付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	12061006
Study ID	HOPE303
Manufacturer's Control Number	E7080-00962-CLI-JP
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Lipase increased

A 65-year-old Japanese female was diagnosed with Stage TxNxMx papillary thyroid cancer (PTC) in 1977. In 2003, the subject was diagnosed with metastatic disease. The last date of disease progression was on 21 Aug 2012. Significant medical history included left lobe of thyroid gland resection, left neck dissection, survival total thyroidectomy, bilateral neck dissection, left axillary lymphadenectomy, bilateral lymph node dissection, hypertension, diabetes mellitus, insomnia, anxiety disorder, secondary hypothyroidism, cancer pain, and rhinitis seasonal. At Screening, tumor assessments of target/non-target lesions via CT scan showed adenopathy in right and left axillary lymph node, right paratracheal lymph node,mass in middle lobe of right lung and mass in lower lobe of left lung. The subject received prior curative radio iodine therapy. Concomitant medications included metformin, brotizolam, lorazepam, loxoprofen, paracetamol, ketoprofen, olopatadine, aczym, metoclopramide, loperamide, carvedilol, candesartan, amlodipine and levothyroxine. ECOG performance status was 1 at screening.

On 05 Sep 20[redacted] (Day 1), treatment with study drug was initiated.

On 19 Sep 20[redacted] (Day 15), the subject had increased lipase (375 U/L(NR 0-120 U/L)(Grade 4) and the study drug was interrupted.
On 24 Sep 20[redacted] (Day 20), the lipase level improved to 127 U/L (Grade 3). On 26 Sep 20[redacted] (Day 22), the lipase level improved to 91 U/L (Grade 2). On 28 Sep 20[redacted] (Day 24), the repeat lipase level improved to 78 U/L (Grade 1). The Investigator assessed the event of increased lipase as serious and possibly related to study drug. The study drug was resumed on 29 Sep 20[redacted] (Day 25) at a reduced dose of 20 mg due to this event.

On 10 Oct 20[redacted] (Day 36), the subject underwent abdominal ultrasound which showed no pancreatitis and on 17 Oct 20[redacted] (Day 43), lipase was 118 u/L. On 21 Nov 20[redacted] (Day 78), the study drug at a reduced to 14 mg due to lipase increased (Grade 2). On 13 Feb 翌年* (Day 162), the study drug was reduced to 10 mg due to proteinuria (Grade 2).

After the unblinding, the subject received lenvatinib and treatment. The subject remained in the study at the time of data cut-off.

*新薬承認情報提供時に置き換え

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	13011005
Study ID	HOPE303
Manufacturer's Control Number	E7080-00868-CLI-AU
Randomized treatment	Lenvatinib 24 mg QD
Death due to PD	Yes
Non-Fatal SAE(s)	Wound secretion, Osteoarthritis

A 65-year-old White female was diagnosed with Stage III T3N0Mx metastatic poorly differentiated papillary thyroid cancer (PTC) on 20 Aug 2010. The last date of disease progression was on 12 Sep 2011. Significant medical history included tonsillectomy, appendectomy, surgery on retroverted uterus, ectopic pregnancy, salpingo-oophorectomy, osteotomy left knee, osteotomy right knee, hysterectomy, total left knee replacement, fractured left wrist, dyslipidaemia, rosacea, hypertension, blood uric acid increased, biopsy thyroid gland, total thyroidectomy, hypothyroidism, osteoporosis, chilblains both hands, oedema peripheral, laparoscopy, varicose veins stripping of left leg, osteoarthritis right knee, and raynaud's phenomenon. At Screening, tumor assessments of target/non-target lesions via CT scan showed mass in upper, middle and lower lobe of right lung, mass in upper, lower, and lingular lobe of left lung, and mass in left lateral, right lower, left medial/quadrate, caudate and right lobe of liver. The subject had received prior curative radio iodine therapy. Concomitant medications included atorvastatin, vitamin-D, allopurinol, estrogens conjugated, ibuprofen, loperamide, biotene, naproxen, nystatin, lidocaine, glycerol, triamcinolone, paracetamol, loratadine, other therapeutic products, influenza vaccine, escitalopram, ropivacaine, cefalotin, enoxaparin, promethazine, bisacodyl, panadeine Co, lactulose, rivaroxaban, cefalexin, vancomycin, diclofenac, silybum marianum (herbal remedy), gezor and levothyroxine. ECOG performance status was 0 at screening.

On 20 Sep 20[redacted] (Day 1), treatment with study drug was initiated. On 02 Apr 翌年* (Day 196), the study drug was interrupted and resumed at a reduced dose of 20 mg on 06 Apr 20[redacted] (Day 200) due to blisters on heels (Grade 2).

On 05 Jul 20[redacted] (Day 290), the study drug was interrupted due to worsening of right knee pain (Grade 2). On 12 Jul 20[redacted] (Day 297), the subject was hospitalized for worsening osteoarthritis (Grade 2) of right knee. On the same day, she underwent right knee replacement surgery. She was treated with ropivacaine, paracetamol, cefalotin, enoxaparin, and panadeine Co. On 18 Jul 20[redacted] (Day 303), the subject was recovered from the osteoarthritis and discharged. The Investigator assessed the event of osteoarthritis as serious and not related to study drug. The study drug was restarted on 24 Jul 20[redacted] (Day 309).

On 31 Aug 20[redacted] (Day 347), the subject was hospitalized for wound secretion (Grade 2) of right knee. She was treated with vancomycin, paracetamol and cephalexin. The study drug was interrupted on 01 Sep 20[redacted] (Day 348) due to wound secretion. On 16 Sep 20[redacted] (Day 363), the subject was recovered from the event. The Investigator assessed wound secretion as serious and not related to study drug. The study drug was resumed on 23 Sep 20[redacted] (Day 370).

The subject received the last dose of study drug on 13 Nov 20[redacted] (Day 421). Tumor assessment showed disease progression by independent radiological review.

On 20 Jul 翌々年* (Day 670, 249 days after the last dose), the subject died due to disease

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progression. After the unblinding, the subject was found to be randomized to lenvatinib.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	13021004
Study ID	HOPE303
Manufacturer's Control Number	E7080-00689-CLI-AU
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Hypertension

A 66-year-old White female was diagnosed with Stage IVA T4aN0M0 hurthle cell follicular thyroid cancer (FTC) on 20 Dec 2007. On 25 Aug 2008, the subject was diagnosed with metastatic disease. The last date of disease progression was on 09 Jan 2012. Significant medical history included oropharyngeal squamous cell carcinoma, Dukes B colorectal cancer, osteonecrosis of jaw, meniere's post XRT, palpitations related to thyroxine treatment, dyspnoea exertional, chest discomfort, allergy to morphine-itch, menopausal symptoms, thyroidectomy, diverticulum, allergy to vaccine (Tettox-oedema), and vaginal haemorrhage. At Screening, tumor assessments of target/non-target lesions via CT scan showed mass in upper and lower lobe of right lung and innumerable lung mets. The subject received prior curative radiotherapy to tonsil, curative radiotherapy to upper cervical, lower cervical, prior curative and palliative radio iodine therapy. Previous anti-cancer therapy included capecitabine. Concomitant medications included estrogens conjugated, medroxyprogesterone, betahistine, acetylsalicylic acid, metoprolol, paracetamol, prochlorperazine, loperamide, mycolog, domperidone, ranitidine, esomeprazole, haloperidol, ramipril, hydralazine, Prazosin, amlodipine, hydrochlorothiazide, telmisartan, and levothyroxine. ECOG performance status was 0 at screening.

On 19 Mar 20[redacted] (Day 1), treatment with study drug was initiated.

On 28 Mar 20[redacted] (Day 10), the subject experienced hypertension (Grade 3) with a headache (Grade 2). Blood pressure readings were recorded as 130/70 and 120/70 mmHg. She was treated with ramipril. On 31 Mar 20[redacted] (Day 13), the subject was hospitalized due to worsening hypertension (Grade 3) with severe headache (Grade 2), visual disturbance (Grade 1) peripheral and facial edema (Grade 1), proteinuria (Grade 2), and confusion (Grade 1). BP was recorded as 221/105 mmHg. Treatment included metoprolol, hydralazine, fentanyl and prazosin. On 01 Apr 20[redacted] (Day 14), the study drug was interrupted, and the subject was discharged from the hospital. The Investigator assessed hypertension (Grade 3) as serious and probably related to study drug. On 12 Apr 20[redacted] (Day 25), the study drug was resumed at a reduced dose of 20 mg due to this event.

After the unblinding, the subject was found to be randomized to lenvatinib. The subject remained in the study at the time of data cut-off.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	13031002
Study ID	HOPE303
Manufacturer's Control Number	E7080-00537-CLI-AU, E7080-01046-CLI-AU, E7080-01226-CLI-AU
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Renal impairment, Diarrhoea

A 71-year-old White female was diagnosed with Stage IVC T4aM1 Hurthle cell follicular thyroid cancer (FTC) on 09 May 2007. On 25 May 2007, the subject was diagnosed with additional metastatic disease. The last date of disease progression was on 29 Sep 2011. Significant medical history included hypertension, gout, abdominal hernia repair, cataract surgery, near total thyroidectomy, angle closure glaucoma, cholelithiasis, sigmoid diverticulosis, right hearing impairment, female sterilization, appendectomy, mole on left ear lobe, chronic mild intermittent thrombocytopenia, and cataract operation. At Screening, tumor assessments of target/non-target lesions via CT scan showed mass in upper, lingular (medial lingula), lower (inferior lingula) lobe of left lung; and middle and lower lobe of right lung. The subject received previous curative radio iodine therapy. Concomitant medications included sodium chloride, potassium, oxycodone, cefalexin, trimethoprim, influenza vaccine, enoxaparin, metoclopramide, vitamins, thiamine, timolol, candesartan, candesartan w/hydrochlorothiazide, and levothyroxine. ECOG performance status was 0 at screening.

On 20 Oct 20[redacted] (Day 1), treatment with study drug was initiated.

On 25 Oct 20[redacted] (Day 6), the subject was hospitalized for acute renal impairment (Grade 2) with urinary tract infection (Grade 2), fatigue (Grade 1), decreased appetite (Grade 1), oropharyngeal pain (Grade 1), dysphonia (Grade 1), and general malaise. The study drug was interrupted due to renal impairment. The lab findings included serum creatinine of 211 mmol/L (NR: 45-80), estimated GFR 20%, serum potassium 3.2 mmol/L (NR: 3.5-5.0) and urea 13.5 mmol/L (NR: 3.0-8.0). Post void bladder scan revealed 163 ml urine in bladder. Urine cultures showed greater than 100 x10^6 E. Coli per litre. An ultrasound of urinary tract performed on 26 Oct 20[redacted] (Day 7) which confirmed acute renal impairment. She was treated with sodium chloride, potassium, oxycodone, oral cefalexin and Atacand plus (candesartan cilexetil and hydrochlorothiazide tablets). .On 27 Oct 20[redacted] (Day 8), the subject recovered from the event and discharged from the hospital. The Investigator assessed renal impairment as serious and possibly related to study drug. The Investigator assessed urinary tract infection (Grade 2), fatigue (Grade 1), decreased appetite (Grade 1), oropharyngeal pain (Grade 1) and dysphonia (Grade 1) as non-serous and possibly related to study drug. The study drug was resumed on 03 Nov 20[redacted] (Day 15).

On 10 Nov 20[redacted] (Day 22) study drug was reduced to 20 mg due to headache (Grade 2).

On 12 Nov 翌年* (Day 390), the subject was hospitalized for acute renal impairment (Grade 3) with vomiting, lethargy, dehydration and diarrhea (Grade 1). Creatinine was 213 umol/L (NR: 45-80),, urea was 25.8 mmol/L (NR: 3.0-8.0) and low eGFR was 20 mL/min, . The study drug was interrupted on the same day due to renal impairment. She received intravenous hydration, and enoxaparin. On 22 Nov 20[redacted] (Day 400), the subject recovered from the acute renal impairment. The Investigator assessed renal impairment as serious and not related to study drug. The study drug was resumed with a dose of 14 mg on 22 Nov 20[redacted] (Day 400).

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On 08 Apr翌々年* (Day 537), the subject experienced diarrhea (Grade 1) which worsened to grade 3 on 17 Apr 20[redacted] (Day 546) where the subject was hospitalized. The subject experienced vomiting (Grade 1) which recovered after two days with treatment given with metoclopromide. The study drug was interrupted due to diarrhea and the subject was treated with intravenous hydration. The subject was discharged on 20 Apr 20[redacted] (Day 549) and recovered from the event on 23 Apr 20[redacted] (Day 552). The study drug was restarted on 25 Apr 20[redacted] (Day 554) with a reduced dose of 10 mg. The Investigator assessed diarrhea as serious, vomiting as non-serious and both were possibly related to study drug. After the unblinding, the subject was found to be randomized to lenvatinib. The subject remained on study at the time of data cut-off.

*新薬承認情報提供時に置き換え

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	13031005
Study ID	HOPE303
Manufacturer's Control Number	E7080-00625-CLI-AU
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Ischaemic stroke

A 72-year-old White female was diagnosed with Stage IVA T4aN0M0 Follicular thyroid cancer (FTC) on 01 Sep 1988. On 09 Nov 2004, the subject was diagnosed with metastatic disease. The last date of disease progression was on 21 Jan 2011. Significant medical history included hypertension, back pain, gastritis, atrial fibrillation, hypocalcaemia, laryngectomy, osteoporosis - corticosteroid induced, oral candidiasis, insomnia, tracheostomy, vancomycin resistant enterococcal (VRE) infection - rectal, curettage and filling fixation with per articular zimmer Plate, partial pharyngectomy, right hemithyroidectomy, urinary tract infection, haematuria, atrioventricular block first degree, bundle branch block left, strap muscle flap repair, completion thyroidectomy, musculoskeletal chest pain, and vaginal prolapse. At Screening, tumor assessments of target/non-target lesions via CT scan showed left lower lobe lung mass, right lower lobe lung mass, and right upper lobe lung mass. The subject received prior palliative radiotherapy to the pharyngeal and laryngeal area, to right leg, to thoracic area, to left pelvic bone. and prior curative radio iodine therapy. Concomitant medications included calcitriol, esomeprazole, amphotericin-B, glyceryl trinitrate, bepanthen, calcium carbonate, diazepam, trimethoprim, enoxaparin, atorvastatin, coloxyl with senna (herbal remedy), lactulose, acetylsalicylic acid, magnesium, sodium chloride, paracetamol, bupivacaine, triamcinolone, hydroxyzine, furosemide, digoxin, salicylic acid preparations, cefalexin, venlafaxine, propolis, dabigatran, nystatin, povidone-iodine, potassium, urea, asimina triloba (herbal remedy), perindopril, metoprolol, amlodipine, and levothyroxine. ECOG performance status was 1 at screening.

