On 16 Sep 2014 (Day 247), the subject was hospitalized for abdominal pain (worsening of left abdominal pain; Grade 3) and also experienced dyspepsia (Grade 2) and abdominal rigidity (abdominal spasms; Grade 2). Blood culture was performed (results were not reported) and CT scan of abdomen showed interval progression of disease with multiple new masses, new ascites, and new periportal lymphadenopathy. The subject was treated with piperacillin/tazobactam, morphine, pantoprazole, and dicycloverine. Laboratory tests were done and showed AST 123 U/L (NR: 5 – 45), ALT 55 U/L (NR: 7 – 60), ALP 573 U/L (NR: 38 – 126), total bilirubin 35.91 umol/L (NR: 1.71 – 22.23), total protein 82 g/L (NR: 55 – 78), BUN 2.499 mmol/L, and creatinine 44.2 umol/L. On 23 Sep 2014 (Day 254), the subject experienced renal failure (Grade 3) and hypotension (Grade 3). The subject underwent dialysis. Repeat laboratory tests showed BUN 19.635 mmol/L, creatinine 539.24 umol/L, AST 218 U/L, ALP 684 U/L, and total bilirubin 34.2 umol/L. Later that day (Day 254, 29 days after the last dose), the subject died due to cardiopulmonary failure secondary to disease progression. At the time of death, the subject had not recovered from renal failure, abdominal pain, hypotension, dyspepsia, and abdominal rigidity. Autopsy was not performed. The Investigator considered renal failure, cardiopulmonary failure, and abdominal pain serious and not related to the study drug but related to disease progression; hypotension, dyspepsia, and abdominal rigidity nonserious and not related to the study drug.

Subject Number	10151009
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01488-CLI-US
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Acute hepatic failure
Non-Fatal SAE(s)	Liver injury, General physical health deterioration
AE(s) Leading to Discontinuation	Liver injury
Death due to PD	Yes

A 64-year-old Asian male was diagnosed with hepatocellular carcinoma on 05 Mar 2014. Significant medical history included abdominal pain, ascites, drug hypersensitivity (allergy to benadryl, benzocaine, erythromycin, and ibuprofen), clostridium difficile colitis, hepatic cirrhosis, diarrhea, blood aspartate aminotransferase increased, fluid overload, hepatitis C, hypertension, shellfish allergy, and tonsil cancer. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included cefotaxime, cyanocobalamin, dextrose and sodium chloride injection, furosemide, glucose, human albumin, hydrocodone, hydromorphone, levothyroxine, macrogol, midazolam, midodrine, octreotide, oxycodone, pantoprazole, probiotics, rifaximin, sodium polystyrene sulfonate, spironolactone, vancomycin, vicodin, and vitamin k. At Screening, tumor assessments of target/non-target lesions via CT scan showed mass at the limited segment of the colon and bilateral lower lobes of lung. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 7.

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

On 25 Apr 2014 (Day 9), the subject was hospitalized for liver injury (acute; Grade 3). On the same day (Day 9), the subject also experienced increased aspartate aminotransferase (Grade 4) which started as Grade 2 on 26 Mar 2014 (Day –22). See table below. On 25 Apr 2014 (Day 9), the subject also experienced acute kidney injury (Grade 2), decreased appetite (Grade 2), dehydration (Grade 3), hyperkalemia (Grade 3), and hypoglycemia (Grade 1). On the same day (Day 9), the subject was withdrawn from the study due to liver injury secondary to clinical disease progression and received the last dose of the study drug on 24 Apr 2014 (Day 8). Laboratory tests showed ALT 196 U/L (NR: 4 – 45), ALP 168 U/L (NR: 31 – 103), potassium 6.5 mmol/L (NR: 3.6 – 5.4), sodium 128 mmol/L (NR: 135 – 145), and creatinine 203.32 umol/L (NR: 44.2 – 114.92). The subject was treated with glucose, human albumin, dextrose and sodium chloride injection, octreotide, and sodium polystyrene sulfonate. On 26 Apr 2014 (Day 10), the subject experienced ascites (Grade 3), hepatic encephalopathy (Grade 3), and portal vein thrombosis (Grade 2) which was confirmed via ultrasound of the abdomen. Treatment included therapeutic paracentesis, human albumin, rifaximin, and macrogol. The subject recovered from hypoglycemia on 26 Apr 2014 (Day 10). On 30 Apr 2014 (Day 14), the subject recovered from decreased appetite and dehydration. On 01 May 2014 (Day 15), the subject recovered from hyperkalemia. On 02 May 2014 (Day 16), peritoneal pleurex catheter was placed for symptomatic treatment of ascites. On 03 May 2014 (Day 17), the subject experienced cachexia (Grade 3). On 06 May 2014

(Day 20), the subject experienced general physical health deterioration (Grade 4). On 19 May 2014 (Day 33, 25 days after the last dose), the subject died due to acute hepatic failure secondary to clinical disease progression. Autopsy was not performed. At the time of death, the subject had not recovered from increased aspartate aminotransferase, acute kidney injury, liver injury, ascites, portal vein thrombosis, general physical health deterioration, hepatic encephalopathy, and cachexia. The Investigator considered acute hepatic failure, general physical health deterioration, and liver injury serious and not related to the study drug but related to disease progression; ascites, hepatic encephalopathy, increased aspartate aminotransferase, and cachexia nonserious and not related to study drug but related to disease progression; acute kidney injury, decreased appetite, dehydration, hyperkalemia, hypoglycemia, and portal vein thrombosis nonserious and not related to the study drug.

See table below.

Table AST

Laboratory Test Date (Day)	**AST Central Laboratory NR: 10 – 43 U/L Local Laboratory NR: 7 – 36 U/L**
26 Mar 2014 (Screening)	193 CNR
14 Apr 2014 (Day –3)	240 CNR
17 Apr 2014 (Day 1)	219 LNR
25 Apr 2014 (Day 9)	971 LNR
04 May 2014 (Day 18)	150 LNR

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

Subject Number	10151016
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-005913
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Hepatic failure
Non-Fatal SAE(s)	Hepatic failure
Death due to PD	Yes

A 67-year-old white male was diagnosed with hepatocellular carcinoma on 15 Oct 2014. Significant medical history included chronic obstructive pulmonary disease, hepatitis C, hepatic cirrhosis, pain, and splenectomy. Previous anticancer therapy included high frequency ablation. Prior and concomitant medications included diphenhydramine, enoxaparin, fentanyl, lactulose, metoclopramide, midazolam, morphine, olanzapine, ondansetron, pantoprazole, prochlorperazine, rifaximin, and sodium chloride. At Screening, tumor assessments of target/non-target lesions via CT scan showed cardiophrenic and portacaval lymphadenopathies; and liver mass. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 13 Mar 2015 (Day 2), the subject experienced nausea (Grade 2) and vomiting (Grade 2). The subject was treated with ondansetron, metoclopramide, diphenhydramine, pantoprazole, and prochlorperazine. On 26 Mar 2015 (Day 15), the subject experienced increased blood bilirubin (Grade 2), fatigue (Grade 1), dehydration (Grade 1), decreased weight (Grade 1) with body weight 80.5 kg (Baseline: 85.8 kg), and abdominal pain (Grade 2). The subject was treated with sodium chloride and morphine. Laboratory tests showed absolute neutrophil count 8.3 x10^9/L (NR 1.7 – 7.9), ALP 149 U/L (NR: 43 – 115), AST 84 U/L (NR: 10 – 43), total bilirubin 36.1 umol/L (NR: 0 – 18.8), BUN 4.64 mmol/L (NR: 1.78 – 7.14), CRP 27.4 mg/L (NR: 0 – 5), GGT 108 U/L (NR: 10 – 49), and creatinine 35 umol/L (NR: 62 – 124). On the same day (Day 15), the subject recovered from dehydration. On 26 Mar 2015 (Day 15), the study drug was interrupted due to increased blood bilirubin and fatigue. On 01 Apr 2015 (Day 21), the study drug resumed at a reduced dose of 8 mg/day due to increased blood bilirubin and fatigue. The subject did not recover from nausea, vomiting, increased blood bilirubin, abdominal pain, decreased weight, and fatigue. On 04 Apr 2015 (Day 24), the study drug was interrupted due to persistent nausea and vomiting. The Investigator considered increased blood bilirubin, decreased weight, nausea, vomiting, fatigue, dehydration, and abdominal pain nonserious and not related to the study drug.

