付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
腸出血	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
過敏性腸症候群	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
口唇出血	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
口唇痛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
急性膵炎	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
直腸ポリープ	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
直腸潰瘍	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
舌嚢胞	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
舌不快感	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
食中毒	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)
メレナ	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)
大腸炎	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
小腸炎	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
口唇潰瘍	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
膵炎	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
肛門そう痒症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
肛門皮膚垂	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
肛門潰瘍	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
アフタ性潰瘍	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
小腸瘻	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
胃穿孔	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
胃ポリープ	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
出血性胃潰瘍	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
胃十二指腸炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
異所性胃食道	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

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Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
TEAE = Treatment-emergent adverse event.

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
歯肉びらん	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
歯肉紅斑	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
歯肉退縮	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
胃酸過多	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
腹腔内血腫	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
弛緩歯	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
口腔知覚不全	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
口腔扁平苔癬	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
口腔粘膜水疱形成	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
口の錯感覚	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
腹膜出血	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
ひだ舌	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
直腸裂	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
レッチング	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
舌浮腫	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
変色歯	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
一般・全身障害および投与部位の状態	284 (59.7)	48 (10.1)	243 (51.2)	37 (7.8)
疲労	141 (29.6)	18 (3.8)	119 (25.1)	17 (3.6)
発熱	69 (14.5)	0 (0.0)	63 (13.3)	1 (0.2)
末梢性浮腫	66 (13.9)	4 (0.8)	33 (6.9)	1 (0.2)
無力症	54 (11.3)	14 (2.9)	48 (10.1)	11 (2.3)
倦怠感	21 (4.4)	0 (0.0)	9 (1.9)	0 (0.0)
悪寒	11 (2.3)	0 (0.0)	5 (1.1)	0 (0.0)
非心臓性胸痛	11 (2.3)	0 (0.0)	4 (0.8)	0 (0.0)
全身健康状態低下	6 (1.3)	6 (1.3)	5 (1.1)	5 (1.1)

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Study 304
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	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
インフルエンザ様疾患	6 (1.3)	0 (0.0)	5 (1.1)	0 (0.0)
胸部不快感	5 (1.1)	0 (0.0)	4 (0.8)	0 (0.0)
疼痛	4 (0.8)	0 (0.0)	4 (0.8)	1 (0.2)
全身性浮腫	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
末梢腫脹	3 (0.6)	1 (0.2)	6 (1.3)	1 (0.2)
口渇	3 (0.6)	0 (0.0)	5 (1.1)	0 (0.0)
肝疾患による浮腫	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
多臓器機能不全症候群	2 (0.4)	2 (0.4)	1 (0.2)	1 (0.2)
カテーテル留置部位疼痛	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
早期満腹	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
冷感	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
乾燥症	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
胸痛	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
顔面痛	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
突然死	1 (0.2)	1 (0.2)	2 (0.4)	2 (0.4)
顔面浮腫	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
治癒不良	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
限局性浮腫	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
全身性炎症反応症候群	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
突出痛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
死亡	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
薬物不耐性	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
肉芽腫	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
高熱	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
注入部位血管外漏出	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

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Study 304
Safety Analysis Set

	All			
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System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
注射部位内出血	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
小結節	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
臓器不全	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
異物感	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
温度変化不耐症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
歩行障害	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
注射部位漏出	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
腋窩痛	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
炎症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
注入部位腫脹	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
注射部位反応	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
粘膜の炎症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
浮腫	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
活動状態低下	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
肝胆道系障害	85 (17.9)	54 (11.3)	54 (11.4)	37 (7.8)
肝不全	15 (3.2)	15 (3.2)	12 (2.5)	12 (2.5)
肝機能異常	12 (2.5)	8 (1.7)	13 (2.7)	9 (1.9)
高ビリルビン血症	11 (2.3)	6 (1.3)	6 (1.3)	1 (0.2)
胆汁うっ滞性黄疸	9 (1.9)	8 (1.7)	3 (0.6)	3 (0.6)
門脈血栓症	9 (1.9)	4 (0.8)	3 (0.6)	1 (0.2)
肝臓痛	8 (1.7)	1 (0.2)	3 (0.6)	1 (0.2)
黄疸	6 (1.3)	1 (0.2)	7 (1.5)	5 (1.1)
胆管炎	6 (1.3)	3 (0.6)	3 (0.6)	3 (0.6)
肝硬変	4 (0.8)	3 (0.6)	0 (0.0)	0 (0.0)
胆管閉塞	3 (0.6)	3 (0.6)	1 (0.2)	1 (0.2)

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	All			
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System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
胆嚢炎	2 (0.4)	1 (0.2)	1 (0.2)	0 (0.0)
胆管結石	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
急性胆嚢炎	1 (0.2)	1 (0.2)	2 (0.4)	2 (0.4)
胆管狭窄	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
血性胆汁	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
肝腫大	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
肝腎症候群	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
肝損傷	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
黄疸眼	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
急性肝不全	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
胆管拡張	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
後天性胆管拡張症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
胆石症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
胆汁うっ滞	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
慢性肝不全	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
肝出血	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
水腫性胆嚢炎	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
肝障害	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
門脈圧亢進症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
慢性胆嚢炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
肝毒性	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
免疫系障害	3 (0.6)	0 (0.0)	5 (1.1)	0 (0.0)
季節性アレルギー	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
造影剤アレルギー	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
薬物過敏症	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)

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	All			
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System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
過敏症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
感染症および寄生虫症	144 (30.3)	40 (8.4)	134 (28.2)	27 (5.7)
鼻咽頭炎	25 (5.3)	0 (0.0)	19 (4.0)	0 (0.0)
上気道感染	21 (4.4)	1 (0.2)	24 (5.1)	2 (0.4)
肺炎	12 (2.5)	4 (0.8)	9 (1.9)	4 (0.8)
尿路感染	12 (2.5)	1 (0.2)	8 (1.7)	0 (0.0)
胃腸炎	9 (1.9)	3 (0.6)	3 (0.6)	1 (0.2)
インフルエンザ	8 (1.7)	0 (0.0)	2 (0.4)	0 (0.0)
咽頭炎	7 (1.5)	0 (0.0)	6 (1.3)	0 (0.0)
敗血症	7 (1.5)	7 (1.5)	4 (0.8)	4 (0.8)
細菌性腹膜炎	6 (1.3)	4 (0.8)	1 (0.2)	1 (0.2)
膀胱炎	4 (0.8)	0 (0.0)	3 (0.6)	0 (0.0)
気管支炎	3 (0.6)	0 (0.0)	6 (1.3)	1 (0.2)
口腔カンジダ症	3 (0.6)	0 (0.0)	6 (1.3)	0 (0.0)
毛包炎	3 (0.6)	0 (0.0)	4 (0.8)	0 (0.0)
歯肉炎	3 (0.6)	0 (0.0)	3 (0.6)	0 (0.0)
膿疱性皮疹	3 (0.6)	0 (0.0)	3 (0.6)	1 (0.2)
皮膚感染	3 (0.6)	0 (0.0)	2 (0.4)	0 (0.0)
口角口唇炎	3 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)
感染	3 (0.6)	1 (0.2)	1 (0.2)	1 (0.2)
単純ヘルペス	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
肺感染	2 (0.4)	2 (0.4)	5 (1.1)	2 (0.4)
蜂巣炎	2 (0.4)	2 (0.4)	4 (0.8)	1 (0.2)
足部白癬	2 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)
帯状疱疹	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)

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System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
肝膿瘍	2 (0.4)	2 (0.4)	1 (0.2)	1 (0.2)
歯周炎	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
副鼻腔炎	2 (0.4)	1 (0.2)	1 (0.2)	0 (0.0)
細菌性胃腸炎	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
喉頭炎	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
歯感染	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
外陰腟真菌感染	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
結膜炎	1 (0.2)	0 (0.0)	4 (0.8)	0 (0.0)
真菌感染	1 (0.2)	0 (0.0)	4 (0.8)	0 (0.0)
鼻炎	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
扁桃炎	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
肛門膿瘍	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
胆道感染	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
体部白癬	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
せつ	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
ウイルス性胃腸炎	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
ウイルス性消化管感染	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
感染性胸水	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
限局性感染	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
肺膿瘍	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
爪囲炎	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
ウイルス性気道感染	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
敗血症性ショック	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
腹壁感染	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
虫垂膿瘍	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)

