M22-132: Phase 1b/2, Open-Label Study to Evaluate Safety and Tolerability of Epcoritamab in Combination with Anti-Neoplastic Agents in Subjects with Non-Hodgkin Lymphoma

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

1. Subjects or their legally authorized representative, if permitted, must voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

2. Adult **male or female**, at least 18 years old.
3. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:

- Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L (growth factor use is allowed if evidence of bone marrow involvement, but subject must not have received growth factor within 14 days prior to screening labs)
- Hemoglobin ≥ 8.0 g/dL (red blood cell transfusions permitted, but subject must not have received blood transfusions within 7 days prior to screening labs)
- Platelet count ≥ 75 × 10^9/L, or ≥ 50 × 10^9/L if bone marrow infiltration or hypersplenism (platelet transfusions permitted, but subject must not have received blood transfusions within 7 days prior to screening labs)
- Serum aspartate transaminase (AST) AND alanine transaminase (ALT) level ≤ 3 × upper limit of normal (ULN)
- Direct bilirubin must be ≤ 2 × ULN
- Estimated Creatinine Clearance (CrCl) ≥ 50 mL/min (as calculated by Cockcroft-Gault Formula, modified as needed for factors such as body weight)
- Prothrombin time/International normalized ratio (INR)/Activated partial thromboplastin time ≤ 1.5 × ULN, unless receiving anticoagulation (although INR should not be > 4.0)

4. Subject is willing and able to comply with procedures required in this protocol.
5. Subject must be able to tolerate subcutaneous injections.
6. Subject must have available adequate fresh or paraffin-embedded tissue at Screening.

Disease/Condition Activity

7. Diagnosis of:

- (Arms 1, 2, 3, and 4) DLBCL (de novo or histologically transformed from follicular lymphoma or nodal marginal zone lymphoma) with histologically confirmed CD20+ disease, inclusive of the following according to WHO 2016 classification and documented in pathology report:
- DLBCL, NOS
- High-grade B cell lymphoma with MYC and BCL-2 and/or BCL-6 translocations per WHO 2016 ("double-hit" or "triple-hit")

Note: High-grade B-cell lymphomas NOS or other double-/triple-hit lymphomas (with histologies not consistent with DLBCL) are not eligible

- Follicular lymphoma Grade 3B

Or

- (Arm 5) FL with histologically confirmed CD20+ Grade 1 to 3a FL and no evidence of histologic transformation to an aggressive lymphoma at most recent representative tumor

biopsy according to WHO 2016 classification
Or
• (Arms 6 and 7) MCL with histologically confirmed CD20+ disease at most recent representative tumor biopsy according to the WHO 2016 classification with evidence of overexpression of cyclin D1 in association with relevant markers by IHC or evidence of t(11;14) assessed by flow cytometry, FISH, or PCR
• A report from the local laboratory is acceptable if available, however, a tumor block or slides must be sent to the central pathology laboratory for confirmation
8. Subject must have no prior treatment with epcoritamab or any other bispecific antibody targeting CD3 and CD20

9. Subject must have 1 or more measurable disease sites:
• A PET-CT scan demonstrating PET-positive lesion(s)
AND
• At least 1 measurable nodal lesion (long axis > 1.5 cm) or ≥ 1 measurable extra-nodal lesion (long axis > 1.0 cm) on CT scan or MRI
10. Subject must be eligible to receive and have a need for treatment initiation based on symptoms and/or disease burden as per investigator assessment.
11. Subject must have ECOG performance status 0-2, except for Arms 6 and 7 where ECOG performance status must be 0-1.

