Appendix: Supplementary material [posted as supplied by author]

Figure A. Identification of cohort of drugs

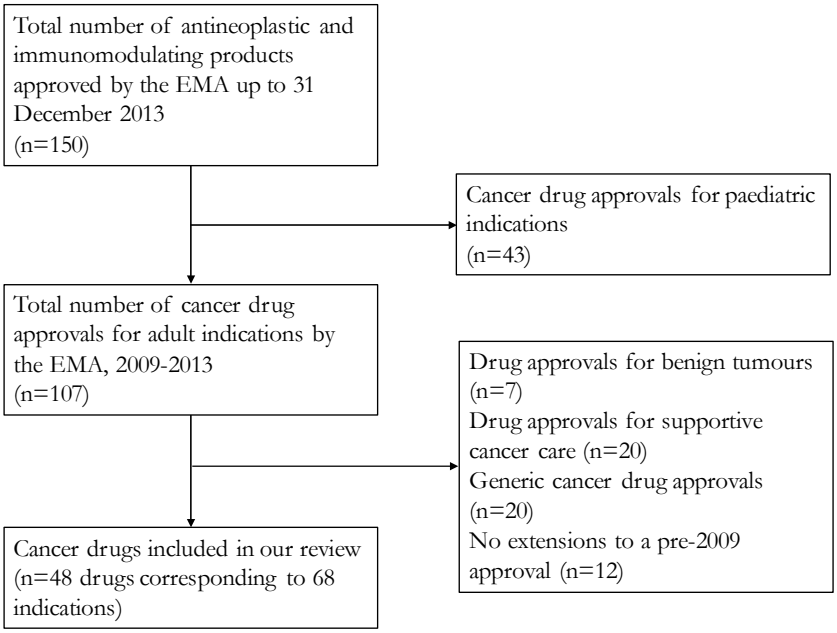

Figure B. Identification and selection of postmarketing studies.

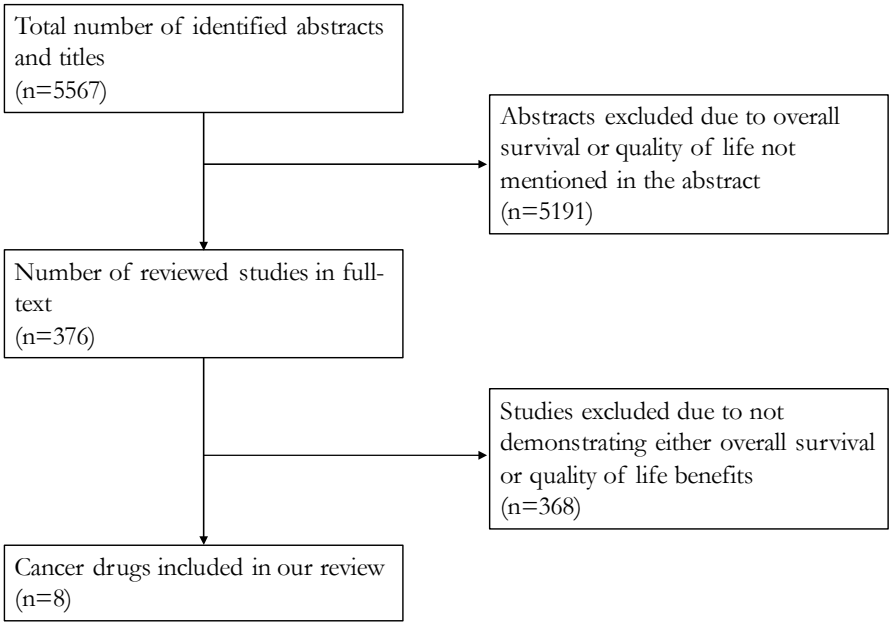

Table A. List of indications for which therapeutic agents received marketing authorisations, 2009-2013.

