Supplementary Online Content

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

Summary of regulatory policy changes in China, 2005-2020

eTable 1. Landmark Regulatory Policies Concerning Drug Approvals in China, 2009-2020

Effective Date	Issuing Organization	Policy Title	Main Policy Content
Jan, 2009	SFDA	Regulations on the Special Review for New Drug Registration	Put forward *Special Review* program, aiming to encourage new drug R&D. For conditions without effective treatments, such as AIDS, cancers, and rare diseases.
Feb, 2013	CFDA	Strengthening the Reform of Drug Review and Approval and Further Encouraging Innovation	To promote drug regulatory reform, improve review efficiency, and encourage R&D of novel drugs and generic drugs with clinical value. Put forward principles of *Accelerated Review* and *Priority Review* programs. Proposed to strengthen the quality management of drug clinical trials and encourage the development of drugs for children.
Aug, 2015	The State Council	Opinions of the State Council on Reform of the System for Evaluation, Review and Approval of Drugs and Medical Devices (No. 44 [2015])	Put forward the primary goals and missions of regulatory system reform, and measures to ensure its implementation. Primary goals: to improve review quality, resolve drug registration backlog, improve quality of generic drugs, encourage new drug R&D, and improve review transparency.
Feb, 2016	CFDA	Resolving the Backlog of Drug Registration Applications and Implementing Priority Review and Approval	Implemented *Priority Review* program. • Rolling review and shorter clock for review of marketing application • Drugs for serious or life-threatening diseases, with early clinical evidence and surrogate endpoint that is reasonably likely to predict clinical benefit could get market authorization under *Conditional Approval*. Certain drugs with clinically meaningful benefit and drugs intended to treat specific diseases were eligible for *Priority Review*, including: • New drugs did not been approved in China or other countries, etc.; • Drugs to treat AIDS, viral hepatitis, rare diseases, cancers, pediatric conditions, specific and frequent diseases of older adults, and others.

Effective Date	Issuing Organization	Policy Title	Main Policy Content
Oct, 2017	General Office of the CPC Central Committee, and the General Office of the State Council	Opinions of the CPC Central Committee and the State Council on Deepening the Reform of the Evaluation and Approval Systems and Encouraging Innovation on Drugs and Medical Devices (No. 42 [2017])	Put forward the primary goals to strengthen the regulatory system reform on the basis of *No. 44 [2015]* and previous work: to encourage innovation, improve industry competitiveness, and meet public clinical needs. Specific opinions: • Reforming clinical trial management; • Accelerating drug and medical devices review and approval; • Encouraging drug innovation and the development of generic drugs; • Strengthening the whole life cycle management of drugs and medical devices; • Improving technical support capabilities; • Strengthening relevant organization and implementation.
Dec, 2017	CFDA	Encouraging Drug Innovation and Implementing Priority Review and Approval	Revised *Priority Review* program, aiming to encourage drug innovation. A drug with clinically meaningful benefit, or a drug intended to treat specific diseases was eligible for *Priority Review* (revised): • New drugs that did not launch in or outside China, and new drugs for which clinical trials were carried out by the National Clinical Medical Research Centre, and others • Drugs to treat AIDS, viral hepatitis, rare diseases, cancers, pediatric conditions, specific and frequent diseases of older adults, and others; • In the case of a major threat to public health, the drug registration application that has obtained a compulsory license will be given *Priority Review* and approval. • Others.
Dec, 2017	CFDA	Publicly Solicit Comments on the *Technical Guidance for the Conditional Approval of Clinically*	Soliciting public comments for the *Technical Guidance for the Conditional Approval of Clinically Urgently Needed Drugs*, to accelerate the approval of urgently needed drugs with clinical value. *Conditional Approval:*

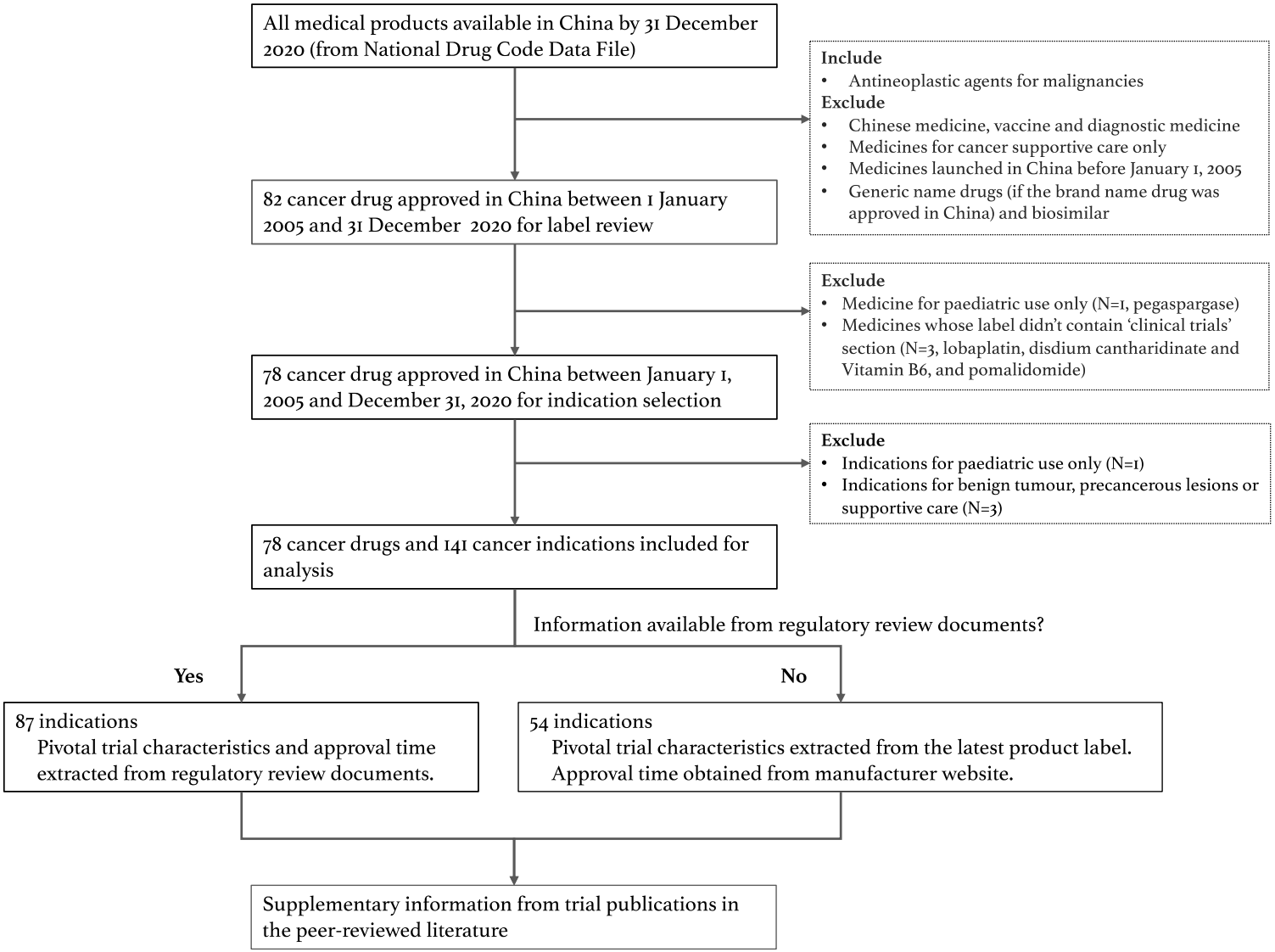
Effective Date	Issuing Organization	Policy Title	Main Policy Content
		Urgently Needed Drugs (Draft for Comments)	• A drug for serious or life-threatening diseases that have no available therapy; • Approval based on surrogate endpoints or preliminary clinical trial evidence that is reasonably likely to predict clinical benefit.
Jul, 2018	NMPA	Announcement of the NMPA on Issuing the *Technical Guidance for Accepting Overseas Clinical Trial Data*	Implemented the opinions put forward in *No. 42 [2017]*, aiming to strengthen the guidance and standardization of the procedure of accepting overseas clinical trials.
Nov, 2018	NMPA	Notice on the Issuance of the First Batch of Clinically Urgently Needed Overseas New Drugs	Listed 40 drugs approved overseas, for which clinically urgently needs were identified in China, including 8 cancer drugs.
Mar, 2019	NMPA	Notice on the Issuance of the Second Batch of Clinically Urgently Needed Overseas New Drugs	Listed 26 drugs approved overseas for which clinically urgently needs were identified in China, including 2 cancer drugs.
Jul, 2020	NMPA	Announcement of the NMPA on Issuing the *Regulatory Review Procedures of Breakthrough Therapy (Trial)* and other three documents	Implemented *Breakthrough Therapy* designation, aiming to encourage R&D of drugs with clinically meaningful benefits. *Breakthrough Therapy (pilot):* • For a drug intended to treat a serious condition, where there is no available therapy, or the drug has an improved effect compared to available therapy; • Preliminary clinical evidence that suggests substantial improvement over existing therapies. Revised *Priority Review* and *Conditional Approval* program, aiming to accelerate approval of drugs with clinically meaningful benefits. *Priority Review* (revised, pilot):

Effective Date	Issuing Organization	Policy Title	Main Policy Content
			• Novel drugs for diseases for which there are clinically urgent needs, major infectious diseases and rare diseases; • New varieties, dosage forms and specifications of childhood drugs; • Vaccines urgently needed for disease prevention and control; • Drugs designated as *Breakthrough Therapy*; • Drugs eligible for *Conditional Approval*; *Conditional Approval* (revised, pilot): • Drugs for the treatment of serious life-threatening diseases for which there are no effective available therapies and with clinical trials that have confirmed efficacy and can predict the drugs' clinical value; • Drugs that are urgently needed in public health, and that have clinical trials that have shown efficacy and can predict the clinical benefit of the drugs; • Vaccines that are urgently needed in response to major public health emergencies or other vaccines that are determined to be urgently needed by the National Health Commission, whose benefits outweigh the risks after assessment.
Nov, 2020	NMPA	Notice on the Issuance of the Third Batch of Clinically Urgently Needed Overseas New Drugs	Listed 7 drugs approved overseas for which there are clinically urgently needs in China, including 2 cancer drugs.

