# Horizon Scanning in Oncology

## Regorafenib (Stivarga®) for heavily pretreated patients with metastatic colorectal cancer

Ludwig Boltzmann Institut
Health Technology Assessment

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# 1 Drug description

### Generic/Brand name/ATC code:

Regorafenib/Stivarga®/L01XE21

### Developer/Company:

Bayer Pharma AG

### Description:

regorafenib inhibits tumor angiogenesis and tumor cell proliferation

Regorafenib (Stivarga®) is a multi-kinase inhibitor that targets angiogenic, stromal and oncogenic receptor tyrosine kinases [1]. It binds to vascular endothelial growth factor receptors (VEGFRs) 2 and 3, which are important for tumor angiogenesis, and to receptor tyrosine kinases RET, KIT, PDGFR and RAF, which are involved in tumor cell signaling. Regorafenib thus inhibits tumor angiogenesis and tumor cell proliferation [2].

oral administration

Regorafenib is administered at a dosage of 160 mg (four 40 mg tablets), once daily for the first 21 days of each 28-day cycle. The drug has to be taken orally, due to effects on pharmacokinetics, with a low-fat breakfast. The treatment should be continued until disease progression or unacceptable toxicity occurs [3].

# 2 Indication

for heavily pretreated patients with mCRC

Regorafenib (Stivarga®) is indicated in patients with metastatic colorectal cancer (mCRC) who have been previously treated with:

- a fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy
- an anti-VEGF therapy
- an anti-EGFR therapy (if KRAS wild-type) [3].

# 3 Current regulatory status

approved by the EMA and the FDA

In August 2013, the EMA granted marketing authorization for Stivarga® for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies (including fluoropyrimidine-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy) [4].

The FDA approved regorafenib (Stivarga®) on September 27, 2012 [5] for patients with mCRC who have been pretreated with:

- A fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy
- an anti-VEGF therapy
- an anti-EGFR therapy (if KRAS wild-type).

In February 2013, the FDA approved regorafenib (Stivarga®) for the treatment of patients with advanced gastrointestinal stromal tumors (GIST) that cannot be surgically removed and no longer respond to other FDA-approved treatments for this disease [6].

In Switzerland, Stivarga® has been approved for the treatment of patients with mCRC who were previously treated with a fluoropyrimidine-, oxaliplatin- and irinotecan-based therapy, anti-VEGF therapy and anti-EGFR (in case of KRAS wild-type) on February 27, 2013 [7]. In Japan, marketing authorization for Stivarga® for the treatment of unresectable advanced or recurrent colorectal cancer was granted on March 25, 2013 [8].

# 4 Burden of disease

Colorectal cancer (CRC) develops in the tissues of the colon and/or rectum. It is the third most common cancer in men and women in the western countries.

incidence rate in Austria 28.1 per 100,000 people per year

Due to early detection and treatment, incidence rates are declining [9]. In Austria, CRC is the third most common malignancy diagnosed in men and the second most common malignancy diagnosed in women. In 2010, the incidence rate in Austria for both men and women was 28.1 (per 100,000 people per year), mortality rate was 11.9 (per 100,000 people per year) [10].

median age at diagnosis: 69 years

Median age at diagnosis for CRC is about 69 years [11]; the 1-year relative survival rate for persons with CRC is 84% and the 5-year relative survival rate is 64% (relative survival compares survival among cancer patients to that of people not diagnosed with cancer who are of the same age, race and sex) [9].

Histologically, more than 95% of CRCs are adenocarcinomas. Less common types are carcinoid tumors, gastrointestinal stromal tumors, lymphomas or sarcomas [12].

