Subject Number	30161005
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-004446
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Hepatic cirrhosis
Non-Fatal SAE(s)	Asthenia, Hepatic cirrhosis
Death due to PD	Yes

A 57-year-old Asian male was diagnosed with hepatocellular carcinoma on 09 Aug 2011. Significant medical history included hepatitis B and hepatic cirrhosis. Previous anticancer therapies included radiotherapy to porta-hepatis lymph node, high frequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included amino acids w/carbohydrates, ascorbic acid, calcium polystyrene sulfonate, chlorphenamine, cimetropium, diosmectite, entecavir, flumazenil, furosemide, glucose, human albumin, hydroxyzine, lactulose, lidocaine, loperamide, midazolam, morphine, mosapride, ornithine, pennel, phytomenadione, silybum marianum, simeticone, spironolactone, thiamine, trimebutine, ursodeoxycholic acid, and vitamin b complex. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe and perihepatic lymphadenopathy. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 19 Feb 2014 (Day 1), treatment with study drug was initiated.

On 20 Feb 2015 (Day 367), the subject experienced decreased appetite (Grade 1). On 25 Feb 2015 (Day 372), the subject was hospitalized for asthenia (Grade 3) and also experienced dizziness (Grade 1), nausea (Grade 1), and decreased platelet count (Grade 1) with platelet count 103 x10^9/L (NR: 150 – 450). On the same day (Day 372), the study drug was interrupted due to asthenia. On 25 Feb 2015 (Day 372), tumor response assessment showed unequivocal progression of an individual lesion. The subject was treated with fresh frozen plasma transfusion, ascorbic acid, phytomenadione, thiamine, vitamin b complex, amino acids w/carbohydrates, glucose, and ornithine. On 04 Mar 2015 (Day 379), the subject recovered from nausea and on 05 Mar 2015 (Day 380), the subject recovered from asthenia and was discharged from the hospital. The subject did not recover from decreased platelet count, decreased appetite, and dizziness. On the same day (Day 380), the study drug was resumed at a reduced dose of 8 mg/day due to asthenia. The Investigator considered asthenia serious and possibly related to the study drug; decreased appetite, nausea, and dizziness nonserious and possibly related to the study drug; decreased platelet count nonserious and not related to the study drug.

On 05 Mar 2015 (Day 380), the subject experienced aggravation of hepatic cirrhosis (Grade 2) and was hospitalized on 06 Mar 2015 (Day 381). The subject underwent abdominal paracentesis for ascites (Grade 3) which was ongoing since 26 Nov 2014 (Day 281). Laboratory tests showed albumin 30 g/L (NR: 33 – 52), AST 112 U/L (NR: 5 – 38), ALT 78 U/L

(NR: 4 – 43), total bilirubin 102.6 umol/L (NR: 3.42 – 20.52), potassium 5.9 mmol/L (NR: 3.5 – 5.1), sodium 122 mmol/L (NR: 135 – 150), and BUN 12.138 mmol/L (NR: 2.856 – 8.211). On 06 Mar 2015 (Day 381), computerized tomogram of liver and thorax showed liver cirrhosis and disease progression. On 07 Mar 2015 (Day 382), the subject experienced abdominal pain (Grade 1). On the same day (Day 382), the study drug was interrupted due to hepatic cirrhosis. The subject was treated with morphine, chlorphenamine, hydroxyzine, spironolactone, and furosemide. On 17 Mar 2015 (Day 392), the subject was withdrawn from study due to disease progression and received the last dose of the study drug on 06 Mar 2015 (Day 381). On the same day (Day 392), laboratory tests showed albumin 29 g/L (NR: 35 – 55), total bilirubin 159.03 umol/L, ALP 278 U/L (NR: 43 – 115), ALT 96 U/L (NR: 10 – 40), AST 208 U/L (NR: 10 – 43), BUN 13.21 mmol/L (NR: 1.78 – 7.14), and total protein 52 g/L (NR: 60 – 80). On 23 Mar 2015 (Day 398, 17 days after the last dose), the subject died due to hepatic cirrhosis secondary to disease progression. Autopsy was not performed. At the time of death, subject had not recovered from abdominal pain and ascites. The Investigator considered hepatic cirrhosis serious and not related to the study drug but related to disease progression; ascites nonserious and possibly related to the study drug; abdominal pain nonserious and not related to the study drug.

Subject Number	30161009
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-002108
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Malignant neoplasm progression
Non-Fatal SAE(s)	Back pain
Death due to PD	Yes

A 57-year-old Asian male was diagnosed with hepatocellular carcinoma on 25 Apr 2014. Significant medical history included back pain, musculoskeletal pain (buttock), chronic hepatitis B, and hepatic cirrhosis. Previous anticancer therapies included transcatheter arterial chemoembolization and radiotherapy to liver and abdominal wall mass. Prior and concomitant medications included almagate, alprazolam, amino acids w/carbohydrates, amlodipine, bupivacaine, cimetropium, dexamethasone, diclofenac, dulcodos, entecavir, famotidine, fentanyl, flumazenil, haloperidol, lactulose, lafutidine, lidocaine, lorazepam, magnesium hydroxide, medilac-s, megestrol, metoclopramide, midazolam, morphine, mosapride, myprodol, nicardipine, oxycodone, pantoprazole, phytomenadione, pregabalin, ranitidine, simeticone, sulperazon, trimebutine, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe; lumbar vertebral mass; left supraclavicular and para-aortic lymphadenopathies. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 23 Oct 2014 (Day 1), treatment with study drug was initiated.

On 01 Dec 2014 (Day 40), the subject was hospitalized for back pain (low back pain; Grade 3) and also experienced decreased appetite (Grade 1). On 02 Dec 2014 (Day 41), tumor response assessment showed disease progression. The subject was treated with morphine, lorazepam, pregabalin, amino acids w/carbohydrates, and megestrol. The study drug dose was not changed. On 11 Dec 2014 (Day 50), the subject underwent nerve block with lidocaine. The subject missed doses of the study drug from 14 Dec 2014 (Day 53) to 15 Dec 2014 (Day 54). On 16 Dec 2014 (Day 55), the subject underwent epidural block with bupivacaine. On the same day (Day 55), the subject was withdrawn from the study due to disease progression and the subject received the last dose of the study drug on 13 Dec 2014 (Day 52). The subject did not recover from back pain and decreased appetite. The Investigator considered back pain serious and not related to the study drug but related to disease progression; decreased appetite nonserious and not related to the study drug but related to disease progression.

On 31 Dec 2014 (Day 70, 18 days after the last dose), the subject died due to malignant neoplasm progression. Autopsy was not performed. The Investigator considered this event serious and not related to the study drug but related to disease progression.

Subject Number	30171014
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-004527
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Sepsis
Non-Fatal SAE(s)	Rhabdomyolysis, Asthenia, Sepsis
Death due to PD	Yes

A 76-year-old Asian male was diagnosed with hepatocellular carcinoma in Jul 2004. Significant medical history included benign prostatic hyperplasia, renal cyst, pulmonary granuloma, hepatitis B, hypertension, hepatic cirrhosis, atelectasis, splenomegaly, tuberculosis, and bronchiectasis. Previous anticancer therapies included cryotherapy and high frequency ablation. Prior and concomitant medications included actifed, alfuzosin, alprazolam, amitriptyline, atorvastatin, betamethasone, cebetabs, cefodizime, chlorphenamine, clarithromycin, claventin, clotiazepam, codena-s, diazepam, domperidone, dopamine, doxofylline, entecavir, epinephrine, fenoverine, fentanyl, furosemide, human albumin, ibuprofen, lactitol, lactulose, lafutidine, lercanidipine, levofloxacin, levosulpiride, magnesium oxide, medilac-s, megestrol, melatonin, meropenem, metoclopramide, nafamostat, norepinephrine, ornithine, oxycodone, paracetamol, pennel, phytomenadione, potassium, propacetamol, prucalopride, rifaximin, silybum marianum, sodium chloride, spironolactone, teicoplanin, ursodeoxycholic acid, vasopressin, venlafaxine, welltamin, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at left lobe of liver and both main portal vein thrombosis. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 29 Jan 2015 (Day 1), treatment with study drug was initiated.

