Document Type:	Study Protocol
Official Title:	Sorafenib Long Term Extension Program (STEP)
NCT Number:	NCT00625378
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Cover page of the integrated protocol[a]

Study title: Sorafenib Long Term Extension Program (STEP)

This protocol version is an integration of the following documents / sections:

- **Original protocol,** Version 1.0, dated 05 JUL 2007
- **Amendment 02 (global amendment described in Section 10.2)** forming integrated protocol Version 3.0, dated 16 MAR 2011
- **Amendment 03 (global amendment described in Section 10.3)** forming integrated protocol Version 4.0, dated 30 MAR 2012
- **Amendment 04 (global amendment described in Section 10.4)** forming integrated protocol Version 5.0, dated 25 MAR 2014
- **Amendment 07 (global amendment described in Section 10.5)** forming integrated protocol Version 6.0, dated 15 MAY 2018
- **Amendment 08 (global amendment described in Section 10.6)** forming integrated protocol Version 7.0, dated 26 MAY 2020

This protocol has also been amended for specific countries:

- **Local Amendment 01, Germany**, dated 07 FEB 2008
- **Local Amendment 05, China**, dated 19 JAN 2016
- **Local Amendment 06, Taiwan,** dated 25 JUL 2017

Amendments not included in the consecutive numbering of amendments are local amendments not forming part of this integrated global protocol.

[a] Cover page was added by Amendment 7. See Section 10.5.6, Modification 6.

Title page – amended

Title:	Sorafenib Long Term Extension Program (STEP)
Test Drug:	Sorafenib/Nexavar® BAY 43-9006
Sponsor:	**Sponsor (Non-US): Bayer AG** **51368 Leverkusen, Germany** **Sponsor (US territory): Bayer US LLC** **100 Bayer Boulevard, P.O. Box 915, Whippany, NJ 07981-0915, USA**[b]
Senior Clinical Development Leader (CDL)[c]:	PPD Müllerstr. 178 13353 Berlin, Germany Phone: PPD
Study Number/Version/Date:	12311/Version 7.0/26 MAY 2020
EudraCT-No.:	2007-002604-17
Development Phase:	3b

The undersigned confirm that they agree to conduct the study under the conditions described in this protocol[e]

PPD	**Date**
PPD	**Date**

[b] The Sponsor's address was updated by Amendment 7. See Section 10.5.1, Modification 1.
[c] The Sponsor's Medical Expert's role name was updated by Amendment 8. See Section 10.6.1, Modification 1.
[d] The Senior Clinical Development Leader's address was updated by Amendment 8. See Section 10.6.1, Modification 1.
e: Changes were made to the Study Manager, Statistician, and Medical Expert under Amendment 3. See Section 10.3, Modification 6.
[f] The Study Manager changed and was modified by Amendment 7 and 8. See Section 10.5.1, Modification 1 and Section 10.6.1, Modification 1.
[g] The Statistician changed and was modified by Amendment 7. See Section 10.5.1, Modification 1.

PPD

Date

i j

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Additional Signatures

Name:[k] Signature: _____

Function: Principal Investigator Date:

Address:

This document is electronically signed. The eSignature is archived in the Trial Master File (TMF) and can be provided upon request.[l]

[h] The signature of the Medical Expert was modified by Amendment 8. See Section 10.6.1, Modification 1.
[i] The Global Clinical Lead changed and was modified by Amendment 7. See Section 10.5.1, Modification 1. The signature of the Global Clinical Lead was removed by Amendment 8. See Section 10.6.1, Modification 1.
j Change of responsibility for the Study Manager and Medical Expert and a line was added for the signature of the Global Clinical Lead under Amendment 4. See Section 10.4, Modification 1.
[k] The Principal Investigator's name and address changed by Amendment 7. See Section 10.5.1, Modification 1.
[l] New eSignature text added with Amendment 8. See Section 10.6.2, Modification 2.

Table of Contents

Glossary and Abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Bid	*Bis in die* (Latin), Twice a day
CRF	Case Report Form either paper or electronic
EC	Ethical Committee
ECOG	Eastern Cooperative Oncology Group
eg	For Example
FU	Follow-up
IB	Investigator's Brochure
GCP	Good Clinical Practice
Gr	Grade
HCT	Hematocrit
Hgb	Hemoglobin
ICH	International Conference on Harmonisation
ie	That is
IRB	Institutional Review Board
MI	Myocardial Infarction
NCI	National Cancer Institute
NCI-CTC	National Cancer Institute – Common Terminology Criteria Version 3.0
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria Adverse Event
NYHA	New York Heart Association
OS	Overall survival
PI	Principal Investigator
PMF	Pregnancy Monitoring Form
RBC	Red Blood Cells
RK	Raf Kinase
RKI	Raf Kinase Inhibitor
SAE	Serious Adverse Event
STEP	Sorafenib Long Term Extension Program
TACE	Transarterial Chemoembolization
TMF	Trial Master File
WBC	White Blood Cells
WHO	World Health Organization

1. Introduction

Experience has shown that in nearly all clinical trials with sorafenib (Nexavar®) there are patients who are continuing to receive sorafenib after the study has met its primary endpoint. The options to provide sorafenib to these patients who have a non-approved/reimbursed tumor type are through a clinical trial, through a Post-Trial Access Program or through any other mechanism (e.g. local access program) in accordance with local legal and compliance rules. [m] The intention of this clinical study 12311 (STEP program) is to enable patients who are still benefiting from ***treatment*** in a completed clinical trial to continue to receive ***treatment***.[n]

Please refer to the sorafenib Investigator Brochure and any additional data supplied by the Sponsor.

2. Study objectives - amended

The primary purpose of the STEP program is to enable patients, currently receiving sorafenib (Nexavar) in a Bayer/Onyx sponsored clinical trial, to continue sorafenib treatment after their respective study has met its primary endpoint and/or has reached the end as defined in the original protocol. Patients will be able to continue treatment until ***(i)*** the treating physician feels the patient is no longer benefiting from the treatment or ***(ii) the treatment***[n] becomes commercially available and reimbursed for the respective indication as applicable in the country in which the patient lives ***and the patient can obtain suitable amounts of drug for treatment through standard mechanisms of commercial availability (ie, there should be no interruption in the patient's treatment schedule when switching to commercially available product)***[o] or (iii) the patient can join a Post-Trial-Access Program, another study or can receive sorafenib through

m: Added Post-Trial Access Program with Amendment 8. See Section 10.6.3, Modification 3.
n: Reference to subjects receiving single-agent sorafenib was modified under Amendment 3 to allow inclusion of subjects receiving sorafenib in combination with other drugs, specifically, subjects from the SEARCH trial receiving sorafenib and erlotinib and subjects from the RESILIENCE trial receiving sorafenib and capecitabine. See Section 10.3, Modification 5.
o: Under Amendment 3, it was clarified that there should be no interruption in a patient's treatment schedule when switching to commercially available product. See Section 10.3, Modification 6.

any other mechanism (e.g. local access program) in accordance with local legal and compliance rules, with no cost to the patient with respect to sorafenib.[p]

An additional objective is the assessment of the safety of Nexavar or Nexavar combination treatment.[q] [r]

3. Investigator(s) and other study participants

Information regarding additional key personnel involved in the conduct of the study, including names and contact details of participating Investigators, monitors, clinical laboratories, technical departments and/or institutions, as well as information on members of additional study committees, will be found in the study files of the Sponsor and on site if requested.

4. Investigational plan

4.1 Study Design and Plan - amended

This is an open label clinical trial that will enable patients receiving sorafenib (Nexavar) in a completed Bayer/Onyx sponsored clinical trial to continue treatment. A completed study is one that has passed the official statistical and regulatory endpoints and/or has reached its end, as outlined in that protocol.

The patients ***in this open-label clinical trial*** will continue receiving single-agent sorafenib (Nexavar)[s] or sorafenib and capecitabine ***combination*** if transferred from Study 12444 (RESILIENCE)[t] at the same dose and schedule as in their original Clinical Trial.

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p: Added clarification for continuation on study drug with Amendment 8. See Section 10.6.5, Modification 5.
q: These additional objectives were added in Amendment 3. See Section 10.3 Modification 1 and Modification 2.
r: Objective modified by Amendment 7 to remove overall survival (OS). See Section 10.5.2, Modification 2.
s: Reference to erlotinib removed since none of the subjects that transferred into this study were assigned to erlotinib from study 12917. See Section 10.4, Amendment 4, Modification 2.
t: Reference to subjects receiving single agent sorafenib was modified under Amendment 3 to allow inclusion of subjects receiving sorafenib in combination with other drugs, specifically, subjects from the SEARCH trial receiving sorafenib and erlotinib and subjects from the RESILIENCE trial receiving sorafenib and capecitabine. See Section 10.3, Amendment 3, Modification 5.

Patients will continue receiving sorafenib (Nexavar; ***as single agent or combination treatment***),[t] as long as the treating physician feels the patient is continuing to benefit from treatment or until sorafenib (***as single agent or combination treatment***) becomes commercially available and reimbursed for the respective indication in the country in which the patient lives or until being switched to any other form of drug supply with no interruption in the patient's treatment schedule.[u] The patient may also continue ***treatment***[v] until he/she withdraws consent, is non-compliant, is lost to follow up, or if an unacceptable toxicity occurs.

Prior to being dispensed study medication for this long term extension clinical trial, patients will be required to complete their End of Treatment visit in their originating study. Once the End of Treatment visit in the originating study is complete, patients will be required to provide informed consent for this long term extension clinical trial. Patients will continue with single agent sorafenib (Nexavar)[w] ***or sorafenib and capecitabine if transferred from Study 12444 (RESILIENCE)***[x] [y]at the same dose and schedule the patient was receiving in their original clinical trial.

Sorafenib (Nexavar) will be provided as 200 mg tablets. [z] ***Capecitabine is available in many countries including generic sources and will be commercially supplied 150 mg and 500mg tablets***[aa] ***for patients receiving the sorafenib/capecitabine combination and transferring from***

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u: Added clarification for continuation on study drug with Amendment 8. See Section 10.6.5, Modification 5.
v: Reference to subjects receiving single agent sorafenib was modified under Amendment 3 to allow inclusion of subjects receiving sorafenib in combination with other drugs, specifically, subjects from the SEARCH trial receiving sorafenib and erlotinib and subjects from the RESILIENCE trial receiving sorafenib and capecitabine. See Section 10.3, Modification 5.
w Reference to erlotinib removed since none of the subjects that transferred into this study were assigned to erlotinib from study 12917. See Section 10.4, Modification 2.
x: Reference to subjects receiving single agent sorafenib was modified under Amendment 3 to allow inclusion of subjects receiving sorafenib in combination with other drugs, specifically, subjects from the SEARCH trial receiving sorafenib and erlotinib and subjects from the RESILIENCE trial receiving sorafenib and capecitabine. See Section 10.3, Modification 5.
y Reference to capecitabine was removed with Amendment 8. See Section 10.6.4, Modification 4.
z Sentence removed since none of the subjects that transferred into this study were assigned to erlotinib. See Section 10.4, Amendment 4, Modification 2.
aa Text changed to clarify that capecitabine will be supplied commercially and not by the sponsor under Amendment 4. See Section 10.4, Modification 3.

Study 12444 (RESILIENCE).[bb] The patient should be evaluated according to Good Medical Practices as well as local therapeutic and diagnostic standards. The patients should be evaluated by a study physician for safety at least once every 8 weeks and more frequently as needed. The protocol allows for a ±7 days window when scheduling any visit. Physicians can choose to continue to see the patients every 8 weeks in a face to face visit. At least every other visit must be a mandatory on site visit for examination and drug dispensing, with the other visit being either in person or as a phone call. It is at the discretion of the investigator based on the patient's current condition and adverse event profile to determine if the next visit will be performed on site or as a phone visit. Any scheduled phone visit is mandatory and it will be at the discretion of the investigator to decide if that phone visit is sufficient. If the patient needs a physical examination, the visit will be performed on site. If the investigator feels the patient is stable with no new safety concerns nor new AEs in between visits, a phone call with labs, ECOG and review of AEs would be enough[cc]. Once every 8 weeks[cc] safety evaluations include vital signs (ie, heart rate, blood pressure, temperature) only when the visit is on site, ***Eastern Cooperative Oncology Group (ECOG) performance status***, laboratory evaluations may be performed by local accredited lab which need to have PI signoff within a week of drawing[dd] (hematology, ALT, AST, lipase and amylase, PT-INR as applicable for anticoagulated patients) and a review of any new or ongoing adverse event or concomitant medications as well as study medication taken during the visit interval. All adverse events, laboratory data, ***ECOG performance status and survival status (dead or alive and date of death or date of last contact)***,[ee] as well as End of Treatment information and study medication taken must be clearly and accurately recorded in the Case Report Form provided. All other data, including but not limited to, vital signs, concomitant

bb: Information on the erlotinib and capecitabine formulations was added under Amendment 3. See Section 10.3, Modification 5. Reference to capecitabine was removed with Amendment 8. See Section 10.6.4, Modification 4.

[cc] Safety follow-up adjusted by Amendment 7 to lessen the travel burden on patients. See Section 10.5.3, Modification 3.

[dd] Laboratory evaluations have been adjusted by Amendment 7 to ensure these are not missed. See Section 10.5.4, Modification 4.

ee: Survival and ECOG performance status were added to the Case Report Form as of Amendment 3. See Section 10.3 Modification 1 and Modification 2.

medications must be recorded in the patient's source documents and may be requested at the discretion of the Sponsor.

Following the End of Treatment assessments from the original study, the following information will be recorded in the long term extension CRF: demography, date of first dose of sorafenib (Nexavar) in originating study[ff] date of first dose of capecitabine if the patient is transferred from RESILIENCE (Study 12444),[gg] originating study number, ***ECOG performance status and survival status (dead or alive and date of death or date of last contact)***[hh] and ongoing adverse events.

In the event the patient experiences a treatment related Serious Adverse Event, based on the definition outlined in Section 7 of this document, this event must be reported to Bayer Global Drug Safety immediately (within 24 hours of awareness) using the forms provided, and recorded in the CRF.

In the event that another mechanism of continued drug supply is established, the present study will end when all patients have transitioned to any new drug supply program or discontinued from this study for another reason (e.g. consent withdrawal, lost to follow-up, death, sponsor decision). Until the transition, patients will continue to follow all the procedures and visits required in the current version of the protocol.[ii]

4.2 Selection of Study Population

Patients who remain ongoing in a Bayer/Onyx sponsored Clinical Trial that has reached its statistical, regulatory and/or study end and who, in the opinion of the Investigator, still benefiting from treatment, will be eligible for entry into this study (STEP program).

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ff Sentence removed since none of the subjects that transferred into this study were assigned to erlotinib. See Section 10.4, Modification 2.

gg: Participation of subjects from the SEARCH trial (Study 12917) or from the RESILIENCE trail (Study 2444) was added under Amendment 3 See Section 10.3, Modification 5.

hh: These additional objectives were added in Amendment 3. See Section 10.3, Modification 1 and Modification 2.

[ii] Added clarification for ending the study with Amendment 8. See Section 10.6.6, Modification 5.

4.2.1 Inclusion Criteria

- Patients, who are participating in a previous Bayer/Onyx sponsored study that has reached its endpoint (statistical and regulatory or study end), and who are, in the opinion of the Investigator, expected to continue to have an overall positive benefit/risk from continuing treatment.
- Patients who have signed informed consent for this long term extension program.
- Women of childbearing potential and men must agree to use adequate contraception prior to study entry and for the duration of study participation, including the 30 days period after last study drug dosing. The investigator should advise the patient how to achieve an adequate contraception.
- Women of childbearing potential who have a negative pregnancy test within 7 days of the first dose of sorafenib in this long term extension program.
- Patient is receiving sorafenib (Nexavar) as a monotherapy in their originating protocol. Patients who were being treated with sorafenib (Nexavar) in combination with other chemotherapies in the original study, but continued on single agent sorafenib (Nexavar) after discontinuation of the combination agent will be eligible.
- Patients who are receiving concurrent combination with sorafenib (Nexavar) and TACE (transarterial chemoembolization) in their originating study will be eligible.[jj] [kk]
- ***Patients who are receiving concurrent combination with sorafenib (Nexavar) and capecitabine in their originating Study 12444 (RESILIENCE) will be eligible.***
- Patients who have completed the End of Treatment assessments in their originating study. Every effort should be made to conduct the End of Treatment visit such that the patient does not have any interruption of sorafenib dosing.

jj: The inclusion criterion regarding eligibility of subjects receiving combination sorafenib and TACE in their originating studies was added under Amendment 2. See Section 10.2.

kk Reference to erlotinib removed since none of the subjects that transferred into this study were assigned to erlotinib from study 12917. See Section 10.4, Modification 2.

4.2.2 Exclusion Criteria

- Any condition that is unstable or that could jeopardize the safety of the patient (please refer to the Investigator Brochure and product labeling safety sections).
- History of cardiac disease: congestive heart failure>NYHA Class 2 (Appendix 11.2) or uncontrolled hypertension
- Myocardial infarction (MI) within the last 3 months
- Symptomatic metastatic brain or meningeal tumors
- Previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study EXCEPT cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors (Ta, Tis & T1) or any cancer curatively treated > 5 years prior to study entry.
- Patients with seizure disorder requiring medication (such as steroid anti-epileptics)
- Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results
- Any condition which could jeopardise the safety of the patient and his/her compliance in the study

Excluded therapies and medications, previous and concomitant:

- Concurrent anti-cancer chemotherapy, except TACE (transarterial chemoembolization)[ll mm nn] and capecitabine

ll: The exclusion criterion regarding concurrent anti-cancer chemotherapy was modified under Amendment 2. See Section 10.2.

- Concurrent immunotherapy (including monoclonal antibodies), during or within 30 days prior to start of study drug[oo]

- Concurrent hormonal therapy, except for bisphosphonates, during or within 30 days prior to start of study drug[oo]

- Concomitant Rifampicin and St John's Wort (Warfarin may be used only with very close monitoring.)

- Radiotherapy during study or within 3 weeks of start of study drug. [Palliative radiotherapy will be allowed as described in the Prior and Concomitant Therapy Section 4.5.8.]

- Concomitant use of potent inhibitors of CYP 3A4 including ketoconazole, itraconazole and ritonavir. Consumption of grapefruit juice should also be avoided.

4.3 Removal of Subjects from Study

Subjects may be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally acceptable representative.

- If, in the Investigator's opinion, continuation in the study would be detrimental to the subject's well-being.

- At the specific request of the Sponsor.

- The patient dies.

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mm Reference to erlotinib removed since none of the subjects that transferred into this study were assigned to erlotinib from study 12917. See Section 10.4, Modification 2.
nn: Participation of subjects from the SEARCH trial (Study 12917) or from the RESILIENCE trial (Study 12444) was added under Amendment 3. In Amendment 4, reference to erlotinib is removed, as no subjects was enrolled into this study from study 12917 taking the combination of erlotinib and sorafenib. Therefore, capecitabine is not an excluded therapy. See Section 10.3, Modification 5.
oo: The exclusion criterion regarding concurrent anti-cancer chemotherapy was modified under Amendment 2. See Section 10.2.

Also subjects must discontinue treatment for the following reasons:

- Substantial non-compliance.
- Patients with clinical signs or laboratory tests results consistent with pregnancy. Pregnancy will be reported by the Investigator on a Pregnancy Monitoring Form (PMF) following the same timelines as a Serious Adverse Event.
- The patient uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with results.
- Occurrence of unacceptable toxicity.
- When Nexavar is commercially available and reimbursed for the respective indication in the country in which the patient lives.
- The patient is lost to follow-up.

In all cases, the reasons for withdrawal must be recorded in the case report form and patient's medical record. All patients who discontinue due to adverse events or clinical laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome recorded.

If any patient should die during the trial or within 30 days of the patient's last dose of sorafenib (Nexavar), the Investigator should inform Bayer by completing the SAE Complimentary Form and Adverse Event page for the study.

The cause and date of death should also be recorded on the End of Treatment page, as applicable.

4.4 Premature Termination of Study/Closure of Centre

The Sponsor has the right to close this study, and the Investigator/Sponsor has the right to close a center, at any time, although this should occur only after consultation between involved parties.

The EC/IRB [pp] must be informed. Should the study/center be closed prematurely, all study materials (except documentation that has to remain stored at site) must be returned to the Sponsor. The Investigator will retain all other documents until notification given by the Sponsor for destruction.

4.5 Treatments

4.5.1 Treatments to be Administered

Sorafenib will be supplied as 200 mg tablets.[qq] [rr] Patients should continue on the same dose as they were receiving in the patient's originating Bayer/Onyx-sponsored Clinical Trial.

The patients' dose may not be increased beyond the dose they were receiving upon entry into this program.

If the patient is receiving a reduced dose upon study entry into STEP due to an adverse event (AE), it is possible to re-escalate this dose after AE resolution. Anyway the maximum dose allowed in the STEP trial is the one the patient had received before AE induced dose reduction in the originating study.

Upon completion of the End of Treatment evaluations in the originating study and registration in this program, the patient should be dispensed a new bottle of medication specific for this long term extension program. Patients should be dispensed enough medication to last until their next scheduled visit.

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pp: As of Amendment 3, additional text was added to include the head of the center for sites in Japan. See Section 10.3 Modification 3. Reference to center for sites in Japan was removed with Amendment 8. See Section 10.6.8, Modification 8.

qq: Information on the erlotinib and capecitabine formulations was added under Amendment 3. See Section 10.3, Modification 5.

rr Reference to erlotinib removed since none of the subjects that transferred into this study were assigned to erlotinib and sorafenib in study 12917 and references to the supply of capecitabine were removed since this drug will not be supplied by the sponsor. See Section 10.4, Modifications 2 and 3.

Every effort should be made to collect all unused medication and empty bottles on the last visit in their original protocol as well at every visit that medication is dispensed in this long term extension program.

4.5.2 Dose Modification[ss]

4.5.2.1 Sorafenib monotherapy

If the starting dose is 600 mg bid the modifications of sorafenib (Nexavar) will follow the pre-defined dose levels:

Dose level 1	600 mg (3 x 200 mg) po q 12 hr
Dose level -1	400 mg (2 x 200 mg) po q 12 hr
Dose level -2	400 mg (2 x 200 mg) po q 24 hr
Dose level -3	400 mg (2 x 200 mg) po q 48 hr

If the starting dose is 400 mg bid the modifications of sorafenib (Nexavar) will follow the pre-defined dose levels:

Dose level 1	400 mg (2 x 200 mg) po q 12 hr
Dose level -1	400 mg (2 x 200 mg) po q 24 hr
Dose level -2	400 mg (2 x 200 mg) po q 48 hr

If a dose reduction by more than two dose levels in relation to the current pertaining standard dose level is required, the patient should be discontinued from the study treatment. Also, at the discretion of the investigator, the dose may be re-escalated to a higher dose level up to the present standard dose level after the resolution of the adverse event. Resolution of an adverse event is

ss: With the inclusion of subjects from the SEARCH study and The RESILIENCE study, this section was modified under Amendment 3 to include information on sorafenib monotherapy, sorafenib/erlotinib combination therapy, and sorafenib/capecitabine combination therapy as separate sub-sections. See Section 10.3, Modification 5.

defined as the disappearance or the decrease of the AE to a lower toxicity grade, at least ≤ Grade 2.

