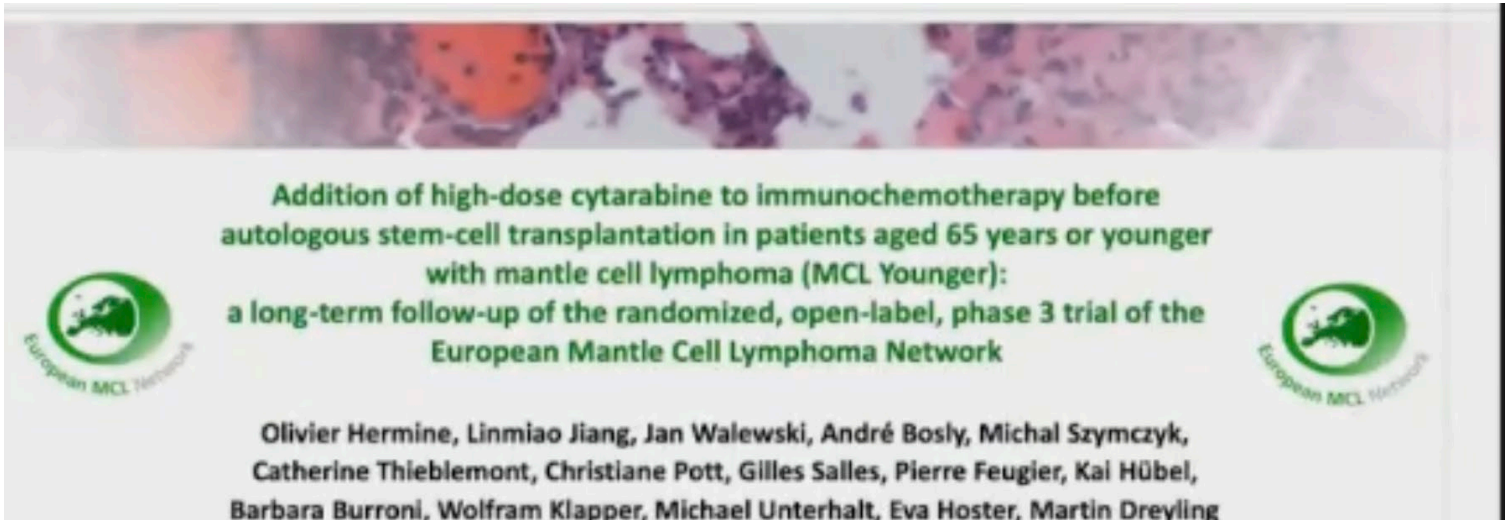
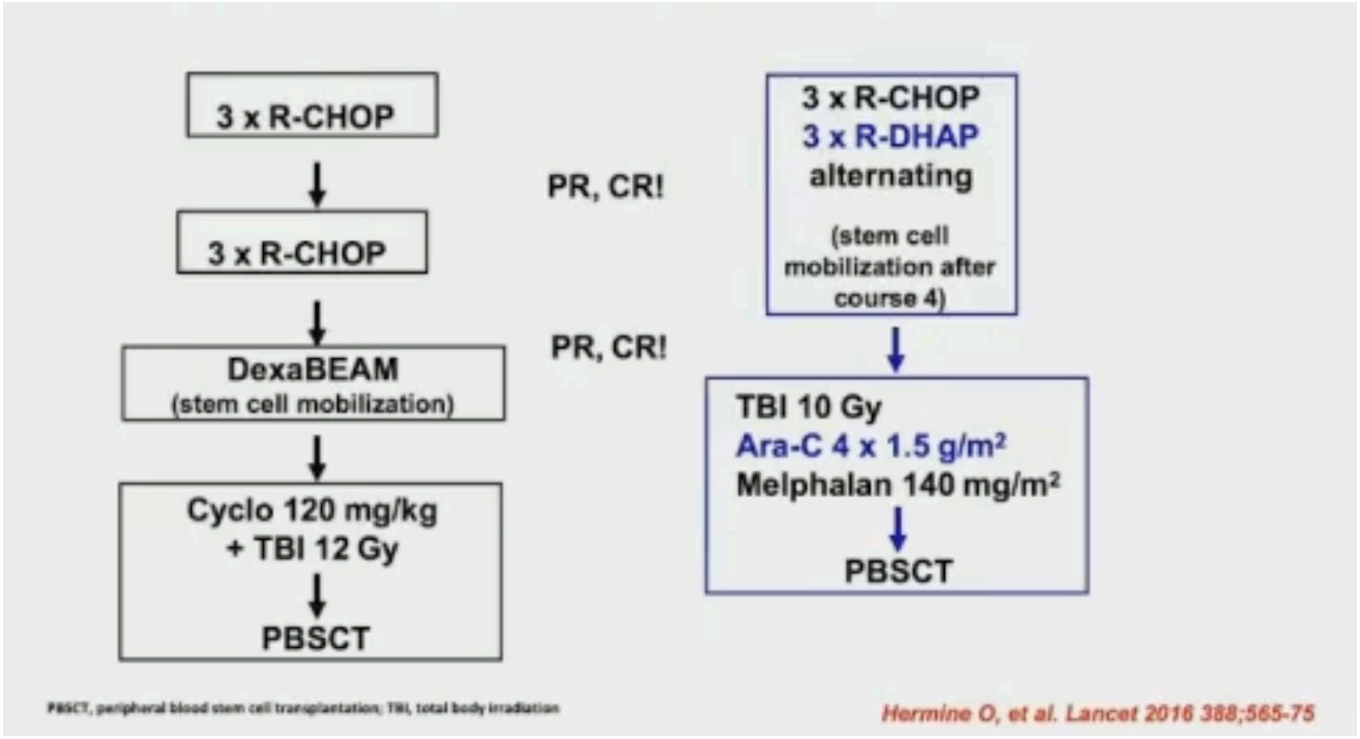
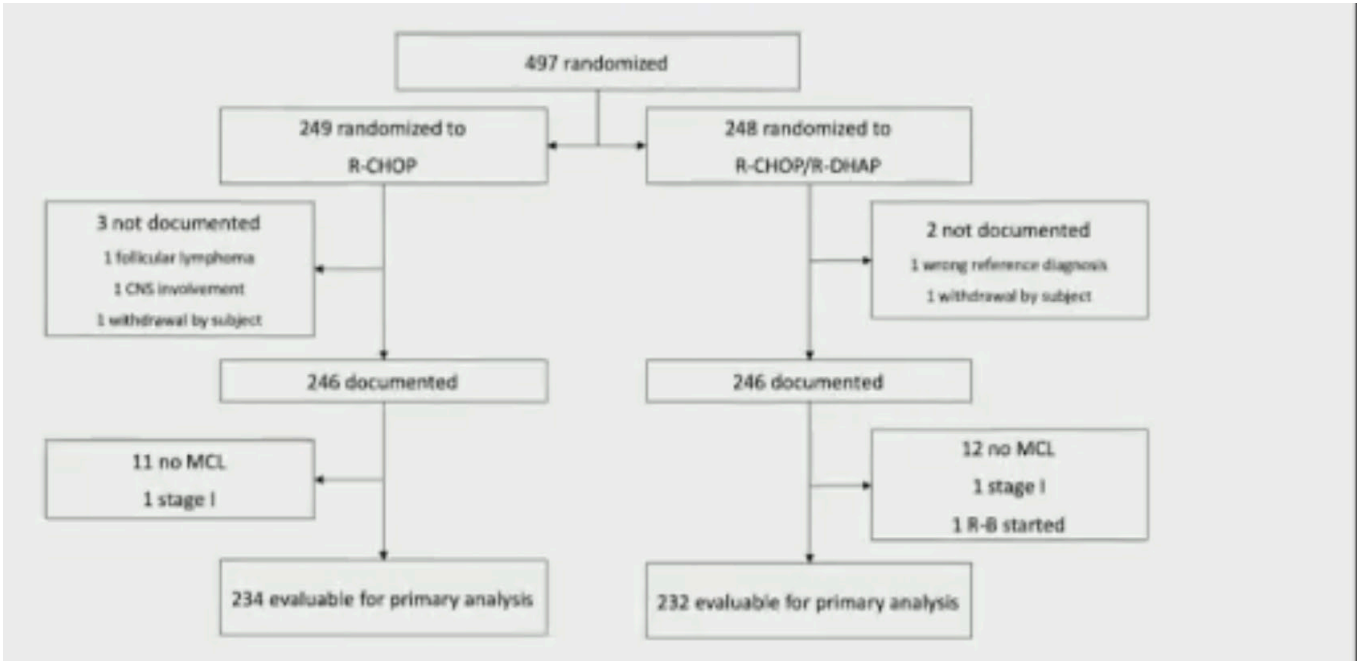
MANTLE HÜCRELİ LENFOMA GÜNCELLEMESİ

Öğr Gör Dr GÜLDANE CENGİZ SEVAL
Ankara Üniversitesi Tıp Fakültesi Hematoloji Bilim Dalı



- Genç hastalarda YD ARA-C içeren indüksiyon+OPKHN ile PFS artmakta ama OS etkisi yok
- Randomize, açık uçlu, paralel-grup, faz III çalışma
- >65 y, Evre III-IV MCL
- Birincil sonlanım noktası: TTF (tedavi başarısızlığına kadar geçen süre)


3 x R-CHOP
3 x R-CHOP
DexaBEAM
(stem cell mobilization)
Cyclo 120 mg/kg
+ TBI 12 Gy
PBSCT
PR, CR!
PR, CR!
3 x R-CHOP
3 x R-DHAP
alternating
(stem cell mobilization after course 4)
TBI 10 Gy
Ara-C 4 x 1.5 g/m²
Melphalan 140 mg/m²
PBSCT
PBSCT, peripheral blood stem cell transplantation; TBI, total body irradiation
Hermine O, et al. Lancet 2016 388;565-75

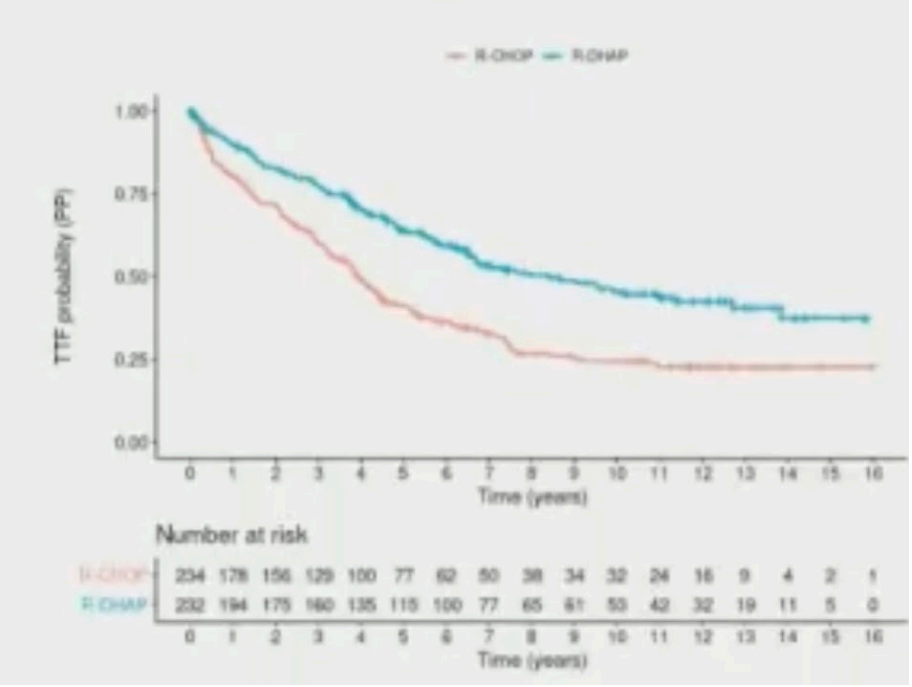

497 randomized
249 randomized to R-CHOP
248 randomized to R-CHOP/R-DHAP
3 not documented
1 follicular lymphoma
1 CNS involvement
1 withdrawal by subject
2 not documented
1 wrong reference diagnosis
1 withdrawal by subject
246 documented
246 documented
11 no MCL
1 stage I
12 no MCL
1 stage I
1 R-B started
234 evaluable for primary analysis
232 evaluable for primary analysis

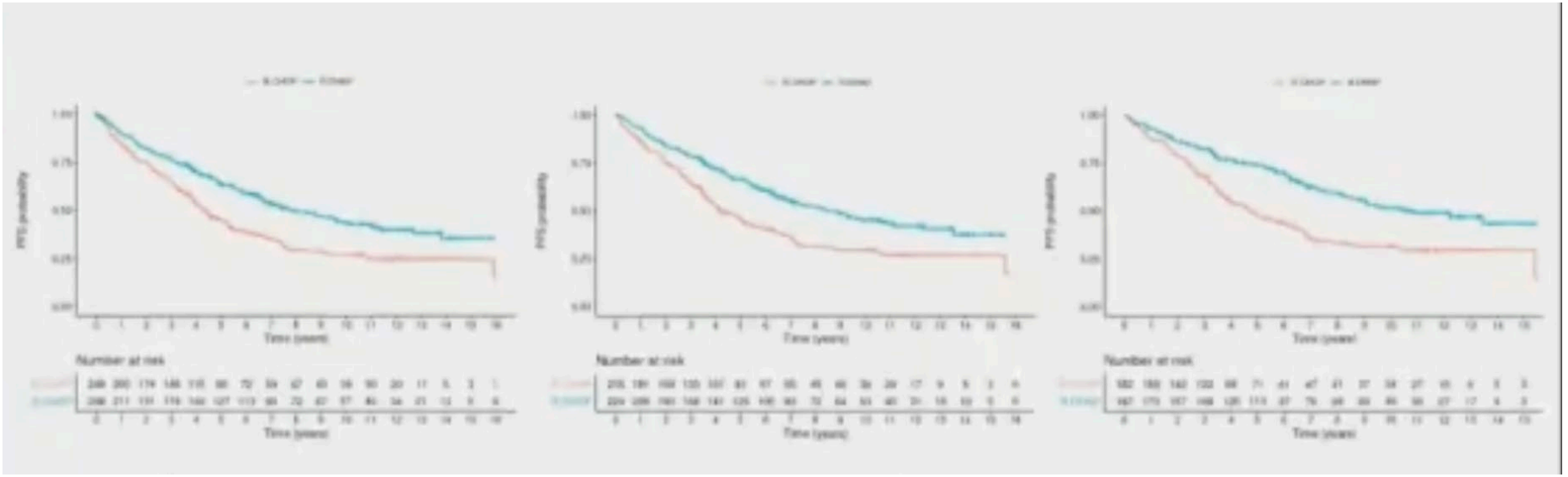
2016 sonuçları (Hermine et al, Lancet 2016)

- Medyan takip 6,1 yıl
- ARA-C ile belirgin uzun TTF (HR 0,56 p=0,038)
- İndüksiyon sonrası ARA-C kolunda daha yüksek TY ve MRD (-)
- ARA-C kolunda daha uzun PFS
- OS farkı yok (HR 0,78 p=0,12)
- ARA-C kolunda artmış G3/4 hematolojik toksisite

2021 güncellenmiş sonuçlar

- Medyan takip 10,6 yıl
- Medyan TTF; R-CHOP 3,9 yıl R-DHAP 8,4 yıl
- 10 yıllık TTF (%95 CI); R-CHOP %25 (%19-%32) R-DHAP %46 (%39-%54)





