Final Report of the Trial MPNSG 02-12

Title	A Phase-Ib/II Study of Ruxolitinib and Pomalidomide Combination Therapy in Patients with Primary and Secondary Myelofibrosis - The POMINC Study –
Project Code	POMINC (MPNSG 02-12)
Active Substances/Finished Products	Ruxolitinib (INCB018424, Jakavi®) Pomalidomide (CC-4047, Imnovid®)
Protocol Number	Version 2.0
Positive initial Vote of the Ethics Committee	23.07.2013
Termination of the Trial	27.04.2024
Sponsor	University Hospital of Ulm, represented by the Chairman of the Board
EudraCT Number	2012-002431-29

1. Name of sponsor/company

1.1 Sponsor

University Hospital of Ulm, represented by the Chairman of the Board

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2. Name of finished product

Ruxolitinib (marketed product name: Jakavi®)

Pomalidomide (marketed product name: Imnovid®)

3. Name of active substances

Ruxolitinib

Pomalidomide

4. Individual study table

Not applicable

5. Title of the study

A Phase-Ib/II Study of Ruxolitinib and Pomalidomide Combination Therapy in Patients with Primary and Secondary Myelofibrosis - The POMINC Study -

Initial approved version of study protocol:

Protocol version V1.1 (Dated: 27.06.2013)

Amendments of the protocol:

Protocol version V1.4 (Dated: 07.01.2014)

Protocol version V2.0 (Dated: 28.03.2017)

This report refers to the current version of study protocol:

Protocol version V2.0 (Dated: 28.03.2017)

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8. Publication reference

Final study results will be published in an international peer-reviewed journal.

9. Studied period

First patient in: 19.08.2013

Last patient last visit: 27.04.2024

Recruitment was interrupted twice during the study period. First interruption was from 25.03.2014 until 02.07.2014 due to a safety assessment after enrolment of the first 6 patients and treatment for at least one cycle of 28 days, each.

The second interruption took place from 06.02.2017 until 10.08.2017 due to a protocol amendment with implementation of a second cohort treated with sequentially increased dosages of pomalidomide.

10. Phase of Development

Phase Ib/II

11. Objectives

Primary Objective

Evaluation of clinical efficacy of ruxolitinib and pomalidomide combination therapy in myelofibrosis patients based on i) consensus criteria of the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT), ii) the criterion red blood cell transfusion independence (RBC-TI), and iii) clinical benefit after 12 28-day-cycles (CB, cohort 2 only)

Secondary Objectives

- Evaluation of response duration, progression-free survival, and overall survival
- Assessment of quality of life

Safety Objectives

Evaluation of the safety of combination therapy with ruxolitinib and pomalidomide

12. Methodology

Study Design

Open-label, single-arm, multi-center, phase Ib/II study with oral pomalidomide and ruxolitinib in adult patients with primary or secondary myelofibrosis as defined in inclusion/exclusion criteria.

In total, 96 patients have been screened of which 92 patients were eligible and enrolled (Figure 1); cohort 1, n=39 (19.08.2013 - 06.02.2017) and cohort 2, n=53 (23.08.2017 - 27.04.2021). Cohort 2 started after approval of protocol amendment version 2.0 with adjustment of pomalidomide dosing and response criteria.

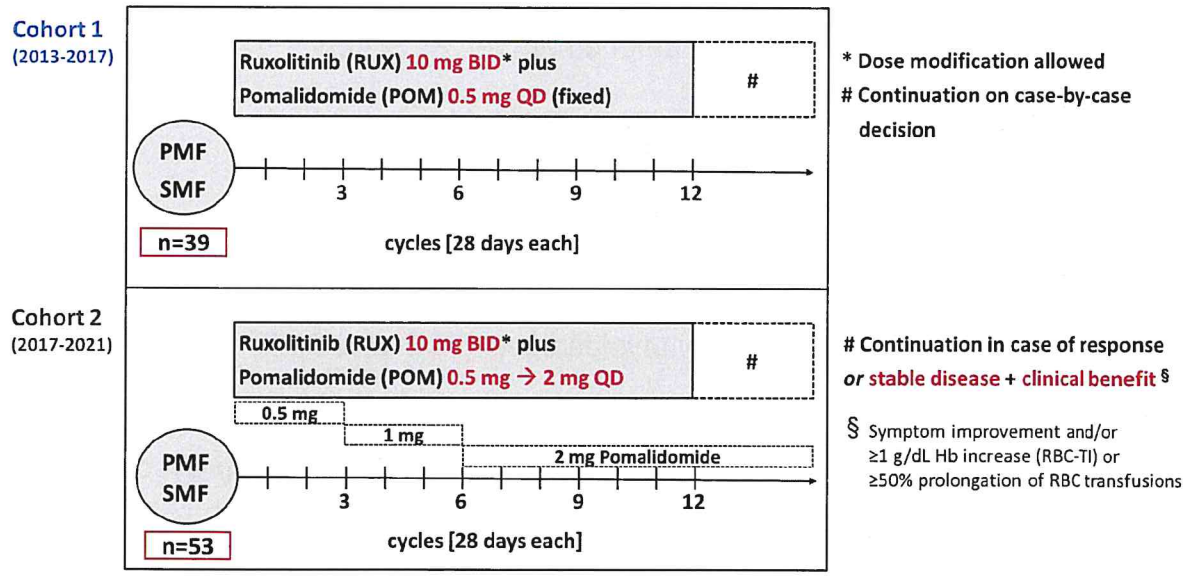

Figure 1. Design of the single-arm, phase-Ib/II combination study with sequential enrolment of 92 patients in two different cohorts. In cohort 2, pomalidomide dosing and response assessment were adjusted (PMF/SMF, primary/secondary myelofibrosis).

