Hematologic Malignancies Tumor Board 2024

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24th Multidisciplinary Management of Cancers: A Case-based Approach

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24th Multidisciplinary Management of Cancers: A Case-based Approach

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Disclosures

Full Name	Role	Type of Financial Relationship	Company Name
Brian Jones	Chair	Advisory Board or Panel	AbbVie, Daiichi Sankyo, Genentech, Kymera, Servier, Rigel
Brian Jones	Chair	Consultant	AbbVie, Daiichi Sankyo, Genentech, Kymera, Servier, Rigel
Brian Jones	Chair	Grants / Research	To my institution from: AbbVie, Amgen, Aptose, AROG, Biomea Fusion, BMS, Celgene, F. Hoffmann-La Roche, Forma, Forty-Seven, Genentech/Roche, Gilead, GlycoMimetics, Hanmi, Immune-Onc, Jazz, Kymera, Loxo, Pfizer, Pharmacyclics, Treadwell
Brian Jones	Chair	Other Financial or Material Support (royalties, patents, etc.)	Travel reimbursement/support from Rigel

Disclosures

Full Name	Role	Type of Financial Relationship	Company Name
Lekha Mikkilileni	Panel	Advisory Board or Panel	Legend Advisory Board at ASH (12/9/23)
Rebecca Olin	Panel	Grants / Research	Reseach: Cellectis; ad board Rigel, Servier
William Shomali	Panel	Consultant	Incyte
William Shomali	Panel	Grants/Research Support	Incyte, Blueprint medicines
Tom Martin, MD	Panel	Advisory Board or Panel	GSK, Pfizer
Tom Martin, MD	Panel	Grants / Research	Sanofi, Janssen, BMS

Case 1: History

- 76 year old male presents to PCP with 1 month of fatigue and easy bruising.
- PMH: Hypertension, Hyperlipidemia, Coronary Artery Disease with prior MI s/p PCI w/ DES x2, and CHF.
- SH: Retired accountant, married, two adult children (both in good healthy), no tobacco/drug use, occasional alcohol
- FH: No history of Hematologic Malignancies
- Physical Exam: general pallor, appearing fatigued, scattered healing ecchymoses on arms and legs, no lymphadenopathy, no hepatosplenomegaly

Case 1: Labs

Lab	Value	Unit
WBC	23	K/μL
Hgb	7.8	g/dL
Hct	21	%
PLT	46	K/μL
Differential:		
Blasts	85	%

Lab	Value	Unit
Potassium	4.0	mmol/L
Creatinine	0.80	mg/dL
Calcium	8.5	mg/dL
Phosphorus	3.7	mg/dL
LDH	350	U/L
Uric Acid	4.8	mg/dL

Case 1: Work-Up

Bone Marrow Biopsy consistent with AML, with 92% blasts

- Immunophenotype CD11c, CD33, CD56 partial, CD64, CD117, MPO+
- Normal Cytogenetics
- FISH: negative for del(5q), monosomy 5, del(7q), monosomy 7, trisomy 8, t(8;21), t(15;17), del(20q), CBFB rearrangement, MLL rearrangement
- Molecular testing: NPM1+, FLT3-ITD negative, IDH1+, IDH2-, CEBPA-

Case 1:

What is the patient's risk status based on cytogenetics and molecular abnormalities?

A. Favorable

B. Intermediate

C. Poor

D. Indeterminate

Bone Marrow Biopsy consistent with AML, with 92% blasts

- Immunophenotype CD11c, CD33, CD56 partial, CD64, CD117, MPO+
- Normal Cytogenetics
- FISH: negative for del(5q), monosomy 5, del(7q), monosomy 7, trisomy 8, t(8;21), t(15;17), del(20q), CBFB rearrangement, MLL rearrangement
- Molecular testing: NPM1+, FLT3-ITD negative, IDH1+, IDH2-, CEBPA-

RISK STRATIFICATION BY BIOLOGICAL DISEASE FACTORS FOR PATIENTS WITH NON-APL AML TREATED WITH INTENSIVE INDUCTION CHEMOTHERAPY[1,*]

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

Case 1: Initial Treatment – 76 y.o. M w/ extensive cardiac Hx and Favorable-Risk AML (NPM1+, IDH1+)

What would first-line therapy be for this patient?

A. 7+3 +/- Gemtuzumab ozogamicin

B. Azacitidine + Venetoclax

C. CPX-351 (Vyxeos)

D. Ivosidenib Monotherapy

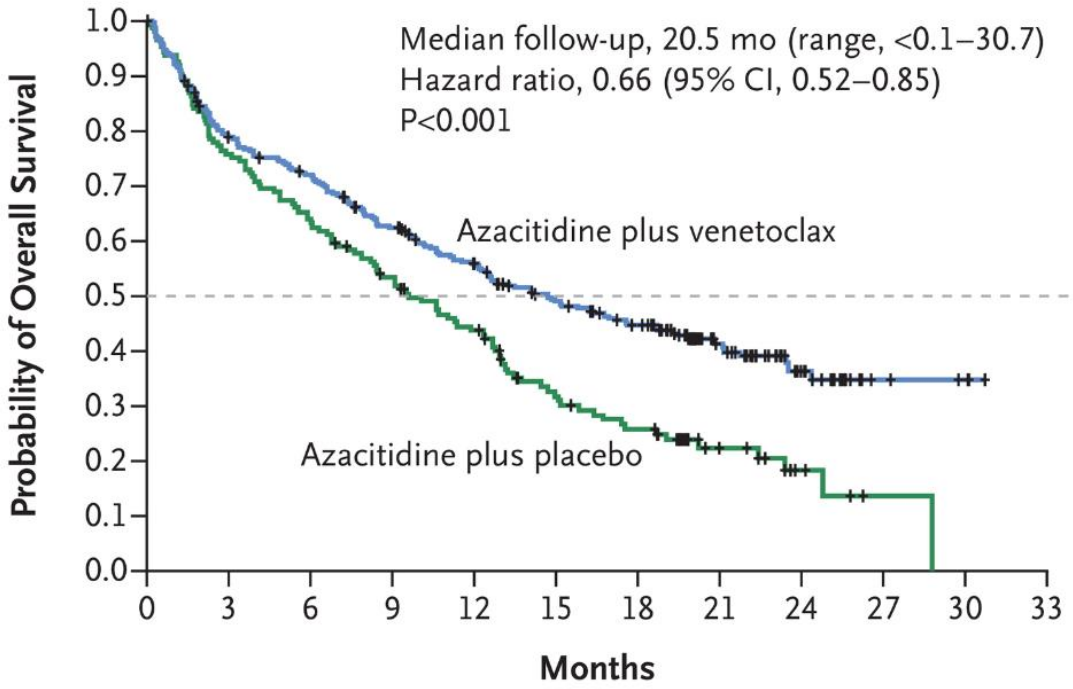
E. Ivosidenib + Azacitidine

Case 1:

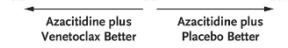
ORIGINAL ARTICLE

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

Courtney D. DiNardo, M.D., Brian A. Jonas, M.D., Ph.D., Vinod Pullarkat, M.D., Michael J. Thirman, M.D., Jacqueline S. Garcia, M.D., Andrew H. Wei, M.B., B.S., Ph.D., Marina Konopleva, M.D., Ph.D., Hartmut Döhner, M.D., Anthony Letai, M.D., Ph.D., Pierre Fenaux, M.D., Ph.D., Elizabeth Koller, M.D., Violaine Havelange, M.D., Ph.D., et al.



Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
All patients	161/286 (56.3)	109/145 (75.2)	0.64 (0.50–0.82)
Sex			
Female	61/114 (53.5)	41/58 (70.7)	0.68 (0.46–1.02)
Male	100/172 (58.1)	68/87 (78.2)	0.62 (0.46–0.85)
Age			
<75 yr	66/112 (58.9)	36/58 (62.1)	0.89 (0.59–1.33)
≥75 yr	95/174 (54.6)	73/87 (83.9)	0.54 (0.39–0.73)
Geographic region			
United States	27/50 (54.0)	21/24 (87.5)	0.47 (0.26–0.83)
Europe	70/116 (60.3)	46/59 (78.0)	0.67 (0.46–0.97)
China	9/24 (37.5)	5/13 (38.5)	1.05 (0.35–3.13)
Japan	10/24 (41.7)	9/13 (69.2)	0.52 (0.20–1.33)
Rest of world	45/72 (62.5)	28/36 (77.8)	0.73 (0.45–1.17)
Baseline ECOG score			
Grade <2	89/157 (56.7)	65/81 (80.2)	0.61 (0.44–0.84)
Grade ≥2	72/129 (55.8)	44/64 (68.8)	0.70 (0.48–1.03)
Type of AML			
De novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51–0.90)
Secondary	41/72 (56.9)	29/35 (82.9)	0.56 (0.35–0.91)
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)
AML with myelodysplasia-related changes			
Yes	56/92 (60.9)	38/49 (77.6)	0.73 (0.48–1.11)
No	105/194 (54.1)	71/96 (74.0)	0.62 (0.46–0.83)
Bone marrow blast count			
<30%	46/85 (54.1)	28/41 (68.3)	0.72 (0.45–1.15)
30 to <50%	36/61 (59.0)	26/33 (78.8)	0.57 (0.34–0.95)
≥50%	79/140 (56.4)	55/71 (77.5)	0.63 (0.45–0.89)



Case 1:

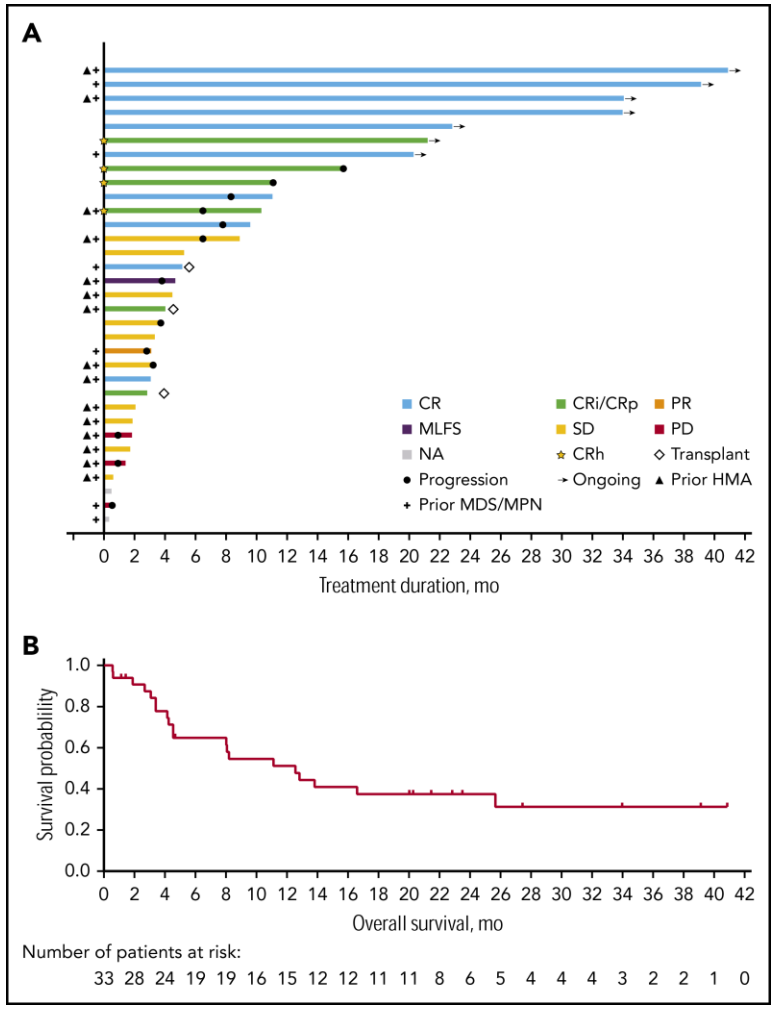
MYELOID NEOPLASIA | FEBRUARY 13, 2020

Ivosidenib induces deep durable remissions in patients with newly diagnosed *IDH1*-mutant acute myeloid leukemia

Clinical Trials & Observations

Gail J. Roboz, Courtney D. DiNardo, Eytan M. Stein, Stéphane de Botton, Alice S. Mims, Gabrielle T. Prince, Jessica K. Altman, Martha L. Arellano, Will Donnellan, Harry P. Erba, Gabriel N. Mannis, Daniel A. Pollyea, Anthony S. Stein, Geoffrey L. Uy, Justin M. Watts, Amir T. Fathi, Hagop M. Kantarjian, Martin S. Tallman, Sung Choe, David Dai, Bin Fan, Hongfang Wang, Vickie Zhang, Katharine E. Yen, Stephanie M. Kapsalis, Denice Hickman, Hua Liu, Samuel V. Agresta, Bin Wu, Eyal C. Attar, Richard M. Stone

Response	Patients (N = 33)
CR + CRh rate	14 (42.4%)
CR rate	10 (30.3%)
ORR	18 (54.5%)
Duration of CR/CRh	Not Reached
Duration of CR	Not Reached