On 01 Mar 2015 (Day 32), the subject was hospitalized for rhabdomyolysis (Grade 3) with increase in CK and CK–MB, and also experienced asthenia (Grade 2). On the same day (Day 32), the study drug was interrupted due to these events. Laboratory tests showed CK 12321 /L (NR: 56 – 244), CK–MB 36 U/L (NR: 0 – 15), albumin 25 g/L (NR: 38 – 52), LDH 3460 U/L (NR: 120 – 520), total protein 60 g/L (NR: 66 – 84), BUN 9.996 mmol/L (NR: 2.856 – 9.282), ALT 138 U/L (NR: 10 – 35), AST 685 U/L (NR: 10 – 35), and total bilirubin 49.59 umol/L (NR: 3.42 – 20.52). The subject was treated with sodium chloride and potassium. On 09 Mar 2015 (Day 40), the subject experienced ileus (Grade 2) and was treated with lactulose, magnesium oxide, and prucalopride. On 12 Mar 2015 (Day 43), the subject experienced pleural effusion (Grade 2) and was treated with furosemide. On 13 Mar 2015 (Day 44), severity of asthenia worsened to Grade 3 and hospitalization was prolonged. The subject was treated with physiotherapy. On the same day (Day 44), the subject was withdrawn from study by choice and received the last dose of the study drug on 28 Feb 2015 (Day 31). On 16 Mar 2015 (Day 47), the subject experienced ascites (Grade 3) which started as Grade 2 on 12 Feb 2015 (Day 15). The subject was treated with rifaximin, furosemide, and spironolactone. On 17 Mar 2015 (Day 48), laboratory tests showed albumin 34 g/L, potassium 3.2 mmol/L

(NR: 3.5 – 5), sodium 150 mmol/L (NR: 135 – 145), BUN 14.994 mmol/L, AST 89 U/L, and total bilirubin 273.6 umol/L. On the same day (Day 48), the subject recovered from rhabdomyolysis. On 19 Mar 2015 (Day 50), the subject experienced sepsis (Grade 4) which further prolonged hospitalization. The subject was treated with meropenem, teicoplanin, norepinephrine, and nafamostat. On 22 Mar 2015 (Day 53), laboratory tests showed Hgb 88 g/L (NR: 130 – 170), Hct 0.262 L/L (NR: 0.3 – 0.5), platelet count 63 x10^9/L (NR: 140 – 400), WBC 25.05 x10^9/L (NR: 3.5 – 10), neutrophil differential 84% (NR: 40 – 70). On the same day (Day 53), the subject was treated for worsening of sepsis with norepinephrine, dopamine, epinephrine, vasopressin, and propacetamol. On 22 Mar 2015 (Day 53, 22 days after the last dose), the subject died due to sepsis secondary to clinical disease progression. Autopsy was not performed. The organism which caused sepsis was unknown. At the time of death, the subject had not recovered from ascites, asthenia, ileus, and pleural effusion. The Investigator considered asthenia and sepsis serious and not related to the study drug but related to disease progression; rhabdomyolysis serious and not related to study drug; ascites, ileus, pleural effusion nonserious and not related to the study drug but related to disease progression.

Subject Number	32021001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-001688
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Circulatory collapse
Non-Fatal SAE(s)	Circulatory collapse
AE(s) Leading to Discontinuation	Circulatory collapse
Death due to PD	No

A 56-year-old Asian male was diagnosed with hepatocellular carcinoma on 22 Jul 2014. Significant medical history included hepatitis B, hypertension, hypothyroidism, and congenital bulbospinal muscular atrophy. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included actifed, amlodipine, amoxicillin, ascorbic acid, augmentin, bromhexine, cetylpyridinium, lamivudine, levothyroxine, neurobion, pseudoephedrine, salicylic acid, urea, and vitamin b complex. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at both lobes of the liver and gastrohepatic and right anterior diaphragm lymph nodes. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 06 Aug 2014 (Day 1), treatment with study drug was initiated. On 03 Oct 2014 (Day 59), Child Pugh score was 7.

On 16 Oct 2014 (Day 72), the subject experienced rhinopharyngitis (Grade 2) which started as Grade 1 on 11 Sep 2014 (Day 37). The subject was treated with actifed, pseudoephedrine, cetylpyridinium, augmentin, and bromhexine. On 10 Nov 2014 (Day 97), the study drug was interrupted. The subject did not recover from the event. The Investigator considered this event nonserious and not related to the study drug.

On 10 Nov 2014 (Day 97), the subject experienced circulatory collapse of unknown cause (Grade 4) with symptoms of persistent drowsiness, confusion, and restlessness. No treatment was provided. The study drug remained interrupted due to circulatory collapse. The subject received the last dose of the study drug on 09 Nov 2014 (Day 96). On 13 Nov 2014 (Day 100, 4 days after the last dose of study drug), the subject died due to circulatory collapse of unknown cause. Autopsy was not performed. The Investigator considered circulatory collapse serious and possibly related to the study drug.

Subject Number	32051001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01472-CLI-TH
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Hepatic failure, Sepsis
Non-Fatal SAE(s)	Decreased appetite, Hepatic failure, Lung infection, Sepsis
AE(s) Leading to Discontinuation	Decreased appetite
Death due to PD	No

A 69-year-old Asian male was diagnosed with hepatocellular carcinoma on 02 Jul 2013. Significant medical history included chronic hepatitis B, hepatic cirrhosis, and hypertension. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, intravenous solutions, lactulose, paracetamol, and tenofovir. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe and aortocaval lymphadenopathy. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 06 Mar 2014 (Day 1), treatment with study drug was initiated.

On 20 Mar 2014 (Day 15), the subject experienced decreased appetite (Grade 2). On 30 Mar 2014 (Day 25), the subject was hospitalized for worsening of decreased appetite (Grade 3) and also experienced fatigue (Grade 3). The subject was treated with intravenous fluids and nasogastric feeding. On 02 Apr 2014 (Day 28), the study drug was interrupted due to decreased appetite. On 03 Apr 2014 (Day 29), the subject experienced hepatic failure (Grade 3) with symptoms of hepatic encephalopathy and mild ascites. On 05 Apr 2014 (Day 31), the subject experienced lung infection (Grade 4) and sepsis (Grade 4). Laboratory tests and treatment details were not reported since source documents could not be obtained. On 07 Apr 2014 (Day 33), the subject was withdrawn from the study due to decreased appetite and received the last dose of study drug on 01 Apr 2014 (Day 27). On 07 Apr 2014 (Day 33, 6 days after the last dose), the subject died due to sepsis and hepatic failure. At the time of death, the subject had not recovered from decreased appetite, lung infection, and fatigue. Autopsy was not performed. The organism which caused the lung infection and sepsis was not specified. The Investigator considered hepatic failure serious and possibly related to study drug; decreased appetite serious and probably related to the study drug; sepsis and lung infection serious and not related to study drug; fatigue nonserious and not related to study drug.

Subject Number	32051003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01546-CLI-TH
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Peritonitis bacterial, Hepatic failure
Non-Fatal SAE(s)	Gastroenteritis, Blood bilirubin increased, Peritonitis bacterial
AE(s) Leading to Discontinuation	Blood bilirubin increased
Death due to PD	No

A 48-year-old Asian male was diagnosed with hepatocellular carcinoma on 01 Aug 2012. Significant medical history included chronic hepatitis B, gastritis, hepatic cirrhosis, and right upper abdominal pain. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included cefdinir, chlorphenamine, combizym, dextrose and sodium chloride injection, diazepam, domperidone, lorazepam, metoclopramide, omeprazole, oral rehydration salt, simeticone, tenofovir, tramadol, ursodeoxycholic acid, and vitamins (multivitamins). At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right lobe of liver; masses at right middle and right upper lobes of lung; portocaval lymphadenopathy; infiltrative hepatocellular carcinoma in superior segment of liver; and tumor thrombus in right hepatic vein. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 08 May 2014 (Day 1), treatment with study drug was initiated.

On 27 Jul 2014 (Day 81), the subject was hospitalized for gastroenteritis (Grade 3) with diarrhea of more than 10 times. Treatment included dextrose and sodium chloride injection, domperidone, omeprazole, metoclopramide, and oral rehydration salt. The study drug dose was not changed. On 30 Jul 2014 (Day 84), the subject recovered from gastroenteritis and was discharged from the hospital. The Investigator considered gastroenteritis serious and not related to study drug.

