Regorafenib indicated as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib

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Rapid assessment of pharmaceutical technologies using the HTA Core Model® for Rapid Relative Effectiveness Assessment

REGORAFENIB INDICATED AS MONOTHERAPY FOR THE TREATMENT OF ADULT PATIENTS WITH HEPATOCELLULAR CARCINOMA WHO HAVE BEEN PREVIOUSLY TREATED WITH SORAFENIB

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Disclaimer

The assessment represents a consolidated view of the EUnetHTA assessment team members and is in no case the official opinion of the participating institutions or individuals.

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Conflict of interest

All authors and reviewers involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA Declaration of interest and confidentiality undertaking (DOICU) statement form.

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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
AFP	alpha-fetoprotein
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BCLC	Barcelona Clinic Liver Cancer
BSC	Best supportive care
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTC	Common terminology criteria for adverse events
DARE	Database of Abstracts of Reviews of Effects
DCR	Disease control rate
DILI	Drug-induced liver injury
DOICU	Declaration of interest and confidentiality undertaking
DOR	Duration of response
EASL	European Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
EFF	Efficacy analysis population
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQoL five dimensions questionnaire
EU	European Union
FACT-hep	Functional Assessment of Cancer Therapy-Hepatobiliary questionnaire
FAS	Full analysis set
GIST	Gastrointestinal stromal tumours
GRADE	Grading of recommendations assessment, development and evaluation
HBeAg	Hepatitis B e antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma

HCS	Hepatobiliary cancer subscale
HCV	Hepatitis C virus
HFSR	Hand–foot skin reaction
HR	Hazard ratio
HRQoL	Health-related quality of life
ICD	International classification of diseases
ILD	Interstitial lung disease
IVRS	Interactive voice response system
LSM	Least squares method
MA	Marketing authorisation
MAH	Marketing authorisation holder
mCRC	Metastatic colorectal cancer
MeDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical subject headings
MI	Myocardial infarction
MID	Minimum important difference
mRECIST	Modified response evaluation criteria in solid tumours
MRI	Magnetic resonance imaging
NASH	Non-alcoholic steatohepatitis
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall Survival
OTR	Objective tumour response
PD	Progressive disease
PFS	Progression free survival
PR	Partial response
PRAC	Pharmacovigilance risk assessment committee
PRES	Posterior reversible encephalopathy syndrome
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols
PRO	Patient reported outcome
PS	Performance score
QoL	Quality of life

RCC	Renal cell cancer
RCT	Randomised controlled trial
REA	Relative effectiveness assessment
RECIST	Response Evaluation Criteria in Solid Tumors.
RMP	Risk management plan
ROW	Rest of the world
SAE	Serious adverse event
SAF	Safety analysis population
SJS	Stevens-Johnson syndrome
SmPC	Summary of product characteristics
SOC	System organ class
TACE	Transcatheter arterial chemoembolisation
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
TMA	Thrombotic microangiopathies
TNM	Classification of Malignant Tumours: - T: tumours, - N: lymph nodes - M: metastasis
TTP	Time to progression
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
WHO-DD	World Health Organization Drug Dictionary

SUMMARY OF RELATIVE EFFECTIVENESS OF REGORAFENIB AS MONOTHERAPY FOR THE TREATMENT OF ADULT PATIENTS WITH HEPATOCELLULAR CARCINOMA WHO HAVE BEEN PREVIOUSLY TREATED WITH SORAFENIB

Scope

The scope can be found here: scope.

Introduction

Description of technology and comparators

On 04 July 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion recommending the extension of indication for STIVARGA® (regorafenib) for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. Before this positive opinion was given, the Marketing Authorisation Holder (MAH) of STIVARGA® (Bayer) requested EUnetHTA to perform an assessment of the relative effectiveness and safety of regorafenib with this new indication. Regorafenib is an oral antineoplastic agent that potently blocks the multiple protein kinases involved in tumour angiogenesis, oncogenesis and the tumour microenvironment. The addition of regorafenib to best supportive care (BSC) in HCC patients who have been previously treated with sorafenib aims to improve the overall survival (OS) in comparison with placebo plus BSC.

Health problem

HCC is the most common type of liver cancer. Its incidence varies from 3 out of 100,000 in western countries to more than 15 out of 100,000 in certain areas of the world. The largest risk factor for HCC, associated with 80-90% of all cases, is cirrhosis of various aetiologies: hepatitis C virus (HCV), hepatitis B virus (HBV), and chronic use of alcohol. Systemic treatment of HCC at an advanced stage depends on a patient's general state. For patients with preserved liver functions and general state, treatment with sorafenib is generally recommended with the objective of increasing survival but not curing the disease. In the case of progression or intolerance to sorafenib, BSC is the preferred option as no antineoplastic treatment was approved or recommended in this situation until regorafenib was available. Therefore, the scoped population of this assessment faces an unmet medical need.

Methods

The authors checked and validated an extensive and detailed literature search for the identification of the scientific evidence of regorafenib in HCC provided by the manufacturer. The systematic literature searches were performed in January 2017 with no time or language limits using the following databases: MEDLINE, EMBASE, the Cochrane Library, clinical trials registries and relevant conference websites. This systematic literature search was restricted to randomised controlled trials (phases II and III), review and meta-analysis (see Appendix 1 for details). The authors updated the literature search on 01 July 2017 using the same research strategy to check whether all relevant information was included in this relative effectiveness assessment (REA). The Cochrane risk of bias assessment was conducted on a study and outcomes level by the authors method was used to assess the quality of evidence (see Appendix 1).

Results (see table S.0.1)

Available evidence

Overall, the body of evidence selected for this REA came from a single pivotal, randomised, double-blind, phase III trial sponsored by the MAH comparing regorafenib (160 mg by mouth once daily in a 3/1 schedule) plus BSC with placebo plus BSC in patients with HCC already treated with sorafenib (the RESORCE trial).

Clinical effectiveness

Overall, 573 patients were randomised in the RESORCE trial: 379 in the regorafenib plus BSC group and 194 in the placebo plus BSC group. The population included in this trial was notably restricted to those who tolerated sorafenib treatment defined as not less than 20 days at a minimum daily dose of 400 mg once daily within the last 28 days prior to withdrawal, with a Child-Pugh score of A and a preserved general state. Demographic and baseline disease characteristics were balanced across both treatment arms. This study met its primary endpoint: OS median OS time was 10.6 months in the regorafenib group and 7.8 months in the placebo group, corresponding to an absolute gain of 2.8 months in favour of regorafenib with a hazard ratio (HR) of 0.627 (95% confidence interval [CI] 0.500, 0.785), p=0.000020. The addition of regorafenib to BSC also induced an improvement in median progression free survival (PFS) from 1.5 months to 3.1 months: HR=0.455 (95% CI 0.371, 0.558), p<0.000001; absolute gain =1.6 months. Data from the RESORCE trial suggested the absence of a clinically relevant difference between the two groups in terms of health-related quality of life (HRQoL) as measured by the following scales: EuroQoL five dimensions questionnaire (EQ-5D) and Functional Assessment of Cancer Therapy-Hepatobiliary questionnaire (FACT-hep).

Safety

More Grade ≥3 drug-related adverse events (AEs) were seen in the regorafenib group (51.9%) than in the placebo group (17.6%); similarly, drug-related serious adverse event (SAE) rates were higher in the regorafenib group (10.4%) than in the placebo group (2.6%). Drug-related AEs leading to the permanent discontinuation of study drug were also greater higher in the regorafenib group (10.4%) than in the placebo group (3.6%).

The most frequent drug-related Grade 3 AEs in the regorafenib group were: hypertension (12.8%), hand–foot skin reaction (HFSR, 12.3%), blood bilirubin increased (5.1%), aspartate transaminase (AST) increased (4.5%) and hypophosphataemia (4.3%).

Table S.0.1: Summary of clinical effectiveness and safety evidence

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (number of studies)	Overall judgment Risk of bias – outcome level	Comments
	Results with placebo + BSC	Results with regorafenib + BSC				
OS	Median OS: 7.8 months (95% CI 6.3, 8.8)	Median OS: 10.6 months (95% CI 9.1, 12.1)	HR=0.627 (95% CI 0.500, 0.785) p =0.000020	573 (1)	Low[a]	Critical outcome
PFS (mRECIST)	Median PFS: 1.5 months (95% CI 1.4, 1.6)	Median PFS: 3.1 months (95% CI 2.8, 4.2)	HR=0.455 (95% CI 0.371, 0.558) p<0.000001	573 (1)	High[a]	Important outcome
HRQoL (EQ-5D index) **Results expressed as LSM time-adjusted (AUC)**	0.77 [0.75; 0.79]	0.76 [0.75; 0.78]	Difference: -0.01 [-0.03; 0.02]	573 (1) Evaluable population (at the end of the treatment: N=110/194 in the placebo group N=178/379 in the regorafenib group	High [a]	Critical outcome
HRQoL (EQ-5D VAS) **Results expressed as LSM time-adjusted AUC**	73.45 [71.84; 75.06]	71.68 [70.46; 72.90]	Difference: -1.77 -3.58; 0.04]	573 (1) Evaluable population (at the end of the treatment: N=110/194 in the placebo group N=180/379 in the regorafenib group	High [a]	Critical outcome
HRQoL (FACT-hep) **Results expressed as LSM time-adjusted AUC**	133.17 [131.21; 135.12]	129.31 [127.84; 130.79]	Difference: -3.85 [-6.06; -1.65]	573 (1) Evaluable population (at the end of the treatment: N=111/194 in the placebo group	High[a]	Critical outcome

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (number of studies)	Overall judgment Risk of bias – outcome level	Comments
	Results with placebo + BSC	Results with regorafenib + BSC				
				N=178/379 in the regorafenib group		
Drug-related grade≥3 AEs	34 (17.6%)	194 (51.9%)	NA	567 (1)	Not applicable	Critical outcome
Drug-related SAEs	5 (2.6%)	39 (10.4%)	NA	567 (1)	Not applicable	Critical outcome
Drug-related permanent discontinuation due to AEs	7 (3.6%)	39 (10.4%)	NA	567 (1)	Not applicable	Critical outcome

[a] see Appendix 1 for details.

Abbreviations: AE=adverse event; AUC=area under the curve; BSC=best supportive care; CI=confidence interval; EQ-5D=EuroQoL five dimensions questionnaire; FACT-hep=functional assessment of cancer therapy questionnaire for patients with hepatobiliary cancer; HRQoL=health-related quality of life; LSM=least squares method; mRECIST=modified response evaluation criteria in solid tumors; NA=not applicable; OS=overall survival; PFS=progression free survival; SAE=serious adverse event; VAS=visual analogue scale.

Source**:** clinical study report

Discussion

This relative assessment is based on a single randomised, double-blind study (RESORCE). Overall, the design of the study is considered acceptable, with a low risk of bias, and the comparator is acceptable. No critical issue was found with the primary endpoint: OS. However, there is a high risk of bias in the assessment of the HRQoLs given the significant amount of missing data and the fact that the safety profile of regorafenib was associated with substantial side effects that might have compromised the blinding of the study.

An evidence gap was identified in patients who did not tolerate sorafenib or had a deteriorated general state and liver function (ECOG >1; Child-Pugh score B) or both, as these patients, included in the scope population, were not eligible for the RESORCE study.

Conclusion

This extension of indication is based on a single randomised pivotal trial (the RESORCE study), which demonstrated that regorafenib plus BSC is more effective than placebo plus BSC in terms of OS in a selected population that tolerated sorafenib treatment and with a preserved general state (ECOG 0-1; Child-Pugh A). However, the addition of regorafenib to BSC induced a modest gain in terms of median OS (+2.8 months) that must be seen in view of the worsened safety profile, notably in terms of Grade ≥3 AEs, SAEs and AEs leading to dose modification or reduction.

Given the poor prognosis of these patients and their general health status observed in clinical practice, HRQoL is also considered as a critical clinical endpoint. In view of the exploratory design of this endpoint, the conclusion on quality of life is greatly limited, which is regrettable.

The stringent eligibility criteria of the RESORCE study result in the non-inclusion of a subset of patients, such as those who did not tolerate sorafenib or those with a deteriorated general health status (ECOG >1) or a Child-Pugh score of B or C, or a combination of these. Therefore, patients included in the RESORCE trial only partially reflect patients seen in clinical practice and the benefit of regorafenib cannot be assessed in these fragile populations. Further research or data collection are deemed necessary to evaluate the use of regorafenib in these specific subgroups.

1 SCOPE

Description	Project scope
Population	Adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. International classification of diseases – version 10 (ICD-10): C22 Medical subject heading (MeSH) term: carcinoma, hepatocellular Tree numbers: C04.588.274.623.160 MeSH unique ID: D006528
Intervention	Regorafenib 160 mg orally once daily for 21 consecutive days followed by 7 days off treatment (schedule 3/1) in combination with best supportive care (BSC) or palliative care. Regorafenib could be administered until: - Disease progression defined by modified response evaluation criteria in solid tumors (mRECIST); - Clinical progression, defined as an Eastern Cooperative Oncology Group (ECOG) performance score ≥3 or symptomatic deterioration, including increased liver function tests; - Unacceptable toxicity. The regorafenib treatment could be continued beyond progression if the investigator judged that the patient would benefit from continued treatment.
Comparison	Placebo in combination with BSC or palliative care.
Outcomes	**Efficacy**: - Critical outcomes: overall survival (OS) and quality of life - Important outcome: progression-free survival (PFS) **Safety**: - Any adverse events (AEs) - Serious AEs (SAEs) - Grade ≥3 AEs - Grade 3 AEs - Grade 4 AEs - Grade 5 AEs - Discontinuation due to AEs - AEs of special interest (important risk identified in the Risk Management Plan).

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment Team

The workload was divided between the author and co-author: the author was responsible for the clinical effectiveness and safety domains and the co-author developed the domains concerning the description and technical characteristics of technology and the health problem and current use of the technology.

The author checked the manufacturer's literature review to verify that all updated and relevant studies and guidelines were included in the assessment.

2.2 Source of assessment elements

The selection of assessment elements was based on the EUnetHTA Core Model® Application for rapid effectiveness assessment (REA) [1]. Further assessment elements from the EUnetHTA Core Model® domains (ETH, ORG, SOC, LEG aspects – relevant for pharmaceuticals) were not included as they were not considered to be relevant for this REA [2]. The selected issues (generic questions) were translated into actual research questions (answerable questions). Some assessment element questions were answered together i.e., questions were listed below each other and a summarised answer was provided.

2.3 Search

The manufacturer presented the findings of an extensive and detailed literature search, identifying the scientific evidence for the use of regorafenib in HCC. The literature search strategy was checked and validated by the author. The reporting of the search followed the EUnetHTA guidelines and the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) statement.

The systematic literature searches were performed by the Marketing Authorisation Holder (MAH) in January 2017, with no time or language limits, in the following databases (platform):

- MEDLINE and EMBASE (ProQuest)
- Cochrane Library, including Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trials (CENTER).
- Relevant conference websites.
- clinicaltrials.gov to identify planned, ongoing or completed studies that had not yet been published.

The inclusion and exclusion criteria that were applied by the MAH are provided in Table 2.1.

Table 2.1: Inclusion and exclusion criteria for the systematic literature review

Inclusion criteria	**Population**: hepatocellular carcinoma (HCC) **Intervention(s):** regorafenib (STIVARGA®) **Comparator(s):** any **Outcomes**: overall survival (OS); time to progression (TTP); progression-free survival (PFS); objective response rate (ORR), disease control; treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), patient reported outcome (PRO) / quality of life (QoL); all patient relevant endpoints **Settings (if applicable):** any **Study design**: randomised controlled trials (RCTs) including phase II and phase III, systematic literature reviews, meta-analysis

	Language restrictions: none **Other search limits or restrictions applied:** none
Exclusion criteria	**Population**: other (oncology) indications not listed in the inclusion criteria **Interventions:** all interventions not listed in the inclusion criteria **Comparator(s):** NA **Outcomes**: NA **Settings (if applicable)**: NA **Study design:** All other study designs not listed in the inclusion criteria **Language restrictions**: NA **Other search limits or restrictions applied:** NA

Abbreviations: HCC=hepatocellular carcinoma; NA=not applicable; OS=overall survival; ORR=objective response rate; PFS=progression-free survival; PRO=patient reported outcome; QoL=quality of life; RCT=randomised controlled trial; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TTP=time to progression.

Source: MAH Submission file

According to the MAH, the selection of articles (based on title/abstract and full text) was made by two reviewers implementing the screening process in parallel:

- Both reviewers performed the titleabstract selection based on the inclusion and exclusion criteria (Table 2.1). The results of this selection were discussed by the reviewers and a selection of articles made for the first review round.

- The full text selection round followed the same process. If the reviewers could not agree on the selection of papers, a third reviewer (a senior team member) was consulted.

The detailed search strategy is provided in Appendix 1.

2.4 Study selection

Through EMBASE, MEDLINE, Cochrane and conferences, a total of 330 records were identified (Figure 1). After removal of 7 duplicates, 323 records were screened.

During the title and abstract selection process, a total of 302 records were excluded, mostly due to the population (n=153), the intervention (n=112), outcomes (n=36) and study design (n=1). The number of records eligible for full text selection was 21. From this batch, 11 publications were excluded because of their outcome (n=7) and study design (n=4), which were not in line with the established selection criteria (details in Appendix 1). Eventually, 10 records were included:

- The first 4 records report on the outcomes of clinical trials. Only one of these records was a full study publication.

- The last 6 of the 10 records consisted of reviews. No additional references were identified through screening the review references.

The flow chart shown in Figure 2.1 illustrates the search and the process by which studies were selected for inclusion in the systematic review.

