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DIPARTIMENTO DI
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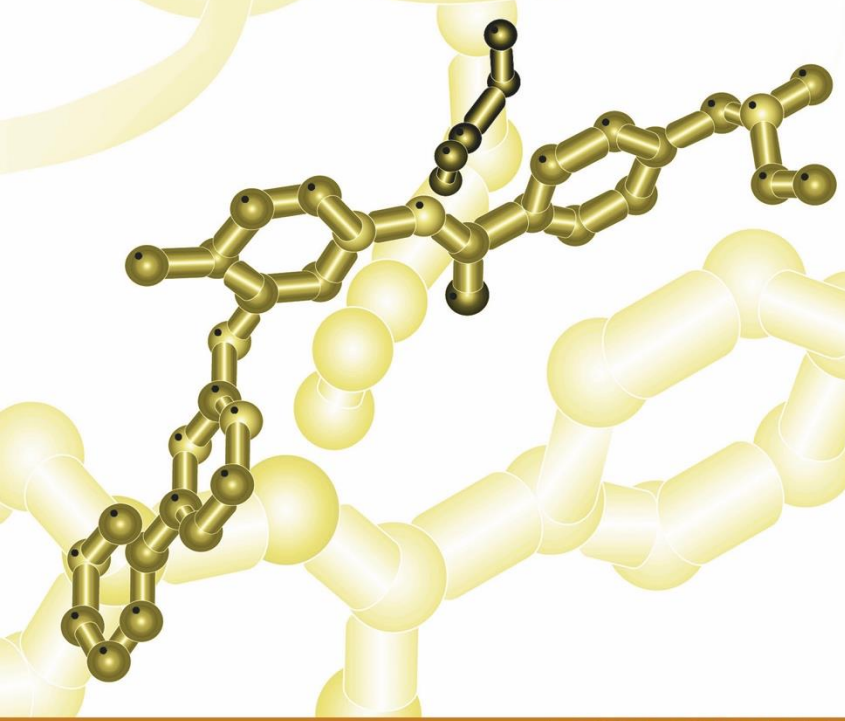

New Drugs in Hematology

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Bologna,
Royal Hotel Carlton
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BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

Zilovertamab vedotin

Paul Barr
University of Rochester

Disclosures of Paul Barr

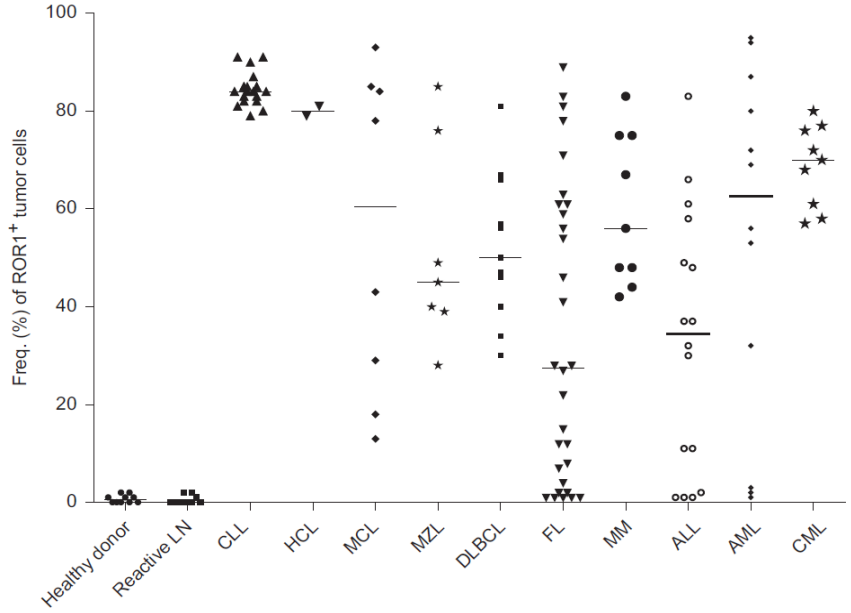
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			X				
Beigene			X				
Genentech			X				
BMS			X				
Seattle Genetics			X				
Janssen			X				
AstraZeneca			x				
Regeneron			X				
Adaptive			X				

