

Lymphoma Review: ASH 2024

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Outline

- Follicular lymphoma
 - inMIND trial: Tafa + R2 in R/R FL
- Mantle cell lymphoma frontline treatment
 - TRIANGLE overall survival update, data for rituximab maintenance
 - EA4151 use of MRD to guide autoSCT
 - ENRICH in transplant ineligible patients



Follicular Lymphoma

inMIND trial for treatment of R/R FL



Landscape of treatment in RR FL

- Most common indolent non-Hodgkin B cell lymphoma (22% of adult NHL)
 - Generally incurable, with most patients experiencing multiple relapses
- 2nd line treatment:
 - Lenalidomide + rituximab (R2)
 - Chemo immunotherapy
- 3rd line treatment:
 - Tazemetostat
 - Zanubrutinib + obinutuzamab
 - Mosunetuzumab
 - Epcoritamab
 - CD19 CART (Axi-cel, Tisa-cel, Liso-cel)



AUGMENT trial in RR FL

- \geq 1 prior line of treatment
 - Required treatment per investigator
- NOT rituximab refractory
 - 84% received prior rituximab
- Lenalidomide 20 mg daily D1-21 q28 days + Rituximab C1-6





Improved ORR, CR and PFS with R2

• ORR 78% (34%) vs. 53% (18%)

- PFS significantly improved for R2: HR 0.46 (0.34 – 0.62)
 - Median PFS 39.4 vs 14.1 mo
- Median duration of response: 39.4 mo vs. 14.1 mo





OS survival benefit with R2

- Median follow up 65.9 months
- Improvement in median OS with R2 (HR 0.59, 95% CI 0.37 – 0.95, p = 0.0285)
- 5 year OS with R2 83.2% vs. 77.3% for rituximab alone
- Median TTNT 73.1 mo vs. 31.8 mo for R2 vs. rituximab alone





Tafasitamab: CD19 monoclonal Ab

- Mechanism of action: induces direct cytotoxicity and enhances NK cell and macrophage immune-mediated mechanisms
- Single agent: ORR 29% in FL
- FDA approved in combination with lenalidomide for 2nd line + R/R DLBCL





inMIND trial: Phase III RCT in RR FL



Stratification Factors (Patients With FL)

- POD24
- Refractoriness to prior anti-CD20 mAb therapy
- Number of prior lines of therapy (1 or ≥2)

Study Endpoints in FL Population (Investigator Assessed Unless Specified)

- Primary study endpoint: PFS
- Key secondary: PET-CR rate in the FDG-avid population, OS
- Select other secondary: PFS by IRC, ORR, DOR, safety, QoL, MRD
- Exploratory:
- TTNT, B-cell recovery, Ig levels, CD19 expression



Improved ORR & CR rates with TafaR2

- N = 548
 - Groups well balanced for age, sex, FL G1-2 vs. G3A, B symptoms, FLIPI score, meeting GELF criteria, number of PLOT, refractory to prior anti CD20 therapy
- ORR 83.5% (CR 52%) for TafaR2
 - vs. ORR 72.4% (CR 40.7%) for R2
 - Statistically significant



Improved PFS, DOR, TTNT with TafaR2



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Time, Months

Consistent PFS benefit across all high risk subgroups

#	Tafasitamab + Len + R # Events/# Patients Censored	Placebo + Len + R # Events/# Patients Cen	sored	Ratio With Confidence Limits	HR (95% CI)		
Subgroup All patients	75/198	<mark>1</mark> 31/144	нн		0.43 (0.32, 0.58)		
Male Female	40/110 35/88	78/71 53/73			0.38 (0.26, 0.56) 0.51 (0.33, 0.80)		
Age group 1 <65 years ≥65 years	29/108 46/90	69/70 62/74			0.35 (0.23, 0.55) 0.53 (0.35, 0.80)		
Age group 2 <75 years ≥75 years	55/164 20/34	102/119 29/25	HH H	H	0.44 (0.31, 0.61) 0.58 (0.30, 1.12)		
Race White Asian Other and miss	61/158 11/29 ing 3/11	106/113 21/21 4/10			0.40 (0.29, 0.55) 0.34 (0.14, 0.81) 0.60 (0.08, 4.41)		
Not Hispanic or Hispanic or Lati Other and missi	Latino 62/166 no 8/23 ing 5/9	112/114 10/14 9/16		 	0.39 (0.28, 0.53) 0.71 (0.24, 2.10) 1.07 (0.25, 4.56)		
Europe North America Rest of the worl	52/124 8/30 Id 15/44	88/105 11/13 32/26			0.53 (0.38, 0.76) 0.12 (0.02, 0.55) 0.33 (0.16, 0.68)		
POD24 Yes No Refractory to priv	29/56 46/142 or anti-CD20	52/36 79/108	⊫⊣ ⊫⊣		0.43 (0.27, 0.69) 0.45 (0.31, 0.65)		
Yes No	45/73 30/125	68/47 63/97	₩-1 H=-1		0.44 (0.30, 0.65) 0.44 (0.28, 0.68)		
1 line ≥2 lines	36/110 39/88	61/86 70/58			0.48 (0.32, 0.74) 0.41 (0.28, 0.61)		
			0 1		6		



