Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Definitions of evidence of OS benefit in FDA-approved labels.

1. With documented OS benefit:

Category	**Detailed definition** [1]
Confirmed or inferred statistically significant overall survival benefit	FDA label included a statement referring to **final or interim trial results** saying that the drug has (statistically significant) (overall) survival benefits in trials with patients for whom the drug is indicated **or** showed numerical data on overall survival in final or interim analyses that allow inference of statistically significant OS benefit: a. FDA label included a statement that the drug does have (statistically significant) (overall) survival benefits in final or interim analyses b. FDA label presented numerical OS data indicating statistically significant OS benefit with at least one of the following: • Survival difference (Kaplan Meier curve) – measured by HR: 95% CI<1 • Number/proportion of deaths by defined time – p<0.05 • Time to death (months) – p<0.05 • Median overall survival (months) – p<0.05

2. Without documented OS benefit:

Category	**Detailed definition**
Confirmed or inferred lack of statistically significant overall survival benefit	FDA label included a statement that the drug did not have (statistically significant) (overall) survival benefits **or** showed numerical data on overall survival, in final or interim analyses. a. FDA label included a statement that the drug did not have (statistically significant) (overall) survival benefits in final or interim analyses b. FDA label showed numerical data that allow inference of lack of statistically significant OS benefit with at least one of the following (not including non-inferiority designs): • Survival difference (Kaplan Meier curve) – measured by HR: 95% CI includes 1 • Number/proportion of deaths by defined time – p>0.05 • Time to death (months) – p>0.05 • Median overall survival (months) – p>0.05

[1] Naci H, Guan XD, Woloshin S, Xu Z, Wagner AK. Communication of Survival Data in US Food and Drug Administration-Approved Labeling of Cancer Drugs. JAMA Intern Med. 2021 Jul 12:e213505.haob.

Category	Detailed definition
Overall survival data obtained from a trial with non-inferiority design	OS data were obtained from a trial with non-inferiority design.
Overall survival not mentioned, or overall survival results not reported or not reported in a way that can support inference	a) The label for the drug-indication pair did not mention (overall) survival (not in text, no data in figures or tables) except to say that it was not measured. b) The label included overall survival among trial endpoints but results are not reported. c) The label included overall survival but results are not reported in a way that can support inference.

eTable 2. Indications approved by the FDA for 44 oral targeted cancer drugs,* 2011-2018.

Drug number	Generic name	Brand name	Date of indication approval	New indication approved	Line of therapy: adjuvant, first line, second line+, any line**
1	Abemaciclib	VERZENIO	20170928	VERZENIO™ is a kinase inhibitor indicated: in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy; as monotherapy for the treatment of adult patients with HRpositive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.	Second line+
2	Abiraterone acetate	ZYTIGA	20110428	ZYTIGA is a CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.	Second line+
2	Abiraterone acetate	ZYTIGA	20121210	In combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).	First line
2	Abiraterone acetate	ZYTIGA	20180207	In combination with prednisone for the treatment of patients with metastatic castration-sensitive prostate cancer (CSPC).	First line
3	Acalabrutinib	CALQUENCE	20171031	CALQUENCE is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.	Second line+
4	Afatinib dimaleate	GILOTRIF	20130712	GILOTRIF is a kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Limitation of Use: Safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations.	First line
4	Afatinib dimaleate	GILOTRIF	20160415	Treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy.	Second line+
5	Alectinib hydrochloride	ALECENSA	20151211	ALECENSA is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.	Second line+
6	Apalutamide	ERLEADA	20180214	ERLEADA is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.	First line
7	Axitinib	INLYTA	20120127	INLYTA is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.	Second line+
8	Binimetinib	MEKTOVI	20180627	MEKTOVI is a kinase inhibitor indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.	Any line

Drug number	Generic name	Brand name	Date of indication approval	New indication approved	Line of therapy: adjuvant, first line, second line+, any line**
9	Bosutinib monohydrate	BOSULIF	20120904	BOSULIF is a kinase inhibitor indicated for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy.	Second line+
10	Brigatinib	ALUNBRIG	20170428	ALUNBRIG is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. This indication is approved under accelerated approval based on tumor response rate and duration of response.	Second line+
11	Cabozantinib s-malate	COMETRIQ	20121129	COMETRIQ is a kinase inhibitor indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).	Second line+
11	Cabozantinib s-malate	CABOMETYX	20160425	CABOMETYX is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior antiangiogenic therapy.	Second line+
12	Ceritinib	ZYKADIA	20140429	ZYKADIA is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.	Second line+
13	Cobimetinib fumarate	COTELLIC	20151110	COTELLIC is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib. Limitation of Use: COTELLIC is not indicated for treatment of patients with wild-type BRAF melanoma.	Any line
14	Crizotinib	XALKORI	20110826	XALKORI is a kinase inhibitor indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test.	First line
15	Dabrafenib mesylate	TAFINLAR	20130529	TAFINLAR is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Limitation of use: TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma.	First line
15	Dabrafenib mesylate	TAFINLAR	20140109	TAFINLAR in combination with trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. The use in combination is based on the demonstration of durable response rate. Improvement in disease-related symptoms or overall survival has not been demonstrated for TAFINLAR in combination with trametinib.	First line
15	Dabrafenib mesylate	TAFINLAR	20170622	TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with: metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test.	Second line+
15	Dabrafenib mesylate	TAFINLAR	20180430	TAFINLAR is indicated, in combination with trametinib, for: the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.	Adjuvant
15	Dabrafenib mesylate	TAFINLAR	20180504	TAFINLAR is indicated, in combination with trametinib, for: the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional	Any line