ROR1 Is Expressed on Multiple Cancers but Not on Normal Tissues

- Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is an oncofetal protein important for embryonic and fetal development [1]
- ROR1 expression attenuates in normal post partum tissues, being largely absent from adult tissues and absent on critical organs
- ROR1 is highly expressed on hematological and solid tumors, including malignant B lymphocytes[2]

CLL	MCL	Lymphomas	Solid Tumors
95%	95%	90%	54-90%

ROR1 Expression on Hematological Cancers

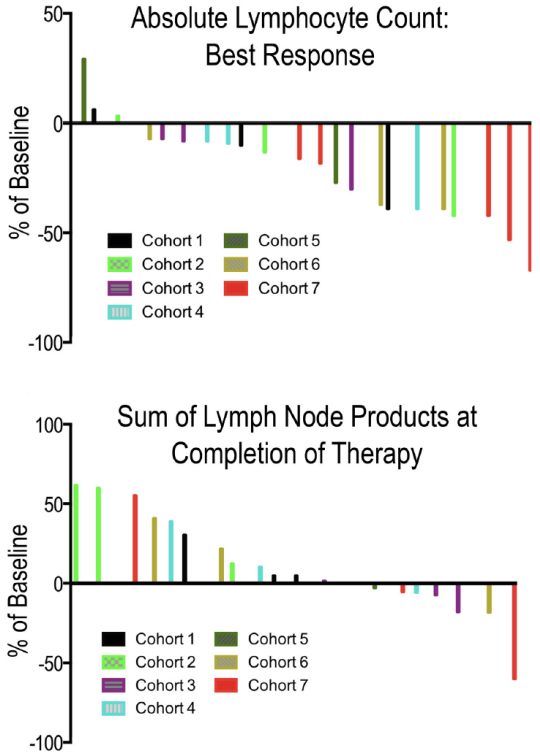


1. Borcherding N et al. Protein Cell. 2014;5:496-502;
2. Danesmanesh AH et al. Leuk Lymphoma. 2013;54:843-850

Zilovertamab

- Zilovertamab (Cirmtuzumab, UC-961)
  - Humanized monoclonal ROR1 antibody

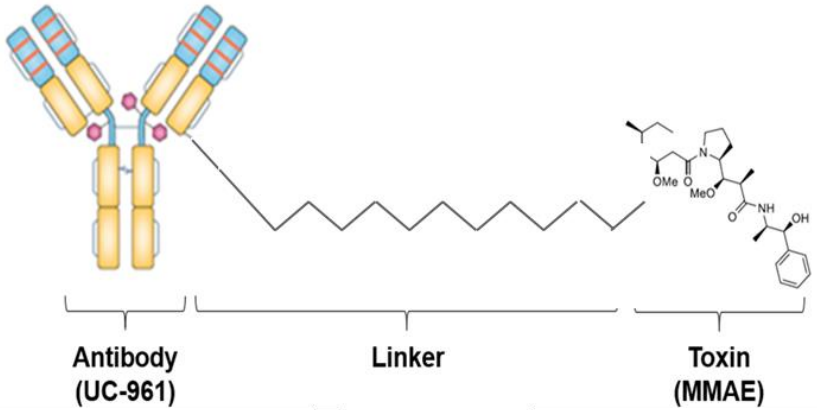
- Phase 1 trial of 4 biweekly infusions
  - Half life of 32 days
  - Evidence of ROR1 down modulation
  - No dose limiting toxicities
  - AEs related to underlying CLL
  - 3 asymptomatic lipase elevations
  - Of 26 CLL patients, 17 had best response of SD



Choi et al. Cell Stem Cell. 2018 Jun 1;22(6):951-959.e3.

