and decreased weight. The Investigator considered decreased weight nonserious and not related to the study drug but related to disease progression; ascites nonserious and not related to the study drug.

On 08 Dec 2015 (Day 405), the subject experienced fatigue (Grade 2) and on 09 Dec 2015 (Day 406), the study drug was interrupted. On 13 Dec 2015 (Day 410, 5 days after the last dose), the subject died due to clinical disease progression of hepatocellular carcinoma at home. Autopsy was not performed. The subject received the last dose of the study drug on 08 Dec 2015 (Day 405). At the time of death, the subject had not recovered from fatigue. The Investigator considered clinical disease progression of hepatocellular carcinoma serious and not related to the study drug but related to disease progression; fatigue nonserious and not related to the study drug but related to disease progression.

Subject Number	19021029
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-022685
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Malignant neoplasm progression
Death due to PD	Yes

A 73-year-old white male was diagnosed with hepatocellular carcinoma on 04 Mar 2014. Significant medical history included hypertension, chronic cholecystitis, chronic gastritis, chronic hemorrhoids, coronary arterial stent insertion, and myocardial infarction (2x). Previous anticancer therapies included transcatheter arterial chemoembolization (2x). Prior and concomitant medications included enalapril. At Screening, tumor assessments of target/non-target lesions via MRI scan showed multiple lesions at right and left lobes of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 13 Apr 2015 (Day 1), treatment with study drug was initiated.

On 19 Jan 2016 (Day 282), tumor response assessment showed disease progression. On 25 Jan 2016 (Day 288), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on the same day (Day 288).

On 21 Feb 2016 (Day 315, 27 days after the last dose), the subject died due to malignant neoplasm progression. The Investigator considered malignant neoplasm progression serious and not related to study drug but due to disease progression.

Subject Number	19021030
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-022628
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Malignant neoplasm progression
AE(s) Leading to Discontinuation	Malignant neoplasm progression
Death due to PD	Yes

A 74-year-old white male was diagnosed with hepatocellular carcinoma on 31 May 2015. Significant medical history included essential hypertension, fatigue, gastritis, increased glucose tolerance, cholecystectomy, and bilateral inguinal hernia repair. Previous anticancer therapy included hepatectomy. Prior and concomitant medications included ademetionine, loperamide, omeprazole, and phospholipids. At Screening, tumor assessments of target/non-target lesions via MRI showed lesion at left lobe and quadrate lobe of liver, and porta-hepatis lymphadenopathy. The BCLC Stage was C, ECOG performance was 1, and Child Pugh score was 5.

On 03 Jun 2015 (Day 1), treatment with study drug was initiated.

On 18 Nov 2015 (Day 169), the subject experienced decreased weight (Grade 2) with body weight of 69 kg (Baseline: 78.7 kg) which started on 23 Sep 2015 (Day 113) as Grade 1 (body weight 75 kg). On 09 Mar 2016 (Day 281), the study drug was reduced to 8 mg/day due to this event. The subject did not recover from decreased weight. The Investigator considered decreased weight nonserious and possibly related to study drug.

On 03 Apr 2016 (Day 306), the subject experienced diarrhea (Grade 2) and was treated with loperamide. On 06 Apr 2016 (Day 309), the subject's decreased weight worsened to Grade 3 with body weight of 58.5 kg. On the same day (Day 309), the study drug was interrupted due to these events. On 10 Apr 2016 (Day 313), the subject recovered from diarrhea. On 16 Apr 2016 (Day 319), the study drug was resumed at same dose. The subject did not recover from decreased weight. The Investigator considered decreased weight and diarrhea nonserious and possibly related to study drug.

On 01 Jun 2016 (Day 365), the subject experienced fatigue (Grade 1). On 06 Jun 2016 (Day 370), the fatigue worsened to Grade 2. On 30 Jun 2016 (Day 394), the study drug was reduced to 4 mg/day due to ongoing decreased weight and fatigue. The subject was recovering from fatigue and did not recover from decreased weight. The Investigator considered decreased weight and fatigue nonserious and possibly related to study drug.

On 27 Jul 2016 (Day 421, 1 day after the last dose), the subject died due to malignant neoplasm progression and received the last dose on 26 Jul 2016 (Day 420). Autopsy was not performed. The Investigator considered malignant neoplasm serious and not related to study drug but related to disease progression.

Subject Number	19021036
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-015742
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Malignant neoplasm progression
Death due to PD	Yes

A 77-year-old white male was diagnosed with hepatocellular carcinoma on 29 Apr 2015. Significant medical history included dyspnea, chronic hepatitis B, essential hypertension, fatigue, dizziness, bilateral inguinal hernia repair, and cholecystectomy. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acetylcysteine, captopril, losartan, moxifloxacin, omeprazole, and phospholipids. At Screening, tumor assessments of target/non-target lesions via CT scan showed bilateral lung masses; MRI showed lesion at right liver lobe. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 10 Jul 2015 (Day 1), treatment with study drug was initiated.

On 20 Aug 2015 (Day 42), the subject experienced decreased weight (Grade 1) with body weight of 74 kg (Baseline: 80.3 kg). On 21 Aug 2015 (Day 43), the subject experienced diarrhea (Grade 1) and fatigue (Grade 2). On 03 Sep 2015 (Day 56), the severity of decreased weight worsened to Grade 2 with body weight of 72 kg. On 11 Sep 2015 (Day 64), the study drug dose was reduced to 8 mg/day due to these events. The subject did not recover from fatigue, diarrhea, and decreased weight. The Investigator considered fatigue, diarrhea, and decreased weight nonserious and possibly related to the study drug.

On 16 Mar 2016 (Day 251), the subject experienced hepatic encephalopathy (Grade 2), worsening of fatigue (Grade 3), worsening of decreased weight (Grade 3) with body weight of 63 kg, and worsened Eastern Cooperative Oncology Group performance status (Grade 3) with score 3. On the same day (Day 251), the study drug was interrupted due to hepatic encephalopathy and decreased weight. Laboratory tests showed albumin 28 g/L (NR: 35 – 55), ALP 158 U/L (NR: 43 – 115), ALT 86 U/L (NR: 10 – 40), AST 73 U/L (NR: 10 – 43), and total bilirubin 45.7 umol/L (NR: 0 – 18.8). No treatment was provided. The subject was still recovering from hepatic encephalopathy, fatigue, and worsened Eastern Cooperative Oncology Group performance status. The subject did not recover from decreased weight. The Investigator considered decreased weight nonserious and possibly related to the study drug but related to disease progression; hepatic encephalopathy nonserious and not related to the study drug but related to disease progression; fatigue and worsened Eastern Cooperative Oncology Group performance status nonserious and not related to the study drug.

On 26 Mar 2016 (Day 261, 11 days after the last dose), the subject died due to malignant neoplasm progression and received the last dose of study drug on 15 Mar 2016 (Day 250). 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	19031011
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-007751
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Cerebrovascular accident
Non-Fatal SAE(s)	Cerebrovascular accident
AE(s) Leading to Discontinuation	Cerebrovascular accident

A 51-year-old white female was diagnosed with hepatocellular carcinoma on 31 Oct 2014. Significant medical history included chronic gastritis, colitis, fatigue, hypertension, and upper abdominal pain. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included ademetionine, dexamethasone, glucose, sodium chloride, and trimetazidine. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes and porta hepatis; multiple lesions in all lobes in both lungs; lymphadenopathies at left from abdominal aorta, posterior of vascular pedicle of left kidney, and left retroperitoneal areas. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 10 Mar 2015 (Day 110), the subject experienced dyspepsia (Grade 1) and was treated with dexamethasone. On 19 Mar 2015 (Day 119), the subject recovered from dyspepsia. On the same day (Day 119), the study drug dose was reduced to 4 mg/day due to this event. The Investigator considered dyspepsia nonserious and possibly related to the study drug.

