ASH 2023

Wichtig zu wissen

ASH Kongress 2023

wichtig zu wissen

- Akute Myeloische Leukämie
- Chronische Lymphatische Leukämie
- Fetale Hämatopoese
- Follikuläres Lymphom
- Hereditäre Hämorrhagische Teleangiektasie
- Mantelzell-Lymphom
- Multiples Myelom
- Myelodysplastische Neoplasien
- Sichelzellkrankheit

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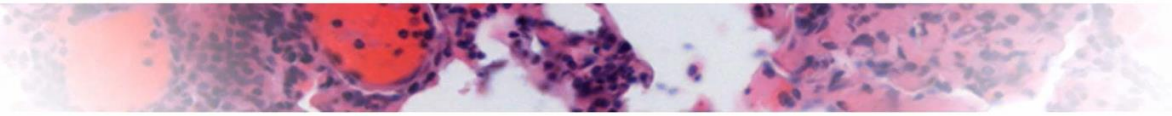
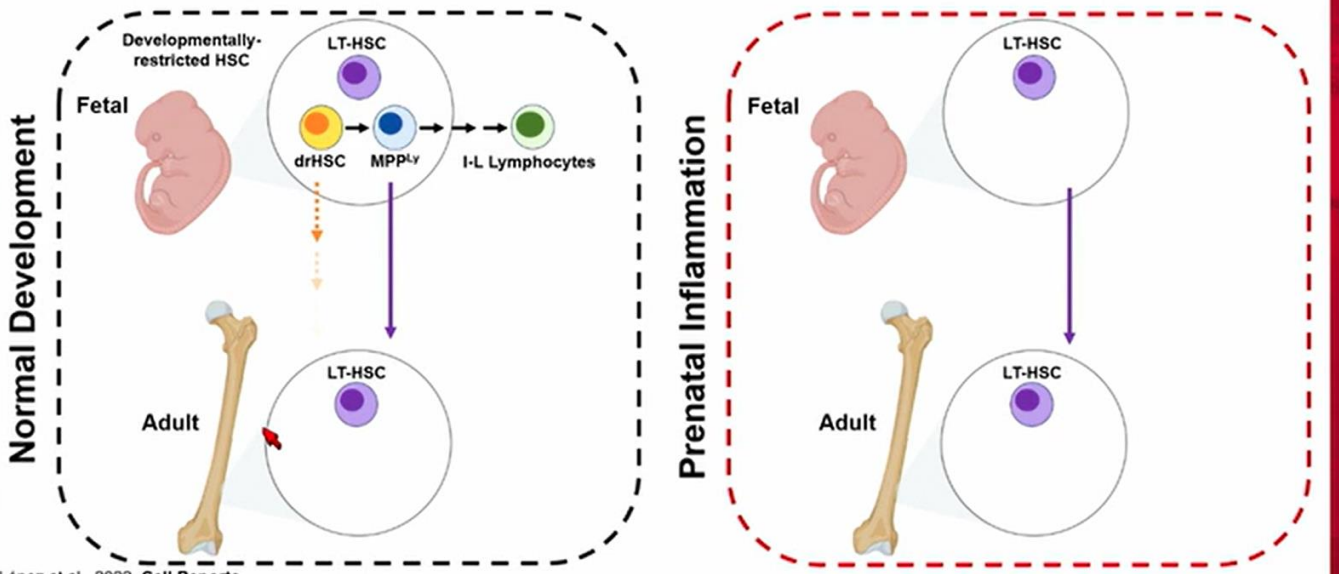


Metabolic Programming of Hematopoietic Stem Cell Function by Prenatal Folate

Brian Krum

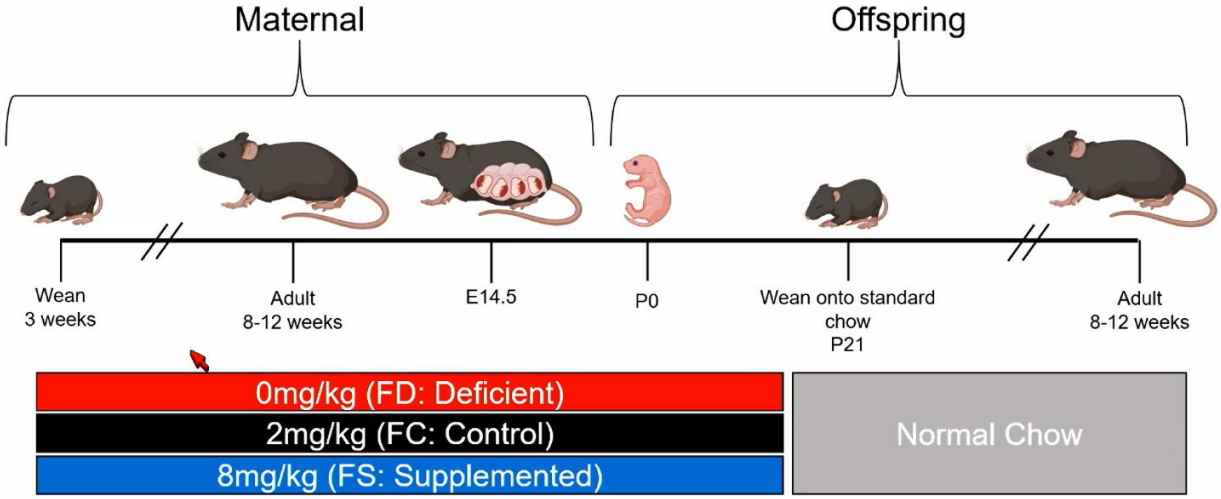
Trista E. North, PhD
Boston Children's Hospital, Harvard Medical School

Adult hematopoiesis is developmentally programmed by prenatal inflammation

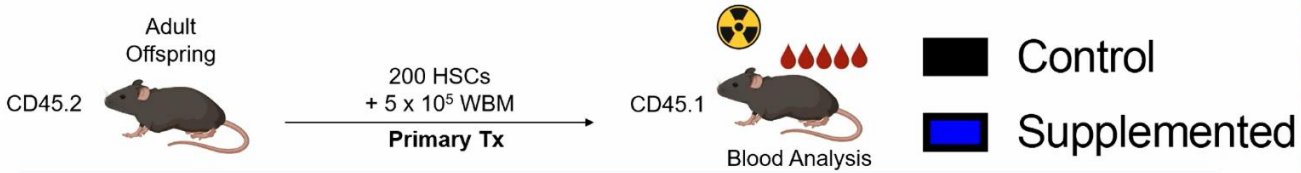


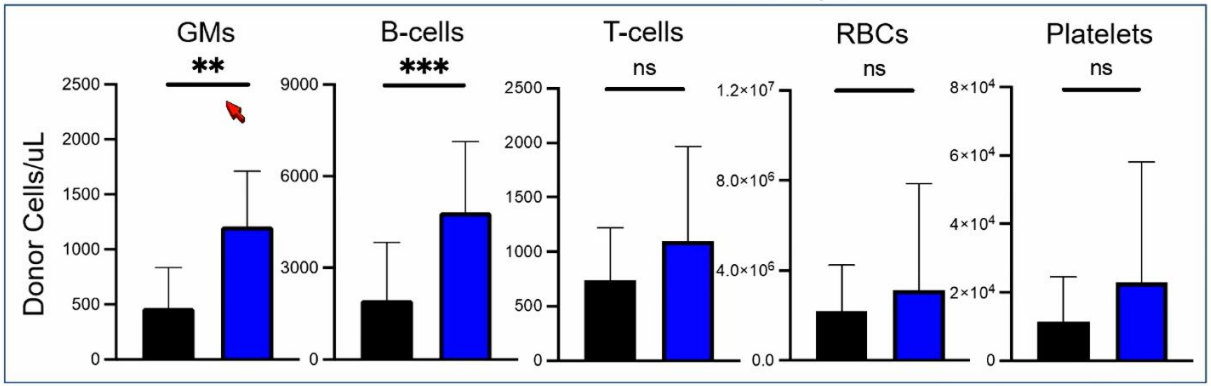
López et al., 2022, **Cell Reports**
Beaudin et al., 2016, **Cell Stem Cell**
Beaudin and Forsberg, 2018, **Blood**
Apostol, Jensen and Beaudin, 2020, **Frontiers of Immunology**

Investigating the effects of prenatal folate status on hematopoiesis in offspring

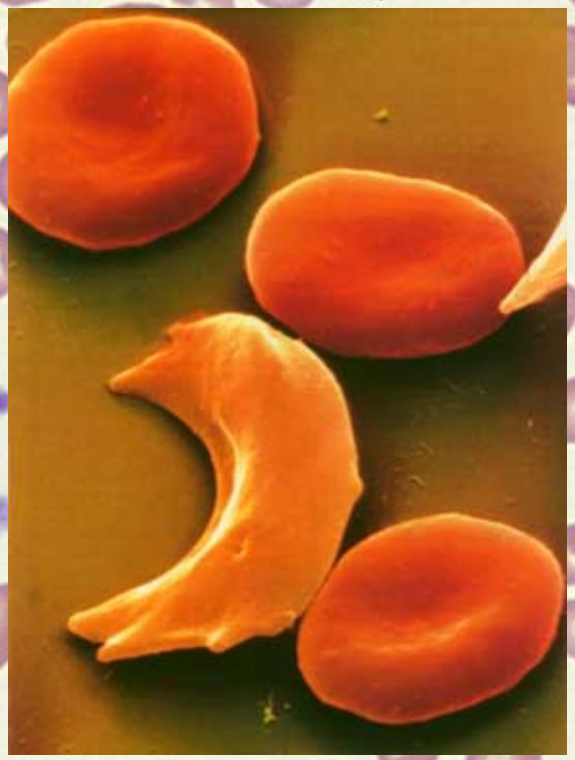


Persistent hematopoietic changes are programmed in adult HSCs by prenatal folate





Unpublished data



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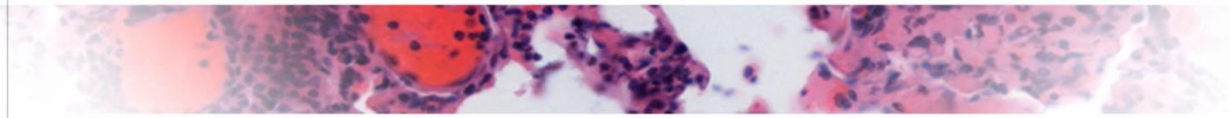


Hydroxyurea Dose Optimization is Safe and Improves Outcomes for Children with Sickle Cell Anemia Living in Sub-Saharan Africa: The REACH Experience

Banu Aygun, MD

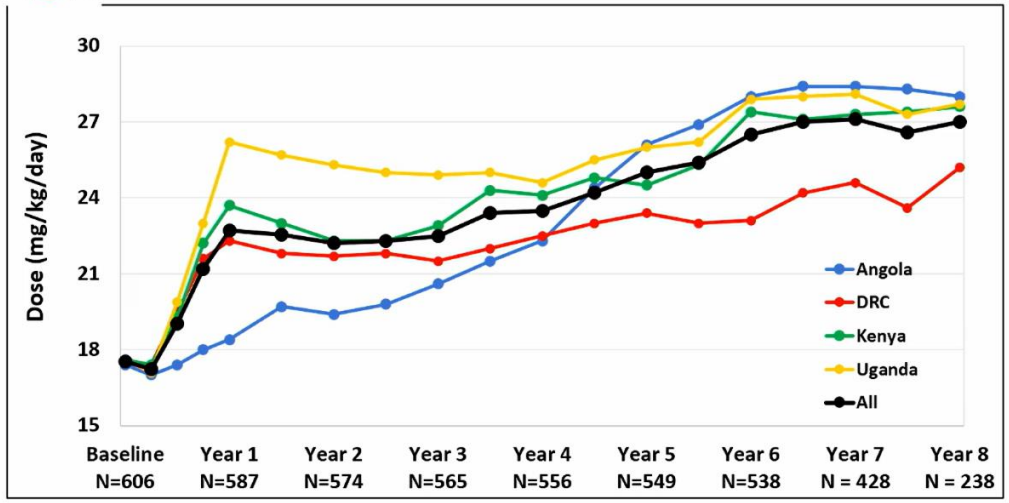
Isaac Odame, MD

The Hospital for Sick Children; University of Toronto

Current Study Objectives

- Treatment effects over time
  - Laboratory parameters
  - Clinical outcomes
- Comparison of hydroxyurea dosing phases
  - Screening (2 months), pre-treatment
  - Fixed dose phase (0-6 months) at 15-20 mg/kg/day
  - Dose escalation phase (7-24 months), increase to MTD
  - MTD phase (>24 months), dose optimization

Hydroxyurea Dose Over Time



	Fixed Dose	MTD		
Clinical Events	Rate	Rate	IRR	p-value
Painful Events	72.7	43.6	0.60	<0.001
Acute Chest	10.0	2.1	0.21	<0.001
Primary Stroke	0.35	0.18	0.52	0.55
Secondary Stroke	18.6	4.5	0.27	0.061
Malaria	32.8	18.8	0.58	<0.001
Non-malarial infections	124.9	64.8	0.52	<0.001
Serious Adverse Events	7.7	3.1	0.42	0.0003
Death	1.3	0.9	0.70	0.50

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Reduced Intensity Conditioning for Haploidentical Bone Marrow Transplantation in Adults with Symptomatic Sickle Cell Disease: BMT CTN 1507

Adetola A. Kassim, MBBS, MS
Hematology/Stem cell Transplant
Vanderbilt University Medical Center
Vanderbilt-Meharry Center for Excellence in Sickle Disease

Engraftment

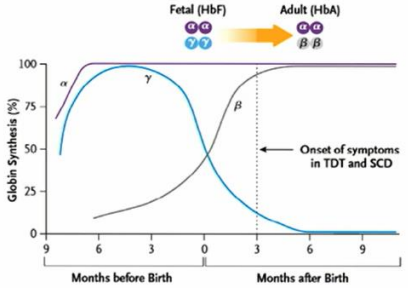
- Cumulative incidence of neutrophil recovery at 42 days
  - 92.9% (95% CI: 77.4%, 97.9%)
- Cumulative incidence of platelet recovery to 50k was
  - at 60 days 88.1% (95% CI: 72.6%, 95.1%)
  - at 100 days 92.9% (95% CI: 77.4%, 97.9%)
- **On Day 28, 88.1% achieved full donor chimerism (donor >95%), and 4.8% had low chimerism (donor <5%)**

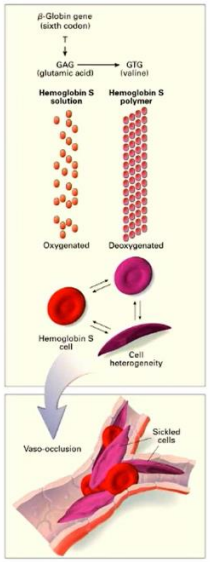
Conclusion

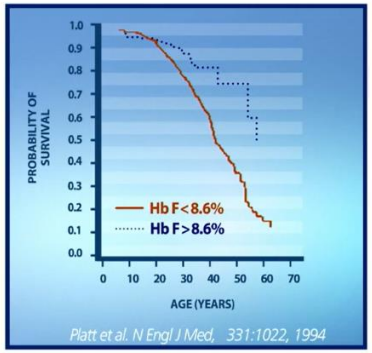
- Reduced intensity haploidentical-BMT in adults with SCD shows durable donor engraftment at 2 years with low mortality.
- The 2-year EFS 88% and OS 95% are comparable to that reported after MSD myeloablative BMT.
- These results support haploidentical BMT with PTCy as a suitable and tolerable curative therapy for adults with SCD and severe end-organ toxicity such as stroke and pulmonary hypertension, a population typically excluded from participating in myeloablative gene therapy and gene editing trials.

Benefits of fetal hemoglobin (HbF) in sickle cell disease

- Naturally occurring mutations produce hereditary persistence of fetal hemoglobin
- Absence of SCD symptoms in newborn period
- HbF expression effective treatment strategy
- Hemoglobin switching to design effective treatment for SCD



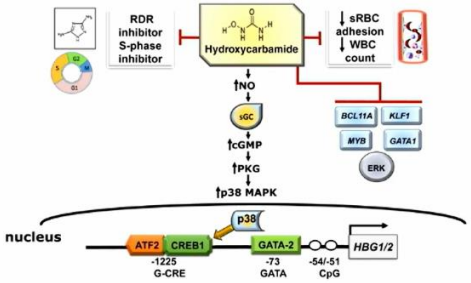




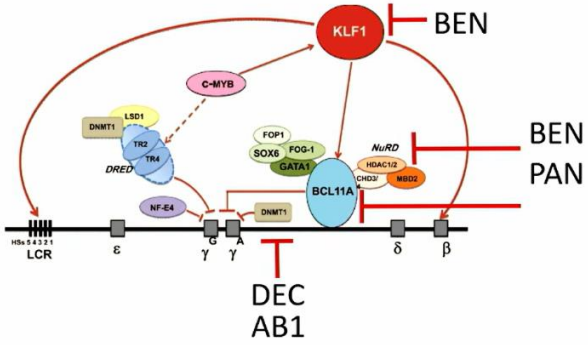
H Frangoul et al. N Engl J Med 2021;384:252-260.

