

# Beyond Ruxolitinib: Fedratinib and Other Emergent Treatment Options for Myelofibrosis

This article was published in the following Dove Press journal:  
*Cancer Management and Research*

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**Abstract:** Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by clonal proliferation of differentiated myeloid cells leading to bone marrow fibrosis, cytopenias and extramedullary hematopoiesis. In late 2019, the FDA approved the highly selective JAK2 inhibitor, fedratinib, for intermediate-2 or high-risk primary or secondary MF, making it the second drug approved for MF after ruxolitinib, a JAK1/2 inhibitor, which was approved for MF in 2011. The approval of fedratinib was based on phase II trials and the phase III JAKARTA trial, in which the drug significantly reduced splenomegaly and symptom burden compared to placebo, including some patients previously treated with ruxolitinib. The main side effects of fedratinib include anemia, gastrointestinal symptoms, and elevations in liver transaminases. Fedratinib also has a black box warning for encephalopathy, although this occurred only in about 1% of the treated patients, most of which were ultimately felt not to represent Wernicke's encephalopathy. Nonetheless, monitoring of thiamine levels and supplementation are recommended especially in high-risk patients. This concern has led to a prolonged clinical hold and delayed the drug approval by several years during which the drug exchanged manufacturers, highlighting the need for meticulous investigation and adjudication of serious, but rare, adverse events in drug development that could end up preventing drugs with favorable risk/benefit ratio from being approved. In this review, we discuss the pharmacokinetic data and efficacy, as well as the toxicity results of clinical trials of fedratinib. We also review ongoing trials of JAK inhibitors in MF and explore future treatment options for MF patients who are refractory to ruxolitinib.

**Keywords:** fedratinib, ruxolitinib, myelofibrosis, MF, JAK2

## Introduction

Myeloproliferative neoplasms (MPNs) are clonal, BCR-ABL1 negative hematopoietic diseases that are characterized by abnormal proliferation of terminally differentiated myeloid cells and comprise essential thrombocytosis (ET), polycythemia vera (PV), and primary myelofibrosis (PMF).<sup>1-3</sup> These entities occur on a wide spectrum of clinical presentations ranging from asymptomatic elevations of hemoglobin/hematocrit and platelet count to progressive bone marrow failure and a variable risk of transformation to acute myeloid leukemia (AML).<sup>2</sup> While the life-expectancy in patients with ET can be normal in (very) low-risk disease, many ET and PV patients have an inferior survival compared to age-matched and sex-matched controls mainly due to thromboembolic events.<sup>4,5</sup> Outcomes in patients with myelofibrosis are significantly poorer with progressive bone marrow failure and progression to AML as drivers for morbidity and mortality.<sup>6-8</sup> In a large cohort study of 1054 patients with myelofibrosis, the median OS was 69 months but varied

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substantially based on patient (age, constitutional symptoms) and disease factors (hemoglobin, circulating blast, and leukocyte levels).<sup>9</sup>

Clonal expansion of hematopoietic stem cells driven by somatic mutations in Janus kinase 2 (*JAK2*), calreticulin (*CALR*), and myeloproliferative leukemia virus oncogene (*MPL*) have been classically associated with MPNs.<sup>3</sup> However, patients with a triple-negative status can be seen, which has been associated with an adverse prognosis in patients with PMF.<sup>8,10</sup> Mutational status in these genes has also been shown to be a prognostic marker for AML progression and overall prognosis.<sup>8,11</sup> With advances in diagnostic techniques, additional high-risk mutations with prognostic significance such as *ASXL1*, *SRSF2*, *EZH2*, and *IDH1/2* have been identified especially in PMF and might have a role in risk stratification and treatment selection in MPN patients.<sup>12–15</sup>

The JAK/signal transducer and activation of transcription (STAT) pathway is a key regulator of cytokine receptor signaling and plays a critical role in hematopoiesis and immune responses.<sup>16,17</sup> The *JAK2* V617F variant, which is located on exon 14 and induces constitutive activation of STAT, is identified in 95% of patients with PV (and post-PV MF) and 50–60% of patients with primary MF and ET (and post-ET MF) making it the most prevalent mutation in MPNs.<sup>18,19</sup> This gain-of-function mutation leads to the constitutive activation of the tyrosine kinase domain of *JAK2* which underlies the hypersensitivity of erythroid precursor cells to hematopoiesis-stimulating cytokines and erythropoietin-independent proliferation.<sup>16</sup> In PV patients, the presence of a *JAK2* V617F mutation has been linked to a higher rate of thromboembolic and hemorrhagic complications as well as progression to secondary myelofibrosis and AML.<sup>19</sup> Of note, small clonal populations harboring *JAK2* V617F mutations are frequently encountered in healthy individuals, but variant allele frequencies of 50% or greater are typical for MPNs.<sup>3,11,20</sup> In up to 10% of PV patients, *JAK2* mutations affecting exon 12 are encountered which presents with a different phenotype (higher hemoglobin and lower platelet levels) but does not appear to have an adverse prognosis with regard to thromboembolic complications or progression to myelofibrosis and AML.<sup>21,22</sup>

Given its high prevalence and pathogenetic significance, aberrant *JAK2* signaling has been a promising target for drug development. Ruxolitinib, an oral *JAK1/2* inhibitor, was the first agent approved for the treatment of MF after it was shown to decrease spleen size and disease-related

symptoms compared to placebo in the double-blind COMFORT-I trial of 309 patients with intermediate-2 or high-risk myelofibrosis.<sup>23</sup> Significant improvements in symptom burden and splenomegaly for treatment with ruxolitinib compared to physician choice have also been reported (COMFORT-II).<sup>24</sup> Five-year follow-up data of these trials have not only shown durable responses to ruxolitinib but even a significant survival benefit with about 30% relative risk reduction for death compared to best available treatment after 5 years of follow-up (HR, 0.69; 95% CI, 0.50–0.96;  $P = 0.025$ ).<sup>25,26</sup> However, thrombocytopenia and anemia can be dose- or even treatment-limiting adverse events and patients who discontinue ruxolitinib have dismal outcomes, making this situation an area of significant unmet need.<sup>23,24</sup>

Fedratinib is a selective oral *JAK2*-kinase inhibitor that was recently FDA approved for adults with intermediate-2 or high-risk primary or secondary MF based on favorable results from placebo-controlled, randomized phase II and III clinical trials showing significant symptom improvement and reduction in spleen size.<sup>27–30</sup> This makes fedratinib the second drug to be approved in this disease state with additional clinical efficacy in patients who were ruxolitinib-resistant or intolerant.<sup>27</sup> In this article, we review the pharmacokinetics, safety, and efficacy of fedratinib in MF and discuss treatment options for ruxolitinib-refractory patients. Other *JAK1/2* inhibitors such as pacritinib and momelotinib are also in advanced clinical development and could add to the treatment armamentarium for MF should they be approved as well.<sup>31,32</sup> Table 1 summarizes major clinical trials of *JAK1/2* inhibitors in MF.

