Input from external expert and manufacturer on the 2nd Draft Assessment "Regorafenib as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib"

Project ID: PTJA02

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

The objective of this reviewer form is to standardise the process of reviewing rapid relative effectiveness assessments.

The 2nd version of the Rapid Assessment on Regorafenib as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib was open to review by external reviewer(s) between **between 25/09 and 02/10/2017**.

Comments received from

Clinical expert
Ulm University Hospital
Manufacturer
Bayer

All received comments are formally responded in this combined document, to be published on the EUnetHTA website, name of organisation/institution (or individual names of the reviewers/affiliations) disclosed.

Comments from clinical expert

Page	Line	Organisation	Comment	Reply from author
12		Ulm University Hospital	Drug related AEs>3 and SAEs: the columns habe been mixed up. Drug related AeEs>3 and SAEs are 51.9% and 10.4% for Rego and not for Placebo	This mistake was corrected in the final version
83		Ulm University Hospital	Product has been withdrawn by Bayer due to lower reimbursement than expected after the GBA evaluation	It is state in table A8 that there is no reimbursment of STIVARGA in Germany due to Negative opinion for both mCRC and GIST indication by G-BA
19		Ulm University Hospital	Last paragraph/2.8: Please check whether D0011 is correct	Yes it is correct. However, this sentence was modified in the final version for clarity.
18		Ulm University Hospital	Typo last paragraph: Applicability	This typo was corrected in the final version
10		Ulm University Hospital	Typo 2nd paragraph: already	This typo was corrected in the final version
22		Ulm University Hospital	Typo: Unresectable	This typo was corrected in the final version
23		Ulm University Hospital	Typo first paragraph: Previously	This typo was corrected in the final version
36		Ulm University Hospital	Typo under Results: May	This typo was corrected in the final version
41		Ulm University Hospital	Typo under Biomarker analysis: Retrospective	This typo was corrected in the final version
42		Ulm University Hospital	Typo first paragraph: Regorafenib	This typo was corrected in the final version

38		Ulm University Hospital	Typo last paragraph: exept	This typo was corrected in the final version
55		Ulm University Hospital	regorafenib or Regorafenib is both used throughout the text	This typo was corrected in the final version

Comments from Manufacturer

Page	Line	Organisation	Comment	Reply from author
13	19	Bayer AG	Topic: The authors stated that the addition of regorafenib to BSC induced a modest gain in terms of OS There is an inconsistency between the conclusion of the EUnetHTA authors on the OS gain and available medical benchmarks. According to ESMO-MCBS criteria (Cherny et al, 2015 and 2017) the gain in OS receives a Grade 4 which represents drugs with “a high level of proven clinical benefit.” The OS benefit is graded based on a dual rule: 1) the lower limit of the 95% confidence interval (CI) of the HR is below 0.65 and 3.0 gain in median OS or 2) the observed absolute incremental survival of 10% within 2 years is achieved. The observed absolute incremental survival at 24 months is 10% in the RESORCE trial (EUnetHTA dossier July 21st, Table x). In addition, the 37% reduction in risk of mortality is clinically relevant to patients in a population with expected survival ranging from 6 to 20 months, 5-year survival less than 5% (EUnetHTA dossier July 21st), and a history of negative trials in the 2L setting (Attachment a). This level of significant reduction in mortality risk is typically viewed as clinically meaningful. For example, adding bevacizumab to fluorouracil-based combination chemotherapy resulted in a significant reduction in death (HR 0.66), which is widely considered as a clinically meaningful improvement in survival (Hurwitz, 2004).	This comment is not related to a factual mistake but is about divergences in terms of results interpretation. Justifications that lead HTA bodies to these conclusions are already in the report.

