The subject did not recover from perihepatic abscess. The Investigator considered perihepatic abscess nonserious and not related to study drug but related to disease progression.

On 09 Jun 2014 (Day 140), subject was hospitalized for infected neoplasm (tumor site infection; Grade 3) with temperature of 40.2 ºC and epigastric pain. The CT of abdomen showed some infection at tumor site. On 12 Jun 2014 (Day 143), chest x-ray showed pleural effusion in the right lung secondary to tumor infection. The subject was treated with ampicillin/sulbactam, furosemide, and augmentin. On 14 Jun 2014 (Day 145), chest x-ray and CT of chest showed worsening pleural effusion with interstitial pneumonia shadows. The subject did not recover from infected neoplasm. On 15 Jun 2014 (Day 146, 33 days after the last dose), the subject died due to respiratory failure. Autopsy was not performed. The Investigator considered infected neoplasm serious and not related to the study drug but related to disease progression.

Subject Number	12031002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01352-CLI-JP
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Blood pressure decreased, Pneumonia

A 72-year-old Japanese male was diagnosed with hepatocellular carcinoma on 20 May 2008. Significant medical history included chronic gastritis, cataract, cholecystectomy, chronic hepatitis B, diabetes mellitus, hypertension, and superior mesenteric artery dissection. Previous anticancer therapies included hepatectomy, percutaneous ethanol injection, pneumonectomy, radiofrequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included acetated ringer, adefovir, amlodipine, bifidobacterium lactis, bisoprolol, fluorometholone, influenza vaccine, insulin lispro, lamivudine, levofloxacin, levothyroxine, loxoprofen, neostigmine, pirenoxine, rabeprazole, urea, and verapamil. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe; mass at bilateral upper lobe of lung; left hilar and left mediastinal lymphadenopathies. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 08 Aug 2013 (Day 1), treatment with study drug was initiated.

On 13 Aug 2013 (Day 6), the subject experienced atrial fibrillation (Grade 2) as confirmed by ECG. The subject was treated with verapamil, acetated ringer, and the study drug dose did not change. On 14 Aug 2013 (Day 7), the severity of atrial fibrillation improved to Grade 1 with heart rate of 70 bpm and blood pressure of 124/79 mmHg. On 17 Aug 2013 (Day 10), the severity of atrial fibrillation worsened to Grade 2 with heart rate of 130 – 140 bpm and systolic blood pressure of 110 mmHg. On 20 Aug 2013 (Day 13), the subject was started on bisoprolol and experienced decreased blood pressure (Grade 1) with reading of 102/63 mmHg and the subject was hospitalized. Due to decreasing blood pressure, subject's concomitant antihypertensive medication, amlodipine, was discontinued. On 26 Aug 2013 (Day 19), the subject recovered from decreased blood pressure with blood pressure of 127/76 mmHg and was discharged. On 04 Sep 2013 (Day 28), the subject recovered from atrial fibrillation and ECG showed heart rate of 64 bpm. The Investigator considered decreased blood pressure serious and not related to the study drug; atrial fibrillation nonserious and possibly related to the study drug.

On 09 Apr 2015 (Day 610), tumor response assessment showed disease progression. On 15 Apr 2015 (Day 616), the subject was withdrawn from study due to disease progression and received the last dose of study drug on 13 Apr 2015 (Day 614) as subject missed dose on 14 Apr 2015 (Day 615).

On 04 May 2015 (Day 635), the subject experienced fever with temperature of 37.8 °C. On 11 May 2015 (Day 642), the subject was hospitalized with a diagnosis of obstructive pneumonia (Grade 2). On the same day (Day 642), the laboratory test showed WBC 7.38 x10^9/L (NR: 3.3 – 8.8), and CT of chest showed atelectasis associated with metastases to the left lung and infection surrounding regions. The subject was treated with levofloxacin,

ampicillin/sulbactam, and meropenem. On 27 May 2015 (Day 658), the subject recovered from obstructive pneumonia. The Investigator considered obstructive pneumonia serious and not related to the study drug but related to disease progression.

On 30 Nov 2015 (Day 845, 231 days after the last dose), the subject died due to disease progression.

Subject Number	12031003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-000761
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Cerebral infarction
AE(s) Leading to Discontinuation	Cerebral infarction

A 67-year-old Japanese male was diagnosed with hepatocellular carcinoma on 31 Jul 2013. Significant medical history included alcoholic hepatitis, chronic gastritis, colon adenoma, right bundle branch block, diabetes mellitus, diverticulitis, granuloma annulare, hypertension, insomnia, and cerebral infarction. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acetokeep 3g, amlodipine, apixaban, candesartan, carbazochrome, carbohydrates w/potassium chloride/sodium, cefazolin, cefdinir, cilnidipine, dabigatran, difenidol, difluprednate, dimeticone, edaravone, furosemide, glycerol, gualenic acid, heparin, herbal emollients and protectives (Chinese medicine), human insulin, influenza vaccine, insulin aspart, insulin detemir, insulin glargine, ketoprofen, lac-b granular powder n, lansoprazole, levofloxacin, lidocaine, loxoprofen, magnesium oxide, midazolam, mitiglinide, neurobion, new lecicarbon, pa, pabron s gold, paracetamol, pentazocine, pilsicainide, povidone-iodine, pronase, rabeprazole, risperidone, salicylic acid, sennoside a+b, sodium bicarbonate, sodium picosulfate, solacet f, solifenacin, solita-t1, stomatological preparations (diclofenac sodium), suvorexant, tiquizium, tranexamic acid, triazolam, urea, ursodeoxycholic acid, veen d, zolpidem, and zopiclone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right, left, and quadrate liver lobes. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 08 Sep 2013 (Day 18), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 2) and was treated with urea and difluprednate. On 16 Sep 2013 (Day 26), the study drug was interrupted. On 17 Sep 2013 (Day 27), the severity of palmar-plantar erythrodysesthesia syndrome worsened to Grade 3. On 24 Sep 2013 (Day 34), the severity of palmar-plantar erythrodysesthesia syndrome improved to Grade 1 and the study drug dose was resumed at a reduced dose of 8 mg/day due to this event. On 10 Nov 2013 (Day 81), the study drug was interrupted due to persistence of palmar-plantar erythrodysesthesia syndrome. On 11 Nov 2013 (Day 82), the severity of palmar-plantar erythrodysesthesia syndrome worsened to Grade 3 and treatment with urea and difluprednate were continued. On 22 Nov 2013 (Day 93), palmar-plantar erythrodysesthesia syndrome improved to Grade 1 and study drug dose was resumed at a reduced dose of 4 mg/day due to palmar-plantar erythrodysesthesia. The subject did not recover from palmar-plantar erythrodysesthesia syndrome. The Investigator considered palmar-plantar erythrodysesthesia syndrome nonserious and probably related to the study drug.

