# TECH-VER

## Input Calculations

*Completeness:*

* Input calculations for transition probabilities for progression, death: the extrapolation parameters obtained from survival regression are in the “*Extrapolation\_Ind*” sheet. However the details of the survival regression (outputs, etc) and the codes/ data inputs used in the regression were not provided. The %PFS and %OS were also provided in this sheet (Columns N-P). The % PFS and %OS values and the pseudo patient level data used in survival regression are from the OS and PFS KM curves from the RESORCE trial (Appendix 1 of the description document).
* Input calculations for transition probabilities for time on treatment: the percentages of the patients on regorafenib treatment are in the “*ToT*” sheet (Colum E).
* Input calculations for regorafenib costs: The cost calculations (drug costs, hospitalization, medical staff visits, One-off progression costs and tests) including resource use frequency and unit costs are given in the “Rego\_Cost\_Input” sheet for the progression free and progressed disease states together with their sources.
* Input calculations for BSC costs: The cost calculations (drug costs, hospitalization, medical staff visits, One-off progression costs and tests) including resource use frequency and unit costs are given in the “Pla\_Cost\_Input” sheet for the progression free and progressed disease states together with their sources
* Input calculations for AE costs: The AE costs were calculated in the “AEs” sheet. The overall weighted AE costs are calculated for the BSC and regorafenib
* Utility inputs: In the “parameters” sheet, no calculations for state utilities and AE disutilities but taken from company submission.
* Summary of the Inquire® output:



* No hidden sheets
* Some named items with errors
* Some formulas with errors
* Some formula with hardcoded parameters

*Consistency*

* # in PF is taken from min(PFS,OS)
* AE weights are found from Table 38 from CS
* Unit costs for resource use can be found from Table 49 but some of the unit costs used in the model are different from the ones reported in Table 49 ( for instance A&E admission in the model is 204 whereas in the CS it was reported as 138)
* Resource use frequency values were from the ERG report Table 26 in TA 514
* TTD log-logistic curve could be traced back in the ERG report (Figure 17) where it is assumed that patients on treatment on the latest data cut off were considered as censored
* OS (independent Weibull) and PFS (KM) extrapolation curves are in line with the ERG preferred choices in the ERG report.

**Black-box tests**

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| *Pre-analysis calculations* | |
| Does the technology (drug/device, etc.) acquisition costs increase with higher prices? | Yes. When “Rego\_Cost\_Input” Sheet, Cell range: “B5” is changed with a higher value, Drug related costs (“Analysis” Sheet, Cell range: “C27” also increases) |
| Does the drug acquisition cost increase for higher weight or body surface area? | No, dose was not considered as a function of weight or body surface area, but it is in line with the license |
| Does the healthcare resource use costs increase with higher unit costs/ higher resource use frequency? | Yes. For instance when “Rego\_Cost\_Input” Sheet, Cell range: “B8” or “C8” is changed with a higher value, Resource use related costs (“Analysis” Sheet, Cell range: “D27” also increases) |
| Does the AE costs increase with higher unit costs/ higher AE incidence frequency? | Yes. For instance when “AE” Sheet, Cell range: “E11” or “B16” is changed with a higher value, AE related costs (“Analysis” Sheet, Cell range: “E27” also increases) |
| Does the probability of an event, derived from an odds ratio (OR)/ relative risk (RR) / hazard ratio (HR) and baseline probability, increases with higher OR/RR/HR? | Not applicable (Independently fitted models were used and no OR, RR, HR were applied.) |
| In a partitioned survival model, does the progression free survival curve or the time on treatment curve crosses the overall survival curve? | No for PFS, as the no of nonprogressed and alive uses min(OS,PFS) at any time (“Regorafenib” sheet column “J” and “Placebo” sheet column “H”)  Such a control for ToT was not implemented (“Regorafenib” sheet column “H”) |
| If survival parametric distributions are used in the extrapolations or time-to-event calculations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (the Weibull or Gamma) distribution(s) after replacing/transforming some of the parameters? | Yes, Weibull formula can generate the exponential distribution results as well (e.g. when cells “I7:I8” in the “Extrapolation\_Ind” sheet are made equal to “H7:H8”, Weibull extrapolation in column “I” is equal to the exponential extrapolation in column “H”). Generalised gamma not used. |
| Is hazard ratio calculated from Cox proportional hazards model applied on top of the parametric distribution extrapolation found from the survival regression? | Not applicable (Independently fitted models were used and no OR, RR, HR were applied.) |
| For the treatment effect inputs, if the model uses outputs from WINBUGs, are the OR, HR and RR values all within plausible ranges? (should be all non-negative and the average of these WINBUGs outputs should give the mean treatment effect) | Not applicable (No WinBUGS output was used.) |

