

---

# Avapritinib in Patients With Advanced Systemic Mastocytosis (AdvSM): Efficacy and Safety Analysis From the Phase 2 PATHFINDER Study With 3-year Follow-up

**Andreas Reiter,<sup>1</sup> Jason Gotlib,<sup>2</sup> Deepti H. Radia,<sup>3</sup> Iván Alvarez-Twose,<sup>4</sup> Michael W. Deininger,<sup>5</sup> Tracy I. George,<sup>6</sup> Jens Panse,<sup>7</sup> Kristen M. Pettit,<sup>8</sup> Alessandro M. Vannucchi,<sup>9</sup> Uwe Platzbecker,<sup>10</sup> Olivier Hermine,<sup>11</sup> Amro Elshoury,<sup>12</sup> Christina Bulai Livideanu,<sup>13,14</sup> Ruben Mesa,<sup>15</sup> Celalettin Ustun,<sup>16</sup> Massimo Triggiani,<sup>17</sup> Ingunn Dybedal,<sup>18</sup> Joseph Jurcic,<sup>19</sup> Roberta Zanotti,<sup>20</sup> Lambert F. Span,<sup>21</sup> Stephen T. Oh,<sup>22</sup> Abdulraheem Yacoub,<sup>23</sup> Elizabeth O. Hexner,<sup>24</sup> Prithviraj Bose,<sup>25</sup> Stephanie Lee,<sup>26,27</sup> Wolfgang R. Sperr,<sup>28</sup> Elizabeth A. Griffiths,<sup>29</sup> Matthew Butler,<sup>30</sup> Ilda Bidollari,<sup>31</sup> Hui-Min Lin,<sup>31</sup> Svetlana Rylova,<sup>32</sup> Javier I. Muñoz-González,<sup>32</sup> and Daniel J. DeAngelo<sup>33</sup>**

<sup>1</sup>Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany; <sup>2</sup>Division of Hematology, Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA, USA; <sup>3</sup>Guy's & St Thomas's NHS Foundation Trust, London, UK; <sup>4</sup>Institute of Mastocytosis Studies of Castilla-La Mancha, Spanish Reference Center of Mastocytosis, Toledo, Spain; <sup>5</sup>Versiti Blood Research Institute, Milwaukee, WI, USA; <sup>6</sup>ARUP Laboratories, University of Utah, Salt Lake City, UT, USA; <sup>7</sup>Department of Oncology, Hematology, Hemostaseology and Stem Cell Transplantation, University Hospital Aachen, Medical Faculty, RWTH Aachen University, Aachen, Germany; <sup>8</sup>Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI, USA; <sup>9</sup>Center for Research and Innovation of Myeloproliferative Neoplasms – CRIMM, Azienda Ospedaliera Universitaria Careggi, University of Florence, Florence, Italy; <sup>10</sup>Leipzig University, Leipzig, Germany; <sup>11</sup>Department of Hematology, CEREMAST, Necker–Enfants Malades Hospital, APHP, and Imagine Institute, INSERM U1163, Paris University, Paris, France; <sup>12</sup>WNY BloodCare, Buffalo, NY, USA; <sup>13</sup>Department de Dermatologie Expert Centre of Mastocytosis (CEREMAST) CHU de Toulouse, Toulouse, France; <sup>14</sup>Toulouse University Hospital - Larrey Hospital, Toulouse, France; <sup>15</sup>Mays Cancer Center at UT Health San Antonio MD Anderson, San Antonio, TX, USA; <sup>16</sup>Rush Medical College, Chicago, MI, USA; <sup>17</sup>Division of Allergy and Clinical Immunology, University of Salerno, Salerno Italy; <sup>18</sup>Department of Hematology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; <sup>19</sup>Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA; <sup>20</sup>IRCCS Ospedale Sacro Cuore Don Calabria di Negrar, Medicine Unit, University of Verona, Verona, Italy; <sup>21</sup>Department of Hematology, University Medical Center, Groningen, The Netherlands; <sup>22</sup>Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, Saint Louis, MO, USA; <sup>23</sup>University of Kansas Medical Center, Kansas City, KS, USA; <sup>24</sup>Abramson Cancer Center, University of Pennsylvania, Perelman Center for Advanced Medicine Philadelphia, PA, USA; <sup>25</sup>The University of Texas MD Anderson Cancer Center, Houston, TX, USA; <sup>26</sup>Temerty Faculty of Medicine, University of Toronto, Toronto, Canada; <sup>27</sup>Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada; <sup>28</sup>Department of Medicine, Medical University of Vienna, Vienna, Austria; <sup>29</sup>Leukemia Division, Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; <sup>30</sup>Department of Medicine, Mays Cancer Center, San Antonio, TX, USA; <sup>31</sup>Blueprint Medicines Corporation, Cambridge, MA, USA; <sup>32</sup>Blueprint Medicines Corporation, Zug, Switzerland; <sup>33</sup>Dana-Farber Cancer Institute, Boston, MA, USA

