CLINICAL STUDY PROTOCOL

An Open-Label, Phase 1/2 Study Evaluating Immunomodulatory AVM0703 in Patients with Lymphoid Malignancies (the OPAL Study)

Investigational Product: AVM0703
Protocol Number: AVM0703-001

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SIGNATURE PAGE

STUDY TITLE: An Open-Label, Phase 1/2 Study Evaluating Immunomodulatory AVM0703 in Patients With Lymphoid Malignancies (the OPAL Study)

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
_____	_____

Theresa A. Deisher, PhD
President & Chief Scientific Officer
AVM Biotechnology, LLC.

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by AVM Biotechnology, LLC. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to AVM Biotechnology, LLC. and that it may not be further disclosed to third parties. I understand that the study may be terminated, or enrollment suspended at any time by AVM Biotechnology, LLC., with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board Regulations, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: An Open-Label, Phase 1/2 Study Evaluating Immunomodulatory AVM0703 in Patients with Lymphoid Malignancies (the OPAL Study)

PROTOCOL NUMBER: AVM0703-001

INVESTIGATIONAL PRODUCT: AVM0703

PHASE: 1/2

INDICATION(S): Lymphoid malignancies

OBJECTIVES:

Phase 1

The primary objective of the Phase 1 portion of the study is to determine the safety, tolerability, and maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of AVM0703.

The secondary objectives of the Phase 1 portion of the study are the following:

- To assess the preliminary efficacy of AVM0703 in patients with lymphoid malignancies; and
- To assess the pharmacokinetics (PK) of ascending doses of AVM0703.

The exploratory objectives of the Phase 1 portion of the study are the following:

- To assess reduction in lymphocyte counts; and
- To assess potential biomarkers indicative of AVM0703 antitumor activity in peripheral blood or tumor samples if available.

Phase 2

The primary objective of the Phase 2 portion of the study is to determine the preliminary efficacy of AVM0703 in specific patient cohorts when administered at one or more RP2D dose levels based on the Phase 1 results. Cohorts will include repeat RP2D infusions in 21 day intervals.

The secondary objective of the Phase 2 portion of the study is to obtain additional characterization of the safety and efficacy of AVM0703 when administered at a RP2D in specific patient cohorts.

The exploratory objectives of the Phase 2 portion of the study are the following:

- To assess changes in immune status; and
- To assess potential biomarkers indicative of AVM0703 antitumor activity in peripheral blood or tumor samples if available.

POPULATION:

Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Age ≥12 years and weight >40 kg ;
2. Histologically confirmed diagnosis per 2016 World Health Organization (WHO) classification of lymphoid neoplasms (1) and per the 2016 WHO classification of acute leukemia (2) (3)of the following indications:

- Diffuse large B-cell lymphoma (DLBCL), including arising from follicular lymphoma;
  - Preceding indolent lymphoma must be transformed histologically to DLBCL or high-grade B cell lymphoma (4) and have met generally accepted criteria for rapid progression and treatment, defined by the following:
    a. Progressive or bulky or symptomatic nodal disease; or
    b. Compromise of normal organ function due to progressive or bulky disease; or
    c. Presence of B symptoms (i.e., fevers, weight loss, night sweats); or
    d. Presence of symptomatic extranodal disease, such as effusions; or
    e. Cytopenias due to extensive bone marrow infiltration, autoimmune hemolytic anemia, or thrombocytopenia, or hypersplenism;
- High-grade B-cell lymphoma;
  - Preceding indolent lymphoma must meet criteria as defined above;
- Mantle cell lymphoma (MCL) with high-risk prognosis defined as scoring ≥6 points on the 11-point MCL International Prognostic Index (MIPI) scale and have met criteria for transformed indolent lymphoma as defined above;
- Primary mediastinal large B-cell lymphoma;
- Primary DLBCL of the central nervous system (CNS);
- Burkitt or Burkitt-like lymphoma/leukemia;
- Chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL) that met at least 1 of the criteria for active disease indicating need for treatment according to the International Workshop on CLL (iwCLL) (5) criteria as follows:
    a. Evidence of progressive marrow failure such as hemoglobin <10 g/dL and/or platelet count $<100 \times 10^9$/L; or
    b. Massive (i.e., ≥6 cm below left costal margin) or progressive or symptomatic splenomegaly; or
    c. Massive (i.e., ≥10 cm in the longest diameter) or progressive or symptomatic lymphadenopathy; or

d. Progressive lymphocytosis with an increase of ≥50% over a 2-month period or lymphocyte doubling time <6 months; or

e. Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids; or

f. Symptomatic or functional extranodal involvement; or

g. Disease-related symptoms, defined by any of the following:

- Unintentional weight loss (≥10%) within the previous 6 months; or
- Significant fatigue (i.e., Eastern Cooperative Oncology Group performance scale 2 or worse); or
- Fevers ≥100.5°F for ≥2 weeks without evidence of infection; or
- Night sweats for ≥1 month without evidence of infection.

- B-cell leukemia/lymphoma, T-cell leukemia/lymphoma, acute leukemias of ambiguous lineage, or natural killer (NK) cell lymphoblastic leukemia/lymphoma, advanced or aggressive lymphoma/lymphoproliferative disease per 2016 World Health Organization classification of lymphoid malignancies;

3. Patients must have relapsed or refractory (R/R) disease with prior therapies defined below: For Phase 1;

- DLBCL and high-grade B-cell lymphoma:

a. R/R after autologous hematopoietic cell transplant (HCT); or

b. R/R after chimeric antigen receptor T-cell (CAR T) therapy; or

c. Patients not eligible for autologous HCT or CAR T therapy; or

d. R/R after ≥2 lines of therapy including anti-20 antibody and for whom no standard therapy is available. Patients must have failed or have been intolerant or ineligible for polatuzamab vedotin;

- MCL:

a. R/R after autologous HCT; or

b. Patients not eligible for autologous HCT must be R/R after ≥2 lines of therapy including at least 1 of the following: a Bruton's tyrosine kinase (BTK) inhibitor, bortezomib, or lenalidomide; and for whom no standard therapy is available;

- Primary mediastinal large B-cell lymphoma: R/R after ≥1 line of therapy and are not eligible for or have recurred after autologous HCT or CAR T cell therapy and for whom no standard therapy is available;

- Primary DLBCL of the CNS: R/R after ≥1 line of therapy including methotrexate (unless intolerant to methotrexate) and are not eligible for or have recurred after autologous HCT or CAR T cell therapy and for whom no standard therapy is available;
- Burkitt or Burkitt-like lymphoma/leukemia: R/R after ≥1 line of therapy including methotrexate (unless intolerant to methotrexate) and are not eligible for or have recurred after autologous HCT or CAR T cell therapy and for whom no standard therapy is available;
- CLL/SLL: patients who have active disease requiring treatment and who are deemed at high-risk for disease progression by the investigator or have high risk features per the iwCLL criteria, such as primary resistance to first-line chemo(immune)therapy, or progression of disease <3 years after fludarabine-based chemo(immune)therapy, or leukemia cells with del(17p)/TP53 mutation, must be:
    a. R/R after autologous or allogeneic HCT; or
    b. Patients not eligible for HCT; or
    c. R/R after ≥2 lines of therapy including at least 1 of the following: a BTK inhibitor, venetoclax, idelalisib, or duvelisib and for whom no standard therapy is available;
- Acute lymphoblastic leukemia (ALL):
    a. R/R after allogeneic HCT and for whom no standard therapy is available; or
    b. Patients not eligible for allogeneic HCT must be R/R according to the following disease-specific specifications:
        - B-cell lymphoblastic leukemia/lymphoma: ≥2 lines of therapy including approved CAR T cell therapies, inotuzumab ozogamicin, or blinatumomab and for whom no standard therapy is available;
        - T-cell lymphoblastic leukemia/lymphoma: ≥2 lines of therapy including nelarabine and for whom no standard therapy is available;
        - NK cell leukemia/lymphoma: ≥1 line of therapy and for whom no standard therapy is available;
- All other diagnoses: R/R after autologous or allogeneic HCT; or R/R after at least one line of therapy and for whom no standard therapy is available

For Phase 2 expansion cohorts:

Patients must have relapsed or refractory (R/R) disease with prior therapies defined below:

- DLBCL and high-grade B-cell lymphoma:
    a) R/R after autologous hematopoietic cell transplant (HCT); or
    b) R/R after chimeric antigen receptor T-cell (CAR T) therapy; or
    c) Patients not eligible for autologous HCT or CAR T therapy; or
    d) R/R after ≥2 lines of therapy including anti-CD20 antibody and failed, intolerant or ineligible for polatuzamab vedotin, or for whom no standard therapy is available.
- MCL:

a) R/R after autologous HCT; or

b) Patients not eligible for autologous HCT must have failed acalabrutinib or be R/R after ≥2 lines of therapy including at least 1 of the following: a Bruton's tyrosine kinase (BTK) inhibitor, bortezomib, or lenalidomide; or for whom no standard therapy is available;

- Primary mediastinal large B-cell lymphoma: R/R after ≥1 line of therapy and are not eligible for or have recurred after autologous HCT or CAR T cell therapy, or for whom no standard therapy is available;
- Primary DLBCL of the CNS: R/R after ≥1 line of therapy including methotrexate (unless intolerant to methotrexate) and are not eligible for or have recurred after autologous HCT or CAR T cell therapy, or for whom no standard therapy is available;
- Burkitt or Burkitt-like lymphoma/leukemia: R/R after ≥1 line of therapy including methotrexate (unless intolerant to methotrexate) and are not eligible for or have recurred after autologous HCT or CAR T cell therapy, or for whom no standard therapy is available;
- CLL/SLL: patients who have active disease requiring treatment and who are deemed at high-risk for disease progression by the investigator or have high risk features per the iwCLL criteria, such as primary resistance to first-line chemo(immune)therapy, or progression of disease <3 years after fludarabine-based chemo(immune)therapy, or leukemia cells with del(17p)/TP53 mutation, must be:

  a) R/R after autologous or allogeneic HCT; or

  b) Patients not eligible for HCT; or

  c) R/R after ≥2 lines of therapy including at least 1 of the following: a BTK inhibitor, venetoclax, idelalisib, or duvelisib, or for whom no standard therapy is available;

- Acute lymphoblastic leukemia (ALL):

  a) R/R after allogeneic HCT and for whom no standard therapy is available; or

  b) Patients not eligible for allogeneic HCT must be R/R according to the following disease-specific specifications:

    - B-cell lymphoblastic leukemia/lymphoma: ≥2 lines of therapy including approved CAR T cell therapies, inotuzumab ozogamicin, or blinatumomab, or for whom no standard therapy is available;
    - T-cell lymphoblastic leukemia/lymphoma: ≥2 lines of therapy including nelarabine, or for whom no standard therapy is available;
    - NK cell leukemia/lymphoma: ≥1 line of therapy or for whom no standard therapy is available;

- All other diagnoses: R/R after autologous or allogeneic HCT; or R/R after at least one line of therapy, or for whom no standard therapy is available.

4. Lansky (12 to 15 years of age) or Karnofsky (≥16 years of age) performance status ≥50;

5. Screening laboratory values that meet all of the following criteria:
For Phase 1:

- Absolute neutrophil count ≥0.5 × 10^9/L;
- Platelet count >50 × 10^9/L;
- Hemoglobin ≥8.0 g/dL;
- Aspartate aminotransferase or alanine aminotransferase ≤2.5 × upper limit of normal (ULN), unless due to the disease;
- Total bilirubin ≤1.5 × ULN (if secondary to Gilbert's syndrome, ≤3 × ULN is permitted), unless due to the disease; and
- Serum creatinine ≤1.5 × ULN or glomerular filtration rate ≥50 mL/min (calculated from a 24-hour urine collection);

For Phase 2:

- Absolute neutrophil count ≥0.05 × 10^9/L;
- Platelet count >25 × 10^9/L;
- Hemoglobin ≥6.5 g/dL;
- Aspartate aminotransferase or alanine aminotransferase ≤2.5 × upper limit of normal (ULN), unless due to the disease;
- Total bilirubin ≤1.5 × ULN (if secondary to Gilbert's syndrome, ≤3 × ULN is permitted), unless due to the disease; and
- Glomerular filtration rate ≥30 mL/min ; except for patients on metformin at baseline for whom GFR must be ≥45 mL/min; *GFR can be calculated by the Cockcroft-Gault formula (Appendix C*);

6. Minimum level of pulmonary reserve defined as <Grade 2 dyspnea and pulse oximetry ≥92% on room air;

7. Females of childbearing potential must have a negative serum pregnancy test at screening. Females of childbearing potential and nonsterile males must agree to use medically effective methods of contraception from the time of informed consent/assent through 1 month after study drug infusion, which must, at a minimum, include a barrier method; and

8. The ability to understand and willingness to sign a written informed consent form and the ability to adhere to the study schedule and prohibitions. Patients under the age of 18 years (or other age as defined by regional law or regulation) must be willing and able to provide written assent and have a parent(s) or guardian(s) willing and able to provide written, signed informed consent after the nature of the study has been explained and prior to performance of any study-related procedure.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study for Phase 1:

9. History of another malignancy, except for the following:
   - Adequately treated local basal cell or squamous cell carcinoma of the skin;
   - Adequately treated carcinoma in situ without evidence of disease;
   - Adequately treated papillary, noninvasive bladder cancer; or
   - Other cancer that has been in complete remission for ≥2 years. Patients with low-grade prostate cancer, on active surveillance, and not expected to clinically progress over 2 years are allowed;
10. Significant cardiovascular disease (e.g., myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to the start of AVM0703 administration, angina requiring therapy, symptomatic peripheral vascular disease, New York Heart Association Class III or IV congestive heart failure, left ventricular ejection fraction <30%, left ventricular fractional shortening <20%, or uncontrolled ≥Grade 3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥150 mmHg) despite antihypertensive therapy for patients ≥18 years of age, or uncontrolled stage 2 hypertension (diastolic blood pressure ≥90 mmHg or systolic blood pressure ≥140 mmHg) despite antihypertensive therapy for patients ≥12 years of age;
11. Significant screening electrocardiogram (ECG) abnormalities, including unstable cardiac arrhythmia requiring medication, atrial fibrillation/flutter, left bundle-branch block, second-degree atrioventricular (AV) block type 2, third-degree AV block, ≥Grade 2 bradycardia, or heart rate corrected QT interval using Fridericia's formula >480 msec;
12. Known gastric or duodenal ulcer;
13. Uncontrolled type 1 or type 2 diabetes;
14. Known hypersensitivity or allergy to the study drug or any of its excipients;
15. Untreated ongoing bacterial, fungal, or viral infection (including upper respiratory tract infections) at the start of AVM0703 administration, including the following:

- Positive hepatitis B surface antigen and/or hepatitis B core antibody test plus a positive hepatitis B polymerase chain reaction (PCR) assay. Patients with a negative PCR assay are permitted with appropriate antiviral prophylaxis;
- Positive hepatitis C virus antibody (HCV Ab) test. Patients with a positive HCV Ab test are eligible if they are negative for hepatitis C virus by PCR;
- Positive human immunodeficiency virus (HIV) antibody test with detectable HIV load by PCR, or the patient is not able to tolerate antiretroviral therapy; or
- Positive tuberculosis test during screening;

16. Received live vaccination within 8 weeks of screening;

17. Pregnant or breastfeeding;
18. Concurrent participation in another therapeutic clinical study (except AVM0703-001); or
19. Manic-depressive disorder, schizophrenia, or a history of severe depression or substance abuse.

Patients who meet any of the following criteria will be excluded from participation in the study for Phase 2:

1. History of another malignancy, except for the following:
   - Adequately treated local basal cell or squamous cell carcinoma of the skin;
   - Adequately treated carcinoma in situ without evidence of disease;
   - Adequately treated papillary, noninvasive bladder cancer; or
   - Other cancer that has been in complete remission for ≥2 years. Patients with low-grade prostate cancer, on active surveillance, and not expected to clinically progress over 2 years are allowed;
2. Significant cardiovascular disease (e.g., myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to the start of AVM0703 administration, angina requiring therapy, symptomatic peripheral vascular disease, New York Heart Association Class III or IV congestive heart failure, left ventricular ejection fraction <30%, left ventricular fractional shortening <20%, or uncontrolled ≥Grade 3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥150 mmHg) despite antihypertensive therapy for patients ≥18 years of age, or uncontrolled stage 2 hypertension (diastolic blood pressure ≥90 mmHg or systolic blood pressure ≥140 mmHg) despite antihypertensive therapy for patients ≥12 years of age;
3. Significant screening electrocardiogram (ECG) abnormalities, including unstable cardiac arrhythmia requiring medication, atrial fibrillation/flutter, second-degree atrioventricular (AV) block type 2, third-degree AV block, ≥Grade 2 bradycardia, or heart rate corrected QT interval using Fridericia's formula >480 msec;
4. Known gastric or duodenal ulcer;
5. Uncontrolled type 1 or type 2 diabetes;
6. Known hypersensitivity or allergy to the study drug or any of its excipients;
7. Untreated ongoing bacterial, fungal, or viral infection (including upper respiratory tract infections) at the start of AVM0703 administration, including the following:
   - Positive hepatitis B surface antigen and/or hepatitis B core antibody test plus a positive hepatitis B polymerase chain reaction (PCR) assay. Patients with a negative PCR assay are permitted with appropriate antiviral prophylaxis;
   - Positive hepatitis C virus antibody (HCV Ab) test. Patients with a positive HCV Ab test are eligible if they are negative for hepatitis C virus by PCR;
- Positive human immunodeficiency virus (HIV) antibody test with detectable HIV load by PCR, or the patient is not able to tolerate antiretroviral therapy; or

- Positive tuberculosis test during screening; test must be positive and not indeterminate due to anergy; if the result is indeterminate due to anergy the patient must not have a history of recent exposure to tuberculosis. Patients in Phase 2 repeat dosing cohorts should not travel to any destination where they might be exposed to tuberculosis during their entire treatment period with AVM0703.

8. Received live vaccination within 8 weeks of screening;
9. Pregnant or breastfeeding;
10. Concurrent participation in another therapeutic clinical study (except AVM0703-001); or
11. Uncontrolled bipolar disorder or schizophrenia. Patients with a diagnosis, past or current, of bipolar disorder or schizophrenia or having a history of severe depression or substance abuse must be prophylactically treated with circadian physiologic hydrocortisone per section 5.5.3.3 CNS prophylaxis, without exception.

STUDY DESIGN AND DURATION:

This is an open-label, Phase 1/2 study designed to characterize the safety, tolerability, PK, and preliminary antitumor activity of AVM0703 administered as a single intravenous (IV) infusion to patients with lymphoid malignancies.

Phase 1

The Phase 1 portion of the study will enroll patients into a 3+3 dose-escalation design to assess the dose-limiting toxicities (DLTs) and establish an MTD/RP2D. AVM0703 dose cohorts are planned as shown in the table below. In each cohort, 3 to 6 patients will be treated. Each patient in the 6, 9, 12, and 18 mg/kg cohorts will be sequentially enrolled after 48-hours of observation. Dose escalation will be permitted after 3 patients have completed a 7 day DLT assessment period with no reported DLTs or after 6 patients have completed the 7 day DLT assessment period with no more than 1 DLT. Patients in the 21 mg/kg cohort will be sequentially enrolled after 7 days of observation, and will be observed for DLTs for 21 days.

The dose escalation will use the following rules for evaluating dose levels:

- If none of the first 3 evaluable patients in a cohort experience a DLT, that dose level will be deemed safe, and another 3 patients will be enrolled into the next dose level;
- If 1 of the first 3 patients in a cohort experiences a DLT, 3 more patients will be treated at the same dose level.

If ≥2 of the 3 to 6 patients in any dose level experience a DLT, that dose level will be considered to have exceeded the MTD and dosing will stop at that level. If the previous dose level did not already have 6 patients treated with ≤1 DLT, enrollment and dosing will then resume in the previous dose level with additional patients up to a total of 6 patients. If >1 evaluable patients in the 18 mg/kg cohort experience a DLT, the DSMC will review all available data (safety, PK and pharmacodymanics) before recommending if intermediate dose levels between 12 mg/kg and 18 mg/kg (e.g., 15 mg/kg) or if alternative dosing schedules or alternative doses should be explored.

- The highest dose level at which no more than 1 of 6 evaluable patients has experienced a DLT in the 7-day or 21-day DLT assessment period (as described above) will be considered the MTD for AVM0703; and
- If ≤1 patient experience(s) a DLT at the highest dose level tested, an MTD will not have been established, but sufficient data may be available to select an RP2D based on the overall safety profile.
- In the event of disease progression, patients may be retreated, according to section 5.5.3.2.

Dose Escalation Plan

Dose Cohort	AVM0703 Dose[a]
1	6 mg/kg
2	9 mg/kg
3	12 mg/kg
4	18 mg/kg
5	21 mg/kg

a. Expressed as dexamethasone phosphate.

Dose-limiting toxicity criteria will be defined separately for patients with acute leukemia and those with NHL or CLL. A DLT is defined as any of the treatment-emergent adverse events listed below that occur within the first 7 (6, 9, 12 and 18 mg/kg cohorts) or 21 days (21 mg/kg cohort) after AVM0703 administration (as describe above).

Phase 2

For Phase 2, one or more patient cohort(s) will receive repeat RP2D infusions in 21 day intervals until intolerance, unacceptable toxicity or disease progression, to determine the number of repeat infusions that are safe, effective and tolerable in this patient population. PK assessments will be made at sites participating in both Phase 1 and Phase 2 after each repeat infusion for the first 6 patients enrolled into each repeat dosing cohort. Full PK assessments will be made as per Phase 1 after the 1st (first) and 6th (sixth) repeat infusions, while for the second to fifth doses (2nd to 5th) PK assessments will be made pre-infusion, at end of infusion, 15 minutes and 48 hours after end of infusion. At least 6 patients will be enrolled in each RP2D repeat dosing cohort. The DSMC will monitor unacceptable toxicities during Phase 2 and halting/stopping criteria are outlined in Table 6. After 6 patients, who have had PK assessments, have reached intolerance, unacceptable toxicity, or disease progression, or they have received 6 infusions without intolerance, unacceptable toxicity, or disease progression, the Data Safety Monitoring Committee will review an integrated interim analysis of all available PK, PD, efficacy, safety and tolerability data and determine whether repeat dosing should continue or be limited to a certain number of infusions. Ongoing DSMC review will occur at least every 6 months. Based on integrated analysis, including dose-response and exposure-response, the DSMC will determine the optimal dose and dosing schedule for repeat dosing with AVM0703.

For Phase 2, RP2D cohorts will be included that do not require repeat 21 day interval dosing for patients who cannot comply with the visit schedule for repeat dosing. These patients can be retreated according to section 5.5.3.2.

For Phase 2, patients should be carefully monitored for tumor flare/pseudoprogression reactions. While tumor flare can induce symptoms requiring medical management, tumor flare has been associated with best long term outcomes (6).

Symptoms of tumor flare/pseudoprogression are summarized below:

Patterns of pseudoprogression include; i) extremely rapid tumor growth by palpation, patient symptoms or imaging that is not consistent with the known growth rate of the patient's cancer, ii) increased edema by imaging around the lesion, iii) enhanced PET signal or even evidence of new lesions that subsequently regress or disappear, and iv) evidence of disease progression without accompanying clinical deterioration (7).

Tumor flare in patients may include rapid, often painful, self-limited increase in the size of lymph nodes, often accompanied by fever, lymphocytosis, rash, and bone pain. (8). Bruton tyrosine kinase and phosphatidylinositol 3-kinase targeting agents may cause a rapid reduction in lymph node size and spleen mass, often with improvement of cytopenias, but associated with lymphocytosis. This finding, which relates to a redistribution of lymphocytes from tissue sites to the peripheral blood, may persist for a year or longer without signs or symptoms associated with disease progression and does not represent a suboptimal response to therapy (8).

<u>NHL/CLL DLT criteria:</u>

- Any Grade 5 toxicity not clearly caused by the NHL/CLL;
- Grade 4 neutropenia lasting more than 5 days (without cytokine support, such as filgrastim);
- Febrile neutropenia (i.e., absolute neutrophil count $<1.0 \times 10^9$/L and fever >38.5°C);
- Grade 4 thrombocytopenia, ≥Grade 3 thrombocytopenia with ≥Grade 2 bleeding, or Grade 3 thrombocytopenia lasting >7 days;
- Any ≥Grade 3 non-hematologic toxicity, except for alopecia and nausea controlled by medical management; and
- Liver injury as defined by Hy's law (9) (defined as alanine aminotransferase or aspartate aminotransferase >3 × ULN and total bilirubin >2 × ULN and no evidence of intra- or extra-hepatic obstruction [elevated alkaline phosphatase] or Gilbert's syndrome);

The following will not be considered unacceptable toxicities for Phase 2:

- Grade 3 symptoms associated with tumor flare/pseudoprogression that resolve to ≤Grade 2 spontaneously within 7 days or within 72 hours with standard medical management; and
- Grade 3 hyperglycemia that resolves with appropriate medical management to ≤Grade 2 within 72 hours; and
- Grade 3 hypertension that resolves with appropriate medical management to ≤Grade 2 within 72 hours.

<u>Acute leukemia DLT criteria:</u>

- Any treatment-related death;
- Grade 4 neutropenia lasting ≥42 days from infusion in the absence of active leukemia; and

- Any ≥Grade 3 non-hematologic toxicity not clearly resulting from the underlying malignancy EXCEPT:
- Alopecia;
- Grade 3 fatigue, asthenia, anorexia, fever, or constipation;
- Grade 3 nausea, vomiting, or diarrhea not requiring tube feeding, total parenteral nutrition, or hospitalization; or
- Infection, bleeding, or other expected direct complications of cytopenias due to active underlying malignancy.

The following will not be considered unacceptable toxicities for Phase 2:

- Grade 3 symptoms associated with tumor flare/pseudoprogression that resolve to ≤Grade 2 spontaneously within 7 days or within 72 hours with standard medical management; and
- Grade 3 hyperglycemia that resolves with appropriate medical management to ≤Grade 2 within 72 hours; and
- Grade 3 hypertension that resolves with appropriate medical management to ≤Grade 2 within 72 hours.

The following will not be considered DLTs:

- Confusion/cognitive disturbance that resolves to ≤Grade 1 within 24 hours;
- Grade 3 or Grade 4 hypogammaglobulinemia; and
- Grade 3 or Grade 4 isolated electrolyte abnormalities that resolve with or without intervention ≤Grade 2 within 72 hours.
- Greater than or equal to grade 3 toxicities will not be counted as a DLT if same toxicity was a part of patient's medical history at baseline and there was no grade change.

In addition to the above not considered DLTs, the following will also not be considered unacceptable toxicities for Phase 2:

- Grade 3 symptoms associated with tumor flare/pseudoprogression that resolve to ≤Grade 2 spontaneously within 7 days or within 72 hours with standard medical management; and
- Grade 3 hyperglycemia that resolves with appropriate medical management to ≤Grade 2 within 72 hours; and
- Grade 3 hypertension that resolves with appropriate medical management to ≤Grade 2 within 72 hours.

For Phase 1, all potential DLTs will be reviewed by the Safety Review Committee (SRC) for a final determination and for the SRC to make recommendations regarding the study, including cohort expansion and dose escalation. The SRC will also consider adverse events (AEs) that may have occurred in patients in any cohort (even beyond the DLT assessment period) when making decisions/recommendations to proceed to the next higher dose level. The SRC may review data (safety, PK, and pharmacodynamics) and recommend exploration of alternative dosing schedules

or alternative doses. The SRC will consist of the Principal Investigators, Sponsor representatives, and the Medpace Medical Monitor(s). A DSMC will meet approximately every 6 months to independently monitor subject safety and to represent the overall interests of the study participants. The DSMC may review data (safety, PK, and pharmacodynamics) and recommend exploration of alternative dosing schedules or alternative doses. The DSMC will monitor unacceptable toxicities during Phase 2 and halting/stopping criteria are outlined in Table 6.

An 18 mg/kg dose has been approved by the SRC for an RP2D. The 21 mg/kg dose-escalation cohort remains open for dose-escalation enrollment. For sites participating in both Phase 1 and Phase 2, patients will be enrolled into the 21 mg/kg dose-cohort unless i) no slot is available, ii) the patient cannot logistically comply with the PK blood draw requirements, iii) the cohort has been fully enrolled, or iv) the patient is enrolled into a Phase 2 repeat dosing RP2D cohort.

In the event of disease progression, a patient may be retreated as described in section 5.5.3.2.

If additional anticancer therapy is required before Day 28, disease assessment should be performed before they receive any other therapy.

Patients who go on to receive additional anticancer therapy will be followed for survival at 3, 6, and 12 months post-infusion, and yearly thereafter until death, withdrawal of consent/assent, or study closure. Survival information can be obtained via public records, telephone calls, and/or medical records. Any subsequent anticancer therapy that the patients receive will also be collected.

Phase 2

To further assess safety and efficacy of AVM0703, specific expansion cohorts will be opened in the Phase 2 portion of the study to obtain preliminary evidence of clinical activity. The Phase 2 portion of the study will include patients with malignancies that are deemed potentially responsive to AVM0703, such as DLBCL (including DLBCL arising from follicular lymphoma and primary DLBCL of the CNS), high-grade B-cell lymphoma or Burkitt lymphoma, AITCL, PTCL, MCL, CLL/SLL, T-cell lymphoma, or ALL. Up to approximately 18 patients will be enrolled into each of the selected tumor types at the MTD/RP2D defined in the Phase 1 portion of the study. Patients who received the MTD/RP2D dose in Phase 1 may be considered in the Phase 2 disease specific data set. Patients will be closely monitored for toxicity and the study will be halted if non-hematological toxicities exceed 30% of patients in a specific expansion cohort. If there is evidence that a subset of disease has differing safety profiles, a group or groups of disease may be removed from the eligibility criteria for the study based on a recommendation from the independent DSMC.

For Phase 2, one or more patient cohort(s) will receive repeat RP2D doses in 21 day intervals until intolerance, unacceptable toxicity or disease progression. For patients who enroll in repeat dosing cohorts, if they subsequently go on to receive additional anticancer therapy they will be followed for survival at 3, 6, and 12 months post-infusion if appropriate, and yearly thereafter until death, withdrawal of consent/assent, or study closure. Survival information can be obtained via public records, telephone calls, and/or medical records. Any subsequent anticancer therapy that the patients receive will also be collected.

For Phase 2, patients should be carefully monitored for tumor flare/pseudoprogression reactions. While tumor flare can induce symptoms requiring medical management, tumor flare has been associated with best long term outcomes (6).

Symptoms of tumor flare/pseudoprogression are summarized below:

Patterns of pseudoprogression include; i) extremely rapid tumor growth by palpation, patient symptoms or imaging that is not consistent with the known growth rate of the patient's cancer, ii) increased edema by imaging around the lesion, iii) enhanced PET signal or even evidence of new lesions that subsequently regress or disappear, and iv) evidence of disease progression without accompanying clinical deterioration (7).

Tumor flare in patients may include rapid, often painful, self-limited increase in the size of lymph nodes, often accompanied by fever, lymphocytosis, rash, and bone pain. (8). Bruton tyrosine kinase and phosphatidylinositol 3-kinase targeting agents may cause a rapid reduction in lymph node size and spleen mass, often with improvement of cytopenias, but associated with lymphocytosis. This finding, which relates to a redistribution of lymphocytes from tissue sites to the peripheral blood, may persist for a year or longer without signs or symptoms associated with disease progression and does not represent a suboptimal response to therapy (8).

For patients who do not enroll onto a repeat dosing cohort, in the event of disease progression, patients may be retreated, according to section 5.5.3.2. If additional anticancer therapy other than AVM0703 before Day 28 is warranted, disease assessment should be performed before they receive any other therapy. Patients who go on to receive additional anticancer therapy will be followed for survival at 3, 6, and 12 months post-infusion, and yearly thereafter until death, withdrawal of consent/assent, or study closure. Survival information can be obtained via public records, telephone calls, and/or medical records. Any subsequent anticancer therapy that the patients receive will also be collected.

DOSAGE FORM AND ROUTE OF ADMINISTRATION:

AVM0703 is supplied as a sterile solution containing 50 mL of 24 mg/mL dexamethasone phosphate (without preservatives) and will be administered to patients as a single IV infusion at a concentration of 10 mg/mL in normal saline over approximately one hour.

POTENTIAL SIDE EFFECT MITIGATION

For prophylaxis against dexamethasone-induced CNS side effects, hydrocortisone will be dosed orally or by IV for 5 days starting on the day of dexamethasone infusion. Hydrocortisone will be divided into 3 daily doses starting in the morning and spaced 6 to 8 hours apart using the following dosing schedule each day: for pediatric and adolescent patients at 5 mg/m^2 (morning dose), 3 mg/m^2 (mid-day dose), and 2 mg/m^2 dose (evening dose); and for adult patients at 10 mg/m^2 (morning dose), 5 mg/m^2 (mid-day dose), and 5 mg/m^2 dose (evening dose), the last dose administered at hour of sleep.

ENDPOINTS:

Phase 1

The primary endpoint for the Phase 1 portion of the study is the incidence of AEs, including DLTs.

The secondary endpoints include the following:

- Overall response rate (ORR) (complete response [CR] plus partial response [PR]) at 28 days post-infusion;
- CR rate at 28 days post-infusion;
- Progression-free survival at 3, 6, and 12 months post-infusion;
- Overall survival at 3, 6, and 12 months post-infusion;
- Time to response;
- Duration of response (DOR);
- Area under the plasma concentration-time curve (AUC) from time 0 to the last measurable concentration, maximum observed concentration, AUC from time 0 to infinity, half-life, volume of distribution, and clearance;
- Number of platelet and red blood cell transfusions received following AVM0703 administration;
- Lansky (12 to 15 years of age) or Karnofsky (≥16 years of age) performance status;
- Patient-Reported Outcomes Measurement Information System (PROMIS®) Scale v1.2 – Global Health (≥18 years of age);
- PROMIS – Ca Bank v1.1 - Physical Function (≥18 years of age);
- PROMIS Item Bank v2.0 – Cognitive Function (≥18 years of age);
- PROMIS Pediatric Scale v1.0 – Global Health 7 + 2 (<18 years of age) or parent proxy;
- PROMIS Pediatric Item Bank v2.0 – Upper Extremity – Short Form 8a (<18 years of age) or parent proxy;
- PROMIS Pediatric Item Bank v2.0 – Mobility – Short Form 8a (<18 years of age) or parent proxy; and
- PROMIS Pediatric Item Bank v1.0 – Cognitive Function (<18 years of age) or parent proxy.
- For patients with DLBCL (including DLBCL arising from follicular lymphoma); high-grade B-cell lymphoma; MCL; primary mediastinal large B-cell lymphoma; primary DLBCL of the CNS; Burkitt or Burkitt-like lymphoma/leukemia; or B-lymphoblastic leukemia/lymphoma, T-lymphoblastic leukemia/lymphoma, acute leukemia/lymphoma, acute leukemias of ambiguous lineage, or NK cell leukemia/lymphoma, tumor response will be assessed per the Lugano Treatment Response Criteria. For patients with CLL/SLL, tumor response will be assessed per the iwCLL criteria.

The exploratory endpoints include the following:

- Assessment of intercellular adhesion molecule (ICAM) expression, glucocorticoid receptor (GR) expression, B and T lymphocyte levels, myeloid-derived suppressor cell levels, NK cell levels, and natural killer T (NKT) cell levels in peripheral blood and tumor samples if available; and
- Assessment of minimal residual disease.

Phase 2

The primary endpoint for the Phase 2 portion of the study is ORR, defined as the proportion of patients with a best overall response of CR or PR at day 28 for patients not receiving repeat dosing in 21 day intervals. For Phase 2 expansion patients receiving repeat RP2D doses in 21 day intervals the primary endpoint is best ORR (CR or PR) at any time point.

- Patients with DLBCL (including DLBCL arising from follicular lymphoma); high-grade B-cell lymphoma; MCL; primary mediastinal large B-cell lymphoma; Burkitt or Burkitt-like lymphoma/leukemia; or B-lymphoblastic leukemia/lymphoma, T-lymphoblastic leukemia/lymphoma, acute leukemia/lymphoma, acute leukemias of ambiguous lineage, or NK cell leukemia/lymphoma, and PTCL, tumor response will be assessed per the LUGANO classification in support of response and progression endpoints (Appendix D) (8).
- Patients with B- or T-ALL will be assessed per the National Comprehensive Cancer Network (NCCN) guidelines in support of response and progression endpoints.
- For PTCL patients, including CTCL, SS or MF patients with skin involvement, response based on mSWAT (10) (Appendix H) will be combined with Lugano assessment in support of response and progression endpoints.
- For patients with CLL/SLL, tumor response will be assessed per the iwCLL criteria (Appendix G) (5), in support of response and progression endpoints.
- For patients with PCNSL, response will be assessed per the International PCNSL Collaborative Group Response Criteria (iPCNSL CGRC) (Appendix H) (11), in support of response and progression endpoints. Occult systemic disease has been reported in up to 8% of patients initially thought to have isolated PCNSL. As a result, complete systemic staging is warranted in every patient at screening according to Lugano criteria. Patients confirmed to have isolated PCNSL will undergo response assessments per PCNSL only. Patients identified to also have systemic disease at screening will undergo both PCNSL and Lugano response assessments.

