Denver ASH Review

Updates in FL…by extension MZL and MCL in 2025…..

Tycel Phillips, MD
Associate Professor
City of Hope

Division of Hematology

1

Disclosures

- Research Support
  - Abbvie, Bayer, BMS, Genentech
- Advisory Board
  - Abbvie, ADC Therapeutics, AstraZeneca, Bayer, Beigene, BMS, Genmab, Genentech, Gilead, Eli Lily, Epizyme, Incyte, Pharmacyclics, TG Therapeutics, Seattle Genetics
- Strategic Counsel
  - Epizyme, Genmab
- Scientific Board
  - Genentech, Merck, Genmab

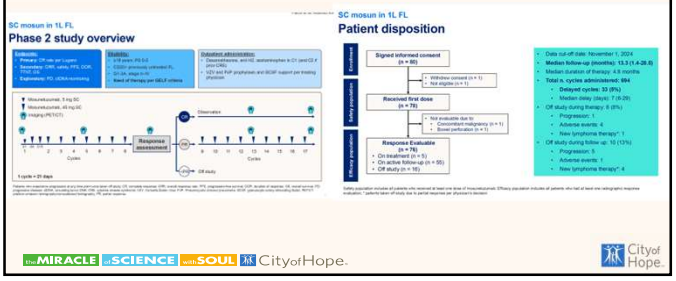
2

What's New in 2025

- Bispecifics in 1L and 2L FL
- 2L…..a new threat to AUGMENT and another option for 3L+
  - inMIND
  - Lonca
- Frontline MCL (Younger)
  - Death of ASCT
    - TRIANGLE
      - More mature follow up.
    - EA4151
      - Initial Presentation
  - Frontline MCL (Older)
    - ENRICH

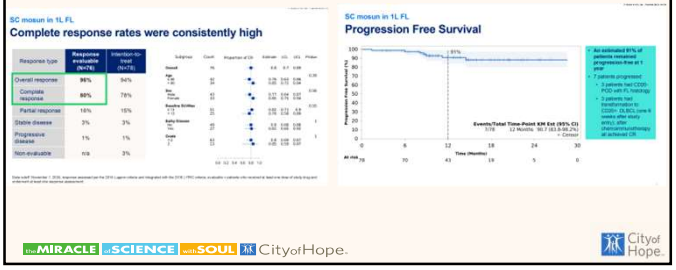
3

Mosun in 1L FL



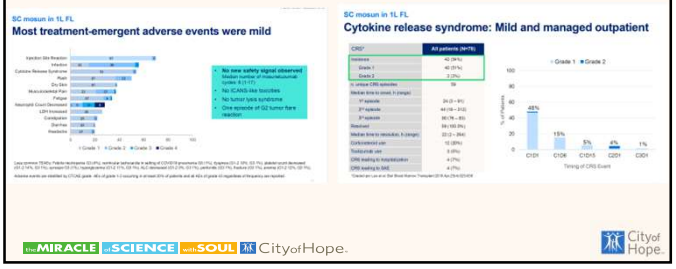
4

Response



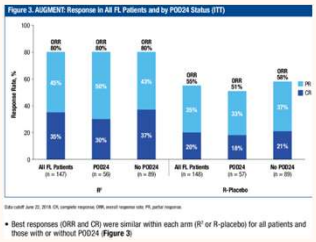
5

AE's of Interest



6

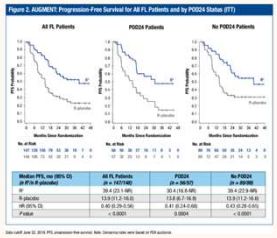
R2 (Augment)

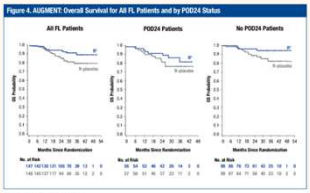


- Best responses (ORR and CR) were similar within each arm (R² or R-placebo) for all patients and those with or without POD24 (**Figure 3**)

- Randomized Phase 3 study of R2 vs. rituximab in R/R FL and MZL (Leonard et al. 2019
- Led to approval of R2 in 2L setting
- Results suggest that treatment is mostly agnostic to POD24 status

7





- At a median follow-up of 28.6 mo (range, 0.5-50.9), OS was not reached in all patients or according to POD24 status (**Figure 4**)

8

Study Design: EPCORE® NHL-2 Arm 2

Key inclusion criteria
- R/R CD20⁺ FL
  - Grade 1–3A
  - Stage II–IV
- ≥1 prior treatment, including an anti-CD20 antibody
- Need for treatment per GELF criteria[1]
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

Concomitant fixed-duration epcoritamab 48 mg + R²
(28-day cycles up to 2 years)

Agent	C1	C2	C3	C4–5	C6–9	C10–12	C13+
2-step-up-dose regimen[a]	Epcoritamab SC 48 mg						
	Cohort A[b]	QW		Q2W		Q4W	
	Cohort B[b]	QW	Q4W				
R²	Rituximab IV 375 mg/m²	QW	Q4W				
	Lenalidomide PO 20 mg/d	D1–21 of each cycle					

Primary endpoint: ORR per Lugano criteria[c]

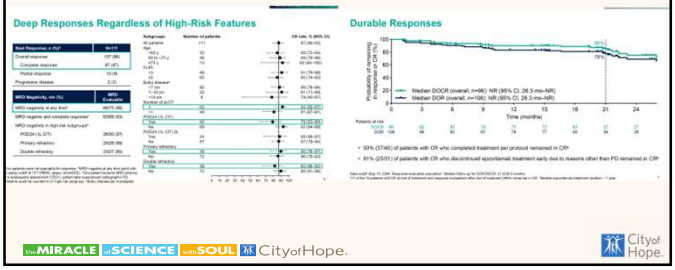
Key secondary endpoints: CR rate, DOR, DOCR, PFS, TTNT, OS, MRD analysis,[d] and safety and tolerability

Data cutoff: May 15, 2024
Median follow-up: 25.3 months

NCT04663347. [a]Patients received epcoritamab with 2 step-up doses (0.16 mg on C1D1 and 0.8 mg on C1D8) before the first full dose on C1D15; corticosteroid prophylaxis to mitigate CRS, and protocol-mandated hospitalization for 24 h after the first full dose. [b]Cohorts A and B enrolled 27 and 84 patients, respectively. [c]Tumor response was evaluated by PET-CT (or separate PET and CT/MRI when PET-CT was not available) obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until disease progression. [d]MRD was assessed in PBMCs using the clonoSEQ® assay (Adaptive Biotechnologies) with a cutoff of 10^{-4}. 1. Brice P, et al. *J Clin Oncol*. 1997;15:11:10-7.

