



ASH 2021

Marginal Zon Lenfomalar

Dr. Deram BÜYÜKTAŞ

Marginal Zon Lenfoma

- ✓ NHL'nin % 10-12'si
- ✓ indolen B-hücreli lenfoma
- ✓ 3 alt grubu var
- Ekstranodal marginal zon lenfoma (EMZL) ; en sık % 70
- Nodal marginal zon lenfoma (NMZL); % 10
- Splenik marginal zon lenfoma (SMZL); % 20

İçerik

1. Parsaclisib & R/R MZL; CITADEL-204
2. Umbralisib+ Ublituximab & R/R MZL; Unity-NHL
3. MIL62+ Lenalidomide & R/R MZL; Phase 1b/2
4. Rituksimab biosimilar+Peg.IF & untreated advanced iB-NHL
5. Igm-2323 & Advanced B-Cell Malignancies
6. Long term outcome of conjunctival extranodal MZL

44 Efficacy and Safety of Parsaclisib in Patients with Relapsed or Refractory Marginal Zone Lymphoma: Primary Analysis from a Phase 2 Study (CITADEL-204)

Tyrel Phillips, MD¹, Abraham Avigdor, MD^{2,3}, Ronit Gurion, MD^{4*}, Caterina Patti, MD^{5*}, Paolo Corradini, MD⁶, Monica Tani, MD^{7*}, Amitkumar Mehta, MD⁸, Izidore S. Lossos, MD⁹, Pier Luigi Zinzani, MD¹⁰, Catherine Thieblemont, MD, PhD¹¹, Wojciech Jurczak, PhD, MD¹², Fred Zheng, MD^{13*}, Erica Rappold, BSN^{13*}, Wanying Zhao, PhD^{13*} and Peter Johnson, MD, FRCP¹⁴

Çalışma özellikleri

- Parsaclisib; PI3K inhibitörü
- Open-label faz 2 çalışma
- BTKi naive, R/R MZL, parsaclisib monoterapi

Dahil etme kriterleri

- ≥ 18 yaş, MZL
- ≥ 1 line tedavi almış
- Progresyon veya refrakter
- ECOG ≤ 2
- Radiolojik olarak ölçülebilir hastalık (nodal, extranodal, splenik)

Çalışma Dizaynı

COHORT 1 (n=10)

- ▀ İbrutinib almış hastalar

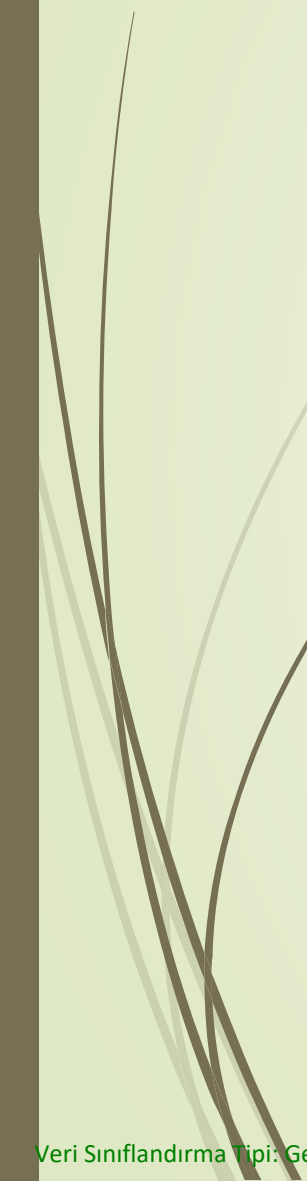
COHORT 2 (n=100)

- ▀ BTKİ almamış hastalar
- ▀ QD(once daily):20 mg, 8 hafta sonrasında
- ✓ WG(weekly):20 mg/haftada bir
- ✓ OD(daily):2.5 mg QD

Primer endpoint:ORR

Sekonder enpoint:DOR, CRR,PFS,OS,tolerabilite,güvenlik

**Sadece Cohort II verileri



	N= 100 (WG=28, DG:72)
Nodal	% 31
Extranodal	% 34
Splenik	% 35
Median yaş	71 (35-95) yıl
Male	% 53
Female	% 47
ECOG≤1	% 49
1 Line	% 49
2 Lines	% 31
≥3 lines	% 20
Relaps	% 46
Refrakter	% 49

	N= 100 (WG=28, DG:72)
Median duration of treatment	13.4 ay (tüm hastalar) 11.6 ay (DG)
Follow-up from first dose to data cut-off	22.8 ay (tüm hastalar) 21 ay (DG)
ORR	% 58 (tüm hasta) % 58.3 (DG) % 57 (WG)
CRR	% 6 (tüm hastalar) % 4.2 (DG) % 10.7 (WG)
Median DOR	12.2 ay (tüm hastalar) 12.2 ay (DG)
Median PFS	16.5 ay (tüm hastalar) 16.5 ay (DG)
Median OS	Was not reached

En sık tedavi gerektiren yan etki	Diare (% 47) Öksürük (%23)
Grade $\geq$ 3 tedavi gerektiren yan etki	Diare (% 12) Nötropeni (%9) Pnömoni (%9) Kolit (%7)
Tedavi kesilmesini gerektiren yan etki (% 29)	Diare (%9) Kolit (%5)
Ciddi (serious) yan etki (%47)	En sık Pnömoni (% 9)
Fatal yan etki (%6)	Febril nötropeni (1 hasta) Sepsis (1 hasta)

Sonuçlar

- *R/R MZL tanılı hastalar Parsaclisib tedavisine hızlı ve uzun süren klinik yanıt göstermiştir.
- *Tedavi iyi tolere edilmiştir.
- * Parsaclisib R/R MZL tanılı hastalarda potansiyel tedavi seçeneğidir.

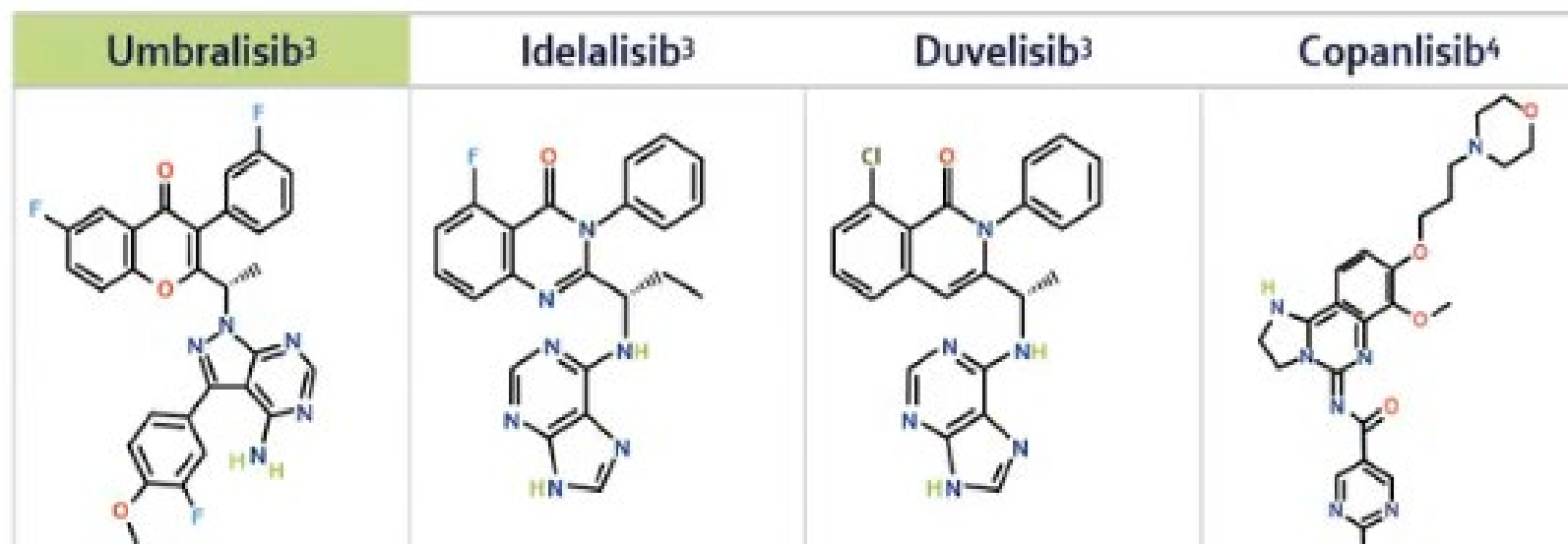
The Combination of Umbralisib Plus Ublituximab is Active in Patients with Relapsed or Refractory Marginal Zone Lymphoma (MZL): Results from the Phase 2 Global UNITY-NHL Trial



Julio C. Chavez, MD, MS¹, Neta Goldschmidt, MD², Felipe Samaniego, MD³, Tomasz Wróbel, MD, PhD⁴, Federica Cavallo, MD, PhD⁵, Gustavo Fonseca, MD⁶, Sung-Soo Yoon, MD⁷, Lubos Drgona, MD⁸, Eliza Hawkes, FRACP, MD, MBBS⁹, Itai Levi, MD¹⁰, Hari P. Miskin, MSc¹¹, Peter Sportelli, BS¹¹, Owen A. O'Connor, MD, PhD¹¹, Nathan H. Fowler, MD³, and Pier Luigi Zinzani, MD, PhD¹²

Umbralisib is a Selective Inhibitor of PI3K δ and CK

- Recent evidence suggests the PI3K-mTOR pathway is sufficient for driving the pathogenesis of MZL¹
- Umbralisib** is a selective PI3K δ and casein kinase-1epsilon (CK1 ϵ) inhibitor that has recently been FDA approved for the treatment of previously treated marginal zone lymphoma (MZL) based on reported data²

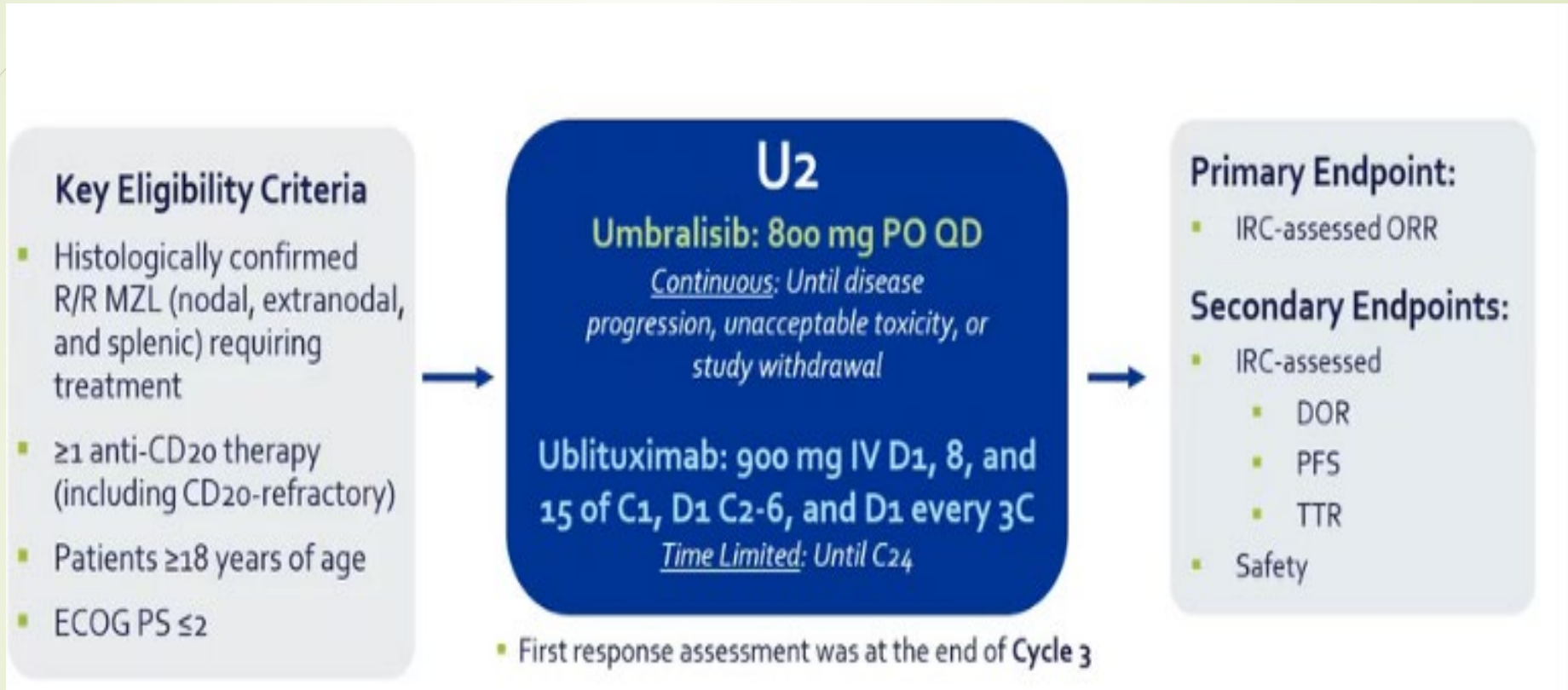


Ublituximab + Umbralisib (U2)