Agent	Cancer site	Indication	Date of marketing authorisation	Type and pathway of marketing authorisation *
abiraterone acetate	Prostate	post-chemo mCRPC (+ pred)	05/09/2011	First MA; R
abiraterone acetate	Prostate	pre-chemo mCRPC (+ pred)	18/12/2012	Type II Variation
afatinib	Lung	TKI-naïve EFGR mut+ mNSCLC	25/09/2013	First MA; R
aflibercept	Colorectal	2nd line mCRC (+ FOLFIRI)	01/02/2013	First MA; R
axitinib	Renal	2nd line advanced RCC	03/09/2012	First MA; R
bevacizumab [a]	Breast	1st line mBC (+ docetaxel)	23/07/2009	Type II Variation
bevacizumab	Breast	1st line mBC (+ capecitabine). No prior taxanes or anthracyclines	29/06/2011	Type II Variation
bevacizumab	Ovary	1st line (+ carboplatin and paclitaxel) in ≥Stage IIIB ovarian, fallopian, or primary peritoneal cancer	19/12/2011	Type II Variation
bevacizumab	Ovary	2nd line (+ carboplatin and gemcitabine) platinum-sensitive ovarian, fallopian, or primary peritoneal cancer. No prior VEGFi	24/10/2012	Type II Variation
bortezomib	Haematological	1st line multiple myeloma eligible for SCT (+dexamethasone or dexamethasone + thalidomide)	31/07/2013	Type II Variation
bortezomib	Haematological	2nd line multiple myeloma ineligible for SCT (monotherapy or + doxorubicin or dexamethasone)	18/12/2013	Type II Variation
bosutinib	Haematological	2nd or 3rd line CP, AP, BP Ph+ CML	27/03/2013	First MA; C; O
brentuximab vedotin	Haematological	relapsed or refractory CD30+ HL after ASCT or 3rd line if ineligible for ASCT	25/10/2012	First MA; C; O
brentuximab vedotin	Haematological	relapsed or refractory systemic ALCL	25/10/2012	First MA; C; O
cabazitaxel	Prostate	hormone refractory mPC (+pred) previously treated with docetaxel	17/03/2011	First MA; R
cetuximab	Colorectal	1st line KRAS WT mCRC (+ FOLFOX)	13/01/2012	Type II Variation
crizotinib	Lung	2nd line ALK+ advanced NSCLC	23/10/2012	First MA; C
dabrafenib	Skin	unresectable or metastatic melanoma w/BRAF V600 mut	26/08/2013	First MA; R
dasatinib	Haematological	1st line Ph+ CML (CP)	06/12/2010	Type II Variation
decitabine	Haematological	1st line AML in chemo-ineligible adults aged 65+	20/09/2012	First MA; R; O
degarelix	Prostate	advanced PC	17/02/2009	First MA; R
docetaxel	Breast	adjuvant treatment of operable node-negative BC (+ doxorubicin and cyclosphamide)	01/07/2010	Type II Variation
enzalutamide	Prostate	mCRPC previously treated with docetaxel	21/06/2013	First MA; R
eribulin	Breast	3rd line mBC	17/03/2011	First MA; R
erlotinib	Lung	maintenance therapy in mNSCLC (previous platinum-based chemo)	27/04/2010	Type II Variation
erlotinib	Lung	1st line EGFR mut+ mNSCLC	24/08/2011	Type II Variation
everolimus	Breast	2nd line HER2/neu-negative BC (+exemetane)	23/07/2012	Type II Variation
everolimus	Pancreas	unresectable or metastatic well or moderately differentiated PNET	24/08/2011	Type II Variation
everolimus	Renal	advanced RCC following VEGF-targeted therapy	03/08/2009	First MA; R; O
gefitinib	Lung	EGFR mut+ mNSCLC	24/06/2009	First MA; R
imatinib	Stomach	adjuvant treatment for high risk GIST	29/04/2009	Type II Variation; O
ipilimumab	Skin	2nd line unresectable or metastatic melanoma	13/07/2011	First MA; R
ipilimumab	Skin	1st line unresectable or metastatic melanoma	31/10/2013	Type II Variation
lapatinib	Breast	HER2+ HR+ mBC (+ aromatase inhibitor). No prior chemo, trastuzumab or AI	05/05/2010	Type II Variation
lapatinib	Breast	HER2+ HR- mBC (+ trastuzumab). Prior trastuzumab + chemo	25/07/2013	Type II Variation

Agent	Cancer site	Indication	Date of marketing authorisation	Type and pathway of marketing authorisation *
mifamurtide	Bone	resectable, non-metastatic osteosarcoma following complete resection (+ chemo)	06/03/2009	First MA; R; O
nab-pactlitaxel	Pancreatic	1st line (+ gemcitabine) metastatic pancreatic adenoca	02/12/2013	Type II Variation
nilotinib	Haematological	newly diagnosed adult Ph+ CML (CP)	20/12/2010	Type II Variation
ofatumumab	Haematological	CLL refractory to fludarabine and alemtuzumab	19/04/2010	First MA; C; O
panitumumab	Colorectal	1st line KRAS WT mCRC (+ FOLFOX)	10/11/2011	Type II Variation
panitumumab	Colorectal	2nd line KRAS WT mCRC (+FOLFIRI)	10/11/2011	Type II Variation
pazopanib	Renal	1st line advanced RCC	14/06/2010	First MA; C
pazopanib	Renal	2nd line advanced RCC (prior cytokine)	14/06/2010	First MA; C
pazopanib	Soft tissue	advanced STS (post-chemo or progressed within 12 months after neo-adjuvant therapy)	03/08/2012	Type II Variation
pemetrexed	Lung	maintenance for mNSCLC (non squam) post platinum-based doublet chemo (w/gemcitabine or taxane)	02/07/2009	Type II Variation
pemetrexed	Lung	maintenance for mNSCLC (non squam) post platinum based chemo	24/10/2011	Type II Variation
pertuzumab	Breast	1st line HER2+ mBC	04/03/2013	First MA; R
pixantrone	Haematological	multiple relapsed or refractory NHL (B-cell)	10/05/2012	First MA; C
pomalidomide	Haematological	3rd line (+ dexamethasone) relapsed and refractory multiple myeloma	05/08/2013	First MA; R, O
ponatinib	Haematological	CML (CP, AP, BP) resistant or intolerant to dasatinib or nilotinib, or with T315I mutation or ineligible for imatinib	01/07/2013	First MA; R; O
ponatinib	Haematological	Ph+ ALL resistant or intolerant to dasatinib, or with T315I mutation or ineligible for imatinib	01/07/2013	First MA; R; O
regorafenib	Colorectal	mCRC either following prior therapy with/or ineligible for 5FU-based chemo or VEGFi or EGFRi therapy	26/08/2013	First MA; R
rituximab	Haematological	1st line CLL (+ chemo)	23/02/2009	Type II Variation
rituximab	Haematological	relapsed/refractory CLL (+ chemo)	21/08/2009	Type II Variation
rituximab	Haematological	maintenance therapy for follicular lymphoma post induction	25/10/2010	Type II Variation
sunitinib	Pancreas	2nd line unresectable or metastatic, well-differentiated PNET	29/11/2010	Type II Variation
tegafur/gimeracil/oteracil	Stomach	advanced GC (+ cisplatin)	14/03/2011	First MA; R
temsirolimus	Haematological	relapsed or refractory MCL	14/10/2009	Type II Variation
trabectedin	Ovary	relapsed (platinum-sensitive) ovarian cancer (+ PLD)	28/10/2009	Type II Variation
trastuzumab	Stomach	1st line HER2+ mGC or mGOJ adenoca	19/01/2010	Type II Variation
trastuzumab	Breast	HER2+ BC (+ taxane) post adjuvant chemo	20/04/2011	Type II Variation
trastuzumab	Breast	HER2+ BC (+ adjuvant chemo)	20/04/2011	Type II Variation
trastuzumab	Breast	HER2+ locally advanced BC (+ neoadjuvant chemo and as monotherapy adjuvantly)	19/12/2011	Type II Variation
trastuzumab emtansine	Breast	HER2+ unresectable or mBC following trastuzumab and/or taxane therapy	15/11/2013	First MA; R
vandetanib	Throid	unresectable or metastatic medullary TC	17/02/2012	First MA; C
vemurafenib	Skin	unresectable or metastatic melanoma (BRAF V600 mut)	17/02/2012	First MA; R
vinflunine	Urinary	advanced or metastatic TCC or the urothelial tract. Prior platinum regimen	21/09/2009	First MA; C
vismodegib	Skin	mBCC	12/07/2013	First MA; C