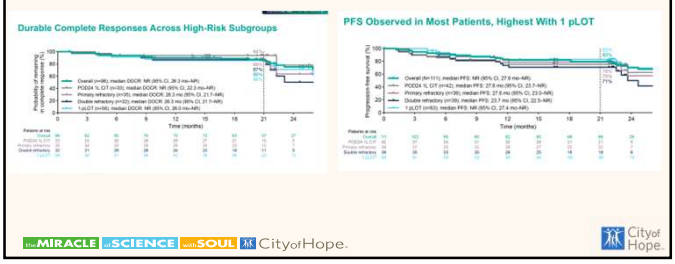
9

Response



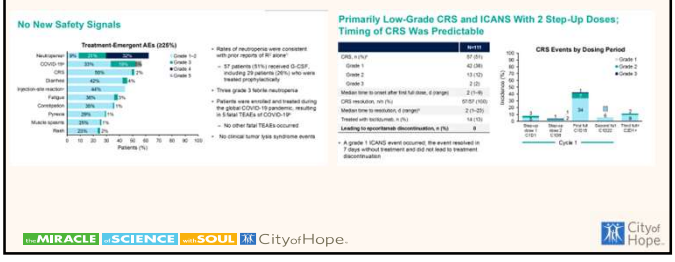
10

Response in High-Risk Groups



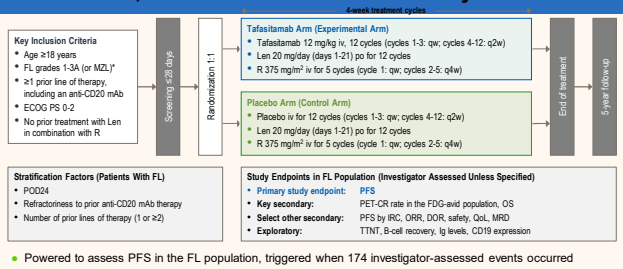
11

AE's of Interest



12

inMIND: Phase 3, Double-Blind, Placebo-Controlled, International, Multicenter Randomized Study

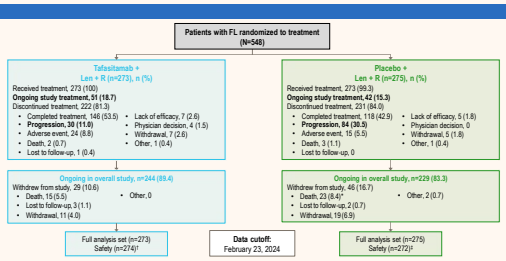


- Powered to assess PFS in the FL population, triggered when 174 investigator-assessed events occurred
- OS analysis planned after 5 years of follow-up

*Limited number of patients with MZL were enrolled but the study was not powered for this population; data for patients with MZL will be presented separately. DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG, fluorodeoxyglucose; FL, follicular lymphoma; Ig, immunoglobulin; IRC, independent review committee; iv, intravenous; Len, lenalidomide; mAb, monoclonal antibody; MRD, minimal residual disease; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PET-CR, positron-emission tomography–complete response; PFS, progression-free survival; po, orally; POD24, disease progression within 24 months of initial diagnosis; QoL, quality of life; qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks; R, rituximab; TTNT, time to next treatment.

13

Patient Disposition



- At primary analysis, median number of cycles received was 12 with tafasitamab and 11 with placebo

*Death for 1 patient was reported but not recorded in the end-of-study form. †One patient randomized to the placebo + len + R group is included in the tafasitamab + len + R safety population because the patient erroneously received tafasitamab. ‡Three patients randomized to the placebo + len + R group are not included in the safety population because they erroneously received tafasitamab (n=1), or did not receive study treatment due to confirmation of R hypersensitivity (n=1), or the patient withdrew from the study (n=1). FL, follicular lymphoma; Len, lenalidomide; R, rituximab.

14

FL Patient Population Comparison

Variable	inMIND Tafasitamab + Len + R (n=273)	inMIND Placebo + Len + R (n=275)	AUGMENT[1] R + Len (n=147)
Median age, years	64	64	62
Male, %	55	54	42
Ann Arbor stage IV at enrollment, %	55	59	30
FL grade 3A, %	25	26	12
FLIPI high risk (score 3-5) , %	50	55	37
ECOG PS 0, %	66	70	67
ECOG PS 1-2, %	34	30	33
B symptoms present, %	23	24	8
High tumor burden per GELF (yes), %	81	84	52
Refractory to last prior regimen, %	41	35	18
Refractory to anti-CD20, %	43	42	–

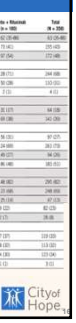
1. Leonard JP, et al. *J Clin Oncol*. 2019;37:1188-1899.
ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; len, lenalidomide; R, rituximab.

15

Baseline Characteristics

ITT population; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; ITT, intent-to-treat; Len, lenalidomide; R, rituximab.

