Abstract: P1092

Title: A PHASE II INVESTIGATOR INITIATED STUDY OF ACALABRUTINIB, LENALIDOMIDE AND RITUXIMAB (AR2) IN PATIENTS WITH PREVIOUSLY UNTREATED HIGH TUMOR BURDEN FOLLICULAR LYMPHOMA

Abstract Type: Poster Presentation

Session Title: Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

Background:

The efficacy of lenalidomide and rituximab (R^2) is comparable to chemoimmunotherapy in patients with previously untreated follicular lymphoma (FL) (*Morschhauser, NEJM 2018*). We previously reported pro-tumoral macrophage enrichment may be associated with resistance to R^2 (*Marques-Piubelli, Blood Adv 2022*). As pre-clinical studies show that BTK inhibition can mitigate the crosstalk between macrophages and FL B cells, we hypothesized that acalabrutinib, a specific BTK inhibitor, may synergize with R^2 without increasing toxicity. In agreement with this, the combination of acalabrutinib and R^2 (aR^2) was shown to be safe and effective in patients with relapsed FL (*Strati P et al, ASH 2022*).

Aims:

Here, we investigated the safety and efficacy of aR^2 in patients with previously untreated high tumor burden FL.

Methods:

This phase 2 single arm study (NCT04404088) was conducted between 09/2020 and 09/2021 (data cutoff 02/2023). Adult patients with previously untreated FL, grade 1 to 3A, stage 3-4, and with high tumor burden (per GELF criteria) were included. Dosing included acalabrutinib 100 mg PO twice a day in a 28-day cycle for 13 cycles, lenalidomide 20 mg PO daily on days 1-21, starting from cycle 2, and rituximab 375 mg/m^2 IV weekly during cycle 2, and on day 1 of subsequent cycles. Response was assessed per Lugano 2014 criteria. The primary endpoint was best complete response (CR) rate, and an exact binomial test was used for sample size calculation (N=24; H_0 50%, H_A 80%, power 80%, 2-sided alpha level 0.05).

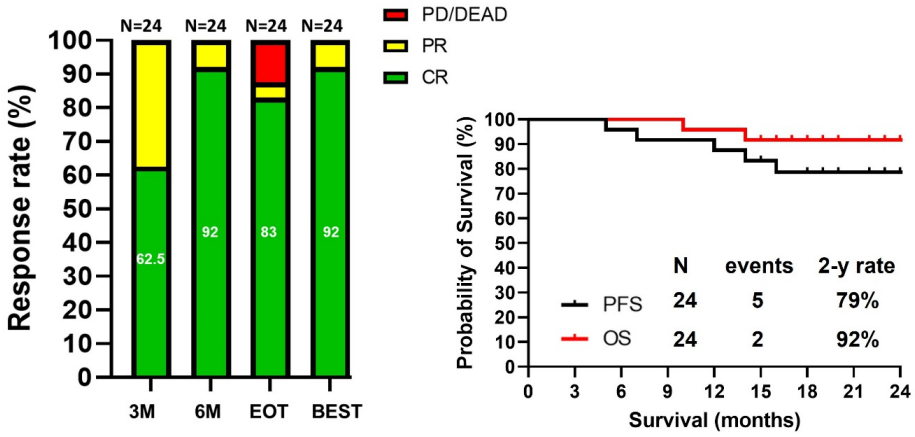
Results:

Twenty-four patients were enrolled. Median age was 62 years (range, 40-82), 18 (75%) were male; median largest lymph node size was 6.2 cm (range, 1.9-15), median SUV_{max} was 14 (range, 6-36), and 17 (61%) patients had an intermediate-high FLIPI. Median number of cycles was 13 (range, 6-13) and 15 (62.5%) patients experienced a cycle delay, due to COVID19 in 11 (46%) cases; 6 (25%) patients required dose reduction of lenalidomide, but none discontinued, and 2 (8%) required dose reduction of acalabrutinib and 1 discontinued. The most common (>5% of patients) grade 3-4 adverse events were neutropenia (58%), liver function test elevation (17%), infection (12.5%; 2 out of 3 related to COVID19), anemia (8%) and skin rash (8%); grade 1-2 infections were observed in 8 (33%) patients, related to COVID19 in 5 cases; 14 (58%) patients needed growth factor support, a median of 2 times (range, 1-8). One patient developed atrial fibrillation, and none had severe bleeding. Best ORR was 100% and best CR rate was 92%, as early as after 6 cycles (**Figure**). After a median follow-up of 22 months (95% CI 20-24 months), 4 patients had disease progression, including 2 who transformed at 5 and 7 months, while in partial response (both with pre-treatment bulky disease and SUVmax > 17), and 1 who transformed at end of treatment, after initial CR. The 2-year PFS rate was estimated at 79% (95% CI, 56%-91%). At data cutoff, 2 patients have died, 1 due to COVID19 (while in CR, at 14 months) and 1 due to transformed lymphoma (at 10 months), both 4 months after study discontinuation. The 2-year OS rate was estimated at 92% (95% CI, 71%-98%) (**Figure**).

Summary/Conclusion:

Our results indicate that aR^2 is a safe and effective frontline non-chemotherapy regimen for FL patients, resulting

in high CR rates. Considering the observed early achievement of CR, the study has been expanded to include 26 additional patients treated with only 6 cycles. Correlative analyses are planned to assess minimal residual disease status and effects on the immune microenvironment.



Keywords: Clinical trial, Follicular lymphoma, Immunotherapy