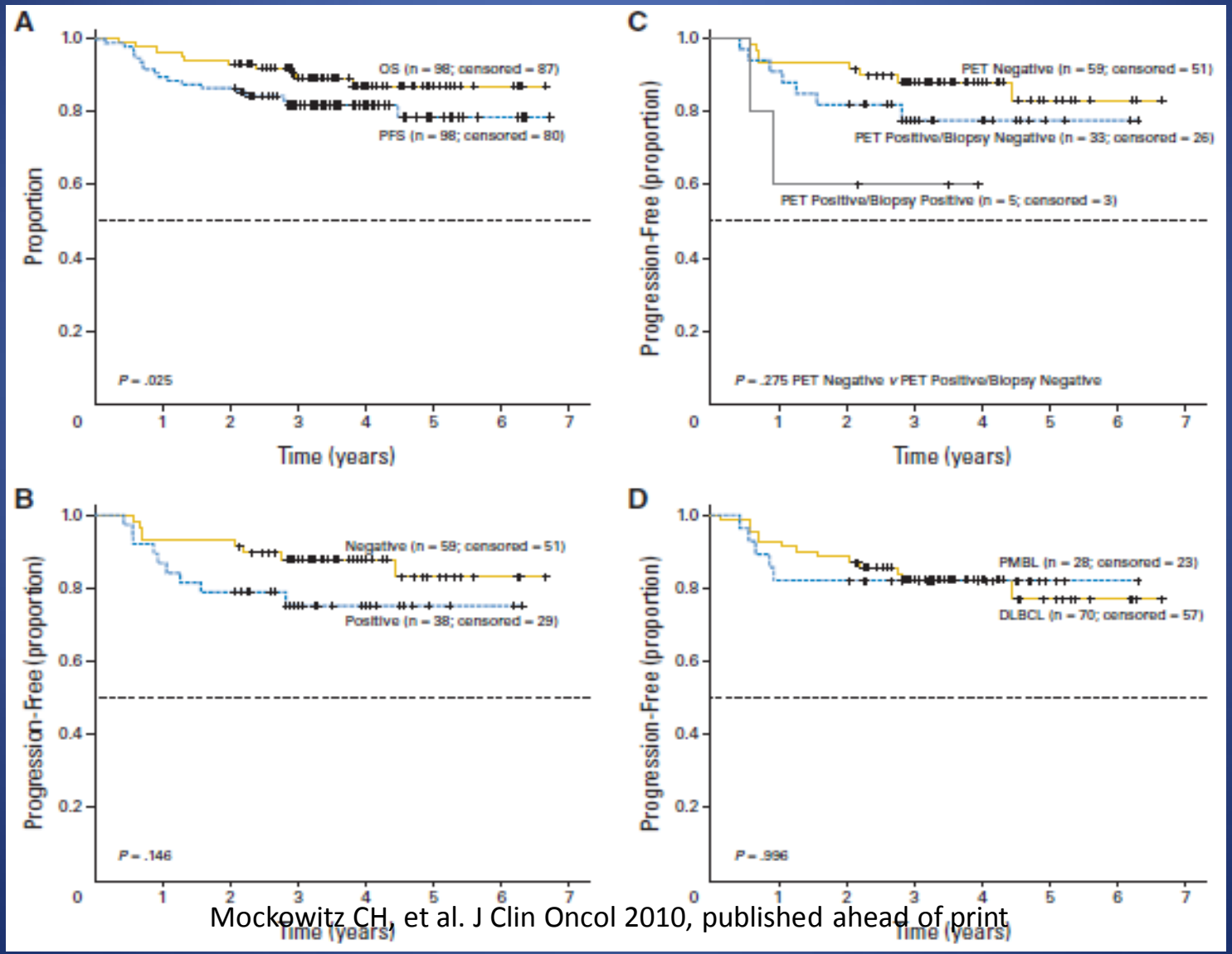
Mockowitz CH, et al. J Clin Oncol 2010, published ahead of print

MSKCC 01-142: Risk-Adapted Tedavi Yüksek yanlış pozitiflik

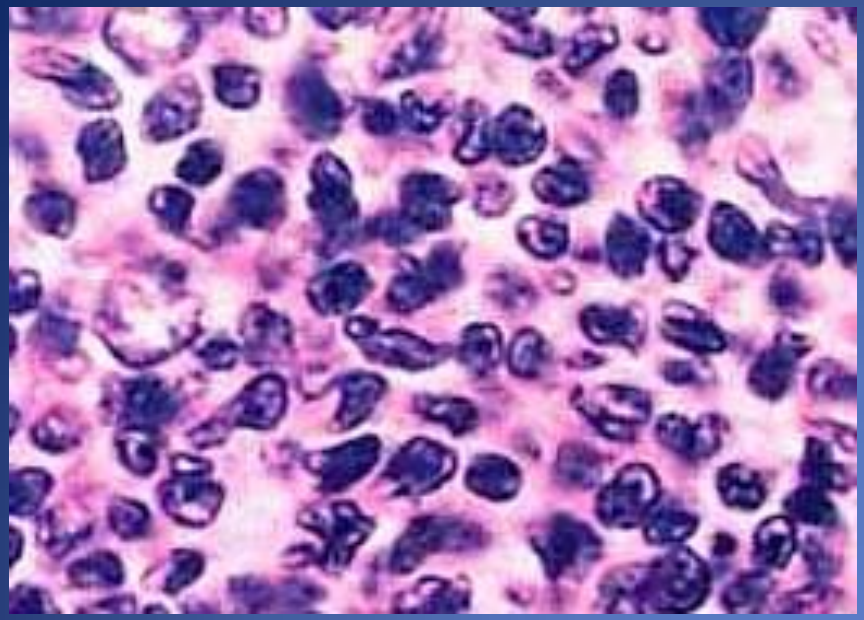


Mockowitz CH, et al. J Clin Oncol 2010, published ahead of print

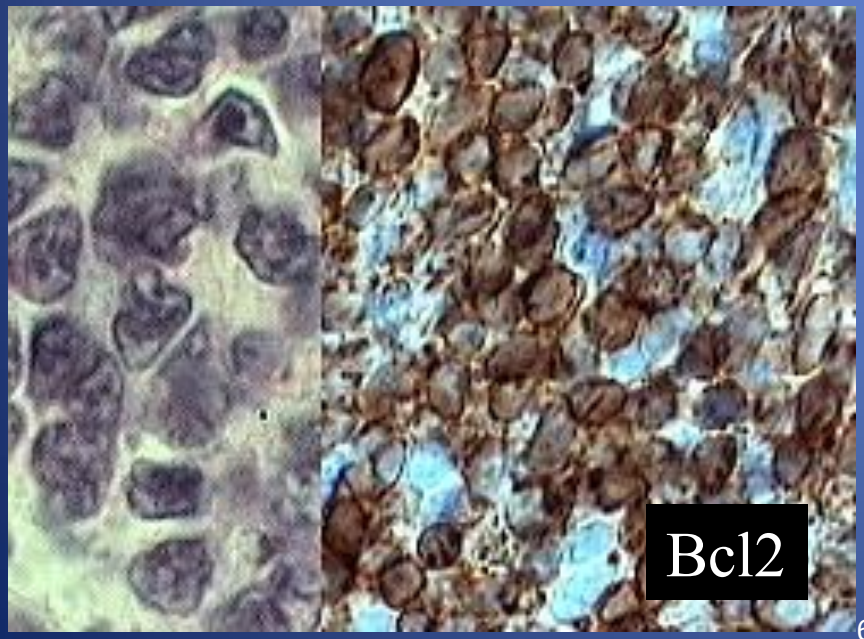
FDG-PET: Risk-Ayarlı Strateji

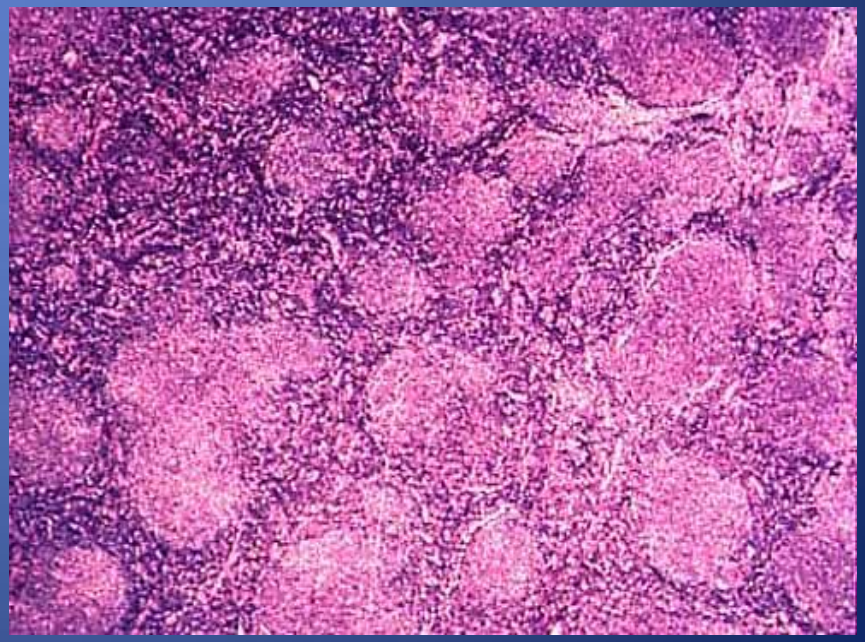


Mockowitz CH, et al. J Clin Oncol 2010, published ahead of print



Folliküler Lenfoma





Folliküler Lenfoma

- Indolent
- Tüm lenfomaların ~%22'sı (Türkiye'de %5-8)
- Genellikle ilk tanıda yaygın hastalık
- Genellikle asemptomatik
- Kürabl değil
- Bcl-2 onkogeni, t(14;18)
- Germinal merkez B hücresinden kaynaklanır

FLIPI prognostik skoru

(Blood. 2004;104:1258-1265)

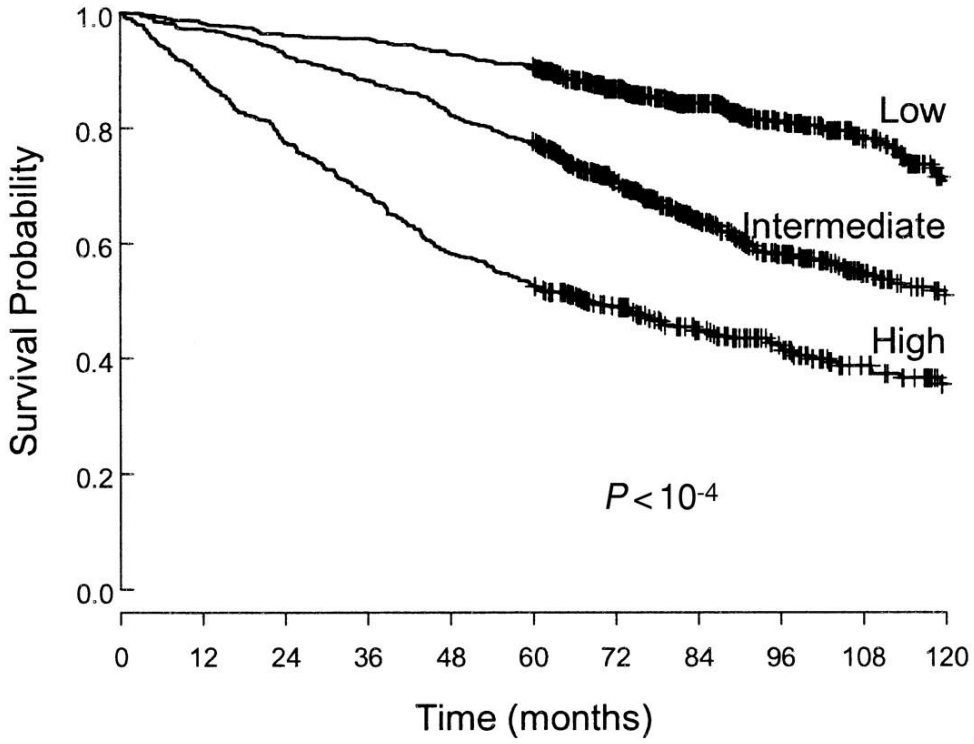
- Yaş > 60
- Ann Arbor evre III – IV
- Hemoglobin level < 12 g/dL
- Nodal alan sayısı > 4
- Serum LDH > normal

FLIPI Risk Group	Adverse Factors, n	Patients, %	5-yr OS, %	10-yr OS, %	RR	95% Confidence Interval
Good	0-1	36	91	71	1.0	
Intermediate	2	37	78	51	2.3	1.9-2.8
Poor	≥ 3	27	53	36	4.3	3.5-5.3

OS, overall survival; RR, response rate.

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Figure 4. Survival of the 1795 patients according to risk group as defined by the Follicular Lymphoma International Prognostic Index



No. of Events											
Low	-	12	25	29	46	60	83	95	106	113	125
Intermediate	-	19	49	79	118	150	192	225	247	255	261
High	-	54	109	152	202	229	245	260	268	274	278

No. at Risk											
Low	641	629	616	612	595	581	450	337	241	157	93
Intermediate	670	651	621	591	552	519	385	263	178	108	68
High	484	430	375	332	282	255	193	139	98	56	33

Solal-Celigny, P. et al. Blood 2004;104:1258-1265

Folliküler Lenfoma: R-KT

KT	Median takip (ay)	R-KT v KT CR/CRu (%)	R-KT v KT ORR (%)	Etkinlik
CVP ± R	30	41 vs 10	81 vs 57	TTP: 32 mo vs 15 mo
CHOP ± R	24	20 vs 17	96 vs 90	2-yr PFS: 84% vs 63%
MCP ± R	30	49 vs 25	92 vs 75	2-yr EFS: 83% vs 43%
CHVP ± R	31	73 vs 44	94 vs 86	2.5-yr EFS: 78% vs 63%
R-FND	30	89	98	3.0-yr FFS: 69%

Bütün karşılaştırmalarda < p 0.001.

