which partially improved pain with an initial overdose (sleepiness, nausea); an anti-inflammatory drug and paracetamol were administered as co-analgesics. On an unspecified date, the Investigator noted the subject was experiencing anorexia, which was not attributed to the treatment.

On 16 Sep 2015 (Day 36), the subject was discharged from the hospital with a plan for adjustment of analgesic treatment. The SAE of Grade 2 **Tumour pain** was considered resolved and was assessed by the Investigator as not related to tazemetostat.

On 22 Sep 2015 (Day 42), the subject experienced the SAE of Grade 2 **Tumour pain** and was hospitalized for pain management. Dosing with tazemetostat 400 mg BID was not modified due to this event. Concomitant medications were as previously described.

On 22 Sep 2015 (Day 42), the subject presented with nausea and increased tumor pain. Further, the non-serious AEs of Grade 1 Asthenia and Nausea worsened to Grade 2, which the Investigator assessed as possibly related to study treatment. The non-serious AEs of Grade 1 Hypomagnesaemia, Grade 1 Hypophosphataemia, Grade 1 Platelet count decreased, and Grade 2 Vomiting were also reported on this same day.

On 25 Sep 2015 (Day 45) the subject was withdrawn from the study due to progressive disease, associated with tumor pain increase, with the last dose of tazemetostat 400 mg BID taken on 24 Sep 2015 (Day 44).

On 29 Sep 2015 (Day 49), appearance of paresthesia at the lower extremities, predominantly on the left, was observed. Palliative radiation therapy was initiated. Laboratory tests were significant for thrombocytopenia (77 g/L; reference range not provided), hypomagnesemia (0.6 mmol/L; reference range not provided), and hypophosphatemia (0.78 mmol/L; reference range not provided), all assessed as unrelated to study drug. Additionally, C-reactive protein was 99 mg/L (reference range not provided), which the Investigator characterized as biological inflammatory syndrome.

On 01 Oct 2015 (Day 51), clinical examination revealed normal cardiopulmonary auscultation; abdomen supple, not rigid, and painless, with bowel sounds noted; no fever; tachycardia with heart rate at 119 beats/minute; hypotensive with blood pressure at 106/58 mmHg; and an edematous left hip, which was painless during palpation, but weight bearing was impossible. Pain management for the SAE of **Tumour pain** included IV oxycodone hydrochloride, anti-inflammatories (diclofenac sodium), and corticosteroids (not specified).

On an unspecified date, a positron emission tomography scan showed multiple hypermetabolic bone targets, namely at the left and right hips. A computed tomography scan revealed clear disease progression at the left hip and appearance of epiduritis at T3-T4-T5 (without visible abnormality in the scan) and appearance of peritoneal carcinomatosis. Clinical reevaluation showed no symptoms of deficiency on either the right or left.

On 01 Oct 2015 (Day 51), the subject was discharged from the hospital with a plan for ongoing radiation therapy of the spine, balanced analgesia, and palliative care.

On 07 Oct 2015 (Day 57), the subject experienced the non-serious AE of Grade 3 General physical health deterioration. On 09 Oct 2015 (Day 59), the AE worsened to Grade 5 **General physical health deterioration**, and the subject died this same day. The cause of death was disease progression.

At the time of death, the SAE of **Tumour pain** was unresolved and was assessed by the Investigator as not related to tazemetostat. At the time of death, the AEs of Vomiting (not related), Platelet count decreased (not related), Asthenia (possibly related), Nausea (possibly related), Hypomagnesaemia (not related), and Hypophosphataemia (not related) were also not resolved.

Subject Number	10021037
Study Name	E7438-G000-101 (Phase 1)
First Dose Date:	09 Sep 2015
Last Dose Date (Study Day):	03 Nov 2015 (Day 56)
Nonfatal SAE	Cervicobrachial syndrome （頚腕症候群）

The subject was a 5[redacted]-year-old white female diagnosed with advanced solid tumor (synovial sarcoma of right thigh) on 27 Jun 2014. Prior treatment for synovial sarcoma included ifosfamide (Sep–Dec 2014), excision of the right thigh sarcoma (Jan 2015), and radiotherapy to right leg/foot (May–Jul 2015).

The subject's ongoing medical history included cervicobrachial syndrome.

Prior to enrollment, in Aug 2015, the subject presented with back pain with radiating, right-sided, cervicobrachial neuralgia. Magnetic resonance imaging was performed on 01 Sep 2015, which showed spinal metastatic disease.

On 09 Sep 2015, the subject started treatment with tazemetostat 800 mg twice daily (BID).

On 23 Sep 2015 (Day 15), the subject experienced the serious adverse event (SAE) of Grade 2 **Cervicobrachial syndrome** and was hospitalized. Also occurring this same day were the non-serious adverse events (AEs) of Grade 2 Constipation and Grade 2 Decreased appetite. Concomitant medications up to 30 days prior to the event included oxycodone and paracetamol.

The subject was hospitalized for a corporectomy of T2 with decompression of the spinal cord. The Investigator noted that the surgery was not planned prior to study enrollment. Treatment for the SAE included ketoprofen and pregabalin; treatment for the AEs was not reported. The SAE of **Cervicobrachial syndrome** was considered resolved this same day and was assessed by the Investigator as not related to tazemetostat.

On 24 Sep 2015 (Day 16), the subject was discharged from the hospital.

On 03 Nov 2015 (Day 56), the subject was withdrawn from the study due to disease progression, with the last dose of tazemetostat 800 mg BID taken this same day.

Subject Number	10021042
Study Name	E7438-G000-101 (Phase 1)
First Dose Date:	14 Oct 2015
Last Dose Date (Study Day):	12 Sep 2016 (Day 335)
Nonfatal SAE	Pancreatitis （膵炎）

The subject was a 6[redacted]-year old white female who was diagnosed with advance solid tumor (ovarian serous carcinoma) on 02 May 2007. Prior treatment for ovarian serous carcinoma included carboplatin/paclitaxel (May–Oct 2007), carboplatin/doxorubicin (Jun–Nov 2009), cisplatin (Feb 2010), paclitaxel (Jul 2011) carboplatin (Jul–Dec 2011), bevacizumab (Jul 2011–May 2012), carboplatin/gemcitabine (Jul 2013–Feb 2014), doxorubicin/ trabectedin (Sep–Nov 2014), and letrozole (Nov 2014–Sep 2015). Prior surgeries for ovarian serous carcinoma included bilateral adnexectomy (May 2007) and exeresis of ovarian lesion (Feb 2010).

The subject's past medical history included herniated disc and urinary cystectomy. Ongoing medical conditions included hypercholesterolemia, hypertension, hypokalemia, and type 2 diabetes.

On 14 Oct 2015, the subject started treatment with tazemetostat 800 mg twice daily (BID).

On 20 Jun 2016 (Day 251), the subject experienced the serious adverse event (SAE) of Grade 2 **Pancreatitis** and was hospitalized. Treatment with tazemetostat 800 mg BID was interrupted due to this SAE, with the last dose taken on 19 Jun 2016 (Day 250). Concomitant medications up to 30 days prior to the event included metoprolol, indapamide with perindopril, pravastatin, lercanidipine, potassium, gliclazide, zolpidem, repaglinide, and insulin glargine.

The subject developed pancreatitis with lipase increased (Grade 4), without any clinical syndrome. Laboratory results revealed lipase 1,794 (reference range: 13-60), units not provided. A computed tomography scan was performed, but results were not provided. The subject was rehydrated, with no food intake to control the event. No treatment medication was administered.

Laboratory investigation for lipase on 21 Jun 2016 (Day 252) was 62, on 22 Jun 2016 (Day 253) was 43, and on 23 Jun 2016 (Day 254) was 47 (no units provided).

On 22 Jun 2016 (Day 253) the SAE of Grade 2 **Pancreatitis** was considered resolved. The Investigator assessed the event as not related to tazemetostat and noted that the event was related to gall stones.

On 23 Jun 2016 (Day 254), the subject was discharged from the hospital.

Tazemetostat 800 mg BID was restarted on 30 Jun 2016 (Day 261).

付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
有害事象発現例数	44 (97.8)	54 (100.0)	98 (99.0)	222 (94.9)	320 (96.1)
胃腸障害	30 (66.7)	32 (59.3)	62 (62.6)	120 (51.3)	182 (54.7)
悪心	9 (20.0)	14 (25.9)	23 (23.2)	47 (20.1)	70 (21.0)
下痢	8 (17.8)	10 (18.5)	18 (18.2)	40 (17.1)	58 (17.4)
腹痛	7 (15.6)	6 (11.1)	13 (13.1)	29 (12.4)	42 (12.6)
嘔吐	5 (11.1)	7 (13.0)	12 (12.1)	36 (15.4)	48 (14.4)
上腹部痛	4 (8.9)	2 (3.7)	6 (6.1)	10 (4.3)	16 (4.8)
便秘	4 (8.9)	3 (5.6)	7 (7.1)	18 (7.7)	25 (7.5)
胃食道逆流性疾患	3 (6.7)	3 (5.6)	6 (6.1)	3 (1.3)	9 (2.7)
腹部不快感	2 (4.4)	0	2 (2.0)	2 (0.9)	4 (1.2)
腹部膨満	2 (4.4)	1 (1.9)	3 (3.0)	1 (0.4)	4 (1.2)
下腹部痛	1 (2.2)	0	1 (1.0)	3 (1.3)	4 (1.2)
アフタ性口内炎	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
齲歯	1 (2.2)	0	1 (1.0)	0	1 (0.3)
口内乾燥	1 (2.2)	1 (1.9)	2 (2.0)	2 (0.9)	4 (1.2)
消化不良	1 (2.2)	0	1 (1.0)	4 (1.7)	5 (1.5)
放屁	1 (2.2)	2 (3.7)	3 (3.0)	0	3 (0.9)
痔核	1 (2.2)	0	1 (1.0)	3 (1.3)	4 (1.2)
鼠径ヘルニア	1 (2.2)	0	1 (1.0)	0	1 (0.3)
腸管腫瘤	1 (2.2)	0	1 (1.0)	0	1 (0.3)
口唇障害	1 (2.2)	0	1 (1.0)	0	1 (0.3)
口腔内潰瘍形成	1 (2.2)	1 (1.9)	2 (2.0)	0	2 (0.6)
口腔内痛	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)

Note: AEs with CTCAE Grade 5 are excluded and summarized under death related tables.
Note: MedDRA v18.1 was used for coding. TEAE = Treatment emergent adverse event.
Note: TEAEs are defined as adverse events that started or worsened in severity on or after the date of first dose of study drug through 30 days after the last dose. A subject is counted at most once within each SOC and PT.
Note: Includes all TEAEs regardless of causality or severity.
FL: Follicular Lymphoa, DLBCL: Diffuse Large B-Cell

付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
腹部ヘルニア	0	0	0	1 (0.4)	1 (0.3)
腹部硬直	0	0	0	1 (0.4)	1 (0.3)
腹部圧痛	0	0	0	2 (0.9)	2 (0.6)
肛門ポリープ	0	1 (1.9)	1 (1.0)	0	1 (0.3)
腹水	0	1 (1.9)	1 (1.0)	3 (1.3)	4 (1.2)
口唇炎	0	0	0	1 (0.4)	1 (0.3)
腸憩室	0	1 (1.9)	1 (1.0)	0	1 (0.3)
十二指腸閉塞	0	0	0	1 (0.4)	1 (0.3)
嚥下障害	0	0	0	2 (0.9)	2 (0.6)
おくび	0	0	0	1 (0.4)	1 (0.3)
便失禁	0	0	0	1 (0.4)	1 (0.3)
機能性胃腸障害	0	0	0	1 (0.4)	1 (0.3)
胃障害	0	1 (1.9)	1 (1.0)	0	1 (0.3)
胃潰瘍	0	0	0	1 (0.4)	1 (0.3)
穿孔性胃潰瘍	0	0	0	1 (0.4)	1 (0.3)
胃炎	0	0	0	4 (1.7)	4 (1.2)
胃十二指腸炎	0	0	0	1 (0.4)	1 (0.3)
胃腸障害	0	0	0	2 (0.9)	2 (0.6)
胃腸出血	0	0	0	2 (0.9)	2 (0.6)
舌炎	0	0	0	1 (0.4)	1 (0.3)
胃排出不全	0	0	0	1 (0.4)	1 (0.3)
腸閉塞	0	0	0	2 (0.9)	2 (0.6)
大腸閉塞	0	0	0	1 (0.4)	1 (0.3)
口唇乾燥	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)

Note: AEs with CTCAE Grade 5 are excluded and summarized under death related tables.
Note: MedDRA v18.1 was used for coding. TEAE = Treatment emergent adverse event.
Note: TEAEs are defined as adverse events that started or worsened in severity on or after the date of first dose of study drug through 30 days after the last dose. A subject is counted at most once within each SOC and PT.
Note: Includes all TEAEs regardless of causality or severity.
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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
下部消化管出血	0	1 (1.9)	1 (1.0)	0	1 (0.3)
メレナ	0	0	0	2 (0.9)	2 (0.6)
嚥下痛	0	0	0	1 (0.4)	1 (0.3)
口腔浮腫	0	0	0	1 (0.4)	1 (0.3)
食道炎	0	0	0	2 (0.9)	2 (0.6)
口腔内不快感	0	0	0	1 (0.4)	1 (0.3)
膵炎	0	0	0	1 (0.4)	1 (0.3)
急性膵炎	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
口の錯感覚	0	0	0	1 (0.4)	1 (0.3)
直腸出血	0	0	0	1 (0.4)	1 (0.3)
小腸出血	0	0	0	1 (0.4)	1 (0.3)
小腸閉塞	0	0	0	1 (0.4)	1 (0.3)
口内炎	0	1 (1.9)	1 (1.0)	3 (1.3)	4 (1.2)
亜イレウス	0	0	0	2 (0.9)	2 (0.6)
歯の脱落	0	0	0	1 (0.4)	1 (0.3)
歯痛	0	0	0	2 (0.9)	2 (0.6)
感染症および寄生虫症	27 (60.0)	30 (55.6)	57 (57.6)	99 (42.3)	156 (46.8)
上気道感染	8 (17.8)	7 (13.0)	15 (15.2)	9 (3.8)	24 (7.2)
気管支炎	6 (13.3)	9 (16.7)	15 (15.2)	15 (6.4)	30 (9.0)
鼻咽頭炎	4 (8.9)	5 (9.3)	9 (9.1)	8 (3.4)	17 (5.1)
尿路感染	4 (8.9)	2 (3.7)	6 (6.1)	17 (7.3)	23 (6.9)
気道感染	3 (6.7)	0	3 (3.0)	2 (0.9)	5 (1.5)
副鼻腔炎	3 (6.7)	5 (9.3)	8 (8.1)	3 (1.3)	11 (3.3)

Note: AEs with CTCAE Grade 5 are excluded and summarized under death related tables.
Note: MedDRA v18.1 was used for coding. TEAE = Treatment emergent adverse event.
Note: TEAEs are defined as adverse events that started or worsened in severity on or after the date of first dose of study drug through 30 days after the last dose. A subject is counted at most once within each SOC and PT.
Note: Includes all TEAEs regardless of causality or severity.
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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
膀胱炎	2 (4.4)	2 (3.7)	4 (4.0)	2 (0.9)	6 (1.8)
胃腸炎	2 (4.4)	0	2 (2.0)	1 (0.4)	3 (0.9)
下気道感染	2 (4.4)	0	2 (2.0)	5 (2.1)	7 (2.1)
口腔ヘルペス	2 (4.4)	2 (3.7)	4 (4.0)	3 (1.3)	7 (2.1)
咽頭炎	2 (4.4)	0	2 (2.0)	3 (1.3)	5 (1.5)
結膜炎	1 (2.2)	2 (3.7)	3 (3.0)	3 (1.3)	6 (1.8)
蓄膿	1 (2.2)	0	1 (1.0)	0	1 (0.3)
大腸菌感染	1 (2.2)	0	1 (1.0)	0	1 (0.3)
ノロウイルス性胃腸炎	1 (2.2)	0	1 (1.0)	0	1 (0.3)
性器感染	1 (2.2)	0	1 (1.0)	0	1 (0.3)
帯状疱疹	1 (2.2)	1 (1.9)	2 (2.0)	1 (0.4)	3 (0.9)
インフルエンザ	1 (2.2)	2 (3.7)	3 (3.0)	3 (1.3)	6 (1.8)
肺感染	1 (2.2)	2 (3.7)	3 (3.0)	4 (1.7)	7 (2.1)
鼻ヘルペス	1 (2.2)	1 (1.9)	2 (2.0)	0	2 (0.6)
口腔真菌感染	1 (2.2)	1 (1.9)	2 (2.0)	4 (1.7)	6 (1.8)
ニューモシスチス・イロベチイ肺炎	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
腎盂腎炎	1 (2.2)	0	1 (1.0)	0	1 (0.3)
鼻炎	1 (2.2)	2 (3.7)	3 (3.0)	8 (3.4)	11 (3.3)
敗血症	1 (2.2)	1 (1.9)	2 (2.0)	3 (1.3)	5 (1.5)
歯感染	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
気管炎	1 (2.2)	0	1 (1.0)	0	1 (0.3)
水痘	1 (2.2)	0	1 (1.0)	0	1 (0.3)
ウイルス性上気道感染	1 (2.2)	2 (3.7)	3 (3.0)	0	3 (0.9)
外陰部腟カンジダ症	1 (2.2)	1 (1.9)	2 (2.0)	1 (0.4)	3 (0.9)

Note: AEs with CTCAE Grade 5 are excluded and summarized under death related tables.
Note: MedDRA v18.1 was used for coding. TEAE = Treatment emergent adverse event.
Note: TEAEs are defined as adverse events that started or worsened in severity on or after the date of first dose of study drug through 30 days after the last dose. A subject is counted at most once within each SOC and PT.
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付録2.7.6-4
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Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
急性扁桃炎	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
細菌性疾患キャリアー	0	0	0	1 (0.4)	1 (0.3)
気管支肺炎	0	0	0	3 (1.3)	3 (0.9)
カンピロバクター感染	0	0	0	1 (0.4)	1 (0.3)
カンジダ感染	0	0	0	2 (0.9)	2 (0.6)
クロストリジウム・ディフィシレ大腸炎	0	1 (1.9)	1 (1.0)	2 (0.9)	3 (0.9)
クロストリジウム・ディフィシレ感染	0	0	0	2 (0.9)	2 (0.6)
耳感染	0	0	0	1 (0.4)	1 (0.3)
脳炎	0	0	0	1 (0.4)	1 (0.3)
腸球菌感染	0	1 (1.9)	1 (1.0)	0	1 (0.3)
丹毒	0	0	0	1 (0.4)	1 (0.3)
大腸菌性腎盂腎炎	0	0	0	1 (0.4)	1 (0.3)
大腸菌性敗血症	0	0	0	1 (0.4)	1 (0.3)
大腸菌性尿路感染	0	0	0	3 (1.3)	3 (0.9)
熱性感染症	0	0	0	1 (0.4)	1 (0.3)
毛包炎	0	1 (1.9)	1 (1.0)	0	1 (0.3)
真菌感染	0	0	0	1 (0.4)	1 (0.3)
皮膚真菌感染	0	2 (3.7)	2 (2.0)	1 (0.4)	3 (0.9)
ウイルス性胃腸炎	0	1 (1.9)	1 (1.0)	0	1 (0.3)
ヘモフィルス感染	0	0	0	1 (0.4)	1 (0.3)
ヘルペスウイルス感染	0	0	0	1 (0.4)	1 (0.3)
麦粒腫	0	0	0	2 (0.9)	2 (0.6)
膿痂疹	0	1 (1.9)	1 (1.0)	0	1 (0.3)
喉頭炎	0	2 (3.7)	2 (2.0)	0	2 (0.6)

Note: AEs with CTCAE Grade 5 are excluded and summarized under death related tables.
Note: MedDRA v18.1 was used for coding. TEAE = Treatment emergent adverse event.
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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
真菌性下気道感染	0	0	0	1 (0.4)	1 (0.3)
好中球減少性敗血症	0	0	0	1 (0.4)	1 (0.3)
食道カンジダ症	0	0	0	1 (0.4)	1 (0.3)
口腔カンジダ症	0	0	0	3 (1.3)	3 (0.9)
外耳炎	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
急性中耳炎	0	0	0	1 (0.4)	1 (0.3)
パラインフルエンザウイルス感染	0	0	0	1 (0.4)	1 (0.3)
肺炎	0	1 (1.9)	1 (1.0)	6 (2.6)	7 (2.1)
クレブシエラ菌性肺炎	0	0	0	1 (0.4)	1 (0.3)
肺炎球菌性肺炎	0	1 (1.9)	1 (1.0)	0	1 (0.3)
膿疱性皮疹	0	1 (1.9)	1 (1.0)	0	1 (0.3)
ＲＳウイルス感染	0	0	0	1 (0.4)	1 (0.3)
ウイルス性気道感染	0	0	0	1 (0.4)	1 (0.3)
ライノウイルス感染	0	0	0	1 (0.4)	1 (0.3)
敗血症性ショック	0	0	0	1 (0.4)	1 (0.3)
皮膚感染	0	0	0	1 (0.4)	1 (0.3)
ブドウ球菌感染	0	0	0	3 (1.3)	3 (0.9)
ブドウ球菌皮膚感染	0	0	0	1 (0.4)	1 (0.3)
ステノトロフォモナス感染	0	0	0	1 (0.4)	1 (0.3)
気管気管支炎	0	1 (1.9)	1 (1.0)	0	1 (0.3)
ブドウ球菌性尿路感染	0	1 (1.9)	1 (1.0)	0	1 (0.3)
尿路性敗血症	0	0	0	1 (0.4)	1 (0.3)
ウイルス感染	0	0	0	2 (0.9)	2 (0.6)

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Note: MedDRA v18.1 was used for coding. TEAE = Treatment emergent adverse event.
Note: TEAEs are defined as adverse events that started or worsened in severity on or after the date of first dose of study drug through 30 days after the last dose. A subject is counted at most once within each SOC and PT.
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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
皮膚および皮下組織障害	21 (46.7)	19 (35.2)	40 (40.4)	38 (16.2)	78 (23.4)
脱毛症	10 (22.2)	7 (13.0)	17 (17.2)	9 (3.8)	26 (7.8)
発疹	4 (8.9)	4 (7.4)	8 (8.1)	7 (3.0)	15 (4.5)
皮膚乾燥	3 (6.7)	1 (1.9)	4 (4.0)	3 (1.3)	7 (2.1)
寝汗	3 (6.7)	1 (1.9)	4 (4.0)	5 (2.1)	9 (2.7)
皮膚変色	2 (4.4)	0	2 (2.0)	0	2 (0.6)
斑状出血	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
紅斑	1 (2.2)	0	1 (1.0)	3 (1.3)	4 (1.2)
毛髪成長異常	1 (2.2)	0	1 (1.0)	0	1 (0.3)
多汗症	1 (2.2)	1 (1.9)	2 (2.0)	2 (0.9)	4 (1.2)
爪甲離床症	1 (2.2)	0	1 (1.0)	0	1 (0.3)
光線過敏性反応	1 (2.2)	0	1 (1.0)	0	1 (0.3)
全身性そう痒症	1 (2.2)	0	1 (1.0)	0	1 (0.3)
紅斑性皮疹	1 (2.2)	1 (1.9)	2 (2.0)	0	2 (0.6)
皮膚腫瘤	1 (2.2)	0	1 (1.0)	0	1 (0.3)
ざ瘡	0	0	0	1 (0.4)	1 (0.3)
湿疹	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
睫毛眉毛脱落症	0	0	0	1 (0.4)	1 (0.3)
爪変色	0	0	0	2 (0.9)	2 (0.6)
爪の障害	0	0	0	1 (0.4)	1 (0.3)
爪破損	0	0	0	1 (0.4)	1 (0.3)
点状出血	0	0	0	1 (0.4)	1 (0.3)
そう痒症	0	3 (5.6)	3 (3.0)	9 (3.8)	12 (3.6)
乾癬	0	0	0	1 (0.4)	1 (0.3)

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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
全身性皮疹	0	1 (1.9)	1 (1.0)	0	1 (0.3)
斑状丘疹状皮疹	0	1 (1.9)	1 (1.0)	2 (0.9)	3 (0.9)
そう痒性皮疹	0	1 (1.9)	1 (1.0)	0	1 (0.3)
皮膚剥脱	0	1 (1.9)	1 (1.0)	0	1 (0.3)
皮膚色素過剰	0	0	0	1 (0.4)	1 (0.3)
皮膚病変	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
皮膚潰瘍	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
一般・全身障害および投与部位の状態	20 (44.4)	27 (50.0)	47 (47.5)	119 (50.9)	166 (49.8)
疲労	8 (17.8)	9 (16.7)	17 (17.2)	32 (13.7)	49 (14.7)
無力症	7 (15.6)	12 (22.2)	19 (19.2)	30 (12.8)	49 (14.7)
末梢性浮腫	3 (6.7)	3 (5.6)	6 (6.1)	22 (9.4)	28 (8.4)
腋窩痛	2 (4.4)	0	2 (2.0)	1 (0.4)	3 (0.9)
発熱	2 (4.4)	8 (14.8)	10 (10.1)	37 (15.8)	47 (14.1)
悪寒	1 (2.2)	1 (1.9)	2 (2.0)	2 (0.9)	4 (1.2)
局所腫脹	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
倦怠感	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
粘膜乾燥	1 (2.2)	0	1 (1.0)	0	1 (0.3)
非心臓性胸痛	1 (2.2)	1 (1.9)	2 (2.0)	3 (1.3)	5 (1.5)
疼痛	1 (2.2)	0	1 (1.0)	4 (1.7)	5 (1.5)
突出痛	0	0	0	1 (0.4)	1 (0.3)
カテーテル留置部位腫脹	0	0	0	1 (0.4)	1 (0.3)
胸痛	0	0	0	2 (0.9)	2 (0.6)
疾患進行	0	0	0	1 (0.4)	1 (0.3)

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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
歩行障害	0	0	0	1 (0.4)	1 (0.3)
全身健康状態低下	0	2 (3.7)	2 (2.0)	19 (8.1)	21 (6.3)
全身性浮腫	0	0	0	1 (0.4)	1 (0.3)
ヘルニア	0	0	0	1 (0.4)	1 (0.3)
インフルエンザ様疾患	0	0	0	1 (0.4)	1 (0.3)
限局性浮腫	0	0	0	1 (0.4)	1 (0.3)
粘膜の炎症	0	1 (1.9)	1 (1.0)	3 (1.3)	4 (1.2)
浮腫	0	0	0	1 (0.4)	1 (0.3)
末梢腫脹	0	0	0	7 (3.0)	7 (2.1)
全身性炎症反応症候群	0	0	0	1 (0.4)	1 (0.3)
乾燥症	0	1 (1.9)	1 (1.0)	0	1 (0.3)
神経系障害	20 (44.4)	18 (33.3)	38 (38.4)	53 (22.6)	91 (27.3)
味覚異常	6 (13.3)	2 (3.7)	8 (8.1)	9 (3.8)	17 (5.1)
浮動性めまい	4 (8.9)	3 (5.6)	7 (7.1)	6 (2.6)	13 (3.9)
頭痛	4 (8.9)	8 (14.8)	12 (12.1)	9 (3.8)	21 (6.3)
記憶障害	2 (4.4)	0	2 (2.0)	1 (0.4)	3 (0.9)
末梢性感覚ニューロパチー	2 (4.4)	0	2 (2.0)	1 (0.4)	3 (0.9)
運動失調	1 (2.2)	0	1 (1.0)	0	1 (0.3)
平衡障害	1 (2.2)	0	1 (1.0)	0	1 (0.3)
灼熱感	1 (2.2)	0	1 (1.0)	0	1 (0.3)
認知障害	1 (2.2)	0	1 (1.0)	0	1 (0.3)
嗜眠	1 (2.2)	1 (1.9)	2 (2.0)	7 (3.0)	9 (2.7)
片頭痛	1 (2.2)	0	1 (1.0)	0	1 (0.3)

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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
末梢性ニューロパチー	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
浸透圧性脱髄症候群	1 (2.2)	0	1 (1.0)	0	1 (0.3)
嗅覚錯誤	1 (2.2)	0	1 (1.0)	0	1 (0.3)
ヘルペス後神経痛	1 (2.2)	0	1 (1.0)	0	1 (0.3)
失神寸前の状態	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
坐骨神経痛	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
副鼻腔炎に伴う頭痛	1 (2.2)	0	1 (1.0)	0	1 (0.3)
失神	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
一過性全健忘	1 (2.2)	0	1 (1.0)	0	1 (0.3)
振戦	1 (2.2)	0	1 (1.0)	0	1 (0.3)
血管性脳症	1 (2.2)	0	1 (1.0)	0	1 (0.3)
味覚消失	0	2 (3.7)	2 (2.0)	0	2 (0.6)
健忘	0	0	0	1 (0.4)	1 (0.3)
脳血管発作	0	1 (1.9)	1 (1.0)	0	1 (0.3)
頚腕症候群	0	0	0	1 (0.4)	1 (0.3)
痙攣	0	1 (1.9)	1 (1.0)	0	1 (0.3)
注意力障害	0	0	0	1 (0.4)	1 (0.3)
異常感覚	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
ジスキネジア	0	1 (1.9)	1 (1.0)	0	1 (0.3)
脳症	0	0	0	2 (0.9)	2 (0.6)
不全片麻痺	0	0	0	1 (0.4)	1 (0.3)
ホルネル症候群	0	0	0	1 (0.4)	1 (0.3)
知覚過敏	0	0	0	1 (0.4)	1 (0.3)
感覚鈍麻	0	1 (1.9)	1 (1.0)	3 (1.3)	4 (1.2)

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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

