Supplemental Materials

Contents

Supplementary Table 1. Information used to classify patients as *de novo* metastatic disease

	1989-93 N (%)	2014-18 N (%)
TNM stage	35873 (69%)	77513 (92%)
EoD stage	4062 (8%)	608 (1%)
Primary site unknown[a]	12210 (23%)	6253 (7%)
Other	118 (0%)	9 (0%)

aDoes not correspond to the numbers in table 1 because pts with melanoma/NETs/GIST also included

Abbreviations: EoD: Extent of disease classification, TNM: tumor node metastases classification, N:All patients (M0+M1), excluding SCC

Supplementary Table 2. Definition of cancer types

Tumor	Description	Details	Topography codes[a]	Morphology	Weight group[1,2]
HNSCC	Lip, Tongue, Gum, Floor of mouth, Palate, Other unspecified parts of mouth, Tonsil, Oropharynx, Nasopharynx, Pyriform Sinus, Hypopharynx, Other and ill- defines sites in lip, oral cavity and pharynx, larynx	Squamous cell carcinoma	C0.03-0.05, C01.0-01.9, C02.0-02.9, C03.0-03.9, C04.0-04.9, C05.0-05.9, C06.0-06.9, C09.0-09.9, C10.0-10.9, C11.0-11.9, C12.0-12.9, C13.0-13.9, C14.0-14.9, C32.0-32.9	8050-8089	1
Esophagus, Cardia	Esophagus, Cardia NOS	Only carcinoma	C15.0-15.9, C16.0	8000-8576, 8940-8950, 8980-8983 Excluding NETs	
Stomach	Stomach	Only carcinoma	C16.1-C16.9		1
Colon	Colon	Only carcinoma	C18.0-18.9		1
Rectum	Rectosigmoid junction, Rectum	Only carcinoma	C19.9, C20.9		1
Hepatocellular	Hepatocellular carcinoma		C22.0	8000-8012, 8014-8040, 8046-8148, 8160-8231, 8250-8573, 8575-8576, 8980, 8982, 9110	1
Gallbladder	Gallbladder	Only carcinoma	C23.9	8000-8576, 8940-8950, 8980-8983	1
Bile Ducts	Intrahepatic bile duct, other and unspecified parts of biliary tract, biliary tract NOS	Only carcinoma	C22.1, C24.0-24.9	8000-8576, 8940-8950, 8980-8983 Excluding NETs	1
Pancreas	Pancreas	Only carcinoma			1
GIST			Before 2001 C15.0-C260 C48.2 C76.2 Whole time period C150-C26.9, C48.1-48.2 C49.4 C76.2	8890- 8896 8936 (since 2000 ICD-0-3 has morphology code 8936/3 for GIST)	1
GEP NET	NET of the appendix		C18.1	8240-8242, 8248-8249	1
	NET of the stomach		C16.0-16.9	8240-8242, 8248-8249, 8150-8153, 8155-8156	
	NET of the small intestine		C17.1-17.9	8240-8242, 8248-8249, 8150-8153, 8155-8156	
	NET of the colon		C18.0, C18.2-18.9, C19.9, C20.9	8240-8242, 8248-8249	
	Gastrointestinal NET other		C15.0-15.9, C26.0-26.9, C48.0-48.9	8240-8242, 8248-8249, 8150-8153, 8155-8156	

	NET of the pancreas		C25.0-25.9	8240-8242, 8248-8249, 8150-8153, 8155-8157	
	NET van duodenum/ampulla of Vater		C17.0, C24.1	8240-8242, 8248-8249, 8150-8153, 8155-8156	
	NET with unknown primary location		C80.9	8240-8242, 8248-8249, 8150-8153, 8155-8156	
NSCLC	NSCLC		C34.0-34.9	8010-8020, 8022-8035, 8046-8230, 8243-8246, 8250-8576, 8972, 8980-8983	1
SCLC	SCLC		C34.0-34.9	8041-8045, 8002, 8021	1
Lung other	Trachea carcinoma & other and unspecified cancers of the lung and trachea Carcinoid of the lung		C33.9 C33.9 / C34.0-34.9 C34.0-34.9	8000-8576, 8940-8950, 8980-8983, 9872 8000-8001, 8003-8005, 8720-8790 8240-8242, 8248-8249	1
Melanoma	Melanoma of the lip, skin, vulva, penis, scrotum NOS, unknown primary	Melanoma	C00.1-00.2, C44.0-44.9, C51,0-51.9, C60.0-60.9, C63.2, C89.0	8720-8790	2
Sarcoma of the bone and soft tissues	Sarcoma of the soft tissues and viscera[b] Note: C70.0-70.9 & C71.0-71.9 (brain), C72.0-72.9 (spinal cord, cranial nerves, and other parts of central nervous system) , C75.1 & C75.3 (pituitary and pineal gland) excluded from analyses		C00-C39, C42, C44, C47-C52, C58-C70, C72-C80	8710-8714, 8800-8830, 8833-8850, 8852-8921, 8935, 8963, 8990-8991, 9040-9045, 9120-9137, 9141-9221, 9230-9342, 9364-9373, 9540-9582	2
			C49	8000-8005, 8982	
	Bones, joints, and articular cartilage		C40.0-40.9, C41.0-41.9	8000-8005, 8710-8714, 8800-8830, 8833-8850, 8852-8921, 8990-8991, 9040-9045, 9120-9137, 9141-9221, 9230-9342, 9364-9373, 9540-9582, 8935, 8963	
Breast	Breast	Only carcinoma	C50.0-50.9	8000-8576, 8940-8950, 8980-8983, 9110	1
Vulva/Vagina	Vulva/ Vagina	SCC / BCC / Merkle cell carcinoma / cutaneous adnexal carcinoma of the vulva	C51.0-51.9 C52.9	8000-8576, 8940-8950, 8980-8983, 9110 8000-8576, 8940-8950, 8980-8983, 9110	1

		Vaginal carcinoma			
Cervix Uteri	Cervix Uteri carcinoma	Only carcinoma	C53.0-53.9	8000-8576, 8940-8951, 8980-8983, 9110	2
Corpus Uteri - endometrium	Corpus uteri, Uterus NOS	Endometrium carcinoma	C54.0-54.9, C55.9		1
Ovary	Epithelial ovarian carcinoma, Extra-ovarian carcinoma Tubal carcinoma	Ovary	C56.0-56.9 C48.1-48.2 C57.0	8000-8239, 8250-8441, 8450, 8452-8461, 8470-8471, 8474, 8480-8576, 8930-8934, 8950-8951, 8980, 8982, 9000-9015, 9110 8000-8046, 8260-8576, 8950-8951, 8140, 8255, 8980, 9110 8000-8576, 8930-8934, 8950-8951, 9000-9015, 8980, 8982, 9110	1
Prostate	Prostate	Only carcinoma	C61.9	8000-8084, 8140-8576, 8940-8950, 8980-8983, 9110	4
Testicular	Testicular	Only germ cell tumors	C62.0-62.9	8000-8005, 9060-9102	3
Kidney	Kidney carcinoma	Only carcinoma	C64.0-64.9	8000-8084, 8140-8576, 8940-8950, 8980-8983, 9110	1
Bladder	Bladder, Renal pelvis, Ureter, Other and unspecified urinary organs	Only carcinoma	C67.0-67.9, C65.9, C66,9, C68.0-68.9 C64.0-64.9	8000-8576, 8940-8950, 8980-8983, 9110, 8120-8131	1
Thyroid	Thyroid Gland includes papillary and follicular, medullary, anaplastic, SCC of the thyroid, other and unspecified thyroid tumors	Only carcinoma	C73.9	8000-8576, 8588, 8589, 8940-8950, 8980-8983	2
Unknown	Unknown primary site		C80.9	Excluding GIST/NET/melanomas specified above	1

Abbreviations: BCC: Basal cell carcinoma; GEP NET: Gastroenteropancreatic neuroendocrine tumor; GIST: Gastrointestinal stromal tumors; HNSCC: Head and neck squamous cell carcinoma; NET: neuroendocrine tumors ; NSCLC: Non-small cell lung cancer; NOS: Not other specified; SCC: Squamous cell carcinoma; SCLC: Small cell lung cancer:
aThe International Classification of Diseases for Oncology (ICD-O) is applied for coding topography and morphology.3 The stage is coded according to the Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) classification, using the edition valid at the point of diagnosis a certain time period (4th–8th edition).4
bFor certain sarcomas the morphology codes slightly differed.

