

**Drug Utilization and Medical Cost Study Focusing on Moisturizers in Cancer Patients Treated with Molecular Targeted Therapy: A Retrospective Observational Study Using Data from a Japanese Claims Database**

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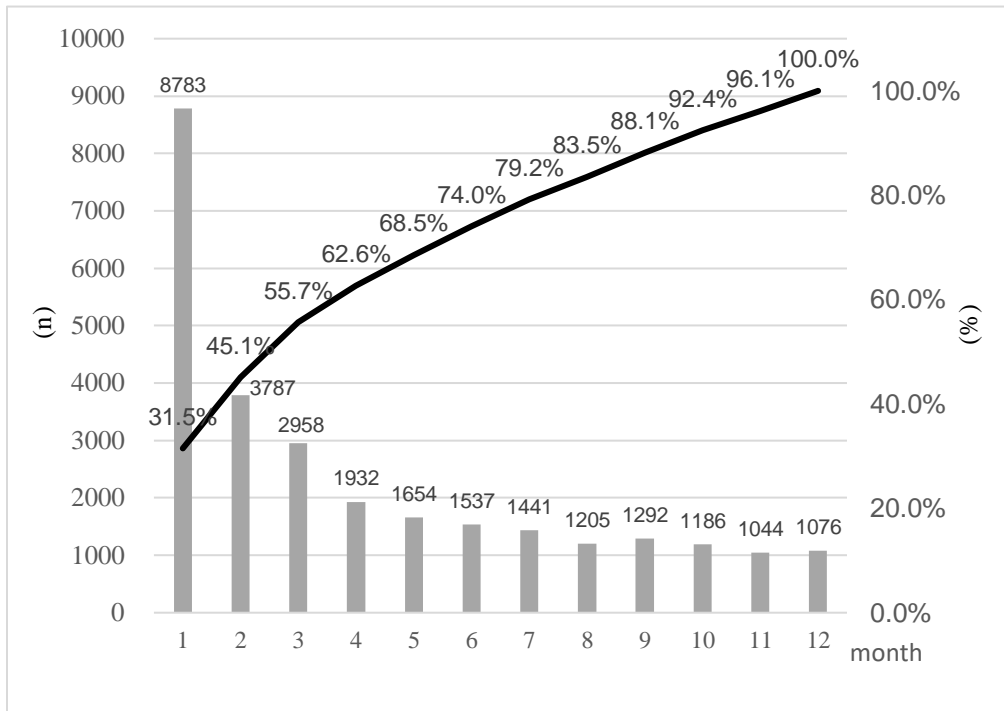
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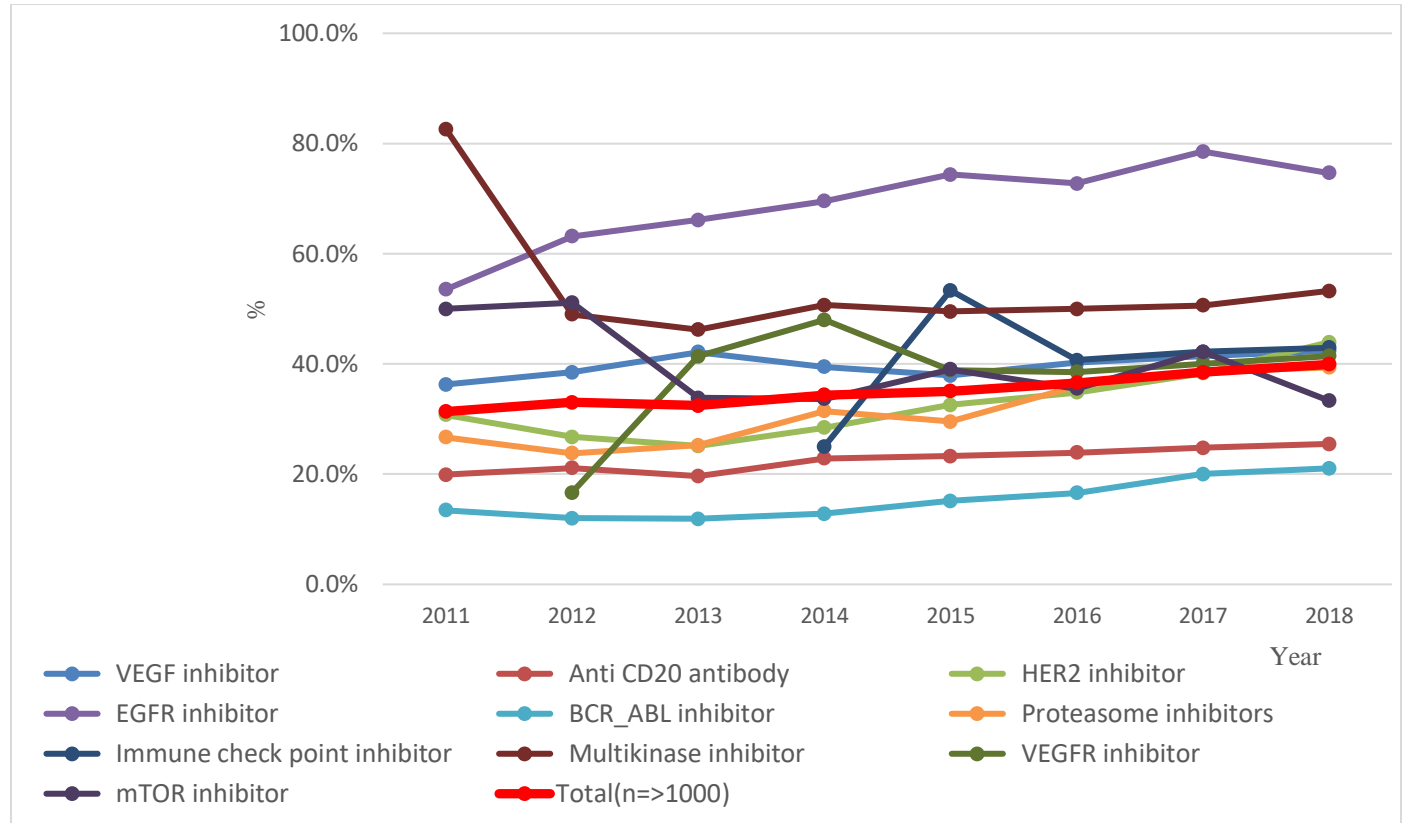
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**Supplementary Figure S1** Timing of moisturizer prescriptions of group M



