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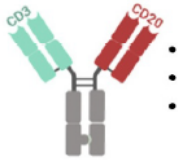
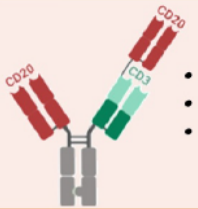
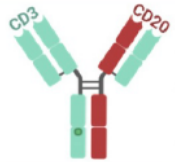
Updates in Hematology

Outline

- Lymphoma
- MM
- Myeloid Neoplasms

Bispecifics

Bi-Specific Antibody	Targets	Design	Ig Fragment Formats	Ref.
mosunetuzumab	CD20 x CD3		• humanized mouse heterodimeric IgG1-based antibody • monovalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	4
glofitamab	$(CD20)_2$ x CD3		• humanized mouse IgG1-based antibody • bivalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	5
odronextamab	CD20 x CD3		• fully human IgG4-based heterodimeric antibody • monovalent CD20 and monovalent CD3ε binding • Fc-dependent effector function-minimized antibody with Fc of the anti-CD3ε heavy chain modified to reduce Protein A binding • common κ light chain from anti-CD3ε mAb	6
epcoritamab	CD20 x CD3		• humanized mouse IgG1-based heterodimeric antibody • monovalent CD20 and monovalent CD3 binding • IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield	7

Ig, immunoglobulin; scFv, single-chain variable fragment; mAb, monoclonal antibody; Fc, fragment crystallizable; FcγR, Fc gamma receptor

[1]Dufner V, *et al*. Blood Adv (2019) 3:2491; [2]Goebeler ME, *et al*. J Clin Oncol (2016) 34:1104; [3]Viardot *et al*. Blood (2016) 127(11):1410; [4]Schuster SJ, *et al*. ASH 2019, Plenary Abstract 6; [5]Hutchings M, *et al*. ASH 2020, Abstract 403; [6]Bannerji R, *et al*. ASH 2020, Abstract 400; [7]Hutchings M, *et al*. ASH 2020, Abstract 406

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What is there currently?

DLBCL

- Approved agents
  - Epcoritamab
  - Glofitamab
- Investigational
  - Single agent
    - Odronextumab
  - Combinations

FL

- Two approved agents
  - Mosunetuzumab
  - Epcoritamab
- Future
  - Odro?
  - Combinations

Efficacy DLBCL

Drug	N	ORR	CR	PFS (median)	DOR	Approved
Epcoritamab	157	63%	39%	4.4 m	15.6 m	Yes
Glofitamab	291	52.6%	35%	4.9 m*	18.4 m	Yes
Odronextamab	130	49.2%*	30.8%*	4.4 m	10.2 m	No

Week 12 response assessment by independent central review	1/20 step-up regimen N=67	0.7/4/20 step-up regimen N=63
ORR	46.3% [95% CI: 34.0–58.9%]	42.9% [95% CI: 30.5–56.0%]
Complete response	26.9%	20.6%

- Median opportunity of follow-up: 21.3 months (range 2.6–29.8)

Drug	post CAR-T patients	Refractory (*R*)	ORR	CR	CR (*R*)
Epcoritamab	61	46	54%	34%	28%
Glofitamab	52	N/A	N/A	35%	N/A
Odronextamab	31		48.4%*	32.3%	N/A

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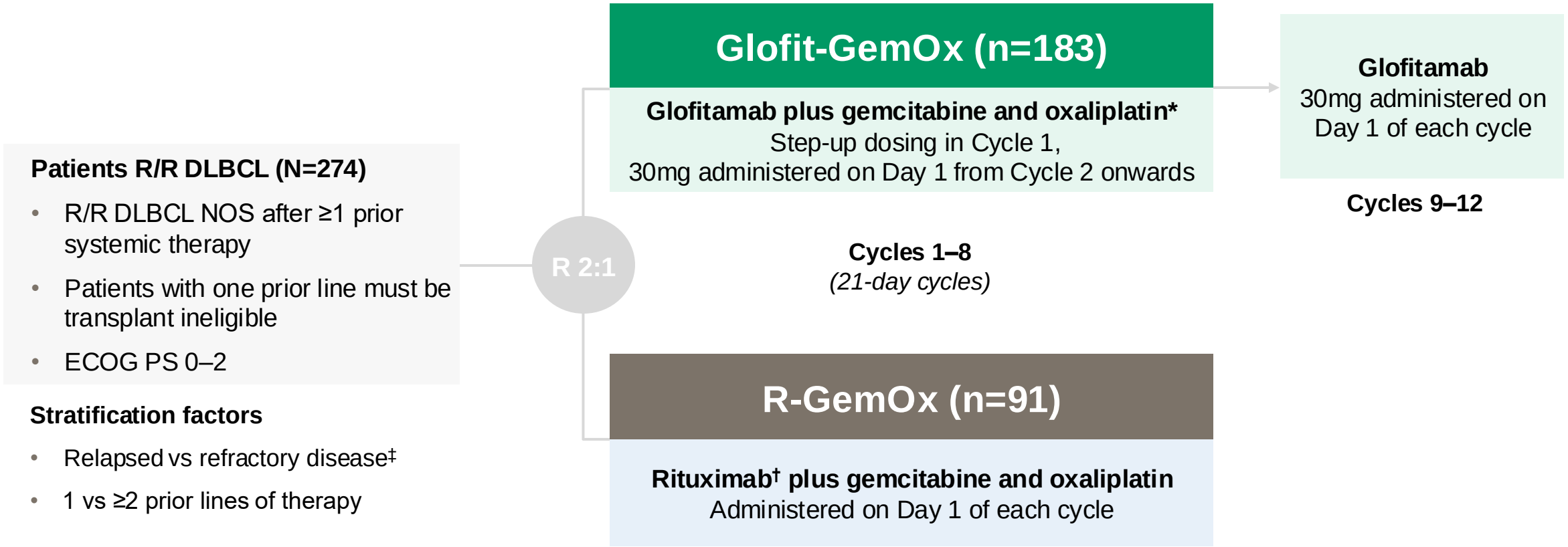
STARGLO: randomized Phase III trial in ASCT-ineligible patients with R/R DLBCL



*Gemcitabine 1000mg/m^2 and oxaliplatin 100mg/m^2. In C1, Gpt administered on D1, GemOx on D2, followed by glofit 2.5mg on D8 and glofit 10mg on D15; in C2–8, glofit 30mg and GemOx are administered on D1. †Rituximab 375mg/m^2. ‡Relapsed disease: recurrence following a response that lasted ≥6 months after completion of the last line of therapy; refractory disease: disease that did not respond to, or that progressed <6 months after, completion of the last line of therapy. ASCT, autologous stem cell transplant; C, cycle; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt, obinutuzumab pre-treatment; NOS, not otherwise specified; R 2:1, patients randomized in a 2:1 ratio.

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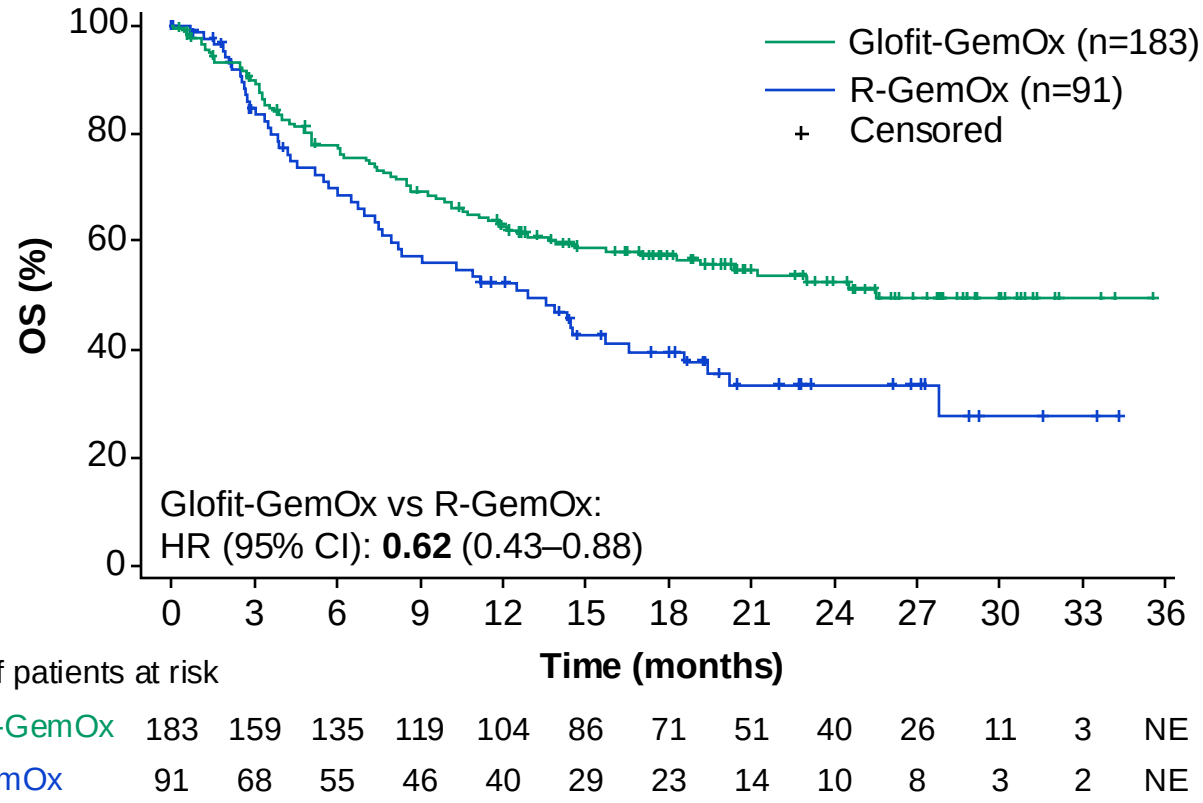
Primary endpoint: overall survival