Zilovertamab Vedotin

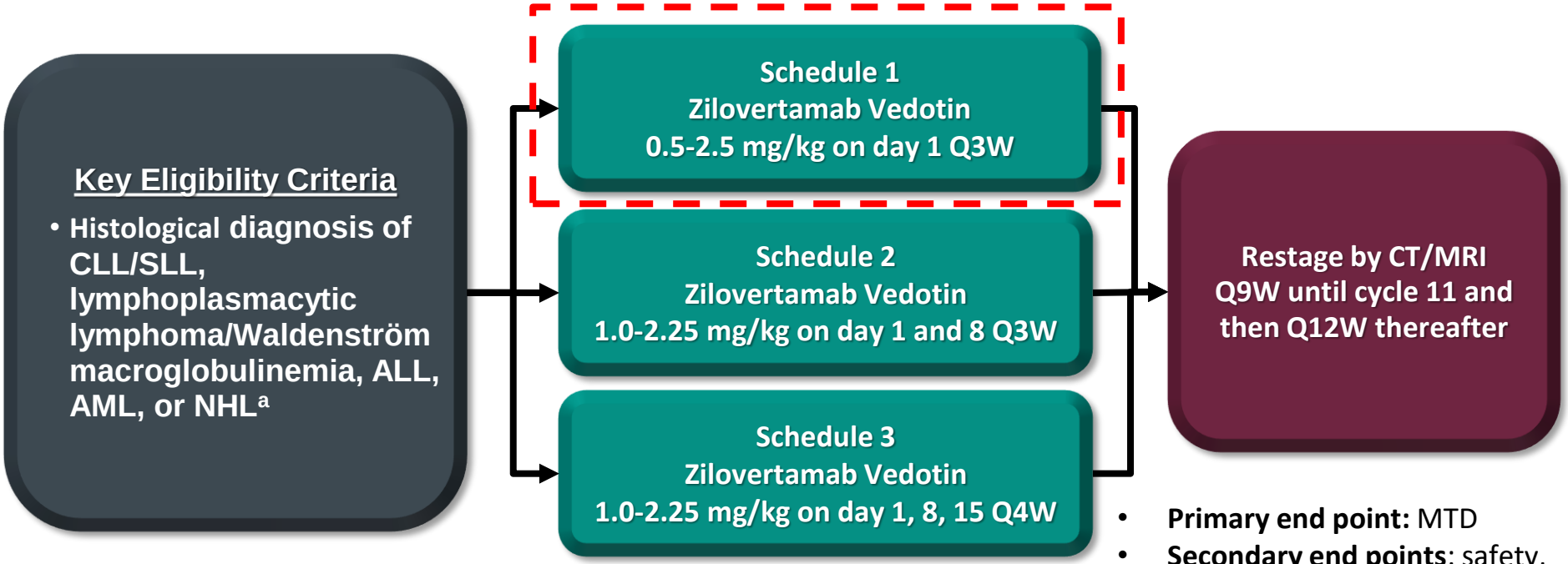
- Zilovertamab vedotin (VLS-101, MK-2140) is an ADC of:
  - The humanized monoclonal antibody, UC-961, with no normal tissue cross-reactivity
  - A cleavable linker and the anti-microtubule toxin, monomethyl auristatin E (MMAE)



- Binding to tumor cell ROR1 causes rapid internalization and lysosomal trafficking to deliver MMAE

Vaisitti T et al. *Blood.* 2021;137:3365-3377.

Phase 1 First In-Human Dose Escalation Study



- **Primary end point:** MTD
- **Secondary end points**: safety, ORR, and DOR

Wang ICML 2023, #427

Baseline Demographics (Schedule 1)

n (%)	All Patients N = 56
Age, median (range), years	70 (40-91)
Type of hematological malignancy	
DLBCL	17 (30)
MCL	17 (30)
Richter's	7 (13)
CLL	7 (13)
FL	3 (19)
AML	3 (5)
MZL	2 (4)

n (%)	Patients
Prior lines of therapy, median (range)	
DLCBL	4 (1-9)
Prior CAR-T	12 (71%)
Prior ASCT	2 (12%)
MCL	4 (1-9)
Prior BTKi	17 (100%)
Prior ASCT	4 (24%)
Richter's	6 (1-10)
Prior BTKi	5 (71%)

