MDS-404

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Population Pharmacokinetics Modeling and Evaluation of Clinical Efficacy and Safety of Sabatolimab: Dose Selection and Dose-Response Analysis

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CONCLUSIONS

- Sabatolimab 400 mg Q2W was predicted to have the highest steady state C_{trough} and TIM-3 occupancy rate when combined with HMA; 800 mg was predicted to be an equivalent Q4W dosing regimen
- Sabatolimab 400 mg Q2W and 800 mg Q4W provided similarly high levels of TIM-3 engagement based on analysis of sTIM-3 concentration and receptor occupancy modeling
- Sabatolimab + HMA showed promising efficacy and good safety/tolerability in patients with vHR/HR-MDS and AML at both 400 mg Q2W and 800 mg Q4W, with no clear relationship between sabatolimab dose/exposure and safety/efficacy
- These results validate the selection of the 400 mg Q2W and 800 mg Q4W dosing regimens for the STIMULUS clinical trial program

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INTRODUCTION

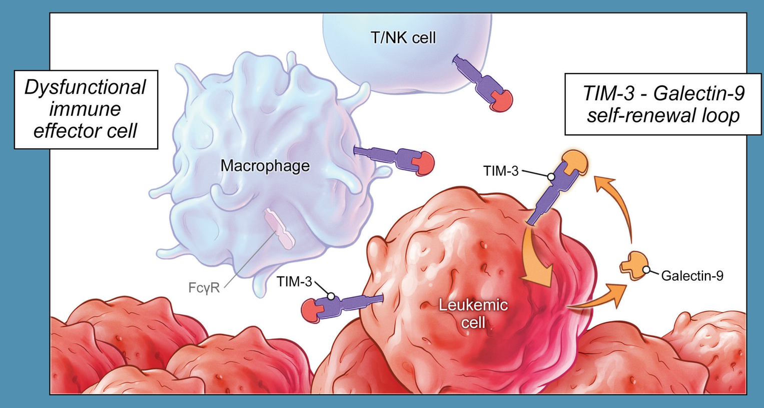
TIM-3

- T-cell immunoglobulin domain and mucin domain-3 (TIM-3) is an inhibitory receptor expressed on macrophages, monocytes, natural killer cells, dendritic cells, and T cells[1,2] (**Figure 1**)
- Involved in regulating innate and adaptive immune responses[1,2]
- Expressed on leukemic stem cells (LSCs)/blasts but not normal hematopoietic stem cells (HSCs),[3,4] making it a promising target in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)[4-6]

Sabatolimab

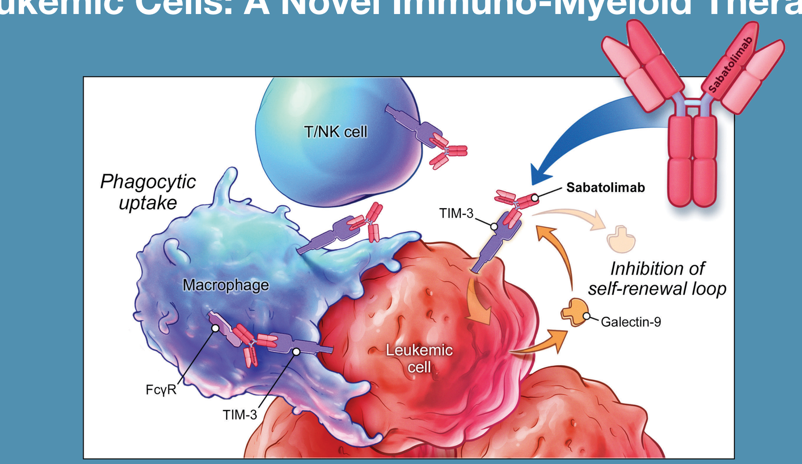
- High-affinity, humanized, immunoglobulin G4 anti–TIM-3 monoclonal antibody[6,7]
- Binds TIM-3 on immune cells, enhancing antileukemic immune activation and phagocytic killing of LSCs and blasts[2,7-9] **(Figure 2)**
- Directly targets TIM-3 on LSCs, inhibiting TIM-3/galectin-9-driven self-renewal[2,9]

Figure 1. TIM-3 is an Inhibitory Receptor Expressed on Immune and Leukemic Cells


T/NK cell
Dysfunctional immune effector cell
TIM-3 - Galectin-9 self-renewal loop
Macrophage
TIM-3
FcγR
TIM-3
Leukemic cell
Galectin-9

