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Date of request: July 8, 2016
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 intermediate or high-risk myelofibrosis (MF). We ask
the Panel to consider for inclusion in the Myeloproliferative Neoplasms Guideline the recently
published/presented longer-term (5-year) efficacy and safety results from two pivotal, Phase 3 studies in
patients with MF, as well as analyses from a separate Phase 3b expanded-access study evaluating
patients with intermediate-1 risk MF.

FDA Clearance: Ruxolitinib, an inhibitor of Janus Associated Kinases (JAKs) JAK1 and JAK2, is FDA-
approved for the treatment of intermediate or high-risk myelofibrosis, including primary myelofibrosis,
post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis (Jakafi
Prescribing Information).

Rationale: The clinical efficacy and safety of ruxolitinib in MF is supported by results from two, Phase 3,
randomized, controlled studies. In the first study (Controlled Myelofibrosis Study with Oral JAK Inhibitor
Treatment I [COMFORT-I]) comparing ruxolitinib with placebo, the primary endpoint was the proportion
of patients with a ≥35% reduction in spleen volume from baseline to Week 24 as measured by magnetic
resonance imaging (MRI) or computed tomography (CT) (Jakafi Prescribing Information; Verstovsek,
2012). Key secondary endpoints included the proportion of patients with a ≥50% reduction in Total
Symptom Score (TSS) from baseline to Week 24 (measured by the modified Myelofibrosis Symptom
Assessment Form [MFSAF] v2.0), change in TSS from baseline to Week 24, and overall survival (OS).

A final pre-planned analysis was conducted to evaluate the long-term efficacy and safety results after all
patients completed the 5-year visit or had discontinued from the study (Gupta, 2016; Verstovsek, 2016).
Among the 92 patients in the ruxolitinib group that achieved a ≥35% spleen volume reduction at any
time point, the median duration of response from time of initial response was 168.3 weeks. The mean
percentage reduction from baseline in spleen volume was 37.6% through 264 weeks for patients who

continued on treatment with ruxolitinib. The median follow-up time for the survival analysis was 268.4 weeks for patients randomized to ruxolitinib and 269.0 weeks for patients randomized to placebo. At data cutoff, 44.5% of patients randomized to ruxolitinib and 53.2% randomized to placebo had died (hazard ratio [HR], 0.69 [95% CI, 0.50-0.96]; p=0.025). The median OS had not been reached in the ruxolitinib group while the median OS was 200 weeks for patients in the placebo group.

The median duration of exposure for patients randomized to ruxolitinib was 149.3 weeks (4.3-296 weeks) and 111 weeks (0.9-256.1 weeks) in the ruxolitinib crossover group. The most common non-hematologic treatment-emergent adverse events (AEs) (all grades) per 100 patient-years of exposure in the ruxolitinib randomized group were fatigue (24.3), diarrhea (18.5), and ecchymosis (12.5); in the ruxolitinib crossover group, fatigue (18.1), diarrhea (12.7), and ecchymosis (11.9); in the placebo group, fatigue (67.6), diarrhea (40.0), and peripheral edema (39.2). The rates of herpes zoster infection (all grades) per 100 patient-years of exposure were higher in the ruxolitinib randomized (3.5) and ruxolitinib crossover (5.8) groups compared to the placebo group (1.0). The rate of basal cell carcinoma per 100 patient-years of exposure was 2.7 in the ruxolitinib randomized group, 4.0 in the ruxolitinib crossover group, and 3.9 in the placebo group. Anemia (worst grade regardless of baseline value) occurred in 98.7% of patients in the ruxolitinib randomized group, 95.5% of patients in the ruxolitinib crossover group, and 88.1% of patients in the placebo group. Thrombocytopenia (worst grade regardless of baseline value) occurred in 83.9% of the ruxolitinib randomized group, 90.1% of ruxolitinib crossover group, and 33.1% of the placebo group.