FL birinci basamak tedavi: R-CVP vs CVP

- Folliküler NHL (IWF B, C, D)
- Evre III–IV
- 18 yas
- Daha önceden tedavi edilmemiş

RANDOMIZASYON

CVP x 4 kür
(3 haftada bir)

MabThera + CVP x 4 kür
(3 haftada bir)

Tekrar Evreleme

CVP x 4 kür
(3 haftada bir)

CR, PR

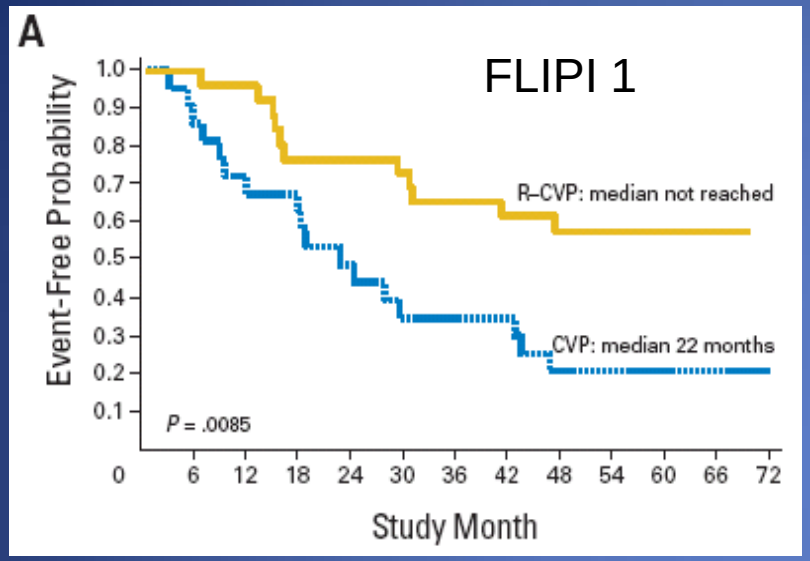
MabThera + CVP x 4 kür
(3 haftada bir)

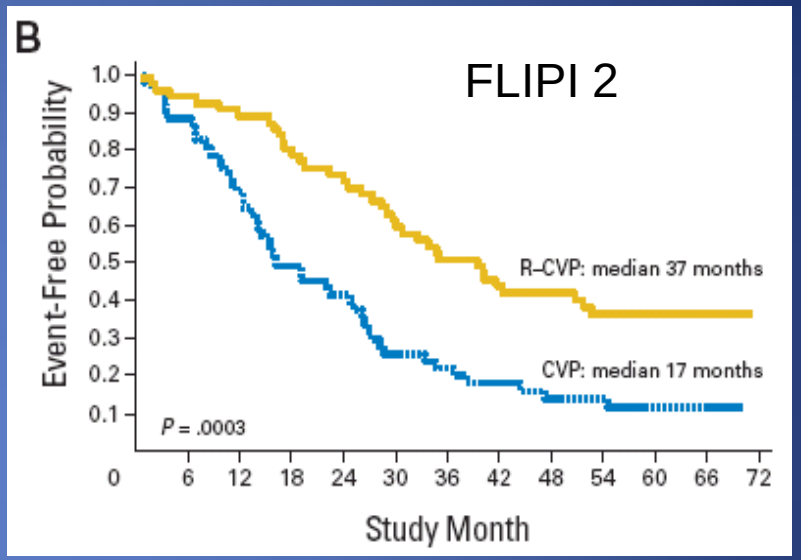
MabThera 375mg/m^2 i.v. 1.gün
Cyclophosphamide 750mg/m^2 i.v. 1.gün
Vincristine 1.4mg/m^2 i.v. 1.gün
Prednisone 40mg/m^2 p.o. 1–5günler

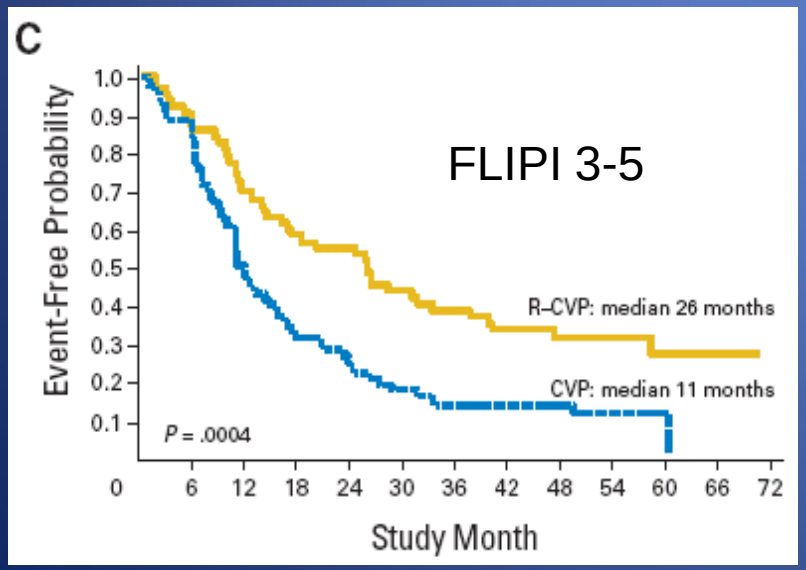
SH, PH tedavi dışı

Marcus R, *et al*. *Blood* 2005; **105:**1417–1423.

R-CVP: 53 aylık takip sonuçları: PFS

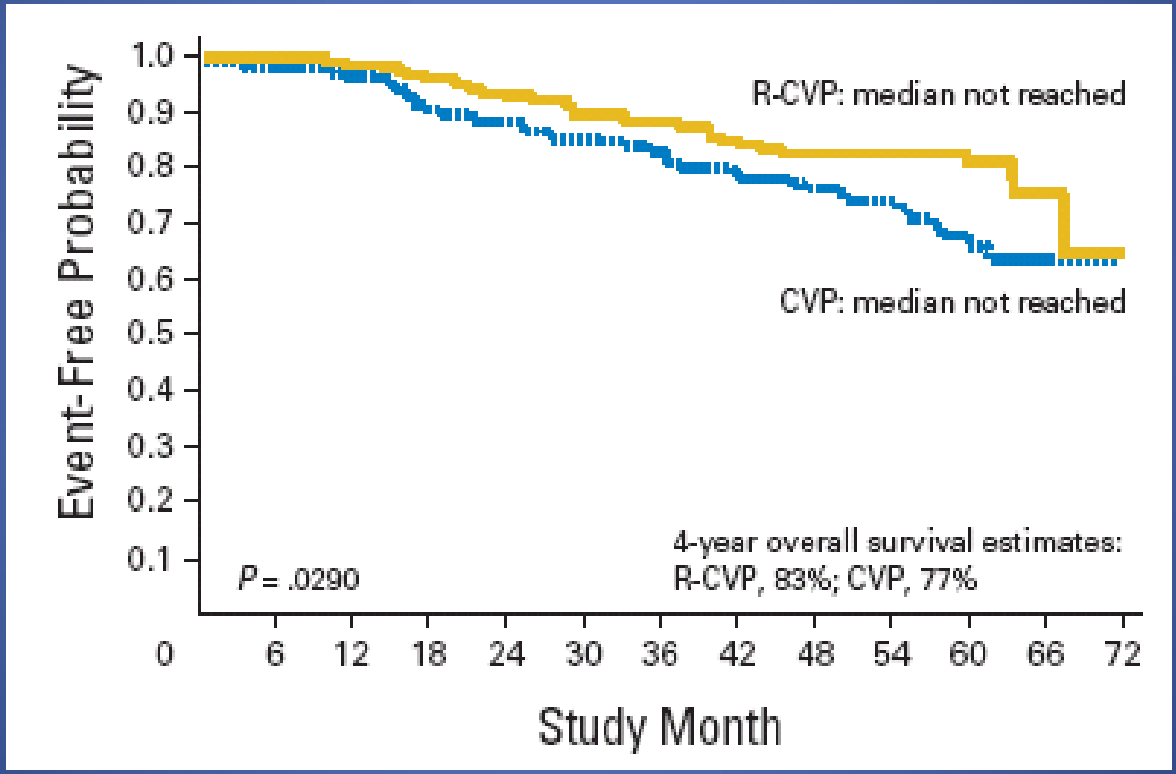






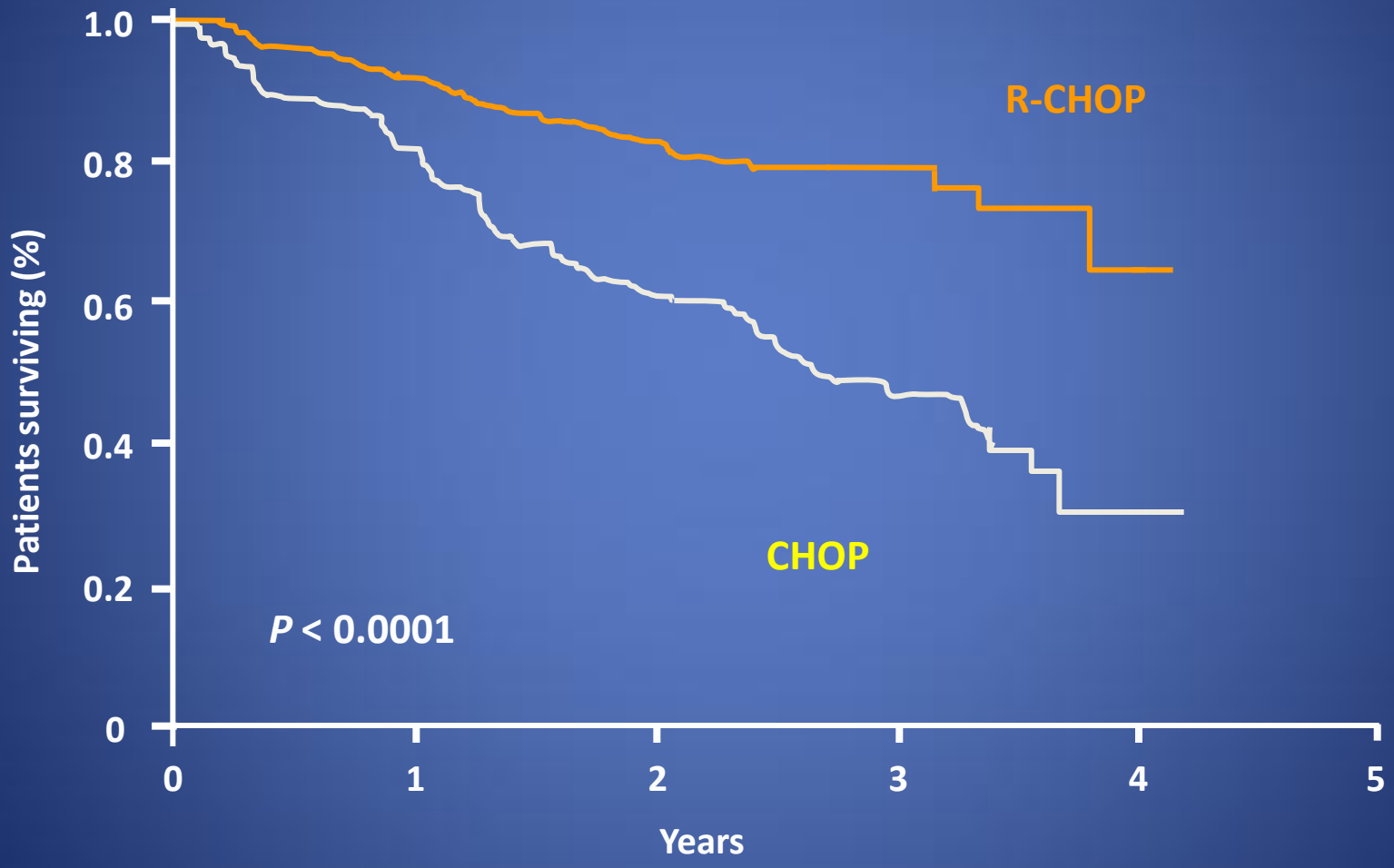
Marcus R et al. J Clin Oncol. 2008 Jul 28.

R-CVP: 53 aylık takip sonuçları: OS



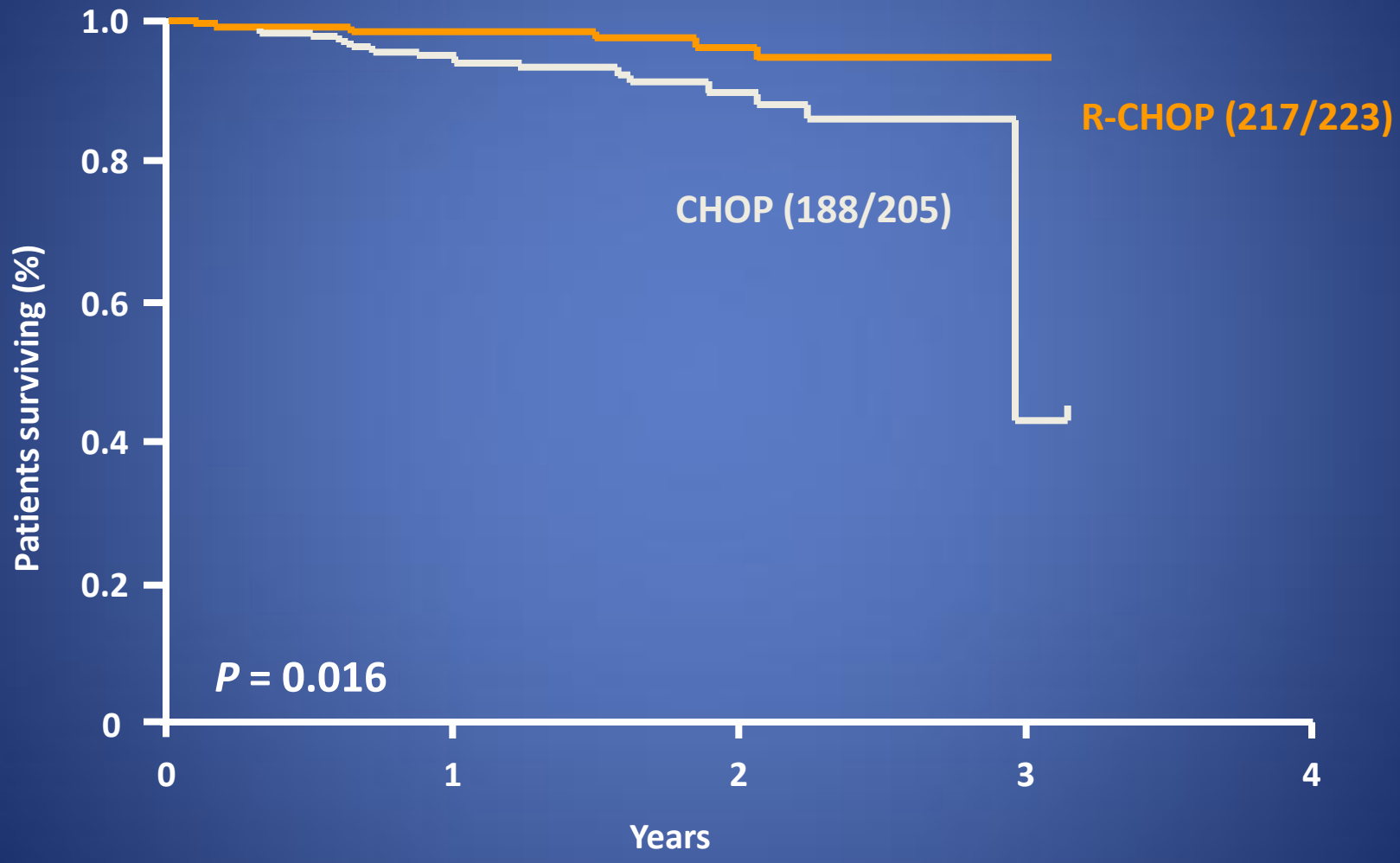
Marcus R et al. J Clin Oncol. 2008 Jul 28.

FL birinci basamak tedavi: CHOP ± R: TTF



Hiddemann W, *et al. Blood* 2005; 106: 3725-32.

FL birinci basamak tedavi: CHOP ± R: OS



Hiddemann W, *et al. Blood* 2005; 106: 3725-32.