On 03 Oct 2014 (Day 408), the subject experienced atrial fibrillation (Grade 2) which started as Grade 1 on 22 Aug 2014 (Day 366). Electrocardiogram showed atrial fibrillation and the subject was treated with pilsicainide. On 06 Oct 2014 (Day 411), the subject experienced pain

in the right temporal region of the head and felt weightless. On 07 Oct 2014 (Day 412), the subject was hospitalized for cerebral infarction (Grade 3) associated with difficulty seeing in the left visual field and ophthalmic examination showed left homonymous hemianopsia and the study drug was interrupted. The CT scan of head showed low absorption area ranging from the right temporal region to the occipital region and MRI of head showed multiple cerebral infarction. Head Diffusion Weighted Imaging-Magnetic Resonance Imaging (DWI-MRI), showed relatively big lesion in the right temporal region significant for acute phase infarction in the right parietal lobe to temporal lobe, fresh lacunar infarct in the left parietal lobe and left cerebellar hemisphere and small lesions with high DWI intensity in the left cerebellar hemisphere, left frontal lobe and big infarction in the left occipital lobe. The subject was treated with edaravone. On 08 Oct 2014 (Day 413), repeat CT scan of head showed neither expansion of infarction area nor hemorrhagic lesion and mild swelling. The subject was treated with dabigatran, heparin, risperidone, and rehabilitation (occupational therapy). On 27 Oct 2014 (Day 432), the severity of cerebral infarction improved to Grade 1 with improved left homonymous hemianopsia. On 28 Oct 2014 (Day 433), the study drug dose was resumed at a reduced frequency of 4 mg every other day due to cerebral infarction. The subject did not recover from this cerebral infarction and atrial fibrillation. The Investigator considered cerebral infarction serious and possibly related to the study drug; atrial fibrillation nonserious and probably related to the study drug.

On 02 Aug 2015 (Day 711), the subject was re-hospitalized for cerebral infarction (Grade 3) with symptoms of giddiness when changing position, as well as swaying on walking, dyslalia, and dysphagia. MRI of head showed high DWI intensity in the medulla oblongata and the right parietal lobe, magnetic resonance angiography showed no findings of cerebrovascular dissection and CT scan of head showed no hemorrhage. The subject underwent nasogastric tube insertion and was treated with heparin, edaravone, neurobion, solita-t1, veen d, and apixaban. On 07 Aug 2015 (Day 716), the subject was withdrawn from the study due to cerebral infarction and received the last dose of study drug on 29 Jul 2015 (Day 707). On 14 Aug 2015 (Day 723), tumor response assessment showed disease progression. On 17 Aug 2015 (Day 726), the subject underwent rehabilitation for dyslalia and pharyngeal movement. On 21 Aug 2015 (Day 730), the subject underwent percutaneous endoscopic gastrostomy. On 23 Aug 2015 (Day 732), sudden motor aphasia occurred without obvious quadriplegia and CT scan of head showed newly-developed cerebral infarction in the left MCA territory and motor aphasia was present. On 05 Mar 2016 (Day 927), the subject recovered with sequelae from cerebral infarction. The Investigator considered cerebral infarction serious and possibly related to the study drug.

On 05 Mar 2016 (Day 927, 220 days after the last dose), the subject died of aspiration pneumonia due to reflux from gastric fistula. It was unknown if an autopsy was performed.

Subject Number	12031004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01393-CLI-JP
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Tumour haemorrhage

A 64-year-old Japanese male was diagnosed with hepatocellular carcinoma on 27 Aug 2013. Significant medical history included asthenopia, cholelithiasis, chronic hepatitis C, gastritis, and insomnia. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included alprazolam, carbazochrome, carbohydrates w/potassium chloride/sodium lactate, cefcapene, cefmetazole, difluprednate, dimeticone, esomeprazole, eufusol, influenza vaccine, levofloxacin, lidocaine, loxoprofen, pronase, rebamipide, sodium bicarbonate, sodium chloride, solita-t1, urea, ursodeoxycholic acid, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left lobes of liver and left adrenal gland mass. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 05 Nov 2013 (Day 47), the subject was hospitalized for tumor hemorrhage (Grade 3) with pain at epigastric region and left hypochondrium and the study drug was interrupted due to this event. The subject also experienced anemia (Grade 2). Contrast-enhanced CT of abdomen confirmed intratumoral hemorrhage. Laboratory tests showed RBC 2.67 x10^12/L (NR: 4.3 – 5.5), WBC 2.75 x10^9/L (NR: 3.3 – 8.8), Hgb 94 g/L (NR: 135 – 170), and Hct 0.268 L/L (NR: 0.397 – 0.51). On 06 Nov 2013 (Day 48), the subject experienced increased blood bilirubin (Grade 1) with total bilirubin 22.23 umol/L (NR: 5.13 – 20.52). The subject was treated with intravenous carbazochrome and cefmetazole. On 08 Nov 2013 (Day 50), the subject recovered from increased blood bilirubin. On 12 Nov 2013 (Day 54), laboratory tests showed RBC 2.46 x10^12/L (NR: 4 – 5.6), WBC 3 x10^9/L (NR: 3.7 – 11), Hgb 91 g/L (NR: 125 – 170), Hct 0.268 (NR: 0.37 – 0.51), and AFP 1178.6 ug/L (NR: 0 – 6.1). On the same day (Day 54), the severity of tumor hemorrhage improved to Grade 1 and the study drug was resumed at reduced dose of 4 mg/day due to tumor hemorrhage. On 10 Dec 2013 (Day 82), the subject recovered from anemia, and on 07 Jan 2014 (Day 110), the subject recovered from tumor hemorrhage. The Investigator considered tumor hemorrhage serious and probably related to study drug; increased blood bilirubin nonserious and probably related to the study drug and anemia nonserious and possibly related to study drug.

On 07 Jan 2014 (Day 110), tumor response assessment showed disease progression. On 10 Jan 2014 (Day 113), the subject was withdrawn from the study due to disease progression. The subject received the last dose of study drug on 09 Jan 2014 (Day 112).

On 12 Jun 2014 (Day 266, 154 days after the last dose), the subject died due to disease progression.