Risk factors for CRC are increasing age, a personal or family history of CRC and/or polyps, a personal history of chronic inflammatory bowel disease as well as hereditary conditions (for example Lynch syndrome and familial adenomatous polyposis). Moreover, type 2 diabetes, obesity, physical inactivity, a diet high in red or processed meat, alcohol consumption, long-term smoking and possibly very low intake of fruit and vegetables are associated with an increased risk for CRC. There are factors that appear to decrease the risk, such as the consumption of milk and calcium or higher blood levels of vitamin D [9].

approximately 20% of patients have metastases at the time of diagnosis

Common symptoms of CRC are bloody or tarry stool, abdominal pain, otherwise unexplained iron deficiency anemia and/or changes in bowel habits. Less common symptoms are abdominal distension, and/or nausea and vomiting. Straining to defecate, rectal pain or small-caliber stools indicate that the tumor is located in the rectum. CRC is a potentially metastatic disease; the most frequently affected sites are the regional lymph nodes, the liver, the lungs and the peritoneum. Approximately 20% of patients have metastases at the time of diagnosis. The preferred staging system for CRC is the TNM classification: primary tumor (T), regional lymph node (N), distant metastasis (M) [13].

# 5 Current treatment

A large number of treatment options are available for CRC. Selection of therapy depends on the site and extent of metastatic disease, performance status, organ function and comorbidity of the patient [14].

**options for first-line therapy**

If patients qualify for intensive therapy, options for the treatment of advanced or metastatic disease are the following [15]:

- FOLFOX (fluorouracil, leucovorin, oxaliplatin) ± bevacizumab
- CapeOX (capecitabine, oxaliplatin) ± bevacizumab
- FOLFOX ± panitumumab (KRAS wild-type gene only)
- FOLFIRI (fluorouracil, leucovorin, irinotecan) + bevacizumab
- FOLFIRI ± cetuximab or panitumumab (KRAS wild-type gene only)
- 5-FU/leucovorin or capecitabine ± bevacizumab
- FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan)

**options after first progression**

In case of disease progression after these first-line therapies, treatment options will be selected according to the first-line regimen and include:

- FOLFIRI ± bevacizumab
- FOLFIRI ± ziv-aflibercept
- Irinotecan ± bevacizumab
- Irinotecan ± ziv-aflibercept
- FOLFIRI ± cetuximab or panitumumab (KRAS wild-type gene only)
- Cetuximab or panitumumab (KRAS wild-type gene only) + irinotecan
- FOLFOX ± bevacizumab
- CapeOX ± bevacizumab

**for further lines of therapy**

Therapy after second progression will again depend on previously used regimens and include:

- Cetuximab or panitumumab + irinotecan
- FOLFOX or CapeOX
- Regorafenib
- Clinical trial
- Best supportive care (BSC)

**very few options for heavily pre-treated patients**

For later lines of therapy, the remaining treatment options are limited:

- Clinical trial
- BSC [15].

# 6 Evidence

A literature search was conducted on the 13th of June 2013 in four databases (Medline, Embase, CRD, and The Cochrane Library). Search terms were "Colorectal Neoplasms/Cancer", "(Neoplasm) Metastasis", "Regorafenib", "Stivarga" and "bay 73".

**one phase III study and one meta-analysis included**

Also, the manufacturer was contacted for any further evidence, and submitted 24 studies. Of these, 16 had already been identified by the systematic literature search, resulting in 8 additional references.

Overall, 87 references were identified of which two have been included in this report:

- a phase III study, assessing the effect of regorafenib on patients with mCRC that keeps progressing after administration of all approved standard therapies (CORRECT trial) [16] and
- a meta-analysis, evaluating the risk of hand-foot skin reactions in patients treated with regorafenib [17].

## 6.1 Efficacy and safety – phase III studies

*Table 1: Summary of efficacy*

| | | | |
|---|---|---|---|
| **Study title**<br>Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial [16]. | | | |
| **Study identifier** | NCT01103323, EudraCTNumber: 2009-012787-14, CORRECT trial | | |
| **Design** | International, multicenter, randomized (2:1 ratio), placebo-controlled | | |
| | Duration | *Enrolment:* 2010-04-30 to 2011-03-22<br>*Median follow-up:* NA<br>*Cut-off dates for second interim analyses:* 2011-07-21 | |
| **Hypothesis** | Superiority<br>(90% power to detect a 33.3% increase in median OS, assuming a 4.5 month median OS for the placebo group (i.e. HR of 0.75 for regorafenib over placebo)) | | |
| **Funding** | Bayer HealthCare Pharmaceuticals | | |
| **Treatment groups** | Intervention (N=505) | Regorafenib 160 mg (oral) once daily for the first 3 weeks of each 4-week cycle + BSC (excluding other investigational antitumor agents or neoplastic chemotherapy, hormonal therapy, and immunotherapy) | |
| | Control (N=255) | Placebo once daily for the first 3 weeks of each 4-week cycle + BSC (excluding other investigational antitumor agents or neoplastic chemotherapy, hormonal therapy, and immunotherapy) | |
| **Endpoints and definitions** | Overall survival (primary outcome) | OS | Time from randomization to death from any cause |
| | Progression-free survival | PFS | Time from randomization to first radiological or clinical observation of disease progression or death from any cause |
| | Objective tumor response rate | ORR | Proportion of patients with complete or partial response |