Abbreviations: *CPC, the Communist Party of China; SFDA, State Food and Drug Administration; CFDA, China Food and Drug Administration; NMPA, National Medical Products Administration; R&D, research and development.*

Methods

eFigure 1. Identification of Sample Indications



eBox 1. Key Words and Research Strategy to Identify Peer-Reviewed Publications of Drug Trials

Key words
#1 NCT number
#2 CTR number
#3 Study name
#4 Generic name
#5 Approved indications (when necessary)
#6 "1900/1/1"[Date - Publication] : "2021/6/30"[Date - Publication]
Research strategies
PubMed: (#1 OR (#3 & #4 [Title/Abstract]) OR (#4 & #5 [Title/Abstract])) AND #6
CNKI: #2 OR #3 OR #4
Clinicaltrial.gov #1 OR #2 OR #3

Note: *CTR, Clinical Trial Registration; CNKI, China National Knowledge Infrastructure.*

eTable 2. Outcome Variables Extracted From Trials

Endpoints (Abbreviation)	Definition
Survival related endpoint	
Overall survival (OS)	The time from randomization to death from any cause.
Progression-free survival (PFS)	The time from randomization to disease progression or death determined by Response Evaluation Criteria in Solid Tumors (RECIST) or other guidelines.
Disease-free survival (DFS)	The time from randomization to disease recurrence, new cancer occurrence, or death from any cause.
Relapse-free survival (RFS)	The time from randomization to disease recurrence or death from any cause.
Tumor response	
Objective response rate (ORR)	The percentage of patients who have complete response or partial response according to RECIST or other guidelines.
Disease control rate (DCR)	The percentage of patients who have complete response, partial response, stable disease or no evidence of disease according to RECIST guidelines or other criteria; also called clinical benefit rate.
Response rate of hematologic malignancy	
Major cytogenetic response (MCyR)	Complete (0 percent Ph-chromosome–positive cells in metaphase in bone marrow) or partial (1 to 35 percent Ph-chromosome–positive cells in metaphase).

eTable 3. Classification of Overall Survival (OS) Benefit

Type	Example
1. Documented OS benefit	
1.1 Overall survival (OS) in the intervention group was statistically significantly longer than that in the comparison group in the pre-planned analysis	e.g., In COU-AA-301 (NCT00638690), pivotal trial of abiraterone (1st-line, metastatic castration-resistant prostate cancer), median OS was 15.8 months vs 11.2 months in abiraterone acetate group and placebo group (HR=0.74, p<0.0001).[1]
1.2 OS in the intervention group was statistically significantly longer than that in the comparison group in pre-planned analysis on subgroup consistent with the indication population	e.g., In LUX-Lung 6 (NCT01121393), pivotal trial of afatinib (1st-line, EGFR mutation-positive lung cancer), median OS was 23.1 months in the afatinib group and 23.5 months in the gemcitabine-cisplatin group (HR 0.93, p=0.61). However, in pre-planned analyses, overall survival was significantly longer for patients with del19-positive tumors in the afatinib group than in the chemotherapy group: 31.4 months vs 18.4 months (HR=0.64, p=0.023).[2]
1.3 OS in the intervention group was statistically significantly longer than that in the control group after adjusting for the crossover	e.g., In VEG105192 (NCT00334282), pivotal trial of pazopanib (1st-line and 2nd-line, advanced and/or metastatic renal cell carcinoma), the difference in final OS between pazopanib- and placebo-treated patients was not statistically significant (22.9 vs 20.5 months, HR=0.91, one-sided P = .224). In inverse probability of censoring weighted analyses, pazopanib decreased mortality (HR=0.504, two-sided P = .002).[3]
2. Documented lack of OS benefit	

Type	Example
2.1 Final OS in the intervention group shows no statistically significant positive difference from or is less than in the comparison group	e.g., In ICOGEN (NCT01040780), pivotal trial of icotinib (1st-line, EGFR mutation lung cancer), there is no significant difference in median OS data between iconitib and gefitinib (13.3 vs 13.9 months, HR=1.02, p=0.57).[4]
2.2 If final OS data is not mature, the latest estimated OS data showed no statistically significant difference between the intervention group and the comparison group	e.g., In SPARTAN (NCT01946204), pivotal trial of apalutamide (1st-line, nonmetastatic castration-resistant prostate cancer), there is no significant difference in estimated median OS data (not reached vs 39.0 months, HR=0.70, p=0.07).[5] e.g. In COMBI-AD (NCT01682083), pivotal trials of dabrafenib (adjuvant therapy, melanoma), the 3-year overall survival rate was 86% vs 77% (HR=0.57, p=0.0006), but this level of improvement did not cross the prespecified interim analysis boundary or P=0.000019.[6]
3. Unknown OS benefit	
3.1 None of the pivotal trials documented OS benefit data	e.g., In FESTnd Study (NCT02204644), pivotal trial of flumatinib (1st-line, newly diagnosed chronic-phase chronic myeloid leukemia), in the latest result published in Sep 2020, OS benefit between flumatinib and imatinib was not mentioned.[7]
3.2 OS data immature or not published by the end of observation	e.g., In NOVA (NCT01847274), pivotal trial of niraparib (maintenance therapy in platinum-sensitive, recurrent ovarian cancer), at the time of the database lock in latest publication, the results for the time until overall survival were not mature.[8]
4. OS benefit not evaluable	

Type	Example
4.1 Indication supported by single arm trial only, that is, OS benefit not evaluable	e.g., Camrelizumab in relapsed or refractory classical Hodgkin lymphoma was approved on SHR-1210-II-204 (NCT03155425), a single-arm phase 2 study.[9]

eBox 2. Key Words and Research Strategy to Identify Peer-Reviewed Publications of Correlations Between Surrogate End Points and Overall Survival

Key words

#1 Cancer site in specific setting

#2 Correlation OR Association OR Validation OR Relationship

#3 Surrogate endpoint in specific cancer site and cancer setting

#4 Overall survival

#5 Trial OR Studies

Research strategies in PubMed

(#1 [Title/Abstract]) AND (#2 [Title/Abstract]) AND (#3 [Title/Abstract]) & (#4 [Title/Abstract]) AND (#5 [Title/Abstract])

e.g., (advanced melanoma[title/abstract]) and ((correlation[title/abstract]) or (association[title/abstract]) or (validation[title/abstract]) or (relationship[title/abstract])) and ((progression-free survival[title/abstract]) or (response rate[title/abstract])) and (overall survival [title/abstract]) and ((trial[title/abstract]) or (studies[title/abstract]))

Note: *the search terms were similar with a previous study*

Results

eTable 4. Sources of Information

Information source	No. Indication (%)
Data sources for pivotal trials	**141 (100)**
Regulatory review document [a]	87 (61.7)
Label [b]	54 (38.3)
Data sources for approval time [c]	
Regulatory review document	87 (61.7)
Label	19 (13.5)
Manufacture website	34 (24.1)
Data sources for overall survival data	
Regulatory review document	87 (61.7)
Label	6 (4.3)
Peer-reviewed publication as supplementary source [a]	128 (90.8)

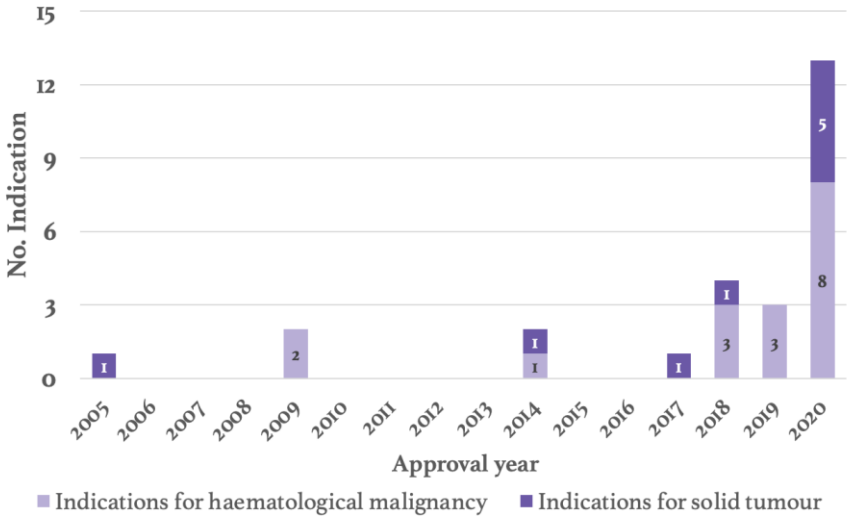
Note:

