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Supplementary information

# Navigating the changing landscape of BTK-targeted therapies for B cell lymphomas and chronic lymphocytic leukaemia

In the format provided by the authors and unedited

**Supplementary Table 1 | Pivotal trials leading to FDA approvals of BTK inhibitors**

| Treatments (BTK inhibitor dose); trial name (phase); | Disease setting[a] (*n*) | ORR | PFS | Common AEs | Ref. |
|---|---|---|---|---|---|
| ***Ibrutinib*** | | | | | |
| Ibrutinib (420 mg or 840 mg OD); PCYC-1102 (Ib/II) | TN CLL/SLL or R/R CLL/SLL after ≥1 prior line of treatment including a purine analogue, in patients ≥65 years old (132) | 89% overall. TN disease subgroup (*n* = 31): ORR 87% (CR rate 35%). R/R disease subgroup (*n* = 101): ORR 89%; (CR rate 10%). | TN disease subgroup: median PFS NR; 7-yr PFS 83%. R/R disease subgroup: median PFS 52 months; 7-yr PFS 34%. | BTK inhibitor class effects: diarrhoea (49–68%), bleeding (contusion in 16%) and afib (10%). Grade ≥3 AEs: bleeding (9–10%), hypertension (28%), afib (6–10%), infection (26–55%), thrombocytopenia (3–11%), anaemia (0–3%), and arthralgia (0–1%). | S1–S3 |
| Ibrutinib (420 mg OD) vs ofatumumab; RESONATE (III) | R/R CLL/SLL after ≥1 prior line of therapy in inappropriate candidates for purine analogues[b] (391) | Initial ORRs: 43% vs 4%. Best ORR at 6 yrs with ibrutinib: 91% (CR rate 11%). | Median PFS 44.1 vs 8.1 months (HR 0.148, 95% CI 0.113–0.196; *P* <0.001) | BTK inhibitor class effects: diarrhoea (~70%), fatigue (~43%), cough (~40%) and arthralgia (~28%). Grade ≥3 AEs: neutropenia (25%), thrombocytopenia (10%), anaemia (9%), pneumonia (21%), hypertension (9%), diarrhoea (7%) and afib (4%). | S4, S5 |
| Ibrutinib (420 mg OD) vs chlorambucil; RESONATE-2 (III) | TN CLL/SLL in patients ≥65 years old (269); del(17p) disease excluded | Initial ORR: 86% vs 35%. Best ORR at 8 yrs: 92% (CR rate 34%) vs 37%. | At median FU of 82.7 months: 7-yr PFS 59% vs 9%; median PFS NR vs 15 months (HR 0.154, 95% CI 0.108–0.220) | BTK inhibitor class effects: diarrhoea (50%), cough (37%), fatigue (37%), infection (overall prevalence unclear based on published data) and arthralgia (>16%). Grade ≥3 AEs: hypertension (12%), afib (6%), haemorrhage (7%). | S6, S7 |
| Ibrutinib (560 mg OD); NA (II) | R/R MCL after 1–5 prior lines of treatment[c] (115) | At 15.3 months of FU: 68% (CR rate 21%) | At median FU of 15.3 months: median PFS 13.9 months | BTK inhibitor class effects: diarrhoea (50%), fatigue (41%) and nausea (31%). Grade ≥3 AEs: neutropenia (16%), thrombocytopenia (11%), anaemia (10%), diarrhoea (6%), pneumonia (6%), fatigue (5%), dyspnoea (5%). | S8 |
| Ibrutinib (560 mg OD); PCYC-1121 (II) | R/R MZL after ≥1 prior line of therapy[d] (63) | At median FU of 19.4 months: ORR 53% (CR rate 7%). At median FU of 33.1 months: ORR 58% (CR rate 10%) | At median FU of 33.1 months: median PFS 15.7 months | BTK inhibitor class effects: bleeding events (68%) diarrhoea (48%), fatigue (46%), anaemia (37%), nausea (32%), arthralgia, peripheral oedema, thrombocytopenia and/or cough (each in ~25%) and afib (8%). Grade ≥3 AEs: infections (22%), anaemia (16%) and pneumonia (8%). | S9, S10 |
| Ibrutinib (420 mg OD); NA (II) | R/R WM after ≥1 prior line of therapy (63) | At median FU of 59 months: best ORR 90.5% (major response rate 79.4%). | 2-yr PFS: 69.1%. 5-yr PFS 54%. | BTK inhibitor class effects: infections (~26% of grade ≥2 reported), bleeding (~6% of grade ≥2 reported) and afib (any grade in 13%). Grade ≥3 AEs: neutropenia (16%), thrombocytopenia (11%) and pneumonia (3%). | S11, S12 |
| ***Acalabrutinib*** | | | | | |
| Acalabrutinib (100 mg BID) + obinutuzumab vs acalabrutinib (100 mg BID) vs chlorambucil + obinutuzumab; ELEVATE-TN (III) | TN CLL/SLL in patients ≥65 years old, or ≥18 years old with CrCl of 30–69 mL/min (535) | At median FU of 28.3 months: 94% vs 86% vs 79%. At median FU of 74.5 months: best ORR 96% vs 90% vs 83% (CR/CRi rates 37% vs 19% vs 14%). | 2-yr PFS: 93% vs 87% vs 47%. 6-yr PFS: 78% vs 62% vs 17%; median NR vs NR vs 27.8 months (HR vs chlorambucil+ obinutuzumab: 0.14 and 0.23, respectively; *P* <0.0001 for both; HR acalabrutinib+ obinutuzumab vs acalabrutinib alone: 0.58; *P*=0.023) | BTK inhibitor class effects: bleeding (49% vs 43% vs 12%), diarrhoea (43% vs 43% vs 21%), headache (40% vs 39% vs 12%), arthralgia (34% vs 12% vs 6%), nausea (25% vs 25% vs 31%) and afib (6% vs 7% vs 1%). Grade ≥3 AEs: neutropenia (31% vs 12% vs 42%), bleeding (4% vs 3% vs 0%) and infections (21% vs 14% vs 8%). | S13, S14 |