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	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
虫垂炎	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
菌血症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
細菌性膣症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
気管支肺アスペルギルス症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
男性外性器蜂巣炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
慢性B型肝炎	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
シトロバクター感染	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
細菌性結膜炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
デング熱	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
憩室炎	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
耳感染	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
大腸菌性敗血症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
肛径部膿瘍	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
肛径部感染	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
B型肝炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
感染性皮膚嚢腫	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
腎感染	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
医療機器使用部位膿瘍	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
爪感染	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
口腔真菌感染	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
口腔ヘルペス	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
中咽頭カンジダ症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
肝周囲膿瘍	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
胸膜感染	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
術後膿瘍	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
肺結核	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
腎盂腎炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
サルモネラ症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
陰嚢感染	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
歯膿瘍	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
気管炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
結核	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
腸球菌性尿路感染	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
尿路性敗血症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
急性副鼻腔炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
アスペルギルス感染	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
細菌感染	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
バクテロイデス感染	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
クロストリジウム・ディフィシレ感染	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
医療機器関連感染	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
糖尿病性足感染	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
眼瞼毛包炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚真菌感染	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
ノロウイルス性胃腸炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
C型肝炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
ヘルペスウイルス感染	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
麦粒腫	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
感染性大腸炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
下気道感染	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
髄膜炎	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
食道カンジダ症	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
眼部単純ヘルペス	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
中耳炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
慢性中耳炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
会陰膿瘍	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
大腸菌性肺炎	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
術後創感染	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
癜風	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
細菌性尿路感染	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
ウイルス感染	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
創傷感染	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
傷害、中毒および処置合併症	30 (6.3)	7 (1.5)	25 (5.3)	4 (0.8)
転倒	8 (1.7)	1 (0.2)	4 (0.8)	0 (0.0)
挫傷	3 (0.6)	0 (0.0)	3 (0.6)	0 (0.0)
皮膚擦過傷	3 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)
偶発的過量投与	2 (0.4)	2 (0.4)	1 (0.2)	0 (0.0)
創傷	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
処置による疼痛	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
外傷後疼痛	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
肋骨骨折	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
脊椎圧迫骨折	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
外傷性血腫	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
大腿骨骨折	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
頭部損傷	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
熱射病	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
切開部位痛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
注入に伴う反応	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
企図的過量投与	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
裂傷	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
四肢損傷	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
処置後血尿	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
処置による悪心	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
放射線性食道炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
放射線性肺臓炎	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
交通事故	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚損傷	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
サンバーン	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
腱断裂	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
胸椎骨折	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
歯牙破折	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
各種物質毒性	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
創傷血腫	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
手首関節骨折	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
創合併症	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)
脊椎骨折	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
動物咬傷	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
節足動物咬傷	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
焼痂	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
眼挫傷	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
体内異物	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
上腕骨骨折	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
腰椎骨折	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
外傷性気胸	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
放射線宿酔症候群	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚創傷	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
ストーマ部出血	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
くも膜下出血	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
熱傷	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
外傷性骨折	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
臨床検査	304 (63.9)	150 (31.5)	255 (53.7)	121 (25.5)
体重減少	147 (30.9)	36 (7.6)	106 (22.3)	14 (2.9)
血小板数減少	87 (18.3)	26 (5.5)	58 (12.2)	16 (3.4)
血中ビリルビン増加	71 (14.9)	31 (6.5)	63 (13.3)	23 (4.8)
アスパラギン酸アミノトランスフェラーゼ増加	65 (13.7)	24 (5.0)	80 (16.8)	38 (8.0)
アラニンアミノトランスフェラーゼ増加	53 (11.1)	16 (3.4)	52 (10.9)	16 (3.4)
白血球数減少	46 (9.7)	12 (2.5)	23 (4.8)	8 (1.7)
好中球数減少	40 (8.4)	15 (3.2)	11 (2.3)	8 (1.7)
γ－グルタミルトランスフェラーゼ増加	37 (7.8)	26 (5.5)	26 (5.5)	19 (4.0)
心電図ＱＴ延長	33 (6.9)	5 (1.1)	24 (5.1)	5 (1.1)
血中アルカリホスファターゼ増加	32 (6.7)	10 (2.1)	29 (6.1)	7 (1.5)
血中甲状腺刺激ホルモン増加	23 (4.8)	0 (0.0)	4 (0.8)	0 (0.0)
国際標準比増加	19 (4.0)	1 (0.2)	14 (2.9)	1 (0.2)
リパーゼ増加	18 (3.8)	13 (2.7)	18 (3.8)	9 (1.9)
Ｃ－反応性蛋白増加	14 (2.9)	0 (0.0)	12 (2.5)	1 (0.2)
血中アルブミン減少	14 (2.9)	1 (0.2)	9 (1.9)	0 (0.0)

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Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
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	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
リンパ球数減少	12 (2.5)	8 (1.7)	10 (2.1)	6 (1.3)
血中乳酸脱水素酵素増加	11 (2.3)	1 (0.2)	12 (2.5)	2 (0.4)
尿中蛋白陽性	11 (2.3)	1 (0.2)	4 (0.8)	0 (0.0)
血圧上昇	11 (2.3)	1 (0.2)	3 (0.6)	1 (0.2)
血中クレアチニン増加	10 (2.1)	0 (0.0)	4 (0.8)	0 (0.0)
血中コレステロール増加	7 (1.5)	0 (0.0)	1 (0.2)	0 (0.0)
体重増加	6 (1.3)	0 (0.0)	1 (0.2)	0 (0.0)
プロトロンビン時間延長	5 (1.1)	0 (0.0)	7 (1.5)	1 (0.2)
アミラーゼ増加	5 (1.1)	2 (0.4)	4 (0.8)	2 (0.4)
血中カリウム減少	5 (1.1)	2 (0.4)	3 (0.6)	1 (0.2)
血中尿素増加	5 (1.1)	0 (0.0)	2 (0.4)	0 (0.0)
尿中ビリルビン増加	5 (1.1)	1 (0.2)	2 (0.4)	0 (0.0)
血中ナトリウム減少	5 (1.1)	4 (0.8)	1 (0.2)	1 (0.2)
ＥＣＯＧパフォーマンスステータス悪化	4 (0.8)	3 (0.6)	1 (0.2)	1 (0.2)
血中クロール減少	2 (0.4)	1 (0.2)	3 (0.6)	0 (0.0)
ヘモグロビン減少	2 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)
血中甲状腺刺激ホルモン減少	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
赤血球数減少	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
尿中血陽性	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
ヘモグロビン増加	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
抱合ビリルビン増加	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
白血球数増加	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
尿中白血球陽性	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
血中カルシウム減少	1 (0.2)	0 (0.0)	4 (0.8)	0 (0.0)
体温上昇	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)

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Study 304
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	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
好中球数増加	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
尿中ウロビリノーゲン増加	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
血中コリンエステラーゼ減少	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
血中クレアチニン減少	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
血中ブドウ糖増加	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
血中カリウム増加	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
尿中ブドウ糖陽性	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
肝酵素上昇	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
尿中亜硝酸塩陽性	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
トランスアミナーゼ上昇	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
尿量減少	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
活性化部分トロンボプラスチン時間短縮	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
アンモニア増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
血中カルシウム増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
血中電解質減少	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
血中フィブリノゲン増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
血圧低下	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
拡張期血圧上昇	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
心雑音	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
クロストリジウム検査陽性	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
薬物スクリーニング陽性	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
心電図ＳＴ部分下降	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
心電図ＳＴ－Ｔ変化	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
心電図異常Ｔ波	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
尿中ブドウ糖	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

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TEAE = Treatment-emergent adverse event.

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
ヘリコバクター検査陽性	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
国際標準比減少	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
リパーゼ減少	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
リンパ球数増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
プロテインC増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
総蛋白減少	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
プロトロンビン量減少	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
プロトロンビン量増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
トリヨードチロニン増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
トロポニンT増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
尿中蛋白／クレアチニン比増加	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
膵酵素増加	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)
活性化部分トロンボプラスチン時間延長	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
α1フェトプロテイン増加	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
血中クレアチンホスホキナーゼ増加	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
血中リン減少	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
チャイルド・ピュー・ターコットスコア増加	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
凝固因子増加	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
凝固時間延長	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
心電図T波逆転	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
肝機能検査値上昇	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
血小板数増加	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
総蛋白増加	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
遊離トリヨードチロニン減少	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
遊離トリヨードチロニン増加	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
尿中ケトン体陽性	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
代謝および栄養障害	220 (46.2)	65 (13.7)	196 (41.3)	38 (8.0)
食欲減退	162 (34.0)	22 (4.6)	127 (26.7)	6 (1.3)
低アルブミン血症	44 (9.2)	4 (0.8)	38 (8.0)	2 (0.4)
低ナトリウム血症	23 (4.8)	20 (4.2)	9 (1.9)	9 (1.9)
脱水	17 (3.6)	4 (0.8)	5 (1.1)	0 (0.0)
低血糖	12 (2.5)	3 (0.6)	2 (0.4)	0 (0.0)
高カリウム血症	11 (2.3)	6 (1.3)	12 (2.5)	2 (0.4)
高アンモニア血症	9 (1.9)	0 (0.0)	3 (0.6)	0 (0.0)
低カリウム血症	8 (1.7)	5 (1.1)	25 (5.3)	12 (2.5)
低マグネシウム血症	5 (1.1)	1 (0.2)	2 (0.4)	0 (0.0)
低カルシウム血症	4 (0.8)	2 (0.4)	4 (0.8)	1 (0.2)
低蛋白血症	4 (0.8)	1 (0.2)	3 (0.6)	0 (0.0)
高血糖	4 (0.8)	1 (0.2)	1 (0.2)	1 (0.2)
高尿酸血症	3 (0.6)	0 (0.0)	3 (0.6)	2 (0.4)
糖尿病	3 (0.6)	1 (0.2)	1 (0.2)	0 (0.0)
高脂血症	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
低リン酸血症	2 (0.4)	2 (0.4)	7 (1.5)	3 (0.6)
高カルシウム血症	2 (0.4)	0 (0.0)	2 (0.4)	1 (0.2)
痛風	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
悪液質	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
過小食	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
高ナトリウム血症	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
低クロール血症	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
アシドーシス	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