## Pharmacokinetics and Pharmacodynamics

Fedratinib competes with wild type *JAK2* as well as the mutated form *JAK2* V617F for ATP binding, which results in inhibition of *JAK2* activation and inhibition of the *JAK*-*STAT* signaling pathway. This pathway becomes overactive in patients with MF due to *JAK2*, *CALR* or *MPL* mutations. Fedratinib has also been noted to inhibit FMS-like tyrosine kinase 3 (*FLT3*) and is reducing B- and T-lymphocyte-mediated cytokine production.<sup>27–30,33</sup>

Pharmacokinetics (PK) of fedratinib have been characterized in both healthy volunteers and patients with MF.<sup>28,30,34,35</sup> It has been shown to have rapid absorption after oral administration with peak plasma concentrations reached within 0.5–4 hrs.<sup>28,30</sup> Fedratinib's PK can be

Table 1 Comparison of Selected Clinical Trials on JAK Inhibitors for Treatment of Myelofibrosis

Drug [TRIAL]	FED [JAKARTA I] <sup>29</sup>	FED [JAKARTA 2] <sup>27</sup>	RUX [COMFORT I] <sup>23</sup>	RUX [COMFORT 2] <sup>24</sup>	PAC [PERSIST I] <sup>54</sup>	PAC [PERSIST 2] <sup>53</sup>	MOM [SIMPLIFY I] <sup>47</sup>	MOM [SIMPLIFY 2] <sup>46</sup>
<b>NCT-Identifier</b>	NCT01437787	NCT01523171	NCT00952289	NCT00934544	NCT01773187	NCT02055781	NCT01969838	NCT02101268
<b>Patient Population</b>	FED (n=193) vs placebo (n=96); JAK inhibitor naive	Single arm FED (n=97); RUX resistant/intolerant	RUX (n=155) vs placebo (n=154)	RUX (n=146) vs BAT (n=73)	PAC (n=220) vs BAT (n=107)	PAC (n=149) vs BAT including RUX (n=72)	MOM (n=215) vs RUX (n=217)	MOM (n=104) vs BAT (n=52)
<b>Outcomes</b>	1.) FED 400 mg = 36%; FED 500 mg = 40%; Placebo = 1%; p<0.001 2.) FED 400 mg = 36%; FED 500 mg = 34%; Placebo = 7%; p<0.001 3.) Not reported	1.) RUX resistant = 53%; RUX intolerant = 63% 2.) RUX resistant = 21%; RUX intolerant = 32% 3.) not reported	1.) RUX = 41.9; Placebo = 0.7; p<0.001 2.) RUX = 45.9; Placebo = 5.3; p<0.001 3.) HR for death: 0.50; 95% CI: 0.25-0.98; P=0.04 for RUX vs placebo	1.) RUX = 32; BAT = 0; p<0.001 2.) not reported 3.) HR for death: 0.70; 95% CI: 0.20-2.49 for RUX vs BAT	1.) PAC: 19%; BAT: 5%; p=0.0003 2.) 25% patients in group vs 7% patients in BAT group, p<0.0001 3.) HR for death: 1.36 (95% CI: 0.89-2.09; p=0.16) PAC vs BAT	1.) PAC: 18%; BAT: 3%; p=0.001 2.) 25% patients in PAC group vs 14% patients in BAT, p=0.08 3.) HR vs BAT for PAC once daily and twice daily: 1.18; 95% CI: 0.57-2.44 and 0.68; 95% CI: 0.30-1.53	1.) MOM: 27%; RUX: 29%; p=0.011 for non-inferiority 2.) MOM: 28%; RUX 42%; p=0.98 for non-inferiority 3.) Not reported	1.) MOM: 7%; BAT: 6%; p=0.9 2.) MOM: 26%; BAT: 6% 3.) not reported
<b>Adverse Events Grade ≥3</b>	FED 400mg: 43% anemia, 21% lymphopenia, 17% thrombocytopenia FED 500mg: 60% anemia, 27% lymphopenia, 27% thrombocytopenia Placebo: 25% anemia, 21% lymphopenia, 9% thrombocytopenia 4 cases of Wernicke encephalopathy	38% anemia, 22% thrombocytopenia, 3% lymphopenia	45% anemia, 13% thrombocytopenia, 5% fatigue in RUX group vs 19% anemia, 12% abdominal pain, 7% fatigue in placebo group	5% anemia, 3% abdominal pain, 2% pyrexia in RUX group vs 5% pneumonia, 4% anemia, 4% dyspnea in BAT group	17% anemia, 12% thrombocytopenia, 5% diarrhea in PAC group vs 15% anemia, 11% thrombocytopenia, 3% dyspnea, 3% hypotension in BAT group	Thrombocytopenia: 31% (once daily PAC) vs 32% (twice daily PAC) vs BAT 18% Anemia: 27% (once daily PAC), 22% (twice daily PAC), 14% (BAT)	MOM: 7% thrombocytopenia, 6% anemia, diarrhea, hypertension, neutropenia (2.8% each) RUX: 23% anemia, neutropenia and thrombocytopenia (4.6% each), hypertension (4.2%)	MOM: 14% anemia, 7% thrombocytopenia BAT: 14% anemia, 6% thrombocytopenia

**Abbreviations:** BAT, best available therapy; CI, confidence interval; FED, fedratinib; HR, hazard ratio; MOM, momelotinib; PAC, pacritinib; RUX, ruxolitinib; SVR, spleen volume reduction; TSS, total symptom score.