On 13 Apr 2015 (Day 33), the subject was hospitalized for hepatic failure (Grade 3). On the same day (Day 33), the subject also experienced hepatic encephalopathy (Grade 3). Laboratory tests showed ammonia 79.2429 umol/L (NR: 27.8421 – 64.251), AST 103 U/L (NR: 7 – 36), ALP 192 U/L (NR: 31 – 103), and total bilirubin 66.69 umol/L (NR: 3.42 – 18.81). The subject was treated with rifaximin. On 13 Apr 2015 (Day 33), the subject was withdrawn from study

due to disease progression and received the last dose of study drug on 03 Apr 2015 (Day 23). On 14 Apr 2015 (Day 34), tumor response assessment showed disease progression. On 22 Apr 2015 (Day 42, 19 days after the last dose), the subject died due to hepatic failure secondary to disease progression. Autopsy was not performed. At the time of death, the subject had not recovered from hepatic encephalopathy. The Investigator considered hepatic failure serious and not related to the study drug; hepatic encephalopathy nonserious and not related to the study drug.

Subject Number	10161001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01416-CLI-US
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Chronic hepatic failure
Non-Fatal SAE(s)	Hepatic encephalopathy (2x), Chronic hepatic failure, Hyperbilirubinaemia
AE(s) Leading to Discontinuation	Chronic hepatic failure
Death due to PD	Yes

A 62-year-old white male was diagnosed with hepatocellular carcinoma on 19 Sep 2013. Significant medical history included alcoholic cirrhosis, Barrett's esophagus, type 2 diabetes mellitus, esophageal varices, cholelithiasis, generalized edema, hepatic encephalopathy, chronic hepatitis C, portal hypertensive gastropathy, hypothyroidism, and thrombocytopenia. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included colecalciferol, human mixtard, insulin lispro, lactulose, levothyroxine, midodrine, novolog mix, nutrients, omeprazole, ondansetron, propranolol, rifaximin, and spironolactone. 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 B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 15 Dec 2013 (Day 26), the subject voided on floor, sleepy, disoriented, and was hospitalized for further evaluation. Laboratory tests showed ammonia 112 umol/L (NR: 11 – 32), albumin 30 g/L (NR: 34 – 50), ALT 165 U/L (NR: 12 – 78), ALP 81 U/L (NR: 45 – 117), AST 161 U/L (NR: 15 – 37), and total bilirubin 46.341 umol/L (NR: 3.42 – 17.1). The subject was diagnosed with hepatic encephalopathy (Grade 3). The CT scan of the brain showed chronic microangiopathic ischemic changes, no acute intracranial hemorrhage or major territorial infarction, and no parenchymal mass or midline shift. The subject was treated with rifaximin. On 17 Dec 2013 (Day 28), the subject recovered from hepatic encephalopathy. The Investigator considered hepatic encephalopathy serious and not related to study drug.

On 18 Jan 2014 (Day 60), the subject experienced hepatic encephalopathy (Grade 1) with symptoms of ‘slower to respond than usual’ and ‘more forgetful’. On 24 Jan 2014 (Day 66), the subject was confused, aggravated, and was hospitalized for hepatic encephalopathy (Grade 3). Laboratory tests showed AST 120 U/L, ALT 122 U/L, total bilirubin 56.43 umol/L, ammonia 97 umol/L, and albumin 32 g/L. The subject was treated with rifaximin and lactulose. On 27 Jan 2014 (Day 69), the subject recovered from the event. The Investigator considered hepatic encephalopathy serious and not related to study drug.

On 17 Apr 2014 (Day 149), the subject was hospitalized for chronic hepatic failure (end stage liver disease, Grade 4). Laboratory tests showed ALT 81 U/L, AST 109 U/L,

ALP 122 U/L, and total bilirubin 327.294 umol/L. On 19 Apr 2014 (Day 151), the study drug was interrupted. On 22 Apr 2014 (Day 154), the subject was discharged from the hospital with total bilirubin 399.114 umol/L and the study drug was resumed at same dose inadvertently by the subject. On 23 Apr 2014 (Day 155), the study drug was interrupted once again by the Investigator due to chronic hepatic failure. The subject did not recover from chronic hepatic failure. The Investigator considered chronic hepatic failure serious and not related to study drug but related to disease progression.

On 25 Apr 2014 (Day 157), the subject was hospitalized for worsening hyperbilirubinemia (Grade 4) with total bilirubin 574.56 umol/L (NR: 1.71 – 20.52). On 30 Apr 2014 (Day 162), the subject was withdrawn from the study due to chronic hepatic failure and received the last dose of the study drug on 22 Apr 2014 (Day 154). Lactulose was continued. The subject was discharged from the hospital under hospice care with poor prognosis. On 05 May 2014 (Day 167, 13 days after the last dose), the subject died due to chronic hepatic failure secondary to clinical disease progression. Autopsy was not performed. The Investigator considered chronic hepatic failure serious and not related to study drug; hyperbilirubinemia serious and not related to study drug.

Subject Number	12121001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01459-CLI-JP
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Renal impairment
Non-Fatal SAE(s)	Decreased appetite, Renal impairment
Death due to PD	Yes

A 70-year-old Japanese male was diagnosed with hepatocellular carcinoma on 17 Apr 2013. Significant medical history included anemia, diabetes mellitus, esophageal varices, abnormal hepatic function, alcoholic liver disease, hypertension, hypoalbuminemia, hepatic cirrhosis, and decreased platelet count. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included human albumin, allopurinol, alogliptin benzoate w/pioglitazone hydrochloride, amlodipine, asphagen, dexamethasone, difluprednate, dimeticone, etilefrine, falkamin, furosemide, glibenclamide, glimepiride, glycerol, haloperidol, heparinoid, iron, lansoprazole, lidocaine, limaprost, loxoprofen, methylprednisolone, paracetamol, pentazocine, pronase, rebamipide, sodium bicarbonate, sodium chloride, sodium thiosulfate, solita-t1, spironolactone, tramadol, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left liver lobe. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 12 Sep 2013 (Day 1), treatment with study drug was initiated.

On 06 Oct 2013 (Day 25), the subject experienced malaise (Grade 2), fatigue (Grade 2), myalgia (Grade 2), stomatitis (lingual margin; Grade 2), rash (beneath the nostrils and periocular area; Grade 2). The subject was treated with methylprednisolone, dexamethasone, and loxoprofen. On 09 Oct 2013 (Day 28), the study drug was interrupted due to these events. Laboratory tests showed WBC 5.1 x10^9/L (NR: 3.7 – 11.0), Hgb 136 g/L (NR: 125 – 170), ALP 168 U/L (NR: 43 – 115), AST 49 U/L (NR: 10 – 43), and GGT 164 U/L (NR: 10 – 49). On 15 Oct 2013 (Day 34), the subject recovered from myalgia. On 16 Oct 2013 (Day 35), the study drug was resumed at a reduced dose of 8 mg/day due to these events. On the same day (Day 35), the severity of fatigue, malaise, stomatitis, and rash decreased to Grade 1. On 06 Nov 2013 (Day 56), the subject recovered from malaise and fatigue; the outcome of rash and stomatitis were unknown. The Investigator considered malaise, fatigue, myalgia, stomatitis, and rash nonserious and probably related to the study drug.

On 29 Dec 2013 (Day 109), the subject experienced decreased appetite (Grade 2). On 28 Jan 2014 (Day 139), the subject experienced constipation (Grade 2) and malaise (Grade 2). On 01 Feb 2014 (Day 143), the study drug was interrupted due to decreased appetite, constipation, and malaise. On 12 Feb 2014 (Day 154), the subject recovered malaise, decreased appetite, and constipation. On the same day (Day 154), the study drug was resumed at a reduced dose of 4 mg/day due to these events. The Investigator considered decreased appetite, constipation, and malaise nonserious and possibly related to the study drug.