Subject History

12. Subject has no toxicities from prior anticancer therapy that have not resolved to Common Terminology Criteria for Adverse Events (CTCAE, v 5.0), Grade 2 or below, with the exception of alopecia. Other eligibility criteria (e.g., laboratory, cardiac criteria) must also be met.
13. Subject has no current evidence of primary central nervous system (CNS) tumor or known CNS involvement, including leptomeningeal disease, at screening.
14. Subject has no history of severe allergic or anaphylactic reactions to anti-CD20 mAb therapy or known significant allergy or intolerance to any component or excipient of epcoritamab or components of study drug combination agents (e.g., lenalidomide, rituximab, etc.)
15. Subject must not have had autologous stem cell transplantation (ASCT) within 3 months prior to screening, and no previous allogeneic hematopoietic stem cell transplant.
16. Subject must not have had any chemotherapy or non-investigational anti-neoplastic agents (except CD20 mAbs) within 4 weeks or 5 half-lives (whichever is shorter) prior to the first dose of epcoritamab (except for Arms 6 and 7, where bridging therapy for MCL is allowed, see Section 5.4)
17. Subject has no clinically significant cardiovascular disease, including:
• Myocardial infarction or stroke within 6 months prior to enrollment,
OR
• The following conditions within 6 months prior to enrollment: unstable or uncontrolled disease/condition related to or affecting cardiac function (e.g., unstable angina, congestive heart failure, New York Heart Association Class III-IV), uncontrolled cardiac arrhythmia, and uncontrolled hypertension)
OR
• Other clinically significant ECG abnormalities within 6 months prior to enrollment unless deemed stable and appropriately treated.
OR
• Left ventricular ejection fraction < 45%
In case of any history of cardiovascular disease, a cardiology consult is required within 60 days of enrollment.
18. Subject has no clinically significant liver disease, including hepatitis, current alcohol abuse, or

cirrhosis.
19. Subject does not have active Hepatitis B Virus or Hepatitis C Virus infection. Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
20. Subject has no known history of Human Immunodeficiency Virus infection. Note: Human immunodeficiency virus testing does not need to be conducted at screening unless it is required per local guidelines or institutional standards.
21. Subject has no known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of the nail beds) requiring intravenous (IV) therapy within 2 weeks prior to enrollment.
22. Subject has no evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results.
23. Subject has no history of other prior malignancies, except for the following:
- Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before the first dose of study drug and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease
- Localized prostate cancer, post-radical prostatectomy with non-rising prostate-specific antigen levels < 0.1 ng/mL

24. Subject has not had radiation therapy to target lesion if only 1 target lesion is involved and no other target lesions that have not received radiation therapy can be followed.
25. Subject has no Grade > 1 neuropathy.
Subject must not have active tuberculosis (TB) or history of completed treatment for active TB within the past 12 months.
Note: Interferon gamma release assay (IGRA) testing does not need to be performed at screening unless active or latent TB is suspected. For subjects with positive IGRA, active pulmonary TB must be excluded with clinical evaluation and radiologic imaging. Subjects with positive IGRA and no evidence of active disease may be enrolled after treatment for latent tuberculosis infection (recommendation isoniazid monotherapy for total of 6 months) has been initiated.
26. Subject does not have active (symptomatic) cytomegalovirus (CMV) disease.
27. Subject has no current autoimmune disease requiring immunosuppressive therapy except for up to 20 mg prednisone daily (or equivalent).

28. Subject has no life-threatening illness, medical condition, or organ system dysfunction that, in the Investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
29. Subject has no current seizure disorder requiring therapy.
30. Subject has no known active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection or have recent known exposure to someone with SARS-CoV infection, they should undergo molecular (e.g., PCR) or 2 negative antigen test results at least 24 hours apart to rule out SARS-CoV-2 infection. Note: SARS-CoV-2 diagnostic tests should be applied following local requirements/regulations.
31. Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria:
- At least 10 days since first positive test result have passed in asymptomatic subjects or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

32. Subject must not have had major surgery within 4 weeks of the first dose of study drug.

33. Subject has a life expectancy of > 3 months from standard of care treatment from time of enrollment
34. Subject has no known history of Progressive Multifocal Leukoencephalopathy (PML).

Contraception

35. For all females of child-bearing potential; a negative serum pregnancy test (beta human chorionic gonadotropin [hCG]) at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug
36. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control that is effective from 30 days prior to enrollment through at least 12 months after the last dose of study drug. Female subjects of non-childbearing potential do not need to use birth control.
37. Female subject who is not pregnant, breastfeeding, donating eggs (ova, oocytes), or considering becoming pregnant during the study or for 12 months after the last dose of study drug.
38. **If male**, and subject is sexually active with female partner(s) of childbearing potential, he must agree, from 30 days prior to enrollment through 12 months after the last dose of study drug, to practice the protocol-specified contraception.
39. Male subject who is not considering fathering a child or donating sperm during the study or for 12 months after the last dose of study drug.

