Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

May 21, 2022

ANCO

Educating and Empowering the Northern California Cancer Community

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Association of Northern California Oncologists (ANCO)
presents

Hematologic Malignancies Updates: Leukemias, Lymphomas. & Myeloma

Saturday, May 21, 2022

8:00 AM Breakfast, Registration, & Exhibits

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

9:05AM Myeloma U*pdate 2022*
Michaela Liedtke, MD, Stanford University

9:50 AM Leukemia U*pdate 2022*
Brian A. Jonas, MD, PhD, FACP, University of California, Davis

10:35AM Coffee Break

11:00 AM *Lymphoma Update 2022*
Bita Fakhri, MD, MPH, University of California, San Francisco

11:45AM Case Presentations Leukemias, Lymphomas. & Myeloma
Eric Kuo, MD, Stanford University

12:30PM ADJOURN

Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Program Faculty

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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Acknowledgement of Financial Support

This activity is supported by:

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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Myeloma U*pdate 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

Disclosures

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

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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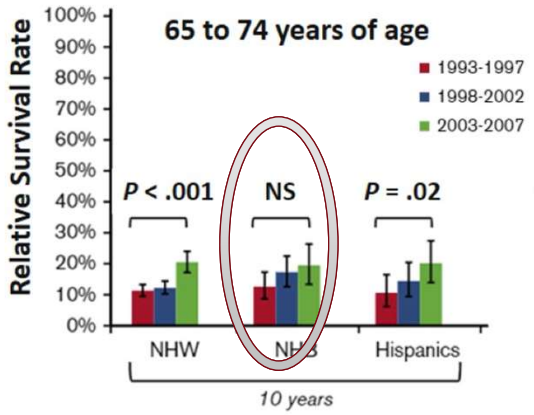
Outcome disparity



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

Costa L, et al. Blood Advances 2017.

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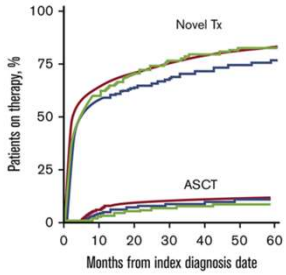
Access disparity



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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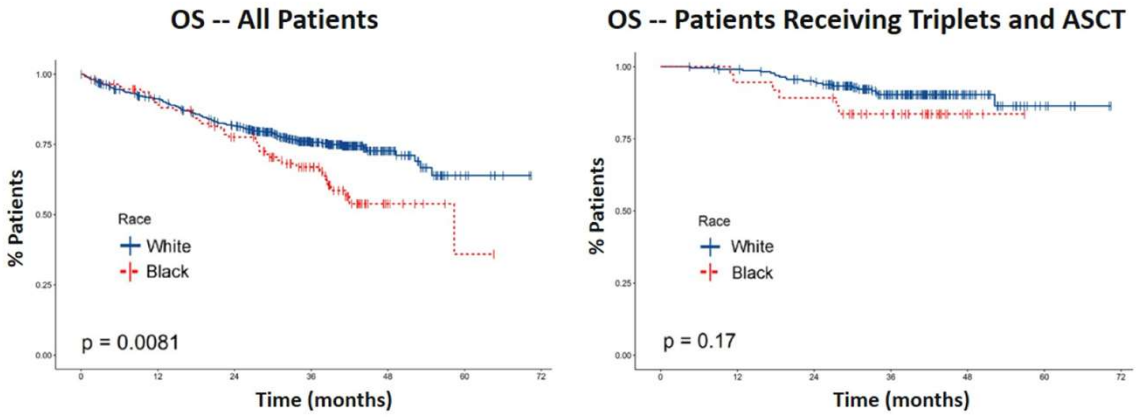
Equal access results in equal outcome



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

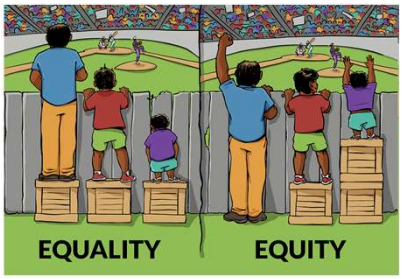
More likely to live in rural areas

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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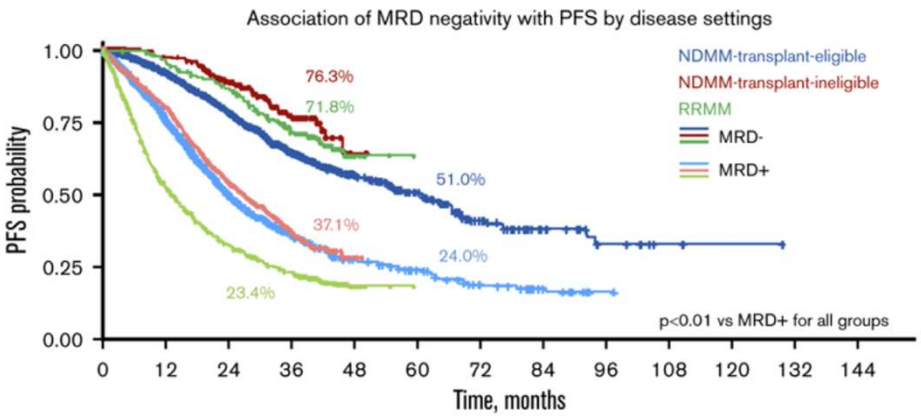
Minimal residual disease



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

NEWLY DIAGNOSED MYELOMA
ASCT-ELIGIBLE UP TO 65 YO

RVD X8
(N = 350)

LENALIDOMIDE
X12 MO

RVD X3
ASCT
RVDX2
(N = 350)

LENALIDOMIDE
X12 MO

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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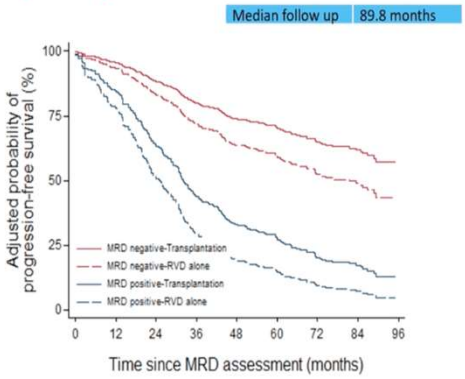
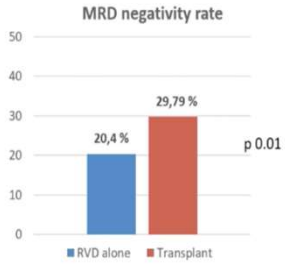
IFM/DFCI 2009: Role of MRD

Subgroup analyses





MRD-negativity is a strong predictor for PFS and OS

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

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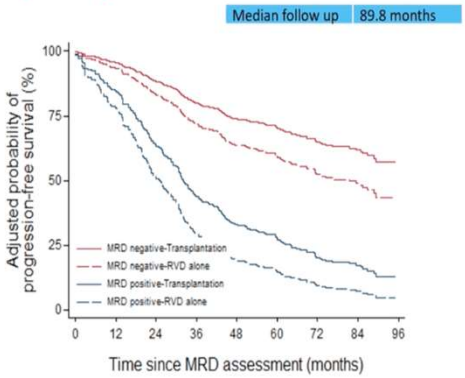
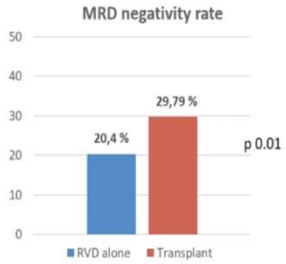
IFM/DFCI 2009: Role of MRD

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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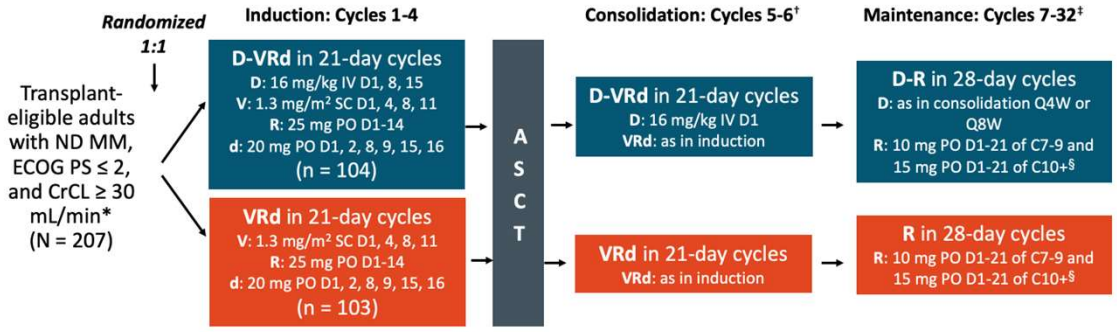
GRIFFIN: Dara-VRd versus VRd



*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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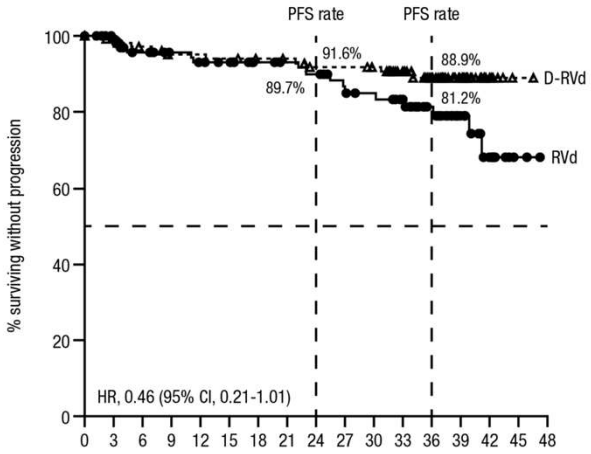
GRIFFIN: D-RVd prolongs PFS



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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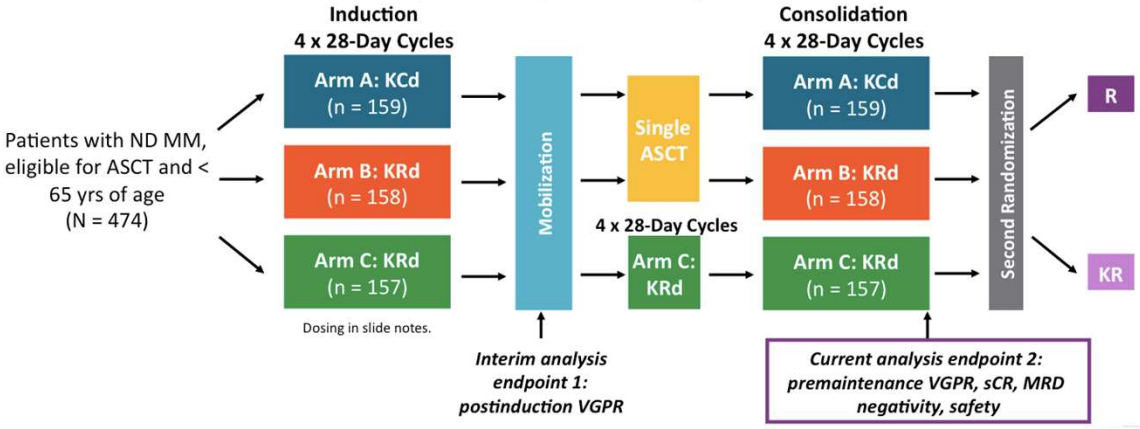
FORTE: KRd +/- ASCT

- Multicenter, randomized, open-label phase II study



Slide credit: clinicaloptions.com

Gay F, et al. Lancet Oncology 2021.

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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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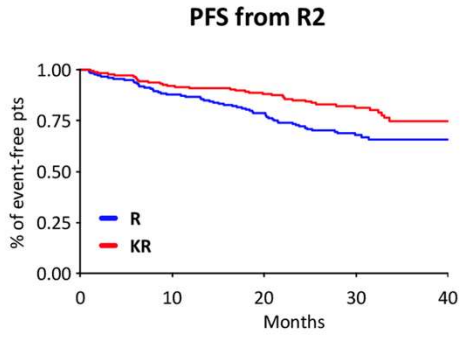
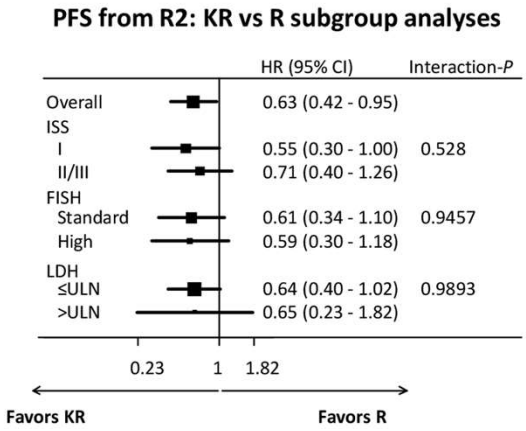
FORTE: Second randomization





KR maintenance increased PFS compared to lenalidomide alone

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

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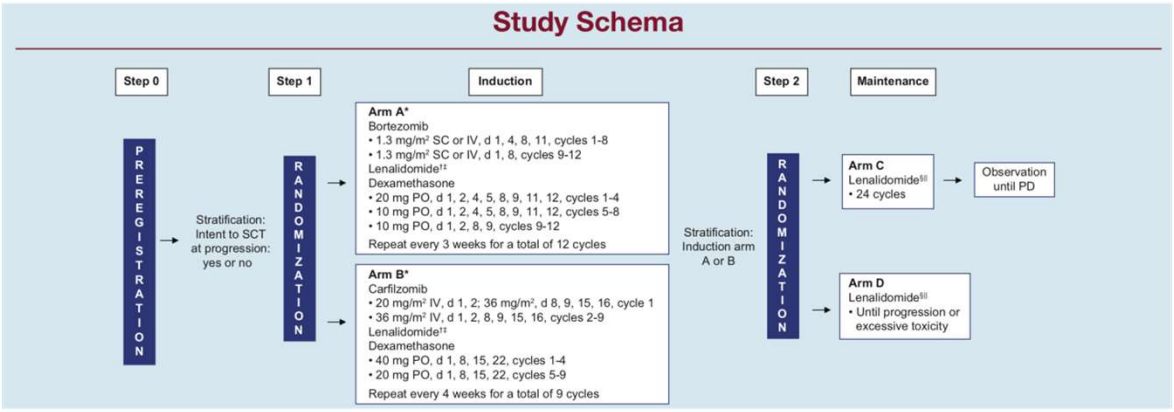
ENDURANCE: KRd versus VRd

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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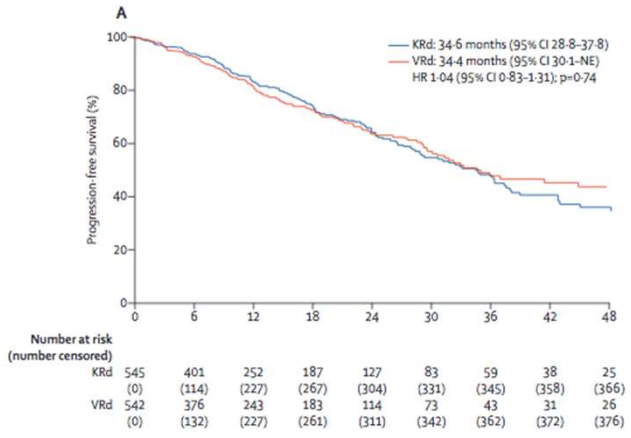
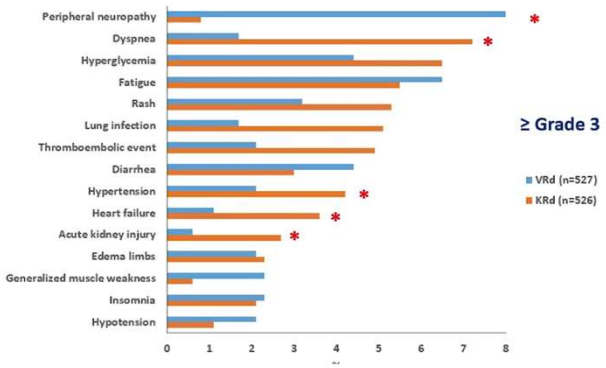
KRd did not improve PFS compared to VRd





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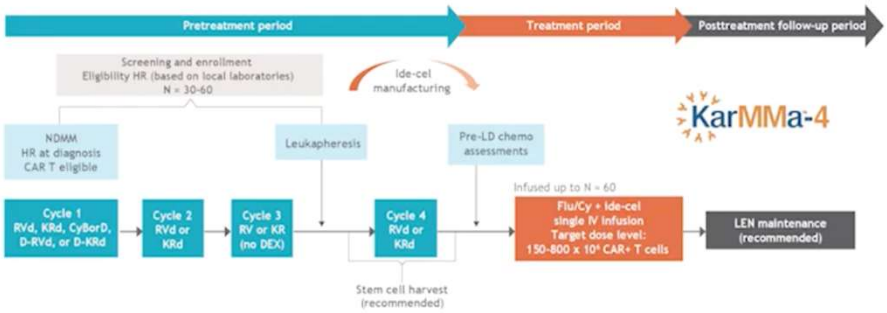
KarMMa-4: upfront CAR-T for high-risk myeloma



High risk (HR) definition
R-ISS III at diagnosis as defined by IMWG¹:
- ISS stage III and
  - Cytogenetic abnormalities t(4;14), del(17p), and/or t(14;16)
  or
  - Serum LDH > ULN

Endpoints
- Primary: Optimal target dose (DLT rate/safety)
- Secondary: CR, MRD negative, ORR, DOR, PFS, TCR, and OS, feasibility and time to start of LEN maintenance, and PK

NCT04196491

Usmani S, et al. ASCO 2021.

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MAIA: Rd +/- daratumumab in upfront myeloma

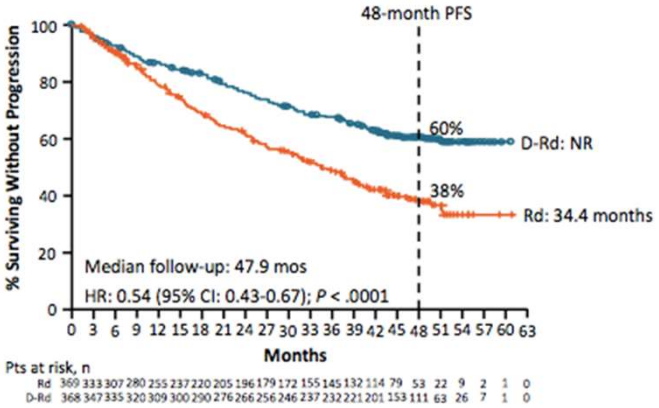
NEWLY DIAGNOSED MYELOMA
ASCT-INELIGIBLE AND ECOG 0-2
MEDIAN AGE 73

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

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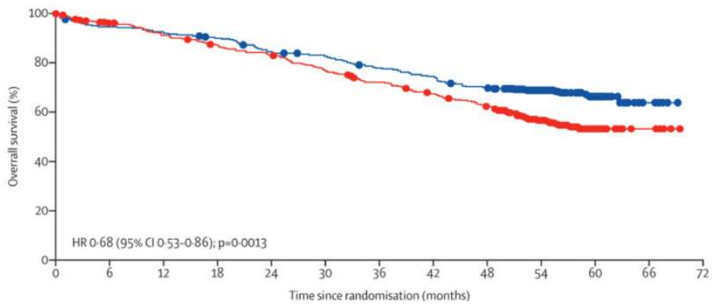

With longer follow-up the trial now demonstrates an overall survival benefit for D-Rd

Facon et al., NEJM 2019 and Lancet Oncology 2021

Slide credit: clinicaloptions.com

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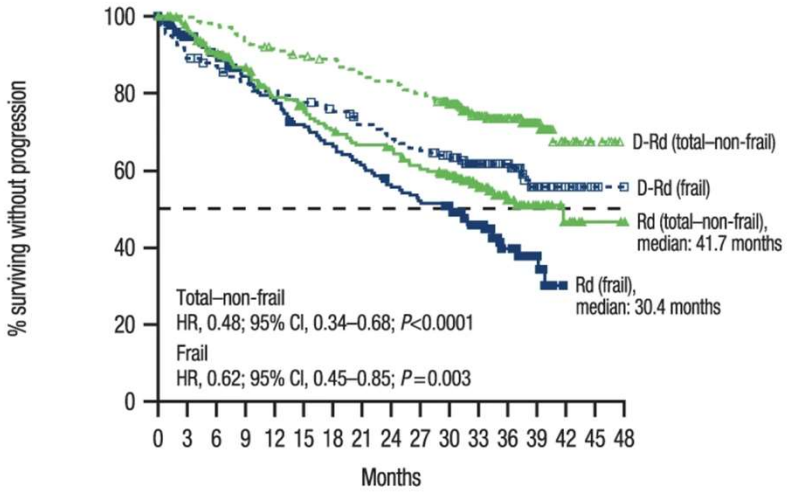
MAIA: Dara-Rd beneficial for frail patients



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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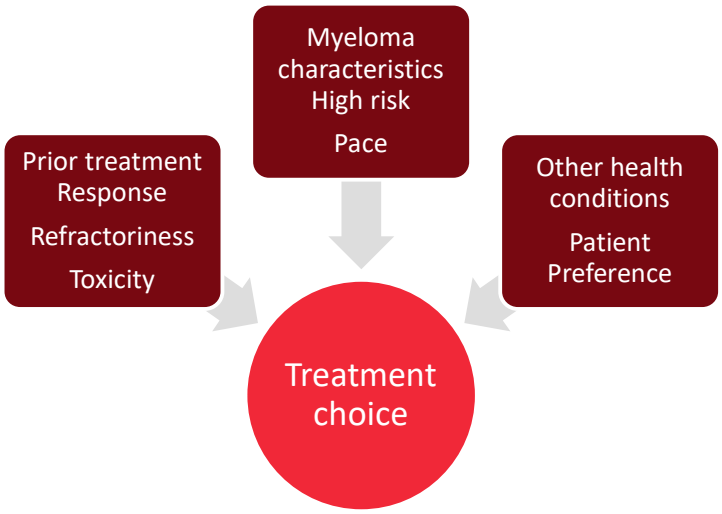
General Treatment Approach at Relapse



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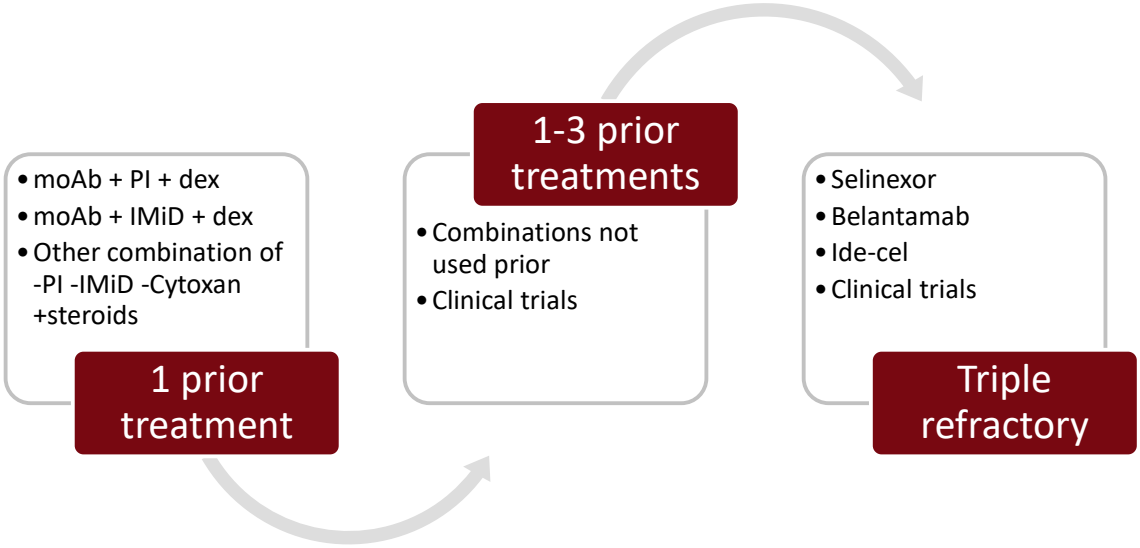
Sequencing Considerations



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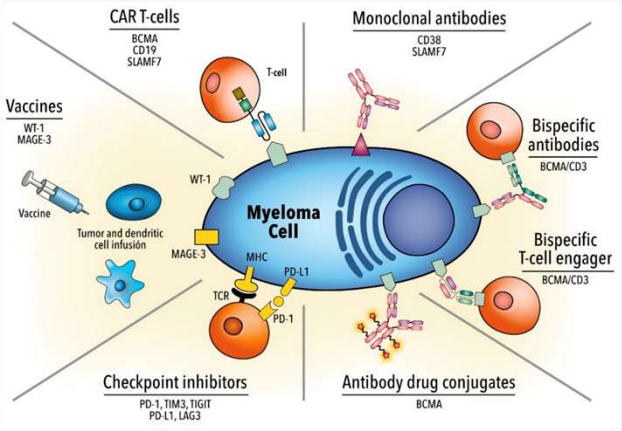
Focus on Immunotherapy

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



Rodriguez-Lobato L, et al. ASH 2021.

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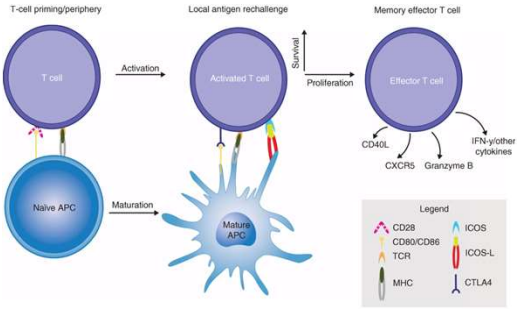
Antibody drug conjugate: belantamab mafodotin plus ICOS-agonist feladilimab

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



Nooka, et al. FutOnc 2021.

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

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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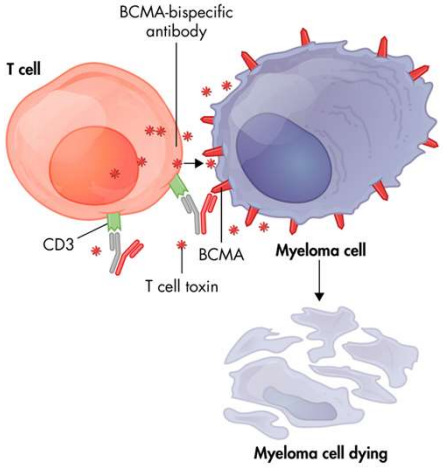
Bispecific antibodies and T-cell engagers

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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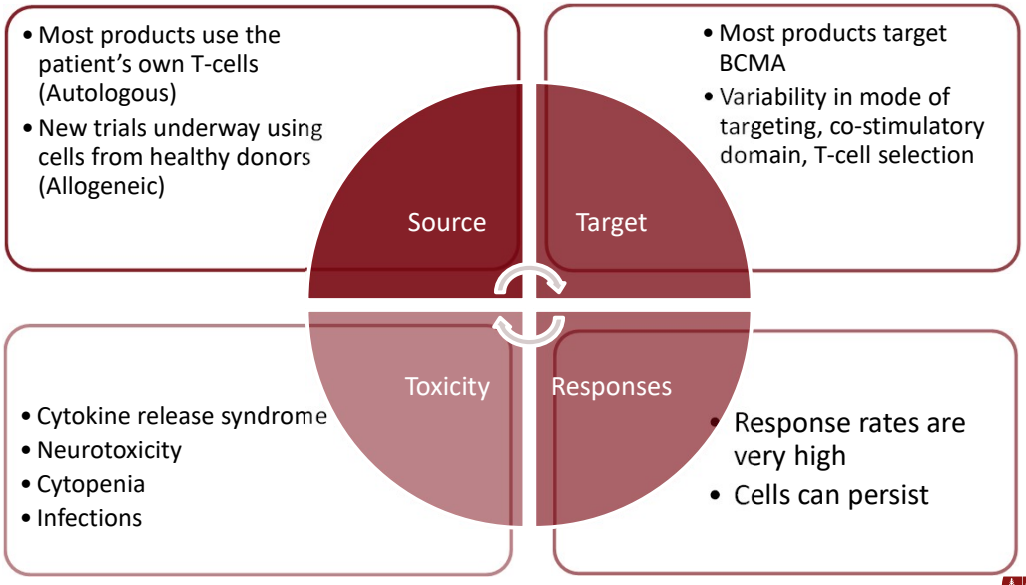
CAR T-cells at a glance



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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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Favor Bispecifics

Off the shelf (immediate use; wider access)	Long manufacturing time
Lower initial cost	Risk of production failure
Lower toxicity	High initial cost
Can interrupt therapy	Restricted to fit patients
Prolonged treatment	Prolonged B-cell aplasia
Duration of response unclear	'One-and-done'
	Longer term experience

Favor CAR-T

Adapted from Patel et al, BJH 2021

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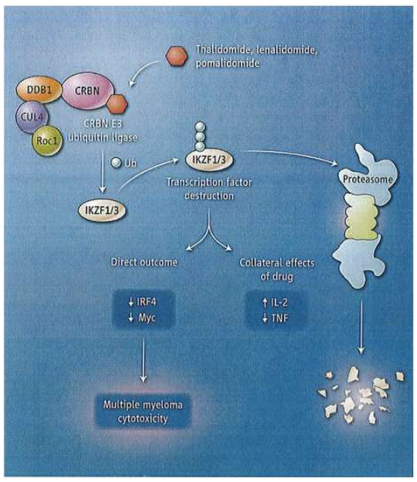
Cereblon E3 ligase modulator (CELMoD): Iberdomide

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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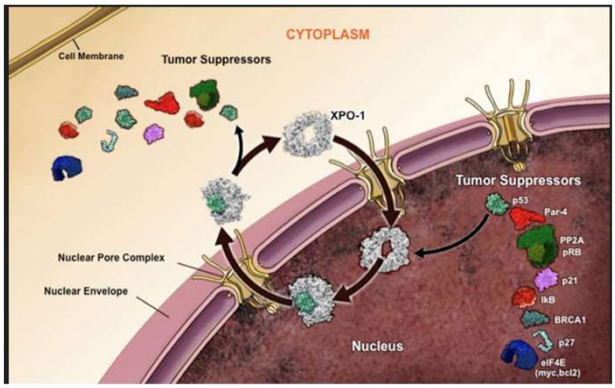
Selinexor in Relapsed/Refractory Multiple Myeloma

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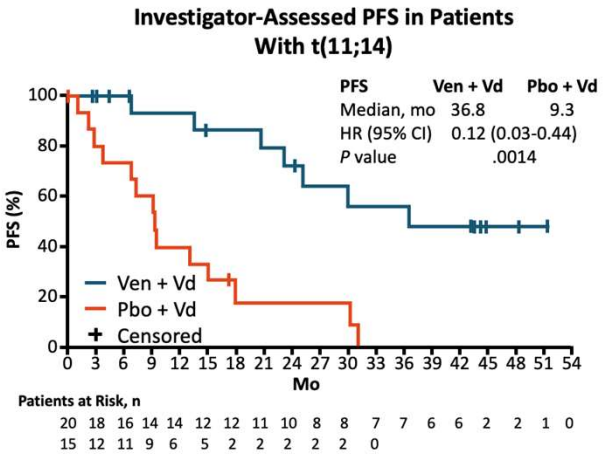
Precision Medicine: Venetoclax for Myeloma with t(11;14)

- 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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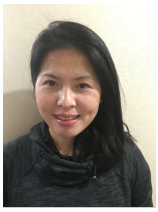
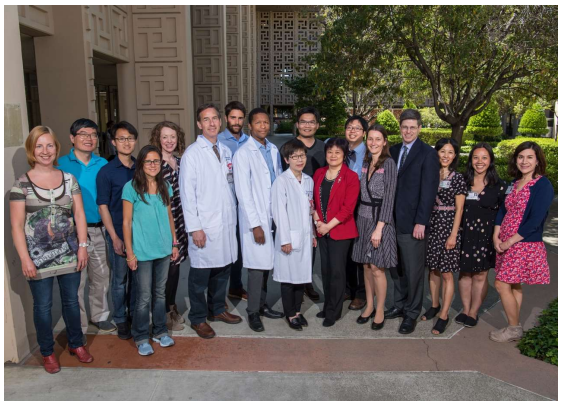
Stanford Myeloma and Amyloid Team



Ren Inthasack

Donirene Ward

Dave Iberri



Surbhi Sidana

Sally Arai

David Kurtz

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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

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
May 21, 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 and ALL
  - Learn about upfront strategies in chronic leukemias, including CML and CLL

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.

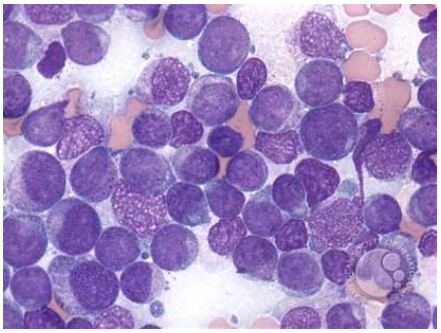
What is this patient's ELN 2017 risk?

How should we treat this patient?

4

Acute Myeloid Leukemia

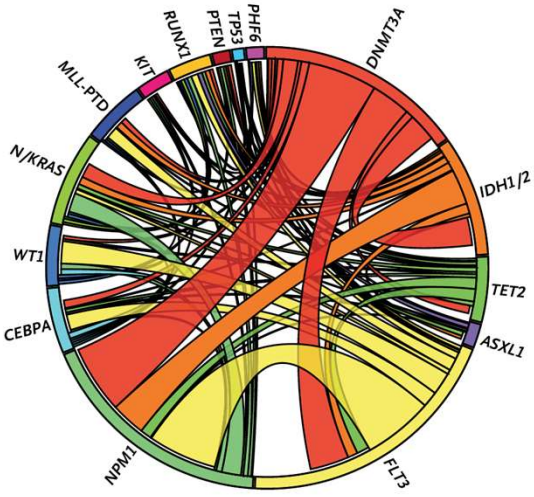
- Clonal expansion of immature myeloid cells
- Heterogeneous disease
- 20,050 new cases (M>F) with 11,540 deaths expected in US in 2022
- Median age 68
- Bleeding, infections, anemia
- High relapse rates



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

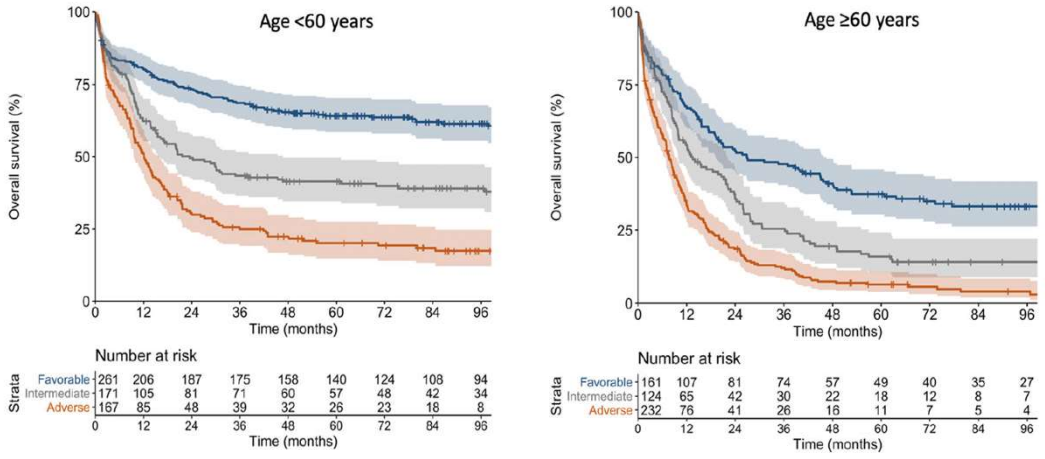
ELN 2017 Risk Stratification

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

7

ELN 2017 Risk Stratification - Validation



Herold et al, Leukemia 2020

8

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.

9

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 ≤50%
3. Documented pulmonary disease with DLCO ≤65% or FEV1 ≤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 ≥3 not related to leukemia
9. Any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy

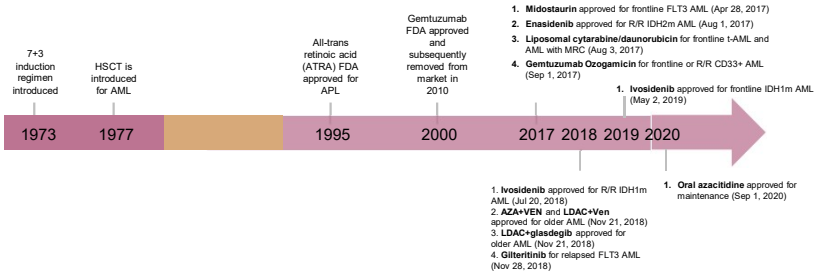
Abbreviations: AML, acute myeloid leukemia; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; FEV1, forced expiratory volume in 1 s.

Ferrara et al, Leukemia 2013.

10

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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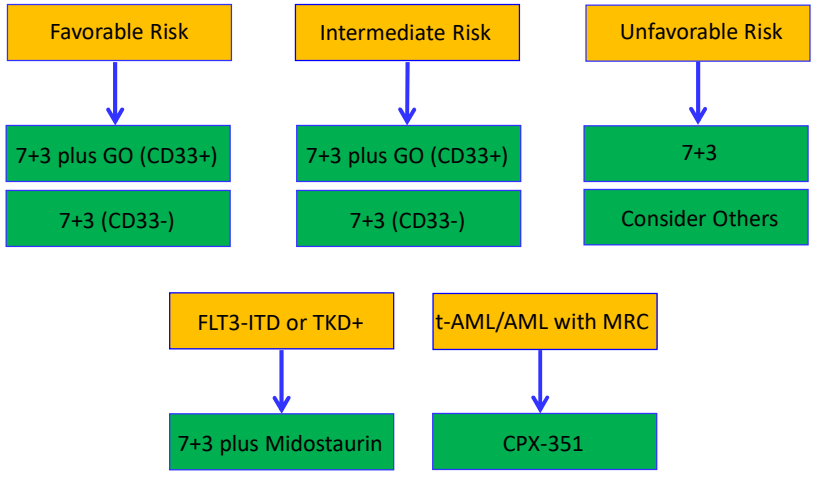
First-Line Treatment of Fit AML in 2022



Based on NCCN guidelines, AML v1.2022

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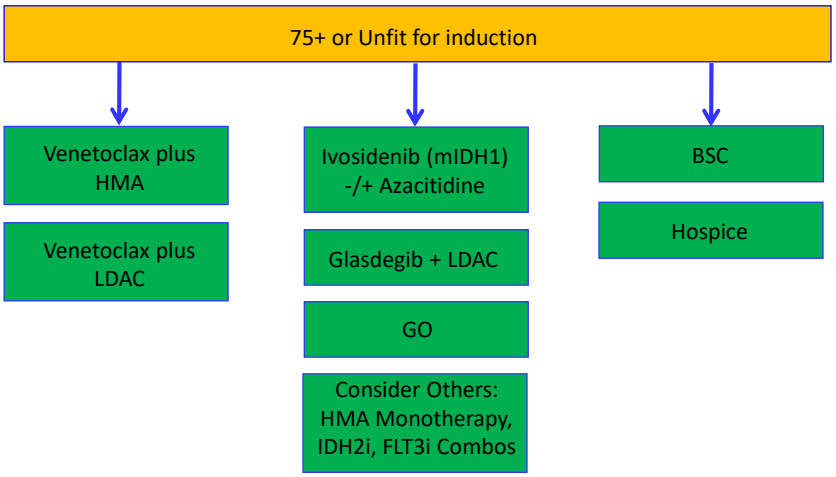
First-Line Treatment of Older/UnFit AML in 2022



Based on NCCN guidelines, AML v1.2022

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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?