On 21 Feb 2014 (Day 163), the subject experienced renal impairment (Grade 1), decreased appetite (Grade 2), and malignant ascites (Grade 2). Ultrasonography of abdomen showed ascites. On 23 Feb 2014 (Day 165), the subject missed a dose of the study drug. On 25 Feb 2014 (Day 167), the subject was hospitalized for renal impairment (aggravated renal function; Grade 2), and worsening decreased appetite (Grade 3). The study drug was interrupted due to these events. On 26 Feb 2014 (Day 168), the subject experienced abdominal pain (Grade 2) and increased blood bilirubin (Grade 2) on 27 Feb 2014 (Day 169). Laboratory tests showed BUN 17.14 mmol/L (NR: 1.78 – 7.14), creatinine 159 umol/L (NR: 62 – 124), total bilirubin 29.1 umol/L (NR: 1.7 – 18.8), and CRP 28.3 mg/L (NR: 0 – 5). The subject underwent bladder catheterization, dialysis, and was treated with intravenous fluids, allopurinol, solita-t1, human albumin, sodium chloride, furosemide, spironolactone, pentazocine, paracetamol, tramadol, and loxoprofen. On 27 Feb 2014 (Day 169), tumor response assessment showed disease progression. On 01 Mar 2014 (Day 171), the subject recovered from increased blood bilirubin. On 03 Mar 2014 (Day 173), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 24 Feb 2014 (Day 166). On 04 Mar 2014 (Day 174, 8 days after the last dose), the subject died due to worsening of renal impairment. Autopsy was not performed. At the time of death, the subject had not recovered from malignant ascites, decreased appetite, and abdominal pain. The Investigator considered renal impairment serious and not related to the study drug, but related to disease progression; decreased appetite serious and possibly related to the study drug; malignant ascites, abdominal pain and increased blood bilirubin nonserious and not related to the study drug but related to disease progression.

Subject Number	12141002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01411-CLI-JP
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Cholangitis
Non-Fatal SAE(s)	Cancer pain, Jaundice cholestatic, Cholangitis
AE(s) Leading to Discontinuation	Ascites, Cancer pain, Cholangitis
Death due to PD	Yes

A 72-year-old Japanese male was diagnosed with hepatocellular carcinoma on 09 Mar 2013. Significant medical history included Barrett's esophagus, benign gastric neoplasm, Brunner's gland hyperplasia, bile duct stent insertion, cancer pain, chronic gastritis, chronic hepatitis C, gastric polyps, gastric xanthoma, gastroesophageal reflux disease, hemorrhoids, hepatitis B, hepatic cirrhosis, large intestine polyp, and renal cyst. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included amino acids w/electrolytes /glucose, amlodipine, betamethasone, bisacodyl, clobetasol, dexamethasone, difluprednate, diphenhydramine, doripenem, ebastine, ethanol, fentanyl, flurbiprofen, gabexate, glucagon, glucose, heparinoid, hydrocortisone, iotalamic acid, lansoprazole, levofloxacin, lidocaine, loxoprofen, magnesium oxide, menthol, metoclopramide, midazolam, neurobion, nutrients, olanzapine, oxycodone, pemoline, prochlorperazine, pronase, propofol, quetiapine, rikkunshito, ringer-lactatis, sennoside a+b, sodium chloride, solita-t1, sulperazon, urea, and white soft paraffin. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right lobe of liver, right lower lobe lung mass, para-aortic and porta-hepatis lymphadenopathies. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 14 Mar 2013 (Day 1), treatment with study drug was initiated.

On 08 Dec 2013 (Day 270), the study drug was interrupted in preparation for endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) for cancer pain. On 09 Dec 2013 (Day 271), the subject was hospitalized for cancer pain (Grade 3). The subject was treated with fentanyl, loxoprofen, and oxycodone. On 10 Dec 2013 (Day 272), the subject underwent EUS-CPN and gastroenterological endoscopy showed multiple metastatic lymph nodes and ascites. Laboratory tests showed total bilirubin 32.49 umol/L (NR: 3.42 – 17.1), ALP 1809 U/L (NR: 85 – 300), AST 586 U/L (NR: 7 – 40), ALT 336 U/L (NR: 0 – 35), and LDH 509 U/L (NR: 100 – 225). On 11 Dec 2013 (Day 273), the abdominal ultrasound showed obstructive jaundice due to displacement of common bile duct by the enlarged lymph node and the subject was diagnosed with cholestatic jaundice (Grade 3). On the same day (Day 273), the subject underwent endoscopic retrograde cholangiopancreatography and bile duct stent insertion. On 17 Dec 2013 (Day 279), the subject experienced ascites (Grade 1). On 18 Dec 2013 (Day 280), the study drug was resumed at the same dose. On 26 Dec 2013 (Day 288), the subject recovered from cholestatic jaundice and did not recover from ascites. On 11 Jan 2014 (Day 304), cancer pain improved to Grade 2 and the subject was discharged from the hospital.

The Investigator considered cholestatic jaundice and cancer pain serious and not related to study drug; ascites nonserious and possibly related to study drug.

On 28 Jan 2014 (Day 321), the subject was hospitalized for cholangitis (Grade 2). Laboratory tests showed ALP 2121 U/L, ALT 145 U/L, AST 195 U/L, GGT 931 U/L (NR: 0 – 80), LDH 330 U/L, and total bilirubin 49.59 umol/L (NR: 3.42 – 17.1). The subject was treated with levofloxacin and doripenem. The study drug was withdrawn due to ascites, cancer pain, and cholangitis which were all secondary to clinical disease progression. The subject received the last dose of the study drug on 28 Jan 2014 (Day 321). On 05 Feb 2014 (Day 329), the subject was withdrawn from the study due to clinical disease progression. On 16 Feb 2014 (Day 340, 19 days after the last dose), the subject died due to cholangitis. Autopsy was not performed. The Investigator considered cholangitis serious and not related to study drug but related to clinical disease progression.

Subject Number	12141007
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01413-CLI-JP
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Disseminated intravascular coagulation, Sepsis
Non-Fatal SAE(s)	Diabetes mellitus, Hypercalcaemia, Disseminated intravascular coagulation, Sepsis
AE(s) Leading to Discontinuation	Disseminated intravascular coagulation, Sepsis
Death due to PD	Yes

A 77-year-old Japanese male was diagnosed with hepatocellular carcinoma on 24 Oct 2011. Significant medical history included cholelithiasis, constipation, diabetes mellitus, hyperplastic cholecystopathy (gallbladder adenomyomatosis), hypertension, intraductal papillary mucinous neoplasm, latent hypoparathyroidism, latent hypothyroidism, hepatic cirrhosis, non-alcoholic steatohepatitis, and seasonal pollen allergy. Previous anticancer therapies included hepatectomy, radiofrequency ablation and transcatheter arterial chemoembolization. Prior and concomitant medications included aminoleban, antithrombin III, betamethasone, carbohydrates w/potassium chloride/sodium, dopamine, doripenem, epinastine, flurbiprofen, furosemide, glimepiride, glucose, gualenic acid, haloperidol, human albumin, hydrocortisone, insulin aspart, insulin human, levothyroxine, lidocaine, lisinopril, loxoprofen, luliconazole, magnesium oxide, metformin, miglitol, neurobion, omeprazole, osmosal, piperacillin/tazobactam, rebamipide, ringer-lactatis, sennoside a+b, sitagliptin, sodium bicarbonate, sodium picosulfate, solita-t1, thrombomodulin alfa, zinc, and zoledronic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed para-caval lymphadenopathy. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 28 Nov 2013 (Day 1), treatment with study drug was initiated.

On 11 Dec 2013 (Day 14), the subject was hospitalized for aggravation of diabetes mellitus (Grade 3) with blood glucose of 235 mg/dL (NR: 65 – 110). The subject was treated with human insulin and insulin aspart. On 05 Feb 2014 (Day 70), the subject recovered from this event. The study drug dose was not changed. The Investigator considered this event serious and not related to the study drug.