| | | | |
|---|---|---|---|
| **Endpoints and definitions** | Disease control rate | DCR | Proportion of patients with a best response of complete or partial response or stable disease; assessment of stable disease had to be made at least 6 weeks after randomization |
| | Safety | - | - |
| | Duration of response and stable disease | DOR | NA |
| | Health-related quality-of-life and health utility values | Hr-QoL | Measured with:<br>• EORTC general health status and QLQ-C30<br>• EQ-5D<br>• EQ-5D VAS |
| **Results and analysis** | | | |
| **Analysis description** | Intention-to-treat analysis<br>OS and PFS: compared between treatment groups with stratified log-rank test<br>HRs (with 95% CI) were calculated with Cox model (adjusting for stratification factors); Kaplan-Meier survival estimates were calculated for each treatment group<br>Objective response and disease control rates were compared between treatment groups with Cochran-Mantel-Haenszel test (adjusting for stratification factors) | | |
| **Analysis population** | Inclusion | • Histological or cytological documentation of adenocarcinoma of the colon or rectum<br>• Prior locally and currently approved standard therapies including fluoropyrimidine, oxaliplatin, irinotecan, beva-cizumab and cetuximab or panitumumab (if KRAS wild-type)<br>• Disease progression during or within 3 months following the last administration of approved standard therapy or discontinuation of standard therapy because of unacceptable toxic effects<br>• Measurable or non-measurable disease according to Response Evaluation Criteria in Solid Tumors criteria, Version 1.1<br>• ECOG performance status of ≤1<br>• Life expectancy of at least 3 months<br>• Adequate bone-marrow, liver and renal function at the start of the trial | |
| | Exclusion | • Prior treatment with regorafenib<br>• Previous assignment to treatment during this study<br>• Previous or concurrent cancer that is distinct in primary site or histology from CRC within 5 years before randomization except for curatively treated cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumors<br>• Major surgical procedures, open biopsy or significant traumatic injury within 28 days before start of study medication | |
| | Characteristics | | Intervention / Control |
| | | Median age/IQR, years | 61/54-67 / 61/54-68 |
| | | Sex, %<br>male/female | 62/38 / 60/40 |
| | | ECOG performance Status, %<br>0/1 | 52/48 / 57/43 |
| | | Primary site of disease<br>Colon/rectum/colon and rectum, % | 64/30/6 / 68/27/5 |

| | | | | |
|---|---|---|---|---|
| **Analysis population** | Characteristics | KRAS mutation, % no/yes/unknown | 41/54/5 | 37/62/2 |
| | | BRAF mutation, % no/yes | 96/4 | 98/2 |
| | | Adenocarcinoma, % | 98 | 96 |
| | | Number of previous systemic anticancer therapies, % 1-2/3/≥4 | 27/25/49 | 25/28/47 |
| | | Previous Bevacizumab, % | 100 | 100 |
| | | Time from diagnosis of metastasis (median, months)/IQR | 31/21-43 | 30/20-46 |