- **Ublituximab** is a novel anti-CD20 monoclonal antibody glycoengineered for enhanced ADCC that targets a unique epitope on CD20¹
- In MZL patients, single agent **umbralisib** demonstrated a 49.3% ORR with 16% CR² and is currently approved for MZL patients who have received a CD20-directed therapy³
- The combination of **umbralisib + ublituximab (U2)** has been shown to be active, with a manageable safety profile in patients with relapsed/refractory (R/R) NHL⁴

UNITY- Design



Characteristic	MZL U2 N=72
Age, median (range), years	70 (40 – 89)
ECOG-PS, 0 1 2, %	49 49 3
Male, n (%)	34 (47)
Stage III-IV, n (%)	53 (74)
MZL subtype, extranodal splenic nodal, %	46 11 43
Prior therapies, median (range)	2 (1 – 9)
Refractory to immediate prior therapy, n (%) ^a	18 (25)
Chemotherapy, n (%)	61 (85)
BTKi, n (%)	6 (8)
Lenalidomide, n (%)	4 (6)
Prior CD20-containing regimens, median (range)	2 (1 – 7)
Refractory to CD20, n (%)	14 (19)
≥3 CD20 containing prior therapy, n (%)	14 (19)

MZL U2

N=72

Treatment status, n (%)

Follow-up, median (range), mos

20 (9 – 29)

Ongoing

34 (47)

Discontinued regimen

38 (53)

Progressive disease

16 (22)

Investigator decision

3 (4)

Death

6 (8)^a

Adverse event

7 (10)

Other

4 (6)

Withdrawal of consent

2 (3)

AEs, n (%)	MZL U2 N=72			
	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	15 (21)	11 (15)	9 (13)	-
Nausea	20 (28)	10 (14)	-	-
Fatigue	15 (21)	7 (10)	5 (7)	-
Headache	15 (21)	5 (7)	-	-
Neutropenia	-	7 (10)	7 (10)	6 (8)
ALT/AST increased	2 (3)	3 (4)	7 (10)	4 (6)
Dizziness	13 (18)	2 (3)	-	-
Back pain	12 (17)	1 (1)	1 (1)	-
Dyspnea	7 (10)	4 (6)	1 (1)	1 (1)
Infusion-related reaction	1 (1)	9 (13)	2 (3)	-
Vomiting	10 (14)	2 (3)	-	-
Decreased appetite	7 (10)	5 (7)	-	-

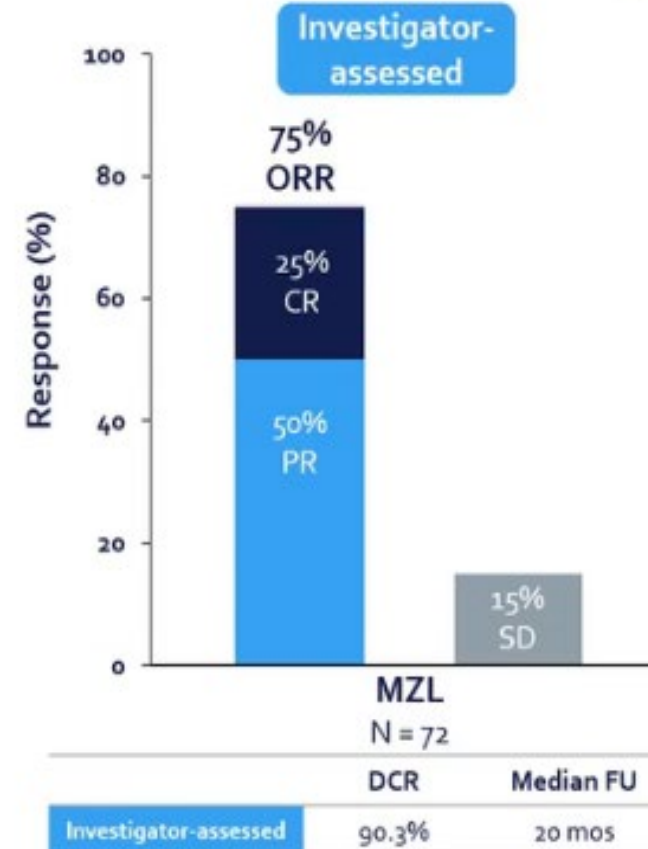
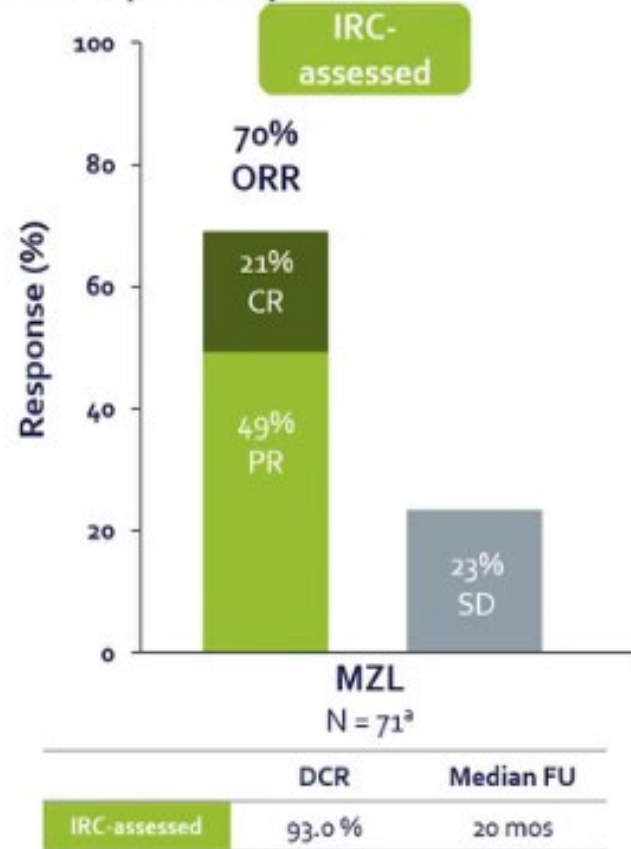
Events of Clinical Interest – PI3K Specific

AEs, n (%)	MZL U2 N=72		
	Any Grade	Grade 3/4	Discontinued U2
Diarrhea	35 (49)	9 (13)	2 (2.8)
Neutropenia	20 (28)	13 (18)	1 (1.4)
ALT/AST increased ^a	16 (22)	11 (15)	2 (2.8)
Rash	9 (13)	-	-
Non-infectious colitis ^b	2 (2.8)	2 (2.8)	-
Pneumonitis	-	-	-

- Median follow-up is 20 months (range 9.5 – 29.3 months)
- Among patients who experienced grade 3/4 diarrhea, only 1 patient was managed with steroids
- 22 (31%) patients were managed with dose reductions
 - Most common AEs leading to dose reduction: ALT/AST 8 (11%) and diarrhea 3 (4%)

Tedavi Yanıtı

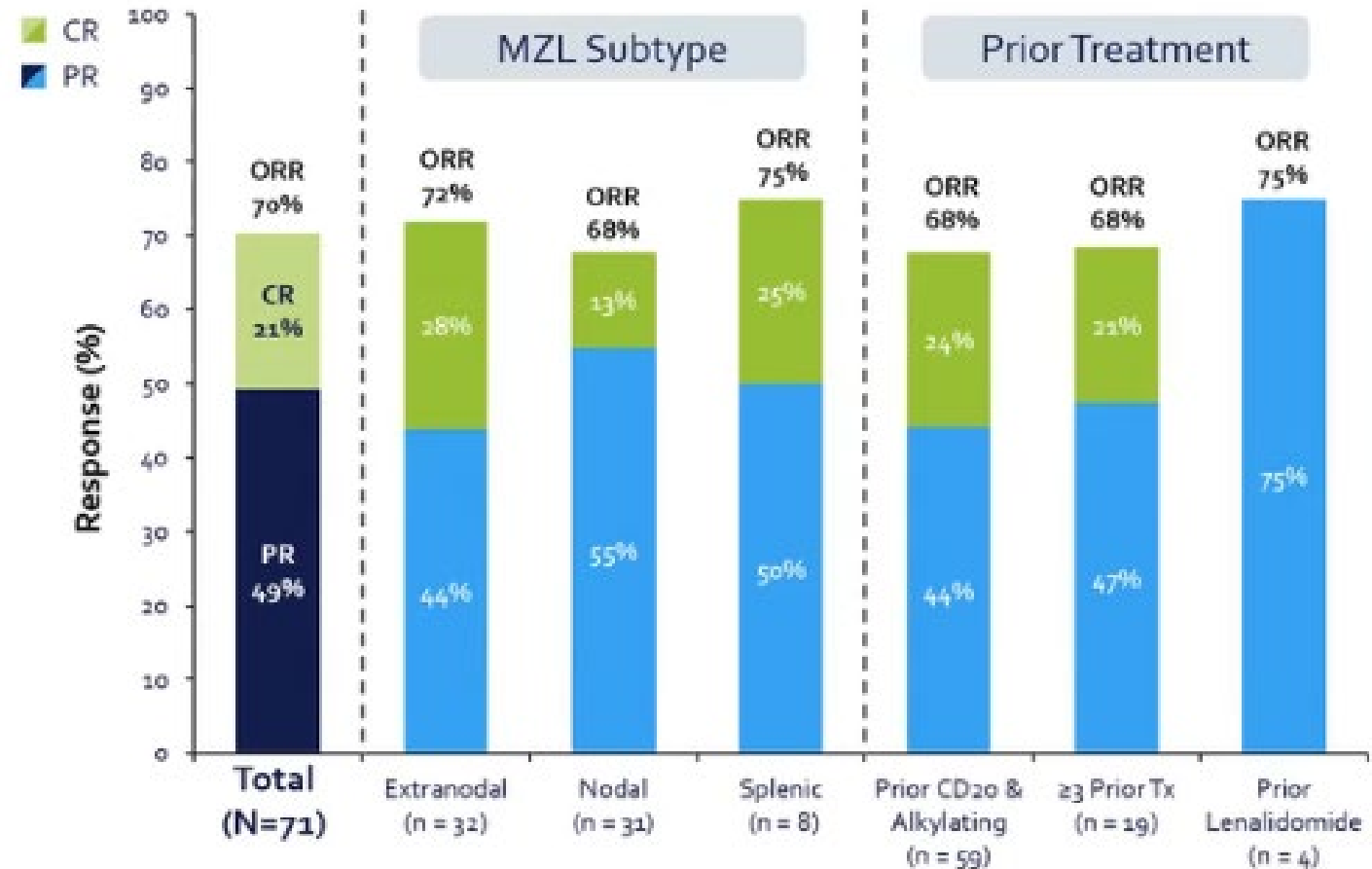
IRC- & Investigator-assessed Overall Response Primary Endpoint



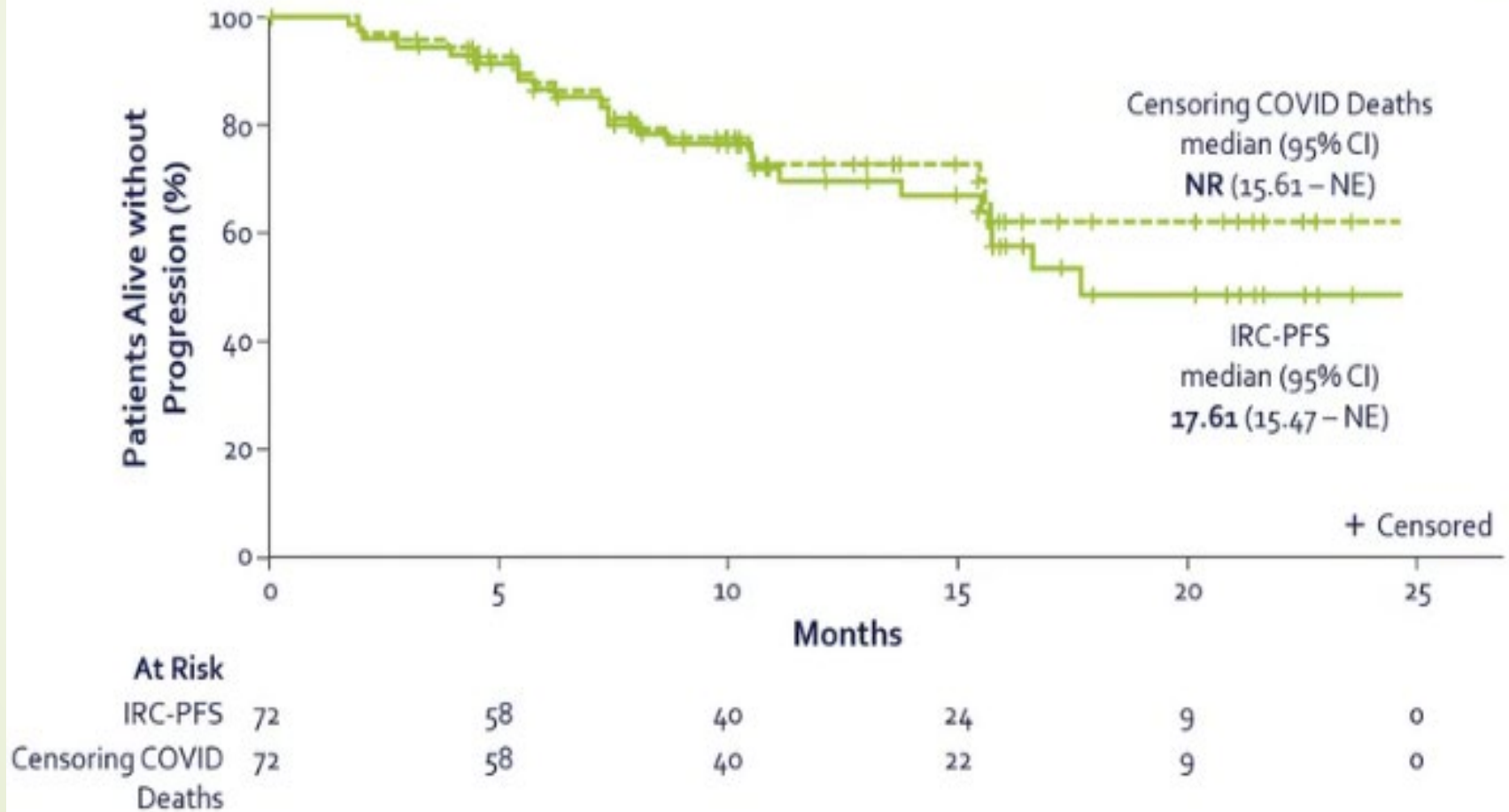
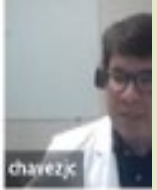
complete response; DCR: disease control rate (CR + PR + SD); FU: follow-up; IRC: independent review committee; mos: months; MZL: marginal zone lymphoma; ORR: overall response rate; PR: partial response; SD: stable disease; ^aPer IRC, one patient had no evaluable disease at baseline therefore is excluded in the overall response assessment