On 20 May 2014 (Day 174), the subject was hospitalized for hypercalcemia (Grade 2) with symptoms of malaise, feeling of weakness, weakness in lower limbs, and decreased appetite. The subject also experienced hypoalbuminemia (Grade 2). Laboratory results showed calcium 3.1 mmol/L (NR: 2.2 – 2.625) and albumin 27 g/L (NR: 36 – 55). On the same day (Day 174), the study drug was interrupted due to hypercalcemia. The subject was treated with furosemide, zoledronic acid, and human albumin. On 22 May 2014 (Day 176), the subject experienced decreased platelet count (Grade 2) with platelet count 72 x10^9/L (NR: 167 – 362) and fever (Grade 1) with temperature 38.9 °C. The subject was treated with flurbiprofen and on 23 May 2014 (Day 177), the subject recovered from fever. On 25 May 2014 (Day 179), the

subject experienced restlessness (Grade 1) and on the following day (Day 180), the subject was diagnosed with gastrointestinal hemorrhage (Grade 3) and paraneoplastic syndrome (Grade 3). Endoscopy showed hemorrhagic tumor in stomach. Laboratory test showed Hgb 137 g/L (NR: 139 – 170). The subject underwent endoscopic mucosal resection and was treated with packed red blood cell transfusion, betamethasone, hydrocortisone, zinc, aminoleban, osmosal, sodium bicarbonate, glucose, and dopamine. On 29 May 2014 (Day 183), the subject experienced sepsis (Grade 4) and disseminated intravascular coagulation (Grade 3). Laboratory tests showed platelet count 28 x10^9/L, INR 1.64 (NR: 0.8 – 1.2), and PT 35.4% (NR: not provided). The subject was treated with antithrombin III, thrombomodulin alfa, piperacillin/tazobactam, and doripenem. On 31 May 2014 (Day 185), the subject recovered from hypercalcemia and gastrointestinal hemorrhage. On 31 May 2014 (Day 185), the subject was withdrawn from the study drug due to sepsis and disseminated intravascular coagulation. The subject received the last dose of the study drug on 19 May 2014 (Day 173). Later that day, (Day 185, 12 days after the last dose), the subject died due to worsening sepsis and disseminated intravascular coagulation. Autopsy was not performed. The organism which caused sepsis was not specified. At the time of death, the subject had not recovered from restlessness, hypoalbuminemia, paraneoplastic syndrome, and decreased platelet count. The Investigator considered sepsis, disseminated intravascular coagulation serious and not related to the study drug but related to the disease progression; hypercalcemia serious and not related to the study drug; hypoalbuminemia nonserious and possibly related to the study drug; decreased platelet count, fever, restlessness, and paraneoplastic syndrome nonserious and not related to the study drug.

Subject Number	12141016
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01547-CLI-JP
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Hepatic failure
Non-Fatal SAE(s)	Hepatic failure
Death due to PD	Yes

An 86-year-old Japanese male was diagnosed with hepatocellular carcinoma on 15 May 2014. Significant medical history included chronic bronchitis, chronic gastritis, esophageal varices, hemorrhoids, hepatitis B, hyperlipidemia, and hypertension. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acetic acid, aczym, amino acids w/vitamins, amlodipine, bakumondoto, esomeprazole, famotidine, fentanyl, furosemide, indigo carmine, lidocaine, loxoprofen, menthol, mosapride, neurobion, posterisan f, pronase, solita-t1, and teprenone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe, masses at right upper and lower lobes of lung. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

On 30 May 2014 (Day 1), treatment with study drug was initiated.

On 22 Jul 2014 (Day 54), tumor response assessment showed disease progression. The subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 22 Jul 2014 (Day 54).

On 22 Jul 2014 (Day 54), the subject experienced ascites (Grade 2), increased blood bilirubin (Grade 2), decreased appetite (Grade 2), and peripheral edema (edema legs; Grade 2). Laboratory tests showed albumin 30 g/L (NR: 35 – 55), ALT 35 U/L (NR: 10 – 40), AST 144 U/L (NR: 10 – 43), and ALP 233 U/L (NR: 43 – 115). On 29 Jul 2014 (Day 61), the subject was hospitalized due to hepatic failure (Grade 3) and also experienced renal impairment (acute renal dysfunction; Grade 2). Laboratory tests showed BUN 19.635 mmol/L (NR: 2.856 – 7.14), creatinine 132.6 umol/L (NR: 61.88 – 114.92), and total bilirubin 9.1 mg/dl (NR: 0.2 – 1.0). On 01 Aug 2014 (Day 64), the subject experienced cancer pain (Grade 2). Treatment included amino acids w/vitamins, furosemide, neurobion, solita-t1, and fentanyl. On the same day (Day 64, 10 days after the last dose), the subject died due to hepatic failure. At the time of death, the subject had not recovered from renal impairment, cancer pain, ascites, increased blood bilirubin, decreased appetite, and peripheral edema. The Investigator considered hepatic failure serious and not related to the study drug but related to disease progression; renal impairment and cancer pain nonserious and not related to study drug but related to disease progression; increased blood bilirubin nonserious and possibly related to study drug; ascites, decreased appetite, and peripheral edema nonserious and probably related to the study drug.

Subject Number	12241004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01427-CLI-JP
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Dyspnoea
Non-Fatal SAE(s)	Decreased appetite, Dyspnoea, Hyponatraemia
AE(s) Leading to Discontinuation	Dyspnoea
Death due to PD	Yes

A 69-year-old Japanese female was diagnosed with hepatocellular carcinoma on 19 Sep 2012. Significant medical history included chronic gastritis, chronic hepatitis C, constipation, cough, esophageal varices, insomnia, left meniscus injury, hepatic cirrhosis, Barrett's esophagus, splenectomy, and splenomegaly. Previous anticancer therapy included hepatectomy. Prior and concomitant medications included acmain, aminoleban, aminoleban en, amlodipine, asphagen, brocin-codeine, canrenoic acid, clobetasol, dextromethorphan, dimeticone, esomeprazole, falkamin, furosemide, glucose, gualenic acid, heparinoid, human albumin, hyoscine, iopamidol, lidocaine, loxoprofen, magnesium oxide, metoclopramide, neolamin 3b, pronase, sennoside a+b, sodium bicarbonate, sodium chloride, solita t, solita-t1, spironolactone, triamcinolone, ursodeoxycholic acid, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe, right lower lobe lung mass, and right mediastinal lymphadenopathy. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 20 Dec 2013 (Day 57), the subject experienced decreased appetite (Grade 3). On 06 Jan 2014 (Day 74), the subject was hospitalized for decreased appetite, dyspnea (due to lymphangiosis carcinomatosa, Grade 4), and also experienced hyponatremia (Grade 3). On 07 Jan 2014 (Day 75), the study drug was interrupted due to decreased appetite and dyspnea. Chest x-ray showed radiolucency associated with lymphangiosis carcinomatosa. On 10 Jan 2014 (Day 78), the hyponatremia worsened to Grade 4 with sodium 117 mmol/L (NR: 138 – 146). The subject was treated with solita t1, acmain (solyugen G, acetated ringer's solution with glucose), neolamin 3b, glucose, and sodium chloride. On 12 Jan 2014 (Day 80), the subject was found with depressed level of consciousness (Grade 2) following a fall in the bathroom. On 13 Jan 2014 (Day 81), the oxygen saturation was 93% and the subject was treated with oxygen supplementation. On 17 Jan 2014 (Day 85), the subject was withdrawn from the study due to dyspnea and received the last dose of the study drug on 06 Jan 2014 (Day 74). On the same day (Day 85, 11 days after the last dose), the subject died due to dyspnea secondary to worsening lymphangiosis carcinomatosa. Autopsy was not performed. At the time of death, the subject had not recovered from decreased appetite, hyponatremia, and depressed level of consciousness. The Investigator considered dyspnea and hyponatremia serious and not related to study drug but related to disease progression; decreased

appetite serious and not related to study drug; depressed level of consciousness nonserious and not related to the study drug.

Subject Number	14021009
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-010350
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Portal vein thrombosis
Non-Fatal SAE(s)	Portal vein thrombosis
Death due to PD	Yes

A 55-year-old white male was diagnosed with hepatocellular carcinoma on 07 Aug 2014. Significant medical history included hepatitis C, and back pain. Previous anticancer therapies included transcatheter arterial chemoembolization (2x). Prior and concomitant medications included ceftriaxone, clorazepic acid, dexeryl, domperidone, esomeprazole, fleet (normacol lavement), furosemide, heparin, human albumin, macrogol, medicated dressings, metoclopramide, metronidazole, morphine, movicol, nefopam, nicardipine, osmotan, other emollients and protectives (uretral gel), paracetamol, phloroglucinol, sodium bicarbonate, sodium chloride, sodium polystyrene sulfonate, sterculia urens, tramadol, and trimebutine. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left lobe of liver, left and right adrenal gland lymphadenopathies. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 21 Jan 2015 (Day 1), treatment with study drug was initiated.