On 31 Jul 2014 (Day 85), the subject was hospitalized for increased blood bilirubin (Grade 3). On 01 Aug 2014 (Day 86), the study drug was interrupted due to this event. Laboratory tests showed total bilirubin 94.4 umol/L (NR: 1.7 – 18.8), albumin 23 g/L (NR: 35 – 55), ALT 40 U/L (NR: 10 – 40), ALP 142 U/L (NR: 43 – 115), and AST 140 U/L (NR: 10 – 43). On 04 Aug 2014 (Day 89), the subject developed large amount of ascitic fluid and underwent abdominal paracentesis. The ascitic fluid showed polymorphonuclear leukocytes >250 (NR: not provided). On the same day (Day 89), the subject was diagnosed with bacterial peritonitis (Grade 4). Treatment was given but specific medications were not provided since source document could not be obtained. On 05 Aug 2014 (Day 90), subject experienced hepatic failure with total bilirubin 244.53 umol/L (NR: not provided), albumin 25 g/L (NR: not provided), AST 618 (units not provided) (NR: not provided), and ALT 128 (units not provided) (NR: not provided). The Child Pugh score was 9 and subject went into coma. The study drug was withdrawn due to increased blood bilirubin and the subject received the last dose of study

drug on 31 Jul 2014 (Day 85). On 05 Aug 2014 (Day 90, 5 days after the last dose), the subject died due to hepatic failure and bacterial peritonitis. At the time of death, the subject had not recovered from increased blood bilirubin. Autopsy was not performed. The Investigator considered increased blood bilirubin, bacterial peritonitis, and hepatic failure serious and not related to study drug.

Subject Number	44031005
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01508-CLI-SG
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Tumour haemorrhage
Non-Fatal SAE(s)	Ascites, Septic shock, Tumour haemorrhage
AE(s) Leading to Discontinuation	Tumour haemorrhage
Death due to PD	Yes

A 58-year-old Asian male was diagnosed with hepatocellular carcinoma on 18 Feb 2014. Significant medical history included diabetes mellitus, hypertension, and hepatic cirrhosis. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included benzocaine, ciprofloxacin, dopamine, esomeprazole, fentanyl, furosemide, glipizide, human albumin, lactulose, lisinopril, loratadine, meropenem, metformin, norepinephrine, omeprazole, paracetamol, piperacillin with tazobactam, propofol, propranolol, red blood cells, sennoside a+b, sodium lactate, spironolactone, stomi equipment (urostomy bag), tramadol, and triamcinolone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right, left, and quadrate lobes of liver. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 21 Mar 2014 (Day 1), treatment with study drug was initiated.

On 30 Apr 2014 (Day 41), the subject experienced hyperbilirubinemia (Grade 2). Laboratory tests showed total bilirubin 49.1 umol/L (NR: 1.7 – 18.8), ALP 228 U/L (NR: 43 – 115), ALT 70 U/L (NR: 10 – 40), and AST 106 U/L (NR: 10 – 43). Treatment for this event was not provided. On 14 May 2014 (Day 55), the severity of hyperbilirubinemia worsened to Grade 3. Repeat laboratory tests showed total bilirubin 65.8 umol/L, ALP 192 U/L, ALT 64 U/L, and AST 103 U/L. On 15 May 2014 (Day 56), the Child Pugh score was 9 and study drug was interrupted due to the hyperbilirubinemia. The subject did not recover from this event. The Investigator considered hyperbilirubinemia nonserious and not related to the study drug.

On 21 May 2014 (Day 62), the subject experienced ascites (Grade 3). Laboratory tests showed albumin 25 g/L (NR: 35 – 55), ALP 189 U/L, ALT 65 U/L, AST 106 U/L, and total bilirubin 86.2 umol/L. On 21 May 2014 (Day 62), the subject was hospitalized for ascites. Ultrasound of abdomen showed ascites and the subject underwent paracentesis. Treatment included piperacillin with tazobactam, furosemide, ciprofloxacin, and spironolactone. On 26 May 2014 (Day 67), the subject recovered from ascites and was discharged from the hospital. Repeat laboratory tests showed albumin 34 g/L, ALP 193 U/L, ALT 50 U/L, AST 82 U/L, and total bilirubin 35.9 umol/L. On 29 May 2014 (Day 70), the study drug was resumed at same dose. The Investigator considered ascites serious and not related to study drug but related to clinical disease progression.

On 04 Jun 2014 (Day 76), the study drug was interrupted due to persistent hyperbilirubinemia (Grade 3). On 05 Jun 2014 (Day 77), the subject was hospitalized for hepatic tumor hemorrhage (Grade 4) with symptoms of worsening abdominal pain, nausea, vomiting, jaundice, hypotension, drowsiness, and metabolic acidosis. The subject also experienced septic shock (Grade 4). Laboratory tests showed AST 1493 U/L (NR: 10 – 50), ALT 575 U/L (NR: 10 – 70), ALP 213 U/L (NR: 40 – 130), creatinine 277 umol/L (NR: 65 – 125), Hgb 103 g/L (NR: 129 – 170), RBC 3.47 x10^12/L (NR: 4.3 – 5.7), and Hct 0.328 L/L (NR: 0.375 – 0.493). The CT scan of abdomen showed increased tumor size, blood in peritoneum, large amount of hemoperitoneum in the right perihepatic space extending to the paracolic gutter and Morrison's pouch. Treatment included fresh frozen plasma transfusion, norepinephrine, fentanyl, propofol, meropenem, human albumin, dopamine, esomeprazole, sodium lactate, and packed RBC. On 06 Jun 2014 (Day 78, 3 days after the last dose), the subject died due to hepatic tumor hemorrhage secondary to clinical disease progression. The subject received the last dose of study drug on 03 Jun 2014 (Day 75). At the time of death, the subject had not recovered from septic shock and hyperbilirubinemia. Autopsy was not performed. The Investigator considered tumor hemorrhage serious and not related to study drug; septic shock serious and not related to study drug; hyperbilirubinemia nonserious and possibly related to study drug and clinical disease progression.

Subject Number	44031007
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01519-CLI-SG
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Myocardial infarction
Non-Fatal SAE(s)	Diarrhoea, Pneumonia, Myocardial infarction
AE(s) Leading to Discontinuation	Pneumonia
Death due to PD	No

An 81-year-old Chinese male was diagnosed with hepatocellular carcinoma on 11 Apr 2014. Significant medical history included mental status changes, diabetes mellitus, hyperlipidemia, hypertension, myocardial ischemia, renal cyst, and unstable angina. Previous anticancer therapy included radiotherapy to the thoracic vertebral lesions (T11 – L4). Prior and concomitant medications included amlodipine, atenolol, atorvastatin, azithromycin, gliclazide, glyceryl trinitrate, irbesartan, isosorbide mononitrate, loperamide, lorazepam, megestrol, metformin w/vildagliptin, midazolam, mirtazapine, morphine, naproxen, panadeine co, piperacillin, ringer-lactate, sodium chloride, tazobactam, telmisartan, tramadol, and vitamins. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at caudate lobe of liver, spleen, portal vein and porta-hepatis lymphadenopathy. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 09 May 2014 (Day 1), the treatment with study drug was initiated.

On 04 Jun 2014 (Day 27), the subject was hospitalized for diarrhea (Grade 3) and study drug was interrupted. Ultrasound of abdomen ruled out any rupture or bleeding and stool culture showed no significant growth. The subject was treated with loperamide and sodium chloride. On 07 Jun 2014 (Day 30), the subject recovered from diarrhea. On 10 Jun 2014 (Day 33), the study drug was resumed at a reduced dose of 4 mg/day due to diarrhea. The Investigator considered diarrhea serious and possibly related to the study drug.

On 03 Jul 2014 (Day 56), the subject experienced hypertension (Grade 3) with BP of 177/80 mmHg. The subject was treated with atenolol, amlodipine, telmisartan, and irbesartan. On the same day (Day 56), the study drug was interrupted due to hypertension. On 17 Jul 2014 (Day 70), the subject recovered from hypertension. The study drug was resumed at a reduced dose of 4 mg every other day. The Investigator considered hypertension nonserious and probably related to the study drug.

On 19 Nov 2014 (Day 195), the subject experienced hyponatremia (Grade 3) with sodium 124 mmol/L (NR: 133 – 145). On 20 Nov 2014 (Day 196), the study drug was interrupted due to this event. On 04 Dec 2014 (Day 210), the subject recovered from hyponatremia. On the same day (Day 210), the study drug was resumed at a reduced dose of 4 mg every 3 days. The Investigator considered hyponatremia nonserious and possibly related to the study drug.

On 23 Dec 2014 (Day 229), the subject presented at the emergency room for breathlessness and was diagnosed with pneumonia (Grade 4) via chest x-ray. On 25 Dec 2014 (Day 231), the study drug was interrupted due to pneumonia. On 30 Dec 2014 (Day 236), the subject was hospitalized for myocardial infarction (Grade 4) and persistent pneumonia. An electrocardiogram showed ST depression and chest x-ray showed left lung consolidation. Laboratory tests showed increased cardiac troponin, WBC 12.56 x10^9/L (NR: 3.4 – 9.6), and neutrophils 11.6 x10^9/L (NR: 1.27 – 6.2). The subject was treated with ringer-lactate, azithromycin, piperacillin, tazobactam, and morphine. On 31 Dec 2014 (Day 237), the subject was withdrawn from the study due to pneumonia. The subject did not recover from pneumonia. Later that day (Day 237, 9 days after the last dose), the subject died due to myocardial infarction. Autopsy was not performed. The subject received the last dose of study drug on 22 Dec 2014 (Day 228). The Investigator considered pneumonia serious and not related to the study drug; myocardial infarction serious and possibly related to the study drug.