Any-Grade Adverse Events in ≥20% of Patients

Any-Grade AEs, n (%)	All Patients N = 51	
	All-Cause	Treatment-Related
Peripheral neuropathy	25 (49)	24 (47)
Fatigue	23 (45)	19 (37)
Nausea	23 (45)	14 (28)
Diarrhea	19 (37)	11 (22)
Dizziness	19 (37)	9 (18)
Decreased neutrophil	18 (35)	16 (31)

Any Grade AEs, n (%)	All Patients N = 51	
	All-Cause	Treatment-Related
Constipation	15 (29)	5 (10)
Myalgia	15 (29)	10 (20)
Pyrexia	14 (28)	4 (8)
Vomiting	12 (24)	5 (10)
Decreased appetite	12 (24)	9 (18)
Dyspnea	11 (22)	8 (16)

Wang et al. NEJM Evidence 2021; 1(1)

Grade 3 or 4 Adverse Events in ≥3 Patients

Grade 3 or 4 AEs, n (%)	All Patients N = 51	
	All-Cause	Treatment-Related
Decreased neutrophil count	16 (31)	16 (31)
Decreased hemoglobin	8 (16)	3 (6)
Febrile neutropenia	4 (8)	2 (4)
Peripheral neuropathy	4 (8)	4 (8)
Decreased platelet count	4 (8)	4 (8)
Diarrhea	3 (6)	2 (4)
Increased lipase	3 (6)	2 (4)
Pneumonia	3 (6)	1 (2)

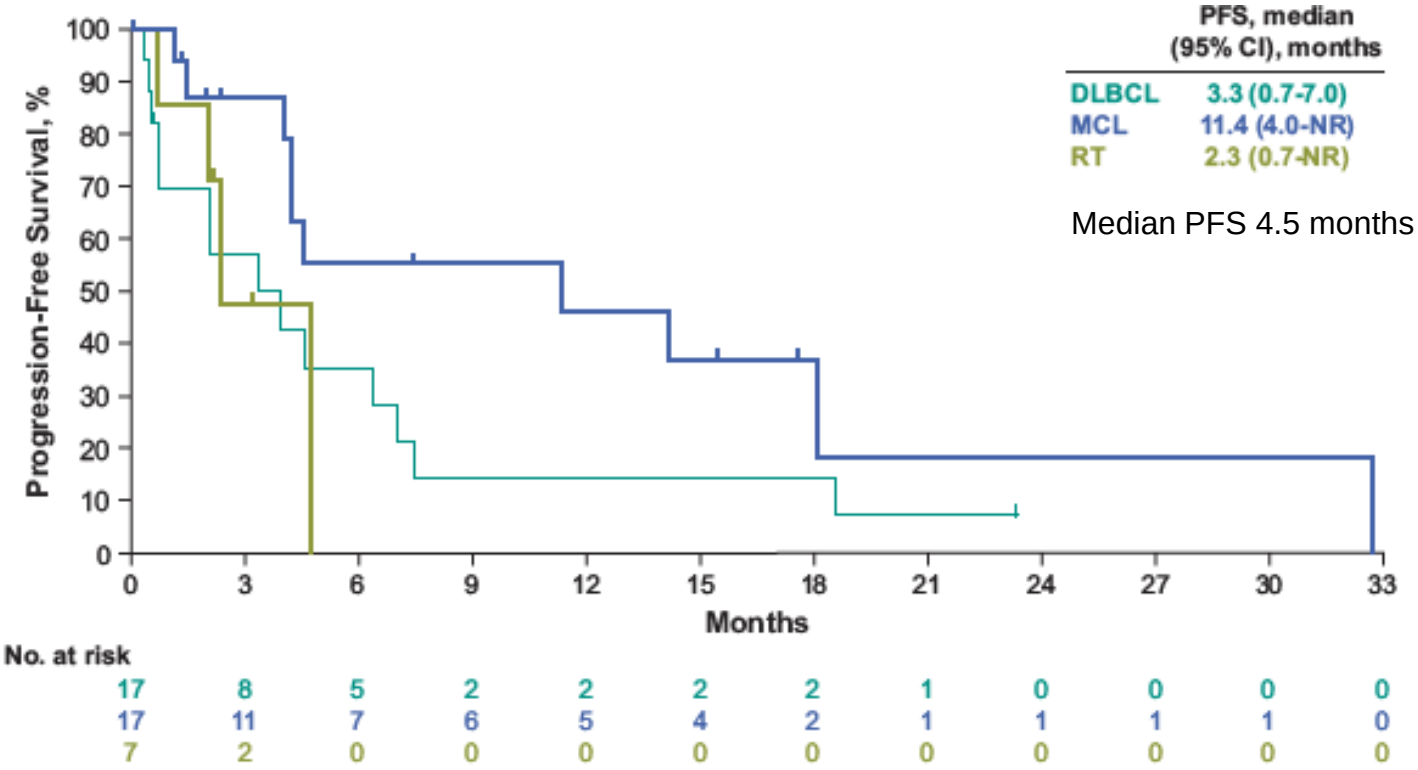
Wang et al. NEJM Evidence 2021; 1(1)