described by a two-compartment model with first-order absorption incorporating a lag time and first-order elimination.<sup>36</sup> Serum levels of fedratinib increased linearly for doses of 200 mg and above. Plasma fedratinib levels reached steady state within 15 days of once-daily dosing.<sup>28</sup> Mean terminal half-life of fedratinib was 62–78 hrs at a single dose of 300–680 mg in healthy patients. Following a single 300 mg fedratinib dose, the area under the curve (AUC) increased by 1.5-fold in subjects with moderate renal function impairment (creatinine clearance [CrCl] 30 to 59 mL/min) and 1.9-fold in subjects with severe (CrCl 15 to 29 mL/min) impairment, compared to that in subjects with normal renal function (CrCl  $\geq$ 90 mL/min). Therefore, dose adjustments based on renal function are recommended in patients with a CrCl  $<$ 30 mL/min. Food intake had minimal impact on the PKs of fedratinib including terminal half-life and AUC. In addition, the tolerability (ie, gastrointestinal toxicities) of this drug was improved when fedratinib was taken following a high-fat breakfast.<sup>35</sup> No clinically meaningful effect on fedratinib PK was observed with regard to body weight, age, race, sex and mild/moderate hepatic impairment.<sup>36</sup>

Although various differences have been noted among patients with MPNs in various studies, phosphorylation of STAT3 and STAT5 has been linked to the presence but not to the allele burden in JAK2 V617F-positive patients and to correlate with disease severity.<sup>37–39</sup> In a phase 2 trial, levels of phosphorylated STAT3 (pSTAT3) were correlated with fedratinib doses and pSTAT3 levels were reduced relative to baseline independent of the fedratinib dose.<sup>28</sup> The greatest reductions on day 1 occurred 2 hrs post-dose, corresponding to the  $t_{max}$  of fedratinib. Inhibition of pSTAT3 then decreased at 6 and 24 hrs, concurrently with reduced fedratinib exposure. This supports that fedratinib acts via suppression of STAT3 signaling and patients with greater levels of pSTAT3 inhibition were more likely to achieve a spleen response.<sup>28</sup>

In the phase I trial, evaluating fedratinib use in MF, although the maximum tolerated dose (680 mg/day) was the most efficacious dose, it was also associated with the highest incidence of adverse events.<sup>30</sup> Therefore, a lower starting dose (400–500 mg) was used in phase II and III trials to provide an optimal risk/benefit balance.

## Efficacy

### Phase II Clinical Trial Data

One phase II dose-ranging study included adult patients with PMF, post-PV MF or post-ET MF who were

intermediate-2 or high risk.<sup>28</sup> Patients were enrolled regardless of JAK2 mutational status. Patients who received prior treatment with a JAK2 inhibitor or any chemotherapy were excluded. Patients were randomized 1:1:1 into 3 dose cohorts (300 mg, 400 mg, and 500 mg). Those in the 300 mg group were permitted to undergo dose escalation to 500 mg if there was a lack of efficacy response and no safety concerns were identified. The primary efficacy endpoint was spleen volume reduction (SVR) by  $\geq$ 35% at 12 weeks (after 3 cycles) on MRI compared to baseline. Thirty-one patients were enrolled and the rate of SVR at 12 weeks was 30.3%, 33.1%, and 43.3% in the 300, 400 and 500 mg dose groups, respectively. Results were similar between 12 and 24 weeks and durable with a median duration of response of  $\sim$ 250 days independent of the fedratinib dose.<sup>28</sup> However, by 24 weeks, spleen size reduction was greater in both the 400 mg and 500 mg groups, compared to 300 mg although the small sample size precluded any formal statistical testing.<sup>28</sup> Additionally, fedratinib led to an improvement in symptom burden as measured by the modified Myelofibrosis Symptom Assessment Form (MPN-SAF) at 12 and 24 weeks with no apparent relationship to the fedratinib dose.<sup>28</sup> In subsets of patients with baseline leukocytosis and thrombocytosis, treatment with fedratinib led to a normalization of peripheral cell counts in up to 44% of patients.<sup>28</sup> Based on these results, the 400 mg and the 500 mg doses were chosen to be further evaluated in the phase III trial.

The single-arm, open-label, non-randomized, multi-center phase II trial [JAKARTA-2] of 97 patients with intermediate-1, intermediate-2, or high-risk PMF, post-PV MF, or post-ET MF who were either resistant to or unable to tolerate ruxolitinib evaluated fedratinib 400 mg once daily for six 28-day cycles.<sup>27</sup> In order to enroll in the trial, patients had to be previously treated with ruxolitinib for at least 14 days. Among 83 evaluable patients, 46 patients (55%) achieved a spleen response ( $\geq$ 35% based on CT-/MRI-imaging) with comparable efficacy in ruxolitinib-refractory (29 out of 55 patients; 53%) and ruxolitinib-intolerant patients (17 out of 27 patients; 63%).<sup>27</sup> Ninety patients were evaluated for symptom response and 26% (23/90) achieved a 50% or greater reduction in total symptom score (TSS) after 6 cycles of treatment. While ruxolitinib-resistant patients seem to have a lower response rate to fedratinib, it is important to note that the study was not powered to detect differences between ruxolitinib-refractory and ruxolitinib-intolerant patients.<sup>27</sup>

A caveat in this trial is that the definitions of ruxolitinib failure or intolerance were not prespecified in the study protocol. In the absence of standardized criteria, patients who discontinued ruxolitinib at any dose after at least 2 weeks of treatment were eligible for the trial. However, both the median duration of prior ruxolitinib treatment of 10.25 months and the fact that 71% of patients had initially received the target dose of 30–40 mg daily suggest that the majority of patients in JAKARTA-2 had indeed received a sufficient therapeutic trial and ruxolitinib was not discontinued prematurely.<sup>27</sup>

As one of the major criticisms of the JAKARTA-2 trial was the definition of ruxolitinib resistance and intolerance, a recently published update from this trial using more stringent definitions as inclusion criteria has been presented recently.<sup>40</sup> Relapsed/refractory disease was defined as at least 3 months of prior treatment with ruxolitinib with an initial response, while ruxolitinib intolerance was defined as the development of RBC transfusion requirements or grade  $\geq 3$  cytopenias after at least 28 days of prior ruxolitinib treatment.<sup>40</sup> In this patient cohort, fedratinib achieved a spleen volume reduction in about 30% of patients with relapsed/refractory disease or ruxolitinib intolerance.<sup>40</sup>

Since thrombocytopenia can be a dose-limiting adverse event to treatment with ruxolitinib, evaluating fedratinib as an alternative in patients with baseline thrombocytopenia is of significant clinical interest. Fifteen percent of patients in the JAKARTA-I and 34% of patients in the JAKARTA-II trial had baseline platelet counts of 50 to  $<100 \times 10^9/L$ .<sup>41</sup> At least 50% symptom reduction was achieved in 31% and 39% in the patient cohorts with baseline platelet counts of 50 to  $<100 \times 10^9/L$  in JAKARTA-I and JAKARTA-II, respectively. SVR  $\geq 35\%$  were seen in 36% in both trials.<sup>41</sup> While grade  $\geq 3$  bleeding events were more common in the patients with baseline platelet counts of 50 to  $<100 \times 10^9/L$ , no new safety signals were reported.<sup>41</sup> Both publications suggest that fedratinib can be a safe and effective alternative in patients who failed or were unable to tolerate ruxolitinib.