| | | | |
|---|---|---|---|
| **Descriptive statistics and estimated variability** | Treatment group | Intervention (Regorafenib + BSC) | Control (Placebo + BSC) |
| | Number of subjects | N = 505 | N = 255 |
| | OS<br>median, months<br>IQR | 6.4<br>3.6-11.8 | 5.0<br>2.8-10.4 |
| | OS rate, %<br>at 3/6/9/12 months | 80.3/52.5/38.2/24.3 | 72.7/43.5/30.8/24.0 |
| | PFS<br>median, months<br>IQR | 1.9<br>1.6-3.9 | 1.7<br>1.4-1.9 |
| | Objective response rate, % | 1.0 | 0.4 |
| | Duration of stable disease<br>median, months<br>IQR | 2.0<br>1.7 - 4.0 | 1.7<br>1.4 - 1.9 |
| | Disease control rate, % | 41 | 15 |
| | EORTC QLQ-C30, score<br>at baseline<br>at end of treatment | 62.6<br>48.9 | 64.7<br>51.9 |
| | EQ-5D, score<br>at baseline<br>at end of treatment | 0.73<br>0.59 | 0.74<br>0.59 |
| | EQ-5D, VAS score<br>at baseline<br>at end of treatment | 65.4<br>55.5 | 65.8<br>57.3 |

| | | | |
|---|---|---|---|
| **Effect estimate per comparison** | *Comparison groups* | | *Intervention vs Control* |
| | OS | HR | 0.77 |
| | | 95% CI | 0.64-0.94 |
| | | P value | 0.0052 |
| | OS in subgroup colon cancer | HR | 0.70 |
| | | 95% CI | 0.56-0.89 |
| | | P value | NR |
| | OS in subgroup rectal cancer | HR | 0.95 |
| | | 95% CI | 0.63-1.43 |
| | | P value | NR |
| | PFS | HR | 0.49 |
| | | 95% CI | 0.42-0.58 |
| | | P value | <0.0001 |
| | PFS in subgroup colon cancer | HR | 0.55 |
| | | 95% CI | 0.45-0.67 |
| | | P value | NR |
| | PFS in subgroup rectal cancer | HR | 0.45 |
| | | 95% CI | 0.33-0.62 |
| | | P value | NR |
| | ORR | HR | NR |
| | | 95% CI | NR |
| | | P value | 0.19 |
| | DCR | HR | NR |
| | | 95% CI | NR |
| | | P value | P<0.0001 |

*Abbreviations: BRAF = B-type Raf kinase, BSC = best supportive care, CI = confidence interval, CRC = colorectal cancer, ECOG = Eastern Cooperative Oncology Group, EORTC = European Organisation for Research and Treatment of Cancer, EQ-5D = EuroQol five dimension, HR = hazard ratio, IQR = interquartile range, KRAS = Kirsten rat sarcoma, NA = not available, NCT = National Clinical Trial, NR = not reported, OS = overall survival, ORR = overall response rate, PFS = progression-free survival, QLQ-C30 = quality-of-life questionnaire, VAS= visual analogue scale*

*Table 2: Most frequent adverse events (occurring in ≥5% of patients in either group from start of treatment to 30 days after end of treatment, safety population)*