Weight group 1: 18-44 year: 7%; 45-54 year: 12%; 55-64 year: 23%; 65-74 year: 29%; 75 year and older: 29%
Weight group 2: 18-44 year: 28%; 45-54 year: 17%; 55-64 year: 21%; 65-74 year: 20%; 75 year and older: 14%
Weight group 3: 18-44 year: 60%; 45-54 year: 10%; 55-64 year: 10%; 65-74 year: 10%; 75 year and older: 10%
Weight group 4: 18-54 year: 4%; 55-64 year: 20%; 65-74 year: 40%; 75-84 year: 30% 85 year and older: 6%

Supplementary Table 3. Number and proportion of patients with de novo metastatic cancer, per tumor, age group and period for cancers with limited numbers of patients in one or more age strata

		1989-93		2014-2018	
		N	**%**	**N**	**%**
HNSCC	18-44	7	7%	4	2%
	45-54	19	20%	23	10%
	55-64	30	31%	78	33%
	65-74	26	27%	96	40%
	75+	15	15%	37	16%
Hepatocellular	18-44	15	13%	15	3%
	45-54	15	13%	33	6%
	55-64	20	17%	117	23%
	65-74	47	41%	198	39%
	75+	18	16%	145	29%
Gallbladder	18-44	8	2%	6	2%
	45-54	21	6%	23	6%
	55-64	57	17%	77	22%
	65-74	115	34%	136	48%
	75+	139	41%	141	85%
GIST	18-44	5	10%	5	3%
	45-54	14	28%	19	12%
	55-64	10	20%	44	28%
	65-74	16	32%	57	36%
	75+	5	10%	35	22%
Lung other	18-44	15	1%	7	0%
	45-54	62	6%	73	3%
	55-64	216	21%	325	11%
	65-74	360	34%	787	27%
	75+	392	38%	1698	59%
Vulva/vagina	18-44	2	7%	2	2%
	45-54	4	15%	10	12%
	55-64	2	7%	7	8%
	65-74	2	7%	28	33%
	75+	17	63%	38	45%
Corpus Uteri	18-44	2	1%	8	1%
	45-54	19	8%	42	6%
	55-64	62	25%	134	20%
	65-74	90	36%	259	39%
	75+	75	30%	229	34%
Testis	18-44	184	88%	238	81%
	45-54	17	8%	41	14%
	55-64	5	2%	9	3%
	65-74	3	1%	5	2%
	75+	1	0%	0	0%

Abbreviations: HNSCC: head and neck squamous cell carcinoma; GIST: Gastrointestinal stromal tumors; N: sample size.

Supplementary Table 4. Number of patients with M0 and M1 disease, per cancer type, per year

Cancer Type	Year	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
HNSCC	M0	1315	1397	1350	1454	1388	1449	1490	1507	1558	1483	1553	1591	1562	1587	1671	1713	1721	1678	1635	1794	1847	1826	1951	1895	1839	1942	1883	1980	1921	1944
	M1	18	16	14	27	22	18	14	27	26	26	25	28	22	39	33	24	37	41	36	37	53	48	31	50	59	35	53	54	49	47
Esophagus/C	M0	830	942	964	926	985	1000	1028	1001	994	1109	1078	1038	1021	1142	1159	1140	1069	1064	1077	1195	1251	1327	1424	1355	1321	1370	1470	1498	1496	1505
ardia	M1	264	308	345	357	372	403	397	416	433	427	476	486	520	558	613	667	717	806	770	866	873	816	757	781	807	847	882	874	861	923
Stomach	M0	1323	1224	1283	1188	1123	1073	1015	974	939	920	915	885	796	888	830	794	755	713	690	698	653	646	658	617	598	589	493	536	432	454
	M1	578	545	553	538	506	524	491	462	432	444	462	424	451	428	403	452	416	396	417	470	466	481	457	469	439	425	430	436	411	446
Colon	M0	3351	3414	3492	3633	3604	3675	3637	3895	3920	3895	4037	4203	4084	4125	4325	4601	4646	4817	4936	5249	5365	5438	5705	5696	5511	6855	7410	7169	6467	6250
	M1	851	920	981	990	1011	1026	995	980	1057	1079	1167	1116	1192	1246	1349	1441	1520	1554	1670	1789	1770	1975	1938	1964	2016	2004	1955	1906	1733	1734
Rectum	M0	2043	1915	1990	2127	2131	2089	2219	2148	2316	2206	2329	2351	2342	2532	2532	2655	2646	2746	2888	2765	2708	2793	2902	2858	2709	3274	3446	3253	3305	3218
	M1	369	355	421	402	409	413	416	444	437	506	488	486	562	548	646	648	658	673	739	717	767	716	815	699	760	770	773	736	711	654
Hepatocellul	M0	123	114	121	137	166	159	140	162	164	170	168	135	198	187	202	188	200	191	237	247	287	291	293	312	330	379	393	385	450	494
ar	M1	22	25	20	24	23	29	23	25	33	21	28	34	31	41	36	47	53	44	47	74	64	71	76	66	91	67	104	105	122	110
Gallbladder	M0	202	180	161	150	155	166	135	123	115	114	100	98	80	84	70	62	84	75	72	78	83	78	85	85	73	69	71	63	55	74
	M1	68	74	80	60	57	60	57	53	70	51	47	57	45	50	47	40	28	49	55	64	72	52	75	60	55	70	75	80	73	85
Bile ducts	M0	307	289	288	300	302	317	293	308	292	294	301	320	318	277	316	309	324	335	381	324	398	334	394	401	415	479	459	450	494	470
	M1	51	49	57	62	70	69	61	59	64	79	61	86	81	71	104	98	95	117	144	124	141	145	161	227	220	248	261	269	296	273
Pancreas	M0	769	778	736	729	685	703	730	674	690	731	705	750	677	719	680	669	759	719	772	775	764	831	806	825	829	867	878	864	908	899
	M1	445	450	496	492	488	466	531	526	503	571	545	584	580	593	630	750	800	761	828	978	1004	1047	999	1054	1080	1172	1184	1305	1283	1279
GIST	M0	32	42	28	35	32	47	48	47	55	57	58	70	69	71	70	108	102	115	112	108	102	123	126	133	113	126	136	115	134	139
	M1	6	4	11	16	13	11	3	12	13	11	11	16	19	13	19	21	26	19	20	27	27	19	25	23	29	34	31	41	32	22
NET	M0	78	151	116	133	125	138	148	131	151	165	150	163	148	137	164	149	203	176	224	198	257	271	315	328	319	330	339	348	357	385
	M1	57	60	61	62	64	66	78	65	83	96	72	84	84	84	105	91	90	118	99	110	119	144	155	163	135	154	167	167	173	179
NSCLC	M0	4365	4345	4397	4353	4367	4249	4419	4318	4198	4070	3855	3809	3642	3633	3629	3646	3584	3645	3698	3691	3652	3584	3709	3471	3607	3455	3595	3511	3446	3649
	M1	1425	1457	1526	1551	1551	1547	1553	1592	1711	1827	1909	2049	2142	2343	2420	2688	2810	3012	3080	3282	3356	3694	3764	3751	3858	3887	4020	3890	3951	4120
SCLC	M0	851	900	831	835	822	803	738	772	741	775	683	657	614	582	612	619	512	542	544	532	521	449	496	465	437	445	449	416	403	387
	M1	657	725	761	706	726	723	660	642	651	635	721	700	705	759	767	823	866	982	920	963	938	1070	1047	994	967	1000	987	978	995	913
Lung other	M0	412	384	428	465	404	437	421	439	460	443	401	429	371	431	454	452	441	496	529	543	601	595	680	690	781	784	1030	1081	1151	1219
	M1	190	189	229	238	199	228	235	198	219	252	280	274	295	331	361	356	366	353	354	402	416	417	438	436	487	428	554	650	597	661
Melanoma	M0	1541	1402	1454	1578	1489	1821	1786	1913	2102	2011	2162	2234	2530	2506	2706	2917	3157	3195	3369	3682	3855	4104	4454	4597	4797	4847	5036	5581	5180	5572
	M1	103	92	88	77	80	93	85	92	115	105	105	126	124	136	136	129	153	150	155	154	177	184	190	181	172	194	205	225	204	213
Sarcoma	M0	494	451	463	471	458	490	437	483	474	453	463	473	465	473	494	461	497	498	500	481	454	478	513	568	486	556	539	564	540	568
	M1	83	68	70	88	81	95	89	90	86	82	96	102	90	93	97	95	95	92	105	90	118	112	107	136	92	112	112	118	98	105