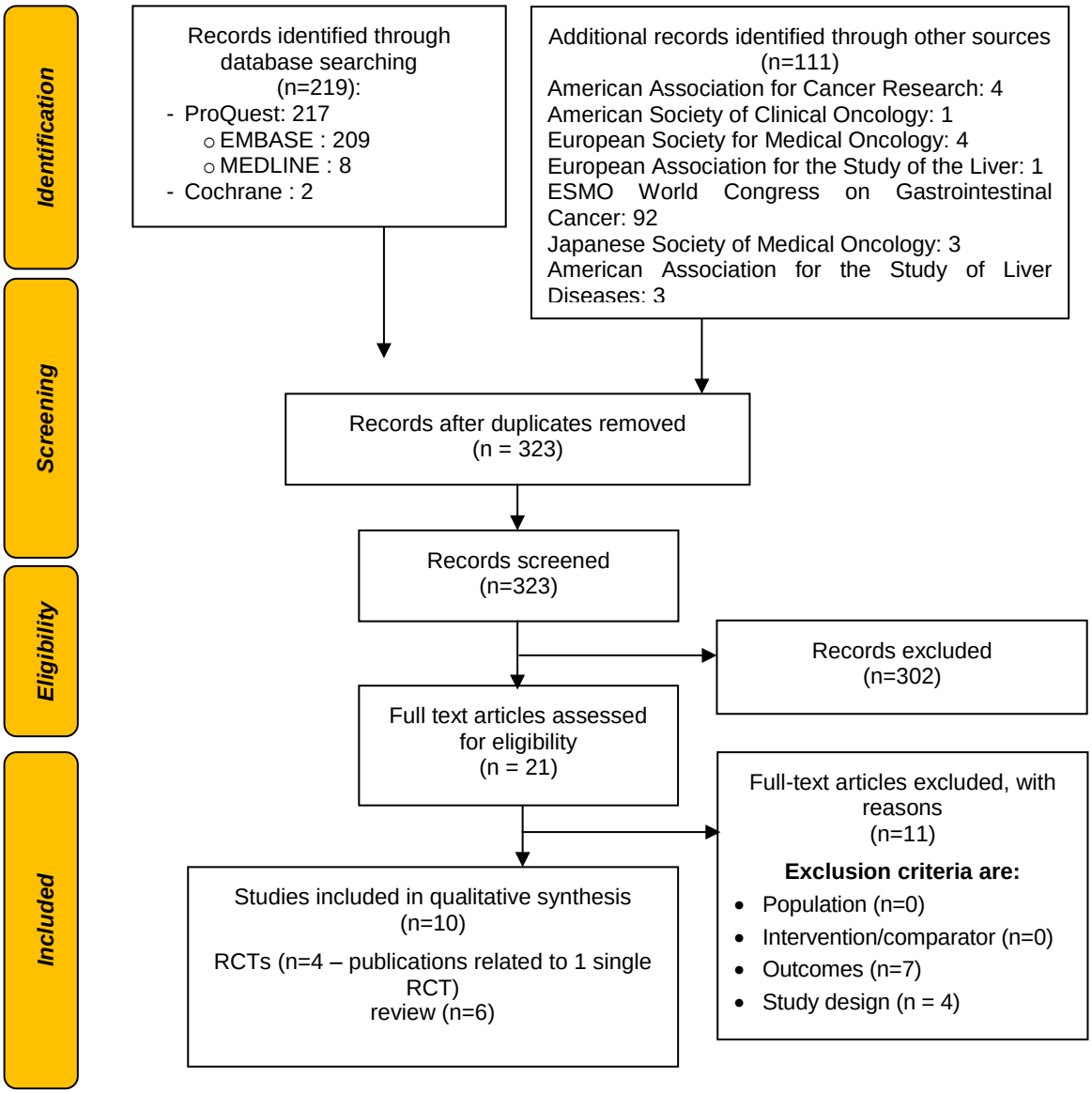


Figure 2.1: Flow chart

Abbreviations: ESMO=European Society for Medical Oncology; RCT=randomised controlled trial

Source: MAH Submission file

In order to check whether all relevant evidence was up-to-date and included in the final report, the authors updated the literature search as of 01 July 2017 using the same research strategy.

Through EMBASE, MEDLINE and Cochrane, a total of 58 records were identified. After removal of 8 duplicates, 50 records were screened.

During the title and abstract selection process, a total of 33 records were excluded, mostly due to the population (n=11), the intervention (n=7) and outcomes (n=15). The number of records eligible for full text selection was 17 of which:

- 9 records reported on the outcomes of clinical trials; all were related to a single trial: the RESORCE study.
- The last 8 of the 17 records consisted of reviews. No additional references were identified through screening the review references.

Overall, no other relevant study was identified with this update.

2.5 Data extraction and analyses

Data used for the EFF and SAF part were extracted from the file submitted by the MAH and verified in the clinical study report (CSR) by the authors. No statistical analysis was performed for this REA. A meta-analysis was not possible as the assessment was based on a single pivotal trial and given the absence of comparators at this stage of the disease.

2.6 Quality rating

The single included study (the RESORCE trial) was assessed independently by the authors for methodological quality. The quality rating tool used was that applied by the Cochrane Collaboration (version 5.1.0; March 2011) for assessing risk of bias in randomised controlled trials (as recommended by the EUnetHTA guideline on internal validity of randomised controlled trials [3]).
This approach classifies risk of bias into 6 different domains:

- Method used to generate the sequence of randomisation (random sequence generation);
- Method used to mask the sequence of allocation to treatment (allocation concealment);
- Measures used to ensure the 'blindness' of the study with respect to treatment assignment (blinding of participants, medical personnel and outcome assessors);
- Completeness of the data for each outcome considered (incomplete outcome data);
- Selective description of the results (selective outcome reporting);
- Other sources of bias (e.g., bias due to the early interruption of the study because of the benefits without an appropriate stopping rule, use of a non-validated measurement instrument, incorrect statistical analysis).

For each domain, assessors were expected to judge the risk of bias ('low risk', 'high risk', or 'unclear') on the basis of the information retrieved from the paper and from the CSR. The results of the risk of bias assessment at both study and outcome level are presented in Table A8 and Table A9 in Appendix 1.

The external validity of the included trial was assessed using the EUnetHTA guideline on applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals [4]), considering the following elements: population, intervention, comparator, outcomes and setting.

The results of the external validity assessment are presented in Table A10 in Appendix 1.

2.7 Description of the evidence used

Table 2.2: Main characteristics of study included

Study name	Study type	Number of patients	Intervention (s)	Main endpoints	Included in clinical effectiveness and/ or safety domain
RESORCE trial	Randomised (2:1 ratio), double-blind, placebo-controlled, phase III trial	573	Regorafenib 160 mg orally once daily for 21 consecutive days followed by 7 days off treatment (schedule 3/1) in combination with best supportive care (BSC) or palliative care Vs placebo (schedule 3/1) in combination with BSC or palliative care	Primary endpoint: OS Secondary: PFS, ORR, QoL, safety	Yes

Abbreviations: BSC=best supportive care; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; QoL=quality of life.

Sources: clinical study report and MAH submission file.

2.8 Deviations from project plan

D0011, D0016 and D0017 were initially selected as relevant research questions in the project plan. During the assessment phase, however, the authors decided that these questions were not informative and decided not to include them in the final report.

Due to time constraint, the grading of recommendations assessment, development and evaluation (GRADE) assessment was not performed by the authors.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What is regorafenib and the comparator(s)?
A0020	For which indications has regorafenib received marketing authorisation?
B0002	What is the claimed benefit of regorafenib in relation to the comparator(s)?
B0003	What is the phase of development and implementation of regorafenib and the comparator(s)?
A0021	What is the reimbursement status of regorafenib?

3.2 Results

Features of the technology and comparators

B0001 – What is regorafenib and the comparator(s)?

Regorafenib
Regorafenib is an oral kinase inhibitor agent that targets a variety of kinases implicated in angiogenic and tumour growth-promoting pathways. Regorafenib potentially targets angiogenic (including the vascular endothelial growth factor [VEGF] receptors 1 to 3, and TIE2), stromal (mutated KIT), metastasis (VEGFR3, PDGFR, FGFR) and oncogenic receptor kinases (KIT, RET, RAF-1, BRAF, BRAFV600E). Its chemical structure is very similar to sorafenib, another oral kinase inhibitor. Regorafenib differs from sorafenib by the addition of one fluorine atom.

Although regorafenib is a targeted therapy, there is no relevant predictive biomarker identified.

Pharmacodynamics/Kinetics
Absorption: a high-fat meal increased the mean area under the curve (AUC) of the drug by 48% compared with the fasted state and decreased the mean AUC of the active metabolites M-2 (N-oxide) by 20% and M-5 (N-oxide and N-desmethyl) by 51%.

A low-fat meal increased the mean AUC of regorafenib by 36%, M-2 by 40%, and M-5 by 23%, compared with the fasted state.

Protein binding: the parent drug and its metabolites (M-2 and M-5) are highly protein bound (99.5% for the parent drug).
Metabolism: the parent drug is metabolised by the liver, via CYP3A4 and UGT1A9, primarily to its active metabolites M-2 and M-5.

Bioavailability: the fraction of the administered dose of unchanged drug that reaches the systemic circulation is 69% for the tablets and 83% for the oral solution.

Half-life elimination: regorafenib: 28 hours (range: 14–58 hours); M-2 metabolite: 25 hours (range: 14–32 hours); M-5 metabolite: 51 hours (range: 32–70 hours)

Time to peak: 4 hours

Excretion: the drug is mainly excreted in the faeces (71%), 47% as parent drug and 24% as metabolites; 19% of the drug is excreted in the urine.

Comparator(s)

On 04 July 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the extension of indication for STIVARGA® (regorafenib) for the treatment of adult patients with HCC who have been previously treated with sorafenib. Currently, no active comparator for regorafenib is recommended or used in clinical practice for the treatment of patients with HCC who have been previously treated with sorafenib, and patients are commonly treated with BSC. BSC in cancer may include assessment and treatment of physical, psychological, social, and spiritual dimensions of suffering [5].

Table 3.1 provides an overview of the technology.

Table 3.1: Features of the intervention and comparators

	Technology	Comparator
Non-proprietary name	Regorafenib	No active comparator is available
Proprietary name	STIVARGA®	
Active substance	Regorafenib	
Galenic Form	40 mg film-coated tablets	
ATC code	L01XE21	

Abbreviations: ATC=anatomical therapeutic chemical; EMA=European Medicines Agency.

Source: EMA 2013.

Administration and dosing of regorafenib is summarised in Table 3.2.

Table 3.2: Administration and dosing of the intervention and comparators

	Technology	Comparator
Administration mode	Oral use It should be taken at the same time each day. The tablets should be swallowed whole with water after a light meal that contains less than 30% fat. An example of a light (low-fat) meal would include 1 portion of cereal (about 30 g), 1 glass of skimmed milk, 1 slice of toast with jam, 1 glass of apple juice, and 1 cup of coffee or tea (520 calories, 2 g fat).	No active comparator is available
Description of packaging	28 film-coated tablets in bottle 84 film-coated tablets (3 x 28) in bottle	
Total volume contained in packaging for sale	28-tablet package of 40 mg regorafenib formulation 112-tablet package of 40 mg regorafenib formulation	
Dosing	Recommended daily dose is 160 mg (4 tablets of 40 mg) taken once daily. Dose interruptions and/or dose reductions may be required based on individual safety and tolerability. Dose modifications are to be applied in 40 mg (1 tablet) steps. The lowest recommended daily dose is 80 mg. The maximum daily dose is 160 mg.	
Recommended duration of treatment	3 weeks of daily regorafenib treatment followed by 1 week off treatment. This 4-week period is considered a treatment cycle. Treatment should continue as long as benefit is observed or until unacceptable toxicity occurs.	
Contraindications	Hypersensitivity to the active substance or to any of the excipients	

Abbreviations: EMA=European Medicines Agency.

Sources: manufacturer's submission file; EMA 2013.

A0020 – For which indications has regorafenib received marketing authorisation?

The approved indications of regorafenib (STIVARGA®) are:

- Patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-epidermal growth factor receptor (EGFR) therapy (approved in the EU on 26 August 2013);
- Unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib (approved in the EU on 28 July 2017).

On 04 July 2017, the CHMP adopted a positive opinion recommending the label extension of regorafenib, indicated as monotherapy for the treatment of adult patients with HCC who have been previously treated with sorafenib [6].
The aim of this report is to perform a relative assessment of the effectiveness and safety of regorafenib in this new indication at the request of the MAH of STIVARGA®.

B0002 – What is the claimed benefit of the regorafenib in relation to the comparator(s)?

The addition of regorafenib to BSC in HCC patients who have been previously treated with sorafenib aims to improve the OS compared with placebo plus BSC. This claimed benefit is based on clinical data (the RESORCE trial) that is presented in Section 5.

B0003 – What is the phase of development and implementation of regorafenib and the comparator(s)?

As of 21 July 2017, regorafenib has regulatory approval in Ecuador, Japan, Korea, and the US for the treatment of adult patients with HCC who have been previously treated with sorafenib; see Table A11 in Appendix 2.

A0021 – What is the reimbursement status of regorafenib?

Reimbursement and pricing decisions are a national responsibility. Thus, the reimbursement status of regorafenib for HCC in different European Union (EU) countries will be decided at the national level after marketing authorisation validation by the European Commission.

Detailed information on the reimbursement status and recommendations for regorafenib in other indications, as of 21 July 2017, are reported in Table A12 in Appendix 2. In summary, regorafenib is reimbursed in most European countries for the treatment of mCRC (15 out of 29 countries) and for GIST (14 out of 29 countries). In the majority of the European countries where it is reimbursed, regorafenib is free of charge.

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for HCC? Are they likely to impact patients' prognostic or treatment choice?
A0004	What is the median survival of patients with HCC? What is the median survival of patients targeted in the claimed MA?
A0005	What are the symptoms and the burden of HCC for the patient, in the targeted population?
A0006	What is the burden of HCC for society in terms of prevalence, incidence, mortality and costs, in the defined population?
A0024	How is HCC currently diagnosed according to published guidelines and in practice?
A0025	How is HCC currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

4.2 Results

Overview of the disease or health condition

A0002 – What is the disease or health condition in the scope of this assessment?

A0003 – What are the known risk factors for HCC? Are they likely to impact patients' prognostic or treatment choice?

The health condition in the scope of this assessment is advanced HCC, specifically, adult patients who have been previously treated with sorafenib.

Liver cancer is the sixth most common cancer (749,000 new cases, about 7% of all cancers) and represents the third-leading cause of cancer-related death (692,000 cases) [7]. HCC is the most common liver cancer (about 90% of the cases). The pattern of HCC occurrence has a clear geographical distribution, with the highest incidence rates in Eastern and South-eastern Asia and in sub-Saharan Black Africans [8], where around 85% of cases occur. HCC has a strong male preponderance with a male to female ratio estimated to be 2.4:1 [9].

HCC usually occurs in the setting of liver cirrhosis, which represents the largest single risk factor present in about 80–90% of all HCC cases [10]. Cirrhosis may be caused by chronic infections with hepatitis B virus (HBV) or hepatitis C virus (HCV), chronic alcohol consumption, non-alcoholic steatohepatitis, or diabetes [11] There are many other risk factors but with lower importance, such as haemochromatosis, aflatoxin B1, tyrosinaemia, galactosaemia, fructosaemia, alpha 1 anti-trypsin deficiency, genetic predisposition, anabolising hormones, oestrogen contraceptives, obesity, and hypothyroidism.

Based on a non-interventional surveillance study in 479 patients (from 39 countries) with unresectable HCC, the aetiology of the underlying liver disease in Europe based on 143 patients was alcohol use in 42%, infection with HCV in 33%, and HBV in 17% [12].

All aetiologic forms of cirrhosis may be complicated by tumour formation, but the risk is higher in patients with hepatitis infection. Overall, one-third of cirrhotic patients will develop HCC during their lifetime.

Several studies have identified HBV-related factors as key predictors of HCC development in patients with chronic hepatitis B infection, such as HBV e antigen (HBeAg) seropositivity, high viral load and genotype C [13]. Identification of mutations in germline DNA that define patients at high risk of developing cancer has become a challenge in HCC; some new findings, such as involvement of single nucleotide polymorphisms or an epidermal growth factor gene polymorphism, need to be further studied and validated.

A0004 – What is the median survival of patients with HCC? What is the median survival of patients targeted in the claimed MA?

Advanced HCC is generally associated with poor prognosis. The median survival time in patients diagnosed with unresectable disease is, depending on stage, estimated to be about 6–20 months, and the 5-year survival rate less than 5% [14]). The median survival of the population scoped in this report (second line of advanced HCC) is estimated to be about 8 months[15] [16] [17].

In a 2009 systematic review of 72 studies, considering patients with cirrhosis and HCC (68 studies with advanced tumours), the most common predictors of mortality in HCC were: portal vein thrombosis (22/72 studies), tumour size (20/72 studies), alpha-fetoprotein (AFP; 20/72 studies), Child–Pugh class (18/72 studies) and bilirubin (15/72 studies) [18].

Effects of the disease or health condition

A0005 – What are the symptoms and the burden of HCC for the patient, in the targeted population?

HCC in the early stages may be asymptomatic, but as the disease progresses, patients may experience one or more clinical symptoms: anorexia/cachexia, ascites, asthenia, early satiety, fatigue, fever, hepatic bruits, hepatic encephalopathy, jaundice, nausea and vomiting, nodular liver, palpable liver mass, peripheral oedema, pruritus, right upper quadrant pain, splenomegaly, variceal bleeding, weight loss.

The stage of the disease together with the occurrence of severe symptoms adds up to a worsened prognosis, which in turn impacts functional status and patient quality of life [19] [20] [21] [22]. Although diagnosis at earlier stages of the disease allows for treatment options with a possibility of cure, even with local therapies of resection and ablation, 5-year survival can be as low as 50% [7] [23]. Further, 63.8% of HCC patients undergoing surgical resection and >70% of those undergoing ablation techniques will have recurrence of HCC tumours 5 years after local therapy [24]. For patients with advanced disease, a cure is generally not expected. They usually experience a variety of symptoms, greatly impacting daily living activities, including pain, deterioration of quality of life and decline of fitness for work. HCC patients scored the lowest in terms of health-related quality of life (HRQoL) on a visual analogue scale (VAS) compared with patients classified with other chronic liver diseases (i.e., chronic hepatitis or cirrhosis) [25]. Overall, the burden of disease for the patient is considered to be very high.

A0006 – What is the burden of HCC for society in terms of prevalence, incidence, mortality and costs, in the defined population?

HCC is the third-leading cause of cancer-related death, and the global incidence is rising, with approximately 700,000 cases diagnosed worldwide in 2012 [26] [27]. In the US, the incidence of HCC is approximately 6.8/2.2 (male/female) 9.18 per 100,000 people, in Southern Europe 9.8/3.2 (male/female), in Western Europe 7.2/2.1 (male/female), and in Northern Europe 3.8/1.6 (male/female) per 100,000 people [28]. The incidence of HCC has risen in the last 10 years and it varies geographically largely due to variations in the incidence of HBV and HCV infection, with the majority

of cases (>80%) occurring in sub-Saharan Africa and eastern Asia. One country alone, China, accounts for 40–50% of worldwide cases.

Since HCC can be considered as a complication of frequent clinical conditions, such as chronic infections with HBV or HCV, chronic alcohol consumption, non-alcoholic steatohepatitis, or diabetes, the consequences for society are strong, namely regarding the consumption of resources (hospitalisations, need of advanced techniques for diagnosis and treatment).

Overall, the burden of the disease for society in the scoped population can be considered as moderate given the prevalence of patients in the second line of advanced HCC. As the development of direct-acting antiviral agents will probably have a positive impact on HCV incidence and may, over time, also impact HCC incidence. Therefore, the burden of HCC for society in Europe may decrease in the coming years.

