Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

November 12, 2022

ANCO

Educating and Empowering the Northern California Cancer Community

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presents

Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Saturday, November 12, 2022

8:00 AM Breakfast, Registration, & Exhibits

9:00AM Welcome & Introductions
Courtney Flookes, ANCO Executive Director

9:05 AM Lymphoma Update 2022
Michael Spinner, MD, University of California, San Francisco

9:50 AM Myeloma Update 2022
Michaela Liedtke, MD, Stanford University

10:35 AM Coffee Break

11:00 AM Leukemia Update 2022
Brian Jonas, MD, PhD, FACP, University of California, Davis

11:45AM Case Presentations Leukemias, Lymphomas. & Myeloma
Vanessa Kennedy, MD, University of California, Davis

12:30PM ADJOURN

Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Lymphoma Update 2022

Michael Spinner, MD

University of California, San Francisco

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Educating and Empowering the Northern California Cancer Community

Updates in Lymphoma

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November 12, 2022
San Francisco, CA

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Disclosures

- No relevant financial disclosures

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Outline

	DLBCL	Mantle cell lymphoma	Hodgkin lymphoma
Frontline therapy	POLARIX	SHINE	ECHELON-1 update
Relapsed/refractory	ZUMA-7 TRANSFORM BELINDA	ZUMA-2 update BRUIN	Choosing first salvage therapy New immunotherapy approaches

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Frontline DLBCL – Phase 3 trials challenging R-CHOP

Trial	Experimental arm	Study population	N	PFS, experimental vs standard arm	Outcome	Reference
LNH03-6B	R-CHOP-14	60-80 y; aaIPI ≥1	602	60% vs 62% (3y)	Negative	Delarue et al[46]
DLCL04	R-CHOP-14 + ASCT	≤65 y; aaIPI ≥2	299	78% vs 77% (5y)	Negative	Chiappella et al[47]
HOVON	R-CHOP + rituximab maintenance	≥18 y; stage II-IV	398	74% vs 71% (3y)	Negative	Lugtenberg et al[52]
PRELUDE	R-CHOP + enzastaurin maintenance	≥18 y; stage II-IV; IPI ≥3	758	70% vs 71% (4y)	Negative	Crump et al[53]
PILLAR-2	R-CHOP + everolimus maintenance	≥18 y; stage II-IV; IPI ≥3	742	77% vs 78% (3y)	Negative	Witzig et al[54]
REMARC	R-CHOP + lenalido-mide maintenance	60-80 y; stage II-IV; aaIPI ≥1	650	80% vs 75% (2y)	Positive, PFS benefit	Thieblemont et al[55]
CALGB 50303	DA-EPOCH-R	≥18 y; stage II-IV	524	79% vs 76% (2y)	Negative	Bartlett et al[56]
GOYA	G-CHOP	≥18 y; stage II-IV	1418	70% vs 67% (3y)	Negative	Vitolo et al[59]
REMoDL-B	R-CHOP + bortezomib	≥18 y; ABC & GCB	918	75% vs 71% (2.5y)	Negative	Davies et al[63]
PHOENIX	R-CHOP + ibrutinib	≥18 y; stage II-IV; non-GCB; IPI ≥2	838	71% vs 68% (3y)	Negative	Younes et al[64]
ROBUST	R-CHOP + lenalido-mide	≥18 y; stage II-IV; ABC; IPI ≥2	570	67% vs 64% (3y)	Negative	Nowakowski et al[66]
POLARIX	R-CHP + polatuzumab vedotin	≥18 y; IPI ≥2	879	77% vs 70% (2y)	Positive, PFS benefit	Tilly et al[91]

Spinner MA, Advani RH. *Oncology* 2022

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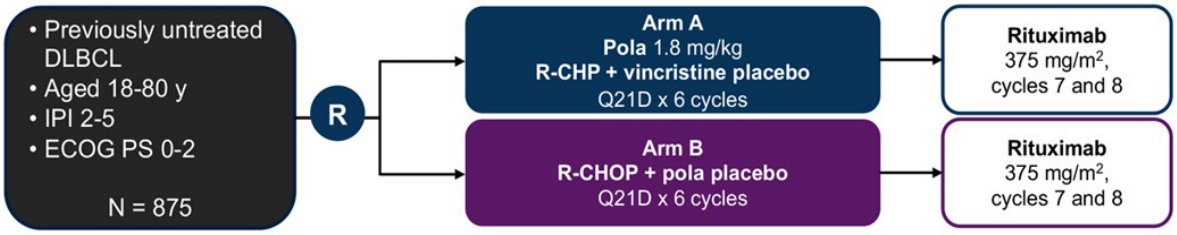
POLARIX trial

- International phase 3 trial comparing**R-CHOP vs polatuzumab vedotin (anti-CD79b ADC) + R-CHP**



- Primary endpoint: **PFS**
- Secondary endpoints: OS, DOR, ORR, CR rate, safety/tolerability

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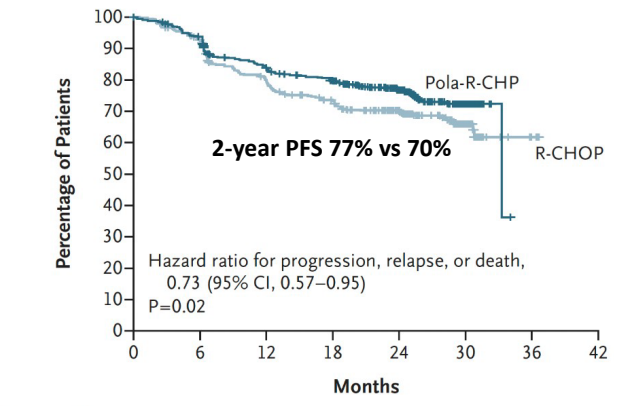
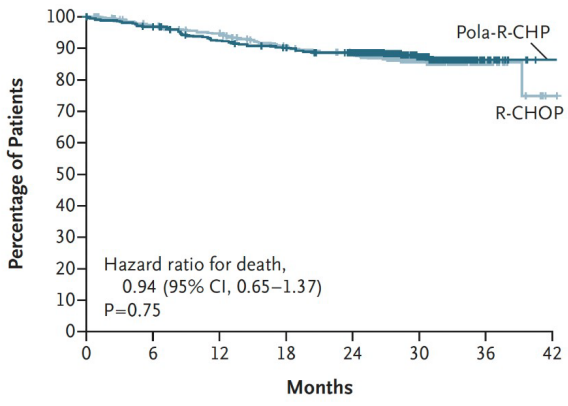
POLARIX efficacy endpoints

Progression-free survival



Overall survival



No. at Risk

Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

440	423	397	384	362	140	15	1	
439	414	401	376	355	132	20	1	

Median follow-up 28 months

Tilly et al, NEJM 2022

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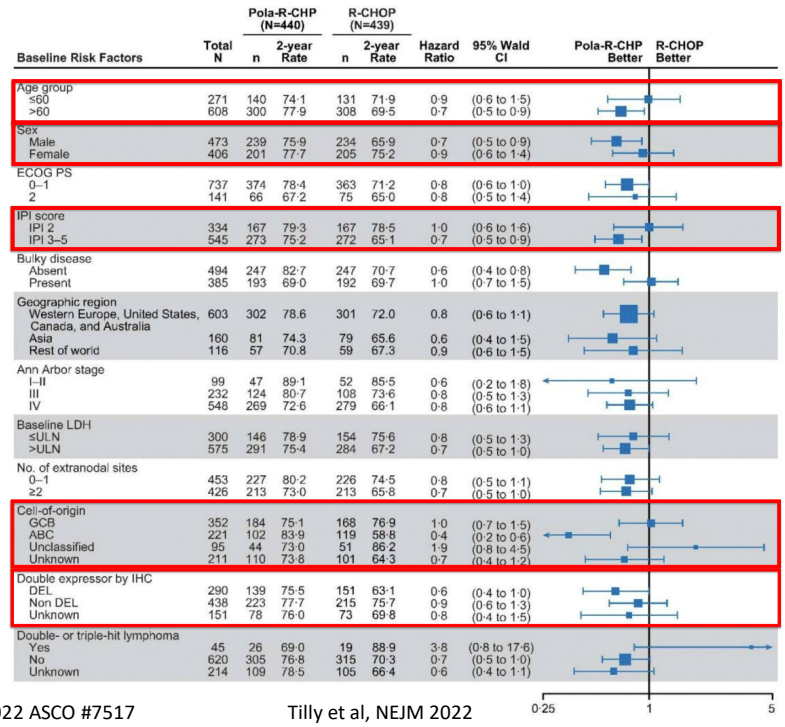
POLARIX - subgroup analysis

Subgroups favoring pola-R-CHP:

- Older adults (age >60)
- Male patients
- High risk IPI 3-5
- ABC subtype
- Double expressor phenotype



Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)

Pola-R-CHP Better | R-CHOP Better

0·25 | 1 | 5

Morschhauser et al, 2022 ASCO #7517 Tilly et al, NEJM 2022

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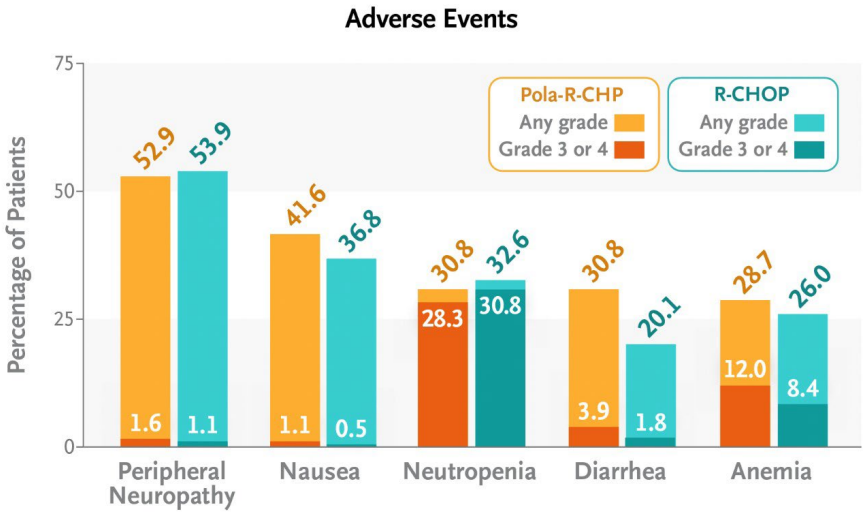
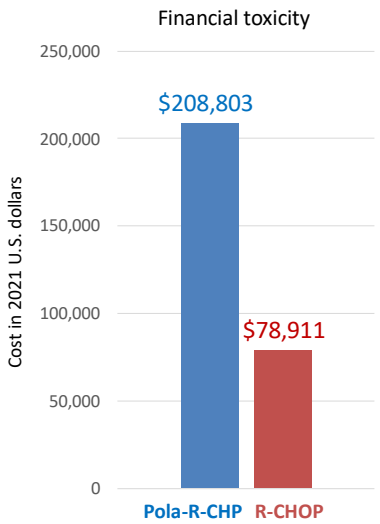
POLARIX – safety/tolerability





Tilly et al, NEJM 2022 Kambhampati et al, Blood 2022

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Other novel frontline approaches for high risk DLBCL

Regimen	Phase	Study population	N	ORR/CR	Reference
DA-EPCH-R + polatuzumab vedotin	1	IPI 3-5 or HGBCL (33%)	18	93%/71%	Lynch et al, 2022 ASCO
R-CHOP + glofitamab	1b	Stage III-IV	13	100%/100%	Ghosh et al, 2021 ASH
R-CHOP + epcoritamab	1/2	IPI 3-5 or HGBCL (25%)	33	100%/90%	Clausen et al, 2022 EHA
CHOP or pola-CHP + mosunetuzumab	2	IPI 2-5	Trial ongoing		NCT03677141
R-CHOP + tafasitamab + lenalidomide	3	IPI 3-5	Trial ongoing		NCT04824092
R-CHOP + acalabrutinib	3	IPI 2-5 & non-GCB COO	Trial ongoing		NCT04529772

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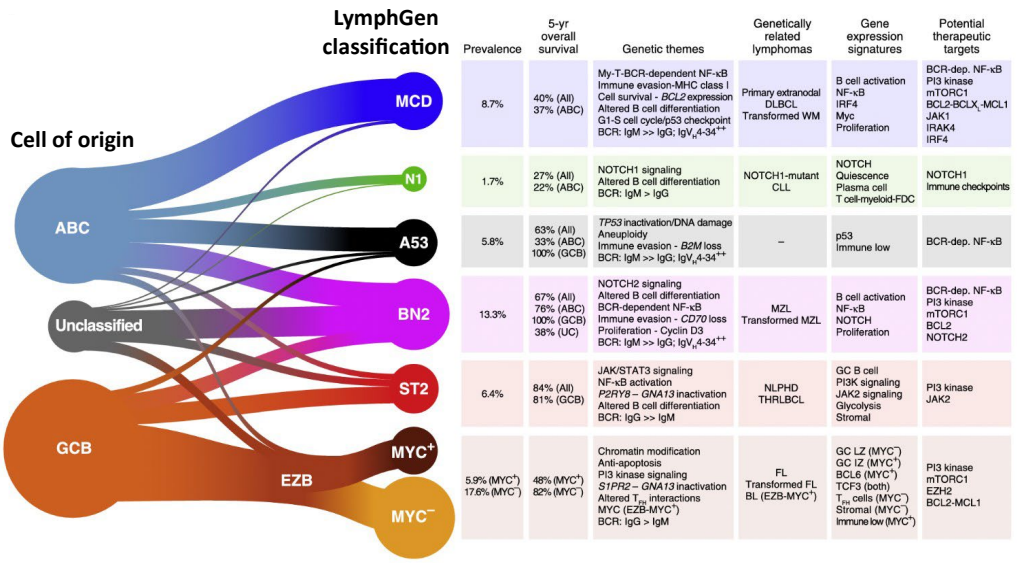
DLBCL genomic subgroups & rational targeted therapies



LymphGen classification	Prevalence	5-yr overall survival	Genetic themes	Genetically related lymphomas	Gene expression signatures	Potential therapeutic targets
MCD	8.7%	40% (All) 37% (ABC)	My-T-BCR-dependent NF-κB Immune evasion-MHC class I Cell survival - *BCL2* expression Altered B cell differentiation G1-S cell cycle/p53 checkpoint BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	Primary extranodal DLBCL Transformed WM	B cell activation NF-κB IRF4 Myc Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 BCL2-$BCLX_L$-MCL1 JAK1 IRAK4 IRF4
N1	1.7%	27% (All) 22% (ABC)	NOTCH1 signaling Altered B cell differentiation BCR: IgM > IgG	NOTCH1-mutant CLL	NOTCH Quiescence Plasma cell T cell-myeloid-FDC	NOTCH1 Immune checkpoints
A53	5.8%	63% (All) 33% (ABC) 100% (GCB)	*TP53* inactivation/DNA damage Aneuploidy Immune evasion - *B2M* loss BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	–	p53 Immune low	BCR-dep. NF-κB
BN2	13.3%	67% (All) 76% (ABC) 100% (GCB) 38% (UC)	NOTCH2 signaling Altered B cell differentiation BCR-dependent NF-κB Immune evasion - *CD70* loss Proliferation - Cyclin D3 BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	MZL Transformed MZL	B cell activation NF-κB NOTCH Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 BCL2 NOTCH2
ST2	6.4%	84% (All) 81% (GCB)	JAK/STAT3 signaling NF-κB activation *P2RY8* – *GNA13* inactivation Altered B cell differentiation BCR: IgG >> IgM	NLPHD THRLBCL	GC B cell PI3K signaling JAK2 signaling Glycolysis Stromal	PI3 kinase JAK2
MYC+ / MYC−	5.9% (MYC^+) 17.6% (MYC^-)	48% (MYC^+) 82% (MYC^-)	Chromatin modification Anti-apoptosis PI3 kinase signaling *S1PR2* – *GNA13* inactivation Altered T_{FH} interactions MYC (EZB-MYC^+) BCR: IgG > IgM	FL Transformed FL BL (EZB-MYC^+)	GC LZ (MYC^-) GC IZ (MYC^+) BCL6 (MYC^+) TCF3 (both) T_{FH} cells (MYC^-) Stromal (MYC^-) Immune low (MYC^+)	PI3 kinase mTORC1 EZH2 BCL2-MCL1

Rational targeted therapies

- BTK inhibitors
  IMiDs
- NOTCH inhibitors
- PD-1 inhibitors
- PI3K inhibitors
- JAK inhibitors
- EZH2 inhibitors
  BCL2 inhibitors

Wright et al, *Cancer Cell* 2020

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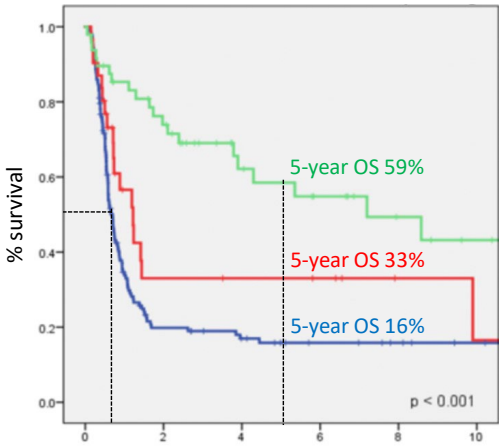
Relapsed/refractory DLBCL

- Outcomes vary by time to relapse after frontline therapy[1]
- Patients with primary refractory disease or early relapse <1 year have poor outcomes
  - ➢ Median OS ~6-8 months[1,2]
  - ➢ Population of interest for second line CAR T-cell therapy

Overall survival from time of relapse/progression



Crump et al, Blood 2017

Ngu et al, 2021 ASH #2499

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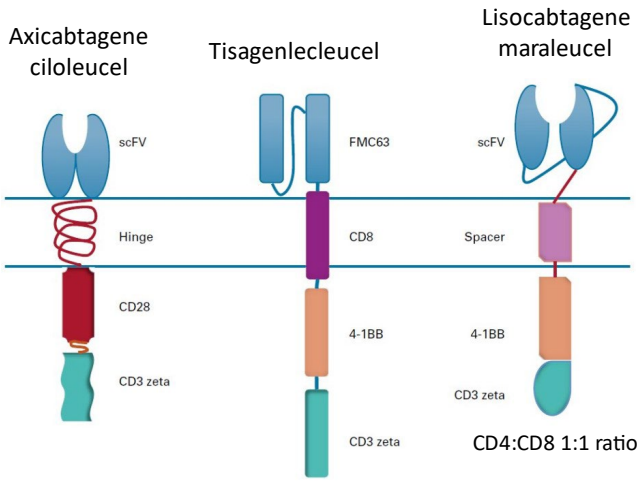
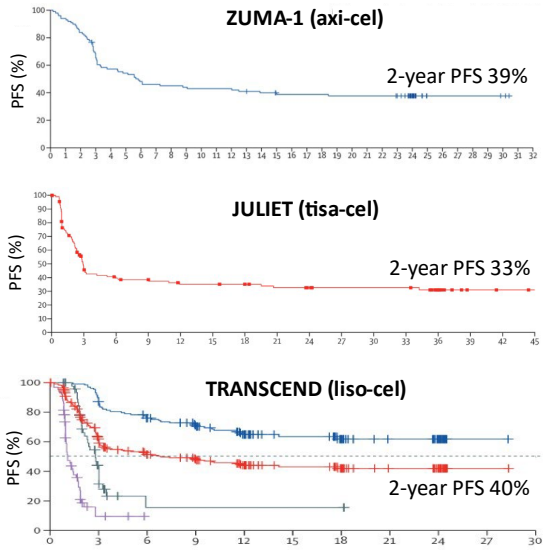
CD19 CAR T-cell products for R/R DLBCL





Locke et al, *Lancet Oncol* 2019

Schuster et al, *Lancet Oncol* 2021

Abramson et al, *Lancet* 2020

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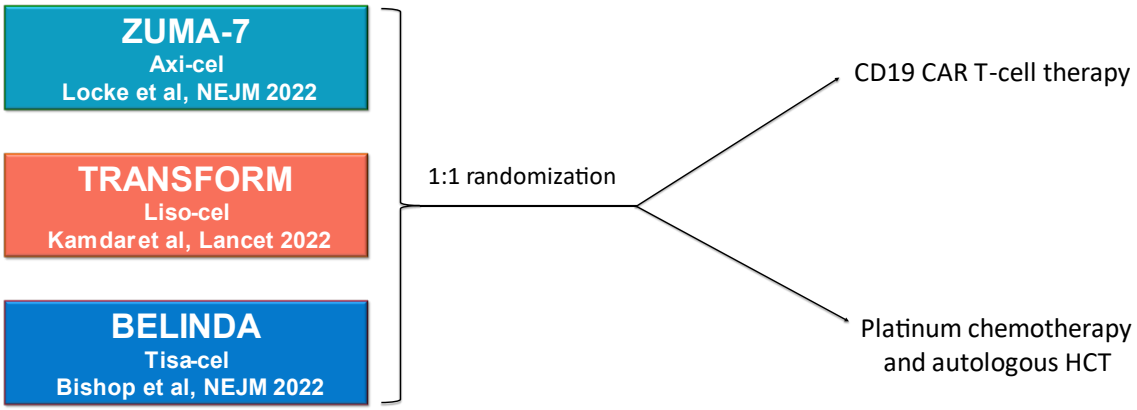
First salvage in DLBCL – CAR-T vs auto HCT

- Three phase 3 trials evaluated CAR -T vs SOC chemotherapy and auto HCT as first salvage
- All trials only included patients with **primary refractory disease or relapse within 1 year**



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Phase 3 CD19 CAR-T trials in R/R DLBCL

	ZUMA-7 (Axi-cel vs SOC)	TRANSFORM (Liso-cel vs SOC)	BELINDA (Tisa-cel vs SOC)
Patient population	Primary refractory Early relapse <1 year	Primary refractory Early relapse <1 year Upper age limit: 75 years	Primary refractory Early relapse <1 year
Bridging therapy	Corticosteroids	Chemotherapy	Chemotherapy
Lymphodepletion	Flu/Cy	Flu/Cy	Flu/Cy or bendamustine
Crossover	Off protocol	On protocol	On protocol
Primary endpoint	EFS	EFS	EFS
EFS definition	Time from randomization to: • PD • Death from any cause • New lymphoma therapy • SD as best response by day 150	Time from randomization to: • PD • Death from any cause • New lymphoma therapy • Not achieving CR/PR by 9 weeks	Time from randomization to: • PD • Death from any cause • New lymphoma therapy • SD as best response at 12 weeks

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Phase 3 CD19 CAR-T trials in R/R DLBCL

	ZUMA-7 (Axi-cel vs SOC)	TRANSFORM (Liso-cel vs SOC)	BELINDA (Tisa-cel vs SOC)
Total # of patients	359	184	322
% receiving CAR-T vs ASCT	**94% vs 36%**	**98% vs 47%**	**96% vs 33%**
% cross over	56%	55%	51%
Median time to CAR-T infusion	29 days	36 days	**52 days**
ORR	**83% vs 50%**	**86% vs 48%**	75% vs 68%
CR rate	**65% vs 32%**	**66% vs 39%**	46% vs 44%
Median EFS	**8.3 vs 2.0 mo.**	**10.1 vs 2.3 mo.**	3.0 vs 3.0 mo.
Median OS	NR vs 35 mo.	**NR vs 16.4 mo.**	--
Median follow-up	24.9 mo.	6.2 mo.	10 mo.

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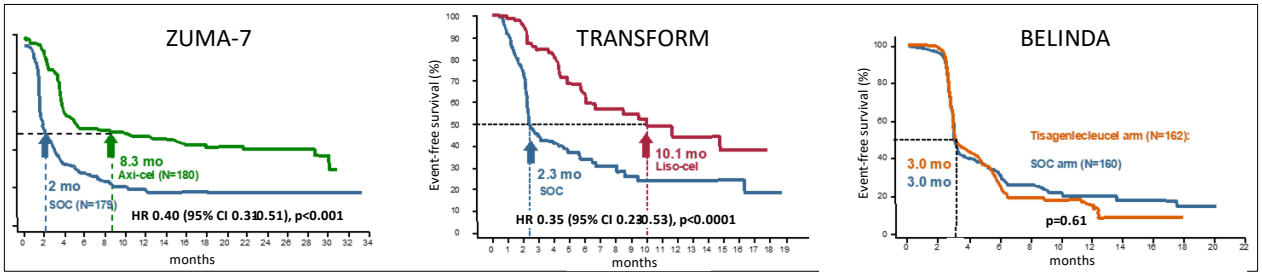
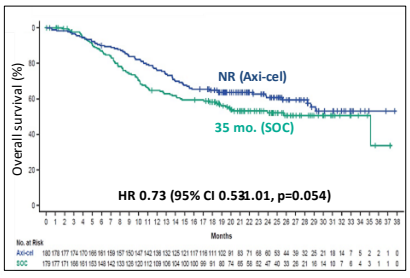
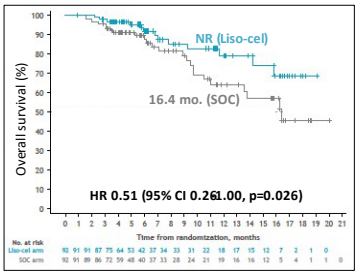
CAR-T vs SOC as first salvage in R/R DLBCL

EFS



OS





CAR-T toxicity

	Axi-cel	Liso-cel	Tisa-cel
CRS, any grade	92%	49%	59%
CRS, grade 3+	6%	1%	5%
ICANS, any grade	60%	12%	10%
ICANS, grade 3+	21%	4%	2%

Locke et al, NEJM 2022

Kamdar et al, *Lancet* 2022

Bishop et al, NEJM 2022

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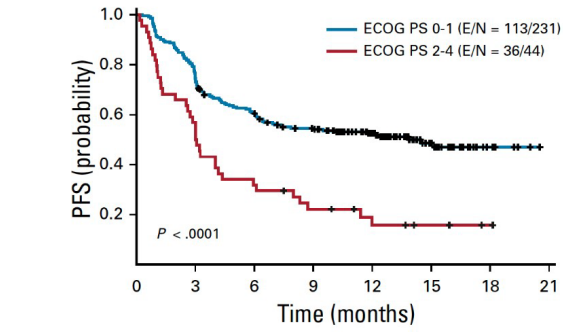
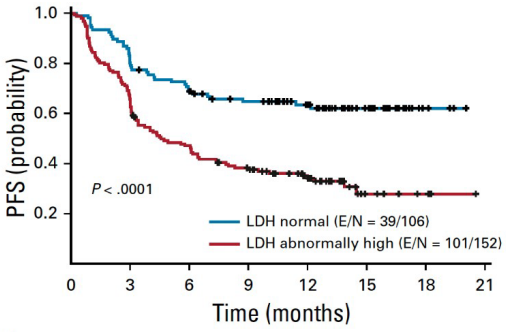
Real world experience with axi-cel

- Comparable efficacy and safety to ZUMA-1 and ZUMA-7 trials; long term PFS ~40%
- Poor performance status and high tumor burden are associated with inferior outcomes



No. at risk:								
ECOG PS 0-1	231	172	137	115	82	31	6	0
ECOG PS 2-4	44	25	14	9	5	3	1	0



No. at risk:								
LDH normal	106	85	72	62	48	24	4	0
LDH abnormally high	152	100	70	53	32	7	3	0

Nastoupil et al, JCO 2020

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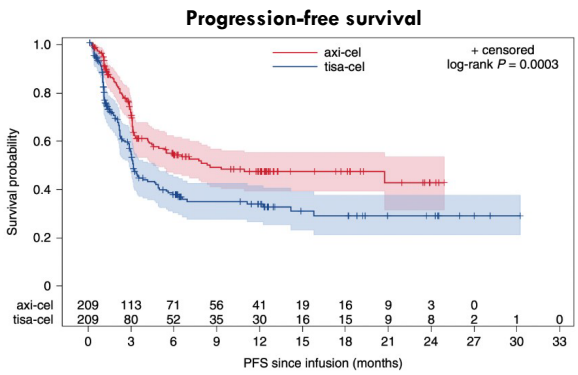
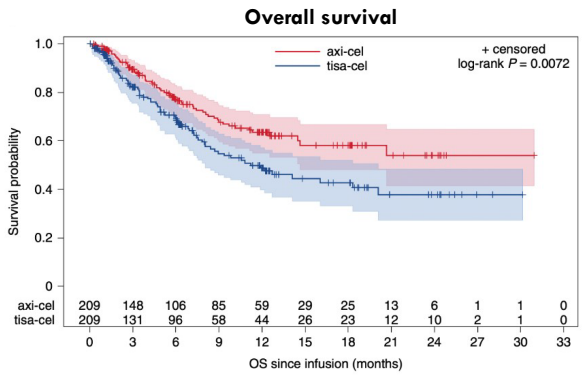
Real world comparison of axi-cel vs tisa-cel

- 418 patients with multiply R/R DLBCL in French DESCAR-T registry who received axi-cel or tisa-cel
- Compared outcomes after 1:1 propensity score matching
- Higher response rates with axi-cel vs tisa-cel: ORR 80% vs 66%; CR 60% vs 42%
- Higher rates of CRS and ICANS (including grade 3-4 ICANS) with axi-cel vs tisa-cel





Bachy et al, *Nature Medicine* 2022

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DLBCL updates – Summary

- Pola-R-CHP is a new frontline option for high-risk DLBCL with IPI 2-5
  - PFS benefit over R-CHOP but similar OS
  - Greater benefit in older adults >60, IPI 3-5, and non-GCB subtype
  - Similar safety profile but much greater financial toxicity withpola-R-CHP
- Ongoing trials are integrating novel agents into frontline therapy, including anti-CD20 BiTEs, Tafa/Len, and acalabrutinib added to an R-CHOP backbone
- Better defined genomic subgroups provide an opportunity for rational targeted therapies added on to an R-CHOP backbone
- Patients with **primary refractory DLBCL and early relapse within 1 year** have poor outcomes with salvage chemotherapy and autoHCT (median OS ~6-8 months)
  - CD19 CAR-T (Axi-cel or Liso-cel) is the new SOC for this patient population

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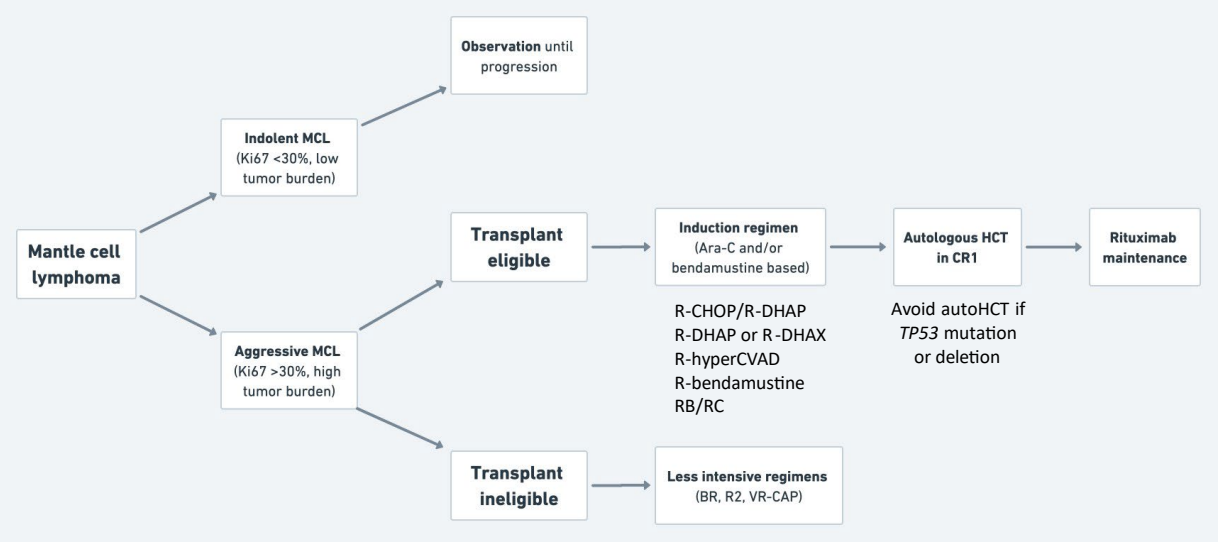
Mantle cell lymphoma – frontline therapy



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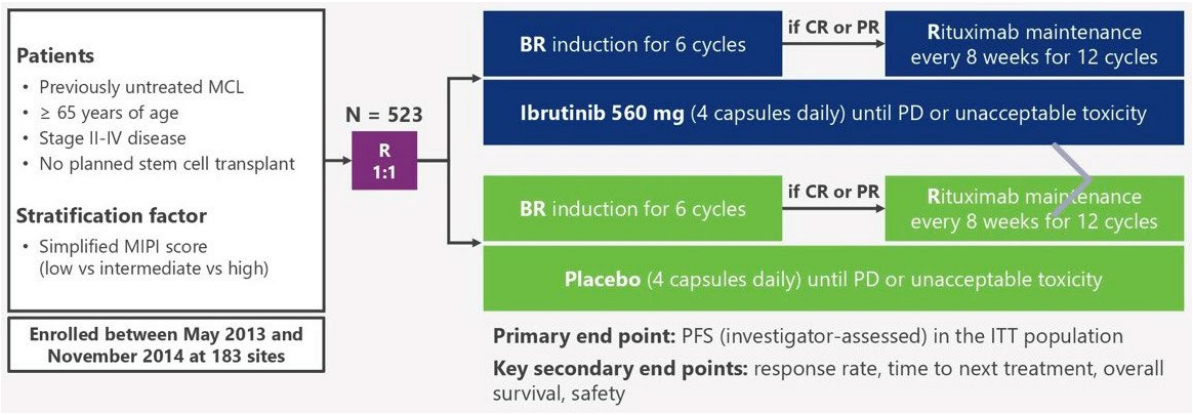
SHINE trial

- Phase 3 trial evaluating **BR with or without ibrutinib** in older adults with transplant ineligible MCL



Wang et al, NEJM 2022

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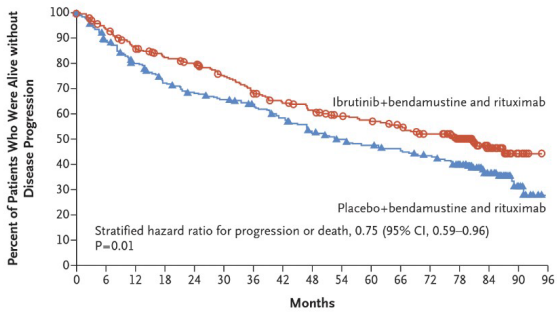
SHINE trial – efficacy endpoints