40. Subject has no active medication use known to decrease T-cell numbers or activity or other concurrent immunosuppressive medication except for up to 20 mg prednisone daily or equivalent, or for disease control during screening.
41. Subject must not have been treated with **any investigational drug** within 30 days or 5 halflives
of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another interventional clinical study or was previously enrolled in this study (agents that have been approved under emergency authorization, e.g., anti-SARS-CoV-2 mAbs, are allowed)
42. Subject has not received vaccination with live-attenuated vaccines within 28 days prior to screening or is expected to need any live-attenuated vaccination during study participation including at least 3 months following the last dose of study treatment. Coronavirus mRNA and adenovirus-based vaccines, which are not live-attenuated vaccines, are permitted.

Additional Eligibility Criteria Specific to Arm 1

43. Subject must have R/R DLBCL
Note: Relapsed disease is defined as disease that previously responded to therapy but progressed ≥ 6 months after completion of therapy. Refractory disease is defined as disease that either progressed during therapy, failed to achieve an objective response to prior therapy, or progressed within 6 months after completion of therapy (including maintenance therapy).
44. Subject must have R/R disease to at least one prior systemic anti-lymphoma therapy (radiotherapy is not considered a systemic therapy) which contains an anti-CD20 monoclonal antibody. Subject who received only prior anti-CD20 monoclonal antibody monotherapy is not eligible.
45. Subject must not be refractory (defined as best response of stable disease [SD] or progressive disease [PD]) to prior CAR-T therapy. Subject should not have received any treatment with CAR-T therapy within 90 days prior to enrollment; any CAR-T related toxicity should have been resolved for at least 30 days.
46. Subjects must have either failed prior ASCT, not be considered eligible for ASCT due to age, performance status, comorbidities and/or insufficient response, or have refused ASCT.
47. Subject must not have documented refractoriness to lenalidomide and must be suitable for

treatment with lenalidomide in the opinion of the investigator.
Note: Refractoriness is defined as:
- Best response to prior regimen(s) of SD or PD, OR
- Progressive disease within 6 months of completion of prior regimen(s)

48. Subject must be willing to take aspirin prophylaxis or prophylactic anticoagulation for thromboembolic event (or per local guidelines for lenalidomide administration).
49. Female subjects of childbearing potential must practice at least 2 protocol-specified methods of birth control that are effective from 30 days prior to enrollment through at least 12 months after the last dose of study drug. Female subjects of non-childbearing potential do not need to use birth control.
50. Subject is willing to adhere to the pregnancy risk minimization plan associated with lenalidomide treatment.
51. Subject must not have had lenalidomide exposure within 12 months prior to screening.
52. Subject must be able to swallow capsules and must not have any disease significantly affecting gastrointestinal function (e.g., resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction).
53. Subjects must agree not to donate blood while receiving, during dose interruptions, and for at least 28 days following the last dose of lenalidomide.

Additional Eligibility Criteria Specific to Arm 2

54. Subject must have R/R (as defined in Criterion #43) DLBCL.
55. Subject must have received at least 1 prior treatment for which must include an anti-CD20 monoclonal antibody in combination with another systemic therapy (radiotherapy is not considered a systemic therapy).
56. Subject must have received prior CAR-T cell therapy, but for those who achieved a response to prior CAR-T, not less than 90 days prior to first dose of epcoritamab, or for those who were refractory to CAR-T, not less than 30 days prior to first dose of epcoritamab.
Note: Refractoriness is defined as:
- Best response to prior regimen(s) of SD or PD, OR
- Progressive disease within 6 months of completion of prior regimen(s)