[a] This indication was subsequently withdrawn.

* **MA**: marketing authorisation; **C**: conditional marketing authorisation; **O**: orphan designation; **R**: regular (full) marketing authorisation.

Abbreviations: **5FU**: 5 fluorouracil; **adenoca**: adenocarcinoma; **AI**: aromatase inhibitor; **ALCL**: anaplastic large cell lymphoma; **ALK**: anaplastic lymphoma kinase; **ALL**: acute lymphoblastic leukaemia; **AML**: acute myeloid leukaemia; **AP**: accelerated phase; **ASCT**: autologous stem cell transplant; **BC**: breast cancer; **BCC**: basal cell carcinoma; **BP**: blast phase; **chemo**: chemotherapy; **CLL**: chronic lymphocytic leukaemia **CML**: chronic myelogenous leukaemia; **CP**: chronic phase; **EFGR**: epidermal growth factor receptor; **FOLFIRI**:

irinotecan/5 fluorouracil/folinic acid; **FOLFOX**: oxaliplatin/5 fluorouracil/folinic acid; **GC**: gastric cancer; **GIST**: gastrointestinal stromal tumours; **HL**: Hodgkin lymphoma; **HR**: hormone receptor; **mBC**: metastatic breast cancer; **MCL**: mantle cell lymphoma; **mCRC**: metastatic colorectal cancer; **mCRPC**: metastatic castration resistant prostate cancer; **mGC**: metastatic gastric cancer; **mGOJ**: metastatic gastric or esophageal junction; **mNSCLC**: metastatic non-small cell lung cancer; **mPC**: metastatic prostate cancer; **mut**: mutation; **NHL**: non-Hodgkin lymphoma; **PC**: prostate cancer; **Ph+**: Philadelphia chromosome positive; **PLD**: pegylated liposomal doxorubicin; **PNET**: pancreatic neuroendocrine tumours; **pred**: prednisone or prednisolone; **RCC**: renal cell carcinoma; **SCT**: stem cell transplantation; **squam**: squaemous; **STS**: soft tissue sarcoma; **TC**: thyroid cancer; **TCC**: transitional cell carcinoma; **TKI**: tyrosine kinase inhibitor; **VEGFi**: vascular endothelial growth factor inhibitor; **WT**: wild-type.

Table B. Characteristics of pivotal trials supporting marketing authorization decisions.

