nature REVIEWS CLINICAL ONCOLOGY

SUPPLEMENTARY INFORMATION

In format as provided by the authors

Simultaneous development of zanubrutinib in the USA and China

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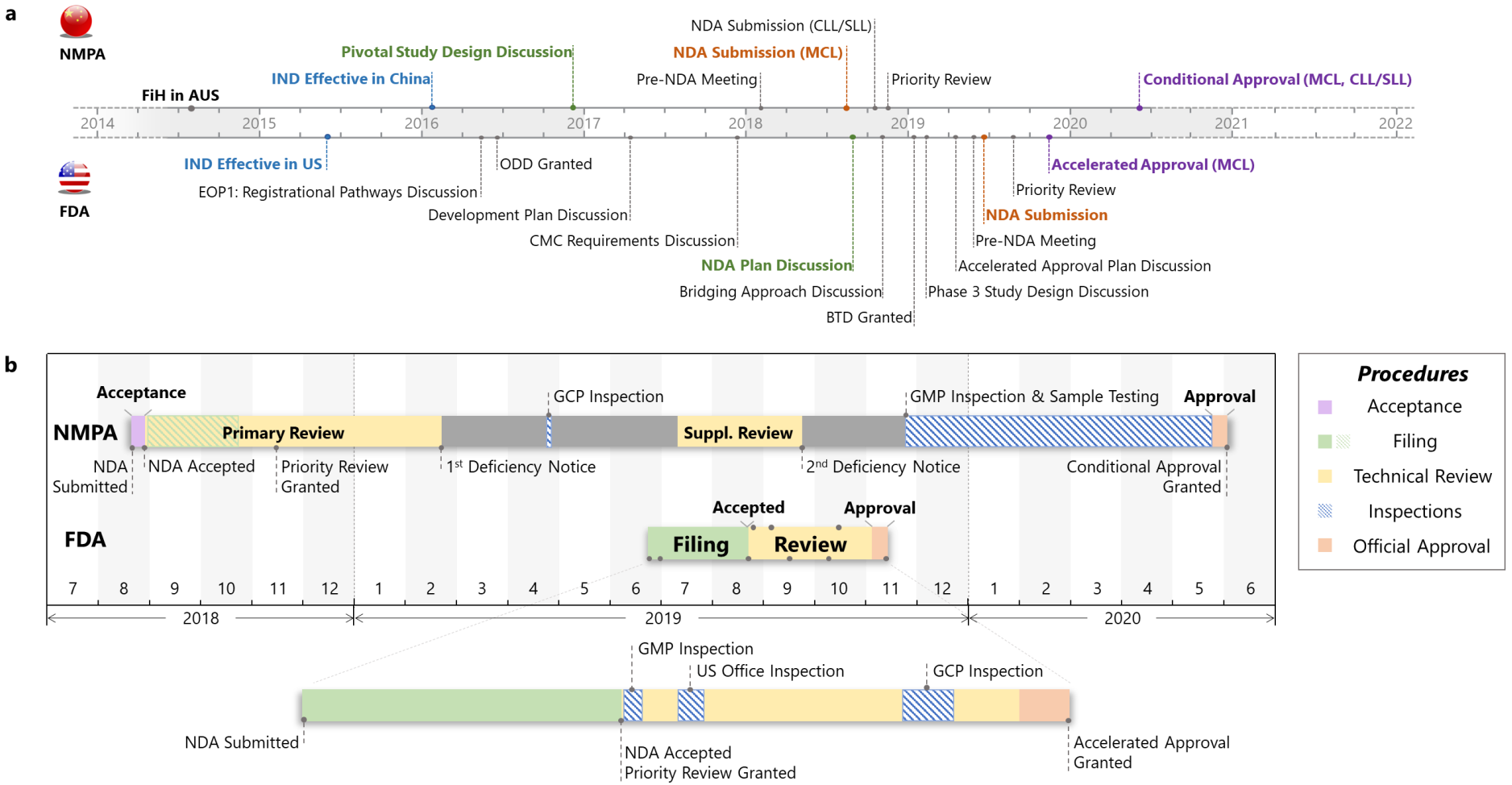
https://doi.org/10.1038/s41571-020-0414-y