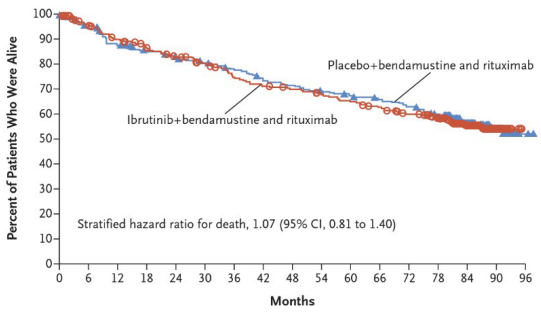
- Adding ibrutinib to BR improved PFS but not OS
- Median PFS 80.6 months vs 52.9 months (median follow-up 84.7 months)

Progression-free survival



BR + ibrutinib	261	228	207	191	182	167	152	139	130	120	115	106	95	78	39	11	0
BR + placebo	262	226	199	177	166	158	148	135	119	109	103	98	90	78	41	11	0

Overall survival



BR + ibrutinib	261	239	221	208	197	187	171	163	158	152	145	138	128	118	70	25	0
BR + placebo	262	244	223	212	203	197	188	177	171	165	159	154	147	137	90	31	2

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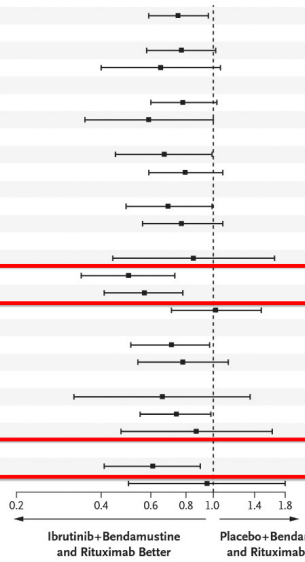
SHINE trial – subgroup analysis

Subgroup	Ibrutinib Group	Placebo Group	Hazard Ratio for Progression or Death (95% CI)
	no. of events/no. of patients		
All patients	116/261	152/262	0.75 (0.59–0.96)
Sex			
Male	88/178	111/186	0.77 (0.58–1.02)
Female	28/83	41/76	0.65 (0.40–1.06)
Race			
White	92/199	118/206	0.78 (0.60–1.03)
Non-White	24/62	34/56	0.59 (0.35–1.00)
Age			
<70 yr	39/99	62/108	0.67 (0.45–0.99)
≥70 yr	77/162	90/154	0.78 (0.58–1.06)
ECOG performance-status score			
0	53/134	72/141	0.69 (0.49–0.99)
1–2	63/127	80/121	0.77 (0.56–1.08)
Simplified MIPI score category at baseline			
Low risk	15/44	21/46	0.85 (0.44–1.65)
Intermediate risk	42/124	76/129	0.50 (0.34–0.73)
Low or intermediate risk	57/168	97/175	0.57 (0.41–0.78)
High risk	59/93	55/87	1.02 (0.71–1.48)
Tumor bulk			
<5 cm in largest diameter	64/165	90/163	0.71 (0.51–0.97)
≥5 cm in largest diameter	51/95	62/98	0.78 (0.54–1.13)
Histologic features			
Blastoid or pleomorphic	12/19	20/26	0.66 (0.32–1.35)
Nonblastoid or nonpleomorphic	86/211	110/201	0.74 (0.55–0.98)
Unknown	18/31	22/35	0.87 (0.47–1.62)
TP53 status			
Nonmutated	42/114	62/105	0.61 (0.41–0.90)
Mutated	21/26	17/24	0.95 (0.50–1.80)



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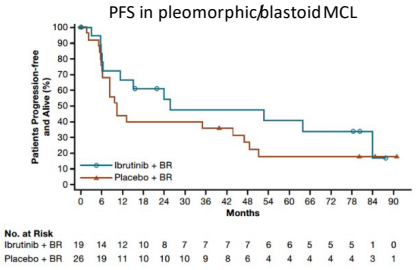
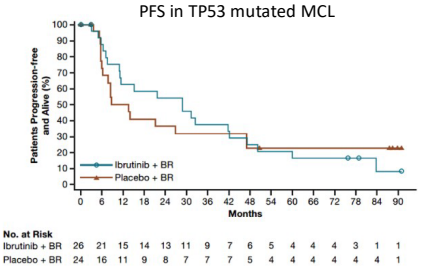
PFS in pleomorphic/blastoid MCL



No. at Risk														
Ibrutinib + BR	19	14	12	10	8	7	7	7	7	6	6	5	5	1	0
Placebo + BR	26	19	11	10	10	10	9	8	6	4	4	4	4	3	1

PFS in TP53 mutated MCL



No. at Risk														
Ibrutinib + BR	26	21	15	14	13	11	9	7	6	5	4	4	4	3	1	1
Placebo + BR	24	16	11	9	8	7	7	7	5	4	4	4	4	4	4	1

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SHINE trial – safety/tolerability

System Organ Class and Preferred Term	Ibrutinib Group (N=259)		Placebo Group (N=260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	259 (100)	211 (81.5)	257 (98.8)	201 (77.3)
Infection or infestation				
Pneumonia	87 (33.6)	52 (20.1)	61 (23.5)	37 (14.2)
Upper respiratory tract infection	71 (27.4)	4 (1.5)	68 (26.2)	4 (1.5)
Bronchitis	38 (14.7)	6 (2.3)	38 (14.6)	6 (2.3)
Urinary tract infection	38 (14.7)	11 (4.2)	33 (12.7)	6 (2.3)
Sinusitis	28 (10.8)	2 (0.8)	34 (13.1)	3 (1.2)
Conjunctivitis	26 (10.0)	0	6 (2.3)	0
Nasopharyngitis	24 (9.3)	0	28 (10.8)	0
Herpes zoster infection	15 (5.8)	2 (0.8)	28 (10.8)	10 (3.8)
Gastrointestinal disorder				
Diarrhea	120 (46.3)	18 (6.9)	96 (36.9)	10 (3.8)
Nausea	107 (41.3)	6 (2.3)	107 (41.2)	3 (1.2)
Vomiting	58 (22.4)	7 (2.7)	48 (18.5)	0
Constipation	51 (19.7)	0	68 (26.2)	1 (0.4)
Abdominal pain	26 (10.0)	6 (2.3)	30 (11.5)	2 (0.8)
General disorder or administration-site condition				
Pyrexia	95 (36.7)	5 (1.9)	83 (31.9)	5 (1.9)
Fatigue	79 (30.5)	8 (3.1)	77 (29.6)	6 (2.3)
Peripheral edema	51 (19.7)	3 (1.2)	42 (16.2)	0
Asthenia	30 (11.6)	2 (0.8)	25 (9.6)	3 (1.2)
Chills	18 (6.9)	1 (0.4)	39 (15.0)	1 (0.4)

System Organ Class and Preferred Term	Ibrutinib Group (N=259)		Placebo Group (N=260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Metabolism or nutrition disorder				
Decreased appetite	56 (21.6)	4 (1.5)	36 (13.8)	3 (1.2)
Hypokalemia	39 (15.1)	19 (7.3)	31 (11.9)	14 (5.4)
Musculoskeletal or connective-tissue disorder				
Arthralgia	45 (17.4)	3 (1.2)	44 (16.9)	0
Back pain	36 (13.9)	2 (0.8)	37 (14.2)	1 (0.4)
Myalgia	31 (12.0)	0	30 (11.5)	3 (1.2)
Nervous system disorder: headache	33 (12.7)	0	40 (15.4)	1 (0.4)
Vascular disorder: hypertension	35 (13.5)	22 (8.5)	29 (11.2)	15 (5.8)
Injury, poisoning, or procedural complication: infusion-related reaction	21 (8.1)	2 (0.8)	30 (11.5)	5 (1.9)
Cardiac disorder: atrial fibrillation	36 (13.9)	10 (3.9)	17 (6.5)	2 (0.8)
Psychiatric disorder: insomnia	29 (11.2)	0	28 (10.8)	0
Blood or lymphatic system disorder†				
Neutropenia	133 (51.4)	122 (47.1)	136 (52.3)	125 (48.1)
Anemia	87 (33.6)	40 (15.4)	64 (24.6)	23 (8.8)
Thrombocytopenia	93 (35.9)	33 (12.7)	69 (26.5)	34 (13.1)
Leukopenia	47 (18.1)	26 (10.0)	44 (16.9)	29 (11.2)
Lymphopenia	47 (18.1)	42 (16.2)	35 (13.5)	31 (11.9)
Skin or subcutaneous tissue disorder				
Rash	98 (37.8)	31 (12.0)	57 (21.9)	5 (1.9)
Pruritus	46 (17.8)	6 (2.3)	56 (21.5)	1 (0.4)

Wang et al, NEJM 2022

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Limitations of the SHINE trial

- Adding ibrutinib to BR improved PFS but increased toxicity (including financial toxicity)
- The lack of an OS benefit suggests that sequential therapy with BR followed by ibrutinib may be as effective with less toxicity
- Newer generation BTK inhibitors (acalabrutinib andzanubrutinib) appear less toxic than ibrutinib with comparable efficacy and may be better options for sequential therapy in some patients[1]
  - Phase 3 ASPEN trial comparing ibrutinib vs zanubrutinib in LPL/WM demonstrated lower rates of Afib, bleeding, pneumonia, diarrhea, and edema in thezanubrutinib arm[2]
- Two Phase 3 trials (ECHO and MANGROVE) are evaluating BR + acalabrutinib or BR +zanubrutinib, respectively, as frontline therapy for older adults with MCL

[1]Byrd et al, JCO 2021 [2]Tam et al, Blood 2020

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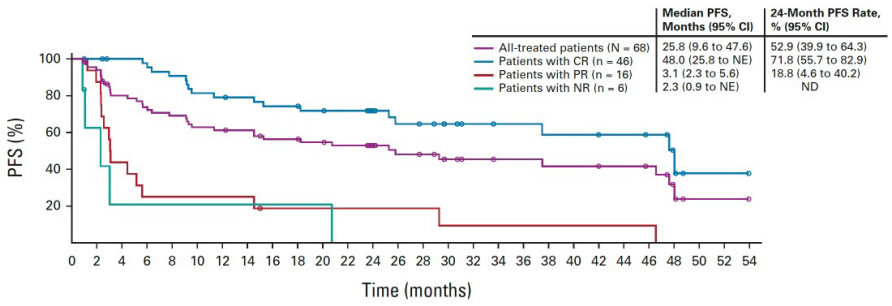
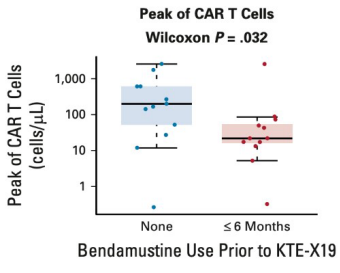
ZUMA-2 trial 3-year update – Brexu-cel in R/R MCL

- Enrolled 68 patients with R/R MCL after BTK inhibitor; received Flu/Cy→ Brexu-cel (2 x 10^6 CAR T cells/kg)
- ORR 91%, CR 68%, median PFS 25.8 months at 3-year follow-up
- Active in high-risk subgroups including TP53 mutation, Ki67 >50%, andblastoid/pleomorphic MCL
- Grade 3-4 CRS and ICANS occurred in 15% and 31%, respectively
- Poorer CAR-T expansion and inferior outcomes with priorbendamustine <6 months before CAR-T





Wang et al, JCO 2022

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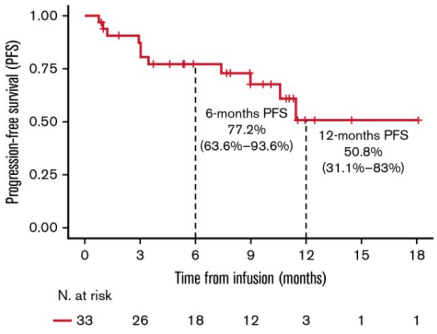
Real world experience with Brexu-cel in R/R MCL

- U.S. CAR-T consortium – 167 patients from 16 centers
- High risk patient population:
  - Median age 67 years
  - Median 3 prior therapies (86% prior BTK inhibitor)
  - 57% had Ki67 >50%
  - 49% had TP53 mutation or deletion
  - 10% had CNS involvement
  - 78% would not have met eligibility criteria for ZUMA2
- Median time from apheresis to LD chemo: 28 days
- Safety/tolerability:
  - CRS 90% (grade 3+ 8%) – 1 fatality
  - ICANS 61% (grade 3+ 32%)
- Efficacy:
  - ORR 89%, CR 70%
  - 6-month PFS 63% (median follow-up 6 months)

Jain et al, ASCO 2022

- Similar real world outcomes from Europe:
  - 33 patients from 11 centers
  - ORR 91%, CR 79%
  - 1-year PFS 51%



Iacoboni et al, *Blood Adv* 2022

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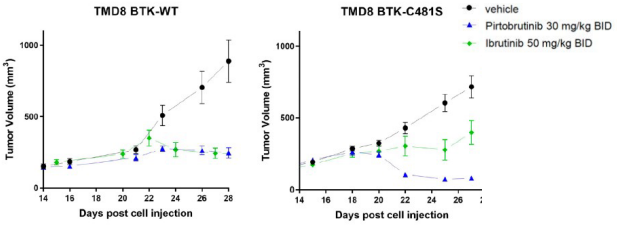
BRUIN trial – Pirtobrutinib (LOXO-305) in R/R MCL

- Pirtobrutinib (LOXO-305) is an oral, highly selective, non-covalent BTK inhibitor
  - ➢ Similar activity to ibrutinib, but retains activity in patients with BTK C481S mutation



- Phase 1/2 BRUIN trial evaluatedpirtobrutinib in R/R CLL, MCL, and other B-cell NHL
- MCL cohort enrolled BTKi refractory and naïve patients

Mato et al, *Lancet* 2021

Characteristics	MCL (n=134)
Median age (range), years	70 (46, 88)
Female / Male, n (%)	30 (22) / 104 (78)
Histology	
Classic	108 (81)
Pleomorphic/Blastoid	26 (19)
ECOG PS, n (%)	
0	82 (61)
1	50 (37)
2	2 (2)
Median number prior lines of systemic therapy (range)	3 (1, 9)
Prior therapy, n (%)	
BTK inhibitor	120 (90)
Anti-CD20 antibody	130 (97)
Chemotherapy	122 (91)
Stem cell transplant[b]	30 (22)
IMiD	23 (17)
BCL2 inhibitor	20 (15)
Proteasome inhibitor	17 (13)
CAR-T	7 (5)
PI3K inhibitor	5 (4)
Reason discontinued prior BTKi[a]	
Progressive disease	100 (83)
Toxicity/Other	20 (17)

Wang et al, 2021 ASH #381

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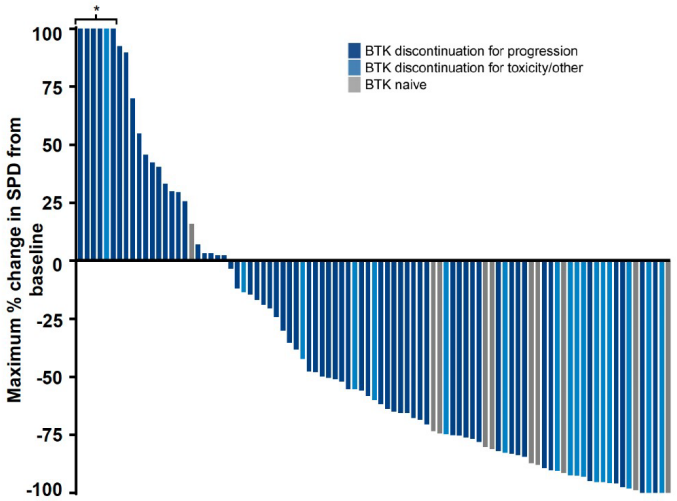
Pirtobrutinib efficacy in R/R MCL



BTK Pre-Treated MCL Patients[a]	n=100
Overall Response Rate[b], % (95% CI)	51% (41-61)
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	**n=11**
Overall Response Rate[b], % (95% CI)	82% (48-98)
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)

Efficacy also seen in patients with prior:
- Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
- CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)

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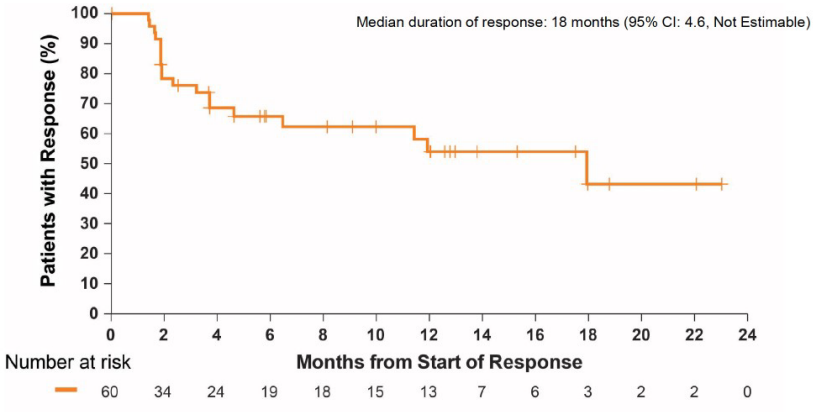
Pirtobrutinib duration of response in R/R MCL



- Median follow-up of 8.2 months (range, 1.0 - 27.9 months) for responding patients
- 60% (36 of 60) of responses are ongoing

Wang et al, 2021 ASH #381

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Pirtobrutinib safety profile in B-cell NHL and CLL

	All doses and patients (n=618)						
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

No DLTs reported and MTD not reached
96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily
1% (n=6) of patients permanently discontinued due to treatment-related AEs

Wang et al, 2021 ASH #381

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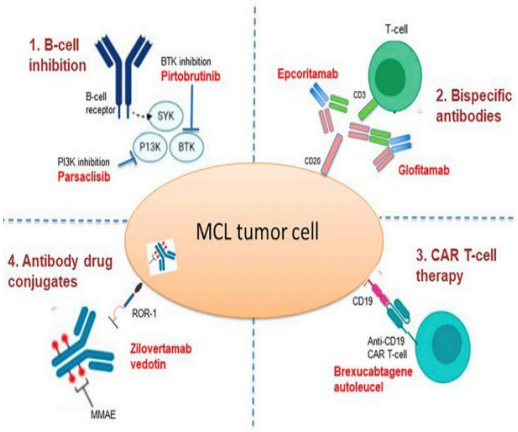
Novel agents and combinations in R/R MCL

Novel therapeutic approaches in R/R MCL



Novel agent(s)	Drug class	Phase	N	ORR	CR	Reference or NCT#
Glofitamab	CD20/CD3 BiTE	1/2	29	81%	67%	Phillips et al, ASH 2021 #130
Epcoritamab	CD20/CD3 BiTE	1/2	4	50%	25%	Clausen et al, ASCO 2021 #7518
Parsaclisib	PI3K delta inhibitor	2	108	69%	18%	Mehta et al, ASH 2021 #382
Zilovertamab vedotin + Ibrutinib	ROR1 ADC + BTKi	2	26	81%	35%	Lee et al, ASCO 2022 #7520
Zilovertamab vedotin + Ibrutinib vs Ibrutinib	ROR1 ADC + BTKi	3	Trial ongoing			NCT05431179
Pirtobrutinib vs SOC covalent BTKi	Non-covalent BTKi	3	Trial ongoing			NCT04662255
LOXO-338 +/- Pirtobrutinib	BCL2 inhibitor +/- non-covalent BTKi	1/2	Trial ongoing*			NCT05024045

Kumar et al, JCO 2022

*trial open at UCSF

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Mantle cell lymphoma updates - Summary

- In older adults with transplant ineligible MCL, adding ibrutinib to BR improves PFS but increases toxicity
  - The lack of an OS benefit suggests that sequential therapy with BR followed by a BTKi at relapse may be as effective with less toxicity
- CAR T-cell therapy (Brexu-cel) is highly active for R/R MCL progressing after a BTKi
  - 3-year follow-up from ZUMA-2 demonstrates durable remissions for patients achieving CR
  - Real world data from the U.S. and Europe demonstrate a similar efficacy/safety profile as ZUMA2
- Pirtobrutinib (LOXO-305) is an active oral therapy for R/R MCL progressing on a covalent BTKi
  - Phase 3 BRUIN MCL-321 trial will compare pirtobrutinib vs investigator's choice of covalent BTKi
- Several novel drug classes appear promising in multiply R/R MCL including anti-CD20/CD3 BiTEs, PI3Ki, ROR1 ADC, and BCL2 inhibitors alone or in combination with pirtobrutinib

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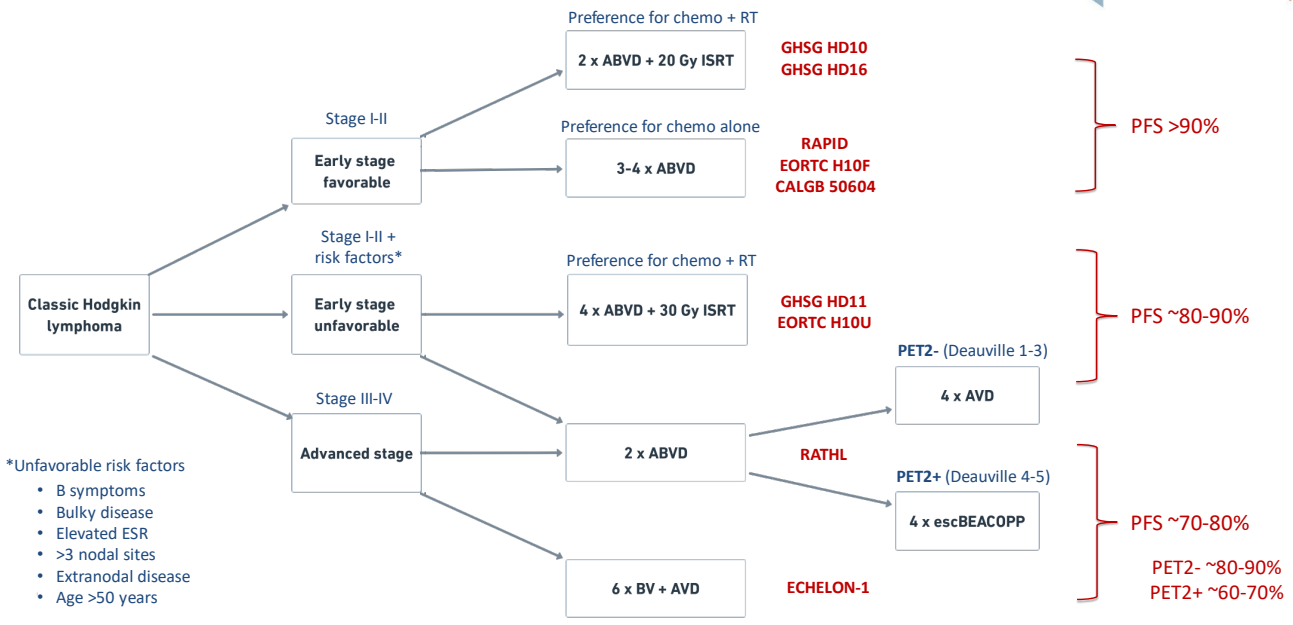
Hodgkin lymphoma – frontline therapy



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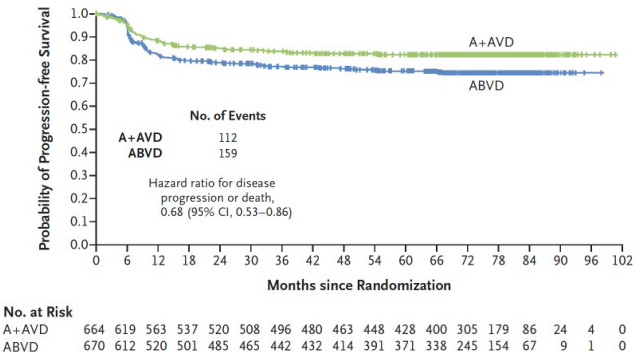
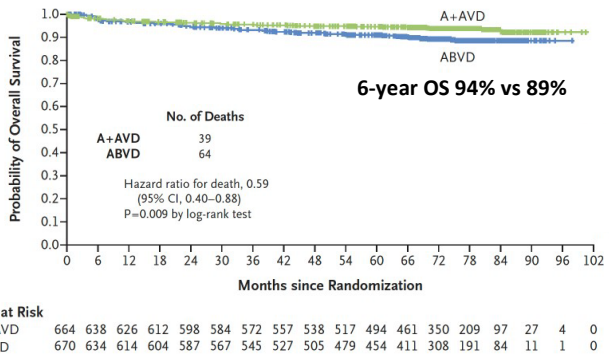
ECHELON-1 6-year update

- Phase 3 trial randomizing 1,334 patients with stage III‡IV HL to receive 6 cycles of ABVD or BV-AVD
- At median follow-up >6 years, PFS and OS were both superior in the BV-AVD arm





Ansell et al, NEJM 2022

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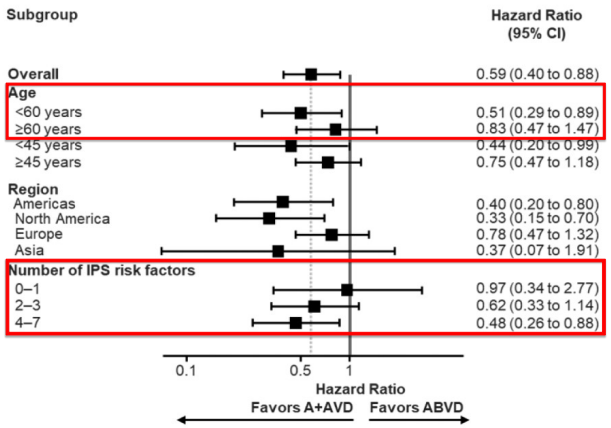
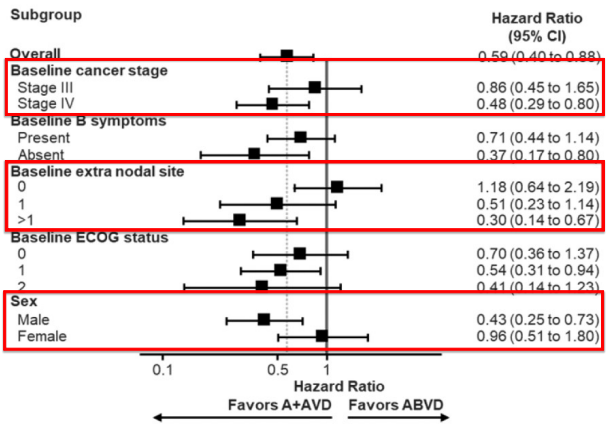
ECHELON-1 subgroup analysis

- Greater benefit of BV-AVD with high-risk disease: stage IV, IPS 47, extranodal involvement
- Less benefit in older adults >60, female patients, and lower risk disease (IPI 01)





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ECHELON-1 – subsequent lymphoma therapy

- Fewer patients in the BV-AVD arm required subsequent therapy including auto-HCT and allo-HCT

	A+AVD (n=662)	ABVD (n=659)	Total (N=1,321)
Patients with ≥1 subsequent anticancer therapy, n (%)	135 (20)	157 (24)	292 (22)
Type of therapy, n (%)			
Chemotherapy regimens	78 (12)	108 (16)	186 (14)
Brentuximab vedotin monotherapy	8 (1)	49 (7)	57 (4)
Brentuximab vedotin + chemotherapy	2 (<1)	20 (3)	22 (2)
Radiation	54 (8)	54 (8)	108 (8)
Chemotherapy + radiation	1 (<1)	4 (<1)	5 (<1)
High-dose chemotherapy + transplant	44 (7)	59 (9)	103 (8)
Allogeneic transplant	4 (<1)	12 (2)	16 (1)
Immunotherapy*	18 (3)	24 (4)	42 (3)
Brentuximab vedotin + nivolumab	0 (0)	4 (<1)	4 (<1)
Nivolumab	15 (2)	18 (3)	33 (2)
Pembrolizumab	2 (<1)	6 (<1)	8 (<1)
Nivolumab combinations	1 (<1)	1 (<1)	2 (<1)

*Immunotherapy was based predominantly on anti-PD-1 agents.

Ansell et al, NEJM 2022

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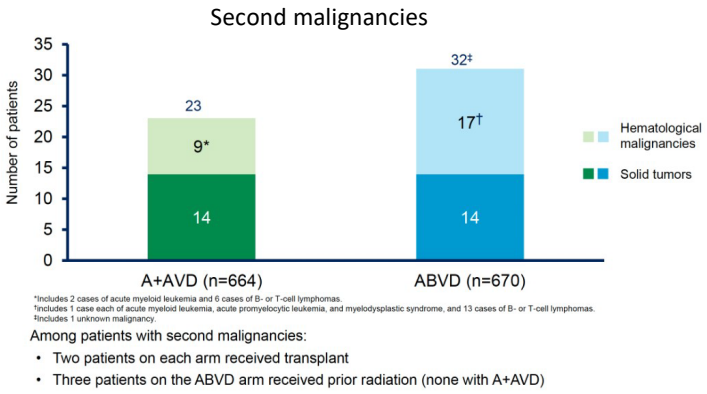
ECHELON-1 – Causes of death

- Most deaths were from progressive disease in both cohorts
- Unexpected high rate of deaths from second cancers in the ABVD arm (mostly NHL)

Table 1. Summary of Causes of Death (Safety Population).*

Cause of Death	A+AVD (N=662)	ABVD (N=659)
Any cause — no. (%)	39 (5.9)	64 (9.7)
Hodgkin's lymphoma or complications — no.	32	45
Second cancer — no.	1	11
Other cause — no.	6	8
Unknown cause	1	5†
Accident or suicide	3	0
Covid-19	0	1
Heart failure	1	1
Intracranial hemorrhage	1	0
Lower respiratory tract infection	0	1



Among patients with second malignancies:

- Two patients on each arm received transplant
- Three patients on the ABVD arm received prior radiation (none with A+AVD)

Ansell et al, NEJM 2022

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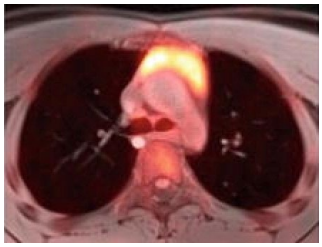
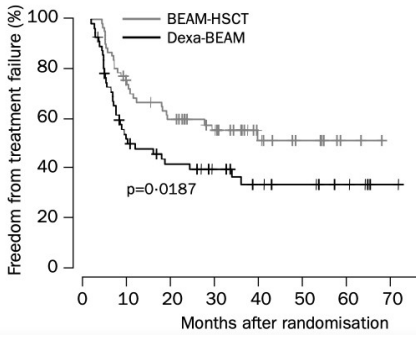
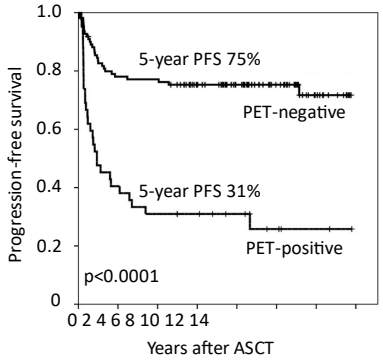
Relapsed/refractory HL

- Rebiopsy is critical to confirm relapse or refractory disease
- Salvage therapy and autologous stem cell transplant (ASCT) is the current standard of care
- Achieving a CR by PET prior to ASCT is a key prognostic factor for PFS



Benign thymic hyperplasia mimicking relapse in mediastinum





Brink et al, *J Nuc Med* 2001

Schmitz et al, *Lancet* 2002

Moskowitz et al, *Blood* 2010

39

Traditional salvage chemotherapy for R/R HL

Regimen	N	ORR	CR rate	PFS	Reference
ICE	65	85%	26%*	58% (3y)	Moskowitz et al, *Blood* 2001
DHAP	102	88%	21%*	59% (3y)	Josting et al, *Ann Oncol* 2002
GVD	91	70%	19%*	52% (4y)	Bartlett et al, *Ann Oncol* 2007
IGEV	91	81%	54%*	53% (3y)	Santoro et al, *Haematologica* 2007
ESHAP	82	67%	50%†	52 mo. (median)	Labrador et al, *Ann Hematol* 2014
BEGEV	58	83%	75%†	59% (5y)	Santoro et al, *J Clin Oncol* 2016

*CR rate assessed by CT

†CR rate assessed by PET

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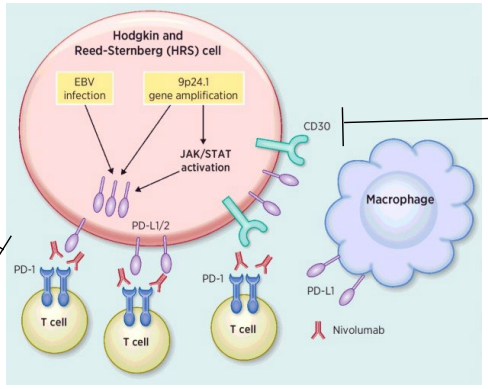
Novel agents have changed the treatment landscape of R/R HL

FDA approved 2016

Nivolumab

Pembrolizumab

FDA approved 2017



Brentuximab vedotin (BV)

FDA approved 2011

Novel agent	N	Median prior Tx	Prior ASCT	ORR	CR rate	Median PFS	Reference
Brentuximab vedotin	102	3.5	100%	75%	34%	9.3 months	Chen et al, *Blood* 2016
Nivolumab	243	4	100%	69%	16%	14.7 months	Armand et al, JCO 2018
Pembrolizumab	210	4	61%*	72%	27%	13.7 months	Chen et al, *Blood* 2019

*Remainder were transplant ineligible and had progression after BV

Figure from SM Ansell, *Clin Cancer Res* 2017

41

Novel salvage regimens incorporating BV and PD-1 inhibitors

Regimen	N	CR rate	PFS (All patients)	PFS (ASCT cohort)	Reference
BV → augmented ICE	65	27% (post BV) 83% (post ICE)	80% (2y)	80% (2y)	Moskowitz et al, *Lancet Oncol* 2015
BV → ICE	56	43% (post BV) 66% (post ICE)	67% (2y)	NR	Herrera et al, *Ann Oncol* 2018
BV + bendamustine	55	74%	63% (2y)	70% (2y)	LaCasce et al, *Blood* 2018
BV + ICE	39	69%	69% (1y)	NR	Stamatoullas et al, ASH 2019
BV + DHAP	61	79%	76% (2y)	NR	Hagenbeek et al, *Haematologica* 2019
BV + ESHAP	66	70%	71% (2y)	NR	Garcia-Sanz et al, *Ann Oncol* 2019
BV + nivolumab	91	67%	77% (3y)	91% (3y)	Advani et al, *Blood* 2021
Nivolumab + ICE	42	91%	72% (2y)	94% (2y)	Mei et al, *Blood* 2022
Pembrolizumab + ICE	37	87%	88% (2y)	NR	Bryan et al, ASH 2021
Pembrolizumab + GVD	38	95%	100% (1y)	100% (1y)	Moskowitz et al, JCO 2021