The secondary endpoints may include the following:

- Incidence of AEs;
- Incidence of tumor flare/pseudoprogression defined by LYRIC criteria or adapted criteria for B- or T-ALL or CLL/SLL or PCNSL, or by symptoms associated with tumor flare/pseudopregression summarized in section 1.2.5 that occur at a time point not scheduled for disease response assessment, or by resolution of clinical symptoms with absence of clinical deterioration despite maintained or potentially increased tumor by imaging assessment.
- CR rate at 28 days after the first AVM0703 infusion or CR rate at any time point for Phase 2 patients receiving repeat doses;
- PR rate at 28 days after the first AVM0703 infusion or PR rate at any time point for Phase 2 patients receiving repeat doses;
- DOR, determined for patients with a best overall response of CR or PR and defined as the time from first achieving a response (CR or PR) to the date of documented disease progression or death;
- Progression-free survival at 3, 6, and 12 months after the first AVM infusion;
- Overall survival at 3, 6, and 12 months after the first AVM0703 infusion;
- Time to response after the first AVM0703 infusion;
- Number of platelet and red blood cell transfusions received after the first AVM0703 infusion;
- Lansky (0 to 15 years of age) or Karnofsky (≥16 years of age) performance status;

The exploratory endpoints may include the following:

- Assessment of immune status by markers of exhaustion, activation, memory and effector function;
- Assessment of plasma or serum cytokines, chemokines, growth factors, cancer antigens and other factors that may be predictive/related to tumor flare (pseudoprogression);
- Assessment of ICAM expression, GR expression, B and T lymphocyte levels, myeloid-derived suppressor cell levels, NK cell levels, and NKT cell levels in peripheral blood and tumor samples if available; and
- Assessment of minimal residual disease.

SAFETY VARIABLES:

Safety parameters for Phase 1 will include all AEs, physical examination findings, vital sign measurements, 12-lead ECG findings, and clinical laboratory assessments (chemistry, hematology, and urinalysis); safety parameters for Phase 2 will include all AEs, physical examination, vital sign measurements, and clinical laboratory assessments.

STATISTICAL ANALYSES:

The Phase 1 dose-escalation portion of the study will determine the safety and tolerability of AVM0703. The Phase 2 dose-expansion portion of the study will enroll 5 or more specific cohorts

at the MTD/RP2D defined in the Phase 1 portion of the study to further characterize the safety and efficacy of AVM0703. Descriptive summaries will be prepared to show the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentages for categorical variables. All details will be described in the Statistical Analysis Plan.

Efficacy Analysis for Phase 1:

ORR and CR rate at 28 days post-infusion as assessed by the Lugano Treatment Response Criteria or iwCLL criteria will be presented along with the 2-sided exact 80% confidence intervals. Time-to-event endpoints, including DOR, progression-free survival, and overall survival, will be summarized using the Kaplan-Meier method.

Safety Analysis

All AEs will be presented in incidence tables coded by the Medical Dictionary for Regulatory Activities preferred term and system organ class. Serious AEs, drug-related AEs, AEs leading to treatment discontinuation, AEs leading to deaths, and adverse events of special interest will be summarized in the same manner.

Laboratory parameters, 12-lead ECG parameters, and vital signs and the corresponding change from baseline over time will be summarized using descriptive statistics.

Pharmacokinetic Analysis

Individual plasma concentrations will be listed and summarized by time point and dose level using descriptive statistics. Linear and semi-logarithmic plots of individual and mean plasma concentration-time profiles as well as spaghetti plots will be presented. The plasma PK parameters of AVM0703 will be calculated using non-compartmental methods with plasma concentrations versus actual sampling time. The PK parameters will also be listed and summarized. Dose proportionality of plasma PK parameters for AVM0703 will be assessed with a power model if data permit. The exposure-response and exposure-AE relationship may also be explored if data permit.

Efficacy Analysis for Phase 2

- ORR and CR and PR rate at 28 days post-infusion, or any time point for patients receiving repeat doses in 21 day intervals, as assessed by the Lugano Treatment Response Criteria, or iwCLL criteria or iPCNSL CGRC, as appropriate, will be presented along with the 2-sided exact 80% confidence intervals. For patients with B- or T-ALL, ORR and CR and PR rate will be assessed consistent with NCCN guidelines, together with response assessed by diagnostic CT, PET/CT or MRI for patients with nodal or extranodal involvement. For B- or T-ALL patients without BM, blood or CSF involvement, Lugano Treatment Response Criteria will be used to determine ORR and CR or PR. For T cell lymphoma (PTCL) patients with skin involvement, mSWAT scores together with Lugano Treatment Response, will be used to determine ORR and CR and PR rate. Sites will incorporate clinical data with the central assessments of imaging for final response determination.

Time-to-event endpoints, including DOR, progression-free survival, and overall survival, will be summarized using the Kaplan-Meier method.

SAMPLE SIZE DETERMINATION:

For the Phase 1 dose-escalation portion of the study, 3 to 6 patients will be needed in each dose cohort based on the 3+3 design. If approximately 6 patients are enrolled in each dose cohort (Cohort 1 to Cohort 5), a total of approximately 30 patients will be enrolled. The actual number of patients enrolled will depend on the observed safety profile for each dose cohort and when the MTD is reached.

The Phase 2 dose-expansion portion of the study will be based on the Simon's 2-stage design. Up to approximately 90 patients will be enrolled, with up to approximately 18 patients in each of the 5 or more specific expansion cohorts (such as DLBCL [including DLBCL arising from follicular lymphoma and primary DLBCL of the CNS], high-grade B-cell lymphoma or Burkitt lymphoma, CLL/SLL, T-cell lymphoma, or ALL) to further characterize the safety and efficacy of AVM0703.

For each expansion cohort, a true ORR of 10% or less is considered insufficient to warrant further study (null hypothesis), whereas a true ORR of 30% or more is considered sufficiently effective (alternative hypothesis). The number of patients evaluated in each stage and the minimum number of responders needed to continue to the next stage were determined based on the Simon's 2-stage optimal design with 80% power and a 1-sided significance level of 10%. For each disease-specific expansion cohort, up to 7 patients may be enrolled in each cohort at stage 1. If no patients achieve CR or PR within a cohort, then enrollment within that cohort will terminate. Otherwise, 11 additional patients will be enrolled within the cohort for stage 2. Upon completion of stage 2, if 4 or more patients out of the 18 enrolled within a cohort achieve CR or PR, then the true response rate for AVM0703 likely exceeds 10%. Alternatively, if 3 or fewer patients achieve CR or PR at the end of stage 2, then the true response rate is likely less than 30% and further evaluation of AVM0703 in that cohort may not be pursued. If the true ORR in a cohort is ≤30%, then the probability of terminating enrollment at the end of the first stage equals 48%.

In cases where preliminary clinical evidence suggests a substantial improvement in ORR for 1 or more disease-specific expansion cohort(s), it is anticipated that the protocol may be amended to allow for enrollment of additional patients in that specific cohort or additional cohorts to further characterize the safety and efficacy of AVM0703.

SITES: Approximately 5 to 7 sites in the United States for the Phase 1 portion of the study; an additional 13-15 sites may be added for the Phase 2 portion of the study in the US and Canada.

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TABLE OF CONTENTS

Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
AITCL/AITL	Angioimmunoblastic T cell lymphoma
ALC	Absolute lymphocyte count
ALCL	Anaplastic large cell lymphoma (T cell lymphoma)
ALL	Acute lymphoblastic leukemia
ASCT	Autologous stem cell transplant
ATCL	Adult T cell lymphoma
AUC	Area under the plasma concentration-time curve
AV	Atrioventricular
B-ALL	B-cell acute lymphoblastic leukemia
BBB	Blood-brain-barrier
BR	Bendamustine and rituximab
BSA	Body Surface Area
BTK	Bruton's tyrosine kinase
CAR T	Chimeric antigen receptor T-cell
CBC	Complete blood count
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CHOEP	Cyclophosphamide, doxorubicin, vincristine, etoposide and prednisolone
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisolone
CI	Confidence Interval
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum observed concentration
CMR	Complete Metabolic Response
CNS	Central nervous system
CR	Complete response
CRA	Clinical Research Associate
CSF	Cerebral spinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T cell lymphoma
CUP	Compassionate Use Program
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DEXA	Dual energy x-ray absorptiometry
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity

Abbreviation	Definition
DSMC	Data Safety Monitoring Committee
DOR	Duration of response
DP	Dexamethasone phosphate
DSP	Dexamethasone sodium phosphate
EATCL	Enteropathy-associated T cell lymphoma e
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
EOS	End of study
EOT	End of Treatment
EPOCH	Etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin
ET	Early termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
GC	Glucocorticoid
GCP	Good Clinical Practice
GI	Gastrointestinal
GR/GCR	Glucocorticoid receptor
HCT	Hematopoietic cell transplant
HCV Ab	Hepatitis C virus antibody
HDAC	Histone deacetylase
HED	Human equivalent dose
HIV	Human immunodeficiency virus
ICAM	Intercellular adhesion molecule
ICF	Informed consent form
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IRIgG	Immune responseImmunoglobulin G
IRB	Institutional Review Board
IV	Intravenous(ly)
iPCNSL CGRCIV	International PCNSL Collaborative Group Response CriteriaIntravenous(ly)
iwCLL	International Workshop on CLL
LD_{50}	Lethal dose 50%
MCL	Mantle cell lymphoma
MIPI	MCL International Prognostic Index
MOA	Mechanism of action

Abbreviation	Definition
Mos	months
MP/MPS	Methylprednisolone
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
MF	Mycosis fungoides
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
NKT	Natural killer T
NKTCL	Natural Killer T cell lymphoma
NOS NKT	Not otherwise specifiedNatural killer T
ORR	Overall response rate
PCNSL	Primary central nervous system lymphoma
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
PMR	Partial Metabolic Response
PR	Partial Response
PRD	Progressive Radiologic Disease
PROMIS	Patient-Reported Outcomes Measurement Information System
PTCL	Peripheral T cell lymphoma
PROMIS	Patient-Reported Outcomes Measurement Information System
R-DHAP	Rituximab, dexamethasone, cytarabine, and cisplatin
R-ESHAP	Rituximab, etoposide, methylprednisolone, cytarabine, and cisplatin
RP2D	Recommended Phase 2 dose
R/R	Relapsed or refractory
SAE	Serious adverse event
SBP	Systolic blood pressure
SLL	Small lymphocytic leukemia
SRC	Safety Review Committee
SRD	Stable Radiologic Disease
SS	Sezary Syndrome
SRC	Safety Review Committee
SCNSL	Secondary central nervous system lymphoma
SUSAR	Suspected Unexpected Serious Adverse Reaction
T-ALL	T-cell acute lymphoblastic leukemia/lymphoma
TBSA	Total Body Surface Area
TCR	T cell receptor
TFHT-ALL	T follicular helperT-cell acute lymphoblastic leukemia/lymphoma
TFR	Tumor Flare Reaction/Pseudoprogression
TLS	Tumor lysis syndrome

Abbreviation	Definition
ULN	Upper limit of normal
VGPRULN	Very good partial responseUpper limit of normal
WHO	World Health Organization
XRT	Radiation Therapy
yoWHO	Years oldWorld Health Organization

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Treatment of Relapsed or Refractory Lymphoid Malignancies

Malignancies that arise from lymphocytes include non-Hodgkin's lymphomas (NHL), acute lymphoblastic leukemia (ALL), and chronic lymphocytic leukemia (CLL). Based on the National Cancer Institute Surveillance, Epidemiology and End Results Program, there will be an estimated 81,560 new cases of NHL, 21,500 new cases of CLL, and 5,690 new cases of ALL in 2021 representing 4.3%, 1.1%, and 0.3% of all new cancer cases, respectively. Initial treatment for a lymphoid malignancy is based upon the risk for relapse, which depends upon the type of cell, stage of the disease, and the presence or absence of biomarkers or genetic mutations. In addition, response to initial therapy may determine the overall course of initial therapy. With current therapies, long-term disease-free survival may be achieved for many patients; however, relapsed or refractory (R/R) lymphomas and leukemias continue to pose a challenge to oncologists as patients with R/R lymphomas and leukemias generally have a very poor prognosis and curative treatment remains an unmet need. NCI estimated 20,720 deaths from NHL in 2021 (3.4% of all cancers), 4,320 from CLL (0.7%), and 1,580 from ALL (0.3%).

Other immunomodulatory drugs show little activity against R/R NHL either as single agents or combination therapy. Nivolumab single agent had ORR of 3-10% and median OS of 5.8 and 12.2 months (autoHSCT-ineligible and auto-HSCT-failed cohorts) (12), while Ipilimumab single agent had 11% ORR (13) in R/R NHL. Combination therapy yielded ORR between 9-22%, did not provide a significant therapeutic benefit (14), and 29% had treatment-related grade 3-4 AEs.

1.1.1 Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of aggressive NHL. Prognosis for patients with R/R DLBCL with salvage chemotherapy alone is poor (15). Commonly accepted salvage regimens include rituximab, gemcitabine, dexamethasone, and cisplatin; rituximab, ifosfamide, carboplatin, and etoposide (15) (16) (17) (18) (19) (20); rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) (15) (21); and rituximab, etoposide, methylprednisolone (MPS), cytarabine, and cisplatin (R-ESHAP). Approximately 50% of patients will achieve sufficient disease response and thus will be eligible for autologous stem cell transplant (ASCT), which offers the best chance for curative therapy with a 4-year survival rate of about 60% (22).

Patients with persistent disease after salvage chemotherapy and therefore not eligible for ASCT, or patients ineligible for ASCT due to co-morbidities, or those with relapse after ASCT, have a particularly poor prognosis (23). A retrospective study (SCHOLAR-1) showed that subsequent chemotherapy resulted in an objective response in only 26% and complete response (CR) in 7%, with the median overall survival being 6.3 months (24).

More recent biologic therapies may offer patients with R/R NHL improved survival. Two CD19-directed chimeric antigen receptor T-cell (CAR T) therapies, YESCARTA™ (axicabtagene ciloleucel) (25) (25) and KYMRIAH™ (tisangenlecleucel) (26), were approved by the Food and Drug Administration (FDA) in 2017 for treatment of R/R DLBCL after at least 2 lines of previous therapy. These approvals in the US were based on Phase 2 studies that

demonstrated high overall response rates (ORRs) and overall survival rates at 12 and 18 months. Likewise, the National Comprehensive Cancer Network (NCCN) recommends CAR T therapy for R/R DLBCL patients (27). Despite high ORR, relapse after approved cluster of differentiation (CD)19 directed CAR T therapy continues to be observed for approximately 60% of patients.

The FDA also recently approved (June 2019) POLIVY™ (polatuzumab vedotin piiq [anti-CD79b antibody drug conjugate]) (28) in combination with bendamustine and rituximab (BR) for treatment of adult patients with R/R DLBCL after at least 2 lines of previous therapy. The accelerated approval was granted following priority review based on ORRs from a randomized, open-label Phase 2 study in which patients were randomized 1:1 to either polatuzumab vedotin-piiq plus BR or BR alone for 6 cycles. The ORRs at the median follow-up of 22 months were 45% and 18%, respectively, for polatuzumab plus BR and BR alone. The CR rates were 40% versus 18% (p=0.026) for the same comparison. The FDA acknowledged a need for more effective, tolerable salvage therapies for DLBCL in their summary basis of review (29). Indeed, it is noteworthy to mention that polatuzumab vedotin was also granted a breakthrough therapy designation by the FDA as well as a Priority Medicines designation in the European Union in 2017 (30). In 2020 FDA also gave accelerated approval to tafasitamab-cxix (31), a CD19-directed cytolytic antibody indicated in combination with lenalidomide for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT) (31). For R/R DLBCL patients not eligible for transplant, Monjuvi® in combination with lenalidomide is reported to have a population adjusted 12 month OS of 62% (32), and from the package insert grade 3+ AEs are present in 49%, grade 4 in 25% and grade 5 in 6.2% of Monjuvi® treated patients.

Other combinations of chemotherapy or immunotherapies, with or without rituxamib, have been studied for treatment of R/R DLBCL. These include blinatumomab (33) (34) (currently approved for treatment of R/R CD19-positive ALL), lenolidomide (35) (36) (37) (38) (currently approved for treatment of R/R mantle cell lymphoma (MCL), bendamustine (39) (40) (41) (currently approved for treatment CLL), ibrutinib (42) (43) (currently approved for treatment of CLL, small lymphocytic leukemia (SLL), and R/R MCL), brentuximab vedotin (44) (currently approved for treatment of R/R Hodgkin lymphoma and anaplastic large cell lymphoma).

Despite occasional success with these agents, the vast majority of patients with R/R DLBCL unresponsive to or ineligible for ASCT will die from disease within 6 to 12 months after disease progression.

1.1.2 MCL

MCL can be treated but not cured. MCL is characterized by translocation (11:14) resulting in dysregulation of the cyclin D1 gene. The MCL International Prognostic Index (MIPI) is used to calculate prognosis, based on presence or absence of elevated white blood counts, high lactate dehydrogenase, older age, and/or poor performance score (45). Treatment for patients with high MIPI includes initial chemotherapy or BR, followed by ASCT for those without significant co-morbidities (46). High-risk patients with R/R disease, those ineligible for ASCT due to co-morbidities, or those with relapse after ASCT, have a particularly poor prognosis. Agents that have been approved for treatment of R/R MCL have been used alone or in combination with varying results. Several studies have shown ORRs of 75% to 90% for patients with R/R MCL treated with the combination of BR (47) (48) (49). Ibrutinib, an inhibitor of Bruton's tyrosine kinase (BTK)

received FDA approval for treatment of R/R MCL that failed initial therapy. Overall response has been reported for 60% to 70% of patients (50) (51) (52). Acalabrutinib and zanabrutinib are second generation BTK inhibitors with similar activity as ibrutinib, both recently approved by the FDA under accelerated approval (53) (54).

Bortezomib, a proteasome inhibitor, has shown response rates of 30% to 50% in patients with R/R MCL, and has received FDA approval for treatment of MCL (55) (56) (57) (58) (59) (60). Lenalidomide also has been approved by the FDA for the treatment of patients with MCL whose disease has relapsed or progressed after 2 prior therapies, including bortezomib and lenalidomide has been reported to yield response rates of approximately 30% (61) (62) (63) (64) (65) (66). Multiple other combinations of chemotherapy, as well as CD20-directed CAR T therapy and allogeneic stem cell transplant have been explored for treatment of patients with R/R MCL.

For MCL patients who fail covalent BTK inhibitors, prognosis is dismal with median OS of 1.9 months without additional therapy, and 5.8 to 8.2 months with additional therapy (67) (68) (69).

1.1.3 Burkitt Lymphoma

Burkitt lymphoma is an aggressive B-cell malignancy requiring intensive chemotherapy using combinations of lympholytic agents in the first-line setting. Examples of standard of care treatment regimens in the US per NCCN Guidelines (27) include (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate), and (ifosfamide, cytarabine, etoposide) as an alternating regimen for medically fit patients, or dose adjusted (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin [EPOCH]) plus rituximab for those at lower risk and those older or less fit. These therapies have been shown to produce 2-year survival rates of at least 70% (70) (71). In contrast, relapsed disease has a very poor prognosis; there are no reported therapies shown to improve survival (72).

1.1.4 ALL

While current risk-adapted chemotherapy regimens cure most pediatric patients with ALL, there remains a subset of patients with high-risk disease and poor prognosis. Patients at high risk for relapse can be identified based upon a number of biologic risk factors, most importantly, unfavorable genetic mutations or persistent disease after induction (73). Adult patients have a worse prognosis than pediatric patients, other than the subset of patients with congenital ALL (diagnosed within the first month of life), when treated with conventional chemotherapy (74) (75). Treatment of children and most adults relies on a risk adapted approach (76), with more intense chemotherapy given to higher-risk patients. Tyrosine-kinase inhibitor therapy is now included for patients with Philadelphia chromosome-positive ALL. Patients with very high-risk features at diagnosis, or those with minimal residual disease after initial chemotherapy, should be considered for allogeneic stem cell transplant in first remission. The prognosis after relapse depends upon the time of relapse and response to re-induction therapy. Children who relapse within 2 years of diagnosis, those with persistent disease after re-induction therapy, as well as most adults, are considered to have poor prognosis. In most instances of relapsed ALL, the goal of salvage therapy is to achieve a second remission followed by allogeneic hematopoietic cell transplant (HCT) (77). Approximately 30% of adults with R/R ALL will achieve a CR to salvage chemotherapy regimens (78) (79) (80) (81) (82). Recent advances in the development of immunotherapies now offer a potentially higher chance of achieving second remission for B lymphoblastic ALL.

These new therapies include antibody drug conjugates (BESPONSA® [inotuzumab ozogamicin]) (83), bi-specific T-cell engagers (BLINCYTO® [blinatumomab]) (84) and CD19-directed CAR T-cell immunotherapies (KYMRIAH [tisagenlecleucel]; YESCARTA [axicabtagene ciloleucel]) (25) (26) (85) (86) (87) (88). Data from CD19 CAR T are the most mature with CR rates of 90% at different institutions and 12 month event-free survival rates approaching approximately 50% (88). For patients with a suitable allogeneic donor, the primary goal with these approaches is to attain remission and bridge to allogeneic HCT. Patients who relapse after allogeneic HCT or after CD19-directed CAR T-cell therapy have a very poor prognosis, with up to 19% survival at 2 years (89) (90) (91).

Patients with R/R precursor T cell acute lymphoblastic leukemia/lymphoma (T-ALL) have much fewer options and very poor prognosis, with <10% 5-year survival. As with B lymphoblastic ALL, re-induction followed by allogenic stem cell transplant is the best option for patients with relapsed T-ALL. There is no agreed standard re-induction approach. Approximately 30% of patients will respond to regimens that include fludarabine, cytarabine, and idarubicin. Nelarabine is licensed for treatment of R/R T-ALL, with response rates around 45% when used alone or in combination with cyclophosphamide (92) (93) (94). Patients with disease unresponsive to nelarabine have few options other than investigational therapies.

1.1.5 CLL

Initial treatment of CLL comprises chemotherapy agents active against lymphocytes, such as fludarabine, bendamustine, and chlorambucil, along with anti-CD20 monoclonal antibodies, such as rituximab. Relapsed CLL is defined as progression of disease 6 or more months after CR or partial response (PR) and refractory disease is defined as failure to achieve a CR or PR within 6 months of therapy (95). Relapsed CLL can be further defined as ‘early relapse’ if progression occurs within 2 to 3 years of initial therapy. Treatment of early relapse generally requires B-lymphocyte-targeted therapies rather than chemotherapy. Ibrutinib has received FDA approval for treatment of R/R CLL (52). When used as a single agent or in combination with other agents, ORRs of 80% to 90% have been reported (96) (97) (98). Calabrutinib, a selective BTK inhibitor, also has been recently approved for treatment of R/R CLL (53).

Venetoclax is an inhibitor of B-cell lymphoma 2 which has also been approved by the FDA for the treatment of R/R CLL (99). Multiple studies have demonstrated ORRs of 60% to 70% with venetoclax given alone or in combination with rituximab (100) (101) (102) (103). Idelalisib is a phosphoinositide 3'-kinase delta inhibitor approved for treatment of R/R CLL in combination with rituximab (104). The efficacy of idelalisib was established in several Phase 3 randomized clinical trials that found ORRs of 70% to 85% (105) (106) (107).

Duvelisib was also recently approved by the FDA for R/R CLL patients who have received at least 2 prior therapies (108). Younger and medically fit patients with relapsed CLL are candidates for autologous or allogeneic HCT, where complete remission has been observed in about 50% of patients with the potential to induce long-term remission (109) (110) (111). Relapse after HCT has a very poor prognosis (112). Corticosteroids are not typically included in modern targeted-therapy regimens for R/R CLL; however, historical experience demonstrates an observed disease response to prednisone or high-dose dexamethasone (113) (114) (115).

Similar to MCL patients, CLL patients who fail the BTK inhibitor Ibrutinib have dismal post-ibrutinib survival with median OS of only 3.1 months (116).

1.1.6 T cell lymphomas/PTCL (including PTCL-NOS, PTCL-TFH, AITCL, CTCL, NKTCL, ATLL, ALCL, EATCL)

T-cell lymphomas are a heterogenous group of uncommon non-Hodgkin's lymphomas (NHLs) which account for approximately 10–15% of all NHLs. The prevalence varies geographically, with the highest incidence in Asia, particularly of natural killer (NK)/T-cell lymphoma and adult T-cell leukemia lymphoma (ATLL) due to variations in exposure and susceptibility to HTLV-1 and EBV. Subtypes which arose from mature T-cells were classified as peripheral T-cell lymphomas (PTCLs) and could be subdivided into clinically indolent or aggressive lymphomas. Historically, these variations in clinical behavior rather than a pathologic basis determined the therapeutic approach. Treatment protocols were chosen to treat aggressive PTCLs owing to their success in treating aggressive B-cell lymphomas; however, outcomes were not as successful.
It is amongst the aggressive group of PTCLs that the most recent WHO classification has incorporated significant advances in the knowledge of the biological heterogeneity of PTCLs to better classify and describe new entities which may help to explain the clinical heterogeneity of these aggressive lymphomas. The relapsed and refractory (RR) setting remains an important population with aggressive disease in which to explore novel targeted approaches prior to moving them into the frontline setting and addressing an unmet need in NHL treatment (117).

Pralatrexate was approved in 2009 for patients with R/R PTCL with median number of prior therapies of 3; 73% of patients had grade 3 or 4 AEs and 1.2% of patients had grade 5 AE (death), PFS and OS are not included in the PI (118). PFS and OS of R/R PTCL (Chinese) with median 2 prior lines of therapy are reported to be 4.8 and 18 months, with 68% experiencing Grade 3 or 4 AEs (119), and PFS and OS of R/R PTCL (Korean) with 45% having only 1-2 prior lines are reported to be 1.8 and 7.7 months, with greater than 34% having Grade 3 or 4 AEs (120). This report summarized real world R/R PTCL response to pralatrexate with PFS of 1.8 (Korean), 4.8 (Chinese), 5.0 (Japanese) and 3.5 (PROPEL Ph II trial) months.

Belinostat, an HDAC inhibitor, was approved in 2014 for patients with a median of 2 prior lines of therapy. ORR was 25.8% and median DOR was 8.4 months. PFS and OS are not given in the PI (121). Published PFS and OS from the BELIEF Ph II trial that led to accelerated approval for belinostat for R/R PTCL were 1.6 and 7.9 months, with about 35% having SAEs of grade 3 or 4 and 1 treatment related death due to liver failure (122).
Romidepsin, an HDAC inhibitor, was approved in 2009 for R/R PTCL who had failed 1 prior line, 35-85% experienced grade 3-4 AEs in four clinical trials. Patients in the trials had a median of 2 prior lines of therapy, ORR was 26%. PFS and OS are not included in the package insert (123). Published median PFS was 4 months (124).

For patients with R/R PTCLwho had failed a median of 2 prior therapies, a 2021 publication described the improved PFS and OS (8 and 20.6 months) for patients treated with a combination of 5-azacytidine and romidepsin that compared favorably with historical data for PFS and OS (3 and 5.5 months) (125). However, 48% of patients still had Grade 3 or 4 AEs and these patients continue to have an unmet medical need for curative therapies with lower side-effects.

1.1.7 Summary

While promising new therapies are available for patients with R/R lymphoid malignancies, a significant proportion will continue to have resistant disease. So called "salvage therapy" for R/R-NHL patients can also consist of stronger chemotherapy but the medical fragility of patients may result in reduced dosing or courses of chemotherapy which may not adequately treat the disease. As with strong chemotherapeutic approaches, cell-based therapies also have serious toxicities, especially in medically fragile patients. Limited effective treatment options and associated side effects coupled with medical fragility associated with some patients, leaves a treatment option void for these patients, or "no-option".

For many of these disorders, the goal of salvage therapy is to achieve disease control in order to proceed to allogeneic or autologous stem cell transplant. For patients who fail to respond to salvage therapy, prognosis remains poor. A novel approach to inducing remission is needed to improve outcome and extend the lives of patients with R/R lymphoid malignancies.

1.2 Overview of AVM0703

1.2.1 AVM0703 and hypothesized immunomodulatory Mechanism of Action

AVM0703 is a patent pending high concentration (24 mg/mL) and high volume (50 mL) formulation of dexamethasone phosphate for injection containing Generally Recognized As Safe (GRAS) excipients (126), permitting administration of a very high, or supra-pharmacologic, acute one hour intravenous infusion. The formulation only contains excipients within the FDA IID List limits: Sodium Citrate (10 mg/mL); Disodium Edetate (0.5 mg/mL); Sodium sulfite, anhydrous (0.035 mg/mL). Compared to other injectable DSP products, it does not contain Benzyl alcohol (10 mg/mL, Fresenius DSP), Methylparaben (1.5 mg/mL, Mylan DSP), and Propylparaben (0.2 mg/mL, Mylan DSP), which are precluded from being used at suprapharmacologic dose due to known toxicities of the excipients (127) (128) (129) (130). Therefore, high doses, up to 21 mg/kg, of DSP from AVM0703 can be safely administered to patients unlike other presentations of DSP which are limited to doses of 6 mg/kg by endotoxin and excipient levels. Endotoxin limits cap the maximum one hour IV infusion of AVM0703 at 21 mg/kg. Additionally, glucocorticoids like methylprednisone (MP or Solu-Medrol would require 6.7 grams for 18 mg/kg DSP equivalent for a 70 kg patient) which activate the mineralocorticoid receptor (MR) cause pancreatitis and can be diabetogenic and cause life-threatening complications at doses of >2 gms (131) (132) (133) (134) (135) (136) (137) (138) (139), while AVM0703 (DSP), in contrast does not activate the MR (140) and prevents diabetes in the gold-standard NOD mouse model (see Diabetes_Report_2022 and section 1.2.3). In contrast to AVM0703, equivalent doses of methylprednisone accelerated diabetes onset in the NOD mouse model.

The Phase 1 dose-escalation has determined a RP2D of 18 mg/kg (1.26 grams over a one hour iv infusion for a 70 kg patient), however, the 21 mg/kg dose-escalation cohort remains open for enrollment. For sites participating in both Phase 1 and Phase 2, patients will be enrolled into the 21 mg/kg dose-cohort unless i) no slot is available, ii) the patient cannot logistically comply with the PK blood draw requirements, iii) the cohort has been fully enrolled, or iv) the patient is enrolled into a Phase 2 repeat dosing RP2D cohort.

Prophylactic hydrocortisone is used to successfully reduce/prevent neuropsychiatric side-effects (141) (142) (143) (144), and only 4 psychiatric side effects of insomnia have been reported; 3 grade 1 and 1 grade 2.

At supra-pharmacologic doses (>6 mg/kg) dexamethasone mobilizes endogenous bispecific gamma delta TCR+ invariant TCR+ Natural Killer T-like cells (γδ+i+ NKT) (PCT/US21/19773), via a non-glucocorticoid receptor pathway, that rapidly home to lymphoma/leukemia cells in murine models, and are directly related to tumor killing. Pre-clinical observations that led to the hypothesis of a non-GCR mechanism responsible for bi-specific γδTCR+iTCR+ NKT-like cell mobilization in response to acute suprapharmacologic >6 mg/kg HED doses include: absence of in vivo effect on pancreas, colon and bone by blinded histopathology, lack of apoptosis in vitro at concentrations equivalent to in vivo 18 mg/kg HED dosing, in vivo activity against cell lines that do not express GCR, and absence of ex vivo apoptosis on whole mouse or human blood samples. Hematology and clinical chemistries from the Phase 1 dose-escalation portion of the trial have confirmed a GCR-independent mechanism of action for AVM0703 one hour iv infusions of 6 mg/kg and higher doses.

Dexamethasone binds moderately to plasma proteins, and in general, is known to distribute rapidly into the kidneys, intestines, skin, liver, and muscle. Metabolism of dexamethasone occurs in the liver, leading to production of inactive metabolites excreted in the urine. The plasma elimination half-life of dexamethasone is approximately 1.8 to 3.5 hours, whereas the biological half-life is 36 to 54 hours (145).

1.2.2 Phase 1 dose-escalation experience with AVM0703 in R/R Non-Hodgkin's Lymphoma/Leukemia

The primary endpoint for the Phase 1 dose-escalation is the incidence of AEs and DLTs. In the Phase 1 portion for patients enrolled and dosed as of 22 Aug 2022, patients were heavily pretreated with a median of 4 prior lines, with 7 of 15 patients having failed HSCT or CarT previously. Three additional patients were enrolled in the 18 mg/kg dose-escalation cohort due to a grade 3 hyperglycemic event in a poorly controlled type II diabetic patient. No additional DLTs were identified and the SRC recommended moving to expansion cohorts at the 18 mg/kg dose level, while leaving the 21 mg/kg dose-escalation cohort open for enrollment. For sites participating in Phase 1, patients will be enrolled into the 21 mg/kg cohort unless i) there is not a slot open, ii) patient cannot logistically provide PK samples, iii) the cohort has been fully enrolled, or iv) the patient is enrolled into a Phase 2 repeat dosing RP2D cohort.

Table 1 Baseline Demographics of all enrolled patients and by dose cohort as of 22 August 2022

	All Cohorts	6 mg/kg	9 mg/kg	12 mg/kg	18 mg/kg
Age (mean)	62.3	63.7	69.3	64.3	57.2
range	39-85	55-69	64-80	60-67	39-85
Gender					
male	10	2	3	2	3
female	5	1	0	1	3
Race					
Asian	2		1		1

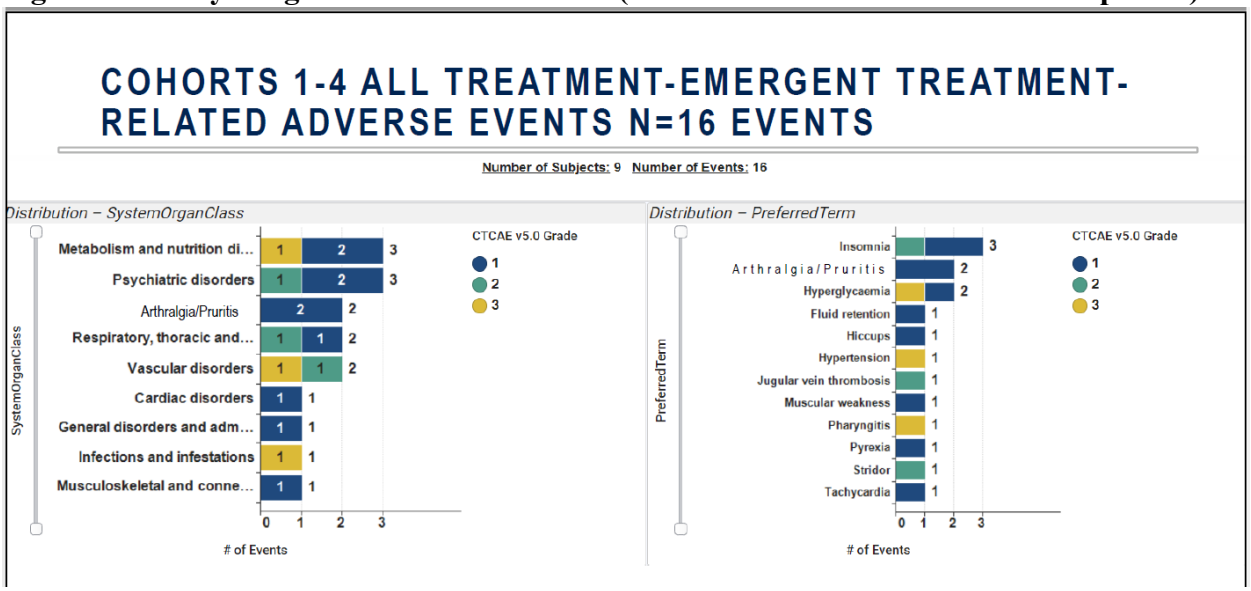
Black	1	1			
Hispanic	6	2	1		3
White	6	0	1	3	2
Prior Lines (mean)	4.3	6.3	5.3	2	4
range	1-9	5-8	2-9	1-3	2-8
Failed HSCT					
one	2	1		1	
two	1	1			
Failed CarT	3		1	1	1
Failed both HSCT and CarT	1				1
Stage at AVM Dosing	1 ND		1 ND		
I	3	1			2
II	2	1			1
III	2			1	1
IV	7	1	2	2	2
ECOG (Karnovsky PS)					
0 (PS 90-100)	8	3	2	1	2
1 (PS 70-80)	6		1	2	3
2 (PS 50-60)					
3 (PS 30-40)	1				1
BM positive	2				2
CSF positive	1		1		
PB positive	1			1	
Spleen positive	1				1
Extranodal	6	2			4
Bulky disease	2		1	1	
NHL subtype					
DLBCL	6		1	1	4
Non-GCB	1		1		
GCB					
with CNS	3				3
Transformed indolent	1			1	
T-ALL	1	1			
B-ALL	2	1			1
CNS B-ALL	1		1		
MCL	2		1	1	
blastoid	1		1		
PTCL	3	1		1	1
PTCL nos	2	1			1
AITCL	1			1	
HbA1c (mean %)	5.3	5.3	4.5	5.4	5.9
range	4.5 – 6.9	5.3	4.5	5.2 – 5.6	5.3 – 6.9
ANC (mean k/uL)	5.2	3.7	8.2	4.7	4.2
range	0.2 – 17.3	1.4 – 6.2	1.5 – 17.3	2.5 – 6.7	0.2 – 6.5

Platelets (mean k/uL)	179	211	112	256	138
range	37-328	179-243	37-194	163-328	59-173

AVM0703 has been generally well tolerated, with only 16 study drug-related adverse events during the DLT 7 day assessment period for the 6-18 mg/kg cohorts: 10 grade 1, 3 grade 2, and 3 grade 3. Physiologic hydrocortisone is required prophylactically to reduce/prevent GC neuropsychiatric side-effects (142), and only 4 neuropsychiatric side-effects of insomnia have been reported, three grade 1 and one grade 2. Additionally, no elevations of alkaline phosphatase have been observed, even with repeat dosing, suggesting risk of osteonecrosis is not elevated with AVM0703. The limitation of side-effects to grades 1-3 is consistent with reports that acute AEs are not increased, and in fact may be reduced after an acute high-dose of GC compared to chronic low doses (146).