Subject Number	12041010
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-000214
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Cancer pain

A 57-year-old Japanese female was diagnosed with hepatocellular carcinoma on 23 Jul 2013. Significant medical history included chronic hepatitis C, diabetes mellitus, dry skin, autonomic nervous system imbalance (dysautonomia), goiter, hypertension, and tumor pain. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, dextromethorphan, difluprednate, dimeticone, etizolam, flumazenil, gliclazide, heparinoid, hyoscine, keishibukuryogan, lidocaine, linagliptin, loxoprofen, magnesium oxide, midazolam, omeprazole, oxycodone, pethidine, procaine, pronase, propranolol, sodium bicarbonate, thiamazole, and urea. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right lobe of liver, right kidney, and bilateral lesions of the lung. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 01 Jul 2014 (Day 1), treatment with study drug was initiated.

On 08 Jul 2014 (Day 8), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 2). On 15 Jul 2014 (Day 15), the severity of palmar-plantar erythrodysesthesia syndrome increased to Grade 3 and the study drug was interrupted. The subject was treated with urea and difluprednate. The subject did not recover from this event. On 23 Jul 2014 (Day 23), the study drug was resumed at a reduced dose of 8 mg/day due to palmar-plantar erythrodysesthesia syndrome. The Investigator considered palmar-plantar erythrodysesthesia syndrome nonserious and probably related to study drug.

On 19 Aug 2014 (Day 50), tumor response assessment showed disease progression and the subject was withdrawn from the study due to disease progression. The subject received the last dose of study drug on 18 Aug 2014 (Day 49).

On 14 Sep 2014 (Day 76), subject was hospitalized for cancer pain (Grade 3). Contrast MRI showed metastases to bones in the right acetabular cartridge and the right femoral neck; and CT scan showed metastases to the brain. The subject was treated with oxycodone and radiotherapy to bones and brain. On 11 Oct 2014 (Day 103), chest x-ray showed aggravation of metastases to lungs. The subject did not recover from this event. The Investigator considered cancer pain serious and not related to study drug, but related to disease progression.

On 15 Oct 2014 (Day 107, 58 days after the last dose), the subject died due to disease progression.

Subject Number	12061003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-004354
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Gastric haemorrhage, Varices oesophageal

A 77-year-old Japanese male was diagnosed with hepatocellular carcinoma on 16 Mar 2006. Significant medical history included cholecystectomy, chronic hepatitis C, hepatic cirrhosis, diabetes mellitus, esophageal varices, gastritis, seasonal allergy (pollinosis), and sinusitis. Previous anticancer therapies included hepatectomy, radiofrequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included actit, alginic acid, atropine, carbazochrome, carbohydrates w/potassium chloride/sodium, cefotiam, cetirizine, diflorasone, dimeticone, famotidine, fexofenadine, gliclazide, glimepiride, heparinoid, hydrocortisone, hydroxyzine, hyoscine, lansoprazole, lidocaine, linagliptin, menthol, mometasone, monoethanolamine oleate, pentazocine, ringer-lactatis, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 04 Sep 2013 (Day 1), treatment with study drug was initiated.

On 01 Dec 2013 (Day 89), the subject experienced decreased appetite (Grade 1). On 02 Sep 2014 (Day 364), the decreased appetite worsened to Grade 2. The subject's body weight was 58.3 kg (Baseline: 59.8 kg). On 01 Oct 2014 (Day 393), the study drug was reduced to 4 mg/day due to decreased appetite. On 11 Mar 2015 (Day 554), the subject recovered from decreased appetite. The Investigator considered decreased appetite nonserious and possibly related to study drug.

On 08 Feb 2015 (Day 523), the subject had black stools for five days. On 17 Feb 2015 (Day 532), laboratory tests showed Hgb 96 g/L (NR: 125 – 170), Hct 0.305 L/L (NR: 0.37 – 0.51), and RBC 3.09 x10^12/L (NR: 4 – 5.6). On 22 Feb 2015 (Day 537), the study drug was interrupted for scrutiny of bleeding. On 23 Feb 2015 (Day 538), the subject was hospitalized for further evaluation. On 24 Feb 2015 (Day 539), upper gastrointestinal tract endoscopy was performed and the subject was diagnosed with gastric hemorrhage (Grade 2), esophageal varices (Grade 3), and the possibility that blood had oozed from erosions in the gastric antrum. On 24 Feb 2015 (Day 539), the study drug was resumed at the same dose. The subject was treated with lansoprazole and monoethanolamine oleate. On 01 Mar 2015 (Day 544), the study drug was interrupted due to esophageal varices. On 03 Mar 2015 (Day 546), the subject underwent an endoscopic sclerotherapy. On the same day (Day 546), the subject recovered from gastric hemorrhage. On 10 Mar 2015 (Day 553), a repeat upper gastrointestinal endoscopy showed sclerotherapy took effect and the subject recovered from esophageal varices. On 12 Mar 2015 (Day 555), repeat laboratory tests showed Hgb 88 g/L, RBC 2.87 x10^12/L, and Hct 0.271 L/L. The Investigator considered gastric hemorrhage and esophageal varices serious and possibly related to study drug.

On 10 Mar 2015 (Day 553), the tumor response assessment showed disease progression, however the scans of 13 Jan 2015 (Day 497) were initially assessed as partial response and were reassessed on 29 Jun 2015 (Day 553) as disease progression. On 10 Mar 2015 (Day 553), the subject was withdrawn from the study due to disease progression and received the last dose on 28 Feb 2015 (Day 543).

Subject Number	12061004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01375-CLI-JP
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Ascites, Non-cardiogenic pulmonary oedema

A 74-year-old Japanese male was diagnosed with hepatocellular carcinoma on 15 Oct 2012. Significant medical history included chronic hepatitis C, esophageal varices, gastritis, hemorrhoids, and hepatic cirrhosis. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, ascorbic acid, asphagen, bepotastine, betamethasone, carbohydrates w/potassium chloride/sodium, diclofenac, dimeticone, drugs for constipation, furosemide, heparinoid, human albumin, hydroxyzine, lactec D, levofloxacin, lidocaine, loxoprofen, meropenem, nifedipine, paracetamol, potassium aspartate, pyridoxal, spironolactone, thiamine, and urea. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and quadrate lobe of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 6.

On 03 Sep 2013 (Day 1), treatment with study drug was initiated.