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Novel salvage regimens increase CR rate and PFS after ASCT

N = 853 patients

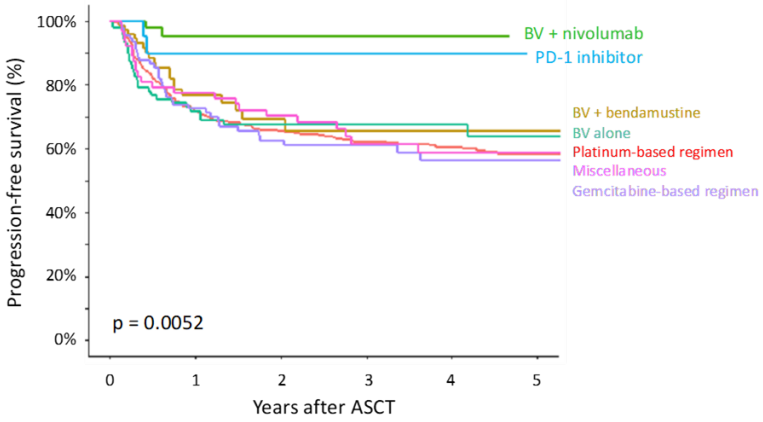
12 U.S. centers

ASCT between 2010-2020

Outcomes compared by salvage regimen:

- Platinum-based regimen (N=451)
- Gemcitabine-based regimen (N=90)
- BV alone (N=87)
- BV + bendamustine (N=76)
- BV + nivolumab (N=48)
- PD-1 inhibitor (N=24)
- Miscellaneous (N=64)

- Higher CR rate with BV+benda (80%) and BV+nivo (67%) vs platinum (49%) (p<0.001)
- Excellent PFS with BV+nivo and PD-1 inhibitors vs platinum regimens (p<0.01)



Desai S, Spinner MA, David KA, et al, 2021 ASH Abstract #878

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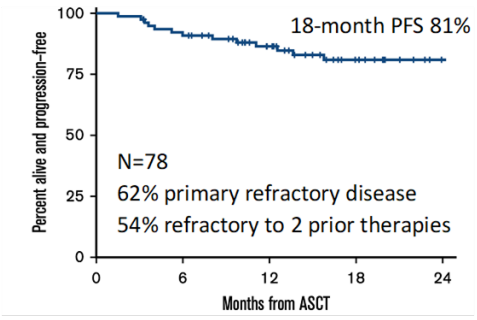
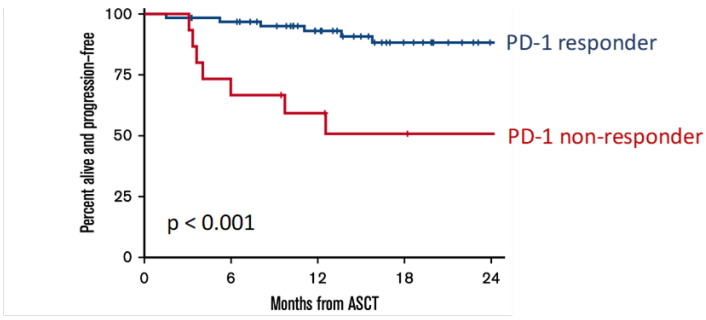
ASCT after PD-1 blockade in R/R HL

- Recent studies suggest that PD-1 inhibitors may sensitize HL to subsequent chemotherapy[1,2]
- Chemorefractory patients who respond to PD-1 inhibitors have excellent outcomes after ASCT[3]
- Response to PD-1 blockade better predicts post-transplant PFS than prior chemosensitivity[3]





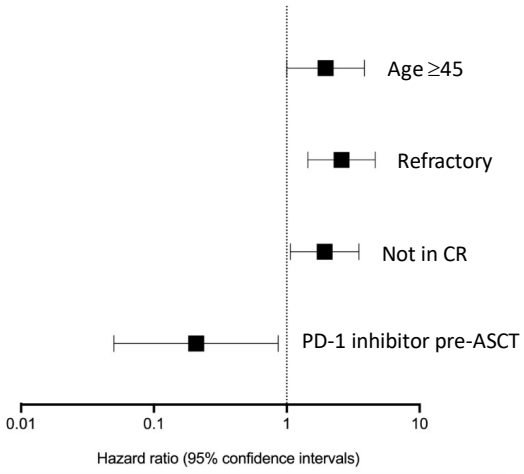
[1]Rossi et al, *Am J Hematol* 2018 [2]Carreau et al, *Oncologist* 2020 [3]Merryman et al, *Blood Adv* 2021

44

PD-1 inhibitors pre-ASCT improve PFS in multivariable analysis

N = 183 patients with R/R cHL transplanted at Stanford from 2011-2020

Variable	N (%)	HR (95% CI)	P value
Age <45	146 (80%)	Reference	
Age ≥45	37 (20%)	**1.961 (1.001-3.841)**	**0.0497**
Relapsed	133 (73%)	Reference	
Refractory	50 (27%)	**2.583 (1.441-4.629)**	**0.00143**
CR	111 (61%)	Reference	
Not in CR	72 (39%)	**1.928 (1.063-3.497)**	**0.0307**
Chemotherapy pre-ASCT	156 (85%)	Reference	
PD-1 inhibitor pre-ASCT	27 (15%)	**0.208 (0.050-0.862)**	**0.0304**

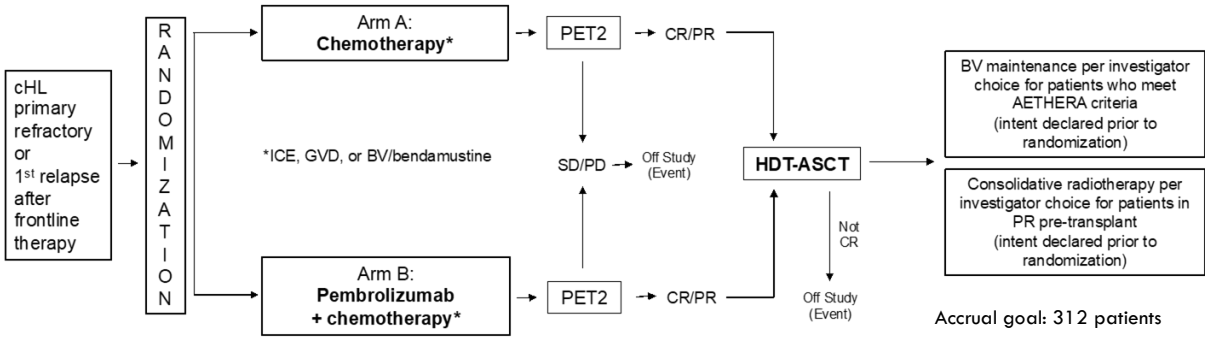


Spinner et al, unpublished data

45

ECOG-ACRIN 4211 trial

- Phase 3 trial comparing SOC chemotherapy vs pembrolizumab + chemotherapy as first salvage for R/R cHL



- Primary endpoint: 2-year PFS
- Secondary endpoints: 2-year OS, CR rate, CR rate after ASCT
- Correlative studies: ctDNA assessments, PB immune cell profiling
- **Planning to open at ALLIANCE cooperative group sites including UCSF in 2023**

Accrual goal: 312 patients

Stratification factors:

- Frontline therapy received
- Age group (<18 or >/=18)
- Intent to use BV maintenance
- Intent to use RT consolidation

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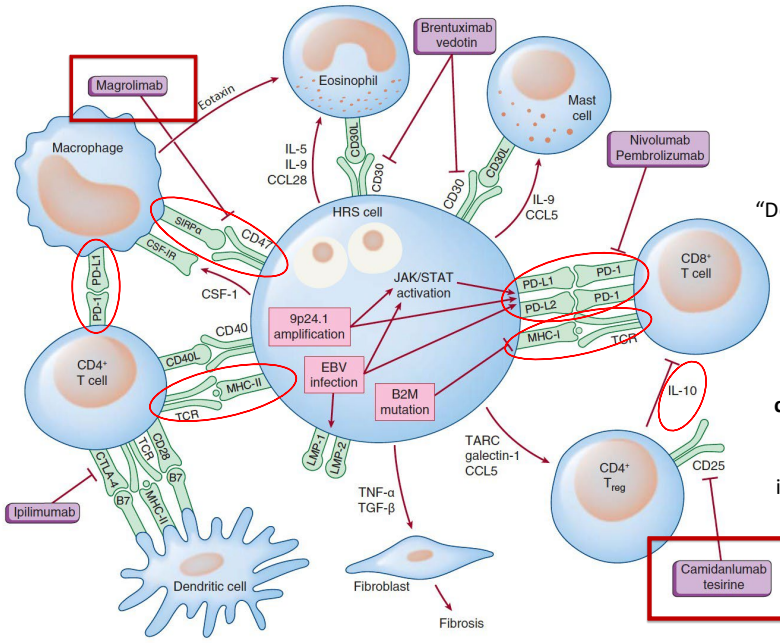
Reed-Sternberg cells evade the immune system through multiple pathways

CD47 overexpression

"Don't eat me" signal

Decreased or absent MHC class I or II expression

Impaired antigen presentation



PD-L1 and PD-L2 overexpression

"Don't find me" signal

Anti-inflammatory cytokine production

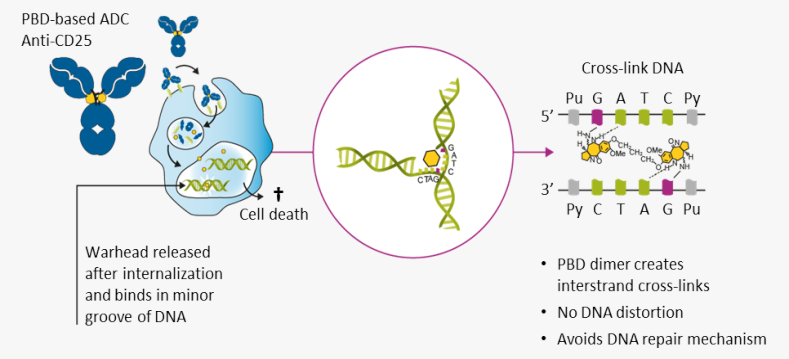
Promoting an immunosuppressive microenvironment

Spinner MA, Mou E, Advani RH. Chapter 96. Hodgkin Lymphoma. Williams Hematology. 2021

47

Depleting immunosuppressive T_{regs} in the tumor microenvironment

- **Camidanlumab tesirine** - anti-CD25 ADC, releases PBD dimer which crosslinks DNA leading to cell death[1]
- Two potential mechanisms of action in Hodgkin lymphoma[2]
  - Death of CD25+ tumor cells (expressed in 60-80% of Reed-Sternberg cells)
  - Depleting immunosuppressive CD25+ regulatory T cells → increased T_{eff}:T_{reg} ratio



[1]Hartley et al, *Expert Opin Investig Drugs* 2011 [2]Flynn et al, *Mol Cancer Ther* 2016

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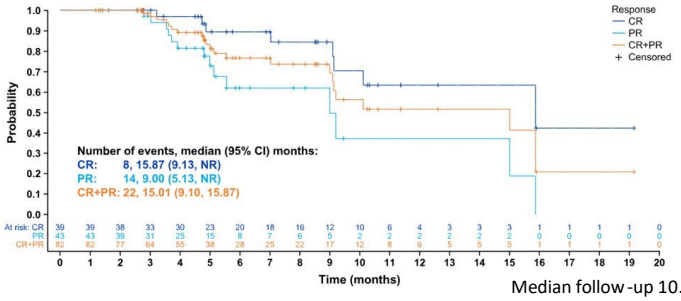
Phase 2 study of camidanlumab tesirine in R/R HL

- Enrolled 117 patients
- Median 5 prior therapies:
  - 100% with prior BV and PD-1 inhibitor
  - 50% with prior autologous HCT
- Dosing schema:
  - Cycle 1-2: 45 mcg/kg IV q3 weeks
  - Cycle 3+: 30 mcg/kg IV q3 weeks
- Activity:
  - **ORR 70%, CR rate 33%**
  - **Median PFS 9.1 months**
  - 14% bridged to auto or allo HCT
- Toxicity profile:
  - **GBS/polyradiculopathy 6.8%**
  - Rash 33%
  - Edema/effusions 17%



Median follow-up 10.7 mo.

Summary of Patients with GBS/polyradiculopathy

Patient	AE by preferred term	Max grade	Duration (days)	IVIG/PLEX/ Steroids	Outcome at last assessment
1	GBS	4	523	Y/Y/Y	Ongoing at grade 1
2	GBS	4	43	Y/Y/N	Recovered
3	GBS	3	50	Y/Y/Y	Not recovered; patient died of sepsis
4	GBS	3	287	Y/N/Y	Ongoing at grade 1
5	GBS	3	111	Y/Y/Y	Ongoing at grade 1[a]
6	GBS	2	119	Y/N/N	Recovered
7	Polyneuropathy[b], Meningitis, Facial paralysis, SIADH	4	72	Y/N/Y	Recovered
8	Radiculopathy	2	165	Y/Y/Y	Recovered

Carlo-Stella et al, 2022 EHA Abstract #S201

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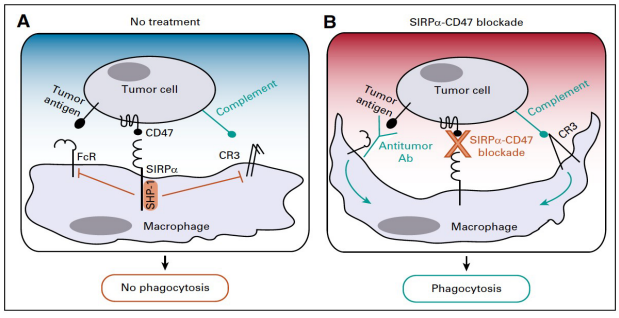
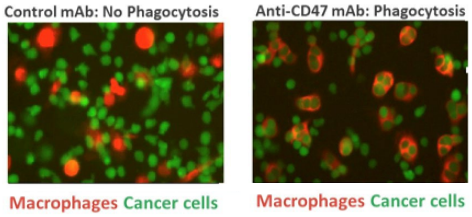
Activating macrophages in the tumor microenvironment

- CD47 is a "don't eat me" signal overexpressed by many cancers to evade phagocytosis[1]
- **Magrolimab** is an anti-CD47 antibody which promotes phagocytic elimination of multiple lymphoma subtypes in preclinical models[2,3]
- Magrolimab + rituximab was active and well tolerated in multiply R/R B-cell NHL with evidence of synergy, enhancing antibody dependent cellular phagocytosis (ADCP)[4]





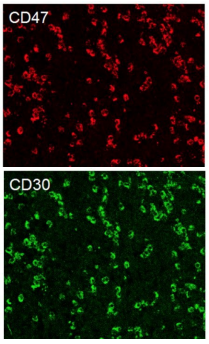
[1]Veillette and Tang, JCO 2019

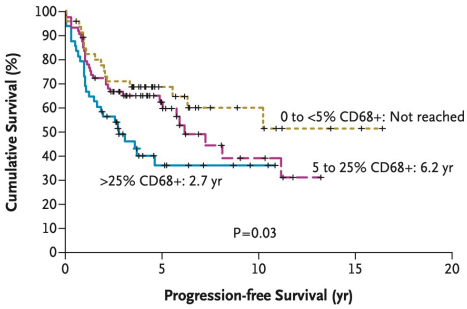
[2]Chao et al, *Cell* 2010
[3]Liu et al, *PLoS One* 2015
[4]Advani et al, NEJM 2018

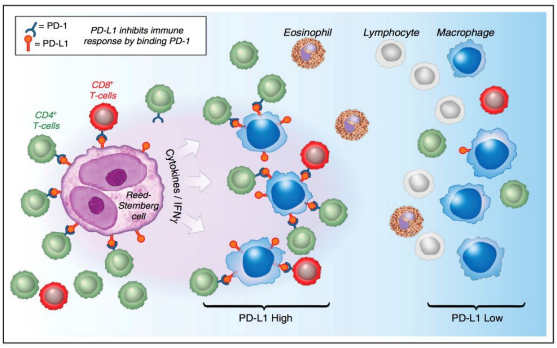
50

Rationale for CD47 blockade and targeting macrophages in HL

- CD47 is consistently overexpressed by Reed-Sternberg cells[1]
- Macrophages are abundant in the HL microenvironment, and an increased number of tumor-associated macrophages is associated with inferior PFS[2,3]
- Topological analysis indicates PD-L1+ macrophages surround Reed-Sternberg cells like a "castle and moat"[4]







[1]Lopez-Pereira et al, *Clin Transl Oncol* 2020 [2]Stiedl et al, NEJM 2010 [3]Tan et al, *Blood* 2012 [4]Carey et al, *Blood* 2017

51

Phase 2 study of magrolimab and pembrolizumab in R/R HL

Eligible patients

Key inclusion criteria
- Adults (age ≥18)
- Biopsy-confirmed R/R cHL
- At least 2 prior lines of therapy

Key exclusion criteria
- Prior Tx with a PD-1 inhibitor within 6 months of enrollment
- Prior allogeneic HCT
- Systemic autoimmune disorder on chronic immunosuppression

REGISTER

Treatment schedule

Cycle 1 (28 days)
Magrolimab 1 mg/kg IV, D1
Magrolimab 30 mg/kg IV, D8, 15, 22
Pembrolizumab 200 mg IV, D8

Cycle 2 (21 days)
Magrolimab 30 mg/kg IV, D1, 8, 15
Pembrolizumab 200 mg IV, D1

Cycle 3 and beyond (21 days)
Magrolimab 45 mg/kg IV, D1
Pembrolizumab 200 mg IV, D1

Progressive disease, unacceptable toxicity, or bridge to SCT, for a maximum treatment period of 24 months

Survival follow up

Currently open at Stanford& DFCI
Accrual goal: 24 patients

- Primary endpoint: **CR rate**
- Secondary endpoints: ORR, DOR, PFS, OS, AEs, immune -related AEs
- Translational correlatives:
  1. Evaluating changes in tumor microenvironment (multiplex immunofluorescence panels of pre-Tx and on-Tx biopsies)
  2. Evaluating potential biomarkers of response (9p24.1 amplification, PD-L1 and CD47 expression, quantitative PET metrics)
  3. Banking serial plasma samples for future correlative studies (ctDNA analysis, single cell RNA sequencing)

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Hodgkin lymphoma updates - Summary

- With mature 6-year follow-up, BV-AVD improves PFS and OS compared to ABVD in stage III-IV HL
  - Greater benefit in the highest risk patients (stage IV, IPS 4-7, extranodal involvement)
  - Fewer patients receiving BV-AVD required auto or allo HCT
  - Now category 1 recommendation in NCCN guidelines
- Numerous options for first salvage, with many regimens incorporating BV and/or PD1 inhibitors
  - Excellent PFS with PD-1 inhibitor-based salvage regimens
  - Phase 3 EA4211 trial will compare chemo vs pembro + chemo as first salvage (**opening at UCSF**)
- Many novel immunotherapy approaches are under investigation for multiply R/R HL
  - Camidanlumab tesirine – anti-CD25 ADC to deplete immunosuppressive T_{regs}
  - Magrolimab – anti-CD47 antibody to enhance phagocytosis (**phase 2 trial open at Stanford**)
  - Many others in development (anti-LAG3 antibody, CD30/CD16A bispecific Ab, CD30 CART)

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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Myeloma Update 2022

Michaela Liedtke, MD

Stanford University

UPDATES IN MULTIPLE MYELOMA

ANCO 2022

Michaela Liedtke, MD

Illustrations on slides courtesy of respective author and/or Clinical Care Options

Stanford University

1

Disclosures

- Advisory Board: GSK, Takeda, Kite, Janssen, Natera

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2

Learning Objectives

- Focus on disparities
- Compare 3 or 4 drugs for patients with newly diagnosed myeloma
- Outline approach to relapsed or refractory myeloma
- Review immunotherapies and other novel agents and experimental strategies
-

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Disease disparity: Myeloma incidence & characteristics

- 2.5-fold higher incidence in black patients
- Family history more common
- Younger age at diagnosis
- Higher rate of comorbidities
- Higher prevalence of myeloma-defining events
- Association with high-risk translocations
-

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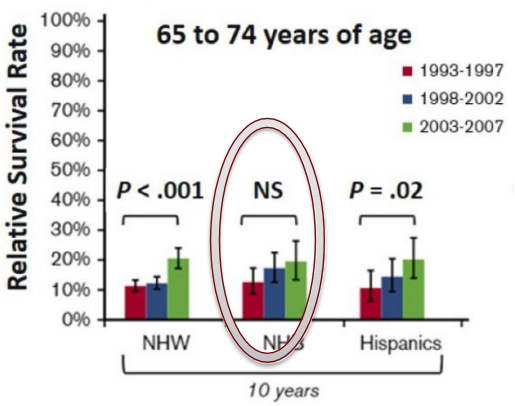
Outcome disparity



No significant improvement in survival for the Non-Hispanic Black population

Costa L, et al. Blood Advances 2017.

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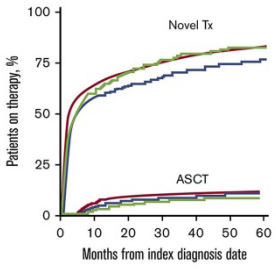
Access disparity



Cohort	N	Mean age (y)	Mean CCI
White	3,504	75.8	2.2
AA	858	71.8	3.2
HISP	468	72.7	2.7
Novel Tx	**Median (months)**	**Log-rank *P* value (vs White)**	
White	2.7	–	
AA	5.2	<0.001	
HISP	4.6	<0.05	
ASCT	**Median (months)**	**Log-rank *P* value (vs White)**	
White	Not reached	–	
AA	Not reached	0.08	
HISP	Not reached	<0.05	

AA, African American; HISP, Hispanic; CCI, Charlson Comorbidity Index; ASCT, autologous stem cell transplant

	White N = 526	Black N = 113	*P* Value
Induction therapy			0.001
Any triplet	384 (73%)	62 (55%)	<0.001
PI+IMiD triplet	240 (46%)	40 (35%)	0.05
Alkylator-based triplet	144 (27%)	22 (20%)	0.1
Doublet	118 (22%)	46 (41%)	<0.001
Other	24 (5%)	5 (4%)	1

Time to novel therapy is twice as long for African Americans compared to Whites

Triplet regimens are less commonly used for African Americans

Ailawadhi S, et al. Blood Advances 2019.

Derman BA, et al. Blood Cancer Journal 2020.

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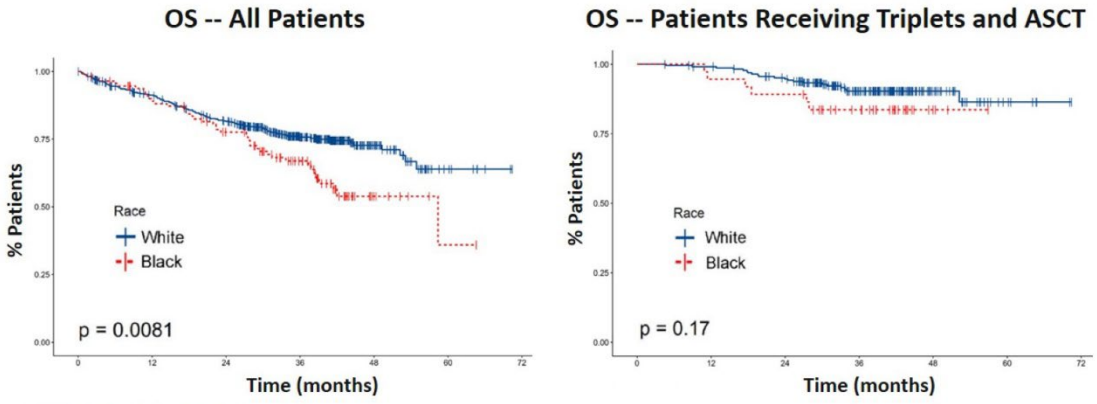
Equal access results in equal outcome



Derman BA, et al. Blood Cancer Journal 2020.

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Identify and address disparities

More likely to be affected by poverty

More likely to be uninsured

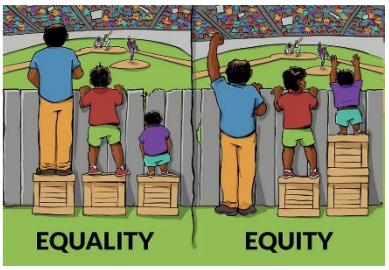
More likely to live in rural areas

Connect patient with resources

Improve understanding of disease

Be sensitive to cultural differences

Adhere to standards



Adapted from 'Interaction Institute for Social Change; Artist: Angus Maguire

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Summary

- Racial disparities are evident in myeloma across a wide spectrum
- Outcome disparities can be overcome by equal access to care
- Awareness and mitigation strategies are needed to identify and address racial disparities

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Newly diagnosed myeloma: Goals of therapy

01	02	03	04
Reduce disease burden	**Prevent or reverse myeloma-related end organ damage**	**Manage symptoms of myeloma and myeloma-treatment**	**Achieve and prolong disease control**

Maximize progression free and overall survival with best possible QOL

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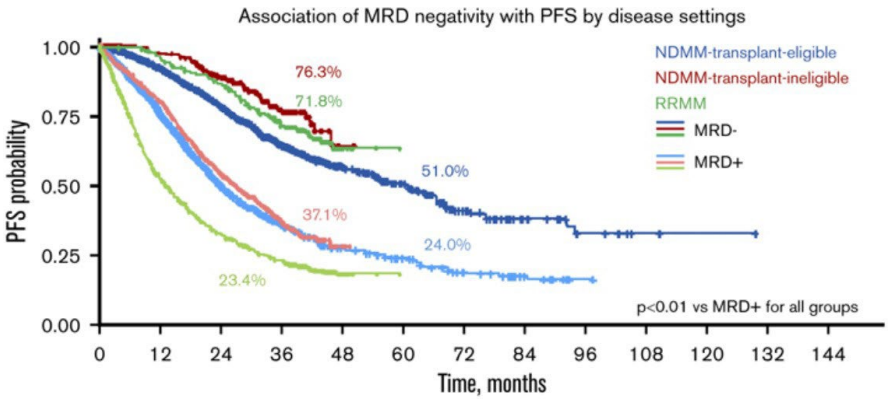
Minimal residual disease



MRD-negativity is associated with longer PFS

Munshi N, et al. Blood Advances 2020.

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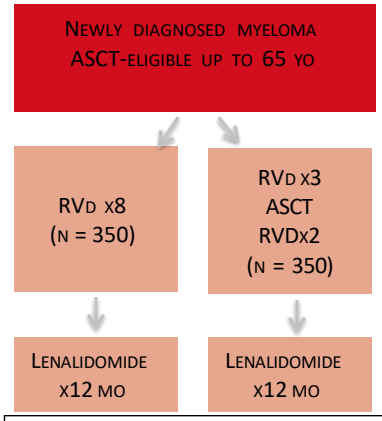
Traditional standard: RVd in IFM/DFCI 2009



Outcome	ARM A (n = 350)	ARM B (n = 350)	HR (95% CI), *P* Value
CR, %	49	59	0.02
MRD - by FCM, %	65	80	0.001
4-yr OS, %	83	81	1.2 (0.7-1.8), NS
4-yr PFS, %	35	47	0.69 (0.56-0.84), < .001

Upfront ASCT improves median PFS from 36 to 50 months

After 8 years of follow-up over 60% of patients are alive in both arms

Attal M, et al. NEJM 2017.

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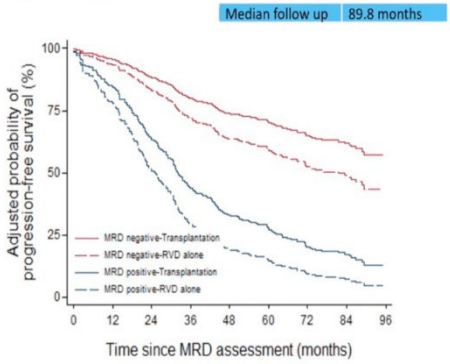
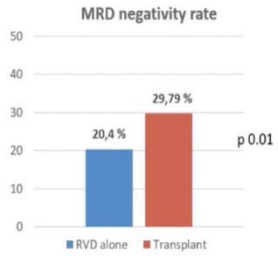
IFM/DFCI 2009: Role of MRD

Subgroup analyses





MRD-negativity is a strong predictor for PFS and OS

Perrot A, et al. ASH 2020. Abstract 143.

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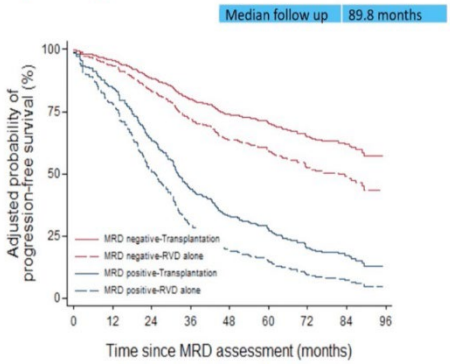
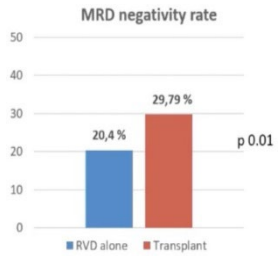
IFM/DFCI 2009: Role of MRD

Subgroup analyses





Can we improve these results?

Perrot A, et al. ASH 2020. Abstract 143.

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Quadruplet therapies in upfront myeloma

01	02	03	04	05
CASSIOPEIA	GRIFFIN	MASTER	GMMG-HD7	DREAMM-9
Dara + VTd	Dara + VRd	Dara + KRd	Isa + VRd	Belamaf + VRd

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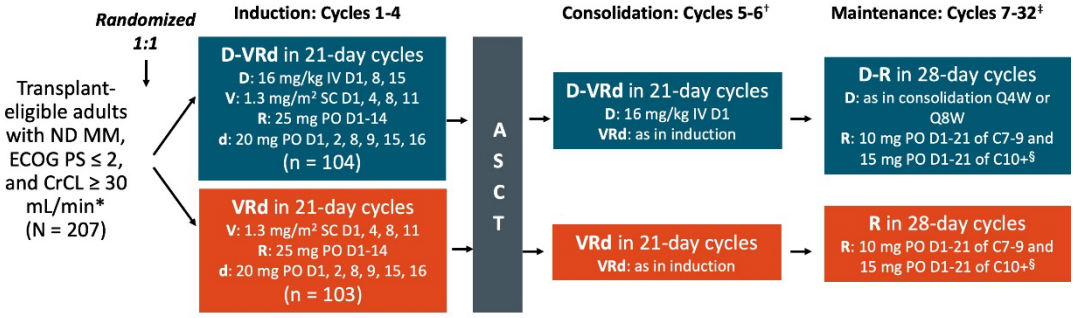
GRIFFIN: Dara-VRd versus VRd



*Lenalidomide dose was adjusted in patients with CrCl ≤ 50 mL/min. †Consolidation began 60-100 days after transplantation. ‡Patients completing maintenance phase were permitted to continue single-agent lenalidomide. §15 mg administered only if tolerable.

Primary endpoint analysis: addition of D to VRd increased sCR by the end of consolidation, 42.4% vs 32.0% (1-sided *P* = .068)

Laubach, et al. ASH 2021. Abstract 79.

Slide credit: clinicaloptions.com

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GRIFFIN: Responses deepen over time

Depth of Response	D-VRd				VRd			
	End of Induction	End of ASCT	End of Consolidation	24 Mos of Maintenance Cutoff	End of Induction	End of ASCT	End of Consolidation	24 Mos of Maintenance Cutoff
sCR	12	21	42	66	7	14	32	47
CR	7	6	9.	16	6	5	10	13
VGPR	53	60	39	14	43	46	31	18
PR	26	12	8	3	35	26	19	14
SD/PD/NE	2	1	1	1	8	8	8	7

After 2 years of maintenance, sCR rate still higher in Dara-VRd

Laubach J, et al. ASH 2021. Abstract 79.

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GRIFFIN: High MRD-negativity rates

MRD status	D-VRd	VRd
ITT MRD-negative	64.4%	30.1%
CR or better and MRD-negative	78%	47.5%
36 mo PFS ITT all pts	88.9%	81.2%

Laubach J, et al. ASH 2021. Abstract 79.

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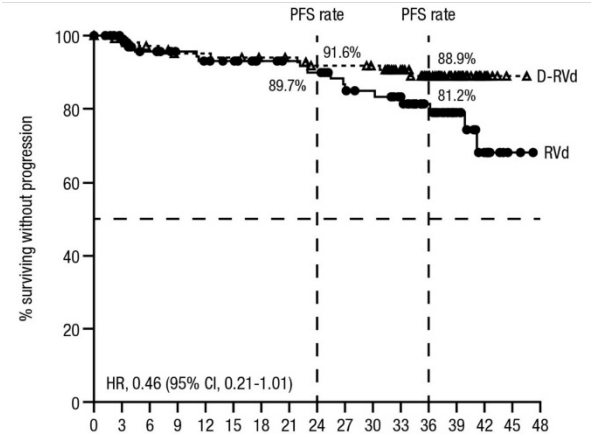
GRIFFIN: D-RVd prolongs PFS



Median PFS/OS not reached in either arm at median follow-up of 38.6 mos

Laubach J, et al. ASH 2021. Abstract 79.

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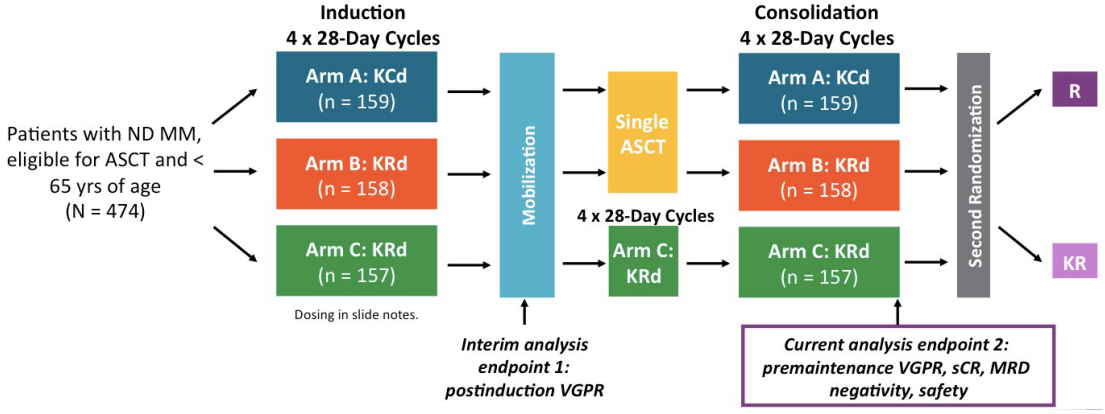
FORTE: KRd +/- ASCT

- Multicenter, randomized, open-label phase II study



Gay F, et al. Lancet Oncology 2021.