# Disclosures

---

- Dr Reiter has received research funding, served on advisory boards, and received honoraria and funding to cover travel expenses from AbbVie, AOP, Blueprint Medicines Corporation, BMS, Cogent, GSK, Incyte, and Novartis

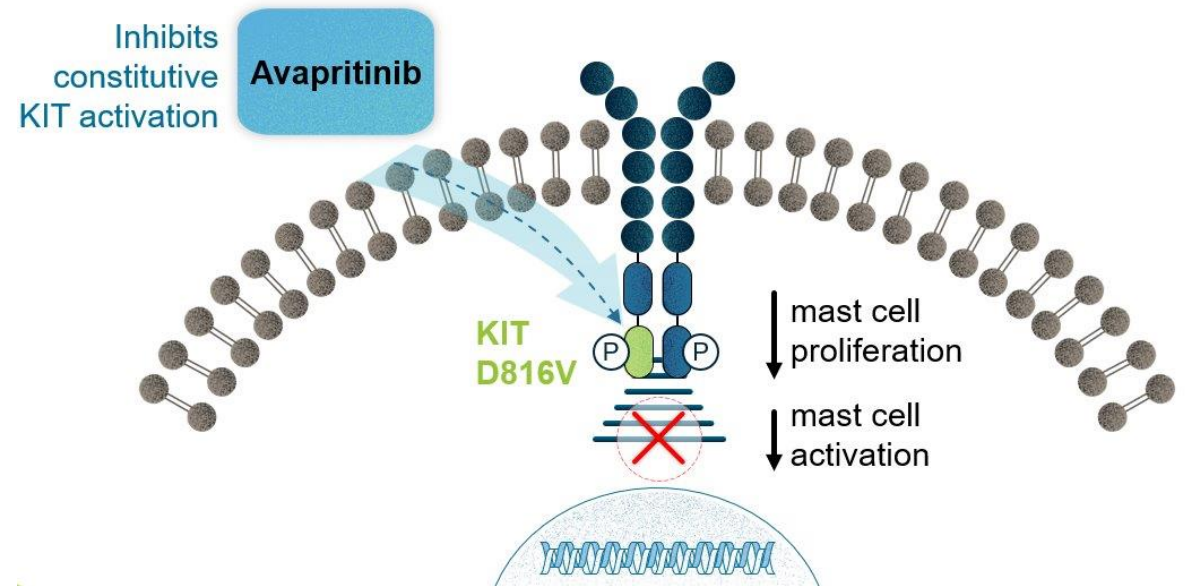
# AdvSM is a clonal hematologic neoplasm driven by the *KIT* D816V mutation in ~95% of cases