Current clinical management of the disease or health condition

A0024 – How is HCC currently diagnosed according to published guidelines and in practice?

A0025 – How is HCC currently managed according to published guidelines and in practice?

This section is supported by clinical practice guidelines from various scientific organisations: EASL-EORTC [11], ESMO-ESDO [7], NCCN [29], and AASLD [30] see Table A5 for details.

Pathological diagnosis of HCC requires a biopsy of the tumour. In some cases, notably for cirrhotic patients, a formal pathological proof is not necessary and the diagnosis can be based on non-invasive imaging criteria for lesion characterisation obtained by 4-phase multidetector computed tomography (CT) scan or dynamic contrast-enhanced magnetic resonance imaging (MRI). Additional immunohistochemical assessment may be helpful such as: staging of glypican-3 (GPC3), neovascularisation (CD34) or potential progenitor cell origin (Keratin 19, EpCAM).

As HCC generally occurs because of cirrhosis, the management of this disease should be global, taking into account the general state of patients and the underlying disease.

When diagnosed at an early stage, patients may be eligible for curative treatments mainly represented by surgical resection, radiofrequency ablation or liver transplantation. At an intermediate (multinodular) stage or for patients who progress to an intermediate stage, transcatheter arterial chemoembolisation (TACE) is generally the preferred option. For patients diagnosed with an advanced tumour or for those who progress to an advanced disease, therapeutic management depends on the general state. Sorafenib is the standard systemic therapy indicated for patients with a well-preserved liver function (Child-Pugh A) and a good performance status (ECOG ≤2) with the objective to increase survival but not to cure the disease. There is little evidence to support the use of sorafenib in Child-Pugh B patients. Although it can be recommended by some scientific societies, with a low strength of evidence sorafenib faces some reimbursement restriction in Child-Pugh B patients[1]. Until the regorafenib extension of indication, no drug was approved or recommended for patients who had been previously treated with sorafenib. Only BSC or inclusion in clinical trials were recommended. For patients with end-stage disease (Child-Pugh C or ECOG >1), only BSC with symptomatic treatment are advocated.

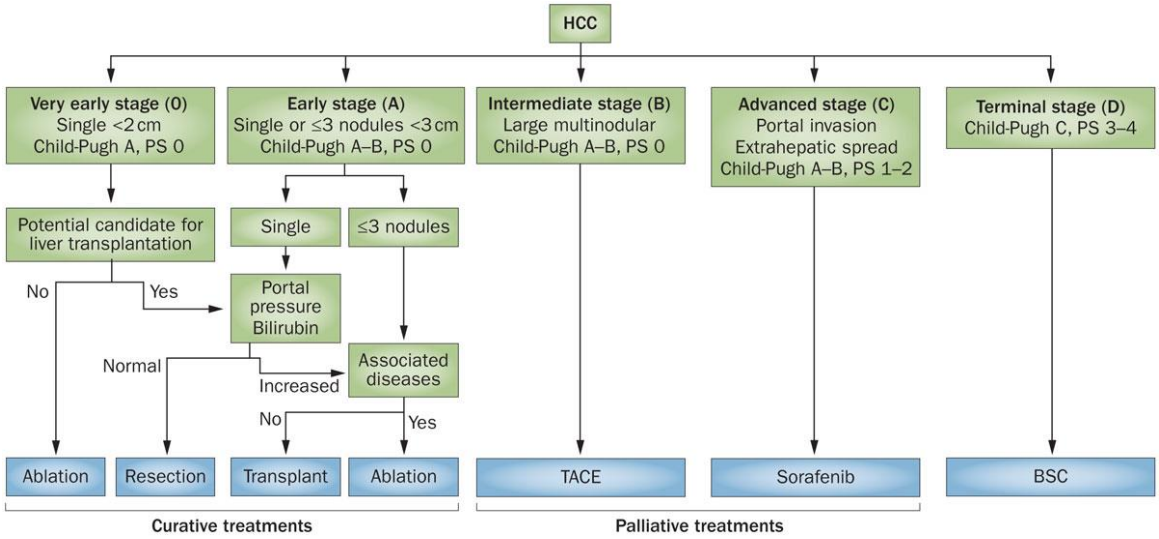
Overall, there is a high unmet need in the population scoped in this report.

Figure 4.1 shows the algorithm included in the guideline of the Barcelona Clinic Liver Cancer (BCLC), which is in agreement with the European Association for the Study of the Liver (EASL) and the European Organisation for Research and Treatment of Cancer (EORTC).

[1] Restricted to Child-Pugh A in France and Italy. Restricted to Child-Pugh A, adequate renal and hematopoietic functions in Croatia.

The BCLC system is widely used and encompasses all HCC patients. It divides HCC patients in 5 stages (0, A, B, C and D) according to pre-established prognostic variables, and allocates therapies according to treatment-related status. Thus, it provides information on both prognostic prediction and treatment allocation. Prognosis prediction is defined by variables related to tumour status (size, number, vascular invasion, N1, M1), liver function (Child–Pugh status) and health status (ECOG). Treatment allocation incorporates treatment-dependent variables, which have been shown to influence therapeutic outcome, such as bilirubin, portal hypertension or presence of symptoms – ECOG [12].

Figure 4.1: Overview of the current clinical pathway for different stages of HCC based on BCLC staging



Abbreviations: BCLC=Barcelona Clinic Liver Cancer; HCC=hepatocellular carcinoma; PS=performance status.
Source: BCLC [31].

For patients requiring second-line therapy, EASL-EORTC [24] and ESMO-ESDO [25] recommended BSC or a clinical trial, while LAASL [27] did not make any recommendation. With recent approval of regorafenib in the US, the NCCN Guideline on Hepatobiliary Cancers was updated and regorafenib is included as the only recommended treatment for progression on or after sorafenib treatment (in patients with Child-Pugh Class A only) [(26].

An overview of European guidelines for HCC treatment is given in Table A5 in Appendix 1.

Target population

A0007 – What is the target population in this assessment?

The target population is that detailed in the summary of product characteristics (SmPC) for regorafenib – clinical particulars: "Stivarga is indicated as monotherapy for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib" (EMA, July 4th, 2017).

A0023 – How many people belong to the target population?

No relevant epidemiological studies were identified in the scientific literature to quantify the number of individuals who belong to the target population. According to the RESORCE study's inclusion and exclusion criteria (cf. section 5), the target population is represented by patients with advanced HCC, who progressed on sorafenib treatment and are eligible to a second- or third-line systemic

treatment: tolerated sorafenib, well-preserved liver function (Child-Pugh A) and a good general state (ECOG 0-1):

- The incidence of HCC in Southern Europe is approximately 9.8/3.2 (male/female), in Western Europe 7.2/2.1 (male/female), and in Northern Europe 3.8/1.6 (male/female) per 100,000 people [28].

- Two subgroups of this target population can be identified:

    - patients with BCLC stage B at diagnosis (approximately 11%) treated by sorafenib after progression on or after TACE [32]

    - patients with BCLC stage C at diagnosis (approximately 51%) treated by sorafenib [32].

Given the poor prognosis of these fragile patients and because of the restricted eligibility criteria for this drug, only a small proportion of patients with advanced HCC can benefit from treatment with regorafenib in clinical practice.

A0011 – How much are the technologies utilised?

There is no published data from Europe regarding utilisation of regorafenib in this extension of indication as this technology has not yet been used for HCC in daily practice in most European countries.

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

Element ID	Research question
D0001	What is the expected beneficial effect of regorafenib on mortality?
D0005	How does regorafenib affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does regorafenib affect progression (or recurrence) of the disease or health condition?
D0012	What is the effect of regorafenib on generic health-related quality of life (EQ-5D)?
D0013	What is the effect of regorafenib on disease-specific quality of life (FACT-hep)?

5.2 Results

Included study

The relative effectiveness assessment of regorafenib in this indication is based on the RESORCE study (NCT01774344) sponsored by the MAH [33]. This pivotal study is a randomised, double-blind, placebo-controlled phase III trial comparing regorafenib plus BSC with placebo plus BSC in patients with HCC who had progressed while on sorafenib.

Inclusion and non-inclusion criteria

Adult patients (≥18 years of age) with this type of cancer were enrolled from 152 centres in 21 countries. The main inclusion and non-inclusion criteria are summarised in Table 5.1.

Table 5.1: Main inclusion and non-inclusion criteria of the RESORCE trial

Main inclusion criteria	Main non-inclusion criteria
• Histological or cytological confirmation of hepatocellular carcinoma (HCC) or non-invasive diagnosis of HCC as per American Association for the Study of Liver Diseases (AASLD) criteria in subjects with a confirmed diagnosis of cirrhosis. • Barcelona Clinic Liver Cancer (BCLC) stage Category B or C that could not benefit from treatments of established efficacy with higher priority such as resection, local ablation, chemoembolisation, or systemic sorafenib. • Failure on prior treatment with sorafenib (defined as documented radiological progression according to the radiology charter). Randomisation needed to be performed within 10 weeks after the last treatment with sorafenib. • Tolerability to prior treatment with sorafenib defined as not less than 20 days at a minimum daily dose of 400 mg once daily within the last 28 days prior to withdrawal. • Liver function status Child-Pugh Class A. • Local or loco-regional therapy of intrahepatic tumour lesions (e.g., surgery, radiation therapy, hepatic arterial embolisation, chemoembolisation, radiofrequency ablation, percutaneous ethanol injection, or cryoablation) must have been completed ≥4 weeks before first dose of study medication. Note: subjects who received sole intrahepatic intra-arterial chemotherapy, without lipiodol or embolising agents, were not eligible. • ECOG Performance Status of 0 or 1. • Adequate bone marrow, liver and renal function • At least one unidimensional measurable lesion by computed tomography (CT) scan or magnetic resonance imaging (MRI) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, and mRECIST for HCC. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, may have been considered measurable if there had been demonstrated progression in the lesion. • Life expectancy of at least 3 months.	• Prior liver transplantation or candidates for liver transplantation. • Prior treatment with regorafenib. Subjects permanently withdrawn from study participation were not allowed to re-enter the study. • Prior and/or concomitant treatment within a clinical study other than with sorafenib during or within 4 weeks of randomisation. • Sorafenib treatment within 2 weeks of randomisation. • Subjects with large oesophageal varices at risk of bleeding that were not being treated with conventional medical intervention: beta blockers or endoscopic treatment. The assessment of oesophageal varices (for subjects in whom conventional medical intervention for known oesophageal varices was already in place), was to be performed by endoscopy as per local standard of care. • Prior systemic treatment for HCC, except sorafenib. • Permanent discontinuation of prior sorafenib therapy due to sorafenib related toxicity. • Permanent discontinuation of prior sorafenib therapy due to any cause more than 10 weeks prior to randomisation. • Past or concurrent history of neoplasm other than HCC, except for in situ carcinoma of the cervix, uteri, and/or non-melanoma skin cancer and superficial bladder tumours (Ta [Non-invasive tumour], Carcinoma in situ [Tis] and T1 [Tumour invades lamina propria]).11 Any cancer curatively treated >3 years prior to study entry was permitted. • Known history or symptomatic metastatic brain or meningeal tumours (head CT or MRI at screening to confirm the absence of central nervous system [CNS] disease if the subject had symptoms suggestive or consistent with CNS disease). • Major surgical procedure or significant traumatic injury within 28 days before randomisation. • Congestive heart failure New York Heart Association (NYHA) ≥ Class 2. • Unstable angina (angina symptoms at rest, new-onset angina i.e., within the last 3 months) or myocardial infarction (MI) within the past 6 months before randomisation. • Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin were permitted).

	• Uncontrolled hypertension. • Subjects with phaeochromocytoma. • Uncontrolled ascites (defined as not easily controlled with diuretic or paracentesis treatment). • Pleural effusion or ascites that caused respiratory compromise (Grade ≥2 dyspnoea). • Persistent proteinuria of NCI-CTCAE Grade 3 or higher. • Ongoing infection > Grade 2. Hepatitis B was allowed if no active replication was present. Hepatitis C was allowed if no antiviral treatment was required. • Clinically significant bleeding Grade 3 or higher within 30 days before randomisation. • Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischaemic attacks), deep vein thrombosis or pulmonary embolism within 6 months before the start of study medication. • Unresolved toxicity higher than Grade 1 (excluding alopecia or anaemia) attributed to any prior therapy/procedure. • Known history of human immunodeficiency virus (HIV) infection. • Seizure disorder requiring medication. • History of organ allograft. • Non-healing wound, ulcer, or bone fracture. • Renal failure requiring haemo- or peritoneal dialysis. • Interstitial lung disease with ongoing signs and symptoms at the time of screening. • Any malabsorption condition.

Abbreviations: AASLD=American Association for the Study of Liver Diseases; BCLC=Barcelona Clinic Liver Cancer; CNS=central nervous system; CT=computed tomography; CTCAE=common terminology criteria for adverse events; HCC=hepatocellular carcinoma; HIV=human immunodeficiency virus; MI=myocardial infarction; mRECIST=modified response evaluation criteria in solid tumors; MRI=magnetic resonance imaging; NCI=National Cancer Institute; NYHA=New York Heart Association; RECIST=response evaluation criteria in solid tumors.

Source: clinical study report

Treatments and randomisation

An interactive voice response system (IVRS) was used to randomly allocate (in a double-blind fashion) in a 2:1 ratio to either:

- regorafenib 160 mg (4 x 40 mg tablets) orally (by mouth) every day for 3 weeks followed by 1 week off treatment (schedule 3/1) plus BSC or
- matching placebo tablets with a 3/1 schedule plus BSC.

BSC included any concomitant medications or treatments such as: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational antitumour agents or antineoplastic chemo/hormonal/immunotherapy.

Subjects could continue on treatment until one of the following main criteria was observed:

- Progressive disease (PD) as defined by mRECIST
- Clinical progression (e.g., defined as worsening of the ECOG performance status (PS) score ≥3 or symptomatic deterioration including increase in liver function tests)
- Death due to any cause
- Unacceptable toxicity
- Subject withdraws consent
- Treating physician determines discontinuation of treatment is in the subject's best interest
- Substantial non-compliance with the protocol
- Or until any other criterion for stopping therapy was met.

Up to two regorafenib dose reductions due to toxicity were allowed (from 160 mg to 120 mg to 80 mg). The dose could be re-escalated to a maximum of 160 mg at the investigator's discretion once toxicities were resolved.

Patients were followed up for tumour assessments every 6 weeks for the first eight cycles and every 12 weeks thereafter during treatment.

Subjects were stratified according to:

- Geographical region (Asia versus the rest of the world [ROW]); the proportion of patients recruited from Asia was limited to 40%
- Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1)
- Alpha-fetoprotein (AFP) levels (<400 ng/mL versus ≥400 ng/mL)
- Extrahepatic disease (presence versus absence)
- Macrovascular invasion (presence versus absence).

Objective and endpoints

The primary objective of the RESORCE trial was to demonstrate the superiority of regorafenib plus BSC versus placebo plus BSC in terms of OS. This primary endpoint is defined as the time from the date of randomisation to death due to any cause.

Other endpoints included:

- Progression-free survival (PFS) defined as the time (in days) from date of randomisation to date of disease progression (radiological or clinical) or death due to any cause (if death occurred before progression was documented). PFS was assessed by the investigators.
- Objective response rate (ORR) defined as the rate of subjects with complete response (CR) or partial response (PR) over all randomised subjects. Subjects prematurely discontinuing without an assessment were to be considered non-responders for the analysis.
- HRQoL assessed using the functional assessment of cancer therapy questionnaire for patients with hepatobiliary cancer (FACT-Hep) and the EuroQoL five dimensions questionnaire (EQ-5D) index and VAS scores.
- Duration of response (DOR) was defined as the time from the first documented objective response of PR or CR, whichever was noted earlier, to disease progression or death (if death occurred before progression was documented).
- Biomarker evaluation.

As a reminder, HTA bodies involved with this REA stated that:
- The critical efficacy outcomes were: OS and HRQoL.
- The important efficacy outcome was: PFS.
- The critical or important safety outcomes were: any AEs, SAEs, grade ≥3 AEs, discontinuation due to AEs and AEs of special interest (Risk Management Plan).

Statistical analysis

Sample size
The sample size was based on the primary efficacy endpoint: OS. The targeted improvement was a 43% increase in median OS compared with placebo (i.e., assuming a median OS under placebo of 8 months, the median under regorafenib was expected to be at least 11.4 months). The associated hazard ratio (HR) of regorafenib over placebo was 0.7. Approximately 370 events were required assuming a one-sided alpha of 0.025, a targeted improvement in median survival of 43%, a power of 90%, and a randomisation ratio of 2:1 between regorafenib and placebo. Approximately 560 patients should have been randomised to conduct the study in a reasonable time frame.

The assumption of 8 months OS in the placebo plus BSC group was based on four previously performed randomised trials that evaluated patients undergoing a second-line treatment [15] [16] [17] [29].

Analysis sets
The primary efficacy analysis was performed using the full analysis set (FAS), which was defined as all randomised patients (intention to treat analysis). The population for the safety analysis (SAF population) comprised all randomised patients who received at least one dose of study medication (regorafenib or placebo).

Endpoints analysis

- *Overall survival*

For each treatment arm, the following parameters and analyses were provided: Kaplan-Meier product-limit estimates of the OS distribution functions and the OS time (median and its 95% confidence interval [CI]). The HR of regorafenib over placebo and its 95% CI were generated from the Cox model. The analysis was performed according to treatment groups as randomised, with stratification as recorded in the IVRS data. A Kaplan-Meier plot displaying the OS curves of the two treatment groups was provided.

A one-sided overall alpha of 0.025 was used for the efficacy analysis of OS. The analysis of OS was planned when approximately 370 deaths were observed (information fraction=1.0).

- *Other endpoints*

PFS was analysed with a one-sided significance level of alpha=0.025. ORR and DOR were analysed descriptively only. For the secondary endpoints, analyses were displayed for both RECIST version 1.1 and mRECIST.

HRQoL was assessed during the trial using a generic scale (EQ-5D index and VAS) and a disease-specific scale (FACT-Hep). The FACT-Hep and EQ-5D were both self-administrated by the subject at baseline, at every cycle, and at the end-of-study visit before seeing the physician.

For the EQ-5D, higher scores represented better health status. A change of at least 0.1 points on the EQ-5D index was considered to be a minimum important difference (MID) (using ECOG PS as the anchor). A change of at least 7 points on the VAS was considered as a MID [34].

The FACT-Hep consisted of the 27-item FACT-G, a core questionnaire designed to measure general aspects of HRQoL in subjects with any form of cancer, and the newly validated 18-item Hepatobiliary Cancer Subscale (HCS), designed to measure specific concerns or problems related to QoL

in subjects with hepatobiliary cancers (FACT-Hep = FACT-G + HCS). It contained five domains: Physical Well-Being, Social Well-Being, Emotional Well-Being, Functional Well-Being and Hepatobiliary Cancer Subscale. A change of at least 8–9 points on the FACT-hep score was considered as a MID [35].