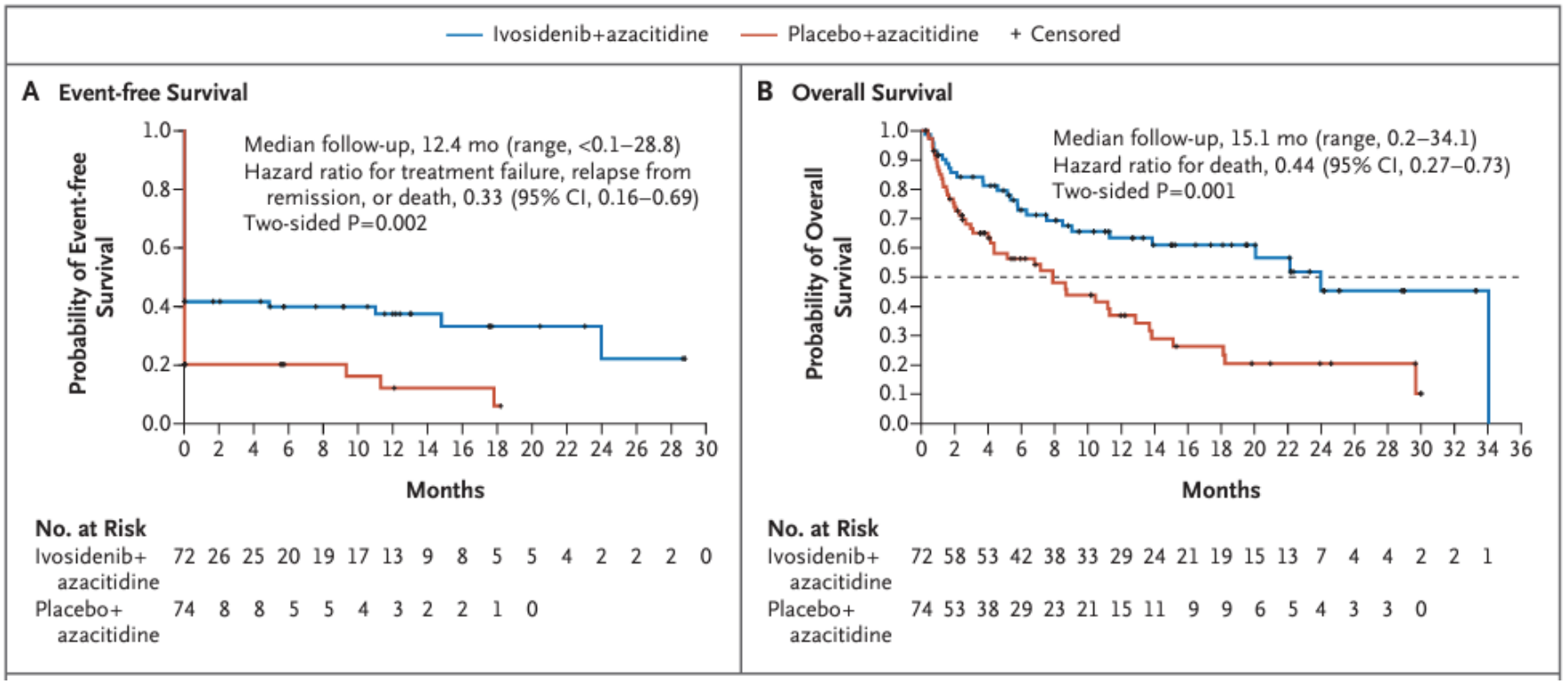


Case 1:

ORIGINAL ARTICLE

Ivosidenib and Azacitidine in *IDH1*-Mutated Acute Myeloid Leukemia

Pau Montesinos, M.D., Ph.D., Christian Recher, M.D., Ph.D., Susana Vives, M.D., Ewa Zarzycka, M.D., Jianxiang Wang, M.D., Giambattista Bertani, M.D., Michael Heuser, M.D., Rodrigo T. Calado, M.D., Ph.D., Andre C. Schuh, M.D., Su-Peng Yeh, M.D., Scott R. Daigle, M.S., Jianan Hui, Ph.D., et al.



Case 1:

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Event	Ivosidenib+Azacitidine (N=71)		Placebo+Azacitidine (N=73)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
	number (percent)			
Any adverse event	70 (99)	66 (93)	73 (100)	69 (95)
Hematologic adverse events	55 (77)	50 (70)	48 (66)	47 (64)
Anemia	22 (31)	18 (25)	21 (29)	19 (26)
Febrile neutropenia	20 (28)	20 (28)	25 (34)	25 (34)
Neutropenia	20 (28)	19 (27)	12 (16)	12 (16)
Thrombocytopenia	20 (28)	17 (24)	15 (21)	15 (21)
Leukocytosis	8 (11)	0	1 (1)	0
Nonhematologic adverse events				
Nausea	30 (42)	2 (3)	28 (38)	3 (4)
Vomiting	29 (41)	0	19 (26)	1 (1)
Diarrhea	25 (35)	1 (1)	26 (36)	5 (7)
Pyrexia	24 (34)	1 (1)	29 (40)	2 (3)
Constipation	19 (27)	0	38 (52)	1 (1)
Pneumonia	17 (24)	16 (23)	23 (32)	21 (29)
QT interval prolonged on ECG	14 (20)	7 (10)	5 (7)	2 (3)
Insomnia	13 (18)	1 (1)	9 (12)	0
Asthenia	11 (15)	0	24 (33)	5 (7)
Hypokalemia	11 (15)	2 (3)	21 (29)	6 (8)
Decreased appetite	11 (15)	1 (1)	19 (26)	6 (8)

Event	Ivosidenib+Azacitidine (N=71)		Placebo+Azacitidine (N=73)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
	number (percent)			
Dyspnea	11 (15)	1 (1)	9 (12)	3 (4)
Differentiation syndrome	10 (14)	3 (4)	6 (8)	3 (4)
Pain in arm or leg	10 (14)	1 (1)	3 (4)	1 (1)
Fatigue	9 (13)	2 (3)	10 (14)	2 (3)
Hematoma	9 (13)	0	1 (1)	0
Edema, peripheral	8 (11)	0	16 (22)	1 (1)
Platelet count decreased	8 (11)	6 (8)	6 (8)	6 (8)
Arthralgia	8 (11)	0	3 (4)	0
Headache	8 (11)	0	2 (3)	0
Bleeding	29 (41)	4 (6)	21 (29)	5 (7)
Infections	20 (28)	15 (21)	36 (49)	22 (30)

Case 1:

- Patient is treated with Ivosidenib + Azacitidine and achieves CR after 2 cycles.

- Continued on 28-day cycle for 12 months until he is found to have relapsed disease.

- Bone Marrow Biopsy consistent with relapsed AML w/ 80% blasts.
- Immunophenotype CD11c, CD33, CD56 partial, CD64, CD117, MPO+
- Normal Cytogenetics
- FISH: negative for del(5q), monosomy 5, del(7q), monosomy 7, trisomy 8, t(8;21), t(15;17), del(20q), CBFB rearrangement, MLL rearrangement
- Molecular testing: NPM1+, FLT3-ITD negative, IDH1+, IDH2-, CEBPA-

Case 1: Second-line therapy – Relapsed AML (NPM1+, IDH1+)

What is the best option for second-line therapy?

A. Gemtuzumab ozogamicin

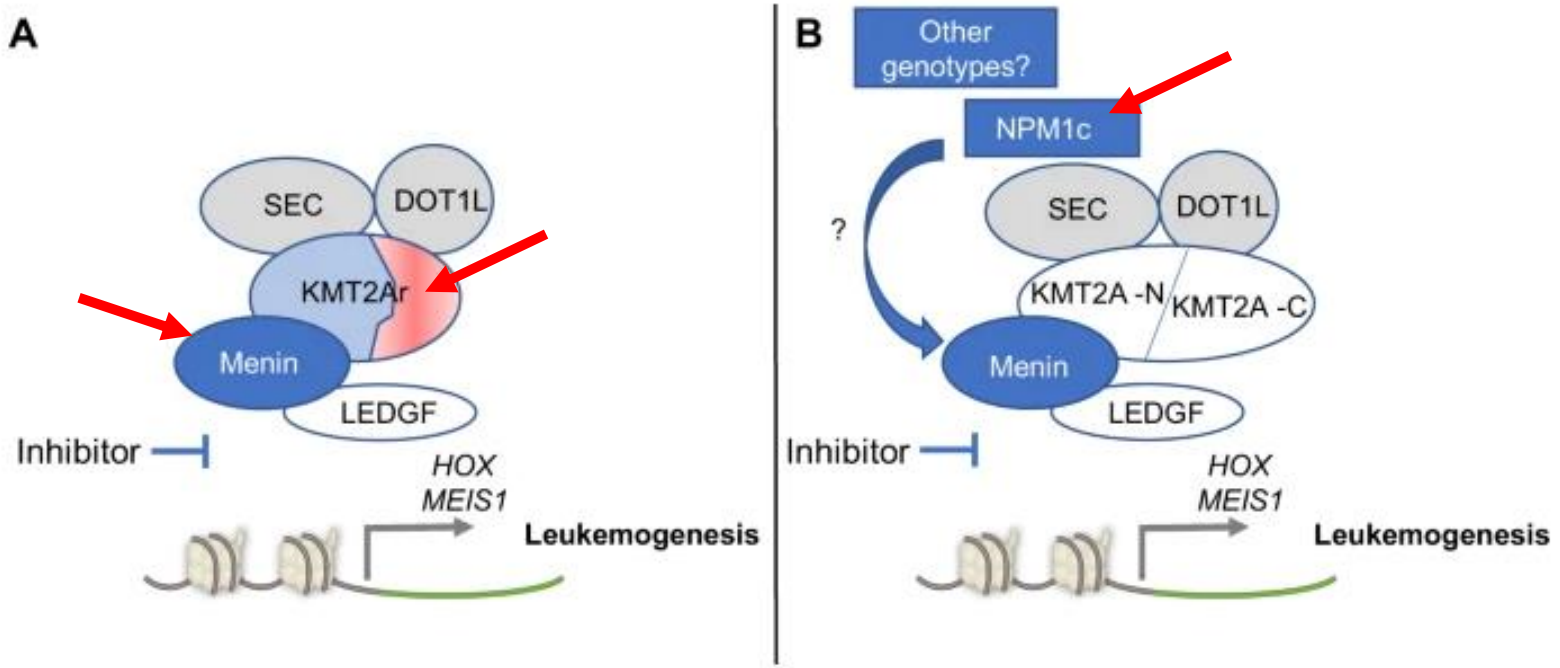
B. Hypomethylating agent +/- Venetoclax

C. Low-Dose Cytarabine +/- Venetoclax

D. Novel Menin inhibitor clinical trial (Ziftomenib, Revumenib)

E. Refer for Stem Cell Transplant

Case 1: Menin inhibition



Case 1: Menin inhibition

LBA-5 Revumenib Monotherapy in Patients with Relapsed/Refractory *KMT2Ar* Acute Leukemia: Topline Efficacy and Safety Results from the Pivotal Augment-101 Phase 2 Study

Program: General Sessions
Session: Late-Breaking Abstracts Session
Hematology Disease Topics & Pathways:
Research, Acute Myeloid Malignancies, AML, MDS, Anticoagulant Drugs, clinical trials, adult, MPN, Non-Biological therapies, elderly, Clinical Research, CML, Chemotherapy, Combination therapy, CMML, Coagulant Drugs, drug development, pediatric, Diseases, Devices, drug-drug interactions, Opioids, therapy sequence, Palliative Care, Myeloid Malignancies, Pharmacology, Surgical, Radiation Therapy, Study Population, Human

Tuesday, December 12, 2023, 9:00 AM-10:30 AM

Ibrahim Aldoss, MD[1], Ghayas C. Issa[2], Michael Thirman[3], John DiPersio[4], Martha Arellano[5], James S. Blachly[6], Gabriel N. Mannis[7], Alexander Perl[8], David S. Dickens[9*], Christine M. McMahon[10], Elie Traer, MD, PhD[11], C. Michel Zwaan[12], Carolyn Grove[13], Richard Stone[14], Paul J. Shami[15], Ioannis Mantzaris[16], Matthew Greenwood[17], Neerav Shukla[18], Branko Cuglievan[2], Yu Gu[19*], Rebecca G. Bagley[19*], Kate Madigan[19*], Soujanya Sunkaraneni[19*], Huy Van Nguyen[19*], Nicole McNeer[19*] and Eytan M. Stein[18]

	Pooled efficacy (n=57)	AML efficacy[b] (n=49)
ORR, n (%)[c]	36 (63.2)	32 (65.3)
Best response, n (%)		
CR	10 (17.5)	9 (18.4)
CRh	3 (5.3)	3 (6.1)
CRi	1 (1.8)	1 (2.0)
CRp	11 (19.3)	9 (18.4)
CRc	25 (43.9) 95% CI, 30.7, 57.6	22 (44.9) 95% CI, 30.7, 59.8
MLFS	10 (17.5)	10 (20.4)
PR	1 (1.8)	-
CR+CRh rate, n (%)	13 (22.8) 95% CI, 12.7, 35.8 *P* value,[d] 0.0036	12 (24.5) 95% CI, 13.3, 38.9
Negative MRD status in CR/CRh, n (%)[e]	7/10 (70.0)	6/9 (66.7)
Negative MRD status in CRc	15/22 (68.2)	13/19 (68.4)

64th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Update on a Phase 1/2 First-in-Human Study of the Menin-KMT2A (MLL) Inhibitor Ziftomenib (KO-539) in Patients with Relapsed or Refractory Acute Myeloid Leukemia

Harry P. Erba, MD PhD[1], Amir T. Fathi, MD[2,3], Ghayas C. Issa, MD[4], Jessica K. Altman, MD[5], Pau Montesinos, MD PhD[6,], Mrinal M. Patnaik, MD MBBS[7], James M. Foran, MD[8], Stephane De Botton, MD PhD[9,*], Maria R. Baer, MD[10], Gary J. Schiller, MD[11], Roland B. Walter, MD PhD MS[12], Marina Kremyanskaya, MD PhD[13], Kristen M. Pettit, MD[14], Stephen A Strickland, MD MSCI[15], Blake Tomkinson, PhD MBA[16,*], Marilyn Tabachri, RN, BSN[16,*], Mollie Leoni, MD[16,*], Stephen Dale, MD[16,*], Eunice S. Wang, MD[17]*

	200 mg (N=12)	600 mg (N = 12)
CR/CRh Rate, n (%)[1]	0	3 (25.0)
95% CI[2]	(0.0, 26.5)	(5.5, 57.2)
Complete Remission Rate, n (%)	0	2 (16.7)
95% CI[2]	(0.0, 26.5)	(2.1, 48.4)
CRc Rate, n(%)[3]	0	4 (33.3)
95% CI[2]	(0.0, 26.5)	(9.9, 65.1)
MRD Negativity Rate, n (%)	0	3 (75.0)
95% CI[2]	(NA, NA)	(19.4, 99.4)
Overall Response Rate, n (%)[4]	0	5 (41.7)
95% CI[2]	(0.0, 26.5)	(15.2, 72.3)
MRD Negativity Rate, n(%)	0	3 (60.0)
95% CI[2]	(NA, NA)	(14.7, 94.7)

Case 1: Take Home Points

- ELN 2022 risk categories now consider FLT3-ITD mutations qualitatively rather than quantitatively and include numerous updated genetic abnormalities compared to the previous 2017 categories.
- IDH1 inhibitors (i.e. Ivosidenib) are approved as monotherapy or in combination with Azacitadine for first-line treatment in patients ≥ 75 years old who are not candidates for intensive induction chemotherapy and can induce deep and durable remissions.
- Menin inhibitors are a novel therapeutic approach for R/R AML with KMT2A alteration and NPM1 mutations with preliminary data showing promising response rates.
- Differentiation syndrome is a common TRAE seen with novel targeted small molecule inhibitors with rates ranging from 5-20%.