Randomizasyondan itibaren medyan PFS

- R-CHOP 4,3 yıl
- R-DHAP 8 yıl (p<0.0001)
- HR 0,61 (0,48-0,78), p<0.0001

İndüksiyondan itibaren medyan PFS

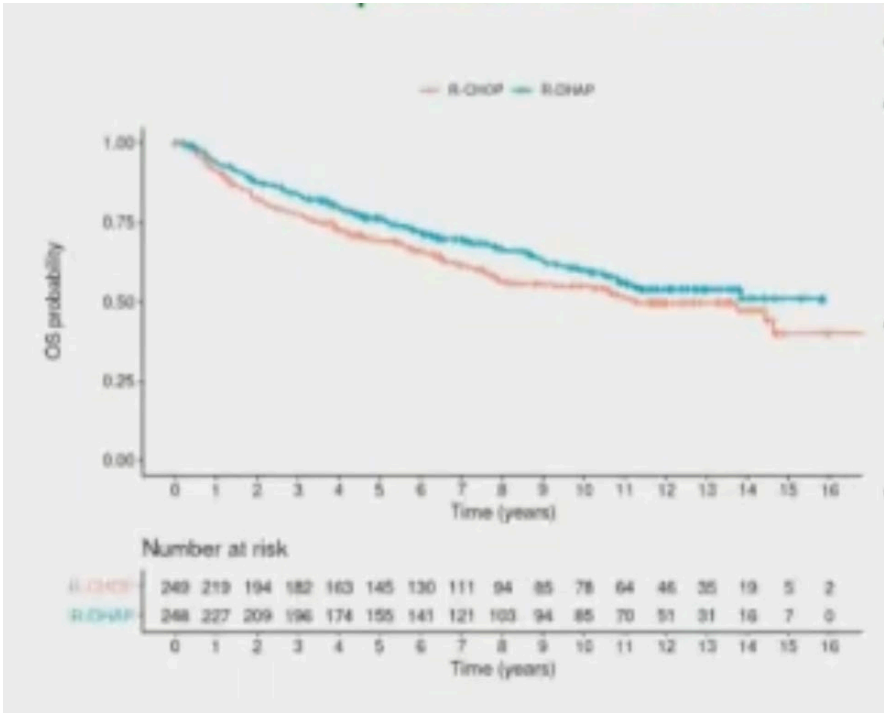
- R-CHOP 4,2 yıl
- R-DHAP 8,5 yıl (p<0.0001)
- HR 0,60 (0,47-0,78), p<0.0001

OPKHN itibaren medyan PFS

- R-CHOP 4,7 yıl
- R-DHAP 10,8 yıl (p<0.0001)
- HR 0,53 (0,40-0,71), p<0.0001

OS

- Medyan takip 11 yıl
- Medyan OS; R-CHOP 11,3 yıl R-DHAP NR (p=0.12)
- 10 yıllık OS (%95 CI); R-CHOP %55 (%48-%62) R-DHAP %60 (%53-%67)



Klinik Önemi:

- YD ARA-C içeren indüksiyon ve OPKHN ile 10. yıldaki sağkalım %60 ve kabul edilebilir toksisite ile
- Yüksek ve düşük riskli hastalarda YD ARA-C etkili
- OS'de belirgin düzelme (MIPI ve/veya Ki-67'ye göre)
- R-CHOP hastalarında kurtarma tedavisi??
- TBI'dan kaçınabilmek ikincil maligniteleri azaltabilir
- Bazı hastalar için optimal küratif tedavi seçeneği

2915 The Intensity of the Induction Regimen Does Not Affect Post-Transplant Survival Among Patients with Newly Diagnosed Mantle Cell Lymphoma

Melhem Solh, MD[1], *Asad Bashey, MD, PhD*[1], *Lawrence E Morris, MD*[1], *H. Kent Holland, MD*[1], *Xu Zhang, PhD*[2*] *and Scott R. Solomon, MD*[1]

[1]*Blood and Marrow Transplant Program, Northside Hospital Cancer Institute, Atlanta, GA*
[2]*Center for Clinical and Transitional Sciences, University of Texas Health Science Center, Houston, TX*

- 2010-2020 arasında 59 hasta OPKHN (+)
- Medyan yaş 60 (45-76)
- %85 Evre IV MCL
- MIPI yüksek risk: %28
- İndüksiyon tedavileri: BR (n=14); RCHOP (n=11); R-Hyper CVAD (n=14); RBAC (n=2); RCHOP/RDHAP (n=18)
- Nakil öncesi %85 TY, %15 KY
- %51 nakil sonrası R idame

	YD ARA-C (+)	YD ARA-C (-)
TY	85%	84%
5 yıllık OS	%82	%69
5 yıllık DFS	%65	%50
NRM	%4	%9
Nüks	%31	%41

MVA: ARA-C etkisi yok (OS, DFS, NRM ve nüks)

Klinik Önemi:

- OPKHN yapılan MCL hastalarında daha ARA-C kullanılan yoğun indüksiyon tedavilerinin uzun dönem sonuçlar üzerine net etkisi gösterilememiş
- Hastalık (MIPI), hasta (ECOG PS) ve nakil sonrası R idame nakil sonrası sonuçlara etkili

1344 Late Effects after Treatment in Mantle Cell Lymphoma: No Difference By Intensity of First-Line Regimens with or without Autologous Stem Cell Transplantation

Sara Ekberg, PhD[1,2*], Karin E. Smedby, MD, PhD[2,3*], Alexandra Albertsson-Lindblad, MD, PhD[4*], Mats Jerkeman, MD, PhD[5], Caroline Weibull, PhD[2*] and Ingrid Glimelius, MD, PhD[1*]

[1]Department of Immunology, Genetics and Pathology, Uppsala University, Sweden, Uppsala, Sweden
[2]Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
[3]Karolinska University Hospital, Stockholm, Sweden
[4]Department of Oncology, Department of Clinical Sciences, Lund University, Skane University Hospital, Lund, Sweden
[5]Department of Oncology, Department of Clinical Sciences, Lund University, Skane University Hospital, Lund, Skaane Laen, Sweden

- Populasyon tabanlı kohort çalışması 1:10 eşleşmeli, 2000-2014 yılları arasında
- 620 MCL, 4,1 yıllık takip
- 280 (%45): OPKHN (+) (medyan yaş 65 (32-69))
- 340 (%55): R-CHOP/R-Benda ve OPKHN(-) (medyan yaş 65 (22-69))
- 4/280 (%1,5): OPKHN sonrası 60 gün içinde ex
- OPKHN yapılan hastalarda yapılmayanlarla göre uzun dönem yan etki oranları benzer
- 5 yıllık kümülatif MCL-spesifik ölüm oranı OPKHN (+) vs (-) 0.23 (%95 CI: 0,18-0,30) vs 0,32 (%95 CI: 0,26-0,38)
- >12 ay yan etki OPKHN grubunda nadir ve çoğunlukla ölüm nedeni hastalık progresyonu, komplikasyon değil

Klinik Önemi:

- OPKHN içeren yoğun bir ilk basamak tedavi ile daha az yoğun tedavilerle benzer uzun dönem YE
- Sağ kalım üzerine olumlu etkileri düşünüldüğünde YD KT+OPKHN etkili bir tedavi !!!

3525 Ibrutinib Plus Rituximab and Venetoclax (IRV) Followed By Risk-Stratified Observation or Short Course R-Hypercvad/MTX in Young Patients with Previously Untreated Mantle Cell Lymphoma – Phase-II Window-2 Clinical Trial

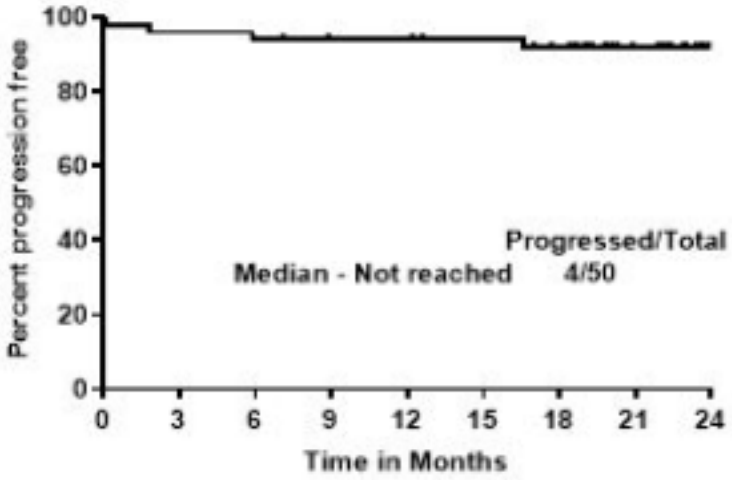
Michael Wang, MD[1], Preetesh Jain, MBBS, MD, DM, PhD[1], Hun Ju Lee, MD[1], Chi Young Ok, MD[2], Holly Hill[1*], Lucy Navsaria, MB BCh BAO[1*], Rashmi Kanagal-Shamanna, MD[3], Luis Malpica-Castillo, MD[1*], Ranjit Nair, MD[1*], Swaminathan Padmanabhan Iyer, MD[1*], Felipe Samaniego, MD[1], Wendy Chen[1*], Onyeka Oriabure[1*], Lei Feng, MS[4*], Selvi Thirumurthi[5*], David Santos[6*], Guilin Tang, MD, PhD[2*], Francisco Vega, MD, PhD[2], Shaoying Li[7*], Michelle Avellaneda[1*], Maria Badillo, MSN, RN, OCN, CCRP[1*] and Christopher R. Flowers[8]

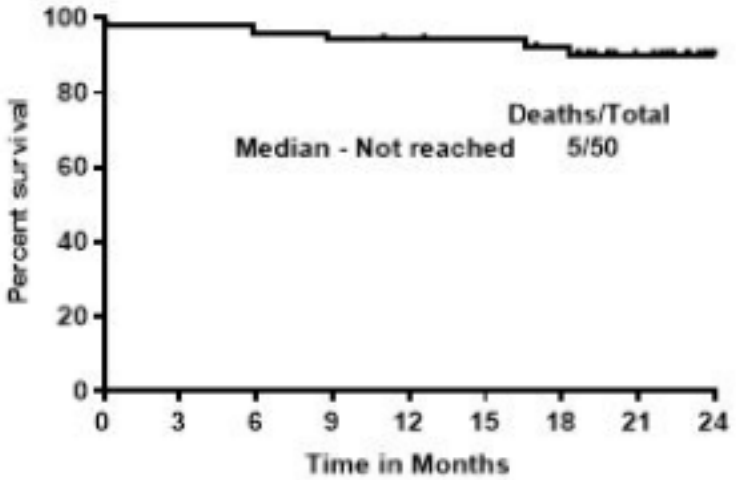
[1]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX
[2]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX
[3]Department of Hematopathology, University of Texas MD Anderson Cancer Center, Houston, TX
[4]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX
[5]Department of Gastroenterology, The University of Texas MD Anderson Cancer Center, Houston
[6]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston
[7]Department of Hematopathology, Division of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX
[8]Department of Lymphoma and Myeloma, MD Anderson Cancer Center, Houston, TX

WINDOW-1 protokolü: IR+ 4xR-HCVAD ile %90 TY
50 hst
4xIR + 8xIRV (5-12. kürlerde) sonrası TY (+) ise 4xIRV (max 12 kür)
Yüksek, orta ve düşük hastalar 4/2/0 R-HCVAD/Mtx-ARA-C ile konsolidasyon
Bütün hastalara IRV ile idame

low risk pts were those with Ki-67 ≤30%, largest tumor mass <3 cm, low MIPI score and no features of high risk disease (Ki-67 ≥50%, mutations in the TP53, NSD2 or in NOTCH genes, complex karyotype or del17p, MYC positive, or largest tumor diameter >5 cm or blastoid/pleomorphic histology or if they remain in PR after 12 cycles of part 1.

- 48 hst IRV (+)
- %92 TY (+)
- 2. kısımı alan hst %92 TY ve %4 KY
- Medyan IRV kür sayısı 8 (2-12)
- Medyan 24 aylık takip sonunda medyan PFS ve OS NR (2 yıllık %92 ve %90)
- Risk kategorilerine göre medyan PFS ve OS NR
- G3-4 toksisite %10 miyelosüpresyon, %10 halsizlik, miyalji ve raş her biri, %3 mukozit, 1 hastada AF


Percent progression free
100
80
60
40
20
0
0
3
6
9
12
15
18
21
24
Time in Months
Progressed/Total
Median - Not reached 4/50


Percent survival
100
80
60
40
20
0
0
3
6
9
12
15
18
21
24
Time in Months
Deaths/Total
Median - Not reached 5/50

Klinik Önemi:

- Kemoterapisiz IRV ile indüksiyon ile genç MCL hst sürekli ve derin yanıt (+)
- Düşük riskli MCL KT ihtiyacı yok ama yakın takip gerekli
- Bütün risk gruplarında etkili

2416 Safety and Efficacy of Acalabrutinib Plus Venetoclax and Rituximab in Patients with Treatment-Naïve (TN) Mantle Cell Lymphoma (MCL)

Michael Wang, MD[1], Tadeusz Robak, MD, PhD[2], Kami J. Maddocks, MD[3], Tycel Phillips, MD[4*], Stephen D. Smith, MD[5], David Gallinson, DO[6*], Roser Calvo[7*], Chuan-Chuan Wun, RPh, PhD[8*], Veerendra Munugalavadla, PhD[8] and Wojciech Jurczak, MD, PhD[9*]

[1]MD Anderson Cancer Center, University of Texas, Houston, TX
[2]Copernicus Memorial Hospital, Medical University of Lodz, Lodz, Poland
[3]The James Comprehensive Cancer Center The Ohio State University, Columbus, OH
[4]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI
[5]University of Washington/Fred Hutchinson Cancer Research Center, Seattle
[6]Summit Medical Group, Florham Park, NJ
[7]AstraZeneca, Gaithersburg, MD
[8]AstraZeneca, South San Francisco, CA
[9]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland

- Devam eden, çok merkezli, açık uçlu faz 1b çalışma
- 21 hst (medyan yaş 65 (51-85)
- Medyan tedavi süresi 16 ay (8-26,2)
- 17 hst (%81) çalışmaya devam ediyor, 1 hst PH ve 3 hst COVID-10 nedeniyle çalışmadan çıkarılmış
- Doz kısıtlayıcı YE yok

ECI Category, % (n) ECI Subcategory	N=21	
	Any Grade	Grade ≥3
Infections	57 (n=12)	29 (n=6)*
Neutropenia	33 (n=7)	24 (n=5)
Hemorrhage	33 (n=7)	0
Major hemorrhage	0	0
Cardiac events	19 (n=4)	0
Atrial fibrillation	0	0
Hypertension	5 (n=1)	5 (n=1)

*Four of the 6 infections were COVID-19 related.

Response	Confirmed by PET/CT Only[b] (N=21)	Confirmed by Lugano with BM Confirmation (N=21)
ORR (CR + PR), % (n) [95% CI[a]]	100 (n=21) [83.9–100]	100 (n=21) [83.9–100]
CR, % (n) [95% CI[a]]	90 (n=19)[b] [69.6–98.8]	38 (n=8) [18.1–61.6]
PR, % (n)	10 (n=2)[b]	62 (n=13)[b]
SD, % (n)	0	0
PD, % (n)	0	0

AVR, acalabrutinib + venetoclax + rituximab; BM, bone marrow; CI, confidence interval; CR, complete response; CT, computed tomography; ORR, overall response rate; PET, positron emission tomography scan; PD, progressive disease; PR, partial response; SD, stable disease.
Note: The best responses displayed in this table are identical to the best responses assessed at the end of cycle 6, with the exception of 2 pts with missing response assessment and PET scans at end of cycle 6; these pts had PR at the end of cycle 3 and stayed as PR at the end of cycles 9 and 12.
[a]95% exact binomial CI.
[b]11 of 13 PR pts had CR by PET (BM biopsy missing to confirm CR).

