Kinase inhibitors in clinical practice: An expanding world

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Deregulation of kinase function is associated with several diseases. Therefore, efforts have been focused on selective targeting of these aberrant kinases in different disease models. These efforts received a boost with the success of ABL kinase inhibitor, Imatinib (also known as Gleevec or STI571), the first kinase targeted therapy in chronic myeloid leukemia (CML). Though Imatinib was not curative in CML; the long term survival of CML patients is now similar to that of age matched population.[1] Imatinib was not as successful in other malignancies driven by its target kinases but it provided the impetus for expanding the repertoire of kinase targeted therapies in oncology. In a short span of 15 years, 28 small molecule kinase inhibitors have been approved by Food and Drug Administration (FDA) for cancer therapy making them possibly the fastest growing class of therapeutics. While on one hand the number of potential kinase targets and their inhibitors in different stages of clinical trials are expanding; on the other hand the kinase inhibitors are finding application in areas other than oncology. Given their importance in immune cell signaling, several of the kinase inhibitors developed for cancer are being applied to disorders involving immune cell hyperactivation (Table 1) and more recently for selective reactivation of immune cell function.

Majority of the kinase inhibitors in clinical trials act by suppressing cytokine dependent immune cell activation frequently observed in auto-immune and inflammatory disorders. Targeting of Janus Kinase 2 (JAK2) and JAK3 has been the

most successful in immunological diseases as they are utilized by multiple cytokines that have either common gp130 or γ chain (Figure 1, Table 1). Thus a single inhibitor is able to block signaling from multiple cytokines involved in inflammatory and autoimmune disorders. JAK3 inhibitor (CP-690550/ Tofacitinib/ Xeljanz) has been approved by FDA for treatment of rheumatoid arthritis and it has entered post marketing surveillance (Table 1). It is now being clinically evaluated in other autoimmune disorders that involve hyperactivated cytokine signaling and immune cell activation (Table 1). In addition to the clinical trials underway for treatment of auto-immune and inflammatory diseases, potential application of kinase inhibitors in other areas such as immune response to microbial or viral infections is also being explored in pre-clinical studies. Gefitinib, a FDA approved receptor tyrosine kinase inhibitor has shown pre-clinical promise in restricting Mycobacterium tuberculosis growth through increased lysosomal targeting and suppressing STAT3 activation.[2] Similarly using kinome profiling of human cytomegalovirus infected cells, researchers have identified potential kinase inhibitors that could find application as anti-virals in clinic in the near future.[3] Similar studies being carried out with other microbes and viruses to restrict their ability to survive and replicate by host directed kinase inhibitors will be extremely helpful in countering increasing drug resistance in infections.

In oncology practice, it has been recently shown that anti-tumor effects of Dasatinib, a tyrosine kinase inhibitor, were mediated in part through increase in frequency of peripheral and intra-tumoral $CD8^+$ T cells.[4] Though the mechanism of action is not clear, the $CD8^+$ T cells showed increase in programmed death 1 (PD-1)

expression with reduced cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) expression. These molecules act as checkpoints to limit immune response to self and are utilized by tumors to evade the immune surveillance. Therefore, checkpoint-blockade therapies reactivate patient's immune system through inhibition of CTLA-4 or (PD-1) activated pathways. Three checkpoint inhibitors have been approved - Ipilimumab (anti-CTLA-4), pembrolizumab (anti-PD-1), and nivolumab (anti-PD-1) as single agents or in combination for the treatment of advanced melanoma and refractory non-small cell lung cancer. However, only 30-40% patients respond to these immune checkpoint blockade therapies. Moreover it is not possible to accurately predict as to which patients are likely to respond. In general, patients with higher intra-tumoral T cell infiltration show a better response with checkpoint blockade therapies. In an analysis of genetic and transcriptional factors from responder and non-responder patients, immunosuppressive and monocyte chemotactic genes were found to be amongst the differentially expressed genes between the 2 groups.[5] This indicates that tumors actively recruit monocytes and macrophages to modulate the tumor microenvironment in a manner that suppresses anti-tumor immune responses and makes them refractory to anti-immune checkpoint therapies.