IRC-assessed Responses by Subgroup



IRC-assessed Progression-free Survival



SONUÇ

Conclusions

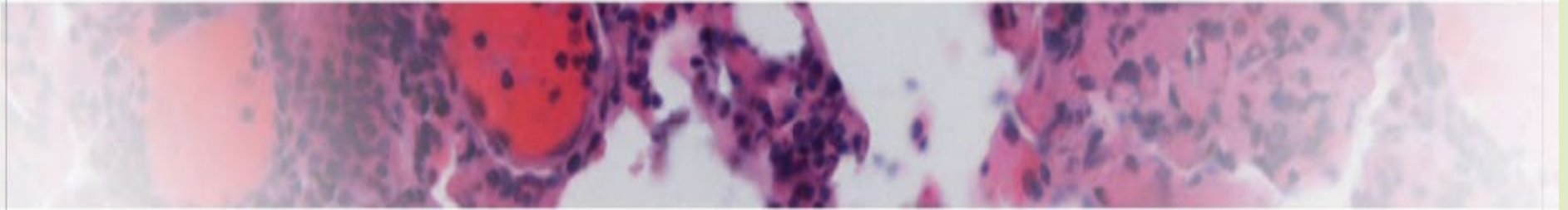


- In the UNITY-NHL study, U2 was highly active in patients with R/R MZL, with durable responses observed
 - U2 treatment resulted in an increased rate of response when compared to a prior cohort of MZL patients treated with umbralisib monotherapy
- The safety profile was acceptable, with low incidence of immune-mediated toxicities and AE-related discontinuations
- The U2 combination demonstrated favorable clinical activity and may constitute a novel non-chemotherapy treatment option for patients with R/R MZL



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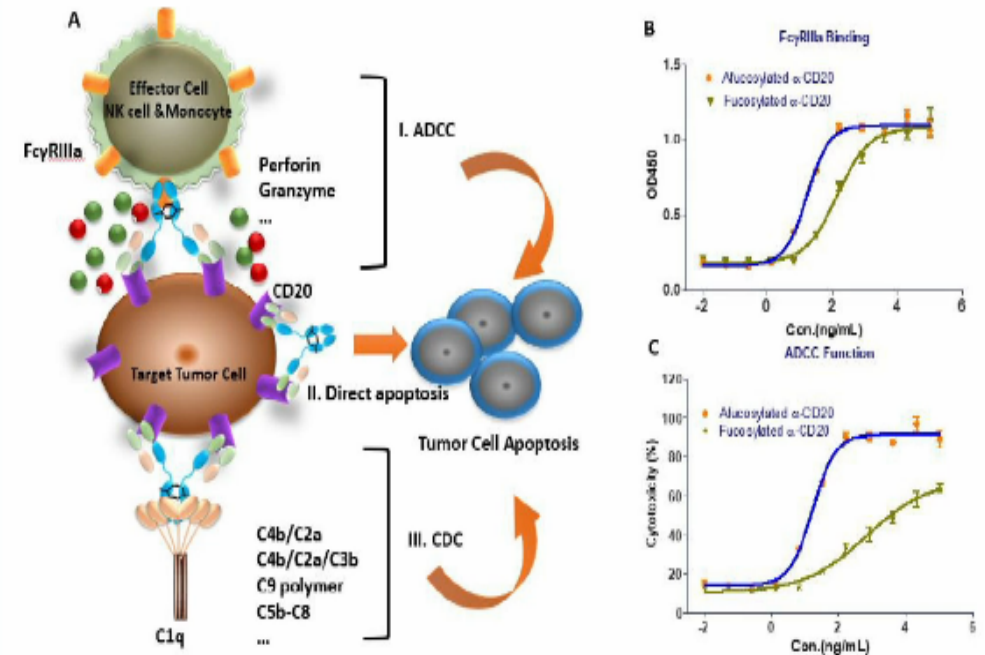
The Type II Glycoengineered Humanized Anti-CD20 Monoclonal Antibody MIL62 Combined with Lenalidomide in Chinese Patients with Relapsed/Refractory Follicular Lymphoma and Marginal Zone Lymphoma: Results of a Multicenter, Single-Arm, Phase 1b/2 Trial

Yuankai Shi¹, MD, Yan Qin¹, MD, Yongping Song², MD, Keshu Zhou², MD, Hui Zhou³, MD, Hongmei Jing⁴, MD, Ying Xiang⁵, Zhao Wang⁶, MD, Zhen Wang⁷, Aimin Zang⁸, MD, Ou Bai⁹,
Zhenyu Li¹⁰, MD, Huilai Zhang¹¹, MD

Background

- MIL62 is a novel glycosylated type II anti-CD20 monoclonal antibody with enhanced affinity for the FcγRIIIa receptors leading to improved ADCC (antibody-dependent cellular cytotoxicity) than rituximab.
- This open-label, multicenter, phase 1b/2 trial aims to explore the efficacy, pharmacokinetics, and safety of MIL62 plus lenalidomide in patients with previously treated relapsed/refractory indolent non-Hodgkin lymphoma.

Mechanism of action of MIL62



ClinicalTrials.gov, identifier NCT04110301

Study Design

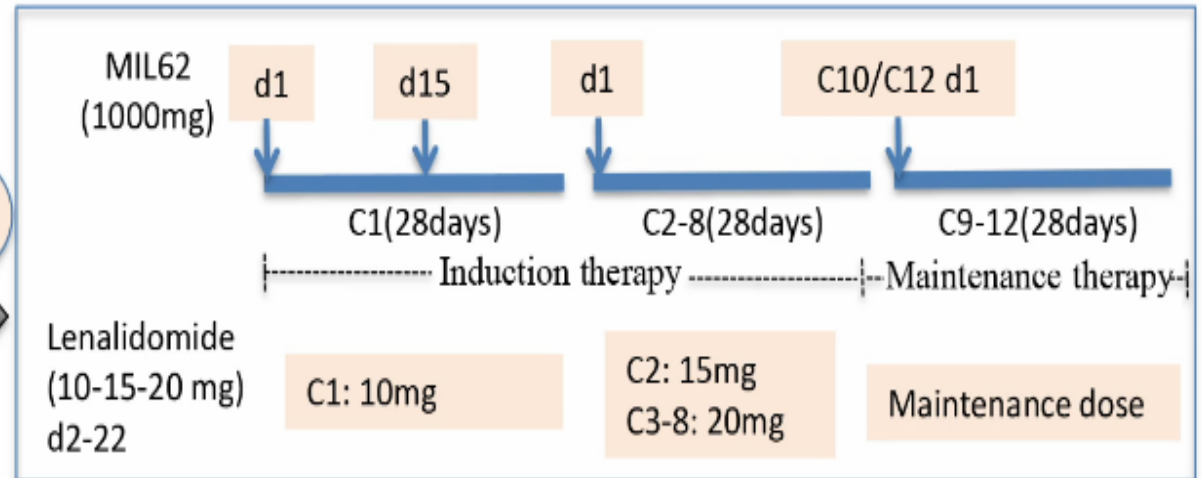
Key inclusion criteria

- CD20 positive MZL or FL of WHO grades 1-3a
- Received one to four prior systemic regimens (with at least one rituximab-containing therapy)
- ECOG PS 0-2
- ≥ 1 measurable lesion (2014 Lugano criteria)
- Adequate organ function

Note: FL: follicular lymphoma; MZL: marginal zone lymphoma; ORR: objective response; DoR: duration of response; DCR: disease control response; PFS: progression-free survival; C: cycle; PK: pharmacokinetics; AEs: adverse events.

N=54

Treatment schedule



Primary end point

- ORR by investigator

Secondary end point

- DoR/DCR
- 12-month PFS rate
- Safety/PK

Study methodology

- Simon's two-stage design
- Efficacy assessment based on 2014 Lugano criteria every 3 cycles
- AEs graded by CTCAE v5.0

Baseline characteristics and prior therapies

From Nov. 2019 to Dec. 2020, 54 patients were enrolled at 11 centers in China.

Patient disposition

Enrolled and recieved treatment
(N=54)

Discontinued treatment (N=16, 29.6%)

- Disease progression (N=11, 20.3%)
- Adverse event (N=3, 5.6%)
- Other reason (N=2, 3.7%)

Complete treatment (N= 21, 38.9%)
Treatment ongoing (N=17, 31.5%)

Baseline characteristics	N=54
Male, n(%)	31 (57.4)
Age, median (years)	50.0(28-85)
ECOG PS	
0, n(%)	27(50.0)
1-2, n(%)	27(50.0)
Histology	
FL Grade 1-2, n(%)	40(74.1)
FL Grade 3a, n(%)	11(20.4)
MZL, n(%)	3 (5.6)
Ann Arbor stage	
I-II, n(%)	13(24.1)
III-IV, n(%)	41(75.9)
Bone marrow involvement	
Yes, n(%)	14(25.9)

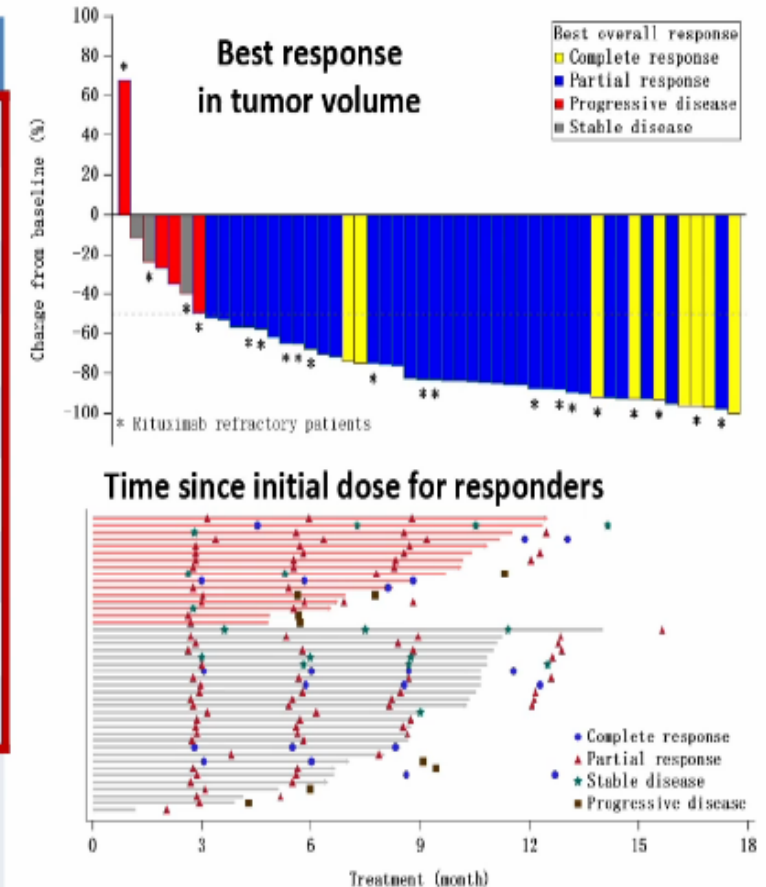
Continued	N=54
Bulk ≥6 cm, n(%)	16(29.6)
Extranodal involvement	
Yes, n(%)	24(44.4)
LDH >ULN, IU/L, n(%)	16(29.6)
FLIPI-2 score	
0-1, n(%)	30(55.6)
2, n(%)	11(20.4)
3-5, n(%)	12(22.2)
unknown, n(%)	1 (1.9)
No. of prior treatments	
median(Min, Max)	1.0(1,4)
1, n(%)	35(64.8)
2-4, n(%)	19(35.2)
Refractory to rituximab	20(37.0)

Efficacy

50 patients were included the efficacy analysis set. The median follow-up time was 12.1 (95%CI: 8.8-12.3) months.

