in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF
HEALTH POLICY & MANAGEMENT

Maastricht University

Pacritinib for treating myelofibrosis

ERRATUM

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This document contains errata in respect of the ERG report in response to the company's factual accuracy check. The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
14	"(HR 1.85, 95% CI 0.39 to 1.86)" changed to "(HR 0.85, 95% CI 0.39 to 1.86)"
20	The sentence "The ICER for the PERSIST-2 BID subgroup was [redacted] lower than the ERG preferred base case ICER." was replaced by "The ICER for the PERSIST-2 BID subgroup was [redacted] lower than the ERG preferred base case ICER."
28	Intervention name corrected.
29	Removed sentence: "However, unlike ruxolitinib it is not a targeted disease-modifying treatment."
49	"(HR 1.85, 95% CI 0.39 to 1.86)" changed to "(HR 0.85, 95% CI 0.39 to 1.86)"
58	"(HR 1.85, 95% CI 0.39 to 1.86)" changed to "(HR 0.85, 95% CI 0.39 to 1.86)"
75	Removed sentence: "It remains unclear though why this additional step of fitting a parametric survival curve was needed since time to death could have been sampled directly from the KM curves."
85	Removed sentence: "Furthermore, as can be seen from Table 34 in the CS, pacritinib patients seem to have more common haematological adverse events, which is in contrast to the RBC transfusion rates (Table 51 in the CS), which were more frequently administered in the BAT arm patients. Therefore, the ERG considers that using RBC transfusion costs as a proxy for the haematological adverse event management costs would not only underestimate the adverse event costs, but also would create a bias in favour of pacritinib."
93	"with 1.65 and 2.27" changed to "with 0.41 and 9.11" Removed sentence: "Furthermore, in the model it was observed that only the outpatient visits were multiplied by three, even though in the CS, it was reported that all resource use was multiplied by three to reflect the characteristics of a clinically worse patient population. Since the impact of this on incremental costs was expected to be small, this was not updated by the ERG."
103	The sentence "The company did not explain the gap between the deterministic and probabilistic PSA ICER values and did not elaborate on the scatterplot and the CEAC results." has been replaced by "The company did not elaborate on the scatterplot and the CEAC results."
126	The sentence "It can be observed that the ICER for the PERSIST-2 BID subgroup is [redacted], thus, [redacted] lower than the ERG preferred base case ICER." Has been replaced by "It can be observed that the ICER for the PERSIST-2 BID subgroup is [redacted], thus, [redacted] lower than the ERG preferred base case ICER."
132	The sentence "The ICER for the PERSIST-2 BID subgroup was [redacted] lower than the ERG preferred base-case ICER." Has been replaced by "The ICER for the PERSIST-2 BID subgroup was [redacted] lower than the ERG preferred base-case ICER."

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B2.10, page 82). When the FDA full clinical hold was imposed, all patients discontinued pacritinib and BAT study treatments, and no patients were allowed to start pacritinib as initial or crossover treatment. Patients continued to be followed for OS and leukaemia-free survival (LFS). The clinical hold caused early termination of the PERSIST-2 study resulting in incomplete data. After review of mature PERSIST-1 and PERSIST-2 data, the hold was removed on 5 January 2017.

[redacted] (CS, Section B.2.11, page 96).

For the severe thrombocytopenic population (≤ 50,000/μL platelet count) in the PERSIST-2 trial, there were no significant differences in OS for pacritinib QD (HR 1.27, 95% CI 0.499 to 3.23) or BID (HR 1.28, 95% CI 0.495 to 3.33) compared to BAT. There were 10 patient deaths (26.3%) with pacritinib QD, 9 (29.0%) with pacritinib BID and eight (25%) with BAT. Progression-free survival (PFS) results in the severe thrombocytopenic population (≤ 50,000/μL platelet count) also showed no statistically significant differences between pacritinib QD (HR 0.85, 95% CI 0.39 to 1.86) or BID (HR 1.02, 95% CI 0.48 to 2.21) and BAT. LFS results favoured BAT in the severe thrombocytopenic population (≤ 50,000/μL platelet count), although, again, none of the differences were statistically significant.