Table 4–1 illustrates dose modifications and delays for hematologic toxicities.

Table 4–1: Hematologic Criteria for Dose Delay and Dose Modification of Bay 43-9006

Grade	Dose Delay	Dose Modification
Grade 0-2	Treat on time	No Change
Grade 3	Treat on time	DECREASE one dose level [b]
Grade 4	DELAY [a] until ≤ Grade 2	DECREASE one dose level [b]

a If no recovery after 30 day delay, treatment will be discontinued unless patient is deriving clinical benefit
b If more than 2 dose reductions are required, treatment will be discontinued

Table 4–2 summarizes the recommendations for dose delays and modifications for all non-hematologic adverse events, except for skin toxicities, which will be detailed separately (Table 4–3 and Table 4–4).

Table 4–2: Non-hematologic Criteria for Dose Delay and Dose Modification of Bay 43-9006 (except skin toxicity)[a]

Grade	Dose Delay	Dose Modification
Grade 0-2	Treat on time	No Change
Grade 3	DELAY[b] until ≤ Grade 2	DECREASE one dose level[c]
Grade 4	OFF protocol therapy	OFF protocol therapy

a Also excludes nausea/vomiting that has not been premedicated, and diarrhea
b If no recovery after 30 day delay, treatment will be discontinued unless patient is deriving clinical benefit
c If more than 2 dose reductions are required, treatment will be discontinued

Only for the purpose of dose modifications, patients experiencing Hand-Foot ***Skin Reactions***[tt] should have their signs and symptoms graded according to the following system (see Table 4–3). Other skin toxicities will be graded according to CTCAE Version 3.0. Please note that Hand-Foot ***Skin Reaction*** will be graded and recorded as an adverse event according to NCI-CTC Version 3.0 in the CRF.

Table 4–3: Grading for Hand-Foot Skin Reaction

Grade 1	Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort, which does not disrupt normal activities.
Grade 2	Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities.
Grade 3	Moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living.

According to the grade and incidence of skin toxicity (including rash and hand-foot syndrome) for a given patient, the following dose modification schedule will be followed (see Table 4–4).

tt: Hand-Foot Syndrome was changed to Hand-Foot Skin Reaction under Amendment 3. See Section 10.3, Modification 6.

Table 4–4: Skin Toxicity Criteria for Dose Delay and Dose Modification of Sorafenib

Toxicity Grade		During a Course of Therapy	Dose for Next Cycle
Grade 1		Maintain dose level	Maintain dose level
Grade 2	1st appearance	Interrupt until resolved to grade 0-1	Maintain dose level
	2nd appearance	Interrupt until resolved to grade 0-1	Decrease by one dose level
	3rd appearance	Interrupt until resolved to grade 0-1	Decrease by two dose levels
	4th appearance	Discontinue treatment permanently	
Grade 3	1st appearance	Interrupt until resolved to grade 0-1	Decrease by one dose level[a]
	2nd appearance	Interrupt until resolved to grade 0-1	Decrease by two dose levels
	3rd appearance	Discontinue treatment permanently	

a For patients who require a dose reduction for grade 3 rash or hand-foot syndrome, the dose of study drug may be increased to the starting dose after one full cycle of therapy has been administered at the reduced dose without the appearance of rash or hand foot syndrome ≥ grade 1.

Patients with discomfort due to hand foot syndrome may be treated with topical emollients, low potency topical steroids, or urea-containing cream.

For patients who require a dose reduction for Grade 3 rash or hand-foot syndrome, the dose of study drug may be increased to the starting dose after one full cycle of therapy has been administered with the reduced dose, without the appearance of rash or hand foot syndrome ≥ Grade 1. ***uu***, ***vv***, ***ww***, xx, ***yy***, zz, aaa, ***bbb***, ccc, ***ddd***, ***eee***, ***fff***, ***ggg***, ***hhh***, ***iii***, ***jjj***, ***kkk***, ***lll***, ***mmm***, ***nnn***

uu Reference to erlotinib removed since none of the subjects that transferred into this study were assigned to erlotinib from study 12917. See Section 10.4, Modification 2..
vv The word placebo was removed to clarify that subjects receiving sorafenib in Study 12444 did not receive placebo under Amendment 4. See Section 10.4, Modification 4.
ww The word placebo was removed to clarify that subjects receiving sorafenib in Study 12444 did not receive placebo under Amendment 4. See Section 10.4, Modification 4.
xx Removed entire Section 4.5.2.2 Sorafenib and capecitabine combination with Amendment 8. See Section 10.6.4, Modification 3.
yy The word placebo was removed to clarify that subjects receiving sorafenib in Study 12444 did not receive placebo under Amendment 4. See Section 10.4, Modification 4.

4.5.2.2 Sorafenib and capecitabine combination

This section extensively described the specific dose modifications for the sorafenib capecitabine combination therapy and is not applicable anymore because all patients treated with this combination are off the study. The entire section and subsections were removed with Amendment 8 to avoid confusion for the remaining patients none of whom are receiving sorafenib and capecitabine .[ooo]

4.5.2.3 Sorafenib and TACE combination

This section described the specific dose modifications for the sorafenib TACE combination therapy and is not applicable anymore because all patients treated with this combination are off

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[zz] Removed entire Section 4.5.2.2.1 Dose reduction levels with Amendment 8. See Section 10.6.4, Modification 4.
[aaa] Removed entire Section 4.5.2.2.2 Dose modification for hematologic toxicities with Amendment 8. See Section 10.6.4, Modification 4.
bbb The word placebo was removed to clarify that subjects receiving sorafenib in Study 12444 did not receive placebo under Amendment 4. See Section 10.4, Modification 4.
[ccc] Removed entire Section 4.5.2.2.3 Dose modification for non-hematologic toxicities with Amendment 8. See Section 10.6.4, Modification 4.
ddd The word placebo was removed to clarify that subjects receiving sorafenib in Study 12444 did not receive placebo under Amendment 4. See Section 10.4, Modification 4.
eee The word placebo was removed to clarify that subjects receiving sorafenib in Study 12444 did not receive placebo under Amendment 4. See Section 10.4, Modification 4.
fff The word placebo was removed to clarify that subjects receiving sorafenib in Study 12444 did not receive placebo under Amendment 4. See Section 10.4, Modification 4.
[ggg] Removed entire Section 4.5.2.2.4 Dose modification and management of sorafenib specific toxicities with Amendment 8. See Section 10.6.4, Modification 4.
[hhh] Removed entire Section 4.5.2.2.5 Dose modification and management of capecitabine specific toxicities with Amendment 8. See Section 10.6.4, Modification 4.
[iii] Removed entire Section 4.5.2.2.6 Dose modification for other non-hematologic toxicities (excluding fatigue, dermatologic toxicities, gastrointestinal toxicities, hypertension and toxicities attributable to capecitabine) with Amendment 8. See Section 10.6.4, Modification 4.
[jjj] Removed entire Section 4.5.2.3 Sorafenib and TACE combination with Amendment 8. See Section 10.6.4, Modification 4.
kkk Added the CTC version used to grade liver function abnormalities. See Section 10.4, Modification 6.
lll Added the CTC version used to grade liver function abnormalities. See Section 10.4, Modification 6.
mmm Addition of a new section to present the guidance on Sorafenib dose modification in combination with TACE. See Section 10.4, Modification 5.
nnn The word placebo was removed to clarify that subjects receiving sorafenib in Study 12444 did not receive placebo under Amendment 4. See Section 10.4, Modification 4.
[ooo] Added explaining text as to why sorafenib capecitabine combination therapy sections were removed with Amendment 8. See Section 10.6.4, Modification 4.

the study. The entire section was removed with Amendment 8 to avoid confusion for the remaining patients none of whom are receiving sorafenib and TACE.[ppp]

4.5.3 Identity of Investigational Product[qqq]

4.5.3.1 Sorafenib

BAY 43-9006 will be packed by the Sponsor and will be labeled according to the requirements of local law and legislation. Label text will be approved according to agreed procedures, and the master labels will be available in the study file(s).

Label text will be approved according to agreed Bayer procedures, and a copy of the labels will be made available to the study site upon request.

Sorafenib (Nexavar) tablets are red in color and are manufactured by Bayer. The 200 mg tablets are packed in bottles containing 140 tablets or in blister packs depending on the climate zone of the respective country.

The active compound of BAY 43-9006 is 4-{4-[3-(4-chloro-3-trifluoromethyl-phenyl) -ureid]-phenoxy}-pyridine-2-carboxylic acid methylamide-4-methylbenzenesulfo-nate, and its molecular weight is 637 Daltons.

The drug is poorly soluble in aqueous media. The tablets need not be protected from light. The formulation is presented as an immediate release dosage form, ie, the active ingredient is completely dissolved under *in-vitro* test conditions within a short period of time.

[ppp] Added explaining text as to why sorafenib TACE combination therapy section was removed with Amendment 8. See Section 10.6.4, Modification 4.

qqq: With the inclusion of subjects from the SEARCH study and the RESILIENCE study, this section was modified under Amendment 3 to include information on sorafenib, erlotinib, and capecitabine as separate sub-sections. See Section 10.3, Modification 5.

Supply, packaging, labeling and storage

BAY 43-9006 tablets will be packed in bottles containing 140 tablets per bottle in countries with climate zones I/II. In case of blister packaging 10 tablets are packed per blister. Fourteen blister strips are packed in one card box, which thus contains 140 tablets in total. [rrr]

Participating countries and centers will be provided with the study medication according to the number of potential patients from other Bayer/Onyx sponsored studies and receipt of the registration form by Bayer. Once the drug has been received, the drug should be kept in a dry, safe place, at controlled room temperature of < 25°C.

The study drug must exclusively be used for the patients specified in this protocol and it will only be accessible to authorized staff.

Only the Investigator or a person assigned by him/her will be allowed to supply and administer the drug to the patient. The dispensing and return of sorafenib (Nexavar) to a patient will be recorded on a Drug Accountability Form maintained either in the Pharmacy or in the patient's files. In addition, dosing information should be captured on the appropriate page(s) in the CRF. ***[sss]***

Capecitabine is commercially approved for breast cancer and readily available in many countries including generic sources. Subjects on treatment with both capecitabine and sorafenib at the end of the 12444 RESILIENCE trial who are switched to the STEP study will switch to commercial supply capecitabine. In addition, subjects will continue to receive sorafenib as clinical supply. [ttt]

[rrr] Reference to study sites in Japan removed with Amendment 8. See Section 10.6.8, Modification 8.
sss Reference to erlotinib removed since at the time of Amendment 4 none of the subjects that transferred into this study were assigned to erlotinib and sorafenib in study 12917. See Section 10.4, Modification 2. At a later time, a patient in Taiwan, who was taking sorafenib in combination with erlotinib was transferred from SEARCH into the STEP trial. This was explained in local Amendment 6, on 25 JUL 2017.
ttt Text changed to clarify that capecitabine will be supplied commercially and not by the sponsor under Amendment 4. See Section 10.4, Modification 3.

4.5.4 Method of Assigning Subjects to Treatment Groups

As the study is an open label allocation, randomization is not required.

4.5.5 Selection of Doses in the Study

Patients will receive sorafenib (Nexavar) 200 mg tablets and should continue receiving the same dose they were receiving in their original trial. ***Patients receiving sorafenib***[uuu] ***or sorafenib/capecitabine combination should continue the same doses as in the originating trial.***[vvv]

4.5.6 Selection and Timing of Dose for Each Subject - amended

The patient should continue receiving the same dose they were receiving in the previous trial. Dose increase beyond the dose the patient is currently receiving is not acceptable.

Sorafenib (Nexavar) [www], ***and capecitabine*** may be decreased in the event of toxicity based on the Dose Modification criteria outlined in Section 4.5.2.[vvv]

4.5.7 Blinding

This study is an open label study therefore blinding is not applicable.

4.5.8 Prior and Concomitant Therapy

Any medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator. This information must be recorded in the patient's source documents.

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uuu Reference to erlotinib removed since none of the subjects that transferred into this study were assigned to erlotinib from study 12917. See Section 10.4, Modification 2.

vvv: Participation of subjects from the SEARCH trial (Study 12917) or the RESILIENCE trial (Study 12444) was added under Amendment 3. See Section 10.3, Modification 5.

www Reference to erlotinib removed since none of the subjects that transferred into this study were assigned to erlotinib from study 12917. See Section 10.4, Modification 2.

Permissible concomitant medication/therapies:

- Patients taking concomitant medications, known to be metabolized by the liver, should be closely observed for side effects. Patients taking narrow therapeutic index medications that are hepatically metabolized (liver P450 system) should be monitored proactively for serum/ plasma levels of warfarin, phenytoin, quinidine, carbamazepine and phenobarbital. Treatment with non-conventional therapies (for example herbs or acupuncture), and vitamin/mineral supplements is acceptable provided that the patient continues to be monitored by the patient's physician.
- In general, patients should be closely monitored for side effects of all concomitant medications regardless of path of elimination, especially those with narrow therapeutic indices, such a digoxin, warfarin, quinidine, phenytoin, phenobarbitol, carbamazepine and cyclosporine.
- Patients may receive palliative and supportive care for any underlying illness. Patients who receive bisphosphonates prophylactically or for bone metastases may continue while on study drug.
- Palliative radiotherapy during the program is permitted. Study drug may be continued during palliative radiotherapy.

Since there is a possibility of decreased sorafenib (Nexavar) efficacy upon chronic co-administration of CYP3A4 inducers with sorafenib (Nexavar), chronic co-administration of CYP3A4 inducers with sorafenib (Nexavar) should be avoided to the extent possible.

Non-permissible concomitant medication/therapies:

- Anticancer chemotherapy, ***except TACE,***[xxx] [yyy] and capecitabine, [zzz] immunotherapy or ***live***[aaaa] vaccines during the study.

4.5.9 Treatment Compliance

An adequate record of receipt, distribution and return (or destruction) of all study medication supplies must be kept in the form of a Drug Accountability Form provided by the sponsor. In addition, information regarding treatment with sorafenib (Nexavar) in this protocol should be recorded on the appropriate page in the CRF.

4.6 Study Variables

The primary objective is to enable patients receiving sorafenib (Nexavar) in a completed Bayer/Onyx-sponsored Clinical Trial to continue treatment in this extension program.

4.6.1 Efficacy Variables - amended

Not applicable.[bbbb] [cccc]

4.6.2 Safety Variables

All observations pertinent to the safety of the study medication will be recorded in the patient's source documents and be made available at the request of the sponsor.

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xxx This text regarding concurrent anti-cancer chemotherapy was modified to add TACE under Amendment 4 to be consistent with the exclusion criteria modified in Amendment 2. See Section 10.4, Modification 5.
yyy Reference to erlotinib removed since none of the subjects that transferred into this study were assigned to erlotinib from study 12917. See Section 10.4, Modification 2.
zzz: Participation of subjects from the SEARCH trial (Study 12917) or the RESILIENCE trial (Study 12444) was added under Amendment 3. Therefore, erlotinib and capecitabine are not excluded therapies. See Section 10.3, Modification 5.
aaaa: In Amendment 3, the information regarding vaccines was clarified to refer to live vaccines. See Section 10.3, Modification 6.
bbbb: Overall survival was added as an efficacy variable by Amendment 3. See Section 10.3, Modification 1.
cccc Efficacy variable modified by Amendment 7 to remove overall survival (OS). See Section 10.5.2, Modification 2.

The following data must be reported in the source documents:[dddd]

- Vital signs (heart rate, blood pressure, temperature)
- Concomitant medications

In addition to the above parameters, the following data must be recorded in the CRF provided and the source documents:

- All treatment related adverse events (any grade)
- All adverse events NCI-CTCAE Version 3.0 Grade 3 or higher (regardless of attribution). [eeee]
- All Serious Adverse Events, regardless of relationship to study drug
- ***ECOG performance status***[j]
- Laboratory parameters
  - Hematology – Hgb, HCT, platelets, RBC, WBC, differential
  - Blood chemistry – ALT, AST, amylase, lipase
  - Coagulation – INR as applicable for patients receiving coagulation therapy
- Start and stop dates of sorafenib (Nexavar) treatment as well as the dose of sorafenib (Nexavar)
- Reason for termination of study medication[ffff]

dddd: ECOG performance status was moved from the list of data that must be reported in the source documents to data the must be recorded in the CRF and the source documents as of Amendment 3. See Section 10.3, Modification 2.

eeee: Language specific to the recording of adverse event information in Japan was added under Amendment 3. See Section 10.3, Modification 2. Language specific to the recording of adverse event information in Japan was removed with Amendment 8. See Section 10.6.8, Modification 8.

ffff: The bullet for Date of death was deleted in Amendment 3. See Section 10.3, Modification 2.

4.6.3 Assessment Periods - amended

Prior to a site's participation [and receipt of open label sorafenib (Nexavar)] in this Long Term Extension Program, Ethics Committee/IB and Regulatory approval must be received.

Only patients participating in a Bayer/Onyx clinical trial may be included in this Long Term Extension Program.

Upon receipt of the medication for the Long Term Extension Program, the patient should be scheduled for a final visit for their original study and the Case Report Form for the original study completed. At the same time, medication should be dispensed for the Long Term Extension Program and requested data transferred from the originating CRF to the CRF for the Long Term Extension Program.

Observations and Measurements

Once enrolled in this program, patients will be evaluated according to local routine practice or at least every 8 weeks (±7 days) for safety. Every other visit must be a mandatory on-site visit for examination and drug dispensing with the other visit being either in person or as a phone call. It is at the discretion of the investigator based on the patient's current condition and adverse event profile to determine if the visit will be performed on site or as a phone visit. Any scheduled phone visit is mandatory and it will be at the discretion of the investigator to decide if a phone visit is sufficient. If the patient needs a physical examination, the visit will be performed on site. If the investigator feels the patient is stable with no new safety concerns nor new AEs in between visits a phone call with labs, ECOG and review of AEs would be enough[gggg]All observations pertinent to the safety of the patient must be recorded in the patient's source documents. The following must be recorded in the CRF provided:

- Assessment of Adverse Events

[gggg] The visit window and safety follow-up have been modified by Amendment 7 to lessen the travel burden on patients. See Section 10.5.3, Modification 3.

- Treatment related event – all CTC grades
- Any CTC Grade 3 or 4 event (regardless of attribution)
- [hhhh]Any Serious Adverse Event (regardless of attribution)

- Study medication (date dispensed and returned, number of tablets dispensed and returned)
- Laboratory Assessments
  - Hematology (hemoglobin, hematocrit, RBC, WBC, platelets, differential)
  - Blood Chemistry (ALT, AST, amylase, lipase)
  - PT-INR (for patients receiving anticoagulation therapy)
- ***Other variables***[iiii]
  - ***ECOG performance status***
  - ***Survival status***

End of treatment

In addition to the above parameters, please record the following in the CRF and source documents:

- The reason for termination
- Date of last dose

hhhh: Language specific to the recording of adverse event information in Japan was added under Amendment 3. See Section 10.3, Modification 2. Language specific to the recording of adverse event information in Japan was removed with Amendment 8. See Section 10.6.8, Modification 8.
iiii: The bullet for other variables and the corresponding sub-bullets for ECOG performance status and survival were added in Amendment 3. See Section 10.3, Modification 1 and Modification 2.

- ***Survival status (dead or alive and date of death or date of last contact)***[jjjj]

Follow-up period

All subjects will be followed until 30 days after the last dose of study drug.[kkkk] [llll]

If a patient discontinues due to an adverse event or clinical laboratory abnormality, the patient should be followed until the event resolves, the patient stabilized, or 30 days, whichever is shorter. If a patient dies within 30 days of the last dose of study medication, the SAE complementary form should be completed and forwarded to Bayer Global Drug Safety.[mmmm]

4.7 Data Quality

Monitoring and auditing procedures defined/agreed by the sponsor will be followed, in order to comply with GCP guidelines. Each center will be visited by a monitor to ensure compliance with the study protocol, GCP and legal aspects. This will include on-site checking of the specific data recorded in the case report forms (CRF) for completeness and clarity, cross-checking with source documents, and clarification of administrative matters, and review of the clinical supplies.

4.8 Documentation

Entries made in the CRF must be either verifiable against source documents, or have been directly entered into the CRF, in which case the entry in the CRF will be considered as the source data. The source data parameter to be verified and the identification of the source document must be documented. The study file and all source data should be retained until notification given by the sponsor for destruction.

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jjjj: This bullet for survival status was added in Amendment 3. See Section 10.3, Modification 1.

kkkk: The text regarding assessment of survival in the follow-up period was added in Amendment 3. See Section 10.3, Modification 1.

[llll] This bullet for survival limiting was added in Amendment 7. See Section 10.5.5 Modification 5.

mmmm: Section 4.6.4, Drug Concentration Measurements, was deleted in Amendment 3. See Section 10.3, Modification 6.

4.9 End of Study

According to Directive EU 2001/20/EC the end of the trial will be notified to the competent authorities of the member states concerned based on the following definition. For the member states involved, the end of trial will be reached when the last visit of the last patient for all centers in the territory of this member state has occurred. This can be reached based on the last patient stopping study medication or being switched to any other form of study drug supply. In the event that any other mechanism of drug supply is established, the present study will end when all patients have transitioned or discontinued from this study for another reason (e.g. consent withdrawal, lost to follow-up, death, sponsor decision). Until the transition, patients will continue to follow all the procedures and visits required in the current version of the protocol.[nnnn] As soon as the end of trial according to this definition has been reached in all participating centers within and outside the community has occurred, the complete end of trial will be reached.

5. Ethical and legal aspects

5.1 Ethics Committee (EC) or Institutional Review Board (IRB)

Documented approval from appropriate Ethics Committee(s)/IRBs will be obtained for all participating centers/countries prior to study start, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the Ethics Committee approval must be obtained and also forwarded to the Sponsor. The Ethics Committees[oooo] must supply to the Sponsor, upon request, a list of the Ethics Committee members involved in the vote and a statement to confirm that the Ethics Committee is organized and operates according to GCP and applicable laws and regulations.