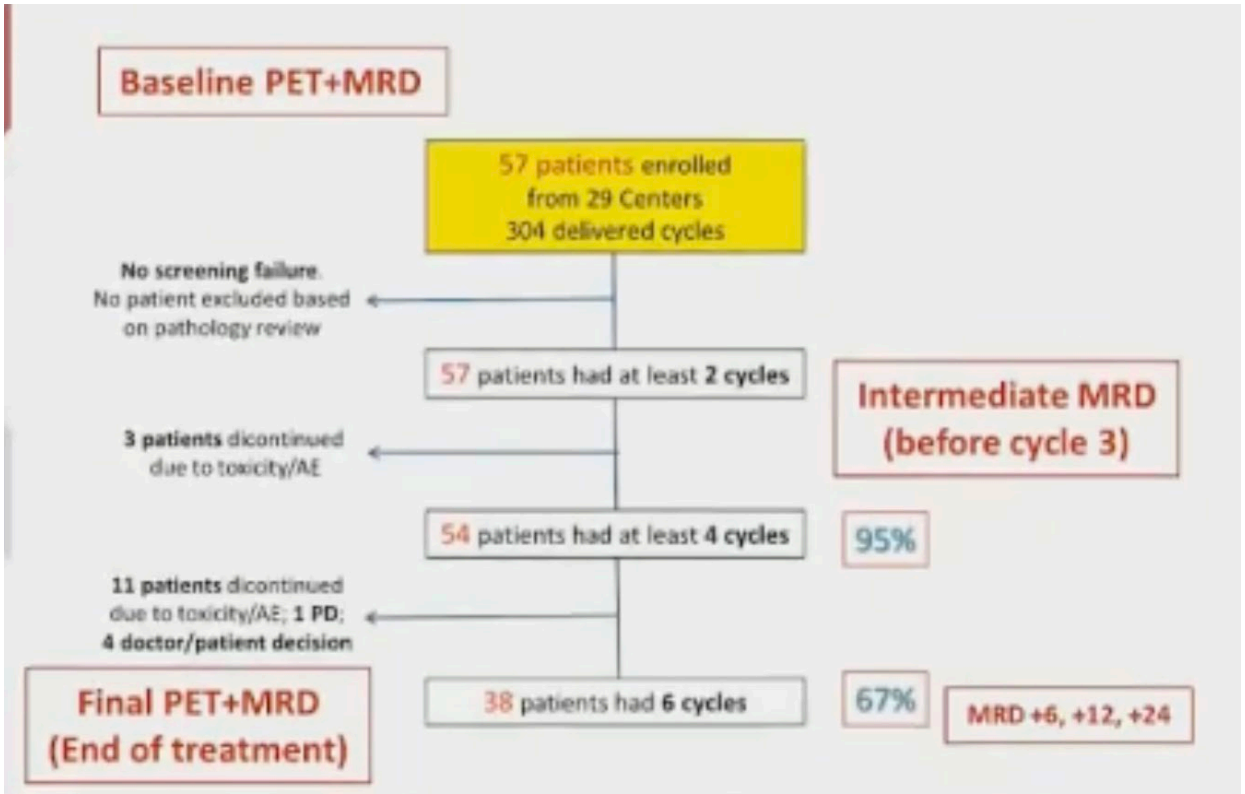
Medyan yanıt süresi 19 ay (%95 CI 71-99)
Medyan PFS ve OS NR
12/16 (%75) hst 6 kür sonunda 10^{-6} MRD(-)

Klinik Önemi:

- AVR ile tedavi edilmemiş MCL hastalarında %100 klinik yanıt, yüksek oranda moleküler yanıt ve güvenli

RITUXIMAB PLUS BENDAMUSTINE AND CYTARABINE (R-BAC) IN ELDERLY PATIENTS WITH NEWLY DIAGNOSED MANTLE CELL LYMPHOMA: LONG TERM FOLLOW-UP AND MRD RESULTS OF A PHASE 2 STUDY FROM THE FONDAZIONE ITALIANA LINFOMI

M.C. Tisi, L. Nassi, C. Patti, M. Spina, S. Ferrero, M. Tani, B. Botto, A.L. Molinari, B. Puccini, E. Cencini, A. Di Rocco, C. Chini, C. Ghiggi, R. Zambello, M. Zanni, R. Sciarra, M. Ferrante, C. Stelitano, A. Re, S. Volpetti, V.R. Zilioli, A. Arcari, F. Merli, C. Visco



2012-2014
Medyan yaş 71 yıl (61-79)
Medyan takip 35 ay (28-52)

R-BAC500

- Tek kollu faz II, çok merkezli çalışma
- Yeni tanı MCL (>65 veya 60-65 OPKHN uygun olmayan)
- İdame tedavi yok
- ARA-C dozu 500 mg/m^2 (800 mg/m^2'den azaltılmış)

Rituximab, bendamustine, and low-dose cytarabine as induction therapy in elderly patients with mantle cell lymphoma: a multicentre, phase 2 trial from Fondazione Italiana Linfomi

Carla Visco, Annalisa Chiappella, Luca Nassi, Gaudenzio Patti, Simone Feresin, Daniela Barbero, Andrea Evangelista, Michela Spina, Annalisa Molinari, Luigi Rigacci, Marsico Toni, Alice Di Rocco, Grazziella Pesaresi, Alberto Fabbri, Renato Zambello, Silvia Finotto, Manuel Gotti, Angelo Al Carello, Flavia Salvi, Stefano A Pileri, Marco Ciofetta, Giovannina Cozzoni, Gianluca Gaidano, Marco Ruggeri, Maurizio Martelli, Umberto Vitolo

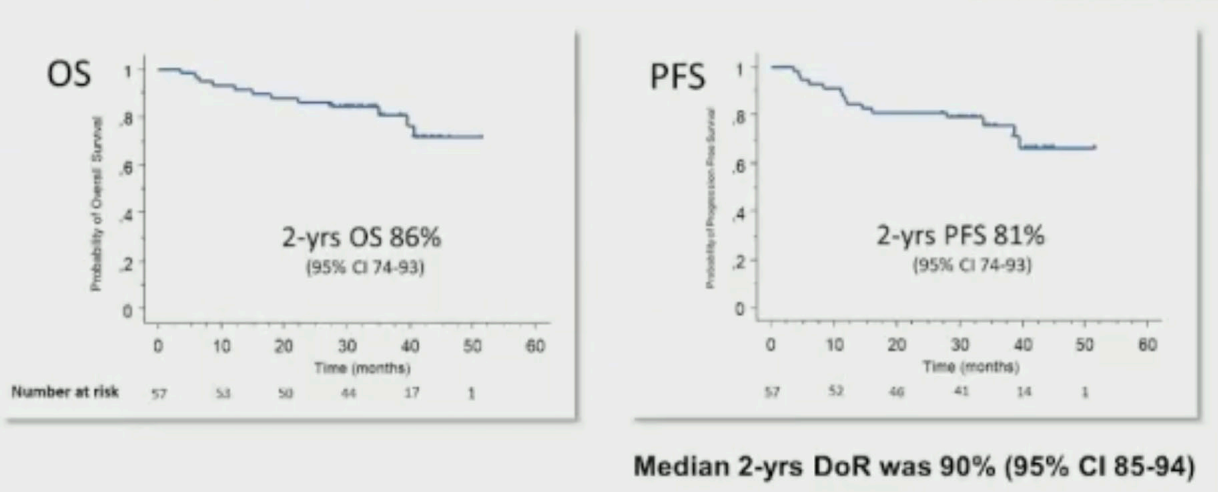
Treatment	Day 1	2	3	4
Rituximab 375 mg/m^2	↓			
Bendamustine 70 mg/m^2		↓	↓	
Ara-C 500 mg/m^2		↓	↓	↓

Visco C, #472, ASH 2016; Lancet Haematol 2017; 4: e15–23

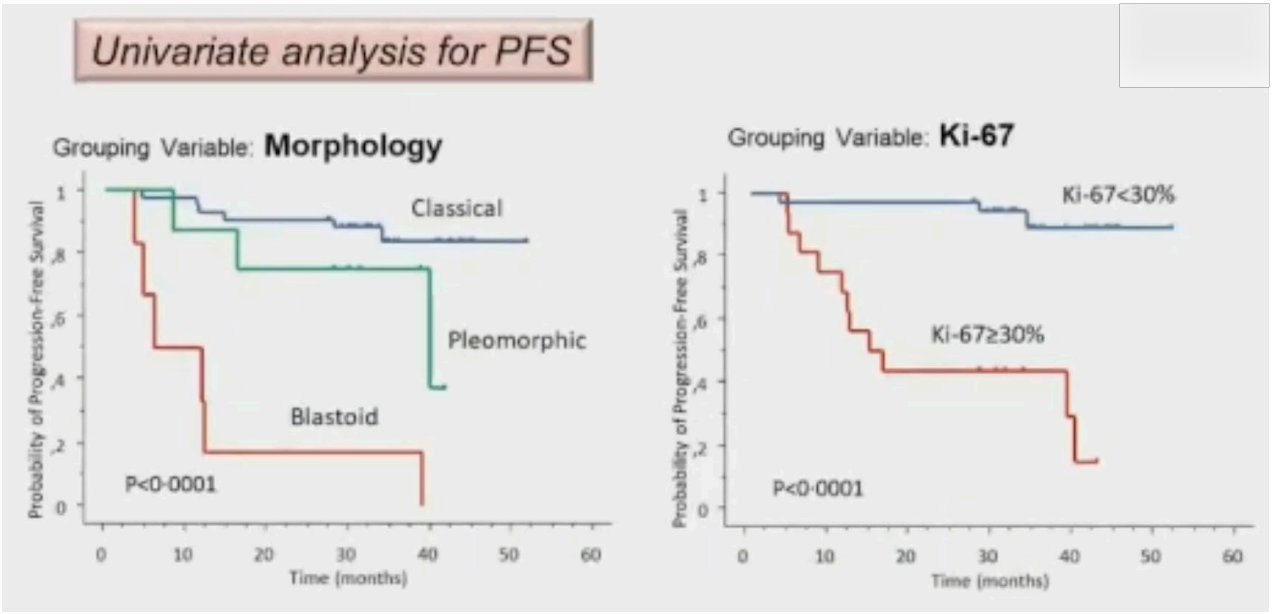
Medyan 35 ay takip sonuçları

End of treatment PET/CT		
	N=57	%
ORR	52	91
CR	52	91
PD	2	4
NA°	3	5

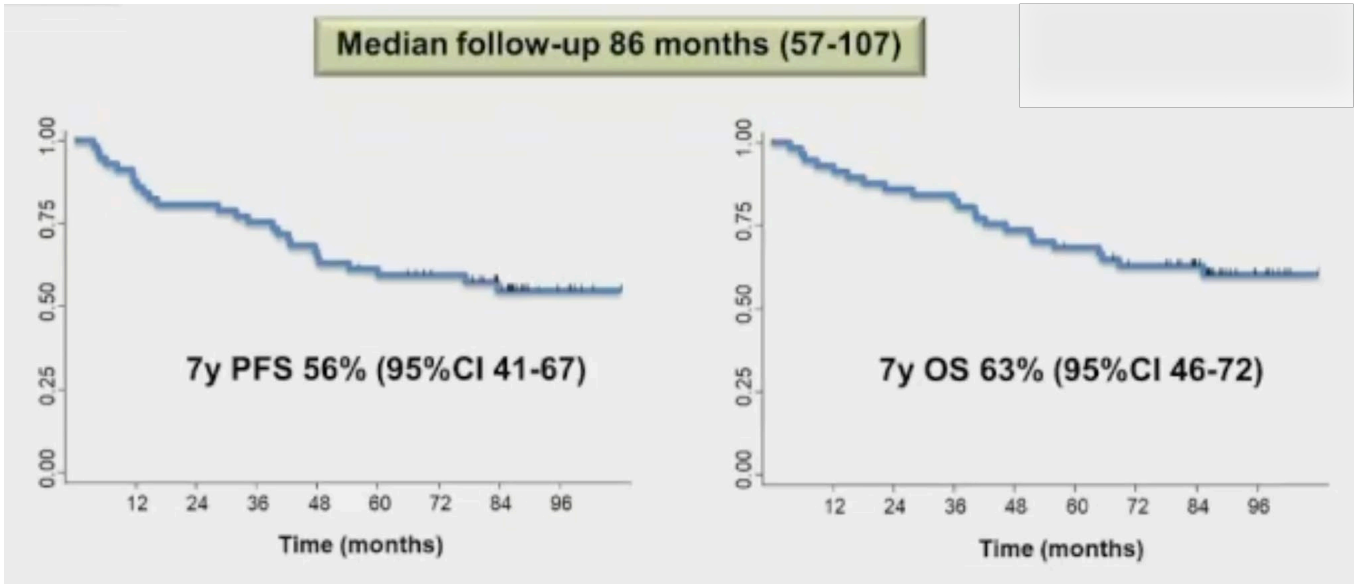
°Three patients were withdrawn for toxicity before cycle 4 and were considered non-responders

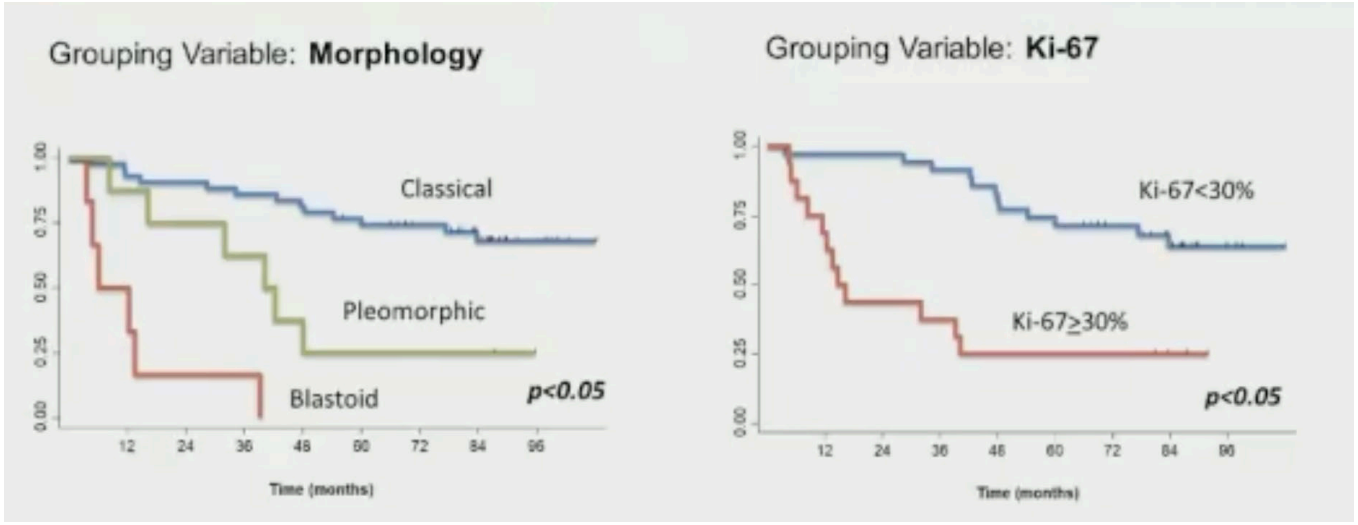


Median 2-yrs DoR was 90% (95% CI 85-94)