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Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
糖尿病性代謝代償不全	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
高トリグリセリド血症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
代謝性アシドーシス	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
高コレステロール血症	0 (0.0)	0 (0.0)	6 (1.3)	2 (0.4)
水分過負荷	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
高アミラーゼ血症	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
高リパーゼ血症	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
高蛋白血症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
テタニー	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
筋骨格系および結合組織障害	180 (37.8)	18 (3.8)	132 (27.8)	14 (2.9)
背部痛	50 (10.5)	1 (0.2)	31 (6.5)	5 (1.1)
筋骨格痛	47 (9.9)	0 (0.0)	24 (5.1)	2 (0.4)
関節痛	42 (8.8)	0 (0.0)	20 (4.2)	1 (0.2)
四肢痛	37 (7.8)	3 (0.6)	18 (3.8)	1 (0.2)
筋肉痛	21 (4.4)	1 (0.2)	8 (1.7)	0 (0.0)
筋痙縮	13 (2.7)	0 (0.0)	18 (3.8)	1 (0.2)
筋力低下	13 (2.7)	2 (0.4)	6 (1.3)	1 (0.2)
筋骨格系胸痛	11 (2.3)	0 (0.0)	7 (1.5)	0 (0.0)
頚部痛	10 (2.1)	2 (0.4)	4 (0.8)	1 (0.2)
側腹部痛	8 (1.7)	0 (0.0)	6 (1.3)	0 (0.0)
骨痛	6 (1.3)	2 (0.4)	5 (1.1)	0 (0.0)
変形性関節症	4 (0.8)	1 (0.2)	2 (0.4)	0 (0.0)
病的骨折	3 (0.6)	2 (0.4)	7 (1.5)	4 (0.8)
筋骨格不快感	3 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)
骨粗鬆症	3 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
関節腫脹	2 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)
関節炎	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
尾骨痛	2 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)
椎間板突出	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
腰部脊柱管狭窄症	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
筋攣縮	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
脊柱管狭窄症	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
脊椎痛	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
脊椎すべり症	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
関節可動域低下	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
筋骨格硬直	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
滑液包炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
痛風性関節炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
運動性低下	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
筋萎縮	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
筋緊張	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
関節周囲炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
横紋筋融解症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
肩回旋筋腱板症候群	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
変形性脊椎症	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
痛風結節	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
筋肉疲労	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
頚部腫瘤	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
顎痛	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
軟部組織腫瘤	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
滑膜炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
腱痛	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	51 (10.7)	28 (5.9)	57 (12.0)	32 (6.7)
癌疼痛	17 (3.6)	4 (0.8)	15 (3.2)	6 (1.3)
悪性新生物進行	10 (2.1)	10 (2.1)	15 (3.2)	15 (3.2)
腫瘍疼痛	4 (0.8)	1 (0.2)	5 (1.1)	2 (0.4)
悪性腹水	3 (0.6)	1 (0.2)	8 (1.7)	1 (0.2)
腫瘍出血	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)
腫瘍熱	3 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)
肝癌破裂	2 (0.4)	2 (0.4)	1 (0.2)	1 (0.2)
悪性胸水	2 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)
脊椎転移	2 (0.4)	2 (0.4)	1 (0.2)	1 (0.2)
中枢神経系転移	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
骨転移	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
腫瘍壊死	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
腫瘍破裂	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
副腎腺腫	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
基底細胞癌	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
感染性新生物	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
頭蓋内腫瘍出血	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
髄膜腫	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
腫瘍随伴症候群	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
腎細胞癌	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
子宮頚部の良性新生物	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
ケラトアカントーマ	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
口唇扁平上皮癌	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
肺の悪性新生物	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
菌状息肉症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
口腔新生物	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
形質細胞性骨髄腫	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
脂漏性角化症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
神経系障害	163 (34.2)	47 (9.9)	106 (22.3)	20 (4.2)
頭痛	46 (9.7)	3 (0.6)	38 (8.0)	0 (0.0)
肝性脳症	38 (8.0)	23 (4.8)	9 (1.9)	7 (1.5)
浮動性めまい	30 (6.3)	1 (0.2)	16 (3.4)	1 (0.2)
味覚異常	22 (4.6)	0 (0.0)	12 (2.5)	0 (0.0)
錯感覚	9 (1.9)	2 (0.4)	6 (1.3)	0 (0.0)
傾眠	7 (1.5)	1 (0.2)	6 (1.3)	0 (0.0)
嗜眠	6 (1.3)	0 (0.0)	3 (0.6)	0 (0.0)
感覚鈍麻	6 (1.3)	0 (0.0)	2 (0.4)	0 (0.0)
末梢性感覚ニューロパチー	4 (0.8)	0 (0.0)	7 (1.5)	1 (0.2)
注意力障害	3 (0.6)	0 (0.0)	2 (0.4)	0 (0.0)
多発ニューロパチー	3 (0.6)	0 (0.0)	2 (0.4)	0 (0.0)
肝性昏睡	3 (0.6)	3 (0.6)	1 (0.2)	1 (0.2)
痙攣発作	3 (0.6)	1 (0.2)	1 (0.2)	0 (0.0)
脳出血	3 (0.6)	3 (0.6)	0 (0.0)	0 (0.0)
脳梗塞	3 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)
失神	3 (0.6)	3 (0.6)	0 (0.0)	0 (0.0)
脳血管発作	2 (0.4)	2 (0.4)	1 (0.2)	0 (0.0)
振戦	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
失語症	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
固定姿勢保持困難	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
意識レベルの低下	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
過眠症	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
睡眠の質低下	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
脊髄圧迫	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
認知障害	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
脳症	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.2)
両麻痺	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
坐骨神経痛	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
意識変容状態	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
健忘	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
運動失調	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
平衡障害	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
灼熱感	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
昏睡	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
ジスキネジア	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
測定障害	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
顔面麻痺	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
蟻走感	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
頭蓋内出血	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
味覚減退	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
第３脳神経麻痺	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
記憶障害	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
末梢性ニューロパチー	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
反回神経麻痺	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
末梢性運動ニューロパチー	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
末梢性感覚運動ニューロパチー	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
可逆性後白質脳症症候群	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
緊張性頭痛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
中毒性ニューロパチー	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
一過性脳虚血発作	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
三叉神経痛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
白質病変	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
失声症	0 (0.0)	0 (0.0)	3 (0.6)	2 (0.4)
知覚過敏	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)
大脳基底核出血	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
脳虚血	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
頭部不快感	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
肋間神経痛	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
頭蓋内圧上昇	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
虚血性脳卒中	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
意識消失	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
代謝性脳症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
神経痛	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
神経毒性	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
ヘルペス後神経痛	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
失神寸前の状態	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
神経根障害	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
下肢静止不能症候群	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
血栓性脳梗塞	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
精神障害	56 (11.8)	6 (1.3)	46 (9.7)	1 (0.2)
不眠症	33 (6.9)	1 (0.2)	27 (5.7)	0 (0.0)
不安	9 (1.9)	0 (0.0)	5 (1.1)	0 (0.0)
うつ病	7 (1.5)	1 (0.2)	6 (1.3)	0 (0.0)
錯乱状態	6 (1.3)	2 (0.4)	4 (0.8)	1 (0.2)
譫妄	4 (0.8)	0 (0.0)	1 (0.2)	0 (0.0)
精神状態変化	3 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)
失見当識	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
睡眠障害	1 (0.2)	0 (0.0)	3 (0.6)	0 (0.0)
無感情	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
抑うつ気分	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
大うつ病	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
精神運動制止遅滞	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
落ち着きのなさ	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
自殺企図	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
激越	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
易刺激性	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
神経過敏	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
人格変化	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
腎および尿路障害	151 (31.7)	38 (8.0)	84 (17.7)	15 (3.2)
蛋白尿	117 (24.6)	27 (5.7)	54 (11.4)	8 (1.7)
血尿	25 (5.3)	1 (0.2)	10 (2.1)	0 (0.0)
急性腎障害	9 (1.9)	4 (0.8)	5 (1.1)	4 (0.8)
腎機能障害	5 (1.1)	1 (0.2)	6 (1.3)	2 (0.4)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
排尿困難	4 (0.8)	0 (0.0)	3 (0.6)	0 (0.0)
ビリルビン尿	3 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)
着色尿	3 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)
尿閉	3 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)
慢性腎臓病	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
白血球尿	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
夜間頻尿	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
腎不全	2 (0.4)	2 (0.4)	1 (0.2)	0 (0.0)
腎仙痛	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
頻尿	1 (0.2)	0 (0.0)	6 (1.3)	0 (0.0)
尿失禁	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
乏尿	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
尿流量減少	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
無尿	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
高窒素血症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
膀胱障害	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
膀胱腫瘤	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
尿路結石	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
非感染性膀胱炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
糖尿	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
ＩｇＡ腎症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
ケトン尿	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
腎炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
腎結石症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
腎梗塞	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
腎尿細管壊死	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
尿意切迫	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
多尿	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
尿路の炎症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
尿路痛	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
生殖系および乳房障害	26 (5.5)	2 (0.4)	19 (4.0)	0 (0.0)
女性化乳房	6 (1.3)	0 (0.0)	1 (0.2)	0 (0.0)
骨盤痛	4 (0.8)	1 (0.2)	0 (0.0)	0 (0.0)
良性前立腺肥大症	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
乳房痛	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
陰嚢紅斑	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
陰嚢潰瘍	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
陰部そう痒症	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
乳頭痛	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
陰嚢血瘤	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
後天性陰嚢水瘤	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
性器発疹	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
不規則月経	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
性器浮腫	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
骨盤液貯留	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
陰茎浮腫	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
前立腺閉塞	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
陰嚢浮腫	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
精巣痛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
無月経	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
乳房分泌	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
線維嚢胞性乳腺疾患	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
性器びらん	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
性器紅斑	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
乳頭の炎症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
前立腺石灰化	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
前立腺炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
陰嚢障害	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
陰嚢腫脹	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
腟出血	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
腟の炎症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
外陰部障害	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
呼吸器、胸郭および縦隔障害	213 (44.7)	25 (5.3)	148 (31.2)	16 (3.4)
発声障害	113 (23.7)	1 (0.2)	57 (12.0)	0 (0.0)
咳嗽	45 (9.5)	0 (0.0)	36 (7.6)	1 (0.2)
呼吸困難	36 (7.6)	9 (1.9)	18 (3.8)	3 (0.6)
鼻出血	34 (7.1)	1 (0.2)	15 (3.2)	0 (0.0)
口腔咽頭痛	21 (4.4)	0 (0.0)	16 (3.4)	0 (0.0)
喀血	9 (1.9)	1 (0.2)	7 (1.5)	0 (0.0)
胸水	9 (1.9)	0 (0.0)	6 (1.3)	2 (0.4)
しゃっくり	4 (0.8)	0 (0.0)	4 (0.8)	1 (0.2)
肺塞栓症	4 (0.8)	4 (0.8)	4 (0.8)	4 (0.8)
湿性咳嗽	3 (0.6)	0 (0.0)	10 (2.1)	1 (0.2)
鼻漏	3 (0.6)	0 (0.0)	4 (0.8)	0 (0.0)
呼吸不全	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
アレルギー性鼻炎	3 (0.6)	0 (0.0)	2 (0.4)	0 (0.0)
誤嚥性肺炎	3 (0.6)	3 (0.6)	1 (0.2)	0 (0.0)
上気道の炎症	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
気胸	2 (0.4)	1 (0.2)	1 (0.2)	0 (0.0)
喘鳴	2 (0.4)	1 (0.2)	1 (0.2)	0 (0.0)
肝肺症候群	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
非心原性肺水腫	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
肺梗塞	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
胸膜炎	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
胸膜痛	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
急性呼吸不全	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
慢性閉塞性肺疾患	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
喉頭の炎症	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
鼻閉	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
鼻乾燥	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
肺臓炎	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
呼吸抑制	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
呼吸窮迫	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
鼻痛	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
無気肺	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
慢性気管支炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
気管支痙攣	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
気管支狭窄	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
労作性呼吸困難	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
低酸素症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
特発性肺線維症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
上気道分泌増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
壊死性細気管支炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
口腔咽頭不快感	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
咽頭びらん	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
肺腫瘤	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
変色痰	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
喀痰増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
痰貯留	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
上気道うっ血	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
上気道咳症候群	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
鼻の炎症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
ラ音	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
咽喉刺激感	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚および皮下組織障害	237 (49.8)	17 (3.6)	353 (74.3)	64 (13.5)
手掌・足底発赤知覚不全症候群	128 (26.9)	14 (2.9)	249 (52.4)	54 (11.4)
発疹	46 (9.7)	0 (0.0)	76 (16.0)	2 (0.4)
そう痒症	34 (7.1)	0 (0.0)	34 (7.2)	1 (0.2)
皮膚乾燥	21 (4.4)	0 (0.0)	19 (4.0)	0 (0.0)
脱毛症	14 (2.9)	0 (0.0)	119 (25.1)	0 (0.0)
過角化	9 (1.9)	0 (0.0)	11 (2.3)	0 (0.0)
紅斑	9 (1.9)	0 (0.0)	10 (2.1)	0 (0.0)
斑状丘疹状皮疹	6 (1.3)	0 (0.0)	19 (4.0)	4 (0.8)
蕁麻疹	6 (1.3)	0 (0.0)	6 (1.3)	0 (0.0)
皮膚剥脱	6 (1.3)	0 (0.0)	3 (0.6)	0 (0.0)