On 29 Nov 20[redacted] (Day 1), treatment with study drug was initiated.

On 28 Jan 翌年* (Day 61), the subject experienced chest pain and dizziness. Her blood pressure was 227/120 mmHg, which later reduced to 180/112 mmHg after administration of glyceryl nitrate. She was admitted to the hospital for moderate ischemic stroke (Grade 2) with left facial droop and mild left hemiparesis affecting left arm. The study drug was interrupted on the same day due to ischemic stroke. CT scan of brain showed focal hypodensities in anterior limb of the right internal capsule, right caudate and the right corona radiata. Electrocardiogram (ECG) showed sinus rhythm with first degree block. Treatment included enoxaparin, atorvastatin, acetylsalicylic acid, and magnesium. On 10 Feb 20[redacted] (Day 74), the subject recovered from the ischemic stroke and discharged from the hospital. The Investigator assessed ischemic stroke as serious and possibly related to study drug. The study drug was resumed on 09 Feb 20[redacted] (Day 73) with a reduced dose of 20 mg.

After the unblinding, the subject was found to be randomized to lenvatinib. The subject remained in the study at the time of data cut-off.

*新薬承認情報提供時に置き換え

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	13031006
Study ID	HOPE303
Manufacturer's Control Number	E7080-00808-CLI-AU, E7080-00972-CLI-AU
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Vocal cord paralysis, Pulmonary embolism, Pleural haemorrhage

A 68-year-old White male was diagnosed with Stage IVA T4aN1bM0 Follicular thyroid cancer (FTC) on 01 Dec 2004. On 27 Nov 2009, the subject was diagnosed with metastatic disease. The last date of disease progression was on 23 Feb 2012. Significant medical history included bronchiectasis, lung-left lower lobectomy, lung- right partial lobectomy, asthma, myocardial infarction, coronary arterial stent insertion, bone graft - right leg, thyroidectomy, dysphonia, deafness, oropharyngeal pain, fatigue, shoulder pain, decreased appetite, dysphagia, myocardial ischaemia, and hypercholesterolaemia. At Screening, tumor assessments of target/non-target lesions via CT scan showed right paratracheal adenopathy, left hilar adenopathy, left lower lobe lung mass, right lower lobe lung mass, left upper lobe lung mass, right middle lobe lung mass, and right lower lobe lung mass. The subject received prior palliative radiotherapy to trunk skin, left humerus, right chest wall, left femur, head/neck skin, left lingular lobe, prior palliative radio iodine therapy and previous anti-cancer therapy was oral fibroblast growth factor inhibitor. Concomitant medications included seretide, acetylsalicylic acid, rosuvastatin, amoxicillin w/clavulanate potassium, nystatin, benzydamine, salbutamol, paracetamol, cefalexin, Progastrit dexamethasone, enoxaparin, antibiotics, warfarin, coloxyl with senna (herbal remedy), lactulose, ceftriaxone, metoclopramide, sodium chloride, oxycodone, morphine, targin, meropenem, salbutamol, prednisolone, bromhexine, prothrombinex, vitamin-K, furosemide, temazepam, pansoral, spektramox, cefuroxime, magnesium, protuss, panadeine co, roxithromycin, ciprofloxacin, amoxicillin, methylprednisolone, metoprolol, perindopril and levothyroxine. ECOG performance status was 1 at screening.

On 08 Mar 20[redacted] (Day 1), treatment with study drug was initiated. On 19 Apr 20[redacted] (Day 43) study drug was reduced to 20 mg due to oral mucositis (Grade 2). On 03 May 20[redacted] (Day 57) study drug was interrupted and resumed on 10 May 20[redacted] (Day 64) at a reduced dose of 14 mg due worsening dysphagia (Grade 2).

On 18 Jun 20[redacted] (Day 103), the subject was hospitalized for right sided lower throat discomfort. Laryngoscopy revealed right vocal cord paralysis (Grade 2). The subject underwent vox-implant as corrective treatment and was treated with hyaluronic acid, progastrit, cefalexin, dexamethasone, salbutamol, paracetamol, and pansoral. On 19 Jun 20[redacted] (Day 104), the subject was discharged from the hospital. On 20 Sep 20[redacted] (Day 197), the event of vocal cord paralysis was recovered with sequelae. The Investigator assessed the event as serious and possibly related to study drug. The study drug dose was not changed.

On 12 Jul 20[redacted] (Day 127) study drug was interrupted due to worsening of fatigue (Grade 2), worsening sore throat (Grade 2), worsening dysphagia (Grade 2), and hoarse voice (Grade 2). On 18 Jul 20[redacted] (Day 133) study drug was resumed at a reduced dose of 10 mg due to worsening dysphagia (Grade 2) and 'ropey saliva' (Grade 2).

On 23 Aug 20[redacted], (Day 169), the subject went for routine visit and was hospitalized due to

pulmonary embolism (Grade 3) in the left lower lobar artery. The embolus was noted during routine CT scan for the study in which CT pulmonary angiogram (CTPA) was performed also as per the request of the subject's respiratory physician. The subject was treated with warfarin, acetylsalicylic acid, and enoxaparin. The study drug was interrupted on 24 Aug 20[redacted] (Day 170) due to the event of pulmonary embolism. The subject was discharged from the hospital on 24 Aug 20[redacted] (Day 170). On 27 Aug 20[redacted] (Day 173), subject was recovered from the event of pulmonary embolism. The Investigator assessed the event, pulmonary embolism as serious and possibly related to study drug. The study drug remained interrupted.

On 26 Aug 20[redacted] (Day 172), the subject experienced pleural hemorrhage (Grade 3) with symptoms of increasing shortness of breath and was re-admitted to the hospital on 29 Aug 20[redacted] (Day 175). On 30 Aug 20[redacted] (Day 176), a right video assisted thoracic surgery was performed to drain the hemothorax. Treatment included sodium chloride, oxycodone, morphine, Targin, paracetamol, prednisolone, bromhexine, prothrombinex, vitamin K, and furosemide. On 05 Sep 20[redacted] (Day 182), the subject was recovered from pleural hemorrhage and discharged from the hospital. The Investigator assessed the pleural hemorrhage as serious and not related to study drug. The study drug was resumed on 06 Sep 20[redacted] (Day 183).

After the unblinding, the subject was found to be randomized to lenvatinib. The subject remained on the study at the time of data cut off.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	13031010
Study ID	HOPE303
Manufacturer's Control Number	E7080-01085-CLI-AU
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Pneumatosis intestinalis

A 64-year-old White female was diagnosed with Stage IVA T4aN1aM0 follicular variant of papillary thyroid cancer (PTC) on 05 Mar 2009. On 09 Aug 2010, the subject was diagnosed with metastatic disease. The last date of disease progression was on 23 Aug 2012. Significant medical history included left hemithyroidectomy & lymph node clearance, left vocal nerve palsy, right completion thyroidectomy, dysphonia, cholangitis, bilateral varicose vein repair, hernia repair, chronic pain syndrome, pethidine dependence, drug allergy – morphine, oxycontin, sulphur drugs and penicillin, cholecystectomy, ischaemic bowel resection, bile duct obstruction, fracture right leg, abdominal pain, femoral hernia repair, urinary incontinence, incisional hernia, abdominal adhesions, recurrent bowel obstructions, anxiety, depression, superficial bilateral varicose veins, abdominal operation, pruritus-associated with fentanyl use, and right ovarian cyst. At Screening, tumor assessments of target/non-target lesions via CT scan showed mass in right lower lobe and left upper lobe of lung. The subject received prior curative radio iodine therapy. Concomitant medications included vitamins, hyoscine, fish oil, metoclopramide, oxycodone, fentanyl, bisacodyl, other cold preparations, panadeine co, cefalexin, budesonide, senna alexandrina (herbal remedy), fexofenadine, morphine, ceftriaxone, metronidazole, paracetamol, enoxaparin, vancomycin, Mylanta, tramadol, microlax, delcoprep, enemas, prucalopride, targin, coloxyl with senna (herbal remedy), movicol, roxithromycin, benzydamine, cefaclor, influenza vaccine, terbinafine, ketoconazole, betamethasone, clotrimazole, chloramphenicol, mirtazapine, ramipril and levothyroxine. ECOG performance status was 1 at screening.

On 11 Sep 20[redacted] (Day 1), treatment with study drug was initiated. On 06 Oct 20[redacted] (Day 26) the subject received study drug at a reduced dose of 20 mg due to the events of hypertension (Grade 2), lethargy (Grade 2), anorexia (Grade 2), and nausea (Grade 2). On 08 Nov 20[redacted] (Day 59) study drug was interrupted and resumed on 15 Nov 20[redacted] (Day66) at a reduced dose of 14 mg due to the event of gastric irritation (Grade 2).

On 30 Nov 20[redacted] (Day 81), the subject experienced severe epigastric pain and general abdominal tenderness and went for checkup. Morphine with IV saline and metoclopramide were given and subject was transferred to local hospital. Abdominal x-ray showed gas in bowel wall. CT abdomen revealed gross intramural gas within a long length of distal ileum and caecal pole, consistent with ischaemia and a perforation evidenced by small locules of extraluminal gas within the right iliac fossa. On 01 Dec 20[redacted] (Day 82), a laparotomy was performed and subject was diagnosed with pneumatosis intestinalis (Grade 3). The study drug was interrupted on the same day (Day 82) due to pneumatosis intestinalis. On 02 Dec 20[redacted] (Day 83), another laparotomy was performed and intra-operative findings revealed a healthy looking small and large bowel. The subject was treated with metoclopramide, intravenous saline of morphine, Mylanta, ceftriaxone, metronidazole, paracetamol enoxaparin, vancomycin and tramadol. On 08 Dec 20[redacted] (Day 89), the subject recovered from the pneumatosis intestinalis and discharged from the hospital. The Investigator assessed the event of pneumatosis intestinalis as serious and not related to study drug. The study drug was resumed on 27 Dec 20[redacted] (Day 108).

After the unblinding, the subject was found to be randomized to lenvatinib. The subject remained in the study at the time of data cut-off.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	14011002
Study ID	HOPE303
Manufacturer's Control Number	E7080-01102-CLI-FR
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Testicular abscess
AEs leading to Discontinuation	Glossitis, Asthenia

A 54-year-old White male was diagnosed with Stage IVA T4aN1bM0 poorly differentiated papillary thyroid cancer (PTC) on 05 May 2009. On 26 Sep 2011, the subject was diagnosed with metastatic disease. The last date of disease progression was on 07 Feb 2012. Significant medical history included nephrolithiasis, diabetes mellitus, hypercholesterolaemia, hypertension, right carpal duct surgery, sleep apnoea syndrome, hypertensive cardiomyopathy, total thyroidectomy, cervical lymph nodes exeresis, hypothyroidism, bilateral jugulo carotidian lymph nodes exeresis, left thyroidectomy field malignant tumor surgery, and nicotine dependence. At Screening, tumor assessments of target/non-target lesions via CT scan showed left lingular lobe lung mass, right lower lobe lung mass, left upper lobe lung mass, middle or lower cervical (left) adenopathy and left hilar adenopathy. The subject received prior palliative radiotherapy to the upper cervical lymph node and curative radio iodine therapy. Concomitant medications included rosuvastatin, escitalopram, metformin, insulin aspart, insulin glargine, esomeprazole, sucralfate, hyaluronic acid, anethole trithione, paracetamol, miconazole, amphotericin-B, Eludril (chlorhexidine/chlorobutanol), aciclovir, amoxicillin, dexeryl, dexpanthenol, lidocaine, salbutamol, beclometasone, cefuroxime, rabeprazole, pristinamycin, calcium carbonate, methylthioninium, furosemide, Coveram (perindopril/amlodipine), Nebicard-H (nebivolol/hydrochlorothiazide), urapidil, and levothyroxine. ECOG performance status was 0 at screening.

On 28 Feb 20[redacted] (Day 1), treatment with study drug was initiated. On 14 Mar 2012 (Day 16), the subject experienced glossitis (Grade 1). On 22 May 20[redacted] (Day 85), the subject experienced asthenia (Grade 1). On 14 Aug 20[redacted] (Day 169), glossitis worsened to Grade 2. On 15 Aug 20[redacted] (Day 170), study drug was reduced to 14 mg due to glossitis (Grade 2). On 28 Aug 20[redacted] (Day 183), glossitis improved to Grade 1.

On 16 Dec 20[redacted] (Day 293), the subject was hospitalized for testicular abscess (Grade 3). Treatment included pristinamycin and surgical drainage was performed. On 20 Dec 20[redacted] (Day 297), the subject recovered from the testicular abscess and discharged from the hospital. .The Investigator assessed the event of testicular abscess serious and not related to study drug. No action was taken with study drug

On 13 Mar 翌年* (Day 380), study drug was interrupted due to asthenia (Grade 2) and stomatitis (Grade 2). On 26 Mar 20[redacted] (Day 393), asthenia improved to Grade 1. On 10 Apr 20[redacted] (Day 408), study drug was restarted at a reduced dose of 10 mg. On 23 Apr 20[redacted] (Day 421), glossitis worsened to Grade 2, asthenia worsened to Grade 3, and study drug was withdrawn. The subject received the last dose of study drug on 23 Apr 20[redacted] (Day 421) due to glossitis and asthenia. On 21 May 20[redacted] (Day 449), the subject was recovered from glossitis (Grade 2) and the event of asthenia was reported as not recovered. The Investigator assessed the events of glossitis (Grade 2) and asthenia (Grade 3) non-serious and probably related to study drug.