Breast	M0	7022	7472	7823	8468	8762	9121	8715	8987	9053	9328	10189	10281	10638	10538	10738	10957	10947	11289	11733	11808	11928	12129	12666	12845	12806	12902	12875	12933	13149	12872
	M1	528	575	575	563	567	555	516	535	539	566	560	553	575	591	528	593	591	600	535	632	639	562	582	664	727	731	756	780	754	805
Vulva/Vagin	M0	224	219	231	225	202	226	212	253	203	240	237	225	230	231	264	245	256	268	300	272	334	317	367	347	315	370	338	372	377	390
a	M1	5	6	6	3	7	6	5	5	5	11	11	6	6	9	5	7	13	9	15	17	15	14	19	9	14	17	17	20	9	22
Cervix Uteri	M0	685	729	685	694	674	662	671	663	667	695	654	615	544	597	545	613	611	607	657	610	626	646	627	623	568	617	582	679	666	724
	M1	26	25	26	38	29	31	37	34	37	32	29	43	36	33	45	49	47	44	57	59	65	53	71	61	57	81	86	83	58	65
Corpus	M0	1138	1063	1130	1146	1079	1176	1154	1180	1248	1272	1234	1241	1284	1287	1358	1473	1496	1345	1438	1552	1459	1531	1518	1481	1532	1505	1491	1487	1593	1514
Uteri	M1	45	52	54	43	54	40	45	39	47	46	50	49	58	58	52	68	65	80	82	92	98	89	103	107	127	125	139	128	138	142
Ovary	M0	883	882	976	976	954	950	1003	939	937	968	944	876	858	868	834	860	807	825	846	872	864	926	870	860	822	809	835	800	842	848
	M1	203	218	218	208	213	183	192	201	196	192	167	178	222	213	210	256	222	228	284	248	257	295	243	252	282	286	285	313	297	336
Prostate	M0	2808	2914	3057	3407	3860	4707	5000	5061	4980	5171	5259	5434	5516	5915	6630	7600	7172	7858	7917	7880	8308	8456	9291	9062	8728	7718	7990	8506	8710	8971
	M1	1077	1016	1023	1192	1169	1154	1092	1052	989	1012	928	1010	1014	986	1082	1143	1120	1108	1137	1159	1296	1298	1343	1267	1309	1364	1569	1599	1821	2138
Testicular	M0	284	280	286	305	347	335	341	387	362	401	431	430	508	453	461	516	503	536	528	609	582	599	628	670	645	693	637	742	725	755
	M1	42	45	34	44	45	46	46	62	46	66	56	48	53	61	66	44	67	63	59	63	64	50	70	49	50	53	54	61	63	62
Kidney	M0	842	826	802	906	886	883	835	908	908	894	848	878	937	922	989	1041	1004	1163	1294	1251	1351	1312	1419	1412	1455	1418	1493	1691	1628	1724
	M1	269	298	301	319	302	314	344	331	330	308	375	348	324	363	374	366	405	447	439	417	459	473	433	464	430	443	446	463	421	432
Bladder	M0	2019	1978	2035	2061	1991	2102	2075	2099	2088	2044	2184	2143	2146	2169	2189	2192	2354	2328	2421	2539	2456	2526	2452	2500	2459	2512	2486	2631	2659	2549
	M1	97	91	125	122	114	111	123	125	119	130	148	149	157	182	181	196	205	233	231	231	233	269	290	296	317	305	321	361	381	400
Thyroid	M0	256	283	246	241	254	262	276	240	272	295	296	289	286	327	312	340	358	339	378	412	417	444	482	508	548	554	533	528	562	582
Gland	M1	34	39	33	37	39	27	30	29	26	31	39	29	32	36	33	36	45	45	37	47	44	43	35	44	40	48	50	60	43	58
Other	M0	34	39	33	37	39	27	30	29	26	31	39	29	32	36	33	36	45	45	37	47	44	43	35	44	40	48	50	60	43	58
	M1	905	977	896	931	926	948	947	1060	1041	1133	1087	1099	1098	1038	1059	1159	1171	1123	1203	1287	1271	1286	1326	1301	1289	1288	1323	1337	1354	1444
Unknown	M1	2219	2373	2308	2421	2338	2343	2469	2341	2402	2458	2458	2379	2498	2438	2288	2282	2167	1970	1808	1816	1610	1559	1533	1388	1337	1042	989	1106	1044	1099

Supplementary Table 5. Net survival per time period and change over time for *de novo* metastatic cancer, per cancer type

	1 year NS (%)				5 year			
	1989-93 *(95% CI)*	**2014-18 *(95% CI)***	**Change**	**P**	**1989-93 (95% CI)**	**2014-18 *(95% CI)***	**Change**	**P**
Pancreas	5 *(4-5)*	10 *(10-11)*	6	<0.01	0 (0-1)	1 *(1-2)*	1	<0.01
Gallbladder[a]	5 *(3-6)*	15 *(12-19)*	11	<0.01	1 *(0-2)*	1 *(1-3)*	1	0.10
Hepatocellular[b]	6 *(4-8)*	13 *(11-16)*	7	<0.01	1 *(0-3)*	1 *(1-3)*	0	0.16
Bile Ducts	8 *(6-10)*	18 *(16-19)*	10	<0.01	0 *(0-0)*	1 *(0-1)*	1	<0.01
Long other[a]	9 *(8-11)*	11 *(9-14)*	2	<0.01	1 *(0-2)*	3 *(2-4)*	2	<0.01
NSCLC	9 *(9-10)*	28 *(27-28)*	18	<0.01	1 *(0-1)*	7 *(6-7)*	6	<0.01
Stomach	12 *(11-13)*	20 *(19-21)*	8	<0.01	1 (1-2)	2 *(1-3)*	1	0.05
Esophagus/Cardia	12 *(11-13)*	23 *(22-24)*	11	<0.01	1 *(1-2)*	3 *(2-3)*	2	<0.01
SCLC	13 *(13-14)*	22 *(21-23)*	9	<0.01	1 *(0-1)*	2 *(2-2)*	1	<0.01
Unknown	14 *(14-14)*	16 *(15-16)*	2	<0.01	4 *(3-4)*	7 *(6-8)*	3	<0.01
Other	17 *(15-19)*	32 *(30-34)*	16	<0.01	5 *(3-6)*	11 *(9-13)*	7	<0.01
Bladder	19 *(16-22)*	25 *(24-27)*	6	<0.01	3 *(2-5)*	7 *(5-8)*	3	<0.01
HNSCC[a]	23 *(17-29)*	28 *(22-34)*	5	<0.01	7 *(3-13)*	6 *(3-9)*	-1	0.60
Kidney	28 *(26-30)*	42 *(40-44)*	14	<0.01	6 (5-7)	12 *(11-14)*	7	<0.01
Colon	28 *(27-29)*	51 *(50-52)*	23	<0.01	4 *(3-5)*	14 *(13-15)*	10	<0.01
Sarcoma	32 *(28-36)*	45 *(41-49)*	14	<0.01	7 *(5-10)*	14 *(10-17)*	6	<0.01
Cervix Uteri	33 *(27-40)*	54 *(49-59)*	21	<0.01	9 *(5-14)*	22 *(17-27)*	13	<0.01
Rectum	34 (33-36)	59 *(58-61)*	25	<0.01	4 *(3-5)*	14 *(13-16)*	11	<0.01
GIST[a]	36 (26–46)	86 *(78-91)*	50	<0.01	8 *(3-15)*	53 *(42-63)*	46	<0.01
Corpus Uteri[a]	38 *(33-43)*	49 *(45-53)*	11	<0.01	18 (13-23)	16 *(12-20)*	-2	0.18
Ovary	41 *(38-43)*	62 *(60-64)*	21	<0.01	6 (5-8)	16 *(14-18)*	10	<0.01
Melanoma	48 *(44-52)*	62 *(59-65)*	14	<0.01	23 *(20-27)*	39 *(35-43)*	16	<0.01
Vulva/vagina[b]	50 *(23-71)*	23 *(15-32)*	-27	0.03	9 (3-18)	6 *(2-13)*	-3	0.34
NET	59 *(54-64)*	84 *(81-87)*	25	<0.01	26 *(21-31)*	57 *(52-62)*	32	<0.01
Breast	60 *(58-62)*	76 *(74-77)*	15	<0.01	14 (13-16)	33 *(31-35)*	18	<0.01
Thyroid	60 *(52-67)*	63 *(57-68)*	3	0.26	32 *(23-41)*	49 *(42-56)*	17	<0.01
Testicular[c]	77 *(68-84)*	87 *(75-94)*	10	<0.01	66 *(55-74)*	84 *(71-91)*	18	<0.01
Prostate	79 *(78-80)*	89 *(88-99)*	10	<0.01	23 *(22-24)*	42 *(41-44)*	19	<0.01

a Age strata with < 10 patients in one or more diagnostic groups but analyses not adjusted because NS could be estimated. See supplemental table 7 for unweighted results for these groups. b Cancers form whom NS could not be estimated and thus, the diagnostic groups were adjusted: Hepatocellular, vulva/vagina, bile ducts: 2014-2017 instead of 2014-2018. c Testicular cancer: Adjusted weight groups because barely any patients aged 75+ with testicular cancer and 0 in 2014-18: changed from 60% 18-44, 10% 45-55, 10% 55-65, 10% 65-75, 10% 75+ to 60% 18-44, 10% 45-55, 10% 55-65, 20% 65+

Abbreviations: CI: confidence intervals; HNSCC: head and neck squamous cell carcinoma; NET: Neuroendocrine Tumors; NS: Net survival: GIST: Gastrointestinal stromal tumors; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer.