Summary of efficacy outcomes		
Best Overall Response	N=50	Rituximab refractory N=20
CR, n(%)	9 (18.0)	4 (20.0)
PR, n(%)	34 (68.0)	12 (60.0)
SD, n(%)	3 (6.0)	2 (10.0)
PD, n(%)	4 (8.0)	2 (10.0)
ORR, n(%), 95%CI	43 (86.0), (73.3, 94.2)	16 (80.0), (56.3, 94.3)
DCR, n(%), 95%CI	46 (92.0), (80.8, 97.8)	18 (90), (68.3, 98.8)
9-month DoR rate (%), 95%CI	74.6 (54.3, 86.9)	73.3 (43.6, 89.1)
12-month PFS rate (%), 95%CI	69.0 (51.9, 81.1)	64.9 (36.0, 83.2)

Note: CI: confidence interval; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate; mDoR: median duration of response; PFS: median progression-free survival.



Safety

- The median treatment time of MIL62 and lenalidomide was 38.0 weeks and 38.9 weeks, respectively.
- In total, 53 (98.1%) patients reported treatment-related adverse events (TRAEs).
- Serious TRAEs occurred in 11 patients (20.4%) and recovered with appropriate supportive care.
- Dose adjustment for lenalidomide occurred in 10 patients (18.5%).
- No treatment-related deaths occurred during the study period.

Most common MIL62 related AEs (≥10%, all grades), n (%)	All patients N=54	
Preferred Term (PT)	All grades	Grade 3/4
Neutropenia	47 (87.0)	28 (51.9)
Leukopenia	43 (79.6)	10 (18.5)
Thrombocytopenia	31 (57.4)	9 (16.7)
Lymphopenia	15 (27.8)	4 (7.4)
Infusion-related reaction	9 (16.7)	1 (1.9)
ALT increased	8 (14.8)	0 (0.0)
AST increased	7 (13.0)	0 (0.0)

Note: AEs: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase

Conclusions

- An effective chemo-free combination therapy:
 - MIL62 combined with lenalidomide showed promising efficacy in both relapsed and rituximab refractory Chinese patients with CD20 positive MZL or FL.
 - ✓ All patients: ORR: 86%, 9-month DoR rate: 74.6%
 - MIL62 could overcome the problem of rituximab resistance according to the clinically meaningful efficacy result.
 - ✓ Rituximab refractory patients: ORR: 80%, 9-month DoR rate: 73.3%
- The safety profile was acceptable and manageable.
- This phase Ib/II data warrant further clinical studies of MIL62 plus lenalidomide.



2021ASH poster presentation(#1359)

Chemotherapy-free initial Treatment of Rituximab Biosimilar (Henliritux®) plus Pegylated Interferon α -2b (Pegberon®) in pts with Untreated Advanced Indolent B-cell Non-Hodgkin's Lymphoma: Preliminary Results from a Multicenter, Single-Arm, Phase II Study(RIPPLE trial)

Gao Yan¹; Wu jianqiu²; Huang yunhong³; Zhou hui⁴; Feng ru⁵; Li fei⁶; Wang xiaoxiao¹; Bai bing¹; Huang yuhua⁷; He haixia⁸; Ping liqin¹; He yanxia¹; Huang cheng¹; Li jibin⁹; Mao jiaqing¹; Huang huiqiang¹

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Introduction



- Indolent B-cell lymphoma (iBCL) are clinically heterogeneous and accounts for 10-15% of all kind of subtypes in NHL in China.
- Majority of advanced iBCL is considered incurable. The favorable activity and safety profile of rituximab monotherapy in the initial treatment of iBCL has been proven.
- Clinical combination of rituximab and IFN- α was associated with fewer early treatment failures compared to single agent rituximab.
- Peginterferon- α -2(peg-IFN- α 2) has a longer half-life with less toxicity. It is also recommended as one of the therapeutic options for chronic hepatitis B virus (CHB) infection.



Aim

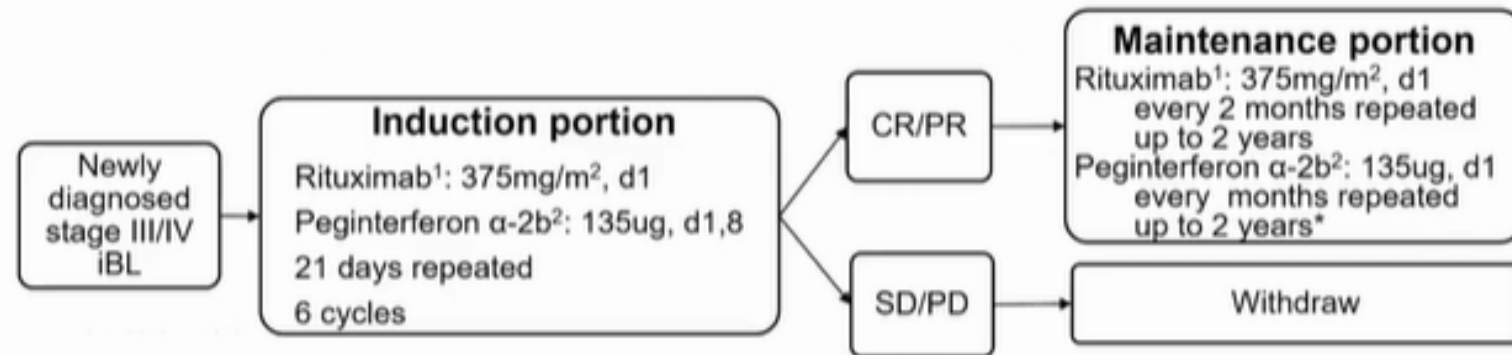


- The purpose of this study is to evaluate the efficacy and safety of rituximab biosimilar combined with pegylated Interferon α -2b as initial treatment in patients with treatment-naïve iBCL.



Study design

Figure 1. Trial flow chart



*Hepatitis B virus pts orally treated with entecavir continuously



Key eligibility



Inclusion Criteria

1. ≥ 18 years
2. iBL confirmed by histopathology examination including FL(grade 1-2,3a) and MZL
3. Treatment-naïve
4. Stage III-IV
5. ECOG score: 0-2
6. At least one evaluable or measurable lesion that meets the Lugano 2014[#] Lymphoma criteria
7. Adequate organ and bone marrow function
8. HBsAg positivity with HBV DNA load < 3000 IU/mL

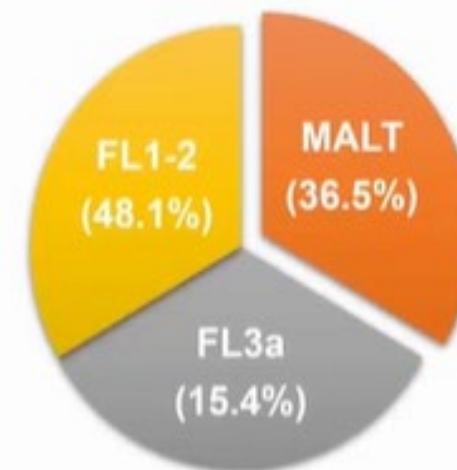
Exclusion Criteria

1. Central nervous system involvement
2. Transformed iBL
3. Requiring systemic glucocorticoid therapy or other immunosuppressive therapy for a given condition within 14 days before treatment
4. Active infection
5. Uncontrollable complications
6. Active hepatitis B



Characteristics

Key Characteristic		Total(n=52)
Age(years),Median(range) ≥60y,n(%)		54(29-79) 8(26.7)
Gender,n(%)	Male	22(42.3)
	Female	30(57.7)
Status,n(%)	Newly diagnosed	52(100)
ECOG performance,n(%)	0-1	52(98.7)
	2	1(1.3)
Ann Arbor stage,n(%)	Stage III	21(40.4)
	Stage IV	31 (59.6)
Serum LDH level	Normal	44(84.6)
	Elevated	8(15.4)
FLIPI score,n(%)	Low (0-1)	8(15.4)
	Intermediate (2)	22(42.3)
	High(≥3)	22(42.3)
Symptomatic,n(%)	Yes	20(38.5)
	No	32(61.3)
Bone marrow involvement, n(%)	Yes	14(26.9)
	No	38(73.1)
Hepatitis B, n(%)	Yes	6(11.5)
	No	46(88.5)



Abstract #1359



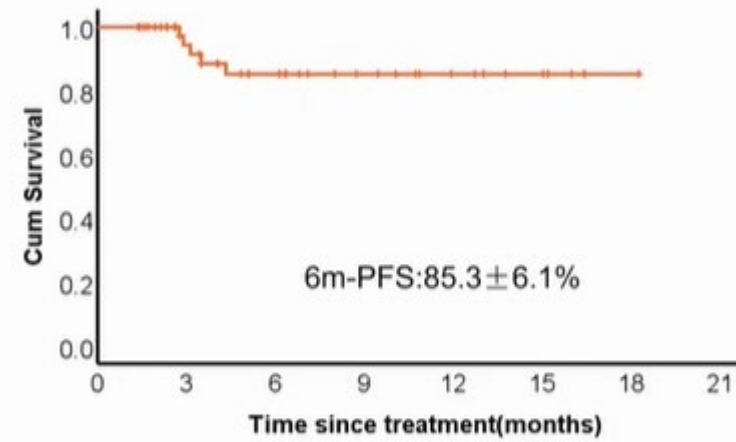
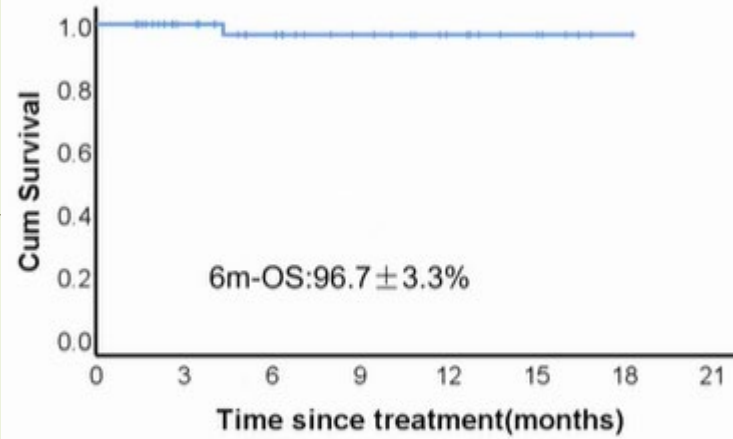
Efficacy



	Whole cohort(N=52)			
	FL1-2(n=25)	FL3a(n=8)	MALT(n=19)	Whole cohort(N=52)
ORR	14(56%)	6(75%)	11(58%)	31(60% [46-73])
CR	7(28%)	5(62.5%)	7(37%)	19(37%[23-50])
PR	7(28%)	1(12.5%)	4(21%)	12(22%)
SD	10(40%)	2(25%)	6(32%)	18(33%)
PD	0	0	1(5%)	1(2%)
NE	1(4%)	0	1(5%)	2(4%)
Responses were assessed in the per protocol set(n=40) according to the International Working Group consensus response evaluation criteria in lymphoma (Lugano 2014).				
Table 2: Best overall response (per protocol population)				



Survival



Median follow-up time: 6.2(IQR:3.3-12.1)

- Median TTR was 3.0months (1.5-5.2months)
- Median HBV DNA load clearance time was 1.8 months (1.3-2.1months)
- no hepatitis B virus reactivation reported.

Abstract #1359



Safety



	Treatment-related adverse events(n=52)	
	Grade 3-4 N(%)	Any grade N(%)
Neutropenia	9(17.3)	33(63.5)
Anemia	4(7.7)	18(34.6)
Thrombocytopenia	0	15(28.8)
Fever	0	15(28.8)
Transaminase elevated	0	15(28.8)
Fatigue	0	14(26.9)
Hectic fever	0	10(19.2)
Infusion reaction	0	8(17.4)
Data are n (%). Grade 1–2 adverse events reported in at least 10% of patients and all grade 3–4 events are shown. *Including serious adverse events		
Treatment-related adverse events		



Conclusion



- Rituximab biosimilar(Henliritux®) plus pegylated interferon α -2b(Pegberon®) provided favorable response in newly diagnosed advanced iBCL
 - ORR: 60%
 - CR: 37%
 - 6m-OS: $96.7 \pm 3.3\%$
 - 6m-PFS: $85.3 \pm 6.1\%$
- Rituximab biosimilar plus pegylated interferon α -2b was well tolerated.
- No hepatitis B virus reactivation was observed.
- Further investigation is warranted.