Uzun dönem sonuçları: 7 yıl



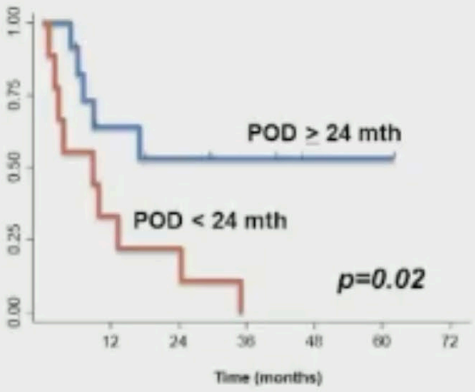


Adverse predictive factors affecting PFS

Multivariate analysis for PFS

Variable	HR	P>|z|	[95% C.I.]
Blastoid	4.5	0.030	1.15-17.62
MIPI	1.9	0.188	0.73- 5.07
Ki-67	3.1	0.027	1.14- 8.5

OS in Early Progression Of Disease (POD-24)



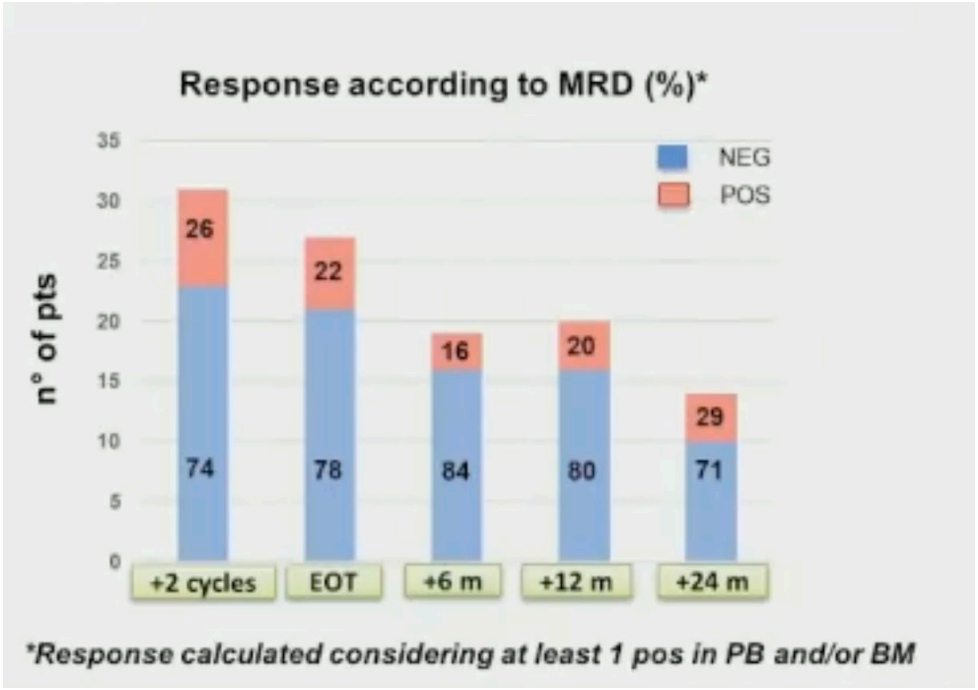
R-BAC sonrası 25 hst nüks

TREATMENT REGIMEN	n of pts
No other treatment	8 (32%)
Ibrutinib monotherapy[1]	6 (24%)
CHOP or CHOP-like[2]	4 (16%)
Various treatment[3]	7 (28%)

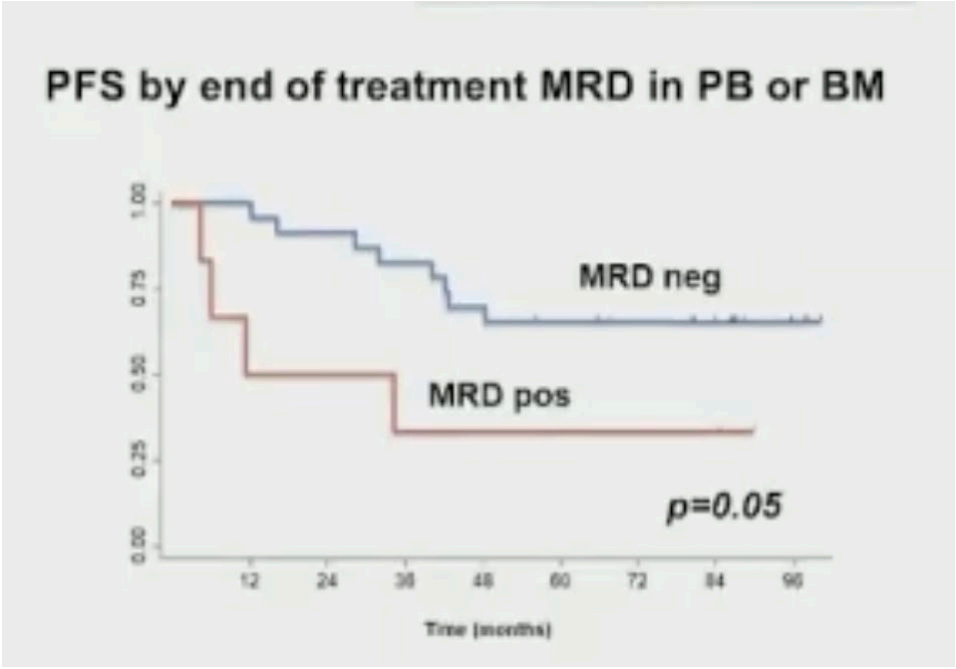
[1]4/6 (67%) responded to Ibrutinib (3 are still in CR)
[2]only PR to CHOP
[3]*R-Benda, HD-MTX, Lenalidomide, RT*

8 hst (%14) ikincil malignite (+)

1 parotid heteroplazisi
1 parotid nodüler hiperplazi
1 prostat kanseri
1 mesane kanseri
1 larinks kanseri
1 tiroid kanseri
1 AC kanseri
1 sekonder AML



*Response calculated considering at least 1 pos in PB and/or BM



Klinik Önemi:

- R-BAC ile uzun dönem takipte de süreğen bir etkinlik
- Yaşlı hastalarda hematolojik toksisiteyi arttırmamak için doz azaltımı gerekli
- Yüksek doz Ki-67 ve blastoid varyant ile daha kötü sonuçlar, devam eden V-RBAC çalışma sonucunda konsolidasyon/idame gerekliliği ???
- R-BAC sonrası MRD (+) ile yüksek nüks riski var, bu hastalar için konsolidasyon tedavisi gerekli olabilir
- RBAC500'ün yaşlı hastalarda kullanımını desteklemekte

2427 Rituximab, Bendamustine and Cytarabine Followed By Venetoclax (V-RBAC) in High-Risk Elderly Patients with Mantle Cell Lymphoma

Carlo Visco, MD[1], Valentina Tabanelli[2*], Claudia Peracchio[3*], Andrea Evangelista[4*], Maria Chiara Tisi, MD[5*], Anna Merli[6*], Costanza Fraenza, MD[7*], Stefano Fiori, MD[2*], Alessandro Re, MD[8*], Claudia Castellino[9*], Vittorio Ruggero Zilioli, MD[10*], Francesco Piazza[11], Paolo Corradini, MD[12], Stefan Hohaus, MD[13*], Gerardo Musuraca[14*], Valeria Ferla[15*], Benedetta Puccini, MD[16*], Federica Cavallo, MD, PhD[17*], Filippo Ballerini[18*], Roberta Sciarra, MD[19*], Alice Di Rocco[20*], Annalisa Arcari[21*], Carola Boccomini, MD[22*], Francesco Merli, MD[23*], Guido Gini, MD[24], Monica Tani, MD[25*], Riccardo Bruna[26*], Vincenzo Pavone[27*], Andrés J M Ferreri, MD[28], Armando Santoro[29*], Caterina Patti[30*], Giacomo Loseto, MD[31*], Marco Ladetto, MD[32], Michele Merli, MD[33*], Michele Spina, MD[34], Pier Luigi Zinzani, MD, PhD[35], Pietro Maria Stefani[36*], Sara Veronica Usai[37*], Caterina Stelitano, MD[38*], Stefano Volpetti[39*], Stefano A Pileri[2] and Monica Balzarotti, MD[40*]*

Factor	Level	Low Risk	High Risk	p-value
N		79	48	
Sex	Male	60 (76%)	35 (73%)	0.70
	Female	19 (24%)	13 (27%)	
Age on Enrollment calc, median (IQR)		72 (68, 74)	73 (69, 75.5)	0.25
Variant type	Classic / Pleomorphic	79 (100%)	37 (77%)	
	Blastoid	0 (0%)	11 (23%)	
P53 mutation	No	79 (100%)	20 (43%)	
	Yes	0 (0%)	27 (57%)	
P53 deletion	No	79 (100%)	31 (66%)	
	Yes	0 (0%)	16 (34%)	
Proliferation index Ki 67 ≥ 30%	No	79 (100%)	18 (38%)	
	Yes	0 (0%)	30 (63%)	
Systemic B symptoms	Absent	64 (81%)	39 (81%)	0.97
	Present	15 (19%)	9 (19%)	
Ann Arbor Stage	II	3 (4%)	2 (4%)	0.76
	III	6 (8%)	2 (4%)	
	IV	69 (88%)	42 (91%)	
ECOG Performance Status	0	58 (73%)	33 (69%)	0.33
	1	19 (24%)	11 (23%)	
	2	2 (3%)	4 (8%)	
Bone marrow involvement	Positive	57 (72%)	35 (73%)	0.52
	Negative	17 (22%)	12 (25%)	
	Not done	5 (6%)	1 (2%)	
LDH abnormal	No	59 (77%)	27 (56%)	**0.017**
	Yes	18 (23%)	21 (44%)	
MIPI high	No	53 (67%)	23 (48%)	0,09
	Yes	26 (33%)	25 (52%)	
SUV max of lesion , median (IQR)		8.8 (7, 13)	10.9 (8.8, 15.6)	**0.032**
Type of lesion	Nodal	34 (76%)	13 (62%)	0.25
	Extranodal	11 (24%)	8 (38%)	

Blastoid
Ki67 expr >%30
TP53 mut/TP53 del

} Yüksek risk %40

4xR-BAC
4 ay konsolidasyon Vntx 800 mg/gün
20 ay idame Vntx 400 mg/gün

Rituximab-Lenalidomide(R2) maintenance is superior to rituximab maintenance after first Line Immunochemotherapy in Mantle Cell Lymphoma: results of the MCL R2 Elderly clinical trial

V. Ribrag[1], V. Safar[2], Hanneke C. Kluin-Nelemans[3], L.Oberic[4], P.Feugier[5], O.Casasnovas[6], C. Thieblemont[7], N.Daguindau[8], G. Damaj [9], W. Klapper[10], E. Hoster[11], L. Fischer von Weikersthal[12], M.Hänel [13], M. André [14], M. Gomes Da Silva [15], F. Carnicero [16], A. Marin-Niebla [17], M. Taszner [18], J. Walewski [19], R. Boersma [20], I. Houtenbos [21], MH. Delfau-Larue [22], S. Le Gouill[23], M. Dreyling[11]

on behalf of the European MCL Network

1 Institut Gustave Roussy, 2 CHLS Lyon-Sud, 3 University Medical Center Groningen, 4 IUCT Oncopole, 5 CHU Brabois, 6 CHU Dijon, 7 Hopital Saint Louis, 8 CHU Annecy, 9 CHU Caen, 10 University Kiel, 11LMU University Munich,12 Klinikum St Marien Amberg, 13 Klinicum Chemnitz, 14 CHU Namur St Godine, 15 Institut de Oncologia Lisboa, 16 San Pedro de Alcantara, 17 VHIO, 18 Gdansk, 19 Varszawa, 20 Breda, 21 Hoofddorp, 22 CHU Henri Mondor, 23 Service d'hématologie clinique du CHU de Nantes, INSERM CRCINA Nantes-Angers, NeXT Université de Nantes, Nantes, France.

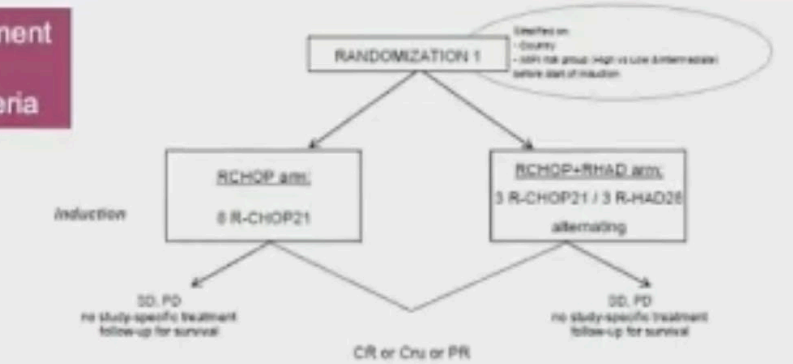
MCL-R2 Yaşlı: Dahil edilme kriterleri

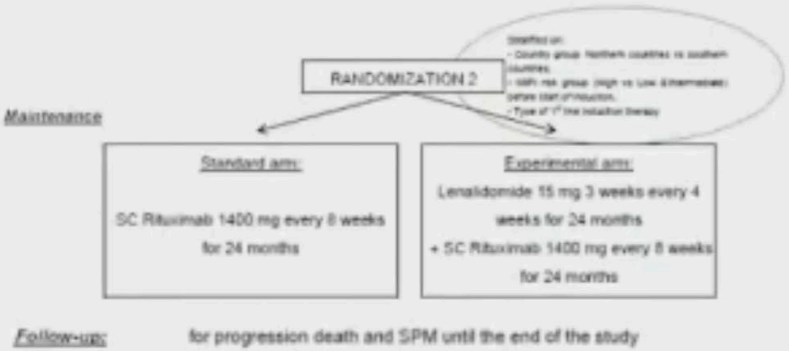
- MCL: siklin D1 overekspresyonu veya (11;14)(q13;q32)
- >60 y ve nakil adayı olmamak
- Ann Arbor evre II-IV
- Tedavi edilmemiş olmak
- ECOG PS <2