Updated analysis



No. of patients at risk

Glofit-GemOx	183	159	135	119	104	86	71	51	40	26	11	3	NE
R-GemOx	91	68	55	46	40	29	23	14	10	8	3	2	NE

	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 11.3 months)		
OS, median (95% CI); months	9 (7.3–14.4)	NE (13.8–NE)
HR (95% CI)	**0.59** (0.40–0.89)	
p-value*	0.011	
Updated analysis (median follow-up: 20.7 months)		
OS, median (95% CI); months	12.9 (7.9–18.5)	25.5 (18.3–NE)
HR (95% CI)	**0.62** (0.43–0.88)	
p-value*	0.006	
24-month OS (95% CI)	33.5% (22.2–44.9)	52.8% (44.8–60.7)

Statistically significant and clinically meaningful **OS benefit for Glofit-GemOx** vs R-GemOx

24-month OS not reported at the primary analysis as data were not sufficiently mature.
*p-value is alpha controlled at the primary analysis and descriptive at updated analysis. CI, confidence interval; HR, hazard ratio; NE, not evaluable.

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Epcoritamab

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Trial Design: Pivotal EPCORE™ NHL-1 Study

Epcoritamab in R/R FL

Dose expansion

Key inclusion criteria[a]:

- R/R CD20+ mature B-cell neoplasm
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 anti-CD20 mAb
- Prior treatment with an alkylating agent or lenalidomide
- FDG-avid disease by PET/CT
- Prior CAR T allowed

Data cutoff: April 21, 2023
Median follow-up: 17.4 mo

Step-up dosing[b]

Epcoritamab SC RP2D 48 mg
Treatment until PD[c] or unacceptable toxicity
R/R FL grade 1–3A expansion cohort, N=128

SC injections in minutes

QW		Q2W						Q4W	
C1	2	3	4	5	6	7	8	9	10
Wk 0	4	8	12	16	20	24	28	32	36

- **Primary endpoint:** ORR by independent review committee (IRC)
- **Key secondary endpoints:** MRD[d], DOR, TTR, PFS, OS, CR rate, and safety/tolerability

C1 optimization

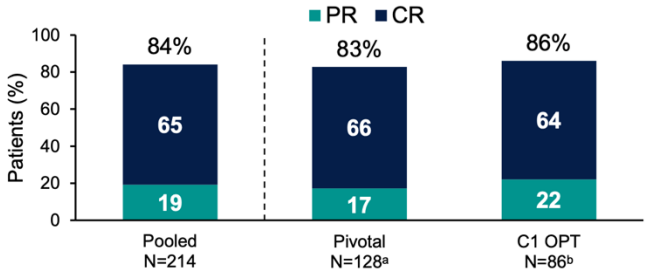
CRS prophylaxis with dexamethasone 15 mg

- C1D22 — First full dose: 48 mg
- C1D15 — SUD 3: 3 mg
- C1D8 — SUD 2: 0.8 mg
- C1D1 — SUD 1: 0.16 mg

Recommendations for adequate hydration

- Hospitalization not mandated in this setting
- **Primary objective:** Assess impact on risk and severity of CRS

High Rates of Complete Response and MRD Negativity



MRD-Negativity Rate	n (%)
Pooled (n=135)	89 (66)
Pivotal (n=91)	61 (67)
C1 OPT (n=44)	28 (64)

Based on MRD-evaluable population per clonoSEQ® PBMC assay with 10^{-6} cutoff.

- At 6 mo in C1 OPT, an estimated 86% of patients with CR remained in CR
- No impact on time to response in C1 OPT
  - Median time to response was 1.4 mo in both cohorts[c]
  - Median time to complete response was 1.5 mo in both cohorts[d]

Phase 1/2 trial. [a]Patients enrolled in this trial (and excluded from trials of other T-cell–engaging therapies) included those with worse anemia, lymphopenia, and/or renal function. [b]Step-up dosing (SUD; priming [SUD 1] 0.16 mg and intermediate [SUD 2] 0.8 mg dosing before first full dose) and corticosteroid prophylaxis were used to mitigate CRS. [c]≥2 measurable (by CT/MRI) and FDG PET–positive lesions; radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter. [d]MRD was assessed in peripheral blood using the clonoSEQ® (Adaptive Biotechnologies, Seattle, WA) next-generation sequencing assay. ClinicalTrials.gov: NCT03625037; EudraCT: 2017-001748-36.

CR was complete metabolic response (ie, PET negativity). CR, complete response; PBMC, peripheral blood mononuclear cell; PR, partial response. [a]Three patients (2%) were not evaluable. [b]Five patients (6%) were not evaluable. [c]Range: 1.2–4.4 in C1 OPT, 1.0–3.0 in pivotal. [d]Range: 1.2–4.7 in C1 OPT, 1.2–11.1 in pivotal.

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Safety

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C1 Optimization Reduced Risk and Severity of CRS

	Pivotal Cohort N=128	C1 Optimization Cohort[a] N=50
CRS, n (%)[b]	85 (66)	24 (48)
Grade 1	51 (40)	20 (40)
Grade 2	32 (25)	4 (8)
Grade 3	2 (2)	0
Treated with tocilizumab, n/n (%)	31/85 (36)	6/24 (25)
Leading to epcoritamab discontinuation, n (%)	**0**	**0**
CRS resolution, n/n (%)	**85/85 (100)**	**24/24 (100)**
Median time to resolution, d (range)	2 (1–54)	3 (1–14)

- Patient baseline characteristics were consistent between cohorts
- C1 optimization substantially reduced rate and severity of CRS
- In both cohorts, CRS was mostly confined to C1
- Similar response rates were observed in the C1 optimization cohort
- There were no cases of ICANS in the C1 optimization cohort; 8 cases were observed in the pivotal cohort (all grade 1–2 and resolved; none led to discontinuation)

[a]Data cutoff: September 21, 2023. Median follow-up: 3.8 mo (range, 1.9–8.7). [b]Graded by Lee et al 2019 criteria.[1] **1.** Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-38.

➢ Linton et al. ASH 2023

Summary of Response FL

Drug	N	ORR	CR	PFS 24 m	OS 24 m	mDOR
Mosunetuzumab	90	78%	60%	48%	87%	NR
Odronextamab	121	81.8%	75.2%	55.3%*	N/A	20.5 m
Epcoritamab	128	82%	63%	N/A	N/A	NR

*18 months

Drug	DOR 12 m	DOCR 12 m	DOR 24 m	DOCR 24 m
Mosunetuzumab	67%	82%	53%*	63%
Odronextamab	68.8%	72.2%	55%*	59.1%*
Epcoritamab	N/A	N/A	N/A	N/A

*18 months

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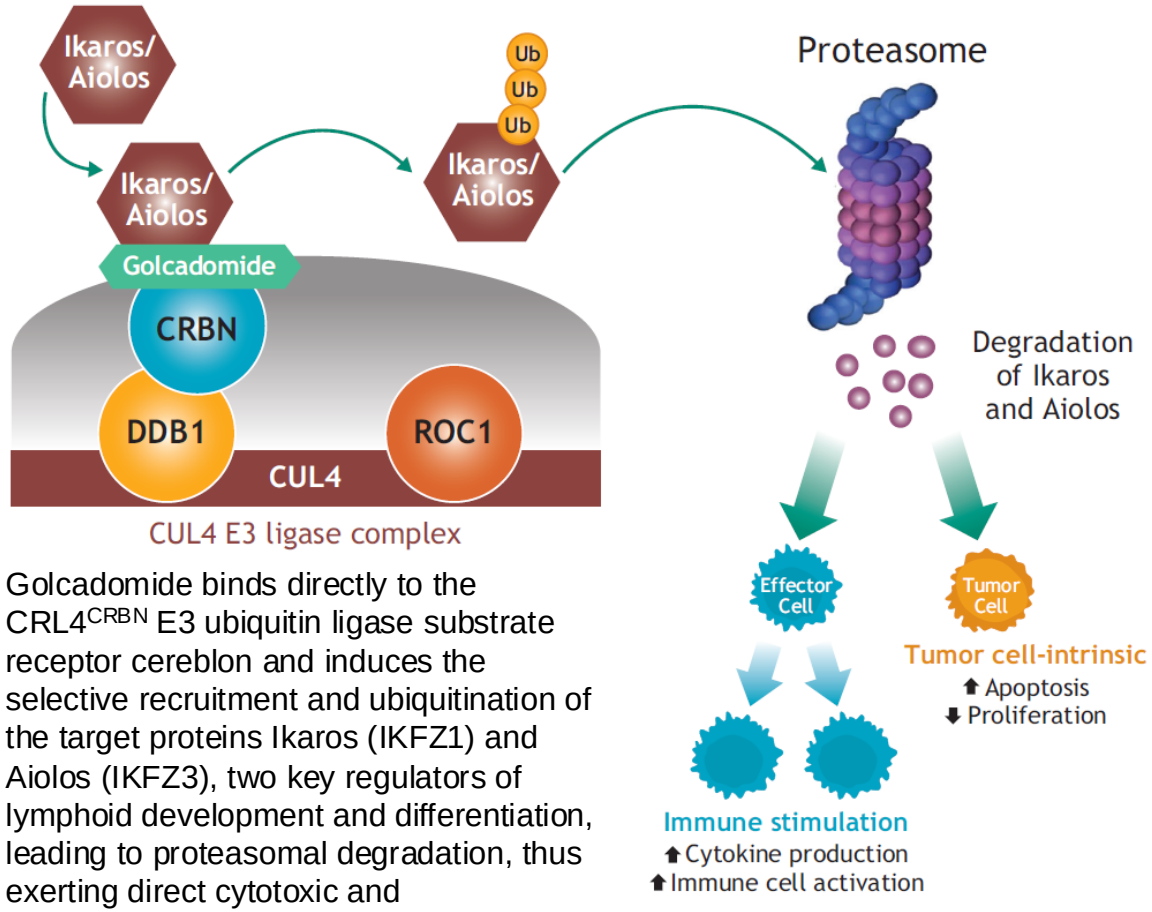
Summary

