Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

September 17, 2022

ANCO

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Northern California Cancer Community

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Association of Northern California Oncologists (ANCO)
presents

Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Saturday, September 17, 2022

8:00 AM Breakfast, Registration, & Exhibits

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

9:05 AM Leukemia Update 2022
Brian A. Jonas, MD, PhD, FACP, University of California, Davis

9:50 AM Lymphoma Update 2022
Michael Spinner, MD, University of California, San Francisco

10:35 AM Coffee Break

11:00 AM Myeloma Update 2022
Michaela Liedtke, MD, Stanford University

11:45AM Case Presentations Leukemias, Lymphomas. & Myeloma
Tamar Othman, Fellow, University of California, Davis

12:30PM ADJOURN

Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

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Acknowledgement of Financial Support

This activity is supported by:

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ADC Therapeutics

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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Leukemia Update 2022

Brian A. Jonas, MD, PhD, FACP

University of California, Davis

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UCDAVIS COMPREHENSIVE CANCER CENTER

ANCO Hematologic Malignancies Updates
September 17, 2022

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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

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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?

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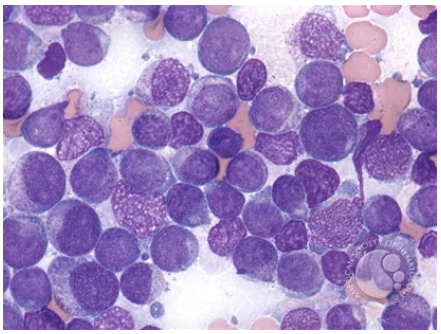
Acute Myeloid Leukemia

- 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.

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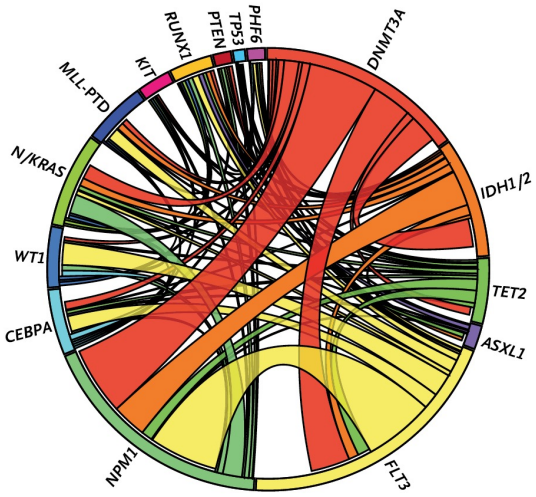
Recurrent Mutations in AML



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.

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ELN 2017 Risk Stratification

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

Dohner et al, Blood 2017

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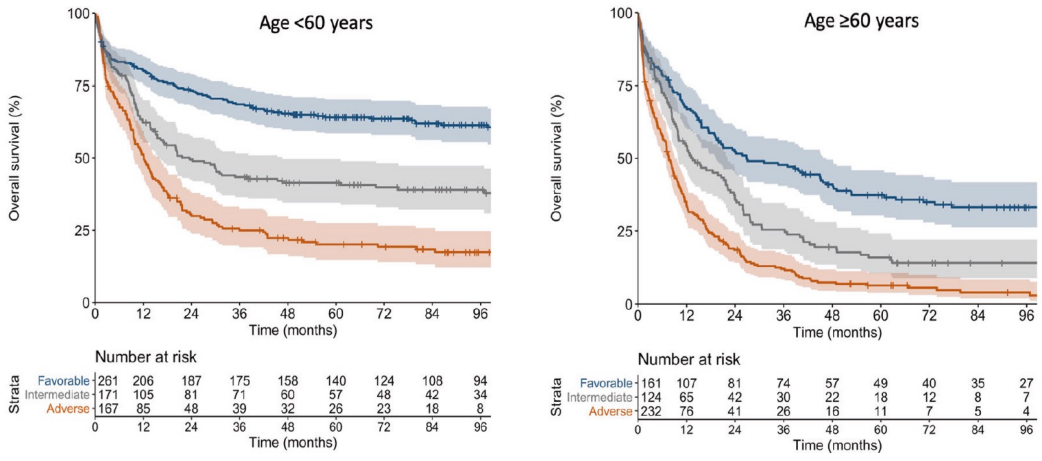
ELN 2017 Risk Stratification - Validation



Herold et al, Leukemia 2020

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ELN 2022 Risk Stratification

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

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

* Changes from ELN 2017

Dohner et al, Blood 2022

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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.

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Ferrara Criteria to Define Unfitness for Intense Chemotherapy for AML

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

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

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

Ferrara et al, Leukemia 2013.

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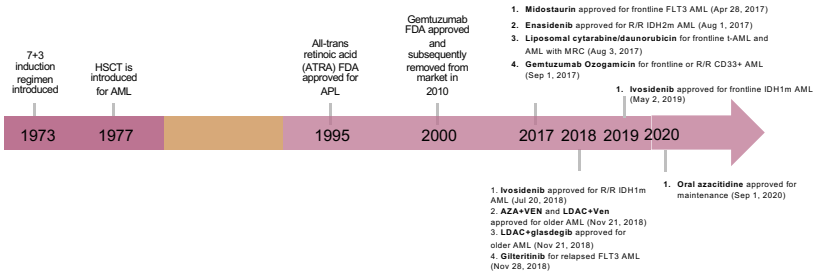
Recent FDA Approvals for AML

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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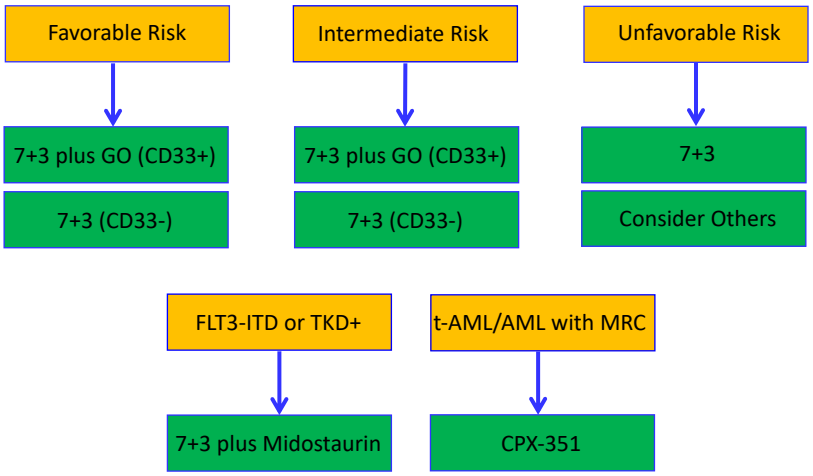
First-Line Treatment of Fit AML in 2022



Based on NCCN guidelines, AML v1.2022

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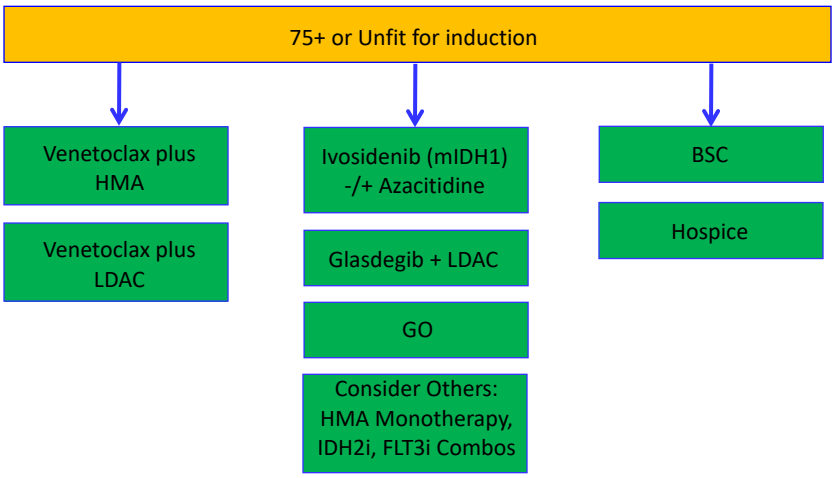
First-Line Treatment of Older/UnFit AML in 2022



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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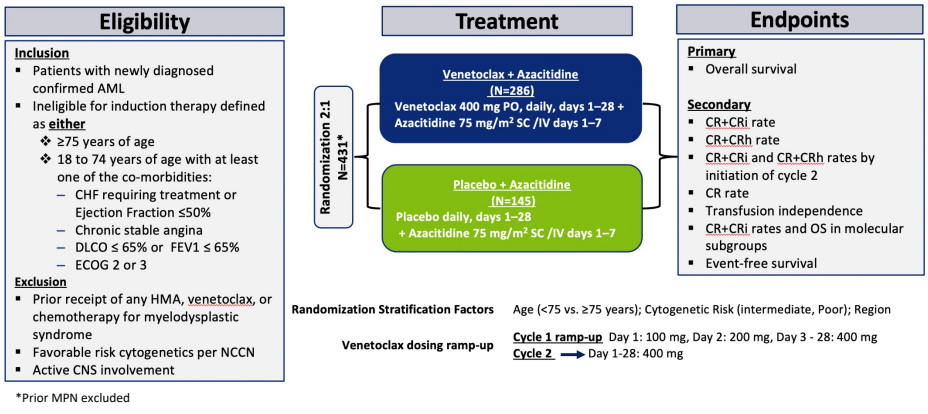
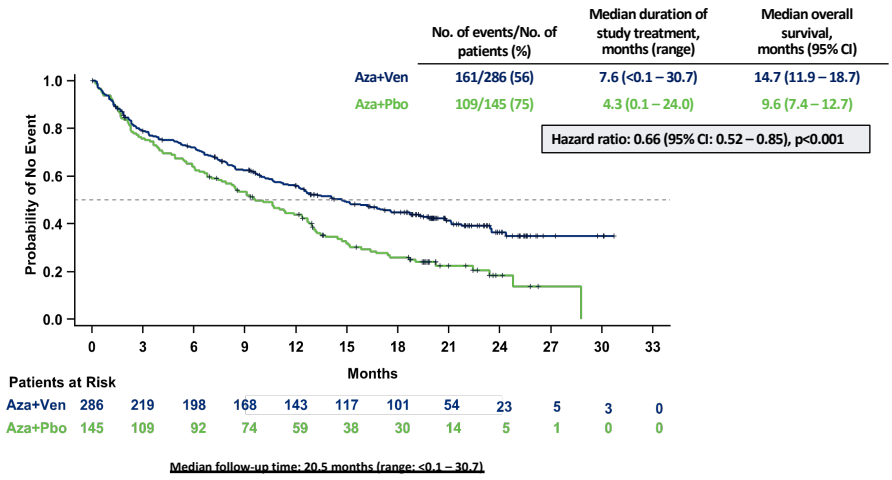
VIALE-A: Azacitidine plus Venetoclax vs Aza-PBO



DiNardo et al, NEJM 2020.

16

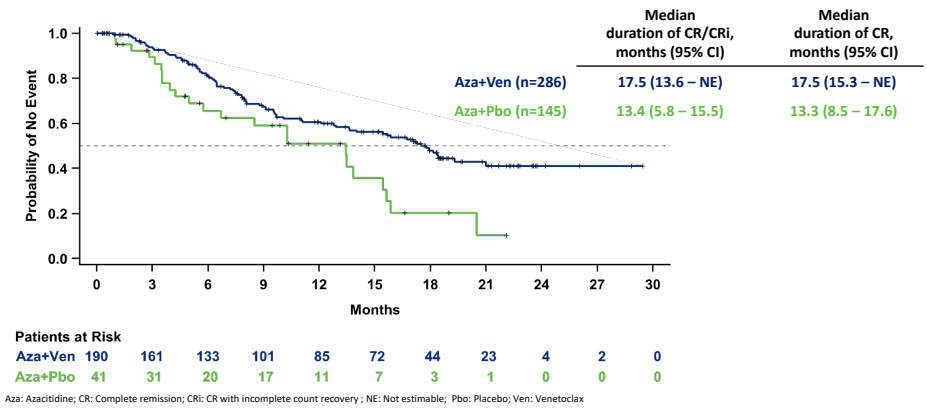
Aza-Ven vs Aza-PBO: OS



DiNardo et al, NEJM 2020.

17

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



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

DiNardo et al, NEJM 2020.

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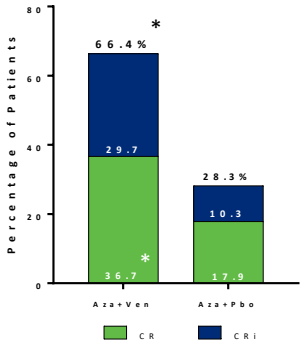
Aza-Ven vs Aza-PBO: Responses



	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.

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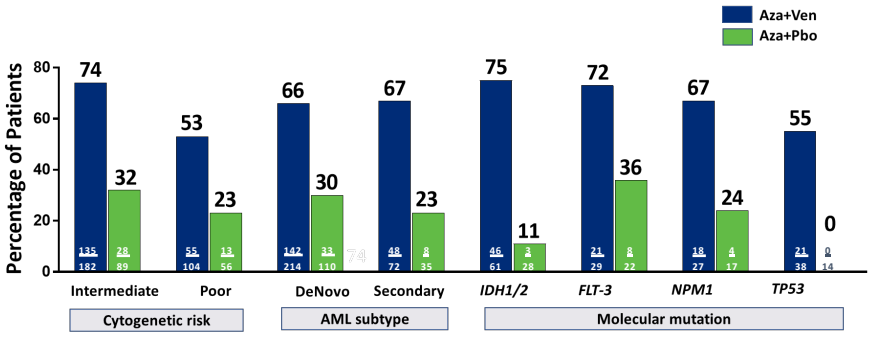
Aza-Ven vs Aza-PBO: Responses by Subgroup



DiNardo et al, NEJM 2020.

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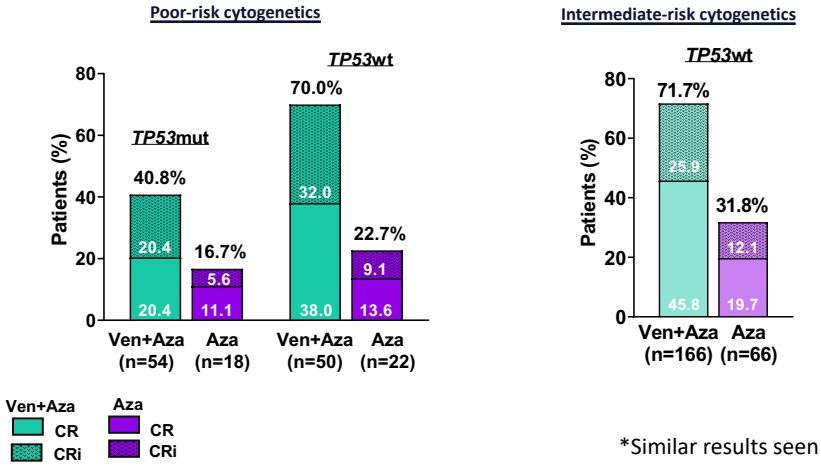
Aza-Ven vs Aza-PBO: Responses in Poor-risk Cytogenetics -/+ TP53 Mutation



*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.

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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?

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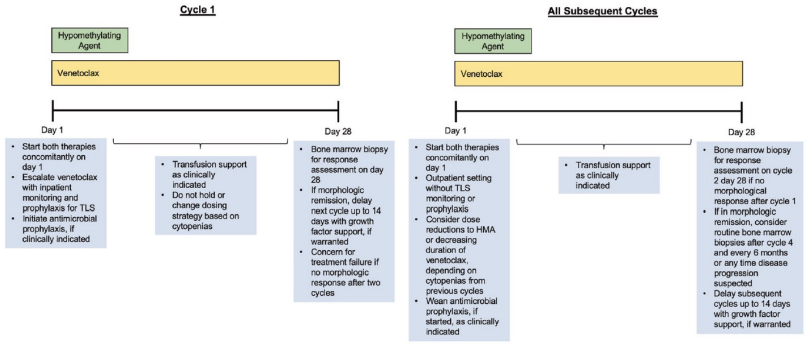
Leukemia
https://doi.org/10.1038/s41375-019-0612-8

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

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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.

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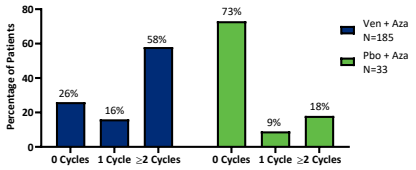
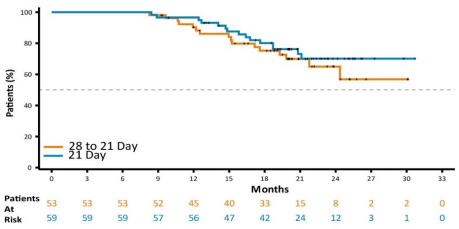
Cytopenia Management on the VIALE-A Trial

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)

Number of Patients Who Achieved CR/CRh Who Had Post-remission Cycles With a Reduction in Dosing Duration and/or Cycle Delay ≥7 Days Related to Cytopenia



Overall Survival Among Patients Who Acheived CR/CRh in VIALE-A (Converted to 21-Day Dosing After 1st Grade 4 Cytopenia)



Pratz et al, ASH 2020, Abstract 1944.

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Timing of Response to HMA-Ven

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

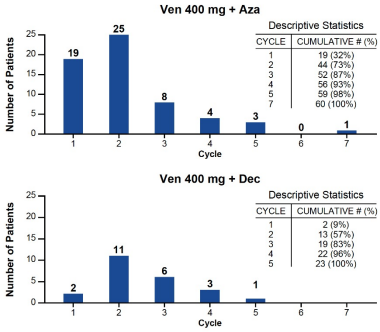
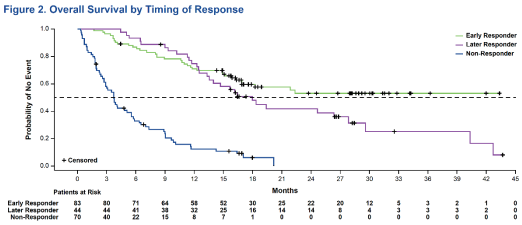


Figure 2. Overall Survival by Timing of Response



Jonas et al, ASCO 2020.

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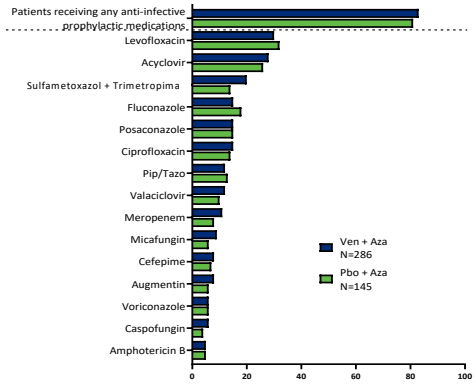
Use of CYP3A4i on the VIALE-A Trial

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

Prophylactic Anti-infective Use in VIALE-A*



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

Jonas et al, ASH 2020, Abstract 2846.

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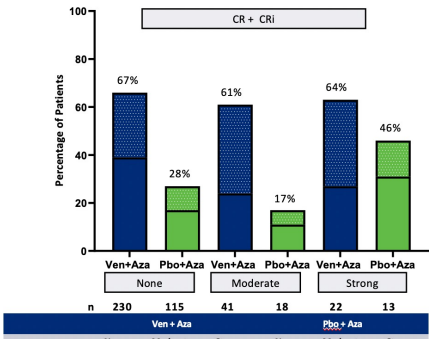
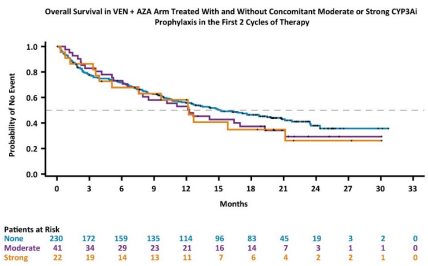
Use of CYP3A4i on the VIALE-A Trial



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

Overall Survival in Ven + Aza



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

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

Jonas et al, ASH 2020, Abstract 2846.

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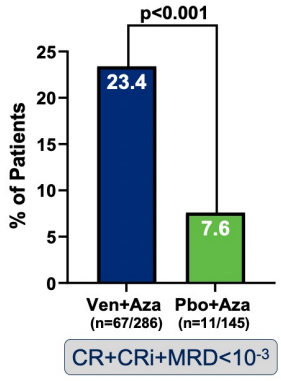
Case 2, Continued

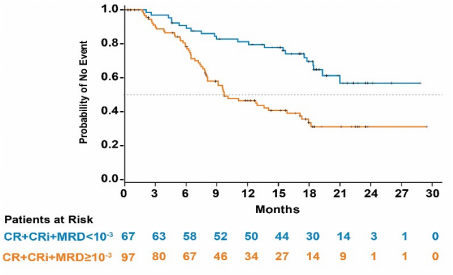
Our 76yo M with newly diagnosed AML with NPM1 and IDH2 R140Q mutations is is treated with venetoclax and decitabine and achieves a MRD positive CR after cycle 1. He continues on treatment and his end of cycle 4 bone marrow biopsy shows an MRD negative CR.

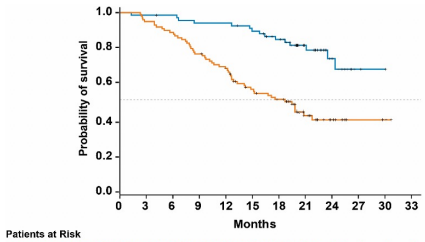
He asks about the impact of her MRD status as well as if there is a role for transplant in her care.

30

VIALE-A Trial: MRD Response, DoR and OS







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

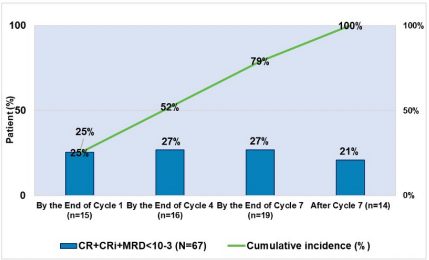
Overall survival	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median OS, months (95% CI)
CR+CRi+MRD<10-3	15	94.0 (84.7, 97.7)	84.6 (73.3, 91.4)	NR (24.4 – NR)
CR+CRi+MRD≥10-3	52	67.9 (57.6, 76.2)	50.1 (39.6, 59.8)	18.7 (12.9 – NR)

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

31

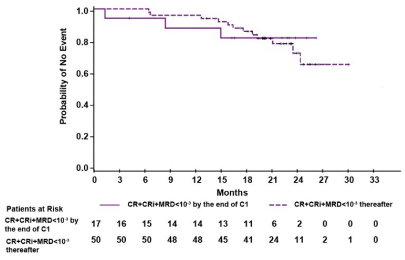
VIALE-A Trial: Timing of MRD Response and OS

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.

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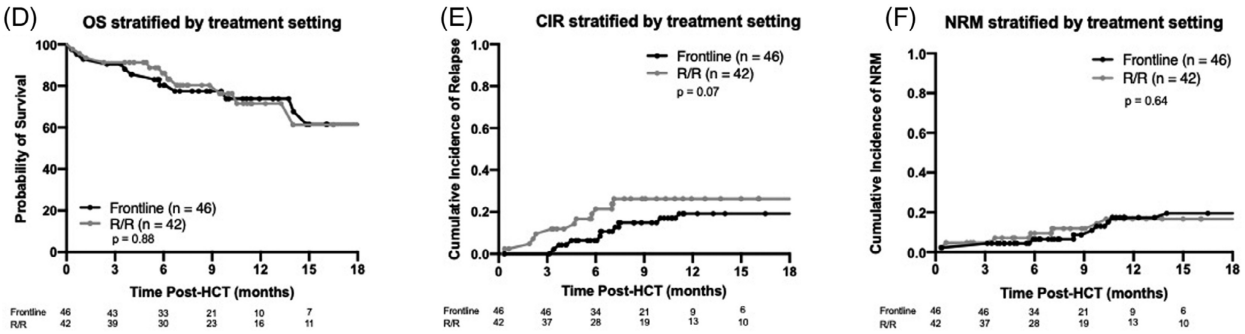
Allo-HCT is Feasible after HMA plus Venetoclax in Frontline and r/r AML



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

Kennedy et al, AJH 2022.

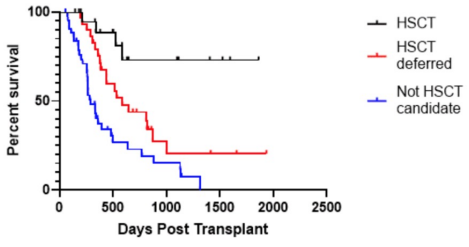
33

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

Table 1: Disease status characteristics

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

Figure 1: Overall survival



Pollyea et al, ASH 2020, Abstract 78.

