1. SYNOPSIS

Name of Sponsor/Company: MEI Pharma, Inc	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not Applicable		
Name of Active Ingredient: Zandelisib		

Title of Study:

A Multicenter, Open-Label, Single-Arm, Phase 2 Study of Zandelisib (ME 401) in Subjects with Follicular Lymphoma or Marginal Zone Lymphoma After Failure of Two or More Prior Systemic Therapies – The TIDAL Study

Principal Investigator: PPD

PPD

Investigators and Study Centers:

This study was conducted at 124 centers worldwide.

Publications (reference):

None.

Studied period (years):	**Phase of development:**
Date first patient enrolled: 25 June 2019 Date last patient completed: 24 Mar 2023	Phase II

Primary Objective:

To evaluate the objective response rate (ORR) of zandelisib in relapsed or refractory follicular lymphoma (FL) or marginal zone lymphoma (MZL), based on the Modified Lugano Response Criteria, and determined by an Independent Response Review Committee (IRRC).

Secondary Objectives:

- To evaluate the efficacy of zandelisib as assessed by an IRRC:
  - Duration of response (DOR)
  - Complete response (CR) rate
  - Progression-free survival (PFS)
  - Recapture of response
  - Duration of recaptured response (DORR)
- To evaluate the efficacy of zandelisib as assessed by the Investigator:
  - Objective response rate (ORR)
  - Duration of response (DOR)
  - Complete response (CR) rate
  - Progression-free survival (PFS)
  - Time to treatment failure (TTF)
  - Recapture of response
  - Duration of recaptured response (DORR)
- To evaluate overall survival (OS)
- To evaluate the safety profile of zandelisib
  - Overall incidence of treatment-emergent adverse events (TEAEs)

- Incidence of adverse event(s) of special interest (AESIs)
- Time to occurrence of AESIs

- To evaluate the pharmacokinetics (PK) of zandelisib

Study Design:

This is a global, multicenter, open-label, single-arm, Phase 2 study of the PI3Kδ inhibitor zandelisib in subjects with relapsed/refractory FL or MZL after failure of ≥2 prior therapies for lymphoma, including chemotherapy and anti-CD20 monoclonal antibody. Zandelisib was administered orally at a dose of 60 mg given once a day. A cycle of treatment is 28 days in duration. Treatment with zandelisib was administered initially on two regimens; a continuous daily dosing schedule (CS) and an intermittent dosing schedule (IS). In the original protocol subjects were randomized 1:1 to the CS or IS arm. At Amendment 2, the CS arm was closed to enrollment, all ongoing subjects randomized to the CS arm were switched to intermittent dosing after completing the first 2 cycles of daily doing, and all new subjects were enrolled in the IS arm. Subjects randomized to the CS arm and who were subsequently switched to IS after cycle were analyzed in the CS intent-to-treat population.

The IS regimen includes:

- continuous daily dosing for the initial 2 cycles of treatment
- intermittent dosing (ID) that begins at Cycle 3, with zandelisib administered daily for the first 7 days of every 28-day cycle (7 days on treatment and 21 days off treatment)

The first day of treatment is designated as Day 1. Zandelisib was administered until progressive disease (PD), development of unacceptable toxicity (despite zandelisib modified dosing schedule), or subject withdrawal.

Review of maturing data from the ongoing Phase 1b study ME-401-002 evaluating CS and IS dosing schedules for zandelisib in subjects with relapsed/refractory FL and other B-cell malignancies showed improved risk-benefit profile of the IS over CS regimen, with improved tolerability without loss in efficacy, as assessed by ORR and DOR.

Therefore, the design of this study was amended (Amendment 2) and the CS treatment arm was closed to enrollment, and all new subjects were enrolled to receive therapy on the IS arm only. If subjects randomized to the CS arm had already completed the 2 initial cycles of therapy, they were switched to ID, and if they had not yet completed the first 2 cycles of therapy they were switched to ID after completion of the first two cycles of daily dosing. Subjects who had achieved an objective response and then progressed on ID dosing could be switched to daily dosing to recapture disease control.

