Myeloproliferative Neoplasien, CML und MDS

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Disclosures

Vortragshonorare: Janssen, Pfizer, Novartis, BMS

Beratertätigkeit: Janssen, Sanofi, Abbvie, Amgen,

Übersicht

1. MDS
    1. Abstract #85; Makishima et al.: Impact of DDX41 Mutations in Myeloid malignancies
    2. Abstract #459; Platzbecker et al., Imetelstat in Lower-Risk Myelodysplastic Syndrome (LR-MDS)

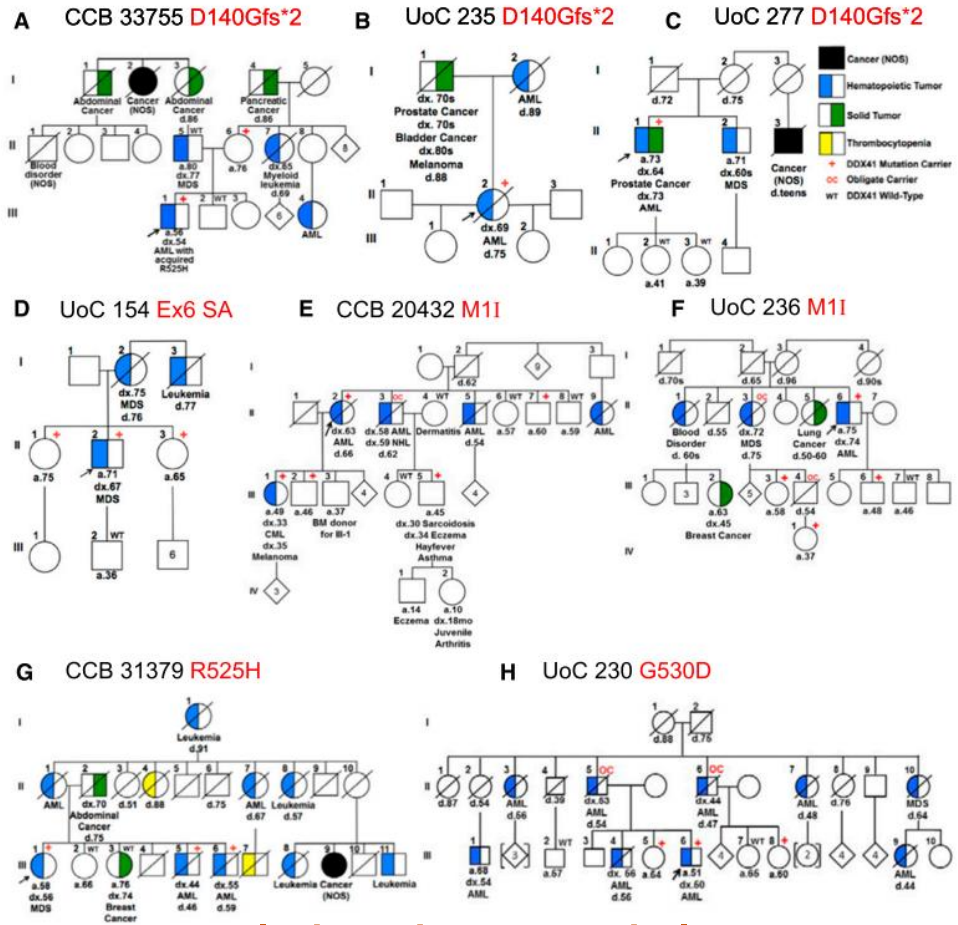
2. Chronische myeloische Leukämie
    1. Abstract #79; Yeung et al., Frontline Asciminib in chronic Phase ALLG CML13 Ascend CML
    2. Abstract #80; Cortes et al Efficacy and safety Results from ASC4MORE-Novartis

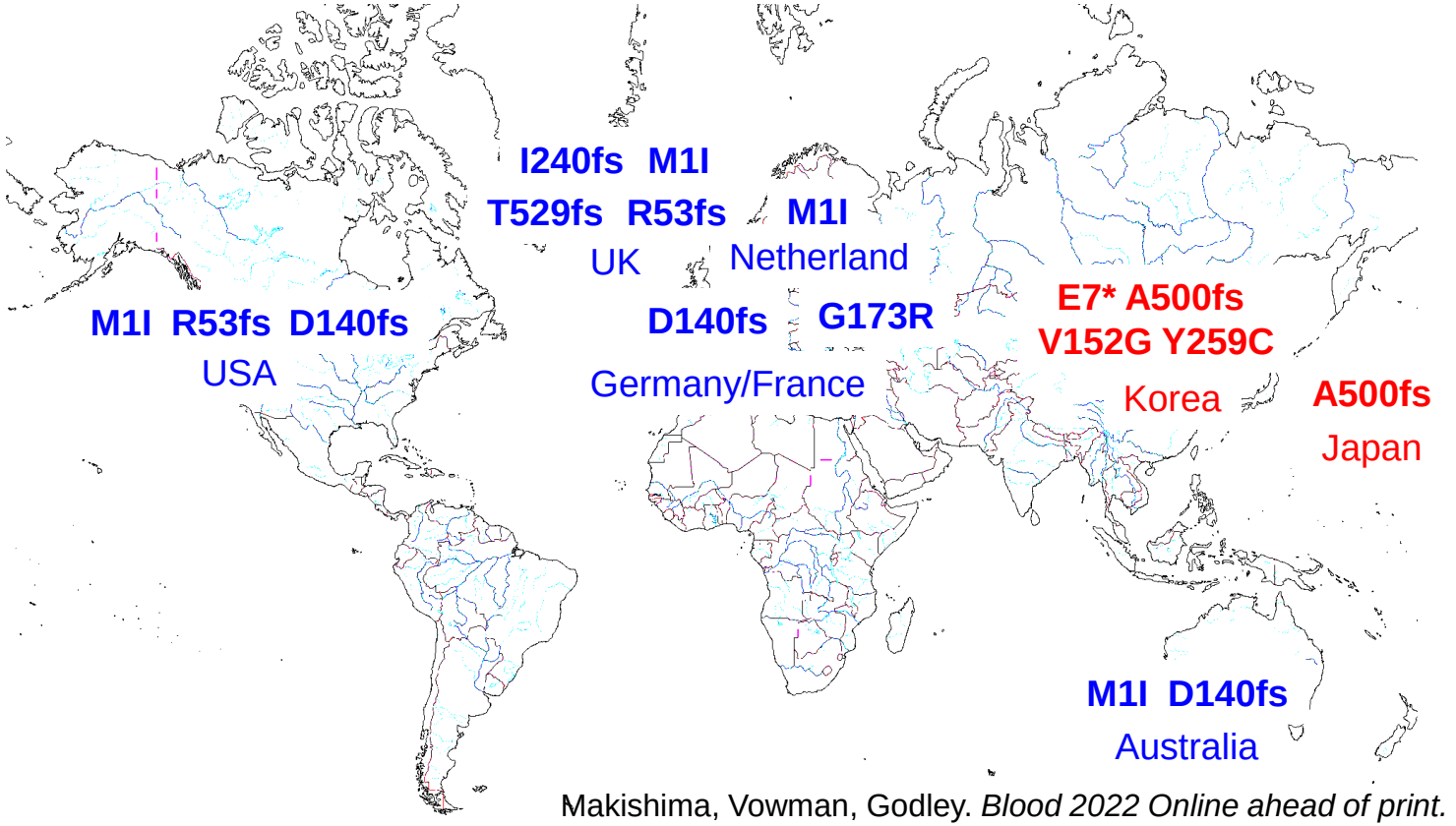
3. Myeloproliferative Neoplasien
    1. Abstract #6; Reis et al.; Monoclonal Antibody against Mutatnt Calreticulin
    2. Abstract #627; Gerds et. al., Momelotinib (MMB) Versus Danazol (DAN) in Myelofibrosis

#85, Makishima et. al

Germline Risks and Clinical Impacts of *DDX41* Mutations in Myeloid Malignancies.

Germline mutations of *DDX41* identified in autosomal dominant and non-familial adult-onset MDS/AML





Makishima, Vowman, Godley. *Blood 2022 Online ahead of print.*

Autosomal dominant adult-onset MDS/AML

Polprasert et al. Cancer Cell. 2015.
Lewinsohn et al. Blood. 2016

Non-familial adult-onset MDS/AML

Cardoso et al. Leukemia. 2016. Berger et al. Leukemia. 2017.
Kobayashi et al. Leukemia. 2017. Sebert et al. BLOOD. 2019.
Qu et al. BJH. 2020. Choi et al. Haematologica. 2021.

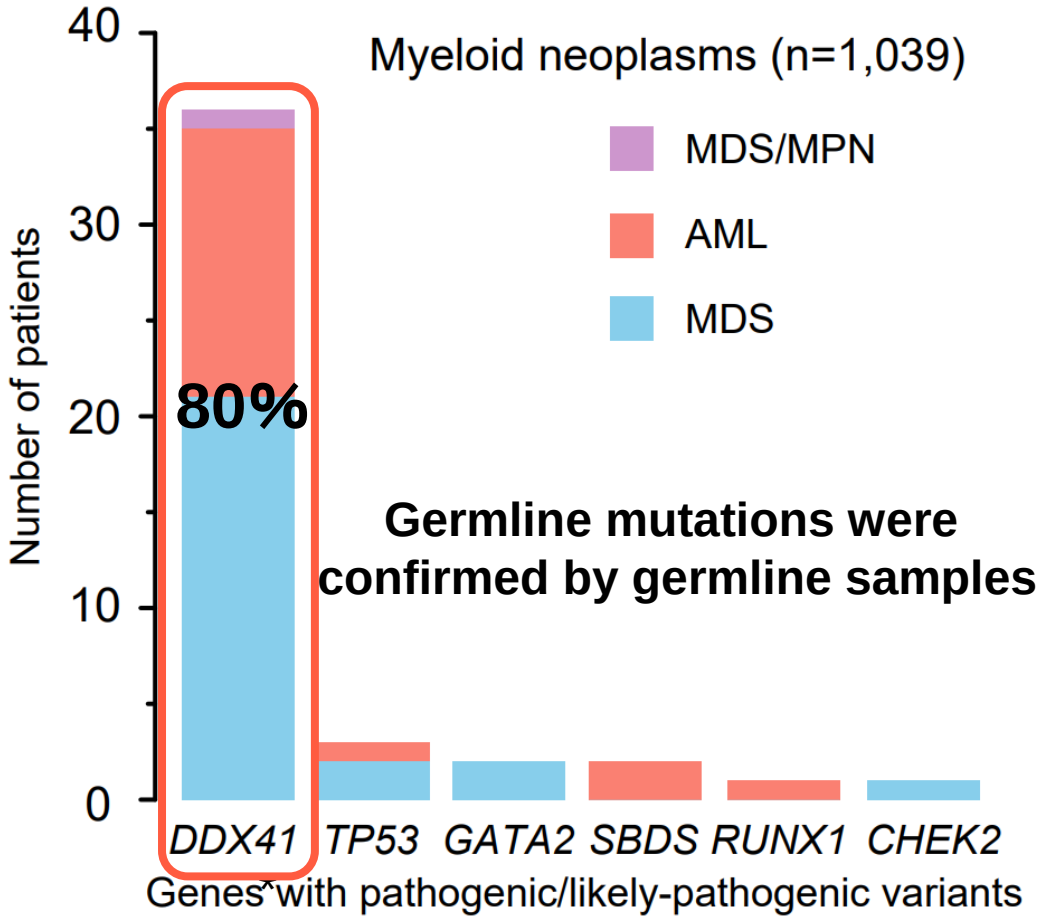
- ✓ **Long latency with a mean patients' age of 62 years at onset.**
- ✓ **Frequent second-hit mutations, typically somatic mutations in cases with truncating (loss of function) germline mutations.**
- ✓ **Mainly MDS and AML MRC. CMMLs are also reported.**
- ✓ **Disease risks are not fully assessed.**
- ✓ **Prognostic implications remain unclear.**

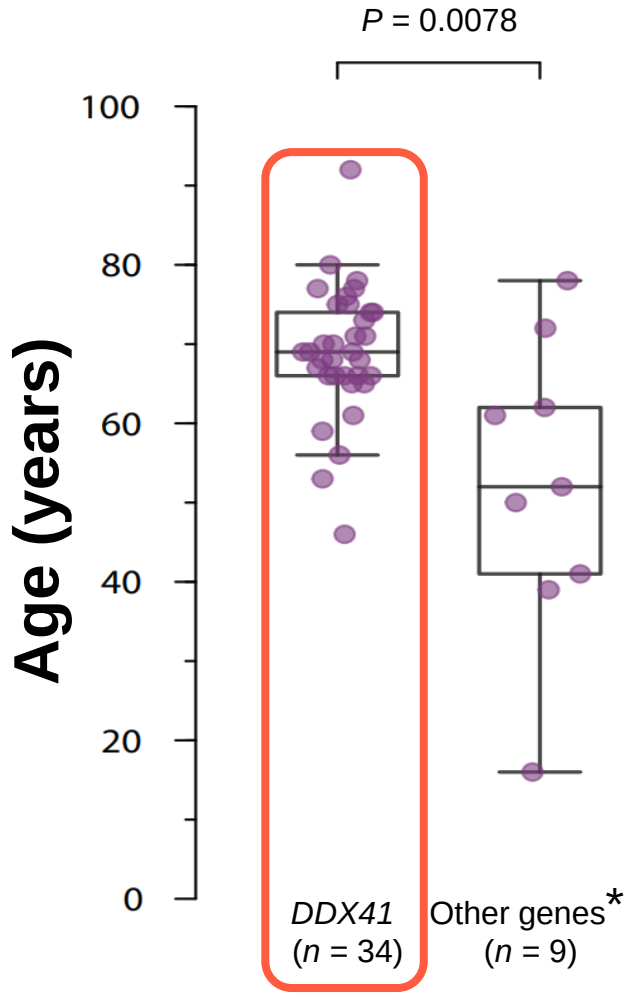
Targeted sequencing for *DDX41* mutations (N = 9,082) in various myeloid malignancies

↓

346 out of 9,082 (3.8%) cases were positive for any *DDX41* mutation.
53/346 somatic mutations

Evaluation of relative impact of *DDX41* on the risk of MNs among the genes known to be associated with predisposition of myeloid neoplasms





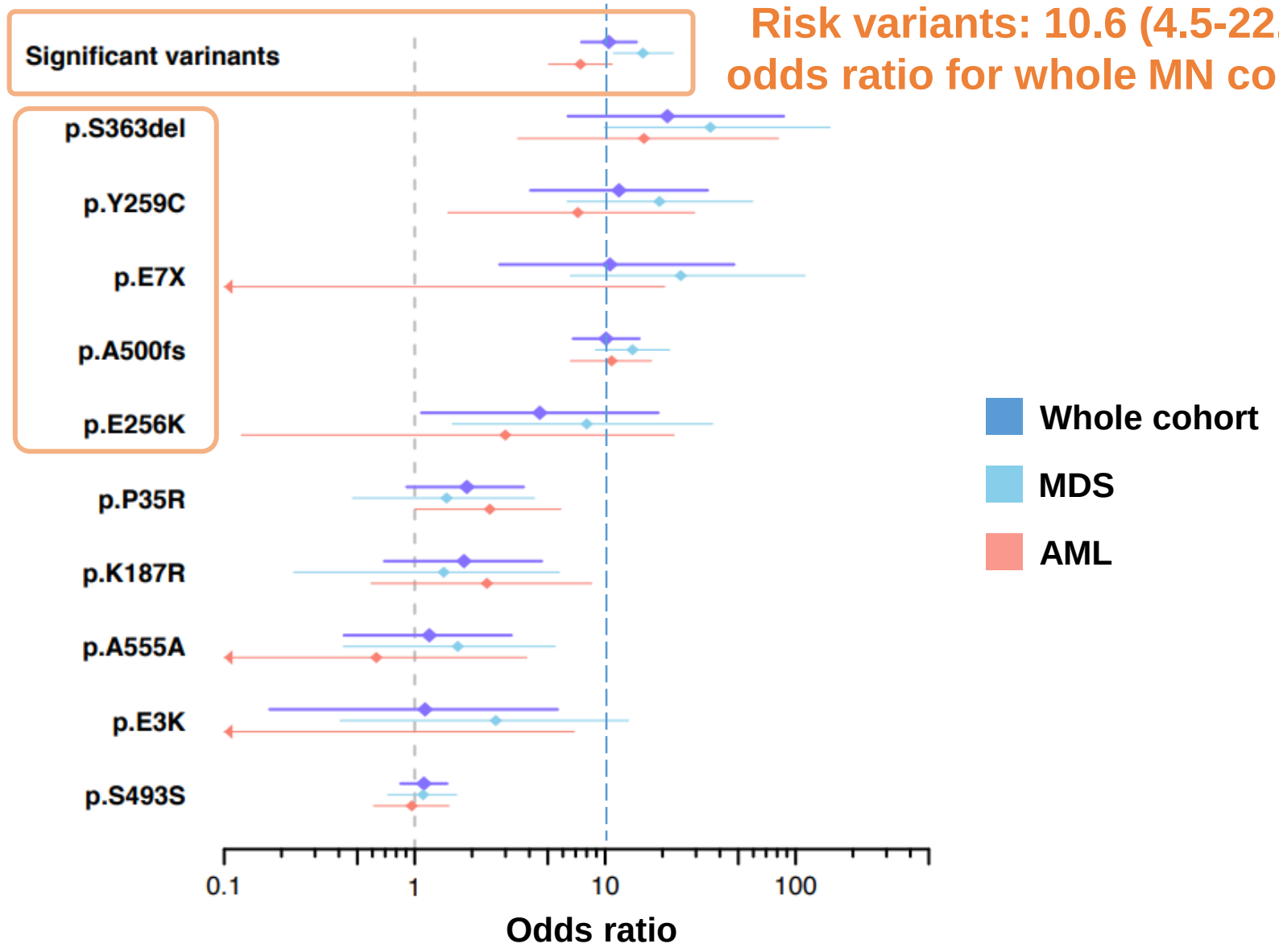
*Godley & Shimamura. Blood 2017

Makishima *et al. Blood Online ahead of print.*

Comparison of frequencies of 10 Japanese *DDX41* germline variants (3,672 Japanese MN cases *VS.* 20,238 Japanese healthy individuals)

Combined

Germline mutation



Risk variants: 10.6 (4.5-22.8)
odds ratio for whole MN cohort

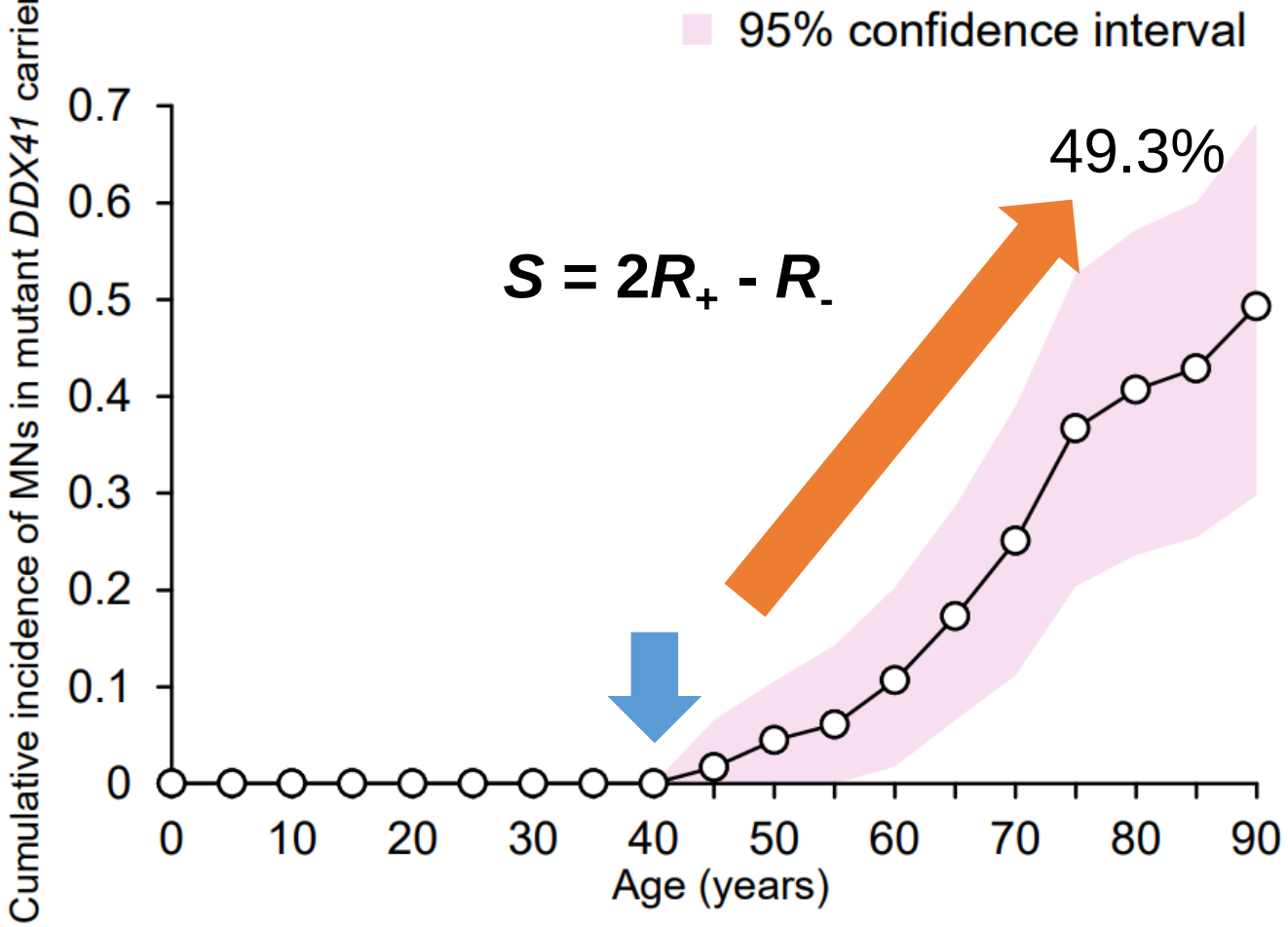
Whole cohort

MDS

AML

Calculation of the penetrance (2*R*(+)-*R*(-))