- Two Bispecifics approved for R/R DLBCL and FL respectively
  - Drugs have far more similarities than differences
  - Whether indefinite vs. finite is best will be determined by time and further analysis of results
- Moving forward we are likely to get
  - An approval for odronextumab
  - Several combinations with chemotherapy and other antibody partners.
- With time and community usage of drugs we will get better idea of true ORR
  - REAL WORLD DATA

Figure 1. Golcadomide is a potent first-in-class lymphoma CELMoD with pleotropic MoA

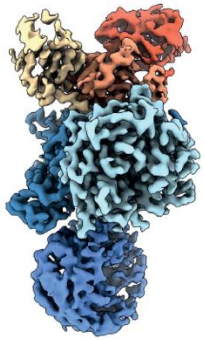


Golcadomide binds directly to the CRL4^{CRBN} E3 ubiquitin ligase substrate receptor cereblon and induces the selective recruitment and ubiquitination of the target proteins Ikaros (IKFZ1) and Aiolos (IKFZ3), two key regulators of lymphoid development and differentiation, leading to proteasomal degradation, thus exerting direct cytotoxic and immunomodulatory effects

Allosteric regulation of cereblon[1]

Inactive/open cereblon
No Ikaros/Aiolos bound

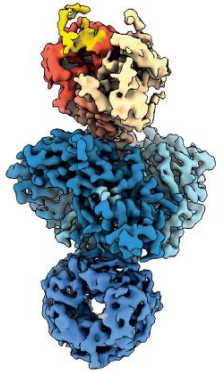
Active/closed cereblon
Ikaros/Aiolos bound



75% **Lenalidomide** 25%

50% **Iberdomide** 50%

0% **Golcadomid** 100%

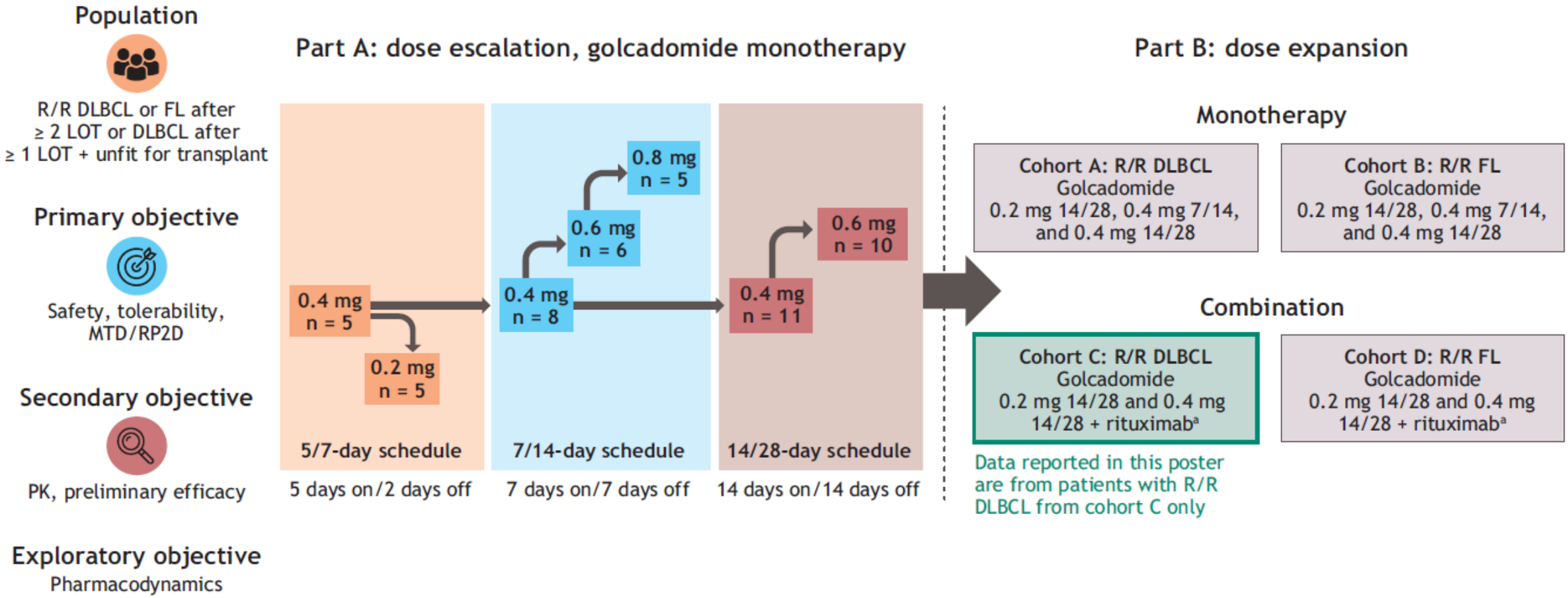


- Recent cryo-EM data indicates that the cereblon complex has both an ***open, inactive state*** and a ***closed, active state,*** and that IMiDs and CELMoDs drive the closed conformation[1]
- Due to the unique binding modes of golcadomide, it is more efficient than lenalidomide at driving the closed conformation,[1] leading to deeper and more rapid degradation of Ikaros/Aiolos

1. Watson ER, et al. *Science* 2022;378:549-553.

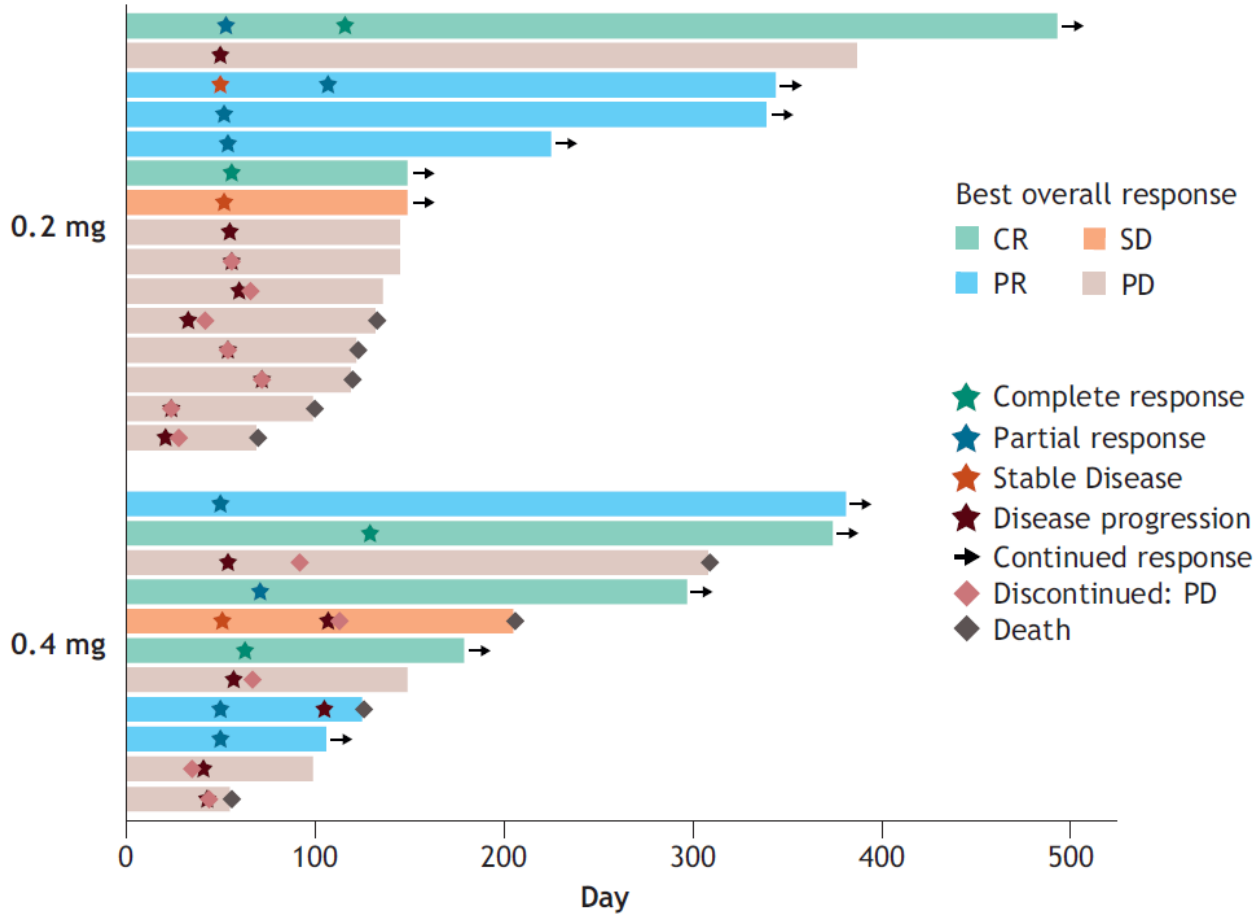
CELMoD, cereblon E3 ligase modulator; CRBN, cereblon; cryo-EM, cryogenic electron microscopy; CUL4, cullin 4; DDB1, DNA damage-binding protein 1; IMiD, immunomodulatory drug; MoA, mechanism of action; ROC1, regulator of cullins 1; Ub, ubiquitin.

