Pirtobrutinib *versus* venetoclax in covalent Bruton tyrosine kinase inhibitor-pretreated chronic lymphocytic leukemia: a matching-adjusted indirect comparison

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Supplementary content: Sensitivity analyses

An unanchored MAIC relies on the assumption of conditional constancy of relative effects and assume that the relative treatment effects are constant between studies.[19] Meeting this stringent assumption is extremely difficult for all MAIC analysis; therefore, to achieve reliable predictions, adjustment methods in these studies should account for all effect modifiers and prognostic variables.[28] Therefore, for the unanchored MAIC, unbalanced prognostic factors may contribute to the outcome and thus become confounders. As a result, it was crucial that all factors that directly or indirectly affect outcomes by impacting the effect the treatment has on that outcome (e.g., including even the non-effect-modifying prognostic factors) were balanced. The primary analysis utilized an informed covariate approach. To ensure that this did not introduce bias into the study findings, sensitivity analyses were conducted balancing the cohorts on all available baseline factors (the primary covariates listed above plus the additional covariates of ECOG performance status 0/1 versus 2, percent of patients with bulky disease, and patient sex) to evaluate the potential impact of informed versus uninformed covariate selection. Additional sensitivity analyses were conducted in the case of the identification of extreme weights, where those patients were excluded, and analyses were re-run for each efficacy outcome.

Supplementary Table 1. Search strategy terms used to identify trials of venetoclax

A systematic literature review was conducted in MedLine, EMBASE, EBM Reviews, clinicaltrials.gov, and a series of conference proceedings through June 2022. Studies were included in this review if they enrolled patients with CLL who had prior cBTKi exposure, and if at least one clinical outcome of overall survival (OS), PFS, or tumor response (including ORR) were reported.

S.No.	Search strings
1.	lymphoma, non-hodgkin/
2.	(chronic lymphocytic leukemia or chronic lymphocytic leukaemia).mp.
3.	chronic lymphatic leukemia.mp.
4.	(chronic lymphocytic or CLL).mp.
5.	(small lymphocytic lymphoma or small-lymphocytic lymphoma).mp.
6.	small lymphocytic lymphoma.mp.
7.	(small lymphocytic or SLL).mp.
8	((chronic or small) adj3 (lymph* or leuk* or NHL)).mp.
9	(chronic lymphocytic leukemia or small lymphocytic lymphoma).mp.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	exp salvage therapy/
12	((salvage adj3 (chemotherap* or treatment* or therap*)) or (resistant adj3 (chemotherap* or treatment resistant))).mp.
13	(second line or 2nd line or 2?nd line or second-line or (second adj4 line)).ti,ab.
14	(third line or third-line or 3?rd line or 3rd line or (third adj4 line)).ti,ab.
15	(refractory or refractor* or relaps* or recurrent or (previously adj3 treated or previous* adj3 treat*) or (drug adj3 resistan*) or pre-treated or pretreated).ti,ab.
16	((failed or failure or discontinue or discontinu*) and (treatment* or therap* or prior or previous)).mp.
17	((chemotherap* or treatmen* or regime* or medication* or therap*) adj7 (refractory or recurrent or resistant or rescue or salvage or failed or failure)).mp.
18	11 or 12 or 13 or 14 or 15 or 16 or 17
19	10 AND 18
20	Bruton Tyrosine Kinase inhibitor.mp.
21	(bruton's tyrosine kinase inhibitor or bruton tyrosine kinase inhibitor or bruton s tyrosine kinase inhibitor or inhibitor of bruton s tyrosine kinase inhibitor or inhibitor of bruton's tyrosine kinase inhibitor or inhibitor of bruton tyrosine kinase inhibitor or BTK inhibitors or BTKI or BTKi or BTKinhibitors or BTK?inhibitors or BTK).mp.
22	exp Agammaglobulinaemia Tyrosine Kinase/
23	(ibrutinib or imbruvica or "cra 032765" or cra032765 or cra-032765 or "pci 32765" or pci32765 or "pci 32765-00" or "pci 32765 00" or pci3276500 or PC-32765 or PC32765 or "PC 32765").mp.
24	(acalabrutinib or "calquence acp 196" or acp196 or acp-196 or Acp-196).mp.
25	(zanubrutinib or brukinsa or BGB-3111 or Bgb-3111 or "BGB 3111" or BGB3111).mp.
26	(Tirabrutinib or GS-4059 or Gs-4059 or "GS 4059" or GS4059 or ONO-4059 or Ono-4059 or ONO4059 or "ONO 4059").mp.

