nature portfolio

https://doi.org/10.1038d41573-021-00080-0

Supplementary information

Characteristics of expedited programmes for cancer drug approval in China

In the format provided by the authors

Supplementary Box 1 | Data sources and analysis

Data extraction

All cancer new drugs that received marketing authorization in China between January 1, 2016, and December 31, 2020, were collected from the Pharmcube database (one of the most authoritative platforms of drug information in China), which is curated largely from official databases of China's National Medical Products Administration (NMPA) (https://www.nmpa.gov.cn/yaopin/index.html) and Center for Drug Evaluation (CDE) (http://www.cde.org.cn/) and other public resources. Basic and regulatory characteristics were extracted and manually verified, including origins (discovered in China [domestic] or outside China [imported]), indications for use, dates of investigational new drug (IND) submission (indicating the commencement of clinical development phase), new drug application (NDA)/ biologic license application (BLA) submission (indicating the beginning of drug review of marketing authorization), and the first approval in China (i.e., the end of drug review).

Drugs that were originally discovered outside China and in-licensed to domestic pharmaceutical companies after entering the clinical phase were counted as imported drugs in this analysis. Only one drug, niraparib, fell into this category. When a drug has multiple approved indications, the approval date of the first cancer indication was used. Drugs were also classified based on the expedited programmes (EP) granted by the authority (Supplementary Table 1), including Priority Review (PR, effective as of Dec 2015), Conditional Approval (CA, Dec 2017), and Urgently Needed Overseas Drugs (UNOD, Oct 2018). Breakthrough Therapy (BT) Designation took effect in July 2020, and there have not yet been drugs approved under this program. The Special Review (SR, effective between Oct 2007-June 2020) programme was introduced to provide intensive guidance from the authority, creating a mechanism of communication historically. However, it was not included in this analysis due to its limited impact in practice on expediting drug development and review. Special Approval (effective as of November 2005) is another expedited programme for drugs needed for major areas of public health, but was excluded from this analysis given it does not cover cancer indications. Imported drugs were further categorized into three groups according to the clinical development strategies in China, including bridging studies (one or more supplemental studies in China) defined according to International Council on Harmonisation (ICH) - E5, joining multi-regional clinical trials (MRCT) groups and waiving trials in China (no Chinese data required).

Analysis of drug review length, total development length and drug lag

Drug review length was calculated as the period from the NDA/BLA submission to approval for the first cancer indication. Total development length, defined as the time from clinical development to approval in China, was calculated as the period from the date of the IND application in China to the first approval. Total development length and drug review length were compared between EP-designated versus non-EP-designated drugs.

To evaluate the drug lags of imported drugs in China compared to the United States, we collected the imported drugs approved in China from 2010 to 2020 with the first US approval time later than 2006, on the basis of the US Food and Drug Administration (FDA)'s database: (https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases). The drug lag was defined as the time between a new drug being approved by the US FDA and the time it was subsequently approved in China.

Statistical analysis

Numerical data are presented with median and interquartile ranges. A non-parametric Mann-Whitney-Wilcoxon (MWW) test was performed to examine the differences of total development length and drug review length between expedited programs (EP)-designated versus non-EP-designated drugs, and drug lag between different development strategies. Statistical analyses were performed using R version 4.0.2 and GraphPad Prism version 7.0. A two-tailed p-value <0.05 was considered statistically significant.

