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Sabatolimab (MBG453) Dose Selection and Dose-Response Analysis in Myelodysplastic Syndrome/ Acute Myeloid Leukemia: Population Pharmacokinetics Modeling and Evaluation of Clinical Efficacy/Safety by Dose

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Disclosures

AHW reports consultancy for Servier, BMS; honoraria for AbbVie, Servier, Novartis, AstraZeneca, Pfizer, BMS, Janssen, Amgen, Astellas, Genentech, and Celgene; research funding from Abbvie, Servier, Novartis, AstraZeneca, BMS, Amgen, and Celgene; speakers bureau for AbbVie, BMS, and Novartis; patents and royalties from Walter and Eliza Hall Institute of Medical Research; membership on an entity's Board of Directors or advisory committees for Astellas, Genentech, and Celgene. **KP** reports consultancy for Novartis; honoraria and research funding from Novartis and BMS/Celgene. **SK** reports honoraria, membership on an entity's Board of Directors or advisory committee and research funding for Novartis. **GG-M** reports consultancy for Acceleron Pharmaceuticals, Astex Pharmaceuticals, Bristol-Myers Squibb, Celgene, Helsinn Therapeutics, Jazz Pharmaceuticals, and Genentech; honoraria for AbbVie, Acceleron Pharmaceuticals, Astex Pharmaceuticals, Celgene, and Helsinn Therapeutics; research funding from AbbVie, Amphivena Therapeutics, Astex Pharmaceuticals, Bristol-Myers Squibb, Celgene, Helsinn Therapeutics, H3 Biomedicine, Merck, Novartis, Genentech, and Onconova; membership on an entity's Board of Directors or advisory committees for Genentech. **MW** reports honoraria for MacroGenics. **JJ** reports honoraria for Novartis, Pfizer, and Incyte; research funding from Novartis, and BMS, membership on an entity's Board of Directors or advisory committees for Novartis, Pfizer, AbbVie, and Incyte; Founder of the HematologyApp which is supported by Janssen, BMS Incyte, MDS, Pfizer, Daiichi-Sankyo, Roche and Takeda. **ET** reports consultancy for AbbVie, and Notable Labs; research funding for Incyte; membership on an entity's Board of Directors or advisory committees for Agios, Genentech, AbbVie, Astellas, and Daiichi Sankyo; current equity holder in private company with Notable Labs. **RN** reports current spouse employment with Sanofi-Genzyme; prior spouse employment within 24 months with Takeda; prior spouse employment within 24 months and prior spouse equity divested within past 24 months with Genentech. **MK** reports consultancy with Astellas; research funding with AbbVie; membership on an entity's Board of Directors or advisory committees with Jazz Pharma, Astellas, Novartis, and Celgene; speakers bureau with Novartis, and Celgene. **OO** reports honoraria for Novartis, Amgen, Celgene, Fusion Pharma, and Incyte; research funding from Amgen, Celgene, and Incyte. **MLR** reports employment at Novartis and consultancy for Qiagen. **AMB** reports consultancy for Acceleron Pharma Inc., Biogen, Celgene/BMS, Forty Seven, Inc., Jazz Pharma, Novartis, Takeda, and Xcenda, research funding from Celgene/BMS, Novartis, Takeda, GSK, Janssen, and AstraZeneca. **UB** reports research funding from Takeda, Novartis, Jazz Pharmaceuticals, and Pfizer; membership on an entity's Board of Directors or advisory committees for Genentech, Daiichi Sankyo, Takeda, Novartis, and Pfizer; investigator in AbbVie-funded clinical trials. **SX**, **AL**, **AS**, **FK**, **PN**, **WH**, **AM**, and **HS** are employees at Novartis. All other authors had nothing to disclose

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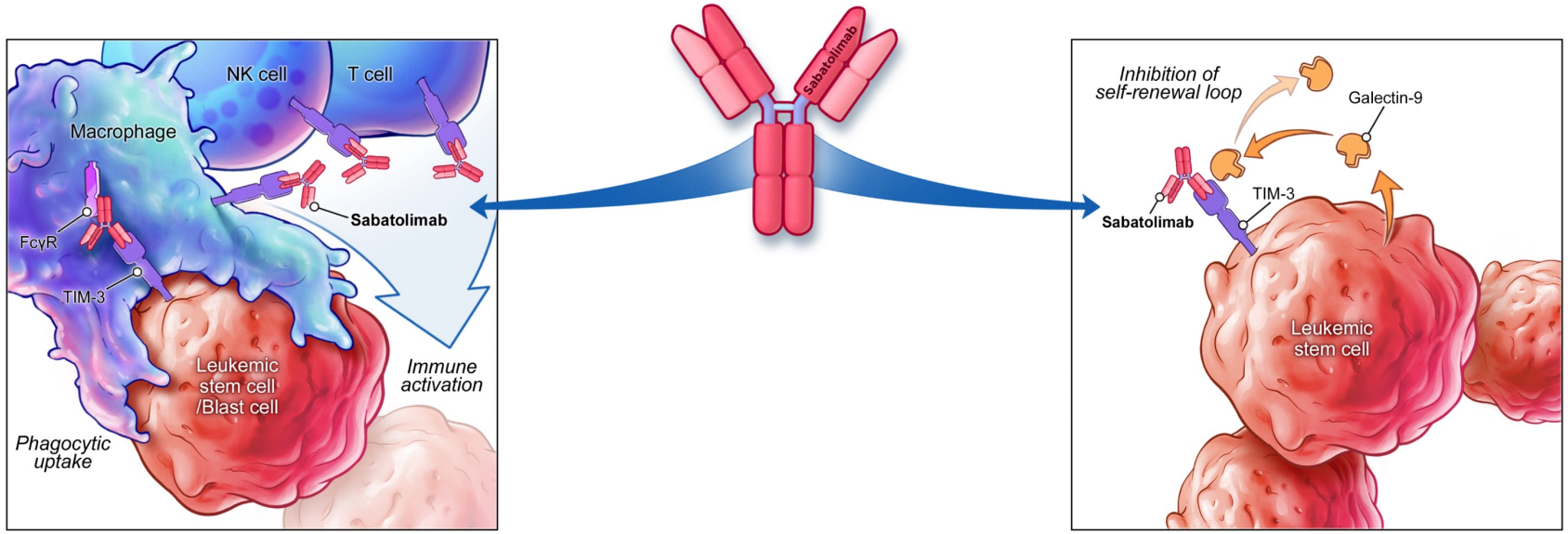
Sabatolimab (MBG453) Provides Dual Targeting of TIM-3 on Immune and Leukemic Cells