Agent (EPAR reference)	Cancer site	Indication	Design[a]	Crossover[b]	Intervention and control groups	Primary endpoint[c]	OS or QoL as secondary endpoints[d]
abiraterone acetate (EMEA/H/C/ 002321)	Prostate	post-chemo mCRPC (+ pred)	PBO, DB, RCT	NR	Group 1: abiraterone acetate + pred (n=797) Group 2: PBO + pred (n=398)	OS	NA
abiraterone acetate (EMEA/H/C/ 002321/II/0004/G)	Prostate	pre-chemo mCRPC (+ pred)	PBO, DB, RCT	Yes	Group 1: abiraterone acetate + pred (n=546) Group 2: PBO + pred (n=542)	OS, PFS	QoL
afatinib (EMEA/H/C/ 002280)	Lung	TKI-naïve EFGR mut+ mNSCLC	AC, OL, RCT	Yes	Gruop 1: afatinib (n=230) Group 2: pemetrexed + cisplatin (n=115)	PFS	OS, QoL
aflibercept (EMEA/H/C/ 002532)	Colorectal	2nd line mCRC (+ FOLFIRI)	PBO, DB, RCT	No	Group 1: aflibercept followed by FOLFIRI (n=612) Group 2: PBO followed by FOLFIRI (n=614)	OS, PFS	
axitinib (EMEA/H/C/ 002406)	Renal	2nd line advanced RCC	AC, OL, RCT	NR	Group 1: axitinib (n=361) Group 2: sorafenib (n=362)	PFS	OS, QoL
bevacizumab (EMEA/H/C/ 000582/II/0041)	Ovary	1st line (+ carboplatin and paclitaxel) in ≥Stage IIIB ovarian, fallopian, or primary peritoneal cancer	PBO, DB, RCT	No	Group 1: bevacizumab + carboplatin and paclitaxel chemo followed by PBO alone (n=625) Group 2: bevacizumab + carboplatin and paclitaxel chemo followed by bevacizumab alone (n=623) Group 3: PBO + carboplatin and paclitaxel chemo followed by PBO alone (n=625)	Originally OS, then changed to PFS	OS, QOL
bevacizumab (EMEA/H/C/ 000582/II/0041)	Ovary	1st line (+ carboplatin and paclitaxel) in ≥Stage IIIB ovarian, fallopian, or primary peritoneal cancer	Add-on, OL, RCT	No	Group 1: bevacizumab + carboplatin and paclitaxel chemo followed by bevacizumab alone (n=764) Group 2: carboplatin and paclitaxel chemo (n=764)	PFS	OS, QOL
bevacizumab (EMEA/H/C/ 000582/II/0046)	Ovary	2nd line (+ carboplatin and gemcitabine) platinum-sensitive ovarian, fallopian, or primary peritoneal cancer. No prior VEGFi	PBO, DB, RCT	Yes	Group 1: carboplatin and gemcitabine + concomitant and extended bevacizumab (n=242) Group 2: carboplatin and gemcitabine + concomitant and extended PBO (n=242)	PFS	OS

bevacizumab [e] (EMEA/H/C/ 582/II/0024)	Breast	1st line mBC (+docetaxel) [e]	PBO, DB, RCT	Yes	Group 1: bevacizumab 7.5mg/kg + docetaxel (n=248) Group 2: bevacizumab 15 mg/kg + docetaxel (n=247) Group 3: PBO + docetaxel (n=241)	PFS	OS, QOL
bevacizumab (EMEA/H/C/ 000582/II/0033)	Breast	1st line mBC (+ capecitabine). No prior taxanes or anthracyclines	PBO, DB, RCT	Yes	Group 1: capecitabine + bevacizumab (n=409) Group 2: capecitabine + PBO (n=206)	PFS	OS
bortezomib (EMEA/H/C/ 000539/II/0059)	Haematological	1st line multiple myeloma eligible for SCT (+dexamethasone or dexamethasone + thalidomide)	AC, OL, RCT	NR	Group 1: bortezomib, andriamycin, and dexamethasone (n=417) Group 2: vincristine, adriamycin, and dexamethasone (n=416)	PFS	OS
bortezomib (EMEA/H/C/ 000539/II/0059)	Haematological	1st line multiple myeloma eligible for SCT (+dexamethasone or dexamethasone + thalidomide)	AC, OL, RCT	NR	Group 1: bortezomib and dexamethasone (n=240) Group 2: vincristine, adriamycin, and dexamethasone (n=242)	CR+nCR rate	OS
bortezomib (EMEA/H/C/ 000539/II/0059)	Haematological	1st line multiple myeloma eligible for SCT (+dexamethasone or dexamethasone + thalidomide)	Add-on, AC, OL, RCT	NR	Group 1: vincristine, bis-chloronitrosourea, melphalan, cyclophosphamide, prednisone-vincristine, bis-chloronitrosourea, adriamycin, dexamesthasone/bortezomib (n=129) Group 2: bortezomib/thalidomide/dexamethasone (n=130) Arm 3: thalidomide/dexamethasone (n=127)	CR+nCR+PR, and CR+nCR rate	OS
bortezomib (EMEA/H/C/ 000539/II/0063/G)	Haematological	2nd line multiple myeloma ineligible for SCT (monotherapy or + doxorubicin or dexamethasone)	AC, OL, RCT	NR	Group 1: caelyx + bortezomib (n=324) Group 2: bortezomib (n=322)	TTP	OS
bosutinib (EMEA/H/C/ 002373)	Haematological	2nd or 3rd line CP, AP, BP Ph+ CML	SAT	NA	Group 1: bosutinib (n=546) Group 2: none	MCyR (PCyR or CCyR)	OS
brentuximab vedotin (EMEA/H/C/ 002455)	Haematological	relapsed or refractory CD30+ HL after ASCT or 3rd line if ineligible for ASCT	SAT	NA	Group 1: brentuximab vedotin (n=102) Group 2: none	ORR	OS
brentuximab vedotin (EMEA/H/C/ 002455)	Haematological	relapsed or refractory systemic ALCL	SAT	NA	Group 1: brentuximab vedotin (n=58) Group 2: none	ORR	OS