Case 1: End of Case

Case 2: History

- 76 year old female presents to PCP with 2 months of dyspnea with exertion and fatigue. She denies bleeding or bruising issues.
- PMH: Type 2 DM.
- SH: Retired teacher. Lives with spouse alone. Has 1 adult child in good health who lives nearby. Non-smoker. No alcohol.
- FH: No history of Hematologic Malignancies
- Physical Exam: appearing stated age, no scleral icterus, appears slightly fatigued from walking from car to the office, otherwise unremarkable without splenomegaly or lymphadenopathy appreciated.

Case 2: Labs

Lab	Value	Unit
WBC	3.6	K/μL
Hgb	6.8	g/dL
Hct	20.1	%
MCV	102	fL
PLT	115	K/μL
Differential:		
ANC	2400	K/μL

Bone Marrow Biopsy:

- Hypercellular marrow (~50%) with trilineage hematopoiesis. Megaloblastic changes noted in erythroids.
- Blasts 2%, >15% ringed sideroblasts
- Cytogenetics: negative for del(5q), del(7q)
- Molecular studies: SF3B1+, TP53 normal

Case 2:

WHO 2022

CLASSIFICATION OF MYELODYSPLASTIC NEOPLASMS (MDS)[a,†,‡]

WHO 2022[†]	WHO 2016[‡,1]	Blasts
MDS, genetically defined		
• MDS-5q (low blasts)[b]	MDS-del(5q)	<5% BM, <2% PB
• MDS-SF3B1 (low blasts)[c]	MDS-RS	<5% BM
• MDS-bi*TP53*[d]	-	<20% BM, PB
MDS, morphologically defined		
• MDS with low blasts (MDS-LB)	MDS-SLD, MDS-MLD	<5% BM, 2%–4% PB
• MDS, hypoplastic (MDS-h)[e]	-	<5% BM
• MDS with increased blasts (MDS-IB)		
▸ MDS-IB1 ▸ MDS-IB2[f]	MDS-EB1 MDS-EB2	5%–9% BM or 2%–4% PB 10%–19% BM or 5%–19% PB, Auer rods
▸ MDS with fibrosis (MDS-f)	-	5%–19% BM, 2%–19% PB
• AML	AML	WHO: ≥20% BM[g,2] ICC: ≥20% BM blasts or ≥10% with defining molecular abnormalities[g,3]

International Consensus Classification 2022

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

Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation* or *TP53* mutation (VAF > 10%) and complex karyotype often with loss of 17p†
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF > 10%)
AML with mutated *TP53*	Not required	≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia	Any somatic *TP53* mutation (VAF > 10%)

Case 2:

Which Prognostic Scoring System is most useful in assessing this patient's risk of progression to AML?

A. IPSS

B. IPSS-R

C. IPSS-M

D. IDK?

Case 2: Prognostic Scoring Systems

REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R[2])

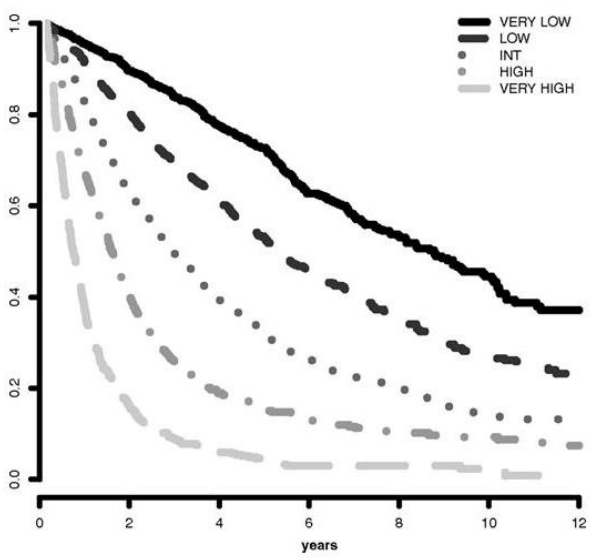
	Score Value						
Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetic[e]	Very good	—	Good	—	Intermediate	Poor	Very poor
Marrow blasts (%)	≤2	—	>2-<5	—	5-10	>10	—
Hemoglobin	≥10	—	8-<10	<8	—	—	—
Platelets	≥100	50-<100	<50	—	—	—	—
ANC	≥0.8	<0.8	—	—	—	—	—

IPSS-R Risk Category (% IPSS-R pop.)	Overall Score	Median Survival (y) in the Absence of Therapy	25% AML Progression (y) in the Absence of Therapy
VERY LOW (19)	≤1.5	8.8	Not reached
LOW (38)	>1.5-≤3.0	5.3	10.8
INT[3] (20)	>3.0-≤4.5	3	3.2
HIGH (13)	>4.5-≤6.0	1.6	1.4
VERY HIGH (10)	>6.0	0.8	0.7

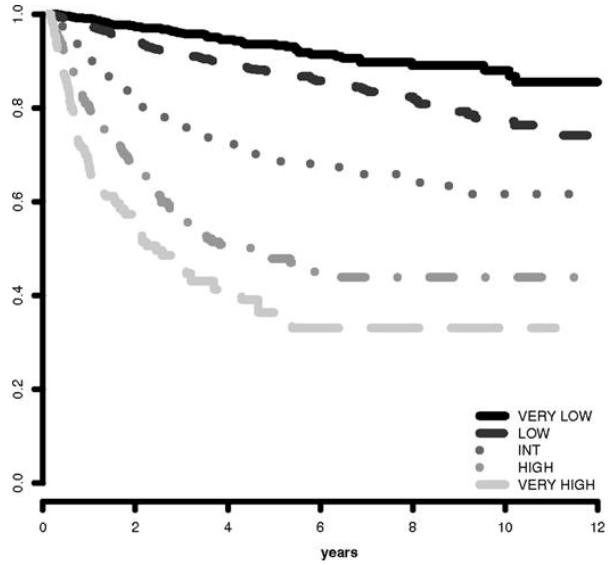
For IPSS-R: Very Low/Low/Intermediate, see MDS-3 through MDS-5
For IPSS-R: Intermediate/High/Very High, see MDS-6

[e] Cytogenetic risks: Very good = -Y, del(11q); Good = normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate = del(7q), +8, +19, i(17q), any other single or double independent clones; Poor = -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities; Very poor = complex: >3 abnormalities.

Survival

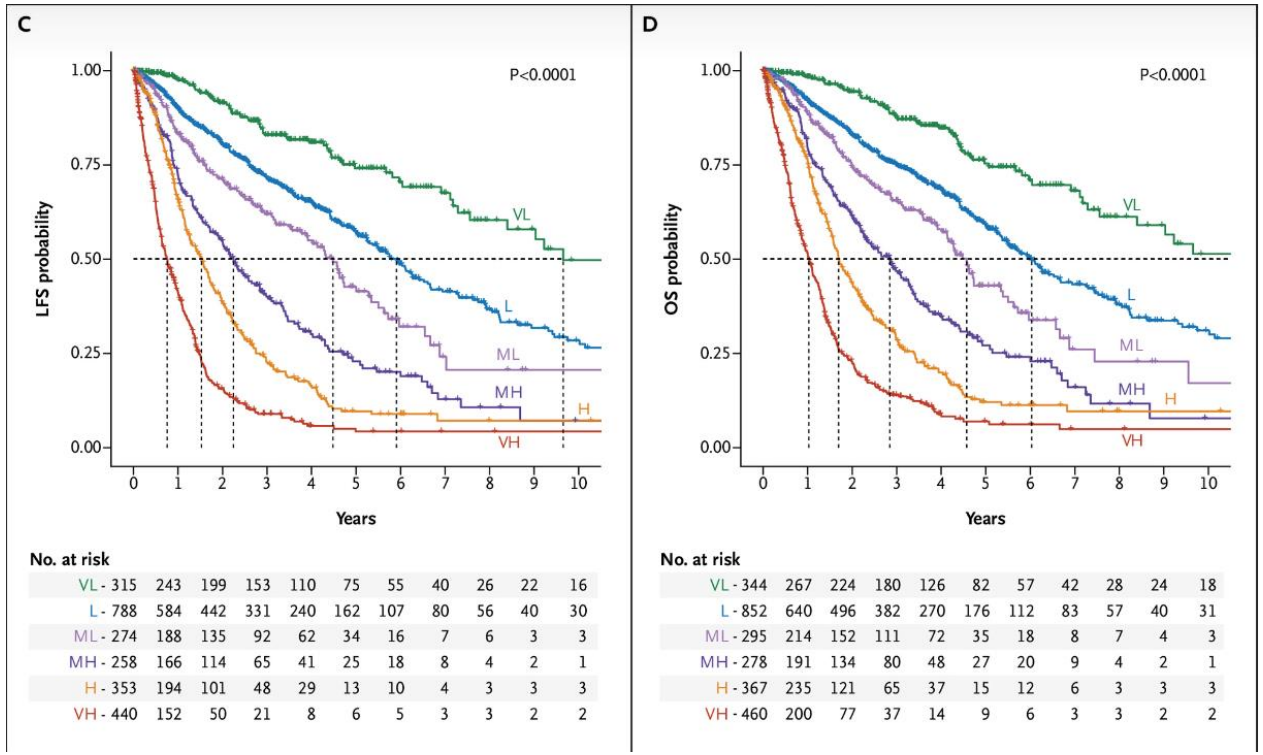


AML Evolution

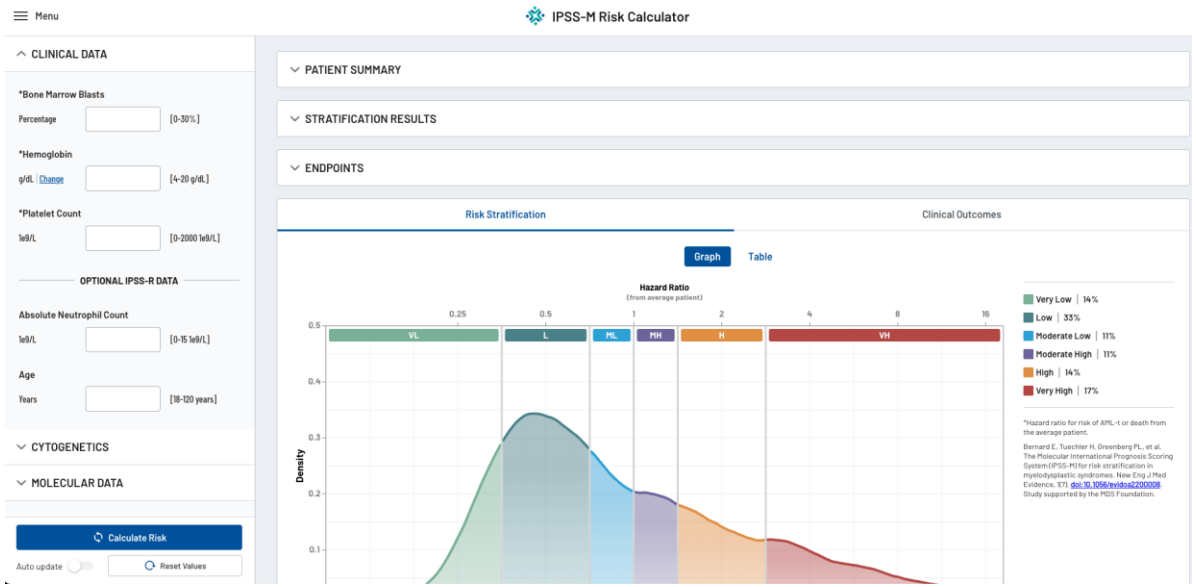


Outcomes / Risk	Very Low	Low	Intermediate	High	Very High
mOS (years)	8.8	5.3	3.0	1.6	0.8
AML evolution (25%, years)	NR	10.8	3.2	1.4	0.73

Case 2: IPSS-M



mds-risk-model.com



Case 2: Our patient with MDS-SF3B1 is considered Low-Risk by IPSS-R (score 2.5) and Moderate-Low by IPSS-M (score -0.39). She is noted to have >15% ringed sideroblasts with her primary issue being symptomatic, transfusion-dependent anemia. Which first-line treatment option should be considered first?

