Supplementary

Table S1. Formulas and signal detection criteria for ROR.

Formula	**Signal standard**
ROR = (ad/bc)	**· Lower limit of ROR95%CI>1;** **· a≥3**
$\mathbf{ROR95\%CI = e^{\ln(ROR)\pm 1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}}$	

a: number of specific adverse events to the target drug; b: number of other adverse events to the target drug; c: number of specific adverse events to background drugs; d: number of other adverse events to the background drug;

ROR: reporting odds ratio, CI: confidence interval

Table S2. All positive Preferred Terms associated with Zanubrutinib.

soc	PT	n	ROR (95%CI)
Blood and lymphatic system disorders	Myelosuppression	39	19.7 (14.4-27.1)
	Febrile neutropenia	14	4.4 (2.6-7.4)
	Neutropenia	13	1.8 (1-3)
	Increased tendency to bruise	5	13.7 (5.7-33.1)
	Haemorrhagic diathesis	4	29.7 (11.1-79.2)
	Cytopenia	4	5.2 (1.9-13.8)
	Haemolysis*	3	11.1 (3.6-34.4)
Cardiac disorders	Atrial fibrillation	21	4.9 (3.2-7.6)
	Pericardial effusion*	7	7.4 (3.5-15.5)
	Atrioventricular block	3	9.9 (3.2-30.8)
	Ventricular tachycardia	3	5 (1.6-15.5)
Ear and labyrinth disorders	Ear discomfort*	3	6.9 (2.2-21.5)
Eye disorders	Eye haemorrhage	5	9.7 (4-23.2)
Gastrointestinal disorders	Dysphagia	14	4 (2.4-6.8)
	Dyspepsia*	8	2.1 (1-4.2)
	Intestinal perforation*	4	9.5 (3.6-25.4)
	Faeces discoloured	3	3.8 (1.2-11.7)
	Haematemesis	3	3.3 (1.1-10.2)
	Tooth disorder*	3	3.2 (1-10.1)
General disorders and administration site conditions	Fatigue	50	1.4 (1-1.8)
	Asthenia	30	2 (1.4-2.9)
	Peripheral swelling	18	2 (1.3-3.2)
	Oedema peripheral	12	3.4 (1.9-5.9)
	Oedema	5	2.6 (1.1-6.3)
	Mass*	3	4.9 (1.6-15.2)
Hepatobiliary disorders	Hepatic function abnormal	5	3.2 (1.3-7.6)
Infections and infestations	Urinary tract infection	19	2.4 (1.6-3.8)
	Infection	15	2.2 (1.3-3.6)
	Cellulitis	10	4.8 (2.6-8.9)
	Sepsis	9	2 (1-3.8)
	Pneumonia fungal	6	23.7 (10.6-53)
	Hepatitis B	4	21.8 (8.2-58.3)
	Meningitis cryptococcal	3	40.1 (12.9-124.9)
	Hepatitis b reactivation	3	13.1 (4.2-40.7)
	Pneumocystis jirovecii pneumonia	3	5.5 (1.8-17.2)
	Skin infection	3	5.4 (1.7-16.8)
Injury, poisoning and procedural complications	Contusion	68	17.2 (13.5-21.9)
	Subdural haematoma	5	9.7 (4-23.4)
Investigations	Platelet count decreased	29	5.7 (4-8.3)
	White blood cell count decreased	24	4.4 (2.9-6.6)

