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Leukemia insights

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What's Next Beyond Ruxolitinib for Primary Myelofibrosis?

INTRODUCTION

JAK2 inhibitors represent an important milestone in the development of effective drug therapy for patients with myelofibrosis (MF). Spurred by the discovery of the JAK2V617F mutation in 2005, these drugs have been shown to dramatically reduce splenomegaly and improve systemic symptoms such as bone pain, itching, night sweats and fatigue, leading to an improved quality of life of these patients. Two prospective randomized clinical trials have demonstrated the superiority of the JAK2 inhibitor ruxolitinib (Jakafi; Incyte, Wilmington, DE) versus placebo and best available therapy for MF, respectively. Even though JAK2V617F is found in only about 60% of patients with MF, JAK2 inhibitors are effective both in patients with and without the mutation. This is for 2 reasons, a) JAK2 inhibitors are not specific for mutated JAK2, and b) the underlying pathobiologic abnormality in all patients with MF is deregulated JAK-STAT (Signal Transducer and Activator of Transcription) signaling, regardless of the JAK2V617F mutational status. Besides ruxolitinib, there are several other JAK2 inhibitors in clinical development as therapy for patients with MF and other myeloproliferative neoplasms.

However, even though JAK inhibitors are an effective therapeutic option for patients with MF, it is clear that there is still work to be done. Therapy with JAK2 inhibitors does not eradicate the malignant clone, as most studies do not demonstrate clinically relevant and consistent reductions in the allelic burden of JAK2V617F-mutated clones, and patients who stop therapy rapidly become symptomatic again. Also, there is no improvement in the bone marrow (BM) fibrosis, and the effect of JAK2 inhibitors on the incidence of leukemic transformation is still unclear. Some patients do not respond to JAK2 inhibitors, while others develop secondary resistance. It is thus clear that JAK2 inhibitors are not curative therapy for MF. They may control signs and symptoms of the disease very well and prolong life of patients with advanced features but new drugs are needed if we are to pursue the cure of this neoplasm. Herein, we review the clinical results and future development program of major JAK inhibitors, including ruxolitinib combinations, CYT387, SAR302503, lestaurtinib, pacritinib, XL-019, LY2784544, BMS-911543, and NS-018. We will detail inclusion and exclusion criteria of certain clinical trials ongoing at our institution.

In This Issue

Combination Studies of Ruxolitinib

Studies of ruxolitinib in combination with other drugs active in MF are underway. Currently, two studies (NCT01693601 and NCT01433445) are testing the combination of ruxolitinib and panobinostat (LBH589). In mouse models of JAK2V617F driven disease, the combination of ruxolitinib and panobinostat showed promising activity, with ruxolitinib decreasing STAT5 phosphorylation, and panobinostat decreasing total STAT5 level. Other studies are evaluating the combination of ruxolitinib with either lenalidomide (NCT01375140) or pomalidomide (NCT01644110), based on the single-agent activity of immunomodulatory drugs in MF.

Dual blockade of JAK2 and a pathway co-activated by aberrant JAK2 signaling may increase target specificity. Pre-clinical evaluation of JAK2 inhibitor and a panel of 15 kinase inhibitors identified dual JAK2 and PI3K blockade as showing synergism in cells and in mouse models. A second group reported pre-clinical synergism between ruxolitinib and BEZ235, a dual PI3K and mTOR inhibitor. Together, these studies suggest that simultaneous inhibition of JAK2 and PI3K may increase treatment efficacy while allowing potentially for the use of both drugs at lower doses. At present, at least one clinical trial (NCT01730248, ruxolitinib and BKM120) is currently evaluating this therapeutic combination in patients with MF. At our institution, 3 phase II trials combining ruxolitinib with other agents are ongoing. These studies are:

1- Ruxolitinib and lenalidomide, closed for new patient entry
2- Ruxolitinib and thrombomimetic agents (eltrombopag)
3- Ruxolitinib and hypomethylathing agents (azacitidine)

SAR302503 (Formerly TG101348)

SAR302503 (Sanofi S.A., Paris) is a JAK2-selective inhibitor (IC50 = 3 nM) with little activity against JAK1 (105 nM) or other JAK family members. It is equally selective for wildtype JAK2 and V617F-mutant JAK2. Interestingly, in a murine model of JAK2V617F MPN, SAR302503 was effective not only in ameliorating disease manifestations, but also caused a substantial fall in JAK2V617F allele burden (a phenomenon uncommonly observed in humans with current JAK inhibitors).