13	20	Bayer AG	Topic: The authors stated that "...in view of the worsen safety profile notably in terms of grade ≥3 AEs, serious AEs and AEs leading to dose modification or reduction" The increase in AEs, which typically occurs with all anti-cancer therapies needs to be considered in light of the 37% reduction in mortality. The absence of evidence for a decline in health-related quality of life suggests a very positive benefit-risk profile for regorafenib. HCC patients previously treated with sorafenib have a high unmet medical need due to the low survival rate and deteriorated quality of life. Patients who have benefited from sorafenib in 1L treatment now have with regorafenib a treatment option in 2L. Regorafenib is associated with typical TKI-related TEAEs, which are manageable. These findings suggest that patients will be able to continue their activities of daily living as patients on regorafenib did not experience any clinically meaningful decline in health-related quality of life.	This comment is not related to a factual mistake but is about divergences in terms of results interpretation. Justifications that lead HTA bodies to these conclusions are already in the report.
13	25	Bayer AG	Topic: It was mentioned that "In view of the exploratory design of this endpoint the conclusion on quality of life is strongly limited, which is regrettable" It appears that the conclusions of the evaluators are based on the missing data from the EOT visit. Please note that the QoL analyses were not based on the EOT visit assessments but on a LSM time-adjusted AUC across all scheduled visits. AUC analyses uses all available data from patients rather than data based on a single time point (reference tables with completion rates in Attachment b). Completion rates are noted below in response to Page 54, Line 10 and were provided in the EUnetHTA Dossier of July 21st. The results do not appear to be impacted by missing data in particular during the time period while patients were on study drug when AEs would have been expected to impact QoL. Although, regorafenib is associated with a higher rate of TEAEs, a negative impact on the QoL cannot be inferred from the PRO data.	This comment is not related to a factual mistake but is about divergences in terms of interpretation. Justifications that lead HTA bodies to these conclusions are already in the report.

21	19	Bayer AG	Topic: Currently no active comparator of regorafenib is… used in clinical practice…": From a strictly regulatory point of view, no other treatment is currently approved or recommended by international guidelines for treatment in 2L uHCC. As a result, placebo plus BSC was the only appropriate comparator for the RESORCE clinical trial but clinical practice may vary from country to country. It needs to be noted that the fact that certain drugs may be used in certain patients and countries after sorafenib does not necessarily constitute a meaningful "clinical practice" that should be considered for the design of clinical trials. The contrary may actually be true: unproven or untested drugs such as chemotherapy in this setting, while sometimes given to patients, may lead to deterioration of the underlying liver dysfunction and could be associated with shortened survival, unless otherwise proven. Therefore, the incorporation or acceptance of unproven and untested drugs as control arm may lead to shorter OS in the control arm and may lead to a perceived false OS improvement of an experimental treatment. This practice would likely lead to rejection of study protocol by Health Authorities or Ethic Committees. Consequently, BSC was the only appropriate comparator in the RESORCE trial.	This comment is not related to a factual mistake but is about divergences in terms of interpretation. As stated in the report, placebo + BSC was considered as a relevant comparator. Please refer to the EUnetHTA guideline on comparator for more information about comparators selection by HTA bodies.
27	23	Bayer AG	Topic: ".... sorafenib faces some reimbursement restriction in Child-Pugh B patients" We suggest adding to this statement: "More than two-thirds of EU markets (18) reimburse sorafenib for the full label, including Child-Pugh B patients: England & Wales, Germany, Spain, Netherlands, Denmark, Norway, Sweden, Finland, Latvia, Lithuania, Estonia, Greece, Bulgaria, Portugal, Romania, Czech Rep, Slovakia, Slovenia."	This comment is not related to a factual mistake but is about divergences in terms of interpretation.