FcγR, Fc gamma receptor; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

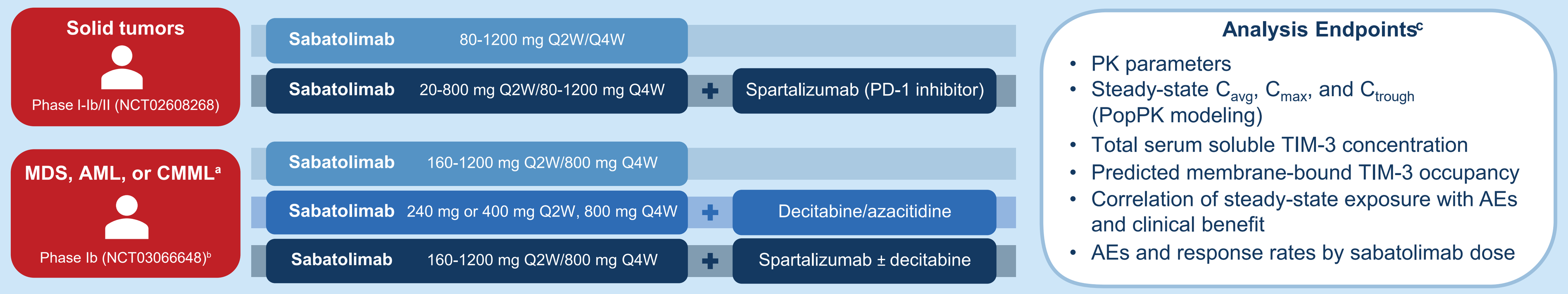
Figure 2. Sabatolimab Targets TIM-3 on Immune and Leukemic Cells: A Novel Immuno-Myeloid Therapy


Sabatolimab
T/NK cell
Phagocytic uptake
Sabatolimab
TIM-3
Inhibition of self-renewal loop
Macrophage
Leukemic cell
Galectin-9
FcγR
TIM-3

FcγR, Fc gamma receptor; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

METHODS

Figure 3. Evaluation of Sabatolimab Pharmacokinetics and Dose Response in Early Clinical Studies