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| Acalabrutinib (100 mg BID) vs IdR or BR; ASCEND (III) | R/R CLL/SLL after ≥1 prior line of therapy in patients ≥18 years old (310) | At median FU of 16.1 months: 81% vs 75%.<br>At median FU of 46 months: best ORR 83% vs 84% (CR rate 5% in each arm). | 1-yr PFS: 88% vs 68%.<br>3.5-yr PFS: 62% vs 19%; median NR vs 16.8 months<br>(HR 0.28, 95% CI 0.20–0.38;<br>*P* <0.001). | BTK inhibitor class effects: infections (68% vs 67%), bleeding/haemorrhage (31% vs 8%), headache (23% vs 5%), diarrhoea (21% vs 44%), cough (18% vs 13%), arthralgia (13% vs 5%), afib (8% vs 3%) and hypertension (8% vs 5%).<br>Grade ≥3 AEs: infections (29% vs 29%, pneumonia in 10% vs 8.5%) neutropenia (19% vs 38%) and anaemia (13% vs 7%). | S15, S16 |
| Acalabrutinib (100 mg BID); ACE-LY-004 (II) | R/R MCL after ≥1 prior lines of therapy (124) | At median FU of 15.2 months:<br>81% ORR (CR rate 40%, increasing to 48% after a median follow-up of 38.1 months) | 1-yr PFS: 67%.<br>3-yr PFS: 37%; median 22.0 months | BTK inhibitor class effects: infections (68%), headache (39%), diarrhoea (38%), fatigue (30%), cough (23%) myalgia (22%), nausea (22%), arthralgia (10%), hypertension (4%) and afib (2%).<br>Grade ≥3 AEs: infections (17%, pneumonia in 7%), neutropenia (11%), anaemia (11%) and major haemorrhage (4%). | S17, S18 |
| ***Zanubrutinib*** | | | | | |
| Zanubrutinib (160 mg BID) vs BR; SEQUOIA (III) | TN CLL/SLL without del(17p13.1) in patients aged ≥65 years or with contraindications to FCR and (479). A separate cohort (group C) included 111 patients with TN CLL/SLL with del(17p13.1) who all received zanubrutinib. | ORR 95% (CR rate 7%) vs 85% (CR rate 15%).<br>Group C: ORR 90% (CR rate 6%). | 2-yr PFS: 85.5% vs 69.5% (HR 0.42, 95% CI 0.28–0.63; *P* <0.0001).<br>Group C: 2-yr PFS 88.9%. | BTK inhibitor class effects: bleeding events (45–51% vs 11%), infections (e.g. URTI in 17–21% vs 12%), diarrhoea (14–17% vs 13%), arthralgia (13–20% vs 9%), neutropenia (15–18% vs 57%), hypertension (9–12% vs 9%), fatigue (9–12% vs 16%), cough (11–13% vs 10%), headache (11% vs 7%) and afib (3% vs 3%).<br>Grade ≥3 AEs: infection (16% vs 19%), neutropenia (11–15% vs 51%), major bleeding (5–7% vs 2%) and hypertension (5–6% vs 5%). | S19 |
| Zanubrutinib (160 mg BID) vs ibrutinib (420 mg OD); ALPINE (III) | R/R CLL/SLL after ≥1 prior line of therapy (652) | At median FU of 29.6 months: ORR 83.5% (89.9% including PR-L; CR/CRi rate 7.0%) vs 74.2% (PR-L 82.5%; CR/CRi rate 4.9%).<br>At median FU of 36.3 months: ORR 85.0% (90.2% including PR-L; CR/CRi rate 10.1%) vs 74.8% (82.8% including PR-L; CR/CRi rate 7.4%). | 2-yr PFS: 78.4% vs 65.9% (HR 0.65, 95% CI 0.49–0.86; *P* = 0.002).<br>3-yr PFS: 65.8% vs 54.3% (HR: 0.67, 95% CI 0.52–0.86; *P* = 0.002). | BTK class effects: infections (including COVID-19 in 37% vs 26% and URTI in 26% vs 17%), diarrhoea (18% vs 26%, neutropenia (23% vs 18% at 29.6-month FU), hypertension (22% vs 20% at 29.6-month FU), anaemia (15% vs 16% at 29.6-month FU), arthralgia (15% vs 16% at 29.6-month FU), contusion (14% vs 10% at 29.6-month FU), cough (12% vs 10% at 29.6-month FU), fatigue (10% vs 13% at 29.6-month FU), afib (6.2% vs 16%).<br>Grade ≥3 AEs: neutropenia (17% vs 16%), hypertension (15% vs 12%), afib (4% vs 2% at 29.6-month FU); serious infections in 31% with each agent. | S20, S21 |
| Zanubrutinib (160 mg BID); MAGNOLIA (II) | R/R MZL after ≥1 prior line of therapy, including an anti-CD20 antibody (68) | At median FU of 15.7 months: 68.2% (CR 25.8%); 76.0%, 66.7%, 64.0% and 50.0% for nodal, splenic, extranodal and unknown subtypes, respectively. Rates unchanged at median FU of 27.4 months. | 12 and 15-month PFS: 82.5%.<br>2-year PFS: 70.9% | BTK inhibitor class effects: infections (56%), bleeding (41%)/contusion (24%), neutropenia (16%), thrombocytopenia (16%), arthralgia (15%), anaemia (6%), hypertension (4%) and afib (3%).<br>Grade ≥3 AEs: infections (22%), neutropenia (9%), thrombocytopenia (4%), anaemia (3%), hypertension (3%) and afib (1%). | S22, S23 |
| Zanubrutinib (160 mg BID) + obinutuzumab vs obinutuzumab; ROSEWOOD (II) | R/R grade I–IIIA FL after ≥2 lines of therapy, including an anti-CD20 antibody and an alkylating agent (217) | ORR 69% vs 46% | Median 28.0 vs 10.4 months<br>(HR 0.50, 95% CI 0.33–0.75;<br>*P* <0.001) | BTK inhibitor class effects: infection (55% vs 41%), thrombocytopenia (36% vs 24%), neutropenia (29% vs 28%), bleeding (28% vs 13%), diarrhoea (18% vs 17%), fatigue (15% vs 14%), cough (13% vs 13%), hypertension (3% vs 6%) and afib (3% vs 1%).<br>Grade ≥3 AEs: neutropenia (24% vs 23%) thrombocytopenia (15% vs 7%), pneumonia (10% vs 4%), COVID-19 (6% vs 3%), anaemia (5% vs 6%) and diarrhea (3% vs 1%). | S24 |