MCL-R2 Elderly: study design

MCL ELDERLY R²

Response assessment according to Cheson 1999 criteria

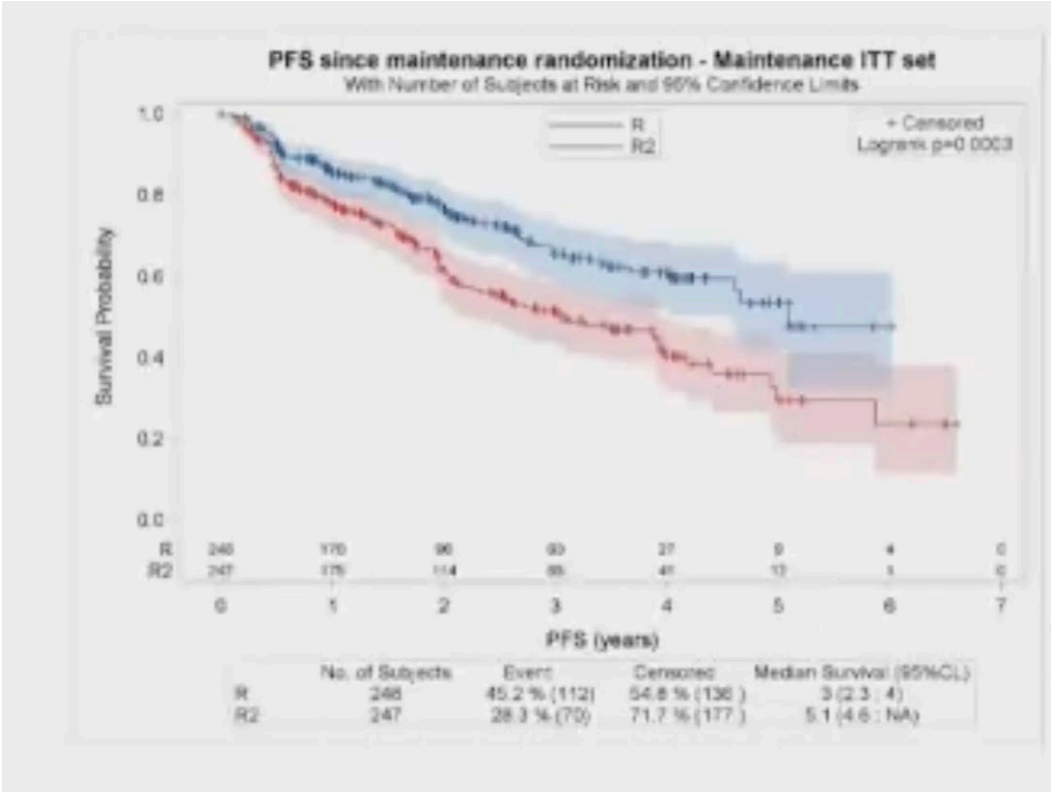




Follow-up: for progression death and SPM until the end of the study

	Maintenance actual arm				Maintenance mITT set	
	R		R2			
	N=227		N=220		N=447	
Age (years)						
Median	71.0		71.0		71.0	
Sex						
Male	161	(70.9%)	154	(70.0%)	315	(70.5%)
Ann arbor stage						
III	12	(5.3%)	13	(5.9%)	25	(5.6%)
IV	201	(88.5%)	199	(90.5%)	400	(89.5%)
LDH > upper limit	89	(39.6%)	79	(36.4%)	168	(38.0%)
Complete response (CR/CRu)	110	(49.1%)	93	(42.9%)	203	(46.0%)
Overall response	223	(99.6%)	216	(99.5%)	439	(99.5%)

	R N=250	R2 N=238
Blood and Lymphatic System Disorders	68 (117 events)	140 (471 events)
Neutropenia > grade 2	47 (64 events)	119 (315 events)
Anemia > grade 2	1 (1 event)	7 (7 events)
Infections and Infestations	6 (7 events)	26 (33 events)
SPM	26 (32 events)	32 (59 events)



Klinik Önemi:

- Lenalidomid eklenmesi ile PFS'de uzama (RR: 0,579; 95% CI: 0,429-0,781; p=0.003)
- İndüksiyon randomizasyonundan itibaren OS farkı yok (medyan takip 32,4 ay)
- İdame randomizasyonundan itibaren OS farkı yok (medyan 25,2 ay takip)
- R^2 kolunda daha fazla hematolojik YE
- R^2 kolunda 1 toksik ölüm

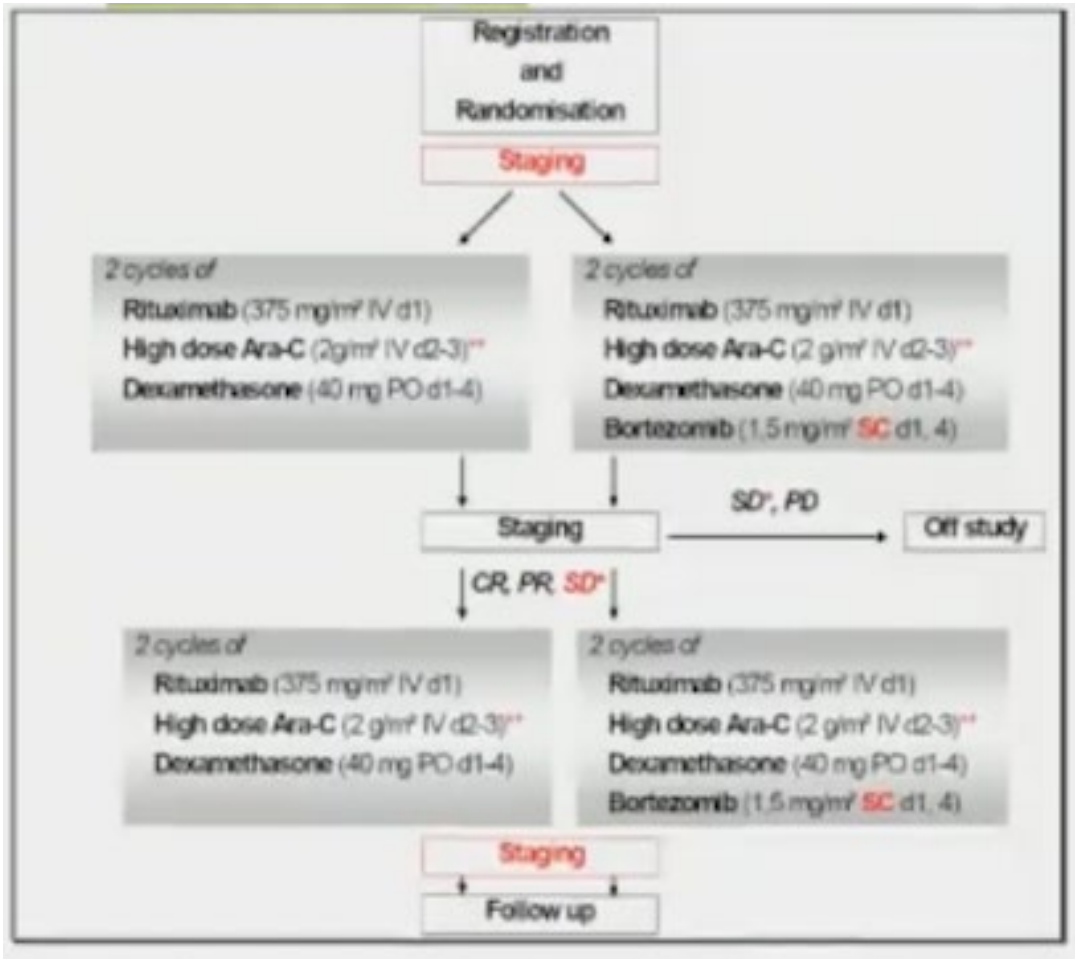
R-high dose Cytarabine/Dexamethasone (R-HAD) plus Bortezomib is superior to R-HAD only in relapsed mantle cell lymphoma

A randomized phase 3 trial of the European MCL Network

M. Dreyling[1], E. Hoster[2], K. Bouabdallah [3], J. Dürig[4], Ch. Schmidt[1], S. Stilgenbauer[5], S. Bologna [6], C. W. Scholz[7], W. Klapper[8], V. Ribrag[9]

on behalf of the European MCL Network

[1] LMU Hospital, [2] IBE, LMU, [3] Centre Francois Magendie, [4] University Hospital Essen, [5] University Hospital Ulm, [6] CHU Brabois, [7] Vivantes Hospital am Urban, [8] Institute of Pathology, University Kiel, [9] Institut Gustave Roussy

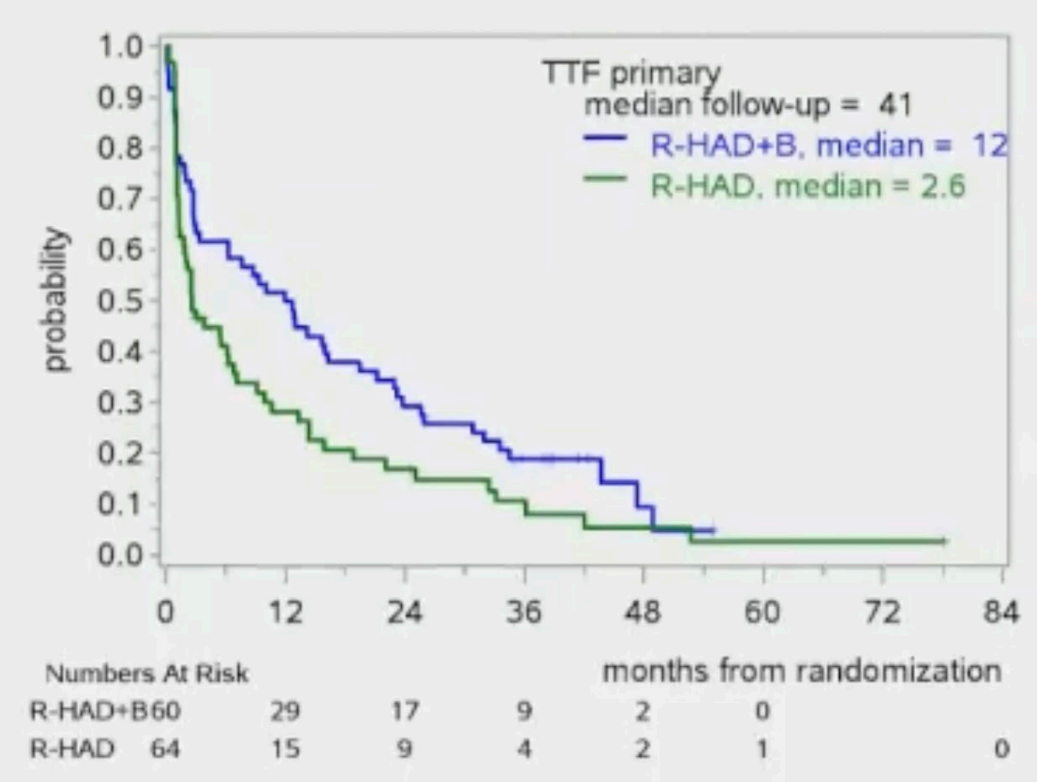


Faz III çalışma
1-3 sıra tedavi almış hst

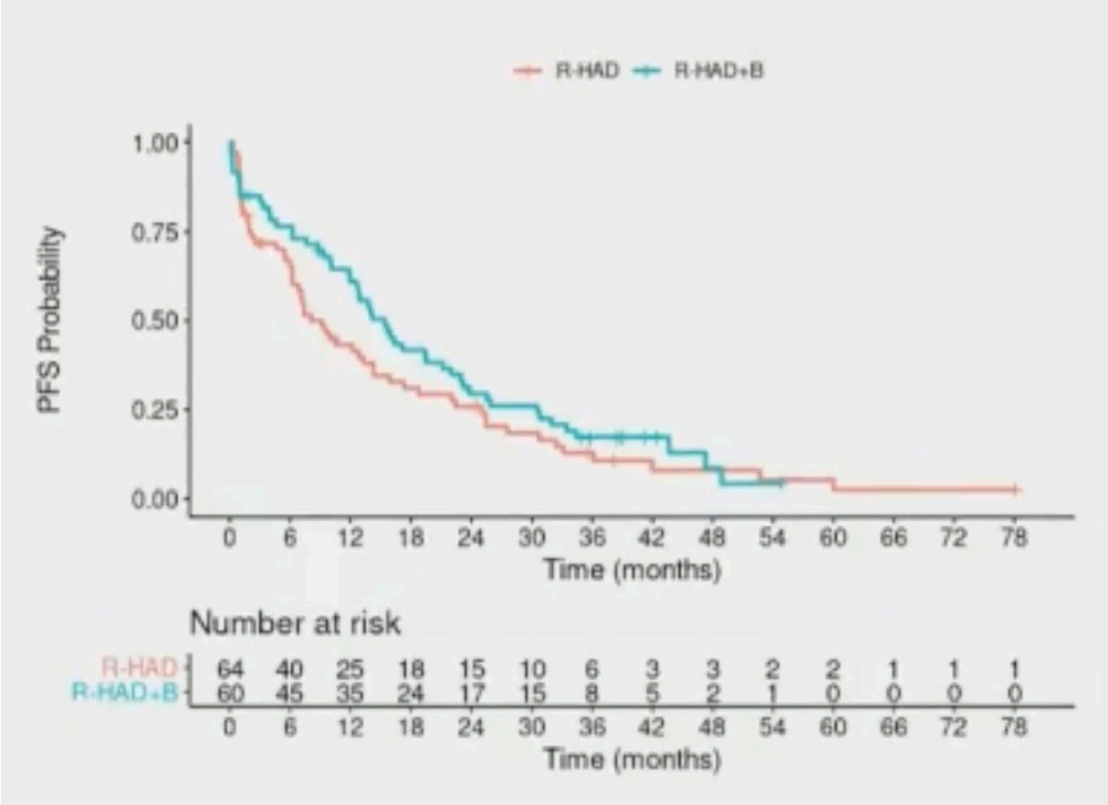
Variable	Value	R-HAD (n=64)	R-HAD+B (n=63)	P value
Age	Median (min-max)	71 (41-85)	69 (41-85)	0.49
Sex	Male	80%	71%	0.31
Ann Arbor Stage	I	6%	8%	0.54
	II	8%	13%	
	III	8%	14%	
	IV	77%	65%	
ECOG Performance Status	0	45%	38%	0.18
	1	45%	59%	
	2	9%	3%	
LDH ratio	Median (min-max)	0.95 (0.51-5.79)	0.92 (0.57-6.74)	0.91
MIPI Risk Group (at trial entry)	Low	17%	25%	0.35
	Intermediate	34%	38%	
	High	48%	37%	
Years from 1. diagnosis	Median (min-max)	3.7 (0-14)	3.9 (0-11)	0.31
No. of previous lines	1	62%	79%	0.13
	2	27%	14%	
	3	11%	6%	
Previous high-dose cytarabine	Yes	34%	38%	0.71
Previous ASCT	Yes	38%	41%	0.72
Previous Remission	Yes	95%	97%	>0.99
Primary salvage treatment	Yes	2%	3%	0.62

	R-HAD (N=64)		R-HAD+B (N=60)		P value
Complete remission (CR)	8	12%	17	28%	0.043
Complete remission (CR+CRu)	12	19%	25	42%	0.0062
Overall response (CR, CRu, PR)	29	45%	38	63%	0.049