On 17 Sep 2013 (Day 15), the subject experienced decreased platelet count (Grade 2) with platelet count 50 x10^9/L (NR: 141 – 327). On 30 Sep 2013 (Day 28), the severity of decreased platelet count worsened to Grade 3 with platelet count 48 x10^9/L. On 01 Oct 2013 (Day 29), the study drug was interrupted due to decreased platelet count. On 04 Oct 2013 (Day 32), the subject was hospitalized for ascites (Grade 2). On 05 Oct 2013 (Day 33), the subject experienced non-cardiogenic pulmonary edema (Grade 3) with oxygen saturation 85 – 87% (NR: >95). Chest x-ray and chest CT showed pleural effusion (Grade 2), atelectasis, and cardiac enlargement. On 07 Oct 2013 (Day 35), CT scan of chest showed pneumonia (Grade 2). Laboratory tests showed AST 103 U/L (NR: 13 – 33), ALT 53 U/L (NR: 8 – 42), and total bilirubin 76.95 umol/L (NR: 5.13 – 18.81). Treatment included oxygen, furosemide, human albumin, spironolactone, meropenem, hydroxyzine, and subject underwent bladder catheterization. On 11 Oct 2013 (Day 39), repeated chest CT showed decreased pleural effusion. On 12 Oct 2013 (Day 40), the subject experienced hypokalemia (Grade 3) with potassium 2.5 mmol/L (NR: 3.7 – 4.8) and was treated with potassium aspartate. On 21 Oct 2013 (Day 49), decreased platelet count improved to Grade 1 with a count of 81 x10^9/L. On 22 Oct 2013 (Day 50), the subject started rehabilitation therapy. On 23 Oct 2013 (Day 51), tumor response assessment showed disease progression and the subject was withdrawn from the study due to disease progression. The subject received the last dose of the study drug on 30 Sep 2013 (Day 28). On 23 Oct 2013 (Day 51), the subject recovered from pleural effusion; on 24 Oct 2013 (Day 52), the subject recovered from decreased platelet count; on 29 Oct 2013 (Day 57), the subject recovered from pneumonia and on 02 Nov 2013 (Day 61), the subject recovered from ascites and non-cardiogenic pulmonary edema. The subject did not recover from hypokalemia. The Investigator considered ascites serious and probably related to the study drug and related to disease progression; non-cardiogenic pulmonary edema serious and probably related to the study drug; pleural effusion and pneumonia nonserious and possibly related to the

study drug; hypokalemia nonserious and not related to the study drug; and decreased platelet count nonserious and probably related to the study drug.

On 18 Nov 2013 (Day 77, 49 days after the last dose), the subject died due to disease progression.

Subject Number	12071003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-001445
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Pyrexia, Cholangitis, Bile duct stone

A 79-year-old Japanese male was diagnosed with hepatocellular carcinoma on 14 Aug 2001. Significant medical history included benign prostatic hyperplasia, depression, arthralgia, constipation, chronic sinusitis, skin cyst excision, hepatitis C, hyperuricemia, insomnia, benign monoclonal hypergammaglobulinemia, and duodenal ulcer. Previous anticancer therapies included hepatectomy, percutaneous ethanol injection therapy, radiotherapy to liver, high frequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, ascorbic acid, asphagen, bisacodyl, brotizolam, carbazochrome, carbohydrates w/potassium chloride/sodium, clindamycin, dextrose and sodium chloride injection, diazepam, dimeticone, dutasteride, falkamin, famotidine, felbinac, flomoxef, flunitrazepam, fluorometholone, furosemide, glucagon, glycerol, human albumin, lactec d, lidocaine, mentha spp., meropenem, nifedipine, ofloxacin, paracetamol, pentazocine, piperacillin/tazobactam, pyridoxal, riboflavin, ringer-lactatis, sennoside a+b, silodosin, spironolactone, thiamine, tranexamic acid, and ulinastatin. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe; bilateral lung masses; right hilar and mediastinal lymphadenopathies. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 28 May 2014 (Day 1), treatment with study drug was initiated.

On 20 Aug 2014 (Day 85), the subject experienced proteinuria (Grade 2) with urine protein dipstick 2+ and on 21 Aug 2014 (Day 86), 24h urine protein was 1.9689 g/24hr. On 17 Sep 2014 (Day 113), the proteinuria worsened to Grade 3 with urine protein dipstick 3+ and 24h urine protein was not done. On 07 Oct 2014 (Day 133), the study drug was interrupted due to proteinuria. On 15 Oct 2014 (Day 141), the proteinuria improved to Grade 2 and the subject experienced peripheral edema (Grade 2) which was ongoing since 28 Jun 2014 (Day 32) as Grade 1. Laboratory tests showed BUN 5.71 mmol/L (NR: 1.78 – 7.14), creatinine 80 umol/L (NR: 62 – 124), sodium 131 mmol/L (NR: 133 – 145), potassium 4.6 mmol/L (NR: 3.5 – 5), calcium 2.12 mmol/L (NR: 2.12 – 2.62). The subject was treated with furosemide and spironolactone. On 22 Oct 2014 (Day 148), the study drug was resumed at the same dose. The subject did not recover from proteinuria and peripheral edema. On 29 Oct 2014 (Day 155), the study drug was resumed at a reduced dose of 8 mg/day due to peripheral edema. The Investigator considered proteinuria nonserious and probably related to the study drug; peripheral edema nonserious and possibly related to the study drug.

On 03 Nov 2014 (Day 160), the subject was hospitalized for pyrexia (Grade 1) with temperature of 39 ºC associated with chills and the study drug was interrupted due to pyrexia. On 04 Nov2014 (Day 161), the blood cultures showed gram-negative bacilli. Laboratory tests showed WBC 14.9 x10^9/L (NR: 3.4 – 9.2), CRP 20.6 mg/L (NR: 0 – 3), GGT 893 U/L

(NR: 9 – 109), AST 207 U/L (NR: 13 – 33), ALT 181 U/L (NR: 8 – 42), and ALP 1777 U/L (NR: 117 – 350). The subject was treated with piperacillin/tazobactam and paracetamol. On 05 Nov 2014 (Day 162), magnetic resonance cholangiopancreatography (MRCP) showed dilatation of common bile duct and calculus in the lower common bile duct. The subject remained hospitalized due to cholangitis (Grade 3) and bile duct stone (Grade 3). The subject underwent endoscopic retrograde cholangiopancreatography (ERCP) and had an insertion of biliary drainage tube. The bile culture was positive for Aeromonas species. Additional treatments were clindamycin and meropenem. On 07 Nov 2014 (Day 164), laboratory tests showed AST 1557 U/L, ALT 686 U/L, and ALP 1694 U/L. On 10 Nov 2014 (Day 167), the subject underwent repeat MRCP which showed previously inserted biliary drainage tube and dilated bile duct where drainage was inhibited by stricture of the hepatic portal region. On 18 Nov 2014 (Day 175), tumor response assessment showed disease progression. On 19 Nov 2014 (Day 176), the subject was withdrawn from study due to disease progression and received the last dose on 02 Nov 2014 (Day 159). On 21 Nov 2014 (Day 178), the total bilirubin was 244.53 umol/L (NR: 5.13 – 18.81). The subject underwent repeat ERCP and biliary drainage tube was replaced. The subject was recovering from these events. The Investigator considered pyrexia, cholangitis, and bile duct stone serious and possibly related to the study drug.