| NCT01103323 | | | | | | |
|---|---|---|---|---|---|---|
| **Adverse Event** (according to NCI-CTCAE version 3.0) | **Regorafenib + BSC (N=500)** | | | **Placebo + BSC (N=253)** | | |
| | Any grade n (%) | Grade 3 n (%) | Grade 4 n (%) | Any Grade n (%) | Grade 3 n (%) | Grade 4 n (%) |
| Any event | 465 (93) | 253 (51) | 17 (3) | 154 (61) | 31 (12) | 4 (2) |
| Fatigue | 237 (47) | 46 (9) | 2 (<1) | 71 (28) | 12 (5) | 1 (<1) |
| Hand-foot skin reaction | 233 (47) | 83 (17) | 0 | 19 (8) | 1 (<1) | 0 |
| Diarrhea | 169 (34) | 35 (7) | 1 (<1) | 21 (8) | 2 (1) | 0 |
| Anorexia | 152 (30) | 16 (3) | 0 | 39 (15) | 7 (3) | 0 |
| Voice changes | 147 (29) | 1 (<1) | 0 | 14 (6) | 0 | 0 |
| Hypertension | 139 (28) | 36 (7) | 0 | 15 (6) | 2 (1) | 0 |
| Oral mucositis | 136 (27) | 15 (3) | 0 | 9 (4) | 0 | 0 |
| Rash or desquamation | 130 (26) | 29 (6) | 0 | 10 (4) | 0 | 0 |
| Nausea | 72 (14) | 2 (<1) | 0 | 28 (11) | 0 | 0 |
| Weight loss | 69 (14) | 0 | 0 | 6 (2) | 0 | 0 |
| Fever | 52 (10) | 4 (1) | 0 | 7 (3) | 0 | 0 |
| Constipation | 42 (8) | 0 | 0 | 12 (5) | 0 | 0 |
| Dry skin | 39 (8) | 0 | 0 | 7 (3) | 0 | 0 |
| Alopecia | 36 (7) | 0 | 0 | 1 (<1) | 0 | 0 |
| Taste alteration | 35 (7) | 0 | 0 | 5 (2) | 0 | 0 |
| Vomiting | 38 (8) | 3 (1) | 0 | 13 (5) | 0 | 0 |
| Sensory neuropathy | 34 (7) | 2 (<1) | 0 | 9 (4) | 0 | 0 |
| Nose bleed | 36 (7) | 0 | 0 | 5 (2) | 0 | 0 |
| Dyspnea | 28 (6) | 1 (<1) | 0 | 4 (2) | 0 | 0 |
| Muscle pain | 28 (6) | 2 (<1) | 0 | 7 (3) | 1 (<1) | 0 |
| Headache | 26 (5) | 3 (1) | 0 | 8 (3) | 0 | 0 |
| Pain, abdomen | 25 (5) | 1 (<1) | 0 | 10 (4) | 0 | 0 |
| Thrombocytopenia | 63 (13) | 13 (3) | 1 (<1) | 5 (2) | 1 (<1) | 0 |
| Hyperbilirubinemia | 45 (9) | 10 (2) | 0 | 4 (2) | 2 (1) | 0 |
| Proteinuria | 35 (7) | 7 (1) | 0 | 4 (2) | 1 (<1) | 0 |
| Anemia | 33 (7) | 12 (2) | 2 (<1) | 6 (2) | 0 | 0 |
| Hypophosphatemia | 25 (5) | 19 (4) | 0 | 1 (<1) | 1 (<1) | 0 |

*Abbreviations: NCI= National Cancer Institute, CTCAE= Common Terminology Criteria for Adverse Events*

**efficacy and safety of regorafenib were evaluated in 760 heavily pretreated patients**

The aim of the CORRECT trial, an international, multicenter, placebo-controlled phase III trial, was to assess the efficacy and safety of regorafenib in patients with mCRC that progressed after administration of approved standard therapies. A total of 760 patients were randomized to receive either regorafenib (N=505) plus BSC or placebo (N=255) plus BSC. Regorafenib was administered orally at a daily dosage of 160 mg for the first three weeks of each 4-week cycle; mean duration of treatment was 2.8 months for the regorafenib group and 1.8 months for the placebo group.

Patients in both groups had a median age of 61 years and ECOG performance status ≤1 was an inclusion criterion. Enrolled patients were heavily pretreated with a median number of 3 prior lines of therapy. 25% of patients (regorafenib group) and 28% of patients (placebo group) had 3, 49% of patients in the regorafenib group and 47% of patients in the placebo group received ≥4 previous systemic anticancer therapies and all patients had had previous anti-VEGF treatment with bevacizumab. In the placebo group, more patients progressed on previous treatment with bevacizumab, irinotecan and oxaliplatin than in the regorafenib group. There was a lower proportion of patients with a KRAS mutation in the regorafenib group: 54% of patients assigned to regorafenib and 62% assigned to placebo. 4% of regorafenib group patients and 2% of placebo group patients showed BRAF mutations. Histologically, 98% (regorafenib group) and 96% (placebo group) of patients had adenocarcinomas. The primary endpoint of this trial was OS; secondary endpoints were PFS, objective tumor response rate, disease control rate and safety. Duration of response and stable disease, health-related quality-of-life and health utility values were determined as tertiary endpoints. During the study, plasma and tissue samples were collected for biomarker analysis within a substudy.