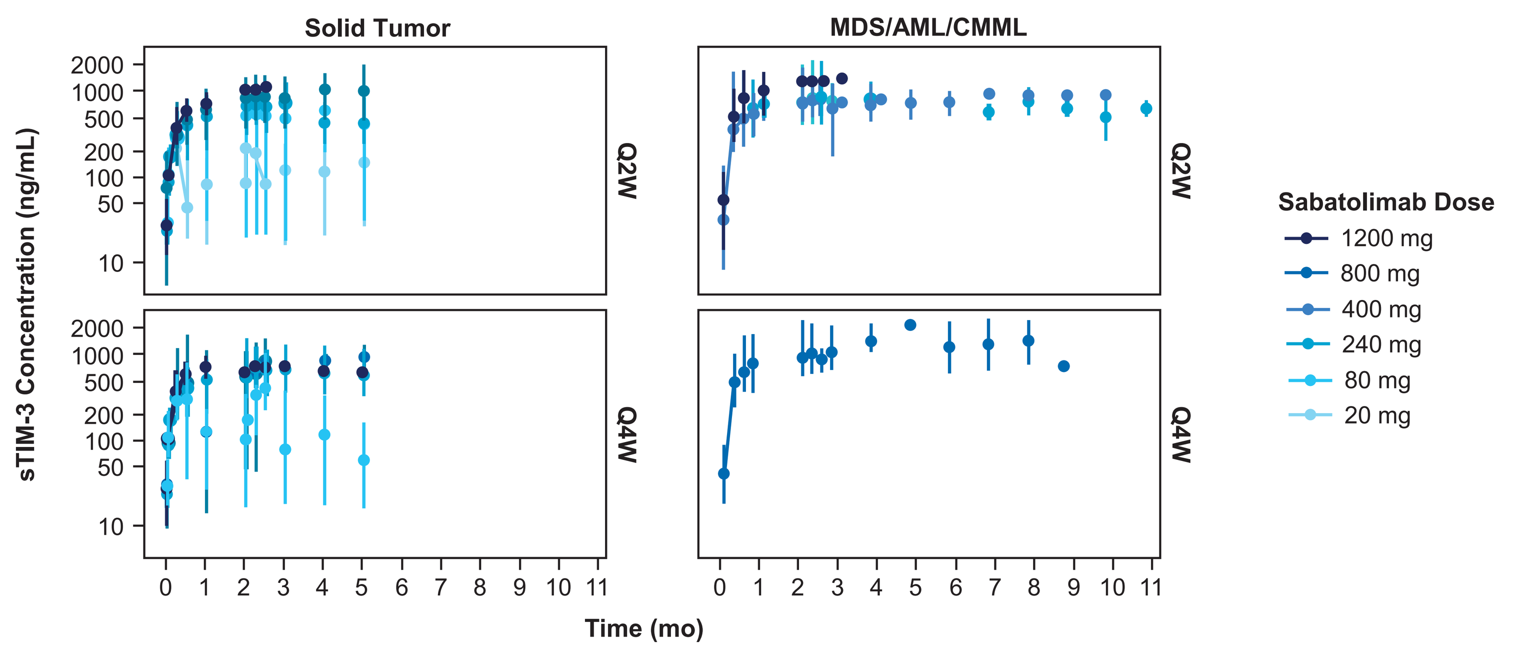

Solid tumors
Phase I-Ib/II (NCT02608268)
Sabatolimab 80-1200 mg Q2W/Q4W
Sabatolimab 20-800 mg Q2W/80-1200 mg Q4W + Spartalizumab (PD-1 inhibitor)
MDS, AML, or CMML[a]
Phase Ib (NCT03066648)[b]
Sabatolimab 160-1200 mg Q2W/800 mg Q4W
Sabatolimab 240 mg or 400 mg Q2W, 800 mg Q4W + Decitabine/azacitidine
Sabatolimab 160-1200 mg Q2W/800 mg Q4W + Spartalizumab ± decitabine
Analysis Endpoints[c]
PK parameters
Steady-state Cavg, Cmax, and Ctrough (PopPK modeling)
Total serum soluble TIM-3 concentration
Predicted membrane-bound TIM-3 occupancy
Correlation of steady-state exposure with AEs and clinical benefit
AEs and response rates by sabatolimab dose

AE, adverse event; AML, acute myeloid leukemia; C_{avg}, average concentration; C_{max}, maximum concentration; C_{trough}, trough concentration; CMML, chronic myelomonocytic leukemia; HR, high-risk; MDS, myelodysplastic syndrome; PD-1, programmed death-1; PK, pharmacokinetics; Pop, population; Q2W, every 2 weeks; Q4W, every 4 weeks; TIM-3, T-cell immunoglobin domain and mucin-3; vHR, very high-risk.
[a] Sabatolimab + decitabine/azacitidine arm included adult patients with vHR/HR-MDS or AML who were ineligible for intensive chemotherapy. [b] Dosing used in vHR/HR-MDS and AML patients was based on findings from the NCT02608268 study. [c] All endpoints had a data cutoff date of November 27, 2019, except for AEs and response rates by sabatolimab dose, which had a data cutoff date of September 22, 2020.

RESULTS

- Saturation of soluble TIM-3 (sTIM-3) was achieved with sabatolimab doses ≥240 mg every 2 weeks (Q2W) and ≥800 mg every 4 weeks (Q4W) (**Figure 4**)
- In patients with solid tumors, sabatolimab doses ≥240 mg Q2W or ≥800 mg Q4W showed:
 - Plateau in accumulated total sTIM-3
 - Proportional dose-exposure relationship
- Similar results were observed in the study in patients with MDS/AML/chronic myelomonocytic leukemia (CMML)