Slide credit: clinicaloptions.com

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FORTE: Initial randomization

Outcome	KCd-ASCT	KRd12	KRd-ASCT
At least CR, %	42	57	54
MRD – 10^{-5}, % (ITT)	43	56	62
4-yr PFS, %	51	56	**69**
Median PFS	53 mo	55.3 mo	Not reached
3-yr OS%	83	90	90

KRd-ASCT increased rate of MRD-negativity and 4-yr PFS

Gay F, et al. Lancet Oncology 2021.

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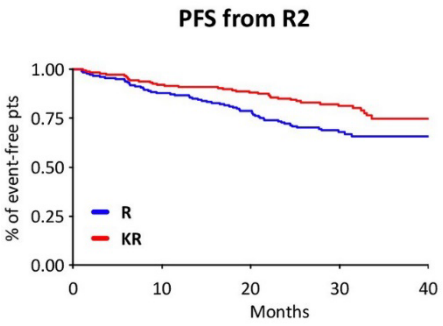
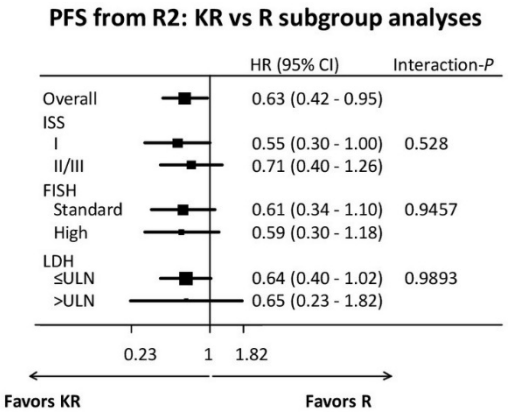
FORTE: Second randomization





KR maintenance increased PFS compared to lenalidomide alone

Gay F, et al. ASH 2020. Abstract 141.

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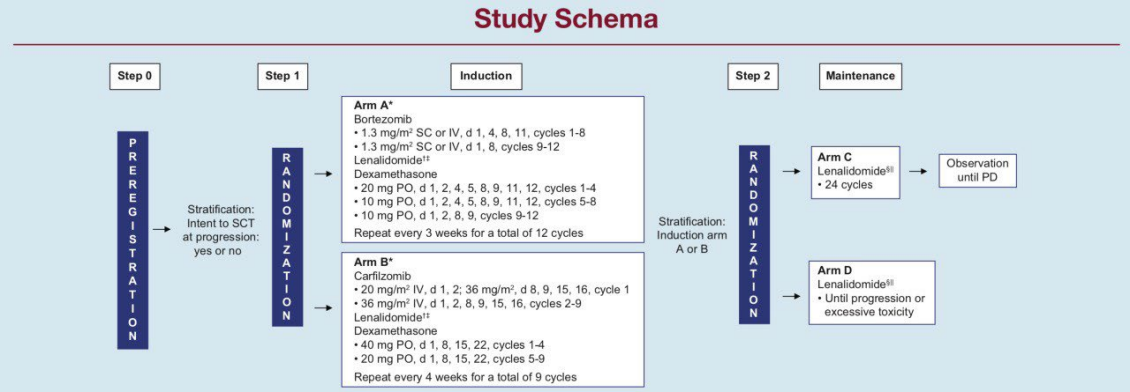
ENDURANCE: KRd versus VRd

Study enrolled >1,000 patients with standard risk myeloma not planned for ASCT



KRd was associated with deeper responses: VGPR or better 74% vs 65%

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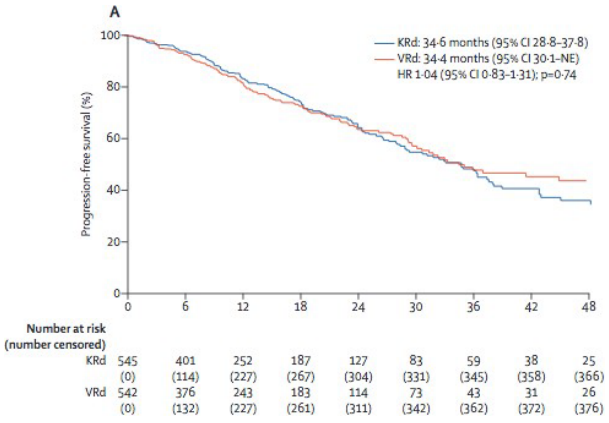
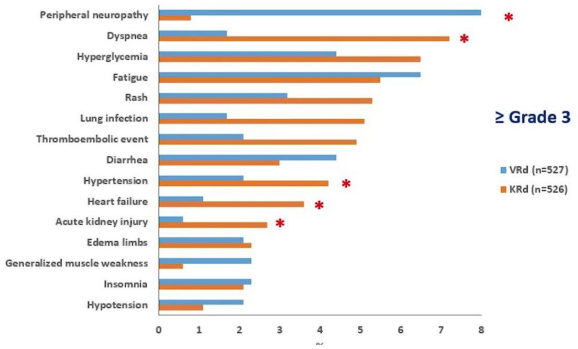
KRd did not improve PFS compared to VRd





Subgroup analysis did not identify benefit based on age or disease characteristics

Rate of cardio-pulmonary and renal toxicity is higher with carfilzomib

Kumar S, et al. Lancet Oncology 2020.

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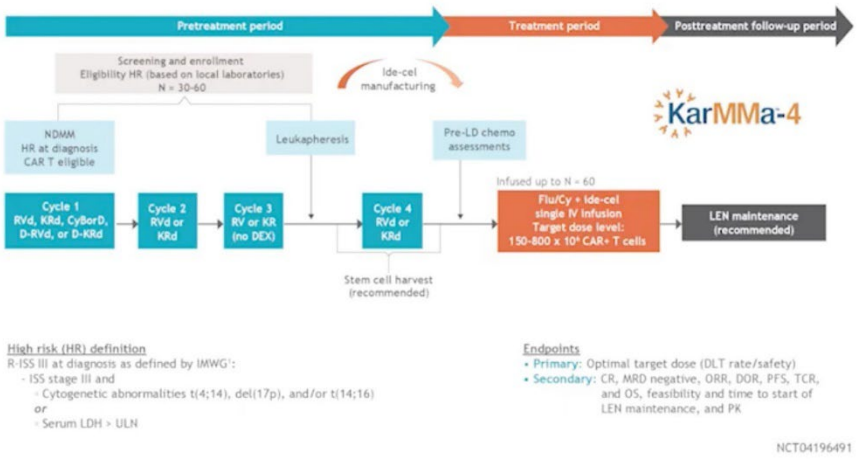
KarMMa-4: upfront CAR-T for high-risk myeloma



Usmani S, et al. ASCO 2021.

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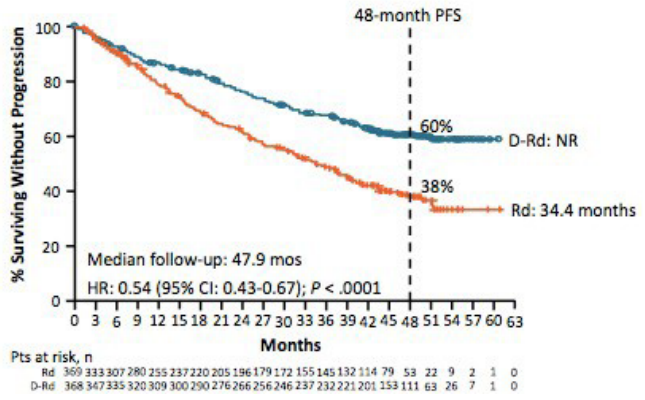
MAIA: Rd +/- daratumumab in upfront myeloma

NEWLY DIAGNOSED MYELOMA
ASCT-INELIGIBLE AND ECOG 0-2
MEDIAN AGE 73

DARATUMUMAB+ REVLIMID + DEX (N = 368)	Revlimid + dex (n = 369)
MEDIAN DOT 42.8 MO	MEDIAN DOT 22.6 MO



In primary analysis addition of daratumumab to Rd reduced risk of progression or death by 44% and increased MRD-negativity rates (24.2% vs 7.3%)

Facon et al., NEJM 2019 and Lancet Oncology 2021

Slide credit: clinicaloptions.com

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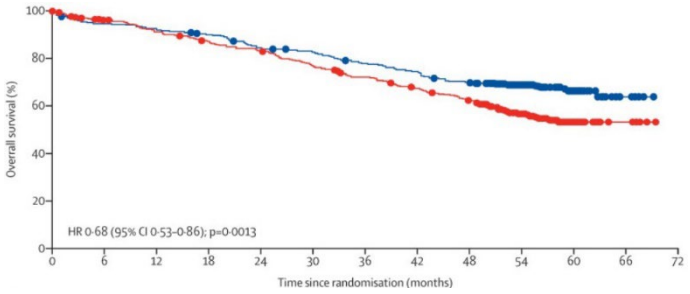
MAIA: Rd +/- daratumumab in upfront myeloma

NEWLY DIAGNOSED MYELOMA
ASCT-INELIGIBLE AND ECOG 0-2
MEDIAN AGE 73

DARATUMUMAB+ REVLIMID + DEX (N = 368)	Revlimid + dex (n = 369)
MEDIAN DOT 42.8 MO	MEDIAN DOT 22.6 MO



With longer follow-up the trial now demonstrates an overall survival benefit for D-Rd

Facon et al., NEJM 2019 and Lancet Oncology 2021

Slide credit: clinicaloptions.com

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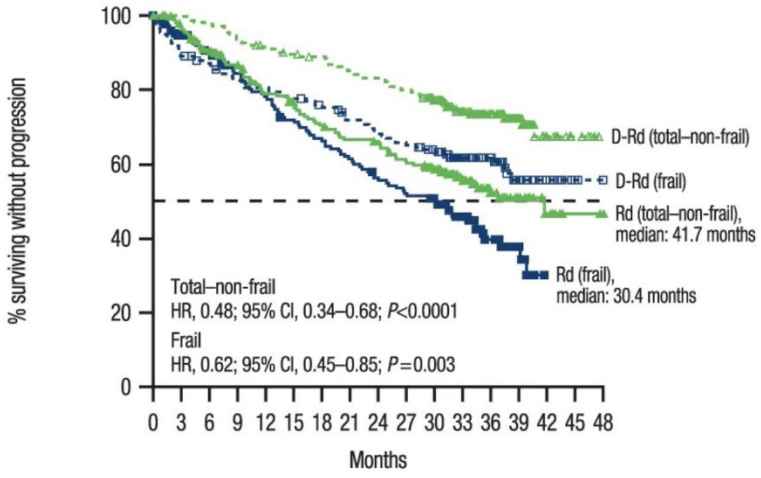
MAIA: Dara-Rd beneficial for frail patients



Facon T, et al. Leukemia 2021.

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Induction regimens in upfront myeloma

	n	Best Response	1-year PFS	2-year PFS
Attal 2017 RVd; ASCT	350	59% ≥CR 88% ≥VGPR	88%	75%
Kaufman 2020 GRIFFIN: D-RVd	104	82% ≥CR (post 1-yr maint) 96% ≥VGPR	97%	95%
Gay 2020 FORTE: KRd-ASCT	158	60% ≥CR 89% ≥VGPR	92% at 1.5-yr	78% at 3-yr
Costa 2019 MASTER: D-KRd	81	**95% ≥CR** **100% ≥VGPR**	NR	NR
Durie SWOG0777	242	24% ≥CR 75%≥VGPR	Median 3.5-yr	
Kumar 2020 MAIA: D-Rd	368	51% ≥CR (at 48 mo) 81% ≥VGPR	86%	76%

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Summary

- Depth of response affects survival outcomes
- Daratumumab-based quadruplet regimens entering clinical practice
- KRd-ASCT produces deep and durable responses
- RVd and KRd are equivalent in standard risk myeloma
- VRd and daratumumab-Rd prolong overall survival compared to Rd alone

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Relapse: Available Agents

Chemo-therapy	IMiD	Proteasome inhibitor	Steroids	MoAb	Other	CAR-T
Melphalan	Revlimid	Bortezomib	Dexamethasone	Daratumumab	Selinexor	Idecel
Cyclophosphamide	Thalidomide	Carfilzomib	Prednisone	Elotuzumab	Venetoclax	Ciltacel
Anthracycline	Pomalidomide	Ixazomib		Isatuximab	Clinical trials	
				Belantamab		

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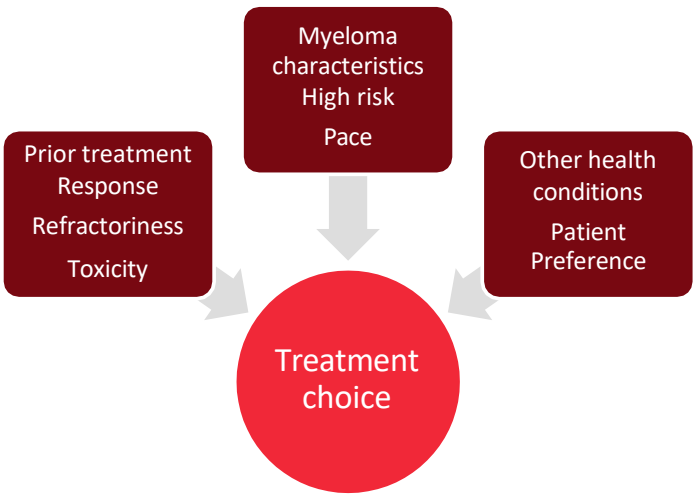
General Treatment Approach at Relapse



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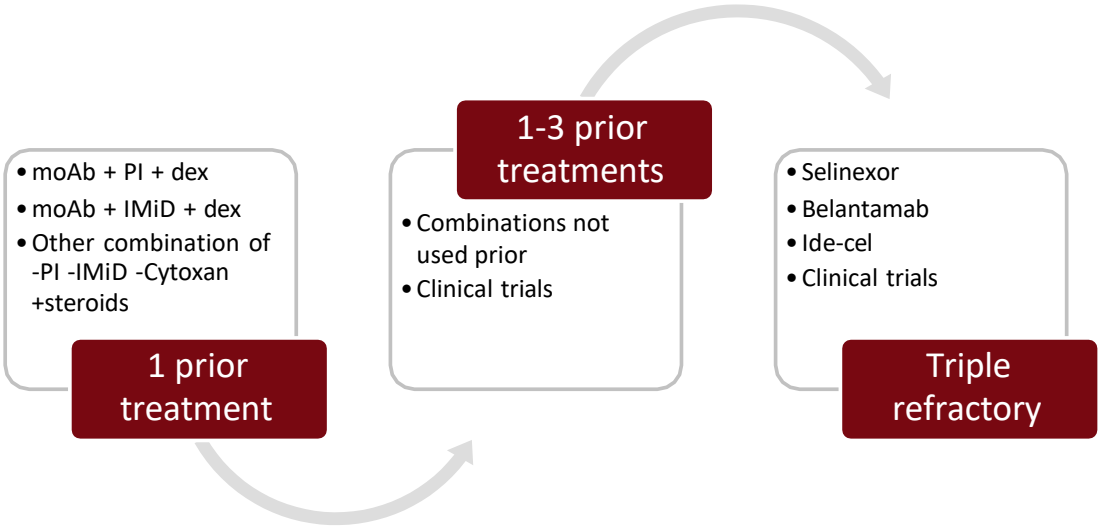
Sequencing Considerations



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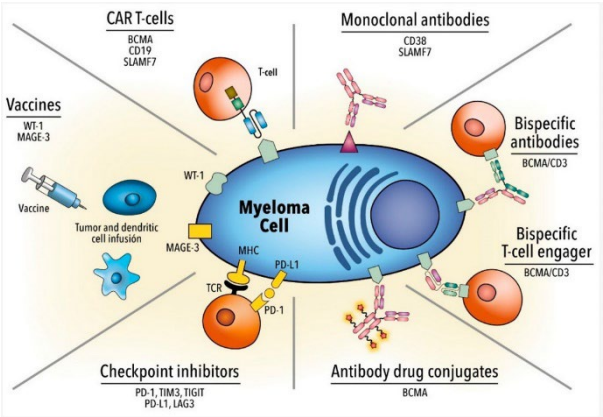
Focus on Immunotherapy

- Naked antibodies
- **Antibody-drug conjugates**
- **Bispecific/T-cell engager**
- **CAR T-cells**



Rodriguez-Lobato L, et al. ASH 2021.

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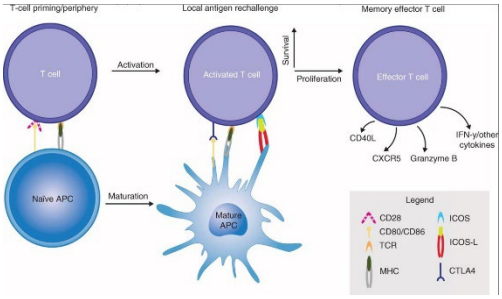
Antibody drug conjugate: belantamab mafodotin plus ICOS-agonist feladilimab

Belantamab mafodotin is an ADC targeting BCMA

ICOS (inducible co-stimulator) is a co-stimulatory receptor of CD28 superfamily on T-cells
Feladilimab is an ICOS agonist that promotes T-cell anti-tumor activity

Intravenous infusion q3weeks
Eye exam prior to every infusion



Efficacy	N=23
ORR	48%
PR	22%
VGPR	17%
CR	8%

Nooka, et al. FutOnc 2021.

Callander, et al. ASH 2021. Abstract 897.

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DREAMM-5: Adverse Events/Ocular Toxicity

Overview of Adverse Events, n (%)	Cohort A Belamaf 1.9 mg/kg + aICOS 8mg N=9	Cohort B Belamaf 2.5 mg/kg + aICOS 8mg N=10	Cohort C Belamaf 2.5 mg/kg + aICOS 24 mg N=4	Total Population N = 23
Any AE	9 (100)	9 (90)	4 (100)	22 (96)
AEs leading to permanent discontinuation of study treatment	1 (11)	1 (10)	0	2 (9)
AEs leading to dose reduction	0	4 (40)	2 (50)	6 (26)
AEs leading to dose delay	5 (56)	6 (60)	1 (25)	12 (52)
Grade 3 or 4 AEs	6 (67)	7 (70)	2 (50)	15 (65)
Grade 3 or 4 AEs related to belamaf	3 (33)	5 (50)	1 (25)	9 (39)
Any SAE	3 (33)	3 (30)	0	6 (26)
Fatal SAEs	0	0	0	0
Adverse Events Related to Study Treatment				
Any Grade AEs	7 (78)	8 (80)	4 (100)	19 (83)
Grade ≥3 AEs	4 (44)	6 (60)	2 (50)	12 (52)
Any grade ocular AEs*	5 (56)	8 (80)	3 (75)	16 (70)
Grade ≥3 ocular AEs	3 (33)	5 (50)	1 (25)	9 (39)

Callander, et al. ASH 2021. Abstract 897.

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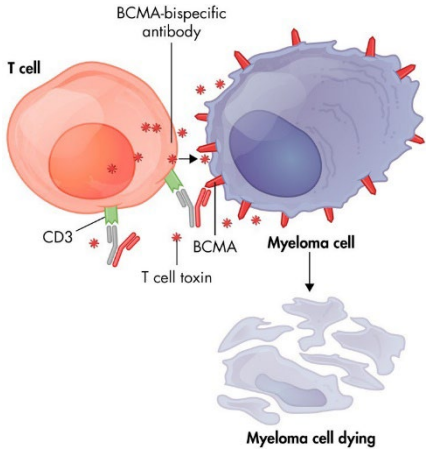
Bispecific antibodies and T-cell engagers

Medication	In Clinical Trials
Formulation	Subcutaneous Intravenous
Targets	BCMA GPCR5 FCRH5
Response rates	55-80+%



SF Cho, Front Immunology;9:821

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Bispecifics in Myeloma

Trial	Teclistamab	REGN5458	TNB-383B	Talquetamab	Cevostamab
Target	BCMA	BCMA	BCMA	GPRC5D	FcRH5
Patients #	165	73	118	55	161
Prior lines #	5 (2-14)	5 (2-17)	5 (1-15)	6 (2-17)	6 (2-18)
ORR, %	62	75	81	69	57
CR, %	29	16	39	16	8
CRS, % (grade 3/4)	72 (1)	38 (0)	54 (3)	75 (5)	80 (1.2)
Neurotox, % (G 3/4)	13 (0)	4 (0)	Not reported	Not reported	14 (1)
Median PFS, mo	59% at 9 mo	Not reported	Not reported	Not reported	Not reported

ASH 2021-abstract 896; ASH 2021-abstract 160 ; ASH 2021-abstract 900; ASH 2021-abstract 158; ASH 2021-abstract 157

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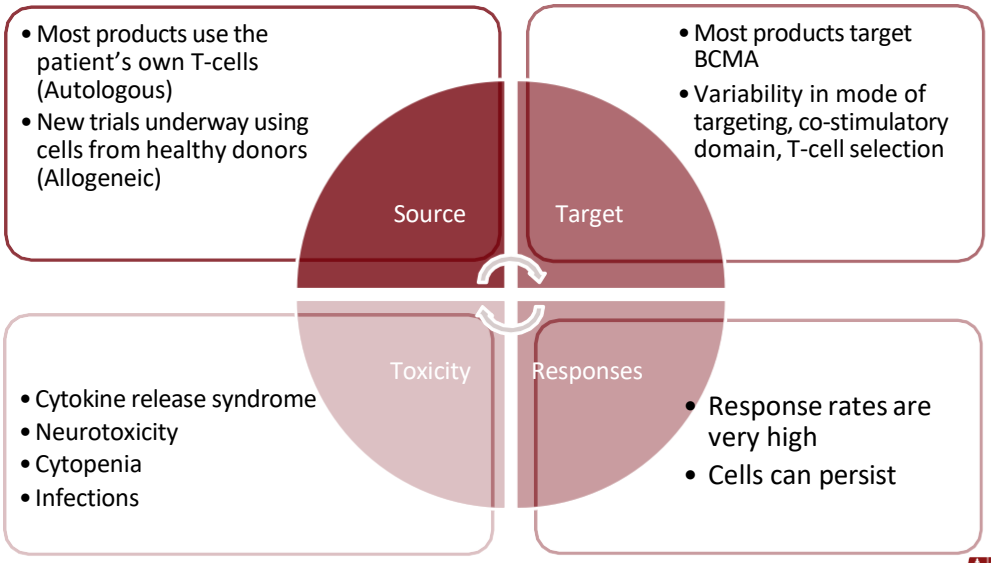
CAR T-cells at a glance



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BCMA-targeted CAR T-cell Therapy

Trial	KarMMa Ide-cel	CARTITUDE-1 Cilta-cel	CT103A	UNIVERSAL ALLO-715
Patients #	128 (54*)	97	79	31
Prior lines #	6 (3-16)	6 (3-18)	4 (3-13)	5 (3-11)
ORR, %	82*	98	95	60
CR or better, %	39*	82.5	58.2	Not reported
CRS, % (grade 3/4)	96 (6)*	95 (4)	95 (3)	45 (0)
Neurotox, % (grade 3/4)	20 (6)*	21 (10)	1.3 (0)	0
Response duration, mo	11.3*	21.8	Not reported	Not reported
Median PFS, mo	12.1*	Not reached	71% at 12mo	Not reported

ASH 2020-abstract 136; ASH 2021-abstract 549; ASH 2021-abstract 547; ASH 2020-abstract 129

*at highest dose level

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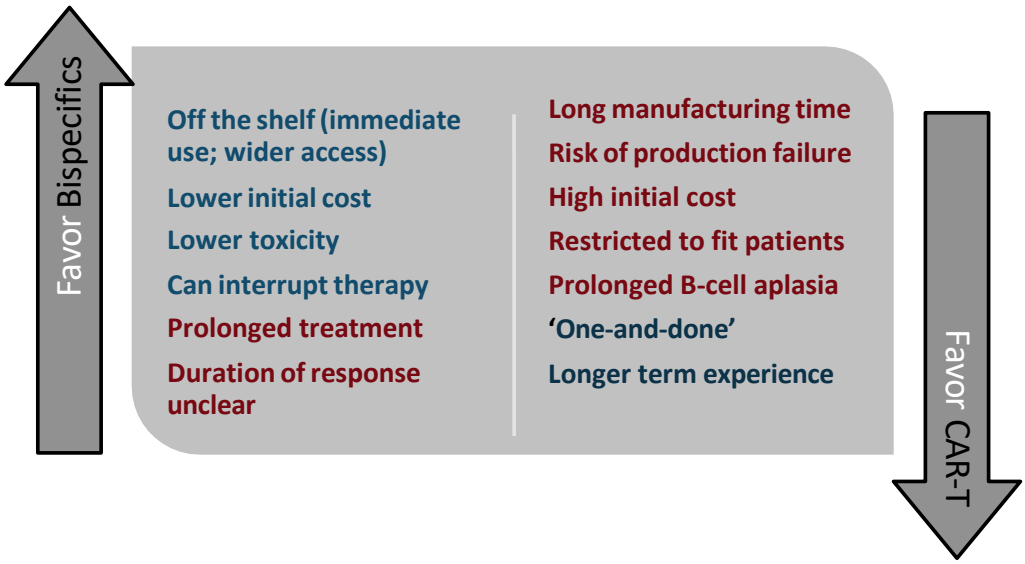

Adapted from Patel et al, BJH 2021

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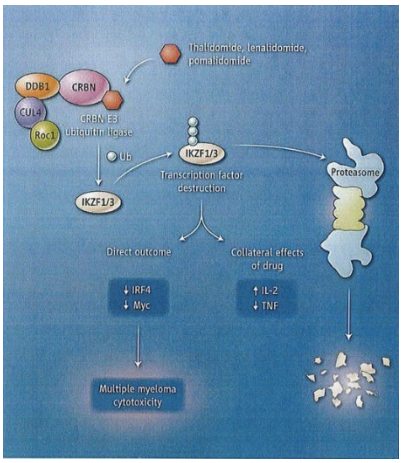
Cereblon E3 ligase modulator (CELMoD): Iberdomide

Iberdomide is an oral CELMoD
enhances degradation of Ikaros and Aiolos

Phase I/II trial in 107 pts
Median 6 prior lines
97% triple refractory

In combination with dexamethasone



Neutropenia common:
Grade 3/4: 45%
Infection:
Grade 3/4: 27%

Overall response rate:
All pts: 26%
Prior BCMA: 25%

Median DOR: 7 mo

Lonial, et al. ASH 2021. Abstract 162.

Stewart, Science 2014.

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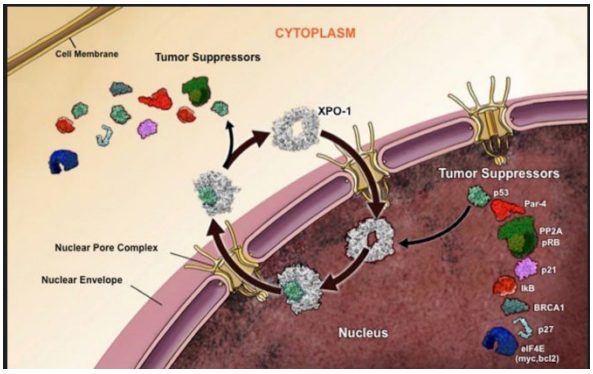
Selinexor in Relapsed/Refractory Multiple Myeloma

- XPO-1 is the main nuclear exporter for tumor suppressors
- Selinexor is a first in class XPO-1 inhibitor
- Toxicity: GI, fatigue, low platelets
- In combination with pomalidomide and dex, weekly Selinexor achieved ORR of 65% (XPd-60)



D White et al, ASH 2021-abstract 2748

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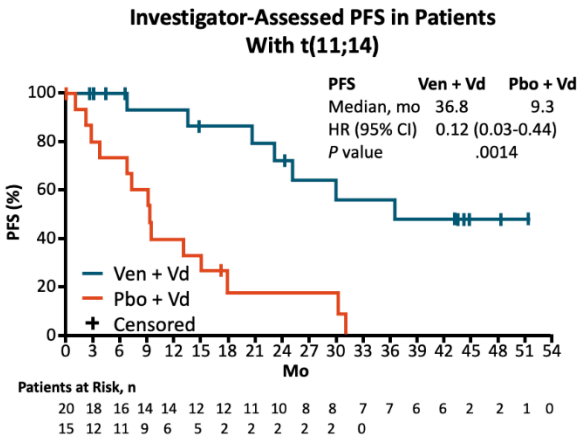
Precision Medicine: Venetoclax for Myeloma with t(11;14)

- Myeloma cells with t(11;14) have higher expression of the anti-apoptotic protein BCL-2
- Venetoclax is a BCL-2 inhibitor
- Bellini phase III trial compared bortezomib/dex +/- venetoclax
- In patients with t(11;14) Venetoclax significantly prolonged PFS (36.8 vs 9.3 mo)



Kumar. ASH 2021. Abstr 84.

Slide credit: clinicaloptions.com

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MyDRUG: Myeloma-Developing Regimens Using Genomics

6-arm, nonrandomized phase I/II study

Patients with RR MM after 1-3 prior therapies including a PI and an IMiD; in early relapse*; 30% mutation in *CDKN2C, FGFR3, KRAS, NRAS, BRAF V600E, IDH2* or t(11;14)
(Planned N = 228)
*within 3 yrs of ASCT on maintenance or 18 months if no maintenance, or within 18 months of initial non-ASCT-based therapy

- Primary endpoint: ORR with actionable genetic alteration
- Secondary endpoint: ORR with nonactionable genetic alteration

All patients received ixazomib/ pomalidomide/dexamethasone, plus:

- *CDK2* alteration: Abemaciclib (Planned n = 38)
- *IDH2* mutation: Enasidenib (Planned n = 38)
- *RAF/RAS* mutation: Cobimetinib (Planned n = 38)
- *FGFR3* mutation: Erdafitinib (Planned n = 38)
- t(11;14): Venetoclax (Planned n = 38)
- "Nonactionable genetic abnormality": Daratumumab (Planned n = 38)

ClinicalTrials.gov. NCT03732703.

Slide credit: clinicaloptions.com

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Summary

- Immunotherapy is taking center stage in myeloma
- CAR T cells and Bispecifics are highly active and share side effect profile of CRS and neurotoxicity
- Agents with novel mechanisms of action are being developed
- Precision Medicine is used to target defined genetic Multiple Myeloma subsets
- Response & Survival rates are improving due to new treatment approaches

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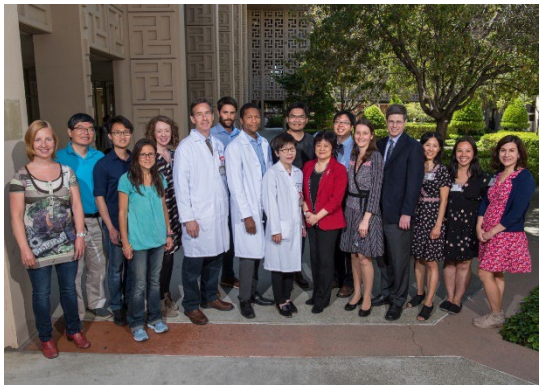
Stanford Myeloma and Amyloid Team

Ren Inthasack

Donirene Ward

Dave Iberri



Surbhi Sidana

Sally Arai

David Kurtz

Stanford MEDICINE

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Leukemia Update 2022

Brian A. Jonas, MD, PHD, FACP

University of California, Davis

Leukemia Update 2022

Brian A. Jonas, MD, PhD, FACP
Associate Professor
University of California, Davis

UCDAVIS COMPREHENSIVE CANCER CENTER

ANCO Hematologic Malignancies Updates
November 12, 2022

1

Disclosures

For the past 12 months:

- **Consulting/Advising**: AbbVie, BMS, Genentech, Gilead, GlycoMimetics, Pfizer, Servier
- **Grant/Research support to my institution**: 47, AbbVie, Amgen, AROG, Celgene, Daiichi Sankyo, F. Hoffmann-La Roche, Forma, Genentech/Roche, Gilead, GlycoMimetics, Hanmi, Immune-Onc, Incyte, Jazz, Loxo, Pfizer, Pharmacyclics, Sigma Tau, Treadwell

2

Learning Objectives

- Using a case-based approach:
  - Review standard and emerging treatment options for AML
  - Discuss current approaches to treating MDS

3

Case 1

A 65-year-old woman is diagnosed with AML after presenting with SOB and bruising. CBC showed WBC 25, Hgb 6, Plt 20, and 60% circulating blasts. BMBx showed 65% myeloblasts, trisomy 8 and mutations in RUNX1 and ASXL1. She is fit for induction chemotherapy.

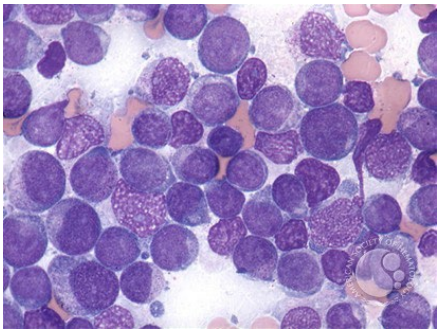
What is this patient's ELN 2017 risk?

How should we treat this patient?

4

Acute Myeloid Leukemia

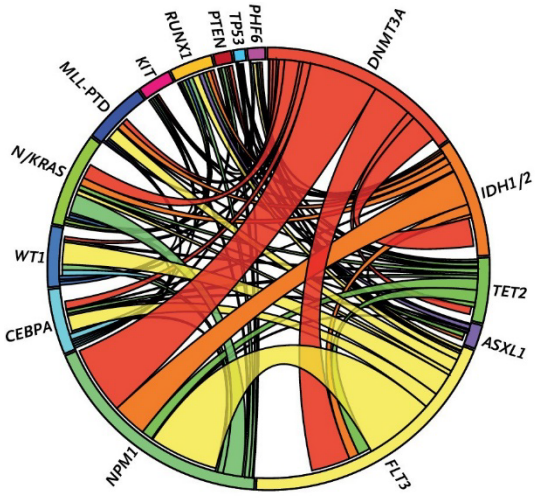
- Clonal expansion of immature myeloid cells
- Heterogeneous disease
- 20,050 new cases (M>F) with 11,540 deaths expected in US in 2022
- Median age 68
- Bleeding, infections, anemia
- High relapse rates



ACS Cancer Statistics, 2022.
ASH Image Bank.

5

Recurrent Mutations in AML



Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

Patel et al. NEJM 2012.