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前兆を伴う片頭痛	0	0	0	1 (0.4)	1 (0.3)
神経系障害	0	0	0	1 (0.4)	1 (0.3)
神経痛	0	0	0	4 (1.7)	4 (1.2)
錯感覚	0	2 (3.7)	2 (2.0)	4 (1.7)	6 (1.8)
パーキンソニズム	0	0	0	1 (0.4)	1 (0.3)
末梢性運動ニューロパチー	0	0	0	2 (0.9)	2 (0.6)
下肢静止不能症候群	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
傾眠	0	0	0	3 (1.3)	3 (0.9)
脊髄圧迫	0	0	0	1 (0.4)	1 (0.3)
一過性脳虚血発作	0	1 (1.9)	1 (1.0)	0	1 (0.3)
第７脳神経麻痺	0	0	0	1 (0.4)	1 (0.3)
筋骨格系および結合組織障害	14 (31.1)	19 (35.2)	33 (33.3)	59 (25.2)	92 (27.6)
背部痛	5 (11.1)	6 (11.1)	11 (11.1)	23 (9.8)	34 (10.2)
関節痛	3 (6.7)	4 (7.4)	7 (7.1)	7 (3.0)	14 (4.2)
筋痙縮	3 (6.7)	6 (11.1)	9 (9.1)	9 (3.8)	18 (5.4)
筋肉痛	3 (6.7)	2 (3.7)	5 (5.1)	4 (1.7)	9 (2.7)
四肢痛	3 (6.7)	1 (1.9)	4 (4.0)	10 (4.3)	14 (4.2)
末梢部痛	2 (4.4)	0	2 (2.0)	1 (0.4)	3 (0.9)
側腹部痛	1 (2.2)	1 (1.9)	2 (2.0)	1 (0.4)	3 (0.9)
関節硬直	1 (2.2)	0	1 (1.0)	0	1 (0.3)
関節腫脹	1 (2.2)	1 (1.9)	2 (2.0)	2 (0.9)	4 (1.2)
四肢不快感	1 (2.2)	1 (1.9)	2 (2.0)	0	2 (0.6)
筋骨格系胸痛	1 (2.2)	1 (1.9)	2 (2.0)	2 (0.9)	4 (1.2)

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筋骨格不快感	1 (2.2)	0	1 (1.0)	0	1 (0.3)
筋骨格痛	1 (2.2)	2 (3.7)	3 (3.0)	5 (2.1)	8 (2.4)
筋骨格硬直	1 (2.2)	0	1 (1.0)	0	1 (0.3)
頚部痛	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
顎痛	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
腱炎	1 (2.2)	0	1 (1.0)	0	1 (0.3)
骨痛	0	0	0	3 (1.3)	3 (0.9)
滑液包炎	0	0	0	1 (0.4)	1 (0.3)
筋膜炎	0	0	0	1 (0.4)	1 (0.3)
筋力低下	0	0	0	3 (1.3)	3 (0.9)
変形性関節症	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
腰筋徴候	0	0	0	1 (0.4)	1 (0.3)
脊椎痛	0	1 (1.9)	1 (1.0)	0	1 (0.3)
顎関節症候群	0	0	0	1 (0.4)	1 (0.3)
代謝および栄養障害	13 (28.9)	11 (20.4)	24 (24.2)	53 (22.6)	77 (23.1)
食欲減退	6 (13.3)	2 (3.7)	8 (8.1)	24 (10.3)	32 (9.6)
高カリウム血症	2 (4.4)	1 (1.9)	3 (3.0)	0	3 (0.9)
高トリグリセリド血症	2 (4.4)	0	2 (2.0)	0	2 (0.6)
低リン酸血症	2 (4.4)	1 (1.9)	3 (3.0)	6 (2.6)	9 (2.7)
脱水	1 (2.2)	0	1 (1.0)	3 (1.3)	4 (1.2)
高血糖	1 (2.2)	0	1 (1.0)	7 (3.0)	8 (2.4)
高ナトリウム血症	1 (2.2)	0	1 (1.0)	0	1 (0.3)
鉄欠乏	1 (2.2)	0	1 (1.0)	0	1 (0.3)

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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

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糖尿病	0	1 (1.9)	1 (1.0)	0	1 (0.3)
糖尿病性代謝代償不全	0	1 (1.9)	1 (1.0)	0	1 (0.3)
葉酸欠乏	0	0	0	2 (0.9)	2 (0.6)
食物不耐性	0	0	0	1 (0.4)	1 (0.3)
耐糖能障害	0	1 (1.9)	1 (1.0)	0	1 (0.3)
痛風	0	1 (1.9)	1 (1.0)	0	1 (0.3)
高カルシウム血症	0	1 (1.9)	1 (1.0)	7 (3.0)	8 (2.4)
高コレステロール血症	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
高尿酸血症	0	2 (3.7)	2 (2.0)	4 (1.7)	6 (1.8)
低アルブミン血症	0	0	0	1 (0.4)	1 (0.3)
低カルシウム血症	0	0	0	2 (0.9)	2 (0.6)
低カリウム血症	0	1 (1.9)	1 (1.0)	6 (2.6)	7 (2.1)
低マグネシウム血症	0	0	0	4 (1.7)	4 (1.2)
低ナトリウム血症	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
低尿酸血症	0	0	0	1 (0.4)	1 (0.3)
乳酸アシドーシス	0	0	0	2 (0.9)	2 (0.6)
栄養障害	0	1 (1.9)	1 (1.0)	3 (1.3)	4 (1.2)
代謝症候群	0	1 (1.9)	1 (1.0)	0	1 (0.3)
多飲症	0	0	0	1 (0.4)	1 (0.3)
ビタミンD欠乏	0	0	0	2 (0.9)	2 (0.6)
臨床検査	9 (20.0)	6 (11.1)	15 (15.2)	41 (17.5)	56 (16.8)
血中クレアチンホスホキナーゼ増加	2 (4.4)	0	2 (2.0)	2 (0.9)	4 (1.2)
アミラーゼ増加	1 (2.2)	1 (1.9)	2 (2.0)	5 (2.1)	7 (2.1)

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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
血中クレアチニン増加	1 (2.2)	1 (1.9)	2 (2.0)	2 (0.9)	4 (1.2)
血中免疫グロブリンG減少	1 (2.2)	0	1 (1.0)	0	1 (0.3)
血圧上昇	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
血清フェリチン減少	1 (2.2)	0	1 (1.0)	0	1 (0.3)
トランスアミナーゼ上昇	1 (2.2)	0	1 (1.0)	0	1 (0.3)
体重減少	1 (2.2)	2 (3.7)	3 (3.0)	11 (4.7)	14 (4.2)
白血球数減少	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
アラニンアミノトランスフェラーゼ増加	0	0	0	2 (0.9)	2 (0.6)
アスパラギン酸アミノトランスフェラーゼ増加	0	0	0	1 (0.4)	1 (0.3)
抱合ビリルビン増加	0	0	0	1 (0.4)	1 (0.3)
血中アルカリホスファターゼ増加	0	0	0	3 (1.3)	3 (0.9)
血中ビリルビン増加	0	0	0	2 (0.9)	2 (0.6)
血中乳酸脱水素酵素減少	0	0	0	1 (0.4)	1 (0.3)
血中乳酸脱水素酵素増加	0	0	0	2 (0.9)	2 (0.6)
血中リン減少	0	0	0	2 (0.9)	2 (0.6)
血中カリウム減少	0	0	0	2 (0.9)	2 (0.6)
血中尿酸増加	0	0	0	2 (0.9)	2 (0.6)
Ｃ－反応性蛋白増加	0	0	0	2 (0.9)	2 (0.6)
腎クレアチニン・クリアランス異常	0	0	0	1 (0.4)	1 (0.3)
心電図ＱＴ延長	0	2 (3.7)	2 (2.0)	3 (1.3)	5 (1.5)
全身健康状態異常	0	0	0	2 (0.9)	2 (0.6)
ヘモグロビン減少	0	0	0	2 (0.9)	2 (0.6)
国際標準比増加	0	0	0	1 (0.4)	1 (0.3)
肝機能検査異常	0	0	0	1 (0.4)	1 (0.3)

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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
リンパ球数減少	0	0	0	1 (0.4)	1 (0.3)
単球数減少	0	0	0	1 (0.4)	1 (0.3)
血小板数減少	0	0	0	8 (3.4)	8 (2.4)
呼吸器、胸郭および縦隔障害	9 (20.0)	17 (31.5)	26 (26.3)	76 (32.5)	102 (30.6)
咳嗽	5 (11.1)	11 (20.4)	16 (16.2)	40 (17.1)	56 (16.8)
発声障害	2 (4.4)	0	2 (2.0)	5 (2.1)	7 (2.1)
呼吸困難	2 (4.4)	6 (11.1)	8 (8.1)	12 (5.1)	20 (6.0)
気管支肺症	1 (2.2)	0	1 (1.0)	0	1 (0.3)
鼻出血	1 (2.2)	3 (5.6)	4 (4.0)	2 (0.9)	6 (1.8)
低酸素症	1 (2.2)	0	1 (1.0)	5 (2.1)	6 (1.8)
鼻閉	1 (2.2)	0	1 (1.0)	3 (1.3)	4 (1.2)
胸水	1 (2.2)	2 (3.7)	3 (3.0)	8 (3.4)	11 (3.3)
湿性咳嗽	1 (2.2)	1 (1.9)	2 (2.0)	1 (0.4)	3 (0.9)
肺塞栓症	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
鼻漏	1 (2.2)	2 (3.7)	3 (3.0)	2 (0.9)	5 (1.5)
副鼻腔うっ血	1 (2.2)	0	1 (1.0)	0	1 (0.3)
急性肺水腫	0	0	0	2 (0.9)	2 (0.6)
急性呼吸窮迫症候群	0	0	0	1 (0.4)	1 (0.3)
無気肺	0	0	0	1 (0.4)	1 (0.3)
気管支障害	0	0	0	1 (0.4)	1 (0.3)
慢性閉塞性肺疾患	0	0	0	1 (0.4)	1 (0.3)
労作性呼吸困難	0	0	0	2 (0.9)	2 (0.6)
喀血	0	0	0	1 (0.4)	1 (0.3)

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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
喉頭の炎症	0	0	0	1 (0.4)	1 (0.3)
肺障害	0	0	0	3 (1.3)	3 (0.9)
縦隔障害	0	0	0	1 (0.4)	1 (0.3)
鼻の炎症	0	0	0	1 (0.4)	1 (0.3)
閉塞性気道障害	0	1 (1.9)	1 (1.0)	0	1 (0.3)
口腔咽頭痛	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
咽頭紅斑	0	0	0	1 (0.4)	1 (0.3)
誤嚥性肺炎	0	0	0	1 (0.4)	1 (0.3)
肺臓炎	0	0	0	1 (0.4)	1 (0.3)
肺腫瘤	0	1 (1.9)	1 (1.0)	0	1 (0.3)
呼吸不全	0	0	0	1 (0.4)	1 (0.3)
アレルギー性鼻炎	0	1 (1.9)	1 (1.0)	2 (0.9)	3 (0.9)
頻呼吸	0	0	0	1 (0.4)	1 (0.3)
咽喉刺激感	0	0	0	1 (0.4)	1 (0.3)
扁桃肥大	0	0	0	1 (0.4)	1 (0.3)
血液およびリンパ系障害	7 (15.6)	18 (33.3)	25 (25.3)	95 (40.6)	120 (36.0)
血小板減少症	4 (8.9)	6 (11.1)	10 (10.1)	54 (23.1)	64 (19.2)
貧血	3 (6.7)	11 (20.4)	14 (14.1)	42 (17.9)	56 (16.8)
好中球減少症	3 (6.7)	4 (7.4)	7 (7.1)	36 (15.4)	43 (12.9)
白血球減少症	1 (2.2)	2 (3.7)	3 (3.0)	8 (3.4)	11 (3.3)
大赤血球症	1 (2.2)	0	1 (1.0)	0	1 (0.3)
有熱性骨髄無形成	0	0	0	1 (0.4)	1 (0.3)
発熱性好中球減少症	0	0	0	4 (1.7)	4 (1.2)

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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
溶血	0	0	0	1 (0.4)	1 (0.3)
貪食細胞性組織球症	0	0	0	1 (0.4)	1 (0.3)
免疫性血小板減少性紫斑病	0	0	0	1 (0.4)	1 (0.3)
リンパ節痛	0	0	0	1 (0.4)	1 (0.3)
リンパ球減少症	0	2 (3.7)	2 (2.0)	5 (2.1)	7 (2.1)
汎血球減少症	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
血小板増加症	0	1 (1.9)	1 (1.0)	0	1 (0.3)
腎および尿路障害	7 (15.6)	1 (1.9)	8 (8.1)	22 (9.4)	30 (9.0)
夜間頻尿	2 (4.4)	0	2 (2.0)	0	2 (0.6)
慢性腎臓病	1 (2.2)	0	1 (1.0)	0	1 (0.3)
尿意切迫	1 (2.2)	0	1 (1.0)	0	1 (0.3)
腎結石症	1 (2.2)	0	1 (1.0)	0	1 (0.3)
頻尿	1 (2.2)	0	1 (1.0)	3 (1.3)	4 (1.2)
尿失禁	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
急性腎不全	0	0	0	1 (0.4)	1 (0.3)
無尿	0	0	0	1 (0.4)	1 (0.3)
排尿困難	0	0	0	2 (0.9)	2 (0.6)
糖尿	0	1 (1.9)	1 (1.0)	0	1 (0.3)
血尿	0	0	0	4 (1.7)	4 (1.2)
水腎症	0	0	0	1 (0.4)	1 (0.3)
乏尿	0	0	0	1 (0.4)	1 (0.3)
腎仙痛	0	0	0	1 (0.4)	1 (0.3)
腎不全	0	0	0	4 (1.7)	4 (1.2)

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SOC/PT別の有害事象発現率
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急性腎不全	0	0	0	3 (1.3)	3 (0.9)
腎機能障害	0	0	0	1 (0.4)	1 (0.3)
尿閉	0	0	0	1 (0.4)	1 (0.3)
血管障害	7 (15.6)	7 (13.0)	14 (14.1)	27 (11.5)	41 (12.3)
大腿動脈閉塞	1 (2.2)	0	1 (1.0)	0	1 (0.3)
ほてり	1 (2.2)	1 (1.9)	2 (2.0)	0	2 (0.6)
高血圧	1 (2.2)	3 (5.6)	4 (4.0)	7 (3.0)	11 (3.3)
リンパ浮腫	1 (2.2)	0	1 (1.0)	0	1 (0.3)
起立性低血圧	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
末梢冷感	1 (2.2)	0	1 (1.0)	0	1 (0.3)
静脈炎	1 (2.2)	0	1 (1.0)	0	1 (0.3)
鎖骨下静脈血栓症	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
深部静脈血栓症	0	0	0	3 (1.3)	3 (0.9)
塞栓症	0	0	0	1 (0.4)	1 (0.3)
血腫	0	1 (1.9)	1 (1.0)	2 (0.9)	3 (0.9)
低血圧	0	0	0	5 (2.1)	5 (1.5)
腹腔内血腫	0	0	0	1 (0.4)	1 (0.3)
頸静脈血栓症	0	0	0	1 (0.4)	1 (0.3)
神経原性ショック	0	0	0	1 (0.4)	1 (0.3)
蒼白	0	0	0	1 (0.4)	1 (0.3)
骨盤静脈血栓症	0	1 (1.9)	1 (1.0)	0	1 (0.3)
末梢血管障害	0	0	0	1 (0.4)	1 (0.3)
上大静脈症候群	0	0	0	2 (0.9)	2 (0.6)

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付録2.7.6-4
SOC/PT別の有害事象発現率
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Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
表在性血栓性静脈炎	0	0	0	1 (0.4)	1 (0.3)
血栓症	0	0	0	1 (0.4)	1 (0.3)
静脈瘤	0	0	0	1 (0.4)	1 (0.3)
静脈血栓症	0	1 (1.9)	1 (1.0)	0	1 (0.3)
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）	6 (13.3)	4 (7.4)	10 (10.1)	15 (6.4)	25 (7.5)
急性骨髄性白血病	1 (2.2)	0	1 (1.0)	0	1 (0.3)
網膜の良性新生物	1 (2.2)	0	1 (1.0)	0	1 (0.3)
線維腫	1 (2.2)	0	1 (1.0)	0	1 (0.3)
悪性黒色腫	1 (2.2)	0	1 (1.0)	0	1 (0.3)
甲状腺新生物	1 (2.2)	0	1 (1.0)	0	1 (0.3)
腫瘍疼痛	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
基底細胞癌	0	1 (1.9)	1 (1.0)	4 (1.7)	5 (1.5)
癌疼痛	0	0	0	5 (2.1)	5 (1.5)
再発びまん性大細胞型Ｂ細胞性リンパ腫	0	0	0	1 (0.4)	1 (0.3)
肺転移	0	0	0	1 (0.4)	1 (0.3)
骨髄異形成症候群	0	1 (1.9)	1 (1.0)	0	1 (0.3)
骨髄線維症	0	1 (1.9)	1 (1.0)	0	1 (0.3)
腫瘍合併症	0	0	0	1 (0.4)	1 (0.3)
悪性心嚢液貯留	0	0	0	1 (0.4)	1 (0.3)
脂漏性角化症	0	0	0	1 (0.4)	1 (0.3)
皮膚乳頭腫	0	0	0	1 (0.4)	1 (0.3)
扁平上皮癌	0	1 (1.9)	1 (1.0)	0	1 (0.3)
皮膚有棘細胞癌	0	0	0	1 (0.4)	1 (0.3)

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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
精神障害	6 (13.3)	9 (16.7)	15 (15.2)	24 (10.3)	39 (11.7)
不眠症	4 (8.9)	3 (5.6)	7 (7.1)	5 (2.1)	12 (3.6)
異常な夢	1 (2.2)	0	1 (1.0)	0	1 (0.3)
不安	1 (2.2)	3 (5.6)	4 (4.0)	9 (3.8)	13 (3.9)
錯乱状態	1 (2.2)	0	1 (1.0)	5 (2.1)	6 (1.8)
うつ病	1 (2.2)	1 (1.9)	2 (2.0)	2 (0.9)	4 (1.2)
激越	0	0	0	2 (0.9)	2 (0.6)
歯ぎしり	0	1 (1.9)	1 (1.0)	0	1 (0.3)
譫妄	0	0	0	1 (0.4)	1 (0.3)
抑うつ気分	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
失見当識	0	0	0	1 (0.4)	1 (0.3)
易刺激性	0	0	0	1 (0.4)	1 (0.3)
気分変化	0	0	0	1 (0.4)	1 (0.3)
気分動揺	0	1 (1.9)	1 (1.0)	0	1 (0.3)
神経過敏	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
精神症状	0	1 (1.9)	1 (1.0)	0	1 (0.3)
睡眠障害	0	0	0	2 (0.9)	2 (0.6)
自殺念慮	0	0	0	1 (0.4)	1 (0.3)
傷害、中毒および処置合併症	3 (6.7)	3 (5.6)	6 (6.1)	17 (7.3)	23 (6.9)
転倒	2 (4.4)	0	2 (2.0)	5 (2.1)	7 (2.1)
裂傷	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
四肢損傷	1 (2.2)	0	1 (1.0)	0	1 (0.3)
足関節部骨折	0	0	0	1 (0.4)	1 (0.3)

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SOC/PT別の有害事象発現率
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Safety Analysis Set

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擦過傷	0	0	0	1 (0.4)	1 (0.3)
大腿骨頸部骨折	0	0	0	1 (0.4)	1 (0.3)
足骨折	0	0	0	1 (0.4)	1 (0.3)
手骨折	0	1 (1.9)	1 (1.0)	0	1 (0.3)
股関節部骨折	0	1 (1.9)	1 (1.0)	0	1 (0.3)
注入に伴う反応	0	1 (1.9)	1 (1.0)	0	1 (0.3)
靱帯捻挫	0	0	0	1 (0.4)	1 (0.3)
過量投与	0	0	0	1 (0.4)	1 (0.3)
眼窩周囲出血	0	0	0	1 (0.4)	1 (0.3)
腰椎穿刺後症候群	0	0	0	1 (0.4)	1 (0.3)
放射線損傷	0	0	0	1 (0.4)	1 (0.3)
硬膜下出血	0	0	0	1 (0.4)	1 (0.3)
各種物質毒性	0	0	0	1 (0.4)	1 (0.3)
上肢骨折	0	0	0	1 (0.4)	1 (0.3)
創傷	0	0	0	2 (0.9)	2 (0.6)
創傷出血	0	0	0	1 (0.4)	1 (0.3)
心臓障害	2 (4.4)	4 (7.4)	6 (6.1)	16 (6.8)	22 (6.6)
狭心症	1 (2.2)	1 (1.9)	2 (2.0)	0	2 (0.6)
動悸	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
不整脈	0	1 (1.9)	1 (1.0)	0	1 (0.3)
心房細動	0	0	0	2 (0.9)	2 (0.6)
徐脈	0	0	0	1 (0.4)	1 (0.3)
心障害	0	0	0	1 (0.4)	1 (0.3)

Note: AEs with CTCAE Grade 5 are excluded and summarized under death related tables.
Note: MedDRA v18.1 was used for coding. TEAE = Treatment emergent adverse event.
Note: TEAEs are defined as adverse events that started or worsened in severity on or after the date of first dose of study drug through 30 days after the last dose. A subject is counted at most once within each SOC and PT.
Note: Includes all TEAEs regardless of causality or severity.
FL: Follicular Lymphoa, DLBCL: Diffuse Large B-Cell

付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
心不全	0	0	0	2 (0.9)	2 (0.6)
拡張機能障害	0	0	0	1 (0.4)	1 (0.3)
左室不全	0	0	0	1 (0.4)	1 (0.3)
心筋虚血	0	1 (1.9)	1 (1.0)	0	1 (0.3)
心嚢液貯留	0	0	0	1 (0.4)	1 (0.3)
収縮性心膜炎	0	1 (1.9)	1 (1.0)	0	1 (0.3)
洞性頻脈	0	0	0	3 (1.3)	3 (0.9)
頻脈	0	1 (1.9)	1 (1.0)	2 (0.9)	3 (0.9)
心室性期外収縮	0	0	0	1 (0.4)	1 (0.3)
眼障害	2 (4.4)	3 (5.6)	5 (5.1)	6 (2.6)	11 (3.3)
黄斑変性	1 (2.2)	0	1 (1.0)	0	1 (0.3)
霧視	1 (2.2)	0	1 (1.0)	0	1 (0.3)
硝子体剥離	1 (2.2)	0	1 (1.0)	0	1 (0.3)
硝子体浮遊物	1 (2.2)	0	1 (1.0)	0	1 (0.3)
眼精疲労	0	1 (1.9)	1 (1.0)	0	1 (0.3)
白内障	0	0	0	1 (0.4)	1 (0.3)
結膜出血	0	0	0	1 (0.4)	1 (0.3)
複視	0	0	0	1 (0.4)	1 (0.3)
眼瞼紅斑	0	0	0	1 (0.4)	1 (0.3)
眼球浮腫	0	0	0	1 (0.4)	1 (0.3)
眼充血	0	0	0	1 (0.4)	1 (0.3)
黄疸眼	0	0	0	1 (0.4)	1 (0.3)
眼窩周囲浮腫	0	1 (1.9)	1 (1.0)	0	1 (0.3)

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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
視力低下	0	2 (3.7)	2 (2.0)	1 (0.4)	3 (0.9)
耳および迷路障害	1 (2.2)	2 (3.7)	3 (3.0)	4 (1.7)	7 (2.1)
片耳難聴	1 (2.2)	0	1 (1.0)	0	1 (0.3)
耳痛	0	0	0	1 (0.4)	1 (0.3)
鼓膜穿孔	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
回転性めまい	0	1 (1.9)	1 (1.0)	2 (0.9)	3 (0.9)
内分泌障害	1 (2.2)	1 (1.9)	2 (2.0)	3 (1.3)	5 (1.5)
甲状腺機能低下症	1 (2.2)	1 (1.9)	2 (2.0)	0	2 (0.6)
副腎機能不全	0	0	0	1 (0.4)	1 (0.3)
自己免疫性甲状腺炎	0	0	0	1 (0.4)	1 (0.3)
悪性腫瘍に伴う高カルシウム血症	0	0	0	1 (0.4)	1 (0.3)
免疫系障害	1 (2.2)	4 (7.4)	5 (5.1)	6 (2.6)	11 (3.3)
低γグロブリン血症	1 (2.2)	3 (5.6)	4 (4.0)	6 (2.6)	10 (3.0)
体液性免疫不全	0	1 (1.9)	1 (1.0)	0	1 (0.3)
生殖系および乳房障害	1 (2.2)	2 (3.7)	3 (3.0)	7 (3.0)	10 (3.0)
外陰膣乾燥	1 (2.2)	1 (1.9)	2 (2.0)	0	2 (0.6)
乳房障害	0	0	0	1 (0.4)	1 (0.3)
性器浮腫	0	0	0	1 (0.4)	1 (0.3)
骨盤不快感	0	1 (1.9)	1 (1.0)	0	1 (0.3)
骨盤痛	0	0	0	1 (0.4)	1 (0.3)
陰茎腫脹	0	0	0	1 (0.4)	1 (0.3)

Note: AEs with CTCAE Grade 5 are excluded and summarized under death related tables.
Note: MedDRA v18.1 was used for coding. TEAE = Treatment emergent adverse event.
Note: TEAEs are defined as adverse events that started or worsened in severity on or after the date of first dose of study drug through 30 days after the last dose. A subject is counted at most once within each SOC and PT.
Note: Includes all TEAEs regardless of causality or severity.
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付録2.7.6-4
SOC/PT別の有害事象発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
前立腺炎	0	0	0	1 (0.4)	1 (0.3)
陰嚢浮腫	0	0	0	1 (0.4)	1 (0.3)
精巣痛	0	0	0	1 (0.4)	1 (0.3)
精巣腫脹	0	0	0	1 (0.4)	1 (0.3)
膣分泌物	0	0	0	1 (0.4)	1 (0.3)
膣出血	0	0	0	1 (0.4)	1 (0.3)
肝胆道系障害	0	1 (1.9)	1 (1.0)	3 (1.3)	4 (1.2)
胆管閉塞	0	1 (1.9)	1 (1.0)	0	1 (0.3)
黄疸	0	0	0	1 (0.4)	1 (0.3)
胆汁うっ滞性黄疸	0	0	0	1 (0.4)	1 (0.3)
門脈圧亢進症	0	0	0	1 (0.4)	1 (0.3)
外科および内科処置	0	0	0	1 (0.4)	1 (0.3)
単径部ヘルニア修復	0	0	0	1 (0.4)	1 (0.3)

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Note: TEAEs are defined as adverse events that started or worsened in severity on or after the date of first dose of study drug through 30 days after the last dose. A subject is counted at most once within each SOC and PT.
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付録2.7.6-5
SOC/PT別の副作用発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
副作用発現例数	38 (84.4)	42 (77.8)	80 (80.8)	131 (56.0)	211 (63.4)
胃腸障害	19 (42.2)	16 (29.6)	35 (35.4)	59 (25.2)	94 (28.2)
悪心	8 (17.8)	11 (20.4)	19 (19.2)	27 (11.5)	46 (13.8)
下痢	6 (13.3)	6 (11.1)	12 (12.1)	16 (6.8)	28 (8.4)
嘔吐	3 (6.7)	3 (5.6)	6 (6.1)	12 (5.1)	18 (5.4)
上腹部痛	2 (4.4)	2 (3.7)	4 (4.0)	2 (0.9)	6 (1.8)
腹部不快感	2 (4.4)	0	2 (2.0)	0	2 (0.6)
腹痛	2 (4.4)	0	2 (2.0)	7 (3.0)	9 (2.7)
放屁	0	2 (3.7)	2 (2.0)	0	2 (0.6)
口腔内潰瘍形成	1 (2.2)	1 (1.9)	2 (2.0)	0	2 (0.6)
腹部膨満	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
アフタ性口内炎	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
便秘	1 (2.2)	0	1 (1.0)	3 (1.3)	4 (1.2)
口内乾燥	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
口腔内痛	1 (2.2)	0	1 (1.0)	0	1 (0.3)
腹部硬直	0	0	0	1 (0.4)	1 (0.3)
消化不良	0	0	0	2 (0.9)	2 (0.6)
穿孔性胃潰瘍	0	0	0	1 (0.4)	1 (0.3)
胃炎	0	0	0	1 (0.4)	1 (0.3)
胃食道逆流性疾患	0	0	0	1 (0.4)	1 (0.3)
腸閉塞	0	0	0	1 (0.4)	1 (0.3)
口唇乾燥	0	0	0	1 (0.4)	1 (0.3)
メレナ	0	0	0	1 (0.4)	1 (0.3)

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付録2.7.6-5
SOC/PT別の副作用発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
口腔内不快感	0	0	0	1 (0.4)	1 (0.3)
直腸出血	0	0	0	1 (0.4)	1 (0.3)
口内炎	0	0	0	1 (0.4)	1 (0.3)
歯痛	0	0	0	1 (0.4)	1 (0.3)
一般・全身障害および投与部位の状態	15 (33.3)	15 (27.8)	30 (30.3)	33 (14.1)	63 (18.9)
無力症	7 (15.6)	8 (14.8)	15 (15.2)	13 (5.6)	28 (8.4)
疲労	6 (13.3)	6 (11.1)	12 (12.1)	14 (6.0)	26 (7.8)
発熱	1 (2.2)	1 (1.9)	2 (2.0)	3 (1.3)	5 (1.5)
粘膜乾燥	1 (2.2)	0	1 (1.0)	0	1 (0.3)
非心臓性胸痛	1 (2.2)	0	1 (1.0)	0	1 (0.3)
末梢性浮腫	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
乾燥症	0	1 (1.9)	1 (1.0)	0	1 (0.3)
倦怠感	0	0	0	1 (0.4)	1 (0.3)
粘膜の炎症	0	0	0	1 (0.4)	1 (0.3)
神経系障害	16 (35.6)	8 (14.8)	24 (24.2)	12 (5.1)	36 (10.8)
味覚異常	6 (13.3)	2 (3.7)	8 (8.1)	4 (1.7)	12 (3.6)
頭痛	2 (4.4)	3 (5.6)	5 (5.1)	2 (0.9)	7 (2.1)
浮動性めまい	3 (6.7)	0	3 (3.0)	1 (0.4)	4 (1.2)
嗜眠	1 (2.2)	1 (1.9)	2 (2.0)	1 (0.4)	3 (0.9)
記憶障害	2 (4.4)	0	2 (2.0)	0	2 (0.6)
味覚消失	0	1 (1.9)	1 (1.0)	0	1 (0.3)
認知障害	1 (2.2)	0	1 (1.0)	0	1 (0.3)