S.No.	Search strings
27	(pirtorutinib or LOXO-305 or "LOXO 305" or Loxo-305 or "Loxo 305" or LY-3527727 or "LY 3527727" or LY3527727 or RXC-005 or RXC005 or "RXC 005").mp.
28	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29	19 AND 28
30	exp adolescent/ or exp child/ or exp infant/ or (infant disease* or childhood disease*).ti,ab,kf. or (adolescen* or babies or baby or boy? or boyfriend or boyhood or child* or girl? or infant* or juvenil* or kid? or minors or minors* or neonat* or neonat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kf.
31	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt.
32	(nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.
33	29 not (30 or 31 or 32)
34	(venetoclax or “BCL-2” or BCL2).ti.ab
35	33 and 34

Supplementary Table 2. Venetoclax trials identified in the literature review and eligibility assessment

A total of 14 publications representing 8 single-arm trials were identified.

Citation	Population	Intervention	Outcomes	Included or Excluded (with reason)
Jones, Mato et al. 2018[9] NCT02141282	91 patients who received venetoclax after ibrutinib	Venetoclax initiated at 20 mg daily, intra-patient ramp-up to 400 mg daily.	ORR/tumor response DOR PFS OS Safety	Included
Anderson, Tan et al. 2017[28] NCT01328626, NCT01889186, and/or NCT01682616	67 heavily pre-treated patients enrolled to various early phase trials	Venetoclax (n=51 monotherapy; n=16 venetoclax+rituximab,)	Time to progression Post-venetoclax outcomes	Excluded (Data were combined between monotherapy and combined therapy regimens)
Blombery, Thompson et al. 2020; 2022[29,30]	92/89 patients enrolled to various clinical trials	Venetoclax (trials not specified)	BAX mutations	Excluded (No efficacy or safety outcomes reported)
Coutre, Choi et al 2018[31] NCT02141282	36 patients who received venetoclax after idealisib	Venetoclax initiated at 20 mg daily, intrapatient ramp-up to 400 mg daily.	ORR/tumor response MRD Safety	Excluded (same study as Jones at al, 2018 but limited to post-idelalisib which is not comparable to BRUIN)
Coutre, Wierda et al 2016[32] NCT02141282	38 patients who received venetoclax after ibrutinib, 10 after idealisib	Venetoclax initiated at 20 mg daily, intrapatient ramp-up to 400 mg daily.	ORR/tumor response Safety	Excluded (Same study as Jones et al. 2018)
Davids, Hallek et al 2018[33] NCT01328626, NCT01889186, NCT02141282	350 patients enrolled to various phase 1/2 clinical trials	400 mg daily venetoclax monotherapy	Safety	Excluded (No efficacy outcomes reported)
Jones, Mato et al. 2015[34] NCT02141282	22 patients who received venetoclax after ibrutinib, 6 after idealisib	Venetoclax initiated at 20 mg daily, intrapatient ramp-up to 400 mg daily.	ORR/tumor response Safety	Excluded (Same study as Jones et al. 2018)