[a] *By June 30, 2021*

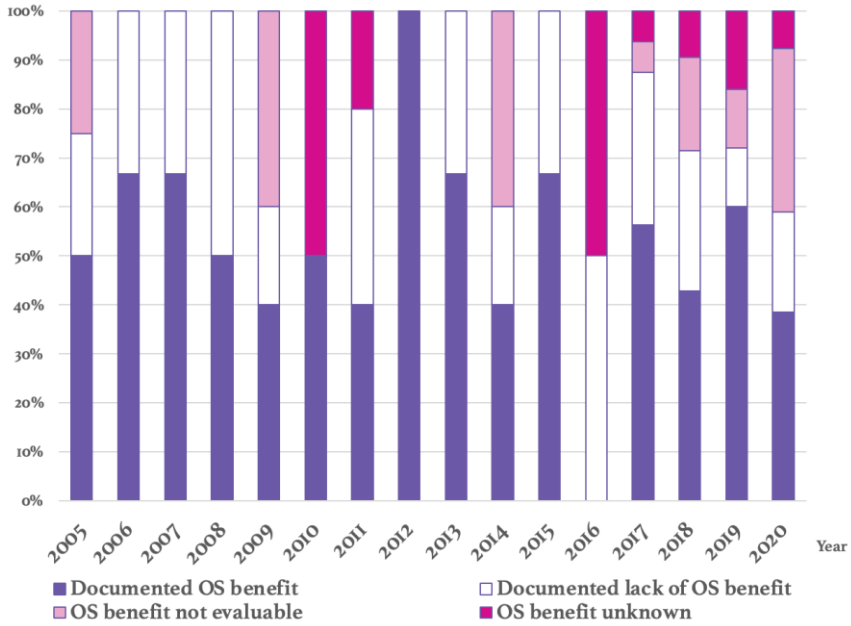
[b] *By December 31, 2020*

[c] *All the data were crosschecked using a commercial dataset (http://db.pharmcube.com/database/drugde/main).*

eFigure 2. Approval Year of Indications Supported Only by Single-Arm or Dose-Optimization Trials



eFigure 3. Classification of Overall Survival (OS) Benefit for Cancer Indications Approved in China, by Approval Year



eTable 5. Line of Therapy of Cancer Indications of Drugs Approved in China Only and Drugs Also Approved in the United States or the European Union

Line of therapy	Indications, n (%)	Indications, n (%)	
		Of cancer drugs approved in China only [a]	Of cancer drugs also approved in the US or Europe[a]
Total	**141 (100)**	**30 (100)**	**111 (100)**
First-line therapy	67 (47.5)	8 (26.7)	59 (53.2)
Later therapy	67 (47.5)	22 (73.3)	45 (40.5)
Adjuvant/neoadjuvant therapy	7 (5.0)	0	7 (6.3)

[a] *By June 30, 2021; drug indications for more than one line of therapy were classified by the earliest line (neoadjuvant/adjuvant before first before later line).*

eTable 6. Classification of Overall Survival and ESMO-MCBC Score of Cancer Drugs

Overall survival benefit type	Indication, n (%)	Applicable to ESMO-MCBS		
		Indications with ESMO-MCBS score, n (%, of all indications)		Indications with clinically meaningful benefit, n (%, of indications with ESMO-MCBS score)
Total	**141 (100)**	**66 (46.8)**		**38 (57.6)**
Documented OS benefit	68 (48.2)	42 (61.8)		29 (69.0)
Documented lack of OS benefit	34 (24.1)	18 (52.9)		8 (44.4)
OS benefit unknown	13 (9.2)	5 (38.5)		1 (20.0)
OS benefit not evaluable	26 (18.4)	1 (3.8)		0

Note: *European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) scores were obtained from ESMO website in June 30, 2021 (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards). ESMO-MCBS score A/B in the curative setting or 5/4 in the non-curative setting were considered clinically meaningful benefits. ESMO-MCBS scores are only available for solid tumor indications.*

eTable 7. Magnitude of Documented Overall Survival (OS) Benefit for 68 Indications, by Cancer Type

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	OS data (month) [a]	OS benefit (month) [a]	HR (95% CI)	Note
Lung										
1	Afatinib	1st-line advanced or metastatic NSCLC with EGFR mutations	LUX-Lung 6[2]	NCT01121393	afatinib	gemcitabine + cisplatin	31.4 vs 18.4	13.0	0.64 (0.44-0.94)	del19-positive tumors
2	Afatinib	2nd-line advanced or metastatic NSCLC	LUX-Lung 8[10]	NCT01523587	afatinib	erlotinib	7.9 vs 6.8	1.1	0.81 (0.69-0.95)	
3	Alectinib	ALK mutation positive advanced or metastatic NSCLC	ALEX[11]	NCT02075840	alectinib	crizotinib	NR vs 57.4	NA	0.67 (0.46-0.98)	
4	Atezolizumab	1st-line ES-SCLC, in combination with carboplatin and etoposide	IMpower133[12]	NCT02763579	atezolizumab	placebo	12.3 vs 10.3	2.0	0.70 (0.54-0.91)	
5	Anlotinib (China-only approval)	3rd-line advanced or metastatic NSCLC	ALTER 0303[13]	NCT02388919	anlotinib	placebo	9.5 vs 6.4	3.1	0.70 (0.55-0.89)	
6	Anlotinib (China-only approval)	3rd-line progressed or relapse SCLC	ALTER 1202	NCT03059797	anlotinib	placebo	7.3 vs 4.9	2.4	0.53 (0.30-0.92)	Data obtained from label
7	Osimertinib	1st-line advanced or metastatic NSCLC with EGFR mutation (exon 19 deletion or L858R allele)	FLAURA[14]	NCT02296125	osimertinib	standard EGFR-TKI	38.6 vs 31.8	6.8	0.80 (0.64-1.00)	
8	Bevacizumab	1st-line, non-squamous NSCLC, in combination with platinum-based chemotherapy	BEYOND[15]	NCT01364012	Bevacizumab + cisplatin + gemcitabine	Placebo + cisplatin + gemcitabine	24.3 vs 17.7	6.6	0.68 (0.50-0.93)	
9	Dacomitinib	1st-line, advanced or metastatic NSCLC with EGFR mutation (exon 19 deletion or L858R allele)	ARCHER 1050[16]	NCT01774721	dacomitinib	gefitinib	34.1 vs 27.0	7.1	0.75 (0.59-0.95)	

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	OS data (month) [a]	OS benefit (month) [a]	HR (95% CI)	Note
10	Durvalumab	Maintenance treatment, unresectable stage III NSCLC following platinum-based chemotherapy and radiation therapy	PACIFIC[17]	NCT02125461	durvalumab	placebo	NR vs 29.1	NA	0.69 (0.55-0.86)	
11	Erlotinib	Maintenance treatment, locally advanced or metastatic NSCLC, following 4 cycles platinum-based chemotherapy	SATURN[18]	NCT00556712	erlotinib	placebo	12.0 vs 11.0	1.0	0.81 (0.70-0.95)	
12	Erlotinib	2nd line, locally advanced or metastatic NSCLC	BR.21	NCT00036647	erlotinib	placebo	6.7 vs 4.7	2.0	0.70 (0.58-0.85)	
13	Crizotinib	ALK mutation positive locally advanced or metastatic NSCLC	PROFILE 1014[19]	NCT01154140	crizotinib	pemetrexed + cisplatin/carboplatin	NR vs 47.5	NA	0.35 (0.08-0.72)	adjusted for crossover
14	Nivolumab	2nd-line, EGFR and ALK mutation negative, locally advanced or metastatic NSCLC, after platinum-based chemotherapy	CheckMate 017[20]	NCT01642004	nivolumab	docetaxel	9.2 vs 6.0	3.2	0.59 (0.44-0.79)	
15	Pembrolizumab	1st-line, metastatic non-squamous NSCLC with EGFR and ALK mutation negative, in combination with pemetrexed and platinum-based chemotherapy	KEYNOTE-189[21]	NCT02578680	pembrolizumab	placebo	22.0 vs 10.7	11.3	0.56 (0.45-0.70)	
16	Pembrolizumab	1st-line, locally advanced or metastatic NSCLC expressing	KEYNOTE-042 （China study）[22]	NCT03850444	pembrolizumab	chemotherapy	20.2 vs 13.5	6.7	0.67 (0.50-0.89)	

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	OS data (month) [a]	OS benefit (month) [a]	HR (95% CI)	Note
		PD-L1 TPS≥1, with EGFR and ALK mutation negative								
17	Pembrolizumab	1st-line, metastatic NSCLC, in combination with carboplatin and paclitaxel	KEYNOTE-407[23]	NCT02775435	pembrolizumab	placebo	17.1 vs 11.6	5.5	0.71 (0.58-0.88)	
18	Pemetrexed	1st-line, locally advanced or metastatic NSCLC, in combination with cisplatin	H3E-MC-JMDB[24]	NCT00087711	pemetrexed+ cisplatin	gemcitabine+ cisplatin	11.8 vs 10.4	1.4	0.81 (0.70-0.94)	
19	Pemetrexed	Maintenance treatment, locally advanced or metastatic non-squamous NSCLC, following 4 cycle platinum-based chemotherapy	H3E-MC-JMEN[25]	NCT00102804	pemetrexed+ best supportive care	placebo+ best supportive care	13.4 vs 10.6	2.8	0.79 (0.65-0.95)	
20	Recombinant Human Endostatin (China-only approval)	1st-line, stage III/IV NSCLC, in combination with vinorelbine and cisplatin	A Phase 3 study	NA	Recombinant Human Endostatin+ vinblastine+ cisplatin	vinblastine+ cisplatin	14.9 vs 9.9	5.0	Not mentioned	Data obtained from label
Prostate										
21	Abiraterone	mCRPC	COU-AA-301[1]	NCT00638690	abiraterone acetate + prednisone	placebo + prednisone	15.8 vs 11.2	4.6	0.74 (0.64-0.86)	
22	Abiraterone	Newly diagnosed mHSPC	LATITUDE[26]	NCT01715285	androgen-deprivation therapy + abiraterone acetate + prednisone	androgen-deprivation therapy + dual placebos	53.3 vs 36.5	16.8	0.66 (0.56-0.78)	