6

ELN 2017 Risk Stratification

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Dohner et al, Blood 2017

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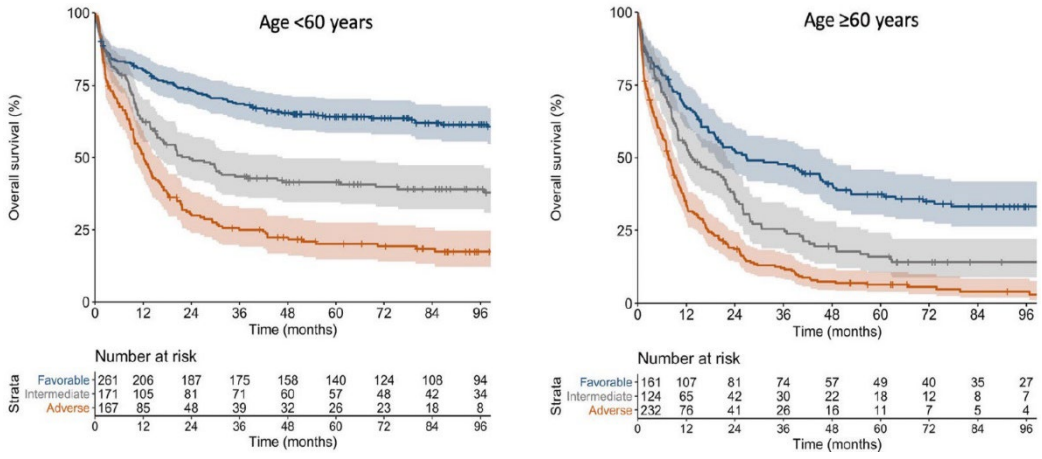
ELN 2017 Risk Stratification - Validation



Herold et al, Leukemia 2020

8

ELN 2022 Risk Stratification

Risk Category[b]	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*[b,c] • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*[b,c] • * Mutated *NPM1*[b,d] without *FLT3*-ITD • * bZIP in-frame mutated *CEBPA*[e]
Intermediate	• * Mutated *NPM1*[b,d] with *FLT3*-ITD • * Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*[b,f] • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK::NUP214* • t(v;11q23.3)/*KMT2A*-rearranged[g] • t(9;22)(q34.1;q11.2)/*BCR::ABL1* • * t(8;16)(p11;p13)/*KAT6A::CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)* • * t(3q26.2;v)/*MECOM(EVI1)*-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype,[h] monosomal karyotype[i] • * Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*[j] • Mutated *TP53*[k]

[a] Frequencies, response rates and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.
[b] Mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course based on the results from analyses of measurable residual disease.
[c] Concurrent of *KIT* and/or *FLT3* gene mutation does not alter risk categorization.
[d] AML with *NPM1* mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.
[e] Only in-frame mutations affecting the basic leucine zipper (bZIP) region of *CEBPA*, irrespective whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome.
[f] The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
[g] Excluding *KMT2A* partial tandem duplication (PTD).
[h] Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.
[i] Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML).
[j] For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
[k] *TP53* mutation at a variant allele fraction of at least 10%, irrespective of the *TP53* allelic status (mono- or biallelic mutation); *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

* Changes from ELN 2017

Dohner et al, Blood 2022

9

Determining "Fitness" for AML Patients

- Disease-related prognostic factors
  - Adverse risk mutations
  - Multidrug-resistance
  - Antecedent hematologic disorders
- Patient-related prognostic factors
  - Comorbidities
  - Psychosocial factors

Ossenkoppele and Lowenberg, Blood 2015.

10

Ferrara Criteria to Define Unfitness for Intense Chemotherapy for AML

Table 3. Operation criteria to define unfitness to intensive chemotherapy in AML

1. An age older than 75 years
2. Congestive heart failure or documented cardiomyopathy with an EF $\leq$50%
3. Documented pulmonary disease with DLCO $\leq$65% or FEV1 $\leq$65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
4. On dialysis and age older than 60 years or uncontrolled renal carcinoma
5. Liver cirrhosis Child B or C, or documented liver disease with marked elevation of transaminases (>3 times normal values) and an age older than 60 years, or any biliary tree carcinoma or uncontrolled liver carcinoma or acute viral hepatitis
6. Active infection resistant to anti-infective therapy
7. Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
8. ECOG performance status $\geq$3 not related to leukemia
9. Any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy

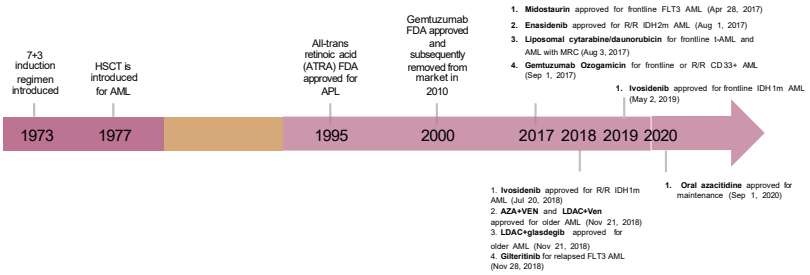
Abbreviations: AML, acute myeloid leukemia; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; FEV1, forced expiratory volume in 1 s.

Ferrara et al, Leukemia 2013.

11

Recent FDA Approvals for AML

Since its introduction in the early 1970s, 7+3 therapy (Cytarabine for 7 days + Anthracycline for 3 days) has been the standard of care for AML



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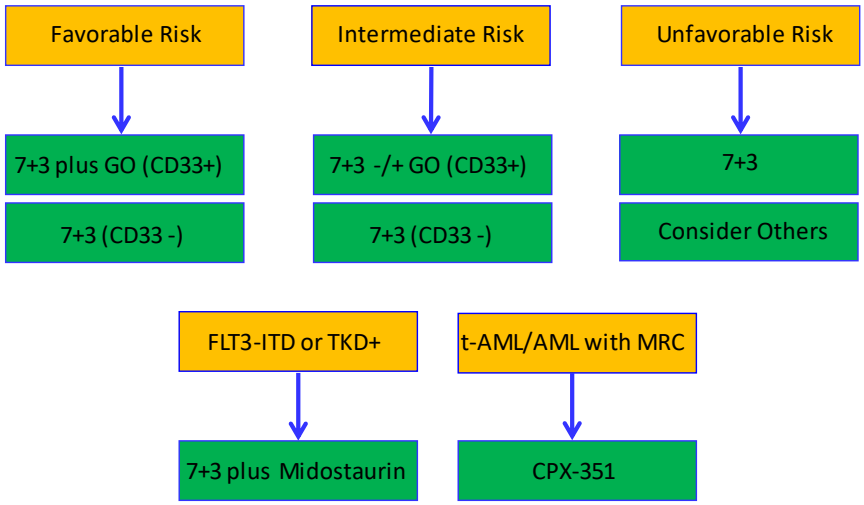
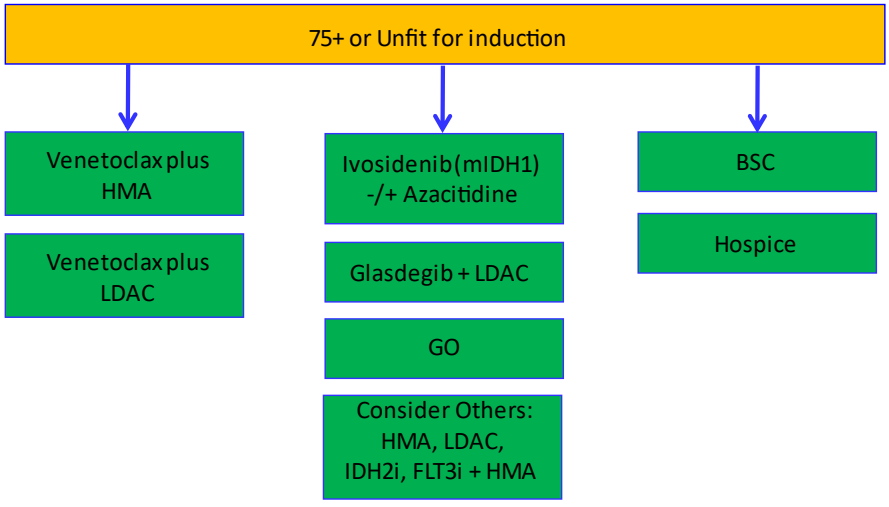
First-Line Treatment of Fit AML in 2022



Based on NCCN guidelines, AML v2.20

13

First-Line Treatment of Older/ UnFit AML in 2022



Based on NCCN guidelines, AML v2.20

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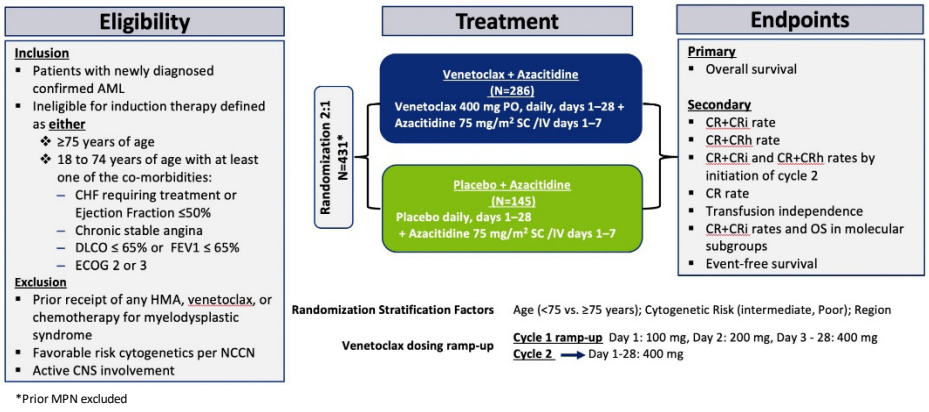
Case 2

A 76-year-old man is diagnosed with AML after presenting with fatigue and dyspnea. CBC showed WBC 15, Hgb 6, Plt 75, and 60% blasts. BMBx showed 90% blasts, normal cytogenetics and mutations in NPM1 and IDH2 R140Q.

How should we treat this patient?

15

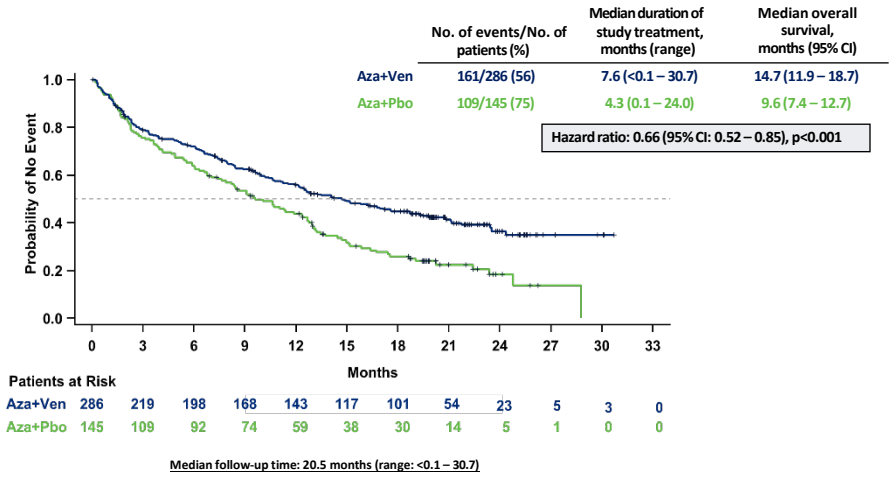
VIALE-A: Azacitidine plus Venetoclax vs Aza-PBO



DiNardo et al, NEJM 2020.

16

Aza-Ven vs Aza-PBO: OS

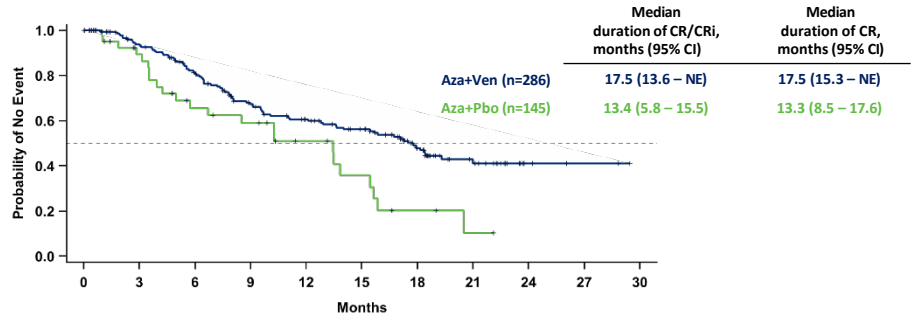


Median follow-up time: 20.5 months (range: <0.1 – 30.7)

DiNardo et al, NEJM 2020.

17

Aza-Ven vs Aza-PBO: DoR after CR/CRi

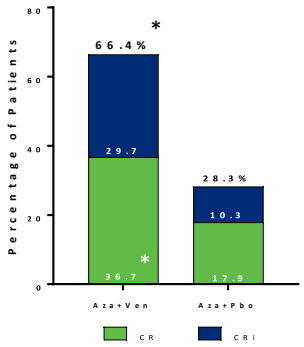


Aza: Azacitidine; CR: Complete remission; CRi: CR with incomplete count recovery ; NE: Not estimable; Pbo: Placebo; Ven: Venetoclax

DiNardo et al, NEJM 2020.

18

Aza-Ven vs Aza-PBO: Responses



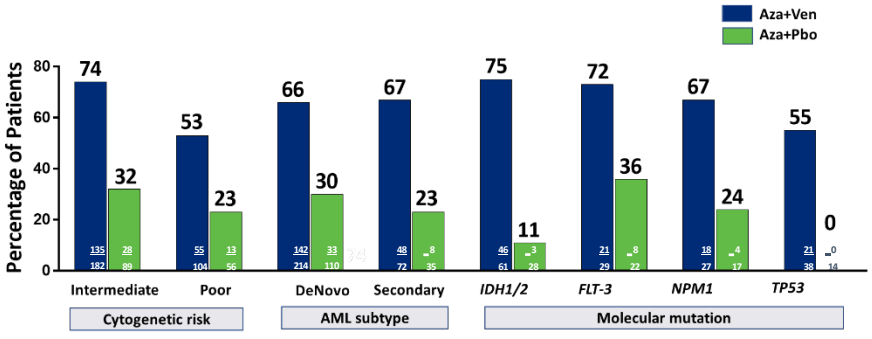
	No. of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR+CRi by initiation of Cycle 2, n (%)
Aza+Ven (n=286)	7.0 (1.0 – 30.0)	1.3 (0.6 – 9.9)	124 (43.4)
Aza+Pbo (n=145)	4.5 (1.0 –26.0)	2.8 (0.8 – 13.2)	11 (7.6)

*CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with p<0.001 by CMH test

DiNardo et al, NEJM 2020.

19

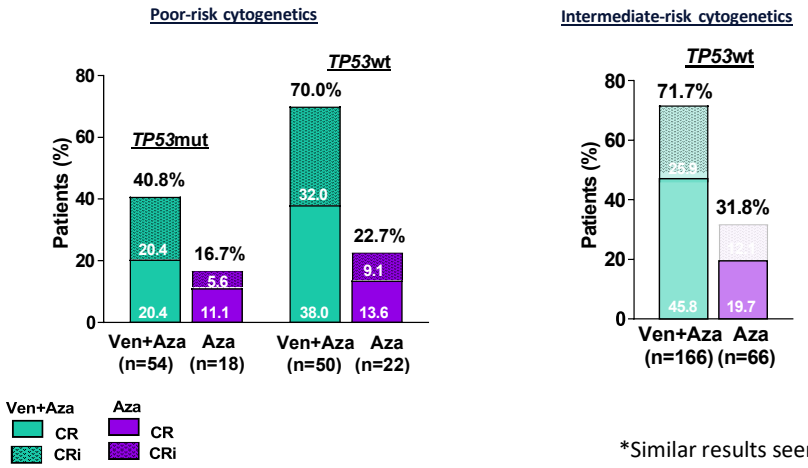
Aza-Ven vs Aza-PBO: Responses by Subgroup



DiNardo et al, NEJM 2020.

20

Aza-Ven vs Aza-PBO: Responses in Poor-risk Cytogenetics -/+ TP53 Mutation



*Similar results seen for DoR and OS

Aza, azacitidine; CI, confidence interval; CR, complete remission; CRi, CR+ incomplete hematological remission; mut, mutation; Ven, venetoclax; wt, wild-type

Pollyea et al, ASH 2021 Abstract #224.

21

Case 2, Continued

Our 76yo M with newly diagnosed AML with NPM1 and IDH2 R140Q mutations is admitted and started on azacitidine and venetoclax with TLS prophylaxis and dose ramp up. He completes cycle 1. End of cycle 1 bone marrow biopsy shows MLFS.

What should we do now? Start cycle 2 now? Delay the start of cycle 2 for count recovery? Use G-CSF?

How should we dose cycle 2? Future cycles?

Should we be using antifungal prophylaxis?

22

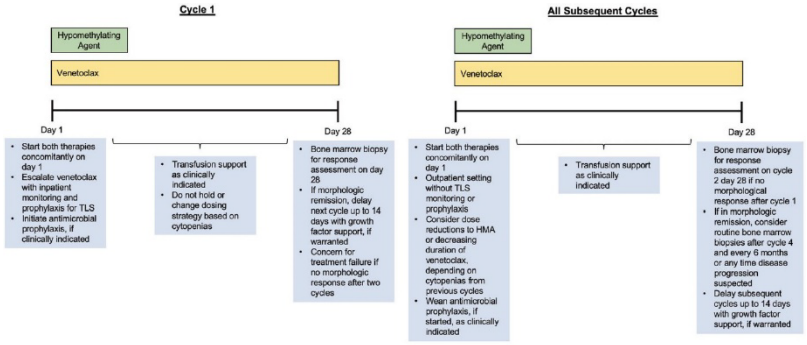
Leukemia
https://doi.org/10.1038/s41375-019-0612-8

PERSPECTIVE

Acute myeloid leukemia

How we use venetoclax with hypomethylating agents for the treatment of newly diagnosed patients with acute myeloid leukemia

Brian A. Jonas[1] · Daniel A. Pollyea[2]



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Aza-Ven vs Aza-PBO: TEAE

	Aza+Ven		Aza+Pbo	
Adverse events^, n (%)	All grade* n=283	Grade 3/4** n=276	All grade* n =144	Grade 3/4** n =136
All AEs	**283 (100)**	**279 (99)**	**144 (100)**	**139 (97)**
Hematologic AEs	**236 (83)**	**233 (82)**	**100 (69)**	**98 (68)**
Thrombocytopenia	130 (46)	126 (45)	58 (40)	55 (38)
Neutropenia	119 (42)	119 (42)	42 (29)	41 (29)
Febrile neutropenia	118 (42)	118 (42)	27 (19)	27 (19)
Anemia	78 (28)	74 (26)	30 (21)	29 (20)
Leukopenia	58 (21)	58 (21)	20 (14)	17 (12)
Non-hematologic AEs	**47 (17)**	**46 (17)**	**44 (31)**	**44 (31)**
Nausea	124 (44)	5 (2)	50 (35)	1 (1)
Constipation	121 (43)	2 (1)	56 (39)	2 (1)
Diarrhea	117 (41)	13 (5)	48 (33)	4 (3)
Vomiting	84 (30)	6 (2)	33 (23)	1 (1)
Hypokalemia	81 (29)	30 (11)	41 (29)	15 (10)
Peripheral edema	69 (24)	1 (0)	26 (18)	0
Pyrexia	66 (23)	5 (2)	32 (22)	2 (1)
Fatigue	59 (21)	8 (3)	24 (17)	2 (1)
Decreased appetite	72 (25)	0	25 (17)	0

AE, adverse event, ^Includes all patients who received at least one dose of either of the treatment *Adverse events shown were reported in ≥20% of patients in either treatment arms; ** Grade 3 or 4 AEs ≥10% occurrence.

DiNardo, Jonas, Pullarkat et al, EHA 2020 Abstract# LB2601.
DiNardo, Jonas, Pullarkat et al, NEJM 2020.

24

Aza-Ven vs Aza-PBO: TEAE

Serious AEs in ≥5% of patients, n (%)	Aza+Ven N = 283	Aza+Pbo N = 144
All serious AEs	**235 (83)**	**105 (73)**
Febrile neutropenia	84 (30)	15 (10)
Anemia	14 (5)	6 (4)
Neutropenia	13 (5)	3 (2)
Atrial fibrillation	13 (5)	2 (1)
Pneumonia	47 (17)	32 (22)
Sepsis	16 (6)	12 (8)
Any AE leading to:		
Dose discontinuation	69 (24)	29 (20)
Dose interruption*	204 (72)	82 (57)
Dose reduction†	7 (3)	6 (4)
Deaths, n (%)		
≤30 days after first dose of study drug	21 (7)	9 (6)
≤60 days after first dose of study drug	43 (15)	24 (17)
Other, n (%)		
Tumor lysis syndrome††	3 (1)	0

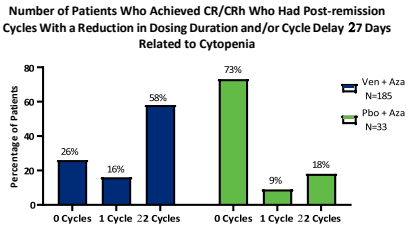
*Dose interruptions commonly due to neutropenia (19%/10%), febrile neutropenia (20%/4%), and thrombocytopenia (10%/4%); interruptions include delays between cycles and reduced duration from 28 to 21 days per cycle for count recovery after marrow leukemia clearance; †Dose reduction for AEs or other medications; †† 3 cases of TLS during ramp up.

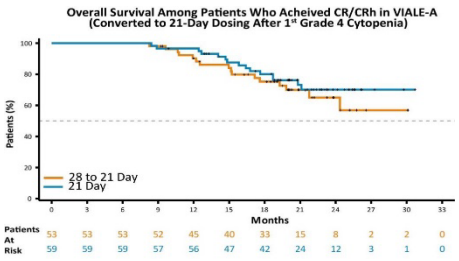
DiNardo, Jonas, Pullarkat et al, EHA 2020 Abstract# LB2601.
DiNardo, Jonas, Pullarkat et al, NEJM 2020.

25

Cytopenia Management on the VIALE-A Trial

Patients with best response of CR or CRh with a post-remission Grade 4 cytopenia lasting ≥7 days, n (%)	Ven + Aza (n=185)	Pbo + Aza (n=33)
0 events	24 (13)	18 (55)
1 event	36 (19)	8 (24)
≥2 events	125 (68)	7 (21)





Pratt et al, ASH 2020, Abstract 1944.

26

Timing of Response to HMA-Ven

Figure 1A. Time to First Response of CR/CRi in M14-358

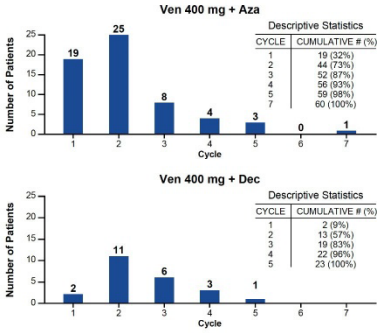
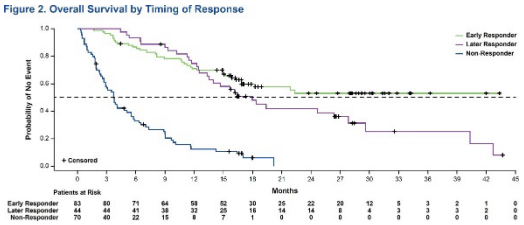


Figure 2. Overall Survival by Timing of Response



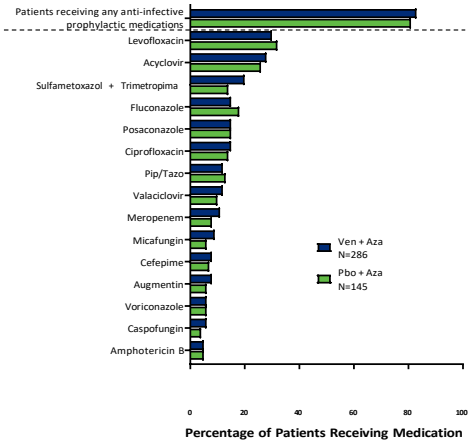
Jonas et al, ASCO 2020.

27

Use of CYP3A4i on the VIALE-A Trial

- Anti-infective prophylaxis was required for patients with absolute neutrophil count <500/µL
- Common anti-infective CYP3Ai include moderate inhibitors such as fluconazole, isavuconazole, ciprofloxacin, and strong inhibitors such as itraconazole, posaconazole, and voriconazole

Prophylactic Anti-infective Use in VIALE-A*

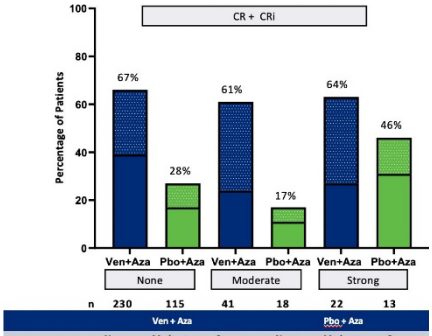


*Medications listed were used in ≥ 5% of patients receiving anti-infective prophylaxis (list not exclusive to CYP3A inhibitors).

Jonas et al, ASH 2020, Abstract 2846.

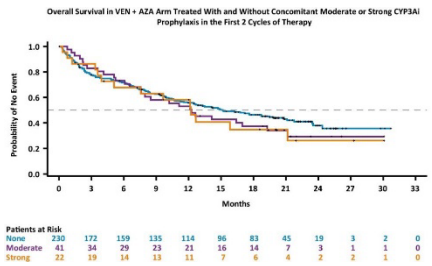
28

Use of CYP3A4i on the VIALE-A Trial



	Ven + Aza			Pbo + Aza		
Outcome†	None (n=153)	Moderate (n=25)	Strong (n=14)	None (n=32)	Moderate (n=3)	Strong (n=6)
Median time to CR+CRi, mo (range)	1.2 (0.6–9.9)	1.4 (1.0–5.5)	1.4 (0.9–5.4)	2.8 (0.8–13.2)	2.8 (1.1–6.3)	2.8 (1.0–5.3)

Overall Survival in Ven + Aza



	Survival Estimate (%) (95% CI)			Median (Months)
Events	Month 6	Month 12	Month 24	(95% CI)
126	71.7 (65.3, 77.1)	55.8 (49.0, 62.1)	37.9 (30.2, 45.6)	15.2 (11.2, 20.8)
27	73.2 (56.8, 84.1)	53.0 (36.6, 66.9)	29.4 (15.1, 45.3)	12.3 (7.6, 19.3)
14	67.9 (44.1, 83.2)	58.2 (34.9, 75.7)	26.2 (8.1, 48.9)	12.2 (3.9, 21.1)

- There was not a major impact on response rate, time to response, OS, frequency of infections or treatment discontinuation with moderate or strong CYP3Ai compared to no CYP3Ai

Jonas et al, ASH 2020, Abstract 2846.

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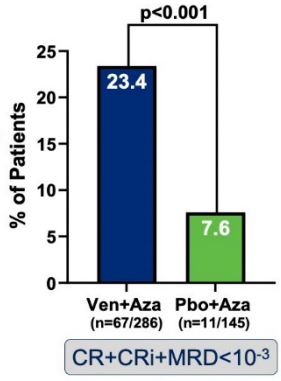
Case 2, Continued

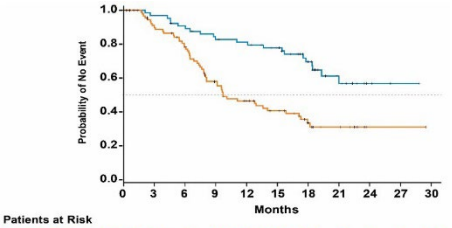
Our 76yo M with newly diagnosed AML with NPM1 and IDH2 R140Q mutations is is treated with venetoclax and decitabine and achieves a MRD positive CR after cycle 1. He continues on treatment and his end of cycle 4 bone marrow biopsy shows an MRD negative CR.

He asks about the impact of her MRD status as well as if there is a role for transplant in her care.

30

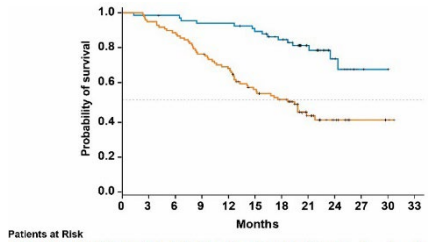
VIALE-A Trial: MRD Response, DoR and OS





Patients at Risk

CR+CRi+MRD<10-3	67	63	58	52	50	44	30	14	3	1	0
CR+CRi+MRD≥10-3	97	80	67	46	34	27	14	9	1	1	0



Patients at Risk

CR+CRi+MRD<10-3	67	66	65	62	62	58	52	30	13	2	1	0
CR+CRi+MRD≥10-3	97	92	86	74	64	49	42	21	10	3	2	0

Duration of remission	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median DoR, months (95% CI)
CR+CRi+MRD<10-3	22	81.2 (69.3, 88.9)	69.6 (55.9, 79.8)	NR (19.3 – NR)
CR+CRi+MRD≥10-3	54	46.6 (35.6, 56.8)	33.5 (22.9, 44.5)	9.7 (8.0 – 15.8)

Overall survival	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median OS, months (95% CI)
CR+CRi+MRD<10-3	15	94.0 (84.7, 97.7)	84.6 (73.3, 91.4)	NR (24.4 – NR)
CR+CRi+MRD≥10-3	52	67.9 (57.6, 76.2)	50.1 (39.6, 59.8)	18.7 (12.9 – NR)

Pratz et al, ASCO 2021, Abstract 7018.
Pratz et al, EHA 2021, Abstract S137.

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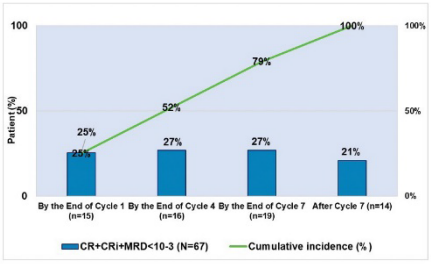
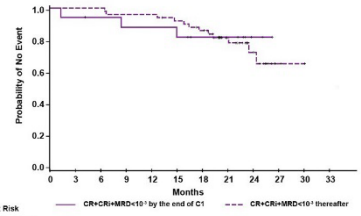
VIALE-A Trial: Timing of MRD Response and OS

MRD by treatment cycles



Note: End of cycle (C) 1: MRD<10-3 from C1 Day (D) 1 to end day of C1+7 days
End of C4: MRD<10-3 from end day of C1+8D to min (End day of C4, last dose +7 days)
End of C7: MRD<10-3 from end day of C4+1D to min (end day of C7, last dose +7 days
After C 7: End day of C7+1D and onward up to cutoff date: Jan 04, 2020.

OS by treatment cycles



Patients at Risk

CR+CRi+MRD<10-3 by the end of C1	17	16	15	14	14	13	11	6	2	0	0	0
CR+CRi+MRD<10-3 thereafter	50	50	50	48	48	45	41	24	11	2	1	0

Overall survival	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median OS, months (95% CI)
CR+CRi+MRD<10-3 by end of cycle 1	3	87.8 (59.5, 96.8)	81.6 (53.0, 93.7)	NR (NR – NR)
CR+CRi+MRD<10-3 thereafter	12	96.0 (84.9, 99.0)	85.8 (72.5, 93.0)	NR (24.4 – NR)

NR: Not reached; OS: Overall survival

Pratz et al, ASCO 2021, Abstract 7018.
Pratz et al, EHA 2021, Abstract S137.

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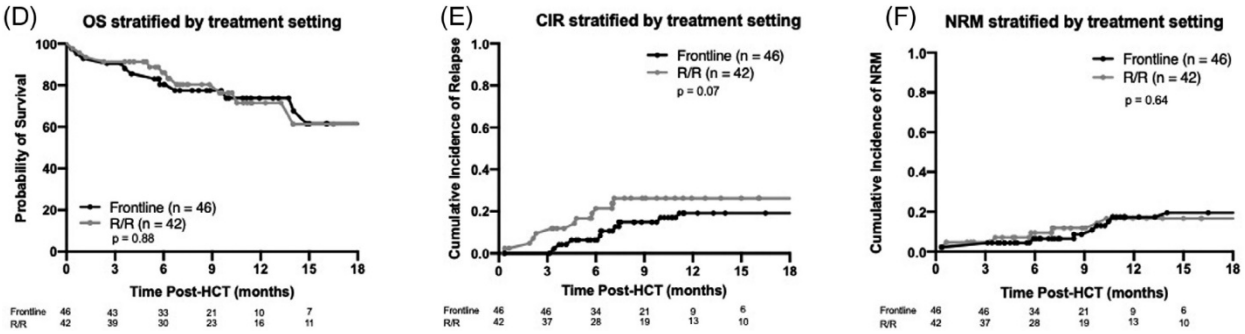
Allo-HCT is Feasible after HMA plus Venetoclax in Frontline and r/r AML



Pooled retrospective data from UC Davis, UCSF, UCLA, UCSD, and Stanford

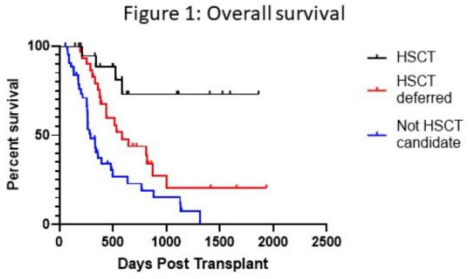
Kennedy et al, AJH 2022.

33

Outcomes of AML Patients Treated with Aza/Ven Are Improved After HSCT Compared to Maintenance Aza/Ven

Table 1: Disease status characteristics

ELN risk	SCT patients	SCT deferred patients
High	15	16
Intermediate	3	4
Favorable	3	10
Disease status at SCT consult		
CR/CRi without MRD	2	11
CR/CRi with MRD	11	11
MLFS/Aplasia/persistent disease	6	6
Disease status at time of SCT		
CR/CRi without MRD	7	
CR/CRi with MRD	10	
MLFS/Aplasia	4	
Best response in non-SCT patients		
CR/CRi without MRD		21
CR/CRi with MRD		8
MLFS/Aplasia		1



Pollyea et al, ASH 2020, Abstract 78.

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Case 3

- An 80-year-old woman is diagnosed with AML after presenting with fevers and progressive shortness of breath. CBC showed WBC 1, Hgb 7.4, Plt 60, and 20% blasts. BMBx showed 40% blasts and normal cytogenetics and mutations in IDH1 R132C and ASXL1. CXR is clear.

What should we offer as first line treatment for this patient?