Objective Response Rates

	All patients	DLBCL	MCL	RT
	N= 56	n = 17	n = 17	n = 7
ORR, % (95% CI)	32 (20-46)	29 (10-56)	53 (28-77)	57 (18-90)
Best overall response, n (%)				
CR	7 (13)	3 (18)	2 (12)	2 (29)
PR	11 (20)	2 (12)	7 (41)	2 (29)
SD	14 (25)	4 (24)	3 (18)	0 (0)
PD	14 (25)	6 (35)	2 (12)	2 (29)
NE	10 (18)	2 (12)	3 (18)	1 (14)

Wang et al. ICML 2023, #427

Progression free survival



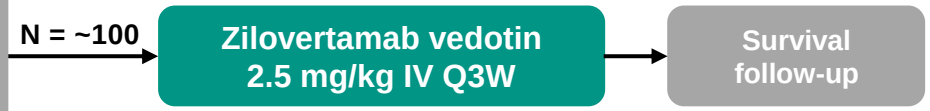
Median PFS 4.5 months

Wang et al. ICML 2023, #427

Phase 2 R/R DLBCL (waveLINE-004)

Key Eligibility Criteria

- Age ≥18 years
- DLBCL per WHO classification[a]
- Radiographically measurable disease per Lugano 2014 criteria
- PET-positive disease by BICR
- ECOG PS of 0-2
- Progressed after ≥2 prior lines of therapy, including an alkylating agent, anthracycline, and an anti-CD20 antibody
- Progressed after or ineligible for ASCT and CAR-T therapy



- **Primary end point:** ORR per Lugano 2014 criteria
- **Secondary end points:** DOR per Lugano 2014 criteria and safety and tolerability
- **Exploratory end points:** DCR and PFS per Lugano 2014 criteria and OS

Assessments and statistical analyses

- Safety and OS were evaluated in all patients who received ≥1 dose of study treatment (APaT population)
- ORR, DOR, and PFS were evaluated in all patients who received ≥1 dose of study treatment and had ≥1 postbaseline scan (efficacy analysis population)

Ozcan et al. ASH 2023, #1720

Baseline Characteristics

	Zilovertamab vedotin N = 98
Age, median (range), years	66 (19-88)
≥65 years	53 (54)
Male	63 (64)
Cell of origin (IHC)	
GCB	38 (39)
Non-GCB	35 (36)
unknown	25 (16)
Ann Arbor stage	
II	16 (16)
III	9 (9)
IV	60 (61)
Missing	13 (13)