---

- Advanced systemic mastocytosis (AdvSM) encompasses aggressive SM (ASM), SM with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL)<sup>1–5</sup>
- AdvSM is characterized by the proliferation and infiltration of neoplastic mast cells (MCs) and variably, hematologic neoplasms in various organs that can result in life-threatening organ damage and reduced survival<sup>6,7</sup>
- Hyperactivation and MC mediator release often lead to severe and debilitating symptoms associated with functional impairment and reduced quality of life<sup>6,7</sup>
- Patients with AdvSM have a poor prognosis
  - Reported median overall survival (OS) of 3.4–6.2 years in ASM, 2.0–2.9 years in SM-AHN, and 0.2–1.9 years in MCL<sup>8–10</sup>

# Avapritinib is a highly potent and selective KIT D816V inhibitor

- Avapritinib is approved for adult patients with AdvSM or indolent systemic mastocytosis (ISM)
  - AdvSM approval was based on the phase 1 EXPLORER and phase 2 PATHFINDER studies<sup>a,1-4</sup>
  - ISM approval was based on outcomes of the phase 2 PIONEER trial<sup>b,1,2,5</sup>



**Potently and selectively inhibits the autophosphorylation of KIT D816V, with an IC<sub>50</sub> of 0.27 nanomolar in selective cellular assays<sup>6</sup>**

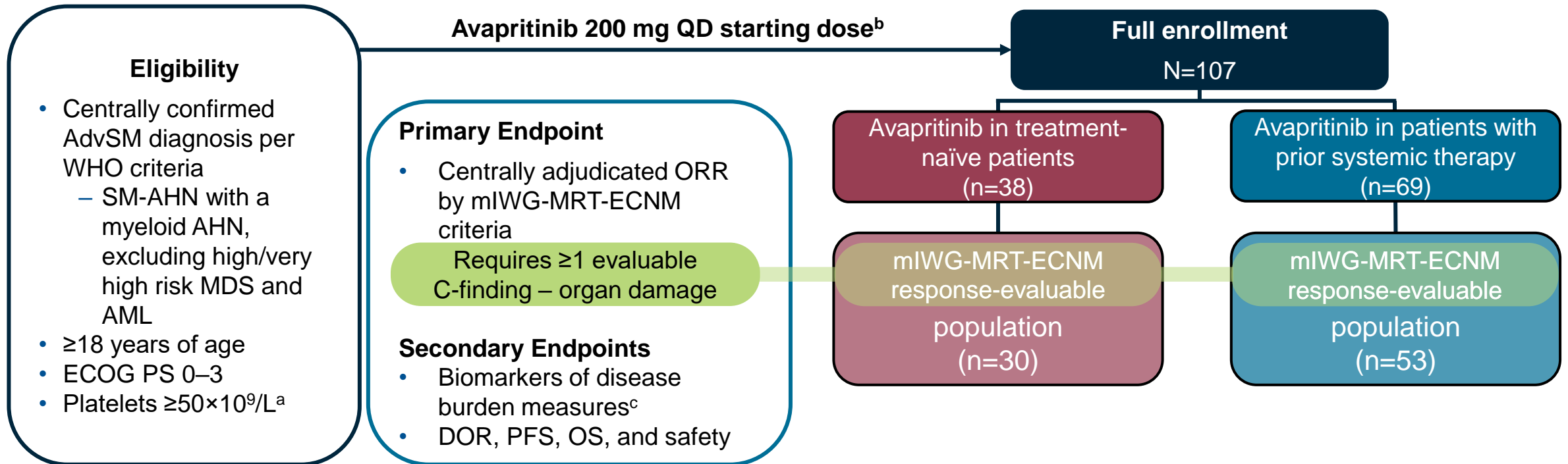
<sup>a</sup>Avapritinib is approved in the USA for adult patients with AdvSM irrespective of prior therapy and in Europe for adult patients with AdvSM after ≥1 systemic therapy. <sup>b</sup>Avapritinib is approved in the USA for adult patients with ISM and in Europe for adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment.