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VIALE-A: Azacitidine plus Venetoclax vs Aza-PBO

Eligibility

Inclusion
- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ❖ ≥75 years of age
  - ❖ 18 to 74 years of age with at least one of the co-morbidities:
    - – CHF requiring treatment or Ejection Fraction ≤50%
    - – Chronic stable angina
    - – DLCO ≤ 65% or FEV1 ≤ 65%
    - – ECOG 2 or 3

Exclusion
- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

*Prior MPN excluded

Treatment

Randomization 2:1 N=431*

- **Venetoclax + Azacitidine (N=286)**: Venetoclax 400 mg PO, daily, days 1–28 + Azacitidine 75 mg/m² SC /IV days 1–7
- **Placebo + Azacitidine (N=145)**: Placebo daily, days 1–28 + Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary
- Overall survival

Secondary
- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors: Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region

Venetoclax dosing ramp-up: **Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg; **Cycle 2** → Day 1-28: 400 mg

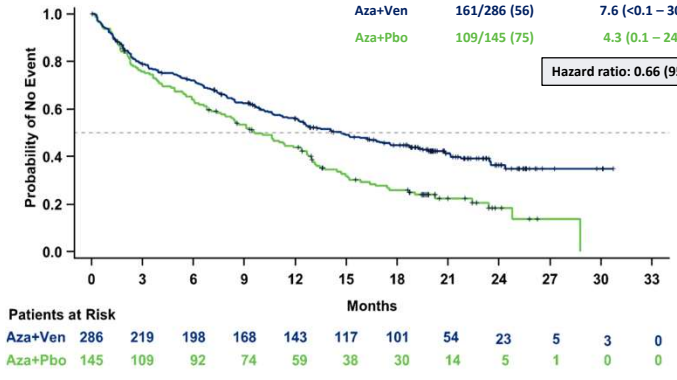
DiNardo et al, NEJM 2020.

15

Aza-Ven vs Aza-PBO: OS

	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), p<0.001



Patients at Risk												
Aza+Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza+Pbo	145	109	92	74	59	38	30	14	5	1	0	0

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

DiNardo et al, NEJM 2020.

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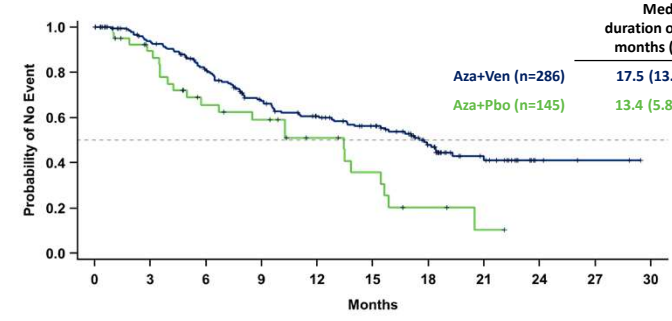
Aza-Ven vs Aza-PBO: DoR after CR/CRi



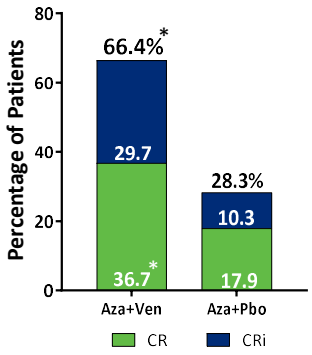
	Median duration of CR/CRi, months (95% CI)	Median duration of CR, months (95% CI)
Aza+Ven (n=286)	17.5 (13.6 – NE)	17.5 (15.3 – NE)
Aza+Pbo (n=145)	13.4 (5.8 – 15.5)	13.3 (8.5 – 17.6)

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

DiNardo et al, NEJM 2020.

17

Aza-Ven vs Aza-PBO: Responses



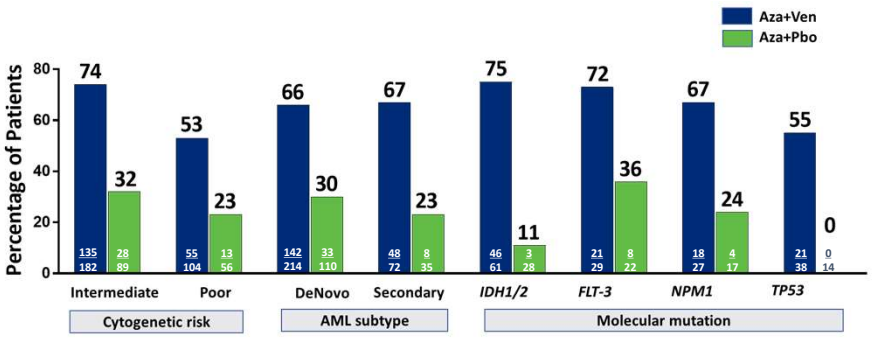
	No. of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR+CRi by initiation of Cycle 2, n (%)
Aza+Ven (n=286)	7.0 (1.0 – 30.0)	1.3 (0.6 – 9.9)	124 (43.4)
Aza+Pbo (n=145)	4.5 (1.0 –26.0)	2.8 (0.8 – 13.2)	11 (7.6)

*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.

18

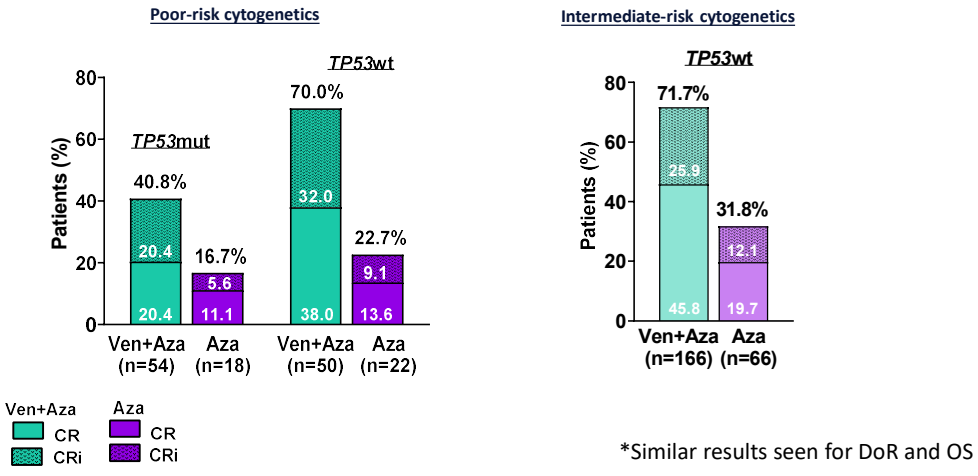
Aza-Ven vs Aza-PBO: Responses by Subgroup



DiNardo et al, NEJM 2020.

19

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.

20

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?

21

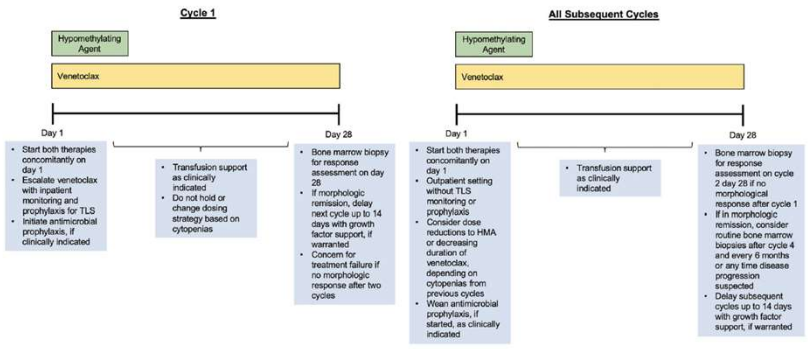
Leukemia
https://doi.org/10.1038/s41375-019-0612-8

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

Adverse events^, n (%)	Aza+Ven All grade* n=283	Aza+Ven Grade 3/4** n=276	Aza+Pbo All grade* n =144	Aza+Pbo 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.

23

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

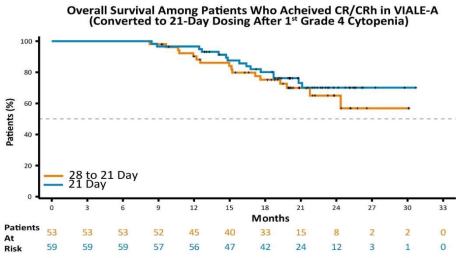
*Dose interruptions commonly due to neutropenia (19%/10%), febrile neutropenia (20%/4%), and thrombocytopenia (10%/4%); interruptions include delays between cycles and reduced duration from 28 to 21 days per cycle for count recovery after marrow leukemia clearance; †Dose reduction for AEs or other medications;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

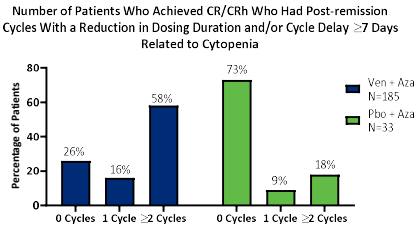
DiNardo, Jonas, Pullarkat et al, EHA 2020 Abstract# LB2601.
DiNardo, Jonas, Pullarkat et al, NEJM 2020.

24

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)

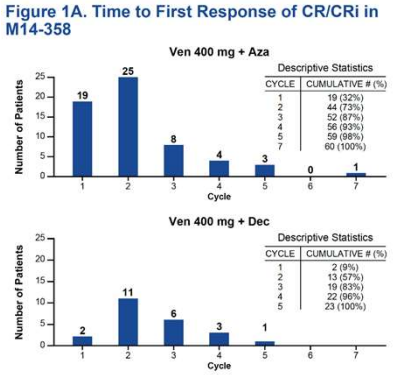


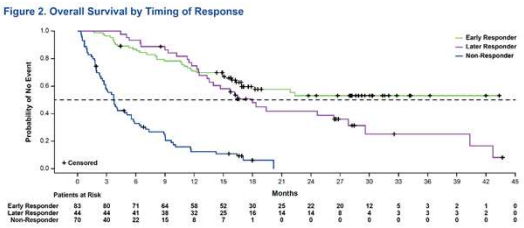


Pratz et al, ASH 2020, Abstract 1944.

25

Timing of Response to HMA-Ven



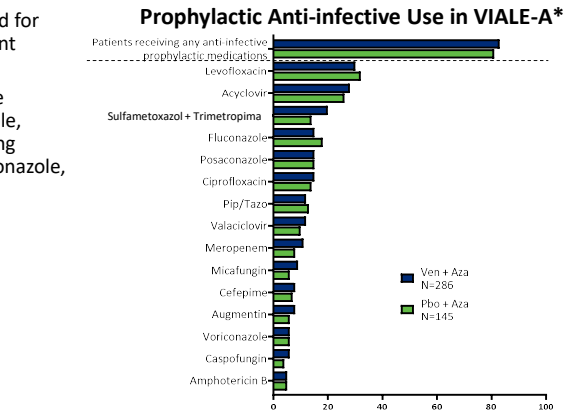


Jonas et al, ASCO 2020.

26

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

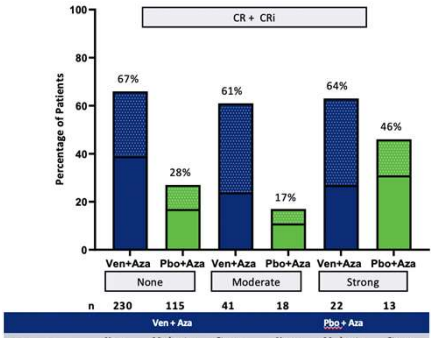


*Medications listed were used in ≥ 5% of patients receiving anti-infective prophylaxis (list not exclusive to CYP3A inhibitors).

Jonas et al, ASH 2020, Abstract 2846.

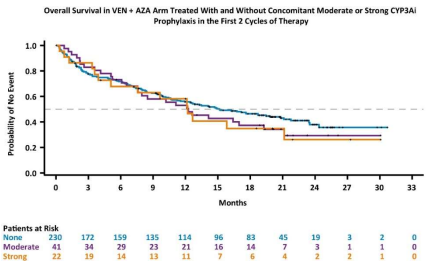
27

Use of CYP3A4i on the VIALE-A Trial



n	230	115	41	18	22	13
	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



Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) (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.

28

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.

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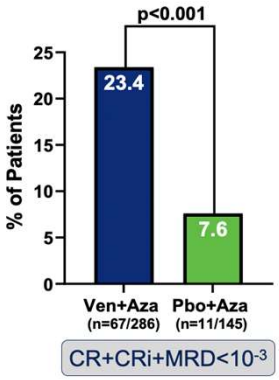
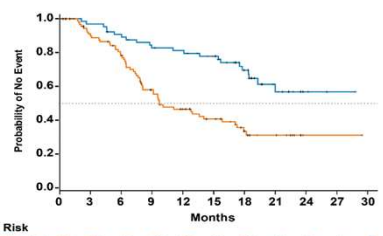
VIALE-A Trial: MRD Response, DoR and OS

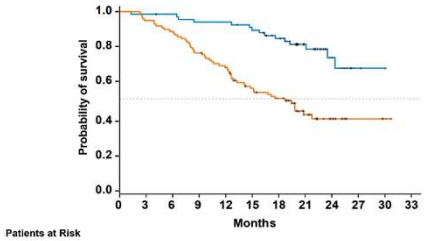




Patients at Risk

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

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)



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

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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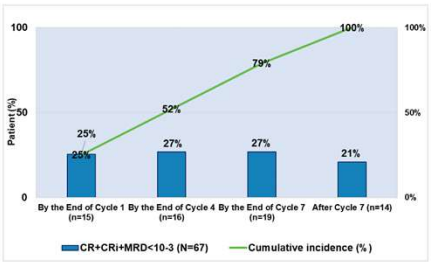
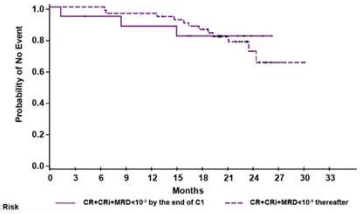
VIALE-A Trial: Timing of MRD Response and OS

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



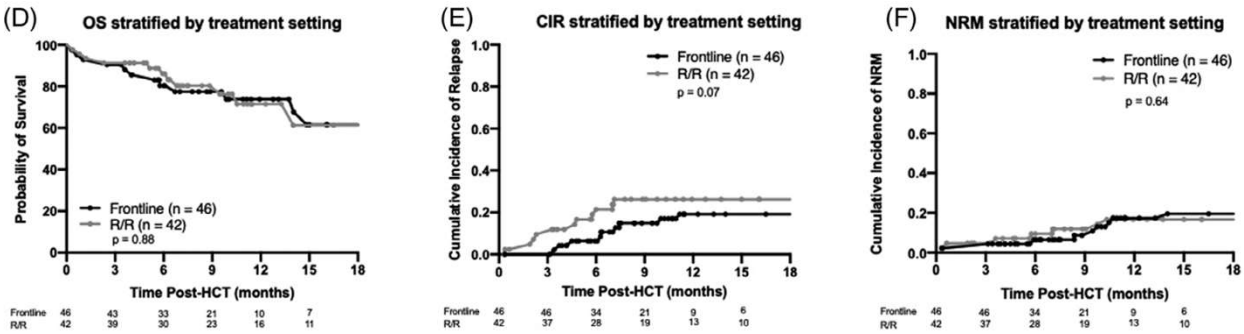
Overall survival	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median OS, months (95% CI)
CR+CRi+MRD<10^{-3} by end of cycle 1	3	87.8 (59.5, 96.8)	81.6 (53.0, 93.7)	NR (NR – NR)
CR+CRi+MRD<10^{-3} thereafter	12	96.0 (84.9, 99.0)	85.8 (72.5, 93.0)	NR (24.4 – NR)

NR: Not reached; OS: Overall survival

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

31

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.

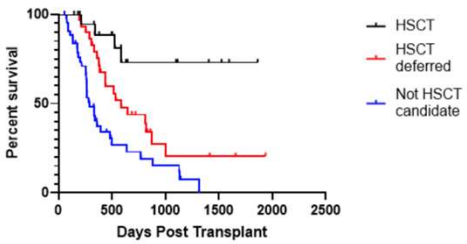
32

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

Figure 1: Overall survival



Pollyea et al, ASH 2020, Abstract 78.

33

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?

34

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)

Patients with untreated AML (WHO criteria); centrally confirmed *IDH1* mutation status; ineligible for IC; ECOG PS 0-2 (planned N = 200)

→ **Ivosidenib** 500 mg PO QD + **Azacitidine** 75 mg/m² SC or IV (n = 72)*

→ **Placebo** PO QD + **Azacitidine** 75 mg/m² SC or IV (n = 74)*

*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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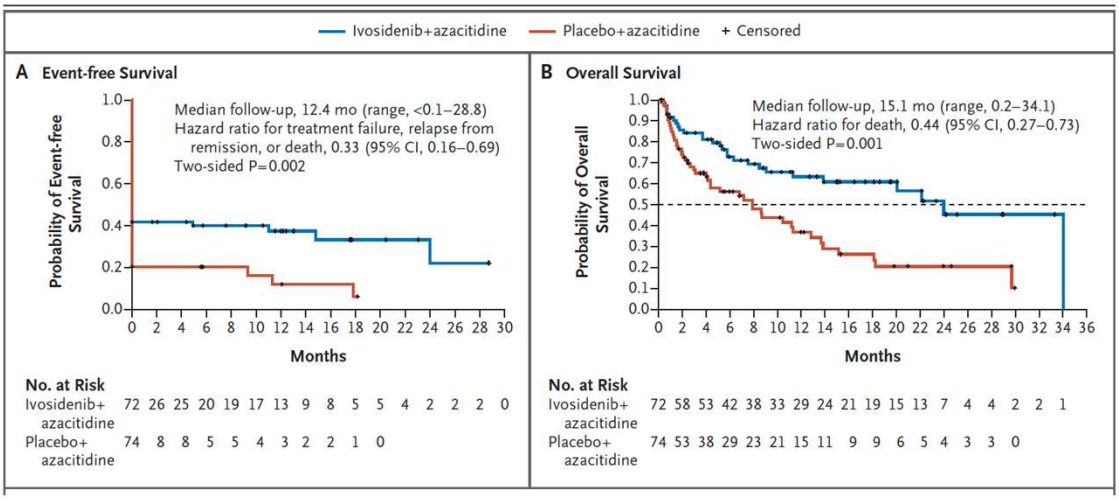
AGILE: OS and EFS



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?

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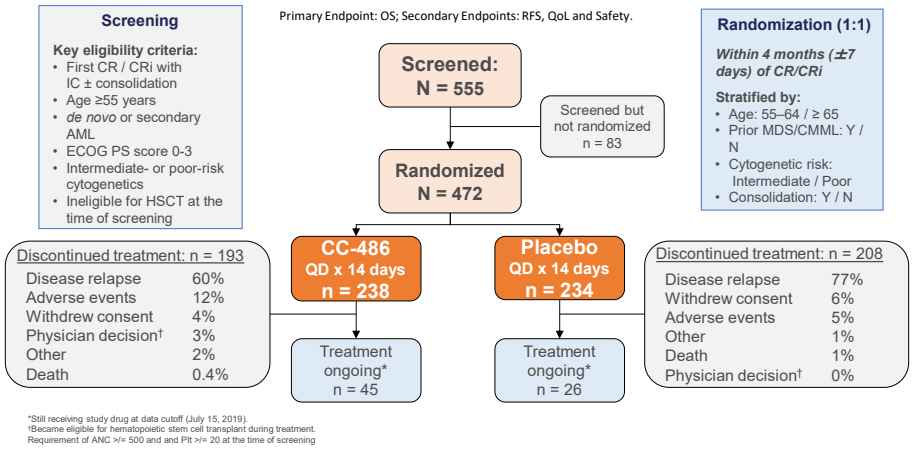
QUAZAR AML-001 Maintenance Trial CC-486 (Oral Azacitidine)

Patient DISPOSITION / SCHEMA



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

40

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.

	CC-486 n = 236		Placebo n = 233	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Preferred term	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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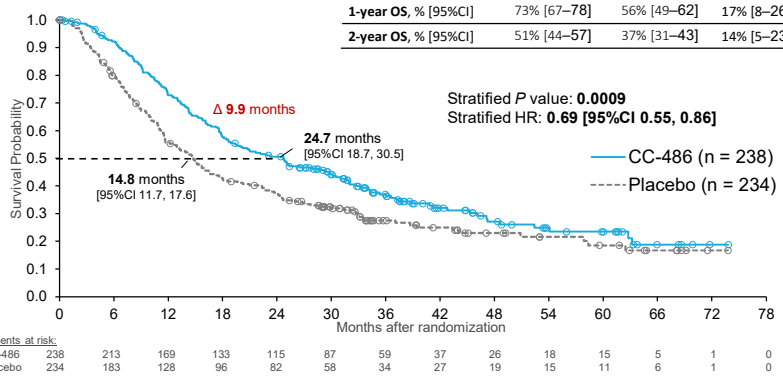
QUAZAR Trial – Primary Endpoint OS

- 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]



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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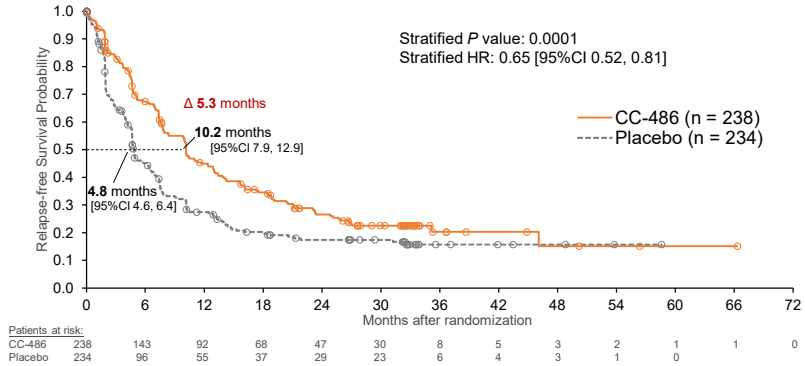
QUAZAR Trial – Secondary Endpoint RFS



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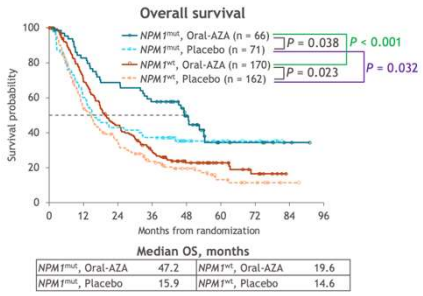
QUAZAR AML-001 Trial: Effects of NPM1 and FLT3-ITD mutations

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).

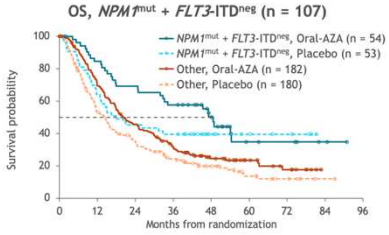
Presence of *FLT3*-ITD at Dx had a negative prognostic influence, as suggested by differences in OS results in the PBO arm

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)



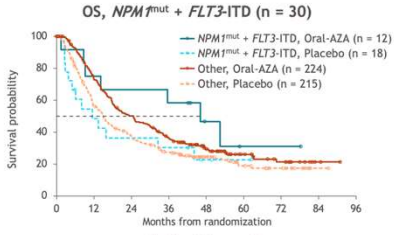
Median OS, months

NPM1^{mut}, Oral-AZA	47.2	*NPM1*^{wt}, Oral-AZA	19.6
NPM1^{mut}, Placebo	15.9	*NPM1*^{wt}, Placebo	14.6



Median OS, months

NPM1^{mut} *FLT3-ITD*^{neg}, Oral-AZA	48.6	Other, Oral-AZA	20.2
NPM1^{mut} *FLT3-ITD*^{neg}, Placebo	18.0	Other, Placebo	14.6



Median OS, months

NPM1^{mut} *FLT3*-ITD, Oral-AZA	46.1	Other, Oral-AZA	24.7
NPM1^{mut} *FLT3*-ITD, Placebo	11.5	Other, Placebo	14.9

Döhner et al, EHA 2021. Abstr S131.

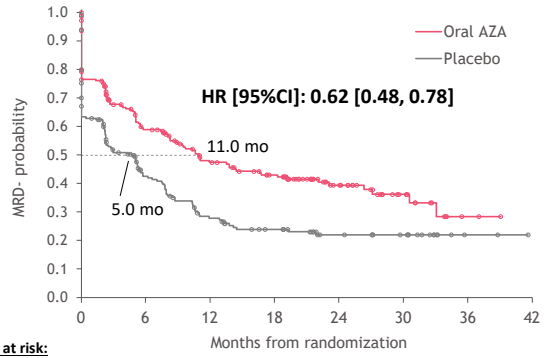
45

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?

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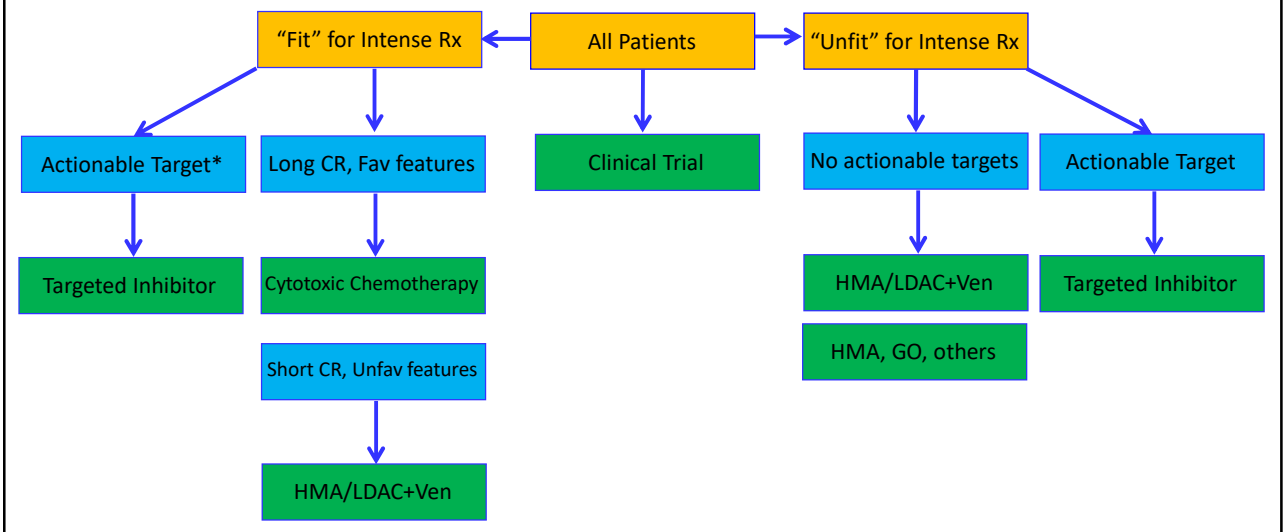
Current Options for the Treatment of r/r AML



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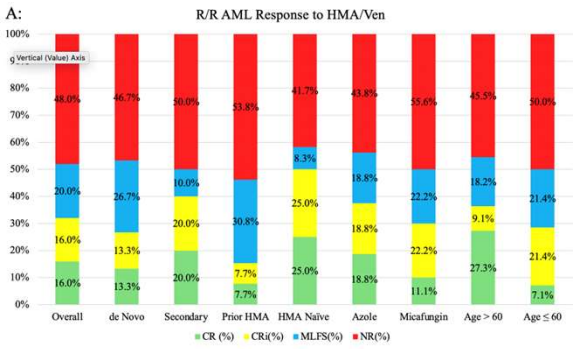
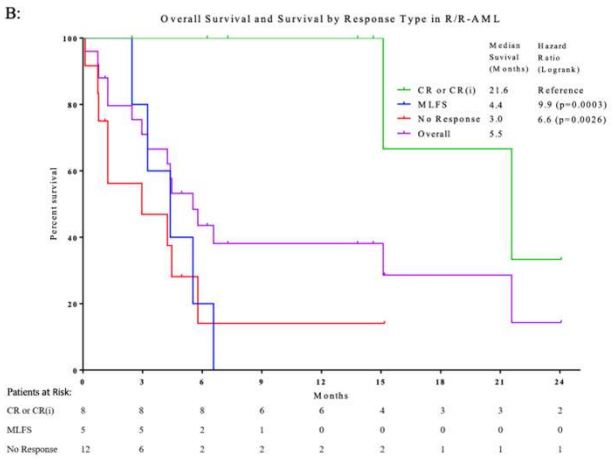
HMA plus Venetoclax in r/r AML

- 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.

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

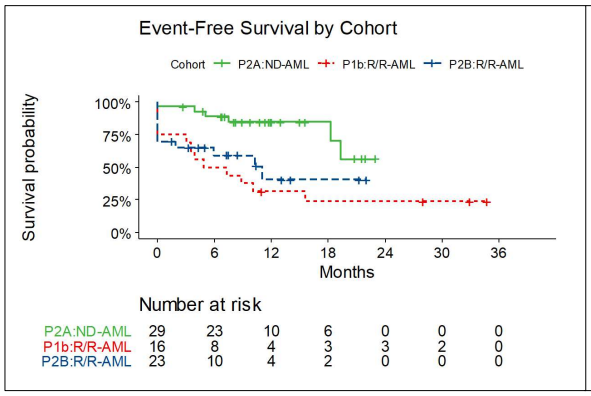
Parameter	All (N=68)	Phase 2A ND-AML (N=29)	R/R-AML (N=39)	Phase Ib R/R-AML (N=16)	Phase 2B R/R-AML (N=23)
Overall Response	56 (82%)	28 (97%)	28 (72%)	12 (75%)	16 (70%)
Composite CR	52 (76%)	26 (90%)	26 (67%)	12 (75%)	14 (61%)
CR	37	20	17	6	11
CRh	10	5	5	2	3
CRi	5	1	4	4	-
MRD negative (FC)	43 (83%)	25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

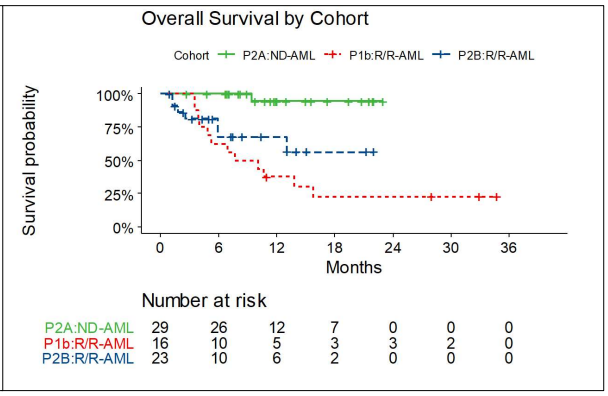
Composite CR (CRc): Complete response + Complete response with partial hematologic recovery (CRh: ANC ≥ 500 and platelet count ≥ 50,000) + Complete response with incomplete hematologic recovery (CRi: ANC ≥ 1000 or platelet count ≥ 100,000); Morphologic Leukemia Free State (MLFS: Bone marrow blasts <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

DiNardo et al, JCO 2021 and ASH 2020.

50

FLAG-Ida-Ven: EFS and OS





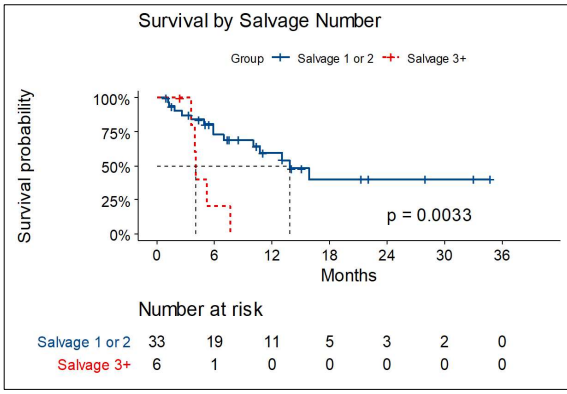
12mo OS 68% P2B

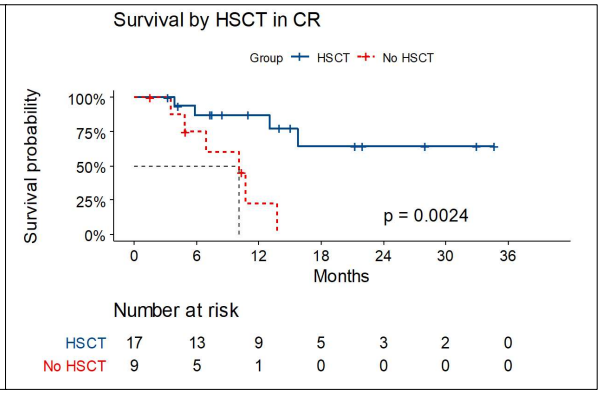
UCD FLAG	Present study	42	52	CR + CRi, 62 (CR, 47.6)	10	12	24.6	1-51	38.1% at 12 months

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

51

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



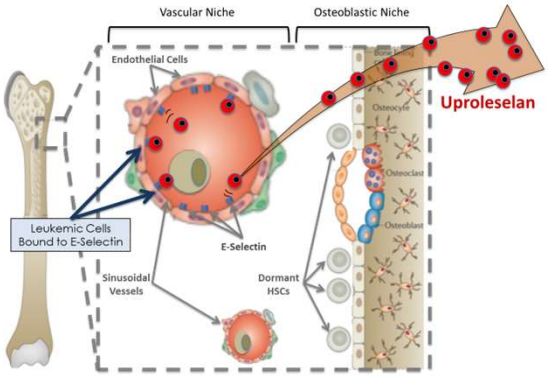


46% bridged to allo-HCT
12mo OS 87%

DiNardo et al, JCO 2021 and ASH 2020.

52

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.

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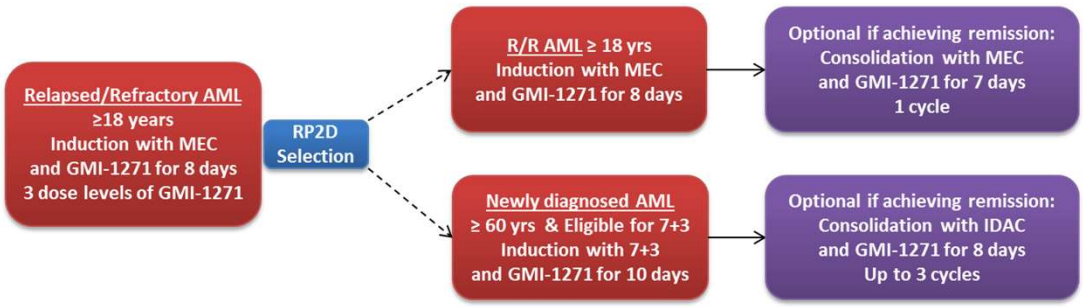
Phase 1/2 Uproleselan Study Schema



DeAngelo et al, Blood 2022.

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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)	
Duration of prior remission <6 mos	6/19 (32)	
Duration of prior remission ≥ 24mos	6/7 (86)	

RR RP2D Cohort:
MRD Evaluable n=13
Negative 9 (69%)

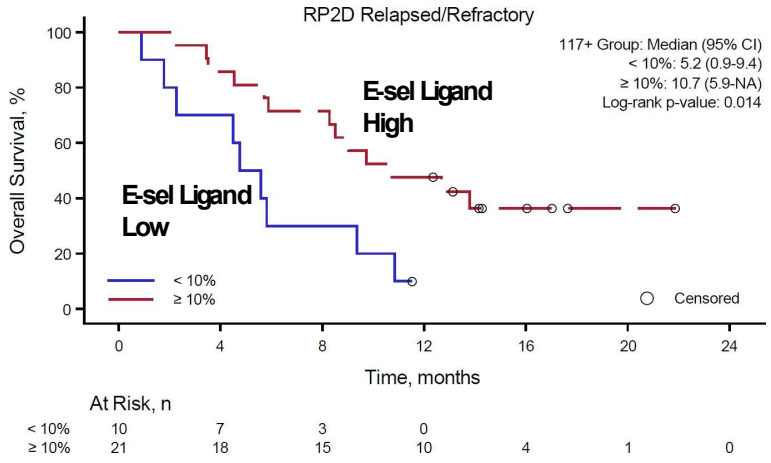
G3 mucositis with Uproleselan+ MEC in rel/ref cohort ~2 %

DeAngelo et al, Blood 2022.

55

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.

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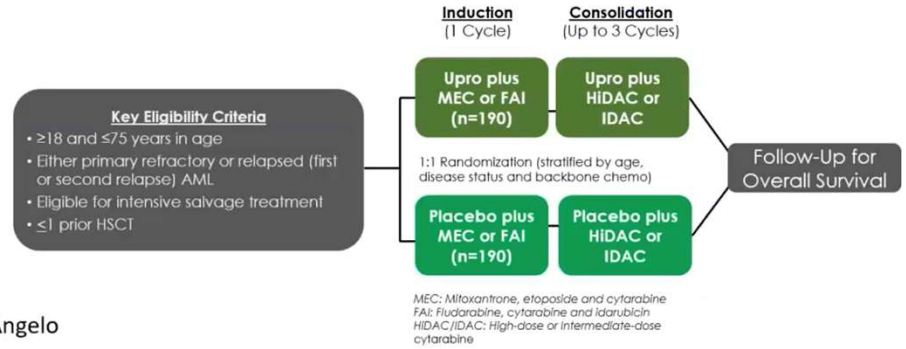
Phase 3 Study of Uproleselan in r/r AML

NCT#03616470



PI: DeAngelo

Primary Endpoint: OS

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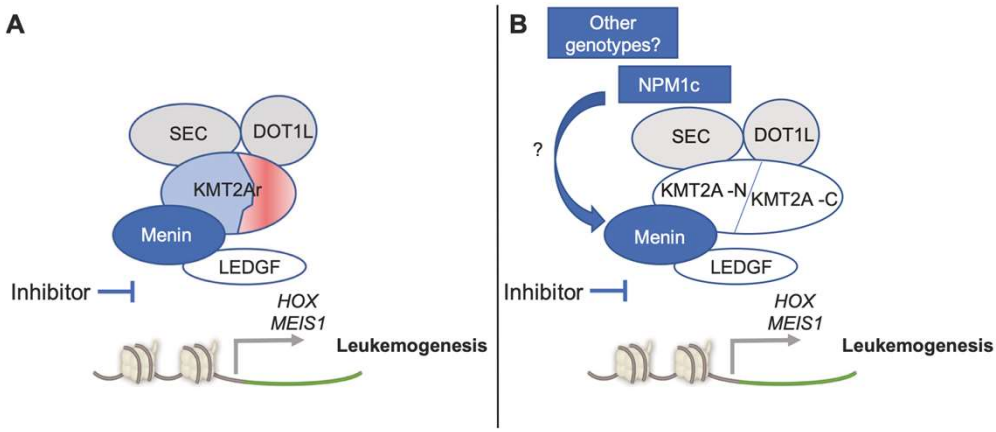
Menin Inhibition for AML with MLL Rearrangements and NPM1c Mutations



Issa et al, Leukemia 2021.

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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.

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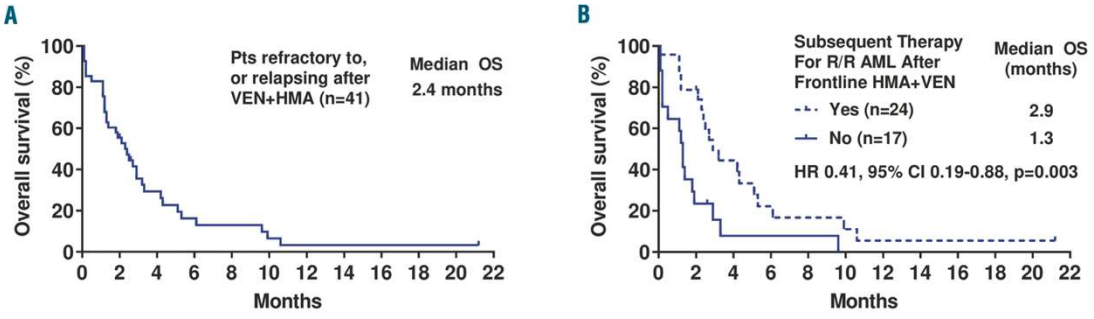
R/R AML after Ven-HMA has Very Poor Outcomes



- **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.