In the second pivotal study, COMFORT-II, which compared ruxolitinib with best available therapy (BAT), the primary endpoint was the proportion of patients with a ≥35% reduction in spleen volume from baseline at Week 48 as measured by MRI or CT (Jakafi Prescribing Information; Harrison, 2012). The key secondary endpoint was the proportion of patients who achieved a ≥35% spleen volume reduction from baseline to Week 24.

A final pre-planned analysis was conducted to evaluate the long-term efficacy and safety after 5 years of ruxolitinib treatment (Harrison, 2015; Harrison, 2016). Overall, 97.1% of patients with post baseline spleen assessments randomized to ruxolitinib experienced some degree of spleen volume reduction, with 53.4% achieving a ≥35% reduction at any time on treatment. Of the patients who crossed over from BAT, 75.6% experienced spleen volume reduction after crossover to ruxolitinib, and 42.2% had ≥35% reduction at any time. Spleen volume reductions ≥35% among ruxolitinib-randomized patients were sustained for a median duration of 3.2 years; the probability of maintaining a spleen response for patients randomized to ruxolitinib was 0.48 at 5 years (95% CI, 0.35-0.60). Overall, deaths were reported in 40.4% and 47.9% of patients randomized to ruxolitinib and BAT, respectively. Median OS was not reached in the ruxolitinib group and was 4.1 years in the BAT group. The Kaplan-Meier estimated probability of survival at 5 years was 56% with ruxolitinib and 44% with BAT (hazard ratio [HR] = 0.67 [95% CI, 0.44-1.02]; P = 0.06).

The median duration of exposure was 2.6 years in the ruxolitinib randomized group and 1.2 years in the BAT group after crossover. As in COMFORT-I, no relevant increase in the incidence of AEs was noted with longer exposure, and there were no new or unexpected AEs at the time of the 5-year analysis. The most common non-hematologic treatment-emergent AEs (all grades) per 100 patient-years of exposure in the ruxolitinib randomized group were diarrhea (13.7), peripheral edema (13.4), and bronchitis (10.0); in the ruxolitinib crossover group, diarrhea (15.1), dyspnea (15.1), and pain in extremity (13.8); in the BAT group, peripheral edema (31.4), dyspnea (22.4), and abdominal pain (19.4), diarrhea (19.4), and pruritus (19.4). Exposure-adjusted rates of herpes zoster infection per 100 patient-years were higher in

the ruxolitinib randomized (3.9) and ruxolitinib crossover (6.3) groups compared to the BAT group (0). The rate of nonmelanoma skin cancer per 100 patient-years of exposure was 6.1 in the ruxolitinib randomized group, 1.3 in the ruxolitinib crossover group, and 3.0 in the BAT group. When adjusted for exposure, the most common Grade 3/4 AEs per 100 patient-years of exposure occurring in patients who received ruxolitinib at any time included anemia (8.8), thrombocytopenia (5.9), pneumonia (2.2), general physical health deterioration (1.6), and acute renal failure (1.4).

The clinical efficacy and safety of ruxolitinib in MF was also evaluated in the Phase 3b JUMP (JAK Inhibitor RUxolitinib in Myelofibrosis Patients) study (Al-Ali, 2016). JUMP is an expanded-access study for patients in countries without access to ruxolitinib outside of a clinical study. In an initial analysis of 1144 patients with International Prognostic Scoring System (IPSS) high, intermediate-2, or intermediate-1 risk MF, at Weeks 24 and 48, 56.9% and 62.3% of evaluable patients achieved a ≥50% reduction from baseline in palpable spleen length, respectively. The median time to the first ≥50% reduction in palpable spleen length was 5.1 weeks (range, 0.1-53.1 weeks). The Kaplan-Meier estimated probability of maintaining a spleen response for 24 weeks and 48 weeks was 93% (95% CI, 91%-95%) and 72% (95% CI, 54%-84%), respectively. The most common non-hematologic AEs (in ≥5% of patients) were primarily Grade 1/2, and included diarrhea, pyrexia, fatigue, and asthenia. The most common hematologic AEs were anemia (all grades, 56.3%; Grade 3/4, 33.0%) and thrombocytopenia (all grades, 42.2%; Grade 3/4, 12.5%).