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A phase 1 dose-escalation study of IGM-2323, a novel anti-CD20 x anti-CD3 IgM T-cell engager in patients with advanced B-cell malignancies

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IGM-2323 is a novel engineered high-affinity, high-avidity CD20xCD3 IgM bispecific T-cell engager

IGM-2323 is a novel bispecific antibody, based on an engineered pentameric IgM framework, with a recombinant J-chain that is fused to an anti-CD3 scFv

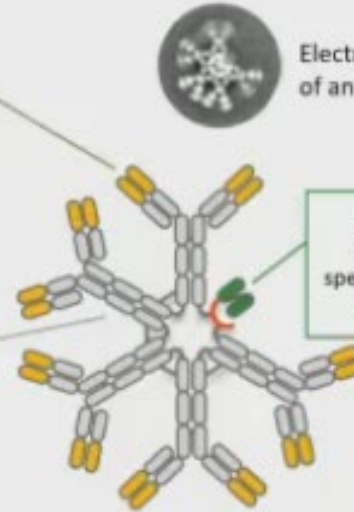
In preclinical studies, **IGM-2323** has been shown to bind irreversibly to CD20-expressing cells, including cancer cells expressing very low levels of CD20, and eliminate them through cell-dependent (TDCC) and cell-independent mechanisms (CDC)^{1,2}

Anti-CD20
10 high affinity, high-specificity binding sites to CD20

Complement
IgM mediates >100x greater complement dependent killing of bound cancer cells

Electron micrograph of an IgM molecule

Anti-CD3
Single high-specificity binding site to CD3



CD, cluster of differentiation; CDC, complement dependent cytotoxicity; IgG/M, immunoglobulin G/M; scFv, single-chain variable fragment; TDCC, T cell-dependent cytotoxicity

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1. Baliga R, et al. Blood 2019;134(Suppl. 1):1574
2. Baliga R, et al. PEGS 2016



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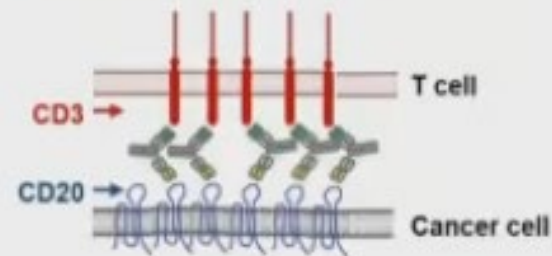
Ig M-2323

- First engineered, high –affinity, high-avidity bispecific Ig M monoclonal antibody T cell engager (TCE)
- 10 domain CD 20'ye, 1 domain CD 3'e bağlı
- Mekanizma
 - ✓ CD'20 ye irreversibl bağlanma
 - ✓ T hücre stimülasyonu
 - ✓ T-hücre ilişkili sitotoksisite
 - ✓ Kompleman bağımlı sitotoksisite
 - ✓ IFN gamma dominant sitokin stimulasyonuna bağlı artmış immunomodulasyon

IGM-2323 engagement of T cells

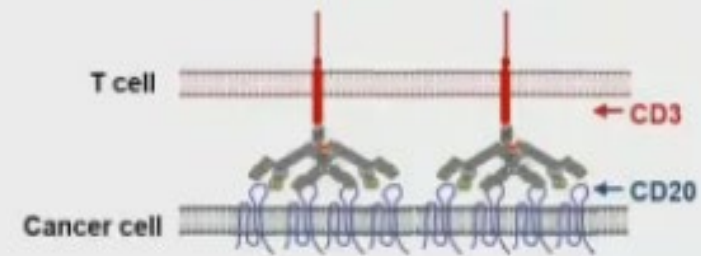
Existing bispecific T-cell engaging antibodies:
IgG or single chain

Supraphysiologic T-cell stimulation



Novel bispecific T-cell engaging antibodies:
IgM

More physiologic T-cell stimulation



IGM-2323 may provide more controlled T-cell activation
compared with existing bispecific T-cell engaging antibodies¹⁻³

1. Faroudi et al. Proc Natl Acad Sci U S A. 2003;100:14145-50
2. Purbhoo et al. Nat Immunol. 2004;5:524-30
3. Itoh et al. J Exp Med 1997;186:757-6



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Faz I, doz eskalasyon

Dahil etme kriterleri

- R/R CD20+ B-NHL
- ≥ 2 line tedavi almış
- Organ fonks. İyi
- ECOG:0-1

Uygulama

- IGM-2323; i.v. ;q3w

D1, D8, D15

Progresyon veya intolerabl toksisite gelişinceye kadar

IGM-2323-001: Phase 1 study design

Phase 1

- Single-patient cohorts followed by standard 3+3 design
- R/R B-cell NHL (DLBCL, FL, MCL, MZL)
- 1 cycle: 21 days
- Weekly dosing: D1, D8, D15
- Dexamethasone premedication
- DLT window C1 d1–21
- Q3 week dosing allowed once CR achieved
- All planned dose escalation cohorts completed. Currently enrolling in limited dose-expansion cohorts.
- Intra-patient dose escalation allowed

Titration dosing*

Dose escalation

IGM-2323 (50/1000 mg)*

IGM-2323 (50/600 mg)*

IGM-2323 (50/300 mg)*

IGM-2323 (50/200 mg)*

IGM-2323 (50/100 mg)*

IGM-2323 (100 mg)

IGM-2323 (30 mg)

IGM-2323 (10 mg)

IGM-2323 (2.5 mg)

IGM-2323 (0.5 mg)

Limited dose expansion (n = up to 10 per cohort)

IGM-2323 (15/1000 mg)*

IGM-2323 (15/600 mg)*

IGM-2323 (15/300 mg)*

IGM-2323 (15/100 mg)*

IGM-2323 (30 mg)

Expansion doses administered in outpatient clinic

Single
patient
cohorts

*First dose and maximum dose for
each titration dose are described

Some patients in dose expansion
started at 50 mg initial dose

MABEL (Minimally Active Biologic Effect Level)



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Fixed doz

- 0.5 mg
- 2.5 mg
- 10 mg
- 10 mg
- 30 mg
- 100 mg

Titration levels

- 50/100
- 50/200
- 50/300
- 50/600
- 50/1000 mg

Baseline demographics

Characteristic	Dosed patients (n=40)
Median age, years (range)	64 (36–84)
Gender, n (%)	
Male / Female	28 (70%) / 12 (30%)
Region, n (%)	
United States / Australia / South Korea	29 (73%) / 6 (15%) / 5 (13%)
Tumor type, n (%)	
DLBCL / MCL	18 (45%) / 4 (10%)
FL / MZL	14 (35%) / 4 (10%)
Disease stage at study entry, n (%)	
I–II	7 (18%)
III–IV	33 (82%)
Prior CAR-T therapy, n (%)	8 (20%)
Prior ASCT, n (%)	3 (8%)
Median prior lines of treatment (range)	3 (2–9)
No. of prior lines of treatment, n (%)	
2 / 3 / ≥4	14 (35%) / 10 (25%) / 16 (40%)
Median time from last treatment, months (range)	3.4 (0.6–37.2)
No. of patients who were refractory to last treatment, n (%)	25 (63%)



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Disposition/exposure

	Dosed patients (n=40)
Median duration of treatment, months (range)	3.2 (0.0–16.3)
Median duration of study follow-up, months (range)	7.8 (0.4–23.7)
Number of patients ongoing, n (%)	12 (30%)
Discontinued from treatment, n (%)	
Progression	23 (58%)
Investigator/patient decision	5 (13%)
Adverse Event	0
Deaths*, n (%)	
Any cause	0
Related to study drug	0

*Within 30 days of last dose of study drug



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Most common treatment-related adverse events (events occurring in >10% of patients)

Non-laboratory AEs, n (%)	Titration dose levels (n=28)		All dose levels (n=40)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Infusion-related reaction	7 (25)	1 (4)	12 (30)	2 (5)
Cytokine release syndrome	5 (18)	1 (4)	10 (25)	1 (3)
Nausea	7 (25)	0	10 (25)	0
Fatigue	6 (21)	0	7 (18)	0
Anemia	2 (7)	1 (4)	6 (15)	2 (5)
Back pain	5 (18)	1 (4)	5 (13)	1 (3)
Laboratory AEs, n (%)	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Hypophosphatemia	6 (21)	1 (4)	9 (23)	1 (3)

*Cytokine release syndrome graded by ASTCT Consensus Grading (Lee et al. Biol Blood Marrow Transplant 2019)



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Adverse events of special interest

Titration cohorts (n=28)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
CRS*	3 (11)	1 (4)	1 (4)	0	0
ICANS [^]	0	0	0	0	0
Neutropenia	1 (4)	0	0	0	0
IRR	3 (11)	3 (11)	1 (4)	0	0
All patients (n=40)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
CRS*	7 (18)	2 (5)	1 (3)	0	0
ICANS [^]	0	0	0	0	0
Neutropenia	1 (3)	0	1 (3)	1 (3)	0
IRR	3 (8)	7 (18)	2 (5)	0	0

Data cut off: September 10, 2021

Cytokine release syndrome graded by ASTCT Consensus Grading (Lee et al. Biol Blood Marrow Transplant 2019)

[^]ICANS: immune effector cell-associated neurotoxicity syndrome

Distinction between CRS and IRR were made by the treating investigator

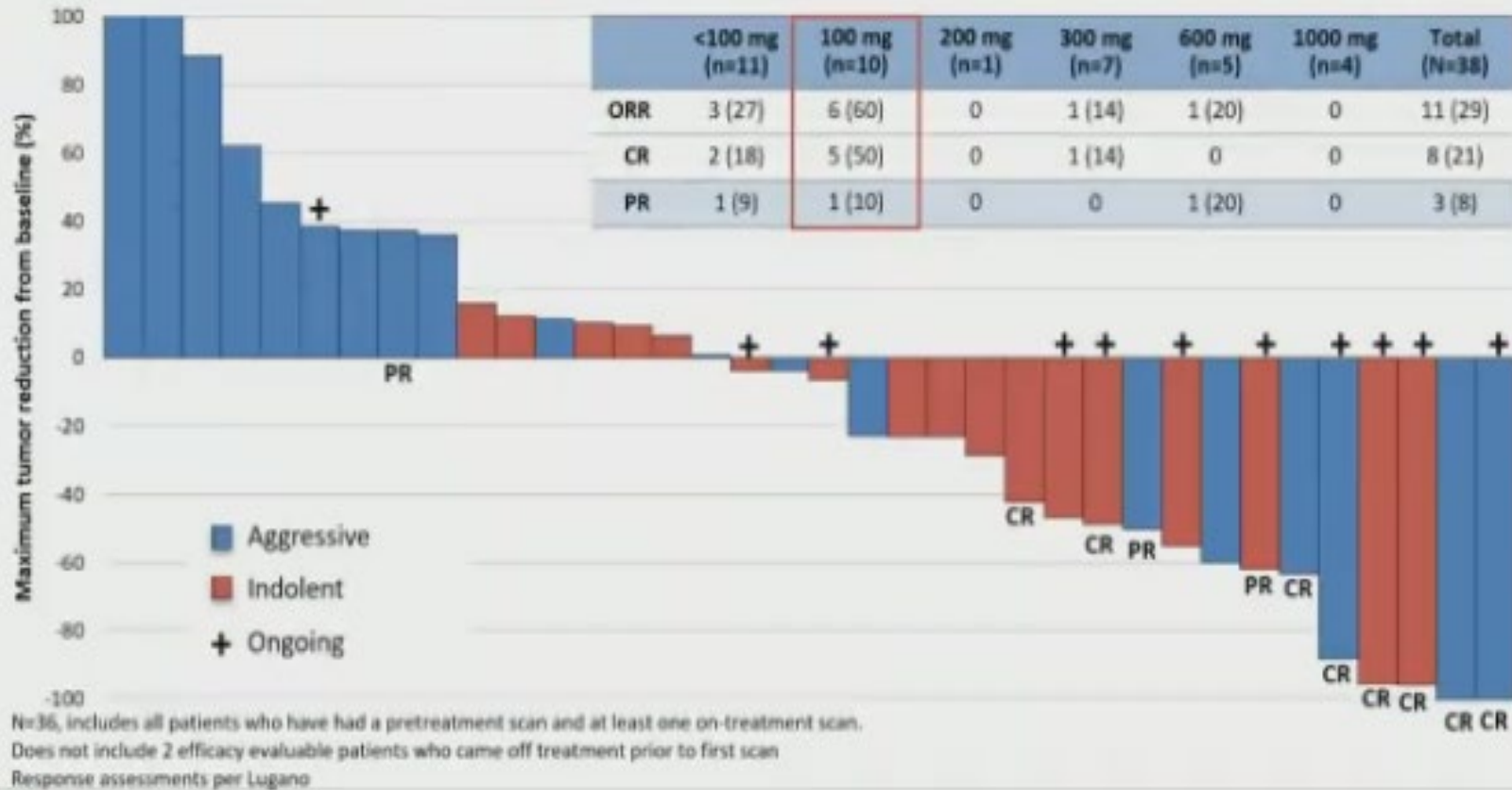
* 3 of 5 CRS cases in titration cohorts and 8 of 10 overall occurred in the first cycle

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Overall NHL cohort: best post-baseline tumor reduction and responses