Jones, Choi et al 2016[35]	43 patients who received venetoclax after ibrutinib, 21 after idealisib	Venetoclax initiated at 20 mg daily, intrapatient ramp-up to 400 mg daily.	ORR/tumor response Safety	Excluded (Same study as Jones et al. 2018)
Jones, Wierda et al 2016[36]	41 patients who received venetoclax after ibrutinib, 13 after idealisib	Venetoclax initiated at 20 mg daily, intrapatient ramp-up to 400 mg daily.	ORR/tumor response Safety	Excluded (Same study as Jones et al. 2018)
Murayama, Izutsu et al 2021[37] NCT0226573	12 Japanese patients with R/R CLL/SLL	Patients enrolled in phase 1 received 400 mg/day venetoclax monotherapy. Patients enrolled in phase 2 received 400 mg/day venetoclax, plus rituximab.	ORR in phase 2 only Safety	Excluded (Phase 1 data only for venetoclax monotherapy)
Roberts, Seymour et al 2016[8,38] NCT02141282, NCT01 889186, NCT01328626, and/or NCT01682616	387 patients enrolled to various phase 1/2 clinical trials	Venetoclax monotherapy Venetoclax + rituximab Venetoclax doses ranged from 150 mg/day to 1200 mg/day	ORR/tumor response MRD DOR PFS	Excluded (Data were combined between monotherapy and combined therapy regimens)
Roberts, Davis et al. 2016[39] NCT01328626	166 patients with R/R CLL	Phase 1 dose escalation phase, phase 2 expansion phase-weekly stepwise ramp-up in doses as high as 400 mg per day	ORR/response Safety PFS DOR	Excluded (Phase 1 data only for venetoclax monotherapy)
Stilginbauer, Eichorst et al 2016[40] NCT01889186	107 patients with R/R CLL	Once daily venetoclax with a weekly dose ramp-up schedule (20, 50, 100, 200, 400 mg) over 4–5 weeks, ramp up to 400 mg daily	ORR/response Safety PFS OS	Excluded (Phase 1 data only for venetoclax monotherapy)
Wierda, Davids et al, 2017[41]	28 patients who received venetoclax after more than one prior BCRi (including ibrutinib, idelalisib, and investigational agents).	Venetoclax initiated at 20 mg daily, intrapatient ramp-up to 400 mg daily.	ORR/tumor response PFS OS Safety	Excluded (Same study as Jones et al. 2018)

MAIC=matching adjusted indirect comparison; CLL=chronic lymphocytic leukemia; ORR=objective response rate; DOR=duration of response; PFS=progression-free survival; OS=overall survival; BCRi = B-cell receptor pathway inhibitors

Supplementary Table 3. Prior therapies received by patients included in this analysis

Prior Systemic Therapies, n (%)	**Venetoclax (N=91)**	**Pirtobrutinib (N=146)**
Prior BTK	91 (100.0)	146 (100.0)
Prior anti-CD20 Antibody	Not reported	120 (82.2)
Prior Chemotherapy	Not reported	108 (74.0)
Prior PI3K Agent	11 (12.1)	17 (11.6)
Prior Lenalidomide	Not reported	11 (7.5)
Prior CAR-T	Not reported	2 (1.4)
Other Systemic Therapy	Not reported	24 (16.4)

Supplementary Table 4. Sensitivity analyses using all available baseline covariates