Mild increased toxicity with TafaR2

Preferred Term, n (%)	Tafasitamab + Len + R (n=274)*	Placebo + Len + R (n=272) [†]		
Any adverse event	272 (99.3)	270 (99.3)		
Neutropenia	133 (48.5)	123 (45.2)		
Diarrhea	103 (37.6)	77 (28.3)		
COVID-19	86 (31.4)	64 (23.5)		
Constipation	80 (29.2)	67 (24.6)		
Rash	60 (21.9)	58 (21.3)		
Fatigue	58 (21.2)	43 (15.8)		
Cough	52 (19.0)	47 (17.3)		
Pyrexia	52 (19.0)	44 (16.2)		
Muscle spasms	49 (17.9)	49 (18.0)		
Nausea	49 (17.9)	38 (14.0)		
Infusion-related reaction	43 (15.7)	41 (15.1)		
Thrombocytopenia	37 (13.5)	42 (15.4)		
Pruritus	44 (16.1)	28 (10.3)		

- No significant increase in G3/4 cytopenias
- Similar dose interruptions/discontin uations due to toxicity
- Similar len discontinuations and dose reductions
- Median len dose intensity 86 vs. 87%



InMIND vs. AUGMENT

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	-	



Management of RR FL

- Summary of inMIND trial:
 - Tafa + R2 improved ORR, CR, PFS, DOR, TTNT. No difference in overall survival.
 - Minimal increase in toxicity without affecting lenalidomide dose intensity
 - Cumbersome infusion schedule of Tafa: weekly C1-3, q2w C4-12
- <u>My approach</u>: Consider addition of Tafa to R2 in 2nd line + setting in patients who are able to manage the travel/frequency of infusion schedule
- Eagerly await results of CD20/CD3 bispecific antibodies + lenalidomide:
 - CELESTIMO: Mosun + len
 - EPCORE FL-1: Epco + R2



Mantle cell lymphoma

Rapidly evolving frontline treatment landscape



MCL: remains incurable but outcomes improved with Tx advances

- Represents 5-7% of all lymphomas
- Median PFS/OS varies based on MIPI score
- Predictors of worse outcomes:
 - Blastoid/pleomorphic variants
 - Ki67 >30%
 - TP53 mutations/deletions



Figure 4. Overall Survival of Patients with Mantle-Cell Lymphoma from the Time of Diagnosis.



Frontline MCL Treatment pre 12/2023





Frontline MCL data

- Transplant eligible: questioning the role of autoSCT
 - TRIANGLE updated data
 - Role for rituximab maintenance with or without BTKi
 - EA4151 MRD guided autoSCT
- Transplant ineligible: questioning the role for chemoimmunotherapy
 - ENRICH: Ibrutinib + Rituximab (IR) vs. chemoimmunotherapy



Transplant Eligible MCL



TRIANGLE: role of ASCT and BTKi in frontline MCL treatment





Improved FFS with BTKi maintenance



- Improve FFS in Groups A+ I and I
- No difference in OS at last publication



OS Benefit to BTKi maintenance





No specific population that benefited from Auto + I

Subgroup (interaction p-value)	No. of patients	No. of events	Hazard ratio (1-sided 98.33% Cl)		
AU	562	134	0.90 (0 - 1.30)		
Sea (p=0.71)					
Familia	1/68	30	± no (0 · 2 33)		
Mary	444	104	D.88 (0 - (.33)		
MIP					
Low	-336	62	0.76 (0 - 1.01)		
Intermediate (p=0.33)	107	37	1 15 (0 -2 38)		trend towards superiority
Hgh (p=0.55)	(be)	35	1.00 (0 - 2.12)		a dia tanàna a sapanang
Cytology (pe0.15)					of A+Lover Lin patients
North-Diseases	401	22	1.00 (0 - 1.56)		or A rover rin patients
(Reating)	RS	27	R 558 (0 - 1.52)		in high rick patients:
KJ-67 (p=0.41)					in high hisk patients.
Low	357	11	1.05 (0 - 1.24)		1/1 67 > 200/
righ	164	54	0.79 (0 1.42)		- KI-07 >30%
P53 expression (p=0.43)		-			All shakes and a family see
LOW	342		0.63 (0 - 1.41)		- blastold cytology of
Jegn			0.04 (0.4) 440		
High Hak biology (p=0.33)			1000 (D) 1000	4	 high p53 expression
11-m		24	D.00 (0 - 1.00)		
E maintenance (TT (n=0.091)	-	-	E.e. (9 - 1.28)		
No	1100		5.97 (0. 9.14)		
Van	340	0.0	0.00/0 - 1.171		
R maintenarice mAT (n=0.14)	-				
No	228	76	3 10 00 - 3 900	-	
Yos	354	58	0.71 (0 - 1.24)		
0.22	-92.5		and the second second	and the set of the set	