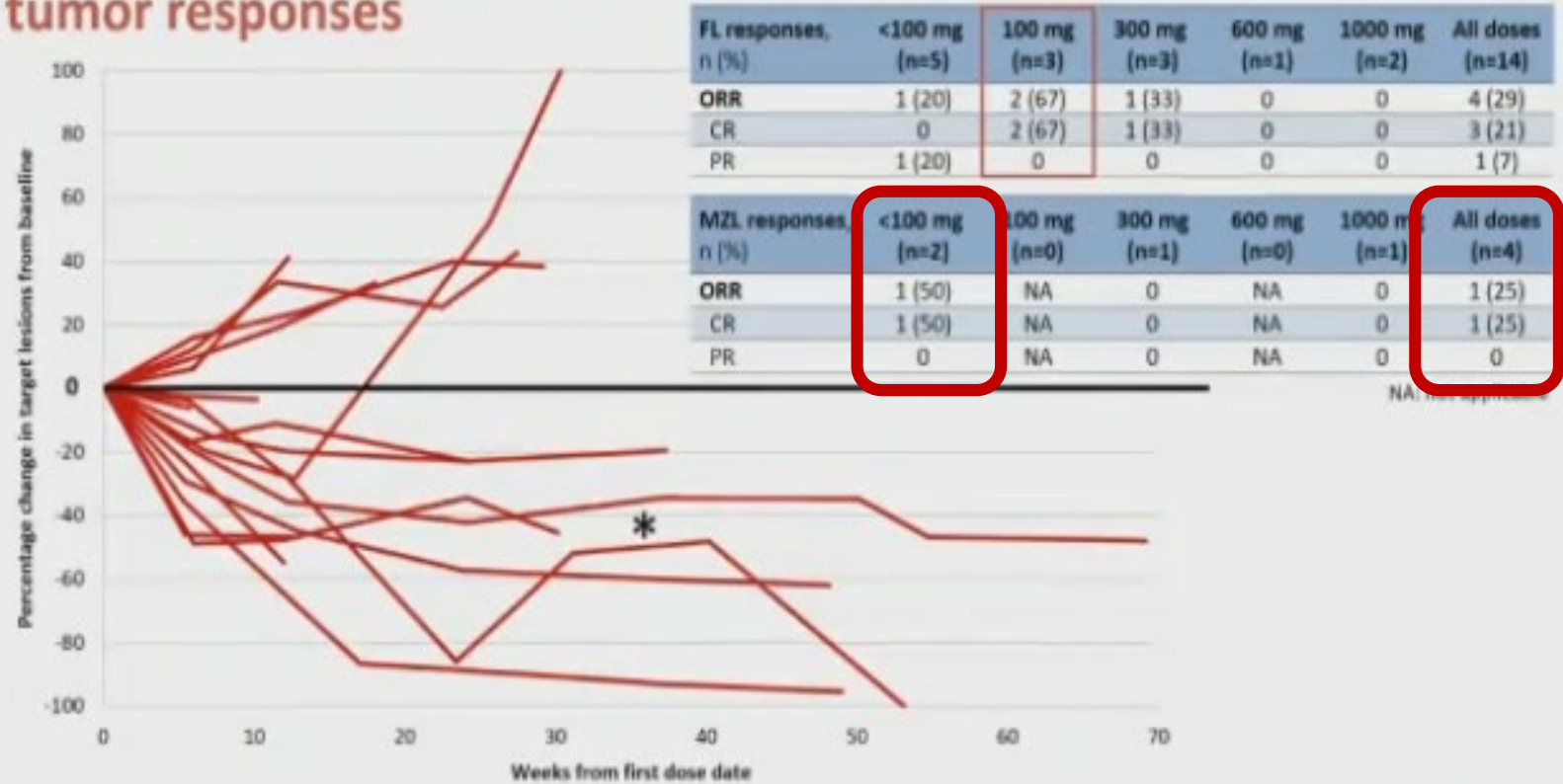


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Indolent NHL cohort (FL and MZL): tumor responses



*FL patient with CR, possible pseudoprogression, and continued treatment with ongoing benefit

Data cut off: September 10, 2021

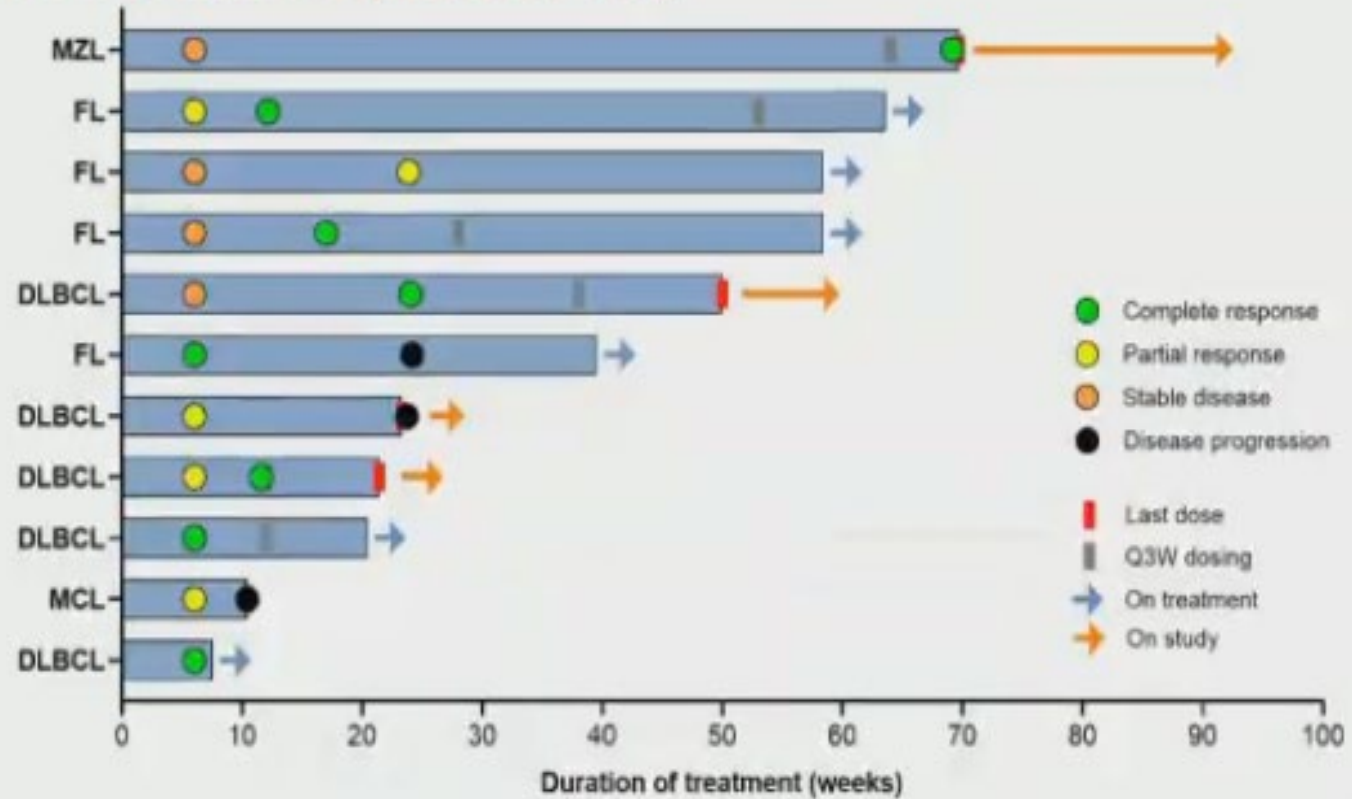


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Patient status: responders only



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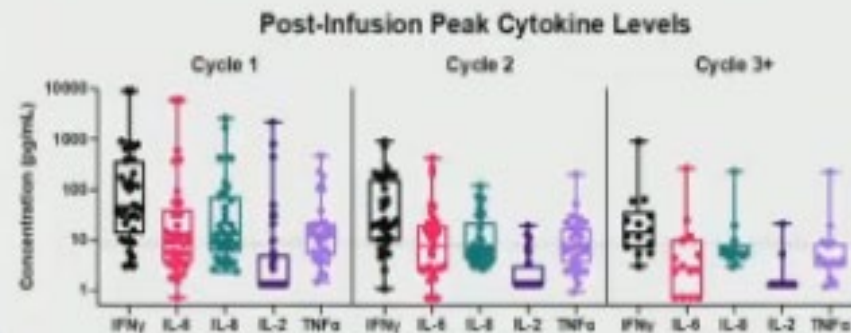


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IGM-2323 induces potent T-cell effector cytokines while minimizing cytokines associated with CRS

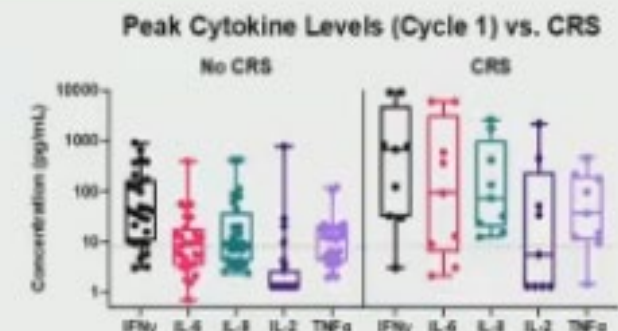
IGM-2323 induces IFN γ dominant immune activity in majority of patients

- Biologically active dose starting at 10 mg
- Transient cytokine elevations (~2-12 hours) over multiple infusions



Poly-cytokine response may be associated with CRS

- Timing of poly-cytokine increase matches CRS onset



Date cut off: 27 October 2021 (n=39 patients)

Box plots show highest concentration of plasma cytokines from n=39 patients. Dotted line indicates median of baseline cytokine levels

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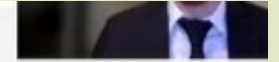
Conclusions

IGM-2323 is active against R/R NHLs and demonstrates a highly favorable safety profile

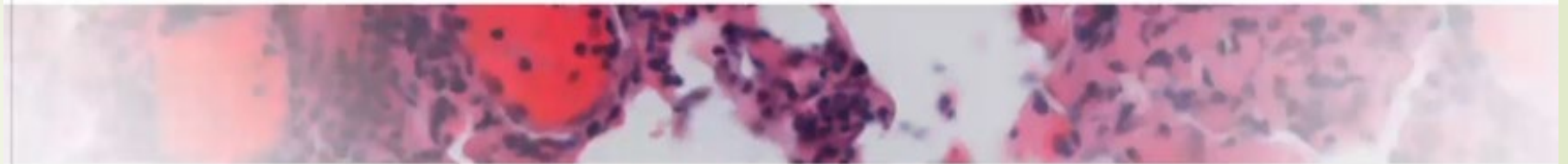
- Active in heavily pre-treated NHLs with evidence of prolonged DOR as a single agent, including those who have received prior CAR-T
- Low rates of grade 2 or higher CRS, no ICANS, and minimal neutropenia
- repeatable IFN γ dominant T cell activation due to a potentially more physiologic immune stimulation, which is in contrast to other T cell engagers



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LONG-TERM OUTCOMES OF CONJUNCTIVAL EXTRANODAL MARGINAL ZONE LYMPHOMA: A LARGE SINGLE INSTITUTION EXPERIENCE

Authors, Eduardo Edelman Saul, MD; Juan Pablo Alderuccio, MD; Isildinha M. Reis, PhD; Zhao Wei; Amrita Desai, MD; Derek M. Isrow, MD, PhD; Arnold M. Markoe, MD; Izidore S. Lossos, MD



Background

- The most common subtype of B-cell lymphomas presenting in the conjunctiva is extranodal marginal zone lymphoma (EMZL), accounting for ~80% of cases.
- Most patients present with localized disease, and radiation therapy (RT) is the preferred treatment strategy.

Aims of present study

- We aimed to retrospectively analyze our single-institution experience to provide further insight into the characteristics and long-term outcomes of conjunctival EMZL.

Methods

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- Included patients diagnosed with conjunctival EMZL between 01/1995 and 12/2020 at the University of Miami Health Care System.
- Primary endpoints were progression-free survival (PFS) and overall survival (OS), estimated using the Kaplan-Meier method, and compared using the log rank test and the univariable Cox regression analysis.
- Performed a competing risk univariable analysis assessing predictors of cumulative incidence of relapse/progression, with death without relapse as a competing risk, using the Fine and Gray regression analysis.

Results – Baseline characteristics

	All		Stage I	
Variable	N.	%	N	%
Total	72	100	63	100
Age, years				
<=60 years	34	47.2	33	52.4
>60 years	38	52.8	30	47.6
Sex				
Female	46	63.9	40	63.5
Male	26	36.1	23	36.5
Ethnicity				
White	37	51.4	33	52.4
Hispanic/Latino	25	34.7	20	31.7
Black	5	6.9	5	7.9
Other	2	2.8	2	3.2
n/a	3	4.2	3	4.8
Location				
Unilateral conjunctival	56	77.8	51	81.0
Bilateral conjunctival	16	22.2	12	19.0
TNM				
T1N0M0	62	86.1	62	98.4
TxN1-2M0	4	5.6	1	1.6
TxNxM1	6	8.3	0	0
Ann Arbor				
IAE	63	87.5	63	100.0
IIAE	3	4.2	0	0
IVAE	6	8.3	0	0
MALT-IPI score				
0	43	59.7	41	65.1
1 or 2	29	40.3	22	34.9