*新薬承認情報提供時に置き換え

After the unblinding, the subject was found to be randomized to lenvatinib.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	14021004
Study ID	HOPE303
Manufacturer's Control Number	E7080-01258-CLI-FR
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Pathological fracture

A 55-year-old White male was diagnosed with Stage IVC TxNxM1 metastatic follicular variant papillary thyroid cancer (PTC) on 14 Nov 2006. The last date of disease progression was on 20 Jan 2012. Significant medical history included hypertension, back pain, hypothyroidism, total thyroidectomy, depression, iliac cementoplasty, and right condyle cementoplasty. At Screening, tumor assessments of target/non-target lesions via CT scan showed left mediastinal thoracic adenopathy, and multiple lung masses. The subject received prior palliative radiotherapy to pelvic bone and prior palliative radio iodine therapy. Concomitant medications included esomeprazole, paroxetine, metopimazine, loperamide, Diprospan, Movicol, morphine, ketoprofen, fentanyl, Spasfon, ondansetron, cortivazol, alprazolam, pregabalin, candesartan w/hydrochlorothiazide, candesartan, and levothyroxine. ECOG performance status was 1 at screening.

On 15 May 20[redacted] (Day 1), treatment with study drug was initiated. On 06 Jun 20[redacted] (Day 23) the study drug was reduced to 20 mg due to arthralgia (Grade 2). On 13 Jun 20[redacted] (Day 30) study drug was further reduced to 14 mg due to arthralgia (Grade 2). On 02 Jul 20[redacted] (Day 49), study drug was reduced dose to 10 mg due to nausea (Grade 2), fatigue (Grade 3), and arthralgia (Grade 2).

On 05 Apr 翌年* (Day 326), the study drug was interrupted due to diarrhea (Grade 3). On 09 Apr 20[redacted] (Day 330), the subject was hospitalized due to pathologic fracture of femoral bone (Grade 3) and underwent resection of femoral bone the following day. On 26 Apr 20[redacted] (Day 347), the subject recovered from the event of pathologic fracture of femoral bone. The Investigator assessed the event of pathological fracture of femoral bone as serious and not related to the study drug. On 15 May 20[redacted] (Day 366), the study drug was resumed.

After the unblinding, the subject was found to be randomized to lenvatinib. The subject remained in the study at the time of data cut-off.

*新薬承認情報提供時に置き換え

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	14021007
Study ID	HOPE303
Manufacturer's Control Number	E7080-01152-CLI-FR
Randomized treatment	Lenvatinib 24 mg QD
Death due to PD	Yes
Non-Fatal SAE	Nephrotic syndrome

A 61-year-old White female was diagnosed with Stage I T4aN0M0 poorly differentiated papillary thyroid cancer (PTC) on 21 May 1996. On 27 Oct 2005, the subject was diagnosed with metastatic disease. The last date of disease progression was on 10 Feb 2012. Significant medical history included thyroidectomy, hypothyroidism, anxiety, left pulmonary metastasis exeresis, and right pulmonary metastasis resection. At Screening, tumor assessments of target/non-target lesions via CT scan showed left upper lobe lung mass, right lower lobe lung masses, and a peritoneal/omental mass. The subject received prior palliative and curative radiotherapy to brain, prophylactic radiotherapy to thyroid and prior palliative radio iodine therapy. Prior anti-cancer therapy included cisplatin and doxorubicin. Concomitant medications included alprazolam, escitalopram, alfacalcidol, calcium carbonate, fluconazole, macrogol, Titanoreine xerial, diflucortolone, urea, emollients and protectives, nicardipine, nebivolol, and levothyroxine. ECOG performance status was 1 at screening.

On 18 Jul 20[redacted] (Day 1), treatment with study drug was initiated. On 23 Nov 20[redacted] (Day 129) study drug was reduced to 20 mg due to hand foot syndrome (Grade 3). The subject received the last dose of study drug on 07 Jan 翌年* (Day 174). Tumor assessment showed disease progression by independent radiological review.

On 07 Jan 20[redacted] (Day 174), the subject's albumin was 20 g/L (NR 33-49 g/L) and urine protein was 3+. On 08 Jan 20[redacted] (Day 175) the subject was diagnosed with nephrotic syndrome (Grade 2). On 04 Feb 20[redacted] (Day 202), albumin was 12 g/L and urine protein 3+ and 0.17 g/24H urine protein. The event was not recovered. On 19 Feb 20[redacted] (Day 217, 43 days after the last dose), the subject died due to disease progression. The Investigator assessed the event of nephrotic syndrome as medically significant and probably related to the study drug.

After the unblinding, the subject was found to be randomized to lenvatinib.

*新薬承認情報提供時に置き換え

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	14021013
Study ID	HOPE303
Manufacturer's Control Number	E7080-01128-CLI-FR, E7080-01259-CLI-FR
Randomized treatment	Lenvatinib 24 mg QD
Death due to PD	Yes
Non-Fatal SAEs	Constipation, General physical health deterioration

A 70-year-old White male was diagnosed with Stage IVA T4aN1aM0 oxyphil papillary thyroid cancer (PTC) on 16 Sep 2011. In Jun 2012, the subject was diagnosed with metastatic disease. The last date of disease progression was 14 Aug 2012. Significant medical history included total thyroidectomy, diabetes mellitus, insomnia, benign prostatic hyperplasia, hypothyroidism, anxiety, bone pain, and Dupuytren's contracture. At Screening, tumor assessments of target/non-target lesions via CT scan showed right para larynx adenopathy, left paratracheal adenopathy, left lateral lobe liver mass, right lower lobe liver mass, and multiple lung masses. The subject received prior palliative radiotherapy to dorsal vertebra (C5-D5) and prior curative and palliative radio iodine therapy. Concomitant medications included gliclazide, zopiclone, alfuzosin, pregabalin, paracetamol, oxycodone, prednisolone, macrogol, Eductyl, lansoprazole, amoxicillin, sterculia urens (herbal remedy), trimebutine, Augmentin, metopimazine, ceftriaxone, amlodipine, and levothyroxine. ECOG performance status was 2 at screening.

On 25 Sep 20[redacted] (Day 1), treatment with study drug was initiated.

On 30 Sep 20[redacted] (Day 6), the study drug was interrupted due to constipation (Grade 3) and asthenia (Grade 2). Treatment for constipation included Macrogol and Eductyl. On 23 Oct 20[redacted] (Day 29), the subject recovered from constipation and restarted the study drug at the reduced dose of 20 mg. The Investigator assessed the event of constipation and asthenia as non-serious and probably related to study drug.

On 09 Jan 翌年* (Day 107), the subject was hospitalized with abdominal pain (Grade 1) and diagnosed with constipation (Grade 3). Treatment included sterculia urens and trimebutine. On 11 Jan 20[redacted] (Day 109), constipation resolved. The Investigator assessed the event of constipation as serious and possibly related to the study drug. No action taken on the study drug.

On 16 Feb 20[redacted] (Day 145), study drug was interrupted due to asthenia (Grade 2) and decreased appetite (Grade 3). On 04 Mar 20[redacted] (Day 161), study drug was resumed at a reduced dose of 14 mg.

The subject received the last dose of study drug on 16 Apr 20[redacted] (Day 204). Tumor assessment showed disease progression by Independent radiological review.

On 07 May 20[redacted] (Day 225), the subject experienced general physical health deterioration (Grade 3), secondary to underlying malignancy, and was hospitalized for palliative care. The event of general physical health deterioration did not resolve. The Investigator assessed the event of general physical health deterioration as serious and not related to the study drug.

On 07 Jun 20[redacted] (Day 256, 52 days after the last dose), the subject died due to disease progression. After the unblinding, the subject was found to be randomized to lenvatinib.

*新薬承認情報提供時に置き換え

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	14051004
Study ID	HOPE303
Manufacturer's Control Number	E7080-00713-CLI-FR
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Blood uric acid increased

A 67-year-old White female was diagnosed with Stage IVC T4aN1aM1 clear cell follicular thyroid cancer (FTC) with metastatic disease on 20 Jun 2010. The last date of disease progression was 16 May 2012. in Nov 2011. Significant medical history included hypertension, hypercholesterolemia, asthma, hysterectomy, gastric banding, anxiety, insomnia, hypothyroidism, blood uric acid increased, cervical pains, upper limb bone pains, back pain, total thyroidectomy, right cervical adenopathy resection, dyslipidemia, moderate effort dyspnea, and dry mouth. At Screening, tumor assessments of target/non-target lesions via CT scan showed head/neck lesion, trunk lesion, left upper lobe lung mass, left lingular lobe lung mass, and pulmonary node lesions. The subject received prior curative radio iodine therapy. Prior anti-cancer therapy included cisplatin and carboplatin. Prior anthracycline therapy included doxorubicin. Concomitant medications included alprazolam, antacids, atorvastatin, bromazepam, captopril, cefpodoxime, colecalciferol, Desitin, Dexeryl, diosmectite, Dynamag, fluticasone, irbesartan, Karvea hct, lansoprazole, levothyroxine, loperamide, mometasone, nicardipine, paracetamol, paroxetine, Spasfon, verapamil, and zolpidem. ECOG performance status was 0 at screening.

On 09 Feb 20[redacted] (Day 1), treatment with study drug was initiated.

On 04 Apr 20[redacted] (Day 56), the subject experienced increased blood uric acid (Grade 4). On 04 Apr 20[redacted] (Day 56), blood urea nitrogen (BUN) was 13.1 mmol/L (NR: 1.4-8.6 mmol/L) and creatinine was 111 umol/L (NR: 31-101 umol/L). On 26 Apr 20[redacted] (Day 78), blood uric acid increased improved to grade 1. On 16 May 20[redacted] (Day 98), the study drug was resumed. On 30 May 20[redacted] (Day 112), the blood uric acid level worsened to Grade 4. On 21 Jun 20[redacted] (Day 134), blood uric acid increased was reported as resolved. The Investigator assessed the events of increased blood uric acid (Grade 4) as serious (important medical event) and not related to the study drug. On 27 Jun 20[redacted] (Day 140), the subject received a reduced dose of 20 mg due to asthenia (Grade 3).

The subject received the last dose of study drug on 25 Oct 20[redacted] (Day 260). Tumor assessment showed disease progression by independent radiological review. After the unblinding, the subject was found to be randomized to lenvatinib.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	14051006
Study ID	HOPE303
Manufacturer's Control Number	E7080-01324-CLI-FR
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Confusional state, Renal failure acute, Urinary retention, Urinary tract infection

A 63-year-old White male was diagnosed with Stage IVC T3NxM1 insular follicular thyroid cancer (FTC) on 28 Sep 1998. In Aug 2003, the subject was diagnosed with additional metastatic disease. The last date of disease progression was in Apr 2012. Significant medical history included right crural pain, total thyroidectomy, 9 and 10 ribs head resection, surgery for a hip prosthesis, surgical decompression of the D10 vertebra, hypothyroidism, and arrhythmia. At Screening, tumor assessments of target/non-target lesions via CT scan showed left thyroid lodge node, paravertebral nodule T5, sub carinal ganglion lesion, and left iliac wing lesion. The subject received prior prophylactic radiotherapy to left pelvic bone lesion, sacrum, femur, spine, left femur, right scapula, and trunk; and prior curative radiotherapy to right sacro iliac and left rib lesion. The subject received prior curative radio iodine therapy and previous anticancer were sorafenib and doxorubicin. Concomitant medications included alfuzosin, Augmentin, celecoxib, diosmectite, duloxetine, Eludril, fentanyl, ketoprofen, lactulose, levofloxacin, levothyroxine, loperamide, mebeverine, Meteospasmyl, metoprolol, metronidazole, Movicol, omeprazole, oxycodone, pregabalin, probiotics, Rhodogil (espiramicina and metronidazole), sodium bicarbonate, solutions affecting the electrolyte balance, Spasfon, tobramycin, and tramadol. ECOG performance status was 1 at screening.

On 05 Jul 20[redacted] (Day 1), treatment with study drug was initiated.

On 24 Jul 翌年* (Day 385), the subject was hospitalized for confusional syndrome (Grade 3). Blood tests revealed subject had acute renal failure (Grade 3) and acute urine retention (Grade 3) with a creatinine of 192 µmol/L (NR 70-115) and uric acid of 532 µmol/L (NR 262-452). The subject was treated with alfuzosin for acute urine retention. On 25 Jul 20[redacted] (Day 386), the subject recovered from acute urine retention and confusional syndrome. The study drug was interrupted due to the events. On 27 Jul 20[redacted] (Day 388), the subject recovered from the acute renal failure. On 29 Jul 20[redacted] (Day 390), hospitalization was prolonged by urinary tract infection (Grade 2) from catheterization for the acute urinary retention. Treatment included intravenous solutions for electrolyte balance, levofloxacin, and Augmentin. On 31 Jul 20[redacted] (Day 392), the subject recovered from the urinary tract infection. On 01 Aug 20[redacted] (Day 393), the subject was discharged from the hospital. The Investigator assessed the events of confusional syndrome, acute renal failure, and acute urinary retention as serious and possibly related to the study drug. The Investigator assessed the event of urinary tract infection as serious and not related to the study drug. On 08 Aug 20[redacted] (Day 399), the subject resumed study drug at a reduced dose of 20 mg.

After the unblinding, the subject was found to be randomized to lenvatinib. The subject remained on the study at the time of data cut-off.

*新薬承認情報提供時に置き換え

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	14051007
Study ID	HOPE303
Manufacturer's Control Number	E7080-01289-CLI-FR
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Back pain

A 52-year-old White female was diagnosed with Stage II T2NxM0 insular follicular thyroid cancer (FTC) on 18 Aug 2007. On 18 May 2012, the subject was diagnosed with metastatic disease and the last date of disease progression was on 16 May 2012. Significant medical history included hypothyroidism, thyroidectomy, asthenia, esophageal pain, and anxiety. At Screening, tumor assessments of target/non-target lesions via CT scan showed mass in right upper and left lower lobe of lung and pulmonary nodules. The subject had received prior radio iodine therapy. Concomitant medications included citalopram, paracetamol, dexeryl, sodium bicarbonate, loperamide, diosmectite, metopimazine, xerial, esomeprazole, domperidone, omeprazole, general nutrients, ornithine, oxycodone, amlodipine, enalapril, zaneril, nicardipine, olmesartan, aldactazine, verapamil, and levothyroxine. ECOG performance status was 0 at screening.

On 25 Jul 20[redacted] (Day 1), treatment with study drug was initiated. On 15 May 翌年* (Day 295) the subject had experienced pain in right upper back (Grade 1). The pain persisted and increased in severity. The subject was hospitalized for pain in right upper back (Grade 3) on 17 Jun 20[redacted] (Day 328) and was treated with oxycodone. The subject recovered from the event on 22 Jul 20[redacted] (Day 363). The Investigator assessed the event of right upper back pain as serious and not related to study drug. The study drug dose was not modified.