Penetrance of MNs for *DDX41* germline mutation carriers



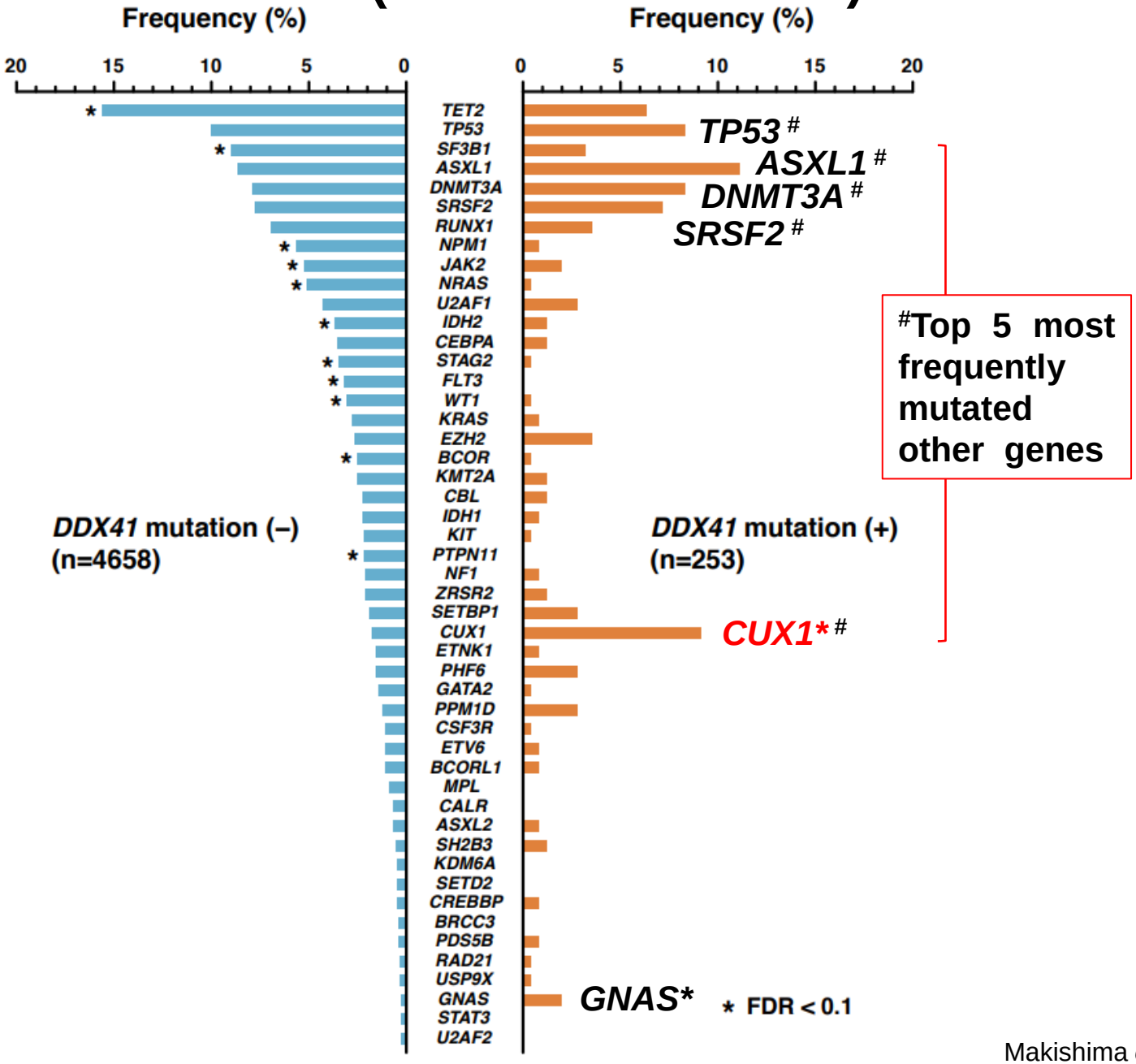
Makishima *et al. Blood Online ahead of print.*

✓ Co-occurring somatic events were reported in cases with *DDX41* mutations

1. Mutations in *TP53* were most frequently identified (Cancer Cell 2015).
2. Mutations in *TP53*, *ASXL1*, and *JAK2* were recurrently identified (AJH 2019).
3. Mutations in *ASXL1*, *EZH2*, *SRSF2*, *SETBP1*, and *CUX1* were frequent (BLOOD 2019).
4. Most common mutations were in *ASXL1*, *TP53*, *EZH2*, *SRSF2*, *PHF6*, and *TET2* (BJH 2020).

➡ Wild-type controls have not been assessed.

Co-mutations (*DDX41*-WT *vs.* Mut)

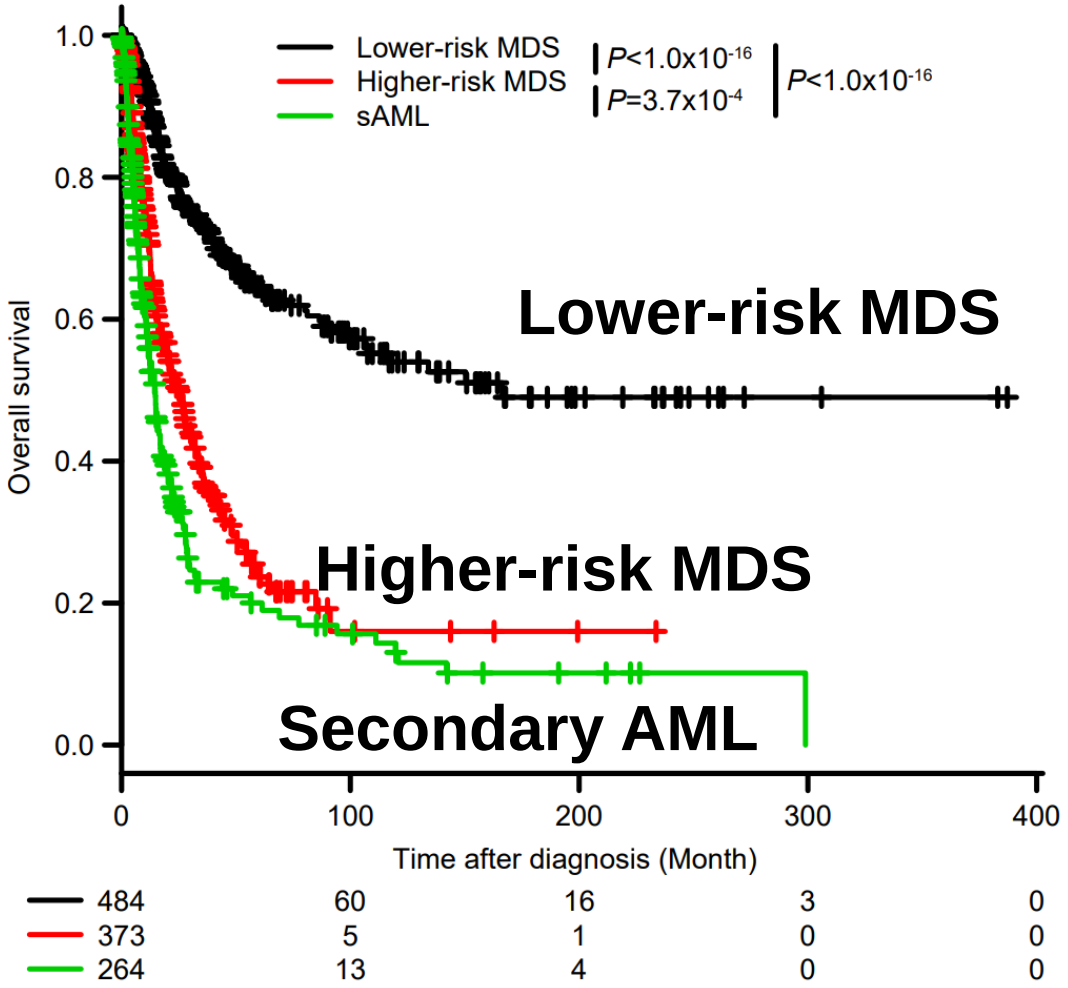


Makishima *et al. Blood Online ahead of print.*

Prognostic stratification of overall survival in *DDX41*-mutated cases

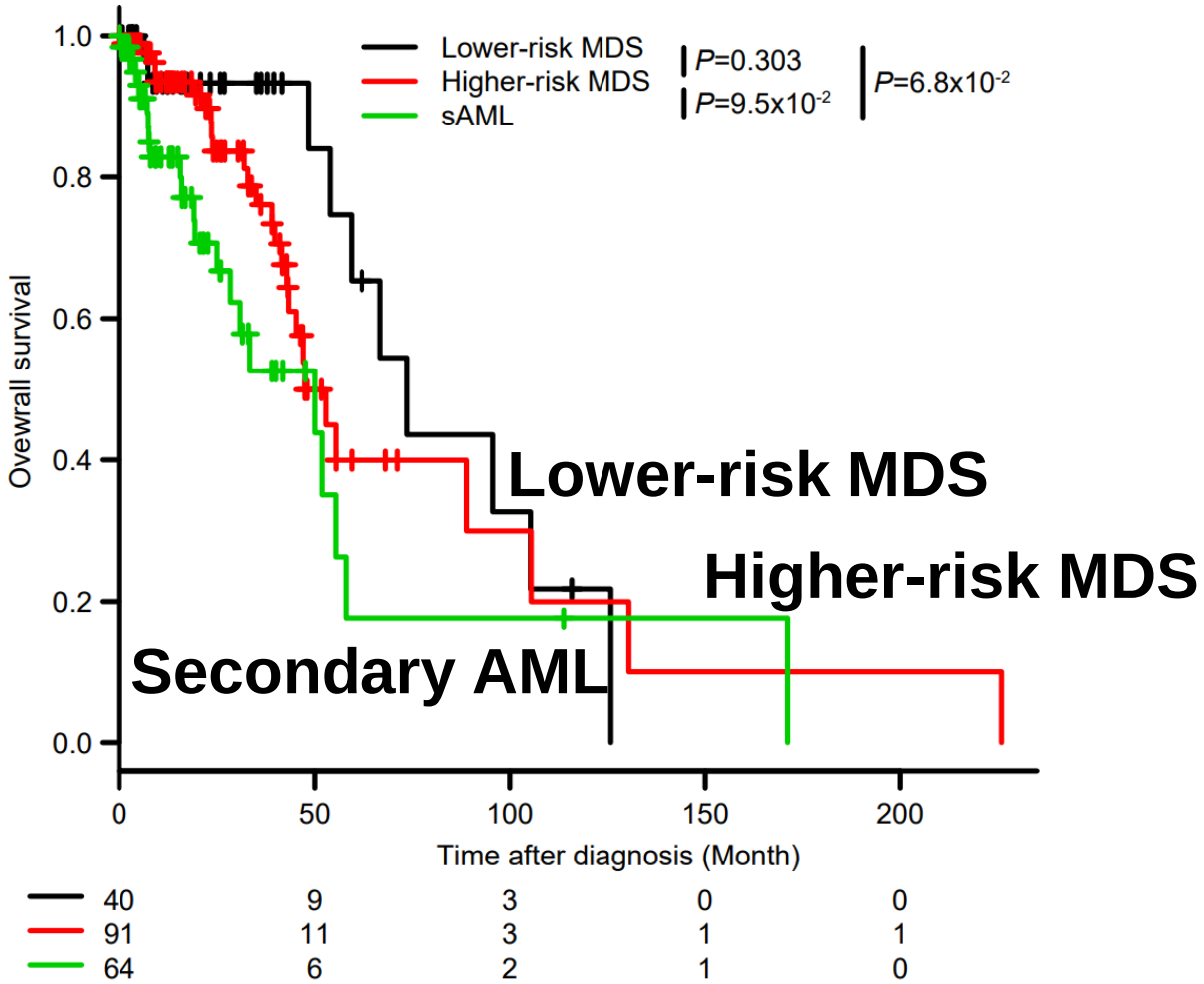
[Disease status]

