Table 3. Pivotal studies for treatment-naïve CLL.

Study	Population[a]	Design	PFS benefit for experimental arm?	OS benefit for experimental arm?
Alliance A041202 (phase 3)[40]	Fit, older patients (>65 years), del(17p) allowed	BR vs Ibru vs IR	YES, IR superior 2-year PFS rate: 74% (BR) vs 87% (I) vs 88% (IR)	NO 2-year OS rate: 95% (BR) vs 90% (I) vs 94% (IR)
CLL5 (phase 3)[66]	Treatment-naïve, ≥65, Binet stage C, ECOG 0–2	F vs Clb	NO 19 months for F vs 18 months for Clb	NO 46 months for F vs 64 months for Clb
CLL8 (phase 3)[29]	Treatment-naïve, physically fit, age 30–80, CD20+	FC vs FC+R	YES, FC+R superior 3-year PFS rate: 65% (FCR) vs 45% (FC)	NO not reached for FCR vs 86.0 months for FC
CLL10 (phase 3)[76]	Treatment-naïve, physically fit, age 30–80, no del(17p)	FCR vs BR	YES, FCR superior PFS 41·7 months BR and 55·2 months	NO
CLL12 (phase 3)[20]	Treatment-naïve, Binet stage A, ECOG 0–2	Observational: no treatment Treatment: I vs placebo	YES 3-year PFS rate: 80.9% (Ibru) vs 28.5%	-
CLL13 (GAIA) (phase 3)[57]	Fit, no *TP53* aberrations	CIT: FCR or BR V combinations: VR vs VO vs VO+I	YES, VO+I most superior 3-year PFS rate: 90.5% (VO+I) vs 87.7% (VO) vs 80.8% (VR) vs 75.5% (CIT)	NO 3-year OS rate: 95.3% (VO+I) vs 96.3% (VO) vs 96.5% (VR) vs 95.0% (CIT)
CLL14 (phase 3)[47]	Unfit (CIRS >6 or CrCl <70)	VO vs Clb-O	YES, VO superior 3-year PFS rate: 82% (VO) vs 50% (Clb-O)	NO 24-month OS rate 92% (VO) vs 93% (Clb-O)
CAPTIVATE (phase 2)[55]	Treatment-naïve, ≥70 years	I+V	YES 24-month PFS rate 95%	YES 24-months OS rate 98%
E1912 (phase 3)[39,59]	Fit, no del(17p)	FCR vs I+R	YES, IR superior 3-year PFS rate: 73% (FCR) vs 89% (IR)	YES 3-year OS rate: 92% (FCR) vs 99% (IR)
GAGE[77]	Treatment-naïve CLL	O 1000 mg vs 2000 mg	YES, but not superior	-
ELEVATE-TN (phase 3)[38,41]	Unfit (CIRS >6 or CrCl <70)	A vs A+O vs Clb-O	YES. A+O superior Estimated 24-month PFS rate: 93% (A+O) vs 87% (A) vs 47% (Clb-O)	YES Estimated 24-month OS rate: 95% (A+O) vs 95% (A) vs 92% (Clb-O)

Table 3. Pivotal studies for treatment-naïve CLL. (Cont'd)

Study	Population[a]	Design	PFS benefit for experimental arm?	OS benefit for experimental arm?
FLAIR (phase 3)[58]	Treatment-naive, fit to receive FCR, age 18–75, WHO performance status ≤2, and treatment required from iwCLL criteria	I+V vs I vs FCR	YES. I+V superior to FCR. Estimated 3-year PFS rate: 97.2% (I+V) vs 76.8% (FCR)	YES 3-year OS rate: 98.0% (I+V) vs 93.0% (FCR)
GLOW (phase 3)[48]	≥65 years OR CIRS >6	I+V vs Clb-O	YES, I+V superior Estimated 30-month PFS rate 80.5% (I+V) vs 35.8% (Clb-O)	NO
HDMP+R[78]	Treatment-naïve	HDMP+R	YES PFS 30.5 months	YES 3-years OS rate 96%
iLLUMINATE (phase 3)[61]	Unfit (CIRS>6 or CrCl<70) or *TP53* del/mut	I+V vs Clb-O	YES Estimated 30-month PFS rate 79% (I+V) vs 31% (Clb-O)	NO Estimated 30-month OS rate: 86% (I+V) vs 85% (Clb-O)
RESONATE-2 (phase 3)[60]	≥65 without del(17p)	I vs Clb	YES 5-year PFS rate: 70% (I) vs 12% (Clb)	YES 5-year OS rate: 83% (I) vs 68% (Clb)
Rituximab (phase 2)[65]	Treatment-naïve	R	YES 1- and 2-year PFS rates were 62% and 49%, respectively	YES
RO5072759 [GA101] (phase 3)[64]	Treatment-naïve, CIRS >6	Clb-O vs Clb vs Clb-R	YES, Clb superior Median PFS 26.7 months (Clb-O) vs 11.1 months (Clb) vs 16.3 months (Clb-R)	YES OS rate 9% (Clb-O) vs 20% (Clb) vs 15% (Clb-R)
SEQUOIA (phase 3)[42]	Untreated, ≥65 years, ECOG 0–2	Z vs BR	Median PFS not reached in either arm. Z showed longer PFS.	NO Estimated 24-month OS rate 94.3% (Z) vs 94.6% (BR)

[a] Fit patients are defined as those aged <65 years with a CIRS score <6 and CrCl ≥70 mL/min

A: acalabrutinib; B: bendamustine; Clb: chlorambucil; CLL: chronic lymphocytic leukaemia; CIT: chemoimmunotherapy; CrCl: creatine clearance; CIRS: Cumulative Illness Rating Scale; C: cyclophosphamide; ECOG: Eastern Cooperative Oncology Group; F: fludarabine; HDMP: high-dose methylprednisolone; FCR: fludarabine + cyclophosphamide + rituximab; I: ibrutinib; iwCLL: International Workshop on CLL; PFS: progression-free survival; O: obinutuzumab; OS: overall survival; R: rituximab; V: venetoclax; WHO: World Health Organization; Z: zanubrutinib