On 20 Apr 2015 (Day 151), the subject experienced loss of consciousness and was hospitalized for cerebrovascular accident (Grade 4). The study drug was interrupted due to this event and other treatment information was not provided. The subject received the last dose of the study drug on 19 Apr 2015 (Day 150). On 22 Apr 2015 (Day 153, 3 days after the last dose), the subject died due to cerebrovascular accident. Autopsy confirmed the diagnosis of stroke. The Investigator considered cerebrovascular accident serious and not related to the study drug.

Subject Number	19061007
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-008798
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Pancreatitis acute, Multiple organ dysfunction syndrome, Bile duct obstruction, Hepatic failure
Non-Fatal SAE(s)	Pancreatitis acute, Hepatic failure, Bile duct obstruction
AE(s) Leading to Discontinuation	Pancreatitis acute, Hepatic failure, Multiple organ dysfunction syndrome, Bile duct obstruction
Death due to PD	Yes

A 67-year-old white male was diagnosed with hepatocellular carcinoma on 24 Sep 2012. Significant medical history included ischemic stroke, coronary artery arteriosclerosis, chronic gastritis, cholecystectomy, coronary artery disease, duodenitis, duodenogastric reflux, essential hypertension, portal hypertension, and esophageal varices. Previous anticancer therapies included transcatheter arterial chemoembolization (6x), hepatectomy of segments 5, 6, and 7. Prior and concomitant medications included acetylsalicylic acid, ademetionine, aprotinin, atorvastatin, bisoprolol, calcium chloride, furosemide, glucose, human albumin, insulin, isosorbide dinitrate, magnesium sulfate, menadione, octreotide, ornithine, sodium chloride, ursodeoxycholic acid, and valsartan. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left lobes of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 10 Mar 2016 (Day 225), the subject experienced hepatic failure (Grade 3), acute pancreatitis (Grade 1), and bile duct obstruction (Grade 3). The study drug was interrupted due to these events. Laboratory tests showed albumin 30 g/L (NR: 35 – 55), ALP 733 U/L (NR: 43 – 115), ALT 84 U/L (NR: 10 – 40), AST 103 U/L (NR: 10 – 43), GGT 522 U/L (NR: 10 – 49), creatinine 18 umol/L (NR: 62 – 124), and total bilirubin 229 umol/L (NR: 0 – 18.8). Amylase and lipase laboratory results were not provided. The subject was treated with ademetionine, human albumin, calcium chloride, glucose, insulin, magnesium sulfate, ornithine, sodium chloride, aprotinin, octreotide, and menadione. On 15 Mar 2016 (Day 230), the subject was hospitalized for hepatic failure (Grade 4) and acute pancreatitis (Grade 4). Laboratory tests showed total bilirubin 543 umol/L (NR: 3.4 – 17.1). Nuclear magnetic resonance imaging of abdomen showed stricture of the common bile duct, big cyst of head of pancreas, ascites, and syndrome of portal hypertension. On 16 Mar 2016 (Day 231), the event of bile duct obstruction worsened to Grade 4. Laboratory tests showed total bilirubin 587 umol/L (NR: 3.4 – 17.1), AST 139.3 U/L (NR: 11 – 50), ALT 96 U/L (NR: 11 – 50), ALP 972.3 U/L (NR: 36 – 92), albumin 29.4 g/L (NR: 30 – 55), and total amylase 43.1 U/L (NR: not provided). The subject underwent bile duct stent insertion. On 17 Mar 2016 (Day 232), the subject was withdrawn from the study due to these events and the subject received the last dose of the study drug on 09 Mar 2016 (Day 224). On the same day (Day 232, 8 days after the last dose),

the subject died due to multiple organ dysfunction syndrome, hepatic failure, bile duct obstruction, and acute pancreatitis. Autopsy was not performed. The Investigator considered multiple organ dysfunction syndrome, hepatic failure, and acute pancreatitis serious and not related to the study drug; bile duct obstruction serious and not related to the study drug but related to disease progression.

Subject Number	20021003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-003331
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Hepatic encephalopathy
Non-Fatal SAE(s)	Hepatic encephalopathy
AE(s) Leading to Discontinuation	Hepatic encephalopathy
Death due to PD	Yes

An 84-year-old white male was diagnosed with hepatocellular carcinoma on 26 Nov 2014. Significant medical history included ascites, hemochromatosis, hepatitis C, decreased gastric acid, and hepatic cirrhosis. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included furosemide, nadroparin, pantoprazole, and spironolactone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right lobe of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 7.

On 12 Jan 2015 (Day 1), treatment with study drug was initiated.

On 15 Jan 2015 (Day 4), the subject experienced hepatic encephalopathy (Grade 4) and on 18 Jan 2015 (Day 7), the subject was hospitalized for hepatic encephalopathy with a blood pressure of 199/117 mmHg, and symptoms of overall decline, with weakness, and inability to walk or stand up. Laboratory tests showed ALP 148 U/L (NR: 38 – 126), ALT 139 U/L (NR: 21 – 72), AST 166 U/L (NR: 17 – 59), total bilirubin 82.08 umol/L (NR: 3.42 – 22.23), ammonia 10.7085 umol/L (NR: 10.7085 – 39.9784), and GGT 59 U/L (NR: 15 – 73). On 19 Jan 2015 (Day 8), tumor response assessment showed disease progression. On the same day (Day 8), the subject was withdrawn from study due to hepatic encephalopathy and received the last dose of the study drug. On 23 Jan 2015 (Day 12, 4 days after the last dose), the subject died due to hepatic encephalopathy. Autopsy was not performed. The Investigator considered this event serious and not related to the study drug but related to disease progression.

Subject Number	24011009
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01552-CLI-CN
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Pulmonary infarction
Non-Fatal SAE(s)	Pulmonary infarction
AE(s) Leading to Discontinuation	Pulmonary infarction
Death due to PD	No

A 57-year-old Chinese male was diagnosed with hepatocellular carcinoma on 04 May 2014. Significant medical history included blood bilirubin increased, cholecystitis, chronic hepatitis B, hepatic cirrhosis, jaundice, hepatic pain, and decreased blood potassium. Previous anticancer therapy included high frequency ablation. Prior and concomitant medications included adefovir, ademetionine, amino acids, aminomethylbenzoic acid, andrographis paniculata, anisodamine, atropine, bifendate, bucinnazine, celecoxib, dalteparin, domperidone, dopamine, epinephrine, esomeprazole, etamsilate, fats (medium and long chain fat emulsion), furosemide, glutathione, glycyrrhizic acid, human albumin, hyaluronic acid, lidocaine, lobeline, marzulene s, multivitamin, nikethamide, norepinephrine, omeprazole, oxycodone, phytomenadione, potassium, proliv, promethazine, sodium bicarbonate, sodium chloride, succinic acid, torasemide, tramadol, and unspecified herbal and traditional medicine (kangfuxin solution). At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes, abdomen, left adrenal gland, and near left iliac blood vessels; gastrohepatic and retroperitoneal lymphadenopathies, and ascites. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 20 Jun 2014 (Day 1), treatment with study drug was initiated.

On 28 Jul 2014 (Day 39), the subject experienced dental ulcer (Grade 3), which started as Grade 1 on 16 Jun 2014 (Day –4). On 29 Jul 2014 (Day 40), the study drug was interrupted due to dental ulcer. The subject was treated with etamsilate, aminomethylbenzoic acid, and phytomenadione. The subject did not recover from this event. The Investigator considered this event nonserious and probably related to the study drug.