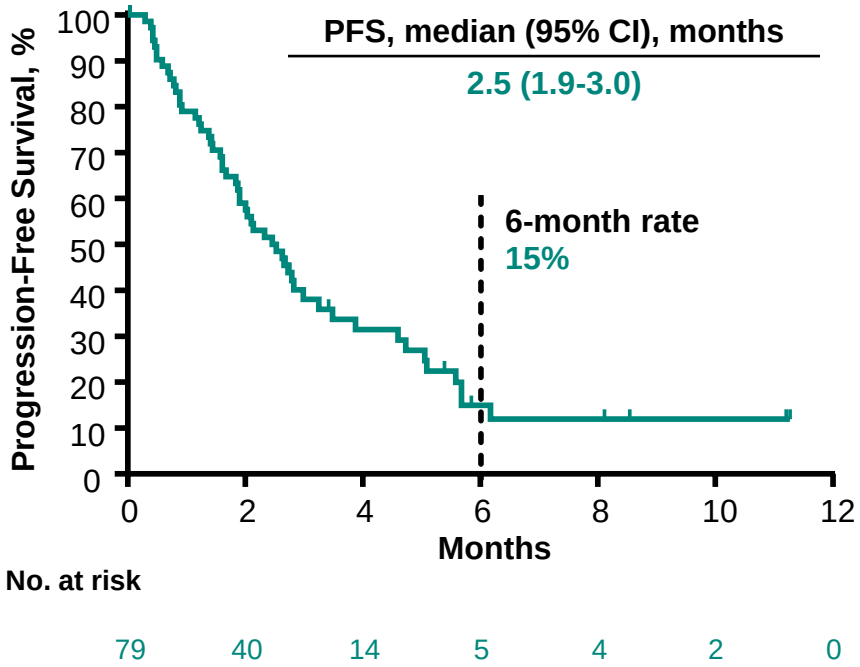
	Zilovertamab vedotin N = 98
Prior lines of therapy	
≤2	28 (29)
≥3	70 (71)
Prior ASCT/CAR-T	
ASCT	15 (15)
CAR-T	18 (18)
ASCT and CAR-T	5 (5)
ASCT / CAR-T ineligible	57 (58)
Missing	3 (3)

Ozcan et al. ASH 2023, #1720

Efficacy of Zilovertamab Vedotin in Relapsed Refractory DLBCL

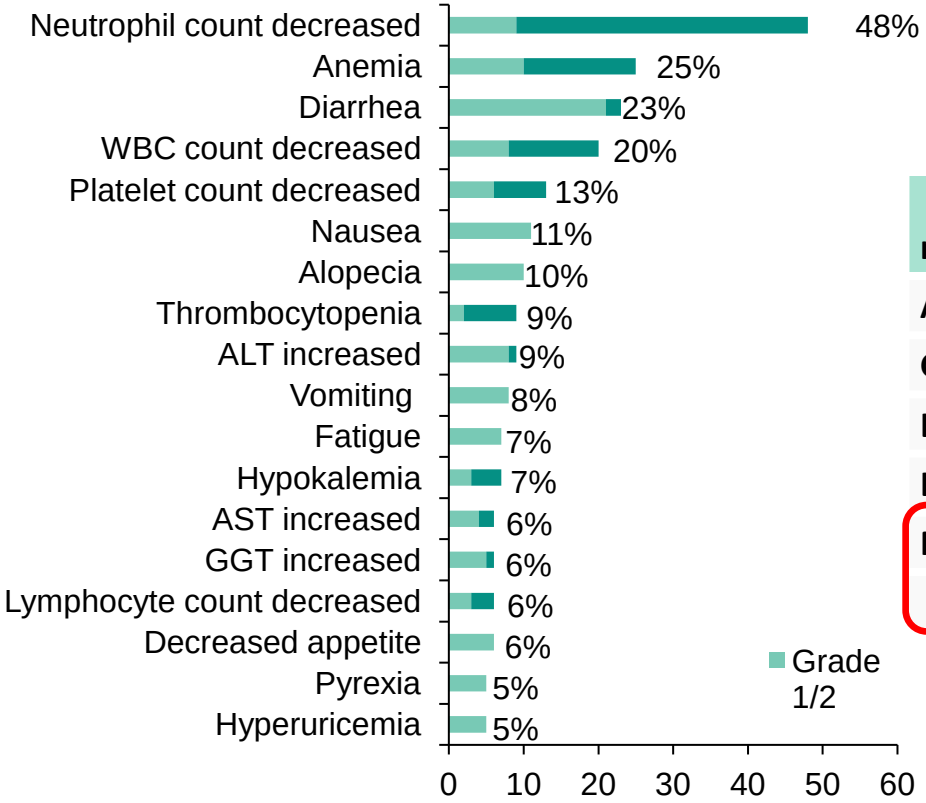
	Zilovertamab vedotin n = 79
ORR (CR + PR), % (95% CI)	29 (19-40)
DCR (CR + PR + SD), % (95% CI)	42 (31-53)
Best overall response, n (%)	
CR	10 (13)
PR	13 (16)
SD	10 (13)
PD	30 (38)
Not evaluable	1 (1)
Not assessed	15 (19)*

