15. Refer to Appendix E for reproductive criteria for male participants.
16. The participants must provide written informed consent.

PF-08046040 + azacitidine combination cohort in relapsed/refractory (HMA-failure) MDS or MDS/AML (Parts D and F):

17. Participants with diagnosis of MDS or MDS/AML according to ICC 2022 (Arber et al, 2022) criteria.
18. Disease which has relapsed, failed to respond after minimum of 6 cycles, or progressed following an HMA in the immediately preceding line of therapy.
    - Participants who received HMA combination therapies are eligible.
    - Participants may only have had exposure to one HMA (either azacitidine or decitabine, or equivalent) prior to enrollment.
19. Participants who are eligible for continued therapy with, and not deemed intolerant of, azacitidine.
20. Must be off any other systemic treatments for AML/MDS; must be off HMA therapy ≥2 weeks and must be off any other systemic treatments for MDS for ≥4 weeks prior to first dose of PF-08046040; growth factors (eg, G-CSF, erythropoietin and thrombopoietin) and transfusions are allowed before and during the study as clinically indicated.
21. Age ≥18 years.
22. ECOG Performance Status 0–2.

PF-08046040 + azacitidine combination cohort in previously untreated higher-risk MDS (Parts D and E):

23. Participants with diagnosis of MDS or MDS/AML according to ICC 2022 (Arber et al, 2022) criteria, previously untreated.
    - Participants with MDS/AML should not have AML-defining cytogenetics.
24. Participants with higher-risk per IPSS-M (Moderate High, High, or Very High) MDS and MDS/AML (Bernard et al, 2022) (IPSS-M Risk Calculator at https://mds-risk-model.com).
25. Age ≥18 years.
26. ECOG Performance Status of 0–2.

PF-08046040 + azacitidine + venetoclax combination cohort in previously participants with untreated AML who are unfit for induction therapy (Part G):

27. Participants with diagnosis of AML according to International Consensus Classification (ICC) 2022 (Arber et al, 2022), with ≥20% bone marrow blasts, participants with AML-defining genetic events per ICC 2022 (Appendix G) must have ≥10% bone marrow blasts. Participants must be previously untreated, ineligible

for treatment with standard cytarabine/anthracycline based induction regimens due to age or comorbidities.

Note: Participants in the dose finding phase of Part G must have adverse risk features as per 2022 ELN risk classification (Appendix H). Participants in the dose expansion phase of Part G may be enrolled irrespective of genetic risk classification (please refer to Appendix O.3 for US-specific requirements on initiation of dose expansion).

28. Participants must be considered ineligible for induction therapy defined by the following:
    - ≥75 years of age;

OR

    - ≥ 18 to 74 years of age with at least one of the following comorbidities:
        - Cardiac disorder (e.g. congestive heart failure requiring treatment, ejection fraction ≤ 50%, or chronic stable angina)
        - Severe pulmonary disorder (e.g. DLCO ≤ 65% or FEV1 ≤ 65%)
        - Creatinine clearance ≥30 mL/min to < 45 ml/min
        - Hepatic disorder with total bilirubin > 1.5 to ≤3 x upper limit of normal
        - Any other comorbidity that the investigator judges to be incompatible with intensive therapy must be reviewed and approved by the medical monitor
29. Age ≥18 years.
30. ECOG Performance Status of 0–2.

4.2. Exclusion Criteria

All Participants

1. History of another malignancy within 3 years before the first dose of study intervention or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (eg, 5-year OS ≥90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.
2. Previous exposure to CD70-targeted agents.
3. Prior allogeneic hematopoietic stem cell transplant, for any condition.
4. Central nervous system leukemia based on imaging or documented positive cytology in cerebral spinal fluid.
5. Any uncontrolled Grade 3 or higher (per the National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI CTCAE], version 5.0) viral, bacterial, or fungal infection within 14 days prior to the first dose of study treatment.

Antimicrobial prophylaxis or ongoing treatment of resolving/controlled infection is permitted.