**White-box testing**

The input cost calculations (Rego\_Cost\_Input and Pla\_Cost\_Input sheets) were checked line by line, no issues were detected

The input effectiveness calculations for OS and PFS (Extrapolation\_Ind sheet) were checked line by line. It was found out that the OS extrapolation coefficients for Regorafenib Weibull are using the cycle number (28 days) whereas the extrapolation coefficients for BSC Weibull are using the month for time units. This difference was discussed with the modeler. It appeared that the modeler used the KM curves from January 23rd 2017 dataset (overall survival) for regorafenib (Figure 1 from Response to the CL in TA514 p290), whereas for placebo, the KM curves from the 5th August 2016 dataset was used (Figure 4 in the CS in TA514 ). It was not clear which PFS data was used (which data cut-off used not clear).

**Replication-based testing:**

None, as the issues identified in the previous stages are resolved/ their root cause is found.

## Event/state calculations

*Completeness:*

* calculation of the distribution of cohorts among different health states at a given cycle in a state transition model

% of ToT/ number of patient under tx🡪 was calculated in columns G in “Regorafenib” sheet

% of Progression free/ number of patients progression free🡪 is calculated in column “J” in “Regorafenib” sheet and column “H” in “Placebo” sheet.

% of PD / number of patients in PD🡪 is calculated in column “K” in “Regorafenib” sheet and column “I” in “Placebo”

% of Death/ number of patients in Death🡪 is calculated in column “L” in “Regorafenib” sheet and column “J” in “Placebo” sheet.

% newly progressed / number of patients in newly progressed🡪 is calculated in column “N” in “Regorafenib” sheet.

* assignment of costs/QALYs/other health outcomes to the relevant states or events in the electronic model.

Assignment of Costs:

Regorafenib drug acquisition costs: in “regorafenib” sheet, columns “Q-X” with different PAS schemes (W-X more the DCF from the drug sales)

Placebo drug acquisition costs: in “placebo” sheet, column “N” with different PAS schemes (W-X more the DCF from the drug sales)

Regorafenib hospitalization, medical staff visit, lab test, radiological test, adverse event costs: in “regorafenib” sheet, columns “Y:AC” for progression free state, for progressed disease, columns “AD-AH”.

Placebo hospitalization, medical staff visit, lab test, radiological test, adverse event costs: in “placebo” sheet, columns “O:S” for progression free state, for progressed disease, columns “U-X”.

Assignment of Utilities:

QALY assignment: For regorafenib🡪 “Regorafenib” sheet: “AN:AO” columns for PF and PD states and column: “AP” for Adverse Events utility decrements. For placebo🡪“Placebo” sheet: “AD:AE” columns for PF and PD states and column:”AF” for Adverse Events utility decrements.

*Consistency*

* # in PF is taken from min(PFS,OS) (this was not mentioned in the technical report)
* # patients in death is calculated in line with the report
* # patients in PD is calculated in line with report
* The AE incidence probability calculation is not in line with the report (in the report it was mentioned that conversion was applied from *rate to probability* however these were not rates but proportions, and those were applied directly in the model. Also AE incidences were applied to both PF and PD states, even though it was not mentioned in the report)