cabazitaxel (EMEA/H/C/ 002018)	Prostate	hormone refractory mPC (+pred) previously treated with docetaxel	AC, OL, RCT	NR	Arm 1: cabazitaxel + pred (n=378) Arm 2: mitoxantrone + pred (n=377)	OS	NA
cetuximab (EMEA/H/C/ 000558/II/0047)	Colorectal	1st line KRAS WT mCRC (+ FOLFOX)	AC, OL, RCT	NR	Group 1: cetuximab + FLOX (n=194) Group 2: cetuximab + intermittent FLOX (n=187) Group 3: FLOX (n=185)	PFS	OS
crizotinib (EMEA/H/C/ 002489)	Lung	2nd line ALK+ advanced NSCLC	SAT	NA	Group 1: crizotinib (response evaluable n=121) Group 2: none	ORR	OS
dabrafenib (EMEA/H/C/ 002604/0000)	Skin	unresectable or metastatic melanoma w/BRAF V600 mut	AC, OL, RCT	Yes	Group 1: dabrafenib (n=187) Group 2: dacarbazine (n=63)	PFS	OS, QoL
dasatinib (EMEA/H/C/ 000709/II/23)	Haematological	1st line Ph+ CML (CP)	AC, OL, RCT	NR	Group 1: dasatinib (n=259) Group 2: imatinib (n=260)	cCCyR	OS
decitabine (EMEA/H/C/ 002221)	Haematological	1st line AML in chemo-ineligible adults aged 65+	AC, OL, RCT	NR	Group 1: decitabine and/or supportive care (n=242) Group 2: cytarabine and/or supportive care (n=243)	OS	QoL - tertiary
degarelix (EMEA/H/C/ 000986)	Prostate	advanced PC	AC, OL, RCT (non-inferiority)	NR	Group 1: degarelix (n=409) Group 2: leuprorelin (n=201)	Testosterone ≤0.5 ng/mL	QoL
docetaxel (EMA/H/C/ 000073/II/0090)	Breast	adjuvant treatment of operable node-negative BC (+ doxorubicin and cyclosphamide)	AC, OL, RCT	NR	Group 1: docetaxel + doxorubicin and cyclophosphamide (n=539) Group 2: 5-fluorouracil + doxurubicin and cyclophosphamide (n=521)	DFS	OS, QOL
enzalutamide (EMEA/H/C/ 002639)	Prostate	mCRPC previously treated with docetaxel	PBO, DB, RCT	Yes	Group 1: MDV3100 – enzalutamide (n=800) Group 2: PBO (n=399)	OS	QoL
eribulin (EMEA/H/C/ 002084)	Breast	3rd line mBC	AC, OL, RCT	NR	Group 1: eribulin (n=508) Group 2: physician's choice (n=254)	OS	NA
erlotinib (EMEA/H/C/ 000618/II/0017)	Lung	maintenance therapy in mNSCLC (previous platinum-based chemo)	PBO, DB, RCT	No	Group 1: platinum-based chemo + erlotinib (n=438) Group 2: platinum-based chemo + PBO (n=451)	PFS	OS, QOL

erlotinib (EMEA/H/C/ 000618/II/0020)	Lung	1st line EGFR mut+ mNSCLC	AC, OL, RCT	Yes	Group 1: erlotinib (n=77) Group 2: chemo (cisplatin + docetaxel, cisplatin + gemcitabine, docetaxel, gemcitabine) (n=77)	PFS	OS, QOL
everolimus (EMEA/H/C/ 001038)	Renal	advanced RCC following VEGF-targeted therapy	PBO, DB, RCT	Yes	Group 1: everolimus + BSC (n=272) Group 2: PBO + BSC (n=138)	PFS	OS, QOL
everolimus (EMEA/H/C/ 001038/II/0008)	Pancreas	unresectable or metastatic well or moderately differentiated PNET	PBO, DB, RCT	Yes	Group 1: everolimus (n=207) Group 2: PBO (n=203)	PFS	OS
everolimus (EMEA/H/C/ 001038/II/0020)	Breast	2nd line HER2/neu-negative BC (+exemetane)	PBO, DB, RCT	No	Group 1: exemestane + everolimus (n=485) Group 2: exemestane + PBO (n=239)	PFS	OS, QOL
gefitinib (EMEA/H/C/ 001016)	Lung	EGFR mut+ mNSCLC	AC, OL, RCT (non-inferiority)	Yes	Group 1: gefitinib (n=609) Group 2: carboplatin and paclitaxel chemo (n=608)	PFS	OS, QOL
gefitinib (EMEA/H/C/ 001016)	Lung	EGFR mut+ mNSCLC	AC, OL, RCT (non-inferiority)	Yes	Group 1: gefitinib (n=733) Group 2: docetaxel (n=733)	OS	QOL as a subsection of secondary endpoint
gefitinib (EMEA/H/C/ 001016)	Lung	EGFR mut+ mNSCLC	PBO, DB, RCT	NR	Group 1: gefitinib + BSC (n=1129) Group 2: PBO + BSC (563)	OS	QoL
imatinib (EMEA/H/C/ 406/II/0048)	Stomach	adjuvant treatment for high risk GIST	PBO, DB, RCT	Yes	Group 1: imatinib (n=359) Group 2: PBO (n=354)	Originally OS, then changed to RFS	OS
ipilimumab (EMEA/H/C/ 002213)	Skin	2nd line unresectable or metastatic melanoma	PBO, DB, RCT	NR	Group 1: ipilimumab + gp100 (n=403) Group 2: gp100 + PBO (n=136) Group 3: ipilimumab + PBO (n=137)	OS	QoL
ipilimumab (EMEA/H/C/ 002213/II/0008)	Skin	1st line unresectable or metastatic melanoma	PBO, DB, RCT	NR	Group 1: dacarbazine + ipilimumab (n=250) Group 2: dacarbazine + PBO (n=252)	OS	QoL
lapatinib (EMA/H/C/ 795/II/0004)	Breast	HER2+ HR+ mBC (+ aromatase inhibitor). No prior chemo, trastuzumab or AI	PBO, DB, RCT	NR	Group 1: letrozole + lapatinib (n=111) Group 2: letrozole + PBO (n=108)	PFS	OS, QOL
lapatinib (EMEA/H/C/	Breast	HER2+ HR- mBC (+ trastuzumab).	AC, OL, RCT	Yes	Group 1: lapatinib + trastuzumab (n=148) Group 2: lapatinib (n=148)	PFS	OS, QOL