**Supplementary Figure S2** Changes in the proportion of moisturizer users over time in the molecular targeted therapy (MTT) groups



	2011	2012	2013	2014	2015	2016	2017	2018
VEGF inhibitor	36.3%	38.5%	42.2%	39.5%	37.9%	40.2%	41.4%	42.4%
Anti CD20 antibody	19.9%	21.1%	19.6%	22.8%	23.3%	23.9%	24.8%	25.5%
HER2 inhibitor	30.8%	26.7%	25.1%	28.4%	32.5%	34.8%	38.3%	43.9%
EGFR inhibitor	53.5%	63.2%	66.1%	69.5%	74.4%	72.7%	78.5%	74.7%
BCR-ABL inhibitor	13.5%	12.0%	11.9%	12.8%	15.2%	16.6%	20.0%	21.1%
Proteasome inhibitors	26.7%	23.8%	25.2%	31.5%	29.5%	36.0%	38.6%	39.4%
Immune check point inhibitor				25.0%	53.3%	40.7%	42.2%	42.9%
Multikinase inhibitor	82.6%	49.0%	46.2%	50.7%	49.5%	50.0%	50.6%	53.3%
VEGFR inhibitor		16.7%	41.4%	48.0%	38.9%	38.5%	40.0%	41.4%
mTOR inhibitor	50.0%	51.1%	33.8%	33.7%	39.0%	35.5%	42.2%	33.3%
Total (n=>1000)	31.4%	33.0%	32.4%	34.4%	35.0%	36.6%	38.5%	39.9%