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Maintenance BTKi +/- rituximab



- Retrospective analysis of RM outcomes in TRIANGLE study
 - Non randomized use of rituximab on study
 - No significant diff in baseline characteristics between groups
- Use of RM:
 - A: 68%
 - A+I: 64%
 - I: 61%



PFS benefit to RM in all arms



- Improvement in 4 years PFS with use of RM in all arms
 - Slightly greater benefit in ASCT containing arms (A and A+I)





Cost of RM: increased toxicity

- Higher rate of G3-5 AE
 - Infections
 - Increased neutropenia only in ASCT arm
- No diff in death due to toxicity
- No diff in OS with RM in all groups



EA4151: role for autoSCT in MRD- CR1

- Transplant eligible
 - Age 18 70
- ClonoSeq 1x10 -6
- N = 650
 - 257/259 randomized
 - Arm C, N = 49
 - Arm D, N = 85





No diff in PFS and OS for arms A and B

MRD negative: with (A) or without (B) autoSCT

- 3 year PFS
 - 76.6% vs. 77.4%



- 3 year OS:
 - 82.1% vs. 82.7%





Outcomes in Arms C & D

- Arm C: PR or MRD +
 - 3 year PFS: 76.9%
 - 3 year OS: 81.9%
- Arm C: MRD indeterminate
 - 3 year PFS: 73.4%
 - 3 year OS: 85.1%
- Outcomes of C/D appear similar to A/B!





Arm C: Outcomes by MRD status post transplant

- If converted to MRD negative post auto, improved 3 year PFS and OS:
 - PFS: 100% vs. 48.8% in MRD+ vs. MRD- patients
 - OS: 63.6% vs. 100% in MRD+ vs MRD – patients
- Only 2 patients on the whole trial received BTKi maintenance
 - How much of this can negative impact of MRD + disease can be overcome by BTKi maintenance vs. autoSCT?





Transplant Ineligible MCL



ENRICH trial

- Randomized Phase II/III trial
 - N = 397
- Stage II- IV MCL, in need of treatment
- Maintenance:
 - R-chemo: Rituximab q2 mo x 2 years
 - IR: Ibrutinib + rituximab q2 mo x2 years
 - Ibrutinib 560 mg daily until progression



R-chemoimmunotherapy (BR vs. RCHOP)



PFS benefit with IR or R-chemo

- Median follow up 47.9 mo
- Median PFS 63.3 vs 42.4 mo Favoring IR



• Test of interaction for choice of chemotherapy regimen...



PFS benefit largely driven by poor performance of RCHOP arm

PFS for RCHOP choice

• SS difference in 5 year PFS:

Progression-free survival probability

- IR 52.4%
- RCHOP 19.2%



Number at risk (number censored)



PFS for BR choice:

- No SS difference in 5 year PFS:
 - IR 50.8%
 - BR 47.4%





No SS difference in OS, similar toxicity

- 5 year OS:
 - IR 57.7%
 - R-chemo 54.5%
- Toxicity:
 - Similar G3/4 AE
 - 22% G3/4 cardiac toxicity with ibrutinib
 - Higher neutropenia with R-chemo (15% G3/4 NF with RCHOP)
- QOL: "Earlier improvement in QOL with IR treatment"
 - How will this hold up long term with time limited vs. ongoing treatment with IR





Summary of MCL at ASH 2024

- BTKi and rituximab maintenance improves overall survival in young, transplant eligible patients
 - No difference in FFS or OS in patients who received auto vs. no auto (A+I vs. I)
- No benefit to transplant in MRD negative patients at end of induction
- Frontline treatment of elderly patient: R-BTKi superior to RCHOP, equivalent to BR
 - Ongoing MANGROVE study or R-zanu vs. BR in same population



Frontline MCL: Clear as mud

- Q: Which transplant eligible patients still may benefit from autoSCT?
- Q: In the era of BTKi maintenance, should we still use cytarabine based induction without autoSCT?
 - ECOG 4181 study: BR/RC vs. BR/RC + acala vs. BR + acala only
- Q: Which transplant ineligible patients should receive frontline BR vs. BTKi vs. combination BR + BTKi?
 - Trend towards worse outcomes in blastoid patients with IR treatment vs. R-Chemo in ENRICH trial
- Q: Which patients should be treated with frontline multiagent targeted therapy?
 - OASIS II trial: R + BTKi +/- Venetoclax, improved CR with ven addition but no diff in PFS
- A: Use 2nd generation BTKi in leu of ibrutinib: Acala vs. Zanu
 - Acalabrutinib now FDA approved for 1st line MCL (ECHO trial)