After the unblinding, the subject was found to be randomized to lenvatinib. The subject remained on the study at the time of data cut off.

*新薬承認情報提供時に置き換え

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	14061006
Study ID	HOPE303
Manufacturer's Control Number	E7080-00874-CLI-FR, E7080-00994-CLI-FR
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Blood uric acid increased, Renal failure

A 69-year-old White female was diagnosed with Stage I T1NxM0 Hürthle cell papillary thyroid cancer (PTC) on 17 Oct 2006. On 03 Nov 2010, the subject was diagnosed with metastatic disease. The last date of disease progression was on 09 Jan 2012. Significant medical history included breast operation, breast cancer, digestive polyp exeresis, hypertension, dyslipidaemia, post-surgical hypothyroidism, dyspnoea, post-surgery radiotherapy for breast cancer treatment, uterine leiomyoma, and total thyroidectomy. At Screening, tumor assessments of target/non-target lesions via CT scan showed left mediastinal adenopathy, barety adenopathy, sub carina adenopathy, right upper lobe lung mass, left upper anterior trunk lesion, right mediastinal adenopathy, right middle lobe lung mass, and right iliac lesion. The subject received prior curative radiotherapy to left breast, prior curative and post-surgery radio iodine therapy and previous anti-cancer therapy were anastrozole and sorafenib. Concomitant medications included acetorphan, alfacalcidol, amlodipine, amoxicillin, antacids, calcium carbonate, Cistina-B6, diosmectite, esomeprazole, furosemide, hydrochlorothiazide w/olmesartan, iron, Lenoltec with codeine No. 1, levothyroxine, loperamide, magnesium, nicardipine, olmesartan, omeprazole, paracetamol, potassium, Prazepam, Prazosin, rosuvastatin, silicon dioxide, solutions affecting the electrolyte balance, Sotalol, and Titanoreine. ECOG performance status was 0 at screening.

On 20 Mar 20[redacted] (Day 1), treatment with study drug was initiated. On 16 Apr 20[redacted] (Day 28), the subject experienced the event of uric acid increased (Grade 4) (level was not reported). On 13 May 20[redacted] (Day 55), the subject recovered from the event of uric acid increased. The Investigator assessed the event of blood uric acid increased as serious (important medical event) and not related to the study drug. No action was taken with the study drug.

On 01 Oct 20[redacted] (Day 196), the subject had proteinuria (Grade 2). Creatinine and BUN were within normal limits. On 02 Oct 20[redacted] (Day 197), the study drug was reduced to 20 mg due to asthenia (Grade 2) and on 04 Oct 20[redacted] (Day 199), study drug was interrupted due to proteinuria (Grade 2).

On 06 Oct 20[redacted] (Day 201), the subject was hospitalized due to severe renal failure (Grade 3) with history of vomiting (Grade 1) for the past 3 days. Creatinine level was 324 µmol/L (NR 8-125 µmol/L) and creatinine clearance was 12 mL/min. The subject also had hyperkalemia (Grade 3) (potassium level not reported). The subject was treated with rehydration therapy. On the same day, the hypertensive treatment of Sotalol and hydrochlorothiazide with olmesartan were interrupted. On 10 Oct 20[redacted] (Day 205), the subject recovered from the renal failure and hyperkalemia, and was discharged from hospital. The Investigator assessed the event of renal failure as serious and probably related to the study drug. The Investigator assessed the event of hyperkalemia as non-serious and not related to the study drug but to the renal failure.

After the unblinding, the subject was found to be randomized to lenvatinib. The subject remained on the study at the time of data cut-off.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	14101002
Study ID	HOPE303
Manufacturer's Control Number	E7080-00774-CLI-FR
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Femur fracture

A 53-year-old White female was diagnosed with Stage IVC T3N0M1 metastatic vascular invasion papillary thyroid cancer (PTC) on 18 Oct 2004. The last date of disease progression was on 24 Aug 2011. Significant medical history included poliomyelitis, hypertension, hypercholesterolaemia, drug hypersensitivity (penicillin, roxithromycin), appendicectomy, tonsillectomy, oophorectomy bilateral, cholecystectomy, total thyroidectomy, pyramidectomy (Lalouette's pyramid), hypothyroidism, and osteoporosis. At Screening, tumor assessments of target/non-target lesions via CT scan showed thoracic right paratracheal adenopathy, subcarinal adenopathy, right upper lobe lung mass, right middle lobe lung mass, and left lower lobe lung mass. The subject received prior curative radio iodine therapy. Concomitant medications included amlodipine, atenolol, atorvastatin, cetirizine, colecalciferol, Cystine B6 Bailleul, dalteparin, Dexeryl, domperidone, hydrochlorothiazide, Lamaline, lercanidipine, levothyroxine, loperamide, morphine, nefopam, nicardipine, ondansetron, Panadeine Co (codeine and paracetamol), paracetamol, Prazepam, ramipril, sodium bicarbonate, tinzaparin, and Vaseretic (enalapril and hydrochlorothiazide). ECOG performance status was 1 at screening.

On 15 Mar 20[redacted] (Day 1), treatment with study drug was initiated.

On 29 Mar 20[redacted] (Day 15), the study drug was reduced to 20 mg due to hypertension (Grade 3). On 28 May 20[redacted] (Day 75), the subject was hospitalized for femur fracture (Grade 3) due to an accidental fall. On 29 May 20[redacted] (Day 76), the subject underwent orthopedic surgery and kinesitherapy. The study drug was interrupted. Treatment included nefopam, morphine, tinzaparin, Panadeine Co, Lamaline, dalteparin, and paracetamol. On 08 Jun 20[redacted] (Day 86), the subject was transferred to rehabilitation center for physiotherapy. . On 31 Aug 20[redacted] (Day 170), the subject returned home where further session of physiotherapy was carried out. On 15 Jun 翌年* (Day 458), the subject stopped physiotherapy and recovered from the femur fracture. The Investigator assessed the event of femur fracture as serious and not related to the study drug. On 22 Jun 同年* (Day100), the study drug was resumed.

The subject received the last dose of study drug on 24 Oct 同年* (Day 224). Tumor assessment showed disease progression by independent radiological review. .

After the unblinding, the subject was found to be randomized to lenvatinib.

*新薬承認情報提供時に置き換え

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	14141003
Study ID	HOPE303
Manufacturer's Control Number	E7080-00902-CLI-FR, E7080-01057-CLI-FR
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Pyelonephritis, Bronchitis

An 89-year-old White female was diagnosed with Stage IVA T4aN0M0 tall cell papillary thyroid cancer (PTC) on 07 Apr 1993. On 10 Jul 2000, the subject was diagnosed with metastatic disease. The last date of disease progression was on 25 Jun 2012. Significant medical history included thyroidectomy, hypothyroidism, left cervical fistula (neck), hypercholesterolaemia, tumour pain, bilateral cervical resection (neck), right cervical node resection, left mandibular node resection, and left cervical resection (neck). At Screening, tumor assessments of target/non-target lesions via CT scan showed left axillary adenopathy, and left axial lesion. The subject received prior curative radiotherapy to left upper cervical lymph nodes and prior curative radio iodine therapy. Concomitant medications included rosuvastatin, paracetamol, potassium, ciprofloxacin, ceftriaxone, cefixime, tinzaparin, carbohydrates with fats/minerals, enoxaparin, Spektramox, irbesartan, rilmenidine, and levothyroxine. ECOG performance status was 1 at screening.

On 16 Jul 20[redacted] (Day 1), treatment with study drug was initiated.

On 06 Aug 20[redacted] (Day 22), the subject experienced confusional state with temporo-spatial disorientation, subfebrile temperature, and speech disturbances with pre-existing left peripheral facial palsy. On 09 Aug 20[redacted] (Day 25), the subject was initially hospitalized for suspected ischemic attack. On admission blood pressure was noted as 174/85 mmHg. .Laboratory result showed a urine culture with positive multi-sensitive E-coli. and C-reactive protein of 185. The subject was diagnosed with acute pyelonephritis (Grade 3) and the treating physician ruled out ischemic stroke. On 10 Aug 20[redacted] (Day 26), the study drug was interrupted due to pyelonephritis . Treatment included irbesartan ciprofloxacin, ceftriaxone, cefixime, and Oroken. On 03 Sep 20[redacted] (Day 50), pyelonephritis improved to Grade 2. ,. The Investigator assessed the event of pyelonephritis as serious and not related to the study drug and the study drug was resumed at the reduced dose of 20 mg due to this event.

On 15 Nov 20[redacted] (Day 123), the subject was hospitalized due to bronchitis (Grade 3) and associated with asthenia (Grade 2). Treatment included Spektramox. On 27 Nov 20[redacted] (Day 135), bronchitis was resolved. The Investigator assessed the event of bronchitis as serious and not related to the study drug. The study drug dose was not changed due to this event.

On 20 Nov 20[redacted] (Day 128), the study drug was interrupted due to asthenia (Grade 2) and resumed on 27 Nov 20[redacted] (Day 135) at a reduced dose of 14 mg.

The subject received the last dose of study drug on 20 May 翌年* (Day 309). Tumor assessment showed disease progression by Independent Radiological Review. After the unblinding, the subject was found to be randomized to lenvatinib.

*新薬承認情報提供時に置き換え

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	15021002
Study ID	HOPE303
Manufacturer's Control Number	E7080-00897-CLI-IT
Randomized treatment	Lenvatinib 24 mg QD
Death due to PD	Yes
Non-Fatal SAE(s)	Alanine aminotransferase increased, Aspartate aminotransferase increased

A 63-year-old White male was diagnosed with Stage IVA T4aN1aM0 tall cell papillary thyroid cancer (PTC) on 27 Jan 2009. On 18 Mar 2009, the subject was diagnosed with metastatic disease. The last date of disease progression was on 15 Mar 2012. Significant medical history included hypertension, essential thrombocythaemia, nephrolithiasis, total thyroidectomy, hypothyroidism, and arthralgia. At Screening, tumor assessments of target/non-target lesions via CT scan showed right lower lobe lung mass, right parapharyngeal lesion, right middle or lower cervical adenopathy, and multiple diffuse lung masses. The subject received prior palliative radiotherapy to the right parapharynx, prior curative radio iodine therapy and previous anti-cancer therapy were cisplatin and doxorubicin. Concomitant medications included acetylsalicylic acid, amlodipine, Azor (sevicar olmesartan and amlodipine), beclometasone, carbomer, cardiazol-paracodina, Corti-Fluoral, nebivolol, nimesulide, olmesartan, Panadeine Co, ramipril, mucosamyn spray, Ialoclean spray, and levothyroxine. ECOG performance status was 0 at screening.

On 05 Apr 20[redacted] (Day 1), treatment with study drug was initiated. On 14 Jul 20[redacted] (Day 101), the study drug was interrupted due to stomatitis (Grade 2).

On 24 Jul 20[redacted] (Day 111), laboratory results showed an increase in alanine aminotransferase (ALT) (Grade 3) to 370 U/L (NR 6-43 U/L), alkaline phosphatase (ALP) of 252 U/L (NR 35-125 U/L) and aspartate aminotransferase (AST) (Grade 3) to 316 U/L (NR 11-36 U/L). On the same day, the study drug was resumed at a reduced dose of 20 mg. On 26 Jul 20[redacted] (Day 113), the study drug was interrupted due to the events of an increased ALT and increased AST. On 30 Jul 20[redacted] (Day 117), lab results showed decreased in severity of ALT to 62 U/L, ALP to 126 U/L and AST to 28 U/L. The events of increased ALT and increased AST were resolved. The Investigator assessed the events of alanine aminotransferase increased and aspartate aminotransferase increased as serious and probably related to the study drug. On 31 Jul 20[redacted] (Day 118), the study drug was resumed.

On 11 Dec 20[redacted] (Day 251), the study drug was reduced to 14 mg due to stomatitis (Grade 2). On 30 Mar 翌年* (Day 360), the study drug was interrupted due to dysphonia (Grade 3), palmar-plantar erythrodysaesthesia syndrome (Grade 3), glossitis (Grade 3), oropharyngeal pain, and dysphagia (Grade 3) and resumed the study drug on 05 Apr 20[redacted] (Day366) at a reduced dose of 10 mg.

The subject received the last dose of study drug on 01 May 20[redacted] (Day 392). Tumor assessment showed clinical disease progression.

On 13 Aug 20[redacted] (Day 496, 104 days after the last dose), the subject died due to disease progression.

*新薬承認情報提供時に置き換え

After the unblinding, the subject was found to be randomized to lenvatinib.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	15021003
Study ID	HOPE303
Manufacturer's Control Number	E7080-00756-CLI-IT, E7080-00915-CLI-IT, E7080-00930-CLI-IT
Randomized treatment	Lenvatinib 24 mg QD
Death due to PD	Yes
Non-Fatal SAE(s)	Pneumonitis, Epilepsy, Pyrexia, Intestinal obstruction
AEs leading to Discontinuation	Epilepsy

An 80-year-old White male was diagnosed with Stage IVC T3N0M1 unspecified variant papillary thyroid cancer (PTC) on 09 Jun 2009. On 08 Apr 2009, thesubject was diagnosed with additional metastatic disease. The last date of disease progression was on 25 Jan 2012. Significant medical history included benign prostatic hyperplasia, thyroid carcinoma parietal lobe metastasis resection, total thyroidectomy and IV level lymphadenectomy, hypothyroidism, left arm joint range of motion decreased, left foot motor and sensory neuropathy, inguinal hernia, and nephrolithiasis. At Screening, tumor assessments of target/non-target lesions via CT scan showed subcarinal adenopathy, right hilar adenopathy, right lower lobe lung mass, right peri-hilar region lesion, left shoulder blade lesion, left IV rib single mass, left XI rib single mass, D10 single vertebral mass, left lower lobe lung mass. The subject received prior palliative radiotherapy to left shoulder bone lesion. and prior palliative and curative radio iodine therapy. Concomitant medications included terazosin, dutasteride, paracetamol, Cernevit, teicoplanin, meropenem, Cacit, Meritene, Fleet, calcium gluconate, Ultralan, Augmentin, promethazine, minerals with vitamins, clotrimazole, fosfomycin, bromazepam, reviparin, esomeprazole, cefaclor, clarithromycin, and levothyroxine. ECOG performance status was 1 at screening.