*VEGF* vascular endothelial growth factor, *CD20* cluster of differentiation, *HER2* human epidermal growth factor receptor, *EGFR* epidermal growth factor receptor, *BCR-ABL* BCR-ABL oncogene, *VEGFR* VEGF receptor, *mTOR* mammalian target of rapamycin

**Supplementary Table S1** List of molecular targeted therapies (MTTs) by type

Category	Generic name
EGFR inhibitor	afatinib, cetuximab, dacomitinib, erlotinib, gefitinib, osimertinib, panitumumab
HER2 inhibitor	lapatinib, pertuzumab, trastuzumab
mTOR inhibitor	everolimus, temsirolimus
Multikinase inhibitor	lenvatinib, pazopanib, regorafenib, sorafenib, sunitinib, vandetanib
VEGF inhibitor	aflibercept, bevacizumab
VEGFR inhibitor	axitinib, ramucirumab
Anti-CD20 antibody	obinutuzumab, ofatumumab, rituximab
Anti-CD38 antibody	daratumumab
Anti-CD52 antibody	alemtuzumab
Bisppecific CD19-directed CD3 T cell engager antibody construct	blinatumomab
Anti-CCR4 antibody	mogamulizumab
Immune check point inhibitor	atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, pembrolizumab
Anti-SLAMF7 antibody	elotuzumab
Antibody–drug conjugate (ADC)	brentuximab vedotin, gemtuzumab ozogamicin, inotuzumab ozogamicin, trastuzumab emtansine
Radioisotope-labeled antibody	ibritumomab tiuxetan
BCR-ABL inhibitor	bosutinib, dasatinib, imatinib, nilotinib, ponatinib
FLT3-AXL inhibitor	gilteritinib
Proteasome inhibitors	bortezomib, carfilzomib, ixazomib
ALK inhibitor	alectinib, ceritinib, crizotinib, lorlatinib
BTK inhibitor	ibrutinib
JAK inhibitor	ruxolitinib
BRAF inhibitor	dabrafenib, encorafenib, vemurafenib
MEK inhibitor	binimetinib trametinib
CDK 4/6 inhibitor	abemaciclib, palbociclib
PARP inhibitor	olaparib
Histone deacetylase inhibitors	panobinostat, romidepsin, vorinostat
Retinoid	bexarotene, tamibarotene, tretinoin

*EGFR* epidermal growth factor receptor, *HER2* human epidermal growth factor receptor, *mTOR* mammalian target of rapamycin, *VEGF* vascular endothelial growth factor, *VEGFR* VEGF receptor, *CD* cluster of differentiation, *CCR4* CC chemokine receptor 4, *SLAMF7* signaling lymphocytic activation molecule F7, *BCR-ABL* oncogene, *FLT3-AXL* FMS-like tyrosine kinase 3/receptor tyrosine kinase AXL, *ALK* anaplastic lymphoma kinase, *BTK* Bruton's tyrosine kinase, *JAK* Janus kinase, *BRAF* B-raf oncogene, *MEK*, Mitogen-activated extracellular signalregulated kinase, *CDK 4/6* cyclin-dependent kinases 4/6, *PARP* poly (ADP-ribose) polymerase