Clinical trials for small molecule drug development

- Epigenetic modifiers – HDAC & DNMT1 inhibitors
- Cell signaling pathways/kinases – p38, ERK MAPK, cGMP, HRI, etc.
- Hydroxyurea standard of care in SCD



Pace et al. BJH 2021

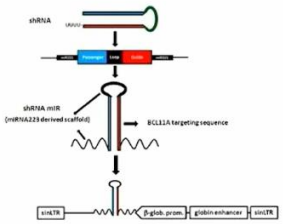


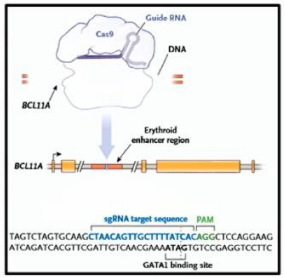
Clinical trials in progress

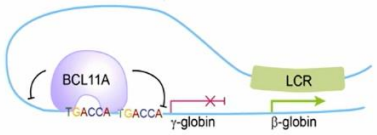
- Decitabine/THU (DEC)
- AB1 (Shah et al ASH 2023)
- Benserazide (BEN)
- Panobinostat (PAN)
- FTX-6058 (PRC2 inhibitor)

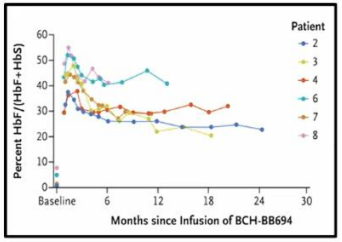
Gene therapy targeting *BCL11A* to induce fetal hemoglobin

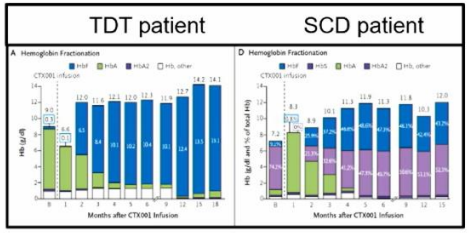
- GWAS identified BCL11A as HbF modifier (Uda et al PNAS, 2008)
- BCL11A – repressor of γ-globin (Sankaran et al Science 2008)
- Erythroid enhancer region (Bauer et al Science 2013)
- Strategies for *BCL11A* gene silencing:
  - ✓ Lentivirus shRNA BCL11A vector
  - ✓ CRISPR-Cas9 gene editing











EB Esrick et al. N Engl J Med 2021;384:205-215.

H Frangoul et al. N Engl J Med 2021;384:252-260.

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Targeted Degradation of the WIZ Transcription Factor for Gamma Globin De-repression

Pamela Y. Ting, PhD
Novartis Institutes for BioMedical Research

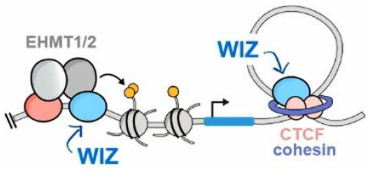
Betty S. Pace, MD
Augusta University

WIZ degradation results in selective gene activation with associated decrease in repressive histone marks

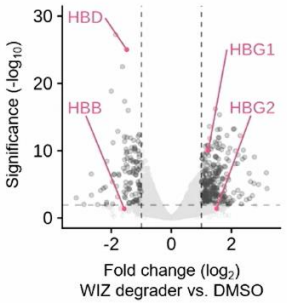
WIZ is a transcription factor

Ubiquitously expressed and resides in the nucleus

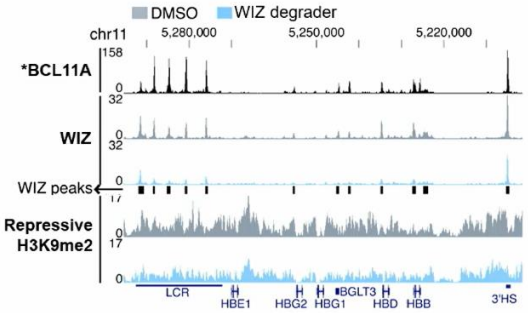
Associates with complexes involved in histone methylation and DNA looping



Transcriptome changes



WIZ binds in the β-globin locus



CD34+ HSPC from healthy human donors were treated with dWIZ-2 and erythroid differentiated for 4-7 days *in vitro*
*BCL11A CUT&RUN data from Liu et al *Cell*. 2018 Apr 5; 173(2): 430–442.e17

Phenotypic screen of CRBN-biased library identified dWIZ-1, a small molecule fetal hemoglobin (HbF) inducer

High-throughput flow cytometry screen in primary human erythroblasts

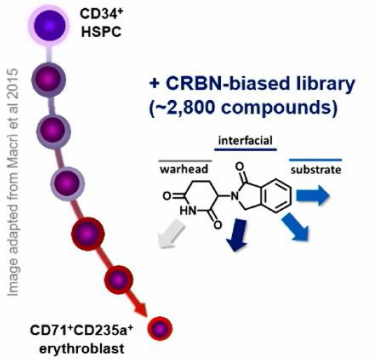
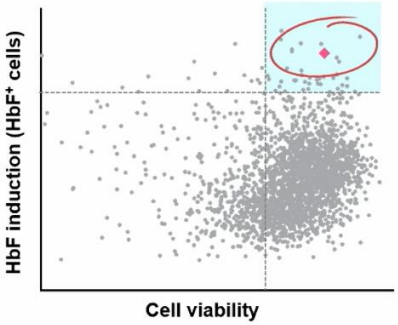
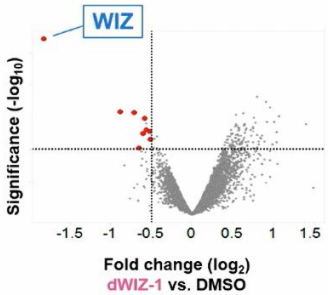


Image adapted from Macari et al 2015

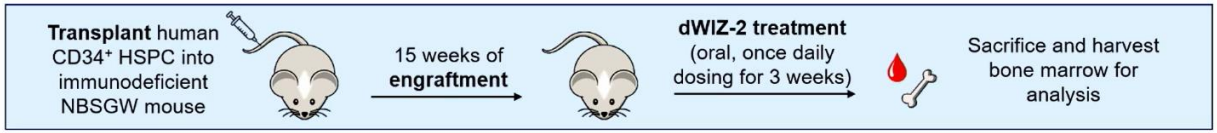
Chemical hits that induce HbF while sparing cell growth & differentiation

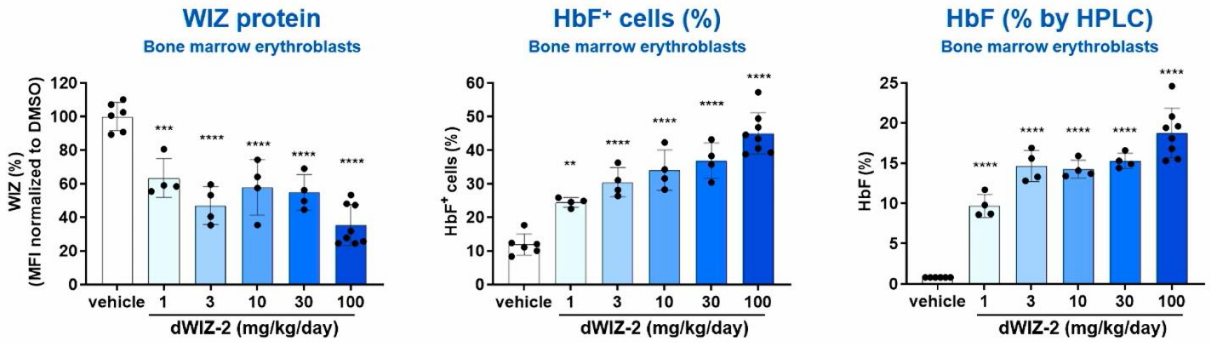


Global proteomics identifies potential target



dWIZ-2 induces HbF in a mouse xenotransplantation model





Data are presented as mean and standard deviation. Each point represents one mouse. Statistical significance in reference to vehicle control was determined by one-way ANOVA with Dunnett's multiple comparisons. P values: ≤ 0.001 (***); ≤ 0.0001 (****).

Moderate Incidence but striking Correlation with TBI of Secondary Malignancies after HSCT in Children with ALL: Long-term Follow-Up from the Prospective International BFM- and FORUM-Trials

A. Lawitschka

St. Anna Children ‘s Hospital

Children ‘s Cancer Research Institute

Vienna, Austria

U. Pötschger, J-H. Dalle, H. Arnardottir, P. Sedlacek, J. Buechner, M. Ifversen, P. Svec, T. Güngör, J. Toporski, C. Diaz-de-Heredia, M. Bierings, R. Meisel, M. Ansari, A. Balduzzi, F. Locatelli, C. Peters and P. Bader

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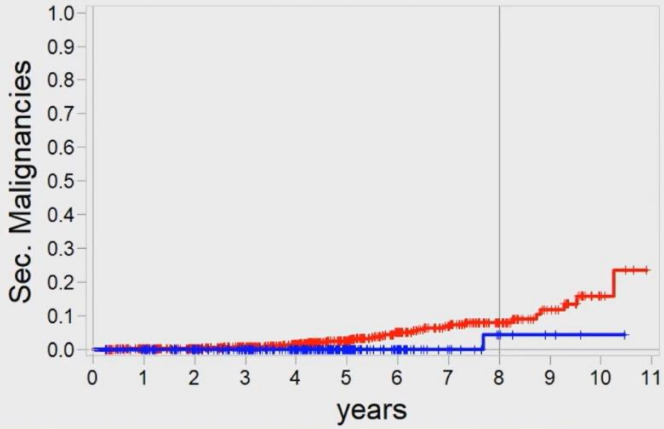
Significant Correlation of SM with TBI



p= 0.004

		Relapses		NRM		Secondary malignancies		
	N	Relapse	8-y CIR	Death	8-y NRM	SM	8-y SM	8-y EFS
TBI	1429	253	0.21±0.01	108	0.09±0.01	41	0.08±0.02	0.62±0.02
CHC	722	256	0.38±0.02	68	0.10±0.01	1	0.04±0.04	0.48±0.05
p-value			<0.001		0.244		0.004	<0.001

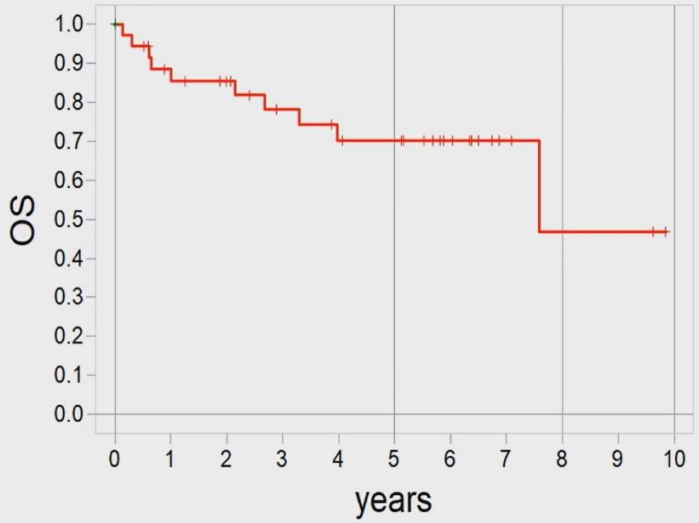
Type of SM

* If n <= 3: individual values are given

	Total		Post relapse	HSCT to SM years, med. (range)*	Age at HSCT							
					<=2 y		2-4 y		4-10 y		> 10 y	
	46		4	5.12 (0.4-13.4)	0		4		20		22	
Thyroid cancer	18	39%	1	5.8 (3.3-11.3)			3	75%	11	55%	4	18%
MDS	4	9%		4.3 (0.4-5.0)			0	0%	1	5%	3	14%
Osteosarcoma	4	9%		7.4 (3.5-8.8)			1	25%	1	5%	2	9%
Basal cell carcinoma	3	7%		5,5 /6.9 /9,5					1	5%	2	9%
Glioblastoma	3	7%		6.4 /6.5 /8.7					1	5%	2	9%
Melanoma	3	7%	1	0.4 /1.1 /2.2					1	5%	2	9%
Breast cancer	2	4%	2	0.5 /1.6					0	0%	2	9%
Colon cancer	2	4%		3.6 /3.9					2	10%	0	0%
AML	1	2%		2.6					0	0%	1	5%
Ewing sarcoma	1	2%		2.3					0	0%	1	5%
Hodgkin lymphoma	1	2%		4.6					0	0%	1	5%
Inflammatory myofibroblastic tumor	1	2%		2.1					1	5%	0	0%
Parotid carcinoma	1	2%		5.2					1	5%	0	0%
Rhabdomyosarcoma	1	2%		5.1					0	0%	1	5%
Squamous cell carcinoma	1	2%		13.4					0	0%	1	5%

OS of patients with SM

5-y OS	8-y OS	10-y OS
0.70±0.09	0.47±0.20	0.47±0.20



- All patients with glioblastoma died within 10 months after diagnosis of SM
- 17/18 (94%) of the patients with thyroid cancer were alive at last FU (1-10 y)

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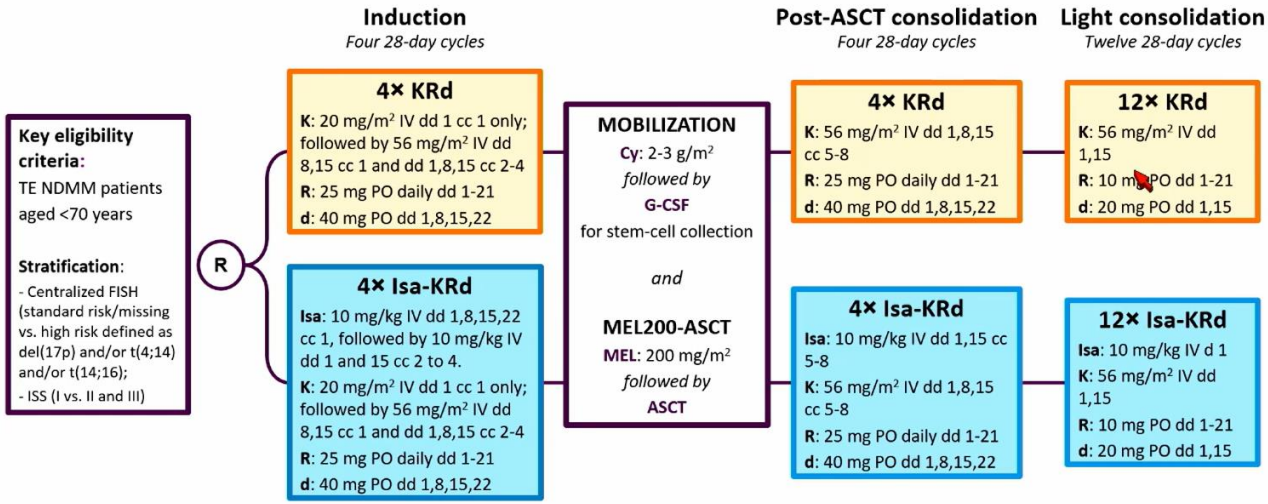
Results of the Phase III Randomized Iskia Trial: Isatuximab-Carfilzomib-Lenalidomide-Dexamethasone vs Carfilzomib-Lenalidomide-Dexamethasone as Pre-Transplant Induction and Post-Transplant Consolidation in Newly Diagnosed Multiple Myeloma Patients

Francesca Gay, M.D., Ph.D.

Peter Voorhees, M.D.
Levine Cancer Institute
Atrium Health Wake Forest Baptist Comprehensive Cancer Center

IsKia EMN24 Study Design

42 active sites; enrollment: Oct 7, 2020 – Nov 15, 2021



The EMN24 IsKia trial is registered with ClinicalTrials.gov: NCT04483739; it was sponsored by the European Myeloma Network (EMN).
All patients provided informed consent. This presentation includes discussion of the off-label use of a drug or drugs for the treatment of multiple myeloma.