For the 15 patients in the 6, 9, 12, and 18 mg/kg cohorts, median OS has not been reached (11 of 15 patients have ongoing survival) and median follow up is 7 months as of 30 Sep 2022. Patients ranged in age from 39 to 85 and 10 were male, 5 were female, 6 were Hispanic, 1 was black, 2 were Asian, and 6 were white.

Figure 1 Study drug related adverse events (informal unlocked data as of 16 Sep 2022)

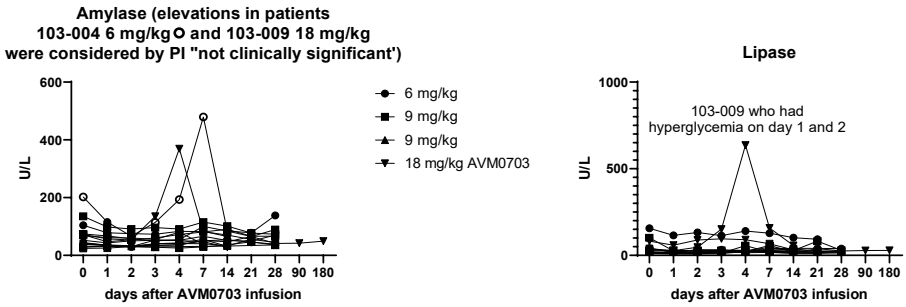


Notably, a compassionate use patient who did not qualify for the AVM0703-001 clinical trial because of history of significant bi-polar disorder was treated at 18 mg/kg under CUP with 6 monthly AVM0703 infusions as of 31 Oct 2022 with very good ongoing and deepening partial response and no neuropsychiatric side-effects (section 1.2.2).

Glucose: Two patients have had glucose elevations above 250 mg/dl.

For patient 103-007 dosed at 12 mg/kg, blood glucose levels rose to 299 mg/dl approximately 8-9 hours after the infusion that resolved without intervention to 108 mg/dl within 24 hours. Patient 103-007 has a history of ongoing pancreatitis since 2014. For patient 103-009 dosed at 18 mg/kg, blood glucose rose to 462 mg/dl on day 1 and 481 mg/dl on day 2 and was resolved after insulin administration down to 131 mg/dl on day 3. This patient has a history of poorly controlled type II diabetes mellitus and had HbA1c of 6.9% at screening on 03 Jun 2022. The patient was dosed on 28 June 2022. Patient 103-009 also had transient elevations in amylase and lipase on day 4 after AVM0703 infusion that were considered 'not clinically significant.'

Figure 2 Amylase and lipase levels

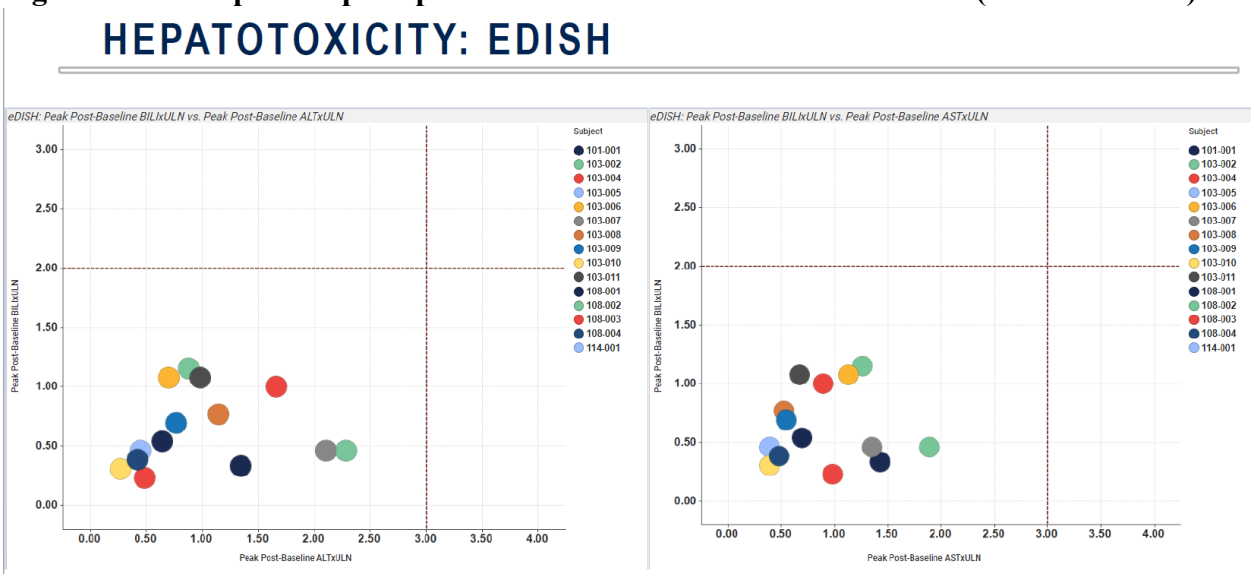


In the other patients, slight glucose elevations that stayed below 250 mg/dL, were observed that resolved without intervention within 24-48 hours (Figure 5). There have been no clinically significant elevations of HbA1c in any patient, except for patient 103-009, an uncontrolled type II diabetic, who had baseline HbA1c of 6.9% that rose to 8.1% on day 7 after AVM0703 dosing.

Five SAEs have been reported (as of 16 Sep 2022): Two patients had symptoms of suspected tumor flare/pseudoprogression (discussed later) requiring hospitalization; a grade 3 pharyngitis (108-003 AITCL patient with neck LN involvement) and a grade 3 headache (103-008 DLBCL with CNS corpus callosum tumor). One patient had a grade 1 fever and was hospitalized although fever was not elevated upon admittance (108-003). As discussed above, patient 103-009 who also has type II diabetes, had glucose elevations on day 1 and day 2 after 18 mg/kg AVM0703 infusion that resolved to 131 mg/dl on day 3 after insulin administration. Patient 108-002 was hospitalized in January 2022, 4.5 months after 18 mg/kg AVM0703, for a COVID-19 infection unrelated to study drug.

There have been no clinically significant ECG abnormalities during the one hour infusion or the dose-escalation 4 hour post-infusion monitoring window. EGFR, creatinine, BUN, ALT and AST have not been impacted except for one 12 mg/kg patient who experienced a clinically significant moderate elevation in ALT on day 14 after AVM0703 infusion which resolved without intervention. Evaluating liver effects by Hy's law using EDISH plots does not indicate any instance of liver toxicity at any dose, as of 16 Sep 2022. All values fall in the lower left quadrant demonstrating absence of liver injury.

Figure 3 EDISH plots of peak post-infusion ALT and AST versus BUN (ratios of ULNs)



1.2.3 Risk of Osteonecrosis: No Alkaline Phosphatase Increases after AVM0703

Glucocorticoids have also been associated with ON in up to 45% of treated patients. In pediatric and adolescent ALL, Mattano et. al. demonstrated that risk of ON is related to duration of DEX dosing, rather than cumulative dose (147) . In this study, patients dosed on a continuous DEX schedule (10 mg/m^2/day on Days 0 to 20) displayed significantly higher ON rates than those randomized to receive two delayed intensification phases with an alternate-week DEX dosing

schedule (10 mg/m^2/day on Days 0 to 6 and Days 14 to 20) (17.0 ± 2.9% [64/403] versus 8.7 ±·1.2% [34/420], p = 0.0005). This study observation was despite the fact that patients given alternate-week dosing received more DEX overall (280 versus 210 mg/m^2). AVM has measured clinical chemistries after acute high dose DP at HED DP doses up to 21.67 mg/kg and has not observed increases in alkaline phosphatase in either male nor female mice (AVM_LYDEP_11 and AVM_LYDEP_15).

There have been no indications of alkaline phosphatase increases from the patients enrolled in the dose-escalation phase of the clinical trial, even with repeat dosing.

Figure 4 Alkaline Phosphatase levels from patients enrolled in the dose-escalation cohorts

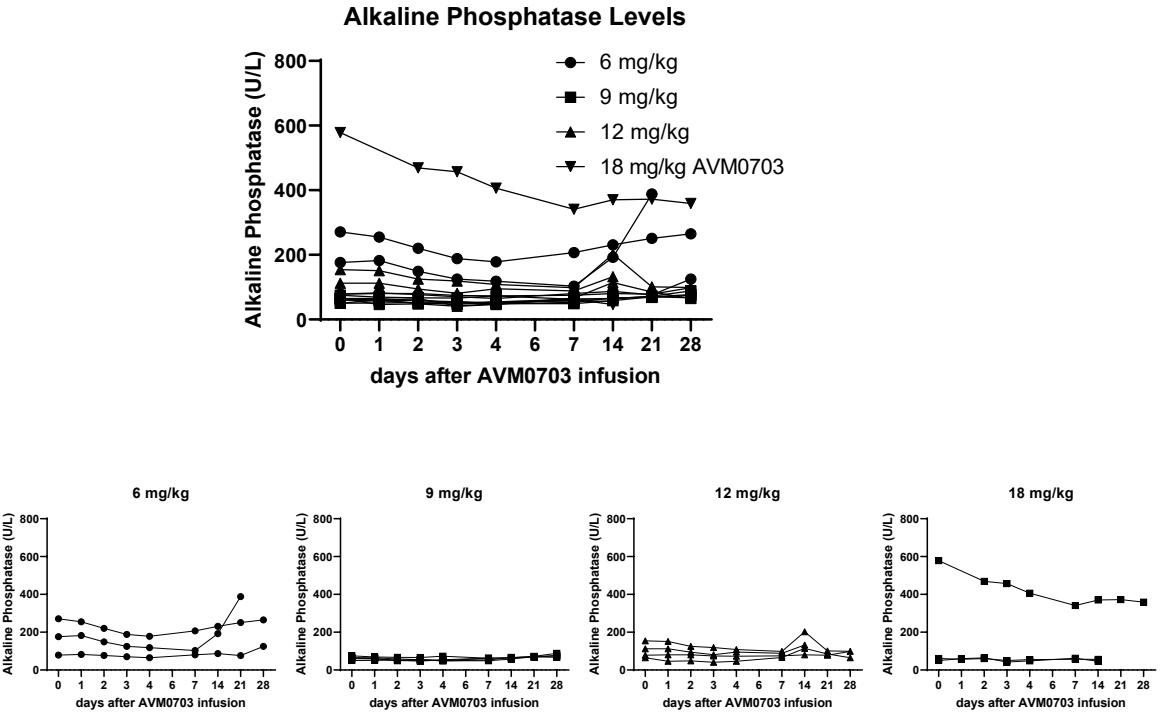
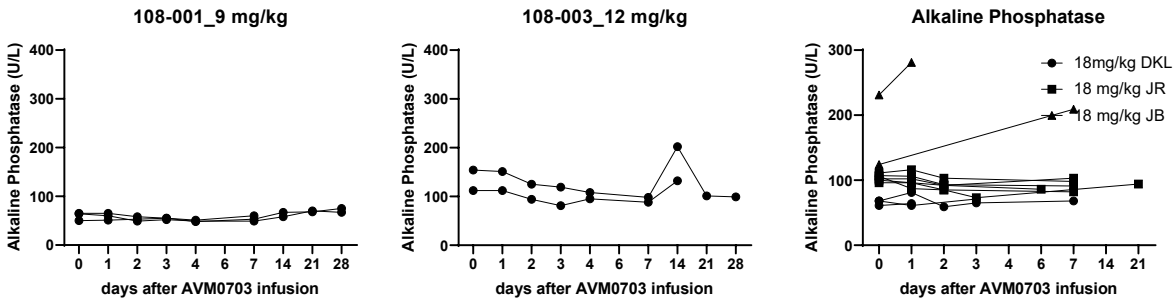


Figure 5 Alkaline Phosphatase levels for patients repeat dosed, including Expanded Access patients



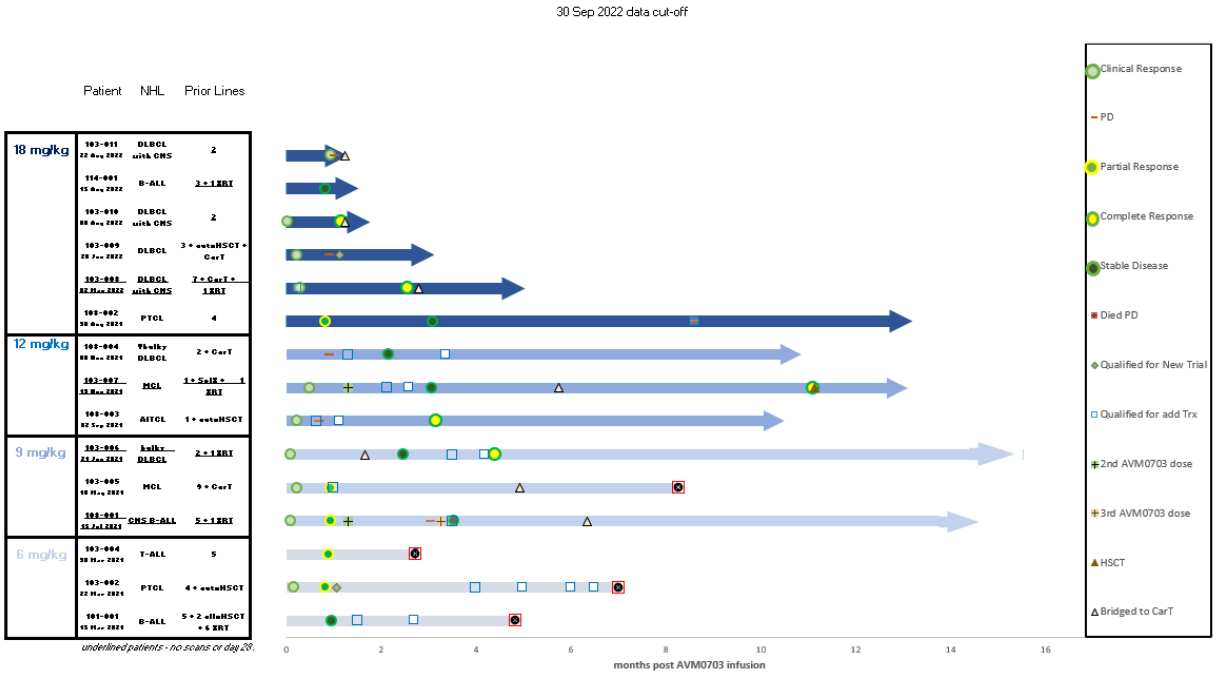
Some patients have received repeat doses at ~28-day intervals without safety concerns, and notably, one Expanded Access compassionate use (CUP) prostate cancer patient received 13 doses (7 at 18 mg/kg) over a 14-month period, without safety concerns.

All patients in the 18 mg/kg dose-escalation cohort were dosed only once with AVM0703 and achieved significant clinical benefits. At the 18 mg/kg RP2D there have been; 1 durable 8.5 month PR (PTCL NOS patient 108-002; 1 B-ALL patient (114-001) with very good PR by local read; significant reduction of symptom causing CNS tumors in 2 patients (DLBCL patient 103-010 with a CR who also had reversal of grade 4 cytopenia, and DLBCL patient 103-011 who had overall PD despite a very good PR of the symptom causing CNS tumor); two week mass stabilization and pain reduction allowing DLBCL patient 103-009 to stabilize his type II diabetes and qualify for another clinical trial; and a DLBCL with CNS involvement only, patient 103-008, who obtained complete remission of corpus callosum lesion by 2.5 month PET/CT with ibrutinib added on day 7 after AVM0703 infusion.

Seven of 9 patients had documented clinical responses at the 6, 9 and 12 mg/kg doses; PTCL patient 103-002 dosed at 6 mg/kg had PI reported reduction in visible lymph node and a PR by day 28 PET/CT scan; T-ALL patient 103-004 dosed at 6 mg/kg had a PR by day 28 PET/CT scan; B-ALL with only CNS involvement patient 108-001 dosed at 9 mg/kg had a PR as determined by PI with vision restored within 72 hours and platelets increased from 39 to 90 k/uL by day 28 after his first AVM0703 infusion. This patient received 3 repeat 9 mg/kg AVM0703 infusions and platelets were above 100 k/uL from day 21 after the second AVM0703 infusion and ongoing; MCL patient 103-005 dosed at 9 mg/kg had HgB increase and a PR by day 28 PET/CT; DLBCL patient 103-006 dosed at 9 mg/kg had two week greater than 50% reduction in LDH from 1400 down to 451 nadir; AITCL patient 108-003 dosed at 12 mg/kg had pharyngitis believed to be a tumor flare reaction associated temporally with palpably softer and smaller neck lymph nodes; MCL patient 103-007 dosed at 12 mg/kg had lymphocytosis reversed from 10.2 to 2.4 k/uL by day 7.

The Swimmer Plot summarizes the diagnosis, prior lines, overall survival after AVM0703 infusion (from the date of first infusion for the two patients who had repeat infusions), response from blinded central lab reads of PET/CT scans according to Lugano criteria (except for patient 103-008 who has had a local read only as of 06 Dec 2022), objective clinical responses from patient symptoms and laboratory assessments, and any additional anti-cancer therapy they received after AVM0703.

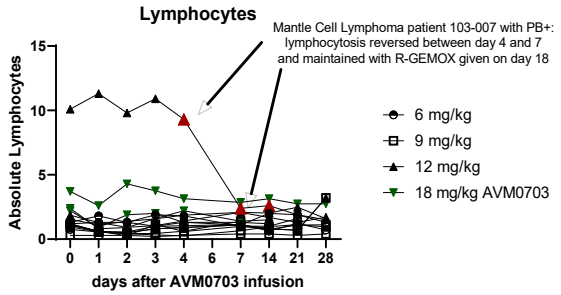
Figure 6 Swimmer plot from PhI dose escalation as of 30 Sep 2022



Hematology and clinical chemistries from the Phase 1 dose-escalation portion of the clinical trial support the non-GCR nature of the mechanism of action of suprapharmacologic AVM0703. In contrast to lower dexamethasone doses that cause lymphopenia (148) (149) and thrombocytopenia (61) (150) in human patients, AVM0703 did not reduce platelets (Figure 6) or non-cancerous (normal) circulating lymphocytes (Figure 5) at any dose between 6-18 mg/kg, supporting a unique mechanism of action, independent of canonical GR alpha activation, for doses greater than 6 mg/kg. Also included in the figure are absolute lymphocyte counts after retreatment. One patient was retreated twice at 9 mg/kg and 1 patient was retreated once at 12 mg/kg. CBCs and clinical chemistries showed no trend to any changes upon retreatment.

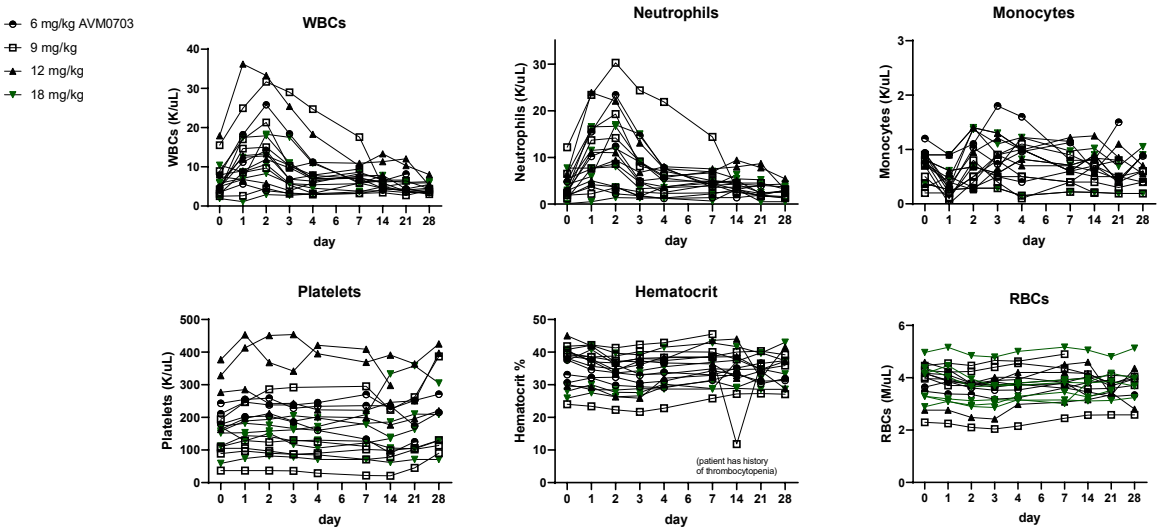
One Mantle Cell Lymphoma Patient had peripheral blood involvement and the lymphocytosis was reduced to normal lymphocyte levels between day 4 and 7 after a 12 mg/kg AVM0703 infusion, suggesting that AVM0703 immune activation preferentially recognizes cancerous cells and spares normal blood cells, including lymphocytes, monocytes, platelets and RBCs (Figure 6). Hematocrit and hemoglobin were also spared, and hemoglobin was actually clinically significantly increased after 9 mg/kg AVM0703 infusion in a R/R MCL patient.

Figure 7 Absolute lymphocyte counts (ALC) demonstrating AVM0703 reduced lymphocytes only in one patient who had baseline lymphocytosis.



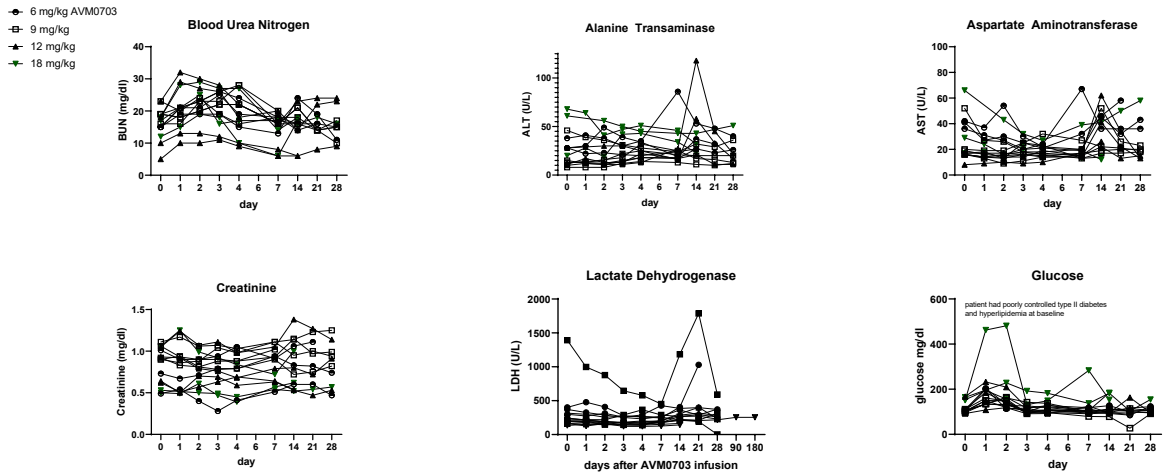
Absence of lymphocytopenia in response to AVM0703 supports a glucocorticoid receptor (GCR) independent mechanism of action (MOA) as discussed in section 1.2.4.

Figure 8 Monocytes, platelets, hematocrit and RBCs were also not reduced after AVM0703 dosing.



Absence of effect on platelets also supports a GCR-independent MOA. Leukocytosis was also observed, evident for 7-14 days after dosing.

Figure 9 Clinical Chemistries from PhI Dose-Escalation



Clinical chemistries from the Phase 1 dose-escalation were generally unremarkable and not clinically significant. Glucose levels demonstrate a mild glucose elevation, below 250 mg/dl for the pre-specified timed blood draws, that resolved without intervention, except for one patient with poorly controlled type II diabetes and hyperlipidemia.

Preliminary evidence also suggests that AVM0703 suprapharmacologic dosing improves immune status, reducing markers of immune exhaustion such as TIM3 and transforming previously unqualified patients into candidates to manufacture autologous CarT therapies from. Four patients dosed at the 9 mg/kg (2), 12 mg/kg (1), and 18 mg/kg (1) cohorts, who were not candidates to manufacture autologous CarT therapies at the time of enrollment in the AVM0703-001 trial, subsequently qualified for autologous CarT therapy after AVM0703 treatment.

Preliminary PK

Dexamethasone concentrations after AVM0703 infusions were determined at MBL Labs and demonstrated linear Cmax compared to published reports of Cmax for lower dexamethasone IV infusions. While nonclinical and clinical data supports AVM's hypothesized GCR-independent MOA, the Cmax values are linear compared to lower dose IV infusions, and thus acute suprapharmacologic dosing does not appear to have altered the pharmacokinetics of dexamethasone IV infusion.

ICAM3 was identified as a potential low affinity receptor for dexamethasone suprapharmacologic concentrations through literature and Human Proteome database searching and confirmed by molecular docking studies conducted by two independent outside consultants. ICAM3 has been reported to be shed after dexamethasone binding (151), and we hypothesize that this binding is covalent at suprapharmacologic doses, preventing AVM0703 from binding to GCRs and explaining why GCR activation is not observed as AVM0703 is 'apparently' cleared from the blood from the PK analysis. AVM0703 covalently bound to shed ICAM3 would be found in the plasma/serum fraction of blood and bound AVM0703 would be released (and thus detectable) from the ICAM3 during LC-MS/MS analysis performed by MBL Labs, but prevented from binding to and activating GCRs. Alternatively, AVM0703's structure could be modified after ICAM3 binding such that it can no longer bind GCRs even if free in the blood. AVM is

collaborating with Cold Spring Harbor Labs to define the MOA responsible for GCR-independent activity.

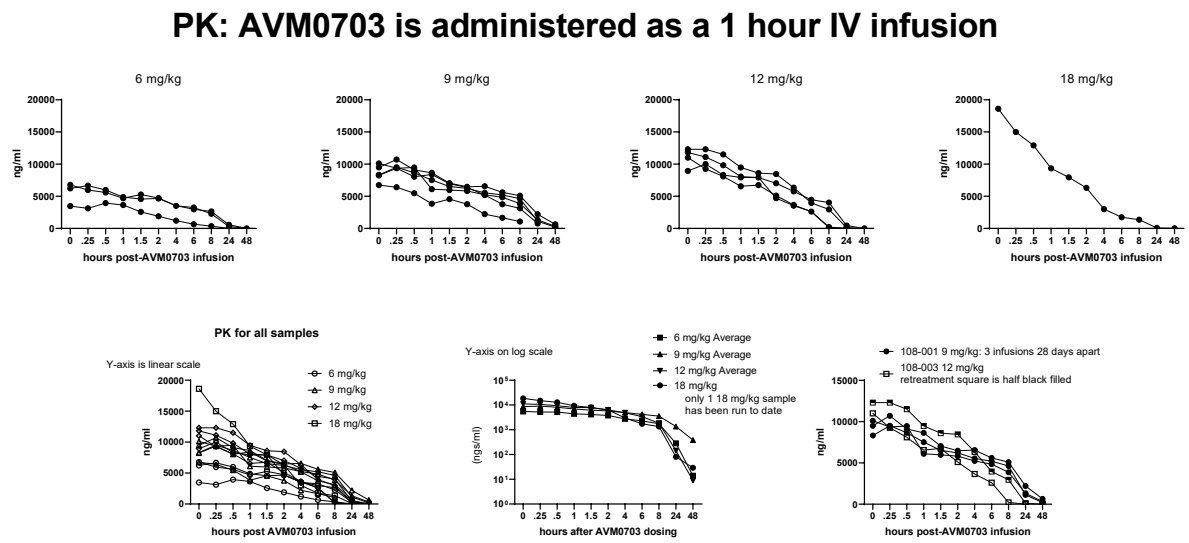
The 9 mg/kg AVM0703 PK clearance appears delayed due to slower clearance by a CNS only B-ALL patient 108-001 who received 3 doses and had an impressive clinical response of vision restoration within 72 hours after the first 9 mg/kg AVM0703 infusion, but slower clearance at the 24 and 48 hour time points after all 3 infusions. There is no trend towards altered PK curves for the two patients who were retreated (bottom right Figure 8). The Cmax for the 6, 12 and 18 mg/kg cohorts was at time 0, while the Cmax for the 9 mg/kg cohort was at 15 minutes. The estimated half-life for each individual patient ranged from 1-8 hours, with an average of about 3.8 hours for 13 infusions. While only 1 patient dosed at 18 mg/kg has had PK analysis, the half-life for this patient was about 1 hour, with estimated half-life at the 6, 9 and 12 mg/kg doses was between 2 and 4 hours for all patients except for patient 108-001 who had 3 infusions and estimated half-lives of 6, 6, and 8 hours.

AUC values and Cmax calculated using Prism GraphPad version 9.0 are listed in the table below.

Table 2 AUC values and Cmax for 13 infusions during the dose-escalation phase

	6 mg/kg	9 mg/kg	12 mg/kg	18 mg/kg
N	3	5	4	1
AUC (mg/L)	44.639	102.251	59.331	51.060
AUC 95% CI	22.841 – 66.437	70.674 – 133.827	27.249 – 91.413	
Cmax (mg/L)	5.49	9.064	11.01	18.6
Cmax STDEV	1.762	1.587	1.480	

Figure 10 AVM0703 Pharmacokinetics measured by LC-MS/MS



1.2.4 Compassionate Use experience with AVM0703 in R/R Non-Hodgkin's Lymphoma/Leukemia and solid tumors :

AVM Biotechnology supports an Expanded Access-Single Patient IND CUP program in compliance with FDA Guidance. Patients dosed include R/R NHL not eligible for AVM0703-001 clinical trial, late-stage glioblastoma, prostate cancer, breast cancer, colon cancer, sarcoma and squamous cell CNS carcinoma.

Of relevance to the AVM0703-001 trial for R/R NHL, an Anaplastic T-cell NHL patient who had previously failed 6 cycles of R-CHOP and romidepsin, had a VGPR to a single 18 mg/kg AVM0703 infusion with complete resolution of 30 Mar 2022 PET/CT documented head and neck, chest, abdomen and pelvis hypermetabolic lymphadenopathy by day 22 post AVM0703 infusion PET/CT, and overall decrease in metastatic osseous hypermetabolic lesions. This patient received additional 18 mg/kg AVM0703 infusions on 15 June 2022, 15 July 2022, 12 Aug 2022 and 12 Sep 2022 with no reports of adverse events of any concern. PET/CT taken on 13 Sep 2022 demonstrated continued resolution of all lymphadenopathy and stable if not further reduced osseous hypermetabolic activity.

Another CUP patient of relevance to the enrolling clinical trial was a critically ill, hospitalized DLBCL patient with CNS involvement facing fatal PD within days on 25 Mar 2022 who had previously failed RCHOP, MTX, DHAP, Ibrutinib, and did not meet clinical trial AVM0703-001 inclusion criteria. The patient was dosed with RP2D 18 mg/kg AVM0703 on 28 March 2022. Side-effects included mild hypothermia that resolved and slight pruritis reported. The patient was reported to be 'stable' with continued hospitalization on 06 Apr 2022. However, on 06 May 2022 the patient had CMV-reactivation precluding any additional AVM0703 infusions or any other anti-cancer therapy and experienced PD; this patient, who was critically ill and imminently terminal per MD submission to FDA when they were dosed at RP2D 18 mg/kg AVM0703 on 28 Mar 2022 lived until 20 May 2022.

Another CUP patient of relevance to the clinical trial was first dosed at 6 mg/kg in the dose-escalation phase of the trial. This B-ALL patient who had only multiple extramedullary masses at baseline had an explosive peripheral blood lymphocytosis after 6 mg/kg AVM0703 with 70-80% blasts, consistent with other reports of tumor flare/pseudoprogression, and subsequent stable disease after early progression, however, patient was taken off-study due to apparent progression. However, day 28 PET/CT read ~12 months later showed the patient had SD at the time of early study termination. The patient was dosed at 18 mg/kg 6 weeks after the 6 mg/kg dose but did not respond to 18 mg/kg nor to subsequent vincristine and passed away 4.8 months after the first 6 mg/kg AVM0703 dose. This patient had previously failed 5 prior lines, 6 XRT and 2 alloHSCT.

Activity against prostate cancer, squamous cell carcinoma and breast cancer, in addition to NHL, also supports a non-GCR mechanism of action and is consistent with the known nature of gamma delta TCR expressing T cells to recognize phosphoantigens produced by most if not all cancer cells. The gamma delta TCR+ nature of the bispecific immune cells induced and mobilized by AVM0703 suprapharmacologic DP dosed from 6-18 mg/kg over a one hour infusion (section 2.1.3) is consistent with observed anti-cancer activity against a range of cancer types. Non-NHL expanded access patients have received repeat 18 mg/kg doses (an RP2D) in 28 day intervals without accumulating safety concerns: two patients have received 7 repeat doses, two patients have received four repeat doses, two patients have received three repeat doses, and two patients have received two repeat doses as of 30 Nov 2022.

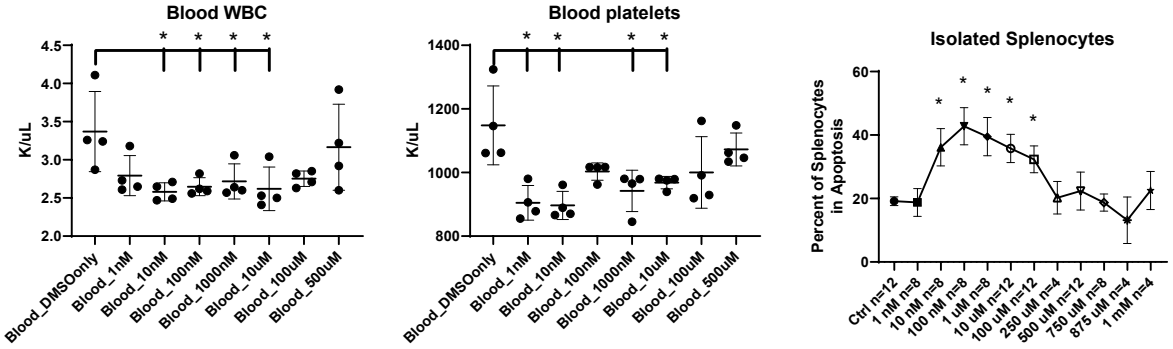
Clinical experience with acute high-dose dexamethasone (AVM0703) is consistent with nonclinical evidence that supra-pharmacologic doses act independently of GRs to mobilize patient's immune cells, in particular a bi-specific gamma delta TCR+ invariant TCR+ Natural Killer T-like cell discussed in the next section.