On 08 Jul 2015 (Day 407, 248 days after the last dose), the subject died due to disease progression.

Subject Number	12081013
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01449-CLI-JP
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Hepatic encephalopathy, Hepatopulmonary syndrome

A 74-year-old Japanese male was diagnosed with hepatocellular carcinoma on 16 Jan 2014. Significant medical history included cataract, chronic gastritis, constipation, diabetes mellitus, esophageal varices, glaucoma, insomnia, alcoholic cirrhosis, and stroma related pneumonia. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included aminoleban, betamethasone, breo ellipta, cefmenoxime, diclofenac, dimeticone, eszopiclone, etizolam, falkamin, fluorometholone, glimepiride, glucose, heparin, human insulin, kanamycin, ketoprofen, lactulose, levofloxacin, lidocaine, loxoprofen, magnesium oxide, methylprednisolone, morihepamin, omeprazole, oxybuprocaine, pabron s, prednisolone, pronase, salbutamol, sennoside a+b, seretide, sitagliptin, sodium bicarbonate, tetracaine, tiotropium, tobramycin, urea, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed right lobe liver lesion, right mediastinal lymphadenopathy, and right upper lung lobe mass. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 12 Feb 2014 (Day 7), the subject was dazed, had flapping tremor, and had ammonia 123.5047 umol/L (NR: 8.5668 – 47.1174). The subject was hospitalized for hepatic encephalopathy (Grade 3). The subject was treated with aminoleban, glucose, and kanamycin. The study drug was interrupted due to this event. On 17 Feb 2014 (Day 12), repeat ammonia was 95 mcg/dL (NR: 12 – 66). On 18 Feb 2014 (Day 13), the subject recovered from hepatic encephalopathy and on the same day (Day 13) the study drug was resumed at a reduced dose of 8 mg/day due to hepatic encephalopathy. The Investigator considered hepatic encephalopathy serious and probably related to the study drug.

On 07 Mar 2014 (Day 30), the subject experienced hyperammonemia (Grade 2) with ammonia 120.6491 umol/L (NR: 8.5668 – 47.1174). The subject was treated with lactulose and the study drug was interrupted due to this event. On 12 Mar 2014 (Day 35), the subject recovered from hyperammonemia with ammonia 66.3927 umol/L (NR: 8.5668 – 47.1174), and the study drug was resumed at a reduced dose of 4 mg/day due to hyperammonemia. The Investigator considered hyperammonemia nonserious and probably related to the study drug.

On 26 May 2014 (Day 110), the subject experienced hyperammonemia (Grade 2) with ammonia 129.2159 umol/L (NR: 8.5668 – 47.1174). The subject was treated with kanamycin and lactulose and the study drug was interrupted due to this event. On 04 Jun 2014 (Day 119), the subject recovered from hyperammonemia with repeat test showing ammonia level 92.807 umol/L (NR: 8.5668 – 47.1174) and the study drug dose was resumed at a reduced

frequency of 4 mg every other day due to hyperammonemia. The Investigator considered hyperammonemia nonserious and probably related to the study drug.

On 15 Oct 2015 (Day 617), the subject experienced increased blood bilirubin (Grade 2) with total bilirubin 31.3 umol/L (NR: 0 – 18.8) and decreased weight (Grade 2) with body weight 67.1 kg (Baseline: 76 kg). The study drug dose was not changed. On 28 Oct 2015 (Day 630), the subject experienced hepatopulmonary syndrome (Grade 2) and symptoms of dyspnea, with SpO2 93% on recumbency and SpO2 87% on exertion. The subject was treated with tiotropium, seretide, and prednisolone. On 12 Nov 2015 (Day 645), the subject recovered from increased blood bilirubin. The subject did not recover from decreased weight and hepatopulmonary syndrome. The Investigator considered hepatopulmonary syndrome, increased blood bilirubin, and decreased weight nonserious and not related to the study drug.

On 03 Dec 2015 (Day 666), the subject was hospitalized for worsening hepatopulmonary syndrome (Grade 3) with SpO2 on exertion 88% to 91%. Treatment included oxygen, tiotropium, seretide, breo ellipta, prednisolone, methylprednisolone, and salbutamol. On 09 Dec 2015 (Day 672), the subject experienced abnormal hepatic function (Grade 2) with ALP 147 U/L (NR: 43 – 115), ALT 121 U/L (NR: 10 – 40), AST 113 U/L (NR: 10 – 43), GGT 357 U/L (NR: 10 – 49), total bilirubin 16.6 umol/L (NR: 0 – 18.8), and creatinine 35 umol/L (NR: 62 – 124). The study drug dose was not changed. On 17 Dec 2015 (Day 680), echocardiography showed microbubbles in the left atrium within 7 heartbeats. On 25 Dec 2015 (Day 688), severity of hepatopulmonary syndrome improved to Grade 2, and the subject was discharged from hospital. The subject did not recover from hepatopulmonary syndrome and abnormal hepatic function. The Investigator considered hepatopulmonary syndrome serious and not related to the study drug; abnormal hepatic function nonserious and not related to the study drug.

On 29 Jan 2016 (Day 723), tumor response assessment showed disease progression. On 04 Feb 2016 (Day 729), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 03 Feb 2016 (Day 728).

On 05 May 2016 (Day 820, 92 days after the last dose), the subject died due to unknown cause.

Subject Number	12081014
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01555-CLI-JP
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Upper gastrointestinal haemorrhage
AE(s) Leading to Discontinuation	Upper gastrointestinal haemorrhage

A 74-year-old Japanese female was diagnosed with hepatocellular carcinoma on 26 Mar 2012. Significant medical history included chronic gastritis, chronic hepatitis C, constipation, esophageal varices, insomnia, muscle spasms, hepatic cirrhosis, blepharitis, osteoporosis, and sarcoidosis. Previous anticancer therapies included hepatectomy, high frequency ablation, radiotherapy to porta-hepatis lymph nodes, and transcatheter arterial chemoembolization. Prior and concomitant medications included, amlodipine, butenafine, carbohydrates w/potassium chloride/sodium, clostridium butyricum, dimeticone, domiphen, eszopiclone, falkamin, famotidine, furosemide, glucose injection, heparinoid, human albumin, iron, kanamycin, lactitol, lidocaine, magnesium oxide, neomycin, neurobion, omeprazole, paracetamol, pronase, rabeprazole, restamin cortizon, risedronic acid, risperidone, sennoside a+b, shakuyakukanzoto, sodium bicarbonate, sodium picosulfate, urea, ursodeoxycholic acid, and zopiclone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at left liver lobe; left upper lung lobe mass, and right mediastinal lymphadenopathy. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

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

On 09 Mar 2014 (Day 18), the subject experienced diarrhea (Grade 2). On 12 Mar 2014 (Day 21), the study drug was interrupted due to diarrhea and the subject was treated with clostridium butyricum. On 16 Mar 2014 (Day 25), the subject recovered from diarrhea. On 18 Mar 2014 (Day 27), the study drug was resumed at a reduced dose of 4 mg/day due to this event. The Investigator considered diarrhea nonserious and probably related to the study drug.