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付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
褥瘡性潰瘍	5 (1.1)	1 (0.2)	2 (0.4)	0 (0.0)
ざ瘡様皮膚炎	4 (0.8)	0 (0.0)	8 (1.7)	0 (0.0)
湿疹	4 (0.8)	1 (0.2)	6 (1.3)	0 (0.0)
多汗症	4 (0.8)	0 (0.0)	2 (0.4)	0 (0.0)
皮膚反応	4 (0.8)	0 (0.0)	1 (0.2)	0 (0.0)
爪変色	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
水疱	3 (0.6)	0 (0.0)	5 (1.1)	1 (0.2)
皮膚炎	3 (0.6)	0 (0.0)	2 (0.4)	0 (0.0)
寝汗	3 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)
丘疹性皮疹	2 (0.4)	0 (0.0)	6 (1.3)	2 (0.4)
水疱性皮膚炎	2 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)
多形紅斑	2 (0.4)	0 (0.0)	3 (0.6)	1 (0.2)
そう痒性皮疹	2 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)
皮膚潰瘍	2 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)
ざ瘡	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
点状出血	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚嚢腫	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚びらん	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚疼痛	1 (0.2)	0 (0.0)	4 (0.8)	0 (0.0)
乾癬	1 (0.2)	0 (0.0)	4 (0.8)	1 (0.2)
皮膚刺激	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
皮膚病変	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
顔面腫脹	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
斑状出血	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
爪線状隆起	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
手掌紅斑	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
紫斑	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
脂漏性皮膚炎	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
皮膚障害	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚色素減少	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
毛細血管拡張症	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
乾皮症	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚血管炎	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
接触皮膚炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
異汗性湿疹	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
環状肉芽腫	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
間擦疹	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
爪床圧痛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
爪の障害	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
爪破損	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
白色粃糠疹	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
紅斑性皮疹	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
くも状母斑	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
薬疹	0 (0.0)	0 (0.0)	4 (0.8)	1 (0.2)
全身性そう痒症	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
痂皮	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
アレルギー性皮膚炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
糖尿病性足病変	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
剥脱性発疹	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
全身紅斑	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

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Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
ヘノッホ・シェーンライン紫斑病	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
汗疹	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
陰茎潰瘍形成	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
斑状皮疹	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚癒着	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚変色	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚不快感	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚亀裂	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚硬結	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚腫瘤	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚感作	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
線状出血	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
血管障害	214 (45.0)	116 (24.4)	152 (32.0)	73 (15.4)
高血圧	201 (42.2)	111 (23.3)	144 (30.3)	68 (14.3)
低血圧	6 (1.3)	2 (0.4)	5 (1.1)	2 (0.4)
起立性低血圧	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
潮紅	2 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)
循環虚脱	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
静脈炎	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
大静脈血栓症	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
大動脈解離	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
動脈硬化症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
動脈解離	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
深部静脈血栓症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
静脈塞栓症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

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Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
ほてり	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
リンパ浮腫	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
起立性高血圧	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
血栓性静脈炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
静脈瘤	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
大動脈狭窄	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
充血	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
血液量減少性ショック	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
末梢冷感	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
ショック	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
表在性血栓性静脈炎	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
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TEAE = Treatment-emergent adverse event.

付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
Subjects with Any Related TEAEs	447 (93.9)	270 (56.7)	452 (95.2)	231 (48.6)
血液およびリンパ系障害	59 (12.4)	21 (4.4)	49 (10.3)	11 (2.3)
血小板減少症	31 (6.5)	7 (1.5)	24 (5.1)	4 (0.8)
好中球減少症	18 (3.8)	6 (1.3)	6 (1.3)	0 (0.0)
貧血	14 (2.9)	4 (0.8)	25 (5.3)	7 (1.5)
白血球減少症	13 (2.7)	1 (0.2)	10 (2.1)	1 (0.2)
骨髄機能不全	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
リンパ球減少症	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
白血球増加症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
リンパ節症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
汎血球減少症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
赤血球増加症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
ビタミンＢ１２欠乏性貧血	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
心臓障害	19 (4.0)	3 (0.6)	14 (2.9)	2 (0.4)
洞性徐脈	3 (0.6)	0 (0.0)	2 (0.4)	0 (0.0)
心筋梗塞	3 (0.6)	3 (0.6)	0 (0.0)	0 (0.0)
心房細動	2 (0.4)	0 (0.0)	4 (0.8)	1 (0.2)
心筋虚血	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
動悸	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
上室性期外収縮	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
左室肥大	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
頻脈	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
心室性期外収縮	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
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TEAE = Treatment-emergent adverse event.

付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
第一度房室ブロック	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
左脚ブロック	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
期外収縮	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
プリンツメタル狭心症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
洞性不整脈	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
洞性頻脈	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
徐脈性不整脈	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
右脚ブロック	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
心不全	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
心臓弁狭窄	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
心室性不整脈	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
耳および迷路障害	10 (2.1)	0 (0.0)	4 (0.8)	1 (0.2)
耳鳴	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
回転性めまい	3 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)
難聴	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
耳不快感	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
耳の障害	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
耳管開放	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
聴覚過敏	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
聴力低下	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
内分泌障害	74 (15.5)	0 (0.0)	10 (2.1)	0 (0.0)
甲状腺機能低下症	70 (14.7)	0 (0.0)	8 (1.7)	0 (0.0)
甲状腺機能亢進症	4 (0.8)	0 (0.0)	2 (0.4)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
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TEAE = Treatment-emergent adverse event.

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付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
甲状腺炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
自己免疫性甲状腺炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
眼障害	5 (1.1)	0 (0.0)	3 (0.6)	0 (0.0)
眼痛	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
眼刺激	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
眼瞼浮腫	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
眼瞼そう痒症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
眼充血	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
眼乾燥	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
眼窩周囲浮腫	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
胃腸障害	281 (59.0)	38 (8.0)	291 (61.3)	42 (8.8)
下痢	143 (30.0)	20 (4.2)	197 (41.5)	17 (3.6)
悪心	65 (13.7)	2 (0.4)	54 (11.4)	3 (0.6)
口内炎	43 (9.0)	1 (0.2)	54 (11.4)	2 (0.4)
嘔吐	43 (9.0)	2 (0.4)	23 (4.8)	5 (1.1)
腹水	31 (6.5)	7 (1.5)	7 (1.5)	2 (0.4)
腹痛	30 (6.3)	2 (0.4)	32 (6.7)	5 (1.1)
上腹部痛	30 (6.3)	1 (0.2)	19 (4.0)	1 (0.2)
口内乾燥	28 (5.9)	0 (0.0)	8 (1.7)	0 (0.0)
便秘	26 (5.5)	0 (0.0)	19 (4.0)	0 (0.0)
消化不良	20 (4.2)	0 (0.0)	11 (2.3)	0 (0.0)
腹部膨満	15 (3.2)	0 (0.0)	8 (1.7)	0 (0.0)
歯肉腫脹	8 (1.7)	0 (0.0)	2 (0.4)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
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付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
歯肉出血	6 (1.3)	0 (0.0)	6 (1.3)	0 (0.0)
歯肉痛	6 (1.3)	0 (0.0)	3 (0.6)	0 (0.0)
鼓腸	5 (1.1)	0 (0.0)	6 (1.3)	0 (0.0)
痔核	4 (0.8)	0 (0.0)	5 (1.1)	1 (0.2)
口腔内潰瘍形成	4 (0.8)	1 (0.2)	3 (0.6)	0 (0.0)
食道静脈瘤出血	4 (0.8)	4 (0.8)	0 (0.0)	0 (0.0)
歯痛	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
口腔内痛	3 (0.6)	0 (0.0)	3 (0.6)	0 (0.0)
上部消化管出血	3 (0.6)	2 (0.4)	3 (0.6)	2 (0.4)
舌痛	3 (0.6)	0 (0.0)	2 (0.4)	0 (0.0)
口腔内出血	3 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)
直腸炎	3 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)
おくび	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
胃潰瘍	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
歯周病	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
胃炎	2 (0.4)	0 (0.0)	3 (0.6)	1 (0.2)
舌炎	2 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)
排便回数増加	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
消化器痛	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
痔出血	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
嚥下痛	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
直腸出血	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
腹部不快感	1 (0.2)	0 (0.0)	4 (0.8)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
胃出血	1 (0.2)	0 (0.0)	2 (0.4)	2 (0.4)
胃食道逆流性疾患	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
食道静脈瘤	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.2)
肛門の炎症	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
出血性十二指腸潰瘍	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
嚥下障害	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
心窩部不快感	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
軟便	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
消化管運動障害	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
裂肛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
口唇のひび割れ	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
十二指腸潰瘍	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
排便障害	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
糞塊	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
歯肉潰瘍	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
口唇痛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
舌不快感	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
大腸炎	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
口唇潰瘍	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
下部消化管出血	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)
膵炎	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
下腹部痛	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
肛門そう痒症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