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付録2.7.6-5
SOC/PT別の副作用発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
異常感覚	0	1 (1.9)	1 (1.0)	0	1 (0.3)
感覚鈍麻	0	1 (1.9)	1 (1.0)	0	1 (0.3)
片頭痛	1 (2.2)	0	1 (1.0)	0	1 (0.3)
錯感覚	0	1 (1.9)	1 (1.0)	2 (0.9)	3 (0.9)
嗅覚錯誤	1 (2.2)	0	1 (1.0)	0	1 (0.3)
末梢性感覚ニューロパチー	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
失神寸前の状態	1 (2.2)	0	1 (1.0)	0	1 (0.3)
一過性全健忘	1 (2.2)	0	1 (1.0)	0	1 (0.3)
振戦	1 (2.2)	0	1 (1.0)	0	1 (0.3)
頚腕症候群	0	0	0	1 (0.4)	1 (0.3)
前兆を伴う片頭痛	0	0	0	1 (0.4)	1 (0.3)
傾眠	0	0	0	1 (0.4)	1 (0.3)
皮膚および皮下組織障害	15 (33.3)	9 (16.7)	24 (24.2)	18 (7.7)	42 (12.6)
脱毛症	10 (22.2)	4 (7.4)	14 (14.1)	7 (3.0)	21 (6.3)
皮膚乾燥	2 (4.4)	1 (1.9)	3 (3.0)	3 (1.3)	6 (1.8)
発疹	2 (4.4)	1 (1.9)	3 (3.0)	4 (1.7)	7 (2.1)
斑状出血	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
毛髪成長異常	1 (2.2)	0	1 (1.0)	0	1 (0.3)
多汗症	0	1 (1.9)	1 (1.0)	0	1 (0.3)
寝汗	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
爪甲離床症	1 (2.2)	0	1 (1.0)	0	1 (0.3)
光線過敏性反応	1 (2.2)	0	1 (1.0)	0	1 (0.3)
そう痒症	0	1 (1.9)	1 (1.0)	3 (1.3)	4 (1.2)

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付録2.7.6-5
SOC/PT別の副作用発現率
外国101試験；第2相パート
Safety Analysis Set

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全身性そう痒症	1 (2.2)	0	1 (1.0)	0	1 (0.3)
紅斑性皮疹	1 (2.2)	0	1 (1.0)	0	1 (0.3)
全身性皮疹	0	1 (1.9)	1 (1.0)	0	1 (0.3)
そう痒性皮疹	0	1 (1.9)	1 (1.0)	0	1 (0.3)
皮膚病変	0	1 (1.9)	1 (1.0)	0	1 (0.3)
湿疹	0	0	0	1 (0.4)	1 (0.3)
睫毛眉毛脱落症	0	0	0	1 (0.4)	1 (0.3)
爪破損	0	0	0	1 (0.4)	1 (0.3)
点状出血	0	0	0	1 (0.4)	1 (0.3)
乾癬	0	0	0	1 (0.4)	1 (0.3)
斑状丘疹状皮疹	0	0	0	1 (0.4)	1 (0.3)
血液およびリンパ系障害	6 (13.3)	12 (22.2)	18 (18.2)	63 (26.9)	81 (24.3)
貧血	2 (4.4)	7 (13.0)	9 (9.1)	20 (8.5)	29 (8.7)
血小板減少症	4 (8.9)	4 (7.4)	8 (8.1)	37 (15.8)	45 (13.5)
好中球減少症	3 (6.7)	3 (5.6)	6 (6.1)	28 (12.0)	34 (10.2)
白血球減少症	1 (2.2)	2 (3.7)	3 (3.0)	6 (2.6)	9 (2.7)
大赤血球症	1 (2.2)	0	1 (1.0)	0	1 (0.3)
汎血球減少症	0	1 (1.9)	1 (1.0)	0	1 (0.3)
発熱性好中球減少症	0	0	0	2 (0.9)	2 (0.6)
リンパ球減少症	0	0	0	2 (0.9)	2 (0.6)
感染症および寄生虫症	10 (22.2)	7 (13.0)	17 (17.2)	20 (8.5)	37 (11.1)
気管支炎	2 (4.4)	1 (1.9)	3 (3.0)	2 (0.9)	5 (1.5)

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付録2.7.6-5
SOC/PT別の副作用発現率
外国101試験；第2相パート
Safety Analysis Set

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下気道感染	2 (4.4)	0	2 (2.0)	0	2 (0.6)
口腔ヘルペス	2 (4.4)	0	2 (2.0)	0	2 (0.6)
膀胱炎	1 (2.2)	0	1 (1.0)	0	1 (0.3)
毛包炎	0	1 (1.9)	1 (1.0)	0	1 (0.3)
皮膚真菌感染	0	1 (1.9)	1 (1.0)	0	1 (0.3)
性器感染	1 (2.2)	0	1 (1.0)	0	1 (0.3)
膿痂疹	0	1 (1.9)	1 (1.0)	0	1 (0.3)
肺感染	1 (2.2)	0	1 (1.0)	0	1 (0.3)
鼻ヘルペス	1 (2.2)	0	1 (1.0)	0	1 (0.3)
口腔真菌感染	1 (2.2)	0	1 (1.0)	0	1 (0.3)
咽頭炎	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
肺炎	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
膿疱性皮疹	0	1 (1.9)	1 (1.0)	0	1 (0.3)
副鼻腔炎	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
気管炎	1 (2.2)	0	1 (1.0)	0	1 (0.3)
気管気管支炎	0	1 (1.9)	1 (1.0)	0	1 (0.3)
上気道感染	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
尿路感染	1 (2.2)	0	1 (1.0)	5 (2.1)	6 (1.8)
水痘	1 (2.2)	0	1 (1.0)	0	1 (0.3)
カンピロバクター感染	0	0	0	1 (0.4)	1 (0.3)
結膜炎	0	0	0	1 (0.4)	1 (0.3)
丹毒	0	0	0	1 (0.4)	1 (0.3)
大腸菌性腎盂腎炎	0	0	0	1 (0.4)	1 (0.3)

Note: AEs with CTCAE Grade 5 are excluded and summarized under death related tables.
Note: MedDRA v18.1 was used for coding. TEAE = Treatment emergent adverse event.
Note: TEAEs are defined as adverse events that started or worsened in severity on or after the date of first dose of study drug through 30 days after the last dose. A subject is counted at most once within each SOC and PT.
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SOC/PT別の副作用発現率
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MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
ヘモフィルス感染	0	0	0	1 (0.4)	1 (0.3)
インフルエンザ	0	0	0	1 (0.4)	1 (0.3)
鼻咽頭炎	0	0	0	1 (0.4)	1 (0.3)
好中球減少性敗血症	0	0	0	1 (0.4)	1 (0.3)
食道カンジダ症	0	0	0	1 (0.4)	1 (0.3)
ニューモシスチス・イロベチイ肺炎	0	0	0	1 (0.4)	1 (0.3)
鼻炎	0	0	0	1 (0.4)	1 (0.3)
皮膚感染	0	0	0	1 (0.4)	1 (0.3)
ステノトロフォモナス感染	0	0	0	1 (0.4)	1 (0.3)
代謝および栄養障害	10 (22.2)	2 (3.7)	12 (12.1)	14 (6.0)	26 (7.8)
食欲減退	4 (8.9)	1 (1.9)	5 (5.1)	8 (3.4)	13 (3.9)
低リン酸血症	2 (4.4)	1 (1.9)	3 (3.0)	2 (0.9)	5 (1.5)
高カリウム血症	2 (4.4)	0	2 (2.0)	0	2 (0.6)
高トリグリセリド血症	2 (4.4)	0	2 (2.0)	0	2 (0.6)
高尿酸血症	0	1 (1.9)	1 (1.0)	0	1 (0.3)
高血糖	0	0	0	2 (0.9)	2 (0.6)
低カリウム血症	0	0	0	1 (0.4)	1 (0.3)
低マグネシウム血症	0	0	0	1 (0.4)	1 (0.3)
低ナトリウム血症	0	0	0	1 (0.4)	1 (0.3)
筋骨格系および結合組織障害	6 (13.3)	5 (9.3)	11 (11.1)	11 (4.7)	22 (6.6)
筋痙縮	3 (6.7)	3 (5.6)	6 (6.1)	5 (2.1)	11 (3.3)
筋肉痛	2 (4.4)	0	2 (2.0)	3 (1.3)	5 (1.5)

Note: AEs with CTCAE Grade 5 are excluded and summarized under death related tables.
Note: MedDRA v18.1 was used for coding. TEAE = Treatment emergent adverse event.
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MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
関節痛	0	1 (1.9)	1 (1.0)	0	1 (0.3)
関節腫脹	0	1 (1.9)	1 (1.0)	0	1 (0.3)
筋骨格痛	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
背部痛	0	0	0	2 (0.9)	2 (0.6)
側腹部痛	0	0	0	1 (0.4)	1 (0.3)
筋力低下	0	0	0	1 (0.4)	1 (0.3)
四肢痛	0	0	0	1 (0.4)	1 (0.3)
臨床検査	7 (15.6)	2 (3.7)	9 (9.1)	10 (4.3)	19 (5.7)
アミラーゼ増加	1 (2.2)	1 (1.9)	2 (2.0)	1 (0.4)	3 (0.9)
血中クレアチンホスホキナーゼ増加	2 (4.4)	0	2 (2.0)	0	2 (0.6)
血中クレアチニン増加	1 (2.2)	0	1 (1.0)	0	1 (0.3)
血中免疫グロブリンG減少	1 (2.2)	0	1 (1.0)	0	1 (0.3)
心電図ＱＴ延長	0	1 (1.9)	1 (1.0)	2 (0.9)	3 (0.9)
トランスアミナーゼ上昇	1 (2.2)	0	1 (1.0)	0	1 (0.3)
体重減少	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
白血球数減少	1 (2.2)	0	1 (1.0)	2 (0.9)	3 (0.9)
アラニンアミノトランスフェラーゼ増加	0	0	0	1 (0.4)	1 (0.3)
血中アルカリホスファターゼ増加	0	0	0	1 (0.4)	1 (0.3)
ヘモグロビン減少	0	0	0	1 (0.4)	1 (0.3)
単球数減少	0	0	0	1 (0.4)	1 (0.3)
血小板数減少	0	0	0	4 (1.7)	4 (1.2)
精神障害	4 (8.9)	2 (3.7)	6 (6.1)	1 (0.4)	7 (2.1)

Note: AEs with CTCAE Grade 5 are excluded and summarized under death related tables.
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Note: TEAEs related to study drug are those that the investigator classified as "possibly related", "probably related", or "related" or relationship was missing to that study drug.
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付録2.7.6-5
SOC/PT別の副作用発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
不眠症	2 (4.4)	1 (1.9)	3 (3.0)	1 (0.4)	4 (1.2)
異常な夢	1 (2.2)	0	1 (1.0)	0	1 (0.3)
錯乱状態	1 (2.2)	0	1 (1.0)	0	1 (0.3)
気分動揺	0	1 (1.9)	1 (1.0)	0	1 (0.3)
神経過敏	0	1 (1.9)	1 (1.0)	0	1 (0.3)
呼吸器、胸郭および縦隔障害	3 (6.7)	2 (3.7)	5 (5.1)	9 (3.8)	14 (4.2)
咳嗽	1 (2.2)	1 (1.9)	2 (2.0)	5 (2.1)	7 (2.1)
発声障害	1 (2.2)	0	1 (1.0)	0	1 (0.3)
呼吸困難	0	1 (1.9)	1 (1.0)	0	1 (0.3)
肺塞栓症	1 (2.2)	0	1 (1.0)	0	1 (0.3)
労作性呼吸困難	0	0	0	1 (0.4)	1 (0.3)
喉頭の炎症	0	0	0	1 (0.4)	1 (0.3)
肺臓炎	0	0	0	1 (0.4)	1 (0.3)
頻呼吸	0	0	0	1 (0.4)	1 (0.3)
血管障害	3 (6.7)	1 (1.9)	4 (4.0)	4 (1.7)	8 (2.4)
ほてり	1 (2.2)	1 (1.9)	2 (2.0)	0	2 (0.6)
リンパ浮腫	1 (2.2)	0	1 (1.0)	0	1 (0.3)
末梢冷感	1 (2.2)	0	1 (1.0)	0	1 (0.3)
高血圧	0	0	0	2 (0.9)	2 (0.6)
腹腔内血腫	0	0	0	1 (0.4)	1 (0.3)
起立性低血圧	0	0	0	1 (0.4)	1 (0.3)

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Note: TEAEs related to study drug are those that the investigator classified as "possibly related", "probably related", or "related" or relationship was missing to that study drug.
Note: Includes all TEAEs regardless of severity.
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付録2.7.6-5
SOC/PT別の副作用発現率
外国101試験；第2相パート
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
心臓障害	0	3 (5.6)	3 (3.0)	3 (1.3)	6 (1.8)
狭心症	0	1 (1.9)	1 (1.0)	0	1 (0.3)
不整脈	0	1 (1.9)	1 (1.0)	0	1 (0.3)
心筋虚血	0	1 (1.9)	1 (1.0)	0	1 (0.3)
心房細動	0	0	0	1 (0.4)	1 (0.3)
心不全	0	0	0	1 (0.4)	1 (0.3)
拡張機能障害	0	0	0	1 (0.4)	1 (0.3)
眼障害	0	2 (3.7)	2 (2.0)	0	2 (0.6)
眼窩周囲浮腫	0	1 (1.9)	1 (1.0)	0	1 (0.3)
視力低下	0	1 (1.9)	1 (1.0)	0	1 (0.3)
免疫系障害	1 (2.2)	1 (1.9)	2 (2.0)	4 (1.7)	6 (1.8)
体液性免疫不全	0	1 (1.9)	1 (1.0)	0	1 (0.3)
低ガンマグロブリン血症	1 (2.2)	0	1 (1.0)	4 (1.7)	5 (1.5)
腎および尿路障害	1 (2.2)	1 (1.9)	2 (2.0)	1 (0.4)	3 (0.9)
糖尿	0	1 (1.9)	1 (1.0)	0	1 (0.3)
夜間頻尿	1 (2.2)	0	1 (1.0)	0	1 (0.3)
腎不全	0	0	0	1 (0.4)	1 (0.3)
耳および迷路障害	0	1 (1.9)	1 (1.0)	0	1 (0.3)
回転性めまい	0	1 (1.9)	1 (1.0)	0	1 (0.3)

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Note: TEAEs are defined as adverse events that started or worsened in severity on or after the date of first dose of study drug through 30 days after the last dose. A subject is counted at most once within each SOC and PT.
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付録2.7.6-5
SOC/PT別の副作用発現率
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Safety Analysis Set

MedDRA System Organ Class Preferred Term	Mutant Type FL Population N=45 n (%)	Wild Type FL Population N=54 n (%)	FL Population N=99 n (%)	DLBCL Population N=234 n (%)	Overall Population N=333 n (%)
内分泌障害	0	1 (1.9)	1 (1.0)	1 (0.4)	2 (0.6)
甲状腺機能低下症	0	1 (1.9)	1 (1.0)	0	1 (0.3)
自己免疫性甲状腺炎	0	0	0	1 (0.4)	1 (0.3)
傷害、中毒および処置合併症	1 (2.2)	0	1 (1.0)	0	1 (0.3)
転倒	1 (2.2)	0	1 (1.0)	0	1 (0.3)
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）	0	1 (1.9)	1 (1.0)	0	1 (0.3)
骨髄異形成症候群	0	1 (1.9)	1 (1.0)	0	1 (0.3)
生殖系および乳房障害	1 (2.2)	0	1 (1.0)	1 (0.4)	2 (0.6)
外陰腟乾燥	1 (2.2)	0	1 (1.0)	0	1 (0.3)
前立腺炎	0	0	0	1 (0.4)	1 (0.3)

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付録 2.7.6-6　死亡又は重篤な有害事象の被験者ごとの叙述（外国 101 試験；第 2 相パート）

FL の死亡又は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。

被験者識別コード	有害事象 MedDRA（PT）Version 18.1	死亡に至った有害事象	死亡以外の重篤な有害事象
FL-MT			
10042004	胸水		X
10052001	ニューモシスチス・イロベチイ肺炎		X
10052010	悪性黒色腫		X
20042035	蓄膿		X
30032003	急性骨髄性白血病		X
40022001	浸透圧性脱髄症候群，大腿動脈閉塞，鎖骨下静脈血栓症		X
40042002	慢性腎臓病	X	X
60012023	低酸素症		X
60022023	敗血症		X
80022025	帯状疱疹，ヘルペス後神経痛，失神		X
80062009	一過性全健忘		X
FL-WT			
10012001	胃障害		X
10012010	好中球減少症		X
10012018	発熱		X
10032005	股関節部骨折		X
10032020	急性膵炎		X
10032035	腹水		X
10032036	下部消化管出血		X
10032038	浮動性めまい		X
10042019	貧血，リンパ球減少症，血小板減少症，全身健康状態低下		X
10052013	高尿酸血症		X
10102001	貧血，汎血球減少症，収縮性心膜炎，全身健康状態低下，肺感染，敗血症，低カリウム血症		X
10102007	腹痛		X
20012014	嘔吐		X
20032003	不整脈，骨髄異形成症候群，脳血管発作		X
50022007	悪寒		X
60012009	胆管閉塞		X

Subject Number	10042004
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	14 Dec 2015 (Day 1)
Last Dose Date (Study Day):	03 Apr 2016 (Day 112)
Nonfatal SAE	Pleural effusion（胸水）

Subject 10042004 is a 5[redacted]-year-old male who was diagnosed with follicular lymphoma on 29 Jun 2005. On 19 Nov 2015, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects with Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with cyclophosphamide/doxorubicin/ methylprednisolone/rituximab/vincristine/prednisolone (Sep 2005 to Jan 2006), etoposide/rituximab/carboplatin/ifosfamide (May 2007 to Jul 2007), methylprednisolone/ etoposide/ifosfamide/rituximab/cyclophosphamide/doxorubicine/vincristine/prednisolone (Aug 2007 to Oct 2007), rituximab/ibritumomab tiuxetan (Nov 2007), carmustine/cytarabine/etoposide/melphalan (Jan 2008 to Feb 2008), rituximab (Oct 2008), anti-CD20 investigational drug (Mar 2009 to Aug 2009), anti-CD19 investigational drug (Mar 2010 to May 2010), gemcitabine/oxaliplatin/rituximab (Oct 2010), bendamustine/rituximab (Apr 2012 to Aug 2012), BTK inhibitor investigational drug/lenalidomide (May 2013 to Jul 2013), PI3K inhibitor investigational drug (Sep 2013 to Aug 2015), and unspecified investigational drug (Sep 2015 to Dec 2015).

Relevant past medical history included anal fissure (Jul 2007), anal sphincterotomy (Nov 2007), fistula repair (Mar 2008), herpes zoster (Oct 2010), and visual acuity reduced (06 May 2010 to 14 Jun 2010). Relevant ongoing medical conditions included tobacco abuse (Mar 1975), anxiety (29 Jun 2005), asthenia (2015), and cancer pain (2015). The subject received the first dose of tazemetostat 800 mg BID on 14 Dec 2015 (Study Day 1).

Concomitant medications taken within 14 days of the start of **Pleural effusion** included bromazepam, clonazepam, lamaline, and oxazepam.

On 19 Mar 2016 (Study Day 97), the subject had non-serious adverse event (AE) of Grade 2 Pleural effusion.

On 01 Apr 2016 (Study Day 110), the same day as the most recent dose of tazemetostat, non-serious AE of Grade 2 Pleural effusion worsened and the subject was hospitalized due to Grade 3 **Pleural effusion**. The subject had received 189 doses of tazemetostat (151,200 mg total) prior to the onset of the Grade 3 **Pleural effusion**. A pleural puncture was done and pleural fluid analysis confirmed the event of pleural effusion was due to lymphoma. A pleural tap was performed and 1 liter of purulent liquid removed. Bacterial examination of the purulent liquid was negative, but the cytology revealed large B cells. No action was taken with study drug due to the Grade 3 **Pleural effusion**. The subject was treated with amoxicillin sodium/clavulanate potassium, amoxicillin, fentanyl, and dexamethasone.

On 04 Apr 2016 (Study Day 113), study drug was discontinued due to disease progression with the last dose taken on 03 Apr 2016 (Study Day 112).

On 06 Apr 2016 (Study Day 115), the subject was transferred to “MB1” unit. On admission, the subject was in a good general condition and with symptoms of night sweats. The subject did not have fever in the evening and no weight loss. Cardiopulmonary examination showed a known heart murmur and decreased vesicular breath sounds which came up to one-third of the

left lung field. The abdomen was soft and pain-free with no palpable organomegaly.

On 07 Apr 2016 (Study Day 116), the subject started treatment with rituximab/etoposide/ ifosfamide/methylprednisolone. The subject had an immediate response and clinical tolerance to the treatment with no tumor lysis syndrome and stability of the left pleural effusion.

On 22 Jun 2016 (Study Day 192), the event of Grade 3 **Pleural effusion** was considered resolved.

The investigator reported the event of **Pleural effusion** was not related to tazemetostat. The investigator reported the event was due to disease progression.

On 28 Nov 2016 (Study Day 351), the subject died due to progressive disease.

Subject Number	10052001
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	07 Dec 2015 (Study Day 1)
Last Dose Date (Study Day):	13 Dec 2017 (Study Day 738)
Nonfatal SAE	Pneumocystis jirovecii pneumonia （ニューモシスチス・イロベチイ肺炎）

Subject 10052001 is a 6[redacted]-year-old male who was diagnosed with follicular lymphoma on 19 Nov 2007. On 10 Nov 2015, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with doxorubicin/cyclophosphamide/ methylprednisolone/vincristine/rituximab (Nov 2007 to May 2008), cytarabine/etoposide/ifosfamide/rituximab (Nov 2010 to Feb 2011), carmustine/cytarabine/etoposide/melphalan (Apr 2011), rituximab (Aug 2013 to Sep 2013), bendamustine/rituximab (Nov 2013 to Apr 2014), and bendamustine/rituximab (May 2014 to Oct 2015).

Relevant past medical history included viral hepatitis (unknown 1974 to unknown 1974).

The subject received the first dose of tazemetostat 800 mg BID on 07 Dec 2015 (Study Day 1).

Concomitant medication taken within 14 days of the start of **Pneumocystis jirovecii pneumonia** was levofloxacin.

Study drug was interrupted on 23 Mar 2016 (Study Day 108) due to Grade 3 fatigue.

On 06 Apr 2016 (Study Day 122), 14 days since the most recent dose of tazemetostat, the subject was hospitalized due to Grade 2 **Pneumocystis jirovecii pneumonia**. The subject had received 216 doses of tazemetostat (172,800 mg total) prior to the onset of the Grade 2 **Pneumocystis jirovecii pneumonia**. On admission, the subject was experiencing acute respiratory distress and hypoxia, which were considered consequences of the **Pneumocystis jirovecii pneumonia**. No action was taken with study drug due to the **Pneumocystis jirovecii pneumonia**.

On 07 Apr 2016 (Study Day 123), bronchoscopy was positive for pneumocystis. The subject was treated with sulfamethoxazole/trimethoprim, piperacillin/tazobactam, and prednisone.

On 13 Apr 2016 (Study Day 129), the event of Grade 2 **Pneumocystis jirovecii pneumonia** was considered resolved, and the subject was discharged from the hospital.

The investigator reported the event of **Pneumocystis jirovecii pneumonia** was not related to tazemetostat.

Study drug was resumed on 19 Apr 2016 (Study Day 135).

Study drug was discontinued on 14 Dec 2017 (Study Day 739) due to disease progression, with the last dose taken on 13 Dec 2017 (Study Day 738).

Subject Number	10052010
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	14 Sep 2016 (Study Day 1)
Last Dose Date (Study Day):	04 Sep 2018 (Study Day 721, entered rollover study)
Nonfatal SAE	Malignant melanoma（悪性黒色腫）

Subject 10052010 is a 6[redacted]-year-old female who was diagnosed with follicular lymphoma on 16 Jan 1996. On 24 Aug 2016, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. She was previously treated with chloraminophene/prednisone (Mar 1998 to Aug 1998), doxorubicin/rituximab/cyclophosphamide/methylprednisolone/vincristine (Aug 2007 to Jan 2008), and voxtalisib (Mar 2012 to Aug 2016).

Relevant past medical history included lyme disease (08 Jul 2014 to 22 Oct 2014) and tonsillectomy (24 Nov 2011). Relevant ongoing medical conditions included diarrhoea (2014) and hypercholesterolaemia (14 Sep 2016).

The subject received the first dose of tazemetostat 800 mg BID on 14 Sep 2016 (Study Day 1).

Concomitant medications taken within 14 days of the start of **Malignant melanoma** (first episode) included pentamidine, valaciclovir, magnesium w/vitamin B6, yeast, and loperamide.

On 01 Sep 2017 (Study Day 353), the same day as the most recent dose of tazemetostat, the subject experienced a medically important event of Grade 4 **Malignant melanoma**. The subject had superficial spreading melanoma (SSM) level 4. The subject had received 702 doses of tazemetostat (561,600 mg total) prior to the onset of the Grade 4 **Malignant melanoma**. On the same day, the subject underwent excision of left shoulder melanoma. On an unknown date, the subject underwent lymphoscintigraphy. No action was taken with study drug due to the **Malignant melanoma** (first episode).

On 01 Sep 2017 (Study Day 353), the event of Grade 4 **Malignant melanoma** was considered resolved.

The investigator reported the event of **Malignant melanoma** (first episode) was not related to tazemetostat. The investigator reported the event was due to concomitant disease.

Concomitant medications taken within 14 days of the start of **Malignant melanoma** (second episode) included pentamidine, valaciclovir, magnesium w/vitamin B6, yeast, and loperamide.

Study drug was interrupted on 18 Oct 2017 (Study Day 400) per investigator decision due to upcoming surgery for Grade 4 **Malignant melanoma**.

On 19 Oct 2017 (Study Day 401), 2 days since the most recent dose of tazemetostat, the subject again experienced Grade 4 **Malignant melanoma** and was hospitalized due to enlargement of the initial excision. The subject had received 796 doses of tazemetostat (636,800 mg total) prior to the onset of the Grade 4 **Malignant melanoma**. That day, the subject underwent surgical reprise of the scar of the initial excision of left shoulder melanoma performed on 01 Sep 2017 (Study Day 353).

On 21 Oct 2017 (Study Day 403), the event of Grade 4 **Malignant melanoma** was considered resolved and the subject was discharged from the hospital with no evidence of metastatic

melanoma.

The investigator reported the event of **Malignant melanoma** (second episode) was not related to tazemetostat. Tazemetostat was resumed on 27 Oct 2017 (Study Day 409).

On 05 Sep 2018 (Study Day 722), the subject enrolled into the EZH-501 rollover study with the last dose taken in this study on 04 Sep 2018 (Study Day 721).

Subject Number	20042035
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	31 Dec 2018 (Study Day 1)
Last Dose Date (Study Day):	Ongoing
Nonfatal SAE	Empyema （蓄膿）

Subject 20042035 is a 7[redacted]-year-old male who was diagnosed with follicular lymphoma (FL) in 1994. The diagnosis was confirmed at screening on 20 Nov 2018. On 17 Dec 2018, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with cyclophosphamide/mitoxantrone/prednisone/vincristine (1994), cyclophosphamide/rituximab/vincristine (17 Apr 2012 to 08 May 2012), prednisolone (17 Apr 2012 to 12 May 2012 and 04 Mar 2015 to 21 Jun 2015), gemcitabine (03 Oct 2012 to 13 Mar 2013), rituximab (04 Mar 2015, 25 Mar 2015 to 17 Jun 2015, 31 Jul 2015 to 01 Jul 2016, and 26 Oct 2017), cyclophosphamide/vincristine (04 Mar 2015 to 17 Jun 2015), and investigational antineoplastic drugs (lilotomab; 09 Nov 2017).

No relevant past medical history was reported. Relevant ongoing medical conditions included Type 2 diabetes mellitus (2000).

The subject received the first dose of tazemetostat 800 mg BID on 13 Dec 2018 (Study Day 1).

Concomitant medications taken within 14 days of the start of the **Empyema** were not reported.

On 05 Mar 2019 (Study Day 65), 2 days after the most recent dose of tazemetostat, the subject experienced a serious adverse event (SAE) of Grade 3 **Empyema** and was admitted to the respiratory ward on the same day. A chest drain was placed and intravenous amoxicillin was started. Additional treatment included oral clarithromycin for lower respiratory tract infection, which was later stopped on the advice of sub-principal investigator as per protocol recommendation. The subject had received 128 doses of tazemetostat (102,400 mg total) prior to the onset of the Grade 3 **Empyema**. No action was taken with study drug due to the **Empyema**.

On 20 Mar 2019 (Study Day 80), relevant laboratory results revealed hemoglobin of 93, leukocytes of 12.1, platelets of 283, albumin of 25, and C- reactive protein of 116 (units and reference ranges not provided). Urea, electrolytes and liver function test were reported as normal.

On 22 Mar 2019 (Study Day 82), the event of Grade 3 **Empyema** was considered resolved and the subject was discharged from the hospital.

The investigator reported the event of **Empyema** was not related to tazemetostat. The long lasting underlying cancer, prior anti-cancer therapies, and subject's age were confounding factors.

The subject continued on the study drug throughout the aforementioned event and at the time of the data cutoff.

Subject Number	30032003
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	24 Aug 2016 (Study Day 1)
Last Dose Date (Study Day):	24 Sep 2018 (Study Day 762)
Nonfatal SAE	Acute Myeloid Leukaemia （急性骨髄性白血病）

Subject 30032003 is a 6[redacted]-year-old male who was diagnosed with follicular lymphoma (FL) on 29 Apr 2008. The diagnosis was confirmed at screening on 19 May 2016. On 26 Jul 2016, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with chlorambucil (09 Sep 2008 to 21 Nov 2008), cyclophosphamide (14 Dec 2008 to 31 Mar 2009), doxorubicin/rituximab/vincristine (17 Dec 2008 to 31 Mar 2009), and rituximab (16 Dec 2009 to 08 Feb 2011).

Relevant past medical history included cerebrovascular accident (Mar 2008). Relevant ongoing medical conditions included back pain (2000), asthma and Type 2 diabetes mellitus (2006), depression, hyperlipidaemia, and hypertension (2008), hemiparesis (Mar 2008), and gastrooesophageal reflux disease (2011).

The subject received the first dose of tazemetostat 800 mg BID on 24 Aug 2016 (Study Day 1). Tazemetostat was interrupted on 03 Apr 2018 (Study Day 588) due to Grade 3 Thrombocytopenia (platelets 42×10^9/L [reference range: 150-500$\times10^9$/L]), and resumed at a reduced dose of 600 mg BID on 08 May 2018 (Study Day 623) due to Grade 1 Thrombocytopenia. On 25 Sep 2018 (Study Day 763), tazemetostat was interrupted due to Grade 3 Thrombocytopenia. The day prior, platelet count was 47×109/L.