[nnnn] Added clarification on the definition of the end of study with Amendment 8. See Section 10.6.7, Modification 7.
oooo: Additional text was added in Amendment 3 to include the head of the center for sites in Japan. See Section 10.3, Modification 3. Text to include the head of the center for study sites in Japan removed with Amendment 8. See Section 10.6.8, Modification 8.

5.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigator abide by Good Clinical Practice Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the Sponsor representatives and/or Regulatory Authority representatives at any time. The Investigator must agree to the inspection of study-related records by the Regulatory Authority/Sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/Sponsor representatives.

The study site will be monitored by Bayer Representatives to verify the timely and accurate reporting of treatment related Serious Adverse Events, dispensing of Clinical Supplies to appropriate patients and accurate maintenance of CRF as well as Study and Regulatory Documents.

Modifications to the study protocol will not be implemented by either the Sponsor or the Investigator without agreement by both parties. However, the Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior EC/IRB/Sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the EC/IRB/Sponsor. Any deviations from the protocol must be fully explained and documented by the Investigator.

Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/notifications, where required, must be in place and fully documented prior to study start.

5.3 Subject Information and Consent

A core information and Informed Consent Form will be provided. Prior to the beginning of the study, the Investigator must have the ECs/IRB written approval/favorable opinion of the written Informed Consent Form and any other written information to be provided to subjects. The written approval of the EC/IRB together with the approved subject information/Informed Consent Forms must be filed in the study files.

Written informed consent must be obtained before any study specific procedure takes place in this program. To ensure continuing administration of medication, patients will be consented and registered for this program while still participating in their original trial (see Section 4.6.3).

Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files.

5.4 Insurance

All subjects participating in the study will have insurance coverage by the Sponsor, which is in line with applicable laws and/or regulations.

5.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject number will be recorded on any study related documents or forms, and if the subject name appears on any other document (eg, pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the Sponsor, EC/IRB, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The Investigator will maintain a list to enable subjects' records to be identified.

6. Statistical methods and determination of sample size

6.1 Statistical and Analytical Plans- amended

After the end of the study[pppp], ***descriptive analyses***[qqqq] of demography, adverse events (including serious), laboratory data, and reasons for termination of treatment[rrrr] ***ssss*** will be provided in the form of a written report.[tttt] [uuuu]

6.2 Determination of Sample Size

Not applicable

7. Adverse events

7.1 Warnings/Precautions

As outlined in the Investigator Brochure and Safety Sections of the Product Labeling.

7.2 Adverse Event Monitoring

Subjects must be carefully monitored for adverse events. This monitoring also includes specified clinical laboratory tests. Adverse events should be assessed in terms of their seriousness, severity

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pppp: The timepoint was corrected with Amendment 8. See Section 10.6.9, Modification 9.
qqqq: Text regarding the presentation of data was modified under Amendment 3. See Section 10.3, Modification 6.
rrrr: Duration of treatment and overall survival were added in Amendment 3. See Section 10.3, Modification 1 and Modification 6.
ssss Statistical and Analytical Plans were modified by Amendment 7 to remove overall survival (OS). See Section 10.5.2, Modification 2.
tttt: Date of enrollment will be used for cases in which the originating trial was not randomized.
uuuu: Information regarding the analysis of survival data was added in Amendment 3. See Section 10.3, Modification 1.

and relationship to study medication. ***Adequate medical care will be provided to the subjects for any adverse events, and the events will be followed up until resolution or stabilization***.[vvvv]

7.3 Adverse Event Definitions

7.3.1 Adverse Event

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The adverse event does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

Adverse events associated with the use of a drug in humans, whether or not considered drug related, include the following:

- An adverse event occurring in the course of the use of a drug product in professional practice.
- An adverse event occurring from an overdose whether accidental or intentional.
- An adverse event occurring from drug abuse.
- An adverse event occurring from drug withdrawal.
- An adverse event where there is a reasonable possibility that the event occurred purely as a result of the subject's participation in the study (eg, adverse event or serious adverse event due to discontinuation of anti-hypertensive drugs during wash-out phase) must also be reported as an adverse event even if it is not related to the investigational product.

vvvv: Sentence regarding the follow-up of adverse events was added in Amendment 3. See Section 10.3, Modification 4.

The clinical manifestation of any failure of expected pharmacological action is not recorded as an adverse event if it is already reflected as a data point captured in the CRF. If, however, the event fulfills any of the criteria for a "serious" adverse event, it must be recorded and reported as such.

If progressive disease leads to signs and symptoms that meet the "serious" criteria (ie, hospitalization, disability, death or an important medical event), the signs and symptoms should be reported as an SAE and not the underlying cause (ie, progressive disease).

7.3.2 Serious Adverse Event

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event.

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an adverse event in which the patient was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours [wwww]

  OR

wwww: The exception regarding Japan was added in Amendment 3. See Section 10.3, Modification 4. The exception regarding Japan was removed with Amendment 8. See Section 10.6.8, Modification 8.

- The admission is pre-planned (ie, elective or scheduled surgery arranged prior to the start of the study).

  OR

- The admission is not associated with an adverse event (eg, social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfil the criteria of 'medically important' and as such may be reportable as a serious adverse event dependant on clinical judgement. In addition where local Regulatory authorities specifically require a more stringent definition, the local regulation takes precedent

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Important medical event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the "WHO Adverse Reaction Terminology – Critical Terms List". These terms either refer to or might be indicative of a serious disease state.

Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

7.3.3 Unexpected Adverse Event

An unexpected adverse event is any adverse drug event, the specificity or severity of which is not consistent with the current Investigator Brochure (or Package Insert for marketed products). Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. ***The expectedness of AEs will***

be determined by the Sponsor according to the applicable reference document and according to all local regulations.[xxxx]

7.3.4 Relationship of Adverse Event to Investigational Product

The assessment of the relationship of an adverse event to the administration of study drug is a clinical decision based on all available information at the time of the completion of the case report form.

An assessment of 'No' would include:

- The existence of a clear alternative explanation, eg, mechanical bleeding at surgical site.

  OR

- Non-Plausibility, eg, the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of 'Yes' indicates that there is a reasonable suspicion that the adverse event is associated with the use of the investigational drug.

xxxx: The sentence regarding expectedness of AEs was added in Amendment 3. See Section 10.3, Modification 4.

Factors to be considered in assessing the relationship of the adverse event to study drug include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subjects response after drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- Known response pattern for this class of drug:
- The pharmacology and pharmacokinetics of the test drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual subject's pharmacodynamics should be considered.

7.3.5 Severity of the Serious Adverse Event

The following classification should be used:

The intensity or severity of serious adverse events should be documented using the National Cancer Institute-Common Terminology Criteria, Version 3.0 (NCI-CTC v. 3.0).

Treatment related Serious adverse events (SAEs), as assessed by the investigator, including laboratory test abnormalities fulfilling the definition of serious, after signing the informed consent

and during follow-up period must immediately (within 24 hours of the investigator's awareness) be reported to the person detailed in the study file. A serious adverse event Form must also be completed within 24 hours of the investigator awareness and forwarded to the designated person as detailed in the study file. Each serious adverse event must be followed up until resolution or stabilization by submission of updated reports to the designated person.

7.3.6 Adverse Event Documentation

All treatment related adverse events or adverse events NCI-CTCAE Version 3.0 Grade 3 or higher (regardless of attribution) occurring after the subject has signed the informed consent must be fully recorded in the subject's case record form.

[yyyy]Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, eg, causing the subject to withdraw from the study, requirement treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

7.4 Reporting of Serious Adverse Events/Pregnancy

Serious adverse events (SAEs), including laboratory test abnormalities fulfilling the definition of serious, after signing the informed consent and during the follow-up period must immediately (within 24 hours of the investigator's awareness) be reported to the person detailed in the study file. A serious adverse event form must also be completed within 24 hours of the investigator's awareness and forwarded to the designated person as detailed in the study file. Each serious adverse event must be followed up until resolution or stabilization by submission of updated reports to the designated person. An isolated laboratory abnormality that is assigned Grade 4, according to CTC definition, is not reportable as an SAE, unless the investigator assesses that the

yyyy: Language specific to the recording of adverse event information in Japan was added under Amendment 3. See Section 10.3, Modification 2. Language specific to the recording of adverse event information in Japan was removed under Amendment 8. See Section 10.6.8, Modification 8.

event meets standard ICH criteria for an SAE. CTC Grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria. If an investigator is in doubt about the applicable reporting obligations, he/she should consult with the study monitor for the Sponsor.

CTC Grade 4 lab abnormalities will be documented in the lab data and will be reviewed on a regular basis.

When required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to Bayer within the same timelines as a serious adverse event on a Pregnancy Monitoring Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse.

8. Use of data and publication

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, whilst free to utilize the data derived from the study for scientific purposes, must discuss any publication with the sponsor prior to release and obtain written consent of the sponsor on the intended publication. The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to the sponsor thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between the

sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties.

9. References

Investigator's brochure BAY 43-9006/Raf Kinase Inhibitor, Safety Section of the Product Information leaflet

10. Protocol amendments

The original study protocol was dated 05 July 2007 and a local protocol amendment (Amendment 1) was instituted in Germany on 07 February 2008. The changes made to the protocol under Amendment 1 are described in Section 10.1. However, as Amendment 1 was a local amendment only, the changes applicable to Germany are not incorporated into the body of this integrated protocol.

A global amendment (Amendment 2) was instituted in February 2011. The changes made to the protocol under Amendment 2 are described in Section 10.2 and are incorporated into the body of this integrated protocol.

Another global amendment (Amendment 3) was instituted in March 2012. The changes made to the protocol under Amendment 3 are described in Section 10.3 and are incorporated into the body of this integrated protocol.

A further global amendment (Amendment 4) was instituted in March 2014. The changes made to the protocol under Amendment 4 are described in Section 10.4 and are incorporated into the body of this integrated protocol.

In addition, a local protocol amendment (Amendment 5) was instituted in China on 19 JAN 2016. The reason for Amendment 5 was the following: A statement was added to allow patients in China who reached End of Treatment in their originating Bayer/Onyx sponsored study, but who continued to receive sorafenib funded by a Bayer-sponsored program, to enter the STEP trial at

any time. This change was made so that these patients may continue to receive sorafenib and be monitored for safety through the STEP trial.

A further local protocol amendment (Amendment 6) was instituted in Taiwan on 25 JUL 2017. The global protocol amendments are described below. The reason for Amendment 6 was the following: The rationale for this amendment is the transfer of ongoing Taiwanese patients from SEARCH (sorafenib + erlotinib in HCC) into the STEP trial. The amendment allows for combination therapy with erlotinib and sorafenib for subjects in the STEP trial.

A global amendment (Amendment 7) was instituted on 15 MAY 2018. The changes made to the protocol under Amendment 7 are described in Section 10.5 and are incorporated into the body of this integrated protocol.

A global amendment (Amendment 8) was instituted on 26 MAY 2020. The changes made to the protocol under Amendment 8 are described in Section 10.6 and are incorporated into the body of this integrated protocol.

The changes for all global amendments are described below.

10.1 Amendment 1

10.1.1 Overview of Changes

Modification 1: Inclusion and Exclusion Criteria

The inclusion criterion regarding the use of contraception by men and women of childbearing age was clarified to state that the investigator should advise the patient regarding what form of contraception he/she feels is most appropriate for the patient.

The exclusion criterion regarding the concomitant use of potent inhibitors of CYP 3A4 was clarified to state that the consumption of grapefruit should also be avoided during treatment with study drug.

The protocol sections affected by these changes are Section 4.2.1, Inclusion Criteria, and Section 4.2.2, Exclusion Criteria.

Modification 2: Prior and Concomitant Therapy

The paragraph describing the proactive monitoring of patients using concomitant narrow therapeutic index medications that are hepatically metabolized (liver P450 system) was modified to include INR (International Normalized Ratio) measurements for warfarin and phenprocoumon as part of the recommended monitoring.

The statement providing examples of concomitant medications with narrow therapeutic indices was modified to add phenprocoumon to the list of medications.

The protocol section affected by these changes is Section 4.5.8, Prior and Concomitant Therapy.

10.1.2 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the protocol version preceding this amendment (ie, protocol version 5.2). Deletions are ~~crossed out~~ in the "old text" and additions are underlined in the "new text" (ie, Amendment 1/Version 1.0).

Section 4.2.1, Inclusion Criteria

Old text:

Women of childbearing potential and men must agree to use adequate contraception prior to study entry and for the duration of study participation, including the 30 days period after last study drug dosing. The investigator should advise the patient how to achieve an adequate contraception.

New text:

Women of childbearing potential and men must agree to use adequate contraception prior to study entry and for the duration of study participation, including the 30 days period after last study drug dosing. The investigator should advise the patient how to achieve an adequate contraception with methods he feels to be most appropriate for the patient.

Section 4.2.2 Exclusion Criteria

Old text:

Concomitant use of potent inhibitors of CYP 3A4 including ketoconazole, itraconazole and ritronavir. Consumption of grapefruit juice should also be avoided.

New text:

Concomitant use of potent inhibitors of CYP 3A4 including ketoconazole, itraconazole and ritronavir. Consumption of grapefruits and grapefruit juice should also be avoided.

Section 4.5.8 Prior and Concomitant Therapy

Old text:

Patients taking concomitant medications, known to be metabolized by the liver, should be closely observed for side effects. Patients taking narrow therapeutic index medications that are hepatically metabolized (liver P450 system) should be monitored proactively for serum/ plasma levels of warfarin, phenytoin, quinidine, carbamazepine and phenobarbital.

In general, patients should be closely monitored for side effects of all concomitant medications regardless of path of elimination, especially those with narrow therapeutic indices, such a digoxin, warfarin, quinidine, phenytoin, phenobarbitol, carbemazepam and cyclosporine.

New text:

Patients taking concomitant medications, known to be metabolized by the liver, should be closely observed for side effects. Patients taking narrow therapeutic index medications that are hepatically metabolized (liver P450 system) should be monitored proactively with INR (International Normalized Ratio) measurements for warfarin and phenprocoumon; and for serum/ plasma levels for phenytoin, quinidine, carbamazepine and phenobarbital.

In general, patients should be closely monitored for side effects of all concomitant medications regardless of path of elimination, especially those with narrow therapeutic indices, such as digoxin, warfarin, phenprocoumon, quinidine, phenytoin, phenobarbitol, carbamazepine and cyclosporine.

10.2 Amendment 2

10.2.1 Overview of Changes

Modification: Inclusion and Exclusion Criteria

An inclusion criterion was added to allow subjects who received combination treatment with sorafenib (Nexavar) and TACE (transarterial chemoembolization) in their originating study to be eligible for this extension study. The exclusion criterion regarding concurrent anti-cancer chemotherapy was, therefore, modified to clarify that the exclusion did not apply to subjects being treated with sorafenib in combination with TACE.

This change was made to allow subjects from the SPACE study to continue to receive sorafenib under this extension protocol. The SPACE study, a randomized, double-blind study of sorafenib vs placebo in patients with hepatic cellular carcinoma who are receiving TACE treatment, will be closed in the near future. Subjects from this study who are receiving sorafenib and continue to benefit from the therapy may now, under this amendment protocol be enrolled in the STEP program may continue to receive TACE along with sorafenib.

In addition, this single criterion covering concurrent anti-cancer chemotherapy, concurrent immunotherapy, and concurrent hormonal therapy was split into three distinct bullets. This change was made clarity and does not represent a change to study conduct.

The protocol sections affected by these changes are Section 4.2.1, Inclusion Criteria, and Section 4.2.2, Exclusion Criteria.

10.2.2 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of sections follows the structure of the original protocol. In the display of modifications, the “old text” refers to the protocol version preceding this amendment (ie, protocol version 5.2). Deletions are ~~crossed out~~ in the “old text” and additions are <u>underlined</u> in the “new text” (ie, Amendment 2/Version 6.0).

Section 4.2.1, Inclusion Criteria

Old text:

Patient is receiving sorafenib (Nexavar) as a monotherapy in their originating protocol. Patients who were being treated with sorafenib (Nexavar) in combination with other chemotherapies in the original study, but continued on single agent sorafenib (Nexavar) after discontinuation of the combination agent will be eligible.

New text:

Patient is receiving sorafenib (Nexavar) as a monotherapy in their originating protocol. Patients who were being treated with sorafenib (Nexavar) in combination with other chemotherapies in the original study, but continued on single agent sorafenib (Nexavar) after discontinuation of the combination agent will be eligible.

Patients who are receiving concurrent combination with sorafenib (Nexavar) and TACE **(transarterial chemoembolization)** in their originating study will be eligible.

Section 4.2.2, Exclusion Criteria

Old text:

Concurrent anti-cancer chemotherapy, immunotherapy (including monoclonal antibodies) or hormonal therapy, except for bisphosphonates, during or within 30 days prior to start of study drug

New text:

- Concurrent anti-cancer chemotherapy, except TACE (transarterial chemoembolization)
- Concurrent immunotherapy (including monoclonal antibodies), during or within 30 days prior to start of study drug

- Concurrent hormonal therapy, except for bisphosphonates, during or within 30 days prior to start of study drug

10.3 Amendment 3

10.3.1 Overview of Changes

Modification 1: Inclusion of an Evaluation of Overall Survival

It is now planned that data from the STEP trial will be transferred to the Integrated Sorafenib Database. Data from individual patients from their originating trial are already part of that database; therefore collecting survival status for this cohort is felt to be valuable for future descriptive data analysis and publication.

The protocol sections affected by this change are Section 2, Study Objectives; Section 4.1, Study Design and Plan; Section 4.6.1, Efficacy Variables; Section 4.6.3, Assessment Periods; Section 6.1, Statistical and Analytical Plans; and Section 11, Study Flow Chart

Modification 2: Evaluation of Safety

Publication of the safety results of the collected data from STEP is now planned. Therefore, including safety as a stated objective is needed. The main objective of this program remains unchanged.

The protocol section affected by this change is Section 2, Study Objectives,

The inclusion of an assessment of ECOG performance status was added to Section 4.1, Study Design and Plan, for consistency with the rest of the protocol. In addition, for consistency, ECOG performance status was added to Section 4.6.3, Assessment Periods under Safety Variables.

The CRF was has been modified to collect information on the ECOG performance status in the CRF as well as the subject's source documentation. Therefore, the ECOG performance status must now also be captured in the subject's CRF.

The protocol section affected by this change is Section 4.6.2, Safety Variables

Date of death was removed from the safety variables as survival status (including date of death when applicable) is collected elsewhere

The protocol section affected by this change is Section 4.6.2, Safety Variables.

Finally, in accordance with Japanese regulatory requirements for the recording of adverse event data, the protocol was modified to require the recording of ALL adverse events regardless of NCI-CTCAE grade and regardless of attribution for patients treated at study sites in Japan.

The protocol sections affected by this change are Section 4.6.2, Safety Variables, Section 4.6.3, Assessment Periods, and Section 7.3.6, Adverse Event Documentation.

Modification 3: Head of the Center for Sites in Japan

In accordance with local regulatory requirements, specific mention of the head of the center for sites in Japan has been added to Section 4.4, Premature Termination of Study/Closure of Centre and Section 5.1, Ethics Committee (EC) or Institutional Review Board (IRB).

Modification 4: Adverse Events

In accordance with local regulatory requirements in Japan, specific language has been added to Section 7.2, Adverse Event Monitoring and Section Section 7.3.3, Unexpected Adverse Event

In accordance with local Japanese regulatory requirements, Section 7.3.2, Serious Adverse Event, was modified to clarify that, in Japan, any adverse event leading to hospitalization or

prolongation of hospitalization is to be considered as serious regardless of the length of hospitalization or prolongation of hospitalization.

Modification 5: Inclusion of Subjects From the SEARCH Study (Study 12917) and the RESILIENCE Study (Study 12444)

The Sponsor has made the decision to allow patients from the SEARCH study, in which patients receive sorafenib in combination with erlotinib, or the RESILIENCE Study, in which patients receive sorafenib in combination with capecitabine, to receive continued treatment in the Sorafenib Long Term Extension Program (STEP). Therefore, all necessary information regarding the inclusion of these subjects into STEP has been included in the protocol under this amendment (Amendment 3).

The protocol sections affected by the inclusion of these subjects are Section 1, Introduction, Section 2, Study Objectives, Section 4.1, Study Design and Plan, Section 4.2.1, Inclusion Criteria, Section 4.2.2, Exclusion Criteria, Section 4.5.1, Treatments to be Administered, Section 4.5.2, Dose Modification, Section 4.5.3, Identity of Investigational Product(s), Section 4.5.5, Selection of Doses in the Study, Section 4.5.8, Prior and Concomitant Therapy, and Section 11, Study Flow Chart.

Modification 6: Minor Changes

Contact names for the Study Manager, Statistician, and Medical Expert were updated on the title page of the protocol.

The information in Section 2 regarding the conditions whereby patients may receive treatment under this protocol was modified slightly to clarify that, if switching to commercially available product, there should be no interruption in the patient's treatment schedule.

The text regarding presentation of data as "a summary" was modified in Section 6.1, Statistical and Analytical Plans, to clarify that descriptive analysis would be performed. Duration of treatment was added to list of variables for which such analyses would be prepared.

Patients receiving long-term sorafenib may be appropriate candidates for vaccination. However, there are no safety data available with live vaccines and, given the propensity for sorafenib to cause lymphopenia, it is felt that administering live vaccine to patients receiving sorafenib may represent a safety risk.

The protocol section affected by this change is Section 4.5.8, Prior and Concomitant Therapy.

An editorial change was made to delete Section 4.6.4, which is not applicable to this protocol.

In Section 4.5.2, Dose Modification, reference to "Hand-Foot syndrome" was change to "Hand-Foot Skin Reaction."

10.3.2 Changes to the Protocol Text

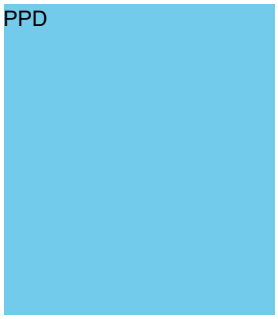
In this section, all affected protocol sections are detailed; the sequence of sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the protocol version preceding this amendment (ie, protocol version 6.0). Deletions are ~~crossed out~~ in the "old text" and additions are <u>underlined</u> in the "new text" (ie, Amendment 3/ Version 7).

Title Page

Old text:

PPD

New text:



Section 1, Introduction

Old text:

The only process to provide sorafenib to these patients who have a non-approved/reimbursed tumor type is through a clinical trial. The intention of this program is to enable these patients who are still benefiting from ~~sorafenib~~ in a completed clinical trial to continue to receive ~~sorafenib~~.