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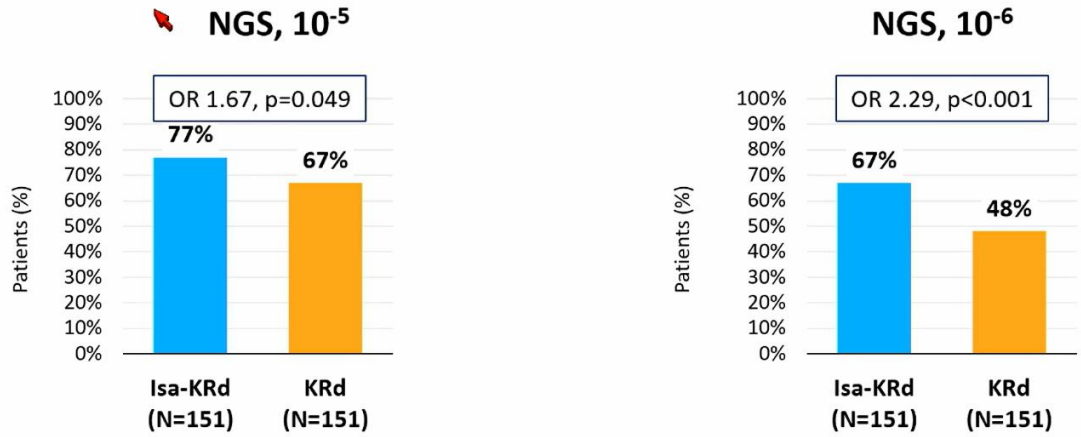
TE, transplant-eligible; NDMM, newly diagnosed multiple myeloma; FISH, fluorescence *in situ* hybridization; del, deletion; t, translocation; ISS, International Staging System stage; R, randomization; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; IV, intravenous; dd, days; cc, cycles; PO, orally; Cy, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; MEL, melphalan; ASCT, autologous stem-cell transplantation; MRD, minimal residual disease; NGS, next-generation sequencing; PFS, progression-free survival.

Primary Endpoint: Post-consolidation MRD negativity (ITT analysis)



≥VGPR after consolidation was 94% in both arms; ≥CR 74% vs 72% and sCR 64% vs 67% in the IsaKRd vs KRd arms.
High MRD compliance and sample quality (97-100% of sample evaluable at 10^{-5} and 10^{-6} cut-offs).
Consistent MRD results were detected by next-generation flow
In the logistic regression analysis, ORs, 95% CIs, and p-values were adjusted for stratification factor.

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MRD, minimal residual disease; ITT, intention to treat; NGS, next-generation sequencing; OR, odds ratio; p, p-value; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; CI, confidence interval.

Conclusions

- **Isa-KRd significantly increased post-consolidation 10^{-5} and 10^{-6} MRD negativity,** as compared with KRd
- Isa-KRd significantly increased **10^{-5} and 10^{-6} MRD negativity after each treatment phase** (Induction, Transplantation, Consolidation) .
- Isa-KRd consistently increased MRD negativity at 10^{-5} and 10^{-6} in all subgroups of patients, including **high-risk and very high-risk disease**.
- **Isa-KRd** treatment was **tolerable**, with a toxicity profile similar to that in previous reports.
- **10^{-6} MRD negativity cut-off** is more informative.
- 1-year sustained MRD negativity will be available in 2024
- **With a longer follow-up**, this trial can offer the opportunity to explore the **correlation** between depth of **MRD negativity and PFS/OS**.

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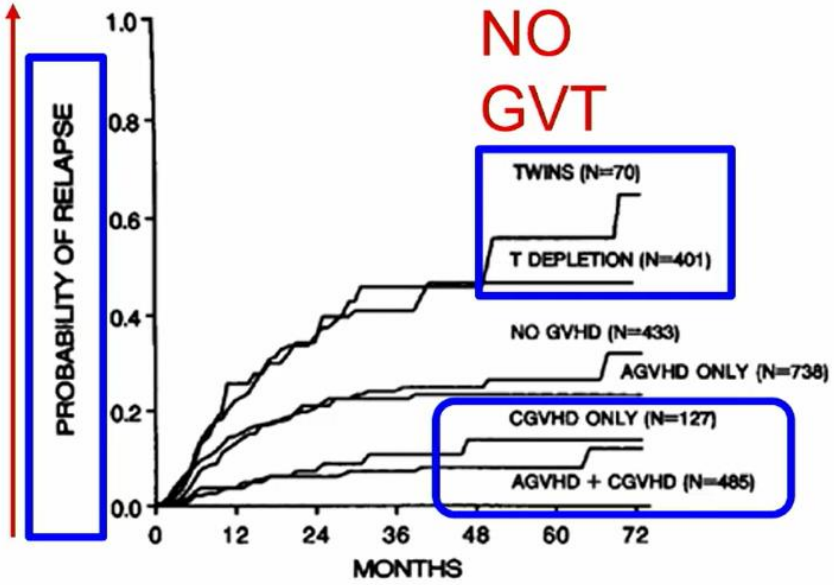
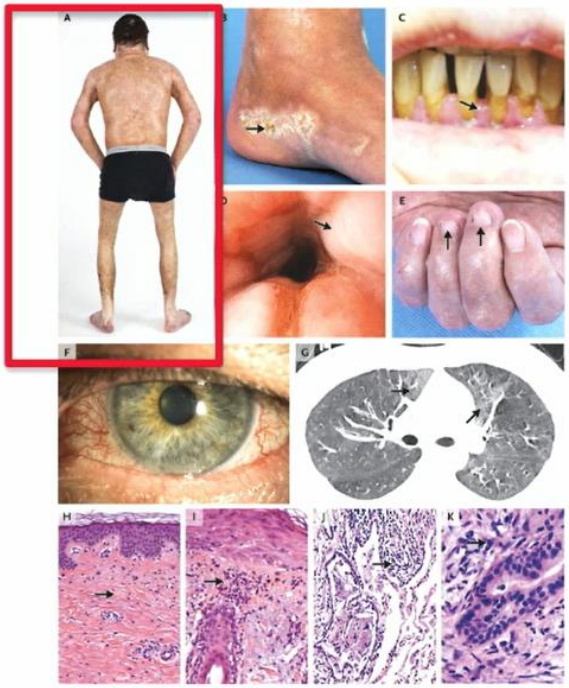
Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; MRD, minimal residual disease; PFS, progression-free survival; OS, overall survival.

Chronic GVHD <–> Cancer Cure

Prevalence ~50+K patients worldwide



Horowitz MM, Gale RP, Paul M, et al. Blood. 1990;75:555-62.



Zeiser R et al. N Engl J Med N Engl J Med 2017; 377:2565-2579.

Safety and Efficacy of Axatilimab at 3 Different Doses in Patients with Chronic Graft-Versus-Host Disease (AGAVE-201)

Daniel Wolff*, MD, PhD; Corey Cutler,* MD, MPH, FRCPC; Stephanie J. Lee, MD, MPH; Iskra Pusic, MD; Henrique Bittencourt MD, PhD; Jennifer White MD, MSc, FRCPC; Mehdi Hamadani MD; Sally Arai, MD; Amandeep Salhotra, MD; Jose A. Perez-Simon, MD; Amin Alousi, MD; Hannah Choe, MD; Mi Kwon, MD; Arancha Bermúdez, MD; Inho Kim, MD, PhD; Gerard Socie, MD, PhD; Vedran Radojcic, MD; Timothy O'Toole, MS; Chuan Tian, PhD; Peter Ordentlich, PhD; Zachariah DeFilipp,† MD; and Carrie L. Kitko,† MD

*/†Authors contributed equally to this work.

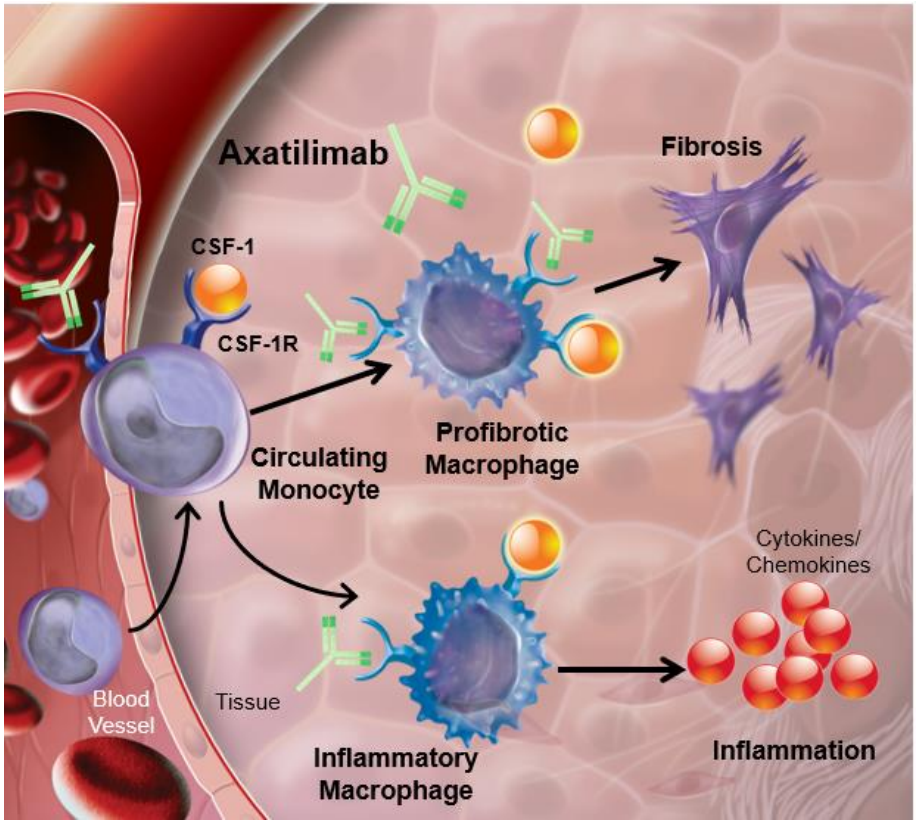
ASH Plenary Session, December 10, 2023

Axatilimab Targets Key Mediators of cGVHD Pathology

- CSF-1R–dependent monocytes and macrophages mediate inflammation and fibrosis[1,2]
- Axatilimab is an investigational monoclonal antibody that targets CSF-1R on monocytes and macrophages[2]
- Axatilimab has shown favorable safety and promising efficacy in recurrent/refractory cGVHD, with an ORR of 67% in the first 6 cycles[2]

cGVHD, chronic graft-versus-host disease; CSF-1R, colony-stimulating factor 1 receptor; ORR, overall response rate.

Axatilimab Mechanism of Action[1-3]



1. MacDonald et al. *Blood.* 2017;129:13-21. **2.** Kitko et al. *J Clin Oncol.* 2022;41:1864-1875. **3.** Jardine et al. *J Clin Invest.* 2020;130:4574-4586.

AGAVE-201: Study Design and Methods

Key eligibility criteria

- Age ≥2 years with ≥2 prior lines of systemic therapy
- Active cGVHD defined per 2014 NIH Consensus Criteria[1]
- Concomitant use of corticosteroids (65%), calcineurin inhibitors (28%), or mTOR inhibitors (12%) was allowed but not required
- No additional systemic cGVHD therapy was allowed

Primary endpoint

- ORR in the first 6 cycles as defined by NIH 2014 Consensus Criteria[1]
- Endpoint was met if lower bound of 95% CI >30%

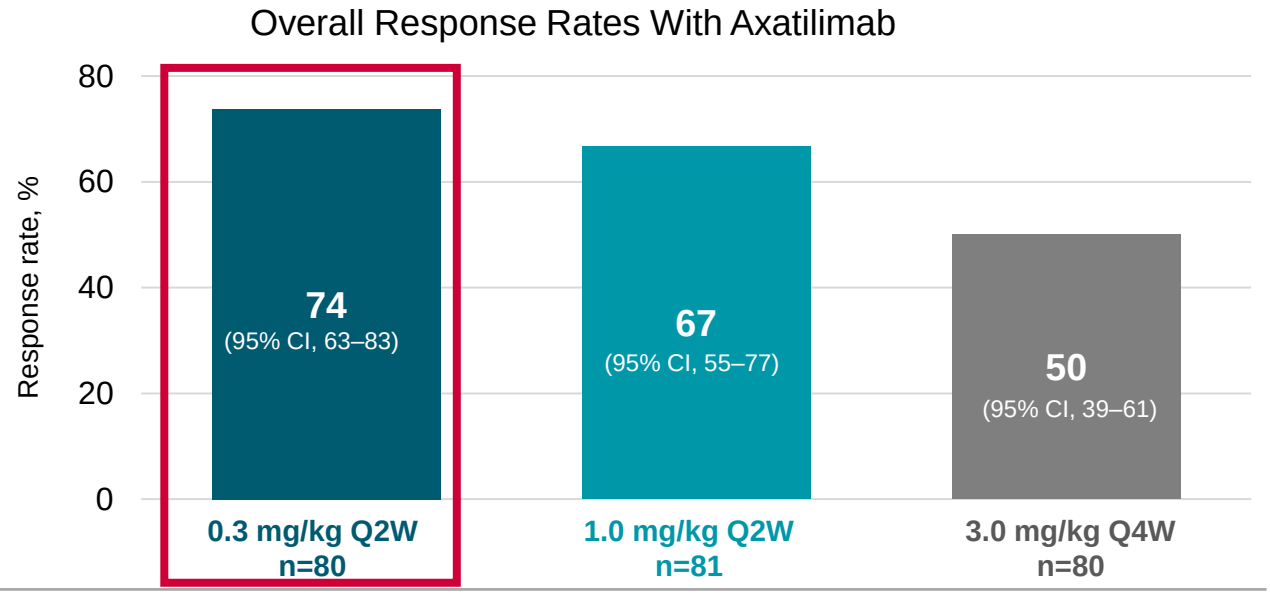
Secondary and exploratory endpoints

- Clinically meaningful improvement in mLSS (≥7 points)
- Organ-specific response rates, DOR, FFS, OS
- Safety

DOR, duration of response; FFS, failure-free survival; mLSS, modified Lee Symptom Scale; mTOR, mammalian target of rapamycin; NIH, National Institutes of Health; OS, overall survival.

1. Jagasia et al. *Biol Blood Marrow Transplant.* 2015;21:389-401.

Primary Efficacy Endpoint[a] Met in All Cohorts

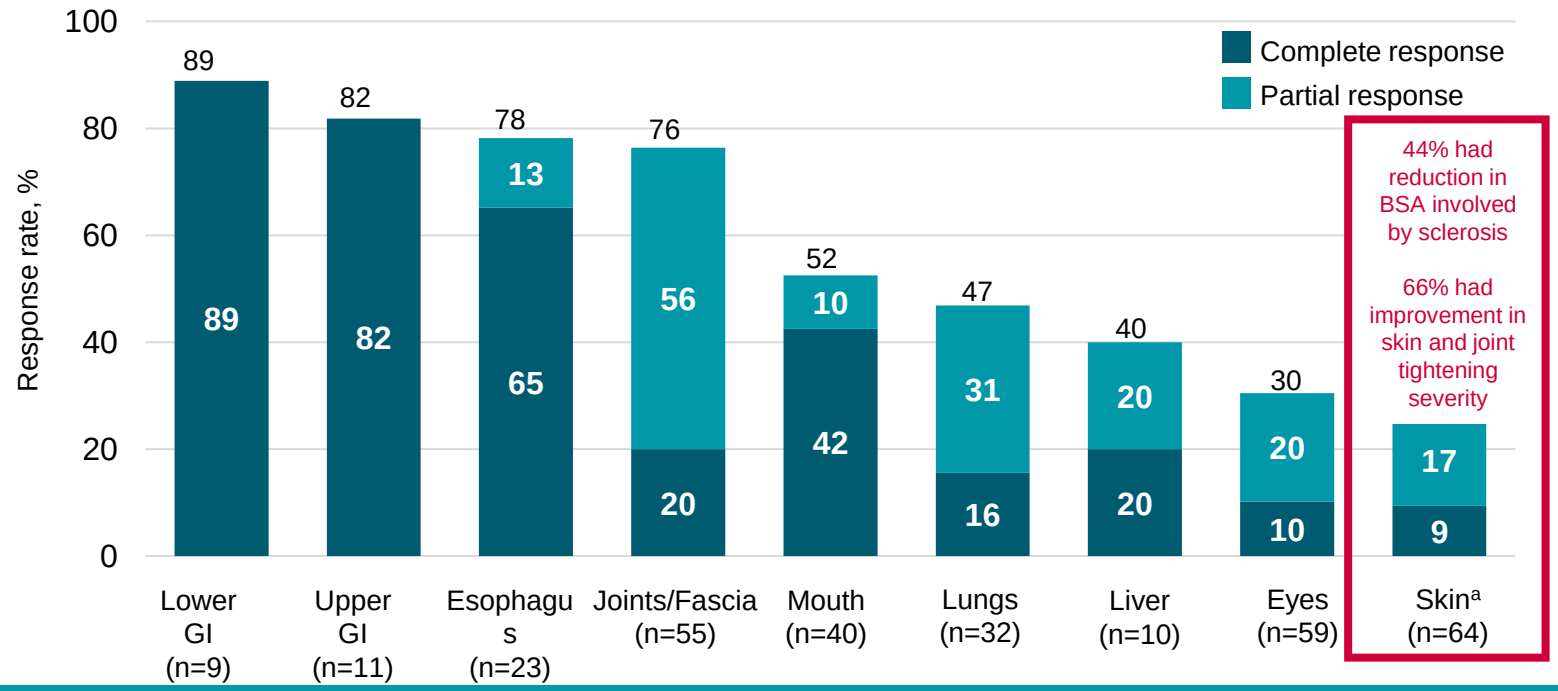


	0.3 mg/kg Q2W n=80	1.0 mg/kg Q2W n=81	3.0 mg/kg Q4W n=80
Time to response, median months (range)	1.7 (0.9–8.1)	1.9 (0.9–8.6)	1.4 (0.9–5.6)
Response maintained for ≥12 months, % (95% CI)	60 (43–74)	60 (43–74)	53 (30–71)