STiL: FL, Indolent, ve MCL birinci basamak tedavisinde Bendamustin + Rituksimab

Evre III-IV CD20+ lenfoma

(N = 549)

Bendamustine-Rituksimab
Bendamustine 90 mg/m^2 1, 2 günler
+ **Rituksimab** 375 mg/m^2 1. gün
Maksimum 6 kür, 4 haftada bir
(n = 260)

R-CHOP
Maksimum 6 kür, 3 haftada bir
(n = 253)

- Primer sonlanım noktası: noninferiority (bendamustine-rituksimab vs R-CHOP)
- İkincil sonlanım noktaları: Cevap oranları, 2. basamak tedaviye kadar geçen zaman, EFS, OS, yan etkiler, infeksiyonlar

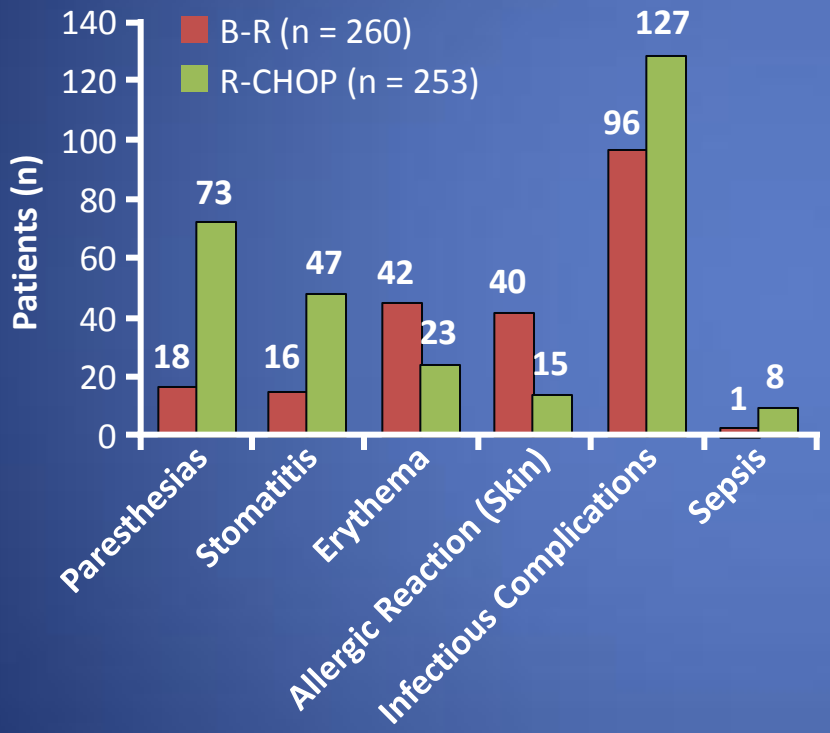
Rummel MJ, et al. ASH 2009. Abstract 405.

STiL: Sonuçlar

- Primer sonlanım: bendamustine-rituksimab > R-CHOP
  - PFS: 54.9 vs 34.8 ay (*P* = .00012)
- Altgrup analizleri: B-R > R-CHOP
  - FL (*P* = .0281), MCL (*P* = .0146), ve Waldenström's (*P* = .0024)
- Sekonder sonlanım: B-R > R-CHOP
  - CR (39.6% vs 30.0%, *P* = 0.26)
  - Bir sonraki tedaviye kadar geçen zaman (ulaşılamadı vs 37.5 ay, *P* = .001)

Rummel MJ, et al. ASH 2009. Abstract 405.

STiL: Yan etkiler

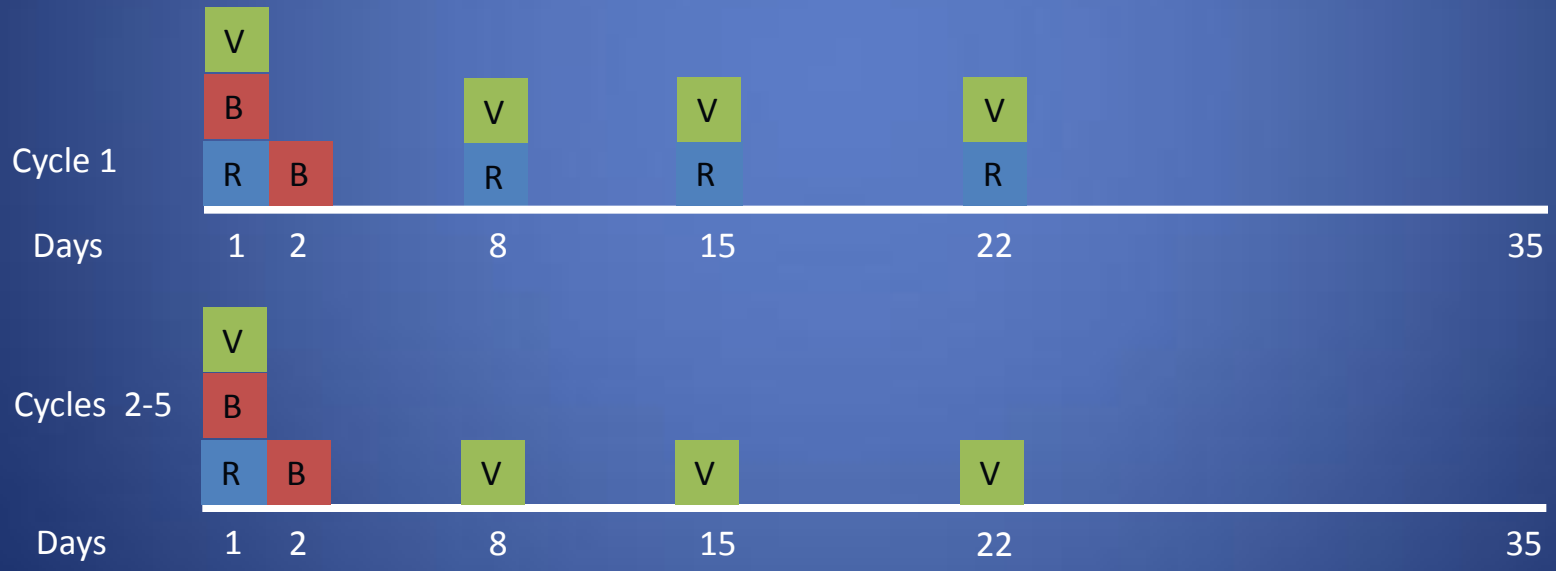


- Myelosupresyon grade 3/4; B-R vs R-CHOP (%), *P* < .0001
  - Nötropeni: 10.7% vs 46.5%
  - Lökositopeni: 12.1% vs 38.2%
  - G-CSF kullanımı: 4.0% vs 20.0%
- Diğer BR yan etkileri
  - Daha az alopesi (*P* < .001)
  - Paresthesia (*P* < .001)
  - Infeksiyonlar (*P* = .0025)

Rummel MJ, et al. ASH 2009. Abstract 405.

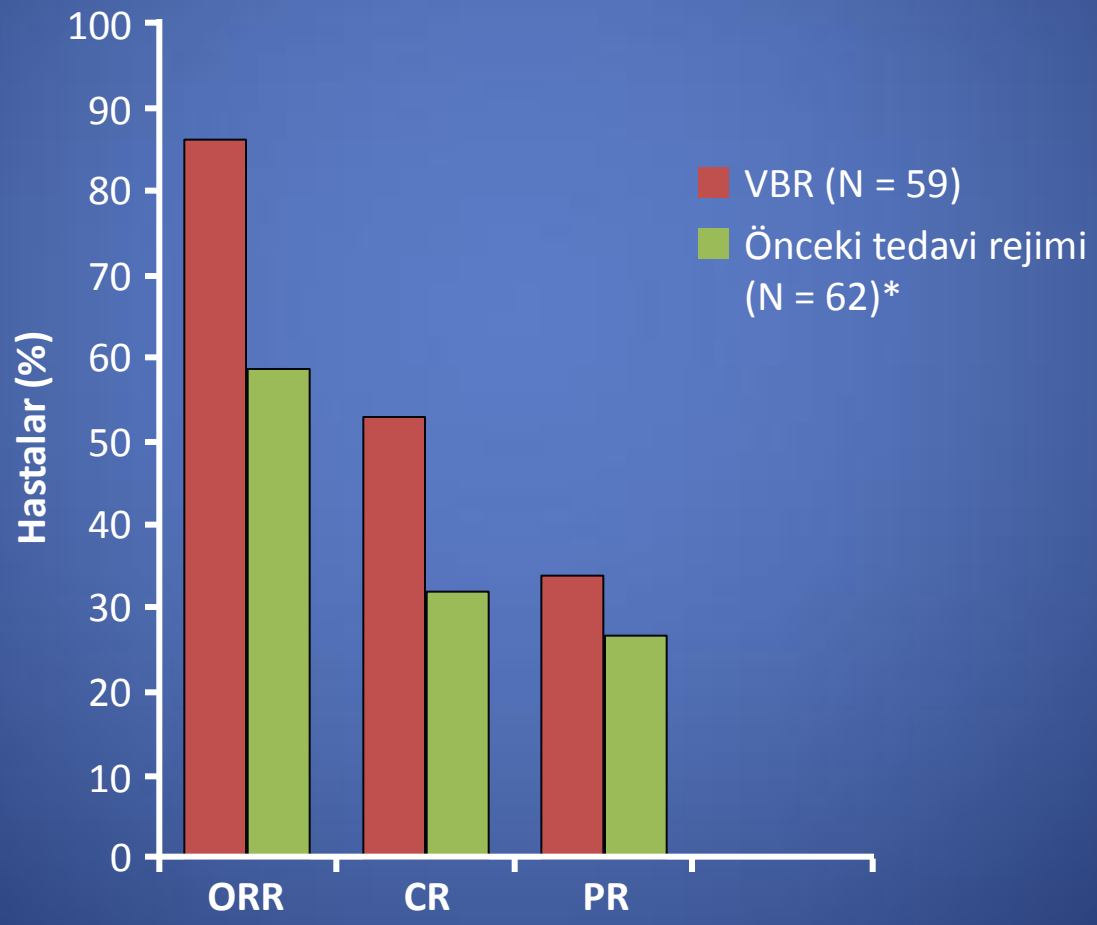
VERTICAL: Rel/Ref FL Tedavisinde Bortezomib + Bendamustine + Rituximab (VBR)

- Faz 2 açık etiketli, multicenter çalışma; doz-eskalasyonu yapılmış
  - Bendamustine 50, 70, and 90 mg/m^2/gün
  - Faz II: 90 mg/m^2
  - Bortezomib 1.6 mg/m^2
  - Rituximab 375 mg/m^2
- Bütün hastalar 5 kür tedavi almış



Fowler N, et al. ASH 2009. Abstract 933.

VERTICAL: Sonuçlar



Fowler N, et al. ASH 2009. Abstract 933.

VERTICAL: Yan etkiler

- Tedaviye bağlı: 100%
  - ≥ grade 3: 60%
    - Nötropenia: 27%
    - Trombosipeni: 6%
    - Anemi: 3%
    - Periferik nöropati, ≥ grade 3: 10%
  - Ölüm: 2%
- Ciddi yan etkiler: 32%
  - Tedavi kesilmesine sebep olan nöropati: 3%
- Kümülatif hematolojik toksisite yok

Fowler N, et al. ASH 2009. Abstract 933.

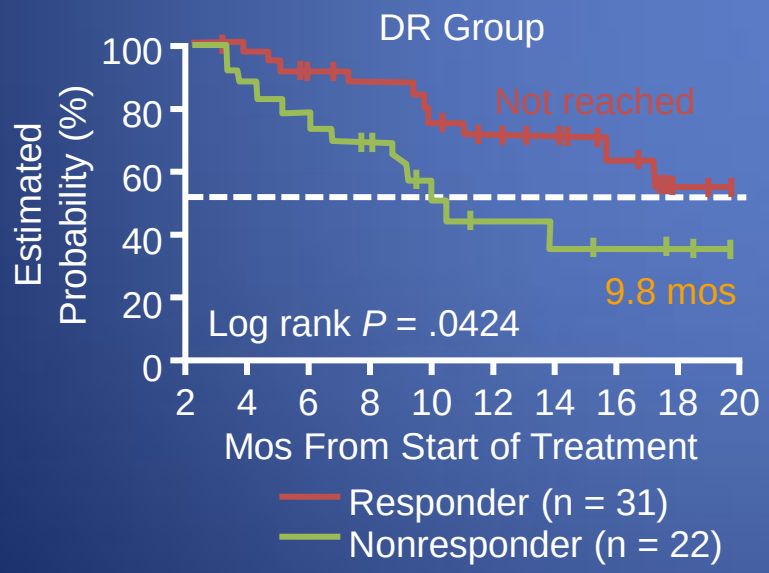
VERTICAL: Sonuç

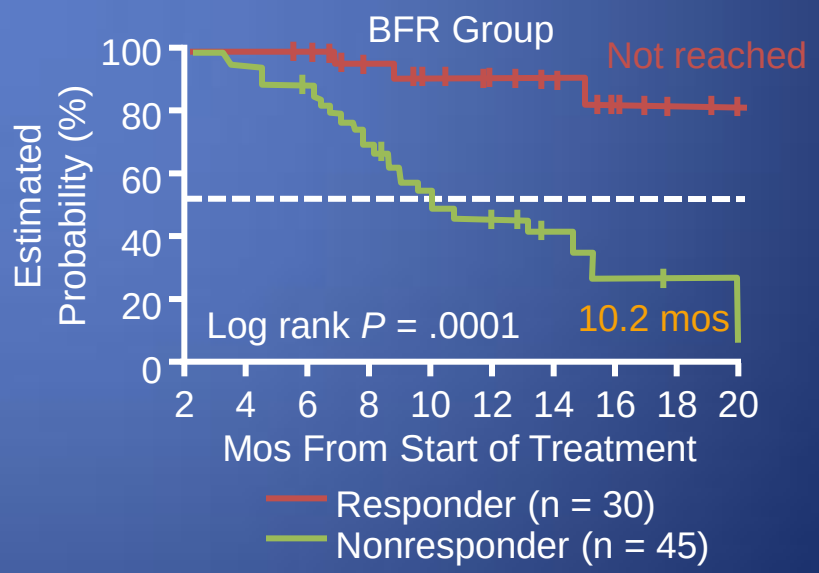
- VBR relaps/refrakter FL tedavisinde etkilidir
  - VBR cevap oranlarını ve tam cevap oranlarını artırmıştır
- VBR iyi tolere edilmiştir
  - Tedaviye bağlı yan etkiler genellikle grade ½
- PFS ve OS bekleniyor

Fowler N, et al. ASH 2009. Abstract 933.

Ofatumumab

- İnsan anti-CD20 monoklonal antikoru
  - İn vitro rituksimab dan daha etkili
- Fludarabin-refrakter KLL hastalarında Faz III çalışma[1]
  - %58 ORR - alemtuzumab refrakter hastalar (DR)
  - %47 ORR – alemtuzumab bulky LAP nedeni ile kullanılamayan hastalar (BFR)





Österborg A, et al. ASH 2008. Abstract 328.

Galiximab

- Anti-CD80 IgG_1 MAb
  - CD80 immün costimülatuar molekül – FL hücrelerinde bulunur
- Relapse/refrakter FL hastalarında Faz II:
  - Galiximab (500 mg/m^2) + rituximab (N = 64)
  - ORR: %64
  - Median PFS: 12.2 ay (%20 > 2 yıl)
  - Ek tedavi ≥ 2 yıl boyunca gerektirmeyenler: %37
  - Bir dahaki tedaviye kadar geçen zaman > 3 yıl: %28
- DLT yok

Friedberg JW, et al. ASH 2008. Abstract 1004.

Epratuzumab

- Hümanize anti-CD22
  - ORR: epratuzumab + rituximab: %47-67[1]
- Faz I/II doz artırımı çalışmaları [2,3]: DLT yok
  - En sık toksisite: Bulantı (22%) ve fatigue (23%)

1. Strauss SJ, et al. J Clin Oncol. 2006;24:3880-3886.
2. Leonard JP, et al. J Clin Oncol. 2003;21:3051-3059.
3. Leonard JP, et al. Clin Cancer Res. 2004;10:5327-5334.