Variable	Tafasitamab + Len + R (n=273)	Placebo + Len + R (n=275)	Total (N=548)
Median age, years (range)	64.0 (36, 88)	64.0 (31, 85)	64.0 (31, 88)
≥75, n (%)	54 (19.8)	54 (19.6)	108 (19.7)
Male sex, n (%)	150 (54.9)	149 (54.2)	299 (54.6)
Median time since initial diagnosis of FL, years (range)	5.2 (0, 34)	5.5 (1, 33)	5.3 (0, 34)
ECOG PS at screening, n (%)			
0	181 (66.3)	192 (69.8)	373 (68.1)
1-2	92 (33.7)	83 (30.2)	175 (31.9)
Ann Arbor stage, n (%)			
I or II	52 (19.0)	50 (18.2)	102 (18.6)
III or IV	221 (81.0)	225 (81.8)	446 (81.4)
FL grade, n (%)			
1 or 2	203 (74.4)	203 (73.8)	406 (74.1)
3A	67 (24.5)	71 (25.8)	138 (25.2)
B symptoms, n (%)	63 (23.1)	67 (24.4)	130 (23.7)
FLIPI score, n (%)			
0-1	57 (20.9)	57 (20.7)	114 (20.8)
2	79 (28.9)	67 (24.4)	146 (26.6)
3-5	137 (50.2)	150 (54.5)	287 (52.4)
GELF criteria, n (%)	222 (81.3)	232 (84.4)	454 (82.8)
FL diagnosis confirmed by central pathology, n (%)	256 (93.8)	259 (90.5)	505 (92.2)



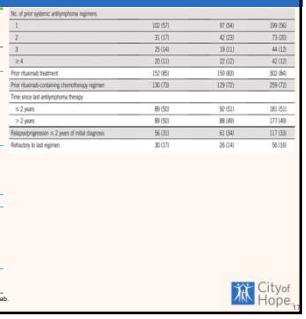
•John P. Leonard et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. JCO 37, 1188-1199(2019) DOI: 10.1200/JCO.19.00010

16

Treatment History

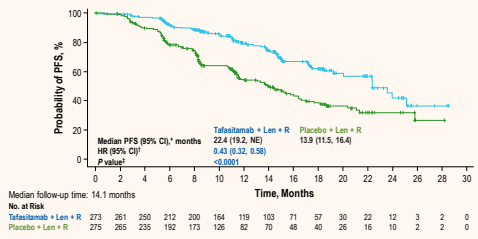
Variable	Tafasitamab + Len + R (n=273)	Placebo + Len + R (n=275)	Total (N=548)
Median number of prior lines of therapy (range)	1.0 (1, 7)	1.0 (1, 10)	1.0 (1, 10)
Number of prior lines of therapy, n (%)			
1	147 (53.8)	153 (55.6)	300 (54.7)
2	66 (24.2)	71 (25.8)	137 (25.0)
3	39 (14.3)	30 (10.9)	69 (12.6)
≥4	21 (7.7)	21 (7.6)	42 (7.7)
Time since last anti-lymphoma therapy, n (%)			
≤2 years	147 (53.8)	157 (57.1)	304 (55.5)
>2 years	126 (46.2)	118 (42.9)	244 (44.5)
POD24, n (%)	85 (31.1)	88 (32.0)	173 (31.6)
Relapsed/refractory status to last therapy, n (%)			
Relapsed	148 (54.2)	164 (59.6)	312 (56.9)
Refractory	112 (41.0)	97 (35.2)	209 (38.1)
Undetermined	13 (4.8)	14 (5.1)	27 (4.9)
Refractory to prior anti-CD20 therapy, n (%)	118 (43.2)	115 (41.8)	233 (42.5)

ITT population. ITT, intent-to-treat; Len, lenalidomide; POD24, disease progression within 24 months of initial diagnosis; R, rituximab.



17

Primary Endpoint: PFS by Investigator Assessment

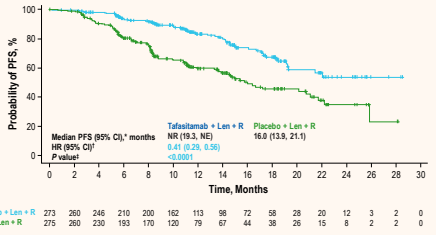


Significant improvement in PFS was observed with tafasitamab

ITT population. *Estimated using Kaplan-Meier method. †Estimated using a stratified Cox proportional hazard model. ‡Stratified log-rank test with a 2-sided significance level of 5%. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Len, lenalidomide; NE, not evaluable; PFS, progression-free survival; R, rituximab.

18

PFS by Independent Review Committee



Significant PFS benefit was confirmed by independent review committee

ITT population. *Estimated using Kaplan-Meier method. †Estimated using a stratified Cox proportional hazard model. ‡Nominal *P* value; stratified log-rank test with a 2-sided significance level of 5%. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Len, lenalidomide; NE, not evaluable; NR, not reached; PFS, progression-free survival; R, rituximab.

19

PET-CR and ORR

PET-CR (FDG-Avid Population)	Tafasitamab + Len + R	Placebo + Len + R
Patients with FDG-avid disease at baseline	251	254
Patients with postbaseline PET assessments, n (%)*	201/251 (80.1)	205/254 (80.7)
Best metabolic response based on PET, n (%)†		
CMR	124 (49.4)	101 (39.8)
PMR	37 (14.7)	39 (15.4)
NMR/SD	19 (7.6)	12 (4.7)
PMD	19 (7.6)	51 (20.1)
Not done	50 (19.9)	46 (19.3)
PET-CR rate, % (95% CI)	**49.4** (43.1, 55.8)	**39.8** (33.7, 46.1)
Odds ratio (95% CI)	**1.5 (1.04, 2.13)**	
Nominal *P* value	**0.0286**	

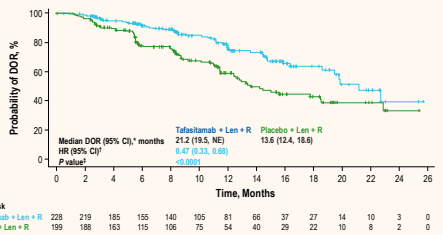
ORR (ITT Population)	Tafasitamab + Len + R	Placebo + Len + R
Patients, n	273	275
Best overall response, n (%)‡		
CR	142 (52.0)	112 (40.7)
PR	86 (31.5)	87 (31.6)
SD	28 (10.3)	46 (16.7)
PD	7 (2.6)	20 (7.3)
NE	2 (0.7)	0
Not done	8 (2.9)	10 (3.6)
ORR, % (95% CI)	**83.5** (78.6, 87.7)	**72.4** (66.7, 77.6)
Odds ratio (95% CI)	**2.0 (1.30, 3.02)**	
Nominal *P* value	**0.0014**	