Upon confirmation of meeting eligibility criteria, subjects were enrolled and were treated with zandelisib within a reasonable time frame (within 5 days).

The study was closed prematurely for business reasons. Investigators were informed on 06 December 2022 of the study premature closure, and that zandelisib could not be dispensed to ongoing subjects after 02 February 2023. Last subject last visit occurred on 24 March 2023.

Methodology:

Safety was assessed by laboratory safety tests including hematology (complete blood count), serum chemistry, and cytomegalovirus using quantitative polymerase chain reaction (PCR); and clinical assessments including physical examination, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead electrocardiogram (ECG). Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

For details of methodologies employed refer to the study protocol.

Number of Patients (planned and analyzed):

A total of 169 subjects were enrolled in the study, 138 with FL and 32 with MZL.

Per amendment 2, the study was planned to enroll 120 subjects with FL in the IS arm. Enrollment in the FL IS arm was closed on 30 August 2021 after meeting its enrollment goal with 121 subjects enrolled.

Per the original protocol, the study was planned to enroll 75 subjects with FL in each of the CS and IS arm. Enrollment in the CS arm was closed per Amendment 2 with a total of 16 subjects randomized in the FL CS arm.

Per Amendment 3, the MZL cohort was opened to enrollment with the plan to enroll 64 subjects in the MZL IS arm. Enrollment in the MZL arm was closed prematurely on 18 August 2022 due to poor enrollment, with a total of 32 subjects enrolled in the MZL IS arm.

Diagnosis and Main Criteria for Inclusion:

For inclusion into the trial, subjects were required to fulfill all of the following criteria:

1. Signed informed consent.
2. Age ≥18 years (or age of majority).
3. Histologically confirmed diagnosis as defined in the World Health Organization (WHO) classification (Swerdlow 2016) of:
   - FL limited to Grade 1, 2, or 3a; or
   - MZL, including nodal, extranodal, and splenic MZL (histopathological report confirming diagnosis must be available during screening procedures).
4. Subjects with relapsed or refractory FL or MZL who received ≥2 prior therapy regimens. A previous regimen is defined as one of the following: at least two months of single-agent therapy or at least two consecutive cycles of polychemotherapy, autologous transplant, or radioimmunotherapy. Prior therapy must have included an anti-CD20 monoclonal antibody and an alkylating agent(s). Relapsed or refractory disease was defined as:
   - Relapsed disease: disease progression after a response (CR or PR) lasting ≥6 months
   - Refractory disease: no response to therapy (no CR or partial response [PR]), or response lasting <6 months
5. At least one bi-dimensionally measurable nodal lesion >1.5 cm or extranodal lesions >1 cm in its longest diameter by computed tomography (CT) scan as defined by the Modified Lugano Classification.
   - Previously irradiated lesions could be selected as target lesions only in cases of unequivocal evidence of progression.
   - For subjects with splenic MZL only: diffuse spleen involvement with splenomegaly, which is defined as the splenic vertical length greater than 13 cm.
6. ECOG performance status of 0 to 1 (Oken 1982).
7. Adequate hematologic parameters at screening unless abnormal values are due to lymphoma per Investigator assessment:
   - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L ($\geq$1,000/mm^3)
   - Platelet count $\geq 75.0 \times 10^9$/L ($\geq$75,000/mm^3)
8. Adequate renal and hepatic function per local laboratory reference range at screening as follows:
   - Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic-pyruvate transaminase (SGPT) ≤3.0 × upper limit of normal (ULN)
   - Total bilirubin ≤2.0 × ULN or ≤3 × ULN for subjects with Gilbert's syndrome
   - Serum creatinine ≤1.5 × ULN or estimated glomerular filtration rate (eGFR) >50 mL/min using the Cockcroft-Gault equation (Appendix 2 of Protocol)
9. QT-interval corrected according to Fridericia's formula (QTcF) ≤450 milliseconds (msec); subjects with QTc >450 msec but <480 msec could be enrolled provided the QTc prolongation is due to a right bundle branch block, left bundle branch block, or pacemaker and is confirmed stable by a cardiologist.
10. Left ventricular ejection fraction (LVEF) ≥45% as measured by echocardiogram (ECHO) or multigated acquisition scan (MUGA). If LVEF <45% by ECHO, a repeat measurement could be conducted within the screening period.
11. Subjects must have completed any prior systemic anti-cancer treatment within ≥4 weeks of Cycle 1 Day 1 (or ≥5 times the half-life [t½], whichever is longer); ≥8 weeks for antibody agents; ≥2 weeks for radiation therapy; and ≥3 months for high dose therapy with stem cell transplantation or CAR T-cell therapy or radioimmunotherapy.