There were differences between treatment arms in the overall proportion of patients achieving a ≥35% spleen volume reduction (SVR) from baseline to week 24, favouring pacritinib. Differences were statistically significant for the comparisons QD+BID vs BAT and for BID vs BAT, but not for QD vs BAT. The proportion of patients in the severe thrombocytopenic population (≤ 50,000/μL platelet count) who achieved a ≥50% reduction in MPN-SAF TSS 2.0 from baseline to week 24 was higher in the pacritinib arms compared to the BAT arm. However, these differences were not statistically significant.

For patients with baseline severe thrombocytopenia (≤ 50,000/μL) in the PERSIST-1 trial, at week 24 in the ITT population, 8 (23%) patients in the pacritinib group had achieved a SVR of 35% or more versus none in the BAT group (p=0.0451). None of the other outcomes reported for the severe thrombocytopenia population showed statistically significant differences between the pacritinib and BAT groups.

Regarding quality of life, changes over time were generally small and similar across groups. Pacritinib showed worsening of appetite loss, insomnia, fatigue and pain at 24 weeks; while BAT showed worsening of insomnia and pain at 24 weeks. None of the differences between groups were statistically significant.

In the CS adverse events for the population with ≤ 50,000/μL baseline platelet count are only reported for the PERSIST-2 trial. In this subgroup (PC ≤ 50,000/μL at baseline), the incidence of Treatment-emergent adverse events (TEAEs) was higher in the pacritinib (99%) arms, including the QD arm (100%) and the BID arm (97.9%), compared to the BAT arm (90.5%), and treatment-related TEAEs occurred at a greater frequency in the pacritinib arms compared to the BAT arm (pacritinib pooled QD + BID, 85.6%; pacritinib QD, 86.0%; pacritinib BID, 85.1%; and BAT, 40.5%). The most common TEAEs (>50% occurrence) among pacritinib and BAT patients in the ≤ 50,000/μL baseline platelet count subgroup were gastrointestinal disorders and blood and lymphatic system disorders. The incidence of serious adverse events (SAEs) was 56.7% in the pacritinib arm (QD, 54.0%; BID, 59.6%) as compared to 38.1% in the BAT arm. The incidence of TEAEs with an outcome of death was 16.5% in the pacritinib QD + BID pooled arms, as compared to a rate of 19.0% in the BAT arm, with a higher rate in the QD arm (20.0%) compared to the BID arm (12.8%).

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indicative of the great uncertainty inherent in the overall survival estimates. The ERG also explored several scenarios showing inconsistencies (according to the ERG) in the results, for which the ERG was unable to determine the cause of such inconsistencies within the time frame of this appraisal. While this might indicate that the model is not error-free, the impact of correcting these potential flaws on the ICER is not expected to be as large as the impact regarding overall survival. Finally, the ERG explored the impact of using EQ-5D instead of MF-8D for deriving utilities, including wastage costs for pacritinib and a subgroup analysis for the expected license population (PERSIST-2 BID). Using EQ-5D instead of MF-8D increased the ICER by [redacted]. The scenario assuming wastage costs for pacritinib resulted in a minor increase of the ICER. The ICER for the PERSIST-2 BID subgroup was [redacted] lower than the ERG preferred base-case ICER. However, results for this subgroup are more uncertain due to the limited number of BID patients in the trial.

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3.1 Population

The population defined in the scope is: People with thrombocytopenia and primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF).[25] The population in the CS is limited to 'adult patients with PMF, PPV-MF or PET-MF who have platelet count ≤50,000/μL (severe thrombocytopenia)'.[11]

According to the company the decision problem addressed in the company submission has a narrower population than the NICE scope, in line with the anticipated license for pacritinib, as advised by the EMA. However, [redacted] Therefore, the relevant population for this appraisal is unclear.

The anticipated license is for adult patients with PMF, PPV-MF, or PET-MF who have severe thrombocytopenia (PC ≤ 50,000/μL) and are intermediate-1, intermediate-2 or high risk (according to the DIPSS).

3.2 Intervention

The intervention (pacritinib) is in line with the scope.