**Black-box testing**

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| Calculate the sum of the number of patients at each health state | Should add up to the cohort size.  Yes, “Regorafenib” sheet column “M”, “Placebo” sheet column “K” sums up to 1000. |
| Check if all probabilities and number of patients in a state are greater than or equal to zero | There are no probabilities but it is an area under the curve model. However all of the PFS and OS are larger than or equal to zero |
| Check if all probabilities are smaller than or equal to one | There are no probabilities but it is an area under the curve model. However all of the PFS and OS are smaller than or equal to one. |
| Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods? | Should be larger  no  The number of death is increasing (“Regorafenib” sheet column “O”; “Placebo” sheet column “L”).  The number of progression free is decreasing for placebo (“Placebo” sheet column “G”) however progression free is not always decreasing for regorafenib (“Regorafenib” sheet column “N”) particularly look at cell N22. Probably due to entering the wrong number. |
| In case of lifetime horizon, check if all patients are dead at the end of the time horizon | Yes  Look at “Regorafenib” sheet cell “L204” and “Placebo” sheet cell “J203” , all patients are dead. |
| *Discrete event simulation specific:* sample one of the “time to event” types used in the simulation from the specified distribution. Plot the samples and compare the mean and the variance from the sample | Not applicable, as it is not a DES model |
| Set all utilities to one  Set all utilities to zero | The QALYs accumulated at a given time would be the same as the life years accumulated at that time  Yes, when “Parameters” sheet Cell D24🡪1, D25🡪0, D28, D29🡪0, then all QALYs = LYs (“Regorafenib” sheet columns “AK:AM”=”AN:AP” and “Placebo” sheet columns “AA:AC”=”AD:AF”).  No utilities will be accumulated in the model  Yes, when “Parameters” sheet Cell D24🡪0, D25🡪0, D28, D29🡪0, then all QALYs=0 (“Regorafenib” sheet columns “AK:AM”=0 and “Placebo” sheet columns “AA:AC”=0). |
| Decrease all state utilities simultaneously (but keep event based utility decrements constant) | Lower utilities will be accumulated each time  Yes, when “Parameters” sheet Cell D24🡪0.811/2 then total QALYs are decreased in “Analysis” sheet cells “E15:E16”. |
| Set all costs to zero | No costs will be accumulated in the model at any time  Yes, when “Parameters” sheet Cell D39:D131 are changed to zero then total costs are zero for both regorafenib and BSC as can be seen in “Analysis” sheet cells “C15:C16” |
| Put mortality rates to 0 | Patients never die  Not applicable as there are no “mortality rates” but with OS, yes  If OS are all changed to 1 (“Regorafenib” sheet column “D”🡪1, then number of death are all zero in column “L”), OR (“Placebo” sheet column “D”🡪1, then number of death are all zero in column “J”) |
| Put mortality rate extremely high | Patients die in the first few cycles  Not applicable as there are no “mortality rates” but with OS, yes  If OS are changed to zero after the first cycle, all patients are diead after the first cycle  (“Regorafenib” sheet column D🡪0 after 1st cycle, then number of death is 1000 in column “L” after cycle 1)  (“Placebo” sheet column “D”🡪 0 after 1st cycle, then number of death is 1000 after 1st cycle in column “J”). |
| Set the effectiveness, utility and safety related model inputs for all treatment options equal | Same life years and QALYs should be accumulated for all treatment at any time  No  When “Placebo” sheet column “D” and column “F” were made equal to “Regorafenib” sheet column “D” and column “F”, respectively, and when the “Parameters” sheet cell “B34” value is set equal to “B33” then we expect the QALYs and LYs to be the same on “Analysis” sheet “E15:E16” and “G15:G16”.  Difference can be seen in further decimals…  However undiscounted QALYs in the “AQ” and “AG” columns in the “Regorafenib” and “Placebo” sheets are the same so the issue is not caused by event/state calculations |