Frontline MCL Treatment in 2/2025





Tip of the lymphoma iceberg at ASH



- DLBCL:
 - Longer follow up with CD20/CD3 bispecifics as single agent in R/R DLBCL and combination treatment in FL with impressive DOR
 - Novel agents in RR disease: promising data for golcadomide and CD19/CD3 bispecifics
- FL:
 - Lonca in R/R disease
- Hodgkins:
 - ctDNA utility in prognostication
 - Pembro maintenance in leu of autoSCT in R/R setting
- PTLD:
 - Tab-cel for EBV+ disease



While I can't bring you the warm San Diego beaches...

...hopefully brought you the practice changing lymphoma data from ASH 2024

Thank you! karimiy@med.umich.edu





Extra Slides



Which patients benefit from ASCT?

Subgroup (interaction p-value)	No. of patients	No. of events	Hazard ratio (1-sided 98.33% Cl)	0
Al	562	134	0.90 (0 - 1.30)	n +
Sex (pu0.71)				
Familia	1/68	30	± 107 (0 · 2 330	· · · · · · · · · · · · · · · · · · ·
Max	444	104	0.88 (0 - (.33)	6 * · · · · · · · · · · · · · · · · · ·
MIP				
Low	336	62	0.76 (0 - 1.01)	
Intermediate (p=0.38)	107	37	1 15 (0 - 2 32)	strend towards super
High (p=0.55)	(det)	35	1.00 (0 - 2.12)	
Cytology (p=0.15)				of A+Lover Lin potio
Nett-blaster2	401	92	1.00 (0 - 1.56)	in A tover i in pare
(Read) as	85	27	R 549 (0 - 1.58)	to black what we show to be
KJ-67 (p=0.41)				in nigh risk patients:
Low	357	11	1.05 (0 - 1.34)	
High	164	57	0.79 (0 - 1.42)	• - KI-67 >30%
P53 expression (p=0.43)				
Low	342	67	0.83 (0)-1.41)	 blastoid cytology o
Han	199	21	0.67 (D.+ 1.400)	· · · · · · · · · · · · · · · · · · ·
High risk biology (p=0.33)				 high p53 expression
Low	423	10	D.00 (0 - 1.03)	
1kge	64	34	D.61 (0 - 1-29)	(
R maintenance (TT (p=0.081)				
No	1946	-90	5.27 (0 - 2.54)	a) •
Yes	360	0.11	D 688 (D - 1 87)	
R maintenance mAY (p=0,14)				
No	226	76	■ ## (0 - 1 193)	
Yes	864	58	0.71 (0 - 1.24)	



But again comes at a cost...





Which patients benefit most from IR?

-0.00

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



Blastold subgroup (n=25) PFS 6.9 (95% CI 1.9 to NE) months for IR vs 21.1 (95% CI 9.8 to NE) months for immunochemotherapy)

HR 2.33, 95% CI 0.83 to 6.52



Progression-free survival subgroups



Median PFS for those treated with IR was 18.5 (95% CI 4.2 to 46.2) months versus

8.9 (95% CI 2.9 to 25.7) months for those treated with immunochemotherapy: HR of 0.77 (95% CI 0.40 to 1.52)



Which patients benefit more from RM?

- More improvement with RM in low risk MIPI
- No diff based on classical/pleo morphic cytology or Ki67

Cyto

Varia Adjus respo

Rm vs

	MIPI category						
	Variables		HR (95% CT)				
	Adjusted for Ki67, cytolog response after induction	gy, treatment arn /ASCT	1,	i.			
Rm vs. noRm in MIFI LR		m MIFI LR 0.22 (0.14 - 0.36) -					
	Rm vs. noRm in MIPI IR		0.62 (0.33 - 1.15)				
	Rm vs. noRm in MIPI HR		0.43 (0.21 0.90)				
				0.4 1 2.7			
logy			Ki67	favors Rm favors r	ioRm		
bles	HR (95% CI)		Variables		HR (95% CI)		
ited for MIPI, treatment arm, onse after induction/ASCT			Adjusted for MI	PI, treatment arm nduction/ASCT	N		
, noRm in cytology small cell/classical	0.40 (0.28 - 0.57)	-	Rm vs. noRm in K	(167 < 30%	0.33 (0.22 - 0.51)	1
noRm in cytology pleamorph/blasto	id 0.29 (0.14 - 0.62)		Rm vs. noRm in K	(167 >= 30%	0.33 (0.20 - 0.54	• •	1
		0.2 0.611.6				0.4	2.7
		favors Rm favors	noRm			favors Rm	favors noRm

Rm appears more beneficial in patients with a low MIPI category