34

Case 3

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

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

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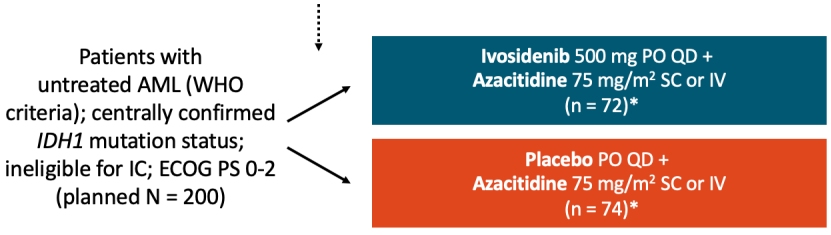
AGILE: Ivosidenib+Azacitidine vs PBO+Aza for Newly Diagnosed AML with mIDH1

- Multicenter, double-blind, randomized phase III trial

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



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

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

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

Slide credit: clinicaloptions.com

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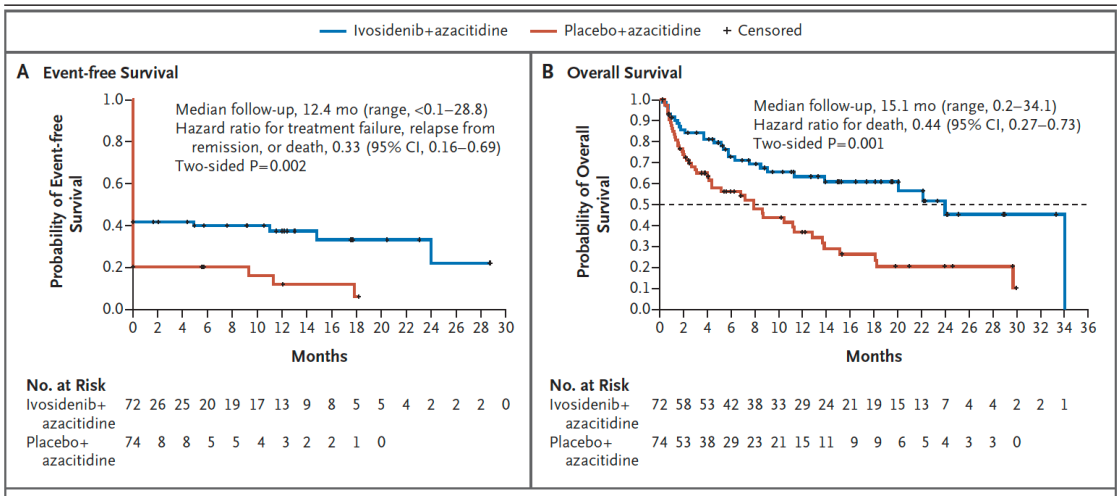
AGILE: OS and EFS



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

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AGILE: Responses

Response	IVO + AZA (n = 72)		PBO + AZA (n = 74)
CR rate, n (%) [95% CI]	34 (47.2) [35.3-59.3]		11 (14.9) [7.7-25.0]
▪ OR (95% CI); *P* value		4.8 (2.2-10.5); <.0001	
▪ Median duration of CR, mo (95% CI)	NE (13.0-NE)		11.2 (3.2-NE)
▪ Median time to CR, mo (range)	4.3 (1.7-9.2)		3.8 (1.9-8.5)
CR + CRh, n (%) [95% CI]	38 (52.8) [40.7-64.7]		13 (7.6) [9.7-28.2]
▪ OR (95% CI); *P* value		5.0 (2.3-10.8); <.0001	
▪ Median duration of CR + CRh, mo (95% CI)	NE (13.0-NE)		9.2 (5.8-NE)
▪ Median time to CR + CRh, mo (range)	4.0 (1.7-8.6)		3.9 (1.9-7.2)
ORR, n (%) [95% CI]	45 (62.5) [50.3-73.6]		14 (18.9) [10.7-29.7]
▪ OR (95% CI); *P* value		7.2 (3.3-15.4); <.0001	
▪ Median duration of response, mo (95% CI)	22.1 (13.0-NE)		9.2 (6.6-14.1)
▪ Median time to response, mo (range)	2.1 (1.7-7.5)		3.7 (1.9-9.4)
***mIDH1* 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.

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AGILE: AEs

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

*Occurring in >20% of patients.

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

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

Slide credit: clinicaloptions.com

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Case 4

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

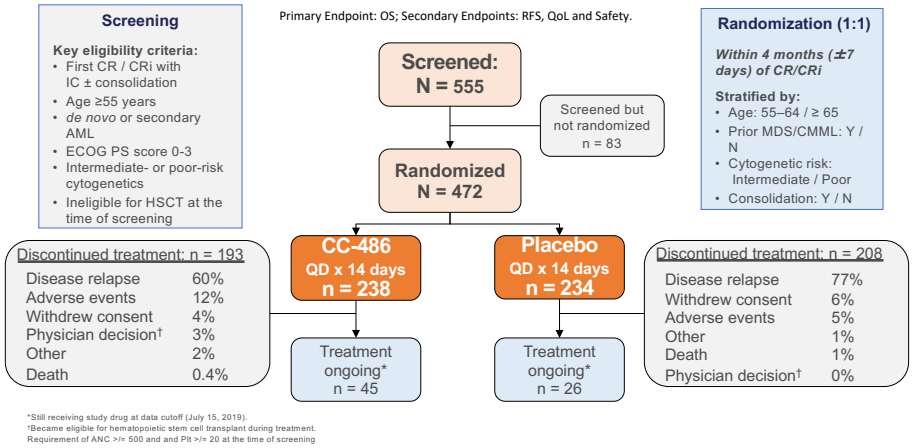
He is induced with 7+3 and achieves an MRD negative CR. He has one cycle of intermediate dose cytarabine for consolidation but tolerates it poorly and it is determined not to pursue additional chemotherapy. He is now unfit for transplant and he currently has no identified donor. He has an end of treatment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

What is the next step: Surveillance or maintenance?

40

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

Patient DISPOSITION / SCHEMA



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

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QUAZAR Trial – Patient Characteristics

Table 1. Baseline Demographic and Disease Characteristics.*

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

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

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QUAZAR Trial – Safety

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

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

	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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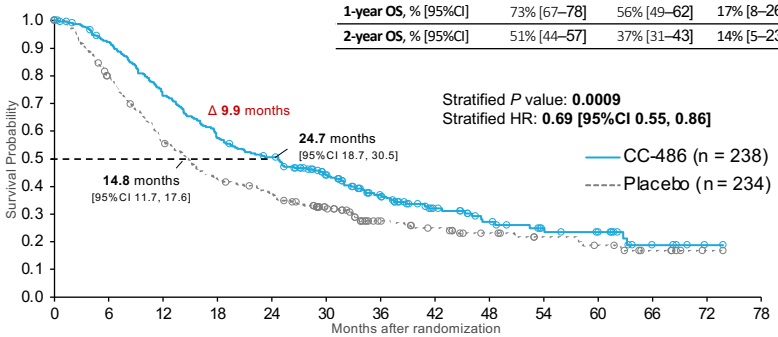
QUAZAR Trial – Primary Endpoint OS

- 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]



Patients at risk:

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

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

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

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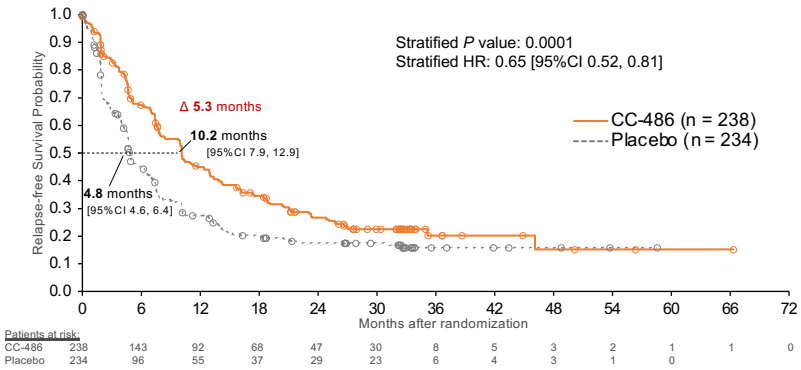
QUAZAR Trial – Secondary Endpoint RFS



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

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

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

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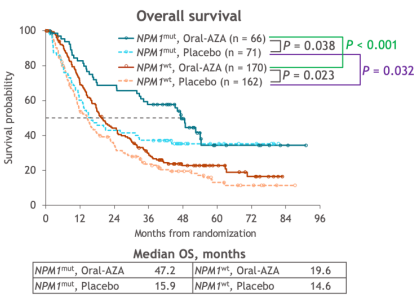
QUAZAR AML-001 Trial: Effects of NPM1 and FLT3-ITD mutations

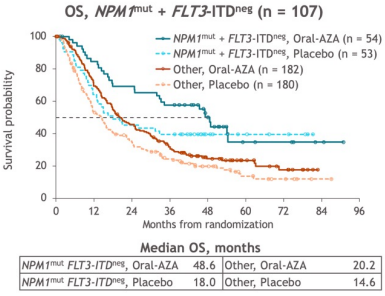
NPM1 mutational status at AML Dx was prognostic for OS and RFS, and predictive of a survival benefit for pts treated with Oral-AZA (vs. PBO).

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



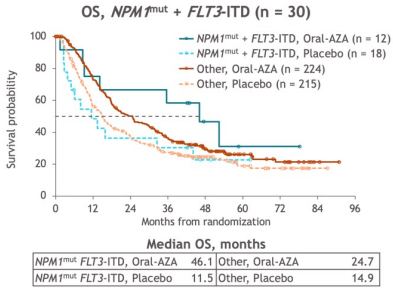
Median OS, months

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.

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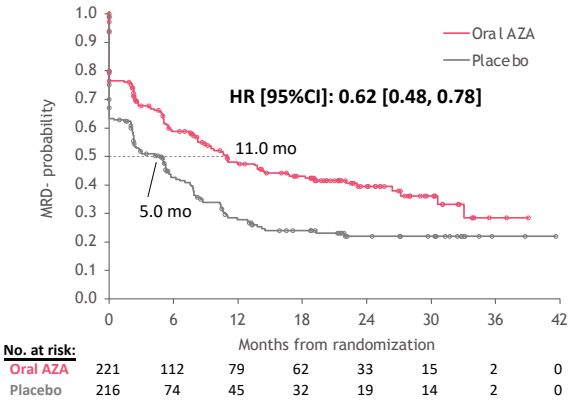
QUAZAR AML-001: MRD Responses

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

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

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



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

Roboz et al, ASH 2020 Abstract #692

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Case 5

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

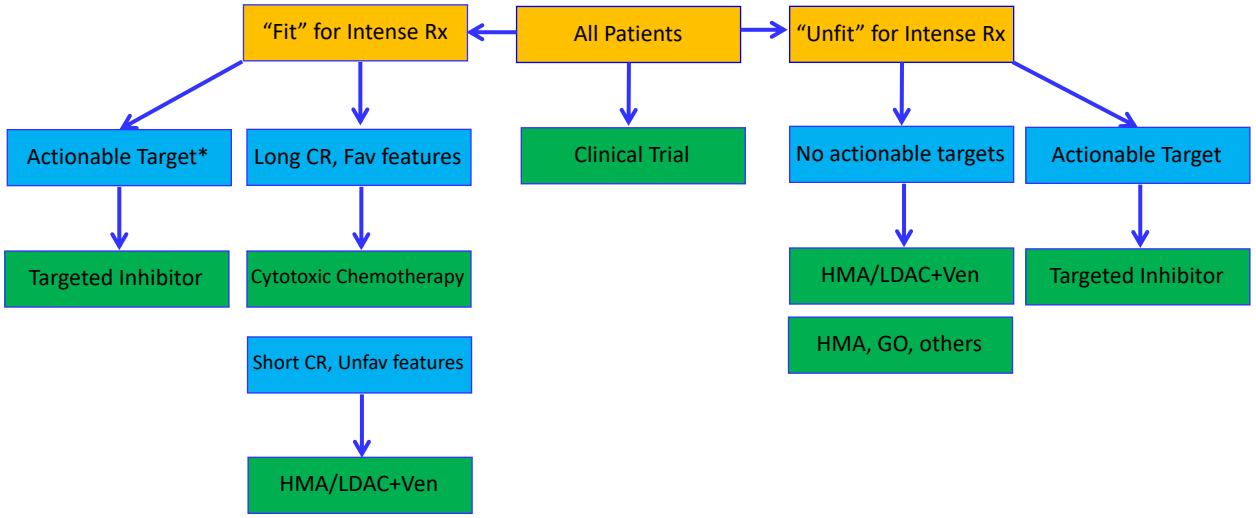
13 months after achieving CR, she presented with mild neutropenia and thrombocytopenia and flow on the PB flow revealed reappearance of abnormal myeloblasts. A BMBx showed relapsed AML with 30% blasts. Cytogenetics and an NGS-based myeloid mutation panel again showed del(9q) and mutations in CEBPA (biallelic),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

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

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

48

Current Options for the Treatment of r/r AML

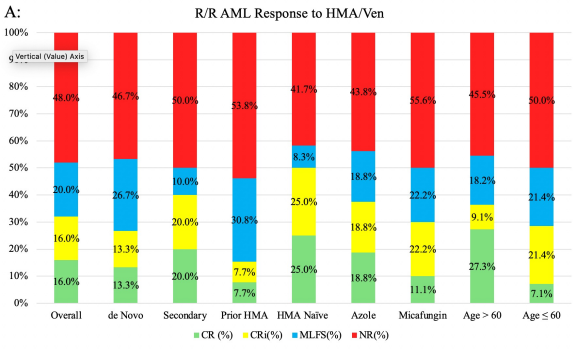


49

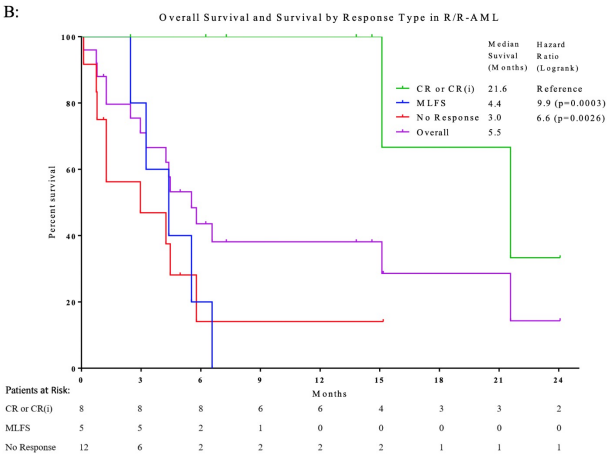
HMA plus Venetoclax in r/r AML

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

UCD Experience:



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



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

50

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

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

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

DiNardo et al, JCO 2021 and ASH 2020.

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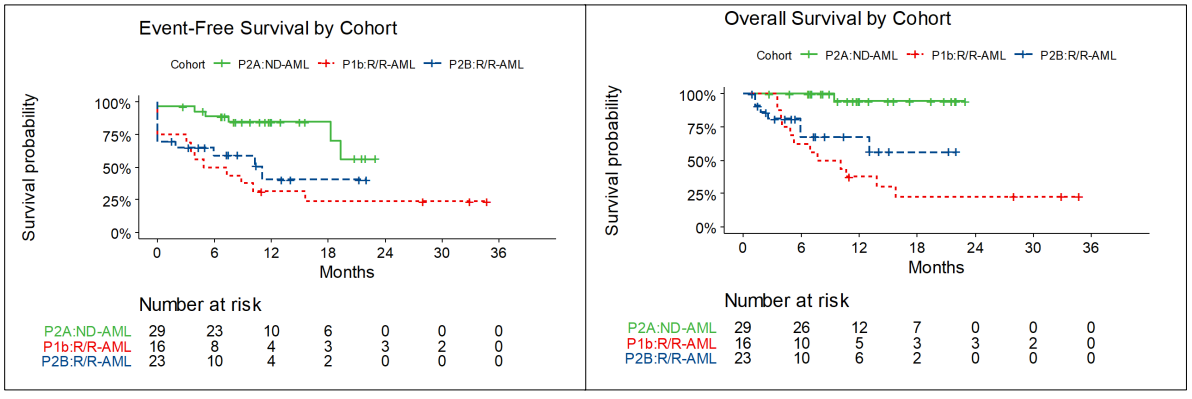
FLAG-Ida-Ven: EFS and OS



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.

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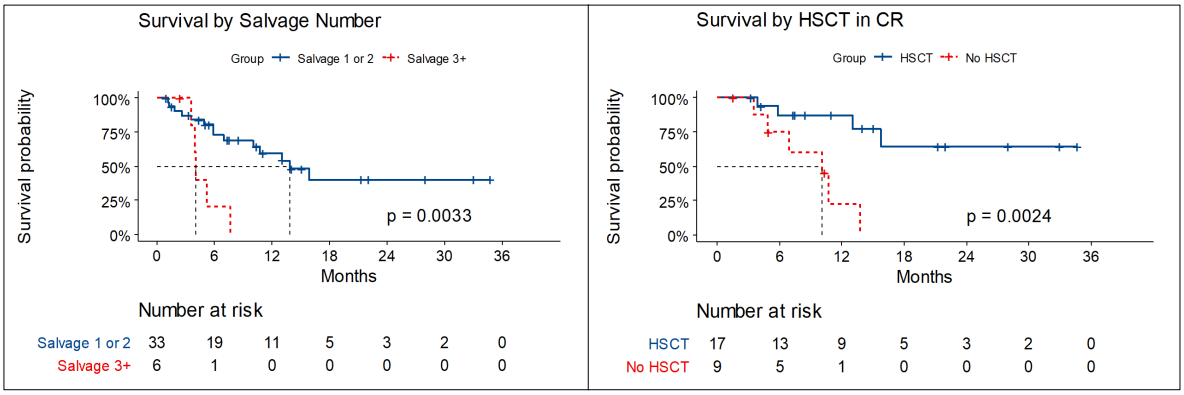
FLAG-Ida-Ven: OS by Salvage and After Allo-HCT for r/r AML

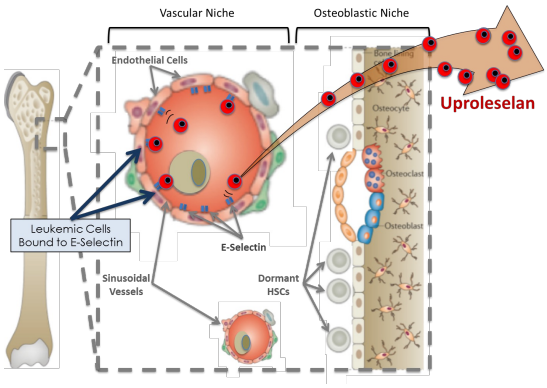


46% bridged to allo-HCT
12mo OS 87%

DiNardo et al, JCO 2021 and ASH 2020.

53

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



E-selectin –

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

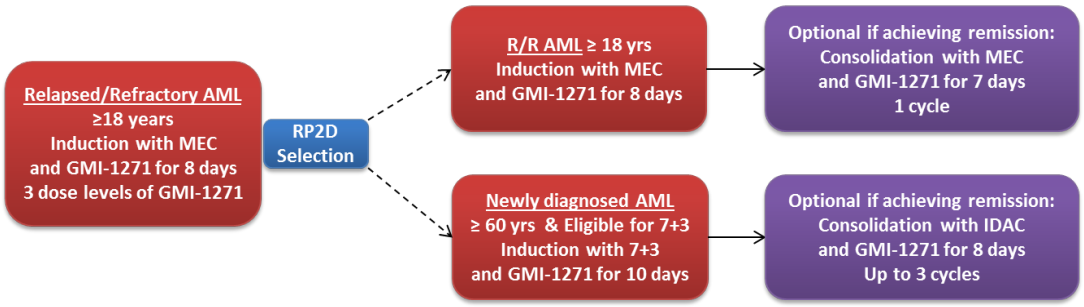
Uproleselan, an E-selectin antagonist –

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

Barbier, et al, Nature Communications 2020.

54

Phase 1/2 Uproleselan Study Schema



DeAngelo et al, Blood 2022.

55

Phase 1/2 Uproleselan Study: Responses

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

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

DeAngelo et al, Blood 2022.

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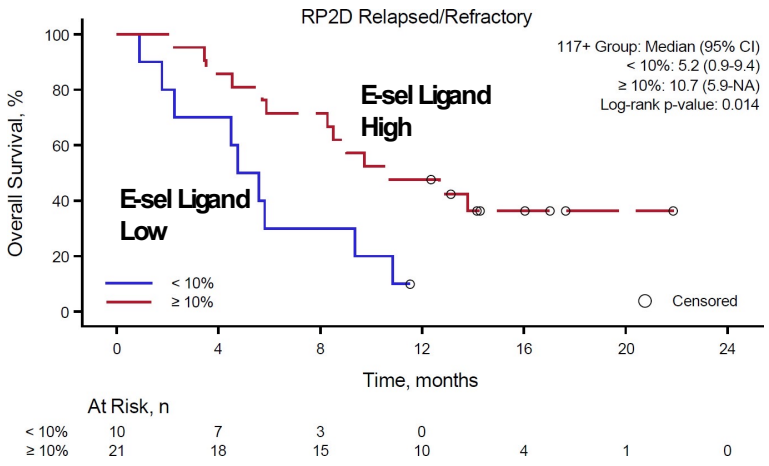
Phase 1/2 Uproleselan Study: OS Based on E-Selectin Ligand Expression

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

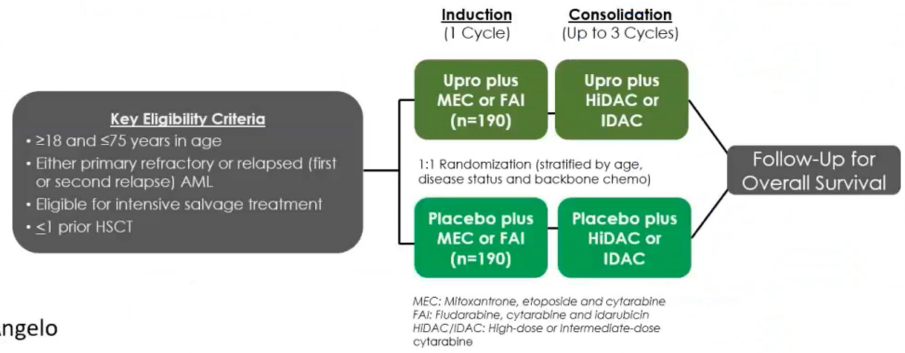


DeAngelo et al, ASH 2018.
DeAngelo et al, Blood 2022.

57

Phase 3 Study of Uproleselan in r/r AML

NCT#03616470



PI: DeAngelo

Primary Endpoint: OS

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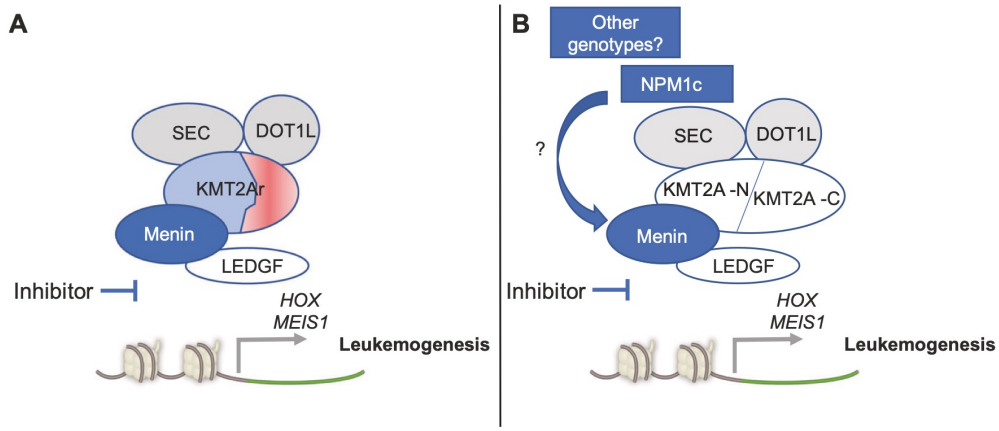
Menin Inhibition for AML with MLL Rearrangements and NPM1c Mutations



Issa et al, Leukemia 2021.

