付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	1022-1014
Cycle/dose regimen last received:	Cycle 16
Overall duration of study drug:	11 February 20[redacted], ongoing as of cutoff date*
Reason for narrative:	
Nonfatal SAE(s)	Myocardial Ischemia Carotid Artery Stenosis Hypotension

A 70-year-old White male with medullary thyroid cancer originally was diagnosed on 12 July 2006 (Stage IVa at diagnosis). The date of last disease progression was on 03 February 2010. Significant medical history included a neck dissection (right side), total thyroidectomy, postoperative hypothyroidism, resection of submandibular lymph nodes, hoarseness, hyperlipidemia, hypertension, coronary artery disease, right ventricular hypertrophy, right bundle branch block, left ventricular systolic dysfunction, subendocardial infarction, coronary artery bypass graft (CABG), lightheadedness, type 2 diabetes mellitus, alcohol abuse, weight loss, and tuberculosis. Bone scan was normal. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan included supraclavicular adenopathy (right) and liver masses (right anterior and left lateral lobes). The ECOG performance status and NYHA functional class were reported as 0 and 1, respectively. The screening ECG was abnormal but not clinically significant, and an echocardiogram showed a baseline ejection fraction of 42.5%. No previous radiotherapy was reported. Previous anticancer therapy included sorafenib, tipifarnib, and "XL 184." Concomitant medications included acetylsalicylic acid, calcium with vitamin D, hydrocodone, multivitamin, ezetimide/simvastatin, rosuvastatin, metformin, levofloxacin, lansoprazole, famotidine, omeprazole, fenofibrate, ergocalciferol, acetylcysteine, bivalirudin, atropine, diphenhydramine, amoxicillin clavulanate, and cefpodoxime. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included lisinopril, hydrochlorothiazide, and carvedilol.

On 11 February 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 08 April 20[redacted], the dose was reduced to 20 mg QD due to elevated AST (Grade 2) and elevated ALT (Grade 3) (both nonserious and possibly related).

The study drug was interrupted on 25 October 20[redacted] (Day 257), as on the next day 26 October 20[redacted] (Day 258), the subject underwent carotid ultrasound which showed carotid artery stenosis (right side) (serious, Grade 3, not related) and carotid artery stenosis (left side) (nonserious, Grade 1, not related). He was subsequently diagnosed with cardiac ischemia with left ventricular systolic dysfunction (serious, Grade 2, not related). The subject was hospitalized and was treated with lisinopril. On 09 November 20[redacted] (Day 272), the subject underwent a left heart catheterization with coronary angiography and graft. The following day the subject had a carotid angiogram with right internal carotid stenting and left ventriculogram. On 10 November 20[redacted] (Day 273), the subject developed hypotension (serious, Grade 3, not related). Treatment included clopidogrel and dopamine. The subject recovered and was discharged from the hospital. The study drug was resumed on 18 November 20[redacted] (Day 281) at 20 mg QD. The subject was still receiving study drug at the data cutoff date of [redacted] 20[redacted].

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	1022-1017
Cycle/dose regimen last received:	Cycle 7
Overall duration of study drug:	28 May 20[redacted] to 29 November 20[redacted]
Reason for narrative:	
Nonfatal SAE(s)	Echocardiogram, Abnormal Dehydration Renal Failure, Acute Accidental Overdose Pneumonia Aspiration
AE(s) leading to treatment discontinuation	Flank Pain

A 40-year-old White male with medullary thyroid cancer was originally diagnosed on 30 September 2004 (Stage IVa at diagnosis). The date of last disease progression was on 09 March 2010. Significant medical history included laryngeal thyroplasty, complete thyroidectomy, post-operative hypothyroidism, postoperative hypocalcemia, subtotal thymectomy, neck dissections (left and right side), modified radical neck dissection (left side), cough, shortness of breath, insomnia, internal jugular vein dissection, rupture of left carotid artery, patch repair (Hemashield) to left carotid artery, tracheal stent, neck pain, malignant endotracheal obstruction, esophageal perforation and repair with sternocleidomastoid flap, ligation of thoracic duct, YAG laser destruction of endotracheal tumor, hypertension, tachycardia, anxiety, fatigue, myalgia, depression, gastroesophageal reflux disease (GERD), dysphagia, diarrhea, peripheral neuropathy, and spinal stenosis. Bone scan showed the etiology of uptake was due to trauma. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan showed other adenopathy. The ECOG performance status and NYHA functional class were reported as 1 and 1, respectively. The ECG was reported as abnormal (not clinically significant), and his body weight was 87.2 kg. No previous radiotherapy was reported. Previous anticancer therapy included sorafenib, tipifarnib, and salirasib. Concomitant medications and treatments during the study included ibuprofen, pregabalin, propofol, acetaminophen, hydrocodone, acetaminophen with codeine, morphine, fentanyl, oxycodone, lorazepam, alprazolam, bupivacaine, triamcinolone, haloperidol, risperidone, ciclesonide, loratadine, diphenhydramine, ipratropium, acetylcysteine, phenylephrine, escitalopram, acetaminophen with hydrocodone, zoledronic acid, docusate, Fleets enema, simethicone, loperamide, magnesium, Alka Seltzer, lansoprazole, furosemide, Caltrate and vitamin D, multivitamin, heparin, potassium, insulin, gabapentin, tamsulosin, dexmedetomidine, pamidronic acid, dicloxacillin, and packed red blood cells (RBC) for anemia. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included lisinopril and metoprolol.

On 28 May 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 15 September 20[redacted] (Day 111), the subject underwent a 2D echocardiogram that showed an aortic valve density (serious, Grade 1, not related). On 16 September 20[redacted], the subject was admitted to the hospital for transesophageal echocardiogram under sedation which revealed no aortic valvular vegetation, normal size left ventricle, trace mitral regurgitation, and trace tricuspid regurgitation. The subject was given fentanyl, midazolam, lyrica, and hydrocodone. On 17 September 20[redacted] (Day 113), the subject recovered from the event and was discharged home. No dose change occurred to the study drug.

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

On 09 November 20[redacted] (Day 166), the subject complained of bilateral flank pain (Grade 1) radiating to the lower abdomen. The following day, the subject reported intermittent constipation (Grade 1), worsening hypertension (BP 156/100 mmHg) (Grade 2) and microscopic hematuria (16-29/HPF) (Grade 1). On 12 November 20[redacted] (Day 169), the subject had hematochezia (Grade 2), and on 22 November 20[redacted] (Day 179), he experienced urinary urgency (Grade 1). On 24 November 20[redacted] (Day 181), the subject underwent IV pyelogram (results not provided). Treatment included milk of magnesia and lisinopril dose was increased from 10 to 20 mg and tamsulosin. On 26 November 20[redacted] (Day 183), the subject claimed that the bilateral flank pain radiating to the abdomen was continuing and had increased in intensity (Grade 2) and he was noted to have anemia (Grade 1) and vomiting (Grade 1). Treatment and diagnostic procedures were not specified. The events were resolved subsequently. The investigator considered the events, constipation, hematuria, urgency, flank pain, hypertension, hematochezia, anemia and vomiting to be nonserious. The events, constipation, hematuria and urgency were assessed as not related to the study drug and the flank pain, hypertension, hematochezia, anemia, and vomiting were assessed as possibly related to the study drug. The last dose was received on 29 November 20[redacted] (Day 186) as the study drug was withdrawn due to bilateral flank pain radiating to lower abdomen.

On 02 December 20[redacted] (Day 189, 3 days after the last dose), the subject was taken to the emergency room for unusual behavior, non-cardiac chest pain (Grade 1) and was found to be confused and it suspected that the subject might have had an unintentional narcotic overdose (Grade 4) and rhadomyolysis (Grade 2). Upon further work up, he was also diagnosed with acute renal failure (Grade 3) secondary to dehydration (Grade 3), hyperkalemia (Grade 2), and aspiration pneumonia (Grade 4) and was hospitalized. Treatments included piperacillin with tazobactam, vancomycin, fluconazole, albuterol, alteplase, salbutamol, albuterol with ipratopium, and intravenous fluid hydration. On 03 December 20[redacted], his BUN was 17 g/dL with creatinine of 0.8 mg/dL, and the dehydration and acute renal failure were considered to have resolved. Blood tests showed elevated ALT (Grade 1), elevated AST (Grade 2), thrombocytopenia (Grade 1), hypoalbuminemia (Grade 2), anemia (Grade 2), and hyperglycemia (Grade 1). He was found with left nephrolithiasis (Grade 1). The subject became increasingly agitated (Grade 2) and had metabolic acidosis (Grade 1). He was treated for narcotic withdrawal and the subject required intubation/ventilation. On 05 December 20[redacted] (Day 192), a chest CT scan revealed bilateral pleural effusions with consolidation (Grade 1), cardiomegaly (Grade 1), and hepatomegaly (Grade 1). CT scan of the brain was negative. On 09 December 20[redacted] (Day 196), a PICC line was placed. On 12 December 20[redacted] (Day 199), the subject underwent percutaneous bronchoscopic assisted tracheostomy tube placement due to respiratory failure and a PEG tube was placed. He was continued on multiple antibiotics and antifungals. On 16 December 20[redacted] (Day 203), the subject began to improve and reportedly had no neurological deficits and the next day was transferred to a rehabilitation center for physical therapy and weaning from ventilation machine. An MRI of the brain was negative for intracranial metastasis. He recovered from the accidental overdose but had neurological sequelae (described as agitation and occasional disorientation to place and sundowning). On 30 December 20[redacted] (Day 217), he became increasingly anemic and attempts at pain medication weaning caused further agitation and labile mood changes, and he continued to need some assistance with activities of daily living and had difficulty with problem solving and expression. On 12 January 翌年* (Day 230), it was decided to discharge the subject under hospice care. The investigator considered the dehydration, acute renal failure, accidental overdose (narcotic), and aspiration pneumonia to be serious and not related to study drug. The events, elevated ALT, elevated AST, thrombocytopenia, hypoalbuminemia, anemia, hyperglycemia, left nephrolithiasis, agitation, and metabolic acidosis, were nonserious and considered not related to the study drug.

On 26 February 20[redacted] (Day 275) (≥30 days after the last dose of study drug), the subject expired. The cause of death was reported as unknown.

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	3001-1001
Cycle/dose regimen last received:	Cycle 20
Overall duration of study drug:	12 October 20[redacted], ongoing as of cutoff date*
Reason for narrative:	
Nonfatal SAE(s)	Amenorrhea (three events)

A 37-year-old White female with medullary thyroid cancer was originally diagnosed on 04 September 2000 (Stage IVa at diagnosis). The date of last disease progression was on 14 September 2009. Significant medical history included total thyroidectomy, neck dissection (right side), fall from horse, fractures to lumbar spine (L-2 to L-4), pain in lumbar spine, groin muscle strain, menorrhagia, laparoscopy, hysteroscopy, polycystic ovaries, pregnancy from *in vitro* fertilization, emergency Caesarian section, childbirths, tonsillectomy, fatigue, and chronic diarrhea. Bone scan was normal. Screening tumor assessments of target/non-target lesions assessed via MRI included liver masses (left lateral and right anterior lobes). Previous radiotherapy included curative radiotherapy to the lymph nodes in the neck (right side). No previous anticancer therapy was reported. Concomitant medications included paracetamol, ibuprofen, povidine-iodine cream, terbinafine cream, diclofenac cream, salicylic acid cream, guaifenesin, amoxicillin, erythromycin, and cefalexin. Concomitant thyroxine suppression therapy was not reported. The subject received no concomitant antihypertensive therapy.

On 12 October 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 23 November 20[redacted] (Day 43), the subject experienced amenorrhea (serious [important medical event], Grade 1, probably related). No treatment was provided for the amenorrhea. On 01 February 翌年*, blood follicle stimulating hormone (FSH) (53.3 IU/L) and blood luteinizing hormone (LH) (41.6 IU/L) were within the postmenopausal range with premature ovarian failure. Urine pregnancy test was negative. The study drug was continued without modification. On 19 July 20[redacted] (Day 281), the subject had one episode of menstrual period and laboratory tests showed values within the normal range; FSH levels were 3.7 IU/L and LH levels were 5.7 IU/L. Urine pregnancy tests were negative. The amenorrhea was reported resolved on 22 July 20[redacted] (Day 284).

On 27 July 20[redacted] (Day 289), a second episode of amenorrhea was reported (serious [important medical event], Grade 1, probably related). The study drug was continued without modification. On 28 February 翌々年*, repeat tests showed FSH of 33.1 IU/L and LH levels of 47.6 IU/L. The event was reported resolved on 17 March 20[redacted] (Day 527).