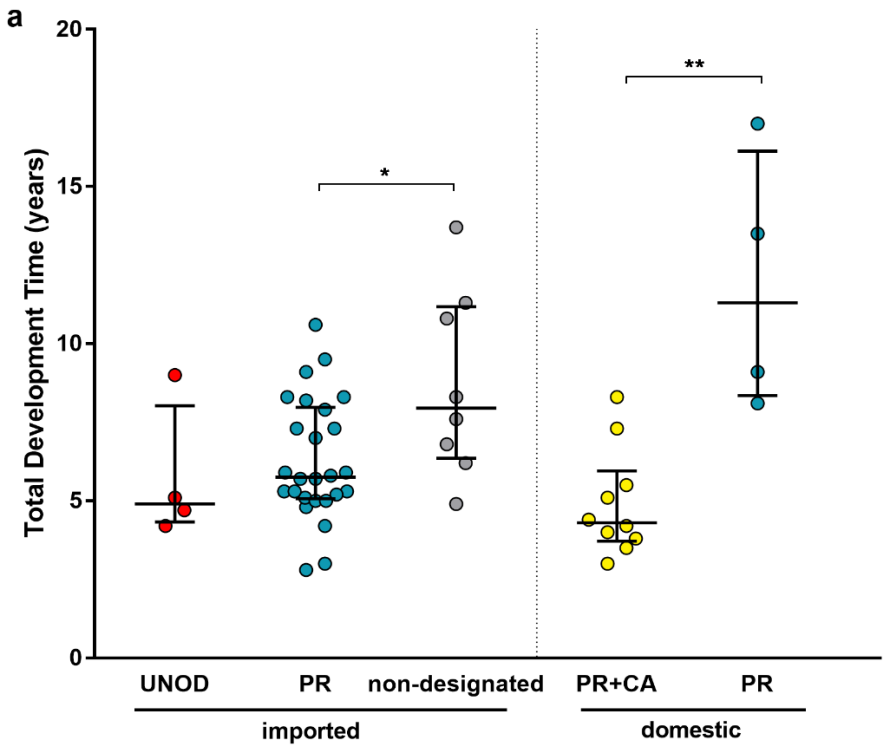
Limitations

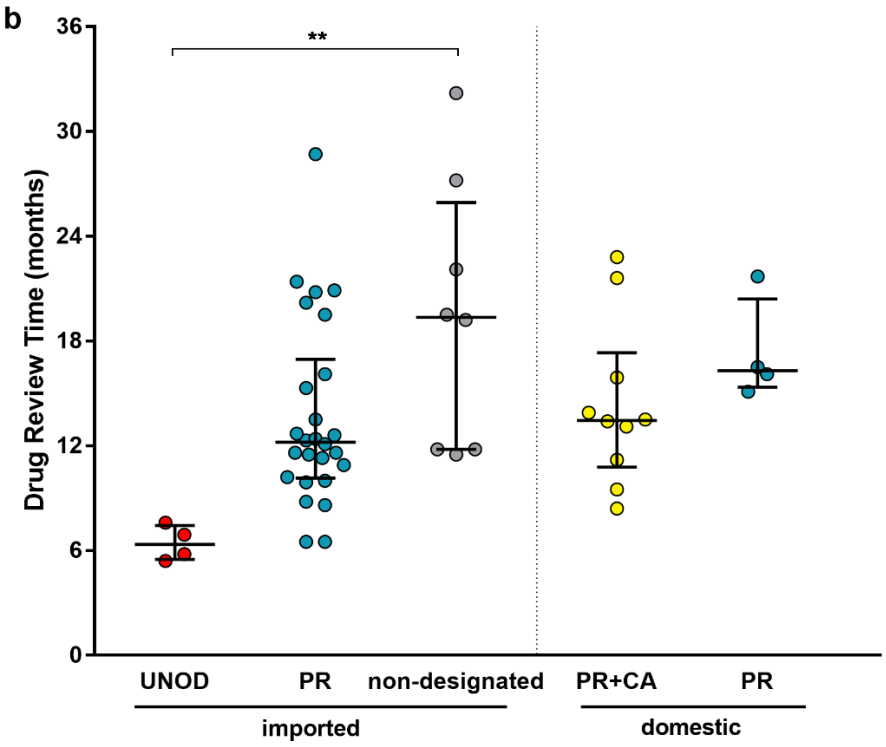
This study has some limitations. First, we extracted the dates of the first IND and first marketing approval to estimate total development time regardless of indications. Second, drug development length can be affected by factors other than new regulations and programmes, such as development strategy, teamwork efficiency, patient size, and collaboration. Causal inferences may not be made between designated status and faster development or review time length, given the existence of additional unobserved predictors or cofounders.