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	OS data (month) [a]	OS benefit (month) [a]	HR (95% CI)	Note
23	Apalutamide	metastatic castration-sensitive prostate cancer	TITAN[27]	NCT02489318	apalutamide+ androgen-deprivation therapy	placebo++and rogen-deprivation therapy	NR vs NR	NA	0.67 (0.51-0.89)	
24	Enzalutamide	mCRPC	PREVAIL[28]	NCT01212991	enzalutamide	placebo	36.0 vs 31.0	5.0	0.83 (0.75-0.93)	
25	Enzalutamide	Non-metastatic CRPC with a high risk of metastasis	PROSPER[29]	NCT02003924	enzalutamide	placebo	67.0 vs 56.3	10.7	0.73 (0.61-0.89)	
26	Radium (223Ra) Dichloride	mCRPC with symptomatic bone metastasis and no visceral metastasis	ALSYMPCA[30]	NCT00699751	radium-223	placebo	14.9 vs 11.3	3.6	0.70 (0.58-0.83)	
Colon and rectum										
27	Bevacizumab	mCRC, in combination with fluorouracil-based chemotherapy	AVF2107g[31]	NCT00109070	bevacizumab + IFL	placebo + IFL	20.3 vs 15.6	4.7	0.66	
28	Fruquintinib (China-only approval)	3rd line, mCRC	FRESCO[32]	NCT02314819	fruquintinib	placebo	9.3 vs 6.6	2.7	0.65 (0.51-0.83)	
29	Trifluridine and Tipiracil	3rd line, mCRC	RECOURSE[33]	NCT01607957	trifluridine/tipiracil	placebo	7.1 vs 5.3	1.8	0.68 (0.58-0.81)	
30	Regorafenib	3rd line, mCRC	CONCUR[34]	NCT01584830	regorafenib	placebo	8.8 vs 6.3	2.5	0.55 (0.40-0.77)	
31	Cetuximab	1st-line, RAS wild-type mCRC, in combination with FOLFOX or FOLFIRI	TAILOR	NCT01228734	cetuximab+FOLFOX-4	FOLFOX-4	20.8 vs 16.5	4.3	0.76 (0.61-0.95)	Data obtained from regulatory review document
Multiple myeloma										
32	Lenalidomide	untreated and unsuitable for transplantation multiple myeloma, in	FIRST[35]	NCT00689936	continuous lenalidomide+ dexamethasone	melphalan+ prednisone+ thalidomide	59.1 vs 49.1	10.0	0.78 (0.67-0.92)	

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	OS data (month) [a]	OS benefit (month) [a]	HR (95% CI)	Note
		combination with dexamethasone								
33	Lenalidomide	2nd-line, multiple myeloma, in combination with dexamethasone	MM-009[36]	NCT00056160	lenalidomide	placebo	29.6 vs 20.2	9.4	0.44 (0.30-0.65)	
34	Bortezomib	multiple myeloma relapsed after at least one treatment	APEX[37]	NCT00048230	bortezomib	dexamethasone	29.8 vs 23.7	6.1	0.77	
35	Bortezomib	untreated and unsuitable for high-dose chemotherapy and myelosuppression multiple myeloma, in combination with melphalan and prednisone	VISTA[38 39]	NCT00111319	bortezomib+ melphalan+ prednisone	melphalan+ prednisone	56.4 vs 43.1	13.3	0.70 (0.57-0.85)	
36	Ixazomib	2nd-line, multiple myeloma, in combination with lenalidomide and dexamethasone	TOURMALINE-MM1 Chinese expansion[40]	NCT01564537	ixazomib+ lenalidomide+ dexamethasone	placebo+ lenalidomide+ dexamethasone	25.8 vs 15.8	10.0	0.42 (0.24-0.73)	
Breast										
37	Eribulin	3rd-line advanced or metastatic breast cancer after anthracycline and taxane-based chemotherapy	EMBRACE[41]	NCT00388726	eribulin	treatment of physician's choice	13.1 vs 10.6	2.5	0.81 (0.66-0.99)	
38	Pyrotinib (China-only approval)	2nd line relapsed or metastatic HER2 positive breast cancer after anthracycline and taxane-based chemotherapy, in	HR-BLTN-I/II-MBC	NCT02422199	pyrotinib + capecitabine	lapatinib + capecitabine	NR vs 16.2	NA	0.36 (0.16-0.82)	Data obtained from regulatory review document

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	OS data (month) [a]	OS benefit (month) [a]	HR (95% CI)	Note
		combination with capecitabine								
39	Pertuzumab	metastatic or unresectable locally relapsed HER2-positive breast cancer, in combination with trastuzumab and docetaxel	CLEOPATRA[42]	NCT00567190	pertuzumab +trastuzumab + docetaxel	placebo+ trastuzumab+ docetaxel	57.1 vs 40.8	16.3	0.69 (0.58-0.82)	
40	Abemaciclib	HR positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy, in combination with fulvestrant	MONARCH 2	NCT02107703	abemaciclib + fulvestrant	placebo + fulvestrant	46.7 vs 37.3	9.4	0.757 (0.606-0.945)	
Stomach										
41	Apatinib (China-only approval)	3rd-line gastric cancer	A Phase 2 study[43]	NCT00970138	apatinib 850 mg once daily or 425mg twice daily	placebo	4.8 vs 4.3 vs 2.5	2.3 (850mg); 1.8 (425mg)	0.51 (0.32-0.83)	850mg group
42	Nivolumab	3rd line, advanced or relapsed gastric or gastroesophageal junction cancer	ONO-4538-12[44]	NCT02267343	nivolumab	placebo	5.3 vs 4.1	1.2	0.63 (0.51-0.78)	
43	Tegafur, Gimeracil and Oteracil Potassium	unresectable locally advanced or metastatic gastric cancer	SC-101	NCT00202969	S-1+cisplatin	fluorouracil+ cisplatin	14.4 vs 10.3	4.1	Not mentioned	Data obtained from label
Head and neck										
44	Nivolumab	2nd-line, relapsed or refractory HNSCC expressing PD-L1 TPS≥1, with disease	CheckMate 141	NCT02105636	nivolumab	standard, single-agent systemic therapy	12.5 vs 5.9	6.6	0.38 (0.19-0.77)	Asian subgroup, data obtained

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	OS data (month) [a]	OS benefit (month) [a]	HR (95% CI)	Note
		progression after or during platinum-containing regimens				(methotrexate, docetaxel, or cetuximab)				from regulatory review document
45	Pembrolizumab	1st-line, metastatic or unresectable relapsed HNSCC expressing PD-L1 CPS ≥1	KEYNOTE-048[45]	NCT02358031	pembrolizumab + platinum+ 5-fluorouracil	cetuximab+ platinum+ 5-fluorouracil	14.7 vs 11.0	3.7	0.60 (0.45-0.82)	
46	Cetuximab	1st-line, recurrent and/or metastatic HNSCC, in combination with platinum and fluorouracil chemotherapy	EXTREME[46]	NCT00122460	cetuximab+ cisplatin/carboplatin+ fluorouracil	cisplatin/carboplatin+ fluorouracil	10.1 vs 7.4	2.7	0.80 (0.64-0.99)	
Leukemia										
47	Azacitidine	CMML	AZA PH GL 2003 CL 001[47]	NCT00071799	azacitidine	conventional care	24.5 vs 15.0	9.5	0.58 (0.43-0.77)	
48	Ibrutinib	chronic lymphocytic leukemia/small lymphocytic lymphoma	RESONATE[48]	NCT01578707	ibrutinib	ofatumumab	67.7 vs 65.1	2.6	0.24 (0.11-0.55)	
49	Blinatumomab	relapsed or refractory precursor B-cell acute lymphoblastic leukemia	TOWER[49]	NCT02013167	blinatumomab	standard-of-care chemotherapy	7.7 vs 4.0	3.7	0.71 (0.55-0.93)	
Melanoma										
50	Dabrafenib	unresectable or metastatic melanoma with BRAF V600E or V600K mutations, in combination with trametinib	COMBI-d[50]	NCT01584648	dabrafenib + trametinib	dabrafenib + placebo	25.1 vs 18.7	6.4	0.71 (0.55-0.92)	

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	OS data (month) [a]	OS benefit (month) [a]	HR (95% CI)	Note
51	Trametinib	unresectable or metastatic melanoma with BRAF V600E or V600K mutations, in combination with dabrafenib	COMBI-d[50]	NCT01584648	dabrafenib+ trametinib	dabrafenib+ placebo	25.1 vs 18.7	6.4	0.71 (0.55-0.92)	
52	Vemurafenib	unresectable or metastatic melanoma with BRAF V600 mutations	BRIM-3[51]	NCT01006980	vemurafenib	dacarbazine	13.6 vs 10.3	3.3	0.81 (0.68-0.96)	
Liver										
53	Apatinib (China-only approval)	advanced HCC failed or untolerated to at least first-line systemic treatment	AHELP[52]	NCT02329860	apatinib	placebo	8.7 vs 6.8	1.9	0.79 (0.62-1.00)	
54	Atezolizumab	unresectable HCC without previous systemic treatment, in combination with bevacizumab	IMbrave150[53]	NCT03434379	atezolizumab+ bevacizumab	sorafenib	NR vs 13.2	NA	0.58 (0.42-0.79)	
55	Regorafenib	HCC who has been previously treated with sorafenib	RESORCE[34]	NCT01774344	regorafenib	placebo	10.6 vs 7.8	2.8	0.63 (0.50-0.79)	
56	Sorafenib	unresectable or metastatic HCC	SHARP[54]	NCT00105443	sorafenib	placebo	10.7 vs 7.9	2.8	0.69 (0.55-0.87)	
Esophagus										
57	Camrelizumab (China-only approval)	2nd-line, locally advanced or metastatic esophageal squamous cell carcinoma	ESCORT[55]	NCT03099382	camrelizumab	investigator's choice of chemotherapy	8.3 vs 6.2	2.1	0.71 (0.57-0.87)	
58	Pembrolizumab	2nd-line, locally advanced or metastatic esophageal squamous	KEYNOTE-181 (China expansion study)	NCT03933449	pembrolizumab	investigator's choice of paclitaxel,	12.0 vs 5.3	6.7	0.34 (0.17-0.69)	Data obtained from