The recommended dose of pacritinib is expected to be 200mg twice daily according to the CS. However, a dose of 400mg once daily is also an option in the CS. There are considerable differences in effectiveness and adverse events between the two doses. In the response to the clarification letter (Question A11), the company stated that "the recommended dose of pacritinib is 200mg BID. However, in line with the trial protocol, dose reductions to 300mg total daily dose (100mg in the morning, 200mg in the evening), 100mg BID, or 100mg QD are available for patients who experience haematological toxicities, severe diarrhea or bleeding etc. 400mg once daily is not an option being applied for."[26]

The following additional tests must be performed before the initiation of therapy in patients with severe thrombocytopenia and should be monitored as clinically indicated: a baseline cardiogram; a complete blood cell count, with a white blood cell count differential, platelet count, and coagulation testing including prothrombin, international normalised ratio, partial thromboplastic and thrombin time.

3.3 Comparators

The description of the comparators in the NICE scope is as follows: Ruxolitinib (for people with intermediate-2 risk or high-risk disease) and established clinical practice (including but not limited to hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion). However, ruxolitinib is not indicated for patients with fewer than 50,000 platelets per μL; therefore, this may not be a relevant comparator.

In addition, the company states that splenectomy and radiation therapy are rarely used and that they were excluded from the ruxolitinib submission (TA386). In TA386, the committee did not consider the exclusion of splenectomy and radiation therapy as possible comparators problematic; these two treatments were not mentioned in the ACD or the FAD.

In the two PERSIST trials, best available therapy (BAT) included: hydroxyurea [hydroxycarbamide], watch and wait, prednisone, interferon-α, thalidomide, danazol, prednisolone, busulfan, cytarabine, peg-interferon α2A, or other (in PERSIST-1); or the aforementioned, with the addition of ruxolitinib and decitabine (in PERSIST-2).

3.4 Outcomes

The NICE final scope lists the following outcome measures:

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- spleen size
- symptom relief (including itch, pain and fatigue)
- overall survival
- progression-free survival
- response rate
- hematologic parameters (including red blood cell transfusion and blood count)
- adverse effects of treatment
- health-related quality of life.

These were all assessed in the PERSIST trials. In addition, RBC transfusion was included as an outcome measure.

3.5 Other relevant factors

According to the company "pacritinib is an innovative selective inhibitor of JAK2, FLT3 and IRAK1, providing potent antiproliferative activity and an ability to promote apoptosis and inhibit the STAT pathway".

[redacted]

According to the company, pacritinib meets the NICE end of life criteria for the treatment of MF (see: CS, Table 38, page 101). The ERG is not sure there is robust evidence to assess this (see chapter 7 in this report).

According to the company no equality concerns have been identified or are anticipated with the introduction of pacritinib (CS, section B.1.4, page 34).

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4.2.5 Results

4.2.5.1 PERSIST-2

A summary of the primary and secondary endpoints for the population with severe thrombocytopenia is presented in Table 4.7.

For the severe thrombocytopenic population (≤ 50,000/μL platelet count), there were differences between treatment arms in the overall proportion of patients achieving a ≥35% SVR from baseline to week 24, favouring pacritinib. Differences were statistically significant for the comparisons QD+BID vs BAT and for BID vs BAT, but not for QD vs BAT.

The proportion of patients in the severe thrombocytopenic population (≤ 50,000/μL platelet count) who achieved a ≥50% reduction in MPN-SAF TSS 2.0 from baseline to week 24 was higher in the pacritinib arms compared to the BAT arm. However, these differences were not statistically significant. The company points out that "the ability to show a statistically significant difference in TSS response between pacritinib and BAT was reduced by the early termination of the study due to the clinical hold, coupled with a higher than anticipated use of ruxolitinib in the BAT arm" (CS, page 66).[11]

OS results favoured BAT in the severe thrombocytopenic population (≤ 50,000/μL platelet count), although none of the differences were statistically significant. The company states that it was expected that OS would be similar across the three arms, due to trial exclusion criteria requiring patients to have a life expectancy of at least six months, prior to week 24. There were no significant differences in OS for pacritinib QD (HR 1.27, 95% CI 0.499 to 3.23) and BID (HR 1.28, 95% CI 0.495 to 3.33) compared to BAT. There were 10 patient deaths (26.3%) with pacritinib QD, nine (29.0%) with pacritinib BID and eight (25%) with BAT.

ERG comment: The OS results should be treated with a high degree of caution due to the trial inclusion criteria specifying that patients should have a life expectancy of at least six months, the impact of the FDA clinical hold and the high percentage of BAT patients switching to pacritinib at or after week 24.