DDX41 WT



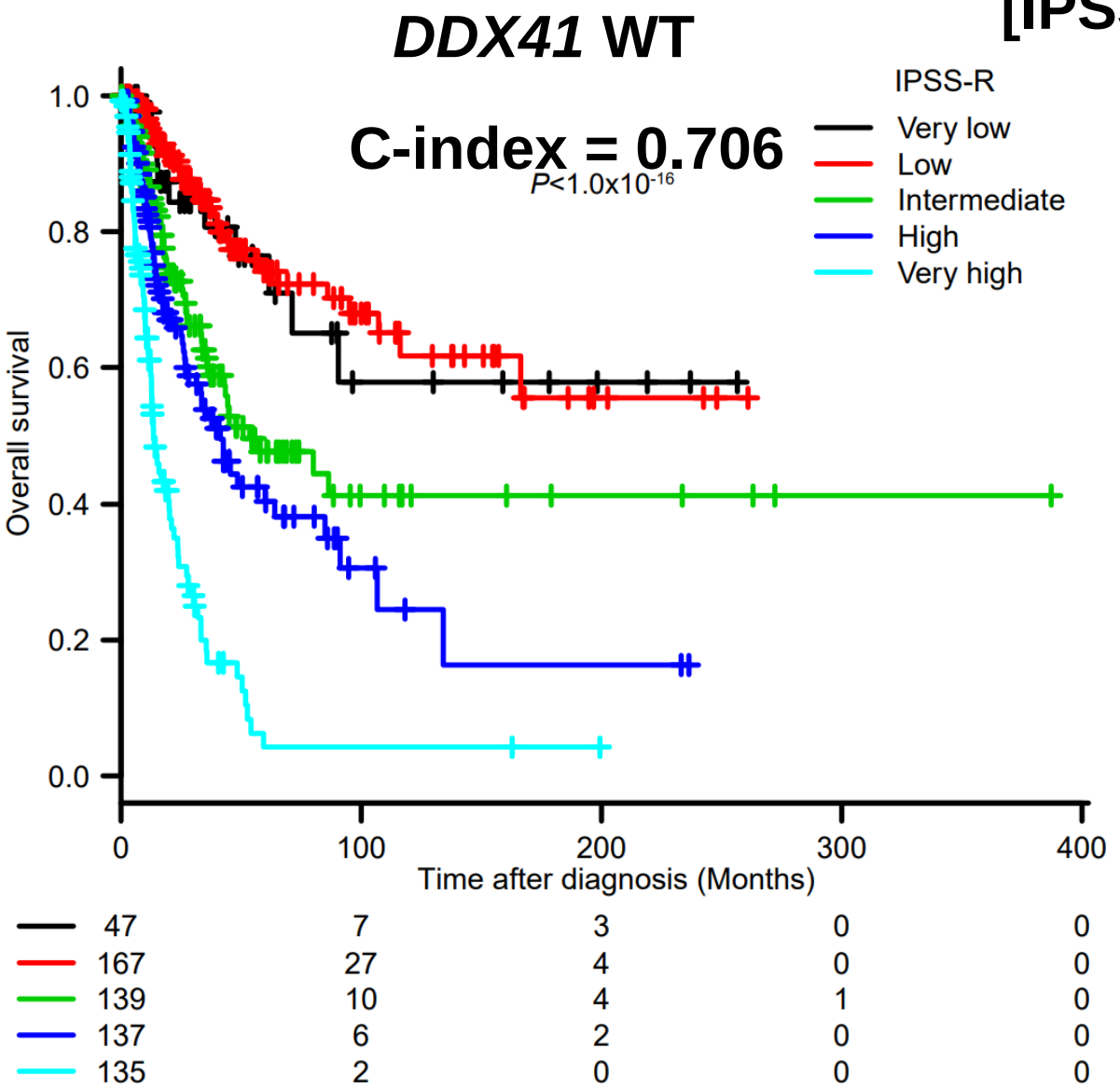
➢ As usual, significantly stratified

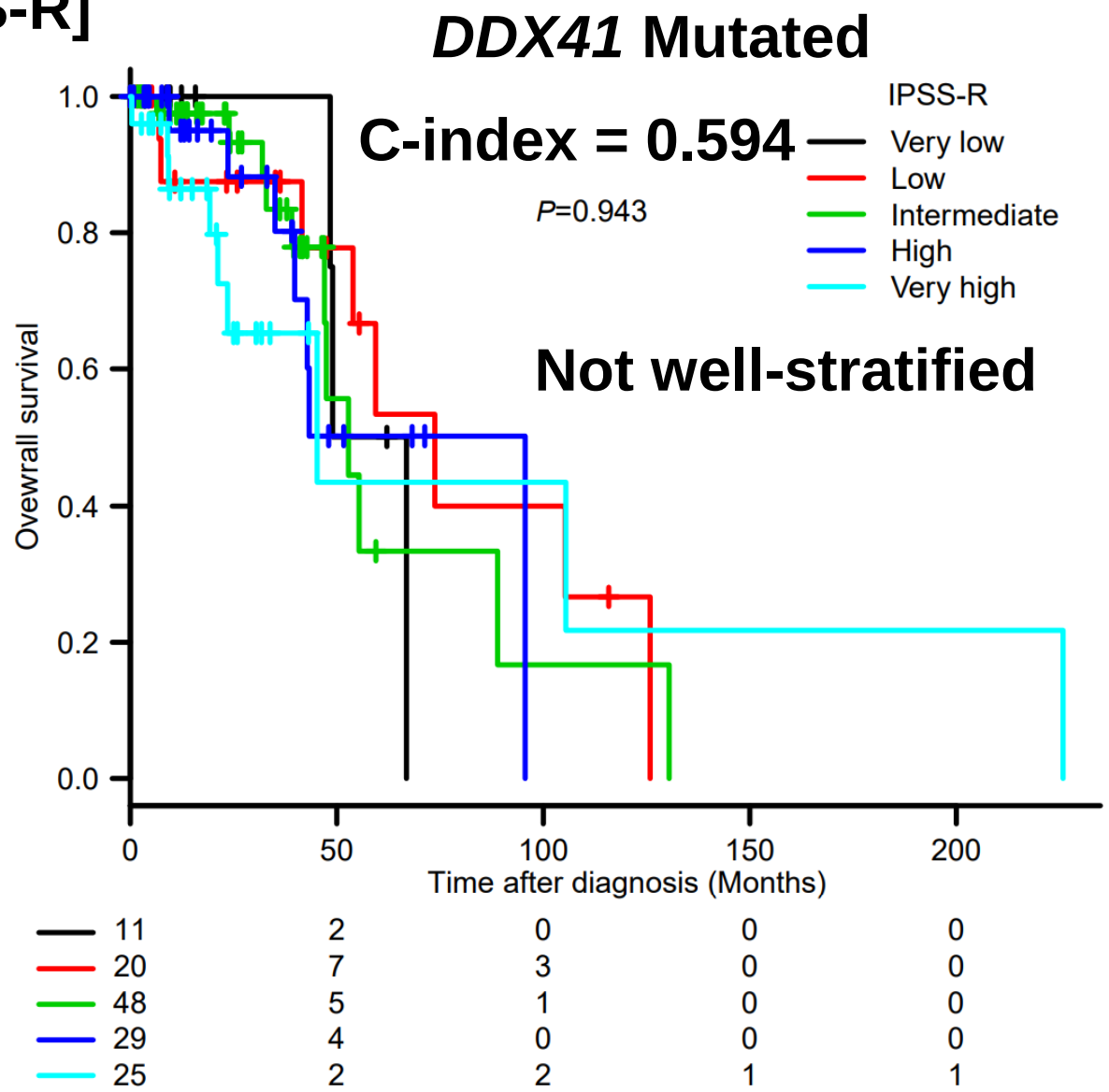
DDX41 Mutated



➢ Not well-stratified

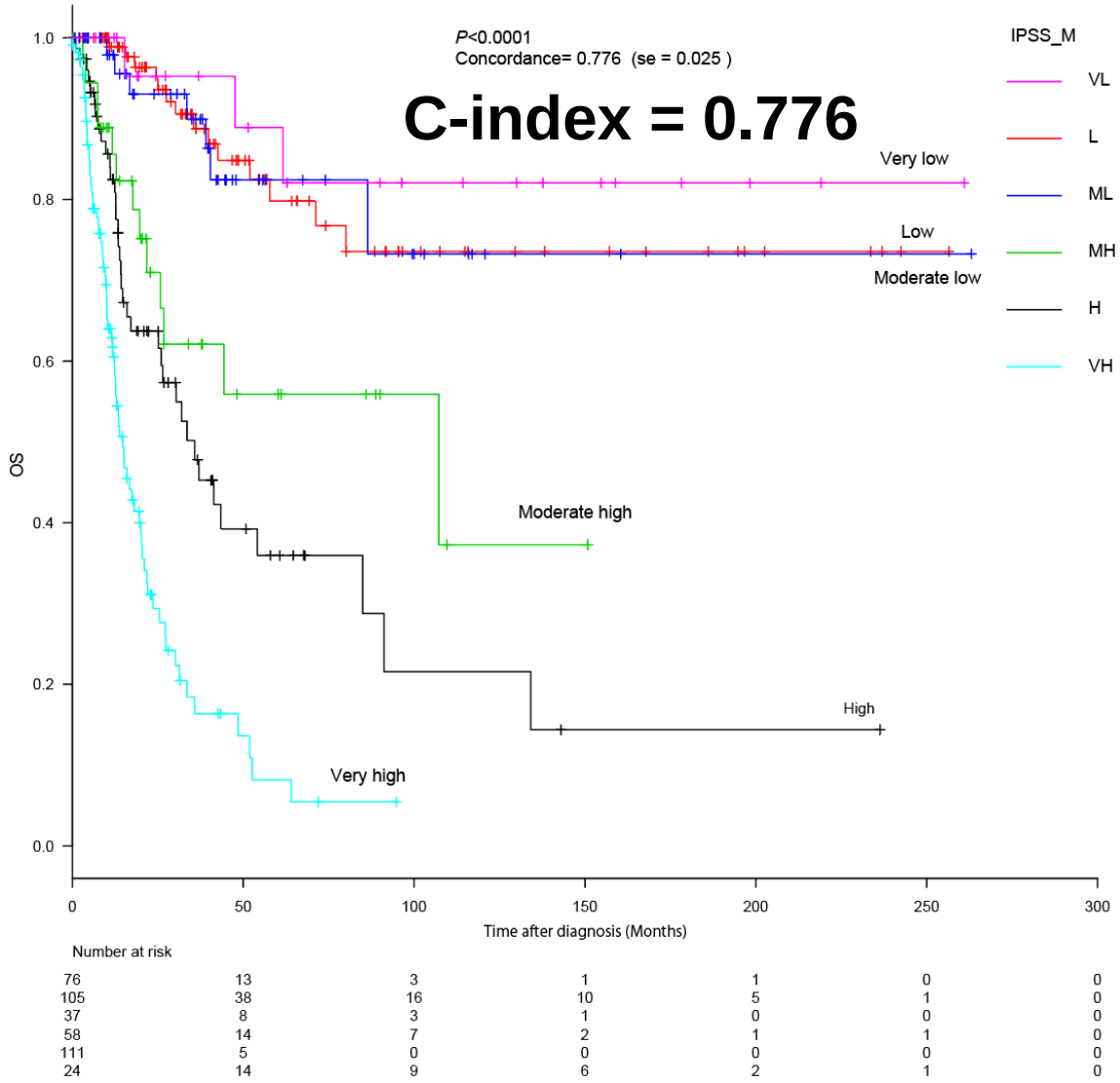
Prognostic stratification of overall survival in *DDX41*-mutated cases [IPSS-R]



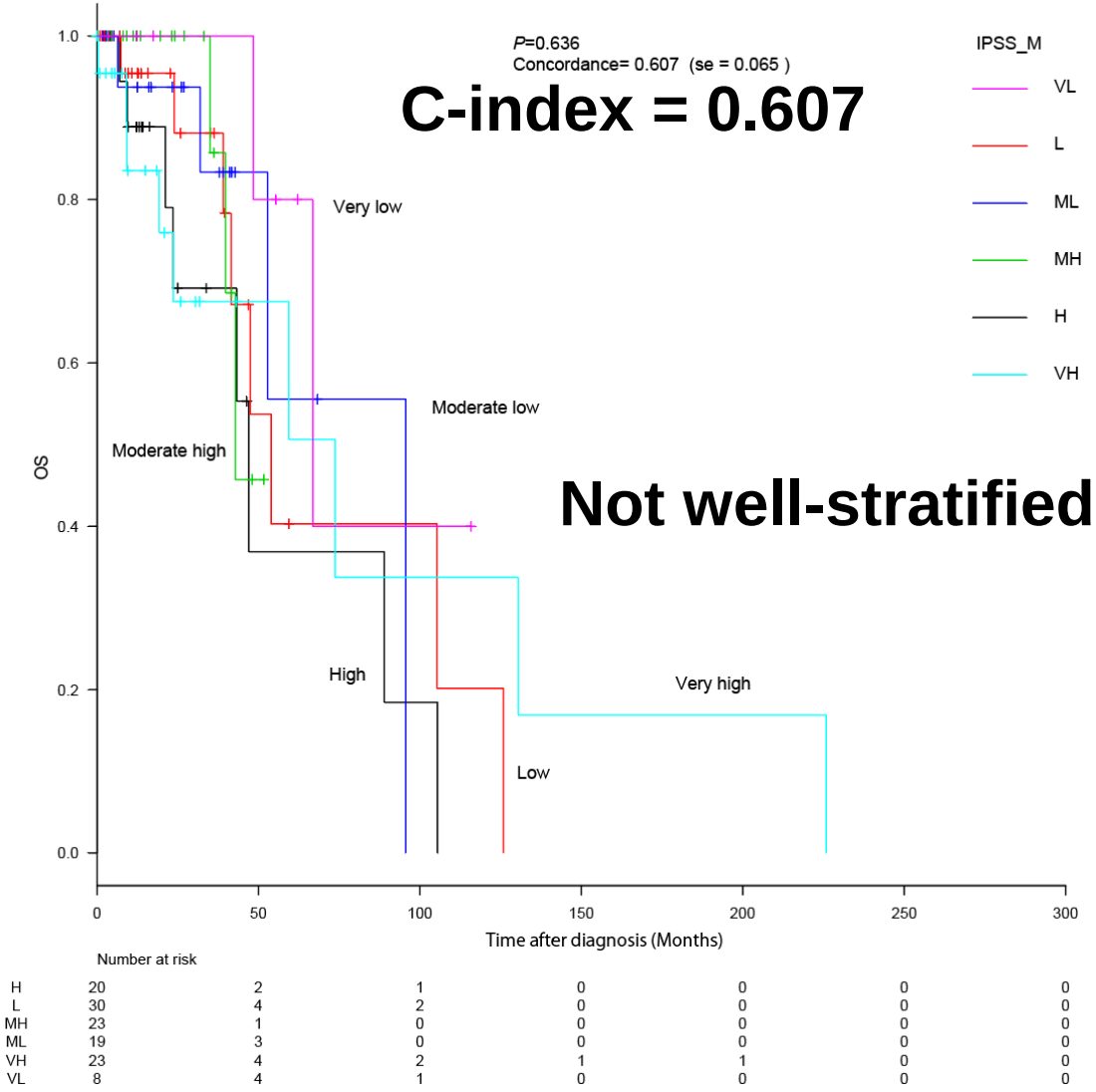


Prognostic stratification of overall survival in *DDX41*-mutated cases [IPSS-M (NEJM Evidence 2022)]

DDX41 WT



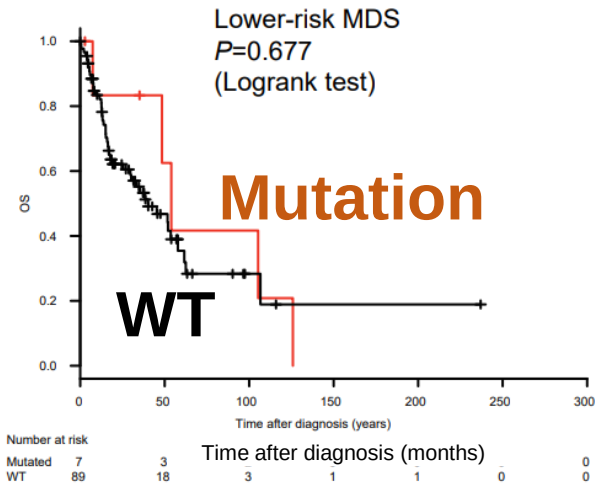
DDX41 Mutated

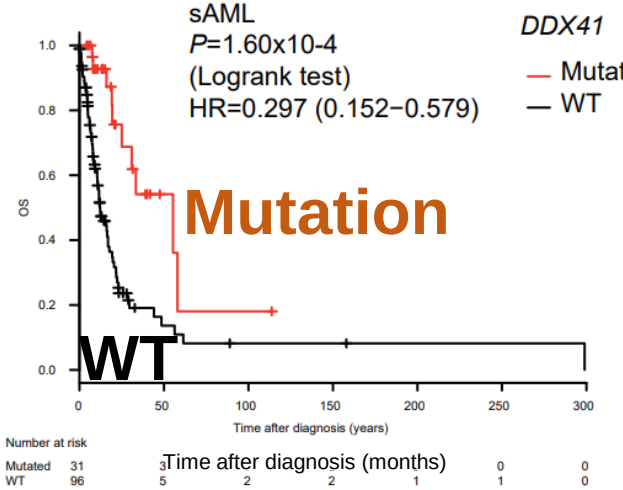


Not well-stratified

Possibly better response in *DDX41*-mutated cases to hypomethylating agents (HMA) treatment (HSCT-censored)

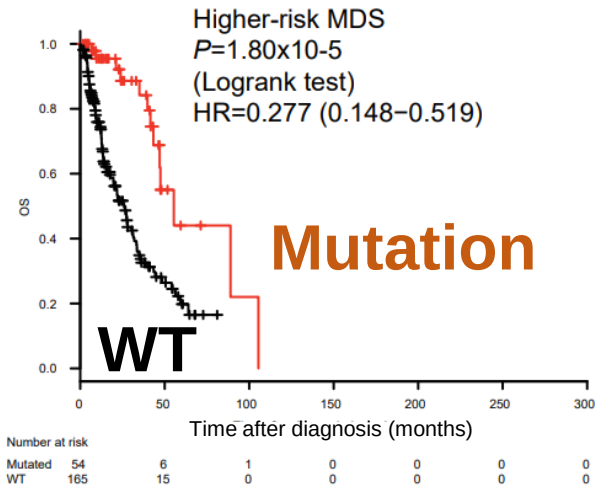
Lower-risk MDS

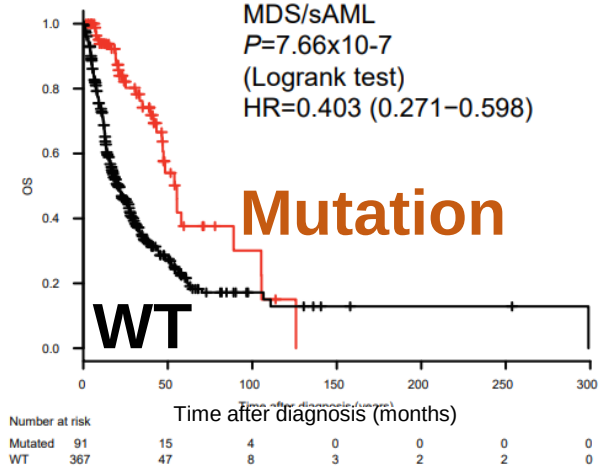




Secondary AML

Higher-risk MDS





Higher-risk MDS + Secondary AML

➢ ***DDX41*** **mutation is a better prognostic factor in higher-risk diseases**

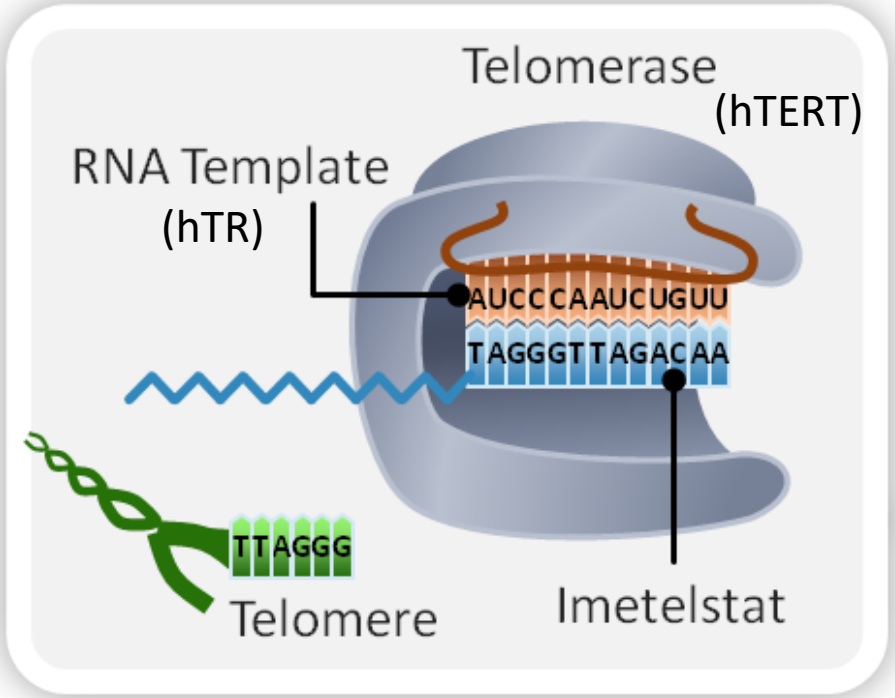
Makishima *et al. Blood Online ahead of print.*

#459, Platzbecker et. al

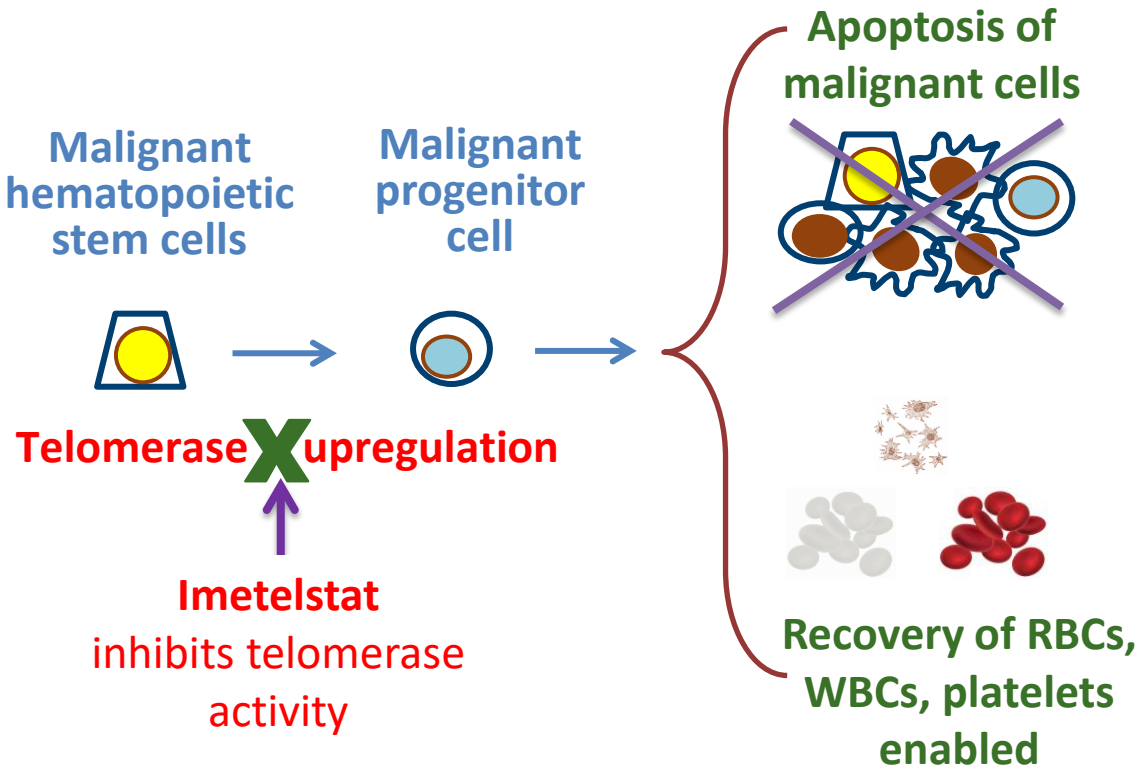
Imetelstat Achieved Prolonged, Continuous Transfusion Independence in Patients With Heavily Transfused Non-Del(5q) Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory to Erythropoiesis Stimulating Agents Within the IMerge Phase 2 Study

Imetelstat: First-in-Class Telomerase Inhibitor

- Imetelstat is a direct and competitive inhibitor of telomerase activity[1,2]



- Imetelstat has disease-modifying potential to selectively kill malignant stem and progenitor cells, enabling recovery of blood cell production[3,4]



hTERT, human telomerase reverse transcriptase; hTR, catalytic component; RBC, red blood cell; WBC, white blood cell.

1. Asai A, et al. *Cancer Res.* 2003;63(14):3931-3939; 2. Herbert BS, et al. *Oncogene.* 2005;24(33):5262-5268; 3. Mosoyan G, et al. *Leukemia.* 2017;31(11):2458-2467; 4. Wang X at al. *Blood Adv.* 2018;25;2(18):2378-2388.

IMerge (MDS3001; NCT02598661) Phase 2/3 Study Design

Part 1[1,2]
Phase 2, single-arm, open-label
Overall N=57

Target population of non-del(5q)/len/HMA-naive
N=38
Enrollment Complete

Imetelstat
7.5 mg/kg IV q4w

Part 2
Phase 3, randomized, double-blind, placebo-controlled
N=170
Enrollment complete; Top line results early Jan 2023

Stratification: transfusion burden (≤6 vs >6 units); IPSS risk group (low vs intermediate-1)

- **Patients with LR-MDS**[1,2]
  - IPSS low or intermediate-1
  - Relapsed/refractory to ESA or sEPO >500 mU/mL
  - Transfusion dependent: ≥4 units RBC/8 weeks over the 16-week prestudy period
  - Non-del5(q), len/HMA-naive
- **Primary endpoint**: ≥8-week RBC TI
- **Key secondary endpoints**: safety, ≥24-week TI rate, HI-E, OS, PFS, and time to progression to AML

Treatment continues until disease progression, unacceptable toxicity, or withdrawal of consent
Pre-medication: diphenhydramine, hydrocortisone 100-200mg (or equivalent)
Supportive care: transfusions, myeloid growth factors per local guidelines

AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; IV, intravenous; len, lenalidomide; LR, lower-risk; MDS, myelodysplastic syndromes; OS, overall survival; PFS, progression-free survival; q4w, every 4 weeks; RBC, red blood cell; sEPO, serum erythropoietin; TI, transfusion independence.

1. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56. 2. Platzbecker U, et al. Presented at: ASH Annual Meeting 2020; Abstract 3113.