Figure 4. sTIM-3 Levels Over Time by Sabatolimab Dose

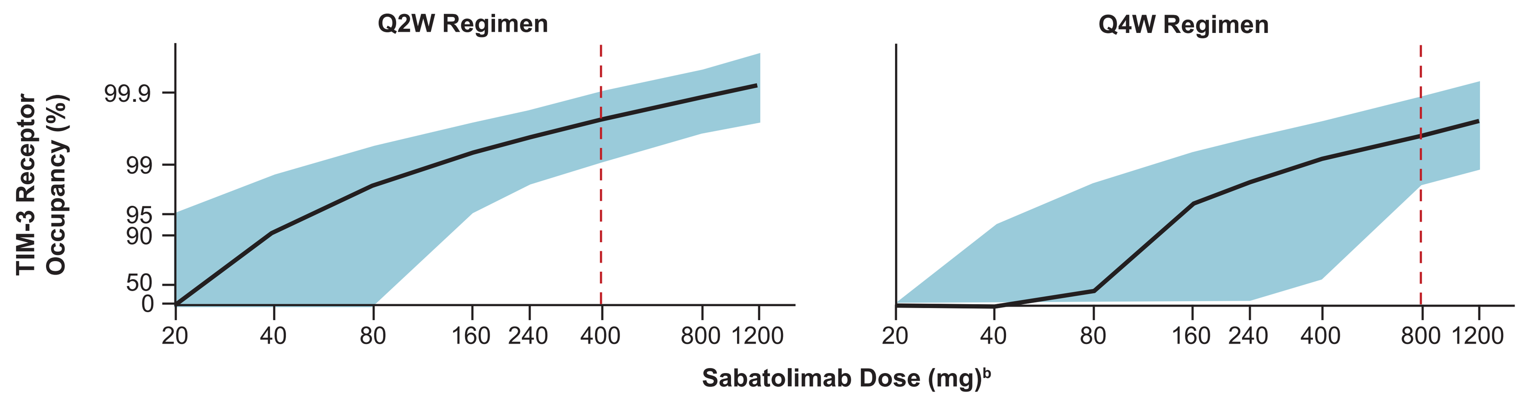

Solid Tumor
MDS/AML/CMML
sTIM-3 Concentration (ng/mL)
2000
1000
500
200
100
50
10
Q2W
Q4W
0 1 2 3 4 5 6 7 8 9 10 11
Time (mo)
Sabatolimab Dose
1200 mg
800 mg
400 mg
240 mg
80 mg
20 mg

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; Q2W, every 2 weeks; Q4W, every 4 weeks; sTIM-3, soluble T-cell immunoglobulin domain and mucin domain-3.

Population PK Modeling with Sabatolimab + HMA Regimens

- 400 mg Q2W had the highest trough concentration (C_{trough}) at steady state
- 800 mg was predicted to be an equivalent Q4W dosing regimen
- Both doses had similar steady-state average concentration (C_{avg})
- Receptor occupancy modeling indicated similarly high levels of TIM-3 engagement with sabatolimab 400 mg Q2W and 800 mg Q4W (**Figure 5**)
 - Greater than 95% occupancy rate in bone marrow in ≥95% of patients with very high-risk (vHR)/high-risk (HR)-MDS, AML, or CMML

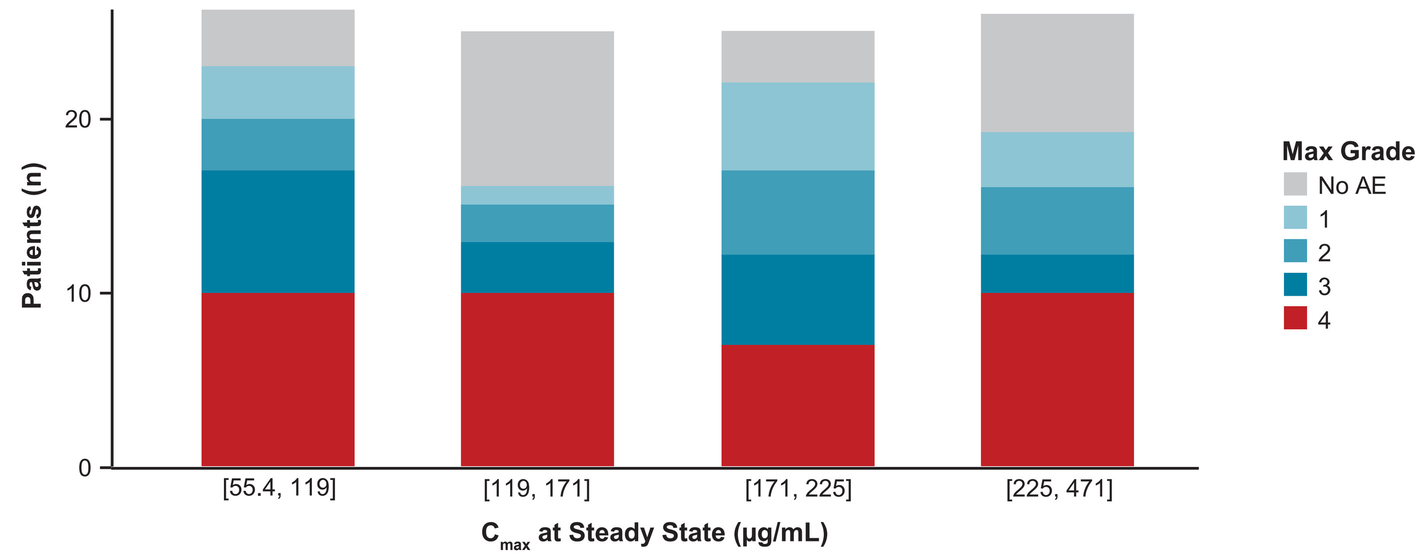
Figure 5. Simulated Steady-State Occupancy of Membrane-Bound TIM-3 in Bone Marrow[a]