59

Menin Inhibitors in Development

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

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

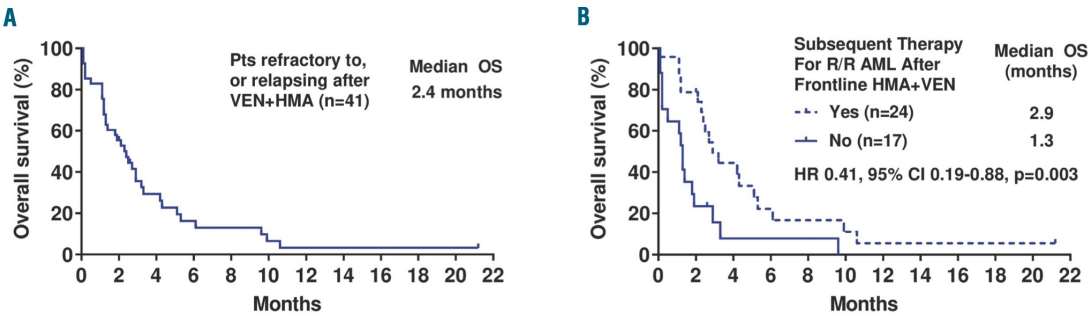
Clinical trial/status	Drug	Dosing	Min. age	Phase 2 expansion cohorts
AUGMENT-101	SNDX-5613	PO BID	30 d	A. ALL or MPAL with *KMT2Ar*
NCT04065399				B. AML with *KMT2Ar*
Syndax (recruiting)				C. AML with *NPM1c*
KOMET-001	KO-539	PO daily	18 yr	A. AML with *KMT2Ar*
NCT04067336				B. AML with *NPM1c*
Kura (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 enrollment, *d* days, *yr* years, *Mini-HCVD* dose reduced combination of cyclophosphamide and dexamethasone, methotrexate, and cytarabine.

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

60

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



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

Maiti et al, Haematologica 2021.

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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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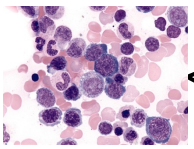
Treatment Approaches in MDS



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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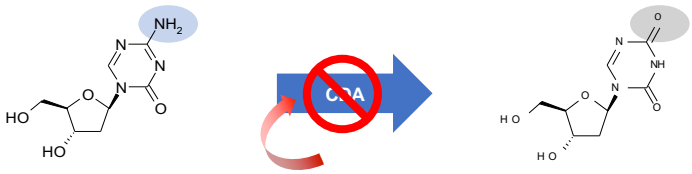
Oral Decitabine + Cedazuridine (DEC-C)

- 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



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

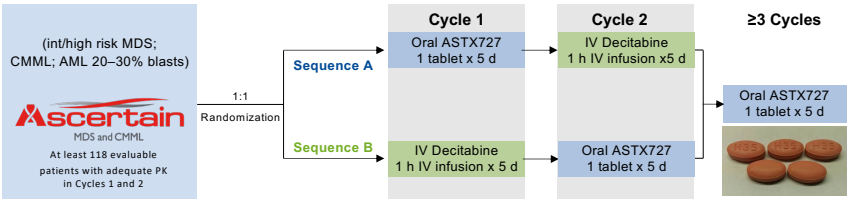
- Cedazuridine is a novel, potent, and safe CDA inhibitor
  - Large safety margin, with no adverse events at up to 200 mg/kg in monkeys (~2400 mg/m^2 human equivalent)

CDA, cytidine deaminase.

Savona et al. Lancet Hematogy 2019.

64

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



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

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

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

Garcia-Manero et al. Abstract 846 ASH 2019

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

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

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

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

Garcia-Manero et al. Abstract 846 ASH 2019

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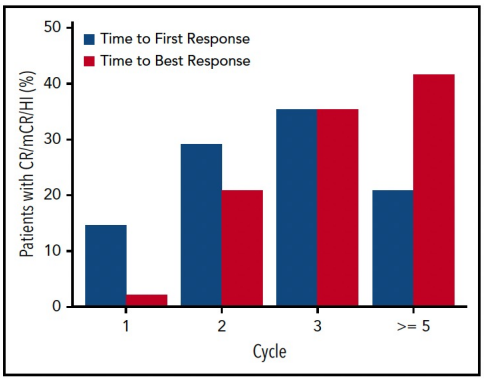
ASTX727-01-B: DEC-C Responses in MDS/CMML

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



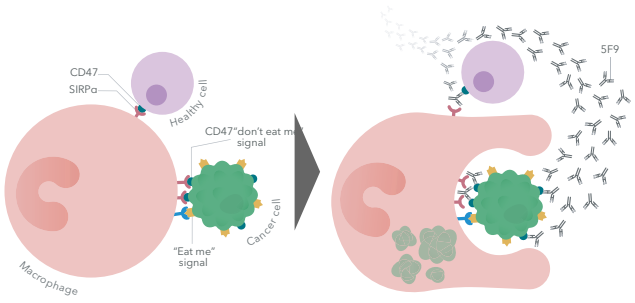
- Comparable safety was seen between IV decitabine and PO DEC-C

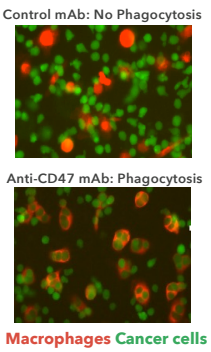
Garcia-Manero et al. Blood 2020.

67

Magrolimab for MDS and AML: MOA

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





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

Sallman et al, ASH 2019. Abstr 569.

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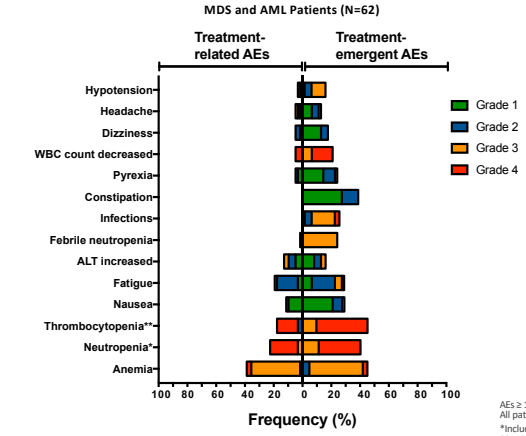
Magrolimab for MDS and AML: Safety



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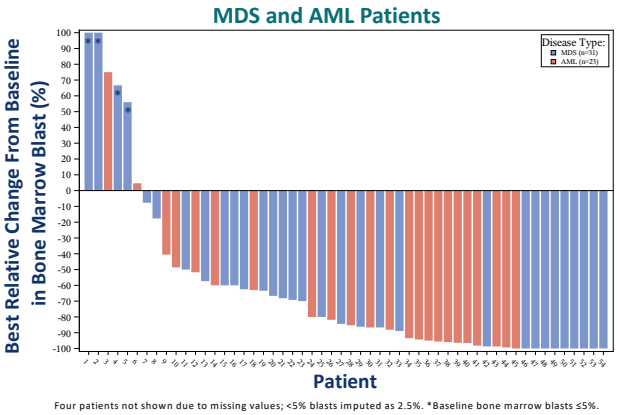
Magrolimab for MDS and AML: Activity

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

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New in 2022: IPSS-M

61 Molecular International Prognosis Scoring System for Myelodysplastic Syndromes

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

Saturday, December 11, 2021: 9:30 AM

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

Bernard et al, ASH 2021 Abstract #61.

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International Prognostic Scoring System – Molecular

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

Category and Variable	Adjusted Hazard Ratio (95% CI)†	Model Weight‡
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — x10^9/l	0.998 (0.997–0.999)	−0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	−0.171
Cytogenetic		
IPSS-R cytogenetic category§	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)¶		
TP53^{multhit}	3.27 (2.38–4.48)	1.18
MLL^{PTD}	2.22 (1.49–3.32)	0.798
FLT3$^{ITD+TKD}$	2.22 (1.11–4.45)	0.798
SF3B1^{5q}	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B1$^{\alpha}$	0.92 (0.74 1.16)	−0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖		
min(Nres,2)	1.26 (1.12–1.42)	0.231

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

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

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

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

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

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

Bernard et al, NEJM Evidence 2022.

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IPSS-M, Continued

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

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

Bernard et al, NEJM Evidence 2022.

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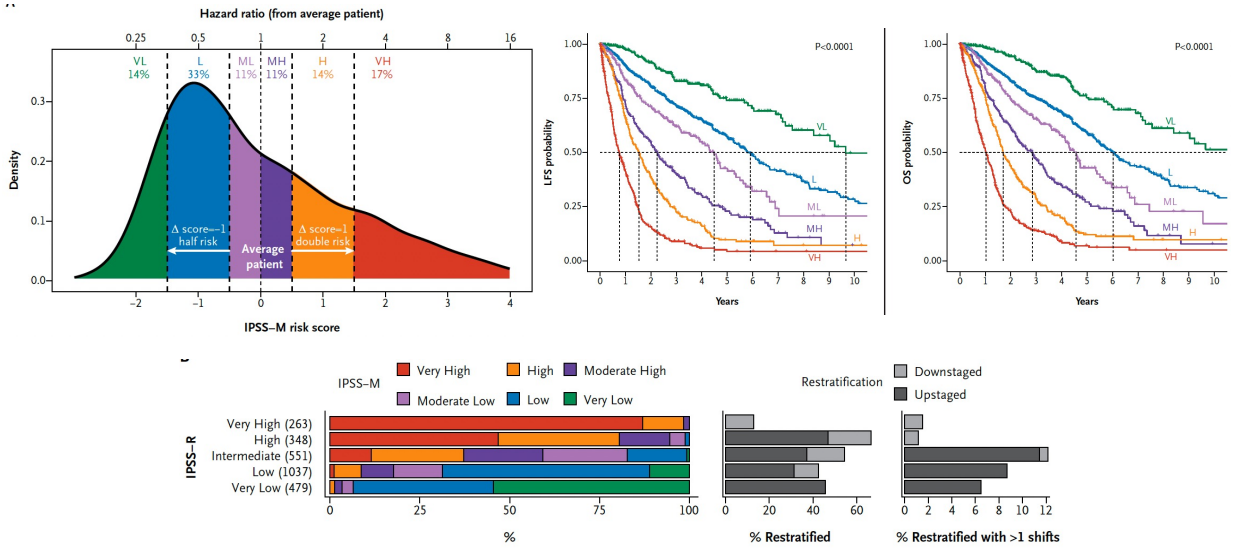
IPSS-M, Continued



Bernard et al, NEJM Evidence 2022.

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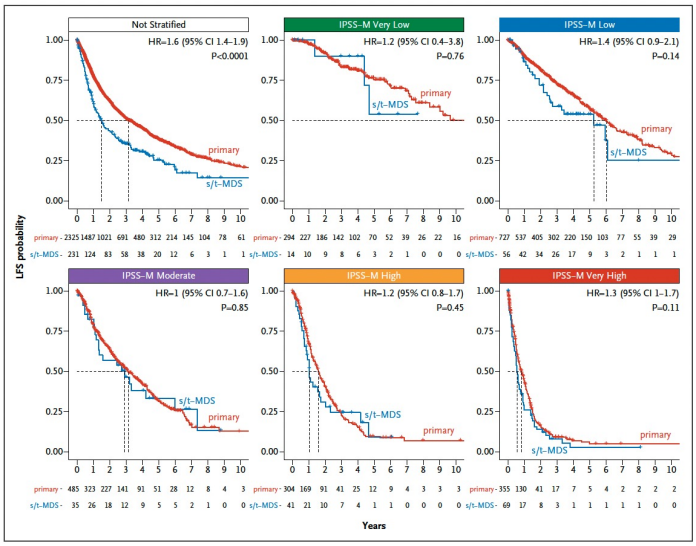
IPSS-M – Therapy-Related MDS



Bernard et al, NEJM Evidence 2022.

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New/Updated Classification Systems

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

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

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WHO 2022 - MDS

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

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

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

Khoury et al, Leukemia 2022

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ICC - MDS

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

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

[a]Cytoses: Sustained white blood count ≥13 x 10^9/L, monocytosis (≥0.5 x 10^9/L and ≥10% of leukocytes), or platelets ≥450 x 10^9/L; thrombocytosis is allowed in MDS-del(5q) or in any MDS case with inv(3) or t(3;3) cytogenetic abnormality.
[b]*BCR::ABL1* rearrangement or any of the rearrangements associated with myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions exclude a diagnosis of MDS, even in the context of cytopenia.
[c]Although dysplasia is typically present in these entities, it is not required.
[d]Although 2% PB blasts mandates classification of an MDS case as MDS-EB, the presence of 1% PB blasts confimed on two separate occasions also qualifies for MDS-EB.
[e]For pediatric patients (<18 years), the blast thresholds for MDS-EB are 5-19% in BM and 2-19% in PB, and the entity MDS/AML does not apply.
[f]AML-defining cytogenetics are listed in the AML section.

Arber et al, Blood 2022

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WHO 2022 – AML

Table 7. Acute myeloid leukaemia.

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

Summary Box:

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

Summary Box:

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

Khoury et al, Leukemia 2022

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ICC - AML

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

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

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

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

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

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

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Summary and Future Directions

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

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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Lymphoma Update 2022

Michael Spinner, MD

University of California, San Francisco

ANCO

Educating and Empowering the Northern California Cancer Community

Updates in Lymphoma

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September 17, 2022
Sacramento, CA

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Disclosures

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- No relevant financial disclosures

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Outline

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

3

Frontline DLBCL – Phase 3 trials challenging R-CHOP

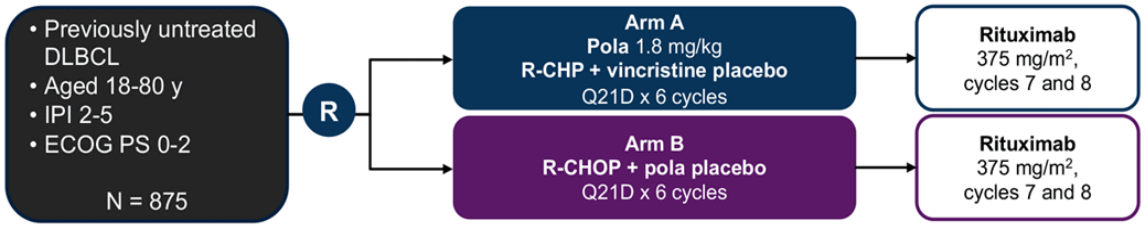
Trial	Experimental arm	Study population	N	PFS, experimental vs standard arm	Outcome	Reference
LNH03-6B	R-CHOP-14	60-80 y; aaIPI ≥1	602	60% vs 62% (3y)	Negative	Delarue et al[46]
DLCL04	R-CHOP-14 + ASCT	≤65 y; aaIPI ≥2	299	78% vs 77% (5y)	Negative	Chiappella et al[47]
HOVON	R-CHOP + rituximab maintenance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

Spinner MA, Advani RH. *Oncology* 2022

4

POLARIX trial

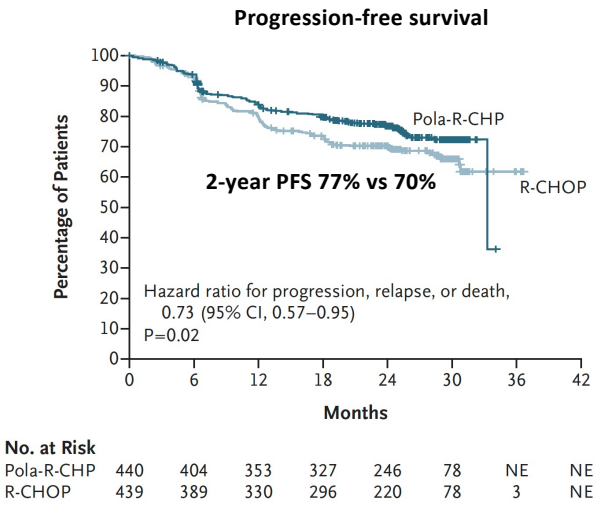
- International phase 3 trial comparing **R-CHOP vs polatuzumab vedotin (anti-CD79b ADC) + R-CHP**

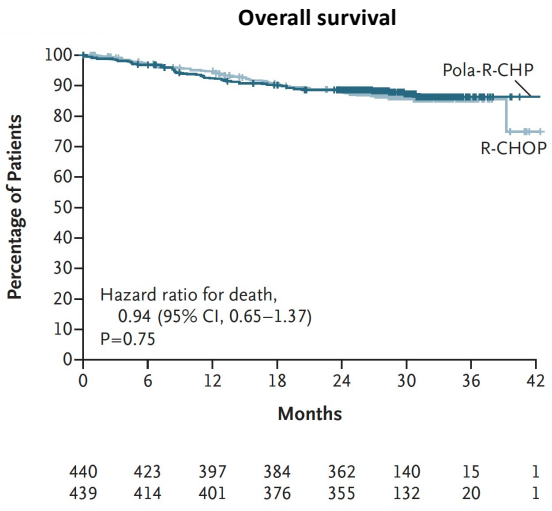


- Primary endpoint: **PFS**
- Secondary endpoints: OS, DOR, ORR, CR rate, safety/tolerability

5

POLARIX efficacy endpoints





Median follow-up 28 months

Tilly et al, NEJM 2022

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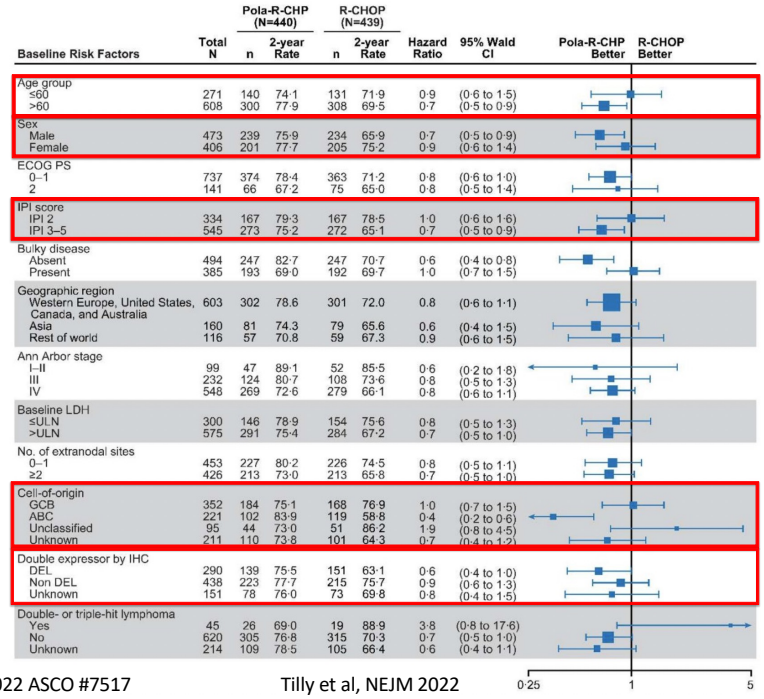
POLARIX - subgroup analysis

Subgroups favoring pola-R-CHP:

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



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

Morschhauser et al, 2022 ASCO #7517

Tilly et al, NEJM 2022

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POLARIX – safety/tolerability

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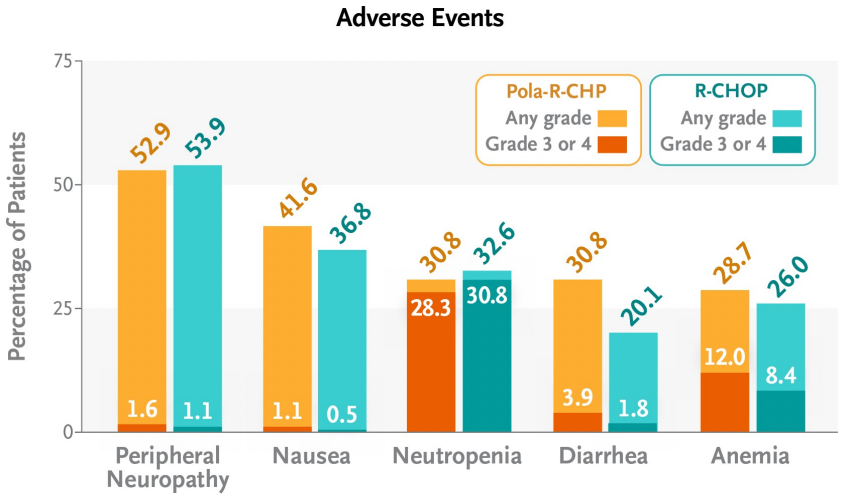

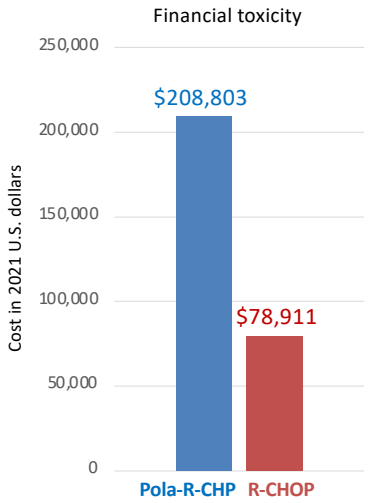

Tilly et al, NEJM 2022

Kambhampati et al, Blood 2022

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Other novel frontline approaches for high risk DLBCL

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

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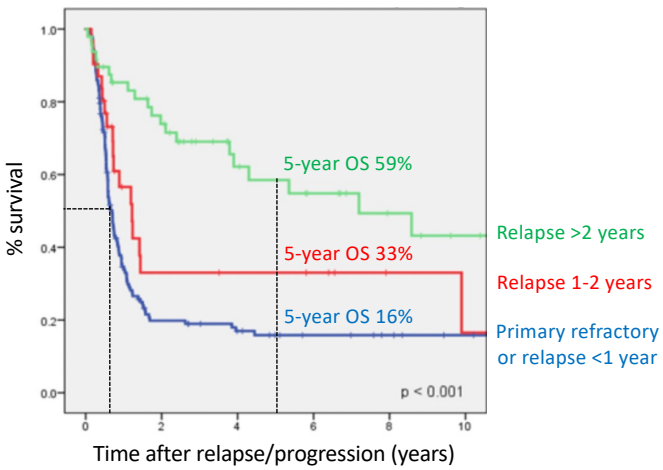
Relapsed/refractory DLBCL

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

Overall survival from time of relapse/progression



Crump et al, Blood 2017

Ngu et al, 2021 ASH #2499

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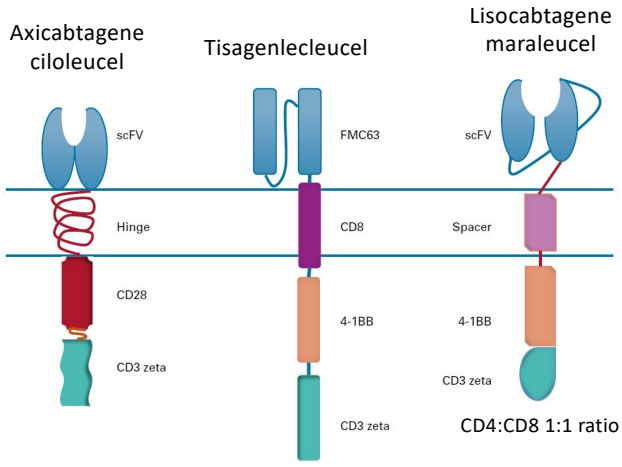
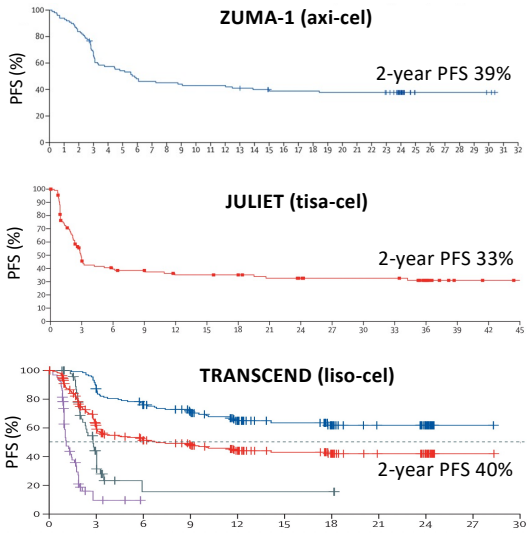
CD19 CAR T-cell products for R/R DLBCL



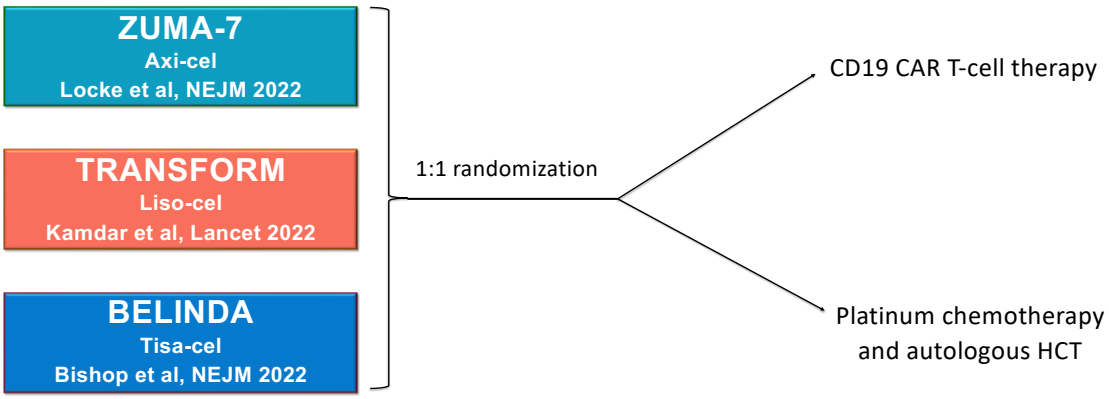


Locke et al, *Lancet Oncol* 2019 Schuster et al, *Lancet Oncol* 2021 Abramson et al, *Lancet* 2020