## Data from Phase III Clinical Trials

Based on the clinical benefit demonstrated in those early phase trials, the safety and efficacy of fedratinib in patients with primary or secondary (post PV or ET) MF was evaluated in a multi-center, randomized, double-blind, placebo-controlled phase III clinical trial (JAKARTA-).<sup>29</sup> Patients were randomized to receive oral fedratinib

400 mg, 500 mg or placebo once daily for at least six consecutive 28-day treatment cycles with continuation until disease progression/relapse or excess toxicity. Of the total 289 patients who were enrolled at the data analysis cutoff date, 64 (67%), 59 (61%) and 1 (1%) of patients in the fedratinib 400 mg, 500 mg, and placebo groups were still receiving treatment as originally assigned, respectively. A total of 70 patients crossed over from placebo to fedratinib after 24 weeks of treatment or at the time of disease progression.<sup>29</sup>

The primary endpoint was the proportion of patients who achieved at least a 35% reduction in spleen volume on CT or MRI imaging from baseline to the end of cycle 6 (week 24) and confirmed 4 weeks later. Secondary endpoints included the proportion of patients with at least a 50% reduction in TSS based on six key symptoms using the modified MPN-SAF as well as 35% SVR regardless of confirmation. The primary endpoint was reached in 35 patients (36%) in the fedratinib 400 mg group and 39 patients (40%) in the fedratinib 500 mg group. This was significantly higher than the placebo group, in which a spleen response was achieved in 1 patient (1%) [ $p < 0.001$ ].<sup>29</sup> A spleen response without confirmation at 4 weeks was seen in 47%, 49% and 1% of the fedratinib 400 mg, 500 mg and placebo group, respectively.<sup>29</sup> Responses were higher in the fedratinib groups compared with placebo irrespective of patient characteristics including baseline platelet count, disease subtype, risk category and *JAK 2* mutation status.<sup>29</sup> A reduction of at least 50% in TSS from baseline to week 24 was noted in 36% in the fedratinib 400 mg group, 34% in the 500 mg group and 7% in the placebo group, respectively.<sup>29</sup> Based on the efficacy results from these phase II and phase III trials, fedratinib became the second FDA approved treatment for intermediate-2 or high-risk primary or secondary MF. Table 1 is comparing reported results to date from landmark clinical trials for ruxolitinib, momelotinib, pacritinib and fedratinib in patients with MF.

## Safety and Adverse Event Profile of Fedratinib

Phase II studies showed an adverse effect (AE) profile similar to that seen in phase I trials.<sup>27,28,30</sup> The most common AEs reported in the phase II dose-ranging study were gastrointestinal (GI) events, fatigue, peripheral edema, dyspnea, and treatment-related anemia.<sup>28</sup> However, no grade 3/4 amylase elevations were observed at the 400 or 500 mg dose, while they were previously observed at the 800 mg dosing during

phase I. All patients had at least one treatment-emergent adverse event (TEAE). All patients in the 500 mg group had grade 3/4 TEAEs. The most common nonhematologic TEAEs were GI disorders, fatigue, peripheral edema, dyspnea, and pain in extremity. Grade 3/4 asymptomatic lipase elevations were seen in 6 patients but were reversible after dose reduction. While grade 3/4 amylase elevations were observed at a dose of 800 mg in the phase I trial, they were not seen with the 400 or 500 mg dose.<sup>28,30</sup> The prevalence of GI TEAEs decreased over time. The most common hematologic AE was anemia with grade 3/4 seen in up to 58% of patients.<sup>27–29</sup> Treatment discontinuation secondary to adverse events was necessary in 8–20% mostly due to gastrointestinal side effects and thrombocytopenia in the various clinical trials.<sup>27–29</sup>

## Wernicke's Encephalopathy

A concerning adverse event seen in clinical trials of fedratinib is Wernicke's encephalopathy (WE), which is caused by thiamine (vitamin B1) deficiency. Of a total of more than 600 patients with MF, PV, or solid tumors who received fedratinib, eight cases of severe neurologic adverse events were suspicious for WE.<sup>29</sup> Due to this risk, the clinical development of fedratinib was placed on hold in 2013. However, after further analysis, only one of those cases was confirmed to be WE and the FDA lifted the hold on fedratinib development.

The underlying pathophysiology of how fedratinib may cause WE has been proposed to be that it may exacerbate malnutrition in patients due to its common GI adverse effects such as nausea, vomiting, and diarrhea. Preclinical data with Caco-2 cells showed that fedratinib may inhibit thiamine transporter (THTR) in a protein-free culture media environment suggesting impaired cellular thiamine uptake as a potential mechanism of WE.<sup>42</sup> Studies in rats treated with fedratinib at doses comparable to those used for the treatment of myelofibrosis in humans did not show any neurologic deficits.<sup>43</sup> This supports the finding that fedratinib, even at much higher doses than those used in the phase III study, does not affect thiamine levels or cause thiamine deficiency-related disorders.<sup>42,43</sup>

Given the concern for WE, 81 patients during the extended safety follow-up of 90 days after study discontinuation in the JAKARTA-2 trial received thiamine supplementation. No cases of encephalopathy or heart failure were reported during the extended safety follow-up.<sup>27</sup> However, in the fedratinib 500 mg cohort of JAKARTA-1, a total of 4 cases of WE were confirmed by an

independent expert safety panel based on either clinical features and imaging (3 patients) or clinical features alone (1 patient). These symptoms developed 6 to 44 weeks after initiation of treatment and were thought to be in the setting of elevated mean drug levels in two patients based on pharmacokinetic analysis, which was not performed for the other 2 patients, as they were placebo crossovers. Fedratinib was permanently discontinued in all 4 patients and intravenous thiamine was administered with residual cognitive deficits remaining in all patients at the time of the study report. Of note, no cases of WE were seen in the 400-mg fedratinib group. This led to the early termination of the JAKARTA-1 study and clinical development of fedratinib.<sup>29</sup>

Despite this conflicting evidence, fedratinib is FDA-approved at a dose of 400 mg for the treatment of myelofibrosis but encephalopathy remains a rare, but serious concern and is a listed black box warning. Especially, in patients with baseline risk factors for WE such as chronic diarrhea, weight loss, malnutrition, or chronic alcohol use, fedratinib use should be monitored very closely and thiamine supplementation can be considered.