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付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
アフタ性潰瘍	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
小腸炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
食中毒	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
胃穿孔	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
びらん性胃炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
胃十二指腸炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
胃腸出血	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
歯肉びらん	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
血便排泄	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
胃酸過多	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
メレナ	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
口腔知覚不全	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
口腔扁平苔癬	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
口腔粘膜水疱形成	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
腹膜出血	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
ひだ舌	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
門脈圧亢進性胃障害	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
レッチング	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
一般・全身障害および投与部位の状態	198 (41.6)	24 (5.0)	163 (34.3)	21 (4.4)
疲労	111 (23.3)	10 (2.1)	99 (20.8)	12 (2.5)
無力症	36 (7.6)	9 (1.9)	33 (6.9)	7 (1.5)
末梢性浮腫	31 (6.5)	1 (0.2)	9 (1.9)	0 (0.0)
発熱	28 (5.9)	0 (0.0)	23 (4.8)	1 (0.2)

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付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
倦怠感	21 (4.4)	0 (0.0)	6 (1.3)	0 (0.0)
悪寒	6 (1.3)	0 (0.0)	2 (0.4)	0 (0.0)
全身性浮腫	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
肝疾患による浮腫	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
口渇	2 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)
疼痛	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
全身健康状態低下	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
非心臓性胸痛	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
乾燥症	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
インフルエンザ様疾患	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
胸痛	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
顔面浮腫	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
治癒不良	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
薬物不耐性	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
早期満腹	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
冷感	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
高熱	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
小結節	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
温度変化不耐症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
顔面痛	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
歩行障害	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
粘膜の炎症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
活動状態低下	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

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付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
突然死	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
肝胆道系障害	38 (8.0)	23 (4.8)	26 (5.5)	16 (3.4)
肝機能異常	8 (1.7)	6 (1.3)	11 (2.3)	8 (1.7)
高ビリルビン血症	8 (1.7)	3 (0.6)	5 (1.1)	1 (0.2)
肝不全	6 (1.3)	6 (1.3)	3 (0.6)	3 (0.6)
門脈血栓症	4 (0.8)	1 (0.2)	2 (0.4)	1 (0.2)
黄疸	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)
胆管炎	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
胆嚢炎	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
肝臓痛	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
胆汁うっ滞性黄疸	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
胆管結石	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
後天性胆管拡張症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
血性胆汁	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
肝硬変	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
肝腎症候群	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
肝障害	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
門脈圧亢進症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
肝毒性	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
肝損傷	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
免疫系障害	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)
薬物過敏症	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
季節性アレルギー	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

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付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
感染症および寄生虫症	36 (7.6)	7 (1.5)	28 (5.9)	5 (1.1)
咽頭炎	4 (0.8)	0 (0.0)	2 (0.4)	0 (0.0)
毛包炎	3 (0.6)	0 (0.0)	3 (0.6)	0 (0.0)
口角口唇炎	3 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)
肺炎	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)
歯肉炎	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
鼻咽頭炎	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
膿疱性皮疹	2 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)
胃腸炎	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
口腔カンジダ症	1 (0.2)	0 (0.0)	4 (0.8)	0 (0.0)
上気道感染	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
結膜炎	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
爪囲炎	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
気管支肺アスペルギルス症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
膀胱炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
耳感染	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
細菌性胃腸炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
インフルエンザ	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
腎感染	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
肺感染	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
爪感染	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
術後膿瘍	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
陰嚢感染	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)

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付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
敗血症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
副鼻腔炎	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
皮膚感染	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
歯感染	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
気管炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
尿路感染	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
蜂巣炎	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
鼻炎	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
気管支炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
医療機器関連感染	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
眼瞼毛包炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
帯状疱疹	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
麦粒腫	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
感染	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
食道カンジダ症	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
足部白癬	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
癜風	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
傷害、中毒および処置合併症	1 (0.2)	0 (0.0)	3 (0.6)	1 (0.2)
サンバーン	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
転倒	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
ストーマ部出血	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
創傷	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
臨床検査	228 (47.9)	92 (19.3)	196 (41.3)	74 (15.6)

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付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
体重減少	86 (18.1)	19 (4.0)	66 (13.9)	6 (1.3)
血小板数減少	66 (13.9)	21 (4.4)	47 (9.9)	12 (2.5)
血中ビリルビン増加	44 (9.2)	14 (2.9)	32 (6.7)	9 (1.9)
アスパラギン酸アミノトランスフェラーゼ増加	40 (8.4)	10 (2.1)	53 (11.2)	22 (4.6)
好中球数減少	38 (8.0)	13 (2.7)	9 (1.9)	6 (1.3)
白血球数減少	36 (7.6)	8 (1.7)	16 (3.4)	6 (1.3)
アラニンアミノトランスフェラーゼ増加	33 (6.9)	9 (1.9)	37 (7.8)	11 (2.3)
血中甲状腺刺激ホルモン増加	22 (4.6)	0 (0.0)	4 (0.8)	0 (0.0)
γ－グルタミルトランスフェラーゼ増加	19 (4.0)	13 (2.7)	13 (2.7)	9 (1.9)
血中アルカリホスファターゼ増加	18 (3.8)	3 (0.6)	12 (2.5)	1 (0.2)
心電図ＱＴ延長	16 (3.4)	1 (0.2)	20 (4.2)	4 (0.8)
リパーゼ増加	12 (2.5)	7 (1.5)	16 (3.4)	9 (1.9)
血圧上昇	9 (1.9)	1 (0.2)	3 (0.6)	1 (0.2)
尿中蛋白陽性	9 (1.9)	1 (0.2)	2 (0.4)	0 (0.0)
リンパ球数減少	8 (1.7)	4 (0.8)	9 (1.9)	5 (1.1)
血中アルブミン減少	8 (1.7)	0 (0.0)	5 (1.1)	0 (0.0)
血中乳酸脱水素酵素増加	8 (1.7)	0 (0.0)	5 (1.1)	1 (0.2)
Ｃ－反応性蛋白増加	8 (1.7)	0 (0.0)	5 (1.1)	0 (0.0)
国際標準比増加	7 (1.5)	0 (0.0)	8 (1.7)	0 (0.0)
血中コレステロール増加	6 (1.3)	0 (0.0)	1 (0.2)	0 (0.0)
アミラーゼ増加	5 (1.1)	2 (0.4)	3 (0.6)	1 (0.2)
血中クレアチニン増加	5 (1.1)	0 (0.0)	1 (0.2)	0 (0.0)
血中尿素増加	4 (0.8)	0 (0.0)	1 (0.2)	0 (0.0)

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Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
プロトロンビン時間延長	3 (0.6)	0 (0.0)	2 (0.4)	0 (0.0)
血中甲状腺刺激ホルモン減少	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
赤血球数減少	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
尿中ビリルビン増加	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
抱合ビリルビン増加	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
ヘモグロビン増加	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
体重増加	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
尿中白血球陽性	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
血中カルシウム減少	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
尿中ウロビリノーゲン増加	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
血中カリウム減少	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
血中ナトリウム減少	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
尿中ブドウ糖陽性	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
肝酵素上昇	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
アンモニア増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
血中クレアチニン減少	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
血中フィブリノゲン増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
拡張期血圧上昇	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
体温上昇	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
ＥＣＯＧパフォーマンスステータス悪化	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
心電図ＳＴ部分下降	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
心電図異常Ｔ波	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
尿中ブドウ糖	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

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Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
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Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
国際標準比減少	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
リパーゼ減少	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
リンパ球数増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
好中球数増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
総蛋白減少	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
プロトロンビン量増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
トランスアミナーゼ上昇	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
トリヨードチロニン増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
トロポニンT増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
尿中蛋白／クレアチニン比増加	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
白血球数増加	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
ヘモグロビン減少	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)
血中クロール減少	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
膵酵素増加	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)
血中リン減少	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
心電図T波逆転	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
肝機能検査値上昇	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
遊離トリヨードチロニン増加	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
代謝および栄養障害	149 (31.3)	33 (6.9)	124 (26.1)	14 (2.9)
食欲減退	122 (25.6)	16 (3.4)	100 (21.1)	4 (0.8)
低アルブミン血症	21 (4.4)	2 (0.4)	13 (2.7)	0 (0.0)
脱水	10 (2.1)	2 (0.4)	2 (0.4)	0 (0.0)
低ナトリウム血症	8 (1.7)	8 (1.7)	3 (0.6)	3 (0.6)