On 04 Aug 2014 (Day 46), the subject experienced pulmonary infarction (Grade 4) associated with sudden onset of dyspnea (Grade 3), hypotension (Grade 3) with BP of 90/57 mmHg, acidosis (Grade 1), increased serum bilirubin (Grade 3), hyperhidrosis (Grade 2), and aspartate aminotransferase increased (Grade 2). Laboratory tests showed a positive d-dimer test, total bilirubin 72.8 umol/L (NR: 0 – 20.5), and AST 157 U/L (NR: 0 – 50). The subject was treated with dalteparin, atropine, dopamine, epinephrine, lobeline, lidocaine, norepinephrine, nikethamide, promethazine, succinic acid, and sodium bicarbonate. The study drug remained interrupted due to hypotension and dyspnea. On 05 Aug 2014 (Day 47), the subject experienced cardiogenic shock (Grade 3) and cancer breakthrough pain (Grade 2). The subject was treated with lidocaine and the study drug remained interrupted due to cardiogenic shock. On the same

day (Day 47), the subject recovered from cancer breakthrough pain and hyperhidrosis. The subject was withdrawn from the study due to pulmonary infarction and received the last dose of the study drug on 28 Jul 2014 (Day 39). On 06 Aug 2014 (Day 48, 9 days after the last dose), the subject died due to pulmonary infarction. Autopsy was not performed. At the time of death, the subject had not recovered from cardiogenic shock, dyspnea, hypotension, acidosis, increased aspartate aminotransferase, and increased serum bilirubin. The Investigator considered pulmonary infarction serious and not related to study drug; increased aspartate aminotransferase and cardiogenic shock nonserious and not related to the study drug but related to disease progression; hypotension, dyspnea, acidosis, hyperhidrosis, increased serum bilirubin, and cancer breakthrough pain nonserious and not related to study drug.

Subject Number	24031019
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006249
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Coma hepatic
Death due to PD	Yes

A 63-year-old Chinese female was diagnosed with hepatocellular carcinoma on 18 Jan 2015. Significant medical history included hepatic cirrhosis, hepatitis B, and splenomegaly. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included glucose injection, glycyrrhizic acid, omeprazole, other emollients and protectives (shen huang shuang, traditional Chinese medicine), polyene phosphatidylcholine, sodium chloride, unspecified herbal and traditional medicine (shuganning), and yinzhihuang (yinzhihuang oral liquid). At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right lobe of liver and inferior vena cava cancer embolus. 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 26 Feb 2015 (Day 29), the subject experienced increased blood bilirubin (Grade 2). Laboratory tests showed albumin 26 g/L (NR: 35 – 55), ALP 124 U/L (NR: 30 – 115), ALT 62 U/L (NR: 10 – 33), AST 45 U/L (NR: 10 – 36), GGT 65 U/L (NR: 5 – 32), total bilirubin 38.1 umol/L (NR: 0 – 18.8), and CRP 78.3 mg/L (NR: 0 – 5). The study drug dose was not changed. On 25 Mar 2015 (Day 56), severity of increased blood bilirubin worsened to Grade 3 with total bilirubin 74.6 umol/L and CRP 92.8 mg/L. The subject was treated with yinzhihuang. On 28 Mar 2015 (Day 59), the study drug was interrupted. The subject did not recover from this event. The Investigator considered increased blood bilirubin nonserious and not related to the study drug.

On 16 Apr 2015 (Day 78, 20 days after the last dose), the subject died due to hepatic coma. Autopsy was not performed. The subject received the last dose of the study drug on 27 Mar 2015 (Day 58). The Investigator considered hepatic coma serious and not related to the study drug but related to disease progression.

Subject Number	24041001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-007030
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Cerebral haemorrhage, Upper gastrointestinal haemorrhage, Respiratory failure
Non-Fatal SAE(s)	Cerebral haemorrhage
AE(s) Leading to Discontinuation	Cerebral haemorrhage
Death due to PD	Unknown

A 65-year-old Chinese male was diagnosed with hepatocellular carcinoma on 25 Mar 2008. Significant medical history included calculous cholecystitis, cerebral hemorrhage, chronic gastritis, hepatitis B, cerebrovascular operation (post operation for cerebrovascular malformation), and tricuspid valve incompetence. Previous anticancer therapy included hepatectomy. Prior and concomitant medications included adefovir, polyene phosphatidylcholine, and potassium. 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 21 Mar 2014 (Day 1), treatment with study drug was initiated.

On 27 Mar 2014 (Day 7), the subject experienced increased transaminases (Grade 3). Laboratory tests showed AST 562 U/L (NR: 8 – 38) and ALT 228 U/L (NR: 4 – 44). On the same day (Day 7), the study drug was interrupted. The subject was treated with polyene phosphatidylcholine. On 31 Mar 2014 (Day 11), the severity of increased transaminases decreased to Grade 2 with AST 199 U/L and ALT 143 U/L. On 08 Apr 2014 (Day 19), the subject recovered from this event and the study drug resumed at same dose. The Investigator considered this event nonserious and probably related to the study drug.

On 20 May 2015 (Day 426), the subject experienced sudden coma and CT scan of the head showed hemorrhage at right temporoparietal lobe, occipital lobe, and subarachnoid areas. The subject was diagnosed with cerebral hemorrhage (Grade 4) and was hospitalized. Laboratory tests and treatment details were not obtainable. On 21 May 2015 (Day 427), the subject was withdrawn from study due to cerebral hemorrhage and received the last dose of the study drug on 20 May 2015 (Day 426). On 21 May 2015 (Day 427, 1 day after the last dose), the subject died due to cerebral hemorrhage, respiratory failure, and upper gastrointestinal hemorrhage. Autopsy was not performed. It was noted that the subject did not suffer any trauma or sepsis prior to these events and no additional lab tests were performed. The Investigator considered cerebral hemorrhage, respiratory failure, and upper gastrointestinal hemorrhage serious and possibly related to the study drug.

Subject Number	24111012
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-002827
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Respiratory failure
Death due to PD	Yes

A 78-year-old Chinese male was diagnosed with hepatocellular carcinoma in Mar 2014. Significant medical history included appendectomy, benign meningiomas, increased blood pressure, gastric ulcer hemorrhage, hepatitis C, and gastrectomy. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included aceglutamide, amlodipine, aztreonam, coenzyme complex, deoxyribonucleic acid, folic acid, glucose injection, glycyrrhizic acid, hydrochlorothiazide, invert sugar, karvea hct, liver therapy, metronidazole, montmorillonite, nifedipine, telmisartan, and thymopentin. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left lobes of liver and multifocal areas in liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 15 Aug 2014 (Day 1), treatment with study drug was initiated.

On 03 Dec 2014 (Day 111), tumor response assessment showed disease progression. On 06 Dec 2014 (Day 114), the subject was withdrawn from the study due to disease progression and received the last dose of study drug on 05 Dec 2014 (Day 113).

On 26 Dec 2014 (Day 134, 21 days after the last dose), a family member informed the site that the subject died. The cause of death was respiratory failure. No further information was provided. Autopsy was not performed. The Investigator considered respiratory failure serious and not related to study drug but related to disease progression.

Subject Number	24111014
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-014600
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Organ failure
AE(s) Leading to Discontinuation	Organ failure
Death due to PD	No

A 65-year-old Chinese male was diagnosed with hepatocellular carcinoma on 27 Nov 2012. Significant medical history included hepatitis B and hypertension. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, enalapril, entecavir, folic acid, hydrochlorothiazide, norfloxacin, and unspecified herbal and traditional medicine (pill of six ingredients with rehmannia). At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe and at the top of the liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 22 Aug 2014 (Day 1), treatment with study drug was initiated.

On 12 Feb 2016 (Day 540), the study drug was interrupted by subject's choice.

On 19 Feb 2016 (Day 547, 8 days after the last dose), the subject died due to organ failure (unknown). The subject received the last dose of study drug on 11 Feb 2016 (Day 539). Autopsy was not performed. The Investigator considered the event serious and not related to the study drug.

Subject Number	24111029
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-014411
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Upper gastrointestinal haemorrhage
AE(s) Leading to Discontinuation	Upper gastrointestinal haemorrhage
Death due to PD	No

A 33-year-old Chinese male was diagnosed with hepatocellular carcinoma on 28 Nov 2014. Significant medical history included hepatitis B. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included ademetionine, entecavir, esomeprazole, glutathione, montmorillonite, and polyene phosphatidylcholine. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe and right branch of portal vein. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 05 Dec 2014 (Day 1), treatment with study drug was initiated.

On 11 Feb 2016 (Day 434), the subject ran out of study drug and missed a dose.