Drug number	Generic name	Brand name	Date of indication approval	New indication approved	Line of therapy: adjuvant, first line, second line+, any line**
				treatment options. Limitations of Use: TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF NSCLC, or wild-type BRAF ATC.	
16	Enasidenib mesylate	IDHIFA	20170801	IDHIFA is an isocitrate dehydrogenase-2 inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA approved test.	Second line+
17	Encorafenib	BRAFTOVI	20180627	BRAFTOVI is a kinase inhibitor indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test. Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma.	First line
18	Enzalutamide	XTANDI	20120831	XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.	Second line+
19	Gilteritinib fumarate	XOSPATA	20181128	XOSPATA is a kinase inhibitor indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test.	Second line+
20	Idelalisib	ZYDELIG	20140723	Zydelig is a kinase inhibitor indicated for the treatment of patients with: relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.	Second line+
20	Idelalisib	ZYDELIG	20140723	Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies. Accelerated approval was granted for FL and SLL based on overall response rate. Improvement in patient survival or disease related symptoms has not been established. Continued approval for these indications may be contingent upon verification of clinical benefit in confirmatory trials.	Second line+
20	Idelalisib	ZYDELIG	20140723	Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies. Accelerated approval was granted for FL and SLL based on overall response rate. Improvement in patient survival or disease related symptoms has not been established. Continued approval for these indications may be contingent upon verification of clinical benefit in confirmatory trials.	Second line+
21	Ivosidenib	TIBSOVO	20180720	TIBSOVO is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test.	Second line+
22	Ixazomib citrate	NINLARO	20151120	NINLARO is a proteasome inhibitor indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.	Second line+
23	Larotrectinib	VITRAKVI	20181126	VITRAKVI is a kinase inhibitor indicated for the treatment of adult and pediatric patients with solid tumors that: have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment. This indication is approved under accelerated approval based on overall response rate and duration of response.	Second line+

Drug number	Generic name	Brand name	Date of indication approval	New indication approved	Line of therapy: adjuvant, first line, second line+, any line**
				Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.	
24	Lenvatinib mesylate	LENVIMA	20150213	LENVIMA is a kinase inhibitor indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.	Second line+
24	Lenvatinib mesylate	LENVIMA	20160513	Renal Cell Cancer (RCC): in combination with everolimus, for patients with advanced RCC following one prior anti-angiogenic therapy.	Second line+
24	Lenvatinib mesylate	LENVIMA	20180815	For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).	First line
25	Lorlatinib	LORBRENA	20181102	LORBRENA is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease; or alectinib as the first ALK inhibitor therapy for metastatic disease; or ceritinib as the first ALK inhibitor therapy for metastatic disease. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.	Second line+
26	Midostaurin	RYDAPT	20170428	RYDAPT is a kinase inhibitor indicated for the treatment of adult patients with: newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. Limitations of Use: RYDAPT is not indicated as a single-agent induction therapy for the treatment of patients with AML.	First line
26	Midostaurin	RYDAPT	20170428	Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).	First line
27	Neratinib maleate	NERLYNX	20170717	NERLYNX is a kinase inhibitor indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.	Adjuvant
28	Niraparib tosylate	ZEJULA	20170327	ZEJULA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.	Second line+
29	Olaparib	LYNPARZA	20141219	LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.	Second line+
29	Olaparib	LYNPARZA	20170817	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy.	Second line+

Drug number	Generic name	Brand name	Date of indication approval	New indication approved	Line of therapy: adjuvant, first line, second line+, any line**
29	Olaparib	LYNPARZA	20180112	In patients with deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.	Second line+
29	Olaparib	LYNPARZA	20181219	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy.	Second line+
30	Osimertinib mesylate	TAGRISSO	20151113	TAGRISSO is a kinase inhibitor indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutationpositive non-small cell lung cancer (NSCLC), as detected by an FDA approved test, who have progressed on or after EGFR TKI therapy. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.	Second line+
30	Osimertinib mesylate	TAGRISSO	20180418	The first-line treatment of patients with metastatic NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.	First line
31	Palbociclib	IBRANCE	20150203	IBRANCE is a kinase inhibitor indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. This indication is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.	First line
32	Panobinostat lactate	FARYDAK	20150223	FARYDAK, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.	Second line+
33	Pomalidomide	POMALYST	20130208	POMALYST is a thalidomide analogue indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.	Second line+
34	Ponatinib hydrochloride	ICLUSIG	20121214	ICLUSIG is a kinase inhibitor indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy. This indication is based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with Iclusig.	Second line+

Drug number	Generic name	Brand name	Date of indication approval	New indication approved	Line of therapy: adjuvant, first line, second line+, any line**
35	Regorafenib	STIVARGA	20120927	STIVARGA is a kinase inhibitor indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an antiVEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.	Second line+
35	Regorafenib	STIVARGA	20130225	Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.	Second line+
35	Regorafenib	STIVARGA	20170427	Hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.	Second line+
36	Ribociclib succinate	KISQALI	20170313	KISQALI is a kinase inhibitor indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.	First line
37	Rucaparib camsylate	RUBRACA	20161219	RUBRACA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA. This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.	Second line+
37	Rucaparib camsylate	RUBRACA	20180406	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.	Second line+
38	Ruxolitinib	JAKAFI	20111116	JAKAFI is a kinase inhibitor indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.	Second line+
38	Ruxolitinib	JAKAFI	20141204	Polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.	Second line+
39	Sonidegib phosphate	ODOMZO	20150724	ODOMZO is a hedgehog pathway inhibitor indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.	First line
40	Talazoparib tosylate	TALZENNA	20181016	TALZENNA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA.	Second line+
41	Trametinib dimethyl sulfoxide	MEKINIST	20130529	MEKINIST is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.	Any line
41	Trametinib dimethyl sulfoxide	MEKINIST	20170622	MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with: metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test.	Any line