On 08 May 20[redacted] (Day 1), treatment with study drug was initiated.

On 11 May 20[redacted] (Day 4), the subject experienced fever (Grade 1). On 15 May 20[redacted] (Day 8), the subject was hospitalized for pneumonitis (Grade 2) with asthenia (Grade 2) and fever (Grade 1). Treatment included intravenous (IV) antibiotics (meropenem, teicoplanin, Augmentin) and hydration. On 16 May 20[redacted] (Day 9), the study drug was interrupted due to pneumonitis (Grade 2) and asthenia (Grade 2). Fever resolved on 18 May 20[redacted] (Day 11). On 25 May 20[redacted] (Day 18), the event of pneumonitis resolved. . The Investigator assessed the event pneumonitis (Grade 2) as serious and not related to the study drug. The investigator assessed fever and asthenia as non-serious, asthenia as probably related and fever as not related to study drug. On 30 May 20[redacted] (Day 23), the study drug was resumed at the reduced dose of 20 mg.

On 15 Aug 20[redacted] (Day 100), the subject was hospitalized due to epileptic seizure (Grade 4) where treatment was unspecified. On 24 Aug 20[redacted] (Day 109), the subject recovered from epilepsy and was discharged from the hospital. The Investigator assessed the event of epilepsy as serious and possibly related to the study drug. The study drug was withdrawn due to this event. The subject received the last dose of blinded study drug on 14 Aug 20[redacted] (Day 99).

On 26 Aug 20[redacted] (Day 111), the subject was hospitalized for a fever (Grade 2) at 40 degrees

Celsius. Treatment included cefaclor. On 30 Aug 20[redacted] (Day 115), pyrexia was resolved and the subject was discharged from hospital. The Investigator assessed pyrexia (Grade 2) as serious and not related to the study drug.

On 03 Sep 20[redacted] (Day 119), the subject was hospitalized for intestinal obstruction (Grade 2) and pneumonitis (Grade 2). Treatment included clarithromycin. On 05 Sep 20[redacted] (Day 121), both events resolved and the subject was discharged from the hospital. The Investigator assessed the event of epilepsy as serious and possibly related to the study drug. The Investigator assessed the events of intestinal obstruction and pneumonitis as serious and not related to the study drug.

On 29 Aug 翌年* (Day 479, 380 days after the last dose), the subject died due to disease progression. After the unblinding, the subject was found to be randomized to lenvatinib.

*新薬承認情報提供時に置き換え

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	15021009
Study ID	HOPE303
Manufacturer's Control Number	E7080-01132-CLI-IT, E7080-01191-CLI-IT
Randomized treatment	Lenvatinib 24 mg QD
Death due to PD	Yes
Non-Fatal SAE(s)	Platelet count decreased, Alanine aminotransferase increased, Aspartate aminotransferase increased

A 55-year-old White female was diagnosed with Stage IVC T3N0M1 follicular papillary thyroid cancer (PTC) on 08 Sep 2003. On 31 Oct 2003, the subject was diagnosed with additional metastatic disease. The last date of disease progression was on 14 Jun 2012. Significant medical history included amenorrhea, cervicobrachial syndrome, frontal parietal pain, hypothyroidism, hypertension, and thyroidectomy. At Screening, tumor assessments of target/non-target lesions via CT scan showed left hilar adenopathy, right lower lobe VII segment liver mass, right lower lobe VI segment liver mass, multiple parenchymal lung mass lesions, multiple mediastinal adenopathies, and multiple hepatic lesions. The subject received prior palliative radiotherapy to a single sternal lesion, L4 vertebral lesion, and cranial base, prior palliative and curative radio iodine therapy and previous anticancer therapy was sorafenib. Concomitant medications included calcitriol, calcium gluconate, clonazepam, colecalciferol, dexamethasone, fentanyl, Hyzaar (losartan and hydrochlorothiazide), ketorolac, lekovit ca, levothyroxine, losartan, Meritene, metoclopramide, minerals w/vitamins, omeprazole, ondansetron, Oxycocet, pregabalin, ranitidine, and zoledronic acid. ECOG performance status was 1 at screening.

On 30 Aug 20[redacted] (Day 1), treatment with study drug was initiated.

On 20 Dec 20[redacted] (Day 113), the subject experienced an increase in alanine aminotransferase (AST) (Grade 3) and aspartate aminotransferase (ALT) (Grade 3). Lab results showed AST was 303 U/L (NR 9-34 U/L), alkaline phosphatase (ALP) of 147 U/L (NR 35-123 U/L) and ALT was 648 U/L (NR 6-34 U/L). No treatment was given for the adverse event. No other symptoms and causes of hepatic dysfunction were reported. On 25 Dec 20[redacted] (Day 118), the study drug was interrupted due to AST and ALT increase. On 27 Dec 20[redacted] (Day 120), the subject recovered from AST and ALT increase. The Investigator assessed the events of alanine aminotransferase increased and aspartate aminotransferase increased as serious (important medical event) and not related to the study drug. On 09 Jan 翌年* (Day 133), the study drug was resumed

The subject received the last dose of study drug on 26 Feb 20[redacted] (Day 181). Tumor assessment showed disease progression by independent radiological review.

On 12 Mar 20[redacted] (Day 195, 14 days after the last dose), the subject was hospitalized due to decreased platelet count (severity grading was not provided). The subject had cutaneous petechial lesions on the trunk and arms since 01 Feb 20[redacted] (Day 156). Laboratory test and treatment were not reported for the event. The events were not recovered. The Investigator considered the event of platelet count decreased as serious and not related to the study drug and the event, petechial was considered non-serious and not related to the study drug.

On 29 Mar 20[redacted] (Day 212, 31 days after the last dose), the subject died due to disease

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progression.

After the unblinding, the subject was found to be randomized to lenvatinib.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	15021012
Study ID	HOPE303
Manufacturer's Control Number	E7080-01110-CLI-IT
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Hyperuricaemia

A 58-year-old White male was diagnosed with Stage I T2N0M0 papillary thyroid cancer (PTC) on 23 Apr 1998. On 18 Dec 2006, the subject was diagnosed with metastatic disease. The last date of disease progression was on 14 Jun 2012. Significant medical history included hypertension, post-surgical hypothyroidism, total thyroidectomy, right laterocervical lymph nodes dissection, left laterocervical lymph node dissection, colon adenomas asportation, and hand and foot dyshidrosis. At Screening, tumor assessments of target/non-target lesions via CT scan showed right lower lobe lung mass and multiple lung lesions. The subject received prior palliative radio iodine therapy and prior anticancer therapy was sorafenib. Concomitant medications included allopurinol, paracetamol, throat preparations, methylprednisolone, cetirizine, doxazosin, amlodipine, Tenoretic (atenolol and chlorthalidone), and levothyroxine. ECOG performance status was 1 at screening.

On 12 Sep 20[redacted] (Day -16), the subject experienced hyperuricemia (Grade 4). Treatment included allopurinol. On 11 Oct 20[redacted] (Day 14), the event of hyperuricemia resolved. The Investigator assessed the event of hyperuricemia as serious (important medical event) and not related to the study drug

On 28 Sep 20[redacted] (Day 1), treatment with study drug was initiated.

After the unblinding, the subject was found to be randomized to lenvatinib. The subject remained in the study at the time of data cut-off.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	15031011
Study ID	HOPE303
Manufacturer's Control Number	E7080-01192-CLI-IT
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Perineal abscess
AEs leading to discontinuation	General physical health deterioration

A 62-year-old White male was diagnosed with Stage IVB T4bN0M0 poorly differentiated with insular areas and Hürthle cells papillary thyroid cancer (PTC) in May 2008. In Mar 2009, the subject was diagnosed with metastatic disease. The last date of disease progression was on 04 Apr 2012. Significant medical history included total thyroidectomy, removal of left laterocervical and supraclavicular lymph nodes, surgical excision of lumbar metastatic lesions, surgical excision of metastatic lesion of the right kidney, hypothyroidism after total thyroidectomy, back pain, dilatation of the pancreatic duct of Wirsung, hyperamylasemia due to secondary lesion of the pancreas, anaemia, colorectal cancer, colorectal resection, vitamin-D deficiency, peritonitis as a complication of colorectal resection, left jugular vein thrombosis, weight loss, and decreased appetite. At Screening, tumor assessments of target/non-target lesions via CT scan showed sovrajugular right anterior lesion, right middle lobe lung mass, left lower lobe lung mass, pancreatic mass, right kidney mass, pelvis bone mass, and gluteus mass. The subject received prior palliative radiotherapy to the right gluteus-lumbar region, prior curative and palliative radio iodine therapy and previous anti-cancer therapy were carboplatin and epirubicin. Concomitant medications included tramadol, pregabalin, iron, dexamethasone, colecalciferol, fondaparinux, atorvastatin, loperamide, ciprofloxacin, nitrofurantoin, ceftriaxone, levofloxacin, paracetamol, Targin, Augmentin, and levothyroxine. ECOG performance status was 1 at screening.

On 24 Apr 20[redacted] (Day 1), treatment with study drug was initiated.

On 09 Oct 20[redacted] (Day 169), the study drug was interrupted due to diarrhea (Grade 2) and on 16 Oct 20[redacted] (Day 176), the study drug was resumed at a reduced dose of 20 mg. On 31 Oct 20[redacted] (Day 191), the study drug was interrupted due to suspected enterovesical fistula (Grade 3) and resumed on 17 Dec 20[redacted] (Day 238) at a reduced dose of 14 mg.

On 10 Feb 翌年* (Day 293), the subject experienced perianal fistula (Grade 3). A surgical visit diagnosed a complication of pelvic perineal abscess (Grade 3) and surgical treatment with "demolition coloanal and definitive colostomy" was advised. On 17 Mar 20[redacted] (Day 328), the subject was hospitalized for surgery. On 18 Mar 20[redacted] (Day 329), the subject underwent distal colon resection, left colostomy, mucosectomy of the anal canal, and curettage pararectal and scrotal abscess. On 29 Mar 20[redacted] (Day 340), perineal abscess resolved with sequelae. The Investigator assessed the event of perineal abscess as serious and not related to the study drug. The investigator assessed the event of perianal fistula as non-serious and not related to study drug. The study drug was interrupted and was not resumed.

The subject received the last dose of study drug on 11 Feb 20[redacted] (Day 294). Tumor assessment showed disease progression by independent radiological review.

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On 11 Apr 20[redacted] (Day 353), the subject was withdrawn from the study due to general physical health deterioration (Grade 3) resulting from complication of perianal abscess. The Investigator assessed the event as non-serious and not related to the study drug. After the unblinding, the subject was found to be randomized to lenvatinib.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	15031012
Study ID	HOPE303
Manufacturer's Control Number	E7080-01160-CLI-IT
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Bacteraemia

A 60-year-old White male was diagnosed with Stage IVA T4aN1bM0 tall cell papillary thyroid cancer (PTC) on 06 Feb 2004. In Mar 2007, the subject was diagnosed with metastatic disease. The last date of disease progression was on 12 Apr 2012. Significant medical history included total thyroidectomy; surgical removal of supraclavicular, sub mandibular, perirecurrential lymph nodes; Graves' disease, surgical removal of thyroid metastatic retrosternal lymph nodes, percutaneous thermo-ablation of right paratracheal thyroid metastatic lesions, paralysis of right vocal cord, severe dyspnea due to paralysis of the right vocal cord, left cordotomy by CO_2 laser, paralysis of left vocal cord, hypothyroidism post thyroidectomy, hypertension, bilateral latero-cervical lymphadenectomy, hiatal hernia, gastric ulcer, depression, appendicectomy, post-trauma vertebral compression treated with surgery, intermittent toothache, vitamin-D deficiency, and osteopenia. At Screening, tumor assessments of target/non-target lesions via CT scan showed paraesophageal adenopathy, right supraclavicular adenopathy, right lower lobe lung mass, left upper lobe lung mass, upper pretracheal adenopathy, right cranial paratracheal adenopathy, right low paratracheal adenopathy, and lower right paratracheal adenopathy. The subject received prior curative and palliative radio iodine therapy. Concomitant medications included allopurinol, amlodipine, amoxi-clavulanico, calcium carbonate, colecalciferol, dexamethasone, domperidone, doxycycline, erythropoietin, esomeprazole, iron, ketorolac, levofloxacin, levothyroxine, nifedipine, Oxycocet, pantoprazole, paracetamol, paroxetine, piperacillina/tazobactam, pregabalin, ramipril, Vea Oris, Targin, teicoplanin, and tigecycline. ECOG performance status was 0 at screening.

On 03 May 20[redacted] (Day 1), treatment with study drug was initiated.

On 20 Sep 20[redacted] (Day 141), the study drug was interrupted due to pain in extremity (Grade 2) and excoriation (Grade 2). On 22 Sep 20[redacted] (Day 143), the study drug was reduced dose of 20 mg due to excoriation.

On 27 Jan 翌年* (Day 270), the subject was hospitalized due to persistent fever (Grade 1) of unknown cause.. On 29 Jan 20[redacted] (Day 272), laboratory findings showed white blood cells (WBC) of 15.93x10^9/L (NR 3.8-10.7 x10^9/L). Urine sultures were positive for staphylococcus haemolyticus, rothia dentocariosa and staphylococcus epidermidis. The subject was diagnosed with bactetremia (Grade 3). Treatment included Oromorph, doxycycline, Tygacil, piperacillina/tazobactam, and Targosid . On 05 Mar 20[redacted] (Day 307), the subject recovered from the event of bacteremia. The Investigator assessed the event of bacteremia as serious and possibly related to the study drug. On 05 Feb 20[redacted] (Day 279), the study drug was interrupted due to back pain (Grade 2) and on 04 Mar 20[redacted] (Day 306), study drug was resumed at a dose of 14 mg.

After the unblinding, the subject was found to be randomized to lenvatinib. The subject remained in the study at the time of data cut-off.