Q2W, every 2 weeks; Q4W, every 4 weeks.
[a]Primary endpoint was overall response rate in the first 6 cycles as defined by NIH 2014 Consensus Criteria.[1]

1. Lee at al. *Biol Blood Marrow Transplant*. 2015;21:984-999.

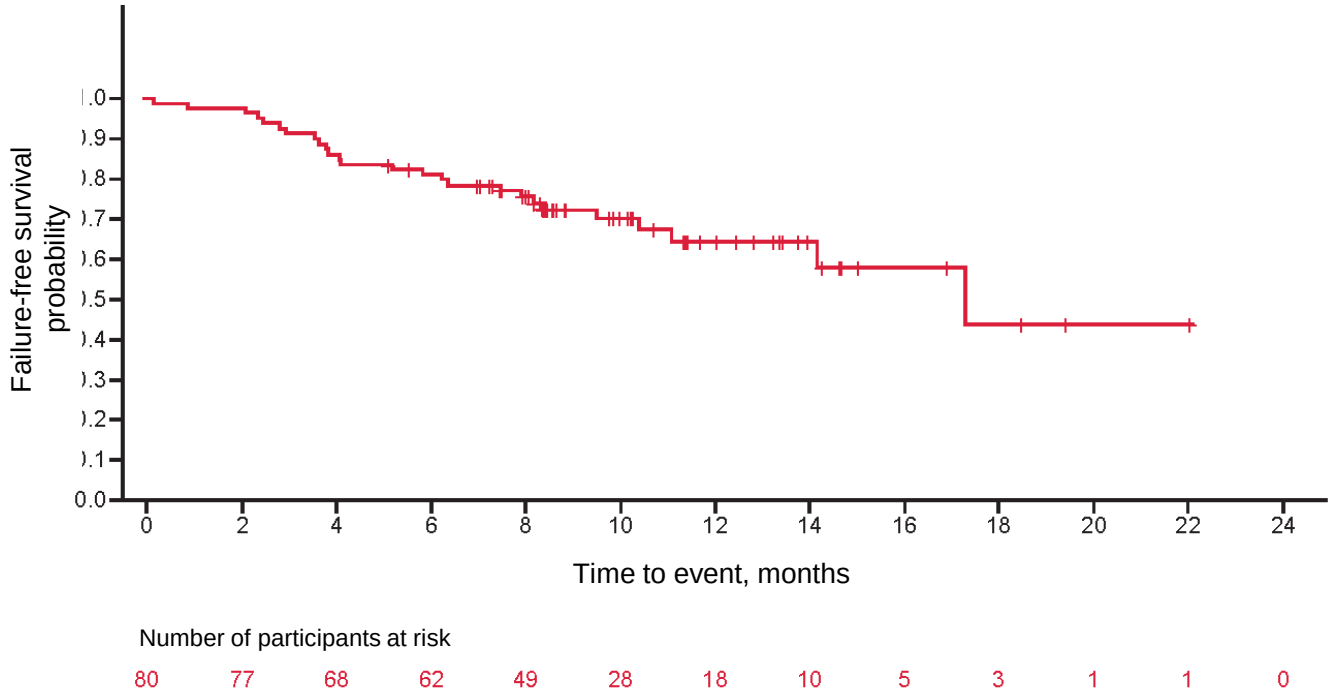
Organ Responses in 0.3 mg/kg Q2W



Responses were notable in fibrosis-dominated organs, including esophagus (78%), joints and fascia (76%), lung (47%), and skin (27%)

BSA; body surface area; GI, gastrointestinal; Q2W, every 2 weeks. [a]Due to rounding, complete response and partial response numbers may not add up to total response rate.

Failure-free Survival[a] in 0.3 mg/kg Q2W



Median FFS was 17.3 (95% CI, 14.2–NE) months

NE, not estimable; Q2W, every 2 weeks.
[a]Defined as time from randomization to death or new systemic cGVHD therapy, where axatilimab dose increase is not considered new therapy.

Conclusions

- Axatilimab at 0.3 mg/kg Q2W is highly effective and has a manageable safety profile in recurrent/refractory cGVHD
- Rapid and durable responses were documented in all organs and patient subgroups
- Significant reduction of symptom burden was reported by most patients, including those with fibrotic cGVHD manifestations
- Adverse events were mostly low grade, reversible, and increased with higher doses
- Unique mechanism of action may represent a new therapeutic strategy in cGVHD

Q2W, every 2 weeks.

Ibrutinib Plus Venetoclax with MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI Flair Study

Peter Hillmen, David Cairns, Adrian Bloor, David Allsup, Kate Cwynarski, Andrew Pettitt, Shankara Paneesha, Christopher Fox, Toby Eyre, Francesco Forconi, Nagah Elmusharaf, Ben Kennedy, John Gribben, Nicholas Pemberton, Oonagh Sheehy, Gavin Preston, Anna Schuh, Dena Howard, Anna Hockaday, Sharon Jackson, Natasha Greatorex, Sean Girvan, Sue Bell, Julia M Brown, Nichola Webster, Surita Dalal, Ruth de Tute, Andrew Rawstron, Piers EM Patten, Talha Munir
on behalf of the NCRI CLL Subgroup.

Abstract No: 631, Oral Presentation, ASH Annual Meeting
Sunday, December 10th 2023

NCRI National Cancer Research Institute

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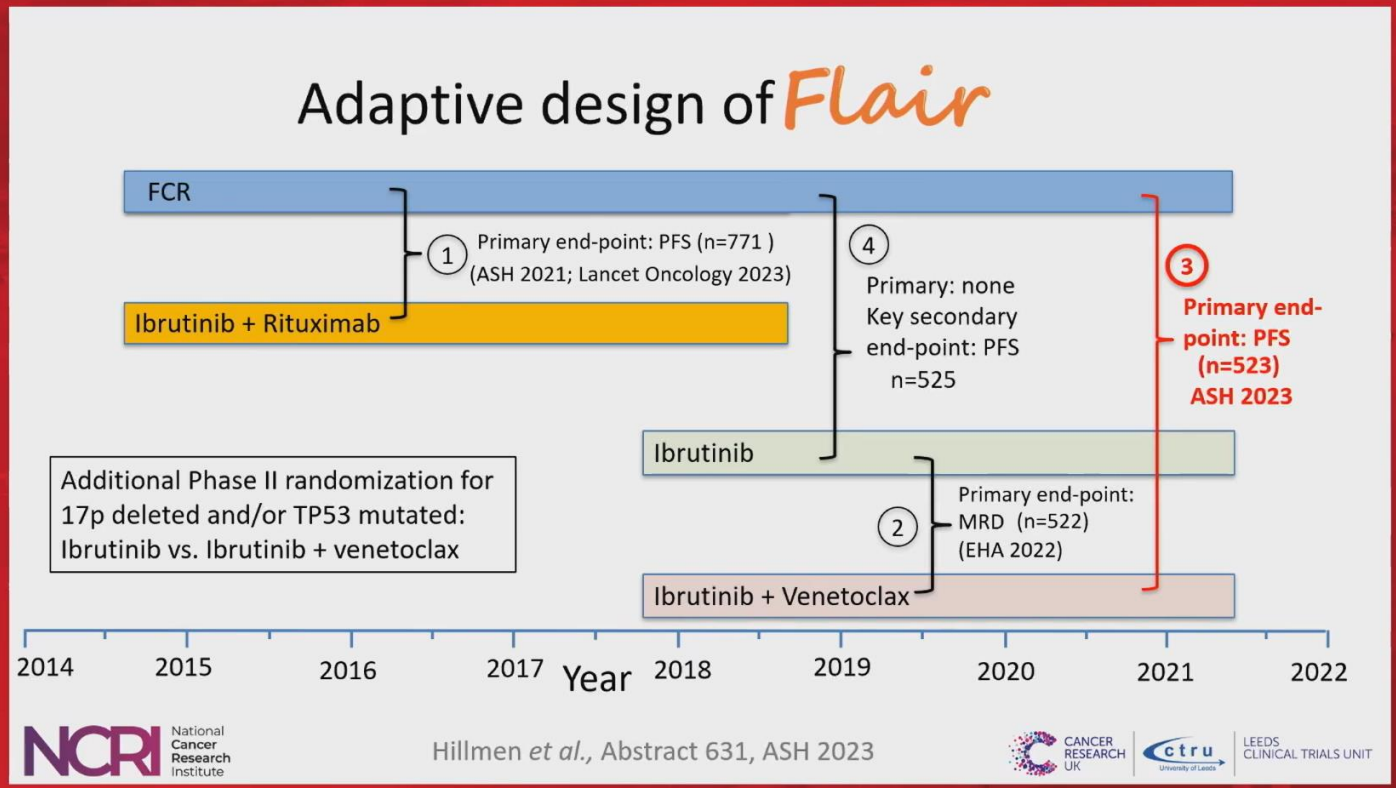
Adaptive design of Flair



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Hillmen *et al.*, Abstract 631, ASH 2023

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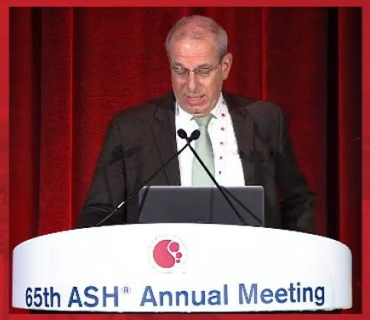
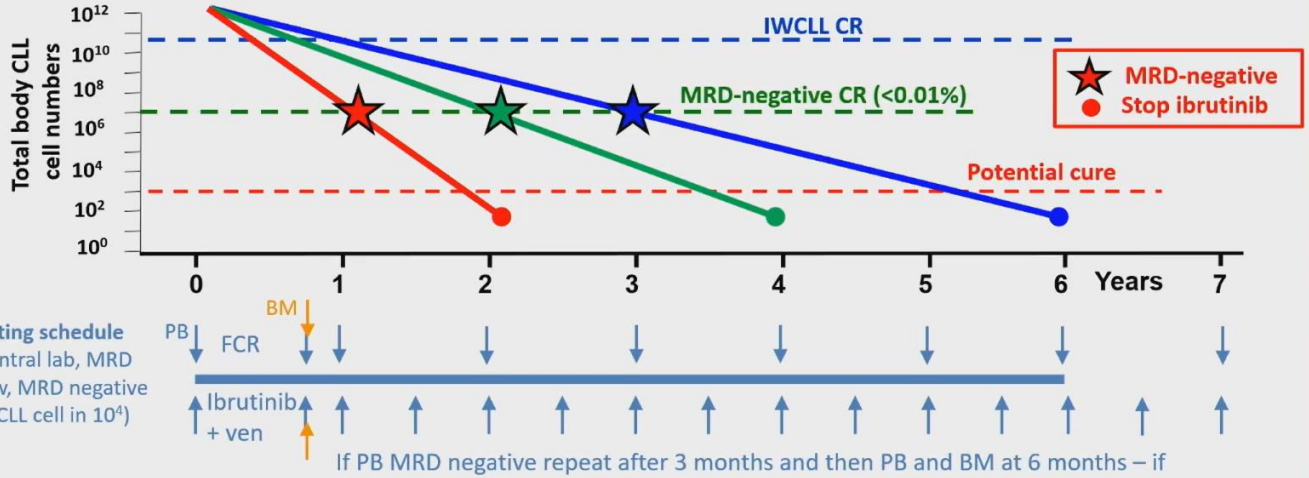


Stopping rules for ibrutinib + venetoclax in Flair



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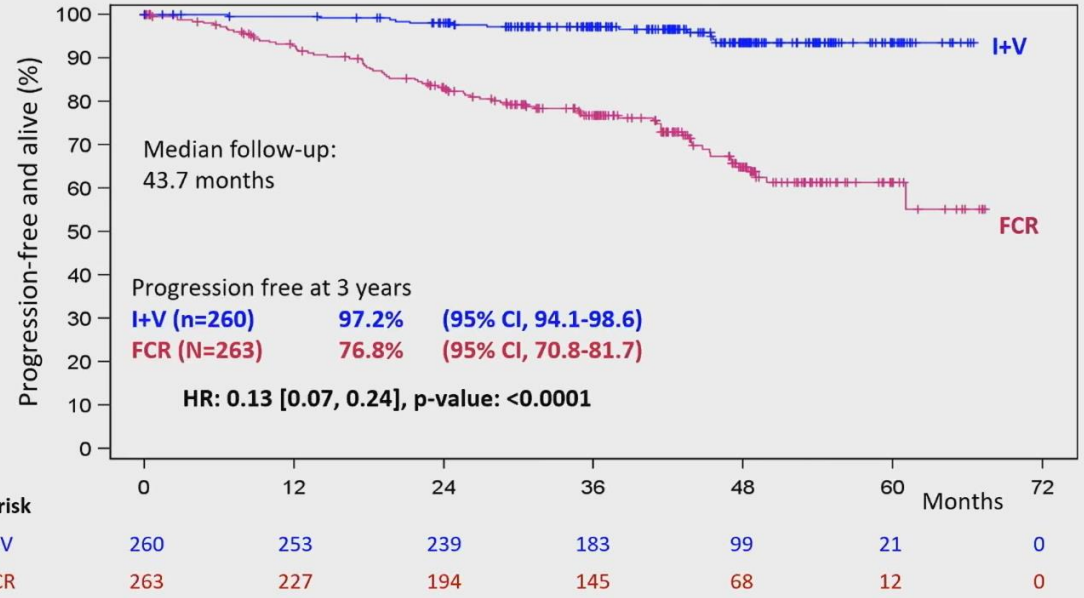
Flair

Primary end-point: PFS for FCR versus I+V



No. at risk							
I+V	260	253	239	183	99	21	0
FCR	263	227	194	145	68	12	0

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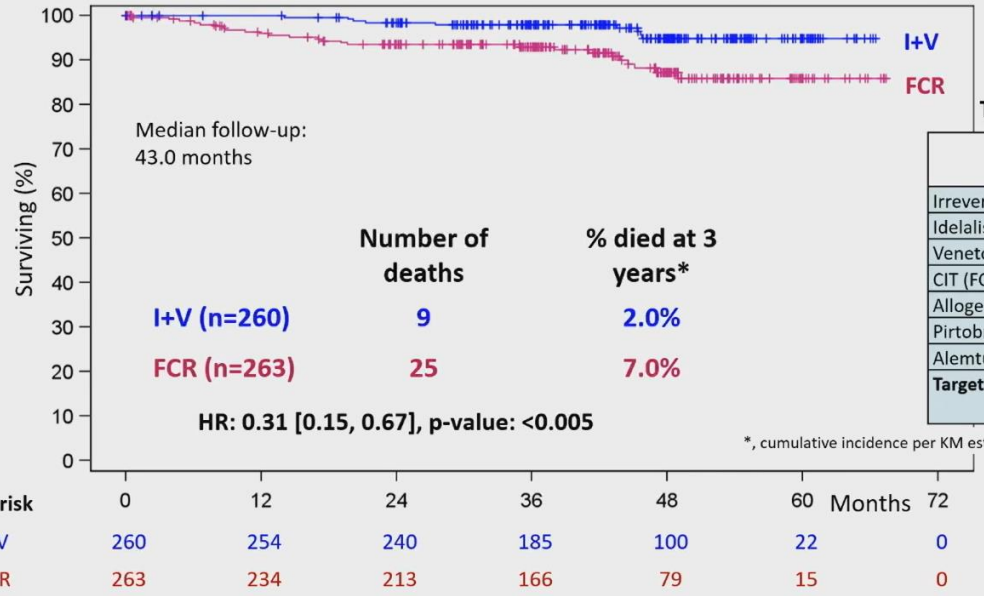
Overall Survival in FCR versus I+V



Treatment after progression

	FCR (n=42)	I+V (n=5)
Irreversible BTKi	23	2
Idelalisib + R	1	0
Venetoclax + R	11	0
CIT (FCR/BR/ChlR)	6	1
Allogeneic SCT	1	0
Pirtobrutinib	0	1
Alemtuzumab	0	1
Targeted therapy for CLL	**35/42 (83%)**	**3/5 (60%)**

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Hillmen *et al.*, Abstract 631, ASH 2023