Treatment

All patients in cohort 1 received oral pomalidomide 0.5 mg once daily (QD); ruxolitinib was started per os at 10 mg twice daily (BID). While pomalidomide dosing was fixed in cohort 1, dose adjustments of ruxolitinib (increase or decrease) were allowed in case of myelosuppression and/or persisting symptoms of myelofibrosis. Tolerability and response were evaluated every 28 days until end of cycle 12 and three-monthly thereafter. Treatment was continued beyond cycle 12 on a case-by-case decision.

In cohort 2, ruxolitinib treatment was started at 10 mg BID with the possibility of dose adjustments like in cohort 1, while pomalidomide was increased from 0.5 to 1 mg QD after three and 2 mg QD after six cycles, respectively. As in cohort 1, tolerability and response were assessed every 28 days until end of cycle 12 and three-monthly thereafter. Treatment continuation beyond cycle 12 was intended in patients with on-going IWG-MRT or RBC-TI response and in patients with stable disease plus clinical benefit (CB).

CB in cohort 2 was defined as prolongation of RBC transfusion intervals by at least 50% compared to baseline in transfusion dependent patients or by an at least 1 g/dL hemoglobin (Hb) increase in the absence of RBC transfusions and/or by an improvement of symptoms according to the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): one symptom improved by ≥50% and/or two symptoms ≥25%.

13. Number of patients

Number of patients planned (before amendment no. 2): n=72

Number of patients recruited (before amendment no. 2): n=41 (cohort 1; n=1 not eligible, n=1 not evaluable)

Number of patients planned (after amendment no. 2): cohort 1: n=37; cohort 2: n=53

Number of patients recruited (after amendment no. 2): cohort 1: n=41 (n=1 not eligible; n=1 not evaluable); cohort 2: n=55 (n=2 not eligible)

Number of patients analysed: cohort 1: n=39; cohort 2: n=53

14. Diagnosis and main criteria for inclusion/exclusion

Diagnosis: Primary and secondary myelofibrosis (PMF and SMF)

Inclusion Criteria:

1. Age ≥18 years at the time of voluntarily signing an IRB/IEC-approved informed consent
2. Diagnosis of Myeloproliferative Neoplasms (MPN) either de novo myelofibrosis according to current WHO criteria (PMF), secondary myelofibrosis (post-PV MF and post-ET MF) according to the IWG-MRT consensus terminology
3. Anemia with hemoglobin level of <10 g/dL or transfusion-dependent anemia (last transfusion within the last 28 days)
4. Splenomegaly (>11 cm total diameter) and/or leukoerythroblastosis

5. Adequate organ function, i.e. ALT and/or AST <3 x upper limit of normal (ULN), total bilirubin <3 x ULN, and serum creatinine <2 mg/dL
6. Subject must be willing to receive transfusion of blood products
7. ECOG performance status <3
8. Females of childbearing potential (FCBP) must undergo repetitive pregnancy testing (serum or urine) and pregnancy results must be negative
9. Reliable contraception should be maintained throughout the study and for 28 days after study treatment discontinuation
10. Unless practicing complete abstinence from heterosexual intercourse, sexually active FCBP must agree to use adequate contraceptive methods
11. Males (including those who have had a vasectomy) must use barrier contraception (condoms) when engaging in sexual activity with FCBP. Males must agree not to donate semen or sperm
12. All subjects must:
    - understand that the investigational product (in particular pomalidomide) has potential teratogenic risk.
    - be regularly counselled about pregnancy precautions and risk of fetal exposure.
    - agree to abstain from donating blood while receiving investigational product, during dose interruptions and for at least 28 days after last dose.
    - agree not to share study medication with another person and to return all unused study drug to the investigator

Exclusion Criteria:

1. Patients eligible for hematopoietic stem cell transplantation (suitable candidate and suitable donor is available)
2. Patients with response to standard therapy as recommended by the Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO/Onkopedia)
3. Pregnant or breast-feeding females
4. *BCR/ABL*-positivity
5. Diagnosis of ET (according to WHO 2016 criteria)
6. Diagnosis of PV (according to WHO 2016 criteria)
7. >20% blasts in peripheral blood or bone marrow
8. thrombocytopenia <100/nL or transfusion-dependent thrombocytopenia
9. neutropenia <0.5/nL
10. Known positive status for HIV, HBV or HCV
11. Prior treatment with immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide) or with Interferon-alpha within a 3-months time-period before Screening-phase
12. Patient treatment with ruxolitinib within 14-days before screening-phase
13. History of thrombosis or pulmonary embolism within 6 months prior to study entry
14. Peripheral neuropathy >grade 1 CTC
15. No consent for registration, storage and processing of the individual disease-characteristics and course as well as information of the family physician about study participation
16. Presence of any medical/psychiatric condition or laboratory abnormalities which may limit full compliance with the study, increase the risk associated with study participation or study drug administration, or may interfere with the interpretation

of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study
17. Drug or alcohol abuse within the last 6 months
18. History of malignancy except for i) adequately treated local basal cell or squamous cell carcinoma of the skin, ii) asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥1 year prior to randomization, or iii) any other cancer that has been in complete remission for ≥5 years
19. Patients undergoing treatment with hematopoietic growth factor receptor agonists (i.e., erythropoietin [EPO], granulocyte colony stimulating factor [G-CSF], romiplostim, eltrombopag [TPO]) within a 4-weeks period prior to screening-phase
20. Patients receiving any medication listed in the Appendix V of protocol "Prohibited Medications" (within 7 days prior to the first dose of study drug)
21. Patients with clinically significant bacterial, fungal, parasitic or viral infection which require therapy. Patients with acute bacterial infections requiring antibiotic use should delay screening/enrolment until the course of antibiotic therapy has been completed
22. Patients under ongoing treatment with another investigational medication or having been treated with an investigational medication within 28 days of screening
23. No consent for biobanking
24. Patients who cannot adhere to the Pregnancy Prevention Plan

15. Test product, dose and mode of administration, batch number

The Investigational Medicinal Products (IMP) in this study were pomalidomide (Imnovid®) and ruxolitinib (Jakavi®).

