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Editorial

New Agents for B-Cell Malignancies: Convergence of Targeting B-Cell Receptor Signaling and FDA Breakthrough Therapy Designations

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Editorial

The recent approval of several novel agents and new treatment options for chronic lymphocytic leukemia; CLL has been recognized by the American Society of Clinical Oncology; ASCO as the Advance of the Year in Clinical Cancer in 2015. Two of the four new approved agents target B- cell receptor; BCR signaling e.g., ibrutinib and idelalisib. What accounts for this remarkable progress in the management of CLL and the rapid pace of new emerging agents for other B-cell malignancies? One of the major driving forces in accelerating oncology drug development is the convergence of the successful translation of the molecular biology of BCR signaling and the implementation of the FDA Breakthrough Therapy designation; BTD program.

B-cell receptor signaling is biologically important for normal B-cell activation and proliferation as well as for initiation and progression of B-cell lymphoproliferative disorders. Briefly, the BCR consists of two parts: the ligand binding domain which is in essence a membrane bound antibody that recognizes antigen and the signal transduction moiety (a disulfide –linked heterodimer; CD79) which contains an immune receptor tyrosine-based activation motif; ITAM. Binding of antigen to the membrane –associated immunoglobulin triggers phosphorylation of ITAM tyrosine residues by the Tyrosine-protein kinase Lyn and Spleen tyrosine kinase; Syk that initiates a second messenger cascade through activation of Syk, Lyn and Bruton tyrosine kinase; BTK with subsequent propagation through phosphor inositol 3-kinase; PI3K, Mitogen-activated protein kinases; MAPK, and nuclear factor kappa-light- chain-enhancer of activated B cells; NF-KB pathways resulting in B-cell activation and proliferation [1].

To date, small molecule inhibitors of specific kinases such as Bruton tyrosine kinase; BTK and the delta isoform of phosphoinositol 3-kinase; PI3K namely ibrutinib and idelalisib respectively, have been the most successfully and rapidly translated into clinical practice and were among the first agents to be granted the FDA Breakthrough Therapy designation. It is noteworthy that while these two agents were initially approved for treatment-resistant CLL, ibrutinib has more recently been approved in the first- line setting in subjects 65 years or older with CLL and small lymphocytic lymphoma; SLL. Ibrutinib is also approved for treatment of refractory mantle cell lymphoma and Waldenstrom's macroglobinemia. In addition, idelalisib is also approved for relapsed follicular B-cell non-Hodgkin lymphoma and SLL.

The FDA Breakthrough Therapy designation; BTD established in 2012 has been helping to accelerate the process of approval for several new drugs including ibrutinib, idelalisib and the novel agent venclexta, recently approved for previously treated patients with CLL and a 17p deletion . According to the FDA, this designation is met if a drug is intended to treat a serious or life-threatening condition and if preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Thus clinical endpoints such as overall response rates, durable responses and progression free survival; PFS are being used in these drug approvals. A key consideration is that conferring this designation results in the FDA commitment to speed development and review similar to the Fast Track approval process but with additional benefits. This includes providing advice on how to efficiently gather the nonclinical and clinical data necessary for approval, helping with clinical trial design and coordinating the review of the development program. This intense guidance during the drug approval process distinguishes the BTD from other FDA designations [2].

In conclusion, it is postulated that the revolution in the understanding and exploitation of the molecular biology of BCR signaling coupled with innovative regulatory science initiatives such as the FDA BTD program bode well for future significant advances in the management of B-cell malignancies .There are a number of promising agents in development including immune checkpoints inhibitors which may be applicable to B-cell lymphoproliferative disorders. While it is still currently the standard of care in the first- line setting for physically fit patients with CLL to use chemo immunotherapy regimens e.g. fludarabine, cyclophosphamide, rituxan; FCR, it is anticipated that agents targeting BCR signaling pathways combined with novel agents targeting a different mechanism of action such as immune checkpoint inhibitors may come to fruition for younger patients in the near future.

References

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