SAR302503 was evaluated in a phase I-II trial of 59 patients with MF. The MTD was 680 mg per day, and the dose-limiting toxicity was a reversible and asymptomatic rise in amylase level (a marker for pancreatitis) at 800 mg daily. In total, 40 patients were treated at 680 mg daily, of whom 70% required dose reductions, primarily due to cytopenias. The myelosuppression effects of SAR302503 were significant, with grade 3+ anemia and thrombocytopenia occurring in 54% and 28% of patients, respectively, at MTD. Common low-grade side-effects included nausea, diarrhea and vomiting. Responses were similar to that of ruxolitinib: IWG splenic responses occurred in 50% at MTD, and over half of patients had resolution of constitutional symptoms. Modest reductions in JAK2 allele burden were observed: of 20 patients with baseline JAK2V617F ≥ 20%, 9 (45%) had a ≥ 50% relative decrease in allele burden. In contrast to the experience with ruxolitinib, no consistent cytokine modulation effect was observed in measurements of IL-2, IL-6, IL-8 and TNF-a. The authors hypothesized that selective targeting of JAK2 may account for the lack of cytokine modulation, and an apparent effect in reducing JAKV617F burden.

A follow-up randomized phase 2 study evaluated three doses of SAR302503 (300 mg vs. 400 mg vs. 500 mg daily) in order to explore the effectiveness and toxicity of lower doses, specifically in regards to reducing myelotoxicity. An analysis of 31 enrolled patients reported splenic responses in 30%, 50% and 64% at 300 mg, 400 mg and 500 mg daily, respectively. The highest dose group also had the highest rate of grade 3+ anemia (55%, vs. 30 – 33% for lower doses). No information regarding JAK2 allele burden was reported in this abstract. Similar to ruxolitinib, testing of SAR302503 in PV and ET has begun (NCT01420783).

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Lestaurtinib (CEP701)

Lestaurtinib (Cephalon, Frazer, PA) is a FLT3 inhibitor that has been evaluated in FLT3 mutant acute myeloid leukemia. As part of a counter screen for additional activities, lestaurtinib was identified to also be a potent inhibitor of JAK2 (IC50 = 0.9 nM), with clear activity against JAK2V617F positive cell lines and primary samples from patients with MPN.

A phase 2 study was performed in 22 patients with primary or post-PV/ET MF, using a dose of 80 mg BID (based on AML studies). Splenic responses occurred in 4 (18%) patients, and a further 2 (9%) became transfusion independent. There was no change in JAK2V617F allele burden in responding patients. Compared to ruxolitinib and SAR302503, lestaurtinib appeared less myelosuppressive. However, gastrointestinal toxicity including diarrhea (73%) and nausea (50%) precluded further development of the drug as a JAK inhibitor, particularly in view of its modest clinical activity in comparison to other agents. In contrast to ruxolitinib, lestaurtinib did not show any modulation of inflammatory cytokines.

Pacritinib (SB1518)

Pacritinib (SB1518, S*BIO, Singapore) is an inhibitor of JAK2 (IC50 = 22 nM) and FLT3 (IC50 = 22 nM), and has activity in cell lines and JAK2V617F mouse models. In humans, target inhibition was demonstrated even at the starting dose of 100 mg daily. Phase I testing explored doses between 100 mg and 600 mg daily, with DLT (gastrointestinal symptoms) being encountered at 600 mg daily. Importantly, there was little evidence of myelotoxicity. Clinical activity was seen in phase I testing, with IWG spleen responses recorded in 44%, and PFS of 67% at 1 year.

Phase 2 testing evaluated 400 mg daily, in patients with MF; patients with thrombocytopenia were permitted to enroll (including patients with platelets <50 K/uL). There was little evidence of myelosuppression, with no new onset of anemia or change in transfusion requirements, and no dose reductions due to thrombocytopenia. Two patients met IWG criteria for improvement in hemoglobin, including one who became transfusion independent. Splenic shrinkage by IWG criteria (≥50% by physical examination) was recorded in 41%, and by MRI criteria (≥35% reduction in volume) in 24%. The reduction in JAK2V617F burden was modest: at 24 weeks, reduction of allele burden was observed in 3 of 11 patients.