On 07 March 20[redacted], the study drug was reduced to 20 mg QD due to blisters (feet) which was reported on 01 February 20[redacted] (Day 478) as nonserious, Grade 2, and probably related. On 22 March 20[redacted] (Day 527), the subject again experienced amenorrhea (serious [important medical event], Grade 1, probably related). No treatment was given and study drug dose was not modified. Both the blisters and amenorrhea were ongoing at the time of data cutoff ([redacted] 20[redacted]), and the subject was still receiving study drug at that time.

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	3001-1004
Cycle/dose regimen last received:	Cycle 13
Overall duration of study drug:	19 April 20[redacted] to 22 March 翌年*
Reason for narrative:	
Nonfatal SAE(s)	Gallbladder Obstruction (two events)

A 28-year-old White male with medullary thyroid cancer was originally diagnosed on 04 October 2006 (Stage IVb at diagnosis). The date of last disease progression was on 22 March 2010. Significant medical history included total thyroidectomy, hypothyroidism, radical neck dissection (right side), pain and paresthesia in right arm, wasting of right pectoral muscles, left ventricular hypertrophy, Horner's syndrome, and diarrhea. Bone scan was reported as marked by malignant lesion(s). Screening tumor assessments of target/non-target lesions assessed via spiral CT scan or MRI showed bilateral paratracheal adenopathy and liver masses (left medial and right anterior lobes). Previous radiotherapy included prophylactic and palliative radiotherapy to the thyroid gland and cervicothoracic spinal cord, respectively. Previous anticancer therapy included sunitinib. Concomitant medications included codeine, paracetamol, ibuprofen, nystatin, Codral, Diflam, loperamide, and heparin. Concomitant thyroxine suppression therapy included levothyroxine. The subject received no antihypertensive therapy.

On 19 April 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 27 May 20[redacted] (Day 39), the dose was reduced at 20 mg QD due to laryngitis (nonserious, Grade 3, probably related).

On 09 July 20[redacted] (Day 82), the subject experienced gastrointestinal upset (nonserious, Grade 1, possibly related) and elevated bilirubin (nonserious, Grade 2, not related). No treatment was given and both events were reported resolved. On 12 July 20[redacted] (Day 85), the subject experienced elevated ALT (nonserious, Grade 2, not related) and proteinuria (nonserious, Grade 2, possibly related). The subject recovered from both events. The study drug was interrupted due to the elevated bilirubin and elevated ALT.

On 20 July 20[redacted] (Day 93), the subject was admitted to the hospitalized for a possible gallbladder obstruction (serious, Grade 2, possibly related) due to gallstones. The radiologist confirmed that the subject had gallstones at screening but these were not reported. Treatment included metoclopramide, morphine, and codeine. On 22 July 20[redacted] (Day 95), the subject recovered and was discharged home. A surgery to remove the gallstones was scheduled. The study drug remained interrupted due to obstruction GI gallbladder and resumed on 28 July 20[redacted] (Day 101) at 20 mg QD.

On 14 August 20[redacted] (Day 118), study drug was interrupted. On 20 August 20[redacted] (Day 124), the subject was hospitalized for cholecystectomy due to gallbladder obstruction (second report) (serious, Grade 1, possibly related). Treatment included heparin, paracetamol, oxycodone, and cephalothin. On 21 August 20[redacted] (Day 125), the subject recovered and was discharged home. The study drug was restarted at 14 mg QD on 10 September 20[redacted] (Day 145). On 22 December 20[redacted] (Day 248), the dose was reduced to 10 mg QD due to anorexia (nonserious, Grade 3, probably related). The last dose was received on 22 March 翌年* (Day 338). On 31 March 20[redacted] (Day 347), the subject was discontinued from the study due to progressive disease.

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	3002-1004
Cycle/dose regimen last received:	Cycle 4
Overall duration of study drug:	22 June 20[redacted] to 11 October 20[redacted]
Reason for narrative:	
Nonfatal SAE(s)	Spinal Osteoarthritis

A 53-year-old White male with medullary thyroid cancer was originally diagnosed on 07 December 2009 (Stage IVc at diagnosis). The date of last disease progression was on 26 May 2010. Significant medical history included traumatic rib fractures, tachycardia, soft ejection systolic murmur, raised venous jugular pressure, peripheral edema, shortness of breath on exertion, hepatomegaly, and proximal myopathy. Bone scan was reported as marked by malignant lesion(s). Screening tumor assessments of target/non-target lesions assessed via spiral CT scan showed liver masses (right anterior and left medial lobes) and right upper lobe lung mass. The subject received no previous radiotherapy. Previous anticancer therapy included doxorubicin. Concomitant medications included esomeprazole, oxycodone, dexamethasone, and temazepam. Concomitant thyroxine suppression therapy included levothyroxine. The subject received no concomitant antihypertensive therapy.

On 22 June 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 17 August 20[redacted] (Day 57), the study drug dose was reduced to 20 mg QD due to desquamation of feet (skin exfoliation) (nonserious, Grade 1, probably related). On 16 September 20[redacted], the study drug dose was further reduced to 14 mg QD due to desquamation of hands and feet (nonserious, Grade 1, probably related).

The last dose was received on 11 October 20[redacted] (Day 112) and the next day (12 October 20[redacted]), the subject was discontinued from the study due to progressive disease. On 13 October 20[redacted] (Day 114, 3 days after the last dose), the subject was hospitalized with increasing back pain and was subsequently diagnosed with degenerative spinal disease (spinal osteoarthritis) (serious, Grade 3, not related) which was confirmed by a CT scan. Treatment was not reported. On 18 October 20[redacted] (Day 119), the subject was discharged from the hospital. The spinal osteoarthritis was noted as continuing.

On 16 December 20[redacted] (Day 178) (≥30 days after the last dose of study drug), the subject expired and the cause of death was reported as unknown.

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	3003-1001
Cycle/dose regimen last received:	Cycle 19
Overall duration of study drug:	19 November 20[redacted], ongoing as of cutoff date*
Reason for narrative:	
Nonfatal SAE(s)	Angioedema

A 60-year-old White male with medullary thyroid cancer was originally diagnosed on 01 March 2007 (Stage IVa at diagnosis). The date of last disease progression was on 06 November 2009. Significant medical history included thyroidectomy, Hodgkin's lymphoma, esophageal reflux, and lumbar spondylosis. Bone scan was reported as marked by degenerative disease. Screening tumor assessments of target/non-target lesions assessed via conventional CT scan included lung masses (left upper and right lower lobes) and liver masses (left medial and lateral lobe). Previous radiotherapy included radiotherapy to the thyroid gland and lymph nodes in the neck. Previous anticancer therapy was not reported. Concomitant medications included pantoprazole, selenium, vitamin E, zinc, magnesium chelate, calcium carbonate, glucosamine, folic acid, vitamin C, paracetamol, codeine, metronidazole, cefalexin, roxithromycin, Spektramox, Codral, and loperamide. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included irbesartan, ramipril, metoprolol, and amlodipine.

On 19 November 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 26 November 20[redacted] (Day 8), the subject developed mild hypertension (170/102 mmHg) (nonserious, Grade 1, probably related) and was treated with ramipril. On 22 December 20[redacted], irbesartan was added for control of the hypertension. Blood pressure range was 150-180/102-110 mmHg. On 26 December 20[redacted] (Day 38), the subject presented to the emergency department with increasing swelling of the lips and right side of the face and was hospitalized with a diagnosis of angioedema secondary to irbesartan (serious, Grade 2, not related). Treatment included hydrocortisone, promethazine, prednisolone, metoprolol, and ranitidine, and irbesartan was stopped. On 27 December 20[redacted] (Day 39), amlodipine was added to the metoprolol. He subsequently recovered from the angioedema and was discharged home. The hypertension was ongoing and on 01 June 翌年* (Day 195), the dose was reduced to 20 mg QD. On 22 March 翌々年*, the dose was further reduced to 14 mg QD due diarrhea, weight loss, anorexia, and intermittent vomiting (all nonserious, Grade 2, probably related).

The subject was still receiving study drug at the data cutoff date of [redacted] 20[redacted].

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	3003-1003
Cycle/dose regimen last received:	Cycle 11
Overall duration of study drug:	21 June 20[redacted], ongoing as of cutoff date*
Reason for narrative:	
Nonfatal SAE(s)	Pulmonary Embolism

A 72-year-old White male with medullary thyroid cancer originally diagnosed in December 2005 (Stage IVa at diagnosis). The date of last disease progression was on 01 June 2010. Significant medical history included total thyroidectomy, total pharyngolaryngectomy, esophageal reflux, diverticulitis, frequent bowel movements, hyperlipidemia, and coronary artery bypass. Bone scan was reported as marked by degenerative disease. Screening tumor assessments of target/non-target lesions assessed via conventional CT scan showed liver masses (left lateral, right anterior, and caudate lobes). ECOG performance status and NYHA functional class were reported as 0 and 1, respectively. The ECG was reported as normal, and his body weight was 73.3 kg. Previous radiotherapy included radiotherapy to the lymph nodes in the neck and pelvic bone. Previous anticancer therapy was not reported. Concomitant medications included ezetimibe, calcium, vitamin D, Extralife Clements Iron, lansoprazole, calcitriol, magnesium, codeine, cholestyramine, pyridoxine, and zoledronic acid. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included irbesartan.

On 21 June 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 29 November 20[redacted] (Day 162), the subject had a routine disease restaging CT scan which revealed a bilateral pulmonary embolism (serious, Grade 2, probably related). He was hospitalized and was treated with enoxaparin. On 03 December 20[redacted] (Day 166), the subject recovered from the event and was discharged home on enoxaparin. The study drug was continued on a reduced dose of 20 mg QD. The subject was still receiving study drug at the data cutoff date of [redacted] 20[redacted].

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	3003-1005
Cycle/dose regimen last received:	Cycle 4
Overall duration of study drug:	27 August 20[redacted] to 25 November 20[redacted]
Reason for narrative:	
Non- fatal SAE(s)	Decreased Appetite Constipation
AE(s) leading to treatment discontinuation	Decreased Appetite

A 69-year-old White male with medullary thyroid cancer was originally diagnosed on 25 July 2001 (Stage IVa at diagnosis). The date of last disease progression was on 23 August 2010. Significant medical history included neck dissection, Cushing's disease, Gilbert's syndrome, osteoporosis, vertebral fractures, chronic back pain secondary to osteoporosis, scoliosis, and diarrhea. Bone scan was reported as marked by trauma (healed fracture). Screening tumor assessments of target/non-target lesions assessed via conventional CT scan included bilateral hilar adenopathy, left paratracheal adenopathy, and liver masses (left lateral and right anterior lobes). Previous radiotherapy included curative radiotherapy to the lymph nodes and neck. Previous anticancer therapy was not reported. Concomitant medications included potassium, octreotide, paracetamol, ketoconazole, and Coloxyl with senna. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy was not reported.

On 27 August 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 30 August 20[redacted] (Day 4), the subject began to experience decreased appetite (serious, Grade 3, probably related). On 22 September 20[redacted] (Day 27), the subject was diagnosed with adrenal insufficiency (nonserious, Grade 2, not related) which was described as steroid insufficiency (Addisonian incident or low cortisol). Treatment included cortisone. On the same day, he was found to have lumbar vertebral fracture (nonserious, Grade 2, not related). Treatment included oxycodone. No diagnostic test was reported. He was hospitalized on 27 September 20[redacted] (Day 32) for the decreased appetite and was treated with intravenous fluid replacement and the study drug was interrupted. On 30 September 20[redacted] (Day 35), he recovered from the event. On 30 September 20[redacted] (Day 35), the dose was reduced to 20 mg QD due to the decreased appetite. On 03 October 20[redacted] (Day 38), the subject experienced constipation (serious, Grade 3, possibly related) and was hospitalized on 06 October 20[redacted] (Day 41). Treatment included a laxative and study drug was interrupted. The pain resolved after bowel movement. On 08 October 20[redacted] (Day 43), the event was reported resolved.

On 25 October 20[redacted] (Day 60), the subject again experienced decreased appetite (nonserious, Grade 2, possibly related). On 29 October 20[redacted] (Day 31), the dose was further reduced to 14 mg QD due to constipation (nonserious, Grade 2, possibly related). The decreased appetite was reported resolved on 20 November 20[redacted] (Day 86). The last dose was received on 25 November 20[redacted] (Day 91). On 30 November 20[redacted] (Day 96), the subject was discontinued from the study due to decreased appetite. The subject recovered from the adrenal insufficiency on 01 December 20[redacted] (Day 97) but had not recovered from the lumbar vertebral fracture.