Concomitant medications taken within 14 days of the start of the **Acute Myeloid Leukaemia** included acetylsalicylic acid, cholecalciferol, ezetimibe, metoprolol, pantoprazole, paracetamol, Pritor Plus, rosuvastatin, and Telsar-A.

On 18 Oct 2018 (Study Day 786), 24 days after the last dose date, the subject was diagnosed with Grade 4 **Acute Myeloid Leukaemia**. The event was considered a serious adverse event of special interest. A bone marrow aspirate and trephine biopsy were performed from left posterior superior iliac spine under local anesthesia and intravenous sedation. Tissue resistance to the aspirate was found normal and the samples were sent for flow cytometry and molecular studies. The marrow aspirate showed fragments and trails to be mildly hypercellular. Myelopoiesis was increased in activity with 53% myeloblasts and a little more maturation was speculated. The blasts were small to intermediate in size with an inconspicuous nucleolus, with some nuclear folding and a small amount of basophilic cytoplasm with fine azurophilic granules and small vacuoles. Erythropoiesis was relatively preserved in activity, with mild dyserythropoiesis including nuclear cytoplasmic asynchrony and occasional multinucleate forms. Megakaryocytes showed reduction in the number with a normal morphology. Lymphocytes represented 5% of the nucleated cells with unremarkable morphology. Macrophages were marked as unremarkable too. Iron stores were trace and ringed sideroblasts were nil. Relevant laboratory results included blasts 53%, promyelocytes <1%, myelocytes <1%, metamyelocytes 1%, bands 1%, eosinophils 2%, neutrophils 1%, lymphocytes 4%, plasma cells <1%, monocytes 1%, and erythroid cells 36% (reference ranges not provided). The trephine biopsy report revealed a trephine core measuring 14×2 mm. Microscopy revealed

the marrow as normal to mildly hypercellular. Myeloid activity was observed to be mildly increased with left shifted maturation and excess of intermediate sized blasts. Erythrocyte activity was normal and megakaryocytes numbers were reduced with normal morphology according to the microscopy reports. No abnormal lymphoid aggregates were seen, and bone trabeculae were normal. The result of Next Generation Sequencing (NGS) myeloid panel and results of the bone marrow cytogenetics were awaited. The pathologist concluded that the bone marrow and flow cytometry were consistent with acute myeloid that was presumed to be related with the prior cyclophosphamide therapy. The subject had received 1440 doses of tazemetostat (109,600 mg total) prior to the onset of the Grade 4 **Acute Myeloid Leukaemia**. Study drug was discontinued due to **Acute Myeloid Leukaemia**. No treatment medication was reported.

On 22 Oct 2018 (Study Day 790), relevant laboratory results included hemoglobin 119 g/L (reference range: 125-175 g/L), neutrophils 0.3×10^9/L (reference range: $2\text{-}8\times10^9$/L), and platelets 50×10^9/L.

On 23 Oct 2018 (Study Day 791), the physician stated due to the subject's condition, any intensive induction chemotherapy would be contraindicated. Primula therapy (azacytidine and paracinostat/placebo) was suggested as a non-curative but better tolerated therapy. The trial therapy of primula was expected to prolong survival for at least 12 months. The consent form of the therapy was given to the subject and on his agreement the therapy was to be started. The subject was stated to be stable with an ECOG performance status of 0. The event remained ongoing at the time of data cutoff.

The investigator reported the event of **Acute Myeloid Leukaemia** was not related to tazemetostat. It was due to the prior rituximab, cyclophosphamide, oncovin (vincristine), prednisone (R-CHOP) therapy.

Subject Number	40022001
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	12 Apr 2017 (Study Day 1)
Last Dose Date (Study Day):	12 Jul 2018 (Study Day 457)
Nonfatal SAE	Osmotic demyelination syndrome （浸透圧性脱髄症候群） Femoral artery occlusion（大腿動脈閉塞） Subclavian vein thrombosis （鎖骨下静脈血栓症）

Subject 40022001 is a 5[redacted]-year-old white male who was diagnosed with follicular lymphoma on 22 Oct 2015. On 15 Mar 2017, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with bendamustine/rituximab (Dec 2015 and Feb 2016) and cyclophosphamide/prednisone/rituximab/vincristine (May 2016 to Nov 2016).

Relevant ongoing medical conditions included cholelithiasis (Oct 2011), hypertension (2006), nicotine dependence (1970), and back pain (2002).

The subject received the first dose of tazemetostat 800 mg BID on 12 Apr 2017 (Study Day 1).

Concomitant medications taken within 14 days of the start of **Femoral artery occlusion** included nebivolol, ramipril, and gabapentin.

On 22 Oct 2017 (Study Day 194), the same day as the most recent dose of tazemetostat, the subject was hospitalized due to Grade 3 **Femoral artery occlusion**. The subject had received 386 doses of tazemetostat (308,800 mg total) prior to the onset of the Grade 3 **Femoral artery occlusion**.

On 24 Oct 2017 (Study Day 196), a chest x-ray showed lung parenchyma without infiltrations. Study drug was interrupted due to the **Femoral artery occlusion**. The subject was treated with sodium chloride, acetylsalicylic acid, cefazolin, clopidogrel, enoxaparin, estazolam, simethicone, sodium dihydrophosphate/sodium hydrophosphate, atorvastatin, and clopidogrel.

On 25 Oct 2017 (Study Day 197), the event of Grade 3 **Femoral artery occlusion** was considered resolved, and the subject was discharged from the hospital. Study drug was reinitiated at the same prior dose level on that day.

The investigator reported the event of **Femoral artery occlusion** was not related to tazemetostat.

In addition to previous medications, concomitant medications taken within 14 days of the start of the **Osmotic demyelination syndrome** and S**ubclavian vein thrombosis** included acetylsalicylic acid, atorvastatin, clopidogrel, paracetamol/tramadol, phospholipids, and herbal preparations.

Study drug was interrupted on 22 Nov 2017 (Study Day 225) and reinitiated on 29 Nov 2017 (Study Day 232) at a reduced dose of 600 mg BID due to Grade 3 Transaminases increased.

On 11 Jul 2018 (Study Day 456), a computerized tomography scan showed a new lesion and lymph nodes progression (Richter transformation).

On 13 Jul 2018 (Study Day 458), 1 day since the most recent dose of tazemetostat, the subject was hospitalized due to Grade 3 **Osmotic demyelination syndrome** and Grade 3 **Subclavian vein thrombosis**. The subject had received 898 doses of tazemetostat (628,000 mg total) prior to the onset of the Grade 3 **Osmotic demyelination syndrome** and Grade 3 **Subclavian vein thrombosis**. Symptoms included diplopia. Magnetic resonance imaging suggested that within the bridge and midbrain capsule, there were banded hyper-reversible changes, which could correspond to central myelinolysis of the bridge or other atypical demyelization. Study drug was discontinued due to disease progression with the last dose taken on 12 Jul 2018 (Study Day 457). The subject was treated with enoxaparin.

On 24 Jul 2018 (Study Day 469), another magnetic resonance imaging scan showed regression of pontine.

On 28 Aug 2018 (Study Day 504), the subject was discharged from the hospital.

The investigator reported the events of **Osmotic demyelination syndrome** and **Subclavian vein thrombosis** were not related to tazemetostat. There was massive infiltration of lymphoma at the same location as the **Subclavian vein thrombosis**.

On 18 Sep 2018 (Study Day 525), the subject died due to disease progression. It was unknown if an autopsy was performed. The events of **Osmotic demyelination syndrome** and **Subclavian vein thrombosis** were ongoing at the time of death.

Subject Number	40042002
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	17 May 2018 (Study Day 1)
Last Dose Date (Study Day):	15 Jan 2019 (Study Day 244)
Fatal SAE	Chronic kidney disease（慢性腎臓病）
Nonfatal SAE	Chronic kidney disease（慢性腎臓病）

Subject 40042002 is a 7[redacted]-year-old female who was diagnosed with follicular lymphoma (FL) on 26 Aug 2016. On 23 Apr 2018, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. She was previously treated with cyclophosphamide/vincristine (27 Sep 2016 to 02 Jan 2017), prednisone/rituximab (27 Sep 2016 to 28 Feb 2017), cyclophosphamide/doxorubicin/vincristine (23 Jan 2017 to 28 Feb 2017), and bendamustine hydrochloride (23 Mar 2018 to 24 Mar 2018).

Relevant past medical history included cholecystectomy (1996), thyroidectomy (2000), intestinal resection and large intestine polyp (2015), thoracic cavity drainage (Sep 2016), pneumonia (Nov 2016), and skull fracture (Feb 2017). Relevant ongoing medical conditions included hypertension and obesity (1960), abdominal hernia and hypothyroidism (2000), acute coronary syndrome, myocardial ischaemia, and Type 2 diabetes mellitus (2002), osteoarthritis (2013), gout (2014), lymphoedema and renal failure chronic (2016), Klebsiella urinary tract infection (Feb 2017), central venous catheterization (25 May 2017), and insomnia (Apr 2018).

The subject received the first dose of tazemetostat 800 mg BID on 17 May 2018 (Study Day 1).

Concomitant medications taken within 14 days of the start of the **Chronic kidney disease** included acetylsalicylic acid, allopurinol, amoxi-clavulanico, bisoprolol, calcium, desloratadine, enoxaparin, hydroxyzine, insulin human, insulin lispro, ipratropium, levothyroxine, pantoprazole, ramipril, and torasemide.

On 19 Dec 2018 (Study Day 217), relevant laboratory results included creatinine 1.81 mg/dL (reference range not provided).

On 14 Jan 2019 (Study Day 243), the subject visited the emergency department due to weakness. Laboratory results (not provided) revealed exacerbation of renal failure and the subject was hospitalized for serious adverse event (SAE) of Grade 4 **Chronic kidney disease**. The subject had a medical history of chronic renal failure since 2016 which was suspected to be due to diabetes. Given the prior anticancer therapies for lymphoma had included many kidney toxic drugs and the medical history of urinary tract infections, the subject was constantly monitored for creatinine and estimated glomerular filtration rate (eGFR) during her tazemetostat treatment and had been found to be stable. The subject required dialysis, which had never previously been required. The subject had received 486 doses of tazemetostat (388,800 mg total) prior to the onset of the Grade 4 **Chronic kidney disease**. Treatment for the event given from 14 Jan 2019 to 28 Jan 2019 included acetylsalicylic acid, amiodarone, calcium chloride, enoxaparin, fentanyl, fluconazole, insulin, levothyroxine, magnesium chloride, malic acid, meropenem, norepinephrine, potassium, propofol, sodium chloride, and sodium citrate. The treatments included multiple anti-infectives (fluconazole, meropenem); however, the exact reason for these medications was not reported. The report notes an ongoing urinary tract infection and the occurrence of sepsis.

On 15 Jan 2019 (Study Day 244), study drug was discontinued due to Grade 4 **Chronic kidney disease**, with the last dose taken that day. Additional treatment given from 31 Jan 2019 to 04 Feb 2019 included acetylsalicylic acid, albumin human, allopurinol, bisoprolol, calcium chloride, ceftriaxone, dextromethorphan, dopamine, drotaverine, electrolytes not otherwise specified, fluconazole, furosemide, glucose, heparin, insulin bovine, insulin glargine, insulin glulisine, insulin lispro, levothyroxine, mannitol, morphine, omeprazole, pantoprazole, potassium, ramipril, sodium bicarbonate, sodium chloride, and torsemide.

On 04 Feb 2019 (Study Day 264), the subject's Grade 4 **Chronic kidney disease** worsened. The subject died that day due to **Chronic kidney disease** (Grade 5). The subject had received 488 doses of tazemetostat (390,400 mg total) prior to the onset of the Grade 5 **Chronic kidney disease**.

The investigator reported the event of **Chronic kidney disease** was not related to tazemetostat. It was due to the subject's ongoing urinary tract infection which resulted in dialysis and sepsis.

Subject Number	60012023
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	05 Dec 2018 (Study Day 1)
Last Dose Date (Study Day):	Ongoing
Nonfatal SAE	Hypoxia（低酸素症）

Subject 60012023 is a 6[redacted]-year-old female who was diagnosed with follicular lymphoma (FL) on an unknown date. The diagnosis was confirmed at screening on 15 Jan 2014. On 14 Nov 2018, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. She was previously treated with cyclophosphamide/prednisone/rituximab/08191301 (07 Mar 2013 to 22 Nov 2013), bendamustine (05 Mar 2014 and 06 Mar 2014 to 25 Jul 2014), obinutuzumab (05 Mar 2014 to 25 Jul 2014 and 22 Sep 2014 to Jul 2016), and investigational antineoplastic drugs (BTCT4465A; 28 Sep 2018 to 06 Nov 2018).

Relevant past medical history included pyrexia (04 Dec 2018 to 05 Dec 2018). Relevant ongoing medical conditions included coronary arterial stent insertion (Oct 2013), chest pain (2015), dyslipidaemia (2017), swelling face (02 Aug 2018), pleural effusion (13 Aug 2018), dyspnoea exertional (01 Sep 2018), neutropenia (21 Nov 2018), and Herpes zoster (26 Nov 2018).

The subject received the first dose of tazemetostat 800 mg BID with prednisolone on 05 Dec 2018 (Study Day 1).

Concomitant medications taken within 14 days of the start of the **Hypoxia** included bisoprolol, acetylsalicylic acid, trandolApr, pantoprazole, glyceryl trinitrate, rosuvastatin, valaciclovir, docusate, sennoside A+B, pregabalin, and mupirocin.

On 05 Jan 2019 (Study Day 32), the subject experienced a non-serious adverse event (AE) of Grade 1 Dyspnoea that was ongoing at the time of the SAE of **Hypoxia**.

On 14 Jan 2019 (Study Day 41), the subject experienced an event of Grade 3 **Hypoxia** and was hospitalized on the same day. It was noted that the subject had relapsed in Aug 2018 with pleural effusions due to lymphoma involvement and pleural effusions were noted as non-target lesions at study baseline. A pleural tap was performed under interventional radiology that day (14 Jan 2019). The subject's oxygen level was below 90% (at rest), pre-pleural tap. After draining about 1.5 L of fluid from the subject's right chest, the oxygen level decreased to 85% and the oxygen flow was increased to 5 L. Cytology was performed on the pleural fluid which confirmed lymphoma involvement. The subject had received 82 doses of tazemetostat (65,600 mg total) prior to the onset of the Grade 3 **Hypoxia**. No action was taken with study drug due to the **Hypoxia**. Treatment for the event included furosemide.

On 15 Jan 2019 (Study Day 42), the subject's oxygen saturation was at 91%. A computed tomography (CT) scan performed that day revealed bilateral pleural effusions. The oxygen flow was maintained between 1L to 4L per minute during hospitalization (from 14 Jan 2019 to 06 Feb 2019).

On 06 Feb 2019 (Study Day 64), the event of Grade 3 **Hypoxia** was considered resolved. The oxygen level was back at baseline level (93%) and the subject was discharged from the hospital.

The investigator reported the event of **Hypoxia** was not related to tazemetostat. It was due to

the subject's known history of pleural effusion which was related to the underlying lymphoma. The subject was continuing on study drug at the time of data cutoff.

Subject Number	60022023
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	12 Jul 2018 (Study Day 1)
Last Dose Date (Study Day):	Ongoing
Nonfatal SAE	Sepsis（敗血症）

Subject 60022023 is a 6[redacted]-year-old female who was diagnosed with follicular lymphoma (FL) on 15 May 2014. On 06 Jul 2018, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. She was previously treated with bendamustine/rituximab (27 Apr 2015 to 22 Jun 2015), bendamustine (20 Jul 2015-Oct 2015), and cyclophosphamide/doxorubicin/prednisone/vincristine (Oct 2016 to Feb 2017). The subject also received radiotherapy for lymphadenopathy at the following sites: abdominal and pelvic/inguinal in 2014, abdominal and pelvic at right groin and right pelvis on 17 Jun 2016, and thoracic adenopathy at right axilla and neck on 19 Jan 2018.

No past medical history was reported. Relevant ongoing medical conditions included blood cholesterol increased and hypertension (1999), osteoporosis (2010), muscular weakness (2014), fatigue and hyperparathyroidism (2015), asthma (2016), rhinitis allergic (2017), and oedema peripheral (Jan 2017).

The subject received the first dose of tazemetostat 800 mg BID on 12 Jul 2018 (Study Day 1).

Concomitant medications taken within 14 days of the start of **Sepsis** included fosavance, perindopril, prochlorperazine, rosuvastatin, and amlodipine/amlodipine besilate.

On 29 Oct 2018 (Study Day 110), the same day as the most recent dose of tazemetostat, the subject experienced a serious adverse event (SAE) of Grade 4 **Sepsis**. That day, the subject was assessed at a local emergency department for a nonserious adverse event (AE) of Grade 3 Urinary Tract Infection. The subject had a history of urinary tract infection on study. No hospitalization was required. The subject was in her usual state of health up until about 2 days prior to her presentation to the emergency department when she developed some generalized malaise and fevers, as well as possible right-sided flank pain. There was no headache, neck stiffness, visual disturbances, chest pain, shortness of breath, cough, nausea, vomiting, diarrhea, constipation or irritative urinary symptoms or hematuria. There were no rashes or active joints. There was no recent surgery or instrumentation or a dental procedure as such. A blood culture performed that day was positive for *Streptococcus bovis*. Relevant laboratory results included blood creatinine 52, hemoglobin 113, platelets 159, and white blood cells 15.5 (units and reference ranges not provided). Urinalysis was considered abnormal with 21 to 50 white blood cells per high power field and greater than 100 red blood cells per high power field. An electrocardiogram revealed sinus tachycardia with a normal PR interval at 154 msec. The subject had received 220 doses of tazemetostat (176,000 mg total) prior to the onset of the Grade 4 **Sepsis**. No action was taken with study drug due to the **Sepsis**. Treatment for the event included amoxicillin, amoxicillin with clavulanate potassium, and ceftriaxone.

On 30 Oct 2018 (Study Day 111), the SAE of Grade 4 **Sepsis** was considered resolved. Blood cultures performed that day were negative for *Streptococcus bovis*. Relevant laboratory results included normal routine electrolytes, creatinine normal, liver enzymes normal, troponin negative, lactate normal, hemoglobin 114, platelets 135 and white blood cells 11.5 (units and reference ranges not provided). A chest X-ray was normal. The subject's fever and flank pain

was resolved. Her condition was better, and she felt good otherwise.

The investigator reported the event of **Sepsis** was not related to tazemetostat.

On 31 Oct 2018 (Study Day 112), relevant laboratory results included creatinine 64 µmol/L (reference range: 50–98), hemoglobin 114 g/L (reference range: 120–160), platelets 166×10^9/L (reference range: 150–400), and white blood cells 5.1×10^9/L (reference range: 4–11). Vital signs included blood pressure 149/75 mmHg, heart rate 93 bpm, and temperature 36.5 °C.

The subject was hospitalized on 02 Nov 2018 (Study Day 114) to facilitate antibiotic administration, to expedite investigations and consultation by specialist regarding the *Streptococcus bovis* bacteremia. A physical examination performed that day revealed no stress; vital signs included temperature 36.9 °C, pulse 72 bpm, blood pressure 149/74 mmHg, respiration 18 breaths per minute, and oxygen saturation 100% at room air. Heart sounds were normal with no extra sounds or murmurs. Jugular nervous pressure was not elevated. She presented symptoms of lymphedema like changes in the lower extremities. Lungs were clear to auscultation with no crackles or wheeze. Abdomen was soft and nontender with no obvious organomegaly or masses. There was no costovertebral angle tenderness. Oropharynx was clear.

On 03 Nov 2018 (Study Day 115), the subject was completely asymptomatic. Her myalgia and dysuria were resolved and she had been eating well. She denied nausea or vomiting, rigors and was ambulating. Relevant laboratory results included leukocyte count 3.6, hemoglobin 97, platelets 135, creatinine 40, and normal electrolytes (units and reference ranges not provided). A computed tomography (CT) scan of the abdomen and pelvis revealed no significant interval change compared to a previous scan performed on 25 Oct 2018. There was no evidence of abdominal adenopathy which was consistent with the subject's lymphoma history and no trace of abscess as well.

On 04 Nov 2018 (Study Day 116), an echocardiogram did not reveal any clinically significant results. The subject was discharged from the hospital.

The subject was continuing in the study at the time of data cutoff.

Subject Number	80022025
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	02 Oct 2017 (Study Day 1)
Last Dose Date (Study Day):	ongoing
Nonfatal SAE	Herpes zoster（帯状疱疹） Post herpetic neuralgia（ヘルペス後神経痛） Syncope（失神）

Subject 80022025 is a 5[redacted]-year-old white female who was diagnosed with follicular lymphoma on 21 Jan 2015. On 31 May 2017, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. She was previously treated with bendamustine/rituximab (Feb 2015 to Dec 2015).

Relevant past medical history included cough (2017 to 02 Oct 2017). Relevant ongoing medical conditions included anxiety (03 May 2017), arthralgia (2015), asthma (2015), back pain (26 Oct 2016), depression (2015), dyspnoea (2015), eczema (08 Jun 2017), fatigue (16 Mar 2015), gastrooesophageal reflux disease (2015), glaucoma (2015), hypertension (2015), nausea (31 May 2017), psoriasis (10 May 2017), hot flush (unknown), and migraine (unknown).

The subject received the first dose of tazemetostat 800 mg BID on 02 Oct 2017 (Study Day 1).

Concomitant medications taken within 14 days of the start of **Herpes zoster** and **Post herpetic neuralgia** included acetylsalicylic acid, esomeprazole, salbutamol, diphenhydramine, latanoprost, montelukast, budesonide/formoterol fumarate, meloxicam, ondansetron, prochlorperazine, clobetasol, sulfadiazine, olanzapine, and fluoxetine.

On 06 Jan 2018 (Study Day 97), the same day as the most recent dose of tazemetostat, the subject was hospitalized due to Grade 3 **Herpes zoster** of the left arm, affecting dermatomes C7 and C8. The subject had received 188 doses of tazemetostat (150,400 mg total) prior to the onset of the Grade 3 **Herpes zoster**. Vital signs showed blood pressure 174/95 mmHg, heart rate 91 bpm, respiratory rate 18 breaths per minute, and temperature 36.9ºC. Treatment included valaciclovir hydrochloride and aciclovir for **Herpes zoster**, in addition to intravenous (IV) morphine sulfate and oxycodone.

On 10 Jan 2018 (Study Day 101), the subject went into urgent care due to worsening pain. Study drug was interrupted due to **Herpes zoster**. Oxycodone, morphine sulfate, aciclovir, and valaciclovir continued.

On 12 Jan 2018 (Study Day 103), the event of Grade 3 **Herpes zoster** was considered resolved. On 15 Jan 2018 (Study Day 106), study drug was restarted.

The investigator reported the event of **Herpes zoster** was not related to tazemetostat.

On 22 Jan 2018 (Study Day 113), the same day as the most recent dose of tazemetostat, the subject was hospitalized for pain management of Grade 3 **Post herpetic neuralgia** to the left arm following herpes zoster infection. The subject also experience Grade 2 Peripheral sensory neuropathy that day. The subject had received 212 doses of tazemetostat (169,600 mg total) prior to the onset of the Grade 3 **Post herpetic neuralgia**. No action was taken with study drug due to the **Post herpetic neuralgia**. Treatment included oxycodone, ibuprofen, and

gabapentin.

On 27 Jan 2018 (Study Day 118), the event of Grade 3 **Post herpetic neuralgia** improved to Grade 2. Treatment included amitriptyline, petrolatum, and lidocaine cream. The event of Grade 2 Post herpetic neuralgia was considered resolved on 16 Apr 2018 (Study Day 197).

The investigator reported the event of **Post herpetic neuralgia** was not related to tazemetostat. The investigator considered **Post herpetic neuralgia** to be related to Herpes zoster.

Concomitant medications taken within 14 days of the start of **Syncope** included acetylsalicylic acid, amlodipine, budesonide with formoterol fumarate, diphenhydramine, esomeprazole, fluoxetine, ibuprofen, latanoprost, meloxicam, montelukast, olanzapine, ondansetron, pantoprazole, prochlorperazine, rosuvastatin, and salbutamol.

On 29 Oct 2018 (Study Day 393), the same day as the most recent dose of tazemetostat, the subject reported an episode of loss of consciousness and was diagnosed with Grade 3 **Syncope**. The subject described that the episode manifested while having dinner when she took a large bite. Based on the subject's medical history, **Syncope** was more likely due to vasovagal syncope, swallowing syncope from excessive distension of the vagus nerve after large bite of food and further exacerbated by a large gulp of carbonated beverage consumption. The subject had prior syncope episodes which appeared to be vasovagal/anxiety related and with infrequent palpitations that appeared to be related to stress. Transthoracic echocardiogram was reviewed and was found to be normal. The subject had Grade 3 Blood pressure increased from 28 Aug 2018 (Study Day 331) to 24 Sep 2018 (Study Day 358) and Grade 3 hypertension in the morning (no adverse event reported), which was resolved in the evening after taking amlodipine; amlodipine dosage was increased to 10 mg by cardiology on 23 Oct 2018. No action was taken with the study drug due to **Syncope**. The subject had received 770 doses of tazemetostat (616,000 mg total) prior to the onset of the Grade 3 **Syncope**. No treatment was given for the event. The event resolved on the same day.

The subject was continuing on study drug at the time of the data cutoff.

Subject Number	80062009
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	26 Jan 2018 (Study Day 1)
Last Dose Date (Study Day):	Ongoing
Nonfatal SAE	Transient global amnesia （一過性全健忘）

Subject 80062009 is a 5[redacted]-year-old male who was diagnosed with follicular lymphoma (FL) on 20 Jun 2016. On 19 Jan 2018, the subject was enrolled in E7438-G000-101: An Open- Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with rituximab/cyclophosphamide/doxorubicin/ vincristine (20 Jul 2016 to 02 Nov 2016), prednisone (20 Jul 2016 to Nov 2016), and idelalisib (15 Nov 2017 to 10 Jan 2018).

Relevant past medical history included vasectomy (1987). Relevant ongoing medical conditions included bradycardia and nausea (2016), pollakiuria (19 Jan 2018), deafness and erectile dysfunction (unknown).

The subject received the first dose of tazemetostat 800 mg BID on 26 Jan 2018 (Study Day 1).

Concomitant medications taken within 14 days of the start of the **Transient global amnesia** included ibuprofen, paracetamol, rosuvastatin, and tadalafil.

On 09 Aug 2018 (Study Day 196), 1 day after the most recent dose of tazemetostat, the subject experienced a serious adverse event (SAE) of Grade 1 **Transient global amnesia** and was hospitalized on the same day. The subject's wife called the clinic and informed that for 4 hours the subject could not remember that he was on treatment for lymphoma or any details from the previous day. As per advice, they proceeded to the emergency department of a local hospital. A computed tomography scan of the head performed that day (09 Aug 2018) was within the normal limits and a carotid Doppler test showed no significant disease. The subject had received 390 doses of tazemetostat (312,000 mg total) prior to the onset of the Grade 1 **Transient global amnesia**. No action was taken with study drug due to the **Transient global amnesia**. The event of Grade 1 **Transient global amnesia** was considered resolved on the same day.

On 10 Aug 2018 (Study Day 197), the subject was discharged from the hospital on prophylactic baby aspirin (acetylsalicylic acid) and atorvastatin. On 17 Aug 2018 (Study Day 204), a brain magnetic resonance imaging showed no evidence of acute intracranial hemorrhage, edema, hydrocephalus or mass effect. The subject was examined again on 05 Sep 2018 (Study Day 223), and there were no subsequent episodes of amnesia and no cognitive changes, neurologic symptoms, or other concerning symptoms during continued treatment with tazemetostat.

The investigator reported the event of **Transient global amnesia** was possibly related to tazemetostat. Increased age and the use of tadalafil were confounding factors.

The subject was continuing on study drug at the time of the data cutoff.

Subject Number	10012001
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	09 Jul 2015 (Study Day 1)
Last Dose Date (Study Day):	22 Sep 2015 (Study Day 76)
Nonfatal SAE	Gastric disorder（胃障害）

Subject 10012001 is a 7[redacted]-year-old female who was diagnosed with follicular lymphoma on 19 Nov 2008. On 10 Jun 2015, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma (DLBCL). At study entry, the subject's current diagnosis was reported as DLCBL. She was previously treated with doxorubicin/cyclophosphamide/vincristine/rituximab/ methylprednisolone (Apr 2009 to Sep 2009) and everolimus/rituximab (Mar 2012).

Relevant past medical history included partial thyroidectomies (1970 and 19 Nov 2008) and cataract (1995 and 1998). Relevant ongoing medical conditions included hypercholesterolaemia (2000), hypothyroidism (1970), intervertebral disc protrusion (1991), varicose vein operation (1998), osteoarthritis (2015), depression (Jan 2015), and goitre (unknown start).

The subject received the first dose of tazemetostat 800 mg BID on 09 Jul 2015 (Study Day 1).

Concomitant medications taken within 14 days of the start of Grade 2 **Gastric disorder** included levothyroxine, atorvastatin, venlafaxine, and paracetamol.

Study drug was interrupted on 23 Sep 2015 (Study Day 77) due to non-serious adverse events (AEs) of Grade 2 Nausea and Grade 2 Asthenia and was not reinitiated.

On 02 Oct 2015 (Study Day 86), 10 days since the most recent dose of tazemetostat, the subject was hospitalized due to Grade 2 **Gastric disorder**, with symptoms of nausea, constipation, and pain. The subject had received 152 doses of tazemetostat (121,600 mg total) prior to the onset of the Grade 2 **Gastric disorder**. On admission, disease progression was radiologically confirmed. The subject was treated with prednisone, lactulose, and phloroglucinol/trimethyl phloroglucinol. Additional treatment included alprazolam, zopiclone, and allopurinol. Study drug was discontinued due to disease progression with the last dose taken on 22 Sep 2015 (Study Day 76). No hospital discharge date was provided.

On 29 Oct 2015 (Study Day 113), the event of Grade 2 **Gastric disorder** was considered resolved.

The investigator reported the event of **Gastric disorder** was not related to tazemetostat. The symptoms were due to disease progression.