Q2W Regimen
Q4W Regimen
TIM-3 Receptor Occupancy (%)
99.9
99
95
90
50
0
20 40 80 160 240 400 800 1200
Sabatolimab Dose (mg)[b]

TIM-3, T-cell immunoglobin domain and mucin domain-3; Q2W, every 2 weeks; Q4W, every 4 weeks.
[a] Compared to baseline. [b] Shaded region denotes 5% to 95% prediction interval.

- Pharmacokinetic (PK) exposure-response analyses with sabatolimab + hypomethylating agents (HMA) showed similar safety and efficacy across sabatolimab exposure levels (**Figures 6 and 7**)
- Patients were categorized into 4 exposure quartiles based on steady-state maximum concentration (C_{max}) and C_{avg}
 - No relationship between steady-state C_{max} or C_{avg} and treatment-related adverse events (AEs)

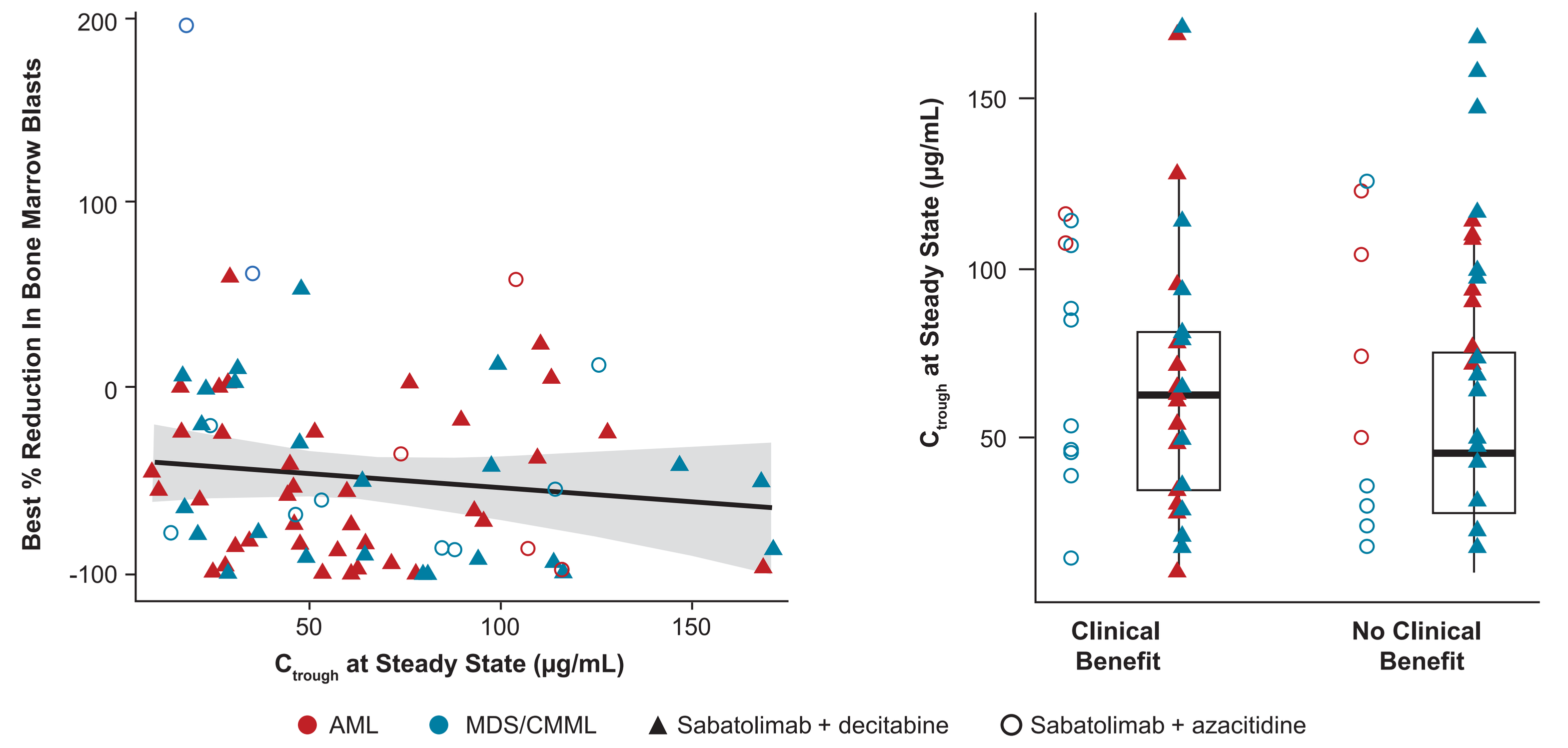
Figure 6. PK Exposure-AE Relationship (n=102[a])