Figure 2. CC-99282-NHL-001 study design



[a]Rituximab dosing was 375 mg/m^2 IV on Days 1, 8, 15, and 22 of Cycle 1, and Day 1 of Cycles 2–5.
DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IV, intravenous; LOT, line of therapy; MTD, maximum tolerated dose; PK, pharmacokinetics; R/R, relapsed or refractory; RP2D, recommended phase 2 dose.

Figure 3. Disposition for individual efficacy evaluable patients at 0.2 and 0.4mg doses[a]



- Median duration of response was 7.5 months (range, 1.8–14.5), including a durable response > 14 months in 1 patient

[a]Each bar shows time from treatment start to earliest of death date, cutoff date, and last known alive date. Continued response is defined as censored duration of response/duration of stable disease. First assessment shown for best overall response for ongoing patients and up to treatment discontinuation for discontinued patients. First efficacy assessment in C3D1 and every 2 cycles during active treatment.

Table 4. TEAEs related to golcadomide reported in ≥ 2 patients at the 0.2-mg and 0.4-mg doses

- In the safety population neutropenia was the most TEAE, occurring in 22 (50%) patients, all of which were grade 3/4
  - All neutropenia was considered related to golcadomide, comprising 10/24 (42%) patients treated at the 0.2-mg and 12/20 (60%) patients treated at the 0.4-mg dose level
  - Febrile neutropenia occurred in 2 (5%) patients, 1 patient at each dose level
  - Granulocyte colony-stimulating factors were used in 22 (50%) patients

TEAE, n (%)	Golcadomide 0.2 mg + RTX (n = 24)		Golcadomide 0.4 mg + RTX (n = 20)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with at least one TRAE	16 (67)	11 (46)	14 (70)	12 (60)
Neutropenia	10 (42)	10 (42)	12 (60)	12 (60)
Diarrhea	4 (17)	0	0	0
Constipation	2 (8)	0	2 (10)	0
Anemia	1 (4)	0	3 (15)	3 (15)
Asthenia	2 (8)	1 (4)	1 (5)	0
Fatigue	1 (4)	0	2 (10)	1 (5)
Pyrexia	1 (4)	0	2 (10)	1 (5)
Lymphopenia	0	0	3 (15)	0
Thrombocytopenia	0	0	3 (15)	3 (15)

- Six patients had SAEs related to golcadomide; the only SAEs occurring in > 1 patient were pneumonia and pyrexia (both n = 2)
- Four grade 5 TEAEs occurred (infection, n = 3; tubulo-interstitial nephritis, n = 1); only 1 (pneumonia) was considered related to study treatment
- TEAEs led to golcadomide discontinuation in 5 (11%) patients (0.2 mg, n = 3; 0.4 mg, n = 2) and rituximab discontinuation in 5 (11%) patients

RTX, rituximab; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

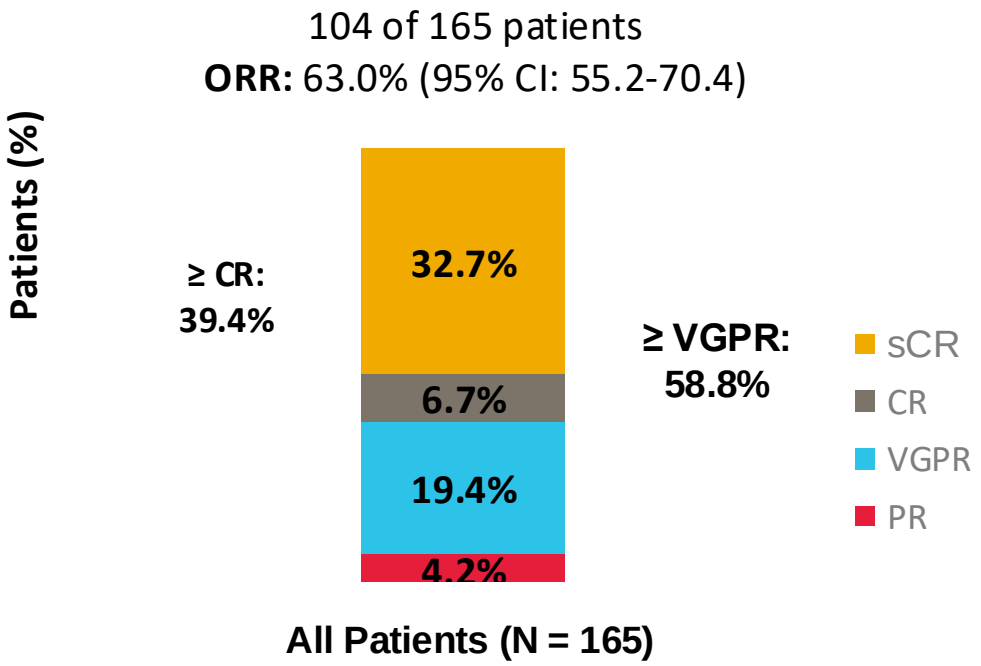
Myeloma

MajesTEC-1: Phase I/II Study of Teclistamab for R/R MM After ≥3 Previous Lines of Therapy

- Patients with R/R MM after ≥3 lines of therapy, including exposure to IMiD, PI, and anti-CD38 mAb
  - 77.6% triple-class refractory
  - 26% high-risk cytogenetics
  - 17% extramedullary disease
- **Teclistamab**: 1.5 mg/kg SQ weekly, after step-up doses

Event	All Patients (N = 165)
MRD negativity at 10^{-5}, n (%; 95% CI)	44 (26.7; 20.1-34.1)
Median DoR, mo (95% CI)	18.4 (14.9-NE)
Median PFS, mo (95% CI)	11.3 (8.8-17.1)
Median OS, mo (95% CI)	18.3 (15.1-NE)

Response to Teclistamab



Median follow-up: 14.1 mo (range: 0.3-24.4)

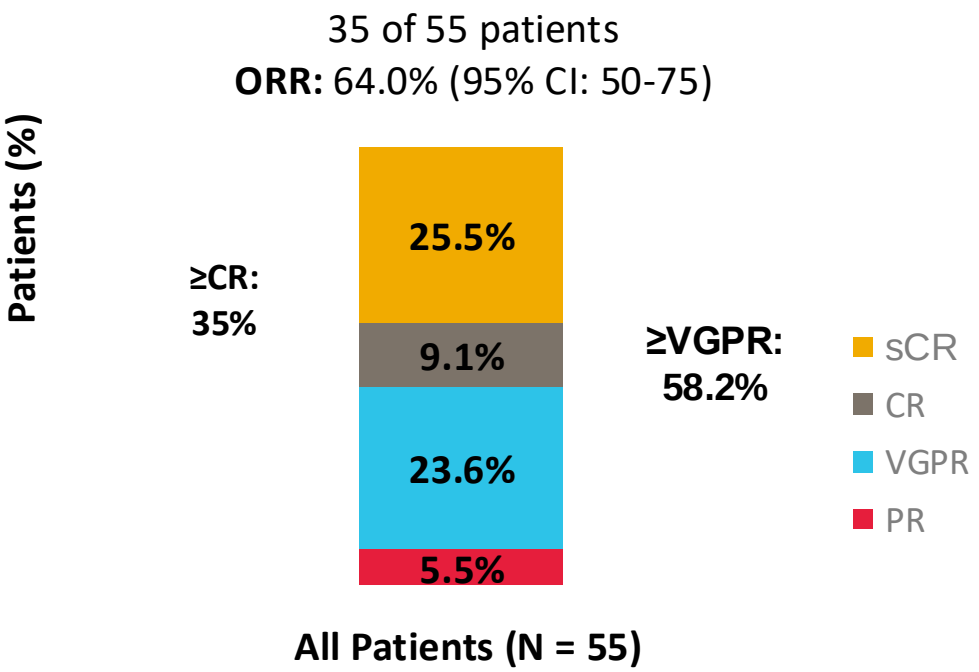
Moreau. NEJM. 2022;387:495.