000795/II/0022)		Prior trastuzumab + chemo					
mifamurtide (EMEA/H/C/ 000802)	Bone	resectable, non-metastatic osteosarcoma following complete resection (+ chemo)	Add-on, OL, RCT	NR	Group 1: maintenance therapy with induction chemo + L-MTP-PE (n=167) Group 2: maintenance therapy with induction chemo + cisplatin + L-MTP-PE (n=171) Group 3: maintenance therapy with induction chemo (n=174) Group 4: maintenance therapy with induction chemo + cisplatin (n=166)	DFS	OS
nab-pactlitaxel (EMEA/H/C/ 000778/II/0055)	Pancreas	1st line (+ gemcitabine) metastatic pancreatic adenoca	Add-on, OL, RCT	Yes	Group 1: abraxane (paclitaxel) + gemcitabine (n=431) Group 2: gemcitabine (n=430)	OS	NA
nilotinib (EMEA/H/C/ 000798/II/0029)	Haematological	newly diagnosed adult Ph+ CML (CP)	AC, OL, RCT	NR	Group 1: nilotinib (300 mg) (n=282) Group 2: nilotinib (400 mg) (n=281) Group 3: imatinib (400 mg) (n=283)	MMR Rate	OS
ofatumumab (EMEA/H/C/ 001131)	Haematological	CLL refractory to fludarabine and alemtuzumab	SAT	NA	Group 1: ofatumumab (n=154) Group 2: none	RR	OS, QoL
panitumumab (EMEA/H/C/ 000741/II/0017)	Colorectal	1st line KRAS WT mCRC (+ FOLFOX)	Add-on, OL, RCT	No	Group 1: panitumumab + FOLFOX (n=593; WT KRAS=325) Group 2: FOLFOX (n=590; WT KRAS=331)	PFS	OS, QoL - tertiary
panitumumab (EMEA/H/C/ 000741/II/0017)	Colorectal	2nd line KRAS WT mCRC (+FOLFIRI)	Add-on, OL, RCT	No	Group 1: panitumumab + FOLFIRI (n=591; WT KRAS=303) Group 2: FOLFIRI (n=595; WT KRAS=294)	PFS, OS	NA
pazopanib (EMEA/H/C/ 001141/II/0007)	Soft tissue	advanced STS (post-chemo or progressed within 12 months after neo-adjuvant therapy)	PBO, DB, RCT	NR	Group 1: pazopanib (n=246) Group 2: PBO (n=123)	PFS	OS, QoL (exploratory endpoint)
pazopanib (EMEA/H/C/ 001141)	Renal	1st line advanced RCC & 2nd line advanced RCC (prior cytokine)	PBO, DB, RCT	Yes	Group 1: pazopanib (n=290) Group 2: PBO (n=145)	PFS	OS; QoL (tertiary endpoint)
pemetrexed (EMEA/H/C/ 000564/II/0015)	Lung	maintenance for mNSCLC (non squam) post platinum-based doublet chemo (w/gemcitabine or taxane)	PBO, DB, RCT	NR	Group 1: pemetrexed + BSC (n=441) Group 2: placebo + BSC (n=222)	PFS	OS, QOL