	Venetoclax (N=91)	Pirtobrutinib (unweighted) (N=146)	Unweighted OR/HR (95% CI), p-value	Pirtobrutinib (weighted)	Weighted OR/HR (95% CI), p-value
Clinical outcomes					
ORR (%)	64.8	69.9	1.26 (0.69-2.27), p = 0.47	84.2	2.88 (1.46-5.76), p = 0.001
PFS, median (95% CI) months	24.7 (19.2 - NE)	22.1 (19.5 - NE)	1.06 (0.70-1.61), p = 0.77	19.4 (18.6 – NE)	1.15 (0.66-2.01), p=0.62
OS, median (95% CI) months	NE (27.8 - NE)	NE (33.9 - NA)	0.78 (0.42-1.44), p = 0.43	NE (NE-NE)	0.88 (0.34-2.29), p = 0.78
Safety outcomes, grade ≥3 (%)					
Anemia	28.6	5.5	0.15 (0.05-0.35), p<0.001	1.1	0.04 (0.00-0.16), p<0.001
Febrile neutropenia	13.2	1.4	0.09 (0.01-0.43), p < 0.001	1.8	0.10 (0.01-0.47), p < 0.001
Neutropenia	50.5	19.9	0.24 (0.13-0.45), p<0.001	21.3	0.26 (0.14-0.49), p<0.001
Thrombocytopenia	28.6	1.4	0.04 (0.00-0.15), p<0.001	1.8	0.04 (0.00-0.16), p<0.001
Pneumonia	6.6	5.5	0.82 (0.24-2.98), p = 0.78	0.8	0.11 (0.00-0.92), p = 0.02
Treatment discontinuation due to adverse events	6.6	7.5	1.15 (0.37-3.95), p = 1.00	2.6	0.44 (0.09-1.92), p = 0.32

NE=not evaluable

Supplementary Table 5. Percent of patients with any grade treatment-emergent adverse events

	Venetoclax (N=91)	Pirtobrutinib (unweighted) (N=146)	Unweighted OR (95% CI), p-value	Pirtobrutinib (weighted)	Weighted OR (95% CI), p-value
Anemia	52.7	11.0	0.11 (0.05-0.22), <0.001	5.1	0.05 (0.02-0.12), <0.001
Febrile neutropenia	13.2	1.4	0.09 (0.01- 0.43), <0.001	1.4	0.10 (0.01 – 0.47), <0.001
Neutropenia	61.5	26.7	0.23 (0.13-0.41), <0.001	29.4	0.26 (0.14 – 0.47), <0.001
Thrombocytopenia	47.3	3.4	0.04 (0.01 – 0.11), <0.001	2.3	0.03 (0.004 – 0.09), <0.001
Pneumonia	11.0	10.3	0.93 (0.37 – 2.43), 1.0	3.9	0.32 (0.08-1.07), 0.05

Supplementary Table 6. Listing of number (%) of all adverse events reported similarly from both trials