Pomalidomide was supplied in capsules of 0.5 mg, 1 mg and 2 mg and taken orally once daily. Ruxolitinib was provided in capsules of 5 mg and taken orally twice a day. Pomalidomide was supplied by Celgene and after completed takeover by Bristol-Myers Squibb (BMS). Celgene resp. BMS was responsible for the labeling of the study drug according to legal requirements. Pomalidomide was shipped from Celgene resp. BMS to the pharmacy at the University Hospital Ulm after order by the pharmacist. The IMP was stored at the pharmacy under controlled conditions and sent to each site after order for each patient and each cycle separately.

Ruxolitinib was supplied by Novartis. Novartis was responsible for the labeling of the study drug according to legal requirements. Ruxolitinib was sent to each site after order for each patient and each cycle separately directly from Novartis.

The following batch numbers were used:

Pomalidomide:

12F0709, 13F0005, 14F0801, 16F1637, 16F1640, 16F2321, 16F2399, 18F0376, 18F0411, 18F0412, 18F0738, 19F0058, 19F0262, 19F0268, 20F0074, 20F0083, 20F0865, 21F0228, 21F0231, 22F0410, 23F0134

Ruxolitinib:

H927LH, S0001, S0002C, S0013A, S0013X, S0024, S0032, S0035, SAUL2, SDE95, SELR9, SER34, SHC61, SHP17, SHXY3, SJ599, SJUY7, SKM43, SKVX7, SNE16, SPY80, SVW42, SWA34, SWD53, SX886

16. Duration of treatment

The estimated treatment duration of an individual patient was 12 28-day-cycles. Treatment was continued beyond cycle 12 in selected patients as outlined before (see **12. Methodology** → Treatment). A follow-up observation period of up to 3 years after stop of study treatment was intended.

17. Reference therapy, dose and mode of administration, batch number

Not applicable.

18. Criteria for evaluation: efficacy, safety

The frequency and timing of efficacy and safety measurements were defined in the study protocol.

Efficacy Measurements

Efficacy assessments were based on analysis of full blood count, bone marrow histology and clinical examination.

Analysis of full blood count was done at baseline, day 1, day 14, day 28 and every 28 days thereafter. During the follow-up period it was done every 3 months.

Bone marrow histology was done at baseline, at the end of cycle 6 and 12 and once a year thereafter.

Clinical examination was obtained at the end of each cycle and 3-monthly during the follow-up period.

The response to treatment was evaluated based on criteria defined by the IWG-MRT and on the criterion RBC-TI. After implementation of amendment version 2.0 the response criteria were extended by the explorative criterion clinical benefit after 12 28-day-cycles (CB, see Appendix A).

Primary Efficacy Variable

The primary efficacy variable for this trial was treatment response according to IWG-MRT (complete remission, CR, partial remission, PR, and clinical improvement, CI) as well as RBC-TI.

Secondary Efficacy Variables

Secondary efficacy variables were clinical benefit (CB), progression-free survival, overall survival, and quality of life. Quality of life was assessed using the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF).

Safety Measurements

Safety endpoint variables in this study were:

- Hematological (thrombocytopenia, anemia, and neutropenia) and non-hematological toxicities. All adverse events / toxicities are graded according to NCI CTCAE Version 3.0

In this study, safety was assessed by evaluating the following: reported (serious) adverse events, clinical laboratory test results, vital signs measurements, physical examination findings. For each safety parameter, all findings (whether normal or abnormal) were recorded in the case report form (CRF).

19. Statistical methods

Response criteria are defined in Appendix A.

Response subsumes CR, PR, CI, and RBC-TI for cohort 1, and CR, PR, CI, RBC-TI, and SD (stable disease) + CB for cohort 2.

Response duration: Time from first response including RBC-TI, CI, PR and CR to date of loss of response. Times of patients without loss of response are censored at last follow up.

Progression-free survival (PFS): Time from study entry to

1. in responding patients to date of loss of response.

2. in patients with SD to date of progressive disease (PD).

Patients without events are censored at last follow up. Death during SD or response is an event.

Overall survival (OS): Time from study entry to the last date known to be alive or death. Survival times of patients alive at last follow-up are censored.

According to amendment version 2.0, the study requires additional 53 subjects to decide whether the proportion responding, p, is less than or equal to 0.300 or greater than or equal to 0.500. If the number of responses is 22 or more, the hypothesis that $p \leq 0.300$ is rejected with a target error rate of 0.100 and an actual error rate of 0.049. If the number of responses is 21 or less, the hypothesis that $p \geq 0.500$ is rejected with a target error rate of 0.100 and an actual error rate of 0.084.

- Intended patient sample size cohort 1: n=37

- Intended patient sample size cohort 2: n=53

- Total intended patient sample size: n= 90

Based on data from previous studies evaluating ruxolitinib and pomalidomide as single agents in myelofibrosis, a response rate of below 30% is estimated as ineffective and above 50% as success. The sample size calculation is based on a one-stage A'Hern design. The one-stage design tests the null hypothesis that $p \leq 0.3$ versus the alternative that $p \geq 0.5$ has a probability of early termination of 0.396. If the drug is not effective, there is a 0.084 probability of concluding that it is. If the drug is effective, there is a 0.049 probability of concluding that it is not.

CB, PFS, and OS are analysed in an explorative manner. Quality of life is assessed using MPN-SAF, EORTC QLQ-C30 and FACT-Lym.

The analysis on the primary and secondary outcome variables in correlation to genetic data is performed using multivariable regression models. Since a substantial number of variables will be included into the regression models, a penalization might be necessary (van Houwelingen, Stat Med 2005; Fan Ann Statist 2002).

Adverse events (AE) were summarized according to type, frequency, severity (graded using the NCI CTCAE Version 3.0), timing and relatedness of adverse events and laboratory abnormalities observed during different treatment cycles.

Incidence rates of adverse events were tabulated and summarised.

For patients with multiple occurrences of the same adverse event, the maximum (worst) grade was used. Summaries are provided for all grades and for grade ≥3 (including grade 5). Missing grades, if any, will be included in the "all grades" category.

Serious AE (SAE) summaries are presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and Preferred Term (PT) version 27.0.

20. Summary: efficacy results, safety results, and conclusion

20.1 Efficacy results

Clinical characteristics: A total of 92 patients were registered and treated, 39 in cohort 1 and 53 in cohort 2. Median age was 72 (cohort 1) and 70 years (cohort 2), respectively. Overall, most patients had PMF (69.6%), were ECOG 0-1 (94.5%) and at intermediate-2 risk (71.7%) according to the Dynamic International Prognostic Scoring System (DIPSS). While median baseline Hb was 8.6 g/dL in both cohorts, 25.6% in cohort 1 and 35.8% in cohort 2 were RBC transfusion-dependent (no statistically significant difference between cohort 1 and 2). Median platelet count was 248/nL. Patients in cohort 2 were significantly more frequently pre-treated with ruxolitinib than patients in cohort 1 (43.4% vs. 15.4%, p=0.006).

Baseline mutation profile: More than 90% of the patients had a driver mutation: 57.6% were *JAK2* V617F, 12.0% *MPL* W515L/K, and 23.9% *CALR* Exon 9 mutated. Regarding additional high-molecular risk (HMR) gene mutations detected by next-generation sequencing analysis, 64.1% (cohort 1) and 58.5% (cohort 2) of patients showed at least one HMR mutation in *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*, *U2AF1*, or *TP53*.

Primary objective and efficacy data: To evaluate the clinical efficacy of ruxolitinib and pomalidomide combination therapy, IWG-MRT/RBC-TI response was assessed after 12 28-day-cycles (patients who did not finish 12 cycles of treatment were counted as non-responders). In cohort 1, 8 patients (20.5%) responded according to one of the following criteria (best response listed): PR, n=1, CI, n=6, and RBC-TI, n=1. In cohort 2 (extended by the criterion CB), 22 patients (41.5%) showed response: CI, n=4, RBC-TI, n=1, CB, n=16.

Duration of treatment/response: Median treatment duration was 12 cycles in both cohorts (cohort 1: range 2-126 cycles, cohort 2: range 4-78 cycles). In cohort 2, pomalidomide dose was increased to 1 mg QD after 3 cycles in 73% and to 2 mg QD after 6 cycles in 40% of patients; 69.2% of patients in cohort 1 and 58.5% in cohort 2 completed 12 cycles of combination treatment; 23.1% of patients in cohort 1 (n=9) 7.5% in cohort 2 (n=4) were treated for more than 40 cycles (Figure 2). Median duration of response was 15 28-day-cycles in cohort 1 (range 8-126) and 9 in cohort 2 (range 2-77).

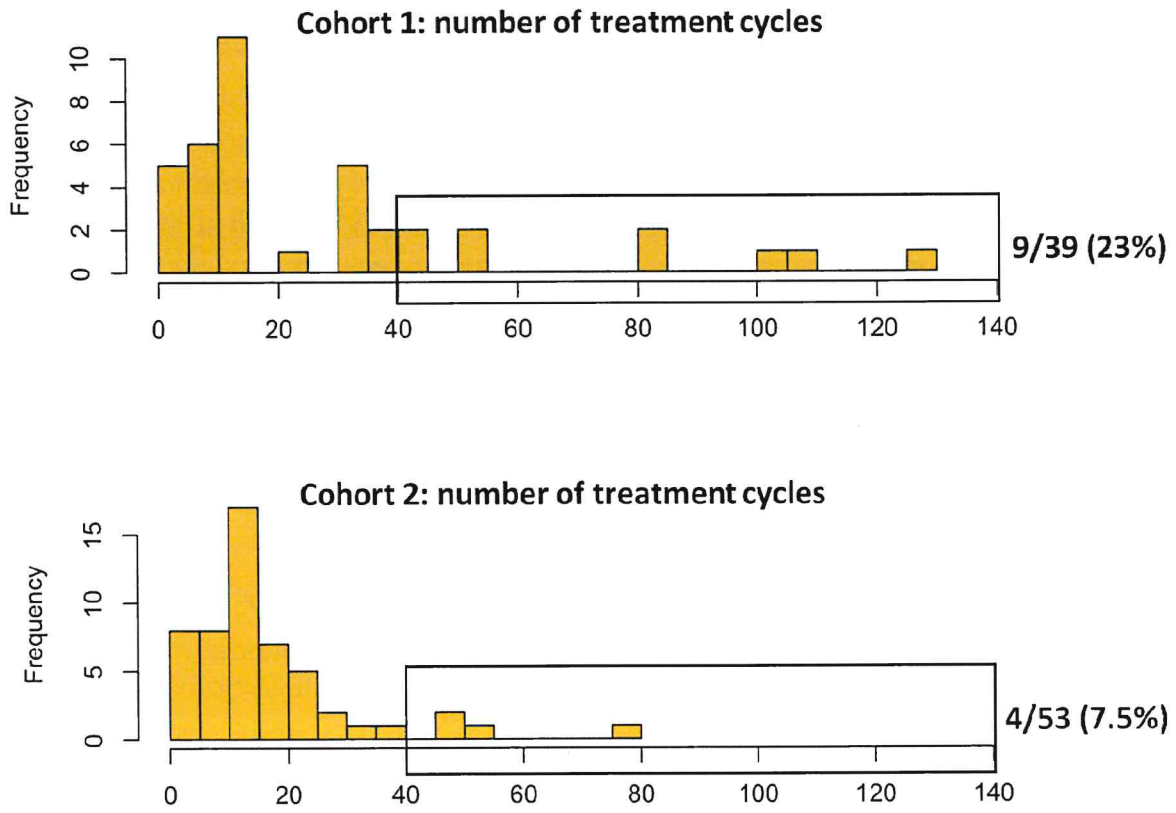

Figure 2: Number of treatment cycles in cohort 1 and 2, respectively. The black rectangle illustrates patients who were treated for more than 40 28-day-cycles.

Overall Survival (OS): Median follow-up was 52.9 months in cohort 1 and 37.3 months in cohort 2. Median OS was 38.4 in cohort 1 and 60.8 months in cohort 2, respectively (Figure 3).

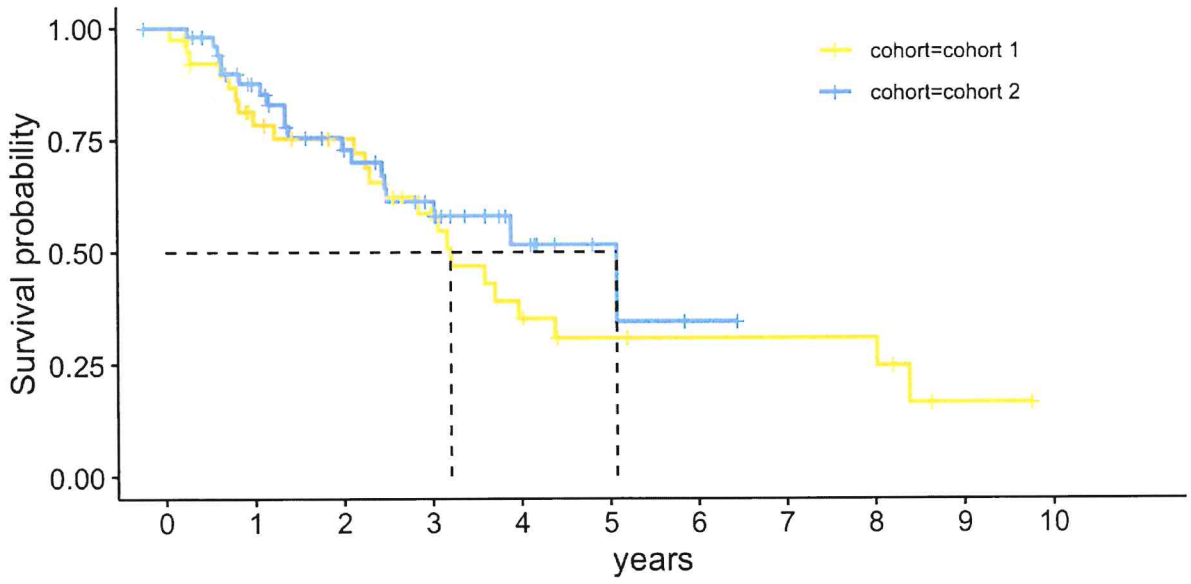

Figure 3: Overall survival probabilities of cohort 1 and 2.

Progression-free survival (PFS): Median PFS was 29.8 months in cohort 1 and 34.3 months in cohort 2 (Figure 4).

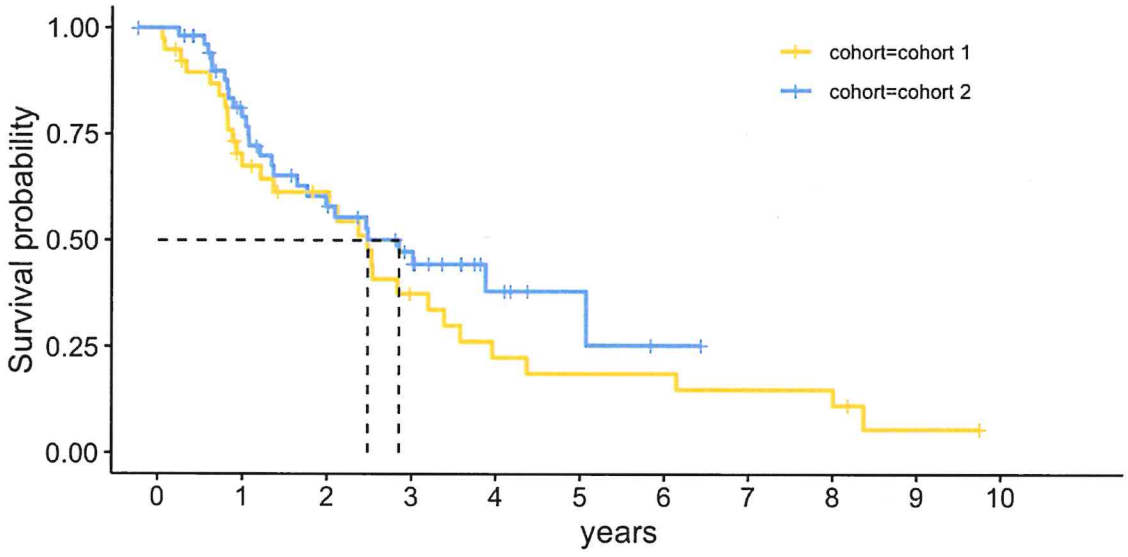

Figure 4: Progression-free survival probabilities of cohort 1 and 2.

Quality of life (QOL): To assess QOL, the mean total MPN-SAF symptom score (27 items, each scaled from 0 [absent] -10 [worst imaginable]) at baseline was compared with the mean symptom score after 12 cycles of combination treatment. In cohort 1, mean baseline score decreased from 2.98 to 2.29 at end of cycle 12 (no statistically significant difference), whereas in cohort 2, the corresponding mean values remained at comparable levels: 2.62 (baseline) and 2.56 (end of cycle 12).

20.2 Safety results

Adverse events (AE): Overall and for all cycles, 1,002 AE were reported in 91/92 (99%) patients of which 390 (38.9%) in 81 patients were considered treatment-related (relation to either of the IMP at least "possible"); 23 AE (2.3%) led to premature termination of study treatment (cohort 1, n=9 and cohort 2, n=14).

AE occurred most frequently in the CTCAE categories ´infection´ (66.3% of the patients), ´blood/bone marrow´ (64.1%), ´pain´ (62.0%), and ´constitutional symptoms´ (51.1%). Regarding AE with a CTCAE grade ≥3, the category ´blood/bone marrow´ was most frequently affected, followed by ´infection´ (28.3%), ´renal/genitourinary´ (13.0%), and ´metabolic/laboratory´ (12.0%).

Other frequently occurring AEs regardless of the CTCAE grade were ´dyspnea´ in 37.0% of patients (30.8% in cohort 1 vs. 41.5% in cohort 2), ´musculoskeletal cramps´ in 31.5% (38.5% in cohort 1 vs. 26.4% in cohort 2), and ´fatigue´ in 31.5% (43.6% in cohort 1 vs. 22.6% in cohort 2).

The most frequently reported AE CTCAE grade ≥3 was ´hemoglobin decreased´ in 38.0% of patients (35.9% in cohort 1 vs. 39.6% in cohort 2), followed by ´infection-

pneumonia´ in 15.2% (12.8% in cohort 1 vs. 17.0% in cohort 2) and ´platelet count decreased´ in 8.7% (10.3% in cohort 1 vs. 7.5% in cohort 2).

Transformation in secondary AML was more frequent in cohort 1 (n=6, 15.4%) than in cohort 2 (n=1, 1.9%) whereas ´neutrophil count decreased´ occurred more often in cohort 2 (11.3%) than in cohort 1 (2.6%).

Serious AE (SAE): Overall, 65 patients (70.6%) had serious adverse events (SAE), n=30 (76.9%) in cohort 1 and n=35 (66.0%) in cohort 2. The most frequent SAE occurring during the whole treatment period were pneumonia (n=12, 13.0% [at least possibly IMP-related, n=4]), acute myeloid leukemia (n=7, 7.6% [possibly IMP-related, n=1]), sepsis (n=6, 6.5% [possibly IMP-related, n=1]) and cerebral ischemia (n=4, 4.3% [IMP-unrelated]).

Deaths: There were 12 (13.0%) deaths reported during study treatment (6 patients, each, in cohort 1 and cohort 2). In cohort 1, four patients died due to infections (pneumonia, n=2, and sepsis, n=2), two patients due to cardiac problems (cardiorenal syndrome, n=1, and cardiac decompensation, n=1). In cohort 2, two patients died due to infections (pneumonia, n=1, COVID-19, n=1) and 4 patients due to other problems with (upper gastrointestinal hemorrhage, sudden death, CNS ischemia, and neurology-paraplegia [n=1, each]).

20.3 Conclusion

Discussion: In cohort 1 of our single-arm, phase-Ib/II trial with pomalidomide and ruxolitinib in MF patients, response rate of the combination treatment was 20.5% after 12 28-day-cycles according to IWG-MRT/RBC-TI criteria. Less patients responded in cohort 2 (11.3%) despite an intensification of pomalidomide dosing when identical response criteria were applied. However, implementation of the criterion ´clinical benefit´(CB) increased the response rate to 41.5% in patients of cohort 2 showing stable disease at end of cycle 12.

Median duration of response (15 cycles in cohort 1 and 9 cycles in cohort 2) was similar to our previous MPNSG 01-09 trial investigating single-agent pomalidomide in MF patients with cytopenia at daily dosages of 0.5 and 2 mg +/- prednisolone, respectively (Schlenk RF, Stegelmann F, et al., Leukemia 2017).

These data underline the feasibility and usefulness of the combination treatment in elderly MF patients who were not suitable for allogeneic transplantation, had an adverse genetic risk, and lacked other options for the treatment of anemia than regular RBC transfusions diminishing quality of life. One needs to keep in mind that the combined JAK2/ACVR1-inhibitor momelotinib alleviating anemia in a subset of MF patients was not yet approved when patients were treated within our MPNSG 02-12 trial.

Median progression-free (~2.5-3 years) and overall survival (~3-4.5 years) of our study population was in the expected range when taking into account that most patients were at intermediate-2 risk according to DIPSS.

One explanation for the superior objective response rates according to IWG-MRT and RBC-TI criteria in cohort 1 might be the significantly higher number of ruxolitinib treatment naive patients in cohort 1 vs cohort 2 (15.4% vs. 43.4%). The mechanism of anemia in patients under JAK-inhibitor may rather reflect – at least in part – drug-induced hematologic toxicity than MF-related anemia caused by the bone marrow

disease *per se*. In addition, to what extent pretreatment with ruxolitinib could contribute to possible resistance mechanism with respect to anemia response is currently unclear.

For safety reasons and due to lack of experience with the combination treatment, patients with co-existing low platelet counts (<100/nL) were excluded from the study. Although a decrease of platelets, neutrophils and hemoglobin was observed in a subset of patients during treatment, the combination therapy was in general feasible in most patients and rarely interrupted or discontinued due to hematologic toxicity. Moreover, further safety data of our trial did not raise new concerns with the use of either of the drugs in patients with advanced MF.

There was a subset of patients in our study showing very good (e.g. one patient with PR in cohort 1) and/or long-term response to the combination treatment (e.g. 23.1% of patients in cohort 1 were treated for >40 cycles). These data suggest that a subset of patients benefits the most from treatment with ruxolitinib and pomalidomide. Ongoing explorative analyses including data from next-generation sequencing analysis will significantly contribute to better characterize and identify such patients.

Overall conclusion: Combination treatment with ruxolitinib and pomalidomide was safe and feasible in our highly advanced MF study population. Best results were obtained in JAK-inhibitor naïve patients with low-dose pomalidomide (0.5 mg QD) and ruxolitinib 10 mg BID. The subset of patients achieving best response and long-term benefit from combination therapy remains to be identified and will be explored in ongoing studies.

21. Date of Report

Date 22.04.2025

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Appendix A: Response Criteria

International Working Group for Myelofibrosis Research and Treatment Response (IWG-MRT) Criteria *(Tefferi A et al, Blood 2006)*

Complete remission (CR):

- Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly.
- Peripheral blood count remission defined as hemoglobin level at least >11 g/dL, platelet count at least 100 x 10^9/L, and absolute neutrophil count at least 1.0 x 10^9/L. In addition, all 3 blood counts should be no higher than the upper normal limit.
- Normal leukocyte differential including disappearance of nucleated red blood cells and immature myeloid cells in the peripheral smear, in the absence of splenectomy.*
- Bone marrow histologic remission defined as the presence of age-adjusted normocellularity, no more than 5% myeloblasts, and an osteomyelofibrosis grade no higher than 1.**

Partial remission (PR):

Requires all of the above criteria for CR except the requirement for bone marrow histologic remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill criteria for CR.

Clinical improvement (CI):

Requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment (CI response is validated only if it lasts for no fewer than 8 weeks).

- A minimum 2 g/dL increase in hemoglobin level or becoming transfusion independent (applicable only for patients with baseline hemoglobin level of less than 10 g/dL).§
- Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable.§§
- A minimum 100% increase in platelet count and an absolute platelet count of at least 50 x 10^9/L (applicable only for patients with baseline platelet count below 50 x 10^9/L).
- A minimum 100% increase in ANC and an ANC of at least 0.5 x 10^9/L (applicable only for patients with baseline absolute neutrophil count below 1 x 10^9/L).

Progressive disease (PD):

Requires one of the following: ¶

- Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at greater than 5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of greater than 10 cm.
- Leukemic transformation confirmed by a bone marrow blast count of at least 20%.
- An increase in peripheral blood blast percentage of at least 20% that lasts for at least 8 weeks.

Stable disease (SD):

None of the above.

Relapse (RD):

Loss of CR, PR, CI and RBC-TI. In other words, a patient achieving CR, PR, CI or RBC- TI is considered to have undergone relapse when the criterion RBC-TI as the weakest response criterion is no longer fulfilled. However, changes in response graduation are documented and reported.

* Because of subjectivity in peripheral blood smear interpretation, CR does not require absence of morphological abnormalities of red cells, platelets, and neutrophils.

** In patients with CR, a complete cytogenetic response is defined as failure to detect a cytogenetic abnormality in cases with a pre-existing abnormality. A partial cytogenetic response is defined as 50% or greater reduction in abnormal metaphases. In both cases, at least 20 bone marrow- or peripheral blood derived metaphases should be analyzed. A major molecular response is defined as the absence of a specific disease- associated mutation in peripheral blood granulocytes of previously positive cases. In the absence of a cytogenetic/ molecular marker, monitoring for treatment-induced inhibition of endogenous myeloid colony formation is encouraged. Finally, baseline and post-treatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process.

§ Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the last month for a hemoglobin level of less than 8.5 g/dL that was not associated with clinically overt bleeding. Similarly, during protocol therapy, transfusions for a hemoglobin of 8.5 g/dL or more is discouraged unless it is clinically indicated.

§§ In splenectomized patients, palpable hepatomegaly is substituted with the same measurements.

¶ It is acknowledged that worsening cytopenia might represent progressive disease but its inclusion as a formal criterion was avoided because of the difficulty distinguishing disease-associated from drug-induced myelosuppression. However, a decrease in hemoglobin of ≥2 g/dL, a 100% increase in transfusion requirement, and new development of transfusion dependency, each lasting for more than 3 months after the discontinuation of protocol therapy can be considered disease progression.