**Supplementary Table S2** Clinical characteristics (most frequent cancer diagnoses) in all patients and subgroups

ICD10 Code	Disease name	Overall* <sup>1</sup> , n, %* <sup>2</sup>		All (no moisturizer), n, %		All (with moisturizer), n, %		Heparinoid, n, %		Petrolatum, n, %		Urea, n, %		Combination, n, %	
C76-C80	Malignant neoplasms of ill-defined, secondary and unspecified sites	31,387	40.1%	17,213	54.8%	14,174	45.2%	10,720	75.6%	1567	11.1%	1480	10.4%	407	2.9%
C81-C96	Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	27,108	34.7%	20,581	75.9%	6527	24.1%	3915	60.0%	1751	26.8%	739	11.3%	122	1.9%
C15-C26	Malignant neoplasms of digestive organs	21,183	27.1%	11,509	54.3%	9674	45.7%	7550	78.0%	818	8.5%	1012	10.5%	294	3.0%
C50	Malignant neoplasm of breast	14,583	18.7%	9881	67.8%	4702	32.2%	3489	74.2%	619	13.2%	478	10.2%	116	2.5%
C30-C39	Malignant neoplasms of respiratory and intrathoracic organs	13,090	16.7%	6820	52.1%	6270	47.9%	4880	77.8%	735	11.7%	505	8.1%	150	2.4%
C64-C68	Malignant neoplasms of urinary tract	2656	3.4%	1446	54.4%	1210	45.6%	761	62.9%	114	9.4%	291	24.0%	44	3.6%
C51-C58	Malignant neoplasms of female genital organs	2271	2.9%	1653	72.8%	618	27.2%	461	74.6%	83	13.4%	48	7.8%	26	4.2%
C60-C63	Malignant neoplasms of male genital organs	1019	1.3%	656	64.4%	363	35.6%	260	71.6%	60	16.5%	36	9.9%	7	1.9%
C45-C49	Malignant neoplasms, mesothelial and soft tissue	734	0.9%	488	66.5%	246	33.5%	173	70.3%	35	14.2%	25	10.2%	13	5.3%
C73-C75	Malignant neoplasms of thyroid and other endocrine glands	574	0.7%	327	57.0%	247	43.0%	170	68.8%	26	10.5%	33	13.4%	18	7.3%
C69-C72	Malignant neoplasms of eye, brain, and other parts of central nervous system	545	0.7%	373	68.4%	172	31.6%	114	66.3%	46	26.7%	8	4.7%	4	2.3%
C00-C14	Malignant neoplasms of lip, oral cavity and pharynx	527	0.7%	243	46.1%	284	53.9%	215	75.7%	39	13.7%	19	6.7%	11	3.9%
C43-C44	Melanoma and other malignant neoplasms of skin	263	0.3%	148	56.3%	115	43.7%	82	71.3%	24	20.9%	8	7.0%	1	0.9%
C40-C41	Malignant neoplasms of bone and articular cartilage	82	0.1%	64	78.0%	18	22.0%	13	72.2%	3	16.7%	0	0.0%	2	11.1%
Total*		116,022		71,402	61.5%	44,620	38.5%	32,803	73.5%	5920	13.3%	4682	10.5%	1215	2.7%

\*<sup>1</sup> A patient diagnosed with  $\geq$  two cancer categories was counted in each category. *ICD10* International Classification of Diseases version 10

\*<sup>2</sup> Percentage of overall was calculated by number of patients in each group / study cohort (78,190)