PRO data as measured by FACT-Hep and EQ-5D were analysed to assess differences in HRQoL and health utility values between treatment arms based on time adjusted AUC using all available data. Statistical tests were performed using a 2-sided type I error of 5%.

In case of missing responses for one or more items, subscale scores were permitted to be prorated:

- For FACT-Hep, this was done by multiplying the sum of the subscale by the number of items in the scale, then dividing the number of items actually answered. Prorating of scores was considered acceptable as long as more than 50% of the items were answered (assuming that the score of missing items was similar to those of non-missing items). If less than or equal to 50% of the items were answered for any domain, then the score of that domain was set to missing. The total score was then calculated as the sum of the unweighted subscale scores. Moreover, the FACT-Hep total score was set to missing if the related overall item response rate was less than or equal to 80%.

- For EQ-5D, if there was a missing or ambiguous answer (i.e., marking of more than one answer) on the five dimension questions, then the index score was marked as missing.

Neither hierarchy nor other adjustment for multiplicity analysis was planned to control for type I error.

Results

The main results presented in this report are based on the primary analysis (with a cut-off date in February 2016; database lock in August 2016). Data reported in this REA are based on the CSR provided by the MAH. Authors were notified that between database lock and May 2017 some individual data were rectified leading to minor variations on efficacy and safety outcomes and explaining slight differences between this report and the SmPC.

Overall, 573 patients were randomised in the RESORCE trial: 379 in the regorafenib plus BSC group and 194 in the placebo plus BSC group. Demographic and baseline disease characteristics were balanced across both treatment arms (see Table 5.2).

Table 5.2: Demographic and baseline characteristics

	Placebo N=194 (100%)	Regorafenib N=379 (100%)
Sex		
Male	171 (88.1%)	333 (87.9%)
Female	23 (11.9%)	46 (12.1%)
Calculated age at enrolment (years)		
N	194	379
Median (range)	62.0 (23-83)	64.0 (19-85)
Age group		
<65 years	116 (59.8%)	199 (52.5%)
≥65 years	78 (40.2%)	180 (47.5%)
Geographic region (from stratification)		
Asia	73 (37.6%)	143 (37.7%)
Rest of the world	121 (62.4%)	236 (62.3%)
Baseline value of ECOG Performance Status		
0	130 (67%)	247 (65%)
1	64 (33%)	132 (35%)
Weeks since initial diagnosis to start of study treatment		
N	173	335
Median (range)	87.9 (10.9-531.1)	92.7 (8.7-1129.0)
Weeks since the most recent progression/relapse to start of study treatment		
N	193	374
Median	5.1 (0.6-32.4)	5.4 (0.3-33.9)
Aetiology of HCC		
Alcohol use	55 (28.4%)	90 (23.8%)
Hepatitis B	73 (37.6%)	143 (37.7%)
Hepatitis C	41 (21.1%)	78 (20.6%)
Genetic/metabolic	6 (3.1%)	16 (4.2%)
Non-alcoholic steatohepatitis (NASH)	13 (6.7%)	25 (6.6%)
Unknown	32 (16.5%)	66 (17.4%)
Other	4 (2.1%)	12 (3.2%)
TNM stage at study entry		
Stage I	0	2 (0.5%)
Stage II	12 (6.2%)	27 (7.1%)
Stage IIIA	16 (8.3%)	36 (9.5%)
Stage IIIB	18 (9.3%)	41 (10.8%)
Stage IIIC	0	5 (1.3%)
Stage IVA	17 (8.8%)	22 (5.8%)
Stage IVB	130 (67.0%)	245 (64.6%)
BCLC stage at study entry		
A (early stage)	0	1 (0.3%)
B (intermediate stage)	22 (11.3%)	53 (14.0%)
C (advanced stage)	172 (88.7%)	325 (85.8%)
Alpha-fetoprotein (AFP) (ng/ml)		
<400 ng/mL	107 (55.2%)	217 (57.3%)
≥400 ng/mL	87 (44.9%)	162 (42.7%)
Macrovascular invasion		
Absence	140 (72.2%)	269 (71.0%)
Presence	54 (27.8%)	110 (29.0%)
Extrahepatic disease		
Absence	47 (24.2%)	114 (30.1%)
Presence	147 (75.8%)	265 (69.9%)
Child-Pugh Score		
Missing	0	1 (0.3%)
A	188 (96.9%)	373 (98.4%)
B	6 (3.1%)	5 (1.3%)
Liver cirrhosis (medical history)		
No	50 (25.8%)	94 (24.8%)
Yes	144 (74.2%)	285 (75.2%)

Abbreviations: AFP=alpha-fetoprotein; BCLC=Barcelona Clinical Liver Cancer classification; ECOG=Eastern Cooperative Oncology Group; HCC=hepatocellular carcinoma; NASH=non-alcoholic steatohepatitis; TNM=classification of Malignant Tumours

Sources: clinical study report and MAH submission file.

The numbers of patients with at least one concomitant medication are reported in Table 5.3. A trend to a higher rate of concomitant medications in the regorafenib group is observed.

Table 5.3: Concomitant medication

ATC class WHO-DD version (3q2005)	Placebo N=194	Regorafenib N=379
Number of subjects (%) with at least 1 concomitant medication	187 (96.4%)	372 (98.2%)
Alimentary tract and metabolism	148 (76.3%)	330 (87.1%)
Anti-infectives for systemic use	93 (47.9%)	220 (58.0%)
Antineoplasic and immunomodulating agents	26 (13.4%)	60 (15.8%)
Antiparasitic products, insecticides and repellents	7 (3.6%)	22 (5.8%)
Blood and blood forming organs	110 (56.7%)	237 (62.5%)
Cardiovascular system	149 (76.8%)	321 (84.7%)
Dermatologicals	76 (39.2%)	213 (56.2%)
Genitourinary system and sex hormones	88 (45.4%)	190 (50.1%)
Musculoskeletal system	66 (34.0%)	146 (38.5%)
Nervous system	136 (70.1%)	265 (69.9%)
Respiratory system	68 (35.1%)	182 (48.0%)
Sensory organs	74 (38.1%)	183 (48.3%)
Systemic hormonal preparations, excl. sex hormones and insulin	50 (25.8%)	126 (33.2%)
Unclassifiable	2 (1.0%)	6 (2.1%)
Various	96 (49.5%)	192 (50.7%)

Abbreviations: ATC=anatomical therapeutic chemical; WHO-DD=World Health Organization Drug Dictionary.

Sources: clinical study report and MAH submission file.

Mortality

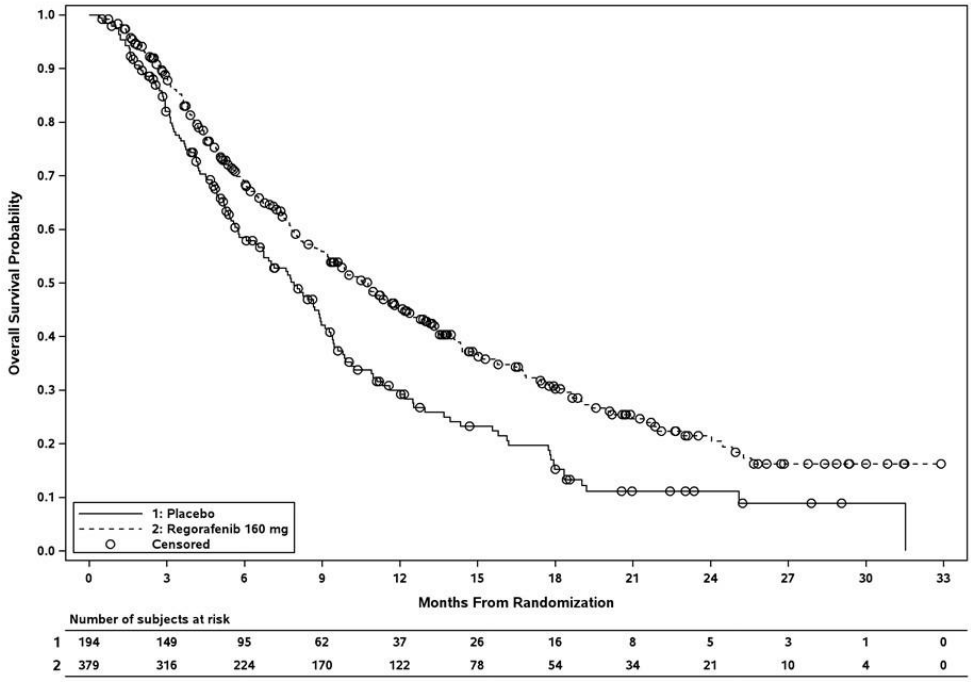
D0001 – What is the expected beneficial effect of regorafenib on mortality?

The median OS time was 10.6 months (95% CI 9.1, 12.1 months) in the regorafenib group compared with 7.8 months (95% CI 6.3, 8.8 months) in the placebo group with an HR of 0.627 (95% CI 0.500, 0.785), one sided p-value from the log rank test stratified =0.00002. The absolute gain was 2.8 months in favour of regorafenib.

Following the authors' request, the MAH provided a bootstrap analysis to estimate the mean and 95% CI of the difference of OS median times at the time of the primary analysis. At this time, the mean difference in terms of OS median times between the two arms was: 2.7 months (95% CI 0.8, 5.0).

A Kaplan-Meier analysis for OS for the FAS is presented in Figure 5.1.

Figure 5.1: Kaplan-Meier curves of OS (FAS population)

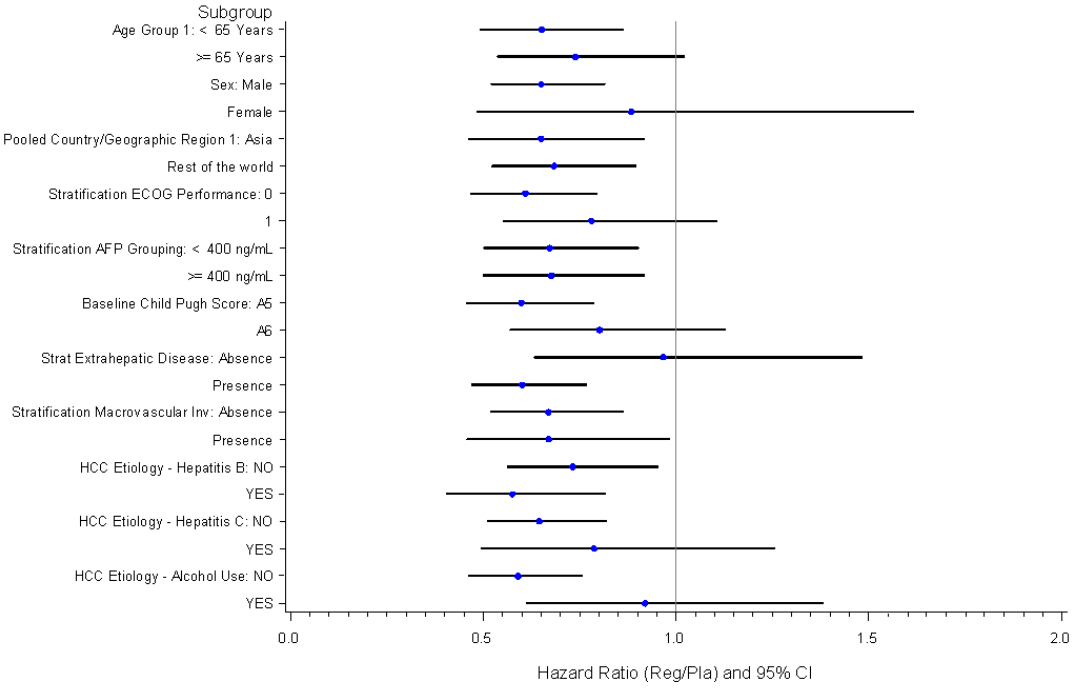


Abbreviations: FAS=full analysis set; OS=overall survival.

Sources: clinical study report and MAH submission file.

Subgroup analysis suggested a consistent effect of regorafenib in almost every subgroup, expect females, absence of extrahepatic disease, HCC aetiology hepatitis C, Child-Pugh score A6, ECOG =1, age ≥65 years old, and alcohol use. However, considering the reduced size in these subgroups, these data are to be interpreted with caution (see Figure 5.2 and Table 5.4).

Figure 5.2: Forest plot of subgroup analyses: OS



Abbreviations: AFP=alpha-fetoprotein; ECOG=Eastern Cooperative Oncology Group; HCC=hepatocellular carcinoma; OS=overall survival.

Sources: clinical study report and MAH submission file.

Table 5.4: Summary subgroup analyses of OS – inferential statistics

					Hazard Ratio (Reg/Pla)		Median (Days)	
Variable	Subgroup	N	# Events	# Censored	Estimate	95% CI	Placebo	Regorafenib
Age Group	<65 years	315	205	110	0.653	(0.493, 0.865)	211 (156, 267)	298 (232, 341)
	≥ 65 years	258	168	90	0.740	(0.536, 1.021)	260 (202, 307)	354 (278, 405)
Sex	Male	504	327	177	0.651	(0.520, 0.815)	241 (173, 280)	324 (269, 383)
	Female	69	46	23	0.884	(0.484, 1.616)	233 (148, 297)	292 (114, 499)
Geographical Region	Asia	216	142	74	0.651	(0.462, 0.916)	158 (112, 268)	278 (214, 354)
	ROW	357	231	126	0.684	(0.523, 0.895)	253 (211, 288)	332 (278, 425)
ECOG PS (RAVE)	0	377	231	146	0.610	(0.468, 0.795)	260 (202, 288)	388 (323, 451)
	1	196	142	54	0.781	(0.551, 1.107)	192 (126, 260)	194 (161, 278)
AFP Grouping (RAVE)	<400 ng/mL	324	194	130	0.673	(0.502, 0.902)	282 (233, 366)	405 (343, 493)
	≥400 ng/mL	249	179	70	0.677	(0.499, 0.919)	174 (142, 244)	223 (178, 261)
Baseline Child Pugh Score	A5	362	222	140	0.599	(0.455, 0.788)	244 (174, 283)	360 (303, 432)
	A6	199	141	58	0.802	(0.570, 1.127)	228 (146, 268)	264 (184, 339)
Extrahepatic Disease (RAVE)	Absence	161	103	58	0.968	(0.632, 1.482)	296 (234, 430)	326 (261, 421)
	Presence	412	270	142	0.601	(0.470, 0.769)	196 (157, 260)	313 (248, 369)
Macrovascular Invasion (RAVE)	Absence	409	259	150	0.670	(0.520, 0.862)	260 (208, 284)	344 (293, 403)
	Presence	164	114	50	0.670	(0.457, 0.983)	157 (106, 253)	232 (180, 332)
HCC Etiology - Hep B	N	357	238	119	0.732	(0.562, 0.953)	260 (202, 296)	332 (278, 401)
	Y	216	135	81	0.576	(0.406, 0.817)	161 (127, 268)	269 (223, 366)
HCC Etiology - Hep C	N	454	295	159	0.646	(0.510, 0.819)	230 (167, 268)	313 (272, 372)
	Y	119	78	41	0.788	(0.494, 1.257)	267 (174, 294)	331 (225, 472)
HCC Etiology - Alcohol Use	N	428	273	155	0.591	(0.461, 0.757)	202 (161, 253)	313 (260, 366)
	Y	145	100	45	0.920	(0.613, 1.381)	296 (230, 484)	339 (240, 405)

Abbreviations: AFP = alpha fetoprotein; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; FAS = full analysis set; HCC = hepatocellular carcinoma; Hep = hepatitis virus; IVRS = interactive voice response system; Pla = placebo; RAVE = validated electronic system for data collection; Reg = regorafenib (160 mg); ROW = rest of the world.
A hazard ratio <1 indicates superiority of Regorafenib 160 mg (experimental) over Placebo (control). Hazard ratio and CIs are based on an unstratified Cox Regression Model.

Abbreviations: AFP=alpha-fetoprotein; ECOG=Eastern Cooperative Oncology Group; HCC= hepatocellular carcinoma; OS=overall survival; PS=performance score.

Sources: clinical study report and MAH submission file.

An updated analysis was performed by the MAH almost 1 year later (with a cut-off date of 23 January 2017). On this date, 4 of the 194 patients randomised into the placebo group had switched to regorafenib. Overall, this updated analysis was consistent with the primary analysis: HR=0.614 (95% CI 0.501, 0.753), p=0.000001. The updated median OS was 10.7 months in the regorafenib group and 7.9 months in the placebo group.

Morbidity

D0005 – How does regorafenib affect symptoms and findings (severity, frequency) of the disease or health condition?

D0006 – How does regorafenib affect progression (or recurrence) of the disease or health condition?

PFS (by investigators)

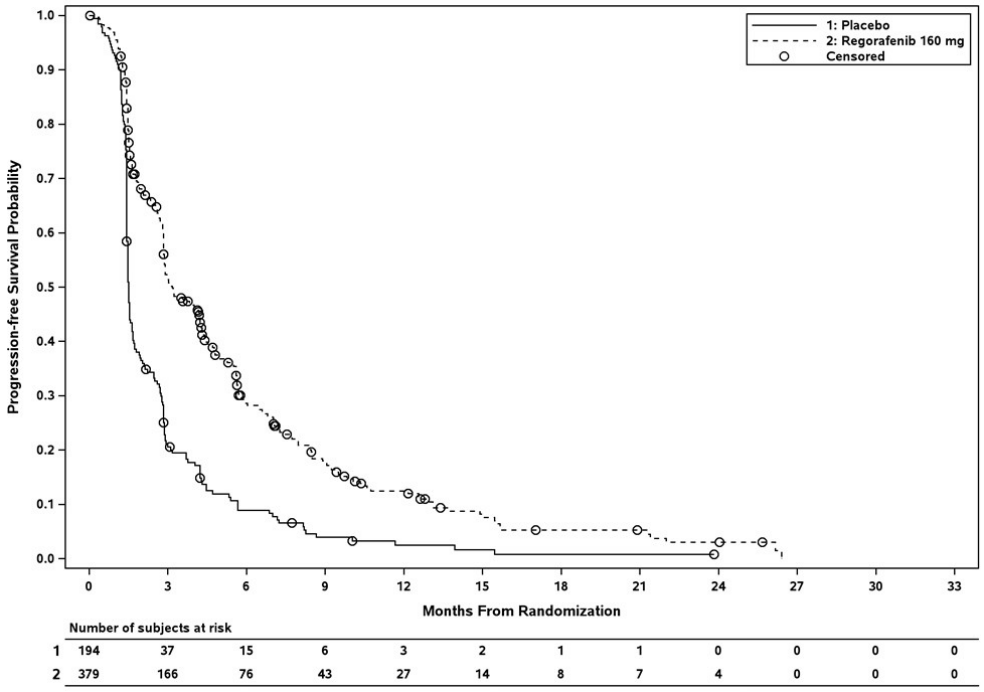
The median PFS time using mRECIST was 3.1 months (95% CI 2.8, 4.2) in the regorafenib group compared with 1.5 months (95% CI 1.4, 1.6) in the placebo group: HR=0.455 (95% CI 0.371, 0.558). The absolute gain was 1.6 months in favour of regorafenib (see Figure 5.3).

