Phase II consortium trial shows positive results for ibrutinib-use in R/R FL

Sara Valente

Ibrutinib is an irreversible, small molecule inhibitor of Bruton's Tyrosine Kinase (BTK) with efficacy in B-cell malignancies including chronic lymphocytic leukemia (CLL) and small lymphocytic, lymphoplasmacytic, marginal zone (MZL), and mantle cell lymphoma (MCL). In a previous phase I study of ibrutinib in relapsed or refractory (R/R) B-cell malignancies, 6 out of 11 patients with follicular lymphoma (FL) achieved objective response.

In a phase II multicentre, open-label study, Nancy L. Bartlett *et al.* from the Division of Oncology and Siteman Cancer Center, Washington University School of Medicine, St. Louis MO, USA, investigated the response rates to ibrutinib in patients with R/R FL.

Key highlights:

- 40 patients (pts) with R/R FL were enrolled; median age = 64 years, pts had histologically-confirmed grade 1, 2 or 3A FL, recurring after one or more chemotherapy regimens
- Pts were treated with ibrutinib 560 mg/day until progression or intolerance

Efficacy:

- Overall response rate (ORR): 37.5% (95% CI, 22.7-54.2)
- Response rates by disease status:
  - Rituximab-naïve pts: 66.7% (95% CI, 9.4-99.2)
  - Rituximab-sensitive pts: 52.6% (95% CI, 28.9-75.6)

    - Rituximab-refractory pts: 16.7% (95% CI, 3.6-41.4)
- Overall complete response (CR) rate: 12.5%
- Overall partial response (PR): 25%
- Median progression free survival (PFS): 14 months (95% CI, 7.4-16.3), 2-year PFS: 20.4% (95% CI, 10.7-38.6)
- Median overall survival (OS) has not been reached, 2-year OS: 79% (95% CI, 67-93.2)

Safety:

- ≥ Grade 3 adverse events with 42.5% of the pts:
    - Neutropenia: 10%
    - Lymphopenia: 7.5%
    - Anemia: 7.5%
    - Infection: 7.5%
- One death occurred during treatment in a patient from a massive upper gastrointestinal haemorrhage due to cryptogenic cirrhosis

In summary, the authors concluded that ibrutinib is a well-tolerated treatment with modest activity in R/R FL but larger trial data is needed to confirm this. Given the favorable side effect profile in most patients, namely the lack of myelosuppression, it was concluded that ibrutinib may be beneficial in patients who will require multiple future lines of therapy. The authors added that somatic mutations such as *CARD11* may influence response to ibrutinib and should be evaluated in further trials.

Abstract

Most patients with follicular lymphoma experience multiple relapses necessitating subsequent lines of therapy. Ibrutinib, a Bruton tyrosine kinase inhibitor approved for the treatment of several B-cell malignancies, showed promising activity in follicular lymphoma in a Phase 1 study. We report the results of a Phase 2 trial evaluating ibrutinib in recurrent follicular lymphoma. Forty patients with recurrent follicular lymphoma were treated with ibrutinib, 560 mg/day until progression or intolerance. The primary endpoint was overall response rate. Exploratory analyses

included correlations of outcome with recurrent mutations identified in a cancer gene panel using next-generation sequencing in pretreatment biopsies from 31 patients and results of early interim PET/CT scans in 20 patients. Overall response rate was 37.5% with complete response rate of 12.5%, median progression free survival (PFS) 14 months and 2-year PFS 20.4%. Response rates were significantly higher among patients whose disease was sensitive to rituximab (52.6%) compared to those who were rituximab refractory (16.7%) (p=0.04). CARD11 mutations were present in 16% (5/31) of patients and predicted resistance to ibrutinib with only wild-type patients responding (p=0.002). SUVmax at cycle 1 day 8 correlated with response and PFS. Ibrutinib was well-tolerated with a toxicity profile similar to labeled indications. Ibrutinib is a well-tolerated treatment with modest activity in relapsed follicular lymphoma. Evaluation of BTK inhibitors in earlier lines of therapy may be warranted based on improved response rates in rituximab sensitive disease. Somatic mutations such as *CARD11* may impact response to ibrutinib and inform clinical decisions and should be evaluated in larger data sets.