Subject Number	10012010
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	04 Nov 2015 (Study Day 1)
Last Dose Date (Study Day):	15 Feb 2017 (Study Day 470)
Nonfatal SAE	Neutropenia（好中球減少症）

Subject 10012010 is a 6[redacted]-year-old male who was diagnosed with follicular lymphoma in 2004. On 30 Sep 2015, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with doxorubicin/cyclophosphamide/rituximab/ methylprednisolone/vincristine/prednisone (Aug 2008 to Feb 2009), etoposide/ rituximab/carboplatin/ifosfamide (Apr 2010 to Jun 2010), carmustine/cytarabine/etoposide/ melphalan (Jul 2010), cisplatin/cytarabine/dexamethasone/rituximab (Oct 2011 to Dec 2011), rituximab (Feb 2012 to Dec 2013), and an investigational drug (abexinostat, Mar 2014 to Sep 2015). The subject received radiotherapy to the left inguinal lymph node (2005) and right inguinal lymph node (04 Mar 2010 to 05 Mar 2010); in addition this subject underwent left sub maxillary exeresis (2006) and tubulus adenocarcinoma exeresis (Apr 2008).

Relevant ongoing medical conditions included type 2 diabetes mellitus (2011) and folliculitis (2015).

The subject received the first dose of tazemetostat 800 mg BID on 04 Nov 2015 (Study Day 1).

Concomitant medications taken within 14 days of the start of Thrombocytopenia included metformin and paracetamol.

On 19 Jan 2017 (Study Day 443), the same day as the most recent dose of tazemetostat, the subject experienced a non-serious adverse event (AE) of Grade 2 Thrombocytopenia (platelet count 64 x 10^9/L, reference range: 150-400). The subject had received 884 doses of tazemetostat (707,200 mg total) prior to the onset of the Grade 2 Thrombocytopenia.

On 01 Feb 2017 (Study Day 456), the same day as the most recent dose of tazemetostat, the subject experienced a non-serious AE of Grade 3 Neutropenia (neutrophil count 0.642 ×10^9/L, reference range: 1.847-6.138). The subject had received 874 doses of tazemetostat (699,200 mg total) prior to the onset of the Grade 3 Neutropenia.

On 16 Feb 2017 (Study Day 471), platelet count was reported to be 54 × 10^9/L, and study drug was interrupted due to ongoing Thrombocytopenia.

On 23 Feb 2017 (Study Day 478), Thrombocytopenia worsened to Grade 3 event (platelet count 46 ×10^9/L).

On 02 Mar 2017 (Study Day 485), Thrombocytopenia improved to a Grade 1 event (platelet count 83 ×10^9/L). The non-serious AE of Grade 1 Thrombocytopenia remained ongoing and study drug remained interrupted.

The investigator reported the event of Thrombocytopenia was probably related to tazemetostat.

Concomitant medications taken within 14 days of the start of **Neutropenia** included metformin and paracetamol.

On 02 Mar 2017 (Study Day 485), 15 days since the most recent dose of tazemetostat, the event of **Neutropenia** (neutrophil count 0.3×10^9/L), was upgraded to Grade 4 and was considered

medically important and reported as a serious adverse event. The subject had received 940 doses of tazemetostat (752,000 mg total) prior to the onset of the Grade 4 **Neutropenia**. No action was taken with study drug as it was previously interrupted. The subject was treated with lenograstim.

On 16 Mar 2017 (Study Day 499), the SAE of Grade 4 **Neutropenia** improved to a non-serious Grade 2 AE (neutrophil count 1.2 $\times 10^9$/L).

On 22 Mar 2017 (Study Day 505), non-serious Grade 2 Neutropenia worsened to a non-serious Grade 3 event (neutrophil count 0.7 $\times 10^9$/L) and remained ongoing.

The investigator reported the event of **Neutropenia** was probably related to tazemetostat.

On 23 Mar 2017 (Study Day 506), study drug was discontinued due to Thrombocytopenia, with the last dose taken on 15 Feb 2017 (Study Day 470).

On 02 Dec 2017 (Study Day 760), the subject died due to progressive disease.

Subject Number	10012018
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	03 Aug 2016 (Study Day 1)
Last Dose Date (Study Day):	24 Jan 2017 (Study Day 175)
Nonfatal SAE	Pyrexia（発熱）

Subject 10012018 is a 4[redacted]-year-old male who was diagnosed with follicular lymphoma on 02 Apr 2012. On 06 Jul 2016, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with cyclophosphamide/doxorubicin/vincristine/ rituximab (Jun 2012 to Jul 2013), dexamethasone/oxaliplatin/rituximab (Aug 2013 to unknown 2013), cytarabine/bendamustine/etoposide/melphalan/rituximab (May 2014 to unknown 2014), and idelalisib/rituximab (Jun 2015 to Dec 2015).

Relevant past medical history included cyst removal (1974) and splenic rupture (04 Jan 2016 to 04 Jan 2016).

The subject received the first dose of tazemetostat 800 mg BID on 03 Aug 2016 (Study Day 1). Tazemetostat was interrupted on 31 Aug 2016 (Study Day 29) due to Grade 2 Thrombocytopenia and resumed at a reduced dose of 600 mg BID on 14 Sep 2016 (Study Day 43). Study drug was interrupted on 25 Jan 2017 (Study Day 176) due to Grade 2 Anaemia (hemoglobin: 86 g/L; reference range: 130-170).

Concomitant medications taken within 14 days of the start of **Pyrexia** included valaciclovir, paracetamol, and phenoxymethylpenicillin.

On 29 Jan 2017 (Study Day 180), 5 days since the most recent dose of tazemetostat, the subject experienced a non-serious adverse event of Grade 2 Pyrexia. The subject had received 318 doses of tazemetostat (195,600 mg total) prior to the onset of the Grade 2 Pyrexia.

On 02 Feb 2017 (Study Day 184), 9 days since the most recent dose of tazemetostat, the Grade 2 **Pyrexia** became serious and the subject was hospitalized with suspicion of infection. The subject had received 321 doses of tazemetostat (203,800 mg total) prior to the onset of the Grade 2 **Pyrexia**. On admission, the subject's temperature was 39.5 °C and hemoglobin was 81 g/L. No action was taken with study drug as it was previously interrupted. No infection or etiology for the fever was found. The subject was treated with paracetamol.

On 03 Feb 2017 (Study Day 185), the subject was discharged from the hospital. On 04 Feb 2017 (Study Day 186), the SAE of Grade 2 **Pyrexia** improved to non-serious Grade 1 Pyrexia. The Grade 1 Pyrexia remained ongoing.

The investigator reported the event of Pyrexia was not related to tazemetostat.

Concomitant medications taken within 14 days of withdrawal from study drug included valaciclovir, paracetamol, and phenoxymethylpenicillin.

On 06 Feb 2017 (Study Day 188), study drug was discontinued per subject choice with the last dose taken on 24 Jan 2017 (Study Day 175). Ongoing events at the time of discontinuation included Grade 2 Anaemia and Grade 1 Pyrexia.

On 09 Jul 2018 (Study Day 706), the subject died. The cause of death was reported as graft versus host disease.

Subject Number	10032005
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	26 Aug 2015 (Study Day 1)
Last Dose Date (Study Day):	03 Sep 2015 (Study Day 9)
Nonfatal SAE	Hip fracture（股関節部骨折）

Subject 10032005 is an 8[redacted]-year-old female who was diagnosed with follicular lymphoma on 06 Jun 2002. On 12 Aug 2015, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. She was previously treated with doxorubicin/cyclophosphamide/interferon/ prednisone/vincristine (Aug 2002 to Jul 2003), fludarabine/mitoxantrone/rituximab (Sep 2003 to Dec 2003), veltuzumab (Dec 2006), bendamustine/rituximab (Sep 2008 to Nov 2008), rituximab (Dec 2011 to Jan 2012), abexinostat (Feb 2012 to Mar 2012), monoclonal antibodies (May 2012 to Jan 2013), and copanlisib (Mar 2014 to Aug 2014).

Relevant past medical history included Basedow's disease (1951 to 1956), hysterectomy and oophorectomy (1974), psoriasis (1994 to Dec 2004), squamous cell carcinoma (14 Aug 2009 to 25 Mar 2010), and cholecystectomy (Jan 1993). Relevant ongoing medical conditions included hypothyroidism (1956), polyarthritis (05 Jan 2004), rheumatic disorder (17 Jan 2005), hypercalcaemia (25 Aug 2015), and osteoporosis (unknown).

The subject received the first dose of tazemetostat 800 mg BID on 26 Aug 2015 (Study Day 1).

Concomitant medications taken within 14 days of the start of the **Hip fracture** included levothyroxine, tramadol, aluminum hydroxide/magnesium carbonate, and pamidronic acid.

On 04 Sep 2015 (Study Day 10), 1 day since the most recent dose of tazemetostat, the subject was hospitalized due to a Grade 2 **Hip fracture**. The fracture was a result of a fall at home. The subject had received 18 doses of tazemetostat (14,400 mg total) prior to the onset of the Grade 2 **Hip fracture**. The subject received midazolam and fentanyl for pain. Study drug was withdrawn that day as the subject withdrew consent from study participation, with the last dose taken on 03 Sep 2015 (Study Day 9). She was placed under palliative care.

The investigator reported the event of **Hip fracture** was not related to tazemetostat.

On 25 Sep 2015 (Study Day 31), the subject died due to disease progression. No autopsy was performed. The Grade 2 **Hip fracture** remained ongoing at the time of death.

Subject Number	10032020
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	04 May 2016 (Study Day 1)
Last Dose Date (Study Day):	25 Jun 2017 (Study Day 418)
Nonfatal SAE	Pancreatitis acute（急性膵炎）

Subject 10032020 is a 6[redacted]-year-old female who was diagnosed with follicular lymphoma on 22 Oct 2010. On 29 Feb 2016, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. She was previously treated with doxorubicin/cyclophosphamide/prednisone/ vincristine/rituximab (Jan 2011 to May 2011; rituximab to Jun 2013), lenalidomide (May 2011 to Jun 2011), cisplatin/dexamethasone/cytarabine (Apr 2014 to May 2014), and idelalisib (Oct 2014 to Jun 2015).

Relevant ongoing medical conditions included drug hypersensitivity (sulfamethoxazole/ trimethoprim) (2010), hypertension (2010), oedema peripheral (18 Feb 2016), renal failure (May 2014), and type 2 diabetes mellitus (2006).

The subject received the first dose of tazemetostat 800 mg BID on 04 May 2016 (Study Day 1).

Concomitant medications taken within 14 days of the start of **Pancreatitis acute** included insulin glargine.

On 15 May 2017 (Study Day 377), the subject experienced non-serious adverse events (AEs) of Grade 1 Anal polyp and Grade 1 Diverticulum intestinal.

On 12 Jun 2017 (Study Day 405), the subject experienced non-serious Grade 2 Weight decreased (weight not reported).

On 19 Jun 2017 (Study Day 412), the subject experienced Grade 2 Acute tonsillitis and Grade 2 Pyrexia (temperature not reported), for which she received treatment with paracetamol.

On 26 Jun 2017 (Study Day 419), 1 day after the most recent dose of tazemetostat, the subject was hospitalized with abdominal pain, pyrexia, and glycemic troubles (glucose level not reported); the Grade 2 Acute tonsillitis resolved but the Grade 2 Pyrexia remained ongoing (temperature not reported). An unspecified scan showed sigmoidal diverticulosis, with an increase in the number of retroperitoneal and coelio mesenteric adenopathies. The subject was diagnosed with Grade 3 **Pancreatitis acute**. The subject had received 836 doses of tazemetostat (668,800 mg total) prior to the onset of Grade 3 **Pancreatitis acute**. The subject also experienced eating difficulties and a 6 kg weight loss. Study drug was interrupted on the day of hospital admission due to the **Pancreatitis acute**. Study drug was not reinitiated due to disease progression, with the last dose taken on 25 Jun 2017 (Study Day 418). Treatment for the **Pancreatitis acute** included tramadol and nefopam.

On 29 Jun 2017 (Study Day 422), the subject experienced a non-serious AE of Grade 2 Urinary tract infection staphylococcal, for which she received treatment with intravenous (IV) ceftriaxone sodium, cefalexin, and IV cloxacillin sodium. She also received metronidazole for the ongoing pyrexia, as well as macrogol 3350/potassium chloride/sodium bicarbonate/sodium chloride as a prophylaxis against constipation.

On 30 Jun 2017 (Study Day 423), the subject experienced a non-serious AE of Grade 2 Anaemia (hemoglobin not reported), for which she received transfusion with packed red blood

cells (number of units not reported).

On 08 Jul 2017 (Study Day 431), the event of Grade 2 Urinary tract infection staphylococcal resolved.

On 10 Jul 2017 (Study Day 433), the event of Grade 3 **Pancreatitis acute** was considered resolved and the subject was discharged from the hospital on the same day.

On 19 Jul 2017 (Study Day 442), the event of Grade 2 Pyrexia resolved (temperature not reported).

The investigator reported the event of **Pancreatitis acute** was not related to tazemetostat. The investigator considered the **Pancreatitis acute** to be related to follicular lymphoma progression.

The subject died on 22 Mar 2018 (Study Day 688) due to disease progression. The Grade 1 Anal polyp, Grade 1 Diverticulum intestinal, Grade 2 Weight decreased, and Grade 2 Anaemia were ongoing at the time of death.

Subject Number	10032035
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	18 Oct 2016 (Study Day 1)
Last Dose Date (Study Day):	12 Dec 2016 (Study Day 56)
Nonfatal SAE	Ascites（腹水）

Subject 10032035 is a 5[redacted]-year-old male who was diagnosed with follicular lymphoma of unknown grade on 30 Mar 2015. On 06 Oct 2016, the subject was enrolled in E7438-G000 101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with cyclophosphamide/etoposide/prednisone/rituximab (Apr 2015 to Jan 2016), obinutuzumab/atezolizumab (May 2016 to Jun 2016), and dexamethasone/oxaliplatin/ cytarabine (Jul 2016 to Aug 2016).

Relevant ongoing medical conditions included alcohol abuse (unknown) and tobacco user (1976).

The subject received the first dose of tazemetostat 800 mg BID on 18 Oct 2016 (Study Day 1).

Concomitant medications taken within 14 days of the start of Ascites included sulfamethoxazole/trimethoprim, folinic acid, and valaciclovir.

On 13 Dec 2016 (Study Day 57), 1 day after the most recent dose of tazemetostat, the subject experienced a serious adverse event (SAE) of Grade 3 **Ascites** and was hospitalized for lymphomatous ascites. The subject had received 112 doses of tazemetostat (89,600 mg total) prior to the onset of the Grade 3 **Ascites**. Vital signs showed blood pressure 120/60 mmHg, heart rate 83 bpm, temperature 36.8℃, and weight 71 kg. Study drug was discontinued that day due to disease progression, with the last dose taken on 12 Dec 2016 (Study Day 56). No treatment medications were reported for the **Ascites**.

On 16 Dec 2016 (Study Day 60), an ascites puncture revealed 93% lymphocytes, 3% neutrophils, and 5000 elements/mm^3 due to the progression of lymphoma.

On 23 Dec 2016 (Study Day 67), the event of Grade 3 **Ascites** was reported as having improved to a non-serious adverse event (AE) of Grade 2 Ascites. The subject was discharged from the hospital on an unknown date with discharge medications of spironolactone and furosemide.

The investigator reported the event of **Ascites** was not related to tazemetostat. The investigator considered the **Ascites** to be related to non-Hodgkin's lymphoma.

The subject died on 03 Jul 2017 (Study Day 259) due to disease progression. The Grade 2 Ascites was ongoing at the time of death.

Subject Number	10032036
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	18 Oct 2016 (Study Day 1)
Last Dose Date (Study Day):	31 May 2017 (Study Day 226)
Nonfatal SAE	Lower gastrointestinal haemorrhage （下部消化管出血）

Subject 10032036 is a 6[redacted]-year-old female who was diagnosed with diffuse large B cell lymphoma on 09 Jun 2009. On 06 Oct 2016, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. She was previously treated with cyclophosphamide/doxorubicin/prednisone/ rituximab/vincristine (Jun 2009 to Nov 2009), bendamustine/rituximab (Mar 2012 to Jun 2012), etoposide/ifosfamide/rituximab (Dec 2013 to Feb 2014), and idelalisib (Nov 2015 to May 2016).

Relevant past medical history included appendicectomy (1969), myocardial infarction (2004 and 2006 to 2009), pulmonary embolism (Jun 2016), and dyspepsia (21 Sep 2016 to unknown). Relevant ongoing medical conditions included abdominal pain (22 Oct 2015), anxiety (unknown), constipation (29 Mar 2016), decreased appetite (17 Jun 2009), hypercholesterolaemia (2009), hypertension (unknown), hypothyroidism (Nov 2014), neutrophil count increased (06 Oct 2016), and type 2 diabetes mellitus (unknown).

The subject received the first dose of tazemetostat 800 mg BID on 18 Oct 2016 (Study Day 1).

On 29 Mar 2017 (Study Day 163), the subject's hemoglobin was 75 g/L (reference range: 115-151) and a non-serious AE of Grade 3 Anaemia was reported. The subject was treated with 2 units of packed red blood cells the following day. The event resolved on 31 Mar 2017 (Study Day 165) (hemoglobin value not reported).

On 05 Apr 2017 (Study Day 170), hemoglobin was 110 g/L, a non-serious AE of Grade 1 Anaemia was reported, and study drug dosing was reduced from 800 mg BID to 600 mg BID due to the event.

On 18 Apr 2017 (Study Day 183), hemoglobin was 90 g/L and the event of Anaemia worsened to Grade 2.

On 05 May 2017 (Study Day 200), hemoglobin was 79 g/L and the event of Anaemia worsened to Grade 3. On 10 May 2017 (Study Day 205), hemoglobin decreased further to 74 g/L and the subject was treated with 4 units of packed red blood cells on 10 May 2017 and 25 May 2017 (2 units per day).

Concomitant medications taken within 14 days of the start of **Gastrointestinal haemorrhage** included bisoprolol, furosemide, fluindione, pravastatin, levothyroxine, candesartan, gliclazide, acetylsalicylic acid, *Sterculia urens*, omeprazole, and oxazepam.

On 31 May 2017 (Study Day 226), the same day as the most recent dose of tazemetostat, the subject experienced Grade 4 **Gastrointestinal haemorrhage** and was hospitalized on the same day for hematemesis and melena with hemodynamic instability and ongoing Grade 3 Anaemia (hemoglobin level not reported); all of the symptoms were related to disease progression. The subject had received 450 doses of tazemetostat (337,600 mg total) prior to the onset of the Grade 4 **Gastrointestinal haemorrhage**. The subject was treated with 2 units of packed red

blood cells.

On 01 Jun 2017 (Study Day 227), study drug was discontinued due to disease progression, with the last dose received on 31 May 2017 (Study Day 226). Treatment for the **Gastrointestinal haemorrhage** included intravenous (IV) esomeprazole magnesium, IV tranexamic acid as a prophylaxis against hemorrhage, 2 units of packed red blood cells, and fresh frozen plasma transfusion.

On 02 Jun 2017 (Study Day 228), the subject experienced a non-serious AE of Grade 2 Convulsion that resolved the same day.

On 06 Jun 2017 (Study Day 232), the event of Grade 4 **Gastrointestinal haemorrhage** was considered resolved and the subject was discharged from the hospital on an unspecified date.

On 14 Jun 2017 (Study Day 240), the subject underwent a digestive fibroscopy, which confirmed gastritis without an ulcer.

On 16 Jun 2017 (Study Day 242), hemoglobin was 83 g/L.

The investigator reported the event of **Gastrointestinal haemorrhage** was not related to tazemetostat. The investigator considered the event to be related to disease progression.

The subject died on 28 Aug 2017 (Study Day 315) due to disease progression. Grade 3 Anaemia was ongoing at the time of death.

Subject Number	10032038
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	09 Nov 2016 (Study Day 1)
Last Dose Date (Study Day):	31 Jan 2018 (Study Day 449)
Nonfatal SAE	Dizziness（浮動性めまい）

Subject 10032038 is a 6[redacted]-year-old female who was diagnosed with follicular lymphoma on 06 Mar 2014. On 10 Oct 2016, the subject was enrolled in E7438G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. She was previously treated with lenalidomide/ rituximab (Oct 2014 to Nov 2014) and cyclophosphamide/doxorubicin/prednisone/vincristine (Dec 2014 to Mar 2015).

Relevant past medical history included cerebral infarction (23 Mar 2013) and Henoch-Schonlein purpura (24 Oct 2014 to 05 Nov 2014 and 07 Nov 2014 to 20 Nov 2014). Relevant ongoing medical conditions included dyspepsia (2014) and fatigue (2016).

The subject received the first dose of tazemetostat 800 mg BID on 09 Nov 2016 (Study Day 1).

Concomitant medications taken within 14 days of the start of **Dizziness** included acetylsalicylic acid and arsenic trioxide w/bryonia alba/cinchona pube.

On 06 Dec 2016 (Study Day 28), 1 day since the most recent dose of tazemetostat, the subject was hospitalized due to Grade 3 **Dizziness**. The subject also experienced a non-serious adverse event (AE) of Grade 2 Hypertension (blood pressure not reported). The subject had received 54 doses of tazemetostat (43,200 mg total) prior to the onset of the Grade 3 **Dizziness**. Study drug was interrupted due to Grade 3 **Dizziness**. Cerebral magnetic resonance imaging was performed which was normal and no additional laboratory tests were performed. The subject was treated with acetylleucine.

On 08 Dec 2016 (Study Day 30), the event of Grade 3 **Dizziness** was considered resolved and the subject was discharged from the hospital. The non-serious AE of Grade 2 hypertension was ongoing. Study drug was resumed on the same day.

The investigator reported the event of **Dizziness** was not related to tazemetostat.

Study drug was discontinued on 31 Jan 2018 (Study Day 449) due to disease progression with last dose taken on the same day.

Subject Number	10042019
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	07 Nov 2016 (Study Day 1)
Last Dose Date (Study Day):	04 Dec 2016 (Study Day 28)
Nonfatal SAE	Anaemia（貧血） Lymphopenia（リンパ球減少症） Thrombocytopenia（血小板減少症） General physical health deterioration （全身健康状態低下）

Subject 10042019 is a 4[redacted]-year-old male who was diagnosed with follicular lymphoma in 2013. On 12 Oct 2016, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with doxorubicin/prednisone/rituximab/vincristine/cyclophosphamide (Jun 2013 to Oct 2013), dexamethasone/rituximab/cisplatin/cytarabine (Mar 2015 to Jun 2015; rituximab until Feb 2016), carboplatin/ifosfamide/etoposide/rituximab (Apr 2016 to Jun 2016), idelalisib (Jul 2016 to Aug 2016), rituximab/bendamustine (Aug 2016), gemcitabine/oxaliplatin/rituximab (Sep 2016), and doxorubicin/etoposide/ methylprednisolone/rituximab/vincristine/cyclophosphamide (Oct 2016 to Oct 2016).

Relevant ongoing medical conditions included abdominal pain and asthenia (12 Oct 2016), neutropenia (07 Nov 2016), and anaemia, constipation, lymphopenia, pleural effusion, and thrombocytopenia (unknown).

The subject received the first dose of tazemetostat 800 mg BID on 07 Nov 2016 (Study Day 1).

Concomitant medications taken within 14 days of the start of the **Anaemia**, **Thrombocytopenia**, **Lymphopenia**, and **General physical health deterioration** included glycerol, valaciclovir, alprazolam, chlorpromazine, enoxaparin, erythropoietin, metoclopramide, pantoprazole, paracetamol, paraffin, and potassium.

On 01 Dec 2016 (Study Day 25), the same day as the most recent dose of tazemetostat, the subject was hospitalized due to Grade 3 **Anaemia** (hemoglobin 67 g/L, reference range: 130-170) and Grade 4 **Thrombocytopenia** (platelet count 24 × 10^9/L, reference range: 150-500), which was considered life-threatening. Additional laboratory results that day included lymphocytes 0.24 × 10^9/L (reference range: 1-4) and neutrophils 1.11 × 10^9/L (reference range: 2-7.5). The subject had received 48 doses of tazemetostat (38,400 mg total) prior to the onset of the Grade 3 **Anaemia** and Grade 4 **Thrombocytopenia**.

On 02 Dec 2016 (Study Day 26), the subject was transfused 1 bag of platelets and 2 bags of red blood cells. The subject was discharged from the hospital that same day.

On 05 Dec 2016 (Study Day 29), 1 day since the most recent dose of tazemetostat, laboratory results showed Grade 4 **Lymphopenia** (lymphocytes 0.16 × 10^9/L), which was considered medically significant. Additional laboratory results that day included hemoglobin 76 g/L, platelet count 20 × 10^9/L (reference range: 150-400), and neutrophils 0.85 × 10^9/L (reference range: 1.8-7.5) (Grade 3 Neutropenia). The subject had received 56 doses of tazemetostat (44,800 mg total) prior to the onset of the Grade 4 **Lymphopenia**. No action was taken with study drug due to the Grade 3 **Anaemia**, Grade 4 **Thrombocytopenia**, or Grade 4

Lymphopenia. Study drug was discontinued due to disease progression, with the last dose taken on 04 Dec 2016 (Study Day 28). The subject was treated with filgrastim.

On 13 Dec 2016 (Study Day 37), the subject was hospitalized due to Grade 4 **General physical health deterioration**. The subject also experienced a non-serious adverse event of Grade 2 Hypogammaglobulinaemia. The subject had received 56 doses of tazemetostat (44,800 mg total) prior to the onset of the Grade 4 **General physical health deterioration**. No action was taken with study drug due to the Grade 4 **General physical health deterioration** as it was previously discontinued. The subject underwent thoracentesis, revealing that the follicular lymphoma had transformed into diffuse large B-cell lymphoma (DLBCL) in a pleural effusion. Treatment included prednisolone.

On 14 Dec 2016 (Study Day 38), the subject was treated with a red blood cells transfusion (number of units not reported) and the event of Grade 3 **Anaemia** was considered resolved the same day. The subject was treated with a single dose of human immunoglobulins on 15 Dec 2016 (Study Day 39) and the Grade 2 Hypogammaglobulinaemia resolved the same day.

On 18 Dec 2016 (Study Day 42), the subject was treated with platelet transfusion (number of units not reported). The events of Grade 4 **Thrombocytopenia**, Grade 4 **Lymphopenia**, Grade 3 Neutropenia, and Grade 4 **General physical health deterioration** resolved on 19 Dec 2016 (Study Day 43). Hospital discharge date was not provided.

The investigator reported the events of **Anaemia**, **Thrombocytopenia**, **Lymphopenia**, and **General physical health deterioration** were not related to tazemetostat. The events were symptoms of lymphoma progression.

The subject began new anticancer therapy with rituximab/etoposide/prednisone/vincristine/ cyclophosphamide/doxorubicin on 03 Jan 2017 (Study Day 58).

The subject died on 06 Apr 2017 (Study Day 151) due to pneumopathy. It was not known if an autopsy was performed.

Subject Number	10052013
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	16 Dec 2016 (Study Day 1)
Last Dose Date (Study Day):	09 Feb 2017 (Study Day 56)
Nonfatal SAE	Hyperuricaemia （高尿酸血症）

Subject 10052013 is a 7[redacted]-year-old male who was diagnosed with follicular lymphoma in 1994. On 16 Nov 2016, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with cyclophosphamide/prednisolone/mitoxantrone/ vincristine (Feb 1998 to Jun 1998), doxorubicin/cyclophosphamide/methylprednisolone/ rituximab/vincristine (Mar 2009 to Jul 2009), bendamustine/rituximab (Jun 2012 to Nov 2012), and lenalidomide/obinutuzumab (May 2015 to Nov 2015).

Relevant past medical history included aortic aneurysm (1999), arterial rupture (1999), cancer surgery (Sep 2015), bone prosthesis insertion (05 Sep 2016), and thrombocytopenia (06 Dec 2016 to 26 Jan 2017). Relevant ongoing medical conditions included cardiac failure chronic (2015), peripheral sensorimotor neuropathy (2015), thrombosis in device (Sep 2016), cough (Oct 2016), bronchial disorder, cataract, dyspnoea, fatigue, gout, hypercholesterolaemia, hypertension, lung disorder, lymphadenopathy, oedema peripheral, open angle glaucoma, supraventricular extrasystoles, and type 2 diabetes mellitus (unknown).

Urate at Screening was 490 µmol/L (reference range: 143–339).

The subject received the first dose of tazemetostat 800 mg BID on 16 Dec 2016 (Study Day 1).

Concomitant medications taken within 14 days of the start of **Hyperuricaemia** included allopurinol, levofloxacin, clarithromycin, acetylsalicylic acid, insulin glargine, lercanidipine, pantoprazole, clopidogrel, pravastatin, seretide, metformin, and nebivolol/hydrochlorothiazide.

On 30 Dec 2016 (Study Day 15), the same day as the most recent dose of tazemetostat, the subject, who had a history of hyperuricemia, experienced a medically important event of Grade 4 **Hyperuricaemia**. Laboratory results included urate 640 µmol/L. The subject had received 28 doses of tazemetostat (22,400 mg total) prior to the onset of the Grade 4 **Hyperuricaemia**. No action was taken with study drug due to the **Hyperuricaemia**. The subject was treated with allopurinol.

On 13 Jan 2017 (Study Day 29), laboratory results included urate 360 µmol/L and the event of Grade 4 **Hyperuricaemia** was considered resolved.

The investigator reported the event of **Hyperuricaemia** was not related to tazemetostat. The investigator reported the event was due to other unspecified alternative causes.

On 10 Feb 2017 (Study Day 57), study drug was discontinued due to radiologically confirmed disease progression with last dose taken on 09 Feb 2017 (Study Day 56).

On 13 Jun 2017 (Study Day 180), the subject died due to disease progression.

Subject Number	10102001
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	01 Feb 2016 (Study Day 1)
Last Dose Date (Study Day):	18 Mar 2016 (Study Day 47)
Nonfatal SAE	Anaemia（貧血） Pancytopenia（汎血球減少症） Pericarditis constrictive（収縮性心膜炎） General physical health deterioration （全身健康状態低下） Lung infection（肺感染） Sepsis（敗血症） Hypokalaemia（低カリウム血症）

Subject 10102001 is a 4[redacted]-year-old male who was diagnosed with follicular lymphoma on 07 Jun 2013. On 07 Jan 2016, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas. He was previously treated with rituximab/lenalidomide (Jun 2013 to Oct 2013), cyclophosphamide/ doxorubicin/vincristine/prednisone/rituximab (Oct 2013 to Jan 2014), carmustine/cytarabine/etoposide/melphalan (Feb 2014 to Mar 2014), rituximab/oxaliplatin/cytarabine/dexamethasone (Feb 2015 to Mar 2015), doxorubicin/ifosfamide/etoposide (Apr 2015 to Aug 2015), and bendamustine (Sep 2015 to Oct 2015).