Similar results were observed using RECIST 1.1: the median PFS time was 3.4 months (95% CI 2.9, 4.2) in the regorafenib group compared with 1.5 months (95% CI 1.4, 1.5) in the placebo group: HR=0.427 (95% CI 0.348, 0.524). The absolute gain was 1.9 months in favour of regorafenib.

A consistent effect on PFS was observed across the subgroup analysis (not detailed in this report).

No PFS assessment was performed by an independent review committee.

Figure 5.3: Kaplan-Meier curves of PFS (FAS) (mRECIST)



Abbreviations: FAS=full analysis set; mRECIST=modified response evaluation criteria in solid tumors; PFS=progression free survival.

Sources: clinical study report and MAH submission file.

Objective response rate (ORR) and duration of response (DOR)

The ORR to treatment according to mRECIST was 10.6% in the regorafenib group compared with 4.1% in the placebo group: difference =-6.61% (95% CI -10.84, -2.39). Most of the responses were partial; only two patients reach a CR in the regorafenib group.

The ORR to treatment according to RECIST 1.1 was 6.6% in the regorafenib group compared with 2.6% in the placebo group: difference =-4.15% (95% CI -7.55, -0.75). The responses were exclusively partials.

The median DOR according to mRECIST was 3.5 months (106 days) in the regorafenib group compared with 2.7 months (81 days) in the placebo group.

The median DOR according to RECIST 1.1 was 5.9 months (179 days) in the regorafenib group compared with 5.6 months (169 days) in the placebo group.

Biomarker analysis

An exploratory and retrospective analysis of biomarkers using a proteomic approach was performed and submitted by the MAH. This preliminary analysis was conducted on 499 patients representing 87% of the total RESORCE population. The baseline plasma levels of 5 proteins (Ang1, Cystatin B, LAP-TGFβ, Lox1 and MIP1α) are potentially predictive for regorafenib treatment effect for OS (after adjustment for multiplicity) when analysed as continuous variables suggesting that an increase in protein levels correlates with reduced benefit from regorafenib treatment. However, given the low level of evidence of this analysis (exploratory, retrospective), no formal conclusion can be drawn on a potential biomarker to predict regorafenib efficacy or safety.

Post-study treatment

During the follow-up, 130 patients (22.7%) were treated with another antineoplastic agent after progression of the disease: 76 patients in the regorafenib group and 54 patients in the placebo group.

Health-related quality of life

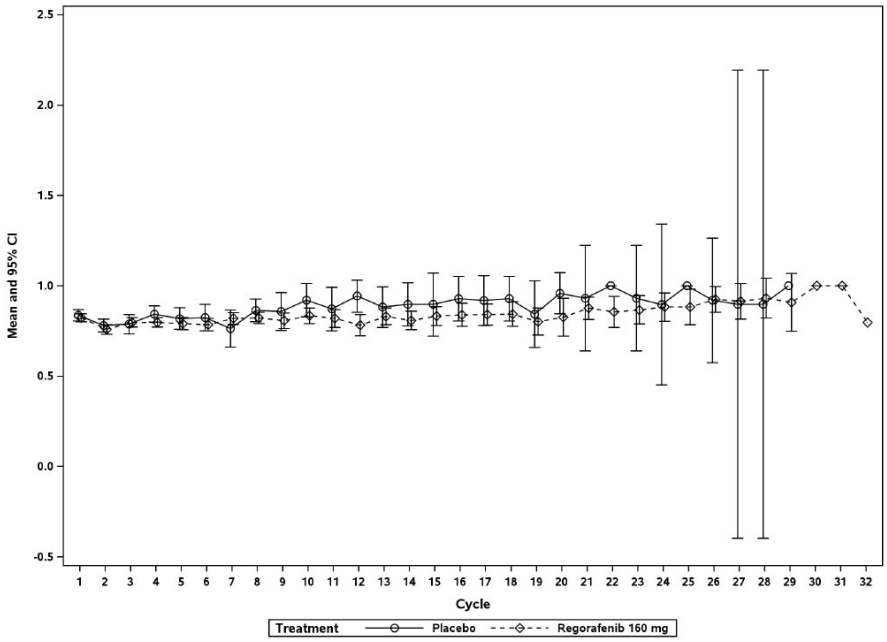
D0012 – What is the effect of regorafenib on generic health-related quality of life (EQ-5D)?

D0013 – What is the effect of regorafenib on disease-specific quality of life (FACT-hep)?

At the end of the treatment (EOT), only half of the patients were evaluated:
- Completion rate for the EQ-5D index at EOT: 56.7% (n=110/194) in the placebo group and 47.0% (n=178/379) in the regorafenib group;
- Completion rate for the EQ-5D VAS at EOT: 57.7% (n=112/194) in the placebo group and 47.5% (n=180/379) in the regorafenib group;
- Completion rate for the FACT-Hep scale at EOT: 57.2% (n=111/194) in the placebo group and 47.0% (n=178/379) in the regorafenib group.

The exploratory analysis of HRQoL suggested the absence of a clinically meaningful difference between regorafenib and placebo as measured by the EQ-5D and FACT-hep scales; see Figures 5.4, 5.5, 5.6 and Table 5.5. However, no formal conclusion can be drawn on HRQoL given the non-optimal level of evidence.

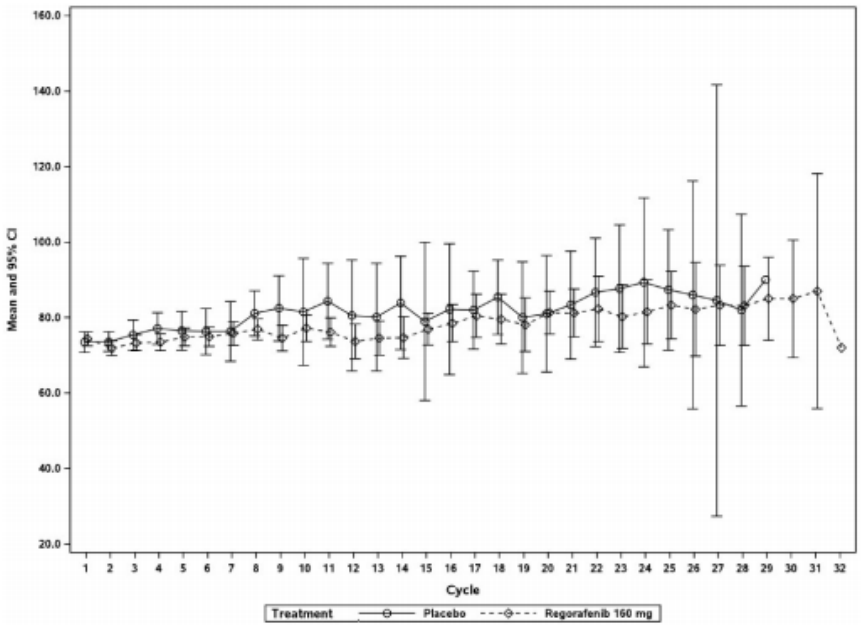
Figure 5.4: EQ-5D – means with 95% CI: EQ-5D index score (evaluable population)



Abbreviations: CI=confidence interval; EQ-5D=EuroQoL five dimensions questionnaire.

Sources: clinical study report and MAH submission file.

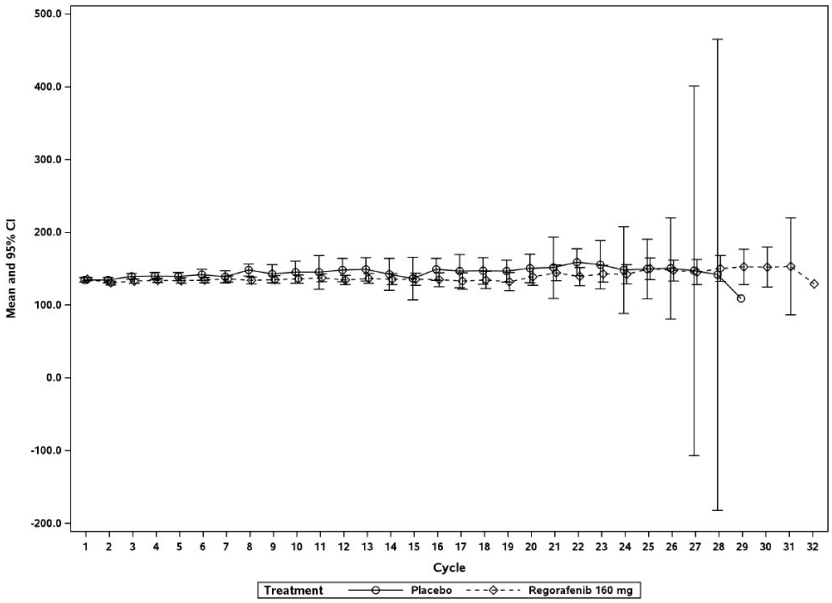
Figure 5.5: EQ-5D – means with 95% CI: EQ-5D VAS (evaluable population)



Abbreviations: CI=confidence interval; EQ-5D=EuroQoL five dimensions questionnaire; VAS=visual analogue scale.

Sources: clinical study report and MAH submission file.

Figure 5.6: FACT-Hep – means with 95% CI: FACT-Hep Total (evaluable population)



Abbreviations: CI=confidence interval; FACT-Hep=functional assessment of cancer therapy questionnaire for patients with hepatobiliary cancer.

Sources: clinical study report and MAH submission file.

Table 5.5: Patient reported outcomes (evaluable population)

	Placebo N=194	Regorafenib N=379	difference	p-value	MID
EQ-5D index	0.77 (0.75, 0.79)	0.76 (0.75, 0.78)	-0.01 (-0.03, 0.02)	0.47	0.1
EQ-5D VAS	73.45 (71.84, 75.06)	71.68 (70.46, 72.90)	-1.77 (-3.58, 0.04)	0.06	10
FACT-Hep total	133.17 (131.21, 135.12)	129.31 (127.84, 130.79)	-3.85 (-6.06, -1.65)	0.0006	8-9

Results expressed as LSM time-adjusted AUC (95% CI)

Abbreviations: AUC=area under the curve; CI=confidence interval; EQ-5D=EuroQoL five dimensions questionnaire; FACT-Hep=functional assessment of cancer therapy questionnaire for patients with hepatobiliary cancer; LSM=least squares method; MID=minimally important differences; VAS=visual analogue scale.

Sources: clinical study report and MAH submission file.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
C0008	How safe is regorafenib in relation to the comparator?
D0011	What is the effect of regorafenib on patients' body functions?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of regorafenib?

6.2 Results

Included study

The relative safety assessment of regorafenib in this indication was based on the randomised, double-blind, placebo-controlled phase III RESORCE trial. Safety variables were analysed in all randomised patients who received at least one dose of study medication: regorafenib or placebo.

The overall median duration of treatment (including time interrupted) was considerably longer for the 374 patients in the regorafenib group (15.6 [0.1-0.128] weeks) than for the 193 patients in the placebo group (8.4 [0.7-0.119] weeks).

Only half of the regorafenib group received the full protocol dose (160 mg/day) with no dose reductions: 184 of 374 (49.2%).

Patient safety

C0008 – How safe is regorafenib in relation to the comparators?

D0011 – What is the effect of regorafenib on patients' body functions?

Treatment-emergent adverse events (TEAEs)
Adverse events (AEs) occurred in all 374 of the 374 patients (100%) receiving regorafenib and in 179 out of 193 patients (92.7%) receiving placebo. These AEs were related to study drug in 92.5% of patients in the regorafenib group and in 51.8% patients in the placebo group.

The most frequently reported TEAEs (>25%) in the regorafenib group were hand–foot skin reaction (HFSR) (51.3% in the regorafenib and 6.7% in the placebo group), diarrhoea (41.2% in the regorafenib and 15.0% in the placebo group), decreased appetite (30.7% in the regorafenib and 14.0% in the placebo group), hypertension (30.7% in the regorafenib and 6.2% in the placebo group), and fatigue (28.6% in the regorafenib and 24.4% in the placebo group); see Table 6.1.

Table 6.1: Most frequently reported TEAEs (>25%) (SAF population)

System organ class (SOC) preferred term	TEAE		Drug-related TEAE	
	Regorafenib N=374(100%)	Placebo N=193 (100%)	Regorafenib N=374 (100%)	Placebo N=193 (100%)
Blood and lymphatic disorders				
Anemia	51 (13.6%)	21 (13.6%)	22 (5.9%)	2 (1.0%)
Endocrine disorders				
Hypothyroidism	24 (6.4%)	0	-	-
Gastrointestinal disorders			-	-

Abdominal distension	18 (4.8%)	10 (5.2%)	-	-
Abdominal pain	79 (21.1%)	30 (15.5%)	26 (7.0%)	4 (2.1%)
Abdominal pain upper	47 (12.6%)	17 (8.8%)	-	-
Ascites	58 (15.5%)	31 (16.1%)	-	-
Constipation	65 (17.4%)	21 (10.9%)	24 (6.4%)	3 (1.6%)
Diarrhea	154 (41.2%)	29 (15.0%)	125 (33.4%)	18 (9.3%)
Dry mouth	21 (5.6%)	9 (4.7%)	-	-
Nausea	64 (17.1%)	26 (13.5%)	40 (10.7%)	13 (6.7%)
Stomatitis	31 (8.3%)	4 (2.1%)	28 (7.5%)	3 (1.6%)
Vomiting	47 (12.6%)	13 (6.7%)	27 (7.2%)	5 (2.6%)
General disorders and administration site conditions				
Asthenia	56 (15.0%)	18 (9.3%)	42 (11.2%)	11 (5.7%)
Edema peripheral	56 (15.0%)	26 (13.5%)	-	-
Fatigue	107 (28.6%)	47 (24.4%)	79 (21.1%)	26 (13.5%)
General physical health deterioration	44 (11.8%)	27 (14.0%)	-	-
Malaise	22 (5.9%)	5 (2.6%)	-	-
Pyrexia	74 (19.8%)	13 (6.7%)	-	-
Investigations				
Alanine aminotransferase increased	54 (14.4%)	21 (10.9%)	28 (7.5%)	8 (4.1%)
Aspartate aminotransferase increased	92 (24.6%)	38 (19.7%)	49 (13.1%)	15 (7.8%)
Blood alkaline phosphatase increased	22 (5.9%)	8 (4.1%)	-	-
Blood bilirubin increased	91 (24.3%)	31 (16.1%)	59 (15.8%)	5 (2.6%)
GGT increased	22 (5.9%)	12 (6.2%)	-	-
Lipase increased	27 (7.2%)	6 (3.1%)	-	-
Platelet count decreased	34 (9.1%)	2 (1.0%)	-	-
Weight decreased	50 (13.4%)	8 (4.1%)	26 (7.0%)	2 (1.0%)
Metabolism and nutrition disorders				
Decreased appetite	115 (30.7%)	27 (14.0%)	88 (23.5%)	11 (5.7%)
Hypoalbuminemia	52 (13.9%)	14 (7.3%)	-	-
Hypokalemia	26 (7.0%)	5 (2.6%)	-	-
Hyponatremia	21 (5.6%)	6 (3.1%)	-	-
Hypophosphatemia	36 (9.6%)	4 (2.1%)	22 (5.9%)	2 (1.0%)
Musculoskeletal and connective tissue disorders				
Arthralgia	14 (3.7%)	11 (5.7%)	-	-
Back pain	45 (12.0%)	17 (8.8%)	-	-
Muscle spasms	38 (10.2%)	4 (2.1%)	23 (6.1%)	1 (0.5%)
Musculoskeletal pain	17 (4.5%)	11 (5.7%)	-	-
Pain in extremity	26 (7.0%)	6 (3.1%)	-	-
Nervous system disorders				
Headache	24 (6.4%)	12 (6.2%)	-	-
Psychiatric disorders				
Insomnia	24 (6.4%)	8 (4.1%)	-	-
Renal and Urinary disorders				
Proteinuria	32 (8.6%)	2 (1.0%)	21 (5.6%)	2 (1.0%)
Respiratory, thoracic and mediastinal disorders				
Cough	41 (11.0%)	13 (6.7%)	-	-
Dysphonia	67 (17.9%)	3 (1.6%)	59 (15.8%)	2 (1.0%)
Dyspnea	28 (7.5%)	15 (7.8%)	-	-
Pleural effusion	15 (4.0%)	11 (5.7%)	-	-
Skin and subcutaneous tissue disorders				
Alopecia	26 (7.0%)	5 (2.6%)	25 (6.7%)	5 (2.6%)
Palmar-plantar erythrodysesthesia syndrome	192 (51.3%)	13 (6.7%)	190 (50.8%)	11 (5.7%)
Pruritus	19 (5.1%)	14 (7.3%)	-	-
Rash	20 (5.3%)	14 (7.3%)	-	-
Vascular disorders				
Hypertension	115 (30.7%)	12 (6.2%)	86 (23.0%)	9 (4.7%)

Abbreviations: SAF=safety analysis population; SOC=system organ class; TEAE=treatment-emergent adverse event.

Sources: clinical study report and MAH submission file.

Grade ≥3 AEs

More Grade ≥3 AEs were observed in the regorafenib group (n=298, 79.7%; 51.9% drug-related) than in the placebo group (n=113, 58.5%; 17.6% drug-related); see Table 6.2.

The five most frequent drug-related Grade 3 TEAEs in the regorafenib group were: hypertension (12.8%), HFSR (12.3%), blood bilirubin increased (5.1%), AST increased (4.5%) and hypophosphataemia (4.3%). The five most frequent drug-related Grade 4 TEAEs in the regorafenib group were: alanine transaminase (ALT) increased (0.5%), hypophosphataemia (0.5%), anaemia (0.3%), thrombocytopenia (0.3%) and acute coronary syndrome (0.3%).

Table 6.2: Worst CTCAE grade of any AE and any drug-related AE

Worst CTCAE grade	Placebo N=193	Regorafenib N=374
Any AE		
Grade 1	30 (15.5%)	16 (4.3%)
Grade 2	36 (18.7%)	60 (16.0%)
Grade 3	61 (31.6%)	208 (55.6%)
Grade 4	14 (7.3%)	40 (10.7%)
Grade 5 (death)	38 (19.7%)	50 (13.4%)
Grade ≥3	113 (58.5%)	298 (79.7%)
Any drug-related AE		
Grade 1	43 (22.3%)	42 (11.2%)
Grade 2	23 (11.9%)	110 (29.4%)
Grade 3	31 (16.1%)	173 (46.3%)
Grade 4	1 (0.5%)	14 (3.7%)
Grade 5 (death)	2 (1.0%)	7 (1.9%)
Grade ≥3	34 (17.6%)	194 (51.9%)

Abbreviation: AE=adverse event; CTCAE=common terminology criteria for adverse events.