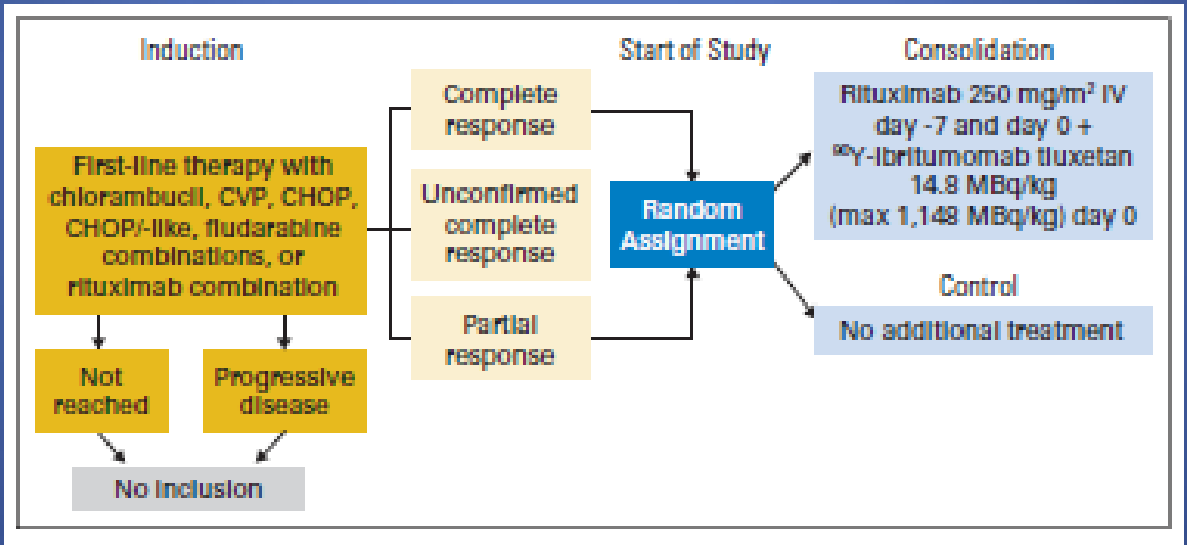
Radyoimmünoterapi: ^{90}Y-Ibritumomab

- Relaps refrakter FL ve transforme NHL için onaylanan ilk radyoimmünokonjugat
  - ORR: %74-84[1]
- Sitopeniler MDS'ye yol açabiliyor (%2.5) [2]

1. Cheson B, et al. Blood. 2003;101:391-398.
2. 2. Czuczman MS, et al. J Clin Oncol. 2007;25:4285-4292.

FL'da ^{90}Y-Ibritumomab Konsolidasyonu

Phase III Trial of Consolidation Therapy With Yttrium-90–Ibritumomab Tiuxetan Compared With No Additional Therapy After First Remission in Advanced Follicular Lymphoma



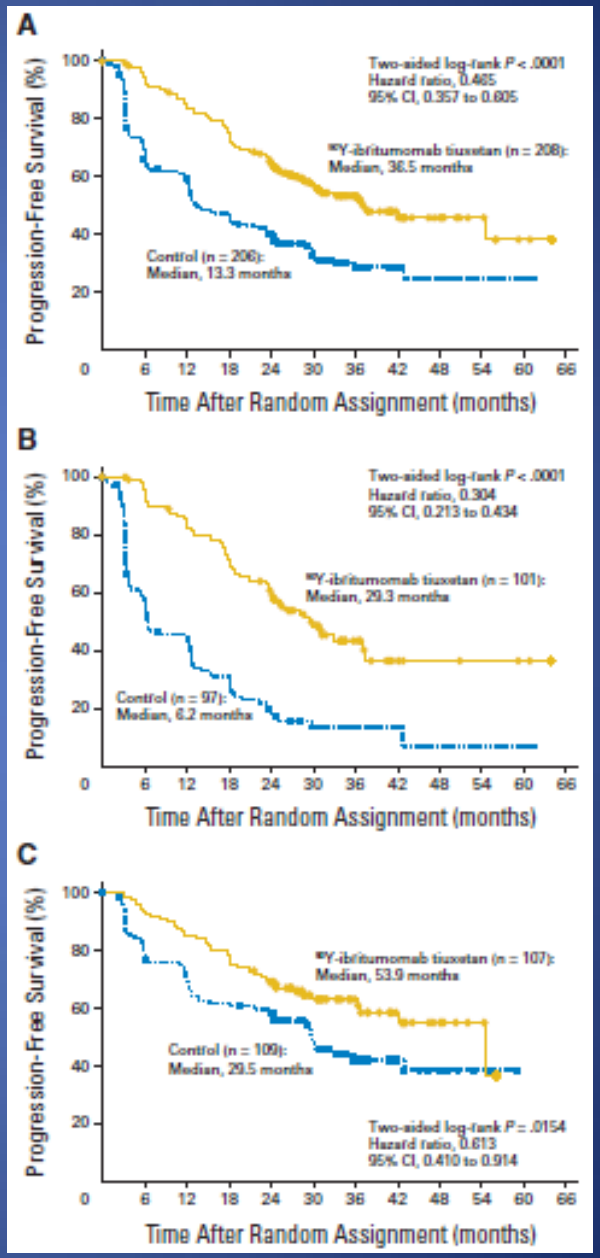
Morschhauser F, et al. J Clin Oncol 2008; 26:5156-64.

^{90}Y-Ibritumomab Konsolidasyonu

Tüm hastalar

Birinci basamak tedavide PR

Birinci basamak tedavide CR/CRu



Morschhauser F, et al. J Clin Oncol 2008; 26:5156-64.

Rituksimab
İdame Tedavisi

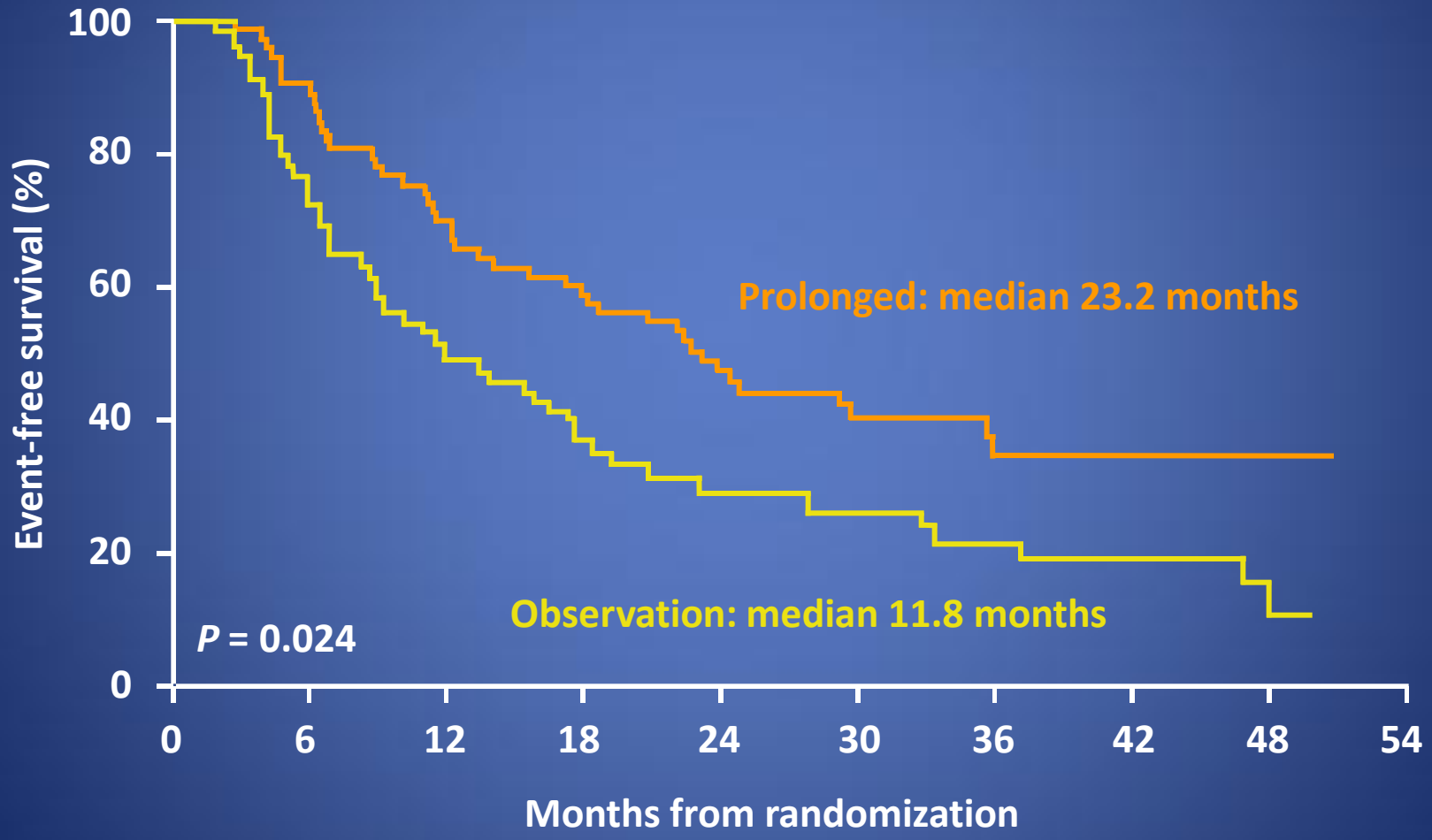
Rituksimab İdamesi

Çalışma grubu	Dizayn	Basamak	İndüksiyon	Rituksimab idame
SAKK 35/98[1]	Ph III	1st/2nd	Rituksimab	EFS ↑ ~ 190%
ECOG 1496[2]	Ph III	1st	CVP	PFS ↑ ~ 280%
EORTC 20981[3]	Ph III	2nd	CHOP ± R	PFS ↑ ~ 250%
GLSG[4*]	Ph III	2nd	FCM ± R	RD ↑ ~ 200%

* MCL hastaları da var

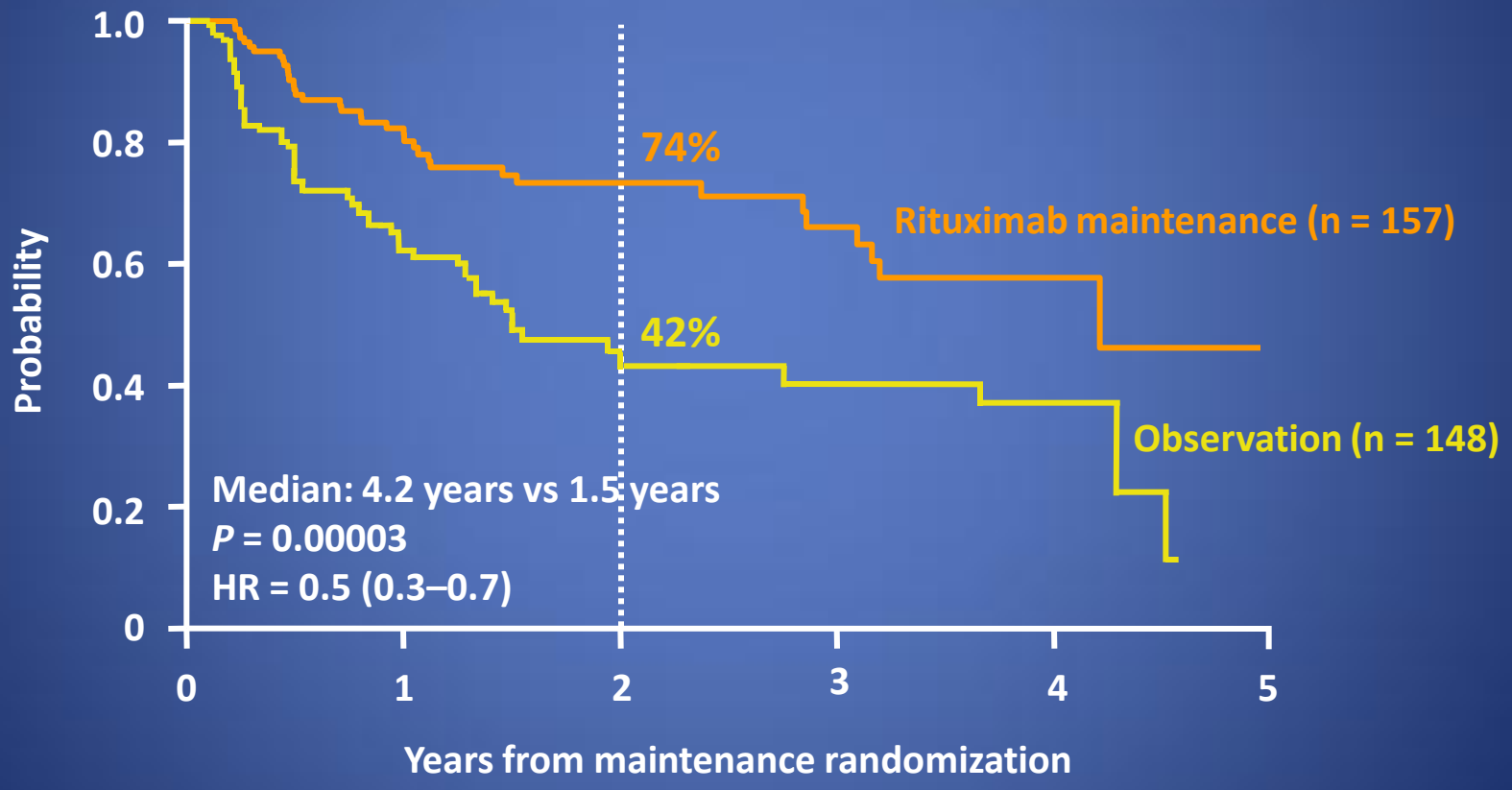
1. Ghielmini M, *et al*. *Blood* 2004; 103:4416–4423.
2. Hochster HS, *et al*. *Proc Am Soc Clin Oncol* 2004; 22:Abstract 6502.
3. van Oers M, *et al*. *Blood* 2006; 108: 3295-301.
4. Forstpointner R, *et al. Blood 2006;108: 4003-8.*