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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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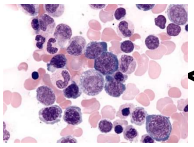
Treatment Approaches in MDS



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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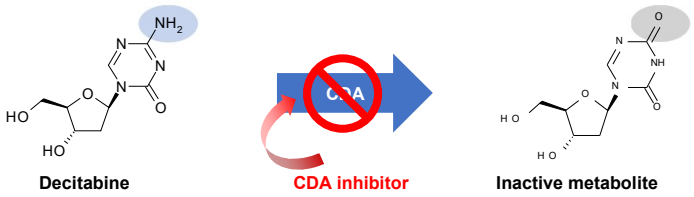
Oral Decitabine + Cedazuridine (DEC-C)

- 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



- 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/m^2 human equivalent)

CDA, cytidine deaminase.

Savona et al. Lancet Hematogy 2019.

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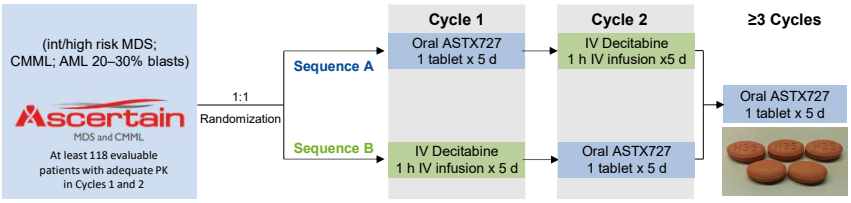
ASTX727-02 trial of DEC-C in MDS/CMML: Randomized Cross-Over Trial



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_{0-24} (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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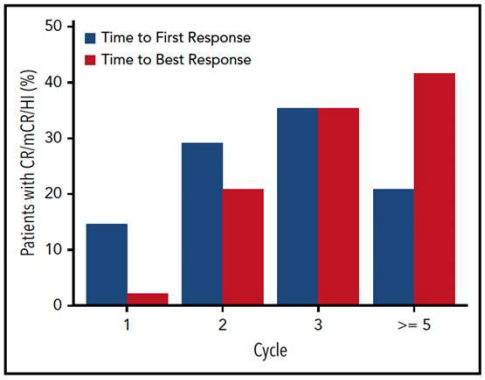
ASTX727-01-B: DEC-C Responses in MDS/CMML

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.

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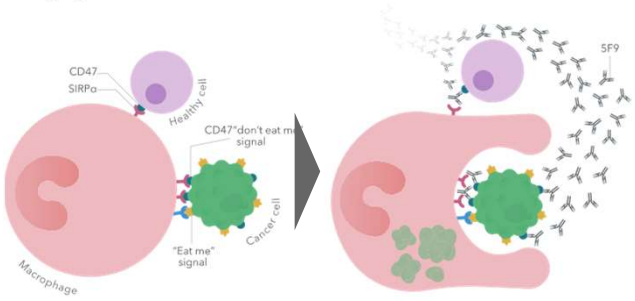
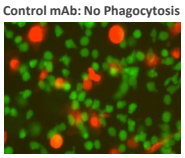
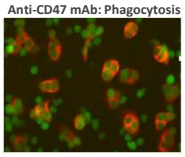
Magrolimab for MDS and AML: MOA

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







Macrophages Cancer cells

- 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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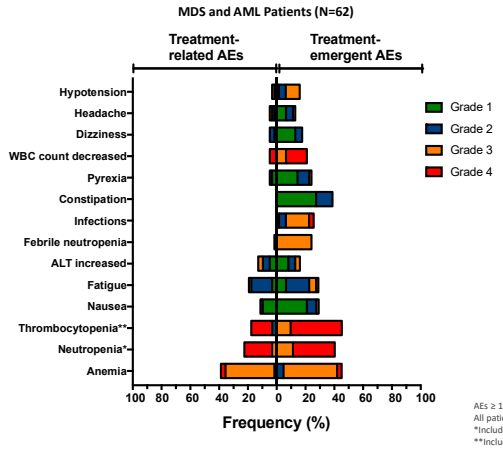
Magrolimab for MDS and AML: Safety



- No MTD was reached; magrolimab+AZA profile consistent with AZA monotherapy
- No significant cytopenias, infections, or autoimmune AEs were observed (most patients 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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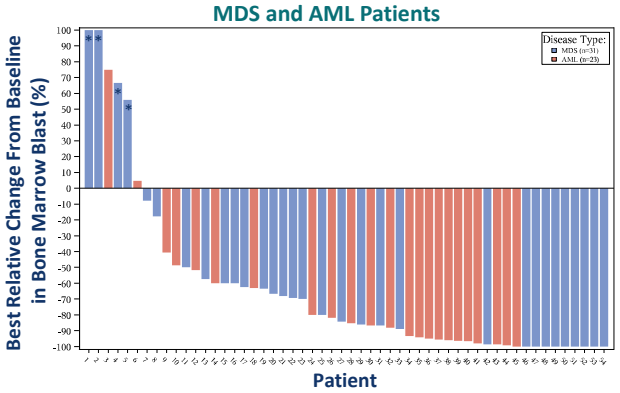
Magrolimab for MDS and AML: Activity

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

69

Coming Soon 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.

70

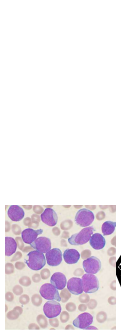
Case 7

A 35-year-old woman is diagnosed with B-cell ALL after presenting with fatigue and bruising. She has no other medical history. CBC shows WBC 40, Hgb 6, Plt 30, and 85% circulating B-lymphoblasts. BMBx shows 90% B-lymphoblasts expressing CD19 and CD22 but negative for CD20. Cytogenetics, FISH and molecular studies are pending.

Which treatment regimen do we recommend to this patient?

71

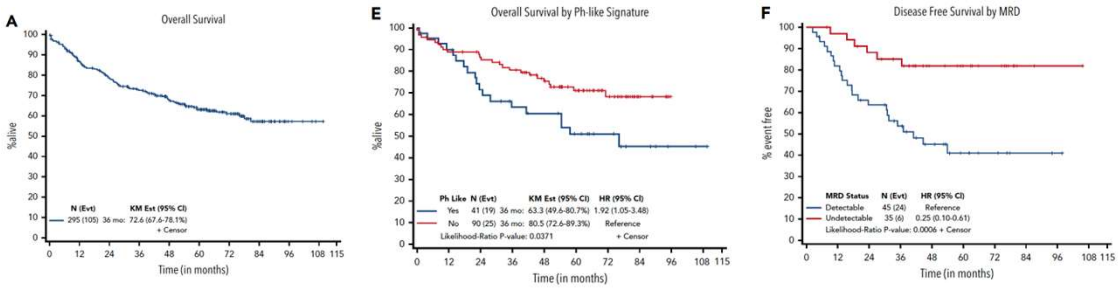
Current Upfront Treatment Approach for ALL



Based on NCCN Guidelines, ALL, v1.2022.

72

Pediatric-Inspired CALGB 10403 Regimen Outcomes

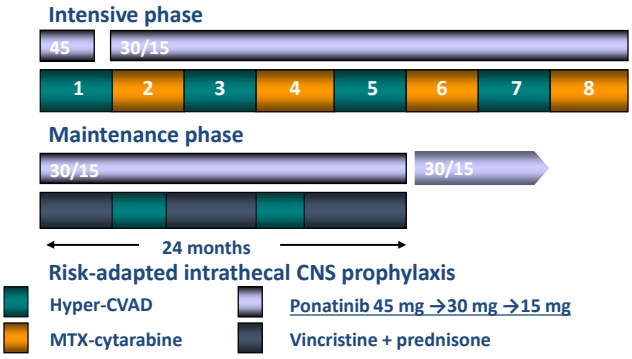


Age 18-40 (n=296)
Similar results for B- and T-cell disease (EFS, DFS, OS)
3% induction death rate
Obese pts did less well
Main toxicities were thrombosis and hyperbilirubinemia
Historically, Hyper-CVAD leads to ~40% 5yr OS
ASH 2020 update – dose reductions allow use in up to age 60

Stock et al. ASH 2014 Abstract# 796.
Stock et al. Blood 2019.
Patel et al. ASH 2020 Abstract# 2796.
Kantarjian et al. Cancer 2004.

73

(R)-Hyper-CVAD plus Ponatinib Regimen for Ph+ ALL



After the emergence of vascular toxicity, protocol was amended:
Beyond induction, ponatinib 30 mg daily, then 15 mg daily once in CMR

Current Hyper-CVAD+TKI regimens are using 12 doses of IT chemo (d2 and d7 cycles 1-6) for all patients and 8 doses of R (cycles 1-4) for CD20+ in 20% of blasts

ASH 2016 Abstract #757.
Rausch et al, Cancer 2020.

74

Outcomes of (R)-Hyper-CVAD plus Ponatinib for Ph+ ALL

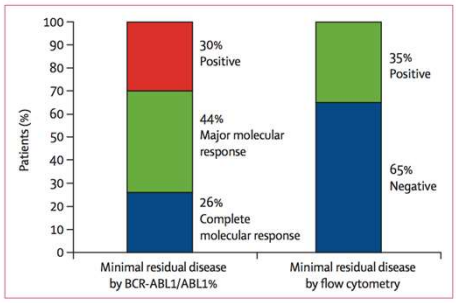


Figure 1: **Levels of residual disease after one cycle of protocol therapy in complete response**
Minimal residual disease after one cycle at complete remission by BCR-ABL1/ABL1 percentage and flow cytometry.

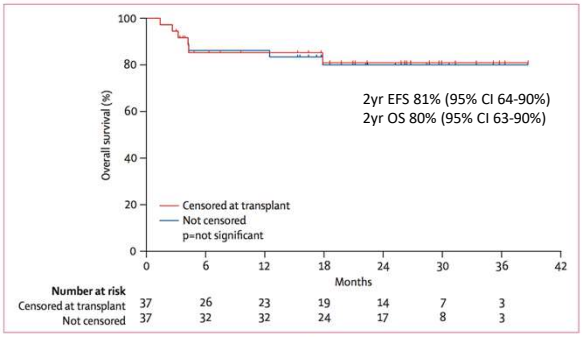


Figure 4: **Overall survival with and without censoring for allogeneic stem-cell transplantation**

Toxicities:
6 died in CR, 3 from MI
Infections, LFTs, Rash, pancreatitis

Jabbour et al Lancet Oncology 2015.

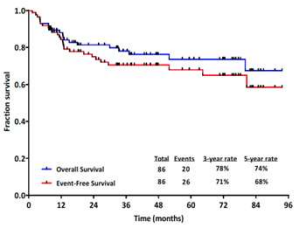
75

Updated Results of (R)-Hyper-CVAD plus Ponatinib for Ph+ ALL

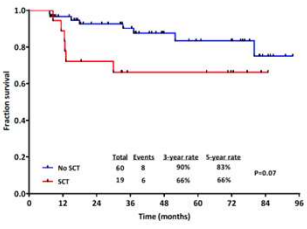
Response	n/N (%)
CR*	68/68 (100)
CCyR^	58/58 (100)
MMR#	80/85 (94)
CMR#	73/85 (86)
Flow negativity#	83/85 (95)
Early death	0

74% CMR at 3 months

EFS and OS



Impact of alloHCT: 6 month landmark



19 (22%) underwent Allo-HCT in CR1

3 relapses on ponatinib and no CNS relapses (12 IT ppx)
Toxicities– VTE (13%), Arterial CV events (7%), pancreatitis (15%), hyperbilirubinemia (15%), AST/ALT elevation (29%)
73% of VTE events at 45mg Pon; 67% of arterial CV events at 30-45mg Pon
No treatment related deaths after amendment of Pon dosing (2 prior)

Short et al. ASH 2019 Abstract #283.

76

Ponatinib plus Blinatumomab for Ph+ ALL

- Single arm P2 study at MDACC
- Newly diagnosed or relapsed/refractory Ph+ ALL
  - 28 treated (19 first line), median age 59 (25-83)
- Treatment:
  - Blinatumomab up to 5 cycles
  - Ponatinib 30mg daily during C1 then 15mg daily after CMR and for 5 years after blina completed
  - 12 doses of IT chemo ppx
- Outcomes:
  - 95% ORR (100% in ND cohort and 88% in R/R cohort)
  - Median time to CMR 1mo (1-13mo)
  - 1yr OS 94% and EFS 81% (1yr 100% OS and EFS in ND and 88% OS and 55% EFS in R/R)
  - No ND underwent allo-HCT; 4 (44%) of R/R pts underwent allo-HCT
- Safety: well-tolerated, no pts dc'd ponatinib due to toxicity, no early deaths in first 4 weeks
- Potentially effective, chemotherapy-free regimen

Short et al. ASCO 2021 Abstract #7001.

77

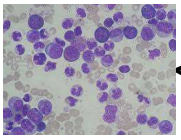
Case 8

A 44-year-old man is diagnosed with chronic phase CML after presenting with bone pain, abd pain and hyperleukocytosis. He has no other medical history. CBC showed WBC 249.6, Hgb 9.8, Plt 178, 1% eos, 1% basos, 1% blasts. Spleen palpable 12cm below the costal margin. BMBx confirms CP-CML. Molecular confirms expression of the p210 isoform. Sokal risk is intermediate.

Which TKI to we recommend for this patient?

78

Treatment Approach in CML



Diagnosis of CML CP

Low Risk
Sokal, Hasford, EUTOS

Non-low Risk

Primary Treatment

- Imatinib

or 2nd gen TKI
- Bosutinib
- Dasatinib
- Nilotinib

Also Consider:
- Comorbidities
- TKI Toxicity profile
- Potential DDI
- Pt preference

2nd gen TKI preferred
- Bosutinib
- Dasatinib
- Nilotinib

or
- Imatinib

Based on NCCN Guidelines, CML, v 3.2022.

79

Asciminib for CML

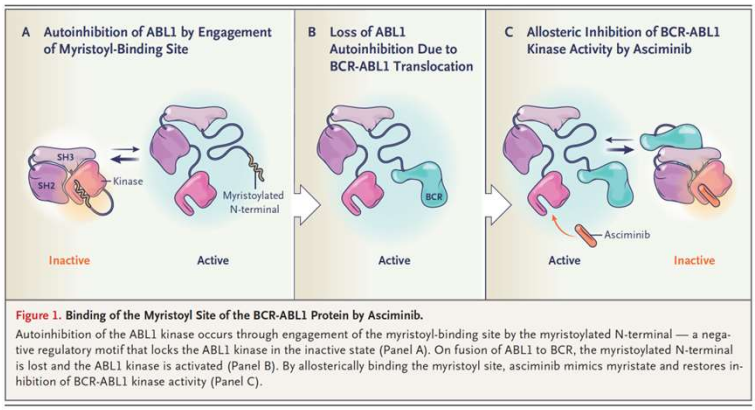


Figure 1. Binding of the Myristoyl Site of the BCR-ABL1 Protein by Asciminib.
Autoinhibition of the ABL1 kinase occurs through engagement of the myristoyl-binding site by the myristoylated N-terminal — a negative regulatory motif that locks the ABL1 kinase in the inactive state (Panel A). On fusion of ABL1 to BCR, the myristoylated N-terminal is lost and the ABL1 kinase is activated (Panel B). By allosterically binding the myristoyl site, asciminib mimics myristate and restores inhibition of BCR-ABL1 kinase activity (Panel C).

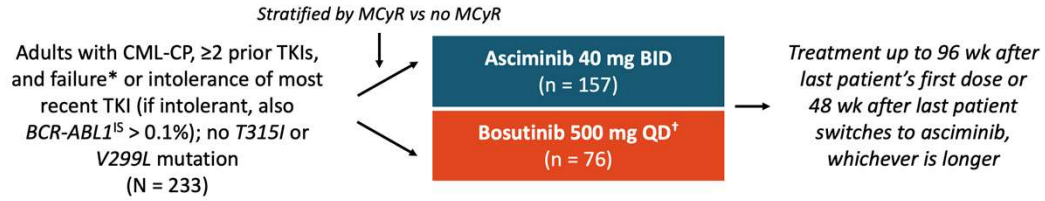
- FDA Approved 10/29/21 for R/R CML
- Active in heavily pretreated CML
- MMR 48% by 12mo overall
- Includes T315I and ponatinib failures
- Dose-limiting effects: asymptomatic lipase elevations and clinical pancreatitis
- Common AEs: fatigue, HA, arthralgia, HTN and thrombocytopenia.

Hughes et al, NEJM 2019.

80

ASCEMBL Trial: Asciminib vs Bosutinib

- Multicenter, open-label, randomized phase III trial (data cutoff: January 6, 2021)



Median follow-up: 19.2 mo. *Per 2013 ELN recommendations. †Switch to asciminib 40 mg BID allowed for treatment failure.

- Primary endpoint: MMR rate at Wk 24 (meeting no tx failure criteria before Wk 24)
- Secondary endpoints: MMR rate at Wk 96 (meeting no tx failure criteria before Wk 96), safety and tolerability, CCyR/MMR rates, time to and duration of CCyR/MMR, time to treatment failure, PFS, OS, and pharmacology parameters

Slide credit: clinicaloptions.com

Mauro et al, ASH 2021 Abstract #310.

81

ASCEMBL Trial: Asciminib vs Bosutinib

Outcome, %	Asciminib (n = 157)	Bosutinib (n = 76)	Common Treatment Difference,* % (95% CI)
MMR at Wk 48	29.3	13.2	16.1 (5.7-26.6)
▪ If used third line	30.5 (n/N = 25/82)	26.7 (n/N = 8/30)	
▪ If used fourth line	31.8 (n/N = 14/44)	6.9 (n/N = 2/29)	
▪ If used ≥ fifth line	22.6 (n/N = 7/31)	0 (n/N = 0/17)	
Outcome,† %	**Asciminib (n = 142)**	**Bosutinib (n = 72)**	**Treatment Difference**
BCR:ABL1IS ≤1%	42.3	19.4	22.9

*Adjusted for MCyR status at baseline. †Based on patients without this level of response at baseline.

Outcome	Asciminib (n = 157)	Bosutinib (n = 76)
Cumulative incidence of MMR at Wk 48, %	33.2	18.6
Probability of maintaining MMR for ≥48 wk, % (95% CI)	96.1 (85.4-99.0)	90.0 (47.3-98.5)
Maintained MMR at last assessment, n/N	60/62	17/18
Cumulative incidence of *BCR:ABL1IS ≤1%* at Wk 48, %	50.8	33.7

Slide credit: clinicaloptions.com

Mauro et al, ASH 2021 Abstract #310.

82

ASCEMBL Trial: Asciminib vs Bosutinib

AE, %	Asciminib (n = 156)		Bosutinib (n = 76)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	91.0	54.5	97.4	67.1
Fatal AEs	1.3	1.3	1.3	1.3
AEs leading to: Discontinuation*	7.1	6.4	25.0	18.4
Dose reduction	23.1		44.7	
Dose interruption	40.4		60.5	

*Included thrombocytopenia (3.2%), neutropenia (2.6%) with asciminib; increased ALT (5.3%) and neutropenia (3.9%) with bosutinib.

AEs Occurring in ≥20% of Patients, %	Asciminib (n = 156)	Bosutinib (n = 76)
Thrombocytopenia	29.5	19.7
Neutropenia	23.1	21.1
Diarrhea	11.5	71.1
Nausea	11.5	46.1
Rash	7.7	23.7
Vomiting	7.1	26.3
Increased ALT	3.8	28.9
Increased AST	5.1	21.1

- Median duration of exposure 15.4 mo for asciminib (range: 0-37.3), 6.8 mo for bosutinib (range: 0.2-34.3)

Arterial occlusive events: 7 with Asciminib vs 1 with Bosutinib

Slide credit: clinicaloptions.com

Mauro et al, ASH 2021 Abstract #310.

83

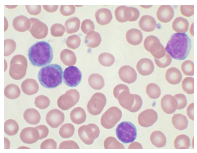
Case 9

A 59-year-old man is diagnosed with Rai Stage 1 CLL and followed with a watch and wait approach. Nearly 10 years later, he presents with progressive anemia and thrombocytopenia and treatment of his CLL is indicated. He has del(13q). He has no other medical history.

Which first line treatment do you recommend for this patient?

84

Initial Treatment Approach in CLL



Diagnosis of CLL requiring treatment

Without del(17p)/TP53

Preferred Primary Treatment

Older or frail pts
- Acalabrutinib -/+ Obinutuzumab
- Ibrutinib
- Venetoclax plus Obinutuzumab
- Zanubritinib

Younger pts
- Acalabrutinib -/+ Obinutuzumab
- Ibrutinib
- Venetoclax plus Obinutuzumab
- Zanubritinib

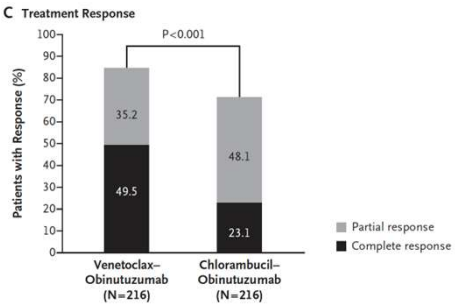
With del(17p)/TP53
- Acalabrutinib -/+ Obinutuzumab
- Ibrutinib
- Venetoclax plus Obinutuzumab
- Zanubritinib

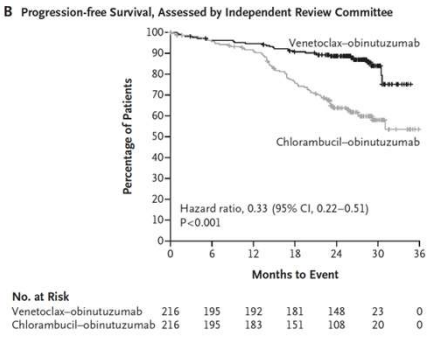
Based on NCCN Guidelines, CLL, v 2.2022.

85

Venetoclax plus Obinutuzumab for 1st Line CLL

CLL14 Trial
Ven-Obinu vs Chlorambucil-Obinu
- Fixed duration treatment
  - 12 x 28 d cycles
  - Obinu x 6 cycles
  - Ven C1D22 onwards
- Benefit also seen with TP53 and IgVH unmutated
- Nonsignificant increases in cytopenias and infections





Fischer et al, NEJM 2019.

86

Summary and Future Directions

- Exciting time for new treatments for leukemias 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

Lymphoma Update 2022

Bita Fakhri, MD, MPH
University of California, San Francisco

ANCO

Educating and Empowering the Northern California Cancer Community

Updates in Lymphoma

Bita Fakhri, MD, MPH
Assistant Professor, UCSF Medical Center

Outline

- Zuma7 – axi-cel vs SOC in 1st ref/early relapse
- Transform – liso-cel vs SOC in 1st ref/early relapse
- Belinda – tisa-cel vs SOC in 1st ref/early relapse
- Zuma5 – CART in FL, MZL
- BiTe Mosunetuzumab for FL
- BiTE Glofitamab for MCL
- Polarix
- Alliance (da-EPOCH-R+ven in DHL)

CLL

- Sequoia trial (zanu vs BR; zanu for 17p del; zanu + ven)
- Captivate, Vision and Glow trials (MRD-directed time-limited therapy ibr + ven)
- CLL13: FCR vs RVe vs OVe vs OIVe
- Pirtobrutinib
- MK-1206 (ARQ531)

Relapsed/Refractory Aggressive B-cell Lymphoma

- ~1/3 of pts with aggressive B-NHL
- Standard treatment is:
  - Salvage/2L chemo-immunotherapy
  - Autologous stem cell transplantation (ASCT) for chemosensitive pts
- ASCT cures about half of pts

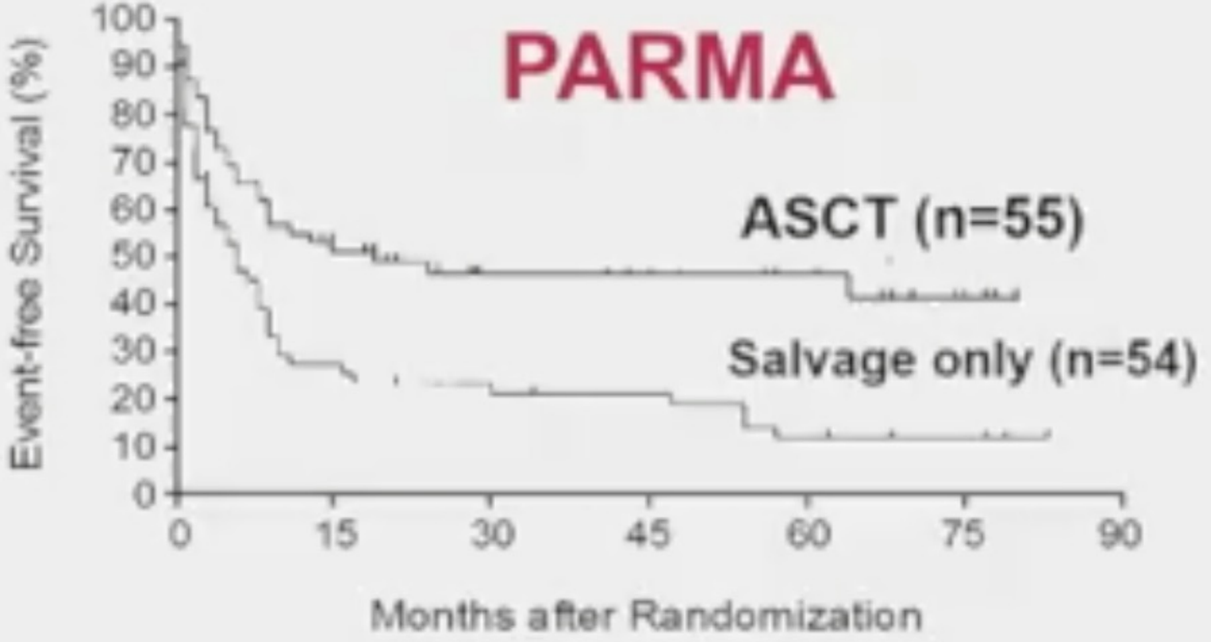

Figure 1. Kaplan–Meier Curves for Event-free Survival of Patients in the Transplantation and Conventional-Treatment Groups.

Philip et al. *NEJM*. 1995.

Relapsed/Refractory Aggressive B-cell Lymphoma

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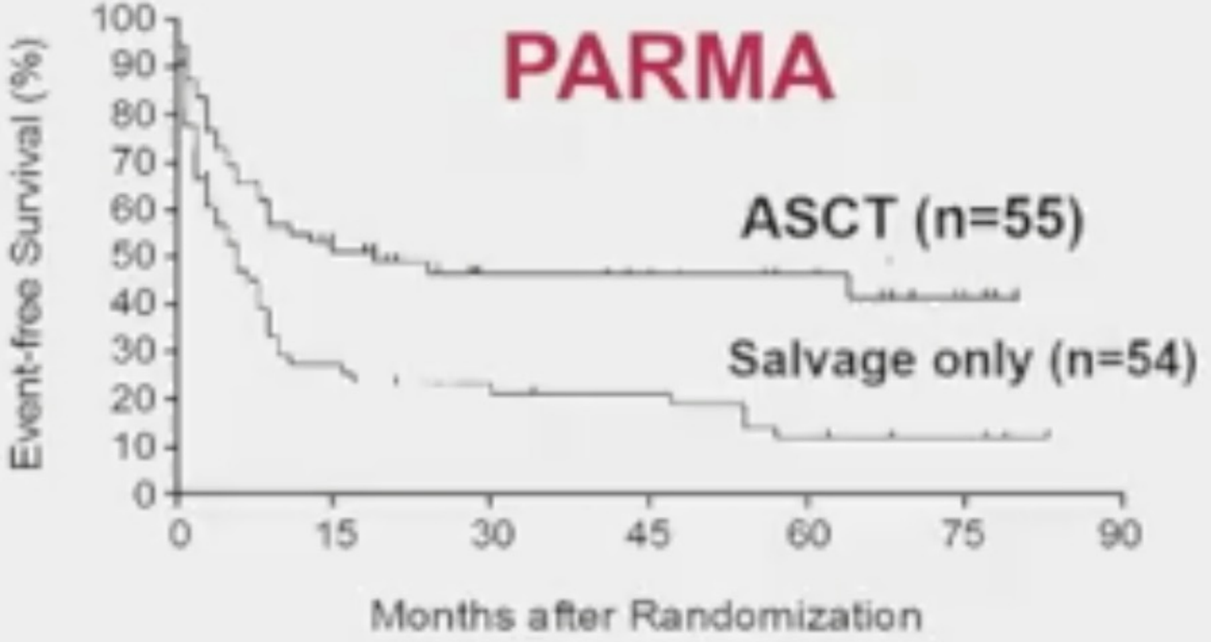


Figure 1. Kaplan–Meier Curves for Event-free Survival of Patients in the Transplantation and Conventional-Treatment Groups.

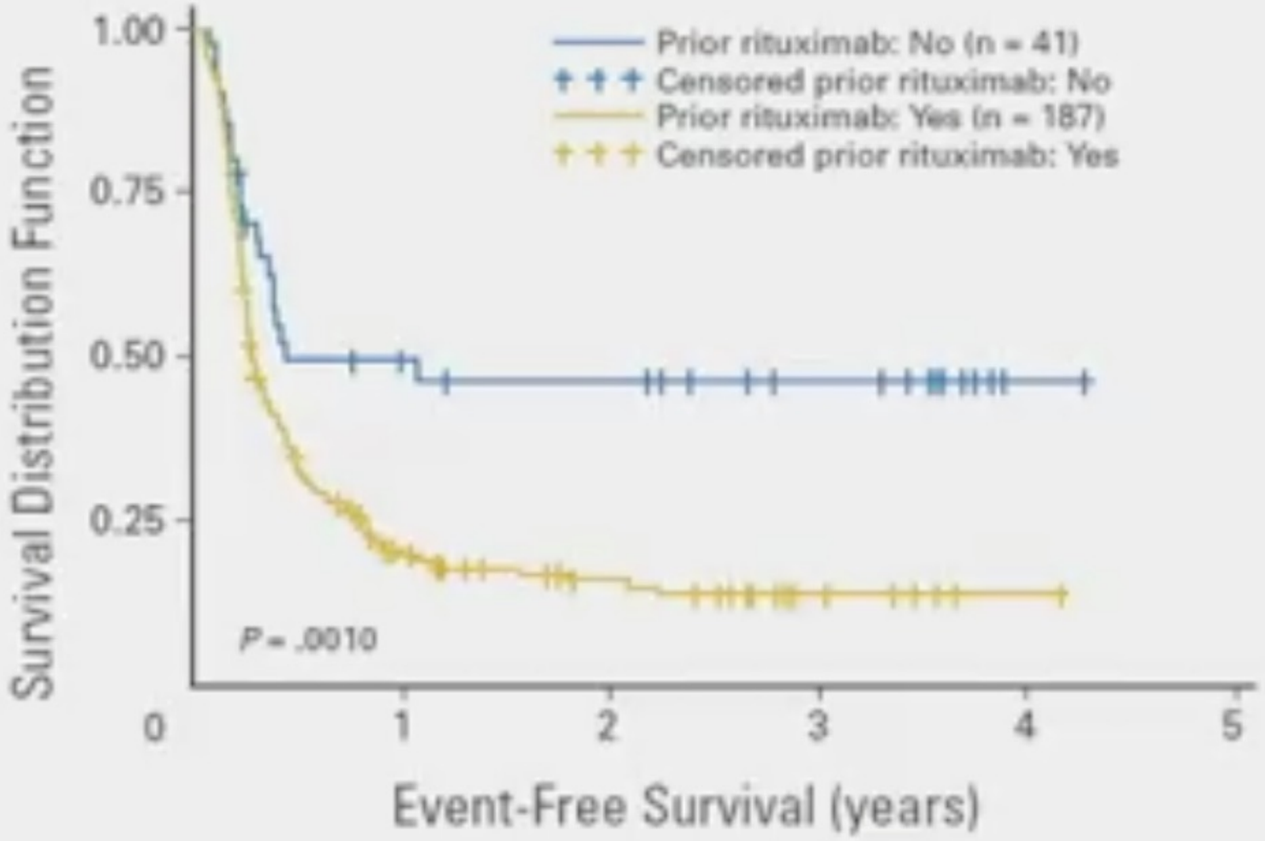
Philip et al. *NEJM*. 1995.

Early relapse after R-CHOP → dismal outcomes

1° refractory/early relapse after prior rituximab

- 2L salvage intent-to-transplant outcomes:
  - ORR 46%
  - 3y EFS 20%
  - 3y OS 39%

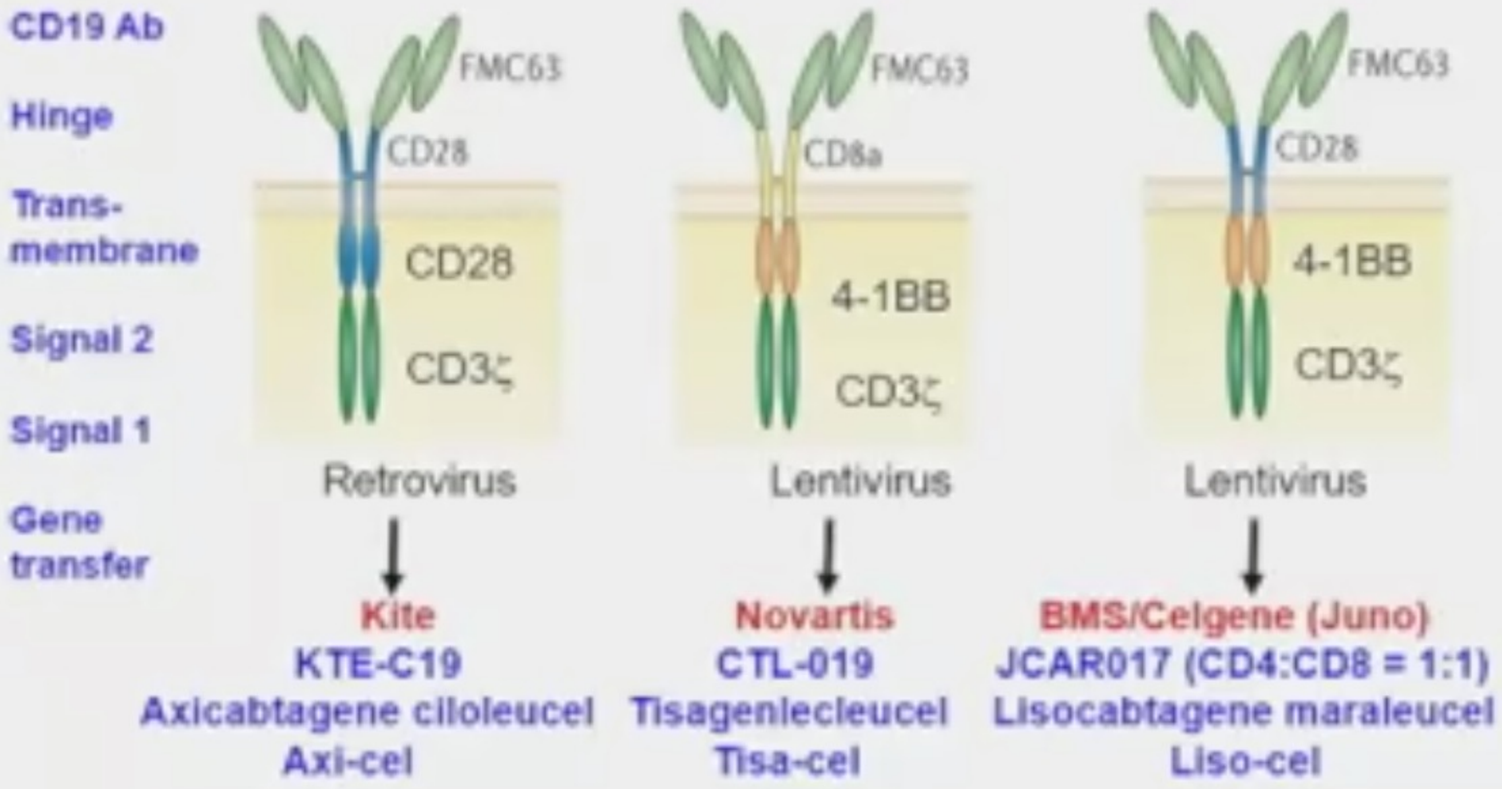
CORAL



Gisselbrecht et al. *JCO* 2010

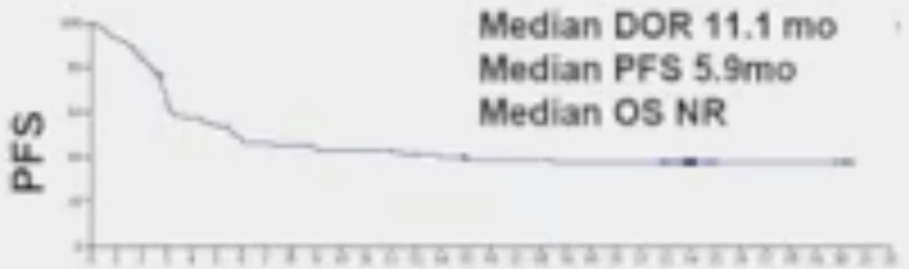
CD19 CAR T-cells: A New Hope?