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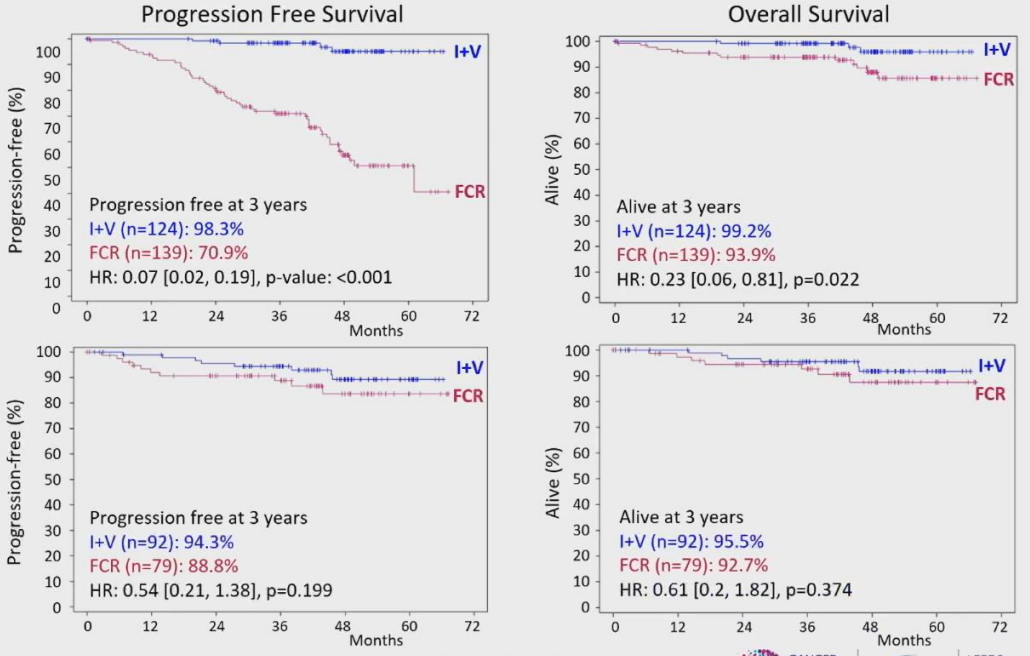
Flair

Outcome by IGHV mutation status



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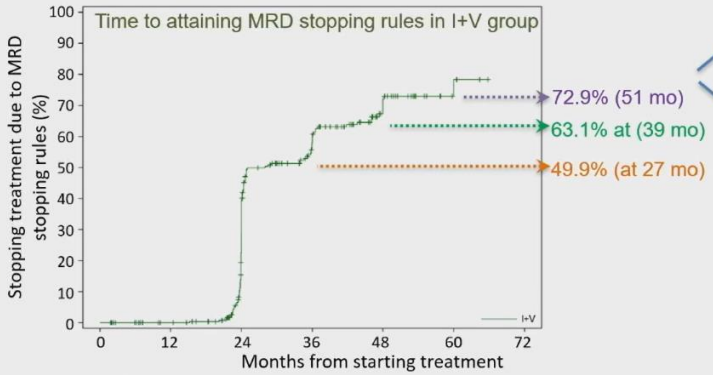
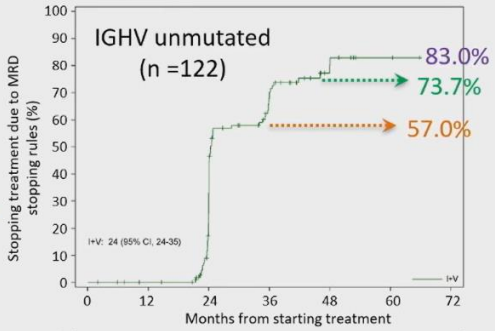
Flair

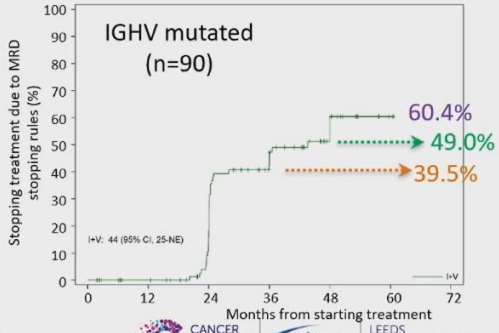
iwCLL response and MRD stopping rules

iwCLL Responses

	Complete Response/CRi		Overall Response		BM uMRD
	9 months	Anytime	9 months	Anytime	Anytime
FCR	49%	71.5%	76.4%	83.7%	40.3%
I+V	59.2%	92.3%	86.5%	95.4%	61.9%
	Odds ratio: 1.51 P<0.05		Odds ratio: 2.0 P<0.005		







National Cancer Research Institute

Hillmen *et al.*, Abstract 631, ASH 2023

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Ibrutinib Combined With Venetoclax in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results From the Randomized Phase 3 SYMPATICO Study

Michael Wang, MD[1], Wojciech Jurczak, MD, PhD[2], Marek Trneny, MD[3], David Belada, MD[4], Tomasz Wrobel, MD, PhD[5], Nilanjan Ghosh, MD, PhD[6], Mary-Margaret Keating, MD[7], Tom van Meerten, MD, PhD[8], Ruben Fernandez Alvarez, MD[9], Gottfried von Keudell, MD, PhD[10], Catherine Thieblemont, MD, PhD[11], Frederic Peyrade, MD[12], Marc Andre, MD[13], Marc Hoffmann, MD[14], Edith Szafer-Glusman, PhD[15], Jennifer Lin, MS, MA[15], James P. Dean, MD, PhD[15], Jutta K. Neuenburg, MD, PhD[15], Constantine S. Tam, MD, MBBS[16]

[1]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Maria Skłodowska-Curie National Research Institute of Oncology, Kraków, Poland; [3]General University Hospital in Prague, Prague, Czech Republic; [4]4th Department of Internal Medicine - Haematology, Charles University, Hospital and Faculty of Medicine, Hradec Králové, Czech Republic; [5]Wrocław Medical University, Wrocław, Poland; [6]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [7]Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada; [8]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [9]Hospital Universitario de Cabueñes, Asturias, Spain; [10]Beth Israel Deaconess Medical Center, Boston, MA, USA; [11]Université de Paris, Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Louis, service d'hémato-oncologie, Paris, France; [12]Centre Antoine Lacassagne, Nice, France; [13]CHU UCL Namur Mont-Godinne, Yvoir, Belgium; [14]University of Kansas Cancer Center, Westwood, KS, USA; [15]AbbVie, North Chicago, IL, USA; [16]Peter MacCallum Cancer Centre, Alfred Health and Monash University, Melbourne, Victoria, Australia

65th ASH Annual Meeting and Exposition; December 9–12, 2023; San Diego, CA, USA

SYMPATICO Study Design

- SYMPATICO (NCT03112174) is multinational, randomized, double-blind, placebo-controlled, phase 3 study

SYMPATICO (N=267)
- Age ≥18 years
- R/R MCL
- 1–5 prior therapies for MCL
- ≥1 prior rituximab/ anti-CD20-containing regimen
- ECOG PS 0–2

Randomized 1:1

Ibrutinib + venetoclax (n=134)
Ibrutinib 560 mg once daily + venetoclax 5-week ramp-up to 400 mg once daily for 24 months

Ibrutinib + placebo (n=133)
Ibrutinib 560 mg once daily + placebo once daily for 24 months

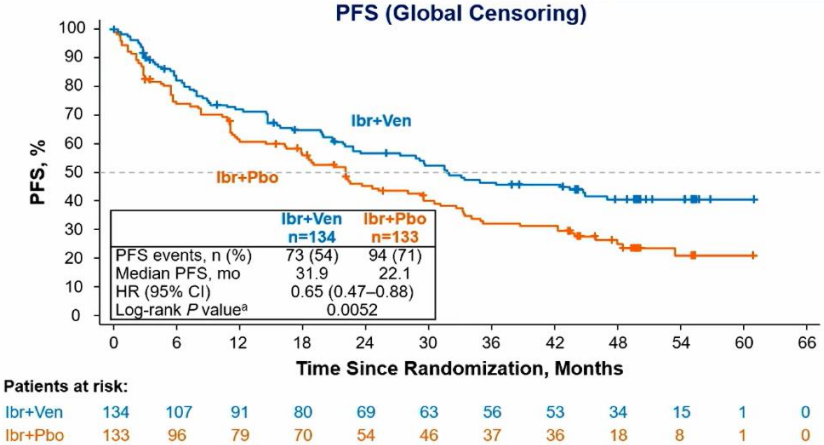
Single-agent ibrutinib 560 mg once daily until PD or unacceptable toxicity

Stratification: ECOG PS, prior lines of therapy, TLS risk[a]

- **Primary endpoint:**
  - PFS by investigator assessment using Lugano criteria
- **Secondary endpoints (tested hierarchically in the following order):**
  - CR rate by investigator assessment
  - TTNT[b]
  - OS (interim analysis)
  - ORR by investigator assessment

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; TLS, tumor lysis syndrome; TTNT, time to next treatment.
[a]Increased TLS risk was defined as at least 1 lesion >10 cm, or at least 1 lesion >5 cm with circulating lymphocytes >25,000 cells/mm^3, and/or creatinine clearance <60 mL/min. [b]For hierarchical testing per US FDA censoring, TTNT was tested after OS.

Primary Endpoint: Investigator-Assessed PFS Was Significantly Improved With Ibrutinib + Venetoclax Versus Ibrutinib + Placebo



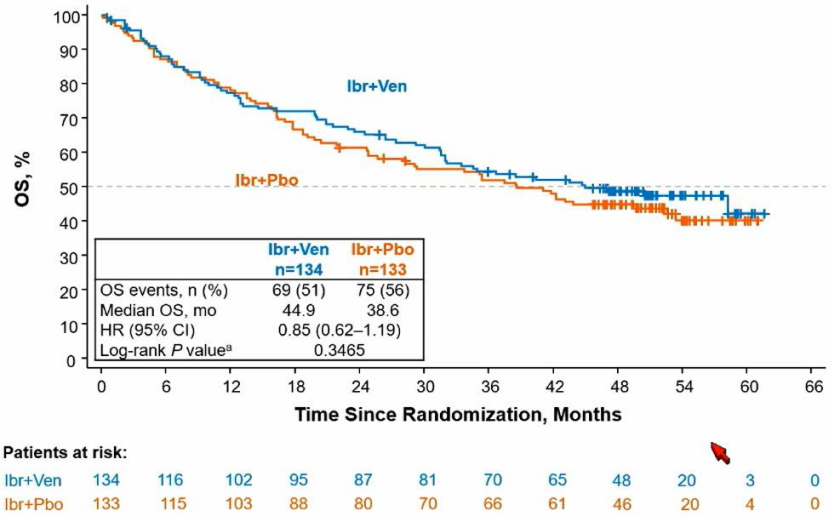
Patients at risk:

Ibr+Ven	134	107	91	80	69	63	56	53	34	15	1	0
Ibr+Pbo	133	96	79	70	54	46	37	36	18	8	1	0

Median PFS, mo	Global Censoring[b]				US FDA Censoring[c]			
	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank *P* value[a]	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank *P* value[a]
Investigator assessment	31.9	22.1	0.65 (0.47–0.88)	0.0052	42.6	22.1	0.60 (0.44–0.83)	0.0021
IRC assessment	31.8	20.9	0.67 (0.49–0.91)	0.0108	43.5	22.1	0.63 (0.45–0.87)	0.0057

HR, hazard ratio; Ibr, ibrutinib; Pbo, placebo; Ven, venetoclax.
[a]*P* values were determined by stratified log-rank test (stratification factors: prior lines of therapy [1–2 vs ≥3] and TLS risk category [low vs increased risk]). [b]Censoring at last non-PD assessment for patients without PD or death. [c]Patients were censored at last non-PD assessment before start of subsequent anticancer therapy or missing ≥2 consecutive visits prior to a PFS event, whichever occurred first.

OS Was Numerically Improved At This Interim Analysis



	Ibr+Ven n=134	Ibr+Pbo n=133
OS events, n (%)	69 (51)	75 (56)
Median OS, mo	44.9	38.6
HR (95% CI)	0.85 (0.62–1.19)	
Log-rank *P* value[a]	0.3465	

Patients at risk:

Ibr+Ven	134	116	102	95	87	81	70	65	48	20	3	0
Ibr+Pbo	133	115	103	88	80	70	66	61	46	20	4	0

[a]*P* values were determined by stratified log-rank test (stratification factors: prior lines of therapy [1–2 vs ≥3] and TLS risk category [low vs increased risk]).

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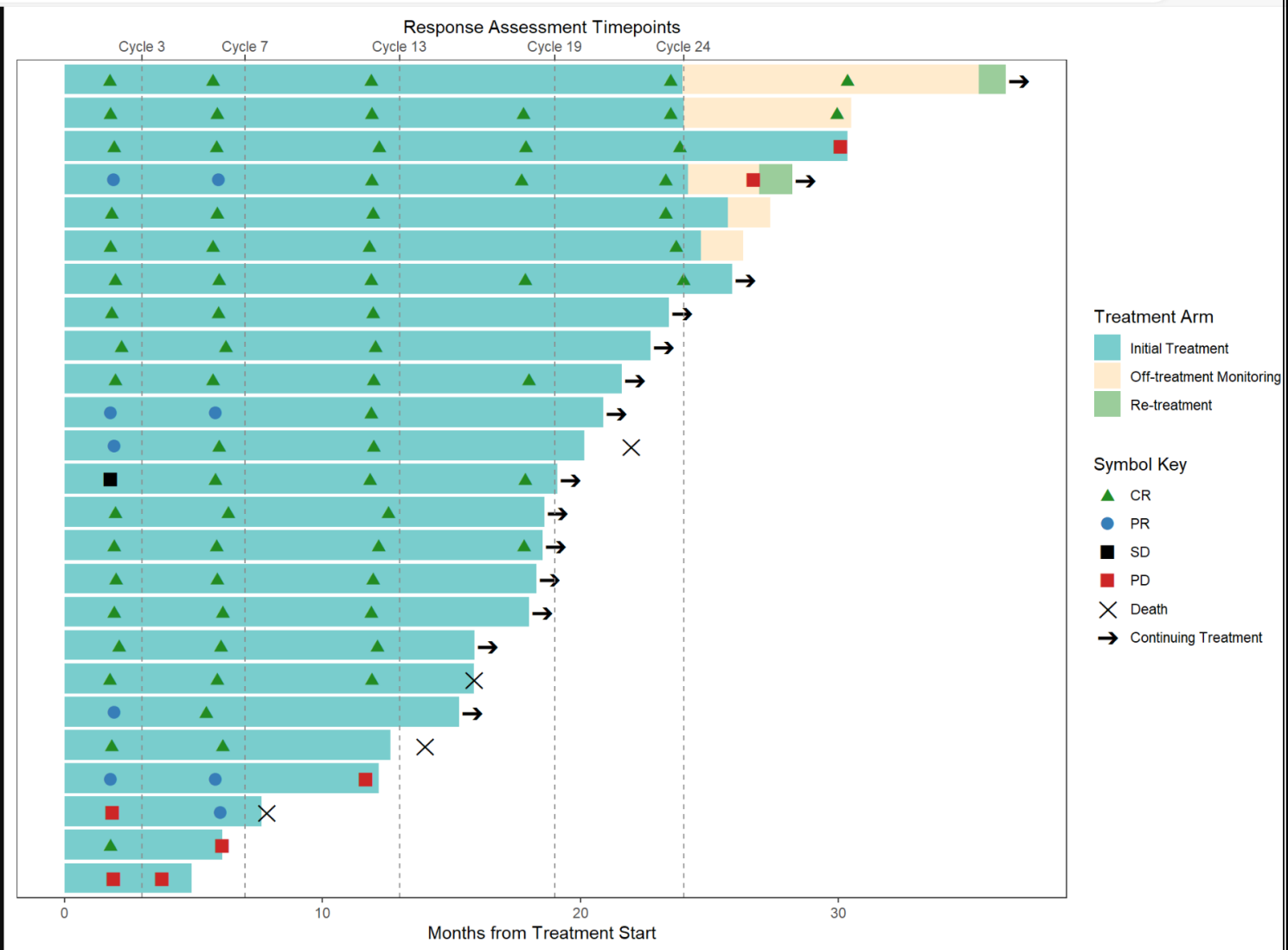

Kumar et al.,

Abstract 738

MCL, TP53

Erstlinie

Zanubrutinib +

Obinutuzumab +

Venetoclax

22.12.2023

ILyAD: A Phase III Double Blind, Randomized Trial Evaluating Vitamin D (Cholecalciferol) in Patients with Low Tumor-Burden Indolent Non-Hodgkin Lymphoma Treated with Rituximab Therapy

Jonathan W. Friedberg, Michael T. Brady, Myla S. Strawderman, Brad S. Kahl, Izidore S. Lossos, Jonathon B. Cohen, Patrick M. Reagan, Carla Casulo, Barbara L. Averill, Brian K. Link, Paul M. Barr, John P. Leonard, John M. Ashton, Derick R. Peterson, Loretta J. Nastoupil