Meaningful and Durable TI With Imetelstat Treatment

- Of 57 patients treated in the phase 2 study, 38 patients were non-del(5q) and lenalidomide/HMA naive (target patient population)[1,2]

Efficacy parameters	Target population N=38[2]
8-week TI, n (%)	16 (42)
Median duration of TI, weeks (95% CI)[a]	88.0 (23.1-140.9)
24-week TI, n (%)	12 (32)
TI ≥1 year, n (%)	**11 (29)**

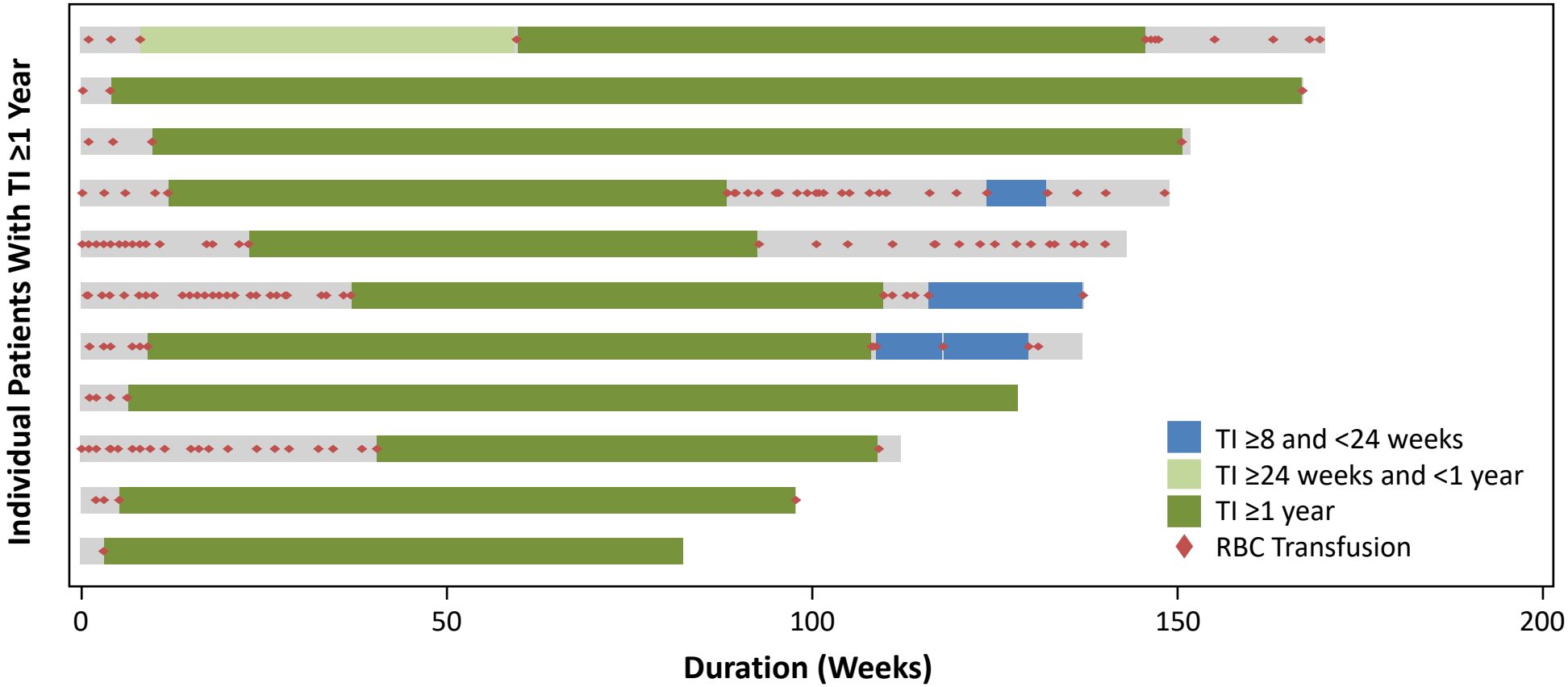
Disposition and Treatment Exposure for Imetelstat-Treated Patients With TI ≥1 Year

	Patients with TI ≥1 year (n=11)
Median time on study,[a] months (range)	57.3 (19.0-57.8)
Median treatment duration, weeks (range)	126.1 (70.1-168.1)
Median treatment cycles, n (range)	27.0 (18-40)
Median relative dose intensity,[b] % (range)	98.9 (85.5-102.4)

[a]Based on the Kaplan Meier method. HMA, hypomethylating agent; MDS, myelodysplastic syndromes; RS+, ring sideroblast-positive; TI, transfusion independence.

1. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56. 2. Platzbecker U, et al. Presented at: ASH Annual Meeting 2020; Abstract 658.

LR-MDS Patients Treated With Imetelstat Achieved Sustained, Continuous TI ≥1 Year



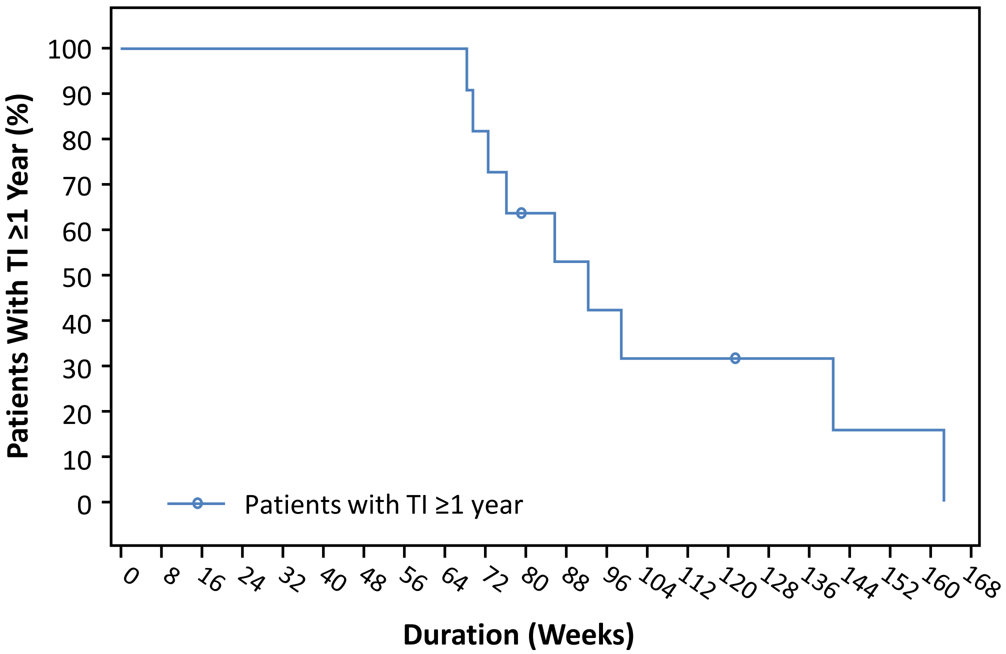
- Median onset of 8-week TI was 9.29 weeks (range, 3.3-40.7)

Data cutoff: October 13, 2022.
LR, lower-risk; MDS, myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence.

Durable TI Accompanied by Substantial Increase in Hgb in TI ≥1-Year Responders

Median TI duration: 92.4 weeks[a]
(95% CI, 69.57-140.86)

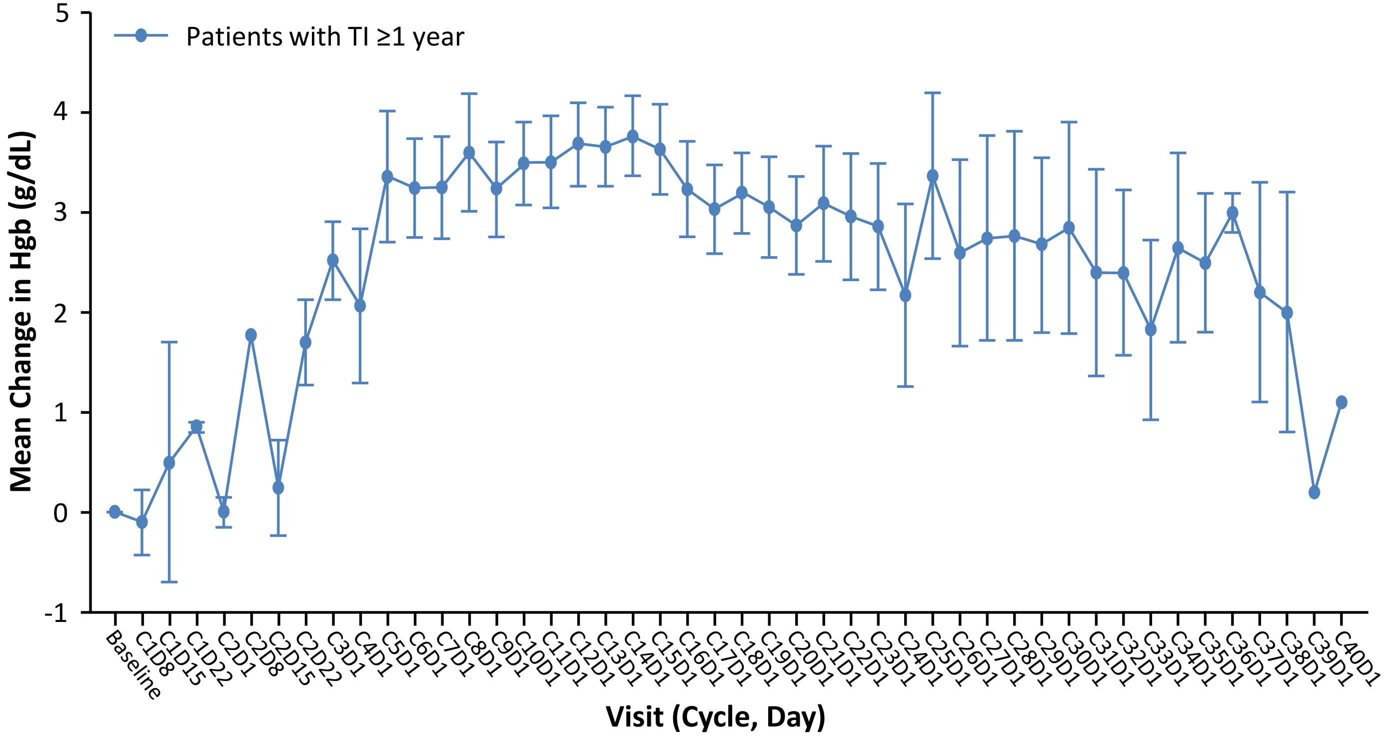
Duration of TI[a]



Patients at Risk

n	11	11	11	11	11	11	11	11	11	9	6	5	4	3	3	3	2	2	1	1	1	0

Mean Change in Hgb[b]

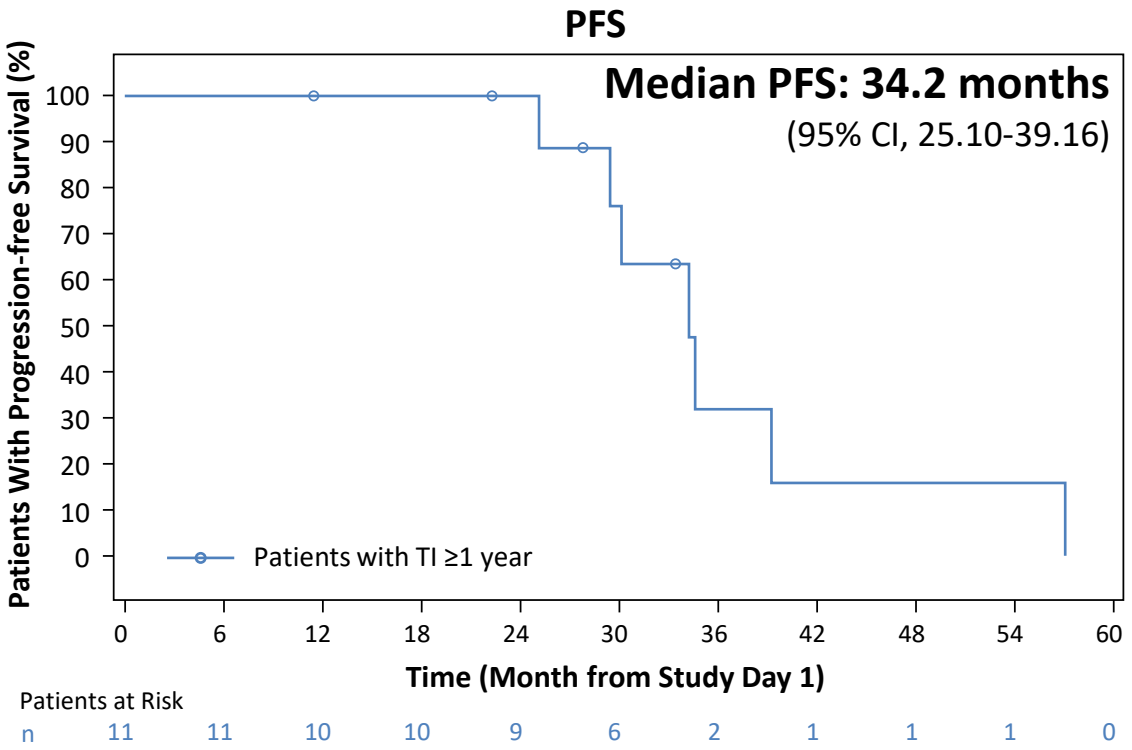


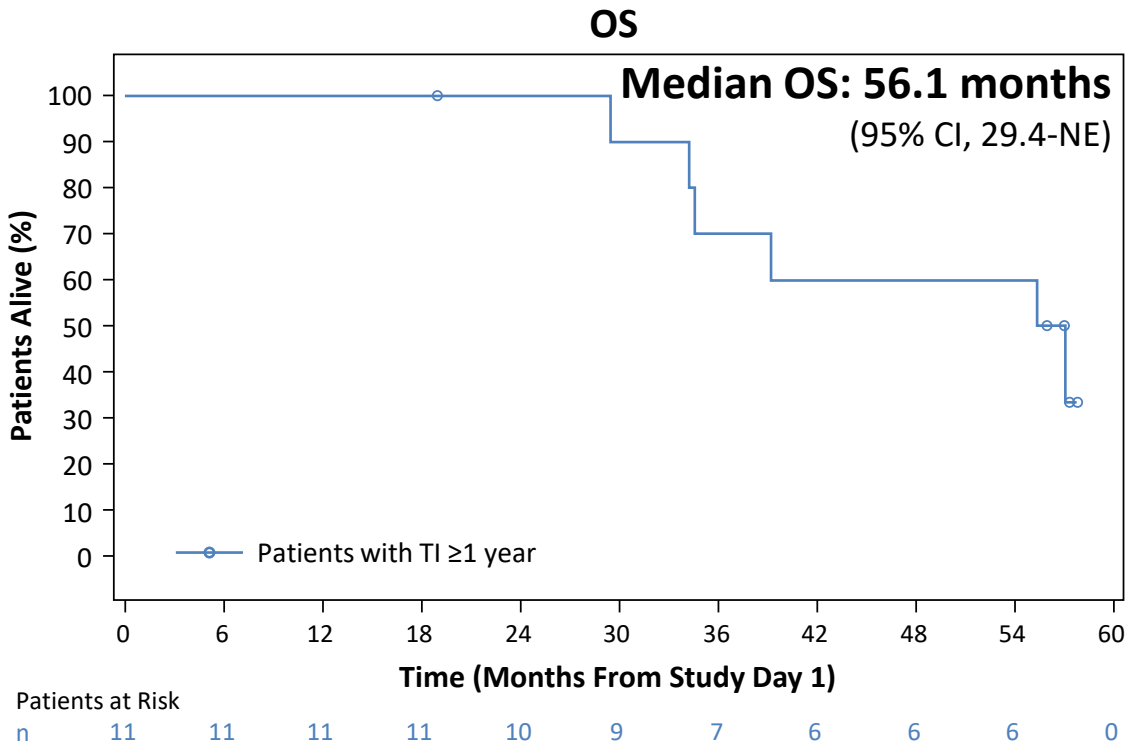
Patients at Risk

n 11 4 2 2 3 1 3 4 6 9 9 10 10 10 11 10 10 11 11 11 11 11 11 11 9 10 9 9 9 8 6 6 5 5 4 4 4 4 4 2 2 2 2 2 1 1

Data cutoff: October 13, 2022.
[a]Based on the Kaplan Meier method. [b]The mean changes from the minimum hgb of the values in the 8 weeks prior to the first dose date are shown and values that within 14 days of RBC transfusions were excluded. This plot does not include the values from unscheduled visits.
Hgb, hemoglobin; RBC, red blood cell; TI, transfusion independence.

Robust PFS and Survival of Imetelstat-Treated Patients With TI ≥1 Year





- After a median follow-up of 57 months, no progressions to AML were observed among the ≥1-year TI responders

Parameter	Patients with TI ≥1 year (n=11)	Others (n=27)	Target population (N=38)
Median PFS, months (95% CI)	34.2 (25.1, 39.2)	25.5 (11.5, 44.2)	34.2 (25.1, 41.4)
Median OS, months (95% CI)	56.1 (29.4, NE)	47.1 (38.1, NE)	55.2 (38.1, 67.1)

Data cutoff: October 13, 2022.
Based on the Kaplan-Meier method.
AML, acute myeloid leukemia; NE, not evaluable; OS, overall survival; PFS, progression-free survival; TI, transfusion independence.

Updated Phase 2 Safety Profile in Imetelstat-Treated Patients Similar to Previous Reports[1,2]

Grade 3/4 Cytopenias n (%)	>1 year TI N=11	Target population N=38
Thrombocytopenia	7 (63.6)	23 (60.5)
Neutropenia	6 (54.5)	21 (55.3)
Anemia	2 (18.2)	8 (21.2)
Leukopenia	2 (18.2)	7 (18.4)

- >97% of grade 3/4 thrombocytopenia and neutropenia within the >1 year TI population resolved to grade 2 or lower within 4 weeks (consistent with target population)
- Events were manageable with dose holds (n= 10/11) and reduction (n=7/11) as specified in the protocol with limited clinical consequences
- Imetelstat-related cytopenias are on-target effects based on the selective reduction of malignant cells through telomerase inhibition[2]

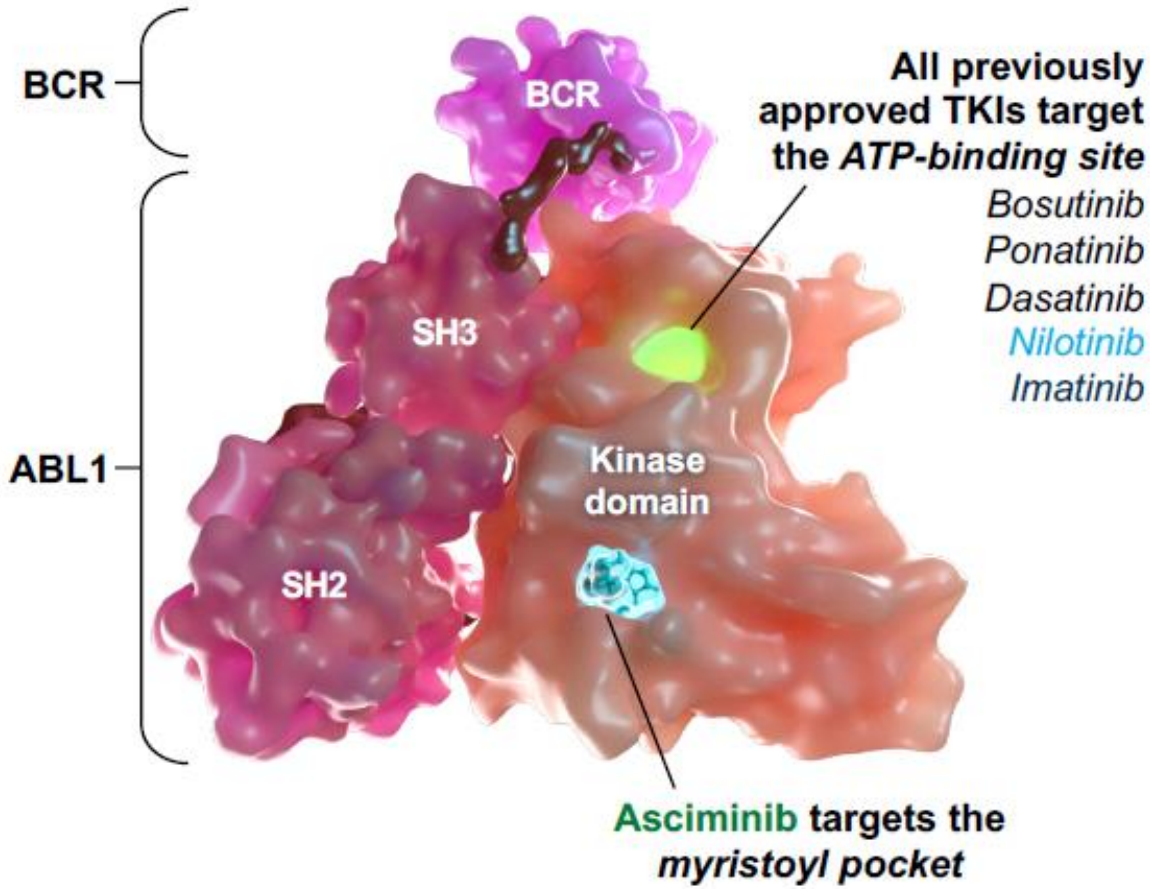
Data cutoff: October 13, 2022.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; TI, transfusion independence.
1. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56. ; 2. Mascarenhas J, et al. Presented at: EHA Annual Meeting 2021; Abstract EP0116.