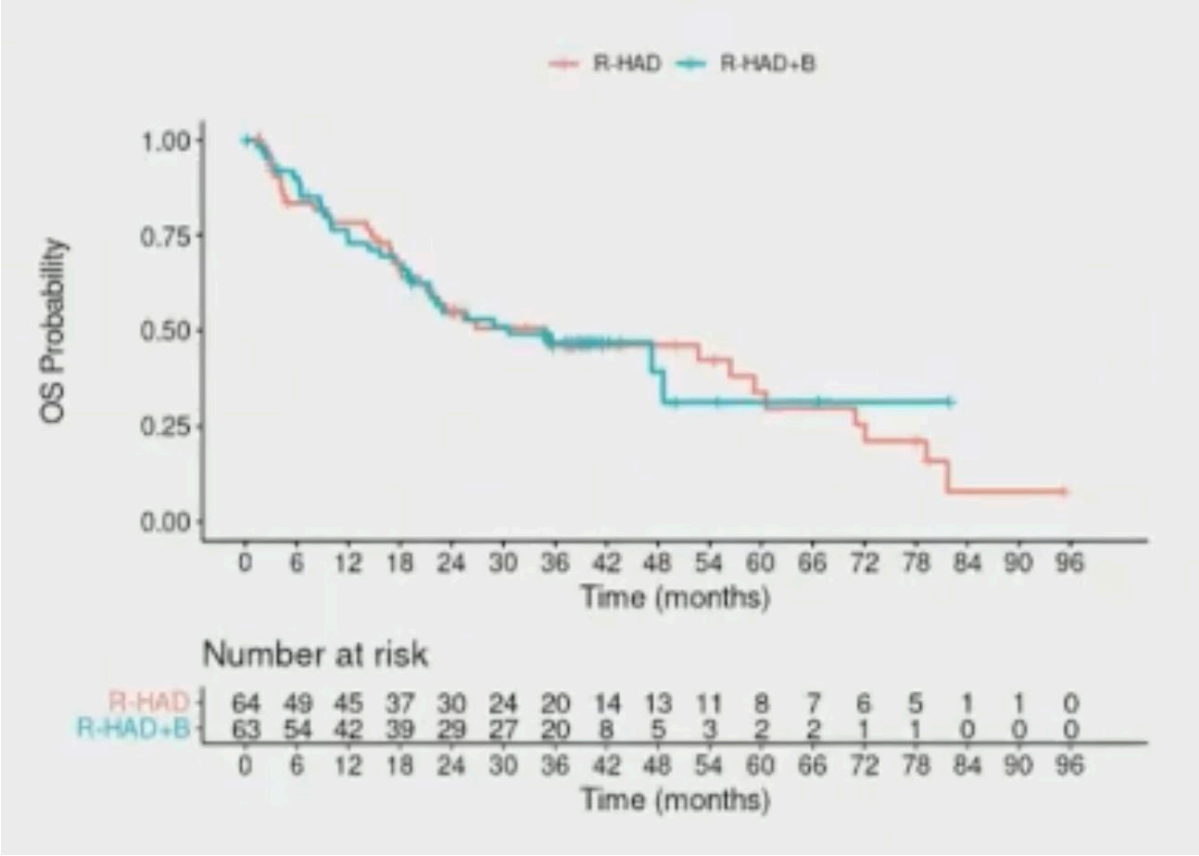
	R-HAD	R-HAD+B	Total
SAEs Overall	50	34	84
Infections	9	9	18
Hematology	11	3	14
Fever	3	6	9
Pneumonia	6	1	7
GI bleeding	5	0	5
Thrombosis/Embolism	2	1	3
Syncope	2	1	3
Nausea	0	2	2
Lung disorder / Respiratory distress	2	0	2
Cardiac failure	1	2	3
Infusion related reaction	1	0	1
Splenic rupture	1	0	1
Intestine perforation	0	1	1
Small cell lung cancer	0	1	1
Other	7	7	14



Medyan takip süresi 41,3 ay
Medyan TTF: R-HAD 2,6 ay ve R-HAD+B 12 ay



Medyan PFS: R-HAD 9,2 ay ve R-HAD+B 15,4 ay (p=0,2)



Medyan OS: R-HAD 35 ay ve R-HAD+B 30,7 ay (p=0,93)

Klinik Önemi:

- KT tabanlı rejimler nüks MCL'de etkili
- R-HAD'a bortezomib eklenmesi R/R MCL'de TTF süresini uzatmakta (HR yaklaşık 0,7)
- Benzer remisyon süresinde yüksek yanıt oranları (+)
- Uzun dönem etkileri olarak sağ kalım veya toksisite açısından fark görülmedi

Efficacy and Safety of Parsaclisib in Patients With Relapsed or Refractory Mantle Cell Lymphoma Not Previously Treated With a BTK Inhibitor: Primary Analysis From a Phase 2 Study (CITADEL-205)

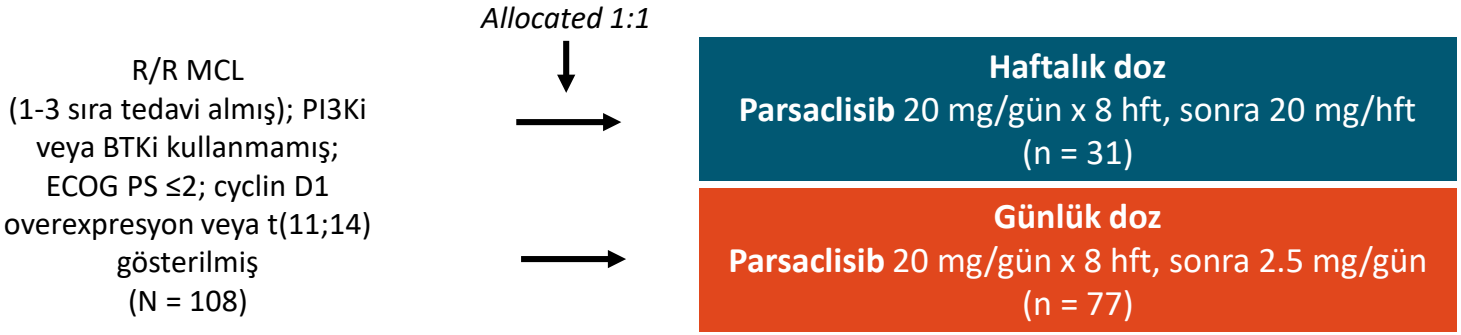
Amitkumar Mehta,[1] Marek Trněný,[2] Jan Walewski,[3] Vincent Ribrag,[4] Caroline Dartigeas,[5] Jacob Haaber Christensen,[6] Fabrizio Pane,[7] Guillermo Rodriguez,[8] Michal Taszner,[9] Parameswaran Venugopal,[10] Vittorio Ruggero Zilioli,[11] Fred Zheng,[12] Douglas J. DeMarini,[12] Wei Jiang,[12] Pier Luigi Zinzani[13]

[1]UAB School of Medicine, Birmingham, AL, USA; [2]Charles University, General Hospital, Prague, Czech Republic; [3]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [4]Institut Gustave Roussy, Villejuif, France; [5]CHRU Tours, Tours, France; [6]University of Southern Denmark, Odense, Denmark; [7]University of Naples Federico II, Naples, Italy; [8]Hospital Universitario Virgen del Rocio, Seville, Spain; [9]Medical University of Gdansk, Gdansk, Poland; [10]Rush University, Chicago, IL, USA; [11]ASST Grande, Ospedale Metropolitano Niguarda, Milan, Italy; [12]Incyte Corporation, Wilmington, DE, USA; [13]Institute of Hematology "Seràgnoli", University of Bologna, Bologna, Italy

Presented at the 63rd ASH Annual Meeting & Exposition • Atlanta, GA, USA • December 11–14, 2021 (Abstract #382)

CITADEL-205: Kohort 2 Çalışma Şeması

- Açık uçlu, Faz II çalışma BTKi kullanmamış R/R MCL (hasta alımı sonlanımı: 15 Ocak 2021)



- **Birincil sonlanım noktası:** ORR
- **İkincil sonlanım noktası:** CRR, DoR, PFS, OS, hedef lezyonda bazale göre en iyi oranda küçülme, güvenlik ve tolerabilite

Mehta. ASH 2021. Abstr 382. NCT03235544.

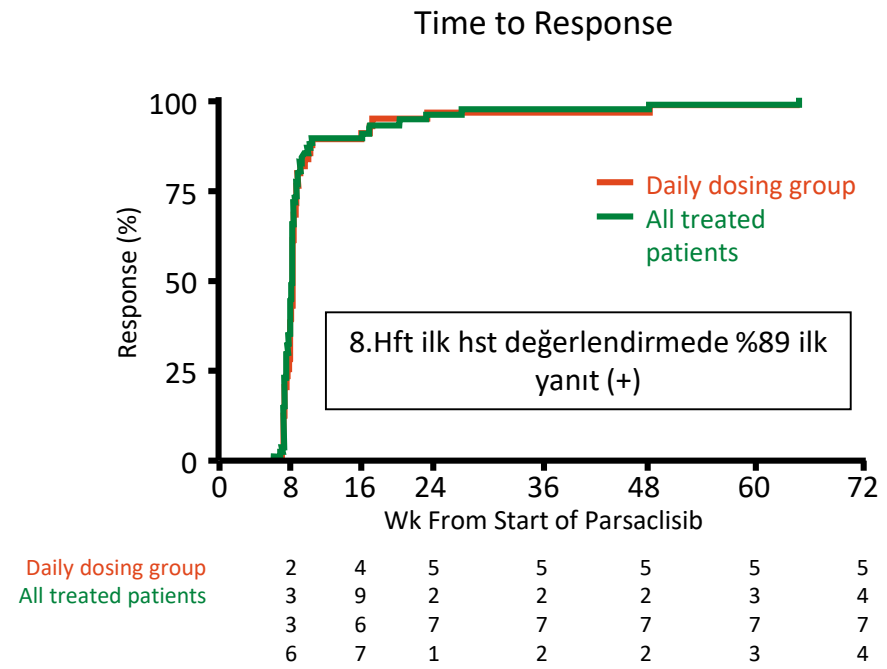
CITADEL-205: Hasta düzeni

n (%)	Bütün hastalar (N = 108)	Günlük doz (n = 77)
İlacı bırakma, n (%)	78 (72)	56 (73)
▪ PH	49 (45)	30 (39)
▪ Yan etki	25 (23)	23 (30)
▪ Kesilme/Dr kararı	3 (3)	2 (3)
▪ Ölüm	1 (1)	1 (1)
Parsaclisib devam eden, n (%)	30 (28)	21 (27)
Tedavi medyan süresi, ay (aralık)	8.3 (0.1-30.0)	7.0 (1.7-27.4)
Takip medyan süresi, ay (aralık)	22.9 (11.6-35.9)	18.2 (11.6-35.9)

Mehta. ASH 2021. Abstr 382.

CITADEL-205: ORR (Birincil sonlanım noktası)

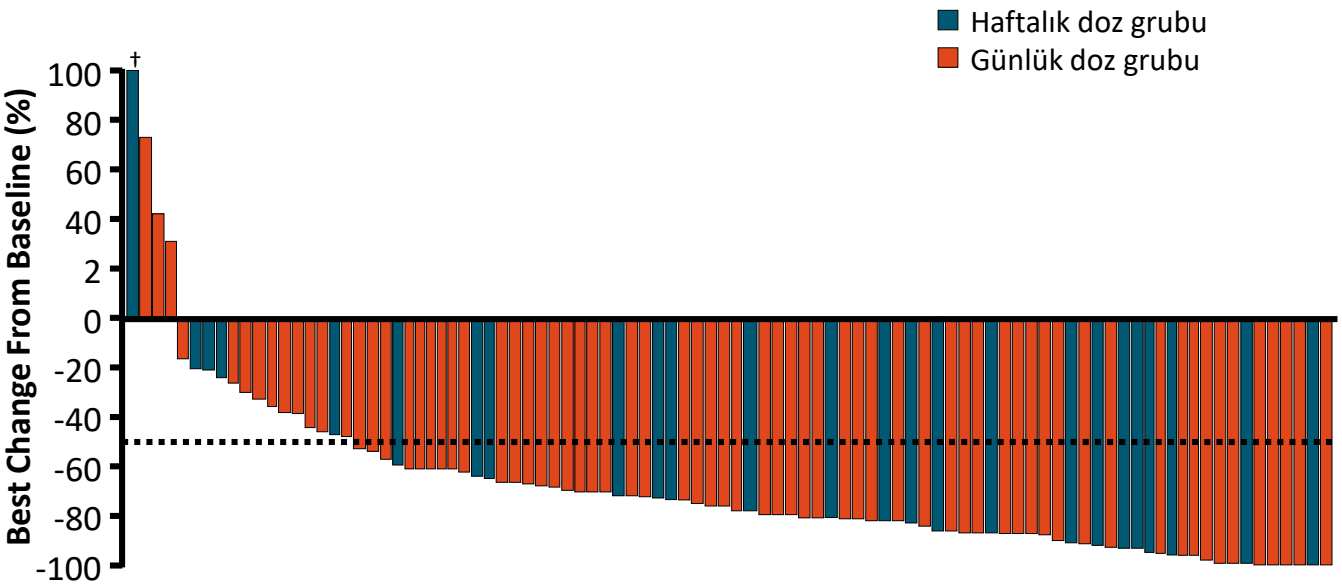
	Bütün hastalar (N = 108)	Günlük doz (n = 77)
ORR /bağımsız değerlendirme komitesi, % (95% CI)	68.5 (58.9-77.1)	70.1 (58.6-80.0)
▪ TY, %	18	16
▪ KY, %	51	55
▪ SH, %	19	21
ORR/araştırmacı, %	79.6	81.8



Mehta. ASH 2021. Abstr 382. Reproduced with permission.

CITADEL-205: Change in Size of Target Lesion From Baseline by IRC

- Değerlendirilebilen hastaların %96'sında hedef lezyonlarda küçülme
  - Hedef lezyonlarda küçülme olan hastaların %84'ünde (76/90) lezyonlarda >50% küçülme



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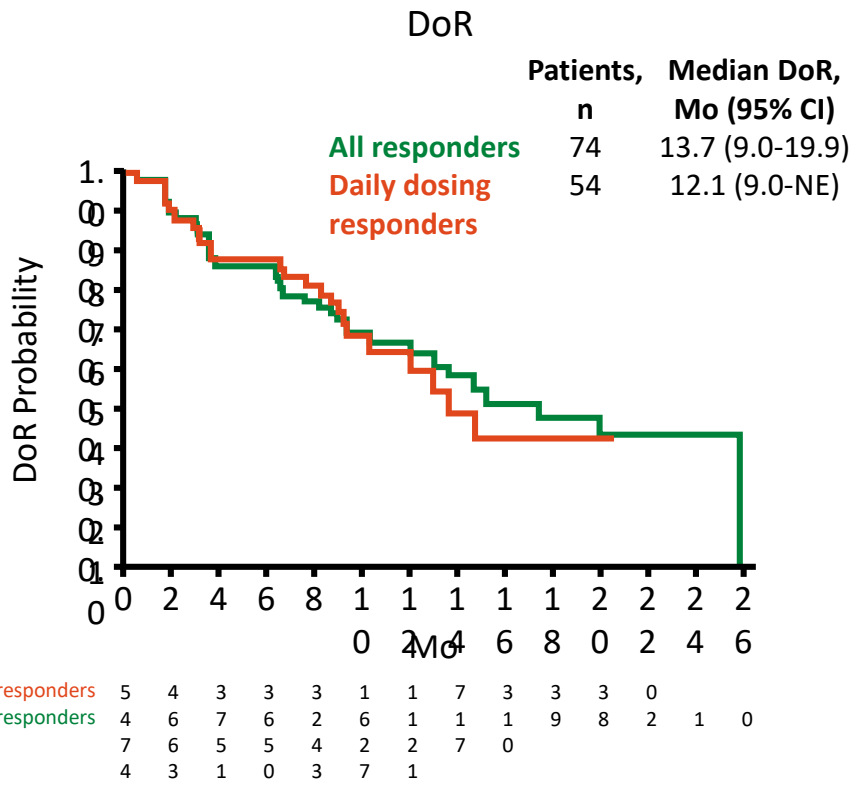
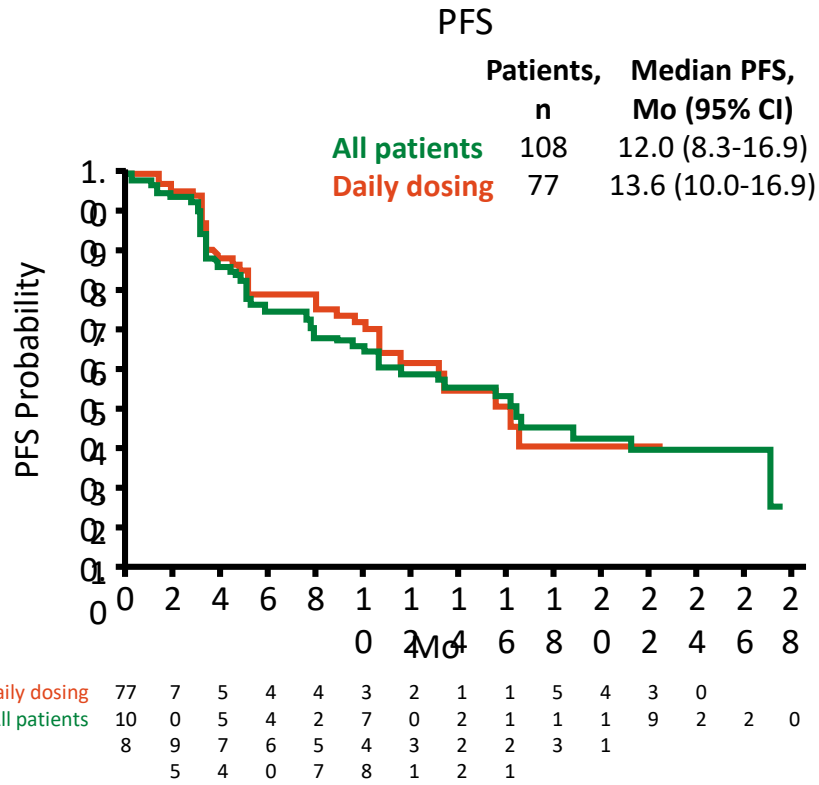
CITADEL-205: Bağımsız değerlendirme komitesine göre DoR ve PFS





Mehta. ASH 2021. Abstr 382.