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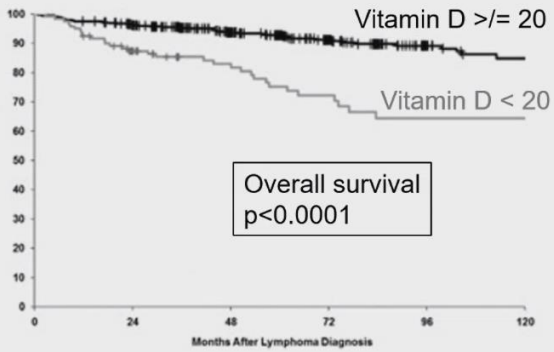
Vitamin D and FL outcome

- Low vitamin D levels are reproducibly associated with inferior outcomes (PFS and OS) in patients with FL treated with chemotherapy and anti-CD20 therapy.
- Magnitude of impact > FL-IPI factors

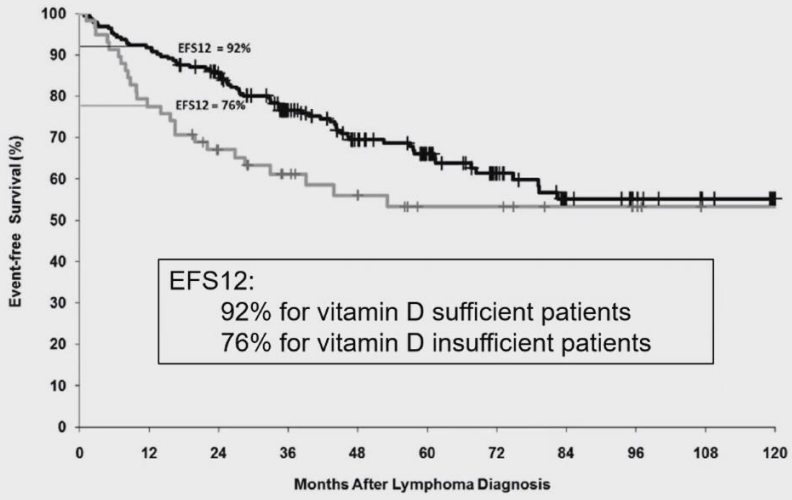


	SWOG Vitamin D Deficient = <20 ng/mL	LYSA Vitamin D Deficient = <10 ng/mL
PFS	1.97 (1.10 – 3.53)	1.50 (0.93-2.42)
OS	4.16 (1.66-10.44)	1.92 (0.72-5.13)

UR MEDICINE
WILMOT CANCER INSTITUTE

Tracy et al., *Blood Cancer J*, 7:e595 2017
Kelly et al, *J Clin Oncol* 33: 1482 2015

Vitamin D <20 ng/mL predicts early treatment failure after chemoimmunotherapy in FL: Mayo Clinic dataset



EFS12:
92% for vitamin D sufficient patients
76% for vitamin D insufficient patients

UR MEDICINE
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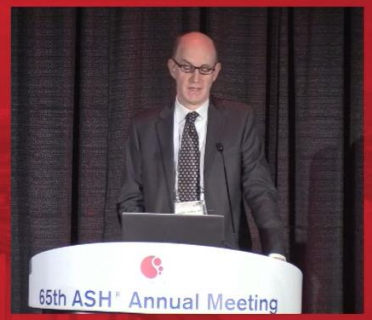
Tracy SI et al., *Blood Cancer J* 7:e595 2017

ILyAD trial: Randomized, placebo controlled, double blind study for patients with indolent NHL



Low tumor burden indolent NHL
No symptoms requiring therapy
Exclude: clinically evident low vitamin D, stones, hyperPTH

→ RANDOMIZE →

- Rituximab 375 mg/m2 qw x 4
  Vitamin D 2000IU/day x 3 yrs
- Rituximab 375 mg/m^2 qw × 4
  Placebo daily x 3 years

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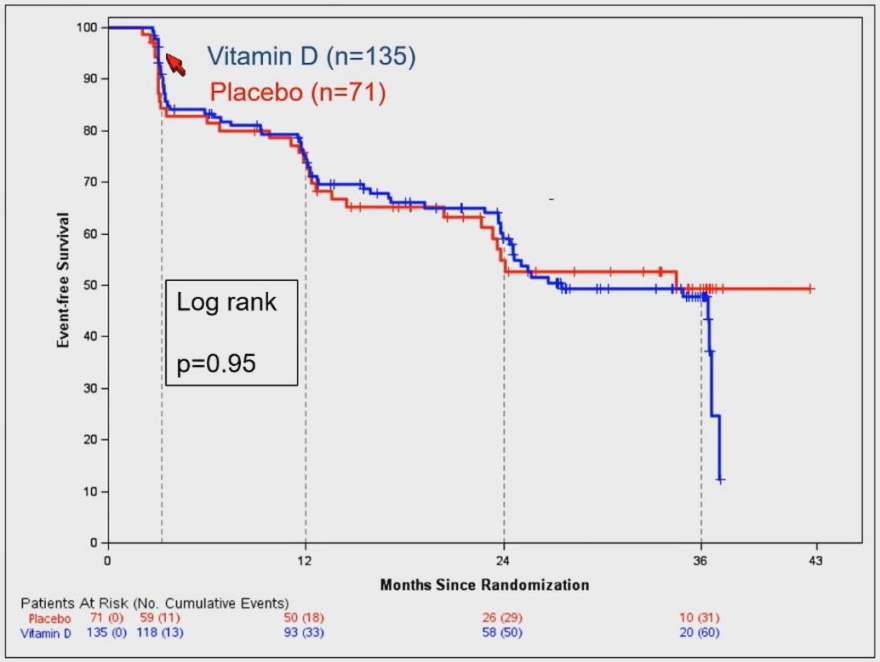
ILyAD Primary Analysis: Event-free survival by arm



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Phase 3 Randomized Study of Daratumumab + Bortezomib, Lenalidomide, and Dexamethasone (VRd) Versus VRd Alone in Patients With Newly Diagnosed Multiple Myeloma Who Are Eligible for Autologous Stem Cell Transplantation: Primary Results of the PERSEUS Trial*

*ClinicalTrials.gov Identifier: NCT03710603; sponsored by EMN in collaboration with Janssen Research & Development, LLC.

Pieter Sonneveld,[1] Meletios A. Dimopoulos,[2] Mario Boccadoro,[3] Hang Quach,[4] P. Joy Ho,[5] Meral Beksac,[6] Cyrille Hulin,[7] Elisabetta Antonioli,[8] Xavier Leleu,[9] Silvia Mangiacavalli,[10] Aurore Perrot,[11] Michele Cavo,[12] Angelo Belotti,[13] Annemiek Broijl,[1] Francesca Gay,[14] Roberto Mina,[14] Inger S. Nijhof,[15,16] Niels W.C.J. van de Donk,[15] Eirini Katodritou,[17] Fredrik Schjesvold,[18] Anna Sureda Balari,[19] Laura Rosiñol,[20] Michel Delforge,[21] Wilfried Roeloffzen,[22] Tobias Silzle,[23] Annette Vangsted,[24] Hermann Einsele,[25] Andrew Spencer,[26] Roman Hajek,[27] Artur Jurczyszyn,[28] Sarah Lonergan,[1] Tahamtan Ahmadi,[29] Yanfang Liu,[30] Jianping Wang,[30] Diego Vieyra,[30] Emilie M.J. van Brummelen,[30] Veronique Vanquickelberghe,[30] Anna Sitthi-Amorn,[30] Carla J. de Boer,[30] Robin Carson,[30] Paula Rodriguez-Otero,[31] Joan Bladé,[32] Philippe Moreau[33]

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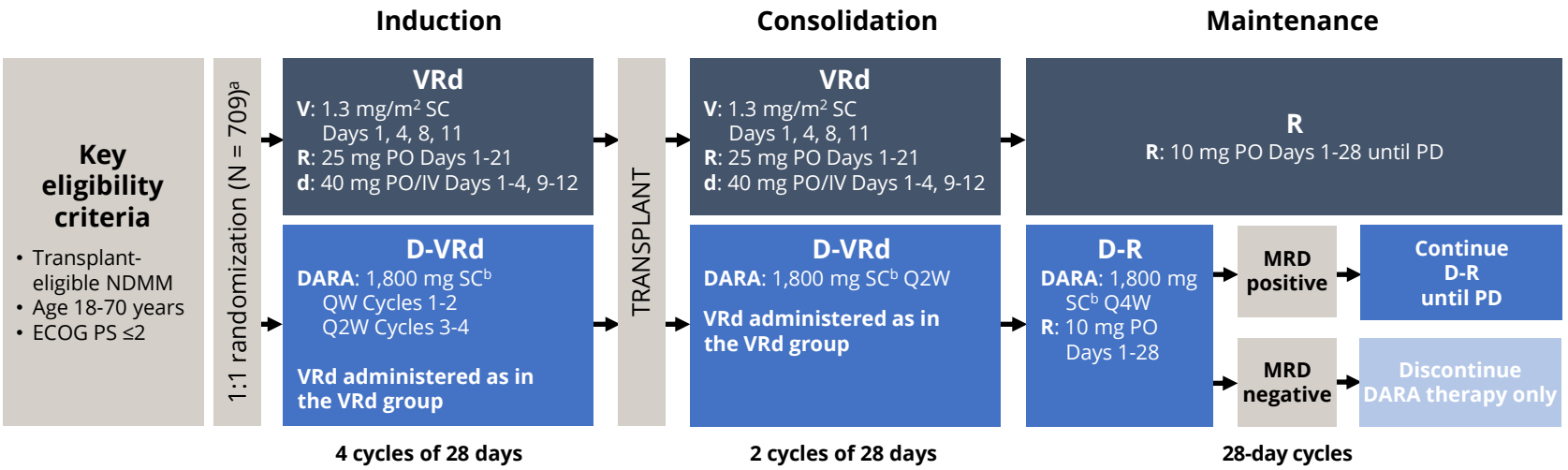
Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

PERSEUS: Study Design



Primary endpoint: PFS[c]

Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate,[d] OS

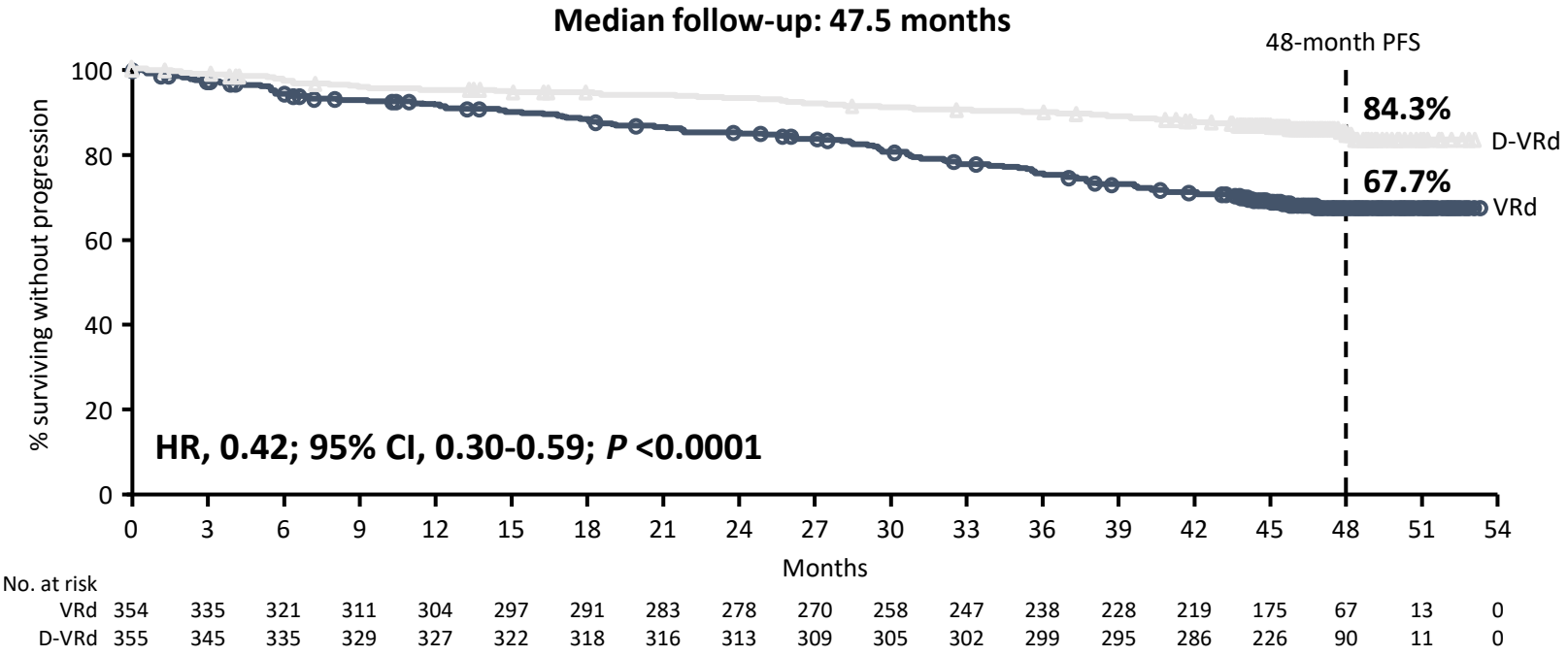
Discontinue DARA therapy only after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity

Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; MRD, minimal residual disease; OS, overall survival; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response. [a]Stratified by ISS stage and cytogenetic risk. [b]DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA).

[c]Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. [d]MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time.

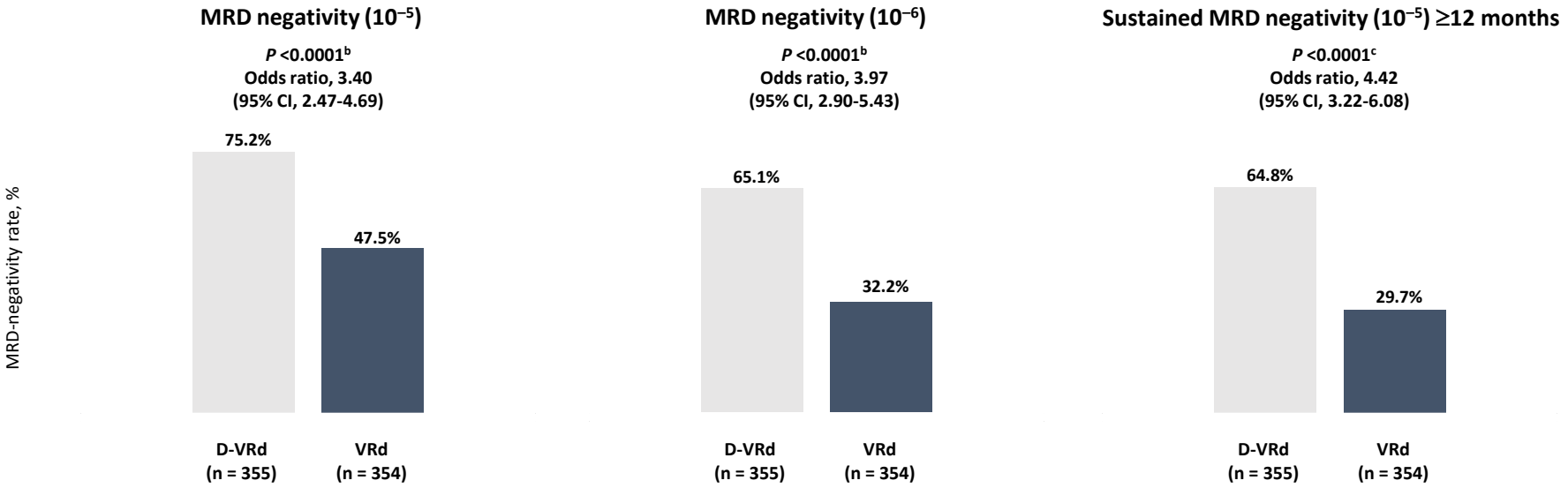
PERSEUS: Progression-free Survival



- **58% reduction in the risk of progression or death in patients receiving D-VRd**

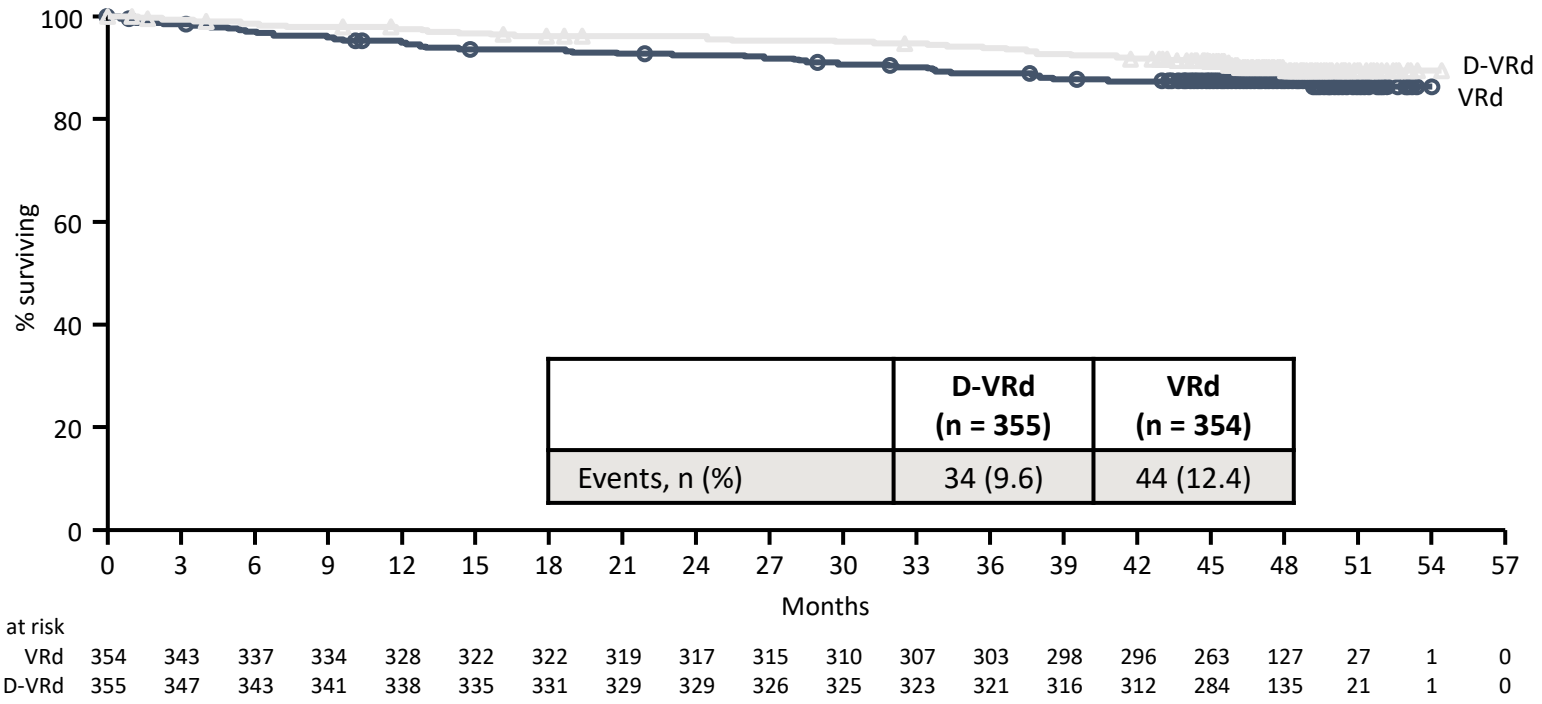
HR, hazard ratio; CI, confidence interval.