**Supplementary Table S3** Duration of MTT by MTT group during the follow-up period (in days)

MTT group	Administration	Overall		All (no moisturizer)		All (with moisturizer)		Heparinoid		Petrolatum		Urea		Combination	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
ALK inhibitor	Oral	846	284.9 (106.2)	661	291.16 (101.72)	185	262.52 (118.51)	151	261.3 (118.3)	20	254.55 (122.95)	10	294.00 (105.64)	4	269.25 (169.74)
BCR-ABL inhibitor	Oral	6412	300.4 (93.7)	5422	308.80 (87.55)	990	254.62 (111.21)	673	258.4 (110.1)	186	235.04 (113.30)	115	262.04 (115.59)	16	269.25 (84.02)
BRAF inhibitor	Oral	17	141.5 (98.9)	10	139.00 (91.26)	7	145.00 (116.54)	2	60.5 (84.2)	4	166.00 (130.56)	1	230.00	0	-
BTK inhibitor	Oral	90	187.6 (137.7)	65	217.78 (138.74)	25	109.04 (100.43)	15	118.6 (105.7)	5	147.00 (114.46)	4	46.00 (26.62)	1	28.00
Bispecific CD19-directed CD3 T cell engager antibody construct	Injection	1	62.0	0	-	1	62.00	0	-	1	62.00	0	-	0	-
CDK 4/6 inhibitor	Oral	474	124.8 (87.2)	313	133.31 (90.32)	161	108.29 (78.45)	112	108.4 (77.7)	29	117.00 (85.25)	17	98.00 (79.97)	3	77.33 (30.29)
EGFR inhibitor	Oral	5818	243.4 (111.9)	1901	225.45 (120.29)	3917	252.09 (106.44)	3150	254.6 (105.6)	315	243.83 (110.61)	332	242.48 (107.64)	120	233.98 (110.17)
	Injection	2959	11.5 (9.6)	358	8.99 (8.77)	2601	11.86 (9.67)	2228	11.8 (9.5)	127	11.59 (10.24)	138	13.07 (10.80)	108	12.29 (10.26)
FLT3-AXL inhibitor	Oral	1	18.0	1	18.00	0	-	0	-	0	-	0	-	0	-
HER2 inhibitor	Oral	327	127.0 (106.3)	111	147.83 (123.69)	216	116.24 (94.69)	152	113.1 (96.5)	18	108.44 (72.77)	37	123.32 (93.03)	9	156.33 (112.41)
	Injection	12,085	15.1 (6.4)	8114	15.24 (6.55)	3971	14.80 (6.20)	3035	14.8 (6.0)	447	14.68 (6.82)	392	15.06 (7.19)	97	15.13 (5.35)
JAK inhibitor	Oral	458	302.0 (100.2)	409	306.81 (97.63)	49	261.67 (113.15)	35	251.23 (115.65)	13	283.46 (109.16)	1	344.00	0	-
MEK inhibitor	Oral	15	116.3 (97.2)	9	118.44 (98.78)	6	113.00 (103.98)	2	49.50 (68.59)	3	116.33 (117.41)	1	230.00	0	-
PARP inhibitor	Oral	30	98.4 (75.6)	21	103.33 (76.28)	9	86.89 (77.27)	9	86.89 (77.27)	0	-	0	-	0	-
VEGFR inhibitor	Oral	837	188.6 (119.2)	391	199.64 (118.15)	446	178.88 (119.34)	250	179.22 (115.64)	36	143.36 (114.87)	144	187.83 (125.22)	16	173.06 (128.10)
	Injection	2909	8.9 (6.9)	1598	9.64 (7.29)	1311	7.95 (6.18)	1036	7.99 (6.28)	147	7.37 (5.40)	101	8.65 (6.49)	27	6.78 (4.65)
VEGF inhibitor	Injection	21,102	11.5 (6.5)	12,260	11.64 (6.49)	8842	11.22 (6.43)	6788	11.28 (6.43)	959	10.28 (6.37)	846	11.82 (6.44)	249	11.20 (6.13)
mTOR inhibitor	Oral	1379	171.1 (117.8)	829	181.76 (118.90)	550	154.93 (114.21)	373	161.82 (115.89)	66	147.97 (112.96)	99	137.67 (108.58)	12	121.75 (102.77)
	Injection	114	16.4 (13.8)	43	18.56 (14.64)	71	15.15 (13.13)	47	14.79 (12.78)	9	19.44 (15.22)	13	15.31 (13.70)	2	3.50 (3.54)
Histone deacetylase inhibitors	Oral	66	41.3 (69.8)	42	32.43 (54.28)	24	56.79 (90.05)	13	62.46 (94.21)	7	69.57 (109.18)	4	16.00 (9.38)	0	-
	Injection	4	3.0 (1.4)	2	2.00 (1.41)	2	4.00 (0.00)	2	4.00 (0.00)	0	-	0	-	0	-