* No assessments postbaseline



Ozcan et al. ASH 2023, #1720

Treatment-Related AEs With Incidence ≥5%



n (%)	Zilovertamab vedotin N = 98
Any grade	78 (80)
Grade 3-5	51 (52)
Led to death	2 (2)
Led to discontinuation	4 (4)
Peripheral neuropathy	15 (15)
Grade 3/4	2 (2)

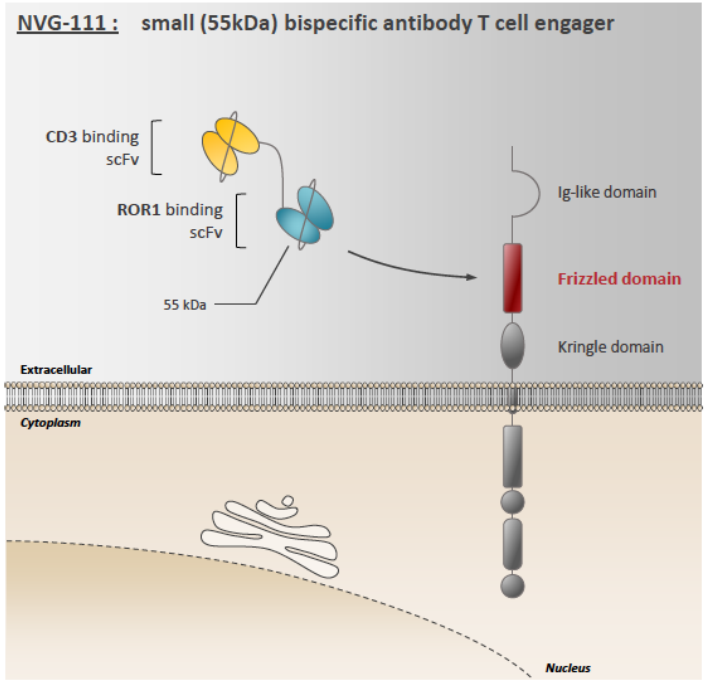
Ozcan et al. ASH 2023, #1720

Ongoing Trials with Zilovertamab Vedotin

Agents	Phase	Disease	NCT
Zilovertamab	Phase 2	Solid tumors	NCT04504916
Zilovertamab + Nemtabrutinib	Phase 2 basket	NHL	NCT05458297
Zilovertamab + R-CHP	Phase 2	DLBCL	NCT05406401
GemOx or BR +/- Zilovertamab	Phase 2/3	R/R DLBCL	NCT05139017

Clinicaltrials.gov

NVG-111: A First in Class ROR1 x CD3 T Cell Engager



- **NVG-111** is a bispecific humanized tandem scFv T cell engager (TCE) targeting **ROR1xCD3**
- NVG-111 mediates **potent killing of ROR1⁺ tumors**[1,2] by:
  - Binding to a **unique** membrane proximal Frizzled domain epitope
  - Possessing an optimized **geometry of binding** for efficient synapse formation
  - Redirecting T cells via the humanized CD3 binder, which is **optimized for efficient tumor killing** and **attenuated cytokine release**

References
1. Gohil *et al*, Oncoimmunol 2017, 6:e1326437
2. Gohil *et al*, Br J Haematol 2019, 186:380