## Other JAK Inhibitors in Clinical Trials

Currently, fedratinib is the only FDA-approved second-line JAK inhibitor and presents a new option for patients who have experienced a treatment failure with ruxolitinib. The National Comprehensive Cancer Network (NCCN) designates fedratinib as a category 2A option for ruxolitinib-refractory/intolerant patients and as a category 2B recommendation for upfront use in ruxolitinib naïve patients with intermediate-2 or high-risk MF.<sup>44</sup> However, both momelotinib and pacritinib have been successfully in clinical trials as well but their uptake has been hampered by concerns about associated adverse events.<sup>2,32,45</sup>

Momelotinib is a selective JAK1/2 inhibitor that has been compared in phase III clinical trials to both ruxolitinib in treatment-naïve patients with myelofibrosis (SIMPLIFY 1; NCT01969838) and to best available therapy (BAT) in patients previously treated with ruxolitinib (SIMPLIFY 2; NCT02101268).<sup>46</sup> In both trials, a 35% reduction in spleen volume after 24 weeks of treatment was chosen as the primary endpoint. Results of both trials have had lackluster results with momelotinib being not superior to BAT in terms of SVR (7% in momelotinib vs 6% in BAT group) but higher rates of at least 50% reduction in TSS compared to BAT (26% with

momelotinib vs 6% with BAT;  $p=0.0006$ ) in SIMPLIFY-2.<sup>46</sup> Comparison with ruxolitinib in the SIMPLIFY-1 trial did not show benefits to treatment with momelotinib with regard to spleen size reduction and symptom improvement (spleen response: 26.5% in momelotinib group and 29% of the ruxolitinib group ( $p=0.011$  for non-inferiority);  $\geq 50\%$  reduction in total symptom score: 28.4% for momelotinib vs 42.2% for ruxolitinib [noninferiority not met;  $p=0.98$ ]).<sup>46,47</sup> Adverse event profiles were comparable for momelotinib, ruxolitinib, and BAT with peripheral neuropathy (in up to 50% of patients) and myelosuppression being the most frequent adverse events seen with momelotinib.<sup>46,48,49</sup> In single-arm studies of mostly treatment-naïve patients, momelotinib achieved clinical/symptom responses in up to 57.6% and spleen responses in 45% of patients, respectively, and no survival benefit compared to risk-matched patients not receiving momelotinib was seen.<sup>48–50</sup> However, momelotinib unexpectedly improved anemia in patients with myelofibrosis, which can be a dose- or even treatment-limiting side effect with other JAK inhibitors.<sup>46,47</sup> In the SIMPLIFY-1 and -2 trials, rates of RBC transfusion independence were higher with momelotinib in both treatment-naïve and ruxolitinib-pretreated patients.<sup>46,47</sup> While the exact mechanism has not been fully elucidated, animal models have suggested that momelotinib reduces hepcidin production in the liver by inhibiting the ACVR1 pathway leading to greater iron availability for hematopoiesis.<sup>51</sup> Based on the favorable effect on anemia, momelotinib will be tested against danazol in the randomized, double-blind phase III MOMENTUM trial for the treatment of anemia in myelofibrosis (NCT04173494). Patient recruitment for this trial has not begun yet.

Pacritinib is another oral multikinase inhibitor that inhibits not only JAK2 but is also targeting FLT3, IRAK1, and CSF1R.<sup>52</sup> In the randomized phase III trial of pacritinib vs BAT including ruxolitinib (45% of patients) for thrombocytopenic patients with myelofibrosis (PERSIST-2; NCT02055781), twice-daily treatment with pacritinib led to significant improvements in both spleen volume reduction by  $\geq 35\%$  and  $\geq 50\%$  reduction in TSS over BAT (SVR: 16 patients [22%] vs 2 patients [3%];  $p=0.001$ ;  $\geq 50\%$  reduction in TSS: 24 patients [32%] vs 10 patients [14%];  $p=0.01$ ).<sup>53</sup> In PERSIST-1 (NCT01773187) patients were randomized to either pacritinib or BAT other than ruxolitinib with higher rates of spleen responses seen in the pacritinib treated group (42 patients [19%] vs 5 patients [5%];  $p=0.0003$ ).<sup>54</sup> The most common adverse events with pacritinib were thrombocytopenia and anemia which seemed to be less profound than with other treatment modalities.<sup>55</sup>

Although the exact mechanism why pacritinib appears to be less myelosuppressive than ruxolitinib is not known, the lack of JAK1 inhibition with pacritinib has been proposed as a potential explanation.<sup>45,53,56</sup> While prior treatment with a JAK inhibitor was allowed in PERSIST-2, patients in PERSIST-1 had to be JAK inhibitor-naïve in order to be eligible for trial enrollment.<sup>53,54</sup> Similar to fedratinib, development was briefly placed on hold in February 2016 after reports of patients dying of heart failure and intracranial hemorrhage in the PERSIST trials.<sup>57</sup> However, after an additional review of those cases, the development hold on pacritinib was lifted.<sup>45</sup>

As the PERSIST-2 trial showed the efficacy of pacritinib also in patients previously treated with ruxolitinib, the phase II PAC203 trial was designed and randomized patients who failed or were intolerant of treatment with ruxolitinib to various doses of pacritinib. One hundred and sixty-four patients were included in this trial with 68% being intolerant of and 73% having failed treatment with ruxolitinib with a median treatment duration of 1.4 years preceding trial enrollment.<sup>58</sup> Abstract data from this trial demonstrated that SVR  $\geq 35\%$  and TSS improvement of  $\geq 50\%$  were observed in 9.3% and 7.4% of patients, respectively, at a dose of 200 mg pacritinib twice daily with lower response rates seen with lower doses.<sup>58</sup> Thrombocytopenia (32%), anemia (22%) and gastrointestinal adverse events were the most common treatment-emergent adverse events.<sup>58</sup>