57. Subjects must have either failed prior ASCT, not be considered eligible for ASCT due to age, performance status, comorbidities and/or insufficient response, or have refused ASCT.
58. Subject must not have documented refractoriness to lenalidomide and must be suitable for treatment with lenalidomide in the opinion of the investigator.
59. Subject must not have had prior treatment with ibrutinib and must be suitable for treatment with ibrutinib in the opinion of the investigator.
60. Subject must not have had lenalidomide exposure within 12 months prior to screening.
61. Subject must not have known bleeding diathesis (e.g., von Willebrand's disease) or hemophilia.
62. Subject must not require treatment with a strong cytochrome P450 (CYP) 3A inhibitor.
63. Subject must not have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit for at least 3 days prior to Cycle 1 Day 1.
64. Subject must be willing to take aspirin prophylaxis or prophylactic anticoagulation for thromboembolic event (or per local guidelines for lenalidomide administration).
65. Female subjects of childbearing potential must practice at least 2 protocol-specified methods of birth control that are effective from 30 days prior to enrollment through at least 12 months after the last dose of study drug. Female subjects of non-childbearing potential do not need to use birth control.

66. Subject is willing to adhere to the pregnancy risk minimization plan associated with lenalidomide treatment.
67. Subject must be able to swallow capsules and must not have any disease significantly

affecting gastrointestinal function (e.g., resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction).
68. Subjects must agree not to donate blood while receiving, during dose interruptions, and for at least 28 days following the last dose of ibrutinib or lenalidomide.

Additional Eligibility Criteria Specific to Arm 3

69. Subject must have newly diagnosed, treatment-naïve (not including prior treatments for indolent lymphoma that has transformed) DLBCL.
70. Subject must be suitable for treatment with polatuzumab, rituximab, cyclophosphamide, doxorubicin, and prednisone in the opinion of the investigator.
71. Subject must have International Prognostic Index score of 2 - 5.

Additional Eligibility Criteria Specific to Arm 4

72. Subject must have R/R (as defined in Criterion #43) DLBCL.
73. Subject must have R/R disease to at least one prior systemic anti-lymphoma therapy (radiotherapy is not considered a systemic therapy) which contains an anti-CD20 monoclonal antibody. Subject who received only prior anti-CD20 monoclonal antibody monotherapy is not eligible.
74. Subject must not be refractory (defined as best response of stable disease [SD] or progressive disease [PD]) to prior CAR-T therapy. Subject should not have received any treatment with CAR-T therapy within 90 days prior to enrollment; any CAR-T related toxicity should have been resolved for at least 30 days.
75. Subjects must have either failed prior ASCT, not be considered eligible for ASCT due to age, performance status, comorbidities and/or insufficient response, or have refused ASCT.
76. Female subjects of childbearing potential must practice at least 2 protocol-specified methods of birth control (at least one highly effective method and one effective method) at the same time from 30 days prior to enrollment through at least 12 months after the last dose of epcoritamab.
77. Subject must be willing to adhere to the pregnancy risk minimization plan associated with CC-99282 treatment.
78. Subject must be able to swallow capsules and must not have any disease significantly affecting gastrointestinal function (e.g., resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction).
79. Subject must not have received prior treatment with CC-99282 or CC-220 (iberdomide).
80. Subjects must agree not to donate blood while receiving CC-99282, during dose interruptions and for at least 28 days following the last dose of CC-99282.

Additional Eligibility Criteria Specific to Arm 5

81. Subject must have R/R (as defined in Criterion #43) FL.
82. Subject must have Stage II-IV disease.
83. Subject must have a need for treatment initiation per investigator determination based on symptoms and/or disease burden.
84. Subject must have R/R disease to at least one prior systemic anti-lymphoma therapy (radiotherapy is not considered a systemic therapy) which contains an anti-CD20 monoclonal antibody. Subjects who received only prior anti-CD20 monoclonal antibody monotherapy are not eligible.
85. Subject must not be refractory (defined as best response of stable disease [SD] or progressive disease [PD]) to prior CAR-T therapy. Subject should not have received any treatment with CAR-T therapy within 90 days prior to enrollment; any CAR-T related toxicity should have been resolved for at least 30 days.