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	4001-1005
Cycle/dose regimen last received:	Cycle 9
Overall duration of study drug:	18 August 20[redacted], ongoing as of cutoff date*
Reason for narrative:	
Nonfatal SAE(s)	Cholecystitis, Acute

A 69-year-old White male with medullary thyroid cancer was originally diagnosed on 06 June 2008 (Stage IVa at diagnosis). The date of last disease progression was on 04 August 2010. Significant medical history included total thyroidectomy, hypothyroidism, cervical discomfort, asthma, dyslipidemia, arterial hypertension, and lumbar pain. Bone scan was not performed. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan showed a liver mass (left lateral lobe). His body weight was 79 kg. Previous radiotherapy was not reported. Previous anticancer therapy was not reported. Concomitant medications included Seretide, phloroglucinol, pravastatin, modafinil, Gaviscon, and alfacalcidol. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included verapamil and perindopril.

On 18 August 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 06 October 20[redacted] (Day 50), the dose was reduced to 20 mg QD due to vomiting (nonserious, Grade 2, probably related). On 14 November 20[redacted] (Day 89), the subject complained of abdominal pain. Ultrasound revealed acute cholecystitis (serious, Grade 2, probably related) without lithiasis, and he was hospitalized the next day.

On 18 November 20[redacted], the dose was reduced to 14 mg QD due to anorexia, asthenia (both nonserious, Grade 2, probably related) and the acute cholecystitis (serious, Grade 2, probably related). On 03 January 翌年* (Day 139), the subject underwent cholecystectomy and the acute cholecystitis was reported resolved on the same day. The study drug was interrupted due to the surgery and resumed on 09 January 20[redacted] (Day 146) at 14 mg QD.

The subject was still receiving study drug at the data cutoff date of [redacted] 20[redacted].

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	5002-1012
Cycle/dose regimen last received:	Cycle 4
Overall duration of study drug:	28 January 20[redacted] to 18 May 20[redacted]
Reason for narrative:	
Nonfatal SAE(s)	Dyspnea
Fatal SAE(s) occurring > 30 days after the last dose	General Physical Health Deterioration

A 51-year-old White female with medullary thyroid cancer was diagnosed in December 2007 (Stage IVa at diagnosis). The date of last disease progression was on 16 December 2009. Significant medical history included hypothyroidism, adenopathy pain, asthenia, transient ischemic attack (TIA), phlebitis of the leg, diarrhea, dental abscess, lumbar pain, herniated disc, depression, total thyroidectomy, upper mediastinal node dissection, bilateral neck dissection, appendectomy and shoulder surgery. Bone scan was reported as marked by malignant lesions. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan included liver mass (left lateral lobe), right hilar and right mediastinal adenopathy, and other adenopathy. Previous radiotherapy included palliative radiotherapy to the shoulder girdle, arm/hand bones, and right tibia. Prior anticancer therapy for advanced disease included epirubicin, cisplatin, etoposide, gemcitabine, lanreotide, CEP 18770, cabozantinib (XL184), and carboplatin. Concomitant medications included ranitidine, bromazepam, oxycodone, dexamethasone, morphine, zoledronic acid, stomatological mouthwash, metronidazole, levofloxacin, nystatin, nadroparin, fentanyl, fluconazole, ceftriaxone, lansoprazole, esomeprazole, and rabeprazole. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy was not reported.

On 28 January 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 12 May 20[redacted] (Day 105), the subject was diagnosed with portal vein thrombosis (nonserious, Grade 3, probably related) and was treated with seleparine. The event remained ongoing. No change was made to the study drug. The last dose of study drug was administered on 18 May 20[redacted] (Day 111).

On 19 May 20[redacted] (Day 112, 1 day after the last dose), laboratory tests showed the following: low RBCs 3.58 x 10^{12}/L (normal range: 3.7-5.2 x 10^{12}/L), increased alkaline phosphatase of 152 U/L (normal range: 30-90 u/L), increased ALT of 83 U/L (normal range: 10-33 U/L), increased AST of 114 U/L (normal range: 10-36 U/L), T4 of 16.8 pmol/L (normal range: 9-28.4 pmol/L), decreased TSH of 0.071 mIU/L (normal range: 0.0-5 mIU/L), increased calcitonin of 23542 pg/mL (normal: -5 pg/mL), and increased CEA of 797.6 mcg/L (normal: -2.5 mcg/L). A CT scan showed progressive disease and the subject was subsequently discontinued from the study due to disease progression.

On 02 June 20[redacted] (Day 126, 14 days after the last dose), the subject experienced dyspnea (serious, Grade 2, not related) and was hospitalized for general physical health deterioration (serious, Grade 3, not related), tachycardia (nonserious, Grade 1, not related) and epigastric pain (nonserious, Grade 2, not related). On 04 June 20[redacted] (Day 128), laboratory tests revealed an infection (nonserious, Grade 3, not related) and she was treated with levofloxacin and ceftriaxone. She recovered from the dyspnea after a blood transfusion. Laboratory tests on 07 June 20[redacted] showed low RBC of 3.08 x 10^{12}/L (normal range: 3.7-5.2 x 10^{12}/L) and low hemoglobin of 96 g/L (normal range: 110-155 g/L). Additional treatments included polygeline, iron, potassium, dexamethasone, and haloperidol. On 08 June 20[redacted] (Day 132), she was discharged from the hospital and moved to palliative care. On 05 July 20[redacted] (Day 159, 48 days after the last dose), the subject died as result of worsening of general condition due to progressive disease.

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	5006-1002
Cycle/dose regimen last received:	Cycle 9
Overall duration of study drug:	25 May 20[redacted] to 28 January 翌年*
Reason for narrative:	
Nonfatal SAE(s)	Lung Infection

A 62-year-old White male with medullary thyroid cancer was originally diagnosed on 10 July 2008 (Stage IVa at diagnosis). The date of last disease progression was on 19 October 2009. Significant medical history included total thyroidectomy, hypothyroidism, hypertension, hypercholesterolemia, low sugar tolerance, systemic degenerative arthropathy. Bone scan was reported as marked by degenerative disease. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan showed liver masses (right anterior lobe), right paratracheal adenopathy, and other adenopathy. Previous radiotherapy was not reported. Previous anticancer therapy included XL-184-301. Concomitant medications included smectite, paracetamol/codeine, ambroxol, lactobacillus fermentum, flunisolide, fitostimoline, omeprazole, allantoin, paracetamol, dutasteride, amoxicillin, loperamide, tamsulosin, and levofloxacin. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included nebivolol, perindopril, and atenolol.

On 25 May 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 19 November 20[redacted] (Day 179), the subject reported a dental abscess (nonserious, Grade 2, not related). On 29 November 20[redacted] (Day 186), the study drug was interrupted due to the abscess. The abscess was resolved on 12 December 20[redacted] (Day 202). On 15 December 20[redacted] (Day 205), the subject had a fever (nonserious, Grade 1, not related) and was hospitalized with a diagnosis of pulmonary infection (serious, Grade 1, not related). Chest x-ray showed parenchymal consolidation of the right lobe and WBC was within normal limits. Treatment included paracetamol, ceftriaxone, and levofloxacin. The study drug was resumed on 17 December 20[redacted] (Day 207) without dose modification. On 24 December 20[redacted] (Day 214), the subject recovered from the fever and pulmonary infection.

The last study dose was received on 28 January 翌年* (Day 249). On 29 January 20[redacted] (Day 250), the subject was discontinued from the study due to progressive disease.

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted]日カットオフデータ–

Subject:	5006-1003
Cycle/dose regimen last received:	Cycle 9
Overall duration of study drug:	16 July 20[redacted] to 22 March 翌年*
Reason for narrative:	
Nonfatal SAE(s)	Premature Menopause

A 34-year-old White female with medullary thyroid cancer was originally diagnosed on 20 November 2003 (Stage IVa at diagnosis). The date of last disease progression was on 18 June 2010. Significant medical history included total thyroidectomy, laterocervical lymph node dissection, postsurgical parahypothyroidism, anemia, appendectomy, abdominal pain, biliary sludge (no cholecystitis), diarrhea, joint pain, compression of lumbar vertebra, and polycystic ovaries. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan included liver masses (left medial, left lateral, and right anterior lobes). Previous radiotherapy was not reported. Previous anticancer therapy included motesanib. Concomitant medications included calcitriol, calcium, pregabalin, lansoprazole, ursodeoxycholic acid, diclofenac, loperamide, thiocolchicoside, methylprednisolone, chlorphenamine, hydromorphone, and prednisone. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy was not reported.

On 16 July 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 18 July 20[redacted] (Day 3), the subject experienced absence of menstrual cycle (nonserious, Grade 1, possibly related) which was reported to have increased in severity on 08 October 20[redacted] (Day 85) (nonserious, Grade 2, possibly related). No treatment was given for amenorrhea. Pregnancy tests were negative. The event amenorrhea was reported resolved. On 03 December 20[redacted] (Day 141), the subject had a blood tests showed hypergonadotropic hypogonadism, with abnormal levels of FSH, LH, and anti-Müllerian hormone (0.7 ng/mL, reference range: 2.0 to 6.8). She was diagnosed with premature ovarian failure –infertility (premature menopause) (serious [an important medical event], Grade 3, possibly related). On 03 January 翌年* (Day 172), repeat blood tests confirmed the hypergonadotropic hypogonadism. Levels of anti-Müllerian hormone were undetectable which was consistent with loss of the follicle reserve. A repeat pregnancy test (urine or serum) were negative. Treatment included drospirenone with ethinyl estradiol, ibuprofen, dydrogesterone, and estradiol. The subject did not recover from the premature menopause. Study drug was continued without modification.

The last dose was received on 22 March 20[redacted] (Day 250). On 25 March 20[redacted] (Day 253), the subject was discontinued from the study due to progressive disease.

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	5006-1005
Cycle/dose regimen last received:	Cycle 10
Overall duration of study drug:	05 August 20[redacted], ongoing as of cutoff date*
Reason for narrative:	
Non- Fatal SAE(s)	Premature Menopause

A 38-year-old White female with medullary thyroid cancer was originally diagnosed on 02 December 1994 (Stage IVa at diagnosis). The date of last disease progression was on 27 July 2010. Significant medical history included total thyroidectomy, laterocervical lymph node dissection, parathyroidectomy, hypothyroidism, hypertension, appendectomy, diarrhea, uterine fibroids, and pheochromocytoma. Bone scan was marked by malignant lesions. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan included liver masses (right anterior and left medial lobes) and a visceral mass. Previous radiotherapy was not reported. Previous anticancer therapy included motesanib. Concomitant medications included calcitriol, cortisone, bromazepam, loperamide, nimesulide, amoxicillin, polyethylene glycol, Gelclair, paroxetine, aciclovir, and Bucogel. There was no report of contraceptive use. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included doxazosin and nebivolol.

On 05 August 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. The same day, the subject experienced absence of menstrual cycle (amenorrhea) (nonserious, Grade 1, possibly related). No treatment was given for amenorrhea. On 25 November 20[redacted] (Day 113), the amenorrhea increased in severity (nonserious, Grade 2, possibly related). A pregnancy test was negative and the amenorrhea was resolved. On 16 December 20[redacted] (Day 134), blood tests showed hypergonadotropic hypogonadism, with abnormal levels of FSH (70 IU/L), LH (23 IU/L), and anti-Müllerian hormone. She was diagnosed with premature ovarian failure (premature menopause) (serious [an important medical event], Grade 3, possibly related). On 22 December 20[redacted] (Day 140), a repeat test showed her anti-Müllerian hormone levels were undetectable, consistent with loss of the follicle reserve. The study drug was continued without modification.

The subject was still receiving study drug at the data cutoff date of [redacted] 20[redacted].

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	6001-1002
Cycle/dose regimen last received:	Cycle 13
Overall duration of study drug:	27 November 20[redacted] to 23 November 翌年*
Reason for narrative:	
Non- Fatal SAE(s)	Blood Calcitonin Increased Hypertension
AE(s) leading to treatment discontinuation	Leukopenia Lymphopenia

A 55-year-old White female with medullary thyroid cancer was originally diagnosed in 1989 (stage at diagnosis was not provided). The date of last disease progression was on 05 October 2009. Significant medical history included hypothyroidism, left thyroid lobe excision, mediastinal lymphadenectomy, excision of tumor from left lung, excision of left supraclavicular tumor, meteorism, cholecystectomy, abdominal discomfort, diarrhea, joint stiffness in both hands, arterial hypertension, and subarachnoid hemorrhage. Bone scan was reported as marked by sacral bone uptake (further described by the investigator as possible but not unequivocal metastasis). Screening tumor assessments of target/non-target lesions assessed via spiral CT scan included bilateral paratracheal and right para-aortic adenopathy. Previous radiotherapy included radiotherapy to the lymph nodes in the neck and mediastinum. Previous anticancer therapy included doxorubicin, cyclophosphamide, vincristine, cisplatin, carboplatin, etoposide, and iodine (I-131). Concomitant medications included potassium, loperamide, omeprazole, sucralfate, simethicone, mebeverine, ascorbic acid, pyridoxine, Thiocodin, ketoprofen, calcium, omeprazole, drotaverine, octreotide, lansoprazole, carbamazepine, akritoin, Strepsils, nystatin, metamizole, Neospasmina, folic acid, hydroxyzine, clindamycin, clarithromycin, alfacalcidol, and tianeptine. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included enalapril, metoprolol, ramipril, doxazosin, nebivolol, bisoprolol, and furosemide.