#79 Yeung et. al

Early and Deep Molecular Responses Achieved with Frontline Asciminib in Chronic Phase CML – Interim Results from the ALLG CML13

Asciminib is the first BCR::ABL1 inhibitor to

Specifically Target the ABL Myristoyl Pocket (STAMP)[6,7]



ASCEND-CML Treatment Schema

Inclusion:
- CML-CP
- Aged 18+
- Good organ fx
- ECOG 0-2
- e13/14a2 or e1a2

Asciminib 40mg BID

3 months	6 months	12 months	18 months
BCR::ABL1 > 10%	*BCR::ABL1* > 10%	*BCR::ABL1* > 1%	*BCR::ABL1* > 1%

Asciminib + addition of either nilotinib, dasatinib or imatinib (physician discretion)

	BCR::ABL1 1.1 - 10%	*BCR::ABL1* 0.11 – 1%	*BCR::ABL1* 0.011 – 1%

Asciminib 80mg BID

BCR::ABL1 ≤10%	*BCR::ABL1* ≤1%	*BCR::ABL1* ≤0.1%	*BCR::ABL1* ≤0.01%

Asciminib 40mg BID (80mg QD)

ASCEND-CML, ASH 2022, Abst 79

Adverse Events (I)

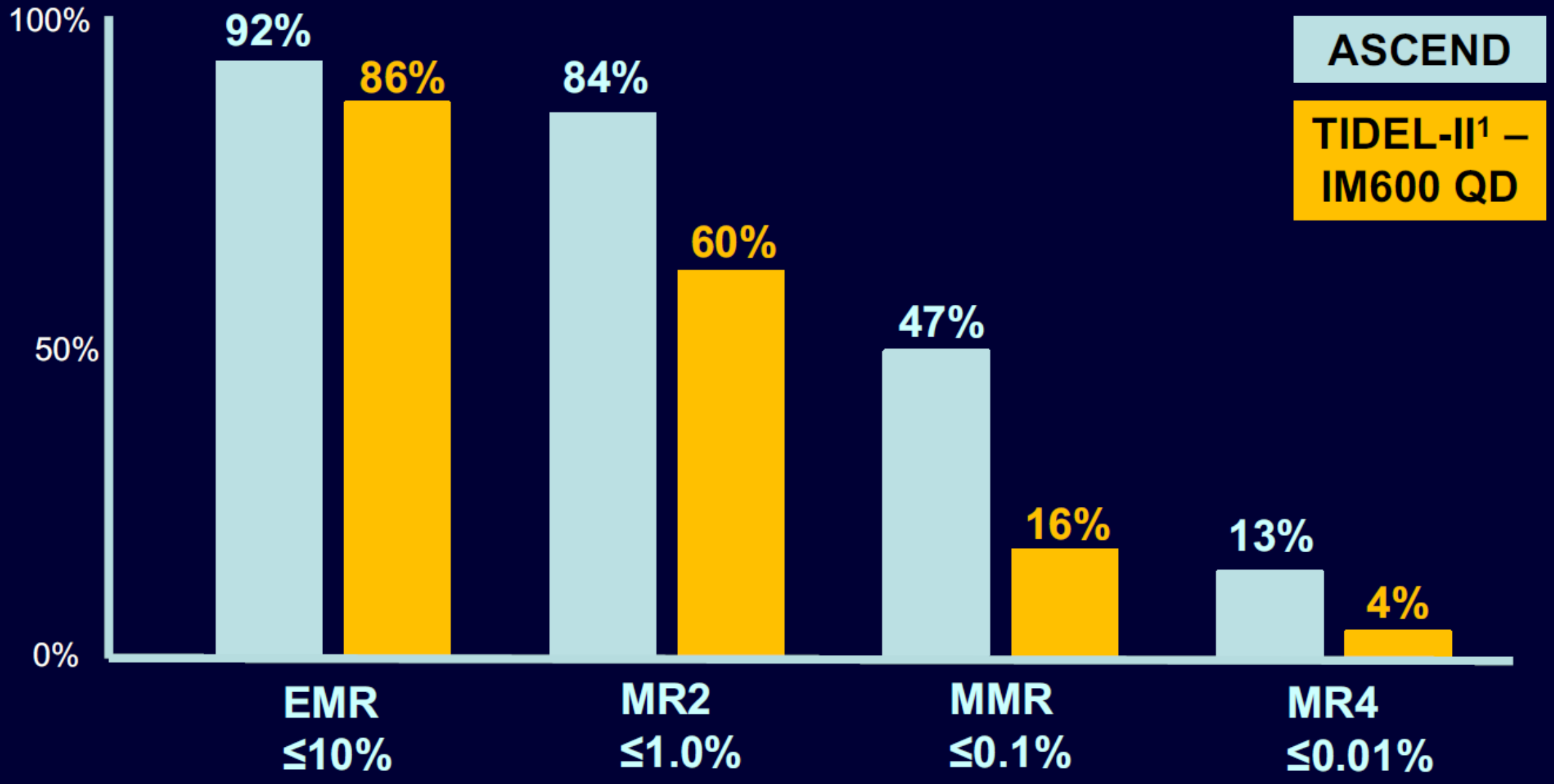
	All grades	Grade 3 / 4
Thrombocytopenia	14%	5.4%
Neutropenia	6.5%	6.5%
Anaemia	8.5%	2.2%
Lipase elevations	16.1%	6.5%
Liver Enzyme ↑	6%	1%

ASCEND-CML, ASH 2022, Abst 79

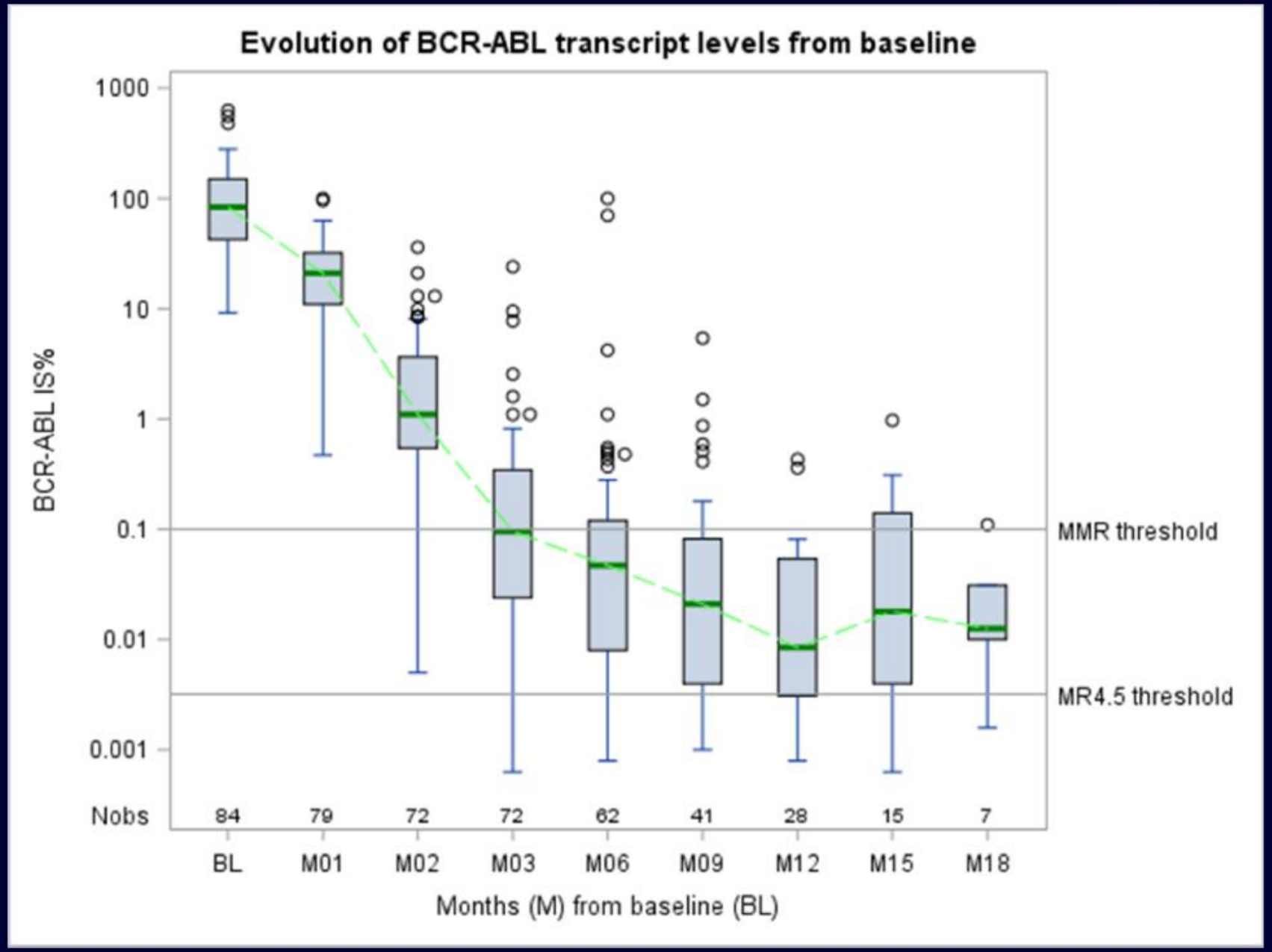
Adverse Events (II)

	All grades (>10% frequency)	Grade 3 / 4
Fatigue / lethargy	20.4%	
Infection	17.2%	1.1%
Abdominal Pain	12.9%	1.1%
Skin Disorder	12.9%	
Nausea / Vomiting	12.9%	
Arthralgia / Myalgia	10.8%	
Pulmonary embolism		1.1%
Arterial Vascular Occlusive Events	0	0

Molecular response at 3 months N=76



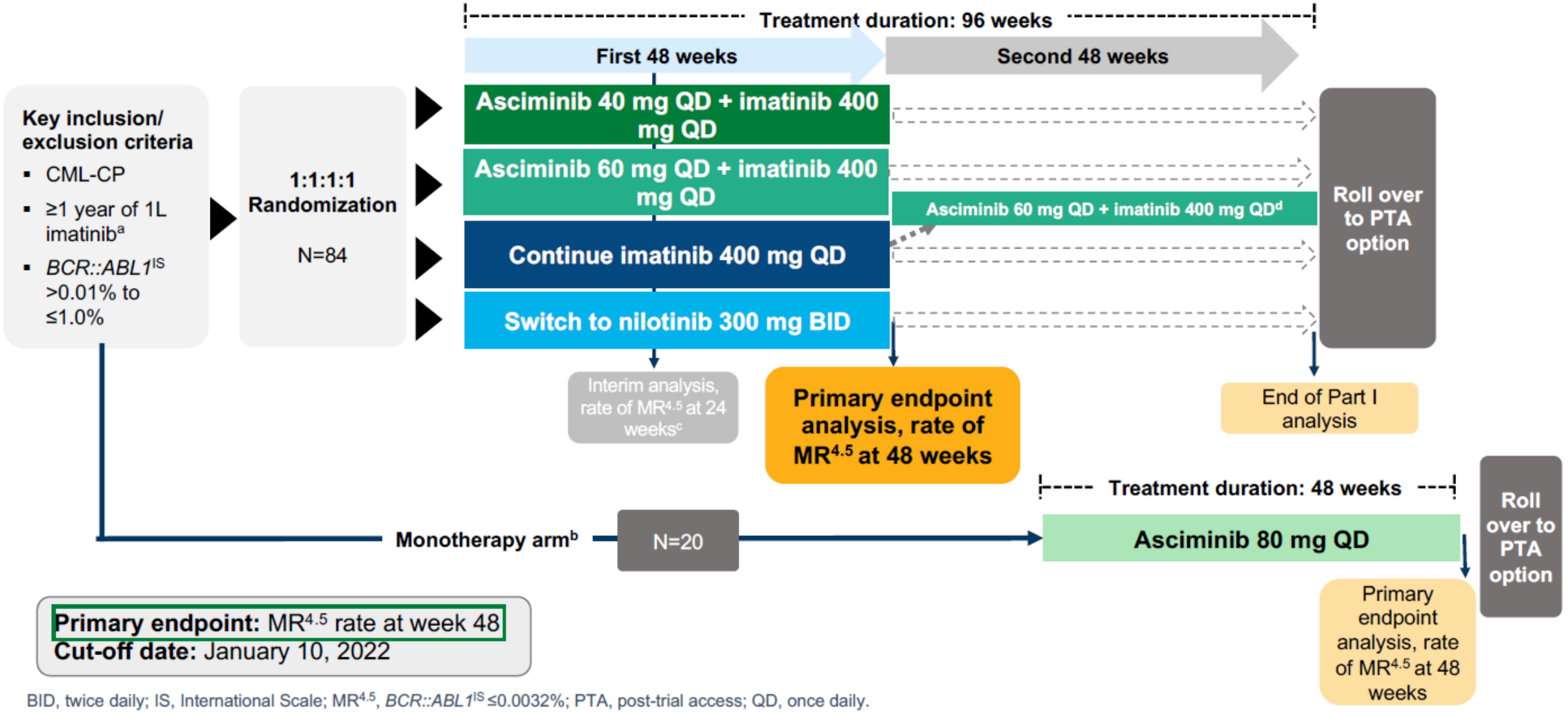
1. Yeung et al Blood 2015


Evolution of BCR-ABL transcript levels from baseline
BCR-ABL IS%
1000
100
10
1
0.1
0.01
0.001
MMR threshold
MR4.5 threshold
Nobs
84
79
72
72
62
41
28
15
7
BL
M01
M02
M03
M06
M09
M12
M15
M18
Months (M) from baseline (BL)

#80 Cortes et. al

Efficacy and Safety Results From ASC4MORE, a Randomized Study of Asciminib Add-On to Imatinib, Continued Imatinib, or Switch to Nilotinib in Patients With Chronic-Phase Chronic Myeloid Leukemia Not Achieving Deep Molecular Responses With ≥1 Year of Imatinib

ASC4MORE Study Design



Primary endpoint: MR$^{4.5}$ rate at week 48
Cut-off date: January 10, 2022

BID, twice daily; IS, International Scale; MR$^{4.5}$, *BCR::ABL1*^{IS} ≤0.0032%; PTA, post-trial access; QD, once daily.

[a] With no change of dose in the past 3 months. [b] The monotherapy arm was added in a protocol amendment on July 12, 2022 to estimate the safety and efficacy of single agent asciminib and is now enrolling. [c] Patients may discontinue treatment at the time of interim analysis if there is excessive toxicity without added benefit is observed in 1 of the observational arms. Patients who choose to discontinue in the asciminib 60 mg add-on arm will have the opportunity to continue the study in the asciminib 40 mg add-on arm if the investigator believes it is in the best interest of the patient. [d] Crossover allowed for patients who have not achieved MR$^{4.5}$ (not included in this analysis).

Oral presentation at: 64th ASH Annual Meeting & Exposition. December 10-13, 2022; New Orleans, LA, and virtual.

Demographics and Baseline Characteristics

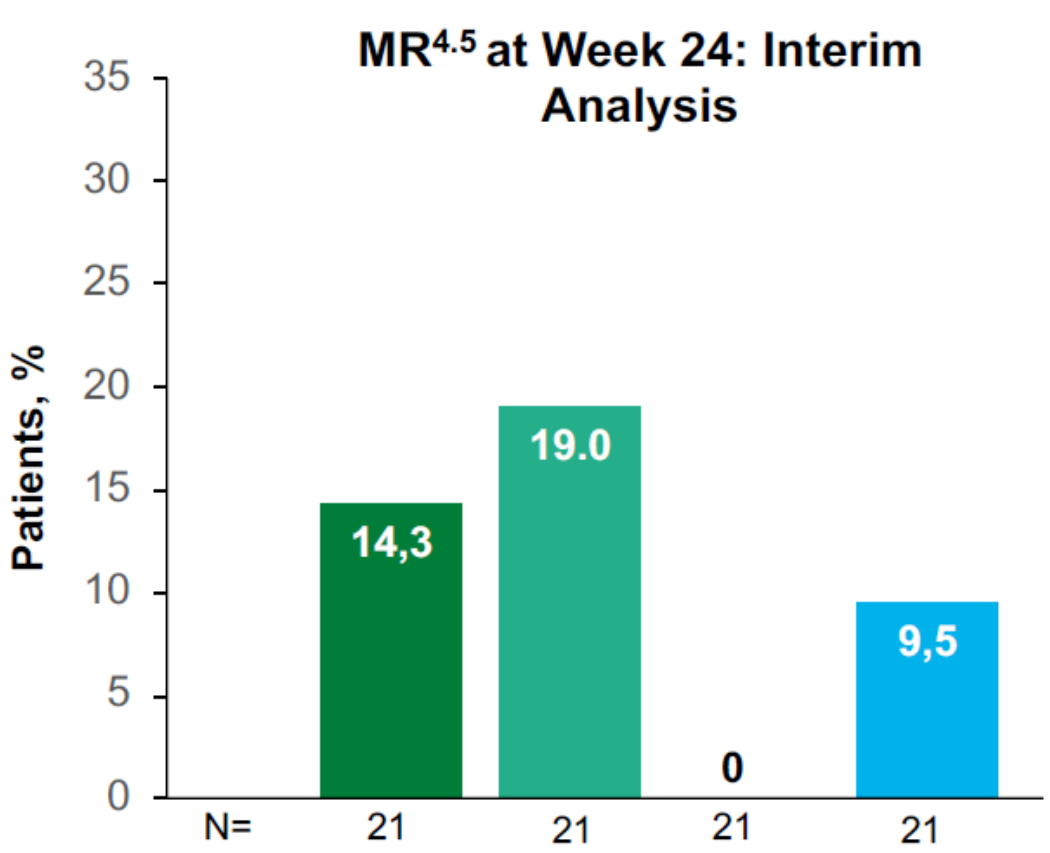
	ASC 40 + IMA N=21	ASC 60 + IMA N=21	IMA N=21	NIL N=21
Age, years				
Median (range)	48 (20-72)	37 (19-72)	51 (28-76)	40 (20-68)
Age category, n (%)				
18 to <65 years	18 (85.7)	19 (90.5)	16 (76.2)	19 (90.5)
65 to ≤85 years	3 (14.3)	2 (9.5)	5 (23.8)	2 (9.5)
Sex, n (%)				
Female	8 (38.1)	5 (23.8)	5 (23.8)	6 (28.6)
Prior duration of imatinib, years				
Median (range)	2.4 (1.1-12.1)	2.3 (1.1-14.4)	2.8 (1.1-15.6)	2.2 (1.2-18.2)
***BCR::ABL1* levels at baseline, n (%)**				
>0.1% to ≤1%	11 (52.4)	13 (61.9)	6 (28.6)	7 (33.3)
>0.01% to ≤0.1% (MMR)	10 (47.6)	8 (38.1)	15 (71.4)	14 (66.7)

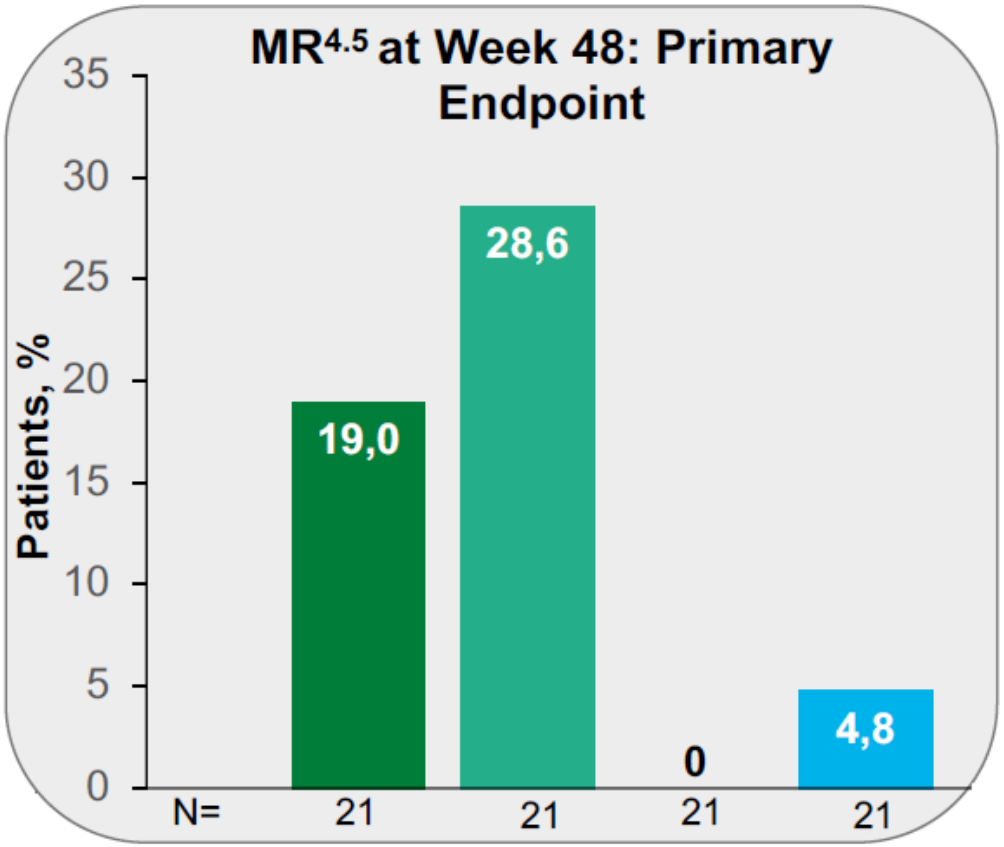
- More patients in the continued **imatinib** and **nilotinib** arms were in MMR at baseline than in the **asciminib add-on** arms, where more patients were in MR^2

ASC, asciminib; IMA, imatinib; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); MR^2, *BCR::ABL1*^{IS} ≤1%; NIL, nilotinib.