30-40% durable response as 3L+



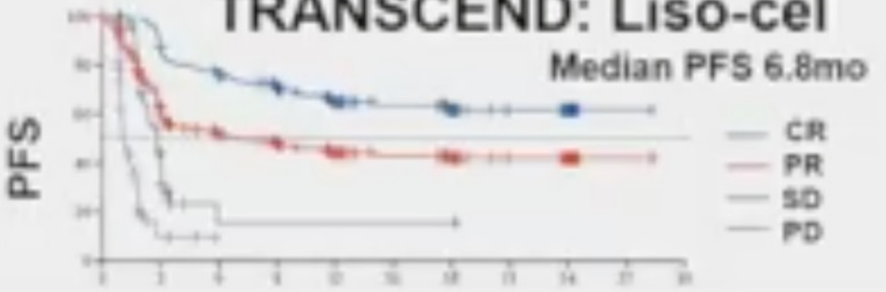
Adapted from van der Steegen et al. Nat Rev Drug Discov 2015

ZUMA-1: Axi-cel



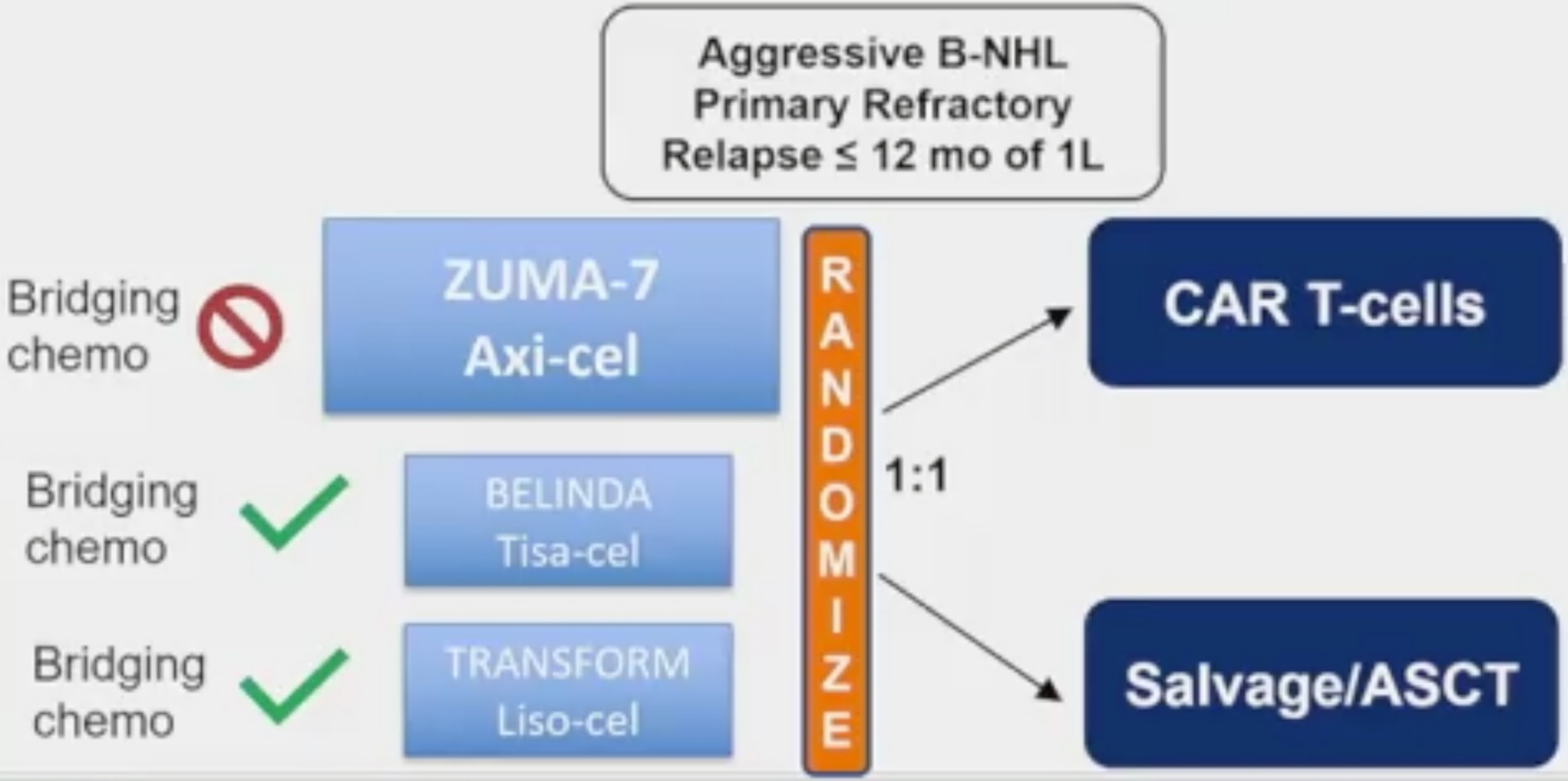
JULIET: Tisa-cel

TRANSCEND: Liso-cel



Locke FL, et al Lancet Oncol 2019. Schuster SJ, et al. Lancet Oncol 2021. Abramson JS, et al. Lancet 2020

ZUMA-7: Uncharted Territory



Primary Analysis of ZUMA-7: a Phase 3 Randomized Trial of Axicabtagene Ciloleucel versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma

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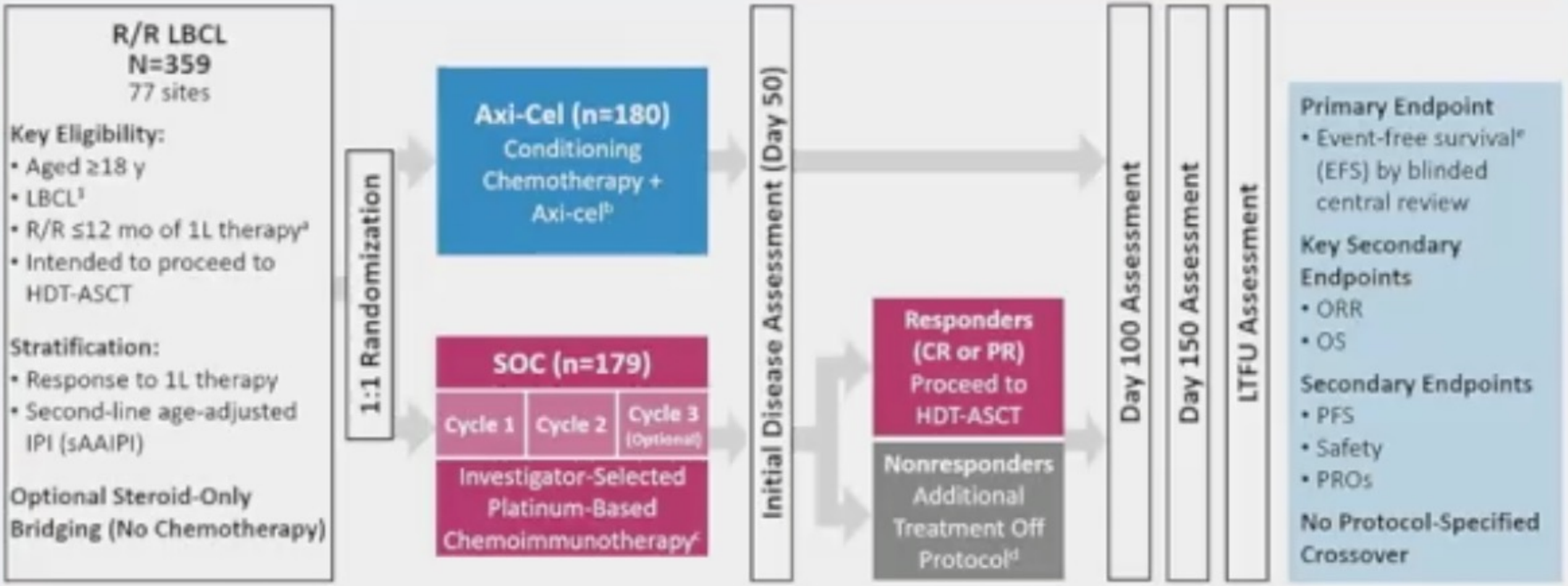
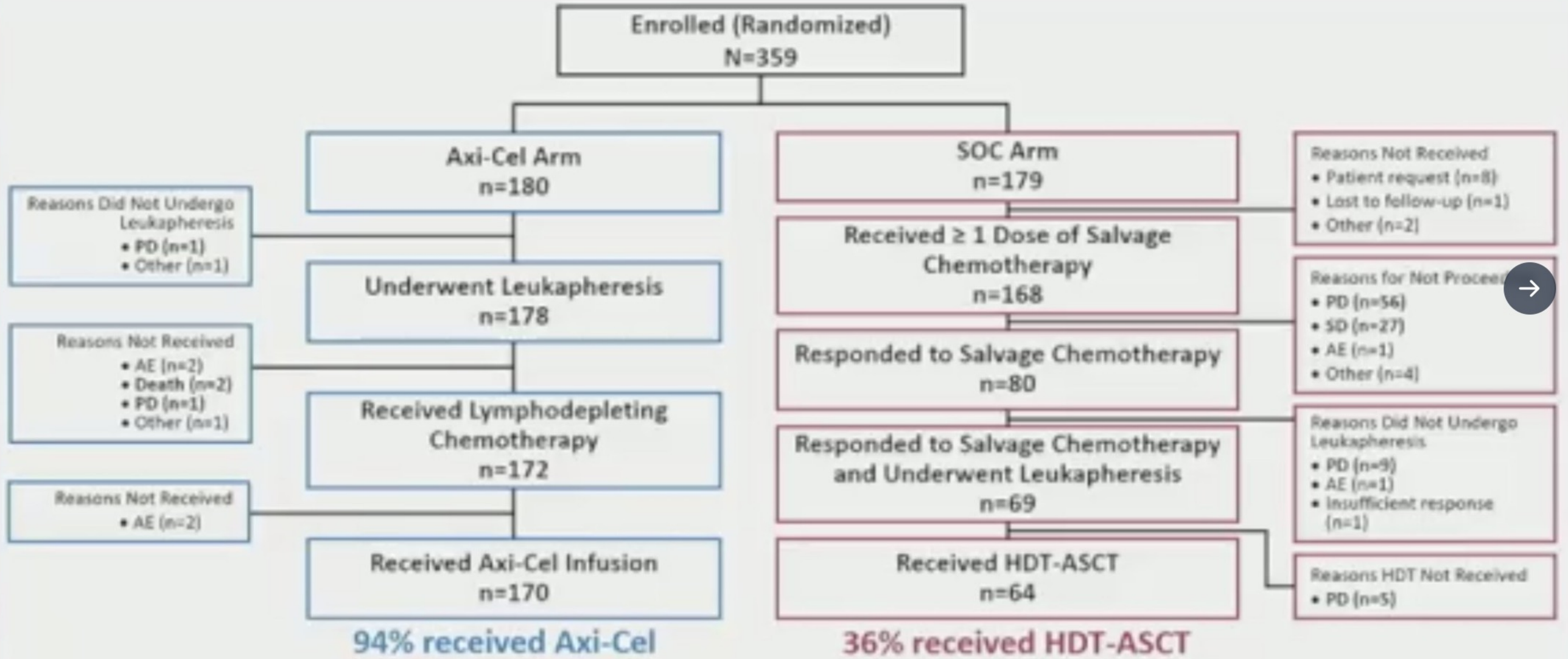
ZUMA-7 Study Schema and Endpoints: Axi-Cel Versus SOC as Second-Line Therapy in Patients With R/R LBCL



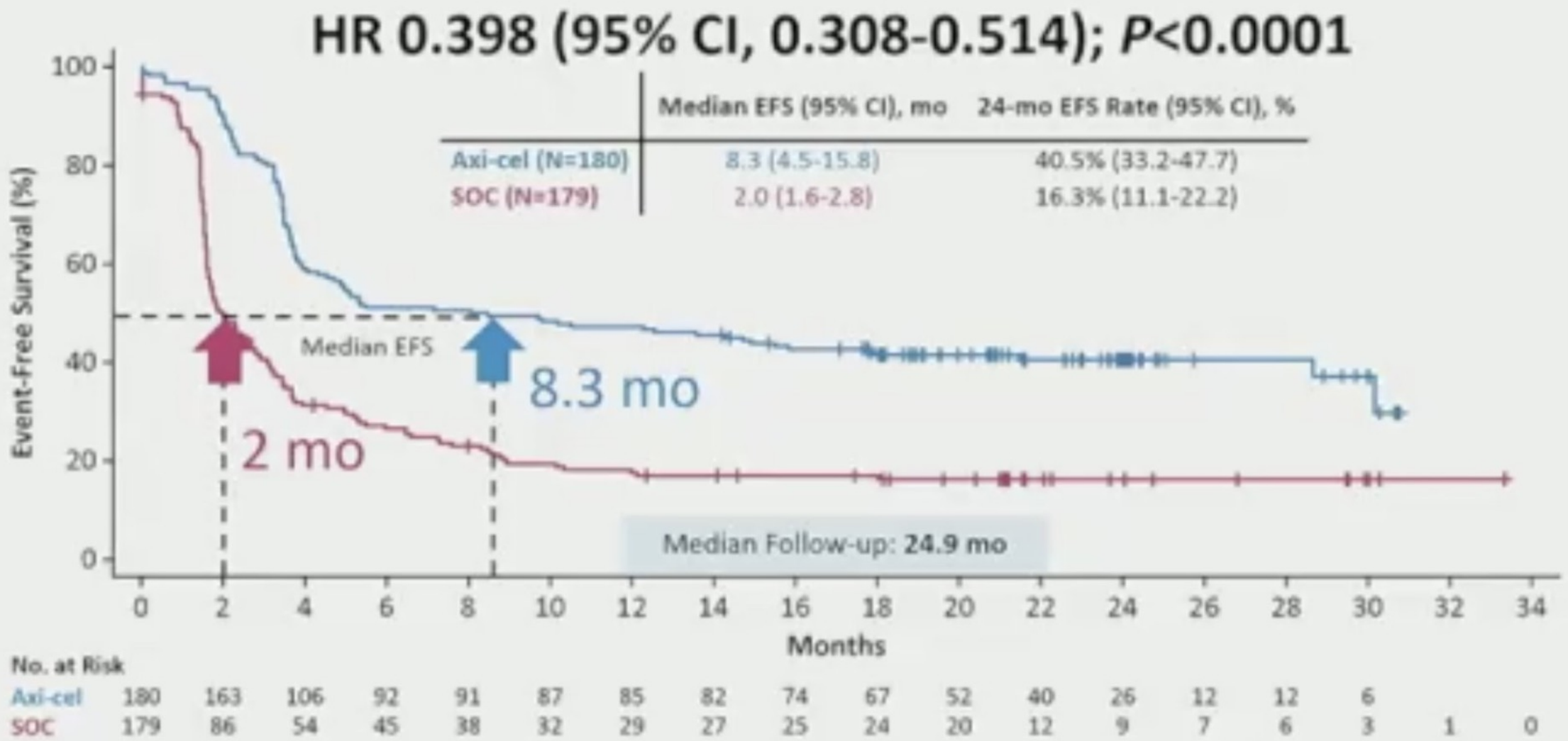
[a] Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10^6 CAR T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] 56% of patients received subsequent cellular immunotherapy. [e] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[2] commencement of new lymphoma therapy, or death from any cause.

1. Swerdlow SH, et al. *Blood*. 2016;127:2375-2390. 2. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

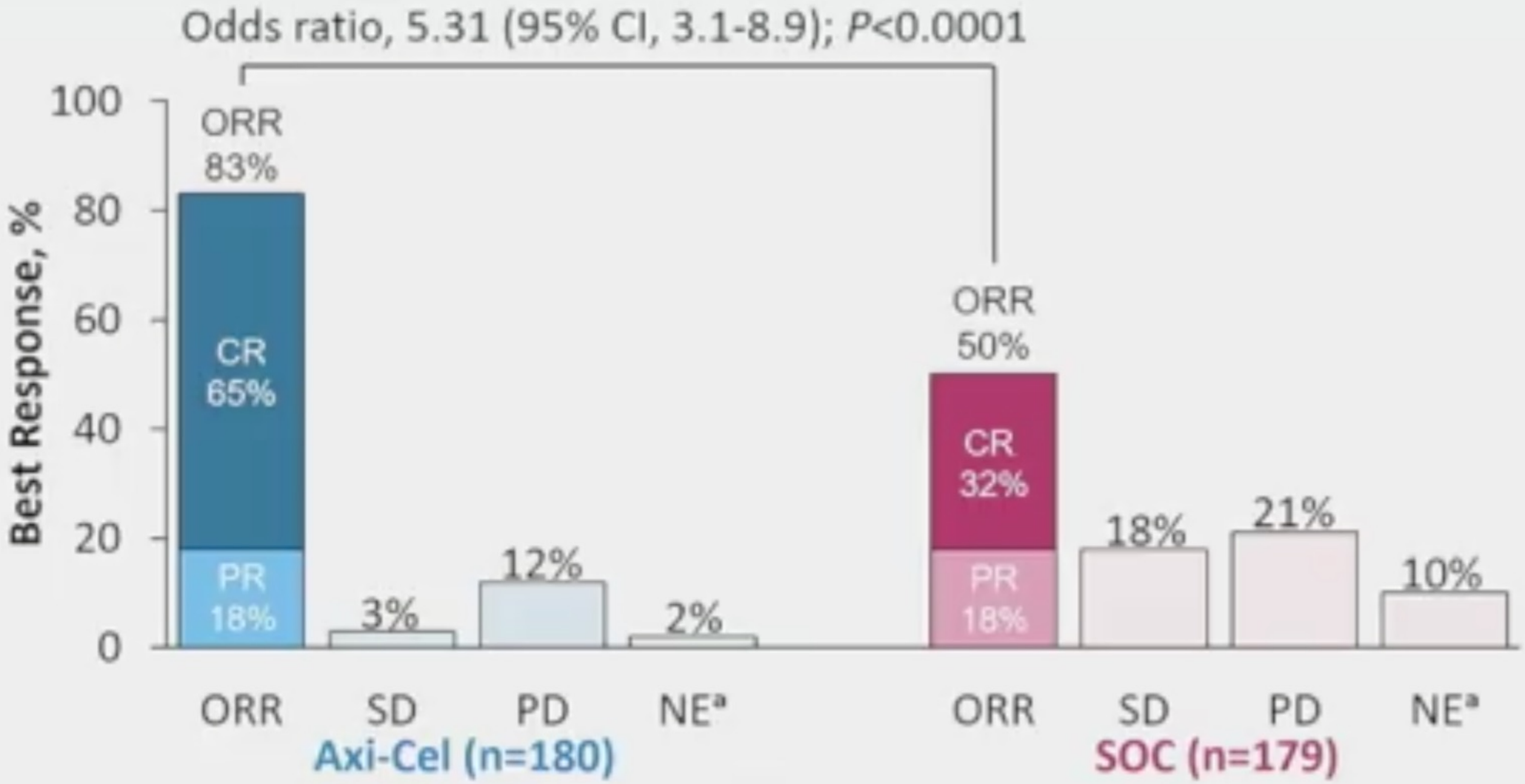
Patient Disposition: Nearly 3× as Many Axi-Cel Patients Received Definitive Therapy Versus SOC Patients



Primary EFS Endpoint: Axi-Cel Is Superior to SOC

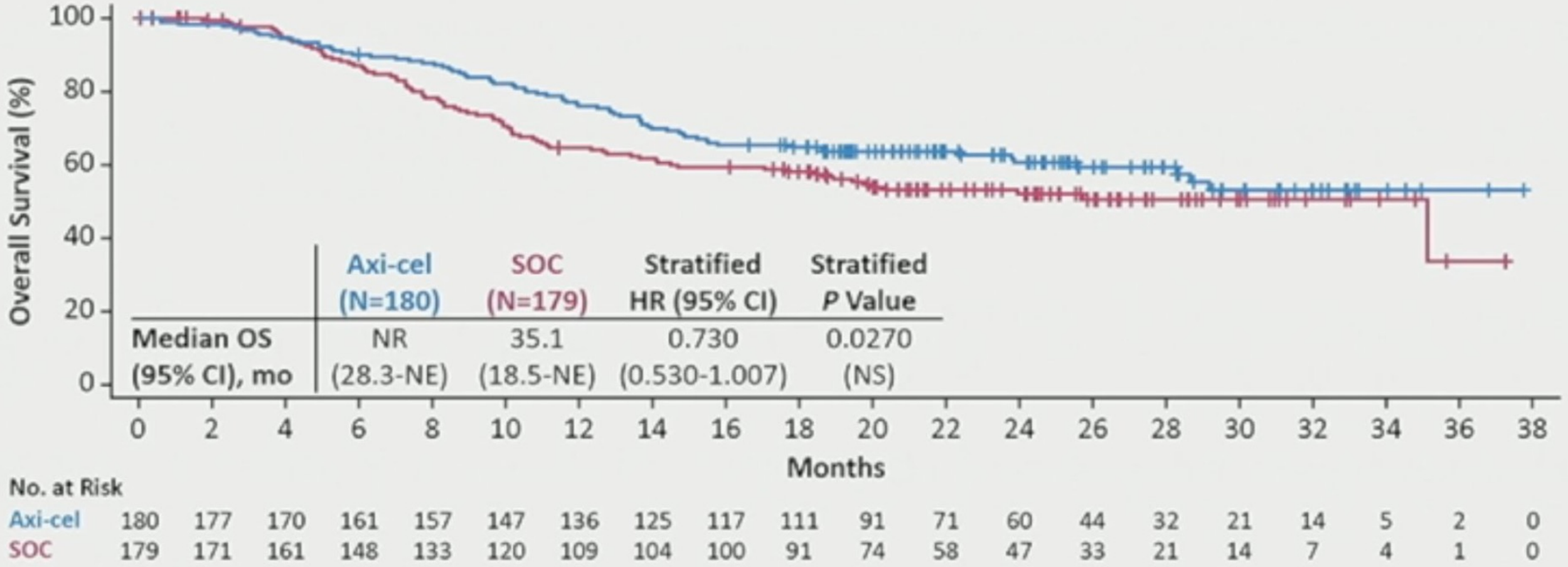


ORR Was Significantly Higher in Axi-Cel Versus SOC Patients



[a] Not evaluable (NE): In the axi-cel arm, response assessments were not done for 4 patients. In the SOC arm, there were 4 patients with undefined disease and 14 who did not have response assessments done.

Median OS, Evaluated as an Interim Analysis, Was Not Reached for Axi-Cel Versus 35.1 Months for SOC



- 56% of SOC patients received subsequent cellular immunotherapy (off protocol)
- Preplanned sensitivity analysis[a] suggests an OS benefit, likely confounded by SOC treatment switching

[a] Analysis utilized the validated and commonly used Rank Preserving Structural Failure Time model, which preserves randomization as described by Robins and Tsiatis (*Commun Stat Theory Methods*. 1991;2609-2631) and revealed the difference in treatment effect if SOC patients did not receive subsequent cellular immunotherapy. Stratified hazard ratio was 0.580 (95% CI, 0.416-0.809).

Grade ≥3 CRS and Neurologic Events Were Generally Consistent With Third-Line Treatment of Patients[1]

CRS Parameter	Axi-Cel n=170
CRS, n (%)[a]	
Any grade	157 (92)
Grade ≥3	11 (6)
Grade 5	0
Most common any-grade symptoms, n/n (%)	
Pyrexia	155/157 (99)
Hypotension	68/157 (43)
Sinus tachycardia	49/157 (31)
AE management[d], n (%)	
Tocilizumab	111 (65)
Corticosteroids	40 (24)
Vasopressors	11 (6)
Median time to onset, days	3
Median duration of events, days	7

Neurologic Event Parameter	Axi-cel n=170	SOC n=168
Neurologic events, n (%)[b]		
Any grade	102 (60)	33 (20)[c]
Grade ≥3	36 (21)	1 (1)
Grade 5	0	0
Most common any-grade symptoms, n (%)		
Tremor	44 (26)	1 (1)
Confusional state	40 (24)	4 (2)
Aphasia	36 (21)	0
AE management[d], n (%)		
Corticosteroids	54 (32)	-
Median time to onset, days	7	23
Median duration of events, days	9	23

1. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-2544. 2. Lee DW, et al. *Blood.* 2014;124:188-195. 3. Topp MS, et al. *Lancet Oncol.* 2015;16:57-66.

[a] CRS was graded according to Lee et al.[2] [b] Neurologic events were identified per prespecified search list based on methods used in the blinatumomab registrational study.[3] Neurologic events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. [c] Other preferred terms reported in the SOC arm (in ≤2 patients) included somnolence, agitation, hypoesthesia, lethargy, depressed level of consciousness, cognitive disorder, memory impairment, bradyphrenia, taste disorder, hallucination, hallucination visual, nystagmus, head discomfort, and neuralgia. [d] Toxicity management followed ZUMA-1 pivotal arms.

Conclusions

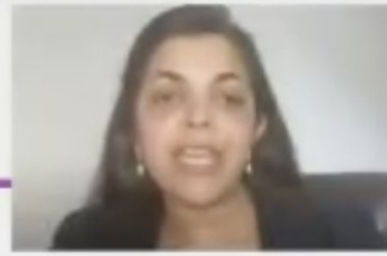
- ZUMA-7 is the first randomized CAR T-cell trial and has 24.9 months median follow-up
- ZUMA-7 met its primary EFS endpoint, demonstrating statistically significant and clinically meaningful improvement in efficacy with axi-cel versus second-line SOC in R/R LBCL
- Axi-cel showed superiority over SOC

>4-fold greater median EFS	2.5-fold greater 2-year EFS	33% higher ORR	Double the CR rate	EFS improvements across key subgroups

- Nearly 3× the number of patients in the axi-cel arm received definitive therapy versus the SOC arm
- Axi-cel had a manageable safety profile that was consistent with previous studies[1,2]
- Paradigm shift: Axi-cel should be the new standard for patients with second-line R/R LBCL

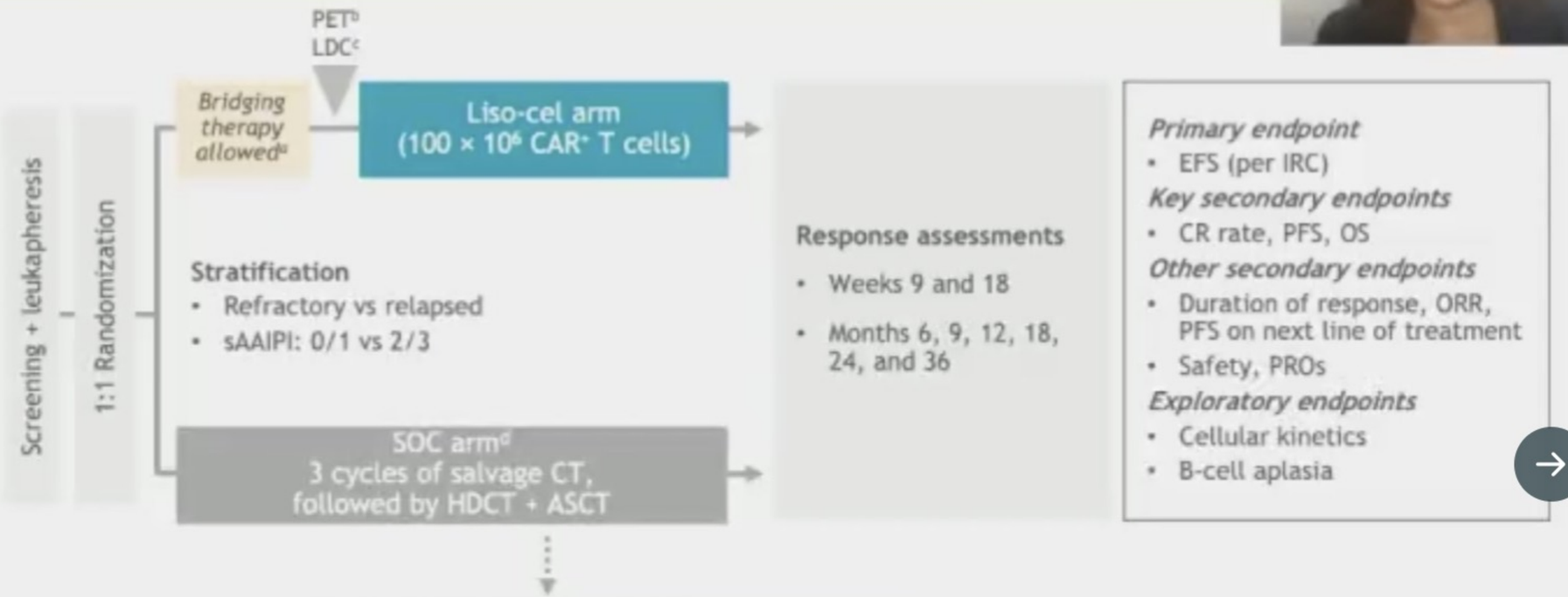
1. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544. 2. Locke FL, et al. *Blood*. 2017;130:2826.

TRANSFORM study design



Key eligibility

- Age 18–75 years
- Aggressive NHL
  - DLBCL NOS (de novo or transformed from indolent NHL), HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL
- Refractory or relapsed ≤ 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS ≤ 1
- Eligible for HSCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum absolute lymphocyte count



Crossover to liso-cel allowed

- Failure to respond by 9 weeks post-randomization
- PD at any time
- Start of new antineoplastic therapy after ASCT

TRANSFORM PRO data
Poster (Abs 3845)
Abramson et al.
Dec 13, 2021, 6:00 pm (EST)

- **EFS is defined as time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurs first**

[a]Patients may have received a protocol-defined SOC regimen to stabilize their disease during liso-cel manufacturing; [b]Only for patients who received bridging therapy; [c]Lymphodepletion with fludarabine 30 mg/m² and cyclophosphamide 300 mg/m² for 3 days; [d]SOC was defined as physician's choice of R-DHAP, R-ICE, or R-GDP.
DLBCL, diffuse large-B cell lymphoma; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; LDC, lymphodepleting chemotherapy; NOS, not otherwise specified; PD, progressive disease; PMBCL, primary mediastinal large B-cell lymphoma; PRO, patient-reported outcome; sAAIPI, secondary age-adjusted International Prognostic Index; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma.

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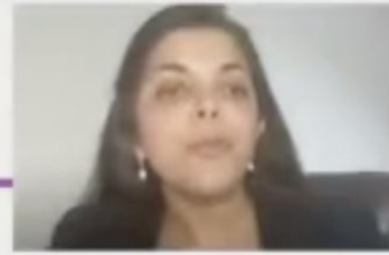
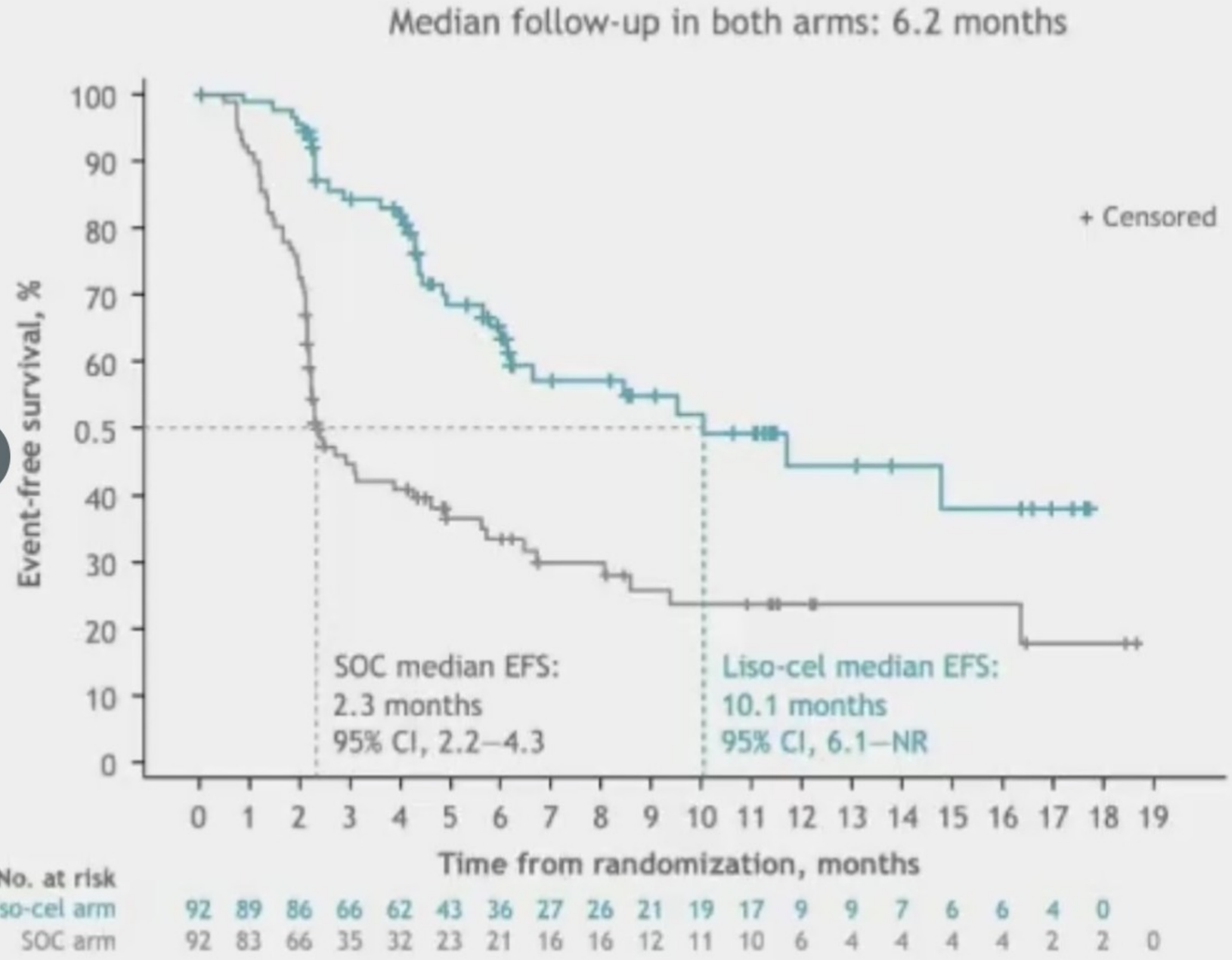
TRANSFORM: Event-free survival per IRC (ITT set; primary endpoint)





	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	0.349 (0.229–0.530)	
	P < 0.0001	
6-month EFS rate, % (SE)	63.3 (5.77)	33.4 (5.30)
Two-sided 95% CI	52.0–74.7	23.0–43.8
12-month EFS rate, % (SE)	44.5 (7.72)	23.7 (5.28)
Two-sided 95% CI	29.4–59.6	13.4–34.1

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

EFS is defined as the time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization or start of a new antineoplastic therapy due to efficacy concerns, whichever occurs first.
CI, confidence interval; HR, hazard ratio; NR, not reached; SE, standard error.

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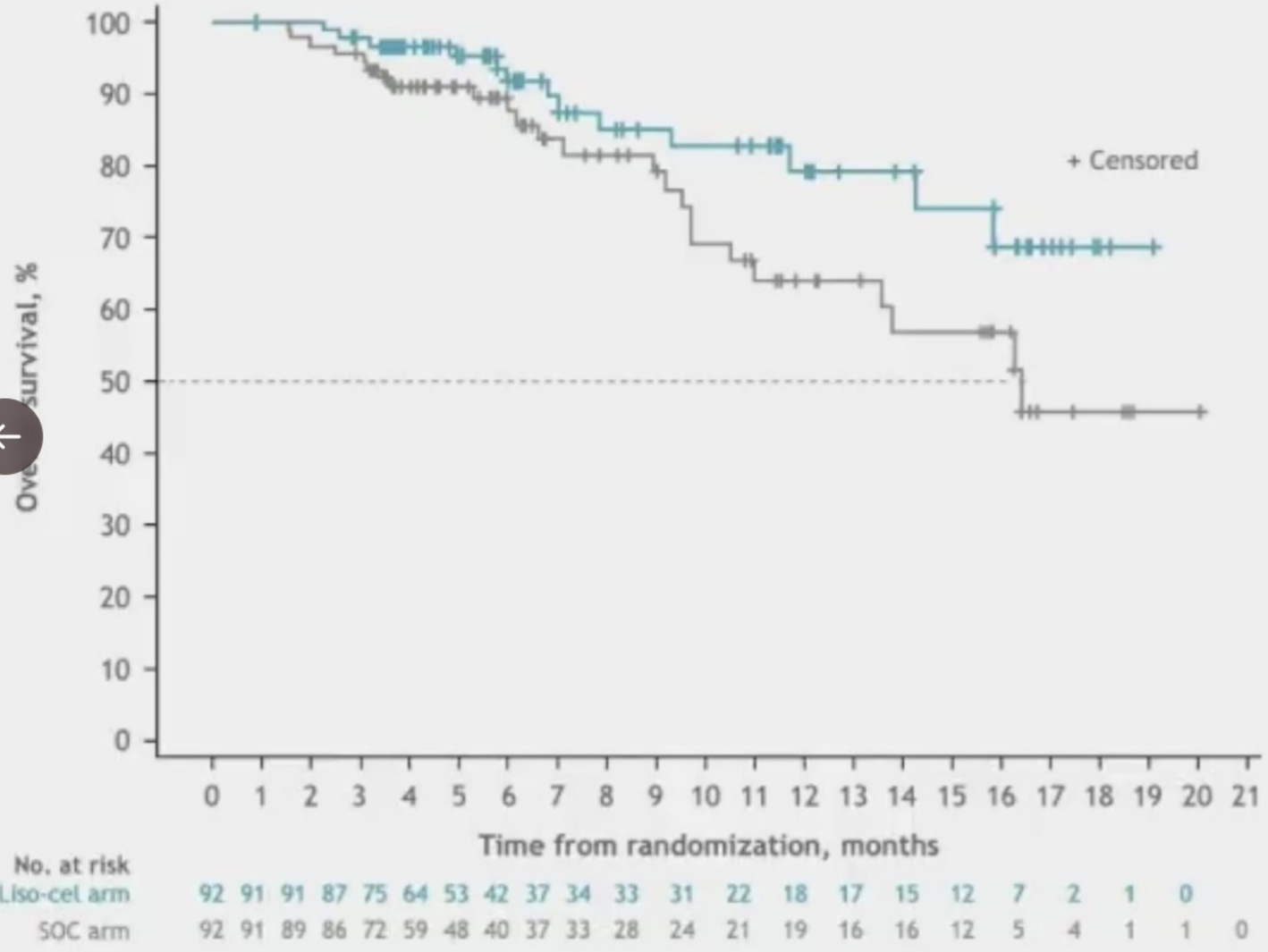
TRANSFORM: Overall survival (ITT set)



	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	13	24
Stratified HR (95% CI)	0.509 (0.258–1.004) *P* = 0.0257	
Median OS (95% CI), months	NR (15.8–NR)	16.4 (11.0–NR)
6-month OS rate, % (SE)	91.8 (3.29)	89.4 (3.36)
Two-sided 95% CI	85.4–98.2	82.9–96.0
12-month OS rate, % (SE)	79.1 (6.13)	64.2 (6.99)
Two-sided 95% CI	67.1–91.1	50.5–77.9

Patients in the SOC arm that crossed over to receive liso-cel continue to be followed for OS in the SOC arm

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

OS is defined as the time from randomization to death from any cause.

