**PFIZER INC.**

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

**PROPRIETARY DRUG NAME® / GENERIC DRUG NAME**: Inlyta® / Axitinib

**PROTOCOL NO.**: A4061058

**PROTOCOL TITLE**: A multicentre, global, randomized, double-blind study of axitinib plus best supportive care versus placebo plus best supportive care in patients with advanced hepatocellular carcinoma following failure of one prior antiangiogenic therapy.

**Study Centers**: 70 centers in 13 countries worldwide: Belgium (2 centers), China (7 centers), France (11 centers), Germany (3 centers), United Kingdom (5 centers), Hong Kong (2 centers), Hungary (2 centers), Italy (7 centers), Japan (9 centers), Korea (3 centers), Slovakia (3 centers), Taiwan (7 centers), and United States of America (9 centers).

**Study Initiation Date and Primary Completion or Final Completion Dates:** Study Initiation Date: 06 December 2010
Primary completion date: 03 March 2014
Final Completion Date: This study is still ongoing.

**Phase of Development**: Phase 2

**Study Objectives:** This study is being conducted in two parts (randomized and non-randomized) and had the following objectives.

**Non-randomized Portion (Selected Sites Only)**

- To evaluate the plasma pharmacokinetics (PK) of axitinib in subjects with advanced hepatocellular carcinoma (HCC) following failure of one prior antiangiogenic therapy and
- To determine the tolerability and recommended starting dose of axitinib in subjects with advanced HCC with Child-Pugh Class B disease (score 7) following failure of one prior antiangiogenic therapy.

**Randomized Portion (All Sites)**

Primary Objective:

- To compare the overall survival (OS) of subjects with advanced HCC receiving axitinib + Best Supportive Care (BSC) versus placebo + BSC following failure of one prior antiangiogenic therapy.

Secondary Objectives:

- To compare progression-free survival (PFS) between both arms;
- To compare time to progression (TTP) between both arms;
- To compare overall response rate (ORR) between both arms;
- To evaluate duration of response (DR) within each treatment arm;
- To compare Clinical Benefit Rate (CBR) between both arms;
- To evaluate the safety and tolerability of axitinib in this subject population;
- To evaluate the PK of axitinib in this subject population;
- To compare subjects' health-related quality of life (HRQoL) and health status between both arms;
- To evaluate baseline blood vascular endothelial growth factor (VEGF) - C level as a potential predictive biomarker of axitinib efficacy; and
- To evaluate blood soluble protein concentrations and ribonucleic acid (RNA) transcripts associated with angiogenesis or tumor growth.

## METHODS

### Study Design

Non-randomized portion (selected sites only)

This was an open-label, non-randomized portion of this study at selected sites only. Subjects were assigned to 2 cohorts according to Child-Pugh score. It was planned to have an equal number of subjects (12) in each of the 2 cohorts.

Cohort 1: Subjects with advanced HCC and Child-Pugh Class A disease, score 5 or 6.

Cohort 2: Subjects with advanced HCC and Child-Pugh Class B disease, score 7 without ascites or encephalopathy.

Subjects with Child-Pugh Class A disease (score 5 or 6) could have been enrolled into either the non-randomized (Cohort 1) portion at selected sites to characterize the PK of axitinib or to the randomized portion of this study at a starting axitinib dose of 5 mg twice daily (BID).

Subjects with Child-Pugh Class B disease (score 7) were initially enrolled at selected sites into the non-randomized portion of this study to determine the recommended starting dose of axitinib for this population. Following determination of the recommended axitinib starting dose based on tolerability and PK assessments, subjects with Child-Pugh Class B disease (score 7) were to begin enrollment into the randomized portion of the study.

Initially, 6 subjects with Child-Pugh Class B disease (score 7) at selected sites were enrolled into Cohort 2 of the non-randomized portion at a 2 mg BID axitinib starting dose. The maximum tolerated dose (MTD) was defined as the dose level in which 0/6 subjects or 1/6 subjects experience dose limiting toxicity (DLT) during Cycle 1 of treatment with the next higher dose level having 2 or more subjects experiencing DLT within their first treatment cycle.

- If 0/6 or 1/6 subject experienced DLT during Cycle 1 (4 weeks) of treatment with 2 mg BID axitinib starting dose, then 5 mg BID axitinib starting dose was explored in 6 subjects. If 0/6 or 1/6 subject at 5 mg BID dose level experience DLT during Cycle 1, then 5 mg BID was the recommended starting dose for the randomized portion unless the PK data indicated a lower starting dose should be used. If 2/6 or more subjects at 5 mg BID dose level experienced DLT during Cycle 1, then the recommended starting dose was 2 mg BID for the randomized portion for Child-Pugh Class B (score 7) subjects.

- If 2/6 or more subjects experienced DLT during Cycle 1 of treatment with 2 mg BID axitinib starting dose, then 6 additional subjects were enrolled at the next lower starting dose level (1 mg BID). If 0/6 or 1/6 subject at 1 mg BID dose level experienced DLT during Cycle 1, then 1 mg BID was the recommended starting dose for the randomized portion of the study for Child-Pugh Class B (score 7) subjects. If 2/6 or more subjects at 1 mg BID dose level experienced DLT during Cycle 1, a lower dose level may have been explored with concurrence of the sponsor and investigator following examination of the PK data.

Provided there was no unacceptable safety or tolerability and with concurrence of the investigators and sponsor, subjects within each cohort were allowed to continue their current dosing for the first cycle and then dose titration may have been performed according to the dose titration guideline until progressive disease (PD) was documented. All subjects enrolled into the non-randomized portion were assessed and followed up following the same schedule (except for assessment of soluble proteins, RNA transcripts, and Subject Reported Outcomes [PROs]) as subjects in the randomized portion.

Randomized portion (all sites)

The randomized portion of the study was a multicenter, double-blind, parallel-arm clinical trial to compare the efficacy of axitinib + BSC versus placebo + BSC in subjects with advanced HCC whose disease had progressed after or were intolerant to one prior antiangiogenic therapy. Subjects were randomized (2:1 ratio) to receive either axitinib + BSC or placebo + BSC and were stratified by tumor invasion (presence vs absence of extrahepatic spread and/or vascular invasion) and geographic region (Asia vs non-Asia).

Schedule of activities can be found in Table 1.

## Table 1: Schedule of Activities

| Observation | Screening Day –28 to Day 0 | Day 1 (Predose) | Every 2 Wks X 2, then Every 4 Wks* | Every 8 Wks by Calendar | Post Treatment | |
|---|---|---|---|---|---|---|
| | | | | | End of Study Treatment/Withdrawal | Follow-up Day 28 after last dose |
| Informed consent[a] | X | | | | | |
| Medical history[b] | X | | | | | |
| Concomitant treatment[c] | Throughout the study period | | | | | |
| Physical exam[d] | X | X** | X | | X | X |
| Weight, height, temperature, heart rate [e] | X | X | X | | X | X |
| Blood pressure[f] | X | X | X | | X | X |
| Home blood pressure monitoring[g] | | Throughout the study period | | | | |
| ECOG performance status[h] | X | X | X (every 4 weeks) | | X | X |
| Hematology[i] | X(Day –7 to 0) | X** | X (every 4 weeks) | | X | |
| Chemistry, AFP[j] | X(Day –7 to 0) | X** | X | | X | |
| HBV panel, anti-HCV antibodies [k] | X | | | | | |
| Coagulation test [l] | X(Day –7 to 0) | X** | X | | X | |
| Thyroid function tests [m] | X(Day –7 to 0) | X** | X | | | |
| Urine analysis [n] | X(Day –7 to 0) | | X (every 4 weeks) | | X | |
| 12-Lead electrocardiogram[o] | X | | | | | |
| Tumor assessments including CT/MRI[p] | X | | | X | X | |
| Serum or urine pregnancy test [q] | X (Day –7 to 0) | | | | | |
| Endoscopy or upper GI imaging [r] | X | | | | | |
| Study randomization [s] | X (Day –7 to 0) | | | | | |
| Child-Pugh class, CLIP score, BCLC class | X | | | | | |
| Pharmacokinetics[t] | | X (Non-randomized portion: C1D15; Randomized portion: C1D1, C2D1 and C3D1) | | | | |
| Plasma VEGF-C and other soluble proteins [u] | | X | X (C2D1 only) | | X | |
| Blood RNA transcripts [v] | | X | X (C2D1 only) | | X | |
| Safety assessment (adverse events) [w] | | Throughout the study period | | | | |
| Survival[x] | Until at least 2 year after the randomization of the last patient | | | | | |
| Patient reported outcomes: FACT-Hep and EQ-5D[y] | | X | X (every 4 weeks) | | X | X |

Note: Tests and procedures were to be done on schedule, but occasional changes by ±4 days (only +4 days for tests and procedures to be done at "Follow-up Day 28 after last dose" visit) were allowable for holidays, vacations, and other administrative reasons.

* Cycle length was 4 weeks. Subjects enrolled into the non-randomized portion were to follow the same schedule of activities as the randomized portion.
** Unnecessary to repeat before first dose if the assessment was performed within 7 days prior to first dose
[a] Informed consent: Prior to any procedures performed solely for this study.
[b] Medical history: Including information on prior systemic first-line treatment and pre-study tumor assessment data showing disease progression according to RECIST criteria if applicable.
[c] Concomitant treatment: collected from screening to the follow-up period.
[d] Physical exam: Examination of major body systems (including neurological examination). Abnormalities from subsequent history and physical examinations were to be recorded as AEs.
[e] Height was not required to be collected after the first measurement.
[f] BP was to be measured with the subject in the seated position after the subject had been sitting quietly for 5 minutes; 2 BP readings were required at each clinic visit. It was acceptable not to collect the second BP reading at follow-up clinic visit only if there were no BP elevations observed by home BP monitoring and the first BP reading in clinic was normal.
[g] Home BP monitoring: All subjects (in both study arms) were provided a BP monitoring device. Subjects were to take BP at least twice daily prior to taking each dose of medication and BP was to be recorded in a subject diary. Subjects were to be instructed by the study staff to contact their physician for guidance if their systolic BP rose above 140 mm Hg, diastolic BP rose above 90 mm Hg, or if they developed symptoms perceived to be related to elevated BP (eg, headache, visual disturbance). A different BP threshold for contacting physician may have been used according to the physician's clinical judgment.
[h] Eastern Cooperative Oncology Group (ECOG) performance status.
[i] Hematology: Hemoglobin, white blood cells with differential count, and platelets required within 7 days prior to the start of study treatment.
[j] Chemistry, alpha-fetoprotein: blood urea nitrogen, creatinine, sodium (Na+), potassium (K+), chloride (Cl-), calcium (Ca+), alkaline phosphatase, gamma-glutamyl-transpeptidase, lactate dehydrogenase, alanine aminotransferase (or serum Glutamate-Pyruvate Transferase), aspartate aminotransferase (or serum Glutamate-Oxalate Transferase), total protein, albumin, total bilirubin, glucose, phosphate, and alpha-fetoprotein.
[k] HBV panel, anti-HCV antibodies: HBsAg, HBe, anti-HBc, and anti-HCV.
[l] Coagulation test: Prothrombin time or International Normalized Ratio required within 7 days prior to the start of study treatment.
[m] Thyroid Function Tests (free T3, free T4, and thyroid stimulating hormone): was to be performed for all non-randomized and randomized subjects (in both study arms) on Cycle 1 Day 1 before dosing or within 7 days of pre-dose. Subsequently, thyroid stimulating hormone was to be done at Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, then every 8 weeks thereafter starting from Cycle 6 Day 1. Free T3 and/or free T4 was to be performed when clinically indicated. Subjects
were to be monitored for signs and symptoms of hypothyroidism, such as fatigue, deepening of voice, cold intolerance, constipation, anorexia, periorbital edema, myxedema, or changes in skin or hair. Hypothyroidism was to be treated per standard medical practice to maintain euthyroid state.
[n] Urine analysis: Protein, glucose, and blood required within 7 days prior to the start of study treatment. If protein ≥2+ by semiquantitative method (eg, urine dipstick) then quantitate by 24-hour urine collection. Dose adjustment may have been required (adjustment of the dose once subject is on trial. This did not depend on baseline proteinuria).
[o] ECGs: A single ECG measurement was collected at screening. If the mean QTc interval was prolonged (>500 msec), then the ECGs were to be re-read by a cardiologist or other qualified person at the site for confirmation. Additional ECGs may have been performed as clinically indicated.
[p] Tumor assessments including CT/MRI: Pre-study objective evidence of disease progression per RECIST or intolerance to prior therapy was to be confirmed by the investigator and documented in the subject's medical record. Baseline (screening) tumor assessments required CT/MRI (no chest x-ray) of the chest and abdomen at the minimum. A bone scan and CT/MRI of the pelvis may have been performed if clinically indicated at baseline and at follow up visits. If the interval between any of the baseline tumor assessments and randomization was >28 days, the expired baseline tumor imaging was to be repeated. For all subjects, CT/MRI (covering the same anatomy as the baseline scans) was required every 8 weeks by calendar from the date of randomization. Response (CR/PR) required confirmation with CT/MRI

at least 4 weeks after the response is first noted.

[q] Serum or urine pregnancy test: Female subjects of childbearing potential must have had a negative pregnancy test within 7 days prior to treatment and all subjects must have been using appropriate birth control or practicing abstinence. Pregnancy testing may have been repeated as per request of IRB/IECs or if required by local regulations.

[r] Endoscopy or upper gastrointestinal imaging (screening): to exclude subjects with esophageal varices of greater than grade 2 according to Paquet classification or esophageal varices in the presence of any red signs (grade 2 allowed only if on prophylactic treatment).

[s] Study randomization: Subject number, randomization, and axitinib bottle number assignments were obtained via centralized randomization. Required information: site and subject identifiers, demographic information, and stratification variables including tumor invasion (presence versus absence of extrahepatic spread and/or vascular invasion), geographic region (Asia versus non-Asia). Study treatment was to begin within 7 days of randomization.

[t] Pharmacokinetics:

*Non-randomized portion (selected sites only)*: Axitinib samples were to be collected from all subjects on Cycle 1 Day 15 at the following time points: pre-dose, 1, 2, 3, 4, 6 and 8 hours after axitinib dosing. Subjects were instructed to hold the morning dose of axitinib until the pre-dose sample was drawn.

*Randomized portion (all sites)*: Population PK samples for axitinib/placebo were to be obtained from subjects on Day 1 of Cycle 1, 2 and 3. On Cycle 1 Day 1, one sample will be obtained 2 to 3 hours after the first axitinib/placebo dose in clinic. The exact time of the first dose was to be noted. On Day 1 of Cycle 2 and 3, two samples were to be collected: 1 sample just before (within 15 minutes) the morning axitinib/placebo dose (taken in the clinic) and another 2 to 3 hours after the morning axitinib/placebo dose. The exact time of the clinic visit dose and the dose taken prior to that were to be noted.

[u] Plasma soluble proteins: Ang-2, MMP-2, VEGF-A, VEGF-C, sVEGFR2, SVEGFR3, HGF, sMET, SCF, sKIT, NGAL, SDF-1, IL-6, IL-8, E-selectin, MCP-3, MIF, CCL5 (also referred to as RANTES)were only measured in randomized subjects. On Cycle 1 Day 1 and at end of study treatment/withdrawal, samples were to be collected at predose. On Cycle 2 Day 1, samples were to be collected at 2 to 3 hours after the morning axitinib/placebo dose.

[v] Blood RNA samples: Blood samples for RNA analysis were to be collected from randomized subjects only. On Cycle 1 Day 1 and at end of study treatment/withdrawal, samples were to be collected at predose. On Cycle 2 Day 1, samples were to be collected at 2 to 3 hours after the morning axitinib/placebo dose.

[w] Safety assessment: AEs were to be collected from the first day of study treatment throughout the study period until at least 28 days after the last dose of study drug and followed until resolution or stabilization. SAEs were to be monitored and reported from the time the subject provided informed consent.