On 12 Feb 2016 (Day 435, 2 days after the last dose), the subject died at home and the cause of death was upper gastrointestinal hemorrhage. No diagnostic tests were done and no treatment was provided. Autopsy was not performed. The subject received the last dose of the study drug on 10 Feb 2016 (Day 433). The Investigator considered the event serious and not related to the study drug.

Subject Number	24111035
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-004981
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Cerebral haemorrhage
Non-Fatal SAE(s)	Aortic dissection
AE(s) Leading to Discontinuation	Cerebral haemorrhage
Death due to PD	No

A 60-year-old Chinese male was diagnosed with hepatocellular carcinoma on 09 Dec 2014. Significant medical history included chronic atrophic gastritis, hepatitis B, and liver arteriogram. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acetylsalicylic acid, alanyl glutamine, cefamandole, deproteinised calf blood injection (blood, calf, deprot, lmw portion), entecavir, esomeprazole, glycyrrhizic acid, metoprolol, neurobion, nifedipine, pantoprazole, pidotimod, and reserpine compound. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right lobe of liver. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 06 Mar 2015 (Day 84), the subject had BP of 145/89 mmHg. On 15 Mar 2015 (Day 93), the subject was hospitalized for aortic dissection (Grade 3) and the study drug was interrupted on the following day (Day 94). Computerized tomogram abdomen confirmed aortic dissection. The subject underwent aortic stent insertion on 17 Mar 2015 (Day 95) and was also treated with acetylsalicylic acid, metoprolol, nifedipine, and pidotimod. On 23 Mar 2015 (Day 101), the subject recovered from this event. On 02 Apr 2015 (Day 111), the study drug was resumed at a reduced dose of 8 mg/day due to aortic dissection. The Investigator considered the event serious and possibly related to the study drug.

On 10 Jul 2015 (Day 210), the subject died due to cerebral hemorrhage. The relatives refused to provide further information. Autopsy was not performed. The subject received the last dose of the study drug on 10 Jul 2015 (Day 210). The Investigator considered the event serious and possibly related to the study drug.

Subject Number	24111043
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-016865
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Hepatic failure
Death due to PD	Yes

A 51-year-old Chinese male was diagnosed with hepatocellular carcinoma on 08 Jan 2015. Significant medical history included abdominal pain and hepatitis. The subject did not receive any previous anticancer therapies. Prior and concomitant medication included omeprazole. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe, sternum, thoracolumbar spine, and pelvis. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 30 Jul 2015 (Day 195), the subject experienced increased blood alkaline phosphatase (Grade 3). Laboratory tests showed ALP 663 U/L (NR: 43 – 115), ALT 111 U/L (NR: 10 – 40), AST 173 U/L (NR: 10 – 43), total bilirubin 27.9 umol/L (NR: 0 – 18.8), CRP 78.5 mg/L (NR: 0 – 5), and GGT 830 U/L (NR: 10 – 49). On 31 Jul 2015 (Day 196), the subject's Child Pugh score was 6. 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 26 Aug 2015 (Day 222), the subject experienced increased aspartate aminotransferase (Grade 2). Laboratory tests showed albumin 32 g/L (NR: 35 – 55), ALP 679 U/L, ALT 109 U/L, AST 211 U/L, total bilirubin 29.6 umol/L, CRP 76.5 mg/L, and GGT 735 U/L. 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 21 Sep 2015 (Day 248), the subject withdrew from study by choice but continued to take the remaining study drug until 25 Sept 2015 (Day 252). The subject received the last dose of the study drug on 25 Sep 2015 (Day 252).

On 03 Oct 2015 (Day 260, 8 days after the last dose), the subject died at home due to hepatic failure. Autopsy was not performed. The subject's relatives refused to provide any further information. The Investigator considered this event serious and not related to the study drug but related to disease progression.

Subject Number	24131019
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-005780
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Cerebrovascular accident
Non-Fatal SAE(s)	Cerebrovascular accident
AE(s) Leading to Discontinuation	Cerebrovascular accident
Death due to PD	No

A 53-year-old Chinese male was diagnosed with hepatocellular carcinoma on 03 Jun 2013. Significant medical history included cholecystectomy, chronic cholecystitis, esophageal varices, gastric ulcer, hepatitis B, hepatic cirrhosis, spleen artery embolism, and splenomegaly. Previous anticancer therapies included radiotherapy to portal vein, hepatectomy, hepatic intra-arterial chemotherapy, high intensity focused ultrasound, brachytherapy, and transcatheter arterial chemoembolization. Prior and concomitant medications included aluminium phosphate, amino acids w/polypeptide, entecavir, esomeprazole, fentanyl, flurbiprofen, glucose injection, human albumin, hydrotalcite, insulin, levoglutamide, mosapride, omeprazole, oxycocet, pantoprazole, potassium, proliv, propranolol, ribonucleic acid, and unspecified herbal and traditional medicine (huoxiang zhengqi, shenqifuzheng, and shenmai). At Screening, tumor assessments of target/non-target lesions via MRI showed lesions at right and left lobe of liver. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 25 Sep 2014 (Day 1), treatment with study drug was initiated.

On 27 Sep 2014 (Day 3), the subject experienced fatigue (Grade 1). On 02 Mar 2015 (Day 159), the event worsened to Grade 2. On 12 Mar 2015 (Day 169), severity of fatigue worsened to Grade 3 and the study drug was interrupted. On 17 Mar 2015 (Day 174), the severity of fatigue improved to Grade 2 and the study drug was resumed at a reduced dose of 8 mg/day due to this event. The subject did not recover from fatigue. The Investigator considered fatigue nonserious and probably related to the study drug.

On 11 Feb 2015 (Day 140), the subject experienced hypertension (Grade 2) with BP of 135/95 mmHg and the subject recovered from the event without treatment with BP of 125/90 mmHg. On 10 Mar 2015 (Day 167), repeat BP was 108/72 mmHg. On 06 Apr 2015 (Day 194), the subject experienced sudden loss of consciousness and was diagnosed with cerebrovascular accident (Grade 4). The study drug was withdrawn due to this event. The subject's family refused further examination. On 07 Apr 2015 (Day 195, 2 days after the last dose), the subject died at home due to cerebrovascular accident. Autopsy was not performed. The subject received the last dose of the study drug on 05 Apr 2015 (Day 193). The Investigator considered cerebrovascular accident serious and possibly related to the study drug; hypertension nonserious and probably related to the study drug.

Subject Number	24161015
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-023048
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Malignant neoplasm progression
Death due to PD	Yes

A 62-year-old Chinese male was diagnosed with hepatocellular carcinoma on 20 Jun 2014. Significant medical history included cholecystectomy, chronic cholecystitis, and gastritis. Previous anticancer therapies included hepatectomy and transcatheter arterial chemoembolization. Prior and concomitant medications included domperidone. At Screening, tumor assessments via CT scan showed lesion at right liver lobe. The BCLC Stage was B, ECOG performance was 0, and Child Pugh score was 5.

On 07 Nov 2014 (Day 1), treatment with study drug was initiated.

On 02 Dec 2015 (Day 391), tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on the same day (Day 391).

On 20 Dec 2015 (Day 409, 18 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	24161019
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-011120
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Death
AE(s) Leading to Discontinuation	Death
Death due to PD	Yes

A 50-year-old Chinese male was diagnosed with hepatocellular carcinoma on 08 Dec 2014. Significant medical history included chronic hepatitis B. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included amlodipine, armillarisin a, dexamethasone, diclofenac, lamivudine, polypeptide, rabeprazole, and ubenimex. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right lobe of liver, L1 and L4 lumbar vertebral masses. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 25 Dec 2014 (Day 1), treatment with study drug was initiated.