Sources: clinical study report and MAH submission file.

Serious adverse events (SAEs)

The overall incidence of SAEs was broadly similar in the two groups: 44.4% (n=166) in the regorafenib group (10.4% drug-related) and 46.6% (n=90) in the placebo group (2.6% drug-related). Most of the SAEs observed in the regorafenib group were related to the following SOCs: general disorders and administration site conditions (49 events, 13.1%), gastrointestinal disorders (32 events, 8.6%), and hepatobiliary disorders (22 events, 5.9%).

Grade 5 AEs (deaths)

In total, at the time of the database cut-off, there were 9 TEAEs with a fatal outcome (Grade 5) within 30 days of last study drug that were reported as treatment-related in the clinical database: 7 in the regorafenib group and 2 in the placebo group. Causes of TEAEs with a fatal outcome in the regorafenib group were: duodenal perforation, meningorrhagia, shock haemorrhagic, hepatic encephalopathy, myocardial infarction, general physical health deterioration, and one unexplained death.

Discontinuation and dose modification due to adverse events

Dose modification (treatment interruption or dose reduction) because of an AE was required in 68.2% of patients receiving regorafenib compared with 31.1% of patients receiving placebo. AEs leading to permanent discontinuation of the drug were also more frequently recorded in the regorafenib group (24.9% versus 19.2%); see Table 6.3.

TEAEs leading to discontinuation of study drug in at least 2% of subjects in the regorafenib group were: general physical health deterioration (3.7%), AST increased (2.4%), and blood bilirubin increased (2.1%).

Table 6.3: Adverse events leading to dose modification or discontinuation of the drug (SAF population)

	Placebo N=193	Regorafenib N=374
Any AE		
Leading to a dose modification	60 (31.1%)	255 (68.2%)
Leading to permanent discontinuation of study drug	37 (19.2%)	93 (24.9%)
Any drug-related AE		
Leading to a dose modification	20 (10.4%)	202 (54.0%)
Leading to permanent discontinuation of study drug	7 (3.6%)	39 (10.4%)

Abbreviation: AE=adverse event; SAF=safety analysis population.

Sources: clinical study report and MAH submission file.

Adverse events of special interest (RMP)

The Pharmacovigilance Risk Assessment Committee (PRAC) and the CHMP endorsed the risk management plan (RMP) with the ongoing safety concerns detailed in Table 6.4.

Table 6.4: Risk management plan

Important identified risks	Severe drug-induced liver injury (DILI) Cardiac ischaemic events Hypertension and hypertensive crisis Haemorrhage Hand–foot skin reaction (HFSR) Posterior reversible encephalopathy syndrome (PRES) Gastrointestinal perforation and fistulae Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN)
Important potential risks	Wound healing complications Interstitial lung disease (ILD) Atrial fibrillation Reproductive and developmental toxicity Renal failure Phototoxicity Thrombotic microangiopathies (TMA)
Missing information	Safety in severe hepatic impairment Safety in children Safety in patients with a cardiac history Safety in severe renal impairment Interaction with antibiotics Interaction with BCRP substrates Activity in KRAS mutated tumours or other biomarker defined tumour sub-types Long-term safety in GIST patients

Abbreviations: BRCP=breast cancer resistance protein; DILI=drug-induced liver injury; EMA=European Medicines Agency; HFSR=hand–foot skin reaction; ILD=interstitial lung disease; PRES=posterior reversible encephalopathy syndrome; SJS=Stevens-Johnson syndrome; TEN=toxic epidermal necrolysis; TMA=thrombotic microangiopathies.

Source: EMA.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of regorafenib?

Differences in terms of safety profile were observed across races groups. Table 6.5 details the most common TEAEs (incidence of >10% overall in the regorafenib group) by race: White, Asian, or not reported. Incidences of HFSR in the regorafenib group were 66.5% for Asian patients and 42.2% for White patients. Other AEs reported more frequently in Asian patients in the regorafenib group included: ALT increased, AST increased, and hypoalbuminaemia. AEs reported more frequently in White subjects included: fatigue and hypothyroidism.

No other subgroups were identified that are more likely to be harmed.

Table 6.5: Most common TEAEs by race (>10% overall in regorafenib treatment group) (SAF)

	Placebo						Regorafenib					
	Asian N = 78		White N = 68		Not reported[b] 44		Asian N = 155		White N = 135		Not reported[b] 76	
MedDRA PT, v. 19.0	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Palmar-plantar erythrodysesthesia syndrome [a]	9	(11.5)	4	(5.9)	0		103	(66.5)	57	(42.2)	29	(38.2)
Diarrhoea	6	(7.7)	12	(17.6)	10	(22.7)	62	(40.0)	53	(39.3)	37	(48.7)
Hypertension	3	(3.8)	6	(8.8)	3	(6.8)	43	(27.7)	45	(33.3)	25	(32.9)
Decreased appetite	15	(19.2)	8	(11.8)	4	(9.1)	46	(29.7)	39	(28.9)	28	(36.8)
Fatigue	14	(17.9)	23	(33.8)	10	(22.7)	26	(16.8)	51	(37.8)	26	(34.2)
AST increased	23	(29.5)	7	(10.3)	8	(18.2)	57	(36.8)	18	(13.3)	16	(21.1)
Blood bilirubin increased	19	(24.4)	7	(10.3)	5	(11.4)	43	(27.7)	34	(25.2)	12	(15.8)
Abdominal pain	9	(11.5)	13	(19.1)	8	(18.2)	24	(15.5)	33	(24.4)	21	(27.6)
Pyrexia	9	(11.5)	3	(4.4)	1	(2.3)	37	(23.9)	27	(20.0)	9	(11.8)
Dysphonia	0		2	(2.9)	1	(2.3)	26	(16.8)	25	(18.5)	13	(17.1)
Nausea	14	(17.9)	8	(11.8)	3	(6.8)	18	(11.6)	26	(19.3)	18	(23.7)
Constipation	8	(10.3)	9	(13.2)	4	(9.1)	23	(14.8)	22	(16.3)	20	(26.3)
Ascites	12	(15.4)	11	(16.2)	8	(18.2)	26	(16.8)	20	(14.8)	10	(13.2)
Asthenia	4	(5.1)	6	(8.8)	8	(18.2)	6	(3.9)	16	(11.9)	31	(40.8)
Oedema peripheral	5	(6.4)	12	(17.6)	9	(20.5)	22	(14.2)	20	(14.8)	14	(18.4)
ALT increased	10	(12.8)	4	(5.9)	7	(15.9)	32	(20.6)	11	(8.1)	10	(13.2)
Anemia	10	(12.8)	9	(13.2)	2	(4.5)	28	(18.1)	13	(9.6)	10	(13.2)
Hypoalbuminemia	11	(14.1)	2	(2.9)	1	(2.3)	36	(23.2)	8	(5.9)	8	(10.5)
Weight decreased	3	(3.8)	2	(2.9)	3	(6.8)	17	(11.0)	17	(12.6)	14	(18.4)
Abdominal pain upper	3	(3.8)	7	(10.3)	7	(15.9)	12	(7.7)	21	(15.6)	12	(15.8)
Vomiting	6	(7.7)	5	(7.4)	2	(4.5)	17	(11.0)	19	(14.1)	10	(13.2)
Back pain	6	(7.7)	7	(10.3)	4	(9.1)	13	(8.4)	18	(13.3)	14	(18.4)
General physical health deterioration	11	(14.1)	10	(14.7)	6	(13.6)	14	(9.0)	14	(10.4)	16	(21.1)
Cough	8	(10.3)	2	(2.9)	3	(6.8)	17	(11.0)	16	(11.9)	8	(10.5)
Muscle spasms	0		2	(2.9)	2	(4.5)	8	(5.2)	18	(13.3)	12	(15.8)
Hypothyroidism	0		0		0		5	(3.2)	18	(13.3)	1	(1.3)

a: Hand foot skin reaction (HFSR) per CTCAE v 3.0 terminology.
b: Missing or not reported. Some participating countries did not require/allow reporting of race.
Of note, most common AEs in regorafenib group (≥10%) of Study 15982 (Pool 2) are shown, along with those with a >10 percentage higher incidence in a race category. There were only 8 Black or African American subjects and 3 "Other" subjects in Study 15982 (Pool 2); please refer to the source table for these subgroups.
AE = Adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; SAF = safety analysis set; CTCAE = Common Terminology Criteria for Adverse Events

Abbreviations:ALT= alanine transaminase, AST= aspartate transaminase; MedDRA= Medical Dictionary for Regulatory Activities

Sources: clinical study report and MAH submission file.

7 POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL, AND LEGAL ASPECTS (ETH, ORG, SOC, LEG)

Not applicable.

8 PATIENT INVOLVEMENT

WP4 emphasises the importance of including the patient's perspective in producing Joint Assessments. For this specific Joint Assessment, several patient organisations have been contacted to assist in identifying patients who may be interested in participating in the Joint Assessment. However, no response from patients has been received.

9 DISCUSSION

On 04 July 2017, the CHMP adopted a positive opinion recommending the extension of indication for STIVARGA® (regorafenib) for the treatment of adult patients with HCC who have been previously treated with sorafenib. In March 2017, the MAH of STIVARGA® (Bayer) requested EUnetHTA to perform a relative assessment of the effectiveness and safety of regorafenib in this new indication. The aim of this report is to provide a common assessment basis that can be used by European HTA bodies for their national appraisal of reimbursement decisions.

Like sorafenib, regorafenib is an oral antineoplastic agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis, oncogenesis and the tumour microenvironment. Its chemical structure differs from sorafenib by the addition of one fluorine atom. Regorafenib has been previously granted marketing approval for the treatment of adult pretreated patients with mCRC and unresectable or metastatic GIST[2].

HCC is the most common type of liver cancer. Its incidence varies from 3 out of 100,000 in western countries to more than 15 out of 100,000 in certain areas of the world [7]. Cirrhosis of various aetiologies (HCV, HBV, alcohol use) is the largest risk factor for HCC associated with 80–90% of all cases. As the prognosis of patients with HCC is generally poor, it represents the third-leading cause of cancer-related death in the world. When diagnosed at an early stage, patients may generally be eligible for curative treatments mainly represented by surgical resection, radiofrequency ablation or liver transplantation. When diagnosed at an intermediate stage (multinodular) or for patients who progress to an intermediate stage, TACE is generally the preferred option. For patients diagnosed with an advanced tumour or for those who progress to an advanced disease, therapeutic management depends on the general state. Sorafenib is the standard systemic therapy indicated for patients with a well-preserved liver function (Child-Pugh A) and a good performance status (ECOG 0-1) with the objective to increase survival but not to cure the disease. There is little evidence to support the use of sorafenib in Child-Pugh B patients. Although it can be recommended by some scientific societies, with a low strength of evidence sorafenib faces some reimbursement restriction in Child-Pugh B patients[3]. For patients with a Child-Pugh C status or a PS >2 (or ECOG>1) only BSC with symptomatic treatment are recommended. Patients who progress on or after sorafenib treatment are only eligible for BSC as no other treatment is currently approved or recommended in this situation, emphasising a medical need in the population scoped in this report.

This REA is based on a pivotal, randomised, double-blind phase III trial sponsored by the MAH comparing regorafenib (160 mg by mouth once daily in a 3/1 schedule) plus BSC versus placebo plus BSC in patients with HCC who had progressed while on sorafenib: the RESORCE trial [33]. The overall design of this pivotal trial is appropriate with a low risk of bias; the authors conducted a risk of bias assessment on a study and outcome level for RCTs. As previously stated, no treatments are currently approved or recommended for patients previously treated with sorafenib; therefore, placebo plus BSC is considered to be an acceptable comparator. However, the population included in this trial was restricted to those who tolerated sorafenib treatment defined as not less than 20 days at a minimum daily dose of 400 mg once daily within the last 28 days prior to withdrawal and to those with a well-preserved general state (ECOG 0-1; Child-Pugh A). Hence, the population included in the RESORCE trial represents only a subgroup of the scoped population. The primary endpoint was OS. Secondary endpoints included: PFS, objective tumour response rate, median DOR and HRQoL (EQ-5D and FACT-hep). In accordance with dedicated reviewers, authors and co-authors selected OS and HRQoL as critical efficacy outcomes in this disease and PFS as an important efficacy outcome. Conclusions on PFS and HRQoL are, however, limited in the absence of adjustment for multiplicity analysis performed in the trial.

Overall, 573 patients were randomised in the RESORCE trial: 379 in the regorafenib group and 194 in the placebo group. Demographic and baseline disease characteristics were balanced across both treatment arms. The mean age was approximately 63 years in both treatment groups. At study entry, most of the patients had an ‘advanced’ BCLC stage (88.7% in the placebo group and 85.8%

[2] See summary of product characteristics for exact indications.

[3] Restricted to Child-Pugh A in France and Italy. Restricted to Child-Pugh A, adequate renal and hematopoietic functions in Croatia.

in the regorafenib group), an ECOG performance score of 0 (65% and 67%) and 1 or 2 target lesions (mRECIST) (63.9% and 61.4%). The vast majority of the patients included had a Child-Pugh A score (97–98%). Most frequent aetiologies of HCC were: hepatitis B (37.7% in the regorafenib group and 37.6% in the placebo group), hepatitis C (20.6% and 21.1%) and alcohol use (23.8% and 28.4%). As HCC in western countries is mostly caused by alcohol use, hepatitis C (although this is tending to decrease) and obesity, the RESORCE population does not fully reflect the European population. However, this potential limit is not considered to have an impact on trial validity.

This study met its primary endpoint: the median OS time was 10.6 months (95% CI 9.1, 12.1 months) in the regorafenib group and 7.8 months (95% CI 6.3, 8.8 months) in the placebo group, corresponding to an absolute gain of 2.8 months in favour of regorafenib: HR=0.627 (95% CI 0.500, 0.785), one sided p-value =0.000020.

The addition of regorafenib to BSC was also superior in terms of PFS: 3.1 months (95% CI 2.8, 4.2) versus 1.5 months (95% CI 1.4, 1.6) corresponding to an absolute gain of 1.6 months: HR=0.455 (95% CI 0.371, 0.558), p<0.000001.

Regarding safety, more Grade ≥3 AEs were seen in the regorafenib group than in the placebo group: 51.9% versus 17.6%. Similarly, SAE rates were higher in the regorafenib group: 10.4% versus 2.6%. Dose modifications due to AEs (interruption or reduction) were more frequently required in the regorafenib group (68.2%) than in the placebo group (31.1%).

The most frequent drug-related Grade 3 AEs in the regorafenib group were: hypertension (12.8%), HFSR (12.3%), blood bilirubin increased (5.1%), AST increased (4.5%) and hypophosphataemia (4.3%). Important risks identified in the RMP (all indications) were: severe drug-induced liver injury, cardiac ischaemic events, hypertension and hypertensive crisis, haemorrhage, HFSR, PRES, gastrointestinal perforation and fistulae, SJS and TEN.

The exploratory analysis of HRQoL as measured by the EQ-5D and FACT-hep scales suggested the absence of a clinically relevant difference between the two study groups for these criteria. However, an important amount of missing data was observed (about 50% of the patients were evaluated at the end of treatment) limiting the conclusion on HRQoL. Furthermore, in a less selected population more representative of patients seen in a real-life setting, given the safety profile of this drug, regorafenib is likely to have an impact on patients' quality of life.

10 CONCLUSION

The market authorisation of regorafenib was recently extended to the treatment of patients with HCC who have been previously treated with sorafenib. So far, no active drug was authorised or used in clinical practice in these patients, emphasising a high unmet medical need in the scoped population.

This extension of indication is based on a single randomised pivotal trial (the RESORCE study), which demonstrated that regorafenib plus BSC is more effective than placebo plus BSC in terms of OS in a highly selected group of patients previously treated with sorafenib, who had a preserved general state (ECOG 0 or 1), a well-preserved liver function (Child-Pugh A) and who tolerated sorafenib[4]. However, the addition of regorafenib to BSC induced a modest gain in terms of OS (+2.8 months in median) at the expense of a worsened safety profile, notably in terms of Grade ≥3 drug-related AEs, drug-related SAEs and dose reduction or discontinuation due to AEs. Given the amount of missing data and the absence of adjustment for multiple analyses, there is insufficient evidence to determine the relative impact of regorafenib on HRQoL in comparison with placebo. As clinical management of end-stage patients must aim to improve or maintain quality of life, this is particularly regrettable.

In addition, it is important to point out that no data are available in patients who progressed on sorafenib treatment but did not tolerate sorafenib or with a deteriorated general state (ECOG >1) or a Child-Pugh score of B (not eligible for the RESORCE trial) or a combination of these; hence, the clinical benefit of regorafenib cannot be assessed in these fragile populations. Given the broad marketing authorisation wording (indicated as monotherapy for the treatment of adult patients with HCC who have been previously treated with sorafenib), further research or data collection are deemed necessary to evaluate the use of regorafenib in these specific subgroups.

[4] Defined as not less than 20 days at a minimum daily dose of 400 mg once daily within the last 28 days prior to withdrawal.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES

Search Strategy (done by the MAH)

ProQuest

Table A1: Search terms in ProQuest

Topic	Search number	Search String	Result hits (10/01/2017)
HCC	S1	TI,AB((hepatic OR liver) AND cell AND (cancer OR carcinoma OR neo-plasm))	99975*
	S2	TI,AB(malignant NEAR/3 hepatoma)	398°
	S3	TI,AB(hepatocarcinoma OR "hepatocellular carcinoma" OR "HCC ")	168566*
	S4	TI,AB(HCC)	97375*
	S5	EMB.EXACT("liver cell carcinoma")	125648*
	S6	MESH.EXACT("Carcinoma, Hepatocellular")	68082*
	S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	298802*
Intervention	S8	TI,AB(regorafenib)	887°
	S9	TI,AB(Stivarga)	32°
	S10	TI,AB("bay 73 4506" OR "bay 73-4506" OR "bay 734506" OR "bay73 4506" OR "bay73-4506" OR "bay734506")	44°
	S11	EMB.EXACT("regorafenib")	1533°
	S12	S8 OR S9 OR S10 OR S11	1612*
Total	S13	S7 AND S12	217°

* Duplicates are removed from the search, but included in the result count.

° Duplicates are removed from the search and from the result count.