[x] Survival: All subjects were to be followed for survival at least every 3 months after discontinuing study treatment until at least two years after randomization of the last subject.

[y] Patient reported outcomes: FACT-Hep and EQ-5D (patient reported outcome) questionnaires were to be administered on Cycle 1 Day 1 before dosing and before any other clinical assessments, then every 4 weeks thereafter while on study, at end of study treatment/withdrawal, and follow-up, Day 28 after last dose in BOTH treatment arms. PROs were to be administered to randomized subjects only.

Abbreviations: AFP=Alpha-fetoprotein; Ang-2=Angiopoietin 2; BP=Blood pressure; BCLC=Barcelona Clinic Liver Cancer; CCL5=Chemokine (C-C motif) ligand 5; CLIP=Cancer of the Liver Italian Program; CT=Computed tomography; ECG=Electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EQ-5D=EuroQoL 5 dimensions; FACT-Hep=Functional Assessment of Cancer Therapy –Hepatobiliary questionnaire; GI=Gastrointestinal; HBV=Hepatitis B virus; HCV=Hepatitis C virus; HGF=Hepatocyte growth factor; IL-6=Interleukin 6; IL-8=Interleukin 8; MCP-3=Monocyte chemotactic protein; MIF=Migration inhibitory factor; MMP-2=Matrix metalloproteinase 2; MRI=Magnetic resonance imaging; NGAL=Neutrophil gelatinase-associated lipocalin; PK=Pharmacokinetic; RANTES=Regulated upon Activation Normal T cell Expressed and presumably Secreted; RECIST=Response Evaluation Criteria in Solid Tumors; RN=Ribonucleic Acid; SAE=Serious adverse event; sKIT=Soluble stem cell factor receptor; SCF=Stem cell factor; SDF-1=stromal cell-derived factor 1 ; sVEGFR2=Soluble vascular endothelial growth factor receptor 2; sVEGFR3=Soluble vascular endothelial growth factor receptor 3; VEGF=Vascular endothelial growth factor; VEGF-A=Vascular endothelial growth factor A; VEGF-C=Vascular endothelial growth factor C.

**Number of Subjects (Planned and Analyzed)**

Non-randomized portion (selected sites only)

Planned: approximately 24 subjects (12 in the Child-Pugh A cohort and 12 in the Child-Pugh B [score 7] cohort);
Analyzed: enrolled 22 subjects (15 in the Child-Pugh A cohort and 7 in the Child-Pugh B cohort).

Randomized portion (all sites)

Planned: 198 subjects (132 in the axitinib arm and 66 in the placebo arm).
Analyzed: enrolled 202 subjects (134 in the axitinib arm and 68 in the placebo arm).

**Diagnosis and Main Criteria for Inclusion**

Subjects with locally advanced or metastatic HCC, failure of one prior antiangiogenic therapy including sorafenib, bevacizumab and brivanib, and Child-Pugh disease A (score 5 or 6) or B (score 7 only) disease were enrolled in this study.

**Study Treatment**

Study treatment was to begin within 7 days of randomization. All subjects enrolled were to receive treatment with axitinib or placebo during the study depending on their participation in either the non-randomized or randomized part of the study. Study treatment was administered in cycles of 4 weeks in duration. Axitinib/placebo was administered beginning on Day 1 of the study. Each medication dose was to be taken with food as close to 12 hours apart as possible and at approximately the same times each day on a continuous schedule.

Test product

*Non-randomized Portion*

Subjects with Child-Pugh Class A disease (score 5 or 6) were enrolled into the non-randomized portion at selected sites only at a starting axitinib dose of 5 mg BID.
Subjects with Child-Pugh Class B disease (score 7) at selected sites were initially enrolled only into the non-randomized portion of this study to determine the recommended starting dose of axitinib for this population.

*Randomized Portion*

Subjects with Child-Pugh Class A disease (score 5 or 6) were enrolled into the randomized portion at a starting axitinib dose of 5 mg BID. Subjects with Child-Pugh Class B disease (score 7) were to begin enrollment into the randomized portion of the study following determination of the recommended axitinib starting dose in the non-randomized portion.

Subjects were randomized (2:1 ratio) in a double-blind fashion (using a centralized registration system) to receive axitinib+BSC (Arm A) or placebo+BSC (Arm B).

Randomization was stratified by tumor invasion (presence versus absence of extra hepatic spread, and/or vascular invasion) and geographic region (Asia versus non-Asia).

Reference Therapy

Matching placebo was supplied as 1 mg and 5 mg immediate-release, film-coated tablets for oral administration.

The criteria for dose modification for study drug-related AEs are summarized in Table 2.

**Table 2: Criteria for Dose Modification for Study Drug-related Adverse Events**

| Related Adverse Event | Intervention/Management |
|---|---|
| **Axitinib-related adverse events other than hypertension or proteinuria** | |
| Grade 1 | Continued at same dose level |
| Grade 2 | Continued at same dose level |
| Grade 3 hematologic treatment-related toxicity | Continued at same dose level |
| Grade 3 nonhematologic treatment-related toxicity[a] | Decreased dose to 1 lower dose level |
| Grade 4 nonhematologic treatment-related toxicity or Grade 4 hematologic toxicity[b] | Interrupted dosing; restarted at 1 lower dose level as soon as improvement to NCI CTCAE Grade ≤2 |
| **Hypertension** | |
| 2 BP readings separated by ≥1 hour showed systolic BP >140 mmHg **or** 2 BP readings separated by ≥1 hour showed diastolic BP >90 mmHg | If not on maximal antihypertensive treatment, instituted new or additional antihypertensive medication and maintained dose of axitinib/placebo.<br>If on maximal antihypertensive treatment, reduced axitinib to 1 lower dose level/placebo. |
| 2 BP readings separated by ≥1 hour showed systolic BP >160 mmHg **or** 2 BP readings separated by ≥1 hour showed diastolic BP >105 mmHg | Interrupted dosing[c]; adjusted antihypertensive medication; as soon as BP was less than 140/90 mmHg, restarted axitinib/placebo at 1 lower dose level. |
| **Proteinuria** | |
| >2+ proteinuria (dipstick) | Performed 24-hour urine collection. Dosing could continue while waiting for test results. |
| ≤3.5 g proteinuria/24 hours | Continued dosing at the same dose level. |
| >3.5 g proteinuria/24 hours | Held dosing and repeated 24-hour urine collection for proteinuria and creatinine clearance (interval at investigator discretion) until proteinuria was ≤3.5 g/24 hours. Restarted axitinib/placebo at the same dose or 1 lower dose level at the discretion of the investigator. |

[a] Subjects who developed Grade 3 nonhematologic toxicities that were controlled with symptomatic medications or who developed Grade 3 asymptomatic biochemistry laboratory abnormalities continued at the same dose level at the discretion of the investigator.
[b] Subjects who developed Grade 4 lymphopenia or Grade 4 asymptomatic biochemistry laboratory abnormalities continued study treatment without interruption.
[c] If axitinib/placebo was held, subjects receiving antihypertensive medications were to be monitored closely for hypotension. The plasma half-life of axitinib is 2 to 4 hours and BP usually decreases within 1 to 2 days following dose interruption.
Abbreviations: BP=Blood pressure; NCI CTCAE=National Cancer Institute Common Terminology Criteria For Adverse Events.

## Efficacy, Pharmacokinetic, Pharmacodynamic, or Outcomes Research Endpoints

*Non-randomized Portion*

- Plasma PK [maximum plasma concentration ($C_{max}$); area under the plasma concentration-time curve (AUC) from time 0 to 24 hours ($AUC_{0-24}$); area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration ($AUC_{last}$); time to first occurrence of $C_{max}$ ($T_{max}$); terminal phase elimination half-life ($t_{1/2}$); apparent oral clearance (CL/F); apparent volume of distribution of the drug during the elimination Phase ($V_z$/F)], and tolerability of single-agent axitinib following continuous dosing.

*Randomized Portion*

- Primary
- OS.
- Secondary
- PFS;
- TTP;
- ORR;
- DR;
- CBR;
- Axitinib population PK analysis;
- Patient-Reported Outcomes (PRO) of HRQoL and disease-related symptoms as measured by the Functional Assessment of Cancer Therapy – Hepatobiliary Questionnaire (FACT-Hep) and health status measured by the EuroQol EQ-5D Self-Report Questionnaire (EQ-5D);
- Plasma soluble proteins (angiopoietin 2 [Ang-2], matrix metalloproteinase 2 [MMP-2], VEGF-A, VEGF-C, soluble vascular endothelial growth factor receptor 2 [sVEGFR2], sVEGFR3, hepatocyte growth factor [HGF], c-MET, stem cell factor [SCF], soluble stem cell factor receptor [sKIT], neutrophil gelatinase-associated lipocalin [NGAL], stromal cell-derived factor 1 [SDF-1], interleukin 6 [IL-6], interleukin 8 [IL-8], E-selectin, monocyte chemotactic protein [MCP-3], migration inhibitory factor [MIF], chemokine (C-C motif) ligand 5 [CCL5; also referred to as Regulated upon Activation Normal T cell Expressed and presumably Secreted (RANTES)];
- Plasma micro-RNA transcripts associated with angiogenesis and tumor growth.

## Safety Evaluations

<u>Non-randomized portion</u>

- First-cycle DLT; Child-Pugh Class B, score 7 population only.
- Type, incidence, severity, timing, seriousness, and relatedness of AEs, laboratory abnormalities based upon the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0.

Randomized portion

- Type, incidence, severity (graded by the NCI CTCAE, Version 3.0), timing, seriousness, and relatedness of AEs and laboratory abnormalities.

**Statistical Methods**

Analysis Sets

*Full Analysis Population:*

The full analysis set (FAS) was to include all randomized subjects, and subjects were classified according to the randomized treatment arm regardless of what treatment, if any, was received. This was to be the primary population for evaluating all efficacy endpoints as well as subject characteristics.

*Safety Analysis Population:*

The safety analysis population was to include all randomized subjects who received at least 1 dose of study drug with treatment assignments designated according to actual study treatment received. This population was to be the primary population for evaluating treatment administration/compliance and safety.

*Pharmacokinetic Analysis Sets:*

The PK concentration set was to include all subjects who were treated and had at least 1 measured concentration on at least 1 day of PK assessment.

The PK parameter analysis set was to include all subjects treated who had at least 1 estimated PK parameter of primary interest.

*Pharmacodynamic Analysis Sets:*

The soluble protein analysis set was to include all subjects in the safety analysis set who had a baseline soluble protein assessment.

The microRNA (miRNA) analysis set was to include all subjects in the safety analysis set who had a baseline miRNA assessment.

Efficacy analyses

Primary Analysis

The primary objective of this study was to compare OS of axitinib+BSC versus placebo+BSC in subjects with advanced HCC, whose disease had progressed on/after or were intolerant to one prior antiangiogenic therapy. The study was designed to detect a hazard ration (HR) of 0.6 in OS for axitinib over placebo.

*Overall survival:* OS was defined as the time from the date of randomization to the date of death due to any cause. OS (in months) was calculated as (date of death − first randomization date +1)/30.4. OS was summarized in the FAS using Kaplan-Meier (KM) methods. A stratified log-rank test (1-sided, α=0.025) was used to compare OS between the 2 treatment arms. The median event time and 2-sided 95% CI for the median was to be provided. The HR and its 95% CI were also estimated. The 1-year survival probability was also estimated using the KM method and a 2-sided 95% CI for the log [-log (1-year survival probability)] was calculated using a normal approximation and then back transformed to give a CI for the 1-year survival probability itself. A Cox regression model was used to explore the potential influences of the stratification factors on the primary OS endpoint. OS was calculated using the following censoring method: OS data were censored at the date of last contact at which the subject was known to be alive, or the date the subject crossed to another chemotherapy, whichever came first. Sensitivity analyses using an unstratified log rank test were also performed.

Secondary Analyses

*Progression-free survival:* PFS was defined as the time from date of first dose of study drug to first documentation of objective tumor progression, or to death due to any cause, whichever occurred first. PFS (in months) was calculated as (first event date – date of first dose of study drug+1)/30.4. PFS in each arm was assessed using the KM method in the FAS and compared with a 1-sided stratified log-rank test at α=0.025 significance level. Median and 95% CIs for each treatment arm were to be provided. As an additional sub-analysis, an unstratified log-rank test was calculated along with the above mentioned supporting summary statistics.

*Time to progression:* TTP was defined as the time from randomization to first documentation of objective tumor progression. TTP (in months) was calculated as (first event date − first randomization date +1)/30.4. TTP in each arm was assessed using the KM method in the FAS and compared with a 1-sided stratified log-rank test, at α=0.025 significance level. Median and 95% CIs for each treatment arm were to be provided. As an additional sub-analysis, an unstratified log-rank test was to be calculated along with the above mentioned supporting summary statistics.

*Overall response rate:* ORR was defined as the percent of subjects with confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria, relative to all randomized subjects who had baseline measurable disease. ORR for the 2 treatment arms was compared with using Cochran-Mantel-Haenszel (CMH) test for stratified analyses (α=0.025 significance level).

*Duration of response:* DR was defined as the time from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed to the first documentation of PD or to death due to any cause, whichever occurs first. DR (in months) was calculated as (the end date for DR − first CR or PR that was subsequently confirmed +1)/30.4. Estimates of the DR were evaluated using the KM method. Median and 95% CIs for each treatment arm were provided.

*Clinical benefit rate:* CBR was defined as the proportion of subjects with confirmed CR or confirmed PR or a best response of stable disease ≥8 weeks according to RECIST criteria, relative to all randomized subjects who had baseline measurable disease. CBR for the 2 treatment arms was compared using CMH test for stratified analyses (α=0.025 significance level).

Pharmacokinetic analysis

Axitinib PK parameters were estimated using non-compartmental methods. The axitinib PK data were summarized and reported based on Child-Pugh class as well as the dose administered. Descriptive statistics (n, mean, standard deviation (SD), % coefficient of variation (CV), median, minimum, maximum) of plasma concentrations for axitinib were presented in tabular form by study day, Child-Pugh class, dose and nominal time. PK parameters for axitinib were listed and summarized using descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, and geometric mean, its associated 95% CI and geometric %CV) by Child-Pugh class. PK parameters with zero values were to be excluded from the calculation of geometric means, its associated 95% CI and geometric %CV.

Population PK modeling using data from both serial (non-randomized portion) and sparse (randomized portion) sample collections in this study are intended to be reported separately, and are not included in this document.

Biomarker analyses

Separately for miRNA and soluble proteins, p-values were assessed for significance for both an unadjusted comparison (α=0.05) and the adjusted comparison where α=0.05/# of analytes assayed.

*RNA Transcript Analysis:* Subjects were to be classified as clinical benefit responder/non-responder based on achieving or failing to achieve clinical benefit. A responder was defined as a subject with a confirmed CR or confirmed PR or a best response of stable disease ≥8 weeks according to RECIST and a non-responder was defined as a subject with a best response of stable disease <8 weeks, PD, symptomatic deterioration, early death, and interminate response. Summaries by responder/non-responder were to be used to identify biomarkers associated with clinical outcome. Probe sets with significant associations with CBR were to be summarized by p-values, odds ratios, or other appropriate statistics. OS data were to be summarized stratifying on baseline biomarkers using KM methods. A stratified log-rank test (1-sided, α=0.025) was to be used to compare OS between the two baseline biomarker categories within a treatment arm, if appropriate. The median event time and 2-sided 95% CI for the median were to be provided, along with the HR and its 95% CI.

P-values from statistical hypothesis tests were to be compared to alpha using unadjusted and adjusted comparisons and the false discovery rate (FDR) were to be provided.

Presentations for all miRNA biomarkers were to include the following as data permitted:

- Summary of baseline biomarkers by treatment group and the comparison of axitinib to placebo using Wilcoxon Rank-Sum test.
- Summary of biomarker values versus CBR category by treatment arm.