On 27 November 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 28 November 20[redacted] (Day 2), the subject experienced hypertension (BP not provided) (nonserious, Grade 2, probably related). Metoprolol was increased from 25 mg to 50 mg and enalapril was increased from 5 mg to 10 mg. In December 20[redacted], the blood pressure (BP) was in a range of 100-130 to 70-90 mmHg. The hypertension was reported as recovering.

On 03 January 翌年* (Day 38), the subject experienced another episode of increase in hypertension (serious, Grade 2, probably related). Her BP was 190/130 mmHg and she was subsequently hospitalized. The antihypertensive medications were modified and the subject was treated with bisoprolol and ramipril. On 08 January 20[redacted] (Day 43), study drug was temporarily interrupted. Her blood pressure returned to normal (BP not reported). On 11 January 20[redacted] (Day 46), she was discharged from the hospital. On 15 January 20[redacted] (Day 50), study drug was restarted.

On 27 February 20[redacted] (Day 93), the subject experienced diarrhea (nonserious, Grade 1, not related). Treatment included loperamide. On 12 March 20[redacted] (Day 106), the diarrhea was reported to have increased in severity (nonserious, Grade 2, probably related). The subject continued to take loperamide. On 18 March 20[redacted] (Day 112), leukopenia (nonserious, Grade 2, possibly related) and lymphopenia (nonserious, Grade 3, possibly related) were reported. See table below for white blood cell and lymphocyte counts throughout the study period. These events were ongoing through the end of the study period. On 20 March 20[redacted] (Day 114), the study drug was reduced to 20 mg QD due to diarrhea. That same day, the grade of the diarrhea decreased to Grade 1 (nonserious, not related).

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

On 04 May 20[redacted] (Day 159), the subject experienced periodontitis (nonserious, Grade 1, not related) which was treated with clindamycin. The event resolved on 10 May 20[redacted] (Day 165). Diarrhea was reported again on 12 May 20[redacted] (Day 167) as nonserious and Grade 3 and possibly related to study drug but probably due to clindamycin treatment. On 14 May 20[redacted] (Day 169), it was reported as Grade 1 and possibly related. The diarrhea was resolved on 24 June 20[redacted] (Day 210). The subject was admitted to the hospital the following day (25 June 20[redacted] [Day 211]) due to diarrhea suspected to be secondary to hypercalcitonemia (blood calcitonin increased) (serious, Grade 3, possibly related). A physical examination revealed slight dehydration, and weight was 63 kg. There were no serious findings in laboratory results. Treatment included loperamide, potassium, multi-electrolyte solution, octreotide, and lanreotide. Study drug was interrupted on 28 June 20[redacted] (Day 214) due to the hypercalcitoninemia. On 07 July 20[redacted] (Day 223), she recovered from the event and study drug was restarted at a reduced dosage of 14 mg QD.

The last study dose was received in 23 November 20[redacted] (Day 362). On 22 December 20[redacted] (Day 391, 29 days after the last dose), the subject was discontinued due to the ongoing leukopenia (nonserious, Grade 2, possibly related) and lymphopenia (nonserious, Grade 3, possibly related). The secondary reason for discontinuation was subject choice.

Subject 6001-1002 – White Blood Cell and Lymphocyte Counts

Date	White Blood Cells ($x 10^9$/L) Normal range: 3.7 – 11 x 10^9/L	Lymphocytes ($x 10^9$/L) Normal range: 0.9 - 3.6 x 10^9/L
19MAR20[redacted]	2.2	0.3
16APR20[redacted]	2.5	0.2
14MAY20[redacted]	2.5	0.2
11JUN20[redacted]	2.5	0.3
05AUG20[redacted]	2.3	0.2
02SEP20[redacted]	2.6	0.4
30SEP20[redacted]	2.7	0.3
28OCT20[redacted]	2.5	0.3
25NOV20[redacted]	3.0	0.3

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	6001-1006
Cycle/dose regimen last received:	Cycle 18
Overall duration of study drug:	09 December 20[redacted], ongoing as of cutoff date*
Reason for narrative:	
Non- Fatal SAE(s)	Abdominal Pain Pneumonia, Staphylococcal

A 57-year-old White male with medullary thyroid cancer was originally diagnosed on 15 January 1998 (Stage II at diagnosis). The date of last disease progression was on 14 October 2009. Significant medical history included total thyroidectomy, right-sided lymphadenopathy (not further specified), tracheostomy, and diarrhea. Bone scan was reported as normal. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan included middle or lower cervical adenopathy (right) and supraclavicular adenopathy (right). Previous radiotherapy included radiotherapy to the parapharyngeal space, lymph nodes, and neck. Previous anticancer therapy was not specified. Concomitant medications included loperamide, omeprazole, ketoprofen, acetylsalicylic acid, hydrocortisone cream, Terra-Cortril, hydroxyzine, clindamycin, Neosporin, megestrol, diosmin, tranexamic acid, drotaverine, Ferro-Folsan, cetirizine, glycerol, ethamsylate, furosemide, magnesium, potassium, and GIK solution (10% glucose/insulin/KCL). Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included metoprolol, ramipril, and amlodipine.

On 09 December 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 29 July 翌年* (Day 233), the subject experienced abdominal pain (serious, Grade 2, not related). He took unspecified pain medication, and due to persistence of pain, he consulted a surgeon on 02 August 20[redacted] (Day 237) and was admitted to the hospital for a suspected appendicitis. Study drug was interrupted starting on 02 August 20[redacted] (Day 237). Abdominal ultrasound showed a renal stone on the left side, without any other significant abnormalities. Hematology values and urinalysis were within the normal limits. Treatment included 5% glucose solution, multi-electrolyte solution, and analgesics (unspecified). On 05 August 20[redacted] (Day 240), he was discharged home. On 11 August 20[redacted] (Day 246), study drug was resumed without dose modification. The abdominal pain gradually improved and resolved on 17 August 20[redacted] (Day 252).

On 15 September 20[redacted] (Day 281), CT scan per protocol requirement showed radiological changes and the subject was subsequently diagnosed with staphylococcal pneumonia (serious, Grade 2, not related). No treatment was given. His temperature and white blood cell (WBC) counts on 15 September 20[redacted] (Day 281) and on 13 October 20[redacted] (Day 309) were 35.7ºC and 37.4ºC and 11.5 x 10^9/L and 14.6 x 10^9/L, respectively. On 13 October 20[redacted] (Day 309), he was hospitalized for further evaluation. The following day, the subject was examined by a pulmonologist on suspicion of tuberculosis. Chest X-ray showed a cave (7 cm in diameter) with the fluid level localized in apex of the right lung), inflammatory infiltration of the upper lobe, and enlarged lymph nodes in the mediastinum and near the hilus of the right lung. Bronchoalveolar lavage showed the absence of mycobacterium tuberculosis absent, and the QuantiFERON TB test and BACTEC test were negative. No treatment was initiated. On 18 October 20[redacted] (Day 314), the subject was discharged home. On 01 January 翌々年* (Day 389), the pneumonia was resolved.

The subject was still receiving study drug at the data cutoff date of [redacted] 20[redacted].

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	6001-1013
Cycle/dose regimen last received:	Cycle 7
Overall duration of study drug:	17 February 20[redacted] to 11 August 20[redacted]
Reason for narrative:	
Nonfatal SAE(s)	Hypercalcemia (predose)
	Hypercalcemia (postdose)

A 47-year-old White male with medullary thyroid cancer was originally diagnosed on 14 February 2007 (Stage IVa at diagnosis). The date of last disease progression was on 02 December 2009. Significant medical history included total thyroidectomy, excision of lymph nodes in the neck, hypothyroidism, paralysis of the brachial plexus after the thyroidectomy, vocal cord paralysis, meniscal surgery, and tachycardia. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan included lung masses (left upper and lower lobes and right upper lobe) and liver masses (left medial and right anterior lobes). The ECOG performance status and NYHA functional class were reported as 2 and 2, respectively. The ECG was reported as abnormal (not clinically significant), and his body weight was 81 kg. Previous radiotherapy included curative radiotherapy to the thyroid gland, mediastinal, supraclavicular, and infraclavicular lymph nodes. Previous anticancer therapy included XL 184 via a clinical study. Concomitant medications included loperamide, megestrol, etamsylate, carbamazepine, phytomenadione, paracetamol, clodronic acid, fentanyl, drotaverine, spironolactone hydroxyzine, dexamethasone, potassium, magnesium carbonate, 10% glucose intravenous infusion, omeprazole, and metoclopramide. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included metoprolol.

On 28 January 20[redacted] (predose), the subject had an elevated calcium 3.15 mmol/L (normal range: 2.12 - 2.62 mmol/L), and on 05 February 20[redacted] (Day -12, predose), the subject experienced hypercalcemia (serious, Grade 3, not related). Treatment consisted of forced diuresis and administration of bisphosphonates, including pamidronic acid, 0.9% NaCl IV infusion, and furosemide. On 17 February 20[redacted], calcium was normal (2.58 mmol/L) and the event was reported resolved. On that same day, 17 February 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated.

On 14 July 20[redacted] (Day 148), the subject was diagnosed with hypercalcemia (nonserious, Grade 1, not related) (laboratory results not provided). On 28 July 20[redacted] (Day 162), a CT scan revealed disease progression. Serum calcium was 2.8 mmol/L 28 July 20[redacted] (Day 162) and was 2.98 mmol/L on 11 August 20[redacted] (Day 176). On 11 August 20[redacted], the last dose was received and the subject was discontinued from the study due to progressive disease. On 17 August 20[redacted] (Day 182), the subject received a 90-mg dose of pamidronate. On 18 August 20[redacted] (Day 183, 7 days after the last dose), he was hospitalized due to hypercalcemia (serious, Grade 3, not related) secondary to hypothyroidism. Treatment included forced diuresis and bisphosphonates (0.9% NaCl IV infusion, furosemide, and pamidronic acid), but despite this, normalization of calcium levels was not achieved. On 02 September 20[redacted] (Day 198), he received a 90-mg dose of pamidronate. On 22 September 20[redacted] (Day 218), his hypercalcemia was reduced to Grade 1 and he was switched to ambulatory treatment.

On 30 September 20[redacted] (Day 226) (≥30 days after the last dose of study drug), the subject expired and the cause of death was reported as unknown.

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	6001-1015
Cycle/dose regimen last received:	Cycle 10
Overall duration of study drug:	22 July 20[redacted], ongoing as of cutoff date*
Reason for narrative:	
Nonfatal SAE(s)	Bronchitis

A 27-year-old White male with medullary thyroid cancer was originally diagnosed on 25 May 2009 (Stage IVc at diagnosis). The date of last disease progression was on 21 June 2010. Significant medical history included radical resection of the thyroid gland, bilateral cervical lymphadenectomy, postoperative hypothyreosis, bronchial asthma, arterial hypertension, and diarrhea. Bone scan was reported as marked by malignant lesions. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan included right hilar adenopathy, liver mass (right anterior lobe), and a pancreatic mass. Previous radiotherapy was not reported. Previous anticancer therapy was not reported. Concomitant medications included calcium, alfacalcidol, ibuprofen, loperamide, nystatin, amoxicillin, omeprazole, and potassium. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included propranolol.

On 22 July 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated.

On 27 January 翌年* (Day 190) the subject developed bronchitis (serious, Grade 2, not related) and was hospitalized. Treatment included amoxicillin and clavulanate. On 31 January 20[redacted] (Day 194), the bronchitis was resolved. No modification occurred to the dose of study drug. The subject was still receiving study drug at the data cutoff date of [redacted] 20[redacted].