TIM-3

- Inhibitory receptor expressed on macrophages, monocytes, NK cells, dendritic cells, and T cells[1,2]
- Involved in regulating innate and adaptive immune responses[1,2]
- Expressed on LSCs/blasts but not normal HSCs,[3,4] making it a promising target in MDS/AML[4-6]

Sabatolimab

- High-affinity, humanized, IgG4 anti–TIM-3 monoclonal antibody[6,7]
- Enhances antileukemia immune activation and phagocytic uptake, facilitating immune cell-mediated killing of LSCs/blasts[2,7-9]
- May inhibit TIM-3/galectin-9–driven LSC self-renewal via blockade of TIM-3 on LSCs[2-9]



AML, acute myeloid leukemia; FcγR, Fc gamma receptor; HSC, hematopoietic stem cell; IgG4, immunoglobulin G4; LSC, leukemic stem cell; MDS, myelodysplastic syndrome; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

1. Wolf Y, et al. *Nat Rev Immunol*. 2020;20(3):173-85; 2. Acharya N, et al. *J Immunother Cancer*. 2020;8(1):e000911; 3. Haubner S, et al. *Leukemia*. 2019;33(1):64-749; 4. Asayama T, et al. *Oncotarget*. 2017;8(51):88904-917; 5. Kikushige Y, et al. *Cell Stem Cell*. 2015;17(3):341-52; 6. Mach N, et al. *Ann Oncol*. 2019;30(suppl 5):abstract 1202P; 7. Borate U, et al. *HemaSphere*. 2020;4(suppl 1):abstract S185; 8. Borate U, et al. EHA 2020. Oral presentation; 9. Sabatos-Peyton C, et al. SITC 2020. Abstract 439.

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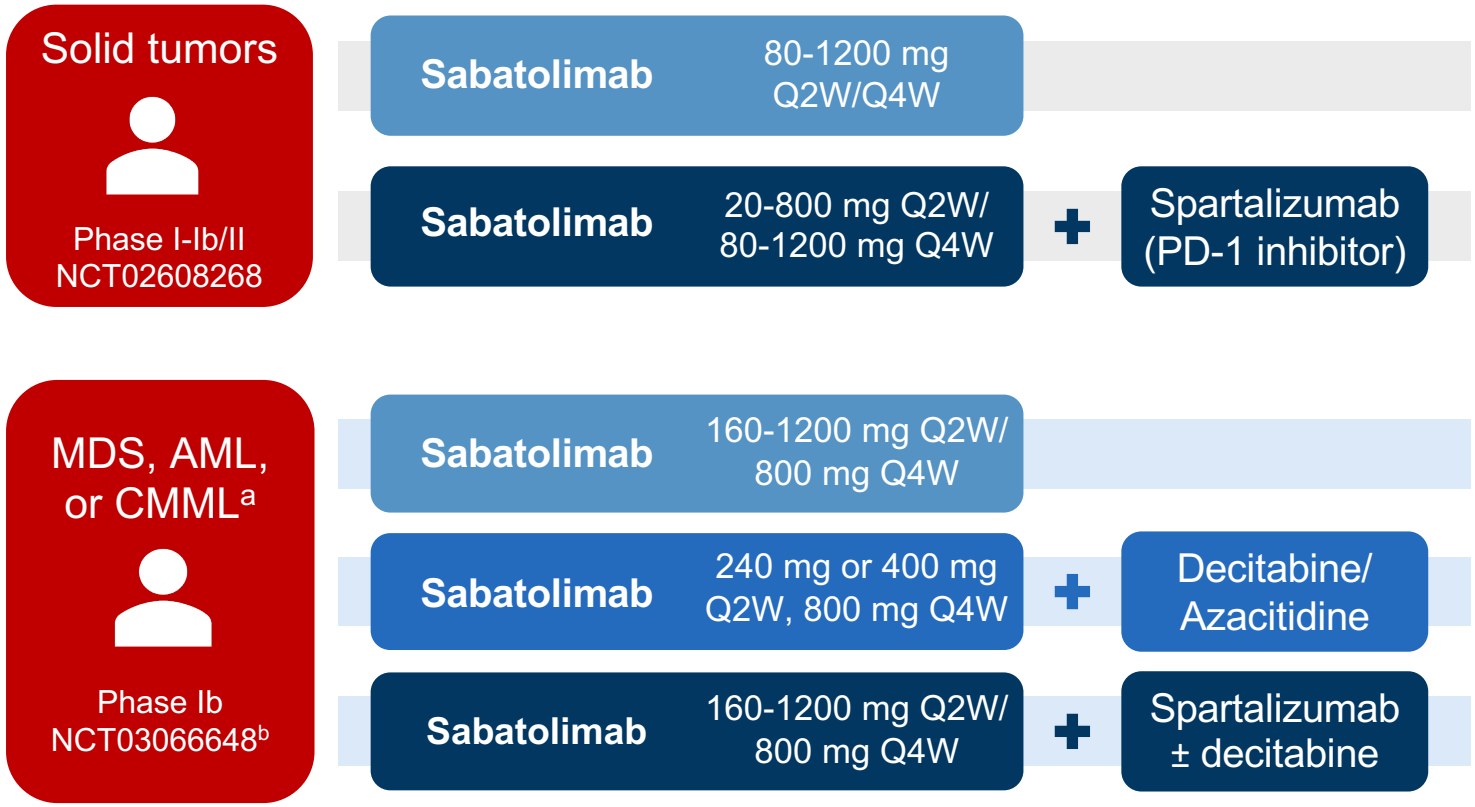
Evaluation of Sabatolimab Pharmacokinetics and Dose Response in Early Clinical Studies