PERSEUS: Overall and Sustained MRD-negativity Rates[a]



- **Deep and durable MRD negativity was achieved with D-VRd**
- **64% (207/322) of patients receiving maintenance in the D-VRd group discontinued DARA after achieving sustained MRD negativity per protocol[d]**

PERSEUS: Overall Survival



	D-VRd (n = 355)	VRd (n = 354)
Events, n (%)	34 (9.6)	44 (12.4)

No. at risk

VRd	354	343	337	334	328	322	322	319	317	315	310	307	303	298	296	263	127	27	1	0
D-VRd	355	347	343	341	338	335	331	329	329	326	325	323	321	316	312	284	135	21	1	0

- **OS data trend favorably for D-VRd**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

P. Sonneveld, M.A. Dimopoulos, M. Boccadoro, H. Quach, P.J. Ho, M. Beksac, C. Hulin, E. Antonioli, X. Leleu, S. Mangiacavalli, A. Perrot, M. Cavo, A. Belotti, A. Broijl, F. Gay, R. Mina, I.S. Nijhof, N.W.C.J. van de Donk, E. Katodritou, F. Schjesvold, A. Sureda Balari, L. Rosiñol, M. Delforge, W. Roeloffzen, T. Silzle, A. Vangsted, H. Einsele, A. Spencer, R. Hajek, A. Jurczyszyn, S. Lonergan, T. Ahmadi, Y. Liu, J. Wang, D. Vieyra, E.M.J. van Brummelen, V. Vanquickelberghe, A. Sitthi-Amorn, C.J. de Boer, R. Carson, P. Rodriguez-Otero, J. Bladé, and P. Moreau, for the PERSEUS Trial Investigators*

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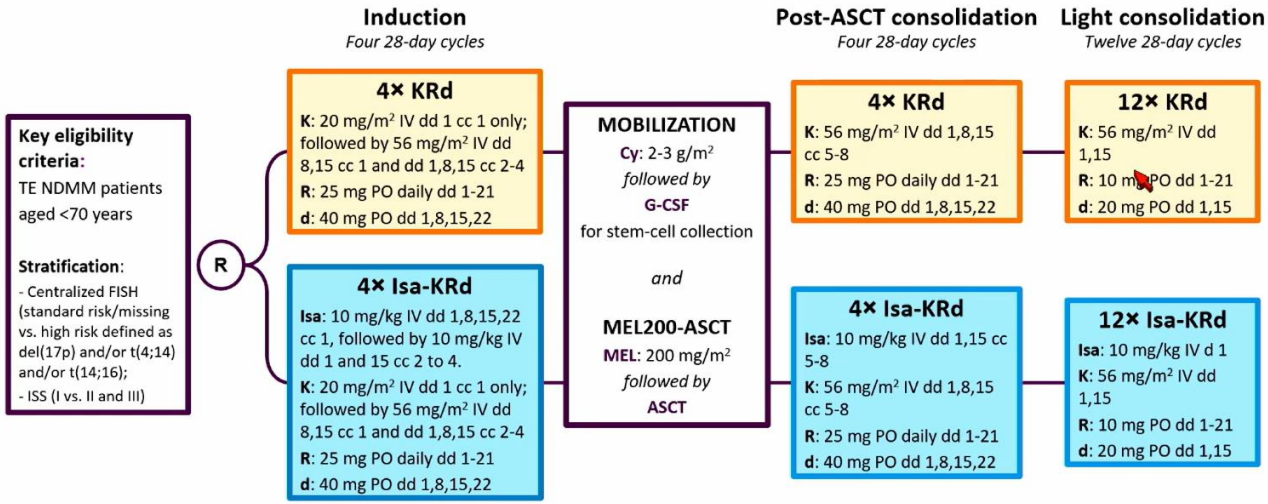
Results of the Phase III Randomized Iskia Trial: Isatuximab-Carfilzomib-Lenalidomide-Dexamethasone vs Carfilzomib-Lenalidomide-Dexamethasone as Pre-Transplant Induction and Post-Transplant Consolidation in Newly Diagnosed Multiple Myeloma Patients

Francesca Gay, M.D., Ph.D.

Peter Voorhees, M.D.
Levine Cancer Institute
Atrium Health Wake Forest Baptist Comprehensive Cancer Center

IsKia EMN24 Study Design

42 active sites; enrollment: Oct 7, 2020 – Nov 15, 2021



The EMN24 IsKia trial is registered with ClinicalTrials.gov: NCT04483739; it was sponsored by the European Myeloma Network (EMN).
All patients provided informed consent. This presentation includes discussion of the off-label use of a drug or drugs for the treatment of multiple myeloma.

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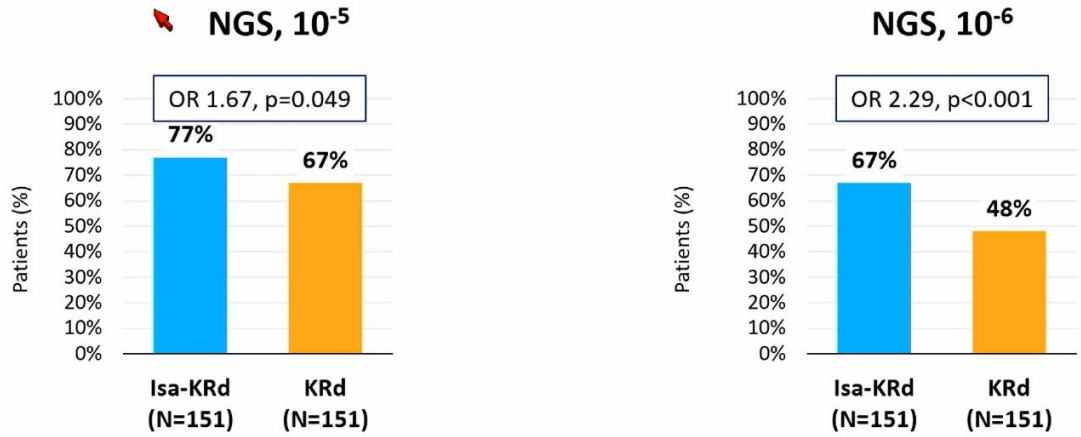
TE, transplant-eligible; NDMM, newly diagnosed multiple myeloma; FISH, fluorescence *in situ* hybridization; del, deletion; t, translocation; ISS, International Staging System stage; R, randomization; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; IV, intravenous; dd, days; cc, cycles; PO, orally; Cy, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; MEL, melphalan; ASCT, autologous stem-cell transplantation; MRD, minimal residual disease; NGS, next-generation sequencing; PFS, progression-free survival.

Primary Endpoint: Post-consolidation MRD negativity (ITT analysis)



≥VGPR after consolidation was 94% in both arms; ≥CR 74% vs 72% and sCR 64% vs 67% in the IsaKRd vs KRd arms.
High MRD compliance and sample quality (97-100% of sample evaluable at 10^{-5} and 10^{-6} cut-offs).
Consistent MRD results were detected by next-generation flow
In the logistic regression analysis, ORs, 95% CIs, and p-values were adjusted for stratification factor.

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MRD, minimal residual disease; ITT, intention to treat; NGS, next-generation sequencing; OR, odds ratio; p, p-value; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; CI, confidence interval.

Conclusions

- **Isa-KRd significantly increased post-consolidation 10^{-5} and 10^{-6} MRD negativity,** as compared with KRd
- Isa-KRd significantly increased **10^{-5} and 10^{-6} MRD negativity after each treatment phase** (Induction, Transplantation, Consolidation) .
- Isa-KRd consistently increased MRD negativity at 10^{-5} and 10^{-6} in all subgroups of patients, including **high-risk and very high-risk disease**.
- **Isa-KRd** treatment was **tolerable**, with a toxicity profile similar to that in previous reports.
- **10^{-6} MRD negativity cut-off** is more informative.
- 1-year sustained MRD negativity will be available in 2024
- **With a longer follow-up**, this trial can offer the opportunity to explore the **correlation** between depth of **MRD negativity and PFS/OS**.

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Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; MRD, minimal residual disease; PFS, progression-free survival; OS, overall survival.

Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive patients with transfusion-dependent lower-risk myelodysplastic syndromes: full analysis of the COMMANDS trial

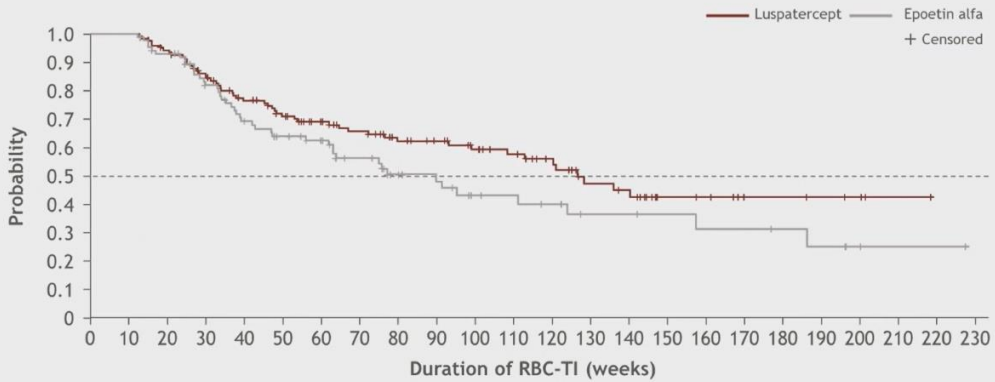
Guillermo Garcia-Manero,[1] Uwe Platzbecker,[2] Valeria Santini,[3] Amer M. Zeidan,[4] Pierre Fenaux,[5] Rami S. Komrokji,[6] Jake Shortt,[7] David Valcarcel,[8] Anna Jonasova,[9] Sophie Dimicoli-Salazar,[10] Ing Soo Tiong,[11] Chien-Chin Lin,[12] Jiahui Li,[13] Jennie Zhang,[13] Ana Carolina Giuseppi,[13] Sandra Kreitz,[14] Veronika Pozharskaya,[13] Karen L. Keeperman,[13] Shelonitda Rose,[13] Thomas Prebet,[13] Andrius Degulys,[15,16] Stefania Paolini,[17] Thomas Cluzeau,[18] Matteo Giovanni Della Porta[19,20]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany; [3]MDS Unit, Hematology, University of Florence, AOUC, Florence, Italy; [4]Department of Internal Medicine, Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; [5]Service d'Hématologie Séniors, Hôpital Saint-Louis, Université Paris 7, Paris, France; [6]Moffitt Cancer Center, Tampa, FL, USA; [7]Monash University and Monash Health, Melbourne, VIC, Australia; [8]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [9]Medical Department Hematology, Charles University General University Hospital, Prague, Czech Republic; [10]Hôpital Haut-Lévêque, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France; [11]Malignant Haematology & Stem Cell Transplantation, The Alfred, Melbourne, VIC, Australia; [12]Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan; [13]Bristol Myers Squibb, Princeton, NJ, USA; [14]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland; [15]Hematology, Oncology and Transfusion Medicine Center, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania; [16]Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [17]IRCCS Azienda Ospedaliero-Universitaria di Bologna - Istituto di Ematologia "Seràgnoli", Bologna, Italy; [18]Département d'Hématologie Clinique, Université Cote d'Azur, CHU Nice, Nice, France; [19]Cancer Center IRCCS Humanitas Research Hospital, Milan, Italy; [20]Department of Biomedical Sciences, Humanitas University, Milan, Italy

ASH 2023, Presentation 193

COMMANDS: duration of RBC-TI ≥ 12 weeks (week 1–EOT)

Duration, median (95% CI), weeks	Luspatercept	Epoetin alfa	HR (95% CI)
ITT	126.6 (99.0-NE)	89.7 (61.9-123.9)	0.586 (0.380-0.904)



No. at risk

Luspatercept	124	124	115	100	86	76	67	59	50	46	40	35	28	20	18	10	9	5	5	4	3	1
Epoetin alfa	88	88	79	65	54	47	43	32	23	20	15	14	12	9	9	7	6	6	5	4	2	1	1

Data cutoff date: September 28, 2023.
CI, confidence interval; EOT, end of treatment; HR, hazard ratio; NE, not estimable.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

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Efficacy of Imetelstat in Achieving Red Blood Cell Transfusion Independence Across Different Risk Subgroups in Patients With Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory to Erythropoiesis-Stimulating Agents in IMerge Phase 3 Study

Rami Komrokji,[1] Valeria Santini,[2] Pierre Fenaux,[3] Michael R. Savona,[4] Yazan F. Madanat,[5] Tymara Berry,[6] Laurie Sherman,[7] Shyamala Navada,[6] Faye Feller,[6] Libo Sun,[6] Qi Xia,[6] Ying Wan,[6] Fei Huang,[6] Amer M. Zeidan,[8] and Uwe Platzbecker[9]

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IMerge Phase 3 Trial Design

Phase 3
Double-blind, randomized
118 clinical sites in 17 countries

Patient population (ITT; N = 178)
- IPSS low-risk or intermediate-1–risk MDS
- R/R[a] to ESA or EPO >500 mU/mL (ESA ineligible)
- Transfusion-dependent: ≥4 U RBCs/8 wk over 16 wk before study
- Non-del(5q)
- No prior treatment with lenalidomide or HMAs

R 2:1

Imetelstat
7.5 mg/kg IV every 4 wk
(n = 118)

Stratification
- Transfusion burden (4-6 U vs >6 U)
- IPSS risk category (low vs intermediate-1)

Supportive care, including RBC and platelet transfusions, myeloid growth factors (eg, G-CSF), and iron chelation therapy administered as needed on study per investigator discretion

Placebo
(n = 60)

Primary end point
- 8-wk RBC-TI[b]

Key secondary end points
- 24-wk RBC-TI[b]
- Duration of TI
- HI-E
- Safety

Key exploratory end points
- VAF changes
- Cytogenetic response
- PRO: fatigue measured by FACIT-Fatigue

Safety population (treated; N = 177)
Imetelstat (n = 118)
Placebo (n = 59)

[a]Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 U, epoetin beta ≥30,000 U, darbepoetin alfa 150 µg, or equivalent per week) without Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U/8 wk or transfusion dependence or reduction in Hb by ≥1.5 g/dL after HI-E from ≥8 weeks of ESA treatment. [b]Percentage of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (8-week TI); percentage of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (24-week TI).
EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FACIT, Functional Assessment of Chronic Illness Therapy; G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HI-E, hematologic improvement–erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; ITT, intent-to-treat; IV, intravenous; MDS, myelodysplastic syndromes; PRO, patient-reported outcome; R, randomization; RBC, red blood cell; R/R, relapsed/refractory; TI, transfusion independence, VAF, variant allele frequency.
Platzbecker U, et al. *Lancet*. Published Online December 1, 2023. https://doi.org/10.1016/S0140-6736(23)01724-5.