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	6001-1016
Cycle/dose regimen last received:	Cycle 5
Overall duration of study drug:	31 August 20[redacted] to 27 December 20[redacted]
Reason for narrative:	
Nonfatal SAE(s)	Iron Deficiency Anemia Weight Decreased
AE(s) leading to treatment discontinuation	Weight Decreased

A 71-year-old White male with medullary thyroid cancer was originally diagnosed on 18 December 2008 (Stage IVc at diagnosis). The date of last disease progression was on 25 June 2010. Significant medical history included radical resection of the thyroid gland, bilateral cervical lymphadenectomy, postoperative hypothyreosis, surgery for medullary thyroid cancer, anemia, arterial hypertension, cholecystectomy, appendectomy, and diarrhea. Bone scan was reported marked by malignant lesions. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan included middle or lower cervical adenopathy (right), left mediastinal and left supraclavicular adenopathy. His body weight was 64 kg. Previous radiotherapy was not reported. Previous anticancer therapy was not reported. Concomitant medications included loperamide, zolpidem, ferrous sulfate with ascorbic acid, megestrol, methylprednisolone, omeprazole, calcium, and alfacalcidol. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included indapamide, amlodipine, and perindopril.

On 31 August 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. The subject was noted to be experiencing a slow but constant weight reduction throughout the study (see table below for weights), and he was started on megestrol. On 15 September 20[redacted] (Day 16), his weight improved and the event was considered resolved. The investigator considered the event nonserious and not related to the study drug. The study drug was continued without modification.

On 27 December 20[redacted] (Day 119), the subject experienced weight reduction (nonserious, Grade 2, not related). The subject's weight was 56.5 kg. On 27 December 20[redacted] (Day 119), the last dose of study drug was received because of the weight decrease. On 05 January 翌年* (Day 128, 8 days after the last dose), the subject was admitted to the hospital due to continuing weight reduction (54.0 kg [serious, Grade 3, probably related]) and the subject was diagnosed as having sideropenic anemia (iron deficiency anemia) (serious, Grade 3, probably related) (see table below for hemoglobin and hematocrit values throughout the study period). Treatment included albumin, omeprazole, and numerous red blood cell (RBC) transfusions (2 units/transfusion) on 05 January 20[redacted] (Day 128), 07 January 20[redacted] (Day 130), and 14 January 20[redacted] (Day 137). The megestrol dose was increased. The subject underwent a colonoscopy on 12 January (Day 135) and 24 January 20[redacted] (Day 147). The gastroscopy was negative for bleeding. The subject's weight was noted to have increased by 5 kg and the iron deficiency anemia improved. The outcome for both events was reported as recovering. On 25 January 20[redacted] (Day 148), the subject was discontinued from the study due to weight decreased. On 01 February 20[redacted], the subject was discharged from the hospital

*新薬承認情報提供時に置き換え

付録 2.7.6-30　死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject 6001-1016 – Weight, Hemoglobin, and Hematocrit

Date	Weight (kg)	Hemoglobin (g/L) Normal Range: 125 - 170 g/L	Hematocrit (%) Normal Range: 37 – 51 %
30AUG20[redacted] Screening	64	98 CTC= 2　L	28.6 L
31AUG20[redacted]	64	100 CTC= 1　L	29.2 L
08SEP20[redacted]	61	96 CTC= 2　L	27.9 L
15SEP20[redacted]	62	94 CTC= 2　L	28.1 L
22SEP20[redacted]	62	99 CTC= 2　L	29.7 L
29SEP20[redacted]	62	101 CTC= 1　L	30.3 L
27OCT20[redacted]	62	105 CTC= 1　L	31.4 L
24NOV20[redacted]	60	102 CTC= 1　L	31 L
22DEC20[redacted]	56.5	Not done	Not done
20JAN翌年*	54	104 CTC= 1　L	30.2

CTC = CTC = common terminology criteria, L= low.

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	7001-1001
Cycle/dose regimen last received:	Cycle 2
Overall duration of study drug:	23 March 20[redacted] to 02 May 20[redacted]
Reason for narrative:	
Nonfatal SAE(s)	Ascites
AE(s) leading to treatment discontinuation	Malaise

A 70-year-old Black Caribbean female with medullary thyroid cancer was originally diagnosed on 17 October 2007 (Stage IVc at diagnosis). The date of last disease progression was on 25 February 2010. Significant medical history included total thyroidectomy, type 2 diabetes mellitus, hypertension, hypercholesterolemia, adrenal adenoma (left side), osteoarthritis, tinnitus (right side), and hysterectomy. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan included liver masses (left medial and lateral and right anterior lobes) and an adrenal mass (left). Her body weight was 62.6 kg. Previous radiotherapy was not reported. Previous anticancer therapy was not reported. Concomitant medications included simvastatin, acetylsalicylic acid, amoxicillin, ciprofloxacin, calcium with ergocalciferol, cyclizine, metoclopramide, Fresubin, insulin glargine, gliclazide, ondansetron, domperidone, codeine, senna, docusate, glycerol suppositories, diamorphine, ibuprofen, nystatin, omeprazole, haloperidol, midazolam, potassium, Movicol, tinzaparin, paracetamol, and amitriptyline. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included amlodipine, doxazosin, candesartan, and eprosartan.

On 23 March 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. The same day (23 March 20[redacted], the subject experienced ascites (nonserious, Grade 1, not related). No treatment was given. On 30 March 20[redacted] (Day 8), the ascites worsened (serious, Grade 3, not related) and was treated with laxatives (Movicol). She was hospitalized for further evaluation. The last dose was received on 02 May 20[redacted] (Day 41). On 05 May 20[redacted] (Day 44), the subject was noted to be too unwell to take the study drug (malaise) (nonserious, Grade 2, not related). The study drug was withdrawn due to malaise. On 28 May 20[redacted] (Day 67), an ascites drain was inserted under radiological guidance. The subject did not recover from the ascites and malaise.

On 11 May 20[redacted] (Day 50), the subject was discontinued from the study primarily due to progressive disease and also due to subject choice. The subject died on 08 June 20[redacted] (Day 78) (≥30 days after the last dose of study drug). The cause of death was reported as unknown.

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	7002-1003
Cycle/dose regimen last received:	Cycle 12
Overall duration of study drug:	24 May 20[redacted], ongoing as of cutoff date*
Reason for narrative:	
Nonfatal SAE(s)	Osteolysis Lytic Bony Lesion Vertebroplasty (spinal disorder)

A 44-year-old White female with medullary thyroid cancer was originally diagnosed on 11 June 2002 (Stage IVa at diagnosis). The date of last disease progression was on 04 May 2010. Significant medical history included thyroidectomy, resection of a neck lesion, latrogenic hypothyroidism due to thyroidectomy, lethargy, neck/shoulder pain, back pain, and polycystic ovaries. Bone scan was reported as marked by malignant lesions. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan included left supraclavicular adenopathy and a liver mass (right anterior lobe). Previous radiotherapy included prophylactic radiotherapy to the thyroid gland. Previous anticancer therapy was not reported. Concomitant medications included alfacalcidiol, calcium, diclofenac, paracetamol, panadeine, omeprazole, fluconazole, amoxicillin, ibuprofen, and hyoscine. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included amlodipine.

On 24 May 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 15 July 20[redacted] (Day 53), the subject developed lytic bone lesion (osteolysis) (serious, Grade 1, not related) and lytic bony lesion vertebroplasty (preferred term-spinal disorder) (serious, Grade 1, not related). On 20 July 20[redacted] (Day 58), the study drug was dose was reduced to 20 mg QD due to splinter hemorrhage (nonserious, Grade 1, probably related).

On 10 October 20[redacted] (Day 140), the study drug was interrupted due to the osteolysis and vertebroplasty. On 13 October 20[redacted] (Day 143), the subject was hospitalized overnight to undergo vertebroplasty and she received lidocaine, fentanyl, midazolam, tramadol, cyclizine, cefuroxime, and dihydrocodeine associated with the procedure. On 14 October 20[redacted] (Day 144), the event resolved and she was discharged home without complication. On 15 October 20[redacted] (Day 145), study drug was resumed.

On 13 December 20[redacted] (Day 204), the dose was further reduced to 14 mg QD due to multiple Grade 1 toxicities. The subject was still receiving study drug at the data cutoff date of [redacted] 20[redacted].

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

(4)中止に至った有害事象

Histology: DTC

Subject:	1022-1002
Cycle/dose regimen last received:	Cycle 16
Overall duration of study drug:	23 November 20[redacted] to 06 January 翌々年*
Reason for narrative:	
AE(s) leading to treatment discontinuation	Performance Status Decreased

A 63-year-old White male with differentiated thyroid cancer (papillary classical) was originally diagnosed on 30 November 1998 (Stage IVc at diagnosis). The date of last disease progression was on 12 August 2009. Significant medical history included anaemia, diabetes mellitus, thyroglobulin increased, fatigue, dysphonia, neuropathy peripheral, renal failure chronic, dry mouth, blood uric acid increased, hypomagnesaemia, cardiac murmur (Grade V6 systolic murmur), hyperlipidaemia, hypertension, hypothyroidism, pollakiuria, arthritis, renal oncocytoma, spinal osteoarthritis, vocal cord paralysis, pharyngeal oedema, splenomegaly, benign prostatic hyperplasia, metastases to lung, pleural effusion, thyroid mass, arthritis, and temporal bone lesion. Bone scan was reported as malignant lesion on the left clavicle and left frontal skull and a degenerative disease on T7 and T8 vertebrae. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan showed a lung mass (right upper and middle lobe). ECOG performance status and NYHA functional class were reported as 0 and 1, respectively. ECG results were not reported, and her body weight was 60.6 kg. Previous radiotherapy included prophylactic radiotherapy to left clavicle. Previous anticancer therapy included celecoxib, radioactive iodine (131), iodine 200, sorafenib and tipifarnib. Concomitant medications included allopurinol, alteplase, atropine, glucose, epinephrine, exactacain, fentanyl, furosemide, heparin, homatropine, loperamide, ristfor, rositagliptin, levosalbutamol, lidocaine, magnesium, midazolam, mineral oil emulsion, megestrol, guaifenesin, valaciclovir and zolendronic acid. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included amlodipine, carvedilol, valsartan, hydrochlorothiazide and lisinopril.

On 23 November 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 02 February 翌々年* (Day 437), the subject experienced decreased performance status (nonserious, Grade 3, not related). The study drug was withdrawn due to this event. The last dose was received on 06 January 20[redacted] (Day 409). No treatment was given and the event remained ongoing at the data cutoff date.

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	1022-1005
Cycle/dose regimen last received:	Cycle 8
Overall duration of study drug:	03 December 20[redacted] to 11 August 翌年*
Reason for narrative:	
AE(s) leading to treatment discontinuation	Diarrhea

A 57-year-old White female with differentiated thyroid cancer (papillary variants) was originally diagnosed in December 1997 (Stage IVc at diagnosis). The date of last disease progression was on 03 November 2009. Significant medical history included papillary thyroid cancer with metastasis to the lungs, total thyroidectomy and neck dissection, surgical hypothyroidism, intermittently elevated thyroglobulin, hypertension, nausea, gastroesophageal reflux disease (GERD), and vomiting. Bone scan was reported as normal. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan showed left hilar and subcarinal adenopathy and bilateral lung masses (upper and lower lobes). Previous radiotherapy included prophylactic radiotherapy to the neck base of the skull. Previous anticancer therapy included gemcitabine, sorafenib, Celebrex (celecoxib) trial, tipifarnib, AZD-8330 (investigational drug), and I-131. Concomitant medications included pyroxidine, esomeprazole, fexofenadine, hydrocodone, azithromycin, loperamide, ondansetron, tincture of opium, Metamucil, promethazine, mirtazapine, diphenoxylate and atropine, prochlorperazine, gabapentin, metronidazole, piperacillin with tazobactam, and magnesium. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included doxazosin, enalapril, telmisartan, and candesartan.

On 03 December 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 18 December 20[redacted] (Day 16), the subject experienced diarrhea (nonserious, Grade 2, not related) which resolved in two days without treatment. There was no change in the study drug.

On 09 January 翌年* (Day 38), the dose was reduced to 20 mg QD due to thrombocytopenia (nonserious, Grade 2, probably related) and hyperbilirubinemia (nonserious, Grade 2, possibly related). From 23 January 20[redacted] (Day 52) to 26 July 20[redacted] (Day 236), the subject experienced several episodes of diarrhea (nonserious, Grades 1 and 2, possibly and probably related). The subject received treatment and the events resolved. On 10 May 20[redacted] (Day 159), the dose was reduced to 14 mg QD due to diarrhea (nonserious, Grade 2, probably related).

On 01 August 20[redacted] (Day 242), the diarrhea worsened (nonserious, Grade 3, possibly related). The study drug was withdrawn due to this event and the last dose was received on 11 August 20[redacted] (Day 252). On 12 August 20[redacted] (Day 253), the subject was discontinued from the study. The subject recovered from the diarrhea on 04 November 20[redacted] (Day 337, 85 days after the last dose).