	White blood cell count increased	22	16.1 (10.6-24.5)
	Haemoglobin decreased	14	3.4 (2-5.8)
	Blood urine present	9	12.7 (6.6-24.4)
	Blood creatinine increased	8	3 (1.5-6.1)
	Red blood cell count decreased	6	4.4 (2-9.7)
	Haemoglobin abnormal	3	9.5 (3.1-29.6)
	Blood iron decreased*	3	4.7 (1.5-14.7)
Metabolism and nutrition disorders	Tumour lysis syndrome	5	11.1 (4.6-26.8)
	Hypernatraemia*	3	15 (4.8-46.6)
	Increased appetite*	3	4.7 (1.5-14.7)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	4	2.8 (1.1-7.6)
	Haemarthrosis	3	4.7 (1.5-14.7)
Nervous system disorders	Hypersomnia*	4	3.3 (1.2-8.8)
	Haemorrhage intracranial	3	6.3 (2-19.6)
Renal and urinary disorders	Haematuria	8	5.9 (3-11.9)
	Dysuria	5	3.5 (1.4-8.3)
Reproductive system and breast disorders	Penile haemorrhage	3	112.6 (35.9-352.6)
Respiratory, thoracic and mediastinal disorders	Pleural effusion	14	6.2 (3.7-10.5)
	Epistaxis	8	2.7 (1.3-5.4)
	Sinus disorder	4	4.4 (1.6-11.7)
Skin and subcutaneous tissue disorders	Rash	48	2.4 (1.8-3.2)
	Haemorrhage subcutaneous	25	190.8 (128-284.5)
	Petechiae	16	40.7 (24.8-66.5)
	Skin discolouration*	10	5.1 (2.7-9.5)
	Rash macular	9	5.8 (3-11.2)
	Ecchymosis	8	34.6 (17.3-69.4)
	Night sweats	6	4.5 (2-10)
	Rash pruritic	6	2.8 (1.2-6.2)
	Blood blister	5	40.3 (16.7-97.2)
	Skin lesion	4	3.1 (1.2-8.4)
	Purpura	3	10 (3.2-31.1)
	Hair texture abnormal*	3	4.9 (1.6-15.2)
	Skin haemorrhage	3	4.6 (1.5-14.3)
Vascular disorders	Haemorrhage	18	4.4 (2.7-6.9)

* unexpected adverse event

SOC, system organ class; PT, preferred term; ROR, reporting odds ratio; CI, confidence interval.

Table S3. Subgroup Disproportionality Analysis by Indications

PT	n	ROR (95%CI)
Mantle cell lymphoma		
Haemorrhage subcutaneous	4	32.2 (9.4-110.3)
Chest pain	5	7.6 (3.0-19.5)
White blood cell count increased	4	7.0 (2.5-20.0)
Myelosuppression	6	5.1 (2.2-11.9)
Contusion	8	4.8 (2.3-9.9)
Pain	6	4.2 (1.8-9.6)
Dizziness	7	4.1 (1.9-8.9)
Oedema peripheral	3	3.7 (1.1-11.8)
Dyspnoea	11	3.6 (2.0-6.7)
Peripheral swelling	5	3.5 (1.4-8.6)
Platelet count decreased	10	3.2 (1.7-6.0)
Asthenia	7	2.7 (1.3-5.9)
Nausea	7	2.7 (1.2-5.7)
Rash	11	2.6 (1.4-4.8)
Chronic lymphocytic leukemia or small lymphocytic lymphoma		
Haemorrhage subcutaneous	8	41.3 (19.0-89.6)
Atrioventricular block	3	26.7 (7.9-90.4)
Skin infection	3	6.9 (2.2-21.8)
Haematochezia	3	6.0 (1.9-19.1)
Blood creatinine increased	5	6.0 (2.4-14.6)
Petechiae	4	4.0 (1.5-10.8)
Erythema	6	3.7 (1.6-8.3)
Rash pruritic	3	3.5 (1.1-11.1)
Pericardial effusion	3	3.5 (1.1-10.8)
Contusion	21	3.4 (2.2-5.3)
Visual impairment	3	3.4 (1.1-10.5)
Skin discolouration	3	3.2 (1.0-9.9)
Anxiety	5	3.1 (1.3-7.6)
Dehydration	6	3.1 (1.4-6.9)
Cardiac failure	4	3.0 (1.1-8.1)
White blood cell count increased	13	2.9 (1.7-5.1)
Abdominal discomfort	5	2.9 (1.2-7.0)
Waldenström's macroglobulinemia		
Haemorrhage subcutaneous	8	46.6 (12.3-175.9)
Drug-induced liver injury	3	10.4 (2.5-43.6)
Petechiae	8	8.7 (3.7-20.5)
Vertigo	3	8.7 (2.2-34.8)
Eye haemorrhage	4	7.7 (2.4-25.1)
Blood urine present	4	6.3 (2.0-19.9)
Blood blister	4	5.8 (1.9-18.0)

Sinus disorder	3	5.8 (1.6-21.4)
Depressed mood	3	5.2 (1.4-19.0)
Gait inability	3	4.7 (1.3-17.0)
Cellulitis	4	4.3 (1.5-13.0)
Gastroesophageal reflux disease	4	4.3 (1.5-13.0)
Musculoskeletal stiffness	3	4.3 (1.2-15.4)
Night sweats	3	3.7 (1.1-13.0)
Erythema	5	3.6 (1.4-9.5)
Rash	18	3.4 (2.0-5.6)
Abdominal discomfort	4	3.3 (1.1-9.7)
Contusion	25	3.0 (1.9-4.6)
Pruritus	7	2.8 (1.3-6.3)