*新薬承認情報提供時に置き換え

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	15041001
Study ID	HOPE303
Manufacturer's Control Number	E7080-00831-CLI-IT, E7080-01218-CLI-IT
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Atrial fibrillation, Atrial flutter

A 70-year-old White male was diagnosed with Stage II T3N0M1 poorly differentiated papillary thyroid cancer (PTC) on 11 Jan 1982. On 07 May 1995, the subject was diagnosed with additional metastatic disease. The last date of disease progression was on 16 Nov 2011. Significant medical history included hypertension , peripheral arterial occlusive disease, diverticulum oesophageal, prostate cancer, pollakiuria, constipation, dyspnoea, dry mouth, musculoskeletal chest pain, dyslipidaemia, hypothyroidism, hypocalcaemia, total thyroidectomy, surgical asportation of mediastinal mass , surgical asportation of laterocervical bilateral lymphadenopathy, thromboendarterectomy, left carotid artery stent, bilateral knee pain, hand foot pain, haemorrhoids, and poliomyelitis. At Screening, tumor assessments of target/non-target lesions via CT scan showed two right lower lobe lung masses, left upper lobe lung mass, left lower lobe lung mass, multiple lung sub-centimeter lesions, right lobe liver mass, and two right mediastinal adenopathies. The subject received prior palliative radiotherapy to right mediastinal adenopathies ,curative radiotherapy to neck adenopathy and curative radio iodine therapy. Concomitant medications included acetylsalicylic acid, acyclovir, alfacalcidol, ambroxol, atenolol, atorvastatin, Augmentin, azithromycin, barnidipine, beclometasone, betamethasone, bisoprolol, calcium carbonate, candesartan, canrenone, carbocysteine, ceftriaxone, activated charcoal, clarithromycin, clopidogrel, diltiazem, doxazosin, enoxaparin, flecainide, furosemide, ipratropium, iron, lacidipine, levofloxacin, levothyroxine, losartan, macrogol, magaldrate, magnesium sulfate, mesalazine, methylprednisolone, metoclopramide, nifedipine, omeprazole, pantoprazole, paracetamol, prednisone, propafenone, rivaroxaban, rosuvastatin, salbutamol, valsartan, verapamil, and vitamins. ECOG performance status was 1 at screening.

On 30 Nov 20[redacted] (Day 1), treatment with the study drug was initiated.

On 01 Jul 翌年* (Day 215), the subject was hospitalized for atrial fibrillation (Grade 2), and the study drug was interrupted. The subject has been experiencing uncontrolled blood pressure and was found to have hypertension (Grade 2) during hospitalization. On 17 Jul 20[redacted] (Day 231), atrial fibrillation worsened to Grade 3. ECG showed phases of bradycardia and tachyarrhythmias. Heart palpitations resolved spontaneously. Treatment included enoxaparin, magnesium sulfate, diltiazem, verapamil, and atenolol. On 18 Jul 20[redacted] (Day 232), a pacemaker was implanted. Further treatment included clarithromycin, and propafenone. On 03 Sep 20[redacted] (Day 279), the atrial fibrillation improved to Grade 1. The Investigator assessed the event of atrial fibrillation as serious and not related to the study drug. The investigator assessed the event of hypertension as non-serious and possibly related to study drug. On 25 Jul 20[redacted] (Day 239), the study drug was resumed at a reduced dose of 14 mg.

On 01 Dec 20[redacted] (Day 368), the study drug was reduced to 10 mg due to lymphopenia (Grade 2).

On 09 Apr 翌々年* (Day 497), the subject was hospitalized for atrial flutter (Grade 2) in conjunction with elevated blood pressure (200/100 mmHg). The subject failed to take antiarrythmic therapy

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by mistake. The subject was treated with Lacirex.. On 11 Apr 20[redacted] (Day 499), atrial flutter (Grade 2) recovered. The Investigator assessed the event of atrial flutter as serious and not related to the study drug. The study drug dose was not changed. The subject received the last dose of study drug on 03 Jul 20[redacted] (Day 582). Tumor assessment showed disease progression by Independent Radiological Review. After the unblinding, the subject was found to be randomized to lenvatinib.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	15041002
Study ID	HOPE303
Manufacturer's Control Number	E7080-01390-CLI-IT
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Musculoskeletal chest pain

A 60-year-old White female was diagnosed with Stage IVC T3N0M1 poorly differentiated papillary thyroid cancer (PTC) on 20 Oct 2010. On 10 Jan 2011, the subject was diagnosed with additional metastatic disease. The last date of disease progression was on 16 Nov 2011. Significant medical history included hypertension, epilepsy, hiatus hernia, gastric ulcer, arthralgia, headache, dyspnoea, total thyroidectomy, caesarean section, right knee ligament rupture, left knee ligament rupture, irritable bowel syndrome, menopause, and asthma. At Screening, tumor assessments of target/non-target lesions via CT scan showed right lower lobe lung masses, right upper lobe lung masses, left upper lobe lung masses, left lingular lobe lung mass, and left lower lobe lung mass. The subject received prior curative radio iodine therapy. Concomitant medications included acetylsalicylic acid, avena sativa, beclometasone, betamethasone, bisoprolol, calcium carbonate, cetirizine, clodronic acid, dihydrocodeine, enalapril, furosemide, glucomannan, hydrochlorothiazide, inulin, ipratropium, isosorbide dinitrate, lansoprazole, lercanidipine, levothyroxine, lidocaine, loperamide, loratadine, megestrol, methylprednisolone, nebivolol, omeprazole, otilonium, Panadeine Co (codeine phosphate and paracetamol), paracetamol, probiotics, pyridoxine, ramipril, salbutamol, topiramate, L-tryptophan, vitamin-B complex, vitamin-D, and vitamins. ECOG performance status was 1 at screening.

On 30 Nov 20[redacted] (Day 1), treatment with study drug was initiated. On 20 Apr 翌年* (Day 143), the study drug dose was reduced to 20 mg due to anorexia (Grade 1) and weight loss (Grade 1). On 13 Jun 20[redacted] (Day 197), the study drug dose was reduced to 14 mg.

On 01 Feb 翌々年* (Day 430), the subject began experiencing thoracic pain of musculoskeletal origin (Grade 1). The subject felt thoracic pain sometimes in cardiac site, sometimes in breast region, and sometimes in right arm during mild work or/and at rest for about 1-2 hours. Sometimes it disappeared spontaneously, and sometimes nitrate use was necessary. On 25 Oct 20[redacted] (Day 696), the subject was hospitalized due to thoracic pain of musculoskeletal origin (Grade 1), and the study drug was interrupted. On admission, the subject was asymptomatic, in good general condition, apyretic, eupneic, with rhythmic cardiac action of 84 beats per minute; and a Levine 2/6 systolic murmur with a rough quality. ECG showed left axis deviation. The subject was treated with isosorbide dinitrate. On 30 Oct 20[redacted] (Day 701), the study drug was resumed at 14 mg. On 31 Oct 20[redacted] (Day 702), ECG stress test was negative. On 04 Nov 20[redacted] (Day 706), stress-rest myocardial perfusion single-photon emission computed tomography (SPECT), first pass angiocardio scintigraphy, quantitative analysis stress-rest myocardial perfusion scintigraphy was performed showed negative results. The maximum stress test with myocardial scintigraphy was negative for stress-induced myocardial ischemia. On 07 Nov 20[redacted] (Day 709), the study drug was interrupted. Basal echocardiogram was performed showed negative results. The subject was discharged. On 08 Nov 20[redacted] (Day 710), the study drug was resumed. Musculoskeletal chest pain (Grade 1) was reported as not resolved. The Investigator assessed the event of musculoskeletal chest pain serious and not related to the study drug.

*新薬承認情報提供時に置き換え

The subject remained on the study at the time of data cut-off. After the unblinding, the subject was found to be randomized to levatinib.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	15061002
Study ID	HOPE303
Manufacturer's Control Number	E7080-00640-CLI-IT
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Abdominal pain upper
AEs leading to Discontinuation	Fatigue, Abdominal pain upper

A 63-year-old White male was diagnosed with Stage IVC T1NxM1 capsulized papillary thyroid cancer (PTC) on 12 Nov 2002. On 13 Aug 2002(as the initial manifestation of the disease), the subject was diagnosed with metastatic disease. The last date of disease progression was on 12 Jan 2012. Significant medical history included cholecystectomy, glucose tolerance impaired, obesity, osteoporosis, total thyroidectomy, first radio frequency ablation of pelvis lesion, second radio frequency ablation of the pelvis lesion, third radio frequency ablation of pelvis lesion, surgical resection of left iliac wing and bone engraft, cholangitis due to biliary route lithiasis, cholelithiasis, endoscopic papillotomy, and endoscopic removal of biliary stones. At Screening, tumor assessments of target/non-target lesions via CT scan showed left ischiopubic ramus lesion. The subject received prior curative radio iodine therapy. Concomitant medications included pregabalin, ursodeoxycholic acid, lansoprazole, vitamin-D, risedronic acid, paracetamol, omeprazole, antacids, Spasfon, hyoscine, pantoprazole, metoclopramide, metformin, valsartan, hydrochlorothiazide, and levothyroxine. ECOG performance status was 1 at screening.

On 09 Feb 20[redacted] (Day 1), treatment with study drug was initiated.

On 14 Feb 20[redacted] (Day 6), the subject presented with stomach ache (Grade 2) and dyspepsia (Grade 2) and radiated posteriorly. The subject was treated with proton pump inhibitor had relief of symptoms. On 15 Feb 20[redacted] (Day 7), the study drug was interrupted due to dyspepsia (Grade 2), upper abdominal pain (Grade 2), and constipation (Grade 1). On 17 Feb 20[redacted] (Day 9), the subject had a new episode of stomach ache associated with constipation (Grade 1). On 18 Feb 20[redacted] (Day 10), the subject was hospitalized for upper abdominal pain (Grade 2). Treatment included pantoprazole, hyoscine, metoclopramide, antacids, Spasfon and Josmine bromure. Abdominal x-ray excluded abdominal occlusion. Abdominal ultrasound excluded biliary route obstruction. Cholangitis and laboratory exams documented only mild elevation of pancreatic lipase to 635 U/L (NR: 23-393 U/L) and total bilirubin 1.98 mg/dL (normal range not provided). On the same day, upper abdominal pain was considered resolved and the subject was discharged. Mild upper abdominal pain continued but general condition was good. On 01 Mar 20[redacted] (Day 22), the study drug was resumed. On 16 Mar 20[redacted] (Day 37), the subject experienced upper abdominal pain (Grade 2), and received the last dose of the study drug. On 22 Mar 20[redacted] (Day 43), fatigue and upper abdominal pain were resolved. The Investigator assessed the event of upper abdominal pain serious and probably related to the study drug. On 17 Mar 20[redacted] (Day 38), the study drug was withdrawn due to fatigue (Grade 2) and upper abdominal pain (Grade 2).

On 03 Sep 20[redacted] (Day 208, 172 days after the last dose), the subject died on undetermined cause. After the unblinding, the subject was found to be randomized to lenvatinib.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	15121003
Study ID	HOPE303
Manufacturer's Control Number	E7080-01075-CLI-IT
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Osteoarthritis, Atrial fibrillation, Renal failure acute

A 76-year-old White female was diagnosed with Stage III T3NxMx insular follicular thyroid cancer (FTC) on 04 Oct 2006. On 23 May 2011, the subject was diagnosed with metastatic disease. The last date of disease progression was on 13 Jul 2012. Significant medical history included giant urticaria, menopause, cholecystectomy, left knee prosthesis, polymyalgia rheumatica, right knee prosthesis, hip prosthesis, hypertension, parossistic atrial fibrillation, thyroidectomy, hypoparathyroidism, hip pain, and coxarthrosis. At Screening, tumor assessments of target/non-target lesions via CT scan showed right acromion lesion, bilateral lung mass, and mediastinal lymph node lesion. The subject received prior curative radio iodine therapy. Concomitant medications included amlodipine, bisoprolol, Cacit, calcitriol, ceftriaxone, clodronic acid, enoxaparin, Etrafon-D, glycerol, ibuprofen, ketorolac, lansoprazole, levosulpiride, levothyroxine, methylprednisolone, metoclopramide, olmesartan, omeprazole, paracetamol, potassium, sodium chloride, and tramadol. ECOG performance status was 1 at screening.

On 02 Aug 20[redacted] (Day 1), treatment with study drug was initiated. On 17 Aug 20[redacted] (Day 16), the study drug was reduced to a dose of 20 mg due to dry mouth (Grade 3) and oral dysesthesia (Grade 3). On 31 Aug 20[redacted] (Day 30), the study drug was reduced to a dose of 14 mg due to dry mouth (Grade 3) and oral dysesthesia (Grade 3). On 19 Sep 20[redacted] (Day 49), the study drug was reduced to a dose of 10 mg due to oral dysesthesia (Grade 3). On 06 Nov 20[redacted] (Day 97), the study drug was interrupted due to oral dysaesthesia (Grade 2).

On 20 Nov 20[redacted] (Day 111), the subject was hospitalized for hip prosthesis surgery planned before randomization of the study. Surgery was for worsening of coxarthrosis of right hip (Grade 2). On the same day, the subject experienced an episode of progressive atrial fibrillation (Grade 2), which was treated with bisoprolol. The subject recovered from atrial fibrillation that same day, but surgery had to be postponed. On 26 Nov 20[redacted] (Day 117), surgery for right hip prosthesis was done. Treatment included ceftriaxone, enoxaparin, paracetamol metoclopramide, ketorolac and tramadol. On 03 Dec 20[redacted] (Day 124), the subject recovered from worsening of coxarthrosis (right hip) and was discharged from hospital. The Investigator assessed the events of osteoarthritis and atrial fibrillation as serious and not related to the study drug. On 12 Dec 20[redacted] (Day 133), the study drug was resumed at the reduced dose of 8 mg due to oral dysaesthesia (Grade 2).