Cochrane

Table A2: Search terms in the Cochrane Library

Search Type	Search Number	Search String	Result hits (10/01/2017)
HCC	#1	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees	1308
	#2	“HCC”: ti,ab,kw	1307
	#3	"hepatic cell carcinoma":ti,ab,kw	2
	#4	"hepatic cell cancer":ti,ab,kw	1
	#5	"liver cell carcinoma":ti,ab,kw	899
	#6	“liver cell cancer":ti,ab,kw	2
	#7	"hepatocarcinoma":ti,ab,kw	45
	#8	"hepatocellular carcinoma":ti,ab,kw	2219
	#9	malignant near/3 hepatoma:ti,ab,kw	4
	#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	2762
	#11	"Regorafenib":ti,ab,kw	117
	#12	"Stivarga":ti,ab,kw	3
	#13	#11 OR #12	117
	#14	#10 AND #13	3
Results by database		**Cochrane Database of Systematic Reviews (CDSR)**	**0**
		Database of Abstracts of Reviews of Effects (DARE)	**0**
		Cochrane Central Register of Controlled Trials (CENTRAL)	**2**
		Cochrane Methodology Register (CMR)	0
		Health Technology Assessments Database (HTA)	1
		NHS Economic Evaluations Database (EED)	0
		Cochrane Groups	0

Conferences

Table A3: Search terms in Conference websites and clinicaltrials.gov

Organization	Search string	Results hits (16/01/2017)
American Association for Cancer Research (AACR)	“hepatocellular carcinoma”; “HCC”; "regorafenib”	4
American Society of Clinical Oncology (ASCO)	"hepatocellular carcinoma" AND "regorafenib"	1
ASCO Gastrointestinal Cancers Symposium (ASCO GI)	"hepatocellular carcinoma" AND "regorafenib"	0
European Society for Medical Oncology (ESMO)	"hepatocellular carcinoma" AND "regorafenib"	4
International Liver Cancer Association (ILCA)	"regorafenib"*	0**
European Society of Digestive Oncology (ESDO)	“hepatocellular carcinoma”; “HCC”*	0
European Association for the Study of the Liver (EASL)	“hepatocellular carcinoma” AND "regorafenib"	1
ESMO World Congress on Gastrointestinal Cancer (WCGIC)	"hepatocellular carcinoma"; “HCC”; "regorafenib"*	92
Japanese Society of Medical Oncology (JSMO)	“hepatocellular carcinoma” AND "regorafenib"	3
Chinese Society of Clinical Oncology (CSCO)	“hepatocellular carcinoma”; “HCC”; "regorafenib”*	0
American Association for the Study of Liver Diseases (AASLD)	“hepatocellular carcinoma” AND "regorafenib"	3
Clinicaltrials.gov	"hepatocellular carcinoma" AND "regorafenib"	3

*No search engine function was available to search for relevant abstracts, therefore search term was limited to "hepatocellular carcinoma"

**Only 2016 abstract book meeting is accessible, abstract books for 2015 and 2014 were not available online.

Studies for full-text selection

Table A4: References screened during full-text selection

Authors	Journal	Title	Final decision FT	Comment
Bolondi, Tak et al. (2011)	European Journal of Cancer (2011), 47, S464	Phase II safety study of the oral multikinase inhibitor regorafenib (BAY 73-4506) as second-line therapy in patients with hepatocellular carcinoma	Excluded, did not meet study design criteria	
Ravi and Singal (2014)	Core Evidence (2014) 9, 81-87	Regorafenib: An evidence-based review of its potential in patients with advanced liver cancer	Excluded, did not meet study design criteria	
(Bruix, Merle et al. 2016a)	Annals of Oncology (2016), 27	Efficacy, safety, and health-related quality of life (HRQoL) of regorafenib in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: Results of the international, double-blind phase 3 RESORCE trial	Included	
(Bruix, Tak et al. 2013)	European Journal of Cancer (2013), 49, *(16)* 3412-3419	Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: Multicentre, open-label, phase II safety study	Excluded, did not meet study design criteria	
(Bruix, Merle et al. 2016)	Annals of Oncology (2016), 27, ii140-ii141	Efficacy and safety of regorafenib versus placebo in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: Results of the international, randomized phase 3 RESORCE trial	Included	
(Bruix, Qin et al. 2017)	The Lancet (2017)	Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomized, double-blind, placebo-controlled, phase 3 trial	Included	

Authors	Journal	Title	Final decision FT	Comment
Yu, Su et al. (2016)	IEEE/ACM transactions on computational biology and bioinformatics (2016)	Prediction of novel drugs for hepatocellular carcinoma based on multi-source random walk	Included	
Cheng, Finn et al. (2013)	Journal of Clinical Oncology (2013), 31 *(15)*	Regorafenib (REG) in patients with hepatocellular carcinoma (HCC) progressing following sorafenib: An ongoing randomized, double-blind, phase III trial	Excluded, did not meet the outcome criteria	No outcomes were reported (poster, regarding study design of RESORCE)
Bruix, Finn et al. (2014)[5]	Journal of Clinical Oncology (2014), 32 *(15)*	RESORCE: An ongoing randomized, double-blind, phase III trial of regorafenib (REG) in patients with hepatocellular carcinoma (HCC) progressing on sorafenib (SOR)	Excluded, did not meet the outcome criteria	No results were reported (only study design of RESORCE)
Ribeiro de Souza, Reig et al. (2016)	Expert Opinion on Pharmacotherapy (2016), 17 *(14)*, 1923-1936	Systemic treatment for advanced hepatocellular carcinoma : the search of new agents to join sorafenib in the effective therapeutic armamentarium	Excluded, did not meet the outcome criteria	No results were reported (review)
Woo, Yoo et al. (2017)	Expert Opinion on Pharmacotherapy (2017), 18 *(1)*, 35-44	New chemical treatment options in second-line hepatocellular carcinoma : what to do when sorafenib fails?	Included	
Trojan and Waidmann (2016)	Journal of hepatocellular carcinoma (2016), 3 31-36	Role of regorafenib as second-line therapy and landscape of investigational treatment options in advanced hepatocellular carcinoma	Included	
von Felden, Schulze et al. (2016)	Diagnostics (Basel, Switzerland) (2016), 6 *(4)*	First- and Second-Line Targeted Systemic Therapy in Hepatocellular Carcinoma -An Update on Patient Selection and Response Evaluation	Included	

[5] Found twice in the systematic literature review (one abstract and one poster)

Authors	Journal	Title	Final decision FT	Comment
(Bruix 2016)	Hepatic Oncology (2016), 3 *(3)*, 187-189	Regorafenib and the RESORCE trial: A new second-line option for hepatocellular carcinoma patients	Excluded, did not meet the study design criteria	Interview
Kudo (2016)	Liver Cancer (2016), 5, 1	Recent advancement in HCC treatment	Excluded, did not meet the outcome criteria	No results were reported (presentation, without references)
Abou-Alfa (2016)	Liver Cancer (2016), 5, 43	An odyssey from doxorubicin to nivolumab with sorafenib and regorafenib in between	Excluded, did not meet the outcome criteria	No results were reported (no references)
Killock (2017)	Nature reviews. Clinical oncology (2016)	Liver cancer: Regorafenib - a new RESORCE in HCC	Included	
Finn (2016)	Liver Cancer (2016), 5, 7	Highlights on targeted therapy for HCC	Excluded, did not meet the outcome criteria	No results were reported (no references)
US National Institutes of Health (2016)	Clinicaltrials.gov (2016)	Study of Regorafenib After Sorafenib in Patients With Hepatocellular Carcinoma	Included	
US National Institute of Health (2015)	Clinicaltrials.gov (2015)	Safety Study of BAY73-4506 in Patients With Hepatocellular Carcinoma	Excluded, did not meet study design criteria	

DESCRIPTION OF THE EVIDENCE USED

Guidelines for diagnosis and management

Table A5: Overview of guidelines

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation and Level of evidence (A,B,C) / class of recommendation (I, IIa, IIb, III)

EASL-EORTC (Llovet 2012)	2012	Europe	First Line treatment:
			• Anatomical resections are recommended for patients with solitary tumors and very well preserved liver function (normal bilirubin with hepatic venous pressure gradient ≤10 mmHg or platelet count ≥100, 000). (3A/2C)
			• Liver transplantation is considered for patients with single tumors less than 5 cm or ≤3 nodules ≤3 cm (Milan criteria) not suitable for resection. (2A/1A)
			  ○ Neo-adjuvant treatment can be considered for loco-regional therapies if the waiting list exceeds 6 months due to good cost-effectiveness data and tumor response rates, even though impact on long-term outcome is uncertain. (2D/2B)
			  ○ Living donor liver transplantation is an alternative option in patients with a waiting list exceeding 6-7 months, and offers a suitable setting to explore extended indications within research programs. (2A/2B)
			  ○ Down-staging policies for HCCs exceeding conventional criteria cannot be recommended and should be explored in the context of prospective studies aimed at survival and disease progression. (2D/2C)
			Local ablation for BCLC 0-A tumors not suitable for surgery:
			• Radiofrequency ablation is recommended in most cases where the tumors are less than 5 cm due to a significantly better control of the disease. (1iD/1A)
			• Ethanol injection is recommended in cases where radiofrequency ablation is not technically feasible (around 10-15%)
			Chemoembolization and transcatheter therapies:
			• Chemoembolization is recommended for patients with BCLC stage B, multinodular asymptomatic tumors without vascular invasion or extra-hepatic spread. (1iiA/1A)
			• Chemoembolization is discouraged in patients with decompensated liver disease, advanced liver dysfunction, macroscopic invasion or extra-hepatic spread. (1iiA/1B)
			• Bland embolization is not recommended
			• Internal radiation with ^{131}I or ^{90}Y glass beads not recommended as standard therapy. (2A/2B)
			• Selective intra-arterial chemotherapy or lipiodolization are not recommended. (2A/2B)

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation and Level of evidence (A,B,C) / class of recommendation (I, IIa, IIb, III)
			Systemic therapies: • Sorafenib is indicated for patients with well-preserved liver function (Child-Pugh A class) and with advanced tumors (BCLC C) or those tumors progressing upon loco-regional therapies. (1iA/1A) • Systemic chemotherapy, tamoxifen, immunotherapy, antiandrogen, and herbal drugs are not recommended for the clinical management of HCC patients. 1-2A/1A/B) • BSC or the inclusion of patients in clinical trials is recommended for patients with intolerance or failure to sorafenib. (Recommendation 2B) • In specific circumstances, radiotherapy can be used to alleviate pain in patients with bone metastasis (3A/2C) Palliative support including management of pain, nutrition and psychological support should be rendered to patients at BCLC D stage
ESMO-ESDO (Verslype 2012)	2012	Europe	For use of radical therapies for management of localized disease: • Resection is recommended for patients without advanced fibrosis, as long as an R0 resection can be carried out without causing postoperative liver failure due to a too small liver remnant (III/B) • In the case of cirrhosis, resection is effective and safe in early BCLC stages (0 and A) provided that one is dealing with a single lesion, a good performance status and no clinically important portal hypertension (III/B) • For patients with small nodules <2 cm, BCLC stage 0 or those in early stages that are not candidates for resection, RFA and PEI can be considered alternatives to resection (III/B) • RFA provides better local control than PEI, especially in HCCs >2 cm (II/A) • The number and diameter of lesions treated by RFA should not exceed five and 5 cm, respectively (III/B) • Neo-adjuvant or adjuvant therapies are not recommended to improve outcome of patients treated with resection or local ablation (II/B) • Liver transplantation should be considered in patients with a solitary lesion of <5 cm or three nodules <3 cm that are not suitable for resection (II/A) • In the case of a long anticipated waiting time (>6 months) for liver transplant, patients may be offered resection, local ablation or TACE transarterial chemoembolization in order to minimise the risk of tumor progression and to offer a 'bridge' to transplant (III/B) For use of palliative treatments for management of locally advanced/metastatic disease: • TACE is recommended for patients with BCLC stage B, or those with an excellent liver function and multinodular asymptomatic tumors without macroscopic vascular invasion or extra hepatic

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation and Level of evidence (A,B,C) / class of recommendation (I, IIa, IIb, III)
			spread (I/A) • The combination of TACE with systemic agents such as sorafenib—either sequential or concomitant—cannot be recommended today in clinical practice • Sorafenib is recommended for patients with advanced HCC and well-preserved liver function (BCLC stage C) and those with intermediate-stage HCC who progress following TACE (I/A) • In the case of progression or intolerance to sorafenib, BSC is preferred or patients should be included in clinical trials • Systemic chemotherapy, tamoxifen, immunotherapy, anti-androgen or somatostatin analogues are not recommended for the clinical management of HCC patients (I–II/A–B) For patients with end-stage disease with heavily impaired liver function or a poor performance status (both due to the tumor involvement of the liver), only symptomatic treatment is advocated, as they will die within 6 months (III/B)
NCCN	Update May 2017	United States	• **Section Unresectable HCC (HCC-5):** • Evaluation whether patient is a candidate for transplant (UNOS criteria HCC-4) • Not a transplant candidate: o Locoregional therapy (Ablation, Arterially directed therapies, EBRT) o Systemic therapy ▪ sorafenib, Child-Pugh Class A or B ▪ chemotherapy o Clinical trial o Best supportive care • *Regorafenib if progression on or after sorafenib (Child-Pugh Class A only)*(Category 1) • **Section Local disease, metastatic disease, extensive liver burden (HCC-6):** • Inoperable, local disease or Local disease with minimal extrahepatic disease only (HCC-6): o Locoregional therapy (Ablation, Arterially directed therapies, EBRT) o Systemic therapy ▪ sorafenib, Child-Pugh Class A or B ▪ chemotherapy o Clinical trial o Best supportive care • *Regorafenib if progression on or after sorafenib (Child-Pugh Class A only)* (Category 1) • • Metastatic disease or extensive liver tumor burden (HCC-6): o Systemic therapy ▪ sorafenib, Child-Pugh Class A or B ▪ chemotherapy

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation and Level of evidence (A,B,C) / class of recommendation (I, IIa, IIb, III)
			○ Clinical trial ○ Best supportive care • *Regorafenib if progression on or after sorafenib (Child-Pugh Class A only)* (Category 1) (note: NCCN discussion section update is in progress)
LAASL (Méndez-Sánchez 2014)	2014	Latin America	• Indicates liver transplant as first line treatment for patients within Malian criteria (single tumor criteria ≤5 cm or ≥ nodules ≤3 cm) and not suitable for resection. Class of evidence 1, level of evidence A • Liver transplant may be considered after successful downstaging to meet the Malian criteria. Class of evidence 2a, level of evidence B • Indicates resection for patients with solitary nodular tumor and preserved liver function; tumor size, presence of satellite lesions, and vascular involvement should be considered. Class of evidence 2a, level of evidence B • In patients with esophageal varices, diuretic therapy to control ascites, and high bilirubin level should not be considered for resection. Class of evidence 2a, level of evidence B • Resection margins should aim for >2 cm margins, except in patients with reduced parenchymal reserve. Class of evidence 3, level of evidence B • For patients with BCLC 0-A not suitable for surgery, the standard of care is local ablation with RFA or PEI. Class of evidence 2a, level of evidence B • Indicates RFA for tumors <5 cm, and PEI in cases where RFA is technically not feasible (about 10 to 15% of patients). Class of evidence 1, level of evidence A • Indicates chemoembolization for patients with BCLC stage B without portal invasion. Class of evidence 1, level of evidence A • Preoperative TACE should not be considered the standard of care. Class of evidence 1, level of evidence A • Indicates sorafenib as the standard systemic treatment for HCC patients with child-Pugh class A underlying cirrhosis and advanced tumor (BCLC stage C) or tumor progression after locoregional therapy. Class of evidence 1, level of evidence A • No alternative treatment for patients with intolerance or failure to respond to sofafenib. Class of evidence 2, level of evidence B

Abbreviations: ADT - arterially directed therapies; BCLC - Barcelona Clinic Liver Cancer; BSC - Best supportive care; DEB – drug-eluting beads; EASL-EORTC - European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer; EBRT - external beam radiation therapy; ESMO–ESDO – European Society for Medical Oncology, European Society of Digestive Oncology; HCC – hepatocellular carcinoma; IMRT - intensity modulated radiation therapy; LAASL - Latin American Association for the Study of the Liver; PBT – proton beam therapy; PEI - percutaneous ethanol injection; RE - radioembolisation; RFA - radiofrequency ablation; SBRT - stereotactic body radiation therapy; TACE - transarterial chemoembolization; TAE - transarterial bland embolization; UNOS, United Network for Organ Sharing

Sources:
EASL- EORTC
ESMO – ESDO
LAASL
NCCN

Evidence tables of individual studies included for clinical effectiveness and safety

Table A6: Characteristics of randomised controlled studies

Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial			
Study identifier	NCT01774344, RESORCE		
Design	randomised, double-blind, placebo-controlled phase III trial		
	First subject first visit: Last subject Last visit		May 14, 2013 February 29, 2016
Hypothesis	Superiority		
Treatments groups	Regorafenib plus BSC		160 mg (4 x 40 mg tablets) orally (p.o.) every day for 3 weeks followed by 1 week off treatment (schedule 3/1) plus BSC; N= 379
	Placebo plus BSC		4 matching placebo tablets with a 3/1 schedule plus BSC; N= 194
Endpoints and definitions	Primary endpoint	OS	Time from the date of randomisation to death due to any cause
	Secondary endpoint	PFS	Time (days) from date of randomization to date of disease progression (radiological or clinical) or death due to any cause, if death occurs before progression is documented
	Exploratory endpoint	HRQoL	Assessed using the FACT-Hep and the EQ-5D questionnaires
Database lock	August 5, 2016		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	regorafenib	placebo
	Number of subject	379	194
	Primary endpoint OS (median, months)	10.6	7.8
	(95 % CI)	(9.1, 12.1)	(6.3, 8.8)
	PFS (median, months)	3.1	1.5

Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial			
Study identifier	NCT01774344, RESORCE		
	(95 % CI)	(2.8, 4.2)	(1.4, 1.6)
	EQ-5D index	0.76	0.77
	(95 % CI)	(0.75; 0.78)	(0.75, 0.79)
	EQ-5D VAS	71.68	73.45
	(95 % CI)	(70.46; 72.90)	(71.84, 75.06)
	FACT-hep	129.31	133.17
	(95 % CI)	(127.84; 130.79)	(131.21, 135.12)
Effect estimate per comparison	Primary endpoint OS	Comparison groups	Regorafenib vs placebo
		Hazard ratio	0.627
		95%CI	0.500, 0.785
		One-sided p-value	p<0.0001
	Secondary endpoint PFS (mRECIST)	Comparison groups	Regorafenib vs placebo
		Hazard ratio	0.455
		95%CI	0.371, -0.558
		One-sided p-value	p<0.000001
	Exploratory endpoint Exploratory endpoint EQ-5D index (LSM time-adjusted AUC)	Comparison groups	Regorafenib vs placebo
		Difference	-0.01
		95%CI	-0.03, 0.02
		One-sided p-value	0.47
	Exploratory endpoint EQ-5D VAS (LSM time-adjusted AUC)	Comparison groups	Regorafenib vs placebo
		Difference	-1.77
		95%CI	-3.58, 0.04
		One-sided p-value	0.06
	Exploratory endpoint FACT-hep (LSM time-adjusted AUC)	Comparison groups	Regorafenib vs placebo
		Difference	-3.85
		95%CI	-6.06, -1.65
		One-sided p-value	0.0006
Notes	This study was conducted in a selected population with a preserved general state, a Child-Pugh score of A and who tolerated sorafenib treatment (cf inclusion/exclusion criteria). Given the number of missing data observed (about 50% of the patients were evaluated at the end of treatment) and the exploratory nature of HRQoL, no formal conclusion can be made on this critical outcome.		