pemetrexed (EMEA/H/C/ 000564/II/0033)	Lung	maintenance for mNSCLC (non squam) post platinum based chemo)	PBO, DB, RCT	NR	Group 1: pemetrexed + BSC (n=359) Group 2: PBO + BSC (n=180)	PFS	OS, QOL
pertuzumab (EMEA/H/C/ 002547/0000)	Breast	1st line HER2+ mBC	PBO, DB, RCT	No	Group 1: pertuzumab + trastuzumab + docetaxel (n=402) Group 2: placebo + trastuzumab + docetaxel (n=406)	PFS	OS; QoL
pixantrone (EMEA/H/C/ 002055)	Haematological	multiple relapsed or refractory NHL (B-cell)	AC, OL, RCT	NR	Group 1: pixantrone (n=70) Group 2: physician's choice (n=70)	CR and CRu	OS
pomalidomide (EMEA/H/C/ 002682)	Haematological	3rd line (+ dexamethasone) relapsed and refractory multiple myeloma	AC, OL, RCT	Yes	Group 1: pomalidomide + low dose dexamethasone (n=302) Group 2: high dose dexamethasone (n=153)	PFS	OS, QoL
ponatinib (EMEA/H/C/ 002695/0000)	Haematological	CML (CP, AP, BP) resistant or intolerant to dasatinib or nilotinib, or with T315I mutation or ineligible for imatinib & Ph+ ALL resistant or intolerant to dasatinib, or with T315I mutation or ineligible for imatinib	SAT	NA	Group 1: ponatinib (Cohort A (n=203) CP-CML with disease resistant to, or intolerant to dasatinib or nilotinib. Cohort B (n=64) CP-CML with T315I mut. Cohort C (n=65) AP-CML. Cohort D (n=18) AP-CML with T315I mut. Cohort E (n=48) BP/Ph+ALL. Cohort F (n=46) BP-CML / Ph+ALL with T315I mut) Group 2: none	Cohorts A-B MCyR; Cohorts C-F MaHR	OS
regorafenib (EMEA/H/C/ 002573/0000)	Colorectal	mCRC either following prior therapy with/or ineligible for 5FU-based chemo or VEGFi or EGFRi therapy	PBO, DB, RCT	Yes	Group 1: regorafenib + BSC (n=505) Group 2: PBO + BSC (n=255)	OS	QoL (tertiary endpoint)
rituximab (EMEA/H/C/ 165/II/0060)	Haematological	1st line CLL (+ chemo)	Add-on, OL, RCT	Yes	Group 1: rituximab + fludarabine and cyclophosphamide (n=408) Group 2: fludarabine and cyclophosphamide (n=409)	PFS	OS
rituximab (EMEA/H/C/ 165/II/0064)	Haematological	relapsed/refractory CLL (+ chemo)	Add-on, OL, RCT	NR	Group 1: rituximab + fludarabine and cyclophosphamide (n=276) Group 2: fludarabine and cyclophosphamide (n=276)	PFS	OS, QoL (not stated as secondary

							but results reported)
rituximab (EMEA/H/C/ 000165/II/0069)	Haematological	maintenance therapy for follicular lymphoma post induction	Add-on, OL, RCT	NR	Group 1: rituximab maintenance (n=505) Group 2: no treatment (observation) (n=513)	PFS	OS, QOL
sunitinib (EMA/H/C/ 000687/II/0021)	Pancreas	2nd line unresectable or metastatic, well-differentiated PNET	PBO, DB, RCT	Yes	Group 1: sunitinib (n=86) Group 2: PBO (n=85)	PFS	OS, QOL
tegafur/ gimeracil/ oteracil (EMEA/H/C/ 0001242)	Stomach	advanced GC (+ cisplatin)	AC, OL, RCT (switched to non-inferiority post-hoc)	NR	Group 1: tegafur/gimeracli/oteracil + cisplatin (n=527) Group 2: 5-FU+cisplatin (n=526)	OS	
temsirolimus (EMEA/H/C/ 000799/II/0001)	Haematological	relapsed or refractory MCL	AC, OL, RCT	Yes	Group 1: temsirolimus (n=108) Group 2: investigator's choice (n=54)	PFS	OS
trabectedin (EMEA/H/C/ 000773/II/0008)	Ovary	relapsed (platinum-sensitive) ovarian cancer (+ PLD)	Add-on, OL, RCT	NR	Group 1: pegylated liposomal doxorubicin followed by trabectedin (n=337) Group 2: pegylated liposomal doxorubicin (n=335)	PFS	OS, QoL - tertiary
trastuzumab (EMEA/H/C/ 000278/II/0053)	Breast	HER2+ BC (+ taxane) post adjuvant chemo	Add-on, OL, RCT	Yes	Group 1: doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab (n=1058) Group 2: doxorubicin + cyclophosphamide followed by paclitaxel (n=1061)	DFS	OS
trastuzumab (EMEA/H/C/ 000278/II/0053)	Breast	HER2+ BC (+ taxane) post adjuvant chemo	Add-on, OL, RCT	Yes	Group 1: doxorubicin and cyclophosphamide followed by paclitaxel followed by trastuzumab (n=814) Group 2: doxorubicin and cyclophosphamide followed by paclitaxel (n=819)	DFS	OS
trastuzumab (EMEA/H/C/ 000278/II/0053)	Breast	HER2+ BC (+ adjuvant chemo)	Add-on, OL, RCT	No	Group 1: doxorubicin and cyclophosphamide followed by trastuzumab (n=1074) Group 2: docetaxel, carboplatin and trastuzumab (n=1075) Group 3: doxorubicin and cyclophosphamide followed by docetaxel (n=1073)	DFS	OS, QoL
trastuzumab (EMEA/H/C/ 278/II/0047)	Stomach	1st line HER2+ mGC or mGOJ adenoca	Add-on, OL, RCT	NR	Group 1: trastuzumab + fluropyrimidine (5-FU or capecatebine) and cisplatin (n=294) Group 2: fluropyrimidine (5-FU or capecatebine) and cisplatin (n=290)	OS	QoL