On 22 Oct 翌年* (Day 447), the study drug was interrupted due to asthenia (Grade 2), oral dysesthesia (Grade 2), and decreased appetite (Grade 3). On 25 Oct 20[redacted] (Day 450), the subject had mild acute renal failure (Grade 1) and hypokalemia (Grade 1). Lab findings showed creatinine was 2.62 mg/dL (NR: 0.5–1.1) and potassium was 3.1 mEg/L(NR; 3.5-4.5). Treatment included intravenous (IV) hydration including 40 mmol potassium chloride and sodium chloride solution. On 26 Oct 20[redacted] (Day 451), the subject received an additional 500 mL of physiologic saline solution. Repeat laboratory showed potassium of 3.3 mEq/L and creatinine of 1.6 mg/dL. The event of acute renal failure was resolved and the subject was discharged. . The Investigator assessed the event of acute renal failure as serious and not

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related to the study drug. On 07 Nov 20[redacted] (Day463), the study drug was resumed at the reduced dose of 4 mg due to oral dysesthesia (Grade 3) and asthenia (Grade 3) After the unblinding, the subject was found to be randomized to lenvatinib. The subject remained on the study at the time of data cut-off.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	15151001
Study ID	HOPE303
Manufacturer's Control Number	E7080-01178-CLI-IT
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Cerebrovascular accident
AEs leading to Discontinuation	Cerebrovascular accident

A 71-year-old White female was diagnosed with Stage IVC T1N0M1 follicular variant papillary thyroid cancer (PTC) on 11 Nov 2010. On 26 May 2011, the subject was diagnosed with additional metastatic disease. The last date of disease progression was on 04 May 2012. Significant medical history included hypertension, hysterectomy, thyroidectomy, dorsal and lumbar dorsal arthrodesis, bone pain, and legs paresthesia. At Screening, tumor assessments of target/non-target lesions via CT scan showed anterior left trunk lesion, right trunk lesion and left lower lobe lung mass. The subject received prior curative radio iodine therapy. Concomitant medications included acetylsalicylic acid, amlodipine, benzydamine, bromazepam, choline alfoscerate, clopidogrel, duloxetine, enoxaparin, furosemide, levothyroxine, loperamide, metoclopramide, Nebacetin (neomycin/ bacitracin), nifedipine, nutrients with vitamins (integration of glutathione, vitamin C, vitamin E and thioctic acid), omeprazole, ranitidine, rupatadine, and Vaseretic (enalapril/ hydrochlorothiazide). ECOG performance status was 2 at screening.

On 25 May 20[redacted] (Day 1), treatment with study drug was initiated. On 04 Aug 20[redacted] (Day 72), the study drug dose was reduced to 20 mg due to proteinuria (Grade 3). On 27 Oct 20[redacted] (Day 156), the study drug dose was reduced to 14 mg due to nausea (Grade 2). On 07 Dec 20[redacted] (Day 197), the study drug dose was reduced to 10 mg due to nausea (Grade 3) and palmar-plantar erythrodysasthesia syndrome (Grade 3).

On 27 Feb 翌年* (Day 279), the subject was hospitalized to perform a scheduled CT scan assessment. While hospitalized, the subject experienced right arm paresis (Grade 1) where the subject was treated with enoxaparin and clopidogrel. On 01 Mar 20[redacted] (Day 281), brain CT scan showed small blurred hypodense lesions in the left periventricular region, close to the thalamus, possible ischemic focus; ventricular system and extra-ventricular cerebrospinal fluid spaces of normal morphology and size; and no midline shift. The subject was diagnosed with ictus cerebri (cerebrovascular accident, Grade 2). On 04 Mar 20[redacted] (Day 284), a second brain CT scan confirmed the cerebrovascular accident. During hospitalization, neurological evaluation documented paresis of the right arm with the necessity of rehabilitation and therapy with enoxaparin. On 08 Mar 20[redacted] (Day 288), the subject was stable and the event was considered to have resolved with sequelae. The subject was discharged on the same day. The Investigator assessed the event of cerebrovascular accident as serious and possibly related to the study drug. The subject received the last dose of study drug on 28 Feb 20[redacted] (Day 280). The subject was withdrawn from the study due to this event.

After the unblinding, the subject was found to be randomized to lenvatinib.

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付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	15151003
Study ID	HOPE303
Manufacturer's Control Number	E7080-01142-CLI-IT
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Weight decreased, Vomiting

A 64-year-old White female was diagnosed with Stage III T3NxMx tall cell papillary thyroid cancer (PTC) on 21 Sep 2004. In Sep 2006, the subject was diagnosed with metastatic disease. The last date of disease progression was on 11 May 2012. Significant medical history included thyroidectomy, diabetes mellitus, menopause, and cough. At Screening, tumor assessments of target/non-target lesions via CT scan showed right hilar adenopathy, right upper lobe lung mass, and bilateral lung masses. The subject received prior curative radio iodine therapy and previous anticancer was sorafenib. Concomitant medications included metformin, Paracodina tranexamic acid, levofloxacin, metoclopramide, dexamethasone, albumin human, glutathione, propranolol, olmesartan, furosemide, and levothyroxine. ECOG performance status was 0 at screening.

On 31 May 20[redacted] (Day 1), treatment with study drug was initiated.

On 03 Sep 20[redacted] (Day 97), the study drug dose was reduced to 20 mg due to asthenia (Grade 1), decreased appetite (Grade 1), and maculopapular rash (Grade 1). On 18 Oct 20[redacted] (Day 141), the study drug dose was reduced to 14 mg due to asthenia (Grade 3) and nausea (Grade 3). The subject was reported not recovered from asthenia on 03 Sep 20[redacted], recovered from decreased appetite and maculopapular rash and recovering from nausea and the second asthenia event. The Investigator assessed all these events non-serious and probably related to study drug.

On 29 Jan 翌年* (Day 244), the study drug was interrupted due to vomiting (Grade 3) and nausea (Grade 3), treated with metoclopramide. On 04 Feb 20[redacted] (Day 250), the subject was hospitalized due to persisting vomiting (Grade 3) and consequent weight loss (Grade 3). Treatment with metoclopramide was continued, and additional treatment with dexamethasone and glutathione was started. Gastroscopy and abdomen ultrasonography results were negative. On 07 Feb 20[redacted] (Day 253), the subject's weight was 50 kg, which was decreased by 18 kg from baseline. On 11 Feb 20[redacted] (Day 257), vomiting was resolved, weight loss improved, and the subject was discharged from hospital. On 07 Mar 20[redacted] (Day 281), the subject's weight increased to 57 kg, and the event of weight loss improved to Grade 2. The Investigator assessed the events of vomiting and weight decreased as serious and probably related to the study drug. The study drug was resumed on 11 Feb 20[redacted] (Day 257) at a reduced dose of 10 mg due to these events.

The subject received the last dose of study drug on 19 Mar 20[redacted] (Day 293). Tumor assessment showed disease progression by independent radiological review. After the unblinding, the subject was found to be randomized to lenvatinib.

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付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	16011009
Study ID	HOPE303
Manufacturer's Control Number	E7080-01219-CLI-PL
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Right ventricular hypertrophy

A 63-year-old White female was diagnosed with Stage IVA T4aNxM0 papillary thyroid cancer (PTC) variants on 25 Feb 2011. On 03 Oct 2011, the subject was diagnosed with metastatic disease. The last date of disease progression was on 07 May 2012. Significant medical history included subtotal bilateral strumectomy, palliative resection of left part of the right thyroid lobe, iatrogenic hypothyroidism, varicose veins of the legs, atrioventricular block first degree, palpitations, vertigo, left eye cataract operation, cataract of right eye, skin neoplasm excision, and congenital atrial septal defect type II. At Screening, tumor assessments of target/non-target lesions via CT scan showed left middle or lower cervical adenopathy, right mediastinal adenopathy, right upper lobe lung mass, left lower lobe lung mass, left thyroid bed lesion, right thyroid bed lesion, a structure below cricoid cartilage probably a lymph node lesion, bilateral lymph node lesions in submandibular region, bilateral mediastinal adenopathy, and disseminated lung masses in both lungs. The subject received prior palliative radio iodine therapy. Concomitant medications included amoxicillin, norfloxacin, metoprolol, omeprazole, loperamide, megestrol, ciprofloxacin, akritoin, naproxen, metoclopramide, paracetamol, Ascorutin, torasemide, spironolactone, ramipril, and levothyroxine. ECOG performance status was 0 at screening

On 02 Jul 20[redacted] (Day 1), treatment with study drug was initiated. On 22 Oct 20[redacted] (Day 113), the study drug was interrupted due to decreased appetite (Grade 2), diarrhea (Grade 2), nausea (Grade 2), vomiting (Grade 2), and weight decreased (Grade 2). The study drug was resumed at 24 mg on 05 Nov 20[redacted] (Day 127). On 05 Dec 20[redacted] (Day 157), the dose of the study drug was reduced to 20 mg due to palmar-plantar erythrodysaesthesia syndrome (Grade 1) and weight decreased (Grade 1).

On 12 Mar 翌年* (Day254), the subject experienced right ventricular hypertrophy (Grade 1). On 30 Mar 20[redacted] (Day 272), the study drug was interrupted due to vomiting (Grade 3) and diarrhea (Grade 3). On 08 Apr 20[redacted] (Day 281), the study drug was resumed at reduced dose of 14 mg. On 12 Apr 20[redacted] (Day 285), the subject was hospitalized for right ventricular hypertrophy (Grade 1). Pulmonary microembolism was suspected due to elevated level of D-dimer and right ventricular hypertrophy found on routine echocardiogram, although the subject was asymptomatic. Pulmonary microembolism was excluded based on results of CT pulmonary angiogram scan performed on the day of admission, and lower levels of D-dimer. On 19 Apr 20[redacted] (Day 292), further examinations confirmed the diagnosis of congenital atrial septal defect type II with left to right shunt, mild tricuspid valve incompetence and good systolic function of left and right ventricle. The subject remained asymptomatic and was discharged from the hospital on the same day. The event right ventricular hypertrophy (Grade 1) was not resolved. No action was taken with the study drug. The Investigator assessed the event of right ventricular hypertrophy as serious and not related to the study drug. . On 03 Jun 20[redacted] (Day 337), the study drug was interrupted due to decreased appetite (Grade 2). On 01 Jul 20[redacted] (Day 365), the study drug was resumed at a reduced dose of 10 mg due to weight decreased (Grade 2).

The subject received the last dose of study drug on 27 Aug 20[redacted] (Day 422). Tumor assessment

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showed disease progression by independent radiological review. After the unblinding, the subject was found to be randomized to lenvatinib.

付録 2.7.6-32　死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	16011012
Study ID	HOPE303
Manufacturer's Control Number	E7080-01157-CLI-PL, E7080-01291-CLI-PL
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Anal fistula, Functional gastrointestinal disorder

A 58-year-old White female was diagnosed with Stage TxNxMx poorly differentiated papillary thyroid cancer (PTC) on 21 May 2001. In Jan 2011, the subject was diagnosed with metastatic disease. The last date of disease progression was on 28 Jun 2012. Significant medical history included total resection of left thyroid lobe, resection of mediastinal lymph nodes, resection of right lung benign tumor, cholecystectomy, acute hemorrhagic pancreatitis, resection of benign uterine polyp, surgical neck exploration, hypertension, hypothyroidism, postoperative hypoparathyroidism, subtotal resection of right thyroid lobe, and removal of right renal stone. At Screening, tumor assessments of target/non-target lesions via CT scan showed right side thyroid bed lesion, left upper lobe lung mass, multiple bone metastases, bilateral mediastinum adenopathy, right pleural effusion, and right adrenal mass. The subject received prior prophylactic radiotherapy to mediastinal adenopathy, neck adenopathy, and thyroid bed and prior curative radio iodine therapy. Concomitant medications included acetylsalicylic acid, alfacalcidol, amlodipine, amoxicillin, captopril, carbamazepine, cefuroxime, cetirizine, Co-Diovan (valsartan and hydrochlorothiazide), etamsilate, ibuprofen, indapamide, ketoprofen, levothyroxine, megestrol, nebivolol, omeprazole, potassium, ramipril, Spektramox (amoxicillin, trihydrate, and clavulanic acid), and Thiocodin®. ECOG performance status was 0 at screening.

On 14 Aug 20[redacted] (Day 1), treatment with study drug was initiated. On 20 Nov 20[redacted] (Day 99), the dose of the study drug was reduced to 20 mg due to stomatitis (Grade 3).

On 10 Feb 翌年* (Day 181), the subject was hospitalized with a perianal fistula (Grade 2) of moderate severity, and the study drug was interrupted. C-reactive protein was 123.5 mg/L (normal range not reported), and bacteriologic examination of the fistula revealed *Candida albicans* and *Escherichia coli*. Treatment included pain-relief drugs, intravenous infusions and a local surgical intervention which led to gradual improvement. On 15 Feb 20[redacted] (Day 186), anal fistula improved and the subject was discharged. On 27 Feb 20[redacted] (Day 198), there was gradual fistula healing with no symptoms of local inflammation present. On 07 Mar 20[redacted] (Day 206), anal fistula improved to Grade 1 and study drug was resumed at a reduced dose of 14 mg due to perianal fistula. On 03 Apr 20[redacted] (Day 233), anal fistula (Grade 1) was recovered. The Investigator assessed the event of anal fistula as serious and possibly related to the study drug.

On 03 Jun 20[redacted] (Day 294), the subject had a respiratory tract infection (Grade 2), which was treated with Spektramox, cefuroxime and cetirizine. The event of respiratory tract infection was reported as recovering. On 12 Jun 20[redacted] (Day 303), the subject was hospitalized due to abdominal pain. Abdominal ultrasound showed renal stones, and colonoscopy excluded significant abnormalities. Diagnosis was functional intestinal disturbances (Grade 2) related to antibacterial treatment of respiratory tract infection (Grade 2). On 14 Jun 20[redacted] (Day 305), functional gastrointestinal disorder (Grade 2) was recovered and the subject was discharged home. The Investigator assessed the event of functional gastrointestinal disorder as serious and not related to the study drug. No action was taken with the study drug.

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The subject remained on the study at the time of data cut-off. After the unblinding, the subject was found to be randomized to lenvatinib.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	16021002
Study ID	HOPE303
Manufacturer's Control Number	E7080-01126-CLI-PL
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Pancreatitis

A 71-year-old White female was diagnosed with Stage III T3N0M0 poorly differentiated insular type papillary thyroid cancer (PTC) on 07 Sep 2010. On 16 Jun 2011, the subject was diagnosed with metastatic disease. The last date of disease progression was on 06 Jul 2012. Significant medical history included hypertension, type 2 diabetes mellitus, cholecystectomy, spinal osteoarthritis, post-operative hypothyroidism, left crural varices, transient hypokalemia, depressed mood, insomnia, obesity, and thyroidectomy. At Screening, tumor assessments of target/non-target lesions via CT scan showed right middle lobe lung mass, left lower lobe lung mass, and multiple small lesions in both lungs. The subject received prior curative radiotherapy to the bilateral middle and cervical lymph nodes and thyroid bed and prior curative radio iodine therapy. Concomitant medications included akritoin, amlodipine, amoxicillin with clavulanate potassium, amoxicillin, ascorbic acid, azithromycin, Bactrim, benzydamine, Bilastine, bisoprolol, boric acid, bromhexine, calcium, carbocysteine, cefuroxime, cetirizine, chlorhexidine, chlorquinaldol, cyproheptadine, diosmectite, drotaverine, estazolam, Fludronef, Gastrolit, glucose, Sterofundin BRAUN intravenous, hyaluronic acid, hydrocortisone, ibuprofen w/paracetamol, ibuprofen, insulin human, ketoprofen, lactobacillus acidophilus, levodropropizine, levothyroxine, lisinopril, loperamide, metformin, methylprednisolone, montelukast, Nature's Way Primadophilus Original, nifuroxazide, norfloxacin, nystatin, ornithine, Pectosol, potassium, prednisone, saccharomyces boulardii, salicylic acid, Sinupret, sodium chloride, Solcoseryl Dental, spironolactone, telmisartan, Thiocodin, torasemide, and triamcinolone (throat preparations). ECOG performance status was 0 at screening.