Supplementary Figure 1 | Timeline of events and NDA approvals of zanubrutinib for MCL at China's NMPA and the US FDA. a | Regulatory events with China's NMPA and the US FDA are shown above or below the scale, respectively. **b |** Timelines of NDA review and approval for zanubrutinib. Time lengths for each process were based on the available FDA approval packages[1] and estimates based on Pharmcube database for NMPA. General processes of NDA priority review at the NMPA comprise acceptance (purple), technical review (yellow) including filing review, primary and supplemental reviews, inspections including sample testing (blue) and approval (orange). NDA priority review at the FDA includes filing review (green, indicating accepted), technical review (yellow) in parallel to inspections (blue), and approval (orange). Grey box represents data preparation of the sponsor in response to deficiency notices. AUS, Australia; BTD, breakthrough therapy designation; CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; CMC, chemical manufacturing control; EOP1, end of phase I; FDA, Food and Drug Administration; FiH, first-in-human study; GCP, Good Clinical Practice; GMP, Good Manufacturing Practice; IND, investigational new drug; MCL, mantle cell lymphoma; NDA, new drug application; NMPA, National Medical Products Administration; ODD, orphan drug designation.

Supplementary Table 1 | Summary of Bruton tyrosine kinase (BTK) inhibitors on the market or in development

Drug name	Approved Indications	Registrational status for MCL in USA	Registrational status for MCL in China	Key studies and results in MCL
Ibrutinib[2,3] (PCI-32765, JNJ-54179060, CRA-032765）	CLL/SLL, MCL, WM, cGvHD and MZL	Approved	Approved	Pooled analysis of 7.5-year follow-up data of phase II SPARK (NCT01599949), phase III RAY (NCT01646021), and phase II PCYC-1104 (NCT01236391) R/R MCL: ORR 70% (CR rate 28%, PR rate 42%); mPFS 12.5 months
Acalabrutinib[4,5] (ACP-196）	MCL and CLL/SLL	Approved	Phase III	Phase II (NCT02213926) R/R MCL: ORR 81% (CR rate 40%, PR rate 41%)
Zanubrutinib[6,7] (BGB-3111）	MCL and CLL/SLL	Approved	Approved	Phase II (NCT03206970) R/R MCL: ORR 84% (CR rate 59%, PR rate 24%); mDoR 19.5 months
Orelabrutinib[8] (ICP-022）	NDA filed for CLL/SLL and MCL	Phase I	Phase II	Phase II (NCT03494179) R/R MCL: ORR 83% (CR rate 25%, PR rate 58%); mDoR and mPFS not reached
Vecabrutinib[9] (SNS-062)	NA	Phase Ib/II	NA	Phase Ib/II (NCT03037645) CLL and other B cell malignancies: ongoing
Fenebrutinib[10] (RG7845)	NA	NA	NA	NA
Spebrutinib[11] (CC-292, AVL-292)	NA	NA	NA	NA
Tirabrutinib[12] (GS-4059)	R/R PCNSL; NDA filed for WM	NA	NA	NA

C481, cysteine 481; cGVHD, chronic graft-versus-host disease; CLL, chronic lymphocytic leukaemia; CR, complete response; MCL, mantle cell lymphoma; mDoR, median duration of response; mPFS, median progression-free survival; MZL, marginal zone lymphoma; ORR, objective response rate; NA, not available; NDA, new drug application; PR, partial response; R/R MCL, relapsed and/or refractory mantle cell lymphoma; R/R PCNSL, relapsed and/or refractory primary central nervous system lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinaemia.

Supplementary Table 2 | Clinical studies relevant to NDA dossiers for zanubrutinib submitted to China's NMPA and the US FDA