trastuzumab (EMEA/H/C/ 000278/II/57)	Breast	HER2+ locally advanced BC (+ neoadjuvant chemo and as monotherapy adjuvantly)	Add-on, OL, RCT	Yes	Group 1: neoadjuvant trastuzumab + neoadjuvant chemo followed by adjuvant trastuzumab (n=116) Group 2: neoadjuvant chemo for HER2+ disease (n=99) Group 2: neoadjuvant chemo for HER2– disease (n=99)	EFS	OS
trastuzumab emtansine (EMEA/H/C/ 002389/0000)	Breast	HER2+ unresectable or mBC following trastuzumab and/or taxane therapy	AC, OL, RCT	Yes	Group 1: trastuzumab emtansine (n=495) Group 2: lapatinib + capecitabine (n=496)	PFS, OS	QoL
vandetanib (EMEA/H/C/ 002315//0000)	Thyroid	unresectable or metastatic medullary TC	PBO, DB, RCT	Yes	Group 1: vandetanib (n=231) Group 2: PBO (n=100)	PFS	OS
vemurafenib (EMEA/H/C/ 002409)	Skin	unresectable or metastatic melanoma (BRAF V600 mut)	AC, OL, RCT	Yes	Group 1: vemurafenib (n=337) Group 2: dacarbazine (n=338)	OS, PFS initially planned as secondary	QoL
vinflunine (EMEA/H/C/ 000983)	Urinary	advanced or metastatic TCC or the urothelial tract. Prior platinum regimen	Add-on, OL, RCT	NR	Group 1: vinflunine + BSC (n=253) Group 2: BSC (n=117)	OS	QoL
vismodegib (EMEA/H/C/ 002602)	Skin	mBCC	SAT	NA	Group 1: vismodegib (n=96) Group 2: none	ORR	OS

[a] **AC**: active-comparator; **DB**: double-blind; **OL**: open-label; **PBO**: placebo; **RCT**: randomised controlled trial; **SAT**: single-arm trial.

[b] **NA**: not applicable; **NR**: not reported.

[c] **CR**: complete remission; **CCyR**: complete cytogenetic response; **CRu**: unconfirmed complete response; **DFS**: disease-free survival; **EFS**: event-free survival; **MaHR**; major haematological response; **MCyR**; major cytogenetic response; **MMR**: major molecular response; **nCR**: near-complete remission; **ORR**: overall response rate; **OS**: overall survival; **PCyR**; partial cytogenetic response; **PFS**: progression-free survival; **PR**: partial response; **RFS**: relapse-free survival; **RR**: response rate; **TTP**: time-to-progression.

[d] **NA**: not applicable; **OS**: overall survival; **QoL**: quality of life.

[e] This indication was subsequently withdrawn.

Abbreviations: **5FU**: 5 fluorouracil; **adenoca**: adenocarcinoma; **AI**: aromatase inhibitor; **ALCL**: anaplastic large cell lymphoma; **ALK**: anaplastic lymphoma kinase; **ALL**: acute lymphoblastic leukaemia; **AML**: acute myeloid leukaemia; **AP**: accelerated phase; **ASCT**: autologous stem cell transplant; **BC**: breast cancer; **BCC**: basal cell carcinoma; **BP**: blast phase; **BSC**: best supportive care; **chemo**: chemotherapy; **CLL**: chronic lymphocytic leukaemia **CML**: chronic myelogenous leukaemia; **CP**: chronic phase; **EFGR**: epidermal growth factor receptor; **FOLFIRI**: irinotecan/5 fluorouracil/folinic acid; **FOLFOX**: oxaliplatin/5 fluorouracil/folinic acid; **GC**: gastric cancer; **GIST**: gastrointestinal stromal tumours; **HL**: Hodgkin lymphoma; **HR**: hormone receptor; **mBC**: metastatic breast cancer; **MCL**: mantle cell lymphoma; **mCRC**: metastatic colorectal cancer; **mCRPC**: metastatic castration resistant prostate cancer; **mGC**: metastatic gastric cancer; **mGOJ**: metastatic gastric or esophageal junction; **mNSCLC**: metastatic non-small cell lung cancer; **mPC**: metastatic prostate cancer; **mut**: mutation; **NHL**: non-Hodgkin lymphoma; **PC**: prostate cancer; **Ph+**: Philadelphia chromosome positive; **PLD**: pegylated liposomal doxorubicin; **PNET**: pancreatic neuroendocrine tumours; **pred**: prednisone or prednisolone; **RCC**: renal cell carcinoma; **SCT**: stem cell transplantation; **squam**: squaemous; **STS**: soft tissue sarcoma; **TC**: thyroid cancer; **TCC**: transitional cell carcinoma; **TKI**: tyrosine kinase inhibitor; **VEGFi**: vascular endothelial growth factor inhibitor; **WT**: wild-type.