Analysis endpoints[c]

- PK parameters
- Steady-state C_{avg}, C_{max}, and C_{trough} (PopPK modeling)
- Total serum soluble TIM-3 concentration

[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 were 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.

AE, adverse event; C_{avg}, average concentration; C_{max}, maximum concentration; C_{trough}, trough concentration; CMML, chronic myelomonocytic leukemia; HR, high-risk; PD-1, programmed death-1; PK, pharmacokinetics; Pop, population; Q2W, every 2 weeks; Q4W, every 4 weeks; vHR, very high-risk.

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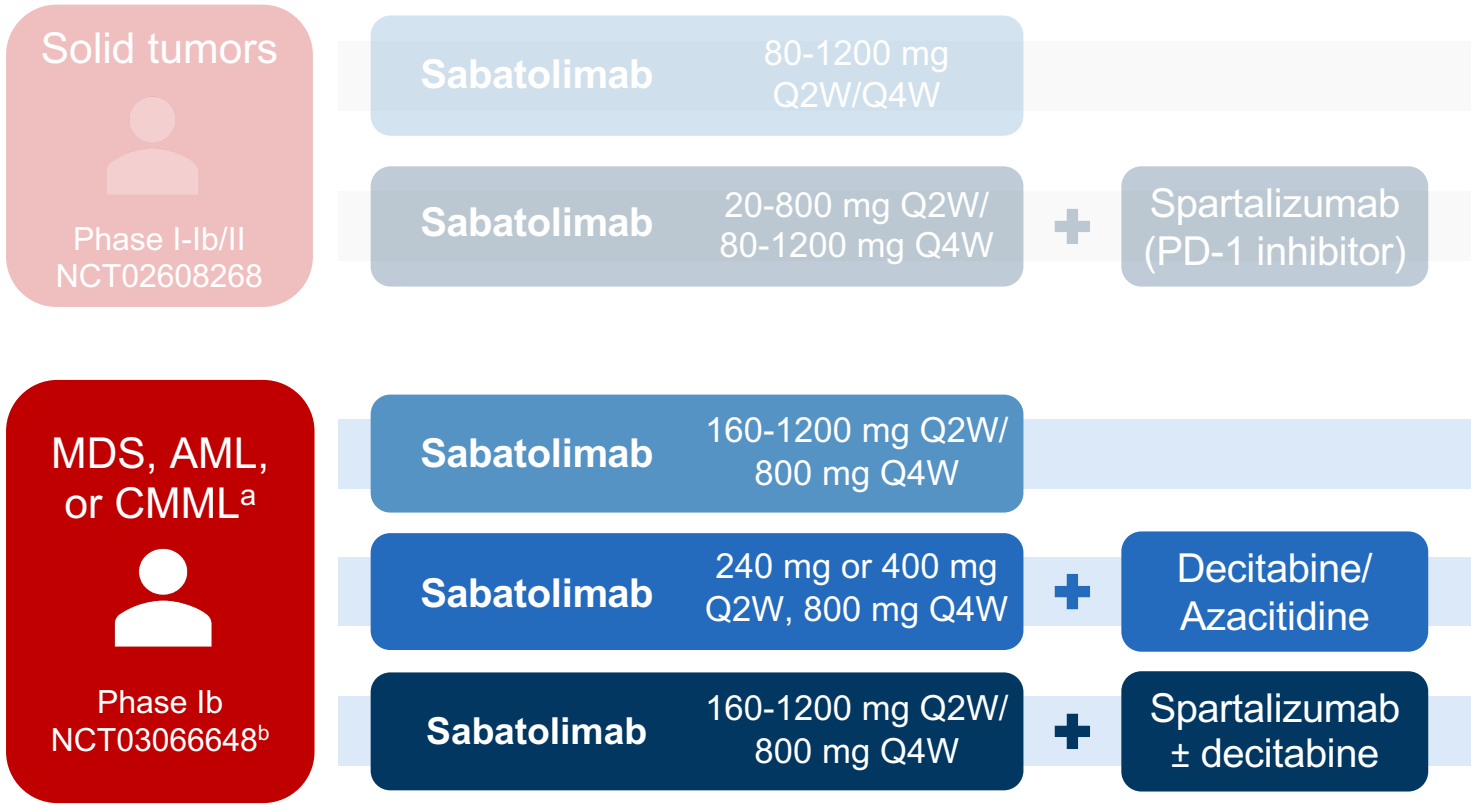
Evaluation of Sabatolimab Pharmacokinetics and Dose Response in Early Clinical Studies