New text:

The only process to provide sorafenib to these patients who have a non-approved/reimbursed tumor type is through a clinical trial. The intention of this program is to enable these patients who are still benefiting from treatment in a completed clinical trial to continue to receive treatment.

Section 2, Study Objectives

Old text:

The primary purpose of program is to enable patients, currently receiving ~~single agent~~ sorafenib (Nexavar) in a Bayer/Onyx sponsored clinical trial, to continue sorafenib treatment after their respective study has met its primary endpoint and/or has reached the end as defined in the original protocol. Patients will be able to continue ~~sorafenib (Nexavar®)~~ treatment until the treating physician feels the patient is no longer benefiting from the treatment or ~~sorafenib~~

~~(Nexavar®)~~ becomes commercially available, and reimbursed for the respective indication as applicable in the country in which the patient lives.

New text:

The primary purpose of program is to enable patients, currently receiving sorafenib (Nexavar) in a Bayer/Onyx sponsored clinical trial, to continue sorafenib treatment after their respective study has met its primary endpoint and/or has reached the end as defined in the original protocol. Patients will be able to continue treatment until (i) the treating physician feels the patient is no longer benefiting from the treatment or (ii) the treatment becomes commercially available and reimbursed for the respective indication as applicable in the country in which the patient lives and the patient can obtain suitable amounts of drug for treatment through standard mechanisms of commercial availability (ie, there should be no interruption in the patient's treatment schedule when switching to commercially available product).

Additional objectives include assessment of the safety of Nexavar or Nexavar combination treatment and evaluation of overall survival (OS).

Section 4.1, Study Design and Plan

Old text:

This is an open label program that will enable patients receiving sorafenib (Nexavar) in a completed Bayer/Onyx sponsored clinical trial to continue ~~single agent sorafenib (Nexavar®)~~ treatment. A completed study is one….

The patients will continue receiving single agent sorafenib (Nexavar) at the same dose and schedule as in their original Clinical Trial.

Patients will continue receiving ~~single agent~~ sorafenib (Nexavar) as long as the treating physician feels the patient is continuing to benefit from treatment or until sorafenib becomes commercially

available and reimbursed for the respective indication in the country in which the patient lives. The patient may also continue ~~sorafenib~~ until he/she withdraws consent, is non-compliant, is lost to follow up, or if an unacceptable toxicity occurs.

Prior to being dispensed study medication …. Patients will continue with single agent sorafenib (Nexavar) in this program at the same dose and schedule the patient was receiving in their original clinical trial.

Sorafenib (Nexavar) will be provided as 200 mg tablets. The patient should be evaluated according to Good Medical Practices as well as local therapeutic and diagnostic standards……..Bimonthly safety evaluations include vital signs (ie, heart rate, blood pressure, temperature), ECOG performance status, laboratory evaluations (hematology, ALT, AST, lipase and amylase, PT-INR as applicable for anticoagulated patients) and a review of any new or ongoing adverse event or concomitant medications as well as study medication taken during the visit interval. All adverse event, ~~and~~ laboratory data as well as End of Treatment information and study medication taken must be clearly and accurately recorded in the Case Report Form provided. All other data, including but not limited to, vital signs, ~~ECOG performance status,~~ concomitant medications ~~and date of death~~ must be recorded in the patient's source documents and may be requested at the discretion of the Sponsor.

Following the End of Treatment assessments from the original study, the following information will be recorded in the long term extension CRF: demography, date of first dose of sorafenib (Nexavar) in originating study, originating study number, ECOG performance status and survival status (dead or alive and date of death or date of last contact) and ongoing adverse events…..

New text:

This is an open label program that will enable patients receiving sorafenib (Nexavar) in a completed Bayer/Onyx sponsored clinical trial to continue treatment. A completed study is one…..

The patients will continue receiving single agent sorafenib (Nexavar), sorafenib and erlotinib if transferred from study 12917 (SEARCH), or sorafenib and capecitabine if transferred from Study 12444 (RESILIENCE), at the same dose and schedule as in their original Clinical Trial.

Patients will continue receiving single agent sorafenib (Nexavar; as single agent or combination treatment) as long as the treating physician feels the patient is continuing to benefit from treatment or until sorafenib (as single agent or combination treatment) becomes commercially available and reimbursed for the respective indication in the country in which the patient lives. The patient may also continue treatment until he/she withdraws consent, is non-compliant, is lost to follow up, or if an unacceptable toxicity occurs.

Prior to being dispensed study medication ….. Patients will continue with single agent sorafenib (Nexavar), sorafenib and erlotinib if transferred from study 12917 (SEARCH), or sorafenib and capecitabine if transferred from Study 12444 (RESILIENCE), in this program at the same dose and schedule the patient was receiving in their original clinical trial.

Sorafenib (Nexavar) will be provided as 200 mg tablets. Erlotinib will be provided as 150 mg, 100 mg, and 25 mg tablets for patients receiving the sorafenib/erlotinib combination and transferring from Study 12917 (SEARCH). Capecitabine will be provided as 150 mg and 500 mg tablets for patients receiving the sorafenib/capecitabine combination and transferring from Study 12444 (RESILIENCE). The patient should be evaluated according to Good Medical Practices as well as local therapeutic and diagnostic standards……..Bimonthly safety evaluations include vital signs (ie, heart rate, blood pressure, temperature), Eastern Cooperative Oncology Group (ECOG) performance status, laboratory evaluations (hematology, ALT, AST, lipase and amylase, PT-INR as applicable for anticoagulated patients) and a review of any new or ongoing adverse event or concomitant medications as well as study medication taken during the visit interval. All adverse events, laboratory data, ECOG performance status and survival status (dead or alive and date of death or date of last contact), as well as End of Treatment information and study medication taken must be clearly and accurately recorded in the Case Report Form provided. All other data,

including but not limited to, vital signs, concomitant medications must be recorded in the patient's source documents and may be requested at the discretion of the Sponsor.

Following the End of Treatment assessments from the original study, the following information will be recorded in the long term extension CRF: demography, date of first dose of sorafenib (Nexavar) in originating study, date of first dose of erlotinib if the patient is transferred from SEARCH (study 12917), date of first dose of capecitabine if the patient is transferred from RESILIENCE (Study 12444), originating study number, ECOG performance status and survival status (dead or alive and date of death or date of last contact) and ongoing adverse events.

Section 4.2.1, Inclusion Criteria

Old text:

- Patients, who are participating in a previous Bayer/Onyx sponsored study that has reached its endpoint (statistical and regulatory or study end)……
- Patients who are receiving concurrent combination with sorafenib (Nexavar) and TACE (transarterial chemoembolization) in their originating study will be eligible.
- Patients who have completed the End of Treatment assessments in their originating study…...

New text:

- Patients, who are participating in a previous Bayer/Onyx sponsored study that has reached its endpoint (statistical and regulatory or study end)……
- Patients who are receiving concurrent combination with sorafenib (Nexavar) and TACE (transarterial chemoembolization) in their originating study will be eligible.
- Patients who are receiving concurrent combination with sorafenib (Nexavar) and erlotinib in their originating study 12917 (SEARCH) will be eligible.

- Patients who are receiving concurrent combination with sorafenib (Nexavar) and capecitabine in their originating study 12444 (RESILIENCE) will be eligible.

- Patients who have completed the End of Treatment assessments in their originating study…...

Section 4.2.2, Exclusion Criteria

Old text:

Excluded therapies and medications, previous and concomitant:

- Concurrent anti-cancer chemotherapy, except TACE (transarterial chemoembolization)…….

New text:

Excluded therapies and medications, previous and concomitant:

- Concurrent anti-cancer chemotherapy, except TACE (transarterial chemoembolization), erlotinib, and capecitabine

Section 4.4, Premature Termination of Study/Closure of Centre

Old text:

The Sponsor has the right to close this study, and the Investigator/Sponsor has the right to close a center, at any time, although this should occur only after consultation between involved parties. The EC/IRB must be informed.……..

New text:

The Sponsor has the right to close this study, and the Investigator/Sponsor has the right to close a center, at any time, although this should occur only after consultation between involved parties. The EC/IRB (or the head of the center for sites in Japan) must be informed.

Section 4.5.1, Treatments to be Administered

Old text:

~~The study drug~~ will be supplied as 200 mg tablets. Patients should continue on the same dose as they were receiving in the patient's originating Bayer/Onyx-sponsored Clinical Trial.

New text:

Sorafenib will be supplied as 200 mg tablets. Erlotinib will be supplied as 150 mg, 100, and 25 mg tablets and capecitabine will be provided as 150 mg and 500 mg tablets. Patients should continue on the same dose as they were receiving in the patient's originating Bayer/Onyx-sponsored Clinical Trial.

Section 4.5.2, Dose Modification

Old text:

If the starting dose is 600 mg bid the modifications of sorafenib (Nexavar) will follow the pre-defined dose levels:

Dose level 1 600 mg (3 x 200 mg) po q 12 hr…….

Only for the purpose of dose modifications, patients experiencing Hand-Foot ~~syndrome~~ should have their signs and symptoms graded according to the following system (see Table 4-3). Other skin toxicities will be graded according to CTCAE Version 3.0. Please note that Hand Foot ~~Syndrome~~ will be graded and recorded as an adverse event according to NCI-CTC Version 3.0 in the CRF.

Table 4-3: Grading for Hand-Foot ~~Syndrome~~

Grade 1	Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort, which does not disrupt normal activities……

New Text:

4.5.2.1 Sorafenib monotherapy

If the starting dose is 600 mg bid the modifications of sorafenib (Nexavar) will follow the pre-defined dose levels:

Dose level 1 600 mg (3 x 200 mg) po q 12 hr.....

Only for the purpose of dose modifications, patients experiencing Hand-Foot Skin Reaction should have their signs and symptoms graded according to the following system (see Table 4-3). Other skin toxicities will be graded according to CTCAE Version 3.0. Please note that Hand Foot Skin Reaction will be graded and recorded as an adverse event according to NCI-CTC Version 3.0 in the CRF.

Table 4-3: Grading for Hand-Foot Skin Reaction

Grade 1	Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort, which does not disrupt normal activities……

4.5.2.2 Sorafenib and erlotinib combination

Doses will be delayed or reduced for clinically significant hematologic and non-hematologic toxicities that are related to protocol therapy according to the guidelines shown in the Dose Delays/Dose Modifications table that follows. Dose modifications will follow predefined dose levels: Dose adjustments for hematologic toxicity are based on the blood counts obtained in preparation for the day of treatment.

Table 4-5: Dose Modification Levels for Sorafenib

Dose	Sorafenib
Starting Dose	400 mg twice daily
-1	400 mg once daily
-2	400 mg every other day

Table 4-6: Dose Modification Levels for Erlotinib

Dose	Erlotinib
Starting Dose	150 mg once a day
-1	100 mg once a day
-2	50 mg once a day

- Except for an event of hypertension, the first agent to dose reduce for the 1st episode of any toxicity will be erlotinib
- If a subject experiences more than one toxicity, dose reduction should be according to the toxicity with the highest grade
- In the case of two or more toxicities of the same grade, the investigator may dose reduce according to the toxicity deemed most causally related to study treatment
- Subjects for whom one agent is held may continue to receive the other agent if all the protocol-defined dose modification steps have been taken and, in the opinion of the treating investigator, the subject may continue to benefit from treatment
- Subjects with toxicities that are manageable with supportive therapy may not require dose reductions (eg, nausea/vomiting may be treated with antiemetics, diarrhea may be treated with loperamide rather than by dose reduction). A subject will be withdrawn from the study if he/she fails to recover from a treatment-related toxicity to CTCAE Grade 0-1, or tolerable

grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) within 30 days, unless the investigator and sponsor agree that the subject should remain in the study because the investigator believes the subject is/may derive benefit from continuing study treatment.

Table 4-7: Dose Modification Plan for Hematologic Toxicities

NCI CTC V3.0	**Dose Interruption**	**Dose Reduction**	
		Sorafenib	**Erlotinib**
Gr 1	Treat on time	No change in dose	No change in dose
Gr 2	No change		
Gr 3*	Treat on time Re-evaluate weekly	1st episode: no change in dose 2nd episode: reduce **sorafenib** to level -1 (400mg once daily) 3rd episode: no change to above modified dose 4th episode: reduce **sorafenib** to level -2 (400mg every other day)	1st episode: reduce **erlotinib** to level -1 (100mg once a day) 2nd episode: no change to above modified dose 3rd episode: reduce **erlotinib** to level -2 (50mg once a day) 4th episode: no change to above modified dose

Table 4-7: Dose Modification Plan for Hematologic Toxicities

NCI CTC V3.0	Dose Interruption	Dose Reduction	
		Sorafenib	**Erlotinib**
Gr 4*	Hold[a] both agents until <Gr 2 Re-evaluate weekly	1st episode: no change in dose upon continuation of treatment	1st episode: reduce **erlotinib** to level -1 (100mg once a day) upon continuation of treatment
		2nd episode: reduce **sorafenib** to level -1 (400mg once daily) upon continuation of treatment	2nd episode: no change to above modified dose upon continuation of treatment
		3rd episode: no change to above modified dose upon continuation of treatment	3rd episode: reduce **erlotinib** to level -2 (50mg once a day) upon continuation of treatment
		4th episode: reduce **sorafenib** to level -2 (400mg every other day) upon continuation of treatment	4th episode: no change to above modified dose upon continuation of treatment

[a]If no recovery after 30 day delay, treatment will be discontinued unless subject is deriving clinical benefit.

*Intervention/Supportive care regarding Gr 3 or 4 Heme toxicity as per investigator.

If more than 4 dose reductions are required, study treatment will be discontinued.

Table 4-8: Dose Modification Plan for non-Hematologic Toxicity except ILD, and Hypertension

NCI CTC V3.0	Dose Interruption	Dose Reduction	
		Sorafenib	**Erlotinib**
Gr 1	Treat on time	No change in dose	No change in dose
Gr 2	No change		
Gr 3*	Hold[a] **both agents** until <Gr 2 Initiate supportive care Re-evaluate weekly	1st episode: no change in dose upon continuation of treatment 2nd episode: reduce **sorafenib** to level -1 (400mg once daily) upon continuation of treatment 3rd episode: no change to above modified dose upon continuation of treatment 4th episode: reduce **sorafenib** to level -2 (400mg every other day) upon continuation of treatment	1st episode: reduce **erlotinib** to level -1 (100mg once a day) upon continuation of treatment 2nd episode: no change to above modified dose upon continuation of treatment 3rd episode: reduce **erlotinib** to level -2 (50mg once a day) upon continuation of treatment 4th episode: no change to above modified dose upon continuation of treatment
Gr 4*	REMOVE FROM STUDY		

[a] If no recovery after 30 day delay, treatment will be discontinued unless subject is deriving clinical benefit.

If more than 4 dose reductions, study treatment will be discontinued. Excludes alopecia, nausea/vomiting that has not been pre-medicated, and diarrhea not treated with supportive care/loperamide.

4.5.2.2.1 Anti-rash and Anti-diarrhea Therapies

Skin rash or dermatosis has been observed in many subjects during treatment with erlotinib. No clinical trials have formally evaluated treatments for rash induced by erlotinib, and there are currently no evidence-based recommendations for its management.

Subjects who develop a mild rash characterized by pustules or raised, red areas may be treated with topical therapy, such as corticosteroids. If the rash is more severe or there is indication of secondary infection, topical clindamycin or tetracycline, or oral minocycline may be used at the discretion of the investigator. (NOTE: minocycline is known to interfere with anticoagulants and oral contraceptives. Therefore, subjects treated with minocycline who are taking anticoagulants and/or oral contraceptives should be monitored accordingly). Guidance concerning modification of study drug dosing is provided in Table 4-8.

Because the pathology of such a rash is not related to acne pathology, retinoids and other acne medications, such as benzoyl peroxide, are not recommended, because these agents are more likely to exacerbate the rash due to their drying effects on the skin.

Anti-diarrhea medications may be introduced if symptoms occur. Previous trials have shown that the frequency and severity of diarrhea rarely hindered the administration of erlotinib and that the diarrhea could be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until the subject is diarrhea-free for 12 hours.

Table 4-9: Dose Modification Plan for Hypertension

Grade	Dose Interruption	Dose Reduction		Antihypertensive Therapy	Blood Pressure Monitoring	Hypertensive NCI CTCAE V3
		Sorafenib	Erlotinib			
Gr 1	Treat on time Initiate supportive care	No change in dose	No change in dose	None	Routine	Asymptomatic, transient, (<24hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated.
Gr 2	Treat on time Initiate supportive care	No change in dose	No change in dose	**(asymptomatic)** Initiate monotherapy (suggest dihydropyridine calcium-channel blocker). **(symptomatic /persistent)** **OR** **Diastolic BP > 110 mmHg** Add agent(s): • Ca++ channel blocker (if not already used) • K+ channel opener (angiotensin blockers), • Beta-blocker Thiazide diuretic	**(asymptomatic)** Increase frequency and monitor (by health professional) every 2 days until stabilized. **(symptomatic/ persistent)** **OR** **Diastolic BP > 110 mmHg** Increase frequency and monitor (by health professional) every 2 days until stabilized.	Recurrent or persistent (>24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to > 150/100 if previously WNL; monotherapy may be indicated.

Table 4-9: Dose Modification Plan for Hypertension

Grade	Dose Interruption	Dose Reduction		Antihypertensive Therapy	Blood Pressure Monitoring	Hypertensive NCI CTCAE V3
		Sorafenib	Erlotinib			
Gr 3	• Hold both agents until ≤ Gr 2 • Initiate supportive care Re-evaluate weekly	1st episode: reduce **sorafenib** to level –1 (400 mg once daily) upon continuation of treatment. 2nd episode: no change in dose upon continuation of treatment. 3rd episode: reduce **sorafenib** to level –2 (400 mg every other day) upon continuation of treatment. 4th episode: no change in dose upon continuation of treatment.	1st episode: no change in dose upon continuation of treatment. 2nd episode: reduce **erlotinib** to level –1 (100 mg once a day) upon continuation of treatment. 3rd episode: no change in dose upon continuation of treatment. 4th episode: reduce **erlotinib** to level –2 (50 mg once a day) upon continuation of treatment.	Add agent(s): • Ca++ channel blocker (if not already used) • K+ channel opener (angiotensin blockers) • Beta-blocker Thiazide diuretic	Increase frequency and monitor (by health professional) every 2 days until stabilized.	Requiring more than one drug or more intensive therapy than previously.
Gr 4	REMOVE FROM STUDY					Life-threatening consequences (e.g., hypertensive crisis)

4.5.2.2.2 Dose Modification for Hand-Foot Skin Reaction

Subjects experiencing Hand-Foot Skin Reaction should have their signs and symptoms graded according to the following system (see Table 4-10). Other skin toxicities will be graded according to CTCAE Version 3.0.

At first occurrence of hand foot skin reaction, independent of grade, **prompt institution** of supportive measures such as topical emollients, low potency steroids, or urea-containing cream should be administered.

Table 4-10: Grading for Hand-Foot Skin Reaction

Grade 1	Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort, which does not disrupt normal activities.
Grade 2	Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the subject's activities.
Grade 3	Moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the subject to be unable to work or perform activities of daily living.

Table 4-11: Dose Modification Plan for Hand Foot Skin Reaction

NCI CTC V3.0	Dose Interruption	Dose Reduction		HFSR NCI CTCAE V3.0
		Sorafenib	Erlotinib	
Gr 1	Treat on time	No change of dose	No change of dose	Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort, which does not disrupt normal activities.
Gr 2	No change			Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the subject's activities.
Gr 3	Hold[a] both agents until <Gr 2 Initiate supportive care Re-evaluate weekly	1st episode: no change in dose upon continuation of treatment. 2nd episode: reduce **sorafenib** to level -1 (400 mg once daily) upon continuation of treatment. 3rd episode: no change to above modified dose upon continuation of treatment. 4th episode: reduce **sorafenib** to level -2 (400 mg every other day) upon continuation of treatment.	1st episode: reduce **erlotinib** to level -1 (100 mg once a day) upon continuation of treatment. 2nd episode: no change to above modified dose upon continuation of treatment. 3rd episode: reduce **erlotinib** to level -2 (50 mg once a day) upon continuation of treatment. 4th episode: no change to above modified dose upon continuation of treatment.	Moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the subject to be unable to work or perform activities of daily living.
Gr 4	REMOVE FROM STUDY			

[a] If no recovery after 30 day delay, treatment will be discontinued unless subject is deriving clinical benefit.

4.5.2.2.3 Dose Modification for Keratitis

For all grades of suspected keratitis, the erlotinib dose should be held and supportive measures instituted. Subjects with dry eyes should be advised to use an ocular lubricant. Subjects who continue to wear contact lenses may have an increased risk of ocular AEs (eg, keratitis). Subjects may continue to wear contacts but should discuss this issue with their treating oncologist before entering the study. In addition, any elective ophthalmological surgery while the subject is taking study drug must first be discussed between the investigator and the Sponsor.

4.5.2.2.4 Dose Modification for Interstitial Lung Disease

For **all grades** of suspected interstitial lung disease (ILD), the erlotinib dose should be held and supportive measures instituted. If ILD is confirmed, erlotinib and sorafenib **must** be discontinued permanently. Acute dyspnea or cough may be signs of ILD. If a subject presents with acute dyspnea or cough, interruption of treatment with erlotinib may be considered, at the discretion of the treating physician, until resolution of symptoms or until ILD can be ruled out. If a subject presents with symptoms such as shortness of breath, dyspnea, cough, or fever, a chest X-ray or chest CT and, if needed, additional tests to evaluate pulmonary function, as clinically indicated, should be considered as part of the work up. If a diagnosis of ILD is confirmed, appropriate treatment measures according to best medical practice and local standards should be initiated.

4.5.2.3 Sorafenib and capecitabine combination

Doses of capecitabine or sorafenib/placebo may be reduced/interrupted in the setting of any AE that is:

- Not controlled by optimal supportive care, or

- Not tolerated due to symptomatology, disfigurement, or interference with normal daily activities, regardless of severity.

Dose modifications will be based on the worst grade of an AE or laboratory abnormality during a given cycle. If multiple AEs are observed, the dose modification should be based on the most severe (ie, worst grade) event.

Dose modifications should take into consideration AEs and dose modifications already occurred in study 12444 (RESILIENCE).

Treatment delays of sorafenib/placebo for up to 21 days are acceptable in order to allow for resolution of symptoms to NCI-CTCAE v3.0 Grade 1 or less. For subjects with NCI-CTCAE v3.0 Grade 2 or greater toxicities at baseline (screening), resolution of symptoms to baseline severity (ie, Grade 2 or greater) is acceptable.