| In addition to the inputs above, set cost related model inputs for all treatment options equal | Same costs, life years and QALYs should be accumulated for all treatment at any time  No  When the resource use frequency values in the “Rego\_Cost\_input” sheet are set equal to the resource use frequency values in the “Pla\_Cost\_Input” and the AE weights and in the “AEs” sheet for Regorafenib and BSC are set equal to each other, still a difference exists, which can be seen on the “Analysis” sheet cells: “C15:C17” and in the undiscounted costs in the “Y” and “AI” columns in the “Placebo” and “Regorafenib” sheets |
| Change around the effectiveness, utility and safety related model inputs between two treatment options | Accumulated life years and QALYs in the model at any time should be also reversed  No.  When the number of progression free and death patient calculations in columns “J” and “K” of the “Regorafenib” sheet uses the PFS and OS values from the “Placebo” sheet in columns “D” and “E” and when the number of progression free and death patient calculations in columns “H” and “I” of the “Placebo” sheet uses the PFS and OS values from the “Regorafenib” sheet in columns “D” and “E” and the AE treatment specific incidence probabilities on the “Parameters” sheet cells “B33” and “B34” are reversed🡪  The LYs and QALYs on the “Analysis” sheet, cells “E15:E16” and “G15:G16” are not reversed.  However, undiscounted QALYs in the “AQ” and “AG” columns of the “Regorafenib” and “Placebo” sheets were reversed so the problem is not in the event/state calculations |
| Check if the number of alive patients estimate at any cycle is in line with general population life table statistics | At any given age, the % alive should be lower or equal in comparison to the general population estimate  Yes  The mortality rates “Regorafenib” sheet column “P” and “Placebo” sheet column “M” are always higher than the age-specific mortality rates from the UK life tables in the “life tables” sheet (highlighted cells) |
| Check if the QALY estimate at any cycle is in line with general population utility estimates | At any given age, the utility assigned in the model should be lower or equal in comparison to the general population estimate  No  The utility values used in the model are a bit higher than the age specific UK utility values from Ara et al as shown in the columns “X:Y” of the “life tables” sheet after a certain age. |
| Set the inflation rate of the previous year higher | The costs (which are based on a reference from previous years) assigned at each time will be higher  Not applicable (inflation rate was not applied, as the goal was to replicate the model where the decision of TA555 was based on) |
| Calculate the sum of all ingoing and outgoing transition probabilities | Not applicable as it is an AUC type model, no conventional transition probabilities were used. |
| Calculate the number of patients entering and leaving a tunnel state throughout the time horizon | Not applicable as there is no tunnel state |
| Check if the time conversions for probabilities were conducted correctly. | Yes  In the “Extrapolation\_Ind” sheet, the Weibull function in columns “I” and “E” use the corresponding time units (cycles, months) where the time to event regressions were conducted. |
| *Decision tree specific:* calculate the sum of the expected probabilities of the terminal nodes | Not applicable as it is not decision tree model |
| *Patient-level model specific:* check if common random numbers are maintained for sampling for the treatment arms? | Not applicable as it is not a patient level model |
| *Patient-level model specific:* check if correlation in patient characteristics is taken into account when determining starting population? | Not applicable as it is not a patient-level model |
| Increase the treatment acquisition cost | Costs accumulated at a given time will increase during the period when the treatment is administered  Yes  When the regorafenib cost in “Rego\_Cost\_Input” “B5” is increased, accumulated drug acquisition costs in the “Regorafenib” sheet column “Q” is also increased. |
| *Population model specific:* set the mortality and incidence rates to zero | Not applicable as it is not population specific model |