On 23 Apr 2014 (Day 63), the subject experienced diarrhea (Grade 1) and on 10 Jun 2014 (Day 111) the diarrhea worsened to Grade 2. The subject was treated with clostridium butyricum and the study drug dose was reduced to 4 mg every other day due to diarrhea. On 24 Jun 2014 (Day 125), the subject recovered from diarrhea. The Investigator considered diarrhea nonserious and probably related to the study drug.

On 18 Jul 2014 (Day 149), the subject experienced upper gastrointestinal hemorrhage (Grade 3). On 25 Jul 2014 (Day 156), the subject underwent upper gastrointestinal tract endoscopy which showed capillarectasia at the antrum of the stomach. Laboratory tests showed Hgb 97 g/dL (NR: 110 – 160), and platelets 94 x10^9/L (NR: 160 – 410). On 08 Aug 2014 (Day 170), the subject was hospitalized for further evaluation and the study drug was interrupted due to upper gastrointestinal hemorrhage. Repeat Hgb was 62 g/L (NR: 110 – 155) and the subject underwent a repeat endoscopy which showed capillarectasia and capillary hemorrhage at the antrum of the stomach. The subject was treated with glucose injection, iron, neurobion,

carbohydrates w/potassium chloride/sodium, human albumin, paracetamol, and was transfused with irradiated red blood cells "NISSEKI". On 15 Aug 2014 (Day 177), the upper gastrointestinal hemorrhage improved to Grade 1. On 18 Aug 2014 (Day 180), the subject experienced ascites (Grade 3) and underwent abdominal cavity drainage. On 18 Aug 2014 (Day 180), the subject was withdrawn from the study due to upper gastrointestinal hemorrhage. The subject received the last dose of the study drug on 07 Aug 2014 (Day 169). On 19 Aug 2014 (Day 181), the subject recovered from upper gastrointestinal hemorrhage and did not recover from ascites. The Investigator considered upper gastrointestinal hemorrhage serious and possibly related to the study drug and ascites nonserious and not related to the study drug but related to disease progression.

On 26 Aug 2014 (Day 188), the subject experienced anemia (Grade 3) with Hgb 66 g/L (NR: 110 – 160). On same day (Day 188), the subject received irradiated red blood cells, leukocytes reduced "NISSEKI". The subject was recovering from this event. The Investigator considered this event as nonserious and possibly related to study drug.

On 01 May 2015 (Day 436, 267 days after the last dose), the subject died due to disease progression.

Subject Number	12101007
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-003097
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Cholangitis (2x), Liver abscess

A 73-year-old Japanese male was diagnosed with hepatocellular carcinoma on 27 Dec 2010. Significant medical history included bile duct stenosis, nephrolithiasis, depression, diabetes mellitus, esophageal varices, hepatic steatosis, gastritis, hyperlipidemia, insomnia, and prostatomegaly. Previous anticancer therapies included transcatheter arterial chemoembolization and hepatectomy (2x). Prior and concomitant medications included alogliptin, amoxicillin, atorvastatin, augmentin, brotizolam, chlorphenamine, dexchlorpheniramine, difluprednate, ecabet, etizolam, felbinac, fexofenadine, flumazenil, glimepiride, hochuekkito, human insulin, imidafenacin, ketoprofen, lansoprazole, levofloxacin, lorazepam, loxoprofen, maalox, midazolam, mosapride, muhi-s, nafamostat, olopatadine, pethidine, piperacillin/tazobactam, retinol, silodosin, sulperazon, triazolam, ursodeoxycholic acid, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 06 Jan 2015 (Day 1), treatment with study drug was initiated.

On 07 Jan 2015 (Day 2), the subject experienced cholangitis (Grade 2). The subject was treated with piperacillin/tazobactam, loxoprofen, and levofloxacin. On 09 Jan 2015 (Day 4), the study drug was interrupted due to cholangitis. On 13 Jan 2015 (Day 8), body temperature was 38.7 °C and WBC 9.9 x10^9/L (NR: 4 – 9). Ultrasound of abdomen showed intrahepatic biliary dilatation. On 14 Jan 2015 (Day 9), the subject was hospitalized for cholangitis (Grade 3) with body temperature of 38.1 °C. The subject underwent endoscopic retrograde cholangiopancreatography (ERCP) which showed cholangitis from the upper common bile duct to the external area, severe stenosis, and yellowish-white colored bile with semi-solid substances suggesting biliary obstruction. The subject underwent implantation of endoscopic biliary stent. Bile culture revealed positive for Enterococcus faecium. On 18 Jan 2015 (Day 13), the subject recovered from cholangitis and was discharged from the hospital. On 03 Feb 2015 (Day 29), the study drug was resumed at the same dose. The Investigator considered cholangitis serious and not related to the study drug.

On 07 Feb 2015 (Day 33), the subject experienced cholangitis (Grade 2) and was treated with unspecified antibiotics in another clinic. On 09 Feb 2015 (Day 35), the study drug was interrupted due to cholangitis. On 10 Feb 2015 (Day 36), the subject was hospitalized for cholangitis (Grade 3). Laboratory tests showed total bilirubin 18.81 umol/L (NR: 3.42 – 15.39) and WBC 15.7 x10^9/L. The subject underwent ERCP to remove the endoscopic biliary stent and endoscopic nasobiliary drainage was implanted. On 13 Feb 2015 (Day 39), the subject complained that the subject was no longer able to tolerate the nasal tube used for endoscopic nasobiliary drainage. The subject underwent repeat ERCP for removal of the endoscopic nasobiliary drainage; a new endoscopic biliary stent for biliary drainage was implanted. The

subject was also treated with augmentin, amoxicillin, and piperacillin/tazobactam. On 16 Feb 2015 (Day 42), cholangitis improved to Grade 1 and the subject was discharged from the hospital. The subject did not recover from cholangitis. The Investigator considered cholangitis serious and not related to the study drug.