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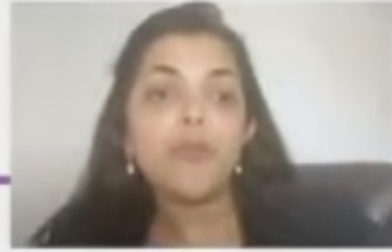
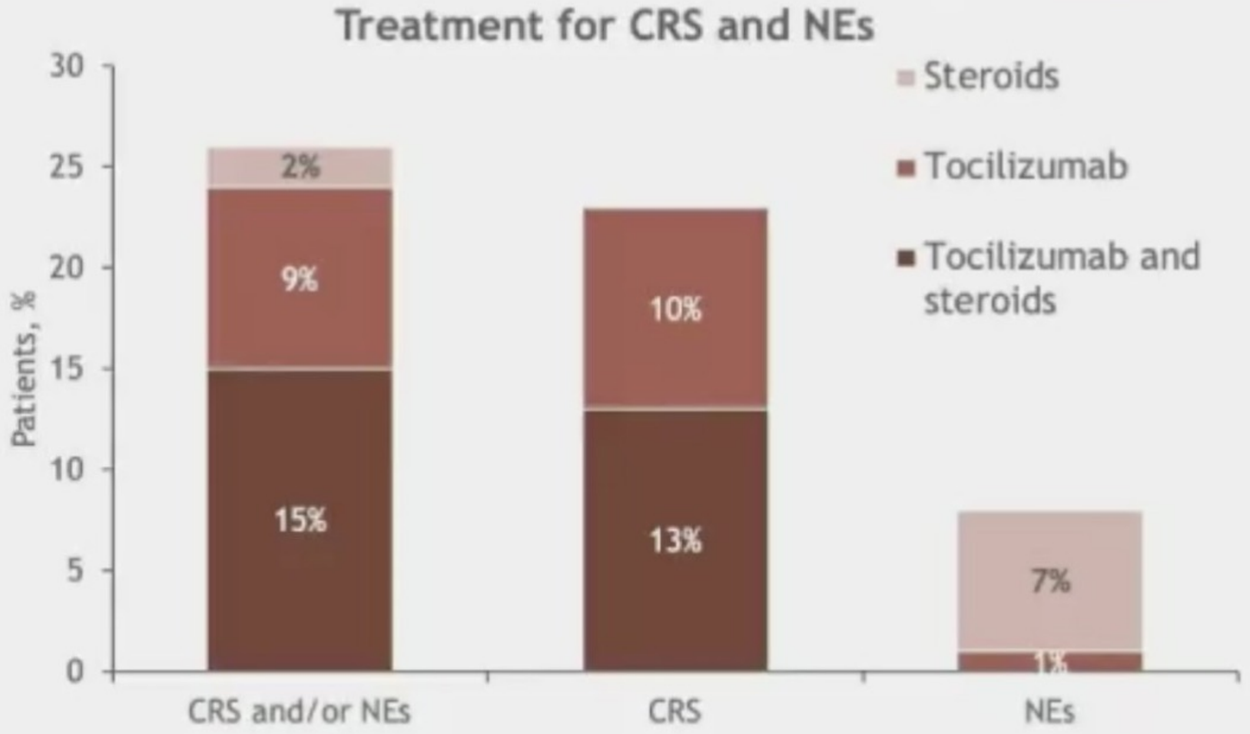
TRANSFORM: TEAEs of special interest (safety set)



Patients with CRS and NEs	Liso-cel arm (n = 92)
CRS,[a] n (%)	
Any grade	45 (49)
Grade 1	34 (37)
Grade 2	10 (11)
Grade 3	**1 (1)[b]**
Grade 4/5	**0**
Time to onset, days, median (range)	5 (1–63)
Time to resolution, days, median (range)	4 (1–16)
NE,[c] n (%)	
Any grade	11 (12)
Grade 1	5 (5)
Grade 2	2 (2)
Grade 3	**4 (4)**
Grade 4/5	**0**
Time to onset, days, median (range)	11 (7–25)
Time to resolution, days, median (range)	6 (1–30)



Other adverse events of special interest	Liso-cel arm (n = 92)	SOC arm (n = 91)
Prolonged cytopenia[d]	40 (43)	3 (3)
Grade ≥ 3 infection	14 (15)	19 (21)

[a]Graded according to the Lee 2014 criteria; [b]Grade 3 CRS event due to hypertransaminasemia, which resolved 2 days later; [c]Defined as investigator-identified neurological adverse events related to liso-cel. These were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03; [d]Grade ≥ 3 anemia, neutropenia, or thrombocytopenia at 35 days after liso-cel infusion for the liso-cel arm or at 35 days after the start of the last CT for the SOC arm.

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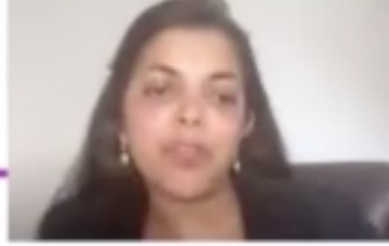
Conclusions



- Liso-cel demonstrated superiority over SOC, with highly statistically significant and clinically meaningful improvements in EFS, CR rate, and PFS as 2L therapy in patients with LBCL primary refractory to or relapsed ≤ 12 months after 1L therapy
  - The primary endpoint was met showing an EFS HR of 0.349 ($P < 0.0001$), which represents a 65% reduction in risk of events versus SOC
  - OS data were immature at this data cutoff, but a numerical trend favoring liso-cel has been observed
- Safety results in the 2L setting were consistent with the liso-cel safety profile in 3L or later LBCL, with very low rates of severe CRS and NE, and no new liso-cel safety concerns were identified
  - Only 1 case of grade 3 CRS, with no grade 4/5 events reported
  - Low incidence of any-grade NEs (12%) and grade 3 NEs (4%)
- In this phase 3, randomized, controlled trial, liso-cel improved outcomes versus salvage CT followed by HDCT and ASCT and exhibited a favorable safety profile, providing support for liso-cel as a potential new standard of care for 2L treatment in patients with R/R LBCL

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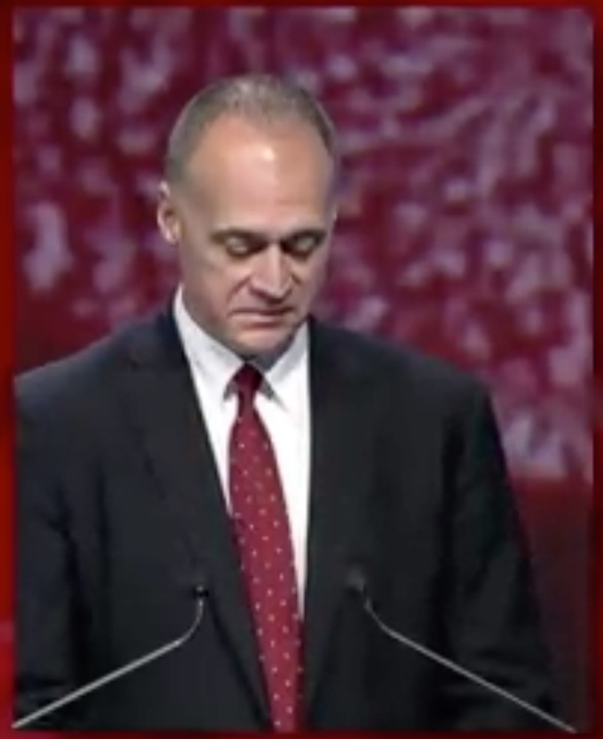

LBA #6

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Tisagenlecleucel vs Standard of Care as Second-Line Therapy of Primary Refractory or Relapsed Aggressive B-Cell Non-Hodgkin Lymphoma: Analysis of the Phase III BELINDA Study

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*Dr. Borchmann and Dr. Westin are co-senior authors. #At the time of the present work, now affiliated with Institut Curie, Paris, France

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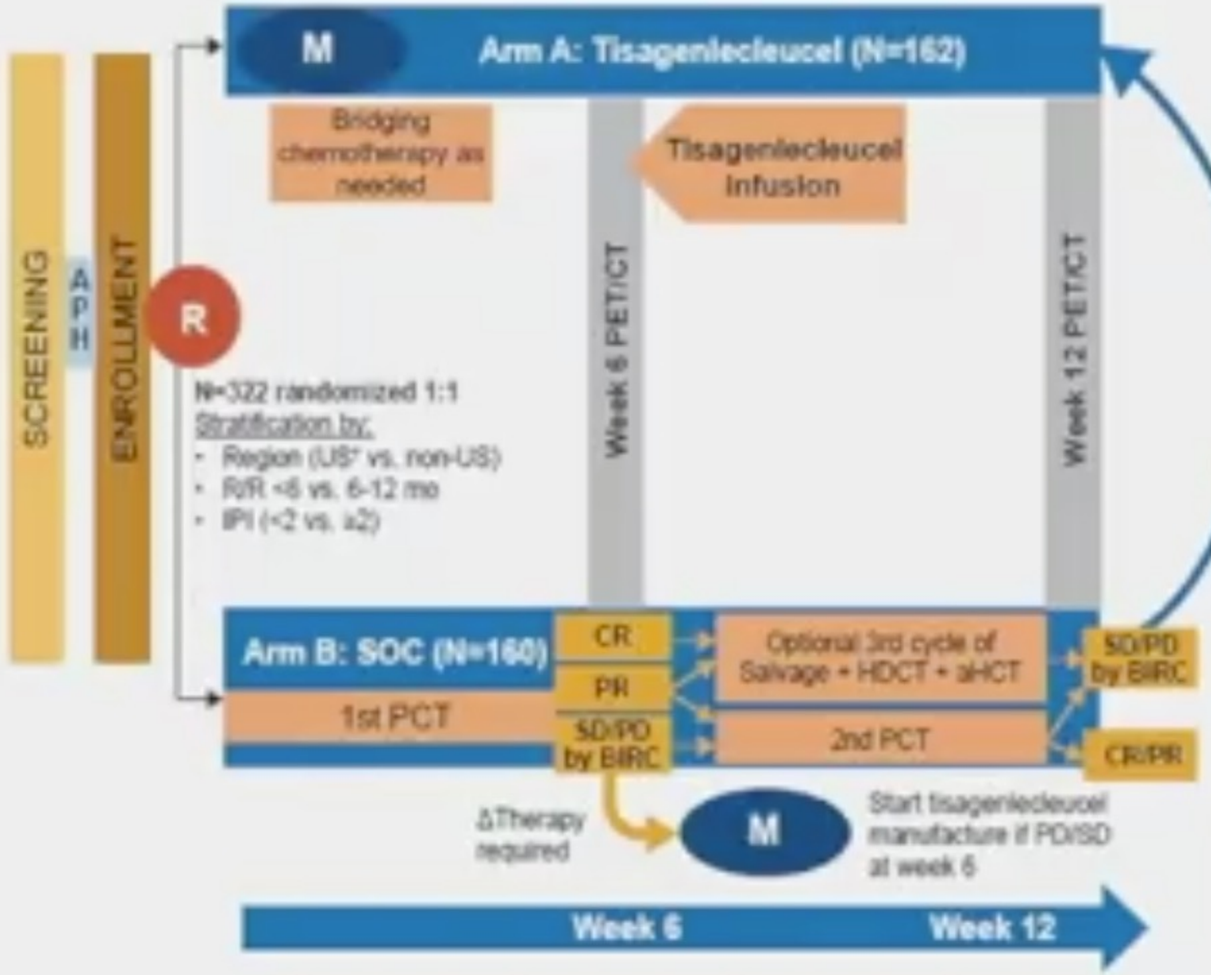
Presented at the 2021 ASH Annual Meeting, 11-14 December, 2021, Georgia World Congress Center – Atlanta, GA

BELINDA Study Design

Key eligibility criteria:

- ≥18 years-old
- Histologically-confirmed aNHL r/r within 12 months of first-line treatment
- autoHCT eligible
- ECOG PS 0-1



Data cutoff: May 6, 2021

Primary Endpoint:
Event-free Survival
EFS Event:

- **SD/PD by BIRC at/after week 12 ± 1 week**
- **Death at any time**

Secondary Endpoints:

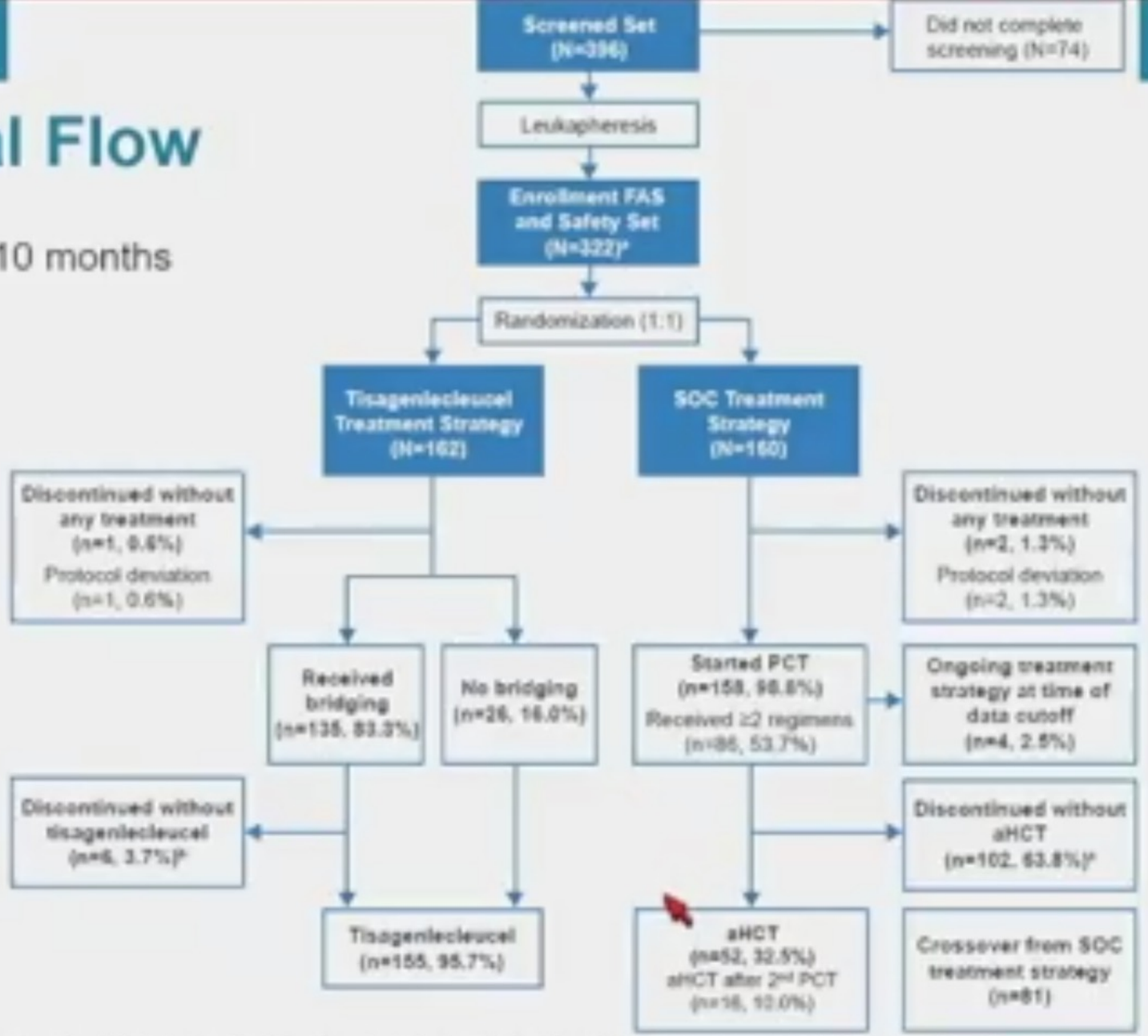
- ORR: Best overall response at/after week 12
- Safety
- Cellular kinetics

aHCT, autologous hematopoietic cell transplantation; aNHL, aggressive non-Hodgkin lymphoma; APH, leukapheresis; BIRC, blinded independent review committee; CR, complete response; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDCT, high-dose chemotherapy; IPI, International Prognostic Index; M, manufacturing; ORR, overall response rate; OS, overall survival; PCT, platinum-based immunochemotherapy; PD, progressive disease; PET, positron emission tomography; PR, partial response; q3mo, every 3 months; q6mo, every 6 months; R, randomization; SD, stable disease; SOC, standard of care; US, United States.

Presented at the 2021 ASH Annual Meeting, 11-14 December, 2021; Georgia World Congress Center - Atlanta, GA

Patient Trial Flow

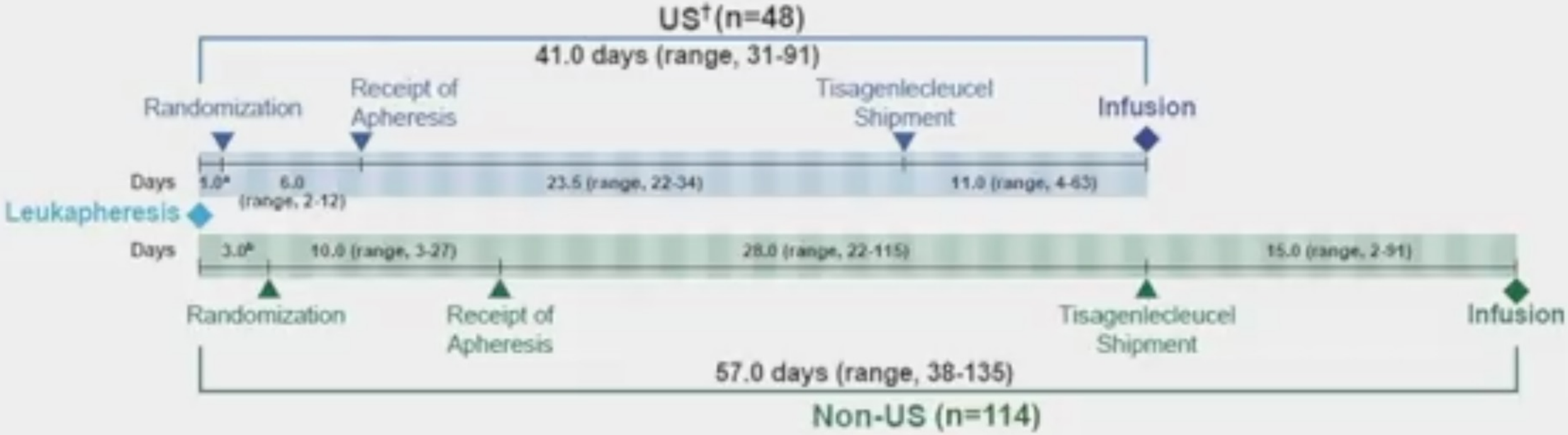
- Median follow-up: 10 months (range, 2.9-23.2)



[a]FAS and safety sets used to compare efficacy and safety between the 2 treatment strategies during the safety comparison period, defined as from day of randomization to the earlier of 56 days after last dose of study treatment or start date of new anticancer therapy. [b]Reasons for discontinuation without tisagenlecleucel infusion include physician decision (n=2, 1.2%), PD (n=2, 1.2%), Manufacturing issue (n=1, 0.6%), and patient decision (n=1, 0.6%). [c]Reasons for discontinuation without aHCT include PD (n=76, 47.5%), physician decision (n=14, 8.8%), death (n=7, 4.4%), patient decision (n=2, 1.3%), technical problems (n=2, 1.3%), and protocol deviation (n=1, 0.6%). aHCT, autologous hematopoietic cell transplantation; FAS, full analysis set; PCT, platinum-based immunochemotherapy; SOC, standard of care.

Time to Tisagenlecleucel Infusion

- Median time to infusion for all patients on the Tisagenlecleucel arm was 52 days (range, 31-135)



†North America was a stratification factor, and all enrolled patients in this group were from the United States (US).
ªrange, 1-6 days, ᵇrange, 1-17 days

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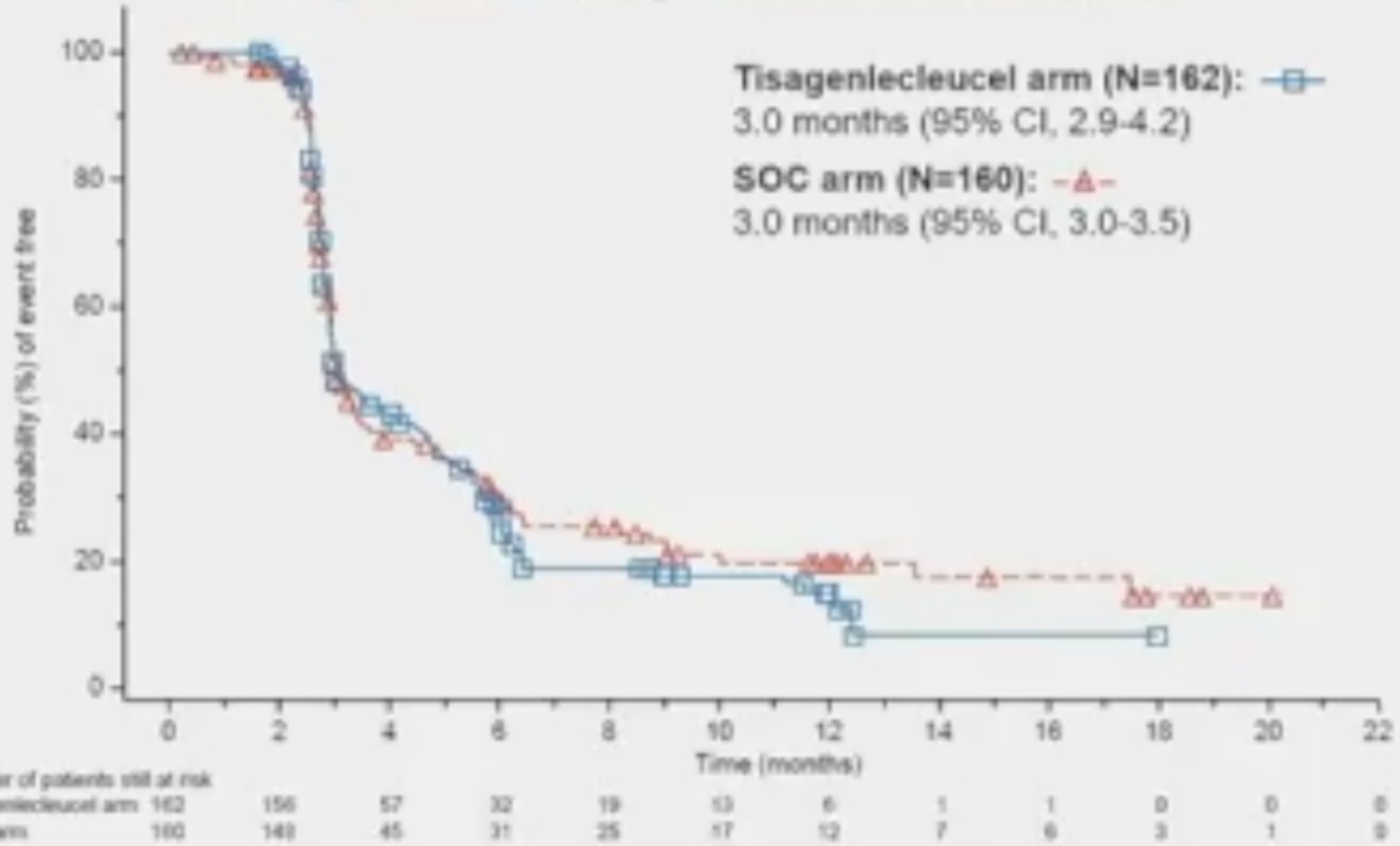
No Difference in EFS Between Treatment Arms

EFS per BIRC in Tisagenlecleucel and SOC Arms



Number of patients still at risk

Tisagenlecleucel arm	162	156	57	32	19	13	6	1	1	0	0	0
SOC arm	160	149	45	31	25	17	12	7	6	3	1	0

- EFS[a] was not significantly different between treatment arms
  - Primary analysis: Stratified unadjusted HR: 1.07 (95% CI, 0.82-1.40, p[b]=0.69)
  - Supportive analysis: Stratified adjusted[c] HR: 0.95 (95% CI, 0.72-1.25)
  - 6 patients responded to tisagenlecleucel infusion, but were captured as an EFS event due to SD/PD before or soon after infusion[d]

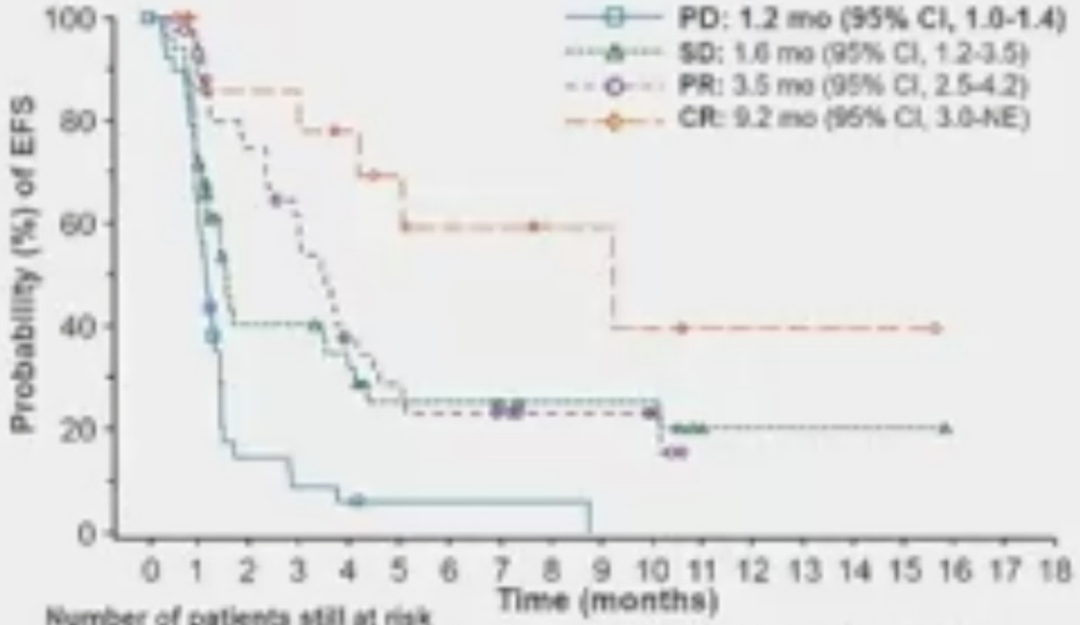
[a]EFS events defined as PD/SD after day 71 or death at any time. [b]p-value derived from 1-sided stratified log-rank test. [c]Adjusted for for potential imbalances in patient characteristics with pre-specified covariates of age, sex, race, ECOG performance status, histological subgroup, disease stage, and disease subtype. [d]Stratified adjusted HR accounting for delayed responses in both arms yield HR of 0.84 (95% CI: 0.63, 1.12).

BIRC, blinded independent review committee; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; OS, overall survival; PD, progressive disease; SD, stable disease; SOC, standard of care.

Presented at the 2021 ASH Annual Meeting, 11-14 December, 2021; Georgia World Congress Center – Atlanta, GA

EFS by Pre-infusion Response Status and Disease Diagnosis in the Tisagenlecleucel Arm

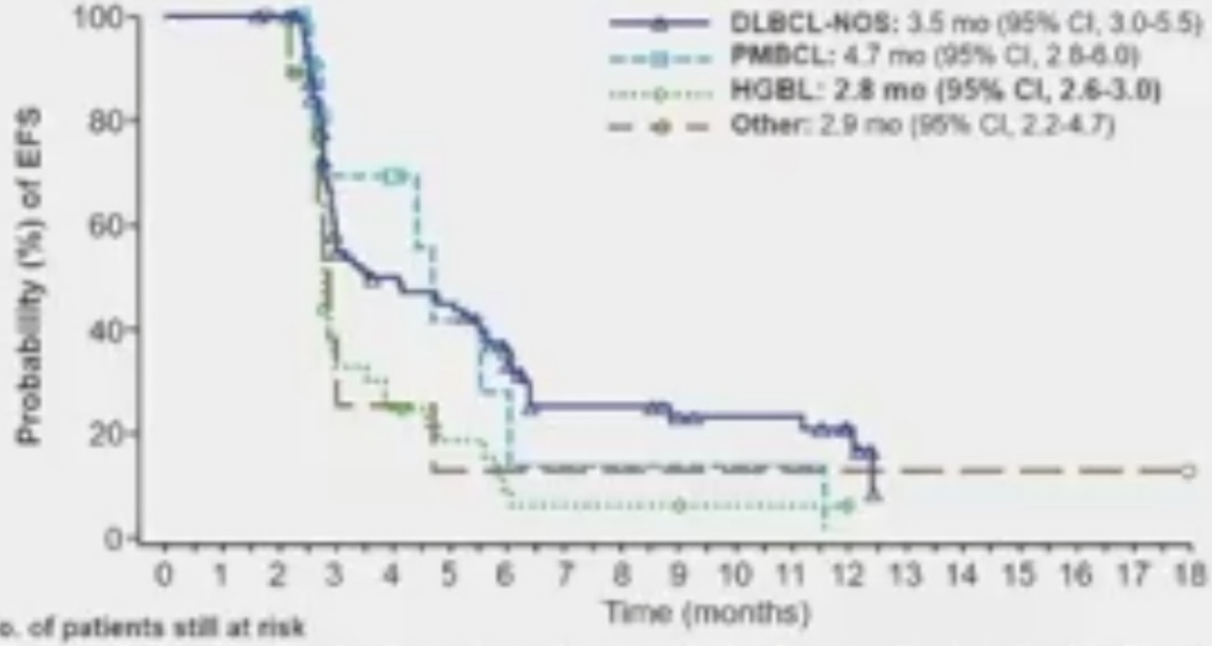
EFS[a] by per BIRC Response Status Pre-infusion



Number of patients still at risk

PD	41	25	5	3	2	1	1	1	1	0	0	0	0	0	0	0	0
SD	50	37	15	15	11	7	7	6	5	5	5	2	1	1	1	1	0
PR	42	39	29	23	13	10	8	7	5	5	3	0	0	0	0	0	0
CR	17	12	11	11	9	7	5	5	3	3	2	1	1	1	1	1	0

EFS per BIRC by Disease Diagnosis[b]



No. of patients still at risk

DLBCL NOS	101	101	99	49	40	36	26	15	15	12	10	10	5	0	0	0	0	0	0
PMBCL	12	12	12	6	6	3	2	1	1	1	1	1	0	0	0	0	0	0	0
HBGL	39	39	36	12	9	6	3	2	2	2	1	1	0	0	0	0	0	0	0
Other	10	10	9	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	0

[a]Time is relative to date of tisagenlecleucel infusion Median time from pre-infusion disease assessment to infusion was 10 days (range, 2-57; Q1-Q3, 8-15). [b]EFS events defined as PD/SD after day 71 from randomization or death at any time.

BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; DLBCL NOS, diffuse large B-cell lymphoma not otherwise specified; EFS, event-free survival; HGBL, high-grade B-cell lymphoma; mEFS, modified event-free survival; NE, not estimable; PD, progressive disease; PMBCL, primary mediastinal B-cell lymphoma; PR, partial response; SD, stable disease; SOC, standard of care

Safety

	Tisagenlecleucel Arm (N=162)		SOC Arm (N=160)	
	All Grades no. (%)	Grade ≥3 no. (%)	All Grades no. (%)	Grade ≥3 no. (%)
AEs[a]	160 (98.8)	136 (84.0)	158 (98.8)	144 (90.0)
Treatment-related[a]	152 (93.8)	121 (74.7)	151 (94.4)	137 (85.6)
Serious AEs[a]	76 (46.9)	58 (35.8)	82 (51.3)	68 (42.5)
Treatment-related[a]	61 (37.7)	44 (27.2)	58 (36.3)	50 (31.3)
Hematological Disorders[a,c]	127 (78.4)	125 (77.2)	142 (88.8)	141 (88.1)
Anemia	80 (49.4)	54 (33.3)	115 (71.9)	92 (57.5)
Thrombocytopenia	59 (36.4)	52 (32.1)	79 (49.4)	76 (47.5)
Neutropenia	67 (41.4)	65 (40.1)	65 (40.6)	63 (39.4)
Febrile neutropenia	21 (13.0)	21 (13.0)	40 (25.0)	40 (25.0)
Infections[a,c]	63 (38.9)	28 (17.3)	55 (34.4)	24 (15.0)
CRS and NE Post tisagenlecleucel infusion (N=155)				
CRS[b]	95 (58.6)	8 (4.9)	NA	NA
NE[d]	16 (10.3)	3 (1.9)	NA	NA

- 52 (32.1%) and 45 (28.1%) patients in tisagenlecleucel and SOC arms died on study
  - 42 (25.9%) and 32 (20.0%) died from PD, respectively
  - 10 (6.2%) and 13 (8.1%) died from AEs, respectively

[a]During safety comparison period, defined as from day of randomization to the earlier of: 56 days after last dose of study treatment or start date of new anticancer therapy.
[b]Related to any part of treatment strategy. [c]Per Lee grading scale. [c]AEs in >20% of patients in either arm. [d]Median time to onset of a NE was 5 days (range, 3-93), and median time to resolution was 9 days (95% CI, 3-14).
AEs, adverse events; CI, confidence interval; CRS, cytokine release syndrome; NA, not applicable; NEs, neurological events; PD, progressive disease; SOC, standard of care.

Conclusions

- EFS was not significantly different between tisagenlecleucel and SOC treatment strategies in patients with aggressive NHL that was refractory or relapsed early after first-line therapy
- Our findings suggest the importance of preventing PD prior to infusion
  - A higher proportion of patients had PD at week 6, prior to CAR T-cell infusion, in the tisagenlecleucel arm
- Effective bridging prior to CAR T-cell infusion and a shorter time to infusion for this chemotherapy-refractory patient population could be critical to improve outcomes
- Insights from this randomized Phase III study should help guide optimal use of CAR T-cells in patients with r/r aggressive NHL requiring second-line therapy and design of future CAR-T trials

CAR, chimeric antigen receptor; EFS, event-free survival; NHL, non-Hodgkin lymphoma; PD, progressive disease; r/r, refractory or relapsed; SOC, standard of care.

Presented at the 2021 63th Annual Meeting, 11-14 December, 2021, Georgia World Congress Center - Atlanta, GA

Phase-3 trials of CAR-T vs SOC in transplant eligible patients with aggressive B-cell lymphoma

	ZUMA-7	TRANSFORM	BELINDA
POPULATION	1L (R/R ≤ 12 months)	1L (R/R ≤ 12 months)	1L (R/R ≤ 12 months)
RANDOMIZATION	1:1	1:1	1:1
STRATIFICATION	Response to 1L aaIPI	N.A.	DOR to 1L IPI Geographic region
CROSS-OVER ALLOWED	NO	YES	YES
BRIDIGNIG THEARPY	Steroids only	Yes (SOC regimen)	Yes (SOC regimen)
LD CHEMO	Flu-Cy	Flu-Cy	Flu-Cy (generally)
PRIMARY END-POINT	EFS	EFS	EFS
	Locke, F. ASH21 (#2)	*Kamdar, M. ASH21 (#91)*	*Bishop, M. ASH21 (#LBA-6)*

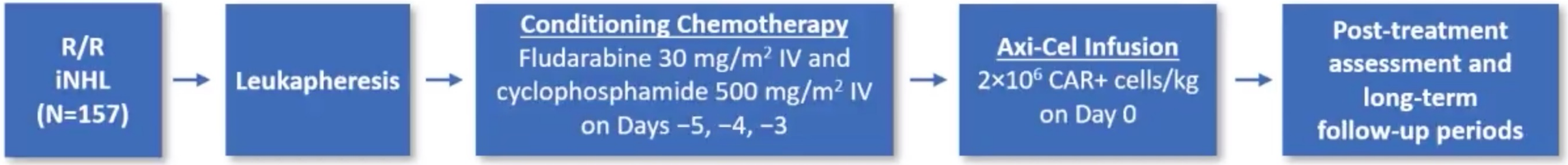
EFS definitions in Phase-3 trials of CAR-T vs SOC in transplant eligible patients with aggressive B-cell lymphoma

	ZUMA-7	TRANSFORM	BELINDA
EFS	**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.	**1)** SD or PD at or after week 12 **2)** Death (any time)
EFS TIME	From randomization	From randomization	From randomization

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Locke, F. ASH21 (#2) *Kamdar, M. ASH21 (#91)* *Bishop, M. ASH21 (#LBA-6)*

ZUMA-5 Study Design



Key ZUMA-5 Eligibility Criteria

- R/R FL (Grades 1–3a) or MZL (nodal or extranodal)[a]
- ≥2 Prior lines of therapy that must have included an anti-CD20 mAb combined with an alkylating agent[b]

Primary Endpoint

- ORR (IRRC assessed per the Lugano classification[1])

Key Secondary Endpoints

- CR rate (IRRC assessed)
- Investigator-assessed ORR[a]
- DOR, PFS, OS
- AEs
- CAR T-cell and cytokine levels

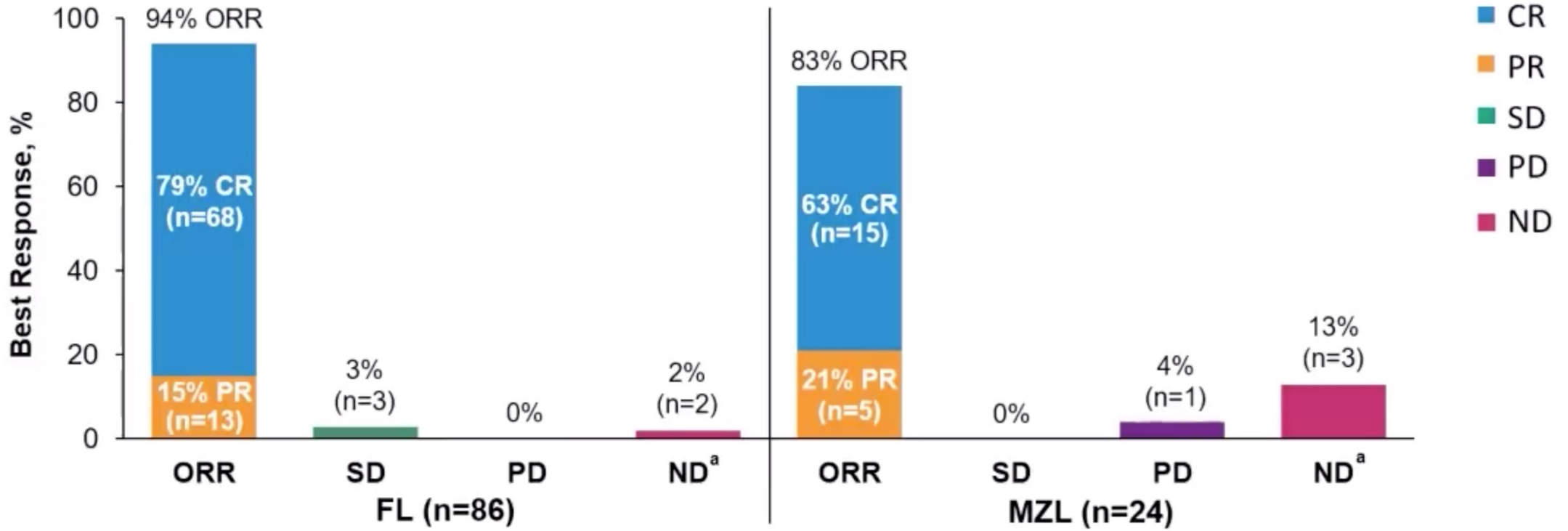
[a] Patients with stable disease (without relapse) >1 year from completion of last therapy were not eligible.
[b] Single-agent anti-CD20 antibody did not count as line of therapy for eligibility.
1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IRRC, Independent Radiology Review Committee; IV, intravenous; mAb, monoclonal antibody; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

Updated Analysis

- The updated efficacy analysis occurred when ≥80 treated patients with FL had ≥24 months of follow-up, per protocol[a]
- Efficacy analyses are reported in the 110 efficacy-eligible patients (86 with FL; 24 with MZL)[a]
  - The median follow-up for patients with FL was 30.9 months (range, 24.7–44.3)
  - The median follow-up for patients with MZL was 23.8 months (range, 7.4–39.4)
- Safety data are reported for all 149 patients treated with axi-cel (124 with FL; 25 with MZL)
- Data cutoff date: March 31, 2021

[a] Efficacy-eligible patients (inferential analysis set) included ≥80 treated patients with FL who had ≥24 months of follow-up after axi-cel infusion and treated patients with MZL who had ≥4 weeks of follow-up after axi-cel infusion as of the data cutoff date.
Axi-cel, axicabtagene ciloleucel; FL, follicular lymphoma; MZL, marginal zone lymphoma.