**White-box testing**

Calculation of the distribution of cohorts among different health states:

In “Regorafenib” sheet, columns “J” to “O” and in “Placebo” sheet, “H” to “L” were checked.

The calculations seem to be correct.

Only in the “Newly Progressed” calculations in the column “N” of the “Regorafenib” sheet is calculated from (PFS(t) – PFS(t+1)). This is an overestimate of the newly progressed, as this value corresponds to newly progressed and newly dead.

Calculation of the assignment of utilities

The utility assignment calculations columns “AN:AQ” in the “Regorafenib” sheet and the columns “AD:AG” in the “Placebo” sheet are checked seem to be correct.

Only it was realized that the AE event utility decrements were calculated, assuming that the AE incidences can be both in the progression free and progressed disease states (column “AP” for Regorafenib and column “AF” in Placebo)

Calculation of the assignment of the costs

The cost assignment calculations of regorafenib (“Regorafenib” sheet, columns “Y:AI” and “Placebo” sheet, columns “N:Y”) are checked.

It was realized that the AE event costs were calculated assuming that AE incidences can be both in the progression free and progressed disease states.

Also the formulae between the regorafenib and BSC for the “medical staff visit” costs in the progression free state are different (“Regorafenib” sheet column “Z” and “Placebo” sheet column “P”) and the lab test for PD states (“Regorafenib” sheet column “AG” and “Placebo” column “W”) are different. The resource use frequency that were zero are automatically dropped from the formulae, but this caused the one of the black box tests to fail.Even though the cost inputs between Regorafenib and Placebo are reversed, the cost results were not reversed.

Additionally, it was mentioned that full dose was assumed in the base case while calculating the drug acquisition costs of regorafenib in the report, but it is realized that a mean dose adjustment of 0.901 is applied in the base case

**Replication-based testing:**

None, as the issues identified in the previous stages are resolved/ their root cause is found.

## Results Calculations

Summation of the accumulated costs, QALYs, and life years or other outcomes over time to obtain total costs, QALYs, and life years or other total outcomes

Completeness/consistency

* The calculation and the interpretation of the incremental results and ICER(s)

Columns “AI, AM, AQ” in the “Regorafenib” and columns “Y,AC, AG” in the “Placebo”

“Analysis” sheet

“Results for the paper” sheet

“Results” sheet

* Applying half cycle correction/ discount rates

Columns “AI:AS” in the “Placebo” sheet and columns ”AS:BE” in the “Regorafenib” sheet

* Disaggregation of total costs and total QALYs

“Regorafenib” sheet columns “AW:BO”

“Placebo” sheet “AU:BM”

The results in Table1, Table2, Table 4 in the “Regorafenibmodel\_description\_.docx” could have been replicated.