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	3001-1002
Cycle/dose regimen last received:	Cycle 1
Overall duration of study drug:	23 November 20[redacted] to 12 December 20[redacted]
Reason for narrative:	
AE(s) leading to treatment discontinuation	Abdominal Pain Nausea

A 70-year-old Asian male with differentiated (papillary classical) thyroid cancer was originally diagnosed on 19 April 2007 (Stage IVc at diagnosis). The date of last disease progression was on 26 October 2009. Significant medical history included subtotal thyroidectomy, hypothyroidism and hypoparathyroidism (post thyroidectomy), fine needle aspiration biopsy of lung, hyperlipidemia, right bundle branch block, and stroke. Bone scan was marked by malignant lesions. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan showed left hilar adenopathy, lung masses (left upper and lower and right upper lobes), and a liver mass (right anterior lobe). Previous radiotherapy included palliative radiotherapy to the thyroid gland. No prior anticancer therapy was reported. Concomitant medications included beclomethasone, Asasantin, atorvastatin, pantoprazole, calcitriol, and calcium. Concomitant thyroxine suppression therapy included levothyroxine. No antihypertensive therapy was taken.

On 23 November 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 11 December 20[redacted] (Day 19) the subject experienced abdominal pain (Grade 3) and the following day, the subject experienced nausea (Grade 2). Both events were considered nonserious and possibly related to study drug. No treatment was given. The study drug was withdrawn because of the abdominal pain and nausea, and the last dose was received on 12 December 20[redacted] (Day 20). On 17 December 20[redacted] (Day 25), the subject recovered from the abdominal pain and nausea. On 15 December 20[redacted] the subject was discontinued from the study primarily due to subject's choice and secondary due to the abdominal pain and nausea.

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	5002-1006
Cycle/dose regimen last received:	Cycle 5
Overall duration of study drug:	30 November 20[redacted] to 07 April 翌年*
Reason for narrative:	
AE(s) leading to treatment discontinuation	Proteinuria (11 events)

A 66-year-old White male with differentiated (clear cell) thyroid cancer was originally diagnosed on 06 December 2000 (Stage IVb at diagnosis). The date of last disease progression was on 11 November 2009. Significant medical history included thyroidectomy, laryngectomy, pharyngectomy, thoracic surgery, esophagectomy, hypothyroidism, dorsal pain, anemia, and hiatal hernia. Bone scan was reported as marked by malignant lesions. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan showed thoracic/dorsal vertebral masses. Previous radiotherapy included curative and palliative radiotherapy to the mediastinal lymph nodes and lumbar vertebra, respectively. Prior anticancer therapy included doxorubicin, cisplatin, radioiodine therapy, and 90 Y dotatate. Concomitant medications included oxycodone, calcitriol, and panadeine. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included losartan/hydrochlorothiazide.

On 30 November 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 10 December 20[redacted] (Day 11), the subject experienced proteinuria, with a urine protein of 30 mg/dL (nonserious, Grade 1, possibly related) (see table below for reports of proteinuria throughout the study period). No treatment was given. On 16 December 20[redacted] (Day 17), the proteinuria increased in severity (nonserious, Grade 2, possibly related), with a urine protein of 300 mg/dL. On 23 December 20[redacted] (Day 24), the proteinuria increased in severity again (nonserious, Grade 3, probably related) with a urine protein ≥ 2000 mg/dL. Subsequently on 30 Dec 20[redacted] (Day 31), the proteinuria improved (nonserious, Grade 2, possibly related) with urine protein of 100 mg/dL. The study drug was interrupted from 24 December 20[redacted] (Day 24) until 16 March 翌年* (Day 107). On 16 February 20[redacted] (Day 79), the study drug was reduced to 20 mg QD due to proteinuria (nonserious, Grade 1, probably related). On 17 March 20[redacted] (Day 108), the study drug was further reduced to 14 mg QD due to proteinuria (nonserious, Grade 1, probably related).

On 24 March 20[redacted] (Day 115), the subject experienced another episode of proteinuria (nonserious, Grade 2, probably related) with a urine protein of 300 mg/dL. Study drug was withdrawn due to the proteinuria and the last dose of study drug was administered on 07 April 20[redacted] (Day 129). On 13 April 20[redacted] (Day 135, 5 days after the last dose), the proteinuria improved (Grade 1) and on 14 April 20[redacted] (Day 136), the urine protein was 30 mg/dL. The proteinuria was considered ongoing and on 14 April 20[redacted] the subject was withdrawn from the study due to proteinuria.

On 06 October 20[redacted], the subject was reported to have developed progressive disease.

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject 5002-1006 - Proteinuria

Adverse Event	Start Date	Stop Date	CTCAE Grade	Serious Event	Relationship to Study Drug	Action Taken
PROTEINURIA	10DEC20[redacted]		1	No	Possibly related	Dose not changed
PROTEINURIA	16DEC20[redacted]		2	No	Possibly related	Drug interrupted
PROTEINURIA	23DEC20[redacted]	29DEC20[redacted]	3	No	Probably related	Drug interrupted
PROTEINURIA	30DEC20[redacted]	12JAN翌年*	2	No	Probably related	Drug interrupted
PROTEINURIA	13JAN20[redacted]	19JAN20[redacted]	1	No	Probably related	Dose not changed
PROTEINURIA	20JAN20[redacted]	09FEB20[redacted]	2	No	Probably related	Drug interrupted
PROTEINURIA	10FEB20[redacted]	21FEB20[redacted]	1	No	Probably related	Dose reduced
PROTEINURIA	22FEB20[redacted]	09MAR20[redacted]	2	No	Possibly related	Dose not changed
PROTEINURIA	10MAR20[redacted]	23MAR20[redacted]	1	No	Probably related	Dose reduced
PROTEINURIA	24MAR20[redacted]	13APR20[redacted]	2	No	Probably related	Drug withdrawn
PROTEINURIA	13APR20[redacted]	ongoing	1	No	Probably related	Not applicable

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

HISTOLOGY: MTC

Subject:	1021-1009
Cycle/dose regimen last received:	Cycle 3
Overall duration of study drug:	18 June 20[redacted] to 25 August 20[redacted]
Reason for narrative:	
AE(s) leading to treatment discontinuation	Palmar-plantar Erythrodysaesthesia Syndrome

A 55-year-old White female with medullary thyroid cancer was originally diagnosed on 27 March 2007 (Stage IVc at diagnosis). The date of last disease progression was on 04 June 2010. Significant medical history included hypothyroidism, lump on left side of neck, voice changes, left vocal cord paralysis, tracheostomy, tonsillectomy, asthma, bronchitis, pneumonia, mumps, dry cough, fatigue, obstructive sleep apnea, back pain, endometrial ablation, Peg tube, constipation, diarrhea, inability to hold urine, ruddy complexion, memory loss, dizziness, and hypertension. Bone scan was reported as marked by degenerative disease. Screening tumor assessments of target/non-target lesions assessed via spiral CT scan showed a visceral mass, a liver mass (left lateral lobe), right hilar adenopathy, left supraclavicular adenopathy, and other adenopathy. Previous radiotherapy included radiotherapy to the left side of the neck. Prior anticancer therapy included sorafenib. Concomitant medications included seretide, ipratropium with albuterol, hydroxyzine, hydrocortisone cream, ibuprofen, loperamide, famotidine, urea 20% cream, calcitriol, calcium, and multivitamin. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included lisinopril.

On 18 June 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 20 June 20[redacted] (Day 3), the subject experienced palmar-plantar erythrodysaesthesia syndrome (Investigator term hand/foot skin reaction) (nonserious, Grade 1, possibly related), and rash/desquamation on the abdomen, face, and legs (nonserious, Grade 2, possibly related). The subject was treated with Atarax and the palmar-plantar erythrodysaesthesia syndrome resolved after two days. The rash/desquamation on the abdomen, face, and legs resolved on 02 July 20[redacted] (Day 15).

On 28 June 20[redacted] (Day 11), the subject experienced another episode of palmar-plantar erythrodysaesthesia syndrome (nonserious, Grade 3, possibly related) and photopsia (nonserious, Grade 1, possibly related). No treatment was given. The photopsia were resolved on 30 June 20[redacted] (Day 13). On 02 July 20[redacted], the subject again had rashes/desquamation on the face and abdomen (nonserious, Grade 1, possibly related). The subject was treated with cortisone cream and the study drug was interrupted from 02 July to 05 July 20[redacted]. On 06 July 20[redacted] (Day 19), the palmar-plantar erythrodysaesthesia syndrome was reported lesser in severity (Grade 1, nonserious, possibly related) and another episode of rashes/desquamation of the arm occurred (nonserious, Grade 1, possibly related) On 06 July 20[redacted] (Day 19), the study drug was reduced to 20 mg QD due to the palmar-plantar erythrodysaesthesia syndrome. The rash/desquamation in the abdomen and face was reported resolved on 09 July 20[redacted] (Day 22).

On 12 July 20[redacted] (Day 25), the palmar-plantar erythrodysaesthesia syndrome increased in severity to Grade 3. The subject also experienced dyspnea on exertion (nonserious, Grade 2, possibly related) and tongue sensitivity (nonserious, Grade 2, probably related). On 14 July 20[redacted] (Day 27), the subject reported fatigue (nonserious, Grade 3, possibly related). No treatment was given. The events, dyspnea on exertion, tongue sensitivity and fatigue, were reported resolved by 19 July 20[redacted] (Day 32). On 19 July 20[redacted], the palmar-plantar erythrodysaesthesia syndrome was reported as Grade 1. On 14 July (Day 27), the subject had blurred vision (nonserious, Grade 2, possibly related) which was ongoing until 06 Aug 20[redacted] (Day 50). The study drug was interrupted from 15 July to 18 July 20[redacted] and restarted at a reduced dose of 14 mg QD on 19 July 20[redacted] (Day 32) due to the palmar-plantar erythrodysaesthesia syndrome and dyspnea.

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

On 26 July 20[redacted] (Day 39), the palmar-plantar erythrodysaesthesia syndrome became Grade 2 and another episode of rash on face (nonserious, Grade 1, possibly related) occurred. The following day, it was noted that the palmar-plantar erythrodysaesthesia syndrome increased in severity to Grade 3 and the rash on the face became Grade 2. Treatment included urea cream and cyproheptadine. The study drug was interrupted from 27 July to 05 August 20[redacted]. On 29 July 20[redacted] (Day 42), the palmar-plantar erythrodysaesthesia syndrome was improved to Grade 2 and on 04 August 20[redacted] (Day 48) to Grade 1. On 06 August 20[redacted] (Day 50), the dose was further reduced to 10 mg QD due to fatigue (nonserious, Grade 3, possibly related). The palmar-plantar erythrodysaesthesia syndrome increased in severity on 24 August 20[redacted] (Day 68) to Grade 3. The subject was treated with cyproheptadine. The subject received the last dose of study drug on 25 August 20[redacted] (Day 69) and study drug was withdrawn due to the palmar-plantar erythrodysaesthesia syndrome. The palmar-plantar erythrodysaesthesia syndrome decreased in severity on 01 September 20[redacted] (Day 76, 6 days after the last dose) to Grade 2 and the event was reported resolved on 17 December 20[redacted] (Day 183).

On 01 October 20[redacted], the subject developed progressive disease.

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	4001-1001
Cycle/dose regimen last received:	Cycle 7
Overall duration of study drug:	23 June 20[redacted] to 29 December 20[redacted]
Reason for narrative:	
AE(s) leading to treatment discontinuation	Diarrhea

A 66-year-old White male with medullary thyroid cancer was originally diagnosed on 22 June 2000 (Stage III at diagnosis). The date of last disease progression was on 05 November 2009. Significant medical history included total thyroidectomy, dissection of left subclavicular node, laterotracheal mass, hypothyroidism, hypertension, leg edema, aortic murmur, iliac vein thrombosis, diarrhea, biliary cyst, and kidney junction syndrome. Bone scan was marked by malignant lesion(s). Screening tumor assessments of target/non-target lesions assessed via spiral CT scan included common iliac adenopathy (left) and other adenopathy. Previous radiotherapy included palliative radiotherapy to the rib, cervical vertebra, and ischium. Prior anticancer therapy included fluorouracil and dacarbazine. Concomitant medications included ibuprofen, acetylsalicylic acid, fluconazole, betamethasone dipropionate, and tinzaparin. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included nebivolol, manidipine, and Vaseretic (enalapril maleate/hydrochlorothiazide).

On 23 June 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. On 30 July 20[redacted] (Day 38), the subject experienced diarrhea (nonserious, Grade 1, probably related) which resolved without treatment on 11 August 20[redacted] (Day 50). On 11 August 20[redacted], the study drug dose was reduced to 20 mg QD due to hypertension (nonserious, Grade 3, possibly related).