Several clinical trials studying pacritinib in the pre-transplant setting (NCT03645824) and in patients previously treated with ruxolitinib (NCT03165734) are currently ongoing. Finally, the phase III PACIFICA trial that randomizes thrombocytopenic (platelet count  $< 50,000/\text{mL}$ ) patients with primary or secondary myelofibrosis to pacritinib or physician's choice (low-dose [ $\leq 5$  mg] ruxolitinib, lenalidomide, corticosteroids, hydroxyurea) is anticipated to start enrollment shortly.<sup>59</sup>

## Novel JAK Inhibitor-Based Combination Treatments

As anemia is a common dose-limiting side effect with ruxolitinib, combinations of ruxolitinib with erythropoiesis-stimulating agents such as the immunomodulators thalidomide and pomalidomide as well as the activin receptor ligand trap sotatercept, which inhibits signaling via the transforming growth factor (TGF)- $\beta$  pathway, are currently ongoing. Especially the immunomodulator pomalidomide with or without prednisone has been successfully tested to

treat cytopenias (anemia, thrombocytopenia) in patients with MPN-associated myelofibrosis.<sup>60–62</sup> While the clinical trial (NCT01375140) of ruxolitinib in combination with lenalidomide had to be terminated early due to lack of therapeutic benefit and significant side effects necessitating dose interruptions in all 20 trial patients, preliminary data showed mixed results with such combinations but data should be interpreted cautiously until fully published.<sup>63–65</sup>

Epigenetic changes such as abnormal DNA methylation patterns have been identified in patients with myelofibrosis leading to clinical trials combining the hypomethylating agents (HMAs) azacitidine and decitabine with ruxolitinib.<sup>3,66,67</sup> While both azacitidine and decitabine have only limited clinical activity if used as monotherapies, the combination therapy of ruxolitinib and azacitidine has led to ORR of 72% in a phase II study (NCT01787487).<sup>68</sup> Notably, 95% of the responding patients maintained a spleen response (>50% reduction in spleen length) by week 48 of the trial. Furthermore, 57% of patients had improvements in the extent of bone marrow reticulin fibrosis which may suggest a disease-modifying effect of this combination.<sup>68</sup> Combining ruxolitinib with HMAs might be especially effective in patients with MDS/MPN-overlap since HMA remains the standard of care for MDS patients especially in the setting of high-risk features such as elevated bone marrow blast percentage.<sup>69</sup> This is further supported by a recent phase I study of ruxolitinib and decitabine in MPNs in accelerated or blast phase.<sup>70</sup> In this trial median OS among the 21 patients was 7.9 months (95%-CI: 4.1 months – not reached) with an ORR (CR, CRi, partial remission) of 42.9% (9 out of 21 patients) in the intention-to-treat analysis.<sup>70</sup> Based on these results, the combination of decitabine and ruxolitinib has been studied in a phase II trial (NCT02076191).

The hedgehog pathway is involved in the early stages of hematopoiesis and combinations of ruxolitinib and hedgehog inhibitors such as vismodegib and glasdegib have been shown to have synergistic effects in in-vitro experiments.<sup>71,72</sup> However, results from a phase Ib/II clinical trial (NCT02226172) of glasdegib and ruxolitinib in 21 patients with JAK inhibitor-refractory MF have been disappointing. None of the trial patients achieved the secondary endpoint of SVR $\geq$ 35% and only 2 patients had at least 50% improvement in symptom burden leading to the early termination of the study.<sup>73</sup> Slightly better responses have been reported from a phase Ib trial (NCT02593760) combining vismodegib with ruxolitinib in 8 patients with MF that showed spleen responses in 3 patients and

symptom improvement in 5 patients.<sup>74</sup> Although the combination was safe, it will not be further developed for MF.<sup>74</sup>

After the B-cell lymphoma 2 (BCL-2) inhibitor venetoclax has shown impressive results in combination with HMA and low-dose cytarabine in AML, inhibition of the anti-apoptotic effects of BCL-2 by navitoclax,<sup>75,76</sup> a related orally bio-available small-molecule BCL-2 inhibitor, has been tested in combination with ruxolitinib in a recent phase II trial in patients with myelofibrosis (NCT03222609).<sup>77</sup> Abstract data for the week 24 endpoint showed that 29% and 20% of the 24 evaluable patients achieved an SVR $\geq$ 35% and symptomatic improvement, respectively.<sup>77</sup> However, all patients had treatment-emergent adverse events with 77% experiencing grade  $\geq$ 3 adverse events with thrombocytopenia (82%), diarrhea (62%), fatigue (53%), anemia (27%), and nausea (27%) being most common.<sup>77</sup> Notably, the combination of navitoclax and ruxolitinib also led to a decrease in the VAF of driver mutations and improvements in bone marrow fibrosis, suggesting a potential disease-modifying effect of the combination.<sup>77</sup>

Another potential candidate for combination therapy with ruxolitinib is CPI-0610, a Bromodomain and Extraterminal Domain (BET) inhibitor, which modulates NF $\kappa$ B and TGF- $\beta$  signaling pathways and has been shown to have synergistic effects with ruxolitinib in vitro.<sup>78</sup> The MANIFEST study uses a two-arm design with one arm being CPI-0610 monotherapy in ruxolitinib-refractory/intolerant patients, and the other arm of CPI-0610 in combination with ruxolitinib (NCT02158858). Preliminary data showed that 94% of the 31 patients (both arms combined) achieved an SVR (median best change: -17% [range: -50.7, 10.2]; rate of  $\geq$ 35% SVR not reported) and 39% had a  $\geq$ 50% symptom reduction.<sup>79</sup> Treatment was well tolerated with anemia (8.3%) and thrombocytopenia (8.3%) being the most common grade  $\geq$ 3 treatment-emergent adverse events.<sup>79</sup>

Finally, in-vitro studies have shown synergistic effects for the combination of ruxolitinib with the tyrosine kinase inhibitor nilotinib and prednisone as well as the telomerase inhibitor imetelstat.<sup>80,81</sup> While imetelstat has been successfully tested as monotherapy in MF even in JAK inhibitor-refractory patients,<sup>82</sup> no clinical trial data for either combination are available yet and a study combining nilotinib and ruxolitinib in patients with chronic myelogenous leukemia has been temporarily suspended (NCT02973711). Other current phase II clinical trials in JAK inhibitor-refractory patients with myelofibrosis are testing the oral MDM2



inhibitor KRT-232 (NCT03662126) and selinexor (NCT03627403; ESSENTIAL trial) but neither of them has published results yet. Ongoing clinical trials of JAK inhibitor-based combination therapies are outlined in Table 2.