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	OS data (month) [a]	OS benefit (month) [a]	HR (95% CI)	Note
		cell carcinoma expressing PD-L1 CPS ≥1				docetaxel, or irinotecan				Review Document
Ovary										
59	Olaparib	Maintenance treatment, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy	SOLO2 (D0816C00002)[56]	NCT01874353	olaparib	placebo	51.7 vs 35.4	16.3	0.56 (0.35-0.97)	adjust for subsequent PARP inhibitor therapy in the placebo group
60	Niraparib	Maintenance treatment, advanced epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer, after platinum-based chemotherapy	PRIMA[57]	NCT02655016	niraparib	placebo	81% vs 59%	22%	0.51 (0.27-0.97)	24-month OS rate
Lymphoma										
61	Bortezomib	untreated and unsuitable for hematopoietic stem cell transplantation MCL, in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone	LYM-3002[58]	NCT00722137	VR-CAP (rituximab+ cyclophosphamide+ doxorubicin+ bortezomib+ prednisone)	R-CHOP (rituximab+ cyclophosphamide+ doxorubicin+ vincristine+ prednisone)	90.7 vs 55.7	35.0	0.66 (0.51-0.85)	
62	Lenalidomide	previously treated follicular lymphoma, in combination with a rituximab product	AUGMENT	NCT01938001	lenalidomide+ rituximab	placebo+ rituximab	Estimated 2-year OS% 95% vs 86%	9%	0.45 (0.22-0.92)	Data obtained from regulatory review document

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	OS data (month) [a]	OS benefit (month) [a]	HR (95% CI)	Note
Brain										
63	Temozolomide	1st-line, newly diagnosed glioblastoma multiforme, in combination with radiotherapy, and then as maintenance therapy	EORTC-NCIC[59]	NCT00006353	temozolomide+ radiotherapy	radiotherapy	14.6 vs 12.1	2.5	0.63 (0.52-0.75)	
Kidney										
64	Pazopanib	1st-line or 2nd-line advanced RCC	VEG105192[3]	NCT00334282	pazopanib	placebo	22.9 vs 20.5	2.4	0.50 (0.32-0.76)	adjusted for crossover
Mesothelioma										
65	Pemetrexed	unresectable malignant pleural mesothelioma, in combination of cisplatin	JMCH[60]	NCT00005636	pemetrexed disodium+ cisplatin	cisplatin	12.1 vs 9.3	2.8	0.77 (0.61-0.96)	
Nasopharynx										
66	Nimotuzumab (China-only approval)	stage III/IV nasopharyngeal cancer with EGFR mutation, in combination with radiotherapy	A Phase 2 study	NA	nimotuzumab+ radiation	radiation	36-month OS % 84.3% vs 77.6%	6.7%	NA	Data obtained from label; mean survival month: 35.8 vs 32.2
Other										
67	Sunitinib	progressive, well-differentiated pNET, with unresectable locally advanced or metastatic disease	A6181111[61 62]	NCT00428597	sunitinib+ best supportive care	placebo+ best supportive care	38.6 vs 16.3	22.3	0.40 (0.23-0.71)	Censoring at crossover
68	Sunitinib	GIST, after disease progression on or intolerance to imatinib mesylate	A6181004[63]	NCT00075218	sunitinib	placebo	NR vs NR	NA	0.49 (0.29-0.83)	

Abbreviation: *HR, hazard ratio; NR, not reached; NA, not applicable; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, high-risk metastatic endocrine therapy-sensitive prostate cancer; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; SCLC, small cell lung cancer; ES-SCLC, extensive-stage small cell lung cancer; mCRC, metastatic colorectal cancer; IFL, irinotecan, bolus fluorouracil, and leucovorin; PD-1, programmed cell death receptor-1; HNSCC, head and neck squamous cell cancer; TPS, tumor proportion score; CPS, combined positive score; RCC, renal cell carcinoma; MCL, mantle cell lymphoma; HCC, hepatocellular carcinoma; GIST, gastrointestinal stromal tumor; pNET, pancreatic neuroendocrine tumors; FOLFOX, leucovorin, fluorouracil, and oxaliplatin; FOLFIRI, leucovorin, fluorouracil, and irinotecan; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.*

Note: *for indications with more than one pivotal trial showing overall survival benefit, the maximum survival gain was extracted for analysis.*

[a] *OS benefit measured in months unless otherwise indicated.*

eTable 8. Results of Pivotal Trials Supporting 34 Indications With Documented Lack of Statistically Significant Overall Survival (OS) Benefit

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	Primary Endpoint	Primary Endpoint Results (month, HR [95%CI])	OS data (month) [a]	OS HR (95% CI)	Note
Lung											
1	Camrelizumab (China-only approval)	1st-line, unresectable locally advanced or metastatic non-squamous NSCLC with EGFR and ALK mutation negative, in combination with pemetrexed and carboplatin	CameL[64]	NCT03134872	camrelizumab+ carboplatin+ pemetrexed	carboplatin+ pemetrexed	PFS	11.3 vs 8.3 HR=0.60 (0.45-0.79)	NR vs 20.9	0.73 (0.53-1.02)	
2	Ceritinib	1st-line, locally advanced or metastatic NSCLC with ALK mutation positive	ASCEND-4[65]	NCT01828099	ceritinib	chemotherapy	PFS	16.6 vs 8.1 HR=0.55 (0.42-0.73)	NR vs 26.2	0.73 (0.50-1.08)	
3	Ceritinib	2nd-line, locally advanced or metastatic NSCLC with ALK mutation positive	ASCEND-5[66]	NCT01828112	ceritinib	chemotherapy (pemetrexed/docetaxel)	PFS	5.4 vs 1.6 HR=0.49 (0.36-0.67)	18.1 vs 20.1	1.0 (0.67-1.49)	
4	Erlotinib	1st-line, maintenance or 2nd line, locally advanced or metastatic NSCLC with	ENSURE[67]	NCT01342965	erlotinib	gemcitabine+ cisplatin	PFS	11.0 vs 5.5 HR=0.34 (0.22-0.51)	26.3 vs 25.5	0.91 (0.63-1.31)	

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	Primary Endpoint	Primary Endpoint Results (month, HR [95%CI])	OS data (month) [a]	OS HR (95% CI)	Note
		EGFR mutation positive									
			EURTAC[68]	NCT00446225	erlotinib	standard chemotherapy	PFS	9.7 vs 5.2 HR=0.37 (0.25-0.54)	19.3 vs 19.5	1.04 (0.65-1.68)	
			OPTIMAL[69 70]	NCT00874419	erlotinib	gemcitabine+ carboplatin	PFS	13.1 vs 4.6 HR=0.16 (0.10-0.26)	22.8 vs 27.2	1.19 (0.83-1.71)	
5	Icotinib (China-only approval)	1st-line, locally advanced or metastatic NSCLC with EGFR mutation	ICOGEN[4]	NCT01040780	icotinib	gefitinib	PFS	4.6 vs 3.4 HR=0.84 (0.67-1.05)	13.3 vs 13.9	1.02 (0.82-1.27)	
6	Osimertinib	2nd-line, locally advanced or metastatic NSCLC with EGFR T790M mutation positive	AURA3[71 72]	NCT02151981	osimertinib	platinum+ pemetrexed	PFS	10.1 vs 4.4 HR=0.30 (0.23-0.41)	26.8 vs 22.5	0.87 (0.67-1.12)	
7	Pemetrexed	2nd-line, locally advanced or metastatic non-squamous NSCLC	H3E-MC-JMID[73]	NCT00391274	pemetrexed	docetaxel	OS	11.7 vs 12.2 HR=1.14 (0.78-1.68)	11.7 vs 12.2	1.14 (0.78-1.68)	
			JMEI[74]	NCT00004881	pemetrexed	docetaxel	OS	8.3 vs 7.9 HR=0.99 (0.82-1.20)	8.3 vs 7.9	0.99 (0.82-1.20)	
Breast											
8	Abemaciclib	initial endocrine-based therapy, locally advanced or metastatic breast cancer with HR positive,	MONARCH 3[75 76]	NCT02246621	abemaciclib+ non-steroidal aromatase inhibitor	placebo+ non-steroidal aromatase inhibitor	PFS	28.2 vs 14.8 HR=0.54 (0.42-0.70)	NR vs NR	1.06 (0.68-1.63)	Data obtained from label

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	Primary Endpoint	Primary Endpoint Results (month, HR [95%CI])	OS data (month) [a]	OS HR (95% CI)	Note
		HER2 negative, in combination with an aromatase inhibitor									
			MONARCH plus Cohort A[77]	NCT02763566	abemaciclib+ non- steroidal aromatase inhibitor	placebo+ non-steroidal aromatase inhibitor	PFS	NR vs 14.7 HR=0.50 (0.35-0.72)	NR vs NR	Not reported	
9	Lapatinib	2nd-line, HER2 positive advanced or metastatic breast cancer, in combination with capecitabine	EGF100151[78 79]	NCT00078572	lapatinib+ capecitabine	capecitabine	TTP	6.2 vs 4.3 HR=0.57 (0.43-0.77)	18.8 vs 16.2	0.87 (0.71-1.08)	
10	Pertuzumab	adjuvant therapy HER2-positive early breast cancer at high risk of recurrence, in combination with trastuzumab and chemotherapy	APHINITY[80 81]	NCT01358877	pertuzumab+ standard adjuvant chemotherapy+ trastuzumab	placebo+ standard adjuvant chemotherapy + trastuzumab	3-year IDFS	92.3% vs 90.6% HR=0.81 (0.66-1.00)	6-year OS% 95% vs 94%	0.81 (0.66-1.00)	
11	Trastuzumab Emtansine	adjuvant therapy, residual invasive HER2-positive early breast cancer, after taxanes plus trastuzumab based neoadjuvant therapy	KATHERINE[82]	NCT01772472	trastuzumab emtansine	trastuzumab	DFS	88.3% vs 77.0% HR=0.50 (0.39-0.64)	NR vs NR	0.70 (0.47–1.05)	
Kidney											
12	Axitinib	advanced RCC after failure of	A4061051[83 84]	NCT00920816	axitinib	sorafenib	PFS	6.5 vs 4.8 HR=0.73	21.7 vs 23.3	1.00 (0.73-1.36)	