Drug number	Generic name	Brand name	Date of indication approval	New indication approved	Line of therapy: adjuvant, first line, second line+, any line**
41	Trametinib dimethyl sulfoxide	MEKINIST	20180430	MEKINIST is indicated, in combination with dabrafenib, for: the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.	Adjuvant
41	Trametinib dimethyl sulfoxide	MEKINIST	20180504	MEKINIST is indicated, in combination with dabrafenib, for: the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options.	Any line
42	Vandetanib	CAPRELSA	20110406	CAPRELSA is a kinase inhibitor indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of vandetanib in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib.	First line
43	Venetoclax	VENCLEXTA	20160411	VENCLEXTA is a BCL-2 inhibitor indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.	Second line+
43	Venetoclax	VENCLEXTA	20181121	In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. This indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.	First line
44	Vismodegib	ERIVEDGE	20120130	ERIVEDGE capsule is a hedgehog pathway inhibitor indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.	First line

Notes: *Oral targeted cancer drugs with only cancer indications; ** First line therapy: "The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. When used by itself, first-line therapy is the one accepted as the best treatment. If it doesn't cure the disease or it causes severe side effects, other treatment may be added or used instead. Also called induction therapy, primary therapy, and primary treatment." (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/first-line-therapy); adjuvant therapy: "Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy." (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/adjuvant-therapy)

eTable 3. Trials of drugs with information on OS benefit reported in FDA-approved labels, 2011-2018.

eTable 3a. Trials of drugs with documented OS benefit in FDA-approved labels, 2011-2018.

Generic name	Date of trial results documented in the label	Trial at approval	Enrolled patients	Treatment arm			Control arm			Hazard ratio (95% CI)	p value
				Treatment	Number of deaths/ Sample size	Median OS in months (95% CI)	Control	Number of deaths/ Sample size	Median OS in months (95% CI)		
Abiraterone acetate	20110428	yes	Patients with metastatic castration-resistant prostate cancer (CRPC) who had received prior docetaxel chemotherapy	Abiraterone	501/797	15.8 (14.8, 17.0)	Placebo	274/398	11.2 (10.4, 13.1)	0.74 (0.64, 0.86)	<0.0001
	20150320 (update)	no	Patients with metastatic castration-resistant prostate cancer (CRPC) who had not received prior cytotoxic chemotherapy	Abiraterone	354/546	34.7 (32.7, 36.8)	Placebo	387/542	30.3 (28.7, 33.3)	0.81 (0.70, 0.93)	0.003
	20180207	no	Patients with metastatic high-risk castration-resistant prostate cancer (CRPC).	Abiraterone+ Prednisone	169/597	NE	Placebos	237/602	34.7 (33.1, NE)	0.621 (0.509, 0.756)	< 0.0001 **
Afatinib dimaleate	20160415	yes	Patients were required to have histologically documented, metastatic squamous NSCLC and have experienced disease progression following an adequate course (≥ 4 cycles) of a platinum-based doublet chemotherapy regimen.	Afatinib	307/398	7.9 (7.2, 8.7)	Erlotinib	325/397	6.8 (5.9, 7.8)	0.81 (0.69, 0.95)	0.008
Cabozantinib s-malate	20160425	yes	Patients with advanced renal cell carcinoma (RCC) who had received at least 1 prior anti-angiogenic therapy	Cabozantinib (Cabometyx)	NM/330	21.4 (18.7, NE)	Everolimus	NM/328	16.5 (14.7, 18.8)	0.66 (0.53, 0.83)	0.000
Cobimetinib	20180126 (update)	yes	Patients with previously untreated, BRAF V600 mutation-positive, unresectable or metastatic, melanoma	Cobimetinib+Vemurafenib	114/247	22.3 (20.3, NE)	Placebo+ Vemurafenib	141/248	17.4 (15.0, 19.8)	0.69 (0.54,0.88)	0.0032
Dabrafenib mesylate	20151120	no	Patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E or V600K	Dabrafenib+ Trametinib	99/211	25.1 (19.2, NR)	Dabrafenib plus placebo	123/212	18.7 (15.2, 23.1)	0.71 (0.55, 0.92)	0.010