Supplementary Table 6. Net survival for patients with de novo metastatic cancer, not standardized by age, per time period and change. For cancers with < 10 patients in at least one of the age strata in 1989-1993 and/or 2014-2018

	1 year NS (%)			5 year NS (%)		
	1989-93 *(95% CI)*	**2014-18 *(95% CI)***	**Change**	**1989-93 *(95% CI)***	**2014-18 *(95% CI)***	**Change**
HNSCC[a]	26 *(19-33)*	27 *(23-32)*	1	8 *(4-14)*	6 *(4-10)*	-1
Hepatocellular[a]	7 *(5-10)*	13 *(11-15)*	6	1 *(0-4)*	1 *(0-2)*	-1
Gallbladder[a]	4 *(3-5)*	13 *(11-16)*	9	1 *(0-2)*	2 *(0-4)*	1
GIST[a]	47 *(33-59)*	86 *(79-90)*	39	10 *(4-20)*	51 *(41-61)*	41
Lung other[b]	8 *(7-9)*	8 *(8-9)*	0	1 *(0-1)*	2 *(1-3)*	1
Vulva/vagina	42 *(25-58)*	30 *(22-39)*	-12	12 *(3-28)*	8 *(3-16)*	-5
Corpus Uteri	40 *(34-46)*	48 *(44-52)*	8	18 *(13-23)*	13 *(10-16)*	-5
Testicular[a]	88 *(82-92)*	94 *(90-96)*	6	77 *(71-82)*	87 *(83-91)*	10

aLimited number (<20) of patients in several age strata: HNSCC, Gallbladder, GIST, Vulva/vagina (max 38 pts in one group), Testicular (0 in group 75+ in 2014-18), Hepatocellular; bLimited number of patients (<20) in one age stratum: Lung other in age group 18-44, Corpus uteri in age group 18-44

Abbreviations: CI: Confidence Interval; HNSCC: head and neck squamous cell carcinoma; NS: Net survival; GIST: Gastrointestinal stromal tumors.

Supplementary Table 7. Survival of patients with *de novo* melanoma, a comparison of net survival and changes with and without unknown primary tumors in the analyses

	1 year NS (%)			5 year NS (%)		
	1989-93 *(95% CI)* N=440	**2014-18 *(95% CI)*** N=1041	**Change**	**1989-93 *(95% CI)*** N=440	**2014-18 *(95% CI)*** N=1041	**Change**
Melanoma with unknown primary	48 (44-52)	62 (59-65)	14	23 *(20-27)*	39 *(35-43)*	16
	1989-93 *(95% CI)* N= 129	**2014-18 *(95% CI)*** N= 259	**Change**	**1989-93 *(95% CI)*** N= 129	**2014-18 *(95% CI)*** N= 259	**Change**
Melanoma without unknown primary	44 *(36-52)*	57 *(51-64)*	13	21 *(14-28)*	23 *(16-30)*	2

Abbreviations: CI: Confidence Interval; N: Sample size; NS: Net survival.

Supplementary Table 8. Median survival (months) of patients diagnosed in 1989-1993 and in 2014-2018, per cancer type

	Median survival in months		
	1989-1993	**2014-2018**	**Change**
Prostate	22.8	39.4	16.6
Testicular	n.a.	n.a.	n.a.
Thyroid	8.7	10.2	1.5
Breast	16.9	35.2	18.3
NET	22.3	64.4	42.1
Vulva/vagina	6.0	5.1	-0.9
Melanoma	10.1	18.1	8.0
Ovarian	8.6	16.5	7.9
Corpus uteri	6.9	10.9	4.0
GIST	9.0	51.8	42.8
Rectum	7.6	16.1	8.5
Cervix uteri	7.4	13.2	5.8
Sarcoma	5.7	8.6	2.9
Colon	5.5	11.4	5.9
Kidney	5.2	8.1	2.9
HNSCC	5.5	5.6	0.1
Bladder	3.8	4.3	0.5
Other solid cancers	1.9	1.5	-0.4
Cancers with an unknown primary site	2.8	5.3	2.5
SCLC	4.3	5.7	1.4
Esophagus/Cardia	3.7	5.2	1.5
Stomach	2.9	4.0	1.1
NSCLC	3.1	5.0	1.9
Lung other	1.8	1.4	-0.4
Bile Ducts	2.3	3.7	1.4
Hepatocellular	1.9	2.3	0.4
Gallbladder	2.2	3.4	1.2
Pancreas	2.0	2.3	0.3
Total	4.1	6.9	2.8

Abbreviations: GIST: Gastrointestinal stromal tumors; HNSCC: head and neck squamous cell carcinoma; NETs: Neuroendocrine Tumors; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer

Supplementary Table 9. Search methods to identify cancer medicines introduced in the Netherlands and the year of introduction for the different types of cancers

The Netherlands Cancer Registry does not collect data about treatment of patients beyond first line. Moreover, it only started collecting information on drug names/classes recently. As such, we collected information (type and date of approval) about the types of cancer medicines per cancer type that were theoretically available for patients with different types of cancers. The approach used is described in the table below. Briefly, we only collected information on newly approved medicines and extensions of indications listed in Summary of Product Characteristics documents. The medicines were categorized by the year of approval or reimbursement and recorded for their first approved use for each cancer type.

Steps	Explanation	
Identification of cancer medicines used in the Netherlands per cancer type		
1	We identified all different types of cancer medicines currently used for the different cancer types in the Netherlands. For this purpose, we consulted the website https://www.bijwerkingenbijkanker.nl/. This website contains information on treatment, treatment regimens, and adverse events related to these treatments. The website is developed by Netherlands Comprehensive Cancer Organization in consultation with several clinical experts and is updated regularly.	[5]
2	We consulted the website of the Association for Medical Oncology in the Netherlands (NVMO). This association has set up a committee since October 1999 and reviews all new European Medicine Association (EMA) approved medicines on clinical value. The objective is to achieve national coordination regarding the use of new and often expensive medicines in clinical practice. On the website, the assessments and final judgment of all new cancer drugs can be found, including a detailed report which describes the considerations for the choice. In our overview of drugs per cancer type, we excluded medicines that received a negative advice from the committee of the NVMO.	[6]
3	For a couple of cancer types, the website (https://www.bijwerkingenbijkanker.nl/) did not contain information regarding treatment. This was the case for vaginal cancer and NET. Information on systemic treatments for NET was obtained from the European Neuroendocrine Tumor Society (ENET) guidelines. Information on systemic treatment for vaginal cancer was obtained from an international website.	[7]
Identification of date of approval of new drugs from 1989-2018		
1	The EMA documentation was consulted to identify the date of approval for each drug and indication. We consulted the EMA 'authorization details' to identify the date of approval for the first indication of a drug. The date of approval of the extension of indications was obtained from the document 'Procedural steps taken and scientific information after the authorization'. It should be noted that the EMA was established in 1995, and thus no information from drugs approved before this date could be obtained from this institute.	EMA
2	For some drugs, the EMA 'Procedural steps taken and scientific information after the authorization' did not provide all extension of indications, especially information on steps taken in EMAs early years was sometimes lacking. If this was the case, we consulted the European Commission (EC) Register of SmPCs per medicine, which can be found on: http://ec.europa.eu/health/documents/community-register/html/reg_hum_act.htm?sort=a. By comparing the changes in the documents over time, it was possible to identify which new extensions of indication were added on a specific date.	[8]
2	The date of approval of drugs for whom no information on the EMA or EC website was obtained from different sources. The first was a personal document created by a professor from the Erasmus School of Health Policy and Management the Netherlands (Erasmus University). This document contained the date of approval of all drugs in the Netherlands since 1989. The document included only the first indication for whom a medicine was approved.	
3.	The second source was the website of the Dutch Medicines Evaluation Board (CBG). This is the national medicines authority in the Netherlands, and information on approval date per drugs can be found on the website. Limitation is that the CBG does not have information on extensions of indications. Therefore, the CBG website was only consulted to identify the date of approval for the first indication and only before 1995.	CBG
4.	The third sources was the publication of Sun et al. 2017 and the website of the Food and Drug Administration (FDA). The publications of Sun et al. reported all FDA approved anti-cancer drugs	FDA

	including the year of approval from 1949 onwards. On the FDA website, information on approval, and extensions of indications can be found. It should be noted that the FDA approves drugs for the United States and thus, the approval date of the FDA is a rough estimate of the introduction date in the Netherlands.	& [9]
5.	The last source we consulted was the website of the ASCO. The ASCO reports a timeline with breakthrough developments for different cancer types, including drugs. This is also an American website and thus only provides a rough estimate of the introduction date in the Netherlands.	[10]
Date of approval of indications for whom a drug is not formally approved but is national and international standard practice		
6.	Some cancer drugs are used in clinical practice based on clinical evidence but used off label because the drug has never been EMA approved for this indication.. This includes mainly the older cytotoxic drugs. These drugs are not listed in de graph of our study because no data is available about the use of these drugs in clinical practice.	
Date of approval of medicines for which reimbursement came later than regulatory approval		
7.	In 2015, the Netherlands government changed their reimbursement procedures. Whereas previously most new inpatient medicines automatically received reimbursement, the government then created an option to postpone reimbursement decisions of new high priced medicines with an expected substantial budget impact. If postponements in reimbursement took place, we used the date of approval of reimbursement in our overview. If medicines were excluded from reimbursement, we assumed they would not be used in clinical practice and thus did not include them in our overview. Reimbursement dates were obtained from the website of the National Health Care institute of the Netherlands.	[12,13]

Abbreviations: ASCO: American society of clinical oncology. CBG: Medicines evaluation board [In Dutch: College ter Beoordeling van Geneesmiddelen] EC: European commission: EMA: European medicines association; ENET: ; FDA: United States Food and Drug Administration: NET: neuroendocrine tumors; NVMO: Association for Medical Oncology in the Netherlands [In Dutch: Nederlandse vereniging voor medische oncologie]; SmPC: Summary of product characteristics.