On 16 December 20[redacted] (Day 177), the subject had another episode of diarrhea (nonserious, Grade 1, possibly related) and anorexia (nonserious, Grade 1, probably related). No treatment was given. On 27 December 20[redacted] (Day 188), the diarrhea increased in severity to Grade 3. Treatment was not reported. His white blood cell (WBC) count was within normal limits. The last dose of study drug was received on 29 December 20[redacted] (Day 190) and the study drug was withdrawn due to the diarrhea. The diarrhea resolved on 31 December 20[redacted] (Day 192). On 05 January 翌年* (Day 197), the subject was discontinued from the study primarily due to subject choice and secondarily due to the diarrhea.

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject:	7004-1008
Cycle/dose regimen last received:	Cycle 3
Overall duration of study drug:	21 July 20[redacted] to 10 October 20[redacted]
Reason for narrative:	
AE(s) leading to treatment discontinuation	Decreased Appetite Hypertension

A 61-year-old White male with medullary thyroid cancer was originally diagnosed on 23 July 2008 (Stage IVa at diagnosis). The date of last disease progression was on 02 July 2010. Significant medical history included total thyroidectomy, radical neck dissection, decreased neck mobility, hypertension, fatigue, facial edema, tingling in hands, gastroesophageal reflux, diarrhea, nasogastric feeding tube, and depression. Bone scan was reported as marked by degenerative disease. Screening tumor assessments of target/non-target lesions assessed via MRI included a liver mass (right anterior lobe). The ECOG performance status and NYHA functional class were reported as 1 and 1, respectively. The ECG was reported as normal, and his body weight was 70.5 kg. Previous radiotherapy included curative radiotherapy to the thyroid gland and lymph nodes in the neck and mediastinum. Prior anticancer therapy was not reported. Concomitant medications included loperamide, citalopram, cod liver oil, omeprazole, calcium, and panadeine. Concomitant thyroxine suppression therapy included levothyroxine. Concomitant antihypertensive therapy included ramipril and bendroflumethiazide.

On 14 July 20[redacted] (Day -7), the subject was noted to have hypertension; his blood pressure was 150/100 mmHg (nonserious, Grade 2, not related) and ramipril 5 mg was started.

On 21 July 20[redacted] (Day 1), treatment with E7080 (24 mg QD) was initiated. The subject's blood pressure was 125/90 mmHg. On 08 September 20[redacted] (Day 49), hypertension was reported (nonserious, Grade 2, and probably related); blood pressure was 136/97 mmHg. See table below for blood pressures during the study period. The subject's cardiologist increased the ramipril dose to 7.5 mg. On both 15 September 20[redacted] (Day 56) and 22 September 20[redacted] (Day 63), his blood pressure was 144/101 mmHg. The cardiologist further increased ramipril to 10 mg.

On 23 September 20[redacted] (Day 64), the dose of study drug was reduced to 20 mg QD due to hypertension. Additional episodes of hypertension (all nonserious, Grade 2, probably related) were reported as follows: on 24 September 20[redacted] (Day 66) until 28 September 20[redacted] (Day 70); 04 October 20[redacted] (Day 76) to 06 October 20[redacted] (Day 78); 07 October 20[redacted] (Day 79) to 14 October 20[redacted] (Day 86). On 07 October 20[redacted], the dose was further reduced to 14 mg QD due to the hypertension, headache (nonserious, Grade 1, probably related), and lightheadedness (nonserious, Grade 2, probably related).

On 11 October 20[redacted] (Day 83), the subject also experienced decreased appetite (nonserious, Grade 1, probably related). No treatment was given for decreased appetite. The last dose was received on 10 October 20[redacted] (Day 82) and the study drug was withdrawn due to hypertension and decreased appetite. On 13 October 20[redacted] (Day 85), the subject was discontinued from the study due to the hypertension. The outcome of the hypertension was reported as recovered with sequelae on 14 October 20[redacted] (Day 86), and the decreased appetite was resolved on 20 October 20[redacted] (Day 92). On 09 February 翌年*, the subject developed progressive disease.

*新薬承認情報提供時に置き換え

付録 2.7.6-30　死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject 7004-1008 - Blood Pressure

Date/Study Day	Blood Pressure	mmHg
14Jul20[redacted]/-7	Sitting SBP	150
	Sitting DBP	100
21Jul20[redacted]/1	Sitting SBP	125
	Sitting DBP	90
08Sep20[redacted]/50	Sitting SBP	136
	Sitting DBP	97
15Sep20[redacted]/57	Sitting SBP	144
	Sitting DBP	101
22Sep20[redacted]/64	Sitting SBP	144
	Sitting DBP	101
29Sep20[redacted]/71	Sitting SBP	129
	Sitting DBP	89
06Oct20[redacted]/78	Sitting SBP	130
	Sitting DBP	90
13Oct20[redacted]/85	Sitting SBP	132
	Sitting DBP	91

DBP = diastolic blood pressure, SBP = systolic blood pressure.

付録 2.7.6-30　死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

Subject Number	Histologic Cohort (DTC or MTC)	Deaths due to SAE n=2	Deaths due to ProgressiveDisease n=0	Non-fatal SAEs n=25	AE(s) leading to study drug discontinuation n=10
10041007	MTC			X	
10041008	MTC			X	
10091001	DTC			X	
10091002	DTC	X		X	X
10161001	MTC			X	
10161006	DTC				X
10161009	MTC			X	
10211001	DTC				X
10221008	DTC			X	
10221013	MTC			X	X
10221016	MTC			X	
10231002	DTC			X	
30011006	MTC			X	
40011002	MTC			X	
40011005	MTC				X
50021010	DTC			X	
50051005	DTC			X	
50061004	MTC			X	X
50061005	MTC			X	X
60011004	MTC			X	X
60011005	DTC			X	
60011006	MTC			X	
60011008	DTC			X	
60011015	MTC			X	
70021003	MTC			X	X
70031001	MTC	X		X	
70041001	MTC			X	
70041007	MTC			X	X

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

(1)死亡

SUBJECT NUMBER	10091002
Study ID	HOPE201
Manufacturer's Control Number	E7080-00502-CLI-US, E7080-00567-CFI-US, E7080-01118-CFI-US, E7080-01145-CFI-US
Assigned treatment	Lenvatinib 24mg QD
Fatal SAE(s)	Acute respiratory failure, Septic shock
Non-Fatal SAE(s)	Sick sinus syndrome, Back pain, Implant site infection, Radiculopathy, Pneumothorax, Septic shock, Acute respiratory failure, Asthenia,
Death due to PD	No
AEs leading to Discontinuation	Sick sinus syndrome, Implant site infection, Radiculopathy, Septic shock, Acute respiratory failure, Asthenia, Atrial fibrillation, Diarrhoea, Vomiting, Mitral valve calcification, Pleural effusion, Generalised oedema, Dehydration, Hypotension, Gastroenteritis, Cardiomegaly, Pneumonia

A 68-year-old White female with Stage IVa T4N1MX papillary variants thyroid cancer was originally diagnosed on 23 Jul 1998. The last date of disease progression was on 16 Oct 2008. Significant medical history included diabetes mellitus, diabetic retinopathy, seasonal allergies, insomnia, hypercholesterolaemia, constipation, headache, dyspepsia, cerebrovascular accident, drug hypersensitivities, gastric operation, anxiety, back muscle spasm, total thyroidectomy, hysterectomy, leg cramps, shoulder surgery, mammogram, tonsillectomy, eye surgery, left modified radical neck dissection, anemia, inguinal hernia, diverticulum intestinal, and pulmonary arterial hypertension. Tumor assessments of target/non-target lesions via conventional CT scan showed multiple lung lesions (right lower lobe and left upper lobe), and multiple mediastinal adenopathy (left and right). Previous anti-cancer therapy included iodine^{131}. Concomitant medications included pravastatin, zolpidem, lorazepam, metformin, asasantin, methocarbamol, calcium, esomeprazole, gabapentin, ferrous sulfate, fexofenadine, insulin, vitamin D, minerals with vitamins, ipratropium/albuterol, vicodin, viscous lidocaine, oasis (spray), mouth preparations, morphine swish & swallow/morphine, artificial saliva lozenges, neosporin (neomycin sulfate), etodolac, lidocaine with epinephrine, saline/iodine mixture, iodoform, oxycocet, diphenoxylate/atropine, ibuprofen, docusate, sulfacetamide, lidocaine patch, doxycycline, rifampin, methylprednisolone, bupivacaine, lidocaine, collagenase, midazolam, toradol, morphine, ondansetron, cyclobenzaprine, omeprazole, antacids, hydromorphone, ibuprofen, pantoprazole, normal saline/sodium chloride, ciprofloxacin, meropenem, probenecid, vitamin B complex, ascorbic acid, multivitamin with minerals, colecalciferol, magnesium with zinc, ensure, atropine, glucerna, methadone, insulin aspart (novolog pen), acetaminophen, piperacillin/tazobactam, insulin glargine, loratadine, cefazolin, vancomycin, dakins solution 0.25, sodium hypochlorite, moxifloxacin, baclofen, bactrim, dexamethasone, neomycin and polymycin b sulfates, tobramycin, diclofenac sodium topical gel 7%), furosemide, citalopram , bacitracin ointment, labetalol, fentanyl, glycopyrronium, ephedrine, metoclopramide, propofol, flebobag ring lact, diphenhydramine, levofloxacin, salbutamol, promethazine with codeine, polysporin sterile ophthalmic, metronidazole, levophed/norepinephrine, aztreonam, fluconazole, levothyroxine, lisinopril, atenolol and diltiazem. ECOG performance status was 1 at screening.

On 24 Nov 20[redacted] (Day 1), treatment with lenvatinib was initiated.

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

On 09 Jun 翌々年* (Day 563) the subject presented to the emergency room with intractable back pain (thoracic) (Grade 3) and was hospitalized. An MRI showed bone spurs and the subject was scheduled for thoracic spine steroid injections to treat the pain. The subject initially had an episode of shortness of breath which also made the pain much worse. A CT was done and pulmonary embolism was ruled out; but there were bilateral mid and lower lung sub pleural cystic changes and traction bronchiectasis compatible with pulmonary fibrosis and right lower lobe nodule was identified. During the hospital stay, the subject was administered a lidocaine patch and hydromorphone which helped with the pain and the subject was able to function and walk. The subject was discharged at unspecified date in 20[redacted] with further follow up for chronic pain management. The subject recovered from the event on 27 Jul 20[redacted] (Day 937). The study drug was not changed during the event. The Investigator considered the event of back pain as serious and not related to study drug.

On 20 Sep 20[redacted] (Day 666) the subject experienced sick sinus syndrome (Grade 3). She presented to the hospital with complaints of shortness of breath and a pressure-like chest pain. She was admitted on 23 Sep 20[redacted] (Day 669). On examination, she was noted to be bradycardic with a rate of 40. Blood tests were all within normal limits. A decision was made to place pacer pads on her. She received intravenous (IV) atropine (2.5mg) without any significant change. Study drug was interrupted on 25 Sep 20[redacted] (Day 671). A permanent atrioventricular sequential pacemaker was inserted on 26 Sep 20[redacted] (Day 672). The subject recovered from the event on 06 Oct 20[redacted] (Day 682). The Investigator considered the event of sick sinus syndrome as serious and possibly related to study drug. The study drug was resumed on 27 Sep 20[redacted] (Day 673).

On 22 Nov 20[redacted] (Day 729) the subject developed an implant site infection (Grade 3) with swelling over her recently inserted pacemaker site in the infraclavicular region and subsequently started to develop redness and yellow pus discharge from the medial and lateral aspects of the incision. Study drug was interrupted on 30 Nov 20[redacted] (Day 737). The subject was hospitalized on 01 Dec 20[redacted] (Day 738). A new pacemaker was inserted and she was treated with antibiotics. The subject was discharged from the hospital on 13 Dec 20[redacted] (Day 778) and recovered from the event of 27 Dec 20[redacted] (Day 764). The Investigator considered the event of implant site infection as serious and not related to study drug. Study drug was resumed on 28 Dec 20[redacted] (Day 765).

On 19 Oct 3年後* (Day 1061) the subject was hospitalized for pneumothorax. She presented with back pain and a CT showed 20% left sided pneumothorax without evidence of mediastinal and tracheal deviation on the contra lateral side. In the background of chronic bilateral interstitial changes, there is bilateral lower lobe airspace disease with prominent hilar lymph nodes, most consistent with an infectious process, pulmonary hypertension, cardiomegaly and anemic state. The subject was treated pain medication and antibiotics. The subject recovered from left sided pneumothorax on 21 Oct 20[redacted] (Day 1063). The Investigator considered the event of pneumothorax as serious and not related to study drug. Study drug was not changed.