Abbreviations: CI=confidence interval; HRQoL=health-related quality of life; OS=overall survival; PFS=progression-free survival; ORR=overall response rate.

Sources: clinical study report.

List of ongoing and planned studies

Table A7: List of ongoing studies with regorafenib

Study Identifier	Time	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02664077 Actively recruiting	Study Start Date: June 2016 Estimated Study Completion Date: January 2025 Estimated Primary Completion Date: November 2023	Interventional; Phase 3	Estimated Enrollment: 1118	Regorafenib (orally once daily for 21 days of a 28 day cycle for a total of 26 cycles)	Placebo	Patients with Stage III (IIIB or IIIC) colon cancer are randomized 1:1 to placebo or the experimental agent regorafenib following completion of at least four months of standard adjuvant therapy (e.g. 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX) , capecitabine, oxaliplatin (CapeOx), and other).	Primary Outcome Measures: DFS Secondary Outcome Measures: OS, toxicity, compliance, tolerability, biomarker, PK
NCT02106858 Actively recruiting	Actual Study Start Date: 25/06/2014 Estimated Study Completion Date: 07/05/2019	Observational; Post-Marketing Surveillance	Estimated enrolment: 190	regorafenib under approved local prescriptions	None	Patients diagnosed with metastatic colorectal cancer or metastatic or unresectable locally advanced GISTby physician.	Primary Outcome Measures: Percentage of patients with serious adverse events Secondary Outcome Measures: Overall response, PFS, OS

Study Identifier	Time	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
	Estimated Primary Completion Date: 07/05/2019						
NCT01933958 Actively recruiting	Actual Study Start Date: 04/09/2013 Estimated Study Completion Date: 25/06/2021 Estimated Primary Completion Date: 25/06/2021	Regulatory post-marketing surveillance in Japan, and it is a local prospective and observational study	Estimated enrolment: 135	Regorafenib under practical manner for gastrointestinal stromal tumors progressed after cancer chemotherapy.	None	Patients who have received Regorafenib for GIST progressed after cancer chemotherapy.	Primary Outcome Measures: Number of patients with adverse drug reactions Secondary Outcome Measures: OS, TTF, tumour response, safety
NCT02042144 On-going not recruiting	Actual Study Start Date: 08/04/2014 Estimated Study Completion Date: 01/12/2017	Observational	Enrollment: 1031 patients	Regorafenib	None	Patients with mCRC who have been previously treated with other approved treatments for metastatic disease and for whom a decision has been made by the physician to treat with regorafenib according to local health authority approved label.	Primary Outcome Measures: Incidence of TEAE Secondary Outcome Measures: OS, PFS, DCR, HRQoL, healthcare resource utilisation

Study Identifier	Time	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
	Estimated Primary Completion Date: 30/09/2017						
NCT01843400 On-going not recruiting	Actual Study Start Date: 22/04/2013 Estimated Study Completion Date: 24/03/2021 Primary Completion Date: 12/09/2016	Regulatory post-marketing surveillance in Japan; local prospective and observational study.	Enrollment: 1306 patients	Regorafenib	None	Patients with unresectable, metastatic or recurrent colorectal cancer	Primary Outcome Measures Number of patients with adverse drug reactions ADRs and SAEs Secondary Outcome Measures: Determination of patient's background to affect the safety and efficacy of Regorafenib using standard observational survey and follow-up survey
NCT01853319 On-going not recruiting	Actual Study Start Date: 24/07/2013 Estimated Study Completion Date: 29/09/2017	Interventional; An Open-label Phase III Study	Enrollment 100 patients	Regorafenib	None	In patients with mCRC who have progressed after all approved standard therapy.	Outcome Measures: safety, PFS,

Study Identifier	Time	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
	Primary Completion Date: 24/04/2015						
NCT01774344 On-going not recruiting	Actual Study Start Date: 14/05/2013 Estimated Study Completion 28/02/2018 Primary Completion Date: 29/02/2016	Interventional; Randomized, Double-blind, Placebo Controlled, Multicenter Phase III Study	Enrollment: 573 patients	Regorafenib	Placebo	Patients with advanced liver cancer who have progressed on sorafenib treatment.	Primary Outcome Measures: OS Secondary Outcome Measures: TTP, PFS, ORR, DCR
NCT01271712 On-going not recruiting	Study Start Date: January 2011 Estimated Study Completion Date: December 2017 Primary Completion Date: January 2012	Interventional; Randomized, double-blind, placebo-controlled phase III study	Enrollment: 199 patients	Regorafenib + BSC	Placebo + BSC	Patients with metastatic and/or unresectable GIST whose disease has progressed despite prior treatment with at least imatinib and sunitinib.	Primary Outcome Measures:PFS Secondary Outcome Measures: OS, TTP, Tumour response, ORR, DCR, DOR

Study Identifier	Time	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02465502 On-going not recruiting	Actual Study Start Date: 21/07/2015 Estimated Study Completion Date: 31/07/2017 Primary Completion Date: 02/05/2017	Interventional; Uncontrolled, Open-label Phase IIb	Enrollment: 59 patients	Regorafenib	None	Patients With Antiangiogenic-naive and Chemotherapy-refractory Advanced Colorectal Cancer	Primary Outcome Measures: Percentage of participants without disease progression or death at the end of 8 weeks Secondary Outcome Measures: PFS, OS, ORR, DCR , safety
NCT00664326 On-going not recruiting	Actual Study Start Date: 30/04/2008 Estimated Study Completion Date: 18/01/2019 Primary Completion Date: 31/05/2009	Interventional; Uncontrolled, open-label, non-randomized Phase II study	Enrollment: 49 patients	Regorafenib	None	Previously Untreated Patients With Metastatic or Unresectable RCC	Primary Outcome Measures: ORR Secondary Outcome Measures: DCR , OS, PFS, TTP, DOR, Duration of Stable Disease .
NCT02085148 On-going not recruiting	Actual Study Start Date: 11/04/2014	Interventional; Multi-center, Open-label, Non-randomized, Phase I	Estimated Enrollment: 77 patients	regorafenib administered orally in combination with backbone chemotherapy (vincristine and irinotecan)	None	Pediatric Patients With Solid Malignant Tumors That Are Recurrent or Refractory to Standard Therapy.	Primary Outcome Measures: safety Secondary Outcome Measures: OS, TTP, ORR, PK

Study Identifier	Time	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
	Estimated Study Completion Date: 24/10/2019 Estimated Primary Completion Date: 24/10/2019	Dose Escalation Study					
NCT02106845 On-going not recruiting	Actual Study Start Date: 22/04/2014 Estimated Study Completion Date: 31/12/2017 Primary Completion Date: 27/04/2015	Interventional Phase I, Multi-center, Non-randomized, Open Label, Drug-drug-interaction Study	Enrollment: 42 patients	Multiple Doses of regorafenib on the Pharmacokinetics of Probe Substrates of Transport Proteins P-gp (Digoxin; Group A) and BCRP (Rosuvastatin; Group B)	None	Patients With Advanced Solid Malignant Tumors	Primary Outcome Measures: PK Secondary Outcome Measures: Tumor Response, safety
NCT01973868 On-going not recruiting	Actual Study Start Date: 21/11/2013 Estimated Study Completion Date: 26/10/2017	Interventional Phase 1b, Multi-center, Non-randomized, Open Label, Dose Escalation	Enrollment: 44 patients	Initial i.v. infusion of cetuximab (loading dose of 400 mg/ m2 BSA) on Pre-cycle Day -7. The treatment of regorafenib in combination with cetuximab maintenance	None	In Patients With Locally Advanced or Metastatic Solid Tumors Who Are Not Candidates for Standard Therapy or in Whom Regorafenib or Cetuximab is Considered as a Standard Treatment	Primary Outcome Measures: Maximum tolerated dose, safety, PK Secondary Outcome Measures: Tumor response

Study Identifier	Time	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
	Estimated Primary Completion Date: 10/08/2017			dose (250 mg/m2 BSA) starts on Cycle 1 Day 1. Cetuximab infusions will be given in a once-weekly dosing-regimen as approved.			
NCT01287598 On-going not recruiting	Actual Study Start Date: 02/08/2011 Estimated Study Completion Date: 29/01/2018 Estimated Primary Completion Date: 31/12/2017	Interventional Phase I, Non-randomized Open-label Study	Enrollment: 40 patients	Experimental Arm 1: regorafenib + warfarin + omeprazole + midazolam Experimental Arm 2: regorafenib + rosiglitazone	None	Patients With Advanced Solid Tumors	Primary Outcome Measures: PK Secondary Outcome Measures: Tumor Response evaluation, safety

Abbreviations: DFS = disease free survival; PFS= progression free survival, OS = overall survival; TTF= time to treatment failure; TEAE= treatment emergent adverse event, DCR= disease control rate; HRQoL= Health related quality of life; ADR= adverse drug reaction; SAE= serious adverse event; AE= adverse event; ORR= objective tumour rate; DCR= disease control rate; DOR= duration of response; mCRC= metastatic colorectal cancer; RCC= renal cell cancer; GIST= gastrointestinal stromal cancer, BSC= best supportive care**.**

Sources:ClinicalTrial.gov

Risk of bias tables

Table A8: Risk of bias – study level (RCTs)

Trial	Random sequence generation	Allocation concealment	Blinding of			Selective outcome reporting	Incomplete outcome data (short-term, long-term)
			Participants	Medicinal personnel	Outcome assessment (patient-reported outcomes, all-		
RESORCE	Low	Low	Unclear[a]	Unclear[a]	Unclear[a]	Low	Low
comments: [a] Given the safety profile of regorafenib with evocative adverse-events (Hand-foot skin reaction, diarrhea, decreased appetite and hypertension notably) blinding could have been broken.							

Abbreviations:

Sources: Clinical study report

Table A9: Risk of bias – outcome level (RCTs)

Outcome Trial	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting	No other aspects according to risk of bias	Overall judgment Risk of bias – outcome level
Overall survival					
RESORCE	Low	Low	Low	Low	Low
Progression free survival					
RESORCE	High[a b]	Low	Low	Low	High
EQ-5D index & VAS					
RESORCE	Unclear[a]	High[c]	Low	Low	High
FACT-hep					
RESORCE	Unclear[a]	High[c]	Low	Low	High
comments: [a] Given the safety profile of regorafenib with evocative adverse-events (Hand-foot skin reaction, diarrhea, decreased appetite and hypertension notably) blinding could have been broken. [b] PFS was assessed by the investigators (absence of independent review committee). [c] substantial number of missing data (about 50% of the patients were evaluated at the end of treatment visit)					

Abbreviations: PFS- progression free survival

Sources: Clinical study report

Applicability tables

Table A10: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The population of the RESORCE trial was highly selected. The inclusion was restricted to those who tolerated sorafenib treatment defined as not less than 20 days at a minimum daily dose of 400 mg QD within the last 28 days prior to withdrawal and to those with a well-preserved general state and liver fonction (ECOG 0-1; Child-Pugh A). Hence, the population included in the RESORCE trial represents only a subgroup of the scoped population. Overall, given the highly selected population of the RESORCE trial, external validity of the trial is limited.
Intervention	The mode of administration, dosing and frequency of cycles used for regorafenib is consistent with the upcoming approved licence. Patients received study treatment until disease progression, unacceptable toxicity, or withdrawal of consent. This is in line with treatment recommendations. All patients received supportive care if indicated as it is done in clinical practice.
Comparators	Currently, no active drug is recommended and/or used in clinical practice for the treatment of patients with HCC who have been previously treated with sorafenib, and patients are commonly treated with BSC. BSC in cancer may include assessment and treatment of physical, psychological, social, and spiritual dimensions of suffering. The appropriateness of BSC as comparator is further supported by clinical practice guide-lines from various scientific organizations (EASL-EORTC (24), ESMO-ESDO (25), NCCN (26), and LAASL (27). No issue regarding intervention applicability was identified
Outcomes	There is evidence regarding OS and clinical benefits that support OS have been demonstrated. Clear limitation related to applicability of the results in terms of outcomes is the lack of interpretable HRQoL data. Given the highly selected population of the RESORCE trial, there is an indirectness issue.
Setting	The RESORCE trial is a multicentre study with approximately 38% of the subjects from Asia and approximately 62% of subjects from the ROW. No issue regarding setting applicability was identified.

Abbreviations: ROW=rest of the world.

Sources: Clinical study report and MAH submission file.

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Table A11: Regulatory status

Country	Institution issuing approval (EMA, FDA, TGA, etc.)	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Date of approval	Type of approval (full, conditional, exceptional)	Launched yes/no If no include date of launch	Marketing authorisation number (if available)
Regorafenib							
EU central procedure	EMA	Yes	STIVARGA® is indicated as monotherapy in adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.	August 2, 2017	Full, indication extension	September 2017	EU/1/13/858
USA	FDA	Yes	STIVARGA® is indicated in patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.	April 27, 2017	Full, indication extension	April 27, 2017	NDA 203085
Ecuador	Ecuador drug regulator agency	Yes	STIVARGA® is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with one systemic therapy.	April 24, 2017	Full	July, 2017	
Japan	PMDA	Yes	STIVARGA® is indicated in unresectable hepatocellular carcinoma progressed after treatment with cancer chemotherapy.	June 26, 2017	Full	June 26, 2017	
Korea	MFDS	Yes	STIVARGA® is indicated in patients in hepatocellular	July 12, 2017	Full	July 12, 2017	

Country	Institution issuing approval (EMA, FDA, TGA, etc.)	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Date of approval	Type of approval (full, conditional, exceptional)	Launched yes/no If no include date of launch	Marketing authorisation number (if available)
			carcinoma (HCC) who have been previously treated with sorafenib				
Switzerland	Swissmedic	No	/	/	/	/	/
Comparator technology: there is no active comparator							
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Abbreviations: EMA=European Medicines Agency; FDA=Food and Drug Administration; MFDS=Ministry Of Food and Drug Safety; PMDA=Pharmaceuticals and Medical Devices Agency.

Sources: Manufacturer's submission file and public information for regulatory agencies.

Table A12: Summary of (reimbursement) recommendations in European countries for the technology

Country and issuing organisation e.g., G-BA, NICE	Reimbursement status (Y, N, Ongoing)	Summary of (reimbursement) recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions
Technology			
Austria	Y	Positive for both mCRC and GIST indication	
Belgium	Y	Positive for both mCRC and GIST indication	
Bulgaria	Ongoing	Ongoing for both mCRC and GIST indication	
Croatia	N	Negative for both mCRC and GIST indication	
Cyprus	Y	Positive for both mCRC and GIST indication	
Czech Republic	Y, N	Postive for mCRC and negative for GIST indication	
Denmark	Y	Positive for both mCRC and GIST indication	
Estonia	N	Negative for both mCRC and GIST indication	
Finland	Y	Positive for both mCRC and GIST indication	
France	Y	Positive for both mCRC and GIST indication	Recommendation for reimbursement in mCRC is limited to patients with ECOG 0-1
Germany	N	Negative for both mCRC and GIST indication	
Greece	Y	Positive for both mCRC and GIST indication	
Hungary	Ongoing	Ongoing for both mCRC and GIST indication	
Ireland	Y	Positive for both mCRC and GIST indication	
Italy	Y	Positive for both mCRC and GIST indication	
Latvia	N	Negative for both mCRC and GIST indication	
Lithuania	N	Negative for both mCRC and GIST indication	
Luxembourg	Y	Positive for both mCRC and GIST indication	
Malta	N	Negative for both mCRC and GIST indication	
Netherlands	Y	Positive for both mCRC and GIST indication	
Norway	Ongoing	Ongoing for both mCRC and GIST indication	

Country and issuing organisation e.g., G-BA, NICE	Reimbursement status (Y, N, Ongoing)	Summary of (reimbursement) recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions
Poland	N	Negative for both mCRC and GIST indication	
Portugal	N, Ongoing	Negative for mCRC and ongoing for GIST indication	
Romania	N	Negative for both mCRC and GIST indication	
Slovakia	N	Negative for both mCRC and GIST indication	
Slovenia	N	Negative for both mCRC and GIST indication	
Spain	Y	Positive for both mCRC and GIST indication	
Sweden	Y	Positive for both mCRC and GIST indication	
Switzerland	Y	Positive for both mCRC and GIST indication	
United Kingdom	N, Y	Negative for mCRC and positive for GIST indication	
Comparator: there is no active comparator - not applicable			
For countries with indication specific reimbursement include only the recommendations for the indication under assessment. **Include a reference to any publically available guidance document**			

Abbreviations: GIST=gastrointestinal stromal tumours; mCRC=metastatic colorectal cancer; N=no; Y=yes.

Source: Manufacturer's submission file.

Table: Benefit assessment based on original ESMO-MCBS and adapted benefit assessment based on adapted ESMO-MCBS

ESMO-MCBS	Active substance	Indication	Intention	PE	Form	MG standard treatment	Efficacy				Safety		AJ	FM
							MG months	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
Adapted ESMO-MCBS	Regorafenib	HCC	NC	OS	2a	≤12 months	+2.8	0.63 0.5-0.79	HR ≤0.65 AND Gain ≥2.0 <3 months	3	+34.3% grade 3–4 AEs[1], +6% DR	no difference	-1	**2**
Original ESMO-MCBS	Regorafenib	HCC	NC	OS	2a	≤12 months	+2.8	0.63 0.5-0.79	HR ≤0.65 AND Gain ≥2.0 <3 months	3	x	no difference	x	**3**

Abbreviations: AEs = adverse events, AJ = Adjustments, CI = confidence interval, DR = discontinued due to adverse events, FM = final adjusted magnitude of clinical benefit grade, HCC = hepatocellular carcinoma, HR = hazard ratio, MG = median gain, NC = non-curative, OS = overall survival, PE = primary endpoint, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life

DISCLAIMER

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: by the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulting from the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI). Hence, we decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut-off values and outcomes that lead to an up- or downgrading seem to be arbitrary. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

[1] downgrade due to a difference of at least 10% in grade ≥3 AEs (+34.3)