11

First salvage in DLBCL – CAR-T vs auto HCT

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



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

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

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

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

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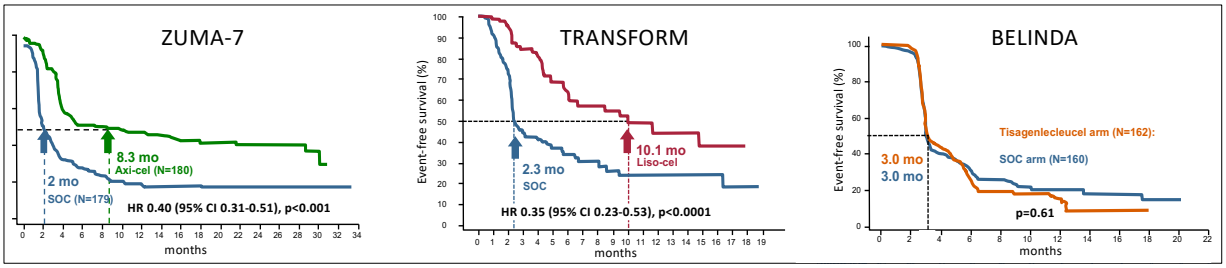
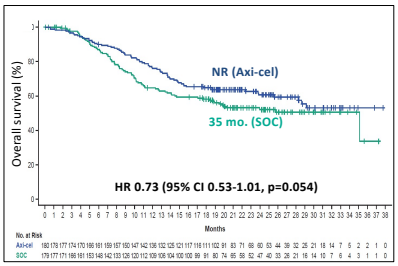
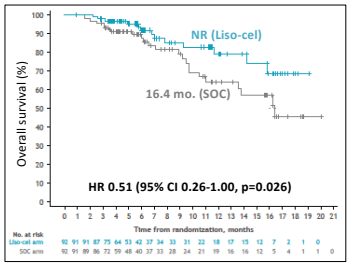
CAR-T vs SOC as first salvage in R/R DLBCL

EFS



OS





CAR-T toxicity

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

Locke et al, NEJM 2022 | Kamdar et al, Lancet 2022 | Bishop et al, NEJM 2022

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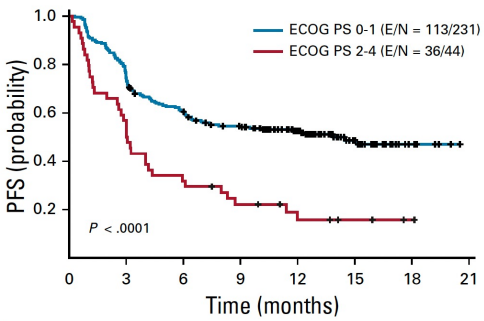
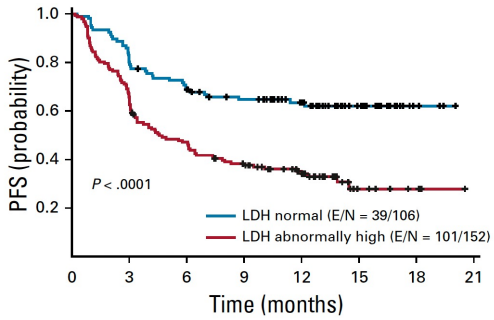
Real world experience with Axi-cel

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



No. at risk:

ECOG PS 0-1	231	172	137	115	82	31	6	0
ECOG PS 2-4	44	25	14	9	5	3	1	0



No. at risk:

LDH normal	106	85	72	62	48	24	4	0
LDH abnormally high	152	100	70	53	32	7	3	0

Nastoupil et al, JCO 2020

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DLBCL updates – Summary

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

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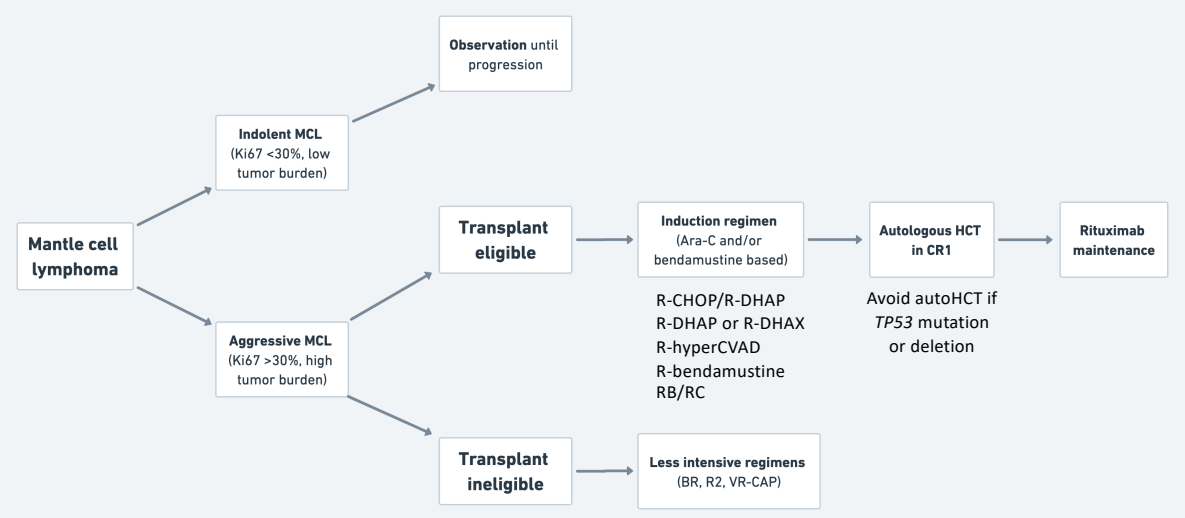
Mantle cell lymphoma – frontline therapy



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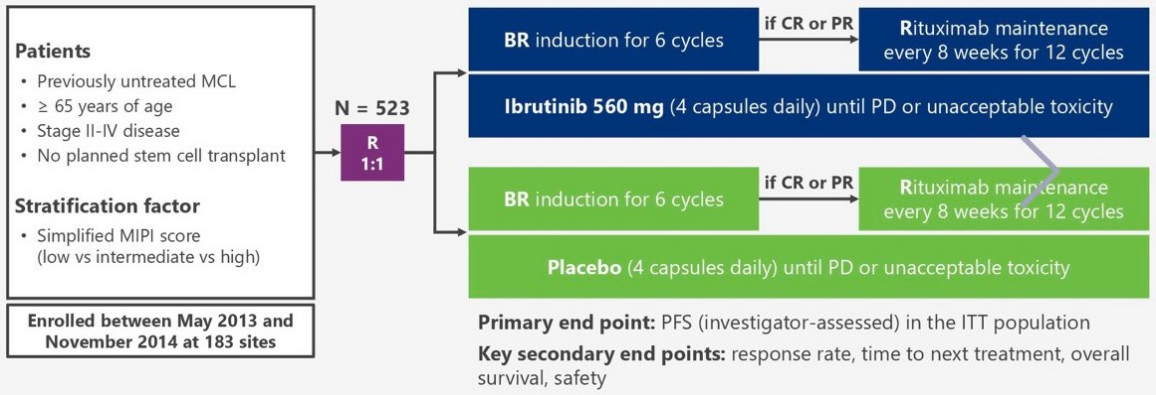
SHINE trial

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



Wang et al, NEJM 2022

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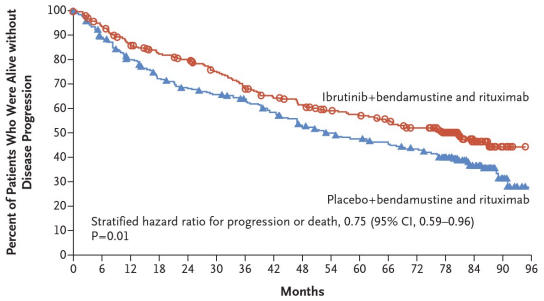
SHINE trial – efficacy endpoints

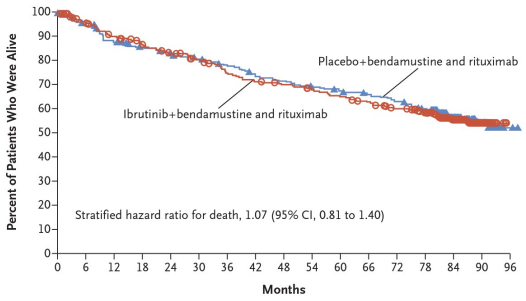
- Adding ibrutinib to BR improved PFS but not OS
- Median PFS 80.6 months vs 52.9 months (median follow-up 84.7 months)

Progression-free survival



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

Overall survival



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

Wang et al, NEJM 2022

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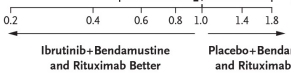
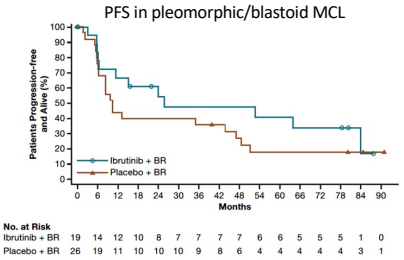
SHINE trial – subgroup analysis

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



ANCO
Educating and Empowering the Northern California Cancer Community

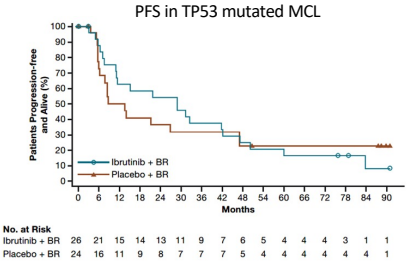
PFS in pleomorphic/blastoid MCL



No. at Risk

Ibrutinib + BR	19	14	12	10	8	7	7	7	7	6	6	5	5	1	0
Placebo + BR	26	19	11	10	10	9	8	6	4	4	4	4	3	1	

PFS in TP53 mutated MCL



No. at Risk

Ibrutinib + BR	26	21	15	14	13	11	9	7	6	5	4	4	4	3	1	1
Placebo + BR	24	16	11	9	8	7	7	7	5	4	4	4	4	4	4	1

Wang et al, NEJM 2022

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SHINE trial – safety/tolerability

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

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

Wang et al, NEJM 2022

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Limitations of the SHINE trial

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

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

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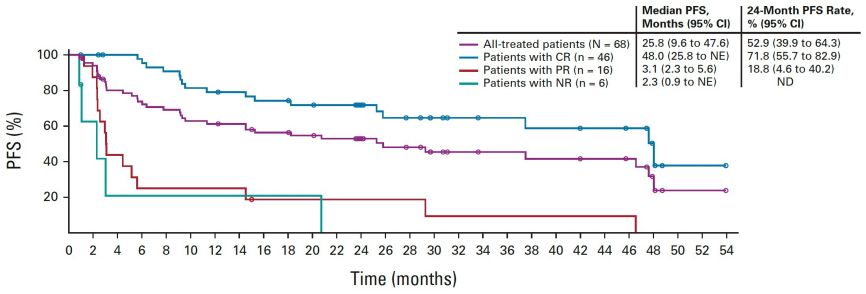
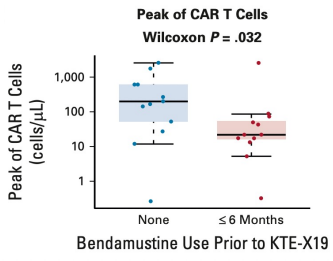
ZUMA-2 trial 3-year update – Brexu-cel in R/R MCL

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





Wang et al, JCO 2022

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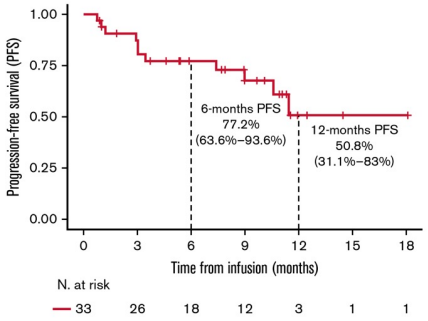
Real world experience with Brexu-cel in R/R MCL

- U.S. CAR-T consortium – 167 patients from 16 centers
- High risk patient population:
  - Median age 67 years
  - Median 3 prior therapies (86% prior BTK inhibitor)
  - 57% had Ki67 >50%
  - 49% had TP53 mutation or deletion
  - 10% had CNS involvement
  - 78% would not have met eligibility criteria for ZUMA-2
- Median time from apheresis to LD chemo: 28 days
- Safety/tolerability:
  - CRS 90% (grade 3+ 8%) – 1 fatality
  - ICANS 61% (grade 3+ 32%)
- Efficacy:
  - ORR 89%, CR 70%
  - 6-month PFS 63% (median follow-up 6 months)

Jain et al, ASCO 2022

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



Iacoboni et al, *Blood Adv* 2022

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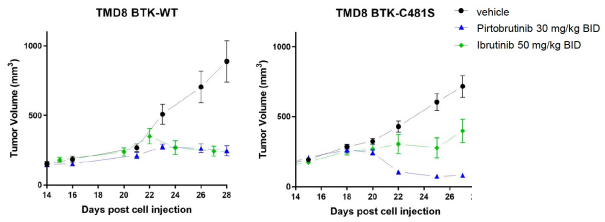
BRUIN trial – Pirtobrutinib (LOXO-305) in R/R MCL

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



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

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

Mato et al, *Lancet* 2021

Wang et al, 2021 ASH #381

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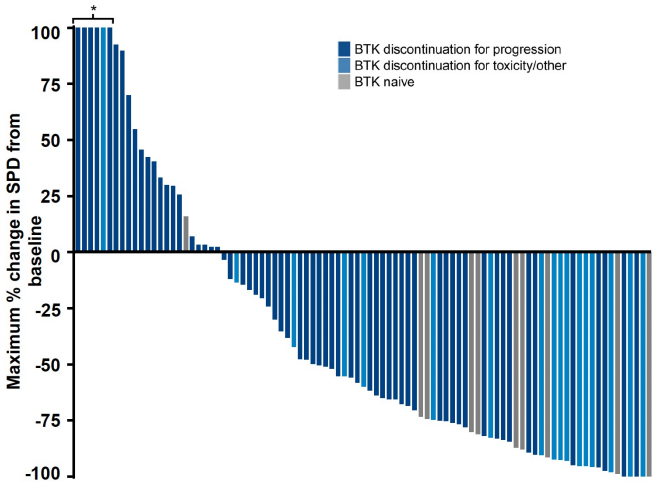
Pirtobrutinib efficacy in R/R MCL



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

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

Wang et al, 2021 ASH #381

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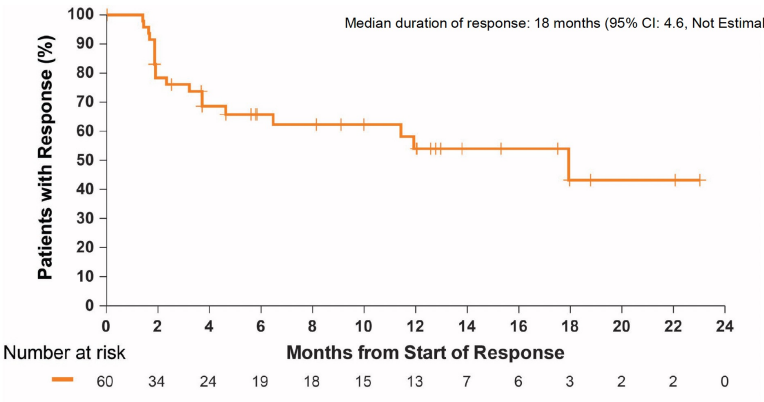
Pirtobrutinib duration of response in R/R MCL



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

Wang et al, 2021 ASH #381

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Pirtobrutinib safety profile in B-cell NHL and CLL

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

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

Wang et al, 2021 ASH #381

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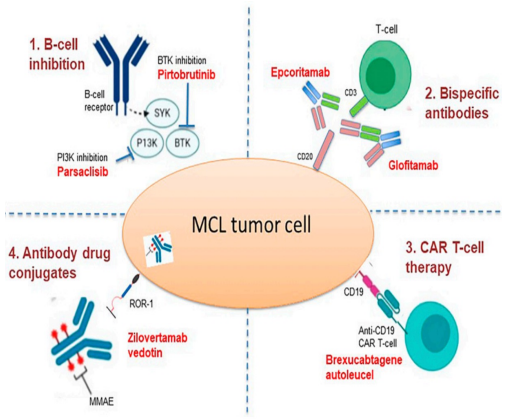
Novel agents and combinations in R/R MCL

Novel therapeutic approaches in R/R MCL



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

Kumar et al, JCO 2022

*trial open at UCSF

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Mantle cell lymphoma updates - Summary

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

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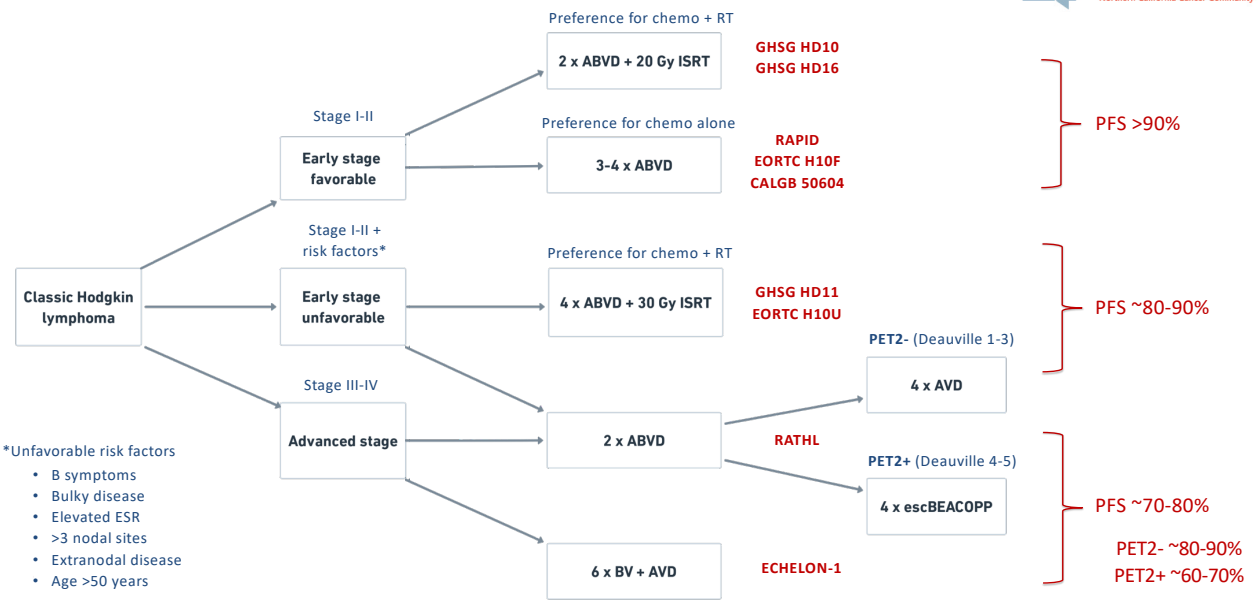
Hodgkin lymphoma – frontline therapy



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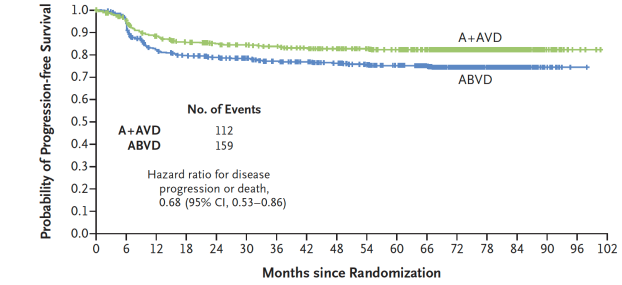
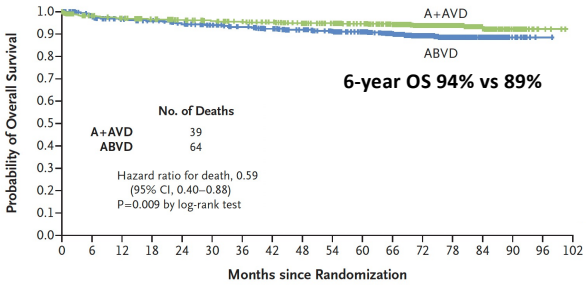
ECHELON-1 6-year update

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





Ansell et al, NEJM 2022

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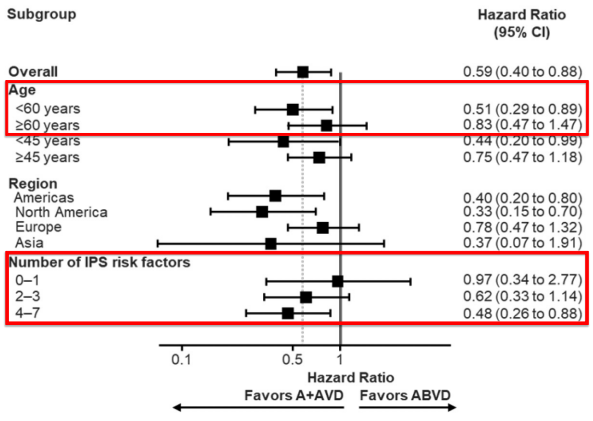
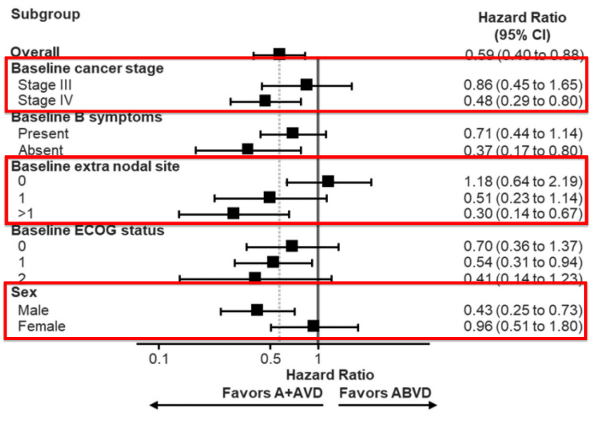
ECHELON-1 subgroup analysis

- Greater benefit of BV-AVD with high-risk disease: stage IV, IPS 4-7, extranodal involvement
- Less benefit in older adults >60, female patients, and lower risk disease (IPI 0-1)





Ansell et al, NEJM 2022

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ECHELON-1 – subsequent lymphoma therapy

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

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

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

Ansell et al, NEJM 2022

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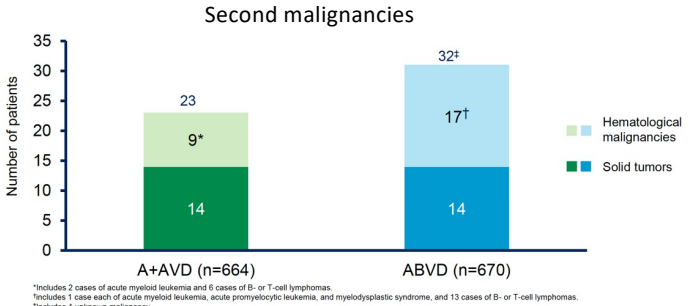
ECHELON-1 – Causes of death

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

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

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



*Includes 2 cases of acute myeloid leukemia and 6 cases of B- or T-cell lymphomas.
†Includes 1 case each of acute myeloid leukemia, acute promyelocytic leukemia, and myelodysplastic syndrome, and 13 cases of B- or T-cell lymphomas.
‡Includes 1 unknown malignancy.