	Venetoclax(n=91)					Pirtobrutinib (n=146)				
n (%)	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Total	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Total
Blood and lymphatic system disorders										
Anaemia	22 (24)	26 (29)	0	0	48 (53)	8(5.5)	8(5.5)	0(0.0)	0(0.0)	16(11.0)
Febrile neutropenia	1 (1)	11 (12)	0	0	12 (13)	0(0.0)	2(1.4)	0(0.0)	0(0.0)	2 (1.4)
Neutropenia	10 (11)	18 (20)	28 (31)	0	56 (62)	5(3.4)	6 (4.1)	6 (4.1)	0(0.0)	17(11.6)
Thrombocytopenia	17 (19)	11 (12)	15 (17)	0	43 (47)	3(2.1)	1 (0.7)	1(0.7)	0(0.0)	5(3.4)
Cardiac Disorders										
Atrial fibrillation	0	1 (1)	0	0	1 (1)	4(2.7)	1(0.7)	1(0.7)	0(0.0)	6(4.1)
Myocardial infarction[a]	0	1 (1)	0	0	1 (1)	0(0.0)	1 (0.7)	0(0.0)	0(0.0)	1 (0.7)
Pericardial effusion	0	1 (1)	0	0	1 (1)	1 (0.7)	0(0.0)	0(0.0)	0(0.0)	1 (0.7)
Ear and labyrinth disorders										
Cataract	0	2 (2)	0	0	2 (2)	1 (0.7)	1 (0.7)	0(0.0)	0(0.0)	2(1.4)
Gastrointestinal disorders										
Abdominal pain	15 (17)	4 (4)	0	0	19 (21)	25(17.1)	2(1.4)	0(0.0)	0(0.0)	27(18.5)
Constipation	19 (21)	0	0	0	19 (21)	27(18.5)	1(0.7)	0(0.0)	0(0.0)	28(19.2)
Diarrhoea	41 (45)	6 (7)	0	0	47 (52)	41(28.1)	1(0.7)	0(0.0)	0(0.0)	42(28.8)
Dysphagia	4 (4)	1 (1)	0	0	5 (6)	7(4.8)	0(0.0)	0(0.0)	0(0.0)	7(4.8)
Haemorrohoids	3 (3)	1 (1)	0	0	4 (4)	4(2.7)	0(0.0)	0(0.0)	0(0.0)	4(2.7)
Intestinal obstruction[b]	0	1 (1)	0	0	1 (1)	0(0.0)	1(0.7)	0(0.0)	0(0.0)	1(0.7)
Nausea	51 (56)	1 (1)	0	0	52 (57)	27(18.5)	0(0.0)	0(0.0)	0(0.0)	27(18.5)
Small intestinal obstruction	1 (1)	1 (1)	0	0	2 (2)	0(0.0)	1(0.7)	0(0.0)	0(0.0)	1(0.7)
Stomatitis	8 (9)	1 (1)	0	0	9 (10)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
Vomiting	20 (22)	1 (1)	0	0	21 (23)	12(8.2)	0(0.0)	0(0.0)	0(0.0)	12(8.2)
General disorders and administration site conditions										
Asthenia	3 (3)	1 (1)	0	0	4 (4)	4(2.7)	0(0.0)	0(0.0)	0(0.0)	4(2.7)
Chills	10 (11)	1 (1)	0	0	11 (12)	6(4.1)	1(0.7)	0(0.0)	0(0.0)	7(4.8)
Fatigue	33 (36)	4 (4)	2 (2)	0	39 (43)	43(29.5)	1(0.7)	0(0.0)	0(0.0)	44(30.1)
Multi-organ failure[c]	0	0	0	1 (1)	1 (1)	0(0.0)	0(0.0)	1(0.7)	0(0.0)	1(0.7)
Peripheral oedema	21 (23)	0	0	0	21 (23)	3(2.1)	0(0.0)	0(0.0)	0(0.0)	3(2.1)
Pyrexia	17 (19)	1 (1)	0	0	18 (20)	13 (8.9)	1 (0.7)	0 (0.0)	0 (0.0)	14 (9.6)
Infections and infestations										
