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Primary Efficacy and Safety Analysis of a Global Phase II Study of Zandelisib Administered by Intermittent Dosing (ID) in Patients with Relapsed or Refractory (R/R) Follicular Lymphoma (FL): The TIDAL Study

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BACKGROUND

- Zandelisib is a potent and selective oral PI3Kδ inhibitor.[1]
- A Phase 1b study evaluated zandelisib at 60, 120 and 180 mg once daily (qd) continuously in patients with R/R FL and chronic lymphocytic leukemia. The MTD was not identified, and 60 mg was selected for further development based on efficacy, safety and PK/PD assessments (NCT02914938).[2]
- Subsequently an intermittent dosing (ID) schedule of 7 consecutive daily doses in a 28-day cycle to allow Treg repopulation during treatment breaks was studied to mitigate immune-mediated adverse events of special interest (AESI) reported with PI3Kδ inhibitors.[3]
- In an expanded cohort of the Phase 1b study, zandelisib 60 mg on ID achieved a high overall response rate (ORR) when given as a monotherapy (76%) or in combination with rituximab (89%) in R/R FL, with median duration of response not reached at a median follow-up of 13.2 months, and the rate on any Grade ≥3 AESI was <10%.[4]

OBJECTIVES

To evaluate efficacy and safety of zandelisib after ≥2 prior lines of therapy in patients with R/R follicular lymphoma

METHODS

- Open-label, phase 2 study (NCT03768505)
- **Eligibility:** ≥18 years, FL Grade I–IIIA, progressive disease after ≥2 prior therapies, which must have included an anti-CD20 antibody and an alkylating agent, no prior PI3K inhibitor, and informed consent
- **Design:** Initially the study was a randomized trial of daily dosing continuously (CS arm) vs. daily for 2 cycles then ID (IS arm). CS arm was closed after maturing data from the Phase 1b study demonstrated better tolerability and similar efficacy with ID compared to continuous dosing.[3] The CS arm (16 patients enrolled) is not reported here
- **Regimen:** In the IS arm, zandelisib was administered at 60 mg qd for 2 cycles, then on ID until disease progression or intolerance (**Figure 1**)
- *Pneumocystis jirovecii* pneumonia prophylaxis was not mandated

Figure 1. Dosing Schema in IS Arm



- **Safety Population:** 121 FL patients on ID
- **Primary Efficacy Population (PEP):** First consecutive 91 patients treated on ID (sample size pre-defined based on hypothesis testing)
- **Primary efficacy endpoint:** ORR in PEP by Lugano criteria, assessed by independent review committee (IRC) and analyzed 6-months after the last patient in the PEP was enrolled
- **Time to events analysis:** To be performed after longer follow-up
- Another arm is still enrolling patients with R/R marginal zone lymphoma (MZL) is not reported here

PATIENT CHARACTERISTICS

- Enrollment occurred between June 2019 and September 2021
- Patients were heavily pre-treated (median 3 prior), and 96% had received prior chemoimmunotherapy (**Table 1**)

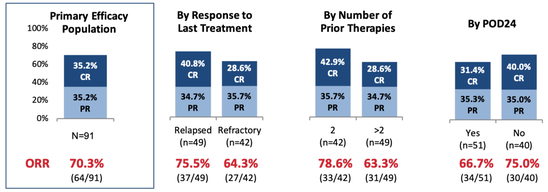
Table 1. Baseline Demographics and Patient Characteristics

	FL Patients (N=121)
Median age, years (range)	64.0 (31-87)
Age ≥65 years, n (%)	59 (48.8)
Male/Female, n (%) / n (%)	74 (61.2) / 47 (38.8%)
ECOG performance status 0 / ≥1, n (%)	78 (64.5) / 42 (34.7)
Stage at enrollment, n (%)	
I-II	21 (17.4)
III-IV	98 (81.0)
Missing	2 (1.7)
Tumor bulk (largest lymphoid mass) , n (%)	
≥5 cm / ≥7 cm	41 (33.9) / 19 (15.7)
Median no. prior systemic therapies, n (range)	3 (2-8)
Prior therapies, n (%)	
Chemoimmunotherapy	116 (95.9)
Combination of anti-CD20 antibody and lenalidomide	20 (16.5)
Myeloablative therapy and stem cell transplant	28 (23.1)
Refractory to last therapy, n (%)	50 (41.3)
POD24, n (%)	68 (56.2)
<6 months since last therapy, n (%)	47 (38.8)