SAKK 35/98: Event-free survival



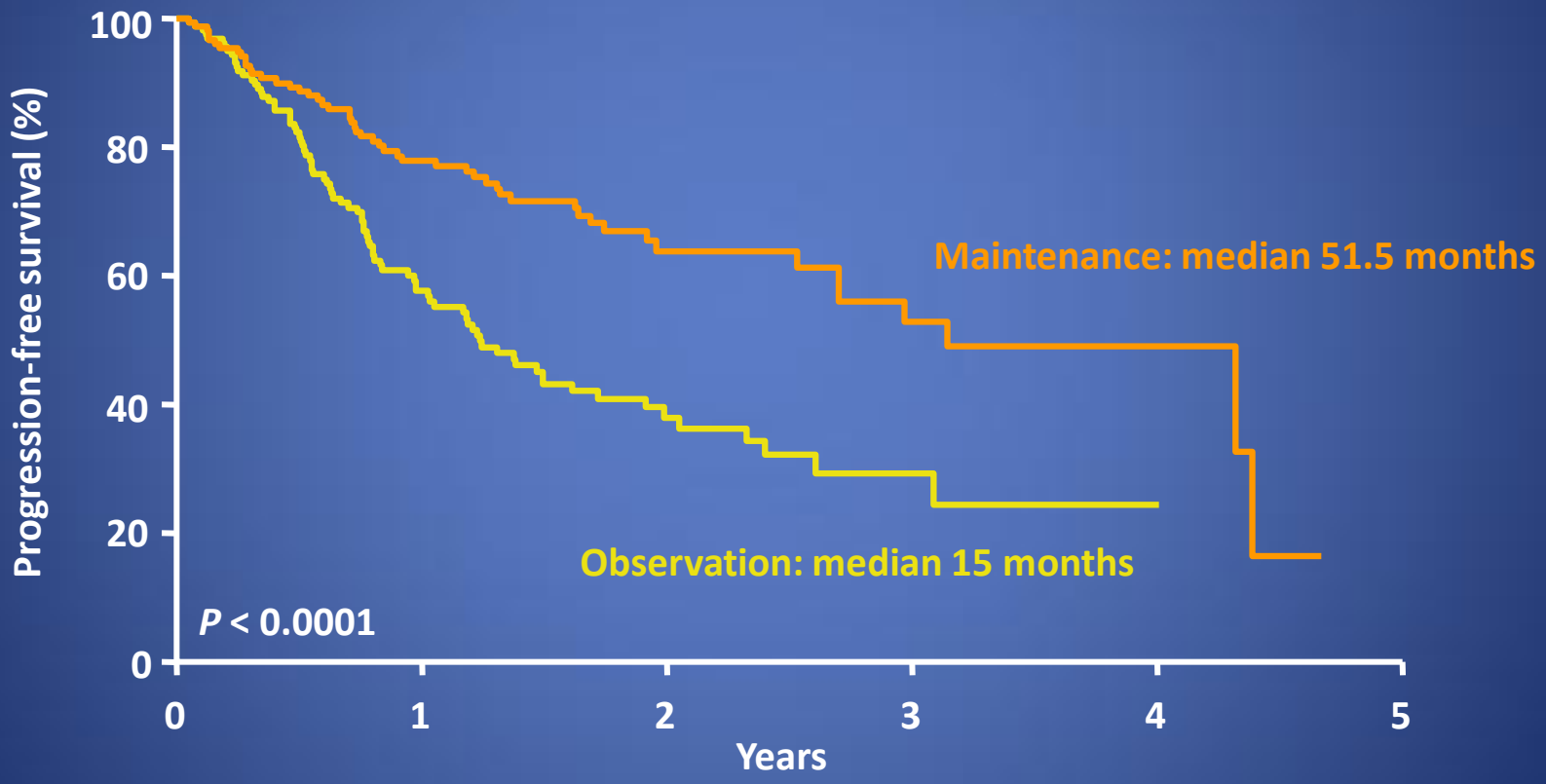
Ghielmini M, *et al*. *Blood* 2004; **103**:4416–4423.

ECOG 1496: PFS



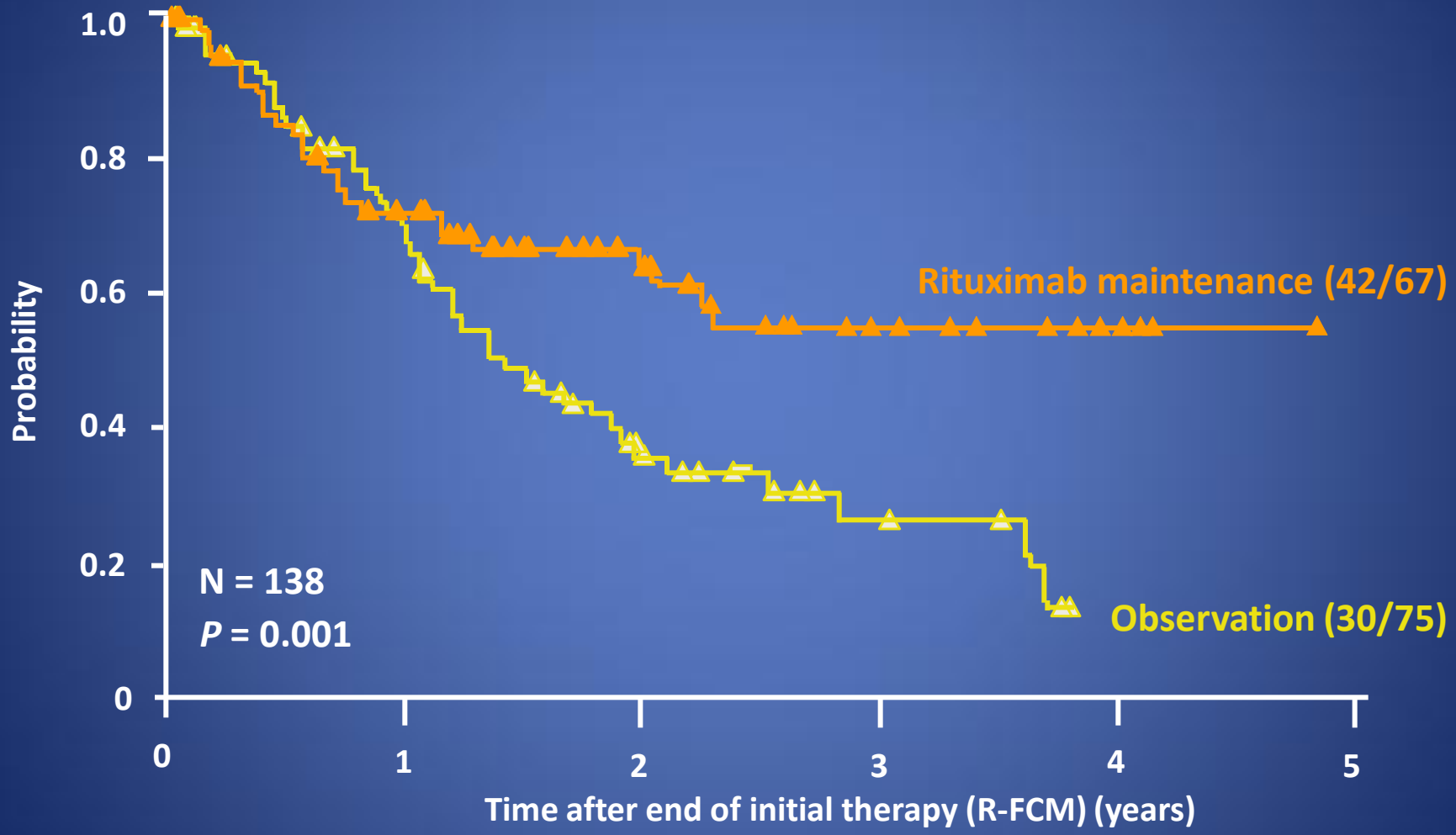
J Clin Oncol. 2009 Apr 1;27(10):1607-14

EORTC 20981: PFS



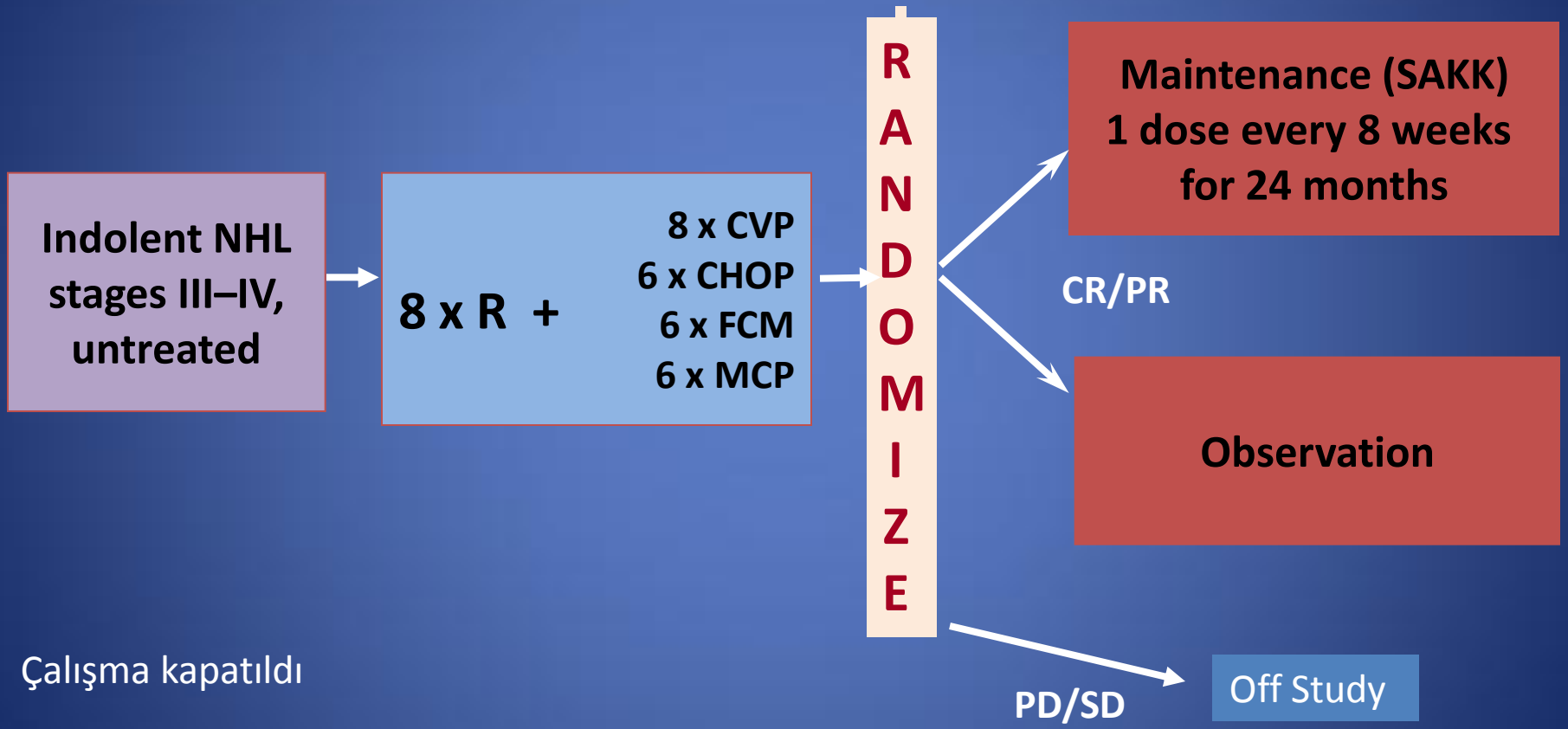
van Oers MHJ, *et al*. *Blood* 2006;108:3295-301.

GLSG: Yanıt süresi



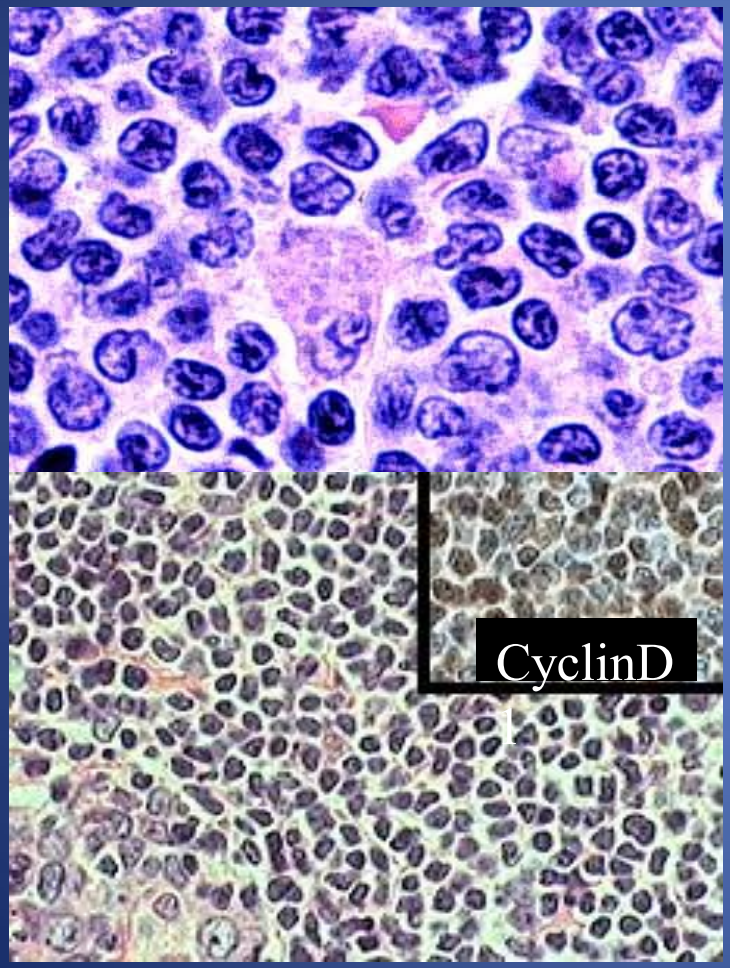
Forstpointner R, et al. Blood 2006;108: 4003-8.

PRIMA Çalışması



Çalışma kapatıldı

Mantle Hücreli Lenfoma

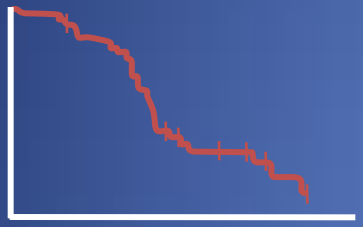


- Agresif
- Tüm lenfomaların ~%6'sı
- Mantle zone B hücresinden kaynaklanır
- Geleneksel tedavilerle inkürabl
- CD19+, CD5+, CD23-
- t(11;14) translokasyonu
  - Siklin D1 (bcl1) gen ekspresyonu
  - Hücre siklusu kontrolü bozulur

Mantle Hücreli Lenfoma: Birinci Basamak tedavi

Standart Kemoterapi

R-CHOP

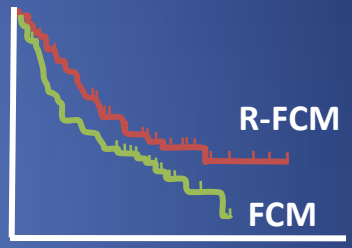


PFS
Howard et al. J Clin Oncol. 2002.

CHOP/R-CHOP

PFS
Lenz et al. J Clin Oncol. 2005.

FCM/R-FCM



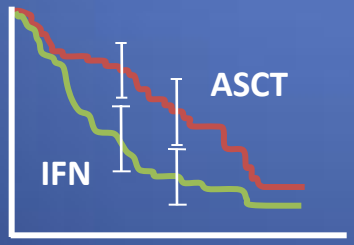
PFS
Forstpointner et al. Blood. 2004.

Yüksek-doz veya doz dense tedaviler

CHOP-DHAP/ASCT

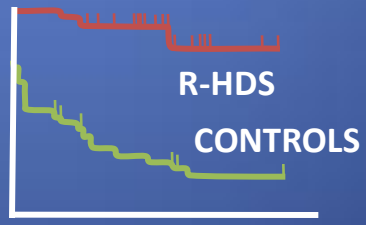
PFS
Lefrére et al.
Leukemia. 2002.

ASCT > CHOP-IFN



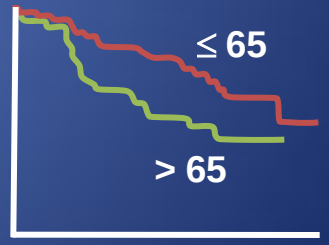
PFS
Dreyling et al.
Blood. 2005.