IC<sub>50</sub>, half-maximal inhibitory concentration.

1. Ayvakit (avapritinib) [package insert]. May 2023. Blueprint Medicines Corporation; 2. Ayvakit (avapritinib) Prescribing Information. 2024. Blueprint Medicines Corporation; 3. DeAngelo DJ et al. *Nat Med.* 2021;27:2183–2191; 4. Gotlib J et al. *Nat Med.* 2021;27:2192–2199. 5. Gotlib J et al. *NEJM Evid.* 2023;2:EVIDoa2200339. 6. Evans EK et al. *Sci. Transl. Med* 2017;9:eaao1690.

# PATHFINDER: 3-year efficacy and safety

- PATHFINDER is an international, multicenter, open-label, single-arm, phase 2 study designed to assess the efficacy and safety of avapritinib in adult patients with a centrally confirmed AdvSM



Data cut-off date: September 15, 2023. <sup>a</sup>Implemented in 2019 to reduce risk of intracranial bleeding. <sup>b</sup>Two patients initiated 100 mg QD avapritinib, all others initiated at 200 mg QD. <sup>c</sup>Biomarkers of disease burden measures include BM MCs, serum tryptase, *KIT* D816V variant allele fraction (VAF), and spleen volume. No type 1 error control for these endpoints.

AdvSM, advanced systemic mastocytosis; AML, acute myeloid leukemia; BM, bone marrow; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; MC, mast cell; MDS, myelodysplastic syndrome; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; ORR, objective response rate; OS, overall survival; PFS, progression free survival; QD, once daily; SM-AHN, systemic mastocytosis with associated hematologic neoplasm; WHO, World Health Organization.

# Patient baseline characteristics

|  | All AdvSM <sup>a</sup><br>(N=107) | Treatment-naïve patients<br>(n=38) | Patients with prior systemic<br>therapy<br>(n=69) |
|--|-----------------------------------|------------------------------------|---|
| <b>Age, median years (range)</b>                               | <b>68 (31–88)</b>                 | 68 (39–88)                         | 68 (31–86)  |
| <b>Female, n (%)</b>   | <b>45 (42)</b>                    | 18 (47)                            | 27 (39)   |
| <b>ECOG performance status, n (%)</b>                          |                                   |                                    |   |
| 2–3 <sup>b</sup>   | <b>28 (26)</b>                    | 7 (18)                             | 21 (30)   |
| <b>AdvSM subtype per central assessment, n (%)</b>             |                                   |                                    |   |
| ASM  | <b>21 (20)</b>                    | 7 (18)                             | 14 (20)   |
| SM-AHN <sup>c</sup>  | <b>71 (66)</b>                    | 28 (74)                            | 43 (62)   |
| MCL (including 4 MCL-AHN) <sup>d</sup>                         | <b>15 (14)</b>                    | 3 (8)                              | 12 (17)   |
| <b>BM MC burden, median percentage (range)</b>                 | <b>40 (1–95)</b>                  | 35 (3–90)                          | 50 (1–95)   |
| <b>Serum tryptase level, median ng/mL (range)</b>              | <b>262 (24–1600)</b>              | 178 (37–1336)                      | 312 (24–1600)                                     |
| <b><i>KITD816V</i> mutation by central assay, n (%)</b>        | <b>103 (96)</b>                   | 36 (95)                            | 67 (97)   |
| <b><i>KITD816V</i> VAF,<sup>e</sup> median percent (range)</b> | <b>16 (0–47)</b>                  | 6 (0–45)                           | 20 (0–47)   |
| <b>S/A/R mutation per central assay,<sup>f</sup> n (%)</b>     | <b>48 (45)</b>                    | 23 (61)                            | 25 (36)   |
| <b>Number of prior antineoplastic therapy, median (range)</b>  | <b>1 (0–6)</b>                    | 0                                  | 1 (0–6)   |
| 1 prior antineoplastic therapy, n (%)                          | <b>42 (39)</b>                    | –                                  | 42 (61)   |
| ≥2 prior antineoplastic therapies, n (%)                       | <b>27 (25)</b>                    | –                                  | 27 (39)   |