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|---|---|---|---|---|---|
| Zanubrutinib (160 mg BID) vs ibrutinib (420 mg OD); ASPEN (III) | R/R WM after ≥1 prior line of therapy (164) or TN WM in unsuitable candidates for standard immunochemotherapy owing to comorbidities or other risk factors (37) | At median FU of 27.4 months: ORR 94% vs 93% (94% vs 94% in R/R group and 95% vs 89% in TN group); VGPR+CR rate 28% vs 19% (29% vs 20% in R/R group and 26% vs 17% in TN group). At median FU of 44 months in entire cohort: ORR 95.1% vs 93.9%; VGPR+CR rate: 36.3% vs 25.3% (no CRs). | 3.5-yr PFS 78.3% vs 69.7% (HR 0.63, 95% CI 0.36–1.12; *P* = 0.12) | BTK inhibitor class effects: infection (79% vs 79%, pneumonia in 5% vs 18%), bleeding (55% vs 62%)/contusion (19% vs 28%), neutropenia (35% vs 20%), fatigue (26% vs 19%), arthralgia (24% vs 24%), diarrhoea (23% vs 35%), cough (19% vs 24%), anaemia (18% vs 22%), thrombocytopenia (17% vs 17%), hypertension (15% vs 26%) and afib (8% vs 23%). Grade ≥3 AEs: infections (22% vs 28%, pneumonia in 19% vs 9%), neutropenia (24% vs 10%), anaemia (12% vs 6%), hypertension (10% vs 20%), bleeding (9% vs 10%), diarrhoea (3% vs 2%) and afib (2% vs 8%). | S25, S26 |
| Zanubrutinib (160 mg BID); pooled data from BGB-3111-206 (I/II) and BGB-3111-AU-003 (II) | R/R MCL after 1–4 prior lines of treatment (112) | At median FU of 25 months: ORR 85% (CR rate 63%); 84.9% (CR rate 24.2% in BGB-3111-AU-003 and 84.8% (CR rate 78.5%) in BGB-3111-206. At median FU of 35.3 months in BGB-3111-206: ORR 83.7% (CR rate 77.9%). | At median FU of 25 months: median PFS 16.0 months in BGB-3111-AU-003 and 25.8 months in BGB-3111-206. At median FU of 35.3 months in BGB-3111-206: median PFS 33.0 months; 2-yr and 3-yr PFS 58.3% and 47.6%, respectively. | BTK inhibitor class effects: infections (including URTI in 35% and pneumonia in 5%), neutropenia (32%), thrombocytopenia (24%), diarrhoea (23%), anaemia (17%), cough (13%), hypertension (12%), contusion (12%) and afib (2%, 0.9% grade ≥3). Grade ≥3 AEs: neutropenia (13%), anaemia (8%), thrombocytopenia (7%), major hemorrhage (5%), pneumonia (4%) and hypertension (3%). | S27–S29 |
| ***Pirtobrutinib*** | | | | | |
| Pirtobrutinib (200 mg OD); BRUIN (I/II) | R/R CLL/SLL (317, including 247 previously treated with a covalent BTK inhibitor) | Covalent BTK inhibitor pretreated group: ORR 73.3%, and 82.2% including PR-L (CR rate 1.6%) | Covalent BTK inhibitor pretreated group: median PFS 19.6 months; 22.1 months in BTK inhibitor-refractory only subgroup, 16.8 months in BTK and BCL-2 inhibitor-refractory subgroup, and 13.8 months in BTK, BCL-2 and PI3K inhibitor-refractory subgroup | BTK inhibitor class effects: infections (71%), bleeding (43%)/contusion (24%)/ haemorrhage (21%, grade ≥3 in 2%), neutropenia (32%), fatigue (32%), diarrhoea (26%), hypertension (14%) and afib (4%, grade ≥3 in 1%). Grade ≥3: infections (28%, COVID-19 in 5%), neutropenia (27%) and anaemia (9%). | S30 |
| Pirtobrutinib (200 mg OD); BRUIN (I/II) | R/R MCL (164, including 152 previously treated with a covalent BTK inhibitor) | Covalent BTK inhibitor pretreated group: ORR 49% (CR rate 16%). TN group: 86% (CR rate 36%) | At median FU of 24.2 months: median PFS 5.6 months in the covalent BTK inhibitor pretreated group. Median PFS NR in the TN group (90% of responses were ongoing at 2 yrs). | BTK inhibitor class effects: fatigue (32%), diarrhoea (22%), and dyspnoea (17.5%) and afib (4%, grade ≥3 in 1%). Grade ≥3 AEs: infections (20%), neutropenia (13%), haemorrhage (2%). | S31, S32 |

