Abstract: LB3439

Title: ACALABRUTINIB PLUS BENDAMUSTINE AND RITUXIMAB IN UNTREATED MANTLE CELL LYMPHOMA: RESULTS FROM THE PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED ECHO TRIAL

Abstract Type: Oral Presentation

Session Title: Late-Breaking Oral Session

Background:

Aggressive first-line therapies for mantle cell lymphoma (MCL) can provide durable responses and prolonged progression-free survival (PFS), but are unsuitable for elderly or unfit patients (pts) due to poor tolerability. The addition of the Bruton tyrosine kinase inhibitor ibrutinib to chemoimmunotherapy (CIT; bendamustine + rituximab [BR]) for first-line treatment of MCL (SHINE) has been shown to prolong PFS, but with detrimental overall survival (OS) due to excess toxicity.

Aims:

To evaluate the combination of acalabrutinib (acala) with BR (ABR) in elderly pts with previously untreated MCL in the randomized, double-blind, placebo-controlled, phase 3 ECHO trial (NCT02972840).

Methods:

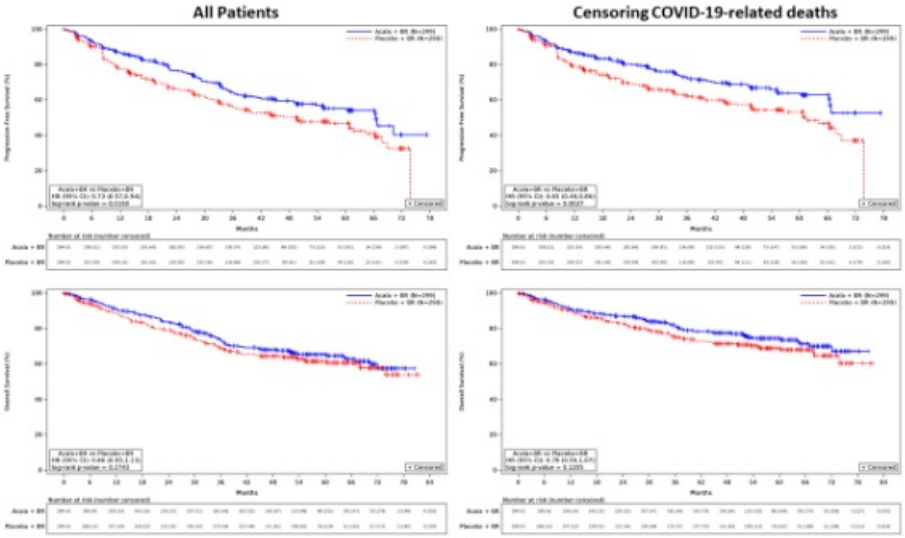
Pts aged ≥65 y with previously untreated MCL and ECOG PS ≤2 were randomly assigned 1:1 to receive ABR or placebo plus BR (PBR). Enrollment occurred between April 2017 and March 2023 from 195 sites globally. BR was administered for 6 cycles followed by rituximab maintenance for 2 y in pts achieving a partial or complete response (PR or CR). Acala (100 mg twice daily) or placebo was administered until disease progression or unacceptable toxicity. Crossover to acala was allowed at disease progression. The primary endpoint was PFS per independent review committee.

Results:

In total, 598 pts were included in this analysis, with 299 pts in each arm. Median age was 71 y; 76% had low/intermediate simplified MIPI and 13% had blastoid/pleiomorphic histology. Patient characteristics were well balanced between arms. With a median 45 months of follow-up, 31.8% and 25.8% of pts continued treatment in the ABR and PBR arms, respectively. Overall response/CR rates were 91.0%/66.6% and 88.0%/53.5% with ABR and PBR, respectively. Median PFS was 66.4 months with ABR and 49.6 months with PBR (hazard ratio [HR] 0.73; 95% CI 0.57, 0.94; *P*=0.0160). OS data showed a positive trend favoring the ABR arm (HR 0.86; 95% CI 0.65, 1.13; *P*=0.27) despite 51 pts crossing over to acala after experiencing progressive disease with PBR. COVID-19 deaths had a relevant impact on the study outcome (**Figure**). After censoring for COVID-19 deaths, median PFS improved in both arms: not reached with ABR vs 61.6 months with PBR (HR 0.65; 95% CI 0.49, 0.86; *P*=0.0027). A similar effect was seen in OS (HR 0.78; 95% CI 0.56, 1.07;*P*=0.12). With respect to safety, grade ≥3 adverse events (AEs)/grade ≥3 serious AEs were comparable and well balanced between both arms and were reported in 88.9%/64.3% and 88.2%/55.9% of pts for ABR and PBR, respectively. Among grade ≥3 AEs of clinical interest, atrial fibrillation was reported in 3.7% and 1.7%, hypertension in 5.4% and 8.4%, neutropenia in 35.4% and 37.0%, infections in 41.1% and 34.0%, and pneumonia in 8.8% and 6.4% of pts in the ABR and PBR arms, respectively. Any-grade COVID-19 events (other than pneumonia) were reported in 30.6% and 20.9% of pts in the ABR and PBR arms, with deaths reported in 2.7% and 2.0% of pts, respectively. COVID-19 pneumonia (any grade) was reported in 15.8% and 12.5% of pts in the ABR and PBR arms, with deaths reported in 5.1% and 3.4% of pts, respectively. Discontinuation of acala due to AEs was reported in 42.8% of pts, which was a difference of 11.8% vs the placebo arm (31.0%); COVID-19 was the primary cause.

Summary/Conclusion:

With only 45 months of median follow-up, the addition of acala to BR in the ECHO trial for elderly patients with untreated MCL demonstrated a statistically significant improvement in PFS with a positive trend in OS, which was more pronounced in patients not affected by COVID-19.



Keywords: Triple therapy, Mantle cell lymphoma, Clinical trial, Phase III