Among patients with second malignancies:

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

Ansell et al, NEJM 2022

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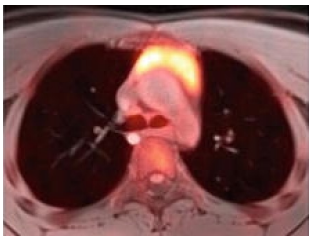
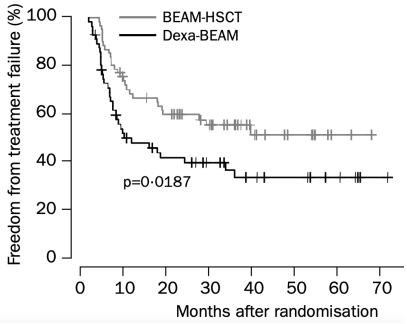
Relapsed/refractory HL

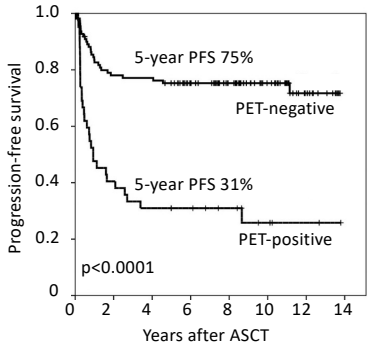
- Rebiopsy is critical to confirm relapse or refractory disease
- Salvage therapy and autologous stem cell transplant (ASCT) is the current standard of care
- Achieving a CR by PET prior to ASCT is a key prognostic factor for PFS



Benign thymic hyperplasia mimicking relapse in mediastinum



Brink et al, *J Nuc Med* 2001



Schmitz et al, *Lancet* 2002

Moskowitz et al, *Blood* 2010

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Traditional salvage chemotherapy for R/R HL

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

*CR rate assessed by CT

†CR rate assessed by PET

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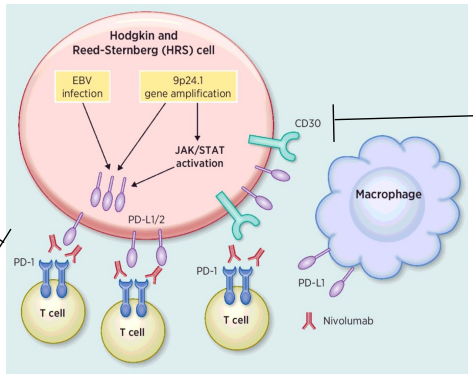
Novel agents have changed the treatment landscape of R/R HL

FDA approved 2016

Nivolumab

Pembrolizumab

FDA approved 2017



Brentuximab vedotin (BV)

FDA approved 2011

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

*Remainder were transplant ineligible and had progression after BV

Figure from SM Ansell, *Clin Cancer Res* 2017

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Novel salvage regimens incorporating BV and PD-1 inhibitors

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

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Novel salvage regimens increase CR rate and PFS after ASCT

N = 853 patients

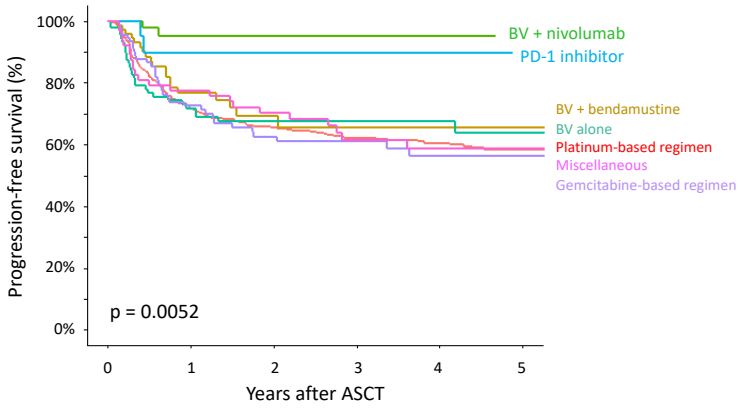
12 U.S. centers

ASCT between 2010-2020

Outcomes compared by salvage regimen:

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

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



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

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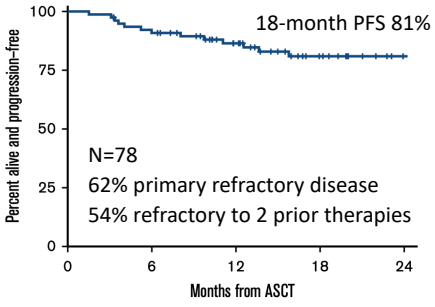
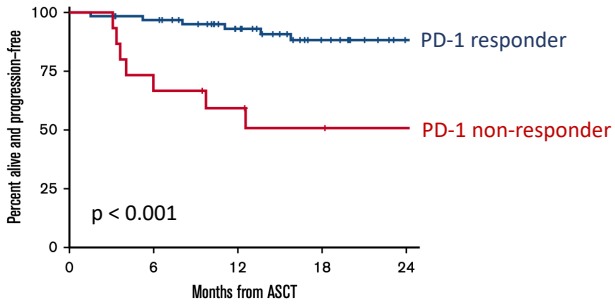
ASCT after PD-1 blockade in R/R HL

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





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

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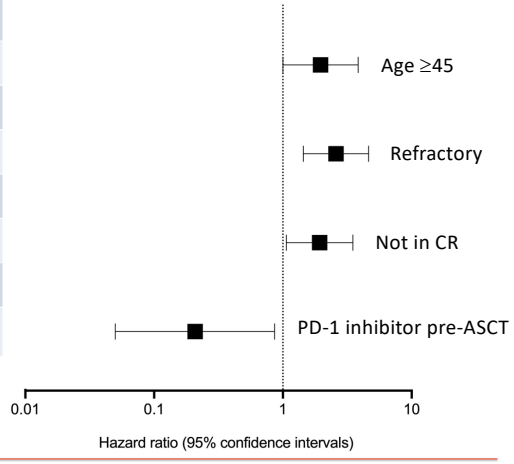
PD-1 inhibitors pre-ASCT improve PFS in multivariate analysis

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

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



Spinner et al, unpublished data

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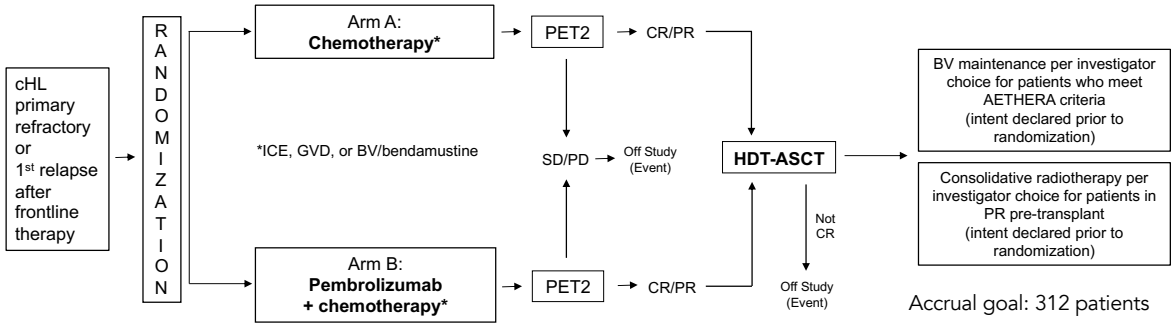
ECOG-ACRIN 4211 trial

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



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

Accrual goal: 312 patients

Stratification factors:

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

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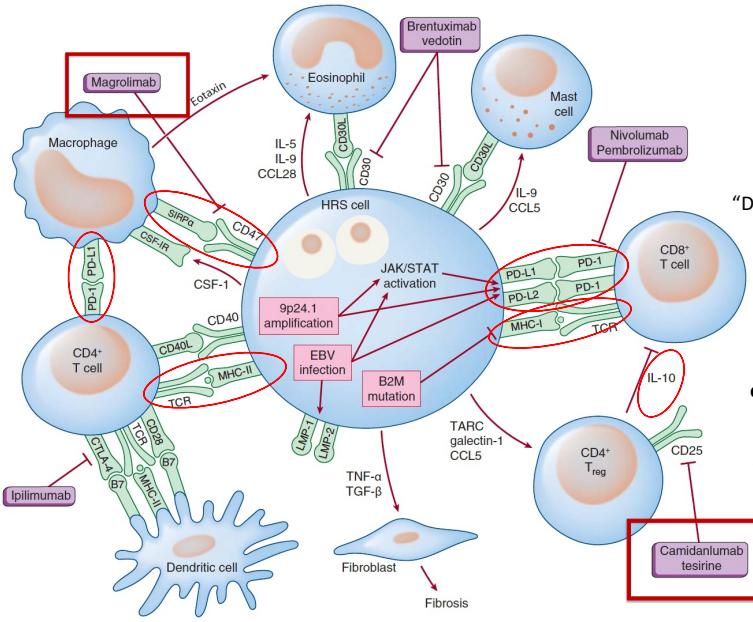
Reed-Sternberg cells evade the immune system through multiple pathways

CD47 overexpression

"Don't eat me" signal

Decreased or absent MHC class I or II expression

Impaired antigen presentation



PD-L1 and PD-L2 overexpression

"Don't find me" signal

Anti-inflammatory cytokine production

Promoting an immunosuppressive microenvironment

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

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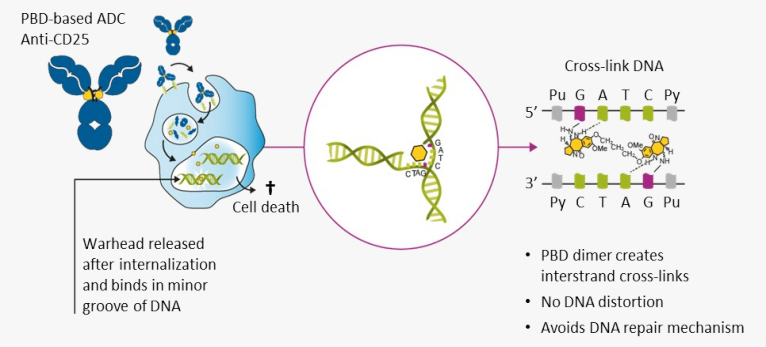
Depleting immunosuppressive T_{regs} in the tumor microenvironment

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



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

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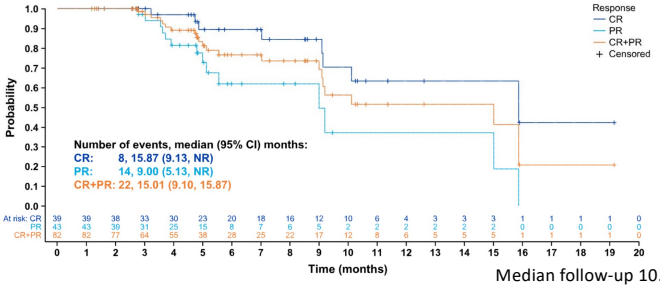
Phase 2 study of camidanlumab tesirine in R/R HL

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



Median follow-up 10.7 mo.

Summary of Patients with GBS/polyradiculopathy

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

Carlo-Stella et al, 2022 EHA Abstract #S201

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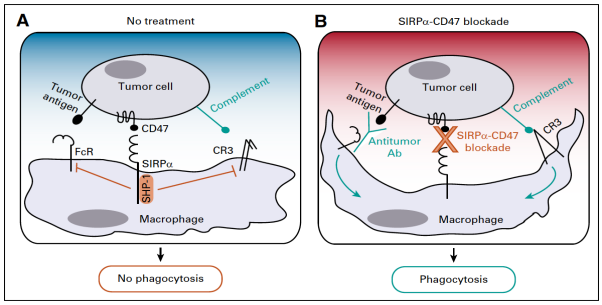
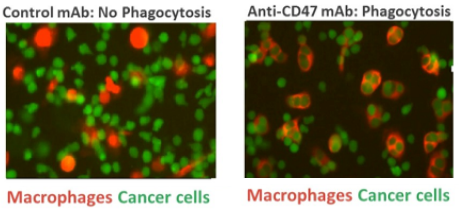
Activating macrophages in the tumor microenvironment

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





[1]Veillette and Tang, JCO 2019

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

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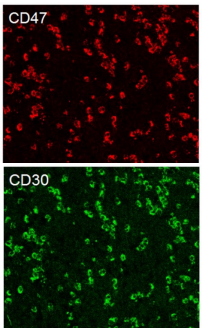
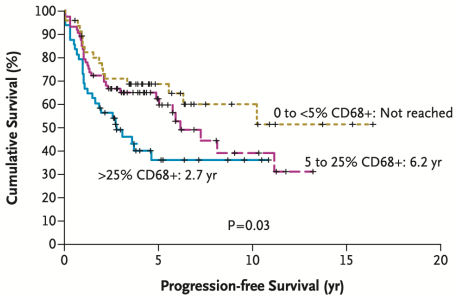
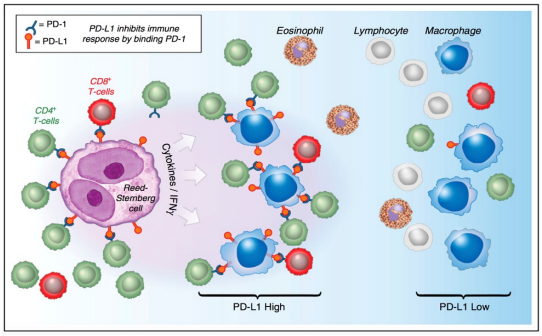
Rationale for CD47 blockade and targeting macrophages in HL

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







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

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

Eligible patients

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

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

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Treatment schedule

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

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

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

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

Survival follow up

Currently open at Stanford & DFCI
Accrual goal: 24 patients

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

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Hodgkin lymphoma updates - Summary

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

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Acknowledgements

UCSF Lymphoma Group
Wei Ai, MD, PhD
Babis Andreadis, MD
Lawrence Kaplan, MD
James Rubenstein, MD, PhD
Madhav Seshadri, MD

Stanford Oncology/BMT
Ranjana Advani, MD
Richard Hoppe, MD
Sally Arai, MD
Robert Lowsky, MD
Robert Negrin, MD

Dana-Farber Cancer Institute
Margaret Shipp, MD
Scott Rodig, MD, PhD
Philippe Armand, MD, PhD
Reid Merryman, MD

Alliance Cooperative Group
Amanda Cashen, MD
Vaishalee Kenkre, MD

Funding Support
Conquer Cancer Foundation of ASCO
Association of Northern California Oncologists

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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Myeloma Update 2022

Michaela Liedtke, MD

Stanford University

UPDATES IN MULTIPLE MYELOMA

ANCO 2022

Michaela Liedtke, MD

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

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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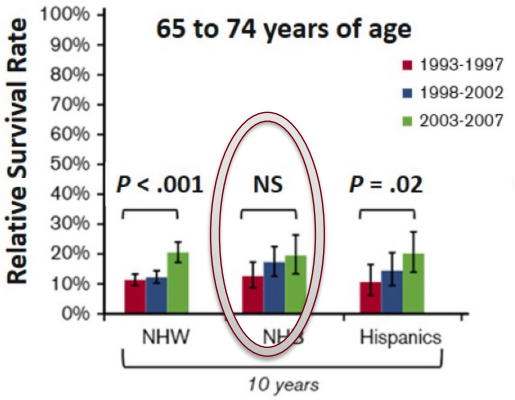
4

Outcome disparity



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

Costa L, et al. Blood Advances 2017.

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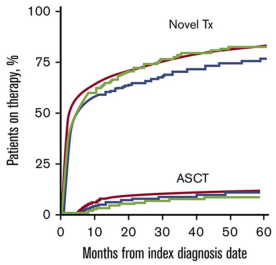
Access disparity



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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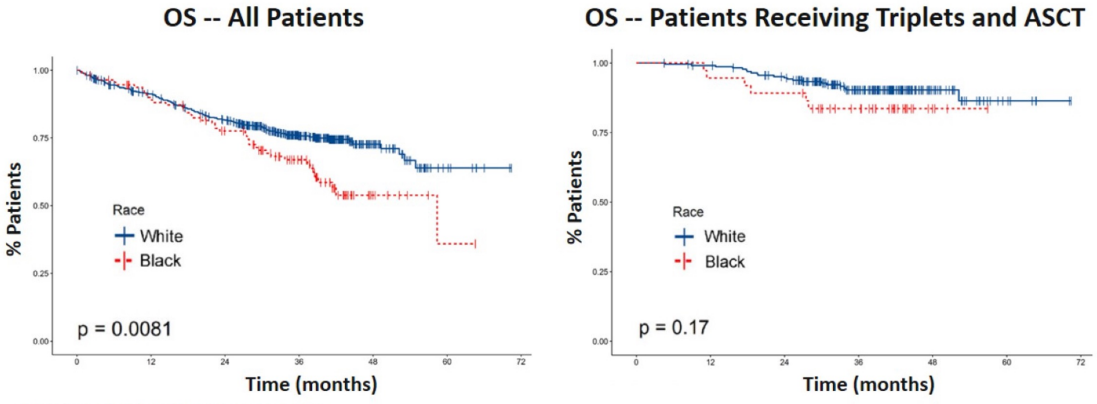
Equal access results in equal outcome



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

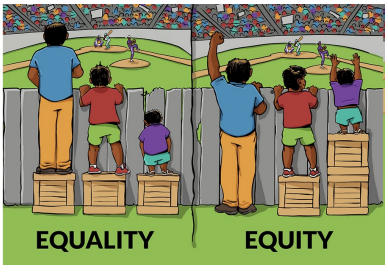
More likely to live in rural areas

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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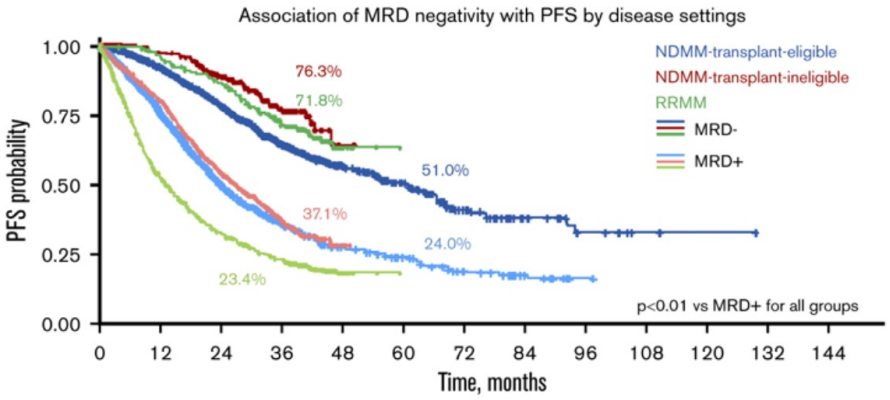
Minimal residual disease



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)

RVD X3
ASCT
RVDX2
(N = 350)

LENALIDOMIDE
X12 MO

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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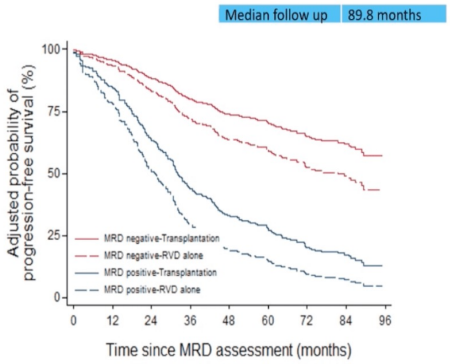
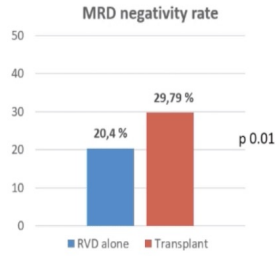
IFM/DFCI 2009: Role of MRD

Subgroup analyses





MRD-negativity is a strong predictor for PFS and OS

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

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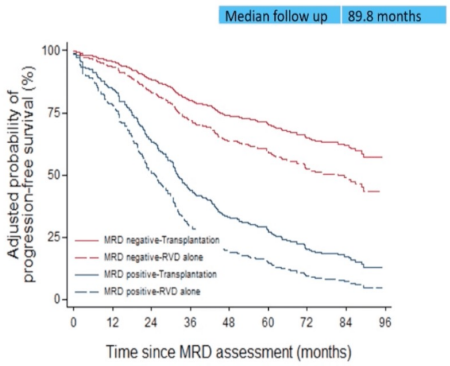
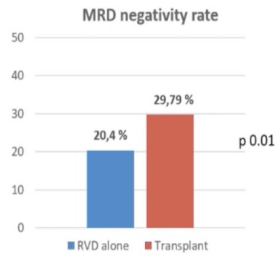
IFM/DFCI 2009: Role of MRD

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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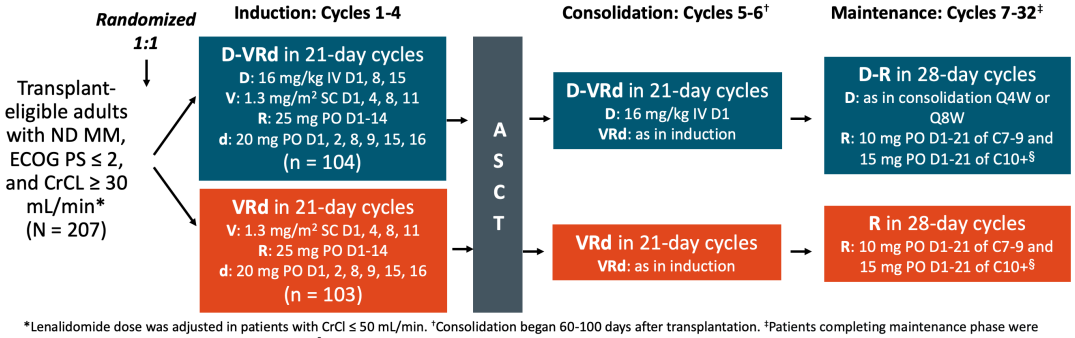
GRIFFIN: Dara-VRd versus VRd



*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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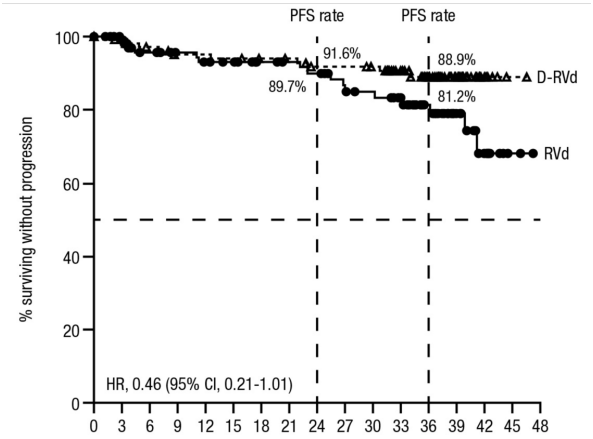
GRIFFIN: D-RVd prolongs PFS



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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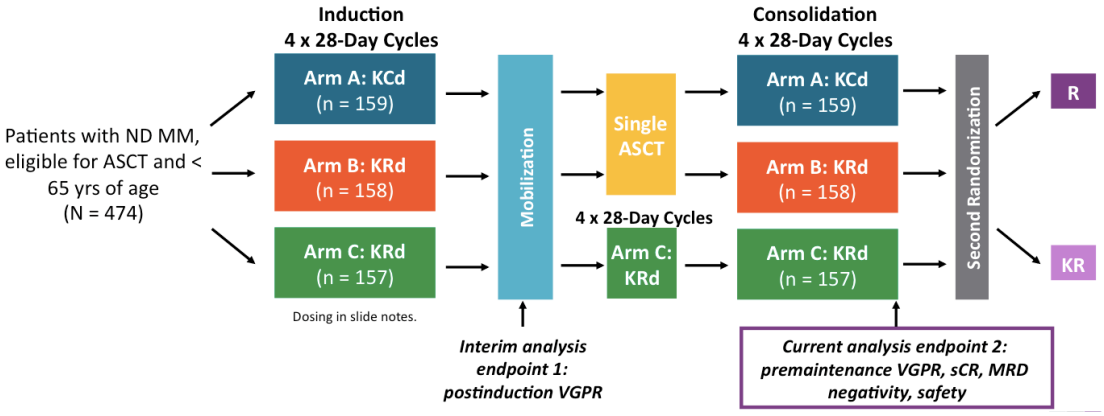
FORTE: KRd +/- ASCT

- Multicenter, randomized, open-label phase II study



Gay F, et al. Lancet Oncology 2021.

Slide credit: clinicaloptions.com

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FORTE: Initial randomization

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

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

Gay F, et al. Lancet Oncology 2021.