Generic name	Date of trial results documented in the label	Trial at approval	Enrolled patients	Treatment arm			Control arm			Hazard ratio (95% CI)	p value
				Treatment	Number of deaths/ Sample size	Median OS in months (95% CI)	Control	Number of deaths/ Sample size	Median OS in months (95% CI)		
			mutation-positive cutaneous melanoma								
	20151120	no	Patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma	Dabrafenib+ Trametinib	100/352	NR (18.3, NR)	Vemurafenib	122/352	17.2 (16.4, NR)	0.69 (0.53, 0.89)	0.005***
Enzalutamide	20120831	yes	Patients with metastatic castration-resistant prostate cancer (CRPC) who had received prior docetaxel-based chemotherapy	Enzalutamide	308/800	18.4 (17.3, NR)	Placebo	212/339	13.6 (11.3, 15.8)	0.63 (0.53, 0.75)	< 0.0001 **
	20150805 (update)	no	Patients with visceral metastases, patients with a history of mild to moderate heart failure (NYHA class I or II), and patients taking medications associated with lowering the seizure threshold.	Enzalutamide	368/872	35.3 (32.2, NR)	Placebo	416/845	31.3 (28.8, 34.2)	0.77 (0.67, 0.88)	<0.0001
Midostaurin	20170428	yes	patients with newly-diagnosed FLT3-mutated acute myeloid leukemia (AML)	Midostaurin+ Standard chemotherapy	NM/360	NE	Placebo+ standard chemotherapy	NM/357	NE	0.77 (0.63, 0.95)	0.016
Olaparib	20170817	yes	Patients with platinum sensitive ovarian cancer who had received 2 or more previous platinum	Olaparib	98/136	29.8	Placebo	112/129	27.8	0.73 (0.55, 0.95)	<0.0001
Pomalidomide	20150423	no	Adult patients with relapsed and refractory multiple myeloma, who had received at least two prior treatment regimens, including lenalidomide and bortezomib, and demonstrated disease progression on or within 60 days of the last therapy	Pomalidomide+ Low-dose dexamethasone	147/302	12.4 (10.4, 15.3)	High-dose dexamethasone	86/153	8.0 (6.9, 9.0)	0.70 (0.54, 0.92)	0.009
Regorafenib	20120927	yes	Patients with previously-treated metastatic colorectal cancer.	Regorafenib+	275/505	6.4 (5.8, 7.3)	Placebo+ Best	157/255	5.0 (4.4, 5.8)	0.77 (0.64, 0.94)	0.010

Generic name	Date of trial results documented in the label	Trial at approval	Enrolled patients	Treatment arm			Control arm			Hazard ratio (95% CI)	p value
				Treatment	Number of deaths/ Sample size	Median OS in months (95% CI)	Control	Number of deaths/ Sample size	Median OS in months (95% CI)		
				Best supportive care			supportive care				
	20170427	yes	Adult patients with Child-Pugh A and Barcelona Clinic Liver Cancer Stage Category B or C hepatocellular carcinoma, with documented disease progression following sorafenib	Regorafenib	233/379	10.6 (9.1, 12.1)	Placebo	140/194	7.8 (6.3, 8.8)	0.63 (0.50, 0.79)	<0.0001
Trametinib dimethyl sulfoxide	20151120	no	Patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma	Trametinib+ Dabrafenib	99/211	25.1 (19.2, NR)	Dabrafenib plus Placebo	123/212	18.7 (15.2, 23.1)	0.71 (0.55, 0.92)	0.010

Note: *Oral targeted drugs indicated only for cancers, with confirmed, statistically significant overall survival benefit or inferred overall survival benefit documented in FDA-approved labels by the end of 2018, OS=Overall survival, NE= Not estimable, NR=Not reached, NM=not mentioned; ** A statistically significant improvement in overall survival was demonstrated at the pre-specified interim analysis; *** P-value is comparing with the allocated alpha of 0.021 for the interim analysis based on 77% information.

eTable 3b. Trials of drugs without documented OS benefit in FDA-approved labels, 2011-2018.

Generic name	Date of trial results documented in the label	Trial at approval	Enrolled patients	Treatment arm			Control arm			Hazard ratio (95% CI)	p value
				Treatment	Number of deaths/ Sample size	Median OS in months (95% CI)	Control	Number of deaths/ Sample size	Median OS in months (95% CI)		
Confirmed or inferred lack of statistically significant overall survival benefit											
Axitinib	20120127	yes	Patients with advanced RCC whose disease had progressed on or after treatment with 1 prior systemic therapy, including sunitinib-,	Axitinib	NM/361	20.1 (16.7, 23.4)	Sorafenib	NM/362	19.2 (17.5, 22.3)	0.97 (0.80, 1.17)	NS

Generic name	Date of trial results documented in the label	Trial at approval	Enrolled patients	Treatment arm			Control arm			Hazard ratio (95% CI)	p value
				Treatment	Number of deaths/ Sample size	Median OS in months (95% CI)	Control	Number of deaths/ Sample size	Median OS in months (95% CI)		
			bevacizumab-, temsirolimus-, or cytokine-containing regimens								
Cabozantinib s-malate	20160520	no	Patients with metastatic medullary thyroid carcinoma (MTC)	Cabozantinib (COMETRIQ)	NM/219	26.6	Placebo	NM/111	21.1	0.85 (0.64, 1.12)	0.2409
Ceritinib	20170526	no	Patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease	Ceritinib	NM/189	NM	Chemotherapy	NM/187	NM	NM	NM**
Crizotinib	20170428	no	Patients with ALK-positive metastatic NSCLC, previously treated with 1 platinum-based chemotherapy regimen	Crizotinib	116/173	21.7 (18.9,30.5)	Chemotherapy	126/174	21.9 (16.8,26.0)	0.85 (0.66, 1.10)	0.2290
	20181130	no	Patients with ALK-positive NSCLC as identified by the FDA-approved assay, Vysis ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit	Crizotinib	71 /172	NR (45.8, NR)	Chemotherapy	81/171	47.5 (32.2, NR)	0.76 (0.55, 1.05)	0.0980
Ixazomib	20151120	yes	Patients with relapsed and/or refractory multiple myeloma who had received at least one prior line of therapy	Ixazomib + Lenalidomide and Dexamethasone	81/360	NM	Placebo + Lenalidomide and Dexamethasone	90/362	NM	NM	NM**
Lenvatinib	20150213	yes	Patients with radioactive iodine-refractory differentiated thyroid cancer	Lenvatinib	71/261	NE (22.1, NE)	Placebo	47/131	NE (20.3, NE)	0.73 (0.50, 1.07)	0.1000
	20160513	no	Patients with advanced or metastatic renal cell carcinoma who have previously received anti-angiogenic therapy	Lenvatinib 18 mg + Everolimus 5 mg	32/51	25.5 (16.4, 32.1)	Everolimus 10 mg	37/50	15.4 (11.8, 20.6)	0.67 (0.42, 1.08)	NM
Panobinostat	20150223	yes	Patients with relapsed multiple myeloma who had received 1 to 3 prior lines of therapy	Panobinostat + bortezomib and dexamethasone	NM/94	NM	Placebo + bortezomib and dexamethasone	NM/99	NM	NM	NM**

