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Clinical Oncology 2018: Development of PI3K inhibitor Copanlisib – New insights and outlook - Ningshu Liu - Bayer AG, Germany

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Statement of the Problem: Follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) are two of the most common non-hodgkin lymp homa (NHL) worldwide with a high unmet medical need for relapsed or refractory disease represents from the frontline treatment. Despite the role of PI3K in NHL and solid tumors has been clinically validated, clinical development of PI3K inhibitors has been challenged with the therapeutic window of both pan- and isoform selective PI3K inhibitors.

Methodology: Copanlisib is the first pan-PI3K inhibitor with intravenous intermittent dosing regimen developed in clinic. Copanlisib has been extensively studied in various preclinical tumor models in vitro and in vivo, as well as investigated in a series of clinical trials in both NHL and solid tumors.

Findings: Investigation of FL and DLBCL patient samples indicates differential and redundant expression of PI3K isoforms. compared to PI3K/AKT selective inhibition, copanlisib showed much stronger and broader anti-tumor activity in NHL by overcoming intrinsic resistance caused by multiple PI3K isoform expression and acquired resistance induced by rebound activation of PI3K/AKT and other oncogenic signaling molecules, such as NFB. These findings have been translated into the significant clinical benefits in FL patients with durable objective responses (59%), which led to an accelerated FDA approval for treatment of relapsed or refractory FL. In addition, copanlisib has also demonstrated significant activity in DLBCL patients. Furthermore, recent preclinical study indicates that pulsatile inhibition of PI3K by copanlisib can also enhance anti-tumor immunity by inhibiting immune suppressive Tregs and M2-TAM and stimulating CD8+ T cells and M1 macrophages, and therefore overcome the resistance to immune checkpoint blocks.

Conclusion & Significance: Pan-PI3K inhibitor copanlisib with intermittent dosing schedule has been successfully developed as an effective and safe therapy for FL. Currently, copanlisib is being investigated in combination with rituximab (CHRONOS-3) or rituximab-chemotherapy (CHRONOS-4) in iNHL, as well as in combination with targeted therapies, such as immune checkpoint inhibitors, in solid tumors.

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