1.2.5 Nonclinical and clinical data for AVM0703 immunomodulatory Mechanism of Action independent of glucocorticoid receptor activation

Pre-clinical observations that led AVM to hypothesize a non-GCR mechanism responsible for bi-specific gamma delta TCR+ invariant TCR+ Natural Killer T-like cells (γδ+i+NKT)induction and mobilization in response to suprapharmacologic AVM0703 >6mg/kg HED dosing include: absence of in vivo effect on pancreas, colon and bone by blinded histopathology, and absence of ex vivo/in vitro apoptosis on whole mouse or human blood samples or mouse splenocytes, or A20 lymphoma cells at concentrations equivalent to in vivo suprapharmacologic dosing. A20 lymphoma cells do not express GRalpha but are killed by in vivo 18 mg/kg HED AVM0703 dosing.

For example, concentration-response curves show the expected apoptotic effect of dexamethasone base on isolated mouse splenocytes and whole blood at concentrations known to bind the transmembrane GCR (10 nM to 100 uM), however, a biphasic curve is observed with apoptosis decreasing as concentration is increased above 100 uM (which is an in vivo equivalent blood concentration peak from about a 2.8 mg/kg human equivalent dose (HED), as seen in Figure 9. Biphasic response curves have been well described for chemokines (152) and growth factors (153) (154), and have been shown to be a result of receptor desensitization/internalization or a new low affinity (152) but very dense receptor soaking up the factor so that it is not available to bind the higher affinity but less accessible receptors (154) (155).

Figure 11 Ex Vivo/In Vitro Dexamaethasone CRC Demonstrating Absence of GCR activation at concentrations equivalent to suprapharmacologic doses



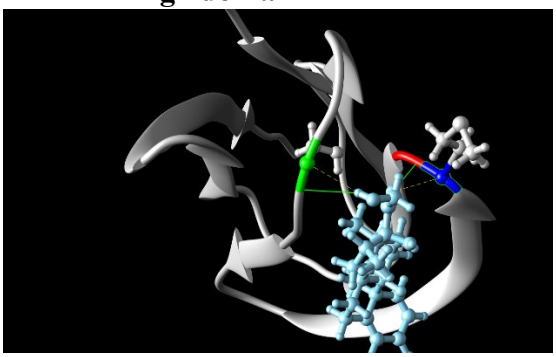
Mouse whole blood (WB) and splenocytes (spl) were incubated for 6 hours with increasing concentrations of dexamethasone base and then cell counts (WB) or apoptosis (spl) was determined by CBC analysis (WB) or flow cytometry (spl) after co-staining for live/dead cells using Viobility™ (Miltenyi Biotec) and eBioscience™ Calcein AM Viability Dye (Invitrogen, ThermoFisher Scientific) Source:LyDep24.1_Ex_Vivo_report_2022

Similarly, from the AVM0703-001 dose-escalation phase in R/R NHL patients, WBCs, lymphocytes, platelets and RBCs were not depleted at doses between 6 mg/kg and 18 mg/kg.

WBCs, platelets, monocytes, lymphocytes and splenocytes are known to express the GCRalpha, consistent with the effects seen on these cell populations at dexamethasone base concentrations between 1 nM and 10 uM. The bi-phasic CRC suggests that a low affinity but very dense non-GCR receptor soaks up the high concentrations, preventing binding and activation of the GCRs (154). RBCs, which do not express the GCRs, had no response to ex vivo dexamethasone base at any concentration (data not shown from study report "LyDep 24.1_Ex_Vivo_report_2022").

ICAM3 was identified as a potential low affinity receptor for dexamethasone suprapharmacologic concentrations through literature and Human Proteome database searching and confirmed by molecular docking studies conducted by two independent outside consultants.

Figure 12 Low affinity hydrogen bonding of dexamethasone to ICAM3 Ig1 domain



The crystallized structure of ICAM3 Ig *domain 1 was cut from the published crystal structure of ICAM3 bound to integrin alphaLbeta2 (LFA-1) and imported into SwissDock docking software. The Dexamethasone PBD structure was loaded to SwissDock as a representation. SwissDock reported a low affinity covalent hydrogen bond found to Ser31 of ICAM3 with 3.522 angstroms length and low affinity oxygen bond to Met49 of ICAM3 with 3.606 angstroms length. High affinity hydrogen bonds typically range from 2.6 to 3.1 angstroms length* (156).

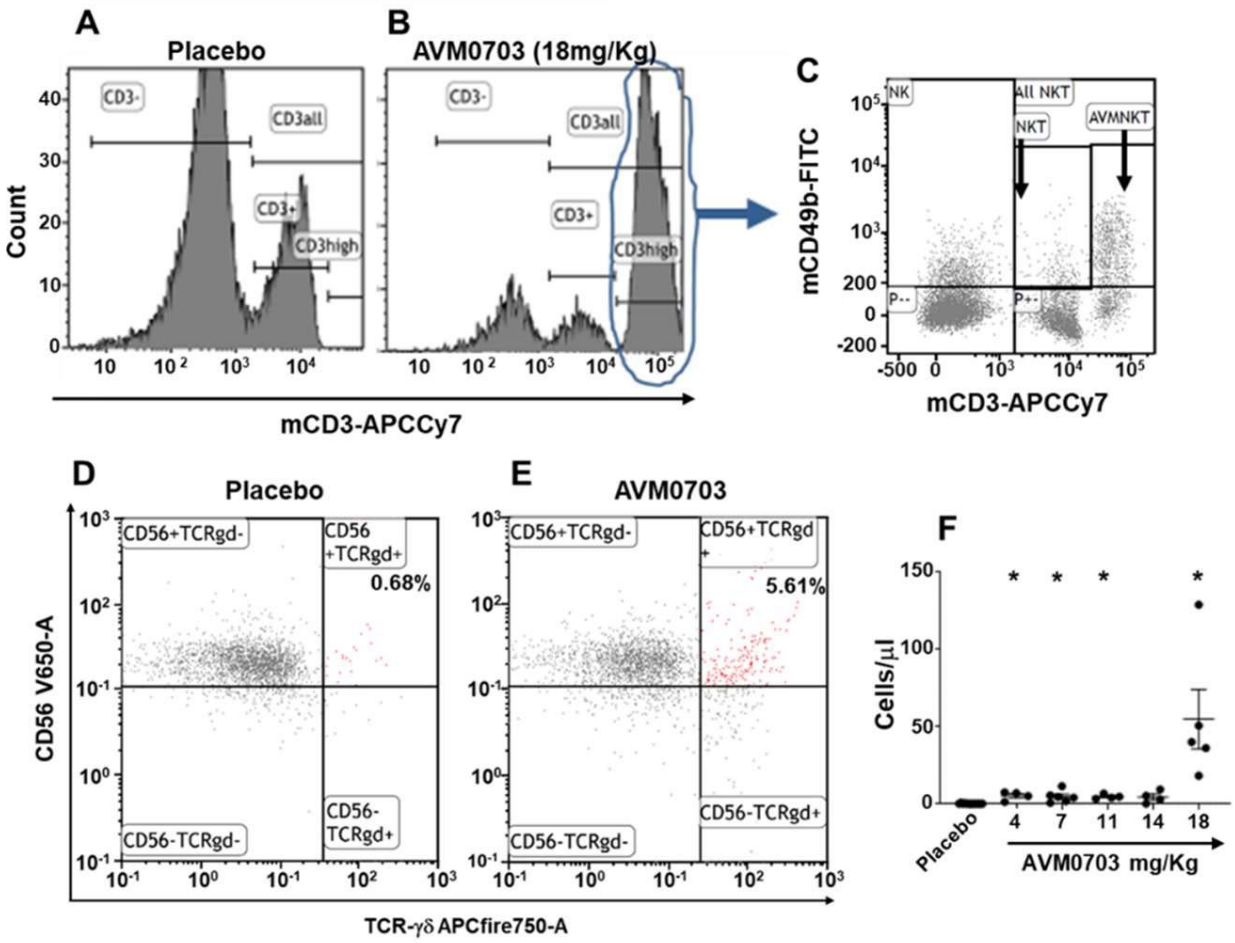
ICAM3 has been reported to be shed after dexamethasone binding (151), and we hypothesize that this binding is nonreversible, preventing AVM0703 from binding to GCRs and explaining why GCR activation is not observed as AVM0703 is 'apparently' cleared from the blood from the PK analysis. AVM0703 irreversibly bound to shed ICAM3 would be found in the plasma/serum fraction of blood and bound AVM0703 would be released from the ICAM3 during LC-MS/MS analysis, but prevented from binding to and activating GCRs. Alternatively, AVM0703's structure could be modified after ICAM3 binding such that it can no longer bind GCRs even if free in the blood. Replacement of the OH group on dexamethasone by chemosts at Cold Spring Harbor Laboratories completely abolished induction of AVM-NKT cells (which are described below) and prevented CBC reductions that are expected in naïve mice, providing confirmatory evidence that low affinity hydrogen bonding is involved in the in vivo activity of suprapharmacologic doses of dexamethasone (AVM0703).

Experiments in naïve C57Bl/6 mice, have shown that a novel CD3 very high/ CD49b+/ Ly6G+ and γδ TCR positive NKT cell population (AVM-NKT) is mobilized at HED above 6 mg/kg with optimal mobilization at doses >18 mg/kg. This cell population appears in the blood of naïve mice 48 hours after AVM0703 administration and in tumor-bearing Balb/c mice within 3 hours and was shown to home to the tumor site in the very immune-resistant A20 lymphoma mouse model. These novel immune cells are not evident in untreated or Placebo treated naïve mice, however, in a tumor environment, these novel immune cells are induced in the spleen but not mobilized to the blood for tumor homing until AVM0703 18 mg/kg HED is dosed. Within 3 hours after AVM0703 dosing, the novel immune cells induced in the spleen are completely mobilized out of the spleen and in 5 out of 6 tumors more than 90% of the tumor cells were found dead as measured by flow cytometry.

Flow cytometry analysis, demonstrated the mobilization of a novel NKT cell population in naïve mice (Figure A-C) shown to be CD3 very bright (one log brighter than other NKTs - Figure B), CD49b+, 100% CD45dim, NK1.1+, CD4 very bright, CD62L+, 10% Ly6G+, 100% Sca1 very bright, CD8dim, CD44+/-, CD69+/-, CD25+/-, B220-, Foxp3-, c-kit+/-, TCR αβ- and TCR γδ+ in naïve C57Bl/6 mice. Expression of Ly6G and TCR γδ suggest that this novel immune population, in addition to described functions of NKT cells, could also have a direct phagocytosis activity on autoreactive lymphocytes, cancer cells, or pathogens. Ly6G indicates a fully mature, differentiated neutrophil or granulocyte which has been shown to be implicated in antitumor responses (157).

These novel NKT immune cells have been identified in humanized mice from different genetic backgrounds and genetic modifications (NOD.Cg-Prkdcscid Il2rgtm1Sug/JicTac and NOD-Prkdc26emCd52Il2rgem26Cd22/NjuCrl and BALB/c Rag2tm1Fwa Il2rgtm1Cgn SirpaNOD Flt3tm1lrl) created using 6 different umbilical cord blood donors. In humanized mice, AVM0703 induced their production and mobilization 72 hours after dosing (n=10). The novel NKT population was observed from all donors but the degree of mobilization varied from 1.12 to 6.7% of the gated human CD45+cells. The novel NKT cells are not optimally-induced in naïve mice at doses below HED 18 mg/kg (Figure 11 F), indicating that mobilization could be achieved thanks to suprapharmacologic doses of DSP, safely possible with AVM0703.

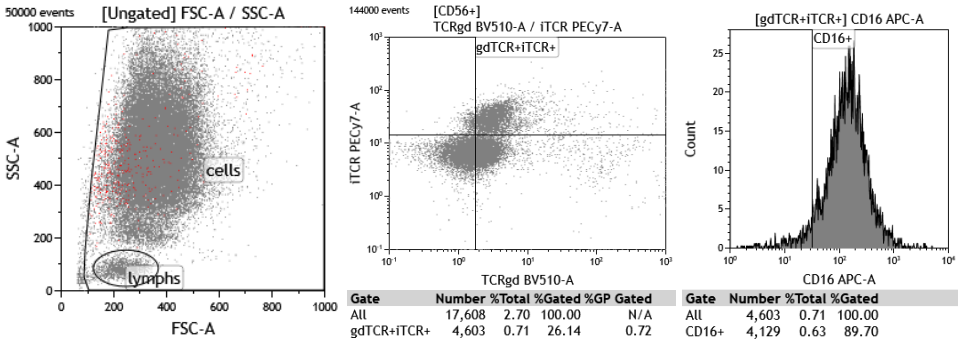
Figure 13 Suprapharmacologic AVM0703 Induces and Mobilizes Novel Immune Cell Populations in Naïve and Humanized Mice



Mobilization of AVM-NKT cells. A-C) Naïve C57Bl/6 mice were orally gavaged with placebo or AVM0703 HED 18 mg/kg. Flow cytometry performed 48 hours later demonstrated the appearance of a novel CD3 very high cell population (C), D-E) AVM-NKT cells in humanized mice 96 hours after placebo (D) or AVM0703 (E) dosing. F) AVM-NKT cells are not optimally-induced in naïve mice at doses below HED 18 mg/kg. In humanized mice and human patients, the novel NKT immune cells are bi-specific for gamma delta TCR and invariant TCR expression.

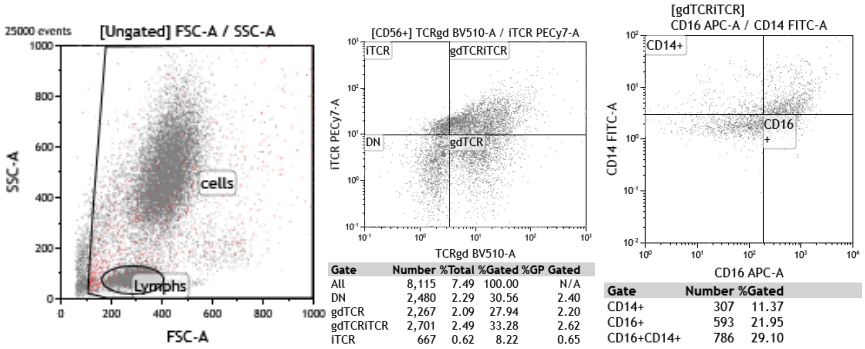
Patients who received AVM0703 also rapidly mobilized a novel double positive (bi-specific) gamma delta^{+} (γδ) invariant TCR^{+} Natural Killer T-like cell (AVM_NKT), measured by flow cytometry, as illustrated in the figures below. As determined in humanized mice, the bi-specific NKT-like cells in human patients express markers of activation including CD16 and NKp44. By size and complexity these immune cells are predominantly large granular lymphocyte-like cells (red dots on FSC vs SSC plot below).

Figure 14 Flow cytometry characterization of CD56+γδTCR+invTCR+ immune cells in patient 108-001 blood one-hour post 9 mg/kg AVM0703 administration who had vision restoration within 72 hours after AVM0703 9 mg/kg dosing.



Lysed whole blood flow cytometry results for AVM0703 treated 108-001 CNS B-ALL patient one hour after dosing with AVM0703, demonstrating double positive γδ TCR^{+} and iTCR^{+} cells from the live cell CD56^{+} gate. Left: Size and complexity (FSC vs SSC) scattergram with these novel immune cells marked as red demonstrates they may be similar to large granular lymphocytes. Middle : CD56^{+} cells are shown on a scattergram for γδ TCR and iTCR. 26% of the CD56^{+} cells are positive for both γδTCR and iTCR. Right: The γδTCR^{+}iTCR^{+} quadrant from the CD56+ gate was then evaluated for CD16 expression. CD16 was expressed on 90% of the γδTCR^{+}iTCR^{+} cells, indicating an activated state. Patient 108-001 had a dramatic response with restoration of vision within 3 days after a single 9 mg/kg AVM0703 infusion. (from Report Summary AVM0703_AVM_NKT)

Figure 15 Flow cytometry characterization of CD56+γδTCR+invTCR+ immune cells of patient 108-002 who has an ongoing durable PR since a single AVM0703 monotherapy infusion 30 August 2021.



Lysed whole blood flow cytometry results for 18 mg/kg AVM0703 PTCL NOS patient 108-002 60 minutes after dosing demonstrating double positive γδ TCR^{+} and iTCR^{+} cells from the live cell CD56^{+} gate. Left: Size and complexity (FSC vs SSC) scattergram with these novel immune cells marked as red demonstrates some are similar to large granular lymphocytesand others are very small, a mixed pattern we have observed in mice as the cells are induced overtime they move from low complexity (low SSC) to high complexity. Middle: CD56^{+} cells are shown on a scattergram for γδ TCR^{+} and iTCR^{+}. 33% of the CD56^{+} cells are positive for both γδTC^{+} and iTCR. Right: The γδTCR+iTCR+ quadrant was then evaluated for CD16 and CD14 expression. CD16 and/or CD14 were expressed on 62% of the γδTCR^{+}iTCR^{+} cells, indicating an activated state. (from Report Summary AVM0703_AVM_NKT)

In summary, suprapharmacologic AVM0703 rapidly mobilizes a novel double positive (bi-specific) gamma delta^{+} (γδ)TCR+ and invariant TCR^{+} Natural Killer T-like cell. The CD56+γδTCR+iTCR+ have been measured in our clinical trial patients at levels up to ~350 cells/uL. Based on the observed very rapid homing of AVM0703 mobilized immune cells to tumor sites in the mouse A20 lymphoma model, measured blood levels 60 minutes after the end of the 1 hour infusion are likely lower than the peak number of immune cells mobilized.

1.2.6 Tumor flare/pseudoprogression after immunomodulatory AVM0703

Tumor flare, also called pseudoprogression or immune Unconfirmed Disease Progression (iUDP), has been observed in response to immunomodulatory drugs such as checkpoint inhibitors, lenalidomide, ibrutinib (7) and CarT therapy (158) , and has been reported in as many as 40-50% of patients with some immunomodulatory drugs (159) (160) (161) (162) (163). Patterns of pseudoprogression include; i) extremely rapid tumor growth by palpation, patient symptoms or imaging that is not consistent with the known growth rate of the patients cancer, ii) increased edema by imaging around the lesion, iii) enhanced PET signal or even evidence of new lesions that subsequently regress or disappear, and iv) evidence of disease progression without accompanying clinical deterioration (7). Tumor flare in CLL patients treated with lenalidomide is common and symptoms include rapid, often painful, self-limited increase in the size of lymph nodes, often accompanied by fever, lymphocytosis, rash, and bone pain. The pathophysiology is speculated to be related in part to an immune phenomenon characterized by natural killer cell activation, modulation of costimulatory (CD80,CD83, CD86) surface molecules on CLL cells, and an increase in levels of tumor necrosis factor-a post-lenalidomide treatment, consistent with an acute inflammatory reaction (8). Bruton tyrosine kinase and phosphatidylinositol 3-kinase targeting agents are associated with major activity in CLL/SLL, mantle cell, and other lymphomas, and are altering treatment paradigms. In patients with CLL/SLL, and less often in other lymphomas, both idelalisib and ibrutinib may cause a rapid reduction in lymph node size and spleen mass, often with improvement of cytopenias, but associated with lymphocytosis. This finding, which relates to a redistribution of lymphocytes from tissue sites to the peripheral blood, may persist for a year or longer without signs or symptoms associated with disease progression and does not represent a suboptimal response to therapy (8).

Responses to immunomodulatory drugs occur very rapidly in some patients which can lead to patient symptoms related to swelling in the area of tumor(s) due to very rapid immune cell infiltration. Immune infiltration and swelling can lead to symptoms such as pain or loss of function around the impacted area. Imaging cannot always distinguish between tumor growth and immune cell infiltration. For some patients, immunomodulatory drugs activate such robust immune responses that previously overlooked sites of tumor suddenly are exposed and appear as new lesions when in fact they are not new but were not picked up by prior imaging.

As clinicians have learned more about tumor flare/pseudoprogression, patients who would have previously been taken off a drug due to apparent disease progression are being continued on the drug, particularly if there is evidence of immune infiltration such as pain or swelling around sites with known tumor or if the patient does not have evidence of clinical deterioration (7) . Distinguishing between tumor flare/pseudoprogression and true disease progression is particularly

important, and especially for patients relapsed or refractory to earlier lines of therapy who may have limited treatment options, because patients with pseudoprogression are responding to the drug and should continue on therapy, while patients with true disease progression require other options. Retrospective analysis of immunomodulatory drug trials have demonstrated that patient's who turned out to have had pseudoprogression have much better outcomes and survival than patients who had true disease progression (164) (165). These observations are quite positive, however they are limited because the publications do not break out outcomes for patients who were taken off therapy versus those who may have continued therapy after pseudoprogression.

Many publications report that patients who experienced tumor flare/pseudoprogression actually have better outcomes than patients who respond to therapy but do not experience tumor flare (166) (167) (168) (169) (170) (165) (171) (172) (173) (6). From the Phase 2 DAWN study of ibrutinib in R/R FL, 7 of 110 patients (6.4%) were confirmed as pseudoprogressors. ORR for the entire trial population was 20%, however, 3 of the 7 (43%) pseudoprogressors had an ORR at 22 weeks, indicating superior short-term response even compared to responders. While a small subset of the overall trial population, pseudoprogressors were also 40% (2 of 5) of the patients with long term PFS at 27 months, indicating that pseudoprogressors also had a superior long-term outcome even compared to responders (7). Solid tumor patients who showed pseudoprogression on ipilimumab anti-CTLA4 therapy have also been reported to have superior outcomes compared to normal responders (174). Brain tumor, particularly glioblastoma patients, who receive Temozolomide with radiotherapy and have pseudoprogression have better outcomes than patients without pseudoprogression (175).

Identification of tumor flare by imaging is not rapid enough to guide patient care decisions and therefore rapid readily measured biomarkers of tumor flare/pseudoprogression are being investigated. For NHL markers that may identify tumor flare/pseudoprogression include reductions in circulating cell free DNA, reductions in circulating IL-8 and reductions in CA125 levels. In some cases with more data points, early increases in these markers were subsequently followed by decreases in patients with pseudoprogression. The early increase followed by subsequent decline is hypothesized to be due to tumor cell killing releasing the markers into the blood (176). Biomarkers that group R/R NHL pseudoresponders with responders rather than true disease progression also include IL4, IP-10, MCP3, and IL-27 (7).

Other immunomodulatory drugs show little activity against R/R NHL either as single agents or combination therapy. Nivolumab single agent for R/R DLBCL had ORR of 3-10% and median OS of 5.8-12.2 months (12), while Ipilimumab single agent B-cell NHL had 11% ORR (13) in R/R NHL. Combination therapy yielded ORR between 9-22% and did not provide a significant therapeutic benefit (14), and 29% had treatment-related grade 3-4 AEs. For comparison to this study the Nivolumab study published in 2019 (12) had median 3 prior lines (vs 4 in AVM0703-001) with 24-29% having 4 or more lines (vs 53% in AVM0703-001). For the combination therapy study (14) published in 2021 for patients with B-NHL and T-NHL median prior lines were 3 and 4 respectively and 6% and 9% had failed cell therapy (vs 47% in AVM0703-001).

From the dose-escalation phase of AVM0703-001 clinical trial in R/R NHL 7 of 15 of AVM0703 patients exhibited indications of tumor flare/pseudoprogression as described in the published literature summarized above which include swelling and pain at known tumor sites, apparent very rapid tumor growth but PR on 1 month PET/CT scans, lymphocytosis following observed clinical responses:

101-001: B-ALL who had only multiple extramedullary masses at baseline who had an explosive peripheral blood lymphocytosis after 6 mg/kg AVM0703 with 70-80% blasts and subsequent stable disease after early progression, however, patient was taken off-study due to apparent progression. However, day 28 PET/CT read ~12 months later showed the patient had SD and no new lesions to AVM0703 monotherapy.

103-002: PI reported tumor size appeared to be shrinking on day 7 after 6 mg/kg AVM0703 infusion, with visible progression on day 21 and patient was taken off study, however, day 28 PET/CT read ~12 months later showed the patient had a PR with stable radiologic disease and partial metabolic response; 2 of 5 LN were smaller and 3 of 5 stable and 18F-FDG uptake decreased and decreased in BM as well and no new lesions to AVM0703 monotherapy.

103-004: apparent tumor growth led to patient being taken off-study after 6 mg/kg AVM0703, however, day 28 PET/CT read ~12 months later showed the patient had a PR with -38% SPD % change from baseline and 18F-FDG uptake reduced for a partial radiologic remission and a partial metabolic response and no new lesions to AVM0703 monotherapy.

103-005: apparent tumor growth after 9 mg/kg AVM0703 led to patient being taken off-study, however, day 28 PET/CT read ~12 months later showed the patient had a PR with stable radiologic disease and partial metabolic response and no new lesions to AVM0703 monotherapy.

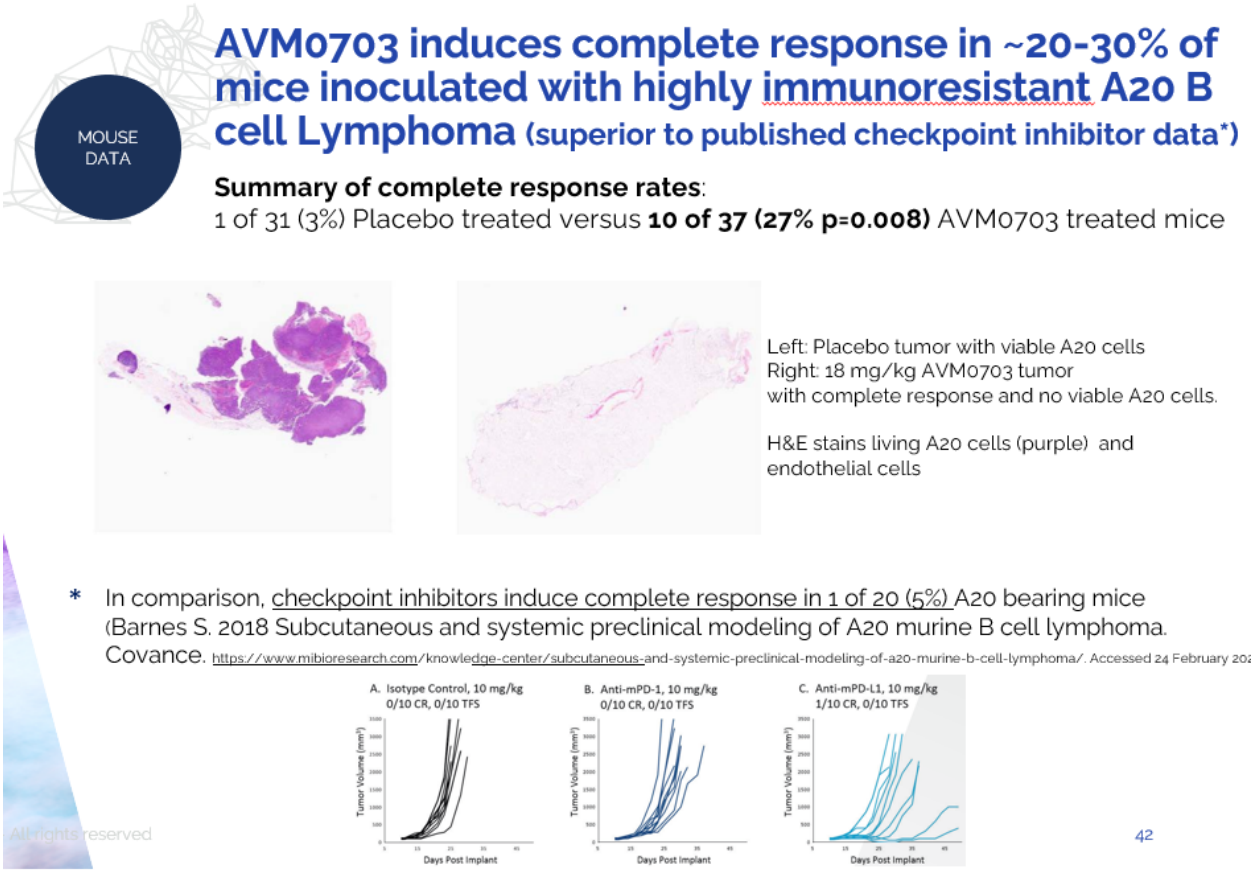
108-003: AITCL disease confined to neck lymph nodes, was dosed at 12 mg/kg AVM0703. The patient was hospitalized on day 14 for a sore throat that had developed since day 1 after 12 mg/kg AVM0703 infusion. The patient was diagnosed with pharyngitis with negative results for bacterial or fungal infection and no visual evidence of infection either. CT scan revealed severe mucosal edema from the oropharyngeal to the tongue and inferior edema involving the vallecula and aryepiglottic folds, which may have been an immune infiltrate of the involved neck lymph nodes. On day 22 a clinic visit showed palpably smaller, softer lymph nodes indicative of response to AVM0703 supporting the hypothesis that the pharyngitis was indicative of immune infiltrate and response to AVM0703 12 mg/kg dosing. Local read of the day 28 PET/CT scan was SD, central read was radiologically SD and PMD. The central read reported a new 18F-FDG positive lesion not observed on the CT, which is consistent with described profiles of pseudoprogression.

103-008: a DLBCL patient (103-008) with brain stem tumor was dosed at 18 mg/kg AVM0703 and had day 9 grade 3 headache and new edema by MRI suggestive of tumor flare/pseudoprogression. Headache was managed with 10 mg dexamethasone IV on 11 May 2022 and 10 mg dexamethasone every 6 hours (X4) on 13 May 2022. Day 28 PET/CT scans were not taken as patient was inadvertently taken off-study due to the headache onset.

103-010: a DLBCL patient with frontal lobe tumor and ECOG 3 was dosed at 18 mg/kg AVM0703. Day 28 MRI showed SRD (stable radiologic disease), and Day 31 PET/CT showed CMR (complete metabolic response) for CR.

Pseudoprogression is also observed in the immune-resistant A20 lymphoma mouse model. The figure below summarizes AVM0703 effect in the A20 model in comparison to published checkpoint inhibitor data and illustrates one example of pseudoprogression, where measureable large tumor was detected, however, histology demonstrated that the A20 cells had been completely killed and resorbed.

Figure 16 Example of Pseudoprogression (also called Tumor Flare) in an AVM0703 18 mg/kg HED treated mouse



1.2.7 Previous Human Experience With High-Dose Dexamethasone

Dexamethasone has been used commercially since US FDA approval for the tablet formulation in 1958 (NDA 011664) (178) followed by the injectable formulation in 1959 (NDA 012071).

Complications of chronic corticosteroid treatments are well known and mainly result from inhibition of the hypothalamic-pituitary-adrenal function and the development of iatrogenic Cushing's syndrome, characterized by truncal obesity, peripheral edema, parchment-like skin, obesity, shortness of breath, sleep apnea, osteopenia, and easy bruising (179) (180) (181). Other complications of chronic corticosteroid therapy include hypertension, hyperglycemia, gastrointestinal (GI) bleed or ulcer, cataracts, aseptic necrosis of bones, myopathy, and development of serious infections (182) (183). Less common, but serious side effects include cardiac disease and pseudotumor cerebri (184) (185). High-dose GCs are associated with neuropsychiatric complications, including mood disorders, psychosis, memory impairment, and rarely, suicidal ideation (186) (187) (188) (189).

There is existing published evidence indicating that side effects from high-dose dexamethasone or other GCs may be less than those generally observed for low dose chronic treatment. A summary

of relevant studies using high-dose corticosteroid therapy is provided in the table below. In all cases where a corticosteroid different from dexamethasone was used, the equivalent dexamethasone dose is provided to allow comparison across studies.

Table 3 Patients Treated With the Equivalent of 6 mg/kg Dexamethasone in Prospective Randomized Studies

Indication	Number of GC-Treated Patients	Route of Administration	Dose	Steroid Used in Study	Total AVM0703 or Equivalent[a]
ALL[123]	369 (1-18 years)	Oral, IV	Highest dose: up to (6 mg/kg × 5 every 24 hours) × 3 weeks	Dexamethasone	6 mg/kg (in 24 hours; 25 kg, 130 cm)
Moderate to severe head injury[139]	147 (15-55 years)	IV	500 mg + (200 mg [t=3 hours]) + (8 × 200 mg every 6 hours)	Dexamethasone	31 mg/kg (2.3 g in 51 hours)
Head trauma[140]	56	IV	Group D (highest dose): 6 mg/kg + 6 mg/kg (every 6 hours) × 1 day + 1 mg/kg (6 hour intervals/ 4 days + tapering doses)	Dexamethasone	30 mg/kg (in 24 hours)
Septic shock[141]	43 dexamethasone, 43 MPS	IV	3 mg/kg × 2 (every 4 hours)	Dexamethasone	3-6 mg/kg (in 24 hours)
Septic shock[142]	21 dexamethasone, 22 MPS	IV	6 mg/kg × 2 cycles if shock persisted	Dexamethasone	6 mg/kg (in 24 hours)
Idiopathic steroid-resistant nephrotic syndrome[143]	81 (1-14 years)	IV	5 mg/kg over 2-3 hours, alternate days for 6 doses	Dexamethasone	5 mg/kg (in 24 hours)

a. Calculation based on dexamethasone concentration.
ALL = acute lymphoblastic leukemia; GC = glucocorticoid; IV = intravenous; MPS = methylprednisolone.

Results of the studies presented in Table 5 are summarized as follows:

- The proposed study of very high dose dexamethasone for treatment of lymphoid malignancies is supported by studies in pediatric patients treated for ALL (190). Schwartz et al reported outcomes for 369 children newly diagnosed with ALL enrolled in a randomized trial that evaluated 4 doses of GCs during induction. Patients were randomly assigned to 1 of 4 dose cohorts: prednisolone 40 mg/m^2/day, dexamethasone 6 mg/m^2/day, dexamethasone 18 mg/m^2/day, or dexamethasone 150 mg/m^2/day (equivalent to 6 mg/kg/day). The GCs were administered during a 3-day, single-drug window before initiation of standard multi-drug

induction therapy. Results showed that high-dose dexamethasone treatment (150 mg/m^2/day or ~6 mg/kg/day) elicited better responses, as measured by the changes in bone marrow and peripheral blood blasts from Day 0 to Day 3, compared to standard dose prednisolone (40 mg/m^2/day) or the lower dexamethasone doses (6 or 18 mg/m^2/day). Further, high-dose dexamethasone was equally effective for steroid-responsive and steroid-resistant patients, as it appeared that high-dose dexamethasone overcame GC resistance. The report did not mention adverse events (AEs) according to treatment group. Dexamethasone was also shown to be superior to prednisone when used for induction or interim maintenance in newly diagnosed children or young adults with high-risk B-cell acute lymphoblastic leukemia (B-ALL) (191). While the dexamethasone doses were not as high as the Schwartz et al study, patients who received dexamethasone had higher 5-year event-free survival rates compared to those given prednisone. However, for the patients >10 years, the benefits were negated by an increased risk for osteonecrosis. Based on the results from this study, the authors recommended replacement of prednisone with dexamethasone in the induction regimen for high-risk B-ALL patients <10 years.

- Ultra-high-dose dexamethasone was studied for treatment of acute brain injury in a prospective randomized placebo-controlled study that enrolled 300 patients. Parameters such as age, severity of trauma (including central nervous system [CNS] trauma) were well-balanced between the 2 groups. Patients were given a total of 2.3 g of dexamethasone (equivalent to ~31 mg/kg) intravenously (IV) within a 51-hour time period (i.e., 1 dose of 500 mg) within the first 3 hours after trauma, then 1 dose of 200 mg 3 hours later and then 200 mg every 6 hours for 8 more doses. The primary endpoints included the modified Glasgow Coma Scale (Day 5), the modified Glasgow Outcome Scale 10 to 14 months after injury, and time interval until consciousness improved above a level of Modified Glasgow Coma Scale ≥8. Secondary outcome measures included computed tomography scan, and neurological and laboratory data. No statistically significant differences were observed between the dexamethasone and placebo groups with regard to primary endpoints for efficacy and safety. No differences in the incidence of death between the 2 groups were observed. Importantly, there were no statistically significant differences in the incidence of upper GI bleeding (1% versus 1.3%), infection (28.5% versus 25.6%), thrombosis (0% versus 0.7%), intracranial complications (4.1% versus 6.6%), or other complications (9.5% versus 6%) when the dexamethasone-treated group was compared to placebo, respectively. There was a trend toward a higher incidence of hyperglycemia (serum glucose >220 mg/dL) in the dexamethasone-treated cohort (47.6% versus 30.4%) (192).
- A randomized placebo-controlled study of high-dose dexamethasone conducted in 70 patients with head trauma requiring ventilation. Patients were randomized to 1 of 4 cohorts: placebo (Group A), 6 mg/kg dexamethasone IV upon admission (Group B), 6 mg/kg dexamethasone IV followed by 0.1 mg/kg IV every 6 hours for 5 days (Group C), and 6 mg/kg dexamethasone IV followed by 6 mg/kg IV every 6 hours for 1 day followed by 1 mg/kg IV every 6 hours for 4 days (Group D). Incidence of pneumonia was reported according to treatment group. Overall 22 (7%) patients developed pneumonia. The multivariate analysis found no significant association between the dose of dexamethasone and risk for pneumonia; nor was there a statistically significant difference in the incidence of pneumonia when comparing placebo

(Group A) to the combined dexamethasone-treated patients (Groups B, C, and D). The study did not report on the incidence of other AEs (193).