PFS results in the severe thrombocytopenic population (≤ 50,000/μL platelet count) showed no statistically significant differences between pacritinib QD (HR 0.85, 95% CI 0.39 to 1.86) or BID (HR 1.02, 95% CI 0.48 to 2.21) and BAT. LFS results favoured BAT in the severe thrombocytopenic population (≤ 50,000/μL platelet count), although, again, none of the differences were statistically significant. The Kaplan-Meier curves for OS, PFS and LFS were not reported for the severe thrombocytopenic population (≤ 50,000/μL platelet count), only for the ITT population.

Another limitation caused by the clinical hold was that only approximately 70% of the participants were included in the ITT analyses for SVR ≥ 35% and reduction in TSS ≥ 50% from baseline to week 24. As not all randomised patients were included, these analyses are also at a high risk of bias.

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adverse events from the PERSIST-1 trial for the population with ≤ 50,000/μL baseline platelet count (see response to clarification letter[26]).

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company considered performing an indirect comparison; however, it was concluded that "Due to a lack of evidence in the target population of MF patients with platelet counts ≤ 50,000/μL, no appropriate comparisons could be made" (CS, page 82).[11]

ERG comment: The ERG agrees that the two PERSIST trials are the best available evidence for a comparison with BAT in the population of MF patients with platelet counts ≤ 50,000/μL and an indirect comparison would not provide reliable additional information.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No further additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The two PERSIST trials are the best available evidence for a comparison with BAT in the population of MF patients with platelet counts ≤ 50,000/μL and an indirect comparison would not provide reliable additional information.

For the severe thrombocytopenic population (≤ 50,000/μL platelet count) in the PERSIST-2 trial, there were no significant differences in OS for pacritinib QD (HR 1.27, 95% CI 0.499 to 3.23) and BID (HR 1.28, 95% CI 0.495 to 3.33) compared to BAT. There were 10 patient deaths (26.3%) with pacritinib QD, nine (29.0%) with pacritinib BID and eight (25%) with BAT. Progression-free survival (PFS) results in the severe thrombocytopenic population (≤ 50,000/μL platelet count) also showed no statistically significant differences between pacritinib QD (HR 0.85, 95% CI 0.39 to 1.86) or BID (HR 1.02, 95% CI 0.48 to 2.21) and BAT. LFS results favoured BAT in the severe thrombocytopenic population (≤ 50,000/μL platelet count), although, again, none of the differences were statistically significant.

There were differences between treatment arms in the overall proportion of patients achieving a ≥35% SVR from baseline to week 24, favouring pacritinib. Differences were statistically significant for the comparisons QD+BID vs BAT and for BID vs BAT, but not for QD vs BAT. Of note, however, the company highlighted that a strong correlation between SVR and symptom reduction has not been established in the published literature (CS, page 31). The proportion of patients in the severe thrombocytopenic population (≤ 50,000/μL platelet count) who achieved a ≥50% reduction in MPN-SAF TSS 2.0 from baseline to week 24 was higher in the pacritinib arms compared to the BAT arm. However, these differences were not statistically significant.

For patients with baseline severe thrombocytopenia (≤ 50,000/μL) in the PERSIST-1 trial, at week 24 in the ITT population, eight (23%) patients in the pacritinib group had achieved a SVR of 35% or more versus none in the BAT group (p=0.0451). None of the other outcomes reported for the severe thrombocytopenia population showed statistically significant differences between the pacritinib and BAT groups.