A. Supportive Care

B. ESA

C. Lenalidomide

D. Luspatercept

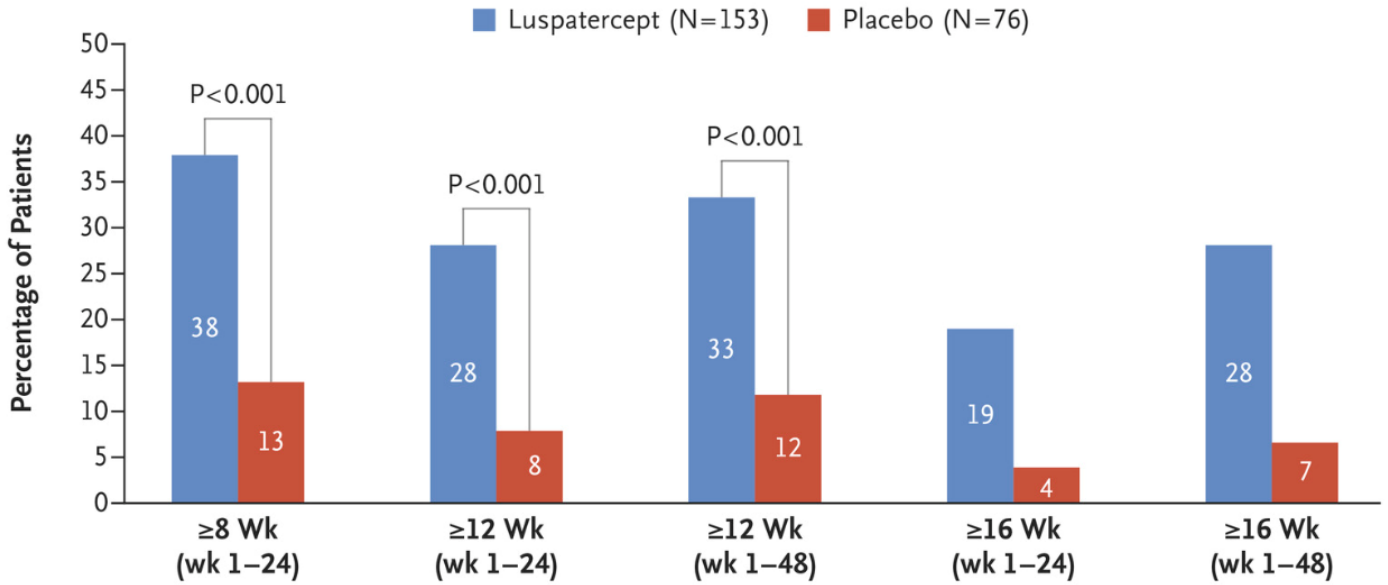
E. HMA

Case 2:

ORIGINAL ARTICLE

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

Pierre Fenaux, M.D., Ph.D., Uwe Platzbecker, M.D., Ghulam J. Mufti, F.R.C.P., Guillermo Garcia-Manero, M.D., Rena Buckstein, M.D., Valeria Santini, M.D., María Díez-Campelo, M.D., Ph.D., Carlo Finelli, M.D., Mario Cazzola, M.D., Osman Ilhan, M.D., Mikkael A. Sekeres, M.D., José F. Falantes, M.D., et al.



No. of Patients with Response (% [95% CI])					
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

Case 2:

ORIGINAL ARTICLE

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

Pierre Fenaux, M.D., Ph.D., Uwe Platzbecker, M.D., Ghulam J. Mufti, F.R.C.P., Guillermo Garcia-Manero, M.D., Rena Buckstein, M.D., Valeria Santini, M.D., María Díez-Campelo, M.D., Ph.D., Carlo Finelli, M.D., Mario Cazzola, M.D., Osman Ilhan, M.D., Mikkael A. Sekeres, M.D., José F. Falantes, M.D., et al.

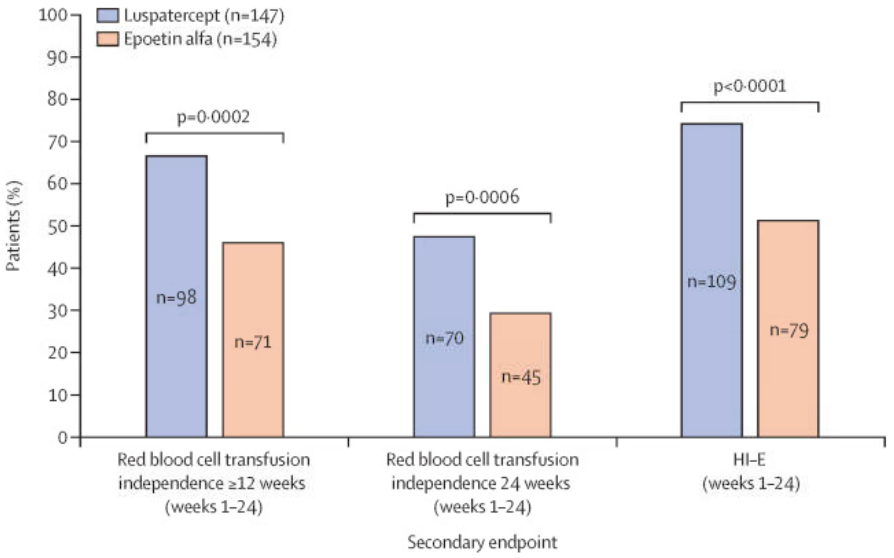
Table 2. Erythroid Response and Increase in Mean Hemoglobin Levels.

End Point	Luspatercept (N=153)	Placebo (N=76)
Erythroid response during wk 1–24*		
No. of patients (% [95% CI])	81 (53 [45–61])	9 (12 [6–21])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	52/107 (49)	8/56 (14)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	29/46 (63)	1/20 (5)
Erythroid response during wk 1–48*		
No. of patients (% [95% CI])	90 (59 [51–67])	13 (17 [9–27])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	58/107 (54)	12/56 (21)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	32/46 (70)	1/20 (5)
Mean increase in hemoglobin level of ≥1.0 g/dl — no. (% [95% CI])§		
During wk 1–24	54 (35 [28–43])	6 (8 [3–16])
During wk 1–48	63 (41 [33–49])	8 (11 [5–20])

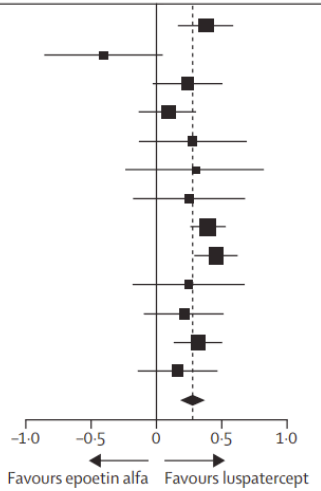
Case 2:

Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial

Uwe Platzbecker, Matteo Giovanni Della Porta*, Valeria Santini, Amer M Zeidan, Rami S Komrokji, Jake Shortt, David Valcarcel, Anna Jonasova, Sophie Dimicoli-Salazar, Ing Soo Tiong, Chien-Chin Lin, Jiahui Li, Jennie Zhang, Ana Carolina Giuseppi, Sandra Kreitz, Veronika Pozharskaya, Karen L Keeperman, Shelonitda Rose, Jeevan K Shetty, Sheida Hayati, Sadanand Vodala, Thomas Prebet, Andrius Degulys, Stefania Paolini, Thomas Cluzeau, Pierre Fenaux†, Guillermo Garcia-Manero†*



	Luspatercept		Epoetin alfa		Risk difference (95% CI)	Weight (%)
	Responders	Total	Responders	Total		
ASXL1	15	31	3	29	0·38 (0·17 to 0·59)	10·5
CBL	0	5	2	5	−0·40 (−0·85 to 0·05)	3·6
DNMT3A	19	28	11	25	0·24 (−0·02 to 0·50)	8·1
DTA.SF3B1.n	12	31	12	40	0·09 (−0·14 to 0·31)	9·8
EZH2	5	10	2	9	0·28 (−0·13 to 0·69)	4·2
IDH2	3	6	1	5	0·30 (−0·23 to 0·83)	2·7
RUNX1	1	4	0	9	0·25 (−0·17 to 0·67)	4·0
SF3B1	64	92	27	90	0·40 (0·26 to 0·53)	15·1
SF3B1α	41	55	16	55	0·45 (0·29 to 0·62)	12·9
SF3B1β	1	4	0	8	0·25 (−0·18 to 0·68)	3·9
SRSF2	5	14	2	14	0·21 (−0·10 to 0·53)	6·4
TET2	30	48	16	53	0·32 (0·14 to 0·51)	11·8
U2AF1	6	16	4	19	0·16 (−0·14 to 0·46)	6·8
Random-effects model		**344**		**361**	**0·27 (0·18 to 0·37)**	**100**



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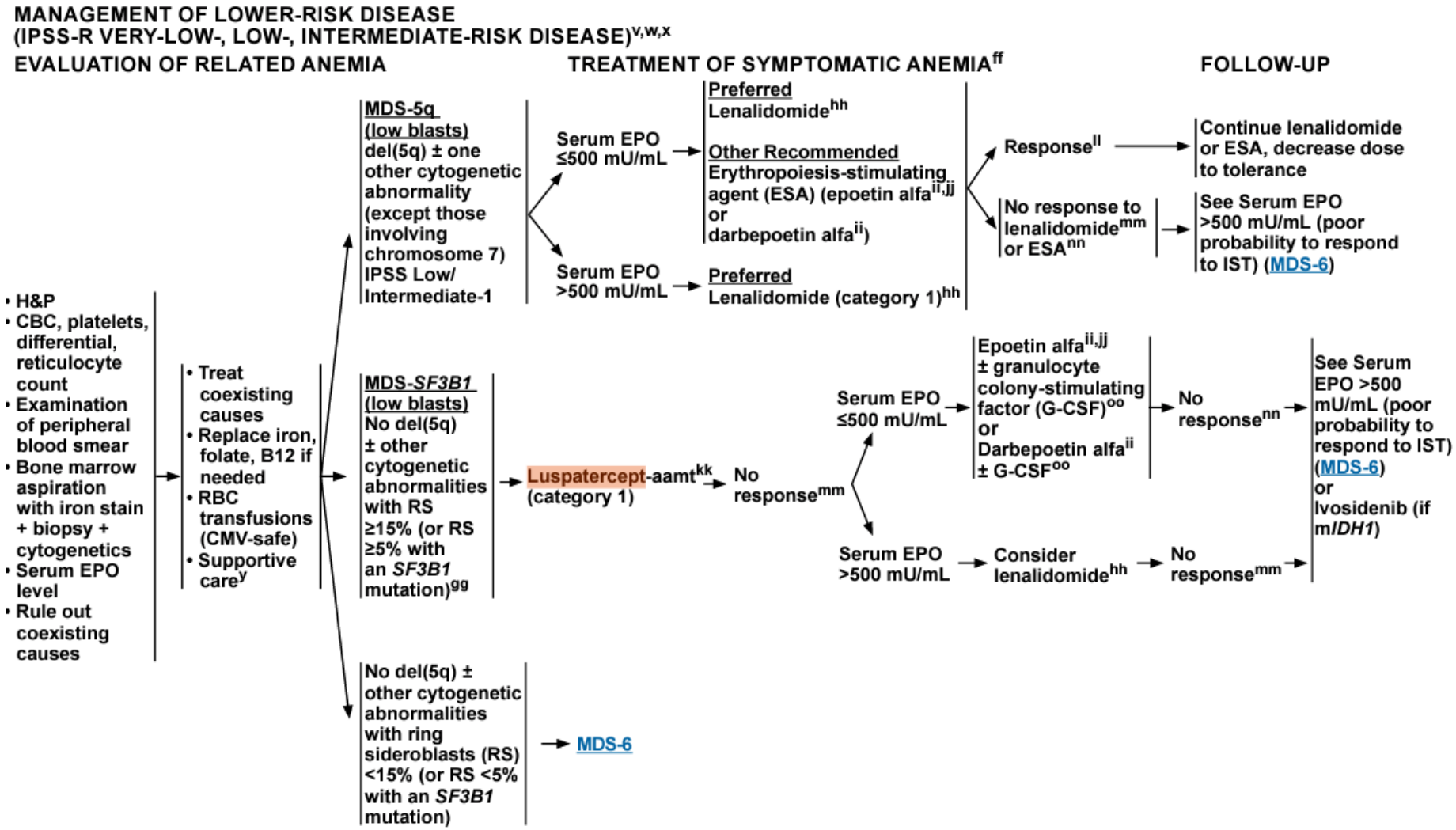
Case 2:


MANAGEMENT OF LOWER-RISK DISEASE
(IPSS-R VERY-LOW-, LOW-, INTERMEDIATE-RISK DISEASE)v,w,x
EVALUATION OF RELATED ANEMIA
TREATMENT OF SYMPTOMATIC ANEMIAff
FOLLOW-UP
• H&P
• CBC, platelets, differential, reticulocyte count
• Examination of peripheral blood smear
• Bone marrow aspiration with iron stain + biopsy + cytogenetics
• Serum EPO level
• Rule out coexisting causes
• Treat coexisting causes
• Replace iron, folate, B12 if needed
• RBC transfusions (CMV-safe)
• Supportive carey
MDS-5q (low blasts) del(5q) ± one other cytogenetic abnormality (except those involving chromosome 7) IPSS Low/ Intermediate-1
Serum EPO ≤500 mU/mL
Preferred Lenalidomidehh
Other Recommended Erythropoiesis-stimulating agent (ESA) (epoetin alfaii,jj or darbepoetin alfaii)
Responsell
Continue lenalidomide or ESA, decrease dose to tolerance
No response to lenalidomidemm or ESAnn
See Serum EPO >500 mU/mL (poor probability to respond to IST) (MDS-6)
Serum EPO >500 mU/mL
Preferred Lenalidomide (category 1)hh
MDS-SF3B1 (low blasts) No del(5q) ± other cytogenetic abnormalities with RS ≥15% (or RS ≥5% with an SF3B1 mutation)gg
Luspatercept-aamtkk (category 1)
No responsemm
Serum EPO ≤500 mU/mL
Epoetin alfaii,jj ± granulocyte colony-stimulating factor (G-CSF)oo or Darbepoetin alfaii ± G-CSFoo
No responsenn
See Serum EPO >500 mU/mL (poor probability to respond to IST) (MDS-6) or Ivosidenib (if mIDH1)
Serum EPO >500 mU/mL
Consider lenalidomidehh
No responsemm
No del(5q) ± other cytogenetic abnormalities with ring sideroblasts (RS) <15% (or RS <5% with an SF3B1 mutation)
MDS-6

Case 2: Therapies on the horizon

RESEARCH ARTICLE | Free Access

Roxadustat for the treatment of anemia in patients with lower-risk myelodysplastic syndrome: Open-label, dose-selection, lead-in stage of a phase 3 study

David H. Henry, John Glaspy, Rosemary Harrup, Moshe Mittelman, Amy Zhou, Hetty E. Carraway, Charles Bradley, Gopal Saha, Katharina Modelska, Pamela Bartels, Robert Leong, Kin-Hung P. Yu

- Roxadustat: first-in-class oral Hypoxia-inducible Factor (HIF) Prolyl Hydroxylase (PH) inhibitor
- Prevents hydroxylation of HIF-α allowing for transcription of the EPO gene
- May 5, 2023 – MATTERHORN study did not meet primary efficacy endpoint.

Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial

Prof Uwe Platzbecker, MD * • Valeria Santini, MD * • Prof Pierre Fenaux, MD • Prof Mikkael A Sekeres, MD • Prof Michael R Savona, MD • Yazan F Madanat, MD • et al. Show all authors • Show footnotes

Published: December 01, 2023 • DOI: https://doi.org/10.1016/S0140-6736(23)01724-5 • Check for updates

- Imetelstat: competitive telomerase inhibitor
- Targets cells with increase telomerase activity, selectively inducing apoptosis in malignant hematopoietic progenitor cells and enabling recovery of bone marrow function (i.e. erythropoiesis).
- IMerge Trial – Lancet 12/2023
  - Imetelstat group: 40% of patients have TI of at least 8 weeks (15% in placebo group)
  - Common grade 3-4 AE's: neutropenia (68%) and thrombocytopenia (62%).

Case 2: Take Home Points

- IPSS-R incorporates cytogenetic features in stratifying patients into risk categories and remains the gold standard prognostic scoring system for MDS.

- IPSS-M adds genetic alterations and may be more useful as more therapies are developed, but needs further validation in making treatment decisions.

- Luspatercept is FDA approved for two specific MDS populations:
  - ESA-naïve adult patients with very low- to intermediate-risk MDS who may require regular RBC transfusions
  - Adult patients with very low- to intermediate-risk MDS with ringed sideroblasts (MDS-RS) who have failed ESA and require 2 or more RBC transfusions over 8 weeks

- Further alternative therapies are currently under development such as HIF-PH inhibition and Telomerase inhibition and may provide improved benefits to a more generalized Low-Risk MDS population

Case 2: End of Case

Case 3: History

- 66 year old male who presents to PCP with abdominal discomfort, distension, 15 lb weight loss, and progressive fatigue x 1 month.
- PMH: Hypertension, Hyperlipidemia, Type 2 Diabetes, CKD 3, alcohol-use disorder (1 episode of acute alcohol withdrawal 3 years ago during a short hospitalization for low-risk surgical procedure).
- SH: Self-employed, divorced, one adult child who lives out of country, prior smoker (quit at age 40), and drinks 2-3 alcoholic beverages on weekdays and 4-5 on weekends.
- FH: No history of prior Hematologic Malignancies
- Physical Exam: abdomen is moderately distended with tenderness in the LUQ, spleen edge appreciated 5-6 cm below left lower rib edge, no fluid wave, no jaundice

Case 3: Labs

Lab	Value	Unit
WBC	3.7	K/μL
Hgb	8.4	g/dL
Hct	26.5	%
PLT	47	K/μL
Differential:		
Blasts: 2%	+ Teardrop cells	Leukoerythroblastosis

Lab	Value	Unit
Creatinine	0.72	mg/dL
AST	65	U/L
ALT	32	U/L
ALP	64	U/L
T bili	0.5	mg/dL
LDH	540	U/L

Case 3: Work-Up

Bone Marrow Biopsy consistent with Primary Myelofibrosis with atypical megakaryocytes, MF-2 reticulin fibrosis, and grade 2 collagen fibrosis.

Normal Karyotype

Molecular tests: +JAK2 V617F mutation, negative for CALR, MPL, IDH1/2. Further NGS-based myeloid panel without targetable or high-risk mutations.

Case 3:

Which prognostic calculator is most helpful in determining this patient's risk category?

A. DIPSS

B. DIPSS-PLUS

C. MIPSS-70

D. MIPSS-70+

Case 3:

RISK STRATIFICATION FOR PATIENTS WITH PMF

DYNAMIC INTERNATIONAL PROGNOSTIC SCORING SYSTEM (DIPSS)[1]

Prognostic Variable	Points		
	0	1	2
Age, y	≤65	>65	
White blood cell count, x10⁹/L	≤25	>25	
Hemoglobin, g/dL	≥10		<10
Peripheral blood blast, %	<1	≥1	
Constitutional symptoms, Y/N	N	Y	

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1 or 2
Intermediate-2 (INT-2)	3 or 4
High	5 or 6

DIPSS-PLUS[2]

Prognostic Variable	Points
DIPSS low-risk	0
DIPSS intermediate-risk 1 (INT-1)	1
DIPSS intermediate-risk 2 (INT-2)	2
DIPSS high-risk	3
Platelets <100 x 10⁹/L	1
Transfusion need	1
Unfavorable karyotype*	1

*Unfavorable karyotype: complex karyotype or sole or two abnormalities that include trisomy 8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3), or 11q23 rearrangement.

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1
Intermediate-2 (INT-2)	2 or 3
High	4 to 6

Case 3:

RISK STRATIFICATION FOR PATIENTS WITH PMF

MUTATION-ENHANCED IPSS (MIPSS-70) FOR PATIENTS WITH PMF AGE ≤70 YEARS[3]

Prognostic Variable	Points
Hemoglobin <10 g/dL	1
Leukocytes >25 x 10^9/L	2
Platelets <100 x 10^9/L	2
Circulating blasts ≥2%	1
Bone marrow fibrosis grade ≥2	1
Constitutional symptoms	1
CALR type-1 unmutated genotype	1
High-molecular-risk (HMR) mutations[a]	1
≥2 HMR mutations	2

Risk Group	Points
Low	0–1
Intermediate	2–4
High	≥5

RISK STRATIFICATION FOR PATIENTS WITH PMF

MUTATION AND KARYOTYPE-ENHANCED IPSS (MIPSS-70+ VERSION 2.0) FOR PATIENTS WITH PMF[4,5]

Prognostic Variable	Points
Severe anemia (Hemoglobin <8 g/dL in women and <9 g/dL in men)	2
Moderate anemia (Hemoglobin 8–9.9 g/dL in women and 9–10.9 g/dL in men)	1
Circulating blasts ≥2%	1
Constitutional symptoms	2
Absence of *CALR* type 1 mutation	2
HMR mutations[b]	2
≥2 HMR mutations	3
Unfavorable karyotype[c]	3
Very-high-risk (VHR) karyotype[d]	4

Risk Group	Points
Very low	0
Low	1–2
Intermediate	3–4
High	5–8
Very high	≥9

Online calculator for MIPSS-70+ Version 2.0 can be found at http://www.mipss70score.it/.

Case 3: Our patient has High-Risk Primary Myelofibrosis (DIPSS 5, DIPSS-PLUS 4). He declines transplant.

What is the best choice for first line therapy for this patient?

A. Supportive Care

B. Ruxolitinib

C. Fedratinib

D. Momelotinib

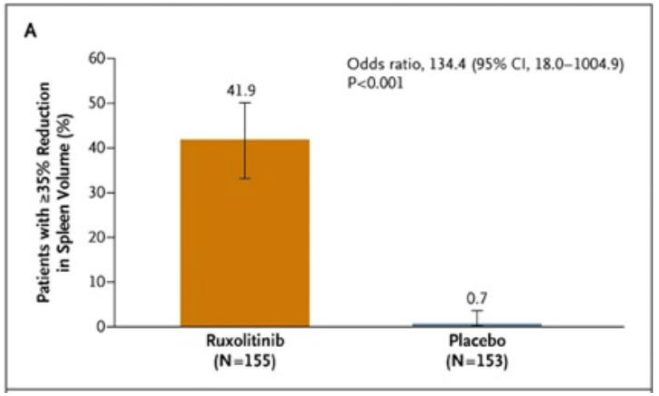
E. Pacritinib

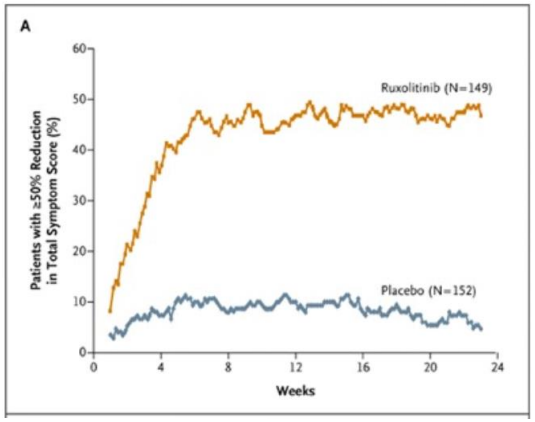
Case 3:

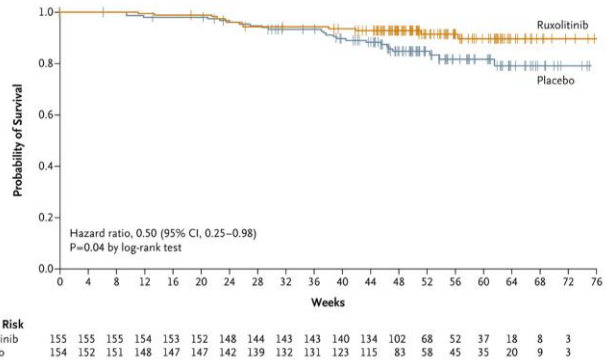
ORIGINAL ARTICLE

A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis

Srdan Verstovsek, M.D., Ph.D., Ruben A. Mesa, M.D., Jason Gotlib, M.D., Richard S. Levy, M.D., Vikas Gupta, M.D., John F. DiPersio, M.D., Ph.D., John V. Catalano, M.D., Michael Deininger, M.D., Ph.D., Carole Miller, M.D., Richard T. Silver, M.D., Moshe Talpaz, M.D., Elliott F. Winton, M.D., et al.



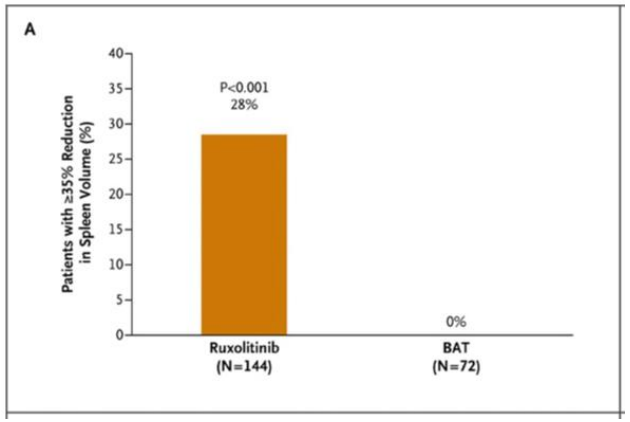


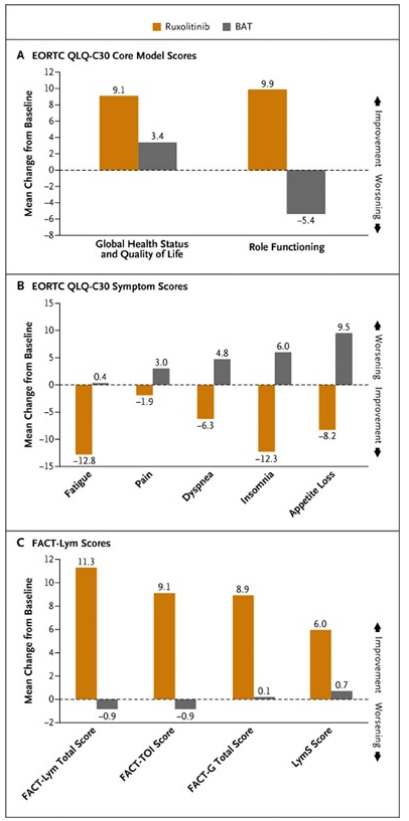


ORIGINAL ARTICLE

JAK Inhibition with Ruxolitinib versus Best Available Therapy for Myelofibrosis

Claire Harrison, D.M., Jean-Jacques Kiladjian, M.D., Ph.D., Haifa Kathrin Al-Ali, M.D., Heinz Gisslinger, M.D., Roger Waltzman, M.D., M.B.A., Viktoriya Stalbovskaya, Ph.D., Mari McQuitty, R.N., M.P.H., Deborah S. Hunter, Ph.D., Richard Levy, M.D., Laurent Knoops, M.D., Ph.D., Francisco Cervantes, M.D., Ph.D., Alessandro M. Vannucchi, M.D., et al.





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Case 3:

August 2015

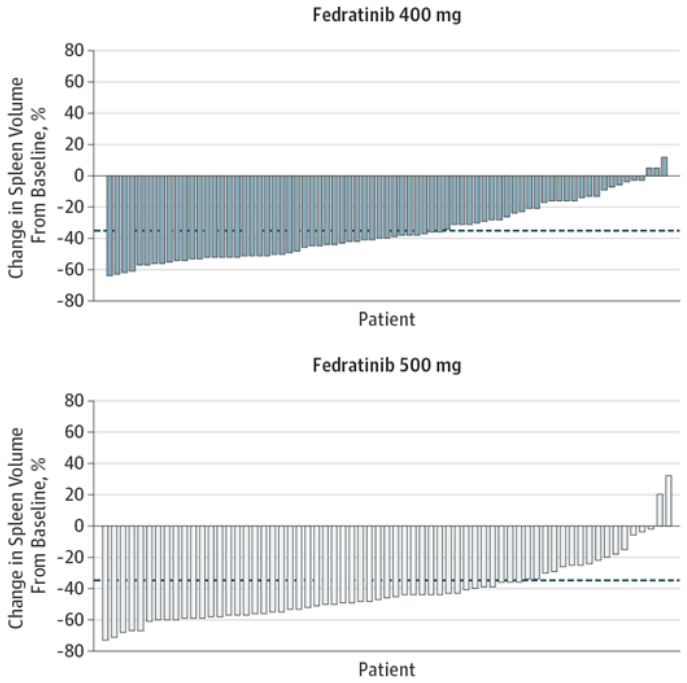
Safety and Efficacy of Fedratinib in Patients With Primary or Secondary Myelofibrosis

A Randomized Clinical Trial

Animesh Pardanani, MD[1]; Claire Harrison, MD[2]; Jorge E. Cortes, MD[3]; et al

» Author Affiliations | Article Information

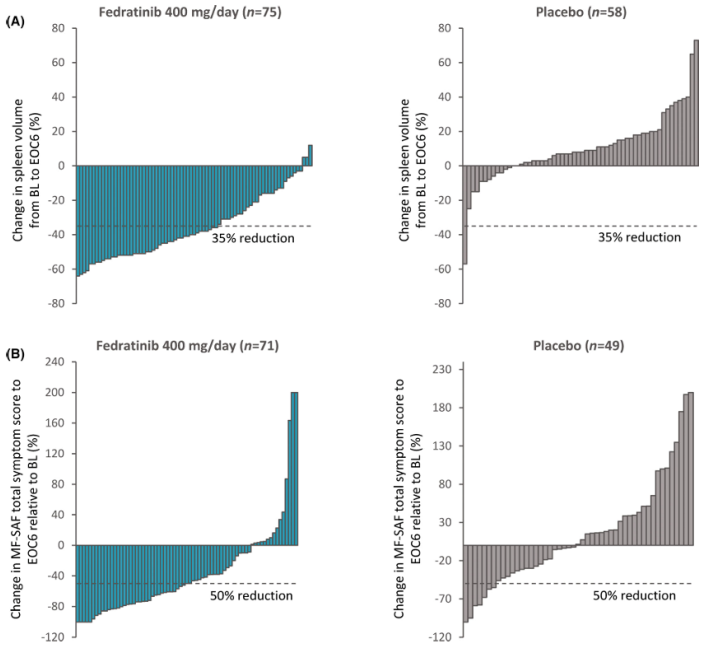
JAMA Oncol. 2015;1(5):643-651. doi:10.1001/jamaoncol.2015.1590



Clinical Trial > Br J Haematol. 2021 Oct;195(2):244-248. doi: 10.1111/bjh.17727. Epub 2021 Jul 30.