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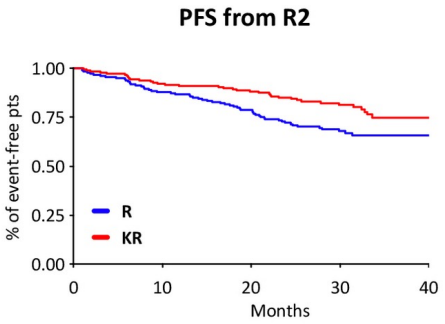
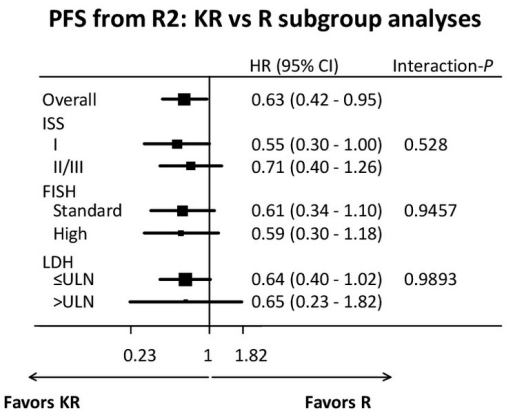
FORTE: Second randomization





KR maintenance increased PFS compared to lenalidomide alone

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

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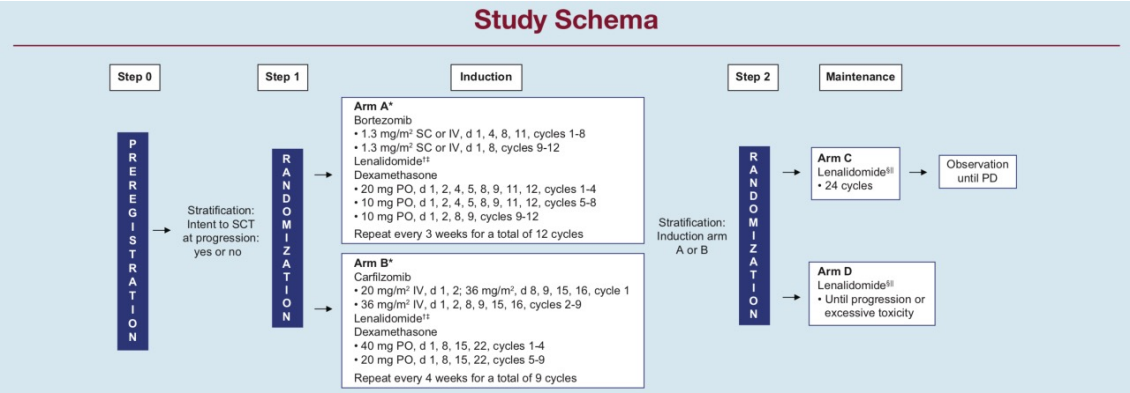
ENDURANCE: KRd versus VRd

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



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

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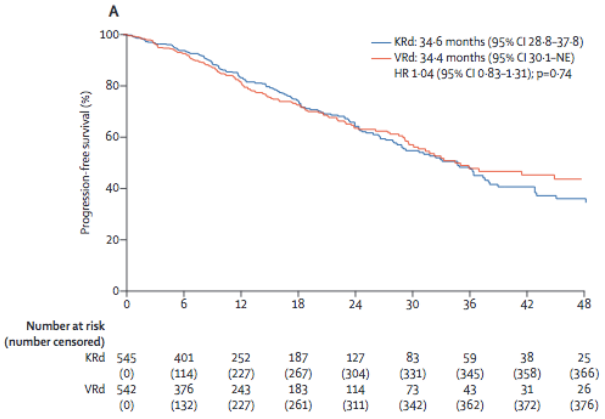
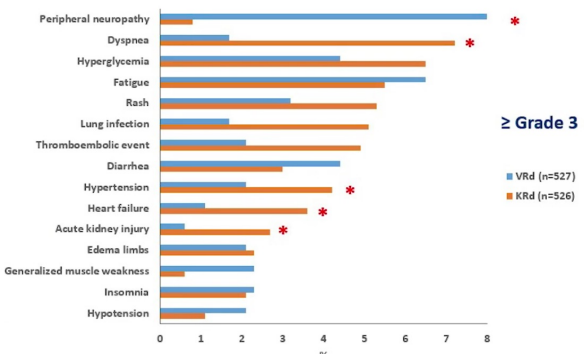
KRd did not improve PFS compared to VRd



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



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

Kumar S, et al. Lancet Oncology 2020.

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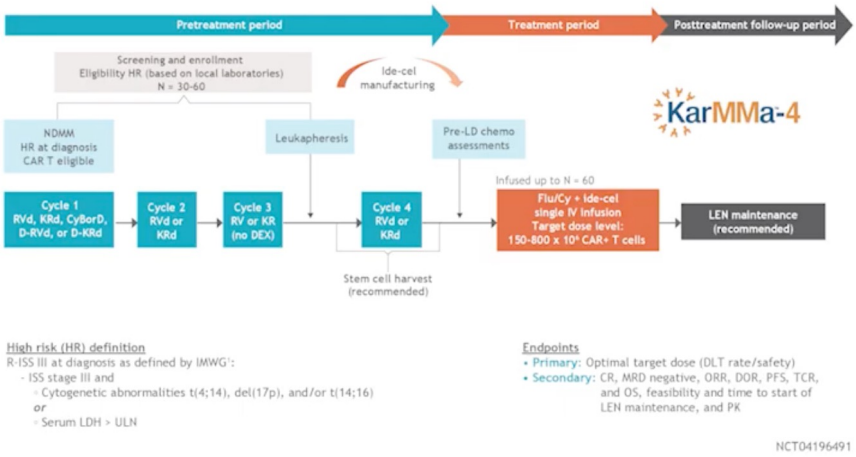
KarMMa-4: upfront CAR-T for high-risk myeloma



Usmani S, et al. ASCO 2021.

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MAIA: Rd +/- daratumumab in upfront myeloma

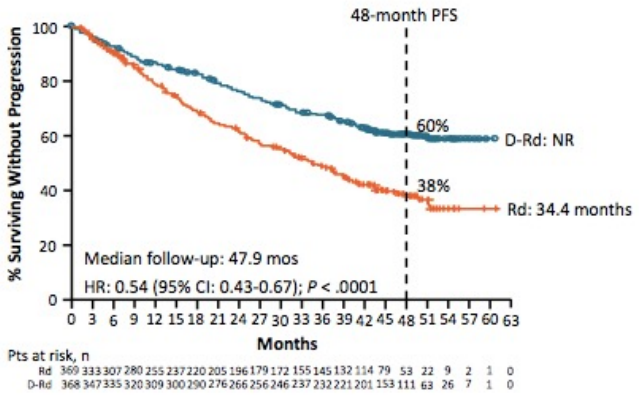
NEWLY DIAGNOSED MYELOMA
ASCT-INELIGIBLE AND ECOG 0-2
MEDIAN AGE 73

DARATUMUMAB+ REVLIMID + DEX (N = 368)

Revlimid + dex (n = 369)

MEDIAN DOT 42.8 MO

MEDIAN DOT 22.6 MO



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

Facon et al., NEJM 2019 and Lancet Oncology 2021

Slide credit: clinicaloptions.com

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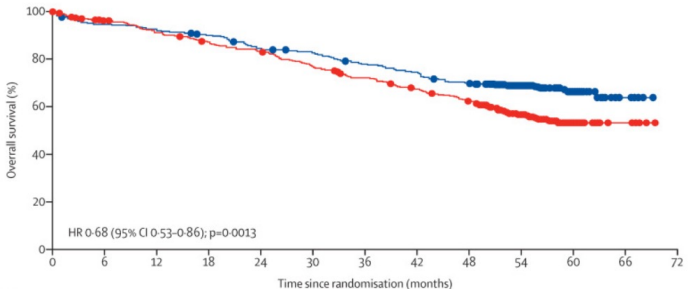
MAIA: Rd +/- daratumumab in upfront myeloma

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

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



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

Facon et al., NEJM 2019 and Lancet Oncology 2021

Slide credit: clinicaloptions.com

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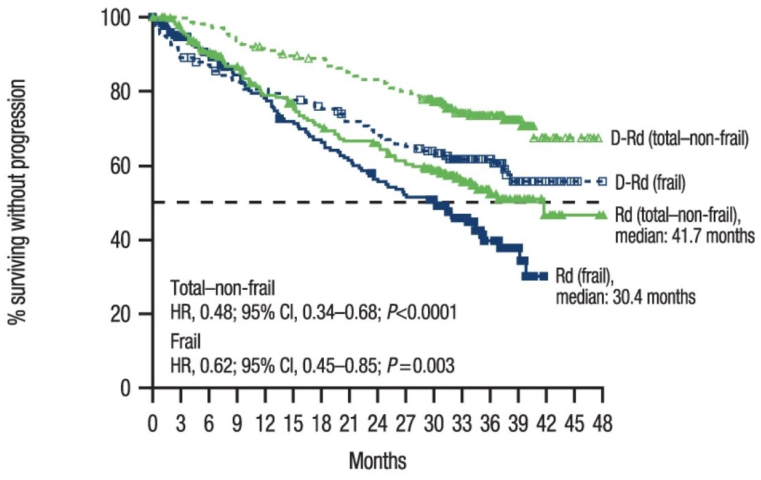
MAIA: Dara-Rd beneficial for frail patients



Facon T, et al. Leukemia 2021.

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Induction regimens in upfront myeloma

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

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Summary

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

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Relapse: Available Agents

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

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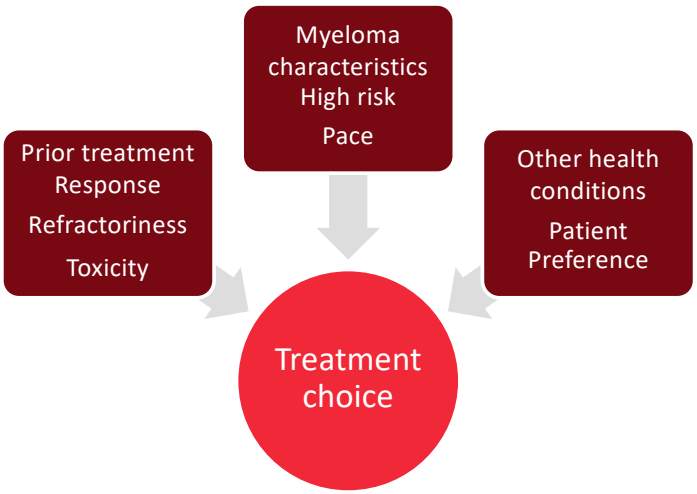
General Treatment Approach at Relapse



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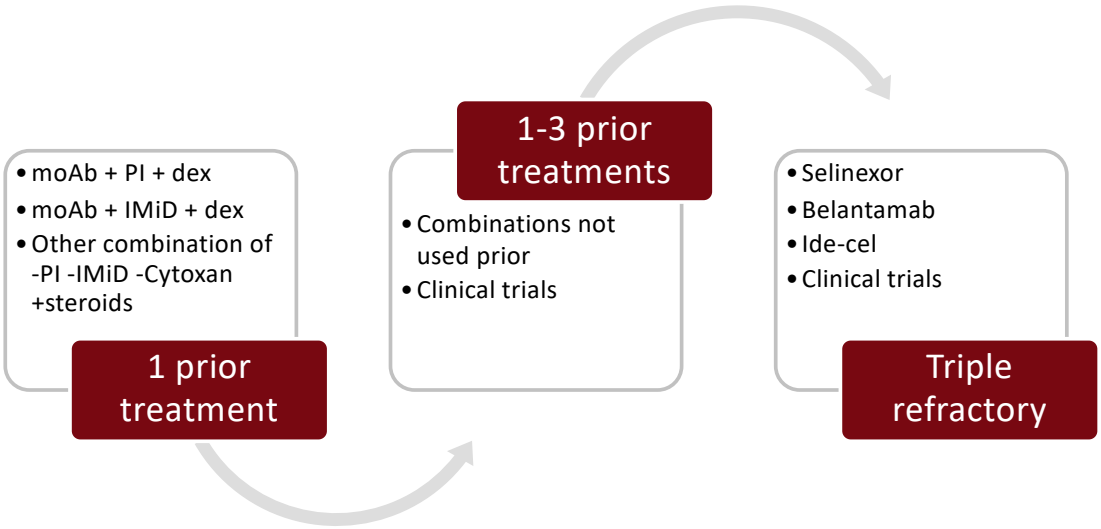
Sequencing Considerations



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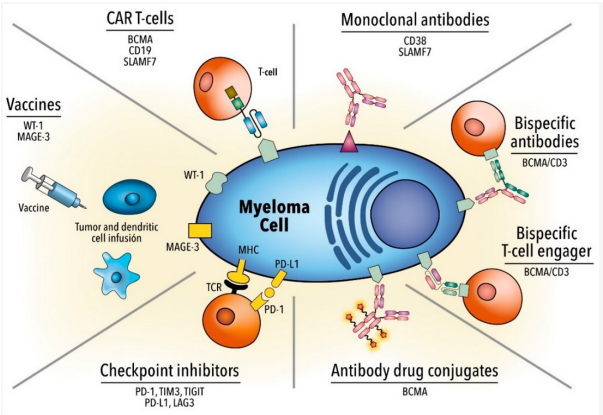
Focus on Immunotherapy

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



Rodriguez-Lobato L, et al. ASH 2021.

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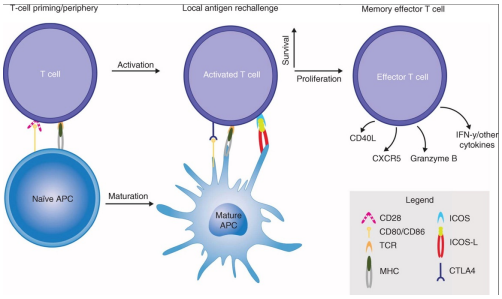
Antibody drug conjugate: belantamab mafodotin plus ICOS-agonist feladilimab

Belantamab mafodotin is an ADC targeting BCMA

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

Intravenous infusion q3weeks
Eye exam prior to every infusion



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

Nooka, et al. FutOnc 2021.

Callander, et al. ASH 2021. Abstract 897.

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DREAMM-5: Adverse Events/Ocular Toxicity

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

Callander, et al. ASH 2021. Abstract 897.

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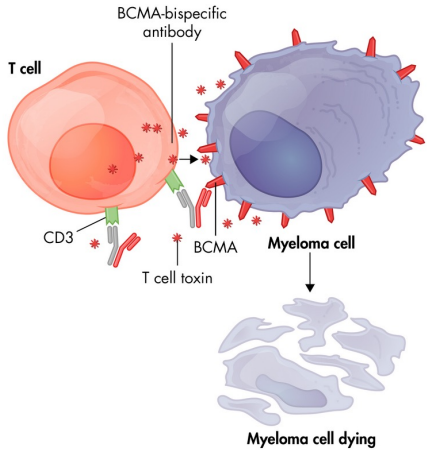
Bispecific antibodies and T-cell engagers

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



SF Cho, Front Immunology;9:821

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Bispecifics in Myeloma

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

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

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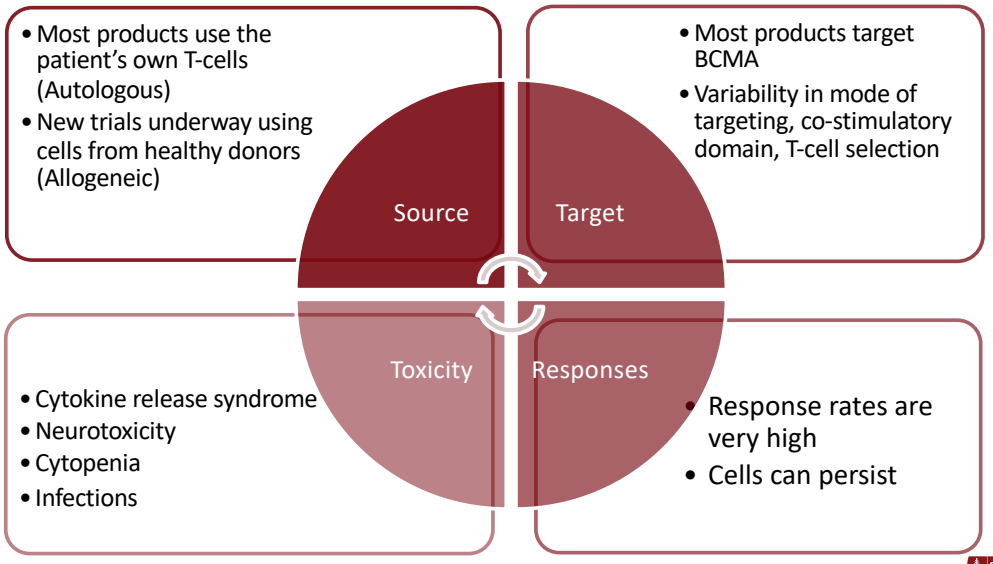
CAR T-cells at a glance



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BCMA-targeted CAR T-cell Therapy

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

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

*at highest dose level

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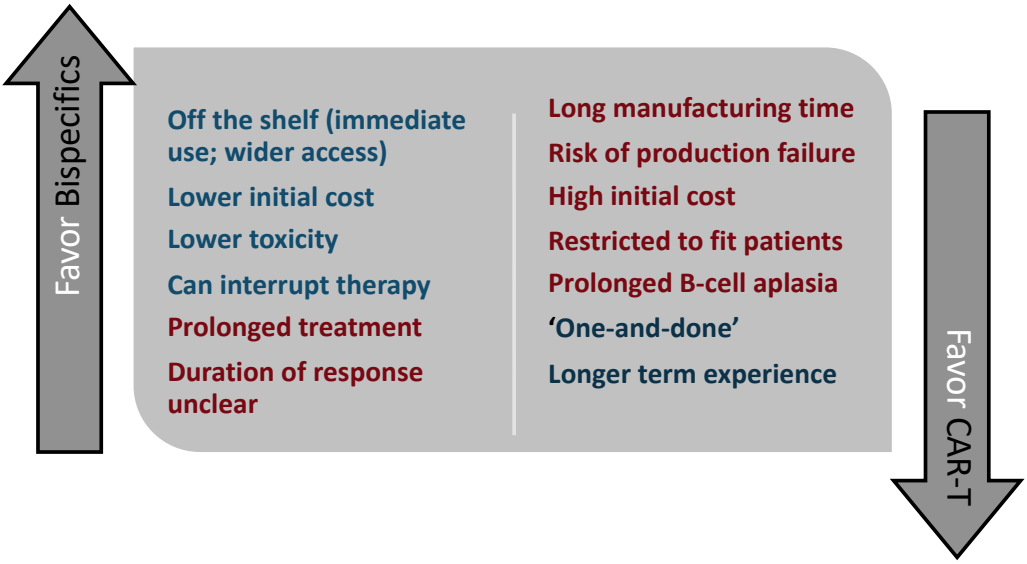

Adapted from Patel et al, BJH 2021

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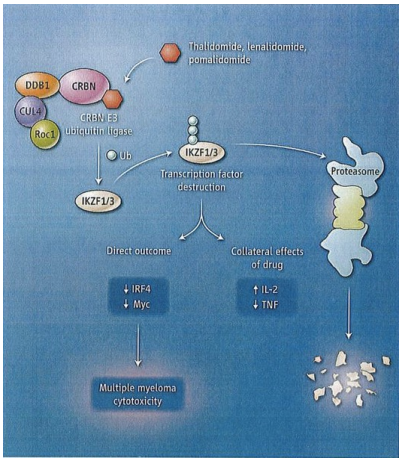
Cereblon E3 ligase modulator (CELMoD): Iberdomide

Iberdomide is an oral CELMoD
enhances degradation of Ikaros and Aiolos

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

In combination with dexamethasone



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

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

Median DOR: 7 mo

Lonial, et al. ASH 2021. Abstract 162.

Stewart, Science 2014.

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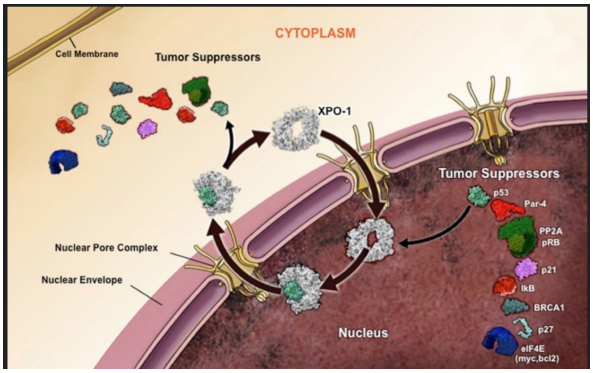
Selinexor in Relapsed/Refractory Multiple Myeloma

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



D White et al, ASH 2021-abstract 2748

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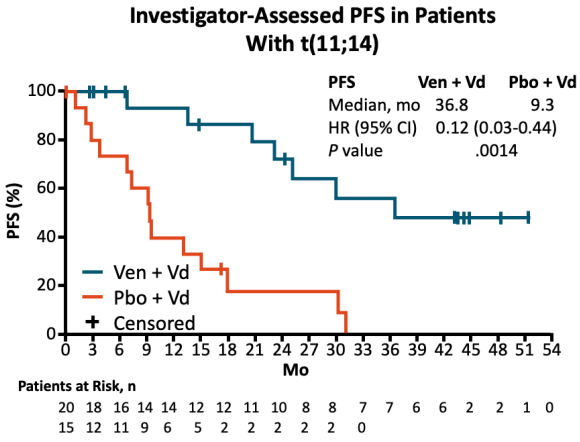
Precision Medicine: Venetoclax for Myeloma with t(11;14)

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



Kumar. ASH 2021. Abstr 84.

Slide credit: clinicaloptions.com

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MyDRUG: Myeloma-Developing Regimens Using Genomics

6-arm, nonrandomized phase I/II study

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

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

All patients received ixazomib/ pomalidomide/dexamethasone, plus:

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

ClinicalTrials.gov. NCT03732703.

Slide credit: clinicaloptions.com

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Summary

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

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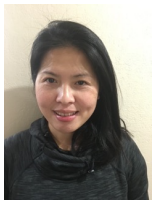
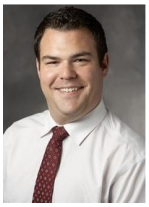
Stanford Myeloma and Amyloid Team

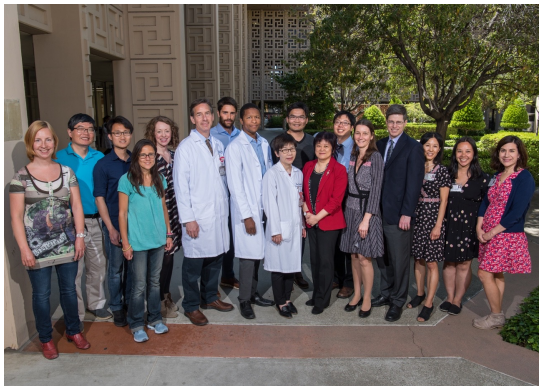


Ren Inthasack

Donirene Ward



Dave Iberri



Surbhi Sidana

Sally Arai

David Kurtz

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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Case Presentations: Leukemias, Lymphomas, Myeloma

Tamar Othman, MD

Fellow, Hematology & Oncology Stanford University

ANCO

Educating and Empowering the Northern California Cancer Community

Hematologic Malignancies Update 2022: Cases

Tamer Othman, MD

1

Case 1

- HPI abridged
  - 61 yo M with a PMH of HTN who presented with a 2-month history of progressive cough, fatigue, dizziness, SOB, 35 lbs unintentional wt loss, and bruising
  - No prior history of malignancies or hematologic disorders
  - ECOG 0
  - Notable physical exam findings
    - Subconjunctival pallor, palatal petechiae
  - Pertinent labs/imaging
    - CBC: WBC 2.3 (ANC 300), Hgb 3.3, MCV 102.7, plts 40
    - Peripheral smear shows 2% blasts. No auer rods visualized.
    - Chemistry: Cr + AST/ALT/AP WNL, Tbili 1.9, K 4.4, Ca 8.7 phos 6.4, uric acid 9.3, LDH 981
    - Coags WNL
    - CXR and TTE without any abnormalities, EF=63%

2

Case 1

- Bone marrow biopsy (aspirate smear and core)
  - Normocellular (45%) with 12% blasts
  - No dysplastic lineages on morphologic assessment
- Flow cytometry on BM
  - Immunophenotyping shows CD33+
- Cytogenetics
  - 46,XY
- Next-gen sequencing
  - NPM1 mutated

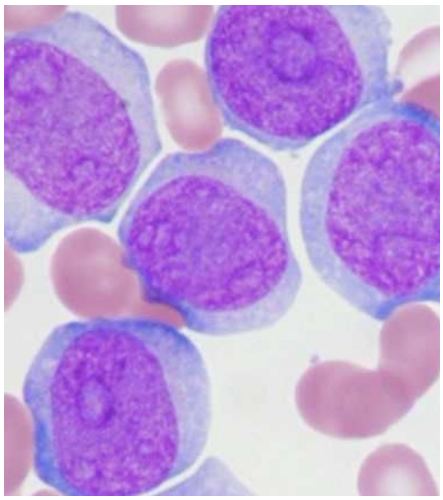


Image credit: https://www.pinterest.co.kr/pin/687784174316025612/

3

Case 1

- Question for the audience:
  - How would you manage this patient?
    - A. Hypomethylating agent
    - B. Supportive care
    - C. 7+3+/- GO
    - D. Clinical trial for MDS-IB1 (formerly MDS-EB1)
    - E. Hypomethylating agent + venetoclax

4

Case 1

- In oncology, a clinical trial is always strongly recommended when available and the patient is eligible
- However in this case, the patient meets the diagnostic criteria of AML, not MDS
- In the 4th edition of WHO myeloid neoplasms and acute leukemia classification, the presence of certain cytogenetic/FISH findings were diagnostic of AML irrespective of the blast %:
  - t(8;21)(q22;q22.1);RUNX1-RUNX1T1
  - inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11
  - APL with PML-RARA

In the 5th edition

Table 7. Acute myeloid leukaemia.