MagnetisMM-1: Phase I Study of Elranatamab for R/R MM After Established Therapy

- Patients with R/R MM who progressed or are intolerant to IMiD, PI, and anti-CD38 mAb
  - 90.9% triple-class refractory
  - 27% high-risk cytogenetics
- **Elranatamab**: 215-1000 µg/kg SQ weekly or Q2W, with priming and/or premedication to reduce CRS

Event	Responders (N = 35)
Patients with sCR/CR and MRD negativity at 10^{-5}, n/N (%)	13/13 (100)
Patients with prior BCMA-targeted therapy and response, n/N (%)	7/13 (54)
9-mo event-free probability after response, % (95% CI)	77 (58-88)

Response to Elranatamab



Median follow-up: 10.6 mo (range: 0.3-24.6)

Jakubowiak. ASCO 2022. Abstr 8014. Dalovisio. EHA 2022. Abstr P897.

Slide credit: clinicaloptions.com

BCMA x CD3 Bispecific Antibodies: Summary

Therapy	Characteristics	N	Population	Safety	Response	DoR/PFS/OS, Mo
Teclistamab[1]	▪ RP2D: 1.5 mg/kg SC once weekly	165	▪ Median of 5 prior lines of tx ▪ 78% triple refractory ▪ 30% penta refractory	▪ CRS 72% (0.6% G3/4) ▪ Neurotox 14% (0.6% G3/4) ▪ ICANS 3% ▪ Infections 76%	ORR: 63% sCR/CR: 39% ≥VGPR: 59%	mDoR: 18.4 mPFS: 11.3 mOS: 18.3
Elranatamab[2,3]	▪ 215-1000 µg/kg SQ weekly or every 2 wk ▪ RP2D: 1000 µg/kg	55	▪ Median of 6 prior lines of tx ▪ 91% triple refractory ▪ 24% prior BCMA-based tx	▪ CRS 87%, no G3-4 (67% with priming and premeds) ▪ ICANS 20% ▪ ISR 56%	ORR: 64% sCR/CR: 35% ≥VGPR: 58.2%	No mature data at 10.6 mo follow-up
Linvoseltamab (REGN5458)[4,5]	▪ IV weekly, then every other wk after Wk 16 ▪ 3-800 mg dose escalation	73	▪ Median of 5 prior lines of tx ▪ 89% triple refractory ▪ 38% penta refractory	▪ CRS 38%, no G3/4 ▪ ICANS 4%	ORR (all doses): 51% ORR (200-800 mg): 75% ≥VGPR (200-800 mg): 58%	mDoR: NR at median 3 mo follow-up
ABBV-383 (TNB-383B)[6]	▪ IV fixed doses, once every 3 wk with no step dosing ▪ 0.025-120 mg dose escalation	124	▪ Median of 5 prior lines of tx ▪ 82% triple refractory ▪ 35% penta refractory	▪ CRS 57%, G3/4: 2% ▪ ICANS 2% ▪ Infections 41%	ORR (all doses): 57% ORR (60 mg exp): 59% ≥VGPR (60 mg exp): 39%	mDoR: NR mPFS: 10.4
Pavurutamab (AMG 701)[7]	▪ IV weekly ▪ 0.005-18 mg dose escalation	85	▪ Median of 6 prior lines of tx ▪ 62% triple refractory	▪ CRS 65% (9% G3) ▪ No ICANS reported ▪ 17% infection SAE	ORR (all doses): 26% ORR (3-18 mg): 36% ORR (most recent cohort): 83%	No mature data at 6.5 mo follow-up

1. Moreau. NEJM. 2022;387:495. 2. Jakubowiak. ASCO 2022. Abstr 8014. 3. Dalovisio. EHA 2022. Abstr P897. 4. Zonder. ASH 2021. Abstr 160. 5. Zonder. IMS 2022. Abstr OAB-056. 6. D'Souza. JCO. 2022;[Epub]. 7. Harrison. ASH 2020. Abstr 181.

Table 3. Recommendations for prevention and management of infections for patients on BiAbs.

	Infection prevention before BCMA bispecific	Infection prevention during BCMA bispecific	Treatment of infection during BCMA bispecific[a]
Bacterial	Vaccinate if appropriate	IVIg q4 weeks	Based on sensitivities
Viral			
Zoster	Vaccinate if appropriate	VZV prophylaxis	Anti VZV therapeutic dosing
Influenza	Vaccinate if due	Hygiene	Antiviral
Hepatitis	Vaccinate if appropriate	Prophylaxis if evidence of Hep B exposure	Per ID input
CMV	N/A	Monitor CMV PCR q monthly	Treat if rising significantly or symptomatic
RSV	N/A	Hygiene	Consider inhaled ribavirin
COVID-19	Vaccinate/Boost	? Preventative monoclonal antibodies based on viral patterns Hygiene Consider monitoring Ab response and continue boosting	Oral or parenteral agents
Fungal	N/A	N/A	As indicated
PCP	N/A	PCP prophylaxis	Per ID Input

Abbreviations: ID, infectious disease; N/A, not applicable; RSV, respiratory syncytial virus; VZV, varicella zoster virus.

[a]Educate patients/caregivers about monitoring for signs and symptoms of infection. In setting of active infection, hold BCMA bispecific until recovery. Consider cytokine release syndrome, hemophagocytic lymphohistiocytosis, Epstein-Barr virus, *Clostridium difficile*, and unusual organisms in differential diagnosis; collaborate closely with ID team.

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ORIGINAL ARTICLE

Talquetamab, a T-Cell–Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma

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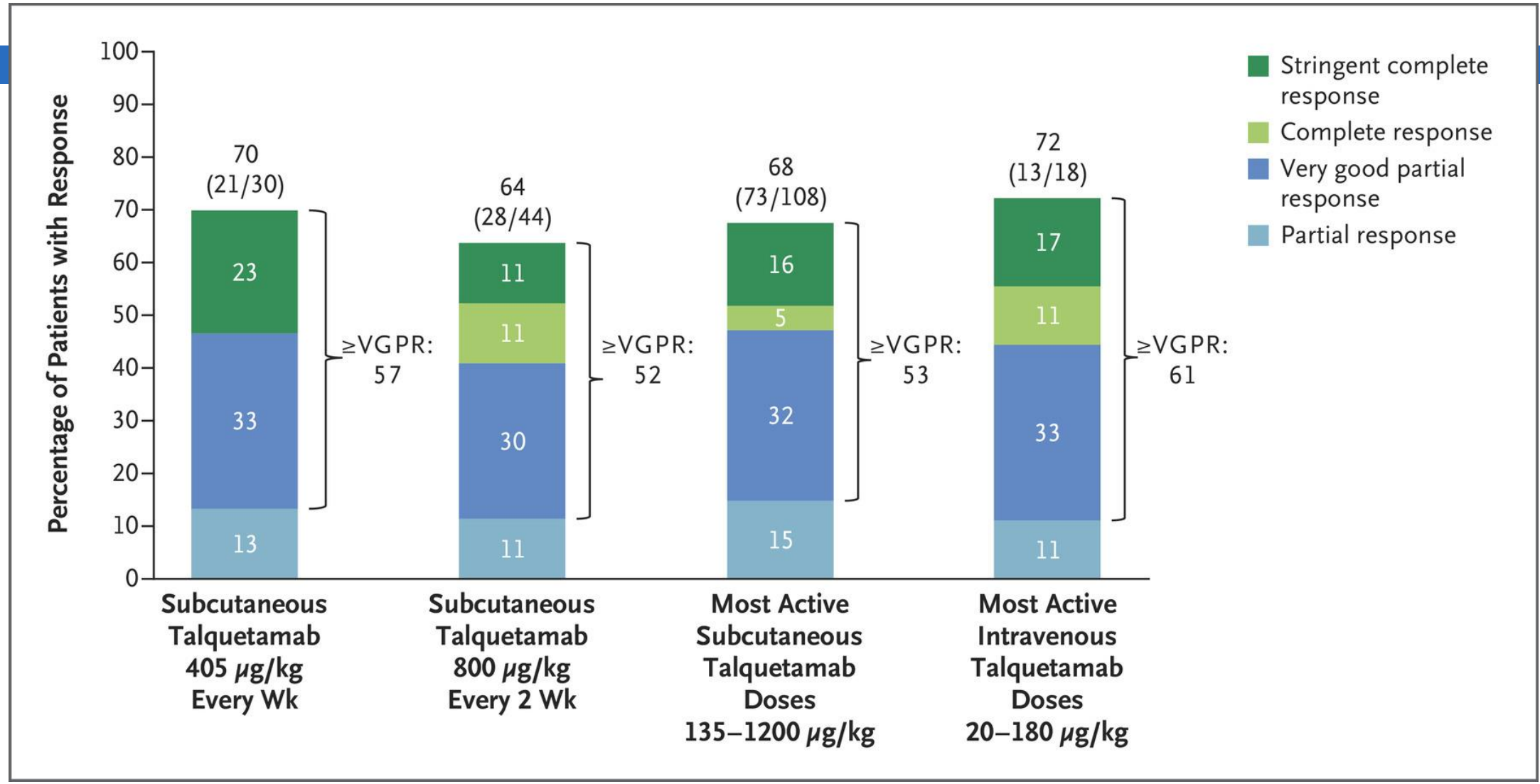
Percentage of Patients with Response
100
90
80
70
60
50
40
30
20
10
0
70
(21/30)
23
33
13
≥VGPR:
57
64
(28/44)
11
11
30
11
≥VGPR:
52
68
(73/108)
16
5
32
15
≥VGPR:
53
72
(13/18)
17
11
33
11
≥VGPR:
61
Stringent complete response
Complete response
Very good partial response
Partial response
Subcutaneous Talquetamab 405 μg/kg Every Wk
Subcutaneous Talquetamab 800 μg/kg Every 2 Wk
Most Active Subcutaneous Talquetamab Doses 135–1200 μg/kg
Most Active Intravenous Talquetamab Doses 20–180 μg/kg