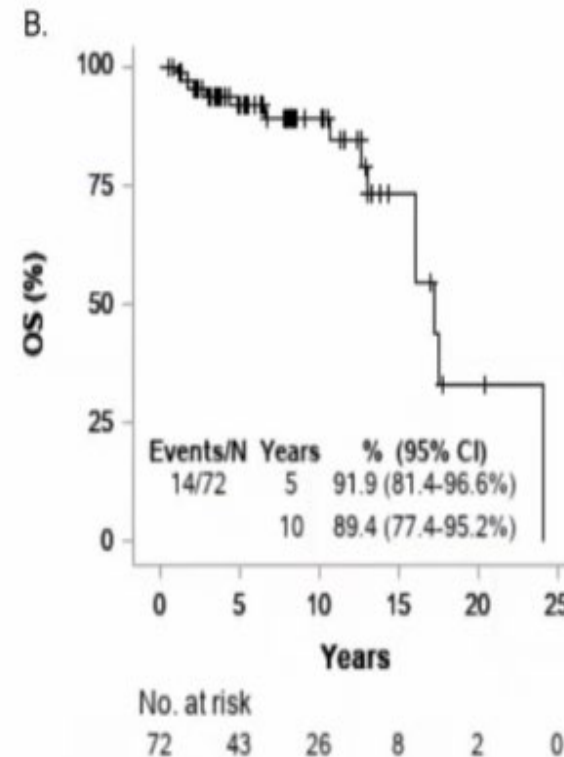
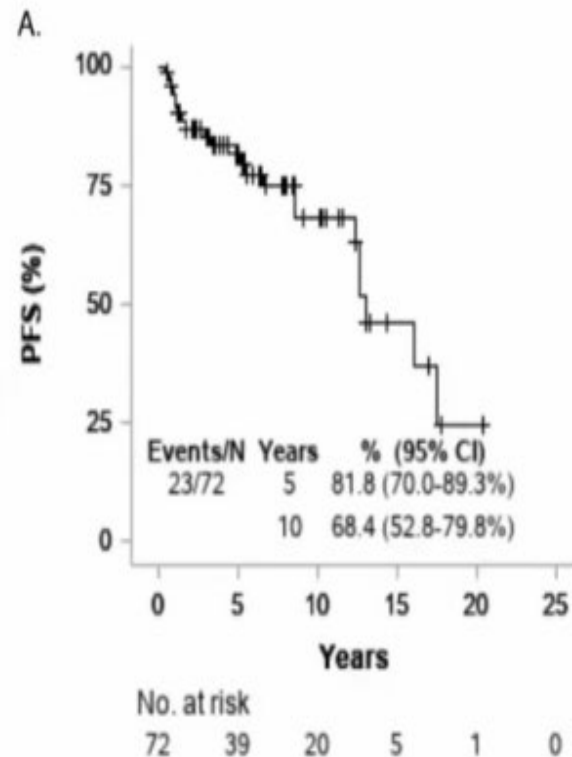
Treatment description

	All		Stage I	
Variable	N.	%	N	%
Total	72	100	63	100
Treatment after surgery				
yes	65	90.3	56	88.9
no	6	8.3	6	9.5
Unknown	1	1.4	1	1.6
Radiation				
yes	51	78.5	48	85.7
Immunochemotherapy (IC)				
IC only	12	18.5	8	14.3
IC + RT	2	3.1	0	n/a

Treatment response and outcomes

	All		Stage I	
Variable	N.	%	N	%
Total	66	100	56	100
First-line treatment response*				
CR	60	92.3	53	94.6
PD	1	1.5	1	1.8
PR	2	3.1	1	1.8
SD	1	1.5	1	1.8
n/a	1	1.5	0	n/a
Relapse**				
yes	14	19.4	10	15.9
no	58	80.6	53	84.1
Relapse within radiation field**				
yes	1	12.5	1	16.7
no	7	87.5	5	83.3
Vital status				
Alive	58	80.6	52	82.5
Dead	14	19.4	11	17.5
*n=only treated patients				
**n=including patients that were not treated				
***n=patients that received RT and relapsed				

Survival analysis

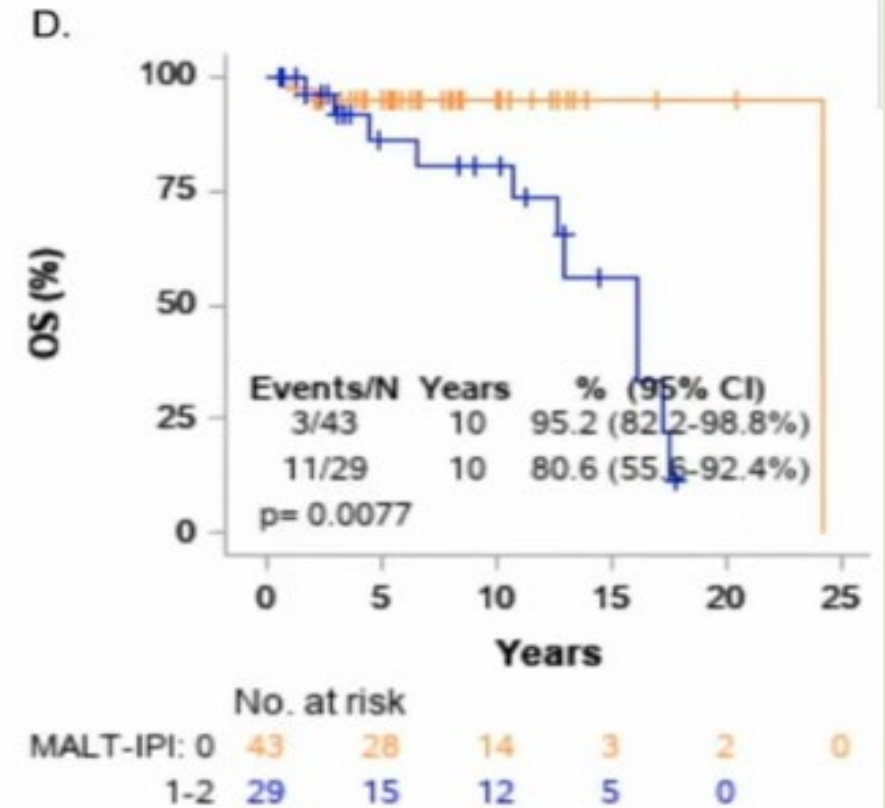
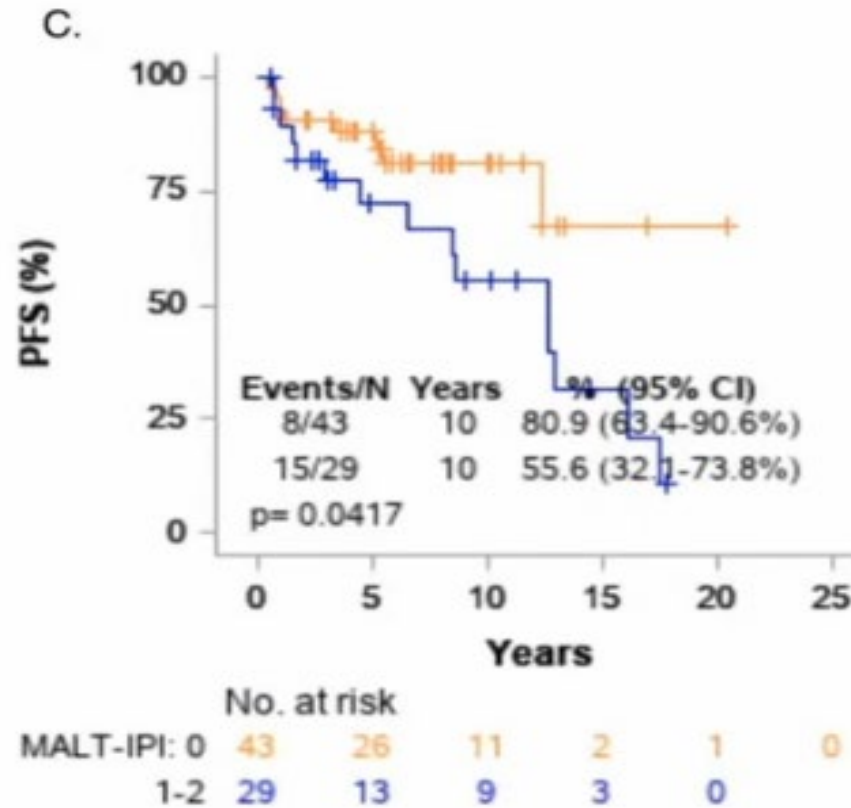


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- Median follow up 6.67 years (0.56-24.13)
- Median PFS and OS for all patients - 5.4 years (range, 0.5-20.4) and 6.7 years (range, 0.6-24.1), respectively



Survival by MALT-IPI score



Univariate analysis Stage I, n=63

		PFS, event=23		OS, event=14	
Variable	Category	HR (95%CI)	p	HR (95%CI)	p
Age	<=60	Ref		Ref	
	>60	2.32 (0.81, 6.70)	0.118	8.01 (1.00, 63.98)	0.05
MALT-IPI	0	Ref		Ref	
	1 or 2	2.37 (0.88, 6.40)	0.088	13.4 (1.67, 107.99)	0.015
Treatment Response	No-CR	Ref		Ref	
	CR	0.15 (0.04, 0.58)	0.006	0.41 (0.05, 3.56)	0.423

Univariate analysis all patients, n=72

		PFS, event=23		OS, event=14	
Variable	Category	HR (95%CI)	p	HR (95%CI)	p
Age	<=60	Ref		Ref	
	>60	2.93 (1.08, 7.95)	0.035	9.07 (1.17, 70.26)	0.035
MALT-IPI	0	Ref		Ref	
	1 or 2	2.42 (1.01, 5.78)	0.048	6.19 (1.35, 28.33)	0.019
Treatment Response	No-CR	Ref		Ref	
	CR	0.13 (0.04, 0.45)	0.001	0.50 (0.06, 4.19)	0.524

UVA Fine and Gray model on time to relapse/progression using death w/o relapse as competing risk



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		No. of Events					Time to relapse	
Variable	Cat.	All	Alive w/o Rel./PD	Alive with Rel./	Dead with Rel./PD	Dead w/o Rel./PD	SHR (95%CI)	p
--	All	72	49	9	5	9		
RT	Yes	53	38	4	4	7	0.33 (0.12, 0.96)	0.041
	No	18	11	5	1	1	Ref	
Treatment Response	CR	63	46	6	4	7	0.11 (0.03, 0.36)	<.001
	No-CR	7	3	3	1		Ref	