Idelalisib, the first FDA approved drug to target a lipid kinase, phosphoinositide 3-kinase δ isoform (PI3K δ) has been shown to act both on tumor cells and their microenvironment.[6] As the PI3K pathway regulates multiple aspects of cancer growth and metastasis through PI3K-AKT-mTOR axis, they are one of the most sought after targets in oncology. IPI-549, a PI3K-γ specific inhibitor is a new member to join the list

of PI3K inhibitors in clinical trials for melanoma. Interestingly, IPI-549 had no effect on growth or viability of melanoma cells but appeared to target the myeloid cells within the tumor microenvironment to enhance anti-tumor cytotoxic T cell responses.[7] Inhibition of the PI3K- γ kinase in the $CD11b^{+}F4/80^{+}CD206^{+}$ M2 type tumor associated myeloid suppressor cells by IPI-549 converted them to $CD11b^{+}F4/80^{+}MHCII^{+}$ inflammatory M1 type cells that are efficient at tumor antigen presentation and lead to upregulation of PD-1 and CTLA4 expression on $CD8^{+}$ T cells.[7] Combination of IP1-549 with anti-PD-1 or anti-CTLA4 therapies was shown to overcome the innate resistance in melanoma, breast and lung cancer models.[7] Complete remissions in 30% of breast cancer and 80% of melanoma bearing mice was observed. Interestingly, the tumor free mice also showed development of an immune memory and were resistant to tumor re-implantation.[7] Similar association between a pro-inflammatory immune profile and increased survival has observed in human papilloma $virus^{+}$ (HPV) head and neck squamous cell carcinoma (HNSCC) patients.[8] The tumor infiltrating myeloid cells mediate immunosuppression through PI3K- γ-AKT-mTOR mediated activation of NF-κB and CCAAT/enhancer binding protein β (C/EBPβ).[8] In this model of HPV^{+} HNSCC too, inhibition or loss of PI3K- γ was associated with enhanced antigen presentation, $CD8^{+}$ T cell anti-tumor response and demonstrated synergism with anti-PD1 therapy.[8] These results advocate for targeting of myeloid suppressor cells in the tumor microenvironment and bring hope for higher success with checkpoint blockade immune therapy.

Though the expanding universe of potential target kinases and their inhibitors in the clinic has brought hope to patients, a word of caution is required. Most of these inhibitors have been in clinical practice for less than a decade and their long term effects are poorly understood. Suppression of PI3K-δ has been reported to increase genomic instability due to increased expression of activation-induced cytidine deaminase (AID).[9] While PI3K-δ inhibitors (Idelalisib, duvelisib, ibrutinib) inhibit proliferation of naïve and leukemic B cells, they also induce increase in somatic mutations, translocations and development of AID dependent tumors.[9] It raises important questions regarding the suitability of these inhibitors for long term use in patients. However, given the limited treatment options that patients have, it is almost certain that kinase inhibitors will be the mainstay in oncology clinical practice and will continue to expand into other disease areas.

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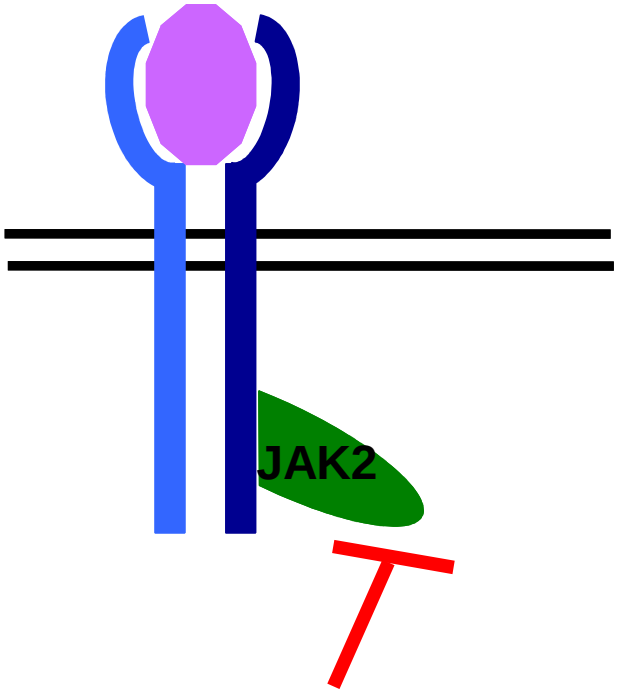
Drug Name	Target	Disease Indication	Clinical Trial Identifier	Stage of development
INCB018424 (Ruxolitinib)	JAK 1/2	Atopic Dermatitis	NCT03011892	Phase 2
INCB018424 (Ruxolitinib)	JAK 1/2	Graft vs Host Disease	NCT02997280 NCT02953678 NCT02913261 NCT03112603	Phase 2 Phase 3
CDZ173	PI3Kδ	Activated PI3Kdelta Syndrome (APDS); p110delta-activating Mutation Causing Senescent T Cells, Lymphadenopathy and Immunodeficiency (PASLI)	NCT02435173	Phase 2/3
PF-06650833	IRAK4	Rheumatoid Arthritis	NCT02996500	Phase 2
CP-690550 (Tofacitinib, Xeljanz)	JAK 3	Rheumatoid Arthritis	NCT02831855 NCT02092467 NCT02321930 NCT02157012 NCT02984020 NCT03011281	Phase 4, post marketing surveillance
CP-690550 (Tofacitinib, Xeljanz)	JAK 3	Juvenile Idiopathic Arthritis	NCT02592434 NCT01500551 NCT03000439	Phase 3