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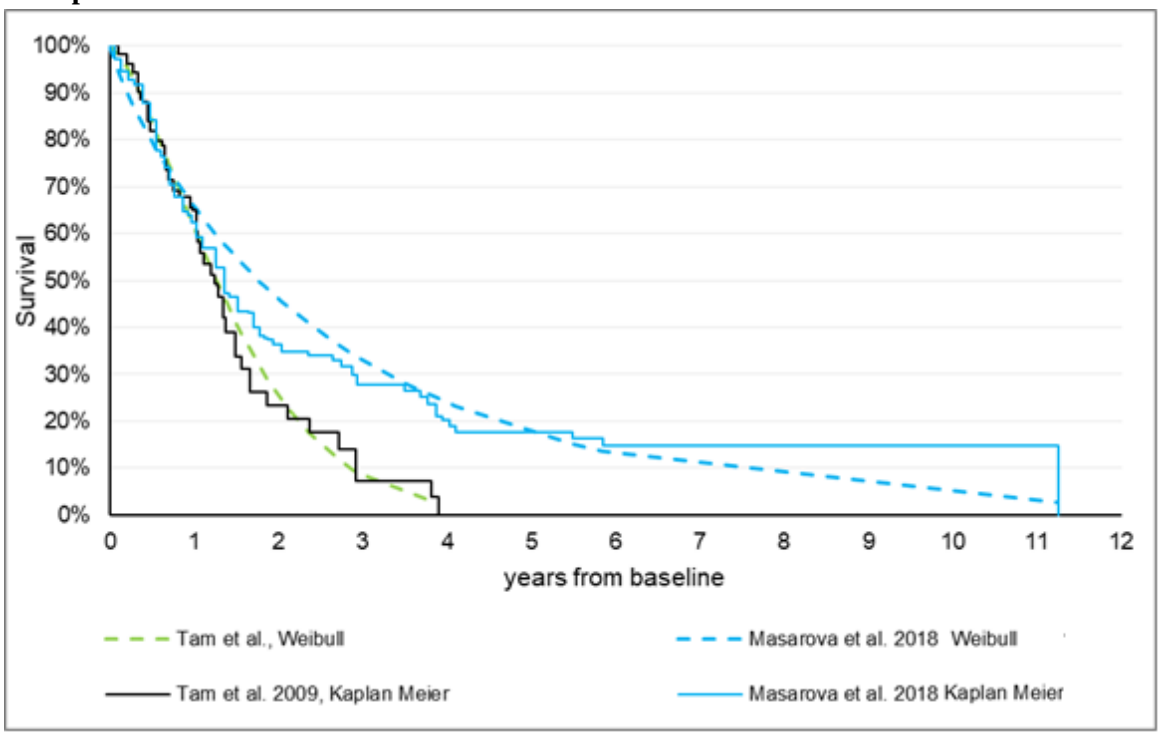
Figure 5.1: Kaplan Meier curves and Weibull extrapolations used to model time to death for BAT patients



Source: Amended Figure 27 in the CS.[11]

ERG comment: As explained in Section 4.2.5.3 of this report, the ERG considers that Masarova et al. 2018[10] might be a better estimate for BAT OS than Tam et al. 2009[3] and that it should be included as preferred option in the base-case analysis. The main reasons for preferring Masarova et al. 2018 data over Tam et al. 2009 data are the following: the data come from a larger population and the data are more recent (and probably a better reflection of current care). Whereas, it is true that some patients in the Masarova et al. 2018 dataset had SCT, which means that results could be more favourable than BAT without SCT, this is only a small proportion (8% of patients had SCT) and this is appropriate given that SCT is standard care for some patients. A comparison of the KM curves indicates that about 20% of the patients in Masarova et al. 2018 are still alive when all Tam et al. 2009 patients have died at 48 months. Thus, it is likely that SCT cannot explain all the additional survival in Masarova et al. 2018. This assumption is also made by the ERG in the preferred base-case analysis presented in Section 5.3.

As mentioned above, the company could not exactly reproduce the KM curves from Tam et al. 2009 and Masarova et al. 2018. The digitised KM curves are then approximations of the real KM curves. There is, therefore, structural uncertainty associated to the BAT OS KM curves which cannot be included in the economic model.

Furthermore, parametric survival curves were fitted to the pseudo-patient-level-data, which constitutes an additional level of uncertainty. However, this type of uncertainty can be quantified by conducting scenario analyses where the parametric survival curves are changed analysis.

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was calculated for both pacritinib and BAT, according to the pooled PERSIST safety dataset and PERSIST-2 BID safety dataset, respectively, by multiplying the mean time on treatment (in years) with the number of patients for each treatment arm in each dataset (see Table 5.9).

Table 5.1: Year at risk of AE calculations for pooled PERSIST and PERSIST-2 safety datasets

	PERSIST POOLED		PERSIST-2 BID	
	Pacritinib	**BAT**	**Pacritinib**	**BAT**
Mean time on treatment (in years)	1.15	0.43	0.763	0.4
N	430	204	106	98
Years at risk of AE	495.04	88.41	80.66	40.15

Source: Electronic model provided in the company's response to the clarification letter on 10 October 2018, after corrections suggested by the ERG.[26]
Abbreviations: AE= adverse event, BAT = best available treatment, BID = bis in die (twice daily)

ERG comment: The ERG has concerns on the company's approach for the haematological adverse events. Firstly, the ERG believes that the RBC transfusion costs were not the only relevant cost items in haematological adverse event management.