12. All AEs and laboratory toxicities related to prior therapy had to be resolve to Grade ≤1 prior to the start of the study therapy (unless otherwise specified in eligibility criteria).
13. For females of childbearing potential, a negative serum human chorionic gonadotropin (hCG) pregnancy test within 28 days of study Day 1 and negative hCG result on study Day 1.
14. Subjects had to agree to use appropriate contraception methods during the clinical study (Appendix 4 of Protocol).
15. Subject must have been willing and able to comply with all scheduled visits, treatment plans, laboratory tests, and other study procedures.

Criteria for Exclusion:

Any of the following was regarded as a criterion for exclusion from the trial.

1. Histologically confirmed FL Grade 3b, or transformed disease (assessed by the Investigator):
    - For subjects with clinical (e.g., marked B-symptoms), laboratory (e.g., high lactate dehydrogenase [LDH]), or radiographic (e.g., high standardized uptake value by positron emission tomography [PET]) signs of rapid disease progression, a fresh tumor biopsy prior to enrollment was required to rule out transformed disease.
2. Known lymphomatous involvement of the central nervous system.
3. Major surgical procedure within 4 weeks prior to study Day 1 (minor surgical procedures, [e.g., lymph node biopsy] performed within 1 day or with an overnight stay are allowed).
4. Prior therapy with PI3K inhibitors.
5. Any uncontrolled clinically significant illness including, but not limited to, active infections requiring systemic antimicrobial therapy, hypertension, angina, arrhythmias, pulmonary disease, or autoimmune dysfunction.
6. Subjects who had tested positive for hepatitis B surface antigen and/or hepatitis B core antibody plus had a positive hepatitis B polymerase chain reaction (PCR) assay; subjects who had previously tested positive with a negative PCR assay were permitted with appropriate anti-viral prophylaxis.
7. Positive hepatitis C virus antibody (HCV Ab); subjects with positive HCV Ab were eligible if they were negative for HCV by PCR.
8. Known history of, or active human immunodeficiency virus (HIV) infection.
9. Ongoing or history of drug-induced pneumonitis.
10. Previous or concurrent cancer that is distinct in the primary site or histology from indolent B-cell non-Hodgkin Lymphoma within 3 years before start of study treatment except for curatively treated cervical cancer in situ, non-melanoma skin cancer, superficial bladder tumors (Ta [non-invasive tumor], Tis [carcinoma in situ], and T1 [tumor invades lamina propria]), and asymptomatic localized prostate cancer with no requirement for systemic therapy (or requiring only hormonal therapy) and with normal prostate-specific antigen values within ≥12 months prior to enrollment.
11. History of clinically significant cardiovascular abnormalities such as congestive heart failure (New York Heart Association classification ≥II [NYHA 1994]), myocardial infarction within 6 months of study entry.
12. History of clinically significant gastrointestinal (GI) conditions, particularly:
    - Known GI condition that would interfere with swallowing or the oral absorption or tolerance of study drug
    - Pre-existing malabsorption syndrome or other clinical situation that would affect oral absorption
13. Females who were pregnant; females who planned to breastfeed during study treatment through 90 days after ending treatment.
14. Psychiatric illness/social situations that would interfere with study compliance.
15. Hypersensitivity or other clinically significant reaction to the study drug or its inactive ingredients.
16. Any other condition for which, in the opinion of the Investigator, participation would not be in the best interest of the subject.