- Analysis of OS using KM method with baseline biomarker by treatment arm.
- P-value for comparison of biomarker category within treatment group.
- Plots of survival curves were to be provided; the 4 groups were to be on one plot, with the two p-values, HR, and 95% CI for HR.
- For KM analyses significant at the 0.05 level (unadjusted) for axitinib, sensitivity/specificity or receiver operating characteristic (ROC) curves predicting OS from the biomarker (actual value) were to be provided.
- Summary table of basic demographic and other characteristics for the biomarker analysis set.
- A listing of miRNA data including, at a minimum, center, subject identification, randomization number, treatment code, accession number, analyte, visit, and result.

*Soluble Protein Analysis:* Presentations for all serum biomarkers were to include the following as data permitted:

- P-value comparisons to alpha were to be done using unadjusted and adjusted comparisons.
- Summary of baseline biomarkers by treatment group comparison of axitinib and placebo for baseline using Wilcoxon Rank-Sum Test.
- Summary of biomarker values versus CBR category by treatment arm.
- Analysis of OS using KM method with baseline biomarker categorized.
- A stratified log-rank test (1-sided, $\alpha$=0.025) was to be used to compare OS between the 2 baseline biomarker categories within treatment arms, if appropriate. The median event time and 2-sided 95% CI for the median were to be provided. The HR and its 95% CI were also to be estimated.
- Plots of survival curves. For KM analyses significant at the 0.05 level (unadjusted) for axitinib, ROC curves prediction OS from the biomarker (actual value) were to be provided.
- A listing of biomarker soluble protein data including, at a minimum, center, subject identification, randomization number, treatment code, accession number, analyte, visit, and result.

Patient Reported Outcomes

The EQ-5D questionnaires were to be scored according to the EQ-5D User's Guide. At each assessment time point and for each treatment arm, the proportion of individuals scoring at each of the 3 levels (no, some, extreme problems) on each of the 5 health dimensions and the score on the EQ-VAS were calculated.

The FACT-Hep questionnaire was scored in accordance with the FACIT Measurement System Manual (Version 4). Overall between treatment comparisons of functional assessment of cancer therapy – hepatobiliary questionnaire (FACT-Hep), EQ-5D, euroQoL visual analogue scale (EQ-VAS), fact hepatobiliary symptom index (FHSI-8), functional assessment of cancer therapy – general (FACT-G), FACT-G subscales, FACT Hep- cancer subscale (CS) 18, and Hep- (trial outcome index) TOI based on the Repeated Measures

Mixed Effects Model is presented in this report. Additionally, time to deterioration analysis has also been presented for FHSI-8.

For the FACT-Hep and EQ-5D, an ambiguous answer to a question was assigned the worst score of the answers circled. For the individual domains of FACT-Hep and FACT-G, a prorated subscale score was calculated as long as more than 50% of the items were answered. The overall FACT-G and FACT-Hep were scored if the overall item response rate was >80% (eg, for FACT-G, at least 22 of the 27 items). Prorated subscale score=[Sum of item scores] x [N of items in subscale] / [N of items answered]. For the EQ-5D, questions not answered were considered to be missing items, and were neither imputed nor utilized. For the EQ-5D, since each dimension had a single item, responses to all 5 items were needed to calculate an index-based summary score.

Safety analyses

Safety data was summarized for the Safety Analysis Set overall. All AEs reported during the study (including 28 days after the final dose of treatment) were considered as treatment-emergent adverse events (TEAEs). All AEs were coded by system organ class (SOC) and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0. The number and percentage of subjects who experienced any adverse event (AE), who experienced any serious adverse event (SAE), who experienced non-serious all causality and treatment related TEAEs, who experienced any treatment-related SAE, and who discontinued because of an AE were presented. Safety data were summarized using descriptive statistics.

## RESULTS

### Subject Disposition and Demography

Subject disposition data in non-randomized and randomized subjects are presented in Table 3 and Table 4 respectively.

*Non-randomized:*

A total of 13 centers from 4 countries screened and assigned 22 subjects (15 in the Child-Pugh A cohort and 7 in the Child-Pugh B cohort) to study treatment between 06 Dec 2010 and 23 Aug 2013. None of them completed the non-randomized phase; however, one subject was ongoing at date of cut-off. The primary reasons for discontinuation from study in the Child-Pugh A and B cohorts were: subject died (14 [93.3%] and 6 [85.7%] subjects, respectively) and subject refused further follow-up (1 [6.7%] and 0 subjects, respectively).

*Randomized:*

A total of 70 centers from 13 countries screened and assigned 202 subjects (134 in the axitinib arm and 68 in the placebo arm) to study treatment between 06 Dec 2010 and 12 Jul 2012. None of them completed the randomized phase. A total of 14 subjects in the axitinib arm and 13 subjects in the placebo arm were ongoing at data cut-off. The primary reasons for discontinuation from study in the axitinib and placebo arms were: subject died (101 [75.4%] and 52 [76.5%] subjects), subject refused further follow-up (11 [8.2%] and 2 [2.9%] subjects) and lost to follow-up (1 [0.7%] and 0 subjects, respectively).

## Table 3: Subject Disposition: Non-randomized Subjects

| | n (%) | | |
|---|---|---|---|
| | **Child-Pugh A (N=15)** | **Child-Pugh B (N=7)** | **Total (N=22)** |
| **Screened** | 22 | | 22 |
| **Assigned to study treatment** | 15 | 7 | 22 |
| Treated | 15 | 7 | 22 |
| Completed | 0 | 0 | 0 |
| Ongoing at date of cut-off | 0 | 1 (14.3) | 1 (4.5) |
| Ongoing in Follow-up | 0 | 1 (14.3) | 1 (4.5) |
| **Primary reason for discontinuation from study** | | | |
| Subject died | 14 (93.3) | 6 (85.7) | 20 (90.9) |
| Subject refused further follow-up | 1 (6.7) | 0 | 1 (4.5) |
| **Primary reason for discontinuation from study treatment** | | | |
| Objective progression or relapse | 11 (73.3) | 5 (71.4) | 16 (72.7) |
| Global deterioration of health status | 1 (6.7) | 0 | 1 (4.5) |
| Adverse event | 1 (6.7) | 1 (14.3) | 2 (9.1) |
| Subject died | 2 (13.3) | 0 | 2 (9.1) |
| No longer willing to participate in study | 0 | 1 (14.3) | 1 (4.5) |
| **Analyzed for Safety** | | | |
| Adverse events | 15 (100.0) | 7 (100.0) | 22 (100.0) |
| Laboratory data | 15 (100.0) | 7 (100.0) | 22 (100.0) |
| **Full Analysis Set[1]** | 15 (100.0) | 7 (100.0) | 22 (100.0) |
| **Safety Analysis Set[2]** | 15 (100.0) | 7 (100.0) | 22 (100.0) |

Number of Subjects Evaluable for adverse events is total number of subjects who received at least one dose of study treatment. Number of Subjects Evaluable for lab is the total number of subjects with at least one post-baseline non missing lab result collected who also received at least one dose of study treatment.
Subjects were treated with axitinib 5 mg BID for Child-Pugh A and 2 mg BID for Child-Pugh B.
[1]: Full Analysis Set includes all subjects who are enrolled with study drug assignment designated, regardless of whether subjects receive study drug or receive different drug from that to which they are randomized.
[2]: Safety Analysis set consists of all subjects who received at least 1 dose of study medication.

**Table 4: Subject Disposition: Randomized Subjects**

| | n (%) | | |
|---|---|---|---|
| | **Axitinib (N=134)** | **Placebo (N=68)** | **Total (N=202)** |
| **Screened** | | | **202** |
| **Assigned to study treatment** | **134** | **68** | **202** |
| Treated | 133 | 68 | 201 |
| Completed | 0 | 0 | 0 |
| Discontinued from Study | 113 (84.3) | 54 (79.4) | 167 (82.7) |
| Ongoing at date of cut-off | 21 (15.7) | 14 (20.6) | 35 (17.3) |
| Ongoing on Treatment | 7 (5.2) | 1 (1.5) | 8 (4.0) |
| Ongoing in Follow-up | 14 (10.4) | 13 (19.1) | 27 (13.4) |
| **Primary reason for discontinuation from study** | | | |
| Subject died | 101 (75.4) | 52 (76.5) | 153 (75.7) |
| Subject refused further follow-up | 11 (8.2) | 2 (2.9) | 13 (6.4) |
| Lost to follow-up | 1 (0.7) | 0 | 1 (0.5) |
| **Primary reason for discontinuation from study treatment** | | | |
| Objective progression or relapse | 70 (52.2) | 50 (73.5) | 120 (59.4) |
| Global deterioration of health status | 6 (4.5) | 2 (2.9) | 8 (4.0) |
| Adverse event | 31 (23.1) | 8 (11.8) | 39 (19.3) |
| Subject died | 5 (3.7) | 3 (4.4) | 8 (4.0) |
| No longer willing to participate in study | 11 (8.2) | 2 (2.9) | 13 (6.4) |
| Other | 4 (3.0) | 2 (2.9) | 6 (3.0) |
| **Analyzed for safety** | | | |
| Adverse events | 133 (99.3) | 68 (100.0) | 201 (99.5) |
| Laboratory data | 133 (99.3) | 67 (98.5) | 200 (99.0) |
| **Full Analysis Set[1]** | 134 (100.0) | 68 (100.0) | 202 (100.0) |
| **Safety Analysis Set[2]** | 133 (99.3) | 68 (100.0) | 201 (99.5) |

[1]:Full Analysis Set includes all subjects who are randomized with study drug assignment designated, regardless of whether subjects receive study drug or receive different drug from that to which they are randomized.
[2]: Safety Analysis set consists of all subjects who received at least 1 dose of study medication at that cycle with treatment assignment designated according to actual study treatment received.

Demographic and baseline characteristics are presented in Table 5 and Table 6 for the non-randomized and randomized subjects respectively. Mean age of the subjects were balanced between the treatment groups in both the phases. Most of the subjects were male in both the non-randomized and randomized phases (77.3% in the non-randomized portion and 82.2% in randomized portion).

## Table 5: Demographic and Baseline Characteristics Based on CRF Data: Non-randomized Subjects

| | Child-Pugh A (N=15) | Child-Pugh B (N=7) | Total (N=22) |
|---|---|---|---|
| **Age (years)** | | | |
| Mean (SD) | 57.8 (13.09) | 59.9 (7.06) | 58.5 (11.38) |
| Median | 59.00 | 62.00 | 59.00 |
| Min, Max | 38, 80 | 51, 70 | 38, 80 |
| **Age (years) [n (%)]** | | | |
| <65 | 9 (60.0) | 5 (71.4) | 14 (63.6) |
| >=65 | 6 (40.0) | 2 (28.6) | 8 (36.4) |
| **Sex [n (%)]** | | | |
| Male | 12 (80.0) | 5 (71.4) | 17 (77.3) |
| Female | 3 (20.0) | 2 (28.6) | 5 (22.7) |
| **Vascular Invasion and/or Extrahepatic Spread** | | | |
| Present | 12 (80.0) | 4 (57.1) | 16 (72.7) |
| Absent | 3 (20.0) | 3 (42.9) | 6 (27.3) |
| **Geographic Region**[1] | | | |
| Asian Sites | 11 (73.3) | 5 (71.4) | 16 (72.7) |
| Hong Kong | 1 (6.7) | 0 | 1 (4.5) |
| Japan | 4 (26.7) | 3 (42.9) | 7 (31.8) |
| Korea | 6 (40.0) | 2 (28.6) | 8 (36.4) |
| Non-Asian Sites | 4 (26.7) | 2 (28.6) | 6 (27.3) |
| USA | 4 (26.7) | 2 (28.6) | 6 (27.3) |

Abbreviations: CRF = case report form; SD = standard deviation; USA = United States of America.

[1]Country information is derived from IMPALA data.

## Table 6: Demographic and Baseline Characteristics (Full Analysis Set): Randomized Subjects

| | Axitinib (N=134) | Placebo (N=68) | Total (N=202) |
|---|---|---|---|
| **Age (years)** | | | |
| Mean (SD) | 61.2 (11.30) | 62.2 (11.81) | 61.5 (11.45) |
| Median | 61.00 | 63.00 | 61.00 |
| Min, Max | 25, 84 | 26, 83 | 25, 84 |
| **Age (years) [n (%)]** | | | |
| <65 | 81 (60.4) | 36 (52.9) | 117 (57.9) |
| >=65 | 53 (39.6) | 32 (47.1) | 85 (42.1) |
| **Sex [n (%)]** | | | |
| Male | 110 (82.1) | 56 (82.4) | 166 (82.2) |
| Female | 24 (17.9) | 12 (17.6) | 36 (17.8) |
| **Vascular Invasion and/or Extrahepatic Spread** | | | |
| Present | 102 (76.1) | 52 (76.5) | 154 (76.2) |
| Absent | 32 (23.9) | 16 (23.5) | 48 (23.8) |
| **Vascular Invasion and/or Extrahepatic Spread[1]** | | | |
| Present | 97 (72.4) | 50 (73.5) | 147 (72.8) |
| Absent | 37 (27.6) | 18 (26.5) | 55 (27.2) |
| **Geographic Region[1]** | | | |
| Asian Sites | 83 (61.9) | 41 (60.3) | 124 (61.4) |
| China | 13 (9.7) | 7 (10.3) | 20 (9.9) |
| Hong Kong | 6 (4.5) | 6 (8.8) | 12 (5.9) |
| Japan | 26 (19.4) | 11 (16.2) | 37 (18.3) |
| Korea | 25 (18.7) | 11 (16.2) | 36 (17.8) |
| Taiwan | 13 (9.7) | 6 (8.8) | 19 (9.4) |
| Non-Asian Sites | 51 (38.1) | 27 (39.7) | 78 (38.6) |
| Belgium | 1 (0.7) | 0 | 1 (0.5) |
| France | 19 (14.2) | 14 (20.6) | 33 (16.3) |
| Germany | 5 (3.7) | 3 (4.4) | 8 (4.0) |
| Hungary | 3 (2.2) | 0 | 3 (1.5) |
| Italy | 7 (5.2) | 1 (1.5) | 8 (4.0) |
| Slovakia | 2 (1.5) | 2 (2.9) | 4 (2.0) |
| USA | 10 (7.5) | 3 (4.4) | 13 (6.4) |
| United Kingdom | 4 (3.0) | 4 (5.9) | 8 (4.0) |

Abbreviation: IVRS=Interactive Voice Response System; SD = standard deviation; USA = United States of America.[1] From IVRS data; Country information is derived from IMPALA data.

## Efficacy, Pharmacokinetic, Pharmacodynamic, or Outcomes Research Results

Efficacy endpoints were not evaluated in the non-randomized subjects. Tabular summaries of the secondary endpoints in randomized subjects are presented in below sections.

## Efficacy results

Primary endpoint

*Overall survival:*

The OS in HCC subjects receiving axitinib+BSC or placebo+BSC are presented in Table 7. Controlling for baseline stratification factors, tumor invasion (presence versus absence of extrahepatic spread and/or vascular invasion) and geographic region (Asian versus non-Asian sites), the estimated stratified HR (axitinib versus placebo) was 0.907 (95% CI: 0.646, 1.274; one-sided p=0.2872). The median OS was 12.7 months (95% CI: 10.2, 14.9) in the axitinib arm and 9.7 months (95% CI: 5.9, 11.8) in the placebo arm. The Axitinib didn't show OS benefit.