AEs, adverse events; afib, atrial fibrillation/flutter; BID, twice daily; BR, bendamustine plus rituximab; CLL, chronic lymphocytic leukaemia; CR, complete response; CrCl, creatinine clearance; CRi, complete response with incomplete count recovery; FCR, fludarabine and cyclophosphamide plus rituximab; FL, follicular lymphoma; FU, follow-up; IdR, idelasib plus rituximab; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; *n*, number of patients; *n*, number of patient; NA, not available or applicable; NR, not reached; OD, once daily; ORR, overall response rate; PFS, progression-free survival; PR-L, partial response with lymphocytosis; R/R relapsed and/or refractory; SLL, small lymphocytic lymphoma; TN, treatment-naive; URTI, upper respiratory tract infection; WM, Waldenström macroglobulinaemia; yr, year. [a]In trials in the setting of CLL/SLL, enrolment of patients with del(17p) and/or *TP53* mutations was permitted, unless stated otherwise. [b]Owing to prior short PFS, co-morbidities, age ≥70 years or 17p13.1 deletions. [c]Patients had to have measurable disease ≥2cm with cyclin D1 overexpression or t(11,14). [d]Patients had to have ≥1 measurable lesion >1.5 cm in longest dimension and prior therapy including an anti-CD20-antibody (either as monotherapy or as chemoimmunotherapy), with documented failure to achieve at least PR or with disease progression after the most recent systemic treatment.