- High-dose GC was studied for adjunctive treatment of culture positive septic shock in a prospective, randomized, double-blind, placebo-controlled study that enrolled 172 patients. Patients were given IV saline (n=86) or high-dose GC given 1 to 2 times IV within the first 4 to 5 hours after admission. Patients given high-dose GCs were divided evenly among those given dexamethasone (3 mg/kg/dose) IV and those given methylprednisolone (MPS) (30 mg/kg/dose) IV. Receipt of GC correlated strongly with survival, with mortality rate of 10.4% compared to 38.4% in the placebo-treated patients ($p<0.001$). There was no significant difference in the percentage or type of AEs observed for high-dose GC-treated patients compared to control. Complications observed in the high-dose GC-treated groups included GI bleeding (2%), non-ketotic hyperglycemia (1%), and psychosis, and the overall proportion of patients with AEs was not statistically different from the control group. Also described in the same report was a retrospective analysis of 328 patients to determine the effects of GC on outcome of septic shock. The retrospective study also included patients treated with multiple infusions of lower dose GC (>24 hours of either dexamethasone 0.25 to 1.5 mg/kg/dose IV or MPS 10 to 30 mg/kg/dose IV). The overall results were consistent with those from the prospective study and showed a significantly lower risk for mortality (14% in GC-treated patients versus 42.5% in placebo-treated patients), with a similar incidence of AEs. Notably, there was a higher incidence of AEs, particularly more GI bleeding events, in patients given prolonged multiple doses of GC compared to a single high-dose (146).
- Effectiveness of high-dose GC for reversal of septic shock was also demonstrated in another prospective, randomized, placebo-controlled study that enrolled 59 patients. Patients were allocated to 1 of 3 treatment groups: MPS 30 mg/kg IV (Group 1), dexamethasone 6 mg/kg IV (Group 2), and placebo (Group 3). Reversal of shock at 24 hours post-treatment was observed in 32% of dexamethasone-treated patients and 19% of MPS-treated patients compared to 0% of placebo-treated patients ($p<0.05$), and mortality within the first 5 days was significantly lower in GC-treated patients compared to placebo-treated patients (40% versus 69%, respectively; $p<0.05$). While overall mortality and complications associated with sepsis were significantly higher in the placebo group, significantly more AEs associated with GC therapy were observed in the GC-treated patients, including super infections and hyperglycemia. GI bleeding was observed in 1 MPS-treated and 2 placebo-treated patients (194).
- High-dose pulse GC was studied in a prospective study for treatment of children with nephrotic syndrome resistant to oral steroids. Children were given either dexamethasone (5 mg/kg) IV or MPS (30 mg/kg) IV once every other day for a total of 6 doses. A total of 81 patients were treated (59 with dexamethasone and 22 with MPS). Complete remission was achieved in 33% and partial remission in 12% of patients. Adverse events were observed in 64% of patients, including serious infections (3.7%), hypertension (50%), hypokalemia (12%), hyponatremia (14%), hyperglycemia (2%), and peritonitis (2%). There was no apparent difference between the treatment groups in the risk for complications (195).

In addition to the above-mentioned prospective, randomized clinical studies, a retrospective meta-analysis was performed on data from 20 clinical studies for treatment of patients with septic shock. The analysis included data from 2063 patients treated with various forms and dosing schemes of GCs. Seven of the studies administered high-dose pulse dexamethasone (≥6 mg/kg)

IV or MPS (≥30 mg/kg) IV to a total of 539 patients, and the remaining gave various courses of lower dose GCs. With respect to efficacy endpoints, the analysis provided more evidence for beneficial effects of low-dose compared to high-dose regimens. Adverse events were described for the entire group of GC-treated patients and compared to that of control-treated patients. GC-treated patients had a statistically significant increased risk for developing hyperglycemia (51.7% versus 45.6%, respectively; $p<0.001$) and hypernatremia (31.4% versus 19.2%, respectively; $p<0.001$); however, there was no statistical difference in the incidence of superinfections (18.7% versus 18.2%, respectively), GI bleeding (7.9% versus 7.3%, respectively), or neuromuscular weakness (1% versus 1.7%, respectively). A subsequent study by the same group updated this analysis to include 33 eligible studies and 4268 patients, which confirmed the findings from the original meta-analysis (196).

Additional complications of pulse high-dose GCs reported in small case series include headache, cardiac arrythmia (bradycardia or tachycardia), flushing, abdominal pain, weakness, malaise, arthritis, osteonecrosis, and insomnia, many of which also are side effects of chronic lower dose GCs.

Taken together, the large clinical experience with pulse high-dose dexamethasone at doses of approximately 6 mg/kg has been acknowledged by regulatory bodies and current US approval suggests doses up to and including 6 mg/kg be used for treatment of unresponsive shock.

1.3 Rationale for Study Design

Patients with R/R NHL are a heterogeneous patient group with a very poor prognosis.

There is an urgent need for new options for patients with R/R lymphoid malignancies who do not respond to chemo-immunotherapy or salvage therapy. A non-cytotoxic treatment identified for R/R lymphoid malignancies that could result in improved remission or as a bridge to ASCT, CarT or other therapies would present an attractive and potentially more positive benefit/risk ratio. Dexamethasone is approved for IV injection for treatment of a variety of indications, at doses up to 6 mg/kg for the treatment of unresponsive shock. AVM proposes to investigate a high-dose dexamethasone formulation, starting at the maximum approved dose, to determine safety and potential efficacy for life-threatening R/R lymphoid malignancies.

AVM has developed AVM0703, a high concentration and high-volume formulation of dexamethasone sodium phosphate (DSP) for IV infusion as an immunomodulatory agent to treat lymphoid malignancies. This new formulation is necessary in order to deliver the higher concentration of drug product since current formulations would result in patients being potentially exposed to safety risks due to higher excipient levels. Based on the biologic properties of high-dose GCs and data from preclinical models of lymphoid malignancies, it was originally hypothesized that a single high or ultra-high-dose of DSP will overcome GC resistance in malignant lymphocytes, resulting in rapid apoptosis, and that rapid clearance of the AVM0703 will mitigate the risk for corresponding increase in toxicity. However, non-clinical and clinical data have demonstrated that ultra-high DSP activity against NHL and various solid tumors appears to be independent of canonical GCR activation and is potentially mediated by the mobilization of a bispecific γδTCR+ invTCR+ Natural Killer T-like cell.

The primary objective of the Phase 1 portion of the study will be to determine the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of AVM0703 in patients with R/R lymphoid malignancies. The starting dose of 6 mg/kg IV is supported by previous studies of pulse high-dose dexamethasone in multiple indications. The MTD will be determined using a 3+3 dose escalation design.

Each patient in the 6, 9, 12 and 18 mg/kg cohorts will be sequentially enrolled after 48-hours of observation. Dose escalation will be permitted after 3 patients have completed a 7-day DLT assessment period with no reported DLTs or after 6 patients have completed the 7-day DLT assessment period with no more than 1 DLT. Patients in the 21 mg/kg cohort will be sequentially enrolled after 7 days of observation, and will be observed for DLTs for 21 days.

Dose escalation decisions will be made by the Safety Review Committee (SRC) after review of the entirety of safety data from the cohort.

The primary objective of the Phase 2 portion of the study will be to gather preliminary evidence of efficacy, defined as ORR. Secondary measures of efficacy will include CR rate at 28 days, duration of response (DOR), overall survival, and progression-free survival.

1.4 Risk/Benefit

There is considerable experience with dexamethasone in patients with hematologic malignancies and other disorders at doses up to the starting dose in this study. Doses higher than 6 mg/kg have not been well studied and therefore pose a potential risk to study participants.

The risk to patients in this study will be minimized by adherence to the eligibility criteria (Section 4), close clinical monitoring, periodic review of the safety data, and guidance for the Investigators in the AVM0703 Investigator's Brochure. Importantly, prophylactic use of physiologic circadian dosed hydrocortisone is required to reduce risks of neuropsychiatric side-effects and use of a proton-pump inhibitor is required to reduce risks of gastric bleeding or ulcer. In the dose-escalation phase of the AVM0703-001 study there have been no increases in alkaline phosphatase, even with repeat dosing, and thus AVM0703 does not appear to increase risks of osteonecrosis. There have been no reports of GI bleeding or ulcer. Study drug-related adverse events at AVM0703 doses between 6 and 18 mg/kg have been limited to 16 events in 9 of 15 patients during the 7 day DLT assessment window; 10 grade 1, 3 grade 2 and 3 grade 3. Only 4 of the recorded adverse events were neuropsychiatric and all were insomnia, three grade 1 and one grade 2. Known safety risks of high-dose dexamethasone are described in the Investigator's Brochure.

Dexamethasone has the potential to cause regression and/or remission of lymphoid malignancies; therefore, it may have anticipated benefits to participants with incurable leukemia or lymphoma who have exhausted all FDA-approved therapies. In the dose-escalation phase of the AVM0703-001 study, patients at all dose levels between 3 mg/kg and 18 mg/kg, have experienced clinically significant responses including reversal of grade 4 cytopenia, elevations of platelets and hemoglobin, reduction in lactate dehydrogenase, improvement in performance status and anti-tumor responses. This potential benefit should be balanced against the potential safety risks in such patients with no other reasonable therapy.

2 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 Phase 1

The primary objective of the Phase 1 portion of the study is to determine the safety, tolerability, and MTD or RP2D of AVM0703.

2.1.2 Phase 2

The primary endpoint for the Phase 2 portion of the study is ORR, defined as the proportion of patients with a best overall response of CR or PR at day 28 for patients who are not repeat dosed in 21 day intervals. For Phase 2 expansion patients receiving repeat RP2D doses in 21 day intervals the primary endpoint is best ORR (CR or PR) at any time point.

2.2 Secondary Objectives

2.2.1 Phase 1

The secondary objectives of the Phase 1 portion of the study are the following:

- To assess the preliminary efficacy of AVM0703 in patients with lymphoid malignancies; and
- To assess the pharmacokinetics (PK) of ascending doses of AVM0703.

2.2.2 Phase 2

The secondary objective of the Phase 2 portion of the study is to obtain additional characterization of the safety and efficacy of AVM0703 when administered at the RP2D in specific patient cohorts.

2.3 Exploratory Objectives

2.3.1 Phase 1

The exploratory objectives of the Phase 1 portion of the study are the following:

- To assess reduction in lymphocyte counts; and
- To assess potential biomarkers indicative of AVM0703 antitumor activity in peripheral blood or tumor samples if available.

2.3.2 Phase 2

The exploratory objectives of the Phase 2 portion of the study are the following:

- To assess changes in immune status; and
- To assess potential biomarkers indicative of AVM0703 antitumor activity in peripheral blood or tumor samples if available.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is an open-label, Phase 1/2 study designed to characterize the safety, tolerability, PK, and preliminary antitumor activity of AVM0703 administered as a one-hour IV infusion to patients with lymphoid malignancies.

Phase 1

The Phase 1 portion of the study will enroll patients into a 3+3 dose-escalation design to assess the DLTs and establish an MTD/RP2D. Up to 5 AVM0703 dose cohorts are planned as shown in Table 6. In each cohort, 3 to 6 patients will be treated. Each patient in the 6, 9, 12 and 18 mg/kg cohorts will be sequentially enrolled after 48-hours of observation. Dose escalation will be permitted after 3 patients have completed a 7-day DLT assessment period with no reported DLTs or after 6 patients have completed the 7-day DLT assessment period with no more than 1 DLT. Patients in the 21 mg/kg cohort will be sequentially enrolled after 7 days of observation, and will be observed for DLTs for 21 days.

The dose escalation will use the following rules for evaluating dose levels:

- If none of the first 3 evaluable patients in a cohort experience a DLT, that dose level will be deemed safe, and another 3 patients will be enrolled into the next higher dose level;
- If 1 of the first 3 patients in a cohort experiences a DLT, 3 more patients will be treated at the same dose level;
- If ≥2 of the 3 to 6 patients in any dose level experience a DLT, that dose level will be considered to have exceeded the MTD and dosing will stop at that level. If the previous dose level did not already have 6 patients treated with ≤1 DLT, enrollment and dosing will then resume in the previous dose level with additional patients up to a total of 6 patients. The highest dose level at which no more than 1 of 6 evaluable patients has experienced a DLT in the DLT assessment period will be considered the MTD for AVM0703; and
- If ≤1 patient experience(s) a DLT at the highest dose level tested, an MTD will not have been established, but sufficient data may be available to select an RP2D based on the overall safety profile.
- In the event of disease progression, patients may retreated according to section 5.5.3.2.

Table 4 Dose Escalation Plan

Dose Cohort	AVM0703 Dose[a]
1	6 mg/kg
2	9 mg/kg
3	12 mg/kg
4	18 mg/kg
5	21 mg/kg

a. Expressed as dexamethasone phosphate.

If >1 evaluable patients in the 18 mg/kg cohort experience a DLT, the DSMC will review all available data (safety, PK and pharmacodymanics) before recommending if intermediate dose levels between 12 mg/kg and 18 mg/kg (e.g., 15 mg/kg) or if alternative dosing schedules or

alternative doses should be explored. The 15 mg/kg cohort was eliminated from the study based on the clinical trial as well as compassionate use data with absence of safety concerns.

Dose-limiting toxicity criteria will be defined separately for patients with acute leukemia and those with NHL or CLL. A DLT is defined as any of the treatment-emergent adverse events listed below that occur within the first 7 days after AVM0703 administration in cohorts 6, 9, 12 and 18 mg/kg and 21-days for the 21 mg/kg cohort.

The following will not be considered unacceptable toxicities for Phase 2:

- Grade 3 symptoms associated with tumor flare/pseudoprogression that resolve to ≤grade 2 spontaneously within 7 days or within 72 hours with standard medical management; and
- Grade 3 hyperglycemia that resolves with appropriate medical management to ≤Grade 2 within 72 hours; and
- Grade 3 hypertension that resolves with appropriate medical management to ≤Grade 2 within 72 hours.

NHL/CLL DLT criteria:

- Any Grade 5 toxicity not clearly caused by the NHL/CLL;
- Grade 4 neutropenia lasting more than 5 days (without cytokine support, such as filgrastim);
- Febrile neutropenia (i.e., absolute neutrophil count $<1.0 \times 10^9$/L and fever >38.5°C);
- Grade 4 thrombocytopenia, ≥Grade 3 thrombocytopenia with ≥Grade 2 bleeding, or Grade 3 thrombocytopenia lasting >7 days;
- Any ≥Grade 3 non-hematologic toxicity, except for alopecia and nausea controlled by medical management; and
- Liver injury as defined by Hy's law (defined as alanine aminotransferase or aspartate aminotransferase >3 × upper limit of normal [ULN] and total bilirubin >2 × ULN and no evidence of intra- or extra-hepatic obstruction [elevated alkaline phosphatase] or Gilbert's syndrome).[1]

The following will not be considered unacceptable toxicities for Phase 2:

- Grade 3 symptoms associated with tumor flare/pseudoprogression that resolve to ≤grade 2 spontaneously within 7 days or within 72 hours with standard medical management; and
- Grade 3 hyperglycemia that resolves with appropriate medical management to ≤Grade 2 within 72 hours; and
- Grade 3 hypertension that resolves with appropriate medical management to ≤Grade 2 within 72 hours.

Acute leukemia DLT criteria:

- Any treatment-related death;
- Grade 4 neutropenia lasting ≥42 days from infusion in the absence of active leukemia; and

- Any ≥Grade 3 non-hematologic toxicity not clearly resulting from the underlying malignancy EXCEPT:
  - Alopecia;
  - Grade 3 fatigue, asthenia, anorexia, fever, or constipation;
  - Grade 3 nausea, vomiting, or diarrhea not requiring tube feeding, total parenteral nutrition, or hospitalization; or
  - Infection, bleeding, or other expected direct complications of cytopenias due to active underlying malignancy.

The following will not be considered unacceptable toxicities for Phase 2:

- Grade 3 symptoms associated with tumor flare/pseudoprogression that resolve to ≤grade 2 spontaneously within 7 days or within 72 hours with standard medical management; and
- Grade 3 hyperglycemia that resolves with appropriate medical management to ≤Grade 2 within 72 hours; and
- Grade 3 hypertension that resolves with appropriate medical management to ≤Grade 2 within 72 hours.

The following will not be considered DLTs:

- Confusion/cognitive disturbance that resolves to ≤Grade 1 within 24 hours;
- Grade 3 or Grade 4 hypogammaglobulinemia; and
- Grade 3 or Grade 4 isolated electrolyte abnormalities that resolve with or without intervention to ≤Grade 2 within 72 hours.
- Greater than or equal to grade 3 toxicities will not be counted as a DLT if same toxicity was a part of patient's medical history at baseline and there was no grade change.

In addition to the above not considered DLTs, the following will also not be considered unacceptable toxicities for Phase 2:

- Grade 3 symptoms associated with tumor flare/pseudoprogression that resolve to ≤grade 2 spontaneously within 7 days or within 72 hours with standard medical management; and
- Grade 3 hyperglycemia that resolves with appropriate medical management to ≤Grade 2 within 72 hours; and
- Grade 3 hypertension that resolves with appropriate medical management to ≤Grade 2 within 72 hours.

All potential DLTs will be reviewed by the SRC for a final determination and for the SRC to make recommendations regarding the study, including cohort expansion and dose escalation. The SRC will also consider AEs that may have occurred in patients in any cohort (even beyond the DLT assessment period) when making decisions/recommendations to proceed to the next higher dose level. The SRC may review data (safety, PK, and pharmacodynamics) and recommend exploration

of alternative dosing schedules or alternative doses. The SRC will consist of the Principal Investigators, Sponsor representatives, and Medpace Medical Monitor.

In the event of disease progression, a patient may be retreated as described in section 5.5.3.2.

If additional anticancer therapy before Day 28 is warranted, disease assessment should be performed before they receive any other therapy. Patients who go on to receive additional anticancer therapy will be followed for survival at 3, 6, and 12 months post-infusion, and yearly thereafter until death, withdrawal of consent/assent, or study closure. Survival information can be obtained via public records, telephone calls, and/or medical records. Any subsequent anticancer therapy that the patients receive will also be collected.

Phase 2

To further assess safety and efficacy of AVM0703, specific expansion cohorts will be opened in the Phase 2 portion of the study to obtain preliminary evidence of clinical activity. The Phase 2 portion of the study will include patients with malignancies that are deemed potentially responsive to AVM0703, such as DLBCL (including DLBCL arising from follicular lymphoma and primary DLBCL of the CNS), AITCL, PTCL, MCL, high-grade B-cell lymphoma or Burkitt lymphoma, CLL/SLL, T-cell lymphoma, or ALL. Up to approximately 18 patients will be enrolled into each of the selected cohorts at an RP2D defined in the Phase 1 portion of the study. Patients who received an RP2D dose in Phase 1 may be considered in the Phase 2 cohort data set. Patients will be closely monitored for toxicity and the study will be halted if non-hematological toxicities exceed 30% of patients. If there is evidence that a subset of disease has differing safety profiles, a group or groups of disease may be removed from the eligibility criteria for the study based on a DSMC recommendation. If there is evidence that 21mg/kg is safe and patients respond to that dose from the Phase 1 portion, then additional cohorts may be added to the Phase 2 portion of the trial dosed at 21 mg/kg RP2D. See Section 9.2.2 for halting rules of the study.

For Phase 2, one or more patient cohort(s) will receive repeat RP2D infusions in 21 day intervals until intolerance, unacceptable toxicity or disease progression, to determine the number of repeat infusions that are safe, effective and tolerable in this patient population. PK assessments will be made at sites participating in both Phase 1 and Phase 2 after each repeat infusion for the first 6 patients enrolled into each repeat dosing cohort. Full PK assessments will be made as per Phase 1 after the 1st (first) and 6th (sixth) repeat infusions, while for the second to fifth doses (2nd to 5th) PK assessments will be made pre-infusion, at end of infusion, 15 minutes and 48 hours after end of infusion. At least 6 patients will be enrolled in each RP2D repeat dosing cohort. The DSMC will monitor unacceptable toxicities during Phase 2 and halting/stopping criteria are outlined in Table 6.

After 6 patients, who have had PK assessments, have reached intolerance, unacceptable toxicity, or disease progression, or they have received 6 infusions without intolerance, unacceptable toxicity, or disease progression, the Data Safety Monitoring Committee will review an integrated interim analysis of all available PK, PD, efficacy, safety and tolerability data and determine whether repeat dosing should continue or be limited to a certain number of infusions. Ongoing DSMC review will occur at least every 6 months. Based on integrated analysis, including dose-response and exposure-response, the DSMC will determine the optimal dose and dosing schedule for repeat dosing with AVM0703.

For Phase 2, RP2D cohorts will be included that do not require repeat 21 day interval dosing for patients who cannot comply with the visit schedule for repeat dosing. These patients can be retreated according to section 5.5.3.2.

For Phase 2, based on evidence from the Phase 1 dose-escalation, patients should be watched for symptoms of tumor flare. While tumor flare can induce symptoms requiring medical management, tumor flare has been associated with best long term outcomes (6).

Symptoms of tumor flare/pseudoprogression are summarized below:

Patterns of pseudoprogression include; i) extremely rapid tumor growth by palpation, patient symptoms or imaging that is not consistent with the known growth rate of the patient's cancer, ii) increased edema by imaging around the lesion, iii) enhanced PET signal or even evidence of new lesions that subsequently regress or disappear, and iv) evidence of disease progression without accompanying clinical deterioration (7).

Tumor flare in patients may include rapid, often painful, self-limited increase in the size of lymph nodes, often accompanied by fever, lymphocytosis, rash, and bone pain (8). Bruton tyrosine kinase and phosphatidylinositol 3-kinase targeting agents may cause a rapid reduction in lymph node size and spleen mass, often with improvement of cytopenias, but associated with lymphocytosis. This finding, which relates to a redistribution of lymphocytes from tissue sites to the peripheral blood, may persist for a year or longer without signs or symptoms associated with disease progression and does not represent a suboptimal response to therapy (8).

In the event of disease progression, patients may be retreated, according to section 5.5.3.2. For Phase 2, some patient cohorts will receive repeat RP2D doses in 21 day intervals.

If additional anticancer therapy before Day 28 is warranted, disease assessment should be performed before they receive any other therapy. Patients who go on to receive additional anticancer therapy will be followed for survival at 3, 6, and 12 months after their first AVM0703 infusion, and yearly thereafter until death, withdrawal of consent/assent, or study closure. Survival information can be obtained via public records, telephone calls, and/or medical records. Any subsequent anticancer therapy that the patients receive will also be collected.

3.2 Data Safety Monitoring Committee

A Data Safety Monitoring Committee (DSMC) will be convened to review accumulating data and monitor safety of patients for the duration of the study. A separate charter further describes the DSMC role and members.

3.3 Study Indication(s)

AVM0703 is being investigated for the treatment of lymphoid malignancies.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Age ≥12 years and weight >40 kg;

    2. Histologically confirmed diagnosis per 2016 World Health Organization (WHO) classification of lymphoid neoplasms[2] and per the 2016 WHO classification of acute leukemia[3] of the following indications:

- DLBCL, including arising from follicular lymphoma;
    - Preceding indolent lymphoma must be transformed histologically to DLBCL or high-grade B cell lymphoma and have met generally accepted criteria for rapid progression and treatment[4,5], defined by the following:
        a. Progressive or bulky or symptomatic nodal disease; or
        b. Compromise of normal organ function due to progressive or bulky disease; or
        c. Presence of B symptoms (i.e., fevers, weight loss, night sweats); or
        d. Presence of symptomatic extranodal disease, such as effusions; or
        e. Cytopenias due to extensive bone marrow infiltration, autoimmune hemolytic anemia, or thrombocytopenia, or hypersplenism;
- High-grade B-cell lymphoma;
    - Preceding indolent lymphoma must meet criteria as defined above;
- MCL with high-risk prognosis defined as scoring ≥6 points on the 11-point MIPI scale[35] and have met criteria for transformed indolent lymphoma as defined above;
- Primary mediastinal large B-cell lymphoma;
- Primary DLBCL of the CNS;
- Burkitt or Burkitt-like lymphoma/leukemia;
- CLL/SLL that met at least 1 of the criteria for active disease indicating need for treatment according to the International Workshop on CLL (iwCLL) criteria[6] as follows:
        a. Evidence of progressive marrow failure such as hemoglobin <10 g/dL and/or platelet count $<100 \times 10^9$/L; or
        b. Massive (i.e., ≥6 cm below left costal margin) or progressive or symptomatic splenomegaly; or
        c. Massive (i.e., ≥10 cm in the longest diameter) or progressive or symptomatic lymphadenopathy; or
        d. Progressive lymphocytosis with an increase of ≥50% over a 2-month period or lymphocyte doubling time <6 months; or

e. Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids; or

f. Symptomatic or functional extranodal involvement; or

g. Disease-related symptoms, defined by any of the following:

- Unintentional weight loss (≥10%) within the previous 6 months; or
- Significant fatigue (i.e., Eastern Cooperative Oncology Group performance scale 2 or worse); or
- Fevers ≥100.5°F for ≥2 weeks without evidence of infection; or
- Night for ≥1 month without evidence of infection;

- B-cell leukemia/lymphoma, T-cell leukemia/lymphoma, acute leukemias of ambiguous lineage, or NK cell leukemia/lymphoma; advanced or aggressive lymphoma/lymphoproliferative disease, per 2016 World Health Organization classification of lymphoid malignancies;

3. Patients must have R/R disease with prior therapies defined below:

ForPhase 1:
DLBCL and high-grade B-cell lymphoma:

a. R/R after autologous HCT; or

b. R/R after CAR T therapy; or

c. Patients not eligible for autologous HCT or CAR T therapy; or

d. R/R after ≥2 lines of therapy including anti-20 antibody and for whom no standard therapy is available. Patients must have failed or have been intolerant or ineligible for polatuzamab vedotin;

- MCL:

a. R/R after autologous HCT; or

b. Patients not eligible for autologous HCT must be R/R after ≥2 lines of therapy including at least 1 of the following: a BTK inhibitor, bortezomib, or lenalidomide; and for whom no standard therapy is available;

- Primary mediastinal large B-cell lymphoma: R/R after ≥1 line of therapy and are not eligible for or have recurred after autologous HCT or CAR T cell therapy and for whom no standard therapy is available;
- Primary DLBCL of the CNS: R/R after ≥1 line of therapy including methotrexate (unless intolerant to methotrexate) and are not eligible for or have recurred after autologous HCT or CAR T cell therapy and for whom no standard therapy is available;
- Burkitt or Burkitt-like lymphoma/leukemia: R/R after ≥1 line of therapy including methotrexate (unless intolerant to methotrexate) and are not eligible for or have recurred after autologous HCT or CAR T cell therapy and for whom no standard therapy is available;

- CLL/SLL: patients who have active disease requiring treatment and who are deemed at high risk for disease progression by the investigator or have high-risk features per the iwCLL criteria,[165] such as primary resistance to first-line chemo(immune)therapy, or progression of disease <3 years after fludarabine-based chemo(immune)therapy, or leukemia cells with del(17p)/TP53 mutation, must be:
    a. R/R after autologous or allogeneic HCT; or
    b. Patients not eligible for HCT; or
    c. R/R after ≥2 lines of therapy including at least 1 of the following: a BTK inhibitor, venetoclax, idelalisib, or duvelisib and for whom no standard therapy is available;
- ALL:
    a. R/R after allogeneic HCT and for whom no standard therapy is available; or
    b. Patients not eligible for allogeneic HCT must be R/R according to the following disease-specific specifications:
        - B-cell lymphoblastic leukemia/lymphoma: ≥2 lines of therapy including approved CAR T cell therapies, inotuzumab, ozogamicin, or blinatumomab and for whom no standard therapy is available;
        - T-cell lymphoblastic leukemia/lymphoma: ≥2 lines of therapy including nelarabine and for whom no standard therapy is available;
        - NK cell leukemia/lymphoma: ≥1 line of therapy and for whom no standard therapy is available;
- All other diagnoses: R/R after autologous or allogeneic HCT; or R/R after at least one line of therapy and for whom no standard therapy is available

For Phase 2 expansion cohorts:

Patients must have relapsed or refractory (R/R) disease with prior therapies defined below:

- DLBCL and high-grade B-cell lymphoma:
    e) R/R after autologous hematopoietic cell transplant (HCT); or
    f) R/R after chimeric antigen receptor T-cell (CAR T) therapy; or
    g) Patients not eligible for autologous HCT or CAR T therapy; or
    h) R/R after ≥2 lines of therapy including anti-CD20 antibody and failed, intolerant or ineligible for polatuzamab vedotin, or for whom no standard therapy is available.
- MCL:
    c) R/R after autologous HCT; or
    d) Patients not eligible for autologous HCT must have failed acalabrutinib or be R/R after ≥2 lines of therapy including at least 1 of the following: a Bruton's tyrosine kinase (BTK) inhibitor, bortezomib, or lenalidomide; or for whom no standard therapy is available;

- Primary mediastinal large B-cell lymphoma: R/R after ≥1 line of therapy and are not eligible for or have recurred after autologous HCT or CAR T cell therapy, or for whom no standard therapy is available;
- Primary DLBCL of the CNS: R/R after ≥1 line of therapy including methotrexate (unless intolerant to methotrexate) and are not eligible for or have recurred after autologous HCT or CAR T cell therapy, or for whom no standard therapy is available;
- Burkitt or Burkitt-like lymphoma/leukemia: R/R after ≥1 line of therapy including methotrexate (unless intolerant to methotrexate) and are not eligible for or have recurred after autologous HCT or CAR T cell therapy, or for whom no standard therapy is available;
- CLL/SLL: patients who have active disease requiring treatment and who are deemed at high-risk for disease progression by the investigator or have high risk features per the iwCLL criteria, such as primary resistance to first-line chemo(immune)therapy, or progression of disease <3 years after fludarabine-based chemo(immune)therapy, or leukemia cells with del(17p)/TP53 mutation, must be:
  d) R/R after autologous or allogeneic HCT; or
  e) Patients not eligible for HCT; or
  f) R/R after ≥2 lines of therapy including at least 1 of the following: a BTK inhibitor, venetoclax, idelalisib, or duvelisib, or for whom no standard therapy is available;
- Acute lymphoblastic leukemia (ALL):
  c) R/R after allogeneic HCT and for whom no standard therapy is available; or
  d) Patients not eligible for allogeneic HCT must be R/R according to the following disease-specific specifications:
    - B-cell lymphoblastic leukemia/lymphoma: ≥2 lines of therapy including approved CAR T cell therapies, inotuzumab ozogamicin, or blinatumomab, or for whom no standard therapy is available;
    - T-cell lymphoblastic leukemia/lymphoma: ≥2 lines of therapy including nelarabine, or for whom no standard therapy is available;
    - NK cell leukemia/lymphoma: ≥1 line of therapy or for whom no standard therapy is available;
- All other diagnoses: R/R after autologous or allogeneic HCT; or R/R after at least one line of therapy, or for whom no standard therapy is available.

4. Lansky (12 to 15 years of age) (Appendix G) or Karnofsky (≥16 years of age) (Appendix H) performance status ≥50;
5. Screening laboratory values that meet all of the following criteria:

For Phase 1:

- Absolute neutrophil count ≥0.5 × 10^9/L;

- Platelet count >50 × 10^9/L;
- Hemoglobin ≥8.0 g/dL;
- Aspartate aminotransferase or alanine aminotransferase ≤2.5 × ULN, unless due to the disease;
- Total bilirubin ≤1.5 × ULN (if secondary to Gilbert's syndrome, ≤3 × ULN is permitted), unless due to the disease; and
- Serum creatinine ≤1.5 × ULN or glomerular filtration rate ≥50 mL/min (calculated from a 24-hour urine collection);

For Phase 2:

- Absolute neutrophil count ≥0.05 × 10^9/L;
- Platelet count >25 × 10^9/L;
- Hemoglobin ≥6.5 g/dL;
- Aspartate aminotransferase or alanine aminotransferase ≤2.5 × ULN, unless due to the disease;
- Total bilirubin ≤1.5 × ULN (if secondary to Gilbert's syndrome, ≤3 × ULN is permitted), unless due to the disease; and
- Glomerular filtration rate ≥30 mL/min ; except for patients on metformin at baseline GFR must be ≥45 mL/min; *GFR can be calculated by the Cockcroft-Gault formula Appendix C*);

6. Minimum level of pulmonary reserve defined as <Grade 2 dyspnea and pulse oximetry ≥92% on room air;
7. Females of childbearing potential must have a negative serum pregnancy test at screening. Females of childbearing potential and nonsterile males must agree to use medically effective methods of contraception from the time of informed consent/assent through 1 month after study drug infusion, which must, at a minimum, include a barrier method; and
8. The ability to understand and willingness to sign a written informed consent form (ICF) and the ability to adhere to the study schedule and prohibitions. Patients under the age of 18 years (or other age as defined by regional law or regulation) must be willing and able to provide written assent and have a parent(s) or guardian(s) willing and able to provide written, signed informed consent after the nature of the study has been explained and prior to performance of any study-related procedure.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

For Phase 1:

1. History of another malignancy, except for the following:
   - Adequately treated local basal cell or squamous cell carcinoma of the skin;

- Adequately treated carcinoma in situ without evidence of disease;
- Adequately treated papillary, noninvasive bladder cancer; or
- Other cancer that has been in complete remission for ≥2 years. Patients with low-grade prostate cancer, on active surveillance, and not expected to clinically progress over 2 years are allowed;

2. Significant cardiovascular disease (e.g., myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to the start of AVM0703 administration, angina requiring therapy, symptomatic peripheral vascular disease, New York Heart Association Class III or IV congestive heart failure, left ventricular ejection fraction <30%, left ventricular fractional shortening <20%, or uncontrolled ≥Grade 3 hypertension (diastolic blood pressure [DBP] ≥100 mmHg or systolic blood pressure [SBP] ≥150 mmHg) despite antihypertensive therapy for patients ≥18 years of age, or uncontrolled stage 2 hypertension (DBP ≥90 mmHg or SBP ≥140 mmHg) despite antihypertensive therapy for patients ≥12 years of age;
3. Significant screening electrocardiogram (ECG) abnormalities, including unstable cardiac arrhythmia requiring medication, atrial fibrillation/flutter, left bundle-branch block, second-degree atrioventricular (AV) block type 2, third-degree AV block, ≥Grade 2 bradycardia, or heart rate corrected QT interval using Fridericia's formula >480 msec;
4. Known gastric or duodenal ulcer;
5. Uncontrolled type 1 or type 2 diabetes;
6. Known hypersensitivity or allergy to the study drug or any of its excipients;
7. Untreated ongoing bacterial, fungal, or viral infection (including upper respiratory tract infections) at the start of AVM0703 administration, including the following:

- Positive hepatitis B surface antigen and/or hepatitis B core antibody test plus a positive hepatitis B polymerase chain reaction (PCR) assay. Patients with a negative PCR assay are permitted with appropriate antiviral prophylaxis;
- Positive hepatitis C virus antibody (HCV Ab) test. Patients with a positive HCV Ab test are eligible if they are negative for hepatitis C virus by PCR;
- Positive human immunodeficiency virus (HIV) antibody test with detectable HIV load by PCR, or the patient is not able to tolerate antiretroviral therapy; or
- Positive tuberculosis test during screening;

8. Received live vaccination within 8 weeks of screening;
9. Pregnant or breastfeeding;
10. Concurrent participation in another therapeutic clinical study (except AVM0703-001); or
11. Manic-depressive disorder, schizophrenia, or a history of severe depression or substance abuse.