Generic name	Date of trial results documented in the label	Trial at approval	Enrolled patients	Treatment arm			Control arm			Hazard ratio (95% CI)	p value
				Treatment	Number of deaths/ Sample size	Median OS in months (95% CI)	Control	Number of deaths/ Sample size	Median OS in months (95% CI)		
Ruxolitinib	20140725	no	Patients with MF (either primary MF, post-polycythemia vera MF or post-essential thrombocythemia-MF)	Ruxolitinib	NM/155	NM	Placebo	NM/154	NM	NM	NM***
	20140725	no	Patients with MF (either primary MF, post-polycythemia vera MF or post-essential thrombocythemia-MF)	Ruxolitinib	NM/146	NM	Best available therapy	NM/73	NM	NM	NM***
Vandetanib	20181012	no	Patients with unresectable locally advanced or metastatic medullary thyroid cancer	Vandetanib	116/231	81.6 (64.6, 98.5)	Placebo	52/100	80.4 (52.5, NE)	0.99 (0.72, 1.38)	0.9750
OS data obtained from a trial with non-inferiority design											
Lenvatinib	20180815	no	Patients with previously untreated unresectable hepatocellular carcinoma (HCC)	Lenvatinib	351/478	13.6 (12.1, 14.9)	Sorafenib	350/476	12.3 (10.4, 13.9)	0.92 (0.79, 1.06)	NM
OS not mentioned, or OS results not reported or not reported in a way that can support inference											
a) The label for the drug-indication pair did not mention (overall) survival (not in text, no data in figures or tables) except to say that it was not measured: With RCT- bosutinib, encorafenib, idelalisib Without RCT- acalabrutinib, brigatinib, enasidenib, gilteritinib, ivosidenib, larotrectinib, lorlatinib, ponatinib, sonidegib, vismodegib											
b) The label included overall survival among trial endpoints but results are not reported: Abemaciclib, alectinib, apalutamide, binimetinib, neratinib, niraparib, osimertinib, palbociclib, ribociclib, rucaparib, talazoparib, venetoclax											

Note: *Oral targeted drugs indicated only for cancers, with statistically non-significant overall survival benefit documented in FDA-approved labels by the end of 2018, OS=Overall survival, NS= Not significant, NR=Not reached, NM=not mentioned; ** A statistically non-significant improvement in overall survival was demonstrated at the pre-specified interim analysis; *** Numerical OS data on the basis of interim analysis suggest statistically significant harm associated with the experimental treatment .

eTable 4. Magnitude of OS benefit and spending associated with oral targeted cancer drugs with documented OS benefit, as reported in FDA-approved labels* in 2018.

Spending rank	**Generic name**	**Spending in 2018 (million USD)**	**First approval year**	**OS primary endpoint**	**Extension of OS (months)**
1	Abiraterone acetate	95.8	2011	yes	4.6
2	Enzalutamide	74.3	2012	yes	4.6
3	Pomalidomide	69.3	2013	no	4.4
4	Cabozantinib s-malate	38.1	2012	no	4.9
5	Olaparib	28.2	2014	no	2.0
6	Trametinib dimethyl sulfoxide	19.0	2013	no	6.4
7	Dabrafenib mesylate	16.3	2013	no	6.4
8	Regorafenib	11.7	2012	yes	2.8
9	Afatinib dimaleate	7.8	2013	no	1.1
10	Midostaurin	6.6	2017	yes	NE
11	Cobimetinib fumarate	1.1	2015	no	4.9

Note: *Oral targeted cancer drugs with only cancer indications; spending= sum of total gross payment associated with dispensings in 2018; OS=evidence of overall survival benefit by end of 2018; OS primary endpoint= OS was the primary endpoint in label-reported pivotal RCTs by the end of 2018; extension of OS benefit=longest extension of OS benefit against the comparator across trials; NE= Not estimable

eTable 5. Spending associated with dispensing events for 44 oral targeted cancer drugs* in 2018.