On 31 Aug 2015 (Day 223), tumor response assessment showed disease progression and the subject received the last dose of the study drug on 30 Aug 2015 (Day 222).

On 02 Sep 2015 (Day 225), the subject was hospitalized for portal vein thrombosis (Grade 3) with the symptoms of abdominal pain and the subject also experienced acute kidney injury (Grade 3). The subject was treated with sodium polystyrene sulfonate, morphine, tramadol, paracetamol, nefopam, heparin, phloroglucinol, trimebutine, human albumin, sodium chloride, and osmotan. On 08 Sep 2015 (Day 231), the subject experienced peripheral edema (Grade 1) and ascites (Grade 1). The subject was treated with furosemide. Laboratory tests showed urea 13 mmol/L (NR: 2.4 – 6.5), creatinine 130 umol/L (NR: 64 – 104), AST 192 U/L (NR: 10 – 45), ALT 85 U/L (NR: 5 – 50), ALP 498 U/L (NR: 40 – 130), total bilirubin 81 umol/L (NR: 3 – 18), potassium 5.19 mmol/L (NR: 3.5 – 5), and sodium 128 mmol/L (NR: 135 – 145). On 9 Sep 2015 (Day 232), subject experienced nausea (Grade 1). The subject was treated with metoclopramide. On 11 Sep 2015 (Day 234), computerized tomogram scan of thorax, abdomen, and pelvis showed portal thrombosis extended to mesenteric vein. On the same day (Day 234), the subject recovered from nausea. On 13 Sep 2015 (Day 236), the subject experienced acute abdomen (Grade 2) and received metronidazole and ceftriaxone. On 19 Sep 2015 (Day 242), the subject experienced dyspnea (Grade 1) and was treated with oxygen. On 21 Sep 2015 (Day 244, 22 days after the last dose), subject died due to portal vein thrombosis secondary to disease progression. Autopsy was not performed. At the time of death, the subject had not recovered from acute kidney injury, peripheral edema, ascites, acute abdomen, and dyspnea.

The Investigator considered portal vein thrombosis serious and not related to the study drug; acute kidney injury, peripheral edema, ascites, nausea, acute abdomen, and dyspnea nonserious and not related to the study drug.

Subject Number	14021013
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006797
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Pneumonia aspiration
Non-Fatal SAE(s)	Decreased appetite, General physical health deterioration, Abdominal pain, Accidental overdose
AE(s) Leading to Discontinuation	General physical health deterioration
Death due to PD	No

A 58-year-old white male was diagnosed with hepatocellular carcinoma on 10 Feb 2015. Significant medical history included alcohol abuse, fatigue, hypertension, ocular hypertension, and esophageal varices. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included carbohydrates w/fatty acids/minerals, carteolol, loperamide, metronidazole, morphine, naloxone, paracetamol, paroxetine, sodium chloride, third-generation cephalosporins, and valsartan. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left liver lobe and mass at left lower lobe of lung. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

On 22 Apr 2015 (Day 1), treatment with study drug was initiated.

On 13 May 2015 (Day 22), the subject was hospitalized for decreased appetite (Grade 2) and also experienced vomiting (Grade 1). The subject was treated with carbohydrates w/fatty acids/minerals and paracetamol. The subject's body weight was 78.5 kg (Baseline: 85.5 kg). The subject recovered from vomiting on the same day (Day 22). On 14 May 2015 (Day 23), the study drug was interrupted due to decreased appetite. On 17 May 2015 (Day 26), the subject recovered from decreased appetite. On 19 May 2015 (Day 28), the study drug was resumed at same dose. The Investigator considered decreased appetite serious and probably related to the study drug; vomiting nonserious and not related to the study drug.

On 08 Jun 2015 (Day 48), the subject was hospitalized for general physical health deterioration (Grade 3) and experienced worsening asthenia (Grade 3). On the same day (Day 48), the subject also experienced acute kidney injury (Grade 2), psychomotor retardation (Grade 1), and vomiting (Grade 1). Laboratory tests showed total bilirubin 79 umol/L (NR: 3 – 18), creatinine 36 umol/L (NR: 64 – 104), AST 132 U/L (NR: 10 – 45), ALP 194 U/L (NR: 40 – 130), and albumin 27.6 g/L (NR: 35.2 – 48). The subject was treated with sodium chloride and paracetamol. The subject recovered from vomiting on the same day (Day 48). On 09 Jun 2015 (Day 49), the study drug was interrupted due to general physical health deterioration. On 11 Jun 2015 (Day 51), the subject recovered from general physical health deterioration and acute kidney injury. The subject did not recover from asthenia and psychomotor retardation. The Investigator considered general physical health deterioration serious and probably related to

the study drug; psychomotor retardation nonserious and not related to study drug but related to disease progression; acute kidney injury, asthenia, and vomiting nonserious and not related to the study drug.

On 13 Jun 2015 (Day 53), the subject was hospitalized for abdominal pain (Grade 3) and was treated with morphine. The subject did not recover from abdominal pain. On 14 Jun 2015 (Day 54), the subject experienced accidental morphine overdose (Grade 3) and pyrexia (Grade 1). The subject was treated with metronidazole, naloxone, and third-generation cephalosporins. On 15 Jun 2015 (Day 55), the subject was withdrawn from the study due to general physical health deterioration and received the last dose of the study drug on 08 Jun 2015 (Day 48). On 15 Jun 2015 (Day 55), the subject recovered from accidental morphine overdose. On the same day (Day 55, 7 days after the last dose), the subject died due to aspiration pneumonia. Autopsy was not performed. At the time of death, the subject had not recovered from abdominal pain and pyrexia. The Investigator considered abdominal pain, aspiration pneumonia, and accidental morphine overdose serious and not related to study drug; pyrexia nonserious and not related to the study drug.

Subject Number	14031006
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006328
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Hepatic encephalopathy
Non-Fatal SAE(s)	Oesophageal varices haemorrhage, Hepatic encephalopathy
Death due to PD	Yes

A 56-year-old white male was diagnosed with hepatocellular carcinoma on 01 Aug 2014. Significant medical history included alcohol use, decreased appetite, anxiety, constipation, depression, esophageal varices, fatigue, glaucoma, hepatic cirrhosis, cancer pain (right chest pain), seasonal allergy, and corneal transplant (right corneal graft). The subject did not receive any previous anticancer therapies. Prior and concomitant medications included ciprofloxacin, clobetasol, dexeryl, dorzolamide, eludril, lactulose, latanoprost, levocetirizine, macrogol, octreotide, oxazepam, oxycodone, paracetamol, prednisolone, propranolol, proteins (fortimel), sodium bicarbonate, spironolactone, timolol, tramadol, urea, and venlafaxine. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe, portal vein thrombosis, masses at right upper lobe of lung, right pleural cavity, and multiple sites of bilateral lungs. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

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

On 25 Nov 2014 (Day 19), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 1). On 25 Feb 2015 (Day 111), the subject's palmar-plantar erythrodysesthesia syndrome worsened to Grade 3. On 26 Feb 2015 (Day 112), the study drug was interrupted due to this event. The subject was treated with dexeryl, urea, and clobetasol. On 11 Mar 2015 (Day 125), the palmar-plantar erythrodysesthesia syndrome improved to Grade 1. On 13 Mar 2015 (Day 127), the study drug was resumed at a reduced dose of 8 mg/day. The Investigator considered palmar-plantar erythrodysesthesia syndrome nonserious and probably related to the study drug.

On 07 Apr 2015 (Day 152), the subject experienced esophageal varices hemorrhage (Grade 3) and was hospitalized on 13 Apr 2015 (Day 158). Laboratory tests showed Hgb 100 g/L (NR: 140 – 175). Gastrointestinal endoscopy showed esophageal varices and the subject underwent venous ligation. The subject was also treated with octreotide, propranolol, and ciprofloxacin. On 14 Apr 2015 (Day 159), the study drug was interrupted due to this event. The subject was recovering from esophageal varices hemorrhage. On 17 Apr 2015 (Day 162), the subject was discharged from hospital. The Investigator considered esophageal varices hemorrhage serious and possibly related to the study drug.

On 17 Apr 2015 (Day 162), the subject was hospitalized for hepatic encephalopathy (Grade 4) and was treated with lactulose. Laboratory tests were not provided. On 21 Apr 2015

(Day 166, 8 days after the last dose), the subject died due to hepatic encephalopathy. Autopsy was not performed. The subject received the last dose of the study drug on 13 Apr 2015 (Day 158). The Investigator considered hepatic encephalopathy serious and not related to the study drug but related to disease progression.

