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NCCN® Guidelines Panel: Myeloproliferative Neoplasms

Dear NCCN Myeloproliferative Neoplasms Guidelines Panel:

On behalf of Incyte Corporation, I respectfully request the NCCN Myeloproliferative Neoplasms Guideline Panel review the enclosed data, in addition to our prior submission from October 2015, pertaining to the use of ruxolitinib in patients with polycythemia vera (PV) who have had an inadequate response to or are intolerant of hydroxyurea. We ask the Panel to consider for inclusion in the Myeloproliferative Neoplasms Guideline recently published long-term (80-week) efficacy and safety results from the pivotal, Phase 3 study in patients with PV that had an inadequate response to or are intolerant of hydroxyurea. In addition, we request that you also consider the results from a separate Phase 3b study in patients with PV, without palpable splenomegaly, who had an inadequate response to or are intolerant of hydroxyurea.

FDA Clearance: Ruxolitinib, an inhibitor of Janus Associated Kinases (JAKs) JAK1 and JAK2, is FDA-approved for treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea (Jakafi Prescribing Information).

Rationale: The clinical efficacy and safety of ruxolitinib in PV was established from the results of a Phase 3, randomized, controlled, open-label study (RESPONSE) that compared ruxolitinib with best available therapy (BAT) in patients with PV who had an inadequate response to or were intolerant of hydroxyurea (HU) (Jakafi Prescribing Information; Vannucchi, 2015). The primary endpoint was the composite of hematocrit (Hct) control and ≥35% reduction in spleen volume at Week 32. Key (type I error–controlled) secondary endpoints included the proportion of patients who had a primary response at Week 32 that was maintained at Week 48, and the proportion of patients who achieved a complete hematologic remission (CHR) (i.e., Hct control, platelet count ≤400 x 10^9/L, and white blood cell [WBC] count ≤10 x 10^9/L) at Week 32.

A second preplanned analysis assessed the durability of efficacy and the long-term safety of ruxolitinib treatment after all patients completed the Week 80 visit or discontinued the study (Verstovsek, 2016). Eighty-three percent of patients randomized to ruxolitinib were still on treatment at the time of this

cutoff with a median exposure of 111 weeks. No patients were actively receiving BAT (median exposure, 34 weeks).

Of the 23% of patients randomized to ruxolitinib who achieved a primary response at Week 32, 76% maintained their response through Week 80 (Jakafi Prescribing Information). The probability of maintaining this response for ≥ 80 weeks was 92% (Verstovsek, 2016). Of the 24% of patients randomized to ruxolitinib who achieved CHR at Week 32, 58% maintained their response through Week 80 (Jakafi Prescribing Information). The probability of maintaining their CHR for ≥80 weeks was 69% (Verstovsek, 2016). In an assessment of the individual components of the primary endpoint, 60% of patients randomized to ruxolitinib and 19% of patients randomized to BAT achieved hematocrit control at Week 32; 77% of hematocrit responders in the ruxolitinib group maintained hematocrit control through Week 80 (Jakafi Prescribing Information). Forty percent of patients randomized to ruxolitinib and <1% of patients randomized to BAT achieved a ≥35% spleen volume reduction at Week 32; 98% of responders in the ruxolitinib group maintained spleen volume reduction through Week 80.

The most common non-hematologic adverse events (AEs- all grades) per 100 patient-years of exposure in patients randomized to ruxolitinib were headache (10.5; BAT 28.5), diarrhea (9.7; BAT 12.2), pruritus (9.7; BAT 32.6), and fatigue (8.3; BAT 23.1) (Verstovsek, 2016). Most events were Grade 1/2. New or worsening hematologic laboratory abnormalities per 100 patient-years of exposure in the ruxolitinib group were decreases in hemoglobin (27.2; BAT 47.6), lymphocytes (27.2; BAT 78.8), and platelets (14.9; BAT 29.9). Among patients randomized to ruxolitinib, the rates of all-grade and Grade 3/4 thromboembolic events per 100 patient-years of exposure were 1.8 (BAT 8.2) and 0.9 (BAT 2.7), respectively. The rate of all-grade infections, adjusted for patient exposure, was 29.4 (Grade 3/4, 4.0) in the ruxolitinib group and 58.4 (Grade 3/4, 4.1) in the BAT group. Among patients randomized to ruxolitinib, the rate of all-grade herpes zoster infection per 100 patient-years of exposure was 5.3 (Grade 3/4, 0.9). There were no cases of herpes zoster infection reported in the BAT group. The rate of non-melanoma skin cancer, adjusted for patient exposure, in the ruxolitinib and BAT groups was 4.4 and 2.7, respectively.