On 24 Feb 2015 (Day 50), the subject was readmitted for cholangitis (Grade 3). Laboratory tests showed WBC 8.9 x10^9/L. On 25 Feb 2015 (Day 51), the subject experienced liver abscess (Grade 3) and was treated with sulperazon and piperacillin/tazobactam. The study drug remained interrupted due to these events. The subject underwent ERCP and endoscopic nasobiliary drainage. On 26 Feb 2015 (Day 52), the bile culture showed a small amount of Klebsiella oxytoca bacteria. On 04 Mar 2015 (Day 58), the subject underwent liver puncture, resection of S3 liver segment, and percutaneous transhepatic abscess drainage. Cytology showed no malignant cells and repeat bile culture showed negative results. On 06 Mar 2015 (Day 60), a repeat ERCP was performed and a dilated balloon was placed at the bile duct stenosis region and two endoscopic nasobiliary drainages were implanted. On 11 Mar 2015 (Day 65), a biliary stent was placed at the abscess cavity and in the biliary duct. On 13 Mar 2015 (Day 67), the subject was recovering from cholangitis and liver abscess and was discharged from the hospital. On 18 Mar 2015 (Day 72), CT scan showed no worsening tendency of cholangitis and the liver abscess. On 08 Apr 2015 (Day 93), the severity of cholangitis and liver abscess improved to Grade 1. The subject was recovering from these events. On 23 Apr 2015 (Day 108), the study drug was resumed at the same dose. The Investigator considered cholangitis and liver abscess serious and not related to the study drug.

On 28 Apr 2015 (Day 113), the subject withdrew from the study by subject's choice and received the last dose of study drug on 26 Apr 2015 (Day 111).

Subject Number	12111012
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-002716
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Jaundice cholestatic, Renal failure, Hepatic failure
AE(s) Leading to Discontinuation	Jaundice cholestatic, Renal failure, Hepatic failure

A 79-year-old Japanese male was diagnosed with hepatocellular carcinoma in Dec 2002. Significant medical history included alcoholic liver disease, benign prostatic hyperplasia, cataract, chronic hepatitis alcohol, chronic hepatitis C, corneal disorder, hypertension, hyperthyroidism, hepatic cirrhosis, radiation-induced gastric ulcer, and type 2 diabetes mellitus. Previous anticancer therapies included radiotherapy to left liver lobe mass, high frequency radioablation (9x) and transcatheter arterial chemoembolization (7x). Prior and concomitant medications included alogliptin, alogliptin benzoate with pioglitazone hydrochloride, bisoprolol, brotizolam, chlorpromazine, choreito, dextromethorphan, dimeticone, esomeprazole, eufusol, flunitrazepam, fluorometholone, haloperidol, heparinoid, human albumin, hyaluronic acid, lidocaine, menatetrenone, nifedipine, olmesartan, oxetacaine, pioglitazone, piperacillin/tazobactam, ringer-lactatis, sodium picosulfate, solita-t1, sucralfate, tamsulosin, thiamazole, ultracet, and intravenous vitamedin. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 14 Oct 2014 (Day 1), treatment with study drug was initiated.

On 22 Dec 2014 (Day 70), the subject was hospitalized for cholestatic jaundice (Grade 4), hepatic failure (Grade 4), and renal failure (Grade 3). A CT scan showed intrahepatic biliary dilatation in the lateral segment of the left hepatic lobe. Laboratory tests showed AST 1320 U/L (NR: 9 – 38), ALT 1747 U/L (NR: 4 – 36), ALP 2063 U/L (NR: 115 – 359), total bilirubin 241.11 umol/L (NR: 5.13 – 22.23), BUN 18.3855 mmol/L (NR: 3.213 – 7.497), and creatinine 156.468 umol/L (NR: 53.04 – 106.08). The subject underwent cholangiostomy and was treated with eufusol, menatetrenone, piperacillin/tazobactam, human albumin, ringer-lactate, solita-t1. The study drug was withdrawn due to these events and the subject received the last dose of study drug on 22 Dec 2014 (Day 70). On 10 Jan 2015 (Day 89), the subject was discharged from the hospital. The subject was recovering from cholestatic jaundice and did not recover from hepatic failure and renal failure. The Investigator considered cholestatic jaundice, hepatic failure serious and possibly related to the study drug and related to disease progression; renal failure serious and possibly related to the study drug.

On 22 Jan 2015 (Day 101), subject was hospitalized again for cholestatic jaundice (Grade 3) and also experienced worsening of renal failure (Grade 4). Laboratory tests showed BUN 36.06 mmol/L (NR: 1.78 – 7.14), creatinine 451 umol/L (NR: 62 – 124), total bilirubin 292.6 umol/L (NR: 0 – 18.8), ALP 139 U/L (NR: 43 – 115), ALT 63 U/L (NR: 10 – 40), and AST 109 U/L (NR: 10 – 43). On the same day (Day 101), tumor response assessment

showed disease progression however, on 22 Dec 2014 (Day 70), the scans were initially assessed as not evaluable and later on, were reassessed on 27 Feb 2015 (Day 137) as progressive disease. The subject did not recover from renal failure and cholestatic jaundice. The Investigator considered cholestatic jaundice serious and possibly related to the study drug and related to disease progression; renal failure serious and possibly related to study drug.

On 08 Feb 2015 (Day 118, 48 days after the last dose), the subject died due to worsening hepatic and renal failure secondary to disease progression. Autopsy was not performed.

Subject Number	12111013
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-002012
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Renal impairment, Hepatic function abnormal, Portal vein thrombosis
AE(s) Leading to Discontinuation	Renal impairment, Hepatic function abnormal, Portal vein thrombosis

A 71-year-old Japanese male was diagnosed with hepatocellular carcinoma in Dec 2006. Significant medical history included alcoholic liver disease, diabetes mellitus, endoscopic variceal ligation, esophageal varices, hypertension, hepatic cirrhosis, back pain (lumbar), lung neoplasm malignant (primary right lung cancer), and thoracic aortic aneurysm. Previous anticancer therapies included hepatectomy (3x), transcatheter arterial chemoembolization, high frequency ablation, and radiotherapy to left liver lobe. Prior and concomitant medications included amlodipine, atenolol, carbohydrates w/potassium chloride/sodium, dimeticone, furosemide, glimepiride, glucose, heparin, heparinoid, human albumin, ketoprofen, lac-B granular powder n, lactulose, levocetirizine, lidocaine, losartan, menatetrenone, rabeprazole, sitagliptin, sodium chloride, solita-t, solita-t1, spironolactone, unspecified herbal and traditional medicine (ajoene), ursodeoxycholic acid, and warfarin. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right 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 31 Oct 2014 (Day 1), treatment with study drug was initiated.