Updated results of the placebo-controlled, phase III JAKARTA trial of fedratinib in patients with intermediate-2 or high-risk myelofibrosis

Animesh Pardanani [1], Ayalew Tefferi [1], Tamás Masszi [2], Elena Mishchenko [3], Mark Drummond [4], Eric Jourdan [5], Alessandro Vannucchi [6], Mindaugas Jurgutis [7], Vincent Ribrag [8], Alessandro Rambaldi [9 10], Liang Piu Koh [11], Shelonitda Rose [12], Jun Zhang [12], Claire Harrison [13]



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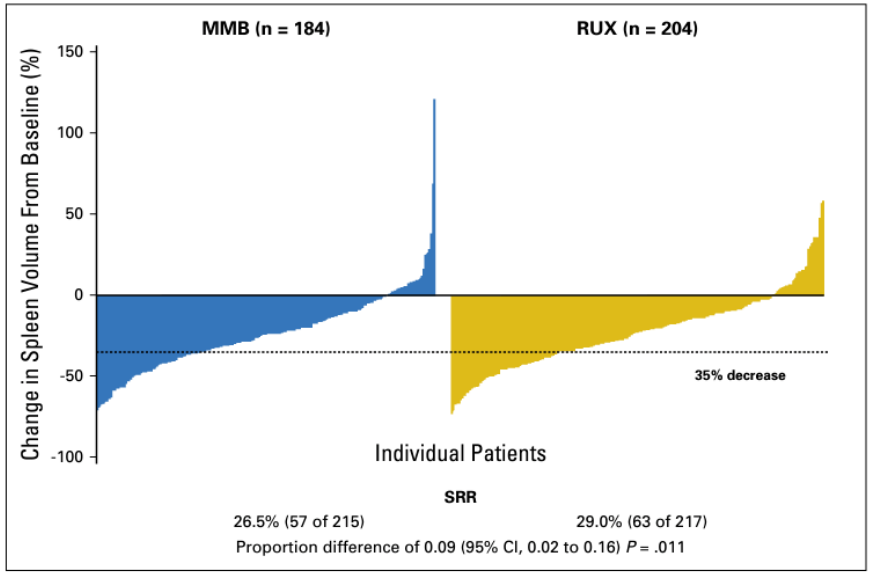
Case 3:

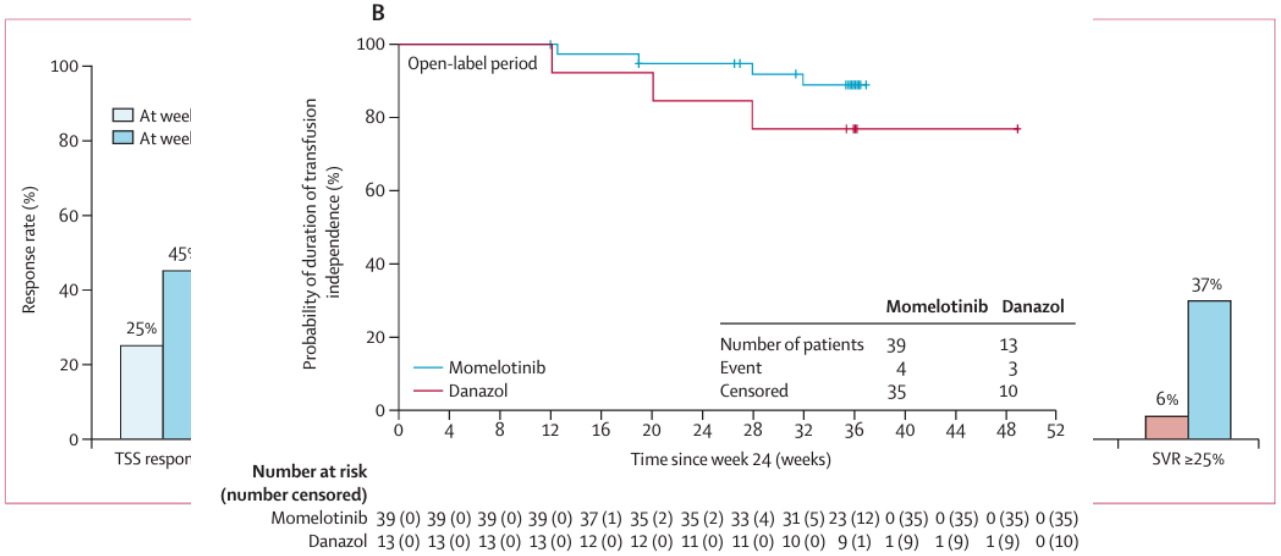
SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor–Naïve Patients With Myelofibrosis

Ruben A. Mesa, Jean-Jacques Kiladjian, John V. Catalano, Timothy Devos, Miklos Egyed, Andrzei Hellmann, Donal McLornan, Kazuya Shimoda, Elliott F. Winton, Wei Deng, Ronald L. Dubowy, Julia D. Maltzman, Francisco Cervantes, and Jason Gotlib



Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis previously treated with a JAK inhibitor (MOMENTUM): an updated analysis of an international, double-blind, randomised phase 3 study

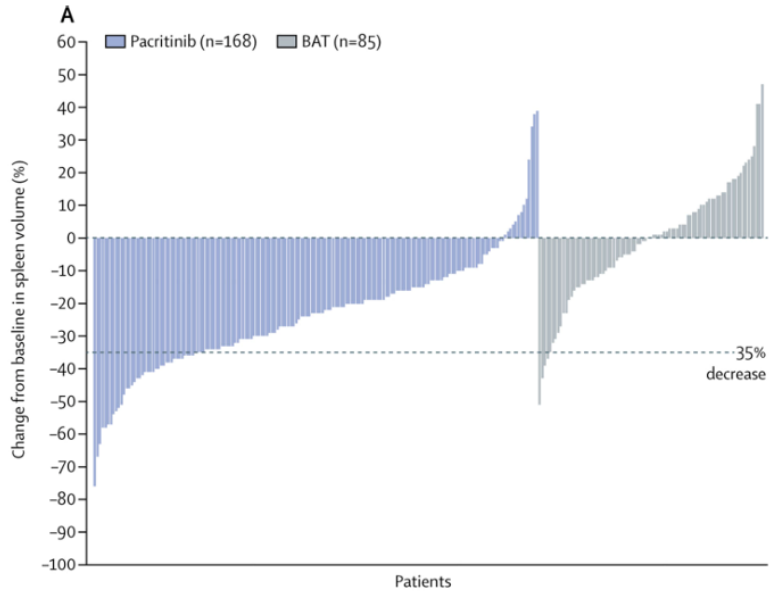
Aaron T Gerds, Srdan Verstovsek, Alessandro M Vannucchi, Haifa Kathrin Al-Ali, David Lavie, Andrew T Kuykendall, Sebastian Grosicki, Alessandra Iurlo, Yeow Tee Goh, Mihaela C Lazaroiu, Miklos Egyed, Maria Laura Fox, Donal McLornan, Andrew Perkins, Sung-Soo Yoon, Vikas Gupta, Jean-Jacques Kiladjian, Nikki Granacher, Sung-Eun Lee, Luminita Ocroteala, Francesco Passamonti, Claire N Harrison, Stephen Oh, Barbara J Klencke, Jing Yu, Rafe Donahue, Jun Kawashima, Ruben Mesa



Case 3:

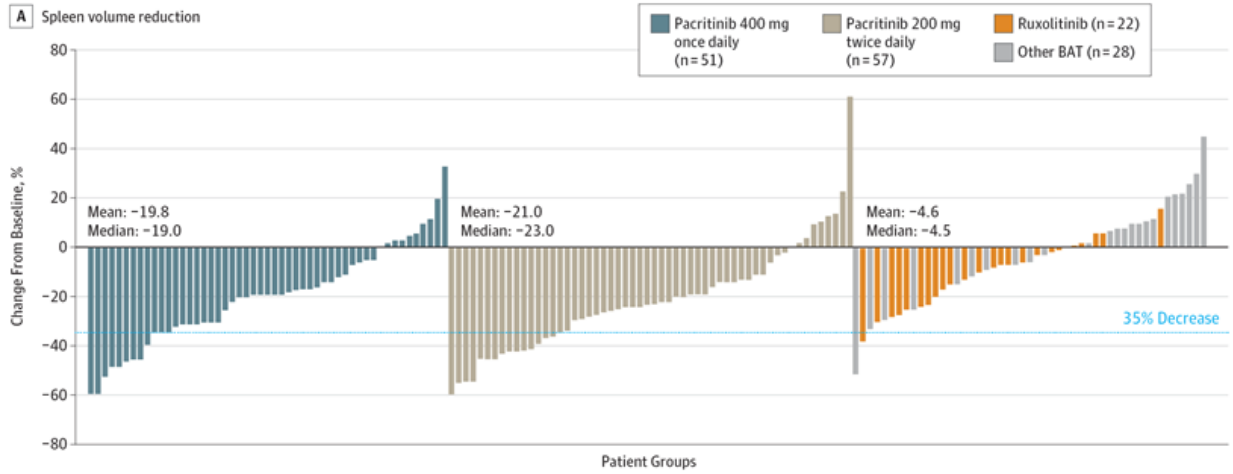
Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial

Ruben A Mesa [1], Alessandro M Vannucchi [2], Adam Mead [3], Miklos Egyed [4], Anita Szoke [5], Aleksandr Suvorov [6], Janos Jakucs [7], Andrew Perkins [8], Ritam Prasad [9], Jiri Mayer [10], Judit Demeter [11], Peter Ganly [12], Jack W Singer [13], Huafeng Zhou [13], James P Dean [13], Peter A Te Boekhorst [14], Jyoti Nangalia [15], Jean-Jacques Kiladjian [16], Claire N Harrison [17]



Pacritinib vs Best Available Therapy, Including Ruxolitinib, in Patients With Myelofibrosis: A Randomized Clinical Trial

John Mascarenhas [1], Ronald Hoffman [1], Moshe Talpaz [2], Aaron T Gerds [3], Brady Stein [4], Vikas Gupta [5], Anita Szoke [6], Mark Drummond [7], Alexander Pristupa [8], Tanya Granston [9], Robert Daly [9], Suliman Al-Fayoumi [9], Jennifer A Callahan [9], Jack W Singer [9], Jason Gotlib [10], Catriona Jamieson [11], Claire Harrison [12], Ruben Mesa [13], Srdan Verstovsek [14]



Case 3:

Symptomatic Therapies in Myelofibrosis

Asymptomatic	Observation
Symptomatic Anemia	ESA Momelotinib Danazol
Constitutional Symptoms / Symptomatic Splenomegaly	JAK inhibitor: Ruxolitinib Fedratinib Pacritinib Momelotinib

Case 3: Take Home Points

- DIPPS-PLUS is helpful in risk stratifying patients for medical management decisions and is commonly used in the clinic.
- MIPPS-70 and MIPPS-70+ were specifically developed for consideration patients who are transplant-eligible age to stratify to transplant vs medical management.
- Ruxolitinib is effective at spleen size reduction and symptom improvement, but is limited by anemia and thrombocytopenia.
- Fedratinib has similar efficacy as ruxolitinib, but there is a risk of Wernicke's Encephalopathy, thus thiamine levels much be monitored with therapy as well as PLT counts. GI AE's can be limiting.
- Momelotinib was non-inferior to ruxolitinib in spleen volume reduction, but was inferior for quality-of-life improvement. It also has benefit in patients with anemia. Peripheral neuropathy is a noted side effect.
- Pacritinib was found to be better than best available therapy (including ruxolitinib) and can be safely given to patients with baseline PLT <50K. GI AE's can be limiting.

Case 3: End of Case

Case 4: History

- 64 year old male who presents with progressive fatigue and back pain.
- PMH: well-controlled hypertension, diabetes.
- SH: Store manager, lives with spouse, two children (healthy), non-smoker, and non-drinker.
- FH: No history of prior Hematologic Malignancies
- Physical Exam: appearing fatigued, point tenderness in lower back over T11 vertebra

Case 4: Labs

Lab	Value	Unit
WBC	3.5	K/μL
Hgb	8.6	g/dL
Hct	26.0	%
PLT	205	K/μL
Differential:		
ANC	1.2	K/μL

Lab	Value	Unit
Creatinine	2.50	mg/dL
Ca	8.2	mg/dL
Albumin	3.0	g/dL
LDH	293	U/L

Case 4: Work-Up

Additional labs:
Beta 2 microglobulin: 6.1; SPEP/IFE M-spike 1.2 (IgA Kappa); total IgA 1100
Kappa 1200, Lambda 5, K:L 240

Bone Marrow Biopsy: 70% kappa restricted plasma cells in a hypercellular (50%) marrow with diminished erythroid and myeloid precursors.