Supplementary Table 10. Novel medicines and extensions of indications per metastatic cancer, for the metastatic cancer types included in our study, year of introduction, source of approval year

Nr.	Tumor	Year	cBOM	Group	Substance	In SmPC	Source approval date
	HNSCC	[a]	n.j.	Cytotoxic	Carboplatin	No	n.a.
1	HNSCC	2006	2008	Cytotoxic	Docetaxel	Yes	EC
2	HNSCC	2008	2009	Targeted Therapy	Cetuximab	Yes	EMA ext
	HNSCC	2017	2017	Immunotherapy	Nivolumab	Yes	EMA ext – cBOM neg
3	HNSCC	2018	2019	Immunotherapy	Pembrolizumab	Yes	EMA ext
	Esophagus/Cardia	[a]	n.j.	Cytotoxic	Carboplatin	No	n.a.
	Esophagus/Cardia	[a]	n.j.	Cytotoxic	Paclitaxel	No	n.a.
	Esophagus/Cardia	[a]	n.j.	Cytotoxic	Epirubicin	No	n.a.
	Esophagus/Cardia	[a]	n.j.	Cytotoxic	Irinotecan	No	n.a.
	Esophagus/Cardia	[a]	n.j.	Cytotoxic	Capecitabine	No	n.a.
	Esophagus/Cardia	[a]	n.j.	Cytotoxic	Oxaliplatin	No	n.a.
1	Esophagus/Cardia	2006	n.j.	Cytotoxic	Docetaxel	Yes	EC
2	Esophagus/Cardia	2010	2010	Targeted Therapy	Trastuzumab	Yes	EMA - ext
3	Esophagus/Cardia	2014	2015	Targeted Therapy	Ramucirumab	Yes	EMA - ext
	Stomach	[a]	n.j.	Cytotoxic	Carboplatin	No	n.a.
	Stomach	[a]	n.j.	Cytotoxic	Irinotecan	No	n.a.
1	Stomach	1997	n.j.	Cytotoxic	Epirubicin	Yes	Estimate
	Stomach	2006	2007	Cytotoxic	Docetaxel	Yes	EMA ext / cBOM neg
2	Stomach	2007	n.j.	Cytotoxic	Capecitabine	Yes	EMA ext
3	Stomach	2007	n.j.	Cytotoxic	Oxaliplatin	Yes	EMA ext
4	Stomach	2010	2010	Targeted Therapy	Trastuzumab	Yes	EMA ext
	Stomach	2011	2012	Cytotoxic	S-1 (Teysuno)	Yes	EMA / cBOM neg
5	Stomach	2014	2015	Targeted Therapy	Ramucirumab	Yes	EMA
1	Hepatocellular carcinoma	2007	n.j.	Targeted Therapy	Sorafenib	Yes	EMA ext
2	Hepatocellular carcinoma	2017	2017	Targeted Therapy	Regorafenib	Yes	EMA ext
3	Hepatocellular carcinoma	2018	2019	Targeted Therapy	Lenvatinib	Yes	EMA ext
	Gallbladder/Bile ducts	[a]	n.j	Cytotoxic	Epirubicin	No	n.a.
	Gallbladder/Bile ducts	[a]	n.j.	Cytotoxic	Etoposide	No	n.a.
	Gall bladder/Bile ducts	[a]	n.j.	Cytotoxic	Cisplatin	No	n.a.
	Gallbladder/Bile ducts	[a]	n.j.	Cytotoxic	Gemcitabine	No	n.a.
	Gallbladder/Bile ducts	[a]	n.j.	Cytotoxic	Oxaliplatin	No	n.a.

	Gallbladder/Bile ducts	[a]	n.j.	Cytotoxic	Capecitabine	No	n.a.
1	Pancreas	1996	2001	Cytotoxic	Gemcitabine	Yes	FDA
2	Pancreas	2007	n.j.	Targeted therapy	Erlotinib	Yes	EMA ext
3	Pancreas	2012	2012	Regime	FOLFIRINOX	Yes	cBOM
4	Pancreas	2013	2015	Cytotoxic	Nab-Paclitaxel	Yes	EMA ext / cBOM neg later pos
5	Pancreas	2016	2017	Cytotoxic	Irinotecan liposomaal	Yes	EC
1	GIST	2002	n.j.	Targeted therapy	Imatinib	Yes	EMA - ext
2	GIST	2006	n.j.	Targeted therapy	Sunitinib	Yes	EMA
3	GIST	2014	2014	Targeted therapy	Regorafenib	Yes	EMA ext
	SCLC	[a]	n.j.	Cytotoxic	Carboplatin	Yes	n.a.
	SCLC	[a]	n.j.	Cytotoxic	Teniposide	??	n.a.
	SCLC	[a]	n.j.	Cytotoxic	Paclitaxel	No	n.a.
	SCLC	[a]	n.j.	Cytotoxic	Docetaxel	No	n.a.
1	SCLC	2006	2008	Cytotoxic	Topotecan	Yes	EMA ext
	NSCLC	[a]	n.j.	Cytotoxic	Carboplatin	Yes	n.a.
	NSCLC	??	n.j.	Cytotoxic	Cisplatin	Yes	n.a.
	NSCLC	[a]	n.j.	Cytotoxic	Paclitaxel	Yes	n.a.
	NSCLC	[a]	n.j.	Cytotoxic	Vinorelbine	Yes	n.a.
1	NSCLC	1998	n.j.	Cytotoxic	Gemcitabine	Yes	FDA
2	NSCLC	2000	2003	Cytotoxic	Docetaxel	Yes	EC
3	NSCLC	2004	2005	Cytotoxic	Pemetrexed	Yes	EMA
4	NSCLC	2005	2006	Targeted therapy	Erlotinib	Yes	EMA
5	NSCLC	2007	2008	Targeted therapy	Bevacizumab	Yes	EMA ext – cBOM only for pts with contra-indication for cisplatin
6	NSCLC	2009	2010	Targeted therapy	Gefitinib	Yes	EMA
7	NSCLC	2012	2013	Targeted therapy	Crizotinib	Yes	EMA
8	NSCLC	2013	2014	Targeted therapy	Afatinib	Yes	EMA
	NSCLC	2014	2016	Targeted therapy	Nintedanib	Yes	EMA / cBOM neg
9	NSCLC	2015	2018	Targeted therapy	Ceritinib	Yes	EMA
10	NSCLC	2015	n.j.	Cytotoxic	Nab-Paclitaxel (Abraxane)	Yes	EC
11	NSCLC	2015/2016[R]	2015	Immunotherapy	Nivolumab	Yes	EMA ext
12	NSCLC	2016	2017	Targeted therapy	Osimertinib	Yes	EMA
13	NSCLC	2016/2017[R]	2017	Immunotherapy	Pembrolizumab	Yes	EMA ext
	NSCLC	2016	2016	Targeted therapy	Ramucirumab	Yes	EMA ext - cBOM neg
14	NSCLC	2017	2018	Targeted therapy	Alectinib	Yes	EMA
15	NSCLC	2017/2018[R]	2018	Immunotherapy	Atezolizumab	Yes	EMA
16	NSCLC	2017	n.j.	Targeted therapy	Trametinib	Yes	EMA ext
17	NSCLC	2017	n.j.	Targeted therapy	Dabrafenib	Yes	EMA ext
18	NSCLC	2018	2020	Targeted therapy	Durvalumab	Yes	EMA
19	NSCLC	2018	2020	Targeted therapy	Brigatinib	Yes	EMA