Exclusion Criteria for Phase 2:

Patients who meet any of the following criteria will be excluded from participation in the study for Phase 2:

1. History of another malignancy, except for the following:
   - Adequately treated local basal cell or squamous cell carcinoma of the skin;
   - Adequately treated carcinoma in situ without evidence of disease;
   - Adequately treated papillary, noninvasive bladder cancer; or
   - Other cancer that has been in complete remission for ≥2 years. Patients with low-grade prostate cancer, on active surveillance, and not expected to clinically progress over 2 years are allowed;
2. Significant cardiovascular disease (e.g., myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to the start of AVM0703 administration, angina requiring therapy, symptomatic peripheral vascular disease, New York Heart Association Class III or IV congestive heart failure, left ventricular ejection fraction <30%, left ventricular fractional shortening <20%, or uncontrolled ≥Grade 3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥150 mmHg) despite antihypertensive therapy for patients ≥18 years of age, or uncontrolled stage 2 hypertension (diastolic blood pressure ≥90 mmHg or systolic blood pressure ≥140 mmHg) despite antihypertensive therapy for patients ≥12 years of age;
3. Significant screening electrocardiogram (ECG) abnormalities, including unstable cardiac arrhythmia requiring medication, atrial fibrillation/flutter, second-degree atrioventricular (AV) block type 2, third-degree AV block, ≥Grade 2 bradycardia, or heart rate corrected QT interval using Fridericia's formula >480 msec;
4. Known gastric or duodenal ulcer;
5. Uncontrolled type 1 or type 2 diabetes;
6. Known hypersensitivity or allergy to the study drug or any of its excipients;
7. Untreated ongoing bacterial, fungal, or viral infection (including upper respiratory tract infections) at the start of AVM0703 administration, including the following:
   - Positive hepatitis B surface antigen and/or hepatitis B core antibody test plus a positive hepatitis B polymerase chain reaction (PCR) assay. Patients with a negative PCR assay are permitted with appropriate antiviral prophylaxis;
   - Positive hepatitis C virus antibody (HCV Ab) test. Patients with a positive HCV Ab test are eligible if they are negative for hepatitis C virus by PCR;
   - Positive human immunodeficiency virus (HIV) antibody test with detectable HIV load by PCR, or the patient is not able to tolerate antiretroviral therapy; or
   - Positive tuberculosis test during screening; test must be positive and not indeterminate due to anergy; if the result is indeterminate due to anergy the patient must not have a history of recent exposure to tuberculosis. Patients in Phase 2 repeat dosing cohorts

should not travel to any destination where they might be exposed to tuberculosis during their entire treatment period with AVM0703.

8. Received live vaccination within 8 weeks of screening;
9. Pregnant or breastfeeding;
10. Concurrent participation in another therapeutic clinical study (except AVM0703-001); or
11. Uncontrolled bipolar disorder or schizophrenia. Patients with a diagnosis, past or current, of bipolar disorder or schizophrenia or having a history of severe depression or substance abuse must be prophylactically treated with circadian physiologic hydrocortisone per section 5.5.3.3 CNS prophylaxis, without exception.

4.3 Withdrawal Criteria

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent/assent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any serious adverse event (SAE), clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;
- Pregnancy;
- Requirement of prohibited concomitant medication;
- Patient failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the End of Treatment (EOT)/Early Termination (ET) Visit. The reason for patient withdrawal must be documented in the electronic case report form (eCRF).

In the case of patients lost to follow-up, attempts to contact the patient should be made and documented in the patient's medical records.

5 STUDY TREATMENTS

5.1 Treatment Groups

Patients will be treated with AVM0703 (DSP).

5.2 Rationale for Dosing

From the phase 1 dose-escalation safety observations and response an 18 mg/kg dose has been approved by the SRC for a Phase 2 expansion RP2D. The 21 mg/kg cohort remains open for dose-escalation enrollment. For sites participating in both Phase 1 and Phase 2, patients will be enrolled into the 21 mg/kg dose-cohort unless i) no slot is available, ii) the patient cannot logistically comply with the PK blood draw requirements, iii) the cohort has been fully enrolled, or iv) the patient is enrolled into a Phase 2 repeat dosing RP2D cohort summarized below.

For Phase 2, one or more patient cohort(s) will receive repeat RP2D infusions in 21 day intervals until intolerance, unacceptable toxicity or disease progression, to determine the number of repeat infusions that are safe, effective and tolerable in this patient population. PK assessments will be made at sites participating in both Phase 1 and Phase 2 after each repeat infusion for the first 6 patients enrolled into each repeat dosing cohort. Full PK assessments will be made as per Phase 1 after the 1st (first) and 6th (sixth) repeat infusions, while for the second to fifth doses (2nd to 5th) PK assessments will be made pre-infusion, at end of infusion, 15 minutes and 48 hours after end of infusion. At least 6 patients will be enrolled in each RP2D repeat dosing cohort. Repeat dosing will be halted according to Table 5 Stopping Boundaries for Unacceptable Toxicities in Expansion Cohorts.

After 6 patients, who have had PK assessments, have reached intolerance, unacceptable toxicity, or disease progression, or they have received 6 infusions without intolerance, unacceptable toxicity, or disease progression, the Data Safety Monitoring Committee will review an integrated interim analysis of all available PK, PD, efficacy, safety and tolerability data and determine whether repeat dosing should continue or be limited to a certain number of infusions. Ongoing DSMC review will occur at least every 6 months. Based on integrated analysis, including dose-response and exposure-response, the DSMC will determine the optimal dose and dosing schedule for repeat dosing with AVM0703.

For Phase 2, RP2D cohorts will be included that do not require repeat 21 day interval dosing for patients who cannot comply with the visit schedule for repeat dosing. These patients can be retreated according to section 5.5.3.2.

There is information in the public domain along with studies conducted by AVM supporting a therapeutic benefit of high-dose corticosteroids in the setting of lymphoid malignancies. Clinical PK of DSP following IV administration is well understood based on information in the public domain and a long history of clinical use. Although DSP is used as a physical substance for the manufacture of AVM0703, the strength/presentation and dosing are expressed in DP equivalent according to the Decadron Phosphate injection label. The dose currently approved for DECADRON phosphate injection (24 mg/mL) for use in septic shock is up to 6 mg/kg DP IV and this will be the starting dose for AVM0703. The dose is supported by multiple nonclinical safety studies as well as the long history of clinical use of the drug product, and supportive information in the public domain.

A range of data supporting DP safety has been collected in the nonclinical setting, including 7-day LD_{50} data in normal and tumor-bearing mice. In normal mice, the oral LD_{50} was 1800 mg/kg in males and 2000 mg/kg in females (197). In tumor-bearing mice, by way of contrast, the oral LD_{50} was 710 mg/kg in males and 1210 mg/kg in females. In normal mice, lethality was not observed (independent of gender) at doses <1400 mg/kg; whereas, in tumor-bearing mice, lethality was not observed (independent of gender) for doses <531 mg/kg. Other Investigators have reported similar findings (e.g., no lethality at doses of DP <1000 mg/kg administered orally) in normal, healthy mice (198).

The lowest observed adverse effect level for dexamethasone after 26 weeks of oral administration of is 2 mg/kg. Target organ toxicity included the adrenal gland and thymus.

Based on the existing published information and dose-escalation data in the 6 and 9 mg/kg cohorts as well as single patient compassionate use IND data at 18 mg/kg doses, AVM believes that there are adequate safety data to support a dose escalation schema for DP with a starting dose of 6 mg/kg, escalation to 9 mg/kg, then 12mg/kg, then18 mg/kg, then 21 mg/kg. From the phase 1 dose-escalation 6, 9, 12, and 18 mg/kg cohorts AVM0703 has been generally well tolerated, with only 16 study drug-related adverse events during the DLT 7 day assessment period for the 6-18 mg/kg cohorts: 10 grade 1, 3 grade 2, and 3 grade 3. Physiologic hydrocortisone is required prophylactically to reduce/prevent GC neuropsychiatric side-effects (142), and only 4 neuropsychiatric side-effects of insomnia have been reported, three grade 1 and one grade 2. The limitation of side-effects to grades 1-3 is consistent with reports that acute AEs are not increased, and in fact may be reduced after an acute high-dose of GC compared to chronic low doses (146).

5.3 Randomization and Blinding

This is an open-label study. No blinding is needed.

5.4 Breaking the Blind

This is an open-label study. No blinding is needed.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The drug product, AVM0703 injection, will be supplied as a 50 mL sterile solution in an amber vial. Each vial contains 24 mg/mL DP in sodium citrate, disodium edetate, and sodium sulfite. The formulation is equivalent to 20 mg/mL dexamethasone base and 26.2 mg/mL DSP. Amber vials are utilized to protect the light-sensitive AVM0703 drug product. The product can be stored for at least 24 months at ambient conditions, and is the subject of an ongoing stability program.

5.5.2 Study Drug Preparation and Dispensing

AVM0703 will be supplied to the pharmacy for preparation. Each dose will be prepared by qualified clinical staff. AVM0703 will be diluted with normal saline (0.9% sodium chloride) to a final concentration of 10 mg/mL for administration. The dose (mg) for each patient will be determined by patient weight and cohort dose level. Please refer to the Pharmacy Manual for complete instructions on preparing the AVM0703 for patient administration.

5.5.3 Study Drug Administration

5.5.3.1 AVM0703

AVM0703 will be administered on an outpatient basis under the supervision of a physician or other study personnel experienced in the use of IV agents. AVM0703 can also be administered on an inpatient basis.

Administer AVM0703 (DSP) as a single IV infusion at a concentration of 10 mg/mL in normal saline. Infuse AVM0703 through a peripheral IV or a central access device using an infusion or syringe pump over a period of approximately 1 hour (must not be infused in less than 1 hour).

If a patient experiences an AE during the administration of study drug, the infusion may be slowed or stopped at the discretion of the Investigator. The infusion may be restarted once the AE has resolved at the discretion of the Investigator. For Phase 2, infusion reactions such as pruritis should be medically managed according to standard institutional practice, and restarting the infusion once the reaction has been controlled.

Do not co-administer other IV drugs concurrently with AVM0703 infusion.

Monitoring

For Phase 1: Patients will be monitored and observed during and for the first 4 hours following AVM0703 administration. Necessary monitoring equipment must be available, including heart monitor. Heart rhythm and vital signs will be monitored during the administration of AVM0703 and during the first 4 hours following AVM0703 administration.

Vital signs, including blood pressure, oxygen saturation, heart rate, respiration rate, and temperature will be obtained within 15 minutes prior to the start of the infusion and every 15 minutes during the first hour of the infusion and then every 30 minutes until the end of the infusion. For the first hour following the end of the infusion, vital signs will be collected every 30 minutes and then hourly thereafter until the end of the 4-hour observation period. All vital signs during and post-infusion will have a ±5-minute window.

For Phase 2: Patients will be monitored and observed during and for the first 1 hour following AVM0703 administration. Necessary monitoring equipment must be available. Vital signs will be monitored during the administration of AVM0703 and during the first 1 hour following AVM0703 administration.

Vital signs, including blood pressure, oxygen saturation, heart rate, respiration rate, and temperature will be obtained within 15 minutes prior to the start of the infusion and every 15 minutes during the one hour of the infusion and then every 30 minutes for 1 hour after the infusion. All vital signs during and post-infusion will have a ±5-minute window.

ECG will not be monitored since no ECG anomalies were reported for patients in Phase I. Blood pressure should be obtained within 15 minutes prior to the start of the infusion and then +/- 15 minutes at the end of infusion and again +/- 15 minutes after the 60 minute post-infusion observation period. If grade 3 or greater hypertension is recorded the patient should be monitored until hypertension has resolved to grade 2 or less or the patient has been prescribed appropriate medical management.

At the discretion of the infusion nurse, MDs or PI, additional post-infusion monitoring may be added based on vital sign readings during and 60 minutes after the AVM0703 RP2D infusion. Patients at risk for hypertension or for hyperglycemia, which includes patients with screening HbA1c levels of 5.7% or greater, fasting blood glucose levels of 110 mg/dL or higher, and patients with a history of glucocorticoid-induced hyperglycemia or pancreatitis, should have additional monitoring per institutional practice.

Age-appropriate emergency medications (crash carts) oxygen and cardiac resuscitation equipment must be immediately available in case an AE, allergic reaction, or anaphylaxis occurs. Site personnel must be qualified to detect and treat allergic reactions and anaphylaxis. If any signs or symptoms of allergic or anaphylactic reaction are observed during the infusion, administration of study drug must be immediately discontinued and the patient treated as appropriate.

5.5.3.2 Retreatment

Patients with a complete or partial response to AVM0703 who subsequently experience disease progression may be considered for repeat AVM0703 treatment, up to a maximum of 8 total infusions. The interval between AVM0703 infusions should be ≥28 days. The patient must meet the original eligibility criteria and undergo disease evaluation before retreatment, and the Investigator must receive approval from the Sponsor for retreatment. The dose level for retreatment may be the original dose level or a higher dose, provided the higher dose level was deemed safe by the SRC, or a lower dose level if the original dose level exceeded the MTD. The patient should be monitored for safety and disease efficacy in the same way as the original infusion.

For Phase 2, one or more patient cohort(s) will receive repeat RP2D infusions in 21 day intervals until intolerance, unacceptable toxicity or disease progression, to determine the number of repeat infusions that are safe, effective and tolerable in this patient population. PK assessments will be made at sites participating in both Phase 1 and Phase 2 after each repeat infusion for the first 6 patients enrolled into each repeat dosing cohort. Full PK assessments will be made as per Phase 1 after the 1st (first) and 6th (sixth) repeat infusions, while for the second to fifth doses (2nd to 5th) PK assessments will be made pre-infusion, at end of infusion, 15 minutes and 48 hours after end of infusion. At least 6 patients will be enrolled in each RP2D repeat dosing cohort. Repeat dosing will be halted according to Table 6 Stopping Boundaries for Unacceptable Toxicities in Expansion Cohorts.

After 6 patients, who have had PK assessments, have reached intolerance, unacceptable toxicity, or disease progression, or they have received 6 infusions without intolerance, unacceptable toxicity, or disease progression, the Data Safety Monitoring Committee will review an integrated interim analysis of all available PK, PD, efficacy, safety and tolerability data and determine whether repeat dosing should continue or be limited to a certain number of infusions. Ongoing DSMC review will occur at least every 6 months. Based on integrated analysis, including dose-response and exposure-response, the DSMC will determine the optimal dose and dosing schedule for repeat dosing with AVM0703.

5.5.3.3 CNS prophylaxis

For prophylaxis against dexamethasone-induced CNS side effects, hydrocortisone will be dosed orally or by IV for 5 days starting on the day of dexamethasone infusion. Hydrocortisone will be

divided into 3 daily doses starting in the morning and spaced 6 to 8 hours apart using the following dosing schedule each day: for pediatric and adolescent patients at 5 mg/m^2 (morning dose), 3 mg/m^2 (mid-day dose), and 2 mg/m^2 dose (evening dose); and for adult patients at 10 mg/m^2 (morning dose), 5 mg/m^2 (mid-day dose), and 5 mg/m^2 dose (evening dose), the last dose administered at hour of sleep.[7] Oral doses may be rounded up to the nearest 1 mg.

5.5.3.4 Required supportive care

- Prophylaxis for GI bleeding: Administer a proton pump inhibitor or H2 blocker starting at least 1 day prior to and for approximately 4 weeks after AVM0703 administration, as per institutional guidelines for Phase 1. For Phase 2, administer a proton pump inhibitor or H2 blocker starting at least 1 day prior to and for 4 days after each AVM0703 administration
- Prophylaxis for (tumor lysis syndrome) TLS: All patients should be assessed for risk of TLS. Patients at high risk for TLS are defined as patients with ALC >25 × 10^9/L and/or who have a lymph node ≥10 cm. For patients at high risk of TLS, recommended prophylaxis is oral and IV hydration and anti-hyperuricemic therapy (e.g., allopurinol or rasburicase) starting before AVM0703 administration per institutional standard practice.
- Prophylaxis for patients not deemed high risk for TLS will be at the discretion of the Investigator.
- Monitoring TLS: High-risk patients should have TLS labs (e.g., potassium, phosphorus, calcium, uric acid, and creatinine) obtained pre-dose, and 4 and 8 hours post-infusion of AVM0703 on Day 0, and at least once on Day 1 (for Phase 1 only). Patients with signs of TLS should be monitored at least daily until all signs of TLS have resolved or are no longer clinically significant.

5.5.4 Treatment Compliance

AVM0703 will be administered only by study personnel by IV infusion at the study site. The administration location, rate, infusion date and start and stop times, any infusion interruptions, and total volume of AVM0703 actually administered will be recorded in the eCRFs.

5.5.5 Storage and Accountability

AVM0703 must be stored at ambient temperature, protected from light, and kept under secure conditions until preparation for use. AVM0703 will be administered according to the instructions given in the Pharmacy Manual.

Accountability procedures for the study drug are described in the Pharmacy Manual. A record will be maintained by the investigational site which will account for all dispensing, destruction, and/or return of any used and unused study drug.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Use of any other investigational drug is excluded during the study.

5.6.2 Restricted Medications and/or Procedures

The following medications are restricted:

- Use of live vaccine within 8 weeks of screening;
- Co-administration of strong or moderate cytochrome P450 (CYP)3A4 inhibitors or strong CYP3A4 inducers (see Appendix C) within 2 weeks post AVM0703 administration. Avoid consuming grapefruit/grapefruit juice and Seville oranges within 2 weeks post AVM0703 administration. If unavoidable, closely monitor for adverse reactions or loss of efficacy. Dexamethasone is a CYP3A4 inducer; therefore, it may interfere with the efficacy of sensitive CYP3A4 substrates that should be monitored for loss of efficacy; and
- Non-steroidal anti-inflammatory medications (e.g., ibuprofen, naproxen, aspirin, cyclooxygenase-2 inhibitors, etc) should be avoided during the first week after AVM0703 infusion and if the patient develops clinically significant thrombocytopenia.

5.6.3 Allowed Medications and/or Procedures

All supportive care measures, medications, and procedures are allowed as clinically indicated, except as outlined in Sections 5.6.1 and 5.6.2.

5.6.4 Required Monitoring Post AVM0703 Infusion

Patients will be monitored on Days 1, 2, 3, 4 (day 4 only for Phase 1), and 7 for the following:

- CNS symptoms/changes including insomnia: Patients are potentially at risk for cognitive, behavioral, and mood changes. Mania-like symptoms are more commonly associated with short-term use of corticosteroids. A detailed history of cognitive, behavioral and mood changes, and sleep will be obtained.
- Hypertension: Hypertension in adult patients will be defined as SBP >140 mm/Hg and DBP >90 mm/Hg and hypertension in pediatric patients will be defined per the 2017 American Association of Pediatrics Definitions for pediatric blood pressure (Appendix F) (199). Blood pressure should be monitored. Anti-hypertensive medication (e.g., calcium channel blockade or angiotensin-converting-enzyme inhibitor) may be adjusted or added as clinically indicated.
- Hyperglycemia: Blood glucose will be obtained, and persistent or significant hyperglycemia will be managed per institutional guidelines. The pathophysiology of hyperglycemia is related to corticosteroid-induced insulin-resistance and is expected to resolve with appropriate medical intervention within 72 hours.
- Metabolic derangements: All patients will have chemistry panel including electrolytes, albumin, calcium, phosphorus, magnesium, and uric acid to monitor for metabolic derangements. Hypocalcemia and hypokalemia will be assessed and managed per institutional guidelines.
- Gastrointestinal bleeding: Monitor patients for signs and symptoms of GI bleeding.
- Renal and liver function: All patients will be monitored for renal function (e.g., creatinine and blood urea nitrogen) and liver function (e.g., alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin).

5.6.5 Recommended Supportive Care Guidelines

5.6.5.1 Antibiotics, antifungals, and antivirals

Patients should be treated prophylactically with an antiviral such as acyclovir until their ALC is $>0.5 \times 10^{\wedge 9}$/L. In addition, *Pneumocystis jirovecii* prophylaxis should be instituted (e.g., with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) before the infusion and for 6 months post-infusion. Prophylaxis with IV immunoglobulin should be considered. Local practices or guidelines regarding infection prophylaxis may be followed.

For patients with a history of fungal infection, miconazole or fluconazole is preferred. Other antifungal prophylaxis, if required, should be used with caution as many antifungals are strong or moderate CYP3A4 inhibitors which are restricted in this study unless unavoidable as described in Section 5.6.2.

Patients who develop an intercurrent infection during the study may receive therapeutic antibacterial, antiviral, or antifungal drugs for intercurrent infections as needed.

5.6.6 Other Supportive Care

5.6.6.1 Osteopenia or osteoporosis/avascular necrosis

Calcium and vitamin D supplementation may be considered. A dual energy x-ray absorptiometry (DEXA) scan will be obtained during screening and at 12 months post-infusion.

5.6.6.2 Visual changes

Visual changes will be assessed as a part of the medical history. Consider referral to ophthalmologist, if indicated.

5.6.6.3 Antiemetics

While prophylactic antiemetics can be considered, it is not expected that antiemetics will be required for this study. Choice of antiemetic therapy should be based on standard practice and/or institutional guidelines.

5.6.6.4 Hematopoietic support

Granulocyte colony-stimulating factor (e.g., filgrastim, filgrastim-snd, peg-filgrastim, or lenograstim) and erythropoietic agents (e.g., erythropoietin or darbepoetin) may be administered as needed at the discretion of the Investigator and per institutional guidelines. Red blood cell or platelet transfusions may be administered as medically indicated.

5.6.6.5 Adrenal insufficiency

After the hydrocortisone prophylaxis is completed, patients may use systemic, enteric, topical, or inhaled corticosteroids as required. Patients with symptoms of adrenal insufficiency should be evaluated (e.g., cortrosyn stimulation test) and given replacement corticosteroids as per institutional guidelines.

5.6.7 Documentation of Prior and Concomitant Medication Use

All prior and concomitant medications (including subsequent anticancer therapies and procedures) will be recorded on the appropriate eCRF.

6 STUDY PROCEDURES

For Phase 2 patients who are enrolled into repeat dosing cohorts, for Cycle 1 study visits will be identical to visits for single dose patients as detailed in section 6.1 to section 6.15 below. For Phase 2 patients enrolled into repeat dosing cohorts in 21 day intervals, study visits for:

Cycle 1 will be Visit 1 (day 0 section 6.3), Visit 2 (day 1 section 6.4), Visit 3 (day 2 section 6.5), Visit 4 (day 3 section 6.6), Visit 5 (day 4) is not required for repeat dosed patients, Visit 6 (day 7) is not required for repeat dosed patients, Visit 7 (day 14 section 6.9), *Visit 8 (day 21) will be visit 1 (day 0 section 6.3) of cycle 2*, Visit 9 (day 28 section 6.11), Visit 10 (3 months section 6.12), visit 11 (6 months section 6.13), visit 12 (12 months section 6.14).

Cycle 2 will be Visit 1 Cycle 2 (day 21 section 6.3), Visit 2 Cycle 2 (day 22 section 6.4), Visit 3 Cycle 2 (day 23 section 6.5), Visit 4 Cycle 2 (day 24 section 6.6), Visit 5 (section 6.7) is not required for repeat dosed patients, Visit 6 (section 6.8) is not required for repeat dosed patients, Visit 7 Cycle 2 (day 35 ±1 day section 6.9), *Visit 8 Cycle 2 (day 42) will be visit 1 (day 0 section 6.3) of cycle 3, and so on.*

- Disease Assessments (including imaging, bone marrow biopsy, skin assessments, CSF, peripheral blood involvement), Survival Status, and Lansky or Karnofsky Performance Status will be obtained on day 28 ±1 day after the first (1st) AVM0703 infusion, 3 months ±7 days after the first (1st) AVM0703 infusion, 6 months ±7 days after the first (1st) AVM0703 infusion, and 12 months ±14 days after the first (1st) AVM0703 infusion.

The tables below list the required visits for each patient calculated from day 0 Visit 1 Cycle 1:

Cycle 1	Visit 1	Visit 2	Visit 3	Visit 4	~~Visit 5~~	~~Visit 6~~	Visit 7
Day after 1st AVM0703 infusion	0	1	2	3			14

Cycle 2	Visit 1	Visit 2	Visit 3	Visit 4	~~Visit 5~~	~~Visit 6~~	Visit 7
Day after 1st AVM0703 infusion	21	22	23	24			35

Cycle 3	Visit 1	Visit 2	Visit 3	Visit 4	~~Visit 5~~	~~Visit 6~~	Visit 7
Day after 1st AVM0703 infusion	42	43	44	45			56

Cycle 4	Visit 1	Visit 2	Visit 3	Visit 4	~~Visit 5~~	~~Visit 6~~	Visit 7
Day after 1st AVM0703 infusion	63	64	65	66			77

Cycle 5	Visit 1	Visit 2	Visit 3	Visit 4	~~Visit 5~~	~~Visit 6~~	Visit 7
Day after 1st AVM0703 infusion	84	85	86	87			98

Cycle 6	Visit 1	Visit 2	Visit 3	Visit 4	~~Visit 5~~	~~Visit 6~~	Visit 7
Day after 1st AVM0703 infusion	105	106	107	108			119

Additional cycles beyond Cycle 6 will be similarly calculated based on day after 1st AVM0703 infusion; for instance, Cycle 7 would begin on day 126, Cycle 8 would begin on day 147. For cycles beyond cycle 6, only Visits 2-4 will be required. Visit 7 (day 14 of each cycle) will not be required.

Phase 2 patients enrolled into single dose cohorts may be retreated according to section 5.5.3.2.

6.1 Informed Consent/Assent

Written informed consent/assent for the study will be obtained from all patients before any study-specific procedures are performed. See Section 11.3 for details on informed consent/assent.

6.2 Screening Visit (Day -28 to Day -1)

The following procedures will be performed at the Screening Visit:

- Obtain informed consent/assent;
- Record demographics and medical history;
- Perform physical examination;
- Assess inclusion/exclusion criteria;
- Obtain vital signs;
- Obtain height and weight;
- Obtain Lansky (12 to 15 years of age) (Appendix G) or Karnofsky (≥16 years of age) (Appendix H) performance status;
- Obtain blood samples for the following local labs: Serum pregnancy test (only for females of childbearing potential); HIV antibody test, hepatitis B surface antigen and/or hepatitis B core

antibody plus hepatitis B PCR assay, HCV Ab test, tuberculosis test; fluorescence in situ hybridization (FISH) (for CLL patients); CBC with differential; serum chemistry; coagulation; HbA1c; and TLS risk assessment and monitoring as per Section 5.5.3.3 and Appendix A;

- Obtain blood sample for the following central lab: Serum biomarkers
- Obtain urine sample for urinalysis;
- Obtain bone marrow biopsy/aspirate;
- Obtain tumor biopsy (optional);
- Perform 12-lead ECG;
- Perform disease assessment;
- Obtain DEXA scan;
- For Phase 2 PROMIS questionnaires will not be obtained. Obtain the following questionnaires: PROMIS Scale v1.2 - Global Health (≥18 years of age); PROMIS – Ca Bank v1.1 - Physical Function (≥18 years of age); PROMIS Item Bank v2.0 – Cognitive Function (≥18 years of age); PROMIS Pediatric Scale v1.0 – Global Health 7 + 2 (<18 years of age) or parent proxy; PROMIS Pediatric Item Bank v2.0 – Upper Extremity – Short Form 8a (<18 years of age) or parent proxy; PROMIS Pediatric Item Bank v2.0 – Mobility – Short Form 8a (<18 years of age) or parent proxy; and PROMIS Pediatric Item Bank v1.0 – Cognitive Function (<18 years of age); and
- Record prior/concomitant medications.

6.3 Treatment Period – Visit 1 (Day 0)

For patients in Phase 2 repeat dosing cohorts in 21 day intervals, Visit 1 will be repeated after each AVM0703 infusion and will be on D0, D21, D42, D63, D84, D105, etc.

The following procedures will be performed at Visit 1 (Day 0):

- Perform symptom-directed physical examination (predose);
- Obtain weight (predose);
- Obtain blood samples for the following local labs: Serum pregnancy test (only for females of childbearing potential); CBC with differential; serum chemistry; coagulation; TLS risk assessment and monitoring as per Section 5.5.3.3 and Appendix A; HbA1c; and immunoglobulin G (IgG) test (predose);
- Obtain blood samples for the following central labs:
  - PBMC/Plasma biomarker (predose and 1 hour post-infusion [±10 min]);
  - Lymphocyte subsets (predose and 1 hour post-infusion [± 10 min]); and
  - PK sampling for Phase 1 and for Phase 2 for the first 6 patients in repeat dosing cohorts after the 1st (first) and 6th (sixth) infusions:

Table 7 PK time points and windows

Timepoint	Window	Timeframe
Predose	Within 60 minutes	Prior to dosing
5 minutes	±5 min	Before the end of infusion
15 minutes	±5 min	After the end of infusion
30 minutes	±10 min	
60 minutes	±10 min	
90 minutes	±10 min	
2 hours	±10 min	
4 hours	±30 min	
6 hours	±30 min	
8 hours	±30 min	

For Phase 2 for the first 6 patients in repeat dosing cohorts after the 2nd (second) to 5th (fifth) infusions

Timepoint	Window	Timeframe
Predose	Within 60 minutes	Prior to dosing
5 minutes	±5 min	Before the end of infusion
15 minutes	±5 min	After the end of infusion

- Obtain urine sample for urinalysis;
- Obtain vital signs (predose [within 15 minutes prior to the start of the infusion], and every 15 minutes during the one hour of the infusion and then every 30 minutes until the end of the infusion. For the first hour following the end of the infusion, vital signs will be collected every 30 minutes and then hourly thereafter until the end of the 4-hour observation period [vital signs during and post-infusion have a ±5-minute window]; For Phase 2 vital signs will only be obtained prior to dosing and at 30±15 minutes and 60±15 minutes after the AVM0703 infusion during the one hour observation period;
- Administer hydrocortisone;
- Administer AVM0703;
- For Phase 1 only: Perform 12-lead ECG (15 ±5 minutes prior to AVM0703 administration and at the end of AVM0703 administration ±5 minutes; and 2 hours ±5 minutes and 4 hours ±5 minutes post AVM0703 administration);
- For Phase 1 only: Obtain the following questionnaires: PROMIS Item Bank v2.0 – Cognitive Function (≥18 years of age) and PROMIS Pediatric Item Bank v1.0 – Cognitive Function (<18 years of age) (predose);
- Assess AEs; and
- Record concomitant medications.

6.4 Visit 2 (Day 1)

For patients in Phase 2 repeat dosing cohorts in 21 day intervals, Visit 2 will be repeated after each AVM0703 infusion and will be on D1, D22, D43, D64, D85, D106, etc.

The following procedures will be performed at Visit 2 (Day 1):

- Record medical history;
- Perform symptom-directed physical examination;
- Obtain vital signs;
- Obtain weight;
- Obtain blood samples for the following local labs: CBC with differential; serum chemistry; coagulation; and TLS risk assessment and monitoring as per Section 5.5.3.3 and Appendix A;
- for Phase 1 and for Phase 2 repeat dosing cohorts after the 1st (first) and 6th (sixth) infusions : Obtain blood sample for the following central lab: PK sampling (24 ±2 hours post end of infusion;
- Obtain urine sample for urinalysis;
- Administer hydrocortisone;
- For Phase 1 only: Obtain the following questionnaires: PROMIS Item Bank v2.0 – Cognitive Function (≥18 years of age) and PROMIS Pediatric Item Bank v1.0 – Cognitive Function (<18 years of age);
- Assess AEs; and
- Record concomitant medications.

6.5 Visit 3 (Day 2)

For patients in Phase 2 repeat dosing cohorts in 21 day intervals, Visit 3 will be repeated after each AVM0703 infusion and will be on D2, D23, D44, D65, D86, D107, etc.

The following procedures will be performed at Visit 3 (Day 2):

- Record medical history;
- Perform symptom-directed physical examination;
- Obtain vital signs;
- Obtain weight;
- Obtain blood samples for the following local labs: CBC with differential and serum chemistry;
- Obtain blood samples for the following central labs: Serum biomarkers and for Phase 1 and for Phase 2 repeat dosing cohorts after each infusion PK sampling (48 ±2 hours post end of infusion);
- Administer hydrocortisone;
- Assess AEs; and
- Record concomitant medications.

6.6 Visit 4 (Day 3)

For patients in Phase 2 repeat dosing cohorts in 21 day intervals, Visit 4 will be repeated after each AVM0703 infusion and will be on D3, D24, D45, D66, D87, D108, etc.

The following procedures will be performed at Visit 4 (Day 3):

- Record medical history;
- Perform symptom-directed physical examination;
- Obtain vital signs;
- Obtain weight;
- Obtain blood samples for the following local labs: CBC with differential and serum chemistry;
- Obtain blood samples for the following central labs: PBMC/Plamsa biomarker and lymphocyte subsets;
- Administer hydrocortisone;
- Assess AEs; and
- Record concomitant medications.

6.7 Visit 5 (Day 4)

Visit 5 will not be required for Phase 2 repeat dosing 21 day interval cohorts.

The following procedures will be performed at Visit 5 (Day 4):

- Record medical history;
- Perform symptom-directed physical examination;
- Obtain vital signs;
- Obtain weight;
- Obtain blood samples for the following local labs: CBC with differential and serum chemistry;
- Administer hydrocortisone;
- Assess AEs; and
- Record concomitant medications.

6.8 Visit 6 (Day 7 ±1 Day)

Visit 6 will not be required for Phase 2 repeat dosing 21 day interval cohorts.

The following procedures will be performed at Visit 6 (Day 7 ±1 day):

- Record medical history;
- Perform symptom-directed physical examination;
- Obtain vital signs;
- Obtain weight;

- Obtain blood samples for the following local labs: CBC with differential; serum chemistry; coagulation; HbA1c; and TLS risk assessment and monitoring as per Section 5.5.3.3 and Appendix A;
- Obtain blood samples for the following central labs: Serum biomarkers;
- Obtain urine sample for urinalysis;
- For Phase 1 only: Obtain the following questionnaires: PROMIS Item Bank v2.0 – Cognitive Function (≥18 years of age) and PROMIS Pediatric Item Bank v1.0 – Cognitive Function (<18 years of age);
- Assess AEs; and
- Record concomitant medications.

6.9 Visit 7 (Day 14) (±1 Day)

For patients in Phase 2 repeat dosing cohorts in 21 day intervals, Visit 7 will be repeated after each AVM0703 infusion and will be on D14, D27, D48, D69, D90, D111, etc.

The following procedures will be performed at Visit 7 (Day 14 ±1 day):

- Perform symptom-directed physical examination;
- Obtain vital signs;
- Obtain weight;
- Obtain blood samples for the following local labs: CBC with differential; serum chemistry; coagulation; HbA1c; and TLS risk assessment and monitoring as per Section 5.5.3.3 and Appendix A;
- Obtain blood samples for the following central labs: Serum biomarkers; PBMC/Plamsa biomarker; and lymphocyte subsets;
- Obtain urine sample for urinalysis;
- For Phase 1 only: Obtain the following questionnaires: PROMIS Item Bank v2.0 – Cognitive Function (≥18 years of age) and PROMIS Pediatric Item Bank v1.0 – Cognitive Function (<18 years of age);
- Assess AEs; and
- Record concomitant medications.

6.10 Visit 8 (Day 21 ±1 Day)

For patients in Phase 2 repeat dosing cohorts in 21 day intervals, Visit 8 will be on D21, D42, D63, D84, D105, etc after each AVM0703 infusion. Procedures for repeat dosing patients will be according to Visit 1 (day 0). Please see Appendix A2: Schedule of Procedures for repeat dosed patient cohorts.

For patients in single dose cohorts the following procedures will be performed at Visit 8 (Day 21 ±1 day):

- Perform symptom-directed physical examination;
- Obtain vital signs;
- Obtain weight;
- Obtain blood samples for the following local labs: CBC with differential; serum chemistry; coagulation; HbA1c; and TLS risk assessment and monitoring as per Section 5.5.3.3 and Appendix A;
- Obtain urine sample for urinalysis;
- For Phase 1 only: Obtain the following questionnaires: PROMIS Item Bank v2.0 – Cognitive Function (≥18 years of age) and PROMIS Pediatric Item Bank v1.0 – Cognitive Function (<18 years of age);
- Assess AEs; and
- Record concomitant medications.

6.11 Visit 9 (Day 28) (±1 Day)

The following procedures will be performed at Visit 9 (Day 28 ±1 day):

- Perform symptom-directed physical examination;
- Obtain vital signs;
- Obtain weight;
- Obtain Lansky (12 to 15 years of age) (Appendix G) or Karnofsky (≥16 years of age) (Appendix H) performance status;
- Obtain blood samples for the following local labs: CBC with differential; serum chemistry; coagulation; HbA1c; and IgG test;
- Obtain urine sample for urinalysis;
- Perform disease assessment;
- For Phase 1 only: Obtain the following questionnaires: PROMIS Scale v1.2 - Global Health (≥18 years of age); PROMIS – Ca Bank v1.1 - Physical Function (≥18 years of age); PROMIS Item Bank v2.0 – Cognitive Function (≥18 years of age); PROMIS Pediatric Scale v1.0 – Global Health 7 + 2 (<18 years of age) or parent proxy; PROMIS Pediatric Item Bank v2.0 – Upper Extremity – Short Form 8a (<18 years of age) or parent proxy; PROMIS Pediatric Item Bank v2.0 – Mobility – Short Form 8a (<18 years of age) or parent proxy; and PROMIS Pediatric Item Bank v1.0 – Cognitive Function (<18 years of age) or parent proxy;
- Assess AEs; and
- Record concomitant medications.