For the inclusion of the non-haematological, less severe adverse events, a 10% threshold criteria was used by the company. The ERG considered that the choice of this threshold level was rather arbitrary, for instance a lower threshold like 5% might have captured other relevant adverse events. Furthermore, it was not clear how this 10% threshold was operationalised, for instance whether the incidences from the pooled or PERSIST-2 BID safety dataset were used, or whether both pacritinib and BAT arm incidences were required to be above 10% simultaneously for an adverse event inclusion or having only one arm incidence above 10% would have sufficed for eligibility.

Finally, the ERG had concerns on the fact that the original safety dataset included patients with blood platelet count higher than 50,000/μL. Therefore, the AE incidences from the safety dataset subpopulation consisting of patients with blood platelet count less than 50,000/μL, in line with pacritinib indication, were provided by the company upon ERG's request. These AE incidences are given in Table A6.3 (grade 3 or 4 adverse events only) and Table A6.4 (less severe grades, more common adverse events with a higher than 10% incidences) below. It can be observed that in Table A6.3 and A6.4, there are a number of adverse events that were not included in the AE tables from the original safety dataset. It was unclear to the ERG why these new adverse events seen in the blood platelet < 50,000/μL subpopulation were not reported as adverse events in the tables from the original safety dataset. For the sake of consistency with the indicated population and completeness, the ERG considers the AE incidences from the blood platelet < 50,000/μL subpopulation safety dataset as more reliable.

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1 and PERSIST-2 population (provided in Table 5.6), multiplied with the estimated annual management cost of AML, derived from TA386 (£46,711.49 per year after inflating to 2017).

5.2.9.7 Other costs

Terminal care costs were applied as a one-off cost at the time of death. This cost item included weekly costs for two blood transfusions and one outpatient visit applied over a duration of 18 weeks (£15,403) as well as a total palliative care cost (e.g. increased pain relief) of £6,865. The first part of the terminal care was based on the assumptions taken in TA386, and the second one was derived from the literature.[48]

ERG comment: In the base case, no wastage costs were assumed for pacritinib. The ERG considers this assumption to be unrealistic. Instead of the arbitrary 5% wastage cost assumption, the ERG requested the company to implement the actual wastage that would have occurred due to the unfinished package/vial at the end of the treatment to the model. An exploratory scenario analysis was conducted to test the impact of the wastage costs in Section 5.3.

In the company base case, the treatment composition for BAT was based on PERSIST-2 trial only, which was reflecting the UK clinical practice more realistically according to the company. For the sake of consistency, the ERG considers that the treatment composition of the BAT arm should be based on pooled PERSIST-1 and PERSIST-2 data, since the model uses other effectiveness and safety estimates from the pooled dataset.

The company applied the percentage resource use reduction from JUMP study to BAT arm resource use estimates. The ERG disagrees with this approach. JUMP study was reporting percentage resource use reduction associated with ruxolitinib in comparison to BAT. It is questionable to what extent these reductions can be generalisable for pacritinib, firstly it is a different drug, secondly BAT arm in PERSIST trials included ruxolitinib and finally patients in PERSIST trials are of a different population (blood platelet count less than 50,000). Hence the ERG deems non-differential resource use estimates more plausible, given lack of evidence.

The company used time-variant treatment specific RBC transfusion rates, however the statistical test results showing the time trend and treatment effect on RBC transfusion rates were not provided in the CS. The impact of using pooled RBC transfusion rates is expected to be small.

The ERG had some difficulties in confirming some of the adverse event costs from their cited sources. Furthermore, the ERG noticed that for some of the adverse events, the unit cost for Grade 3/4 severity and the unit cost for less severe types were the same. The ERG considers this implausible, but expects that the impact of this on incremental results to be small.

The company used pooled LT rates for both pacritinib and BAT treatment arms. However, the incidence rates in Table 5.6 suggest that incidence rates in the pacritinib and BAT treatment arms are different (pacritinib vs. BAT incidence rate ratio: 1.93 with 0.41 and 9.11 as lower and upper Wald confidence intervals, respectively). Therefore, the ERG considers that treatment specific LT rates from Table 5.6 should be used in the model.