Spending rank	Generic name	Spending (million USD)	First approval year	Pivotal RCT	Documented OS benefit	OS primary endpoint	Orphan drug designation	FDA Approval Pathway			
								Fast track	Priority review	Breakthrough therapy	Accelerated approval
1	Palbociclib	209.0	2015	yes	no	no	no	no	yes	yes	yes
2	Abiraterone acetate	95.8	2011	yes	yes	yes	no	no	yes	NA	no
3	Ruxolitinib	75.8	2011	yes	no	no	yes	no	yes	NA	no
4	Enzalutamide	74.3	2012	yes	yes	yes	no	yes	yes	no	no
5	Pomalidomide	69.3	2013	yes	yes	no	yes	yes	no	no	yes
6	Osimertinib mesylate	61.9	2015	yes	no	no	yes	yes	yes	yes	yes
7	Cabozantinib s-malate	38.1	2012	yes	yes	no	yes	yes	yes	no	no
8	Olaparib	28.2	2014	yes	yes	no	yes	no	yes	no	yes
9	Ixazomib citrate	24.5	2015	yes	no	no	yes	no	yes	no	no
10	Alectinib hydrochloride	23.8	2015	yes	no	no	yes	no	yes	yes	yes
11	Neratinib maleate	20.2	2017	yes	no	no	no	no	no	no	no
12	Abemaciclib	19.7	2017	yes	no	no	no	yes	yes	yes	no
13	Trametinib dimethyl sulfoxide	19.0	2013	yes	yes	no	yes	yes	no	no	no
14	Bosutinib monohydrate	16.4	2012	yes	no	no	yes	no	no	no	no
15	Dabrafenib mesylate	16.3	2013	yes	yes	no	yes	yes	no	no	no
16	Lenvatinib mesylate	16.1	2015	yes	no	no	yes	no	yes	no	no
17	Niraparib tosylate	14.4	2017	yes	no	no	yes	yes	yes	yes	no
18	Crizotinib	13.0	2011	yes	no	no	yes	yes	yes	NA	yes
19	Ponatinib hydrochloride	13.0	2012	no	no	no	yes	yes	yes	no	yes
20	Venetoclax	12.9	2016	yes	no	no	yes	no	yes	yes	yes
21	Regorafenib	11.7	2012	yes	yes	yes	no	yes	yes	no	no
22	Rucaparib camsylate	8.7	2016	yes	no	no	yes	no	yes	yes	yes
23	Axitinib	7.8	2012	yes	no	no	no	yes	no	NA	no
24	Afatinib dimaleate	7.8	2013	yes	yes	no	yes	yes	yes	no	no
25	Ribociclib succinate	7.6	2017	yes	no	no	no	no	yes	yes	no
26	Vismodegib	7.2	2012	no	no	no	no	no	yes	NA	no
27	Midostaurin	6.6	2017	yes	yes	yes	yes	yes	yes	yes	no

Spending rank	Generic name	Spending (million USD)	First approval year	Pivotal RCT	Documented OS benefit	OS primary endpoint	Orphan drug designation	FDA Approval Pathway			
								Fast track	Priority review	Breakthrough therapy	Accelerated approval
28	Apalutamide	5.0	2018	yes	no	no	no	yes	yes	no	no
29	Acalabrutinib	3.5	2017	no	no	no	yes	no	yes	yes	yes
30	Brigatinib	3.5	2017	no	no	no	yes	no	yes	yes	yes
31	Enasidenib mesylate	3.5	2017	no	no	no	yes	yes	yes	no	no
32	Idelalisib	3.0	2014	yes	no	no	yes	yes	yes	yes	yes
33	Ceritinib	2.0	2014	yes	no	no	yes	no	no	yes	yes
34	Encorafenib	1.4	2018	yes	no	no	yes	no	no	no	no
35	Binimetinib	1.4	2018	yes	no	no	yes	no	no	no	no
36	Panobinostat lactate	1.2	2015	yes	no	no	yes	no	yes	no	yes
37	Vandetanib	1.1	2011	yes	no	no	yes	yes	yes	NA	no
38	Cobimetinib fumarate	1.1	2015	yes	yes	no	yes	yes	yes	no	no
39	Sonidegib phosphate	0.9	2015	no	no	no	no	no	no	no	no
40	Ivosidenib	0.8	2018	no	no	no	yes	yes	yes	no	no
41	Lorlatinib	0.2	2018	no	no	no	yes	no	yes	yes	yes
42	Larotrectinib	0.1	2018	no	no	no	yes	no	yes	yes	yes
43	Talazoparib tosylate	0.0	2018	yes	no	no	no	no	yes	no	no
44	Gilteritinib fumarate	0.0	2018	no	no	no	yes	yes	yes	no	no

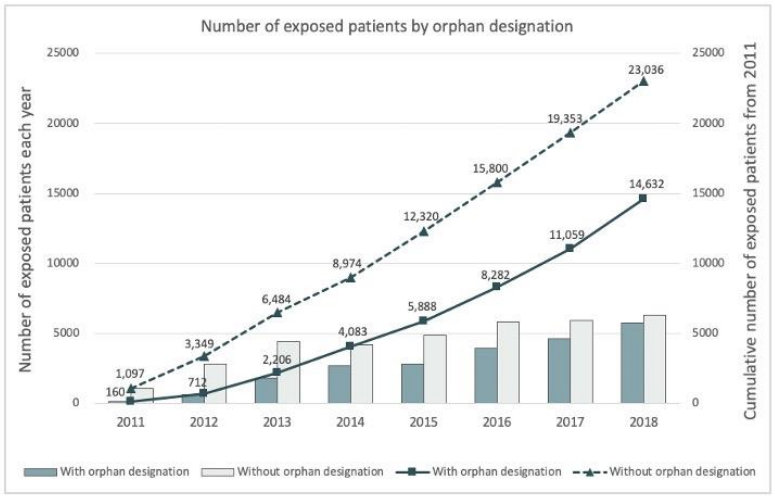
Note: *Oral targeted cancer drugs with only cancer indications; spending= sum of total gross payment associated with dispensings; OS=evidence of overall survival benefit by end of 2018; OS primary endpoint= OS was the primary endpoint in label-reported pivotal RCTs by the end of 2018, NA= not applicable, approval prior to Breakthrough Designation option (2012)

eTable 6. Number of members* per year in the IBM MarketScan Research Databases, 2011-2018.