Data cut-off date: September 15, 2023. <sup>a</sup>Patients with AdvSM initiated avapritinib 200 mg (n=105) or 100 mg (n=2) QD. <sup>b</sup>Remaining patients are ECOG performance status 0–1. <sup>c</sup>SM-AHN subtypes included CMML (30%), MDS (11%), MPN (2%), MDS/MPN-U (14%), CEL (6%), and other (4%). <sup>d</sup>Of the patients with subtype MCL (n=15), 4 were MCL-AHN. <sup>e</sup>Assessed by ddPCR in both peripheral blood and BM (majority were in peripheral blood); limit of detection 0.02%. <sup>f</sup>Assessed by NGS.

ASM, aggressive systemic mastocytosis; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; ddPCR, digital droplet polymerase chain reaction; MCL, mast cell leukemia; MCL-AHN, mast cell leukemia with an associated hematologic neoplasm; MDS/MPN-U, myelodysplastic syndrome/ myeloproliferative neoplasm-unclassifiable; NGS, next-generation sequencing.

# Avapritinib demonstrated a high response rate across subtypes and regardless of prior treatment

|   | All <sup>a</sup><br>(n=83) | AdvSM subtype |                  |               | Treatment-naïve<br>(n=30) | Patients with ≥1<br>prior systemic<br>therapy<br>(n=53) |
|---|----------------------------|---------------|------------------|---------------|---------------------------|---|
|   |                            | ASM<br>(n=13) | SM-AHN<br>(n=55) | MCL<br>(n=15) |                           |   |
| <b>ORR,<sup>b</sup> n (%)</b>   | <b>61 (73)</b>             | 10 (77)       | 41 (75)          | 10 (67)       | 26 (87)                   | 35 (66)   |
| <b>95% CI</b>   | <b>63–83</b>               | 46–95         | 61–85            | 38–88         | 69–96                     | 52–79   |
| <b>Best response</b>  |                            |               |                  |               |                           |   |
| <b>CR or CRh<sup>c</sup></b>  | <b>24 (29)</b>             | 3 (23)        | 18 (33)          | 3 (20)        | 13 (43)                   | 11 (21)   |
| CR  | 13 (16)                    | 1 (8)         | 9 (16)           | 3 (20)        | 7 (23)                    | 6 (11)  |
| CRh   | 11 (13)                    | 2 (15)        | 9 (16)           | 0             | 6 (20)                    | 5 (9)   |
| PR <sup>d</sup>   | 33 (40)                    | 7 (54)        | 19 (35)          | 7 (47)        | 13 (43)                   | 20 (38)   |
| CI  | 4 (5)                      | 0             | 4 (7)            | 0             | 0                         | 4 (8)   |
| SD  | 13 (16)                    | 3 (23)        | 7 (13)           | 3 (20)        | 3 (10)                    | 10 (19)   |
| PD  | 2 (2)                      | 0             | 1 (2)            | 1 (7)         | 0                         | 2 (4)   |
| NE  | 7 (8)                      | 0             | 6 (11)           | 1 (7)         | 1 (3)                     | 6 (11)  |
| <b>Patients with best <i>KIT</i> D816V<br/>VAF response &lt;1%, n (%)<sup>e</sup></b> | <b>55 (67)</b>             | 8 (62)        | 38 (70)          | 9 (60)        | 27 (90)                   | 28 (54)   |