**Black-box testing**

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| *Result calculations* | |
| Check the incremental life years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved? | Yes, higher OS and PFS of Regorafenib led to higher LYs and higher QALYs |
| Check the incremental cost results. Are they in line with the treatment costs? | Yes, higher treatment costs for regorafenib led to higher drug acquisition costs and higher overall costs |
| Total life years > total quality adjusted life years | Yes (Analysis sheet ) |
| Undiscounted results > discounted results | Yes (“Parameters” sheet cells B11:B12🡪 0, the all values in the “analysis” sheet are higher |
| Divide undiscounted total QALYs by undiscounted life years. | This value should be within the outer ranges (maximum and minimum) of the all utility value inputs.  Yes, it is around 0.78 for both placebo and regorafenib, and this value is between 0.81 (utility for PF) and 0.76 (utility for PD) |
| Subgroup analysis results: How do the outcomes change if the characteristics of the baseline change? | Better outcomes for better baseline health conditions and worse outcomes for worse health conditions are expected.  Not applicable, no subgroup analysis were conducted |
| Could you generate all the results in the report from the model (including the uncertainty analysis results)? | Yes (besides the uncertainty analysis) |
| Does the total life years, QALYs and costs decrease if a shorter time horizon is selected? | Not applicable, time horizon not adjustable |
| Is the reporting and contextualization of the incremental results correct? | The use of the terms such as: “dominant”/ “dominated”/ “extendedly dominated”/ “cost-effective” etc. should be in line with the results.  In the incremental analysis table involving multiple treatments, ICERs should be calculated against the next non-dominated treatment.  Yes |
| Are the reported ICERs in the fully incremental analysis non-decreasing? | Yes  Not applicable, only 2 interventions |
| If disentangled results are presented, do they sum up to the total results? (e.g. different cost types sum up to the total costs estimate) | Yes  “Analysis” sheet  C27:E27🡪 sum up to C15  C28:E28🡪 sum up to C16 |
| Check if half cycle correction is implemented correctly (total life years with half cycle correction should be lower than without) | The half cycle correction implementation should be error free. Also check if it should be applied for all costs, for instance if a treatment is administered at the start of a cycle, half cycle correction might be unnecessary.  Yes  “Regorafenib” sheet columns BB:BD and BL:BN and “Placebo” sheets columns AZ:BB and BJ:BL . Indeed drug acquisition costs are not half cycle corrected. |
| Check the discounted value of costs/QALYs after 2 years | Discounted value=undiscounted/(1+r)2  Yes  For instance the discount multiplier “AJ34” in “Regorafenib” sheet is equal to 1/(1+0.035)2 |
| Set discount rates to zero | The discounted and undiscounted results should be the same  Yes  When “Parameters” “B11:B12” are set to zero, columns BU:BW are equal to columns CF:CH in the “Regorafenib” sheet |
| Set mortality rate to zero | The undiscounted total life years per patient should be equal to the length of the time horizon  Yes  When all OS is set to 1 in column D in the “Regorafenib” sheet than the total undiscounted LYs, AM206, is equal to 14.96 years as the time horizon as can be seen in AS204 |
| Put the consequence of adverse event/discontinuation to zero. (zero costs and zero mortality/utility decrements) | The results would be the same as the results when AE rate is set to zero.  Yes  ICER 75778 when AE incidences are zero (can be seen from Analysis sheet E20 after Parameters sheet B33:B34 are set to zero)  ICER 75778 when AE cost and utility are zero (can be seen from Analysis sheet E20 after Parameters sheet B42:B43 and B28:B29 are set to zero) |
| Divide total undiscounted treatment acquisition costs by the average duration on treatment. | This should be similar to treatment related unit acquisition costs  Yes  The total undiscounted drug acquisition cost for regorafenib can be found from Q206 in the “Regorafenib” sheet.  The average ToT was 10.532.  The division would lead to 3065 pounds, slightly lower than the cycle based regorafenib cost of 3371 |
| Set discount rates to a higher value | Total discounted results should decrease  Yes  When discount rates are set to higher values (i.e. twice) from “Parameters” sheet B11: B12, the results decrease as can be seen from the “Analysis sheet” |
| Set discount rates of costs/effects to an extremely high value | Total discounted results should be more or less the same as the discounted results accrued in the first cycles  Yes  When discount rates are set to extremely higher values then in the “Regorafenib” sheet, the discounted costs, Qalys become zero after a number of cycles (columns AW:BE) |
| Put adverse event/discontinuation rates to zero and then to extremely high level. | Less costs higher QALYS/LYs when adverse event rates are 0, higher costs and lower QALYS/LYs when AE rates are extreme  Yes  When adverse events set to zero, (parameters B33:B34) then costs decrease and qalys increase slightly (can be seen from analysis sheet)  When AE utility and cost impacts are increased Parameters B42:B43 and B28:B29, higher costs and lower QALYs (can be seen from the analysis sheet) |
| Double the difference in efficacy and safety between new intervention and comparator and report the incremental results. | Approximately twice of the incremental effect results of the base case. If this is not the case : report and explain the underlying reason/ mechanism  Not applicable, as the PFS, OS are indepenedently modelled and therefore the treatment effect is not quantified like a HR or OR |
| Do the same for a scenario in which the difference in efficacy and safety is halved. | Approximately halve of the incremental effect results of the base case. If this is not the case : report and explain the underlying reason/ mechanism  Not applicable, as the PFs and OS are independently modelled and therefore the treatment effect is not quantified like a HR or OR. |

**White-box testing:**

The half cycle correction, discounting and result calculations were checked in detail (the cell ranges mentioned in the Completeness/consistency part).

In the discounting calculations, it was noticed that the time conversion from year to weeks, different numbers were used in the “Regorafenib” sheet (column AS, 365/7) and in the “Placebo” sheet (column AI, 52).

Specific attention is given to the PAS application calculations in “Regorafenib” sheet columns Q:X.

The optimal PAS parameters were obtained from the VBA macros in Module 3, using goal seek functionality of Excel to put the ICER less than 50,000 by changing the PAS parameters while having the maximum sales from drug acquisition.

**Replication-based testing:**

None, as the issues identified in the previous stages are resolved/ their root cause is found.