6.12 Visit 10 (3 Months Post-Infusion ±7 Days)

The following procedures will be performed at Visit 10 (3 months post-infusion ±7 days):

- Perform symptom-directed physical examination;
- Obtain vital signs;
- Obtain weight;
- Obtain Lansky (12 to 15 years of age) (Appendix G) or Karnofsky (≥16 years of age) (Appendix H) performance status;
- Obtain blood samples for the following local labs: CBC with differential; serum chemistry; coagulation; and IgG test;
- Obtain blood sample for the following central lab: Serum biomarkers
- Obtain urine sample for urinalysis;
- Perform disease assessment;
- For Phase 1 only: Obtain the following questionnaires: PROMIS Scale v1.2 - Global Health (≥18 years of age); PROMIS – Ca Bank v1.1 - Physical Function (≥18 years of age); PROMIS Pediatric Scale v1.0 – Global Health 7 + 2 (<18 years of age) or parent proxy; PROMIS Pediatric Item Bank v2.0 – Upper Extremity – Short Form 8a (<18 years of age) or parent proxy; and PROMIS Pediatric Item Bank v2.0 – Mobility – Short Form 8a (<18 years of age) or parent proxy;
- Assess AEs;
- Obtain overall survival for patients who go on to receive additional anticancer therapy; and
- Record concomitant medications.

6.13 Visit 11 (6 Months Post-Infusion ±7 Days)

The following procedures will be performed at Visit 11 (6 months post-infusion ±7 days):

- Perform symptom-directed physical examination;
- Obtain vital signs;
- Obtain weight;
- Obtain Lansky (12 to 15 years of age) (Appendix G) or Karnofsky (≥16 years of age) (Appendix H) performance status;
- Obtain blood samples for the following local labs: CBC with differential and serum chemistry);
- Obtain blood sample for the following central lab: Serum biomarkers
- Perform disease assessment;
- For Phase 1 only: Obtain the following questionnaires: PROMIS Scale v1.2 - Global Health (≥18 years of age); PROMIS – Ca Bank v1.1 - Physical Function (≥18 years of age); PROMIS Pediatric Scale v1.0 – Global Health 7 + 2 (<18 years of age) or parent proxy; PROMIS Pediatric Item Bank v2.0 – Upper Extremity – Short Form 8a (<18 years of age) or parent proxy; and PROMIS Pediatric Item Bank v2.0 – Mobility – Short Form 8a (<18 years of age) or parent proxy;

- Assess AEs;
- Obtain overall survival for patients who go on to receive additional anticancer therapy; and
- Record concomitant medications.

6.14 EOT Visit (12 Months Post-Infusion) (±7 Days) (For Early Termination or Study Withdrawal, see Section 6.15 for procedures to be performed for EOT Visit).

The following procedures will be performed at the EOT Visit (12 months post-infusion ±7 days):

- Perform physical examination;
- Obtain vital signs;
- Obtain weight;
- Obtain Lansky (12 to 15 years of age) (Appendix G) or Karnofsky (≥16 years of age) (Appendix H) performance status;
- Obtain blood samples for the following local labs: serum pregnancy test (only for females of childbearing potential); CBC with differential; serum chemistry; coagulation; and FISH (for CLL patients);
- Obtain urine sample for urinalysis;
- Obtain bone marrow biopsy/aspirate;
- Obtain tumor biopsy (optional);
- Perform 12-lead ECG;
- Perform disease assessment;
- Obtain DEXA scan;
- For Phase 1 only: Obtain the following questionnaires: PROMIS Scale v1.2 - Global Health (≥18 years of age); PROMIS – Ca Bank v1.1 - Physical Function (≥18 years of age); PROMIS Pediatric Scale v1.0 – Global Health 7 + 2 (<18 years of age) or parent proxy; PROMIS Pediatric Item Bank v2.0 – Upper Extremity – Short Form 8a (<18 years of age) or parent proxy; and PROMIS Pediatric Item Bank v2.0 – Mobility – Short Form 8a (<18 years of age) or parent proxy;
- Assess AEs;
- Obtain overall survival for patients who go on to receive additional anticancer therapy; and
- Record concomitant medications.

6.15 Early Termination Visit and Withdrawal Procedures

The EOT for patients completing the study is the EOT/ET Visit (12 months post-infusion). For patients who are withdrawn from the study prior to completion, all EOT/ET Visit procedures will be performed at an ET visit. These procedures include the following:

- Perform physical examination;
- Obtain vital signs;
- Obtain weight;
- Obtain Lansky (12 to 15 years of age) (Appendix G) or Karnofsky (≥16 years of age) (Appendix H) performance status;
- Obtain blood samples for the following local labs: Serum pregnancy test (only for females of childbearing potential); CBC with differential; serum chemistry; coagulation; and FISH (for CLL patients);
- Obtain urine sample for urinalysis;
- Obtain bone marrow biopsy/aspirate;
- Obtain tumor biopsy (optional);
- Perform 12-lead ECG;
- Perform disease assessment;
- For Phase 1 only: Obtain the following questionnaires: PROMIS Scale v1.2 - Global Health (≥18 years of age); PROMIS – Ca Bank v1.1 - Physical Function (≥18 years of age); PROMIS Pediatric Scale v1.0 – Global Health 7 + 2 (<18 years of age) or parent proxy; PROMIS Pediatric Item Bank v2.0 – Upper Extremity – Short Form 8a (<18 years of age) or parent proxy; and PROMIS Pediatric Item Bank v2.0 – Mobility – Short Form 8a (<18 years of age) or parent proxy;
- Assess AEs;
- Obtain overall survival for patients who go on to receive additional anticancer therapy; and
- Record concomitant medications.

7 ENDPOINTS

7.1 Phase 1

The primary endpoint for the Phase 1 portion of the study is the incidence of AEs, including DLTs.

The secondary endpoints include the following:

- ORR (CR plus partial response [PR]) at 28 days post-infusion;
- CR rate at 28 days post-infusion;
- Progression-free survival at 3, 6, and 12 months post-infusion;
- Overall survival at 3, 6, and 12 months post-infusion;
- Time to response;
- DOR;
- Area under the plasma concentration-time curve (AUC) from time 0 to the last measurable concentration, maximum observed concentration (C_{max}), AUC from time 0 to infinity, half-life, volume of distribution, and clearance;
- Number of platelet and red blood cell transfusions received following AVM0703 administration;
- Lansky (12 to 15 years of age) (Appendix G) or Karnofsky (≥16 years of age) (Appendix H) performance status;
- Patient-Reported Outcomes Measurement Information System (PROMIS®) Scale v1.2 - Global Health (≥18 years of age);
- PROMIS – Ca Bank v1.1 - Physical Function (≥18 years of age);
- PROMIS Item Bank v2.0 – Cognitive Function (≥18 years of age);
- PROMIS Pediatric Scale v1.0 – Global Health 7 + 2 (<18 years of age) or parent proxy;
- PROMIS Pediatric Item Bank v2.0 – Upper Extremity – Short Form 8a (<18 years of age) or parent proxy;
- PROMIS Pediatric Item Bank v2.0 – Mobility – Short Form 8a (<18 years of age) or parent proxy; and
- PROMIS Pediatric Item Bank v1.0 – Cognitive Function (<18 years of age) or parent proxy.
- For patients with DLBCL (including DLBCL arising from follicular lymphoma); high-grade B-cell lymphoma; MCL; primary mediastinal large B-cell lymphoma; primary DLBCL of the CNS; Burkitt or Burkitt-like lymphoma/leukemia; B-lymphoblastic leukemia/lymphoma, T-lymphoblastic leukemia/lymphoma, acute leukemia/lymphoma, acute leukemias of ambiguous lineage, or NK cell leukemia/lymphoma, tumor response will be assessed per the Lugano Treatment Response Criteria (Appendix D).[82] For patients with CLL/SLL, tumor response will be assessed per the iwCLL criteria (Appendix E).[165]

The exploratory endpoints include the following:

- Assessment of intercellular adhesion molecule (ICAM) expression, GR expression, B and T lymphocyte levels, myeloid-derived suppressor cell levels, NK cell levels, and NKT cell levels in peripheral blood and tumor samples if available; and
- Assessment of minimal residual disease.

7.2 Phase 2

The primary endpoint for the Phase 2 portion of the study is ORR, defined as the proportion of patients with a best overall response of CR or PR at day 28 for patients not receiving repeat dosing in 21 day intervals. For Phase 2 expansion patients receiving repeat RP2D doses in 21 day intervals the primary endpoint is best ORR (CR or PR) at any time point.

The following will be used to determine PR, CR and ORR:
Imaging Assessments:

- Patients with DLBCL (including DLBCL arising from follicular lymphoma); high-grade B-cell lymphoma; MCL; primary mediastinal large B-cell lymphoma; Burkitt or Burkitt-like lymphoma/leukemia; or B-lymphoblastic leukemia/lymphoma, T-lymphoblastic leukemia/lymphoma, acute leukemia/lymphoma, acute leukemias of ambiguous lineage, or NK cell lymphoblastic leukemia/lymphoma, or PTCL, tumor response will be assessed per The Lugano Classification (8) in support of response and progression endpoints.
    - Lugano assessments of response and progression require imaging and clinical data assessments:
        - Imaging Data: The following imaging data is required to support Lugano assessments:
            (a) Brain CT or MRI with contrast
                (i) Required during screening for participants with known or suspected CNS involvement
                (ii) Required at all visits for participants with known CNS involvement found during screening
                (iii) Required as clinically indicated for suspected to have developed CNS involvement post- screening.
            (b) Diagnostic Quality CT with contrast (preferred), or MRI with contrast required for all participants at all visits
                (i) During Screening: Neck, chest, abdomen, and pelvis as clinically indicated and any other sites of known or suspected disease involvement
                (ii) On Treatment: All known or suspected sites of disease involvement
            (c) FDG PET/CT (whole body – covering all areas of known or suspected disease)
                (i) Required during screening for all participants

(ii) On Treatment

1. PET Avid Participants: Should be acquired at all visits for FDG avid participants, and is required for an overall response assessment of CR
2. PET Negative Participants: Not required unless clinically indicated

– Clinical Data:

(a) The following clinical data is required to support Lugano (sites will incorporate clinical data with the central blinded assessments of imaging data for final determination of response):

(i) Bone marrow biopsy results

- Patients with B- or T-ALL will be assessed per the National Comprehensive Cancer Network (NCCN) guidelines in support of response and progression endpoints.
  - The National Comprehensive Cancer Network (NCCN) guidelines of response and progression require imaging assessments (for participants with extramedullary disease) and clinical data assessments:
    – Imaging Data: During screening, imaging should cover all areas of known or suspected disease involvement. After screening, the same imaging and anatomical coverage used at screening should be repeated, and any new areas of suspected disease should be covered:

(a) Brain CT or MRI with contrast

(i) Required during screening for participants with known or suspected CNS involvement

(ii) Required at all visits for participants with known CNS involvement found during screening

(iii) Required as clinically indicated for suspected to have developed CNS involvement post- screening.

(b) Diagnostic Quality CT with contrast (preferred), or MRI with contrast required for all participants at all visits

(i) During Screening: Neck, chest, abdomen, and pelvis as clinically indicated and any other sites of known or suspected disease involvement

(ii) On Treatment: All known or suspected sites of disease involvement

(c) FDG PET/CT (whole body – covering all areas of known or suspected disease)

(i) Required during screening for all participants

(ii) On Treatment

1. PET Avid Participants: Should be acquired at all visits for FDG avid participants, and is required to for an overall response assessment of CR
2. PET Negative Participants: Not required unless clinically indicated

(d) Scrotal ultrasound as clinically indicated

- Clinical Data (sites will incorporate clinical data with the central blinded assessments of imaging data for final determination of response):
  (a) The following clinical data is required to support The National Comprehensive Cancer Network (NCCN) guidelines assessments:
    (i) Blood Counts (Absolute neutrophil count, Platelet Count, Lymphoblast)
    (ii) Cerebrospinal Fluid (CSF)
    (iii) Bone marrow biopsy/aspirate results

- Patients with PTCL with skin involvment, including CTCL, SS or MF, will be assessed per mSWAT (12) (Appendix H) combined with Lugano in support of response and progression endpoints.
  - Skin Lesion Assessments
    (a) Performed by site physician according to mSWAT at every visit
  - Imaging Data
    (a) Brain CT or MRI with contrast
      (i) Required during screening for participants with known or suspected CNS involvement
      (ii) Required at all visits for participants with known CNS involvement found during screening
      (iii) Required as clinically indicated for suspected to have developed CNS involvement post- screening.
    (b) Diagnostic Quality CT with contrast (preferred), or MRI with contrast required for all participants at all visits
      (i) During Screening: Neck, chest, abdomen, and pelvis as clinically indicated and any other sites of known or suspected disease involvement
      (ii) On Treatment: All known or suspected sites of disease involvement
    (c) FDG PET/CT (whole body – covering all areas of known or suspected disease)
      (i) Required during screening for all participants
      (ii) On Treatment
        1. PET Avid Participants: Should be acquired at all visits for FDG avid participants, and is required for an overall response assessment of CR
        2. PET Negative Participants: Not required unless clinically indicated
  - Clinical Data
    (a) The following clinical data is required to support Lugano (sites will incorporate clinical data with the central blinded assessments of imaging data for final determination of response):
      (i) Bone marrow biopsy results

- Patients with CLL/SLL be assessed per the iwCLL criteria (Appendix G) (5) in support of response and progression endpoints.
    - iwCLL assessments of response and progression require imaging and clinical data assessments:
        - Imaging Data: The following imaging data is required to support iwCLL assessments:
            (i) Required during screening for participants with known or suspected CNS involvement
            (ii) Required at all visits for participants with known CNS involvement found during screening
            (iii) Required as clinically indicated for suspected to have developed CNS involvement post- screening.
            (b) Diagnostic Quality CT with contrast (preferred), or MRI with contrast of the neck, chest, abdomen and pelvis and any other sites of known or suspected disease involvement
            (i) Required for all participants at all visits
        - Clinical Data (sites will incorporate clinical data with the central blinded assessments of imaging data for final determination of response):
            (a) The following Clinical Data is Required to support iwCLL assessments:
            (i) Constitutional Symptoms
            (ii) Circulating Lymphocyte Count
            (iii) Platelet Count
            (iv) Hemoglobin
            (v) Bone marrow biopsy/aspirate results including presence or absence of B-lymphoid nodules
- Patients with PCNSL will be assessed per the International PCNSL Collaborative Group Response Criteria (iPCNSL CGRC) (Appendix G) (13), in support of response and progression endpoints. Occult systemic disease has been reported in up to 8% of patients initially thought to have isolated PCNSL. As a result, complete systemic staging is warranted in every patient at screening according to Lugano criteria. Patients confirmed to have isolated PCNSL will undergo response assessments per PCNSL only. Patients identified to also have systemic disease at screening will undergo both PCNSL and Lugano response assessments.
    - PCNSL assessments of response and progression require imaging and clinical data assessments:
        - Imaging Data: The following imaging data is required to support PCNSL assessments:
            (a) Brain MRI with contrast (CT with contrast may be used as an alternative if the participant is unable to get an MRI with contrast)

(i) Required for all participants at all visits

– Clinical Data (sites will incorporate clinical data with the central blinded assessments of imaging data for final determination of response):

(a) The following Clinical Data is Required to support PCNSL assessments:

(i) Corticosteroid Dose

(ii) Eye Exam Results

(iii) CSF Cytology

From the Phase 1 dose-escalation 3, 6, 9, 12, and 18 mg/kg cohorts tumor flare /pseudoprogression is suspected in almost half of the patients.
For all Phase 2 cohorts, additional imaging and clinical data assessments may be performed to capture Indeterminate Responses per LYRIC as a secondary endpoint, which indicates possible pseudoprogression/tumor flare, the nature of which must be confirmed at the subsequent imaging visit. The purpose of the LYRIC assessments is to allow participants to remain on study past initial apparent tumor progression in the setting of clinical benefit (Appendix D and E) (8).

– Clinical Data:

(a) The following clinical data may be used to support LYRIC assessments:

(i) Participant Clinical Status

(ii) Lesion Biopsy Results

The secondary endpoints include the following:

- Incidence of AEs;
- Incidence of tumor flare/pseudoprogression defined by LYRIC criteria or adapted criteria for B- or T-ALL or CLL/SLL or PCNSL, or by symptoms associated with tumor flare/pseudopregression summarized in section 1.2.5 that occur at a time point not scheduled for disease response assessment, or by resolution of clinical symptoms with absence of clinical deterioration despite maintained or potentially increased tumor by imaging assessment.
- CR rate at 28 days after the first AVM0703 infusion;
- DOR, determined for patients with a best overall response of CR or PR and defined as the time from first achieving a response (CR or PR) to the date of documented disease progression or death;
- Progression-free survival at 3, 6, and 12 months after the first AVM0703 infusion;
- Overall survival at 3, 6, and 12 months after the first AVM0703 infusion;
- Time to response after the first AVM0703 infusion;
- Number of platelet and red blood cell transfusions received after the first AVM0703 infusion;

- Lansky (0 to 15 years of age) or Karnofsky (≥16 years of age) performance status;

The exploratory endpoints include the following:

- Assessment of immune status by markers of exhaustion, activation, memory and effector function;
- Assessment of plasma or serum cytokines, chemokines, growth factors, cancer antigens and other factors that may be predictive/related to tumor flare (pseudoprogression);
- Assessment of ICAM expression, GR expression, B and T lymphocyte levels, myeloid-derived suppressor cell levels, NK cell levels, and NKT cell levels in peripheral blood and tumor samples if available; and

Assessment of minimal residual disease

7.3 Exploratory Evaluations

Tissue samples and biological specimens may be stored for up to 15 years, or as per local regulations, to conduct exploratory research aimed at addressing scientific questions related either to the study treatment or to the specific tumor type (such as ICAM3, NKT cells, and GR expression, and immune modulation, which could include preclinical xenograft models). Each enrolled patient will have the right to have their specimen material destroyed at any time by contacting the Investigator who in turn can contact the laboratory. The Investigator should provide AVM the study and patient number so that the sample can be identified and destroyed.

For patients who withdraw consent/assent, any samples that were not requested to be returned or destroyed will remain as described in this protocol.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test results, will be monitored and documented from Visit 1 until the EOT/ET Visit. Patients should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study treatment. Beginning at Visit 1, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at screening should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (e.g., ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.1.3 Assessment of Adverse Events by the Investigator

The severity of all AEs should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. For those AE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated; and
- CTCAE Grade 5: Death related to the AE.

Causality Assessment:

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug-

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.1.4 Adverse Events of Special Interest

The Investigator will monitor each patient for clinical and laboratory evidence for pre-defined adverse events of special interest (AESIs) throughout the patient's participation in this study.

The Investigator will assess and record any additional information on the AESI in detail on an AE form which must be submitted within 24 hours of awareness of the event.

For this study, AESIs include the following:

- GI bleeding;
- Neuropsychiatric symptoms: psychiatric event- any psychosis;
- Malignant hypertension: defined as defined as SBP >180 mmHg, DBP >120 mmHg, or CTCAE Version 5.0 Grade 4 hypertension associated with neurologic symptoms, papilledema, visual impairment, chest pain or signs of myocardial ischemia, or acute renal insufficiency;
- Hyperglycemia: For Phase 1 defined as glucose >250 mg/dL that requires either new insulin treatment or an increase over the usual insulin dose and for Phase 2 defined as grade 3 hyperglycemia that does not resolve with appropriate medical management to ≤grade 2 within 72 hours;
- TLS.

During the course of the study, additional AESIs may be identified by the Sponsor.

AESIs must be recorded in the eCRF.

8.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent/assent, or elective treatment of a pre-existing condition that did not worsen from Baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;

- A congenital anomaly/birth defect; or

- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

Note: Events of progression of a patient's underlying cancer, as well as events clearly related to the progression of a patient's cancer (signs/symptoms of progression) should not be reported as an SAE unless the outcome is fatal during the study or within the safety reporting period. If the event has a fatal outcome during that timeframe, the event of Progression of "Type of Cancer" must be recorded as an SAE with CTCAE Grade 5 (fatal) outcome indicated. Diagnosis of progression of disease or hospitalization due to signs and symptoms of disease progression alone should not be reported as an SAE.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from Visit 1 until 30 days following the last administration of study drug must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator considers related to study drug must be reported to Medpace Clinical Safety.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed in Section 8.5) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a patient becomes pregnant while receiving AVM0703 or anytime within 28 days following AVM0703 administration, the patient should be withdrawn from the study; however, overall survival data for these patients will be collected. Upon withdrawal from the study, ET Visit procedures as indicated in Section 6.15 should be implemented. Retreatment of a pregnant patient will not be allowed.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within 28 days following AVM0703 administration, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the FDA, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal product.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
e-mail: medpace-safetynotification@medpace.com

8.6 Clinical Laboratory Evaluations

A detailed list of clinical laboratory analytes assessed during the study is included in Appendix B. Samples for clinical laboratory evaluations will be collected at visits indicated in Appendix A.

Tests for HIV antibody, hepatitis B surface antigen and/or hepatitis B core antibody plus hepatitis B PCR, HCV Ab, and tuberculosis will be performed at the Screening Visit to determine eligibility.

A serum pregnancy test for females of childbearing potential only will be performed at visits indicated in Appendix A.

8.7 Vital Signs

Vital signs (blood pressure, oxygen saturation, heart rate, respiration rate, and temperature) will be assessed at visits indicated in Appendix A.

8.8 Electrocardiograms

ECGs will be performed at visits indicated in Appendix A for screening for Phase 1 and Phase 2, but ECG will only be performed during and after AVM0703 infusion in Phase 1. No ECG abnormalities have emerged during or after AVM0703 infusion during the Phase 1 dose-escalation phase.

8.9 Physical Examinations

A complete physical examination will be performed at the Screening Visit and EOT/ET Visit. The physical examination will consist of an examination of the following systems: general appearance, skin, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart (including any auscultated cardiac murmurs), abdomen, extremities, and neurologic. Symptom-directed physical examinations will be performed at visits indicated in Appendix A.

8.10 Height and Weight

Height will be measured at the Screening Visit only. Weight will be assessed at visits indicated in Appendix A.

9 STATISTICS

9.1 Analysis Populations

9.1.1 Full Analysis Set

The Full Analysis Set (FAS) will consist of all enrolled patients who receive any amount of study drug. The FAS will be used for the summaries of all efficacy data.

9.1.2 DLT Evaluable Set

The DLT Evaluable Set will consist of all patients enrolled in the Phase 1 portion of the study who have a DLT within the first 7 days for the 6, 9, 12, and 18 mg/kg cohorts and 3 weeks (21 days) for the 21 mg/kg cohort on study, or without a DLT but receive at least 75% of the scheduled AVM0703 dose and complete the DLT assessment period.

9.1.3 PK Analysis Set

The PK Analysis Set will consist of all enrolled patients who receive any amount of study drug and have sufficient concentration data to estimate at least 1 PK parameter (e.g., AUC, C_{max}, or half-life). The PK Analysis Set will be used for the summaries of all PK data.

9.1.4 Safety Analysis Set

The Safety Analysis Set will consist of all enrolled patients who receive any amount of study drug. The Safety Analysis Set will be used for the summaries of demographics, baseline, and all safety data.

9.2 Statistical Methods

The Phase 1 dose-escalation portion of the study will determine the safety and tolerability of AVM0703. The Phase 2 dose-expansion portion of the study will enroll 5 or more specific cohorts at an MTD/RP2D defined in the Phase 1 portion of the study to further characterize the safety and efficacy of AVM0703. Descriptive summaries will be prepared to show the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentages for categorical variables. All details will be described in the Statistical Analysis Plan.

9.2.1 Analysis of Efficacy

For Phase 1:

ORR and CR rate at 28 days post-infusion as assessed by the Lugano Treatment Response Criteria or iwCLL criteria will be presented along with the 2-sided exact 80% confidence intervals. Time-to-event endpoints, including DOR, progression-free survival, and overall survival, will be summarized using the Kaplan-Meier method.

For Phase 2:

ORR and CR and PR rate at 28 days post-infusion, or any time point for patients receiving repeat doses in 21 day intervals, as assessed by the Lugano Treatment Response Criteria, or iwCLL criteria or iPCNSL CGRC will be presented along with the 2-sided exact 80% confidence intervals.

For patients with B- or T-ALL, ORR and CR and PR rate will be assessed consistent with NCCN guidelines, together with response assessed by diagnostic CT, PET/CT or MRI for patients with nodal or extranodal involvement. For B- or T-ALL patients without BM, blood or CSF involvement, Lugano Treatment Response Criteria will be used to determine ORR and CR or PR. For T cell lymphoma patients with skin involvement, mSWAT scores together with Lugano Treatment Response, will be used to determine ORR and CR and PR rate. For patients with CNS involvement, CNS disease response may be assessed by MRI imaging, provided both screening and follow-on MRI is available. For Phase 2 patients who receive only one AVM0703 infusion, response at day 28 prior to continuing on to additional anti-cancer therapy will be presented. For Phase 2 patients who receive repeat RP2D doses in 21 day intervals best overall response from any time point will be presented.

Sites will incorporate clinical data with the central assessments of imaging for final response determination.

9.2.2 Analysis of Safety

All AEs will be presented in incidence tables coded by the Medical Dictionary for Regulatory Activities preferred term and system organ class. SAEs, drug-related AEs, AEs leading to treatment discontinuation, AEs leading to deaths, and AESIs will be summarized in the same manner.

Laboratory parameters, 12-lead ECG parameters, and vital signs and the corresponding change from baseline over time will be summarized using descriptive statistics.

A Data Safety Monitoring Committee (DSMC) will be responsible for safeguarding the interests of patients on this study. The DSMC will review safety data on a regular basis, no less frequent than every 6 months after the first patient is enrolled. Continuous monitoring of unacceptable toxicities will be performed for patients enrolled in the expansion phase, where unacceptable toxicities are defined as any toxicity meeting the DLT criteria, as defined in Section 3.1 for the dose-escalation phase, within 28-days following the most recent infusion.

The halting boundaries for unacceptable toxicity rates were determined based on a 1-sided binomial test with a significance level of 0.1 (see Table 3). If the incidence of unacceptable toxicities in an expansion cohort significantly exceeds the acceptable incidence rate of 30%, enrollment will be halted for that expansion cohort and comprehensive review of safety data will be performed by the DSMC. Based on their review, the DSMC may determine that 1 or more disease-specific cohorts should stop or continue enrollment.

Table 8 Stopping Boundaries for Unacceptable Toxicities in Expansion Cohorts

Number of Subjects Enrolled	Stop if Number of Subjects With Unacceptable Toxicity >	Incidence Rate of Unacceptable Toxicities (%)
6	3	50
9	4	44.4
12	5	41.7
15	6	40
18	7	38.9

9.2.3 Pharmacokinetic Analysis

Individual plasma concentrations will be listed and summarized by time point and dose level using descriptive statistics. Linear and semi-logarithmic plots of individual and mean plasma concentration-time profiles as well as spaghetti plots will be presented. The plasma PK parameters of AVM0703 will be calculated using non-compartmental methods with plasma concentrations versus actual sampling time. The PK parameters will also be listed and summarized. Dose proportionality of plasma PK parameters for AVM0703 will be assessed with a power model if data permit. The exposure-response and exposure-AE relationship may also be explored if data permit.

9.2.4 Interim Analysis

No formal interim analysis is planned for the Phase 1 portion of the study except for the assessment of the MTD after each escalation cohort.

For the Phase 2 portion of the study, each expansion cohort will follow a 2-stage Simon design based on ORR, with interim analysis for futility.

For Phase 2 patients in repeat dosing cohorts, after 6 patients, who have had PK assessments, have reached intolerance, unacceptable toxicity, or disease progression, or they have received 6 infusions without intolerance, unacceptable toxicity, or disease progression, the Data Safety Monitoring Committee will review an integrated interim analysis of all available PK, PD, efficacy, safety and tolerability data and determine whether repeat dosing should continue or be limited to a certain number of infusions. Ongoing DSMC review will occur at least every 6 months. Based on integrated analysis, including dose-response and exposure-response, the DSMC will determine the optimal dose and dosing schedule for repeat dosing with AVM0703. Repeat dosing will be halted according to Table 9 Stopping Boundaries for Unacceptable Toxicities in Expansion Cohorts.

9.2.5 Sample Size Determination

For the Phase 1 dose-escalation portion of the study, 3 to 6 patients will be needed in each dose cohort based on the 3+3 design. If approximately 6 patients are enrolled in each dose cohort (Cohort 1 to Cohort 5), a total of approximately 30 patients will be enrolled. The actual number of patients enrolled will depend on the observed safety profile for each dose cohort and when the MTD is reached.

The Phase 2 dose-expansion portion of the study will be based on the Simon's 2-stage design. Up to approximately 90 patients will be enrolled, with up to approximately 18 patients in each of the 5 or more specific expansion cohorts (such as DLBCL [including DLBCL arising from follicular lymphoma and primary DLBCL of the CNS], high-grade B-cell lymphoma or Burkitt lymphoma, CLL/SLL, T-cell lymphoma, or ALL) to further characterize the safety and efficacy of AVM0703.

For each expansion cohort, a true ORR of 10% or less is considered insufficient to warrant further study (null hypothesis), whereas a true ORR of 30% or more is considered sufficiently effective (alternative hypothesis). The number of patients evaluated in each stage and the minimum number of responders needed to continue to the next stage were determined based on the Simon's 2-stage optimal design with 80% power and a 1-sided significance level of 10%. For each specific

expansion cohort, up to 7 patients may be enrolled in each cohort at stage 1. If no patients achieve CR or PR within a cohort, then enrollment within that cohort may terminate. Otherwise, 11 additional patients will be enrolled within the cohort for stage 2. Upon completion of stage 2, if 4 or more patients out of the 18 enrolled within a cohort achieve CR or PR, then the true response rate for AVM0703 likely exceeds 10%. Alternatively, if 3 or fewer patients achieve CR or PR at the end of stage 2, then the true response rate is likely less than 30% and further evaluation of AVM0703 in that cohort may not be pursued. If the true ORR in a cohort is ≤30%, then the probability of terminating enrollment at the end of the first stage equals 48%.

In cases where preliminary clinical evidence suggests a substantial improvement in ORR for 1 or more specific expansion cohort(s), it is anticipated that the protocol may be amended to allow for enrollment of additional patients in that specific cohort or additional cohorts to further characterize the safety and efficacy of AVM0703.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and AEs; and
- WHO Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment for the last patient in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board

The Institutional Review Board (IRB) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent/Assent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation, and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent/assent from each patient before any study-specific activity is performed and should document in the source documentation that consent/assent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs

and procedures for their completion, informed consent/assent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

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APPENDIX A1: SCHEDULE OF PROCEDURES FOR PHASE 1 AND PHASE 2 SINGLE DOSE PATIENTS

Patients may be repeat dosed according to section 5.5.3.2

Visit	Screening	1	2	3	4	5	6	7	8	9	10	11	EOT/ET[q]	EOS
Days	D-28 to D-1	D0	D1	D2	D3	D4	D7	D14	D21	D28	3 Months Post-Infusion	6 Months Post-Infusion	12 Months Post-Infusion	Long-Term Follow-up
Visit Window (Days)							±1	±1	±1	±1	±7	±7	±7	
Informed consent/assent	X													
Inclusion/exclusion criteria	X													
Demographics	X													
Medical history[a]	X		X	X	X	X	X							
Physical examination	X												X	
Symptom-directed examination[d]		X[b]	X	X	X	X	X	X	X	X	X	X		
Vital signs	X	X[b,c]	X	X	X	X	X	X	X	X	X	X	X	
Height/weight[e]	X	X[b]	X	X	X	X	X	X	X	X	X	X	X	
Lansky or Karnofsky performance status	X									X	X	X	X	
Pregnancy test[f]	X	X[g]											X	
HIV testing	X													
Hepatitis B and C testing	X													
Tuberculosis testing	X													
Serum biomarkers[h]	X			X			X	X			X	X		
Bone marrow biopsy/aspiration[i]	X									X			X	
Tumor biopsy (optional)	X												X	
Cytogenetics (FISH)[j]	X												X	

Visit	Screening	1	2	3	4	5	6	7	8	9	10	11	EOT/ET[q]	EOS
Days	D-28 to D-1	D0	D1	D2	D3	D4	D7	D14	D21	D28	3 Months Post-Infusion	6 Months Post-Infusion	12 Months Post-Infusion	Long-Term Follow-up
Visit Window (Days)							±1	±1	±1	±1	±7	±7	±7	
12-lead ECG (D0 for Phase 1 only)	X	X[k]											X	
CBC with differential	X	X[g]	X	X	X	X	X	X	X	X	X	X	X	
Lymphocyte subsets		X[b,r]			X			X						
PBMC/ Plasma biomarkers		X[b,r]			X			X						
Serum chemistry	X	X[g]	X	X	X	X	X	X	X	X	X	X	X	
TLS risk assessment and monitoring[l]	X	X[g]	X				X	X	X					
Coagulation	X	X[g]	X				X	X	X	X	X		X	
HbA1c	X	X[g]					X	X	X	X				
IgG test		X[b]								X	X			
Urinalysis	X	X[g]	X				X	X	X	X	X		X	
DEXA scan	X												X	
AVM0703 administration[m]		X												
Hydrocortisone administration[n]		X	X	X	X	X								
PK sampling[o]		X	X	X										
For Phase 2: Monitor for clinical symptoms of tumor flare[p]			X	X	X	X	X	X						
Disease assessment[q]	X									X	X	X	X	
Phase 1 only: PROMIS® Scale v1.2 – Global Health	X									X	X	X	X	
Phase 1 only: PROMIS – Ca Bank v1.1 – Physical Function	X									X	X	X	X	