## Conclusion and Future Directions

Ruxolitinib continues to be the first-line option for the treatment of symptomatic intermediate- or high-risk MF. Major challenges remain in the treatment of patients after ruxolitinib failure, for which there is not yet a clear-cut definition. Generally, spleen response or progressive increase of blast cells are used in clinical practice to define ruxolitinib-resistance. In the COMFORT-I and COMFORT-II trials, 50% and 75% of ruxolitinib treated patients experienced treatment failure or unacceptable adverse effects at 3 and 5 years, respectively.<sup>23,26</sup> In this setting, clinical trials, allogeneic hematopoietic stem cell transplant (HSCT) or alternative JAK2 inhibitors remain viable options in eligible patients.<sup>1</sup> Reasons for ruxolitinib resistance are poorly understood but include the variable JAK2 V617F VAF among patients, the use of ruxolitinib too late in the disease course, alternative mechanisms of JAK-STAT signaling pathway activation that are not inhibited by ruxolitinib, and a response modifying effect of concurrent mutations such as *ASXL1* or *SRSF2*.<sup>57,83–85</sup> Furthermore, 25–35% of patients in the COMFORT trials discontinued ruxolitinib due to adverse events with anemia, infectious complications, and diarrhea being the most commonly observed side effects in about a third of patients each.<sup>23,25</sup> Prognosis of patients after ruxolitinib failure is poor and additional therapeutic options are highly warranted.

Currently, fedratinib presents the only FDA-approved option for patients who have experienced a treatment failure with ruxolitinib. However, both momelotinib and pacritinib have been successfully tested and could be potential therapeutic options for selected patients. While cytopenias have been a limiting factor for the treatment with ruxolitinib, momelotinib has been shown to reduce transfusion requirements and improve anemia which makes it a potential option for anemic patients.<sup>47</sup> Similarly, pacritinib seems to be safe and effective in patients with treatment-limiting thrombocytopenia but further studies are needed to evaluate safety and efficacy.<sup>55</sup> Of note, none of these second-line JAK inhibitors has shown a survival benefit and the concern about serious treatment-related side effects has stalled further clinical trials. Fedratinib is currently being studied in

a phase 3b trial in 110 patients with intermediate to high-risk MF who have previously received ruxolitinib (FREEDOM; NCT03755518). This is a single-arm, open-label trial examining the efficacy and safety of fedratinib in patients with DIPSS (Dynamic International Prognostic Scoring System)-Intermediate or High-Risk PMF or post PV/post ET MF previously treated with ruxolitinib. The ongoing, randomized phase 3, open-label FREEDOM2 trial (NCT03952039) is comparing fedratinib to the best supportive care and started patient enrollment in September 2019. The primary objective of both studies is to evaluate the percentage of subjects with at least a 35% reduction of spleen volume. Secondary outcome measures include  $\geq 50\%$  reduction in spleen size, durability of symptom and spleen volume response and to evaluate the safety of fedratinib with a focus on GI adverse events, occurrence of confirmed WE events and monitoring and correction of thiamine levels. Results are expected for 2022 and will provide additional information on the role of fedratinib in myelofibrosis. Table 2 provides an overview of currently active clinical trials of JAK inhibitors as monotherapy or combination treatments in myelofibrosis.

The role of Fedratinib in the frontline setting of higher risk MF is less clear. While it is approved for this indication, there have been no published randomized clinical trials to date that compared it head-to-head to ruxolitinib which has been in the market for almost 8 years and has a prolonged clinical experience.

As outlined above future directions in myelofibrosis management include investigation of alternate pathways such as targeting bone marrow fibrosis, and consideration of JAK inhibitor-based combination therapies with other therapeutic classes such as hedgehog inhibitors, immunomodulators, epigenetic agents, and PI3K pathway inhibitors.<sup>32,86</sup> One promising agent is the orally available LSD1 inhibitor IMG-7289 (bomedemstat) that had shown promising effects in animal models and is currently being tested in a phase I/II study in myelofibrosis patients intolerant of or refractory to ruxolitinib (NCT03136185).<sup>87,88</sup> Preliminary results from this trial showed an SVR in 50% of patients (not defined as  $\geq 35\%$  as in other trials) and  $\geq 50\%$  symptom reduction in 21% of patients.<sup>88</sup> However, it remains to be seen what the final results using more stringent response criteria show before the role of IMG-7289 in the treatment landscape of myelofibrosis can be evaluated. LCL161 is another compound that is tested as a single agent in a clinical trial in patients with myelofibrosis (NCT02098161). LCL161 is a second mitochondria-derived activator of caspases