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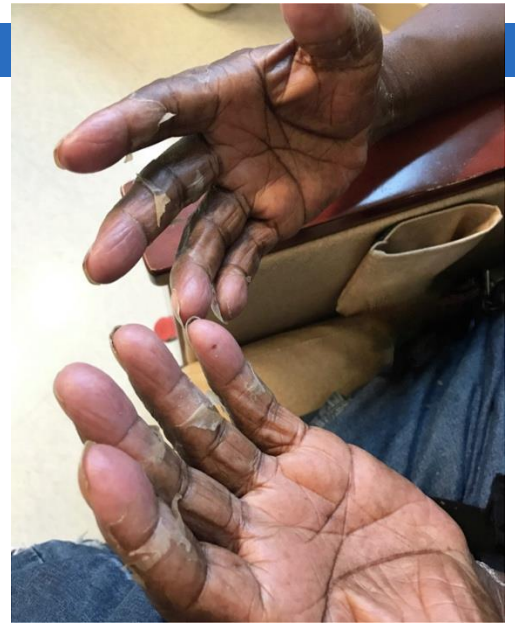

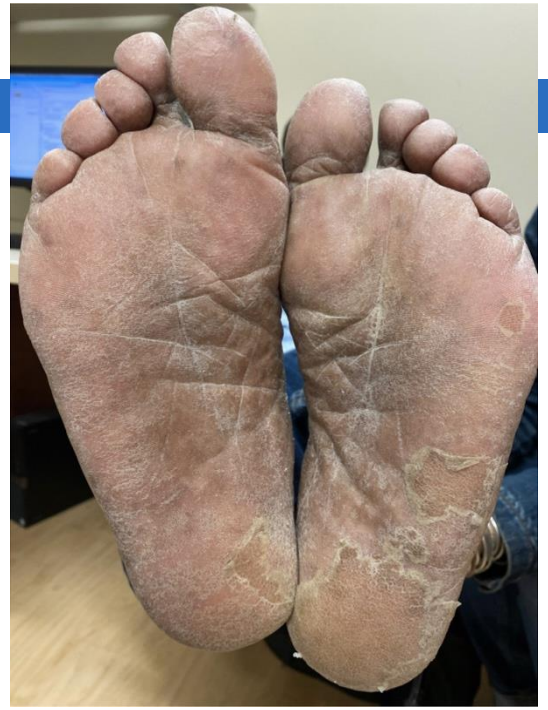

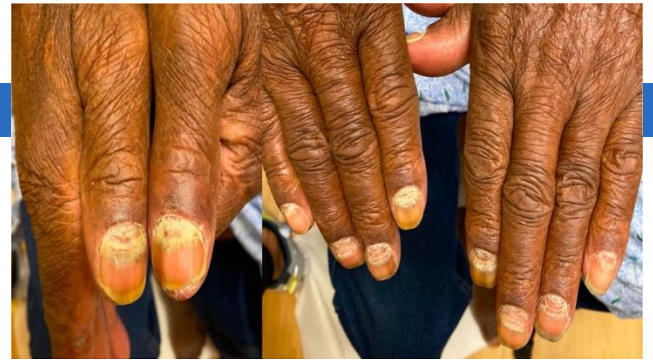

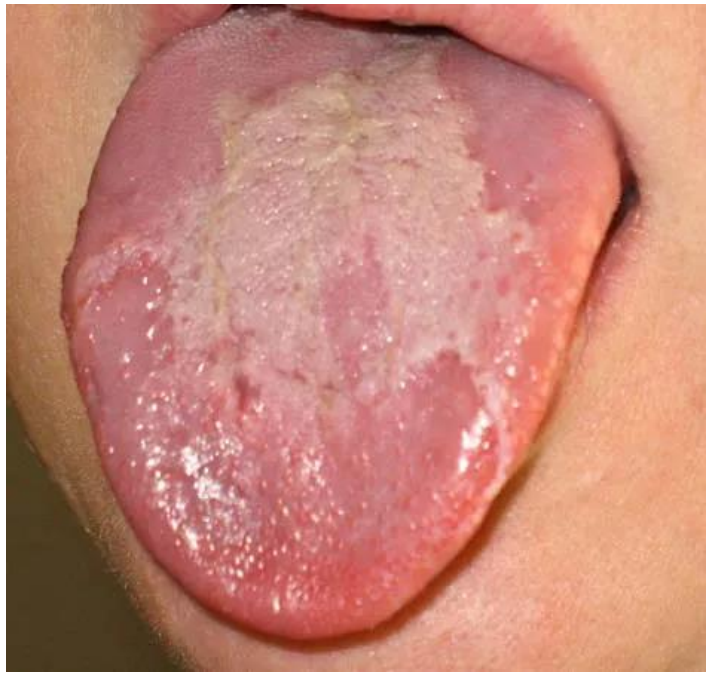

Onychomadesis and palmoplantar keratoderma associated with talquetamab therapy for relapsed and refractory multiple myeloma

Neha Narayan BA , Benjamin Williams MD , Brea Lipe MD , Anna De Benedetto MD

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Novel Bispecific Antibodies

Therapy	Characteristics	N	Population	Safety	Response	mDoR, Mo
Talquetamab[1,2]	▪ G protein-coupled receptor family C group 5 member D (GPRC5D) x CD3 bispecific antibody ▪ RP2D: 405 µg/kg SC once weekly or 800 µg/kg SC once every 2 wk	n = 30 (405 µg/kg QW)	▪ Median of 6 prior lines of tx ▪ 77% triple refractory ▪ 24% penta refractory	▪ CRS 78% (1.4% G3/4) ▪ Infections: 47% (405 µg/kg); 39% (800 µg/kg) ▪ Neutropenia (51%), anemia (51%), thrombocytopenia (28%)	ORR: 70% sCR/CR: 30% ≥VGPR: 57%	10.2
		n = 44 (800 µg/kg Q2W)			ORR: 63.6% sCR/CR: 20% ≥VGPR: 57%	13.0
Cevostamab (BFCR4350A)[3,4]	▪ FcRH5/CD3 bispecific T-cell engager ▪ Q3W IV infusions with single step up or double step-up expansions	161	▪ Median of 6 prior lines of tx ▪ 85% triple refractory ▪ 68% penta refractory	▪ CRS 81% (1.2% G3) ▪ ICANS 14% (0.6% G3) ▪ Neutropenia, anemia, thrombocytopenia most common heme AE	ORR: 57% at 132-198 mg; 36% at 20-90 mg dose level	11.5

1. Minnema. ASCO 2022. Abstr 8015. 2. Minnema. EHA 2022. Abstr S182. 3. Cohen. ASH 2020. Abstr 292. 4. Trudel. ASH 2021. Abstr 157.