Supplementary Table 1 | Summary of expedited programmes in China

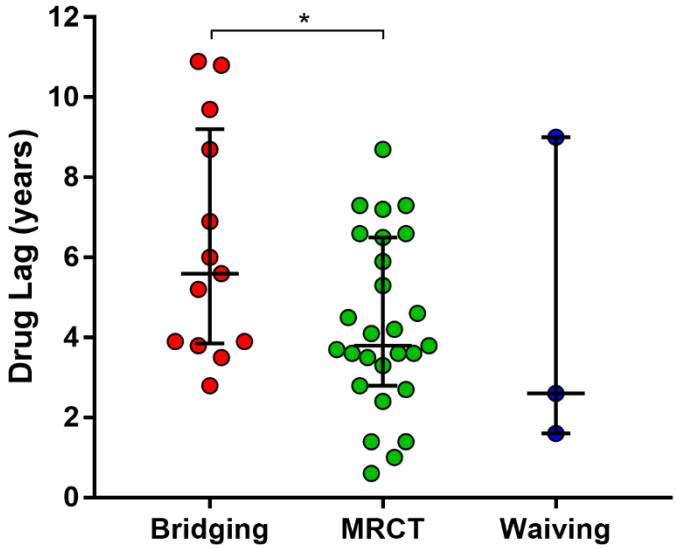
	Special Review	Priority Review[Δ]	Conditional Approval	Urgently Needed Overseas Drugs	Breakthrough Therapy
Effective period	October 2007–June 2020	November 2015–present	December 2017–present	October 2018–present	July 2020–present
Time of application	From IND application to NDA/BLA application	With NDA/BLA application	Discuss potential with the CDE during IND; determined during NDA review	With NDA/BLA application; the NMPA released the qualified drug lists	With or following IND
Drug type	New drugs (not yet launched in any countries)	New drugs (primarily)	New drugs	Overseas approved drugs	New drugs
Major characteristics of qualifying products	• For conditions without effective treatments, such as AIDS /HIV, cancer, and rare diseases; • Favourable non-clinical and clinical data	• Substantial clinical benefits • For urgently needed conditions and diseases such as major infectious diseases and rare diseases • New or modified drugs for pediatrics	• For serious or life-threatening diseases; • Urgently needed drugs; • Early clinical evidence and surrogate end point that is reasonably likely to predict clinical benefit	• For serious or life-threatening diseases; • Efficacy superior to current SoC; • Overseas data without potential ethnic differences	• For serious or life-threatening diseases; • Preliminary clinical evidence that suggests substantial improvement over existing therapies
Benefits					
Shortening NDA review length	No*	No public time limit stipulated prior to June 2020; 130 working days (versus standard 200 working days, starting from July 2020)	Eligible for PR designation	3–6 months	Eligible for PR designation and rolling submission
Possible actions to efficient drug development in China	Receive more intensive guidance	No	Allow NDA approval based on surrogate end points or intermediate results; requirements for completion of post-marketing studies	Allow NDA filing with limited or no data in Chinese population	Receive more intensive guidance

[Δ] Shows the provisions for Priority Review in the revised Drug Registration Regulation (DRR, in effect as of July 2020). As the legistrations have evolved, the priorities of priority review has shifted from resolving the registrational backlog to stimulating innovation. Applicable drug types, which used to include both innovative and generic drugs that were urgently needed, have changed to primarily innovative drugs with clinical benefits. The timing of application was the period between IND application and NDA/BLA application previously, but now only applies to NDA/BLA application.*Special Review was stipulated to shorten the IND review length from 90 to 80 working days and NDA review length from 150 to 120 working days. However, the actual impacts were minimal due to the prolonged review times. AIDS/HIV, acquired immunodeficiency syndrome/human immunodeficiency virus; CDE, Center for Drug Evaluation; IND, investigational new drug; SoC, standard of care; NDA/BLA, new drug application/biologic license application; NMPA, National Medical Products Administration; PR, priority review.


a
Total Development Time (years)
20
15
10
5
0
*
**
UNOD
PR
non-designated
PR+CA
PR
imported
domestic


b
Drug Review Time (months)
36
30
24
18
12
6
0
**
UNOD
PR
non-designated
PR+CA
PR
imported
domestic

Supplementary Figure 1 | Total development time (a) and drug review length (b) of new cancer drugs approved in China between 2016 and 2020. Total development time was calculated as the time between the date of investigational new drug (IND) application in China to the first approval and drug review length was defined as the time between filing of the new drug application/biologic license application (NDA/BLA) to approval for the first cancer indication. Drugs were categories into imported drugs with or without Priority Review (PR) or Urgently Needed Overseas Drugs (UNOD) designations and domestic drugs with PR designation, with or without Conditional Approval (CA) designation. Box plots indicate interquartile ranges in shaded areas and maximum and minimum values in whiskers.



Supplementary Figure 2 | Drug lag for imported new cancer drugs, by clinical development strategies in China. Drug lag was defined as the time between a new drug being approved by the US FDA after 2006 and the time it was subsequently approved in China between 2010 to 2020. Drug were classified into three groups based on clinical development and registration strategies in China, including bridging studies in China after drug approval overseas (Bridging, red), China joining multi-regional clinical trials before approval worldwide (MRCT, green) and waiving trials in China for drugs which are in urgent clinical need (Waiving, blue). *p<0.05.