Analysis endpoints[c]

- PK parameters
- Steady-state C_{avg}, C_{max}, and C_{trough} (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

[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 were 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.
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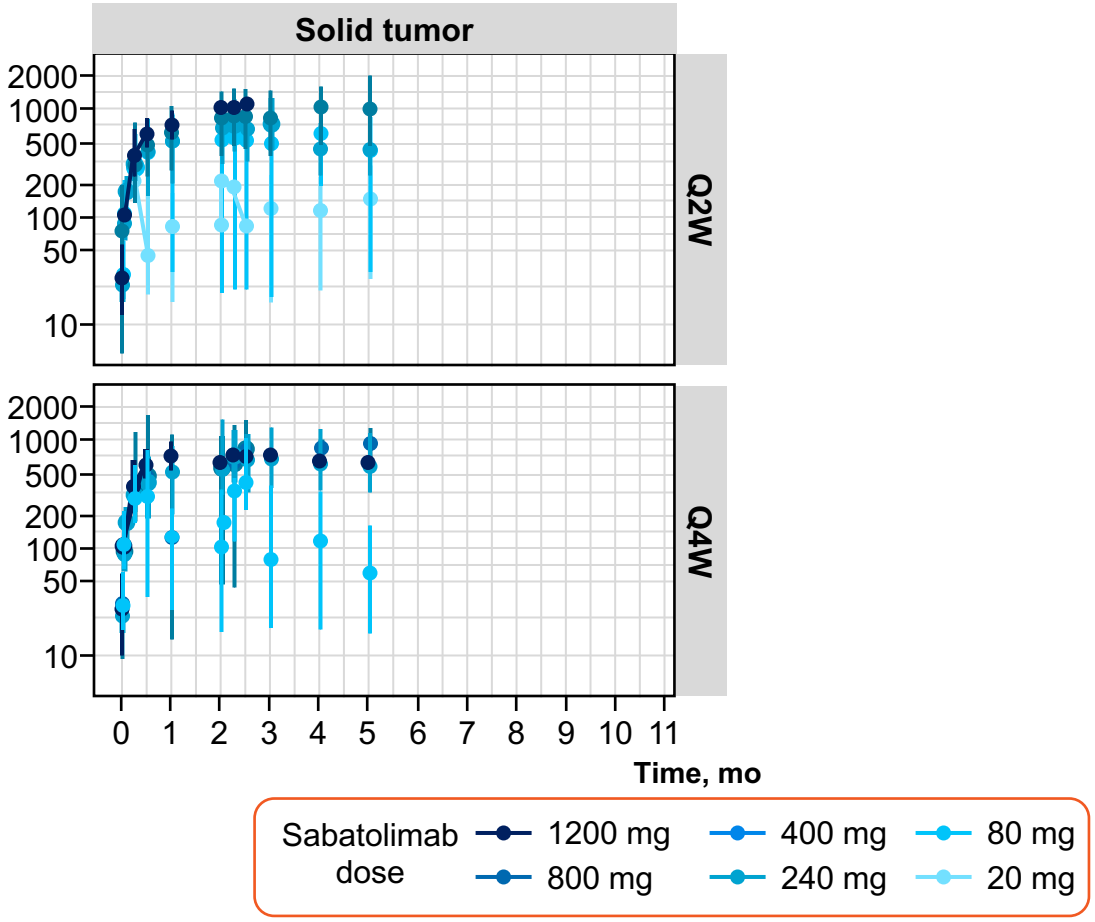
Saturation of sTIM-3 Was Achieved With Sabatolimab Doses ≥240 mg Q2W and ≥800 mg Q4W