Subject Number	45041008
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-005068
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Cachexia
Non-Fatal SAE(s)	Cachexia
Death due to PD	Yes

A 74-year-old Chinese male was diagnosed with hepatocellular carcinoma on 11 Nov 2009. Significant medical history included decreased appetite, cholecystectomy, anemia, arthralgia, asthenia, chronic hepatitis B, chronic hepatitis C, chronic sinusitis, constipation diarrhea, foraminotomy, helicobacter infection, hepatic cirrhosis, hypoesthesia, benign prostatic hyperplasia, hypertension, insomnia, intestinal polyp, internal fixation of spine, nausea, right flank pain, renal stone removal, spinal laminectomy, spinal column stenosis, spondylolisthesis, transurethral prostatectomy, and urinary tract infection. Previous anticancer therapies included hepatectomy and transcatheter arterial chemoembolization. Prior and concomitant medications included azor, benzydamine, bisacodyl, ceftazidime, clindamycin, combivent, dexamethasone, dimeticone, domperidone, dorithricin, dutas-t, famotidine, fosavance, furosemide, human albumin, hydrocortisone, hyoscine, ipratropium, lidocaine, magnesium oxide, medroxyprogesterone, megestrol, meloxicam, methylprednisolone, metoclopramide, morphine, nystatin, prochlorperazine, sennoside a+b, sinbaby, smofkabiven perifer, sulfadiazine, tamsulosin, tramadol, and ultracet. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes; masses at right rib, left and right pelvis. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 21 Nov 2014 (Day 1), treatment with study drug was initiated.

On 13 Jan 2015 (Day 54), the subject experienced anemia (Grade 2), increased aspartate aminotransferase (Grade 1), and hypoalbuminemia (Grade 2) which started as Grade 1 on 16 Dec 2014 (Day 26). Laboratory test showed albumin 28 g/L (NR: 35 – 55), AST 50 U/L (NR: 10 – 43), RBC 2.83 x10^12/L (NR: 4 – 5.6), Hgb 95 g/L (NR: 125 – 170), and Hct 0.291 L/L (NR: 0.37 – 0.51). On 10 Feb 2015 (Day 82), the subject experienced increased alanine aminotransferase (Grade 1) with ALT 71 U/L (NR: 10 – 40). On 13 Feb 2015 (Day 85), the subject experienced cachexia (Grade 2) and decreased weight (Grade 2) with body weight 38.8 kg (Baseline: 43.4 kg). The study drug dose was not changed. The subject did not recover from these events. The Investigator considered cachexia, anemia, increased aspartate aminotransferase, increased alanine aminotransferase, and hypoalbuminemia nonserious and not related to the study drug; decreased weight nonserious and possibly related to the study drug.

On 13 Mar 2015 (Day 113), tumor response assessment showed disease progression. On the same day (Day 113), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 12 Mar 2015 (Day 112).

On 13 Mar 2015 (Day 113), the subject experienced fatigue (Grade 2) and malignant pleural effusion (Grade 1). On 15 Mar 2015 (Day 115), the subject experienced decreased appetite (Grade 2) and received smofkabiven perifer. On 17 Mar 2015 (Day 117), the subject was hospitalized for cachexia (Grade 3) with complaints of malaise, weakness, and decreased appetite. On the same day (Day 117), the subject also experienced worsening of anemia to Grade 3, decreased platelet count (Grade 1), and pneumonia (Grade 2). Laboratory tests showed WBC 3.0 x10^9/L (NR: 3.9 – 10.6), RBC 2.13 x10^12/L (NR: 4.5 – 5.9), Hgb 76 g/L (NR: 135 – 175), platelet count 86 x10^9/L (NR: 150 – 400), albumin 23.4 g/L (NR: 35 – 55), and potassium 4.3 mmol/L (NR: 3.6 – 5). The subject was treated with nutritional support, packed red blood cell transfusion, smofkabiven perifer, ceftazidime, clindamycin, and medroxyprogesterone. On 18 Mar 2015 (Day 118), the subject recovered from anemia with Hgb 116 g/L. On 20 Mar 2015 (Day 120), the severity of decreased platelet count worsened to Grade 2 with platelet count 63 x10^9/L. On 22 Mar 2015 (Day 122), the subject experienced wheezing (Grade 3). On 24 Mar 2015 (Day 124), malignant pleural effusion worsened to Grade 2 and the severity of decreased platelet count improved to Grade 1. Chest x-ray confirmed bilateral pleural effusion. The subject underwent gastrointestinal tube insertion, central venous catheterization, and was also treated with oxygen, inhalation therapy, blood transfusion with albumin, oxygen, ceftazidime, combivent, hydrocortisone, ipratropium, lidocaine, human albumin, methylprednisolone, and furosemide. On 26 Mar 2015 (Day 126), the subject experienced non-cardiogenic pulmonary edema (Grade 2). Chest x-ray showed bilateral pulmonary edema. The subject was treated with furosemide. On 27 Mar 2015 (Day 127), the subject experienced worsening of anemia (Grade 3) with Hgb 71 g/L, RBC 2.29 x10^12/L, and the severity of decreased platelet count again worsened to Grade 2 with platelets 60 x10^9/L. On the same day (Day 127), the subject was discharged from hospital and was admitted to hospice care. On 29 Mar 2015 (Day 129, 17 days after the last dose), the subject died due to cachexia secondary to disease progression. Autopsy was not performed. At the time of death the subject had not recovered from anemia, decreased appetite, fatigue, malignant pleural effusion, decreased platelet count, wheezing, pneumonia, and non-cardiogenic pulmonary edema. The Investigator considered cachexia serious and not related to the study drug but related to disease progression; malignant pleural effusion, and non-cardiogenic pulmonary edema nonserious and not related to the study drug but related to disease progression; anemia, decreased appetite, fatigue, decreased platelet count, pneumonia, and wheezing nonserious and not related to the study drug.

Subject Number	47011010
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-008595
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Respiratory failure
Non-Fatal SAE(s)	Pulmonary embolism, Respiratory failure
AE(s) Leading to Discontinuation	Respiratory failure
Death due to PD	Yes

A 71-year-old Chinese male was diagnosed with hepatocellular carcinoma on 05 Dec 2011. Significant medical history included benign prostatic hyperplasia, calculus bladder, chronic obstructive pulmonary disease, infectious pleural effusion, hypertension, hypokalemia, sleep apnea syndrome, and hepatitis B. Previous anticancer therapies included hepatectomy, radiofrequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included atenolol, augmentin, entecavir, fluocinolone acetonide, furosemide, levothyroxine, nifedipine, piperacillin/tazobactam, potassium, ramipril, tinzaparin, and urea. At Screening, tumor assessments of target/non-target lesions via CT scan showed mass at left lung, lesions at multiple sites of liver, caudate, and left liver lobes. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 19 Nov 2014 (Day 1), treatment with study drug was initiated.

On 03 Dec 2014 (Day 15), the subject experienced proteinuria (Grade 3) with urine protein dipstick 3+ and 24h urine protein 3.9024 g/24hr. On 08 Dec 2014 (Day 20), the study drug was interrupted. On 28 Dec 2014 (Day 40), severity of proteinuria improved to Grade 2 with 24h urine protein 1.1492 g/24hr. On 31 Dec 2014 (Day 43), the study drug was resumed at the same dose. On 14 Jan 2015 (Day 57), severity of proteinuria worsened to Grade 3 with 24h urine protein 3.6659 g/24hr. On 19 Jan 2015 (Day 62), the study drug was interrupted. On 25 Jan 2015 (Day 68), the severity of proteinuria improved to Grade 2 with 24h urine protein 2.3273 g/24hr. On 28 Jan 2015 (Day 71), the study drug was resumed at a reduced dose of 8 mg/day due to proteinuria. The subject did not recover from this event. The Investigator considered proteinuria nonserious and probably related to study drug.