Subjects requiring interruption of study treatment for more than 21 days will be discontinued from study treatment. These subjects will, however, be followed until death or overall completion of the trial, whichever comes first.

Subject requiring further dose reductions beyond 500 mg/m2 BID of capecitabine or 200 mg (1 tablet) twice daily every other day of sorafenib will be discontinued from study drug. In the event a subject meets the criteria to discontinue all study drugs (capecitabine plus sorafenib), the subject will be followed until death or overall completion of the trial, whichever comes first.

NOTE:

- Subjects for whom it is medically appropriate to stop capecitabine administration (eg, due to intolerance) must also discontinue sorafenib.

- Subjects for whom it is medically appropriate to stop sorafenib administration (eg, due to intolerance) may continue to receive capecitabine .

Capecitabine and sorafenib/placebo treatment interruptions are regarded as lost treatment days and missed doses should not be replaced; the planned treatment dosing schedule should be maintained in the event of a treatment interruption.

4.5.2.3.1 Dose-reduction levels

Dose-reduction levels of sorafenib and capecitabine for the management of AEs are outlined in Table 4-12 and Table 4-13, respectively.

Table 4-12: Predefined Dose Levels of Sorafenib

Study drug: Sorafenib	Dose Level 0	-1	-2	-3
Applicable if sorafenib was never escalated higher than 600 mg/d in study 12444	200 mg/1 tablet in the morning, 400 mg/2 tablets in the evening	200 mg/1 tablet twice daily	200 mg/1 tablet twice daily, every other day	—
Applicable if sorafenib was escalated to 800 mg/d following cycle 1 in study 12444	400 mg/2 tablets, twice daily	200 mg/1 tablet in the morning, 400 mg/2 tablets in the evening	200 mg/1 tablet twice daily	200 mg/1 tablet twice daily, every other day

Table 4-13: Predefined Dose Levels of Capecitabine

Study drug: Capecitabine	Dose Level 0	-1	-2	-3
Applicable if capecitabine dose was not escalated to 1,250 mg/m^2 BID daily in study 12444	1,000 mg/m^2 twice daily	750 mg/m^2 twice daily	500 mg/m^2 twice daily	—
Applicable if capecitabine was escalated to 1,250 mg/m^2 BID daily in study 12444	1,250 mg/m^2 twice daily	1,000 mg/m^2 twice daily	750 mg/m^2 twice daily	500 mg/m^2 twice daily

4.5.2.3.2 Dose modification for hematologic toxicities

In general, doses of sorafenib should not be reduced for hematologic events, except for Grade 4 hematologic toxicities. Any subject experiencing any of the following hematologic toxicities should have capecitabine therapy held until the toxicity has resolved to Grade 1 or less.

- Absolute neutrophil count < 1,000/mm3 (≥ Grade 3) for > 7 days and/or febrile neutropenia.
- Platelet count < 50,000/mm3 (≥ Grade 3).

At the re-start of capecitabine following these toxicities, the dose of capecitabine should be reduced by at least one level (see Table 4-7 and Table 4-8). Additional dose reductions may occur as needed in subsequent cycles. If a subject requires dose reduction below capecitabine 500 mg/m2 twice daily or sorafenib/placebo 200 mg twice daily, every other day, study drug must be permanently discontinued.

If the described hematologic toxicity persists for more than 21days, the subject should discontinue capecitabine treatment and, therefore, also sorafenib.

Dose modifications of capecitabine and sorafenib for hematologic toxicities are outlined in Table 4-14 and Table 4-15.

Granulocyte colony stimulating factor and erythropoietic growth factors should not be administered as prophylaxis may be used. The dose of capecitabine must be reduced by two dose levels with the first episode of febrile neutropenia.

Table 4-14: Dose Modifications for Hematologic Toxicities: Neutropenia and Anemia

Toxicity	ANC ($\times 10^9$/L)	Hemoglobin (g/dL)	Capecitabine	Sorafenib
Grade 1	≥ 1.5	< LLN – 10.0	No change	No change
Grade 2	≥ 1.0 to < 1.5	< 10.0 – 8.0	**No change**	No change
Grade 3[a]	≥ 0.5 to < 1.0	< 8.0	Delay drug until toxicity has resolved to Grade 2 or less, then reduce by one dose level	No change
Grade 4[a]	< 0.5	Life-threatening consequence; urgent intervention indicated	Delay drug until toxicity has resolved to Grade 2 or less, then reduce by two dose levels	Delay drug until toxicity has resolved to Grade 2 or less, then reduce by one dose level
Febrile Neutropenia	—	—	Delay drug until toxicity has resolved **(neutropenia to Grade 1 or less and fever resolved)**, then reduce by two dose levels	**Delay drug until toxicity has resolved (neutropenia resolved to Grade 1 or less and fever resolved), then reduce by one dose level**

ANC=Absolute neutrophil count

a: For an ANC of less than 1 x 10^9/L (≥ Grade 3) for > 7 days, drug should be held until toxicity has resolved to Grade 1 or less.

Table 4-15: Dose Modifications for Hematologic Toxicities: Thrombocytopenia

Toxicity	Platelets (x 10^9/L)	Capecitabine	Sorafenib
Grade 1	≥75	No change	No change
Grade 2	≥ 50 to < 75	First occurrence, delay drug until toxicity has resolved to Grade 1 or less, restart at same dose. On subsequent occurrences, delay drug until toxicity has resolved to Grade 1 or less, then reduce by one dose level.	No change
Grade 3	≥ 25 to < 50	Delay drug until toxicity has resolved to Grade 1 or less, then reduce by one dose level	No change
Grade 4	< 25	Delay drug until toxicity has resolved to Grade 1 or less, then reduce by two dose levels	Delay drug until toxicity has resolved to Grade 1 or less, then reduce by one dose level

4.5.2.3.3 Dose modification for non-hematologic toxicities

Dose modification for toxicities common to both sorafenib and capecitabine

Dermatologic toxicities (eg, HFSR, rash), gastrointestinal toxicities (eg, diarrhea), and fatigue are common to both sorafenib and capecitabine. Therefore, because it may not be possible to identify the causative agent should these events present in this trial, a pragmatic approach to dose adjustments has been taken to ensure subject safety.

Hand Foot Skin Reaction

Subjects experiencing HFSR should have their signs and symptoms graded according to Table 4-16.

Subjects with discomfort due to HFSR should be treated with topical emollients, low-potency topical steroids, or urea-containing creams.

Table 4-16: Grading for Hand-Foot Skin Reaction

	Grade 1	Grade 2	Grade 3
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (eg, erythema, edema, or hyperkeratosis) without pain	Skin changes (eg, peeling, blisters bleeding, edema, or hyperkeratosis) with pain; limiting instrumental activities of daily living (ADL)	Severe skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL
Further description / examples of skin changes	Numbness, dysesthesia/paresthesia, tingling, painless swelling, or erythema of the hands and/or feet	Painful erythema and swelling of the hands and/or feet	Moist desquamation, ulceration, blistering, or severe pain of the hands and/or feet
Effect on activities	Does not disrupt normal activities	Limiting instrumental activities of daily life (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money)	Limiting self-care activities of daily life (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications) and not bedridden

a: Palmar-plantar erythrodysesthesia syndrome is a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of hands or the soles of the feet.

The dose-modification schedule outlined below and in Table 4-17 should be followed as appropriate based on (i) the grade of the toxicity(ies), (ii) the incidences of skin toxicity (including rash and HFSR), gastrointestinal toxicity, and fatigue, and (iii) the cycle of treatment.

All dose modifications will follow the predefined dose levels presented in Table 4-12 and Table 4-13 (Section 4.5.2.3.1).

General guidelines for dose modification for toxicities common to both sorafenib and capecitabine

Grade 1:	If any dermatologic toxicities, gastrointestinal toxicities or fatigue occur at grade 1, maintain doses of capecitabine and sorafenib/placebo. No dose modification is required for any occurrence of Grade 1 fatigue, dermatologic toxicity or gastrointestinal toxicity. The investigator should use symptomatic treatment to alleviate the toxicity.
Grade 2 or Grade 3:	If dermatologic toxicities, gastrointestinal toxicities, or fatigue occur at Grade 2 or Grade 3, both drugs (ie, capecitabine and sorafenib) should be held until the toxicity resolves to Grade 1 or less. The algorithm in Table 4-10 should be followed for dose modifications when re-starting study treatment. This algorithm should also be used for each recurrence of these toxicities to determine which drug (ie, capecitabine or sorafenib) should be reduced. Actions to be taken at each occurrence are outlined below. At the first occurrence of Grade 2 or Grade 3 fatigue, dermatologic toxicity, and/or gastrointestinal toxicity, the dose of capecitabine should be reduced by one dose level when restarting

study treatment (see Table 4-6). Sorafenib should be restarted at the same dose as prior to the onset of the event(s).

At the second occurrence of Grade 2 or Grade 3 fatigue, dermatologic toxicity, and/or gastrointestinal toxicity, the dose of sorafenib/placebo should be reduced by one dose level when restarting study treatment (see Table 4-5). Capecitabine should be restarted at the same dose as prior to the onset of the event(s).

As a general rule, at any subsequent occurrence of Grade 2 or Grade 3 fatigue, dermatologic toxicity, and/or gastrointestinal toxicity, if the last dose modification was made for sorafenib/placebo, sorafenib/placebo should be restarted at the same dose as prior to the onset of the event(s), and the dose of capecitabine should be reduced by one dose level. If, on the other hand, the last dose modification was made for capecitabine, capecitabine should be restarted at the same dose as prior to the onset of the event(s), and the dose sorafenib/placebo should be reduce by one dose level.

Subjects who continue to experience toxicity and require a dose reduction below the lowest dose level of capecitabine (500 mg/m^2 twice daily) or

	sorafenib/ placebo (200 mg/1 placebo tablet twice daily every other day) must discontinue study drug.
Grade 4:	Grade 4 toxicities require both study drugs to be discontinued permanently.

Table 4-17: Recommended Dose Modifications for Fatigue, Dermatologic Toxicities and/or GI Toxicities

Grade 1
No interruption of study drugs or dose reductions of study drugs are required for Grade-1 adverse events.

Grade 2 or Grade 3 - FIRST occurrence including occurrences in study 12444				
If dose at onset of event is:		**Then:**	**When event resolves, resume treatment at:**	
Sorafenib	200 mg/1 tablet in the am and 400 mg/ 2 tablets in the pm **OR**[a] 400 mg/ 2 tablets twice daily	Hold both sorafenib and capecitabine until the AE has resolved to Grade 1 or less then resume treatment as directed.[b]	**Sorafenib** Same dose as prior to event	200 mg/1 tablet in the am and 400 mg/ 2 tablets in the pm OR[a] 400 mg/2 tablets twice daily
Capecitabine	1,000 mg/m^2 twice daily **OR**[a] 1,250 mg/m^2 twice daily		**Capecitabine** Reduce dose	750 mg/m^2 twice daily OR[a] 1,000 mg/m^2 twice daily

Grade 2 or Grade 3 - SECOND occurrence including occurrences in study 12444				
If dose at onset of event is:		**Then:**	**When event resolves, resume treatment at:**	
Sorafenib	200 mg/1 tablet in the am and 400 mg/ 2 tablets in the pm, daily **OR**[a] 400 mg/ 2 tablets twice daily	Hold both sorafenib and capecitabine until the AE has resolved to Grade 1 or less then resume treatment as directed.[b]	**Sorafenib** Reduce dose	200 mg/1 tablet twice daily OR[a] 200 mg/1 tablet in the am and 400 mg/ 2 tablets in the pm, daily
Capecitabine	750 mg/m^2 twice daily **OR**[a] 1,000 mg/m^2 twice daily		**Capecitabine** Same dose as prior to event	750 mg/m^2 twice daily OR[a] 1,000 mg/m^2 twice daily

a: The dose at which study drug is resumed is based on the dose being administered at the onset of the AE and must follow the predefined dose levels as specified in Table 4-12 (sorafenib) and Table 4-13(capecitabine).
b: Interruption in administration of either study drug for more than 21 days requires permanent discontinuation of that study drug.

Table 6-10: Recommended Dose Modifications for Fatigue, Dermatologic Toxicities and/or GI Toxicities (continued)

Grade 2 or Grade 3 – THIRD and all SUBSEQUENT occurrences including occurrences in 12444					
If dose at onset of event is:			**Then:**	**When event resolves, resume treatment at:**	
	Sorafenib	200 mg/ 1 tablet twice daily **OR[a]** 200 mg/ 1 tablet in the am and 400 mg/ 2 tablets in the pm, daily	Hold both sorafenib and capecitabine until the AE has resolved to Grade 1 or less then resume treatment as directed.[b]	**Sorafenib** Same dose as prior to event	200 mg/ 1 tablet twice daily OR[a] 200 mg/ 1 tablet in the am and 400 mg/ 2 tablets in the pm, daily
	Capecitabine	750 mg/m^2 twice daily **OR[a]** 1,000 mg/m^2 twice daily		**Capecitabine** Reduce dose	500 mg/m2 twice daily OR[a] 750 mg/m2 twice daily
	Sorafenib	200 mg/ 1 tablet twice daily **OR[a]** 200 mg/ 1 tablet in the am and 400 mg/ 2 tablets in the pm, daily	Hold both sorafenib and capecitabine until the AE has resolved to Grade 1 or less then resume treatment as directed.[b]	**Sorafenib** Reduce dose	200 mg/ 1 tablet twice daily, every other day OR[a] 200 mg/ 1 tablet twice daily
	Capecitabine	500 mg/m^2 twice daily **OR[a]** 750 mg/m^2 twice daily		**Capecitabine** Same dose as prior to event	500 mg/m2 twice daily OR[a] 750 mg/m2 twice daily
	Sorafenib	200 mg/ 1 tablet twice daily	Hold both sorafenib and capecitabine until the AE has resolved to Grade 1 or less then resume treatment as	**Sorafenib** Same dose as prior to event	200 mg/ 1 tablet twice daily
	Capecitabine	750 mg/m^2 twice daily		**Capecitabine** Reduce dose	500 mg/m2 twice daily

			directed.[b]		
	Sorafenib	200 mg/ 1 tablet twice daily, every other day	Hold both sorafenib and capecitabine until the AE has resolved to Grade 1 or less then resume treatment as directed.[b]	**Sorafenib** Same dose as prior to event	200 mg/ 1 tablet twice daily, every other day
	Capecitabine	750 mg/m^2 twice daily		**Capecitabine** Reduce dose	500 mg/m2 twice daily

a: The dose at which study drug is resumed is based on the dose being administered at the onset of the AE and must follow the predefined dose levels as specified in Table 4-12 (sorafenib) and Table 4-13 (capecitabine).

b: Interruption in administration of either study drug for more than 21 days requires permanent discontinuation of that study drug.

Table 6-10: Recommended Dose Modifications for Fatigue, Dermatologic Toxicities and/or GI Toxicities (continued)

	Sorafenib	200 mg/ 1 tablet twice daily, every other day	Discontinue both drugs permanently	=
	Capecitabine	500 mg/m^2 twice daily		
	Grade 4 toxicities require both study drugs to be discontinued permanently.			

4.5.2.3.4 Dose modification and management of sorafenib-specific toxicities

Sorafenib dose modifications or delays will not impact capecitabine therapy. Subjects who require a delay or dose modification of sorafenib/placebo should continue to receive capecitabine as scheduled.

Dose modification and management of sorafenib-specific toxicities should follow Section 4.5.2.1 (Sorafenib monotherapy)

4.5.2.3.5 Dose modification and management of capecitabine-specific toxicities

If the following toxicities occur, they will be deemed to be primarily related to capecitabine. Such toxicities, therefore, warrant specific dose modifications for capecitabine only as described here and in Table 4-18.

Subjects who require a delay or dose modification of capecitabine should continue to receive sorafenib as scheduled.

1) Stomatitis (Grade 2 or higher)

If Grade 2 or 3 stomatitis occurs, administration of capecitabine should be immediately interrupted until the event resolves to Grade 1 or less. The subject should be treated symptomatically. Subsequent doses of capecitabine should be administered in accordance with the algorithm in Table 4-18.

2) Cardiac toxicity

Subjects with cardiac toxicity greater than Grade 2, which is attributable to capecitabine, will be permanently discontinued from capecitabine therapy and withdrawn from study treatment.

3) Dihydropyrimidine dehydrogenase deficiency

If a subject develops clinical manifestations consistent with suspected DHPD deficiency, including Grade 3 or 4 neutropenia, mucositis, diarrhea, and/or encephalopathy, within the first or second cycle of study treatment, the subject should be tested for DHPD levels or genetic polymorphisms if such testing is locally available. If DHPD deficiency is confirmed, the subject should be permanently discontinued from capecitabine and withdrawn from the trial. If such testing is not available and DHPD deficiency is suspected, the subject should be permanently discontinued from capecitabine and withdrawn from study treatment.

Table 4-18: Dose Modification for Stomatitis Associated With Capecitabine

	Grade 2	Grade 3	Grade 4
First occurrence	Interrupt treatment until resolved to Grade 0-1, then continue at same dose with prophylaxis where possible.	Interrupt treatment until resolved to Grade 0-1, then continue at 75% of the original dose.	Discontinue permanently.
Second occurrence	Interrupt treatment until resolved to Grade 0-1, then continue at 75% of the original dose.	Interrupt treatment until resolved to Grade 0-1, then continue at 50% of the original dose.	—
Third occurrence	Interrupt treatment until resolved to Grade 0-1, then continue at 50% of the original dose.	Discontinue permanently.	—
Fourth occurrence	Discontinue permanently.	—	—

Note: For Grade-1 toxicity, maintain current dose of capecitabine. No dose interruption or modification is required.

Occurrences should include events in study 12444

4.5.2.3.6 Dose modification for other non-hematologic toxicities (excluding fatigue, dermatologic toxicities, gastrointestinal toxicities, hypertension and toxicities attributable to capecitabine)

For other non-hematologic toxicities (excluding fatigue, dermatologic toxicities, gastrointestinal toxicities, hypertension and toxicities attributable to capecitabine), dose modifications are to be handled as outlined in Table 4-19. For the toxicities alopecia, altered taste, and nail changes, which are considered unlikely to become serious or life threatening, treatment can be continued at the same dose without reduction or interruption.

Table 4-19: Dose Modification for Other Non-Hematologic Toxicities (Excluding Fatigue, Dermatologic Toxicities, Gastrointestinal Toxicities, Hypertension and Toxicities Attributable to Capecitabine)

Toxicity Grade	Occurrence	Sorafenib		Capecitabine	
		Dose Interruption	Dose Reduction	Dose Interruption	Dose Reduction
Grade 1	Any	None	None	None	None
Grade 2	First	None	None	Delay until resolved to Grade 1 or less	Resume at full dose
	Subsequent	None	None	Delay until resolved to Grade 1 or less	Reduce dose by one dose level[a,b]
Grade 3	Any	Delay until resolved to Grade 1 or less	Reduce dose by one dose level[a,b]	Delay until resolved to Grade 1 or less	Reduce dose by one dose level[a,b]
Grade 4	Any	Discontinue study drug	—	Discontinue study drug	—

a: If recovery is not achieved after 21 days of interruption, study drug should be discontinued.

b: Subjects who continue to experience toxicity and require a dose reduction below the lowest dose level of capecitabine (500 mg/m^2 twice daily) or sorafenib/placebo (200 mg/1 placebo tablet twice daily, every other day) must discontinue study drug.

Occurrences should include events in study 12444

Section 4.5.3, Identity of Investigational Product(s)

Old text:

Section 4.5.3 Identity of Investigational Product(s)

BAY 43-9006 will be packed by the Sponsor and will be labeled according to the requirements of local law and legislation.…….

New text:

Section 4.5.3 Identity of Investigational Product(s)

4.5.3.1 Sorafenib

BAY 43-9006 will be packed by the Sponsor and will be labeled according to the requirements of local law and legislation.…….

4.5.3.2 Erlotinib

Erlotinib tablets are manufactured by Schwartz Pharma Manufacturing, Inc. for OSI Pharmaceuticals, Inc.

The tablet formulation consists of erlotinib and the excipients lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and titanium dioxide. The 25 mg, 100 mg, and 150 mg strengths are supplied as round white, film-coated, bi-convex tablets with no imprint. The active compound of erlotinib is N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-4-quinazolinamine and its molecular weight is 429.90 Daltons.

Supply, packaging, labeling and storage

The erlotinib tablets will be supplied in high-density, polyethylene bottles of 30 tablets each. The bottles will have a tamper-evident seal and a child-resistant cap. Each bottle of erlotinib will have a 1-panel standard label or booklet label affixed. For the 100 mg and 150 mg erlotinib doses, two bottles will be further packaged into a subject pack with a 2-panel standard label or booklet label affixed. For the 50 mg erlotinib dose, four bottles of erlotinib 25 mg tablets will be further packaged into a subject pack with a 2-panel standard label or booklet label affixed. One panel of the label will be permanently attached to the subject pack while the other portion will be a tear-off section that will be appended to the dispensing documentation. This label will contain the study ID, sponsor ID, contents, directions for use, storage requirements, batch, and investigational use statement as well as spaces to record the subject number and date dispensed. The label will also include any other text as required by local law and legislation. Each subject pack label will also have a unique pack number. The labels on the bottles within the pack will have the same pack number. The labels will not contain any unblinding information. Erlotinib must be stored at room temperature and not above 25°C (77°F).

Once the study medication has been received, it must be stored in a dry, secure location (ie, locked cabinet) accessible only to authorized staff.

The study drug must be used exclusively for the investigation specified in this protocol. The investigative site must acknowledge receipt of drug supplies. Generally, acknowledgement for this study will be done using the IVRS/IWRS system. The confirmation of receipt sent by the IVRS/IWRS system must be printed and filed appropriately in the investigative site file. Occasionally, the IVRS/IWRS may not be available. The site will be instructed on using the Dispatch Order Form for acknowledgment in that situation. The CRA will instruct the site on how to sign the Dispatch Order Form and return it to the shipping unit.

Only the investigator or a person(s) assigned will be allowed to dispense the study medications to the subject. To have complete control over the distribution and use of study

drugs, drug accountability must be performed at every subject visit. Empty bottles/blisters must be returned to the investigator along with all unused medication. Drug accountability will be performed throughout the study. Destruction of all unused material (ie, empty bottles, unused tablets, etc) must be documented and performed per standard operating procedures. One copy of the destruction certificate must be kept in the investigator's file and the other copy must be sent to the Bayer representative.