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



sTIM-3, soluble TIM-3

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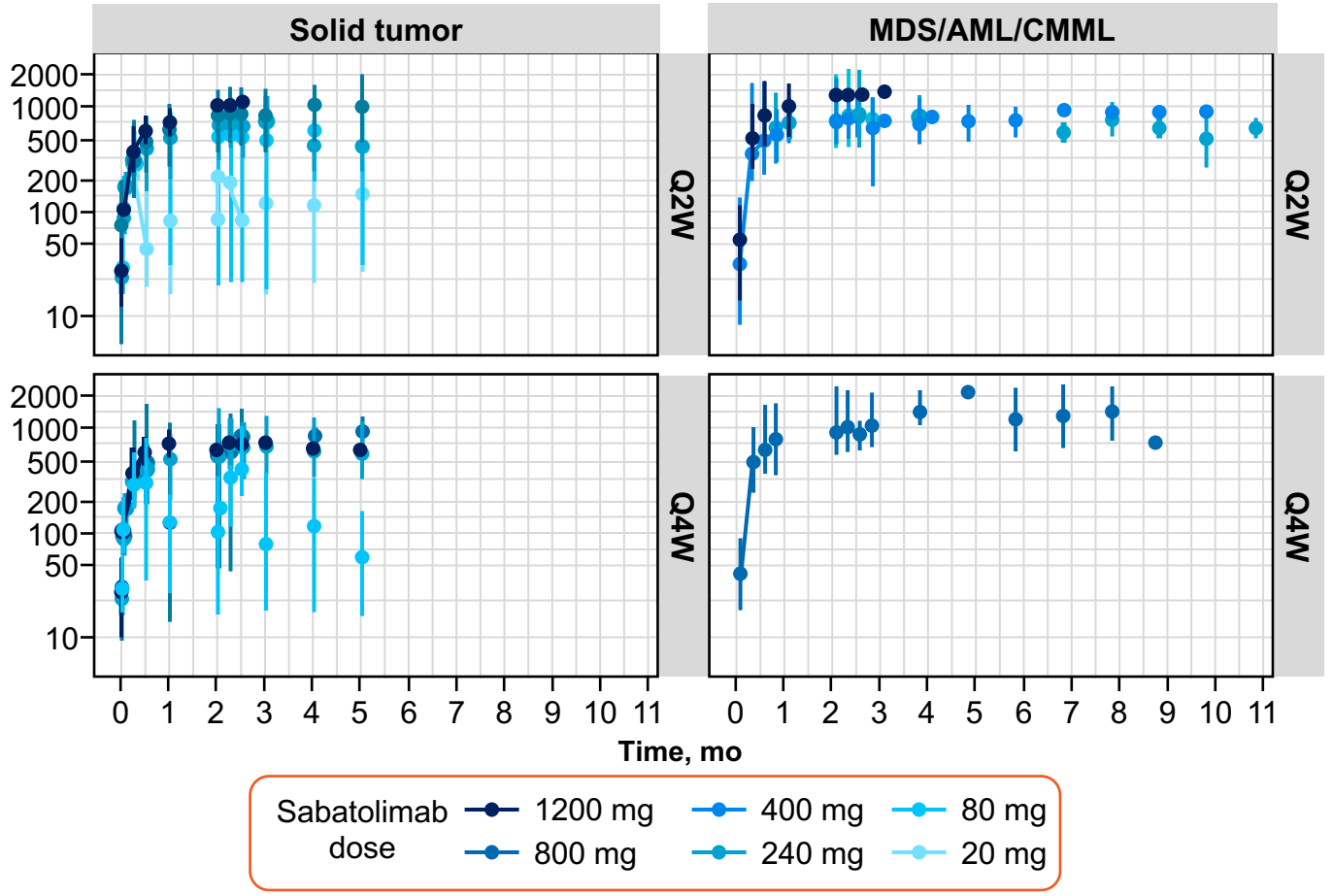
- Plateau in accumulated total sTIM-3
- Proportional dose-exposure relationship

Similar results were observed in the study in patients with MDS/AML/CMML



sTIM-3, soluble TIM-3

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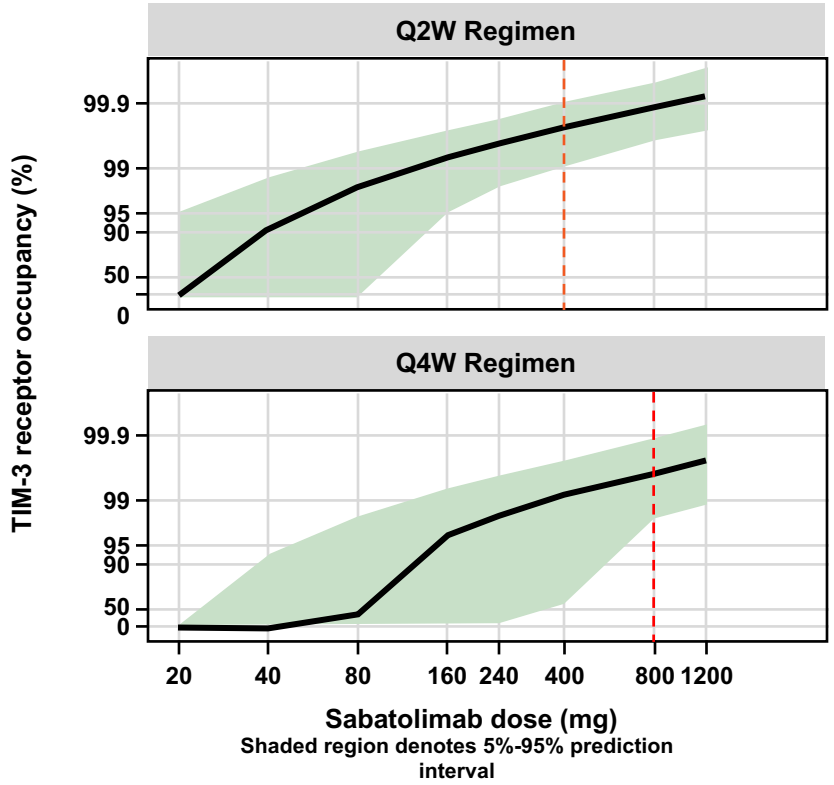
Receptor Occupancy Modeling Indicated Similarly High Levels of TIM-3 Engagement With Sabatolimab 400 mg Q2W and 800 mg Q4W

Population PK modeling with sabatolimab + HMA regimens

- **400 mg Q2W** had the highest C_{trough} at steady state
- **800 mg** was predicted to be an equivalent **Q4W** dosing regimen
- Both doses had similar steady-state C_{avg}

Simulated steady-state occupancy of membrane-bound TIM-3 in bone marrow[a]



- **>95% occupancy rate** in bone marrow **in ≥95% of patients** with vHR/HR-MDS, AML, or CMML

[a]Compared to baseline.
HMA, hypomethylating agent.