Significant improvement in PET-CR rate and ORR was observed with tafasitamab

Analysis by investigator assessment. *Calculated based on patients with a positive PET scan at baseline, defined as having a Deauville score of 4 or 5 at baseline. †Two patients (0.8%) in both arms had PET after confirmed PD or new antilymphoma treatment initiation. ‡Per Lugano 2014 classification. CI, confidence interval; CMR, complete metabolic response; CR, complete response; FDG, fluorodeoxyglucose; ITT, intent-to-treat; Len, lenalidomide; NE, not evaluable; NMR, nonmetabolic response; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PET-CR, positron emission tomography-complete response; PMD, progressive metabolic disease; PMR, partial metabolic response; PR, partial response; R, rituximab; SD, stable disease.

20

Duration of Response

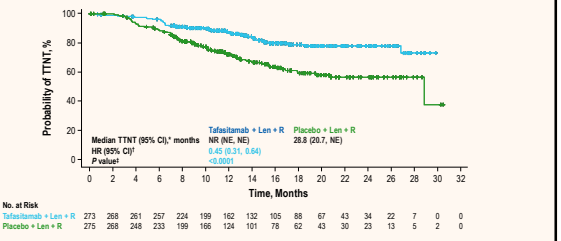


Significant improvement in DOR was observed with tafasitamab

ITT population. Analysis by investigator assessment. *Estimated using Kaplan-Meier method. †Estimated using a stratified Cox proportional hazard model. ‡Nominal *P* value; stratified log-rank test with a 2-sided significance level of 5%. CI, confidence interval; DOR, duration of response; HR, hazard ratio; ITT, intent-to-treat; Len, lenalidomide; NE, not evaluable; R, rituximab.

21

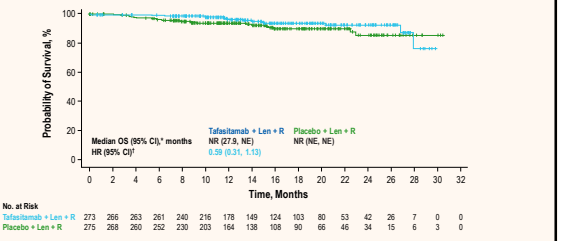
Time to Next Treatment



ITT population. Analysis by investigator assessment. *Estimated using Kaplan-Meier method. †Estimated using a stratified Cox proportional hazard model. ‡Nominal *P* value; stratified log-rank test with a 2-sided significance level of 5%. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; len, Lenalidomide; NE, not evaluable; NR, not reached; R, rituximab; TTNT, time to next treatment.

22

Overall Survival



- OS was tested only for futility at the time of the primary analysis
- After a median follow-up of 15.3 months, the futility threshold was not crossed and a positive trend was observed

ITT population. Analysis by investigator assessment. *Estimated using Kaplan-Meier method. †Estimated using a stratified Cox proportional hazard model. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat;
Len, lenalidomide; NE, not evaluable; NR, not reached; OS, overall survival; R, rituximab.

23

Grade 3 or 4 TEAEs and Dose Modifications

Most Common Grade 3 or 4 TEAEs (≥5% in Any Group)

Preferred Term, n (%)	Tafasitamab + Len + R (n=274)*	Placebo + Len + R (n=272)†	Total (n=546)
Neutropenia	109 (39.8)	102 (37.5)	211 (38.6)
Pneumonia	23 (8.4)	14 (5.1)	37 (6.8)
Thrombocytopenia	17 (6.2)	20 (7.4)	37 (6.8)
Neutrophil count decreased	16 (5.8)	18 (6.6)	34 (6.2)
Anemia	12 (4.4)	16 (5.9)	28 (5.1)
COVID-19	16 (5.8)	6 (2.2)	22 (4.0)
COVID-19 pneumonia	13 (4.7)	3 (1.1)	16 (2.9)

- Tafasitamab and placebo dose interruptions or discontinuations due to TEAEs were similar between treatment arms, n (%):
  - Dose delay or interruption due to TEAEs: 203 (74%) vs 190 (70%)
  - Discontinued study treatment due to TEAEs: 30 (11%) vs 18 (7%)
- Len discontinuations due to TEAEs were similar between tafasitamab and placebo arms, n (%):
  - 39 (14%) vs 31 (11%)
- Len dose reductions were similar between tafasitamab and placebo arms
  - Median relative dose intensity: 86% vs 87%

24

Summary of Deaths and Fatal TEAEs

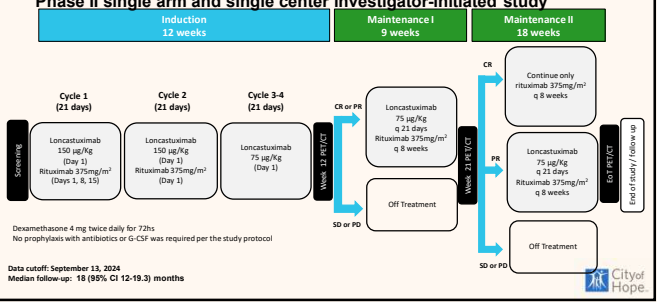
Variable, n (%)	Tafasitamab + Len + R (n=274)*	Placebo + Len + R (n=272)†	Total (n=546)
All deaths	**15 (5.5)**	**23 (8.5)**	38 (7.0)
Disease progression	**5 (1.8)**	**17 (6.3)**	22 (4.0)
Adverse event with fatal outcome	**6 (2.2)**	**6 (2.2)**	12 (2.2)
COVID-19	2 (0.7)	0	2 (0.4)
COVID-19 pneumonia	0	2 (0.7)	2 (0.4)
Sepsis	1 (0.4)	1 (0.4)	2 (0.4)
Adenocarcinoma gastric	1 (0.4)	0	1 (0.2)
Carcinoid tumor (large intestine)	1 (0.4)	0	1 (0.2)
Death‡	1 (0.4)	0	1 (0.2)
Bronchopulmonary aspergillosis	0	1 (0.4)	1 (0.2)
Cardiac failure	0	1 (0.4)	1 (0.2)
Pneumonia	0	1 (0.4)	1 (0.2)
Deaths reported after 90-day follow-up interval	4 (1.5)	0	4 (0.7)
Heart failure	1 (0.4)	0	1 (0.2)
Lung infection	1 (0.4)	0	1 (0.2)
Pneumonia	1 (0.4)	0	1 (0.2)
Respiratory failure	1 (0.4)	0	1 (0.2)

