TUMOR ZENTRUM Oberösterreich

BCR/ABL- negative MPN
MYELOFIBROSE
Medizinische Leitlinie

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Myelofibrose- JAK Inhibitoren

	Ruxolitinib (JAKAVI), Novartis	Fedratinib (INREBIC), BS	Momelotinib (OMJJARA), GSK	Pacritinib (VONJO), CTI Biopharma
Wirkmechanismus	JAK**1/2**	JAK(1)/**2**	JAK**1/2**/**ACVR1**	JAK**2**/**IRAK1**/**ACVR1**
FDA approval	11/ 2011	8/ 2019	9/ 2023	2/ 2022
EMA approval	17/ 2012	3/ 2021	11/2023 (positive opinion)	n.a.
Zugelassene Indikationen	Splenomegalie oder Symptome bei MF	Splenomegalie oder Symptome bei MF	Splenomegalie oder Symptome bei MF mit moderater-schwerer Anämie	n.a.
Dosierung	**Max 25mg 2x/ Tag (abhängig von PLT)**	**400mg/Tag (PLT <50G/L)**	**200mg/ Tag**	**200mg 2x/ Tag (PLT<50G/**L)
Nebenwirkungen	Anämie Thrombopenie Opport. Infektionen Withdrawl Syndrom	Anämie Thrombopenie Anstieg Leberwerte Amylase/ Lipase Wernicke Enzephalopathie (selten)	Thrombopenie Anstieg Leberwerte Amylase/ Lipase PNP Schwindel	Diarrhoe Ödeme Pneumonien Herzinsuffizienz

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Randomized TKI studies in MF

	RUXOLITINIB		FEDRATINIB	MOMELOTINIB			PACRITINIB	
Study name	**COMFORT-1**	**COMFORT-2**	**JAKARTA-1**	**SIMPLIFY-1**	**SIMPLIFY-2**	**MOMENTUM**	**PERSIST-1**	**PERSIST-2**
Enrollment	309	219	289	432	156	195	327	311
Study completion	2015	2015	2014	2019	2019	2022	2016	2016
Study design	Ph3, Randomized, double blind	Ph3, Randomized, Open-label	Ph3, Randomized, double blind	Ph3, Randomized, double blind	Ph3, Randomized, Open label	Ph3, Randomized, double blind	Ph3, Randomized, Open-label	Ph3, Randomized, Open-label
Treatment	Ruxolitinib vs placebo	Ruxolitinib vs BAT, crossover	Fedratinib 400 or 500 mg vs placebo	Momelotinib vs Ruxolitinib	Momelotinib vs BAT	Momelotinib vs Danazol	Pacritinib vs BAT	Pacritinib vs BAT (in pat. with low PLT)

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Cross-Study Comparisons of JAK2 Inhibitors in MF

Table 2 Impact of JAK Inhibitors on Cytopenias in Randomized Myelofibrosis Studies

	PERSIST-1[8] PAC 400 mg QD N = 220	PERSIST-2[5,9] PAC 200 mg BID N = 106	PERSIST-2[5,9] PAC 400 mg QD N = 104	COMFORT-1[3] RUX N = 155	COMFORT-2[4] RUX N = 146	JAKARTA-1[10] FED 400 mg QD N = 96	SIMPLIFY-1[11] MMB N = 215	SIMPLIFY-1[11] RUX N = 217	SIMPLIFY-2[16] MMB N = 104	MOMENTUM[17] MMB N = 130	MOMENTUM[13] PLT <100 × 10⁹/L MMB N = 66 (subgroup)	MOMENTUM[13] PLT <50 × 10⁹/L MMB N = 18 (subgroup)
Prior JAK2 inhibitor	0%	45%	44%	0%	0%	0%	0%	0%	100%	100%	100%	100%
PLT (x10⁹/L) for eligibility	Any	≤100	≤100	≥100	≥100	≥50	≥50	≥50	Any	≥25	≥25 to 100 subgroup	≥25 to 50 subgroup
Baseline PLT x10⁹/L, median	166[a]	55	55[a]	262	244	221	301 (mean)	301.5 (mean)	171 (mean)	97		
Thrombo. (all grade)	23%	34%	33%	70%	68%	63%	19%	29%	13%	76%[b]	35%	44%
Thrombo. (grade 3/4)	17%	32%	31%	13%	8%	17%	7%	5%	7%	28%[b]	33%	44%
Baseline HB g/dL, median	10.6[a]	9.7	9.15[a]	10.5	10.9 (mean)	10.7	10.6 (mean)	10.7 (mean)	9.4 (mean)	8.0	8.1 (mean)	7.7 (mean)
Anemia (all grade)	30.5%	24%	28%	96%	96%	99%	14%	38%	18%	99%[b]	15%	28%
Anemia (grade 3/4)	26%	22%	27%	45%	42%	43%	6%	23%	14%	61%[b]	9%	22%

Abbreviations: BID = twice daily; FED = fedratinib; HB = hemoglobin; MMB = momelotinib; PAC = pacritinib; PLT = platelet; QD = once daily; RUX = ruxolitinib; Thrombo = thrombocytopenia.
[a] Data on file; CTI BioPharma Corp.
[b] Data based on laboratory values. The data shown are for events of the worst grade during the first 24 weeks of study, regardless of whether this grade was a change from baseline.