R-HDS



PFS
Gianni et al.
Blood. 2003.

R-HyperCVAD MTX/ARAC



PFS
Romaguera et al.
J Clin Oncol. 2005.

R-CHOP ve R-DHAP → OKİT: Birinci basamak

- 60 hasta (2000-2003)
- Med yaş 57 ++
- 49/60 OKİT
- 2 hasta dışında hastalar OKİT sırasında CR
- Med takip 67 ay: EFS 83%
- 5-yıl OS: 75%

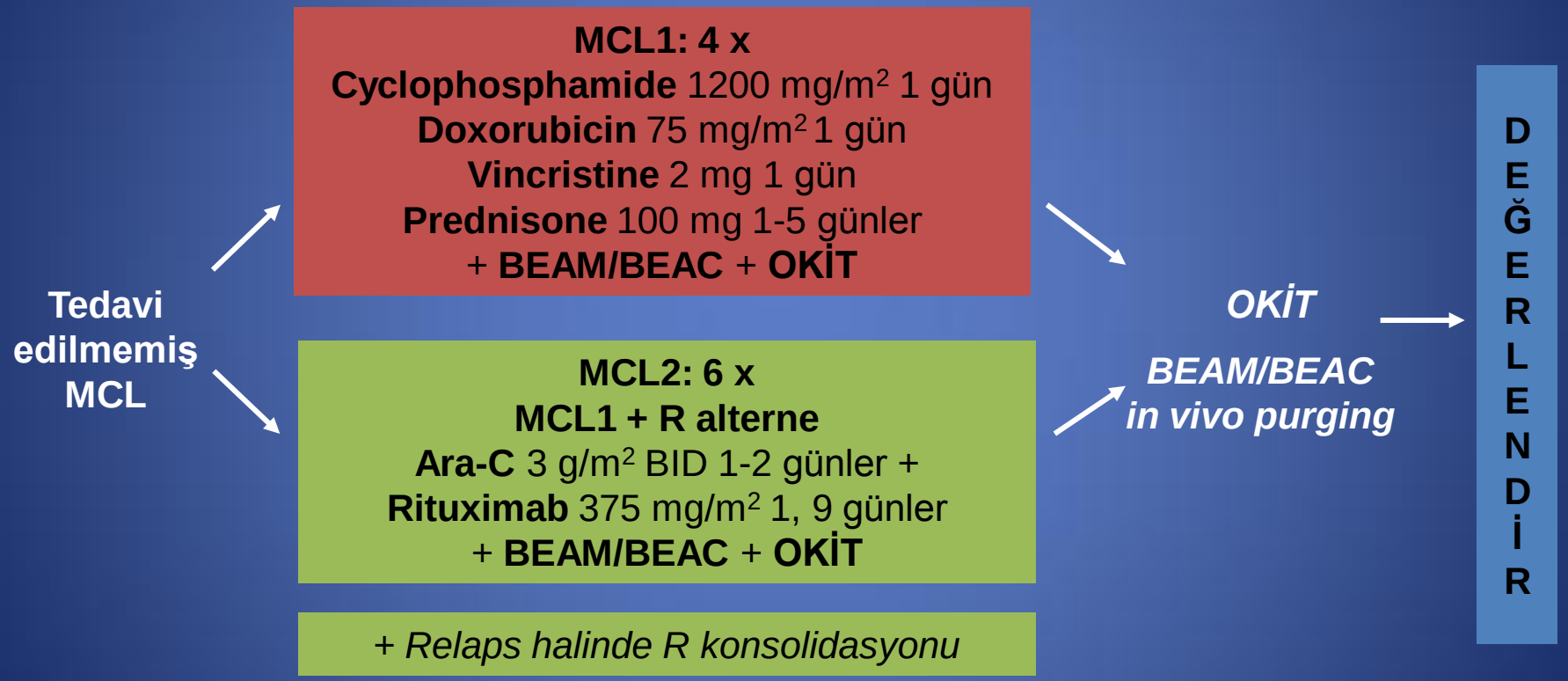
- < 66 yaş, MCL evre III-IV
- 3 CHOP-R alterne 3 R-DHAP
- Mobilizasyon
- OKİT hazırlık: TAM6 (TBI 10Gy, Ara-C 6g/m^2, Mel 140) veya BEAM

Cevap, %	Post R-CHOP	Post R-DHAP
ORR	93	95
CR	12	61

R ve Ara-C faydası gösterildi: CR %12 post R/ %61 R-DHAP
%20 hastaya OKİT yapılamadı

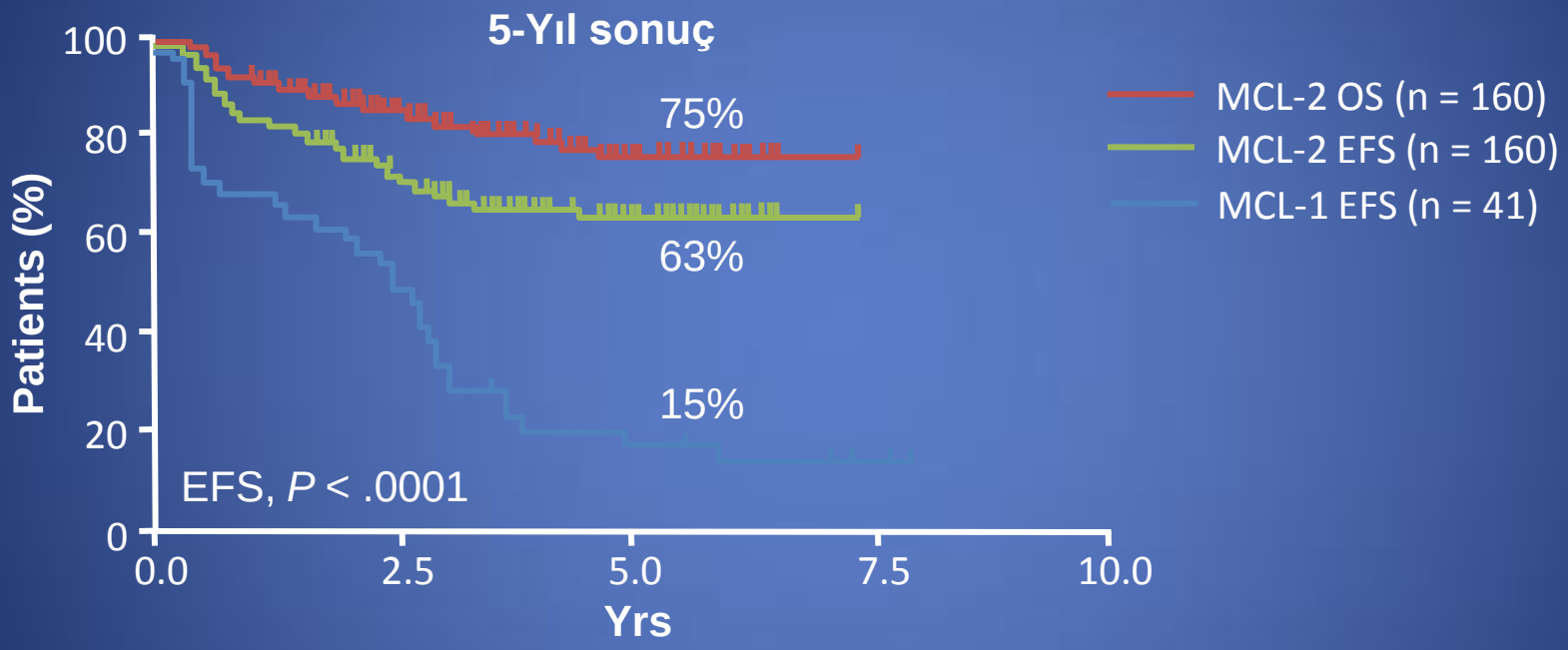
Delarue R, et al. ASH 2008. Abstract 581.

Nordic Grubu: MCL OKİT çalışmaları (MCL-1, MCL-2)



Geisler CH, et al. ASH 2007. Abstract LB1.
Geilser CH, et al. Blood. 2008;112:2687-2693.
Anderson NS, et al. ASH 2007. Abstract 1281.

Nordic Lenfoma Grubu: MCL OKİT çalışmaları (MCL-1, MCL-2)



- Induksiyon: R-hyperCVAD benzeri (methotrexate yok) x 6 kür + OKİT
- Preemptif rituksimab (moleküler monitorizasyon ile) (34 hasta, 13 > 1 yıl)
- Median takip: sadece 3 yıl

Geisler CH, et al. Blood. 2008;112:2687-2693.

NLG MCL-3: ^{90}Y-Ibritumomab Tiuxetan + Yüksek-Doz BEAM/BEAC

- NLG MCL-1 (1996-2000) maxi-CHOP - BEAM/C ve OKİT[1]
  - CR iken OKİT yapılan hastalarda sonuçlar PR olanlara göre aha diyi
  - Yüksek ralps oranı
- NLG MCL-2 (2000-2006) [2]
  - Yüksek doz ARA-C ve rituksimab eklendi(+ maxi-CHOP)
  - MCL-1 çalışmasına göre çok daha iyi sağkalım

1. Andersen NS, et al. Eur J Haematol. 2003;71:73-80. 2. Geisler CH, et al. Blood. 2008;112:2687-2693.

NLG MCL-3: ^{90}Y-Ibritumomab Tiuxetan + Yüksek-Doz BEAM/BEAC

- Indüksiyon MCL-2 aynısı:
  - 6 x Rituximab + alterne maxi-CHOP ve YD Ara-C
- CR hastalar MCL-2 OKİT tedavisine devamn
- CRu veya PR hastaları ^{90}Y-ibritumomab tiuxetan (0.4 mCi/kg) + rituximab 250 mg/m^2 ve BEAM/C-destekli OKİT

Kolstad A, et al. ASH 2009. Abstract 932.

NLG MCL-3: Cevap oranları

- Pre- ve posttransplant ORR MCL-3 = MCL-2
- > %90 hasta OKİT'e gidebilmiş

Pretransplant

Cevap, %	MCL-3 (n = 148)	MCL-2 (n = 160)
ORR	96	96
CR	51	46
CRu	18	9
PR	28	42
SD/PD	3	4
Tedaviye bağlı ölüm	1	0

Posttransplant

Cevap, %	MCL-3 (n = 109)	MCL-2 (n = 145)
CR	83	83
CRu	8	6
PR	4	8
PD	2	1
Tedaviye bağlı ölüm	3*	2

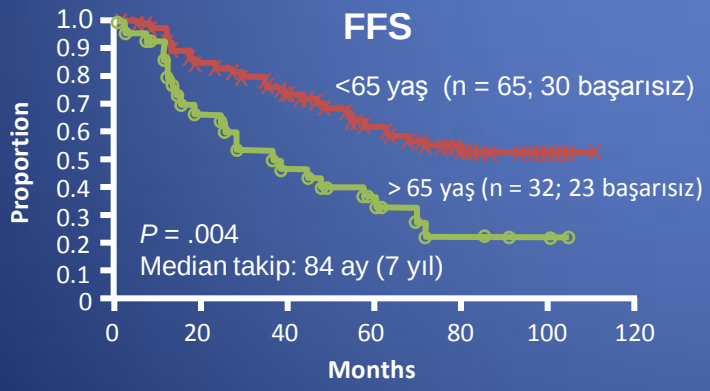
Kolstad A, et al. ASH 2009. Abstract 932.

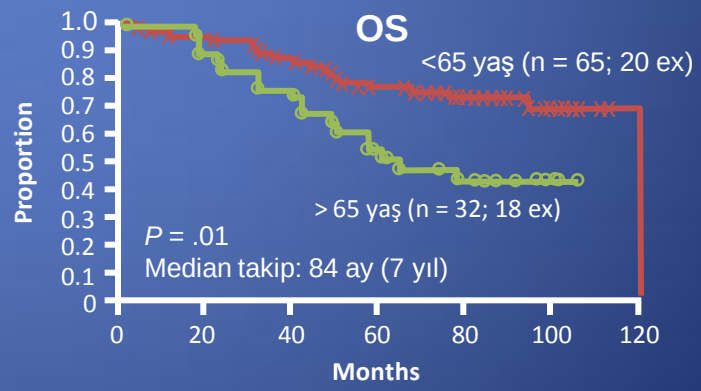
Birinci basamakta R-HyperCVAD: Uzun Dönem Sonuçlar

MDACC, 99 hasta, 6-8 kür, 6 kür sonrası CR ise OKİT yok

Yaş grubu	No.	CR, %	PR, %
Tüm yaşlar	97	87	11
≤ 65 yıl	66	88	9
> 65 yıl	31	84	16

- Prognostik faktörler: yaş, beta-2, LDH, IPI ve MIPI
- Median takip 84 ay (7 y)
- FFS 43% ve OS %60
- < 65 yıl: FFS %52, OS %68





Romaguera JE, et al. ASH 2008. Abstract 833.
Romaguera JE, et al. ASH 2008. Abstract 3051.

Dose Dense ve Yüksek Doz Tedavilerin Karşılaştırılması

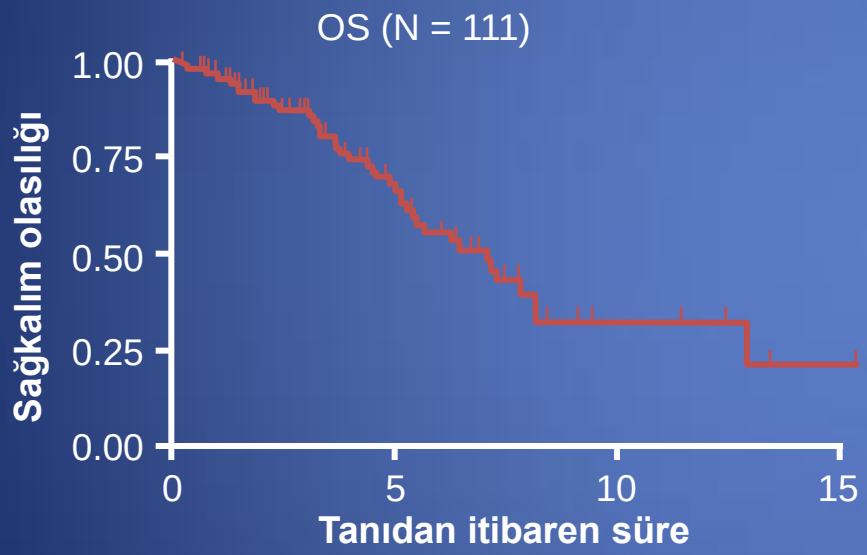
Ara-C–içeren indüksiyonlar

Çalışma	Tedavi	n	Yaş sınırı, Yıl	5-Yıl EFS, %	5-Yıl OS, %	Takip, aylar
Nordic ASH 07	MCL-2 (R+ Ara-C)	160	< 66	63	74	60
GITL ASH 07	(R) HDS-ASCT*	77	< 61	61	74	50
MDACC	R-hyperCVAD	97	<80 (1/3 > 65)	48/FFS	65	50
			< 65	60/FFS	76	50

Geisler CH, et al. ASH 2007. Abstract LB1.
Cortelazzo S. ASH 2007. Abstract 1282.
Romaguera JE, et al. J Clin Oncol. 2005;23:7013-7023.
Fayad L, et al. Clin Lymphoma Myeloma. 2007;8(suppl 2):S57-S62.