Safety population. *One patient randomized to the placebo + len + R group is included in the tafasitamab + len + R safety population because the patient

25

Study Schema

Phase II single arm and single center investigator-initiated study



26

Baseline Patient & Disease Characteristics

39 patients enrolled between January 2022 to June 2024

		n = 39	%
Median age, years (range)		68 (47-89)	
Male		21	53.8
Hispanic		22	56.4
Prior transformed FL		11	28.2
FL grade 3A		11	28.2
Bone marrow involvement		13	33.3
ECOG performance status	0 / 1	29 / 10	74.3 / 25.7
Elevated β2-microglobulin		27	69.2
Ann-Arbor stage	II / III-IV	7 / 32	17.9 / 79.1
FLIPI risk score	0-1 / 2 / 3-5	9 / 6 / 24	23 / 15.4 / 61.6
Progression of disease within 24 months		20	51.5
High-tumor burden by GELF criteria		36	92

27

Prior Treatment Characteristics

	n = 39	%
Refractory to last therapy	20	51
Relapsed FL	19	49
Median no, of prior lines, n (range)	1 (1-6)	
≥3 lines of therapy	11	28
Prior frontline regimens		
• R-CHOP	22	56
• Bendamustine with rituximab	10	26
• Rituximab	6	15
• Fludarabine, mitoxantrone, dexamethasone with rituximab	1	3

28

TEAEs

Most Common (≥10% Overall) Treatment-Emergent Adverse Events

	Adverse event	Grade 1-2, n	%	Grade 3, n	%	Grade 4, n	%	Any grade, n	%
Hematological TEAEs	Neutropenia	10	25.6	4	10.3	1	2.6	15	38.5
	Anemia	14	35.9					14	35.9
	Lymphopenia	5	12.8	5	12.8	3	7.7	13	33.3
	Thrombocytopenia	9	23.1					9	23.1
Non-hematological TEAEs	Hyperglycemia	16	41	1	2.6			17	43.6
	Increased ALP	16	41					16	41
	Increased ALT	14	35.9	1	2.6			15	38.5
	Fatigue	15	38.5	1	3.1			15	38.5
	Increased AST	15	38.5					15	38.5
	Rash maculo-papular	14	35.9					14	35.9
	Localized edema	5	12.8	1	2.6			6	15.4
	Photosensitivity	6	15.4					6	15.4
	Generalized edema	5	12.8	1	2.6			6	15.4
	Diarrhea	6	15.4					6	15.4
	Pleural effusion	5	12.8					5	12.8

29

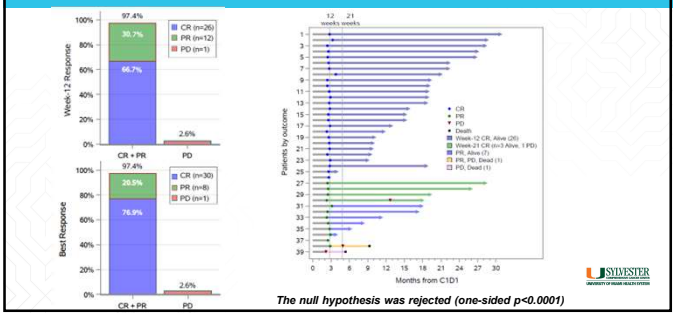
	Grade 1-2, n	%	Grade 3, n	%	Grade 4, n	Any grade n	%
Upper respiratory infection	4	10.3	1	2.6		5	12.6
Infections – Other*	5	12.6				5	12.6
UTI	4	10.3				4	10.3
Skin infection	2	5.1	1	2.6		3	7.7

**Includes 3 cases of covid-19 infection*

- **Disease progression (n=2) was the most common cause of treatment discontinuation (*LBCL on confirmatory biopsies*)**
- **No treatment-related deaths occurred during the study course**
- **Four (10.2%) patients experienced related serious adverse events**
  - Cellulitis after loncastuximab extravasation
  - Febrile neutropenia
  - Dyspnea secondary to pleural effusion
  - Generalized edema

30

Efficacy



The null hypothesis was rejected (one-sided p<0.0001)

31

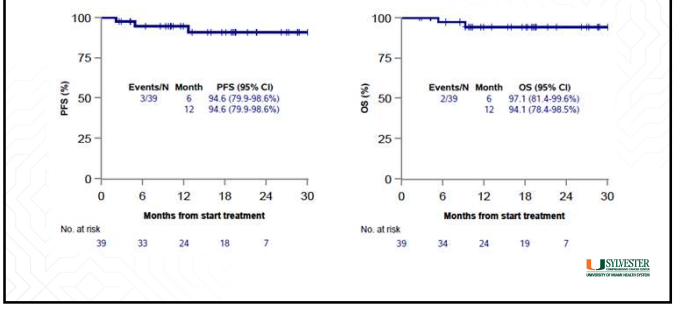
Post-hoc Efficacy Analyses

	n	Best ORR	Best CR rate
POD24*	20	100%	85%
High risk FLIPI score	24	96%	67%
Prior transformed FL	11	100%	73%
Rituximab with an alkylating agent	32	100%	75%