CYT387

CYT387 (YM Biosciences, Mississauga, Canada) inhibits multiple members of the JAK family, including JAK1 (IC50 = 11 nM), JAK2 (18 nM) and TYK (17 nM). Preclinical activity was demonstrated in cell lines, primary patient samples, and animal models.

The phase I/II results of CYT387 were reported in 2010-2011 and updated in 2012. A total of 166 MF patients were recruited. The majority were treated on a 9 month core study at 150 mg daily (n=52), 300 mg daily (n=60) or 150 mg BID (n=42). The DLTs were headache and hyperlipasemia.

CLL Treatment Priorities

1. Untreated

- Fludarabine + Cytoxan + Rituximab (FCR) (2008-0431)
- Ofatumumab (2010-0241/2011-0520)
- Lenalidomide + Rituximab (2011-0509)
- PCI-32765 + Heavy Water (2012-0086)

2. Prior Therapy

- 8-Chloro-Adenosine (2004-0144)
- FBR (2009-0546)
- Sapacitabine + Cytoxan + Rituximab (2010-0516)
- AVL-292 (2011-0513)
- PCI-32765 (2011-0142)
- ABT-199 (2011-0164)
- Lenalidomide + Rituximab (2011-0509)
- GS-1101 + Rituximab (2012-0171)
- Ibrutinib vs. Ofatumumab (2012-0707)

3. Minimal Residual Disease

- Ofatumumab (2010-0266)
- Revlimid (2007-0213)

4. Other

- Hairy Cell: 2CDA + Rituximab (2004-0223)

AML/MDS Treatment Priorities

1. Newly Diagnosed

A. Acute Promyelocytic Leukemia: cytogenetic feature: t(15;17):

- ATRA + Arsenic +/- Gemtuzumab (2010-0981)

B. Cytogenetic feature: Inv16 or t(8:21): Fludarabine + Ara-C + Idarubicin (2007-0147)

C. Younger Patients:

- AC220 + 3 + 7 (2011-0041)
- PF-04449913 with 3 + 7 (2012-0062)

D. Older Patients:

- DAC +/- Clofarabine (2008-0092)
- Vorinostat + Aza (2007-0685)
- Plerixafor + Clofarabine (2009-0536)
- Sapacitabine vs. DAC vs. Both (2010-0727)
- Sorafenib + Azacitidine (2010-0511)
- Omacetaxine + LD Ara-C (2010-0736)
- Tosedostat + Ara-C or AZA (2011-0188)
- Cladribine + LD Ara-C/DAC (2011-0987)
- PF-04449913 with LD Ara-C or DAC (2012-0062)
- LD Ara-C + Lintuzumab (2012-0434)

2. Salvage Programs

- Tamibarotene (2007-0512) in APL
- IA + SAHA (2007-0835)
- Plerixafor + Sorafenib (2008-0501)
- Vidaza + Revlimid (2009-0467)
- Oral Panobinostat + Vidaza (2009-0619)
- PKC 412 + Aza (2010-0374)
- SGI-110 (2010-0615)
- Ara-C +/- Vosaroxin (2010-0692)
- CIA vs FAI (2010-0788)
- Plerixafor + G-CSF (2011-0036)
- CWP232291 (2011-0253)
- MK-8242 (2011-0547)
- Clofarabine + LD Ara-C (2011-0660)
- Crenolanib (2012-0569)

3. Low Risk MDS and CMML with <10% Blasts

- Lenalidomide (2009-0737)
- Deferasirox (2010-0041)
- Alemtuzumab (2010-0187)
- ON 01910 (2010-0209)
- Azacitidine + GM-CSF (2011-1123)
- ARRY-614 (2011-0827)
- DAC vs. Aza (2012-0507)

ALL Treatment Priorities

1. Newly Diagnosed or Primary Refractory

(one non-hyper-CVAD induction)

A. Age <40:Augmented BFM (2006-0375)

B. Age >60: Marquibo (2011-1071)

C. Hyper CVAD + Ofatumumab (2010-0708)

D. Ph+: Hyper CVAD + Dasatinib (SW0G0805)

- Hyper CVAD + Ponatinib +/- Rituximab (2011-0030)