## Uncertainty analysis calculations

OWSA, PSA and VoI calculations and the Scenario analyses

Completeness/ *Consistency*

* “OWSA” calculations and results could not be found in the model, therefore they could not be verified. Also in the model, in the “Parameters” sheet, columns “F” and “G” do not correspond to the upper and lower 95% CI values.
* PSA calculations can be found in the “Parameters” sheet, (column “C” where the parameters are sampled using the standard error data in column “E” and parameters “I” and “J”). “Simulation” sheet, where the results of each sampled iteration is reported. “CE-Plane” and “CEAC” sheets where the PSA results are used to plot the CE plane and CEAC curves. “Simulation()” and “CEAC()” Excel VBA macros, which conducts the PSA calculations automatically
* VoI calculations: Simulation\_EVPI() macro reports the sampled inputs used in the PSA as well as the resulting incremental cost/QALY results in the “EVPI\_Simulation” sheet of the model. Afterwards, the values on this sheet are uploaded to the SAVI online tool and EVPI/ EVPPI and HTA Risk calculations are performed by this SAVI tool. The verification of SAVI tool is out of the scope of this project.

The standard errors and the distributions used in the PSA of the model seem to be consistent with the reported standard errors

It is not clear how the standard error of the PFS and ToT curves were obtained. It was also not explained in the report.

Also in the report it is mentioned that the survival regression coefficients were sampled independently, each using Normal distribution, however, in the model, they were sampled using a multivariate normal distribution, incorporating the correlation between the coefficients.