Relevant past medical history included bile duct stenosis (15 Dec 2015 to 16 Dec 2015), jaundice (10 Dec 2015 to Jan 2016), lung disorder (Unknown 2015 to Dec 2015), and tonsillectomy (date unknown). Relevant ongoing medical conditions included chest pain (2015), Horner's syndrome (Nov 2014), immunosuppression (2015), and pyrexia (Jan 2016). During Screening (20 Jan 2016), the subject experienced Grade 2 Lung disorder (pneumopathy), Grade 2 Non-cardiac chest pain, and Grade 2 Pericardial effusion.

The subject received the first dose of tazemetostat 800 mg BID on 01 Feb 2016 (Study Day 1).

Concomitant medications taken within 14 days of the start of the **Pancytopenia**, **Lung infection**, **Pericarditis constrictive**, and **Sepsis** included omeprazole, paracetamol, prednisone, sulfamethoxazole/trimethoprim, oxycodone, valaciclovir, morphine, and pegfilgrastim.

The subject experienced Grade 3 Anaemia from 08 Feb 2016 (Study Day 8) to 11 Feb 2016 (Study Day 11), Grade 1 Epistaxis from 09 Feb 2016 (Study Day 9) onwards, and Grade 3 Non-cardiac chest pain from 10 Feb 2016 (Study Day 10) to 22 Feb 2016 (Study Day 22).

On 11 Feb 2016 (Study Day 11), the same day as the most recent dose of tazemetostat, the subject experienced medically important Grade 4 **Pancytopenia** and was hospitalized due to a Grade 3 **Lung infection**, Grade 3 **Pericarditis constrictive**, and Grade 4 **Sepsis**. The subject had received 20 doses of tazemetostat (16,000 mg total) prior to the onset of these events. The subject also experienced Grade 1 Dyspnoea, Grade 2 Anxiety, and Grade 2 Enterococcal infection on that day. Relevant laboratory results are provided in the table below. Clinical examination findings included hemodynamic stability, regular heart sounds with moderate tachycardia without audible heart murmur, vesicular murmur at both bases with crackling rale

at bases, normal abdominal examination, and normal neurological examination except for a known Claude Bernard Horner syndrome. The subject was slightly dyspneic on 4 L/min of oxygen, without signs of associated respiratory distress. Computed tomography (CT) scan did not show a pulmonary embolism but did show pleural effusion bilaterally and a decrease in the subject's pericardial effusion with maximum thickness facing the right atrium at 24 mm (versus 34 mm in the past CT scan). There was an increase in the parenchymal condensation lesions at the lower left lobe and the appearance of a lesion in the lower right lobe. Bilateral apical remodeling, probably due to a previous lesion, was observed predominantly on the right lung. The perifissural nodule on the right lung was stable at 25 mm. Blood culture from an implanted device was positive for *Enterococcus faecalis* and *Streptococcus pneumoniae*. A pulmonary angio-scanner showed pulmonary parenchymatous condensation with positive hemoculture and corpoculture. Study drug was interrupted due to the **Pancytopenia**. No action was taken with study drug due to the **Lung infection**, **Pericarditis constrictive**, or **Sepsis**. The subject was treated with platelet and red blood cell transfusions, midazolam, morphine, oxygen, prednisone, ceftriaxone, spiramycin, piperacillin/tazobactam, and alprazolam.

On 12 Feb 2016 (Study Day 12), the subject experienced Grade 2 Clostridium difficile colitis, Grade 3 Hyponatraemia, Grade 1 Oedema peripheral, and Grade 2 Tachycardia. Fecal culture was positive for Clostridium difficile. Laboratory results included red blood cell (RBC) count 2.92 x 10^{12}/L (reference range: 4.7-6.00), hematocrit 27.1% (reference range: 38-50), red cell distribution width (RDW) 17.8% (reference range: 11.5-14.0), eosinophils 0.00 x 10^9/L (reference range: 0.04-0.80), lymphocytes 0.06 x 10^9/L (reference range: 1.30-4.00), monocytes 0.02 x 10^9/L (reference range: 0.2-1), fibrinogen 10.3 g/L (reference range: 2.5-4.5), and C-reactive protein (CRP) around 400 mg/L (reference range not provided). Renal function was normal. The subject was treated with amoxicillin, fidaxomicin, potassium chloride, racecadotril, voriconazole, magnesium sulfate, cilastatin, sodium/imipenem monohydrate, cefepime, gentamicin, and methylprednisolone sodium succinate.

On 13 Feb 2016 (Study Day 13), the subject experienced Grade 2 Pneumonia pneumococcal, which did not resolve. Polymerase chain reaction (PCR) panel by nasal swab for respiratory virus was positive for Enterovirus and Rhinovirus due to pulmonary bacterial superinfection. The subject was treated with vancomycin, voriconazole, and potassium.

On 15 Feb 2016 (Study Day 15), the event of Grade 3 Hyponatraemia improved to Grade 1 and then resolved on 22 Feb 2016 (Study Day 22).

On 19 Feb 2016 (Study Day 19), a culture test from an implanted device was negative. Blood cultures from peripheral blood were negative. A transthoracic echocardiogram showed constrictive pericarditis with an increase in ventricular interdependence. Additional laboratory tests included D-Dimers 1,726 ng/mL (reference range not provided). A disseminated intravascular coagulation profile was negative. There were no schizocytes. Cytobacteriological examination of urine was negative. Aspergillus serology and Aspergillus antigenemia were negative.

On 22 Feb 2016 (Study Day 22), the event of Grade 1 Oedema peripheral worsened to Grade 2 and did not resolve.

On 23 Feb 2016 (Study Day 23), an echocardiogram was performed (results not available). The subject experienced constrictive chest pain, fever, and dyspnea.

Laboratory results on 01 Mar 2016 (Study Day 30) included RBC count 3.51 $\times 10^{12}$/L, hematocrit 33.6%, mean corpuscular hemoglobin concentration (MCHC) 29.8 g/dL (reference range: 32.0–36.0), RDW 18.6%, lymphocytes 0.90 $\times 10^9$/L, partial thromboplastin time (PTT) 45% (reference range: 33–39), and fibrinogen 7.9 g/L.

The subject experienced Grade 3 Non-cardiac chest pain from 02 Mar 2016 (Study Day 31) to 04 Mar 2016 (Study Day 33).

On 04 Mar 2016 (Study Day 33), the event of Grade 4 **Pancytopenia** improved to Grade 3 Pancytopenia. Study drug was reinitiated on that day at the reduced dose of 600 mg BID. The Grade 3 Pancytopenia did not resolve.

The subject experienced Grade 2 Non-cardiac chest pain from 06 Mar 2016 (Study Day 35) to 09 Mar 2016 (Study Day 38).

On 08 Mar 2016 (Study Day 37), the events of Grade 4 **Sepsis** and Grade 2 Clostridium difficile colitis were considered resolved, and the subject was discharged from the hospital. During discharge, oncology support care, such as reflexology and psychological care, were recommended. The subject showed favorable progress with weaning off oxygen.

On 10 Mar 2016 (Study Day 39), the event of Grade 3 **Lung infection** improved to a Grade 2 Lung infection. The Grade 2 Lung infection did not resolve. The events of Grade 3 **Pericarditis constrictive**, Grade 2 Enterococcal infection, and Grade 2 Tachycardia did not resolve.

The investigator reported the event of **Pancytopenia** was probably related to tazemetostat and the events of **Lung infection**, **Pericarditis constrictive**, and **Sepsis** were not related to tazemetostat.

In addition to previous medications (except prednisone, oxycodone, and pegfilgrastim), concomitant medications taken within 14 days of the start of **Anaemia** included oxygen, fidaxomicin, osmotan, hydroxyzine, magnesium sulfate, potassium, vancomycin, primaxin, tramadol, diosmectite, racecadotril, and paracetamol.

On 17 Mar 2016 (Study Day 46), the same day as the most recent dose of tazemetostat, the subject experienced medically important Grade 4 **Anaemia**. The subject had received 48 doses of tazemetostat (33,200 mg total) prior to the onset of the Grade 4 **Anaemia**. Relevant laboratory results are provided in the table below. No action was taken with study drug due to the **Anaemia**. The subject was treated with a red blood cell transfusion (2 units).

Study drug was discontinued on 19 Mar 2016 (Study Day 48) due to disease progression with the last dose taken on 18 Mar 2016 (Study Day 47).

In addition to previous medications, concomitant medications taken within 14 days of the start of the **General physical health deterioration** included piperacillin/ tazobactam.

On 20 Mar 2016 (Study Day 49), 2 days since the most recent dose of tazemetostat, the subject was hospitalized due to Grade 4 **General physical health deterioration**. The subject had received 52 doses of tazemetostat (35,600 mg total) prior to the onset of the Grade 4 **General physical health deterioration**. On that day, the event of Grade 4 **Anaemia** improved to Grade 3. The subject was treated with gentamicin, methylprednisolone, and vancomycin.

In addition to previous medications (except magnesium sulfate), concomitant medications taken within 14 days of the start of the **Hypokalaemia** included cefepime, gentamicin, and methylprednisolone.

On 23 Mar 2016 (Study Day 52), 5 days since the most recent dose of tazemetostat, the subject experienced medically important Grade 4 **Hypokalaemia**. The subject had received 52 doses of tazemetostat (35,600 mg total) prior to the onset of the Grade 4 **Hypokalaemia**. The subject's Dyspnoea worsened to Grade 3 on that day, and the subject also experienced Grade 2 Diarrhoea. Relevant laboratory results are provided in the table below. The subject was treated with racecadotril, diosmectite, tramadol, vancomycin, salbutamol, and potassium.

On 24 Mar 2016 (Study Day 53), the event of Grade 4 **Hypokalaemia** improved to Grade 2 and then resolved. The events of Grade 4 General physical health deterioration, Grade 3 Anaemia, Grade 2 Diarrhoea, and Grade 3 Dyspnoea did not resolve.

The investigator reported the events of **Anaemia**, **General physical health deterioration**, and **Hypokalaemia** were not related to tazemetostat.

On 31 Mar 2016 (Study Day 60), the subject died due to progressive disease. No autopsy was performed.

	WBC Count, x 10^9/L (reference range: 4-10.5 x 10^9/L)	**Neutrophils, x 10^9/L (reference range: 1.8-8 x 10^9/L)**	**Hemoglobin, g/L (reference range: 135-180 g/L)**	**Platelets, x 10^9/L (reference range: 150-450 x 10^9/L)**	**Sodium (reference range: 135-145 mmol/L)**	**Potassium (reference range: 3.6-4.8 mmol/L)**
29 January 2016 Screening	11.23	10.37	96	83	134	3.8
11 February 2016 (Study Day 11)	1.67	1.55	74	32	--	--
12 February 2016 (Study Day 12)	0.8	0.72	90	21	128	4.3
15 February 2016 (Study Day 15)	0.66	0.57	72	13	132	3.6
23 February 2016 (Study Day 23)	3.45	2.52	65	29	--	--
01 March 2016 (Study Day 30)	--	8.18	100	63	--	--
04 March 2016 (Study Day 33)	7.82	6.57	86	94	133	3.6
17 March 2016 (Study Day 46)	4.41	3.71	47	42	129	3.4
23 March 2016 (Study Day 52)	2.85	2.51	70	12	142	2.3 2.8

Subject Number	10102007
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	01 Sep 2016 (Study Day 1)
Last Dose Date (Study Day):	21 Jun 2017 (Study Day 294)
Nonfatal SAE	Abdominal pain（腹痛）

Subject 10102007 is a 6[redacted]-year-old female who was diagnosed with follicular lymphoma in Jul 2009. On 27 Jul 2016, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. She was previously treated with cyclophosphamide/doxorubicin/rituximab/ methylprednisolone/vincristine/prednisone (Jul 2010 to Feb 2011), rituximab (Mar 2011 to Jan 2012), cisplatin/rituximab/cytarabine/dexamethasone (Feb 2012 to May 2012), carmustine/cytarabine/etoposide/melphalan (Jun 2012), and bendamustine/prednisone/ rituximab (Oct 2015 to Feb 2016).

Relevant ongoing medical conditions included mucosal dryness (unknown) and insomnia (2009).

The subject received the first dose of tazemetostat 800 mg BID on 01 Sep 2016 (Study Day 1).

Concomitant medications taken within 14 days of the start of **Abdominal pain** included dexpanthenol, hydroxyzine, omeprazole, and fluconazole.

On 02 Mar 2017 (Study Day 183), the same day as the most recent dose of tazemetostat, the subject was hospitalized due to Grade 3 **Abdominal pain**. The subject had received 364 doses of tazemetostat (291,200 mg total) prior to the onset of the Grade 3 **Abdominal pain**. The subject also had a diarrhea. On admission, vital signs included blood pressure 125/66 mmHg, heart rate 98 beats per minute, and temperature 36.2 °C. No action was taken with study drug due to the **Abdominal pain**. The subject was treated with phloroglucinol, diosmectite, and paracetamol.

On 03 Mar 2017 (Study Day 184), the event of Grade 3 **Abdominal pain** was considered resolved and the subject was discharged from the hospital.

The investigator reported the event of **Abdominal pain** was not related to tazemetostat. The investigator reported the event was due to disease progression.

Study drug was discontinued on 21 Jun 2017 (Study Day 294) due to disease progression with the last dose taken on the same day.

On 12 Sep 2017 (Study Day 377), the subject was considered lost to follow-up.

Subject Number	20012014
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	03 Nov 2016 (Study Day 1)
Last Dose Date (Study Day):	20 Feb 2017 (Study Day 110)
Nonfatal SAE	Vomiting（嘔吐）

Subject 20012014 is a 6[redacted]-year-old white male who was diagnosed with follicular lymphoma on 19 Jul 2012. On 27 Oct 2016, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with prednisolone/cyclophosphamide/doxorubicin/ rituximab/vincristine (Aug 2012 to Nov 2012) and rituximab (Feb 2013 to Feb 2015). The subject also received radiotherapy (visceral, 14 Nov 2013 to 15 Nov 2013).

Relevant past medical history included tonsillectomy (1960).

The subject received the first dose of tazemetostat 800 mg BID on 03 Nov 2016 (Study Day 1).

There were no concomitant medications taken within 14 days of the start of **Vomiting** (both occurrences).

On 01 Feb 2017 (Study Day 91), the subject experienced a non-serious adverse event of Grade 1 Vomiting. He was seen by a general physician and the vomiting resolved on the same day after treatment with prochlorperazine.

On 12 Feb 2017 (Study Day 102), the subject again experienced nausea and vomiting (no adverse events reported).

On 13 Feb 2017 (Study Day 103), the same day as the most recent dose of tazemetostat, the vomiting worsened to Grade 3 **Vomiting**. The subject had received 204 doses of tazemetostat (163,200 mg total) prior to the onset of the Grade 3 **Vomiting**. The subject also experienced weight loss.

On 14 Feb 2017 (Study Day 104), the same day as the most recent dose of tazemetostat, the subject reported to the emergency room with worsening nausea. He was subsequently hospitalized due to ongoing Grade 3 **Vomiting**. An abdominal x-ray confirmed no abdominal obstructions and the subject started treatment with metoclopramide. Study drug was interrupted due to the Grade 3 **Vomiting**.

On 15 Feb 2017 (Study Day 105), the subject started an additional treatment with ranitidine and his symptoms improved. The subject was discharged from the hospital that same day.

On 17 Feb 2017 (Study Day 107), study drug was resumed at the same dose. On 20 Feb 2017 (Study Day 110), a computerized tomogram (CT) revealed lymphoma progression in the brain. A cerebrospinal fluid (CSF) examination confirmed the progression of lymphoma to the central nervous system (CNS), as well as the development of left cranial nerve (CN) VII palsy. The subject received 1 dose of IV methotrexate. Study drug was discontinued due to disease progression with the last dose also received that day. The subject received intravenous (IV) fluids and a blood transfusion on an unspecified date.

On 24 Feb 2017 (Study Day 114), the event of Grade 3 **Vomiting** was considered resolved with sequelae (unspecified). The investigator reported the event of **Vomiting** was not related to tazemetostat. The investigator considered the event related to disease progression of lymphoma

in the brain.

On 06 Mar 2017 (Study Day 124), 14 days since the most recent dose of tazemetostat, the subject presented to the clinic with vomiting and continued weight loss. That same day, the subject was hospitalized due to a second occurrence of Grade 3 **Vomiting** and nausea (adverse event not reported). The subject had received 220 doses of tazemetostat (176,000 mg total) prior to the onset of the second occurrence of Grade 3 **Vomiting**. No action was taken with study drug due to the second occurrence of Grade 3 **Vomiting** as it was previously discontinued.

On an unknown date, the Grade 3 **Vomiting** and nausea improved and subject's mood was brighter. The subject was engaged with physiotherapy and managed mobilization with three trolley. However, 1 week following the methotrexate dose, the subject was noted to have abnormal liver function, and an abdominal ultrasound showed a dilated common bile duct (CBD) with cholecystitis. The subject received treatment with ciprofloxacin.

On an unknown date, the subject experienced a spike in body temperature and methicillin-sensitive *Staphylococcus aureus* (MSSA) was noted in a blood culture. The subject had a new systolic murmur and was started on flucloxacillin as treatment for presumed endocarditis. A transthoracic echocardiogram (TTE) showed high left ventricular outflow tract (LVOT) gradient due to left ventricular hypertrophy.

On 20 Mar 2017 (Study Day 138), a chest x-ray was normal.

On 24 Mar 2017 (Study Day 142), an abdominal ultrasound showed previous right upper lobe resection, and background changes of chronic obstructive pulmonary disease (COPD), with more marked peribronchial thickening and interstitial change, likely edema. No collapse or consolidation was noted.

On 29 Mar 2017 (Study Day 147), a chest/pleural cavity ultrasound with a focus on the left infraclavicular region showed no evidence of a mass lesion. The proximal left axillary vessels appeared of a normal caliber, with no thrombus seen within the left axillary vein at its junction with the subclavian vein.

The subject's condition continued to deteriorate, with the onset of confusion, nausea, and coffee ground emesis. Despite treatment, the subject was considered to have progressive CNS and peripheral disease, and, with the ongoing deterioration, was not well enough for further treatment. On an unknown date, do not attempt resuscitate (DNAR) was signed and the subject was palliated.

The subject died on 02 Apr 2017 (Study Day 151) due to disease progression in the brain. The Grade 3 **Vomiting** was ongoing at the time of death.

The investigator reported the event of **Vomiting** was not related to tazemetostat. The investigator considered the event related to disease progression of lymphoma in the brain.

Subject Number	20032003
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	21 Sep 2016 (Study Day 1)
Last Dose Date (Study Day):	06 Feb 2018 (Study Day 504)
Nonfatal SAE	Arrhythmia（不整脈） Myelodysplastic syndrome （骨髄異形成症候群） Cerebrovascular accident（脳血管発作）

Subject 20032003 is a 6[redacted]-year-old white male who was diagnosed with follicular lymphoma in 1983. On 24 Aug 2016, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with chlorambucil/prednisone/vincristine (1983), chlorambucil/prednisone/vincristine (Jul 1992 to Feb 1993), etoposide/bleomycin/ cyclophosphamide/doxorubicin/methotrexate/vincristine (Mar 1995 to May 1995), locomustine/cytarabine (May 1995), bleomycin/cyclophosphamide/doxorubicin/etoposide/ methotrexate/prednisolone/vincristine (May 2004 to Nov 2004), rituximab/carmustine/ hydrocortisone/melphalan (Nov 2004), dexamethasone/gemcitabine/vinorelbine (May 2009 to Jul 2009), rituximab (Sep 2009 to Jul 2011), and bendamustine/idelalisib/ rituximab (Feb 2014 to Sep 2015).

Relevant past medical history included weight decreased (2015 to 2016). Relevant ongoing medical conditions included asthma (2014), bronchiectasis (2014), hypertension (date unknown), hypogammaglobulinaemia (2014), localised oedema (2014), lung consolidation (2014), platelet count increased (10 Aug 2016), productive cough (date unknown), sinusitis (date unknown), and skin lesion (2007). At Screening, the subject's white blood cell count (8.2 $\times 10^9$/L, reference range: 4.2–10.6) and platelets (426 $\times 10^9$/L, reference range: 130–370) were close to the upper limit of normal but thought to be reactive due to chronic obstructive pulmonary disease and frequent chest infections. Baseline bone marrow biopsy showed mild megakaryocytic dysplastic changes, thought to be related to previous chemo-radiotherapy. The subject had no splenomegaly or other clinical features of a myeloproliferative disorder.

The subject received the first dose of tazemetostat 800 mg BID on 21 Sep 2016 (Study Day 1). On Study Day 1, the subject's white blood cell count was 9.6 x 10^9/L and platelets were 547 $\times 10^9$/L.

In Apr 2017 (approximately Study Day 165), genetic tests for JAK2V617F, CALR, and MPL mutations were all negative.

Concomitant medications taken within 14 days of the start of the **Arrhythmia** included ramipril, azithromycin, immunoglobulins, ibuprofen, salbutamol, tiotropium, and ciclesonide.

On 28 Jun 2017 (Study Day 281), 1 day since the most recent dose of tazemetostat, the subject experienced a medically important Grade 1 **Arrhythmia**. The subject had received 560 doses of tazemetostat (448,000 mg total) prior to the onset of the Grade 1 **Arrhythmia**. Vital signs included heart rate 76 beats per minute and blood pressure 133/75 mmHg. Irregular heartbeat on palpitations was observed while recording vitals; however, the subject was asymptomatic. Laboratory results included white blood cell count 19.2$\times 10^9$/L and platelets 933$\times 10^9$/L. An electrocardiogram (ECG) showed premature ventricular complexes. A second ECG 2 minutes

later showed the same result, but a third ECG 2 minutes later showed sinus rhythm with occasional premature ventricular complex. Study drug was interrupted due to the **Arrhythmia**. A cardiologist determined that no treatment was needed. Twenty-four-hour ECG monitoring showed the presence of ectopic beads, but the subject was asymptomatic.

On 07 Jul 2017 (Study Day 290), an echocardiogram showed overall good biventricular systolic function with no significant valvular disease.

On 12 Jul 2017 (Study Day 295), laboratory results included white blood cell count 23.0 $\times 10^9$/L, neutrophils 1.6 $\times 10^9$/L (reference range: 2–7.1), and platelets 1045.0 $\times 10^9$/L.

Study drug was reinitiated on 14 Jul 2017 (Study Day 297). That day, the event of Grade 1 **Arrhythmia** was considered resolved. The investigator reported the event of **Arrhythmia** was possibly related to tazemetostat.

On 10 Oct 2017 (Study Day 385), the subject experienced a non-serious adverse event (AE) of Grade 2 Transient ischaemic attack. CT, MRI, magnetic resonance angiogram, dopplers, echocardiogram, and Holter were normal. Treatment included clopidogrel.

In addition to previous medications, concomitant medications taken within 14 days of the start of the **Cerebrovascular accident** included clopidogrel.

On 13 Dec 2017 (Study Day 449), 1 day since the most recent dose of tazemetostat, the subject was hospitalized due to a Grade 3 **Cerebrovascular accident**. The subject had received 864 doses of tazemetostat (691,200 mg total) prior to the onset of the Grade 3 **Cerebrovascular accident**. The subject had a scheduled study visit, where he reported fluctuating weakness of the left arm and left lower limb to a lesser degree and numbness on the left side of the mouth. The subject noticed these symptoms 5 days before the visit but did not seek medical attention. The numbness on the left side of the mouth had resolved at the time of the visit. Laboratory results included white blood cell count 21.5 $\times 10^9$/L and platelets 1158 $\times 10^9$/L. Physical examinations were performed, and the subject was admitted to hospital for further observation and investigations. Neurological examination was performed in the specialist clinic. These examinations were not part of routine clinical assessment for the study. Upon examination, there was reduced muscle power of the left arm to level 3 on a scale of 1 to 5 and left leg to a level 4 on a scale of 1 to 5. However, reflexes were normal and symmetrical with no sensory loss. The facial nerve examination and subject's balance were normal. The National Institutes of Health Stroke Scale (NIHSS) score was 2 due to left arm weakness and inattention and Glasgow Coma Scale (GCS) score was 15/15. An urgent CT of the head with contrast appeared unremarkable, but review of neuroradiology was pending. A CT scan showed there was no intracranial hemorrhage; however, there was low density involving the right posterior temporal and lateral occipital regions, which were not present on the previous study that represented a recent infarct. However, the scan results did not correspond to the side of the symptoms and no convincing acute infarct was observed within the left cerebral hemisphere. There was scattered subcortical, and periventricular low density changes were noted. A CT of the abdomen showed there was a minimal irregularity of the right M1 and of the left P1 segments, with a slight reduction in caliber. The intra and extracranial vessels were otherwise unremarkable with no evidence of filling defect to suggest thrombosis and no aneurysmal dilatation. A small amount of calcification was noted at the origin of the vertebral artery while venous sinuses were unremarkable. Results of an MRI suggested right hemispheric embolic infarction. A CT scan and MRI confirmed right middle cerebral artery embolic shower. An echocardiogram was unremarkable with an ejection fraction of 55–60% with no obvious thrombus. Biochemistry was unremarkable, and a blood test showed known secondary thrombocytosis, leukocytosis, and mild anemia. Upon discussion with the stroke team, the subject was admitted to the hospital under stroke team. Study drug was interrupted due to the **Cerebrovascular accident**. The subject was treated with acetylsalicylic acid, atorvastatin, and losartan.

The non-serious AE of Grade 2 Transient ischaemic attack was considered resolved on 14 Dec 2017 (Study Day 450).

On 15 Dec 2017 (Study Day 451), the event of Grade 3 **Cerebrovascular accident** was considered resolved with sequelae (unspecified), and the subject was discharged from the hospital. Transthoracic echocardiography was performed on that day (results not provided).

Study drug was reinitiated on 20 Dec 2017 (Study Day 456). On that day, the subject was independent with his transfers and indoor mobility with no aids and managed stairs independently. He could complete domestic tasks but could not drive for 4 weeks.

The investigator reported the event of **Cerebrovascular accident** was not related to tazemetostat.

In addition to previous medications, concomitant medications taken within 14 days of the start of the **Myelodysplastic syndrome** included acetylsalicylic acid, atorvastatin, and losartan.

On 29 Dec 2017 (Study Day 465), the same day as the most recent dose of tazemetostat, the subject experienced medically important Grade 3 **Myelodysplastic syndrome**. The subject had received 882 doses of tazemetostat (705,600 mg total) prior to the onset of the Grade 3 **Myelodysplastic syndrome**. A bone marrow biopsy showed histological feature of myeloproliferative neoplasm/myelodysplastic syndrome. Repeat genetic testing for JAK2V617F, CALR, and MPL mutations were again negative. Additional genetic testing showed two mutations: one in the E2H2 gene at exon 18 (c.2110G >Tp. (Val740 Phe)) with a variant allele frequency of 83.17% and one in the ASXL1 gene at exon 9 (c. 1926-1927 insGp (Gly646 Trpts Ter/2) confirming a clonal myeloid disorder. Treatment with hydrocarbamide was planned.

Laboratory results on 10 Jan 2018 (Study Day 477) included white blood cell count 21.4 $\times 10^9$/L and platelets 788 $\times 10^9$/L.

The event of Grade 3 **Myelodysplastic syndrome** did not resolve.

The investigator reported the event of **Myelodysplastic syndrome** was possibly related to tazemetostat.

Study drug was discontinued on 06 Feb 2018 (Study Day 504) due to **Myelodysplastic syndrome** with the last dose taken that same day.

On 10 Apr 2018 (Study Day 567), the subject died due to an infection. Autopsy results were unavailable. The **Myelodysplastic syndrome** was ongoing at the time of death.

Subject Number	50022007
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	10 Aug 2016 (Study Day 1)
Last Dose Date (Study Day):	24 Aug 2016 (Study Day 15)
Nonfatal SAE	Chills（悪寒）

Subject 50022007 is a 5[redacted]-year-old white male who was diagnosed with follicular lymphoma in Nov 1995. On 20 Jul 2016, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma. He was previously treated with interferon/chlorambucil (Nov 1995), rituximab/cyclophosphamide/doxorubicin/prednisolone/vincristine (Oct 2009 to Mar 2010), epirubicin/etoposide/ifosfamide (May 2010), ibritumomab tiuxetan/rituximab (Jun 2010 to Jul 2010), fludarabine/mitoxantrone/rituximab (Aug 2011 to Jan 2012), rituximab (Apr 2012 to Oct 2012), bendamustine (Oct 2012 to Jan 2013), lenalidomide/rituximab (Sep 2014 to Nov 2015), and idelalisib (Jan 2016 to Jun 2016).

No relevant past medical history or relevant ongoing medical conditions were reported.

The subject received the first dose of tazemetostat 800 mg BID on 10 Aug 2016 (Study Day 1).

Concomitant medications taken within 14 days of the start of the **Chills** included allopurinol, sulfamethoxazole/trimethoprim, ranitidine, ceftriaxone, and normal human immunoglobulin.

The subject experienced Grade 1 Pyrexia from 15 Aug 2016 (Study Day 6) to 25 Aug 2016 (Study Day 16). The subject was treated with ceftriaxone.

On 25 Aug 2016 (Study Day 16), 1 day since the most recent dose of tazemetostat, the subject experienced Grade 2 **Chills** accompanied by pyrexia (temperature 38.5 °C). The subject had received 30 doses of tazemetostat (24,000 mg total) prior to the onset of the Grade 2 **Chills**.

On 29 Aug 2016 (Study Day 20), the subject was hospitalized due to Grade 2 **Chills** accompanied by Grade 2 Pyrexia (temperature 39.4 °C). The subject also experienced pruritus, erythema, dry skin, asthenia, and pain in the left groin, where there was adenomegaly related to disease progression (no adverse events reported). Study drug was discontinued due to disease progression with the last dose taken on 24 Aug 2016 (Study Day 15). Laboratory results were not available. No treatment was reported.

On 05 Sep 2016 (Study Day 27), the events of Grade 2 **Chills** and Grade 2 Pyrexia were considered resolved, and the subject was discharged from the hospital.

The investigator reported the event of **Chills** was not related to tazemetostat.