Bacteraemia	0	1 (1)	0	0	1 (1)	1(0.7)	0(0.0)	1(0.7)	0(0.0)	2(1.4)
Bronchitis	5 (5)	1 (1)	0	0	6 (7)	3(2.1)	0(0.0)	0(0.0)	0(0.0)	3(2.1)
Cellulitis	2 (2)	3 (3)	0	0	5 (5)	3(2.1)	1(0.7)	0(0.0)	0(0.0)	4(2.7)
Diverticulitis	2 (2)	1 (1)	0	0	3 (3)	1(0.7)	1(0.7)	0 (0.0)	0(0.0)	2(1.4)
Viral gastroenteritis	2 (2)	1 (1)	0	0	3 (3)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
Laryngitis[d]	0	1 (1)	0	0	1 (1)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
Pneumonia	4 (4)	5 (5)	1 (1)	0	10 (11)	7(4.8)	7(4.8)	0(0.0)	1(0.7)	15 (10.3)
Septic shock	0	0	0	1 (1)	1 (1)	0(0.0)	0 0.0)	2(1.4)	1(0.7)	3(2.1)
Upper respiratory tract infection[e]	24 (26)	0	0	0	24 (26)	31(21.2)	0(0.0)	0(0.0)	0(0.0)	31(21.2)
Urinary tract infection	6 (7)	1 (1)	1 (1)	0	8 (9)	17(11.6)	4 (2.7)	0(0.0)	0(0.0)	21(14.4)
Staphylococcal wound infection[f]	0	1 (1)	0	0	1 (1)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
Injury, poising, and procedural complications										
Bruising[g]	15 (17)	0	0	0	15 (17)	32 (21.9)	0(0.0)	0(0.0)	0(0.0)	32(21.9)
Fall	2 (2)	3 (3)	0	0	5 (6)	20(13.7)	0(0.0)	0(0.0)	0(0.0)	20(13.7)
Investigations										
Increased alanine aminotransferase	11 (12)	2 (2)	1 (1)	0	14 (15)	2(1.4)	1 0.7)	0(0.0)	0(0.0)	3(2.1)
Increased aspartate aminotransferase	16 (18)	0	2 (2)	0	18 (20)	5(3.4)	0(0.0)	0(0.0)	0(0.0)	5(3.4)
Increased blood bilirubin	11 (12)	1 (1)	0	0	12 (13)	8 (5.5)	1 (0.7)	0(0.0)	0(0.0)	9 (6.2)
Decreased lymphocyte count	9 (10)	11 (12)	3 (3)	0	23 (25)	1 (0.7)	0(0.0)	0(0.0)	0(0.0)	1 (0.7)
Increased lymphocyte count	4 (4)	4 (4)	0	0	8 (9)	3 (2.1)	1 (0.7)	0(0.0)	0(0.0)	4 (2.7)
Metabolism and nutrition disorders										
Dehydration	6 (7)	2 (2)	0	0	8 (9)	1(0.7)	3(2.1)	0(0.0)	0(0.0)	4 (2.7)
Hyperglycaemia	5 (5)	4 (4)	1 (1)	0	10 (11)	4 (2.7)	1(0.7)	0(0.0)	0(0.0)	5 (3.4)
Hyperkalaemia	13 (14)	1 (1)	0	0	14 (15)	6 (4.1)	0(0.0)	0(0.0)	0(0.0)	6 (4.1)
Hypermagnesaemia	1 (1)	1 (1)	0	0	2 (2)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
Hyperphosphataemia	11 (12)	0	0	0	11 (12)	2 (1.4)	0(0.0)	0(0.0)	0(0.0)	2 (1.4)
Hyperuricaemia	12 (13)	0	0	0	12 (13)	20 (13.7)	0(0.0)	0(0.0)	0(0.0)	20 (13.7)
Hypoalbuminaemia	13 (14)	2 (2)	0	0	15 (17)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
Hypokalaemia	15 (16)	5 (5)	0	0	20 (22)	5 (3.4)	2(1.4)	0(0.0)	0(0.0)	7 (4.8)