MCL: Tartışmalı konular

Median OS: 7.1 yıl

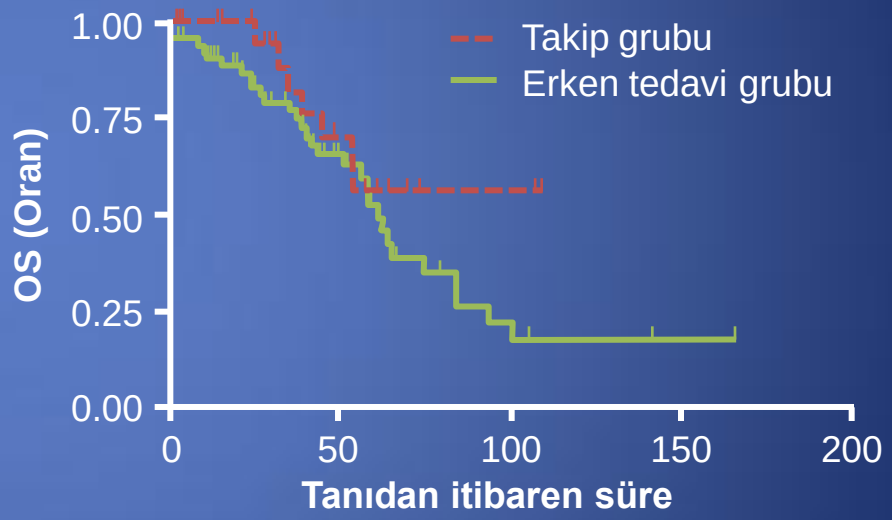


0 yrs: n = 111; 5 yrs: n = 41; 10 yrs: n = 5

Heterojen hastalık, tek merkez sonucu

Martin P, et al. Ann Oncol. 2008;19:1327-1330.

Takip vs Erken tedavi

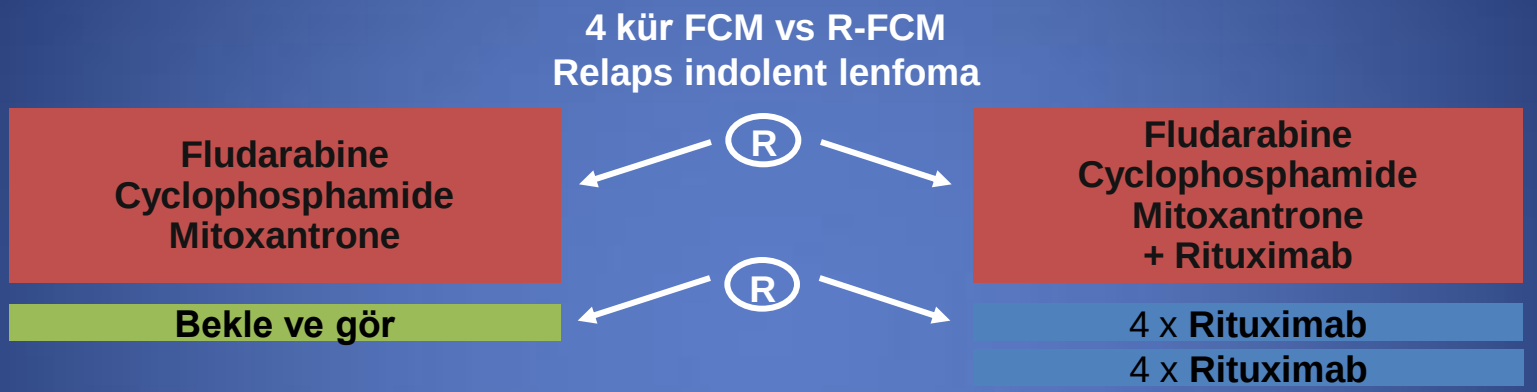


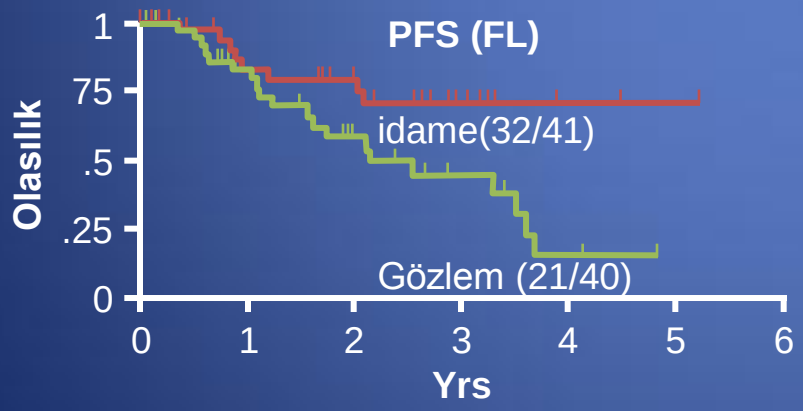
Martin P, et al. J Clin Oncol. 2009;27:1209-1213.

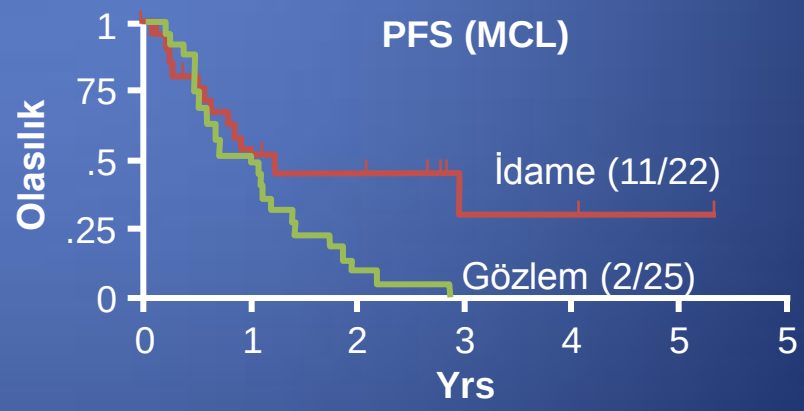
MCL: Indüksiyon tedavisi—Özet

- Standart veya konsensus tedavi yok
- Median OS: 3-5 yıl (son 20 yılda arttı)
- Baştan yoğun tedavi (hyperCVAD veya OKİTASCT) + rituksimab genç hastalarda faydalı görünüyor
- MCL indolent alt grubunda bekle ve gör politikası izlenebilir
- Relaps hastalarda prognoz hala kötü

MCL: Rituksimab İdame





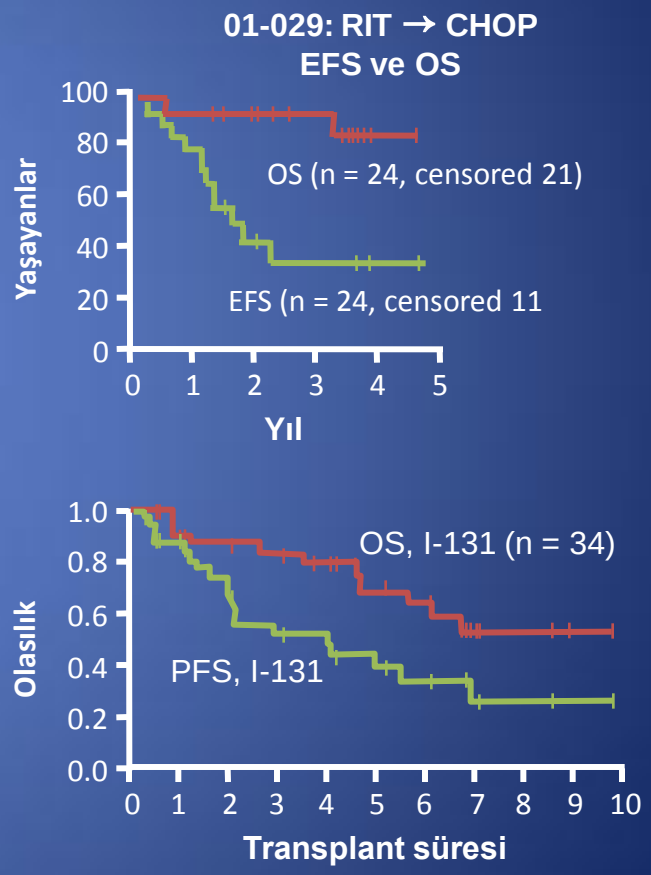


Rituximab idame faydası FL kadar değil

Forstpointner R, et al. Blood. 2006;108:4003-4008.

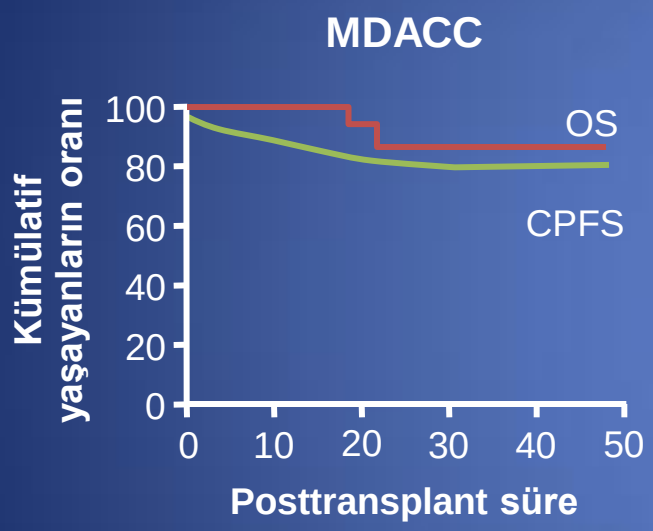
MCL'de Radyoimmünoterapi

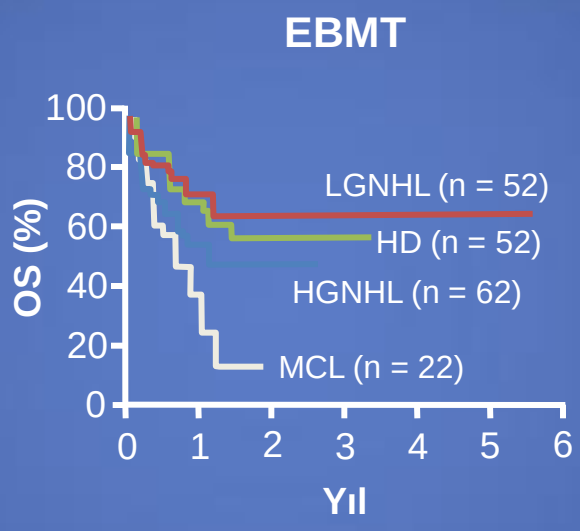
Çalışma	Dizayn	Sonuçlar
Tositumomab + CHOP MSKCC[1]	Tositumomab → 6 CHOP No rituximab	Uygun 1/3 hasta had mol CR post RIT *Post CHOP sonrası fayda?*
R-CHOP + ibritumomab tiuxetan ECOG 1499 [2]	R-CHOP x 4 → ibritumomab tiuxetan	56 hasta/med yaş 61 yıl *CR oranı 3 misli: %45 (R-CHOP sonrası %1*
HDT RIT/ ASCT Hutch [3]	Tositumomab + HDT cyclophosph + etoposide + ASCT	5-yr PFS: 42%

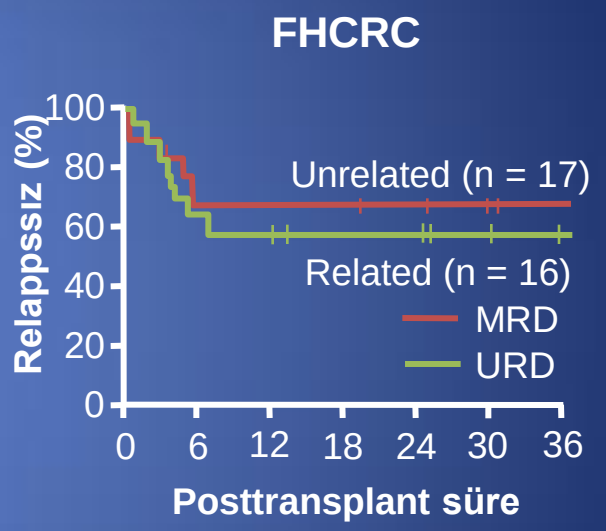


1. Zelenetz A, et al. ASCO 2006. Abstract 7560. 2. Smith M, et al. ASH 2007. Abstract 389.
3. Gopal AK, et al. Blood. 2002;99:3158-3162.

MCL: Allojeneik Transplantasyon







Khouri IF, et al. J Clin Oncol. 2003;21:4407-4412.

Robinson SP, et al. Blood. 2002;100:4310-4316.

Maris MB, et al. Blood. 2004;104:3535-3542.

Potansiyel küratif modalite
Problem: median yaş ve cGVH > 50%

MCL'de Temsirolimus

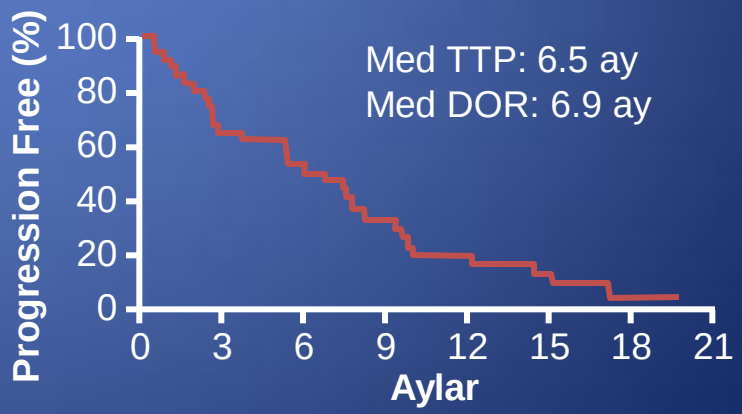
250 mg haftalık

- %38 ORR (13/34)
- 1 CR; 12 PRs
- Median cevaba kadar geçen süre: 1 ay
- Toksisite
  - Grade 3 - 4 %91
  - Trombositopeni (%100), anemi (%66) nötropeni (%77)
  - GI, mucositis, fatigue, hiperglisemi, neuropathy

Cevap oranları, süresi ve TTP benzer

25 mg haftalık

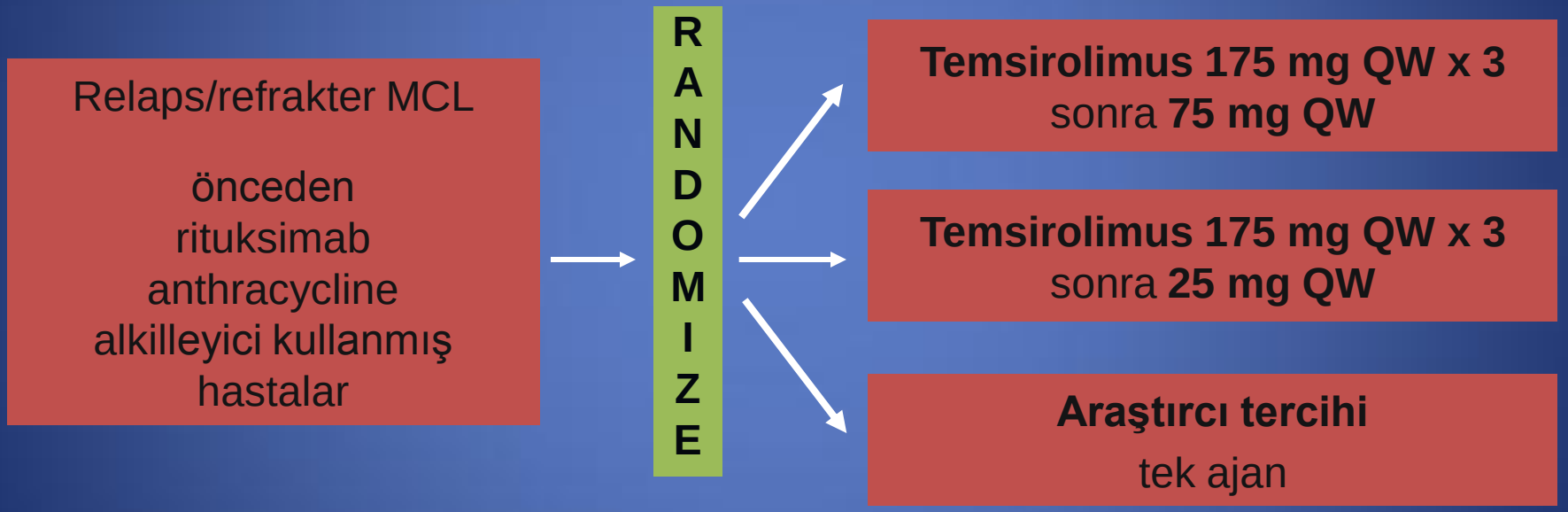
- ORR %41 (11/27)
- 1 CR (%3.7) ve 10 PRs (%37)
- Median 4 tedavi sonrası
- Hematolojik toksisite
  - %50 grade 3, %4 grade 4
  - Thrombositopeni en sık



Witzig T, et al. J Clin Oncol. 2005;23:5347-5356.