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	Primary Endpoint	Primary Endpoint Results (month, HR [95%CI])	OS data (month) [a]	OS HR (95% CI)	Note
		tyrosine kinase inhibitor or cytokine therapy						(0.51-1.06)			
			AXIS[85 86]	NCT00678392	axitinib	sorafenib	PFS	8.3 vs 5.7 HR=0.66 (0.55-0.78)	20.1 vs 19.2	0.97 (0.80-1.17)	
13	Sunitinib	unresectable advanced RCC	A6181034[87]	NCT00083889	sunitinib	interferon alfa	PFS	11.0 vs 5.0 HR=0.42 (0.32-0.54)	28.7 vs 23.7	0.82 (0.67-1.00)	Data obtained from label
14	Sorafenib	unresectable advanced RCC	TARGET[88 90]	NCT00073307	sorafenib	placebo	PFS	5.5 vs 2.8 HR=0.44 (0.35-0.55)	17.8 vs 15.2	0.88 (0.74-1.04)	
15	Everolimus	advanced RCC, after failure of sunitinib or sorafenib therapy	RECORD1[89 90]	NCT00410124	everolimus	placebo	PFS	4.0 vs 1.9 HR=0.30 (0.22-0.40)	14.8 vs 14.4	0.87 (0.65-1.15)	
Melanoma											
16	Dabrafenib	adjuvant therapy, melanoma with BRAF V600 mutations, in combination with trametinib	COMBI-AD[91]	NCT01682083	dabrafenib+ trametinib	placebo	RFS	NR vs 16.6 HR=0.47 (0.39-0.58)	NR vs NR	0.57 (0.42-0.79)	Did not meet protocol-specified analysis boundary

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	Primary Endpoint	Primary Endpoint Results (month, HR [95%CI])	OS data (month) [a]	OS HR (95% CI)	Note
17	Pembrolizumab	2nd-line, unresectable or metastatic melanoma	KEYNOTE-002[92 93]	NCT01704287	pembrolizumab 2 mg/kg pembrolizumab 10 mg/kg	investigator-choice chemotherapy	PFS	2.9 vs 2.7 HR=0.58 (0.46-0.73) 2.9 vs 2.7 HR=0.47 (0.37-0.60)	13.4 vs 11.0 14.7 vs 11.0	0.86 (0.67-1.10) 0.74 (0.57-0.96)	Did not meet protocol-specified boundary
18	Trametinib	adjuvant therapy, melanoma with BRAF V600 mutations, in combination with dabrafenib	COMBI-AD[91]	NCT01682083	dabrafenib+ trametinib	placebo	RFS	NR vs 16.6 HR=0.47 (0.39-0.58)	3-year OS% 86% vs 77%	0.57 (0.42-0.79)	Level of improvement did not cross the prespecified interim analysis boundary
Brain											
19	Bevacizumab	recurrent glioblastoma	AVF3708g[94]	NCT00345163	bevacizumab+ irinotecan	bevacizumab	6-month PFS rate	50.3% vs 42.6% HR not mentioned	9.3 vs 8.8	not reported	
			EORTC26101[95]	NCT01290939	bevacizumab+ lomustine	lomustine	OS	9.1 vs 8.6 HR=0.95 (0.74-1.21)	9.1 vs 8.6	0.95 (0.74-1.21)	

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	Primary Endpoint	Primary Endpoint Results (month, HR [95%CI])	OS data (month) [a]	OS HR (95% CI)	Note
20	Temozolomide	relapse or progressed glioblastoma multiforme or anaplastic astrocytoma	A Phase 2 study[96]	NA	temozolomide	procarbazine	6-month PFS rate	3.1 vs 2.1 HR not mentioned	7.3 vs 5.7	p = 0.33	Data obtained from label
			China registration study[97]	NA	temozolomide	semustine	6-month PFS rate	78.9% vs 55.9% HR not mentioned	6-month OS% 96.9% vs 97.3%	not reported	
Colon and rectum											
21	Raltitrexed	advanced CRC who are not suitable for 5-FU/leucovorin	1694IL/00003[98]	NA	raltitrexed	5-fluorouracil	TTP	4.7 vs 3.6 HR=1.08 (0.89-1.30)	10.3 vs 10.3	1.06 (0.85-1.32)	
			1694IL/0012[99]	NA	raltitrexed	5-fluorouracil+ leucovorin	ORR	18.6% vs 18.1% HR=1.04 (0.65-1.63)	10.9 vs 12.3	1.15 (0.93-1.42)	
			China study[100]	NA	raltitrexed+ oxaliplatin	oxaliplatin+ fluorouracil+ leucovorin	ORR	29.1% vs 17.0% HR not mentioned	not reported	not reported	
22	Cetuximab	EGFR and RAS mutation wild-type mCRC failure to irinotecan-based chemotherapy, in combination with irinotecan	BOND[101]	NA	cetuximab+ irinotecan	cetuximab	ORR	22.9% vs 10.8% HR not mentioned	8.6 vs 6.9	0.91 (0.68-1.21)	
Thyroid											

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	Primary Endpoint	Primary Endpoint Results (month, HR [95%CI])	OS data (month) [a]	OS HR (95% CI)	Note
23	Lenvatinib	locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC	SELECT[102]	NCT01321554	lenvatinib	placebo	PFS	18.3 vs 3.6 HR=0.21 (0.14-0.31)	NR vs NR	0.73 (0.50-1.07)	Data obtained from regulatory review document
24	Sorafenib	locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC	DECISION[103]	NCT00984282	sorafenib	placebo	PFS	10.8 vs 5.8 HR=0.59 (0.45-0.76)	NR vs 36.5	0.88 (0.63-1.24)	Data obtained from regulatory review document
Thyroid											
25	Everolimus	progressive, well-differentiated, non-functional neuroendocrine tumors of gastrointestinal or lung origin that are unresectable, locally advanced or metastatic	RADIANT-4[104]	NCT01524783	everolimus+ supportive care	placebo+ supportive care	PFS	11.0 vs 3.9 HR=0.48 (0.35-0.67)	NR vs NR	0.64 (0.40-1.05)	
26	Everolimus	unresectable, locally advanced or metastatic,	RADIANT-3[105] [106]	NCT00510068	everolimus	placebo	PFS	11.0 vs 4.6 HR=0.35 (0.27-0.45)	44.0 vs 37.7	0.94 (0.73-1.20)	

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	Primary Endpoint	Primary Endpoint Results (month, HR [95%CI])	OS data (month) [a]	OS HR (95% CI)	Note
		well-differentiated, progressive neuroendocrine tumors of pancreatic origin									
Prostate											
27	Apalutamide	nmCRPC, with a high risk of metastasis	SPARTAN[5]	NCT01946204	apalutamide	placebo	MFS	40.5 vs 16.2 HR=0.28 (0.23-0.350	NR vs 39.0	0.70 (0.47-1.04)	
Ovaries											
28	Olaparib	maintenance treatment, advanced epithelial ovarian, fallopian tube or primary peritoneal cancer with deleterious or suspected deleterious germline or somatic BRCA-mutated, who are in complete or partial response to first-line platinum-based chemotherapy	SOLO1[107]	NCT01844986	olaparib	placebo	PFS	49.9 vs 13.8 HR=0.31 (0.23-0.41)	3-year OS% 84% vs 80%	0.95 (0.60-1.53)	
Liver											
29	Lenvatinib	1st-line, unresectable HCC	REFLECT[108]	NCT01761266	lenvatinib	sorafenib	OS	14.7 vs 10.5 HR=0.82 (0.59-1.14)	14.7 vs 10.5	0.82 (0.59-1.14)	Data obtained from

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	Primary Endpoint	Primary Endpoint Results (month, HR [95%CI])	OS data (month) [a]	OS HR (95% CI)	Note
											regulatory review document
Soft Tissue Sarcoma											
30	Anlotinib (China-only approval)	2nd-line, acinar soft tissue sarcoma, clear cell sarcoma and other advanced soft tissue sarcoma	ALTER0203	NCT02449343	anlotinib	placebo	PFS	6.9 vs 1.5 HR=0.32 (0.23-0.45)	14.3 vs 12.8	0.96 (0.64-1.41)	Data obtained from regulatory review document
Lymphoma											
31	Ibrutinib	2nd-line, MCL	MCL-3001[109]	NCT01646021	ibrutinib	temsirolimus	PFS	14.6 vs 6.2 HR=0.28 (0.23-0.35)	NR vs 21.3	0.76 (0.53-1.09)	
32	Ibrutinib	Waldenström's macroglobulinemia, in combination with rituximab	PCYC-1127-CA[110]	NCT02165397	ibrutinib+ rituximab	placebo+ rituximab	PFS	NR vs 20.3 HR=0.20 (0.11-038)	30-month OS% 94% vs 92%	0.62 (0.17-2.19)	
Other											
33	Decitabine	MDS including previously treated and untreated, de novo and secondary MDS of all French-	D-0007[111]	NCT00043381	decitabine	best supportive care	ORR	17% vs 0 HR not mentioned	14.0 vs 14.9	not reported	

No	Generic Name (China-only approval)	NMPA approved indication	Pivotal trial [reference]	Trial ID	Intervention	Comparison	Primary Endpoint	Primary Endpoint Results (month, HR [95%CI])	OS data (month) [a]	OS HR (95% CI)	Note
		American-British subtypes									
34	Regorafenib	2nd-line, locally advanced, unresectable or metastatic gastrointestinal stromal tumor who have been previously treated with imatinib mesylate and sunitinib malate	GRID[112]	NCT01271712	regorafenib	placebo	PFS	4.8 vs 0.9 HR=0.27 (0.19-0.39)	OS% 78% vs 74%	0.77 (0.42-1.41)	