**median age of 61 years and ECOG performance status ≤1**

**49% (regorafenib group) and 47% (placebo group) of patients received ≥4 previous systemic anticancer therapies**

Median OS was 6.4 months in the regorafenib group compared to 5.0 months in the placebo group (HR=0.77, 95% CI 0.64-0.94, p=0.0052). Median PFS was 1.9 months in the regorafenib arm and 1.7 months in the placebo arm (HR=0.49, 95% CI 0.42-0.58, p<0.0001). The OS rate after 3 months of regorafenib treatment was 80.3% compared to 72.7% in placebo group patients. After 6 months, the OS rate was 52.5% in the regorafenib group and 43.5% in the placebo group. After 9 months, the rates were 38.2% in the regorafenib arm and 30.8% in the placebo arm. After 12 months of treatment, the OS rate in both groups was much the same (24.3% in the regorafenib group, 24.0% in the placebo group).

**median OS was extended by 1.4 months in the regorafenib group**

Subgroup analysis according to site of disease showed better results for regorafenib on OS in patients with colon cancer (HR=0.70, 95%CI 0.56-0.89) than in those with rectal cancer (HR=0.95, 95% CI 0.63-1.44). However, regorafenib had almost the same effect on PFS in patients with colon cancer (HR=0.55, 95% CI 0.45-0.67) as in patients with rectal cancer (HR=0.45, 95% CI 0.33-0.62).

Objective response rates were 1.0% for the regorafenib group and 0.4% for the placebo group, no patients achieved complete response. 41% of patients of the regorafenib arm and 15% of placebo arm patients achieved disease control. The median duration of stable disease was 2.0 months in patients assigned to regorafenib and 1.7 months in patients assigned to placebo.

**ORR was 1.0% in the regorafenib group**

Overall, treatment-related adverse events occurred in 93% (regorafenib group) and 61% (placebo group) of patients, mostly during treatment cycles 1-2. Grade 3 or 4 treatment-related adverse events were reported in 54% (regorafenib group) and 14% (placebo group). Within the regorafenib group, the most frequent adverse events of any grade were fatigue and hand-foot skin reaction, the most frequent adverse events of grade 3 or higher were hand-foot skin reaction, fatigue, diarrhea, hypertension and rash or desquamation. Within the placebo group, the most frequent adverse events of any grade were fatigue and anorexia. Serious adverse events occurred in 44% of patients in the regorafenib arm and in 40% of patients in the placebo arm.

**higher rate of treatment-related adverse events of 93% in regorafenib group vs. 61% in placebo group**

During the study, a total of 110 deaths were reported (14% in the regorafenib group, 16% in the placebo group), most of them caused by progression

of underlying disease (12% in regorafenib group, 14% in placebo group). 8 (2%) cases of death in the regorafenib group were attributed to adverse events: pneumonia, gastrointestinal bleeding, intestinal obstruction, pulmonary hemorrhage, seizure and sudden death. In the placebo group, 3 (1%) patients died of pneumonia and sudden death. Liver function tests showed a higher incidence of increased liver transaminases and bilirubin in the regorafenib group; one case compatible with drug-induced liver injury due to regorafenib was reported.

Adverse events were the most common cause leading to dose modification (= dose reduction or dose interruption) in 76% (regorafenib group) and 38% (placebo group) of patients. Most frequently, dermatological, gastrointestinal, constitutional, metabolic or laboratory events were causes for dose modification.

**health-related quality-of-life and health utility values**

Health-related quality-of-life and health utility values were evaluated by:

- European Organisation for Research and Treatment of Cancer (EORTC) general health status and quality-of-life questionnaire QLQ-C30 (possible score: 0-100, higher scores represent better health-related quality of life). At baseline, mean EORTC QLQ-C30 scores were 62.6 in the regorafenib group and 64.7 in the placebo group. At the end of the treatment, mean scores were 48.9 in the regorafenib group and 51.9 in the placebo group.
- EQ-5D (EuroQol five dimension) index questionnaire, where higher scores represent better health status. Analysis at baseline showed mean EQ-5D index scores of 0.73 (regorafenib group) and 0.74 (placebo group) versus 0.59 in both groups at the end of the treatment.
- EQ-5D visual analogue scale evaluation showed scores of 65.4 (regorafenib group) and 65.8 (placebo group) at baseline and 55.5 (regorafenib group) versus 57.3 (placebo group) at the end of the treatment.