GSK2982772	RIP1K	Rheumatoid Arthritis	NCT02858492	Phase 2
Pacritinib	JAK 2, FLT3	Graft Vs Host Disease	NCT02891603	Phase 1/2
Imatinib mesylate (Gleevec)	ABL, BCR-ABL, PDGFRA, c-KIT	Graft Vs Host Disease	NCT01898377	Phase 2
CP-690550 (Tofacitinib, Xeljanz)	JAK 3	Systemic Lupus Erythematosus	NCT02535689 NCT03159936	Phase 1

The clinical trial registry at https://clinicaltrials.gov was queried for active (open) clinical trials with kinase inhibitors in immune diseases. JAK – Janus Kinase; PI3K - Phosphoinositide 3-Kinase; IRAK - Interleukin-1 Receptor Associated Kinase; RIP1K - Receptor-Interacting Protein-1 Kinase; FLT3 - Fms Related Tyrosine Kinase 3; ABL - Abelson murine leukemia viral oncogene homolog 1; BCR – B Cell Receptor; PDGFRA - Platelet-Derived Growth Factor Receptor Alpha

Figure 1: JAK2 and JAK3 inhibitors in clinical trials for immunological disorders. JAK2 and JAK3, non-receptor tyrosine kinases associate with different cytokine receptors have been targets in diseases such as rheumatoid arthritis, graft versus host disease, atopic dermatitis and systemic lupus erythematosus.

Type II cytokine receptor family
gp130 receptor family

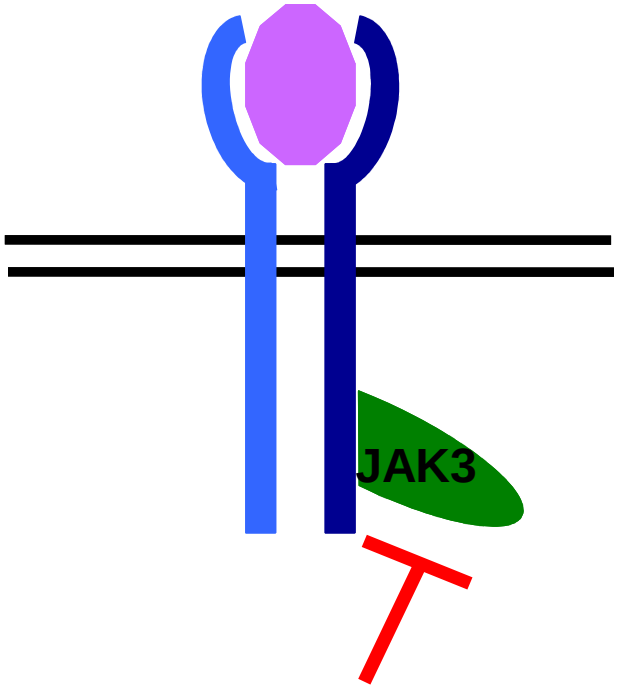


Pacritinib (SB1518)

Ruxolitinib (INCB018424)

Baricitinib (INCB028050)

γ_c Cytokine receptor family



Decernotinib (VX-509)

Tofacitinib (Xeljanz, CP-690550)