Proteasome inhibitors	Oral	176	14.6 (11.6)	111	15.17 (11.55)	65	13.48 (11.62)	46	15.00 (12.15)	13	9.54 (10.37)	5	10.40 (9.10)	1	10.00
	Injection	4064	22.7 (12.9)	2738	23.46 (12.90)	1326	21.23 (12.70)	758	21.34 (12.76)	365	20.82 (12.59)	179	22.12 (12.84)	24	17.42 (11.11)
Multikinase inhibitor	Oral	3233	154.0 (115.8)	1408	171.49 (117.82)	1825	140.41 (112.46)	1159	134.25 (112.16)	135	150.82 (108.55)	429	154.89 (112.93)	102	135.67 (113.96)
Retinoid	Oral	568	76.9 (58.3)	306	71.52 (52.80)	262	83.22 (63.60)	114	80.29 (58.59)	117	86.13 (63.76)	26	70.81 (65.53)	5	146.60 (125.45)
Anti CCR4 antibody	Injection	220	6.51 (3.14)	55	6.60 (3.13)	165	6.48 (3.15)	99	6.49 (2.83)	47	6.02 (3.68)	18	7.50 (3.31)	1	8.00
Anti CD20 antibody	Injection	17,632	6.1 (2.4)	13,526	6.07 (2.34)	4106	6.14 (2.45)	2484	6.17 (2.46)	1095	6.06 (2.40)	451	6.25 (2.50)	76	5.99 (2.69)
Anti CD38 antibody	Injection	153	10.8 (6.2)	85	11.45 (5.80)	68	10.00 (6.50)	41	10.51 (6.82)	18	8.22 (5.76)	7	10.86 (6.62)	2	12.50 (7.78)
AntiCD52 antibody	Injection	4	23.3 (12.8)	2	20.50 (16.26)	2	26.00 (14.14)	1	36.00	1	16.00	0	-	0	-
Anti SLAMF7 antibody	Injection	124	14.4 (8.2)	86	15.33 (8.50)	38	12.39 (7.00)	28	12.79 (6.97)	7	12.57 (8.04)	2	7.00 (7.07)	1	11.00
Antibody–drug conjugate (ADC)	Injection	838	5.8 (4.4)	482	6.30 (4.68)	356	5.19 (3.99)	245	5.31 (3.99)	78	5.01 (4.19)	24	4.75 (2.98)	9	4.67 (4.85)
Radioisotope-labeled antibody	Injection	135	1.9 (0.3)	111	1.95 (0.25)	24	1.88 (0.34)	14	1.93 (0.27)	4	1.75 (0.50)	5	1.80 (0.45)	1	2.00
Immune check point inhibitor	Injection	3984	10.5 (7.4)	2261	10.87 (7.62)	1723	9.96 (7.06)	1340	10.29 (7.17)	248	8.40 (6.42)	104	9.05 (6.55)	31	11.35 (7.05)

*EGFR* epidermal growth factor receptor, *HER2* human epidermal growth factor receptor, *mTOR* mammalian target of rapamycin, *VEGF* vascular endothelial growth factor, *VEGFR* VEGF receptor, *CD* cluster of differentiation, *CCR4* CC chemokine receptor 4, *SLAMF7* signaling lymphocytic activation molecule F7, *BCR-ABL* BCR-ABL oncogene, *FLT3-AXL* FMS-like tyrosine kinase 3/receptor tyrosine kinase *AXL*, *ALK* anaplastic lymphoma kinase, *BTK* Bruton's tyrosine kinase, *JAK* Janus kinase, *BRAF* B-raf oncogene, *MEK*, Mitogen-activated extracellular signalregulated kinase, *CDK 4/6* cyclin-dependent kinases, *PARP* poly (ADP-ribose) polymerase



**Supplementary Table S4** Proportion of patients treated with radiotherapy and descriptive statistics of the duration during the follow-up period

Variable	Overall		All (no moisturizer)		All (with moisturizer)	
Radiotherapy, N (%)						
Yes	7,801	10.0%	4,284	8.5%	3,517	12.6%
No	70,389	90.0%	46,000	91.5%	24,389	87.4%
Number of radiotherapy						
Valid values		7801		4284		3517
Mean (Sd)		22.77 (12.75)		22.55 (12.29)		23.04 (13.30)
95% CI		22.49–23.05		22.19–22.92		22.60–23.48
Median		20		20		22
Q1-Q3		15-26		15-25		13-28