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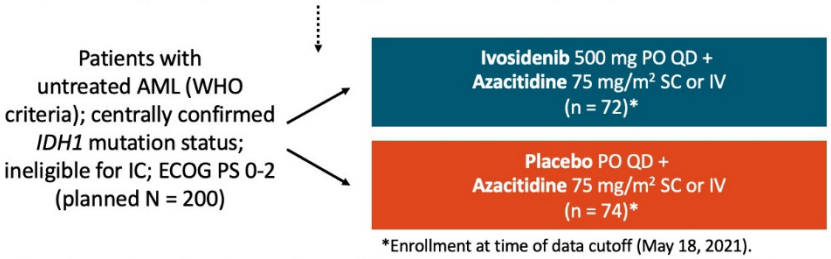
AGILE: Ivosidenib+Azacitidine vs PBO+Aza for Newly Diagnosed AML with mIDH1

- Multicenter, double-blind, randomized phase III trial

Stratified by region (US/Canada vs Western Europe, Israel, and Australia vs Japan vs rest of world) and disease history (de novo vs secondary AML)



*Enrollment at time of data cutoff (May 18, 2021).

- Enrollment halted based on efficacy as of May 12, 2021 (N = 148)
- **Primary endpoint:** EFS with ~173 events (52 mo)
- **Secondary endpoints:** CRR, OS, CR + CRh rate, ORR

Montesinos et al, ASH 2021, Abstract #697.
Montesinos et al, NEJM 2022.

Slide credit: clinicaloptions.com

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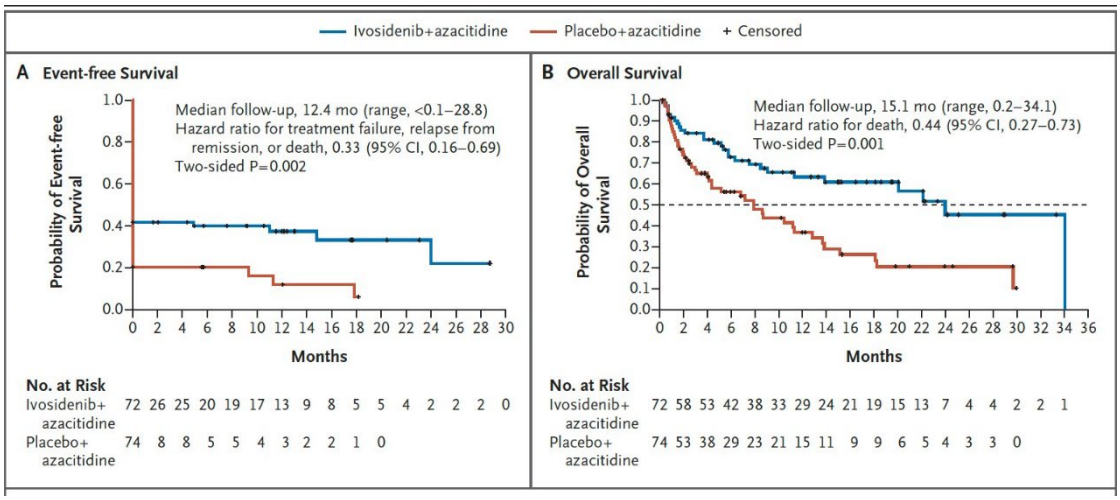
AGILE: OS and EFS



Montesinos et al, ASH 2021, Abstract #697.
Montesinos et al, NEJM 2022.

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AGILE: Responses

Response	IVO + AZA (n = 72)	PBO + AZA (n = 74)
CR rate, n (%) [95% CI]	34 (47.2) [35.3-59.3]	11 (14.9) [7.7-25.0]
▪ OR (95% CI); *P* value	4.8 (2.2-10.5); <.0001	
▪ Median duration of CR, mo (95% CI)	NE (13.0-NE)	11.2 (3.2-NE)
▪ Median time to CR, mo (range)	4.3 (1.7-9.2)	3.8 (1.9-8.5)
CR + CRh, n (%) [95% CI]	38 (52.8) [40.7-64.7]	13 (7.6) [9.7-28.2]
▪ OR (95% CI); *P* value	5.0 (2.3-10.8); <.0001	
▪ Median duration of CR + CRh, mo (95% CI)	NE (13.0-NE)	9.2 (5.8-NE)
▪ Median time to CR + CRh, mo (range)	4.0 (1.7-8.6)	3.9 (1.9-7.2)
ORR, n (%) [95% CI]	45 (62.5) [50.3-73.6]	14 (18.9) [10.7-29.7]
▪ OR (95% CI); *P* value	7.2 (3.3-15.4); <.0001	
▪ Median duration of response, mo (95% CI)	22.1 (13.0-NE)	9.2 (6.6-14.1)
▪ Median time to response, mo (range)	2.1 (1.7-7.5)	3.7 (1.9-9.4)
m*IDH1* Clearance in BMMCs by Response, n/N (%)	**IVO + AZA (n = 43)**	**PBO + AZA (n = 34)**
CR + CRh	17/33 (51.5)	3/11 (27.3)
▪ CR	14/29 (48.3)	2/10 (20)
▪ CRh	3/4 (75)	1/1 (100)
Non-CR + CRh responders	2/4 (50)	0/2 (0)
Nonresponders	1/6 (16.7)	0/21 (0)

Montesinos et al, ASH 2021, Abstract #697.
Montesinos et al, NEJM 2022.

Slide credit: clinicaloptions.com

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AGILE: AEs

TEAEs, n (%)	IVO + AZA (n = 71)		PBO + AZA (n = 73)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	70 (98.6)	66 (93.0)	73 (100)	69 (94.5)
Any hematologic TEAE	55 (77.5)	50 (70.4)	48 (65.8)	47 (64.4)
Most common hematologic TEAEs*				
▪ Anemia	22 (31.0)	18 (25.4)	21 (28.8)	19 (26.0)
▪ Febrile neutropenia	20 (28.2)	20 (28.2)	25 (34.2)	25 (34.2)
▪ Neutropenia	20 (28.2)	19 (26.8)	12 (16.4)	12 (16.4)
▪ Thrombocytopenia	20 (28.2)	17 (23.9)	15 (20.5)	15 (20.5)
Most common TEAEs*				
▪ Nausea	30 (42.3)	2 (3.8)	28 (38.4)	3 (4.1)
▪ Vomiting	29 (40.8)	0	19 (36.0)	1 (1.4)
▪ Diarrhea	25 (35.2)	1 (1.4)	26 (35.6)	5 (6.8)
▪ Pyrexia	24 (33.8)	1 (1.4)	29 (39.7)	2 (2.7)
▪ Constipation	19 (26.8)	0	38 (52.1)	1 (1.4)
▪ Pneumonia	17 (23.9)	16 (22.5)	23 (31.5)	21 (28.8)
Bleeding	29 (40.8)	4 (5.6)	21 (28.8)	5 (6.8)
Infections	20 (28.2)	15 (21.1)	36 (49.3)	22 (30.1)

*Occurring in >20% of patients.

- AEs of special interest (IVO + AZA vs PBO + AZA):
  - Grade ≥2 differentiation syndrome: 14.1% vs 8.2%
  - Grade ≥3 QT prolongation: 9.9% vs 4.1%
- Fewer infections with IVO + AZA vs PBO + AZA (28.2% vs 49.3%)
- No treatment-related deaths

Montesinos et al, ASH 2021, Abstract #697.
Montesinos et al, NEJM 2022.

Slide credit: clinicaloptions.com

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Case 4

A 68-year-old man was diagnosed with AML after presenting with fatigue and SOB. BMBx showed 70% CD33 negative myeloblasts and trisomy 8 and BCOR mutation. He is medically fit for induction and transplant.

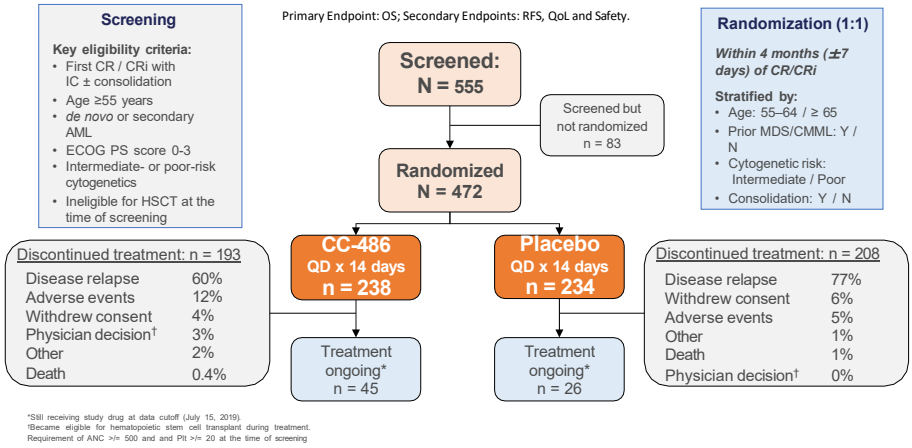
He is induced with 7+3 and achieves an MRD negative CR. He has one cycle of intermediate dose cytarabine for consolidation but tolerates it poorly and it is determined not to pursue additional chemotherapy. He is now unfit for transplant and he currently has no identified donor. He has an end of treatment BMBx that confirms MRD negative CR.

What is the next step: Surveillance or maintenance?

40

QUAZAR AML-001 Maintenance Trial
CC-486 (Oral Azacitidine)

Patient DISPOSITION / SCHEMA



Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

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QUAZAR Trial – Patient Characteristics

Table 1. Baseline Demographic and Disease Characteristics.*

Characteristic	CC-486 (N=238)	Placebo (N=234)	Total (N=472)
Response after induction therapy — no. (%)			
Complete remission	187 (79)	197 (84)	384 (81)
Complete remission with incomplete blood count recovery	51 (21)	37 (16)	88 (19)
Receipt of consolidation therapy — no. (%)			
Yes	186 (78)	192 (82)	378 (80)
No	52 (22)	42 (18)	94 (20)
Median time from induction therapy to randomization (range) — mo	4.0 (1.4–8.8)	4.0 (1.3–15.1)	4.0 (1.3–15.1)
Median time from complete remission to randomization (range) — days‡	84.5 (7–154)	86.0 (7–263)	85.0 (7–263)
Median bone marrow blasts (range) — %§	2.0 (0.0–5.0)	2.0 (0.0–6.5)	2.0 (0.0–6.5)
Positive for measurable residual disease — no. (%)¶	103 (43)	116 (50)	219 (46)
Median platelet count (range) — $\times 10^{-9}$/liter§	154 (22–801)	179 (16–636)	165 (16–801)
Median absolute neutrophil count (range) — $\times 10^{-9}$/liter§	3.0 (0.3–15.9)	2.8 (0.5–9.6)	2.9 (0.3–15.9)

Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

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QUAZAR Trial – Safety

- Median treatment durations:
  - CC-486: 12 cycles (range 1–80)
  - Placebo: 6 cycles (range 1–73)
- CC-486 safety profile was generally consistent with that of injectable AZA[1]
- Gastrointestinal adverse events (AEs) in the CC-486 arm were most common during the first 2 treatment cycles
- Serious AEs were reported for 34% and 25% of patients in the CC-486 and placebo arms, respectively
- No treatment-related deaths

1. Dombret et al. *Blood*. 2015;126(3):291-9.
AE, adverse event; AZA, azacitidine; GI, gastrointestinal.

Preferred term	CC-486 n = 236		Placebo n = 233	
	All Grades	Grade 3–4	All Grades	Grade 3–4
	n (%)			
Patients with ≥1 AE	**231 (98)**	**169 (72)**	**225 (97)**	**147 (63)**
Gastrointestinal				
Nausea	153 (65)	6 (3)	55 (24)	1 (0.4)
Vomiting	141 (60)	7 (3)	23 (10)	0
Diarrhea	119 (50)	12 (5)	50 (22)	3 (1)
Constipation	91 (39)	3 (1)	56 (24)	0
Hematologic				
Neutropenia	105 (45)	97 (41)	61 (26)	55 (24)
Thrombocytopenia	79 (34)	53 (23)	63 (27)	50 (22)
Anemia	48 (20)	33 (14)	42 (18)	30 (13)
Other				
Fatigue	70 (30)	7 (3)	45 (19)	2 (1)
Asthenia	44 (19)	2 (1)	13 (6)	1 (0.4)
Pyrexia	36 (15)	4 (2)	44 (19)	1 (0.4)
Cough	29 (12)	0	39 (17)	0

Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

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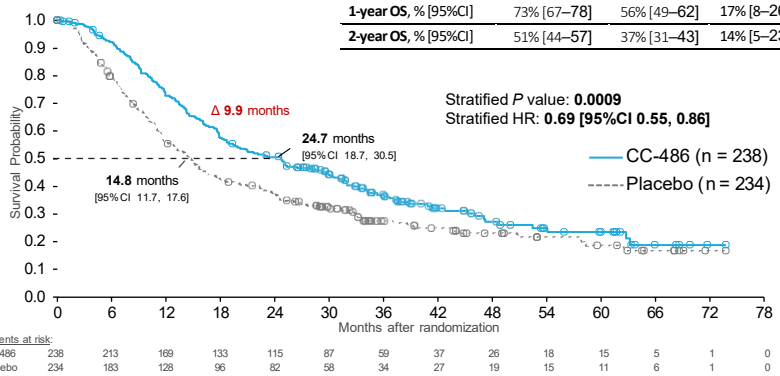
QUAZAR Trial – Primary Endpoint OS

- Median follow-up: 41.2 months

	CC-486	Placebo	Difference
1-year OS, % [95%CI]	73% [67–78]	56% [49–62]	17% [8–26]
2-year OS, % [95%CI]	51% [44–57]	37% [31–43]	14% [5–23]



Patients at risk:

CC-486	238	213	169	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	128	96	82	58	34	27	19	15	11	6	1	0

Data cutoff: July 15, 2019
OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for CC-486 vs. placebo by stratified log-rank test. HRs and 95% CIs were generated using a stratified Cox proportional hazards model.

Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

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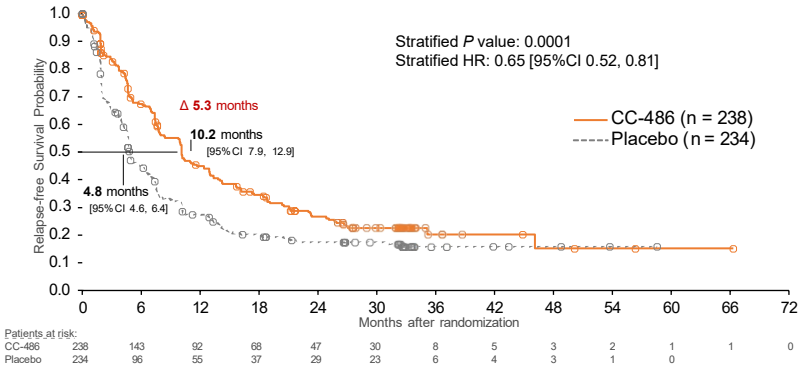
QUAZAR Trial – Secondary Endpoint RFS



- 1-year relapse rate was 53% in the CC-486 arm [95%CI 46, 59] and was 71% in the placebo arm [65, 77]

Data cutoff: July 15, 2019
RFS was defined as the time from randomization to relapse or death by any cause, whichever occurred first. Kaplan-Meier estimated RFS was compared for CC-486 vs. placebo by stratified log-rank test. HRs and 95% CIs were generated using a stratified Cox proportional hazards model.

Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

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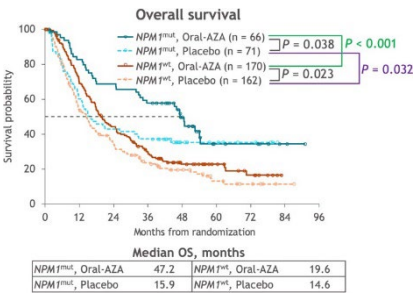
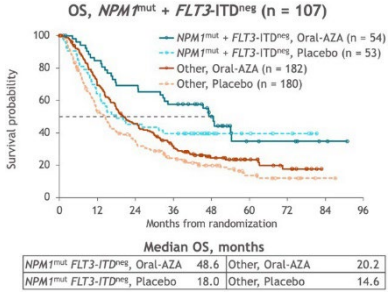
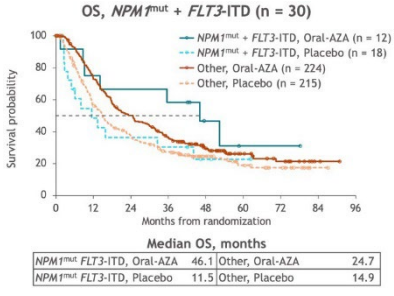
QUAZAR AML-001 Trial: Effects of NPM1 and FLT3-ITD mutations

NPM1 mutational status at AML Dx was prognostic for OS and RFS, and predictive of a survival benefit for pts treated with Oral-AZA (vs. PBO).

Presence of *FLT3*-ITD at Dx had a negative prognostic influence, as suggested by differences in OS results in the PBO arm
Oral-AZA prolonged OS vs. PBO in pts with *NPM1*^{mut} + *FLT3*-ITD^{neg} (48.6 vs. 18.0 mo, respectively), and in pts with both *NPM1*^{mut} + *FLT3*-ITD (46.1 vs. 11.5 mo)







Döhner et al, EHA 2021. Abstr S131.

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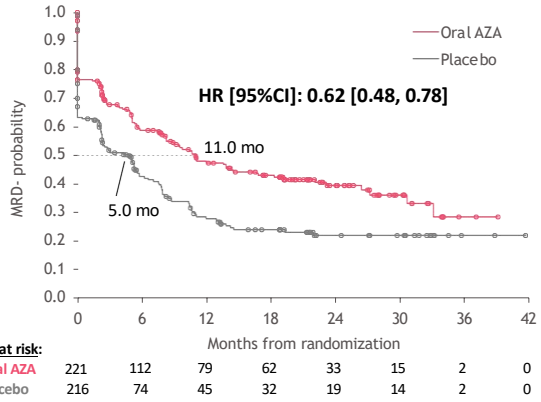
QUAZAR AML-001: MRD Responses

- Oral AZA was associated with a higher rate of MRD response (BL MRD+, became MRD- on-study) vs. PBO: 37% vs. 19%, respectively

MRD Response	Oral AZA	Placebo
MRD+ at screening, n	**103**	**116**
MRD responders, n/N (%)	**38/103 (37%)**	**22/116 (19%)**
Time to MRD response,[a] n/N (%)		
> 3 to ≤ 6 months	7/38 (18%)	6/22 (27%)
> 6 months	9/38 (24%)	1/22 (5%)

- The median duration of MRD negativity overall (BL MRD– and MRD responders) was extended with Oral AZA vs. PBO



No. at risk:								
Oral AZA	221	112	79	62	33	15	2	0
Placebo	216	74	45	32	19	14	2	0

[a]Time from MRD assessment at screening.
95%CI, 95% confidence interval; AZA, azacitidine; BL, baseline; HR, hazard ratio; mo, months; MRD, measurable residual disease; PBO, placebo.

Roboz et al, ASH 2020 Abstract #692

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Case 5

A 55-year-old woman was diagnosed with AML with del(9q) and mutations in CEBPA (biallelic), GATA2 and WT1. She achieved an MFC MRD negative CR with negative molecular studies after induction with 7+3 plus GO. She completed consolidation with HiDAC and transplant was deferred. BMBx after consolidation again confirmed MRD negative CR with negative molecular studies.

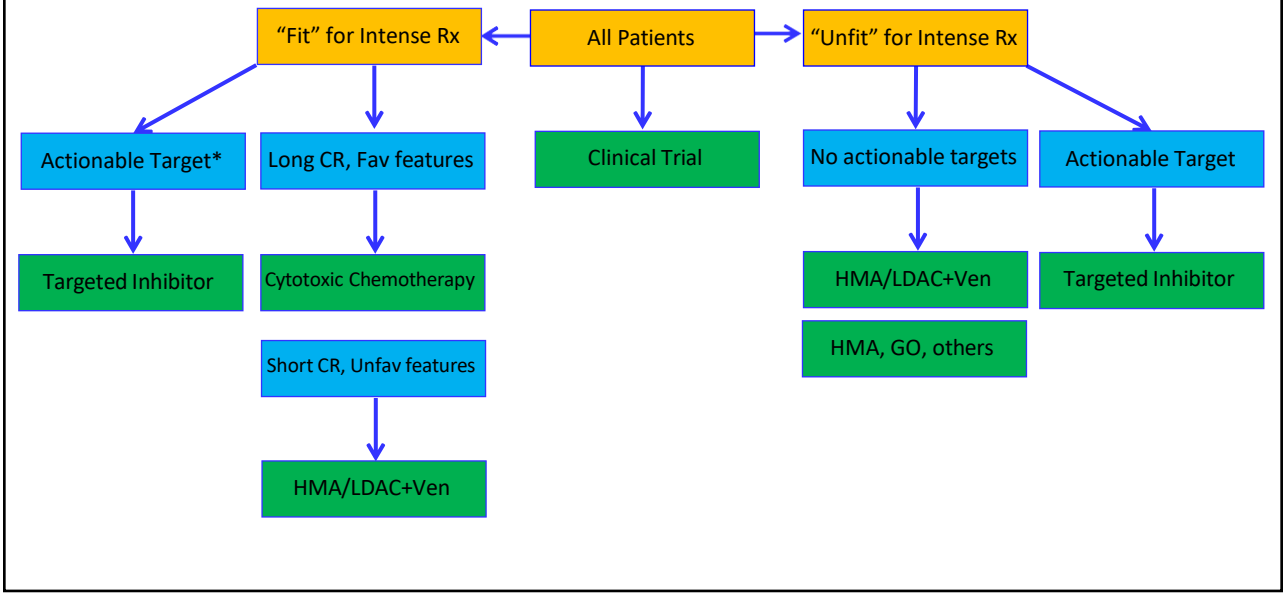
13 months after achieving CR, she presented with mild neutropenia and thrombocytopenia and flow on the PB flow revealed reappearance of abnormal myeloblasts. A BMBx showed relapsed AML with 30% blasts. Cytogenetics and an NGS-based myeloid mutation panel again showed del(9q) and mutations in CEBPA (biallelic), GATA2 and WT1.

What are the typical approaches to treating r/r AML?

What are some of the newer agents and approaches being incorporated?

48

Current Options for the Treatment of r/r AML

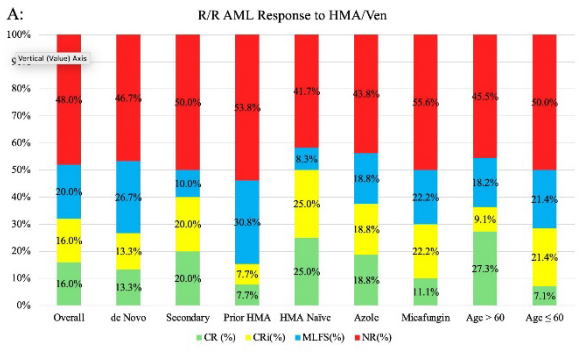


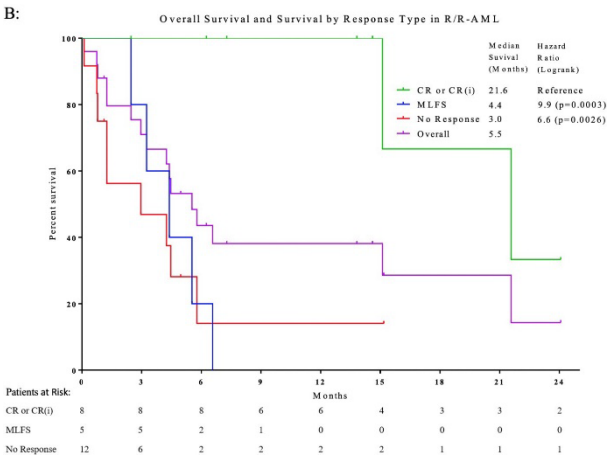
49

HMA plus Venetoclax in r/r AML

- ORR 19% for Ven monotherapy and around 15-20% for Aza monotherapy in r/r AML
- Meta-analysis: ORR 38.7% (31.1% for prior HMA), CR/CRi 32.8%, CR 19% for Ven+HMA/LDAC

UCD Experience:





CR/CRi 50+% with IDH1/2, NPM1 and FLT3-ITD mutations

Tenold et al, Frontiers in Oncology 2021.
Konopleva et al, Cancer Discovery 2016.
Bewersdorf et al, Haematologica 2020.

50

Outcomes for Venetoclax plus FLAG-Ida in r/r AML

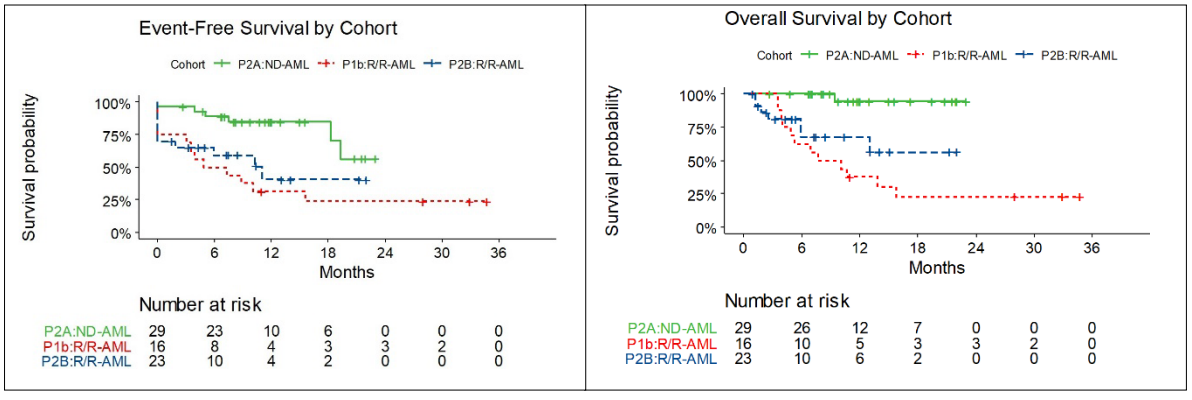
Parameter	All (N=68)	Phase 2A ND-AML (N=29)	R/R-AML (N=39)	Phase Ib R/R-AML (N=16)	Phase 2B R/R-AML (N=23)
Overall Response	56 (82%)	28 (97%)	28 (72%)	12 (75%)	16 (70%)
Composite CR	52 (76%)	26 (90%)	26 (67%)	12 (75%)	14 (61%)
CR	37	20	17	6	11
CRh	10	5	5	2	3
CRi	5	1	4	4	-
MRD negative (FC)	43 (83%)	25 (96%)	18 (69%)	7 (58%)	11 (79%)
MLFS	4	2	2	-	2
No response	12	1	11	4	7

Composite CR (CRc): Complete response + Complete response with partial hematologic recovery (CRh: ANC ≥ 500 and platelet count ≥ 50,000) + Complete response with incomplete hematologic recovery (CRi: ANC ≥ 1000 or platelet count ≥ 100,000); Morphologic Leukemia Free State (MLFS: Bone marrow blasts < 5% no hematologic recovery required); FC: Flow cytometry

DiNardo et al, JCO 2021 and ASH 2020.

51

FLAG-Ida-Ven: EFS and OS



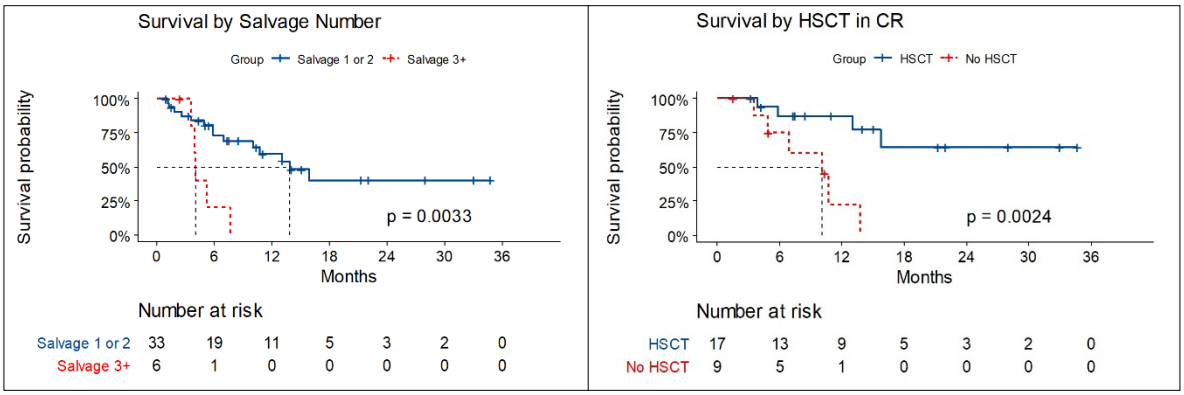
12mo OS 68% P2B

UCD FLAG	Present study	42	52	CR + CRi, 62 (CR, 47.6)	10	12	24.6	1-51	38.1% at 12 months

DiNardo et al, JCO 2021 and ASH 2020.
Tenold et al, Clin Lymph Myelo & Leuk 2021.

52

FLAG-Ida-Ven: OS by Salvage and After Allo-HCT for r/r AML

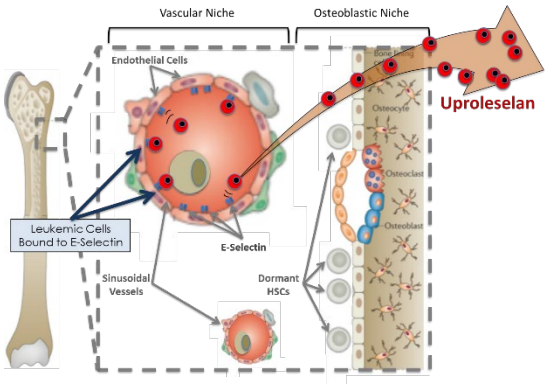


46% bridged to allo-HCT
12mo OS 87%

DiNardo et al, JCO 2021 and ASH 2020.

53

E-Selectin Inhibition with Uproleselan (GMI-1271) in AML



E-selectin –

- An Adhesion molecule constitutively expressed on endothelial cells in the bone marrow microvasculature
- Binds to the E-selectin ligands (Sialyl $Le^{a/x}$) on AML cells
- Promotes environment-mediated drug resistance (EMDR) of leukemic cell

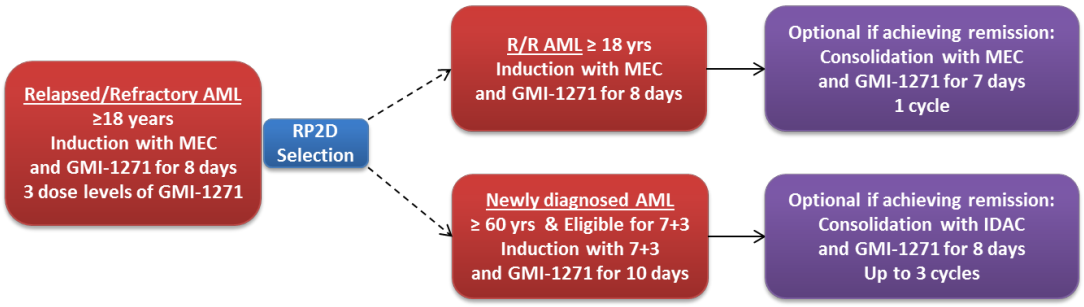
Uproleselan, an E-selectin antagonist –

- Inhibits activation of cancer survival pathways (e.g. NF-KB), disrupting EMDR within bone marrow
- Prolongs survival over chemotherapy alone in animal models
- Protects normal HSCs by enhancing quiescence and ability for self-renewal
- Reduces chemotherapy-associated mucositis

Barbier, et al, Nature Communications 2020.

54

Phase 1/2 Uproleselan Study Schema



DeAngelo et al, Blood 2022.

55

Phase 1/2 Uproleselan Study: Responses

Outcomes, n (%)	Rel/Ref RP2D N=54	Newly Diagnosed N=25
CR/CRi	22 (41)	18 (72)
CR	19 (35)	13 (52)
ORR (CR/CRi/MLFS/PR)	27 (50)	20 (80)
Mortality, All-Cause		
30 days	1 (2)	2 (8)
60 days	5 (9)	2 (12)
Outcomes by Subgroup (CR/CRi Rate and %)		
Primary Refractory	5/17 (29)	
Relapsed (all)	18/37 (49)	RR RP2D Cohort:
Duration of prior remission <6 mos	6/19 (32)	MRD Evaluable n=13
Duration of prior remission > 24mos	6/7 (86)	Negative 9 (69%)

G3 mucositis with Uproleselan+ MECin rel/ref cohort ~2 %

DeAngelo et al, Blood 2022.

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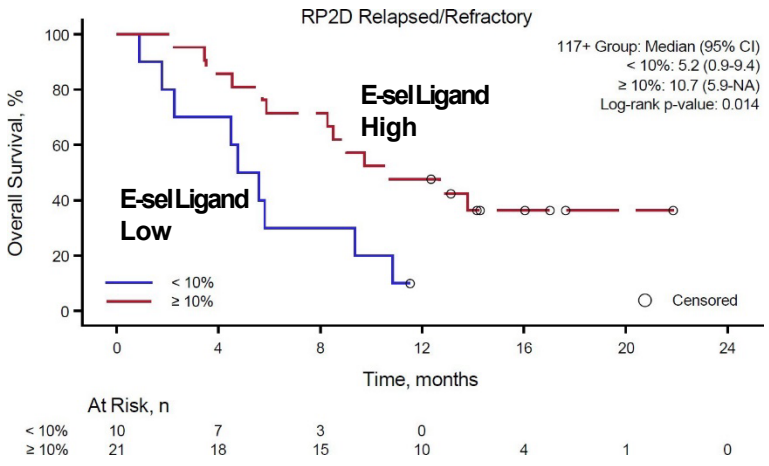
Phase 1/2 Uproleselan Study: OS Based on E-Selectin Ligand Expression

- Median OS 8.8mo
- 12mo OS:
  - All 35%
  - MRD-ve 73%

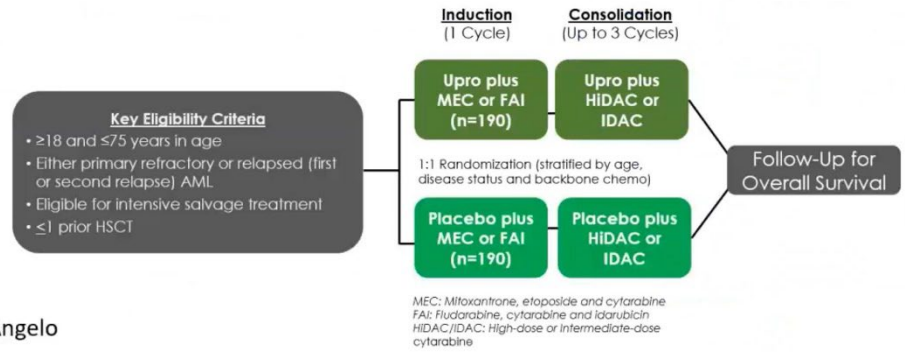


DeAngelo et al, ASH 2018.
DeAngelo et al, Blood 2022.