Test Product, Dose and Mode of Administration, Batch Number:

Zandelisib batch numbers used are available on file.

Duration of Treatment:

Study drug administration, study visits, and protocol-mandated assessments were conducted in 28-day cycles. Subject participation in the study was expected to be approximately 3-4 years, including 28-days for screening, 18 months of dosing with study drug, and up to 3 years of follow-up for survival after discontinuation of study drug. However, the study was terminated for business reasons after 45 months with a total 169 subjects treated.

Study Treatments:

Zandelisib, 60 mg capsule, oral.

Reference Therapy, Dose and Mode of Administration, Batch Number: None

Criteria for Evaluation:

Safety evaluations were conducted at screening, and continuously during the treatment period, and at the safety follow-up visit. During the follow-up period, adverse events (AEs) and serious adverse events (SAEs) were reported for up to 30 days after the last dose of study drug. After 30 days post last dose, only SAEs deemed related to study drug were reported. For the schedule of assessments refer to the table of schedule of events in the study protocol.

Statistical Methods:

Safety analyses is presented and summarized in the safety population for the Primary Analysis for FL, and include overall IS group, IS FL, MZL, and CS group.

Safety IS FL population is used to analyze safety endpoints for the FL Primary Analysis.

SAFETY RESULTS:

Demographics of Subjects and Disposition: A summary of demographic characteristics by treatment Arm is shown in Table 00a. Among total 169 subjects treated, 121 where in the IS FL group, 32 were in IS MZL group, and 16 where in the CS. Of the 169 total subjects 106 (62.7%) where male and 63 (37.3%) were female. Among IS FL and IS MZL groups, the percentages of male and female were similar. Median age was 65.0 years (range: 31,87). Median age in the IS FL group was 64.0 years (range: 31,87), in the IS MZL group 72.0 years (range: 53,87), and in the CS group 63.0 years (range:39, 80).

Seventy-nine (46.7%) subjects where between the ages of 18 and 64, and 90 (53.3%) subjects where 65 years of age or older. In the IS FL arm 62 (51.2%) subjects were between 18 and 64 years old, and 59 (48.8%) were 65 years of age or older. In the IS MZL group 8 (25.0%) subjects were between 18 and 64 years old and 24 (75.0%) were 65 years of age or older. Among the 169 subjects, 129 (76.3%) were White and 24 (14.2%) were Asian. The percentages of White and Asian were similar in the IS FL group and the IS MZL group. The majority of the patients 144 (85.2%) were not Hispanic or Latino.

Safety: A summary of safety is shown in Table 1. In all, 163 (96.4%) subjects reported TEAEs; 118 (97.5%) in the IS FL group, 29 (90.6%) in the IS MZL group, and 16 (100%) in the CS group. Gr 3 TEAEs were reported in 107 (63.3%) subjects; 79 (65.3%) and IS FL group 18 (56.3%) in the IS MZL group, and 10 (62.5%) in the CS group.

Gr 4 TEAEs were reported in 36 (21.3%) subjects; 28 (23.1%) in the IS FL group, 6 (18.8%) subjects in the IS MZL group and 2 (12.5%) subjects in the CS group. Serious TEAEs were reported in 69 (40.8%) of subjects; 51 (42.1%) subjects in the IS FL group, 12 (37.5%) subjects in the IS MZL group, and 6 (37.5%) subjects in the CS group. Among 169 subjects, 32 (18.9%) subjects had AE that led to treatment discontinuation; 23 (19.0%) subjects in the IS FL group, 4 (12.5%) subjects in the IS MZL group, and 5 (31.3%) subjects in the CS group. TEAEs leading to treatment interruption was reported for 89 (52.7%) subjects, 62 (51.2%) subjects in the IS FL group, 19 (59.4%) subjects in the IS MZL group and 8 (50.0%) in the CS group. Gr ≥3 treatment-emergent AESIs were reported for 42 (24.9%) subjects; 29 (24.0%) subjects in the IS FL group, 6 (18.8%) subjects in the IS MZL group, and 7 (43.8%) subjects in the CS group. Gr 5 TEAEs were reported for 11 (6.5%) subjects, 10 (8.3%) subjects in the IS FL group and 1 (6.3%) subject in the CS group.

