Title: An open-label, multicenter, Phase 1b study of JNJ-COMPOUND With Bruton's Tyrosine Kinase Inhibitor (BTKI) in Combination in Relapsed or Refractory B cell Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

Short title: Phase 1b study of JNJ-COMPOUND with BTKI in R/R NHL and CLL

1. PROTOCOL SUMMARY

1.1 Synopsis

An open-label, multicenter, Phase 1b study of JNJ-COMPOUND and Bruton's Tyrosine Kinase Inhibitor (BTKI) in combination in relapsed or refractory B cell non-Hodgkin lymphoma and chronic lymphocytic leukemia.

Introduction

Bruton's tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase that plays a critical role in B cell activation via the B cell receptor (BCR) signaling pathway. BTK is important for normal B cell activation and the pathophysiology of B cell malignancies, and several BTK inhibitors have demonstrated clinical activity in non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). The TKI to be used in this study is a first-in-class BTK inhibitor that has demonstrated broad clinical activity in the treatment of CLL and discrete subtypes of NHL.

JNJ-COMPOUND

This study will evaluate JNJ-COMPOUND in combination with BTKI in a first-in-human study of NHL and CLL.

JNJ-COMPOUND is currently being evaluated in an ongoing, 2-part, Phase 1 FIH study. The study is an open-label study of the safety, PK, and PD of JNJ-COMPOUND in participants with NHL and CLL. The study consists of a dose escalation phase to determine a recommended Phase 2 dose (RP2D) or dose.

Rationale of Combining JNJ-COMPOUND and Bruton's Tyrosine Kinase Inhibitor (BTKI)

Both JNJ-COMPOUND and the BTKI can inhibit activation of the NF-kB pathway. JNJ- COMPOUND has activity in models with commonly seen resistance mechanisms to the BTKI (BTK C481S, PLCG2, CARD11, and BCL10).

Objectives and Endpoints

The primary objectives of the study are to determine the safety (Part 1 and Part 2) and the recommended Phase 2 doses (RP2Ds) (in Part 1) of JNJ- COMPOUND and the BTKI in combination in participants with B cell NHL and CLL.

The secondary objectives are to determine the safety of this combination in focused histologies/participant populations (Part 2) when administered at the RP2D(s) determined in Part 1; to assess the pharmacokinetics (PK) and pharmacodynamics (PD) of the study drugs (Part 1 and Part 2), and to determine preliminary clinical activity of the combination in focused histologies/participant populations (Part 2) when administered at the RP2D(s) determined in Part 1.

The primary endpoint of the study is the type and severity of adverse events, including dose-limiting toxicities (DLTs). The study secondary endpoints include plasma concentration-time profiles, PK parameters of JNJ-COMPOUND and the BTKI in combination, BTK receptor occupancy and cytokine and T cell profiling, overall response rate, time to first response, and duration of response.

Hypothesis

No formal statistical hypothesis testing will be conducted in this study. The study will determine the following:

Dose escalation (Part 1): The RP2D(s) of JNJ-COMPOUND and the BTKI in combination such that the underlying DLT rate is ≤25%.

Cohort Expansion (Part 2): The RP2D(s) determined in Part 1 of JNJ-COMPOUND and the BTKI is safe and shows preliminary anticancer activity in combination in participants with specific subtypes of B cell NHL including MCL and WM.

Overall Design

This is an open-label, multicenter, Phase 1b study of JNJ-COMPOUND and the BTKI in combination in participants with B cell NHL and CLL who have relapsed or refractory disease that requires treatment.

The study will be conducted in 2 parts: Part 1 of the study is designed to determine the RP2Ds of JNJ-COMPOUND and the BTKI in combination in participants with B cell NHL and CLL. Part 2 is designed to further assess the safety as well as preliminary clinical efficacy of the RP2D(s) of JNJ-COMPOUND and the BTKI in combination in participants with specific subtypes of B cell NHL such as MCL and WM. Other histologies may be considered in Part 2 if data from Part 1 or other sources support other cohorts such as DLBCL or follicular lymphoma.

Dose escalation and de-escalation for ongoing participants will be guided by the dose escalation rules and will be decided by the Study Evaluation Team (SET) based on the review of safety, clinical activity, PK, PD, and other relevant data. The end of study is defined as the last scheduled study assessment for the last participant of the study.

Number of Participants

A target of approximately 70 participants will be enrolled in this study. As the number of cohorts to be opened will be informed and affected by the data herein, and emerging clinical data from medical and scientific literature, the final sample size may be different from 70.

1.2 Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. ≥18 years of age.

2. Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1.

3. Participants must have histological documentation of disease: (R/R B-cell NHL or CLL/SLL) requiring therapy (defined below for Part 1 and Part 2). Prior BTK inhibitor treatment is acceptable, provided discontinuation was not due to disease progression during treatment with the BTK inhibitor or poor tolerance of the BTK inhibitor.