Abbreviation: *PFS, progression-free survival; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TTP, time-to-progression; IDFS, invasive-disease–free survival; RCC, renal cell carcinoma; RFS, relapse-free survival; NR, not reached; NA, not applicable; CRC, colorectal cancer; mCRC, metastatic colorectal cancer; ORR, objective response rate; DTC, differentiated thyroid cancer; mCRPC, metastatic castration resistant prostate cancer; MFS, metastasis-free survival; HCC, hepatocellular carcinoma; MCL, mantle-cell lymphoma; MDS, myelodysplastic syndromes*

[a] *OS benefit measured in months unless otherwise indicated.*

eTable 9. Primary End Point and Time From Enrollment to Approval of 13 Indications With Unknown Overall Survival Data by June 30, 2021

No.	Generic Name (China-only approval)	Indication	Approval Time	Pivotal Trials	Comparator	Primary Endpoint	First Enrolment Time	Duration from enrolment to approval (years)
1	Azacitidine	AML	Apr-2017	CALGB8921[113]	supportive care	response rate	Feb-1994	23.2
2	Dasatinib	adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to imatinib	Sep-2011	START-R[114]	imatinib	MCyR%	Feb-2005	6.6
3	Degarelix	advanced prostate cancer	Sep-2018	FE200486 CS21[115]	leuprolide	Cumulative probability of testosterone ≤0.5 ng/mL at any monthly measurement	Feb-2006	12.6
4	Flumatinib (China-only approval)	Philadelphia chromosome-positive chronic phase CML	Nov-2019	FESTnd[7]	imatinib	MMR%	Aug-2014	5.2
5	Fulvestrant	HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy or relapse after or during anti-estrogen adjuvant therapy	Jun-2010	9238IL/0021[116]	anastrozole	TTP	May-1997	13.1
			Jun-2010	D6997L00004[117]	anastrozole	TTP	Nov-2005	4.6
6	Neratinib	after trastuzumab-based adjuvant therapy in HER2-positive breast cancer	Apr-2020	ExteNET[118 119]	placebo	DFS	Jul-2009	10.8
7	Niraparib	maintenance treatment, platinum-sensitive recurrent epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer	Dec-2019	NOVA[8]	placebo	PFS	Aug-2013	6.3
8	Nilotinib	newly diagnosed adult Ph+CML in chronic phase	Jul-2016	CAMN107A2405[120]	imatinib	12month rate of confirmed best cumulative undetectable BCR-ABL1	Jun-2009	7.1
			Jul-2016	ENESTchina[121]	imatinib	MMR%	Apr-2011	5.2

No.	Generic Name (China-only approval)	Indication	Approval Time	Pivotal Trials	Comparator	Primary Endpoint	First Enrolment Time	Duration from enrolment to approval (years)
			Jul-2016	ENESTnd[122 123]	imatinib	12m MMR%	Sep-2007	8.9
9	Pertuzumab	neoadjuvant treatment, early or locally advanced ERBB2-positive breast cancer, in combination with trastuzumab and chemotherapy	Aug-2019	NeoSphere[124 125]	trastuzumab+ docetaxel pertuzumab+ trastuzumab pertuzumab+ docetaxel	pCR	Dec-2007	11.7
			Aug-2019	PEONY[126]	placebo+ trastuzumab+ docetaxel	pCR	Mar-2016	3.4
10	Palbociclib	initial treatment, HR positive, HER2 negative advanced breast cancer, in combination with letrozole	Jul-2018	PALOMA-2[127]	placebo+ letrzole	PFS	Feb-2013	5.5
11	Chidamide (China-only approval)	advanced, hormone receptor-positive breast cancer, in combination with exemestane	Nov-2019	ACE[128]	placebo	PFS	Jul-2015	4.4
12	Inetetamab (China-only approval)	metastatic breast cancer who has received one or more chemotherapy regimens, in combination with vinorelbine	Jun-2020	A Phase 3 study[129]	vinorelbine	PFS	Jan-2009	11.5
13	Sulfatinib (China-only approval)	advanced extrapancreatic neuroendocrine tumors	Dec-2020	SANET-ep[130]	placebo	PFS	Dec-2015	5.1

Abbreviation: *HR, hazard ratio; ER, estrogen-receptor; HER2, human epidermal growth factor receptor 2; PFS, progression-free survival; pCR, pathologic complete response; CML, chronic myeloid leukemia; MMR, major molecular response; IDFS, invasive disease-free survival.*

eTable 10. Results of Single-Arm or Dose-Optimization Trials Supporting Approvals by China National Medical Products Administration, 2005-2020

No.	Generic Name (China-only approval)	Indication	Pivotal trial [reference]	Trials ID	Primary endpoint	Result	Complete Response	Partial Response	Note
Solid tumour									
1	Icotinib (China-only approval)	2nd-line, locally advanced or metastatic NSCLC	BD-IC-III01-V2[131]	NCT02486354	PFS	5.4 months	0.0%	25.8%	ORR was the secondary endpoint
2	Denosumab	unresectable giant cell tumor of bone	Study 20040215[132]	NCT00396279	ORR	86.0%	Not reported	Not reported	
3	Fluazolepali (China-only approval)	advanced epithelial ovarian, fallopian tube or primary peritoneal cancer with deleterious or suspected deleterious germline or somatic BRCA-mutated	HR-FZPL-Ib-OC	NCT03509636	ORR	69.9%	4.4%	65.5%	Data was obtained from label
4	Crizotinib	ROS1 re- arrangement positive advanced NSCLC	A8081063	CTR20140093	ORR	69.3%	11.0%	58.3%	Data was obtained from label
5	Almonertinib (China-only approval)	2nd-line, locally advanced or metastatic NSCLC with EGFR T790M mutation positive	A phase 2 dose expansion study	NA	ORR	68.9%	Not reported	Not reported	Data was obtained from regulatory review document
6	Ensartinib (China-only approval)	crizotinib-resistant locally advanced or metastatic ALK-positive NSCLC	BTP-42322[133]	NCT03215693	ORR	52.0%	0.0%	52.0%	
7	Tislelizumab (China-only approval)	previously treated locally advanced or metastatic urothelial carcinoma with high PD-L1 expression	BGB-A317-204[134]	NCT04004221; CTR20170071	ORR	24.8%	9.6%	14.4%	
8	Camrelizumab (China-only approval)	previously treated advanced HCC	SHR-1210-II/III-HCC[135]	NCT02989922	ORR	17.6%	0.0%	14.7%	
9	Toripalimab (China-only approval)	previously treated advanced melanoma	POLARIS-01[136]	NCT03013101	ORR	17.3%	0.8%	16.5%	
10	Iodine[131I] Metuximab (China-only approval)	unresectable or relapse HCC	A Phase 2 study	NA	ORR	8.2%	0.0%	8.2%	Data was obtained from label
Haematological malignancy									

No.	Generic Name (China-only approval)	Indication	Pivotal trial [reference]	Trials ID	Primary endpoint	Result	Complete Response	Partial Response	Note
11	Bortezomib	relapsed or refractory MCL	PINNACLE[137]	NCT00063713	TTP	6.2 months	6.4%	25.5%	ORR was also reported
12	Tislelizumab (China-only approval)	3rd-line, relapsed or refractory classical Hodgkin lymphoma	BGB-A317-203[138]	NCT03209973	ORR	87.1%	62.9%	24.3%	
13	Brentuximab Vedotin	relapsed or refractory systemic anaplastic large-cell lymphoma	SG035-0004[139]	NCT00866047	ORR	86.0%	56.9%	29.3%	
14	Zanubrutinib	2nd-line, adult MCL	BGB-3111-206[140]	NCT03206970	ORR	83.7%	68.6%	15.1%	
15	Zanubrutinib	2nd-line, adult CLL/SLL	BGB-3111-205[141]	NCT03206918	ORR	84.0%	3.3%	59.3%	
16	Sintilimab (China-only approval)	3rd-line, relapsed or refractory classical Hodgkin lymphoma	ORIENT-1[142]	NCT03114683	ORR	80.4%	33.7%	46.7%	
17	Orelabrutinib (China-only approval)	2nd-line, adult MCL	ICP-CL-00102	NCT03494179	ORR	77.9%	25.6%	52.3%	Data was obtained from label
18	Camrelizumab (China-only approval)	3rd-line, relapsed or refractory classical Hodgkin lymphoma	SHR-1210-II-204[9]	NCT03155425	ORR	76.0%	21.0%	48.0%	
19	Orelabrutinib (China-only approval)	2nd-line, adult CLL/SLL	ICP-CL-00103	NCT03493217	ORR	73.8%	10.0%	63.8%	Data was obtained from label
20	Bendamustine	2nd-line, adult relapsed indolent non-Hodgkin lymphoma	C18083/3076	NCT01596621	ORR	72.5%	18.6%	53.9%	Data was obtained from regulatory review document
21	Venetoclax	newly diagnosed adult AML patients who are not suitable for strong induction chemotherapy due to comorbidities, or who are 75 years and older, in combination with azacitidine	M14-358[143]	NCT02203773	ORR	63.2%	61.4%	1.8%	

No.	Generic Name (China-only approval)	Indication	Pivotal trial [reference]	Trials ID	Primary endpoint	Result	Complete Response	Partial Response	Note
22	Pralatrexate	relapsed or refractory PTCL	FOT12-CN-301[144]	NCT03349333	ORR	52.0%	19.7%	32.4%	
23	Brentuximab Vedotin	relapsed or refractory classical Hodgkin lymphoma	C25007[145]	NCT01990534	ORR	50.0%	11.7%	38.3%	
24	Nilotinib	Philadelphia chromosome-positive CML in chronic phase following imatinib resistance and intolerance	CAMN107A2101[146]	NCT00109707	6-month MCyR	48.0%	31.0%	16.0%	
25	Daratumumab	relapsed or refractory multiple myeloma	SIRIUS[147]	NCT01985126	ORR	29.2%	2.8%	26.4%	
26	Chidamide (China-only approval)	2nd-line, relapsed or refractory PTCL	TG0902CDM confirmatory trial	NA	ORR	29.1%	15.2%	13.9%	Data was obtained from label