Data cut-off date: September 15, 2023. Median follow-up of 38 months. <sup>a</sup>ORR evaluable per mIWG-MRT-ECNM criteria at baseline. <sup>b</sup>Best confirmed response per mIWG-MRT-ECNM criteria. CR+CRh+PR+CI. <sup>c</sup>CRh requires full resolution of all evaluable C-findings, elimination of BM mast cell aggregates, serum tryptase <20 ng/mL, resolution of palpable hepatosplenomegaly, and partial hematologic recovery (defined as absolute neutrophil count >0.5×10<sup>9</sup>/L with normal differential, platelet count >50×10<sup>9</sup>/L, and hemoglobin level >8.0 g/dL). <sup>d</sup>PR requires full resolution of ≥1 evaluable C-findings and ≥50% reduction in both bone marrow mast cells and serum tryptase. <sup>e</sup>82 of 83 patients had baseline and post baseline VAF measurements; 1 patient (SM-AHN with prior systemic treatment) had no post baseline VAF measurement.

95% CI, 95% confidence interval; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; mCR, morphologic complete remission; mCRh, morphologic complete remission with partial recovery of peripheral blood counts; mPR, morphologic partial remission; NR, not reached; PR, partial response; PD, progressive disease; SD, stable disease.

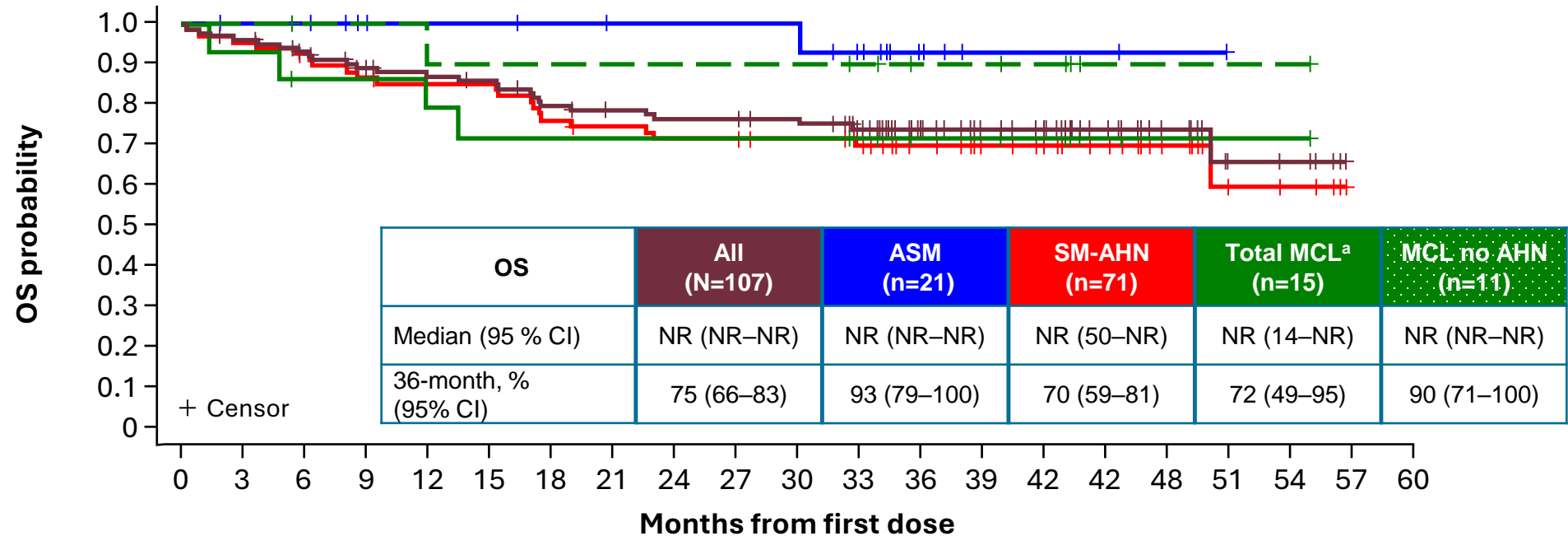
# Avapritinib demonstrated durable sustained responses with no SM progressions