4.5.3.3 Capecitabine

The chemical name for capecitabine is 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine and its molecular weight is 359.35 daltons. Capecitabine is available in 150-mg and 500-mg, film-coated tablets and is supplied as biconvex, oblong tablets. The 150-mg tablet is light peach in color and the 500-mg tablet is peach colored. Each tablet contains the following inactive ingredients: anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate and purified water. The film coating contains hydroxylpropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

Sponsor-supplied capecitabine 150-mg and 500-mg tablets will be supplied in child-resistant blister packs (wallets) of 20 tablets each. Each blister pack of capecitabine will have a 2-panel standard label or booklet label affixed. One portion of the label will be permanently attached to the subject pack while the other portion will be a tear-off section that will be appended to the dispensing documentation. This label will contain the trial ID, sponsor ID, contents, directions for use, storage requirements, batch, and investigational use statement as well as spaces to record the subject number and date dispensed. The label will also include any other text as required by local law and legislation. The capecitabine must be stored in its original, immediate package at a temperature not above 30°C (86°F).

Alternatively, capecitabine may be supplied locally according to institutional procedures or may be supplied by the sponsor to the site in locally available commercial packaging labeled for the study.

Section 4.5.5, Selection of Doses in the Study

Old text:

Patients will receive sorafenib (Nexavar) 200 mg tablets and should continue receiving the same dose they were receiving in their original trial

New text:

Patients will receive sorafenib (Nexavar) 200 mg tablets and should continue receiving the same dose they were receiving in their original trial. Patients receiving sorafenib/erlotinib or sorafenib/capecitabine combination should continue the same doses as in the originating trial.

Section 4.5.6, Selection and Timing of Dose for each Subject

Old text:

Sorafenib (Nexavar) may be decreased in the event of toxicity based on the Dose Modification criteria outlined in Section 4.5.2.[vvv]

New text:

Sorafenib (Nexavar), erlotinib, and capecitabine may be decreased in the event of toxicity based on the Dose Modification criteria outlined in Section 4.5.2.[vvv]

Section 4.5.8, Prior and Concomitant Therapy

Old text:

Non-permissible concomitant medication/therapies:

- Anticancer chemotherapy, immunotherapy or vaccines during the study.

New text:

Non-permissible concomitant medication/therapies:

- Anticancer chemotherapy, except erlotinib and capecitabine, immunotherapy or live vaccines during the study.

Section 4.6.1, Efficacy Variables

Old text:

~~Not applicable~~

New text:

Overall Survival (OS)

Section 4.6.2, Safety Variables

Old text:

~~**Primary objective**~~

All observations pertinent to the safety of the study medication will be recorded in the patient's source documents and available at the request of the sponsor.

The following data must be reported in the source documents:

~~• ECOG performance status~~

- Vital signs (heart rate, blood pressure, temperature)

- ……

In addition to the above parameters, the following data must be recorded in the CRF provided and the source documents:

- All treatment related adverse events (any grade)
- All adverse events NCI-CTCAE Version 3.0 Grade 3 or higher (regardless of attribution).
- All Serious Adverse Events, regardless of relationship to study drug
- Laboratory parameters ……..
- Reason for termination of study medication
- ~~Date of death, as applicable~~

New text:

All observations pertinent to the safety of the study medication will be recorded in the patient's source documents and available at the request of the sponsor.

The following data must be reported in the source documents:

- Vital signs (heart rate, blood pressure, temperature)
- ……

In addition to the above parameters, the following data must be recorded in the CRF provided and the source documents:

- All treatment related adverse events (any grade)
- All adverse events NCI-CTCAE Version 3.0 Grade 3 or higher (regardless of attribution). **Study Sites in Japan:** In accordance with Japanese regulatory requirements ALL adverse events regardless of NCI-CTCAE grade and regardless of attribution are to be recorded.

- All Serious Adverse Events, regardless of relationship to study drug
- ECOG performance status
- Laboratory parameters ……
- Reason for termination of study medication

Section 4.6.3, Assessment Periods

Old text:

Observations and Measurements

Once enrolled in this program……

- Assessment of Adverse Events
  - Treatment related event – all CTC grades
  - Any CTC Grade 3 or 4 event (regardless of attribution)
  - Any Serious Adverse Event (regardless of attribution)
- Study medication (date dispensed and returned, number of tablets dispensed and returned)
- Laboratory Assessments ……

End of treatment

In addition to the above parameters, please record the following in the CRF and source documents:

- The reason for termination
- Date of last dose
- ~~Date of death, if applicable~~

Follow up period

If a patient discontinues due to an adverse event or clinical laboratory abnormality, the patient should be followed until the event resolves, the patient stabilized, or 30 days, whichever is shorter……..

New text:

Observations and Measurements

Once enrolled in this program……

- Assessment of Adverse Events
  - Treatment related event – all CTC grades
  - Any CTC Grade 3 or 4 event (regardless of attribution)

    Study Sites in Japan: In accordance with Japanese regulatory requirements ALL adverse events regardless of NCI-CTCAE grade and regardless of attribution are to be recorded.
  - Any Serious Adverse Event (regardless of attribution)
- Study medication (date dispensed and returned, number of tablets dispensed and returned)
- Laboratory Assessments ……
- Other variables
  - ECOG performance status
  - Survival status

End of treatment

In addition to the above parameters, please record the following in the CRF and source documents:

- The reason for termination
- Date of last dose
- Survival status (dead or alive and date of death or date of last contact)

Follow up period

All subjects will be followed for survival. Assessment of survival status will be performed approximately every 3 months in the follow-up period.

If a patient discontinues due to an adverse event or clinical laboratory abnormality, the patient should be followed until the event resolves, the patient stabilized, or 30 days, whichever is shorter……..

Section 4.6.4, Drug Concentration Measurements

Old text:

~~**Section 4.6.4, Drug Concentration Measurements**~~

~~Not applicable~~

New text:

There is no new text; this section was deleted

Section 5.1, Ethics Committee (EC) or Institutional Review Board (IRB)

Old text:

…….. When necessary, an extension, amendment or renewal of the Ethics Committee approval must be obtained and also forwarded to the Sponsor. The Ethics Committees supply to the Sponsor, upon request, a list of the Ethics Committee members involved in the vote and a statement to confirm that the Ethics Committee is organized and operates according to GCP and applicable laws and regulations.

New text:

…… When necessary, an extension, amendment or renewal of the Ethics Committee approval must be obtained and also forwarded to the Sponsor. The Ethics Committees or the head of the center for sites in Japan must supply to the Sponsor, upon request, a list of the Ethics Committee members involved in the vote and a statement to confirm that the Ethics Committee is organized and operates according to GCP and applicable laws and regulations.

Section 6.1, Statistical and Analytical Plans

Old text:

At the time that the last patient last visit occurs, ~~a summary~~ of demography, adverse events (including serious), laboratory data ~~and~~ reasons for termination of treatment will be provided in the form of a written report. ~~Later on information on overall~~ survival ~~may~~ be ~~provided~~.

New text:

At the time that the last patient last visit occurs, descriptive analyses of demography, adverse events (including serious), laboratory data, reasons for termination of treatment, duration of treatment, and overall survival will be provided in the form of a written report.

Overall survival (OS) will be measured from the date of randomization/date of enrollment[gg] in the originating trial until the date of death due to any cause. If a subject is still alive at the

date of database cutoff, the subject will be censored at the date of the last contact (last time the subject was known to be alive). Subgroup analyses may be performed, if necessary.

gg: Date of enrollment will be used for cases in which the originating trial was not randomized.

Section 7.2, Adverse Event Monitoring

Old text:

….Adverse events should be assessed in terms of their seriousness, severity and relationship to study medication.

New text:

…… Adverse events should be assessed in terms of their seriousness, severity and relationship to study medication. Adequate medical care will be provided to the subjects for any adverse events, and the events will be followed up until resolution or stabilization.

Section 7.3.2, Serious Adverse Event

Old text:

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours

OR……

New text:

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours (because of local regulatory requirements, this exception is not applicable to Japan).

OR……

Section 7.3.3, Unexpected Adverse Event

Old text:

……Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events.

New text:

…… Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. The expectedness of AEs will be determined by the Sponsor according to the applicable reference document and according to all local regulations.

Section 7.3.6, Adverse Event Documentation

Old text:

All treatment related adverse events or adverse events NCI-CTCAE Version 3.0 Grade 3 or higher (regardless of attribution) occurring after the subject has signed the informed consent must be fully recorded in the subject's case record form.

Documentation must be supported by an entry in the subject's file…….

New text:

All treatment related adverse events or adverse events NCI-CTCAE Version 3.0 Grade 3 or higher (regardless of attribution) occurring after the subject has signed the informed consent must be fully recorded in the subject's case record form.

Study Sites in Japan: In accordance with Japanese regulatory requirements ALL adverse events regardless of NCI-CTCAE grade and regardless of attribution are to be recorded.

Documentation must be supported by an entry in the subject's file……..

Section 11, Appendices

Old text:

Activity	Visit 1	Minimum Every 8 weeks	End of Treatment
Demography [a, b] …….	X		
ECOG performance	X	X	X
Adverse events [a] ……	…	…	…
Laboratory evaluations [a] ……..	…	…	…
Dispense/return sorafenib [a]	X	X	X
Reason for termination of treatment [a]			X
~~Date of death, as applicable~~ [a]			~~X~~
Concomitant medications	X	X	X

a Record these data in the CRF and source documents.
b Includes ……..
c For anticoagulated patients only

New text:

Activity	Visit 1	Minimum Every 8 weeks	End of Treatment
Demography [a, b] …….	X		
ECOG performance [a]	X	X	X
Survival status (dead or alive, date of death or		X	X[d]

date of last contact, as applicable)			
Adverse events [a] ……	…	…	…
Laboratory evaluations [a] ……	…	…	…
Dispense/return sorafenib (and erlotinib or capecitabine if applicable)[a]	X	X	X
Reason for termination of treatment [a]			X
Concomitant medications	X	X	X

a Record these data in the CRF and source documents.
b Includes ……..
c For anticoagulated patients only
d For patients in long term follow up, survival status is assessed at a minimum of every 3 months

10.4 Amendment 4

10.4.1 Overview of Changes

Modification 1 Change of responsibility for the Study Manager and Medical Expert.

Contact names for the Study Manager and Medical Expert were updated on the title page of the protocol. A line was also added for the signature of the Global Clinical Lead.

The protocol section affected by this change is the title page.

Modification 2 Removal of all references to erlotinib.

All references to erlotinib were removed since none of the subjects that transferred into this study were assigned to erlotinib+sorafenib in study 12917 (SEARCH). Where entire sections were removed, this also changed the section numbering in subsequent sections and tables.

The protocol sections affected by this change are Section 4.1 Study design and Plan, Section 4.2.1 Inclusion Criteria, Section 4.2.2 Exclusion Criteria, Section 4.5.1 Treatments to be Administered, Section 4.5.2.2 Sorafenib and erlotinib combination therapy, Section 4.5.2.2.1 Anti-rash and Anti-diarrhea Therapies, Section 4.5.2.2.2 Dose Modification for Hand-Foot Skin Reaction, Section 4.5.2.2.3 Dose Modification for Keratitis, Section 4.5.2.2.4 Dose Modification for Interstitial Lung Disease, Section 4.5.3.2 Erlotinib, Section 4.5.5 Selection of Doses in the Study, Section 4.5.6 Selection and Timing of Dose for Each Subject and Section 4.5.8 Prior and Concomitant Therapy.

Modification 3 Clarification regarding the supply of capecitabine for subjects from Study 12444 changing from clinical supply by the sponsor to commercial supply.

The protocol current language suggest that for those subjects who will be transferred from the RESILIENCE study (12444) and taking a combination of capecitabine and sorafenib, both sorafenib and capecitabine will be provided by the sponsor. However, capecitabine is

commercially approved for breast cancer and readily available in many countries including generic sources, the study team proposes to modify the protocol to reflect that capecitabine will NOT be provided by the sponsor but should be sourced from commercial sources for those subjects who are on combination treatment. Only sorafenib will be provided by the sponsor.

The protocol sections affected by this change are Section 4.1 Study design and Plan, Section 4.5.1 and Treatments to be Administered and Section 4.5.3.3 Capecitabine.

Modification 4 Removal of references to placebo in association with sorafenib administration in Study 12444 (RESILIENCE).

In Study 12444 (RESILIENCE), subjects received either capecitabine and sorafenib or capecitabine and placebo. In this protocol, the text as written can be misinterpreted to indicate that subjects from Study 12444 received both sorafenib and placebo and none of the subjects received sorafenib and placebo in Study 12444. This modification removes the word placebo when referring to subjects in Study 12444 who received sorafenib.

The protocol sections affected by this change are Section 4.5.2.2 Sorafenib and capecitabine combination, Section 4.5.2.2.2 Dose modification for hematologic toxicities, Section 4.5.2.2.3 Dose modification for non-hematologic toxicities, Section 4.5.2.2.4 Dose modification and management of sorafenib-specific toxicities and Section 4.5.2.2.6 Dose modification for other non-hematologic toxicities (excluding fatigue, dermatologic toxicities, gastrointestinal toxicities, hypertension and toxicities attributable to capecitabine).

Modification 5 Addition of TACE to the permissible anticancer chemotherapies in Section 4.5.8 Prior and Concomitant Therapy and addition of guidance on Sorafenib dose modification in combination with TACE in Section 4.5.2.3.

One of the changes implemented during Amendment 2 (16 Mar 2011) was to modify the exclusion criteria to allow patients who were receiving TACE and sorafenib in a Bayer

sponsored study to participate in the STEP study. This is reflected in protocol Section 4.2.2 (Exclusion criteria) and in Section 10.2.2 that describes the changes and rationale for the amendment. However, Section 4.5.8(Prior and Concomitant Therapy) was not modified to allow the concomitant use of TACE and sorafenib and is not in line with the intent of Amendment 2 and the related text in Section 4.2.2.

The lack of changing Section 4.5.8to be in line with the other sections of the protocol was an unintentional oversight. The study team issued an administrative letter on 11 Dec 2013 to clarify that since the implementation of Amendment 2, concomitant TACE and sorafenib is permissible as *per the protocol (*Section 4.2.2 and 10.2.2). This discrepancy in Section 4.5.8 is now being corrected in this amendment to reflect that TACE is permissible.

Meanwhile, the guidance on Sorafenib dose modification in combination with TACE is added as the Section 4.5.2.3.

The protocol section affected by this change are Section 4.5.2.3 Sorafenib and TACE combination and Section 4.5.8 Prior and Concomitant Therapy (Non-permissible concomitant medication/therapies).

Modification 6 Clarification of which CTC version was used for the grading of liver function abnormalities.

Since there are differences between CTC versions in the definitions of severity grades for liver function test abnormalities, it was decided to specify the version of CTC used as a reference for the grading.

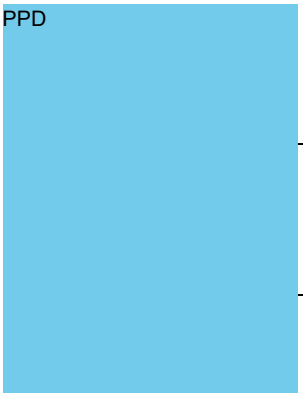
The protocol section affected by this change is Section 4.5.2.3 Sorafenib, Table 4-13 and Table 4-14.

10.4.2 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the protocol version preceding this amendment (ie, protocol version 7.0). Some section numbers and table numbers changed from those in the preceding protocol due to the removal of some section detailed in this section. Deletions are ~~crossed out~~ in the "old text" and additions are underlined in the "new text" (ie, Amendment 4/ Version 8.0).

Title Page

Old text:

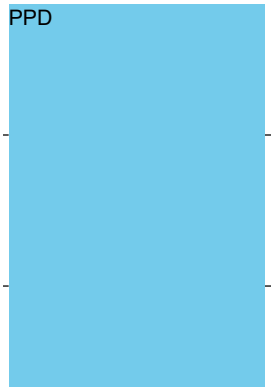


Date

Date

Date

New Text:



Date

Date

Date

Section 4.1, Study Design and Plan

Old text:

The patients ***in this open-label program*** will continue receiving single-agent sorafenib (Nexavar)~~, sorafenib and erlotinib ***combination*** if transferred from study 12917 (SEARCH),~~ or sorafenib and capecitabine ***combination*** if transferred from Study 12444 (RESILIENCE) at the same dose and schedule as in their original Clinical Trial.

Prior to being dispensed study medication for this long term extension program, patients will be required to complete their End of Treatment visit in their originating study. Once the End of Treatment visit in the originating study is complete, patients will be required to provide informed consent for this long term extension program. Patients will continue with single agent sorafenib (Nexavar)~~, ***if transferred from Study 12917 (SEARCH), or sorafenib and capecitabine if transferred from Study 12444 (RESILIENCE)***~~ in this program at the same dose and schedule the patient was receiving in their original clinical trial.

Sorafenib (Nexavar) will be provided as 200 mg tablets. ~~***Erlotinib will be provided as 150 mg, 100 mg, and 25 mg tablets for patients receiving the sorafenib/erlotinib combination and transferring from Study 12917 (SEARCH).***~~ ***Capecitabine will be*** ~~***provided***~~ ***as 150 mg and*** **500mg** ***tablets for patients receiving the sorafenib/capecitabine combination and transferring from Study 12444 (RESILIENCE)***.

New text:

The patients ***in this open-label program*** will continue receiving single-agent sorafenib (Nexavar) or sorafenib and capecitabine ***combination*** if transferred from Study 12444 (RESILIENCE) at the same dose and schedule as in their original Clinical Trial.

Prior to being dispensed study medication for this long term extension program, patients will be required to complete their End of Treatment visit in their originating study. Once the End of Treatment visit in the originating study is complete, patients will be required to provide informed consent for this long term extension program. Patients will continue with single agent sorafenib (Nexavar) ***or sorafenib and capecitabine if transferred from Study 12444 (RESILIENCE)*** in this program at the same dose and schedule the patient was receiving in their original clinical trial.

Sorafenib (Nexavar) will be provided as 200 mg tablets. ***Capecitabine is available in many countries including generic sources and will be commercially supplied as 150 mg and* 500mg *tablets for patients receiving the sorafenib/capecitabine combination and transferring from Study 12444 (RESILIENCE)***.

Section 4.2.1, Inclusion Criteria

Old text:

- ~~***Patients who are receiving concurrent combination with sorafenib (Nexavar) and erlotinib in their originating Study 12917 (SEARCH) will be eligible.***~~

New text:

None

Section 4.2.2, Exclusion Criteria

Old text:

Excluded therapies and medications, previous and concomitant

- Concurrent anti-cancer chemotherapy, except TACE (transarterial chemoembolization)~~,~~ ~~***erlotinib***~~,~~ and capecitabine

New text:

Excluded therapies and medications, previous and concomitant

- Concurrent anti-cancer chemotherapy, except TACE (transarterial chemoembolization) and capecitabine

Section 4.5.1, Treatments to be Administered

Old text:

Sorafenib **will be supplied as 200 mg tablets.** ~~***Erlotinib will be supplied as 150 mg, 100, and 25 mg tablets, and capecitabine will be provided as 150 mg and 500 mg tablet***~~**s.** Patients should continue on the same dose as they were receiving in the patient's originating Bayer/Onyx-sponsored Clinical Trial.

New text:

Sorafenib **will be supplied as 200 mg tablets. Patients should continue on the same dose as they were receiving in the patient's originating Bayer/Onyx-sponsored Clinical Trial.**

Section 4.5.2.2, Sorafenib and erlotinib combination therapy

Old text:

~~**4.5.2.2 Sorafenib and erlotinib combination therapy**~~

~~***Doses will be delayed or reduced for clinically significant hematologic and non-hematologic toxicities that are related to protocol therapy according to the guidelines shown in Table 4-5andTable 4-6. Dose modifications will follow predefined dose levels. Dose adjustments for hematologic toxicity are based on the blood counts obtained in preparation for the day of treatment.***~~

~~***Table 4-5: Dose Modification Levels for Sorafenib***~~

~~***Dose***~~	~~***Sorafenib***~~
~~***Starting Dose***~~	~~***400 mg twice daily***~~
~~***-1***~~	~~***400 mg once daily***~~
~~***-2***~~	~~***400 mg every other day***~~

~~***Table 4-6: Dose Modification Levels for Erlotinib***~~

~~***Dose***~~	~~***Erlotinib***~~
~~***Starting Dose***~~	~~***150 mg once a day***~~
~~***-1***~~	~~***100 mg once a day***~~
~~***-2***~~	~~***50 mg once a day***~~

- ~~***Except for an event of hypertension, the first agent to dose reduce for the 1st episode of any toxicity will be erlotinib***~~

- ~~*If a subject experiences more than one toxicity, dose reduction should be according to the toxicity with the highest grade*~~

- ~~*In the case of two or more toxicities of the same grade, the investigator may dose reduce according to the toxicity deemed most causally related to study treatment*~~

- ~~*Subjects for whom one agent is held may continue to receive the other agent if all the protocol-defined dose modification steps have been taken and, in the opinion of the treating investigator, the subject may continue to benefit from treatment*~~

- ~~*Subjects with toxicities that are manageable with supportive therapy may not require dose reductions (eg, nausea/vomiting may be treated with antiemetics; diarrhea may be treated with loperamide rather than by dose reduction). A subject will be withdrawn from the study if he/she fails to recover from a treatment-related toxicity to CTCAE Grade 0-1, or tolerable grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) within 30 days, unless the investigator and sponsor agree that the subject should remain in the study because the investigator believes the subject is/may derive benefit from continuing study treatment.*~~

~~*Table 4-7: Dose Modification Plan for Hematologic Toxicities*~~

~~*NCI CTC V3.0*~~	~~*Dose Interruption*~~	~~*Dose Reduction*~~	
		~~*Sorafenib*~~	~~*Erlotinib*~~
~~*Gr 1*~~	~~*Treat on time*~~	~~*No change in dose*~~	~~*No change in dose*~~
~~*Gr 2*~~	~~*No change*~~		
~~*Gr 3**~~	~~*Treat on time*~~ ~~*Re-evaluate weekly*~~	~~*1st episode: no change in dose*~~ ~~*2nd episode: reduce sorafenib to level -1 (400 mg once daily)*~~ ~~*3rd episode: no change to*~~	~~*1st episode: reduce erlotinib to level -1 (100 mg once a day)*~~ ~~*2nd episode: no change to above modified dose*~~ ~~*3rd episode: reduce*~~