Mascarenhas J, Mesa R. Cross-Study Comparisons of JAK2 Inhibitors in Myelofibrosis: Risks and Recommendations. Clin Lymphoma Myeloma Leuk. 2023 Oct;23(10):714-718. doi: 10.1016/j.clml.2023.06.004. Epub 2023 Jun 9. PMID: 37357030.

Cross-Study Comparisons of JAK2 Inhibitors in Myelofibrosis

Table 1 JAK Inhibitor Efficacy (Week 24) in Front-Line Myelofibrosis Studies

	PERSIST-1[8] PAC 400 mg QD N = 220	PERSIST-2[9] PAC 200 mg BID N = 43 ruxolitinib naïve	COMFORT-1[3] RUX N = 155	COMFORT-2[4] RUX N = 146	JAKARTA-1[10] FED 400 mg QD N = 96	SIMPLIFY-1[11]	
						MMB N = 215	RUX N = 217
PLT ($x10^9$/L) exclusion	None	Greater than 100	Less than 100	Less than 100	Less than 50	Less than 50	Less than 50
Baseline PLT ($x10^9$/L), median	166[a]	51	262	244	221	301 (mean)	301.5 (mean)
SVR35, (%)	19%	28%	42%	32%	36%	27%	29%
TSS50[b], (%)	NR	37%	46%	N/A	36%	28%	42%

Abbreviations: BID = twice daily; FED = fedratinib; MMB = momelotinib; PAC = pacritinib; PLT = platelets; QD = once daily; RUX = ruxolitinib; SVR35 = spleen volume reduction of ≥35% from baseline; TSS50 = total symptom score response of ≥50% from baseline.

[a] Data on file; CTI BioPharma Corp.

[b] ITT analysis of TSS v2.0, excluding tiredness.

Mascarenhas J, Mesa R. Cross-Study Comparisons of JAK2 Inhibitors in Myelofibrosis: Risks and Recommendations. Clin Lymphoma Myeloma Leuk. 2023 Oct;23(10):714-718. doi: 10.1016/j.clml.2023.06.004. Epub 2023 Jun 9. PMID: 37357030.

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MF- Empfehlung zur Wahl des 1. TKI

Ausgangswert Hb, mg/dl	Ausgangswert PLT, G/L	1. Wahl TKI
>10	>100	Ruxolitinib
>10	50-100	Fedratinib
<10	Any above 25	Momelotinib

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MF Studien OKL Elisabethinen

Entität	Therapie	First line	Second line (Vortherapie)	Ein/Ausschlusskriterien	Start	laufende Patienten
MF	**Navitoclax + Ruxolitinib vs BAT** **(Ph III, M20-178, Transform-2)** LENA		**X** **(Ruxo)**	**INCL**: DIPSS+ mind. interm.-2, Ruxo Intolerance oder suboptimal response, spleen palpable OR spleen volume ≥ 450 cm^3 (MRI) **EXCL**: prior JAK2 inhibitor (except Ruxo), BET inhib.	laufend	**2**
MF	**Luspatercept vs Placebo** **(Celgene, ACE-536-MF-002)** LENA		**X** **(JAK inhib)**	**INCL**: requiring RBC transfusions (4-12 RBC/ 12 weeks), continuous JAK2 inhibitor ≥ 8 months	laufend	**1**
MF	**Imetelstat vs BAT** **(PhIII, Geron Corp. MYF 3001, Impact MF)** ANDREA		**X** **(JAK inhib)**	**INCL**: DIPSS intermediate-2 or high-risk; refractory to JAK-inhibitor treatment, spleen palpable OR spleen volume ≥ 450 cm^3 (MRI/CT) **EXCL**: PB blasts ≥ 10% or BM blasts ≥ 10%	laufend	**1**
MPN	**MyeloPro (Biosampling Study)** ANNA	**X**	**X**	**INCL**: alle CALR oder MPL positiven MPN Pat.	laufend	**60**

Abstimmung durch die Leitliniengruppe

(a) Die Leitlinie wird ohne Einschränkung freigegeben

(b) Die Leitlinie wird nach Umsetzung der protokollierten Inhalte freigegeben

(c) Die Leitlinie wird aufgrund der protokollierten Inhalte / Einwände nicht freigegeben