**Table 7: Overall Survival (Overall Stratified Analysis; Full Analysis Set): Randomized Subjects**

| | Axitinib (N=134) | Placebo (N=68) |
|---|---|---|
| **Number of deaths [n (%)]** | 101 (75.4) | 52 (76.5) |
| **Cause of death [n (%)]** | | |
| Disease Under Study | 91 (90.1) | 47 (90.4) |
| Unknown | 4 (4.0) | 2 (3.8) |
| Other | 6 (5.9) | 4 (7.7) [6] |
| **Number censored [n (%)]** [1] | 33 (24.6) | 16 (23.5) |
| **Reason for censorship [n (%)]** | | |
| Alive | 21 (63.6) | 14 (87.5) |
| Subject No Longer Willing To Participate | 11 (33.3) | 2 (12.5) |
| Lost To Follow-Up | 1 (3.0) | 0 |
| **1-year Survival Probability (95% Confidence Interval)** [2] | 54.8 [45.7, 62.9] | 37.9 [26.4, 49.4] |
| **Kaplan-Meier estimates of Time to Event (Months)** | | |
| **Quartiles (95% Confidence Interval)** [3] | | |
| 25% | 5.5 [4.3, 6.9] | 3.5 [2.7, 5.2] |
| 50% | 12.7 [10.2, 14.9] | 9.7 [5.9, 11.8] |
| 75% | 22.8 [19.0, 26.2] | 19.1 [13.3, -] |
| Hazard Ratio(Axitinib Versus Placebo)[4] | 0.907 | |
| 95% Confidence Interval for Hazard Ratio | [0.646, 1.274] | |
| P-value [5] | 0.2872 | |

Abbreviation: IVRS= Interactive Voice Response System.
Subjects with multiple reasons for death are counted separately for each individual reason in the sub-category counts.
[1] Subjects still alive on the PCD (primary outcome completion) date are censored on PCD date. Subjects with unknown survival status at the PCD date are censored on the date they were last known to be alive prior to PCD date.
[2] Calculated from the log[-log(12-month survival probability)] using a normal approximation and back transformation.
[3] Based on the Brookmeyer and Crowley Method.
[4] Assuming proportional hazards, a hazard ratio <1 indicates reduction in hazard rate to favor Axitinib; hazard ratio >1 indicates reduction to favor Placebo.
[5] For the Overall Stratified Analysis the p-value is from a 1-sided log-rank test of treatment stratified by Tumor Invasion and Geographic Region.
Tumor Invasion is from IVRS data; Geographic region includes Asian Sites/Non-Asian Sites.
[6] Details about death 'other' are reported in Table 29.

## Secondary endpoints

*Progression-free Survival:*

Summary of PFS by treatment (stratified analysis) is presented in Table 8. The estimated HR (axitinib versus placebo) was 0.618 (95% CI: 0.438, 0.871; one-sided p=0.0039) stratified by tumor invasion (present, absent) and geographic region (Asian, non-Asian sites), representing a decrease of 38.2% in risk of progression or death before progression for axitinib over placebo. PFS was statistically significant between the groups (p=0.0039).

*Time to Progression:*

A summary of time to tumor progression by treatment (stratified analysis; derived investigator's assessment) for the FAS is presented in Table 9. The HR (axitinib versus placebo) was 0.621 (95% CI: 0.434, 0.889) indicating TTP was statistically significant between the groups (p=0.006).

*Overall Response Rate:*

A summary of ORR by treatment (stratified analysis) for the FAS is presented in Table 10. The risk ratio (axitinib versus placebo) was 3.172 (95% CI: 0.759, 13.265). ORR between the two treatment arms were not statistically significant (p=0.0914).

*Duration of Response:*

A summary of DR among responders by treatment (unstratified analysis; derived investigator's assessment) for the FAS is presented in Table 11. The median DR was 6.4 months (95% CI: 3.7, 9.3) in the axitinib arm and not evaluable in the placebo arm.

*Clinical Benefit Rate:*

A summary of CBR by treatment (stratified analysis) for the FAS is presented in Table 12. A total of 42 (31.3%) subjects in the axitinib arm and 8 (11.8%) subjects in the placebo arm had an overall clinical benefit response rate (CR+PR+stable disease with ≥8 weeks to treatment failure). The risk ratio (axitinib versus placebo) was 2.650 (95% CI: 1.319, 5.326) and p=0.0025. The difference between the axitinib and placebo arms was statistically significant (p = 0.0025).

## Table 8: Progression-Free Survival (Overall Stratified Analysis; Derived Investigator's Assessment; Full Analysis Set): Randomized Subjects

| | Axitinib (N=134) | Placebo (N=68) |
|---|---|---|
| **Subject observed to have progressed or died due to any cause while on study [n (%)]** [1] | 105 (78.4) | 54 (79.4) |
| Type of event [n (%)] | | |
| Objective progression | 99 (94.3) | 49 (90.7) |
| Increase in Existing Lesion (Target or Non-Target) | 54 (54.5) | 22 (44.9) |
| New Lesion | 24 (24.2) | 7 (14.3) |
| Increase and a New Lesion | 21 (21.2) | 20 (40.8) |
| Death without objective Progression | 6 (5.7) | 5 (9.3) |
| **Subject did not progress or die due to any cause while on study [n (%)]** [1] | 29 (21.6) | 14 (20.6) |
| Reason for censorship [n (%)] | | |
| No adequate baseline assessments | 1 (3.4) | 1 (7.1) |
| No on-study disease assessments | 6 (20.7) | 3 (21.4) |
| Given new anti-cancer treatment prior to tumor progression | 1 (3.4) | 1 (7.1) |
| Off treatment prior to progression | 14 (48.3) | 6 (42.9) |
| Withdrew consent for follow-up | 0 | 1 (7.1) |
| Progressive disease or death occurs after >=2 consecutive, missed assessments | 3 (10.3) | 1 (7.1) |
| In follow-up for progression | 4 (13.8) | 1 (7.1) |
| **Kaplan-Meier estimates of Time to Event (Months)** | | |
| Quartiles (95% Confidence Interval) [2] | | |
| 25% | 1.9 [1.8, 1.9] | 1.8 [1.7, 1.8] |
| 50% | 3.6 [2.3, 4.6] | 1.9 [1.9, 3.5] |
| 75% | 7.4 [7.3, 9.1] | 3.7 [3.5, 6.8] |
| Hazard Ratio(Axitinib Versus Placebo)[3] | 0.618 | |
| 95% Confidence Interval for Hazard Ratio | [0.438, 0.871] | |
| P-value [4] | 0.0039 | |

Abbreviation: IVRS= Interactive Voice Response System.
Subjects are considered to have adequate baseline assessments if all target and non-target lesions with non-missing lesion site are collected within 28 days prior to first treatment date and if all target lesions are measurable.
[1] On study includes treatment plus 28-day follow-up period.
[2] Based on the Brookmeyer and Crowley Method.
[3] Assuming proportional hazards, a hazard ratio <1 indicates a reduction in hazard rate in favor of Axitinib; a hazard ratio >1 indicates a reduction in favor of Placebo.
[4] For the Overall Stratified Analysis the p-value is from a 1-sided log-rank test of treatment stratified by Tumor invasion and Geographic Region.
Tumor invasion is from IVRS data; Geographic region includes Asian Sites/Non-Asian Sites.

## Table 9: Time to Tumor Progression (Overall Stratified Analysis; Derived Investigator's Assessment; Full Analysis Set): Randomized Subjects

| | Axitinib (N=134) | Placebo (N=68) |
|---|---|---|
| **Overall stratified analysis** | **134** | **68** |
| **Number with event [n (%)]** [1] | 99 (73.9) | 49 (72.1) |
| **Number censored [n (%)]** [1] | 35 (26.1) | 19 (27.9) |
| **Reason for censorship [n (%)]** | | |
| No adequate baseline assessments | 1 (2.9) | 1 (5.3) |
| No on-study disease assessments | 11 (31.4) | 6 (31.6) |
| Given new anti-cancer treatment prior to tumor progression | 1 (2.9) | 1 (5.3) |
| Death on treatment without progression | 2 (5.7) | 2 (10.5) |
| Off treatment prior to progression | 12 (34.3) | 5 (26.3) |
| Withdrew consent for follow-up | 2 (5.7) | 2 (10.5) |
| PD or death occurs after >=2 consecutive, missed assessments | 2 (5.7) | 1 (5.3) |
| In follow-up for progression | 4 (11.4) | 1 (5.3) |
| **Kaplan-Meier estimates of Time to Event (Months)** | | |
| Quartiles (95% Confidence Interval) [2] | | |
| 25% | 1.9 [1.8, 1.9] | 1.8 [1.7, 1.9] |
| 50% | 3.7 [2.8, 5.6] | 1.9 [1.9, 3.6] |
| 75% | 7.4 [7.3, 9.2] | 3.9 [3.6, 7.4] |
| Hazard Ratio(Axitinib Versus Placebo)[3] | 0.621 | |
| 95% Confidence Interval for Hazard Ratio | [0.434, 0.889] | |
| P-value [4] | 0.006 | |

Abbreviation: IVRS = Interactive Voice Response System; PD = Progressive disease.
[1] On study includes treatment plus 28-day follow-up period.
[2] Based on the Brookmeyer and Crowley Method.
[3] Assuming proportional hazards, a hazard ratio <1 indicates a reduction in hazard rate in favor of Axitinib; a hazard ratio >1 indicates a reduction in favor of Placebo.
[4] For the Overall Stratified Analysis the p-value is from a 1-sided log-rank test of treatment stratified by Tumor invasion and Geographic Region.
Tumor invasion is from IVRS data; Geographic region includes Asian Sites/Non-Asian Sites.

## Table 10: Objective Response Rate (Overall Stratified Analysis, Derived Investigator's Assessment; Full Analysis Set): Randomized Subjects

| | Axitinib (N=134) | Placebo (N=68) |
|---|---|---|
| **Subjects with Baseline Assessment [n (%)]** | 133 (99.3) | 67 (98.5) |
| **Subjects with Measurable Disease at Baseline [n (%)]** | 131 (97.8) | 66 (97.1) |
| **Best Overall Response [n (%)]** | | |
| Complete Response | 1 (0.7) | 0 |
| Partial Response | 12 (9.0) | 2 (2.9) |
| Stable Disease | 49 (36.6) | 20 (29.4) |
| Progressive Disease | 55 (41.0) | 38 (55.9) |
| Symptomatic deterioration | 1 (0.7) | 0 |
| Early Death [1] | 5 (3.7) | 3 (4.4) |
| Indeterminate | 11 (8.2) | 5 (7.4) |
| **Overall Confirmed Objective Response Rate (Complete Response + Partial Response)** | 13 (9.7%) | 2 (2.9%) |
| 95% Exact Confidence Interval [2] | [5.3%, 16.0%] | [0.4%, 10.2%] |
| **Treatment Comparison (Axitinib vs Placebo)** [3] | 3.172 | |
| 95% Confidence Interval [3] | [0.759, 13.265] | |
| p-value [4] | 0.0914 | |

[1] Early death is defined as death occurring within 8 weeks from start date and prior to new anti-cancer treatment.
[2] Using exact method based on F-distribution.
[3] Risk Ratio and CI based on the Mantel-Haenszel estimator; risk ratio is adjusted for Geographical Region and Vascular Invasion and Extra Hepatic Spread.
[4] P-value is from Cochran-Mantel-Haenszel test of treatment stratified by Geographical Region and Vascular Invasion and Extra Hepatic Spread.

## Table 11: Duration of Response (Overall Unstratified Analysis, Derived Investigator's Assessment (Full Analysis Set): Randomized Subjects

| | Axitinib (N=13) | Placebo (N=2) |
|---|---|---|
| **Subject observed to have progressed or died due to any cause while on study [n (%)]** [1] | 10 (76.9) | 0 |
| **Type of event [n (%)]** | | |
| Objective progression | 10 (100.0) | 0 |
| Death without objective Progression | 0 | 0 |
| **Subject did not progress or die due to any cause while on study [n (%)]** [1] | 3 (23.1) | 2 (100.0) |
| **Kaplan-Meier estimates of Time to Event (Months)** | | |
| Quartiles (95% Confidence Interval) [2] | | |
| 25% | 5.6 [ 1.9, 6.4] | NR |
| 50% | 6.4 [ 3.7, 9.3] | NR |
| 75% | 9.3 [ 5.7, NR ] | NR |

Abbreviation: NR= not reached
[1] On study includes treatment plus 28-day follow-up period.
[2] Based on the Brookmeyer and Crowley Method.

**Table 12: Clinical Benefit Response (Overall Stratified Analysis, Derived Investigator's Assessment; Full Analysis Set): Randomized Subjects**

| | Axitinib (N=134) | Placebo (N=68) |
|---|---|---|
| **Subjects with Baseline Assessment [n (%)]** | 133 (99.3) | 67 (98.5) |
| **Subjects with Measurable Disease at Baseline [n (%)]** | 131 (97.8) | 66 (97.1) |
| **Best Overall Response [n (%)]** | | |
| Complete Response | 1 (0.7) | 0 |
| Partial Response | 12 (9.0) | 2 (2.9) |
| Stable Disease | 49 (36.6) | 20 (29.4) |
| Progressive Disease | 55 (41.0) | 38 (55.9) |
| Symptomatic deterioration | 1 (0.7) | 0 |
| Early Death [1] | 5 (3.7) | 3 (4.4) |
| Indeterminate | 11 (8.2) | 5 (7.4) |
| **Overall Clinical Benefit Response Rate (Complete Response + Partial Response + Stable Disease with >= 8 weeks to treatment failure)** | 42 (31.3%) | 8 (11.8%) |
| 95% Exact Confidence Interval [2] | [23.6% - 39.9%] | [5.2% - 21.9%] |
| **Treatment Comparison (Axitinib vs Placebo)** [3] | 2.650 | |
| 95% Confidence Interval [4] | [1.319, 5.326] | |
| p-value [5] | 0.0025 | |

[1] Early death is defined as death occurring within 8 weeks from start date and prior to new anti-cancer treatment.
[2] Using exact method based on F-distribution.
[3] Risk Ratio and CI based on the Mantel-Haenszel estimator; risk ratio is adjusted for Geographical Region and Vascular Invasion and Extra Hepatic Spread.
[4] For the Overall Stratified Analysis the p-value is from Cochran-Mantel-Haenszel test of treatment stratified by Geographical Region and Vascular Invasion and Extra Hepatic Spread.

## Pharmacokinetic results

*Axitinib pharmacokinetics on cycle 1 day 15 from non-randomized portion:*

PK parameter data from n=12 Child-Pugh A (5 mg BID axitinib dose) and from n=7 Child-Pugh B (2 mg BID axitinib dose) HCC subjects are summarized in Table 13.

**Table 13: Summary of Axitinib Steady-State Pharmacokinetic Parameters Following Administration of Multiple Doses of Axitinib in Subjects with Advanced Hepatocellular Carcinoma**

| Hepatic Impairment status | Axitinib Dose | $C_{max}$ (ng/mL) | $AUC_{0-24}$ (ng.hr/mL) | $T_{max}$ (hr) | CL/F (L/hr) | Vz/F (L) | $t_{1/2}$ (hr) |
|---|---|---|---|---|---|---|---|
| Child-Pugh A; mild hepatic impairment (n=12)[a] | 5 mg BID | 35.7 (59) | 311 (63) | 2.50 (0.00-7.98) | 32.2 (63) | 150 (46) | 4.12 (±3.55) |
| Child-Pugh B; moderate hepatic impairment (n=7)[b] | 2 mg BID | 21.2 (164) | 316 (118) | 1.05 (0.00-4.00) | 12.7 (118) | 81.2 (89) | 4.79 (±2.42) |

Abbreviations: $AUC_{0-24}$=area under the plasma concentration versus time curve from 0 to 24 hr; $C_{max}$=maximum observed plasma concentration; CL/F=apparent oral clearance; %CV=percent coefficient of variation; SD=standard deviation; $t_{1/2}$=terminal plasma elimination half-life; $T_{max}$=time to first occurrence of $C_{max}$; $V_z$/F=apparent oral volume of distribution of the drug during the elimination phase.
Geometric mean (geometric %CV) for $C_{max}$, $AUC_{0-24}$, CL/F and $V_z$/F; arithmetic mean (±SD) for $t_{1/2}$; median with range for $T_{max}$
a $AUC_{0-24}$, CL/F, $V_z$/F and t1/2 were not reported for 4 subjects due to nonestimable half-life.
b $AUC_{0-24}$, CL/F, $V_z$/F and t1/2 was not reported for 1 subject due to nonestimable half-life.