Subject Number	14061009
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-002677
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Pneumonia aspiration, Acute respiratory failure, Multiple organ dysfunction syndrome
Non-Fatal SAE(s)	Anxiety, Accidental overdose, Acute kidney injury, Renal tubular necrosis, Pneumonia aspiration, Acute respiratory failure, Infectious pleural effusion
AE(s) Leading to Discontinuation	Multiple organ dysfunction syndrome
Death due to PD	No

A 67-year-old white male was diagnosed with hepatocellular carcinoma on 19 Nov 2014. Significant medical history included non-alcoholic steatohepatitis, hepatic cirrhosis, obesity, esophageal varices, portal hypertension, type 1 diabetes mellitus, dyslipidemia, dyspepsia, hypertension, and abdominoplasty. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acetylsalicylic acid, amiodarone, antacids, augmentin, bactrim, bisoprolol, co-diovan, esomeprazole, furosemide, hydroxyzine, insulin aspart, insulin glargine, meropenem, morphine, ondansetron, pantoprazole, propranolol, rosuvastatin, sodium polystyrene sulfonate, spiramycin, and tramadol. At Screening, tumor assessments of target/non-target lesions via CT scan showed left upper lung lobe mass, multiple lung masses, and celiac lymphadenopathy; abdominal MRI showed lesion at right liver lobe. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 09 Dec 2014 (Day –14), the subject was hospitalized to minimize anxiety (Grade 2) in performing the study specific procedures. No treatment was provided. On 11 Dec 2014 (Day –12), the subject recovered from anxiety. The Investigator considered this event serious and not related to the study drug.

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

On 23 Dec 2014 (Day 1), the subject misunderstood the instructions in taking the study drug and said he took 30 tablets instead of 3 tablets. The subject was immediately hospitalized for observation in the ICU for the accidental overdose of study drug (Grade 4), and the study drug was interrupted due to this event. The subject underwent endoscopy of upper GI tract and gastric lavage where approximately 6 tablets were removed. Laboratory tests were done and showed AST 324 U/L (NR: 0 – 35), creatinine 87 umol/L (NR: 50 – 120), platelet count 633 x10^9/L (NR: 150 – 400), and uric acid 559 umol/L (NR: 230 – 450). On 28 Dec 2014 (Day 6), during hospitalization, the subject experienced acute kidney injury (Grade 3). Laboratory tests showed creatinine 427 umol/L, BUN 24.1 mmol/L (NR: 3 – 7), potassium 5.7 mmol/L (NR: 3.5 – 4.8), and sodium 134 mmol/L (NR: 135 – 145). On 30 Dec 2014 (Day 8), the subject experienced vomiting (Grade 2). On 31 Dec 2014 (Day 9), the subject underwent kidney biopsy and was diagnosed with renal tubular necrosis (Grade 2). Laboratory tests showed creatinine 263 umol/L (NR: 45 – 97). The study drug remained interrupted. The subject was treated with morphine,

sodium polystyrene sulfonate, tramadol, and ondansetron. On 08 Jan 2015 (Day 17), the subject experienced acute respiratory failure (Grade 4) and aspiration pneumonia (Grade 3). The study drug remained interrupted due to aspiration pneumonia and acute respiratory failure. On 09 Jan 2015 (Day 18), the subject recovered with sequelae from renal tubular necrosis and recovered from vomiting. Repeat laboratory tests showed BUN 33.8 mmol/L, creatinine 196 umol/L (NR: 50 – 120), potassium 3.7 mmol/L, and sodium 147 mmol/L. Beginning 09 Jan 2015 (Day 18), the subject refused (intensive) medical care and received only palliative management for the duration of the hospitalization. On 14 Jan 2015 (Day 23), the subject experienced infectious left pleural effusion (Grade 3) and the study drug remained interrupted. The subject was treated with amiodarone, furosemide, acetylsalicylic acid, augmentin, bisoprolol, hydroxyzine, bactrim, spiramycin, and meropenem. On 22 Jan 2015 (Day 31, 30 days after the last dose), the subject died due to worsening of acute respiratory failure, aspiration pneumonia, and multiple organ dysfunction syndrome. Autopsy was not performed. At the time of death, the subject had not recovered from infectious left pleural effusion and acute kidney injury. The Investigator considered acute kidney injury and acute tubular necrosis serious and probably related to the study drug; acute respiratory failure, aspiration pneumonia, infectious left pleural effusion, accidental overdose, and multi-organ failure serious and not related to the study drug; vomiting nonserious and probably related to the study drug.

Subject Number	14071003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-004063
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Cerebral haemorrhage
Non-Fatal SAE(s)	Atrial fibrillation, Cerebral haemorrhage
AE(s) Leading to Discontinuation	Cerebral haemorrhage
Death due to PD	No

A 68-year-old white male was diagnosed with hepatocellular carcinoma on 20 Aug 2014. Significant medical history included alcoholic cirrhosis, hypertension, chronic bronchitis, bilateral hip arthroplasty, obesity, osteoarthritis, and portal hypertension. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acenocoumarol, augmentin, beclometasone, bi predonium, capozide, digoxin, enoxaparin, esomeprazole, furosemide, magnesium, midazolam, oxomemazine, paracetamol, pentoxifylline, pregabalin, propranolol, salbutamol, sodium chloride, sufentanil, tinzaparin, and ultracet. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at segment 6 and segment 7 of liver; left lingular lung lobe and multiple lung masses; and splenic hilar lymphadenopathy. At Screening, the BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 12 Feb 2015 (Day 15), the subject was hospitalized for atrial fibrillation (Grade 3) confirmed by electrocardiogram. The subject also experienced hypomagnesemia (Grade 2). On the same day (Day 15), the study drug was interrupted due to atrial fibrillation. The subject was treated with enoxaparin, pentoxifylline, magnesium, acenocoumarol, digoxin, and tinzaparin. On 26 Feb 2015 (Day 29), severity of atrial fibrillation improved to Grade 1 and on the same day (Day 29), the study drug was resumed at same dose. The subject did not recover from atrial fibrillation and hypomagnesemia. The Investigator considered atrial fibrillation serious and not related to the study drug; hypomagnesemia nonserious and not related to the study drug.

On 06 May 2015 (Day 98), the subject experienced violent headaches and was hospitalized for cerebral hemorrhage (Grade 4) with Glasgow coma score 6, miotic pupils, and left nonreactive mydriasis. There were no signs of motor deficit. The oxygen saturation was 99%, body temperature 37 ℃, and blood glucose was normal. The subject underwent intubation and mechanical ventilation after rapid-sequence induction. The subject was treated with sodium chloride and was sedated with sufentanil/midazolam. Cerebral and supra-aortic trunk angiography scan showed intraparenchymal hemorrhage located in the midbrain and protuberance invading to V3 and V4, without suspected aneurysmal lesions. On 07 May 2015 (Day 99, 1 day after the last dose), the subject died due to cerebral hemorrhage. Autopsy was not performed. The subject received the last dose of the study drug on 06 May 2015 (Day 98). The Investigator considered cerebral hemorrhage serious and possibly related to the study drug.

Subject Number	15091003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01541-CLI-IT
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	General physical health deterioration
Non-Fatal SAE(s)	Pleural infection
AE(s) Leading to Discontinuation	General physical health deterioration
Death due to PD	Yes

A 59-year-old white male was diagnosed with hepatocellular carcinoma on 22 Dec 2013. Significant medical history included myocardial ischemia, hepatic cirrhosis, and hepatitis B. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included beclometasone, canrenone, clindamycin, enoxaparin, entecavir, furosemide, ketorolac, levofloxacin, omeprazole, oxitropium, parnaparin, and rabeprazole. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right, left, and caudate lobe of the liver. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 27 Jan 2014 (Day 1), treatment with study drug was initiated.