86. Female subjects of childbearing potential must practice at least 2 protocol-specified methods of birth control (at least one highly effective method and one effective method) at the same time from 30 days prior to enrollment through at least 12 months after the last dose of epcoritamab.
87. Subject must be willing to adhere to the pregnancy risk minimization plan associated with CC-99282 treatment.
88. Subject must be able to swallow capsules and must not have any disease significantly affecting gastrointestinal function (e.g., resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction).
89. Subject must not have received prior treatment with CC-99282 or CC-220 (iberdomide).
90. Subjects must agree not to donate blood while receiving CC-99282, during dose interruptions and for at least 28 days following the last dose of CC-99282.

Additional Eligibility Criteria Specific to Arm 6A

91. Subject must have R/R (as defined in Criterion #43) MCL.
92. Subject must have an absolute lymphocyte count < 50 x 10^9/L during screening and < 10 × 10^9/L by Cycle 1 Day 1 (bridging therapy may be needed and is allowed).
93. Subject must have received at least 1 prior treatment for MCL which must include an anti-CD20 monoclonal antibody in combination with another systemic therapy (radiotherapy is not considered a systemic therapy).
94. Subject must not be refractory (defined as best response of stable disease [SD] or progressive disease [PD]) to prior CAR-T therapy. Subject should not have received any treatment with CAR-T therapy within 90 days prior to enrollment; any CAR-T related toxicity should have been resolved for at least 30 days.
95. Subject must be suitable for treatment with ibrutinib in the opinion of the investigator.

96. Subject must not have received prior BTKi therapy.
97. Subject must not have known bleeding diathesis (e.g., von Willebrand's disease) or hemophilia.
98. Subject must not require treatment with a strong cytochrome P450 (CYP) 3A inhibitor.
99. Subject must not have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit for at least 3 days prior to Cycle 1 Day 1.
100. Subject must be able to swallow capsules and must not have any disease significantly affecting gastrointestinal function (e.g., resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction).

Additional Eligibility Criteria Specific to Arm 6B

101. Subject must have R/R (as defined in Criterion #43–35) MCL.
102. Subject must have an absolute lymphocyte count < 50 x 10^9/L during screening and < 10 x 10^9/L by Cycle 1 Day 1 (bridging therapy may be needed and is allowed).
103. Subject must have received at least 1 prior treatment for MCL which must include an anti-CD20 monoclonal antibody in combination with another systemic therapy (radiotherapy is not considered a systemic therapy).
104. Subject must not be refractory (defined as best response of stable disease [SD] or progressive disease [PD]) to prior CAR-T therapy. Subject should not have received any treatment with CAR-T therapy within 90 days prior to enrollment; any CAR-T related toxicity should have been resolved for at least 30 days.
105. Subject must be suitable for treatment with ibrutinib and venetoclax in the opinion of the investigator.
106. Subject must not have received prior BTKi therapy.

107. Subject must not have known bleeding diathesis (e.g., von Willebrand's disease) or hemophilia.
108. Subject must not require treatment with a strong cytochrome P450 (CYP) 3A inhibitor and must not have received a strong CYP3A inhibitor for at least 7 days prior to Cycle 1 Day 1.
109. Subject must not have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit for at least 3 days prior to Cycle 1 Day 1.
110. Subject must not have received prior BCL-2 inhibitor therapy.
111. Subject must be able to swallow capsules and must not have any disease significantly affecting gastrointestinal function (e.g., resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction).

Additional Eligibility Criteria Specific to Arm 7

112. Subject must have treatment-naïve MCL disease.
113. Subject must have an absolute lymphocyte count < 50 x 10^9/L during screening and < 10 × 10^9/L by Cycle 1 Day 1 (bridging therapy may be needed and is allowed).
114. Subject must have refused ASCT, not be Transplant for ASCT (due to age, performance status, comorbidities), OR have high-risk disease characteristics (e.g., TP53 alterations [deletion/mutation], Ki-67 > 30%, blastoid/pleomorphic variant).
115. Subject must be suitable for treatment with ibrutinib and venetoclax in the opinion of the investigator.
116. Subject must not have known bleeding diathesis (e.g., von Willebrand's disease) or hemophilia.
117. Subject must not require treatment with a strong cytochrome P450 (CYP) 3A inhibitor.
118. Subject must not have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit for at least 3 days prior to Cycle 1 Day 1.
119. Subject must be able to swallow capsules and must not have any disease significantly affecting gastrointestinal function (e.g., resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction).