

Title page

Article title: Ruxolitinib versus Best Available Therapy for ET intolerant or resistant to Hydroxycarbamide in a Randomized trial

Short title: Ruxolitinib vs BAT in HC resistant/intolerant ET

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Key Points

- Ruxolitinib showed no significant improvement for attainment of either CR or PR over BAT within the first year of therapy in high-risk ET
- Ruxolitinib significantly improved some disease-related symptoms but rates of thrombosis, hemorrhage or transformation were not different

Abstract

Treatments for high-risk essential thrombocythemia (ET) address thrombocytosis, disease-related symptoms, as well as risks of thrombosis, hemorrhage, transformation to myelofibrosis and leukemia. Patients resistant/intolerant to hydroxycarbamide (HC) have a poor outlook. MAJIC (ISRCTN61925716) is a randomized phase II trial of ruxolitinib (JAK1/2 inhibitor) vs Best Available Therapy (BAT) in ET and polycythemia vera (PV) patients resistant or intolerant to HC. Here findings of MAJIC-ET are reported, where the modified intention-to-treat population included 58 & 52 patients randomized to receive ruxolitinib or BAT respectively. There was no evidence of improvement in complete response within 1 year reported in 27 (46.6%) patients treated with ruxolitinib vs 23 (44.2%) with BAT ($P=.40$). At 2 years rates of thrombosis, hemorrhage and transformation were not significantly different, ~~however between ruxolitinib and BAT. S~~ some disease-related symptoms improved in patients receiving ruxolitinib, ~~more so than~~ relative to BAT. Molecular responses were uncommon; ~~however~~ there were two complete molecular responses (CMR) and one partial molecular response (PMR) in *CALR* positive ruxolitinib-treated patients. Transformation to myelofibrosis occurred in one CMR patient, presumably due to the emergence of a different clone raising questions about the relevance of CMR in ET patients. Grade 3&4 anemia occurred in 19% & 0% of ruxolitinib vs 0% (both grades) BAT arm, grade 3&4 thrombocytopenia in 5.2% & 1.7% of ruxolitinib vs 0% (both grades) of BAT treated patients. Rates of discontinuation or treatment switching did not differ between the two trial arms. The MAJIC-ET trial suggests that ruxolitinib is not superior to current second-line treatments for ET.

Introduction

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm (MPN) characterized by thrombocytosis. Patients are at higher risk of thrombosis and hemorrhage. They also have disease-related symptoms which are difficult to manage with standard therapies. Therapeutic approaches include lowering risks of thrombosis and hemorrhage, without increasing risk of transformation into myelofibrosis (PET-MF) or acute myeloid leukemia (AML), which are also part of the natural history of this disorder¹⁻³. Low-dose aspirin with hydroxycarbamide (HC) is recommended as first line therapy in high-risk patients to reduce both platelet count and thrombotic events, as supported by data from randomized trials^{3,4}. However, approximately 20% of patients with ET become intolerant or resistant to HC and those patients with resistance appear to be at increased risk of disease transformation and significantly reduced overall survival⁵. However, there is a lack of prospective trial data to guide management of ET patients who are resistant or intolerant to HC; current treatment options are limited, and several second-line treatment options are associated with increased risk of disease transformation^{2,3,6}.

The discovery of the Janus kinase (*JAK2V617F*) mutation provided the first genetic marker of the malignant clone in MPN⁷⁻⁹, and highlighted identifying the central role of JAK/STAT activation as a consistent pathological finding, even in those patients without the *JAK2V617F* mutation¹⁰. There is evidence that in ET *JAK2* activation is associated with platelet and leukocyte activation, and risk of thrombosis, especially venous events¹¹. High *JAK2V617F* mutant allele burden is also associated with features of more advanced disease in both polycythemia vera (PV) and ET^{12,13}. Furthermore, other key driver mutations associated with ET, affecting the thrombopoietin receptor *MPL* and calreticulin (*CALR*) also lead to increased *JAK2* signaling¹⁴, highlighting the primacy of *JAK2* signaling in the pathogenesis of ET.

The *JAK1/2* inhibitor, ruxolitinib, was effective in reducing spleen volume, controlling blood counts and improving disease symptoms in patients with MF and PV¹⁵⁻¹⁷. In addition, ruxolitinib treatment may result in a survival advantage for patients with MF^{18,19}. A previous non-randomized study in 39 ET patients with ET, who were resistant or intolerant to HC, demonstrated that ruxolitinib was capable of lowering both platelet and white cell counts and that the most effective starting dose was 25mg bd²⁰.

We conducted a randomized, phase II trial to evaluate the activity and safety of ruxolitinib vs Best Available Therapy (BAT) in two different patient populations (ET and PV) in the MAJIC trial: A

randomized study of best Available therapy versus JAK inhibition in patients with high-risk Polycythemia Vera or Essential Thrombocythaemia who are resistant or intolerant to Hydroxycarbamide (MAJIC). The study utilized an efficient framework of a basket trial design, permitting the separate evaluation of two study populations. Here we present safety and efficacy data for the ET population ~~of the MAJIC study~~, so-called MAJIC-ET.

Trial design

~~A~~Within each arm of the MAJIC trial, an independent, parallel, open-label, randomized controlled trial of ruxolitinib vs BAT was implemented (~~Trial schema~~, Supplemental Figure 1). Patients aged ≥ 18 with high-risk ET or PV, who met modified criteria for intolerance or resistance to HC²¹, (~~Supplemental Table 1~~), were recruited. (~~criteria in Supplemental Table 1~~). The MAJIC-PV arm is ongoing ~~and will be reported separately~~. High-risk ET was defined by standard criteria (Supplemental Table 2), patients were stratified by JAK2V617F status and randomized ~~on a 1:1 ratio~~ to receive either ruxolitinib (starting dose 25mg twice daily (bd) or 20mg bd, if baseline platelets were $100\text{--}200 \times 10^9/\text{L}$) or BAT. Full trial inclusion and exclusion criteria are presented ~~in~~ (Supplemental Table 3). The trial was registered at www.isrctn.com (~~registration number~~ ISRCTN61925716) and ~~was~~ reviewed by an independent research ethics committee. All ~~patients entering the trial~~ gave written informed consent in accordance with the Declaration of Helsinki. Trial data was analyzed by statisticians at the Cancer Research UK Clinical Trials Unit (University of Birmingham), UK and Quality of Life (QoL) analysis performed by statisticians at the Mayo Clinic, Scottsdale, Phoenix, USA. Ruxolitinib was provided free of charge by Novartis. All authors had access to ~~the~~ primary clinical trials data and approved the final version of ~~the~~ manuscript.

Outcome measures

The primary outcome measure was achievement of Complete Response (CR) ~~rates~~ as defined by European Leukemia Net (ELN) criteria within 1 year of treatment²². CR in ET patients was defined by achieving all of the following criteria: platelet count $\leq 400 \times 10^9/\text{L}$; normal spleen size on imaging; white blood cell count $\leq 10 \times 10^9/\text{L}$. Secondary outcomes included Partial Response (PR) ~~rates~~ per ELN criteria within 1 year of treatment, duration of response (both CR and PR) and overall response (i.e. CR&PR), toxicity profile of ruxolitinib based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4, dose intensity, histological response, molecular response ~~as defined by ELN~~; hemorrhagic and thromboembolic event ~~rate~~, disease transformations, QoL and disease symptom burden, overall and progression free survival. The safety population included all patients who received at least one dose of protocol treatment. ~~All~~ hemorrhagic and thrombotic events were ~~collected and~~ centrally reviewed. QoL and symptom assessment

questionnaires; ~~included the~~ 10-item Myeloproliferative Neoplasm Symptom Assessment Form Symptom Score (TSS)²³, EQ-5D²⁴ and M.D. Anderson Symptom Inventory (MDASI)²⁵ and were completed ~~by patients~~ at baseline (~~pre-ior to~~ treatment, 7 consecutive days for the MPN-10 and questionnaires), 2 months and 4 months post randomization and continued 4 monthly whilst on trial (~~once per time point per questionnaire~~). Overall symptom response was defined as at least a (average of the 7 baseline days with at least 4 of 7 days scored) at any post-baseline time point up to Month 12.

Sample size justification and statistical analysis

Sample size calculation were based upon rates obtained from preliminary ~~phase II data with ruxolitinib in PV and ET patients~~²⁰ using an one-sided normal test without continuity correction and unpooled variance. ~~The~~ CR rate for ~~the~~ control group was estimated ~~to beat~~ 30%. A clinically significant improvement was considered to be 20%. Thus, assuming CR rates in the control and treatment group were 30% and 50% ~~respectively~~, 55 patients were required in each arm to detect a clinically significant difference of 20% with 82% statistical power at 10% level of significance. ~~As this is a randomized screening trial to evaluate a direct, but nondefinitive comparison between the two arms, with the aim of screening for promising signal of activity in ruxolitinib, a relaxed one-sided significance level of 10% is utilized (Rubinstein et al 2005).~~ Allowing for a 5% drop out rate, ~~the total number required was~~ 116 patients ~~were required~~.

Commented [CY1]: Please update reference. Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA: Design issues of randomized phase II trials and a proposal for phase II screening trials. J Clin Oncol. 2005;23:7199-7206.

~~A~~ $P < .10$ was considered ~~statistically~~ significant for the primary outcome. For all other analyses, two-sided tests were used and a $P < .05$ was considered ~~statistically~~ significant. ~~The n~~ Number and proportion of patients ~~were~~ reported for categorical variables by treatment group and overall. Descriptive statistics (number of patients, mean, standard deviation (SD), median, Interquartile Range (IQR)) ~~were~~ reported for continuous variables by treatment group and overall. ~~The number and proportion of patients were reported for categorical variables by treatment group and overall.~~ Time-to-event outcomes ~~were~~ analyzed using the method of Kaplan and Meier and differences in survival ~~time analyses were~~ determined using ~~the a~~ Cox's model ~~with adjustment for JAK2V617F status as per baseline data reported by sites~~. ~~Apart from the primary outcome, additional hypotheses testing were exploratory and non pre-specified. These analyses have adjusted for JAK2V617F status.~~ Normal Z-tests were used to assess difference in proportions. ~~We also fitted~~ Univariate and multivariate logistic regression ~~were fitted~~ models to ~~see assess the~~ effect of baseline measures on ~~the~~ primary outcome, transformations and toxicity. ~~Apart from the primary outcome, additional hypotheses testing were exploratory and non pre-specified.~~ All summaries and statistical analyses for efficacy were primarily carried out on a modified intention to treat (mITT)

basis, including patients analyzed according to their randomized treatment allocation, starting treatment within one year of randomization and ~~for which~~ with at least one response ~~was available~~. Summary statistics for safety variables were based on the safety population, which included patients according to the treatment they actually received and who received one or more doses of treatment. All above statistics analyses were performed using Stata version 14.2.

QoL and symptom data were analyzed ~~for the~~ mITT population using SAS version 4. Overall symptom response rate was compared between arms using a chi-squared test, ~~and~~ maximum percentage reduction from baseline during the first 12 months was compared between arms using a Wilcoxon rank-sum test. Symptom response and percentage reduction at each post-baseline time point (or at most recent assessment if no symptom data at the given time point were provided) were similarly compared between arms using chi-squared and Wilcoxon rank-sum tests, ~~respectively~~. Comparisons of mean scores longitudinally employed a linear mixed model for each outcome (~~starting at the~~ from month 2 assessment) using all available data. In addition ~~to a randomized arm covariate~~, each model included a continuous covariate for ~~the~~ baseline value of ~~the~~ outcome and used ~~the~~ planned month of assessment as ~~the~~ categorical time value with compound covariance structure.

Treatment and assessments

Ruxolitinib ~~treatment~~ was initiated ~~at an appropriate dose~~ based on baseline platelet count. BAT was assigned according to physician's choice but had to be an active agent, ~~Patients were permitted to change of~~ BAT therapies ~~was permitted~~ with the aim of achieving a CR. ~~Patients were also allowed to receive a combination of~~ BAT therapies ~~but no other concurrent cytoreductive therapies were~~ ~~was permitted~~, ~~permitted for patients on the ruxolitinib arm~~. No crossover of BAT ~~patients to~~ ruxolitinib was permitted. Low-dose aspirin (75mg od) was ~~also~~ advised ~~for all patients~~ unless contraindicated. Protocol specified dose reductions for ruxolitinib were in place ~~for hematological, renal and hepatic toxicities~~ and patients were allowed to re-escalate following a ~~dose reduction~~ if the toxicity had resolved. ~~The~~ lowest permitted dose of ruxolitinib was 5mg once ~~daily~~. ~~Patients were assessed for hematological response~~ ~~was assessed every~~ 2 weeks for 3 months, ~~and~~ then ~~every~~ 6 weeks ~~during the first year of treatment~~ in order to determine the primary outcome of CR during year 1 (cut-off week 54). Ultrasound was performed at baseline ~~and~~ centrally reviewed, ~~to confirm the presence or absence of splenomegaly~~. ~~Patients with~~ splenomegaly ~~at was present at~~ baseline ~~required a repeat ultrasound showing a normal spleen size~~ resolution was required for ~~to be considered as achieving~~ CR. ~~Patients continued to receive~~ ruxolitinib ~~continued~~ beyond 1 year

moved to the BAT arm for continued follow-up. Patients who underwent transformation to PET-MDS) or AML discontinued the trial but were followed up for survival.

~~In order to achieve the secondary outcome, rate of molecular response, blood samples were taken from patients at baseline and 4 monthly for the duration of the trial.~~ Assays for JAK2V617F, CALR and MPL mutation allele burden was quantified using next generation sequencing as previously described²⁶ An analysis of histological features is currently being performed and this data is not being presented as part of this manuscript.

Results

Patient characteristics

116 patients were recruited in 38 UK centers within the UK between a September 2012 and February 2015, with a median follow up of 2.61 years (range: 0.23 – 4.12). In total 110 were eligible for the mITT analysis. ~~Comprising These consisted of~~ 58 (52%) and 52 (48%) patients recruited to the ruxolitinib and BAT arms respectively. ~~The~~ median age of patients was 64.2 years with 44 (40%) males and 66 (60%) female patients, ~~s enrolled, of which overall~~ 28/110 (25.4%) were resistant to HC, 57/110 (51.8%) intolerant or 25/110 (22.7%) both. Baseline characteristics were balanced between the two groups (Table 1), except for the ruxolitinib arm which had with longer disease duration and lower hemoglobin. ~~Overall~~ 6 patients were excluded from the mITT analysis: 4 withdrew before commencing without treatment (2 did not wish to be in the on BAT arm, one was ineligible, and one had transformed to PET-MF) and 2 did not start treatment within one year from randomization. All list of all CALR indels and MPL mutations detected is are provided in Supplemental Table 4.

Trial Treatment

For patients receiving ruxolitinib, ~~although treatment was initiated at 25mg bd in all patients~~ the median dose intensity of ruxolitinib during year one was 15mg bd (Figure 1). ~~For patients receiving BAT,~~ the most common BAT therapies utilized at least once in the therapeutic scheme of BAT patients included HC in 37/52 (71.1%), anagrelide in 25/52 (48.1%) and interferon in 21/52 (40.4%) patients.

Add comment about prior therapies for BAT arm

Patient disposition at the time of the analysis (2 year follow up) is shown in Figure 2. Thirty BAT patients (57.7%) switched their initially assigned therapy at least once and there were a total of 86 switches across this the BAT group. In total, 45 patients (49.5%) discontinued treatment, with 40

discontinuations occurring within the first treatment year. Thirty-five patients (60.3%) receiving ruxolitinib and 10 patients (19.2%) receiving BAT discontinued treatment. The main reasons for discontinuation in the ruxolitinib arm were loss of response (11/35 (31.4%)) and transformation (9/35 (25.7%)). The main reasons for discontinuation in the BAT arm were transformation (3/10 (30%)) and death (2/10 (20%)). Discontinuations and therapy switches are shown in Table 2.

Efficacy analysis

For patients meeting the criteria for mITT analysis the primary outcome (CR) was achieved in 27 (46.5%) of the patients in the ruxolitinib arm vs 23 (44.2%) in the BAT arm (Unadjusted $P = .40$, adjusted for JAK2V617F status $P = 0.40$) with a difference of proportions -2.3% between BAT and ruxolitinib (80% CI: -15%, 10%). PR occurred in 27 (46.5%) patients in the ruxolitinib arm and 27 (51.9%) patients in the BAT arm (Figure 3A). The Time to first response (CR or PR) between the two arms was significantly different ($P = .01$; Figure 3B) with BAT patients taking longer to reach this point. Although duration of CR appeared shorter for ruxolitinib patients, this was not statistically significant (Figure 3C) and there was no evidence of a difference in duration of overall response (CR and PR) between ruxolitinib and BAT (Figure 3D). Overall survival (OS) and progression free survival (PFS) at 1 year were similar (OS: .98 (95%CI .86, .99) for BAT and .98 (95%CI 0.88, 0.99) for ruxolitinib patients, PFS: .96 (95%CI .85, .99) for BAT and .93 (95%CI .81, .97) for ruxolitinib patients). In multivariate analyses performed to assess baseline factors influencing CR (modelled for: treatment received, HC resistance/intolerance, white cell count, platelets, hemoglobin & JAK2/CALR status) no factor was shown to be significant and did not change the treatment effect (Supplemental Table 54).

Thrombosis, hemorrhage and disease transformation

After 2 years of follow up transformation to PET-MF occurred in 8 ruxolitinib vs. 5 BAT treated patients. Transformation to AML was seen in 1 patient who received ruxolitinib. Transformation free survival event free probability was not significantly different between the two arms ($P = 0.29$; Supplemental Figure S24A). Concerning thrombosis and hemorrhage, following central review, 10 patients (17.2%) on the ruxolitinib arm experienced 11 thrombotic events compared to 3 patients (5.8%) on the BAT arm experiencing 5 events. Hemorrhagic events were 1 (1.7%) vs 5 (8.9%) for ruxolitinib and BAT patients respectively (Table 3). Concerning the thrombosis free survival event free probability, the differences were borderline but not statistically significant ($P = .09$; Supplemental Figure S24B). Hemorrhage was less frequent for patients treated with ruxolitinib, however this difference was not significant ($P = .14$; Supplemental Figure S24C). Since all of these events are considered clinically relevant we performed an analysis of transformation, thrombosis and hemorrhage as a composite endpoint; there was no evidence of a difference ($P = .35$; Supplemental Figure S42D). Most thrombotic and hemorrhagic events occurred in patients in CR or

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PR (Supplemental Figure S32). In a multivariate analysis of factors influencing transformation to PET-MF, this event only occurred in patients with baseline WBC $<10 \times 10^9/L$ (Supplemental Table 65).

Molecular responses (MR)

The mean baseline allele burdens for *JAK2V617F*, *CALR* or *MPL* mutation positive patients are displayed in Table 1. At 12 months, or the last available sample during year 1, the overall mean allele burden had not changed significantly for any mutation in either treatment arm. However, 1 complete molecular response (CMR) and 1 partial molecular response (PMR) per ELN criteria were seen for *JAK2V617F* positive patients on the ruxolitinib arm and 2 CMRs and 1 PMR for *CALR* positive patients on ruxolitinib compared to 0 CMRs/PMRs for patients with these mutations receiving BAT. A *JAK2V617F* positive patient who achieved a PMR on ruxolitinib also had resolution of a cytogenetic abnormality at one year. There was no pattern of MR or progression with complete or partial hematological response or transformation, but 1 *CALR* positive patient who transformed to PET-MF had a CMR.

Impact on ET Related Disease Symptom Burden

Among 110 patients in the mITT cohort, 85 completed the baseline and at least one post-baseline questionnaire (ruxolitinib N=47, BAT N=38). While overall symptom response rate during the first 12 months did not significantly differ between arms (ruxolitinib 12/42 (29%) vs BAT 6/31 (19%), $P=.37$), maximum percentage TSS reduction at any point during the first 12 months of treatment was significantly greater for ruxolitinib compared to BAT (median reduction 32% vs 0%, $P=.03$, Figure 35A). Symptom response was rapid in the ruxolitinib arm (8/42 (19%) at 2 months) as compared to BAT (1/31 (3%) at 2 months, $P=.04$). Longitudinally, mean TSS ($P=.03$) and the individual symptom of pruritus ($P=.01$) were significantly lower for ruxolitinib vs BAT (Figure 35B and 35C), with trends observed for improved concentration ($P=.05$), lower anxiety/depression (EQ5D $P=.09$), and higher ability to perform usual activities (EQ5D $P=.09$) on the ruxolitinib arm compared to BAT.

Safety

All safety analysis has been conducted on the safety population: ~~which includes 115 patients (57 BAT, 58 RUX)~~. A total of 128 Grade 3/4 events occurred in 89 patients on the trial (Supplemental Table 64). Hematological toxicities (36/~~101-128~~) and metabolism/nutrition disorders (17/~~101-128~~ – 10 relating to hyponatremia) were the most common. Grade 3 or 4 anemia occurred in 12/58 (21%) of ruxolitinib patients vs 0/57 (0%) in the BAT patients ($P<.005$), grade 3 or 4 thrombocytopenia in 2/58 (3.4%) of ruxolitinib vs 0/57 (0%) of BAT patients ($P=.32$), and grade 3 (only) infections occurred in 9/58 (15.5%) of patients in the ruxolitinib arm compared to 2/57 (3.5%) (grade 3 and 4) in the BAT arm ($P=.03$). Overall 2 patients discontinued ruxolitinib for anemia; there were no discontinuations related to thrombocytopenia. Blood counts during the trial according to treatment arm are shown in

[Supplemental Figure 46](#), demonstrating equivalent control of leucocytes and platelets but lower hemoglobin from week 4. An unplanned multivariate model (modelled for hemoglobin ($\geq 100\text{g/dl}$) and *JAK2/CALR* status) demonstrated that hemoglobin ($\geq 100\text{g/dl}$) was significant in predicting the occurrence of anemia or thrombocytopenia (OR=.17, 95% CI=.04, .72, P=0.01) (Supplemental Table [86](#)).

There were 5 patient deaths in the ruxolitinib arm and 2 in the BAT arm, none were considered to be treatment related. The deaths in the BAT arm were due to multiple organ failure and cerebral hemorrhage. In the ruxolitinib arm, deaths were due to carcinomatosis combined with esophageal cancer, bowel infarction due to adhesions, acute left ventricular failure, ischemic cardiomyopathy and sepsis combined with pancreatic cancer.

Discussion

ET is often regarded as the most indolent of the Philadelphia negative MPNs. Treatments for high-risk ET offer improvements in blood counts and reduction in risk of thrombosis and hemorrhage with a lack of certainty regarding effects upon transformation to PET-MF and AML^{2,3}. Criteria for resistance or intolerance to standard therapy with HC were originally developed to guide clinicians when to initiate second-line therapies; however, there is now evidence that HC resistant patients have a poor outlook²⁷. In addition, disease-related symptom burden is increasingly recognized as an important disease feature, causing significant morbidity with few effective treatments²⁻⁴. In previous studies patients with MF displayed a survival benefit with ruxolitinib, which also reduced spleen size and symptoms when compared to BAT¹⁸. In the RESPONSE study in HC resistant/intolerant patients with PV there was a suggestion of lower rates of thrombosis in patients receiving ruxolitinib compared with BAT, as well as better control of blood counts, spleen size and symptoms¹⁷.

The MAJIC trial was designed to compare ruxolitinib with BAT in patients with HC intolerance/resistance in two populations, MAJIC-ET and MAJIC-PV. ~~There is~~ [Representing](#) considerable gain in efficiency in terms of resources, labor and time compared to running two separate trials. Also, there is an added advantage of consistency ~~as both studies are run under one protocol~~. Both trial populations are fully recruited and here we report the findings of MAJIC-ET trial. The patients recruited into MAJIC-ET displayed characteristics that were well-balanced between the two arms with the exception of baseline hemoglobin and prior disease duration. Distribution of driver mutations *JAK2V617F*, *MPL* exon 10, *CALR* mutations were as expected. [Our p](#)Patients had a long disease duration (up to 31 years) and some of whom had received multiple therapy lines with up to nine prior therapies. [Some features of advanced disease, for example splenomegaly and leukocytosis were present at baseline however transformation to PET-MF was excluded at trial entry. \[Diagnostic\]\(#\)](#)

~~criteria have been controversial in ET and those in use at trial centres were as follows~~ British Committee for Standards in Haematology (BCSH n=18); WHO 2001/2008 (n=11) and both combined (n=3). The BCSH and WHO criteria were recently shown to perform equally well. [REF]

~~Something here about standard second line therapies~~ Usual therapy choice in the second-line setting for ET would be anagrelide or interferon, however in order to perform a “real-life comparison” we allowed investigator choice overall the majority, 79% (41/52), of BAT patients received one or both agents before or during the study. On-study BAT included in addition busulfan ³²P and remaining on HU several international guidelines recommend busulfan or ³²P for older patients. ~~Some features of advanced disease, for example splenomegaly and leukocytosis were present at baseline however transformation to PET-MF was excluded at trial entry.~~ ~~Diagnostic criteria in use at trial centres were as follows~~

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In MAJIC-ET numbers, proportion of patients reaching CR within one year were not different/similar: 27 (46.5%) in the ruxolitinib arm vs 23 (44.2%) for BAT, with similar data for the achievement of PR rates. Time to any first response (CR or PR) was significantly faster for patients treated with ruxolitinib ($P=0.12$). This finding is particularly interesting finding, as patients in CR who were randomized to receive ruxolitinib had to change therapy and potentially lost any pre-existing response yet managed to attain CR faster than BAT patients who may not have changed therapy and thus only needed to maintain their response. In addition, BAT patients were also allowed to combine or to switch therapies and frequently did so. Importantly however the duration of CR appeared shorter for ruxolitinib patients with a marginally significant value, while the duration of overall response (CR and PR) was not different between both arms. We confirm that HC resistant/intolerant ET patients have a high-risk of thrombosis, hemorrhage and transformation to PET-MF; event rates here being higher than reported in the non-resistant/intolerant population for example the e.g. PT-1 or ANAHYDRET studies^{28,29}. Transformation for may have been more likely for ruxolitinib treated patients due to the higher prevalence of anemia and longer disease duration for this cohort. However, overall thrombosis, hemorrhage or transformation these events when considered separately or together as a composite endpoint were not statistically different between the ruxolitinib and BAT. Furthermore, in a *post hoc* unplanned analysis for factor influencing transformation to PET-MF, only a leucocyte count $<10 \times 10^9/L$ was significant. Several studies have reported that post-randomization exclusions of patients in randomized trials may affect trial results (Montedori et al 2011), with some raising concerns that the investigated therapy might be favored (Tierney et al, 2005; Melander et al 2003). However, in the MAJIC-ET trial, if we were to conduct a pure intention-to-treat (ITT) analysis, this would require imputation of missing response data for 6

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Tierney JF, Stewart LA. Investigating patient exclusion bias in meta-analysis. *Int J Epidemiol* 2005;34:79-87.

Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B. Evidence based medicine—selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *BMJ*. 2003;326:1171–1173. doi: 10.1136/bmj.326.7400.1171

BAT patients. Missing data imputation may bias estimates of treatment effects. A commonly used technique is nonresponder imputation (EMA, 2010), which will attribute all 6 BAT patients as not achieving CR within a year. This will result in a less conservative ITT analysis of 23/58 CR (BAT) vs 27/58 CR (RUX), with p-value of .22 compared to the mITT analysis (p=.4). Our primary findings of no evidence of superiority of Ruxolitinib were however consistent using either mITT or ITT analysis.

Molecular responses were uncommon in the first year of the trial, as ~~has been~~ described previously²⁰. However, ruxolitinib was associated with two CMR and one PMR in a *CALR* positive patient that has not previously been reported. ~~Given the low overall number of molecular responses it is has not been possible to correlate with other clinical endpoints.~~ Transformation to PET-MF in one *CALR* positive patient, who achieved a CMR, presumably occurred due to the emergence of a different clone, consistent with patients reported with *JAK2V617F* positive chronic phase developing *JAK2V617F* negative AML³⁰, and raises questions about the relevance and value of CMR in patients with ET.

Patterns of adverse events with ruxolitinib were similar to those already reported, most prevalent events related to hematological, nutritional and metabolic events. Infections were also more common with ruxolitinib therapy. There was no suggestion of imbalance between the two arms of MAJIC-ET for non-melanoma skin cancer as was previously noted in the RESPONSE trial¹⁷. Treatment discontinuation occurred more frequently for patients treated with ruxolitinib, with 35 patients discontinuing treatment compared to 9 discontinuations in the BAT arm. However, 30 BAT patients switched their initially assigned BAT treatment for various reasons, which indicates a similar rate of treatment ineffectiveness or intolerance. For the first time, we show baseline anemia predicted for treatment emergent anemia and thrombocytopenia.

Patients with ET have a high burden of symptoms, which have been consistently reported to affect their quality of life³¹. The symptom response rate, defined as a 50% reduction in TSS, during the first 12 months did not significantly differ between the two arms. However, maximum percentage TSS reduction during the first 12 months of treatment was significantly greater for ruxolitinib compared to BAT and was more rapid in the ruxolitinib arm. Longitudinally, mean TSS and individual symptom of pruritus were significantly lower for ruxolitinib, with trends observed for improved concentration, lower anxiety/depression and higher ability to perform usual activities for ruxolitinib arm compared to BAT indicating a novel and important benefit to ET patients of ruxolitinib therapy.

Limitations of our trial include that the trial reflected “real life practice” in use of diagnostic criteria and selection of BAT therapies. The majority of our centers used xxxxx diagnostic criteria which....

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EMA (2010). Guideline on missing data in confirmatory clinical trials, European Medicines Agency (EMA), London (2010)

Guidelines recommend anagrelide as second line therapy for ET, many of our patients had already been treated with this drug (25 received anagrelide, 7 interferon and 7 both agents) before study entry. Regarding the choice of BAT therapy 235 patients received anagrelide, 1920 interferon, 54 had both drugs as BAT therapy. both The use of HC as a BAT and frequent switching of BAT therapies which occurred in almost two thirds of the BAT arm. ~~However these factors~~ also reflect real-life constraints and the limited treatment options for ET patients with resistance/intolerance to HC and highlight the need for newer therapies in this field.

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In conclusion, the MAJIC-ET trial suggests there is insufficient evidence that ruxolitinib has improved treatment efficacy compared to BAT for most clinically relevant events. Some symptom responses were superior with ruxolitinib therapy but there was no difference in this study for control of blood counts or other relevant endpoints such as transformation, thrombosis or hemorrhage.

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Authorship Contributions

CH, AJM, MFM and CY designed the MAJIC trial. CH, SF, CY and AH wrote and reviewed the protocol. CY, AP, AH and CH devised the statistical analysis plan. JE, MW, FC, JC, NP, SK and SA recruited patients. AP conducted the statistical analysis, with statistical support from CY and AH. AD, RS and RM conducted the QoL analyses. CH, AM, AP, CY, AH, MFM, RM and AD interpreted the results. CH, SJF, AP, EG and CY drafted the manuscript and all authors reviewed the final version. CH is the guarantor.

Conflict of Interest Disclosures

CH has participated in advisory boards for Novartis, CTI, Baxalta and Celgene; speakers bureau for Novartis, CTI, Baxalta, Shire, Gilead, INCYTE; received honoraria from Novartis, Shire, CTI, Gilead, Baxalta, INCYTE and received research funding and travel, accommodation and expenses from Novartis. AM has participated in advisory boards for Novartis, CTI and Baxalta; received honoraria from Novartis, Gilead, Shire and Baxalta and also received research funding and travel,

accommodation and expenses from Novartis. FC and JC have received travel, accommodation and expenses from Novartis. SK has participated in advisory boards for Novartis; received honoraria from Novartis, Shire and Gilead and received travel accommodation and expense from Novartis and Celgene. SA received honoraria from Novartis and participated in advisory boards for Novartis. AH has participated in advisory boards for Novartis and received speakers bureau from Gilead. NCPC has participated in advisory boards for Novartis, received honoraria from Novartis and research support from Novartis. RM has consulted for Novartis, Ariad, and Galena; received research funding from Incyte, Gilead, CTI, NS Pharma, Celgene, and Promedior. MFM has participated in advisory boards for Novartis and Gilead; received honoraria from Novartis, Shire and Celgene and received travel, accommodation and expenses from Novartis. The remaining authors declare no competing financial interests.

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Figures

Figure 1. Dose of Ruxolitinib received throughout study

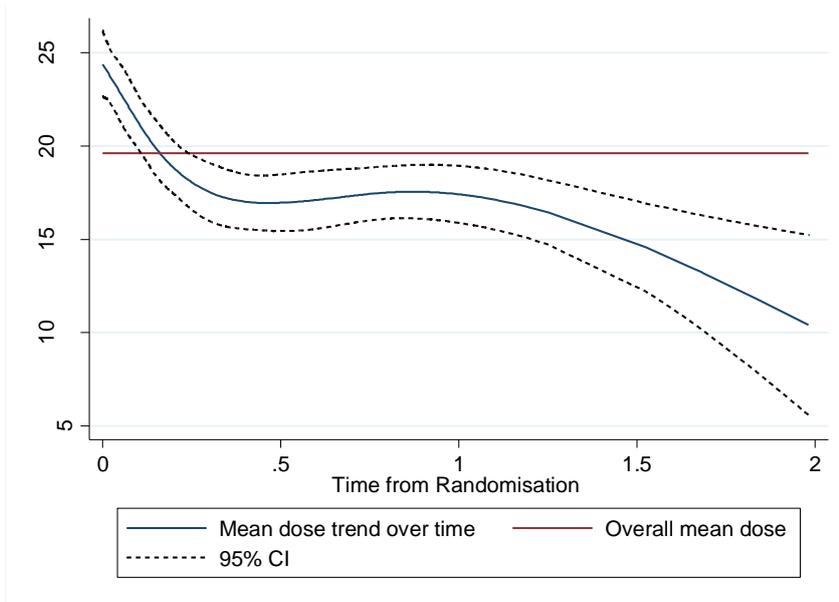
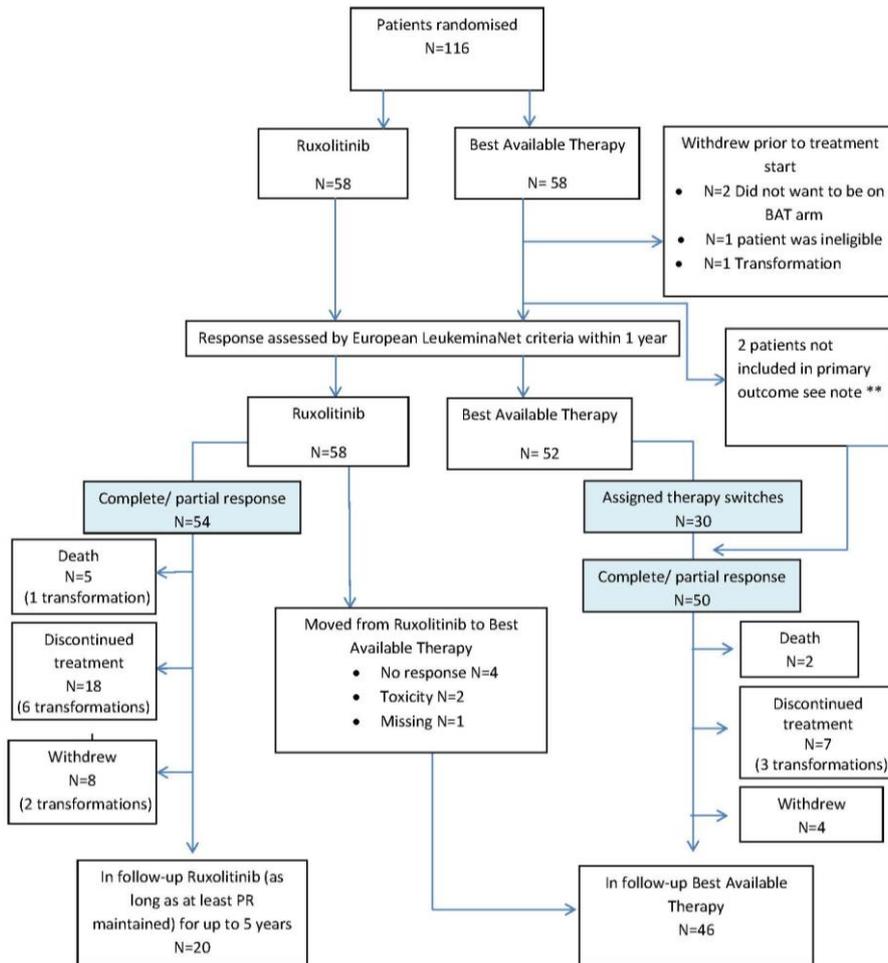


Figure 2. Trial consort diagram at second safety analysis

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Death was recorded as such regardless of prior discontinuation or withdrawal. Patients were clustered as withdrawals regardless of prior discontinuations.

**Note: 1 BAT patient started treatment 1 year after randomisation. 1 other BAT patient did not have a recorded response within 1 year. Both have been excluded from primary analysis, but included in follow-up.

Figure 3. Analyses of response

Figure 4A. Transformation event free probability survival by treatment arm

Figure 53. Changes in ET Related Symptom Burden during year 1 of the MAJIC-ET trial

Figure 53A.

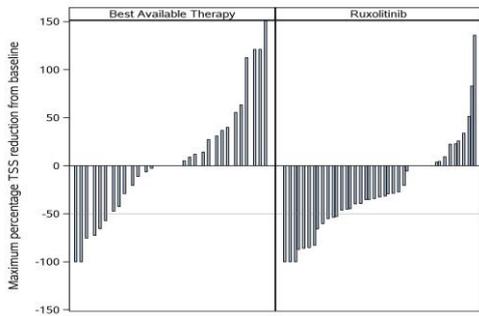


Figure 53B.

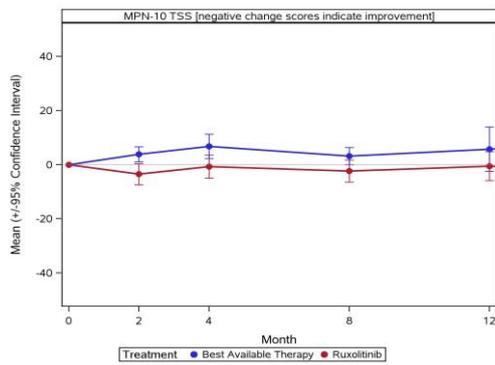


Figure 53C.

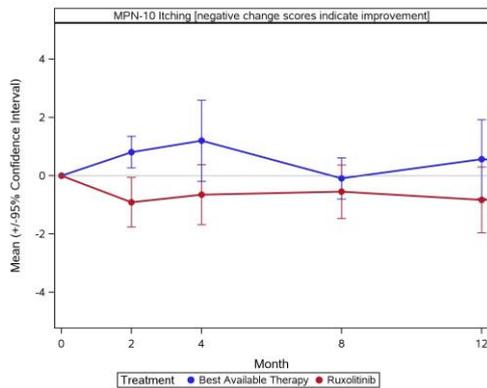


Figure 6. Hematological variables during the first year of the MAJIC-ET trial

Figure 1

Figure illustrating doses of ruxolitinib throughout the MAJIC-ET trial

Figure 2

Trial consort diagram including data to second safety analysis

Figure 3A

Figure 4B

Changes in ET Related Symptom Burden during year 1 of the MAJIC-ET trial

Figure 53A shows a waterfall plot of maximum percentage change in the MPN SAF TSS score, dotted line indicates 50% reduction in TSS

Figure 53B shows mean MPN-SAF TSS throughout the first year of the trial there was a consistent trend for reduction for ruxolitinib

Figure 53C shows the mean MPN-SAF score for itching during the first 12 months of the MAJIC-ET trial

Figure 6

Tables

Table 1. Baseline characteristics by treatment

	Best Available Therapy (52)	Ruxolitinib (58)	Overall (110)
Age			
Mean (sd) [Range]	65.6 (13.5) [37.2, 85.4]	62.9 (12.3) [34.5, 90.5]	64.2 (12.9)[34.5, 90.5]

Gender, n (%)			
Female	30 (57.7)	36 (62.1)	66 (60.0)
Male	22 (42.3)	22 (37.9)	44 (40.0)
Mutation status, n (%)			
JAK2V617F Positive	26 (50.0)	28 (48.3)	54 (49.1)
CALR mutation positive	147 (32.7-26.9)	20 (34.5)	347 (33-630.9)
MPL mutation positive	3 (5.8)	2-3 (3-45.2)	5-6 (4-65.5)
Triple negative	6-7 (11-513.5)	8-6 (13-810.3)	14-13 (12-711.8)
Not run	2 (3.8)	1 (1.7)	3 (2.7)
HC Resistant or Intolerant*, n (%)			
Resistant	25 (48.1)	28 (48.3)	53 (48.2)
Intolerant	27 (51.9)	30 (51.7)	57 (51.8)
Time from diagnosis to randomization, years**			
Mean (sd) [Range]	6.9 (5.8) [.4, 23.6]	10.4 (6.7) [.7, 31.2]	8.8 (6.5)[.4, 31.2]
Hemoglobin, g/L**			
Mean (sd) [Range]	126 (17) [90.0, 160.0]	119 (17) [87.0, 152.0]	122 (17) [87.0, 160.0]
Platelet count x 10⁹ / L			
Mean (sd) [Range]	573.0 (227.1) [166.0, 1406.0]	545.4 (215.3) [89.0, 1139.0]	558.4 (220.4) [89.0, 1406.0]
WBC count x 10⁹ / L			
Mean (sd) [Range]	6.8 (2.7) [2.8, 15.2]	7.5 (4.8) [1.7, 29.8]	7.2 (3.9) [1.7, 29.8]
Hematocrit			
Mean (sd) [Range]	0.4 (0.1) [0.3, 0.5]	0.4 (0.1) [0.3, 0.5]	0.4 (0.1) [0.3, 0.5]
Spleen size			
Enlarged	9	14	23
Normal	38	37	75
Splenectomy	2	3	5
Missing	3	4	7
Number of Previous Therapies, n (%)			
1	15(28.8)	14 (24.1)	28 (26.4)
2	20(38.5)	24 (41.4)	44 (40.0)
3	8 (15.4)	12 (20.7)	20 (18.2)
4	5 (9.6)	5 (8.6)	10 (9.1)
5	2 (3.8)	2 (3.4)	4 (3.6)
6	2 (3.8)	0 (.0)	2 (1.8)
9	0 (.0)	1 (1.7)	1 (.9)
Total number of previous therapies by treatment, number (%)[‡]			
Hydroxycarbamide	59 (52.2)	70 (58.8)	129 (55.6)
Anagrelide	29 (25.7)	31 (26.1)	60 (25.9)
Interferon	7 (6.2)	11 (9.2)	18 (7.8)
Pegylated Interferon	2 (1.8)	2 (1.7)	4 (1.7)
Busulfan	8 (7.1)	1 (.8)	9 (3.9)
32P	3 (2.7)	1 (.8)	4 (1.7)
Pipobroman	1 (.9)	1 (.8)	2 (.9)
Fedratinib	1 (.9)	1 (.8)	2 (.9)
Vorinostat	2 (1.8)	0 (.0)	2 (.9)
Thalidomide	0 (.0)	1 (.8)	1 (.4)
Missing	1 (.9)	0 (.0)	1 (.4)

HC Hydroxycarbamide; WBC white blood cell; *25 patients were both resistant and intolerant. These patients have been included as resistant; **Time from diagnosis to randomization and baseline hemoglobin were different between the two treatment arms; † Patients were allowed to receive multiple therapies, therefore total number of therapies in each category might exceed number of patients

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Table 2. Overview of assigned therapy switches and discontinuations per treatment arm

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	Ruxolitinib	BAT	Total
<i>Assigned therapy switches</i>			
Patients that switched BAT therapy at least once	N/A	30	30
Total number of times BAT therapy was switched	N/A	86	86
<i>Discontinuations</i>			
Transformation	9	3	12
Loss of response	11	0	11
Lack of efficacy	5	1	6
Toxicity	Anemia	2	0
	Other	3	1
Other	3	3	6
Death	1	2	3
Withdrawal of consent	1	0	1
Total	35	10	45

Table 3. Thrombotic and hemorrhagic events

	BAT			Ruxolitinib			Total	
	Grade 1&2	Grade 3&4	Grade 5	Grade 1&2	Grade 3&4	Grade 5		
<i>Hemorrhagic events</i>								
Hematuria	1	0	0	0	0	0	1	
Intracranial hemorrhage	0	0	1	0	0	0	1	
Oral hemorrhage	1	0	0	1	0	0	2	
Rectal hemorrhage	1	1	0	0	0	0	2	
<i>Total</i>	3	1	1	1	0	0	6	
<i>Thrombotic events *</i>								
Chest pain - cardiac	0	1	0	0	0	0	1	
Myocardial infarction	0	0	0	0	2	0	2	
Cerebrovascular ischemia	1	0	0	0	0	0	1	
Retinal vascular disorder	1	0	0	1	0	0	2	
Thromboembolic events	PE	0	0	0	0	3*	0	3
	DVT	0	0	0	1	1	0	2
	Calf vein DVT	0	0	0	0	1	0	1
Transient ischemic attacks	2	0	0	2	0	0	4	
<i>Total</i>	4	1	0	4	7	0	16	

PE Pulmonary Embolism; DVT Deep Vein Thrombosis

* The death of a ruxolitinib treated patient due to ischemic cardiomyopathy occurred more than 30 days past treatment and is therefore not recorded as an event

* 1 patient experienced PE and DVT at the same time, but was counted in the PE category

~~*A sepsis and pancreatic cancer related death of 1 ruxolotinib patient occurred more than 30 days~~