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付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
高アンモニア血症	8 (1.7)	0 (0.0)	2 (0.4)	0 (0.0)
高カリウム血症	4 (0.8)	1 (0.2)	3 (0.6)	0 (0.0)
低マグネシウム血症	3 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)
低カリウム血症	2 (0.4)	1 (0.2)	10 (2.1)	6 (1.3)
低リン酸血症	2 (0.4)	2 (0.4)	5 (1.1)	2 (0.4)
高血糖	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
低カルシウム血症	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
低血糖	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
高尿酸血症	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
糖尿病性代謝代償不全	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
痛風	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
高脂血症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
過小食	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
低蛋白血症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
高アミラーゼ血症	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
高コレステロール血症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
高リパーゼ血症	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
高ナトリウム血症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
高蛋白血症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
低クロール血症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
筋骨格系および結合組織障害	74 (15.5)	1 (0.2)	47 (9.9)	2 (0.4)
関節痛	19 (4.0)	0 (0.0)	6 (1.3)	0 (0.0)
四肢痛	15 (3.2)	1 (0.2)	11 (2.3)	1 (0.2)

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付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
筋肉痛	14 (2.9)	0 (0.0)	5 (1.1)	0 (0.0)
筋骨格痛	10 (2.1)	0 (0.0)	3 (0.6)	0 (0.0)
背部痛	9 (1.9)	0 (0.0)	6 (1.3)	0 (0.0)
筋力低下	7 (1.5)	0 (0.0)	3 (0.6)	0 (0.0)
頚部痛	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
筋痙縮	3 (0.6)	0 (0.0)	8 (1.7)	1 (0.2)
側腹部痛	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
骨痛	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
関節腫脹	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
筋骨格系胸痛	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
筋緊張	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
筋骨格不快感	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
脊椎痛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
関節可動域低下	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
筋肉疲労	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
筋骨格硬直	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
顎痛	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
腱痛	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	2 (0.4)	1 (0.2)	7 (1.5)	3 (0.6)
腫瘍出血	1 (0.2)	1 (0.2)	2 (0.4)	2 (0.4)
腫瘍熱	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
ケラトアカントーマ	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
悪性腹水	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

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付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
脂漏性角化症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
腫瘍壊死	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
腫瘍破裂	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
神経系障害	104 (21.8)	18 (3.8)	67 (14.1)	9 (1.9)
頭痛	24 (5.0)	1 (0.2)	19 (4.0)	0 (0.0)
浮動性めまい	21 (4.4)	0 (0.0)	7 (1.5)	0 (0.0)
味覚異常	19 (4.0)	0 (0.0)	12 (2.5)	0 (0.0)
肝性脳症	18 (3.8)	8 (1.7)	3 (0.6)	2 (0.4)
末梢性感覚ニューロパチー	4 (0.8)	0 (0.0)	6 (1.3)	1 (0.2)
嗜眠	4 (0.8)	0 (0.0)	2 (0.4)	0 (0.0)
傾眠	4 (0.8)	1 (0.2)	2 (0.4)	0 (0.0)
脳出血	3 (0.6)	3 (0.6)	0 (0.0)	0 (0.0)
感覚鈍麻	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
錯感覚	2 (0.4)	0 (0.0)	5 (1.1)	0 (0.0)
多発ニューロパチー	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
失語症	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
脳梗塞	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
脳血管発作	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
平衡障害	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
灼熱感	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
肝性昏睡	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
ジスキネジア	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
顔面麻痺	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)

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付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
蟻走感	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
頭蓋内出血	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
味覚減退	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
末梢性ニューロパチー	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
末梢性運動ニューロパチー	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
末梢性感覚運動ニューロパチー	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
可逆性後白質脳症症候群	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
痙攣発作	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
緊張性頭痛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
中毒性ニューロパチー	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
振戦	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
三叉神経痛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
知覚過敏	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)
失声症	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
大脳基底核出血	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
認知障害	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
注意力障害	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
虚血性脳卒中	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
意識消失	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
代謝性脳症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
神経毒性	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
失神寸前の状態	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
血栓性脳梗塞	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)

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Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
精神障害	15 (3.2)	2 (0.4)	4 (0.8)	1 (0.2)
不眠症	11 (2.3)	0 (0.0)	1 (0.2)	0 (0.0)
錯乱状態	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)
うつ病	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
無感情	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
抑うつ気分	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
易刺激性	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
腎および尿路障害	123 (25.8)	30 (6.3)	51 (10.7)	6 (1.3)
蛋白尿	114 (23.9)	27 (5.7)	44 (9.3)	6 (1.3)
血尿	15 (3.2)	0 (0.0)	5 (1.1)	0 (0.0)
腎機能障害	2 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)
ビリルビン尿	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
急性腎障害	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
着色尿	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
夜間頻尿	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
白血球尿	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
無尿	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
慢性腎臓病	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
排尿困難	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
糖尿	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
腎仙痛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
腎不全	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
腎梗塞	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

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付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
腎尿細管壊死	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
頻尿	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)
多尿	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
生殖系および乳房障害	14 (2.9)	1 (0.2)	9 (1.9)	0 (0.0)
女性化乳房	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
骨盤痛	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
陰嚢潰瘍	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
後天性陰嚢水瘤	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
性器発疹	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
不規則月経	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
骨盤液貯留	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
前立腺閉塞	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
陰部そう痒症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
陰嚢血瘤	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
陰嚢浮腫	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
精巣痛	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
無月経	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
乳房痛	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
性器紅斑	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
乳頭の炎症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
乳頭痛	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
陰嚢障害	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
陰嚢紅斑	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
外陰部障害	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
呼吸器、胸郭および縦隔障害	134 (28.2)	7 (1.5)	84 (17.7)	4 (0.8)
発声障害	104 (21.8)	0 (0.0)	52 (10.9)	0 (0.0)
鼻出血	12 (2.5)	0 (0.0)	7 (1.5)	0 (0.0)
呼吸困難	12 (2.5)	2 (0.4)	5 (1.1)	0 (0.0)
口腔咽頭痛	9 (1.9)	0 (0.0)	7 (1.5)	0 (0.0)
喀血	6 (1.3)	1 (0.2)	2 (0.4)	0 (0.0)
咳嗽	5 (1.1)	0 (0.0)	13 (2.7)	0 (0.0)
胸水	5 (1.1)	0 (0.0)	1 (0.2)	0 (0.0)
肺塞栓症	3 (0.6)	3 (0.6)	2 (0.4)	2 (0.4)
呼吸不全	2 (0.4)	2 (0.4)	1 (0.2)	1 (0.2)
しゃっくり	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
喉頭の炎症	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
鼻痛	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
慢性気管支炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
特発性肺線維症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
壊死性細気管支炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
非心原性肺水腫	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
口腔咽頭不快感	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
肺臓炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
肺梗塞	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
肺腫瘤	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
上気道の炎症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
鼻の炎症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
湿性咳嗽	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚および皮下組織障害	211 (44.3)	16 (3.4)	339 (71.4)	64 (13.5)
手掌・足底発赤知覚不全症候群	126 (26.5)	14 (2.9)	249 (52.4)	54 (11.4)
発疹	38 (8.0)	0 (0.0)	64 (13.5)	2 (0.4)
そう痒症	23 (4.8)	0 (0.0)	25 (5.3)	1 (0.2)
皮膚乾燥	13 (2.7)	0 (0.0)	18 (3.8)	0 (0.0)
脱毛症	12 (2.5)	0 (0.0)	115 (24.2)	0 (0.0)
紅斑	7 (1.5)	0 (0.0)	10 (2.1)	0 (0.0)
斑状丘疹状皮疹	6 (1.3)	0 (0.0)	16 (3.4)	4 (0.8)
ざ瘡様皮膚炎	4 (0.8)	0 (0.0)	8 (1.7)	0 (0.0)
過角化	4 (0.8)	0 (0.0)	7 (1.5)	0 (0.0)
皮膚剥脱	4 (0.8)	0 (0.0)	3 (0.6)	0 (0.0)
皮膚反応	4 (0.8)	0 (0.0)	1 (0.2)	0 (0.0)
爪変色	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
水疱	3 (0.6)	0 (0.0)	4 (0.8)	1 (0.2)
丘疹性皮疹	2 (0.4)	0 (0.0)	5 (1.1)	2 (0.4)
多形紅斑	2 (0.4)	0 (0.0)	3 (0.6)	1 (0.2)
ざ瘡	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
湿疹	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
そう痒性皮疹	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
皮膚炎	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚疼痛	1 (0.2)	0 (0.0)	4 (0.8)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
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Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
蕁麻疹	1 (0.2)	0 (0.0)	4 (0.8)	0 (0.0)
顔面腫脹	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
爪線状隆起	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
手掌紅斑	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
紫斑	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
脂漏性皮膚炎	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
皮膚障害	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚色素減少	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚刺激	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
乾皮症	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚血管炎	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
皮膚嚢腫	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
接触皮膚炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
異汗性湿疹	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
間擦疹	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
寝汗	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
爪破損	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
点状出血	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
紅斑性皮疹	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚びらん	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
薬疹	0 (0.0)	0 (0.0)	4 (0.8)	1 (0.2)
水疱性皮膚炎	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)
多汗症	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)

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Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
乾癬	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
皮膚病変	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
皮膚潰瘍	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
アレルギー性皮膚炎	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
斑状出血	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
剥脱性発疹	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
全身紅斑	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
陰茎潰瘍形成	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
斑状皮疹	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
痂皮	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚癒着	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚変色	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚不快感	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚亀裂	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚硬結	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
皮膚感作	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
毛細血管拡張症	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
血管障害	197 (41.4)	108 (22.7)	135 (28.4)	63 (13.3)
高血圧	191 (40.1)	105 (22.1)	131 (27.6)	62 (13.1)
潮紅	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
循環虚脱	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
大動脈解離	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
動脈解離	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

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TEAE = Treatment-emergent adverse event.