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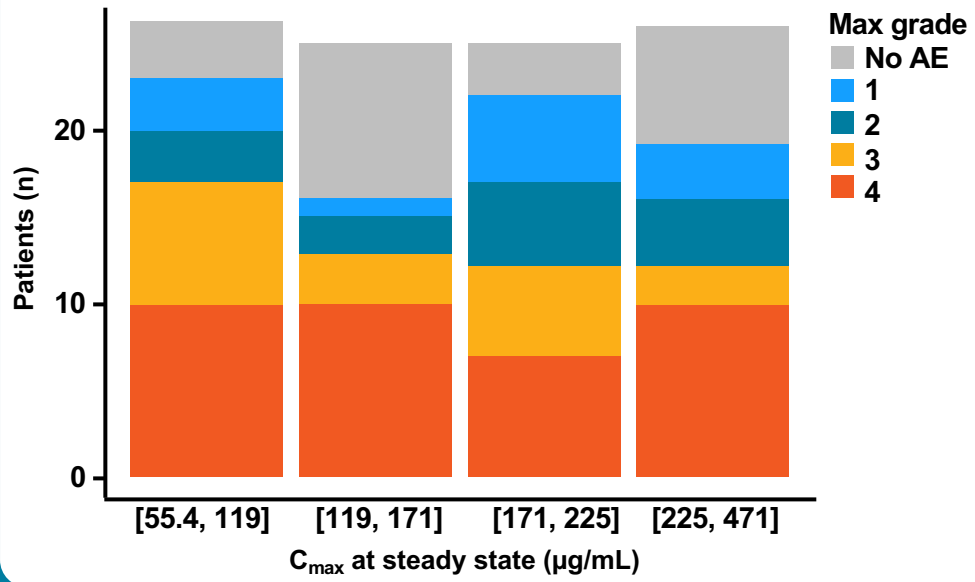
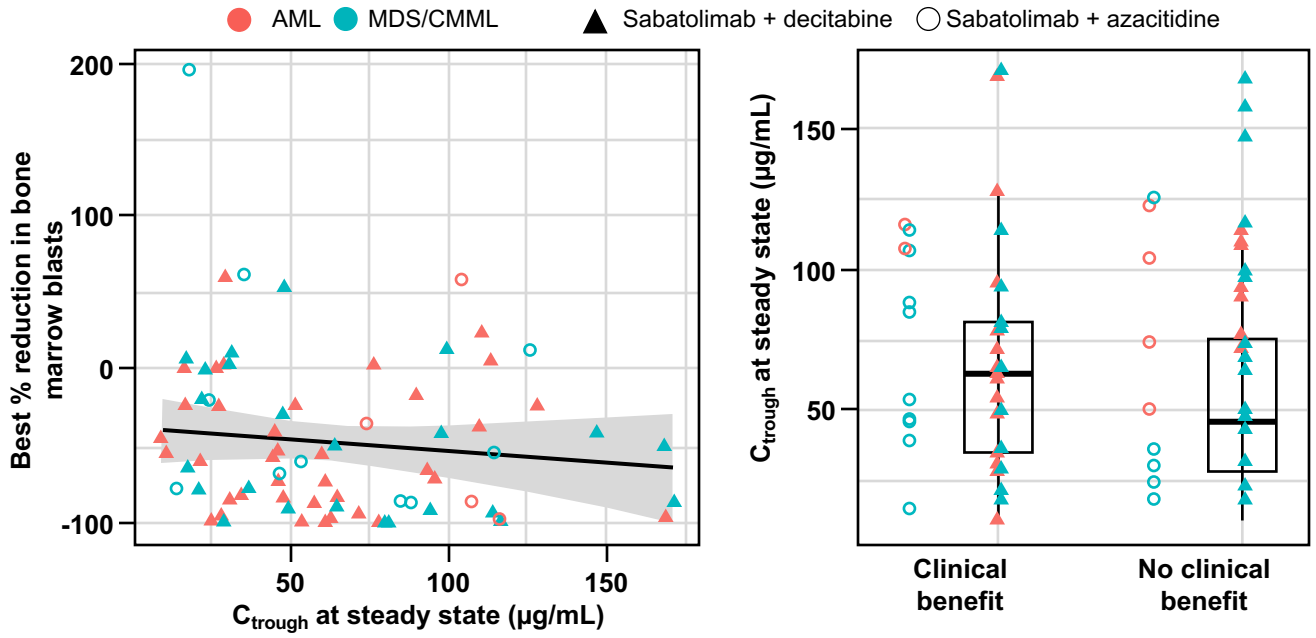
PK Exposure-Response Analyses With Sabatolimab + HMA Showed Similar Safety and Efficacy Across Sabatolimab Exposure Levels

PK exposure-AE relationship (n=102[a])



PK exposure-efficacy relationship (n=92[a])



Patients were categorized into 4 exposure quartiles based on steady-state C_{max} and C_{avg}

- **No relationship** between steady-state C_{max} or C_{avg} and treatment-related AEs

- **No relationship** between steady-state C_{trough} or C_{avg} and % blast cell reduction or clinical benefit (ie, CR, mCR, CRi, and PR)

[a]Includes patients with vHR/HR-MDS, CMML, or AML who were treated with sabatolimab + HMA.
CR, complete remission; CRi, CR with incomplete hematologic recovery; mCR, marrow CR; PR, partial remission.