On 05 Aug 2015 (Day 224), the subject experienced decreased weight (Grade 2) with body weight of 74 kg (Baseline: 85 kg). On 02 Sep 2015 (Day 252), the subject experienced increased alanine aminotransferase (Grade 2), increased aspartate aminotransferase (Grade 3), and increased blood bilirubin (Grade 3). The laboratory tests showed albumin 30 g/L (NR: 35 – 55), ALP 202 U/L (NR: 43 – 115), ALT 121 U/L (NR: 10 – 40), AST 222 U/L (NR: 10 – 43), total bilirubin 98 umol/L (NR: 0 – 18.8), and CRP 30.5 mg/L (NR: 0 – 5). The study drug dose was not changed. The subject did not recover from these events. The Investigator considered decreased weight, increased alanine aminotransferase, increased aspartate aminotransferase, and increased blood bilirubin nonserious and possibly related to the study drug.

On 01 Oct 2015 (Day 281), the subject died due to unknown reason in another hospital. Autopsy was not performed. The subject received the last dose of the study drug on the same day (Day 281). The Investigator considered this event serious and not related to the study drug but related to disease progression.

Subject Number	30011021
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-020573
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Malignant neoplasm progression
Death due to PD	Yes

A 62-year-old Asian male was diagnosed with hepatocellular carcinoma on 01 Jun 2014. Significant medical history included alcoholic cirrhosis, benign prostatic hyperplasia, gastric ulcer, hypertension, musculoskeletal pain (right shoulder pain), and tuberculosis. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included ambroxol, chlorhexidine, glyceryl trinitrate, ketorolac, lactulose, morphine, naloxone w/oxycodone, olmesartan, oseltamivir, osmotan, oxycodone, paracetamol, propacetamol, rabeprazole, silodosin, theobromine, and ultracet. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes, and mass at right lower lobe of lung. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

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

On 31 Mar 2015 (Day 223), tumor response assessment showed disease progression. On 06 Apr 2015 (Day 229), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on the same day (Day 229).

On 11 Apr 2015 (Day 234), the subject experienced abdominal pain (Grade 2) and was treated with oxycodone and rabeprazole. On 19 Apr 2015 (Day 242), the subject experienced cancer pain (cancer related chest pain; Grade 2). The subject was treated with glyceryl trinitrate, morphine, ketorolac, and naloxone w/oxycodone. The subject did not recover from these events. The Investigator considered abdominal pain and cancer pain non serious and not related to the study drug.

On 24 Apr 2015 (Day 247, 18 days after the last dose), the subject died due to malignant neoplasm progression. The Investigator considered this event serious and not related to the study drug but related to disease progression.

Subject Number	30041011
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-003600
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Hepatic failure
Non-Fatal SAE(s)	Pneumothorax, Hepatic failure
Death due to PD	No

A 52-year-old Asian male was diagnosed with hepatocellular carcinoma on 27 Jan 2012. Significant medical history included decreased appetite, hepatitis B, and procedural pain (chest). Previous anticancer therapies included hepatectomy (2x), pulmonary resection of the right lung (2x), lymphadenectomy, mass excision (retroperitoneal), and transcatheter arterial chemoembolization. Prior and concomitant medications included amino acids w/electrolytes, amino acids w/electrolytes and glucose, amlodipine, ascorbic acid w/biotin/calcium/carbohydrate, calcium gluconate, carol-f, cefazolin, chlorphenamine, dexamethasone, factor I (fibrinogen), famotidine, fentanyl, gabapentin, ketorolac, lidocaine, magnesium oxide, megestrol, methylprednisolone, midazolam, morphine, nicardipine, ornithine, oxycodone, paracetamol, pethidine, piroxicam, pregabalin, ranitidine, silybum marianum, sodium chloride, targin, thrombin, ultracet, ursodeoxycholic acid, and vitamins (multivitamin). At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at caudate liver lobe, right retroperitoneal mass, and bilateral multiple lung metastases. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 09 Dec 2014 (Day 19), the subject experienced asthenia (Grade 2), decreased appetite (Grade 2), and fatigue (Grade 2). Treatment included ascorbic acid with biotin/calcium/carbohydrate, megestrol, sodium chloride, and multivitamins. The subject did not recover from these events. The Investigator considered asthenia, decreased appetite, and fatigue nonserious and possibly related to the study drug.

On 12 Jan 2015 (Day 53), the subject experienced pneumothorax (Grade 1), which was found during planned CT scan of the chest performed on 09 Jan 2015 (Day 50). On 01 Feb 2015 (Day 73), the severity of pneumothorax worsened to Grade 3 and the subject was hospitalized. Chest x-ray showed progression of pneumothorax causing collapse of entire left lung. On 02 Feb 2015 (Day 74), the study drug was interrupted due to ongoing asthenia, decreased appetite, and fatigue. On 02 Feb 2015 (Day 74), the subject underwent chest tube insertion for pneumothorax and experienced catheter site pain (pain due to chest tube insertion; Grade 1). On 03 Feb 2015 (Day 75), the subject underwent fibrinogen pleurodesis and was also treated with ketorolac, pethidine, ultracet, calcium gluconate, cefazolin, carol-f, piroxicam, factor I, fentanyl, gabapentin, lidocaine, and morphine. The subject did not recover from pneumothorax and catheter site pain. The Investigator considered pneumothorax serious and not related to the study drug; catheter site pain nonserious and not related to the study drug.

On 06 Feb 2015 (Day 78), tumor response assessment showed disease progression and the subject was withdrawn from the study due to disease progression, and received the last dose of the study drug on 01 Feb 2015 (Day 73).

On 14 Feb 2015 (Day 86), the subject experienced lower gastrointestinal hemorrhage (Grade 1). Liver CT scan showed diffuse homogenous parenchymal enhancement in the liver probably due to parenchymal hemorrhage. The subject was hospitalized for hepatic failure (Grade 4). Treatment included ornithine, silybum marianum, and ursodeoxycholic acid. On 15 Feb 2015 (Day 87), the subject experienced azotemia (Grade 3), hepatic hemorrhage (Grade 3), and rectal hemorrhage (Grade 1). Laboratory tests were performed and showed creatinine 43.316 umol/L (NR: 61.88 – 123.76), AST 7680 U/L (NR: 0 – 40), ALT 19560 U/L (NR: 0 – 40), ALP 804 U/L (NR: 30 – 115), total bilirubin 169.29 umol/L (NR: 3.42 – 20.52), Hgb 103 g/L (NR: 130 – 170), and ammonia 244.8677 umol/L (NR: 10.7085 – 36.4089). On 17 Feb 2015 (Day 89, 16 days after the last dose), the subject died due to hepatic failure. At the time of death, the subject had not recovered from lower gastrointestinal hemorrhage, azotemia, hepatic hemorrhage, and rectal hemorrhage. The Investigator considered hepatic failure serious and possibly related to the study drug; lower gastrointestinal hemorrhage, azotemia, hepatic hemorrhage, and rectal hemorrhage nonserious and not related to the study drug but related to disease progression.

Subject Number	30051004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01496-CLI-KR
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Hepatic failure
Non-Fatal SAE(s)	Hepatic failure
Death due to PD	Yes

A 50-year-old Asian male was diagnosed with hepatocellular carcinoma on 07 Oct 2013. Significant medical history included duodenal ulcer and hepatitis B. Previous anticancer therapies included transcatheter arterial chemoembolization. Prior and concomitant medications included adefovir, amino acids, amlodipine, azithromycin, ceftriaxone, furosemide, gabapentin, godex, hydromorphone, hyoscine, lactulose, lansoprazole, livalavin, megestrol, metoclopramide, morphine, myprodol, naproxen, phytomenadione, pneumococcal vaccine, propacetamol, propofol, sucralfate, targin, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via MRI showed lesions at left and right liver lobes, and porta-hepatis lymphadenopathy; CT scan showed lesion at right iliac bone. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

On 19 Dec 2013 (Day 1), treatment with study drug was initiated.

On 09 Apr 2014 (Day 112), tumor response assessment showed disease progression. On 14 Apr 2014 (Day 117), the subject was withdrawn from study due to disease progression and received the last dose of the study drug on the same day (Day 117).