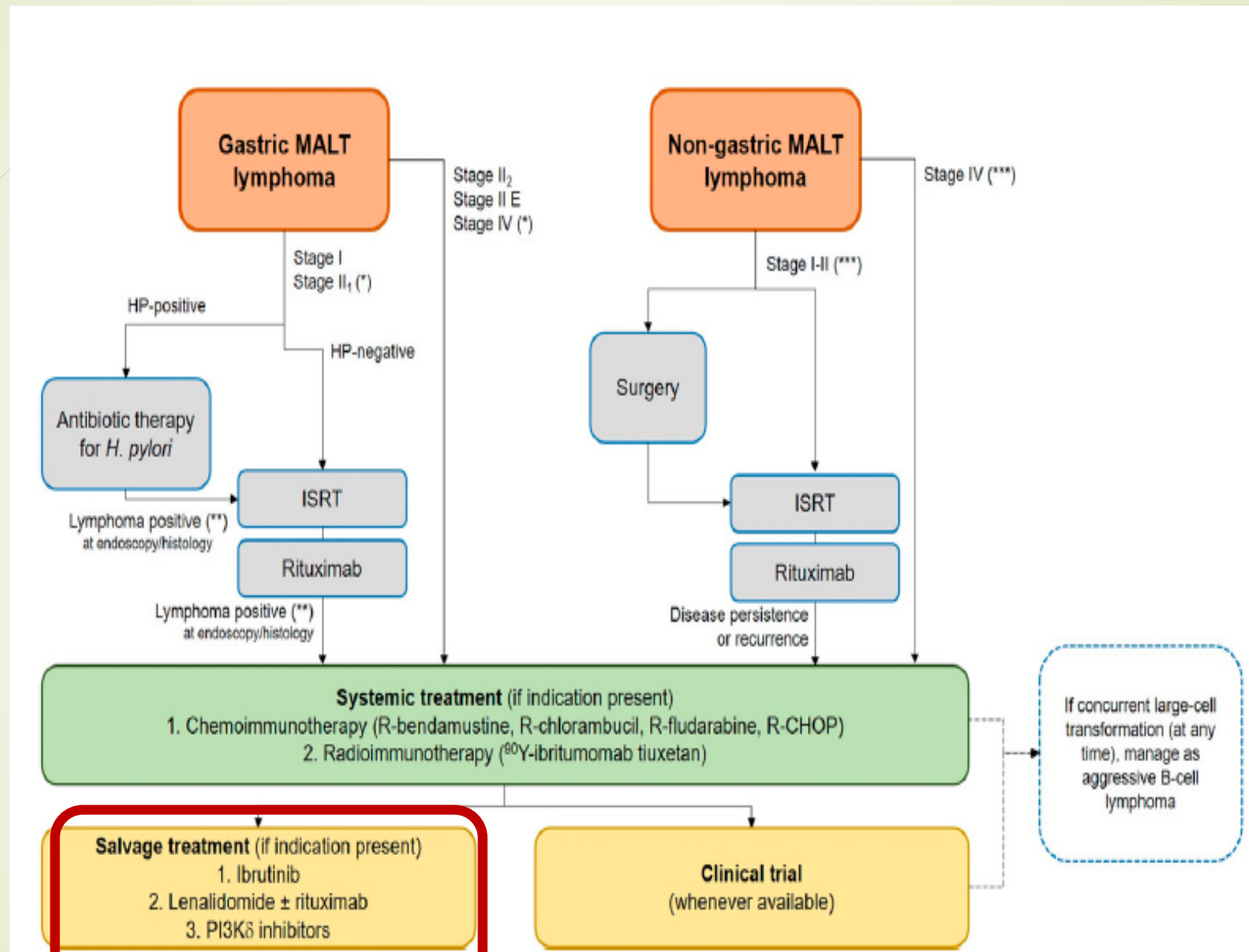
Conclusions

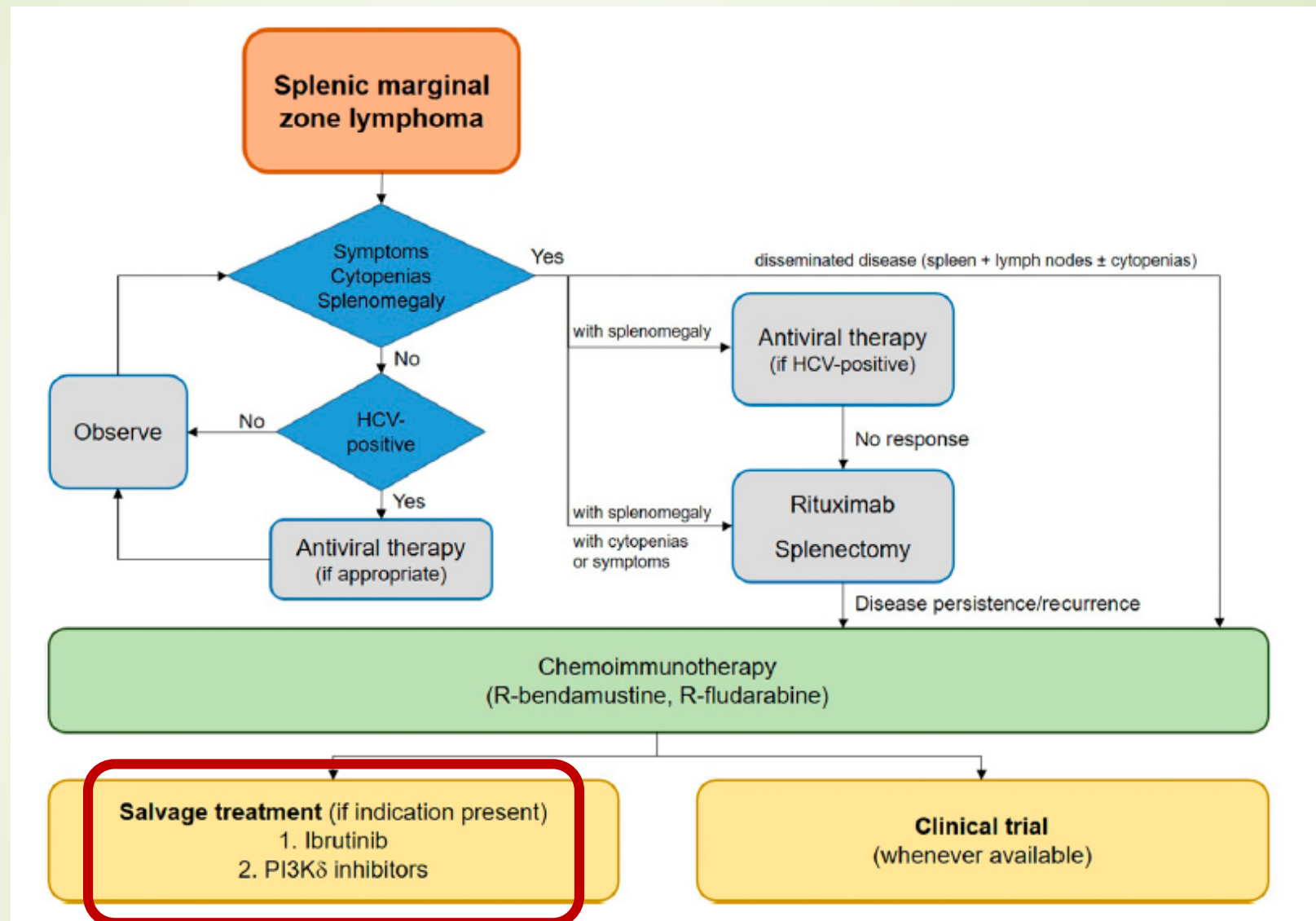
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- Patients with conjunctival EMZL exhibit excellent long-term survival
- RT remains the most effective frontline therapy.
- MALT-IPI appropriately identifies patients at risk for treatment failure.

Take Home Message

- Parsaclisib R/R Ibrutinib- naive MZL hastalarında alternatif olmaya aday bir ajan? (ORR:% 58, CR %6)
- Umbralisib+ Ublituximab R/R MZL hastalarında iyi bir kombinasyondur.
- MIL62+ Lenalidomid relaps ve Rtx refrakter hastalarda etkili tedavi seçeneği olmaya adaydır.
- Rituksimab+ Peg.Interferon alfa-2b ileri evre MZL hastalarında seçenekler arasına girebilir.
- Igm-2323 gibi bispesifik antikorlar MZL de gelecek vadetmektedir.
- Konjunktival EMZL hastalarında RT en efektif frontline tedavidir. MALT-IPI bu hastalarda PFS ve OS ile ilişkilidir.





MZL Targeted and novel agents

Table 4. Experiences with targeted and novel agents in marginal zone lymphomas

Study	Drug	Setting	Patients	ORR %	CR %	Median PFS, mo
Vanazzi et al ⁴⁹	⁹⁰ Y-ibritumomab tiuxetan	MALT relapsed	30	90	77	Not reached*
Samaniego et al ⁵⁰	⁹⁰ Y-ibritumomab tiuxetan	MALT de novo	11	100	—	Not reached
Lossos et al ⁵¹	⁹⁰ Y-ibritumomab tiuxetan	MZL de novo	16	88	56	47.6
Lolli et al ⁵²	⁹⁰ Y-ibritumomab tiuxetan	MALT de novo+relapsed	16	94	63	37.3
Zinzani et al ⁵³	Chemotherapy+ ⁹⁰ Y-ibritumomab tiuxetan	MZL de novo	10	90	90	—
Kiesewetter et al ⁵⁵	Lenalidomide	MALT de novo+relapsed	18	61	33	—
Kiesewetter et al ⁵⁶	Lenalidomide+rituximab ★	MALT de novo+relapsed	46	80	54	—
Becnel et al ⁵⁹	Lenalidomide+rituximab	MZL de novo	30	93	70	59.8
Noy et al ⁶¹	Ibrutinib ★	MZL relapsed	63	48	3	14.2
Gopal et al ⁶²	Idelalisib	MZL relapsed	15	47	7	7.0
Flinn et al ⁶³	Duvelisib	MZL relapsed	18	39	—	—
Dreyling et al ⁶⁴	Copanlisib	MZL relapsed	23	70	9	—
Forero-Torres et al ⁶⁵	Parsaclisib	MZL relapsed	9	78	33	—
Zinzani et al ⁶⁶	Umbralisib ★	MZL relapsed	69	55	10	71%†

*Time-to-treatment failure.

†PFS percentage at 12 months.

ibrutinib (Noy et.al,2017)

Table 2. Summary of adverse events

Event	Total (N = 63)
Most common adverse events of any grade*	
Fatigue	28 (44)
Diarrhea	27 (43)
Anemia	21 (33)
Nausea	16 (25)
Arthralgia	15 (24)
Peripheral edema	15 (24)
Thrombocytopenia	15 (24)
Cough	14 (22)
Dyspnea	13 (21)
Upper respiratory tract infection	13 (21)
AEs grade ≥3†	
Anemia	9 (14)
Pneumonia	5 (8)
Fatigue	4 (6)
Cellulitis	3 (5)
Diarrhea	3 (5)
Hypertension	3 (5)
Lymphocyte count decreased	3 (5)
Neutropenia	3 (5)
Asthenia	2 (3)
Autoimmune hemolytic anemia	2 (3)
Blood bilirubin increased	2 (3)
Muscle spasms	2 (3)
Multiple organ dysfunction	2 (3)
Neutrophil count decreased	2 (3)
Pneumothorax	2 (3)
Sepsis	2 (3)
Serious AEs‡	
Pneumonia	5 (8)
Cellulitis	2 (3)
Autoimmune hemolytic anemia	2 (3)
Pneumothorax	2 (3)
Sepsis	2 (3)

idelalisib (Gopal et al., 2014)

Table 2. Adverse Events during Treatment.*

Event or Abnormality	Grade	
	Any no. (%)	≥3 no. (%)
Adverse event	103 (82)	68 (54)
Diarrhea	54 (43)	16 (13)
Nausea	37 (30)	2 (2)
Fatigue	37 (30)	2 (2)
Cough	36 (29)	0
Pyrexia	35 (28)	2 (2)
Decreased appetite	22 (18)	1 (1)
Dyspnea	22 (18)	4 (3)
Abdominal pain	20 (16)	3 (2)
Vomiting	19 (15)	3 (2)
Upper respiratory tract infection	18 (14)	0
Weight decreased	17 (14)	0
Rash	16 (13)	2 (2)
Asthenia	14 (11)	3 (2)
Night sweats	14 (11)	0
Pneumonia	14 (11)	9 (7)
Peripheral edema	13 (10)	3 (2)
Headache	13 (10)	1 (1)
Hematopoietic laboratory abnormality		
Decreased neutrophils	70 (56)	34 (27)
Decreased hemoglobin	35 (28)	2 (2)
Decreased platelets	32 (26)	8 (6)
Chemical laboratory abnormality		
Increased ALT	59 (47)	16 (13)
Increased AST	44 (35)	10 (8)
Increased alkaline phosphatase	28 (22)	0
Increased bilirubin	13 (10)	0

Umbralisib (Fowler NH,2021)

System Organ Class ^a Preferred Term	Total (N = 208), n (%)	
	Any Grade	Grade ≥ 3
Any TEAE	207 (99.5)	111 (53.4)
Hematopoietic laboratory abnormalities		
Neutropenia	33 (15.9)	24 (11.5)
Any TEAE		
Diarrhea	123 (59.1)	21 (10.1)
Nausea	82 (39.4)	1 (0.5)
Fatigue	64 (30.8)	7 (3.4)
Vomiting	49 (23.6)	1 (0.5)
Cough	43 (20.7)	0 (0.0)
Decreased appetite	39 (18.8)	4 (1.9)
Dizziness	38 (18.3)	1 (0.5)
Headache	33 (15.9)	2 (1.0)
Upper respiratory tract infection	30 (14.4)	0 (0.0)
Insomnia	28 (13.5)	1 (0.5)
Edema peripheral	25 (12.0)	1 (0.5)
Pyrexia	24 (11.5)	0 (0.0)
Chemical laboratory abnormality		
ALT increased	42 (20.2)	14 (6.7)
AST increased	39 (18.8)	15 (7.2)
Blood creatinine increased	29 (13.9)	1 (0.5)

Lenalidomid (Kiesewetter, 2013)

Table 2. Characteristics of hematologic and non-hematologic toxicities.

Adverse event	Grade I + II*	Grade III + IV*
Hematologic		
Anemia	9	0
Thrombopenia	9	1
Leukopenia	6	1
Neutropenia	6	3
Lymphopenia	2	
Non-hematologic		
Anorexia	2	
Biliary colic		SAE
Conjunctivitis	2	
Constipation	3	
Cough	2	1
Edema of the eye	2	
Emesis	2	
Exanthema	5	2 (incl. 1 SAE)
Fatigue	5	
Febrile infection	2	
Fracture (femur)		SAE
Headache	2	
Heartburn	2	
Nausea	4	
Pain joints	2	
Paresthesia	2	
Pneumonia		SAE
Pruritus	7	
Tremor	3	
Vertigo	3	
Others**	14	

R-Lena (Leonard JP, 2019)

Adverse Event	Lenalidomide + Rituximab (n = 176)		Placebo + Rituximab (n = 180)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Neutropenia*	102 (58)	88 (50)	40 (22)	23 (13)
Diarrhea	55 (31)	5 (3)	41 (23)	0
Constipation	46 (26)	0	25 (14)	0
Cough	40 (23)	1 (1)	31 (17)	0
Fatigue	38 (22)	2 (1)	33 (18)	1 (1)
Pyrexia	37 (21)	1 (1)	27 (15)	3 (2)
Leukopenia	36 (20)	12 (7)	17 (9)	3 (2)
Upper respiratory tract infection	32 (18)	2 (1)	23 (13)	4 (2)
Anemia	28 (16)	8 (5)	8 (4)	1 (1)
Headache	26 (15)	1 (1)	17 (9)	0
Infusion-related reaction	26 (15)	4 (2)	24 (13)	0
Thrombocytopenia	26 (15)	4 (2)	8 (4)	2 (1)
Asthenia	24 (14)	2 (1)	19 (11)	1 (1)
Decreased appetite	23 (13)	2 (1)	11 (6)	0
Muscle spasms	23 (13)	1 (1)	9 (5)	1 (1)
Peripheral edema	23 (13)	0	16 (9)	0
Abdominal pain	22 (13)	2 (1)	16 (9)	0
Pruritus	21 (12)	2 (1)	7 (4)	0
Nausea	20 (11)	0	23 (13)	1 (1)
Dyspnea	19 (11)	2 (1)	8 (4)	1 (1)
Rash	19 (11)	2 (1)	7 (4)	1 (1)
Tumor flare	19 (11)	1 (1)	1 (1)	0
Alanine aminotransferase increased	18 (10)	3 (2)	15 (8)	1 (1)
Influenza	17 (10)	1 (1)	8 (4)	0
Vomiting	17 (10)	0	13 (7)	0
Back pain	14 (8)	0	18 (10)	0
Nasopharyngitis	13 (7)	0	18 (10)	0