**Previously treated with rituximab and an alkylating agent*

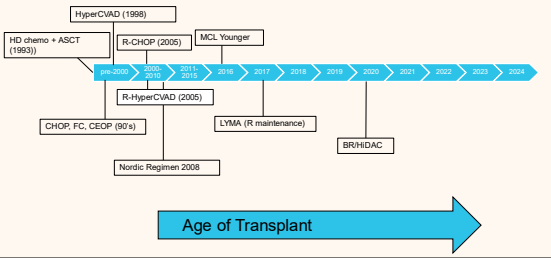
32

Time-to-Event Endpoints



33

Young/Fit……Then

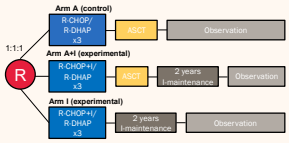


34

TRIANGLE Phase 3 Study of Ibrutinib + SOC as a Substitute for ASCT in Younger Patients With MCL: Study Design and Patients

Key Eligibility Criteria
- Previously untreated stage II-IV MCL
- Age <66 years
- Suitable for HA and ASCT
- ECOG PS 0-2

- R maintenance (± I) was added in all 3 trial arms, following national guidelines. It was initiated in 168 (58%) patients in Arm A; 165 (57%) patients in Arm A+I; and 158 (54%) patients in Arm I



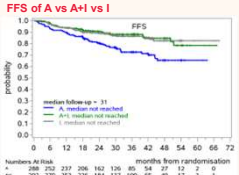
Primary endpoint: FFS
Secondary endpoints: Response rates, PFS, RD, OS, safety

*2 patients aged 66 & 68 years were randomized. †1 CLL, 1 FL. ‡1 NHL NOS, 1 HD, 2 MZL. §1 HCL, 1 DLBCL.
Dreyling M, et al. ASH 2022. Abstract 1.

35

TRIANGLE Phase 3 Study of Ibrutinib + SOC as a Substitute for ASCT in Younger Patients With MCL: Efficacy

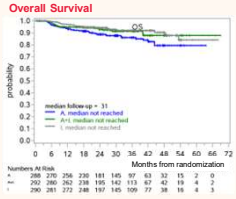
FFS of A vs A+I vs I



- Test for A+I vs I FFS is ongoing

Next Lymphoma Treatment After 1st Treatment Failure, n (%)	A (n=68)	A+I (n=35)	I (n=37)
With ibrutinib	34 (79)	4 (24)	3 (11)
Without ibrutinib	9 (21)	13 (76)	24 (89)
No treatment	25	18	10

Overall Survival

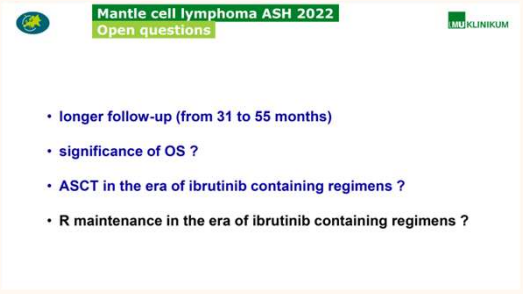


- 3-year OS: A 86%; A+I 91%; I 92%
- Too early to determine statistical significance

Dreyling M, et al. ASH 2022. Abstract 1.