ORR by Central Review

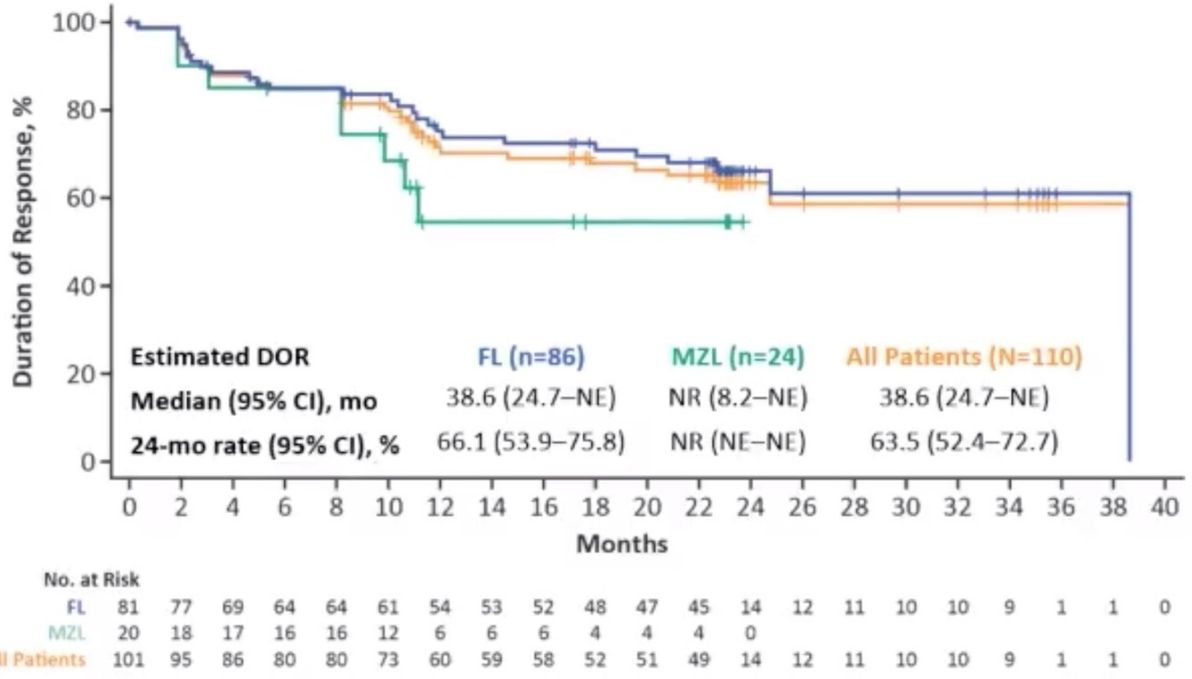


- Among efficacy-eligible patients with iNHL (n=110), the ORR was 92% (95% CI, 85–96), with a 75% CR rate
- Among all treated patients with iNHL (n=149), the ORR was 92% (95% CI, 86–96), with a 77% CR rate

Assessed in efficacy-eligible patients (n=110) by an IRRC according to the Lugano Classification (Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068).
[a] Among the 5 patients reported as ND, 4 (1 FL; 3 MZL) had no disease at baseline and post-baseline per IRRC but were considered with disease by the investigator; 1 patient with FL died before the first disease assessment.
CR, complete response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; ND, not done/undefined; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

DOR and TTNT

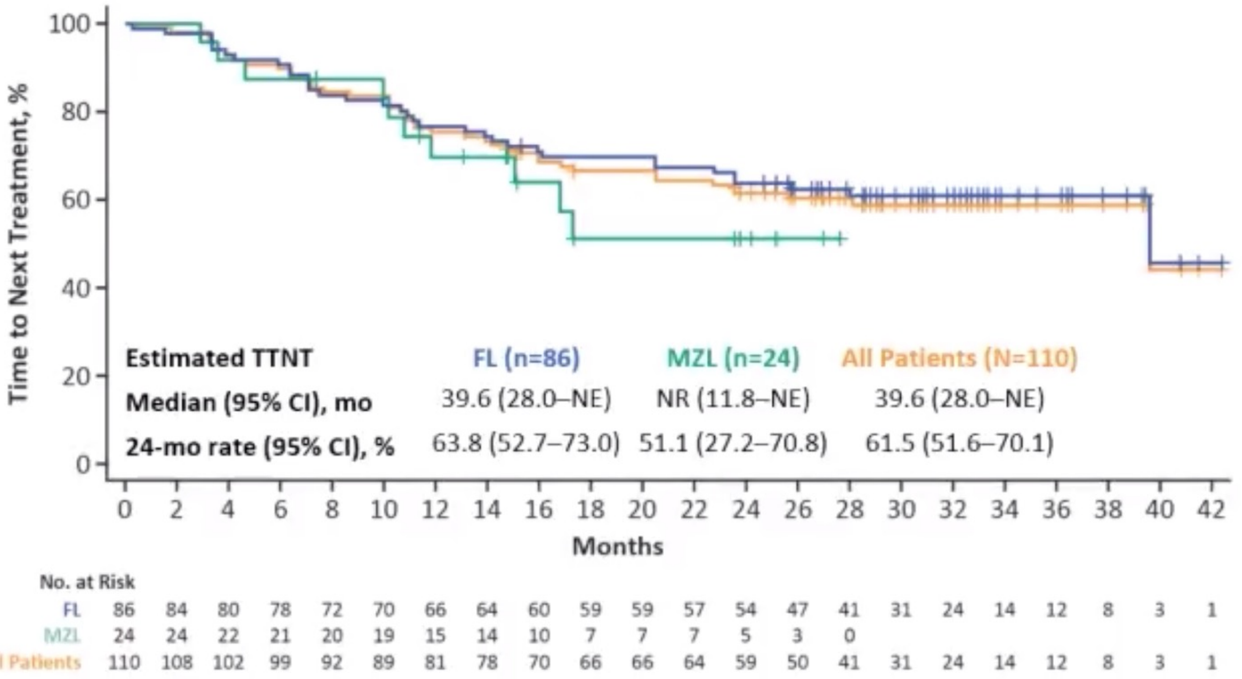
Duration of Response



No. at Risk

FL	81	77	69	64	64	61	54	53	52	48	47	45	14	12	11	10	10	9	1	1	0
MZL	20	18	17	16	16	12	6	6	6	4	4	4	0								
All Patients	101	95	86	80	80	73	60	59	58	52	51	49	14	12	11	10	10	9	1	1	0

Time to Next Treatment[a]



No. at Risk

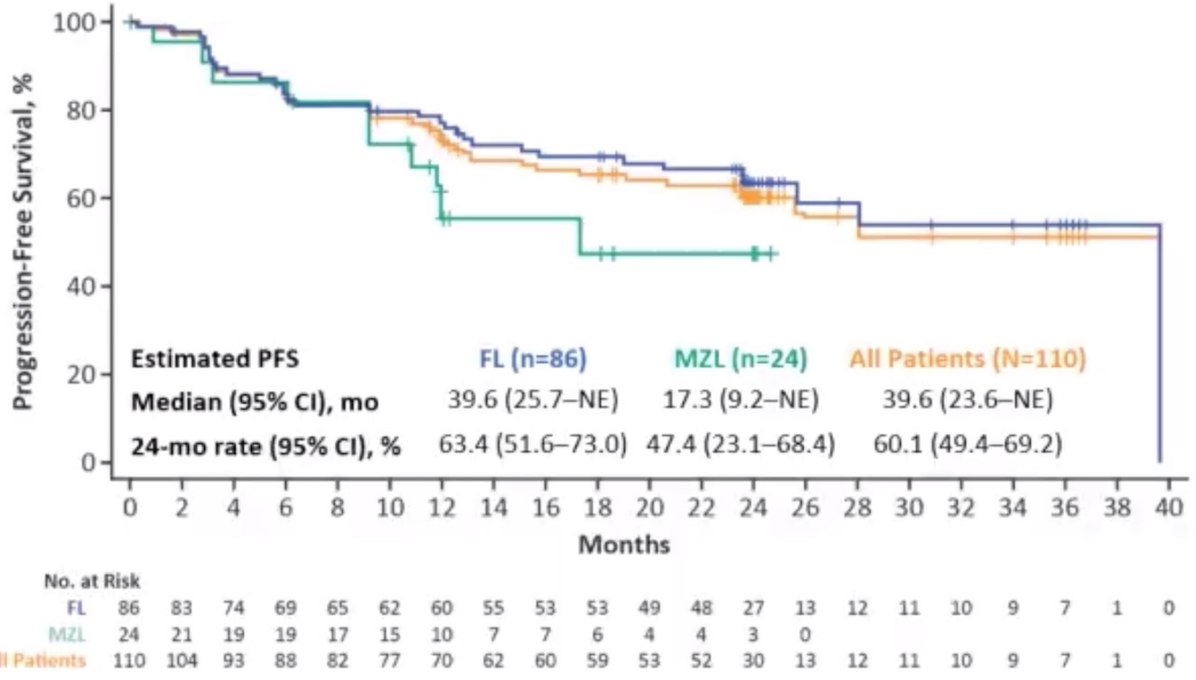
FL	86	84	80	78	72	70	66	64	60	59	59	57	54	47	41	31	24	14	12	8	3	1
MZL	24	24	22	21	20	19	15	14	10	7	7	7	5	3	0							
All Patients	110	108	102	99	92	89	81	78	70	66	66	64	59	50	41	31	24	14	12	8	3	1

- At data cutoff, 57% of efficacy-eligible patients with FL (49 of 86) and 50% of patients with MZL (12 of 24) had ongoing responses
  - Of patients who achieved a CR, 68% of patients with FL (46 of 68) and 73% of patients with MZL (11 of 15) had ongoing responses

[a] A total of 28 efficacy-eligible patients received subsequent treatment, including 18 with new anti-cancer therapy and 10 with axi-cel retreatment. No patients received subsequent SCT.
Axi-cel, axicabtagene ciloleucel; CR, complete response; DOR, duration of response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached, SCT, stem-cell transplantation; TTNT, time to next treatment.

PFS and OS

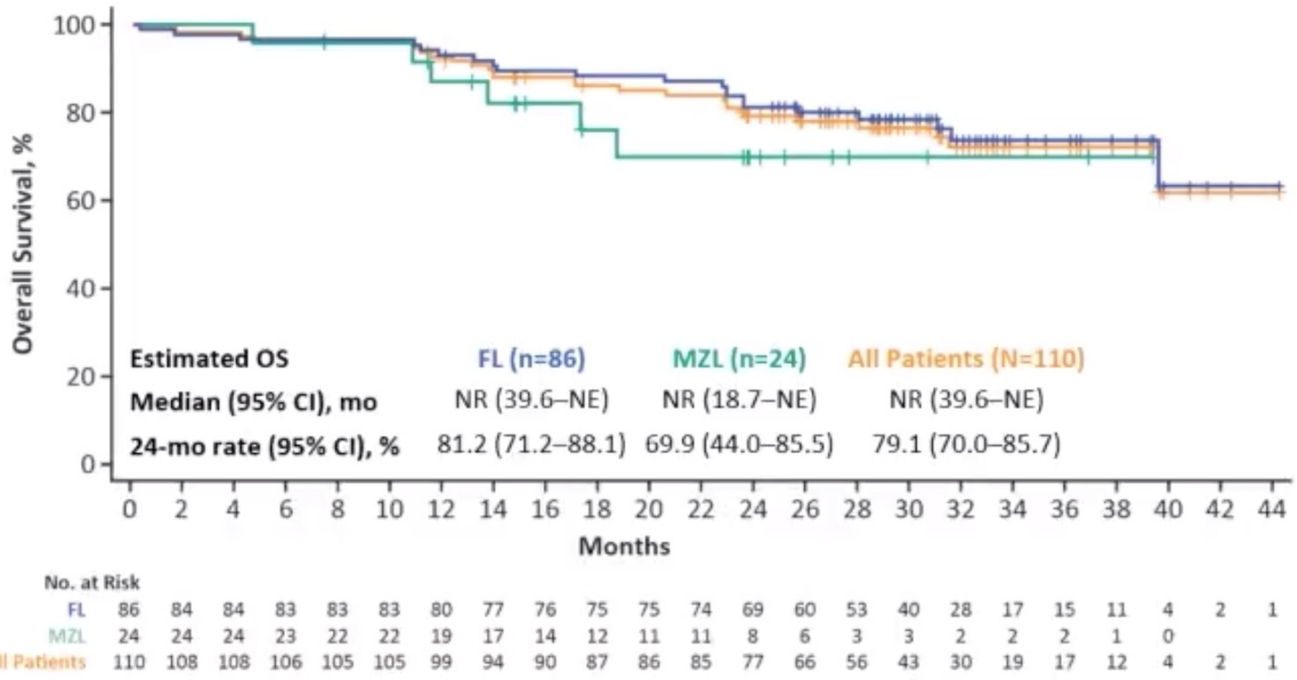
Progression-Free Survival



No. at Risk

FL	86	83	74	69	65	62	60	55	53	53	49	48	27	13	12	11	10	9	7	1	0
MZL	24	21	19	19	17	15	10	7	7	6	4	4	3	0							
All Patients	110	104	93	88	82	77	70	62	60	59	53	52	30	13	12	11	10	9	7	1	0

Overall Survival



No. at Risk

FL	86	84	84	83	83	83	80	77	76	75	75	74	69	60	53	40	28	17	15	11	4	2	1
MZL	24	24	24	23	22	22	19	17	14	12	11	11	8	6	3	3	2	2	2	1	0		
All Patients	110	108	108	106	105	105	99	94	90	87	86	85	77	66	56	43	30	19	17	12	4	2	1

- Median OS was not yet reached in efficacy-eligible patients with FL or MZL
- Among patients with FL, 3 deaths occurred after Month 24[a]; no disease progression events occurred after Month 24

[a] Of the 3 deaths, 2 were from COVID-19 and 1 was from sepsis.

FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival.

Efficacy Outcomes in Patients With FL by POD24 Status

Parameter (95% CI)	Follicular Lymphoma (n=78)[a]	
	With POD24 (n=49)	Without POD24 (n=29)
Median DOR, months	38.6 (14.5–NE)	NR (24.7–NE)
24-month rate, %	61.1 (44.3–74.3)	72.4 (50.2–85.9)
Median PFS, months	39.6 (13.1–NE)	NR (25.7–NE)
24-month rate, %	57.3 (41.2–70.4)	73.0 (51.1–86.2)
Median OS, months	NR (39.6–NE)	NR (NE–NE)
24-month rate, %	77.6 (63.1–86.9)	85.9 (66.7–94.5)

- Patients with FL who had POD24 benefitted from axi-cel, with estimated medians and 24-month rates of DOR and PFS consistent with all efficacy-eligible patients
  - Medians of DOR and PFS among patients without POD24 were not yet reached at data cutoff

[a] Axi-cel–treated patients with FL and available efficacy data on progression after an anti-CD20 mAb + alkylating agent were included in the POD24 analysis.
Axi-cel, axicabtagene ciloleucel; DOR, duration of response; FL, follicular lymphoma; mAb, monoclonal antibody; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; POD24, progression of disease <24 months from initiating the first anti-CD20–containing chemoimmunotherapy

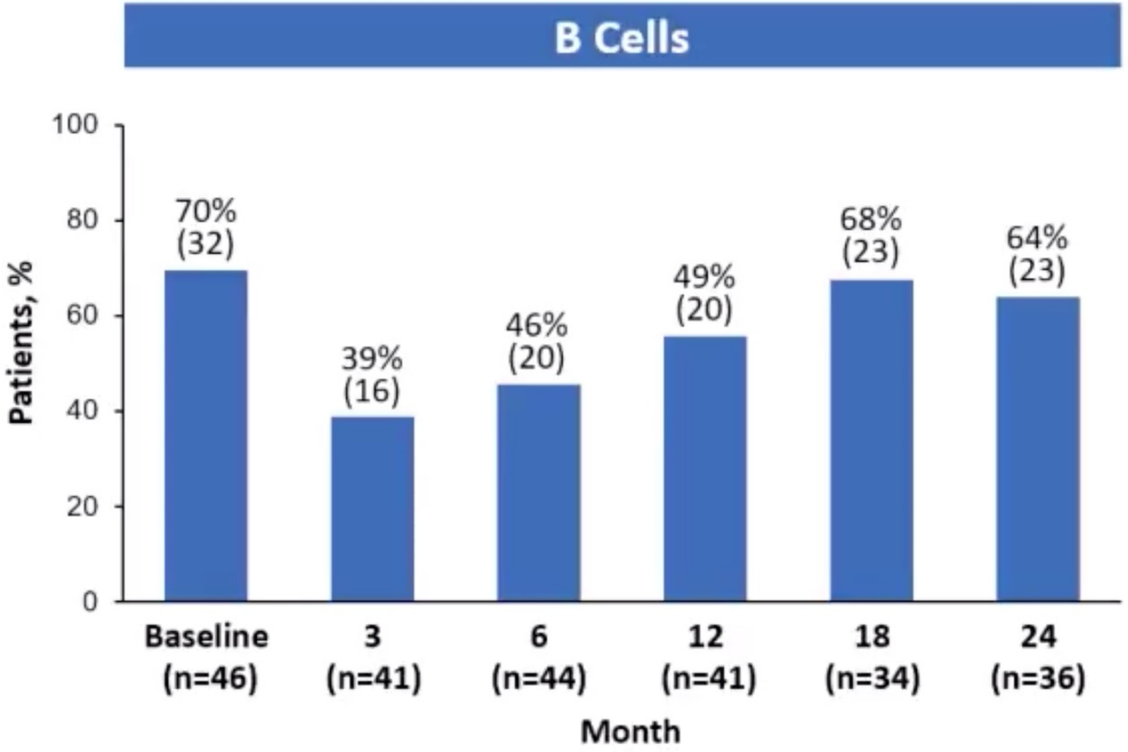
AEs With First Occurrence After the Primary Analysis DCO[a]

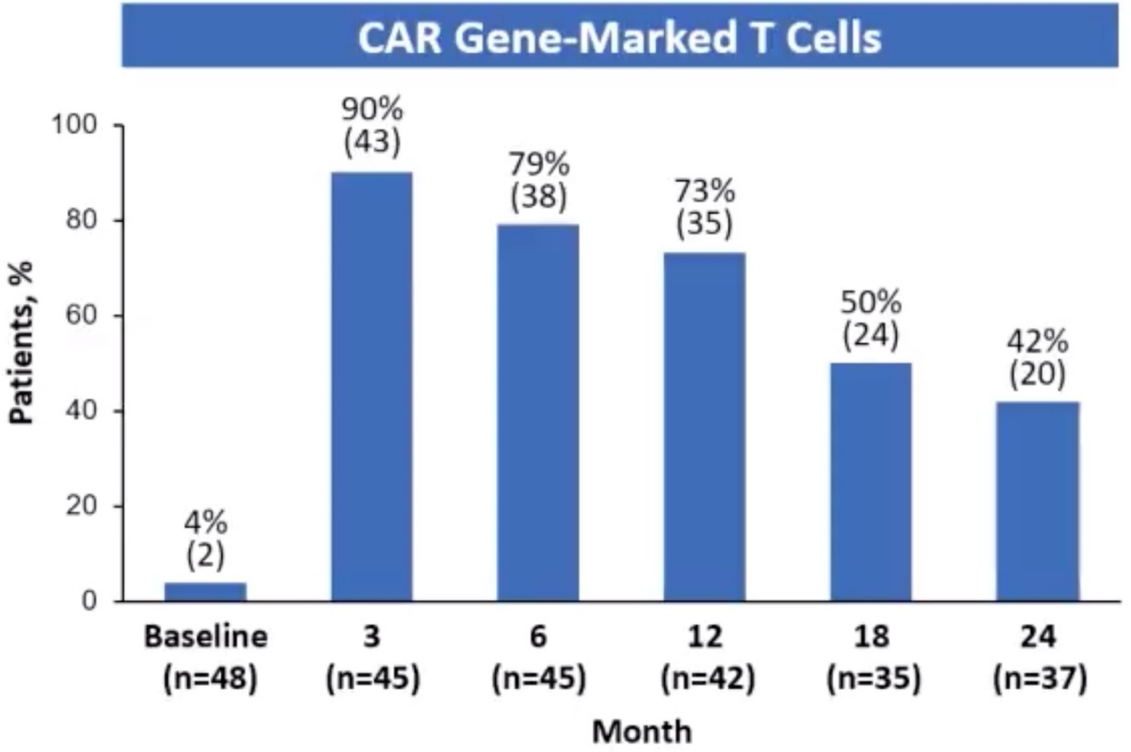
AE, n (%)	Follicular Lymphoma (N=124)		Marginal Zone Lymphoma (N=25)		All Patients (N=149)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	27 (22)	14 (11)	11 (44)	6 (24)	38 (26)	20 (13)
Serious AE	11 (9)	11 (9)	4 (16)	4 (16)	15 (10)	15 (10)
Cytopenia	8 (6)	4 (3)	3 (12)	3 (12)	11 (7)	7 (5)
Infection	18 (15)	7 (6)	7 (28)	4 (16)	25 (17)	11 (7)
CRS	0 (0)	0 (0)	2 (8)	0 (0)	2 (1)	0 (0)
Neurologic event	0 (0)	0 (0)	2 (8)	0 (0)	2 (1)	0 (0)
Hypogammaglobulinemia	2 (2)	0 (0)	2 (8)	0 (0)	4 (3)	0 (0)
Tumor lysis syndrome	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

- Grade 5 AEs occurred in 6 patients after the data cutoff of the primary analysis[b]
  - Grade 5 infectious AEs occurred in 5 patients: 1 COVID-19 (FL, Day 717, unrelated), 1 COVID-19 pneumonia (FL, Day 780, related to axi-cel), 1 PML[c] (FL, Day 697, related to axi-cel and CC) and 2 sepsis (FL, Day 1204; MZL, Day 139; both unrelated)
  - Acute bilineal leukemia occurred in 1 patient (FL, Day 623, CC related)

[a] Includes all AEs that occurred after the primary analysis data cutoff date (March 12, 2020) and by the data cutoff date of the current analysis (March 31, 2021). [b] No Grade 5 AEs were due to progressive disease. [c] The Grade 5 PML event occurred after axi-cel retreatment.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CC, conditioning chemotherapy; CRS, cytokine release syndrome; DCO, data cutoff; FL, follicular lymphoma; MZL, marginal zone lymphoma; PML, progressive multifocal leukoencephalopathy

Detectable B Cells and CAR T Cells Over Time in Patients With FL and Ongoing Responses at 24 Months





- The majority of patients with FL and ongoing responses had detectable B cells by Month 18; by Month 24, less than half had low levels of detectable CAR gene-marked cells
  - The levels of CAR gene-marked T cells were inversely correlated with that of B cells at each timepoint post-infusion

CAR, chimeric antigen receptor; FL, follicular lymphoma.

Conclusions

- With long-term follow-up in ZUMA-5, axi-cel demonstrated substantial and continued benefit in patients with R/R iNHL
  - In FL, high response rates translated to durability after 31 months median follow-up
    - Median DOR was 38.6 months, and 57% of efficacy-eligible patients were in ongoing response at data cutoff
    - Median PFS was nearly 40 months, and median OS was not yet reached
  - In MZL, efficacy outcomes appeared to improve with longer follow-up (median, 24 months)
    - Median DOR and OS not yet reached; median PFS was 17.3 months
    - 50% of patients were in ongoing response at data cutoff
- Axi-cel maintained a manageable safety profile in iNHL, with no new safety signals
- Results of the long-term pharmacokinetic analysis suggest that functional CAR T-cell persistence may not be required for long-term remissions in patients with FL, consistent with prior findings in aggressive lymphomas[1]
- Axi-cel is a highly effective therapeutic approach for patients with R/R iNHL

1. Neelapu SS, et al. ASH 2018. Abstract 2967.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DOR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MZL, marginal zone lymphoma; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

Mosunetuzumab Monotherapy is an Effective and Well-Tolerated Treatment Option for Patients with Relapsed/ Refractory (R/R) Follicular Lymphoma (FL) who have Received ≥2 Prior Lines of Therapy: Pivotal Results from a Phase I/II Study

L Elizabeth Budde,[1] Laurie H Sehn,[2] Matthew Matasar,[3] Stephen J Schuster,[4] Sarit Assouline,[5] Pratyush Giri,[6] John Kuruvilla,[7] Miguel Canales,[8] Sascha Dietrich,[9] Keith Fay,[10] Matthew Ku,[11] Loretta Nastoupil,[12] Michael C Wei,[13] Shen Yin,[13] Michelle Y Doral,[13] Chi-Chung Li,[13] Huang Huang,[14] Raluca Negricea,[15] Elicia Penuel,[13] Carol O'Hear,[13] Nancy L Bartlett[16]

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Accepted as an Oral Presentation at the 63rd ASH Annual Meeting and Exposition

Primary endpoint met: CR rate greater than historical control

Efficacy endpoint[1]	IRF N (%) [95% CI]	Investigator N (%) [95% CI]	Concordance IRF vs investigator
CR	**54 (60%)** [49%, 70%]	54 (60%) [49%, 70%]	93%
ORR	**72 (80%)** [70%, 88%]	70 (78%) [68%, 86%]	96%

- **60% CR rate significantly greater ($p<0.0001$)* than 14% historical control CR rate[2]**

*exact binomial test with two-sided alpha level of 5%; CI, confidence interval

1. Cheson et al. J Clin Oncol 2007;25:579–86
2. Dreyling et al. J Clin Oncol 2017;35:3898–905

Conclusions

- Pivotal Phase II study of mosunetuzumab, a CD20xCD3 T-cell-engaging bispecific antibody, met primary efficacy endpoint (CR rate: 60%, p<0.0001; ORR: 80%)
- Deep and durable responses achieved in heavily pre-treated/high-risk R/R FL with fixed duration treatment
- Favorable tolerability profile, with most CRS confined to Cycle 1 and low Grade; treatment administration without mandatory hospitalization
- First T-cell-engaging bispecific antibody to demonstrate clinically meaningful outcomes in patients with R/R FL in pivotal Phase II setting
  - potentially promising off-the-shelf, outpatient therapy

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Glofitamab Step-Up Dosing Induces High Response Rates in Pts With R/R MCL, most of whom had failed prior BTKi therapy

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

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

Baseline characteristics

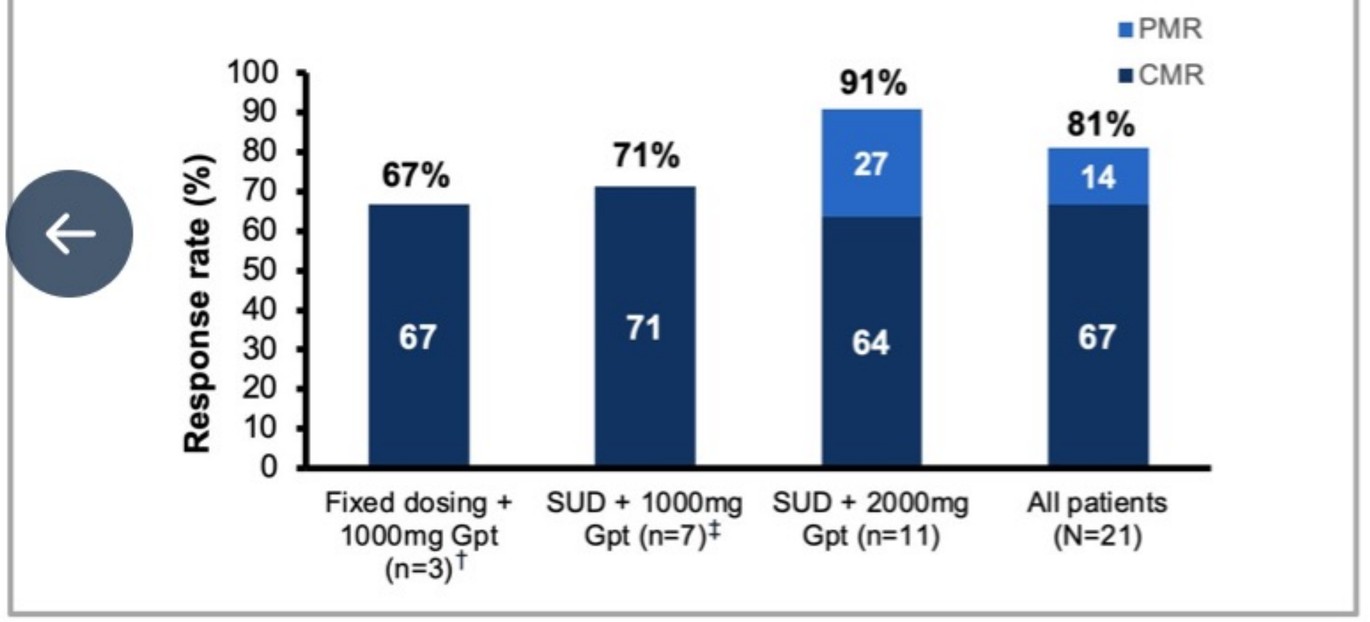
n (%) of patients unless stated		Glofitamab fixed dosing + 1000mg Gpt (n=3)	Glofitamab SUD + 1000mg Gpt (n=7)	Glofitamab SUD + 2000mg Gpt (n=19)	All patients (N=29*)
Median age, years (range)		81.0 (66–84)	69.0 (64–75)	66.0 (41–84)	69.0 (41–84)
Male		2 (66.7)	6 (85.7)	12 (63.2)	20 (69.0)
Ann Arbor stage III–IV at study entry		2 (66.7)	6 (85.7)	16 (84.2)	24 (82.8)
MCL IPI score ≥6 at study entry		3 (100)	3 (42.9)	12 (63.2)	18 (62.1)
Prior therapy	Median time since last therapy, months (range)	1.1 (1.0–8.5)	3.4 (1.2–53.2)	1.6 (0.1–107.5)	1.7 (0.1–107.5)
	Prior lines of therapy, median (range)	3 (2–5)	4 (3–5)	3 (1–6)	3 (1–6)
	BTKi	3 (100)	6 (85.7)	11 (57.9)	20 (69.0)
	Lenalidomide	0	1 (14.3)	3 (15.8)	4 (13.8)
	Chemotherapy	3 (100)	7 (100)	18 (94.7)	28 (96.6)
	Alkylator	0	6 (85.7)	7 (36.8)	13 (44.8)
	Anti-CD20 monoclonal antibody	3 (100)	6 (85.7)	14 (73.7)	23 (79.3)
Refractory status	Refractory to any prior therapy	3 (100)	7 (100)	16 (84.2)	26 (89.7)
	Refractory to prior anti-CD20 therapy	2 (66.7)	3 (42.9)	10 (52.6)	15 (51.7)
	Refractory to first-line therapy	2 (66.7)	2 (28.6)	11 (57.9)	15 (51.7)
	Refractory to last prior therapy	2 (66.7)	5 (71.4)	13 (68.4)	20 (69.0)

- **Most patients had received prior BTKi therapy**

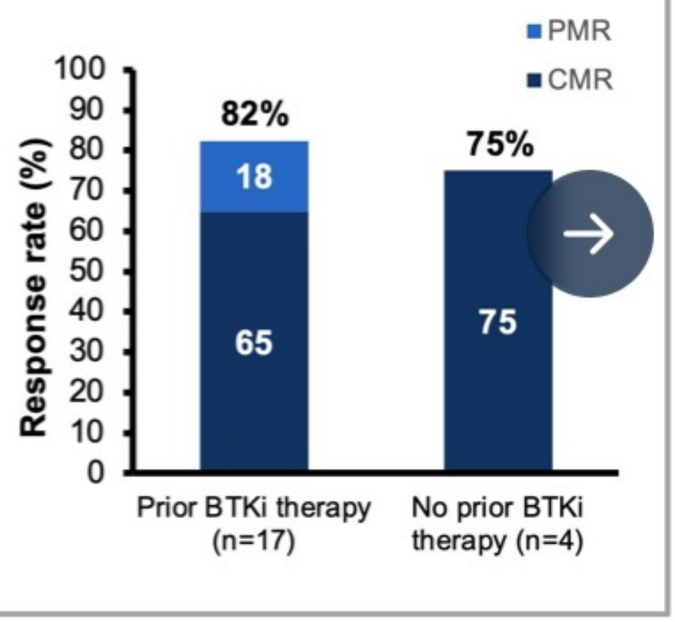
*Three patients were treated with glofitamab in combination with obinutuzumab (G-combo). Gpt, obinutuzumab pretreatment; IPI, International Prognostic Index; SUD, step-up dosing

Response rates

Response rates[1] by glofitamab regimen*



Response rates[1] by prior BTKi therapy*

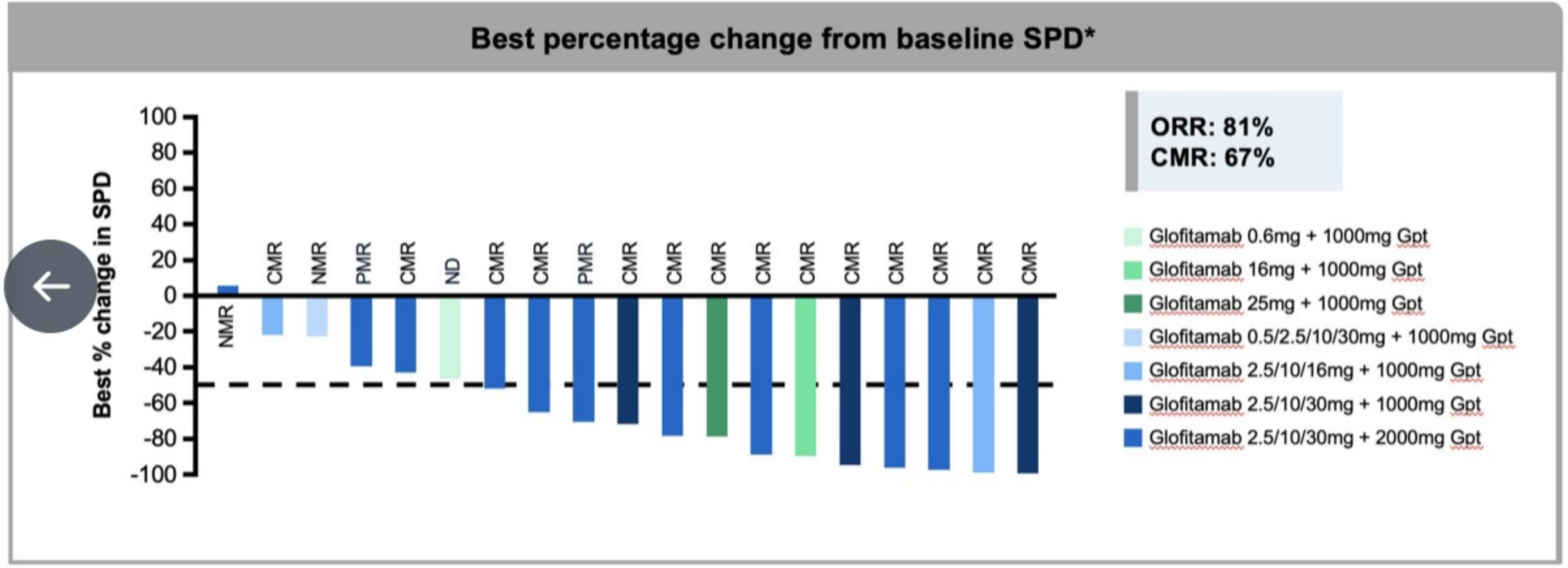


- **Glofitamab resulted in high response rates in patients with R/R MCL**

*21/29 patients were efficacy-evaluable: the secondary efficacy-evaluable population includes all patients who had a response assessment performed (investigator-assessed), or who were still on treatment at the time of their first scheduled response assessment (Lugano 2014 criteria)[1]. †Due to a data issue, the response (CR) from one patient is reported as missing. Two patients treated with a combination of glofitamab and obinutuzumab (G-combo); ‡One patient treated with G-combo. Gpt, obinutuzumab pretreatment; SUD, step-up dosing

1. Cheson, et al. J Clin Oncol 2014

Antitumor activity



- **Activity was observed across glofitamab dosing regimens in R/R MCL**

*Primary efficacy population: includes all patients who have a response assessment performed, who withdrew early from treatment or study, or who are still on treatment at the time of their first scheduled response assessment. Two patients were excluded because they had a missing SPD. Reference line at –50% indicates the reduction required for PR based on computed tomography. CMR, complete metabolic response; Gpt, obinutuzumab pretreatment; ND, not defined; SPD, sum of the product of diameters

LBA-1

The POLARIX Study: Polatuzumab Vedotin with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (Pola-R-CHP) Versus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP) Therapy in Patients with Previously Untreated Diffuse Large B-Cell Lymphoma

Hervé Tilly,[1] Franck Morschhauser,[2] Laurie H. Sehn,[3] Jonathan W. Friedberg,[4] Marek Trněný,[5] Jeff P. Sharman,[6] Charles Herbaux,[7] John M. Burke,[8] Matthew Matasar,[9] Shinya Rai,[10] Koji Izutsu,[11] Neha Mehta-Shah,[12] Lucie Oberic,[13] Adrien Chauchet,[14] Wojciech Jurczak,[15] Yuqin Song,[16] Richard Greil,[17] Larysa Mykhalska,[18] Juan Miguel Bergua Burgués,[19] Matthew C. Cheung,[20] Antonio Pinto,[21] Ho-Jin Shin,[22] Greg Hapgood,[23] Eduardo Munhoz,[24] Pau Abrisqueta,[25] Jyh-Pyng Gau,[26] Jamie Hirata,[27] Yanwen Jiang,[27] Mark Yan,[28] Calvin Lee,[27] Christopher Flowers,[29] Gilles Salles[30]

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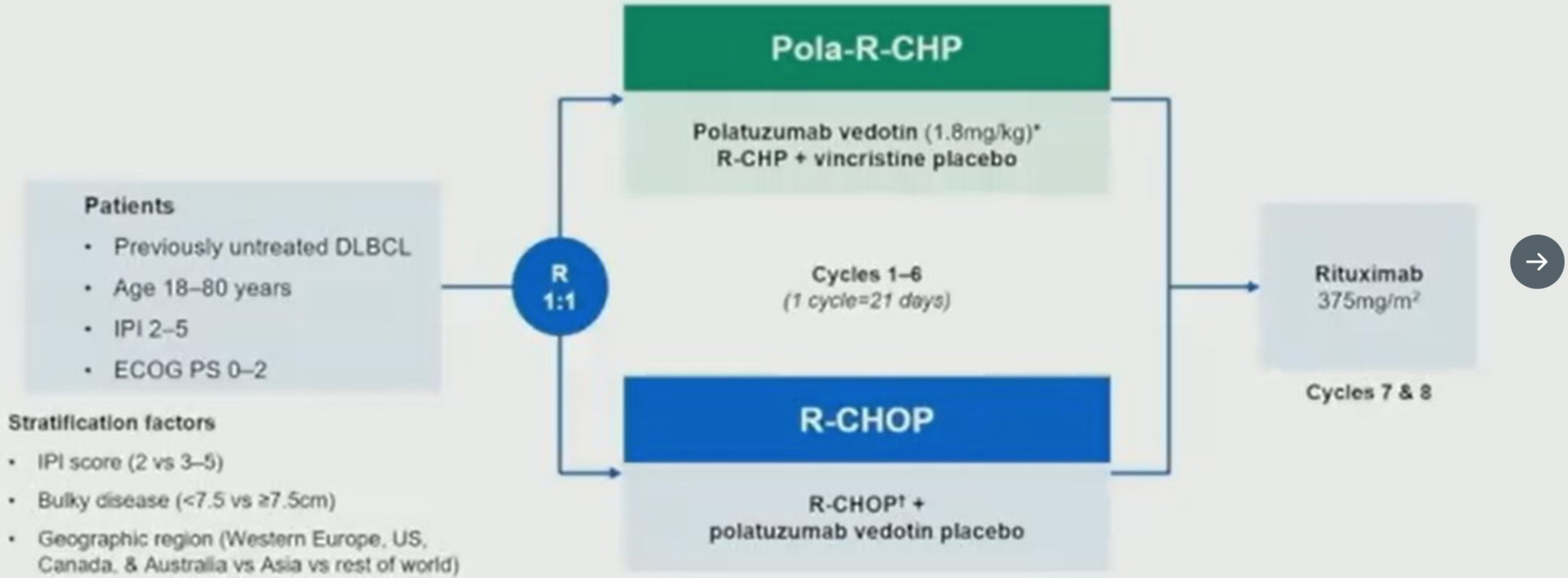
Late-Breaking Abstract Accepted as an Oral Presentation at the 63rd ASH Annual Meeting and Exposition, 11–14 December 2021

POLARIX: A randomized double-blinded study



*IV on Day 1; †R-CHOP: IV rituximab 375mg/m², cyclophosphamide 750mg/m², doxorubicin 50mg/m², and vincristine 1.4mg/m² (max. 2mg) on Day 1, plus oral prednisone 100mg once daily on Days 1–5.
IPI, International prognostic index; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized.