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

On 20 Dec 20[redacted] (Day 1123), during follow up on the pacer pocket wound, the subject complained of right side chest pain. Chest X-ray found possible fluid in the lungs. On 10 Jan [4年後*] (Day 1144), the subject was admitted for acute upper right quadrant and lower ribcage area pain secondary to thoracic spine radiculopathy neuropathy (Grade 3). CT of the abdomen and pelvis contrast was performed. Study drug was interrupted. On 13 Jan 20[redacted] (Day 1147), during consultation, non-remarkable increase in pain with compression of the chest wall on the right side was noted. Acetaminophen and oxycodone 7.5 mg was administered for treatment of right chest pain on 16 Jan 20[redacted]. The pulmonologist ruled out slight lower lung pneumonia as well as chronic active bronchiectasis. Ciprofloxacin hydrochloride was administered for pacer pocket infection. HIDA (hepatobiliary iminodiacetic acid) scan was negative for acute cholecystitis. Right upper quadrant ultrasound showed common bile duct dilation but it was ruled out as cause of the pain, because the pain was in the lower ribs on right side not in the upper quadrant. Pain treatment was carried out with local nerve block insertions of the lower thoracic spine. The subject responded well, and the pain improved. The subject was discharged home with additional concomitant medication of magnesium chloride, levothyroxine sodium and acetylsalicylic acid/dipyridamole. The study medication was reintroduced at a dose of 10 mg per day on 17 Jan 20[redacted] (Day 1151). On 22 Jan 20[redacted] (Day 1156) the subject recovered from acute upper right quadrant and lower ribcage area pain secondary to thoracic spine radiculopathy neuropathy. The Investigator considered the event of radiculopathy as serious and not related to study drug. Study drug was restarted at 10 mg daily on 19 Feb 20[redacted] (Day 1184).

On 29 Apr 20[redacted] (Day 1253) the subject developed gastroenteritis (Grade 3), cardiomegaly (Grade 1) and mitral valve calcification (Grade 1). On 01 May 20[redacted] (Day 1255) the subject developed atrial fibrillation (Grade 1), pleural effusion (Grade 3), generalized edema (Grade 3), and hypotension (Grade 3). The Investigator considered the event of gastroenteritis non-serious and probably related to the study drug; the events of cardiomegaly, mitral valve calcification and atrial fibrillation non-serious and possibly related to the study drug, and the events of pleural effusion, generalized edema, and hypotension as non-serious and not related to study drug. The recovery from these events was not reported. Study drug was withdrawn due to these events and the subject took the last dose of study drug on 28 Apr 20[redacted] (Day 1252).

On 29 Apr 20[redacted] (Day 1253), the subject developed generalized weakness (Grade 3), acute respiratory failure (Grade 3) and severe sepsis with shock (Grade 3). Subject went to see her physician to follow-up on her diarrhea issues, but felt too weak. She subsequently visited the emergency room (ER), and was admitted. She presented with persistent vomiting (Grade 3) and diarrhea (Grade 3) with signs of clinical dehydration (Grade 3). Blood tests came back abnormal (specifics not provided). She received intravenous (IV) fluids to help with her dehydration but developed progressive respiratory distress. Her general condition and weakness worsened during admission, resulting in sepsis and acute respiratory failure (Grade 4). On 01 May 20[redacted] (Day 1255), the subject was moved to the intensive care unit (ICU). Severe sepsis with shock progressed to Grade 4 despite the treatment and the subject's condition continued to worsen. Per sepsis protocol, a right PICC line was inserted. Chest X-ray revealed bilateral interstitial infiltrates, and appeared most likely related to infection. Generalized weakness was considered resolved. On 02 May 20[redacted] (Day 1256), she developed progressive respiratory distress and chest X-ray confirmed multilobular pneumonia (Grade 3). The subject was intubated and placed on assisted ventilation. She was treated empirically with broad-spectrum antibiotics and respiratory therapy treatments. She also underwent enteric tube placement. On 08 May 20[redacted] (Day 1264), the family met with palliative care, and after several discussions and unchanged status of the subject, comfort care and DNR (do not resuscitate) were implemented. All medications were discontinued. On 12 May 20[redacted] (Day 1266, 14 days after the last dose) the subject died due septic shock secondary to pneumonia and acute respiratory failure. The investigator considered both events serious and not related to the study drug.

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

SUBJECT NUMBER	70031001
Study ID	HOPE201
Manufacturer's Control Number	E070-00551-CLI-GB, E7080-00415-CLI-GB, E0780-00670-CLI-GB, E0780-001036-CLI-GB
Assigned treatment	Lenvatinib 24mg QD
Fatal SAE(s)	Oncologic complication
Non-Fatal SAE(s)	Lower respiratory tract infection, Dehydration, Vomiting, Diarrhea, Tachycardia
Death due to PD	No
AEs leading to Discontinuation	Lower respiratory tract infection, Dehydration, Vomiting, Diarrhea, Tachycardia, Oncologic complication

A 37-year-old White female with Stage T2N1BM0 medullary thyroid cancer was originally diagnosed on 22 Feb 1990. The last date of disease progression was on 21 Jul 2010. Significant medical history included thyroidectomy, radical neck dissection, left hemilaryngectomy, excision left pharyngeal mass, excision jugular digastric mass, tracheostomy, pharyngeal haemorrhage, dyspnoea exertional, left facial pain, neck pain, edema peripheral, dyspepsia, lymphadenectomy, resection of recurrent neck malignancy, depression, and amenorrhoea. Tumor assessments of target/non-target lesions via spiral CT scan showed left side of neck, soft tissue non-nodal mass; superior right lung hilar adenopathy, inferior right lung hilar adenopathy, tumour mass right neck, soft tissue non-nodal mass; tumour mass left upper neck, soft tissue non-nodal mass; sub-cardinal adenopathy; lungs, nodular lesions; and paratracheal lymphadenopathy. The subject received previous radiotherapy to anterior left neck and pharynx. Previous anti-cancer therapy were epirubicin and sorafenib. Concomitant medications included antacids, augmentin, calcium carbonate, ciprofloxacin, cyclizine, diclofenac, difflan-mouthwash, domperidone, ferrous sulphate, flucloxacillin, fluoxetine, haloperidol, lansoprazole, levofloxacin, levothyroxine, loperamide, metronidazole,morphine, nystatin, paracetamol, ramipril, and piperacillin/tazobactam, and prochlorperazine. ECOG performance status was 1 at screening.

On 13 Aug 20[redacted] (Day 1), treatment with lenvatinib was initiated.

On 07 Nov 翌年* (Day 452), the subject was admitted to the hospital with lower respiratory tract infection (Grade 2) and fever. On examination, the subject had extensive crackles at the base of the left lung, and a pulse rate of 110 bpm. Chest X-ray showed left lower lobe consolidation, and the sputum culture grew *Serratia marcescens*. The subject was discharged from the hospital on an unknown date with the events still continuing, with treatment medications consisting of morphine sulphate tablets, paracetamol, alfacalcidol, lansoprazole, domperidone, ferrous fumarate, fluoxetine, ramipril, levothyroxine, calichew, saline neb., carbo-cysteine, bactoban-T and octenisan. The study drug was interrupted. The event resolved on 17 Nov 20[redacted] (Day 462). The Investigator considered the event of lower respiratory tract infection serious and not related to study drug. The study drug was resumed unchanged.

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

On 07 Mar 翌々年* (Day 573), the subject experienced vomiting (Grade 1) and the subject's NG tube was removed. She also experienced 3 episodes of diarrhea (Grade 1). On 09 Mar 20[redacted] (Day 579), the subject went to the emergency room because she was feeling unwell. The subject vomited every time she attempted to take in fluids and became dehydrated (Grade 3). Additionally, the subject was tachycardic (Grade 2), with a pulse of 129/min. Other observations were reported to be within normal limits. Urinanalysis showed ++protein, trace blood and trace leukocytes. Her urea was elevated (10.3 mmol/L; NR: 2.5 - 7.83 mmol/L) and she was feeling very tired and sleepy. On 09 Mar 20[redacted] (Day 579) the subject was admitted to the hospital for further investigations and for IV fluid replacements. On the same day, the study medication was interrupted. The event of vomiting and diarrhea resolved on 12 Mar 20[redacted] (Day 578) and the tachycardia and dehydration resolved on 13 Mar 20[redacted] (Day 579). The Investigator considered the events of dehydration, vomiting, diarrhea, and tachycardia serious and possibly related to study drug. Study drug was resumed on to14 Mar 20[redacted] (Day 580).

On 08 Nov 20[redacted] (Day 819), the subject died of left carotid artery hemorrhage due to malignant tumor infiltration and weakening of the left carotid vessel wall (coded as oncologic complication). The subject took the last dose of study drug on 07 Nov 20[redacted] (Day 818).The subject had a pharyngocutaneous fistula (Grade 1) which was a result of tumor response (and not disease progression). The fistula size remained constant through the duration of the study. The subject exsanguinated with blood loss orally and through pharyngocutaneous fistula. The Investigator considered the event of lower respiratory tract infection and oncologic complication serious and not related to study drug and was believed to be due to malignant infiltration of the vessel.

*新薬承認情報提供時に置き換え

付録 2.7.6-30 死亡，その他重篤な有害事象の叙述（外国 201 試験）（続き）
–20[redacted] 年[redacted] 月[redacted] 日カットオフデータ–

(2)死亡以外の重篤な有害事象

SUBJECT NUMBER	10041007
Study ID	HOPE201
Manufacturer's Control Number	E7080- 00741-CLI-US, E7080- 000965-CLI-US, E7080- 000965-CLI-US
Assigned treatment	Lenvatinib 24mg QD
Non-Fatal SAE(s)	Gastroenteritis viral, Pulmonary embolism, Colitis
Death due to PD	No

A 36-year-old White female with Stage IVa T3N1BM0 medullary thyroid cancer was originally diagnosed on 22 Feb 2005. The last date of disease progression was on 23 Feb 2010. Significant medical history included anxiety, insomnia, thyroidectomy, radical neck dissection, liver biopsy, hypothyroidism, herpes simplex, diarrhea, lower back, gallstones and cardiac murmur. Tumor assessments of target/non-target lesions via spiral CT scan showed the following multiple hepatic lesions: right liver mass, right anterior lobe; right #3 liver mass, right # 4 liver mass, and left hepatic lesion, unspecified. Additional lesions were also found via spiral CT in the following regions: left #1 para-aortic adenopathy; left #2 para-aortic adenopathy; multiple small pulmonary nodules; and multiple bone lesions. Previous anti-cancer therapy was sunitinib. . Concomitant medications included oxycodone, zolpidem, diazepam, loperamide, acetaminophen, opium (10% tincture), atropine – diphenoxylate, combipatch, metoclopramide, venlafaxine, sertraline, amoxicillin, tylenol, cyclobenzaprine, lidocaine viscous, bupropion, cephalexin, dextrose with sodium chloride, glucose, morphine, ondansetron, ursodeoxycholic acid, lorazepam, diphenhydramine, psyllium, potassium chloride, clotrimazole, ceftriaxone, oxygen, hydrocodone-acetaminophen, docusate, sodium chloride, heparin, magnesium hydroxide, enoxaparin, medical marijuana, meclizine, pepto-bismol, senna, MS contin, magnesium citrate, ciprofloxacin, metronidazole, sprintec birth control, hydromorphone, promethazine, iopamidol, lactobacillus acidophilus, lomotil, levothyroxine, and nutrisource fiber. ECOG performance status was 0 at screening.

On 26 Mar 20[redacted] (Day 1), treatment with lenvatinib was initiated.

On 08 May 翌々年* (Day 775), the subject presented to the hospital with a 2-day history of right-sided abdominal discomfort, nausea and diarrhea and was subsequently admitted. The diarrhea was profuse and watery with greater than 10 episodes a day. Study drug was interrupted. An ultrasound revealed 2 cm gallstones, with possible non-specific gallbladder wall thickening. Cholecystitis was ruled out given the lack of fever or leukocytosis and relatively rapid resolution of the symptoms. Stool studies (including C-diff toxin) were negative. It was suspected that the subject might have viral gastroenteritis (Grade 3) as she was exposed to children at a school where similar symptoms had occurred. The subject was treated with tincture of opium, psyllium, diphenoxylate/atropine and ursodiol. The subject's symptoms improved gradually and she was able to tolerate an oral diet. She was discharged on 12 May 20[redacted] (Day 779) in a good condition, recovering from the event. The Investigator considered the event of viral gastroenteritis serious and not related to study drug. Study drug was restarted on 18 May 20[redacted] (Day 785).

*新薬承認情報提供時に置き換え