1	Melanoma	2011	2011	Immunotherapy	Ipilimumab	Yes	EMA
2	Melanoma	2012	2012	Targeted therapy	Vemurafenib	Yes	EMA
3	Melanoma	2013	2014	Targeted therapy	Dabrafenib	Yes	EMA
4	Melanoma	2014	2016	Targeted therapy	Trametinib	Yes	EMA
5	Melanoma	2015	2016	Targeted therapy	Cobimetinib	Yes	EMA
6	Melanoma	2015	2015	Immunotherapy	Nivolumab	Yes	EMA
7	Melanoma	2015	2016	Immunotherapy	Pembrolizumab	Yes	EMA
8	Melanoma	2015	2017	Viral therapy	Talimogene laherparepvec	Yes	EMA / cBOM clinical value not assessable
9	Melanoma	2018	2019	Targeted therapy	Binimetinib	Yes	EMA
10	Melanoma	2018	2019	Targeted therapy	Encorafenib	Yes	EMA
	Bone	[a]	n.j.	Cytotoxic	Gemcitabine	No	n.a.
	Sarcoma	[a]	n.j.	Cytotoxic	Docetaxel	No	**
	Sarcoma	[a]	n.j.	Cytotoxic	Gemcitabine	No	**
1	Sarcoma	1998	n.j.	Cytotoxic	Paclitaxel	Yes	Estimate
2	Sarcoma	2006	n.j.	Targeted therapy	Imatinib	Yes	EMA ext
3	Sarcoma	2007	n.j.	Cytotoxic	Trabectedine	Yes	Steenhoek
4	Sarcoma	2012	2013	Targeted therapy	Pazopanib	Yes	EMA ext
5	Sarcoma (Bone)	2014	n.j.	Targeted therapy	Denosumab	Yes	EMA ext
6	Sarcoma	2016	2018	Cytotoxic	Eribulin	Yes	EMA ext
	Sarcoma	2016	2017	Targeted therapy	Olaratumab	Yes	EMA – cBOM neg, no longer authorized by EMA
	Breast	[a]	n.j.	Cytotoxic	Carboplatin	No	n.a.
1	Breast	1995	2000	Cytotoxic	Docetaxel	Yes	EMA
2	Breast	1996	2001	Hormonal therapy	Anastrozol	Yes	Steenhoek
3	Breast	1997	2001	Hormonal therapy	Letrozol	Yes	Steenhoek / SmPC
4	Breast	1999	2001	Hormonal Therapy	Exemestane	Yes	Steenhoek / SmPC
5	Breast	2000	2001	Targeted thearpy	Trastuzumab	Yes	EMA
	Breast	2001	2001	Cytotoxic	Vinorelbine	Yes	cBOM - neg
6	Breast	2002	2003	Cytotoxic	Capecitabine	Yes	EC
7	Breast	2003	2005	Cytotoxic	Doxorubicin (liposomaal)	Yes	EC
8	Breast	2004	2004	Hormonal therapy	Fulvestrant	Yes	EMA
9	Breast	2004	2009	Cytotoxic	Gemcitabine	Yes	ASCO
10	Breast	2007	2008	Targeted therapy	Bevacizumab	Yes	EMA - ext
11	Breast	2008	2008	Targeted therapy	Lapatinib	Yes	EMA
	Breast	2008	2012	Cytotoxic	Nab-Paclitaxel (Abraxane)	Yes	EC / cBOM neg
12	Breast	2011	2011	Cytotoxic	Eribulin	Yes	EMA
13	Breast	2012	2012	Targeted therapy	Everolimus	Yes	EMA ext

14	Breast	2013	n.j.	Targeted therapy	Trastuzumab-Emtansine	Yes	EMA
15	Breast	2013	2013	Targeted therapy	Pertuzumab	Yes	EMA
16	Breast	2016/2017[b]	2017	Targeted therapy	Palbociclib	Yes	EMA
17	Breast	2017/2018[b]	2017	Targeted therapy	Ribociclib	Yes	EMA
18	Breast	2018/2019[b]		Targeted therapy	Abemaciclib	Yes	EMA
	Vulva	[a]	n.j.	Cytotoxic	Capecitabine	No	n.a.
	Vulva	[a]	n.j.	Cytotoxic	Carboplatin	No	n.a.
	Vulva	[a]	n.j.	Cytotoxic	Cisplatin	No	n.a.
	Vulva	[a]	n.j.	Cytotoxic	Docetaxel	No	n.a.
	Vulva	[a]	n.j.	Cytotoxic	Paclitaxel	No	n.a.
	Vulva	[a]	n.j.	Cytotoxic	Topotecan	No	n.a.
		[a]					
	Vaginal	[a]	n.j.	Cytotoxic	Carboplatin	No	n.a.
	Vaginal	[a]	n.j.	Cytotoxic	Cisplatin	No	n.a.
	Vaginal	[a]	n.j.	Cytotoxic	Docetaxel	No	n.a.
	Vaginal	[a]	n.j.	Cytotoxic	Paclitaxel	No	n.a.
	Vaginal	[a]	n.j.	Cytotoxic	Irinotecan	No	n.a.
		[a]					
	Cervix Uteri	[a]	n.j.	Cytotoxic	Carboplatin	No	n.a.
	Cervix Uteri	[a]	n.j.	Cytotoxic	Docetaxel	No	n.a.
	Cervix Uteri	[a]	n.j.	Cytotoxic	Paclitaxel	No	n.a.
1	Cervix Uteri	2006	n.j.	Cytotoxic	Topotecan	Yes	EMA ext
2	Cervix Uteri	2015	2015	Targeted Therapy	Bevacizumab	Yes	EMA ext
	Corpus uteri	[a]		Cytotoxic	Carboplatin	No	n.a.
	Corpus uteri	[a]		Cytotoxic	Paclitaxel	No	n.a.
	Corpus uteri	[a]		Hormonal therapy	Anastrozol	No	n.a.
	Corpus uteri	[a]		Cytotoxic	Topotecan	No	n.a.
	Corpus uteri	[a]		Hormonal therapy	Letrozol	No	n.a.
	Corpus uteri	[a]		Cytotoxic	Docetaxel	No	n.a.
	Corpus uteri	[a]		Cytotoxic	Gemcitabine	No	n.a.
		[a]					
	Ovarian	[a]	n.j.	Cytotoxic	Docetaxel	No	n.a.
	Ovarian	[a]	n.j.	Cytotoxic	Capecitabine	No	n.a.
	Ovarian	[a]	n.j.	Hormonal therapy	Letrozol	No	n.a.
	Ovarian	[a]	n.j.	Hormonal therapy	Anastrozol	No	n.a.
	Ovarian	[a]	n.j.	Hormonal therapy	Exemestane	No	n.a.
	Ovarian	[a]	n.j.	Cytotoxic	Nab-Paclitaxel (Abraxane)	No	n.a.
1	Ovarian	1989	n.j.	Cytotoxic	Carboplatin	Yes	Sun et al.
2	Ovarian	1993	n.j.	Cytotoxic	Paclitaxel	Yes	Steenhoek
3	Ovarian	1996	n.j.	Cytotoxic	Topotecan	Yes	EMA
4	Ovarian	2006	n.j.	Cytotoxic	Gemcitabine	Yes	FDA
	Ovarian	2009	2013	Cytotoxic	Trabectedine	Yes	EMA ext - cBOM neg
5	Ovarian	2011	2013	Targeted therapy	Bevacizumab	Yes	EMA - ext

6	Ovarian	2014	2017	Targeted therapy	Olaparib	Yes	EMA / cBOM
7	Ovarian	2018	2019	Targeted therapy	Rucaparib	Yes	EMA
8	Ovarian	2018	2019	Targeted therapy	Niraparib	Yes	EMA
1	Prostate	1989	n.j.	Hormonal therapy	Gosereline	Yes	Sun et al. 2016*
2	Prostate	1989	n.j.	Hormonal therapy	Flutamide		Sun et al. 2016*
3	Prostate	1995	n.j.	Hormonal therapy	Bicalutamide	Yes	CBG / Steenhoek
4	Prostate	1996	n.j.	Hormonal therapy	Nilutamide (Anandron)	Yes	CBG
5	Prostate	2004	2005	Cytotoxic	Docetaxel	Yes	EC
6	Prostate	2009	n.j.	Hormonal therapy	Degarelix	Yes	EMA
7	Prostate	2011	2012	Hormonal therapy	Abiraterone	Yes	cBOM
8	Prostate	2011	2011	Cytotoxic	Cabazitaxel	Yes	EMA
9	Prostate	2013	n.j.	Therapeutic cancer vaccin	Provenge	Yes	EMA
10	Prostate	2013	2013	Hormonal Therapy	Enzalutamide	Yes	EMA
11	Prostate	2013	2014	Therapeutic radiopharmaceuticals	Radium 223	Yes	EMA
	Testis	[a]	n.j.	Chemotherapy	Paclitaxel	No	n.a.
1	Kidney	1992		Immunotherapy	Interleukin-2 (IL-2)	??	ASCO
2	Kidney	2006	2007	Targeted therapy	Sunitinib	Yes	EMA
3	Kidney	2006	2007	Targeted therapy	Sorafenib	Yes	EMA
4	Kidney	2007	2008	Targeted therapy	Bevacizumab	Yes	EMA ext
5	Kidney	2007	2008	Targeted therapy	Temsirolimus	Yes	EMA
6	Kidney	2009	2010	Targeted therapy	Everolimus	Yes	EMA
7	Kidney	2010	2011	Targeted therapy	Pazopanib	Yes	EMA
	Kidney	2012	2013	Targeted therapy	Axitinib	Yes	EMA / cBOM neg
8	Kidney	2016	2017	Targeted therapy	Lenvatinib	Yes	EMA
9	Kidney	2016	2016	Immunotherapy	Nivolumab	Yes	EMA ext
10	Kidney	2016	2016	Targeted therapy	Cabozantinib	Yes	EMA
11	Kidney	2017	2018	Targeted therapy	Tivozanib	Yes	EMA
12	Kidney	2018	2019	Immunotherapy	Ipilimumab	Yes	EMA ext
13	Kidney	2019	2020	Immunotherapy	Avelumab	Yes	EMA ext
14	Kidney	2019	2020	Immunotherapy	Pembrolizumab	Yes	EMA ext
	Bladder	[a]	n.j.	Cytotoxic	Carboplatin	No	n.a.
1	Bladder	2000	2001	Cytotoxic	Gemcitabine	Yes	ASCO
	Bladder	2009	2010	Cytotoxic	Vinflunin	Yes	EMA / cBOM neg
	Bladder	2017	2018	Immunotherapy	Atezolizumab	Yes	EMA / cBOM neg
2	Bladder	2017	n.j.	Immunotherapy	Nivolumab	Yes	EMA ext
3	Bladder	2017	2017	Immunotherapy	Pembrolizumab	Yes	EMA ext