A summary of exposure is shown in Table 0. From a total of 169 subjects treated, 123 (72.8%) were on study for ≥12 months; 93 (76.9%) in the IS FL group, 17 (53.1%) in the IS MZL group, and 13 (81.3%) in the CS group.

The median duration of exposure was 19.3 (range 1.0 - 37.4) months in the IS FL group, 12.4 (range 2.7 - 19.6) months in the IS MZL group, and 33.5 (range 4.1 - 40.0) months in the CS group. All subjects have been discontinued from the study.

Among the reasons for discontinuation of treatment, 66 (39.1%) subjects discontinued due to progressive disease, 57 (33.7%) subjects due to other reasons (i.e., termination of the study by the Sponsor), and 34 (20.1%) subjects due to AEs.

Among reasons for ending the study, 76 (45.0%) subjects ended due to sponsor's decision, 35 (20.7%) subjects died, and 30 (17.8%) were noted as other reasons; 22 (13.0%) were withdrawn by subject from the study and 6 (3.6%) were lost to follow up.

A summary of TEAE by Dictionary-Derived Term is shown in Table 9b and by System Organ Class and Preferred Term is shown in Table 9a. In all 163 (96.4%) subjects reported TEAEs; 118 (97.5%) subjects in the IS FL group, 29 (90.6%) in the IS MZL group, and 16 (100%) subjects in the CS group. In the IS FL group the most frequently reported (≥15%of subjects in the group) TEAEs were: diarrhea reported in 47 (38.8%) subjects, nausea 28 (23.1%) subjects, fatigue 25 (20.7%) subjects pyrexia 23 (19.0%) subjects, neutropenia 22 (18.2%) subjects, and abdominal pain 21 (17.4%) subjects.

In the IS MZL group the most frequently reported (≥ 15% of group) TEAE was diarrhea in 11 (34.4%) subjects, COVID-19 in 8 (25.0%) subjects, thrombocytopenia 7 (21.9%), nausea, pyrexia,and anemia 5 (15.6%) subjects each, and cytomegalovirus infection was reported in 4 (12.5%) subjects.

In the CS group diarrhea was reported in 8 (50.0%) subjects and nausea in 5 (31.3%) subjects; cough and constipation were reported in 4 (25.0%) subjects each in the CS group.

Subject incidence of TEAEs by grade is shown Table 3.

Gr 3 TEAEs reported in a total of 91 (53.8%) subjects; 66 (54.5%) in the IS FL group, 17 (53.1%) in the IS MZL group and 8 (50.0%) subjects in the CS group. The most frequently reported Gr 3 TEAEs in the IS FL group were diarrhea and neutropenia reported in 7 (5.8%) subjects each, and colitis, anemia, neutrophil count decreased, and pneumonia, and coronavirus disease 2019 (COVID-19) pneumonia were reported for 4 (3.3%) subjects each. The most frequently reported Gr 3 TEAE reported in IS MZL group was anemia in 4 (12.5%) subjects, AST increased was reported for 2 (6.3%) subjects. In the CS group, the most frequent TEAEs reported were diarrhea and colitis in 2 (12.5%) subjects each.

Gr 4 TEAEs were reported for 26 (21.5%) subjects in the IS FL group, 6 (18.8%) subjects in the IS MZL group and 2 (12.5%) subjects in the CS group. The most frequently reported Gr 4 TEAEs in the IS FL group were neutropenia in 9 (7.4%) subjects and neutrophil count decreased in 7 (5.8%) subjects. In the IS MZL group the most frequently reported Gr 4 AEs were neutropenia, neutrophil count decreased, and thrombocytopenia in 2 (6.3%) subjects each. In the CS group Gr 4 AEs were reported in no more than 1 subject each. Subject incidence of related TEAEs by grade is shown in Table 5c.