CCI-779 (Temsirolimus)

Randomize çalışma



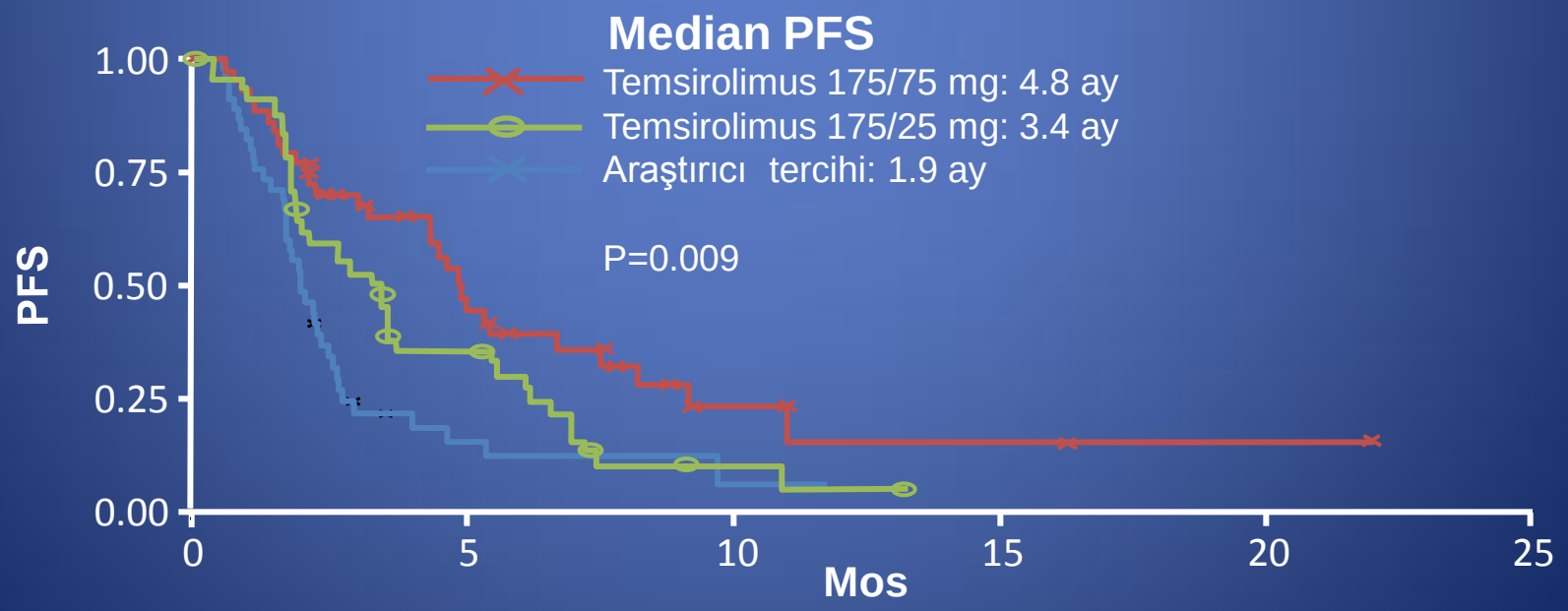
Her kolda 54 hasta; 2-7 öncül tedavi

Temsirolimus tedavisi progresyona, ölüme veya toksisiteye kadar devam edilkecek

Hess G, et al. ASCO 2008. Abstract 8513.

CCI-779 (Temsirolimus) in MCL

Cevap	Temsirolimus 175/75 (n = 54)	Temsirolimus 175/25 (n = 54)	Araştırıcı Tercihi (n = 54)
ORR, %	22	6	2
DOR, ay	7.1	3.6	NA
Median PFS, ay	4.8	3.4	1.9



Hess G, et al. ASCO 2008. Abstract 8513.

Lenalidomide (NHL-002 ve NHL-003)

Tek başına 25 mg PO 21/28-gün siklus – PD veya toksisiteye kadar
Nötropeni, trombositopeni (%20 grade 3-4), fatigue

Parametre	NHL-002 (N = 15)	NHL-003 (N = 22*)
ORR, n (%)	8 (53)	8 (36)
CR, n (%) Cru, n (%) PR, n (5)	3 (20) 0 (0) 5 (33)	0 (0) 2 (9) 6 (27)
Öncül Td, median n (aralık)	4 (1-7)	4 (1-8)
Bortezomib alan hastalarda ORR, n/N (%)	2/5 (40)	3†/6 (50)

Bortezomib: MCL'de etkinlik özeti

	Çalışma	N	CR/CRu	PR	ORR
1.5 mg/m²	O'Connor	37	3/2 (13%)	10 (27%)	40%
	Goy	29	6 (20.5%)	6 (20.5%)	41%
1.3 mg/m²	Strauss Lister	24	1 (4%)	6 (25%)	29%
	Belch	13 tedavisiz/ 15 relaps	0 1	6 6	46% 47%
	PINNACLE*	141	11 (8%)	36 (26%)	47 (33%)
	Total	**259**	**24 (9%)**	**70 (27%)**	**94 (36%)**

O'Connor OA, et al. J Clin Oncol. 2005;23:676-684.
Goy A, et al. J Clin Oncol. 2005;23:667-675.
Strauss SJ, et al. J Clin Oncol. 2006;13:2105-2112.
Belch A, et al. Ann Oncol. 2007;18:116-121.
Fisher RI, et al. J Clin Oncol. 2006;24:4867-4874.

Çalışmalarda benzer ORR

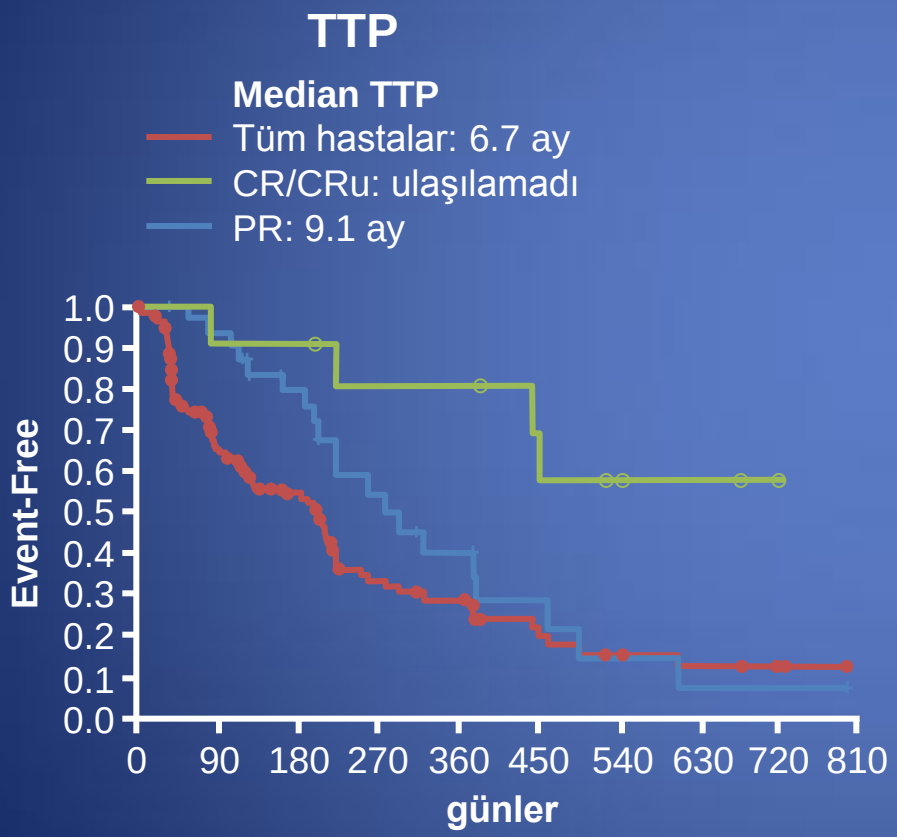
PINNACLE Çalışması Update

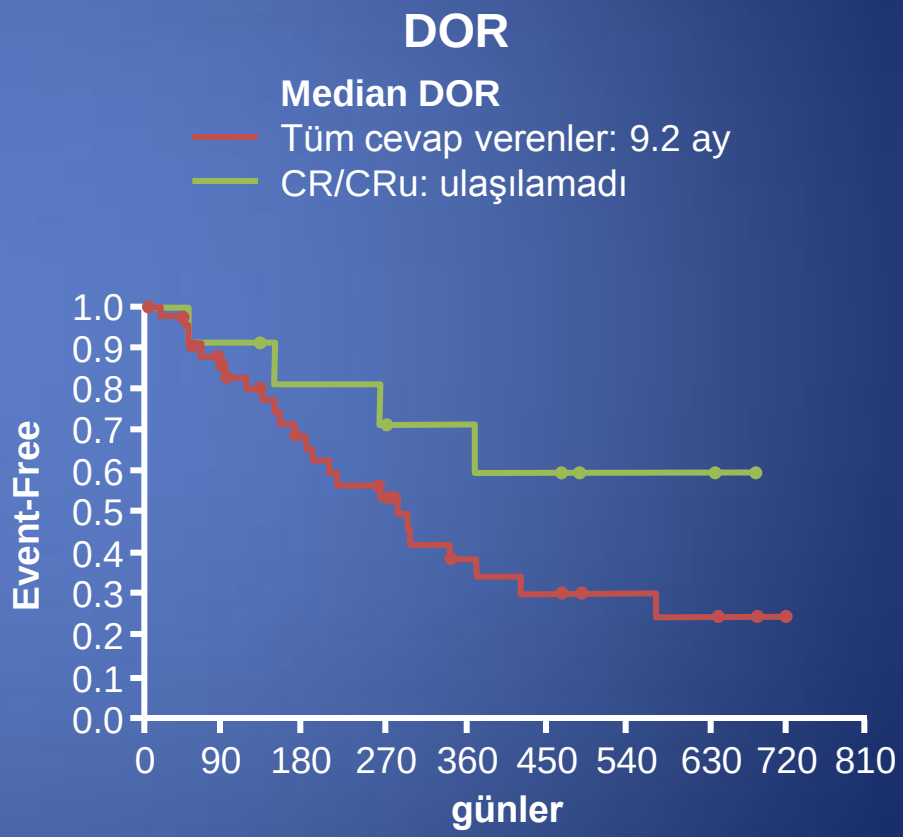
Cevap/altgrup analizi

Parameter	Cevap: değerlendirilebilen(n = 141)	Refrakter MCL* (n = 51)	Önceden yüksek doz tedavi (n = 52)
ORR, %	32	29	25
CR/CRu, %	8	6	10
Median DOR, ay	9.2	5.9	Ulaşılamadı

Goy A, et al. Ann Oncol. 2009;20:520-525.
O'Connor OA, et al. Br J Haematol. 2009;145:34-39.

PINNACLE Çalışması Update



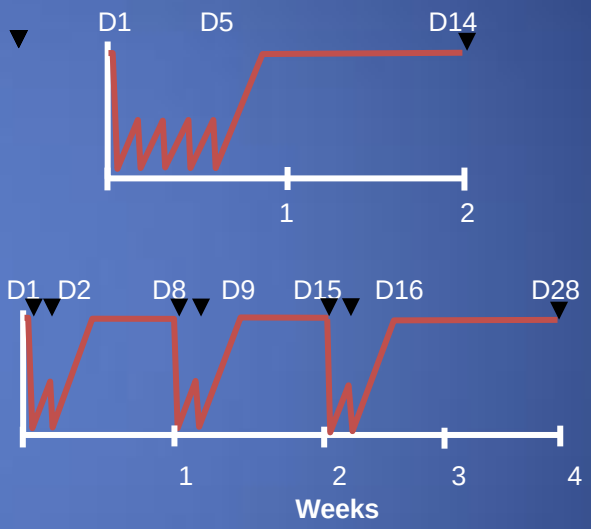


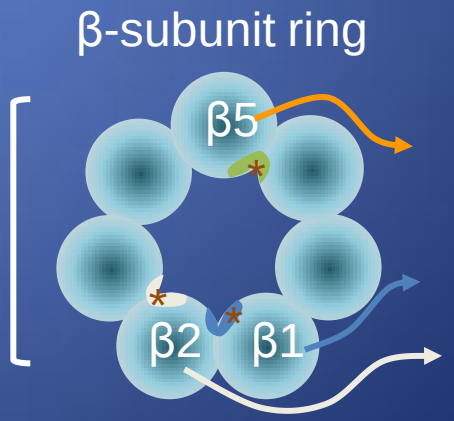
Median takip 26.5 mos

Goy A, et al. Ann Oncol. 2009;20:520-525.

İkinci kuşak Proteasome Inhibitörleri

- **PR-171 (Carfilzomib)**
  - Keto-epoxide tetrapeptide
  - Daha selektif/irreversible
  - MM aktivite var
  - < neuropathy, GI, thrombocytopenia, fatigue, renal
- **NPI-0052**
  - 3 proteolitik bölgeyi inhibe eder
  - Faz I devam ediyor (renal toksisite)
- **Immünoproteasome inhibitörleri/ ligaz specific inhibitörleri**





MCL'de Diğer Novel Ajanlar

İlaç	Mekanizma/Çalışma
Diğer antiangiogenesis ajanları	Thalidomide/rituximab/bevacizumab/VEGF Trap
Anti-TRAIL antikorları (TRM-1)	TRAIL reseptor 1 agonistleri apoptosis/ekstrinsik yolak aktivasyonu
HSP inhibitörleri 17AAG (geldamycin)	bortezomib resistansı geri dönüşümü
IKK inhibitörleri	NF_KB stabilizasyonu
Raf/MEK signal inhibitörleri	Sorafenib Küçük molekül sinyal transdüksiyon inhibitörü
HDAC inhibitörleri (SAHA, depsipeptide)	
Farnesyl transferase inhibitörleri	Tipifarnib
BL22 immunotoxin	Calicheamycin/CD22 (CMC-544)
Diğerleri	Bcl-2 inhibitörleri

Teşekkürler