付録 2.7.6.2
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 304
Safety Analysis Set

	All			
	Lenvatinib (N=476)		Sorafenib (N=475)	
System organ Class Preferred Term	Any Grade n (%)	Grade >= 3 n (%)	Any Grade n (%)	Grade >= 3 n (%)
深部静脈血栓症	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
静脈塞栓症	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
起立性低血圧	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
血栓性静脈炎	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
充血	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
血液量減少性ショック	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
末梢冷感	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
TEAE = Treatment-emergent adverse event.

付録 2.7.6-3　死亡又は重篤な有害事象の被験者ごとの叙述（国際共同304試験）

死亡又は死亡以外の重篤な有害事象が認められた被験者に関する叙述を以下に示した。

被験者番号	投与群	死亡に至った有害事象	死亡以外の 重篤な有害事象
10031004	Lenvatinib		X
10031006	Sorafenib		X
10031009	Sorafenib		X
10031011	Lenvatinib		X
10031013	Lenvatinib		X
10031025	Sorafenib		X
10061007	Lenvatinib		X
10061008	Lenvatinib	X	X
10061014	Lenvatinib		X
10071012	Lenvatinib		X
10091004	Lenvatinib		X
10101002	Sorafenib	X	
10101013	Sorafenib		X
10111001	Lenvatinib	X	X
10121003	Lenvatinib		X
10121004	Sorafenib		X
10141001	Lenvatinib		X
10151002	Lenvatinib		X
10151006	Lenvatinib		X
10151009	Lenvatinib	X	X
10151016	Lenvatinib	X	X
10161001	Lenvatinib	X	X
10161005	Sorafenib		X
12011002	Lenvatinib		X
12011006	Sorafenib		X
12031002	Lenvatinib		X
12031003	Lenvatinib		X
12031004	Lenvatinib		X
12031010	Sorafenib		X
12041006	Sorafenib		X

被験者番号	投与群	死亡に至った有害事象	死亡以外の 重篤な有害事象
12041010	Lenvatinib		X
12061003	Lenvatinib		X
12061004	Lenvatinib		X
12061005	Sorafenib		X
12061007	Sorafenib		X
12071003	Lenvatinib		X
12081004	Sorafenib		X
12081009	Sorafenib		X
12081010	Sorafenib		X
12081011	Sorafenib	X	X
12081013	Lenvatinib		X
12081014	Lenvatinib		X
12081021	Sorafenib		X
12101007	Lenvatinib		X
12111002	Sorafenib		X
12111012	Lenvatinib		X
12111013	Lenvatinib		X
12121001	Lenvatinib	X	X
12121003	Lenvatinib		X
12131003	Sorafenib		X
12131004	Lenvatinib		X
12141002	Lenvatinib	X	X
12141003	Lenvatinib		X
12141004	Sorafenib		X
12141007	Lenvatinib	X	X
12141016	Lenvatinib	X	X
12141020	Lenvatinib		X
12141021	Sorafenib		X
12141025	Sorafenib		X
12151007	Sorafenib		X
12151008	Sorafenib		X
12191009	Lenvatinib		X
12191010	Sorafenib		X

被験者番号	投与群	死亡に至った有害事象	死亡以外の 重篤な有害事象
12201002	Lenvatinib		X
12201008	Lenvatinib		X
12201009	Lenvatinib		X
12211001	Sorafenib		X
12211002	Sorafenib		X
12211004	Sorafenib		X
12211007	Sorafenib	X	
12211008	Lenvatinib		X
12221001	Sorafenib		X
12241001	Lenvatinib		X
12241004	Lenvatinib	X	X
12251001	Lenvatinib		X
12251006	Sorafenib		X
12251007	Lenvatinib		X
12251009	Sorafenib		X
12251010	Lenvatinib		X
14021005	Sorafenib		X
14021008	Lenvatinib		X
14021009	Lenvatinib	X	X
14021013	Lenvatinib	X	X
14021014	Lenvatinib		X
14021016	Sorafenib		X
14031006	Lenvatinib	X	X
14031010	Sorafenib		X
14031012	Sorafenib		X
14061003	Sorafenib		X
14061008	Sorafenib	X	X
14061009	Lenvatinib	X	X
14061016	Sorafenib	X	X
14061017	Lenvatinib		X
14061019	Lenvatinib		X
14061021	Lenvatinib		X
14061023	Sorafenib		X

被験者番号	投与群	死亡に至った有害事象	死亡以外の 重篤な有害事象
14071003	Lenvatinib	X	X
14101003	Sorafenib		X
14101004	Sorafenib	X	X
14121001	Sorafenib		X
14131001	Lenvatinib		X
14131002	Sorafenib		X
14141002	Lenvatinib		X
14141005	Sorafenib	X	X
15041006	Sorafenib	X	
15051008	Lenvatinib		X
15071001	Sorafenib		X
15091003	Lenvatinib	X	X
15091008	Sorafenib		X
16011005	Lenvatinib		X
16011008	Lenvatinib		X
16011024	Sorafenib	X	
16021003	Sorafenib		X
16021004	Sorafenib		X
16021010	Lenvatinib		X
16021017	Sorafenib		X
16021023	Sorafenib		X
16031003	Sorafenib	X	
16031008	Sorafenib		X
16031012	Sorafenib		X
16031014	Sorafenib		X
16031019	Sorafenib	X	X
16031024	Sorafenib		X
17011004	Sorafenib		X
17021001	Sorafenib		X
17021002	Sorafenib		X
17021003	Lenvatinib		X
17021004	Lenvatinib		X
17021007	Lenvatinib		X

被験者番号	投与群	死亡に至った有害事象	死亡以外の 重篤な有害事象
17021008	Sorafenib		X
17021009	Lenvatinib		X
17031002	Lenvatinib		X
17041001	Sorafenib		X
17041006	Lenvatinib		X
17041008	Sorafenib		X
17041014	Sorafenib		X
17061002	Lenvatinib		X
17071004	Lenvatinib		X
18021007	Lenvatinib		X
18041002	Sorafenib		X
18051004	Lenvatinib		X
18051014	Lenvatinib	X	X
18071001	Lenvatinib		X
18071006	Lenvatinib	X	X
18081001	Lenvatinib		X
18081005	Sorafenib		X
19011002	Lenvatinib	X	X
19011005	Sorafenib		X
19011010	Sorafenib		X
19011014	Lenvatinib	X	
19011023	Sorafenib		X
19011028	Lenvatinib		X
19021002	Lenvatinib	X	
19021003	Lenvatinib		X
19021004	Sorafenib	X	X
19021007	Lenvatinib		X
19021017	Lenvatinib	X	
19021020	Lenvatinib	X	
19021029	Lenvatinib	X	
19021030	Lenvatinib	X	
19021031	Sorafenib	X	
19021036	Lenvatinib	X	

被験者番号	投与群	死亡に至った有害事象	死亡以外の 重篤な有害事象
19021037	Sorafenib		X
19031011	Lenvatinib	X	X
19031019	Lenvatinib		X
19061007	Lenvatinib	X	X
20021003	Lenvatinib	X	X
20021005	Lenvatinib		X
21021001	Sorafenib		X
21031005	Lenvatinib		X
21031012	Lenvatinib		X
21041004	Lenvatinib		X
21051001	Lenvatinib		X
24011009	Lenvatinib	X	X
24021003	Sorafenib		X
24021011	Sorafenib	X	X
24031002	Sorafenib	X	X
24031009	Sorafenib	X	
24031014	Lenvatinib		X
24031019	Lenvatinib	X	
24041001	Lenvatinib	X	X
24041009	Sorafenib		X
24041013	Sorafenib	X	
24041014	Sorafenib		X
24071003	Sorafenib		X
24071005	Sorafenib	X	X
24081007	Lenvatinib		X
24101001	Sorafenib		X
24101003	Sorafenib		X
24101010	Sorafenib		X
24101011	Sorafenib	X	
24111005	Lenvatinib		X
24111007	Sorafenib	X	X
24111008	Lenvatinib		X
24111012	Lenvatinib	X	

被験者番号	投与群	死亡に至った有害事象	死亡以外の 重篤な有害事象
24111014	Lenvatinib	X	
24111018	Lenvatinib		X
24111022	Lenvatinib		X
24111029	Lenvatinib	X	
24111035	Lenvatinib	X	X
24111042	Lenvatinib		X
24111043	Lenvatinib	X	
24111045	Sorafenib	X	X
24121006	Lenvatinib		X
24121007	Lenvatinib		X
24121010	Lenvatinib		X
24131003	Sorafenib		X
24131008	Lenvatinib		X
24131009	Lenvatinib		X
24131011	Lenvatinib		X
24131019	Lenvatinib	X	X
24131031	Sorafenib	X	
24151002	Lenvatinib		X
24151015	Lenvatinib		X
24161005	Sorafenib		X
24161015	Lenvatinib	X	
24161016	Sorafenib	X	
24161019	Lenvatinib	X	
24171003	Lenvatinib		X
24181004	Lenvatinib		X
24201004	Lenvatinib		X
24201006	Lenvatinib		X
24201007	Sorafenib		X
24211001	Lenvatinib		X
24221002	Sorafenib	X	
24221003	Lenvatinib		X
24221005	Lenvatinib		X
24231003	Sorafenib	X	