Supplementary Table 2 | List of new cancer drugs approved in China between 2016 and 2020

Trade name	Drug name	Developer	Origin	EP programs	Date of IND submission (China)	Date of NDA/BLA submission (China)	Date of NDA/BLA approval (China)	Date of NDA/BLA approval (US)	Drug lag (US vs. China, years)
GIOTRIF	Afatinib dimaleate	Boehringer Ingelheim	Imported	PR, SR	January 2008	February 2016	February 2017	July 2013	3.6
VOTRIENT	Pazopanib hydrochloride	Novartis	Imported	None	November 2005	April 2015	February 2017	October 2009	7.3
ZELBORAF	Vemurafenib	Roche	Imported	PR	May 2012	April 2016	March 2017	August 2011	5.6
JAKAVI	Ruxolitinib phosphate	Novartis	Imported	PR, SR	June 2011	December 2015	March 2017	November 2011	5.3
TAGRISSO	Osimertinib mesylate	Astrazeneca	Imported	PR, SR	May 2014	August 2016	March 2017	November 2015	1.4
STIVARGA	Regorafenib	Bayer	Imported	PR, SR	December 2009	November 2015	March 2017	September 2012	4.5
VIDAZA	Azacitidine	Celgene	Imported	PR	December 2009	December 2014	April 2017	May 2004	12.9
IMBRUVICA	Ibrutinib	Johnson & Johnson	Imported	PR, SR	July 2012	November 2016	August 2017	November 2013	3.8
NINLARO	Ixazomib citrate	Takeda	Imported	PR, SR	December 2012	July 2016	April 2018	November 2015	2.4
FOCUS V	Anlotinib hydrochloride	Chia Tai-Tianqing	Domestic	PR, SR	April 2010	January 2017	May 2018	n/a	n/a
ZYKADIA	Ceritinib	Novartis	Imported	PR, SR	January 2013	March 2017	May 2018	April 2014	4.1
OPDIVO	Nivolumab	Bristol-Myers Squibb	Imported	UNOD*	May 2013	October 2017	June 2018	December 2014	3.5
KEYTRUDA	Pembrolizumab	Merck Sharp & Dohme	Imported	UNOD*	April 2014	February 2018	July 2018	September 2014	3.9
IBRANCE	Palbociclib	Pfizer	Imported	PR, SR	May 2013	August 2017	July 2018	February 2015	3.5
IRENE	Pyrotinib maleate	Hengrui	Domestic	PR, CA, SR	May 2011	July 2017	August 2018	n/a	n/a

Trade name	Drug name	Developer	Origin	EP programs	Date of IND submission (China)	Date of NDA/BLA submission (China)	Date of NDA/BLA approval (China)	Date of NDA/BLA approval (US)	Drug lag (US vs. China, years)
ALECENSA	Alectinib hydrochloride	Roche	Imported	PR, SR	May 2014	January 2018	August 2018	December 2015	2.7
LYNPARZA	Olaparib	AstraZeneca	Imported	PR, SR	August 2013	November 2017	August 2018	August 2017	1.0
LENVIMA	Lenvatinib mesylate	Eisai	Imported	PR, SR	January 2013	November 2017	September 2018	February 2015	3.6
ELUNATE	Fruquintinib	Hutchison	Domestic	PR	August 2009	June 2017	September 2018	n/a	n/a
FIRMAGON	Degarelix acetate	Ferring	Imported	None	February 2011	January 2016	September 2018	December 2008	9.7
TUOYI	Toripalimab	Junshi	Domestic	PR, CA	December 2014	March 2018	December 2018	n/a	n/a
TREANDA	Bendamustine hydrochloride	Cephalon	Imported	PR	June 2009	March 2017	December 2018	March 2008	10.8
PERJETA	Pertuzumab	Roche/ Genentech	Imported	none	March 2008	December 2017	December 2018	June 2012	6.5
TYVYT	Sintilimab	Innovent	Domestic	PR, CA, SR	December 2015	April 2018	December 2018	n/a	n/a
VIZIMPRO	Dacomitinib	Pfizer	Imported	PR, SR	June 2011	May 2018	May 2019	September 2018	0.6
XGEVA	Denosumab	Amgen	Imported	UNOD	May 2010	October 2018	May 2019	June 2010	9.0
AIRUIKA	Camrelizumab	Hengrui	Domestic	PR, CA, SR	December 2014	April 2018	May 2019	n/a	n/a
DARZALEX	Daratumumab	Johnson & Johnson	Imported	PR, SR	August 2013	October 2018	July 2019	November 2015	3.6
HALAVEN	Eribulin mesylate	Eisai	Imported	None	March 2011	December 2017	July 2019	November 2010	8.7
LONSURF	Tipiracil hydrochloride+Trifluridine	Servier	Imported	SR	November 2012	June 2017	August 2019	September 2015	3.9