On 14 Jul 2014 (Day 169), the subject underwent a chest CT scan which showed right hydropneumothorax and the subject was diagnosed with pneumothorax (Grade 2). On the same day (Day 169), the subject underwent intercostal drainage. The subject was diagnosed with pleural infection (Grade 2) and was hospitalized due to this event. Laboratory tests showed WBC 16 x10^9/L (NR: 3.7 – 11), absolute neutrophils 13.5 x10^9/L (NR: 1.7 – 7.9), and absolute lymphocytes 1.6 x10^9/L (NR: 0.9 – 3.6). The subject was treated with clindamycin, levofloxacin, beclometasone, oxitropium, and the study drug was interrupted due to pleural infection. On 27 Jul 2014 (Day 182), the study drug was resumed at the same dose. On 01 Aug 2014 (Day 187), the subject recovered from pleural infection and did not recover from pneumothorax. The Investigator considered pleural infection serious and not related to study drug; pneumothorax nonserious and not related to study drug.

On 12 Aug 2014 (Day 198), the subject experienced decreased weight (Grade 2) of 58 kg (Baseline: 70 kg), fatigue (Grade 2), sinus tachycardia (Grade 1), and dyspnea (Grade 1). Vital signs showed BP 93/51 mmHg and heart rate 106 bpm. On the same day (Day 198), the study drug was resumed at a reduced dose of 8 mg/day due to decreased weight. The subject did not recover from these events. The Investigator considered decreased weight nonserious and possibly related to the study drug; fatigue, sinus tachycardia, and dyspnea nonserious and not related to the study drug.

On 28 Aug 2014 (Day 214, 1 day after the last dose), the subject was found dead while sitting on the chair. The cause of death was general physical health deterioration related to disease progression. Autopsy was not performed. The subject received the last dose of the study drug

on 27 Aug 2014 (Day 213). The Investigator considered general physical health deterioration serious and not related to study drug.

Subject Number	18051014
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006108
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	General physical health deterioration
Non-Fatal SAE(s)	Blood bilirubin increased, Aspartate aminotransferase increased, Tumour pain
AE(s) Leading to Discontinuation	Blood bilirubin increased
Death due to PD	Yes

A 59-year-old white male was diagnosed with hepatocellular carcinoma on 23 Jan 2015. Significant medical history included aortic arteriosclerosis, hypertension, cholelithiasis, chronic hepatitis B, benign prostatic hyperplasia, inguinal hernia, and splenomegaly. Previous anticancer therapies included hepatectomy (segment resection IVb) and transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, candesartan, clemastine, ibuprofen, tenofovir, tinzaparin, and valoron n. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at segment VI and lateral II segment of liver, left adrenal gland; masses at left and right lower lobes of lung; malignant portal vein thrombosis between liver segment IVa and VIII. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 06 March 2015 (Day 2), the subject experienced fatigue (Grade 3). On 13 Mar 2015 (Day 9), the subject experienced decreased weight (Grade 1) with body weight of 101 kg (Baseline: 108 kg). On the same day (Day 9), the study drug was interrupted due to decreased weight. The subject did not recover from fatigue and decreased weight. The Investigator considered fatigue nonserious and possibly related to the study drug; decreased weight nonserious and possibly related to the study drug and related to disease progression.

On 19 Mar 2015 (Day 15), the subject experienced increased gamma-glutamyltransferase (Grade 3) with GGT 364 U/L (NR: 10 – 49). On 02 Apr 2015 (Day 29), the subject experienced increased alanine aminotransferase (Grade 3), increased blood lactate dehydrogenase (Grade 3), increased blood alkaline phosphatase (Grade 3), increased aspartate aminotransferase (Grade 4), and increased blood bilirubin (Grade 4). Laboratory tests showed albumin 30 g/L (NR: 35 – 55), ALP 1857 U/L (NR: 43 – 115), ALT 726 U/L (NR: 10 – 40), AST 2501 U/L (NR: 10 – 43), LDH 2806 U/L (NR: 0 – 248), total bilirubin 281.3 umol/L (NR: 0 – 18.8), CRP 101.8 mg/L (NR: 0 – 5), GGT 252 U/L, and AFP 1104428 ug/L (NR: 0 – 6.1). On the same day (Day 29), the study drug was withdrawn due to increased blood bilirubin and received the last dose of the study drug on 12 Mar 2015 (Day 8). The subject did not recover from these events. The Investigator considered increased blood bilirubin, increased aspartate aminotransferase serious and not related to the study drug but related to disease progression; increased gamma-glutamyltransferase, increased alanine aminotransferase, increased blood lactate dehydrogenase,

and increased blood alkaline phosphatase nonserious and not related to the study drug but related to disease progression.

On 04 Apr 2015 (Day 31), the subject was hospitalized for tumor pain (Grade 3). The subject was treated with valoron n. On the same day (Day 31, 23 days after the last dose), the subject died due to general physical health deterioration. Autopsy was not performed. At the time of death, the subject had not recovered from tumor pain. The Investigator considered general physical health deterioration and tumor pain serious and not related to the study drug but related to disease progression.

Subject Number	18071006
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-007912
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Sepsis
Non-Fatal SAE(s)	Hepatic enzyme increased, Sepsis
AE(s) Leading to Discontinuation	Sepsis
Death due to PD	No

A 71-year-old white male was diagnosed with hepatocellular carcinoma on 21 Apr 2015. Significant medical history included cardiac pacemaker insertion, coronary artery disease, right ankle joint arthroplasty, hemochromatosis, hip arthroplasty, hypertension, hyperuricemia, hepatic cirrhosis, muscle injury, nephropathy, osteoarthritis, phlebotomy, and spinal fusion surgery. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included allopurinol, candesartan, clarithromycin, enoxaparin, glucose, hemofiltrationsloesung hf (sterofundin), hydromorphone, lactulose, meropenem, mesalazine, morphine, movicol, novo-petrin, pantoprazole, phytomenadione, ringer aguettant (ringer), vancomycin, and zopiclone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left side of psoas muscles, right lobe, and segment 8 of the liver. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 27 Jun 2015 (Day 5), the subject was hospitalized for sepsis (Grade 4). The subject also experienced increased hepatic enzymes (Grade 4), anuria (Grade 4), and dyspnea (Grade 3) with oxygen saturation 95%. Laboratory tests showed Hgb 82 g/L (NR: 130 – 170), WBC 11.14 x10^9/L (NR: 4 – 10), creatinine 388.076 umol/L (NR: 8.84 – 114.92), potassium 4.35 mmol/L (NR 3.5 – 4.8), AST 1540 U/L (NR: 0 – 50), ALT 811 U/L (NR: 0 – 50), ALP 270 U/L (NR: 40 – 130), LDH 1066 U/L (NR: 0 – 248), and total bilirubin 35.91 umol/L (NR: 0 – 17.1). Chest x-ray showed right sided hilar signs of progression; and lung auscultation showed sharpened sounds on both sides, basal crepitations, and right basal side moist rales. Urine dipstick showed moderate amount of leukocytes 2+, nitrite positive, and bilirubin 1+. Treatment included hemodialysis, oxygen supplementation, intravenous fluids, clarithromycin, meropenem, phytomenadione, and vancomycin. On the same day (Day 5), the subject was withdrawn from study due to sepsis and received the last dose of the study drug on 26 Jun 2015 (Day 4). Laboratory tests on 28 Jun 2015 (Day 6) showed WBC 20.71 x10^9/L, creatinine 425.204umol/L, AST 2457 U/L, ALT 1147 U/L, ALP 273 U/L, LDH 1919 U/L, and potassium 5.06 mmol/L. Ultrasound abdomen showed hepatosplenomegaly, multifocal hepatocellular carcinoma, and dilated colon loops with fluid. Blood culture showed positive for gram-negative E. coli. The subject refused further intensive care treatment. Later on that day (Day 6, 2 days after the last dose), the subject died due to sepsis. Autopsy was not performed. At the time of death, the subject had not recovered from increased hepatic enzymes, dyspnea, and anuria. The Investigator considered sepsis and increased hepatic enzymes serious and

possibly related to the study drug; dyspnea and anuria nonserious and possibly related to the study drug.

Subject Number	19011002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01465-CLI-RU
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Portal vein thrombosis, Coma hepatic
Non-Fatal SAE(s)	Portal vein thrombosis, Coma hepatic
AE(s) Leading to Discontinuation	Portal vein thrombosis, Coma hepatic, Encephalopathy
Death due to PD	Yes

A 72-year-old white male was diagnosed with hepatocellular carcinoma on 19 Jun 2013. Significant medical history included arterial hypertension, asthenia, atherosclerosis, irritable bowel syndrome, cholecystectomy, chronic duodenitis, chronic hepatitis B, intestinal diverticulum, diabetes mellitus, gastritis, hiatal hernia, myocardial ischemia, pulmonary fibrosis, portal vein thrombosis, and urinary calculus. Previous anticancer therapy included liver segment IV – V resection. Prior and concomitant medications included amlodipine, bisoprolol, captopril, entecavir, furosemide, gliclazide, perindopril, rabeprazole, and trimetazidine. 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 31 Jan 2014 (Day 1), treatment with study drug was initiated.