Oral presentation at: 64th ASH Annual Meeting & Exposition. December 10-13, 2022; New Orleans, LA, and virtual.

$MR^{4.5}$ at Weeks 24 and 48



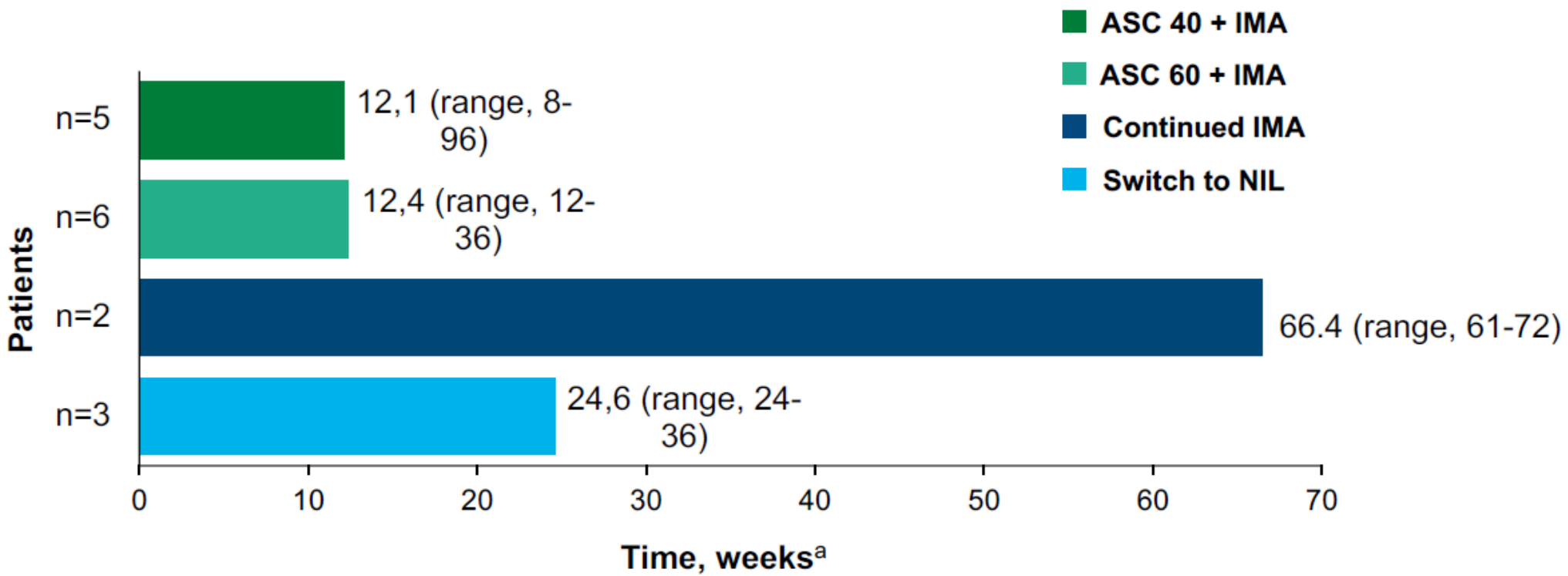


ASC 40 + IMA
ASC 60 + IMA
Continued IMA
Switch to NIL

- More patients were able to achieve $MR^{4.5}$ with **asciminib add-on** to imatinib vs continued **imatinib** or switch to **nilotinib**
- No patients in the continued **imatinib** arm were in $MR^{4.5}$ at week 48, although more patients in this arm were in MMR at baseline than in the **asciminib add-on** arms

Oral presentation at: 64th ASH Annual Meeting & Exposition. December 10-13, 2022; New Orleans, LA, and virtual.

Median Time to $MR^{4.5}$ Among Patients Who Achieved $MR^{4.5}$ at Any Time

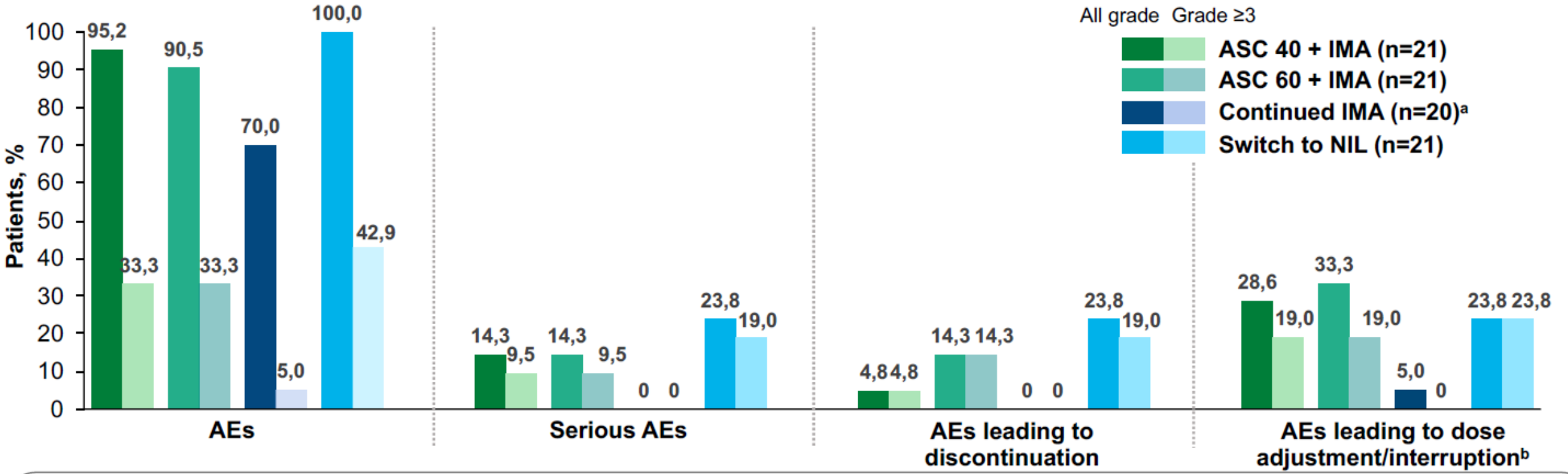


- Patients receiving **asciminib add-on** achieved $MR^{4.5}$ more quickly than those receiving **imatinib** monotherapy or **nilotinib**

[a] Assessments were performed at screening, week 4 and week 8 (not mandatory for patients in the IMA and NIL arms), weeks 12, 24, 36, and 48, and every 12 weeks up to 96/48 weeks after the first dose of the last randomized/enrolled patient (ASC single agent cohort, every 12 weeks up to 48 weeks after the first dose of the last enrolled patient).

Oral presentation at: 64th ASH Annual Meeting & Exposition. December 10-13, 2022; New Orleans, LA, and virtual.

Overview of AEs



- With longer median (range) durations of exposure (**104.7 [27-160]**, **94.0 [1-148]**, **53.4 [50-142]**, and **78.9 [1-146]** weeks for the **asciminib 40 mg QD add-on**, **asciminib 60 mg QD add-on**, **imatinib**, and **nilotinib** arms, respectively), more patients in the **asciminib add-on** arms remained on treatment at data cutoff
- In this population of patients who had been tolerating imatinib ≥1 year prior to study entry, **asciminib add-on** resulted in a slightly higher rate of AEs vs continued **imatinib**, although fewer than switching to **nilotinib**
- Serious AEs and AEs leading to treatment discontinuation occurred more frequently in the **nilotinib** arm vs the **asciminib add-on arms**

AE, adverse event.

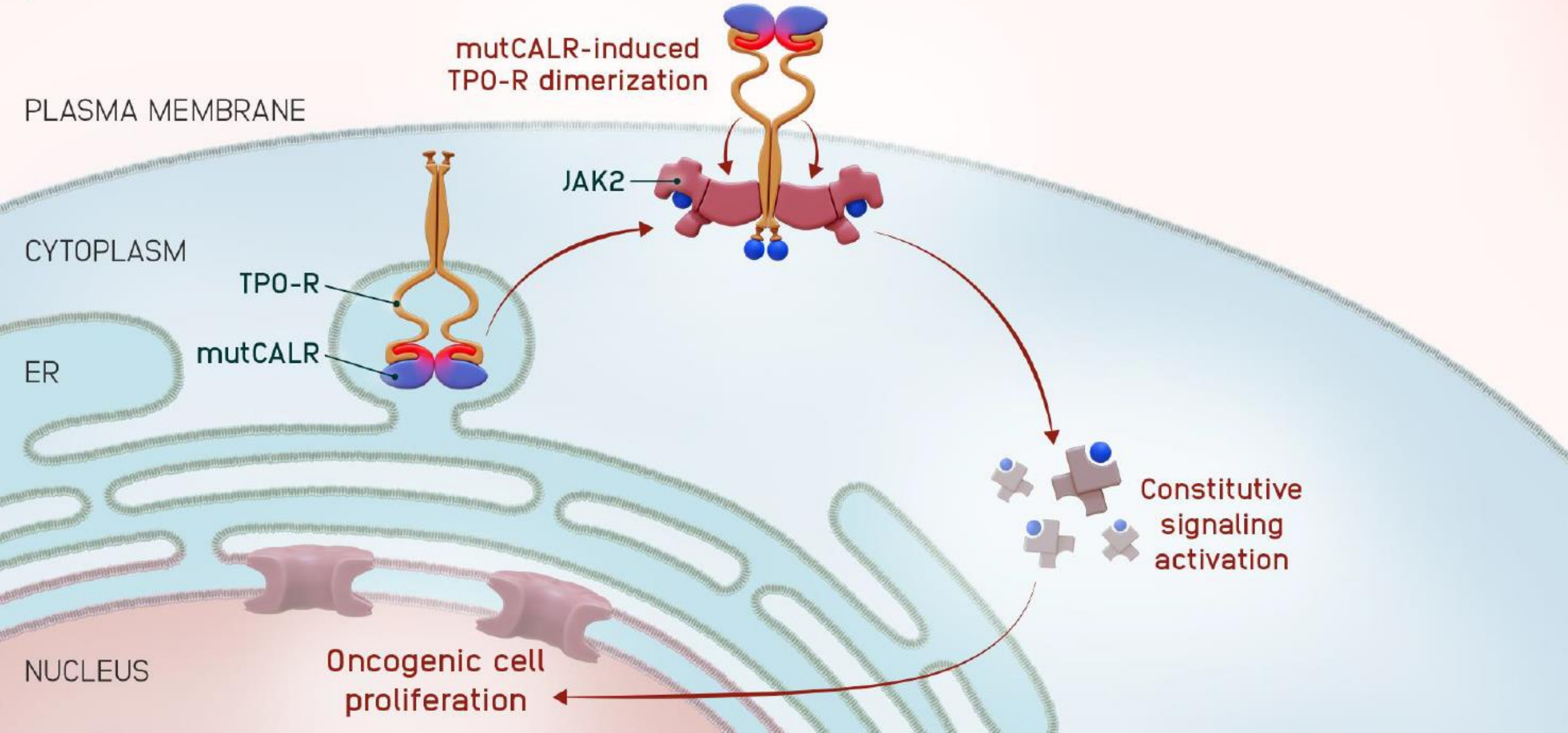
[a] One patient in the continued imatinib arm was not treated due to patient decision. [b] AEs leading to dose adjustments/interruptions in ≥2 patients were neutropenia (n=2) in the asciminib 40 mg add-on arm and Gilbert syndrome and abdominal pain upper (n=2 each) in the nilotinib arm.

Oral presentation at: 64th ASH Annual Meeting & Exposition. December 10-13, 2022; New Orleans, LA, and virtual.

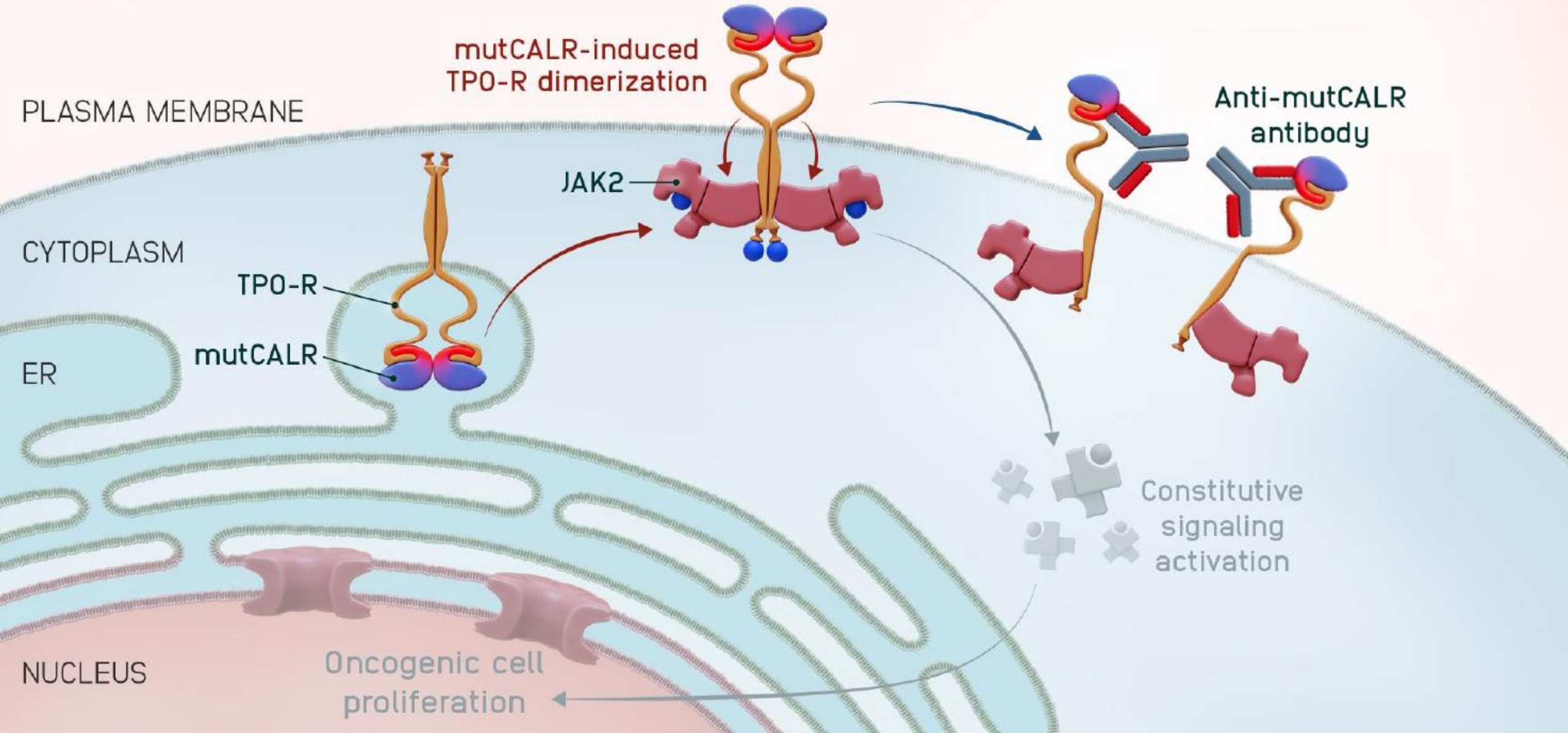
#6 Reis et. al

Discovery of INCA033989, a Monoclonal Antibody That Selectively Antagonizes Mutant Calreticulin Oncogenic Function in Myeloproliferative Neoplasms

Mutant calreticulin (mutCALR) induces oncogenic cell proliferation

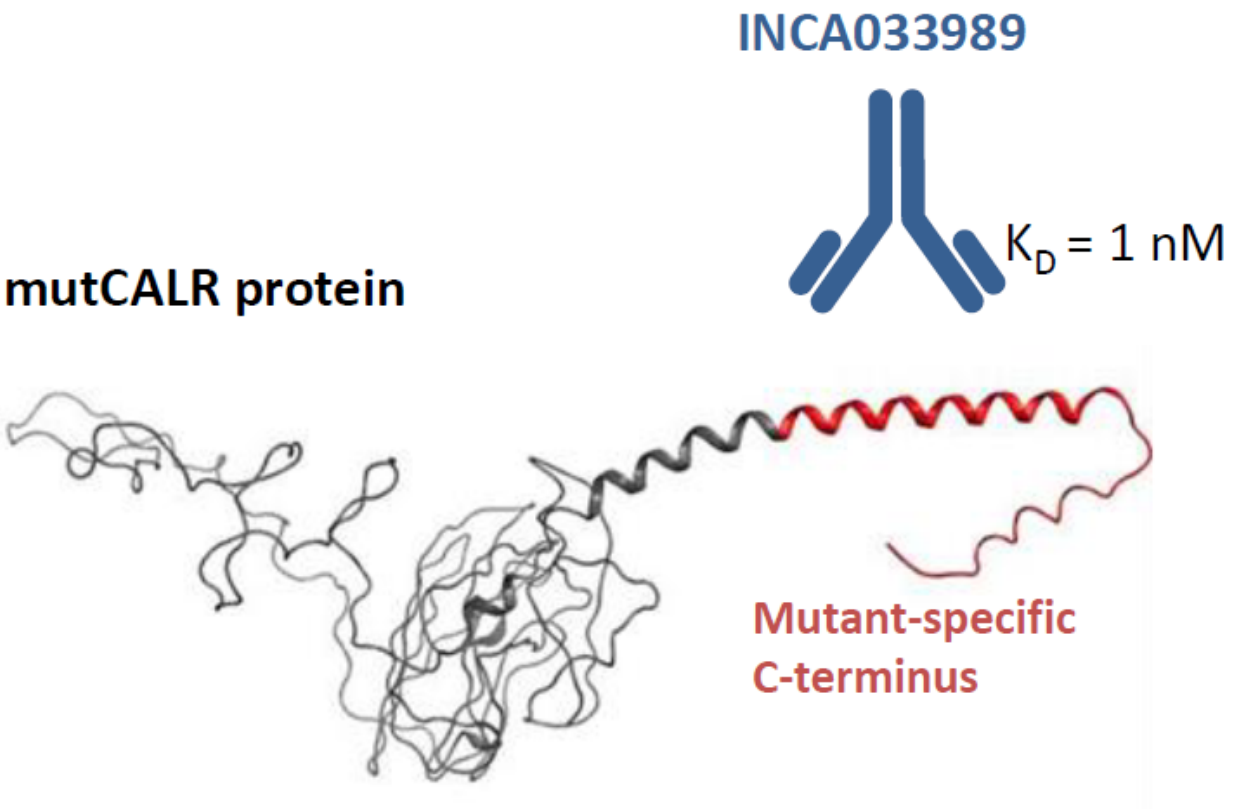


Anti-mutCALR antibody selectivity inhibits oncogenic cell proliferation



INCA033989: a mutCALR-specific monoclonal antibody

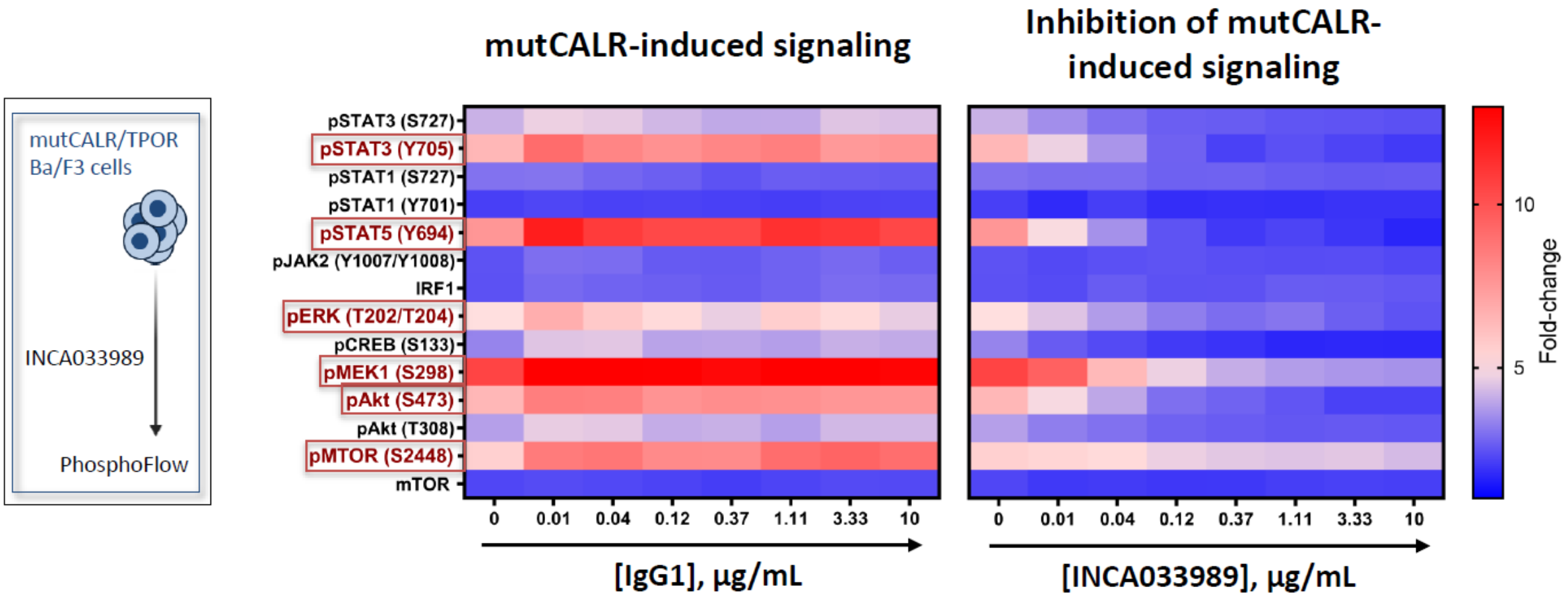
- Fully human IgG1
- Fc-silent
- Selective binding to mutCALR
- Antagonizes mutCALR-induced signaling and oncogenic function



Structure generated with RaptorX (Toyota Technological Institute at Chicago, IL, USA).