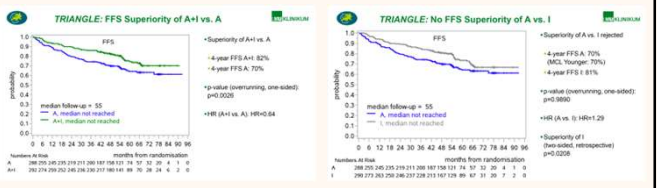
36

Updates from ASH 2024



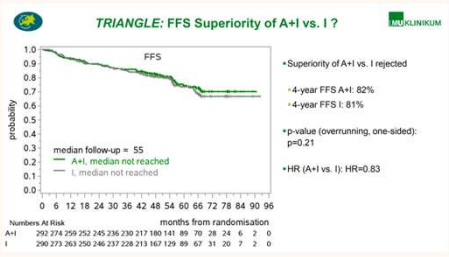
37

Failure Free Survival



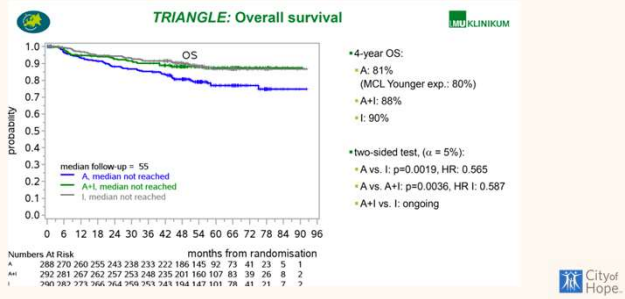
38

Is Transplant needed when using a BTKi in 1L



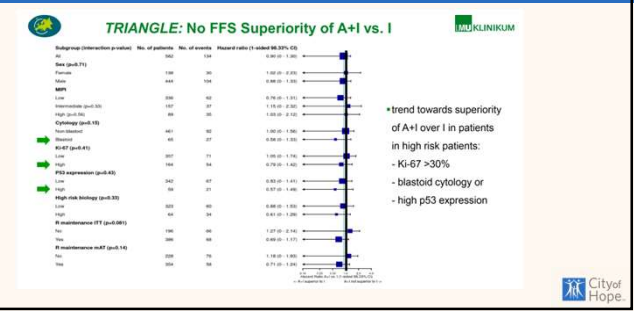
39

Survival



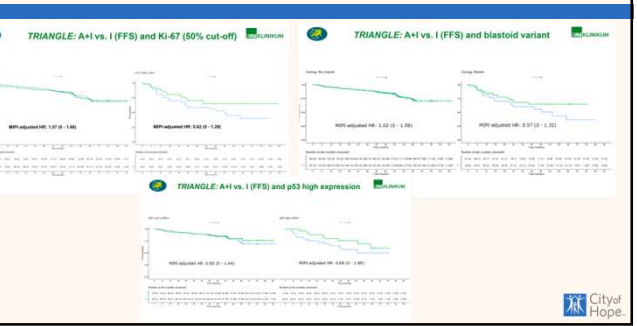
40

Transplant vs. No Transplant in experimental arms



41

Does ASCT benefit (I) in High Risk Groups



42

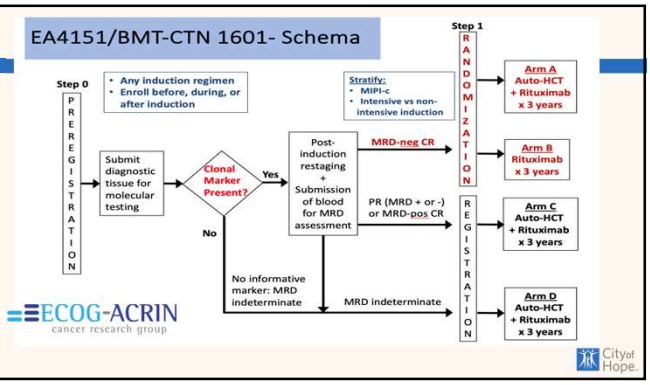
TRIANGLE CONCLUSION

- ASCT w/o any reasonable benefit in 1L MCL
  - SOC w/ inferior FFS/OS vs. both BTKi containing arms
    - No sufficient benefit of ASCT + I vs. I even in high-risk patients
      - Small gain doesn't overcome increase in AE's
- TRIANGLE regimen should be considered new SOC in younger
  - Questions remain??
    - Does exposure to a BTKi in 1L even w/ a finite time frame impact 2L care.
      - IF yes then options are limited currently (post BTKi void)…
    - Substantial benefit in high-risk patients but is this something needed for all patients…..
    - Impact of R maintenance or lack there of…on outcomes in SOC arm.

City of Hope

43

EA4151/BMT-CTN 1601- Schema

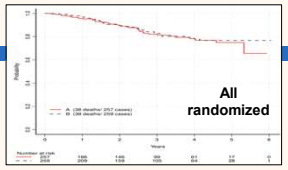


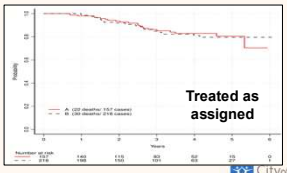
City of Hope

44

OS – Arms A & B

- With median follow up of 2.7 years, the futility boundary was an OS hazard ratio (HR) of 0.984 for Arm A vs B.
- The estimated OS HR for Arm A vs B in all randomized (n=516) and pts treated as assigned (n=375) were 1.11 (CI 0.71-1.74, p=0.66) and 1.00 (CI 0.58-1.74, p=0.99), respectively **and crossed the futility boundary**.
- The 3 year OS for Arms A and B were 82.1% and 82.7% in all randomized pts, and 86.2% and 84.8% in pts treated as assigned.



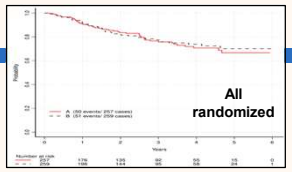


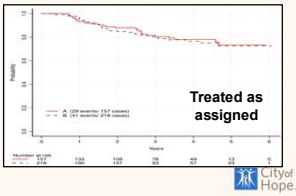
City of Hope

45

PFS – Arms A & B

- The estimated PFS HR for Arm A vs B in all randomized (n=516) and pts treated as assigned (n=375) were 1.05 (CI 0.71-1.56, p=0.79) and 0.95 (CI 0.59-1.54, p=0.84), respectively.
- The 3-year PFS for Arms A and B were 76.6% and 77.4% in all randomized pts, and 81.5% and 80.4% in pts treated as assigned.

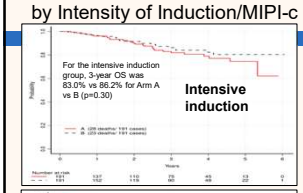


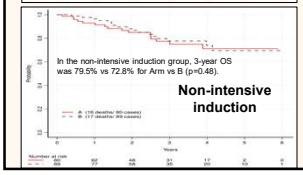


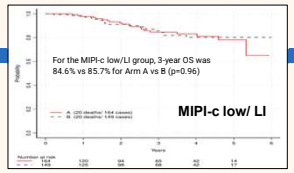
City of Hope

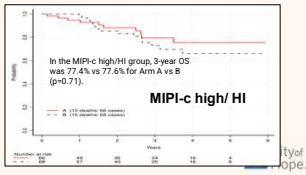
46

OS – Arms A & B
by Intensity of Induction/MIPI-c





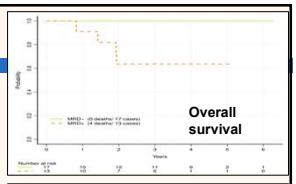


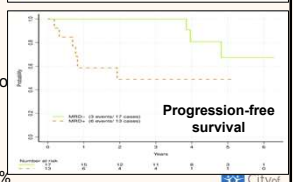


47

Arm C (MRD+ pts)
by post-transplant MRD status

- For Arms C and D, 3 yr OS were 81.9% (CI 69.6-96.4%) and 85.1% (CI 76.0%-95.4%), respectively
- For Arms C and D, 3 yr PFS were 76.9% (CI 64.4-91.7%), and 73.4% (62.7-85.9%), respectively.
- Exploratory analysis of MRD+ pts (Arm C) showed that 3-year OS in pts who converted to uMRD6 post auto-HCT (n=17) was 100%, vs 63.6% in those who remained MRD+
- Similarly, 3-year PFS in pts who converted to uMRD6 post auto-HCT was 100% versus 48.8% in those who remained MRD+





City of Hope

48

EA4151

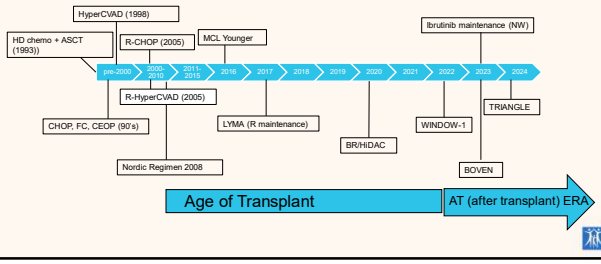
- What to make of this considering study results and recent approval of test by medicare……
  - If patients are MRD negative it appears you can avoid ASCT
    - Appears due to longer f/u being needed to verify that results are maintained due to the incurable nature of MCL…….
  - Test can be now be obtained as SOC (reimbursable for most and company has assistance now for those whose companies will not pay).
  - What to do if your MRD + or indeterminate
    - Study wasn't really designed to address but in those who convert after ASCT outcomes appear favorable but that as a minority of those on study.
    - More work needs to be done to determine effective intervention for these patients