~~*Table 4-7: Dose Modification Plan for Hematologic Toxicities*~~

~~*NCI CTC V3.0*~~	~~*Dose Interruption*~~	~~*Dose Reduction*~~	
		~~*Sorafenib*~~	~~*Erlotinib*~~
		~~*above modified dose*~~ ~~*4th episode: reduce sorafenib to level -2 (400 mg every other day)*~~	~~*erlotinib to level -2 (50 mg once a day)*~~ ~~*4th episode: no change to above modified dose*~~
~~*Gr 4**~~	~~*Hold[a] both agents until <Gr 2*~~ ~~*Re-evaluate weekly*~~	~~*1st episode: no change in dose upon continuation of treatment*~~ ~~*2nd episode: reduce sorafenib to level -1 (400 mg once daily) upon continuation of treatment*~~ ~~*3rd episode: no change to above modified dose upon continuation of treatment*~~ ~~*4th episode: reduce sorafenib to level -2 (400 mg every other day) upon continuation of treatment*~~	~~*1st episode: reduce erlotinib to level -1 (100 mg once a day) upon continuation of treatment*~~ ~~*2nd episode: no change to above modified dose upon continuation of treatment*~~ ~~*3rd episode: reduce erlotinib to level -2 (50 mg once a day) upon continuation of treatment*~~ ~~*4th episode: no change to above modified dose upon continuation of treatment*~~

~~[a]*If no recovery after 30 day delay, treatment will be discontinued unless subject is deriving clinical benefit.*~~
~~**Intervention/Supportive care regarding Gr 3 or 4 Heme toxicity as per investigator. If more than 4 dose reductions are required, study treatment will be discontinued.*~~

~~*Table 4-8: Dose Modification Plan for non-Hematologic Toxicity except ILD, and Hypertension*~~

~~*NCI CTC V3.0*~~	~~*Dose Interruption*~~	~~*Dose Reduction*~~	
		~~*Sorafenib*~~	~~*Erlotinib*~~
~~*Gr 1*~~	~~*Treat on time*~~	~~*No change in dose*~~	~~*No change in dose*~~
~~*Gr 2*~~	~~*No change*~~		
~~*Gr 3**~~	~~*Hold[a] both agents until <Gr 2*~~	~~*1st episode: no change in dose upon continuation of*~~	~~*1st episode: reduce erlotinib to level -1*~~

~~*Table 4-8: Dose Modification Plan for non-Hematologic Toxicity except ILD, and Hypertension*~~

~~*NCI CTC V3.0*~~	~~*Dose Interruption*~~	~~*Dose Reduction*~~	
		~~*Sorafenib*~~	~~*Erlotinib*~~
	~~*Initiate supportive care*~~ ~~*Re-evaluate weekly*~~	~~*treatment*~~ ~~*2nd episode: reduce sorafenib to level -1 (400 mg once daily) upon continuation of treatment*~~ ~~*3rd episode: no change to above modified dose upon continuation of treatment*~~ ~~*4th episode: reduce sorafenib to level -2 (400 mg every other day) upon continuation of treatment*~~	~~*(100 mg once a day) upon continuation of treatment*~~ ~~*2nd episode: no change to above modified dose upon continuation of treatment*~~ ~~*3rd episode: reduce erlotinib to level -2 (50 mg once a day) upon continuation of treatment*~~ ~~*4th episode: no change to above modified dose upon continuation of treatment*~~
~~*Gr 4**~~	~~*REMOVE FROM STUDY*~~		

~~*[a] If no recovery after 30 day delay, treatment will be discontinued unless subject is deriving clinical benefit.*~~

~~*If more than 4 dose reductions, study treatment will be discontinued. Excludes alopecia, nausea/vomiting that has not been pre-medicated, and diarrhea not treated with supportive care/loperamide.*~~

New text (change in section numbering):

Section 4.5.2.2 Sorafenib and capecitabine combination

Section 4.5.2.2.1, Anti-rash and Anti-diarrhea Therapies

Old text:

~~***4.5.2.2.1 Anti-rash and Anti-diarrhea Therapies***~~

~~*Skin rash or dermatosis has been observed in many subjects during treatment with erlotinib. No clinical trials have formally evaluated treatments for rash induced by erlotinib, and there are currently no evidence-based recommendations for its management.*~~

~~*Subjects who develop a mild rash characterized by pustules or raised, red areas may be treated with topical therapy, such as corticosteroids. If the rash is more severe or there is indication of secondary infection, topical clindamycin or tetracycline, or oral minocycline may be used at the discretion of the investigator. (NOTE: minocycline is known to interfere with anticoagulants and oral contraceptives. Therefore, subjects treated with minocycline who are taking anticoagulants and/or oral contraceptives should be monitored accordingly). Guidance concerning modification of study drug dosing is provided inTable 4-8.*~~

~~*Because the pathology of such a rash is not related to acne pathology, retinoids and other acne medications, such as benzoyl peroxide, are not recommended, because these agents are more likely to exacerbate the rash due to their drying effects on the skin.*~~

~~*Anti-diarrhea medications may be introduced if symptoms occur. Previous trials have shown that the frequency and severity of diarrhea rarely hindered the administration of erlotinib and that the diarrhea could be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until the subject is diarrhea-free for 12 hours.*~~

~~*Table 4-9: Dose Modification Plan for Hypertension*~~

~~*Grade*~~	~~*Dose Interruption*~~	~~*Dose Reduction*~~		~~*Antihypertensive Therapy*~~	~~*Blood Pressure Monitoring*~~	~~*Hypertensive NCI CTCAE V3*~~
		~~*Sorafenib*~~	~~*Erlotinib*~~			
~~*Gr 1*~~	~~*Treat on time Initiate supportive care*~~	~~*No change in dose*~~	~~*No change in dose*~~	~~*None*~~	~~*Routine*~~	~~*Asymptomatic, transient, (< 24hrs) increase by > 20 mm Hg (diastolic) or to > 150/100 if previously WNL; intervention not indicated.*~~
~~*Gr 2*~~	~~*Treat on time Initiate supportive care*~~	~~*No change in dose*~~	~~*No change in dose*~~	~~*(asymptomatic) Initiate monotherapy (suggest dihydropyridine calcium-channel blocker). (symptomatic /persistent) OR Diastolic BP > 110 mm Hg Add agent(s):*~~ ~~*• Ca++ channel blocker (if not already used)*~~ ~~*• K+ channel opener (angiotensin blockers),*~~ ~~*• Beta-blocker Thiazide diuretic*~~	~~*(asymptomatic) Increase frequency and monitor (by health professional) every 2 days until stabilized. (symptomatic/ persistent) OR Diastolic BP > 110 mm Hg Increase frequency and monitor (by health professional) every 2 days until stabilized.*~~	~~*Recurrent or persistent (> 24 hrs) or symptomatic increase by > 20 mm Hg (diastolic) or to > 150/100 if previously WNL; monotherapy may be indicated.*~~

~~*Table 4-9: Dose Modification Plan for Hypertension*~~

~~*Grade*~~	~~*Dose Interruption*~~	~~*Dose Reduction*~~		~~*Antihypertensive Therapy*~~	~~*Blood Pressure Monitoring*~~	~~*Hypertensive NCI CTCAE V3*~~
		~~*Sorafenib*~~	~~*Erlotinib*~~			
~~*Gr 3*~~	~~• Hold both agents until ≤ Gr 2~~ ~~• Initiate supportive care~~ ~~Re-evaluate weekly~~	~~*1st episode: reduce sorafenib to level –1 (400 mg once daily) upon continuation of treatment.*~~ ~~*2nd episode: no change in dose upon continuation of treatment.*~~ ~~*3rd episode: reduce sorafenib to level –2 (400 mg every other day) upon continuation of treatment.*~~ ~~*4th episode: no change in dose upon continuation of treatment.*~~	~~*1st episode: no change in dose upon continuation of treatment.*~~ ~~*2nd episode: reduce erlotinib to level –1 (100 mg once a day) upon continuation of treatment.*~~ ~~*3rd episode: no change in dose upon continuation of treatment.*~~ ~~*4th episode: reduce erlotinib to level –2 (50 mg once a day) upon continuation of treatment.*~~	~~*Add agent(s):*~~ ~~• Ca++ channel blocker (if not already used)~~ ~~• K+ channel opener (angiotensin blockers)~~ ~~• Beta-blocker Thiazide diuretic~~	~~*Increase frequency and monitor (by health professional) every 2 days until stabilized.*~~	~~*Requiring more than one drug or more intensive therapy than previously.*~~
~~*Gr 4*~~	~~*REMOVE FROM STUDY*~~					~~*Life-threatening consequences (eg, hypertensive crisis)*~~

New text (change in section numbering):

Section 4.5.2.2.1 Dose-reduction levels

Section 4.5.2.2.2, Dose Modification for Hand-Foot Skin Reaction

Old text:

~~***4.5.2.2.2 Dose Modification for Hand-Foot Skin Reaction***~~

~~***Subjects experiencing Hand-Foot Skin Reaction should have their signs and symptoms graded according to the following system (seeTable 4-10). Other skin toxicities will be graded according to CTCAE Version 3.0.***~~

~~***At first occurrence of hand foot skin reaction, independent of grade, prompt institution of supportive measures such as topical emollients, low potency steroids, or urea-containing cream should be administered.***~~

~~***Table 4-10: Grading for Hand-Foot Skin Reaction***~~

~~***Grade 1***~~	~~***Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort, which does not disrupt normal activities.***~~
~~***Grade 2***~~	~~***Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the subject's activities.***~~
~~***Grade 3***~~	~~***Moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the subject to be unable to work or perform activities of daily living.***~~

Table 4-11: Dose Modification Plan for Hand Foot Skin Reaction

NCI CTC V3.0	***Dose Interruption***	***Dose Reduction***		***HFSR NCI CTCAE V3.0***
		Sorafenib	***Erlotinib***	
Gr 1	***Treat on time***	***No change of dose***	***No change of dose***	***Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort, which does not disrupt normal activities.***
Gr 2	***No change***			***Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the subject's activities.***
Gr 3	***Hold[a] both agents until ≤ Gr 2 Initiate supportive care Re-evaluate weekly***	***1st episode: no change in dose upon continuation of treatment.*** ***2nd episode: reduce sorafenib to level -1 (400 mg once daily) upon continuation of treatment.*** ***3rd episode: no change to above modified dose upon continuation of treatment.*** ***4th episode: reduce sorafenib to level -2 (400 mg every other day) upon continuation of treatment.***	***1st episode: reduce erlotinib to level -1 (100 mg once a day) upon continuation of treatment.*** ***2nd episode: no change to above modified dose upon continuation of treatment.*** ***3rd episode: reduce erlotinib to level -2 (50 mg once a day) upon continuation of treatment.*** ***4th episode: no change to above modified dose upon continuation of treatment.***	***Moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the subject to be unable to work or perform activities of daily living.***
Gr 4	***REMOVE FROM STUDY***			

[a] If no recovery after 30 day delay, treatment will be discontinued unless subject is deriving clinical benefit.

New text (change in section numbering):

Section 4.5.2.2.2 Dose modification for hematologic toxicities

Section 4.5.2.2.3, Dose Modification for Keratitis

Old text:

~~***4.5.2.2.3 Dose Modification for Keratitis***~~

~~***For all grades of suspected keratitis, the erlotinib dose should be held and supportive measures instituted. Subjects with dry eyes should be advised to use an ocular lubricant. Subjects who continue to wear contact lenses may have an increased risk of ocular AEs (eg, keratitis). Subjects may continue to wear contacts but should discuss this issue with their treating oncologist before entering the study. In addition, any elective ophthalmological surgery while the subject is taking study drug must first be discussed between the investigator and the Sponsor.***~~

New text (change in section numbering):

Section 4.5.2.2.3 Dose modification for non-hematologic toxicities

Section 4.5.2.2.4, Dose Modification for Interstitial Lung Disease

Old text:

~~***4.5.2.2.4 Dose Modification for Interstitial Lung Disease***~~

~~***For all grades of suspected interstitial lung disease (ILD), the erlotinib dose should be held and supportive measures instituted. If ILD is confirmed, erlotinib and sorafenib must be discontinued permanently. Acute dyspnea or cough may be signs of ILD. If a subject presents with acute dyspnea or cough, interruption of treatment with erlotinib may be considered, at the discretion of the treating physician, until resolution of symptoms or until ILD can be ruled out. If a subject presents with symptoms such as shortness of breath, dyspnea, cough, or fever, a chest X-ray or chest CT and, if needed, additional tests to evaluate pulmonary function, as clinically indicated, should be considered as part of the work up. If a diagnosis of ILD is confirmed, appropriate treatment measures according to best medical practice and local standards should be initiated.***~~

New text (change in section numbering):

Section 4.5.2.2.2 Dose modification and management of sorafenib-specific toxicities

Section 4.5.2.3, Sorafenib and capecitabine combination

Old text:

Doses of capecitabine or sorafenib~~/placebo~~ may be reduced/interrupted in the setting of any AE that is:

- ***Not controlled by optimal supportive care, or***
- ***Not tolerated due to symptomatology, disfigurement, or interference with normal daily activities, regardless of severity.***

New text:

Section 4.5.2.2 Sorafenib and capecitabine combination

Doses of capecitabine or sorafenib may be reduced/interrupted in the setting of any AE that is:

- ***Not controlled by optimal supportive care, or***
- ***Not tolerated due to symptomatology, disfigurement, or interference with normal daily activities, regardless of severity.***

Section 4.5.2.3, Sorafenib and TACE combination (new section)

New text:

Doses of sorafenib maybe be delayed or reduced for clinically significant hematologic and non-hematologic toxicities that are related to Sorafenib and TACE combination.

Dose modifications should take into consideration AEs and dose modifications already occurred in Study 12918 (SPACE).

Sorafenib dose modification in combination with TACE should follow the sorafenib monotherapy section guidelines (section 4.5.2.1) except dose modification for liver function test abnormalities. The following tables (Table 4–13 and Table 4–14) illustrate dose reductions and interruptions of Sorafenib if ALT or AST increase to CTC Grade 3 or 4 within 72 hours post-TACE along with the instruction for dose re-escalation following dose reduction for TACE related liver function test abnormalities.

Table 4-13: Criteria for Dose Reduction and Dose Interruption of Sorafenib if ALT or AST Increase to CTC Grade 3 or 4 within 72 hours Post TACE

Criteria for Dose Interruption and Dose Modification of Sorafenib if ALT/AST increased to CTC Grade 3 within 72 hours post TACE			
	DURATION of ALT/AST elevation	***ACTION***	***DOSE MODIFICATION***
1	***Grade 3 within 72 h post TACE***	***Continue study drug***	***No***
2	***Grade 3 persists >1 weeks post TACE***	***Continue study drug***	***YES:*** ***Decrease one dose level [a]***
3	***Grade 3 persists >2 weeks post TACE***	***Continue study drug***	***YES:*** ***Decrease dose further [b]***
4	***Grade 3 persists >3 weeks post TACE [c]***	***STOP study drug***	***YES:*** ***OFF Protocol Therapy***
Criteria for Dose Interruption and Dose Modification of Sorafenib if ALT/AST increased to CTC Grade 4 within 72 hours post TACE			
	DURATION of abnormal ALT/AST or bilirubin	***ACTION***	***DOSE MODIFICATION***
5	***Grade 4 AST or ALT for up to 1 week following TACE and bilirubin ≤2x pre-TACE value***	***Continue study drug, check ALT/AST, bilirubin every 1-2 days***	***No change***
6	***Grade 4 AST or ALT at any time within 1 week following TACE and bilirubin >2x pre-TACE value***	***STOP study drug until*** ***a.) bilirubin decreased to ≤2x pre-TACE value, and*** ***b.) ALT and AST decreased to grade 3 (check ALT/AST, bilirubin every 1-2 days)***	***Once bilirubin <2x pre-TACE value and ALT and AST decreased to grade 3 or less within 1 week of TACE, continue study drug at DECREASED dose (one level) [a] and follow grade 3 table above (criteria 3)***
7	***Grade 4 AST or ALT persists >1 week and bilirubin remains at ≤ 2 x pre-TACE value***	***Continue study drug***	***DECREASE one dose level a and follow grade 3 table above (criteria 3)***
8	***Grade 4 AST or ALT persists > 1 week or bilirubin has not decreased to ≤2x pre-TACE value after 1 week***	***STOP study drug***	***OFF Protocol Therapy***

a to 400 mg daily, if pre-TACE dose was full dose (or to 400mg every other day, if pre-TACE dose was 400 mg daily)
b to 400 mg every other day (or discontinue, if pre-TACE dose was 400 mg daily)
c if more than 2 dose reductions are required, patient is off protocol therapy

Note: Liver function test abnormalities will be graded using the CTCAE v. 3.0

Table 4–14: Post-TACE Sorafenib Dose Re-Escalation Scheme

	CAUSE FOR DOSE REDUCTION	*RE-ESCALATE to 400 mg every other day, if*	*RE-ESCALATE to 400 mg every day, if*	*RE-ESCALATE to 400 mg twice daily, if*
1	*Grade 3 ALT or AST persisted >1 week post-TACE*	*N/A*	*N/A*	*Grade 2 (or less) ALT and AST for at least 2 weeks under 400 mg daily*
2	*Grade 3 ALT or AST persisted >2 weeks post-TACE*	*N/A*	*Grade 2 (or less) ALT and AST for at least 2 weeks under 400 mg every other day*	*Grade 2 (or less) ALT and AST for at least 2 additional weeks under 400 mg daily*
3	*Grade 4 ALT or AST persisted >1 week and bilirubin remained at <2x pre-TACE value*	*N/A*	*N/A*	*Grade 2 (or less) ALT and AST, and bilirubin ≤2x pre-TACE value for at least 2 weeks under 400 mg daily*

Note: Liver function test abnormalities will be graded using the CTCAE v. 3.0

The rationale for additional criteria for ALT/AST increase within 72 hours following TACE is as follows:

Transarterial Chemoembolization (TACE) induces necrosis of tumor cells and to some degree affects normal liver tissue near the tumor tissue targeted by the TACE procedure. A common observation after TACE is a transient, reversible rise of liver enzymes peaking at 24-36 hours. One previous study confirmed AST and ALT levels increased 1–3 days after embolization and normalized to near pre-embolization values 1-month post procedure. Therefore, ALT/AST increases within 72 hours after TACE should be handled with different dose modification guidelines, reflecting the duration of Grade 3/4 ALT/AST increases as well as bilirubin levels.

Section 4.5.2.3.2, Dose modification for hematologic toxicities

Old text:

At the re-start of capecitabine following these toxicities, the dose of capecitabine should be reduced by at least one level (see Table 4-14 and Table 4-15). Additional dose reductions may occur as needed in subsequent cycles. If a subject requires dose reduction below capecitabine 500 mg/m2 twice daily or sorafenib~~/placebo~~ 200 mg twice daily, every other day, study drug must be permanently discontinued.

New text:

Section 4.5.2.2.2 Dose modification for hematologic toxicities

At the re-start of capecitabine following these toxicities, the dose of capecitabine should be reduced by at least one level (see Table 4-14 and Table 4-15). Additional dose reductions may occur as needed in subsequent cycles. If a subject requires dose reduction below capecitabine 500 mg/m2 twice daily or sorafenib 200 mg twice daily, every other day, study drug must be permanently discontinued.

Section 4.5.2.3.3, Dose modification for non-hematologic toxicities

Old text:

General guidelines for dose modification for toxicities common to both sorafenib and capecitabine

Grade 1: ***If any dermatologic toxicities, gastrointestinal toxicities or fatigue occur at grade 1, maintain doses of***

capecitabine and sorafenib~~/placebo~~. No dose modification is required for any occurrence of Grade 1 fatigue, dermatologic toxicity or gastrointestinal toxicity. The investigator should use symptomatic treatment to alleviate the toxicity.

Grade 2 or Grade 3: ***If dermatologic toxicities, gastrointestinal toxicities, or fatigue occur at Grade 2 or Grade 3, both drugs (ie, capecitabine and sorafenib) should be held until the toxicity resolves to Grade 1 or less.***

The algorithm in Table 4-17 should be followed for dose modifications when re-starting study treatment. This algorithm should also be used for each recurrence of these toxicities to determine which drug (ie, capecitabine or sorafenib) should be reduced. Actions to be taken at each occurrence are outlined below.

At the first occurrence of Grade 2 or Grade 3 fatigue, dermatologic toxicity, and/or gastrointestinal toxicity, the dose of capecitabine should be reduced by one dose level when restarting study treatment (see Table 4-13). Sorafenib should be restarted at the same dose as prior to the onset of the event(s).

At the second occurrence of Grade 2 or Grade 3 fatigue, dermatologic toxicity, and/or gastrointestinal toxicity, the dose of sorafenib~~/placebo~~ should be reduced by one dose level when restarting study treatment (see Table 4-12).

Capecitabine should be restarted at the same dose as prior to the onset of the event(s).

As a general rule, at any subsequent occurrence of Grade 2 or Grade 3 fatigue, dermatologic toxicity, and/or gastrointestinal toxicity, if the last dose modification was made for sorafenib~~/placebo~~, sorafenib~~/placebo~~ should be restarted at the same dose as prior to the onset of the event(s), and the dose of capecitabine should be reduced by one dose level. If, on the other hand, the last dose modification was made for capecitabine, capecitabine should be restarted at the same dose as prior to the onset of the event(s), and the dose sorafenib~~/placebo~~ should be reduce by one dose level.

Subjects who continue to experience toxicity and require a dose reduction below the lowest dose level of capecitabine (500 mg/m2 twice daily) or sorafenib~~/placebo~~ (200 mg~~/1 placebo~~ tablet twice daily every other day) must discontinue study drug.

Grade 4: ***Grade 4 toxicities require both study drugs to be discontinued permanently.***

New text:

Section 4.5.2.2.3 Dose modification for non-hematologic toxicities

General guidelines for dose modification for toxicities common to both

sorafenib and capecitabine

Grade 1:	***If any dermatologic toxicities, gastrointestinal toxicities or fatigue occur at grade 1, maintain doses of capecitabine and sorafenib. No dose modification is required for any occurrence of Grade 1 fatigue, dermatologic toxicity or gastrointestinal toxicity. The investigator should use symptomatic treatment to alleviate the toxicity.***
Grade 2 or Grade 3:	***If dermatologic toxicities, gastrointestinal toxicities, or fatigue occur at Grade 2 or Grade 3, both drugs (ie, capecitabine and sorafenib) should be held until the toxicity resolves to Grade 1 or less.*** ***The algorithm in Table 4-17 should be followed for dose modifications when re-starting study treatment. This algorithm should also be used for each recurrence of these toxicities to determine which drug (ie, capecitabine or sorafenib) should be reduced. Actions to be taken at each occurrence are outlined below.*** ***At the first occurrence of Grade 2 or Grade 3 fatigue, dermatologic toxicity, and/or gastrointestinal toxicity, the dose of capecitabine should be reduced by one dose level when restarting study treatment (see Table 4-13). Sorafenib should be restarted at the same dose as prior to the onset of the event(s).*** ***At the second occurrence of Grade 2 or Grade 3 fatigue,***

dermatologic toxicity, and/or gastrointestinal toxicity, the dose of sorafenib should be reduced by one dose level when restarting study treatment (see Table 4-12). Capecitabine should be restarted at the same dose as prior to the onset of the event(s).