## 6.2 Safety – further studies

**meta-analysis evaluated overall incidence of HFSR**

This meta-analysis evaluated the overall incidence and the risk of developing hand-foot skin reaction (HFSR) in patients treated with regorafenib [17]. A systematic literature search was conducted and three phase II and two phase III trials (both placebo-controlled) were included in the analysis; data of 1,078 patients having received regorafenib for the treatment of hepatocellular carcinoma, GIST, renal-cell carcinoma and CRC were analyzed. 750 of 1,078 patients received regorafenib as a single agent. In four of five included trials, patients had been pretreated with one or more drugs that could induce HFSR, of which were listed imatinib, sunitinib, bevacizumab, sorafenib and fluoropyrimidines.

**highest incidence in patients with renal cell carcinoma, lowest incidence in patients with mCRC**

The overall incidence of all-grade HFSR was 60.5% (95% CI: 48.3-71.6), the overall incidence of high-grade HFSR was 20.4% (95% CI: 15.4-26.6). Concerning tumor type, the incidence of HFSR varied significantly; the highest incidence was found in patients with renal-cell carcinoma, the lowest in patients with mCRC.

For relative risk (RR) analysis, only phase III randomized, placebo-controlled trials were included; calculation showed an overall RR of 5.4 (95% CI: 3.76-7.76, p<0.001) for all-grade and an RR of 41.99 (95% CI: 5.88-299.93, p<0.001) for high-grade HFSR for regorafenib compared to placebo.

Comparing the incidences of HFSR in patients treated with regorafenib and patients treated with other multi-kinase inhibitors (pazopanib, sunitinib, axitinib and sorafenib), incidences of both all-grade and high-grade HFSRs were significantly higher for patients treated with regorafenib.

higher incidence in patients treated with regorafenib compared to patients treated with other multi-kinase inhibitors

# 7 Estimated costs

Regorafenib (Stivarga®) is administered orally at a dosage of 160 mg per day, for the first 21 days of each 28-day cycle. It is available in the form of 40 mg film-coated tablets [3].

For Austria, no cost estimates are available yet. According to manufacturer's information, the list price for a 28-day supply in the United States is $ 9,350 [18]. Converted into euros, the monthly treatment costs for regorafenib are approximately € 7,035. In Switzerland, the costs for 84 tablets (sufficient for one month of regorafenib treatment) are CHF 5,567 [19], which equals approximately € 4,515.

no cost information for Austria available

In the CORRECT trial, mean duration of treatment was 2.8 months for the regorafenib group [16]. Thus, three months of regorafenib treatment would amount to € 21,105 (U.S. price) and € 13,545 (Swiss price), respectively. Additionally, costs for BSC and management of adverse events incur.

# 8 Ongoing research

In July 2013 a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted; the following phase III trials were identified:

various phase III studies are ongoing

- *NCT01853319*: an open-label phase III study of regorafenib in patients with mCRC who have progressed after standard therapy. The aim of this study is to provide additional information about the safety of regorafenib. The estimated study completion date is July 2014.
- *NCT01786538:* a randomized phase III study of oxaliplatin, fluorouracil and leucovorin (FOLFOX) with or without regorafenib in patients with mCRC having progressed after first-line irinotecan plus fluoropyrimidines. The estimated study completion date is May 2017.
- *NCT01584830*: a randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in Asians with mCRC who have progressed after standard therapy. The estimated study completion date is May 2014.

- N*CT01538680* (EudraCT Number: 2011-005836-25): an open-label phase IIIb study of regorafenib in patients with mCRC who have progressed after standard therapy. The primary endpoint of this expanded-access study will be safety. There are four study locations in Austria. The study completion date has not been specified yet.

Several phase I and phase II studies assessing the use of regorafenib for the first-line or second-line treatment (single-use or combination therapy) of mCRC were identified. For example, one of those studies (NCT01875380, EudraCT Number: 2013-000236-94) aims to evaluate the efficacy and safety of regorafenib in the first-line treatment of patients with mCRC who are frail and/or unfit for polychemotherapy.

Moreover, a database search showed a number of studies investigating the effects of regorafenib on other types of cancer such as gastrointestinal stromal tumors (GIST) or hepatocellular carcinoma.