49

End of an ERA

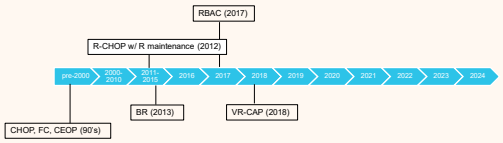
50

Young/Fit……Now



51

Older/Unfit……Then



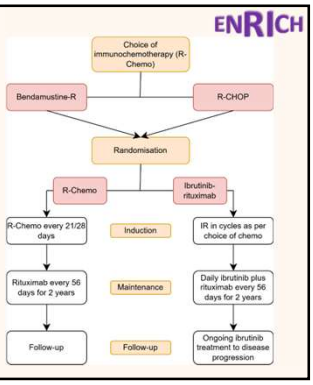
52

Trial design

Inclusion criteria
- 60 years or older
- Pathologically confirmed MCL, including either cyclin D1 overexpression or t(11;14)(q13;q32)
- Previously untreated, measurable (>1.5cm), stage II-IV MCL in need of treatment
- ECOG 0-2

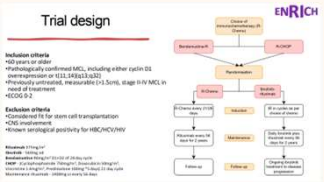
Exclusion criteria
- Considered fit for stem cell transplantation
- CNS involvement
- Known serological positivity for HBC/HCV/HIV

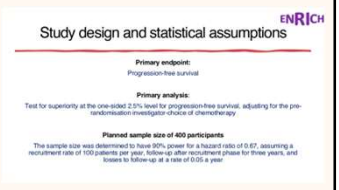
Rituximab 375mg/m²
Ibrutinib - 560mg od
Bendamustine 90mg/m² D1+D2 of 28 day cycle
CHOP - (Cyclophosphamide 750mg/m², Doxorubicin 50mg/m², Vincristine 1.4mg/m², Prednisolone 100mg *5 days) 21 day cycle
Maintenance rituximab - 1400mg sc every 56 days



53

ENRICH

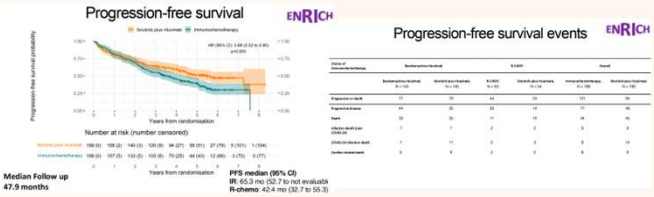




the MIRACLE of SCIENCE with SOUL City of Hope

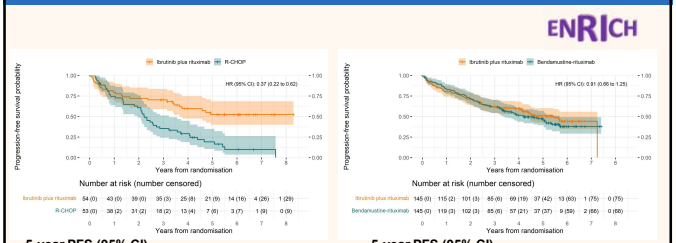
54

Progression-Free Survival



55

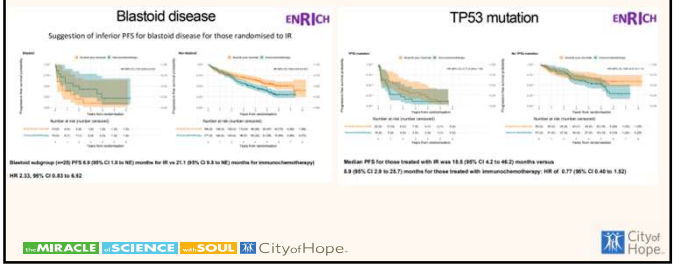
Progression-free survival



56

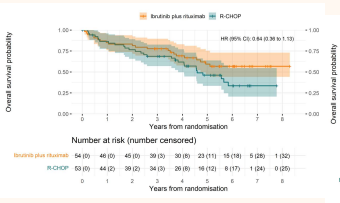
Response in High-Risk Groups

Suggestion of inferior PFS for blastoid disease for those randomised to IR



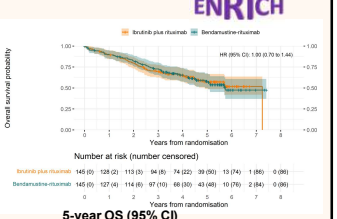
57

Overall survival



5-year OS (95% CI)
IR: 59.4% (46.9% to 75.3%)
R-CHOP: 46.3% (33.5% to 63.8%)

ENRICH



5-year OS (95% CI)
IR: 57.2% (49.0% to 66.8%)
BR: 58.1% (49.9% to 67.6%)

The MIRACLE of SCIENCE with SOUL City of Hope

City of Hope

58

What to make of this

- Easy Answer
  - R-CHOP is a bad 1L regimen for most patients….has been demonstrated in several trials to be inferior to most regimens and needs a lot (ASCT or indefinite maintenance) to have equivalent efficacy to BR and in this case BTKi + R
- Harder Answer
  - Is 1L BTKi the right approach in older patients
    - ECHO w/ improved PFS vs. BR while ENRICH was equivalent
      - Positive: not chemotherapy, better in p53 mutated patients
      - Negative: indefinite therapy vs. finite, likely not better than sequential therapy in non-p53 mutated patients (again indefinite vs finite).
  - Likely need a better but fixed non-chemo based regimen

City of Hope

59

Thank you

City of Hope

60