On 15 Jul 2015 (Day 239), the subject was hospitalized for pulmonary embolism at right lower lung (Grade 3) with oxygen saturation 88% and right side chest air entry was less than the left side. The subject also experienced pneumonia (Grade 2) and worsening dyspnea (Grade 3) which started as Grade 2 on 08 Jul 2015 (Day 232). Computerized tomogram scan of thorax showed segmental pulmonary emboli at right lower lobe of lung, with superimposed infective changes at left lobe and right upper lobe of lung. The study drug was interrupted due to dyspnea and pulmonary embolism. The subject was treated with augmentin, tinzaparin, furosemide, and oxygen. On 17 Jul 2015 (Day 241), the subject recovered from pulmonary embolism and pneumonia with sequelae and was discharged from the hospital. On 18 Jul 2015 (Day 242), the severity of dyspnea improved to Grade 2. On 19 Jul 2015 (Day 243), laboratory

tests showed bicarbonate 19.7 mmol/L (NR: 22.0 – 26.0), PCO2 4.0 kPa (NR: 4.7 – 6.4), and PO2 8.7 kPa (NR: 11 – 14.4). The subject did not recover from dyspnea. The Investigator considered pulmonary embolism serious and possibly related to the study drug; dyspnea nonserious and possibly related to study drug; pneumonia nonserious and not related to study drug.

On 18 Jul 2015 (Day 242), the subject was hospitalized for respiratory failure (Grade 4) secondary to pulmonary embolism and pneumonia with symptoms of increasing dyspnea and blood-stained sputum. The subject was treated with oxygen, tinzaparin, and piperacillin/tazobactam. On 19 Jul 2015 (Day 243, 5 days after the last dose), the subject died due to respiratory failure. Autopsy was not performed. The subject received the last dose of study drug on 14 Jul 2015 (Day 238). The Investigator considered respiratory failure serious and possibly related to study drug and disease progression.

Subject Number	47021006
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-008783
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Escherichia sepsis
Non-Fatal SAE(s)	Gastroenteritis, Escherichia sepsis
AE(s) Leading to Discontinuation	Escherichia sepsis
Death due to PD	Yes

A 56-year-old Chinese male was diagnosed with hepatocellular carcinoma on 16 Jan 2013. Significant medical history included chronic duodenal ulcer, chronic hepatitis B, and epigastric discomfort. Previous anticancer therapies included radiotherapy to right lobe of lung, hepatectomy, and transcatheter arterial chemoembolization. Prior and concomitant medications included amikacin, amlodipine, ampicillin, anidulafungin, augmentin, cefuroxime, ciprofloxacin, dopamine, esomeprazole, famotidine, gabapentin, hydrocortisone, hyoscine, hypromellose, meropenem, metoclopramide, metronidazole, nifedipine, pantoprazole, paracetamol, phytomenadione, piperacillin/tazobactam, sodium chloride, tramadol, and zopiclone. At Screening, tumor assessments of target/non-target lesions via CT scan showed masses at right adrenal, right kidney, and at the second part of duodenum. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 03 Dec 2014 (Day 1), treatment with study drug was initiated.

On 21 Jul 2015 (Day 231), the subject was hospitalized for gastroenteritis (Grade 3) with symptoms of right abdominal pain, chills, rigors, and fever with temperature of 40 ºC. Chest x-ray showed no abnormalities and abdominal x-ray showed dilated bowels, and no intestinal obstruction. The subject was treated with augmentin, ciprofloxacin, and metoclopramide. The study drug dose was not changed. On 25 Jul 2015 (Day 235), the subject recovered from gastroenteritis and was discharged from the hospital. The Investigator considered gastroenteritis serious and not related to the study drug.

On 02 Aug 2015 (Day 243), the subject was hospitalized for Escherichia sepsis (Grade 4) with fever and temperature of 38.1 °C. The subject was treated with sodium chloride, tramadol, metoclopramide, amikacin, augmentin, pantoprazole, piperacillin/tazobactam, meropenem, dopamine, anidulafungin, hydrocortisone, phytomenadione, cefuroxime, metronidazole, and ampicillin. On 03 Aug 2015 (Day 244), the study drug was interrupted due to Escherichia sepsis. Laboratory tests showed WBC 23.4 x10^9/L (NR: 3.9 – 10.7), absolute neutrophils 18.6 x10^9/L (NR: 2.1 – 7.8), Hgb 95 g/L (NR: 134 – 172), platelets 21 x10^9/L (NR: 152 – 358), PT 17.9 sec (NR: 10.4 – 12.6), and creatinine 112 umol/L (NR: 62 – 106). Computerized tomogram scan of abdomen and pelvis showed progressive disease with right adrenal metastasis with invasion into upper pole of right kidney, second part of duodenum, and inferior vena cava, causing tumor thrombus formation in inferior vena cava, and marked submucosal edema with wall thickening affecting the ascending colon with adjacent

inflammatory changes. On 06 Aug 2015 (Day 247), the subject was withdrawn from study due to Escherichia sepsis and received the last dose of the study drug on 02 Aug 2015 (Day 243). On 13 Aug 2015 (Day 254, 11 days after the last dose), the subject died due to Escherichia sepsis secondary to disease progression. Autopsy was not performed. The Investigator considered Escherichia sepsis serious and not related to the study drug.

Arm: Sorafenib

Subject Number	10101002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-015810
Assigned Treatment	Sorafenib 800 mg/day
Fatal SAE(s)	Malignant neoplasm progression
Death due to PD	Yes

A 53-year-old white male was diagnosed with hepatocellular carcinoma on 13 Nov 2013. Significant medical history included abdominal pain, decreased appetite, chronic hepatitis C, esophageal varices, gastric ulcer, hypertension, fatigue, insomnia, and upper gastrointestinal hemorrhage. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included furosemide, lactulose, oxycodone, pantoprazole, propranolol, rifaximin, and spironolactone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe, masses diffusely through all lobes of both lungs, lymphadenopathy at portal nodes, and MRI showed lesions diffusely involving both liver lobes. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

On 10 Feb 2014 (Day 1), treatment with study drug was initiated.

On 07 Apr 2014 (Day 57), tumor response assessment showed disease progression. On 08 Apr 2014 (Day 58), the subject was withdrawn from the study due to disease progression and received the last dose of study drug on the same day (Day 58).

On 02 May 2014 (Day 82, 24 days after the last dose), the subject died due to malignant neoplasm progression. Autopsy was not performed. The Investigator considered malignant neoplasm progression serious and not related to the study drug but related to disease progression.

Subject Number	12081011
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01425-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Fatal SAE(s)	Hepatic failure
Non-Fatal SAE(s)	Hepatic failure
AE(s) Leading to Discontinuation	Hepatic failure
Death due to PD	Yes

A 63-year-old Japanese male was diagnosed with hepatocellular carcinoma in 2003. Significant medical history included cancer pain, chronic gastritis, chronic hepatitis B, headache, and insomnia. Previous anticancer therapies included hepatectomy, percutaneous ethanol injection therapy, and hepatic intra-arterial chemotherapy (2x). Prior and concomitant medications included aminoleban, ascorbic acid, carbohydrates w/potassium chloride/sodium, clobetasol, dextrose and sodium chloride, dimeticone, entecavir, esomeprazole, etizolam, falkamin, fentanyl, glucose, gualenic acid, haloperidol, human albumin, ketoprofen, lactitol, lidocaine, loxoprofen, menatetrenone, metoclopramide, morphine, mosapride, neurobion, other dermatologicals (duo active), oxycodone, prochlorperazine, pronase, rabeprazole, sodium bicarbonate, sodium chloride, teprenone, tramadol, triamcinolone, urea, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right lobe of liver and splenic hilar lymphadenopathy. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 22 Nov 2013 (Day 1), treatment with study drug was initiated.

On 13 Dec 2013 (Day 22), the subject experienced increased aspartate aminotransferase (Grade 3) with AST 358 U/L (see table below) and the study drug was reduced to 400 mg/day due to this event. The subject did not recover from increased aspartate aminotransferase. The Investigator considered increased aspartate aminotransferase nonserious and possibly related to study drug.

On 25 Dec 2013 (Day 34), the subject experienced somnolence (Grade 2) and hypoalbuminemia (Grade 2). Laboratory tests showed albumin 26 g/L, ammonia 54.9703 umol/L (NR: 8.5668 – 47.1174), and CT scan of the brain showed no abnormalities. The subject was also diagnosed with hepatic failure (Grade 2). The study drug was interrupted due to hepatic failure and hypoalbuminemia. The subject was treated with aminoleban, human albumin, and glucose as an outpatient. On 27 Dec 2013 (Day 36), the subject experienced diarrhea (Grade 1), difficulty eating, and persistence of somnolence. On the same day (Day 36), the subject was hospitalized for worsening hepatic failure (Grade 3). Laboratory tests showed albumin 27 g/L and ammonia 104.2294 umol/L. The subject was treated with ascorbic acid, menatetrenone, sodium chloride, metoclopramide, carbohydrates w/potassium chloride/sodium, and neurobion. On 02 Jan 2014 (Day 42), hepatic failure worsened to Grade 4 with laboratory tests of ammonia 112.0823 umol/L and total bilirubin 66.69 umol/L (NR: 3.42 – 20.52). The subject was treated

with haloperidol, dextrose, and sodium chloride. On 06 Jan 2014 (Day 46), the subject was withdrawn from the study due to clinical disease progression. The subject received the last dose of the study drug on 24 Dec 2013 (Day 33). No imaging studies were performed to confirm clinical disease progression. On 08 Jan 2014 (Day 48, 15 days after the last dose), the subject died due to hepatic failure secondary to clinical disease progression. Autopsy was not performed. At the time of death, the subject had not recovered from hypoalbuminemia, somnolence, and diarrhea. The Investigator considered hepatic failure serious and not related to study drug; hypoalbuminemia and somnolence nonserious and possibly related to study drug; diarrhea nonserious and not related to the study drug.