On 04 Sep 20[redacted] (Day 1), treatment with study drug was initiated.

On 20 Jan 翌年* (Day 139), the subject was hospitalized with recurrent severe abdominal pain (Grade 1), poor general condition, and an intense yellow tinge to her skin. Abdomen was tender on palpation, with pain in the right hypochondriac region, no pathological masses, negative peritoneal signs and slow peristalsis. Laboratory tests revealed signs of cholestatic liver injury (Grade 3), with increased lactate dehydrogenase (LDH), creatine phosphokinase (CPK), GGTP and hyperbilirubinemia, and a tendency towards hypokalemia. Physical exam showed icterus with weakened peristalsis. X-ray of the abdomen showed subileus (Grade 3). Ultrasound scan showed cholestasis. Blood and urine amylase was normal. Lipase activity could not be performed. Surgical consultation reported the subject had a 4 day history of abdominal pain, nausea, recurrent vomiting (Grade 1), loose stools passed (discolored) (Grade 1), and yellow tinge to the skin. Abdomen was soft with symptoms of pain in the upper middle section and negative peritoneal signs, with audible peristalsis. On 21 Jan 20[redacted] (Day 140), the study drug was interrupted due to weight decreased (Grade 2), subileus (Grade 3), cholestatic liver injury (Grade 3), and pancreatitis (Grade 3). On 22 Jan 20[redacted] (Day 141), laboratory studies revealed increased blood lipase 859 U/L (NR 0-130 U/L) and amylase 538 U/L (NR: 50-252 U/L), and the initial diagnosis of hepatic failure and subileus was changed to pancreatitis (Grade 3). Cholestatic liver injury and subileus were considered secondary to pancreatitis. The corrective treatment was strict diet (easily digestible) followed by a light, hepatoprotective, diabetic diet;

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intravenous L-ornithini aspartas, intravenous drotaverine, intravenous fluids including 5% glucose, Sterofundin and 0.9% sodium chloride, Kalium chloratum, Hepa-Merz, No-Spa, Bisocard, Aldan, Euthyrox, subcutaneous insulin human, and vitamin-C. On 23 Jan 20[redacted] (Day 142), subileus completely recovered; peristalsis and stool were normal. The subject gained weight. The subject's condition improved, she gradually became less jaundiced and the activity of her liver enzymes decreased. On 25 Jan 20[redacted] (Day 144), the subject started taking Kalipoz prolongatum for transient hypokalemia, Hepatil-l-ornithine aspartate for liver injury secondary to pancreatitis, levothyroxine sodium for iatrogenic hypothyroidism and amlodipine for hypertension. On 28 Jan 20[redacted] (Day 147), liver and pancreas follow-up tests revealed significant improvement, and pancreatitis was resolved. On 29 Jan 20[redacted] (Day 148), the subject was discharged from hospital. The Investigator assessed the event of pancreatitis as serious and probably related to the study drug. The study drug was resumed at the reduced dose of 20 mg due to pancreatitis.

The subject remained on the study at the time of data cut off. After the unblinding, the subject was found to be randomized to lenvatinib.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	16031001
Study ID	HOPE303
Manufacturer's Control Number	E7080-01171-CLI-PL
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Gallbladder mucocoele

A 30-year-old White female was diagnosed with Stage I TxN1bM0 clear cell follicular thyroid cancer (FTC) with metastatic disease on 13 Dec 2008. The last date of disease progression was on 27 Mar 2012. Significant medical history included polycystic ovary syndrome, nodular goitre, lymph node dissection in the neck for thyroid carcinoma metastasis to lymph node, lymph node dissection in the neck, subtotal thyroidectomy, total thyroidectomy, locoregional lymphadenectomy, overweight, mild left shoulder pain, temporary formication left upper limb, and hypothyroidism. At Screening, tumor assessments of target/non-target lesions via CT scan showed medial end left clavicle-upper margin level between left venous angle and posterior-upper clavicle surface lesion, right middle lobe lung mass, anterior mediastinum adenopathy, and left middle or lower cervical adenopathy. The subject received prior curative radio iodine therapy and previous anti-cancer therapy was yttrium (90y) compounds. Concomitant medications included amlodipine, amoxicillin, calcium, clindamycin, dalteparin, diosmectite, drotaverine, GIK solution, glucose, Sterofundin, Hetastarch, hydrochlorothiazide, hydroxyzine, Jeanine, Jonosteril, ketoprofen, levothyroxine, loperamide, metamizole, metoclopramide, omeprazole, papaverine, paracetamol, ramipril, sodium chloride, and Trophicard. ECOG performance status was 0 at screening.

On 17 Apr 20[redacted] (Day 1), treatment with study drug was initiated. On 20 Sep 20[redacted] (Day 157), the study drug dose was reduced to 20 mg due to diarrhea (Grade 3).

On 21 Feb 翌年* (Day 311), the subject was hospitalized for gallbladder mucocele (Grade 3) with hypochondrium pain (Grade 2) radiating to the right shoulder, and vomiting. An abdominal ultrasound confirmed hydrocele of the gallbladder and stone in the gallbladder. The subject was scheduled for surgical resection of the gallbladder. On 22 Feb 20[redacted] (Day 312), the study drug was interrupted in preparation for the surgery. Treatment included 0.9% sodium chloride, metamizole, drotaverine, papaverine, acetaminophen, Jonosteril, Fragmin dalteparin natrium, omeprazole, ketoprofen, 5% glucose, and Haes. On 28 Feb 20[redacted] (Day 318), the subject underwent a cholecystectomy. On 02 Mar 20[redacted] (Day 320), the event of gallbladder mucocele was resolved. The subject was discharged from hospital on drotaverine for abdominal pain. The Investigator assessed the event of gallbladder mucocele as serious and possibly related to the study drug. On 08 Mar 20[redacted] (Day 326), the study drug was resumed at 20 mg.

The subject remained on the study at the time of data cut-off. After the unblinding, the subject was found to be randomized to lenvatinib.

*新薬承認情報提供時に置き換え

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	17031002
Study ID	HOPE303
Manufacturer's Control Number	E7080-00710-CLI-GB
Randomized treatment	Lenvatinib 24 mg QD
Non-Fatal SAE(s)	Headache, Hypertension, Vomiting

A 68 year old White female was diagnosed with Stage IVC T4aN1bM0 widely invasive papillary thyroid cancer (PTC) in 2007. In Jan 2008, the subject was diagnosed with metastatic disease. The last date of disease progression was on 22 Feb 2012. Significant medical history included right leg angioplasty, cholecystectomy, varicose vein surgery, hypertension, hiatus hernia, insomnia, neck, back, hip, and hand pain from cancer, bone pain, dyspepsia, hypercholesterolaemia, nausea, sterilization, total thyroidectomy, sinus congestion, right selective neck dissection, cough, seasonal allergy, blurred vision, and dyspnoea. At Screening, tumor assessments of target/non target lesions via CT scan showed left lobe lung mass, right lobe lung mass, right lower lobe lung mass, left supraclavicular adenopathy, left neck adenopathy, tracheal mass anterolateral to trachea, mass posterior to trachea, single left upper cervical region lesion, and single lesion posteriorly at approximately L1 L2. The subject received prior curative radiotherapy at right upper cervical neck adenopathy and prior curative radio iodine therapy. Concomitant medications included acetylsalicylic acid, amitriptyline, amlodipine, antacids, atorvastatin, beclometasone, benzydamine, Cefalexin, chlorphenamine, citric acid, E 45 cream, ibuprofen, levothyroxine, loperamide, loratadine, metoclopramide, naproxen, nefopam, omeprazole, paracetamol, ramipril, simvastatin, trimethoprim, and zopiclone. ECOG performance status was 1 at screening.

On 12 Mar 20[redacted] (Day 1), treatment with study drug was initiated. On 13 Mar 20[redacted] (Day 2) the subject experienced headache (Grade 1). On 10 Apr 20[redacted] (Day 30), the study drug was interrupted due to hypertension (Grade 3). Treatment included an increase in Ramipril dose and amlodipine. On 16 Apr 20[redacted] (Day 36), the study drug was resumed at the reduced dose of 20 mg due to hypertension (Grade 2) with average blood pressure of 187/97 mmHg. On 18 Apr 20[redacted] (Day 38), the subject was hospitalized for severe headache (Grade 3), nausea (Grade 3), vomiting (Grade 3) and hypertension (Grade 3). Treatment included paracetamol, naproxen, nefopam, and ibuprofen and ramipril dose was again increased.. On the same day, the subject also experienced neck pain (Grade 2), which did not resolve with pain medication. On 19 Apr 20[redacted] (Day 39), blood pressure was stable for 24 hours (149/77 mmHg) and improved to Grade 2, and the subject was discharged from hospital. On 20 Apr 20[redacted] (Day 40), vomiting and headache improved to Grade 1. On 04 May 20[redacted] (Day 54), the study drug was resumed at the reduced dose of 14 mg due to headache (Grade 2) and fatigue (Grade 2). On 21 May 20[redacted] (Day 71), vomiting was resolved. On 22 May 20[redacted] (Day 72), the study drug was interrupted due to fatigue (Grade 3) and nausea (Grade 2). On 01 Jun 20[redacted] (Day 82), the study drug was resumed at the reduced dose of 10 mg due to fatigue (Grade 1). On 11 Jun 20[redacted] (Day 92), the study drug was interrupted due to headache (Grade 2) and fatigue (Grade 2). On 09 Jul 20[redacted] (Day 120), the study drug was resumed at the reduced dose of 8 mg. On 17 Dec 20[redacted] (Day 281), the study drug was interrupted due to dysgeusia (Grade 2). On 31 Dec 20[redacted] (Day 295), the study drug was resumed at the reduced dose of 4 mg. The event of headache was reported as not resolved and hypertension was recovering. The Investigator assessed the events of headache (Grade 3), hypertension (Grade 3), and vomiting (Grade 3) as serious and possibly related to the study drug.

The subject remained on the study at the time of data cut off. After the unblinding, the subject was found to be randomized to lenvatinib.

付録 2.7.6-32 死亡，その他重篤な有害事象の叙述（国際共同 303 試験：無作為化期）（続き）

SUBJECT NUMBER	17041002
Study ID	HOPE303
Manufacturer's Control Number	E7080-00651-CLI-GB, E7080-01112-CLI-GB, E7080-01149-CLI-GB
Randomized treatment	Lenvatinib 24 mg QD
Death due to PD	Yes
Non-Fatal SAE(s)	Back pain, Lower respiratory tract infection, Spinal cord compression

A 57-year-old Black or African American male was diagnosed with Stage IVC T3N0M1 follicular papillary thyroid cancer (PTC) with metastatic disease on 11 Mar 2007. The last date of disease progression was on 24 Jan 2012. Significant medical history included pain to lower back, fatigue, total thyroidectomy, constipation, surgical spine stabilization T8 to T9, left hip replacement, spinal cord compression T9, total hip replacement, abdominal pain, pain to right groin, pain to right shoulder, dysuria, spinal cord decompression T4-T5, spastic paraparesis, intermittent nausea, radiotherapy to spinal cord, erectile dysfunction, modified radical neck dissection, and spinal cord compression. At Screening, tumor assessments of target/non-target lesions via CT scan showed posterior right sided chest wall mass, left anterior chest wall mass, right sided chest wall mass anteriorly positioned, prevertebral T4 Lesion, left iliac mass, right hilar adenopathy, and lesion of lamina, right transverse process and spinous process at T7. The subject received prior palliative radiotherapy of the right and left hip, dorsal thoracic vertebral lesion T-spine, left hemi pelvis, .dorsal thoracic vertebral lesions T2 to T6, right arm proximal humerus, left leg hip and femur and right clavicle, prior palliative radio iodine therapy and previous anticancer was sorafenib. Concomitant medications included alfacalcidol, amoxicillin with clavulanate potassium, amoxicillin, calcitriol, carbocisteine, ciprofloxacin, Cyclizine, dexamethasone, Diprobase, electrolytes w/macrogol emollients and protectives, erythromycin, flucloxacillin, general nutrients, gentamicin, hydrocortisone, ibuprofen, levothyroxine, lidocaine, morphine, Movicol, omeprazole, paracetamol, Pip/Tazo (piperacillin/tazobactam), senna alexandrina (herbal remedy), and trimethoprim. ECOG performance status was 2 at screening.

On 15 Feb 20[redacted] (Day 1), treatment with study drug was initiated.

On 22 Feb 20[redacted] (Day 8), the subject was hospitalized due to increasing back pain (Grade 2). He complained of increasing pain between the shoulder blades radiating anteriorly to the anterior chest wall. The subject was treated with dexamethasone and Zomorph. On 29 Feb 20[redacted] (Day 15), back pain improved to Grade 1 and reported as recovering. On 01 Mar 20[redacted] (Day 16), the subject was discharged home with daily lidocaine patches. The Investigator assessed the event of back pain as serious and not related to the study drug. No action was taken with study drug.

On 12 Sep 20[redacted] (Day 211) the subject received the study drug at a reduced dose of 20 mg due to decreased weight (Grade 2) and wound on penis (Grade 2). On 26 Apr 20[redacted] (Day 72), the subject experienced lower respiratory tract infection (Grade 2). There were multiple episodes of lower respiratory tract infection (Grade 2) on and off which were treated with amoxicillin with clavulanate potassium, flucloxacillin, amoxicillin, erythromycin, trimethoprim, and ciprofloxacin. On 26 Nov 20[redacted] (Day 286), the subject was hospitalized for continuing chest infection (Grade 2)