CITADEL: Yan Etki

- 1 ölüm: lökositoz, AML ve ABY olan bir hasta
- İlaca ara vermeyi gerektiren YE: diare %14, nötropeni %9
- Doz azaltmayı gerektiren YE: raş %3
- İlacı kesmeyi gerektiren YE: diare %16, kolit %6,5

Klinik Önemi:

- CITADEL-205, parsaclisib, BTKi naïve R/R MCL hastalarında etkili bir tedavi
- Önerilen günlük doz grubunda:

➢ ORR: %70,1

➢ medyan yanıt süresi: 12,1 ay

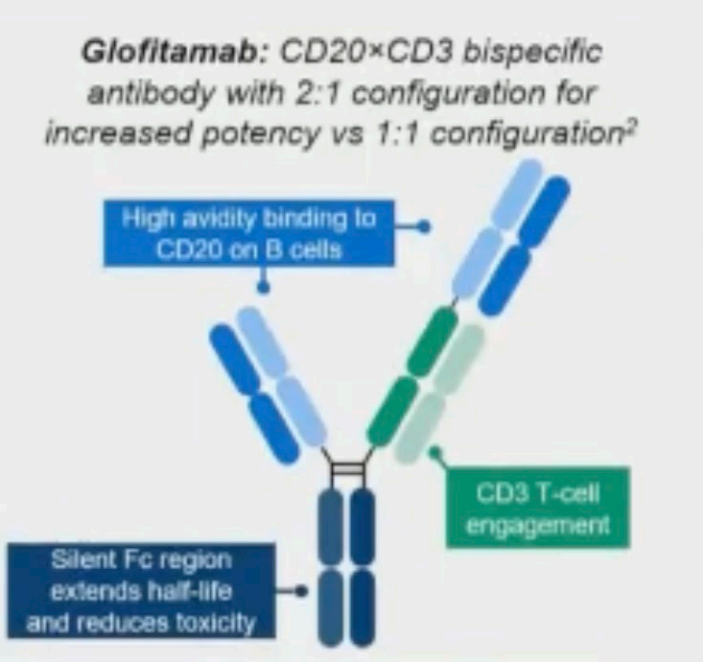
➢ medyan PFS: 13,6 ay

- Genellikle iyi tolere edilen ve kabul edilebilir güvenlik profili olan

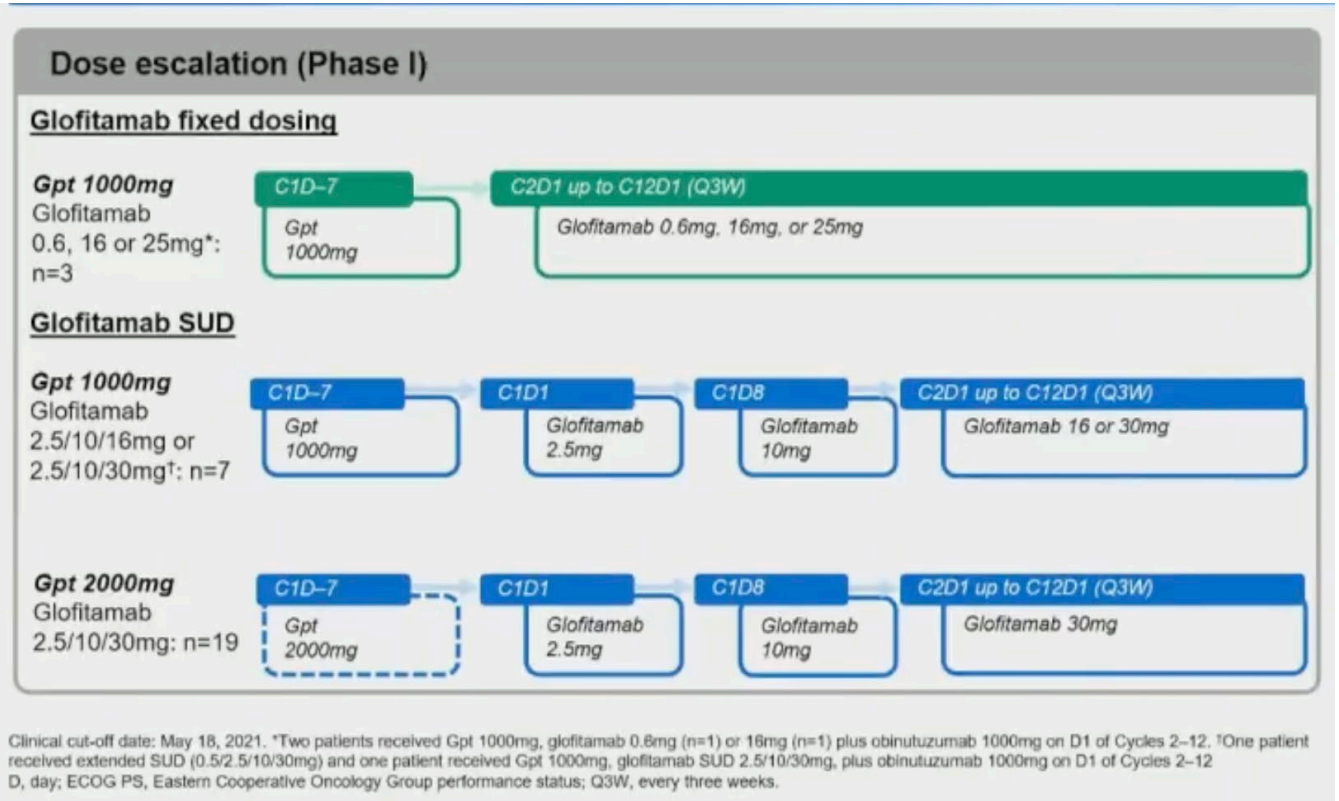
Glofitamab Step-Up Dosing Induces High Response Rates in Pts With R/R MCL, Most of Whom Had Failed Prior BTKi Therapy

Tycel Phillips,[1] Michael Dickinson,[2] Franck Morschhauser,[3] Emmanuel Bachy,[4] Michael Crump,[5] Marek Trněný,[6] Nancy Bartlett,[7] Jan Zaucha,[8] Kathryn Humphrey,[9] David Perez-Callejo,[10] Linda Lundberg,[10] James Relf,[9] Audrey Filezac de L'Etang,[10] David Carlile,[9] Emma Clark,[9] Carmelo Carlo-Stella[11]

[1]University of Michigan Medical School, Ann Arbor, MI, USA; [2]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Australia; [3]CHU Lille, Service des Maladies du Sang, Lille, France; [4]Hospices Civils de Lyon and Université Claude Bernard, Pierre-Bénite, France; [5]Princess Margaret Hospital, Toronto, ON, Canada; [6]1st Faculty of Medicine, Charles University, General Hospital, Prague, Czech Republic; [7]Washington University, Siteman Cancer Center St. Louis, MO, USA; [8]Medical University of Gdańsk, Gdańsk, Poland; [9]Roche Products Ltd, Welwyn Garden City, United Kingdom; [10]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [11]Humanitas University and Humanitas Research Hospital, Milan, Italy.

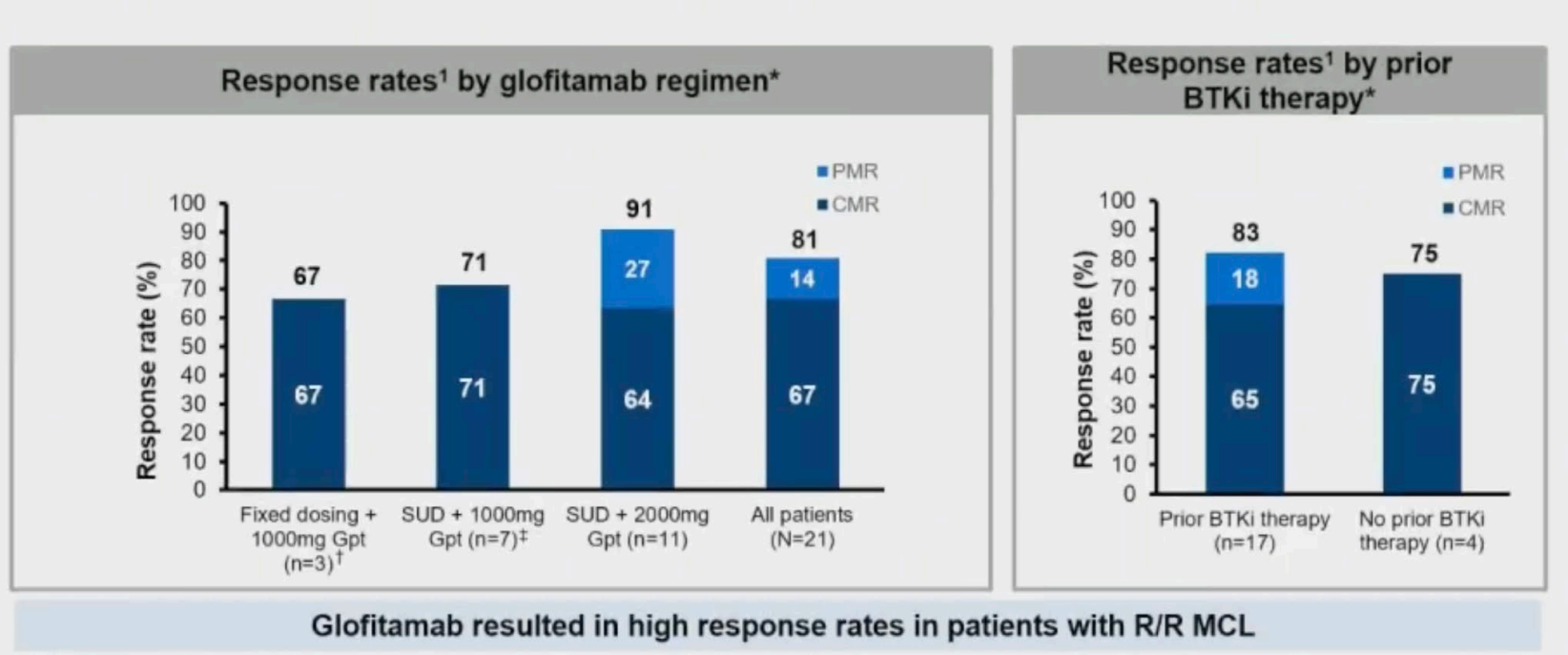


Tedavi Şeması

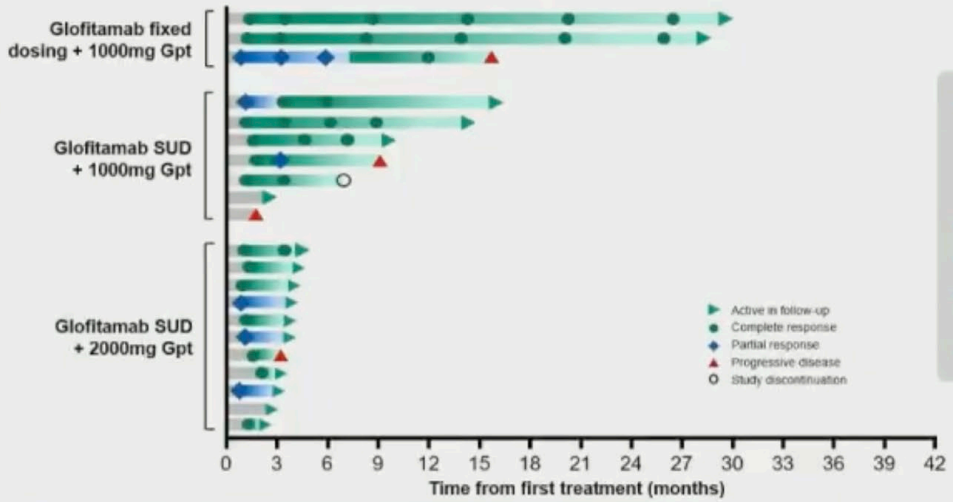


>1 sıra tedavi alan hst

Tedavi Yanıtları



Duration of response in efficacy-evaluable patients*



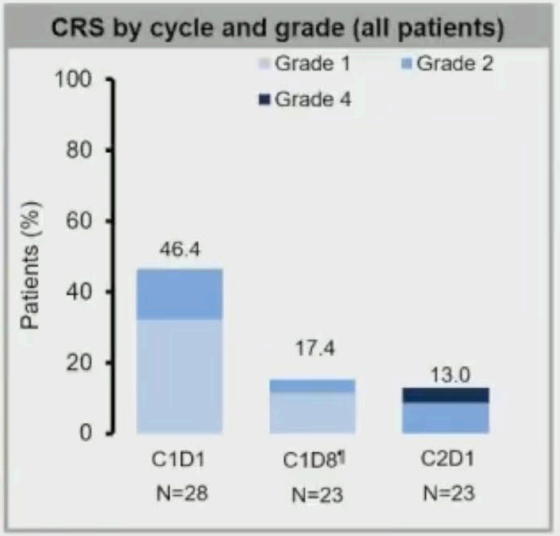
- Median follow-up (months):
  - *Glofitamab fixed dosing + 1000mg Gpt:* ***25.9 months***
  - *Glofitamab SUD + 1000mg Gpt:* ***7.3 months***
  - *Glofitamab SUD + 2000mg Gpt:* ***1.3 months***
  - *All patients:* ***1.4 months***
- Median DOCR follow-up: 2.4 months (range, 0.0–25.0)
- Median DOR follow-up: 2.2 months (range, 0.0–25.0)
- At data cut-off, 85.7% (12/14) of patients with a CR remained in remission
- Median DOR and median DOCR not reached