FISH: +1q (gain), +3, +5, +11, t(4;14)

Case 4:

Multiple Myeloma (Symptomatic)[a,c]

Clonal BMPCs ≥10% or biopsy-proven bony or extramedullary plasmacytoma
and
Any one or more of the following myeloma-defining events:

- **Calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)**
- **Renal insufficiency (creatinine >2 mg/dL) [>177 µmol/L] or creatinine clearance <40 mL/min**
- **Anemia (hemoglobin <10 g/dL or hemoglobin >2 g/dL below the lower limit of normal)**
- **One or more osteolytic bone lesions on skeletal radiography, CT, or FDG-PET/CT**
- **Clonal BMPCs ≥60%**
- **Involved:uninvolved serum FLC ratio (FLCr) ≥100 and involved FLC concentration 10 mg/dL or higher**
- **>1 focal lesions on MRI studies ≥5 mm**

Case 4:

For Those with Newly Diagnosed MM

• R-ISS III (MYEL-B 2 of 2)
• Extramedullary disease
• Circulating plasma cells[a]
• Cytogenetic abnormalities
  ‣ Del(1p32)
  ‣ t(4;14)
  ‣ t(14;16)
  ‣ t(14;20)
  ‣ Del(17p)/monosomy 17/*TP53* mutation
  ‣ 1q21 gain/1q21 amplification[b]
  ‣ MYC translocation
• High-risk gene expression profile

Stage	International Staging System (ISS)	Revised-ISS (R-ISS)[1]	R2-ISS[2,c]
I	Serum beta-2 microglobulin <3.5 mg/L, Serum albumin ≥3.5 g/dL	ISS stage I and standard-risk chromsomal abnormalities by FISH and Serum LDH ≤ the upper limit of normal	Low-risk: 0 points[d] • Not ISS stage II or III • Serum LDH ≤ the upper limit of normal • del(17p), t(4;14), 1q+: Not detected
II	Not ISS stage I or III	Not R-ISS stage I or III	Low-intermediate risk: 0.5–1 points[d] • ISS stage II or • Serum LDH > the upper limit of normal or • del(17p) or t(4;14) or 1q+: Detected
III	Serum beta-2 microglobulin ≥5.5 mg/L	ISS stage III and either high-risk chromosomal abnormalities by FISH or Serum LDH > the upper limit of normal	Intermediate-high risk: 1.5–2.5 points[d] • Any combination of high-risk features which equals a score of 1.5–2.5
IV			High-risk: 3–5 points[d] • Any combination of high-risk features which equals a score of 3–5

Case 4: He is diagnosed with High-Risk Multiple Myeloma (ISS3, rISS 3, R2-ISS 4)

What is the appropriate induction regimen for this patient?

A. Lenalidomide + Dexamethasone (Rd)

B. Daratumumab + Lenalidomide + Dexamethasone (DRd)

C. Bortezomib + Lenalidomide + Dexamethasone (VRd)

D. Daratumumab + Bortezomib + Lenalidomide + Dexamethasone (DVRd)

E. Isatuximab + Carfilzomib + Lenalidomide + Dexamethasone (IKRd)

F. Other

Case 4:

Addition of daratumumab to lenalidomide, bortezomib, and dexamethasone for transplantation-eligible patients with newly diagnosed multiple myeloma (GRIFFIN): final analysis of an open-label, randomised, phase 2 trial

Peter M Voorhees, Douglas W Sborov*, Jacob Laubach, Jonathan L Kaufman, Brandi Reeves, Cesar Rodriguez, Ajai Chari, Rebecca Silbermann, Luciano J Costa, Larry D Anderson Jr, Nitya Nathwani, Nina Shah, Naresh Bumma, Yvonne A Efebera, Sarah A Holstein, Caitlin Costello, Andrzej Jakubowiak, Tanya M Wildes, Robert Z Orlowski, Kenneth H Shain, Andrew J Cowan, Shira Dinner, Huiling Pei, Annelore Cortoos, Sharmila Patel, Thomas S Lin, Saad Z Usmani, Paul G Richardson*

GRIFFIN trial – published Lancet Hematology 9/11/23

- Phase 2 D-VRd vs VRd in transplant-eligible patients

	D-VRd	VRd
Stringent CR	67%	47%
4-yr PFS	87.2%	70.0%
Median OS	Not reached	Not reached

ORIGINAL ARTICLE FREE PREVIEW

Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

Pieter Sonneveld, M.D., Ph.D., Meletios A. Dimopoulos, M.D., Mario Boccadoro, M.D., Hang Quach, M.B., B.S., M.D., P. Joy Ho, M.B., B.S., D.Phil., Meral Beksac, M.D., Cyrille Hulin, M.D., Elisabetta Antonioli, M.D., Ph.D., Xavier Leleu, M.D., Ph.D., Silvia Mangiacavalli, M.D., Aurore Perrot, M.D., Ph.D., Michele Cavo, M.D., et al., for the PERSEUS Trial Investigators*

PERSEUS trial – published NEJM 01/25/24

- Phase 3 D-VRd vs VRd in transplant-eligible patients

	D-VRd	VRd
48-mo PFS	84.3%	67.7%
CR or better	87.9%	70.1%
MRD-negative	75.2%	47.5%

Case 4:

Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone for the Treatment of High-Risk Newly Diagnosed Multiple Myeloma

Lisa B. Leypoldt, MD[1]; Diana Tichy, PhD[2]; Britta Besemer, MD[3]; Mathias Hänel, MD[4]; Marc S. Raab, MD[5]; Christoph Mann, MD[6]; Markus Munder, MD[7]; Hans Christian Reinhardt, MD[8]; Axel Nogai, MD[9]; Martin Görner, MD[10]; Yon-Dschun Ko, MD[11]; Maike de Wit, MD[12]; Hans Salwender, MD[13]; Christof Scheid, MD[14]; Ullrich Graeven, MD, PhD[15]; Rudolf Peceny, MD[16]; Peter Staib, MD, PhD[17]; Annette Dieing, MD[18]; Hermann Einsele, MD[19]; Anna Jauch, PhD[20]; Michael Hundemer, MD[21]; Manola Zago, PhD[22]; Ema Požek, MSc[2]; Axel Benner, Dipl Stat[2]; Carsten Bokemeyer, MD[1]; Hartmut Goldschmidt, MD[23]; and Katja C. Weisel, MD[1]

GMMG-CONCEPT trial – JCO, 9/27/2023

- Phase 2 IKRd for high-risk newly diagnosed Multiple Myeloma
- Enrolled both transplant eligible (TE) and ineligible patients (TIE)

	TE (N=99)	TIE (N=26)
MRD negative	67.7%	54.2%
Median F/up	44 months	33 months
Median PFS and OS	Not reached	Not reached

The 65th ASH Annual Meeting Abstracts

PLENARY ABSTRACTS

PLENARY ABSTRACTS

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, MD PhD[1,2], Wilfried Roeloffzen, MD PhD[3], Meletios A. Dimopoulos, MD PhD[4], Laura Rosiñol, MD PhD[5], Marjolein van der Klift, MD PhD[6], Roberto Mina, MD[1,2], Albert Oriol Rocafiguera, MD[7], Eirini Katodritou, MD[8], Ka Lung Wu, MD PhD[9], Paula Rodriguez Otero, MD PhD[10], Roman Hajek, MD[11,12], Elisabetta Antonioli, MD[13], Mark van Duin, PhD[14], Mattia D'Agostino, MD[2,1], Joaquin Martinez-Lopez, MD PhD[15], Elena M. van Leeuwen-Segarceanu, MD PhD[16], Paola Tacchetti, MD PhD[17], Niels W.C.J. van de Donk, MD PhD[18], Katja Weisel, MD[19], Luděk Pour, MD[20], Jakub Radocha, MD PhD[21], Angelo Belotti, MD[22], Fredrik Schjesvold, MDPhD[23,24], Joan Bladé, MD PhD[25], Hermann Einsele, MD PhD[26], Pieter Sonneveld, MD PhD[14], Mario Boccadoro, MD[27], Annemiek Broijl, MD PhD[14]

ISKIA trial – presented at ASH 2023

- Phase 3 IKRd for new MM as pre-ASCT induction and post-ASCT consolidation vs KRd

	IKRd	KRd
MRD neg (10^{-5}) after consolidation	77%	67%
MRD neg (10^{-6}) after consolidation	67%	48%
MRD-negative	75.2%	47.5%

Case 4: continued

- The patient undergoes 4 cycles of induction therapy with D-VRd and achieves a VGPR (M-spike undetectable, IFE showing IgA Kappa monoclonal band, K:L 1.4, total IgA 250).
- Repeat bone marrow biopsy shows 3% kappa restricted plasma cells.
- Creatinine improves to 1.0, Hgb improves to 10.0
- Treatment complicated by mild neutropenia without infections
- He is treated with monthly zoledronic acid (plan to complete 24 months total)
- He then undergoes Autologous SCT with Melphalan 200mg/m2 prep.

Case 4: continued

At Day +90, what is the most appropriate maintenance regimen for this patient?

A) Lenalidomide

B) Bortezomib

C) Lenalidomide + Bortezomib

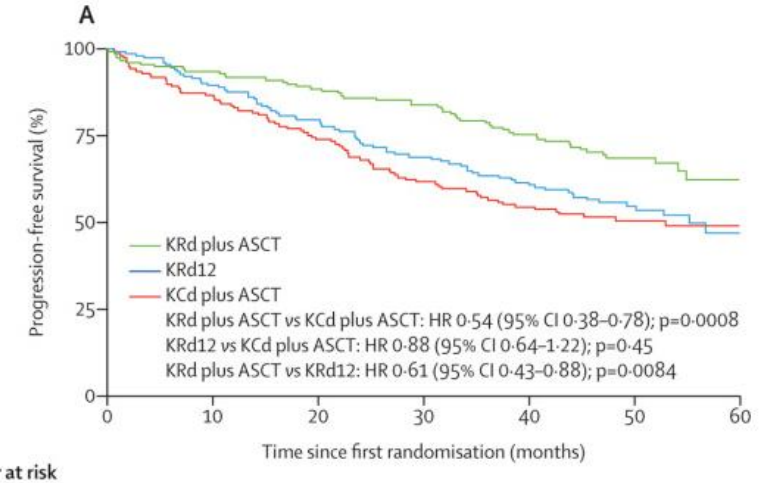
D) Lenalidomide + Carfilzomib

E) Lenalidomide + Daratumumab

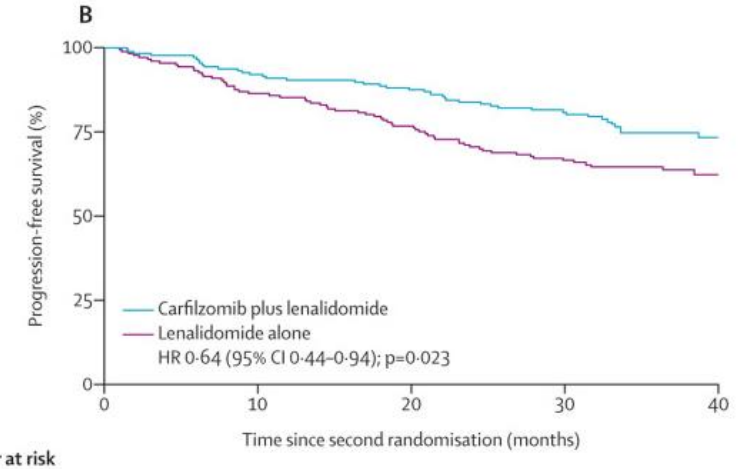
Case 4: continued

Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial

Francesca Gay, PhD * • Prof Pellegrino Musto, MD * • Delia Rota-Scalabrini, MD • Luca Bertamini, MD • Angelo Belotti, MD • Monica Galli, PhD • et al. Show all authors • Show footnotes



Number at risk (number censored)							
KRd plus ASCT	158 (0)	147 (1)	137 (3)	129 (4)	111 (9)	61 (51)	5 (103)
KRd12	157 (0)	135 (6)	120 (6)	103 (7)	90 (9)	51 (39)	5 (81)
KCd plus ASCT	159 (0)	137 (1)	115 (3)	94 (5)	80 (8)	46 (37)	6 (76)



Number at risk (number censored)					
Carfilzomib plus lenalidomide	178 (1)	162 (2)	151 (5)	123 (22)	41 (95)
Lenalidomide alone	178 (0)	154 (0)	135 (2)	108 (11)	39 (75)

Case 4: continued

RECRUITING

S1803, Lenalidomide +/- Daratumumab/rHuPh20 as Post-ASCT Maintenance for MM w/MRD to Direct Therapy Duration (DRAMMATIC)

ClinicalTrials.gov ID NCT04071457

Sponsor SWOG Cancer Research Network

Information provided by SWOG Cancer Research Network (Responsible Party)

Last Update Posted 2023-08-14

Case 4: continued

- The patient receives Daratumumab + Lenalidomide per GRIFFIN trial for 4 years, then has biochemical progression. Patient hoped to avoid transplant and cellular therapies.
  - IgA 950, SPEP: 0.4 g/dL, Kappa 110, lambda 5
  - Creatinine 1.4, Hgb 10.5
  - Repeat bone marrow biopsy FISH shows new del(17q)
- Treatment course:
  - Carfilzomib + Pomalidomide + Dex (KPd), achieves a VGPR for 18 months
  - Ixazomib + Cyclophosphamide + Dex (ICd), achieves a PR for 8 months
  - Selinexor + Pomalidomide + Dex (XPd), achieves VGPR that is ongoing at 4 months
- Kappa free light chains and IgA have now begun rising, but has not formally progressed

- Work-up for CAR-T cell therapy is started, but before insurance authorization can be obtained, his kappa free light chains rise rapidly and creatinine increases from 1.1 to 1.8.

- The patient is then admitted and started on a BCMA/CD3-directed bi-specific antibody

Case 4:

What infectious prophylaxis is best for this patient while receiving BCMA/CD3 bi-specific antibody therapy?

A) Antibacterial prophylaxis

B) Antifungal prophylaxis

C) Antiviral prophylaxis

D) PJP prophylaxis

E) IVIG (when IgG < 400)

F) Antiviral and PJP prophylaxis

G) Antiviral, PJP, and IVIG prophylaxis

Case 4:

Toxicity	Teclistamab (MajesTEC-1)	Elranatamab (MagnetisMM-3)	Talquetamab (MonumenTAL-1)
Infections (bacterial, viral, fungal)	76.4%	69.9%	47% (405 μg dose Q week) 34% (800 μg dose Q 2 week)
Hypogammaglobulinemia (IgG < 500 mg/dL)	74.5%	75.5% (IgG < 400 mg/dL)	87% (405 μg dose Q week) 71% (800 μg dose Q 2 week)
Grade ≥3 Neutropenia	64.2%	48.8%	60% (405 μg dose Q week) 32% (800 μg dose Q 2 week)

Case 4:

Current guidelines for Management of Infections in patients receiving Bispecific Antibody therapy

Bacterial infections:

- Levofloxacin 500mg PO daily; starting with therapy and administer throughout first cycle (recommended for patients with high risk of infection).