Table S4. Subgroup Disproportionality Analysis Results in the United States and China

PT	n	ROR (95%CI)
United States		
Haemorrhage subcutaneous	18	601.7 (369.4-980.3)
Penile haemorrhage	3	176.1 (55.7-556.1)
Petechiae	16	87.7 (53.4-143.9)
Ecchymosis	6	62.3 (27.8-139.4)
Haemorrhagic diathesis	4	51.1 (19.1-136.8)
Hypernatraemia	3	44.8 (14.4-139.8)
Blood blister	5	44.8 (18.6-108.1)
Pneumonia fungal	3	30.1 (9.7-93.8)
Procedural haemorrhage	3	22.7 (7.3-70.5)
Contusion	67	21.6 (17.0-27.6)
Blood urine present	9	16.5 (8.6-31.9)
White blood cell count increased	13	15.8 (9.2-27.3)
Eye haemorrhage	5	15.2 (6.3-36.7)
Increased tendency to bruise	5	13.5 (5.6-32.6)
Subdural haematoma	3	10.7 (3.5-33.3)
Ear discomfort	3	8.4 (2.7-26.0)
Haematuria	6	8.3 (3.7-18.4)

Cardiac operation	3	8.2 (2.7-25.5)
Skin infection	3	8.1 (2.6-25.3)
Platelet count decreased	22	7.2 (4.7-10.9)
Mass	3	7.1 (2.3-22.0)
Blood iron decreased	3	6.6 (2.1-20.5)
Pericardial effusion	3	6.0 (1.9-18.5)
Musculoskeletal pain	4	5.9 (2.2-15.7)
Rash macular	9	5.7 (3.0-11.1)
Faeces discoloured	3	5.6 (1.8-17.4)
Night sweats	5	5.4 (2.3-13.1)
Increased appetite	3	5.4 (1.7-16.8)
Haemorrhage	16	5.3 (3.3-8.7)
Dysphagia	12	5.1 (2.9-9.0)
Oedema	5	5.0 (2.1-12.0)
Skin haemorrhage	3	5.0 (1.6-15.5)
Skin discolouration	9	4.9 (2.6-9.4)
Red blood cell count decreased	5	4.7 (2.0-11.3)
Pleural effusion	5	4.7 (2.0-11.3)
Atrial fibrillation	14	4.7 (2.8-7.9)
Sinus disorder	4	4.6 (1.7-12.2)
Haemoglobin decreased	11	4.5 (2.5-8.1)
Skin lesion	3	4.5 (1.4-13.9)
Joint injury	3	4.2 (1.4-13.2)
Oedema peripheral	7	4.1 (1.9-8.6)
Tooth disorder	3	4.0 (1.3-12.3)
Hair texture abnormal	3	3.9 (1.3-12.1)
Cellulitis	5	3.7 (1.5-8.9)
White blood cell count decreased	15	3.7 (2.2-6.1)
Hypersomnia	4	3.7 (1.4-9.8)
Localised infection	3	3.5 (1.1-10.8)
Depressed mood	5	3.4 (1.4-8.2)
Rectal haemorrhage	3	3.4 (1.1-10.6)
Dysuria	3	3.3 (1.1-10.2)
Blood creatinine increased	5	3.3 (1.4-7.8)
Neck pain	5	3.1 (1.3-7.4)
Productive cough	4	3.1 (1.2-8.2)
Rash pruritic	5	2.9 (1.2-6.9)
Stomatitis	5	2.7 (1.1-6.5)
Infection	11	2.7 (1.5-4.9)
Dyspepsia	8	2.6 (1.3-5.2)
Urinary tract infection	15	2.5 (1.5-4.2)
Neutropenia	9	2.4 (1.3-4.7)