1	Thyroid Gland	2012	2013	Targeted therapy	Vandetanib	Yes	EMA
2	Thyroid Gland	2014	2015	Targeted therapy	Cabozantinib	No	EMA
3	Thyroid Gland	2014	2014	Targeted therapy	Sorafenib	Yes	EMA ext
4	Thyroid Gland	2015	2016	Targeted therapy	Lenvatinib	Yes	EMA ext
1	Colon / Rectum	1999	2001	Cytotoxic	Oxaliplatin	Yes	Steenhoek
2	Colon / Rectum	2000	2000	Cytotoxic	Irinotecan	Yes	FDA / cBOM
3	Colon / Rectum	2001	2001	Cytotoxic	Capecitabine	Yes	cBOM
4	Colon / Rectum	2002	2002	Cytotoxic	S-1 (Teysuno)	No	cBOM
5	Colon / Rectum	2004	2008*	Targeted therapy	Cetuximab	Yes	EMA / cBOM neg 2004 – 62008 pos (2008 in timeline)
6	Colon / Rectum	2005	2005	Targeted therapy	Bevacizumab	Yes	EMA
7	Colon / Rectum	2007	2008	Targeted therapy	Panitumumab	Yes	EMA
	Colon / Rectum	2013	2013	Targeted therapy	Regorafenib	Yes	EMA / cBOM neg
	Colon / Rectum	2016	2016	Targeted therapy	Ramucirumab	Yes	EMA ext / cBOM neg
8	Colon / Rectum	2016	2016	Cytotoxic	Trifluridine/tipiracil TAS 102(Lonsurf)	Yes	EMA
	Anus	[a]	n.j.	Cytotoxic	Capecitabine	No	n.a.
		[a]					
	NET	[a]	n.j.	Cytotoxic	Carboplatin	No	n.a.
	NET	[a]	n.j.	Cytotoxic	Dacarbazine	No	ENET guidelines table 2
	NET	[a]	n.j.	Cytotoxic	Capecitabine	No	ENET guidelines table 2
	NET	[a]	n.j.	Cytotoxic	Oxaliplatin	No	ENET guidelines table 2
	NET	[a]	n.j.	Cytotoxic	Temozolomide	No	ENET guidelines table 2
1	NET	1992	n.j.	SSA	Octreotide	Yes	Qaudevlieg et al. [11]
2	NET	1998		SSA	Octreotide LAR	Yes	FDA
3	NET	2000		Immunotherapy	Interferon alfa 2b	Yes	EC
4	NET	2010	2011	Targeted therapy	sunitinib	Yes	EMA ext
5	NET	2011	2016	Targeted therapy	everolimus	Yes	EMA ext
6	NET	2015	2015	SSA	lanreotide	Yes	cBOM
7	NET	2015	2015	Cytotoxic	Irinotecan	No	cBOM
8	NET	2017	2017	Other	lutetium (177Lu) oxodotreotide	Yes	EC docs

The medicines and corresponding information presented in light grey text, are 1) medicines that are available for use for patients with the specific cancer type, but were most likely approved prior to 1989; 2) medicines that are EMA approved for the indication but are most likely not used in the Netherlands because the professional association gave a negative advise for using this medicine. Abbreviations: ASCO: American Society of Clinical Oncology; cBOM: committee assessment of oncologic agents; EC: European Commission; ENET: European Neuroendocrine Tumor Society; EMA; European Medicines Association; ext: extension of indication; FDA: Food and Drug Administration

(United States); HNSCC: head and neck squamous cell carcinoma; GIST: Gastrointestinal stromal tumors; n.a.: not applicable; neg: negative; NET: Neuroendocrine tumors; n.j.; not judged; NSCLC: non-small cell lung cancer; pos: positive: SCLC: small cell lung cancer; SmPC; summary of product characteristics: SSA: somatostatin analogues.

a year of introduction unknown but likely introduced during the study period as drug was approved for the first indication during the study period or just before. b reimbursement year for medicines for whom drugs required additional evaluations to determine on the reimbursement

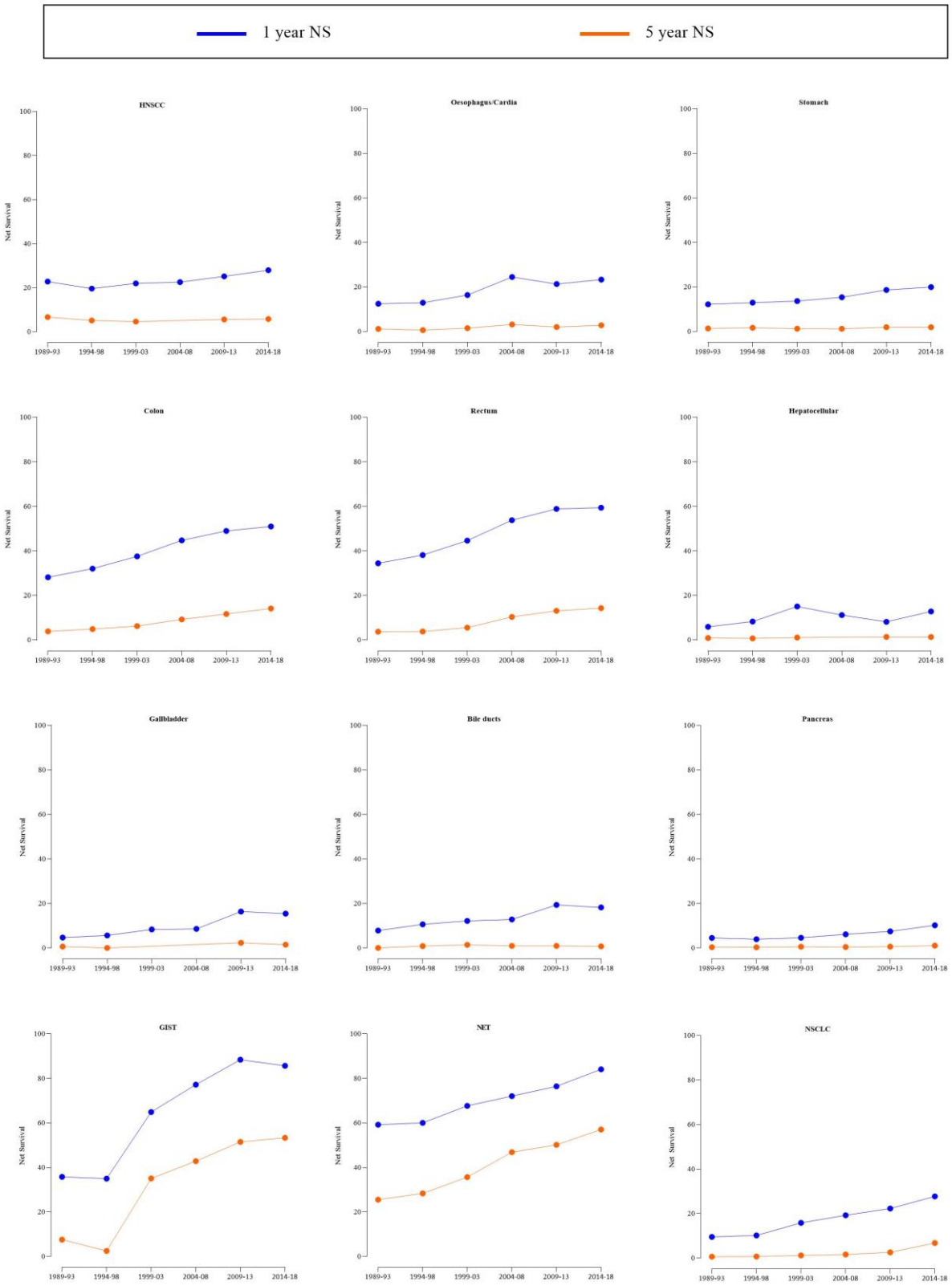
Note: drugs including Bleomycin, Cisplatin, Cyclofosfamide, Dacarbazine, Dactinomycin, Doxorubicin, Etoposide, Fluorouracil (5-FU), Ifosfamide, Leuprorelin, Medroxyprogesterone, Methotrexate, Megestrol, Streptozocin, Tamoxifen, Vinblastine, Vincristine are assumed to be introduced before 1989 for all tumors.