**Supplementary Table 2** | Most frequently reported adverse events associated with approved BTK inhibitors

| | Ibrutinib | | | Acalabrutinib | | | Zanubrutinib | | | Pirtobrutinib | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | All Grades | Grade 3/4 | | All Grades | Grade 3/4 | | All Grades | Grade 3/4 | | All Grades | Grade 3/4 |
| **Hematological** | | | | | | | | | | | |
| Neutropenia | | | | | | | | | | | |
| Thrombocytopenia | | | | | | | | | | | |
| Anemia | | | | | | | | | | | |
| Major Hemorrhage | | | | | | | | | | | |
| **Gastrointestinal Disorders** | | | | | | | | | | | |
| Diarrhea | | | | | | | | | | | |
| Nausea | | | | | | | | | | | |
| Vomiting | | | | | | | | | | NR | |
| Constipation | | | | | | | | | | | |
| **Cardiac Disorders** | | | | | | | | | | | |
| HTN | | | | | | | | | | | |
| Atrial Fibrillation/Flutter | | | | | | | | | | | |
| Peripheral Edema | | | | | | | | NR | | | |
| **Musculoskeletal** | | | | | | | | | | | |
| Myalgias | | | | | | | * | * | | | |
| Arthralgias | | | | | | | * | * | | | |
| Muscle spasms | | | | | | | * | * | | NR | NR |
| Back Pain | | | | | | | * | * | | NR | NR |
| **Skin and Subcutaneous Disorders** | | | | | | | | | | | |
| Rash | | | | | | | | | | | |
| Bruising/Contusion | | | | | | | | | | | |
| **Respiratory Disorders** | | | | | | | | | | | |
| Cough | | | | | | | | | | | |
| Dyspnea | | | | | | | | | | | |
| **Infections** | | | | | | | | | | | |
| Upper Respiratory Tract Infection | | | | | | | | | | | |
| Pneumonia | | | | | | | | | | | |
| Urinary Tract Infection | | | | | | | | | | | NR |
| **Nervous System Disorders** | | | | | | | | | | | |
| Headache | | | | | | | | | | | |
| Dizziness | | | | | | | | | | | |
| Peripheral Neuropathy | | | | NR | NR | | | NR | | | |
| **Other** | | | | | | | | | | | |
| Fatigue | | | | | | | | | | | |
| Pyrexia | | | | | | | | | | | |

HTN, hypertension; NR, not reported

**Legend**

| | |
|---|---|
| <1% | + |
| 2–5% | ++ |
| 6–10% | +++ |
| 11–50% | ++++ |
| 51–100% | +++++ |

*Combined as one category of MSK pain

The incidence data used to create this table were obtained from the following references.
Ibrutinib: S8,S20,S33,S34,S35
Acalabrutinib: S13, S16, S17, S18, S33 and S34
Zanubrutinib: S19, S20, S22 ,S23 and S26
Pirtobrutinib: S30, S31, S32, S36 and S37

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