On 27 Apr 2014 (Day 130), the subject was hospitalized for bone metastasis. On 29 Apr 2014 (Day 132), the subject received radiotherapy to bone (palliative radiotherapy T-spine). On 04 May 2014 (Day 137), the subject experienced hepatic failure (Grade 3) which further prolonged hospitalization. No treatment was provided. On 06 May 2014 (Day 139), laboratory tests showed ALT 194 U/L (NR: 5 – 46), AST 952 U/L (NR: 13 – 34), and total bilirubin 78.66 umol/L (NR: 8.55 – 30.78). On 08 May 2014 (Day 141, 24 days after the last dose), the subject died due to hepatic failure secondary to disease progression. Autopsy was not performed. The Investigator considered hepatic failure serious and not related to the study drug but related to disease progression.

Subject Number	30051005
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01422-CLI-KR
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Malignant neoplasm progression
Non-Fatal SAE(s)	Hiccups, Dyspnoea, Pyrexia
Death due to PD	Yes

A 51-year-old Asian male was diagnosed with hepatocellular carcinoma on 27 Nov 2013. Significant medical history included chronic gastritis, constipation, diabetes mellitus, erosive gastritis, hepatitis B, and hypertension. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included ascorbic acid w/biotin/calcium/carb, augmentin, baclofen, benproperine, benzydamine, bromhexine, carol-f, cefixime, ceftizoxime, ceftriaxone, celecoxib, chlorphenamine, clinimix, codeine, cough and cold preparations (cough syrup), diosmectite, dulcodos, entecavir, erdosteine, falkamin, furosemide, godex, granisetron, human albumin, itopride, lactitol, lactulose, lafutidine, lansoprazole, livalavin, losartan, magnesium oxide, megestrol, metoclopramide, morphine, multitrace, naproxen, oxycodone, pancreatin, paracetamol, pheniramine, pneumococcal vaccine, pregabalin, propacetamol, ramosetron, rani-q, smoflipid, sucralfate, targin, tramadol, tranexamic acid, ultracet, ursodeoxycholic acid, vitamins, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe, axial skeleton, and spleen; portocaval lymphadenopathy. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 10 Dec 2013 (Day –10), the subject experienced cough (Grade 1), sputum (Grade 1) and was treated with erdosteine. On 27 Dec 2013 (Day 8), the subject experienced hiccups (Grade 2). On 30 Dec 2013 (Day 11), the subject was hospitalized for persistent hiccups, dyspnea (Grade 1), and pyrexia (Grade 1) with body temperature of 38.8 °C. The subject also experienced hypoalbuminemia (Grade 2) with albumin 23 g/L (NR: 33 – 53). Treatment included pheniramine, morphine, propacetamol, tramadol, ceftriaxone, ultracet, naproxen, cefixime, albumin human, falkamin, and paracetamol. The subject recovered from dyspnea on the same day (Day 11). On 07 Jan 2014 (Day 19), the subject recovered from hiccups, cough, and sputum. On 15 Jan 2014 (Day 27), the subject was discharged from the hospital. On 03 Feb 2014 (Day 46), the subject recovered from pyrexia with body temperature of 36.9 °C. The study drug dose was not changed. The subject did not recover from hypoalbuminemia. The Investigator considered hiccups serious and possibly related to study drug; pyrexia and dyspnea serious and not related to study drug; cough, sputum, and hypoalbuminemia nonserious and not related to study drug.

On 10 May 2014 (Day 142), the study drug was interrupted because the subject did not visit the site as scheduled.

On 19 May 2014 (Day 151, 10 days after the last dose), the subject died due to malignant neoplasm progression as reported by the subject's family members. Autopsy was not performed. No further information was provided. The subject received the last dose of study drug on 09 May 2014 (Day 141). The Investigator considered malignant neoplasm progression serious and not related to the study drug but related to disease progression.

Subject Number	30051010
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-001186
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Malignant neoplasm progression
Non-Fatal SAE(s)	Pain in extremity, Malignant neoplasm progression
AE(s) Leading to Discontinuation	Pain in extremity
Death due to PD	Yes

A 47-year-old Asian female was diagnosed with hepatocellular carcinoma on 30 Oct 2013. Significant medical history included acalculus cholecystitis, anemia, back pain, benign neoplasm of skin, hepatitis B, menopause, and gastroesophageal reflux disease. Previous anticancer therapies included transcatheter arterial chemoembolization, regional chemotherapy, and radiotherapy to right liver lobe mass (2x). Prior and concomitant medications included acetylcysteine, albis, alginic acid, almagate, aludrox, ambroxol acefyllinate, amino acids w/electrolytes, amlodipine, benproperine, benzydamine, celecoxib, cimetidine, clinimix, codeine, dexamethasone, diosmectite, furosemide, gabapentin, godex, grandpaze f, human albumin, hyoscine, iron, lansoprazole, loperamide, mannitol, megestrol, meloxicam, metoclopramide, metronidazole, morphine, multitrace, naproxen, nature's way primadophilus original, ofloxacin, oxycodone, pancreatin, paracetamol, piperacillin, propofol, propranolol, ranitidine, silybum marianum, smoflipid, spironolactone, sucralfate, targin, tenofovir, tramadol, trimebutine, ursodeoxycholic acid, and vitamins (tamipool). At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right liver lobes, left lower and right upper lung lobes; right rib and thoracic vertebral mass (T4 – T6). The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 20 Oct 2014 (Day 165), the subject was hospitalized for pain in extremity (right thigh pain; Grade 3) due to suspected spine metastasis and cord compression. The subject was treated with dexamethasone, targin, celecoxib, oxycodone, and gabapentin. On 21 Oct 2014 (Day 166), tumor response assessment showed disease progression. On 24 Oct 2014 (Day 169), the subject's hospitalization was further prolonged due to malignant neoplasm progression (Grade 3). On same day (Day 169), the study drug was withdrawn due to pain in extremity secondary to disease progression and the subject received the last dose of the study drug that day. On 30 Oct 2014 (Day 175), the severity of pain in extremity decreased to Grade 2 and the subject was discharged from the hospital. The subject did not recover from the pain in extremity. On 21 Nov 2014 (Day 197, 28 days after the last dose), the subject died due to malignant neoplasm progression. Autopsy was not performed. The Investigator considered the malignant neoplasm progression and pain in extremity serious and not related to the study drug but related to disease progression.

Subject Number	30071011
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01536-CLI-KR
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Sepsis
AE(s) Leading to Discontinuation	Sepsis
Death due to PD	Yes

A 67-year-old Asian male was diagnosed with hepatocellular carcinoma on 18 Nov 2013. Significant medical history included back pain, benign prostatic hyperplasia, bone pain, duodenal ulcer, hepatitis B, hypertension, metastases to spine, metastases to pleura (right), and metastases to bone (right rib). Previous anticancer therapies included transcatheter arterial chemoembolization, radiotherapy to T12 – L2, radiotherapy to L3 – S2, and radiotherapy right rib. Prior and concomitant medications included benzydamine, bisacodyl, candesartan, cebetabs, celecoxib, dexamethasone, domperidone, escitalopram, famotidine, fentanyl, haloperidol, lactulose, losartan, magnesium hydroxide, megestrol, metoclopramide, morphine, naloxone w/oxycodone, oxycodone, pangest f, pantoprazole, paracetamol, pregabalin, sodium bicarbonate, tenofovir, unspecified herbal and traditional medicine (PMC/garlic oil), ursodeoxycholic acid, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at quadrate lobe of liver, multiple lesions in left and right lobe; multiple bone metastases at vertebra, iliac, and sacral bones. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 17 Apr 2014 (Day 1), treatment with study drug was initiated.

On 30 Apr 2014 (Day 14), the subject experienced aggravation of back pain (Grade 2) and bone pain (Grade 2). On 19 May 2014 (Day 33), the subject was hospitalized for a planned radiotherapy for aggravation of the back pain and bone pain. On 21 May 2014 (Day 35), the subject experienced pathological compression fracture at T12 – L2 (Grade 2) due to spine metastasis and confirmed via MRI of whole spine. The study drug dose was not changed. On 22 May 2014 (Day 36), the subject received radiofrequency ablation with radiotherapy to T12. On 26 May 2014 (Day 40), the subject underwent vertebroplasty for pathological compression fracture at T12 – L1. The subject was also treated with dexamethasone, morphine, fentanyl, naloxone w/oxycodone, pregabalin, and oxycodone. On 02 Jun 2014 (Day 47), the subject received palliative radiation therapy to T12 – L2. The subject did not recover from these events. The Investigator considered these events nonserious and not related to study drug.