On 06 Mar 2014 (Day 35), the subject went to emergency room for hypertension (Grade 3), with blood pressure of 170/100 mmHg and encephalopathy (non-hepatic, mixed genesis; Grade 3). The subject was later hospitalized with a diagnosis of portal vein thrombosis (Grade 4) and hepatic coma (Grade 4). Laboratory tests showed albumin 30.3 g/L (NR: 35 – 50), ALT 78.1 U/L (NR: 0 – 40), AST 85.5 U/L (NR: 0 – 37), and total bilirubin 25.8 umol/L (NR: 0 – 20.5). The subject was treated with perindopril, trimetazidine, and amlodipine. On the same day (Day 35), the subject recovered with sequelae from encephalopathy, but did not recover from hypertension, portal vein thrombosis and hepatic coma. On 07 Mar 2014 (Day 36, 1 day after the last dose), the subject died due to portal vein thrombosis and hepatic coma, secondary to clinical disease progression. The autopsy results showed hepatic carcinoma stage IV as the initial cause of death, hepatic coma and portal vein thrombosis as directly leading to death. The subject received the last dose of study drug on 06 Mar 2014 (Day 35). The Investigator considered portal vein thrombosis and hepatic coma serious and not related to study drug; encephalopathy nonserious, and not related to study drug; hypertension nonserious, and possibly related to study drug.

Subject Number	19011014
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006430
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Intestinal haemorrhage
Death due to PD	Yes

A 64-year-old white female was diagnosed with hepatocellular carcinoma on 10 Jun 2014. Significant medical history included ascites, asthenia, chronic atrophic gastritis, hepatic cirrhosis, large intestine polyp, Hodgkin's disease, and right subcostal abdominal pain. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included captopril, furosemide, omeprazole, spironolactone, trophicard, and valsartan. At Screening, tumor assessments of target/non-target lesions via CT scan showed ascites, lesions at quadrate and right lobe of liver; lymphadenopathies at right celiac trunk, porta-hepatis, and retroperitoneal areas. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

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

On 17 Mar 2015 (Day 266), tumor response assessment showed disease progression. On 18 Mar 2015 (Day 267), the subject was withdrawn from study due to disease progression and received the last dose of the study drug on the same day (Day 267).

On 01 Apr 2015 (Day 281), the subject experienced intestinal hemorrhage (Grade 3). On 05 Apr 2015 (Day 285, 18 days after the last dose), the subject died at home due to intestinal hemorrhage. Autopsy was not performed. No additional information was available. The Investigator considered this event serious and not related to the study drug but related to disease progression.

Subject Number	19021002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-010693
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Sudden death
AE(s) Leading to Discontinuation	Sudden death
Death due to PD	Yes

A 57-year-old white male was diagnosed with hepatocellular carcinoma on 12 Dec 2013. Significant medical history included chronic gastritis and hepatitis B. The subject did not receive any previous anticancer therapies. The subject did not receive any prior and concomitant medications. 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 B, ECOG performance score was 0, and Child Pugh score was 5.

On 29 Jan 2014 (Day 1), treatment with study drug was initiated.

On 15 Aug 2015 (Day 579), the Child Pugh Score was 7.

On 21 Sep 2015 (Day 601), the subject's family reported that the subject died suddenly due to unknown cause. Autopsy was not performed. The subject received the last dose of the study drug on the same day (Day 601). The Investigator considered sudden death serious and not related to the study drug but related to disease progression.

Subject Number	19021017
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-001846
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Pulmonary embolism
AE(s) Leading to Discontinuation	Pulmonary embolism
Death due to PD	No

A 67-year-old white male was diagnosed with hepatocellular carcinoma on 01 Sep 2014. Significant medical history included aortic valve disease, atrial fibrillation, dyspnea, bronchiectasis, cough, chronic bronchitis, gout, headache, hypertension, atherosclerosis, myocardial ischemia, right upper abdominal pain, constipation, congenital cystic kidney disease, and urinary calculus. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included ademetionine, clemastine, loperamide, and warfarin. At Screening, tumor assessments of target/non-target lesions via MRI showed lesion at left lobe of liver. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 8.

In 2014 (unknown month and day), the subject started on warfarin for thrombosis prophylaxis and warfarin was discontinued on 01 Sep 2014 (Day –29). On 27 Sep 2014 (Day –3), at Baseline, Child Pugh score was 5.

On 30 Sep 2014 (Day 1), treatment with study drug was initiated.

On 05 Nov 2014 (Day 37, 1 day after the last dose), the subject died at home and the cause of death was pulmonary embolism. No further information was provided. The subject received the last dose of study drug on 04 Nov 2014 (Day 36). Autopsy was performed but the subject's wife refused to provide consent to get the autopsy results. The Investigator considered pulmonary embolism serious and not related to study drug.

Subject Number	19021020
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-013091
Assigned Treatment	Lenvatinib 8 mg/day
Fatal SAE(s)	Malignant neoplasm progression
AE(s) Leading to Discontinuation	Fatigue, Malignant neoplasm progression
Death due to PD	Yes

A 69-year-old white female was diagnosed with hepatocellular carcinoma on 13 Oct 2014. Significant medical history included hypertension, hepatitis B, and uterine leiomyoma. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included aprotinin. At Screening, tumor assessments of target/non-target lesions via MRI showed lesions at right liver lobe and multiple sites of liver. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 30 Oct 2014 (Day 1), treatment with study drug was initiated.

On 13 Nov 2014 (Day 15), the subject experienced increased lipase (Grade 4), increased blood bilirubin (Grade 1), chromaturia (Grade 1), increased amylase (Grade 3), decreased blood sodium (Grade 3), decreased blood albumin (Grade 2), and increased gamma-glutamyltransferase (Grade 1). The laboratory tests showed lipase 442 U/L (NR: 13 – 60), amylase 253 U/L (NR: 35 – 121), sodium 129 mmol/L (NR: 133 – 145), albumin 29 g/L (NR: 35 – 55), ALP 164 U/L (NR: 30 – 115), ALT 43 U/L (NR: 10 – 33), AST 104 U/L (NR: 10 – 36), total bilirubin 24.8 umol/L (NR: 0 – 18.8), and GGT 34 U/L (NR: 5 – 32). The subject was treated with aprotinin. On 14 Nov 2014 (Day 16), the study drug interrupted due to increased lipase. On 27 Nov 2014 (Day 29), severity of increased lipase improved to Grade 3 with lipase 153 U/L and increased amylase improved to Grade 1 with amylase 152 U/L. On the same day (Day 29), the subject recovered from chromaturia, decreased blood sodium, and increased gamma-glutamyltransferase with GGT 29 U/L. On 11 Dec 2014 (Day 43), increased lipase improved to Grade 1 with lipase 75 U/L and the subject recovered from increased amylase with amylase 112 U/L and increased blood bilirubin with total bilirubin 16.2 umol/L. On the same day (Day 43), the study drug resumed at same dose. On 25 Dec 2014 (Day 57), decreased albumin improved to Grade 1 with albumin 34.2 g/L (NR: 35 – 50). On 22 Jan 2015 (Day 85), increased lipase worsened to Grade 3 and the subject recovered from decreased albumin with albumin 39 g/L (NR: 35 – 55). On 27 Jan 2015 (Day 90), the study drug was again interrupted due to persistent increased lipase. On 09 Feb 2015 (Day 103), the subject recovered from increased lipase. On 10 Feb 2015 (Day 104), the study drug resumed at reduced dose of 4 mg/day due to increased lipase. The Investigator considered these events nonserious and possibly related to the study drug.

On 17 Jun 2015 (Day 231), the subject experienced ascites (Grade 1) and the study drug dose was not changed. On 06 Aug 2015 (Day 281), the subject experienced decreased weight (Grade 1) with body weight 48.7 kg (Baseline: 58 kg). The subject did not recover from ascites