E. T cell: Hyper CVAD + Nelarabine (2006-0328)

2. Salvage Programs

- MOAD (2008-0267)
- RAD001 + Hyper CVAD (2009-0100)
- Low Dose Hyper CVAD + CMC-544 (2010-0991)
- SAR3419 (2011-0287)
- BMS-906024 (2011-0382)
- Blinotumimab (2011-0784)
- Inotuzumab Ozogamicin (2012-0151)

CML Treatment Priorities

1. CML Chronic Phase

- Dasatinib (2005-0422)
- Nilotinib (2005-0048)
- Ponatinib (2012-0074)

2. TKI Failures, T315I Mutations or Advanced Phases

- LDE225 + Nilotinib (2011-0394)
- Dasatinib + DAC (2011-0333)

3. Minimal Residual Disease

- PEG-IFN (2011-0184)
- Azacitidine (2011-0254)

Myeloproliferative Disorders

1. Myelofibrosis

- Pomalidomide (2007-0199)
- LY2784544 (2010-0167)
- BMS-911543 (2010-0782)
- INC (2010-0964)
- GS-6624 (2011-0016)
- NS-018 (2011-0090)
- Ruxolitinib + Revlimid (2011-0269)
- Ruxolitinib (2011-0359)
- SAR 302503 (2011-0857)
- INCB039110 (2011-0035)

2. Polycythemia Vera

- INC 424 (2010-0808)

3. Essential Thrombocythemia

4. Systemic Mastocytosis

- Masatinib (2008-0275)

Phase I/II Agents for Hematologic Malignancies

- L-Grb2 Antisense (2003-0578)
- Nelarabine (2009-0717)
- ABT348 (2009-0788)
- TH-302 (2010-0268)
- KB004 (2010-0509)
- BKM120 (2010-0874)
- PM01183 (2010-0965)
- AMG900 (2011-0369)
- PRI-724 (2011-0527)
- AZD1208 (2011-0816)
- DFP-10917 (2012-0262)

XL-019

XL-019 (Exelixis, San Francisco, CA) is a potent and selective JAK2 inhibitor (IC50 = 2.3 nM), with >50-fold selectivity for JAK2 versus a panel of over 100 serine/threonine and tyrosine kinases, including other members of the JAK family.

A phase I study was conducted in 30 patients with MF. There was no evidence of myelotoxicity, but central and peripheral neuropathy was encountered, resulting in termination of the clinical development program. Spleen shrinkage of ≥50% by physical examination was recorded in 20%. Interestingly, there was no modulation of key inflammatory cytokines, including TNF-*a* and IL-6. JAK2V617F allele burden was not substantially altered by XL-019.

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LY2784544

LY2784544 (Eli Lilly, Indianapolis, IN) is unique among currently tested JAK2 inhibitors in that it is possibly specific for the JAK2V617F mutant cells. In in-vitro tests using Ba/F3 cells expressing V617F or wildtype JAK2, the IC50 for inhibition of JAK2-STAT5 signaling was 55 nM for V617F mutant, compared with 2260 nM for the wildtype JAK2.

In a phase I study of 19 patients (1 PV, 18 MF; all JAK2V617F mutated), the dose-limiting toxicity of tumor lysis syndrome was encountered at doses of 200 mg or more daily. Clinical spleen reduction of ≥50% was recorded in 39% of patients with MF. Interestingly, a reduction in marrow fibrosis was observed in 3 of 5 patients with follow-up biopsies. If these observations were confirmed in a larger population of patients, LY2784544 would be the first JAK inhibitor to influence marrow histology. Similar to the other JAK inhibitors, little change in JAK2V617F allele burden was observed. Clinical evaluation of LY2784544 is ongoing (NCT01134120, NCT01520220, NCT01594723).

BMS-911543

BMS-911543 (Bristol-Myers Squibb, New York, NY) is a potent JAK2 selective inhibitor (IC50 = 1.1 nM) with little effects on JAK1 (356 nM), JAK3 (73 nM) or TYK2 (66 nM). It has activity in JAK2V617F expressing cells, and inhibited proliferation of primary CD34+ cells from patients with MPN. Phase I/II evaluation of BMS-911543 in patients with MF is ongoing (NCT01236352).

This is a first in human, multiple-dose study of BMS-911543. The objective of the Phase 1 portion is to determine the maximum tolerated dose and the clinically active dose of BMS-911543. The objective of the Phase 2 portion is to assess the efficacy of the safety and tolerability of a twice daily or once-daily dosing schedule.