On 04 Nov 2014 (Day 5), the subject experienced increased aspartate aminotransferase (Grade 1). On 13 Nov 2014 (Day 14), the subject experienced proteinuria (Grade 3), generalized edema (Grade 1), hematuria (Grade 1), hypertension (Grade 3) with BP 164/98 mmHg, and hypoalbuminemia (Grade 2). The subject was treated with spironolactone. Laboratory tests showed albumin 27 g/L (NR: 35 – 55), ALP 196 U/L (NR: 43 – 115), AST 60 U/L (NR: 10 – 43), total bilirubin 20.9 umol/L (NR: 1.7 – 18.8), and urine protein dipstick 3+. On 17 Nov 2014 (Day 18), 24h urine protein was 6.8986 g/24hr. On 18 Nov 2014 (Day 19), the study drug was interrupted due to proteinuria. On 21 Nov 2014 (Day 22), the subject recovered from hypertension and did not recover from increased aspartate aminotransferase, hypoalbuminemia, generalized edema, and hematuria. The subject was recovering from proteinuria. The Investigator considered increased aspartate aminotransferase, hypertension, hematuria, and hypoalbuminemia nonserious and possibly related to the study drug; generalized edema and proteinuria nonserious and probably related to the study drug.

On 21 Nov 2014 (Day 22), the subject was hospitalized for abnormal hepatic function (Grade 3), portal vein thrombosis (Grade 3), and renal impairment (Grade 2). The study drug remained interrupted due to these events. On the same day (Day 22), the subject also experienced hepatic encephalopathy (Grade 1), decreased appetite (Grade 1), rash (Grade 2), and increased aspartate aminotransferase worsened to Grade 3. Laboratory tests were done and showed total bilirubin 59.85 umol/L (NR: 5.13 – 22.23), albumin 24 g/L (NR: 39 – 49), ammonia 112.0823 umol/L (NR: 8.5668 – 47.1174), creatinine 194.48 umol/L (NR:53.04 – 106.08), BUN 14.0301 mmol/L

(NR: 3.213 – 7.497), ALP 577 U/L (NR: 115 – 359), AST 397 U/L (NR: 9 – 38), and ALT 368 U/L (NR: 4 – 36). On 24 Nov 2014 (Day 25), the severity of increased aspartate aminotransferase improved to Grade 1 and subject recovered from hepatic encephalopathy. A repeat abdominal ultrasound showed that portal blood flow was restored. On 25 Nov 2014 (Day 26), the subject recovered from renal impairment and decreased appetite. On 27 Nov 2014 (Day 28), the subject experienced ascites (Grade 2). The subject was treated with levocetirizine, solita-t1, glucose, albumin, menatetrenone, sodium chloride, lactulose, carbohydrates w/potassium chloride/sodium, spironolactone, furosemide, heparin, and warfarin. On 27 Nov 2014 (Day 28), the subject was withdrawn from the study due to abnormal hepatic function, renal impairment, and portal vein thrombosis. The subject received the last dose of the study drug on 17 Nov 2014 (Day 18). On 01 Dec 2014 (Day 32), the severity of proteinuria improved to Grade 1. On 05 Dec 2014 (Day 36), the subject recovered from hematuria. On 08 Dec 2014 (Day 39), tumor response assessment showed disease progression. On 13 Dec 2014 (Day 44), the subject recovered from generalized edema and on 04 Feb 2015 (Day 97), the subject recovered from abnormal hepatic function. On 25 Feb 2015 (Day 118), the subject recovered from portal vein thrombosis. The subject did not recover from increased aspartate aminotransferase, proteinuria, ascites, and rash. The Investigator considered abnormal hepatic function, portal vein thrombosis serious and possibly related to the study drug; renal impairment serious and probably related to the study drug; ascites nonserious and possibly related to the study drug and related to disease progression; increased aspartate aminotransferase, decreased appetite, hepatic encephalopathy nonserious and possibly related to the study drug; rash nonserious and not related to the study drug.

On 07 Apr 2015 (Day 159, 141 days after the last dose), the subject died due to disease progression. It was unknown if an autopsy was performed.

Subject Number	12121003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01456-CLI-JP
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Upper gastrointestinal haemorrhage

A 68-year-old Japanese female was diagnosed with hepatocellular carcinoma on 18 Dec 2013. Significant medical history included anemia, contrast media allergy, duodenal ulcer, gallbladder cancer, abnormal hepatic function, hepatitis B, and hepatic cirrhosis. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included falkamin, goshajinkigan, l-carbocysteine, omeprazole, paracetamol, polaprezinc, spironolactone, tiotropium, and urea. At Screening, tumor assessments of target/non-target lesions via MRI showed lesion at right lobe of liver, and CT scan showed masses at left upper and lower lobe of lung and multiple sites of lung. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 12 Feb 2014 (Day 6), the subject experienced upper abdominal pain (Grade 1), decreased appetite (Grade 1), diarrhea (Grade 1), and malaise (Grade 1). Treatment included paracetamol. On 13 Feb 2014 (Day 7), the subject recovered from diarrhea. On 14 Feb 2014 (Day 8), laboratory tests showed Hgb level 114 g/L (NR: 113 – 149) and platelet count 84 x10^9/L (NR: 142 – 298). On 15 Feb 2014 (Day 9), the subject was hospitalized for upper gastrointestinal hemorrhage (Grade 2) with symptoms of black stool. On 19 Feb 2014 (Day 13) the study drug was interrupted. The subject underwent upper gastrointestinal tract endoscopy which showed vasodilatation in the gastric antrum and adherence of small blood clotting. The subject recovered from upper gastrointestinal hemorrhage. On 20 Feb 2014 (Day 14), the subject was discharged from the hospital. On 24 Feb 2014 (Day 18), the subject recovered from upper abdominal pain, decreased appetite, and malaise and the study drug was resumed at reduced dose of 8 mg/day due to upper gastrointestinal hemorrhage. The Investigator considered upper gastrointestinal hemorrhage serious and probably related to study drug; upper abdominal pain, decreased appetite, diarrhea, malaise nonserious and probably related to study drug.

On 27 Feb 2014 (Day 21), the subject experienced upper abdominal pain (Grade 2). Treatment included paracetamol. On the same day (Day 21), the study drug was interrupted due to the event. On 01 Mar 2014 (Day 23), the event improved to Grade 1 and the study drug was resumed at reduced dose of 4 mg/day due to this event. The subject did not recover from this event. The Investigator considered upper abdominal pain nonserious and probably related to the study drug.

On 31 Mar 2014 (Day 53), tumor response assessment showed disease progression. On 04 Apr 2014 (Day 57), the subject was withdrawn from the study due to disease progression and received the last dose on 03 Apr 2014 (Day 56).