**Table 2** Ongoing Clinical Trials of JAK Inhibitors in Myelofibrosis

Agent(s)/Regimen	NCT Identifier	Targets	Phase	Population
<b>Ruxolitinib Monotherapy</b>				
Ruxolitinib doses calculated with platelets count and P450 cytochrome inhibitor HSCT for patients with donor	NCT01795677	JAK1-/JAK2-inhibitor	II	Primary or secondary myelofibrosis prior to allogeneic hematopoietic stem cell transplantation
Ruxolitinib Pre-, During- and Post-HSCT for Patients with Primary or Secondary Myelofibrosis	NCT03427866	JAK1-/JAK2-inhibitor	II	Primary or secondary myelofibrosis prior to allogeneic hematopoietic stem cell transplantation
Ruxolitinib vs Allogeneic SCT for Patients with Myelofibrosis According to Donor Availability	NCT0333187	JAK1-/JAK2-inhibitor	II	Primary or secondary myelofibrosis
Ruxolitinib before and after Reduced Intensity Donor Stem Cell Transplant	NCT02917096	JAK1-/JAK2-inhibitor	I	Primary or secondary myelofibrosis prior to allogeneic hematopoietic stem cell transplantation
Ruxolitinib (dose escalation)	NCT01317875	JAK1-/JAK2-inhibitor	I	Myelofibrosis
<b>Ruxolitinib Combinations</b>				
Ruxolitinib + thalidomide	NCT03069326	JAK1-/JAK2-inhibitor + immunomodulator	II	Primary or secondary myelofibrosis
Ruxolitinib + pomalidomide	NCT01644110	JAK1-/JAK2-inhibitor + immunomodulator	I/II	Primary or secondary myelofibrosis
PIM447 (pan-pim inhibitor) + ruxolitinib (doublet), LEE011 (CDK4/6 inhibitor) + ruxolitinib (doublet), PIM447 + ruxolitinib + LEE 011 (triple combination)	NCT02370706	JAK1-/JAK2-inhibitor + pan-pim inhibitor or CDK4/6 inhibitor	Ib	JAK2V617F-positive primary or secondary MF
Open-Label of Navitoclax (ABT-263) Alone or in Combination With Ruxolitinib	NCT03222609	Bcl-2 inhibitor ± JAK1-/JAK2-inhibitor	II	Intermediate or high-risk primary Myelofibrosis, post polycythemia Vera Myelofibrosis or post-essential thrombocythemia myelofibrosis
Pevonedistat (MLN4924) + ruxolitinib	NCT03386214	NEDD8 inhibitor ± JAK1-/JAK2-inhibitor	I	Primary or secondary myelofibrosis classified as high risk, intermediate-2 risk, or intermediate I risk by IPSS; tolerating 3 months of ruxolitinib before enrolment
Itacitinib (INCB039110) in Combination With Low-Dose Ruxolitinib or Itacitinib Alone	NCT03144687	JAK1 inhibitor ± JAK1-/JAK2-inhibitor	II	Primary or secondary myelofibrosis, tolerating 2 months of and response to ruxolitinib before enrolment
Ruxolitinib + azacytidine SC or IV for 5 days for up to 15 28-day cycles	NCT01787487	JAK1-/JAK2-inhibitor + hypomethylating agent	II	Patients with myelofibrosis, myelodysplastic syndromes/ myeloproliferative neoplasms (MDS/MPN), chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia, myelodysplastic syndromes/myeloproliferative neoplasms, unclassifiable (MDS/MPN-U)

(Continued)

**Table 2** (Continued).

Agent(s)/Regimen	NCT Identifier	Targets	Phase	Population
Panobinostat (3 times a week, every other week in 28-day cycles; LBH589) + ruxolitinib	NCT01433445	Histone deacetylase inhibitor + JAK1-/JAK2-inhibitor	I	Primary or secondary myelofibrosis
CPI-0610 + ruxolitinib	NCT02158858	BET inhibitor ± JAK1/JAK2-inhibitor	I/II	Myelofibrosis with or without prior JAK inhibitor therapy
Ruxolitinib + Peg-interferon Alpha-2a	NCT02742324	JAK1/JAK2-inhibitor + IFN	I/II	Primary or secondary myelofibrosis, age 18–65 years
Parsaclisib (INCB050465) + ruxolitinib	NCT02718300	PIK3 inhibitor + JAK1/JAK2-inhibitor	II	Primary or secondary myelofibrosis
TGR-1202 (umbralisib) + Ruxolitinib	NCT02493530	PIK3 inhibitor + JAK1/JAK2-inhibitor	I	Primary or secondary myelofibrosis, MDS/MPN or Polycythemia Vera Resistant to Hydroxyurea
PU-H71 + ruxolitinib	NCT03373877	HSP90 inhibitor + JAK1/JAK2-inhibitor	I	Primary or secondary myelofibrosis
PU-H71 + ruxolitinib	NCT03935555	HSP90 inhibitor + JAK1/JAK2-inhibitor	I	Primary or secondary myelofibrosis
<b>Fedratinib</b>				
Fedratinib vs best available therapy [FREEDOM-2]	NCT03952039	JAK2-inhibitor	III	Primary or secondary myelofibrosis previously treated with ruxolitinib
Fedratinib (single- arm) [FREEDOM]	NCT03755518	JAK2-inhibitor	III	Primary or secondary myelofibrosis previously treated with ruxolitinib
<b>Pacritinib</b>				
Pacritinib	NCT03165734	JAK2/IRAK1-inhibitor	II	Primary or secondary myelofibrosis previously treated with ruxolitinib

(SMAC) mimetic that induces apoptosis in cancer cells, leading to a phase II study that enrolled 43 patients with myelofibrosis. Using less stringent response criteria, 5 and 10 patients experienced anemia and symptom improvement, respectively, while only 1 patient had a spleen response.<sup>89</sup>

While additional clinical trials of these single agents and combination therapies are necessary, the currently available data suggest high ORR especially for the combination of ruxolitinib with hypomethylating agents with an acceptable risk profile.

In conclusion, fedratinib has shown improvement in both spleen size and MF-related symptom burden in the JAKARTA trials with efficacy seen in both frontline and in ruxolitinib-refractory patients. Providers should pay close attention to early detection and management, including pre-emptive interventions especially in high-risk patients,

of rare but serious side effects such as WE. Additional studies are ongoing to inform the role of fedratinib in the treatment landscape for MF and studies to assess synergistic effects with other drug classes are needed.

## Acknowledgments

AMZ is a Leukemia and Lymphoma Society Scholar in Clinical Research and is also supported by an NCI's Cancer Clinical Investigator Team Leadership Award (CCITLA). This research was partly funded by the Dennis Cooper Hematology Young Investigator Award (AZ) and was in part supported by the National Cancer Institute of the National Institutes of Health under Award Number P30 CA016359. The conduction of the study and interpretation of the data are the sole responsibility of the authors.

## Disclosure

SMJ has been employed by Celgene since 10/18/2019. All sections contributed to this manuscript were written and completed during prior employment at Yale New Haven Hospital-Smilow Cancer Center. No payment or services have been received pertaining to any aspect of the submitted work. SA has been employed by Sanofi Genzyme since 7/01/2019. No payment or services have been received pertaining to any aspect of the submitted work. AMZ received research funding (institutional) from Celgene, Acceleron, Abbvie, Otsuka, Pfizer, Medimmune/AstraZeneca, Boehringer-Ingelheim, Trovogene, Incyte, Takeda, and ADC Therapeutics. AMZ had a consultancy with and received honoraria from AbbVie, Otsuka, Pfizer, Celgene, Ariad, Agios, Boehringer-Ingelheim, Novartis, Acceleron, Astellas, Daiichi Sankyo, Trovogene, BeyondSpring, and Takeda. AMZ reports personal fees from Celgene, Acceleron, Abbvie, Otsuka, Pfizer, Medimmune/AstraZeneca, Boehringer-Ingelheim, Trovogene, Incyte, Takeda, ADC Therapeutics, Ariad, Agios, Novartis, Astellas, Daiichi Sankyo, and BeyondSpring, outside the submitted work. The other authors have no conflicts of interest to declare.

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