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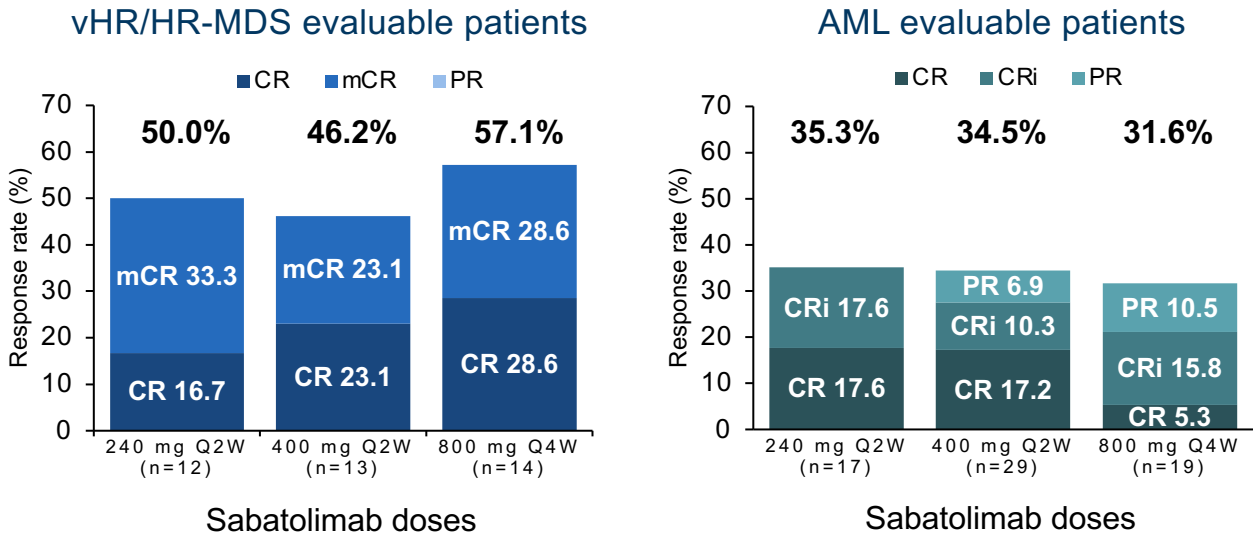
Sabatolimab + HMA Was Safe Overall, With Encouraging Efficacy Across Doses in vHR/HR-MDS or AML

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)

Clinical efficacy by sabatolimab dose (n=104)



- Rates of clinically significant (grade ≥3) TEAEs and possible imAEs related to treatment **did not appear to be dose dependent**
- To date, among the 3 sabatolimab dosing regimens tested:
  - **No notable differences in efficacy**
  - **No significant association with duration of response** (Cox model with dose as a covariate)

[a]Reported in ≥10% of patients in either the vHR/HR-MDS or AML cohort; [b]8 events occurred in 6 patients.
imAE, immune-mediated adverse event; TEAE, treatment-emergent adverse event.

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Conclusions

1. 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

2. 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

3. 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

4. These results validate the selection of the 400 mg Q2W and 800 mg Q4W dosing regimens for the STIMULUS clinical trial program

Updated clinical data from Phase 1b study of sabatolimab + HMA in MDS/AML: Brunner AM et al. Oral presentation #657; Monday, December 7, 2020; 12:30 PM

STIMULUS TiP poster: Zeidan AM, et al; Poster 1294; December 5-8, 2020

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Acknowledgments

- The authors thank the patients who participated in the trial and their families
- This study was funded by Novartis Pharmaceuticals Corporation
- Editorial assistance was provided by Jasmine Javier, MD, of Healthcare Consultancy Group, LLC, and funded by Novartis Pharmaceuticals Corporation

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Supplementary material for associated poster presentation

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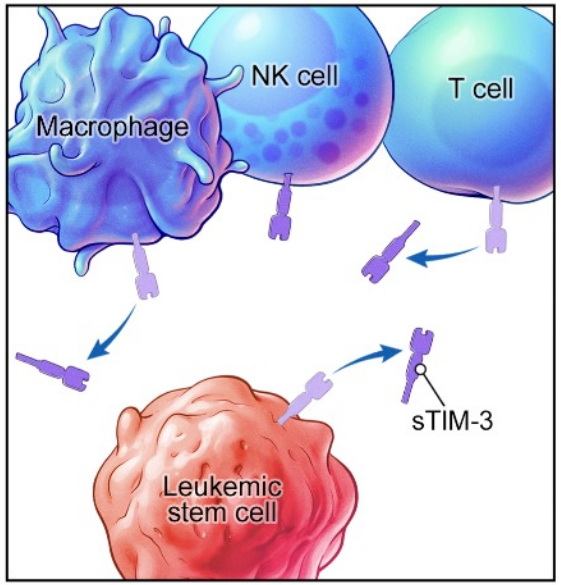
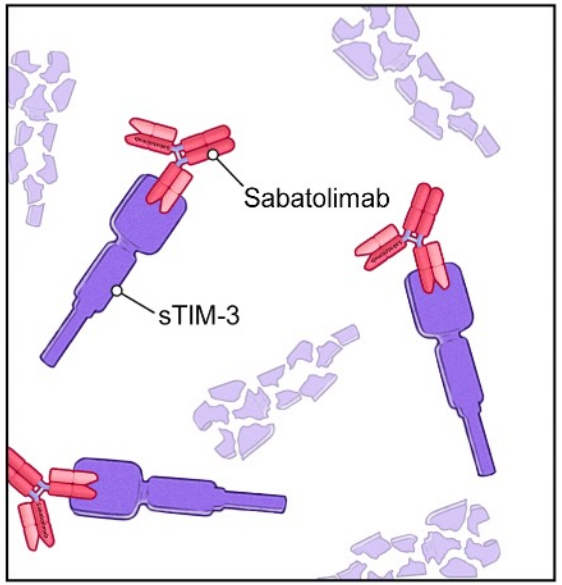
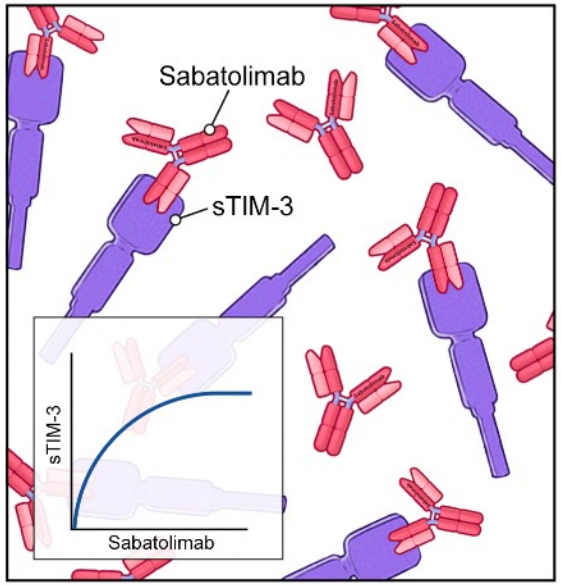
Soluble TIM-3 (sTIM-3) concentration as an indicator of sabatolimab binding to TIM-3 on the cell surface