Trade name	Drug name	Developer	Origin	EP programs	Date of IND submission (China)	Date of NDA/BLA submission (China)	Date of NDA/BLA approval (China)	Date of NDA/BLA approval (US)	Drug lag (US vs. China, years)
ERLEADA	Apalutamide	Johnson & Johnson	Imported	UNOD	January 2015	March 2019	September 2019	February 2018	1.6
XTANDI	Enzalutamide	Astellas	Imported	PR, SR	August 2011	April 2018	November 2019	August 2012	7.2
HANSOH XINFU	Flumatinib mesylate	Hansoh	Domestic	PR, SR	June 2006	July 2018	November 2019	n/a	n/a
IMFINZI	Durvalumab	AstraZeneca	Imported	None	January 2015	December 2018	December 2019	May 2017	2.6
TAFINLAR	Dabrafenib mesylate	GlaxoSmithKline	Imported	PR, SR	January 2014	January 2019	December 2019	May 2013	6.6
MEKINIST	Trametinib	Novartis	Imported	PR, SR	January 2014	January 2019	December 2019	May 2013	6.6
ZEJULA	Niraparib tosylate	Zai Lab	Imported	PR, SR	December 2016	December 2018	December 2019	March 2017	2.8
BAIZE'AN	Tislelizumab	BeiGene	Domestic	CA, PR, SR	October 2015	September 2018	December 2019	n/a	n/a
KADCYLA	Ado-trastuzumab emtansine	Roche	Imported	PR	June 2009	March 2019	January 2020	February 2013	6.9
TECENTRIQ	Atezolizumab	Roche/ Genentech	Imported	None	November 2013	February 2019	February 2020	May 2016	3.7
AMEILE	Almonertinib mesylate	Hansoh	Domestic	CA, PR, SR	June 2016	April 2019	March 2020	n/a	n/a
NERLYNX	Neratinib maleate	Pfizer	Imported	SR	August 2006	September 2018	April 2020	July 2017	2.8
ADCETRIS	Brentuximab vedotin	Takeda	Imported	PR	May 2013	April 2019	May 2020	August 2011	8.7
BRUKINSA	Zanubrutinib	BeiGene	Domestic	CA, PR, SR	December 2014	August 2018	June 2020	November 2019	0.6
CIPTERBIN	Inetetamab	Guojian	Domestic	PR	June 2003	September 2018	June 2020	n/a	n/a

Trade name	Drug name	Developer	Origin	EP programs	Date of IND submission (China)	Date of NDA/BLA submission (China)	Date of NDA/BLA approval (China)	Date of NDA/BLA approval (US)	Drug lag (US vs. China, years)
FOLOTYN	Pralatrexate	Mundipharma	Imported	PR	June 2012	December 2018	August 2020	September 2009	10.9
AIRUIYI	Fluzoparib	Hengrui	Domestic	CA, PR, SR	September 2012	October 2019	December 2020	n/a	n/a
XOFIGO	Radium^{223}	Bayer	Imported	PR	May 2012	November 2018	August 2020	May 2013	7.3
BLINCYTO	Blinatumomab	Amgen	Imported	PR	August 2015	October 2019	December 2020	December 2014	6.0
BEIMEINA	Ensartinib hydrochloride	Betta	Domestic	CA, PR, SR	October 2015	January 2019	November 2020	n/a	n/a
VENCLEXTA	Venetoclax	Abbvie	Imported	PR, SR	November 2015	January 2020	December 2020	April 2016	4.6
YINUOKAI	Orelabrutinib	InnoCare	Domestic	CA, PR, SR	June 2017	November 2019	December 2020	n/a	n/a

CA, conditional approval; EP, expedited programmes; IND, investigational new drug; NDA/BLA, new drug application/biologic license application; PR, priority review; SR, special review; UNOD, urgently needed overseas drugs; n/a., not applicable, not approved in the US yet. *These two drugs were on the proposed list of UNOD and were already approved before the final release of UNOD.