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

Most AML with defining genetic abnormalities may be diagnosed with <20% blasts

Khoury, Leukemia 2022

5

Case 1

- International Consensus Criteria

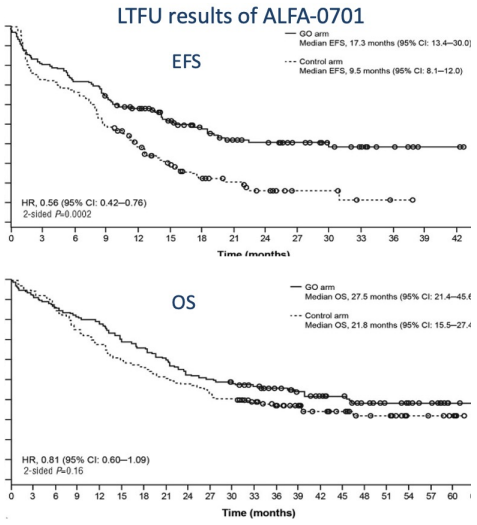
Table 26. Classification of acute myeloid leukemia (AML) with percentage of blasts required for diagnosis

- **Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2)/*PML*::*RARA*** ≥10%
- **APL with other *RARA* rearrangements*** ≥10%
- **AML with t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*** ≥10%
- **AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*** ≥10%
- **AML with t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*** ≥10%
- **AML with other *KMT2A* rearrangements**** ≥10%
- **AML with t(6;9)(p22.3;q34.1)/*DEK*::*NUP214*** ≥10%
- **AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*; *MECOM*(*EVI1*)** ≥10%
- **AML with other *MECOM* rearrangements***** ≥10%
- **AML with other rare recurring translocations (see Supplemental Table 5)** ≥10%
- **AML with t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*‡** ≥20%
- **AML with mutated *NPM1*** ≥10%
- **AML with in-frame bZIP *CEBPA* mutations** ≥10%
- **AML and MDS/AML with mutated *TP53*†** 10-19% (MDS/AML) and ≥20% (AML)
- **AML and MDS/AML with myelodysplasia-related gene mutations** 10-19% (MDS/AML) and ≥20% (AML)
  - Defined by mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
- **AML with myelodysplasia-related cytogenetic abnormalities** 10-19% (MDS/AML) and ≥20% (AML)
  - Defined by detecting a complex karyotype (≥3 unrelated clonal chromosomal abnormalities in the absence of other class-defining recurring genetic abnormalities), del(5q)/t(5q)/add(5q), -7/del(7q), +8, del(12p)/t(12p)/add(12p), i(17q), -17/add(17p) or del(17p), del(20q), and/or idic(X)(q13) clonal abnormalities
- **AML not otherwise specified (NOS)** 10-19% (MDS/AML) and ≥20% (AML)
- **Myeloid Sarcoma**

6

Case 1

- Should GO be added?
  - GO is a CD33-targeting ADC
  - Several trials tested chemo + GO
  - ALFA-0701 trial specifically studied 7+3+GO
    - Initial results showed OS and EFS benefit
    - OS benefit lost in LTFU report
  - 4 meta-analyses were conducted
    - Loke et al
      - ↑ induction deaths but ↓ resistant disease
      - ↑ RFS but no OS benefit
        - » ↑ OS in pts with favorable cytogenetics only
    - Kharfan-Dabaja et al
      - ↑ RFS but also early mortality, no OS benefit
        - » ↑ RFS in favorable/intermediate cytogenetics
    - Li et al
      - ↑ RFS and OS, ↓ resistant disease and relapse
        - » OS benefit only in favorable
    - Hills et al
      - ↓ relapse and ↑ OS
        - » OS benefit in those with favorable/intermediate cytogenetics



Castaigne et al, Lancet 2012; Lambert et al, Haematologica 2019; Hills et al, Lancet Oncol 2014; Li, Ann Oncol 2014; Loke, Ann Hematol 2015; Kharfa-Dabaja, BJH 2013

7

Case 1

- Intensive chemotherapy or low-intensity therapy?
  - Balance chance of disease control and risk of major morbidity/early mortality
  - Intensive induction for pts <60 with favorable/intermediate-risk
  - For pts <60 with unfavorable-risk AML, alternative induction strategies should be considered
    - Clinical trial
    - HMA-Ven
    - 10 days of decitabine
  - For ≥60, factor to consider
    - Organ function
    - Performance status
    - AML risk stratification
  - Pts ineligible for intensive chemo are more appropriate for HMA/Ven or targeted therapy
    - Rapid screening for actionable mutations should also be performed (i.e., FLT3, IDH1/2)

8

Case 1

- GO is recommended in favorable- or intermediate-risk CD33+ AML
- Data suggests benefit in NPM1 mutated AML specifically
  - AMLSG 09-09 trial:
    - GO + intensive chemotherapy in NPM1 mutated AML = ↓NPM1 transcripts by RT-qPCR (MRD) and cumulative incidence of relapse
- No benefit in adverse-risk AML

ELN 2022 risk stratification

Genetic Abnormality

- t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*[b,c]
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*[b,c]
- Mutated *NPM1*[b,d] without *FLT3*-ITD
- bZIP in-frame mutated *CEBPA*[e]

- Mutated *NPM1*[b,d] with *FLT3*-ITD
- Wild-type *NPM1* with *FLT3*-ITD
- t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*[b,f]
- Cytogenetic and/or molecular abnormalities not classified as favor

- t(6;9)(p23;q34.1)/*DEK::NUP214*
- t(v;11q23.3)/*KMT2A*-rearranged[g]
- t(9;22)(q34.1;q11.2)/*BCR::ABL1*
- t(8;16)(p11;p13)/*KAT6A::CREBBP*
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*
- t(3q26.2;v)/*MECOM(EVI1)*-rearranged
- -5 or del(5q); -7; -17/abn(17p)
- Complex karyotype,[h] monosomal karyotype[i]
- Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2,*
- Mutated *TP53*[k]

Dohner, Blood 2022

9

Case 1

- Induction course
  - Pt is started on 7+3+GO
  - C/b LLL pneumonia, strep bacteremia, febrile neutropenia, and sepsis
  - D14 BMBx – 5% cellularity and 1% blasts
  - D28 BMBx – CR: 90% cellularity and 3% blasts with ANC >1000 and plts >100
    - Cytogenetics 46,XY, FISH negative
    - Multicolor flow cytometry (MFC) MRD negative
    - NPM1 real time quantitative polymerase chain reaction (RQ-PCR) negative

10

Case 1

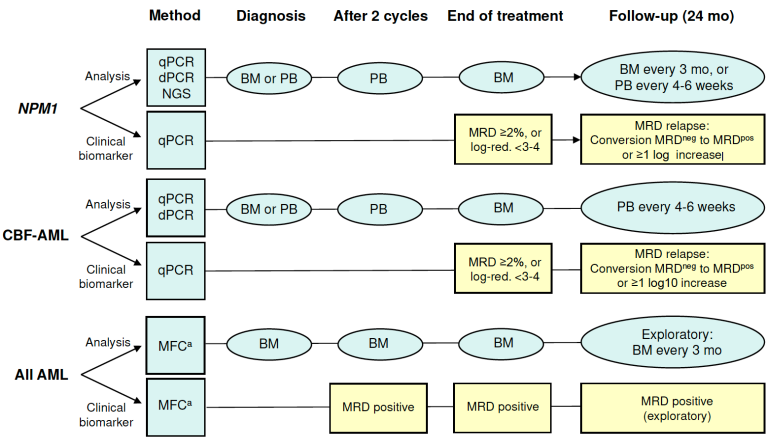
- Role of MRD in AML
  - Still under investigation
  - Assessed with MFC and RQ-PCR
  - Mutations seen in CHIP and with aging (DNMT3A, TET2, ?ASXL1) are not reliable MRD markers
    - Preleukemic mutation detection at CR does not signify residual disease
    - NPM1 mutations, CBFB-MYH11, RUNX1-RUNX1T1, KMT2A-MLLT3, DEK-NUP214, BCR-ABL1 gene fusions, and WT1 expression.
  - Persistently MRD+ is associated with increased risk of morphologic relapse
  - Detectable NPM1 by RQ-PCR and +MRD MFC also correlates with ↓OS
  - MRD status at alloHCT (if indicated)
    - MRD- associated with ↓ relapse and ↑OS
    - Unclear if pre-alloHCT chemo consolidation to achieve MRD- improves outcomes
      - » Equal outcomes post-alloHCT regardless of timing of MRD- CR pre-alloHCT
      - » A small % of pts MRD+ post-induction convert to MRD- with consolidative chemo
      - » Delaying alloHCT to achieve MRD- may lead to morphologic relapse

Morita, J Clin Oncol, 2018; Araki J Clin Oncol, 2016; Lane, Leuk Lymphoma, 2008; Walter, Blood, 2013; Buccisano, Leukemia, 2006; Dohner, Blood 2022

11

Case 1

Figure 2. Algorithm of MRD assessment and time points at which MRD is considered a clinically relevant biomarker



Dohner et al, 2022

12

Case 1

- Question for the audience
  - The patient presents to clinic post-consolidation still feeling weak (ECOG 2) with low appetite. How would next manage this patient?
    - A. Consolidation with ara-C + GO
    - B. Referral for alloHCT in CR1
    - C. Both A and B
    - D. Oral azacitidine maintenance

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Case 1

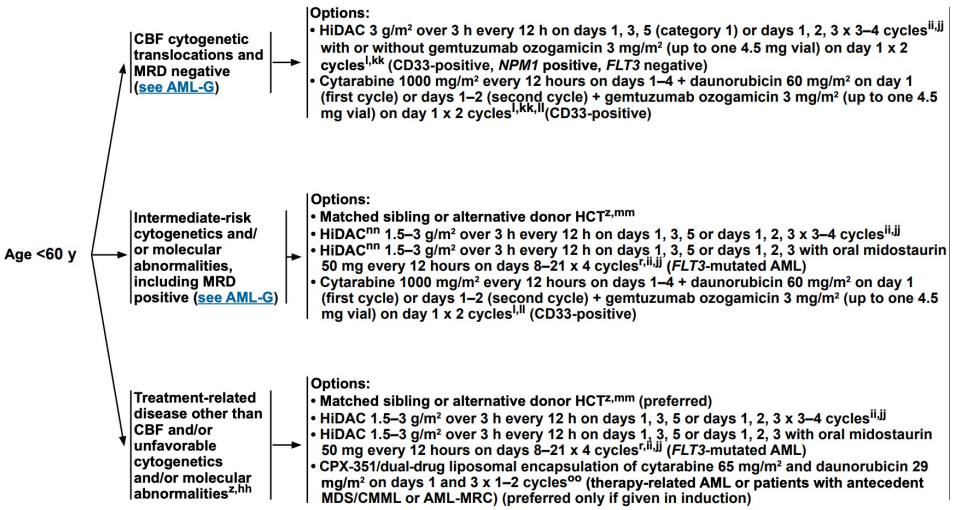
Younger patients (18-60/65 y)	
▪ Favorable-risk genetics	▪ 2-4 cycles of IDAC (1000-1500 mg/m^2 IV over 3 h q12h, d1-3; or 1000-1500 mg/m^2 IV over 3 h d1-5 or 6)
▪ Intermediate-risk genetics	▪ Allogeneic HCT from matched-related or unrelated donor
	▪ 2-4 cycles of IDAC (1000-1500 mg/m^2 IV over 3 h q12h, d1-3; or 1000-1500 mg/m^2 IV over 3 h d1-5 or 6), or
	▪ High-dose therapy and autologous HCT
▪ Adverse-risk genetics	▪ Allogeneic HCT from matched-related or unrelated donor
Older patients (>60/65 y)	
▪ Favorable-risk genetics	▪ 2-3 cycles of IDAC (500-1000 mg/m^2 IV over 3 h q12h, d1-3; or 500-1000 mg/m^2 IV over 3 h d1-5 or 6)
▪ Intermediate/adverse-risk genetics	▪ No established value of intensive consolidation therapy; consider allogeneic HCT in patients with low HCT-Comorbidity Index, or investigational therapy

Generally, patients with favorable-risk AML are not transplanted in CR1, unless there is persistent MRD

Dohner, Blood 2017

14

Case 1



NCCN guidelines

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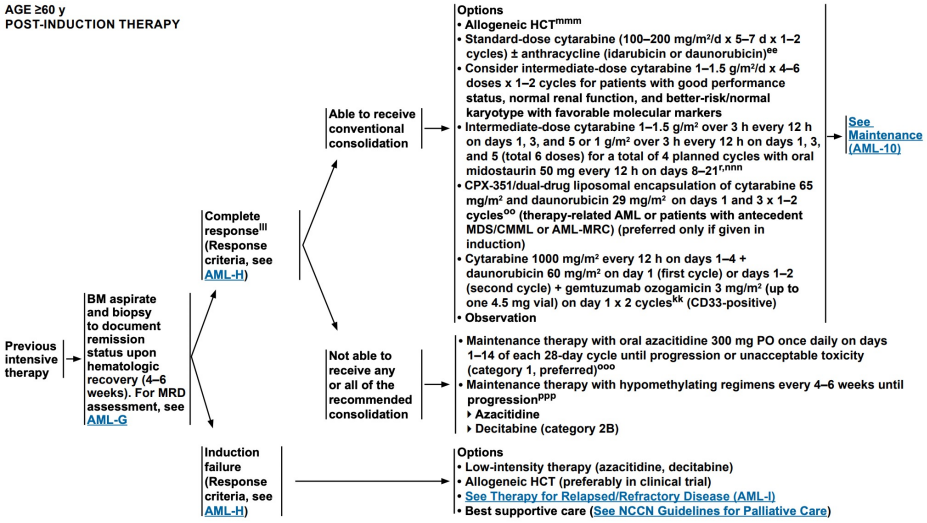
Case 1



NCCN guidelines

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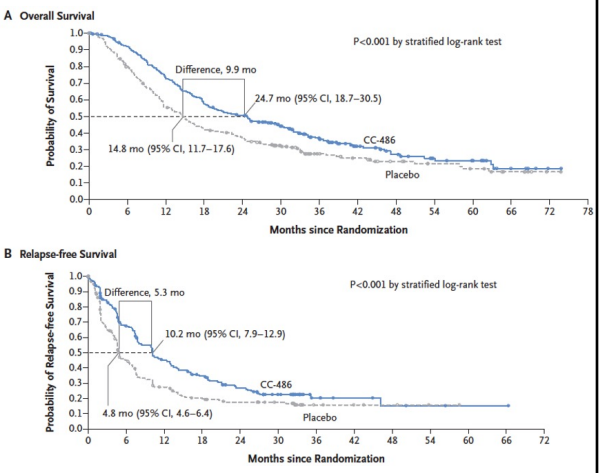
Case 1

- Maintenance post-induction in AML without a FLT3 mutation
  - Oral azacitidine (CC-486) in the QUAZAR trial ↓relapse risk and ↑mOS (14.8 vs 24.7 months) independent of MRD-status by MFC among pts ≥55 years ineligible for alloHCT
  - Approved for continued treatment of pts with AML in first CR/CRi following intensive induction chemotherapy who are unable to complete intensive curative therapy
  - Limitations to the trial design prohibit generalizability of the data:
    - Data regarding the role of oral aza in younger pts or those with CBF-AML are lacking;
    - Only few patients had AML with adverse-risk cytogenetics (14%).
    - The trial did not specify prior induction and consolidation therapy, thus, there was a variability in prior therapy in those selected for maintenance
      - 45% of patients had received 1 consolidation cycle, 31% 2 cycles, and 20% no consolidation



Wei, NEJM 2020; Dohner, Blood 2022

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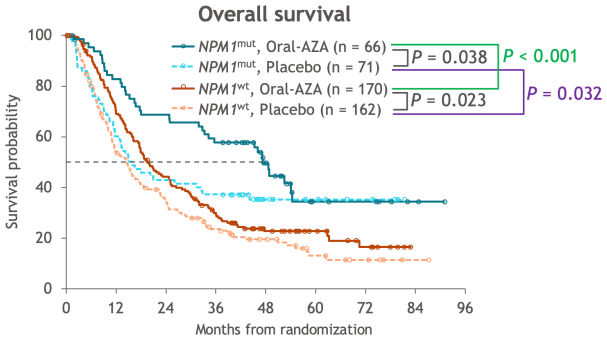
Case 1

- QUAZAR AML-001 Trial: post-hoc analysis on effects on NPM1 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).



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

Döhner et al, EHA 2021. Abstr S131.

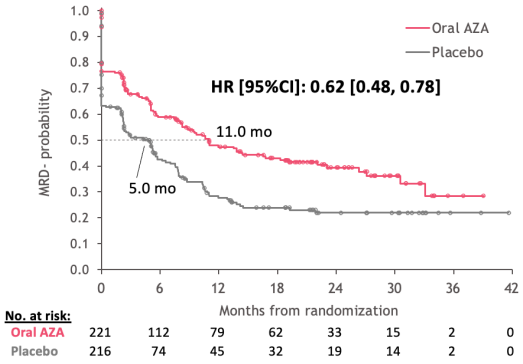
18

Case 1

- 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



[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 1

- The patient is started oral azacitidine maintenance due to his performance status
- NPM1 positive after 1 cycle of oral azacitidine by qPCR on PB, with a new thrombocytopenia noted at this time
- Repeat BMBx showed 26-28% blasts by IHC, aspirate count, and flow, consistent with relapsed AML
- He is started on decitabine/venetoclax

20

Case 1

- HMA/Ven in r/r AML
  - Retrospective data shows ORR 21-64%, mOS 3.4-8 mos
  - One non-randomized phase 2 clinical trial showed an ORR 62%, mOS 7.8 mos

Tenold et al, Front Oncol 2021; Aldoss et al, Haematologica 2018, DiNardo et al, Lancet haematol 2020

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Case 1

- After 1 cycle, patient achieves CR
  - BMBx shows normocellular marrow (30-40%) with 2% blasts by aspirate count
  - RQ-PCR NPM1 undetectable, MRD MFC negative
  - He undergoes alloHCT in CR2 and remains disease-free 1-year post-transplant

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Case 1 Summary

- Not all AML requires 20% blasts and careful attention to molecular assays is needed to inform diagnosis and management
- If CD33+ with favorable- or intermediate-risk cytogenetics, add GO to intensive chemo
- AlloHCT is not required in favorable-risk AML in CR1, but is for poor-risk, select cases of intermediate-risk, and r/r AML if eligible
- Oral azacitidine may have a role as maintenance post-induction in patients with intermediate/poor-risk AML achieving CR/CRi and are ineligible for curative alloHCT
- HMA/Ven has efficacy in the r/r setting

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Case 2

- HPI abridged
  - 61 yo M with no prior PMH
  - P/w enlarging L axillary mass over past 3 mos
  - No fevers, night sweats, unintentional weight loss
  - ECOG 0
- Pertinent physical exam findings
  - B/l cervical, supraclavicular, and L axillary LAD appreciated
  - No tenderness to palpation

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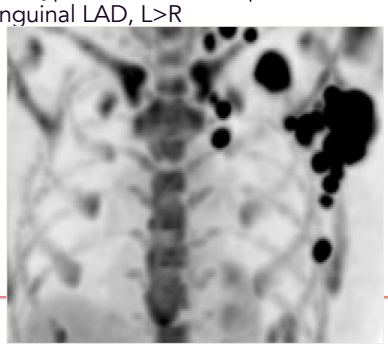
Case 2

- Pertinent labs
  - CBC, CMP WNL, LDH 342
- PET/CT
  - B/l multi-level hypermetabolic cervical + supraclavicular LAD
  - **L axillary bulky LAD 11.5 x 7.5 cm, SUV 29.7 (Deauville 5)**
  - B/l hypermetabolic retroperitoneal, iliac, and inguinal LAD, L>R



- Pathology
  - Excisional biopsy of L axillary mass showed DLBCL, non-GCB subtype
    - IHC with MYC 20% and BCL2 70%
    - EBER ISH negative
    - FISH with BCL6 rearrangement but no MYC or BCL2 rearrangements
  - Bone marrow biopsy negative for lymphoma involvement
- Diagnosis and prognostication
  - Diffuse large B-cell lymphoma, non-GCB, non-DE/DHL
  - Stage III, R-IPI score 3

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Case 2

- He is started on R-CHOP
- Interim PET scan after 2 cycles showed PR (Deauville 4) with size reduction in all lymph nodes, L axillary mass SUVmax=6, 1 cm
- After C4, reports increasing L axillary swelling and night sweats
- LDH 390
- PET scan after C4 shows PD, L axillary mass SUVmax=35 and now 3 cm, only other site of disease is L sub-pectoral major mass, measuring 2.5 cm, SUV=26

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Case 2

- Question for the audience
  - Which of the following would be the next best step of management?
    - A. Platinum-based salvage therapy followed by CAR T infusion
    - B. CAR T-cells with steroid bridge
    - C. Platinum-based salvage therapy, then autoHCT if ≥PR, CAR T-cells if <PR
    - D. Radiation therapy to active disease sites

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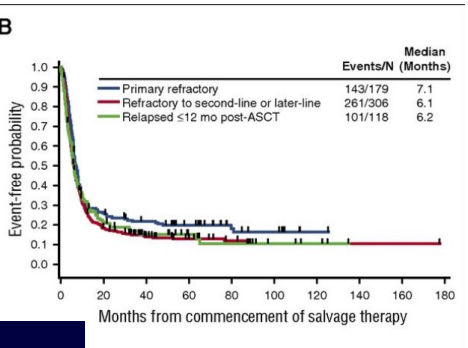
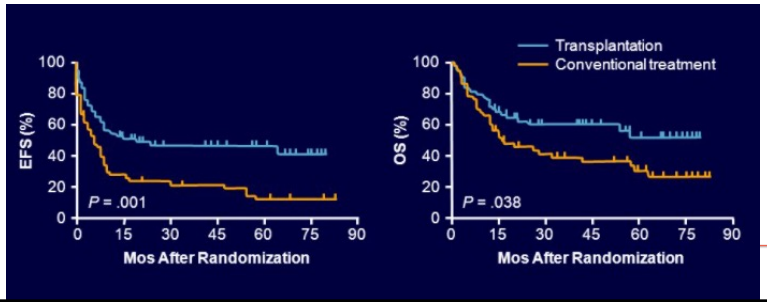
Case 2

- SCHOLAR-1
  - Largest pooled analysis to evaluate responses and OS rates in pts with r/r DLBCL

Endpoint	N=636
ORR to next line of tx	26%
CR to next line of tx	7%
2-y OS	20%





Pre-rituximab era

Crump et al, Blood 2017; Philip et al, NEJM 1995

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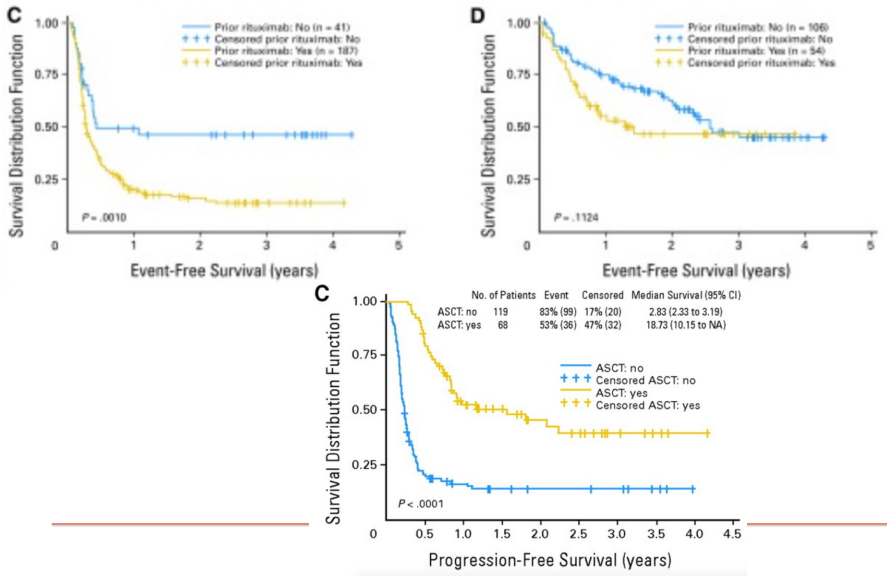
Case 2