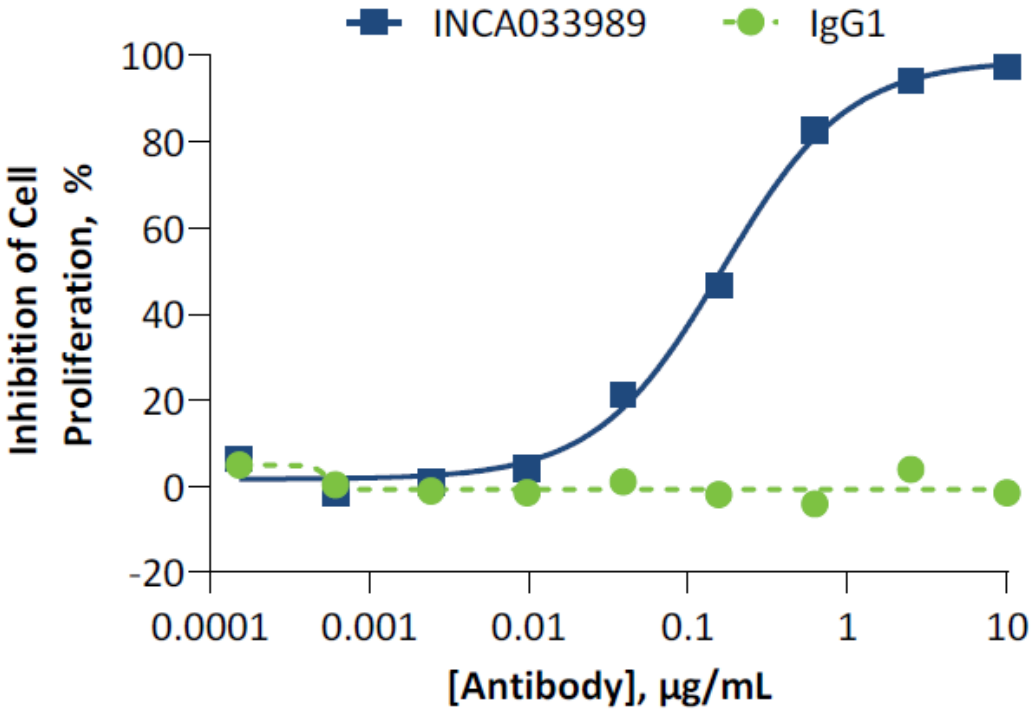
IgG, immunoglobulin G; Fc, fragment crystallizable; K_D, equilibrium dissociation constant.

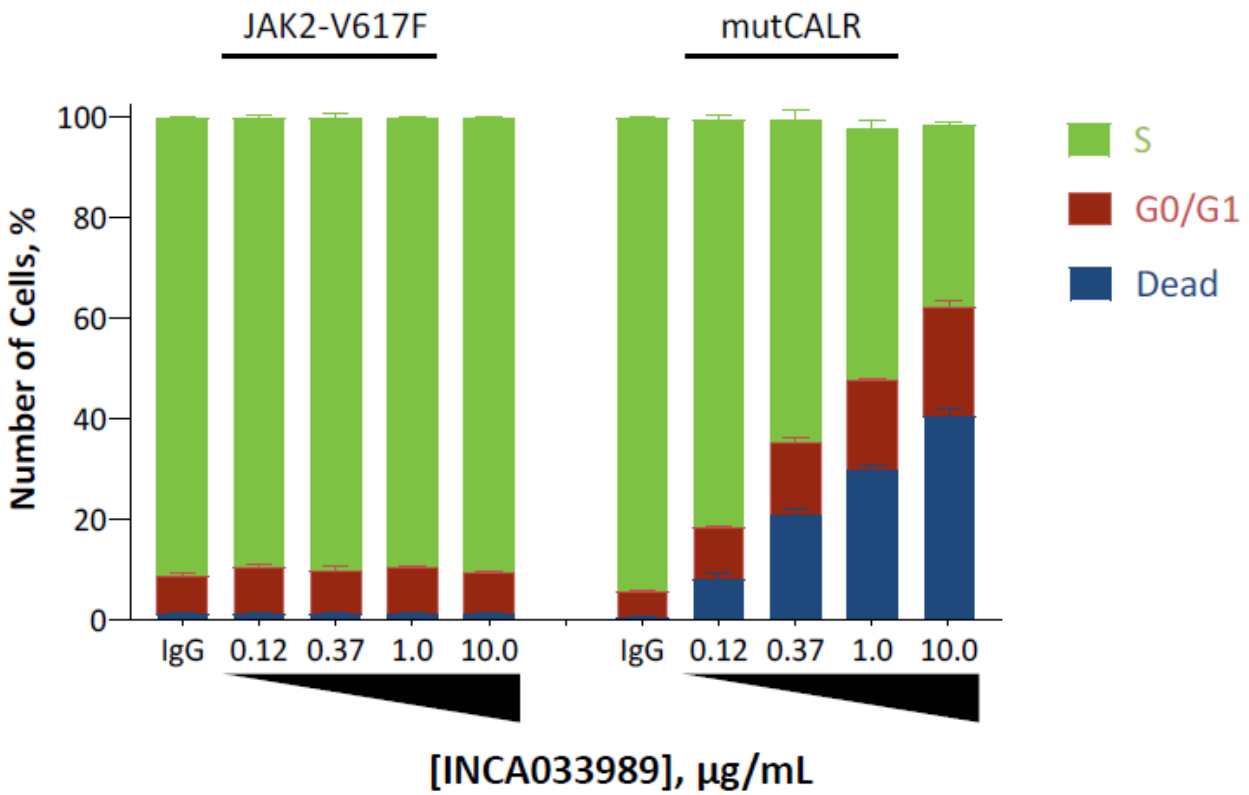
INCA033989 inhibits mutCALR-induced oncogenic signaling



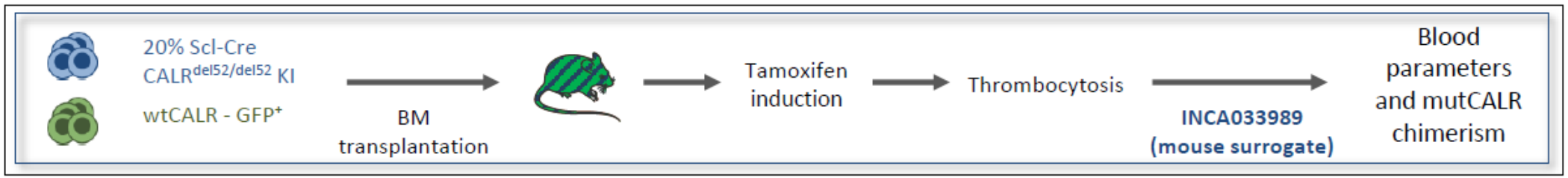
Bianca Lima Ferreira, Ian Hitchcock. York Biomedical Research Institute, University of York.

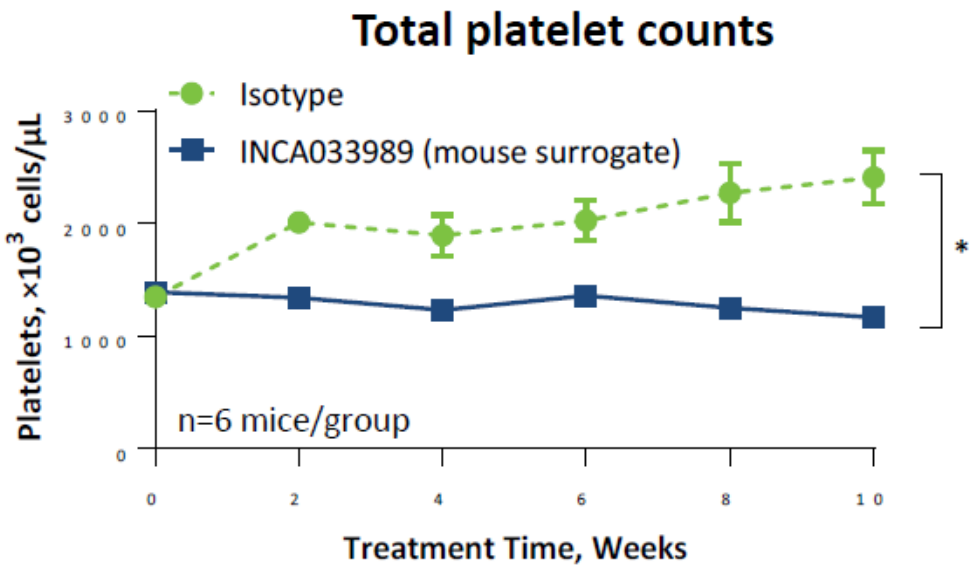
INCA033989 selectively inhibits cell proliferation and induces death of mutCALR^{+} cells

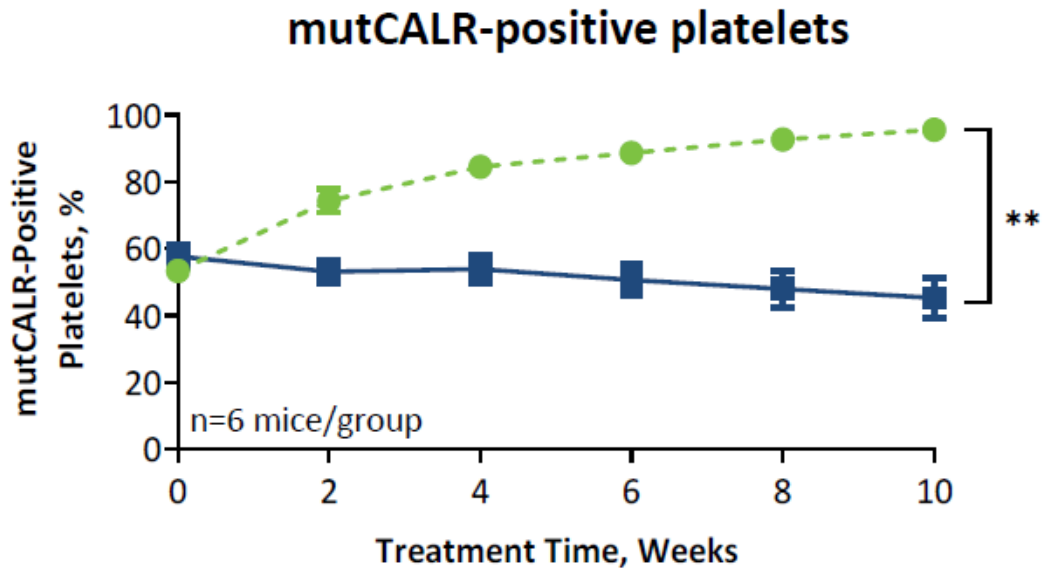




INCA033989 surrogate restores hematologic and molecular responses in a murine model of ET







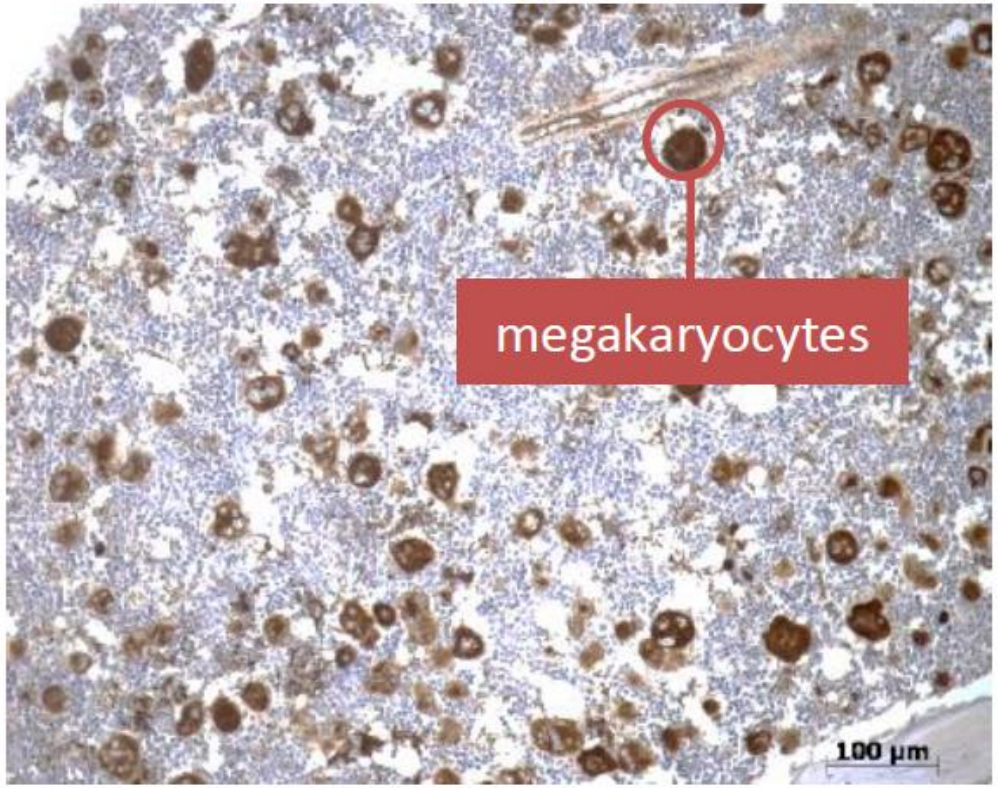
*P<0.001; **P<0.0001.

BM, bone marrow; ET, essential thrombocythemia.

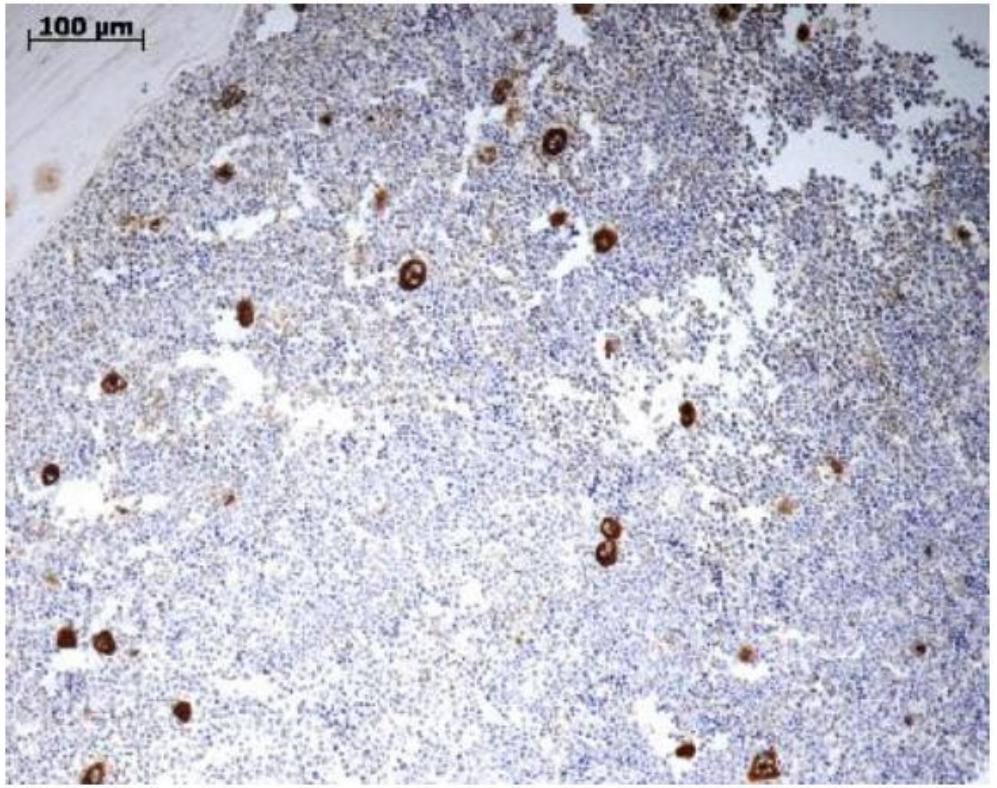
Caroline Marty, Elodie Rosa, Maxime Evrard, William Vainchenker, Isabelle Plo. Gustave Roussy Institute, INSERM, Université Paris-Saclay.

INCA033989 surrogate treatment re-establishes normal megakaryopoiesis

Isotype



INCA033989 (mouse surrogate)



Megakaryocytes stained with anti–von Willebrand factor antibody.

Caroline Marty, Elodie Rosa, Maxime Evrard, William Vainchenker, Isabelle Plo. Gustave Roussy Institute, INSERM, Université Paris-Saclay.