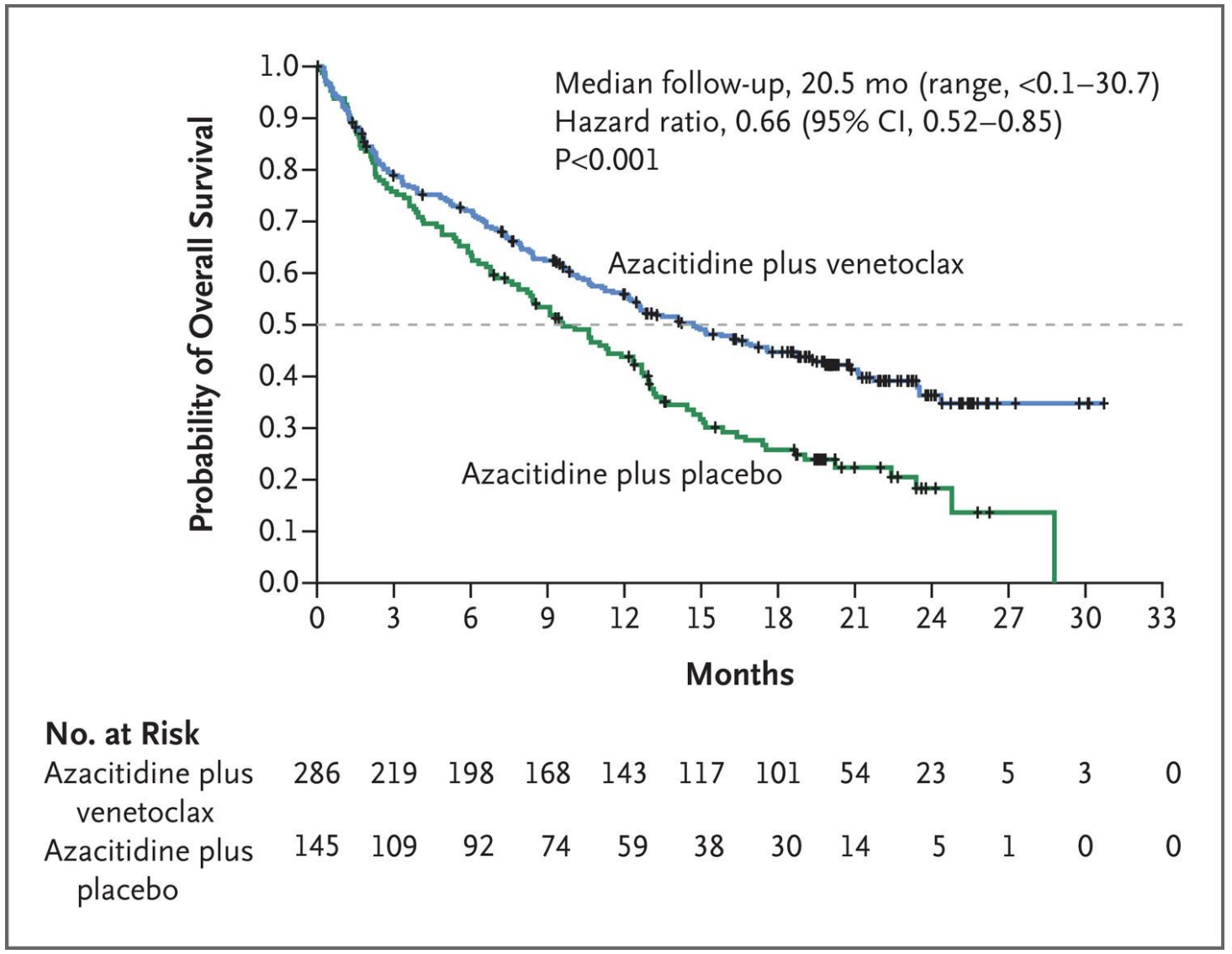
Slide credit: clinicaloptions.com

Summary

- Several Bispecifics in MM
  - Major difference between NHL is the longer hospital requirement with SUD
    - 48 – 72 hrs between doses
  - Unlike Lymphoma Bispecifics before CAR-T with BCMA agents impacts response to CAR
  - Importance of other targets
    - More side effects with Talquetamab
    - Longer ramp up with Cevostamab
- Infections complications a concerns
  - Possibly related to other treatments?
  - Mitigation of infections with IVIG

AML

Venetoclax in AML



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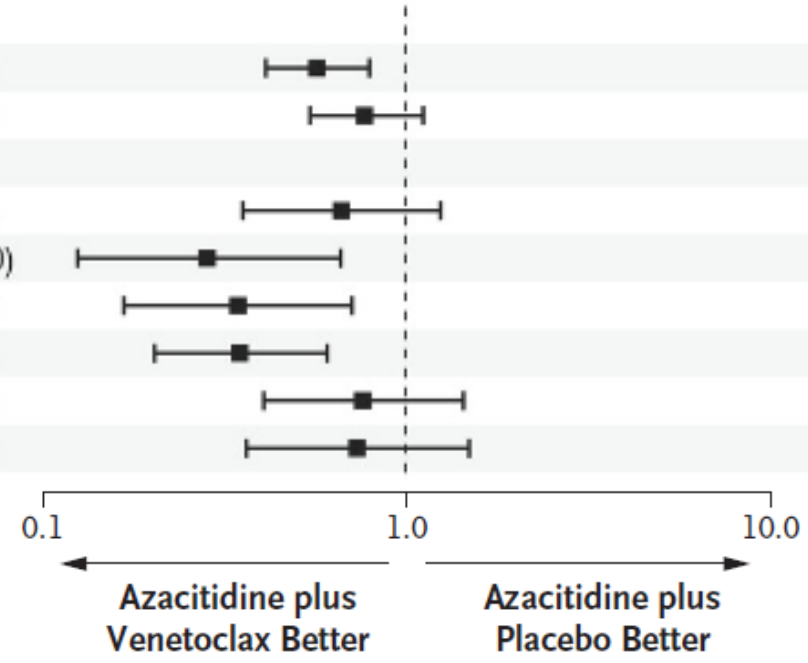
Molecular Subgroups

Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
Cytogenetic risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	0.57 (0.41–0.79)
Poor	77/104 (74.0)	47/56 (83.9)	0.78 (0.54–1.12)
Molecular marker			
FLT3	19/29 (65.5)	19/22 (86.4)	0.66 (0.35–1.26)
IDH1	15/23 (65.2)	11/11 (100.0)	0.28 (0.12–0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16–0.71)
IDH1 or *IDH2*	29/61 (47.5)	24/28 (85.7)	0.34 (0.20–0.60)
TP53	34/38 (89.5)	13/14 (92.9)	0.76 (0.40–1.45)
NPM1	16/27 (59.3)	14/17 (82.4)	0.73 (0.36–1.51)



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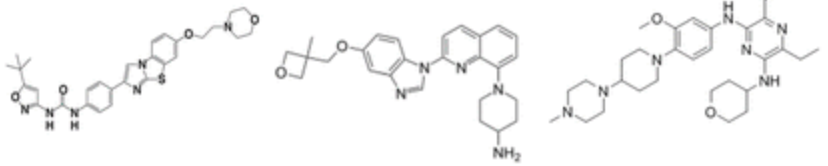
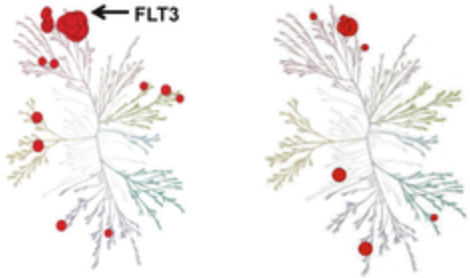
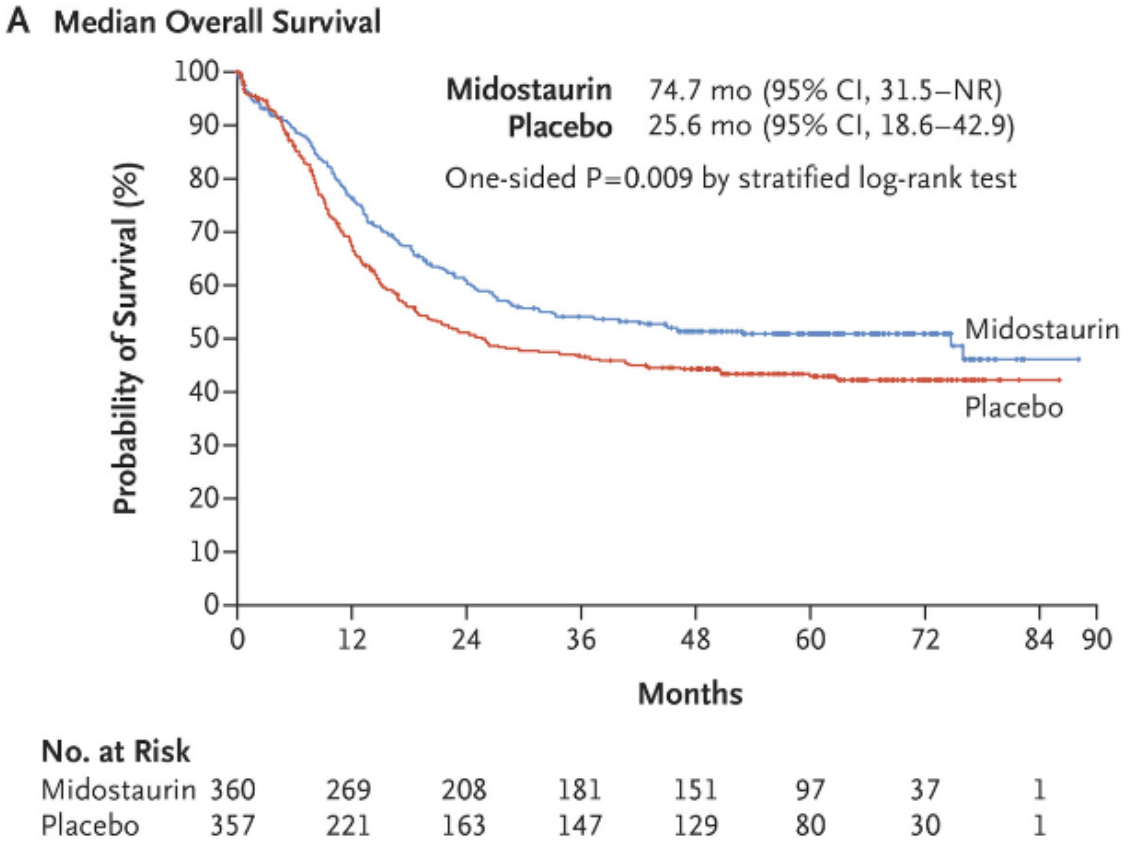
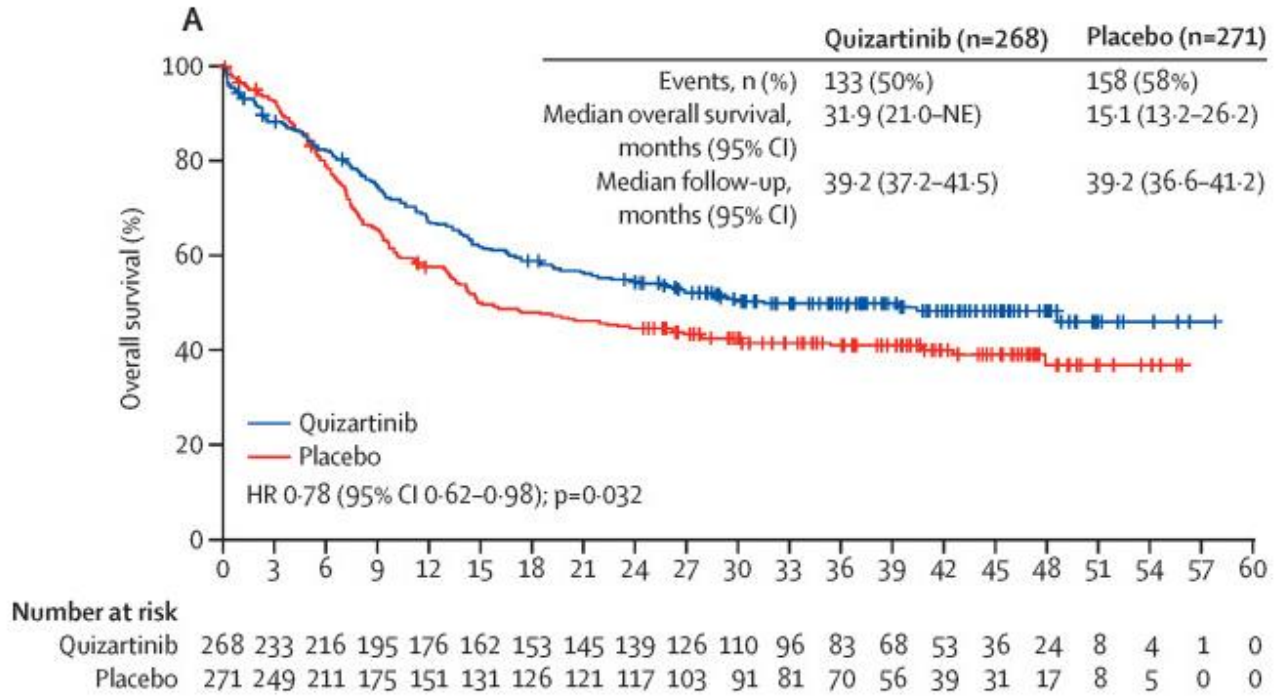
FLT3 mutant