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| *Uncertainty analysis calculations* | |
| Are all parameters subject to uncertainty included in the one-way sensitivity analysis (OWSA)?  Check if the OWSA includes any parameters associated with joint uncertainty (e.g. parts of a utility regression equation, survival curves with multiple parameters). | Cannot be checked as the OWSA calculations were not provided  Cannot be checked as the OWSA calculations were not provided |
| Are the upper and lower bounds used in the one-way sensitivity analysis used confidence intervals based on the statistical distribution assumed for that parameter?  Are the resulting ICER, incremental costs/QALYs with upper and lower bound of a parameter plausible and in line with a priori expectations? | Cannot be checked as the OWSA calculations were not provided  Yes  The directions of the ICER in the tornado diagram seems plausible.  For HR for ToT, a higher HR means lower ToT, hence less drug acquisition costs.  For cost parameters specific to regorafenib (BSC), higher values increase (decrease) ICER  Higher utility value for PFS would decrease the ICER as regorafenib has a more favorable PFS profile |
| Check that all parameters used in the sensitivity analysis have an appropriate associated distributions  - upper and lower bounds should surround the deterministic value (i.e. Upper bound ≥ mean ≥ Lower bound)  - standard error and not standard deviation used in sampling  - Lognormal / gamma distribution for hazard ratios and costs/ resource use  - Beta for utilities and proportions/probabilities  - Dirichlet for multinomial  - Multivariate normal for correlated inputs (e.g. survival curve or regression parameters)  - Normal for other variables as long as samples don’t violate requirement to remain positive when appropriate | \* The lower and upper bounds were not reported in the model.  \* standard errors were used in sampling and not standard deviation  \* the distribution choices seem to plausible (can be seen in the “parameters” sheet column H and in the “Extrapolation\_Ind” sheet.  - Lognormal / for hazard ratios and gamma distribution for costs/ resource use  - Beta for utilities and proportions/probabilities  - Dirichlet for multinomial  - Multivariate normal for correlated inputs (e.g. survival curve or regression parameters) |
| Check PSA output mean costs, QALYs and ICER compared to the deterministic results. Is there a large discrepancy? | No (in general)  The mean PSA results as can be seen in the row 11 of the “Simulation” sheet is very similar to the deterministic results in the “Analysis” sheet. (Also in the report) For instance ICER from deterministic and mean PSA are 76,754 and 78,073, respectively. |
| If you take new PSA runs from the excel model do you get similar results? | Yes, another PSA run had led to similar results, for instance a mean PSA ICER of 78,337. |
| Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier? | Yes, CEAC is in line with the scatter plots, for instance when WTP is zero, the probability that regorafenib is cost effective is around 5%, since 5% of the iterations are in the southeast quadrant. |
| Does the PSA cloud demonstrate an unexpected behavior or has an unusual shape? | No, no strange shape is observed in the PSA cloud, it can be characterized as an ellipse. |
| Is the sum of all CEAC lines equal to 1 for all WTP values? | Yes, for each WTP, CEAC for regorafenib and BSC sum up to 1 as can bes een in the “CEAC” sheet |
| Are the explored scenario analyses provide a balanced view on the structural uncertainty? (i.e. not always looking at more optimistic scenarios) | No, not all the sources of structural uncertainty were explored (for instance the distribution for extrapolation), however the model was also developed to explore how different MEA agreements are performing under different assumptions. |
| Are the scenario analysis results plausible and in line with a priori expectations? | Yes  The MEA agreements provide results as expected. Only simple discount scheme and money-back guarantee scheme resulted in an ICER of 50,000 (and an iNMB of 0), since the decision parameters for these schemes are continuous and the optimal MEA scheme parameters can be chosen that satisfies the ICER=50000 optimally.  The other two schemes have ICER less than 50,000 and therefore have a positive iNMB, since the decision parameter for these schemes is discrete.  In the scenario analysis 1:  Assuming full dose instead of MDI adjusted dose increased the total costs for regorafenib and ICER as expected.  Life treatment acquisition cap provided the best ICER, as this strategy is expected to be more robust on the variations of MDI.  In the scenario analysis 2 &3 :  Changing the interest rate has only impact on DCF and no impact on CE results  In scenario analysis 4:  Assuming a worse prognosis (in terms of PFS and OS) for Regorafenib led to decrease in LYs and QALYs for Regorafenib, decrease in incremental QALYs and an increase for ICER, as expected. The PBRSA type MEA provided the best ICER as this strategy is expected to be more robust on the variations on PFS.  In scenario analysis 5, treatment invariant resource use estimates were used. This led to an increase in resource use frequency of regorafenib and a decrease in resource use costs for BSC. As a result, in this scenario incremental costs and ICER have increased. None of the MEAs were successful in bringing down the ICER to plausible levels, as the source of structural uncertainty were not targeted by none of the MEAs |
| If a certain seed is used for random number generation (or previously generated random numbers are used), check if they are they scattered evenly between 0-1 when they are plotted? | Not applicable, as the seed of the random number generator was not fixated. |
| Compare the mean of the parameter samples generated by the model against the point estimate for that parameter, use graphical methods to examine distributions, functions | The sample means and the point estimates will overlap, the graphs will be similar to the corresponding distribution functions (e.g. Normal, Gamma, etc.)  The sample means and the point estimates are similar to a great extent, as can be seen in the “EVPI\_Simulation” sheet (rows 1 and 4). Only for HR of PFS BSC and ToT, the PSA sample mean deviates from the point estimate substantially (BR1 and BS1 cells).  The ks.test from R of the sampled parameters and the graphical methods were not  Explored due to time. |
| Check if sensitivity analyses include any parameters associated with methodological/ structural uncertainty (e.g. annual discount rates, time horizon). | No  They are not included in the PSA. |
| Value of information analysis if applicable: Was this implemented correctly?  Which types of analysis? Were aggregated parameters used? Which parameters are grouped together? Does it match the write-up’s suggestions?  Is EVPI larger than all individual EVPPI?  Is EVPPI for a (group of) parameters larger than the EVSI of that (group) of parameter(s)?  Are the results from EVPPI in line with OWSA or other parameter importance analysis (e.g. ANCOVA)? | Yes  EVPI is larger than EVPPI values. SAVI web interface was used. |
| Did the electronic model pass the black-box tests of the previous verification stages in all PSA iterations and in all scenario analysis settings? (additional macro can be embedded to PSA code, which stops the PSA when an error such as negative transition probability, is detected) | Not conducted due to time limitations |
| Check the correlation between 2 PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator) | Should be very low (very high) if different (same) random streams are used for different arms  Correlation between regorafenib and BSC costs is -0.056 as can be seen in the Simulation sheet, cell: “D4” |