Subject Number	60012009
Study Name	E7438-G000-101 (Phase 2)
First Dose Date (Study Day):	05 Aug 2016 (Study Day 1)
Last Dose Date (Study Day):	31 Aug 2016 (Study Day 27)
Nonfatal SAE	Bile duct obstruction（胆管閉塞）

Subject 60012009 is a 6[redacted]-year-old white male who was diagnosed with follicular lymphoma in Apr 2013. On 14 Jul 2016, the subject was enrolled in E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma (DLBCL). At study entry, the subject's current diagnosis was reported as DLBCL. He was previously treated with prednisone/rituximab/vincristine/cyclophosphamide/ doxorubicin (Apr 2013 to Sep 2013), cisplatin/etoposide/ methylprednisolone/ rituximab/cytarabine (Sep 2014 to Dec 2014), bendamustine/rituximab (Mar 2015 to Aug 2015), cisplatin/gemcitabine/rituximab/dexamethasone/gemcitabine (Nov 2015 to Dec 2015), and bendamustine/rituximab/carmustine/cytarabine/etoposide (Jan 2016 to Mar 2016).

Relevant ongoing medical conditions included fatigue (2013), groin pain (May 2016), hypoaesthesia (Jun 2016), and malacoplakia gastrointestinal (04 Apr 2016).

The subject received the first dose of tazemetostat 800 mg BID on 05 Aug 2016 (Study Day 1).

Concomitant medications taken within 14 days of the start of **Bile duct obstruction** included paracetamol, bethanechol, sulfamethoxazole/trimethoprim, and ascorbic acid, ibuprofen, and hydromorphone.

On 04 Aug 2016 (Study Day -1), laboratory results showed alanine aminotransferase (ALT) 10 U/L, aspartate aminotransferase (AST) 17 U/L, alkaline phosphatase (ALP) 77 U/L, total bilirubin 4 µmol/L, and direct bilirubin 2 µmol/L (reference ranges not provided).

On 18 Aug 2016 (Study Day 14), laboratory results included ALT 22 U/L, AST 26 U/L, ALP 81 U/L, bilirubin 4 µmol/L, and direct bilirubin 1 µmol/L.

On 01 Sep 2016 (Study Day 28), the same day as the most recent dose of tazemetostat, the subject presented to the clinic with clear signs of jaundice. Laboratory results included ALT 314 U/L, AST 118 U/L, ALP 1138 U/L, bilirubin 283 µmol/L, and direct bilirubin 198 µmol/L. The subject was transferred to the emergency room. That same day, the subject was hospitalized for Grade 4 **Bile duct obstruction**. The subject had received 54 doses of tazemetostat (43,200 mg total) prior to the onset of the Grade 4 **Bile duct obstruction**. Study drug was discontinued due to disease progression, with the last dose taken on 31 Aug 2016 (Study Day 27).

During the subject's hospitalization, treatment of the **Bile duct obstruction** included intravenous (IV) dimenhydrinate, IV ondansetron, pantoprazole, hydromorphone hydrochloride, prochlorperazine, IV furosemide, gabapentin, amitriptyline, sennoside A+B, IV menadione, macrogol, IV piperacillin/tazobactam, IV meropenem, IV potassium chloride, and morphine sulfate. The subject also received IV dexamethasone, IV metoclopramide hydrochloride, and lorazepam.

On 15 Sep 2016 (Study Day 42), relevant laboratory results remained above the upper limit of normal (exact values not provided) and the event of Grade 4 **Bile duct obstruction** was considered resolved with sequelae. The subject was discharged from the hospital on the same

day.

On 27 Sep 2016 (Study Day 54), the subject withdrew consent from study participation because he wanted to be in palliative care.

The investigator reported the event of **Bile duct obstruction** was not related to tazemetostat. The investigator considered the event to be related to disease progression.

付録2.7.6-7
SOC/PT別の有害事象発現率
国内106試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat (N=7) n (%)	
	Any Grade	Grade >= 3
有害事象発現例数	7 (100.0)	4 (57.1)
血液およびリンパ系障害	4 (57.1)	2 (28.6)
血小板減少症	3 (42.9)	2 (28.6)
貧血	2 (28.6)	1 (14.3)
白血球減少症	2 (28.6)	1 (14.3)
好中球減少症	2 (28.6)	1 (14.3)
リンパ球減少症	1 (14.3)	1 (14.3)
眼障害	2 (28.6)	0
ドライアイ	2 (28.6)	0
胃腸障害	6 (85.7)	1 (14.3)
便秘	3 (42.9)	0
口内炎	2 (28.6)	0
腹部不快感	1 (14.3)	0
裂肛	1 (14.3)	0
口唇炎	1 (14.3)	0
心窩部不快感	1 (14.3)	0
胃炎	1 (14.3)	0
腸管穿孔	1 (14.3)	1 (14.3)
悪心	1 (14.3)	0
肛門周囲痛	1 (14.3)	0
歯痛	1 (14.3)	0
一般・全身障害および投与部位の状態	3 (42.9)	1 (14.3)

Percentages are based on the total number of subjects in the Safety/Efficacy Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

付録2.7.6-7
SOC/PT別の有害事象発現率
国内106試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat (N=7) n (%)	
	Any Grade	Grade >= 3
疲労	2 (28.6)	1 (14.3)
無力症	1 (14.3)	0
末梢性浮腫	1 (14.3)	0
感染症および寄生虫症	5 (71.4)	0
上咽頭炎	5 (71.4)	0
インフルエンザ	2 (28.6)	0
口腔ヘルペス	1 (14.3)	0
爪囲炎	1 (14.3)	0
臨床検査	4 (57.1)	2 (28.6)
血中クレアチニン増加	2 (28.6)	0
アラニンアミノトランスフェラーゼ増加	1 (14.3)	0
アスパラギン酸アミノトランスフェラーゼ増加	1 (14.3)	0
血中アルカリホスファターゼ増加	1 (14.3)	0
血中トリグリセリド増加	1 (14.3)	1 (14.3)
γ－グルタミルトランスフェラーゼ増加	1 (14.3)	1 (14.3)
体重減少	1 (14.3)	0
代謝および栄養障害	1 (14.3)	1 (14.3)
低アルブミン血症	1 (14.3)	0
低リン酸血症	1 (14.3)	1 (14.3)
筋骨格系および結合組織障害	4 (57.1)	0
筋痙縮	2 (28.6)	0
関節痛	1 (14.3)	0

Percentages are based on the total number of subjects in the Safety/Efficacy Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

Appendix_2_7_6_7.sas 31MAR2020 14:29

付録2.7.6-7
SOC/PT別の有害事象発現率
国内106試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat (N=7) n (%) Any Grade	Tazemetostat (N=7) n (%) Grade >= 3
滑液包炎	1 (14.3)	0
筋骨格硬直	1 (14.3)	0
滑液嚢腫	1 (14.3)	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 (28.6)	1 (14.3)
舌扁平上皮癌	1 (14.3)	1 (14.3)
腫瘍熱	1 (14.3)	0
神経系障害	4 (57.1)	0
味覚異常	3 (42.9)	0
末梢性ニューロパチー	1 (14.3)	0
末梢性感覚ニューロパチー	1 (14.3)	0
精神障害	2 (28.6)	0
不眠症	2 (28.6)	0
呼吸器、胸郭および縦隔障害	1 (14.3)	0
咳嗽	1 (14.3)	0
皮膚および皮下組織障害	4 (57.1)	0
皮膚乾燥	2 (28.6)	0
発疹	2 (28.6)	0
脱毛症	1 (14.3)	0
爪の障害	1 (14.3)	0
皮膚色素過剰	1 (14.3)	0
皮膚腫脹	1 (14.3)	0

Percentages are based on the total number of subjects in the Safety/Efficacy Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

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付録2.7.6-7
SOC/PT別の有害事象発現率
国内106試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat (N=7) n (%)	
	Any Grade	Grade >= 3
血管障害	2 (28.6)	0
出血	1 (14.3)	0
高血圧	1 (14.3)	0

Percentages are based on the total number of subjects in the Safety/Efficacy Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

Appendix_2_7_6_7.sas 31MAR2020 14:29

付録2.7.6-8
SOC/PT別の副作用発現率
国内106試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat (N=7) n (%) Any Grade	Tazemetostat (N=7) n (%) Grade >= 3
副作用発現例数	6 (85.7)	3 (42.9)
血液およびリンパ系障害	4 (57.1)	2 (28.6)
血小板減少症	3 (42.9)	2 (28.6)
貧血	2 (28.6)	1 (14.3)
白血球減少症	1 (14.3)	0
好中球減少症	1 (14.3)	0
胃腸障害	4 (57.1)	0
口内炎	2 (28.6)	0
腹部不快感	1 (14.3)	0
便秘	1 (14.3)	0
心窩部不快感	1 (14.3)	0
胃炎	1 (14.3)	0
悪心	1 (14.3)	0
一般・全身障害および投与部位の状態	2 (28.6)	1 (14.3)
疲労	2 (28.6)	1 (14.3)
感染症および寄生虫症	1 (14.3)	0
口腔ヘルペス	1 (14.3)	0
爪囲炎	1 (14.3)	0
臨床検査	1 (14.3)	0
血中クレアチニン増加	1 (14.3)	0

Percentages are based on the total number of subjects in the Safety/Efficacy Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).
Treatment-Related TEAEs include TEAEs that were considered by the Investigator to be related to study drug or TEAEs with a missing causality.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

Appendix_2_7_6_8.sas 31MAR2020 14:29

付録2.7.6-8
SOC/PT別の副作用発現率
国内106試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat (N=7) n (%)	
	Any Grade	Grade >= 3
体重減少	1 (14.3)	0
代謝および栄養障害	1 (14.3)	0
低アルブミン血症	1 (14.3)	0
筋骨格系および結合組織障害	3 (42.9)	0
筋痙縮	2 (28.6)	0
筋骨格硬直	1 (14.3)	0
神経系障害	4 (57.1)	0
味覚異常	3 (42.9)	0
末梢性ニューロパチー	1 (14.3)	0
末梢性感覚ニューロパチー	1 (14.3)	0
精神障害	1 (14.3)	0
不眠症	1 (14.3)	0
皮膚および皮下組織障害	4 (57.1)	0
皮膚乾燥	2 (28.6)	0
発疹	2 (28.6)	0
脱毛症	1 (14.3)	0
爪の障害	1 (14.3)	0
皮膚色素過剰	1 (14.3)	0

Percentages are based on the total number of subjects in the Safety/Efficacy Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).
Treatment-Related TEAEs include TEAEs that were considered by the Investigator to be related to study drug or TEAEs with a missing causality.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

付録 2.7.6-9　死亡又は重篤な有害事象の被験者ごとの叙述（国内 106 試験）

死亡又は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。

被験者識別コード	有害事象 MedDRA（PT）Version 22.0	死亡に至った有害事象	死亡以外の重篤な有害事象
10011001	腸管穿孔		X
10011002	舌扁平上皮癌		X

Subject Number	10011001
Study Name	E7438-J081-106 (EZH-106)
Starting Dose	Tazemetostat 800 mg single dose (Cycle 0) Tazemetostat 800 mg twice daily (Cycle 1)
Nonfatal SAE	Intestinal perforation（腸管穿孔）

An 8[redacted]-year old Japanese female was diagnosed with diffuse large B-cell lymphoma (DLBCL), a subtype of B-cell non-Hodgkin's lymphoma (NHL), on 11 Jul 2016. Significant medical history included breast cancer, gastric cancer, hepatitis acute, and tuberculosis. Current medical conditions included anemia, asthenopia, constipation, lymphopenia, musculoskeletal pain, and thrombocytopenia. Previous anticancer therapy included rituximab/cyclophosphamide/doxorubicin hydrochloride/prednisone/vincristine sulfate. Prior medications included sulfamethoxazole, magnesium oxide, and pentamidine. Concomitant medications administered until the date of SAE onset included cyanocobalamin, isoniazid, paracetamol, teprenone, prednisolone, oseltamivir, trazodone, lactulose, oxycodone, sennoside a+b, albumin human, Solita-T1, fluconazole, pip/tazo, omeprazole, prednisolone, micafungin, and fentanyl. At Screening, Ann Arbor Staging was IV, B symptom was absent, and ECOG performance score was 1.

On 23 Jan 2017 (Day 1), the subject received single dose of tazemetostat 800 mg (Cycle 0).

On 26 Jan 2017, treatment with study drug (tazemetostat 800 mg twice daily [1600 mg total daily dose]) was initiated (Cycle 1 Day 1).

On 10 Feb 2017, the subject experienced thrombocytopenia (Grade 2) on Cycle 1 Day 16. Given age-related risk and risk of fall, the subject was assessed to be at high risk of hemorrhage. As a result, treatment with study drug was interrupted.

On 14 Feb 2017, the subject experienced acute abdomen. On examination, rebound tenderness was noted. CT scans showed intraperitoneal free air. Based on these findings, the subject was diagnosed with gastrointestinal perforation (Grade 4). The subject underwent an emergency operation. Visual inspection of the surgical specimen led to the finding of multiple lymphomatous lesions, in some of which perforation was noted. The visual inspection clearly indicated the consistency with the diagnosis. Therefore, the pathologic specimens were not submitted for further examination. The subject underwent irrigation and drainage as well as ileostomy, and moved to the intensive care unit (ICU).

On 16 Feb 2017, the subject returned from the ICU to the general ward.

On 20 Feb 2017, oral intake was started, and the course was favorable.

On 07 Mar 2017, the subject had no progression of anemia or fluctuations in vital signs, while intermittent melena was noted.

On 11 Mar 2017, the subject was recovering from intestinal perforation. The signs and symptoms were stable. The subject was transferred to another facility to receive best supportive care. It was difficult to track the case thereafter. The event was due to aggravation of the underlying disease, and recovery could not be expected. In addition, the signs and symptoms were stable. Therefore, the case tracking was completed.

The investigator classified the event of intestinal perforation as "Not related" to the study medication and commented: “The event was caused by small intestinal invasion of the underlying cancer cells. Given the new onset of the lesion, the subject was considered to have progressive disease (PD). The event was a serious adverse event (SAE) associated with PD; therefore, the causal relationship between the adverse event and the study drug was assessed to be not related.” “The drug compliance of the subject was less than 75% in Cycle 1; therefore, assessment of dose limiting toxicity based on the subject’s data could not be performed.”

Subject Number	10011002
Study Name	E7438-J081-106 (EZH-106)
Starting Dose	Tazemetostat 800 mg single dose (Cycle 0) Tazemetostat 800 mg twice daily (Cycle 1)
Nonfatal SAE	Squamous cell carcinoma of the tongue （舌扁平上皮癌）

A 7[redacted]-year old Japanese female was diagnosed with follicular lymphoma (FL), a subtype of B-cell non-Hodgkin's lymphoma (NHL), in Jun 2006. Significant medical history included hemorrhoids. Current medical conditions included anemia, hyperuricemia, hypogammaglobulinemia, leukopenia, lymphopenia, neutropenia, thrombocytopenia, and tumour pain. Previous anticancer therapy included rituximab/cyclophosphamide/doxorubicin hydrochloride/prednisone/vincristine sulfate, fludarabine/rituximab, ofatumumab, bendamustine/ibrutinib/rituximab, and copanlisib. No prior medications were reported. Concomitant medications administered until the date of SAE onset included aciclovir, bactrim, gualenic acid, hyaluronic acid, ciprofloxacin, and dexamethasone. At Screening, Ann Arbor Staging was II, B symptom was absent, and ECOG performance score was 0.

On 13 Feb 2017 (Day 1), the subject received single dose of tazemetostat 800 mg (Cycle 0).

On 20 Feb 2017, treatment with study drug (tazemetostat 800 mg twice daily [1600 mg total daily dose]) was initiated (Cycle 1 Day 1).

On 18 Aug 2017, the subject experienced stomatitis (Grade 1).

On 04 Sep 2017, intra-oral mass with pain and induration was noted. Stomatitis was considered Grade 2 and intolerable adverse event. Treatment with study drug was interrupted. The subject visited the department of dentistry and department of head and neck oncology of the study site, where a biopsy was performed.

On 13 Sep 2017, pathologic diagnosis suggested that squamous cell carcinoma was highly likely, which was considered operable.

On 02 Oct 2017, stomatitis (Grade 2) persisted. The subject condition did not meet the requirements for resuming the study drug. Therefore, the subject was discontinued from the study.

On 25 Oct 2017, the subject was hospitalized to undergo partial glossectomy and right neck dissection.

On 26 Oct 2017, partial glossectomy and right neck dissection were performed. The subject underwent the operations uneventfully.

On 01 Nov 2017, histopathological findings led to a diagnosis of squamous cell carcinoma.

On 02 Nov 2017, the post-operative course was favorable. The subject was discharged.

On 06 Nov 2017, the subject recovered from squamous cell carcinoma of the tongue.

The investigator classified the event of squamous cell carcinoma of the tongue as "Not related" to the study medication and commented: "Stomatitis was previously diagnosed, the causal relationship of which

to the study drug could not be ruled out. The subject was pathologically suspected to have malignant tongue cancer (squamous cell carcinoma). For a diagnostic therapy, surgical intervention was determined. Thus, the subject was hospitalized." "Histopathologic examination with a resected specimen led to a definitive diagnosis of squamous cell carcinoma of the tongue (Grade 3), the onset date of which was 04 Sep 2017. Therefore, the event was changed from stomatitis to malignant tongue cancer. The subject had a rich pretreatment history with drugs such as bendamustine and fludarabine, which was highly likely to become the inducing factor. Thus, the causal relationship to the study drug was considered not related."

付録2.7.6-10
SOC/PT別の有害事象発現率
国内206試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat FL (N=17) n (%)		Tazemetostat DLBCL (N=3) n (%)		Tazemetostat Total (N=20) n (%)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
有害事象発現例数	17 (100.0)	8 (47.1)	3 (100.0)	0	20 (100.0)	8 (40.0)
血液およびリンパ系障害	8 (47.1)	3 (17.6)	0	0	8 (40.0)	3 (15.0)
リンパ球減少症	5 (29.4)	2 (11.8)	0	0	5 (25.0)	2 (10.0)
好中球減少症	3 (17.6)	1 (5.9)	0	0	3 (15.0)	1 (5.0)
血小板減少症	3 (17.6)	0	0	0	3 (15.0)	0
貧血	2 (11.8)	0	0	0	2 (10.0)	0
白血球減少症	1 (5.9)	0	0	0	1 (5.0)	0
心臓障害	0	0	1 (33.3)	0	1 (5.0)	0
上室性頻脈	0	0	1 (33.3)	0	1 (5.0)	0
眼障害	2 (11.8)	0	0	0	2 (10.0)	0
結膜出血	1 (5.9)	0	0	0	1 (5.0)	0
視力障害	1 (5.9)	0	0	0	1 (5.0)	0
胃腸障害	9 (52.9)	1 (5.9)	0	0	9 (45.0)	1 (5.0)
便秘	4 (23.5)	0	0	0	4 (20.0)	0
悪心	3 (17.6)	0	0	0	3 (15.0)	0
口内炎	3 (17.6)	0	0	0	3 (15.0)	0
腹痛	1 (5.9)	0	0	0	1 (5.0)	0
心窩部不快感	1 (5.9)	0	0	0	1 (5.0)	0
血便排泄	1 (5.9)	0	0	0	1 (5.0)	0
大腸ポリープ	1 (5.9)	0	0	0	1 (5.0)	0

Percentages are based on the total number of subjects in the Safety Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more TEAEs reported in the same system organ class (or with the same preferred term) will be only counted once using the highest CTCAE grade.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

付録2.7.6-10
SOC/PT別の有害事象発現率
国内206試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat FL (N=17) n (%)		Tazemetostat DLBCL (N=3) n (%)		Tazemetostat Total (N=20) n (%)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
機械的イレウス	1 (5.9)	1 (5.9)	0	0	1 (5.0)	1 (5.0)
歯の障害	1 (5.9)	0	0	0	1 (5.0)	0
一般・全身障害および投与部位の状態	3 (17.6)	0	1 (33.3)	0	4 (20.0)	0
疲労	1 (5.9)	0	1 (33.3)	0	2 (10.0)	0
倦怠感	2 (11.8)	0	0	0	2 (10.0)	0
非心臓性胸痛	0	0	1 (33.3)	0	1 (5.0)	0
発熱	1 (5.9)	0	0	0	1 (5.0)	0
感染症および寄生虫症	14 (82.4)	2 (11.8)	1 (33.3)	0	15 (75.0)	2 (10.0)
上咽頭炎	6 (35.3)	0	1 (33.3)	0	7 (35.0)	0
上気道感染	4 (23.5)	0	0	0	4 (20.0)	0
単純ヘルペス	2 (11.8)	0	0	0	2 (10.0)	0
インフルエンザ	2 (11.8)	0	0	0	2 (10.0)	0
肺炎	2 (11.8)	1 (5.9)	0	0	2 (10.0)	1 (5.0)
異型肺炎	1 (5.9)	1 (5.9)	0	0	1 (5.0)	1 (5.0)
気管支炎	1 (5.9)	0	0	0	1 (5.0)	0
胃腸炎	1 (5.9)	0	0	0	1 (5.0)	0
膿痂疹	1 (5.9)	0	0	0	1 (5.0)	0
口腔ヘルペス	1 (5.9)	0	0	0	1 (5.0)	0
爪囲炎	1 (5.9)	0	0	0	1 (5.0)	0
歯周炎	1 (5.9)	0	0	0	1 (5.0)	0
ニューモシスチス・イロベチイ肺炎	1 (5.9)	1 (5.9)	0	0	1 (5.0)	1 (5.0)
尿路感染	1 (5.9)	0	0	0	1 (5.0)	0

Percentages are based on the total number of subjects in the Safety Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more TEAEs reported in the same system organ class (or with the same preferred term) will be only counted once using the highest CTCAE grade.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

付録2.7.6-10
SOC/PT別の有害事象発現率
国内206試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat FL (N=17) n (%)		Tazemetostat DLBCL (N=3) n (%)		Tazemetostat Total (N=20) n (%)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
傷害、中毒および処置合併症	3 (17.6)	0	0	0	3 (15.0)	0
転倒	1 (5.9)	0	0	0	1 (5.0)	0
術後譫妄	1 (5.9)	0	0	0	1 (5.0)	0
処置による疼痛	1 (5.9)	0	0	0	1 (5.0)	0
皮膚裂傷	1 (5.9)	0	0	0	1 (5.0)	0
歯牙破折	1 (5.9)	0	0	0	1 (5.0)	0
外傷性骨折	1 (5.9)	0	0	0	1 (5.0)	0
外傷性頭蓋内出血	1 (5.9)	0	0	0	1 (5.0)	0
臨床検査	10 (58.8)	1 (5.9)	1 (33.3)	0	11 (55.0)	1 (5.0)
血中クレアチンホスホキナーゼ増加	5 (29.4)	0	0	0	5 (25.0)	0
体重減少	3 (17.6)	0	0	0	3 (15.0)	0
アラニンアミノトランスフェラーゼ増加	2 (11.8)	0	0	0	2 (10.0)	0
アミラーゼ増加	2 (11.8)	0	0	0	2 (10.0)	0
アスパラギン酸アミノトランスフェラーゼ増加	2 (11.8)	0	0	0	2 (10.0)	0
血中クレアチニン増加	2 (11.8)	0	0	0	2 (10.0)	0
心電図ＱＴ延長	1 (5.9)	0	1 (33.3)	0	2 (10.0)	0
血圧低下	1 (5.9)	0	0	0	1 (5.0)	0
γ－グルタミルトランスフェラーゼ増加	1 (5.9)	1 (5.9)	0	0	1 (5.0)	1 (5.0)
代謝および栄養障害	6 (35.3)	2 (11.8)	0	0	6 (30.0)	2 (10.0)
高トリグリセリド血症	2 (11.8)	1 (5.9)	0	0	2 (10.0)	1 (5.0)
低リン酸血症	2 (11.8)	0	0	0	2 (10.0)	0

Percentages are based on the total number of subjects in the Safety Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more TEAEs reported in the same system organ class (or with the same preferred term) will be only counted once using the highest CTCAE grade.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

付録2.7.6-10
SOC/PT別の有害事象発現率
国内206試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat FL (N=17) n (%)		Tazemetostat DLBCL (N=3) n (%)		Tazemetostat Total (N=20) n (%)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
高カリウム血症	1 (5.9)	1 (5.9)	0	0	1 (5.0)	1 (5.0)
高尿酸血症	1 (5.9)	0	0	0	1 (5.0)	0
低アルブミン血症	1 (5.9)	0	0	0	1 (5.0)	0
筋骨格系および結合組織障害	4 (23.5)	0	1 (33.3)	0	5 (25.0)	0
関節痛	0	0	1 (33.3)	0	1 (5.0)	0
背部痛	0	0	1 (33.3)	0	1 (5.0)	0
筋骨格系胸痛	1 (5.9)	0	0	0	1 (5.0)	0
筋肉痛	1 (5.9)	0	0	0	1 (5.0)	0
四肢痛	1 (5.9)	0	0	0	1 (5.0)	0
腱障害	1 (5.9)	0	0	0	1 (5.0)	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）	1 (5.9)	0	0	0	1 (5.0)	0
非小細胞肺癌	1 (5.9)	0	0	0	1 (5.0)	0
神経系障害	11 (64.7)	0	1 (33.3)	0	12 (60.0)	0
味覚異常	9 (52.9)	0	1 (33.3)	0	10 (50.0)	0
浮動性めまい	0	0	1 (33.3)	0	1 (5.0)	0
筋痙直	1 (5.9)	0	0	0	1 (5.0)	0
視野欠損	1 (5.9)	0	0	0	1 (5.0)	0
精神障害	1 (5.9)	0	0	0	1 (5.0)	0
不眠症	1 (5.9)	0	0	0	1 (5.0)	0

Percentages are based on the total number of subjects in the Safety Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more TEAEs reported in the same system organ class (or with the same preferred term) will be only counted once using the highest CTCAE grade.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

付録2.7.6-10
SOC/PT別の有害事象発現率
国内206試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat FL (N=17) n (%)		Tazemetostat DLBCL (N=3) n (%)		Tazemetostat Total (N=20) n (%)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
腎および尿路障害	1 (5.9)	0	0	0	1 (5.0)	0
血尿	1 (5.9)	0	0	0	1 (5.0)	0
呼吸器、胸郭および縦隔障害	4 (23.5)	1 (5.9)	0	0	4 (20.0)	1 (5.0)
喘息	1 (5.9)	0	0	0	1 (5.0)	0
発声障害	1 (5.9)	0	0	0	1 (5.0)	0
誤嚥性肺炎	1 (5.9)	1 (5.9)	0	0	1 (5.0)	1 (5.0)
上気道の炎症	1 (5.9)	0	0	0	1 (5.0)	0
皮膚および皮下組織障害	8 (47.1)	0	1 (33.3)	0	9 (45.0)	0
脱毛症	2 (11.8)	0	1 (33.3)	0	3 (15.0)	0
発疹	3 (17.6)	0	0	0	3 (15.0)	0
湿疹	2 (11.8)	0	0	0	2 (10.0)	0
多形紅斑	1 (5.9)	0	0	0	1 (5.0)	0
爪の障害	1 (5.9)	0	0	0	1 (5.0)	0
斑状丘疹状皮疹	1 (5.9)	0	0	0	1 (5.0)	0
皮膚剥脱	1 (5.9)	0	0	0	1 (5.0)	0
血管障害	1 (5.9)	0	0	0	1 (5.0)	0
静脈炎	1 (5.9)	0	0	0	1 (5.0)	0

Percentages are based on the total number of subjects in the Safety Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more TEAEs reported in the same system organ class (or with the same preferred term) will be only counted once using the highest CTCAE grade.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

付録2.7.6-11
SOC/PT別の副作用発現率
国内206試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat FL (N=17) n (%)		Tazemetostat DLBCL (N=3) n (%)		Tazemetostat Total (N=20) n (%)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
副作用発現例数	17 (100.0)	6 (35.3)	3 (100.0)	0	20 (100.0)	6 (30.0)
血液およびリンパ系障害	8 (47.1)	3 (17.6)	0	0	8 (40.0)	3 (15.0)
リンパ球減少症	5 (29.4)	2 (11.8)	0	0	5 (25.0)	2 (10.0)
好中球減少症	3 (17.6)	1 (5.9)	0	0	3 (15.0)	1 (5.0)
血小板減少症	3 (17.6)	0	0	0	3 (15.0)	0
貧血	2 (11.8)	0	0	0	2 (10.0)	0
白血球減少症	1 (5.9)	0	0	0	1 (5.0)	0
心臓障害	0	0	1 (33.3)	0	1 (5.0)	0
上室性頻脈	0	0	1 (33.3)	0	1 (5.0)	0
胃腸障害	4 (23.5)	0	0	0	4 (20.0)	0
口内炎	3 (17.6)	0	0	0	3 (15.0)	0
便秘	2 (11.8)	0	0	0	2 (10.0)	0
悪心	2 (11.8)	0	0	0	2 (10.0)	0
心窩部不快感	1 (5.9)	0	0	0	1 (5.0)	0
歯の障害	1 (5.9)	0	0	0	1 (5.0)	0
一般・全身障害および投与部位の状態	2 (11.8)	0	1 (33.3)	0	3 (15.0)	0
倦怠感	2 (11.8)	0	0	0	2 (10.0)	0
疲労	0	0	1 (33.3)	0	1 (5.0)	0

Percentages are based on the total number of subjects in the Safety Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more TEAEs reported in the same system organ class (or with the same preferred term) will be only counted once using the highest CTCAE grade.
Treatment-Related TEAEs include TEAEs that were considered by the Investigator to be related to study drug or TEAEs with a missing causality.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