As a general rule, at any subsequent occurrence of Grade 2 or Grade 3 fatigue, dermatologic toxicity, and/or gastrointestinal toxicity, if the last dose modification was made for sorafenib, sorafenib should be restarted at the same dose as prior to the onset of the event(s), and the dose of capecitabine should be reduced by one dose level. If, on the other hand, the last dose modification was made for capecitabine, capecitabine should be restarted at the same dose as prior to the onset of the event(s), and the dose sorafenib should be reduce by one dose level.

Subjects who continue to experience toxicity and require a dose reduction below the lowest dose level of capecitabine (500 mg/m2 twice daily) or sorafenib (200 mg tablet twice daily every other day) must discontinue study drug.

Grade 4: ***Grade 4 toxicities require both study drugs to be discontinued permanently.***

Section 4.5.2.3.4, Dose modification and management of sorafenib-specific toxicities

Old text:

Sorafenib dose modifications or delays will not impact capecitabine therapy. Subjects who require a delay or dose modification of sorafenib~~/placebo~~ should continue to receive capecitabine as scheduled.

New text:

Section 4.5.2.2.4 Dose modification and management of sorafenib-specific toxicities

Sorafenib dose modifications or delays will not impact capecitabine therapy. Subjects who require a delay or dose modification of sorafenib should continue to receive capecitabine as scheduled.

Section 4.5.2.3.6, Dose modification for other non-hematologic toxicities (excluding fatigue, dermatologic toxicities, gastrointestinal toxicities, hypertension and toxicities attributable to capecitabine)

Old text:

Table 4-19: Dose Modification for Other Non-Hematologic Toxicities (Excluding Fatigue, Dermatologic Toxicities, Gastrointestinal Toxicities, Hypertension and Toxicities Attributable to Capecitabine)

		Sorafenib		Capecitabine	
Toxicity Grade	***Occurrence***	***Dose Interruption***	***Dose Reduction***	***Dose Interruption***	***Dose Reduction***
Grade 1	***Any***	***None***	***None***	***None***	***None***
Grade 2	***First***	***None***	***None***	***Delay until resolved to Grade 1 or less***	***Resume at full dose***
	Subsequent	***None***	***None***	***Delay until resolved to Grade 1 or less***	***Reduce dose by one dose level[a,b]***
Grade 3	***Any***	***Delay until resolved to Grade 1 or less***	***Reduce dose by one dose level[a,b]***	***Delay until resolved to Grade 1 or less***	***Reduce dose by one dose level[a,b]***
Grade 4	***Any***	***Discontinue study drug***	***—***	***Discontinue study drug***	***—***

a: If recovery is not achieved after 21 days of interruption, study drug should be discontinued.

b: Subjects who continue to experience toxicity and require a dose reduction below the lowest dose level of capecitabine (500 mg/m² twice daily) or sorafenib~~/placebo~~ (200 mg~~/1 placebo~~ tablet twice daily, every other day) must discontinue study drug.

Table 4-19: Dose Modification for Other Non-Hematologic Toxicities (Excluding Fatigue, Dermatologic Toxicities, Gastrointestinal Toxicities, Hypertension and Toxicities Attributable to Capecitabine)

		Sorafenib		Capecitabine	
Toxicity Grade	***Occurrence***	***Dose Interruption***	***Dose Reduction***	***Dose Interruption***	***Dose Reduction***
Occurrences should include events in Study 12444					

New text:

Section 4.5.2.2.6 Dose modification for other non-hematologic toxicities (excluding fatigue, dermatologic toxicities, gastrointestinal toxicities, hypertension and toxicities attributable to capecitabine)

Table 4-12: Dose Modification for Other Non-Hematologic Toxicities (Excluding Fatigue, Dermatologic Toxicities, Gastrointestinal Toxicities, Hypertension and Toxicities Attributable to Capecitabine)

		Sorafenib		Capecitabine	
Toxicity Grade	***Occurrence***	***Dose Interruption***	***Dose Reduction***	***Dose Interruption***	***Dose Reduction***
Grade 1	***Any***	***None***	***None***	***None***	***None***
Grade 2	***First***	***None***	***None***	***Delay until resolved to Grade 1 or less***	***Resume at full dose***
	Subsequent	***None***	***None***	***Delay until resolved to Grade 1 or less***	***Reduce dose by one dose level[a,b]***
Grade 3	***Any***	***Delay until resolved to Grade 1 or less***	***Reduce dose by one dose level[a,b]***	***Delay until resolved to Grade 1 or less***	***Reduce dose by one dose level[a,b]***
Grade 4	***Any***	***Discontinue study drug***	***—***	***Discontinue study drug***	***—***

a: If recovery is not achieved after 21 days of interruption, study drug should be discontinued.

b: Subjects who continue to experience toxicity and require a dose reduction below the lowest dose level of capecitabine (500 mg/m^2 twice daily) or sorafenib (200 mg tablet twice daily, every other day) must discontinue study drug.

Occurrences should include events in Study 12444

Section 4.5.3.2, Erlotinib

Old text:

~~**4.5.3.2 Erlotinib**~~

~~***Erlotinib tablets are manufactured by Schwartz Pharma Manufacturing, Inc. for OSI Pharmaceuticals, Inc.***~~

~~***The tablet formulation consists of erlotinib and the excipients lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and titanium dioxide. The 25 mg, 100 mg, and 150 mg strengths are supplied as round white, film-coated, bi-convex tablets with no imprint. The active compound of erlotinib is N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-4-quinazolinamine and its molecular weight is 429.90 Daltons.***~~

~~***Supply, packaging, labeling and storage***~~

~~***The erlotinib tablets will be supplied in high-density, polyethylene bottles of 30 tablets each. The bottles will have a tamper-evident seal and a child-resistant cap. Each bottle of erlotinib will have a 1-panel standard label or booklet label affixed. For the 100 mg and 150 mg erlotinib doses, two bottles will be further packaged into a subject pack with a 2-panel standard label or booklet label affixed. For the 50 mg erlotinib dose, four bottles of erlotinib 25 mg tablets will be further packaged into a subject pack with a 2-panel standard label or booklet label affixed. One panel of the label will be permanently attached to the subject pack while the other portion will be a tear-off section that will be appended to the dispensing documentation. This label will contain the study ID, sponsor ID, contents, directions for use, storage requirements, batch, and investigational use statement as well as spaces to record the subject number and date dispensed. The label will also include any***~~

~~*other text as required by local law and legislation. Each subject pack label will also have a unique pack number. The labels on the bottles within the pack will have the same pack number. The labels will not contain any unblinding information. Erlotinib must be stored at room temperature and not above 25°C (77°F).*~~

~~*Once the study medication has been received, it must be stored in a dry, secure location (ie, locked cabinet) accessible only to authorized staff.*~~

~~*The study drug must be used exclusively for the investigation specified in this protocol. The investigative site must acknowledge receipt of drug supplies. Generally, acknowledgement for this study will be done using the IVRS/IWRS system. The confirmation of receipt sent by the IVRS/IWRS system must be printed and filed appropriately in the investigative site file. Occasionally, the IVRS/IWRS may not be available. The site will be instructed on using the Dispatch Order Form for acknowledgment in that situation. The CRA will instruct the site on how to sign the Dispatch Order Form and return it to the shipping unit.*~~

~~*Only the investigator or a person(s) assigned will be allowed to dispense the study medications to the subject. To have complete control over the distribution and use of study drugs, drug accountability must be performed at every subject visit. Empty bottles/blisters must be returned to the investigator along with all unused medication. Drug accountability will be performed throughout the study. Destruction of all unused material (ie, empty bottles, unused tablets, etc) must be documented and performed per standard operating procedures. One copy of the destruction certificate must be kept in the investigator's file and the other copy must be sent to the Bayer representative.*~~

New text:

None

Section 4.5.3.3, Capecitabine

Old text:

~~**4.5.3.3 Capecitabine**~~

~~***Sponsor-supplied capecitabine 150-mg and 500-mg tablets will be supplied in child-resistant blister packs (wallets) of 20 tablets each. Each blister pack of capecitabine will have a 2-panel standard label or booklet label affixed. One portion of the label will be permanently attached to the subject pack while the other portion will be a tear-off section that will be appended to the dispensing documentation. This label will contain the trial ID, sponsor ID, contents, directions for use, storage requirements, batch, and investigational use statement as well as spaces to record the subject number and date dispensed. The label will also include any other text as required by local law and legislation. The capecitabine must be stored in its original, immediate package at a temperature not above 30°C (86°F).***~~

~~***Alternatively, capecitabine may be supplied locally according to institutional procedures or may be supplied by the sponsor to the site in locally available commercial packaging labeled for the study***~~

New text:

Capecitabine is commercially approved for breast cancer and readily available in many countries including generic sources. Subjects on treatment with both capecitabine and sorafenib at the end of the 12444 RESILIENCE trial who are switched to the STEP study will switch to commercial supply capecitabine. In addition, subjects will continue to receive sorafenib as clinical supply.

Section 4.5.5, Selection of Doses in the Study

Old text:

Patients will receive sorafenib (Nexavar) 200 mg tablets and should continue receiving the same dose they were receiving in their original trial. ***Patients receiving sorafenib~~/erlotinib~~ or sorafenib/capecitabine combination should continue the same doses as in the originating trial.***

New text:

Patients will receive sorafenib (Nexavar) 200 mg tablets and should continue receiving the same dose they were receiving in their original trial. ***Patients receiving sorafenib or sorafenib/capecitabine combination should continue the same doses as in the originating trial.***

Section 4.5.6, Selection and Timing of Dose for Each Subject

Old text:

The patient should continuing receiving the same dose they were receiving in the previous trial. Dose increase beyond the dose the patient is currently receiving is not acceptable.

Sorafenib (Nexavar)~~, *erlotinib, and capecitabine*~~ may be decreased in the event of toxicity based on the Dose Modification criteria outlined in Section 4.5.2.

New text:

The patient should continuing receiving the same dose they were receiving in the previous trial. Dose increase beyond the dose the patient is currently receiving is not acceptable.

Sorafenib (Nexavar) ***and capecitabine*** may be decreased in the event of toxicity based on the Dose Modification criteria outlined in Section 4.5.2.

Section 4.5.8, Prior and Concomitant Therapy

Old text:

Non-permissible concomitant medication/therapies:

- Anticancer chemotherapy, ***except ~~erlotinib~~*** and capecitabine, immunotherapy or ***live*** vaccines during the study.

New text:

Non-permissible concomitant medication/therapies:

- Anticancer chemotherapy, ***except TACE*** and capecitabine, immunotherapy or ***live*** vaccines during the study.

Section 11.1, Study Flow Chart

Old text:

Activity	Visit 1	Minimum Every 8 weeks	End of Treatment
Demography [a, b]	X		
Pregnancy Test	X		
Vital signs	X	X	X
ECOG performance[a]	X	X	X
Survival status (dead or alive, date of death or date of last contact, as applicable)		*X*	*X*[d]
Adverse events [a]			
All treatment related	X	X	X
All Grade 3 or higher regardless of attribution	X	X	X
All serious adverse events	X	X	X
Laboratory evaluations [a]			
Hematology (Hgb, RBC, WBC,	X	X	X
platelets, differential)	X	X	X
CBC (ALT, AST, amylase, lipase)	X	X	X
PT-INR [c]			
Dispense/return sorafenib *(and ~~erlotinib or capecitabine if applicable~~)*[a]	*X*	*X*	*X*
Reason for termination of treatment [a]			X
Concomitant medications	X	X	X

a Record these data in the CRF and source documents.
b Includes originating study number, patient number and date of first sorafenib dose in originating study.
c For anticoagulated patients only
d For patients in long term follow up, survival status is assessed at a minimum of every 3 months

New text:

Activity	Visit 1	Minimum Every 8 weeks	End of Treatment
Demography [a, b]	X		
Pregnancy Test	X		
Vital signs	X	X	X
ECOG performance[a]	X	X	X
Survival status (dead or alive, date of death or date of last contact, as applicable)		*X*	*X[d]*
Adverse events [a]			
All treatment related	X	X	X
All Grade 3 or higher regardless of attribution	X	X	X
All serious adverse events	X	X	X
Laboratory evaluations [a]			
Hematology (Hgb, RBC, WBC,	X	X	X
platelets, differential)	X	X	X
CBC (ALT, AST, amylase, lipase)	X	X	X
PT-INR [c]			
Dispense/return sorafenib *(and capecitabine if applicable*)[a]	*X*	*X*	*X*
Reason for termination of treatment [a]			X
Concomitant medications	X	X	X

a Record these data in the CRF and source documents.
b Includes originating study number, patient number and date of first sorafenib dose in originating study.
c For anticoagulated patients only
d For patients in long term follow up, survival status is assessed at a minimum of every 3 months

10.5 Amendment 7

Date of amendment: 15 MAY 2018, v6.0.

10.5.1 Modification 1: Change of responsibility for Sponsor's Medical Expert, Study Manager, Statistician, Global Clinical Lead and Principal Investigator

Description of modification to the title page:

On the title page of the protocol, Sponsor's address was updated, Sponsor's address (US territory) was added. Also, the contact names for the Study Manager, Statistician and Global Clinical Lead were updated. In addition, the Principal Investigator's contact name and address were updated.

Rationale:

Personnel change in study team and Principal Investigator.

List of affected section:

Section Title page – amended.

10.5.2 Modification 2: Overall survival (OS) evaluation removed from the study objectives

Description of modification to the study plan:

The overall survival (OS) evaluation has been removed from the study objectives.

Rationale:

Given that the primary study objective is to enable patients receiving sorafenib (Nexavar) in a completed Bayer/Onyx sponsored clinical trial to continue treatment, the data on OS is not being utilized for any analyses. Therefore, to minimize burden to patients and sites, OS data collection at follow up will no longer be performed and OS will be removed as a study objective.

List of effected sections:

Sections 2, 4.6.1, 6.1

10.5.3 Modification 3: Safety visits

Description of modification to the study design and plan:

The patients should be evaluated by a study physician for safety at least once every 8 weeks and more frequently as needed. The protocol allows for a ±7 day window when scheduling any visit. Physicians can choose to continue to see the patients every 8 weeks in a face to face visit. At least every other visit must be a mandatory on site visit for examination and drug

dispensing, with the other visit being either in person or as a phone call. It is at the discretion of the investigator based on the patient's current condition and adverse event profile to determine if the next visit will be performed on site or as a phone visit. Any scheduled phone visit is mandatory and it will be at the discretion of the investigator to decide if that phone visit is sufficient. If the patient needs a physical examination, the visit will be performed on site. If the investigator feels the patient is stable with no new safety concerns nor new AEs in between visits, a phone call with labs, ECOG and review of AEs would be enough.

Rationale:

To lessen the travel burden on patients and enable better compliance at site while ensuring patient's safety. It is at the discretion of the Investigator and based on the patient's current condition to determine if the visit will be performed on site or as a phone call.

The protocol allows for a ±7 day window when scheduling any visit.

List of affected sections:

Sections 4.1, 4.6.3, 11.1

10.5.4 Modification 4: Laboratory evaluations

Description of modification to the study design and plan:

The laboratory evaluations were modified.

Rationale:

To ensure that the laboratory evaluations were not missed.

List of affected section:

Section 4.1

10.5.5 Modification 5: Follow-up period changed

Description of modification to the study objectives:

FU period was changed from until survival to until 30 days after last dose of study drug. Overall survival is removed from the objective.

Rationale:

This would allow some sites with only patients in survival follow-up for years to close, and to minimize burden to patients and to enable better compliance at sites.

List of affected sections:

Sections 4.6.3, 11.1

10.5.6 Modification 6: Editorial changes, corrections and clarifications

Description of modification to the study plan / Rationale:

The minor editorial changes are not shown by footnotes in the body text.

- Cover page added
- Minor text revisions and corrections

List of affected sections:

Sections 1, 2, 3, 4, 4.5.6, 5, 6, 7, 8, 9, 10, 11

10.6 Amendment 8

Date of amendment: 26 MAY 2020, v7.0.

10.6.1 Modification 1: Change of responsibility for Sponsor's Medical Expert, Study Manager, Statistician, Medical Expert, and Global Clinical Lead

Description of modification:

Change of study team members on the title page of the protocol; the Sponsor's Medical Expert's role is now filled by the Clinical Development Leader (CDL), and the respective contact information was updated. Further, contact names for the Study Manager, and Statistician were updated. In addition, the signature of the Global Clinical Lead was removed as this role is now filled by the CDL.

Rationale:

The role name and personnel change in study team.

List of affected section:

Section Title page – amended.

10.6.2 Modification 2: Added new eSignature text

Description of modification:

New eSignature text added.

Rationale:

New eSignature process implemented at Bayer.

List of affected section:

Section Title page – amended.

10.6.3 Modification 3: Added Post-Trial Access Program

Description of modification:

For completeness added that, at least in theory, Sorafenib study patients can continue to receive the treatment (study drug) not only through a subsequent clinical but also through a Post-Trial Access Program or any other mechanism (e.g. local access program).

Rationale:

To provide the investigator with information on further potential post-study drug supply mechanisms for sorafenib that are without costs to the patients.

List of affected sections:

Sections 1.

10.6.4 Modification 4: Removal of the instructions for dose modifications for the combination of sorafenib with capecitabine and TACE

Description of modification:

In Section 4.5.2.2, its subsections and Section 4.5.2.3 the instructions for dose modifications for the combination of sorafenib with capecitabine and TACE were removed.

In addition, explaining text as to why sorafenib combination therapy sections were removed was added to Section 4.5.2.2 and 4.5.2.3.

Rationale:

As of Amendment 8 there are no patients receiving combination therapy with capecitabine or TACE. The sections were removed to avoid confusion for the remaining patients none of whom are receiving capecitabine or TACE.

List of affected sections:

Sections 4.5.2.2, its subsections and 4.5.2.3.

10.6.5 Modification 5: Added clarification for continuation on study drug

Description of modification:

Added further options that can lead to the end of study treatment in the STEP study These are the transfer to a Post-Trial-Access Program, another study or any other mechanism (e.g. local access program) in accordance with local legal without costs to the patient with respect to sorafenib.

Rationale:

To allow physicians to stop the study treatment not only if the patient is no longer benefitting from the treatment or the treatment becomes commercially available/is reimbursed, but also if there is one of the following options available: a Post-Trial-Access Program, another study or any other mechanism (e.g. local access program) in accordance with local legal and compliance rules with no cost to the patient with respect to sorafenib.

List of affected section:

Section 2 and 4.1.

10.6.6 Modification 6: Added clarification for ending the study

Description of modification:

Added option to end this study when all patients have transitioned or discontinued from the study.

Rationale:

To clarify when the STEP study will end if an alternative mechanism of continued drug supply is established.

List of affected section:

Section 4.1.

10.6.7 Modification 7: Added clarification on last patient last visit date

Description of modification:

Added clarification on the definition of the end of study.

Rationale:

To define under what circumstances LPLV for this study will be achieved, which includes patients stopping study drug or being switched to receive treatment through an alternative mechanism of sorafenib supply.

List of affected sections:

Sections 4.9.

10.6.8 Modification 8: Removed reference to Study Sites in Japan

Description of modification:

Removed reference regarding Japanese regulatory requirements for Japanese study sites.

Rationale:

There are no patients on treatment from any Japanese study sites.

List of affected sections:

Sections 4.4, 4.5.3.1, 4.6.2, 4.6.3, 5.1, 7.3.2 and 7.3.6.

10.6.9 Modification 9: Corrected timepoint

Description of modification:

The timepoint of the performance of the analyses was corrected, last patient last visit was changed to “after the end of the study”.

Rationale:

For further clarity.

List of affected section:

Section 6.1.

10.6.10 Modification 9: Editorial changes, corrections and clarifications

Description of modification:

The minor editorial changes are not shown by footnotes in the body text. In addition to the changes summarized above, minor changes were made to correct typographical errors, and add clarity.

List of affected sections:

Sections Cover page of the integrated protocol, Glossary and Abbreviations, 1, 2, 4.1, 4.2, 4.2.2, 4.5.3.1, 10.

11. Appendices

11.1 Study Flow Chart

Activity[zzzz]	Visit 1	Minimum Every 8 weeks (±7 days)[aaaaa]	End of Treatment
Demography [a, b]	X		
Pregnancy Test	X		
Vital signs	X	X	X
ECOG performance[a]	X	X	X
Survival status (dead or alive, date of death or date of last contact, as applicable)[bbbbb]		*X*	*X*[d]
Adverse events [a]			
All treatment related	X	X	X
All Grade 3 or higher regardless of attribution	X	X	X
All serious adverse events	X	X	X
Laboratory evaluations [a]			
Hematology (Hgb, RBC, WBC, platelets, differential)	X	X	X
CBC (ALT, AST, amylase, lipase)	X	X	X
PT-INR [c]	X	X	X
Dispense/return sorafenib *(and capecitabine if applicable* [ddddd])[a]	*X*	*X*	*X*
Reason for termination of treatment [a]			X
Concomitant medications	X	X	X

a Record these data in the CRF and source documents.
b Includes originating study number, patient number and date of first sorafenib dose in originating study.
c For anticoagulated patients only
d The long term follow up period is until 30 days after last dose of study drug.[eeeee] [fffff]

[zzzz]: The text row regarding date of death was deleted in Amendment 3. See Section 10.3, Modification 6.

[aaaaa] The visit window has been modified by Amendment 7. See Section 10.5.3, Modification 3.

[bbbbb]: The text row concerning survival was added in Amendment 3. See Section 10.3, Modification 1.

[ccccc] Reference to erlotinib removed since none of the subjects that transferred into this study were assigned to erlotinib from study 12917. See Section 10.4, Modification 2.

[ddddd]: Participation of subjects from the SEARCH trial (Study 12917) or the RESILIENCE trial (Study 12444) was added under Amendment 3. See Section 10.3, Modification 5

[eeeee]: The table footnote regarding assessment of survival was added in Amendment 3. See Section 10.3, Modification 1.

[fffff] The table footnote was revised to change the FU period to until 30 days after last dose of study drug in Amendment 7. See Section 10.5.5, Modification 5.

11.2 New York Heart Association Criteria

Functional Capacity

Class I: Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.

Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitations, dyspnea, or anginal pain.

Class IV: Patients with cardiac disease resulting in ability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

11.3 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Death