---

- **Median follow-up was 38 months**
- **Median (range) time to response (TTR) was 2.3 (0.3–20.3) months**
  - TTR for MCL was 7.3 (1.7–12.2) months
- **Median duration of response (DOR) and progression-free survival (PFS) were not reached**
- **Rate of disease progression was 14% (15/107<sup>a</sup>) in patients with AdvSM receiving avapritinib**
  - AHN progressions occurred in 11 patients
  - Non-mast cell progressions of undetermined cause occurred in 4 patients



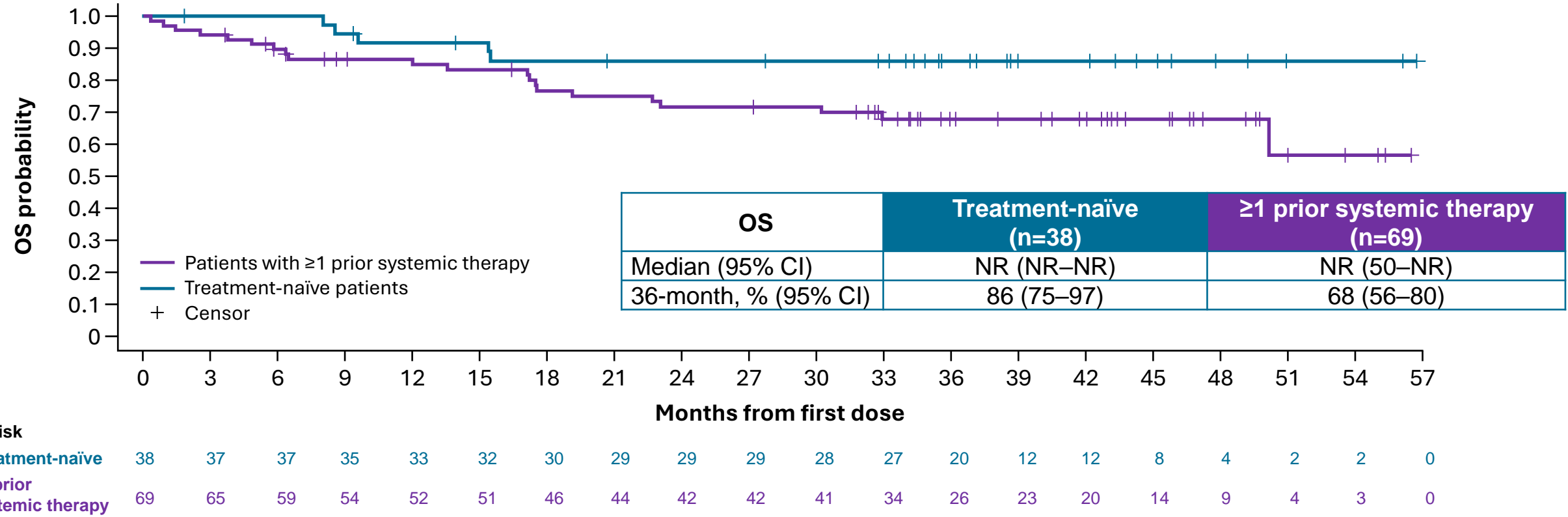
# Median overall survival was not reached regardless of AdvSM subtype