   Part 1:

   B-cell NHL: The following histologies of B-cell NHL that require systemic treatment will be enrolled, with the following disease-specific criteria:

   - Large B Cell Lymphoma and High-grade B cell Lymphoma
   - Follicular Lymphoma

- Mantle Cell Lymphoma or Waldenström Macroglobulinemia
- Marginal Zone Lymphoma (Including MALT Lymphoma)

CLL/SLL: CLL/SLL that meets criteria for systemic treatment per the iwCLL guidelines and is relapsed or progressing/nonresponsive after at least 2 prior systemic therapies, and no other approved therapies that would be considered more appropriate in the investigator's judgement.

Part 2: All above requirements for MCL and WM in Part 1 apply. In addition, participants must have measurable disease as defined by the appropriate disease response criteria.

4. Hematology laboratory parameters within the following ranges. Values must be without transfusions or growth factors for at least 7 days prior to the first dose of study drug.
   a. Hemoglobin ≥ 8 g/dL
   b. Platelets ≥ 100 x 10^9/L or 50 x 10^9/L if bone marrow involvement independent of transfusion support in either situation
   c. Absolute neutrophil count ≥ 1.0 x 10^9/L.
5. Chemistry laboratory parameters within the following range:
   a. AST and ALT ≤ 2.5 × ULN or < 4 × ULN if participant has documented liver involvement with disease
   b. Serum total bilirubin < 1.5 × ULN. Participants with congenital bilirubinemia such as Gilbert's Syndrome may enroll if direct bilirubin is within normal range
   c. Estimated or measured glomerular filtration rate (GFR) ≥40 mL/min.
6. Cardiac parameters within the following range: corrected QT interval using Fridericia formula (QTcF) ≤480 ms based on the average of triplicate assessments performed as close as possible in succession (the full set of triplicates should be completed in less than 10 minutes).
7. Ejection fraction, as measured by the preferred local modality, and within normal range per local parameters.
8. Participants must have tumor tissue available at baseline that is adequate for tumor sequencing (DNA and/or RNA sequencing). The tumor tissue can be from a fresh biopsy or archived tumor tissue, and can be from biopsy of a nodal, extranodal tumor. Bone marrow biopsy is only acceptable if it's known to be extensively infiltrated with lymphoma or CLL.
9. Women of childbearing potential (as defined in Appendix **Fehler! Verweisquelle konnte nicht gefunden werden.**) must agree to all of the following during the study and for 30 days after the last dose of study drug:
   - Use a barrier method of contraception

- Use a highly effective preferably user-independent method of contraception. See Section **Fehler! Verweisquelle konnte nicht gefunden werden.** for acceptable methods of contraception).
- Not to donate eggs (ova, oocytes) or freeze them for future use for the purposes of assisted reproduction during the study.
- Not to plan to become pregnant
- Not to breast-feed

10. A male must agree to all of the following during the study and for 90 days after the last dose of study drug:

    - Wear a condom when engaging in any activity that allows for passage of ejaculate to another person.
    - Not to donate sperm or freeze for future use for the purpose of reproduction.
    - Not plan to father a child

    In addition, the participant should be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.

11. Participants must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and the procedures required for the study, and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard-of-care for the participant's disease.

12. Willing and able to adhere to the lifestyle restrictions specified in this protocol.

1.3 Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study.

1. Prior treatment with JNJ-COMPOUND or a MALT1 inhibitor that is associated with disease progression or intolerable toxicities.

2. Known (active) CNS involvement.

3. Received prior solid organ transplantation.

4. Either of the following:

    - Received an autologous stem cell transplant ≤3 months before the first dose of study drug.
    - Prior treatment with allogenic stem cell transplant ≤6 months before the first dose of study drug, has evidence of GVHD, or requires immunosuppressant therapy for graft versus host disease within the last 4 weeks.

5. (a) Prior chemotherapy, targeted therapy, immunotherapy, radiotherapy (with the exclusion of palliative radiation to limited sites that do not interfere with response assessment based on a

sufficient number of other sites), or treatment with an investigational anti-cancer agent or an investigational drug (including investigational vaccines) within 2 weeks before the first administration of JNJ-COMPOUND and the BTKI.

For other investigational agents where the half-life is known, there should be a treatment-free window of at least 2 weeks or 5 half-lives.

(b) Prior chimeric antigen receptor T (CAR-T) cell therapy and T-cell engaging antibodies within 4 weeks before the first administration of JNJ-COMPOUND and the BTKI.

CAR-T associated toxicities must have been to Grade 1 or baseline before enrollment. Due to paucity of data in post-CAR-T treatment, the investigator should discuss with the sponsor regarding the eligibility.

6. Toxicities from previous anti-cancer therapies that have not resolved to baseline levels, or to Grade <2 (except for alopecia [Grade 2], vitiligo [Grade 2]), and peripheral neuropathy [Grade 1]).