A great deal of the model inputs (e.g. percentage of BAT treatment duration after initially assigned treatment discontinuation, resource use estimates etc.) were based on clinical expert suggestions or from

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Table 5.2: Company base-case PSA cost effectiveness results (discounted)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
Pacritinib	[redacted]	1.90	[redacted]	0.72	[redacted]
BAT	[redacted]	1.18			

Key: ICER, incremental cost effectiveness ratio; Incr., incremental; LYG, life years gained; QALYs, quality-adjusted life years.

The mean ICER from PSA results is [redacted], which is higher than the deterministic ICER of [redacted]. The scatterplot from the PSA iterations (Figure 5.6) suggests that there is a linear relationship between incremental costs and incremental QALYs. Furthermore, the cost effectiveness acceptability curve (CEAC) curve (Figure 5.7) for pacritinib increased until [redacted] per QALY gained and then seemed to be flat between WTP values of [redacted] and [redacted] per QALY gained and started to decrease afterwards. The CEAC is at approximately [redacted] at a willingness to pay threshold of £30,000, and [redacted] at a willingness to pay of £50,000. The company did not elaborate on the scatterplot and the CEAC results.

[redacted] 2: Scatterplot from the probabilistic sensitivity analysis iterations

[redacted]

Source: ERG based on PSA data from the company's model.

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Table 5.3: ERG exploratory analysis – pacritinib wastage costs

Scenarios	Pacritinib		BAT		Inc. Costs (£)	Inc. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
ERG base-case (no wastage)	[redacted]	2.16	[redacted]	1.68	[redacted]	0.48	[redacted]
Scenario (wastage)	[redacted]	2.16	[redacted]	1.68	[redacted]	0.48	[redacted]

Abbreviations: BAT = best available therapy; CS = company submission; ERG = evidence review group; ICER = incremental cost effectiveness ratio; QALYs = quality adjusted life years

Additional scenario 5: PERSIST-2 BID subgroup

In this scenario, the ERG performed a subgroup analysis for the expected license population (PERSIST-2 BID). Unlike the ERG base-case, where the OS survival regression equation for pacritinib was adjusted for response as a covariate, when the BID population is selected, the OS survival regression equation is not adjusted for response. This might be due to the low number of patients (and responders) in the BID arm. Thus, for completeness, the results of the ERG base-case assuming unadjusted OS are also presented in Table 5.33. It can be observed that the ICER for the PERSIST-2 BID subgroup is [redacted], thus, [redacted] lower than the ERG preferred base-case ICER. Whereas it is true that the analysis based on PERSIST-2 BID data only resulted in a substantially lower ICERs it is also true that due to the limited number of BID patients, these results are also more uncertain.

Table 5.4: ERG subgroup analysis – PERSIST-2 BID

Scenarios	Pacritinib		BAT		Inc. Costs (£)	Inc. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
ERG base-case (PERSIST pooled covariate adjusted)	[redacted]	2.16	[redacted]	1.68	[redacted]	0.48	[redacted]
Scenario (PERSIST pooled covariate unadjusted)	[redacted]	1.79	[redacted]	1.68	[redacted]	0.11	[redacted]
Scenario (PERSIST-2 BID covariate unadjusted)	[redacted]	2.43	[redacted]	1.63	[redacted]	0.80	[redacted]

Abbreviations: BAT = best available therapy; CS = company submission; ERG = evidence review group; ICER = incremental cost effectiveness ratio; QALYs = quality adjusted life years

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the results, for which the ERG was unable to determine the cause of such inconsistencies within the time frame of this appraisal. While this might indicate that the model is not error-free, the impact of correcting these potential flaws on the ICER is not expected to be as large as the impact regarding overall survival. Finally, the ERG explored the impact of using EQ-5D instead of MF-8D for deriving utilities, including wastage costs for pacritinib and a subgroup analysis for the expected license population (PERSIST-2 BID). Using EQ-5D instead of MF-8D increased the ICER by [redacted]. The scenario assuming wastage costs for pacritinib resulted in a minor increase of the ICER. The ICER for the PERSIST-2 BID subgroup was [redacted] lower than the ERG preferred base-case ICER. However, results for this subgroup are more uncertain due to the limited number of BID patients in the trial.

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