EFFICACY

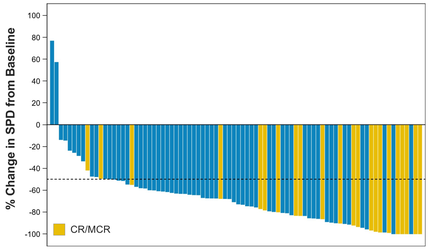
- ORR by IRC in 64 patients (70.3%, 95% CI, 59.8–79.5%) (**Table 2**)
- Complete response (CR) in 32 patients (35.2%, 95% CI, 25.4–45.9%)
- Responses occurred early: 87.5% (n=56) of responses first observed by end of Cycle 2 and 75.0% (n=24) of CRs first observed by end of Cycle 4

Figure 2. Overall Response Rates in PEP and by Subgroup



- Disease control (CR+PR+SD) in 77 patients (85%)
- Follow-up is immature to accurately estimate duration of response
- Investigator assessment of response: ORR = 71.4% (n=65), and CR rate = 24.2% (n=22)
- Best change in SPD from baseline in 84 patients with post baseline disease assessment per investigator (**Figure 4**)

Figure 4. Best Change in SPD from Baseline *



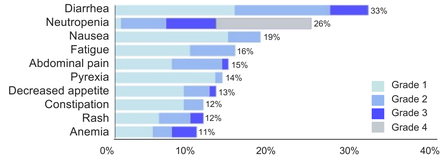
*7 patients not included because they did not have post-baseline imaging scans.

SAFETY

Treatment Emergent AEs (TEAEs)

- Median follow-up for all 121 patients = 9.4 months (0.8–24)
- TEAEs reported in ≥10% of patients in **Figure 2**

Figure 2. TEAEs Occurring in ≥10% of Patients, By Grade



Treatment Discontinuations due to Adverse Events (AEs)

- 16 patients (13.2%) discontinued therapy due to any AE
- 12 patients (9.9%) discontinued therapy due to treatment-related AE
  - Diarrhea/colitis (n=5), CMV colitis (n=1), rash (n=1), non-infectious pneumonitis/NIP (n=1), retinitis (n=1), SIRS (n=1), acute renal injury (n=1), and tumor lysis syndrome/TLS (n=1)
  - Except for TLS, all these events recovered, at a median of 15 days

COVID-19

- Treatment-emergent COVID-19 infections in 10 patients (8.3%)

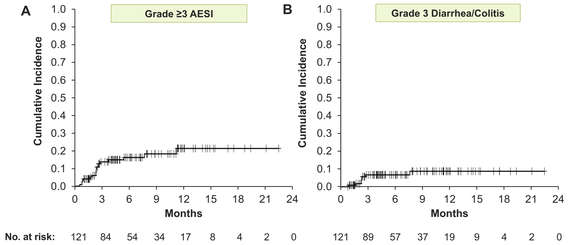
Grade 5 TEAEs

- COVID-19 (n=4), pneumonia (n=1), and TLS (n=1)

Grade 3 Adverse Events of Special Interest (AESI)

- Diarrhea (n=6, 5%), colitis (n=2, 1.7%), rash (n=4, 3.3%), stomatitis (n=3, 2.5%), AST high (n=1, 0.8%), ALT high (n=1, 0.8%), NIP (n=1, 0.8%).
- Grade 3 AESIs occurred primarily (15/18 [83%] for all events) in Cycles 1-3, during the daily dosing period.
  - Substantial decrease in the cumulative incidence of Grade 3 AESI on ID, shown for all AESI (**Figure 3A**) and diarrhea/colitis (**Figure 3B**).

Figure 3. Cumulative Incidence of Time to First Occurrence of (A) Grade ≥3 AESI or (B) Grade 3 Diarrhea/Colitis



Infections Grade 3 Excluding COVID-19

- 2 patients (1.7%) each with pneumonia and febrile neutropenia; 1 patient (0.8%) each with campylobacter gastroenteritis, lower respiratory tract infection, CMV colitis, PJP, urinary tract infection, and vestibular neuronitis.

CONCLUSIONS

- Zandelisib as a single-agent on ID achieved high ORR (70%) and CR rate (35%) in heavily pretreated FL patients
- Discontinuations due to treatment-related adverse events occurred in <10% of patients
- Safety profile includes low rate of Gr 3 AESI and discontinuations due to adverse events and is attributed to the ID administered from Cycle 3 onward
- Longer follow-up is needed to estimate the duration of response and long-term safety of zandelisib on ID
- These data support evaluation of zandelisib on ID as a single agent or in combination in various B-cell malignancies, both in relapsed disease and earlier lines of therapy
- Zandelisib plus rituximab vs chemoimmunotherapy is being studied in the phase 3 trial COASTAL in R/R FL and MZL (NCT04745832).

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