Table ALT, AST, ALP, and Albumin

Laboratory Test Date (Day)	**ALT Central Laboratory NR: 10 – 40 U/L Local Laboratory NR: 4 – 43 U/L**	**AST Central Laboratory NR: 10 – 43 U/L Local Laboratory NR: 7 – 38 U/L**	**ALP Central Laboratory NR: 43 – 115 U/L Local Laboratory NR: 103 – 335 U/L**	**Albumin Central Laboratory NR: 35 – 55 g/L Local Laboratory NR: 38 – 51 g/L**
19 Nov 2013 (Day –3)	59 CNR	163 CNR	332 CNR	38 CNR
06 Dec 2013 (Day 15)	57 CNR	276 CNR	261 CNR	29 CNR
13 Dec 2013 (Day 22)	Not Done	358 LNR	Not Done	Not Done
25 Dec 2013 (Day 34)	Not Done	Not Done	Not Done	26 LNR
27 Dec 2013 (Day 36)	59 LNR	313 LNR	Not Done	27 LNR
02 Jan 2014 (Day 42)	67 LNR	479 LNR	946 LNR	25 LNR

CNR = Central Laboratory Normal Range
LNR = Local Laboratory Normal Range

Subject Number	12211007
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01512-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Fatal SAE(s)	Renal impairment, Hepatic function abnormal
AE(s) Leading to Discontinuation	Renal impairment, Hepatic function abnormal
Death due to PD	Yes

A 60-year-old Japanese male was diagnosed with hepatocellular carcinoma on 28 Feb 2014. Significant medical history included cancer pain, chronic gastritis, chronic hepatitis C, constipation, diabetes mellitus, and back pain. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included amiodarone, amlodipine, bisacodyl, calcium gluconate, candesartan, celecoxib, cortistamin l, epinephrine, fexofenadine, glucose, human insulin, ketoprofen, loxoprofen, miglitol, oxycodone, prochlorperazine, senna, sennoside a+b, sodium picosulfate, terufis, and urea. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at the right liver lobe and thoracic vertebral mass (Th12). The BCLC stage was C, ECOG performance score was 0, and Child Pugh score was 6.

On 10 Apr 2014 (Day 1), treatment with study drug was initiated.

On 24 Apr 2014 (Day 15), the subject experienced cancer pain (Grade 2). The subject was treated with loxoprofen and oxycodone. On 28 Apr 2014 (Day 19), the subject experienced nausea (Grade 2) and vomiting (Grade 1). The subject was treated with prochlorperazine. On the same day (Day 19), the subject recovered from vomiting. On 20 May 2014 (Day 41), the subject stopped taking the study drug by choice. On 22 May 2014 (Day 43), the subject experienced abnormal hepatic function (Grade 4), fatigue (Grade 3), decreased weight (Grade 2), vomiting (Grade 1), and dehydration (Grade 1). The subject was treated with terufis and prochlorperazine. The study drug was interrupted due to abnormal hepatic function and fatigue. On the same day (Day 43), the subject recovered from vomiting. Laboratory tests showed AST 1104 U/L (NR: 10 – 43), ALP 207 U/L (NR: 43 – 115), ALT 727 U/L (NR: 10 –40), total bilirubin 126.4 umol/L (NR: 1.7 – 18.8), albumin 34 g/L (NR: 35 – 55), BUN 21.42 mmol/L (NR: 1.78 – 7.14), creatinine 212 umol/L (NR: 62 – 124), potassium 5.2 mmol/L (NR: 3.5 – 5), total protein 91 g/L (NR: 60 – 80), and GGT 144 U/L (NR: 10 – 49). On 29 May 2014 (Day 50), the subject was supposed to go to emergency room but was too weak. On 30 May 2014 (Day 51), the subject was picked up by the ambulance and while the preparations for transport were being made, the subject lost consciousness. The subject went into cardiopulmonary arrest, and cardiopulmonary resuscitation was performed. In the hospital, the subject was found to have an arrhythmia and underwent defibrillation. The subject was diagnosed with hyperkalemia (Grade 4) and renal impairment (Grade 4). Repeat laboratory tests showed BUN 63.3675 mmol/L (NR: 2.856 – 7.14), creatinine 643.552 umol/L (NR: 53.04 – 97.24), potassium 8 mmol/L (NR: 3.6 – 4.9), AST 718 U/L (NR: 10 – 35), ALT 428 U/L (NR: 5 – 40), and ALP 651 U/L (NR: 110 – 360). The subject was treated with

calcium gluconate, insulin, epinephrine, and amiodarone. On the same day (Day 51), the subject was withdrawn from the study drug due to renal impairment and abnormal hepatic function secondary to clinical disease progression. The subject received the last dose of the study drug on 19 May 2014 (Day 40). Later that day (Day 51, 10 days after the last dose), the subject died due to worsening of renal impairment and abnormal hepatic function. At the time of death, the subject had not recovered from hyperkalemia, nausea, fatigue, cancer pain, decreased weight, and dehydration. Autopsy was not performed. The Investigator considered abnormal hepatic function and renal impairment serious and not related to the study drug but related to disease progression; cancer pain, vomiting and fatigue nonserious and not related to the study drug but related to disease progression; hyperkalemia, decreased weight, and dehydration nonserious and not related to the study drug; nausea nonserious and possibly related to the study drug.

Subject Number	14061008
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-002875
Assigned Treatment	Sorafenib 800 mg/day
Fatal SAE(s)	Septic shock
Non-Fatal SAE(s)	Pneumonia escherichia, Septic shock
AE(s) Leading to Discontinuation	Septic shock
Death due to PD	No

A 68-year-old white male was diagnosed with hepatocellular carcinoma on 09 Oct 2014. Significant medical history included blindness, esophageal varices, cardiac catheterization, pulmonary arterial hypertension, portal hypertension, dyspepsia, hepatic cirrhosis, and hepatitis C. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included amiodarone, ceftriaxone, daclatasvir, nicardipine, norepinephrine, omeprazole, and sofosbuvir. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 13 Nov 2014 (Day 1), treatment with study drug was initiated.

On 03 Jan 2015 (Day 52), the subject was hospitalized for Escherichia pneumonia (Grade 4) and septic shock (Grade 4), and also experienced tachyarrhythmia (Grade 2), acute kidney injury (Grade 3) secondary to septic shock, and pyrexia (Grade 1) with body temperature 39 ºC. On the same day (Day 52), the study drug was interrupted due to Escherichia pneumonia and septic shock. Laboratory tests showed WBC 8.8 x10^9/L (NR: 4 – 10) and platelets 53 x10^9/L (NR: 150 – 400). The subject was treated with amiodarone, ceftriaxone, and norepinephrine. The subject underwent dialysis. On 05 Jan 2015 (Day 54), the subject experienced respiratory distress (Grade 3) and underwent endotracheal intubation, and mechanical ventilation. On 06 Jan 2015 (Day 55), the subject recovered from tachyarrhythmia. On 07 Jan 2015 (Day 56), laboratory tests showed BUN 23.6 mmol/L (NR: 2.8 – 7.6), AST 874 U/L (NR: 5 – 38), and ALT 618 U/L (NR: 5 – 41) and the subject was diagnosed with hepatic failure (Grade 3). On 08 Jan 2015 (Day 57), laboratory tests showed BUN 29.5 mmol/L, creatinine 238 umol/L (NR: 60 – 105), AST 465 U/L, ALT 443 U/L, and total bilirubin 247 umol/L (NR: 1 – 17). On the same day (Day 57), the subject was withdrawn from the study due to septic shock. The subject received the last dose of the study drug on 02 Jan 2015 (Day 51). On 08 Jan 2015 (Day 57, 6 days after the last dose), the subject died due to septic shock. Autopsy was not performed. At the time of death, the subject had not recovered from Escherichia pneumonia, hepatic failure, respiratory distress, pyrexia, and acute kidney injury. The Investigator considered Escherichia pneumonia serious (important medical event) and not related to the study drug; septic shock serious and not related to the study drug; tachyarrhythmia, respiratory distress, hepatic failure, pyrexia, and acute kidney injury nonserious and not related to the study drug.