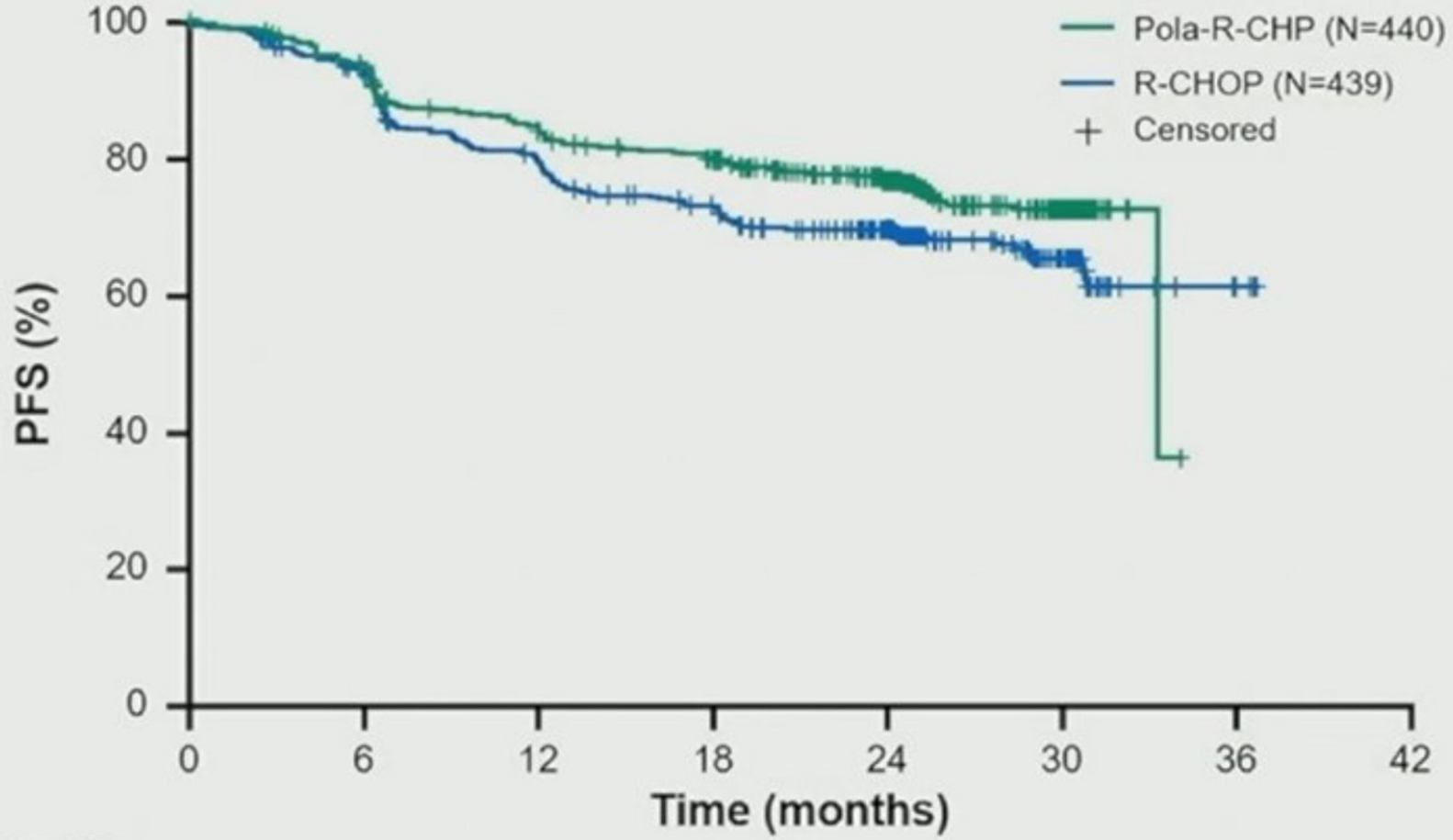
Baseline characteristics

ITT population		Pola-R-CHP (N=440)	R-CHOP (N=439)
Age	Median (range), years	65.0 (19–80)	66.0 (19–80)
Sex, n (%)	Male	239 (54)	234 (53)
ECOG PS, n (%)	0–1	374 (85)	363 (83)
	2	66 (15)	75 (17)
Bulky disease (≥7.5cm), n (%)	Present	193 (44)	192 (44)
Elevated LDH, n (%)	Yes	291 (66)	284 (65)
Time from diagnosis to treatment initiation	Median, days	26	27
n Arbor Stage, n (%)	III–IV	393 (89)	387 (88)
Extranodal sites, n (%)	≥2	213 (48)	213 (49)
IPI score, n (%)	2	167 (38)	167 (38)
	3–5	273 (62)	272 (62)
Cell-of-origin, (%)*	ABC	102 (31)	119 (35)
	GCB	184 (56)	168 (50)
	Unclassified	44 (13)	51 (15)
MYC/BCL2 expression, n (%)*	Double expression	139 (38)	151 (41)
MYC/BCL2/BCL6 rearrangement, n (%)*	Double-/triple-hit	26 (8)	19 (6)

*In the Pola-R-CHP and R-CHOP groups, respectively, the numbers of patients evaluable for cell-of-origin were 330 and 338, with IHC for MYC/BCL2 expression were 362 and 366, and with FISH for *MYC/BCL2/BCL6* rearrangements were 331 and 334.
ABC, activated B-cell; FISH, fluorescence in situ hybridization; GCB, germinal center B-cell; LDH, lactate dehydrogenase.

Primary endpoint: Progression-free survival

Pola-R-CHP significantly improved PFS versus R-CHOP



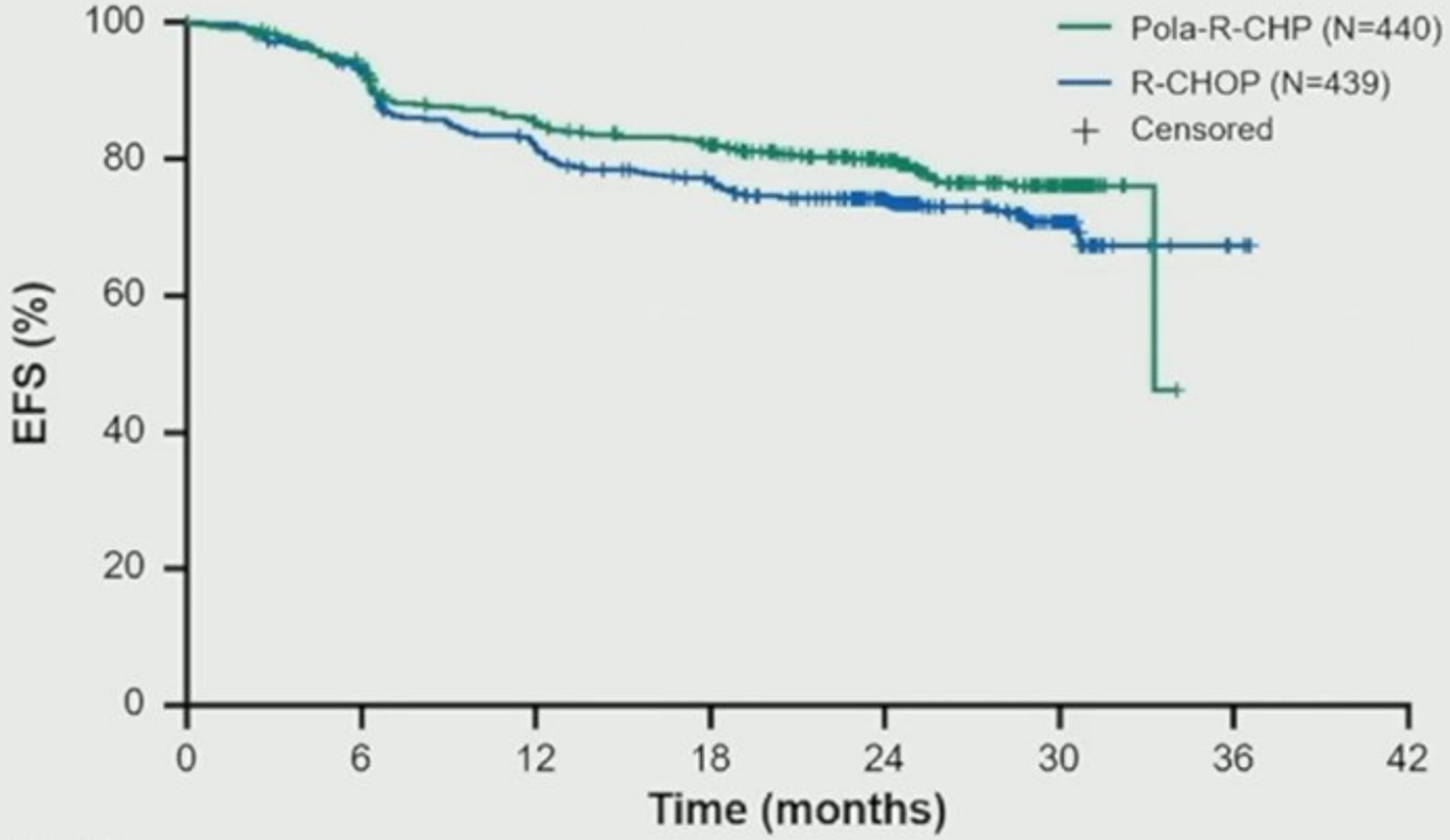
No. of patients at risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

HR 0.73 (P<0.02)
95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP
- **24-month PFS:**
  76.7% with Pola-R-CHP versus
  70.2% with R-CHOP (Δ**=6.5%**)

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
NE, not evaluable.

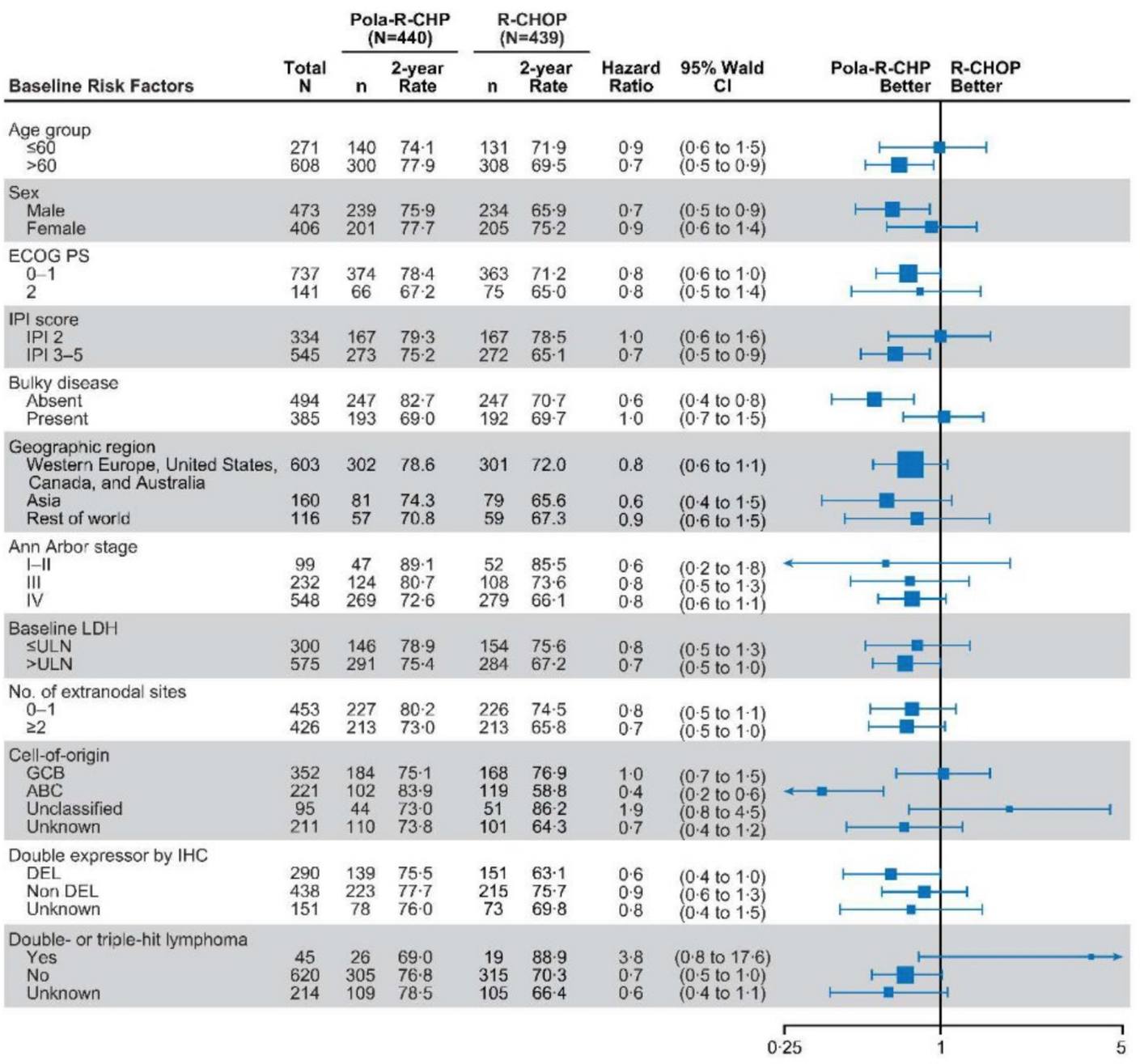
Event-free survival



HR 0.75 (P=0.02)
95% CI: 0.58, 0.96

No. of patients at risk								
Pola-R-CHP	440	402	348	323	243	78	NE	NE
R-CHOP	439	386	327	294	218	78	3	NE

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
EFS, event-free survival.

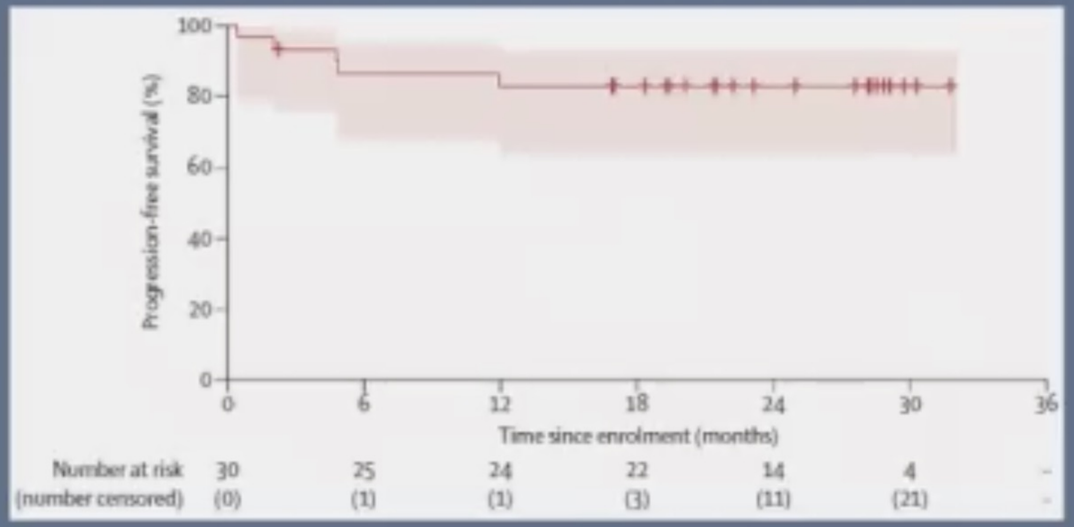


Randomized Phase II/III Study of DA-EPOCH-R +/- Venetoclax in Previously Untreated Double Hit Lymphoma: Initial Results from Alliance A051701

Jeremy S. Abramson, Amy S. Ruppert, Sharmila Giri, Ann Hudson, Eric Hsi, Richard F. Little, Steven Gore, Anusha Vallurupalli, Daniel Landsburg, Brad Kahl, Jonathan W. Friedberg, Nancy L. Bartlett, John P. Leonard

63rd ASH® Annual Meeting and Exposition

Phase I Study of Venetoclax plus DA-EPOCH-R



- Notable grade 3-4 toxicities
  - Neutropenia 83%
  - Thrombocytopenia 70%
  - Neutropenic fever 63%
- Venetoclax 600 mg x 5 days with each cycle declared RP2D

Rutherford, et al. Lancet Haem 2021.

ALLIANCE 051701 (Phase 2/3): Venetoclax plus Chemoimmunotherapy for MYC/BCL-2 Double Hit and Double Expressing Lymphomas

Double-hit lymphoma
Or
Double expressor lymphoma

Patients stratified by IPI, prior cycle of R-chemo, and DHL/DEL subtype

R

Arm 1 → R-chemo† (6 cycles, q21 days) → PD, unacceptable AE, or 6 cycles complete

Arm 2 → Venetoclax‡ + R-chemo† (6 cycles, q21 days) → PD, unacceptable AE, or 6 cycles complete

FU for 10 years or until death

Primary Endpoint

- PFS

Secondary Endpoints

- OS
- Safety
- Response rates (RR)

Exploratory Endpoints

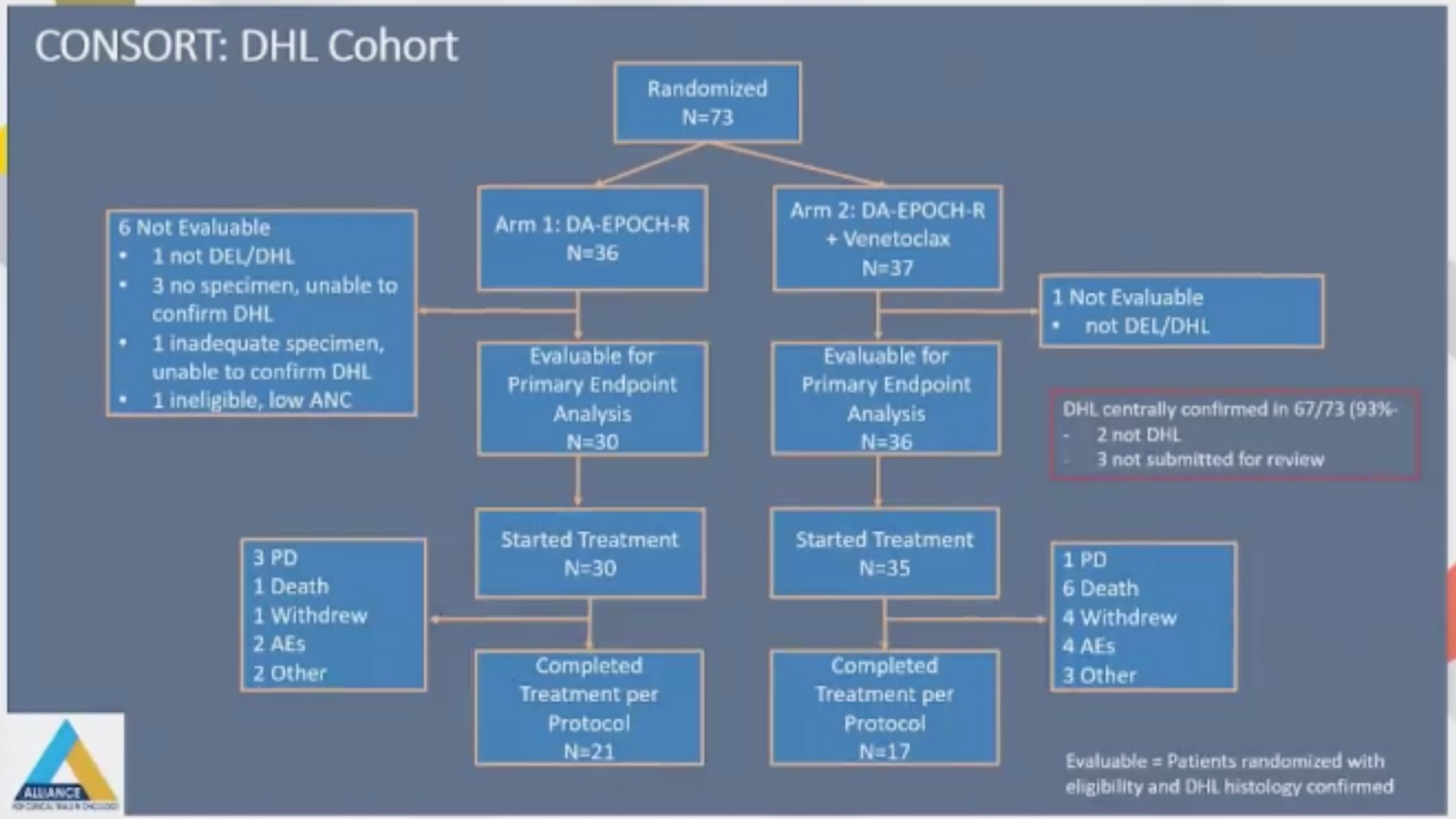
- Expression/genetic profile of DEL/DHL
- Correlation of expression/mutational profiles with known DLBCL profiles, response to treatment, PFS, and OS

- HGBCL with translocations of MYC and BCL-2 (DHL), or DLBCL/HGBCL NOS with protein expression by IHC of both MYC (≥40%) and BCL-2 (≥50%) in the absence of dual translocations (DEL). MYC/BCL-6 DHL are eligible for the DHL cohort only if they have protein expression of BCL-2..
- † R-CHOP in patients with DEL, DA-EPOCH-R in patients with DHL. Patients who received a single cycle of R-CHOP or DA-EPOCH-R prior to randomization will count that towards the 6 total cycles and so will receive 5 cycles of R-chemo +/- venetoclax.
- ‡ Venetoclax given days 4–8 cycle 1, days 1–5 cycles 2–6. Dose is 600 mg/day with DA-EPOCH-R, 800 mg/day with R-CHOP.

Statistical Considerations: DHL Cohort

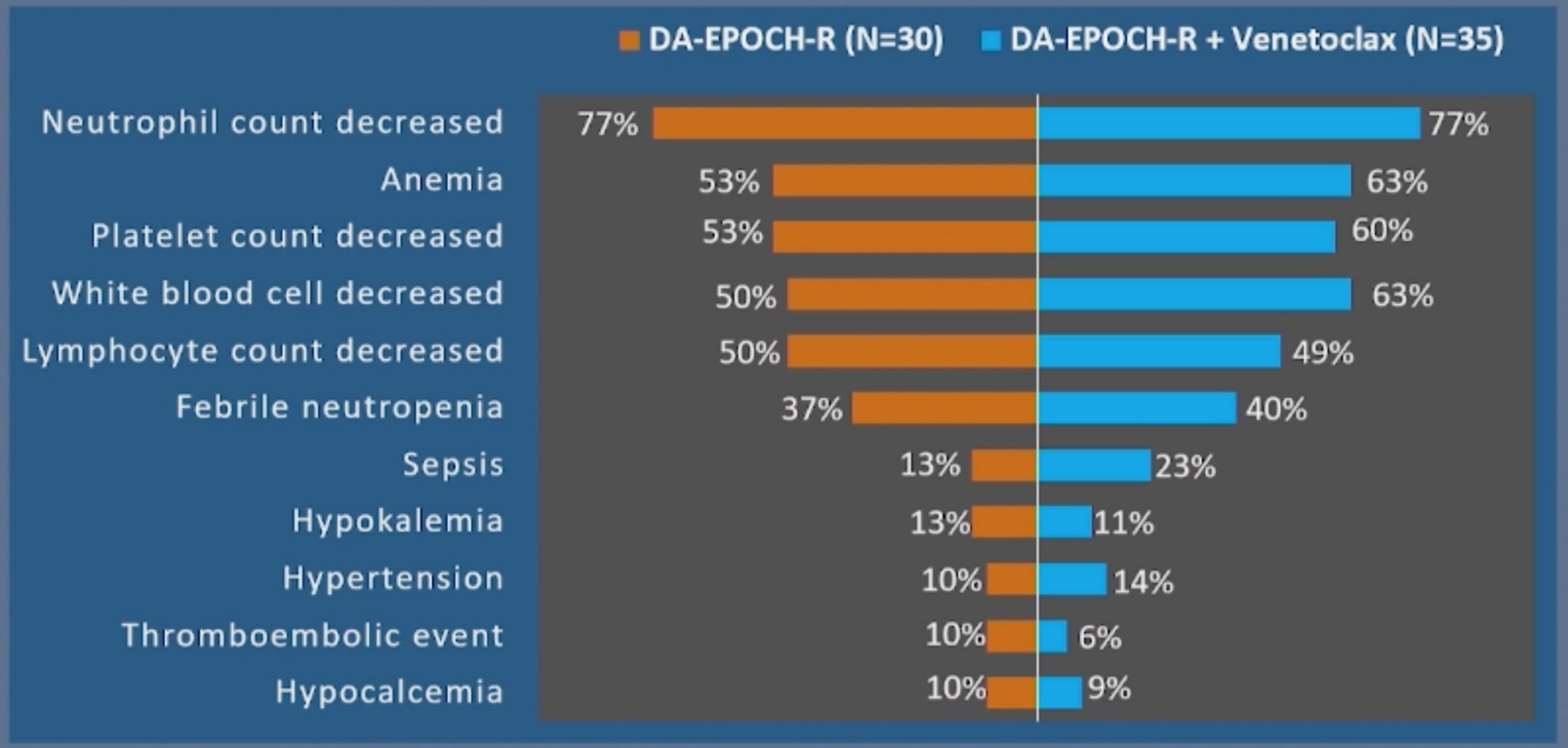
- Phase 2 Primary Endpoint: Progression-free Survival (PFS), defined as the time from randomization until progression or death
- Planned Accrual: 106 patients (53/arm)
  - 53 events ensured 90% power to detect hazard ratio=0.557 (2-year PFS estimates 60% vs 40%)
  - 1-sided $\alpha = 0.20$
- First patient enrolled: Oct 22, 2019
- Safety signal with DA-EPOCH-R + Venetoclax led to led to early closure of the study and the data were released on December 2, 2020
- Data for this analysis was frozen July 8, 2021

CONSORT: DHL Cohort



Common Grade 3+ Adverse Events

Worst Grade, Regardless of Attribution



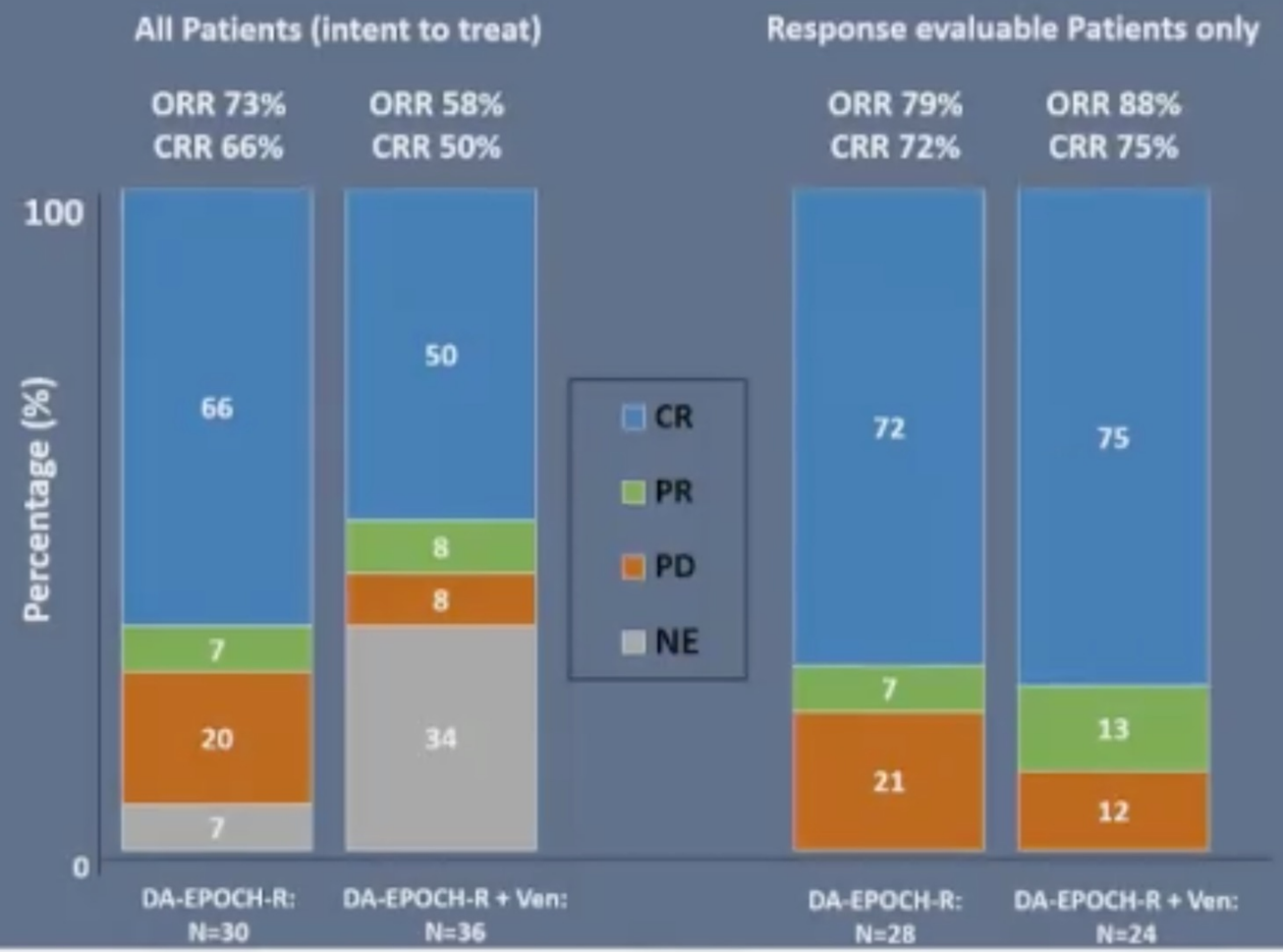
Grade 5 AEs on Treatment or within 30 Days after Treatment

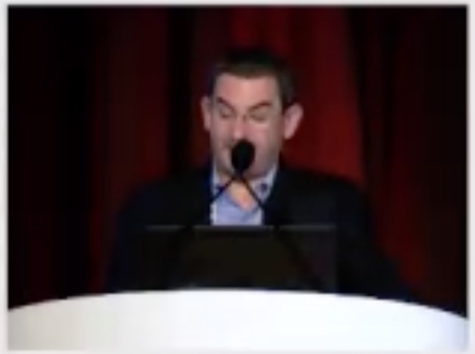
DA-EPOCH-R vs DA-EPOCH-R + Venetoclax: 1/30 (3.3%) vs 6/35 (17.1%)

Grade 5 Adverse Events

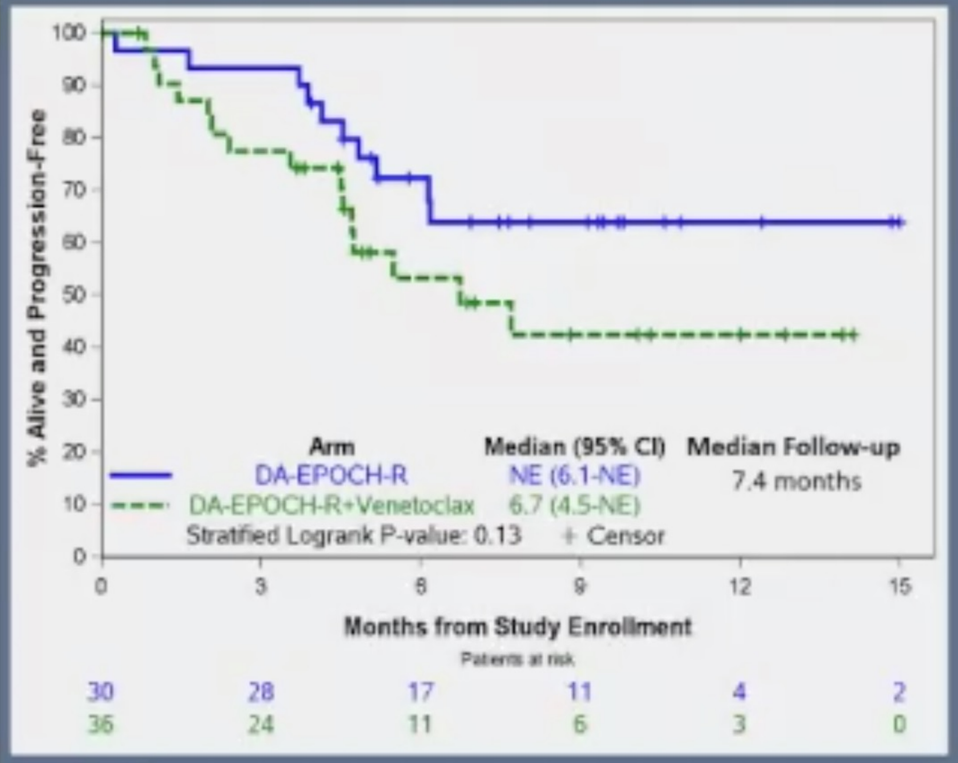
Arm	Age	Gender	Grade 5 Adverse Event	Treatment Cycle (Days after Last Dose)
1: DA-EPOCH-R	78	M	Dyspnea	1
	76	M	Sepsis	(40 days after C3 dose)
2: DA-EPOCH-R + Venetoclax	62	F	Sepsis	1
	80	M	Sepsis	2
	59	M	Sepsis	2
	79	F	Sepsis	3
	68	F	Cardiac arrest	2
	68	M	Cardiac arrest	2
	76	M	Lung infection	(51 days after C3 dose)
	60	M	Hypoxia	(56 days after C5 dose)
	53	M	Sepsis	(57 days after C5 dose)
	65	M	COVID-19	(77 days after C6 dose)

Response at End of Treatment

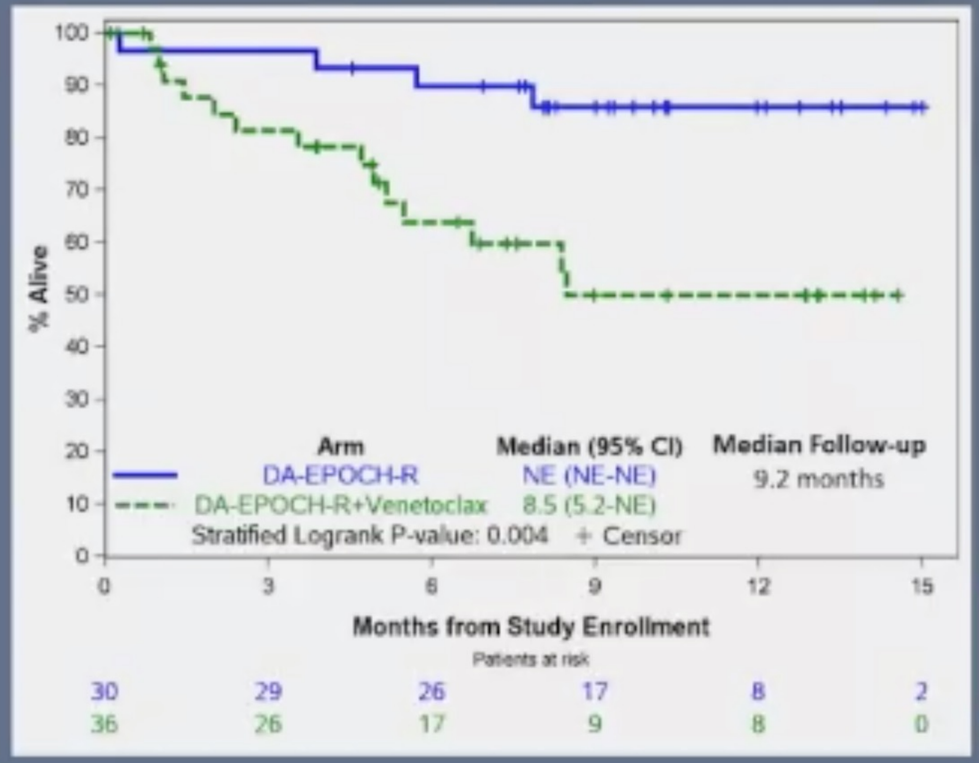




Progression Free Survival



Overall Survival



Conclusions

- Venetoclax added to DA-EPOCH-R resulted in excess treatment-associated toxicity and mortality, prompting early closure of the DHL cohort of A051701
- Prospective trials of DHL are achievable in the cooperative group setting
- DA-EPOCH-R performed well as a control arm, with limited follow up presently
- Accrual based on local path had high concordance with central review
- The DEL cohort of R-CHOP +/- Venetoclax has completed accrual to the phase 2 component of the study

Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Case Presentations: Leukemia, Lymphoma, Myeloma

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ANCO

Educating and Empowering the Northern California Cancer Community

Case Presentations in Leukemia, Myeloma, Lymphoma

Eric Kuo MD
Fellow at Stanford Hematology/Oncology

1

Conflict of Interest

ANCO
Educating and Empowering the Northern California Cancer Community

- None to Declare

2

Case 1

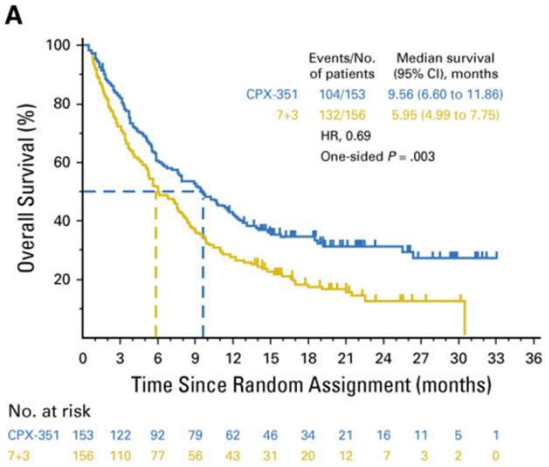
74 yo F with Hx of Early stage ER/PR+ breast cancer diagnosed in 2006 s/p mastectomy/XRT c/b recurrence w/ mets to bone 2017 s/p XRT currently on palbociclib+ letrozole in remission now presenting with neutropenia:

- 2017- Hgb~13, MCV 110
- 12/2021- WBC 2.2, ANC 700 – reduced Palbociclib dose
- 3/25- Developed neutropenia – stopped Palbociclib
- 4/29- Bone marrow – 30% immature monocytes/blasts, IHC for TP53 negative

- New diagnosis of Therapy-related AML (**NPM1+**, IDH1/2-, FLT3-), **ASXL1mut**, normal karyo
- Determined to be **Not FIT** for intensive chemotherapy

3

CPX-351



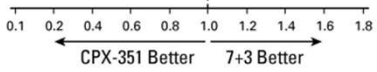
CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia
Jeffrey E. Lancet, Geoffrey L. Uy, Jorge E. Cortes, Laura F. Newell, Tara L. Lin, Ellen K. Ritchie, Robert K. Stuart, Stephen A. Strickland, Donna Hogge, Scott R. Solomon, Richard M. Stone, Dale L. Bixby, Jonathan E. Kolitz, Gary J. Schiller, Matthew J. Wieduwilt, Daniel H. Ryan, Antje Hoering, Kamalika Banerjee, Michael Chiarella, Arthur C. Louie, and Bruno C. Medeiros. Journal of Clinical Oncology 2018 36:26, 2684-2692

4

CPX-351

B

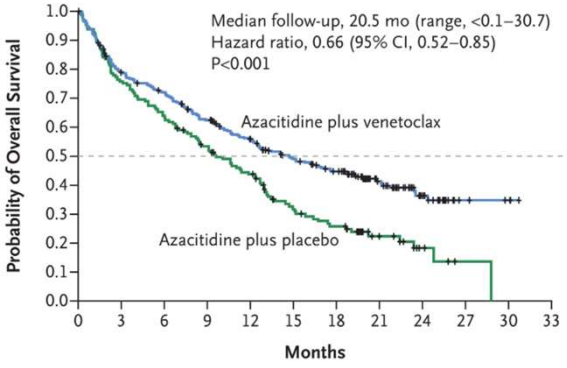
Subgroup	CPX-351 No.	CPX-351 Median OS, months	7+3 No.	7+3 Median OS, months	HR (95% CI) for Death
Age					
60-69 years	96	9.63	102	6.87	0.68 (0.49 to 0.95)
70-75 years	57	8.87	54	5.62	0.55 (0.36 to 0.84)
Type of AML					
Therapy-related AML	30	12.17	33	5.95	0.48 (0.26 to 0.86)
AML with antecedent MDS or CMML	82	7.38	86	5.95	0.70 (0.50 to 0.99)
MDS with prior HMA exposure	50	5.65	55	7.43	0.98 (0.64 to 1.51)
MDS without prior HMA exposure	21	15.74	19	5.13	0.46 (0.21 to 0.97)
CMML	11	9.33	12	2.28	0.37 (0.14 to 0.95)
De novo AML with MDS karyotype	41	10.09	37	7.36	0.71 (0.42 to 1.20)
Cytogenetic risk at screening					
Favorable/intermediate	71	14.72	63	8.41	0.64 (0.41 to 0.99)
Unfavorable	72	6.60	83	5.16	0.73 (0.51 to 1.06)
Baseline *FLT3* mutation status					
FLT3 wild type	116	9.33	120	5.98	0.64 (0.47 to 0.87)
FLT3 mutation	22	10.25	21	4.60	0.76 (0.34 to 1.66)
Overall HMA experience					
All patients with prior HMA exposure*	62	5.65	71	5.90	0.86 (0.59 to 1.26)



CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia
Jeffrey E. Lancet, Geoffrey L. Uy, Jorge E. Cortes, Laura F. Newell, Tara L. Lin, Ellen K. Ritchie, Robert K. Stuart, Stephen A. Strickland, Donna Hogge, Scott R. Solomon, Richard M. Stone, Dale L. Bixby, Jonathan E. Kolitz, Gary J. Schiller, Matthew J. Wieduwilt, Daniel H. Ryan, Antje Hoering, Kamalika Banerjee, Michael Chiarella, Arthur C. Louie, and Bruno C. Medeiros. Journal of Clinical Oncology 2018 36:26, 2684-2692

5

HMA/VEN



No. at Risk												
Azacitidine plus venetoclax	286	219	198	168	143	117	101	54	23	5	3	0
Azacitidine plus placebo	145	109	92	74	59	38	30	14	5	1	0	0

DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, Konopleva M, Döhner H, Letai A, Fenaux P, Koller E, Havelange V, Leber B, Esteve J, Wang J, Pejsa V, Hájek R, Porkka K, Illés Á, Lavie D, Lemoli RM, Yamamoto K, Yoon SS, Jang JH, Yeh SP, Turgut M, Hong WJ, Zhou Y, Potluri J, Pratz KW. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020 Aug 13;383(7):617-629. doi: 10.1056/NEJMoa2012971. PMID: 32786187.