*Randomized portion:*

Results from population PK modeling using data from both serial and sparse sample collections in this study are intended to be reported separately, and are not included in this document.

## Pharmacodynamic Results:

Pharmacodynamic results were evaluated in the randomized portion of this study.

*Micro-RNA Results:*

Baseline samples were analyzed for miRNA transcript analysis. From 181 samples collected, RNA of sufficient quality for Agilent micro-array analysis was generated from 170 subjects. The false discovery rate (a statistical method for adjusting for level of significance with 100s or 1000s of analytes) for potential differences in presence/absence of baseline miRNAs between treatment groups was >0.8 for all 174 miRNAs, indicating high confidence of no differences.

*Soluble Proteins:*

Baseline levels of the soluble proteins analyzed were similar between treatment arms (Table 14).

**Table 14: Concentration of Soluble Proteins at Baseline: Soluble Proteins Analysis Set**

| Mean (SD) | Axitinib (N=120) | Placebo (N=61) | P-value unadjusted[1] | P-value Bonferroni-adjusted[2] |
|---|---|---|---|---|
| IL-6 | 50.67 (102.86) | 50.72 (106.74) | 0.4699 | 1.0000 |
| E-Selectin | 52313.94 (32603.18) | 55430.76 (26723.43) | 0.2060 | 1.0000 |
| IL-8 | 33.35 (47.72) | 27.23 (44.46) | 0.3719 | 1.0000 |
| HGF | 478.84 (712.43) | 406.06 (376.04) | 0.8456 | 1.0000 |
| MMP-2 | 355715.66 (137663.04) | 350979.72 (146323.29) | 0.7054 | 1.0000 |
| SCF | 1352.75 (1534.41) | 1439.71 (2260.89) | 0.7848 | 1.0000 |
| Ang-2 | 662.40 (623.87) | 577.82 (354.42) | 0.8210 | 1.0000 |
| VEGF-A | 102.56 (128.09) | 173.59 (472.19) | 0.2330 | 1.0000 |
| VEGF-C | - | - | - | - |
| sVEGFR2 | 17675.76 (7218.95) | 18273.65 (6836.16) | 0.6135 | 1.0000 |
| sVEGFR3 | 287429.28 (117583.24) | 290338.69 (97830.36) | 0.4704 | 1.0000 |
| SDF1 | 1190.08 (823.03) | 1150.10 (681.04) | 0.9419 | 1.0000 |
| NGAL | 134861.80 (152492.96) | 141383.00 (121747.35) | 0.4401 | 1.0000 |
| MIF | 33057.15 (28256.00) | 32302.99 (21485.01) | 0.4733 | 1.0000 |
| c-MET ELISA | 1664.96 (834.36) | 1641.08 (704.38) | 0.9742 | 1.0000 |
| RANTES | 26412.12 (38682.81) | 26917.76 (27094.12) | 0.2684 | 1.0000 |
| MCP-3 | - | - | | |

'-'% < LLQ was greater than 75% and no summary statistics was provided and those analytes were not included in the count of statistical comparisons for the Bonferroni correction.

[1] P-values from comparison of treatment groups based on the exact two-sided Wilcoxon test, estimated using 1,000,000 Monte Carlo realizations.

[2] Bonferroni-adjusted p-values < 0.05 (or unadjusted p-values < 0.05/15=0.0033) are considered significant.

## Other Results – Patient Reported Outcomes

Patient-Reported Outcomes were evaluated in the randomized portion of this study and are presented in Table 15 and Table 16.

The overall between-treatment comparison for axitinib versus placebo based on the repeated measures mixed effects model was statistically significant favoring placebo for all the PRO variables presented in Table 15 except for FACT-G Subscales SWB and EWB. However, the results were similar between the treatment groups for SWB and EWB.

The time to deterioration based on the composite outcome (death or tumor progression or FHSI-8 mean score decrease ≥3 points, whichever occurred first ) or FHSI-8 mean score decrease alone showed no significant difference between treatment arms (Table 16).

**Table 15: Patient-Reported Outcomes - Overall between Treatment Comparison of FACT-Hep, EQ-5D, EQ-VAS, FHSI-8, FACT-G, FACT-G subscales, FACT Hep-CS18, and Hep-TOI Based on the Repeated Measures Mixed Effects Model - Full Analysis Set**

| | Axitinib (N=134) | Placebo (N=68) |
|---|---|---|
| **FACT-Hep; Estimated Mean (95% CI)** | 123.33 (120.17, 126.50) | 135.22 ( 129.17, 141.27) |
| Overall Comparisons | | |
| Estimated Mean (95% CI) | -11.89 (-18.70, -5.08) | |
| P-Value | 0.0006 | |
| **EQ-5D; Estimated Mean (95% CI)** | 0.67 ( 0.63, 0.70) | 0.79 ( 0.72, 0.86) |
| Overall Comparisons | | |
| Estimated Mean (95% CI) | -0.12 (-0.20, -0.04) | |
| P-Value | 0.0024 | |
| **EQ-VAS; Estimated Mean (95% CI)** | 68.67 (66.11, 71.23) | 75.70 (70.40, 81.00) |
| Overall Comparisons | | |
| Estimated Mean (95% CI) | -7.03 (-12.91, -1.15) | |
| P-Value | 0.0193 | |
| **FHSI-8; Estimated Mean (95% CI)** | 23.42 (22.77, 24.07) | 26.69 (25.35, 28.03) |
| Overall Comparisons | | |
| Estimated Mean (95% CI) | -3.27 (-4.76, -1.78) | |
| P-Value | <.0001 | |
| **FACT-G; Estimated Mean (95% CI)** | 71.20 (69.00, 73.41) | 78.81 (74.68, 82.93) |
| Overall Comparisons | | |
| Estimated Mean (95% CI) | -7.60 (-12.27, -2.94) | |
| P-Value | 0.0014 | |
| **FACT-G Subscale PWB; Estimated Mean (95% CI)** | 19.39 (18.72, 20.07) | 23.13 (21.76, 24.50) |
| Overall Comparisons | | |
| Estimated Mean (95% CI) | -3.74 (-5.26, -2.21) | |
| P-Value | <.0001 | |
| **FACT-G Subscale SWB; Estimated Mean (95% CI)** | 18.94 (18.05, 19.83) | 20.21 (18.66, 21.77) |
| Overall Comparisons | | |
| Estimated Mean (95% CI) | -1.27 (-3.07, 0.52) | |
| P-Value | 0.1642 | |
| **FACT-G Subscale EWB; Estimated Mean (95% CI)** | 17.23 (16.63, 17.84) | 17.71 (16.54, 18.89) |
| Overall Comparisons | | |
| Estimated Mean (95% CI) | -0.48 (-1.80, 0.84) | |

| | | |
|---|---|---|
| P-Value | 0.4759 | |
| **FACT-G Subscale FWB; Estimated Mean (95% CI)** | 15.76 (14.88, 16.65) | 17.83 (16.19, 19.47) |
| Overall Comparisons | | |
| Estimated Mean (95% CI) | -2.07 (-3.92, -0.21) | |
| P-Value | 0.0288 | |
| **FACT Hep-CS18; Estimated Mean (95% CI)** | 51.78 (50.46, 53.10) | 56.74 (54.08, 59.39) |
| Overall Comparisons | | |
| Estimated Mean (95% CI) | -4.96 (-7.93, -1.99) | |
| P-Value | 0.0011 | |
| **FACT Hep-TOI; Estimated Mean (95% CI)** | 87.28 (84.98, 89.58) | 97.73 (93.24, 102.23) |
| Overall Comparisons | | |
| Estimated Mean (95% CI) | -10.45 (-15.49, -5.42) | |
| P-Value | <.0001 | |

Larger values are associated with better health status. Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.
Abbreviations: EQ-5D = EuroQoL 5 Dimensions; EQ-VAS = EuroQoL visual analogue scale; EWB: Emotional well-being; FACT-Hep = Functional assessment of cancer therapy – hepatobiliary questionnaire; FACT Hep-CS18: Functional assessment of cancer therapy - hepatobiliary cancer subscale; FACT-G : Functional assessment of cancer therapy – general; FHSI-8= Fact hepatobiliary symptom index; FWB: Functional well-being; PWB= Physical well-being; SWB= Social/family well-being; TOI = Trial outcome index.

**Table 16: Time to Deterioration (TTD) Based on Composite Endpoint (Death or Tumor Progression or FHSI-8 Mean Score Decrease ≥3 Points, Whichever Comes First) in Randomized Portion: Overall Between-Treatment Comparison Based on Repeated Measures Mixed Effects Model - Full Analysis Set**

| | Axitinib (N=134) | Placebo (N=68) |
|---|---|---|
| **Subject had composite endpoint (death or tumor progression or FHSI-8 decrease >=3 points) while on study [n (%)]** | 131 (97.8) | 63 (92.6) |
| **Subject did not have composite endpoint while on study [n (%)]** | 3 (2.2) | 5 (7.4) |
| **Reason for censorship [n (%)]** | | |
| No adequate assessment of composite endpoint | 0 | 0 |
| Off treatment prior to composite endpoint | 1 (33.3) | 1 (20.0) |
| Subject alive and on study without composite event | 2 (66.7) | 4 (80.0) |
| **Kaplan-Meier estimates of Time to Event (Months)** | | |
| **Quartiles (95% Confidence Interval)** [1] | | |
| 25% | 1.0 [ 1.0, 1.0 ] | 1.7 [ 1.0, 1.8 ] |
| 50% | 1.9 [ 1.8, 1.9 ] | 1.9 [ 1.8, 2.7 ] |
| 75% | 3.7 [ 2.8, 4.4 ] | 3.7 [ 3.3, 6.8 ] |
| **Axitinib Versus Placebo** | | |
| Hazard Ratio [2] | 1.252 | |
| 95% CI for Hazard Ratio [2] | 0.923 - 1.698 | |
| P-value [3] | 0.9182 | |

[1] Based on the Brookmeyer and Crowley Method.
[2] Assuming proportional hazards, a hazard ratio <1 indicates reduction in hazard rate to favor Axitinib, hazard ratio >1 indicates reduction to favor Placebo.
[3] p-value is from a 1-sided, unstratified log-rank test.

**Safety Results:**

Safety overview

Overall summary of all-causality TEAEs in non-randomized and randomized portions are presented in Table 17 and Table 18 respectively. Overview of treatment-related AEs is summarized in Table 19 for the non-randomized subjects and in Table 20 for the randomized subjects.

*Non-randomized:* All subjects in the non-randomized portion experienced TEAEs out of which 14 subjects in the Child-Pugh A cohort and 6 subjects in the Child-Pugh B cohort experienced treatment-related TEAEs.

*Randomized:* TEAEs, SAEs, Grade ≥3 AEs were more frequent in the axitinib arm than in the placebo arm, while the Grade 5 AEs were similar in the two arms. One hundred twenty-eight (128) (96.2%) subjects in the axitinib arm and 40 (58.8%) subjects in the placebo arm experienced treatment-related TEAEs.

**Table 17: Overall Summary of Treatment-Emergent Adverse Events (All Causalities): Non-randomized Subjects**

| | Child-Pugh A (N=15) n (%) | Child-Pugh B (N=7) n (%) |
|---|---|---|
| Subjects evaluable for adverse events | 15 | 7 |
| Subjects with adverse events | 15 (100.0) | 7 (100.0) |
| Subjects with serious adverse events | 10 (66.7) | 3 (42.9) |
| Subjects with ≥Grade 3 adverse events | 13 (86.7) | 5 (71.4) |
| Subjects with Grade 5 adverse events | 4 (26.7) | 1 (14.3) |
| Subjects who discontinued treatment due to adverse events | 4 (26.7) | 1 (14.3) |
| Subjects with dose reduced due to adverse events | 5 (33.3) | 0 (0.0) |
| Subjects with temporary discontinuation due to adverse events | 13 (86.7) | 5 (71.4) |

Subjects were treated with axitinib 5 mg BID for Child-Pugh A and 2 mg BID for Child-Pugh B.
Includes data up to 28 days after last dose of study drug.
CTCAE version 3.
MedDRA (version 17.0) coding dictionary applied.
Abbreviations: BID=Twice daily; CTCAE= Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities.

## Table 18: Overall Summary of Treatment-Emergent Adverse Events (All Causalities) in Randomized Portion: Safety Analysis Set

| | Axitinib (N=133) n (%) | Placebo (N=68) n (%) |
|---|---|---|
| Subjects evaluable for adverse events | 133 | 68 |
| Subjects with adverse events | 131 (98.5) | 63 (92.6) |
| Subjects with serious adverse events | 62 (46.6) | 16 (23.5) |
| Subjects with Grade ≥3 adverse events | 109 (82.0) | 26 (38.2) |
| Subjects with Grade 5 adverse events | 16 (12.0) | 8 (11.8) |
| Subjects who discontinued treatment due to adverse events | 38 (28.6) | 9 (13.2) |
| Subjects with dose reduced due to adverse events | 46 (34.6) | 5 (7.4) |
| Subjects with temporary discontinuation due to adverse events | 87 (65.4) | 17 (25.0) |

Subjects were treated with axitinib+BSC or placebo+BSC.
Includes data up to 28 days after last dose of study drug.
Subjects were counted only once per treatment in each row.
CTCAE version 3.
MedDRA (version 17.0) coding dictionary applied.
Abbreviations: BSC=Best supportive care; CTCAE= Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities.

## Table 19: Overall Summary of Treatment-Related Treatment-Emergent Adverse Events: Non-randomized Subjects

| | Child-Pugh A (N=15) n (%) | Child-Pugh B (N=7) n (%) |
|---|---|---|
| Subjects evaluable for adverse events | 15 | 7 |
| Subjects with adverse events | 14 (93.3) | 6 (85.7) |
| Subjects with serious adverse events | 2 (13.3) | 2 (28.6) |
| Subjects with ≥Grade 3 adverse events | 9 (60.0) | 4 (57.1) |
| Subjects with Grade 5 adverse events | 0 (0.0) | 0 (0.0) |
| Subjects who discontinued treatment due to adverse events | 0 (0.0) | 1 (14.3) |
| Subjects with dose reduced due to adverse events | 5 (33.3) | 0 (0.0) |
| Subjects with temporary discontinuation due to adverse events | 9 (60.0) | 4 (57.1) |

Subjects were treated with axitinib 5 mg BID for Child-Pugh A and 2 mg BID for Child-Pugh B.
Includes data up to 28 days after last dose of study drug.
CTCAE version 3.
MedDRA (version 17.0) coding dictionary applied.
Abbreviations: BID=Twice daily; CTCAE= Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities.

## Table 20: Overall Summary of Treatment-Related Treatment-Emergent Adverse Events in Randomized Subjects: Safety Analysis Set

| | Axitinib (N=133) n (%) | Placebo (N=68) n (%) |
|---|---|---|
| Subjects evaluable for adverse events | 133 | 68 |
| Subjects with adverse events | 128 (96.2) | 40 (58.8) |
| Subjects with serious adverse events | 24 (18.0) | 1 (1.5) |
| Subjects with ≥Grade 3 adverse events | 90 (67.7) | 12 (17.6) |
| Subjects with Grade 5 adverse events | 1 (0.8) | 0 (0.0) |
| Subjects who discontinued treatment due to adverse events | 15 (11.3) | 2 (2.9) |
| Subjects with dose reduced due to adverse events | 46 (34.6) | 4 (5.9) |
| Subjects with temporary discontinuation due to adverse events | 73 (54.9) | 8 (11.8) |

Subjects were treated with axitinib+BSC or placebo+BSC.
Includes data up to 28 days after last dose of study drug.
Subjects were counted only once per treatment in each row.
CTCAE version 3.
MedDRA (version 17.0) coding dictionary applied.
Abbreviations: BSC=Best supportive care; CTCAE= Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary.