Visit	Screening	1	2	3	4	5	6	7	8	9	10	11	EOT/ET[q]	EOS
Days	D-28 to D-1	D0	D1	D2	D3	D4	D7	D14	D21	D28	3 Months Post-Infusion	6 Months Post-Infusion	12 Months Post-Infusion	Long-Term Follow-up
Visit Window (Days)							±1	±1	±1	±1	±7	±7	±14	
Phase 1 only: PROMIS Pediatric Scale v1.0 – Global Health 7 + 2 or parent proxy.	X									X	X	X	X	
Phase 1 only: PROMIS Pediatric Item Bank v2.0 – Upper Extremity – Short Form 8a or parent proxy	X									X	X	X	X	
Phase 1 only: PROMIS Pediatric Item Bank v2.0 – Mobility – Short Form 8a or parent proxy	X									X	X	X	X	
Phase 1 only: PROMIS Item Bank v2.0 – Cognitive Function	X	X[b]	X				X	X	X	X				
Phase 1 only: PROMIS Pediatric Item Bank v1.0 – Cognitive Function or parent proxy	X	X[b]	X				X	X	X	X				
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Overall survival[r]											X	X	X	X

a. A detailed history of cognitive, behavioral and mood changes, sleep, and visual changes will be obtained on Days 1, 2, 3, 4, and 7. A detailed gastrointestinal medical history will also be obtained on Days 1, 2, 3, 4, and 7.
b. Predose.
c. For Phase 1: Patients will be monitored and observed during the first 4 hours following AVM0703 administration. Vital signs, including blood pressure, oxygen saturation, heart rate, respiration rate, and temperature will be obtained within 15 minutes prior to the start of the infusion and every 15 minutes during the first hour of the infusion and then every 30 minutes until the end of the infusion. For the first hour following the end of the infusion, vital signs will be collected every 30 minutes and then hourly thereafter until the end of the 4-hour observation period. All vital signs during and post-infusion will have a ±5 minute window. For Phase 2 : Patients will be monitored and observed during the first 1 hour following AVM0703 administration. Vital signs, including blood pressure, oxygen saturation, heart rate, respiration rate, and temperature will be obtained within 15 minutes prior to the start of the infusion and every 15 minutes during the first hour of the infusion. For the first hour following the end of the infusion, vital signs will be collected every 30 minutes until the end of the 1-hour observation period. All vital signs during and post-infusion should have a ±5 minute window.
d. Symptom-directed physical examination will be performed only as needed/indicated, based on interim history.
e. Height will be measured at screening only.
f. A serum pregnancy test will be performed for females of childbearing potential only.
g. Assessments do not need to be repeated if performed within 72 hours of AVM0703 administration.
h. Serum biomarkers to be analyzed include assessment of ICAM expression, GR expression, B and T lymphocyte levels, myeloid-derived suppressor cell levels, NK cell levels, and NKT cell levels in peripheral blood.
i. Bone marrow aspirate/biopsy to be obtained at screening, at Day 28 Visit and at EOT or at 12 months post-infusion, whichever comes first for all patients, unless not typically performed per standard of care for the disease indication. For patients with CLL, bone marrow aspirate and biopsies should also be obtained per the iwCLL criteria. For patients with DLBCL (including DLBCL arising from follicular lymphoma); high-grade B-cell lymphoma; MCL; primary mediastinal large B-cell lymphoma; primary DLBCL of the CNS; Burkitt or Burkitt-like lymphoma/leukemia; or B-lymphoblastic leukemia/lymphoma, T-lymphoblastic leukemia/lymphoma, acute leukemia/lymphoma, acute leukemias of ambiguous lineage, or NK cell leukemia/lymphoma, bone marrow aspirate and biopsies should be obtained per the Lugano Treatment Response Criteria. Bone marrow aspirate should be sent for histopathology, flow cytometry, cytogenetics, and molecular testing (for disease evaluation, including minimal residual disease).
j. For patients with CLL/SLL, perform cytogenetics (FISH) for del(13q), del(11q), del(17), trisomy 12, and del(6q) on blood or biopsy specimen of histologically confirmed CLL. Assessment will be repeated when patient achieves complete response. The result does not need to be available for enrollment or study initiation.
k. For Phase 1 only: 12-lead ECG will be performed 15 minutes (±5 minutes) prior to AVM0703 administration, end of AVM0703 administration (±5 minutes), and 2 hours (±5 minutes) and 4 hours (±5 minutes) post AVM0703 administration.
l. All patients should be assessed for risk of TLS. High-risk patients should have TLS labs (e.g., potassium, phosphorus, calcium, uric acid, and creatinine) obtained predose, and 4 and 8 hours post-infusion of AVM0703 on Day 0, and at least once on Day 1 (For Phase 1 only). Patients with signs of TLS should be monitored at least daily until all signs of TLS have resolved or are no longer clinically significant.
m. AVM0703 will be administered to patients as a single IV infusion at a concentration of 10 mg/mL in normal saline over a period of approximately 1 hour. Upon disease progression, patients may be retreated according to section 5.5.3.2. If a patient is retreated, they will complete all visits a second time.
n. For prophylaxis against dexamethasone-induced CNS side effects, hydrocortisone will be dosed orally or by IV for 5 days starting on the day of dexamethasone infusion. Hydrocortisone will be divided into 3 daily doses starting in the morning and spaced 6 to 8 hours apart using the following dosing schedule each day: for pediatric and adolescent patients at 5 mg/m^2 (morning dose), 3 mg/m^2 (mid-day dose), and 2 mg/m^2 dose (evening dose); and for adult patients at 10 mg/m^2 (morning dose), 5 mg/m^2 (mid-day dose), and 5 mg/m^2 dose (evening dose), the last dose administered at hour of sleep.
o. For Phase 1 and for Phase 2 infusions one (1) and six (6): Pharmacokinetic samples will be obtained predose (within 60 minutes prior to dosing), 5 minutes (±5 mins) before the end of infusion, and 15 minutes (± 5 mins), 30 minutes (±10 mins), 60 minutes (±10 mins), 90 minutes (±10 mins), 2 hours (±10 mins), 4 hours (±30 mins), 6 hours (±30 mins), 8 hours (±30 mins), 24 hours (±2 hours), and 48 hours (±2 hours) post end of infusion. For Phase 2 infusions two to five (2-5) pharmacokinetic samples will be obtained predose (within 60 minutes prior to dosing), 5 minutes (±5 mins) before the end of infusion, and 15 minutes (± 5 mins), and 48 hours (±2 hours) post end of infusion.
p. For Phase 2: Monitor for clinical symptoms of tumor flare that include pain or swelling of affected sites, Patterns of tumor flare/pseudoprogression include; i) extremely rapid tumor growth by palpation, patient symptoms or imaging that is not consistent with the known growth rate of the patient's cancer, ii) increased edema by imaging around the lesion, iii) enhanced PET (or MRI) signal or even evidence of new lesions that subsequently regress or disappear, and iv) evidence of disease progression without

accompanying clinical deterioration (7). Tumor flare in patients may include rapid, often painful, self-limited increase in the size of lymph nodes, often accompanied by fever, lymphocytosis, rash, and bone pain. (8). For instance, Bruton tyrosine kinase and phosphatidylinositol 3-kinase targeting agents can cause a rapid reduction in lymph node size and spleen mass, often with improvement of cytopenias, but associated with lymphocytosis. This finding, which relates to a redistribution of lymphocytes from tissue sites to the peripheral blood, may persist for a year or longer without signs or symptoms associated with disease progression and does not represent a suboptimal response to therapy (8).

q. For patients with DLBCL (including DLBCL arising from follicular lymphoma); high-grade B-cell lymphoma; MCL; primary mediastinal large B-cell lymphoma; primary DLBCL of the CNS; Burkitt or Burkitt-like lymphoma/leukemia; or B-lymphoblastic leukemia/lymphoma, T-lymphoblastic leukemia/lymphoma, acute leukemia/lymphoma, acute leukemias of ambiguous lineage, or NK cell leukemia/lymphoma, disease assessments will be performed per the Lugano Treatment Response Criteria. For patients with DLBCL (including DLBCL arising from follicular lymphoma) and high-grade B-cell lymphoma, circulating tumor DNA will be sent to detect minimal residual disease. For patients with CLL/SLL, disease assessments will be performed per the iwCLL criteria. For patients with primary DLBCL of the CNS, CSF analysis will be performed. If additional anticancer therapy before Day 28, disease assessment should be performed before they receive any other therapy. For Phase 2: CNS imaging is required at screening for patients with known or suspected CNS involvement. For CNS assessments, CNS assessment at day 28, 3, 6, and 12 months is required for patients with CNS involvement at screening and acquired as clinically indicated for patients suspected to have developed CNS involvement post- screening. The imaging modality used at screening should be the imaging modality used at every follow-up imaging visit. For B- and T-ALL assessments will be consistent with NCCN guidelines; for PTCL with skin involvement assessment will be consistent with mSWAT and LUGANO; for CLL/SLL assessment will be consistent with iwCLL guidelines; for PCNSL response assessments will be consistent with iPCNSL CGRC criteria. For all other NHL subtypes response assessment will be per LUGANO criteria. Secondary LYRIC response assessment may be determined to document tumor flare/pseudoprogression.

r. Patients who go on to receive additional anticancer therapy will be followed for survival at 3, 6, and 12 months post-infusion for Phase 1, and yearly thereafter until death, withdrawal of consent/assent, or study closure. Survival information can be obtained via public records, telephone calls, and/or medical records. Any subsequent anticancer therapy that the patients receive will also be collected. Patients who withdraw prematurely from the study for any reason should have EOT/ET assessments before receiving additional anticancer therapy or at time of study termination. The reason for patient withdrawal should be documented in the eCRF. For Phase 2 patients who receive repeat AVM0703 RP2D infusions in 21 day intervals; patient should not go onto additional anti-cancer therapy until the drug is no longer tolerated, unacceptable toxicity has been reached or the patient has disease progression.

BUN = blood urea nitrogen; CBC = complete blood count; CLL = chronic lymphocytic leukemia; CNS = central nervous system; CSF = cerebrospinal fluid; D = day; del = deletion; DEXA = dual energy x-ray absorptiometry; DLBCL = diffuse large B-cell lymphoma; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOS = End of Study; EOT = End of treatment; ET = Early Termination; FISH = fluorescence in situ hybridization; GR = glucocorticoid receptor; HIV = human immunodeficiency virus; ICAM = intercellular adhesion molecule; IgG = immunoglobulin G; IV = intravenous; iwCLL = International Workshop on CLL; LDH = lactate dehydrogenase; MCL = mantle cell lymphoma; NK = natural killer; NKT = natural killer T; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System for Phase 1 only; SLL = small lymphocytic lymphoma; TLS = tumor lysis syndrome.

APPENDIX A2: SCHEDULE OF PROCEDURES FOR PHASE 2 REPEAT RP2D DOSED PATIENT COHORTS

- Screening will be conducted as detailed in Appendix A1
- Disease Assessments (including imaging, bone marrow biopsy, skin assessments, CSF, peripheral blood involvement), Survival Status, and Lansky or Karnofsky Performance Status will be obtained on day 28 ±1 day after the first (1st) AVM0703 infusion, 3 months ±7 days after the first (1st) AVM0703 infusion, 6 months ±7 days after the first (1st) AVM0703 infusion, and 12 months ±14 days after the first (1st) AVM0703 infusion as detailed in Appendix A1.

The table below summarizes Visits and Procedures after each cycle of AVM0703 infusion:

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Days	**D0, D21, D42, D63, D84, D105, etc**	**D1, D22, D43, D64, D85, D106, etc**	**D2, D23, D44, D65, D86, D107, etc**	**D3, D24, D45, D66, D87, D108, etc**	**D4, D25, D46, D67, D88, D109, etc**	**D7, D28, D49, D70, D91, D112, etc**	**D14, D35, D56, D77, D98, D119, etc**
Visit Window (Days)					**Visit 5 will not be required for repeat dosed patients**	**Visit 6 will not be required for repeat dosed patients**	**±1**
Medical history[a]				X			X
Symptom-directed examination[d]	X[b]			X			X
Vital signs	X[b,c]			X			X
Height/weight[e]	X[b]			X			X
TPregnancy test[f]	X						
CBC with differential	X[b]	X	X	X			X
Lymphocyte subsets	X[b,g]			X			X
PBMC/ Plasma biomarkers	X[b,g]			X			X
Serum chemistry	X[b]	X	X	X			X
Coagulation	X[b]						
HbA1c	X[b]						
IgG test	X[b]						
Urinalysis	X[b]						

Visit	1	2	3	4	5	6	7
Days	D0, D21, D42, D63, D84, D105, etc	D1, D22, D43, D64, D85, D106, etc	D2, D23, D44, D65, D86, D107, etc	D3, D24, D45, D66, D87, D108, etc	D4, D25, D46, D67, D88, D109, etc	D7, D28, D49, D70, D91, D112, etc	D14, D35, D56, D77, D98, D119, etc
Visit Window (Days)					Visit 5 will not be required for repeat dosed patients	Visit 6 will not be required for repeat dosed patients	±1
TLS risk assessment and monitoring[h]	X[b]			X			X
Hydrocortisone administration[i]	X[b]	X	X	X	X taken at home or in-hospital		
AVM0703 administration[j]	X						
[K] PK sampling will be obtained only at sites participating in both Phase 1 and Phase 2 and will only be obtained for six (6) patients enrolled to each repeat dose RP2D cohort.							
PK sampling Cycles 1 and 6	X	X	X				
PK sampling cycles 2 through 5	X		X				
Monitor for clinical symptoms of tumor flare[l]				X			X
Prior and concomitant medications	X			X			X

a. A detailed history of cognitive, behavioral and mood changes, sleep, and visual changes will be obtained on Days 3 and 14 of each cycle. A detailed gastrointestinal medical history will also be obtained on Days 3 and 14 of each cycle.
b. Predose
c. For Phase 2 : Patients will be monitored and observed during the first 1 hour following AVM0703 administration. Vital signs, including blood pressure, oxygen saturation, heart rate, respiration rate, and temperature will be obtained within 15 minutes prior to the start of the infusion and every 15 minutes during the first hour of the infusion. For the first hour following the end of the infusion, vital signs will be collected every 30 minutes until the end of the 1-hour observation period. All vital signs during and post-infusion should have a ±5 minute window.
d. Symptom-directed physical examination will be performed only as needed/indicated, based on interim history.
e. Height will be measured at screening only.
f. A serum pregnancy test will be performed for females of childbearing potential only.
g. Serum biomarkers to be analyzed include assessment of ICAM expression, GR expression, B and T lymphocyte levels, myeloid-derived suppressor cell levels, NK cell levels, and NKT cell levels in peripheral blood.
h. All patients should be assessed for risk of TLS. High-risk patients should have TLS labs (e.g., potassium, phosphorus, calcium, uric acid, and creatinine) obtained predose, and 4 and 8 hours post-infusion of AVM0703 on Day 0. Patients with signs of TLS should be monitored at least daily until all signs of TLS have resolved or are no longer clinically significant.
i. For prophylaxis against dexamethasone-induced CNS side effects, hydrocortisone will be dosed orally or by IV for 5 days starting on the day of dexamethasone infusion. Hydrocortisone will be divided into 3 daily doses starting in the morning and spaced 6 to 8 hours apart using the following dosing schedule each day: for pediatric and adolescent patients at 5 mg/m2 (morning dose), 3 mg/m2 (mid-day dose), and 2 mg/m2 dose (evening dose); and for adult patients at 10 mg/m2 (morning dose), 5 mg/m2 (mid-day dose), and 5 mg/m2 dose (evening dose), the last dose administered at hour of sleep.
j. AVM0703 will be administered to patients as a single IV infusion at a concentration of 10 mg/mL in normal saline over a period of approximately 1 hour in cycles with a 21 day interval.
k. Phase 2 infusions one (1) and six (6): Pharmacokinetic samples will be obtained predose (within 60 minutes prior to dosing), 5 minutes (±5 mins) before the end of infusion, and 15 minutes (± 5 mins), 30 minutes (±10 mins), 60 minutes (±10 mins), 90 minutes (±10 mins), 2 hours (±10 mins), 4 hours (±30 mins), 6 hours (±30 mins), 8 hours (±30 mins), 24 hours (±2 hours), and 48 hours (±2 hours) post end of infusion. For Phase 2 infusions two to five (2-5) pharmacokinetic samples will be obtained predose (within 60 minutes prior to dosing), 5 minutes (±5 mins) before the end of infusion, and 15 minutes (± 5 mins), and 48 hours (±2 hours) post end of infusion.
l. For Phase 2: Monitor for clinical symptoms of tumor flare that include pain or swelling of affected sites, Patterns of tumor flare/pseudoprogression include ; i) extremely rapid tumor growth by palpation, patient symptoms or imaging that is not consistent with the known growth rate of the patient's cancer, ii) increased edema by imaging around the lesion, iii) enhanced PET (or MRI) signal or even evidence of new lesions that subsequently regress or disappear, and iv) evidence of disease progression without accompanying clinical deterioration (7). Tumor flare in patients may include rapid, often painful, self-limited increase in the size of lymph nodes, often accompanied by fever, lymphocytosis, rash, and bone pain. (8). For instance, Bruton tyrosine kinase and phosphatidylinositol 3-kinase targeting agents can cause a rapid reduction in lymph node size and spleen mass, often with improvement of cytopenias, but associated with lymphocytosis. This finding, which relates to a redistribution of lymphocytes from tissue sites to the peripheral blood, may persist for a year or longer without signs or symptoms associated with disease progression and does not represent a suboptimal response to therapy (8).

For Phase 2 patients who receive repeat AVM0703 RP2D infusions in 21 day intervals; patient should not go onto additional anti-cancer therapy until the drug is no longer tolerated, unacceptable toxicity has been reached or the patient has imaging-documented disease progression. Repeat dosed patients who go on to to receive additional anticancer therapy will be followed for survival at 3, 6, and 12 months after the date of the 1st AVM0703 infusion, and yearly thereafter until death, withdrawal of consent/assent, or study closure. Survival information can be obtained via public records, telephone calls, and/or medical records. Any subsequent anticancer therapy that the patients receive will also be collected. Patients who withdraw prematurely from the study for any reason should have EOT/ET assessments before receiving additional anticancer therapy or at time of study termination. The reason for patient withdrawal should be documented in the eCRF.

BUN = blood urea nitrogen; CBC = complete blood count; CLL = chronic lymphocytic leukemia; CNS = central nervous system; CSF = cerebrospinal fluid; D = day; del = deletion; DEXA = dual energy x-ray absorptiometry; DLBCL = diffuse large B-cell lymphoma; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOS = End of Study; EOT = End of treatment; ET = Early Termination; FISH = fluorescence in situ hybridization; GR = glucocorticoid receptor; HIV = human immunodeficiency virus; ICAM = intercellular adhesion molecule; IgG = immunoglobulin G; IV = intravenous; iwCLL = International Workshop on CLL; LDH = lactate dehydrogenase; MCL = mantle cell lymphoma; NK = natural killer; NKT = natural killer T; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System for Phase 1 only; SLL = small lymphocytic lymphoma; TLS = tumor lysis syndrome.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Direct bilirubin
Estimated glomerular filtration rate	Gamma-glutamyl transferase
Glucose	
Lactate dehydrogenase	Lipase
Magnesium	Phosphorus
Potassium	Sodium
Total bilirubin	Total protein
Uric acid	

Additional Chemistry Parameters

Glycosylated hemoglobin (HbA1c)
Cancer Antigen 125 and other cancer antigens as appropriate
Cell free DNA

Tumor Lysis Syndrome Panel

Calcium	Creatinine
Phosphorus	Potassium
Uric acid	

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count

White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Additional Hematology

Mean corpuscular volume

Standard Coagulation Panel

PT	PTT

INR	D-dimer

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

1. Microscopy is performed only as needed based on positive dipstick test results.

Additional Tests for Eligibility

Tests for human immunodeficiency virus antibody, hepatitis B surface antigen and/or hepatitis B core antibody plus a hepatitis B polymerase chain reaction, hepatitis C virus antibody, and tuberculosis.

A serum pregnancy test for females of childbearing potential only will be performed.

APPENDIX C COCKCROFT-GAULT EQUATION FOR CALCULATING ESTIMATED CREATININE CLEARANCE

Serum creatinine units	Gender	Estimated Creatinine Clearance (ml/min)
mg/dl	Males	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)}}{72 \times \text{subject serum creatinine (mg/dl)}}$
	Females	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 0.85}{72 \times \text{subject serum creatinine (mg/dl)}}$
υM/dl	Males	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 01.23}{\text{Subject serum creatinine (υM/dl)}}$
	Females	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 01.04}{\text{Subject serum creatinine (υM/dl)}}$

APPENDIX D: CYTOCHROME P450 3A4 INHIBITORS, INDUCERS, AND SUBSTRATES

A listing of cytochrome P450 3A4 inhibitors, inducers, and substrates can be found using the following link https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm; Tables 3-1, 3-2, and 3-3. . Relevant sections of the tables for P450 CYP3A are found below:

Table 3-1: Examples of clinical substrates for P450-mediated metabolism (for concomitant use clinical DDI studies and/or drug labeling) (12/03/2019)

	Sensitive substrates	Moderate sensitive substrates
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir[f], ebastine, everolimus, ibrutinib, lomitapide, lovastatin[g], midazolam, naloxegol, nisoldipine, saquinavir[f], simvastatin[g], sirolimus, tacrolimus, tipranavir[f], triazolam, vardenafil	alprazolam, aprepitant, atorvastatin[c], colchicine, eliglustat[e], pimozide, rilpivirine, rivaroxaban, tadalafil
	budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir[f], lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	

Table 3-2: Examples of clinical inhibitors for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (03/06/2020)

	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP3A4	boceprevir, cobicistat[h], danoprevir and ritonavir[j], elvitegravir and ritonavir[j], grapefruit juice[k], indinavir and ritonavir[j], itraconazole[h], ketoconazole, lopinavir and ritonavir[h,j], paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[j], posaconazole, ritonavir(h,j), saquinavir and ritonavir[h,j], telaprevir[h], tipranavir and ritonavir[h,j], telithromycin, troleandomycin, voriconazole	aprepitant, ciprofloxacin, conivaptan[l], crizotinib, cyclosporine, diltiazem[m], dronedarone[h], erythromycin, fluconazole[f], fluvoxamine[a], imatinib, tofisopam, verapamil[h]	chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor[h], lomitapide, ranitidine, ranolazine[h], ticagrelor[h]
	clarithromycin[h], idelalisib, nefazodone, nelfinavir[h]	-	-

Table 3-3: Examples of clinical inducers for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (12/03/2019)

	Strong inducers	Moderate inducers	Weak inducers

CYP3A	apalutamide, carbamazepine[e], enzalutamide[g], mitotane, phenytoin[b], rifampin[a], St. John's wort[h]	bosentan, efavirenz[f], etravirine, phenobarbital, primidone	armodafinil, modafinil[i], rufinamide

APPENDIX E: LUGANO TREATMENT RESPONSE CRITERIA

The response criteria per the Lugano classification are described in the table below.

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3[1] with or without a residual mass on 5PS.[2] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤1.5 cm in LDi. No extralymphatic sites of disease.
Nonmeasured lesion	N/A	Absent
Organ enlargement	N/A	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5[2] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease. At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value. When no longer visible, 0 × 0 mm. For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	N/A	Absent/normal, regressed, but no increase
Organ enlargement	N/A	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	N/A

Response and Site	PET-CT-Based Response	CT-Based Response
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	N/A	No increase consistent with progression
Organ enlargement	N/A	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	N/A
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression: An individual node/lesion must be abnormal with: LDi >1.5 cm; and Increase by ≥50% from PPD nadir; and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions; A new node >1.5 cm in any axis; A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma; Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

1. A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

2. PET 5PS: 1, no uptake above background; 2, uptake ≤mediastinum; 3, uptake >mediastinum but ≤liver; 4, uptake moderately >liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; N/A = not applicable; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

Source: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068

Appendix F : Lyric Response Criteria to assess for tumor flare/pseudoprogression

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3[1] with or without a residual mass on 5PS.[2] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤1.5 cm in LDi. No extralymphatic sites of disease.
Nonmeasured lesion	N/A	Absent
Organ enlargement	N/A	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
For patients with baseline CNS/CSF involvement, the CSF should be negative for morphologic evidence of disease (200)		
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5[2] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease. At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value. When no longer visible, 0 × 0 mm. For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	N/A	Absent/normal, regressed, but no increase
Organ enlargement	N/A	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	N/A
For patients with baseline CNS/CSF involvement, there may be persistent morphologic detection of disease in the CSF if this finding was present at diagnosis; however, there should be a 50% reduction in the percentage of lymphoma cells (200).		
Response and Site	**PET-CT-Based Response**	**CT-Based Response**
No response or stable	No metabolic response	Stable disease

disease		
Target nodes/nodal masses, extranodal lesions Nonmeasured lesions Organ enlargement New lesions Bone marrow	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment N/A N/A None No change from baseline	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met No increase consistent with progression No increase consistent with progression None N/A
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Addition of LYRIC to the LUGANO criteria to distinguish pseudoprogression from true progression (8)	with the following exceptions: Immune response (IR) IR(1): >50% increase in SPD on day 28 without clinical deterioration (biopsy is encouraged) IR(2): <50% increase in SPD with a. New lesion(s), or b. <50% increase in PPD of a lesion or set of lesions at any time during treatment IR(3): Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD (biopsy is encouraged)	with the following exceptions: Immune response (IR) IR(1): >50% increase in SPD on day 28 without clinical deterioration (biopsy is encouraged) IR(2): <50% increase in SPD with a. New lesion(s), or b. <50% increase in PPD of a lesion or set of lesions at any time during treatment
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression: An individual node/lesion must be abnormal with: LDi >1.5 cm; and Increase by ≥50% from PPD nadir; and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions; A new node >1.5 cm in any axis; A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma; Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement
For patients without CNS involvement at baseline, PD also applies to any patient who develops new morphologic evidence of CNS disease (200)		
3. A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim		

scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

4. PET 5PS: 1, no uptake above background; 2, uptake ≤mediastinum; 3, uptake >mediastinum but ≤liver; 4, uptake moderately >liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.
5. The decision to continue a patient on AVM0703 treatment with a determination of IR will be at the discretion of the treating physician taking into account the clinical status of each patient.

5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; N/A = not applicable; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions. IR=immune response

Source: Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood. 2016;128(21):2489-2496; Sandlund, J. R. (2015). International Pediatric Non-Hodgkin Lymphoma. *J Clin Oncol, 33*, 2106-2111.

APPENDIX G: RESPONSE CRITERIA PER iwCLL CRITERIA

The response definition after treatment of patients with chronic lymphocytic leukemia (CLL) per the International Workshop on CLL guidelines are described in the table below.

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)[1]	Increase ≥50% from baseline or from response	Change of -49% to +49%
	Liver and/or spleen size[2]	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of -49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of -49% to +49%
B	Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of -49 to +49%
	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11.0 g/dL or increase ≥50% over baseline	Decrease of ≥2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

CR (all of the criteria have to be met); PD (at least 1 of the criteria of group A or group B has to be met); PR (for a PR, at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD (all of the criteria have to be met; constitutional symptoms alone do not define PD).

1. Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).
2. Spleen size is considered normal if <13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.

CLL = chronic lymphocytic leukemia; CR = complete remission; CT = computed tomography; PD = progressive disease; PR = partial remission; SD = stable disease.

Source: Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-2760

APPENDIX H: RESPONSE CRITERIA PER IPCNSL CGRC CRITERIA (11)

(brain MRI with contrast preferred or brain diagnostic CT if MRI not possible) **source:Abrey 2005 [11]**				
Response	**Criteria**			
	Brain Imaging	**Corticosteroid Dose within 2 weeks of assessment**	**Eye examination[a]**	**CSF cytology**
Complete Response CR[b]	**No contrast enhancement**	**None**	**Normal**	**Normal**
Unconfirmed Complete Response CRu	**No contrast enhancement**	**Any**	**Normal**	**Negative**
	Minimal abnormality	**Any**	**Minor RPE abnormality[c]**	**Negative**
Partial Response[d]	**50% decrease in enhancing tumor**	**irrelevant**	**Minor RPE abnormality or normal**	**Negative**
	No contrast enhancement	**irrelevant**	**Decrease in vitreous cells or retinal infiltrate**	**Negative**
Progressive Disease	**25% increase in lesion**	**irrelevant**	**Recurrent or new ocular disease**	**Persistent or suspicious**
	Any new site of disease: CNS or systemic			**Recurrent or positive**

[a] Chronic changes of the retinal pigment epithelium in the setting of a prior retinal or optic nerve infiltrate does not preclude the definition of a CR. Detailed ophthalmologic examination with dilated fundus examination, slit-lamp examination and color photography of the posterior pole, and lumbar puncture for cytology are required only if these studies were initially positive or became positive during treatment and if clinically indicated by new symptoms or signs.
[b] Residual lesions (other than lesions < 10 mm) if presumed to be non-malignant should be further investigated (eg, by PET scans) before CR can be accepted. If there was evidence of PET abnormality suspicious for systemic disease then PET has to be repeated to confirm CR.
[c] Subjects with a persistent minor abnormality on follow-up ophthalmologic examination (persistent non- malignant cells in the vitreous, alteration of the retina/optic nerve that is not consistent with tumor infiltration) may be considered a CRu if this abnormality is unlikely to represent ocular lymphoma.
[d] Ophthalmologic examination should show a decrease in the vitreous cell count or retinal/optic nerve cellular infiltrate but may continue to show persistent malignant or suspicious cells. Color photos of the posterior pole of the eye should be obtained to document improvement in retinal/optic nerve infiltrates. CSF cytologic examination may be negative or continue to show persistent malignant or suspicious cells in subjects with a ≥ 50% decrease in the primary brain lesion. No new sites of disease. In the setting of primary leptomeningeal lymphoma, PR is not recognized; all subjects should be categorized as CR, CRu, stable disease, or progressive disease. Stable disease (SD) is defined as less than a PR but is not progressive disease (PD).
As additional radiographic, laboratory, or functional studies become more widely available and are demonstrated to have predictive value, they may be recommended as well.

APPENDIX I : MODIFIED SEVERITY WEIGHTED ASSESSMENT TOOL (mSWAT) SKIN LESION SCORING FOR MF, SS, ATLL AND CTCL AND GLOBAL RESPONSE SCORE

No patient with a global OR should have less than a PR in the skin if they had skin involvement at screening. As "skin flares" have been described in patients with SS receiving the immunomodulatory drug anti-PD-1 antibody Pembrolizumab ((201)), patients whose only sign of PD is an increase in mSWAT score will continue treatment and be re-evaluated in 2-4 weeks to confirm disease progression. Patients whose PD is not confirmed on re-evaluation will be noted to have had a skin flare.

The body is divided into 12 regions with pre-assigned percentage (%) total body surface area (TBSA) based on the burn literature. The extent of skin disease in each region is quantified by using the patient's palm to measure the %TBSA involvement within region: patient's palm with 4 fingers (excluding the thumb) is 1% of TBSA. Patient's palm without fingers is 0.5% of TBSA. The patient's palm with 4 fingers is traced on a transparency sheet at the baseline visit, using a permanent marker that will not rub off or smear. The transparency of the patient's palm should be used in all mSWAT assessments during the course of the clinical study. The transparency will be labeled with the patient's study ID number kept in the patient's study file on site. Using the baseline visit transparency of the patient's palm, the Investigator will measure and record the %TBSA for each lesion type within each of the 12 regions.

The severity weighting factors will be the following:

- 1= patch (flat erythema or erythema with mild infiltration)
- 2=plaque (elevated erythema or erythema with moderate infiltration)
- 4= tumor or ulceration (erythema with fissuring, ulceration or tumor)

Patch is defined as abnormal skin not elevated from normal skin. A plaque is defined as abnormal skin elevated from normal skin by < 5 mm. A plaque elevated ≥ 5 mm is a tumor.

Calculating Skin Score Lesions:
The sum of %TBSA by lesion is derived by summing the %TBSA from all regions affected by the lesion. The sum of %TBSA across lesion types (patches, plaques and tumors) within each region cannot exceed the %TBSA for the region. For example, the %TBSA for the head region is 7%. The sum of %TBSA across lesion types from head can only range from 0-7%. The skin score subtotal by lesion type are derived by multiplying the sum of %TBSA for patches from all regions by 1, sum of %TBS of plaques from all regions by 2, and the sum of %TBSA of tumors or ulcers from all regions by 4. The skin score total is derived from summing the skin score subtotals for patches, plaques and tumors or ulcers. The skin score total is dimensionless with a scale of 0 to 400.

%TBSA for each lesion type within each of the 12 regions

Region	Percentage TBSA for the region	Percentage TBSA patch (or flat erythema)	Percentage TBSA plaque (or elevated/indurated erythema)	Percentage TBSA tumor/ulceration (or erythema w/fissuring, ulceration
Head	7			
Neck	2			
Anterior Trunk	13			
Posterior Trunk	13			
Buttocks	5			
Genitalia	1			
Upper Arms	8			
Forearms	6			
Hands	5			
Thighs	19			
Lower Leg	14			
Feet	7			
%BSA by category	100			
Severity Weighting factor		×1	×2	×4
Skin Score subtotal				

Abbreviations: TBSA, total body surface area; BSA, body surface area

Responses will be determined by the criteria described in the table below. Progression of disease while on treatment should be confirmed by a second assessment 1 to 4 weeks later so that patients who experience a temporary flare of disease due to skin infection or other intercurrent illnesses are not removed from the study prematurely.

Response	Description
Skin	
Complete Response (CR)	No evidence of disease; 100% clearance of skin lesions.
Partial Response (PR)	≥50% decrease in skin scores compared to baseline and improvement is maintained for a minimum of 4 weeks
Stable Disease (SD)	< 50% decrease in skin scores compared to baseline
Progressive Disease (PD)	≥ 25% increase in skin scores compared to baseline while the patient is actively taking the study drug, *or* new tumor(s) ≥ 1 cm diameter in skin disease only patient, *or* ≥ 50% increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes (should be documented by biopsy) compared to baseline while the patient is actively taking the study drug.
Relapse	Any disease recurrence in those with complete response.
Lymph Nodes (peripheral and central)	
CR	All lymph nodes are now ≤ 1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N_3 classification and ≤ 1.5 cm in their long axis and > 1 cm in their short axis at baseline, must now be ≤ 1 cm in their short axis or biopsy negative for lymphoma

PR	Cumulative reduction > 50% of the SPD of each abnormal lymph node at baseline and no new lymph node > 1.5 cm in the diameter of the long axis or >1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain criteria for CR, PR, or PD
PD	≥ 50% increase in SPD from baseline of lymph nodes *or* Any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N3 histologically *or* Loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR
Relapse	Any new lymph node > 1.5 cm in the long axis in those with CR proven to be N_3 histologically.
Viscera	
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma
PR	≥ 50% regression in any splenic or liver nodules, or in measurable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain criteria for CR, PR, or PD

Response	**Description**
PD	>50% increase in size (SPD) of any organs involved at baseline *or* New organ involvement *or* Loss of response: >50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR
Relapse	New organ involvement in those with CR.
Blood	
CR (a)	B_0: Absence of significant blood involvement, <5% of peripheral blood lymphocytes are atypical cells
PR (b)	>50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD	B0 to B2 or >50% increase from Baseline and at least 5,000 neoplastic cells/μL, or >50% increase from nadir and at least 5,000 neoplastic cells/μL for those with OR who were originally B2 at baseline.

SPD = sum of the maximum linear dimension (major axis) x longest perpendicular dimension (minor axis)

GLOBAL RESPONSE SCORE AND DEFINITIONS OF RESPONSE IN SKIN, LYMPH NODES, VISCERA, AND BLOOD FOR SS, MF, ATLL AND CTCL:

Global Response Score					
Global Score	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any category involved at baseline at least one has a CR or PR		
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease	PD in any category			

(202) (203)

APPENDIX J : B- AND T-ALL RESPONSE CRITERIA

For B- and T-ALL additional response criteria are summarized below: (204) (205) consistent with NCCN guidelines:

Classification of CNS stautus:

CNS-1: No lymphoblasts in CSF regardless of WBC number;
CNS-2: WBC < 5/microL with presence of lymphoblasts;
CNS-3: WBC > 5/microL with presence of lymphoblasts.
If the patient has leukemic cells in the peripheral blood and the LP is traumatic and WBC >5/microL in the CSF with the presence of lymphoblasts, then compare the CSF WBC/RBC ratio to the blood ratio. If the CSF ratio is at least 2-fold greater than the blood ratio then it is CNS-3. If not then CNS-2.

- Complete response is defined as achieving each of the following:

o Bone marrow differential showing ≤5% blast cells,
o Absolute neutrophil count ≥1.0 x 109 /L and platelet count ≥100 x 109 /L,
o Absence of extra-medullary disease by diagnostic CT, PET/CT or MRI according to LUGANO Criteria (adapted as necessary in the imaging guidelines) in Appendix E,
o Patient is independent of red blood cell (RBC) transfusions.
o CNS-1

- Complete response with incomplete blood count recovery is defined as achieving all CR criteria except that that values for ANC may be <1.0 x 109/L and/or values for platelets may be <100 x 109/L.

- Partial response is defined as achieving each of the following:

o ANC ≥1.0 x 109/L and platelet count ≥100 x 109/L,
o Bone marrow differential showing a ≥50% decrease from baseline in the percentage of bone marrow blast cells to a level >5% and ≤25%.
o CNS-2
o Reduction of extramedullary disease by diagnostic CT, PET/CT or MRI according to the LUGANO Criteria (adapted as necessary in the imaging guidelines) in Appendix E

- A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease.

- Progressive Disease is defined as not achieving CR, CRi or PR with extramedullary masses increasing according to the LUGANO Criteria for PD (adapted as necessary in the imaging guidelines) in Appendix E and appearance of circulating leukemic blasts or an increase of at least 25% in the absolute number of circulating or bone marrow blasts and CNS-3.

APPENDIX K: DEFINITIONS FOR PEDIATRIC BLOOD PRESSURE

The updated definitions and blood pressure categories for pediatric patients are described in the table below.

For Children Aged 1 to ≤13 years	For Children Aged ≥13 years
Normal BP: <90th percentile	Normal BP: <120/<80 mmHg
Elevated BP: ≥90th percentile to <95th percentile or 120/80 mmHg to <95th percentile (whichever is lower)	Elevated BP: 120/<80 to 129/<80 mmHg
Stage 1 HTN: ≥95th percentile to <95th percentile + 12 mmHg, or 130/80 to 139/89 mmHg (whichever is lower)	Stage 1 HTN: 130/80 to 139/89 mmHg
Stage 2 HTN: ≥95th percentile + 12 mmHg, or ≥140/90 mmHg (whichever is lower)	Stage 2 HTN: ≥140/90 mmHg
BP = blood pressure; HTN = hypertension. Source: Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3)	

APPENDIX L: LANSKY PERFORMANCE SCALE

Lansky Score	Definition
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of, and less time spent in, active play
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive
Source: Lansky SB, List MA, Lansky LL, et al. The measurement of performance in childhood cancer patients. *Cancer*. 1987;60(7):1651-1656	

APPENDIX M: KARNOFSKY PERFORMANCE SCALE

Karnofsky Score (KS)	Definition
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead
Source: Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In MacLeod CM (Ed), Evaluation of chemotherapeutic agents. Columbia University Press, New York. 1949; 196-196	

APPENDIX N: TRANSLATION OF KARNOFSKY PERFORMANCE SCALE TO ECOG PERFORMANCE STATUS SCALE

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.