39	3	Bayer AG	Topic: Forest plot of subgroup analyses in Overall Survival The forest plot of the subgroup analysis for OS presented in Figure 4 on page 39 is based on the cut-off date February 29, 2016. In the submitted dossier dated July 21st, there was also the forest plot based on the cut-off date January 23, 2017 (Attachment c including Figure i). Although the updated OS analysis was based on more mature data, there was only a minor change in the HR from 0.627 to 0.614 (with no change in the incremental median OS of 2.8 months) between the original data cut-off 2016 and the updated data cut-off 2017. Due to a longer observation period, this updated analysis includes a larger number of events, which increases the statistical power of the subgroup analyses with minimal bias due to very low crossover of patients following the unblinding of the study. As expected, HR's of specific subgroups regressed to the overall mean HR further suggesting the consistency of effects across the trial population. We recommend adding Figure i in addition to Figure 4 (page 39).	This comment is not related to a factual mistake. Please note, that according to the RESORCE protocole, this REA is intentionnally focused on the primary analysis.
51	1	Bayer AG	Topic: Patient involvement The lack of patient input on the results is regrettable given the conclusion that the clinical benefit is labelled modest.	As stated in the report, the absence of patient involvment in particularly regreted by the HTA bodies involved in this REA.
52	5	Bayer AG	Topic: "After the grant of this positive opinion, the MAH of STIVARGA (Bayer) requested EUnetHTA to perform" Bayer AG requested to participate in the EUnetHTA JA3 Work Package 4 for regorafenib on January 20th, 2017. The kick-off for this REA was in March 2017, which is about 4 months before receiving the positive CHMP opinion. Please note that Bayer AG requests this sentence to be changed.	This sentence is modified in the final version.

52	12	Bayer AG	Topic: “Its chemical structure differs from sorafenib by the addition of one fluorine atom.” Regorafenib is structurally different than sorafenib, owing to the presence of a fluorine (Wilhelm S et al. Nat Rev Drug Discov 2006) atom in the central phenyl ring (Ravi S & Singal AK. Core Evid 2014;9;81–87). This minor structural difference has a major impact on potency and functionality, resulting in a broader spectrum of kinase inhibition and a higher inhibition potential than sorafenib in preclinical models. For example, in contrast to sorafenib, regorafenib also inhibits CSF1R, which has been implicated in the regulation of tumor-infiltrating macrophages. Evidence suggests that regorafenib is pharmacologically more potent than sorafenib (Jia JB et al. Oncologist 2010;15:732–743). Bayer AG recommends either removing the sentence focusing on the chemical structure as it may be misleading or adding the context as described here in the comment.	This comment is not related to a factual mistake but is about divergence in terms on interpretation. Chemical differences with sorafenib are important in view of the REA conclusions.
54	14	Bayer AG	Topic: "…regorafenib is likely to have an impact on patients' quality of life." Bayer AG recommends that a more appropriate statement would be that “… a negative impact on QoL cannot be inferred from the PRO data in the RESORCE trial.” The evidence of this conclusion is based on the high completion rate during the period while patients were receiving study drug. In the first 12 cycles for the EQ-5D completion rates ranged between 86.2%-100% for the placebo group and 94.8%-98.9% for the regorafenib group. Similarly, for the first 12 cycles for the FACT-Hep, the completion rates range between 79.3%-89.5% for placebo group and 86.8%-92.4% for the regorafenib group.	This comment is not related to a factual mistake but is about divergences in terms of interpretation. Justifications that lead HTA bodies to these conclusions are already in the report.

55	14	Bayer AG	Topic: "absence of adjustment for multiple analyses, there is insufficient evidence…" Performing multiple analyses (i.e sub-scales of the questionnaires) would require, in order to avoid erroneous inferences, stricter significance thresholds for individual comparisons to compensate for the number of inferences being made. Therefore, a correction for multiple analyses would further reduce the statistical significance of any observed difference in quality of life. In essence, adjusting for multiple analyses as suggested by the authors would strengthen the conclusion regarding the absence of a quality of life difference between the groups. Bayer AG recommends removing "absence of adjustment for multiple analyses" from the statement and reconsidering the conclusions regarding the impact of AEs on QoL given the high completion rates.	This comment is not related to a factual mistake but is about divergences in terms of interpretation. Justifications that lead HTA bodies to these conclusions are already in the report.