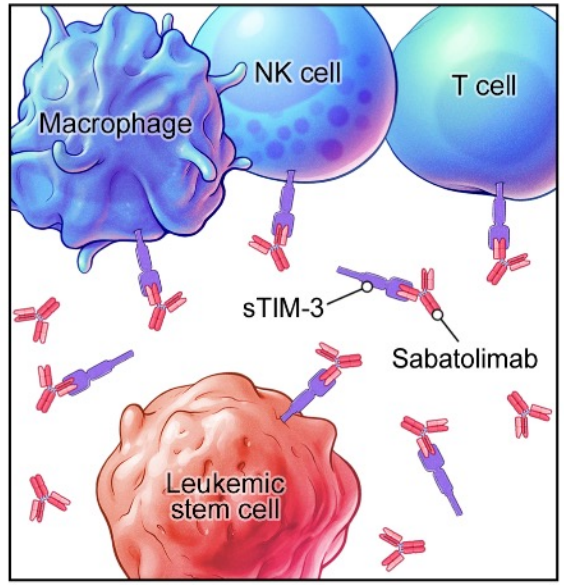
TIM-3 is a cell surface receptor but can be shed from immune and leukemic cells as soluble TIM-3 (denoted “sTIM-3”).



The binding of sabatolimab to sTIM-3 results in the stabilization of sTIM-3.



As sabatolimab increases, more sTIM-3 is bound and the measured concentration of sTIM-3 increases. Saturation of sTIM-3 can be seen as a concentration plateau.



Because sabatolimab binds both soluble and cell surface TIM-3, the saturation of sTIM-3 can be used to infer a high level of engagement of cell surface TIM-3.

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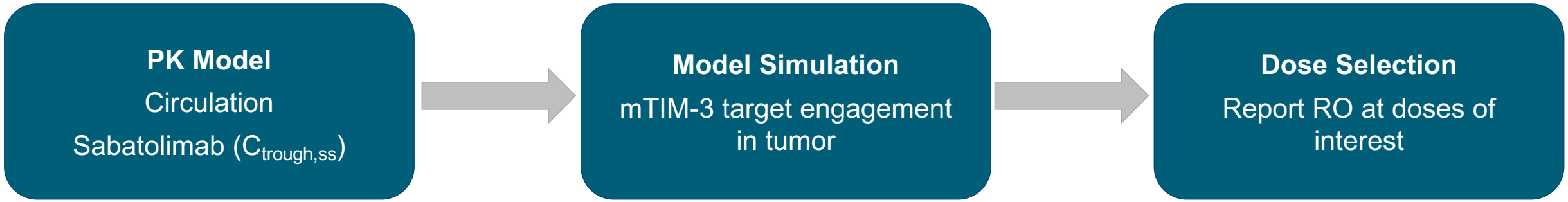
Sabatolimab $C_{trough,ss}$ was simulated from the PopPK model, and used to predict RO and support dose selection



Equation for predicting RO in bone marrow[1]

$$RO \approx \frac{B \cdot C_{trough,ss}}{B \cdot C_{trough,ss} + T_{acc} \cdot K_{ss}}$$

Assumptions for RO Simulation

- Bone marrow drug concentration is 20-40% of circulation concentration (B)
- Membrane-bound TIM-3 after sabatolimab binding is 50-100% its levels at baseline (Tacc)
- Sabatolimab concentration is much greater than TIM-3 concentration
- Binding affinity for mTIM-3 is 0.5 nM (Kss)

1. Ahmed S, et al. *J Pharmacokinet Pharmacodyn.* 2019;46:287-304.

B, bone marrow drug concentration; C, concentration; Kss, quasi-steady-state binding constant for membrane-bound TIM-3; mTIM-3, membrane-bound TIM-3; RO, receptor occupancy; ss, steady state; Tacc, fold change in membrane-bound TIM-3; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

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