6. Participants who have experienced major surgery (defined as requiring general anesthesia and hospitalization for >24 hours) or significant traumatic injury that would place the participant at undue risk from study procedures, in the opinion of the investigator, within 14 days before the first dose of study treatment. Participants must have recovered adequately from the surgery/injury, or complications thereof, prior to starting treatment.
7. Positive for hepatitis B by surface antigen expression. Active hepatitis C infection (positive by PCR or on antiviral therapy for hepatitis C within the last 6 months). Participants who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks.
8. Known to be positive for human immunodeficiency virus (HIV).
9. Known active or latent tuberculosis.
10. History of clinically significant sickle cell anemia, autoimmune hemolytic anemia, or idiopathic thrombocytopenic purpura.
11. History of clinically significant chronic liver disease (eg, liver cirrhosis) and/or ongoing alcohol abuse.
12. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association Class III-IV (Appendix F) within 6 months prior to their first dose of PF-08046040.
13. a. Parts A, B, C, D, and F: Chemotherapy, systemic radiotherapy, biologics, other anti-neoplastic or investigational agents, and/or other antitumor treatment with immunotherapy that is not completed 4 weeks prior to first dose of PF-08046040. Focal radiotherapy that is not completed 2 weeks prior to the first dose of PF-08046040. Hydroxyurea or 6-mercaptopurine used for cytoreduction may be given up to 24 hours prior to treatment.

    b. Part E and Part G: Chemotherapy, systemic radiotherapy, biologics, other anti-neoplastic or investigational agents, and/or other antitumor treatment with immunotherapy for diagnosis of MDS (Part E) or AML (Part G) prior to first dose of PF-08046040. Focal radiotherapy that is not completed 2 weeks prior to the first dose of PF-08046040. Hydroxyurea or 6-MP used for cytoreduction may be given up to 24 hours prior to treatment. For participants who progressed from MDS (Part G): HMA and/or chemotherapy for MDS.
14. Participants with either of the following:
    - A condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications within 2 weeks of first dose of PF-08046040 (inhaled, topical, intraocular, intranasal, and intraarticular steroids are permitted in the absence of active immune disease, and

steroid premedication for prevention of hypersensitivity reactions to radiographic contrast is permitted).

- Active known or suspected clinically significant autoimmune disease or clinically significant autoimmune-related toxicity from prior immune-oncology–based therapy (exceptions include vitiligo, controlled type 1 diabetes mellitus, residual hypothyroidism requiring hormone replacement, and conditions not expected to recur in the absence of an external trigger).

15. Participants who are breastfeeding, pregnant, or planning to become pregnant from time of informed consent until 8 weeks (Parts A, B, and C) or 24 weeks (Parts D, E, F and G) after final dose of study intervention. Please refer to Appendix O.2 for additional clarification relevant to participants in Japan.
16. Known hypersensitivity to any components contained in the drug formulation of PF-08046040 (all Parts), azacitidine (Parts D-G), or venetoclax (Part G).
17. Estimated life expectancy <12 weeks.
18. Other serious underlying medical condition that, in the opinion of the investigator, would impair the participant's ability to receive or tolerate the planned treatment and follow-up.
19. Parts D and F: Participants who have received prior oral HMA or oral HMA-combinations are not eligible.
20. Participant has a chronic respiratory disease that requires continuous oxygen.
21. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

For participants enrolled in (Part G):

22. History of myeloproliferative neoplasm (MPN) including myelofibrosis, essential thrombocytopenia (ET), polycythemia vera, chronic myeloid leukemia (CML) with or without BCR-ABL1 translocation, APL, AML with BCR-ABL1 translocation, and diagnosis of MDS/AML by ICC 2022.
23. Participant has received strong and/or moderate CYP3A inducers within 7 days prior to the initiation of study treatment.
24. Participant has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Starfruit within 3 days prior to the initiation of study treatment.
25. Participant has a malabsorption syndrome or other condition that precludes enteral route of administration for venetoclax.