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. 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.\textsuperscript{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.\textsuperscript{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\textsuperscript{+} T cells.\textsuperscript{4} Though the mechanism of
action is not clear, the CD8\textsuperscript{+} 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. 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. 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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**References:**

2. Sogi MK, Lien KA, Johnson JR, Krogan NJ, Stanley SA. The tyrosine kinase inhibitor Gefitinib restricts *Mycobacterium tuberculosis* growth through increased lysosomal biogenesis and modulation of cytokine signaling. ACS Infect Dis 2017, 10.1021/acsinfecdis.7b00046


### Table 1: Kinase inhibitors in active clinical trials for Immune disorders

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Target</th>
<th>Disease Indication</th>
<th>Clinical Trial Identifier</th>
<th>Stage of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCB018424 (Ruxolitinib)</td>
<td>JAK 1/2</td>
<td>Atopic Dermatitis</td>
<td>NCT03011892</td>
<td>Phase 2</td>
</tr>
<tr>
<td>INCB018424 (Ruxolitinib)</td>
<td>JAK 1/2</td>
<td>Graft vs Host Disease</td>
<td>NCT02997280 NCT02953678 NCT02913261 NCT03112603</td>
<td>Phase 2 Phase 3</td>
</tr>
<tr>
<td>CDZ173</td>
<td>PI3Kδ</td>
<td>Activated PI3Kdelta Syndrome (APDS); p110delta-activating Mutation Causing Senescent T Cells, Lymphadenopathy and Immunodeficiency (PASLI)</td>
<td>NCT02435173</td>
<td>Phase 2/3</td>
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<tr>
<td>PF-06650833</td>
<td>IRAK4</td>
<td>Rheumatoid Arthritis</td>
<td>NCT02996500</td>
<td>Phase 2</td>
</tr>
<tr>
<td>CP-690550 (Tofacitinib, Xeljanz)</td>
<td>JAK 3</td>
<td>Rheumatoid Arthritis</td>
<td>NCT02831855 NCT02092467 NCT02321930 NCT02157012 NCT02984020 NCT03011281</td>
<td>Phase 4, post marketing surveillance</td>
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<tr>
<td>CP-690550 (Tofacitinib, Xeljanz)</td>
<td>JAK 3</td>
<td>Juvenile Idiopathic Arthritis</td>
<td>NCT02592434 NCT01500551 NCT03000439</td>
<td>Phase 3</td>
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<td></td>
<td>Kinase Inhibitors</td>
<td>Disease</td>
<td>Clinical Trial ID</td>
<td>Phase</td>
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<tr>
<td>-----------------</td>
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<td><strong>GSK2982772</strong></td>
<td>RIP1K</td>
<td>Rheumatoid Arthritis</td>
<td>NCT02858492</td>
<td>Phase 2</td>
</tr>
<tr>
<td><strong>Pacritinib</strong></td>
<td>JAK 2, FLT3</td>
<td>Graft Vs Host Disease</td>
<td>NCT02891603</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td><strong>Imatinib mesylate (Gleevec)</strong></td>
<td>ABL, BCR-ABL, PDGFRA, c-KIT</td>
<td>Graft Vs Host Disease</td>
<td>NCT01898377</td>
<td>Phase 2</td>
</tr>
<tr>
<td><strong>CP-690550</strong></td>
<td>JAK 3</td>
<td>Systemic Lupus Erythematosus</td>
<td>NCT02535689</td>
<td>Phase 1</td>
</tr>
<tr>
<td><strong>(Tofacitinib, Xeljanz)</strong></td>
<td></td>
<td></td>
<td>NCT03159936</td>
<td></td>
</tr>
</tbody>
</table>

The clinical trial registry at [https://clinicaltrials.gov](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

γc Cytokine receptor family

- JAK2
- Ruxolitinib (INCB018424)
- Baricitinib (INCB028050)

- JAK3
- Pacrittinib (SB1518)
- Tofacitinib (Xeljanz, CP-690550)