Patients (n)
0
10
20
[55.4, 119]
[119, 171]
[171, 225]
[225, 471]
Cmax at Steady State (μg/mL)
Max Grade
No AE
1
2
3
4

AE, adverse event; AML, acute myeloid leukemia; C_{max}, maximum concentration; CMML, chronic myelomonocytic leukemia; HMA, hypomethylating agent; HR, high-risk; MDS, myelodysplastic syndrome; PK, pharmacokinetics; vHR, very high-risk.
[a] Includes patients with vHR/HR-MDS, CMML, or AML who were treated with sabatolimab + HMA.

- No relationship between steady-state C_{trough} or C_{avg} and % blast cell reduction or clinical benefit (ie, complete remission, marrow complete remission, complete remission with incomplete hematologic recovery, and partial remission) (**Figure 7**)

Figure 7. PK Exposure-Efficacy Relationship (n=92[a])


Best % Reduction In Bone Marrow Blasts
200
100
0
-100
50
100
150
Ctrough at Steady State (μg/mL)
Ctrough at Steady State (μg/mL)
150
100
50
Clinical Benefit
No Clinical Benefit
AML
MDS/CMML
Sabatolimab + decitabine
Sabatolimab + azacitidine

AML, acute myeloid leukemia; C_{trough}, trough concentration; CMML, chronic myelomonocytic leukemia; HMA, hypomethylating agent; HR, high-risk; MDS, myelodysplastic syndrome; PK, pharmacokinetics; vHR, very high-risk.
[a] Includes patients with vHR/HR-MDS, CMML, or AML who were treated with sabatolimab + HMA.

- Rates of clinically significant (grade ≥3) treatment-emergent AEs (TEAEs) and possible immune-mediated AEs (imAEs) related to treatment did not appear to be dose dependent (**Table 1**)