被験者番号	投与群	死亡に至った有害事象	死亡以外の 重篤な有害事象
24231008	Sorafenib	X	X
24231009	Sorafenib	X	
30011001	Lenvatinib		X
30011007	Lenvatinib		X
30011009	Lenvatinib		X
30011017	Lenvatinib		X
30011021	Lenvatinib	X	
30021001	Sorafenib		X
30031002	Sorafenib		X
30041005	Sorafenib		X
30041011	Lenvatinib	X	X
30051001	Lenvatinib		X
30051002	Lenvatinib		X
30051004	Lenvatinib	X	X
30051005	Lenvatinib	X	X
30051008	Lenvatinib		X
30051009	Sorafenib		X
30051010	Lenvatinib	X	X
30051012	Lenvatinib		X
30051013	Sorafenib		X
30051014	Sorafenib		X
30061001	Sorafenib		X
30061003	Lenvatinib		X
30061006	Sorafenib		X
30061008	Sorafenib	X	X
30061010	Lenvatinib		X
30061011	Lenvatinib		X
30061012	Sorafenib		X
30061013	Sorafenib		X
30071003	Sorafenib	X	
30071005	Sorafenib		X
30071006	Lenvatinib		X
30071009	Lenvatinib		X

被験者番号	投与群	死亡に至った有害事象	死亡以外の 重篤な有害事象
30071011	Lenvatinib	X	
30071012	Lenvatinib		X
30071013	Lenvatinib		X
30071014	Sorafenib		X
30071016	Lenvatinib		X
30071018	Sorafenib		X
30081002	Sorafenib		X
30081005	Sorafenib		X
30081006	Sorafenib		X
30091002	Lenvatinib	X	X
30091004	Sorafenib		X
30091011	Lenvatinib		X
30091027	Lenvatinib		X
30101001	Lenvatinib	X	X
30101003	Lenvatinib		X
30101005	Sorafenib		X
30111003	Lenvatinib		X
30111006	Lenvatinib		X
30111008	Lenvatinib	X	X
30121002	Sorafenib	X	X
30121003	Lenvatinib		X
30121005	Lenvatinib		X
30121016	Lenvatinib		X
30121018	Lenvatinib		X
30121027	Lenvatinib	X	X
30131001	Lenvatinib		X
30131002	Sorafenib		X
30131003	Lenvatinib		X
30131004	Lenvatinib		X
30141001	Lenvatinib		X
30141002	Lenvatinib		X
30151001	Sorafenib		X
30161002	Sorafenib		X

被験者番号	投与群	死亡に至った有害事象	死亡以外の 重篤な有害事象
30161004	Sorafenib		X
30161005	Lenvatinib	X	X
30161007	Sorafenib	X	X
30161009	Lenvatinib	X	X
30171005	Lenvatinib		X
30171008	Sorafenib		X
30171010	Sorafenib		X
30171011	Lenvatinib		X
30171014	Lenvatinib	X	X
30181003	Lenvatinib		X
32021001	Lenvatinib	X	X
32041001	Sorafenib		X
32041002	Sorafenib	X	X
32051001	Lenvatinib	X	X
32051003	Lenvatinib	X	X
43011003	Lenvatinib		X
44031004	Sorafenib		X
44031005	Lenvatinib	X	X
44031006	Sorafenib	X	X
44031007	Lenvatinib	X	X
44041001	Sorafenib		X
44051002	Sorafenib		X
44051004	Sorafenib		X
44051006	Lenvatinib		X
45011003	Sorafenib		X
45011004	Sorafenib	X	
45011010	Lenvatinib		X
45021001	Lenvatinib		X
45021002	Lenvatinib		X
45031009	Lenvatinib		X
45041003	Sorafenib		X
45041008	Lenvatinib	X	X
45051008	Sorafenib		X

被験者番号	投与群	死亡に至った有害事象	死亡以外の 重篤な有害事象
45061006	Lenvatinib		X
45061015	Lenvatinib		X
45071009	Lenvatinib		X
45081001	Sorafenib	X	X
45101002	Lenvatinib		X
45121006	Sorafenib	X	X
46031005	Lenvatinib		X
46041004	Lenvatinib		X
47011007	Sorafenib		X
47011010	Lenvatinib	X	X
47021006	Lenvatinib	X	X
47021009	Lenvatinib		X
47031003	Lenvatinib		X
47031011	Sorafenib		X
47031012	Lenvatinib		X
48011002	Lenvatinib		X
48011004	Lenvatinib		X
48021003	Sorafenib		X
48041001	Lenvatinib		X
48051003	Lenvatinib		X
48051004	Sorafenib		X
48051005	Lenvatinib		X

Section I Fatal Serious Adverse Event

Arm: Lenvatinib

Subject Number	10061008
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-004982
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Hepatic failure
Non-Fatal SAE(s)	Dyspnoea, Hepatic failure
AE(s) Leading to Discontinuation	Hepatic failure
Death due to PD	Yes

A 70-year-old white male was diagnosed with hepatocellular carcinoma on 10 Oct 2014. Significant medical history included alcohol use, atrial fibrillation, melanocytic nevus, liver biopsy, hepatic cirrhosis, left renal cyst, peripheral edema, hepatitis C, glomerulonephritis minimal lesion, nephrotic syndrome, obesity, gallbladder polyp, portal hypertension, tobacco use, and hypertension. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included biotene, cough and cold preparations, hydrochlorothiazide, lactulose, levofloxacin, metoprolol, omeprazole, oseltamivir, other emollients and protectives (eucerin), and paracetamol. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left lobe, right lobe, and multiple sites of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 6.

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

On 27 Feb 2015 (Day 73), the subject experienced hepatic failure (Grade 3) and fatigue (Grade 1). On the same day (Day 73), study drug was interrupted due to hepatic failure and the subject was treated with lactulose. Laboratory tests showed albumin 16 g/L (NR: 34 – 50), AST 323 U/L (NR: 15 – 37), ALT 132 U/L (NR: 30 – 65), ALP 327 U/L (NR: 50 – 136), total bilirubin 112.86 umol/L (NR: 0 – 18.81), creatinine 88.4 umol/L (NR: 70.72 – 114.92), and ammonia 51 umol/L (NR: 11 – 32). The subject did not recover from fatigue and hepatic failure. The Investigator considered hepatic failure nonserious and not related to the study drug but related to disease progression; fatigue nonserious and possibly related to the study drug.

On 15 Mar 2015 (Day 89), the subject was hospitalized for dyspnea (Grade 3) and worsening hepatic failure (Grade 4). The subject also experienced hypoglycemia (Grade 2) with glucose 18 mg/dL (NR: 70 – 100). On the same day (Day 89), the study drug remained interrupted due to worsening hepatic failure and dyspnea. The laboratory tests showed anion gap 21.2 mmol/L (NR: 6 – 16), albumin 12 g/L, AST 341 U/L, ALT 138 U/L, ALP 369 U/L, and total bilirubin 117.99 umol/L. On 15 Mar 2015 (Day 89), the subject had atelectasis of lungs (Grade 3) which was confirmed by chest x-ray and CT scan of abdomen showed ill-defined masses within liver, underlying cirrhosis vs capsular retraction. The subject

requested "do-not-resuscitate'' status. On 16 Mar 2015 (Day 90, 18 days after the last dose), the subject died due to hepatic failure secondary to clinical disease progression. Autopsy was not performed. The subject received the last dose of study drug on 26 Feb 2015 (Day 72). At the time of death, the subject had not recovered from dyspnea, hypoglycemia, and atelectasis of lungs. The Investigator considered hepatic failure and dyspnea serious and not related to the study drug but related to disease progression; hypoglycemia and atelectasis of lungs nonserious and not related to study drug.

Subject Number	10111001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01442-CLI-US
Assigned Treatment	Lenvatinib 12 mg/day
Fatal SAE(s)	Cardiopulmonary failure
Non-Fatal SAE(s)	Abdominal pain lower, Nausea, Vomiting, Abdominal pain, Renal failure
Death due to PD	Yes

A 34-year-old white female was diagnosed with hepatocellular carcinoma on 22 Nov 2013. Significant medical history included abdominal pain, decreased appetite, fatigue, hemorrhoids, nausea, obesity, pulmonary embolism, blindness, vomiting, and decreased weight. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included amlodipine, betamethasone, cefepime, dicycloverine, hydrocodone, levofloxacin, metronidazole, morphine, ondansetron, other antiemetics (IV fluids-antiemetics), pantoprazole, paracetamol, piperacillin/tazobactam, promethazine, and rivaroxaban. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe; mass at right lower lobe of lung. The BCLC stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 31 Jan 2014 (Day 19), the subject was hospitalized for lower abdominal pain (right; Grade 3) and also experienced urinary tract infection (Grade 2). Laboratory tests showed WBC 12.4 x10^9/L (NR: 3.6 – 10.8), absolute neutrophil count 10 x10^9/L (NR: 1.8 – 7.7), lipase 78 U/L (NR: 13 – 60), CRP 184.1 mg/L (NR: 0 – 5), and ALP 155 U/L (NR: 30 – 115). On 01 Feb 2014 (Day 20), the study drug was interrupted due to lower abdominal pain. The subject was treated with morphine, levofloxacin, and metronidazole. On 02 Feb 2014 (Day 21), the study drug was resumed at same dose. On 03 Feb 2014 (Day 22), the subject recovered from lower abdominal pain and recovered from urinary tract infection on 08 Feb 2014 (Day 27). The Investigator considered lower abdominal pain serious and not related to the study drug; urinary tract infection nonserious and not related to the study drug.

On 22 Apr 2014 (Day 100), the subject was hospitalized for nausea (Grade 3) and vomiting (Grade 3). On the same day (Day 100), the study drug was interrupted due to nausea and vomiting. Laboratory tests showed BUN 2.142 mmol/L (NR: 2.499 – 6.426) and creatinine 44.2 umol/L (NR: 61.88 – 106.08); Na, K, and Cl were within normal limits. The subject was treated with intravenous fluids and ondansetron. On 24 Apr 2014 (Day 102), the subject recovered from nausea and vomiting. On the same day (Day 102), the study drug was resumed at the same dose. The Investigator considered nausea and vomiting serious and not related to the study drug.

On 26 Aug 2014 (Day 226), tumor response assessment showed disease progression and the subject was withdrawn from the study due to disease progression. The subject received the last dose of the study drug on 25 Aug 2014 (Day 225).