# 9 Commentary

**regorafenib has been approved by the FDA and the EMA**

Regorafenib (Stivarga®) was approved by the FDA in September 2012 [5] for patients with mCRC who have been previously treated with a fluoropyrimidine-, oxaliplatin- and irinotecan based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy (if KRAS wild-type) [3]. In August 2013, the EMA granted marketing authorization for Regorafenib (Stivarga®) for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies (including fluoropyrimidine-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy)[4].

**increase of median OS of 1.4 months in regorafenib group, PFS was improved by 0.2 months in regorafenib group**

**primary effect: delay of tumor progression**

The CORRECT trial [16], an international, multicenter, randomized, placebo-controlled phase III study evaluated the efficacy and safety of regorafenib in patients with mCRC that progressed after administration of approved standard therapies. Analyses showed a gain of 1.4 months in median OS in the regorafenib group compared to the placebo group (HR=0.77, 95% CI 0.64-0.94, p=0.0052). Median PFS was also improved by 0.2 months in the regorafenib group (1.9 months) compared to the placebo group (1.7 months), which results in a hazard ratio of 0.49 (95% CI 0.42-0.58, p<0.0001). The objective response rate was 1.0% in patients in the regorafenib group versus 0.4% in patients in the placebo group, suggesting that delay of tumor progression is the primary effect of the described therapy. 41% of patients receiving regorafenib and 15% of patients receiving placebo achieved disease control; the median duration of stable disease was 2.0 months in the regorafenib group and 1.7 months in the placebo group.

**high incidence of adverse events, occurrence of serious adverse events**

The (small) improvements in prolonging OS and PFS survival, and the positive effects on the disease control rate are in contrast to the high incidence of treatment-related adverse events of any grade (93% in the regorafenib group versus 61% in the placebo group). This led to dose modifications in 76% (regorafenib group) and 38% (placebo group) of patients. Adverse events of grade ≥3 occurred in 54% of patients in the regorafenib group and 14% of patients in the placebo group. 8 cases of death in the regorafenib arm and 3 cases of death in the placebo arm were attributed to adverse events.

In all clinical trials (a total of 1,100 patients received Stivarga®) 0.3% of patients had severe drug-induced liver injury with fatal outcome. Thus, Stivarga® prescribing information includes a boxed warning for hepatotoxicity [3]. Compared to other anti-neoplastic protein kinase inhibitors like pazopanib, sorafenib and sunitinib, the safety profile of regorafenib is similar (including labeled warnings for teratogenicity, hypertension, hemorrhagic events and QTc prolongation) [20].

**no improvement of quality-of-life in both groups**

The phase III study also aimed to evaluate patients' health-related quality of life and health utility values by using questionnaires (EORTC QLQ-C30 and EQ-5D) and VAS scales. Interestingly, the results in both treatment groups – both at baseline and at the end of treatment – were similar, showing that regorafenib treatment is apparently not responsible for a decrease in health status and quality of life, but does not improve quality of life either.

**applicability of results needs to be verified**

In the CORRECT trial, regorafenib was administered to patients who ran out of therapeutic options but still had good performance status [21]; 49% of patients (regorafenib group) and 47% (placebo group) of patients had undergone ≥4 previous systemic anticancer therapies. The median age of study patients in both groups was 61 years, and all patients had ECOG performance status 0 or 1. Considering the fact that the median age at diagnosis for colon and rectum cancer is about 69 years [11] and previous treatment lines also require time, it is questionable how many patients are effectively eligible for this new drug in third or fourth-line therapy. Especially since verification is still needed of regorafenib as being an appropriate therapeutic option for patients with a poorer performance status than ≤1.

**detailed criteria for selecting eligible patients need to determined**

For future research, some questions on regorafenib need to be answered regarding the mechanism of action, its activity in other lines of mCRC therapy and the optimal management of adverse events. Furthermore, identification of biomarkers could help to predict the activity of regorafenib [22]. Based on molecular markers, subgroups of patients who may achieve significantly better survival times on regorafenib need to be identified [23].

**modest survival benefit stands in contrast to high incidence of adverse events and high costs**

In summary, regorafenib may represent a therapeutic option for patients who received all approved standard therapies while maintaining a good performance status. However, the modest gain in OS and PFS survival, the high-risk for adverse events, lack of improvements in QoL and potentially considerable costs of this therapy call into question whether this drug represents a viable treatment option in unselected patients.

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