Subject Number	14061016
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-010092
Assigned Treatment	Sorafenib 800 mg/day
Fatal SAE(s)	Sepsis
Non-Fatal SAE(s)	Sepsis, Asthenia
Death due to PD	No

A 77-year-old white male was diagnosed with hepatocellular carcinoma on 06 Nov 2014. Significant medical history included appendectomy, appendicular abscess, adenocarcinoma of appendix, intestinal diverticulum, hypertension, colectomy, non-alcoholic steatohepatitis, hepatic cirrhosis, hepatic steatosis, esophageal varices, portal hypertension, prostatic adenoma, right knee arthroplasty, splenomegaly, and type 2 diabetes mellitus. Previous anticancer therapies included transcatheter arterial chemoembolization (2x). Prior and concomitant medications included acarbose, allantoin w/amino acids/butyrospermum par, amlodipine, cefotaxime, dexchlorpheniramine, fentanyl, fluconazole, loperamide, losartan, metoclopramide, metronidazole, midazolam, octreotide, other emollients and protectives (moisturizing cream), pantoprazole, proteins, and spiramycin. At Screening, tumor assessments of target/non-target lesions via MRI showed liver lesions at right lobe, left lobe, and left portal vein. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 17 Apr 2015 (Day 1), treatment with study drug was initiated.

On 06 May 2015 (Day 20), the subject experienced asthenia (Grade 2). On 09 May 2015 (Day 23), the subject experienced rash (Grade 2). On 11 May 2015 (Day 25), the study drug was interrupted due to these events and the subject was treated with dexchlorpheniramine. On 18 May 2015 (Day 32), the subject recovered from asthenia and on 01 Jun 2015 (Day 46), the subject recovered from rash. On 02 Jun 2015 (Day 47), the study drug was resumed at a reduced dose of 200 mg/day due to rash. The Investigator considered asthenia and rash nonserious and probably related to the study drug.

On 13 Jun 2015 (Day 58), the study drug dose was increased to 400 mg/day per Investigator's decision.

On 28 Jun 2015 (Day 73), the subject experienced asthenia (Grade 2). On 14 Jul 2015 (Day 89), the study drug dose was again reduced to 200 mg/day due to asthenia. On 07 Aug 2015 (Day 113), the subject experienced esophageal candidiasis (Grade 2) and the severity of asthenia worsened to Grade 3. On 08 Aug 2015 (Day 114), the study drug was interrupted due to asthenia and esophageal candidiasis. On 21 Aug 2015 (Day 127), the severity of esophageal candidiasis worsened to Grade 3 and the subject was treated with fluconazole. The subject did not recover from esophageal candidiasis and asthenia. The Investigator considered asthenia and esophageal candidiasis nonserious and probably related to the study drug.

On 21 Aug 2015 (Day 127), tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of study drug on 07 Aug 2015 (Day 113).

On 27 Aug 2015 (Day 133), the subject was hospitalized for sepsis (severe sepsis related to pulmonary origin; Grade 4) and asthenia (Grade 3). On the same day (Day 133), the subject experienced renal failure (Grade 2). On 28 Aug 2015 (Day 134), the subject experienced aspiration pneumonia (Grade 2), hepatic failure (Grade 3), and malignant ascites (Grade 1). The subject was treated with spiramycin, cefotaxime, and metronidazole. On the same day (Day 134), the subject recovered from renal failure. On 01 Sep 2015 (Day 138), the laboratory results showed WBC 14.52 x10^9/L (NR: 4 – 10), creatinine 139 umol/L (NR: 50 – 120), AST 628 U/L (NR: 0 – 35), ALT 340 U/L (NR: 0 – 43), ALP 421 U/L (NR: 0 – 115), and total bilirubin 126 umol/L (NR: 0 – 17). On 03 Sep 2015 (Day 140, 27 days after the last dose), the subject died due to sepsis. Autopsy was not performed. The organism which caused sepsis was not specified. At the time of death, the subject had not recovered from asthenia and malignant ascites. The outcome of aspiration pneumonia and hepatic failure were unknown. The Investigator considered sepsis and asthenia serious and not related to the study drug; aspiration pneumonia, hepatic failure, malignant ascites, and renal failure nonserious and not related to the study drug.

Subject Number	14101004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-010101
Assigned Treatment	Sorafenib 800 mg/day
Fatal SAE(s)	General physical health deterioration
Non-Fatal SAE(s)	Diarrhoea, Gastrointestinal haemorrhage, General physical health deterioration
AE(s) Leading to Discontinuation	Gastrointestinal haemorrhage, General physical health deterioration
Death due to PD	Yes

A 73-year-old white male was diagnosed with hepatocellular carcinoma on 08 Jul 2015. Significant medical history included large intestinal polypectomy, intervertebral disc protrusion, alcoholism, hypertension, hyponatremia, left facial paralysis, asthenia, diabetes mellitus, ascites, alcoholic cirrhosis, and cerebrovascular accident. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included dextrose and sodium chloride injection, esomeprazole, fenofibrate, furosemide, gabapentin, human albumin, metformin, perindopril, racecadotril, spironolactone, and titanoreine. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right liver lobes. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 30 Jul 2015 (Day 1), treatment with study drug was initiated.

On 01 Aug 2015 (Day 3), the subject experienced gastrointestinal motility disorder (alternating constipation and diarrhea; Grade 1). The study drug dose was not changed. On 28 Aug 2015 (Day 30), the subject recovered with sequelae from gastrointestinal motility disorder. The Investigator considered gastrointestinal motility disorder nonserious and probably related to the study drug.

On 28 Aug 2015 (Day 30), the subject experienced diarrhea (Grade 3) and was hospitalized the following day (Day 31). On 30 Aug 2015 (Day 32), the study drug was interrupted due to diarrhea. Laboratory tests showed urea 16.5 mmol/L (NR: 2.5 – 6.7), creatinine 106 umol/L (NR: 53 – 97), and sodium 125 mmol/L (NR: 135 – 145). The subject was treated with racecadotril. Stool examination showed normal flora and stool culture was negative for bacterial growth. On 03 Sep 2015 (Day 36), the subject recovered from diarrhea. On 04 Sep 2015 (Day 37), the study drug was resumed at reduced dose and frequency of 400 mg every other day due to diarrhea. The Investigator considered diarrhea serious and probably related to the study drug.

On 22 Sep 2015 (Day 55), the subject was hospitalized for gastrointestinal hemorrhage (Grade 2) and general physical health deterioration (progressive disease with patient general impairment; Grade 4). On the same day (Day 55), the subject recovered from gastrointestinal hemorrhage. On 23 Sep 2015 (Day 56), the study drug was interrupted due to both events. Esophagogastroduodenoscopy showed portal hypertensive gastropathy and no hemorrhagic

lesion; sigmoidoscopy showed inflammatory rectal and colonic mucosa. Laboratory tests showed urea 25.4 mmol/L, Hgb 99 g/L (NR: 130 – 170), and Hct 0.297 L/L (NR: 0.4 – 0.54). On 23 Sep 2015 (Day 56), the subject experienced ascites (nonmalignant ascites; Grade 2). On the same day (day 56), the subject underwent paracentesis and recovered from ascites. On 24 Sep 2015 (Day 57), the subject was withdrawn from study due to gastrointestinal hemorrhage, general physical health deterioration, and received the last dose of the study drug on 22 Sep 2015 (Day 55). On 09 Oct 2015 (Day 72, 17 days after the last dose), the subject died due to general physical health deterioration. The Investigator considered general physical health deterioration serious and not related to the study drug but related to disease progression; gastrointestinal hemorrhage serious and possibly related to the study drug; ascites nonserious and not related to the study drug.

Subject Number	14141005
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-009352
Assigned Treatment	Sorafenib 800 mg/day
Fatal SAE(s)	Subarachnoid haemorrhage, Traumatic haematoma
Non-Fatal SAE(s)	Spinal fracture, Subarachnoid haemorrhage, Traumatic haematoma
AE(s) Leading to Discontinuation	Traumatic haematoma
Death due to PD	No

A 60-year-old white male was diagnosed with hepatocellular carcinoma on 08 Oct 2014. Significant medical history included ex-alcoholic, diabetes mellitus, drug dependence, epilepsy, hepatitis C, fracture treatment (knee fracture surgery), hepatic cirrhosis, spinal operation (lumbar surgery), amnesia, musculoskeletal chest pain, nicotine dependence, pulmonary arterial hypertension, dry skin, sleep disorder, traumatic fractured pelvis and rachis, and malnutrition. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included escitalopram, general nutrients (nutritional complement), insulin aspart, insulin glargine, levetiracetam, loperamide, magnesium, other emollients and protectives (neutrogena), paracetamol, potassium, racecadotril, sildenafil, tramadol, urea, and xerial. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left liver lobe and segment VII of the right liver lobe; mass at right upper lobe of lung. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 16 Jun 2015 (Day 1), treatment with study drug was initiated.