Hyponatraemia	11 (12)	6 (7)	0	0	17 (19)	1 (0.7)	1 (0.7)	0(0.0)	0(0.0)	2 (1.4)
Hypophosphataemia	5 (5)	11 (12)	1 (1)	0	17 (19)	2(1.4)	0(0.0)	0(0.0)	0(0.0)	2 (1.4)
Musculoskeletal and connective tissue disorders										
Arthralgia	16 (18)	0	0	0	16 (18)	26 (17.8)	1(0.7)	0(0.0)	0(0.0)	27 (18.5)
Arthritis	1 (1)	1 (1)	0	0	2 (2)	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.1)
Back pain	16 (18)	0	0	0	16 (18)	26 (17.8)	1(0.7)	0(0.0)	0(0.0)	27 (18.5)
Intervertebral disc protrusion	0	1 (1)	0	0	1 (1)	3 (2.1)	1 (0.7)	0(0.0)	0(0.0)	4 (2.7)
Extremity pain	12 (13)	0	0	0	12 (13)	12 (8.2)	0(0.0)	0(0.0)	0(0.0)	12 (8.2)
Spinal column stenosis	0	1 (1)	0	0	1 (1)	2 (1.4)	0(0.0)	0(0.0)	0(0.0)	2 (1.4)
Neoplasms benign, malignant, and unspecified										
Prostate cancer	1 (1)	1 (1)	0	0	2 (2)	0(0.0)	1 (0.7)	0(0.0)	0(0.0)	1 (0.7)
Squamous cell carcinoma of skin	5 (5)	1 (1)	0	0	6 (6)	1 (0.7)	0(0.0)	0(0.0)	0(0.0)	1 (0.7)
Nervous system disorders										
Dizziness	12 (13)	0	0	0	12 (13)	25 (17.1)	0(0.0)	0(0.0)	0(0.0)	25 (17.1)
Headache	18 (20)	1 (1)	0	0	19 (21)	26 (17.8)	0(0.0)	0(0.0)	0(0.0)	26 (17.8)
Spinal cord compression[h]	0	1 (1)	0	0	1 (1)	1 (0.7)	0(0.0)	0(0.0)	0(0.0)	1 (0.7)
Presyncope	2 (2)	0	1 (1)	0	3 (3)	2 (1.4)	0(0.0)	0(0.0)	0(0.0)	2 (1.4)
Syncope	0	2 (2)	0	0	2 (2)	0(0.0)	3 (2.1)	0(0.0)	0(0.0)	3 (2.1)
Renal and urinary disorders										
Acute kidney injury	2 (2)	1 (1)	0	0	3 (3)	0(0.0)	5 (3.4)	1 (0.7)	0 (0.0)	6 (4.1)
Nephrolithiasis	0	1 (1)	0	0	1 (1)	0(0.0)	1 (0.7)	0(0.0)	0(0.0)	1 (0.7)
Respiratory, thoracic, and mediastinal disorders										
Cough	24 (26)	0	0	0	24 (26)	41 (28.1)	0(0.0)	0(0.0)	0(0.0)	41 (28.1)
Dyspnoea	12 (13)	2 (2)	0	0	14 (15)	25 (17.1)	1 (0.7)	0(0.0)	0(0.0)	26 (17.8)
Hypoxia	0	4 (4)	0	0	4 (4)	1 (0.7)	2 (1.4)	0(0.0)	0(0.0)	3 (2.1)
Oropharyngeal pain	11 (12)	0	0	0	11 (12)	9 (6.2)	0(0.0)	0(0.0)	0(0.0)	9 (6.2)
Pleural effusion	3 (3)	1 (1)	0	0	4 (4)	4 (2.7)	0(0.0)	1(0.7)	0(0.0)	5 (3.4)
Pulmonary oedema	0	0	1 (1)	0	1 (1)	1 (0.7)	0(0.0)	0(0.0)	0(0.0)	1 (0.7)
Respiratory failure	0	0	1 (1)	0	1 (1)	0(0.0)	0(0.0)	1 (0.7)	1 (0.7)	2 (1.4)
Wheezing	3 (3)	1 (1)	0	0	4 (4)	2 (1.4)	0(0.0)	0(0.0)	0(0.0)	2 (1.4)
Skin and subcutaneous tissue disorders										
Rash	11 (12)	0	0	0	11 (12)	6 (4.1)	0(0.0)	0(0.0)	0(0.0)	6 (4.1)
Vascular disorders										
Hypertension	5 (5)	6 (7)	0	0	11 (12)	21 (14.4)	4(2.7)	0(0.0)	0(0.0)	25 (17.1)
Hypotension	1 (1)	1 (1)	0	0	2 (2)	3 (2.1)	3(2.1)	0(0.0)	0(0.0)	6 (4.1)

Pirtobrutinib reported as: [a]acute myocardial infarction; [b]large intestinal obstruction; [c]multiple organ dysfunction; [d]reflux laryngitis; [e]respiratory tract infection; [f]staphylococcal skin infection; [g]contusion; [h]nerve compression