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Recent News in the Fast-Paced Field of JAK Inhibitors

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Therapeutic research and development has rarely progressed as rapidly to market as the field of Janus Kinase (JAK) inhibitors. Simultaneous publication [1-4] of the discovery of the JAK2 V617F mutation, prevalent in many patients suffering from impaired hematopoesis, set drug hunters on a race to discover and develop small molecule inhibitors of JAK2. These efforts rapidly produced two marketed drugs in two separate indications, oncology [5] and rheumatoid arthritis [6], fast followed by numerous clinical stage investigative agents. Myelofibrosis (MF), a disease where patients suffer from impaired hematopoesis, has emerged as the primary oncology indication with the November 2011 launch of ruxolitinib (Jakafi), a selective JAK1/2 kinase inhibitor (Novartis/Incyte). Ruxolitnib is indicated for all types of MF, including primary MF, post-polycythemia vera (post-PV) and post- essential thrombocytosis (post-ET) MF. However myelosuppression is dose limiting and presents particular challenges for the treatment of patients with low platelet levels, perhaps 25% of the total population. Although MF is quite rare it is a member of the myeloproliferative neoplasms (MPNs), which include other hematopoetic diseases, such as PV and ET, which encompass larger populations and can lead to serious hematological malignancies such as leukemia. Despite the myelosuppression concerns and debate around the disease-modifying potential of these drugs, Incyte have made progress in addressing both those aspects in MF treatment highlighted in a recent spate of press releases. Given the high unmet need in this population, a strategy to treat patients with low platelet counts with a low dose of ruxolitininb has been approved in a sNDA [7]. Dose increases are then required to achieve pharmacologically active drug levels. How many of these patients can truly benefit from long term ruxolitinib therapy? With such a fine line between clinically meaningful doses and myelosuppression this will be highly challenging. As often happens as more patients are dosed new toxicities emerging: in the case of ruxolitninb progressive multifocal leukoencephalopathy (PML) has been reported in myelofibrosis patients. However intriguing evidence of longer term disease modification is beginning to emerge. Recent data shows that long term (24-48 months) ruxolitinib therapy is improving fibrosis in patients' bone marrow, an important hallmark of disease progression [8]. Furthermore, new analysis of data from the phase 3 'COMFORT-II' study in Europe reveals that ruxolitinib treated patients have benefited from a 52% improvement in progression free survival (PFS) [9]. Significant tolerability concerns still exist for many patients driving the quest for alternative therapeutic options.

In the meantime new JAK inhibiting drugs in phase 3 trials for myelofibrosis from Sanofi and Cell Therapeutics Inc (CTI) are hot on the heels of ruxolitinib. Sanofi have initiated a phase 3 trial 'JAKARTA' to study their selective JAK2 inhibitor, SAR302503, in MF patients. This trial was recently announced to have met its primary endpoint [10] with further data examining the drug's effect on bone marrow fibrosis to be reported in the near future. Both CTI and Sanofi phase 3 trials monitor primary endpoints of number of patients achieving a ≥ 35% reduction in spleen volume measured by MRI or CT at 24 weeks of treatment. In parallel CTI are rapidly developing pacritinib, a selective JAK2/FLT3 inhibitor, which entered the phase 3 'PERSIST-1' trial in December 2012. Pacritinib has the advantage of minimal myelosuppression hence responses and tolerability is unrelated to baseline platelet levels. To confirm the efficacy and tolerability of pacritinib in this population a second phase 3 trial 'PERSIST-2', is planned in patients with low platelet levels. Pacritinib is also being developed for lymphoma with encouraging initial responses and safety reported in a phase 1 trial [11]. Of 31 evaluable patients 55% had a tumor mass reduction of 4-70%, inclusive of 3 partial responses, 2 mantle cell and 1 follicular lymphoma. Further expansion of JAK therapy, either as single agent or combination therapy, into both solid and hematological malignancies are eagerly awaited by physicians and patients alike and bode well for the future of JAK2 inhibitors for the treatment of a range of oncologic conditions.

JAK kinase inhibitors have applicability in a wide range of immunoinflammatory conditions. Upregulation of JAK-driven cytokine pathways in Rheumatoid Arthritis (RA) and psoriasis have led to the development of small molecule inhibitors specifically for these applications. Culminating in Pfizer's November 2012 launch of tofacitinib (Xeljanz) [6], a pan-JAK inhibitor, this strategy is set to potentially revolutionize the treatment of RA, an important indication with significant and growing unmet need. JAK therapy is very attractive to patients compared to regular injections of biological DMARDs (disease-modifying antirheumatic drugs) and as such has tremendous potential. Consequently tofacitinib has been publicized as a potential blockbuster drug for Pfizer. However JAK kinase therapy is usually accompanied by gastrointestinal side effects and myelosuppression, often grade 1/2 but can be more severe, which may not be tolerated by many patients where the disease is not directly life threatening. Further, similar to the concern in MF, there is not yet confidence that these drugs are truly disease modifying in RA. As if to remind Pfizer of the fragility of new RA therapies in today's economic climate, the European Committee for Medicinal Products for Human Use (CHMP) did not approve the marketing of tofacitinib for RA in a recent pronouncement [12], stating that consistent reduction in disease activity and structural damage to joints had not been sufficiently demonstrated. Having achieved approval in US, Japan and Russia, Pfizer are understandably upset and say they will immediately appeal the ruling. However on-going research will be closely studying the rates of serious infections, gastrointestinal perforations and malignancies that so concerned the CHMP. Safety concerns are indeed paramount in the treatment of RA and tofacitinib's pan-JAK inhibition profile may be leaving a door open for competitors. This will not be clear until a larger body of efficacy and safety data is available to compare tofacitinib to another more selective therapy in this population. On the bright side, this may not be so long in coming

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since Incyte are following their success with ruxolitinib in MF with another drug, baricitinib, in RA. Partnered with Lilly, a very recent report highlighted positive Phase 2b data sustained through 52 weeks in RA patients [13]. This encouraging data is tempered somewhat by the safety data, for example, at the lower 4mg dose there were still 10% serious adverse events. In depth analysis will be critical in weighing up the difficult balance between efficacy and safety in this serious condition, and assessing how tofacitinib and baricitinib compare in those respects.

Discovery of the V617F activating mutation in JAK2 8 years ago has catalyzed the creation of an exciting portfolio of drugs to treat several serious diseases. With two drugs on the market and two other differentiated products in phase 3, and others not far behind, the JAK field maturing positively. Being kinase inhibitors efficacy and safety are always expected to be finely balanced. Only the long path of extensive clinical trials and post-marketing data analysis can identify areas for improvement in the next generation of therapies. This fast-moving area is one to watch with new compounds and alternative indications sure to come forward in the near future for the benefit of patients and their families.

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