Analyses of non-serious TEAEs and SAEs (All causality and treatment related)

The treatment-emergent non-serious AEs reported in >=5% of subjects in any of the treatment arm by preferred term and by SOC (all causality and treatment-related) are summarized in Table 21 for the non-randomized subjects and in Table 22 for the randomized subjects.

SAEs by preferred term and by SOC (all-causality and treatment-related) are summarized in Table 23 for the non-randomized subjects and in Table 24 for the randomized subjects.

*Non-randomized:*

The most frequently reported non-serious, all-causality TEAEs in the non-randomized portion of the study were fatigue (80.0% and 28.6% in the Child Pugh A and Child Pugh B cohorts respectively), diarrhoea (60.0% and 14.3% respectively), palmar-plantar erythrodysaesthesia syndrome (53.3% and 28.6% respectively), hypertension (46.7% and 42.9% respectively), decreased appetite (40.0% and 71.4% respectively), dizziness (40.0% and 0% respectively), and dysphonia (40.0% and 42.9% respectively) (Table 21).

The most frequently reported non-serious, treatment-related TEAEs overall in the non-randomized portion of the study were decreased appetite (40.0% and 71.4% in the Child-Pugh A Child-Pugh B cohort), dysphonia (40.0% and 42.9% respectively), fatigue (60.0% and 28.6% respectively), hypertension (46.7% and 42.9% respectively) and palmar-plantar erythrodysaesthesia syndrome (53.3% and 28.6% respectively) (Table 21).

The most frequently reported SAE in subjects in the Child-Pugh A cohort was disease progression (20.0% of subjects), and no SAE preferred term was reported by >1 subject in the Child-Pugh B cohort. Treatment related SAEs were hyponatraemia, encephalopathy (one subject each in the Child-Pugh B cohort) and enterocolitis haemorrhagic and hypertension (one subject each) in the Child-Pugh A cohort (Table 23).

*Randomized:*

The most frequently reported non-serious, all-causality TEAEs were diarrhoea (53.4% and 11.8% in the axitinib and placebo arms respectively), hypertension (54.1% and 13.2% respectively), and decreased appetite (46.6% and 20.6% respectively) (Table 22).

The most frequently reported non-serious, treatment-related TEAEs were hypertension (54.1% and 13.2% in the axitinib and placebo arms respectively), diarrhoea (45.1% and 7.4% respectively), and decreased appetite (37.6% and 11.8% respectively) (Table 22)).

Sixty-two (62) (46.6%) subjects in the axitinib arm and 16 (23.5%) subjects in the placebo arm experienced SAEs. The most frequently reported SAE in either treatment arm was disease progression (Table 24).

**Table 21: Treatment-Emergent Non-Serious Adverse Events Reported in ≥5% Subjects in Any of the Treatment Arm by System Organ Class and Preferred Term (All Causalities and Treatment-Related) - Non-randomized Subjects**

| System Organ Class<br>Preferred Term | Child Pugh A (N=15) n (%) | | Child Pugh B (N=7) n (%) | |
|---|---|---|---|---|
| | All Causalities | Treatment related | All Causalities | Treatment related |
| **With adverse events** | **15 (100.0)** | **14 (93.3)** | **7 (100.0)** | **6 (85.7)** |
| **Blood and lymphatic system disorders** | **1 (6.7)** | **-** | **0** | **-** |
| Anaemia | 1 (6.7) | - | 0 | - |
| **Cardiac disorders** | **1 (6.7)** | **-** | **0** | **-** |
| Atrial fibrillation | 1 (6.7) | - | 0 | - |
| **Congenital, familial and genetic disorders** | **0** | **0** | **1 (14.3)** | **1 (14.3)** |
| Hydrocele | 0 | 0 | 1 (14.3) | 1 (14.3) |
| **Ear and labyrinth disorders** | **1 (6.7)** | **0** | **1 (14.3)** | **1 (14.3)** |
| Ear disorder | 1 (6.7) | 0 | 1 (14.3) | 1 (14.3) |
| **Endocrine disorders** | **4 (26.7)** | **4 (26.7)** | **0** | **0** |
| Hypothyroidism | 4 (26.7) | 4 (26.7) | 0 | 0 |
| **Eye disorders** | **1 (6.7)** | **-** | **0** | **-** |
| Ocular surface disease | 1 (6.7) | - | 0 | - |
| **Gastrointestinal disorders** | **13 (86.7)** | **10 (66.7)** | **4 (57.1)** | **4 (57.1)** |
| Abdominal distension | 2 (13.3) | 1 (6.7) | 0 | 0 |
| Abdominal pain | 6 (40.0) | 3 (20.0) | 1 (14.3) | 1 (14.3) |
| Abdominal pain upper | 2 (13.3) | 2 (13.3) | 1 (14.3) | 0 |
| Anal inflammation | 2 (13.3) | 2 (13.3) | 0 | 0 |
| Ascites | 1 (6.7) | - | 1 (14.3) | - |
| Constipation | 5 (33.3) | 3 (20.0) | 2 (28.6) | 1 (14.3) |
| Diarrhoea | 9 (60.0) | 8 (53.3) | 1 (14.3) | 1 (14.3) |
| Dry mouth | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Dyspepsia | 5 (33.3) | 1 (6.7) | 2 (28.6) | 1 (14.3) |
| Enterocolitis | 0 | - | 1 (14.3) | - |
| Gastritis erosive | 0 | - | 1 (14.3) | - |
| Glossitis | 0 | 0 | 1 (14.3) | 1 (14.3) |
| Nausea | 5 (33.3) | 3 (20.0) | 3 (42.9) | 3 (42.9) |
| Stomatitis | 3 (20.0) | 3 (20.0) | 0 | 0 |
| Varices oesophageal | 0 | - | 1 (14.3) | - |
| Vomiting | 3 (20.0) | 1 (6.7) | 0 | 0 |

| System Organ Class<br>Preferred Term | Child Pugh A (N=15) n (%) | | Child Pugh B (N=7) n (%) | |
|---|---|---|---|---|
| | All Causalities | Treatment related | All Causalities | Treatment related |
| **General disorders and administration site conditions** | **12 (80.0)** | **10 (66.7)** | **6 (85.7)** | **6 (85.7)** |
| Asthenia | 0 | 0 | 2 (28.6) | 2 (28.6) |
| Catheter site pain | 1 (6.7) | - | 0 | - |
| Chest discomfort | 2 (13.3) | - | 0 | - |
| Chest pain | 2 (13.3) | 1 (6.7) | 0 | 0 |
| Chills | 1 (6.7) | - | 1 (14.3) | - |
| Face oedema | 2 (13.3) | - | 0 | - |
| Fatigue | 12 (80.0) | 9 (60.0) | 2 (28.6) | 2 (28.6) |
| Influenza like illness | 1 (6.7) | - | 0 | - |
| Malaise | 0 | 0 | 2 (28.6) | 2 (28.6) |
| Mucosal inflammation | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Oedema | 1 (6.7) | 0 | 1 (14.3) | 1 (14.3) |
| Oedema peripheral | 4 (26.7) | 1 (6.7) | 1 (14.3) | 0 |
| Pain | 5 (33.3) | 3 (20.0) | 0 | 0 |
| Pyrexia | 3 (20.0) | - | 1 (14.3) | - |
| **Hepatobiliary disorders** | **0** | **1 (6.7)** | **1 (14.3)** | **1 (14.3)** |
| Hyperbilirubinaemia | 0 | 0 | 1 (14.3) | 1 (14.3) |
| **Infections and infestations** | **2 (13.3)** | - | **2 (28.6)** | - |
| Bronchitis | 0 | - | 1 (14.3) | - |
| Cystitis | 1 (6.7) | - | 0 | - |
| Nasopharyngitis | 0 | - | 1 (14.3) | - |
| Pneumonia | 1 (6.7) | - | 0 | - |
| **Injury, poisoning and procedural complications** | **4 (26.7)** | **1 (6.7)** | **0** | **0** |
| Contusion | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Fall | 1 (6.7) | - | 0 | - |
| Laceration | 1 (6.7) | - | 0 | - |
| Procedural pain | 1 (6.7) | - | 0 | - |
| **Investigations** | **9 (60.0)** | **8 (53.3)** | **3 (42.9)** | **3 (42.9)** |
| Alanine aminotransferase increased | 2 (13.3) | 2 (13.3) | 0 | 0 |
| Alpha 1 foetoprotein increased | 1 (6.7) | - | 0 | - |
| Ammonia increased | 1 (6.7) | - | 0 | - |
| Aspartate aminotransferase increased | 4 (26.7) | 2 (13.3) | 0 | 0 |

| System Organ Class<br>Preferred Term | Child Pugh A (N=15) n (%) | | Child Pugh B (N=7) n (%) | |
|---|---|---|---|---|
| | All Causalities | Treatment related | All Causalities | Treatment related |
| Blood alkaline phosphatase increased | 2 (13.3) | 1 (6.7) | 0 | 0 |
| Blood bilirubin increased | 1 (6.7) | - | 0 | - |
| Blood creatinine increased | 0 | 0 | 1 (14.3) | 1 (14.3) |
| Blood thyroid stimulating hormone increased | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Gamma-glutamyltransferase increased | 3 (20.0) | 2 (13.3) | 0 | 0 |
| Neutrophil count decreased | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Platelet count decreased | 2 (13.3) | 2 (13.3) | 0 | 0 |
| Weight decreased | 5 (33.3) | 4 (26.7) | 3 (42.9) | 3 (42.9) |
| **Metabolism and nutrition disorders** | **9 (60.0)** | **7 (46.7)** | **5 (71.4)** | **5 (71.4)** |
| Decreased appetite | 6 (40.0) | 6 (40.0) | 5 (71.4) | 5 (71.4) |
| Hypercalcaemia | 0 | 0 | 1 (14.3) | 1 (14.3) |
| Hyperkalaemia | 0 | 0 | 1 (14.3) | 1 (14.3) |
| Hypoalbuminaemia | 4 (26.7) | 1 (6.7) | 2 (28.6) | 1 (14.3) |
| Hypocalcaemia | 1 (6.7) | 0 | 1 (14.3) | 1 (14.3) |
| Hypokalaemia | 0 | 0 | 1 (14.3) | 1 (14.3) |
| Hyponatraemia | 1 (6.7) | 0 | 3 (42.9) | 3 (42.9) |
| Hypophosphataemia | 1 (6.7) | 1 (6.7) | 0 | 0 |
| **Musculoskeletal and connective tissue disorders** | **11 (73.3)** | **4 (26.7)** | **2 (28.6)** | **1 (14.3)** |
| Arthralgia | 2 (13.3) | - | 0 | - |
| Arthropathy | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Back pain | 4 (26.7) | - | 1 (14.3) | - |
| Bone pain | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Flank pain | 4 (26.7) | - | 0 | - |
| Muscle spasms | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Muscular weakness | 0 | 0 | 1 (14.3) | 1 (14.3) |
| Musculoskeletal chest pain | 1 (6.7) | - | 0 | - |
| Musculoskeletal discomfort | 1 (6.7) | - | 0 | - |
| Musculoskeletal pain | 2 (13.3) | - | 0 | - |
| Musculoskeletal stiffness | 1 (6.7) | - | 0 | - |
| Myalgia | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Neck pain | 1 (6.7) | - | 0 | - |
| Pain in extremity | 2 (13.3) | 1 (6.7) | 0 | 0 |

| System Organ Class<br>Preferred Term | Child Pugh A (N=15) n (%) | | Child Pugh B (N=7) n (%) | |
|---|---|---|---|---|
| | All Causalities | Treatment related | All Causalities | Treatment related |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **0** | **-** | **1 (14.3)** | **-** |
| Tumour associated fever | 0 | - | 1 (14.3) | - |
| **Nervous system disorders** | **8 (53.3)** | **7 (46.7)** | **3 (42.9)** | **3 (42.9)** |
| Dysgeusia | 0 | - | 0 | - |
| Dizziness | 6 (40.0) | 5 (33.3) | 0 | 0 |
| Headache | 5 (33.3) | 3 (20.0) | 2 (28.6) | 2 (28.6) |
| Hepatic encephalopathy | 0 | 0 | 1 (14.3) | 1 (14.3) |
| Neuropathy peripheral | 1 (6.7) | - | 0 | - |
| Peripheral sensory neuropathy | 2 (13.3) | 1 (6.7) | 0 | 0 |
| Tremor | 0 | 0 | 1 (14.3) | 1 (14.3) |
| **Psychiatric disorders** | **6 (40.0)** | **3 (20.0)** | **1 (14.3)** | **0** |
| Agitation | 1 (6.7) | - | 0 | - |
| Confusional state | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Depression | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Insomnia | 2 (13.3) | 1 (6.7) | 1 (14.3) | 0 |
| Irritability | 1 (6.7) | - | 0 | - |
| **Renal and urinary disorders** | **6 (40.0)** | **4 (26.7)** | **1 (14.3)** | **1 (14.3)** |
| Chromaturia | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Dysuria | 1 (6.7) | - | 0 | - |
| Pollakiuria | 1 (6.7) | - | 0 | - |
| Proteinuria | 4 (26.7) | 4 (26.7) | 1 (14.3) | 1 (14.3) |
| **Respiratory, thoracic and mediastinal disorders** | **10 (66.7)** | **8 (53.3)** | **4 (57.1)** | **4 (57.1)** |
| Cough | 3 (20.0) | 1 (6.7) | 0 | 0 |
| Dysphonia | 6 (40.0) | 6 (40.0) | 3 (42.9) | 3 (42.9) |
| Dyspnoea | 3 (20.0) | 1 (6.7) | 1 (14.3) | 0 |
| Epistaxis | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Haemoptysis | 1 (6.7) | 0 | 1 (14.3) | 1 (14.3) |
| Interstitial lung disease | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Nasal congestion | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Nasal inflammation | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Oropharyngeal pain | 2 (13.3) | 1 (6.7) | 0 | 0 |
| Productive cough | 0 | 0 | 1 (14.3) | 1 (14.3) |

| **System Organ Class**<br>Preferred Term | **Child Pugh A (N=15) n (%)** | | **Child Pugh B (N=7) n (%)** | |
|---|---|---|---|---|
| | **All Causalities** | **Treatment related** | **All Causalities** | **Treatment related** |
| Upper respiratory tract inflammation | 1 (6.7) | 1 (6.7) | 0 | 0 |
| **Skin and subcutaneous tissue disorders** | **11 (73.3)** | **11 (73.3)** | **3 (42.9)** | **3 (42.9)** |
| Blister | 2 (13.3) | 2 (13.3) | 0 | 0 |
| Dry skin | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Facial wasting | 1 (6.7) | - | 0 | - |
| Nail disorder | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Night sweats | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | 8 (53.3) | 8 (53.3) | 2 (28.6) | 2 (28.6) |
| Petechiae | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Pruritus | 0 | 0 | 1 (14.3) | 1 (14.3) |
| Rash | 2 (13.3) | 2 (13.3) | 2 (28.6) | 2 (28.6) |
| Skin ulcer | 0 | 0 | 1 (14.3) | 1 (14.3) |
| **Vascular disorders** | **8 (53.3)** | **7 (46.7)** | **3 (42.9)** | **3 (42.9)** |
| Hypertension | 7 (46.7) | 7 (46.7) | 3 (42.9) | 3 (42.9) |
| Hypotension | 1 (6.7) | - | 0 | - |

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.
Note: The symbol '-' in the table indicates data not provided in the source table as the subject had not experienced that particular event.
MedDRA (v17.0) coding dictionary applied.