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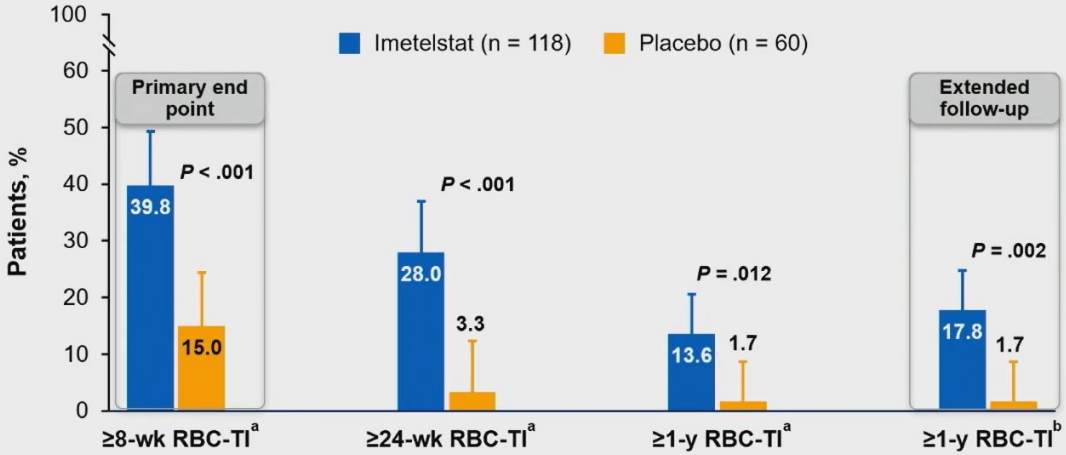
Overall Population: Higher Rates of Longer-Term Duration of RBC-TI With Imetelstat vs Placebo[1,2]



[a]Data cutoff date: October 13, 2022. [b]Data cutoff date: January 13, 2023.
The *P* value was determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC U/8 wk during a 16-week period before randomization) and baseline IPSS (low-risk vs intermediate-1–risk) applied to randomization.
IPSS, International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.
1. Zeidan A, et al. ASCO 2023. Abstr 7004. 2. Platzbecker U, et al. *Lancet*. Published Online December 1, 2023. https://doi.org/10.1016/S0140-6736(23)01724-5.

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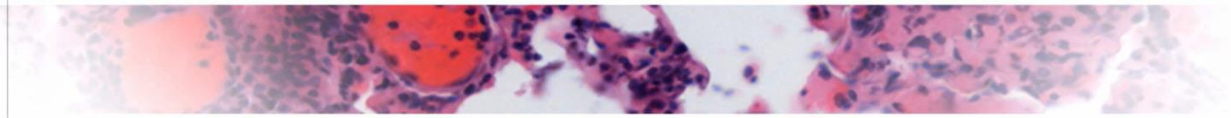
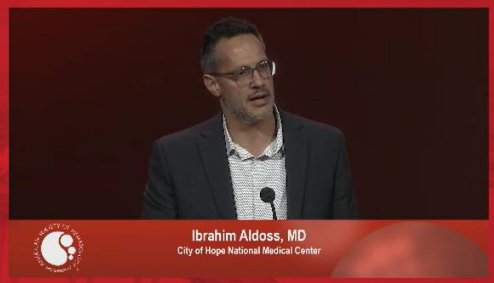


Revumenib Monotherapy in Patients with Relapsed/Refractory *KMT2Ar* Acute Leukemia: Topline Efficacy and Safety Results from the Pivotal AUGMENT-101 Phase 2 Study

Ibrahim Aldoss, Ghayas C. Issa, Michael Thirman, John DiPersio, Martha Arellano, James S. Blachly, Gabriel N. Mannis, Alexander Perl, David S. Dickens, Christine M. McMahon, Elie Traer, C. Michel Zwaan, Carolyn Grove, Richard Stone, Paul J. Shami, Ioannis Mantzaris, Matthew Greenwood, Neerav Shukla, Branko Cuglievan, Yu Gu, Rebecca G. Bagley, Kate Madigan, Soujanya Sunkaraneni, Huy Van Nguyen, Nicole McNeer, Eytan M. Stein



KMT2Ar Acute Leukemia

- Many patients relapse after chemotherapy and/or HSCT[1]
- In adults, remission rates after relapse (CR, 5%) and median OS (2.4 months) after ≥2 salvage therapies remain low[1]
- Outcomes in infants/children after relapse remain poor

No approved targeted therapies for *KMT2Ar* disease

OS in Adult Patients With R/R *KMT2Ar* AML After ≥3rd-Line Therapy

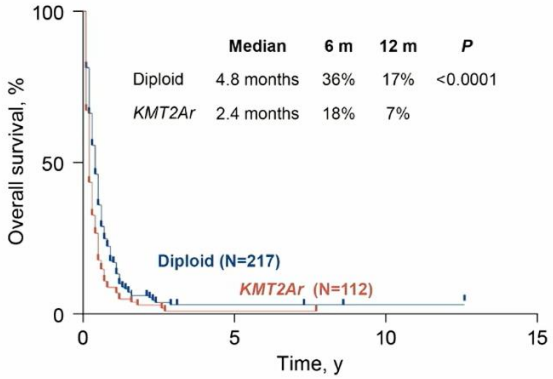


Figure reproduced from Issa GC, Zarka J, Sasaki K, et al. *Blood Cancer J.* 2021;11:162
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AML, acute myeloid leukemia; CR, complete remission; HSCT, hematopoietic stem cell transplant; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; OS, overall survival; R/R, relapsed/refractory.

1. Issa GC, Zarka J, Sasaki K, et al. *Blood Cancer J.* 2021;11:162.

AUGMENT-101 Phase 2 Study Design

Patients aged ≥30 days with R/R acute leukemia

Revumenib RP2D

163 mg (95 mg/m^2 if body weight <40 kg) q12h oral + a strong CYP3A4i in 28-day cycles

- ***KMT2Ar* acute leukemia**
- ***NPM1m* AML**
  Still enrolling, not included in this analysis

- **Primary endpoint**
  - CR+CRh rate*
- **Key secondary efficacy endpoints**
  - CRc
  - ORR

A planned interim analysis of patients with *KMT2Ar* acute leukemia was conducted

*CR+CRh rate >10% in adult evaluable population considered lower efficacy bound

AML, acute myeloid leukemia; CR, complete remission; CRc, CR composite (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; CYP3A4i, cytochrome P450 3A4 inhibitor; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; *NPM1m*, nucleophosmin 1–mutated; ORR, overall response rate; q12h, every 12 hours; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

Response

Parameter	Efficacy population (n=57)
ORR, n (%)	**36 (63)**
CR+CRh rate, n (%)	13 (23)
95% CI	12.7–35.8
P value, 1-sided	0.0036
CRc	25 (44)
95% CI	30.7–57.6
Negative MRD status[a]	
CR+CRh	7/10 (70)
CRc	15/22 (68)

Parameter	Efficacy population (n=57)
Best response, n (%)	
CR	10 (18)
CRh	3 (5)
CRi	1 (1.8)
CRp	11 (19)
MLFS	10 (18)
PR	1 (1.8)
PD	4 (7)
No response	14 (25)
Other[b]	3 (5)

Data cutoff: July 24, 2023. [a]MRD done locally; not all patients had MRD status reported. [b]Includes patients without postbaseline disease assessment.

CR, complete remission; CRc, composite CR (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphological leukemia-free state; MRD, minimal residual disease; ORR, overall response rate (CRc+MLFS+PR); PD, progressive disease; PR, partial remission.

Revumenib Safety Profile (cont)

Any grade TEAEs that occurred in ≥25% patients

All terms, n (%)	Safety population (n=94)[a]
Nausea	42 (45)
Febrile neutropenia	36 (38)
Diarrhea	33 (35)
Vomiting	29 (31)
Differentiation syndrome	26 (28)
Hypokalemia	26 (28)
Epistaxis	25 (27)
QTc prolongation	24 (26)

Grade ≥3 TEAEs that occurred in ≥10% patients

All terms, n (%)	Safety population (n=94)[a]
Febrile neutropenia	35 (37)
Decreased neutrophil count	15 (16)
Decreased white blood cell count	15 (16)
Decreased platelet count	14 (15)
Anemia	17 (18)
Differentiation syndrome	15 (16)
QTc prolongation	13 (14)
Sepsis	11 (12)
Hypokalemia	10 (11)

Data cutoff: July 24, 2023. [a]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib.

No patients discontinued due to differentiation syndrome, QTc prolongation, or cytopenias

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PATH-HHT

A Blinded, Randomized Trial in Hereditary Hemorrhagic Telangiectasia Demonstrates that Pomalidomide Reduces Epistaxis and Improves Quality of Life

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Hereditary Hemorrhagic Telangiectasia

- Characterized by telangiectasia and AVM on mucosal surfaces, and in lung, liver, brain and spinal cord
- Second most common inherited bleeding disorder; incidence ~ 1:5000
- Most clinically significant bleeding disorder in women? (Zhang et al, abstract #0028)
- Pathogenesis involves altered TGF-β signaling; mutations in *ENG*, *ACVRL1*, *SMAD4* in > 90%
- No FDA approved therapies, and no adequately-powered, randomized trials of systemic therapy

2009

- 45-year-old man
- Type IIa vWD
- Severe epistaxis and GI bleeding (ACVRL1 mutation)
- Receiving 2-4 units PRBC and 2-3 doses Humate P weekly
- Dramatic response to thalidomide

Inclusion Criteria

1. **Clinical diagnosis of HHT** as defined by the Curaçao criteria
2. **Epistaxis severity score ≥ 3** over the preceding 3 months
3. **Anemia as determined by local laboratory hgb normal ranges, and/or infusion of at least 250 mg of iron or 1 unit of blood in the preceding 24 weeks**
4. Platelet count ≥ 100 x 10^9/L
5. WBC ≥ 2.5 x 10^9/L
6. INR ≤ 1.4 and normal ± 2 sec activated partial thromboplastin time (aPTT) (except for those on a stable dose of warfarin or DOAC)

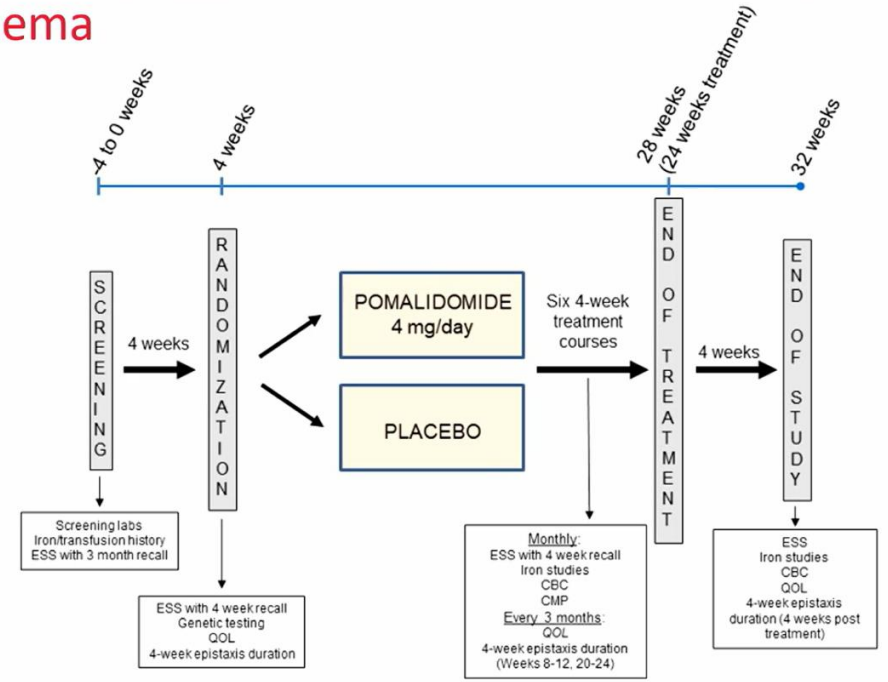
Primary Endpoint

Change of the Epistaxis Severity Score from baseline to week 24

Key Secondary Endpoints

1. Change in the HHT-specific QOL score from baseline to weeks 12 and 24 (key timepoint), and the 4-week post-treatment follow-up visit
2. Change in average daily epistaxis duration from the 4-week screening period prior to randomization to weeks 8-12 and to weeks 20-24, and the 4 weeks post-treatment
3. Amount of parenteral iron administered
4. Number of packed red blood cell transfusions
5. Change in Neuro-QOL™, Satisfaction with Social Roles, and Activities Short Form (V1.1) T-score from baseline to weeks 12 and 24 (key timepoint), and the 4-week post-treatment follow-up visit

Study Schema



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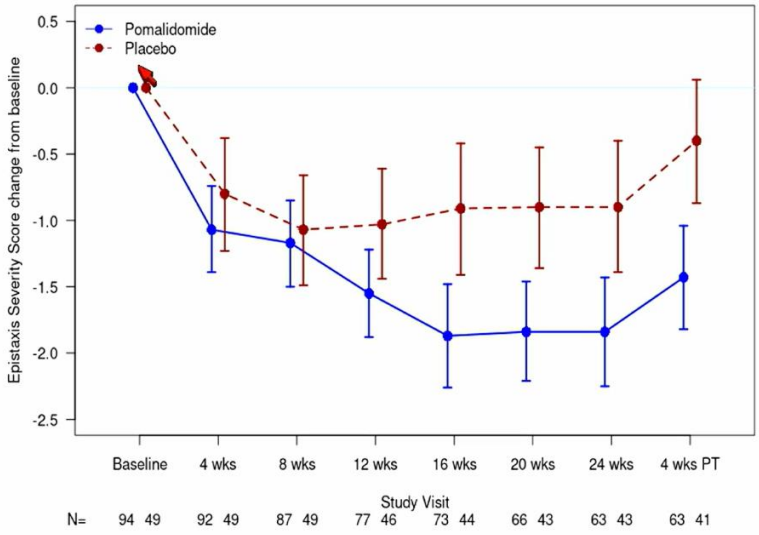
ESS Change from Baseline



Time	Difference (95% CI)	P value
12 weeks	-0.52 (-1.04, -0.01)	0.045
16 weeks	-0.95 (-1.57, -0.34)	0.003*
20 weeks	-0.93 (-1.50, -0.36)	0.002*
24 weeks	-0.95 (-1.58, -0.32)	0.003*
4 weeks post-treat.	-1.05 (-1.63, -0.47)	<0.001*

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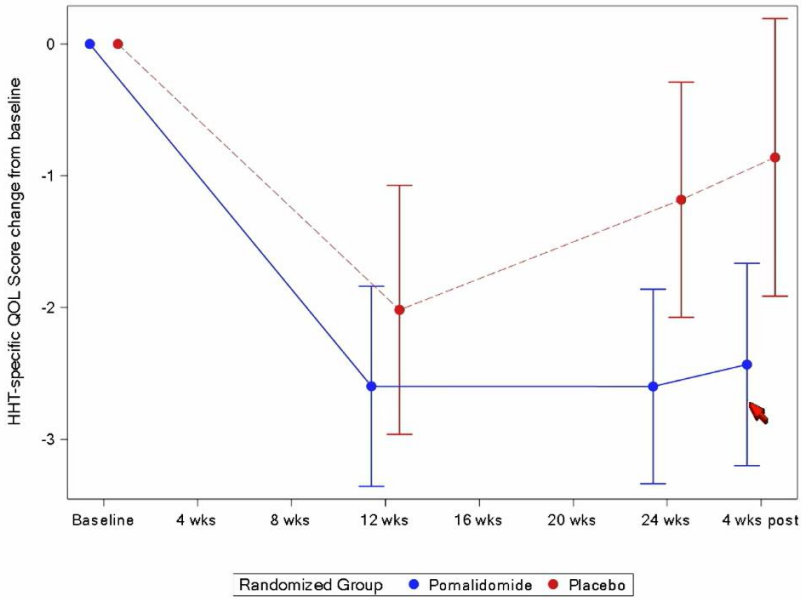
HHT-QOL Score Change from Baseline



Time	Difference (95% CI)	P value
12 weeks	-0.6 (-1.8, 0.6)	0.337
24 weeks	-1.4 (-2.6, -0.3)	0.015
4 weeks post-treatment	-1.6 (-2.9, -0.3)	0.017

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ASH Kongress 2023

wichtig zu wissen

- Akute Myeloische Leukämie
- Chronische Lymphatische Leukämie
- Fetale Hämatopoese
- Follikuläres Lymphom
- Hereditäre Hämorrhagische Teleangiektasie
- Mantelzell-Lymphom
- Multiples Myelom
- Myelodysplastische Neoplasien
- Sichelzellkrankheit