57

Phase 3 Study of Uproleselan in r/r AML

NCT#03616470



PI: DeAngelo

Primary Endpoint: OS

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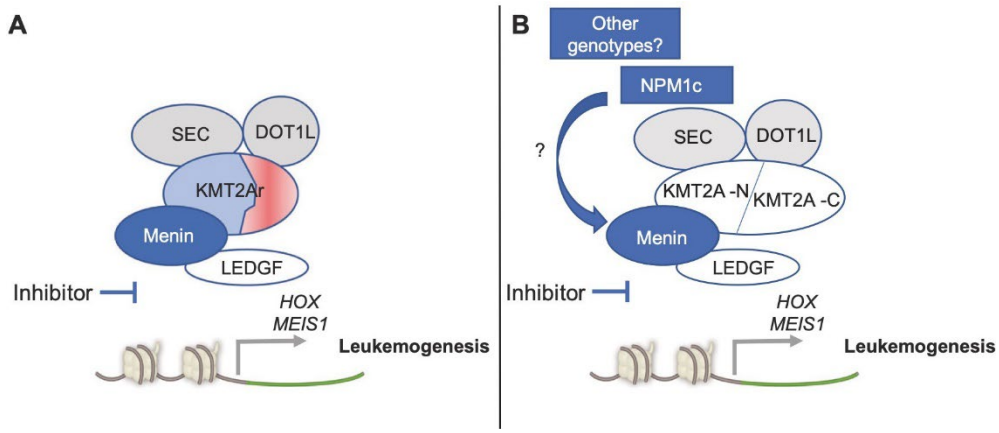
Menin Inhibition for AML with MLL Rearrangements and NPM1c Mutations



Issa et al, Leukemia 2021.

59

Menin Inhibitors in Development

Table 1 Phase 1/2 clinical trials investigating menin inhibitors in refractory acute leukemias.

Clinical trial/status	Drug	Dosing	Min. age	Phase 2 expansion cohorts
AUGMENT-101	SNDX-5613	PO BID	30 d	A. ALL or MPAL with *KMT2Ar*
NCT04065399				B. AML with *KMT2Ar*
Syndax (recruiting)				C. AML with *NPM1c*
KOMET-001	KO-539	PO daily	18 yr	A. AML with *KMT2Ar*
NCT04067336				B. AML with *NPM1c*
Kura (recruiting)				
NCT04752163	DS-1594	PO BID	18 yr	A. *KMTAr* leukemia: single agent
Daiichi Sankyo (recruiting)				B. AML with *NPM1c*: single agent
				C. AML with *KMT2Ar* or *NPM1c*: in combination with azacytidine and venetoclax
				D. ALL with *KMT2Ar*: in combination with mini-HCVD
NCT04811560	JNJ-75276617	PO daily	18 yr	–
Janssen (not yet recruiting)				
Biomea Fusion (IND enabling submission)	BMF-219	PO	–	–

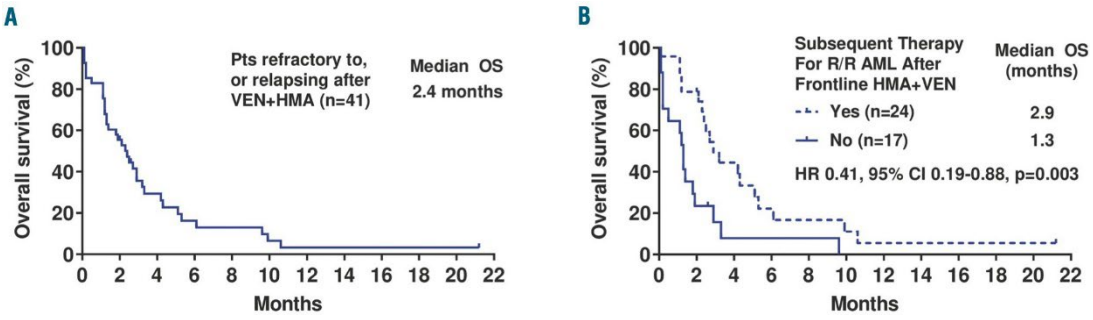
Status of clinical trials as of May 2021. *ALL* acute lymphoblastic leukemia, *MPAL* mixed-phenotype acute leukemia, *KMT2Ar* rearranged *Lysine Methyltransferase 2A*, *AML* acute myeloid leukemia, *NPM1c* mutation of the *Nucleophosmin 1* resulting in a cytoplasmic localization of the protein, *Min. age* minimum age for enrollement, *d* days, *yr* years, *Mini-HCVD* dose reduced combination of cyclophosphamide and dexamethasone, methotrexate, and cytarabine.

Early clinical experience:
Active in r/r AML with MLLr and NPM1c
ORR around ~50% (CR ~20-25%)
Potential AEs
Differentiation syndrome KO-539
QTc prolongation SNDX-5613

Issa et al, Leukemia 2021.
Stein et al, ASH 2021 Abstract # 699.
Wang et al, ASH 2020 Abstract # 115.

60

R/R AML after Ven-HMA has Very Poor Outcomes



- **New major unmet medical need**
- When there is no targetable mutation and no trial option, I have tried chemotherapy, GO, Cladribine-LDAC-/+Ven, continuing Ven-HMA with dose adjustments
- Clinical trials are needed to advance the field: Mcl1i, activated kinase pathway inhibition, TP53-targeting agents, immunotherapy, and other approaches; do we re-use Ven in a new combo?

Maiti et al, Haematologica 2021.

61

Case 6

A 78-year-old man was diagnosed with MDS after presenting with fatigue and macrocytic anemia. He is relatively healthy overall. CBC showed WBC 2, Hgb 7, Plt 75, and ANC 700. BMBx showed 8% blasts, del(5q) and a mutation in DNMT3A. His IPSS-R score is 5.5pts or high risk. He is interested in treatment of his MDS and his hematologist recommends standard azacitidine 75mg/m2 SQ for 7 days every 28 days.

He is interested in seeing if there is an oral option to treat his high risk MDS since he lives relatively far from the nearest infusion center.

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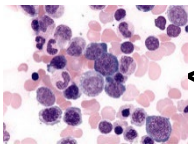
Treatment Approaches in MDS



Diagnosis of MDS

	Treatment Goal	Treatment Options
Higher Risk: IPSS-R Int*, HR, VHR	Alter disease natural history	• Hypomethylating agents (HMA) -/+ Ven • High-intensity chemotherapy (IC) • Allogeneic HCT • Clinical Trial
Lower Risk: IPSS-R VLR, LR, Int	Hematologic improvement	• Growth factors • Luspatercept • Lenalidomide • Immune suppressive therapy (IST) • HMA • Watch and Wait • Clinical Trial

* IPSS-R score > 3.5 points

Based on NCCN Guidelines, MDS, v 3.2022.

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Oral Decitabine + Cedazuridine (DEC-C)

- Current HMA treatment poses significant patient burden due to 5–7 days per month of parenteral administration in a clinic setting
- Oral bioavailability of HMAs decitabine and azacitidine is limited due to rapid degradation by CDA in the gut and liver

Decitabine | **CDA inhibitor** | **Inactive metabolite**

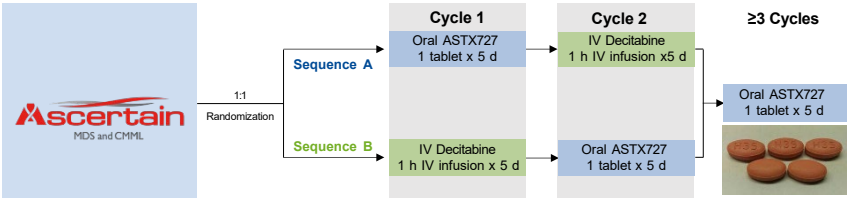
- Cedazuridine is a novel, potent, and safe CDA inhibitor
  - Large safety margin, with no adverse events at up to 200 mg/kg in monkeys (~2400 mg/m² human equivalent)

CDA, cytidine deaminase.

Savona et al. Lancet Hematogy 2019.

64

ASTX727-02 trial of DEC-C in MDS/CMML: Randomized Cross-Over Trial



Major entry criteria
- Candidates for IV decitabine
- ECOG PS 0–1
- Life expectancy of ≥3 months
- Adequate Organ Function
- One prior cycle of HMA is allowed

Primary endpoint
- Total 5-d decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

Secondary endpoints
- Efficacy: Response rate; Transfusion independence; duration of response; Leukemia-free and overall survival
- Safety of ASTX727
- Max LINE-1 demethylation

Garcia-Manero et al. Abstract 846 ASH 2019

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ASTX727-02 Primary Endpoint: 5-day Decitabine AUC Equivalence

Decitabine 5-day $AUC_{0\text{-}24}$ (h·ng/mL)		IV DEC N	IV DEC Geo. LSM	Oral ASTX727 N	Oral ASTX727 Geo. LSM	Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
Primary Analysis	Paired[1]	123	864.9	123	855.7	98.9 (92.7, 105.6)	31.7

[1] Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All Sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

Garcia-Manero et al. Abstract 846 ASH 2019

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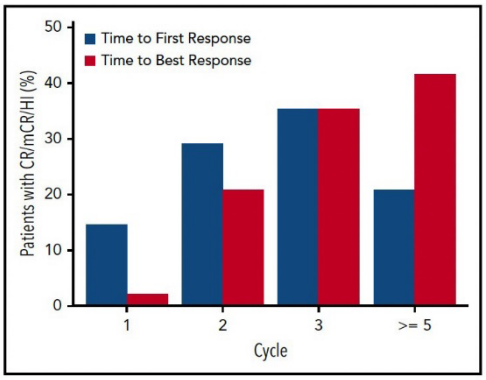
ASTX727-01-B: DEC-C Responses in MDS/CMML

Type of response	Phase 2 overall (N = 80)	
	n (%)	95% CI
CR	17 (21)	13-32
PR	0	
mCR mCR with HI	18 (22) 6 (7)	14-33 3-16
HI HI-E HI-N HI-P	13 (16) 8 (10) 2 (2) 11 (14)	9-26 4-19 0-9 7-23
Overall response* (CR + PR + mCR + HI)	48 (60)	48-71
No response	32 (40)	29-52



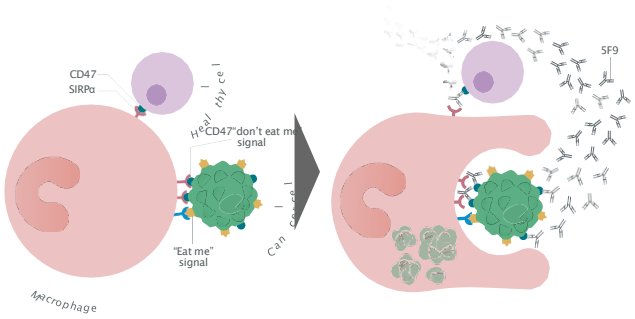
- Comparable safety was seen between IV decitabine and PO DEC-C

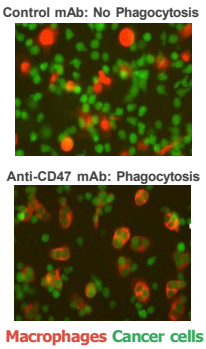
Garcia-Manero et al. Blood 2020.

67

Magrolimab for MDS and AML: MOA

- Magrolimab (Formerly 5F9) is a First-in-class Macrophage Immune Checkpoint Inhibitor Targeting CD47





- Magrolimab is an IgG4 anti-CD47 monoclonal antibody being investigated in multiple cancers
- Magrolimab was well tolerated in a UK Phase 1 trial in r/r AML with no MTD reached (Vyas et al., EHA abs 2018)

Sallman et al, ASH 2019. Abstr 569.

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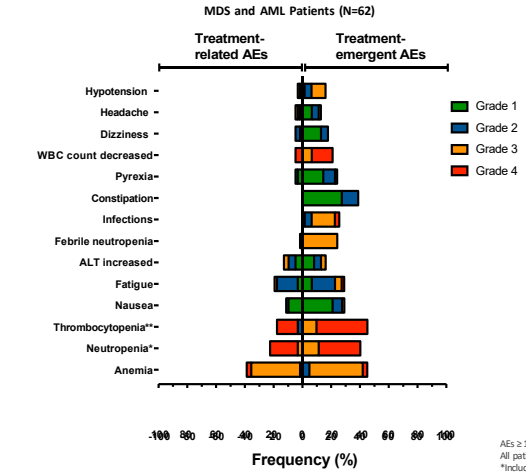
Magrolimab for MDS and AML: Safety



- No MTD was reached; magrolimab+AZA profile consistent with AZA monotherapy
- No significant cytopenias, infections, or autoimmune AEs were observed (most patie* nts cytopenic at baseline)
- No deaths were observed in the first 60 days on therapy
- Treatment discontinuation due to AE occurred in only 1 of 62 (1.6%) of all patients treated with magrolimab + AZA

AEs ≥ 15% or AEs of interest are shown
All patients with at least one magrolimab dose are shown
*Includes neutropenia and neutrophil count decreased
**Includes thrombocytopenia and platelet count decreased

Sallman et al, ASH 2019. Abstr 569.

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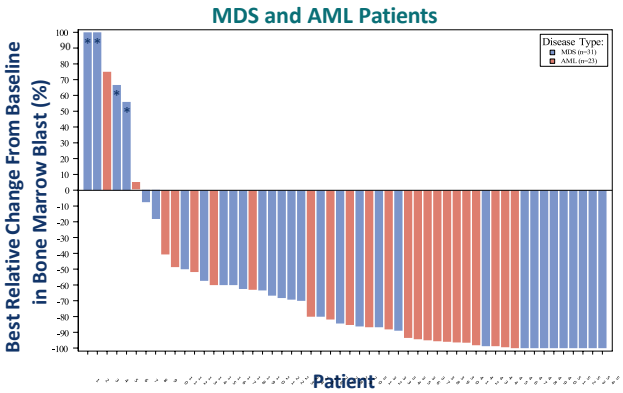
Magrolimab for MDS and AML: Activity

Best Overall Response	1L MDS N=33	1L AML N=25
ORR	30 (91%)	16 (64%)
CR	14 (42%)	10 (40%)
CRi	NA	4 (16%)
PR	1 (3%)	1 (4%)
MLFS/marrow CR	8 (24%) 4 with marrow CR + HI	1 (4%)
Hematologic improvement (HI)	7 (21%)	NA
SD	3 (9%)	8 (32%)
PD	0	1 (4%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML patients (1 AE, 2 early withdrawal).



Four patients not shown due to missing values; <5% blasts imputed as 2.5%. *Baseline bone marrow blasts ≤5%.

- Magrolimab + AZA induces a 91% ORR (42% CR) in MDS and 64% ORR (56% CR/CRi) in AML
- Responses deepened over time with a 56% 6-month CR rate in MDS patients (assessed in all patients 6 months after initial treatment)
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 6-17%[1,2])

1. Azacitidine USPI. 2. Fenaux P, et al. *Lancet Oncol.* 2009 ;10(3):223-232.

Sallman D et al., 2020 ASCO

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New in 2022: IPSS-M

61 Molecular International Prognosis Scoring System for Myelodysplastic Syndromes

Program: Oral and Poster Abstracts
Type: Oral
Session: 637. Myelodysplastic Syndromes – Clinical and Epidemiological: Low Risk Myelodysplastic Syndrome Prognosis and Treatment
Hematology Disease Topics & Pathways:
Adults, Genomics, Translational Research, Clinically Relevant, Diseases, Genomic Profiling, Biological Processes, Myeloid Malignancies, Technology and Procedures, Study Population, Molecular Testing, Clinical Practice (e.g. Guidelines, Health Outcomes and Services, and Survivorship, Value; etc.)

Saturday, December 11, 2021: 9:30 AM

Elsa Bernard, PhD[1], *Heinz Tuechler*[2*], *Peter L. Greenberg, MD*[3], *Robert P. Hasserjian, MD*[4], *Juan Arango Ossa*[5*], *Yasuhito Nannya, MD, PhD*[6], *Sean M Devlin, PhD*[7*], *Maria Creignou, MD*[8*], *Philippe Pinel*[9*], *Lily Monnier*[9*], *Juan S Medina-Martinez*[10*], *Yesenia Werner*[11*], *Martin Jädersten, MD, PhD*[12*], *Ulrich Germing, MD*[13*], *Guillermo Sanz, MD, PhD*[14], *Arjan A. Van de Loosdrecht, MD, PhD*[15], *Olivier Kosmider, PharmD, PhD*[16*], *Matilde Y Follo, PhD*[17*], *Felicitas R Thol, MD*[18], *Lurdes Zamora, PhD*[19*], *Ronald Feitosa Pinheiro, MD, PhD*[20*], *Andrea Pellagatti, PhD*[21*], *Harold Elias, MD*[10*], *Detlef Haase, MD*[22*], *Christina Ganster*[22], *Lionel Ades, MD, PhD*[23], *Magnus Tobiasson, MD*[24*], *Matteo G. Della Porta, MD*[25*], *Akifumi Takaori-Kondo, MD, PhD*[26], *Takayuki Ishikawa, MD, PhD*[27], *Shigeru Chiba, MD, PhD*[28*], *Senji Kasahara, MD, PhD*[29], *Yasushi Miyazaki, MD, PhD*[30], *Pierre Fenaux, MD, PhD*[31], *Monika Belickova*[32*], *Michael R. Savona, MD*[33], *Virginia M. Klimek, MD*[34], *Fabio Pires de Souza Santos, MD*[35], *Jacqueline Boultwood, PhD*[36], *Ioannis Kotsianidis, PhD*[37], *Valeria Santini, MD*[38], *Francesc Solé, PhD*[39], *Uwe Platzbecker, MD*[40], *Michael Heuser, MD*[41], *Peter Valent, MD*[42], *Kazuma Ohyashiki, MD, PhD*[43], *Carlo Finelli, MD*[44*], *Maria Teresa Teresa Voso, MD*[45], *Lee-Yung Shih, MD*[46], *Michaela Fontenay*[47], *Joop H. Jansen, PhD*[48], *José Cervera, MD, PhD*[49*], *Norbert Gattermann, MD*[50], *Benjamin L. Ebert, MD, PhD*[51], *Rafael Bejar, MD, PhD*[52], *Luca Malcovati, MD*[53], *Mario Cazzola, MD, PhD*[54], *Seishi Ogawa*[55,56,57], *Eva Hellström-Lindberg, MD, PhD*[8] *and Elli Papaemmanuil, PhD*[5,58]

Bernard et al, ASH 2021 Abstract #61.

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International Prognostic Scoring System – Molecular

Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.*

Category and Variable	Adjusted Hazard Ratio (95% CI)†	Model Weight‡
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — x10^9/l	0.998 (0.997–0.999)	−0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	−0.171
Cytogenetic		
IPSS-R cytogenetic category§	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)¶		
TP53^{multihit}	3.27 (2.38–4.48)	1.18
MLL^{PTD}	2.22 (1.49–3.32)	0.798
FLT3$^{ITD+TKD}$	2.22 (1.11–4.45)	0.798
SF3B1^{Sq}	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B1^{a}	0.92 (0.74 1.16)	−0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖		
min(Nres,2)	1.26 (1.12–1.42)	0.231

* CI denotes confidence interval; IPSS-M, International Prognostic Scoring System–Molecular; IPSS-R, International Prognostic Scoring System–Revised; ITD, internal tandem duplication; min, minimum; PTD, partial tandem duplication; and TKD tyrosine kinase domain.

† Hazard ratio is for the risk of leukemic transformation or death, adjusted for age, sex, and secondary/therapy-related versus primary myelodysplastic syndrome. Cox regression was performed for 2428 patients with available covariables and leukemia-free survival data.

‡ Model weights were derived from the logarithm of the raw hazard ratios up to three significant digits. The following formula applies: IPSS-M score = $1.15467 + (\sum_{variables\ j} w_j x_j)/\log(2)$, where w_j denotes the weight of variable j, and x_j the value of the variable j observed in a given patient.

§ IPSS-R cytogenetic categories were as follows: 0 denotes very good, 1 good, 2 intermediate, 3 poor, and 4 very poor.

¶ *SF3B1*^{Sq} is the *SF3B1* mutation in the presence of isolated del(5q) — that is, del(5q) only or with one additional aberration excluding -7/del(7q). *SF3B1*^{a} is the *SF3B1* mutation without comutations in *BCOR, BCORL1, RUNX1, NRAS, STAG2, SRSF2,* and del(5q).

‖ Nres is defined as the number of mutated genes within the following list: *BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2,* and *WT1*. The variable min(Nres,2) can therefore take the value 0, 1, or 2.

Bernard et al, NEJM Evidence 2022.

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IPSS-M, Continued

Table 2. Summary of Clinical Outcomes for 2701 Patients by IPSS-M Risk Category.*

Characteristic	IPSS-M Risk Category					
	Very Low	Low	Moderate Low	Moderate High	High	Very High
Patients — No. (%)	381 (14)	889 (33)	302 (11)	281 (11)	379 (14)	469 (17)
Risk score	≤−1.5	>−1.5 to −0.5	>−0.5 to 0	>0 to 0.5	>0.5 to 1.5	>1.5
Hazard ratio (95% CI)†	0.51 (0.39–0.67)	1.0 (Reference)	1.5 (1.2–1.8)	2.5 (2.1–3.1)	3.7 (3.1–4.4)	7.1 (6.0–8.3)
Median LFS (25–75% range) — yr‡	9.7 (5.0–17.4)	5.9 (2.6–12.0)	4.5 (1.6–6.9)	2.3 (0.91–4.7)	1.5 (0.80–2.8)	0.76 (0.33–1.5)
Median OS (25–75% range) — yr	10.6 (5.1–17.4)	6.0 (3.0–12.8)	4.6 (2.0–7.4)	2.8 (1.2–5.5)	1.7 (1.0–3.4)	1.0 (0.5–1.8)
AML-t — %						
By 1 yr	0.0	1.7	4.9	9.5	14.3	28.2
By 2 yr	1.2	3.4	8.8	14.0	21.2	38.6
By 4 yr	2.8	5.1	11.4	18.9	29.2	42.8
Death without AML — %						
By 1 yr	2.2	8.5	12.0	18.0	19.3	30.6
By 2 yr	7.0	16.2	19.8	31.1	39.8	45.6
By 4 yr	15.9	29.5	33.6	51.1	54.2	51.3

Bernard et al, NEJM Evidence 2022.

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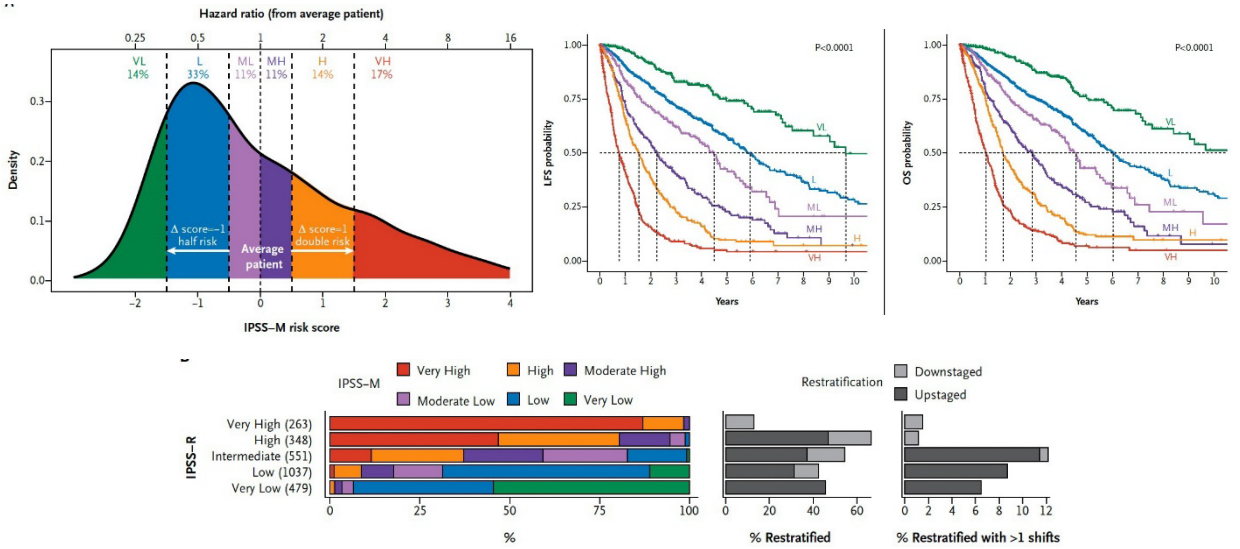
IPSS-M, Continued



Bernard et al, NEJM Evidence 2022.

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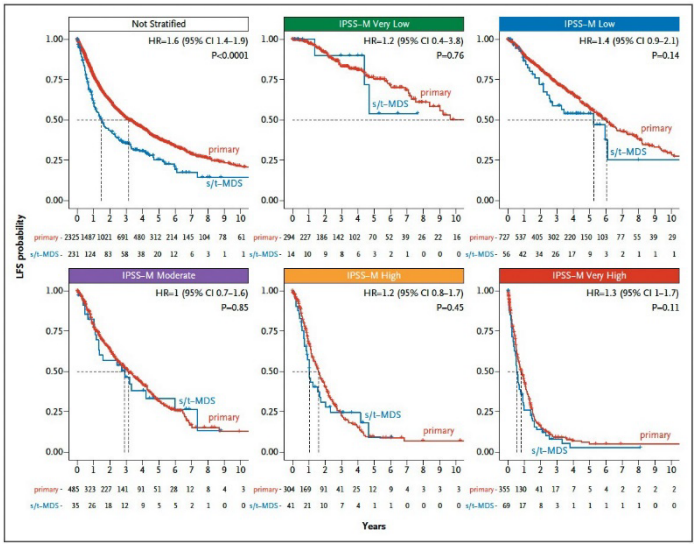
IPSS-M – Therapy-Related MDS



Bernard et al, NEJM Evidence 2022.

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New/Updated Classification Systems

- 2022 Update to the WHO Classification System (WHO 2022)
- The International Consensus Classification of Myeloid Neoplasms and Acute Leukemia (ICC)
- ELN 2022 AML Recommendations

Khoury et al, Leukemia 2022
Arber et al, Blood 2022
Dohner et al, Blood 2022

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WHO 2022 - MDS

Table 3. Classification and defining features of myelodysplastic neoplasms (MDS).

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

Khoury et al, Leukemia 2022

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ICC - MDS

Table 20. Myelodysplastic syndromes (MDS) and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)

	Dysplastic lineages	Cytopenias	Cytoses*	BM and PB Blasts	Cytogenetics[b]****	Mutations
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1[c]	≥1	0	<5% BM <2% PB	Any, except isolated del(5q), -7/del(7q), abn3q26.2, or complex	*SF3B1* (≥10% VAF), without multi-hit *TP53*, or *RUNX1*
MDS with del(5q) [MDS-del(5q)]	Typically ≥1[c]	≥1	Thrombocytosis allowed	<5% BM <2% PB[d]	del(5q), with up to 1 additional, except -7/del(7q)	Any, except multi-hit *TP53*
MDS, NOS - without dysplasia	0	≥1	0	<5% BM <2% PB[d]	-7/del(7q) or complex	Any, except multi-hit *TP53* or *SF3B1* (≥10% VAF)
MDS, NOS - with single lineage dysplasia	1	≥1	0	<5% BM <2% PB[d]	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*;not meeting criteria for MDS-*SF3B1*
MDS, NOS - with multilineage dysplasia	≥2	≥1	0	<5% BM <2% PB[d]	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*,; not meeting criteria for MDS-*SF3B1*
MDS with excess blasts (MDS-EB)	Typically ≥1[c]	≥1	0	5-9% BM, 2-9% PB[d]	Any	Any, except multi-hit *TP53*
MDS/AML	Typically ≥1[c]	≥1	0	10-19% BM or PB[e]	Any, except AML-defining[f]	Any, except *NPM1*, bZIP *CEBPA* or *TP53*

*Cytoses: Sustained white blood count ≥13 x 10^9/L, monocytosis (≥0.5 x 10^9/L and ≥10% of leukocytes), or platelets ≥450 x 10^9/L; thrombocytosis is allowed in MDS-del(5q) or in any MDS case with inv(3) or t(3;3) cytogenetic abnormality.

**BCR::ABL1* rearrangement or any of the rearrangements associated with myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions exclude a diagnosis of MDS, even in the context of cytopenia.

[c]Although dysplasia is typically present in these entities, it is not required.

[d]Although 2% PB blasts mandates classification of an MDS case as MDS-EB, the presence of 1% PB blasts confirmed on two separate occasions also qualifies for MDS-EB.

[e]For pediatric patients (<18 years), the blast thresholds for MDS-EB are 5-19% in BM and 2-19% in PB, and the entity MDS/AML does not apply.

[f]AML defining cytogenetics are listed in the AML section.

Arber et al, Blood 2022

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WHO 2022 – AML

Table 7. Acute myeloid leukaemia.

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML::RARA* fusion
Acute myeloid leukaemia with *RUNX1::RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB::MYH11* fusion
Acute myeloid leukaemia with *DEK::NUP214* fusion
Acute myeloid leukaemia with *RBM15::MRTFA* fusion
Acute myeloid leukaemia with *BCR::ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

Summary Box:

- AML is arranged into two families: AML with *defining genetic abnormalities* and AML *defined by differentiation*. AML, NOS is no longer applicable.
- Most AML with defining genetic abnormalities may be diagnosed with <20% blasts.
- AML-MR replaces the former term AML "with myelodysplasia-related changes", and its diagnostic criteria are updated. AML transformation of MDS and MDS/MPN continues to be defined under AML-MR in view of the broader unifying biologic features.
- AML with rare fusions are incorporated as subtypes under AML with *other defined genetic alterations*.
- AML with somatic *RUNX1* mutation is not recognized as a distinct disease type due to lack of sufficient unifying characteristics.

Summary Box:

- Myeloid neoplasms (MDS, MDS/MPN, and AML) *post cytotoxic therapy* (MN-pCT) require full diagnostic work up; the term replaces *therapy-related.*
- Exposure to PARP1 inhibitors is added as a qualifying criterion for MN-pCT.
- The diagnostic framework for myeloid neoplasm associated with germline predisposition is restructured along a scalable model that can accommodate future refinement and discoveries.

Khoury et al, Leukemia 2022

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ICC - AML

AML and related neoplasms
AML with recurrent genetic abnormalities (requiring ≥10% blasts in BM or PB)[a]
• APL with t(15;17)(q24.1;q21.2)/*PML::RARA*[b]
• AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*
• AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*
• AML with t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*[c]
• AML with t(6;9)(p22.3;q34.1)/*DEK::NUP214*
• AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*[d]
• AML with other rare recurring translocations[e]
• AML with mutated *NPM1*
• AML with in-frame bZIP mutated *CEBPA*[f]
• AML with t(9;22)(q34.1;q11.2)/*BCR::ABL1*[g]
Categories designated AML (if ≥20% blasts in BM or PB) or MDS/AML (if 10-19% blasts in BM or PB)
• AML with mutated *TP53*[g]
• AML with myelodysplasia-related gene mutations Defined by mutations in *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1,* or *ZRSR2*
• AML with myelodysplasia-related cytogenetic abnormalities[h]
• AML not otherwise specified (NOS)
Myeloid sarcoma
Myeloid proliferations related to Down Syndrome
• Transient abnormal myelopoiesis associated with Down syndrome
• Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
• Acute undifferentiated leukemia
• MPAL with t(9;22)(q34.1;q11.2)/*BCR::ABL1*
• MPAL with t(v;11q23.3)/*KMT2A* rearranged
• MPAL, B/myeloid, not otherwise specified
• MPAL, T/myeloid, not otherwise specified

Table 27. Diagnostic qualifiers that should be used following a specific MDS, AML (or MDS/AML) diagnosis*

Therapy-related** • prior chemotherapy, radiotherapy, immune interventions
Progressing from myelodysplastic syndrome • MDS should be confirmed by standard diagnostics
Progressing from myelodysplastic/myeloproliferative neoplasm (specify) • MDS/MPN should be confirmed by standard diagnostics
Germline predisposition

*Examples: Acute myeloid leukemia with myelodysplasia-related cytogenetic abnormality, therapy-related; acute myeloid leukemia with myelodysplasia-related gene mutation, progressed from myelodysplastic syndrome; AML with myelodysplasia-related gene mutation, germline *RUNX1* mutation

**lymphoblastic leukemia/lymphoma may also be therapy-related, and that association should also be noted in the diagnosis

Arber et al, Blood 2022
Dohner et al, Blood 2022

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Summary and Future Directions

- Exciting time for new treatments for AML and MDS
- Standards of care are rapidly evolving
- Clinical trials continue to advance new treatments
- My email: bajonas@ucdavis.edu

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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Case Presentations: Leukemias, Lymphomas, Myeloma

Vanessa Kennedy, MD

Fellow, Hematology & Oncology University of California, San Francisco

ANCO

Educating and Empowering the Northern California Cancer Community

Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Vanessa E. Kennedy, MD
University of California San Francisco

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ANCO
Educating and Empowering the Northern California Cancer Community

CASE PRESENTATIONS

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CASE #1

3

Case 1

- Mr. C: 68 yo M presents with L > R cervical adenopathy, fevers, night sweats
- CT C/A/P: Extensive adenopathy above and below the diaphragm, splenomegaly
- Core biopsy of R axillary node:
  - **DLBCL** (60%) arising in a background of follicular lymphoma (60%)
  - Large B cells are CD19, CD20, CD30, MUM1 and (variable) BCL2 positive
  - FISH positive for BCL2 rearrangement but negative for MYC and BCL6 rearrangements
- Bone marrow biopsy: positive for DLBCL
- Stage IVB disease with IPI 4/5

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Case 1

- Treatment: **R-CHOP**
- PET: After 2 cycles R-CHOP metabolic CR (Deauville 1)
- After 6 cycles of R-CHOP, ongoing metabolic CR
- Surveillance scan 6 months later metabolic CR (Deauville 1)

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Case 1

- 3 months later: Recurrent cervical adenopathy, fatigue and anemia
- CT C/A/P: Recurrent extensive adenopathy
- Repeat BMBx: 10-15% involvement of DLBCL
- Salvage: R-ICE x 2
- Repeat PET-CT: Metabolic CR (Deauville 1-2)

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Case 1

What would you do next?

A. 2 more cycles of R-ICE

B. Autologous HCT

C. Allogeneic HCT

D. CAR T-cell therapy

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Case 1

What would you do next?