A separate analysis of the JUMP study assessed the safety and efficacy of ruxolitinib in 700 patients with Dynamic International Prognostic Scoring System (DIPSS) intermediate-1 MF with ≥1 year follow-up from baseline (Passamonti, 2016). At Week 24, 62% (339/547) of patients had a ≥50% reduction from baseline in palpable spleen length and 21% (117/547) had 25% to 50% reductions. Rates were similar at Week 48. At Weeks 4, 12, 24, and 48, 40% to 50% of patients achieved a clinically meaningful response on the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) total score and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale. The Kaplan-Meier estimated OS probabilities at Week 48 were similar between JUMP (median follow-up, 65 weeks) and the DIPSS database (0.98 [95% CI, 0.97-0.99] versus 0.99 [0.96-1.00]), as expected in intermediate-1 patients given the short time period. The most common non-hematologic AEs included asthenia (all grades, 14.0%; Grade 3/4, 1.6%), pyrexia (all grades, 11.4%; Grade 3/4, 0.9%), and headache (all grades 11.4%; Grade 3/4, 0.3%). The most common hematologic AEs were anemia (all grades, 55.1%; Grade 3/4, 22.0%) and thrombocytopenia (all grades, 39.7%; Grade 3/4 10.3%). Serious AEs occurring in >1% of patients included pneumonia (3.7%), anemia (2.2%), cardiac failure (1.6%), pyrexia (1.6%), dyspnea (1.3%), gastrointestinal hemorrhage (1.1%), and sepsis (1.1%).

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

Literature support:

Al-Ali HK, Griesshammer M, le Coutre P, et al. Safety and efficacy of ruxolitinib in an open-label, multicenter, single-arm phase 3b expanded-access study in patients with myelofibrosis: a snapshot of 1144 patients in the JUMP trial [published online May 31, 2016]. *Haematologica*. doi:10.3324/haematol.2016.143677.

Gupta V, Verstovsek S, Mesa RA, et al. Long-term outcomes of ruxolitinib in patients with myelofibrosis: 5-year update from COMFORT-I. Poster presented at 52nd Annual Meeting of the American Society of Clinical Oncology; June 3-7, 2016; Chicago, IL.

Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366:787-798.

Harrison CN, Vannucchi AM, Kiladjian J-J, et al. Long-term efficacy and safety in COMFORT-II, a Phase 3 study comparing ruxolitinib with best available therapy for the treatment of myelofibrosis: 5-year final study results [presentation]. Presented at: 57th American Society of Hematology Annual Meeting; December 5-8, 2015; Orlando, FL.

Harrison CN, Vannucchi AM, Kiladjian JJ, et al. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis [published online June 17, 2016]. *Leukemia*. doi: 10.1038/leu.2016.148.

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

Passamonti F, Zaritskey A, Giraldo P, et al. Safety and efficacy of ruxolitinib in patients with DIPSS intermediate-1–risk myelofibrosis (MF) from JUMP: an open-label, multicenter, single-arm, expanded-access study [poster]. Presented at: 21st Annual Meeting of the European Hematology Association; June 9-June 12, 2016; Copenhagen, Denmark.

Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366:799-807.

Verstovsek S, Mesa R, Gotlib J, et al. Long-Term Outcomes of Ruxolitinib Therapy in Patients With Myelofibrosis: 5-Year Final Efficacy and Safety Analysis From COMFORT-I [abstract and presentation]. Presented at the 21st Congress of the European Hematology Association; June 9-12, 2016; Copenhagen, Denmark.

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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