Severe hypocalcaemia fatal cases where the causal relationship to RANMARK (denosumab) cannot be ruled out

No.	Sex/ Age	latency to adverse reaction onset from initial dose	Corrected serum calcium levels(mg/dL)			Outcome	Symptoms of hypocalcaemia	Supplementation of calcium or vitamin D	Measures taken	Test for renal function etc.,
			Before administration	At the time of the onset	The lowest level					
1 (non-small cell lung cancer)	Male 50's	10 days	10.7 (9 days before administration)	8.2 (10 days after administration)	5.5 (24 days after administration)	Death (31 days after administration) Cause of death: cancer	None	None	calcium gluconate injection (850mg/day) Inravenous injection	BUN 26.2mg/dL, Serum creatinine level 2.94mg/dL, Albumin 3.5g/dL (9days before administration) At the day 1 of administration,hypercalcaemia was present. (Corrected serum calcium 12.4)
2*	Male	5 days	12.5 (2 days before administration)	8.6 (5 days after administration)	6.9 (18 days after administration)	Death (18 days after administration) Cause of death: pulmonary oedema	None	Calcium *L*-aspartate (600mg/day) Oral administration	keep oral administration of Calcium *L*-aspartate continuously calcium chloride continuous infusion	BUN 27.8mg/dL, Serum creatinine level 1.66mg/dL, Albumin 3.0g/dL (2days before administration)

* This information is provided under agreement.

< Case summary - No.1 >

Sex/ Age	Reason for use (complications)	Daily dose/ Treatment duration to ADR onset	Clinical course and therapeutic measures

Male 50s	Bone lesion due to bone metastases from non-small cell lung cancer (Non-small cell lung cancer) (Venous thrombosis) (Renal disorder)	120 mg/ 10days	Approximately 6 years before administration:
			  The patient developed non-small cell lung cancer. The patient was removed his right upper lobe of lung. CEA 3.4ng/mL.
			Approximately 4 years before administration:
			  Metastasis to lymph nodes was confirmed, and lymphadenectomy and removal of right lung was performed.
			Approximately 1 year before administration:
			  CEA 7.9ng/mL
			18days before administration:
			  CEA 41.4ng/mL
			Day 1 of administration:
			  The patient was diagnosed with multiple metastatic bone tumors and started receiving denosumab for bone lesion due to bone metastases from non-small cell lung cancer. The patient was diagnosed with renal disorder that was attributed to NSAIDs. Supplementation of calcium and vitamin D was not administered because hypercalcaemia (corrected serum calcium level 12.4mg/dL) was present. Phosphorus 5.0mg/dL, serum creatinine 3.9mg/dL. PS2.
			6 days after administration:
			  Corrected serum calcium level 8.5 mg/dL, phosphorus 3.6 mg/dL, serum creatinine 3.2mg/dL. The patient was admitted to the hospital.
			10 days after administration (day of onset):
			  Hypocalcaemia occurred. Corrected serum calcium level 8.2 mg/dL, phosphorus 2.7 mg/dL, serum creatinine 2.7mg/dL
			13 days after administration:
			  Corrected serum calcium level 7.8 mg/dL, phosphorus 2.2 mg/dL, serum creatinine 2.4mg/dL.
			17 days after administration:
			  Corrected serum calcium level 7.2 mg/dL, phosphorus 2.2 mg/dL, serum creatinine 1.8mg/dL. No abnormality was observed in electrocardiogram. There were no clinical symptoms associated with hypocalcaemia.
			19 days after administration:
			  Corrected serum calcium level 6.8 mg/dL, phosphorus 2.3 mg/dL, serum creatinine 1.89mg/dL, CEA 95.5ng/mL.
			20 days after administration:
			  Pre-existing disease was progressed rapidly. ALK lung cancer was suspected (IHC: positive, FISH: indeterminant) and the administration of crizotinib was started, but clinical improvement was not observed within a few days of the treatment.
			24 days after administration:
			  Corrected serum calcium level 5.5 mg/dL, phosphorus 3.4 mg/dL, serum creatinine 2.9mg/dL, PS 3. The patient experienced sudden cardiac arrest, and then circulation was restarted by resuscitation. Respiratory management by mechanical ventilation was started. Calcium gluconate 8.5% (850mg ×1) was intravenously injected.
			25 days after administration:
			  Corrected serum calcium level 6.1 mg/dL, phosphorus 3.1 mg/dL, serum creatinine 3.0mg/dL.
			27 days after administration:
			  Corrected serum calcium level 5.8 mg/dL, phosphorus 10.7 mg/dL, serum creatinine 9.2mg/dL. Calcium gluconate 8.5% (850mg ×1) was intravenously injected.
			28 days after administration:
			  Calcium gluconate 8.5% (850mg ×1) was intravenously injected.

					31 days after administration				
					The patient died. (Cause of death: cancer. According to his physician, a direct cause of death was considered to be an aggravation of non-small cell lung cancer, but the possibility of sudden cardiac arrest due to obvious hypocalcaemia cannot be ruled out.)				

Concomitant medications: ketoprofen tape, sodium rabeprazole, warfarin potassium, flavin adenine dinucleotide sodium, celecoxib, loxoprofen sodium, crizotinib

Laboratory Examination

	9 days before administration	Day 1 of administration	6 days after administration	10 days after administration (day of onset)	13 days after administration	17 days after administration	19 days after administration	24 days after administration	25 days after administration	27 days after administration
Corrected serum calcium (mg/dL)	10.7	12.4	8.5	8.2	7.8	7.2	6.8	5.5	6.1	5.8
Serum calcium (mg/dL)	10.2	12.1	8.2	7.8	7.3	6.8	6.5	5.2	5.7	4.4
Serum albumin (g/dL)	3.5	3.7	3.7	3.6	3.5	3.6	3.7	3.7	3.6	2.6
Serum potassium (mEq/L)	4.5	5.0	4.6	5.7	5.1	4.9	4.2	4.5	4.3	6.0
inorganic phosphorus (mg/dL)	4.8	5.0	3.6	2.7	2.2	2.2	2.3	3.4	3.1	10.7
BUN (mg/dL)	26.2	29.8	34.7	25.7	24.7	18.0	20.8	32.1	32.0	97.3
Creatinine	2.94	3.90	3.20	2.72	2.43	1.81	1.89	2.88	3.01	9.21
eGFR	19	14	17	21	23	32	31	19	18	5

AST (GOT) (IU/L)	36	26	31	28	39	39	33	60	342	447
ALT (GPT) (IU/L)	15	12	11	13	15	15	17	34	112	103
LDH (IU/L)	1060	784	1215	1235	1634	1911	1754	1594	2571	3271
ALP (IU/L)	677	583	616	591	535	525	514	472	590	373
CRP (mg/dL)	4.52	2.91	5.09	8.37	6.05	9.00	12.07	18.85	35.83	19.08
WBC ($\times 10^2/\mu$ L)	132	109	126	106	100	121	125	139	142	220
RBC ($\times 10^4/\mu$ L)	363	377	357	369	331	320	320	278	408	370
PLT ($\times 10^4/\mu$ L)	27.9	29.5	25.0	30.9	31.4	32.5	35.7	38.8	35.4	12.7