Selected Inclusion Criteria:

1) Diagnosis of primary or secondary MF (WHO 2008 Criteria) with intermediate-1, intermediate-2, or high risk disease as assessed using the Dynamic International Prognostic Scoring System (DIPSS) international prognostic scoring system.
2) ECOG performance status 0-2.
3) Platelet count ≥ 25,000.
4) Absolute neutrophil count ≥ 1,000.

Selected Exclusion Criteria:

1) Current active malignancy or a prior history of malignancy with the exception of: adequately treated basal cell carcinoma of the skin, curatively treated in situ carcinoma of the cervix, or other localized malignancy that has undergone potentially curative therapy with no evidence of disease recurrence

≥ 3 years and that is deemed by the investigator to be at low risk of recurrence.

2) Any condition requiring chronic use of moderate/high dose steroids (equivalent to ≥30 mg QD prednisolone). Inhalation or oral steroids for mild pulmonary disease are permitted.
3) Any gastrointestinal surgery that could impact upon the absorption of study drug as judged by the treating physician.
4) Evidence of uncontrolled active infection.
5) Have significant cardiac disease or who have a personal or family history of congenital long QT syndrome, or have a baseline ≥450 msec QTcF abnormality.
6) Uncontrolled or significant inflammatory bowel disease or uncontrolled peptic ulcer disease.
7) Symptomatic CHF, unstable cardiac arrhythmia requiring medication, presence of a significant atrial or ventricular tachyarrhythmia, use of a cardiac pacemaker, complete left bundle branch block, or LVEF < the institutional lower limit of normal by MUGA or ECHO within the past 3 months.
8) Splenic irradiation ≤3 months prior to treatment with study drug.

NS-018

NS-018 (Nippon Shinyaku, Kyoto, Japan) is a JAK2 selective inhibitor (IC50 = 0.72 nM) with >30 fold selectivity for JAK2 over other members of the JAK family. It also has activity against several SRC family kinases including FYN, SRC and YES (4 – 11 fold selectivity over JAK2). In preclinical models, NS-018 showed activity in primary patient samples and JAK2V617F mouse models. Phase I/II testing is ongoing (NCT01423851) at MDACC.

Approximately 24 evaluable patients will be enrolled during the phase 1 portion, with escalating doses until the maximum tolerated dose (MTD) is established. Once the MTD or clinically active dose is determined, a phase 2 portion will include up to an additional 20 patients.

Selected Inclusion Criteria:

1) ≥ 18 years old
2) ECOG performance status of ≤2
3) Estimated life expectancy of ≥12 weeks
4) Estimated creatinine clearance ≥60 ml/min1.73 m2
5) AST and ALT ≤ 3x ULN and total bili ≤1.5xULN
6) Adequate bone marrow reserve as demonstrated by: ANC >1000 µL and platelet count >50,000 µL without assistance of growth factors.
7) QTcB ≤ 480 msec.

Selected Exclusion Criteria:

1) Active, uncontrolled systemic infection
2) Prior treatment with JAK2 inhibitors that necessitated discontinuation specifically due to gastrointestinal toxicity.
3) Currently taking medication that is substantially metabolized by CYP1A2 or CYP3A4 or taking medication known to be strong inhibitors or inducers of CYP3A4.
4) Serious cardiac condition within the past 6 months such as uncontrolled arrhythmias, MI, angina, or heart disease as defined by the NYHA Class III or IV.
5) Radiation therapy for splenomegaly within 6 months prior to study entry.
6) Splenectomy (for phase 2 portion only)
7) Known HIV positive status
8) Known active hepatitis, a history of viral hepatitis B or hepatitis C, or known positive hepatitis B serology's without a history of immunization.

CONCLUSION

JAK inhibitors provide effective relief of signs and symptoms in patients with MPN, but have shown relatively weak effects in modifying the underlying disease clone. The success of the JAK inhibitors has catalyzed interest and activity in the development of targeted therapies in MPN, and lessons from the clinic have uncovered new aspects of MPN biology and provided new targets. It is likely that future targeting of the JAK-STAT pathway will extend beyond simple inhibition of the JAK kinase site.

For information about these studies, MF, or the Myeloproliferative Disorders program in the Leukemia Department, contact Srdan Verstovsek, Elias Jabbour or any Leukemia physician.

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