Gr 5 TEAEs we reported in a total of 11 (6.5%) subjects; 10 (8.3%) in the IS FL group and 1 (6.3%) subject in the CS group. The cause of Gr 5 TEAE in the IS FL group was reported as COVID-19 in 3 (2.5%) subjects, COVID-19 pneumonia in 2 (1.7%) subjects, and cardiac arrest, Pneumocystis jirovecii pneumonia (PJP), pneumonia, respiratory failure and tumor lysis in 1 (0.8%) subject each. There were no Gr 5 AEs reported in IS MZL, In the CS group 1 (6.3%) subject died due to pneumococcal pneumonia.

Subject incidence of SAEs by grade is shown in Table 4. A total of 69 (40.8%) subjects reported SAEs; 51 (42.1%) subjects in the IS FL group, 12 (37.5%) subjects in the IS MZL group, and 6 (37.5%) subjects in the CS group. In the IS FL group Gr 3 SAEs were reported in 40 (33.1%) subjects, 10 (31.3%) subjects in the IS MZL group, and 4 (25.0%) subjects in the CS group. In the IS FL group the most frequently reported Gr 3 SAEs were pneumonia and COVID-19 pneumonia reported in 4 (3.3%) subjects each; colitis was reported for 3 (2.5%) subjects. In the IS MZL and CS groups Gr 3 SAEs were reported in no more than 1 subject each.

Gr 4 SAEs were reported for 11 (6.5%) subjects, 8 (6.6%) in the IS FL group, 2 (6.3%) in the IS MZL group, and 1 (6.3%) in the CS group. In the IS FL group pneumonia was reported for 2 (1.7%) subjects, other Gr 4 SAEs were reported in no more than 1 subject each. In the IS MZL group Gr 4 SAEs of cardiac failure and neutropenic sepsis were reported in 1 subject each. In the CS group Gr 4 SAEs of hepatitis and lung disorder were reported in 1 (6.3%) subject each.

A summary of AEs leading to treatment discontinuation is shown in Table 5a. A total of 32 (18.9%) subjects discontinued treatment due to AEs; 23 (19.0%) subjects in the IS FL group, 4 (12.5%) subjects in the IS MZL group, and 5 (31.3%) subjects in the CS group. In the IS FL group the most frequently reported AE that led to

discontinuation was diarrhea in 4 (3.3%) subjects, Colitis and COVID-19 pneumonia in 2 (1.7%) subjects each. Other AE that led to discontinuation in the IS FL group reported in 1 subject each were: pneumonitis, acute kidney injury, autoimmune enteropathy, COVID-19, cerebral ischemia, cerebrovascular accident, gastritis erosive, cytomegalovirus colitis, mucosal inflammation, pneumonia, rash, rash maculopapular, systemic inflammatory response syndrome, tumor lysis syndrome, and uveitis.

In the IS MZL group, treatment discontinuation due to a TEAE was reported in 1 subject each with diarrhea, pneumonitis, cardiac failure enterocolitis, nausea, neutropenic sepsis, and weight decreased. In the CS group, treatment discontinuation due to a TEAE was reported in 1 subject each with colitis, alkaline phosphate decreased, lung disorder, immune mediated enterocolitis, and pneumonia pneumococcal.

A summary of related AEs leading to treatment discontinuation is shown in Table 5b.