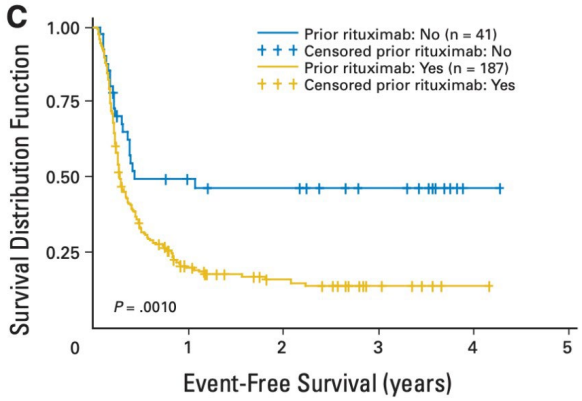
A. 2 more cycles of R-ICE

B. **Autologous HCT…..**

C. Allogeneic HCT

D. CAR T-cell therapy

CORAL



8

Case 1

What would you do next?

A. 2 more cycles of R-ICE

B. Autologous HCT

C. Allogeneic HCT

D. CAR T-cell therapy

Gisselbrecht, *JCO*, 2010

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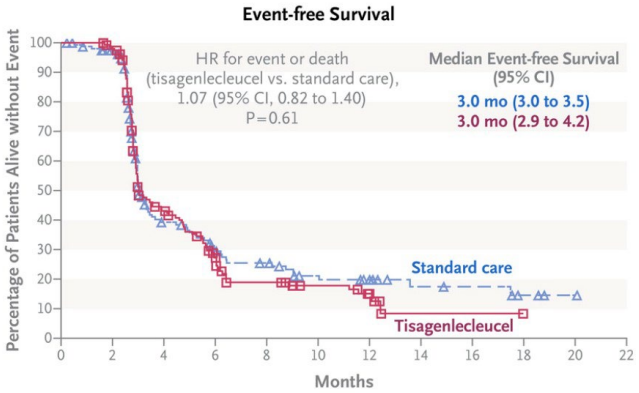
CAR T cell therapy as 2nd line

BELINDA

- 322 patients with aggressive B cell lymphoma (R/R in < 12 months)
- **Tisagenlecleucel** vs standard care



Median EFS 3 months vs 3 months- **No difference**

Bishop et al, *NEJM*, 2022

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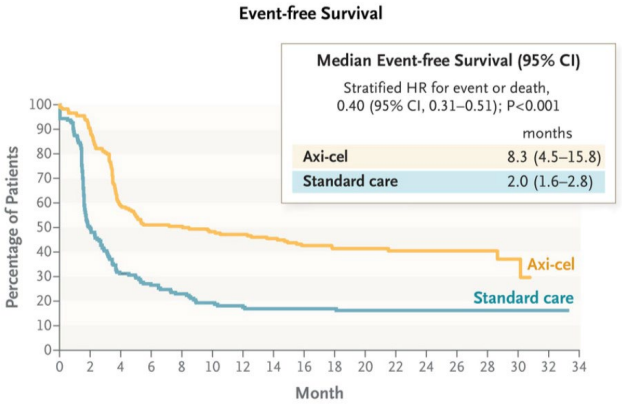
CAR T cell therapy as 2nd line

ZUMA-7

- 359 patients with aggressive B cell lymphoma (R/R in < 12 months)
  - No impending organ compromise
- **Axicabtagene Ciloleucel** vs standard care



Median EFS 8.3 vs 2.0 months- **CAR T significantly better**

Locke et al, *NEJM,*2022

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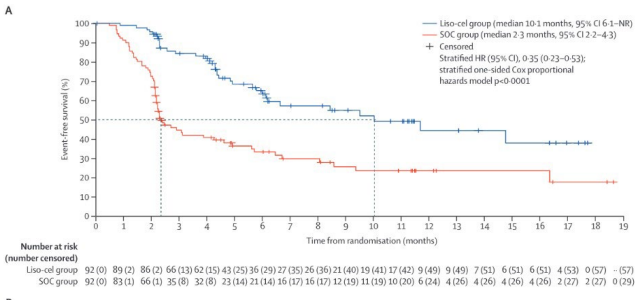
CAR T cell therapy as 2nd line

TRANSFORM

- 184 patients with aggressive B cell lymphoma (R/R in < 12 months)
- **Lisocabtagene maraleucel** vs standard care



Median EFS 10.1 vs 2.3 months- **CAR T significantly better**

Kamdar et al, *Lancet*, 2022

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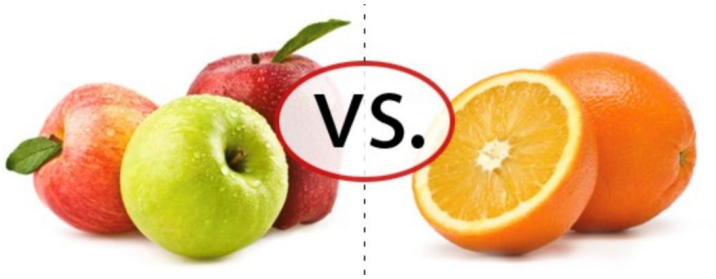
CAR T cell therapy as 2nd line ?

- All 3 trials with similar patient populations
- All 3 trials with 1:1 randomization and roughly similar sample sizes (322, 359, 184)
- All 3 trials with the same primary endpoint (EFS)



But there are still important differences in trial design and interpretation!

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CAR T cell therapy as 2nd line

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CAR T cell therapy as 2nd line

	BELINDA	ZUMA-7	TRANSFORM
Co-Stim			
CART vs ASCT	1) SD or PD at or after week 12 2) Death (any time)	1) Disease progression 2) Death from any cause 3) New therapy started 4) SD as best response within 150 days from randomization	1) Disease progression 2) Death from any cause 3) New therapy started 4) Not achieving CR/PR by 9-weeks.
Crossover			
Bridging Chemo			
	12% 2 lines)		
Median time from apheresis to CAR T	52 days	27 days	36 days
OS	NS	NS	✓
EFS	NS	✓	✓

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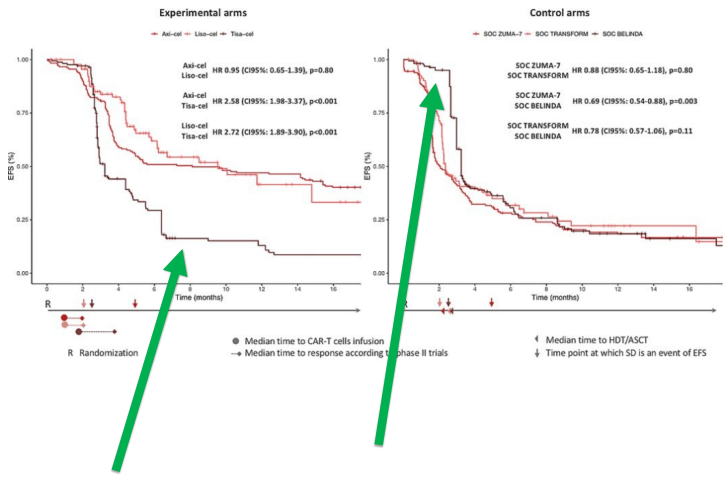
CAR T cell therapy as 2nd line



- **BELINDA: Patients may have been sicker**
- Allowed for patients with impending organ compromise
- 26% of patients on the CAR T arm had **progressive disease prior to CAR T** (and were not excluded from the study)
- 29% with **ABC subtype** (vs 15% on ZUMA-7)
- **Bridging chemotherapy allowed**

Bommier, *Hematological Oncology,* 2022

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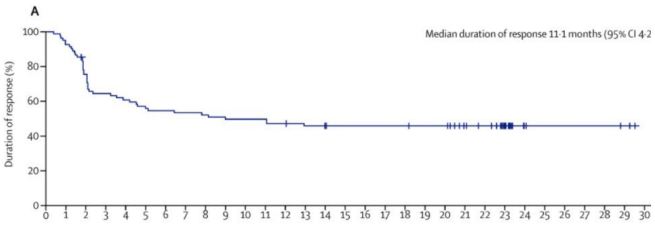
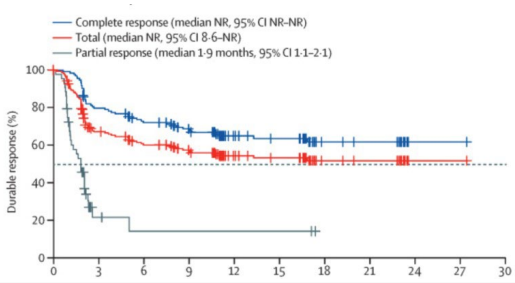
CAR T cell therapy as 2nd line

- 2 products (**Axi-Cel** and **Liso-Cel**) demonstrate superior EFS vs SOC chemotherapy with ASCT as 2 nd line therapy in patients with high risk R/R LBCL
- Approximately **30-40%** pf patients will achieve **long term remissions** with these products based on Phase 2 data

ZUMA-1 (Axi-Cel)



TRANSCEND (Liso-Cel)



Locke, *Lancet Oncology*, 2019; Abramson, *Lancet,* 2020

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Lingering Questions

- What are the clinically meaningful differences between products?
  - Differences in trial design make it challenging to compare differences in products
  - No head-to-head comparisons
- Is there a patient population that benefits most from 2nd line CAR T?
  - Only studied in patients with aggressive (primary refractory or relapsed < 12 months) disease.
  - BELINDA suggest we *may* see less of a benefit in rapidly-progressing, aggressive disease that requires multiple lines of bridging chemotherapy
- What is the optimal sequencing?
  - CAR T after ASCT is well-established; the reverse is not!

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Back to Case 1

- Following his 2 cycles of R-ICE, Mr. C proceeded to **Axi-Cel** CAR T cell therapy
- PET/CT at 3 months demonstrates CR
- 1 year later, remains in CR

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CASE #2

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Case 2

- Ms. S: 67 yo, otherwise healthy, F develops new fatigue and presents to her PCP
  - CBC: Hgb 6.7, Plt 93, WBC 3.2
- She is sent to the ED and admitted
- **BMBx:**
  - Normocellular marrow with markedly abnormal megakaryocytes, 10% Blasts by smear
  - Flow: 15% blasts, CD33+, CD117+
  - Karyotype: Normal
  - NGS: NPM1 mutation

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Case 2

How do you want to treat this patient?

A. Azacitidine indefinitely

B. Azacitidine followed byallo-HCT

C. 7+3 +/- GO induction chemotherapy, followed by consolidation

D. 7+3 +/- GO induction chemotherapy, followed byallo-HCT

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Case 2

How do you want to treat this patient?

A. Azacitidine indefinitely

B. Azacitidine followed byallo-HCT

C. **7+3 +/- GO induction chemotherapy, followed by consolidation**

D. 7+3 +/- GO induction chemotherapy, followed byallo-HCT

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Case 2

How do you want to treat this patient?

Wait…isn't this a recommended option for high-risk MDS?

A. Azacitidine indefinitely

B. Azacitidine followed byallo-HCT

C. **7+3 +/- GO induction chemotherapy, followed by** consolidation

D. 7+3 +/- GO induction chemotherapy, followed byallo-HCT

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What's her diagnosis?

- Previously, this patient would have high-risk MDS-EB2 with IPSS-R 6 (high-risk)
- However, the classification system for myeloid malignancies has changed!
- By both the new 2022 International Consensus Criteria/ELN and the 2022 WHO guidelines,

>10% blasts + Defining Genetic Abnormalities = AML

Dohner et al, *Blood*, 2022

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What's her diagnosis?

WHO

Table 7. Acute myeloid leukaemia.

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML::RARA* fusion
Acute myeloid leukaemia with *RUNX1::RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB::MYH11* fusion
Acute myeloid leukaemia with *DEK::NUP214* fusion
Acute myeloid leukaemia with *RBM15::MRTFA* fusion
Acute myeloid leukaemia with *BCR::ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
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Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

International Consensus Criteria

AML and related neoplams

AML with recurrent genetic abnormalities (requiring ≥10% blasts in BM or PB)*

- APL with t(15;17)(q24.1;q21.2)/*PML::RARA*†
- AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*
- AML with t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*‡
- AML with t(6;9)(p22.3;q34.1)/*DEK::NUP214*
- AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*§
- AML with other rare recurring translocations‖
- AML with mutated *NPM1*
- AML with in-frame bZIP mutated *CEBPA*¶
- AML with t(9;22)(q34.1;q11.2)/*BCR::ABL1**

- Many defining genetic lesions are now defined as AML even without <20% blasts

Dohner et al, *Blood*, 2022; Khoury, *Leukemia*, 2020

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What's her risk stratification?

Table 6.

2022 ELN risk classification by genetics at initial diagnosis*

Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ *CBFB::MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK::NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR::ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ *GATA2, MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*‡‡ • Mutated *TP53*§§

She has favorable risk, NPM1-mutated AML

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Case 2

How do you want to treat this patient?

A. Azacitidine indefinitely

B. Azacitidine followed byallo-HCT

C. 7+3 +/- GO induction chemotherapy, followed by consolidation

D. 7+3 +/- GO induction chemotherapy, followed byallo-HCT

For favorable risk AML, HCT is <u>not</u> recommended in first CR

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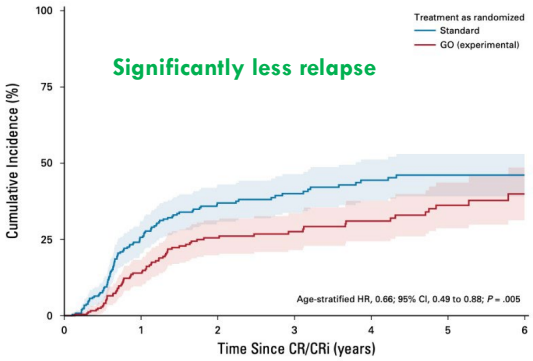
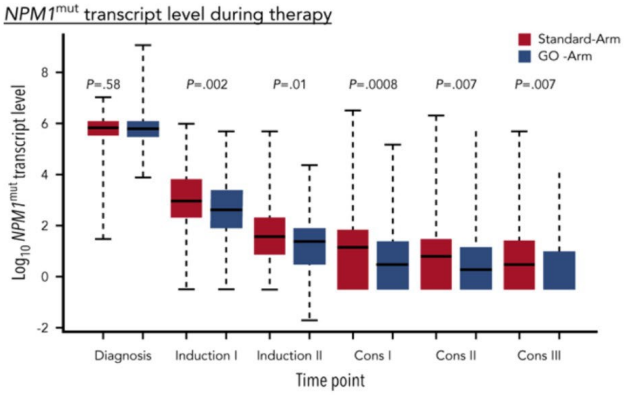
Induction

- Gemtuzumab Ozogamicin should be considered in all CD33+ favorable and intermediate risk AML
- Particular benefit in **NPM1-mutated AML**





Decreased NPM1 transcripts

Schlenk et al, *JCO,* 2019

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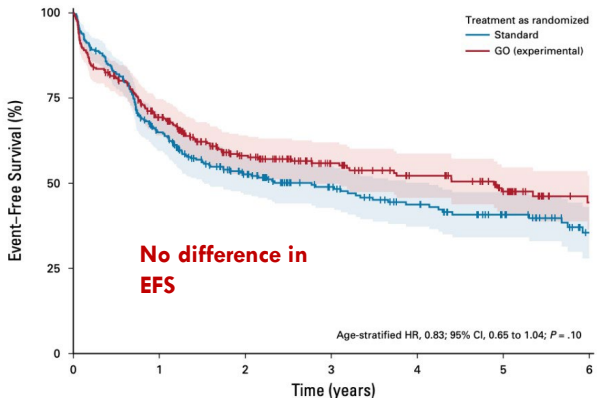
Induction

- AMLSG 09-09 did not meet it's primary endpoint of EFS
- Significantly higher early mortality in the GO arm, mainly driven by infections



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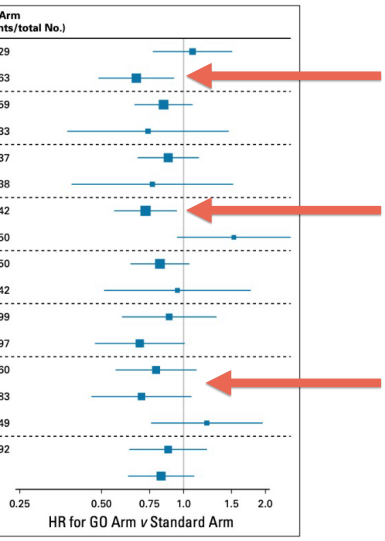
Induction

Variable	HR (95% CI)	Standard Arm (No. of events/total No.)	GO Arm (No. of events/total No.)
Male	1.08 (0.77 to 1.51)	73/144	64/129
Female	0.67 (0.49 to 0.92)	84/152	68/163
De novo	0.84 (0.66 to 1.08)	140/265	116/259
s-AML/t-AML	0.74 (0.37 to 1.47)	17/30	16/33
No normal karyotype	0.88 (0.68 to 1.14)	123/237	106/237
Normal karyotype	0.77 (0.39 to 1.52)	16/32	17/38
FLT3-ITD wild type	0.72 (0.56 to 0.95)	126/247	96/242
FLT3-ITD mutated	1.53 (0.95 to 2.48)	31/49	36/50
FLT3-TKD wild type	0.82 (0.64 to 1.05)	138/262	111/250
FLT3-TKD mutated	0.95 (0.51 to 1.77)	19/34	21/42
DNMT3A wild type	0.89 (0.59 to 1.32)	58/118	41/99
DNMT3A mutated	0.69 (0.47 to 1.01)	56/84	51/97
Age ≤ 60 years	0.79 (0.56 to 1.12)	75/165	58/160
Age 60-70 years	0.7 (0.46 to 1.07)	48/81	39/83
Age > 70 years	1.22 (0.76 to 1.95)	34/50	35/49
WBC LQ	0.88 (0.63 to 1.22)	157/296	132/292
WBC UQ	0.83 (0.62 to 1.1)		



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Case 2

- The patient is induced with 7+3+GO
- She develops febrile neutropenia with a soft tissue infection, but otherwise tolerates therapy well
- Day 29 BMBx:
  - 80% cellularity; 1% blasts
  - Negative: Cytogenetics, FISH, NGS, Flow cytometry
- Proceeds to C1 of consolidation, which is complicated by pneumonia and delirium

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How to monitor?

- Role and timing of MRD in AML is still being determined
- MRD can be monitored via flow cytometry or PCR (only some genetic lesions)
- **PCR: NPM1**, CBFB:MYH11, RUNZ1:RUNX1T1, KMT2A:MLLT3, DEK:NUP214, BCR:ABL1, WT1 expression

Dohner et al, *Blood*, 2022

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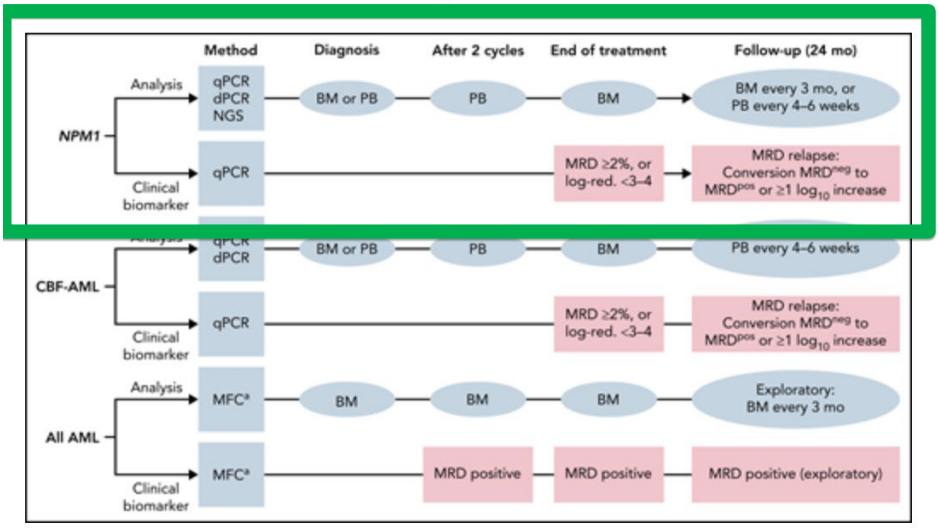
How to monitor?

Figure 2.



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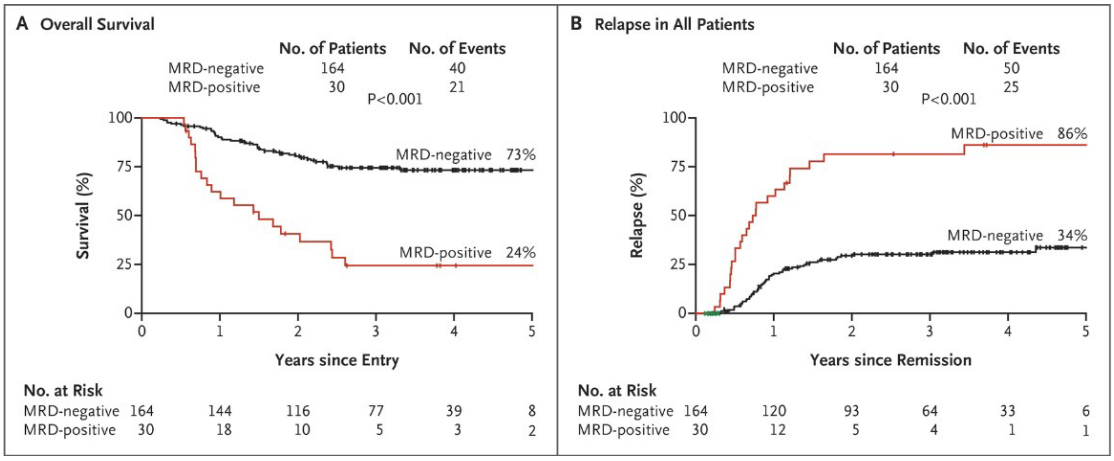
How to monitor?



Ivey et al, NEJM, 2016

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Back to Case 2

- Her counts recover after her first cycle of consolidation, but she is **NPM1 MRD positive**
- She receives her 2nd cycle of consolidation, but then develops persistent cytopenias
- Bone marrow biopsy confirms **relapsed AML**
- She is started on Azacitidine/Venetoclax

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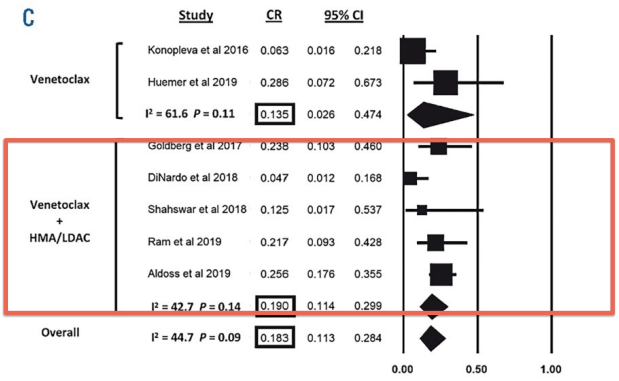
Aza/Ven in Relapsed AML



- She is started on Aza/Ven
- Repeat BMBx after 1 cycle shows CR!
- NPM1 MRD is now negative!
- She is feeling much better and has resumed walking around the pond in Golden Gate Park

Bewersdorf, Hematologica, 2020

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Now what?

What would be your next step in management?

A. Continue Azacitidine/Venetoclax indefinitely with NPM1 monitoring

B. Start oral Azacitidine monotherapy

C. Referral for HCT

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Now what?

What would be your next step in management?

A. Continue Azacitidine/Venetoclax indefinitely with NPM1 monitoring

B. Start oral Azacitidine monotherapy

C. Referral for HCT

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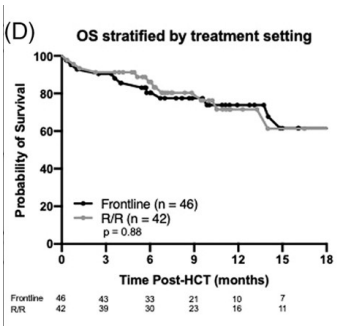
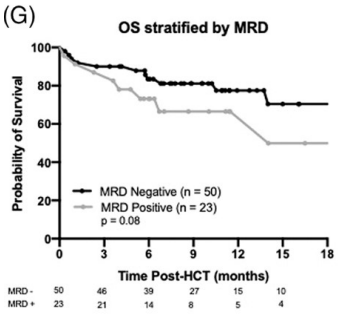
HCT after HMA/Ven

- Limited retrospective data patients who receive HMA/Ven for R/R AML can achieve good outcomes after HCT
- This is especially true for patients who are MRD- prior to transplant





Kennedy et al, AJH, 2022

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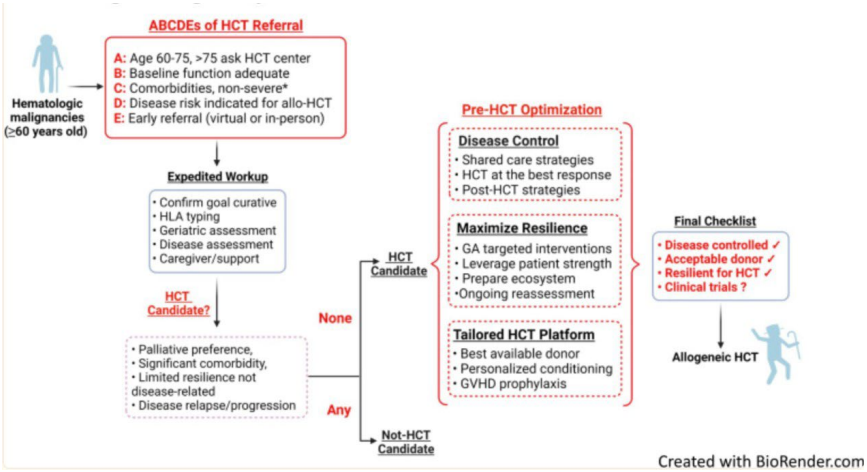
Transplant at 67?

- The patient is referred for transplant
- She is evaluated in a geriatric assessment and confirmed to be fit for transplant
- She undergoes HCT in CR2 and is doing well!



When in doubt, refer

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CASE #3

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Case 3

HPI:

- A 58 yo F, otherwise healthy, noted symptomatic macrocytic anemia with Hgb 9.8
- Further Labs showed:
  - Ca 11.8, Cr 1.0, LDH 400, Beta -2-microglobulin 4.1 mg/L, Albumin 3.8
  - SPEP/SIFE demonstrated M-protein of 3.8 g/dL
  - sFLC demonstrated kappa of 678, lambda 14, k/l ratio 0.02
  - Immunoglobulins: IgG 1030, IgA 117, IgM 45
  - UPEP unremarkable

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Case 3

HPI, continued:

- **BMBx:**
  - 90% atypical IgG lambda -restricted plasma cells
  - FISH: Trisomies involving chromosomes 3 and 11, but no IgH translocation, del(17p) or gain 1q
- **MRI Spine:** Lytic lesions at T9 and L1
- **PET:** Lytic lesions as above

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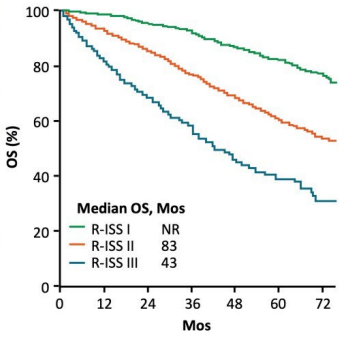
Case 3

HPI, continued:

- **BMBx:**
  - 45% atypical IgG kappa -restricted plasma cells
  - FISH: Trisomies involving chromsomes 3 and 11, but no IgH translocation, del(7p) or gain 1q

ISS Definition	
I	▪ Serum albumin ≥ 3.5 g/dL *AND* ▪ β_2-M < 3.5 mg/L
II	▪ Not stage I or III
III	▪ β_2-M ≥ 5.5 mg/L
R-ISS Definition	
I	▪ ISS stage I *AND* ▪ Normal LDH ▪ No t(4;14), t(14;16), or del(17p)
II	▪ Not stage I or III
III	▪ ISS stage III *AND* ▪ Serum LDH > ULN *OR* ▪ With t(4;14), t(14;16), or del(17p)



Palumbo et al, *J Clin Oncol*, 2015

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Case 3

How would you initially treat this patient?

A. Lenalidomide/Dexamethasone (Rd)

B. Bortezomib/Lenalidomide/Dexamethasone (VRd)

C. Carfilzolib/Lenalidomide/Dexamethasone (KRd)

D. Daratumumab/Bortezomib/Lenalidomide/Dexamethasone (Dara-RVd)

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Case 3

How would you initially treat this patient?

A. Lenalidomide/Dexamethasone (Rd)

B. Bortezomib/Lenalidomide/Dexamethasone (VRd)

C. Carfilzolib/Lenalidomide/Dexamethasone (KRd)

D. Daratumumab/Bortezomib/Lenalidomide/Dexamethasone (Dara-RVd)

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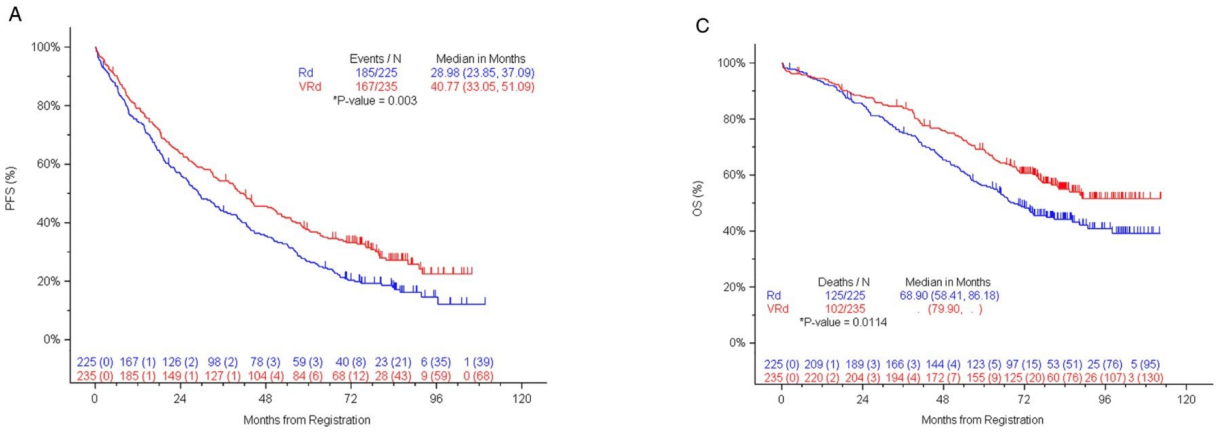
VRd is still the standard, standard risk treatment option..



Durie et al, *Blood Cancer Journal*, 2020

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However….

How would you initially treat this patient?

A. Lenalidomide/Dexamethasone (Rd)

B. Bortezomib/Lenalidomide/Dexamethasone (VRd)

C. Carfilzolib/Lenalidomide/Dexamethasone (KRd)

D. Daratumumab/Bortezomib/Lenalidomide/Dexamethasone (Dara-RVd)

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Can VRd be improved?

- GRIFFIN Trial: **Dara**-VRd vs VRd

Transplant-eligible adults with ND MM ECOG PS ≤ 2, and CrCl ≥ 30 mL/min* (N = 207)

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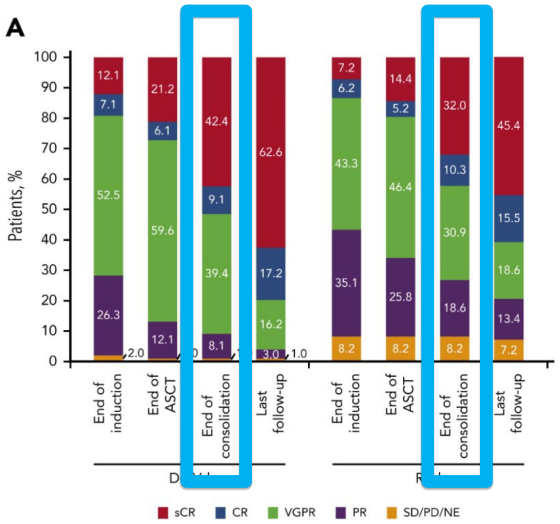
Can VRd be improved?

GRIFFIN



- Primary endpoint: Stringent CR post-consolidation (42% vs 32%)
- **But does this result actually lead to favorable long term outcomes?**

Voorhees et al, *Blood*, August 2020

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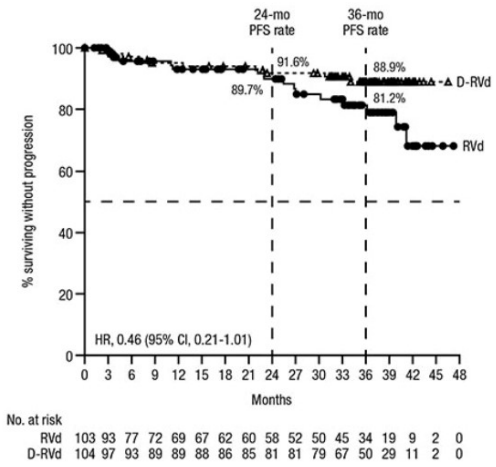
Can VRd be improved?

- After 2 years of maintenance, Dara-RVd had a **greater MRD negativity rate** vs RVd (64% vs 30%)
- **PFS also improved** 88.9% vs 81.2%
- Median OS still not reached for either group



Significantly improved PFS

Sborov et al, 2022 International Myeloma Society Annual Meeting

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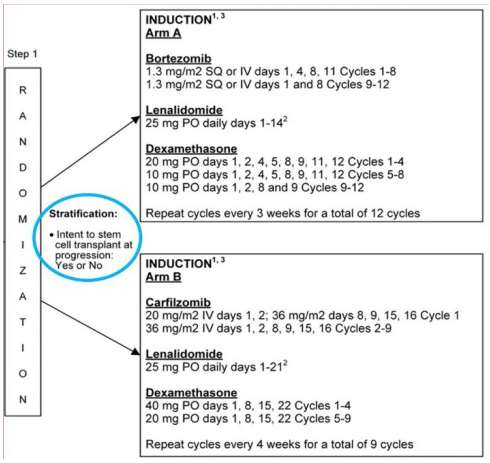
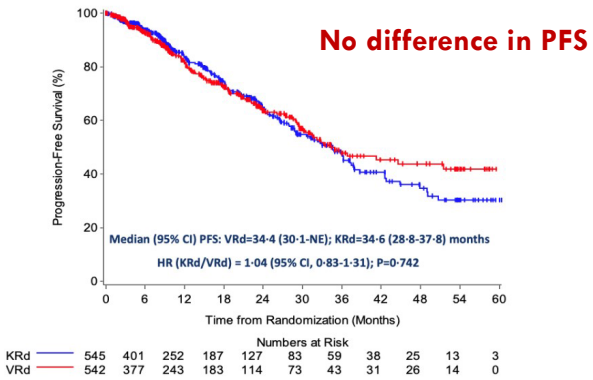
Why not KRd?

ENDURANCE





Kumar et al, *Lancet Oncology*, October 2020

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Thank you!

- Michael Spinner, MD
- Rebecca Olin, MD
- Sandy Wong, MD

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