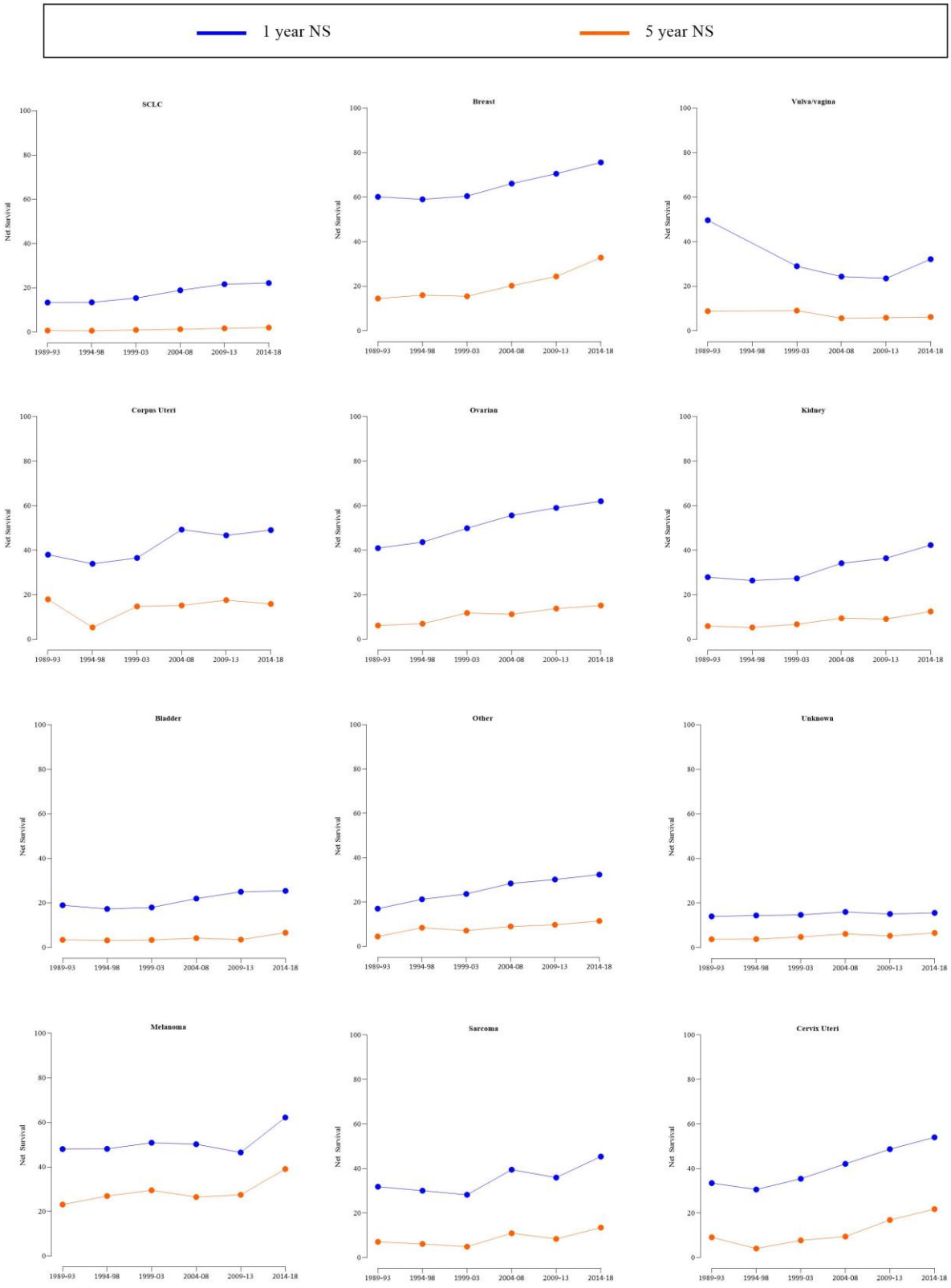
Supplementary Table 11. Initial systemic therapies of patients with GIST and breast cancer, obtained from the Netherlands Cancer Registry

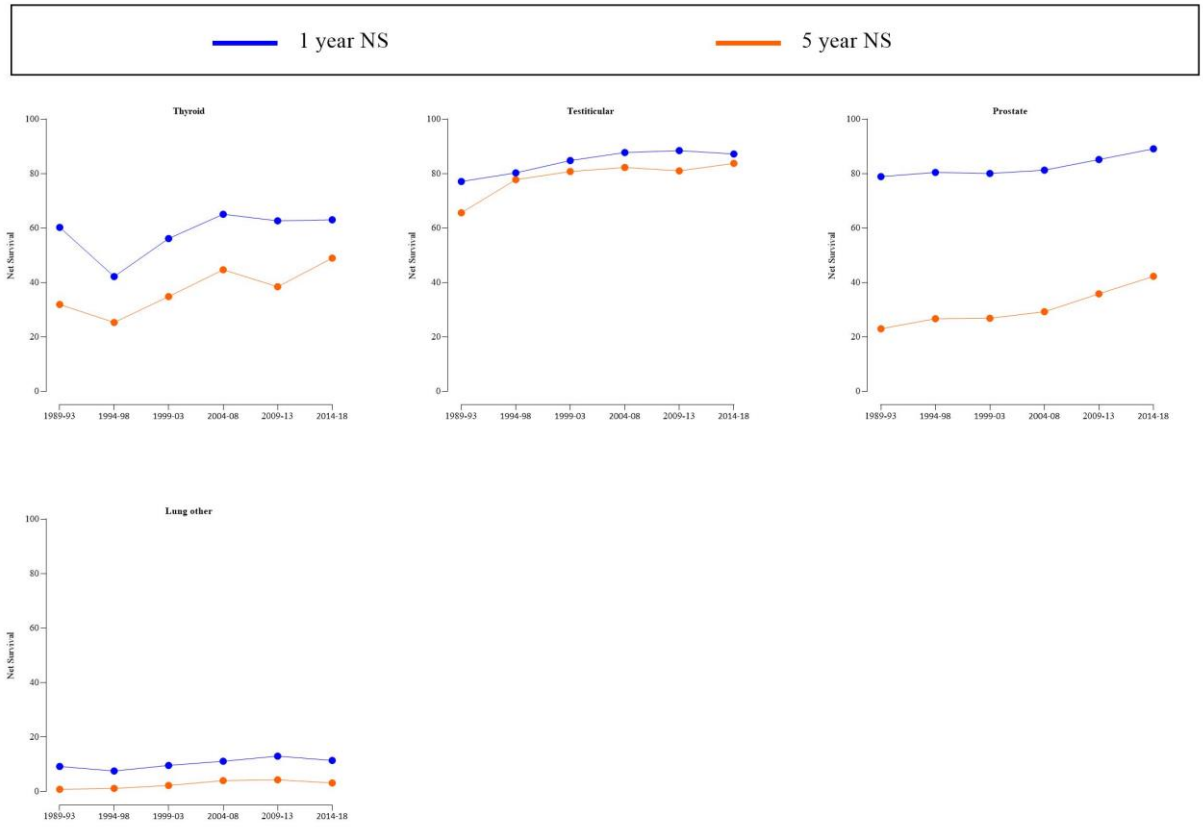
First line therapy	**2014-18**
GIST	**N = 160**
Imatinib	116 (73%)
TKI ns	17 (11%)
Targeted therapy unspecified	2 (1%)
Only surgery	11 (7%)
Other	3 (2%)
No therapy	11 (7%)
Breast cancer HER2+	**N= 808**
HER2 targeted therapy (with or without chemo)	667 (83%)
Only endocrine therapy (HR+/HER2+)	75 (9%)
Only an unspecified targeted therapy / other targeted therapy	4 (0.5%)
Only chemotherapy	6 (1%)
Chemotherapy + endocrine therapy	4 (0.5%)
Other/none	52 (6%)

Abbreviations: GIST: Gastrointestinal stromal tumors: HER2: Human epidermal growth factor receptor 2; HR+: hormone receptor positive; N: Sample size; NCR: Netherlands cancer registry; TKIs: Tyrosine kinase inhibitors.

Supplementary Figure 1. Changes in de novo metastatic cancer survival over time, per cancer type, 1-year and 5-year




1 year NS
5 year NS
SCLC
Breast
Vulva/vagina
Corpus Uteri
Ovarian
Kidney
Bladder
Other
Unknown
Melanoma
Sarcoma
Cervix Uteri
Net Survival
0
20
40
60
80
100
1989-93
1994-98
1999-03
2004-08
2009-13
2014-18



Abbreviations: HNSCC: head and neck squamous cell carcinoma; NET: Neuroendocrine Tumors; NS: Net survival: GIST: Gastrointestinal stromal tumors; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer.

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