#627 Gerds et. al

Updated Results from the Momentum Phase 3 Study of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic and Anemic Myelofibrosis (MF) Patients Previously Treated with a JAK Inhibitor

STUDY BACKGROUND AND METHODS

- Momelotinib (MMB), an oral JAK1, JAK2 inhibitor, showed clinical activity on MF symptoms, red blood cell transfusion requirements (anemia), and spleen volume

- This presentation provides updated efficacy and safety results after 48 weeks

STUDY DESIGN MOMENTUM

Ongoing phase 3 study of MMB vs. DAN in symptomatic, anemic, JAKi-experienced patients

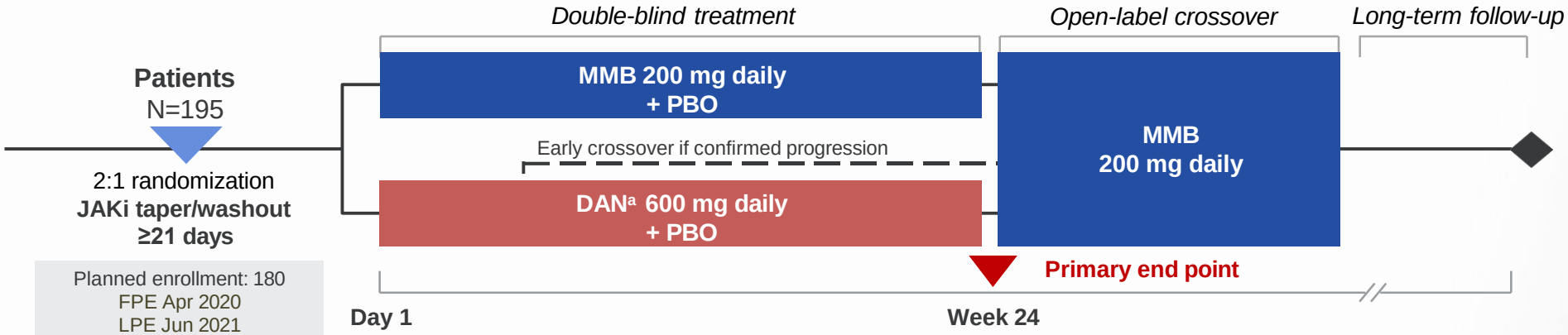
Previously treated with JAKi
Symptomatic (TSS ≥10)
Anemic (Hgb <10 g/dL)
Platelets ≥25×10⁹/L

Stratification:
- TSS
- Palpable spleen length
- Transfused units in prior 8 weeks
- Study site

Patients
N=195

2:1 randomization
JAKi taper/washout ≥21 days

Planned enrollment: 180
FPE Apr 2020
LPE Jun 2021
Database lock Dec 2021



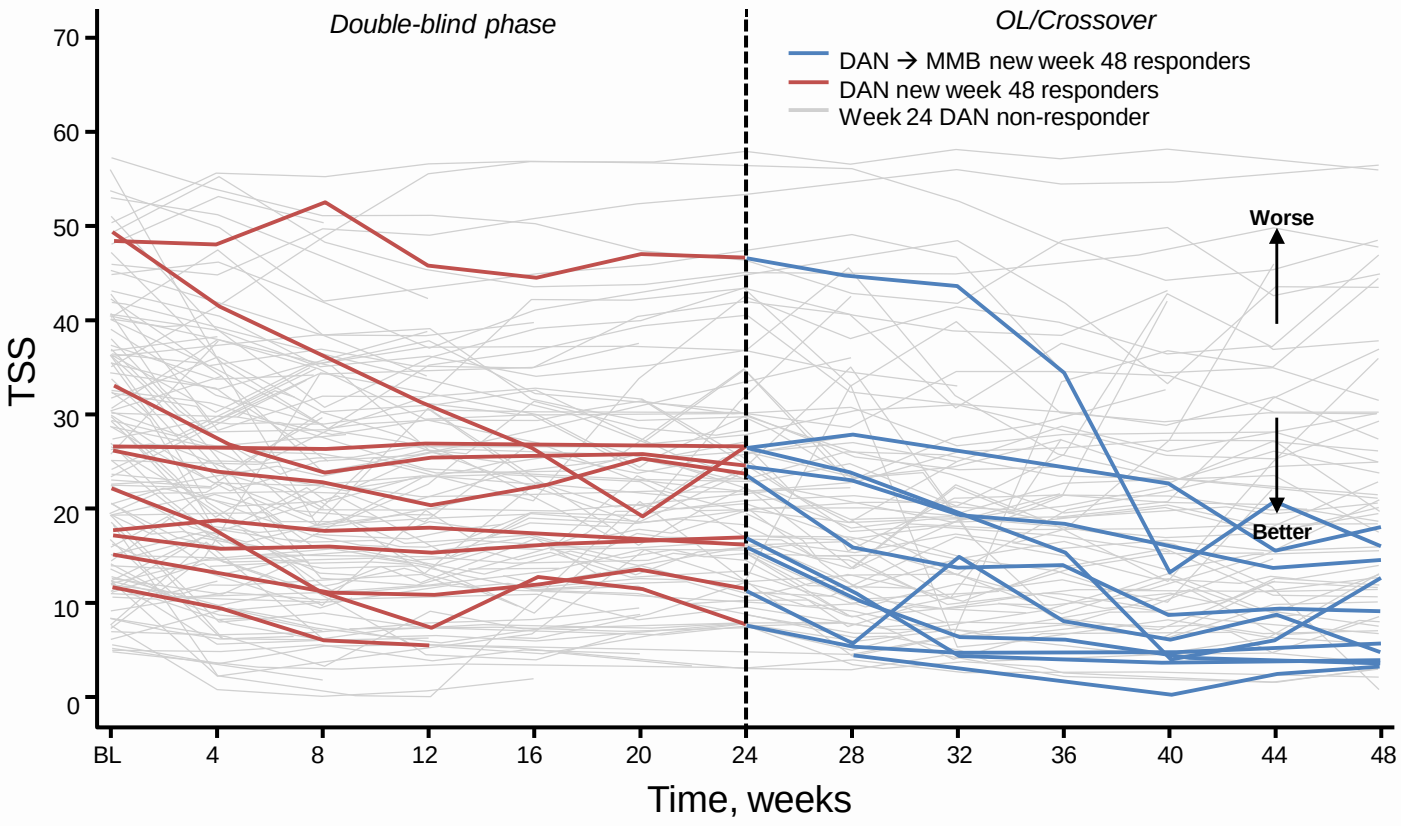
MOMENTUM Topline results at week 24: All primary and key secondary end points met[1,2]

	MFSAF TSS[b] response rate (primary end point)	TI response[c] rate	SRR[d] (35% reduction)
MMB (N=130)	32 (24.6%)	40 (30.8%)	30 (23.1%)
DAN (N=65)	6 (9.2%)	13 (20.0%)	2 (3.1%)
	P=.0095 (superior)	1-sided *P*=.0064 (noninferior)	*P*=.0006 (superior)

EFFICACY – TSS RESPONSE

New week 48 TSS responses were observed for week 24 Danazol non-responders[a]

TSS over time for DAN non-responders who became responders at week 48



- Week 24 TSS response was 25% in the MMB group and 9% in the DAN group
- Week 24 TSS response was maintained in 31 of 32 (97%) MMB→MMB and 6 of 6 (100%) DAN→MMB patients
- 10 of 35 (29%) DAN→MMB week 24 TSS non-responders were new responders at week 48
- 12 of 61 (20%) MMB→MMB week 24 TSS non-responders were also new responders at week 48

[a]Defined as the proportion of patients who achieve <50% reduction in TSS over the 28 days immediately before the end of week 24 compared with baseline. DAN, danazol; MMB, momelotinib; OL, open-label; TSS, total symptom score.

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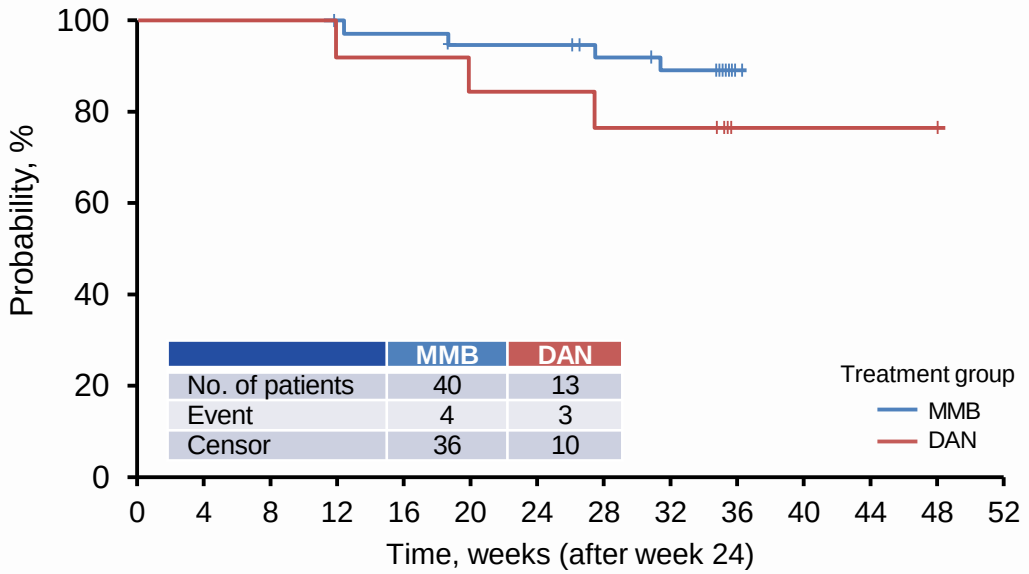
EFFICACY – TI RESPONSES

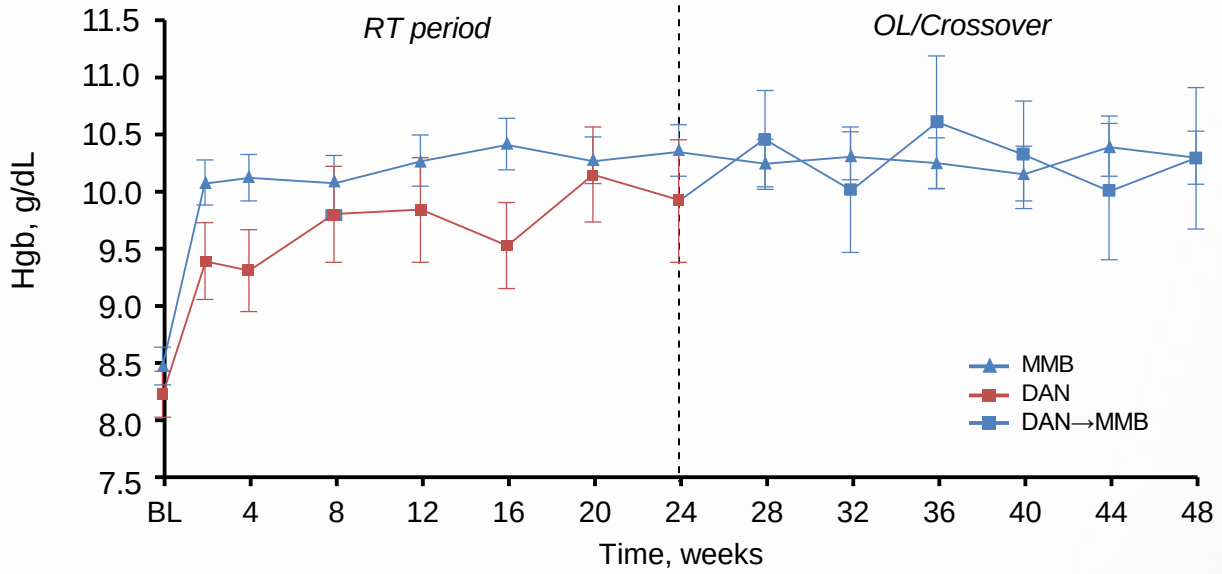
Week 24 TI responses[a] were sustained through week 48

TI duration of response in ITT population



	MMB	DAN
No. of patients	40	13
Event	4	3
Censor	36	10

Mean Hgb over time in TI responders



MMB (n)	40	40	40	40	38	36	36	34	32	23	0			
DAN (n)	13	13	13	13	12	12	11	11	10	9	1	1	1	0

MMB (n)	39	34	32	33	35	36	34	36	37	33	33	34	33	
DAN (n)	13	11	12	11	11	12	10	11	11	7	10	9	10	

- Week 24 TI response was 31% in the MMB group and 20% in the DAN group
  - Consecutive 12-week TI-R[b] was 44.6% in the MMB group and 29.2% in the DAN group (Poster #3028)
- Week 24 TI response was maintained in 36 of 40 (90%) MMB→MMB and 10 of 13 (77%) DAN→MMB patients

[a]Defined as not requiring RBC transfusion in the prior 12 weeks and Hgb levels ≥8 g/dL; [b]Consecutive 12-week TI-R (defined as absence of RBC transfusions and no Hgb measurement below 8 g/dL over any 12-week period through week 24)
BL, baseline; DAN, danazol; Hgb, hemoglobin; ITT, intention-to-treat; MMB, momelotinib; OL, open-label; RBC, red blood cell; RT, randomized treatment; TI, transfusion independence.

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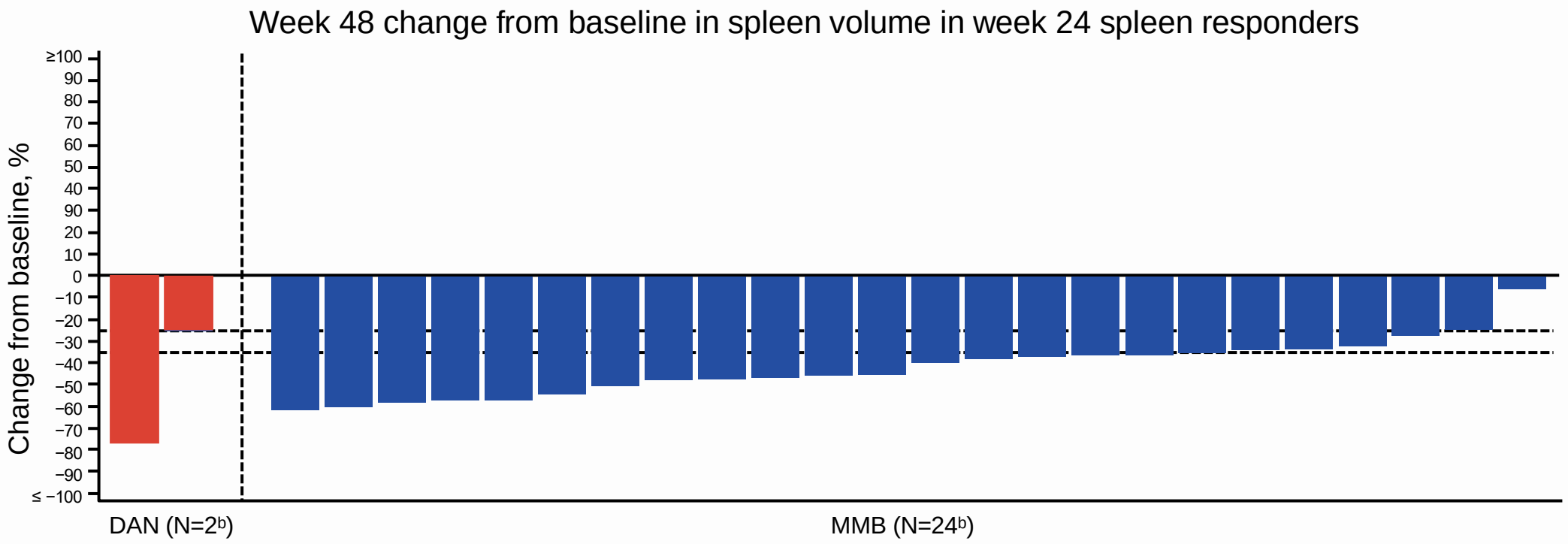
EFFICACY – SPLEEN RESPONSES

Week 24 spleen responses[a] were sustained through week 48



- Week 24 SRR35 response was 23% in the MMB group and 3% in the DAN group
- All SRR35 responders at week 24 maintained spleen volume below baseline (24 of 24 MMB →MMB and 2 of 2 DAN →MMB patients)

[a]Defined as the proportion of patients who have a reduction in spleen volume of ≥35% from baseline. [b]N is the number of patients with percent change in spleen volume at week 48 available.
DAN, danazol; MMB, momelotinib; SRR35, splenic response rate >35%.

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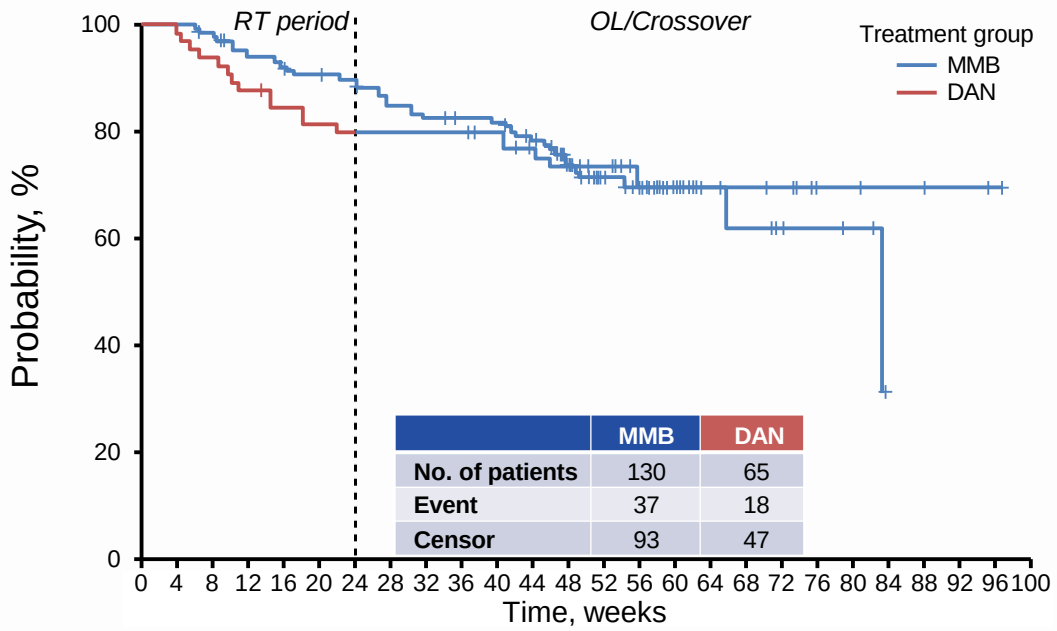
EFFICACY – OS AND LFS

OS and LFS curves for MMB→MMB and DAN→MMB converged after all patients crossed over to open-label MMB at week 24[a]

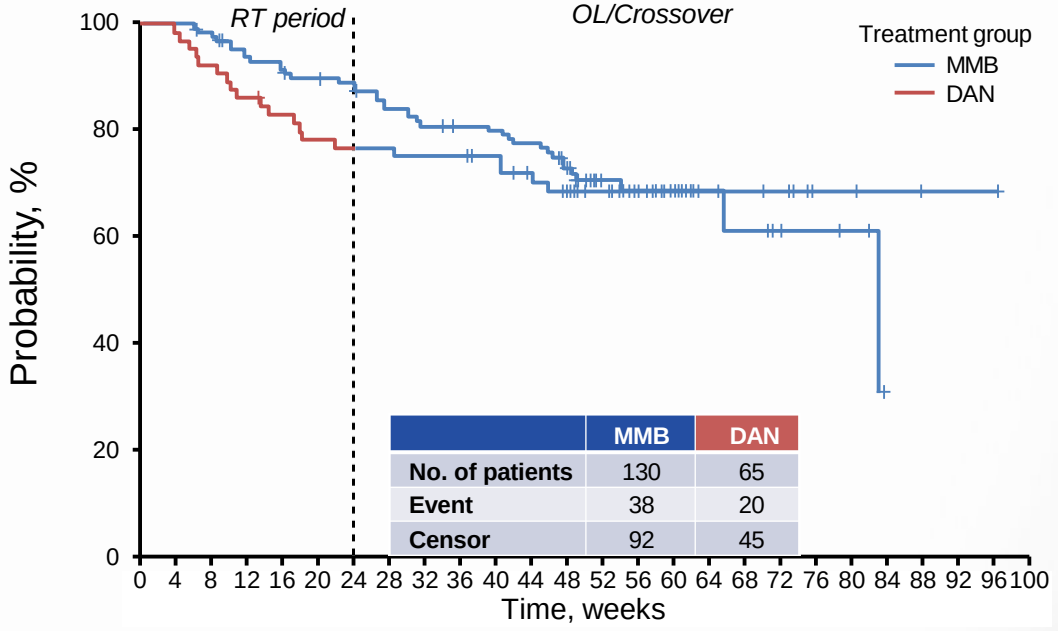
OS in the ITT Population



	MMB	DAN
No. of patients	130	65
Event	37	18
Censor	93	47

MMB (n)	130	130	126	119	117	114	110	104	101	99	98	92	78	40	29	20	10	8	5	4	3	0				
DAN (n)	65	64	61	57	54	52	51	51	51	51	49	45	41	24	17	11	10	9	8	4	4	3	3	2	1	0

LFS in the ITT Population



	MMB	DAN
No. of patients	130	65
Event	38	20
Censor	92	45

MMB (n)	130	130	126	119	116	113	109	103	99	97	96	91	78	40	29	20	10	8	5	4	3	0				
DAN (n)	65	65	60	56	53	50	49	49	48	48	46	42	39	22	16	10	9	8	7	3	3	2	2	1	1	0

- OS was significantly improved for MMB →MMB patients who achieved a week 24 TI response (Poster 3028)

[a]Median follow-up for OS was 51 weeks (range, 6-84 weeks) for MMB-treated and 53 weeks (range, 4-97 weeks) for DAN-randomized patients. DAN, danazol; LFS, leukemia-free survival; MMB, momelotinib; OS, overall survival; RT, randomized treatment.

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TREATMENT-EMERGENT ADVERSE EVENTS

TEAEs in ≥10% of patients during OL MMB treatment with no new safety signals detected

	MMB→MMB (n=93)		DAN→MMB (n=41)	
	% of patients			
Grade ≥3 adverse events	49.5		46.3	
Serious adverse events	31.2		29.3	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
Nonhematologic (preferred term)				
Weight decreased	7.5	0	14.6	0
Diarrhea	14.0	1.1	12.2	0
Pyrexia	14.0	0	7.3	0
Hypertension	3.2	0	12.2	2.4
Asthenia	11.8	3.2	0	0
Hematologic (preferred term)				
Thrombocytopenia	14.0	8.6	17.1	14.6
Anemia	10.8	8.6	7.3	2.4
Neutropenia	5.4	5.4	4.9	0
Other				
COVID-19 (pneumonia)	10.8	5.4	0	0
Peripheral sensory neuropathy	2.2	0	2.4	0

DAN, danazol; MMB, momelotinib; OL, open-label; TEAE, treatment-emergent adverse event.

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Danke für die Aufmerksamkeit!