**BUSINESS RULES TO DEFINE LINE OF TREATMENT IN MYELOFIBROSIS**

**Inclusion/exclusion criteria**

* No other primary cancer diagnosis within the previous 2 years of index diagnosis, or the available lookback period, whichever is shorter
* Clear lookback (no other MF diagnosis or drug usage) of minimum \_\_\_ months
* Age to exceed 18

**Relevant diagnosis codes\*:**

Primary MF: Incidence of Primary MF (ICD9 code 238.76),

Secondary MF: SMF (ICD 9 code 289.83) with prior diagnosis of PV (ICD9 code 238.4) or ET (ICD9 Code 238.71) reported in last 12 months

**Line of Treatment in Myelofibrosis**

1. The usage of each MF drug will be analyzed individually:
2. Treatment period with a drug would be the period from the first date of use to the last date of use as determined after applying days supply to each drug usage (dayssup is assumed to be to be 30 days (in case the data is not present in claims data or dayssup is less than 15 days) for all oral therapies while that for injectable would be the last Rx date plus estimated clinical benefit of 30 days); the latter is the earliest date when there is at least a 60 day gap before the next claim of the same MF drug.
3. A drug used multiple times with a gap of more than 60 days will have multiple treatment periods (start dates and end dates)
4. For an oral therapy, the end date for each treatment period would be the last Rx date in that treatment period + days supply (dayssup is assumed to be to be 30 days (in case the data is not present in claims data or dayssup is less than 15 days) for all oral therapies while that for injectable would be the last Rx date plus estimated clinical benefit of 30 days).

(Analysis of claims data showed that in >95% of drug claims, difference between two consecutive prescriptions is less than 60 days. Therefore, period of 60 days has been considered)- *need to replicate same analysis for MF*

1. Once the different treatment periods of each MF drug have been identified, these periods are lined up such that the entire treatment duration for a patient is broken up into multiple intervals, each with a distinct regimen (i.e. a single drug or a combination of drugs). Each such successive interval is deemed to be a different line of treatment for a patient, subject to the below stipulations:
2. If a regimen comprises of Jakafi (only drug approved to treat MF patients) and any other MF drug, the regimen will be replaced with only Jakafi.
3. If a regimen comprises an ‘other MF drug(s)’ along with a steroid, the regimen will be replaced with only the ‘other MF drug(s)’. In other words, the steroid will be deleted from the regimen. If this regimen is <=30 days, disregard the regimen and replace by a blank
4. If a regimen comprises only a steroid(s), the regimen will be disregarded and replaced by a blank, if the duration of the regimen is <=30 days. Else, the regimen will stand and no change or adjustment will be made
5. Upon completion of each of steps a-c and prior to proceeding to next step, all successive LOTs that are identical (regimens should be exactly the same) and occur without any gap between them will be merged into the same LOT
6. **If there is a blank regimen of less than 30 days:** 
   1. If preceding and succeeding regimens are the same; then the preceding regimen will be deemed to continue till the end date of the regimen succeeding the blank regimen.
   2. If the preceding and succeeding regimens are different then these would be considered as two different regimens and the blank regimen will be disregarded.

(RATIONALE FOR THE ABOVE: During treatment with any regimen, a gap of up to 30 days could exist on account of compliance or adverse events. Therefore, i) if the preceding and succeeding regimens are similar, the 2 periods would be treated as continuous; ii) In all other cases they would be treated as two different regimens- *to be examined*

1. **If there is a blank regimen of between 30 and 60 days:**
2. If preceding and succeeding regimens are the same; then the preceding regimen will be deemed to continue till the end date of the regimen succeeding the blank regimen.
3. Either preceding and succeeding regimens are different then these would be considered as two different regimens and the blank regimen will be disregarded.

(RATIONALE FOR THE ABOVE: During treatment with any regimen, a gap of up to 60 days could exist on account of compliance or adverse events. Therefore, i) if preceding and succeeding regimen are similar, both would be merged, and ii) if preceding and succeeding regimen are not similar then they would be treated as two different regimens- *to be examined*

1. **If there is a blank regimen of more than 60 days:**
2. Preceding and succeeding regimens would be considered as two different regimens irrespective of both being the same or if both are different. The blank regimen will be disregarded.
3. Every LOT so formed (and comprising either Busulphan/ Melphalan/cyclophosphamide, etc) on the basis of 1 and 2 above will be checked to see if there is evidence of allogenic SCT within 15-21 days of the end of the preceding regimen. If there is,
   1. The SCT will be considered part of the same LOT as the MF related drug (which will be the conditioning regimens)

**List of drugs to be considered for MF:-**

For hematological symptoms:

* Erythropoiesis stimulating agents (erythropoietin)
* Androgenic agents (Danazol, Nandrolone, ﬂuoxymesterone, methandrostenolone, and oxymetholone, etc.)
* ImiDs (Thalidomide/lenalidomide/pomalidomide)
* Corticosteroids (Prednisolone) – palliative care in case all the drugs fail

For Splenomegaly:

* Jakafi (Ruxolitinib)
* Hydroxyurea
* Busulphan
* Melphalan

Conditioning regimen before allo-SCT

* Myeloablative SCT: Busulphan and cyclophosphamide
* RIC: Fludarabine and busulphan

\*Reference:

We have considered Post PV-MF and Post ET-MF as SMF based on the following guidances:

         Most of the treatment practice guidelines consider MF post ET and post PV as secondary MF and these patients are essentially treated similar to PMF

(Source: 1. [Cervantes, Blood, 2014, 124 (17)](http://www.bloodjournal.org/content/124/17/2635?sso-checked=true); 2. [Jakafi Label](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202192s009lbl.pdf) for MF patients is in patients with either PMF or post PV-MF and post ET-MF).

         Most of the ongoing trials in MF include patients, who are either PMF or have progressed to MF from PV and ET.

o   Imetelstat trials: [NCT02426086](https://clinicaltrials.gov/ct2/show/NCT02426086); [NCT01731951](https://clinicaltrials.gov/ct2/show/NCT01731951?cond=myelofibrosis&intr=imetelstat&rank=1)

o   Pacritinib trials: [PAC-326](https://clinicaltrials.gov/ct2/show/NCT02055781?cond=myelofibrosis&intr=pacritinib&rank=1); [PERSIST-1/PAC325](https://clinicaltrials.gov/ct2/show/NCT01773187?cond=myelofibrosis&intr=pacritinib&rank=2)

o   Momelotinib trials: [SIMPLIFY-1](https://clinicaltrials.gov/ct2/show/NCT01969838?cond=myelofibrosis&intr=momelotinib&rank=1); [SIMPLIFY-2](https://clinicaltrials.gov/ct2/show/NCT02101268?cond=myelofibrosis&intr=momelotinib&rank=3); [NCT01423058](https://clinicaltrials.gov/show/NCT01423058) ; [NCT02515630](https://clinicaltrials.gov/show/NCT02515630) ; [NCT01236638](https://clinicaltrials.gov/show/NCT01236638)