Registrational package	Efficacy	Efficacy (pivotal)	Safety	Safety	Safety[a]	Safety
Trial name	BGB-3111-AU-003[1,13]	BGB-3111-206[1,6,7]	BGB-3111-1002[1,14]	BGB-3111-205[1,15]	BGB-3111-207[16]	BGB-3111-210[1,17]
Study population	B cell malignancies	R/R MCL after 1–4 prior line of therapy	Part 1: B cell malignancies Part 2: R/R FL/MZL	R/R CLL/SLL	R/R non-GCB DLBCL	R/R WM after at least 1 prior line of therapy
Study design	Phase I/II dose- escalation study with dose expansion phase	Phase II, multicentre, single-arm, open-label study	Phase I, multicentre, open-label study	Phase II, multicenter, single-arm study	Phase II, multicentre, single-arm, open-label study	Phase II, multicentre, single-arm study
Treatment regimen and schedule	40, 80, 160 or 320 mg PO q.d., or 160mg PO b.i.d.	160 mg PO b.i.d.	Part 1:320 mg PO q.d. or 160 mg PO b.i.d. Part 2: 160 mg PO b.i.d.	160 mg PO b.i.d.	160 mg PO b.i.d.	160 mg PO b.i.d.
Population size	376 (32 with R/R MCL)	86	44	91	41	44
Efficacy results	ORR 84% (95% CI 67–95); CR rate 22% (95% CI 9–40); mDoR 18.5 months (95% CI 16.6– NE)	ORR 84% (95% CI 74–91); CR rate 59% (95% CI 48–70); mDoR 19.5 months (95% CI 16.6–NE)[18]	NA	NA	NA	NA
Countries	Australia, New Zealand, South Korea, USA, Italy, and the UK	China	China	China	China	China
Study period	Nov 2014–Dec 2023	Mar 2017–Nov 2020	Jul 2016–Jun 2021	Mar 2017–Dec 2020	June 2017–Jan 2020	Aug 2017–Dec 2021

General information was retrieved based on clinicaltrial.gov and published results. b.i.d., twice a day; CI, confidence interval; CR, complete response; mDoR, median duration of response; NA, not available; NDA, new drug application; NE, not evaluable; ORR, objective response rate; PO, per os (orally); q.d., once a day; R/R CLL/SLL, relapsed and/or refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma; R/R FL/MZL, relapsed and/or refractory follicular lymphoma or marginal zone lymphoma; R/R MCL, relapsed and/or refractory mantle cell lymphoma; R/R non-GCB DLBCL, relapsed and/or refractory non-germinal centre B cell diffuse large B cell lymphoma; R/R WM, relapsed and/or refractory Waldenström macroglobulinaemia. [a]Study BGB-3111-207 was submitted to the NDA dossier at the NMPA by rolling submission during the review. It was not included in the safety dataset for the FDA given the earlier approval of zanubrutinib in the US.

Supplementary Table 3 | Approved drugs for relapsed and/or refractory mantle cell lymphoma

Drug	Mechanism of action	Pivotal study design	Dosing	Efficacy results in pivotal study	Year of FDA approval	Year of NMPA approval
Bortezomib[19]	Proteasome inhibitor	*n* = 155 Single-arm	1.3 mg/m^2 dose i.v. b.i.w. for 2 weeks followed by 10-day drug-free period	ORR 31%; CR rate 8%; mDoR 9.2 months	2006 (regular approval)	2009
Lenalidomide[20]	Antiangiogenesis/IMiD	*n* = 134 Single-arm	25 mg PO q.d. on days 1–21 of repeated 28-day cycles	ORR 26%; CR rate 7.5%; mDoR 16.6 months	2013 (regular approval)	NA
Ibrutinib[2]	BTK inhibitor	*n* = 111 Single-arm	560 mg PO q.d. until disease progression or unacceptable toxicity	ORR 66%; CR rate 21%; mDoR 17.5 months	2013 (accelerated approval)	2017
Acalabrutinib[4]	BTK inhibitor	*n* = 124 Single-arm	100 mg PO b.i.d. until disease progression or unacceptable toxicity	ORR 80%; CR rate 40%; mDoR NR (median follow-up duration 15.2 months)	2017 (accelerated approval)	NA
Zanubrutinib[6]	BTK inhibitor	*n* = 86 Single-arm	160 mg PO b.i.d. or 320 mg PO q.d.	ORR 84%; CR rate 59%; mDoR 19.5 months	2019 (accelerated approval)	2020 (conditional approval)

b.i.d., twice a day; b.i.w., twice a week; BTK, Bruton tyrosine kinase; CR, complete response; mDoR, median duration of response; FDA, Food and Drug Administration; IMiD, immunomodulatory imide drug; i.v., intravenous; NA, not available; NMPA, National Medical Products Administration; NR, not reached; ORR, obejective response rate; PO, per os (orally); q.d., once a day.

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