Hypogammaglobulinemia:

- IVIG 400mg/kg once every 4 weeks; starting with second cycle and thru end of therapy or once serum IgG > 400 mg/dL (whichever is longer).

HSV/VZV:

- Acyclovir 400-800mg PO BID or Valacyclovir 500mg PO daily or BID; for all patients, indefinitely regardless of vaccination status.

Pneumocystis jiroveci pneumonia:

- TMP-SMX; starting with therapy and continued thru therapy or until CD4 $\geq$ 200/mm^3 (whichever is longer)

Fungal:

- Anti-mold azole; recommended in high-risk patients or if ANC < 500

Case 4: Take Home Points

- Addition of anti-CD38 monoclonal antibody therapy to triplet therapy improves response rates, but longer follow-up is needed to assess for survival benefit.
- Both Daratumumab + Lenalidomide and Carfilzomib + Lenalidomide maintenance therapy have shown sustained responses, but have never been compared head-to-head.
- Single-agent maintenance therapy may still have a role in some patients, as doublet therapy has greater toxicity. It is still unknown if patients receiving upfront quadruplet therapies require doublet maintenance (look out for results from DRAMMATIC trial).
- Patients who undergo BCMA/CD3 bispecific antibody therapy should be given antiviral, PJP, and IVIG prophylaxis with consideration of antibacterial and antifungal prophylaxis if at high risk for infections.

Case 4: End of Case

Case 5: History

- 33 year old female with Hx of CML-CP who presents to clinic with plans for pregnancy.
- PMH: typical migraines, acne vulgaris
- SH: Office worker, married, lives with spouse, one child (2 years old, healthy), never smoker, no illicit drug use.
- FH: No history of prior Hematologic Malignancies
- Physical Exam: unremarkable, well-nourished, no lymphadenopathy, no abdominal pain, no organomegaly

Case 5 – Hx continued:

BCR-ABL1 PCR trend:
08/2021 (Dx): 88.8%
2 weeks: 41.7%
3 months: 4.31% (Achieved CHR and EMR)
6 months: 0.0596% (Achieved MMR)
9 months: 0.0296%
12 months: 0.0307%
Every 3 months (x2 years): 0.022%-0.051%

Response/Relapse	Definition
Complete hematologic response (CHR)[1]	• Complete normalization of peripheral blood counts with leukocyte count <10 x 10^9/L • Platelet count <450 x 10^9/L • No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood • No signs and symptoms of disease with resolution of palpable splenomegaly
Cytogenetic response[2,3,4]	• **Complete cytogenetic response (CCyR):** No Ph-positive metaphases • **Major cytogenetic response (MCyR):** 0%–35% Ph-positive metaphases • **Partial cytogenetic response (PCyR):** 1%–35% Ph-positive metaphases • **Minor cytogenetic response:** >35%–65% Ph-positive metaphases
Molecular response[5,6,7]	• **Early molecular response (EMR):** *BCR::ABL1* (IS) ≤10% at 3 and 6 months • **Major molecular response (MMR):** *BCR::ABL1* (IS) ≤0.1% or ≥3-log reduction in *BCR::ABL1* transcripts from the standardized baseline, if qPCR (IS) is not available • **Deep molecular response (DMR): MR4.0:** *BCR::ABL1* (IS) ≤0.01% or **MR4.5:** *BCR::ABL1* (IS) ≤0.0032%
Relapse	• Any sign of loss of hematologic response • Any sign of loss of CCyR or its molecular response correlate (**MR2.0:** *BCR::ABL1* [IS] ≤1%) – defined as an increase in *BCR::ABL1* transcript to >1% • 1-log increase in *BCR::ABL1* transcript levels with loss of MMR[8]

Case 5: She otherwise has no complaints and is planning for pregnancy in the next 3-4 months.

What is the best approach in managing her therapy leading up to pregnancy?

A. Stop dasatinib now.

B. Switch to another TKI now.

C. Switch to PEG-Interferon now.

D. Switch to Hydroxyurea now.

E. Continue current therapy.

F. Recommend against pregnancy.

Case 5: TKI Therapy and Conception

TKI	Data	Reference
Imatinib	-lowers testosterone levels in males after 6 months of therapy -mouse models show effects on placenta maturation and implantation -retrospective report of >40% of patients experienced abortion	-Ghalaut et al. -Salem et al. -Madabhavi et al.
Dasatinib	-reported fetal/infant abnormalities in pregnancies (>10%) -fetal skeletal malformation in mouse models	-Cortes et al. -Barkoulas and Hall
Nilotinib	-fetal skeletal malformation in mouse models	-Barkoulas and Hall
Bosutinib	-retrospective report of >20% experienced abortions with maternal exposure	-Cortes et al.

Case 5:

Successful pregnancies in patients with BCR-ABL-positive leukemias treated with interferon-alpha therapy during the tyrosine kinase inhibitors era

Marie Balsat[1] | Madeleine Etienne[2] | Mohamed Elhamri[2] | Sandrine Hayette[3] | Gilles Salles[1] | Xavier Thomas[1]

-Case series of 12 successful pregnancies managed with IFN-alpha
-all children had normal growth and development
-all patients remained at least in hematological response
-patients had TKI therapy stopped and were placed on IFN for at least 2 months before contraceptives were stopped

Case Reports > Haematologica. 2016 May;101(5):e182-4. doi: 10.3324/haematol.2015.139691. Epub 2016 Jan 27.

Pegylated interferon alpha-2a for essential thrombocythemia during pregnancy: outcome and safety. A case series

Yan Beauverd [1], Deepti Radia [1], Catherine Cargo [2], Steve Knapper [3], Mark Drummond [4], Arvind Pillai [5], Claire Harrison [1], Susan Robinson [6]

> J Cancer Res Clin Oncol. 2021 May;147(5):1481-1491. doi: 10.1007/s00432-020-03430-4. Epub 2020 Nov 2.

Interferon alpha for essential thrombocythemia during 34 high-risk pregnancies: outcome and safety

Lukas Schrickel [1], Florian H Heidel [2 3], Parvis Sadjadian [4], Tatjana Becker [4], Vera Kolatzki [4], Andreas Hochhaus [2], Martin Griesshammer [4], Kai Wille [4]; German Study Group MPN, GSG-MPN

Case 5 continued: Other options

Leukapheresis:
-goal WBC < 100K/μL
-no teratogen exposure
-risk of volume shifts/hypotension

JOURNAL ARTICLE

Successful Pregnancy and Delivery in a Patient with Chronic Myelogenous Leukemia (CML), and Management of CML with Leukapheresis during Pregnancy: a Case Report and Review of the Literature FREE

Ridvan Ali, Fahir Özkalemkas, Vildan Özkocaman, Tülay Özçelik, Ülkü Ozan, Yalçin Kimya, Ahmet Tunali

Japanese Journal of Clinical Oncology, Volume 34, Issue 4, April 2004, Pages 215–217,
https://doi.org/10.1093/jjco/hyh038
Published: 01 April 2004

CASE REPORT

Successful management of chronic myeloid leukaemia with leucapheresis during a twin pregnancy

R. Klaasen[1*], P. de Jong[2], P.W. Wijermans[1]

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Holding TKI:
-Patient who relapsed while holding Imatinib after achieving either CCyR or CMR were able to re-achieve their bast response with resumption of Imatinib.

-Patients who achieved MMR prior to holding Imatinib were more likely to re-achieve MMR upon continuation of therapy.

Original Article: Clinical

Previous best responses can be re-achieved by resumption after imatinib discontinuation in patients with chronic myeloid leukemia: implication for intermittent imatinib therapy

Hyun-Gyung Goh, Yoo-Jin Kim, **Dong-Wook Kim MD, PhD**, Hyeoung-Joon Kim, Soo-Hyun Kim, Se-Eun Jang, ...show all

Pages 944-951 | Received 14 Jan 2009, Accepted 25 Mar 2009, Published online: 21 Jul 2009

CORRESPONDENCE | AUGUST 12, 2010

Poor outcome after reintroduction of imatinib in patients with chronic myeloid leukemia who interrupt therapy on account of pregnancy without having achieved an optimal response

Aya Kuwabara, Anna Babb, Amr Ibrahim, Dragana Milojkovic, Jane Apperley, Marco Bua, Alistair Reid, Letizia Foroni, Katayoun Rezvani, John Goldman, David Marin

Case 5:

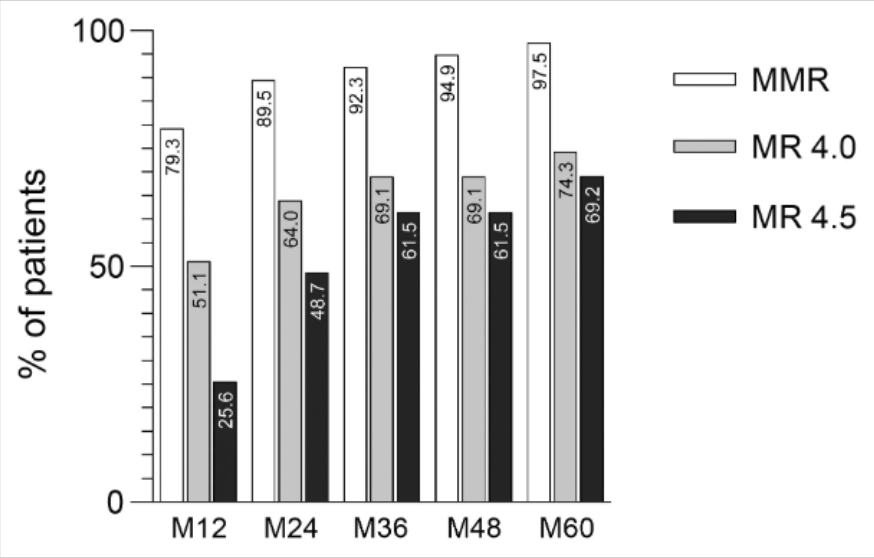
European Journal of Haematology

ORIGINAL ARTICLE | Open Access

Long-term tolerability and efficacy after initial PegIFN-α addition to dasatinib in CML-CP: Five-year follow-up of the NordCML007 study

Hjalmar Flygt, Stina Söderlund, Jesper Stentoft, Johan Richter, Perttu Koskenvesa, Satu Mustjoki, Waleed Majeed, Anna Lübking, Arta Dreimane, Berit Markevärn, Leif Stenke ... See all authors

First published: 21 August 2021 | https://doi.org/10.1111/ejh.13699 | Citations: 4



Dasatinib plus Peg-Interferon alpha 2b combination in newly diagnosed chronic phase chronic myeloid leukaemia: Results of a multicenter phase 2 study (DASA-PegIFN study)

Lydia Roy, Jean-Claude Chomel, Joëlle Guilhot, Agnès Guerci-Bresler, Martine Escoffre-Barbe, Stéphane Giraudier, Aude Charbonnier, Viviane Dubruille, Françoise Huguet ... See all authors

First published: 10 October 2022 | https://doi.org/10.1111/bjh.18486 | Citations: 1

	12 months	24 months
MR (4.5) rate	25%	38%

- 32% sustained MR(4.5) over 2 years
- 46% sustained MR(4.0) over 2 years

Case 5:

Perinatal/Neonatal Case Presentation

Imatinib mesylate and metabolite concentrations in maternal blood, umbilical cord blood, placenta and breast milk

M A Russell ✉, M W Carpenter, M S Akhtar, T F Lagattuta & M J Egorin

Journal of Perinatology **27**, 241–243 (2007) | Cite this article

-Imatinib was detectible in maternal blood, placenta, umbilical cord blood, and breast milk.

-Active metabolite (CGP74588) was detectible in the maternal blood, placenta and breast milk, but not in the umbilical cord blood.

-Imatinib may be safe in the second/third trimester when the placenta has matured.

-Breast feeding should be avoided if patient on imatinib

Case Reports > Mediterr J Hematol Infect Dis. 2018 May 1;10(1):e2018027.
doi: 10.4084/MJHID.2018.027. eCollection 2018.

Breastfeeding in Patients with Chronic Myeloid Leukaemia: Case Series with Measurements of Drug Concentrations in Maternal Milk and Literature Review

Ekaterina Chelysheva [1], Sergey Aleshin [2], Evgenia Polushkina [3], Roman Shmakov [3], Igor Shokhin [2], Ghermes Chilov [4], Anna Turkina [1]

-Both imatinib and nilotinib were detected in maternal milk

-Estimated maximal dose ingest by baby were likely sub-therapeutic

-Impact of low dose chronic exposure remains unknown

Case 5 continued:

-The patient is advised to start PEG-IFN now along with Dasatinib with goal to test tolerability of interferon and improve her molecular response prior to attempting pregnancy.

-Advised to hold Dasatinib upon conception, and resume PEG-IFN if tolerated.

-Plan to check labs every 4 weeks, including BCR-ABL1 PCR.

-In the event of relapse, will then consider managing with leukapheresis or initiating Imatinib therapy depending on the stage of pregnancy.

Case 5: Take Home Points

- There are no clear guidelines to the optimal depth of molecular response in which pregnancy is safe to pursue
- It is recommended to stop TKI therapy prior to and during pregnancy, though Imatinib may be safe in the second and third trimester of pregnancy.
- Leukapheresis is a reasonable management approach where limiting teratogen exposure is of concern.
- Holding TKI with monthly BCR-ABL monitoring is a reasonable option for patients who achieve an initial optimal response (i.e MMR).
- PEG-interferon alpha is a safe option for therapy during pregnancy.
- Combination TKI + PEG-interferon may be an option to achieve deeper responses prior to attempting pregnancy.
- TKI levels are detectible in breast milk, though impact of ingestion by baby remains unknown.
- It is recommended to hold TKI therapy during breast feeding and may be appropriate to hold up to a week post-partum to allow mother to provide colostrum to baby.

Case 5: End of Case

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