Abbreviation: *NMPA, National Medical Products Administration; NSCLC, non-small-cell lung cancer; PFS, progression-free survival; ORR, objective response rate; HCC, hepatocellular carcinoma; MMR, major molecular response; MCL, mantle cell lymphoma; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; PTCL, peripheral T-cell lymphoma; CML, chronic myelogenous leukemia; MCyR, major cytogenetic response; NA, not applicable.*

Note: *ORR usually defined as the proportion of patients achieving complete response (CR) or partial response (PR). In some trials, investigators included unconfirmed complete response (CRu) or unconfirmed partial response (PRu) was in the definition of ORR.*

eTable 11. Published Surrogate Correlation Studies for Cancer Indications Without Documented Overall Survival Benefit

Cancer Site	Setting	Line of therapy	Therapy type	Surrogate measure	Correlation type	Correlation coefficient type	Coefficient	Correlation coefficient (extraction of a root)	Note
Studies obtained from previous umbrella review[148] (No. Indication=32)									
Lung[149]	advanced	not specific	targeted	PFS	PFS-HR and OS-HR	R-squared	0.2269	0.48	≥40% crossover
Lung[150]	advanced	1st-line	targeted	PFS	PFS-HR and OS-HR	R-squared	0.002	0.04	molecularly selected patient trials
Lung[151]	advanced	1st-line	targeted	PFS	PFS-OS	Spearman's r	0.689	0.69	
Lung[152]	advanced	2nd-line	not specific	PFS	PFS-OS	r	0.376	0.38	
Lung[152]	advanced	2nd-line	not specific	PFS	PFS-HR and OS-HR	r	0.415	0.42	
Lung[150]	advanced	not specific	targeted	ORR	ORR-OR and OS-HR	R-squared	0.429	0.65	in trials with molecularly selected patients
Breast[153]	adjuvant setting	adjuvant	not specific	DFS	2-year DFS differences and 5-year OS differences	r	0.62	0.62	base model
Breast[154]	neoadjuvant setting	neoadjuvant	not specific	pCR	logOR(pCR)-logHR(OS)	R-squared	0.09	0.30	
Breast[155]	neoadjuvant setting	neoadjuvant	not specific	pCR	pCR-OS	R-squared	0.24	0.49	trial-level analysis
Breast[156]	advanced	1st-line	targeted	PFS/TTP	PFS/TTP-OS	Spearman's r	0.81	0.81	
Breast[156]	advanced	1st-line	targeted	PFS/TTP	PFS/TTP-HR and OS-HR	Spearman's r	0.73	0.73	
Breast[157]	advanced	not specific	anthracyclines, taxanes, or targeted therapies	PFS	PFS-HR and OS-HR	R-squared	0.18	0.42	weighted multivariate regression analysis
Breast[158]	advanced	not specific	not specific	PFS	PFS gain-OS gain	R-squared	0.3	0.55	
Breast[158]	advanced	not specific	not specific	PFS	PFS-HR and OS-HR	R-squared	0.78	0.88	

Cancer Site	Setting	Line of therapy	Therapy type	Surrogate measure	Correlation type	Correlation coefficient type	Coefficient	Correlation coefficient (extraction of a root)	Note
Breast[159]	advanced	not specific	not specific	PFS/TTP	Progression-HR and OS-HR	R-squared	0.3	0.55	
Breast[160]	advanced	not specific	not specific	PFS/TTP	PFS/TTP-OS	r	0.428	0.43	unweighted Spearman
Breast[161]	advanced	2nd-line or 3rd-line	not specific	PFS/TTP	PFS/TTP-OS	Spearman's r	0.7824	0.78	
Breast[161]	advanced	2nd-line or 3rd-line	not specific	PFS/TTP	Progression-HR and OS-HR	Spearman's r	0.5725	0.57	
Breast[157]	advanced	≥2nd-line	anthracyclines, taxanes, or targeted therapies	PFS	PFS-HR and OS-HR	R-squared	0.4	0.63	weighted multivariate regression analysis
Kidney[162]	advanced	1st-line	targeted	PFS	PFS-OS	Spearman's r	0.869	0.87	
Kidney[162]	advanced	1st-line	targeted	PFS	PFS gain-OS gain	Spearman's r	0.36	0.36	
Kidney[163]	advanced	1st-line	targeted	PFS	3-month PFS-9-month OS	Pearson coefficient	0.82	0.82	
Kidney[163]	advanced	1st-line	targeted	PFS	6-month PFS-12-month OS	Pearson coefficient	0.85	0.85	
Kidney[164]	advanced	not specific	cytokine or targeted therapies	PFS/TTP	-ln HR(PFS/TTP) and -ln HR(OS)	weighted Pearson correlation	0.8	0.80	
Kidney[165]	advanced	not specific	targeted	PFS	PFS gain-OS gain	R-squared	0.44	0.66	targeted therapy ordinary linear regression model
Colon and rectum[166]	advanced	not specific	not specific	TTP	TTP HR and OS HR	Spearman ρ	0.8	0.80	
Colon and rectum[167]	advanced	not specific	chemotherapy	ORR	ORR-OR and OS-HR	r	0.42	0.42	
Colon and rectum[168]	advanced	2nd-line	not specific	PFS/TTP	PFS/TTP-OS	R-squared	0.38	0.62	
Colon and rectum[169]	advanced	2nd-line	chemotherapy	ORR	ORR-OS	r	0.58	0.58	
Colon and rectum[170]	advanced	2nd-line	targeted	ORR	ORR-OR and OS-HR	r	0.169	0.17	

Cancer Site	Setting	Line of therapy	Therapy type	Surrogate measure	Correlation type	Correlation coefficient type	Coefficient	Correlation coefficient (extraction of a root)	Note
Ovaries[158]	advanced	not specific	not specific	PFS	PFS gain-OS gain	R-squared	0.6	0.77	
Ovaries[158]	advanced	not specific	not specific	PFS	PFS-HR and OS-HR	R-squared	0.73	0.85	
Ovaries[171]	advanced	2nd-line or later	not specific	ORR	ORR-OS	R-squared	0.67	0.82	
Urothelial[172]	advanced	not specific	immunotherapy	ORR	ORR-OS	r	-0.12	-0.12	urothelial carcinoma
Prostate[173]	nonmetastatic	1st-line	not specific	MFS	MFS-OS	Kendall's τ	0.91	0.91	weighted linear regression
Prostate[174]	nonmetastatic	1st-line	apalutamide	MFS	MFS-OS	Fleischer method coefficient	0.69	0.69	retrospective analysis of NCT01946204
Studies obtained from additional search (No. Indication=6, see eBox 2 for search terms)									
Melanoma[175]	advanced	not specific	not specific	PFS	PFS-OS	R-squared	0.075	0.27	
Melanoma[176]	advanced	not specific	immunotherapy	PFS	PFS-OS	R-squared	0.82	0.91	in sample size
Melanoma[176]	advanced	not specific	immunotherapy	PFS	PFS-HR and OS-HR	R-squared	0.75	0.87	in sample size
Melanoma[176]	advanced	not specific	immunotherapy	PFS	PFS gain-OS gain	R-squared	0.72	0.85	in sample size
Melanoma[176]	advanced	not specific	immunotherapy	ORR	ORR-OS	R-squared	0.25	0.50	in sample size
Soft tissue sarcoma[177]	advanced	2nd-line	not specific	PFS	PFS-OS	r	0.402	0.40	
Brain-glioblastoma[178]	recurrent	not specific	targeted	PFS	PFS-OS	R-squared	0.15	0.39	
Brain-glioblastoma[179]	newly diagnosed or recurrent	not specific	targeted	PFS	6-month PFS%-12-month OS%	r	0.53	0.53	
Liver[180]	unresectable	1st-line and 2nd-line	not specific	PFS	PFS-OS	r	0.84	0.84	PFS with an HR between 0.6-0.7
Liver[181]	unresectable	not specific	immunotherapy	ORR	ORR-OS	Spearman's r	0.35	0.59	
No relevant study was found by additional search (No. Indication=35)									
Liver	unresectable	1st-line	targeted	ORR					

Cancer Site	Setting	Line of therapy	Therapy type	Surrogate measure	Correlation type	Correlation coefficient type	Coefficient	Correlation coefficient (extraction of a root)	Note
Prostate	advanced	1st-line	not specific	testosterone					
Melanoma	advanced	adjuvant	targeted	RFS					
Brain-anaplastic astrocytoma	relapsed	2nd-line	chemotherapy	PFS					
Head and neck-Thyroid	metastatic	1st-line	targeted	PFS					
Neuroendocrine Tumor	advanced	1st-line	targeted	PFS					
Hodgkin lymphoma	relapsed	2nd-line or later	not specific	ORR					
non-Hodgkin lymphoma	relapsed	2nd-line or later	not specific	ORR					
Gastrointestinal stromal tumor	advanced	2nd-line	targeted	PFS					
Waldenström's macroglobulinemia	not specific	1st-line	targeted	PFS					
Myelodysplastic syndromes	not specific	1st-line	chemotherapy	ORR					
leukemia	not specific	not specific	not specific	ORR					
Bone	not specific	not specific	not specific	ORR					
Multiple myeloma	not specific	not specific	not specific	ORR					

Abbreviation: *OS, overall survival; HR, hazard ratio; PFS, progression-free survival; DFS, disease-free survival; pCR, pathologic complete response; ORR, objective response rate; MFS, metastatic-free survival; TTP, time-to-progression; RFS, relapse-free survival.*

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