Townsend et al. ASH 2023, #329

Best Tumor Reduction from Baseline

12 participants evaluable for efficacy

Dose = µg/day
C = cycle
SUD = step-up dosing

Cohort 2: CLL
C1: 1
C2: 3
C3: 10

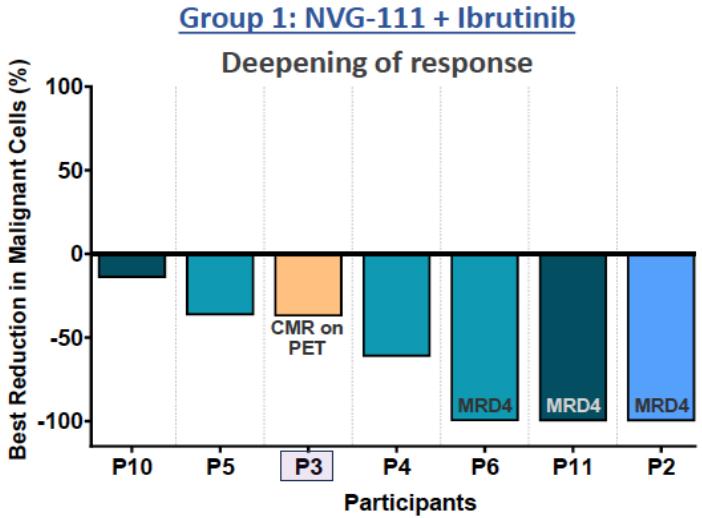
Cohort 3: MCL
C1: 3
C2: 10
C3: 30

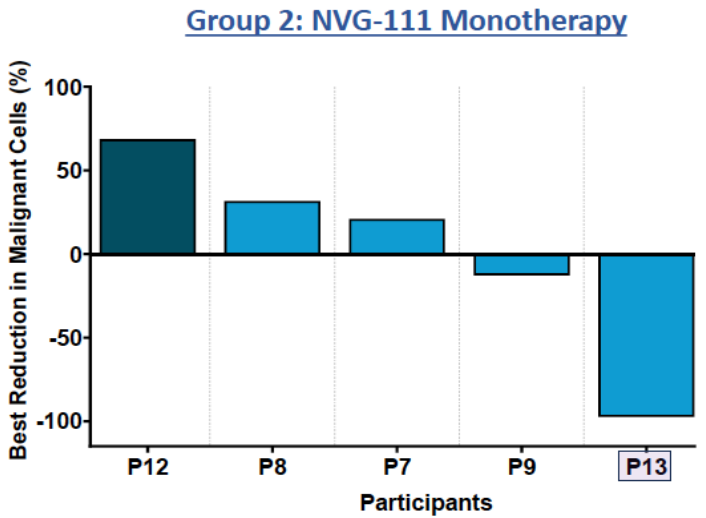
Cohort 4: CLL
C1: 30
C2: 30
C3: 30

Cohort 4b: CLL/MCL
C1: 3/10/30 (SUD)
C2: 30
C3: 30

Cohort 5: CLL
C1: 3/10/45 (SUD)
C2: 45
C3: 45

MCL





Clear evidence of activity in CLL and MCL despite poor T cell fitness[1,2,3]

References
1. Forconi *et al*, Blood 2015, 126:573
2. Yao *et al*, Blood 2020, 136(Suppl 1):16
3. Davis *et al*, Blood Adv 2020, 4:4849

Best reduction in malignant cells (CLL/MCL) out of total nucleated from baseline
Minimal residual disease (MRD4=1 in 10,000 CLL cells); CMR=complete metabolic response assessed by Lugano criteria
PET=positron emission tomography; SUD=step up dose

Townsend et al. ASH 2023, #329

Conclusions

- The distinctive expression of ROR1 make it an attractive target for B-cell malignancies
- Zilovertamab binds to ROR1, with evidence of downstream signaling inhibition
- Zilovertamab vedotin has demonstrated clinical efficacy in MCL and DLBCL with phase 2 dose of 2.5 mg/kg
- The safety profile is consistent with the known profile of MMAE-containing agents
- Combinatorial ZV studies as well as novel strategies targeting ROR1 are ongoing