**Table 22: Treatment-Emergent Non-Serious Adverse Events Reported in ≥5% Subjects in Any of the Treatment Arm by System Organ Class and Preferred Term (All Causalities and Treatment-Related) - Randomized Subjects**

| System Organ Class<br>Preferred Term | Axitinib (N=133) n (%) | | Placebo (N=68) n (%) | |
|---|---|---|---|---|
| | All Causalities | Treatment related | All Causalities | Treatment related |
| **With adverse events** | **130 (97.7)** | **125 (94.0)** | **55 (80.9)** | **33 (48.5)** |
| **Blood and lymphatic system disorders** | **8 (6.0)** | **8 (6.0)** | **0** | **0** |
| Thrombocytopenia | 8 (6.0) | 8 (6.0) | 0 | 0 |
| **Endocrine disorders** | **33 (24.8)** | **31 (23.3)** | **0** | **0** |
| Hypothyroidism | 33 (24.8) | 31 (23.3) | 0 | 0 |
| **Gastrointestinal disorders** | **102 (76.7)** | **84 (63.2)** | **33 (48.5)** | **17 (25.0)** |
| Abdominal distension | 5 (3.8) | - | 7 (10.3) | - |
| Abdominal pain | 45 (33.8) | 23 (17.3) | 12 (17.6) | 2 (2.9) |
| Abdominal pain upper | 17 (12.8) | 7 (5.3) | 3 (4.4) | 3 (4.4) |
| Constipation | 21 (15.8) | 11 (8.3) | 8 (11.8) | 4 (5.9) |
| Diarrhoea | 71 (53.4) | 59 (44.4) | 8 (11.8) | 5 (7.4) |
| Dry mouth | 7 (5.3) | - | 2 (2.9) | - |
| Dyspepsia | 10 (7.5) | 10 (7.5) | 6 (8.8) | 4 (5.9) |
| Nausea | 35 (26.3) | 24 (18.0) | 7 (10.3) | 4 (5.9) |
| Stomatitis | 19 (14.3) | 19 (14.3) | 0 | 0 |
| Vomiting | 26 (19.5) | 20 (15.0) | 7 (10.3) | 3 (4.4) |
| **General disorders and administration site conditions** | **89 (66.9)** | **72 (54.1)** | **26 (38.2)** | **15 (22.1)** |
| Asthenia | 27 (20.3) | 24 (18.0) | 3 (4.4) | 3 (4.4) |
| Fatigue | 46 (34.6) | 40 (30.1) | 18 (26.5) | 11 (16.2) |
| Malaise | 13 (9.8) | 10 (7.5) | 1 (1.5) | 1 (1.5) |
| Mucosal inflammation | 8 (6.0) | 8 (6.0) | 0 | 0 |
| Oedema peripheral | 14 (10.5) | 7 (5.3) | 10 (14.7) | 3 (4.4) |
| Pyrexia | 16 (12.0) | - | 3 (4.4) | - |
| **Infections and infestations** | **9 (6.8)** | **-** | **8 (11.8)** | **-** |
| Nasopharyngitis | 9 (6.8) | - | 8 (11.8) | - |
| **Investigations** | **55 (41.4)** | **29 (21.8)** | **6 (8.8)** | **1 (1.5)** |
| Alanine aminotransferase increased | 8 (6.0) | - | 2 (2.9) | - |
| Aspartate aminotransferase increased | 10 (7.5) | - | 4 (5.9) | - |
| Blood bilirubin increased | 7 (5.3) | - | 0 | - |

| System Organ Class<br>Preferred Term | Axitinib (N=133) n (%) | | Placebo (N=68) n (%) | |
|---|---|---|---|---|
| | All Causalities | Treatment related | All Causalities | Treatment related |
| Blood thyroid stimulating hormone increased | 9 (6.8) | 8 (6.0) | 0 | 0 |
| Weight decreased | 36 (27.1) | 23 (17.3) | 2 (2.9) | 1 (1.5) |
| **Metabolism and nutrition disorders** | **72 (54.1)** | **50 (37.6)** | **17 (25.0)** | **8 (11.8)** |
| Decreased appetite | 62 (46.6) | 50 (37.6) | 14 (20.6) | 8 (11.8) |
| Dehydration | 9 (6.8) | - | 0 | - |
| Hyperkalaemia | 9 (6.8) | - | 2 (2.9) | - |
| Hypoalbuminaemia | 8 (6.0) | - | 1 (1.5) | - |
| Hyponatraemia | 8 (6.0) | - | 3 (4.4) | - |
| **Musculoskeletal and connective tissue disorders** | **30 (22.6)** | - | **13 (19.1)** | - |
| Arthralgia | 7 (5.3) | - | 1 (1.5) | - |
| Back pain | 11 (8.3) | - | 11 (16.2) | - |
| Musculoskeletal pain | 8 (6.0) | - | 4 (5.9) | - |
| Musculoskeletal pain | 8 (6.0) | - | 4 (5.9) | - |
| Pain in extremity | 7 (5.3) | - | 1 (1.5) | - |
| **Nervous system disorders** | **27 (20.3)** | **19 (14.3)** | **3 (4.4)** | **1 (1.5)** |
| Dysgeusia | 9 (6.8) | 8 (6.0) | 0 | 0 |
| Headache | 21 (15.8) | 13 (9.8) | 3 (4.4) | 1 (1.5) |
| **Psychiatric disorders** | **12 (9.0)** | **7 (5.3)** | **3 (4.4)** | **1 (1.5)** |
| Insomnia | 12 (9.0) | 7 (5.3) | 3 (4.4) | 1 (1.5) |
| **Renal and urinary disorders** | **27 (20.3)** | **27 (20.3)** | **1 (1.5)** | **1 (1.5)** |
| Proteinuria | 27 (20.3) | 27 (20.3) | 1 (1.5) | 1 (1.5) |
| **Respiratory, thoracic and mediastinal disorders** | **52 (39.1)** | **39 (29.3)** | **12 (17.6)** | **3 (4.4)** |
| Cough | 16 (12.0) | - | 6 (8.8) | - |
| Dysphonia | 33 (24.8) | 32 (24.1) | 0 | 0 |
| Dyspnoea | 13 (9.8) | 7 (5.3) | 6 (8.8) | 1 (1.5) |
| Epistaxis | 10 (7.5) | 8 (6.0) | 2 (2.9) | 2 (2.9) |
| **Skin and subcutaneous tissue disorders** | **64 (48.1)** | **62 (46.6)** | **17 (25.0)** | **14 (20.6)** |
| Alopecia | 6 (4.5) | 6 (4.5) | 7 (10.3) | 6 (8.8) |
| Palmar-plantar erythrodysaesthesia syndrome | 45 (33.8) | 45 (33.8) | 4 (5.9) | 2 (2.9) |
| Pruritus | 11 (8.3) | 7 (5.3) | 8 (11.8) | 7 (10.3) |

| **System Organ Class**<br>Preferred Term | **Axitinib (N=133) n (%)** | | **Placebo (N=68) n (%)** | |
|---|---|---|---|---|
| | **All Causalities** | **Treatment related** | **All Causalities** | **Treatment related** |
| Rash | 23 (17.3) | 22 (16.5) | 2 (2.9) | 2 (2.9) |
| **Vascular disorders** | **72 (54.1)** | **71 (53.4)** | **9 (13.2)** | **8 (11.8)** |
| Hypertension | 72 (54.1) | 71 (53.4) | 9 (13.2) | 8 (11.8) |

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities
Note: The symbol '-' in the table indicates data not provided in the source table as the subject had not experienced that particular event.
MedDRA (v17.0) coding dictionary applied.

## Table 23: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related) - Non-randomized Subjects

| System Organ Class<br>Preferred Term | Child Pugh A (N=15) n (%) | | Child Pugh B (N=7) n (%) | |
|---|---|---|---|---|
| | All Causalities | Treatment related | All Causalities | Treatment related |
| **With serious adverse events** | **10 (66.7)** | **2 (13.3)** | **3 (42.9)** | **2 (28.6)** |
| **Gastrointestinal disorders** | **2 (13.3)** | **1 (6.7)** | **1 (14.3)** | **0** |
| Abdominal pain | 1 (6.7) | - | 0 | - |
| Enterocolitis haemorrhagic | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Varices oesophageal | 0 | - | 1 (14.3) | - |
| **General disorders and administration site conditions** | **4 (26.7)** | **-** | **0** | **-** |
| Disease progression | 3 (20.0) | - | 0 | - |
| Fatigue | 1 (6.7) | - | 0 | - |
| **Hepatobiliary disorders** | **4 (26.7)** | **-** | **0** | **-** |
| Bile duct stenosis | 1 (6.7) | - | 0 | - |
| Cholecystitis acute | 2 (13.3) | - | 0 | - |
| Hepatic function abnormal | 1 (6.7) | - | 0 | - |
| **Infections and infestations** | **2 (13.3)** | **-** | **1 (14.3)** | **-** |
| Appendicitis | 1 (6.7) | - | 0 | - |
| Peritonitis bacterial | 0 | - | 1 (14.3) | - |
| Pneumonia | 1 (6.7) | - | 0 | - |
| **Metabolism and nutrition disorders** | **1 (6.7)** | **0** | **2 (28.6)** | **1 (14.3)** |
| Decreased appetite | 1 (6.7) | - | 0 | - |
| Electrolyte imbalance | 1 (6.7) | - | 0 | - |
| Hyponatraemia | 0 | 0 | 1 (14.3) | 1 (14.3) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps** | **0** | **-** | **1 (14.3)** | **-** |
| Hepatocellular carcinoma | 0 | - | 1 (14.3) | - |
| **Nervous system disorders** | **1 (6.7)** | **0** | **1 (14.3)** | **1 (14.3)** |
| Cerebral infarction | 1 (6.7) | - | 0 | - |
| Encephalopathy | 0 | 0 | 1 (14.3) | 1 (14.3) |
| **Psychiatric disorders** | **1 (6.7)** | **-** | **0** | **-** |
| Completed suicide | 1 (6.7) | - | 0 | - |
| **Respiratory, thoracic and mediastinal disorders** | **1 (6.7)** | **-** | **0** | **-** |

| **System Organ Class**<br>Preferred Term | **Child Pugh A (N=15) n (%)** | | **Child Pugh B (N=7) n (%)** | |
|---|---|---|---|---|
| | **All Causalities** | **Treatment related** | **All Causalities** | **Treatment related** |
| Dyspnoea | 1 (6.7) | − | 0 | - |
| **Vascular disorders** | **2 (13.3)** | **1 (6.7)** | **0** | **0** |
| Hypertension | 1 (6.7) | 1 (6.7) | 0 | 0 |
| Hypotension | 1 (6.7) | - | 0 | - |

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.
Note: The symbol '-' in the table indicates data not provided in the source table as the subject had not experienced that particular event.
MedDRA (v17.0) coding dictionary applied.

## Table 24: Treatment-Emergent Serious Adverse Events Reported by System Organ Class and Preferred Term (All Causalities and Treatment-Related) - Randomized Subjects

| System Organ Class | Axitinib (N=133) | | Placebo (N=68) | |
|---|---|---|---|---|
| Preferred Term | n (%) | | n (%) | |
| | All Causalities | Treatment related | All Causalities | Treatment related |
| **With serious adverse events** | **62 (46.3)** | **24 (17.9)** | **16 (23.5)** | **1 (1.5)** |
| **Blood and lymphatic system disorders** | **1 (0.7)** | **0** | **1 (1.5)** | **1 (1.5)** |
| Anaemia | 0 | 0 | 1 (1.5) | 1 (1.5) |
| Febrile neutropenia | 1 (0.7) | - | 0 | - |
| **Cardiac disorders** | **3 (2.2)** | **2 (1.5)** | **0** | **0** |
| Acute myocardial infarction | 1 (0.7) | 1 (0.7) | 0 | 0 |
| Bradycardia | 1 (0.7) | - | 0 | - |
| Ventricular tachycardia | 1 (0.7) | 1 (0.7) | 0 | 0 |
| **Eye disorders** | **2 (1.5)** | **2 (1.5)** | **0** | **0** |
| Cataract | 1 (0.7) | 1 (0.7) | 0 | 0 |
| Retinal vein occlusion | 1 (0.7) | 1 (0.7) | 0 | 0 |
| **Gastrointestinal disorders** | 16 (11.9) | 6 (4.5) | 5 (7.4) | **0** |
| Abdominal pain | 3 (2.2) | - | 2 (2.9) | - |
| Ascites | 0 | - | 2 (2.9) | - |
| Colitis | 1 (0.7) | - | 0 | - |
| Diarrhoea | 7 (5.2) | 5 (3.7) | 0 | 0 |
| Gastric ulcer | 1 (0.7) | 1 (0.7) | 0 | 0 |
| Gastrointestinal disorder | 1 (0.7) | - | 0 | - |
| Gastrointestinal haemorrhage | 1 (0.7) | - | 0 | - |
| Haematochezia | 1 (0.7) | - | 0 | - |
| Rectal haemorrhage | 0 | - | 1 (1.5) | - |
| Upper gastrointestinal haemorrhage | 1 (0.7) | - | 1 (1.5) | - |
| **General disorders and administration site conditions** | **16 (11.9)** | **4 (3.0)** | **6 (8.8)** | **0** |
| Asthenia | 4 (3.0) | 3 (2.2) | 0 | **0** |
| Disease progression | 8 (6.0) | - | 4 (5.9) | - |
| General physical health deterioration | 3 (2.2) | - | 0 | - |
| Inflammation | 1 (0.7) | 1 (0.7) | 0 | 0 |
| Oedema peripheral | 0 | - | 1 (1.5) | - |
| Pyrexia | 1 (0.7) | - | 1 (1.5) | - |

| System Organ Class<br>Preferred Term | Axitinib (N=133)<br>n (%) | | Placebo (N=68)<br>n (%) | |
|---|---|---|---|---|
| | **All Causalities** | **Treatment related** | **All Causalities** | **Treatment related** |
| **Hepatobiliary disorders** | 8 (6.0) | 2 (1.5) | 2 (2.9) | **0** |
| Bile duct stone | 1 (0.7) | - | 0 | - |
| Cholangitis | 4 (3.0) | 1 (0.7) | 0 | 0 |
| Cholangitis acute | 1 (0.7) | - | 0 | - |
| Hepatic failure | 2 (1.5) | 1 (0.7) | 0 | 0 |
| Hepatic function abnormal | 0 | - | 1 (1.5) | - |
| Hepatorenal syndrome | 0 | - | 1 (1.5) | - |
| Jaundice cholestatic | 1 (0.7) | - | 0 | - |
| **Infections and infestations** | **9 (6.7)** | - | **4 (5.9)** | - |
| Abscess rupture | 0 | - | 1 (1.5) | - |
| Gastroenteritis | 2 (1.5) | - | 0 | - |
| Otitis media | 1 (0.7) | - | 0 | - |
| Ovarian abscess | 0 | - | 1 (1.5) | - |
| Pneumonia | 1 (0.7) | - | 1 (1.5) | - |
| Sepsis | 1 (0.7) | - | 0 | - |
| Upper respiratory tract infection | 1 (0.7) | - | 1 (1.5) | - |
| Urinary tract infection | 3 (2.2) | - | 0 | - |
| **Injury, poisoning and procedural complications** | **3 (2.2)** | - | **0** | - |
| Femur fracture | 1 (0.7) | - | 0 | - |
| Humerus fracture | 1 (0.7) | - | 0 | - |
| Road traffic accident | 1 (0.7) | - | 0 | - |
| **Investigations** | **1 (0.7)** | **1 (0.7)** | **0** | **0** |
| Alanine aminotransferase increased | 1 (0.7) | 1 (0.7) | 0 | 0 |
| Aspartate aminotransferase increased | 1 (0.7) | 1 (0.7) | 0 | 0 |
| **Metabolism and nutrition disorders** | **8 (6.0)** | **3 (2.2)** | **0** | **0** |
| Cachexia | 1 (0.7) | - | 0 | - |
| Decreased appetite | 1 (0.7) | 1 (0.7) | 0 | 0 |
| Dehydration | 3 (2.2) | 1 (0.7) | 0 | 0 |
| Hyperkalaemia | 2 (1.5) | 1 (0.7) | 0 | 0 |
| Hypovolaemia | 1 (0.7) | - | 0 | - |
| **Musculoskeletal and connective tissue disorders** | 3 (2.2) | 1 (0.7) | 0 | **0** |
| Muscular weakness | 1 (0.7) | 1 (0.7) | 0 | 0 |
| Necrotising myositis | 1 (0.7) | - | 0 | - |