A Phase 3b, open-label study (RESPONSE 2) was recently presented that compared ruxolitinib with BAT in patients with PV who were resistant or intolerant to hydroxyurea, and without palpable splenomegaly (Passamonti, 2016). The primary endpoint was the proportion of patients who achieved hematocrit control at Week 28. The key secondary endpoint (alpha controlled) was the proportion of patients who achieved CHR at Week 28. Other endpoints included patient-reported outcomes (as assessed by the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score [MPN-SAF TSS]), and safety. Patients were randomized 1:1 to receive ruxolitinib 10 mg BID (n=74) or BAT (n=75).

Hematocrit control was achieved in 62.2% and 18.7% of patients randomized to ruxolitinib and BAT, respectively ($p<0.0001$). Complete hematologic remission was achieved in 23.0% and 5.3% of ruxolitinib and BAT-treated patients, respectively ($p=0.0019$). At Week 28, ≥50% improvement in MPN-SAF TSS was achieved in 45.3% of patients randomized to ruxolitinib and 22.7% of patients randomized to BAT; a complete resolution (defined as score reduction ≥10 points from baseline at Week 16 and maintained until Week 28 in patients with a baseline score of ≥20) was achieved in 50.0% of patients randomized to ruxolitinib and 7.7% of patients randomized to BAT.

The median duration of exposure to ruxolitinib and BAT was 42.2 and 28.4 weeks, respectively. The most common (≥10%) non-hematologic AEs in the ruxolitinib and BAT groups, respectively, were headache (12.2% vs. 10.7%), constipation (10.8% vs. 5.3%), hypertension (10.8% vs. 4.0%), pruritus (10.8% vs. 20.0%), and weight increase (10.8% vs. 1.3%). Anemia and thrombocytopenia occurred in

16.2% and 2.7% of patients randomized to ruxolitinib versus 2.7% and 8.0% of patients randomized to BAT; most were Grade 1/2. The rate of all-grade infections among patients randomized to ruxolitinib and BAT was 31.1% (Grade 3/4, 4.1%) and 24.0% (Grade 3/4, 1.3%), respectively. Herpes zoster infection was reported in 1.4% (Grade 3/4, 0%) of patients in the ruxolitinib group and in no patients in the BAT group. The rate of non-melanoma skin cancer was 1.4% in the ruxolitinib group and 1.3% in the BAT group. No deaths were reported in the ruxolitinib group while two patients died in the BAT group.

Additional detail on study design, methodology, analyses and endpoints for the RESPONSE and RESPONSE 2 studies can be found in the following enclosed literature.

Literature support:

Jakafi [Prescribing Information] Wilmington, DE: Incyte. https://www.jakafi.com/pdf/prescribing-information.pdf

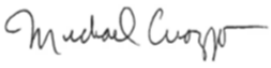
Passamonti F, Griesshammer M, Palandri F, et al. Ruxolitinib proves superior to best available therapy in patients with polycythemia vera resistant to or intolerant of hydroxyurea without splenomegaly: results from RESPONSE-2 [abstract and presentation]. Presented at the 21st Congress of the European Hematology Association; June 9-12, 2016; Copenhagen, Denmark.

Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*. 2015;372(5):426-435.

Verstovsek S, Vannucchi AM, Griesshammer M, et al. Ruxolitinib versus best available therapy in patients with polycythemia vera: 80 week follow up from the RESPONSE trial [published online ahead of print April 21, 2016]. *Haematologica*. doi:10.3324/haematol.2016.143644.

We appreciate the Panel's review and consideration of this submission. Should you have any questions regarding the content of this letter or would like additional information, please do not hesitate to contact me.

Sincerely,



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