7. Participant is taking long-term corticosteroids (>10 mg daily prednisone equivalents).

- A short course (eg, >10 mg daily prednisone equivalents for up to 4 days) of corticosteroids is permitted. Inhaled or topical steroids, and adrenal replacement doses ≤10 mg daily prednisone equivalents, are permitted in the absence of active autoimmune disease.
- If corticosteroids were used to treat immune-related adverse events associated with prior therapy, ≥7 days must have elapsed since the last dose of corticosteroid.

8. Participant has known allergies, hypersensitivity, or intolerance to JNJ-COMPOUND or the BTKI or excipients.

9. History of clinically significant cardiovascular disease within the 6 months prior to the first dose of study drug including, but not limited to:

a. Myocardial infarction
b. Severe or unstable angina
c. Clinically significant cardiac arrhythmias
d. Uncontrolled persistent hypertension (Grade 3 or worse)
e. Stroke or transient ischemic attack
f. Venous thromboembolic events (ie, pulmonary embolism) within 1 month prior to the first dose of study drug; uncomplicated (Grade ≤2) deep vein thrombosis is not considered exclusionary.
g. Congestive heart failure (New York Heart Association class III-IV)
h. Pericarditis or clinically significant pericardial effusion
i. Myocarditis
j. Endocarditis
k. Long QT syndrome

10. Clinically significant pulmonary compromise requiring supplemental oxygen use to maintain adequate oxygenation.

11. Prolonged coagulation values (prothrombin time, international normalized ratio, activated partial thromboplastin time) in the absence of direct oral anti-coagulants treatment, at screening that are clinically significant per investigator discretion, or has a history of subdural hematoma, abnormal bleeding tendency, or congenital bleeding diathesis.

12. Active liver cirrhosis of Child Pugh Class B or Class C.

13. Unable to swallow capsules or tablets or has malabsorption syndrome, disease that significantly affects gastrointestinal function, resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction. If any of these conditions exist, the site should discuss with the sponsor to determine participant eligibility.

14. Evidence of active viral, bacterial, or fungal infection requiring systemic anti-infective treatment within 7 days before the first dose of study drugs.

15. Participant has a known positive test result for human immunodeficiency virus or acquired immune deficiency syndrome, unless viral load is undetectable and CD4 count is above 200 on stable highly active anti-retroviral therapy.

16. Participant has active or chronic hepatitis B or hepatitis C infection.

    Hepatitis B infection is defined by (a) a positive test for hepatitis B surface antigen (HBsAg), or (b) a test panel that is positive for anti-hepatitis B core antigen (HBc) and negative for HBsAg and hepatitis B surface antibody (anti-HBs). Appendix **Fehler! Verweisquelle konnte nicht gefunden werden.** describes the test panels that will not be excluded Specifically, a test panel that is positive for anti-HBc, positive for anti-HBsAb, and negative for anti-HBsAg will be eligible; and for participants enrolled with this panel of results the treating physician should use their discretion and institutional guideline to decide whether (a) PCR based test of hepatitis B virus (HBV) is warranted at screening and repeated during treatment, and (b) prophylactic treatment for HBV reactivation is necessary.

    Hepatitis C infection is defined by a positive hepatitis C virus (HCV) antibody test, with subsequent confirmation with positive HCV RNA test.

17. Clinically significant trauma or major surgery (eg, entailing entry into a major body cavity, or significant blood loss or fluid shifts) within 28 days prior to the first dose of study drug. Note: Participants with planned minor surgical procedures to be conducted under local anesthesia may participate. If a participant undergoes palliative surgery for relieving tumor associated symptoms, such as colectomy, enrollment may be considered without subjecting to the 28-day rule described above, if the participant has recovered. Such case should be approved by the sponsor in addition to endorsement of the investigator and the surgeon who performs the operation.

18. Any serious underlying medical or psychiatric condition (e.g., alcohol or drug abuse, dementia or altered mental status); or any issue that would impair the ability of the participant to receive or tolerate the planned treatment at the investigational site, to understand informed consent, or due to which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, could compromise the participant's well-being) or that could prevent, limit, or confound the protocol-specified assessments.

19. Requires a prohibited medication that cannot be discontinued or substituted, or temporally interrupted during the study; see Section **Fehler! Verweisquelle konnte nicht gefunden werden.** for prohibited therapies.

20. Received a live attenuated vaccine within 1 month before the planned first dose of study drug. The use of vaccines for COVID-19 may be allowed pending emerging data.

21. Active autoimmune disease within the past 2 years that requires systemic immunosuppressive medications (i.e, chronic corticosteroid, methotrexate, or tacrolimus).

22. Malignancy diagnosis other than the disease under study within 1 year prior to the first dose of the study drugs; .exceptions are squamous and basal cell carcinoma of the skin, carcinoma in situ of the cervix and any malignancy that is considered cured or has minimal risk of recurrence within 1 year of first dose of the study drugs in the opinion of both the investigator and sponsor's medical monitor.

    Note: Co-existence of 2 histologies of B cell NHL is not excluded.