- Type 1 (-ITD/TKD)
  - **Midostaurin**
  - **Gilteritinib**
  - Crenolanib
- Type 2 (-ITD2)
  - Sorafenib
  - **Quizartinib**

Inhibitor	Quizartinib	Crenolanib	Gilteritinib
IC_{50} against FLT3 (nM)	1.1	1.3	0.29
Structure			
Kinase dendrogram			not available

OS


A Median Overall Survival
Midostaurin 74.7 mo (95% CI, 31.5–NR)
Placebo 25.6 mo (95% CI, 18.6–42.9)
One-sided P=0.009 by stratified log-rank test
Probability of Survival (%)
Midostaurin
Placebo
Months
No. at Risk
Midostaurin 360 269 208 181 151 97 37 1
Placebo 357 221 163 147 129 80 30 1


A
Quizartinib (n=268) Placebo (n=271)
Events, n (%) 133 (50%) 158 (58%)
Median overall survival, months (95% CI) 31·9 (21·0–NE) 15·1 (13·2–26·2)
Median follow-up, months (95% CI) 39·2 (37·2–41·5) 39·2 (36·6–41·2)
Overall survival (%)
Quizartinib
Placebo
HR 0·78 (95% CI 0·62–0·98); p=0·032
Number at risk
Quizartinib 268 233 216 195 176 162 153 145 139 126 110 96 83 68 53 36 24 8 4 1 0
Placebo 271 249 211 175 151 131 126 121 117 103 91 81 70 56 39 31 17 8 5 0 0

IDH mutant

- Ivosidenib
- Olutasidenib

Response Rate

Response Category	Ivosidenib+Azacitidine (N=72)	Placebo+Azacitidine (N=74)
Best response — no. (%)		
Complete remission	34 (47)	11 (15)
Complete remission with incomplete hematologic or platelet recovery	5 (7)	1 (1)
Partial remission	4 (6)	2 (3)
Morphologic leukemia-free state	2 (3)	0
Stable disease	7 (10)	27 (36)
Progressive disease	2 (3)	4 (5)
Could not be evaluated	1 (1)	2 (3)
Not assessed	17 (24)	27 (36)

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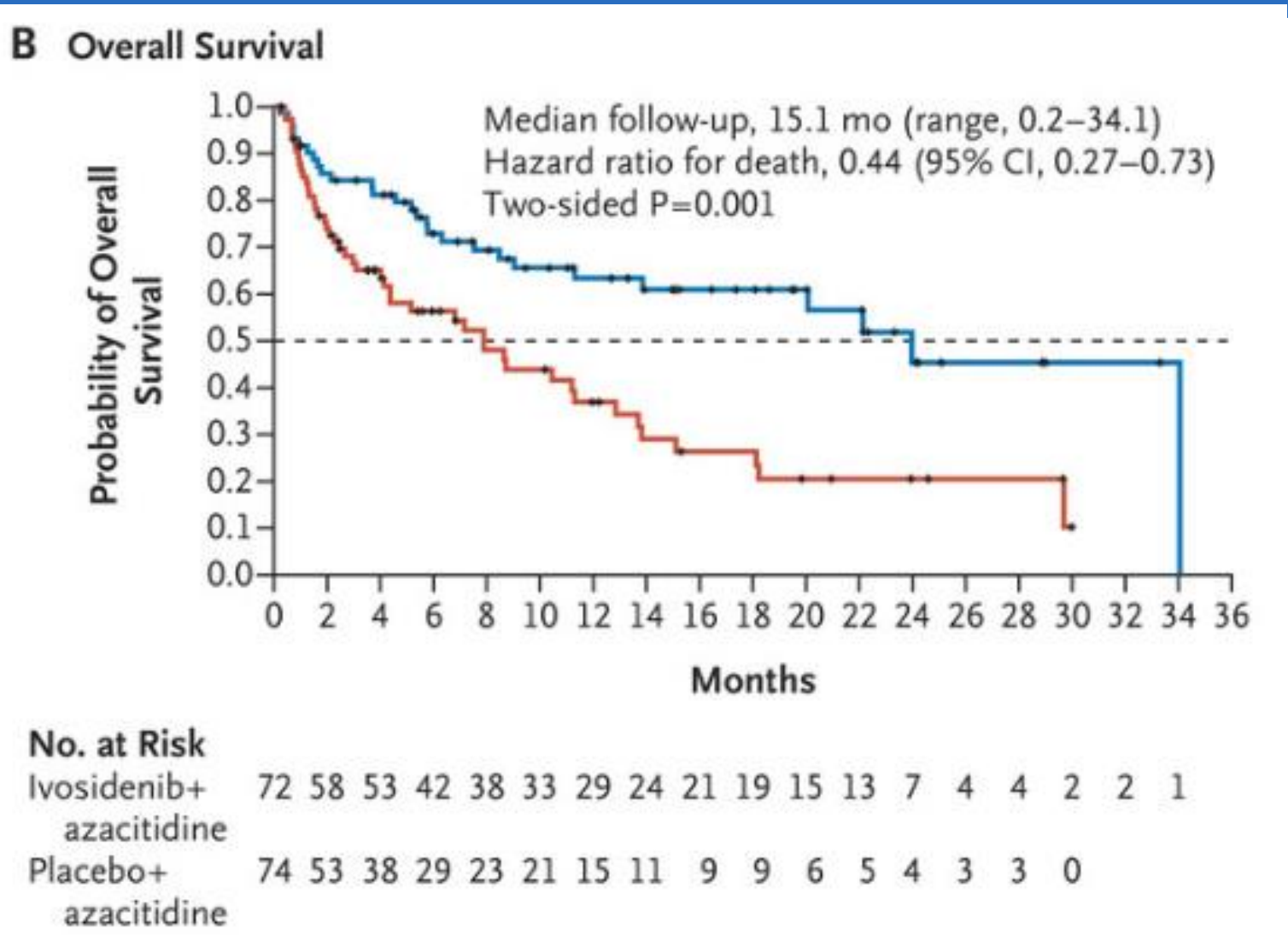
OS

- mOS 24.0 vs 7.9 months



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Summary

- Promising targeted agents in AML
- Importance of molecular testing at diagnosis/relapse

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Lymphoma Center at COH

- Steve Rosen MD
- Larry Kwak MD PhD
- Jasmine Zain MD
- Alex Herrera MD
- Tanya Siddiqi MD
- Matt Mei MD
- Elizabeth Budde MD, PhD
- Lili Wang PhD
- Vu Ngo PhD
- Joo Song MD

- Geoff Shouse MD
- James Godfrey MD
- John Baird MD
- Swetha Kambhampati MD
- Niloufer Khan MD
- Avy Kallam MD
- Lu Chen PhD
- Alexey Danilov MD, PhD
- Leslie Popplewell MD
- CRNs and CRCs

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Questions