付録2.7.6-11
SOC/PT別の副作用発現率
国内206試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat FL (N=17) n (%)		Tazemetostat DLBCL (N=3) n (%)		Tazemetostat Total (N=20) n (%)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
感染症および寄生虫症	8 (47.1)	2 (11.8)	0	0	8 (40.0)	2 (10.0)
上咽頭炎	2 (11.8)	0	0	0	2 (10.0)	0
異型肺炎	1 (5.9)	1 (5.9)	0	0	1 (5.0)	1 (5.0)
気管支炎	1 (5.9)	0	0	0	1 (5.0)	0
単純ヘルペス	1 (5.9)	0	0	0	1 (5.0)	0
膿痂疹	1 (5.9)	0	0	0	1 (5.0)	0
口腔ヘルペス	1 (5.9)	0	0	0	1 (5.0)	0
爪囲炎	1 (5.9)	0	0	0	1 (5.0)	0
ニューモシスチス・イロベチイ肺炎	1 (5.9)	1 (5.9)	0	0	1 (5.0)	1 (5.0)
肺炎	1 (5.9)	1 (5.9)	0	0	1 (5.0)	1 (5.0)
上気道感染	1 (5.9)	0	0	0	1 (5.0)	0
傷害、中毒および処置合併症	1 (5.9)	0	0	0	1 (5.0)	0
転倒	1 (5.9)	0	0	0	1 (5.0)	0
臨床検査	6 (35.3)	0	1 (33.3)	0	7 (35.0)	0
アラニンアミノトランスフェラーゼ増加	2 (11.8)	0	0	0	2 (10.0)	0
アミラーゼ増加	2 (11.8)	0	0	0	2 (10.0)	0
アスパラギン酸アミノトランスフェラーゼ増加	2 (11.8)	0	0	0	2 (10.0)	0
血中クレアチニン増加	2 (11.8)	0	0	0	2 (10.0)	0
心電図ＱＴ延長	1 (5.9)	0	1 (33.3)	0	2 (10.0)	0
体重減少	2 (11.8)	0	0	0	2 (10.0)	0
血中クレアチンホスホキナーゼ増加	1 (5.9)	0	0	0	1 (5.0)	0

Percentages are based on the total number of subjects in the Safety Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more TEAEs reported in the same system organ class (or with the same preferred term) will be only counted once using the highest CTCAE grade.
Treatment-Related TEAEs include TEAEs that were considered by the Investigator to be related to study drug or TEAEs with a missing causality.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

付録2.7.6-11
SOC/PT別の副作用発現率
国内206試験
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tazemetostat FL (N=17) n (%)		Tazemetostat DLBCL (N=3) n (%)		Tazemetostat Total (N=20) n (%)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
代謝および栄養障害	3 (17.6)	1 (5.9)	0	0	3 (15.0)	1 (5.0)
低リン酸血症	2 (11.8)	0	0	0	2 (10.0)	0
高カリウム血症	1 (5.9)	1 (5.9)	0	0	1 (5.0)	1 (5.0)
筋骨格系および結合組織障害	1 (5.9)	0	0	0	1 (5.0)	0
四肢痛	1 (5.9)	0	0	0	1 (5.0)	0
神経系障害	10 (58.8)	0	1 (33.3)	0	11 (55.0)	0
味覚異常	9 (52.9)	0	1 (33.3)	0	10 (50.0)	0
筋痙直	1 (5.9)	0	0	0	1 (5.0)	0
呼吸器、胸郭および縦隔障害	2 (11.8)	0	0	0	2 (10.0)	0
喘息	1 (5.9)	0	0	0	1 (5.0)	0
上気道の炎症	1 (5.9)	0	0	0	1 (5.0)	0
皮膚および皮下組織障害	5 (29.4)	0	1 (33.3)	0	6 (30.0)	0
脱毛症	2 (11.8)	0	1 (33.3)	0	3 (15.0)	0
湿疹	2 (11.8)	0	0	0	2 (10.0)	0
爪の障害	1 (5.9)	0	0	0	1 (5.0)	0
発疹	1 (5.9)	0	0	0	1 (5.0)	0

Percentages are based on the total number of subjects in the Safety Analysis Set.
TEAE is defined as an AE that emerged during time from the first dose of study drug to 30 (+7) days after the subject's last dose.
Subject with two or more TEAEs reported in the same system organ class (or with the same preferred term) will be only counted once using the highest CTCAE grade.
Treatment-Related TEAEs include TEAEs that were considered by the Investigator to be related to study drug or TEAEs with a missing causality.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

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付録 2.7.6-12　死亡又は重篤な有害事象の被験者ごとの叙述（国内 206 試験）

死亡又は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。

被験者識別コード	有害事象 MedDRA（PT）Version 22.0	死亡に至った有害事象	死亡以外の重篤な有害事象
FL			
10011006	上気道の炎症		X
10021006	機械的イレウス，誤嚥性肺炎		X
10031004	外傷性頭蓋内出血		X
10081005	異型肺炎		X
10131011	非小細胞肺癌		X
10231002	ニューモシスチス・イロベチイ肺炎，肺炎		X

Subject Number	10011006
Study Name	E7438-J081-206 (EZH-206)
Starting Dose	Tazemetostat 800 mg twice daily
Nonfatal SAE	Upper respiratory tract inflammation （上気道の炎症）

A 4[redacted]-year old Japanese female was diagnosed with follicular lymphoma (FL), on 18 Jul 2017. Significant medical history included cervix carcinoma. Current medical conditions included seasonal allergy, peripheral sensory neuropathy, and dry skin. Previous anticancer therapy included cyclophosphamide/doxorubicin, and rituximab. Prior medications included heparinoid. Concomitant medications administered until the date of SAE onset included magnesium oxide, bactrim, pregabalin, gualenic acid, miconazole, loratadine, ambroxol, bilastine, dequalinium, loxoprofen, tranexamic acid, l-carbocysteine, paracetamol, cefcapene, amino acids/electrolytes/glucose, ringer-lactate, and cefepime. At Screening, Ann Arbor Staging was III, B symptom was absent, and ECOG performance score was 0.

On 18 Jul 2018 (Cycle 1 Day 1), treatment with study drug (tazemetostat) 800 mg twice daily (BID) [1600 mg total daily dose] was initiated.

On 11 Sep 2019, because of travelling abroad from the same day (11 Sep 2019) to 16 Sep 2019, treatment with study drug was interrupted for the subsequent 6 days.

On 19 Sep 2019, the subject had common cold Grade 1 (nasal discharge and cough).

On 28 Sep 2019, the subject presented to a nearby hospital with persistent pyrexia in the range between 38 °C and 39 °C. The subject was placed under observation with the prescribed medication.

On 30 Sep 2019, the subject emergently visited the study site for a close examination. Blood test and chest X-ray were performed. The findings showed an apparent decrease in the performance status (PS2). The subject was hospitalized to receive treatment for suspected bacterial infection. An antibiotic(s) was administered, and fluid replacement was started. The study drug was interrupted on the same day.

On 02 Oct 2019, persistent defervescence was achieved with continuation of the antibiotic therapy, and the general condition improved (PS1). The meal intake amount was stable. Fluid replacement was completed.

On 03 Oct 2019, improvement of the general condition was ongoing with PS1. Given persistent defervescense, the antibiotic therapy was completed.

On 04 Oct 2019, the subject was discharged. Interruption of the study drug was continued.

On 09 Oct 2019, the subject visited the study site for the protocol-specific evaluation of the study treatment at Cycle 17 Day 1. Resolution of upper respiratory inflammation was noted, and the general condition was evaluated to be favorable (PS 0). Thus, the study drug was resumed at the same dose as that before interruption. The subject recovered from the upper respiratory inflammation.

The investigator classified the event of upper respiratory tract inflammation as "Related" to the study drug and commented: “On 19 Sep 2019, upper respiratory inflammation-like symptoms occurred. At the visit on 25 Sep 2019, the subject’s PS was favorable, and the condition was considered to be common cold. However, high fever occurred on 28 Sep 2019. On 30 Sep 2019, the subject emergently visited the study

site; because of abnormally high levels of the inflammatory reaction and the poor general condition, the subject was emergently hospitalized. Although viral infection was suspected as the cause of upper respiratory inflammation at first, bacterial infection could not be ruled out, resulting in the start of antibiotic therapy. However, cultural tests were negative for both. As the fever went down and the general condition improved rapidly on the following day, infections were ruled out in light of the clinical course. Therefore, it was determined that the causal relationship to the study drug could not be ruled out. As blood tests showed a marked decrease in inflammatory reactions as well, the subject was considered to be recovering from the event on 04 Oct 2019 and discharged. Interruption of the study drug was continued. As the subject was considered to have recovered at an outpatient examination on 09 Oct 2019, the study drug was resumed at the same dose as that before interruption."

Subject Number	10021006
Study Name	E7438-J081-206 (EZH-206)
Starting Dose	Tazemetostat 800 mg twice daily
Nonfatal SAE	Mechanical ileus（機械的イレウス） Pneumonia aspiration（誤嚥性肺炎）

A 7[redacted]-year old Japanese male was diagnosed with follicular lymphoma (FL), on 06 Mar 2007. Significant medical history included gastric cancer and spinal osteoarthritis. Current medical conditions included hypertension and benign prostatic hyperplasia. Previous anticancer therapy included cyclophosphamide/doxorubicin, bendamustine, durvalumab, rituximab, and cyclophosphamide/dexamethasone. Concomitant medications administered until the date of SAE onset included nicardipine, acetylsalicylic acid, lansoprazole, febuxostat, bactrim, naftopidil, pentazocine, pip/tazo, metoclopramide, panthenol, carbohydrates/potassium chloride/sodium, hydroxyzine, solacet f, sodium bicarbonate, and fentanyl. At Screening, Ann Arbor Staging was I, B symptom was absent, and ECOG performance score was 0.

On 27 Sep 2018, treatment with study drug (tazemetostat) 800 mg twice daily was started.

On 15 Nov 2018, the dose of the study drug was changed to 1200 mg daily.

On 13 Feb 2019, the subject had abdominal pain and vomiting around 20:00 and was taken to hospital by ambulance at 21:16. On arrival, the subject had abdominal distention and tenderness centered on the hilum. A decrease in intestinal peristaltic sound was noted. Computed tomography (CT) scans showed a whirl sign, ascites and the enlarged intestinal tract, leading to the diagnosis of strangulation ileus due to internal hernia.

On 14 Feb 2019, at 01:00, the subject underwent an emergency surgery for strangulation ileus (release of ileus). The subject's clinical course was favorable during and after the surgery.

On 15 Feb 2019, when a nurse visited the subject's room after 05:00, a decrease in consciousness level (Japan Coma Scale 30) was noted. As decreased blood pressure (94/52 mmHg), pyrexia (38.9 degree Celsius) and decreased SpO_2 (64%) were noted, CT was performed. CT scans revealed infiltration on the upper lobe of the right lung, leading to the diagnosis of pneumonia. Antibiotic therapy was started. Furthermore, oxygenation was maintained via an oxygen mask (5 L). At 11:27, management with a mechanical ventilator was started under intubation.

On 19 Feb 2019, at 10:00, blood test results and imaging findings showed the improvement in pneumonia, resulted in extubation. After extubation, the subject's respiratory condition was stable.

On 20 Feb 2019, oxygen therapy was stopped.

On 22 Feb 2019, the subject started having a meal again.

On 25 Feb 2019, as there was no image of pneumonia on X-ray films and CRP was negative, the antibiotic therapy ended. The subject had no abdominal symptoms after starting having a meal again, and there were no abnormal findings on imaging tests. The subject recovered from the strangulation ileus and pneumonia aspiration.

On 26 Feb 2019, the subject was discharged.

The investigator classified the event of mechanical ileus as "Not related" to the study drug. The operating surgeon commented: “When pyloric-side gastrectomy with Roux-en-Y reconstruction was performed in 2006, closure of the mesentery defect at the Y-anastomotic site was not performed. Almost all of the small intestine more distal than the Y loop invaginated through the defect to the cavity, leading to internal hernia. Although strangulation of internal hernia was loose, the root of small intestine mesentery invaginated inside out, leading to volvulus. It was thought that lymphatic circulation disorder due to volvulus of the root of the mesentery occurred, resulting in the onset of chylous edema and chylous ascites. Although a mass larger than the fist due to malignant lymphoma was observed surrounding the abdominal aorta during the surgery, it was thought not to be associated with internal hernia mentioned in this case.” The investigator commented: “As of Jan 2019, CT had shown the whirl sign with a rotation slighter than the rotation of the whirl sign observed on 13 Feb 2019. Additionally, the subject complained that the subject had sometimes suffered from temporary abdominal pain for several years. Therefore, it was thought that the subject had had loose internal hernia since before the study drug was started. In this case, it was thought that the small intestine invaginated greatly for some reasons, which led to volvulus, followed by the onset of strangulation ileus. Based on the above statements, strangulation ileus was considered to be due to the past surgery, not due to the study drug.”

The investigator classified the event of pneumonia aspiration as "Not related" to the study drug and commented: “When the subject vomited on 13 Feb 2019, the subject probably experienced aspiration of food; therefore, pneumonia aspiration was thought not to be associated with the study drug.”

Subject Number	10031004
Study Name	E7438-J081-206 (EZH-206)
Starting Dose	Tazemetostat 800 mg twice daily
Nonfatal SAE	Traumatic intracranial haemorrhage （外傷性頭蓋内出血）

An 8[redacted]-year old Japanese female was diagnosed with follicular lymphoma (FL) on 30 Apr 2010. Significant medical history included uterine leiomyoma and myocardial ischaemia. Current medical conditions included hypertension, hypothyroidism, spinal osteoarthritis, arthralgia, insomnia, osteoporosis, scoliosis, depression, and diabetes mellitus. Previous anticancer therapy included cyclophosphamide/prednisone/ritux, bendamustine, and rituximab. Concomitant medications administered until the date of SAE onset included eperisone, ketoprofen, loxoprofen, rebamipide, zestak, minodronic acid, quazepam, lorazepam, mirtazapine, amlodipine, candesartan, rabeprazole, fursultiamine, panvitan, sitagliptin, perampanel, carbazochrome, metoclopramide, pentazocine, tranexamic acid, fosphenytoin, ringer-lactate, nicardipine, sodium chloride, and indometacin. At Screening, Ann Arbor Staging was III, B symptom was absent, and ECOG performance score was 1.

On 25 May 2018, treatment with the study drug (tazemetostat) 800 mg/dose, twice daily, was initiated.

On 20 Jul 2018, the frequency of fall increased after initiation of the study drug. A close-examination with CT of the brain was thus performed. The examination was unremarkable.

On 13 Aug 2018, the frequency of fall due to spasticity increased, and thus, the subject visited the neurology department. Suspected myoclonus was pointed out, and oral perampanel was thus initiated. Testing with magnetic resonance imaging (MRI) of the brain and electroencephalogram were scheduled.

On 17 Aug 2018, at the scheduled visit, the subject fell in the hospital. For the occipital contusion, CT of the head was performed. As a result, traumatic cerebral haemorrhage was diagnosed. The subject was hospitalized for course observation. Since the subject continued to be at a possible risk associated with fall due to spasticity, her withdrawal from the study was decided.

On 20 Aug 2018, MRI of the brain showed no enlargement of the hematoma, based on which continuation of the conservative treatment was decided.

On 11 Sep 2018, imaging test showed the haematoma was reducing, and the disease state was stable. Decreased response was improving but still persisting, and the subject was transferred to another hospital for continuous rehabilitation. The subject was recovering from the traumatic cerebral haemorrhage.

The investigator classified the event of traumatic intracranial haemorrhage as "Not related" to the study drug and commented: “The event occurred while the frequency of fall due to spasticity increased during treatment with the study drug; the study drug was unlikely to be the direct cause of the cerebral haemorrhage and thus the causal relationship of the event to the study drug could be ruled out.”

Subject Number	10081005
Study Name	E7438-J081-206 (EZH-206)
Starting Dose	Tazemetostat 800 mg twice daily
Nonfatal SAE	Atypical pneumonia（異型肺炎）

A 5[redacted]-year old Japanese male was diagnosed with follicular lymphoma (FL), on 09 Jan 2014. Current medical conditions included hepatic function abnormal and hyperglycaemia. Previous anticancer therapy included cyclophosphamide/doxorubicin and rituximab. Concomitant medications administered until the date of SAE onset included aciclovir, bactrim, valisone-g, prednisolone, and esomeprazole. At Screening, Ann Arbor Staging was IV, B symptom was absent, and ECOG performance score was 0.

On 23 Oct 2018, administration of the study drug 800 mg twice daily was initiated.

On 30 Jul 2019, it was the day for the protocol-specific visit for Cycle 11 Day 1. The study drug was continued uneventfully.

On 13 Aug 2019, it was the day for the protocol-specific visit for Cycle 11 Day 15. The vitals showed blood pressure of 102/68, pulse rate of 115, and body temperature of 36.3. The subject had no particular subjective symptoms such as cough and dyspnoea. Because the oxygen saturation with a pulse oximeters at consultation was around 90 %, blood gas (the arterial blood) was measured. As a result, PaO_2 was low at 61.7. Consequently, the subject was hospitalized for a close examination. Because plain computed tomography (CT) of the chest indicated diffuse ground glass opacity in the bilateral lungs, atypical pneumonia such as Pneumocystis pneumonia or viral pneumonia was suspected; a blood test was performed, and beta-D-glucan assay was positive. On the same day, oral Daiphen (sulfamethoxazole/trimethoprim) was initiated (4 tablets per dose, three times a day). Intravenous Predonine (prednisolone) 20 mg at 2 ampules was administered. The regimen was to be switched to oral Predonine from 14 Aug 2019. Oxygen was administered on an as-needed basis. Use of Funguard (micafungin sodium) 50 mg at 3 ampules and Venoglobulin IH 10% IV (polyethylene glycol treated human normal immunoglobulin) at 1 bottle were planned from 14 Aug 2019.

On 14 Aug 2019, no aggravation was noted in the state of the subject. Prednisolone tablet was initiated at a daily dose of 80 mg (until 18 Aug 2019). Venoglobulin IH 10% IV at 1 bottle was administered (administration dates: 14 Aug 2019, 15 Aug 2019, 16 Aug 2019, and 21 Aug 2019). Funguard 50 mg at 3 ampules was administered (administered daily until 26 Aug 2019).

On 19 Aug 2019, chest X-ray findings were not remarkable. Prednisolone tablet was administered at a daily dose of 40 mg (until 23 Aug 2019).

On 20 Aug 2019, tests were negative (-) for cytomegalovirus antigen and Candida mannan antigen.

On 22 Aug 2019, a blood test was performed, and beta-D-glucan assay was negative.

On 23 Aug 2019, oxygen therapy was completed.

On 24 Aug 2019, Prednisolone tablet was administered at a daily dose of 20 mg (until 03 Sep 2019). Even after completion of the oxygen therapy, the subsequent course was uneventful.

On 27 Aug 2019, it was the day for the protocol-specific visit for Cycle 12 Day 1. The protocol-required items other than prescription of the study drug were performed. Additionally, tumour evaluation on contrast-enhanced CT was performed (result: partial remission).

On 03 Sep 2019, the course was favorable, and the physical condition was also good. Therefore, planned discharge on 04 Sep 2019 was decided. The subject showed his willingness for resumption of the study drug. At an outpatient consultation on 10 Sep 2019, final decision whether to resume the study drug would be made.

On 04 Sep 2019, the subject was discharged. The condition was considered to have improved. The severity was updated to Grade 2 from Grade 3. Prednisolone tablet was administered at a daily dose of 10 mg (scheduled to be until 06 Sep 2019), to be followed by a two-day administration at a daily dose of 5 mg from 07 Sep 2019. The regimen of Daiphen was switched to 1 tablet per dose, once a day. The findings of the CT scans taken at the time of hospitalization indicated that any of the following was possible: pneumocystis pneumonia, viral pneumonia, and drug-induced pneumonia. However, given the rapid aggravation in the respiratory condition and increased beta-D-glucan, Pneumocystis pneumonia was most likely, and treatment was performed according to the possibility.

On 10 Sep 2019, the subject visited the study site for the first time after discharge as an outpatient. The physical condition showed no aggravation; thus, the event was assessed as "recovered". While drug-induced pneumonia could not be completely ruled out, and making a choice for other treatment was feasible, resumption of the study drug was too risky. Thus, withdrawal from the study was decided. The visit at withdrawal was performed. The subject recovered from the atypical pneumonia.

The investigator classified the event of atypical pneumonia as "Related" to the study drug and commented: “Initially, treatment was given to the subject for the condition regarded as Pneumocystis pneumonia. However, on the basis of the course, a diagnosis of Pneumocystis pneumonia could not be definitively made. On the other hand, interstitial pneumonia could not be completely ruled out. Considering these, upon reviewing the case, the event term was updated to atypical pneumonia in the previous report. In accordance with the event term update, the causality was updated to "related", based on the following reasons: there was no evidence strong enough to support the causality of the study drug to the event as "not related"; the study drug was the only drug used at the event onset.”

Subject Number	10131011
Study Name	E7438-J081-206 (EZH-206)
Starting Dose	Tazemetostat 800 mg twice daily
Nonfatal SAE	Non-small cell lung cancer（非小細胞肺癌）

A 6[redacted]-year old Japanese male was diagnosed with follicular lymphoma (FL), on 25 Jan 2010. Current medical conditions included dyslipidaemia, hyperuricaemia, pruritus, hypertension, hepatic steatosis, non-small cell lung cancer, glucose tolerance impaired, and emphysema. Previous anticancer therapy included cyclophosphamide/doxorubicin, rituximab, and bendamustine. Prior medications included hydroxyzine. Concomitant medications administered until the date of SAE onset included heparinoid, prednisolone, ezetimibe, clobetasol, rebamipide, febuxostat, fludroxycortide, bepotastine, hydroxyzine, mequitazine, atropa belladonna total alkaloid ex, dequalinium, dextromethorphan, levofloxacin, tranexamic acid, zinc, pa, and diflucortolone. At Screening, Ann Arbor Staging was II, B symptom was absent, and ECOG performance score was 0.

On 02 Oct 2018, treatment with the study drug (tazemetostat) 800 mg twice daily was started.

On 27 May 2019, a study visit was made for Cycle 9 Day 15.

On 06 Jun 2019, the subject noticed hoarseness but continued smoking.

On 10 Jun 2019, a study visit was made for Cycle 10 Day 1. For the treatment of hoarseness, the subject received PL granule (salicylamide, acetaminophen, anhydrous caffeine, promethazine methylenedisalicylate) 3 g daily, Medicon tablet (dextromethorphan hydrobromide hydrate) 45 mg daily and SP troche (dequalinium chloride) as needed.

On 11 Jun 2019, as hoarseness did not improve, the subject stopped receiving PL granule, Medicon tablet and SP troche at the subject's own discretion.

On 01 Jul 2019, as hoarseness did not improve, the subject presented to the department of otolaryngology. There were no abnormal findings suggestive of hoarseness, and the subject was instructed to stop smoking. The subject started receiving SP troche again.

On 08 Jul 2019, a study visit was made for Cycle 11 Day 1.

On 20 Jul 2019, a study visit was made for Cycle 11 Day 15.

On 05 Aug 2019, a study visit was made for Cycle 12 Day 1. The regular enhanced computed tomography was performed. An increase in the non-targeted lesion (left hilar lymph node) and pleural efusion (left) were noted, based on which progressive disease (PD) was determined. However, as shrinkage was maintained in the targeted lesions, the therapy was considered to be beneficial, leading to continuation of the study drug. Oral therapy with the study drug (tazemetostat) 800 mg twice daily was continued. Given that increased hilar lymph node was noted and that the subject was a smoker, a visit to the department of respiratory medicine on 19 Aug 2019 was scheduled, to rule out lung cancer.

On 19 Aug 2019, the subject's medical record was reviewed at the department of respiratory medicine. Endobronchial ultrasound-guided trans-bronchial needle aspiration (EBUS-TBNA) was indicated; however, as the lesion was located in the difficult site, the subject was referred to the department of

medical oncology. When positron emission tomography (PET) was performed, it revealed an abnormal uptake in the left hilar region and swelling of the lymph node, as CT scans revealed. There was an uptake in the interlobar pleura. The subject requested to undergo tests under sedation. One-day hospital stay was planned for EBUS-TBNA of 27 Aug 2019. Thoracentesis of pleural fluid was attempted for the tests, but the pleural fluid was not obtained. Hoarseness persisted, and the symptom of difficulty in sleeping due to coughs before going to bed occurred. In addition to lymph node disease progression, progression of the symptoms was thought to be present. Therefore, withdrawal from the study was determined. The last dosing date of the study drug was 18 Aug 2019.

On 27 Aug 2019, the subject was admitted for EBUS-TBNA. EBUS-TBNA was performed.

On 28 Aug 2019, the subject was discharged.

On 01 Sep 2019, non-small cell lung cancer (squamous cell carcinoma) was diagnosed based on the biopsy report.

On 02 Sep 2019, stage IV lung cancer was diagnosed based on the visit to the medical oncology department and the biopsy results, which was explained to the subject. Chemotherapy with Keytruda (pembrolizumab [genetical recombination]), carboplatin and Abraxane (paclitaxel) for lung cancer was scheduled to be started from 09 Sep 2019. On the same date, a follow-up visit was made to start the next therapy. The disease was determined to be non-small cell lung cancer grade 2.

On 09 Sep 2019, chemotherapy with Keytruda, carboplatin and Abraxane was started. Early after the study drug was started, swollen lymph node and fluorodeoxyglucose (FDG) uptake were observed in the left hilar region, leading to determination of the lymph node lesion. There were progressions of swollen lymph node in the left hilar region and left pleural effusion on CT of 05 Aug 2019. PET and left hilar biopsy led to the diagnosis of lung squamous cell carcinoma. The same lesion was thought to have been present since before the study was started.

The investigator classified the event of non-small cell lung cancer as "Not related" to the study drug and commented: “EBUS-TBNA was performed for the FDG uptake site in the left hilar region in this case. FDG uptake at that site had been present as of the study entry, and lung cancer was detected at the same site. Hence, lung cancer was determined to have been present since before start of the study drug, resulting in no causal relationship between the event of non-small cell lung cancer and the study drug.”

Subject Number	10231002
Study Name	E7438-J081-206 (EZH-206)
Starting Dose	Tazemetostat 800 mg twice daily
Nonfatal SAE	Pneumocystis jirovecii pneumonia （ニューモシスチス・イロベチイ肺炎） Pneumonia（肺炎）

A 6[redacted]-year old Japanese female was diagnosed with follicular lymphoma (FL), on 25 Jun 2014. Significant medical history included eczema. Current medical conditions included postrenal failure, hyperuricaemia, hypogammaglobulinaemia, emphysema, hyperlipidaemia and CD4 lymphocytes decreased. Prior anticancer therapy included cyclophosphamide/doxorubicin, bendamustine, and rituximab. Concomitant medications administered until the date of SAE onset included betamethasone, levofloxacin, bactrim, povidone-iodine, sennoside a+b, sodium picosulfate, domperidone, magnesium oxide, atovaquone, clostridium butyricum, febuxostat, ambroxol hydrochloride, carbocysteine, chlorphe, paracetamol, pip/tazo, osmosal, and gualenic acid. At Screening, Ann Arbor Staging was III, B symptom was absent, and ECOG performance score was 0.

On 30 Aug 2018, treatment with study drug was initiated.

On 11 Oct 2018, the subject visited the study site for Cycle (C) 2 Day (D) 15. The subject reported that she had pyrexia from 02 Oct 2018, but took a wait-and-see attitude since the pyrexia was not persistent. Levofloxacin (levofloxacin hydrate) tablet was prescribed (500 mg/day on 11 Oct 2018 and 250 mg/day from 12 Oct 2018). A blood test was also performed with new test items added.

On 12 Oct 2018, the blood test revealed significant increase in beta-D-glucan. The subject was hospitalized on the same day. Although no apparent source of infection was identified on computed tomography (CT), antifungal therapy was considered necessary, based on the beta-D-glucan level. The study drug was interrupted from the second dose of the same day. Blood test revealed negative for Candida and Aspergillus. Oral Baktar (sulfamethoxazole/trimethoprim) was initiated from the same day.

On 16 Oct 2018, the results of blood tests on 15 Oct 2018 showed increase in beta-D-glucan, for which Baktar was discontinued.

On 22 Oct 2018, tumor response assessment with CT at Week 8 of the treatment was performed.

CT showed findings suggestive of pneumocystis pneumonia and others. In addition, beta-D-glucan further increased. Levofloxacin was discontinued.

On 23 Oct 2018, bronchoscopy was performed. Samtirel (atovaquone) was initiated.

On 26 Oct 2018, polymerase chain reaction (PCR) analysis using the bronchial lavage fluid resulted in positive for Pneumocystis jirovecii, based on which a definite diagnosis was made.

On 01 Nov 2018, the general condition improved and the subject was discharged.

On 08 Nov 2018, no pyrexia, cough symptoms and others were noted after the discharge. CRP remained negative and beta-D-glucan decreased to 86.6 pg/mL. As of the same day, the study drug had been interrupted for 28 days, but continuation of the study was considered desirable. The subject also showed the willingness to continue participating in the study. CT was scheduled on 13 Nov 2018.

On 13 Nov 2018, the subject recovered from the pneumocystis jirovecii pneumonia. No change in the symptoms was noted. CT showed overall improvement of the pneumonia. The study drug was resumed with a one-level dose reduction (1200 mg divided in two doses).

On 26 Jun 2019, pharyngodynia and pyrexia of 37.6 degrees C were present. Respiratory symptom was absent. The subject took over-the-counter oral cold remedy, and the condition was observed.

On 28 Jun 2019, defervescence was indicated.

On the early evening of 01 Jul 2019, the subject reported pyrexia of 38.7 degrees C. The symptoms of cough and sputum had been present since the previous day. Calonal (acetaminophen) and Levofloxacin were orally taken.

On 02 Jul 2019, the subject had body temperature of 38.1 degrees C in the morning and visited the outpatient department. Blood test showed WBC of 31500 and CRP of 21.23; chest X-ray revealed opacity in the right lower lung field. Based on the findings, pneumonia was diagnosed. Treatment with drip infusion was decided to be necessary, and the subject was hospitalized. The event of pneumonia was Grade 3, to which the causal relationship of study drug could not be ruled out. Thus, the study drug was interrupted. Drip infusion with Zosyn (tazobactam/piperacillin hydrate) was initiated.

On 12 Jul 2019, blood test data and clinical manifestations showed improvement, and drip infusion with Zosyn was thus completed (until 11 Jul 2019). Oral Levofloxacin was initiated from the following day. The event was re-evaluated to be Grade 2.

On 17 Jul 2019, blood test data showed improvement, and the subject was thus discharged. Oral Levofloxacin was continued.

On 19 Jul 2019, blood test data showed no inflammation, and thus, oral Levofloxacin was completed. The study drug was resumed with a one-level dose reduction (400 mg/dose, twice/day). The subject recovered from the pneumonia.

The investigator classified the event of pneumocystis, jirovecii pneumonia and pneumonia as "Related" to the study drug and commented: “Given that the pneumocystis pneumonia and pneumonia developed after the initiation of the study drug, the causal relationship between these events and the study drug could not be ruled out.”