| At risk                | 0   | 3   | 6  | 9  | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 42 | 48 | 51 | 54 | 57 | 60 |  |
|------------------------|-----|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|--|
| All AdvSM              | 107 | 102 | 96 | 89 | 85 | 83 | 76 | 73 | 71 | 71 | 69 | 61 | 46 | 35 | 32 | 22 | 13 | 6  | 5  | 0  |    |  |
| ASM                    | 21  | 20  | 20 | 17 | 16 | 16 | 15 | 14 | 14 | 14 | 14 | 11 | 6  | 3  | 3  | 2  | 1  | 0  |    |    |    |  |
| SM-AHN                 | 71  | 68  | 64 | 60 | 58 | 57 | 51 | 49 | 47 | 47 | 45 | 41 | 33 | 25 | 23 | 18 | 11 | 5  | 4  | 0  |    |  |
| Total MCL <sup>a</sup> | 15  | 14  | 12 | 12 | 11 | 10 | 10 | 10 | 10 | 10 | 10 | 9  | 7  | 7  | 6  | 2  | 1  | 1  | 1  | 0  |    |  |
| MCL no AHN             | 11  | 11  | 10 | 10 | 9  | 9  | 9  | 9  | 9  | 9  | 9  | 8  | 6  | 6  | 5  | 1  | 1  | 1  | 1  | 0  |    |  |

Data cut-off date: September 15, 2023. Median (range) follow-up was 38 months (95% CI; 35.5–42.0). <sup>a</sup>Includes subset with no AHN (n=11) and subset with AHN (n=4). Per WHO classification, the diagnostic criteria for subtyping MCL includes BM aspirate smears ≥20% (regardless of the presence of AHN).

# Median overall survival was not reached regardless of treatment history



Data cut-off date: September 15, 2023. Median (range) follow-up was 38 months (95% CI; 35.5–42.0).

# Continued favorable safety profile after more than 3 years of follow-up with avapritinib

Long term safety and tolerability are well characterized and consistent with prior reports<sup>1</sup>:

- AEs were generally managed with dose modifications
  - Dose reductions, interruptions, and discontinuations due to TRAEs occurred in 76%, 63%, and 13% of patients, respectively
- Treatment-related cognitive effects remained similar to previous reports<sup>1</sup> and were mostly Grade 1–2
- No additional intracranial bleeding events since prior data cut-off in September 2022 (n=4 [3.7% of patients])<sup>1</sup>
- No treatment-related deaths occurred

| Most common TRAEs (≥15%), n (%) | Safety population (N=107) |           |
|---------------------------------|---------------------------|-----------|
|                                 | Any grade                 | Grade 3/4 |
| <b>Hematological AEs</b>        |                           |           |
| Thrombocytopenia <sup>a</sup>   | 43 (40)                   | 19 (18)   |
| Anemia <sup>a</sup>             | 34 (32)                   | 14 (13)   |
| Neutropenia <sup>a</sup>        | 20 (19)                   | 18 (17)   |
| <b>Non-hematological AEs</b>    |                           |           |
| Periorbital edema               | 44 (41)                   | 6 (6)     |
| Peripheral edema                | 41 (38)                   | 2 (2)     |
| Cognitive disorder              | 18 (17)                   | 3 (3)     |
| Eyelid edema <sup>a</sup>       | 18 (17)                   | 0 (0)     |
| Hair color changes              | 18 (17)                   | 0 (0)     |
| Face edema                      | 17 (16)                   | 0 (0)     |

# Avapritinib continued to demonstrate a favorable benefit-risk profile after more than 3 years of follow-up

---

- **Avapritinib demonstrated deep and sustained effects regardless of AdvSM subtype or prior therapy including:**
  - High ORR (73%), including 87% in a treatment-naïve setting, by centrally-adjudicated mIWG-MRT-ECNM criteria
  - CR/CRh in 29% of all patients and 43% in treatment-naïve patients
  - Low rate of progression with no MC progressions
  - Median DOR and PFS were not reached
- **Median OS was not reached with OS of 75% at 36 months**
  - Data in treatment-naïve patients suggest better outcomes with earlier treatment
- **Avapritinib maintained a well characterized safety profile with no new safety concerns observed**
  - AEs were effectively managed with dose reductions/interruptions with sustained efficacy

# Acknowledgements

---

- We thank the patients and their families for making the PATHFINDER study possible
- We also thank the investigators and clinical trial teams who participated in the study