A summary of AESIs by maximum grade is shown in Table 2a and subject Incidence of Gr ≥3 treatment-emergent AESIs is shown in Table 2. In all 83 subjects with reported treatment-emergent AESIs during the study, 61 (50.4%) were in the IS FL group, 10 (31.3%) in the IS MZL group, and 12 (75.0%) in the CS group. In the IS FL group, 2 (1.7%) subjects and 1 (6.3%) subject in the CS group were reported with Gr 5 lung infection or pneumonia. There were no Gr 5 AESIs reported in IS MZL group. Grade 4 AESIs of lung infection pneumonia was reported in 2 (1.7%) subjects in the IS FL group. There were no Gr 4 AESIs reported in IS MZL group or the CS group.

Gr 3 AESIs were reported in 25 (20.7%) subjects in the IS FL group, 6 (18.8%) subjects in the IS MZL group, and 6 (37.5%) subjects in the CS group. In the IS FL group the most frequent Gr 3 AESIs were diarrhea/colitis reported for 11 (9.1%) subjects. Gr 3 lung infection or pneumonia was reported in 5 (4.1%) subjects. In the IS MZL group the most frequent Gr 3 AESI reported was diarrhea/colitis, AST increased, and lung infection/pneumonia reported for 2 (6.3%) subjects each. In the CS group 4 subjects (25.0%) subjects reported with Gr 3 diarrhea/colitis.

A summary of Gr ≥3 infections is shown Table 7.1. In all, 35 (20.7%) subjects reported infections; 25 (20.7%) subjects in the IS FL group, 7 (21.9%) subjects in the IS MZL group, and 3 (18.8%) subjects in the CS group. In the IS FL group the most frequently reported Gr ≥3 infections were pneumonia reported for 7 (5.8%) subjects, COVID-19 pneumonia 6 (5.0%) subjects, and COVID-19, 5 (4.1%) subjects. PJP, urinary tract infection, and lower respiratory tract infection reported for 2 (1.7%) subjects each. Other Gr ≥3 last infections were reported in no more than1 subject each. In the IS MZL group Gr ≥3 infections were reported in no more than 1 subject each and were mostly related to respiratory infections. In the CS group Gr ≥3 infections were reported in no more than 1 subject each.

A summary of Covid-19 cases and deaths in patients on treatment by 01JAN2020 is shown in Table 9c. In all 37 (22.0%) subjects were reported with COVID-19; 25 (20.8%) subjects in IS FL group, 11 (34.4%) subjects in IS MZL group, and 1 (6.3%) subject in the CS group. Seven (5.8%) subjects in the IS FL group died due to COVID-19, 5 cases were treatment-emergent.

Subject incidence rate of treatment-emergent ≥Gr 3 lab toxicities is shown in Table 10. Gr ≥3 absolute neutrophil count (ANC) decreased was reported for 37 (21.9%) subjects and lymphocyte count decreased was reported for 20 (11.8%) subjects. In the IS FL group, Gr ≥3 ANC decreased was reported for 30 (24.8%) subjects and lymphocyte count decreased for 15 (12.4%) subjects. In the IS MZL group Gr ≥3 ANC decreased was reported for 5 (15.6%) subjects and lymphocyte count decreased was reported for 4 (12.5%) subjects. In the CS group, Gr ≥3 ANC decreased was reported for 2 (12.5%) subjects.

SUMMARY – CONCLUSIONS:

This study showed that single-agent zandelisib has an acceptable toxicity profile when given with IS dosing. Certain class-specific toxicities such as diarrhea, colitis, lung infection/pneumonia, were observed both with CS schedule and IS; however, IS dosing appears to reduce the risk of Gr ≥3 AESIs. Overall, the AEs observed appear to be tolerable and did not lead to a high rate of discontinuation. COVID-19 infection and infections of all types were reported in approximately 20% of subjects. There were 11 treatment-emergent AE leading to death in the study, the majority were due to COVID-19, COVID-19 pneumonia or other pathogenic pneumonia, 1 due to cardiac arrest, 1 due to tumor lysis syndrome and 1 death due to respiratory failure. Because of the premature termination of the study, efficacy data analysis and follow up was not performed and therefore the risk/benefit profile of single-agent zandelisib in this population cannot be ascertained.

Date of the Report: 04 May 2023