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Changing treatment landscape of Marginal zone lymphoma

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Recent breakthrough therapy designation to copanlisib (a PI3K α/δ inhibitor) for marginal zone lymphoma (MZL) highlights the need to expedite the development of a drug candidate to treat this serious disease [1]. With an annual incidence of approximately 7,500 newly diagnosed patients in the USA, MZL is the third most common B-cell Non-Hodgkin Lymphoma (NHL) accounting for approximately 8% of all NHL cases [2]. Chemotherapy and/or immunotherapy available for the treatment of MZL are often successful, however, treatment options are limited for patients who fail initial chemo-immunotherapy. Therefore, new drugs are needed to fulfil this unmet medical need.

Until recently, MZL has not been a focus of therapeutic development. Approvals of targeted agents in other indolent lymphomas has led to research specifically for, or including, MZL. Ibrutinib (Covalent inhibitor of Bruton's tyrosine kinase (BTK)) is the first targeted therapy that has been approved on January 19, 2017, by US FDA for patients with MZL who require systemic therapy and have received at least one prior anti-CD20-based therapy [3]. This accelerated approval was based on an Objective Response Rate (ORR) of 46% (Complete Response (CR)- 3.2% and Partial Response (PR)- 42.9%) in phase 2, single-arm trial in 63 patients (Study PCYC-1121-CA). Currently, ibrutinib is being evaluated in combination with either BR or R-CHOP in a large phase III, randomised control study (SELENE trial, PCI32765FLR3001) in 400 patients with previously treated follicular lymphoma (FL) or MZL. This trial which is expected to complete in July 2020.

On May 28, 2019, the US FDA approved lenalidomide (an immunomodulator) in combination with rituximab (R^2) for the treatment of patients with previously treated FL or MZL [4]. This is the first chemo-free regimen approved by the FDA for treatment of indolent NHL. The approval of R^2 is based primarily on results from the randomized, double-blind, Phase 3 study (AUGMENT Study) in patients with previously treated FL (n = 295) and MZL (n = 63). In this study, R^2 demonstrated a statistically significant improvement in the PFS as compared to rituximab. The median PFS was 39.4 months for R^2 and 14.1 months for rituximab. This approval seems to have no major impact on the treatment of MZL as the guidelines from National Comprehensive Cancer Network (NCCN) already recommended off-label usage of lenalidomide for MZL and other indolent lymphomas.

Breakthrough therapy designation granted to umbralisib (a PI3K δ inhibitor) in January 2019 for the treatment of MZL patients who have received at least one prior anti-CD20 regimen was based on interim data from the ongoing Phase 2b clinical trial (UNITY-NHL) [5]. So far, umbralisib showed an encouraging response rate in this indication with 52% ORR. Further, durable responses were observed, and toxicity did not appear to worsen with prolonged exposure (median exposure 10.1 months).

The breakthrough therapy designation for copanlisib was granted based on data from MZL subgroup of the pivotal phase 2 study in indolent NHL (CHRONOS-1 study) [1]. This is the trial that lead to an accelerated approval of copanlisib for the treatment of adult patients with relapsed FL in United States. In this study, copanlisib showed preliminary efficacy in indolent NHL patients including 23 patients with relapsed or refractory MZL, who have received at least two prior therapies. At the primary analysis, the ORR was 69.6%. Further, an 18-month follow-up analysis of CHRONOS-1 showed an ORR of 78.3%.

Two other PI3K inhibitors idelalisib (a PI3K δ inhibitor) and duvelisib (a PI3K δ/γ inhibitor) have also been evaluated in large pivotal studies that were planned in patients with iNHL. However, both agents were not approved for the treatment of MZL despite promising response (idelalisib: ORR-47% in 15 patients [6]; duvelisib- ORR-39% in 18 patients in DYNAMO study [7]). Perhaps, the regulatory agency was expecting minimal number of patients as a part of efficacy evaluation, therefore this promising response in few patients was not really considered for an approval. Other PI3k inhibitor parsaclisib (INCB050465) (a PI3K δ inhibitor) also showed the promising efficacy in early clinical stage study with response rate of 78% in MZL. Currently, a phase 2 study is ongoing in 90 patients with relapsed/refractory MZL with or without prior exposure to a BTK Inhibitor (CITADEL-204) and expected to complete in March 2020.

In addition, Obinutuzumab+CHOP was evaluated in GALLIUM study in 195 previously untreated MZL patients. However, patients did not show a clinically relevant difference in PFS between arms (O+CHOP Vs R-CHOP). G-chemo was associated with a higher frequency of grade 3–5 AEs, SAEs and, fatal AEs.

Given the approvals of ibrutinib and R^2 and recent breakthrough designations to copanlisib and umbralisib, it is important to see how the treatment landscape of MZL will change in Asian countries once these targeted therapies approved for this indication.

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