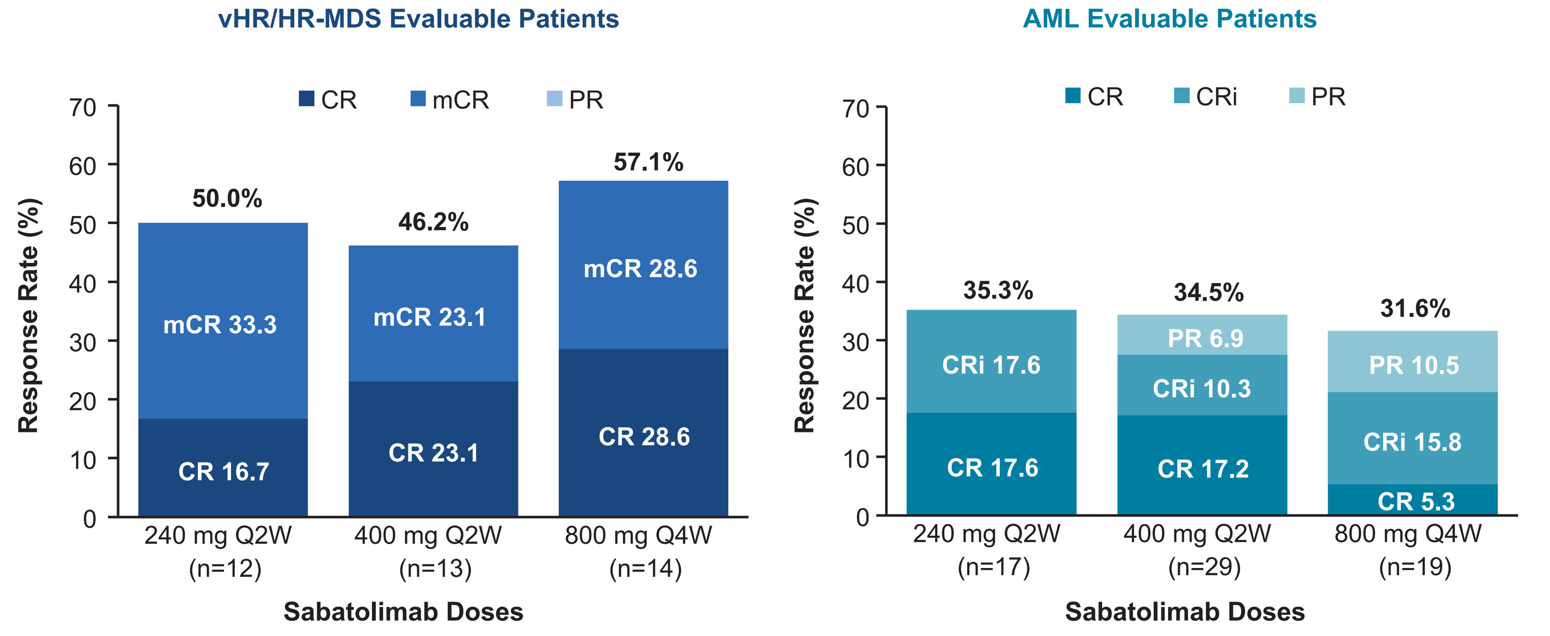
Table 1. Clinical Safety by Sabatolimab Dose (n=118)

	vHR/HR-MDS and AML		
Sabatolimab dose	240 mg Q2W	400 mg Q2W	800 mg Q4W
Safety population, n	30	50	38
Most common[a] TEAEs grade ≥3, n (%)			
Neutropenia	15 (50.0)	20 (40.0)	17 (44.7)
Thrombocytopenia	13 (43.3)	16 (32.0)	20 (52.6)
Febrile neutropenia	17 (56.7)	14 (28.0)	14 (36.8)
Anemia	9 (30.0)	12 (24.0)	14 (36.8)
Pneumonia	2 (6.7)	8 (16.0)	5 (13.2)
Treatment-related possible imAEs grade ≥3,[b] n (%)	4 (13.3)	0	2 (5.3)

AML, acute myeloid leukemia; HR, high-risk; imAE, immune-mediated adverse event; MDS, myelodysplastic syndrome; Q2W, every 2 weeks; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event; vHR, very high-risk.
[a] Reported in ≥10% of patients in either the vHR/HR-MDS or AML cohort. [b] 8 events occurred in 6 patients.

- To date, among the 3 sabatolimab dosing regimens tested (**Figure 8**):
 - No notable differences in efficacy
 - No significant association with duration of response (Cox model with dose as a covariate)
- Sabatolimab + HMA was safe overall, with encouraging efficacy across doses in vHR/HR-MDS or AML

Figure 8. Clinical Efficacy by Sabatolimab Dose (n=104)


vHR/HR-MDS Evaluable Patients
AML Evaluable Patients
CR
mCR
PR
CRi
Response Rate (%)
0 10 20 30 40 50 60 70
50.0%
mCR 33.3
CR 16.7
46.2%
mCR 23.1
CR 23.1
57.1%
mCR 28.6
CR 28.6
240 mg Q2W (n=12)
400 mg Q2W (n=13)
800 mg Q4W (n=14)
35.3%
CRi 17.6
CR 17.6
34.5%
PR 6.9
CRi 10.3
CR 17.2
31.6%
PR 10.5
CRi 15.8
CR 5.3
240 mg Q2W (n=17)
400 mg Q2W (n=29)
800 mg Q4W (n=19)
Sabatolimab Doses

AML, acute myeloid leukemia; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; HR, high-risk; mCR, marrow complete remission; MDS, myelodysplastic syndrome; PR, partial remission; Q2W, every 2 weeks; Q4W, every 4 weeks; vHR, very high-risk.

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