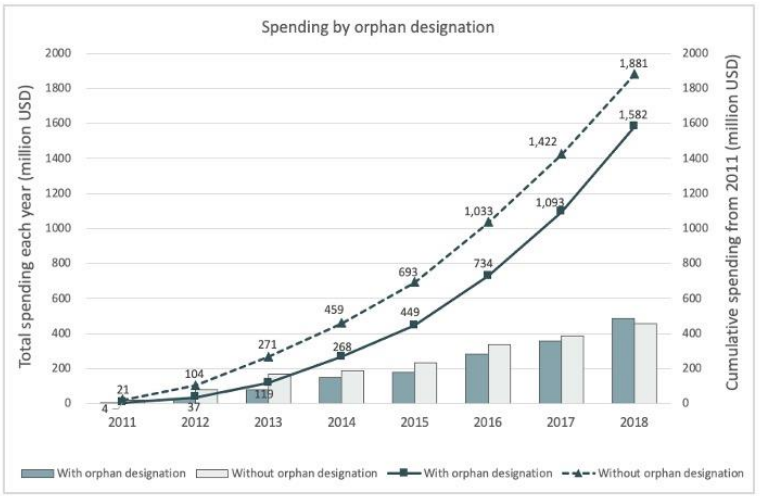
Year	Commercial	Supplementary Medicare	Grand Total
2011	55,559,154	5,243,029	60,802,183
2012	56,466,708	4,922,604	61,389,312
2013	44,180,771	4,272,760	48,453,531
2014	47,258,528	3,868,830	51,127,358
2015	28,348,363	2,199,633	30,547,996
2016	27,895,445	2,098,522	29,993,967
2017	26,146,275	1,473,787	27,620,062
2018	27,685,469	1,076,854	28,762,323

Note: *calculated as sum of unique patient identifiers in a given year.

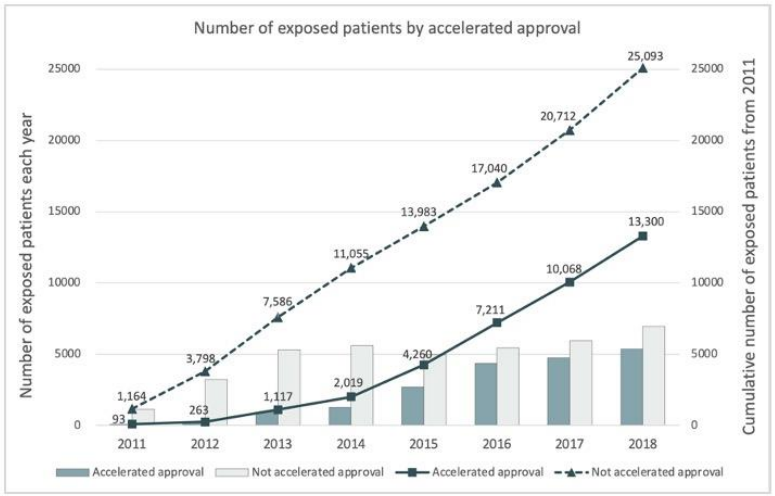
eFigure 1. Annual and cumulative numbers of patients exposed to and spending on 44 oral targeted cancer drugs, by FDA orphan designation and accelerated approval pathway.



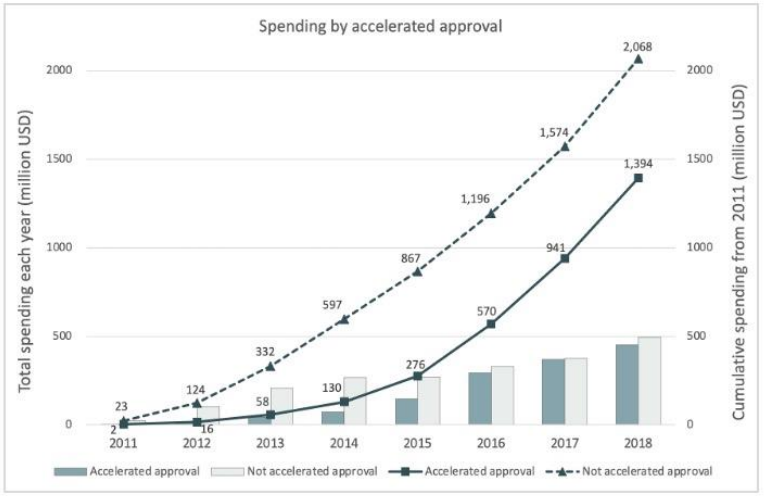
a. Annual and cumulative numbers of patients by orphan designation