On 14 Jun 2014 (Day 59), the subject experienced chills (Grade 1) and was treated with paracetamol. The subject recovered from chills on the same day (Day 59). On 18 Jun 2014 (Day 63), the subject experienced second episode of chills (Grade 1) and recovered on the same day. On 19 Jun 2014 (Day 64), the subject received a follow-up palliative radiation therapy to T12 – L2. On 22 Jun 2014 (Day 67), the subject died at a local hospital due to sepsis. The etiology of sepsis was unknown and there were no details on the

diagnosis and treatment of sepsis. The subject received the last dose of study drug on the same day (Day 67). Autopsy was not performed. The Investigator considered sepsis serious and not related to the study drug but related to disease progression; chills nonserious and not related to study drug.

Subject Number	30091002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-018609
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Metastases to central nervous system
Non-Fatal SAE(s)	Metastases to central nervous system
Death due to PD	Yes

A 38-year-old Asian male was diagnosed with hepatocellular carcinoma on 13 Feb 2013. Significant medical history included hepatitis B and contrast media allergy. Previous anticancer therapies included hepatectomy, cholecystectomy, high frequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included beszyme, biotop, chlorphenamine, dages, dimecrotic acid, diosmectite, dexamethasone, famotidine, godex, hyoscine, loperamide, levetiracetam, mannitol, megestrol, metoclopramide, morphine, nefopam, other therapeutic products (terpenes), otilonium, paracetamol, rifaximin, silybum marianum, tenofovir, tiropramide, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed multiple masses at bilateral lungs. The BCLC stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 25 Oct 2013 (Day 1), treatment with study drug was initiated.

On 04 Jan 2014 (Day 72), the subject experienced abdominal pain (Grade 2) and the study drug was interrupted. Treatment included famotidine. The subject recovered from abdominal pain on the same day. On 05 Jan 2014 (Day 73), the study drug resumed at same dose. The Investigator considered abdominal pain nonserious and probably related to study drug.

On 08 Apr 2014 (Day 166), the tumor response assessment showed disease progression. On 11 Apr 2014 (Day 169), the subject was withdrawn due to disease progression and received the last dose of study drug on the same day.

On 14 Apr 2014 (Day 172), the subject was hospitalized for metastases to central nervous system (Grade 3). The subject was treated with dexamethasone, mannitol, and morphine. On 01 May 2014 (Day 189, 20 days after the last dose), the subject died due to metastases to central nervous system. The Investigator considered metastases to central nervous system serious and not related to study drug but related to disease progression.

Subject Number	30101001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01558-CLI-KR
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Liver carcinoma ruptured
Non-Fatal SAE(s)	Pulmonary embolism, Liver carcinoma ruptured
Death due to PD	Yes

A 47-year-old Asian male was diagnosed with hepatocellular carcinoma on 05 Jun 2010. Significant medical history included alcoholic cirrhosis, diabetes mellitus, diabetic retinopathy, esophageal varices, hypertension, portal hypertensive gastropathy, pulmonary tuberculosis, gastroesophageal reflux disease, subarachnoid hemorrhage, and hepatitis B. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, azithromycin, calcium polystyrene sulfonate, carvedilol, cefpodoxime, ceftriaxone, chlorphenamine, chlorpromazine, cimetropium, ciprofloxacin, demazin, diosmectite, diprogenta, domperidone, entecavir, erdosteine, fentanyl, furosemide, fusidic acid, gliclazide, glucose, lactulose, lidocaine, magnesium oxide, meiji sekidome, metoclopramide, morphine, moxifloxacin, oxycodone, pancreatin, paracetamol, rabeprazole, rebamipide, rivaroxaban, sodium chloride, spironolactone, synatura, targin, tramadol, and tranexamic acid. At Screening, tumor assessments of target/non-target lesions via MRI showed lesions at left lobe of liver, umbilical segment of the left portal vein, and tumor thrombosis in the left hepatic vein. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 10 Jan 2014 (Day –14), the subject experienced pulmonary embolism (Grade 3) at right lower lobar artery and segmental branches as diagnosed by CT scan of chest. The subject was asymptomatic and observation was recommended. The subject did not recover from this event. The Investigator considered pulmonary embolism nonserious and not related to the study drug.

On 24 Jan 2014 (Day 1), treatment with study drug was initiated.

On 18 Mar 2014 (Day 54), the subject was diagnosed with pulmonary embolism (Grade 3) at bilateral inferior pulmonary arteries and segmental branches as found during routine CT scan of the chest. The subject was recommended to receive anticoagulation; however, due to financial constraints the subject did not receive any treatment. The subject did not recover from pulmonary embolism. The Investigator considered pulmonary embolism nonserious and possibly related to the study drug.

On 08 Jul 2014 (Day 166), the subject was diagnosed with pulmonary infarction on right lower lobe (Grade 1) as found during routine CT scan of chest. The subject also experienced right non-cardiac chest pain (Grade 1). The subject was treated with paracetamol. The subject did not recover from these events. The Investigator considered pulmonary infarction and non-cardiac chest pain nonserious and possibly related to the study drug.

On 08 Aug 2014 (Day 197), the subject experienced worsening pulmonary embolism (Grade 3) with symptoms of cough (Grade 1) and hemoptysis (Grade 1). On 10 Aug 2014 (Day 199), the subject recovered from hemoptysis. On 11 Aug 2014 (Day 200), the CT scan of thorax confirmed aggravation pulmonary thromboembolism on both inferior pulmonary arteries and segmental branches, increased right pleural effusion, aggravated infarction on right lower lobe, and multiple nodules, not excluding metastasis. The subject was diagnosed with right pleural effusion (Grade 1), and pulmonary mass (multiple nodules on the lung, unknown; Grade 1). On 14 Aug 2014 (Day 203), the subject was hospitalized for pulmonary embolism. The subject was treated with rivaroxaban, azithromycin, ceftriaxone, and cefpodoxime. The subject did not recover from pulmonary embolism, pleural effusion, pulmonary mass, and cough. The study drug dose did not change. The Investigator considered pulmonary embolism serious and possibly related to the study drug; cough, hemoptysis, pleural effusion, and pulmonary mass nonserious and possibly related to the study drug.

On 02 Sep 2014 (Day 222), the subject experienced anemia (Grade 2) with Hgb 89 g/L (NR: 125 – 170) and RBC 2.6 x10^12/L (NR: 4 – 5.6). On 02 Oct 2014 (Day 252), the severity of anemia worsened to Grade 3 with Hgb 79 g/L and RBC 2.35 x10^12/L. On 07 Oct 2014 (Day 257), the study drug was interrupted due to anemia. The subject was treated with packed red blood cell transfusion. The subject did not recover from this event. The Investigator considered anemia nonserious and possibly related to the study drug.