CORAL = salvage regiments with autoHCT in R/R DLBCL in rituximab era



Worse survival for prior rituximab and relapse <1 y

Gisselbrecht et al, J Clin Oncol 2010

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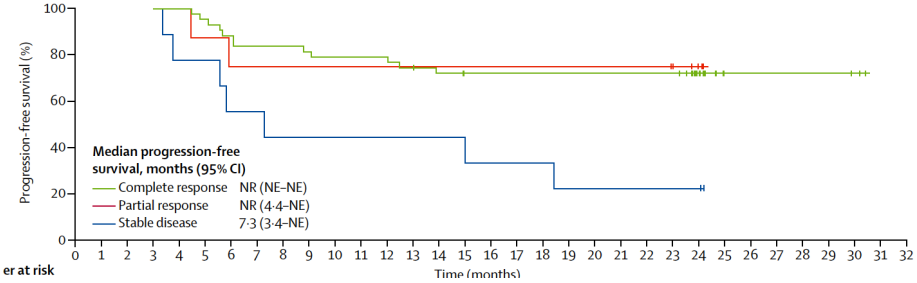
Case 2

- Anti-19 CAR T-cell efficacy in r/r DLBCL
  - Axi-Cel (Yescarta)
  - ZUMA-1 LTFU (median f/u 27 mos)
  - Most pts received >2 lines of tx (97%)

Variable	N=101
ORR	83%
CR	58%
mDOS	11.1 mos
mPFS	5.9 mos
mOS	NR



Locke et al, Lancet Oncol 2018

30

Case 2

- Retrospective CIMBTR study – autoHCT vs CAR T
- N= 411 patients in PR post-salvage
  - AutoHCT (n=266)
  - Axi-Cel (n=145)
  - Primary refractory
    - 160 pts (60%) in autoHCT arm (6 pts/2% missing info)
    - 79 pts (55%) in CAR T arm (22 pts/15% missing info)
    - Time from diagnosis to autoHCT/CAR T
      - ≤12 months:
        - » 103 pts (39%) in autoHCT arm
        - » 64 pts (44%) in CAR T arm
      - >12 months
        - » 162 pts (61%) in autoHCT arm
        - » 81 pts (56%) in CAR T arm
  - # of prior lines
    - Median (range): 2 (1-6) for autoHCT vs 3 (2-11) in CAR T
    - ≥2 lines in 89 pts (33%) in autoHCT arm vs 97 (67%) in CAR T
  - Largest node >5 cm at time of therapy
    - 76 pts (29%) in autoHCT group and 60 pts (41%) in CAR T group (*P*=0.05)

Shadman, Blood 2021

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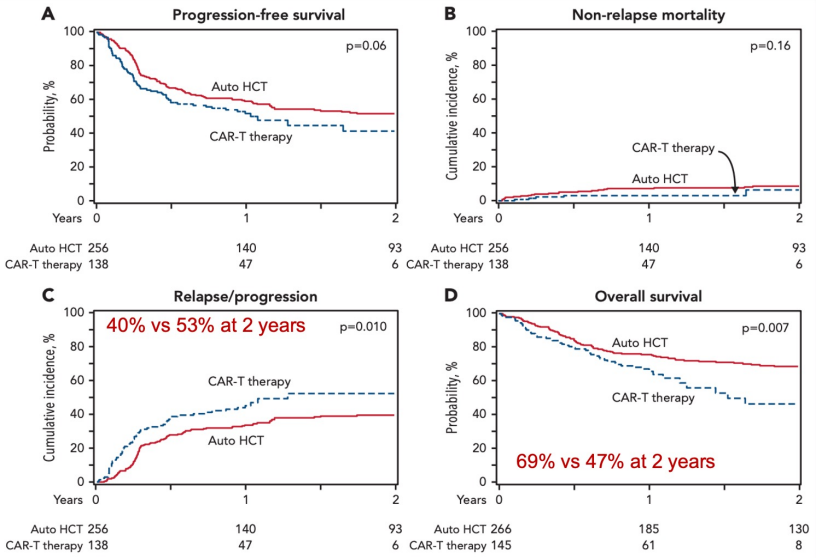
Case 2



Other notable points:

- Propensity score-matched analysis to match disease burden, median # of prior lines of therapy (≥2 lines) = no difference in OS/PFS
- Supports the role of autoHCT in pts with relapsed DLBCL that achieve PR post-salvage, but more data needed for pts with fewer lines of salvage therapy

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Case 2

- Moving CAR T to earlier line of therapy
  - 3 RCTs were conducted to evaluate the efficacy of CAR T-cells earlier in the treatment course of R/R DLBCL
  - Study population for all trials includes:
    - Primary refractory
    - Early relapse (within 12 months of induction)
  - Randomized to receive CAR T-cells or SOC (salvage chemotherapy followed by autoHCT)

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Case 2

Study design

	BELINDA	TRANSFORM	ZUMA-7
CAR T product	Tisa-cel	Liso-cel	Axi-cel
N	322	184	359
Bridging	SOC chemo	SOC chemo	Steroids only
Crossover allowed?	Yes	Yes	No (off-protocol)
Primary endpoint	EFS	EFS	EFS
Lymphodepleting regimen	Flu/Cy or Bendamustine	Flu/Cy	Flu/Cy
Time to blinded central review	Day 150	9-12 weeks	12 weeks

Bishop, N Eng J Med; Kamdar, Lancet Oncol 2022; Locke, N Eng J Med 2021

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Case 2

Efficacy results

	BELINDA	TRANSFORM	ZUMA-7
Received definitive therapy: CAR T vs autoHCT	96% vs 33%	98% vs 47%	94% vs 36%
Received bridging in CAR T arm	83%	63%	36%
Median time from apheresis to CAR T infusion	52 days	36 days	27 days
ORR (%): CAR T vs autoHCT	75% vs 68%	86% vs 48%	83% vs 50%
CRR (%): CAR T vs autoHCT	46% vs 44%	66% vs 39%	65% vs 32%

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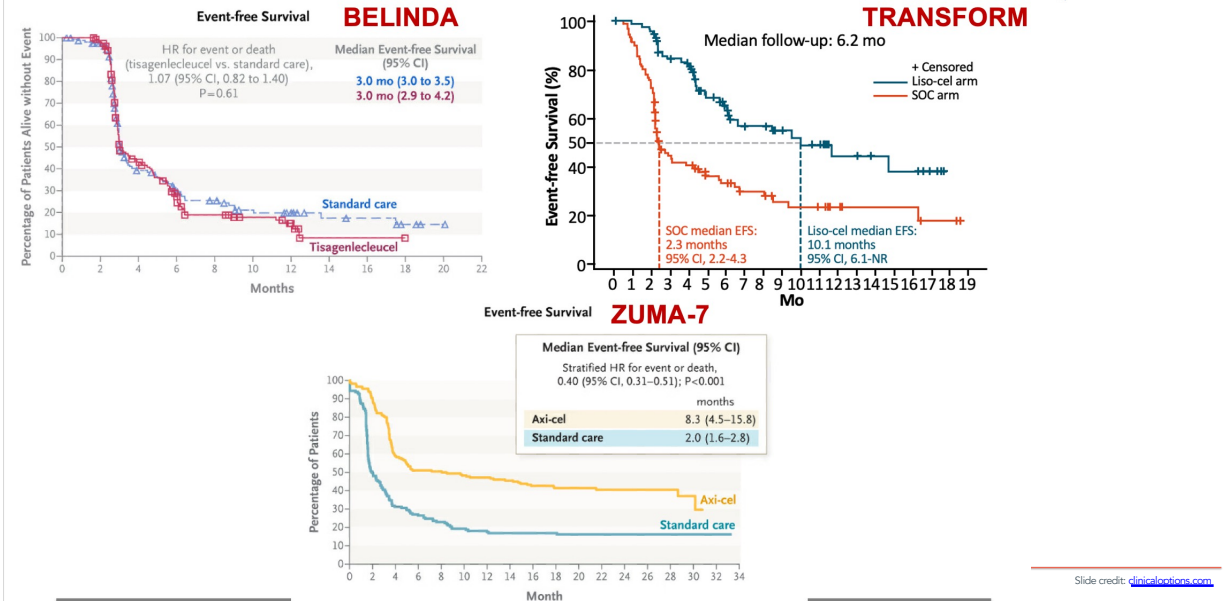
Case 2



Slide credit: clinicaloptions.com

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Case 2

Safety

	BELINDA	TRANSFORM	ZUMA-7
CRS, all grades (%)	59	49	92
CRS, grade ≥3 (%)	5	1	6
ICANS, all grades (%)	10	12	60
ICANS, grade ≥3	2	4	21

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Case 2

- Key limitations to the studies
  - Not designed to address DLBCL pts already achieving a PR in response to salvage therapies
    - Pts are often referred to transplant/CAR T centers after starting salvage
    - CAR T has efficacy post-autoHCT relapse, the reverse is not well described
    - CAR T-capable centers are more limited than autoHCT-capable centers

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Case 2

- The pt received 2 cycles of R-ICE
- Repeat PET/CT shows Deauville 4 (PR) at the left axilla, all other sites of disease show FDG uptake below the liver

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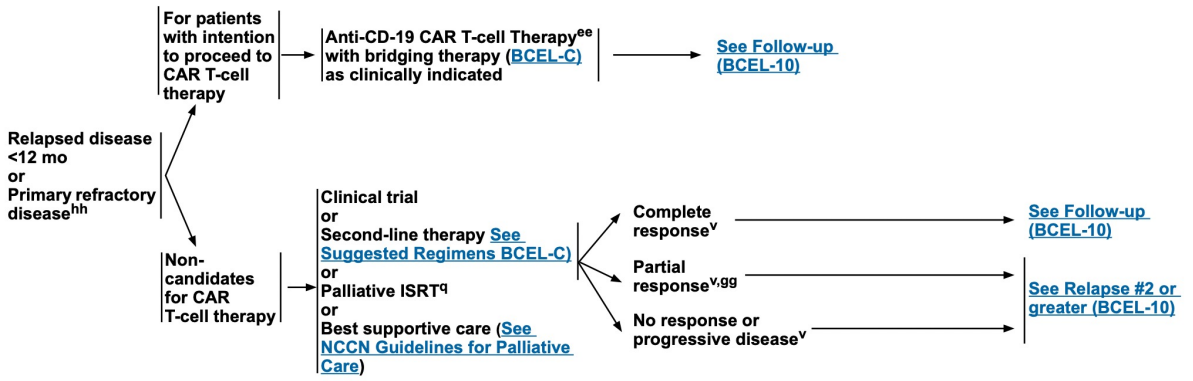
Case 2

- Question for the audience
  - Patient presents to discuss PET/CT results. On exam, he appears well, ECOG 0. Which of the following would be the next best step of management?
    - A. CAR T infusion
    - B. AutoHCT
    - C. Radiation therapy to the left axilla followed by surveillance
    - D. One more cycle of R-ICE then PET re-assessment

40

Case 2



NCCN guidelines

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Case 2

- The patient undergoes Axi-Cel infusion
- 3-month PET/CT demonstrates CR
- Remains in CR at 1-year post-CAR T infusion

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Case 2

- In the 3 RCT trials studying CAR T-cells in the 2nd line management of primary refractory or early relapse DLBCL, Axi-Cel and Liso-Cel improve EFS compared to SOC
- Differences in trial design prohibits the ability to distinguish superiority of one CAR T product over the other
- For patients unable to demonstrate chemosensitive disease, Axi-cel or Liso-cel should be considered earlier in the treatment course
- Consolidative strategy (autoHCT vs CAR T) in primary refractory or early relapse DLBCL is unclear in those achieving PR after salvage
- Getting patients to autoHCT after documented relapsed or refractory disease is difficult, and thus, CAR T-cells may provide select patients a chance at definitive treatment and long-term survival
- Role of CAR T as 2nd line treatment for DLBCL relapse >12 months is not known

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Case 3

- HPI abridged
  - 54 yo M with a PMH of HTN presents to the ED after sudden onset back pain while chopping wood
  - No sx of hyperviscosity: vision changes/impairment, hearing loss, dizziness/vertigo, somnolence, coma, seizures, respiratory compromise, bleeding.
  - ECOG 0
- Physical exam remarkable only for midline tenderness to palpation at T11
- Labs
  - CMP: Cr 4.30, Ca++ 12.2, total protein 12.2, albumin 2.4
  - CBC: Hgb 7.9, MCV 100.2, other counts WNL and differential unremarkable
  - Misc chem: K:L 5.31, serum viscosity 1.89, LDH 330, B2MG 6.5
  - SPEP: M-spike 7.5 g/dL, IFE with 2 IgG kappa bands
  - UPEP: M-spike 4.1 mg/dL
  - IgA 36, IgM <25, IgG 7566

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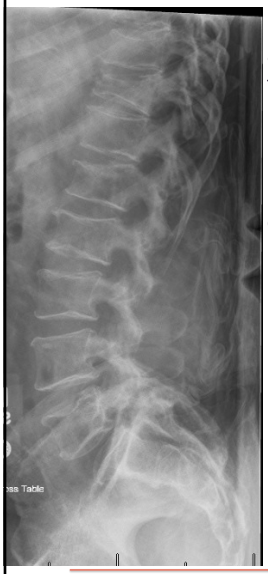
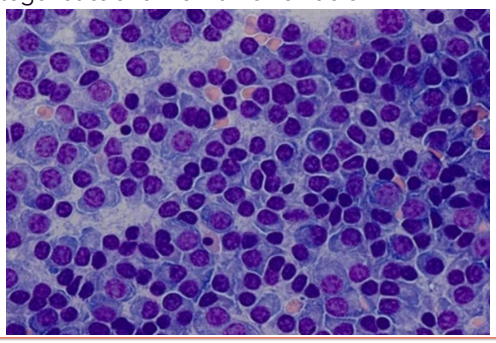
Case 3



Bone survey: Extensive lytic lesions involving the axial and appendicular skeleton, compression fracture at T11

BMBx: Hypercellular with sheets of kappa-restricted plasma cells (90% by CD138 IHC)

Cytogenetics and FISH unremarkable



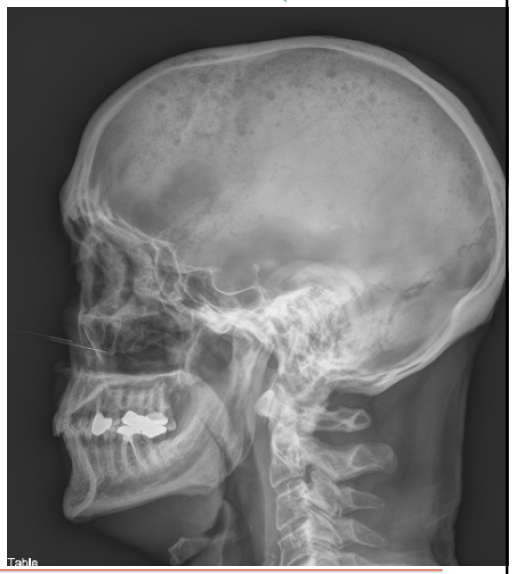


Image credit: doi:10.7759/cureus.5969

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Case 3

- Question to the audience:
  - What induction regimen would you treat him with?
    - A. RVd (lenalidomide, bortezomib, dexamethasone)
    - B. VCd (bortezomib, cyclophosphamide, dexamethasone)
    - C. Rd (lenalidomide, dexamethasone)
    - D. KRd (carfilzomib, lenalidomide, dexamethasone)

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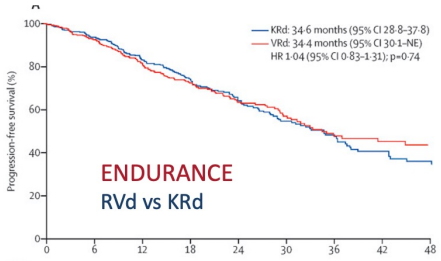
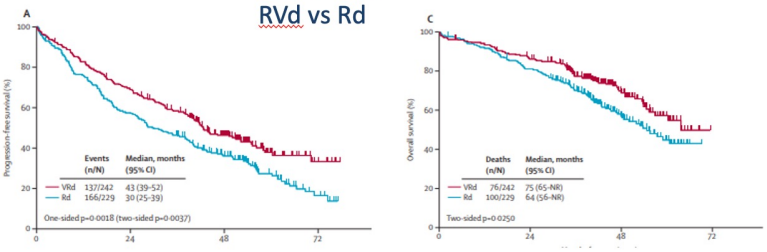
Case 3

- Triplet therapy is SOC for fit pts
- Induction regimen of choice?



SWOG 0777
RVd vs Rd



RVd is still the induction regimen of choice for HCT-eligible patients, but in patients with acute renal injury, VCd is preferred for at least 1 cycle

Kumar et al, Clin lymphoma myeloma leuk 2019; Kumar et al, Lancet Oncol 2020; Voorhees et al, Blood 2020

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Case 3

- The patient receives 1 dose of pamidronate and IVFs
- Evaluated by apheresis and renal, who thought plasmapheresis and HD were not indicated, respectively
- The patient receives CyBorD
- Cr normalizes by C1D7
- He is switched to RVd for C2-C7 with monthly denosumab and achieves VGPR (no BMBx repeated to determine if in CR)
- Receives melphalan 140 mg/m2 and undergoes autoHCT

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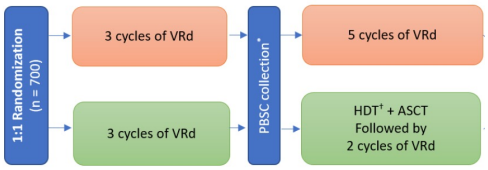
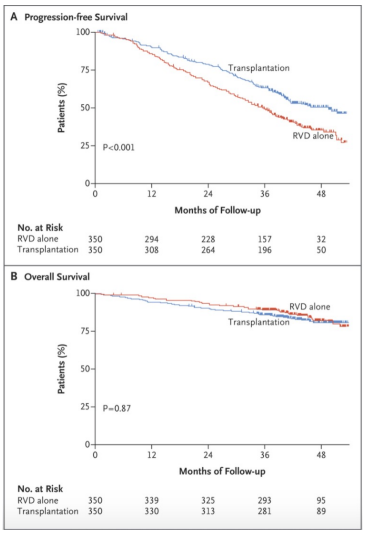
Case 3

- AutoHCT as a standard of care after triplet induction
  - Long-term follow-up of IFM 2009



- Relevance of PFS as an endpoint
  - Post-hoc analysis of 2 phase 3 trials showed of 1,243 pts with PD, 43.7% had morbid PD
  - Prevention of morbid events
    - Fractures
    - Renal injury and HD requirement
    - Cord compression
    - Hypercalcemia



Attal, NEJM 2017; Rosenberg, CLML 2020

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Case 3

- Question for the audience
  - What should he receive as post-autoHCT maintenance?
    - A. Bortezomib until disease progression
    - B. Lenalidomide until disease progression
    - C. Maintenance is not indicated

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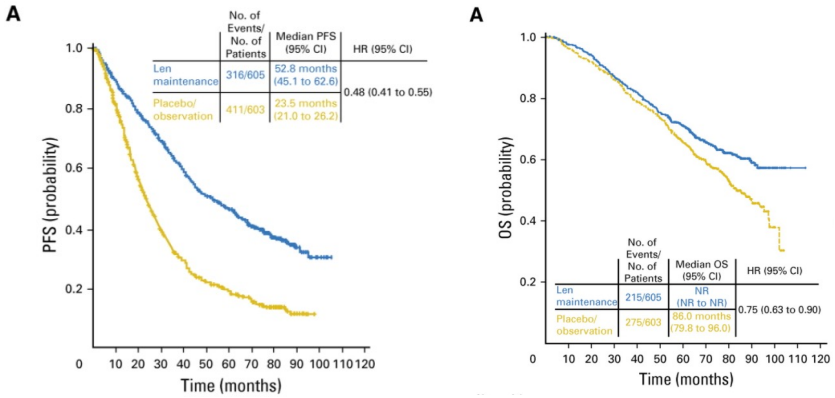
Case 3

Lenalidomide as maintenance therapy



PFS and OS benefit is seen with maintenance lenalidomide, despite the ↑increased risk of SPM

McCarthy et al, J Clin Oncol 2017

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Case 3

- The patient is placed on lenalidomide maintenance and continues it until…
- SPEP shows biochemical progression 4 years post-autoHCT (serum M-protein ↑ by 1.3 g/dL above baseline)

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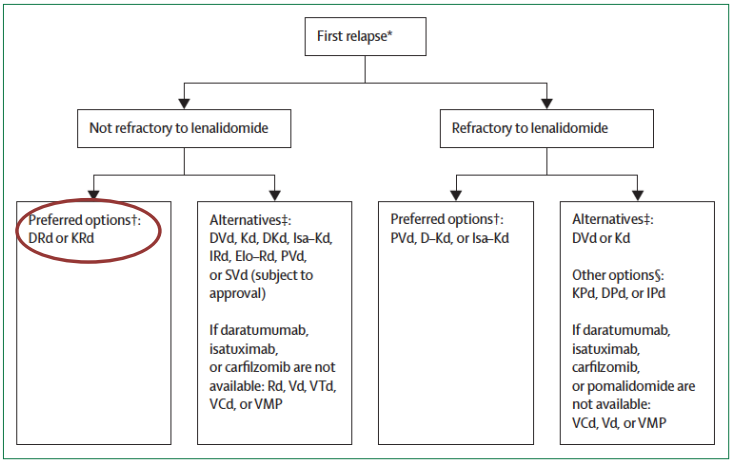
Case 3

- Managing first relapse of myeloma



- Lenalidomide-refractory MM is defined as
  - PD during therapy
  - No response (< PR) to prior lenalidomide-containing therapy, or within 60 days of discontinuation from lenalidomide-containing regimens
  - Does not include low-dose maintenance lenalidomide

Shah, Blood 2015; Moreau, Lancet Oncol 2021

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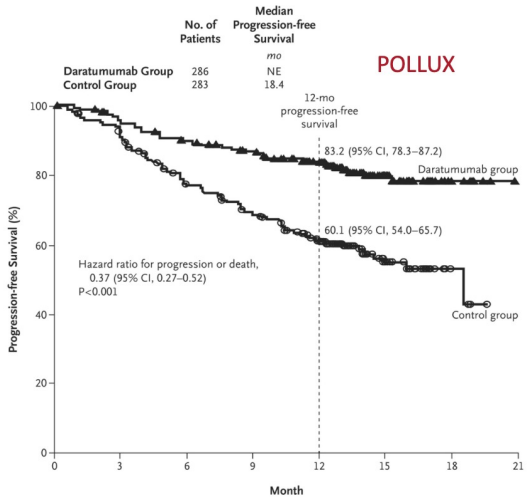
Case 3

He undergoes re-induction with daratumumab, lenalidomide, dexamethasone

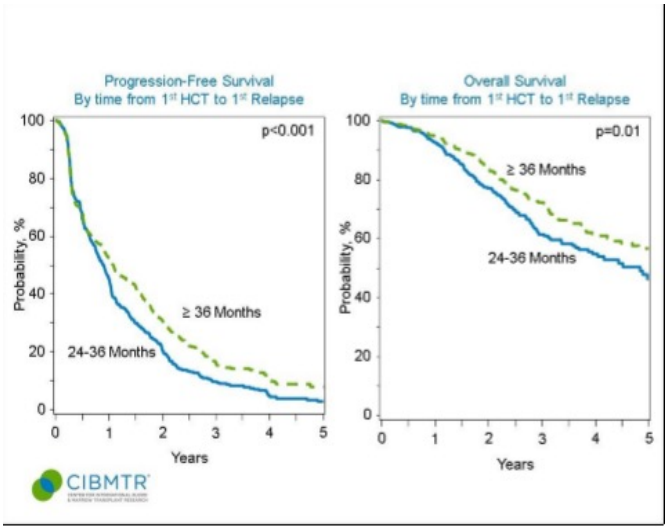


Dimopoulos, NEJM 2016

54

Case 3

He achieves VGPR once again and undergoes 2nd autoHCT with high-dose melphalan conditioning



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Case 3

- Pt outcome
  - Remains in remission 2 years out from autoHCT

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Case 3

- Summary
  - In the absence of an AKI, RVd is the standard frontline treatment for multiple myeloma
  - AutoHCT for MM is still preferred in fit pts directly after induction, although depending on pt preferences, may be delayed until after first relapse
  - Lenalidomide maintenance should be considered for at least 2 years post-autoHCT if pt can tolerate
  - Many options exist for managing r/r MM, and choice should be tailored to prior treatment history and pt-related factors
  - A second autoHCT, especially if PFS ≥3 years after first autoHCT, is an acceptable treatment approach upon disease control with salvage regimens

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Acknowledgements

- Brian A. Jonas, MD, PhD

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