RBC-transfusion dependence (RBC-TD) ***(Gale RP et al., Leuk Res. 2011)***
RBC-transfusion dependence is defined by an average transfusion volume of 2U RBC/month over a 3-month interval.

RBC-transfusion-independence (RBC-TI) ***(Gale RP et al., Leuk Res. 2011)***
RBC-transfusion independence is defined by a 3-month interval to be the shortest appropriate surveillance interval to define a person as being RBC-transfusion-independent after an interval of having been RBC-transfusion-dependent. The definition of RBC-transfusion independence does not require a minimum hemoglobin level nor does it require a minimum hemoglobin increase from baseline.

Clinical benefit (CB):

- **Stable disease (SD) plus hematologic improvement:** prolongation of RBC transfusion intervals by ≥50% compared to baseline in transfusion dependent patients *or* ≥1 g/dL Hb increase in the absence of RBC transfusion dependency *and/or*
- **Stable disease (SD) plus improvement of MF-associated symptoms:** SD plus improvement of at least one MF-associated symptom according to the MPN-SAF / EORTC QLQ-C30 or FACT-Lym by a minimum of 50% *and/or* SD plus improvement of ≥ two MF-associated symptoms according the MPN-SAF / EORTC QLQ-C30 or FACT-Lym by a minimum of 25% each.

Appendix B: Background information and study rationale

Myeloproliferative Neoplasms (MPN) are clonal stem cell disorders derived from multipotent hematopoietic myeloid progenitors. *BCR::ABL1*-positive MPN leading to chronic myeloid leukemia (CML) differ from classical MPN such as essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF). In contrast to CML, *BCR::ABL1*-negative MPN are characterized by a variety of molecular abnormalities leading to aberrant cell proliferation.

ET, PV, and PMF constitute a disease continuum and share common biological and clinical features (Smith CA et al., 2008). The median age at diagnosis is 67 years; thus, MF is primarily a disease of the elderly. The incidence of PMF has been estimated at 1.5 per 100,000 per year.

Myelofibrosis (MF) can either occur *de novo* (PMF) or secondary (SMF) from PV (post-PV MF) or ET (post-ET MF). It is characterized by cytopenia (anemia and/or thrombocytopenia), (hepato-)splenomegaly due to extramedullary hematopoiesis, and debilitating symptoms that include fatigue, weight loss, pruritus, night sweats, fever, and bone, muscle, or abdominal pain. Beside cytopenia, typical laboratory abnormalities are the presence of red and white precursor cells in the peripherals blood as well as elevated serum lactate dehydrogenase levels.

Myelofibrosis is induced by inflammatory cytokines. Hyperplasia of atypical megakaryocytes and an increase of reticulin fibres at a varying degree are histologic findings in the bone marrow. The pro-inflammatory state is mediated by the gain-of function mutation V617F in *JAK2* (50-60%) or by mutated *CALR* (20-30%) or *MPL* (5-10%) leading to constitutive JAK-STAT signaling (Tefferi A et al., 2009a). Thus, evaluation of the bone marrow morphology and analysis of the three driver mutations are crucial steps for the correct diagnostic work-up of MF.

In the last years, the ´DIPSS´ (Dynamic International Prognostic Scoring System) established the following key prognostic parameters as adverse risk factors: anemia (hemoglobin <10 g/dL), increase of white blood cell (WBC) count (>25 x 10^9/L), presence of constitutional symptoms, older age (>65 years), and peripheral blood blasts (≥1%). However, these clinical characteristics alone are not sufficient for reliable prognostication in MF since median survival ranges in different risk groups from 13 to 135 months (Dupriez B et al, 1996; Cervantes F et al., 2009). More recently, high molecular risk (HMR) markers (e.g. mutation in *ASXL1*, *IDH1/2*, *EZH2*, or *SRSF2*) have complemented such clinical scorings and allow for a refined individual risk stratification.

Until today, allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative therapy for MF. However, HSCT is associated with significant treatment-related mortality resulting in an approximately 50% overall survival rate. Moreover, many MF patients are not eligible for HSCT due to co-morbidities and older age. Therefore, the search for alternative and effective therapeutic strategies in MF is still ongoing.

Based on the impressive results of the two phase-III trials with the JAK1/2 inhibitor ruxolitinib, COMFORT-I and COMFORT-II, both demonstrating that ruxolitinib pro-

vides significant clinical benefits by reducing spleen size and disease-related symptoms, the drug has been approved by FDA and EMA in 2012 (Verstovsek S et al, 2012; Harrison C et al, 2012). Although long-term data with ruxolitinib showed an improvement of survival, treatment with JAK inhibitors is not considered to induce remissions of MF. This is also true for fedratinib and momelotinib, other JAK inhibitors approved for symptomatic MF in recent years.

Immunmodulatory drugs (IMiDs) such as thalidomide, lenalidomide or pomalidomide are not approved for MF although they possess multiple immunogenic properties mediating direct or indirect activity against MF. For instance, pomalidomide has shown efficacy regarding anemia and thrombocythemia in different MF studies (e.g. Tefferi A et al., 2009; Begna KH et al, 2011; Mesa R et al, 2010) including a study that has been performed by our group (Schlenk RF, Stegelmann F et al., Leukemia 2016). In all trials, pomalidomide was less toxic compared to thalidomide or lenalidomide.

These data provided the rationale for our study MPNSG 02-12 combining ruxolitinib and pomalidomide in a phase-Ib/II design: to synergistically address the main features of advanced MF, i.e. anemia, disease-associate symptoms, and splenomegaly.

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