On 23 Oct 2014 (Day 273), the subject experienced ruptured liver carcinoma (Grade 2) and worsened upper abdominal pain (Grade 2) which started on 15 Oct 2014 (Day 265) as Grade 1. On 24 Oct 2014 (Day 274), the subject was hospitalized for ruptured liver carcinoma. Abdominal CT confirmed hepatic cell carcinoma rupture without active bleeding, newly developed peritoneal carcinomatosis, aggravation of infiltrative hepatic cell carcinoma at left lobe, and large amount of ascites. The subject was diagnosed with malignant ascites (Grade 3) and bilateral malignant pleural effusion (Grade 2). On the same day (Day 274), tumor response assessment showed disease progression. The subject underwent paracentesis and was treated with glucose, ceftriaxone, furosemide, spironolactone, tranexamic acid, ciprofloxacin, cimetropium, oxycodone, morphine, metoclopramide, moxifloxacin, targin, tramadol, fentanyl, and sodium chloride. On 28 Oct 2014 (Day 278), the subject was withdrawn from study due to disease progression and received the last dose of the study drug on 06 Oct 2014 (Day 256). On 03 Nov 2014 (Day 284), the subject experienced hyperkalemia (Grade 3) with potassium 6.2 mmol/L (NR: 3.5 – 5) and was treated with calcium polystyrene sulfonate. On 05 Nov 2014 (Day 286, 30 days after the last dose), the subject died due to ruptured liver carcinoma. At the time of death, the subject had not recovered from malignant ascites, malignant pleural effusion, upper abdominal pain, and hyperkalemia. Autopsy was not performed. The Investigator considered ruptured liver carcinoma serious and not related to the study drug, but related to disease progression; malignant ascites and malignant pleural effusion nonserious and not related to the study drug, but related to disease progression; upper abdominal pain and hyperkalemia nonserious and not related to the study drug.

Subject Number	30111008
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-007083
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Hepatic failure
Non-Fatal SAE(s)	Hepatic failure
AE(s) Leading to Discontinuation	Blood bilirubin increased
Death due to PD	No

A 43-year-old Asian male was diagnosed with hepatocellular carcinoma on 19 Feb 2014. Significant medical history included abdominal pain, hepatitis B, and hepatic cirrhosis. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included calcium gluconate, calcium polystyrene sulfonate, ceftriaxone, fentanyl, furosemide, human albumin, human insulin, lactobacillus acidophilus, lactulose, levosulpiride, megestrol, metoclopramide, metronidazole, nefopam, ornithine, oxycodone, pennel, phytomenadione, ramosetron, spironolactone, targin, tenofovir, tramadol, ultracet, ursodeoxycholic acid, vitamins, and zenol. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left lobe of liver. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 23 Jan 2015 (Day 1), treatment with study drug was initiated.

On 17 Apr 2015 (Day 85), the subject experienced increased aspartate aminotransferase (Grade 3) and increased alanine aminotransferase (Grade 2). Laboratory tests showed AST 289 U/L (NR: 10 – 43), ALT 157 U/L (NR: 10 – 40), and ALP 184 U/L (NR: 43 – 115). On 15 May 2015 (Day 113), the study drug was interrupted due to increased aspartate aminotransferase and increased alanine aminotransferase. On 19 May 2015 (Day 117), the subject experienced worsening of abdominal pain (Grade 2). On 22 May 2015 (Day 120), the subject was hospitalized for hepatic failure (Grade 4). The subject also experienced increased blood bilirubin (Grade 3), ascites (Grade 3), and the severity of increased alanine aminotransferase worsened to Grade 3. The study drug remained interrupted due to increased blood bilirubin. Laboratory tests showed ALT 293 U/L, AST 529 U/L, ALP 281 U/L, albumin 34 g/L (NR: 35 – 55), and total bilirubin 88.4 umol/L (NR: 0 – 18.8). The subject underwent periodic paracentesis and also was treated with lactulose, calcium polystyrene sulfonate, human albumin, vitamins, calcium gluconate, human insulin, ceftriaxone, metronidazole, nefopam, and phytomenadione. On 29 May 2015 (Day 127), the severity of increased blood bilirubin worsened to Grade 4. Laboratory tests showed total bilirubin 234.27 umol/L (NR: 3.42 – 17.1), AST 657 U/L (NR: 10 – 33), ALT 171 U/L (NR: 4 – 50), ALP 755 U/L (NR: 104 – 338), sodium 120 mmol/L (NR: 134 – 145), potassium 5.8 mmol/L (NR: 3.5 – 5.2), BUN 28.917 mmol/L (NR: 2.856 – 7.14), and creatinine 125.528 umol/L (NR: 53.04 – 106.08). On 29 May 2015 (Day 127), the subject was withdrawn from the study due to increased blood bilirubin and received the last dose on 14 May 2015 (Day 112). On 30 May 2015 (Day 128), repeat laboratory tests showed total

bilirubin 208.62 umol/L (NR: 3.42 – 17.1), AST 2175 U/L (NR: 10 – 33), ALT 304 U/L (NR: 4 – 50), and ammonia 81 umol/L (NR: 0 – 40). The subject's condition worsened and mental status changed from stupor to coma. Later on that day (Day 128, 16 days after the last dose), the subject died due to hepatic failure. Autopsy was not performed. At the time of death, the subject had not recovered from increased aspartate aminotransferase, increased alanine aminotransferase, increased blood bilirubin, abdominal pain, and ascites. The Investigator considered hepatic failure serious and possibly related to the study drug; increased aspartate aminotransferase, increased alanine aminotransferase, and increased blood bilirubin nonserious and possibly related to the study drug; abdominal pain and ascites nonserious and not related to the study drug.

Subject Number	30121027
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-005994
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Malignant neoplasm progression
Non-Fatal SAE(s)	Ascites, Oedema peripheral, Asthenia
AE(s) Leading to Discontinuation	Asthenia
Death due to PD	Yes

A 76-year-old Asian male was diagnosed with hepatocellular carcinoma on 03 May 2012. Significant medical history included decreased appetite, ascites, gastric ulcer, gastritis, gallbladder polyp, hepatic cyst, hemangioma of liver, hepatic cirrhosis, right pelvic pain, and splenomegaly. Previous anticancer therapies included iliac bone radiotherapy, high frequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included albis, amino acids, amlodipine, ascorbic acid with biotin/calcium/chloride (centrum advance), falkamin, furosemide, glucose, megestrol, metoclopramide, minerals w/vitamins (centrum), olmesartan, ornithine, pennel, propofol, silybum marianum, spironolactone, tramadol, ursodeoxycholic acid, and vitamins. At Screening, tumor assessments of target/non-target lesions via MRI showed lesions at right and left lobes of liver and right pelvic mass. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 06 Apr 2015 (Day 61), the subject experienced ascites (Grade 2) and peripheral edema (both legs pitting edema; Grade 2). The CT scan of the abdomen showed newly developed ascites and effusion. The subject was treated with spironolactone and furosemide. On 14 Apr 2015 (Day 69), the subject was hospitalized for peripheral edema and ascites with albumin of 30 g/L (NR: 32 – 48). On 15 Apr 2015 (Day 70), severity of ascites and peripheral edema improved to Grade 1 and the subject was discharged from the hospital. The study drug dose was not changed. The subject did not recover from ascites and peripheral edema. The Investigator considered both events serious and not related to the study drug.

On 10 May 2015 (Day 95), the subject experienced asthenia (Grade 2). On 12 May 2015 (Day 97), the subject was hospitalized for asthenia. Laboratory test showed albumin 27 g/L. The subject was treated with amino acids, ornithine, vitamins, tramadol, glucose, and falkamin. The study drug dose was not changed. On 18 May 2015 (Day 103), severity of asthenia improved to Grade 1 and the subject was discharged from the hospital. The subject did not recover from asthenia. The Investigator considered asthenia serious and not related to the study drug.

On 27 May 2015 (Day 112), the subject experienced worsening of asthenia (Grade 3) and the study drug was interrupted. No treatment was provided. On 10 Jun 2015 (Day 126), laboratory

tests showed RBC 2.72 x10^12/L (NR: 4 – 5.6), Hgb 106 g/L (NR: 125 – 170), albumin 26 g/L (NR: 35 – 55), total protein 53 g/L (NR: 60 – 80), thyrotropin 38.964 mIU/L (NR: 0.3 – 5), and CRP 32.1 mg/L (NR: 0 – 5). On 10 Jun 2015 (Day 126), the subject was withdrawn from study due to asthenia and received the last dose of the study drug on 26 May 2015 (Day 111). The subject did not recover from asthenia. The Investigator considered worsening of asthenia nonserious and not related to the study drug.

On 25 Jun 2015 (Day 141, 30 days after the last dose), the subject died due to malignant neoplasm progression. It was unknown if an autopsy was performed. The Investigator considered this event serious and not related to the study drug but related to disease progression.