Most patients had ongoing responses at the time of the data cut-off

Adverse events, n (%)	Glofitamab fixed dosing + 1000mg Gpt (n=3)	Glofitamab SUD + 1000mg Gpt (n=7)	Glofitamab SUD + 2000mg Gpt (n=19)	All patients (N=29)
Any grade AE	3 (100)	7 (100)	16 (84.2)	26 (89.7)
Glofitamab related	3 (100)	7 (100)	15 (78.9)	25 (86.2)
Serious AE	3 (100)	6 (85.7)	9 (47.4)	18 (62.1)
Glofitamab related	2 (66.7)	6 (85.7)	7 (36.8)	15 (51.7)
Grade 3/4 AE	0	6 (85.7)	6 (31.6)	12 (41.4)
Glofitamab related	0	3 (42.9)	4 (21.1)	7 (24.1)
Grade 5 (fatal) AE	0	0	1*†	0
Glofitamab related	0	0	0	0
AE leading to treatment discontinuation	0	0	0	0
Deaths	0	1 (14.3)*	2 (10.5)*	3 (10.3)*

No AEs leading to treatment discontinuation were reported

n (%) of patients with ≥1 AE unless stated	Glofitamab fixed dosing + 1000mg Gpt (n=3)	Glofitamab SUD + 1000mg Gpt (n=7)	Glofitamab SUD + 2000mg Gpt (n=19)	All patients (N=29)
Any CRS	3 (100)	5 (71.4)	9 (47.4)	17 (58.6)
Grade 1	3 (100)	2 (28.6)	5 (26.3)	10 (34.5)
Grade 2	0	2 (28.6)	4 (21.1)	6 (20.7)
Grade 3	0	0	0	0
Grade 4†	0	1 (14.3)	0	1 (3.4)
Serious AE of CRS (any grade)	2 (66.7)	5 (71.4)	4 (21.1)	11 (37.9)
Median time to first CRS event, hrs (range)	5.5 (3.0–32.7)	9.6 (6.6–21.7)	12.1 (7.7–19.8)	9.9 (3.0–32.7)
Tocilizumab use in patients with CRS	0	4 (57.1)	3 (15.8)	7 (24.1)
CRS events resolved	3 (100)	4 (80)	6 (66)‡	13 (76.5)§
Median time to CRS resolution, hrs (range)	23.0 (10.9–171.4)	38.8 (20.6–49.0)	51.4 (3.8–142.0)	38.8 (3.8–171.4)



Most CRS events occurred during C1, were Grade 1 or 2 and resolved

Grade >2 ICANs YE veya Grade >3 tümör alevlenmesi görülmemiş

Klinik Önemi:

- Glofitamab ile uzun yanıt süresi ve kullanılmaya hazır olması nedeniyle önemli bir tedavi seçeneği
- R/R MCL'de yüksek yanıt oranları, hastaların çoğu BTKi tedavisine yanıtsız
- CRS kontrol edilebilir ve genellikle düşük gradeli; nörolojik yan etki nadir, düşük evreli ve 1 gün içinde düzelmekte
- Glofitamab'ın etkinliği değerlendirilmeye devam edilmekte

U.S. CAR-T Lymphoma CONSORTIUM

Brexucabtagene Autoleucel for Relapsed/Refractory Mantle Cell Lymphoma: Real World Experience from the US Lymphoma CAR T Consortium

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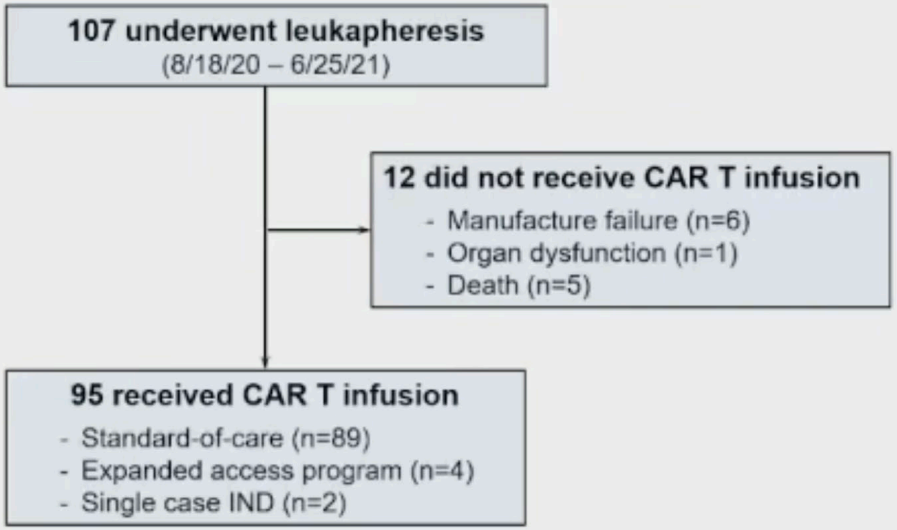
- Brexu-cel; ZUMA-2 çalışmasının sonuçları sonrası R/R MCL hastalarında FDA tarafından onaylandı
- ZUMA-2'ye göre ORR %93, CR %67; 12 aylık PFS ve OS %61 ve %83
- ABD Lenfoma CAR-T Konsersyumu

Brexu-Cel RWE: Consort diagram



Variables	Number	Variables	Number
Age, median (range)	67 (34-89)	**Prior therapies**	
Sex, male	76 (80%)	Total lines, median (range)	3 (1-10)
ECOG PS ≥2	8 (8%)	Prior CD20 antibody	94 (99%)
Simplified MIPI		Prior anthracycline or bendamustine	82 (86%)
Low risk (0-3)	30 (32%)	Prior cytarabine	43 (45%)
Intermediate risk (4-5)	54 (57%)	Prior AutoSCT	27 (28%)
High risk (6-11)	11 (12%)	Prior rituximab maintenance	41 (43%)
Ki-67, ≥50%	50/88 (57%)	Prior BTKi	78 (82%)
Blastoid/pleomorphic	39 (41%)	BTKi-refractory n=69 (73%), BTKi-intolerant n=5 (5%)	
***TP53* mutation or deletion**	31/70 (44%)	Prior lenalidomide	22 (23%)
Complex karyotype	8/28 (29%)	Prior venetoclax	33 (35%)
Stage III-IV	83 (87%)	**Disease status**	
CNS involvement	7 (7%)	Relapsed after last line	53 (56%)
Bone marrow involvement	30/67 (45%)	Refractory to last line	42 (44%)
Bulky disease (≥10 cm)	10 (11%)	**Total (received CAR T infusion)**	**95**

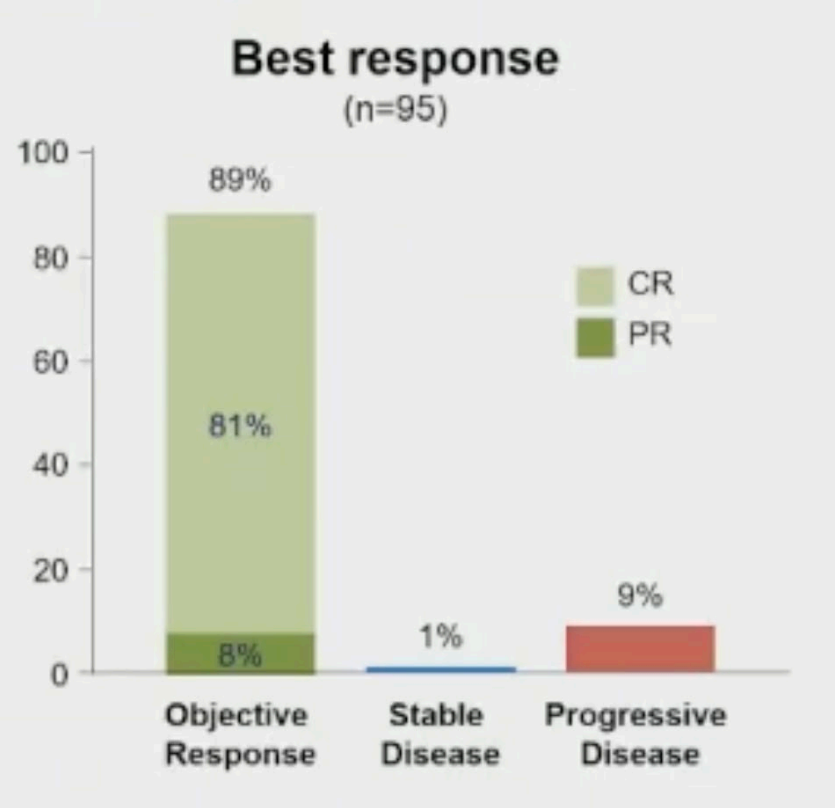
Bruxe-Cel'e köprüleme tedavisi

A total of 64 (67%) patients received bridging therapy.

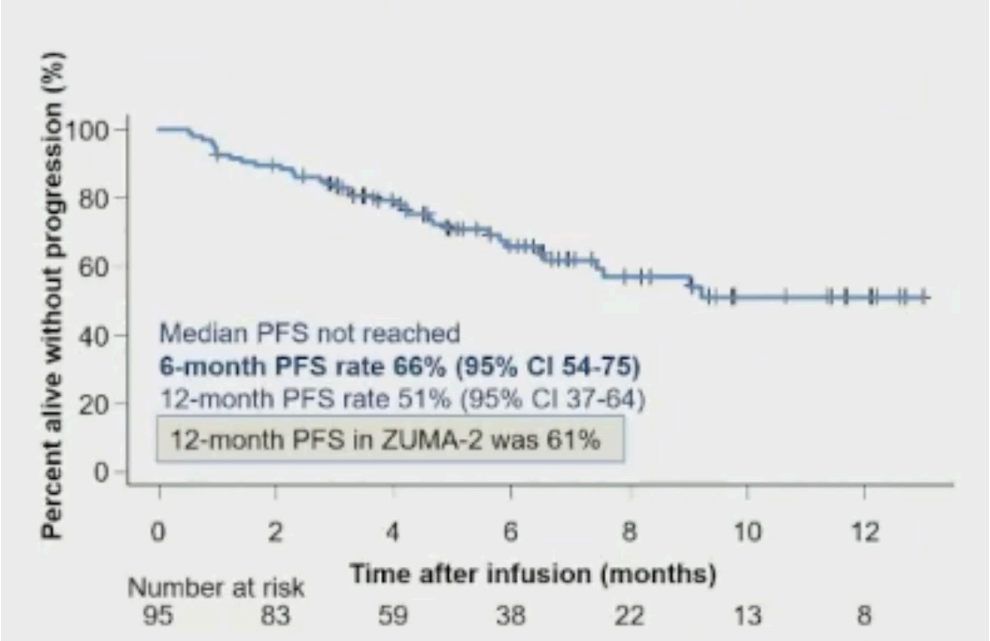
Bridging therapy	Number	Bridging therapy	Number
BTKi-based	**20**	**R-Chemo* ± Steroid**	**16**
BTKi	11	**R-Chemo* + Radiation#**	**3**
BTKi + CD20 ± Steroid	4	**Lenalidomide-based**	**3**
BTKi + (R-)Chemo*	2	Lenalidomide	1
BTKi + Radiation# ± CD20 ± Steroid	3	Lenalidomide + Radiation# ± CD20 ± Steroid	2
Venetoclax ± CD20	**5**	**Radiation# ± Steroid**	**4**
BTKi + Venetoclax-based	**9**	**Steroid**	**3**
BTKi + Venetoclax ± CD20	7	**Steroid + CD20**	**1**
BTKi + Venetoclax + R-Chemo*	1		
BTKi + Venetoclax + Radiation# + Steroid	1	No bridging therapy	31 (33%)

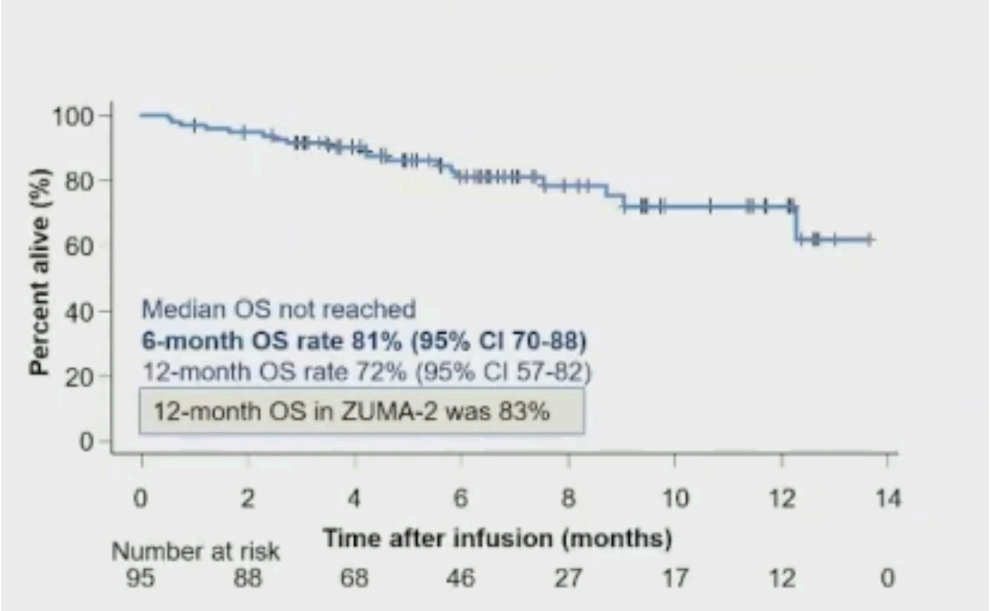
*22 patients received immunochemotherapy #13 patients received radiation therapy

- Median time from leukapheresis to lymphodepletion chemotherapy: 23 days (range 12-54)
- Median time from lymphodepletion chemotherapy to CAR T-cell infusion: 5 days (range 4-12)



- Medyan yanıta kadar süre: 30 gün (16-104)
- 30. Günde ORR (n=92 değerlendirilen) %88 (%66 TY ve %22 KY)
- En iyi yanıta kadar geçen süre medyan 30 gün (16-168)
- En iyi ORR ZUMA-2'de bildirilene benzer (%93)


Percent alive without progression (%)
100
80
60
40
20
0
Median PFS not reached
6-month PFS rate 66% (95% CI 54-75)
12-month PFS rate 51% (95% CI 37-64)
12-month PFS in ZUMA-2 was 61%
0
2
4
6
8
10
12
Time after infusion (months)
Number at risk
95
83
59
38
22
13
8


Percent alive (%)
100
80
60
40
20
0
Median OS not reached
6-month OS rate 81% (95% CI 70-88)
12-month OS rate 72% (95% CI 57-82)
12-month OS in ZUMA-2 was 83%
0
2
4
6
8
10
12
14
Time after infusion (months)
Number at risk
95
88
68
46
27
17
12
0

Klinik Önemi:

Bu çok merkezli retrospektif çalışmaya göre ZUMA-2 ile karşılaştırıldığında;

- Orta/yüksek sMIPI, blastoid/pleomorfik varyant, TP53 alterasyonu ve önceki basamak sayısı fazla olan daha fazla fazla içermekte
- Hst %78'I ZUMA-2'nin dahil edilme kriterlerini karşılamamakta
- Yüksek risk özellikleri içeren hastaların dahil edilmesine rağmen kullanışlı, güvenli ve etkili
- Üretim başarısızlığı düşük
- Üretim süresi uzun
- CRS ve ICAN oranları ZUMA-2 ile karşılaştırılabilir
- ORR (%89) vs ZUMA-2'de %93
- Yüksek riskli hastaların bütün alt gruplarında yüksek yanıt oranları
- Erken yanıt süresi verileri (6. ayda %70) ZUMA-2 ile karşılaştırılabilir

Teşekkürler