6

LDAC/Cladribine+ Ven w/ Alternating 5-Aza

Characteristic	Parameter	N	%	Mutation	N
Age	Median (Range)	68 (57 – 84)		TET2	14
	≥ 70 years	18	38	DNMT3A	13
Cytogenetics	Diploid, -Y	25	52	NPM1	13
	Adverse	12	25	RAS	12
	Intermediate	8	17	IDH2	11
	Insufficient	3	6	SR5F2	11
Bone marrow Blast %	Median (Range)	55 (18– 95)		RUNX1	7
WBC [x10^9/L]	Median (Range)	3 (1 – 23)		BCOR	6
Peripheral Blood Blast %	Median (Range)	18 (0 – 93)		ASXL1	5
Serum Creatinine	Median (Range)	0.87 (0.48 – 1.67)		IDH1	5
Response / Outcome	**N**	**%**	**MRD(-)**	CEBPA	4
Evaluable for Response	48	100		PTPN11	4
CR	37	77	34 (92)	STAG2	4
Cri	8	17	2 (25)	TP53	4
CR + Cri	45	94		BCORL1	3
No Response	3	6		FLT3-D835	3
Died ≤ 4 weeks	0	0		GATA2	3
Died ≤ 8 weeks	1	2		SF3B1	3
Median # of cycles given (Range)	3 (1 – 3)			U2AF1	3
Median # of cycles to response (Range)	1 (1 – 3)			FLT3-ITD	1

Subgroup	Median OS (m)	6-month OS	12-month OS	P-value
Diploid karyotype	NR	95%	88%	
Adverse karyotype	7.8	67%	40%	
Intermediate karyotype	NR	88%	66%	
MRD Negative	NR	94%	86%	0.056
MRD Positive	10.7	88%	38%	
Secondary AML	10.6	80%	43%	0.09
de novo AML	NR	88%	79%	
SCT in CR1	NR	100%	90%	0.099
No SCT in CR1	NR	90%	68%	

*Tapan M. Kadia, MD[1], Gautam Borthakur, MD[1], Naveen Pemmaraju, MD[1],*Phase II Study of Venetoclax Added to Cladribine + Low Dose AraC (LDAC) Alternating with 5-Azacytidine Demonstrates High Rates of Minimal Residual Disease (MRD) Negative Complete Remissions (CR) and Excellent Tolerability in Older Patients with Newly Diagnosed Acute Myeloid Leukemia (AML). ASH Poster Session 2018. https://ash.confex.com/ash/2020/webprogram/Paper142092.html

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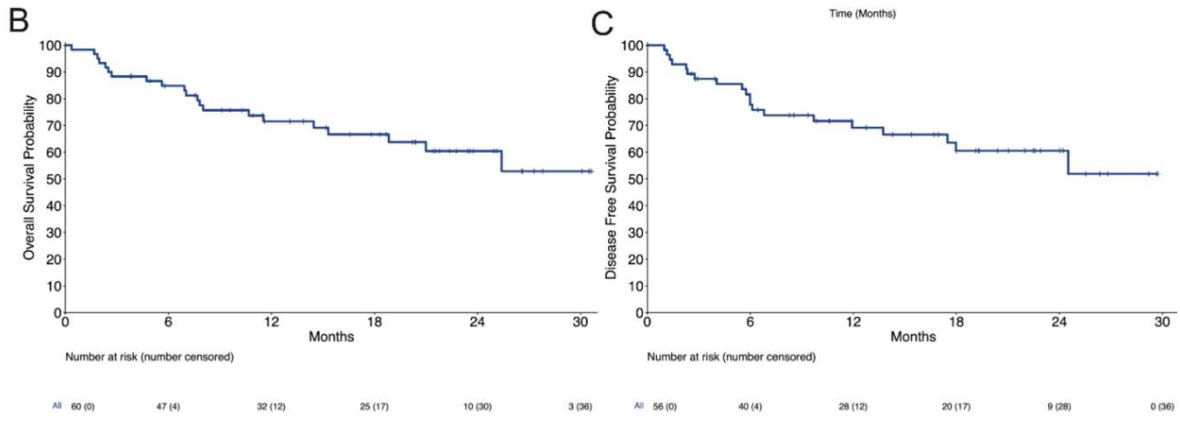
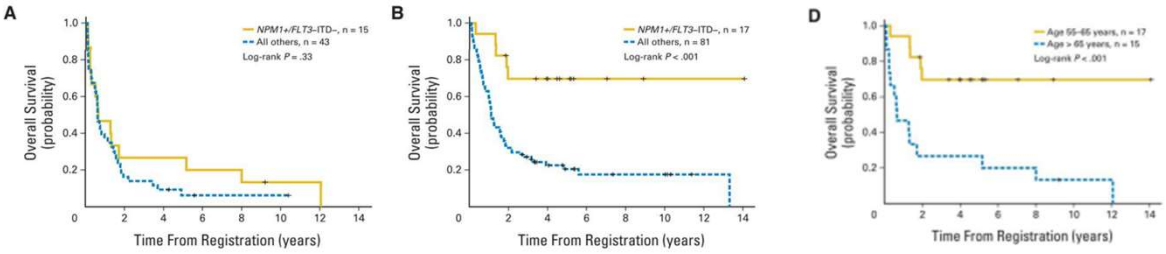
LDAC/Cladribine+ Ven w/ Alternating 5-Aza



Patrick K Reville, Hagop Kantarjian, et al. Farhad Ravandi, Tapan M. Kadia, Phase II Study of Venetoclax Added to Cladribine (CLAD) and Low Dose AraC (LDAC) Alternating with 5-Azacytidine (AZA) in Older and Unfit Patients with Newly Diagnosed Acute Myeloid Leukemia (AML), Blood, Volume 138, Supplement 1,2021,Page 367,ISSN 0006-4971,https://doi.org/10.1182/blood-2021-147360.

8

NPM1 in Older Patients



Ostronoff F, Othus M, Lazenby M, Estey E, Appelbaum FR, Evans A, Godwin J, Gilkes A, Kopecky KJ, Burnett A, List AF, Fang M, Oehler VG, Petersdorf SH, Pogosova-Agadjanyan EL, Radich JP, Willman CL, Meshinchi S, Stirewalt DL. Prognostic significance of NPM1 mutations in the absence of FLT3-internal tandem duplication in older patients with acute myeloid leukemia: a SWOG and UK National Cancer Research Institute/Medical Research Council report. J Clin Oncol. 2015 Apr 1;33(10):1157-64. doi: 10.1200/JCO.2014.58.0571. Epub 2015 Feb 23. Erratum in: J Clin Oncol. 2015 May 20;33(15):1715. PMID: 25713434; PMCID: PMC4372852.

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Case 1

74 yo F with Hx of Early stage ER/PR+ breast cancer diagnosed in 2006 s/p mastectomy/XRT c/b recurrence w/ mets to bone 2017 s/p XRT currently on palbociclib+ letrozole in remission now presenting with neutropenia:

- 2017- Hgb~13, MCV 110
- 12/2021- WBC 2.2, ANC 700 – reduced Palbociclib dose
- 3/25- Developed neutropenia – stopped Palbociclib
- 4/29- Bone marrow – 30% immature monocytes/blasts, IHC for TP53 negative

- New diagnosis of Therapy-related AML (**NPM1+**, IDH1/2-, FLT3-), **ASXL1mut**, normal karyo
- Determined to be **Not FIT** for intensive chemotherapy

- **5/6- Started LDAC/Cladribine + venetoclax alternating with HMA**

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Pearls:

- New Dx of t-AML, Unfit for intensive induction(CPX-351), can consider a less intensive regimen (LDAC/cladribine+ven alternating HMA)

- NPM1+ unlikely to confer favorable risk for those >65

ANCO
Educating and Empowering the Northern California Cancer Community

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Case 2

ANCO
Educating and Empowering the Northern California Cancer Community

75 yo M with Hx of papillary thyroid Ca s/p thyroidectomy/RAI(2009) with High-Risk IgM lambda Multiple Myeloma s/p several lines of therapy at OSH presenting with relapsed/refractory disease

- 7/2012- 60-70% plasma cells, lambda
  - Cytogenetics: Trisomy 9,**13q del, 17p del, t(11;14), BCL2 high**

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Case 2

75 yo M with Hx of papillary thyroid Ca s/p thyroidectomy/RAI(2009) with High-Risk IgM lambda Multiple Myeloma s/p several lines of therapy at OSH presenting with relapsed/refractory disease

- 8/2012-12/2012- **VRD** x6 cycles
- 2/2013- refractory disease- **KRd** x5
- 12/2013- HyperCAD + stem cell collection
- 1/2014- Melphalan + **AutoHSCT** switched to **KRd maintenance**
- 10/2015- BM bx MRD negative clonseq
- 2018- Stopped Dex
- 1/2019- Stopped Revlimid
- 6/2019- Carfilzomib QoW
- 10/2019- Stopped Carfilzomib

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Case 2

75 yo M with history of papillary thyroid Ca s/p thyroidectomy/RAI with High-Risk IgM lambda Multiple Myeloma s/p several lines of therapy with relapsed/refractory disease

- 12/2021- Diagnosed with Metastatic Cecal Adenocarcinoma to liver –
- 1/20/22- C2 cycle of Neoadjuvant FOLFOX/avastin
- 2/2022- admitted for worsening renal function, uptrending M-spike, lambda light chain, PET with lytic lesions throughout appendicular skeleton, ECOG1
- 3/2022-Started **Venetoclax + bortezomib+ dex,** Colon Cancer treatment on Hold

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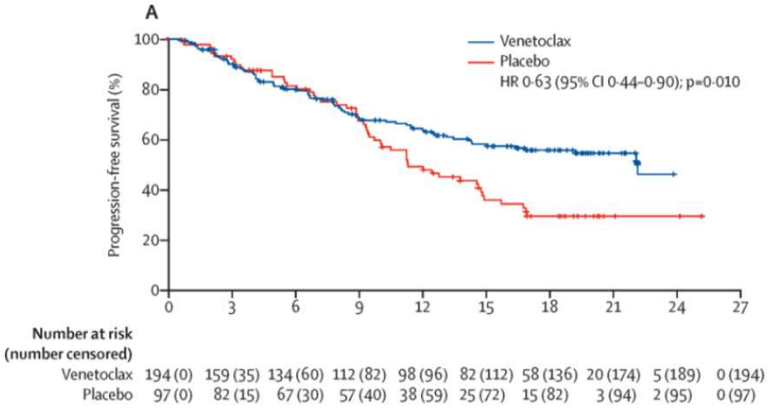
Venetoclax + Bortezomib + dex



Kumar SK, Harrison SJ, Cavo M, de la Rubia J, Popat R, Gasparetto C, Hungria V, Salwender H, Suzuki K, Kim I, Punnoose EA, Hong WJ, Freise KJ, Yang X, Sood A, Jalaluddin M, Ross JA, Ward JE, Maciag PC, Moreau P. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2020 Dec;21(12):1630-1642. doi: 10.1016/S1470-2045(20)30525-8. Epub 2020 Oct 29. PMID: 33129376.

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Venetoclax + Bortezomib + dex

	All patients in intention-to-treat population			Patients with t(11;14) translocation			Patients with high *BCL2* expression		
	Venetoclax group (n=194)	Placebo group (n=97)	p value	Venetoclax group (n=20)	Placebo group (n=15)	p value *	Venetoclax group (n=66)	Placebo group (n=32)	p value *
Stringent complete response	15 (8%)	2 (2%)	0·054	4 (20%)	0	0·102	5 (8%)	0	0·268
Complete response	36 (19%)	3 (3%)	0·00028	5 (25%)	1 (7%)	0·129	19 (29%)	0	0·0019
Very good partial response	63 (32%)	30 (31%)	0·800	5 (25%)	3 (20%)	0·842	23 (35%)	9 (28%)	0·663
Partial response	45 (23%)	31 (32%)	0·112	4 (20%)	3 (20%)	0·560	9 (14%)	15 (47%)	0·00085
Minimal response	3 (2%)	10 (10%)	0·00061	0	4 (27%)	0·0064	0	4 (13%)	0·017
Stable disease	14 (7%)	10 (10%)	0·381	0	3 (20%)	0·035	3 (5%)	2 (6%)	1·00
Progressive disease	10 (5%)	5 (5%)	0·990	0	0	..	2 (3%)	0	0·816
Overall response rate (partial response or better)	159 (82%)	66 (68%)	0·0081	18 (90%)	7 (47%)	0·0038	56 (85%)	24 (75%)	0·367
Very good partial response or better	114 (59%)	35 (36%)	0·00029	14 (70%)	4 (27%)	0·016	47 (71%)	9 (28%)	0·00013
Complete response or better (post-hoc)	51 (26%)	5 (5%)	..	9 (45%)	1 (7%)	..	24 (36%)	0	0·00024
Minimal residual disease									
10^{-4}	37 (19%)	3 (3%)	0·00021	8 (40%)	0	0·0062	18 (27%)	1 (3%)	0·0104
10^{-5}	26 (13%)	1 (1%)	0·00066	5 (25%)	0	0·056	12 (18%)	0	0·025
10^{-6}	14 (7%)	1 (1%)	0·026	4 (20%)	0	0·080	6 (9%)	0	0·190
Median duration of response, months (95% CI)	Not reached (21·0–not reached)	12·8(9·2–15·5)	..	Not reached	12·2 (7·9–not reached)	..	Not reached (21·0–not reached)	8·8(7·6–not reached)	..

Kumar SK, Harrison SJ, Cavo M, de la Rubia J, Popat R, Gasparetto C, Hungria V, Salwender H, Suzuki K, Kim I, Punnoose EA, Hong WJ, Freise KJ, Yang X, Sood A, Jalaluddin M, Ross JA, Ward JE, Maciag PC, Moreau P. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2020 Dec;21(12):1630-1642. doi: 10.1016/S1470-2045(20)30525-8. Epub 2020 Oct 29. PMID: 33129376.

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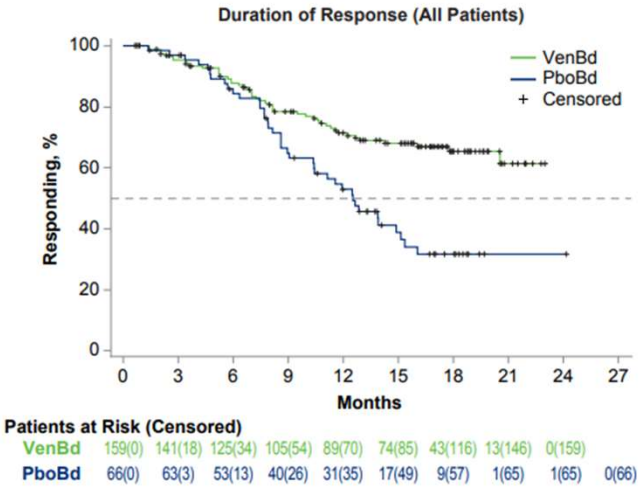
Venetoclax + Bortezomib + dex



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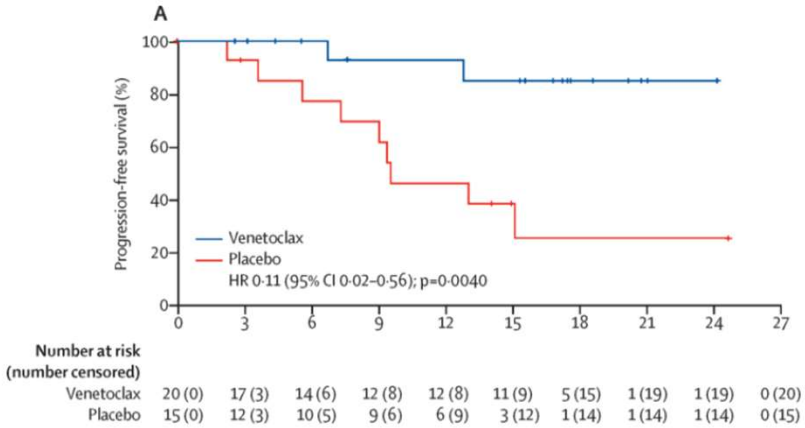
17

Venetoclax + Bortezomib + dex



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Venetoclax + Bortezomib + dex

		No. Events/ No. Patients	Median PFS (95% CI) VenBd	PboBd	HR (95% CI)
All Patients		129/291	22.4 (15.3, NE)	11.5 (9.6, 15.0)	0.63 (0.44, 0.90)
Sex	Male	69/152	19.5 (11.4, NE)	11.4 (9.0, 15.0)	0.67 (0.41, 1.10)
	Female	60/139	NR (17.1, NE)	11.8 (9.6, 17.1)	0.56 (0.33, 0.93)
Age	<65	62/131	22.4 (9.2, NE)	10.2 (7.3, 15.0)	0.66 (0.39, 1.10)
	≥65	67/160	NR (14.5, NE)	12.6 (9.9, 17.2)	0.64 (0.39, 1.04)
ISS Stage	I	56/129	NR (22.4, NE)	11.4 (9.0, 14.0)	0.41 (0.24, 0.71)
	II	47/101	19.5 (11.4, 22.4)	14.8 (9.1, NE)	0.91 (0.49, 1.69)
	III	21/52	12.7 (6.8, NE)	15.1 (5.6, NE)	1.42 (0.55, 3.68)
Prior Lines of Therapy	1 line	62/135	22.4 (12.2, NE)	11.4 (9.0, NE)	0.75 (0.45, 1.26)
	2-3 lines	67/156	NR (14.5, NE)	14.0 (9.5, 15.9)	0.54 (0.33, 0.88)
Prior PI	Sensitive	87/197	22.4 (11.6, NE)	12.6 (9.9, 17.0)	0.75 (0.48, 1.16)
	Naive	39/90	NR (17.1, NE)	10.2 (5.7, 15.0)	0.46 (0.24, 0.88)
Prior IMiD	Refractory	46/100	NR (9.2, NE)	14.8 (9.0, 17.1)	0.75 (0.41, 1.36)
	Sensitive	44/96	NR (10.9, NE)	11.4 (7.3, 15.0)	0.62 (0.33, 1.14)
	Naive	39/93	22.4 (16.6, NE)	11.4 (9.6, NE)	0.61 (0.31, 1.17)
Renal Impairment	None	33/86	22.4 (13.3, NE)	13.0 (8.1, NE)	0.58 (0.29, 1.19)
	Mild	50/109	NR (14.5, NE)	12.2 (11.4, 17.1)	0.57 (0.32, 1.03)
	Moderate	39/84	NR (12.2, NE)	9.9 (9.1, 17.0)	0.60 (0.31, 1.14)
Cytogenetic Risk	Standard	85/213	NR (22.4, NE)	12.2 (9.3, 15.1)	0.54 (0.35, 0.84)
	High	32/49	9.0 (7.4, 19.5)	11.4 (7.0, 17.0)	1.21 (0.58, 2.52)
t(11;14) Status	Positive	11/35	NR (NE, NE)	9.5 (5.6, NE)	0.11 (0.02, 0.56)
	Negative	106/226	22.4 (13.7, NE)	11.4 (9.6, 15.1)	0.67 (0.46, 1.00)
BCL-2 Expr	Low	19/37	11.7 (4.3, NE)	17.0 (2.0, NE)	1.39 (0.43, 4.47)
(IHC)	High	57/140	NR (19.5, NE)	12.2 (9.6, 17.2)	0.50 (0.29, 0.86)
***BCL2* Gene Expr**	Low	33/64	16.6 (11.4, NE)	10.2 (5.6, 17.1)	0.60 (0.29, 1.27)
(Lower QT)	High	79/193	22.4 (19.5, NE)	13.0 (9.6, 17.0)	0.58 (0.37, 0.91)
***BCL2* Gene Expr**	Low	56/128	22.4 (13.3, NE)	13.0 (9.3, 17.1)	0.64 (0.37, 1.10)
(Middle QT)	High	56/129	22.4 (19.5, NE)	10.7 (9.1, 17.0)	0.50 (0.29, 0.85)
***BCL2* Gene Expr**	Low	84/192	22.4 (13.7, NE)	14.0 (9.6, 17.1)	0.69 (0.44, 1.07)
(Upper QT)	High	28/65	22.4 (14.5, NE)	10.2 (7.0, 12.6)	0.34 (0.15, 0.80)
***BCL2* Gene Expr**	Low	81/159	16.6 (11.7, NE)	13.0 (9.6, 17.2)	0.76 (0.48, 1.20)
(BATTing)	High	38/98	22.4 (22.4, NE)	9.9 (9.0, 14.0)	0.24 (0.12, 0.48)

0.01 0.1 1 10

Favour venetoclax Favour placebo

Kumar SK, Harrison SJ, Cavo M, de la Rubia J, Popat R, Gasparetto C, Hungria V, Salwender H, Suzuki K, Kim I, Punnoose EA, Hong WJ, Freise KJ, Yang X, Sood A, Jalaluddin M, Ross JA, Ward JE, Maciag PC, Moreau P. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2020 Dec;21(12):1630-1642. doi: 10.1016/S1470-2045(20)30525-8. Epub 2020 Oct 29. PMID: 33129376.

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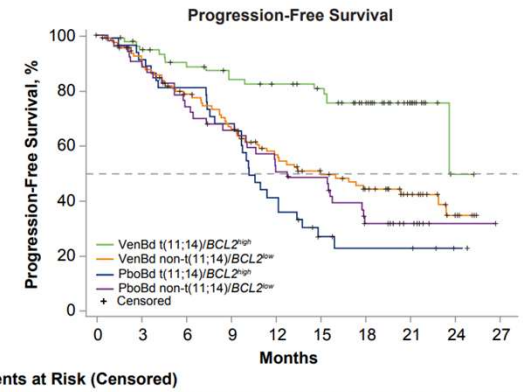
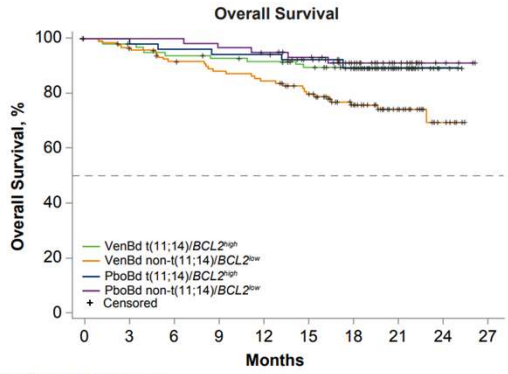
Venetoclax + Bortezomib + dex



Patients at Risk (Censored)

VenBd	74(0)	65(9)	59(15)	54(20)	51(23)	44(30)	29(45)	4(70)	1(73)	0(74)
PboBd	40(0)	35(15)	32(8)	25(15)	14(26)	7(33)	4(36)	1(39)	0(40)	
Ven Bd	110(0)	92(18)	76(34)	61(49)	47(63)	38(72)	29(81)	14(96)	5(105)	0(110)
PboBd	54(0)	46(8)	36(18)	31(23)	24(30)	18(36)	12(42)	2(52)	1(53)	0(54)



Patients at Risk (Censored)

VenBd	74(0)	70(4)	65(9)	63(11)	61(13)	56(18)	39(35)	12(62)	1(73)	0(74)
PboBd	40(0)	39(1)	37(3)	36(4)	36(4)	27(13)	15(15)	6(34)	1(39)	0(40)
Ven Bd	110(0)	106(4)	96(14)	90(20)	86(24)	75(35)	50(60)	22(88)	7(103)	0(110)
PboBd	54(0)	53(1)	53(1)	51(3)	49(5)	45(9)	27(27)	13(41)	3(51)	0(54)

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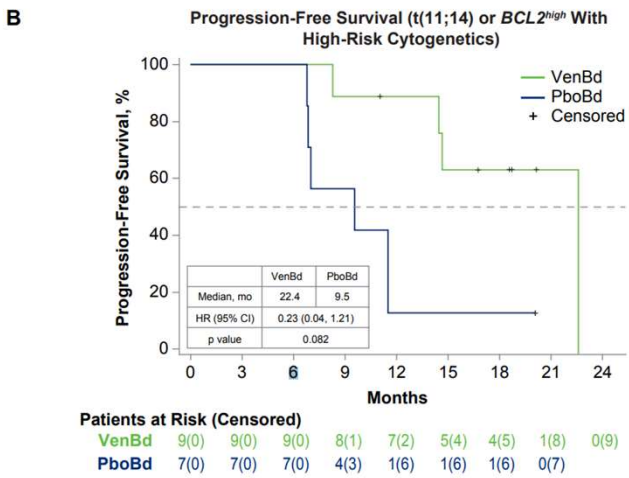
Venetoclax + Bortezomib + dex



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Case 2

75 yo M with Hx of papillary thyroid Ca s/p thyroidectomy/RAI(2009) with High-Risk IgM lambda Multiple Myeloma s/p several lines of therapy at OSH presenting with relapsed/refractory disease

- 12/2021- Diagnosed with Metastatic Cecal Adenocarcinoma to liver –
- 1/20/22- C2 cycle of Neoadjuvant FOLFOX/avastin
- 2/2022- admitted for worsening renal function, uptrending M-spike, lambda light chain, PET with lytic lesions throughout appendicular skeleton, ECOG1->2 thought to be related to MM
- 3/2022-Started **Venetoclax + ixazomib+ dex**, Colon Cancer treatment on Hold

- 4/2022- Admitted for partial SBO, Ixazomib was stopped
- **5/2022- Partial response to therapy, admitted for Non-neutropenic sepsis**

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Pearls:
- R/R Multiple Myeloma w/ t(11;14) can consider use of Ven+Vd

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Case 3

ANCO
Educating and Empowering the Northern California Cancer Community

72 yo M with a Hx of Mantle cell lymphoma c/b relapsed/refractory disease w/ afib RVR:

- 10/2014- L breast mass(15cm) with cervical and thoracic LN
  - Core biopsy- CD20+, **CD5+**, **Cyclin D1**, Ki-67 10-20%, TP53-WT
  - Bone Marrow- 21%, CD19+, CD22+, CD5+, negative for CD10, CD23
  - **Stage IVA, Intermediate risk MIPI score 5**
  - **Multiple Comorbidities thus not candidate for transplant, aggressive therapy**
- 11/2014- C1D1- **BR**
- 4/2015- s/p 6 cycles BR with PET/CT w/ Partial response
- 4/2015- started **ibrutinib** 560mg daily
- 1/2018- Dose reduced 420mg daily due to angioedema/rash
- 11/2019- Progression of disease, increased to 560mg daily
- 2/2020- Hospitalized for **Afib w/ RVR**, stopped ibrutinib, started **Venetoclax**

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Case 3

72 yo M with a history of Mantle cell lymphoma c/b relapsed/refractory disease w/ afib RVR:

- 4/2020- reduced venetoclax to 200mg due to fatigue
- 6/2020- worsening fatigue and lymphadenopathy
- 7/2020- admitted for AIHA – stopped ven, started on C1D1 **Bortezomib/Rituxan/dex (BDR)**
- 9/2020- admitted for severe diarrhea, mCR, stopped bortezomib, continued **Rituxan**
- 3/2021- started **acalabrutinib,** continued Rituxan maintenance q8weeks

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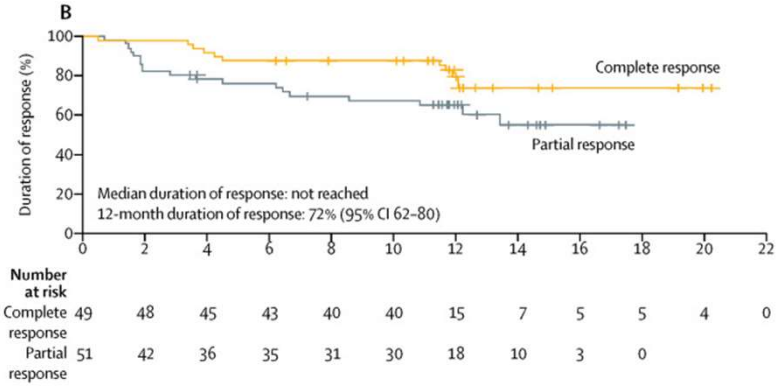
Acalabrutinib



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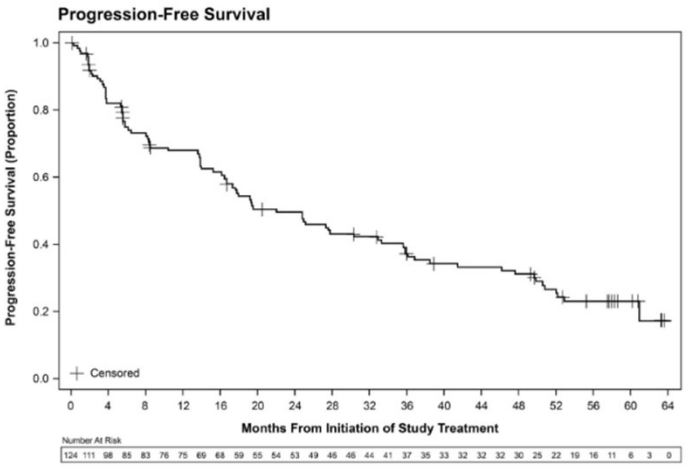
Acalabrutinib



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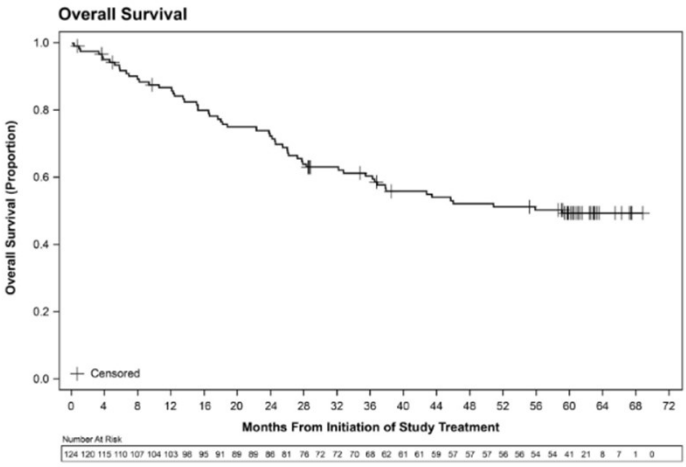
Acalabrutinib



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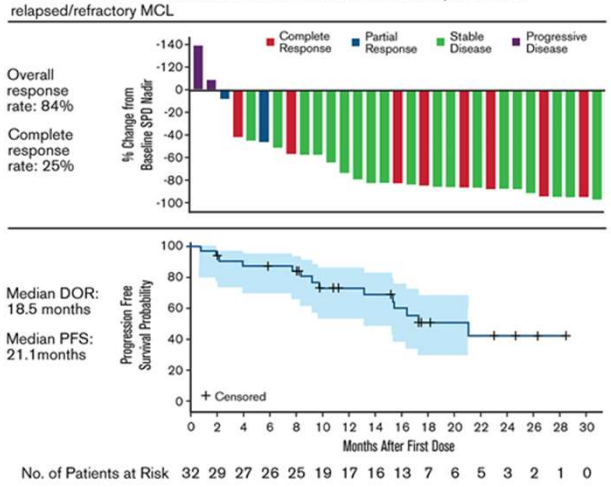
Zanubrutinib

The BTK inhibitor zanubrutinib was effective and well tolerated in patients with relapsed/refractory MCL



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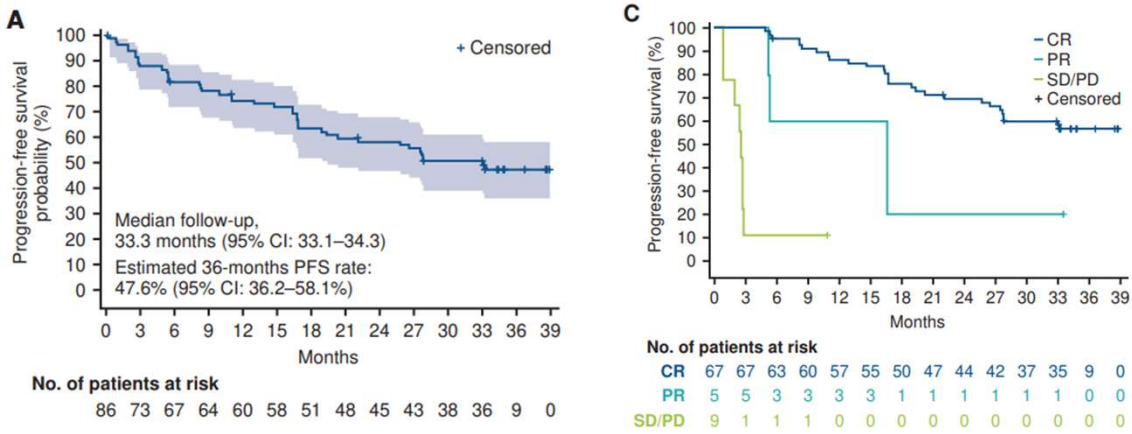
Zanubrutinib



Song Y, Zhou K, Zou DH, Zhou J, Hu J, Yang H, Zhang H, Ji J, Xu W, Jin J, Lv F, Feng R, Gao S, Guo H, Zhou L, Huang J, Novotny W, Kim P, Yu Y, Wu B, Zhu J. Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study. Blood. 2022 Mar 18:blood.2021014162. doi: 10.1182/blood.2021014162. Epub ahead of print. PMID: 35303070.

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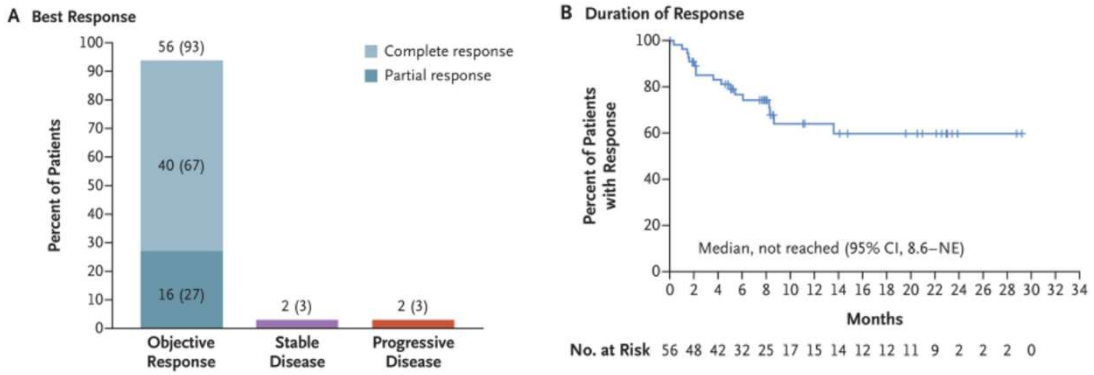
Brexucabtagene Autoleucel (KTE-X19)



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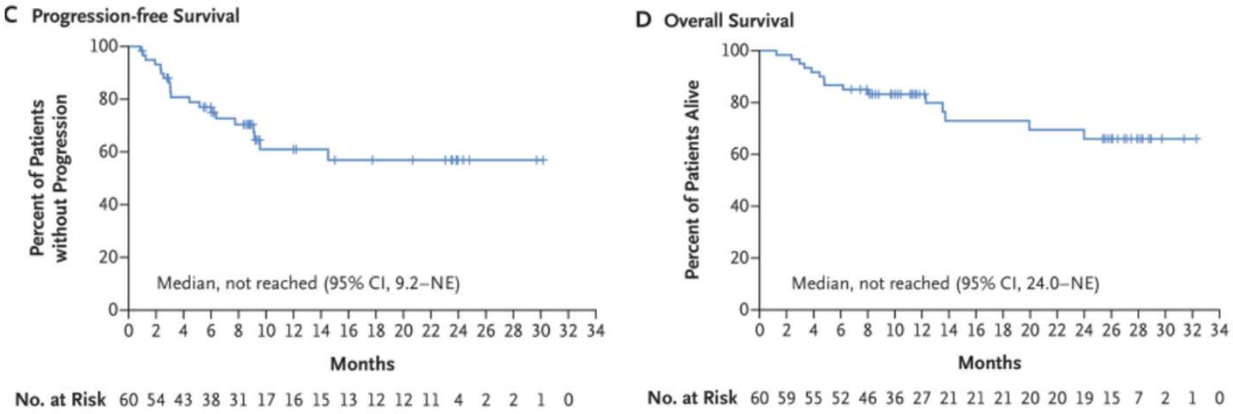
Brexucabtagene Autoleucel (KTE-X19)



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- 3/2021- started **acalabrutinib,** continued Rituxan maintenance q8weeks

- **5/2022- Doing well at clinic visit, referred to NSGY for evaluation of a meningioma for consideration of next steps**

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Pearls

- Acalabrutinib and zanubrutinib have a lower risk for afib compared to ibrutinib

- Can consider CAR-T for R/R Mantle cell lymphoma

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