On 20 Jul 2015 (Day 35), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 3) and was treated with foot care, neutrogena, and urea ointment. On 27 Jul 2015 (Day 42), the study drug dose was reduced to 400 mg/day due to this event. The subject did not recover from palmar-plantar erythrodysesthesia syndrome. The Investigator considered this event nonserious and probably related to the study drug.

On 01 Aug 2015 (Day 47), the subject was run over by a car and was hospitalized. The subject had spinal fracture (Grade 3), traumatic hematoma (cerebral hematoma post run over by car; Grade 3), and subarachnoid hemorrhage (Grade 3). The CT scan showed fractured L2, L3, L4 vertebrae, parietotemporal cerebral hematoma, and subarachnoid hemorrhage. The study drug was withdrawn due to traumatic hematoma. On 05 Aug 2015 (Day 51) brain scan was performed (report was not available). On 13 Aug 2015 (Day 59, 12 days after the last dose), the subject died due to worsening traumatic hematoma and subarachnoid hemorrhage. Autopsy was not performed. The subject received the last dose of the study drug on 31 Jul 2015 (Day 46). At the time of death, the subject had not recovered from spinal fracture. The Investigator considered traumatic hematoma, subarachnoid hemorrhage, and spinal fracture serious and not related to the study drug.

Subject Number	15041006
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2017-023914
Assigned Treatment	Sorafenib 800 mg/day
Fatal SAE(s)	Tumour haemorrhage
AE(s) Leading to Discontinuation	Abdominal pain
Death due to PD	Yes

A 70-year-old white male was diagnosed with hepatocellular carcinoma on 13 Feb 2015. Significant medical history included central pain syndrome, helicobacter gastritis, hepatic cirrhosis, esophageal varices, peptic ulcer, overweight, alcohol use, and helicobacter gastric ulcer. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included furosemide, omeprazole, propranolol, spironolactone, and targin. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right liver lobes, left adrenal mass, and right and left hepatic vein neoplastic thrombosis with caval thrombosis. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 05 Mar 2015 (Day 1), treatment with study drug was initiated.

On 06 Mar 2015 (Day 2), the subject experienced abdominal pain (Grade 3) and vomiting (Grade 3). On the same day (Day 2), the study drug was interrupted due to these events. No treatment was provided. On 07 Mar 2015 (Day 3), severity of abdominal pain improved to Grade 2. On the same day (Day 3), the study drug was resumed at a reduced dose of 400 mg/day due to abdominal pain. On 08 Mar 2015 (Day 4), severity of abdominal pain worsened to Grade 3 and the subject also experienced peripheral edema (Grade 2). The subject was treated with targin, furosemide, and spironolactone. On 09 Mar 2015 (Day 5), the subject recovered from abdominal pain. On the same day (Day 5), the study drug was interrupted due to peripheral edema. On 09 Mar 2015 (Day 5), the subject was withdrawn from study due to abdominal pain and received the last dose of the study drug on 08 Mar 2015 (Day 4). The subject did not recover from vomiting and peripheral edema. The Investigator considered abdominal pain and vomiting nonserious and probably related to the study drug; peripheral edema nonserious and possibly related to the study drug.

On 19 Mar 2015 (Day 15, 11 days after the last dose), the subject was hospitalized and died due to tumor hemorrhage. The Investigator considered tumor hemorrhage serious and possibly related to the study drug and related to clinical disease progression.

Subject Number	16011024
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-012381
Assigned Treatment	Sorafenib 800 mg/day
Fatal SAE(s)	Malignant neoplasm progression
AE(s) Leading to Discontinuation	Malignant neoplasm progression
Death due to PD	Yes

A 79-year-old white male was diagnosed with hepatocellular carcinoma on 02 Jul 2014. Significant medical history included adrenal insufficiency, chronic cardiac failure, chronic hepatitis C, hepatic cirrhosis, pyrexia, hypertension, aortic valve incompetence, and myocardial ischemia. Previous anticancer therapies included transcatheter arterial chemoembolization (4x) and radiotherapy to left adrenal mass. Prior and concomitant medications included acetylsalicylic acid, amlodipine, hydrocortisone, indapamide, metoprolol, and ramipril. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes, bilateral adrenal masses and porta hepatis lymphadenopathy. At Screening, the BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 20 Jul 2015 (Day 1), treatment with study drug was initiated.

On 31 Aug 2015 (Day 43), the subject experienced asthenia (Grade 1). The study drug dose was not changed. The subject did not recover from this event. The Investigator considered this event nonserious and not related to the study drug.

On 12 Oct 2015 (Day 85), the subject experienced hypoalbuminemia (Grade 2). Laboratory tests showed albumin 26 g/L (NR: 35 – 55), total bilirubin 24.6 umol/L (NR: 0 – 18.8), ALP 170 U/L (NR: 43 – 115), ALT 100 U/L (NR: 10 – 40), AST 125 U/L (NR: 10 – 43), GGT 396 U/L (NR: 10 – 49), BUN 11.42 mmol/L (NR: 1.78 – 7.14), creatinine 141 umol/L (NR: 62 – 124), and potassium 3.3 mmol/L (NR: 3.5 – 5). The study drug dose was not changed. The subject did not recover from this event. The Investigator considered this event nonserious and not related to the study drug.

On 28 Oct 2015 (Day 101, 7 days after the last dose), the subject died due to malignant neoplasm progression. Autopsy was not performed. The subject received the last dose of study drug on 21 Oct 2015 (Day 94). The Investigator considered malignant neoplasm progression serious and not related to study drug but related to disease progression.

Subject Number	16031003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01498-CLI-PL
Assigned Treatment	Sorafenib 800 mg/day
Fatal SAE(s)	Malignant neoplasm progression
AE(s) Leading to Discontinuation	Fatigue, Malignant neoplasm progression
Death due to PD	Yes

A 58-year-old white male was diagnosed with hepatocellular carcinoma on 06 Nov 2013. Significant medical history included asthenia, chronic hepatitis C, dysgeusia, hypertension, decreased appetite, decreased weight, right eye injury, right lens disorder (scarring of the right lens), and tobacco user. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included calcium, clemastine, dexamethasone, fluconazole, indapamide, nystatin, potassium, and ramipril. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right liver lobes; mass at the left kidney; porta hepatis, right mediastinal, para-caval, near celiac trunk, and right arm of the low diaphragm lymphadenopathies. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 20 Dec 2013 (Day 1), treatment with study drug was initiated.

On 17 Jan 2014 (Day 29), the subject experienced increased lipase (Grade 4) and decreased weight (Grade 1) with body weight 50 kg (Baseline: 56 kg). Laboratory tests showed ALP 123 U/L (NR: 43 – 115), AST 78 U/L (NR: 10 – 43), lipase 360 U/L (NR: 13 – 60), amylase 236 U/L (NR: 35 – 121), and GGT 83 U/L (NR: 10 – 49). The study drug dose was not changed. On 25 Apr 2014 (Day 127), the subject recovered from increased lipase with lipase 75 U/L but did not recover from decreased weight. The Investigator considered increased lipase nonserious and possibly related to the study drug; decreased weight nonserious and not related to the study drug.

On 21 Mar 2014 (Day 92), the subject experienced increased gamma-glutamyltransferase (Grade 3) and hypokalemia (Grade 3). Laboratory tests showed GGT 514 U/L, ALP 178 U/L, ALT 250 U/L (NR: 10 – 40), AST 216 U/L, lipase 117 U/L, amylase 124 U/L, and potassium 2.7 mmol/L (NR: 3.5 – 5). The subject was treated with potassium. The study drug dose was not changed. On 04 Apr 2014 (Day 106), the subject recovered from hypokalemia and was recovering from increased gamma-glutamyltransferase. The Investigator considered increased gamma-glutamyltransferase and hypokalemia nonserious and possibly related to the study drug.

On 25 Apr 2014 (Day 127), the subject experienced asthenia (Grade 2) with ECOG performance score 1. On 12 May 2014 (Day 144), the subject experienced fatigue (Grade 3). On the same day (Day 144, 1 day after the last dose), the subject died at home due to malignant neoplasm progression. Autopsy was not performed. At the time of death, the subject had not recovered