b. Annual and cumulative spending by orphan designation

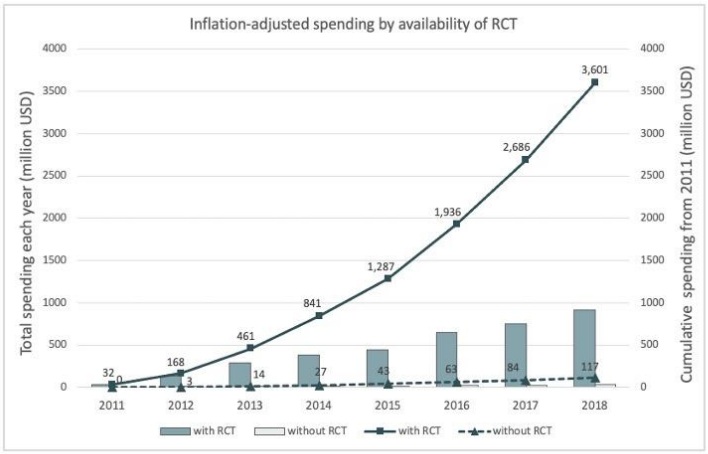


c. Annual and cumulative numbers of patients by accelerated approval

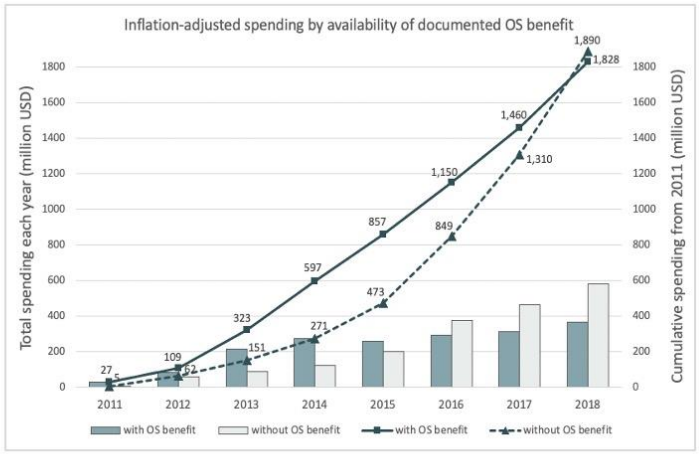


d. Annual and cumulative spending by accelerated approval

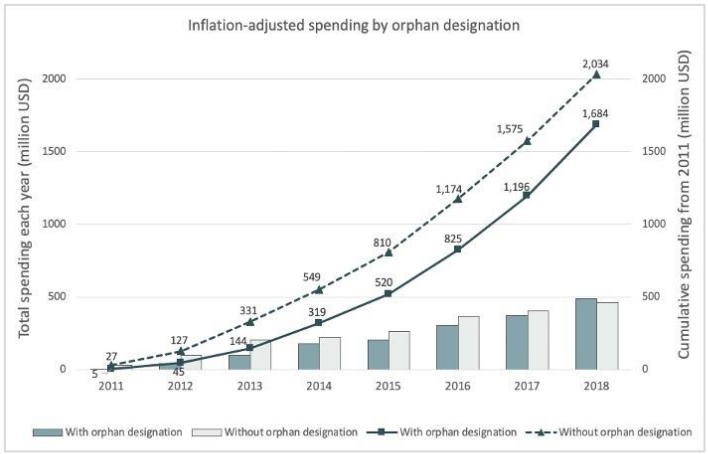
eFigure 2. Annual and cumulative inflation-adjusted spending on 44 oral targeted cancer drugs.



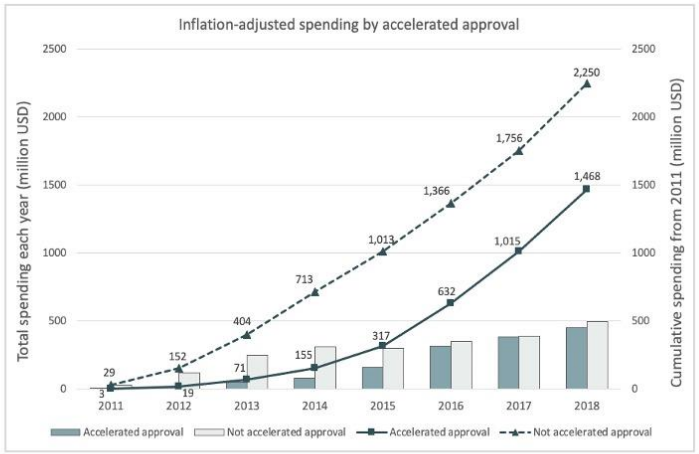
a. Annual and cumulative inflation-adjusted spending by availability of RCT evidence



b. Annual and cumulative inflation-adjusted spending by availability of OS benefit evidence



c. Annual and cumulative inflation-adjusted spending by orphan designation



d. Annual and cumulative inflation-adjusted spending by accelerated approval

Note: RCT=at least one randomized controlled trial supporting approval for at least one indication by end of 2018, OS=evidence of overall survival benefit by end of 2018; we adjusted the spending to 2018 using Consumer Price Index (CPI) for prescription drugs, obtained from the U.S. Bureau of Labor Statistics[2]

[2] U.S. Bureau of Labor Statistics. Prescription drugs in U.S. city average, all urban consumers, not seasonally adjusted. Accessed August 9, 2021. Available from: https://beta.bls.gov/dataViewer/view/timeseries/CUUR0000SEMF01.

eBox 1. Brief summary of the evidence documented in FDA labels for the top 3 drugs by spending in 2018.

Palbociclib was approved to treat (HER2)-negative advanced or metastatic breast cancer in February 2015. Approval was supported by a pivotal RCT with 84 patients (intervention arm) with PFS as outcome measure. By the end of 2018, palbociclib was shown to prolong PFS by an average of 5 to 10 months, supported by 2 RCTs with 791 patients; OS data were not mature.

Abiraterone was approved to treat metastatic prostate cancer in April 2011. Approval was supported by 2 pivotal RCTs with 1,343 patients with an average of 5 months increased OS. Efficacy and safety of abiraterone were demonstrated in 3 RCTs with 1,940 patients by the end of 2018.

Ruxolitinib was approved to treat intermediate or high-risk myelofibrosis in November 2011. Approval was supported by 2 RCTs with 528 patients with reduction in spleen volume as outcome measures. By the end of 2018, ruxolitinib was shown to reduce spleen volume in patients with myelofibrosis and polycythemia vera, supported by 3 RCTs with 750 patients; numerical OS data on the basis of 2 RCT with patients with myelofibrosis were inconclusive.