| System Organ Class<br>Preferred Term | Axitinib (N=133)<br>n (%) | | Placebo (N=68)<br>n (%) | |
|---|---|---|---|---|
| | **All Causalities** | **Treatment related** | **All Causalities** | **Treatment related** |
| Osteoporotic fracture | 1 (0.7) | - | 0 | - |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **2 (1.5)** | - | **1 (1.5)** | - |
| Hepatocellular carcinoma | 1 (0.7) | - | 0 | - |
| Malignant neoplasm progression | 1 (0.7) | - | 0 | - |
| Tumour rupture | 0 | - | 1 (1.5) | - |
| **Nervous system disorders** | 9 (6.7) | 4 (3.0) | 3 (4.4) | **0** |
| Brain stem infarction | 1 (0.7) | - | 0 | - |
| Coma hepatic | 1 (0.7) | 1 (0.7) | 0 | 0 |
| Dizziness | 0 | - | 1 (1.5) | - |
| Encephalopathy | 2 (1.5) | 1 (0.7) | 0 | 0 |
| Epilepsy | 1 (0.7) | - | 0 | - |
| Hepatic encephalopathy | 4 (3.0) | 2 (1.5) | 1 (1.5) | 0 |
| Ischaemic stroke | 0 | - | 1 (1.5) | - |
| Quadriparesis | 0 | - | 1 (1.5) | - |
| **Psychiatric disorders** | **1 (0.7)** | - | **0** | - |
| Dysthymic disorder | 1 (0.7) | - | 0 | - |
| **Renal and urinary disorders** | **3 (2.2)** | **2 (1.5)** | **1 (1.5)** | **0** |
| Renal failure | 1 (0.7) | 1 (0.7) | 1 (1.5) | 0 |
| Renal impairment | 1 (0.7) | 1 (0.7) | 0 | 0 |
| Ureteric obstruction | 1 (0.7) | - | 0 | - |
| **Respiratory, thoracic and mediastinal disorders** | **7 (5.2)** | 1 (0.7) | **1 (1.5)** | **0** |
| Bronchospasm | 0 | - | 1 (1.5) | - |
| Dyspnoea | 3 (2.2) | - | 0 | - |
| Epistaxis | 1 (0.7) | - | 0 | - |
| Lung disorder | 1 (0.7) | - | 0 | - |
| Obstructive airways disorder | 0 | - | 1 (1.5) | - |
| Pulmonary alveolar haemorrhage | 1 (0.7) | 1 (0.7) | 0 | 0 |
| Respiratory failure | 2 (1.5) | - | 0 | - |
| **Skin and subcutaneous tissue disorders** | **1 (0.7)** | - | **0** | - |
| Drug eruption | 1 (0.7) | - | 0 | - |

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.
Note: The symbol '-' in the table indicates data not provided in the source table as the subject had not experienced that particular event.
MedDRA (v17.0) coding dictionary applied.

Permanent discontinuation due to AEs

*Non-randomized:*

Overall, 4 (26.7%) subjects in the Child-Pugh A cohort and 1 (14.3%) subject in the Child-Pugh B cohort experienced TEAEs that led to treatment discontinuation. The AEs that caused permanent treatment discontinuations are presented in Table 25.

*Randomized*:

Overall, 38 (28.6%) subjects in the axitinib arm and 9 (13.2%) subjects in the placebo arm experienced TEAEs that led to treatment discontinuation. The AEs that caused permanent treatment discontinuations are presented in Table 26.

**Table 25: Number (Percentage) of Subjects with Treatment Emergent Adverse Events Leading to Treatment Discontinuation- Non-randomized Subjects**

| **System Organ Class**<br>Preferred Term | **Child Pugh A (N=15) n (%)** | **Child Pugh B (N=7) n (%)** |
|---|---|---|
| **Any AEs** | **4 (26.7%)** | **1 (14.3%)** |
| **General disorders and administration site conditions** | **2 (13.3)** | **0** |
| Asthenia | 0 | 1 (14.3) |
| Disease progression | 2 (13.3) | 0 |
| **Psychiatric disorders** | **1 (6.7)** | **0** |
| Completed suicide | 1 (6.7) | 0 |
| **Infections and infestations** | **1 (6.7)** | **0** |
| Pneumonia | 1 (6.7) | 0 |

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.
Includes data up to 28 days after last dose of study drug.
% = (n/N)*100.
MedDRA (v17.0) coding dictionary applied.

## Table 26: Number (Percentage) of Subjects with Treatment Emergent Adverse Events Leading to Treatment Discontinuation – Safety Analysis Set

| System Organ Class<br>Preferred Term | Axitinib (N=133)<br>n (%) | Placebo (N=68)<br>n (%) |
|---|---|---|
| **Any AEs** | **38 (28.6)** | **9 (13.2)** |
| **Blood and lymphatic system disorders** | **1 (0.8)** | **0** |
| Thrombocytopenia | 1 (0.8) | 0 |
| **Cardiac disorders** | **2 (1.5)** | **0** |
| Acute myocardial infarction | 1 (0.8) | 0 |
| Ventricular tachycardia | 1 (0.8) | 0 |
| **Eye disorders** | **1 (0.8)** | **0** |
| Retinal vein occlusion | 1 (0.8) | 0 |
| **Gastrointestinal disorders** | **4 (3.0)** | **1 (1.5)** |
| Diarrhoea | 2 (1.5) | 0 |
| Gastrointestinal haemorrhage | 1 (0.8) | 0 |
| Intestinal fistula | 1 (0.8) | 0 |
| Upper gastrointestinal haemorrhage | 0 | 1 (1.5) |
| **General disorders and administration site conditions** | **12 (9.0)** | **4 (5.9)** |
| Asthenia | 1 (0.8) | 0 |
| Disease progression | 6 (4.5) | 3 (4.4) |
| Fatigue | 1 (0.8) | 1 (1.5) |
| General physical health deterioration | 3 (2.3) | 0 |
| Malaise | 1 ( 0.8) | 0 |
| **Hepatobiliary disorders** | **3 (2.3)** | **0** |
| Cholangitis | 1 (0.8) | 0 |
| Hepatic failure | 2 (1.5) | 0 |
| **Investigations** | **1 (0.8)** | **0** |
| Alanine aminotransferase increased | 1 (0.8) | 0 |
| **Metabolism and nutrition disorders** | **1 (0.8)** | **0** |
| Dehydration | 1 (0.8) | 0 |
| **Musculoskeletal and connective tissue disorders** | **2 (1.5)** | **0** |
| Muscular weakness | 1 (0.8) | 0 |
| Necrotising myositis | 1 (0.8) | 0 |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **2 (1.5)** | **1 (1.5)** |
| Hepatocellular carcinoma | 1 (0.8) | 0 |
| Malignant neoplasm progression | 1 (0.8) | 0 |

| System Organ Class<br>Preferred Term | Axitinib (N=133)<br>n (%) | Placebo (N=68)<br>n (%) |
|---|---|---|
| Tumour rupture | 0 | 1 (1.5) |
| **Nervous system disorders** | **4 (3.0)** | **1 (1.5)** |
| Coma hepatic | 1 (0.8) | 0 |
| Encephalopathy | 1 (0.8) | 0 |
| Hepatic encephalopathy | 2 (1.5) | 0 |
| Ischaemic stroke | 0 | 1 (1.5) |
| **Psychiatric disorders** | **1 (0.8)** | **0** |
| Confusional state | 1 (0.8) | 0 |
| **Respiratory, thoracic and mediastinal disorders** | **3 (2.3)** | **2 (2.9)** |
| Lung disorder | 1 (0.8) | 0 |
| Obstructive airways disorder | 0 | 1 ( 1.5) |
| Pneumonitis | 0 | 1 ( 1.5) |
| Pulmonary alveolar haemorrhage | 1 ( 0.8) | 0 |
| Respiratory failure | **1 (0.8)** | **0** |
| **Skin and subcutaneous tissue disorders** | 3 (2.3) | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | 3 (2.3) | 0 |
| **Vascular disorders** | **0** | **1 (1.5)** |
| Hypertension | 0 | 1 (1.5) |

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.
Includes data up to 28 days after last dose of study drug.
% = (n/N)*100.
MedDRA (v17.0) coding dictionary applied.

## Dose-limiting toxicities

Dose-limiting toxicities in non-randomized subjects are presented in Table 27. In the Child-Pugh B disease (score 7) cohort (axitinib 2 mg BID) a total of 2 out of 7 subjects experienced DLTs. One subject had proteinuria >3.5 g/24 hours in Cycle 1. The other subject had a Cycle 1 compliance <75% because of treatment-related toxicity, however, upon further review, this subject was considered not fully evaluable for Cycle 1 DLT and was replaced with another candidate.

**Table 27: Subjects with Dose Limiting Toxicity – Non-randomized Subjects**

| Subjects | Cycle | Done/Not Done | Did Subject experience DLT | DLT Details |
|---|---|---|---|---|
| Child Pugh B | | | | |
| Subject AA | Cycle 1 | Done | No | - |
| Subject BB | Cycle 1 | Done | No | - |
| Subject CC | Cycle 1 | Done | Yes | 2011.12.27<br>Urine protein 5.64 G |
| Subject DD | Cycle 1 | Done | No | - |
| Subject EE | Cycle 1 | Done | No | - |
| Subject FF | Cycle 1 | Done | No | - |
| Subject GG | Cycle 1 | Done | Yes | - |

Deaths

The number of subjects who died on the study and during the follow-up and the reasons for the deaths are presented in Table 28 for the non-randomized portion and in Table 29 for the randomized portion.

**Table 28: Summary of Deaths: Non-randomized Subjects**

| | Child-Pugh A (N=15) n (%) | Child-Pugh B (N=7) n (%) | Total (N=22) n (%) |
|---|---|---|---|
| **Subjects Who Died** | **14 (93.3)** | **6 (85.7)** | **20 (90.9)** |
| **Subjects Who Died On-study** [1] | **4 (26.7)** | **1 (14.3)** | **5 (22.7)** |
| Disease Under Study | 3 (20.0) | 1 (14.3) | 4 (18.2) |
| Other | 1 (6.7) | 0 | 1 (4.5) |
| Suicide | 1 (6.7) | 0 | 1 (4.5) |
| **Subjects Who Died During Follow-up** [2] | **10 (66.7)** | **5 (71.4)** | **15 (68.2)** |
| Disease Under Study | 10 (66.7) | 4 (57.1) | 14 (63.6) |
| Unknown | 0 | 1 (14.3) | 1 (4.5) |
| Other | 0 | 1 (14.3) | 1 (4.5) |
| Biliary Sepsis | 0 | 1 (14.3) | 1 (4.5) |

Subjects were treated with axitinib dose 5 mg BID for Child-Pugh A and 2 mg BID for Child-Pugh B.
A subject with multiple reasons for death was counted separately for each individual reason in the sub-category counts.
%=(n/N)×100.
[1] On-study deaths are those that occurred after the first dose of study drug and within 28 days of the last dose of study drug.
[2] Follow-up deaths are those that occurred more than 28 days after the last dose of study drug.
Abbreviations: BID=Twice daily.

**Table 29: Summary of Deaths: Safety Analysis Set (in randomized portion of the study)**

| | Axitinib (N=133) n (%) | Placebo (N=68) n (%) | Total (N=201) n (%) |
|---|---|---|---|
| **Subjects Who Died** | **100 (75.2)** | **52 (76.5)** | **152 (75.6)** |
| **Subjects Who Died On-study** [1] | **16 (12.0)** | **8 (11.8)** | **24 (11.9)** |
| Disease Under Study | 13 (9.8) | 6 (8.8) | 19 (9.5) |
| Other | 3 (2.3) | 2 (2.9) | 5 (2.5) |
| Acute Renal And Liver Failure | 0 | 1 (1.5) | 1 (0.5) |
| AE Pneumopathy | 1 (0.8) | 0 | 1 (0.5) |
| Liver Function Failure | 1 (0.8) | 0 | 1 (0.5) |
| Obstruction Of Airway With Blood Phlegm | 0 | 1 (1.5) | 1 (0.5) |
| Septicaemia | 1 (0.8) | 0 | 1 (0.5) |
| **Subjects Who Died During Follow-up** [2] | **84 (63.2)** | **44 (64.7)** | **128 (63.7)** |
| Disease Under Study | 77 (57.9) | 41 (60.3) | 118 (58.7) |
| Unknown | 4 (3.0) | 2 (2.9) | 6 (3.0) |
| Other | 3 (2.3) | 2 (2.9) | 5 (2.5) |
| Hepatic Failure | 1 (0.8) | 0 | 1 (0.5) |
| Hepatic Insufficiency | 0 | 1 (1.5) | 1 (0.5) |
| Hospitalisation For Fracture Neck Of Femur. Death After Multiple Organ Failure | 0 | 1 (1.5) | 1 (0.5) |
| Pneumonia | 1 (0.8) | 0 | 1 (0.5) |
| Sepsis | 1 (0.8) | 0 | 1 (0.5) |

Subjects were treated with axitinib+BSC or placebo+BSC.
A subject with multiple reasons for death was counted separately for each individual reason in the sub-category counts.
%=(n/N)×100.
[1] On-study deaths are those that occurred after the first dose of study drug and within 28 days of the last dose of study drug.
[2] Follow-up deaths are those that occurred more than 28 days after the last dose of study drug.
Abbreviations: AE=Adverse event; BSC=Best supportive care.

Clinical laboratory evaluations

Abnormal values in the clinical laboratory data that the investigator determined to be clinically significant were reported as AEs and were summarized in Table 21 through Table 24.

## CONCLUSIONS:

*Non-randomized*

- Axitinib steady-state plasma exposures in Child-Pugh B (score 7) subjects receiving 2 mg BID axitinib and Child-Pugh A subjects receiving 5 mg BID axitinib are comparable.

- The safety findings collected in the 6 Child-Pugh Class B (score 7) subjects evaluable for Cycle 1 DLT suggest that 2 mg BID is an appropriate axitinib starting dose for this population.
- The safety profile of axitinib in Child-Pugh A and Child-Pugh B subjects with advanced HCC in this study was consistent with the known safety profile of axitinib or expected based on underlying disease. No new safety signals were identified in this population.

*Randomized*

- The primary endpoint of OS in all randomized subjects did not meet statistical significance. The estimated HR (axitinib versus placebo) was 0.907 (one-sided p=0.2872). The median OS was 12.7 months in the axitinib arm and 9.7 months in the placebo arm.
- The difference between the axitinib and placebo arms was statistically significant for the following secondary endpoints: PFS, TTP and CBR but was not statistically significant for ORR.
- The time to deterioration based on the composite outcome of death, tumor progression, decrease of ≥3 points in FHSI-8 score, whichever occurred first, showed no significant difference between treatment arms. The overall comparison for axitinib versus placebo based on the repeated measures mixed effects model for the estimated mean FHSI-8 scores by cycle post-baseline significantly favored placebo. The PRO data suggest that the expected side effects of axitinib contributed to reduction of HRQoL based on results from FACT-Hep and associated subscales; the only exceptions were the FACT-G subscales social/family well-being and emotional well-being for which results were similar between the treatment groups. In addition, subject responses to disease-related symptoms, or symptoms of liver failure, whether or not the tumor stabilized or regressed, may each have contributed to the time to deterioration outcomes.
- Low levels of IL-6, E-selectin, IL-8, Ang-2, MIF and c-MET were associated with favorable prognosis (OS) for HCC. Low levels of E-selectin and SDF-1 may have baseline predictive value for HCC subjects receiving axitinib.
- Overall, the safety profile of axitinib in subjects with advanced HCC in this study was consistent with the known safety profile of axitinib or expected based on underlying disease. No new safety signals were identified in this population.