Rash	40	2.4 (1.7-3.3)
Myalgia	10	2.4 (1.3-4.4)
Asthenia	24	2.4 (1.6-3.5)
Abdominal distension	7	2.3 (1.1-4.9)
Dehydration	8	2.2 (1.1-4.4)
Hypertension	11	2.1 (1.2-3.8)
Peripheral swelling	13	1.9 (1.1-3.3)
Fatigue	49	1.7 (1.3-2.3)
Cough	16	1.7 (1.01-2.7)
China		
Haemolysis	3	44.8 (13.8-145.0)
Hepatitis B	3	40.0 (12.4-129.1)
Tumour lysis syndrome	3	31.3 (9.8-100.3)
Haemorrhage subcutaneous	6	22.3 (9.8-50.6)
White blood cell count increased	8	19.9 (9.8-40.6)
Pericardial effusion	3	9.3 (3.0-29.1)
Peripheral swelling	3	7.9 (2.5-24.9)
Pleural effusion	5	7.5 (3.1-18.2)
Febrile neutropenia	3	6.4 (2.1-20.1)
Covid-19	3	6.0 (1.9-18.9)
Sepsis	3	5.4 (1.7-17.0)
Oedema peripheral	4	5.1 (1.9-13.7)
Interstitial lung disease	3	4.5 (1.4-14.0)
Myelosuppression	39	3.4 (2.5-4.8)

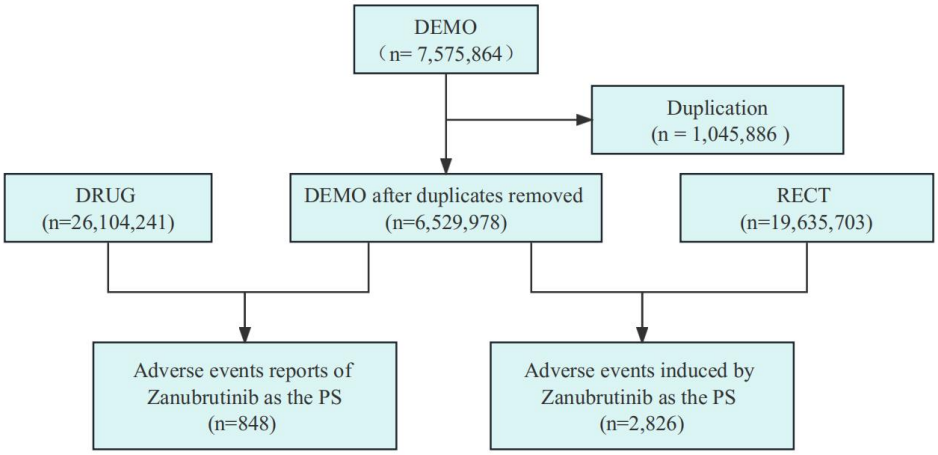

Figure S1. The flow diagram of screening zanubrutinib-related AEs from the FAERS database. DEMO, demographic and administrative information; DRUG, drug information; REAC, adverse event information; PT, preferred term.

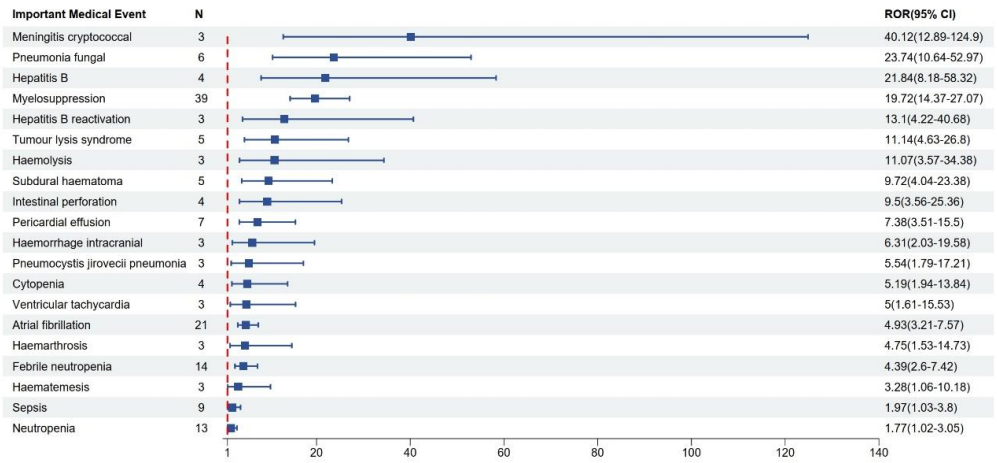

Figure S2. Forest plot of the important medical event signals for zanubrutinib. ROR, reported odds ratio; CI, confidence interval.

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