**Supplementary Table S5** Cost (in JPY) analysis during the first 6 months of follow-up and for the entire 12 months of follow-up

	Group N				Group M			
	<i>n</i>	Mean (SD)	95% CI	% of total medical costs	<i>n</i>	Mean (SD)	95% CI	% of total medical costs
<b>First 6 months of follow-up</b>								
Total medical costs	50,284	3,298,769 (2,069,605)	3280679– 3316859		27,906	3,766,163 (2,317,206)	3,738,975– 3,793,352	
Outpatient costs	49,598	2,126,359 (1,729,972)	2,111,134– 2,141,584	64.5%	27,246	2,087,803 (1,764,503)	2,066,851– 2,108,756	55.4%
Inpatient costs	32,117	1,881,002 (1,948,841)	1,859,688– 1,902,317	57.0%	20,912	2,305,579 (2,393,697)	2,273,134– 2,338,024	61.2%
Drug costs	50,284	2,509,235 (1,757,068)	2,493,877– 2,524,593	76.1%	27,906	2,659,022 (1,812,180)	2,637,760– 2,680,285	70.6%
Defined MTT costs	50,284	1,895,454 (1,617,171)	1,881,319– 1,909,589	57.5%	27,906	1,912,357 (1,665,631)	1,892,814– 1,931,900	50.8%
Moisturizer costs	0	-	-		20,656	4008 (7,453)	3906–4109	0.1%
Other drug costs	49,564	622,697 (777,848)	615,849– 629,545	18.9%	27,864	744,820 (883,418)	734,447– 755,193	19.8%
Radiotherapy costs	2893	269,379 (144,226)	264,121– 274,637	8.2%	2176	274,839 (161,086)	268,067– 281,611	7.3%
<b>Entire 12 months of follow-up</b>								
Total medical costs	50,284	5,135,243 (3,395,783)	5,105,562– 5,164,925	100.0%	27,906	6,164,555 (3,687,885)	6,121,284– 6,207,826	100.0%
Outpatient costs	50,175	3,535,744 (3,039,421)	3,509,149– 3,562,339	68.9%	27,774	3,593,280 (2,962,900)	3,558,433– 3,628,127	58.3%
Inpatient costs	34,939	2,313,020 (2,556,791)	2,286,210– 2,339,831	45.0%	22,995	3,141,044 (3,418,671)	3,096,856– 3,185,233	51.0%
Drug costs								
Defined MTT costs	50,284	2,960,789 (2,772,164)	2,936,559– 2,985,020	57.7%	27,906	3,079,287 (2,722,818)	3,047,340– 3,111,235	50.0%
Moisturizer costs	0	-	-		27,906	6033 (12,344)	5888–6178	0.1%
Other drug costs	49,808	979,841 (1,291,595)	968,498– 991,184	19.1%	27,898	1,246,769 (1,469,595)	1,229,524– 1,264,015	20.2%
Radiotherapy costs	4284	283,912 (151,318)	279,379– 288,444	5.5%	3517	289,301 (166,077)	283,811– 294,792	4.7%

**Supplementary Table S6** Number of patients receiving moisturizers and the total amount of moisturizer prescribed in each year

<b>Year</b>	<b>Total (n)</b>	<b>With moisturizer (n)</b>	<b>% with moisturizer</b>	<b>Total amount of moisturizer (g)</b>	<b>Mean (g)</b>
2011	751	237	31.6%	73,462	310
2012	5547	1824	32.9%	606,297	332
2013	8719	2836	32.5%	969,042	342
2014	12215	4194	34.3%	1,457,762	348
2015	12079	4218	34.9%	1,526,698	362
2016	15549	5652	36.3%	2,153,689	381
2017	18228	6949	38.1%	2,932,977	422
2018	5102	1996	39.1%	756,719	379

2011: Data from October to December

2018: Data from January to April