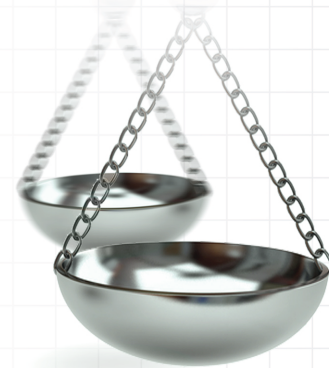




Front-line treatment of patients with chronic lymphocytic leukemia: a systematic review and network meta-analysis

Journal of **Comparative Effectiveness Research**

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Aim: A systematic literature review and network meta-analysis were conducted to determine the relative efficacy and safety of interventions for treatment-naïve chronic lymphocytic leukemia patients, as comparative evidence is scarce. **Materials & methods:** Relative treatment effects of progression-free survival, overall survival and safety outcomes were estimated via network meta-analysis based on data identified via systematic literature review. **Results:** Ibrutinib was superior in all pairwise comparisons for progression-free survival (probability to be better [P] range: overall population: 69–100%; fludarabine-ineligible population: 69–100%) and overall survival (P range: overall: 89–100%; fludarabine-ineligible: 91–100%) and had the highest probability of being best for all outcomes. **Conclusion:** Ibrutinib provides superior benefit in survival and safety compared with other front-line treatments of chronic lymphocytic leukemia.

First draft submitted: 12 October 2017; Accepted for publication: 14 November 2017; Published online: 7 December 2017

Keywords: chronic lymphocytic leukemia • fludarabine-ineligible • front-line • ibrutinib • meta-analysis • systematic literature review • treatment-naïve

Chronic lymphocytic leukemia (CLL) is the most common hematologic malignancy in western countries and occurs mainly in older people. Overall, 4.2 per 100,000 population per year develop the condition, a figure that rises to over 30 per 100,000 per year among those aged over 80 years [1]. The overall 5-year survival rate for people with CLL is 83%, although survival varies widely according to disease stage [2]. Treatment for CLL has evolved rapidly over the past two decades, with the addition of CD20-targeted antibodies, B-cell lymphoma-2 (BCL-2)-targeted treatment and B-cell receptor-targeted treatment resulting in improved outcomes [3–4].

As indicated by both the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network [1,5], there are various management options for CLL, and treatment choices must account for key patient and disease characteristics known to affect therapeutic outcomes. These include patient age [6], fitness/comorbidities [7] and molecular cytogenetics [6,8]. Generally, for fit patients with advanced, symptomatic disease, the so-called ‘full-dose fludarabine-based’ regimen of fludarabine + cyclophosphamide + rituximab (FCR) is recommended [1]. However, for elderly patients and/or those with significant comorbidities, FCR is associated with significant risk of myelosuppression and severe infection [9]. Options are further limited if these individuals also have cytogenetic characteristics associated with poor outcomes from current treatments (such as 17p or 11q deletion, or absence of IgVH mutation). For these patients, ESMO and National Comprehensive Cancer Network guidelines recommend ibrutinib monotherapy [1,5,9].

Given the range of CLL treatment options for people with differing levels of fitness, and the dearth of head-to-head clinical trials comparing front-line treatments, there remains considerable uncertainty regarding the optimal regimen for each patient group. The objectives of the presented systematic literature review (SLR) and network meta-analyses (NMAs) were therefore to determine the relative efficacy and safety of interventions for the front-line

treatment of patients with CLL, and for the subgroup considered ineligible to receive full-dose fludarabine-based treatment.

Materials & methods

Systematic literature review

The SLR involved a search strategy designed to find clinical trials that had investigated front-line treatment of patients with CLL and which had reported efficacy and safety outcomes. Literature searches were conducted on 19 October 2015 in MEDLINE (via PubMed), Medline In-Process (via PubMed), Embase, Embase In-Process, the Cochrane Collection Central Register of Clinical Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects, with no temporal or language limits. An update of this search was conducted in April 2017 to check whether any additional relevant studies or updated data had been published since the original search.

The inclusion criteria targeted prospective, interventional trials (either randomized controlled trials [RCTs], non-RCTs or single-arm studies) that had investigated efficacy or safety outcomes in patients receiving a treatment of interest as front-line therapy for CLL, small cell lymphoma or small lymphocytic lymphoma – conditions that are pathologically very similar to CLL.

Abstracts were screened for inclusion by two independent investigators, with any discrepancies in inclusion eligibility between them being resolved by a third investigator. Full-text versions of those articles that had passed abstract screening were then screened for inclusion by a single investigator, with a second investigator independently verifying whether each rejection by the first investigator had been appropriate, and again, a third investigator resolved any discrepancies. Articles that appeared potentially eligible on abstract screening were subsequently rejected if they were not an RCT or if their full-text version was found to be in a non-English language. The inclusion/exclusion criteria for the interventions/comparators of interest were applied only during full-text screening, with relevant comparators having been determined by considering recommendations in the 2015 ESMO treatment guidelines. Specifically, relevant treatments for elderly and/or unfit patients (who are not eligible for fludarabine-based treatment) included bendamustine, bendamustine + rituximab (BR), obinutuzumab + chlorambucil (Obi-Chl), ofatumumab + chlorambucil (Ofa-Chl), rituximab + chlorambucil (R-Chl) and reduced-dose FCR. By contrast, for young and/or fit patients, full-dose fludarabine-based regimens were also relevant treatments, including fludarabine, fludarabine + cyclophosphamide and FCR.

Information from included full-text articles was extracted by one investigator and validated by a second, and a third investigator was consulted to resolve any discrepancies. Quality-control measures and logic checks were conducted on all extracted data. Quality assessment of RCTs was evaluated using a tool based on the NICE quality assessment summary tables. Studies were categorized into one of the two groups: those conducted in patients eligible for full-dose fludarabine treatment and those conducted in patients ineligible for full-dose fludarabine treatment (typically elderly or unfit patients, per comorbidity status).

Network meta-analysis

A feasibility assessment was conducted to evaluate whether NMAs could be performed for the RCTs identified within the SLR. Two separate networks were established: one which included all studies of patients with CLL receiving front-line therapy (referred to below as the overall front-line population) and another subnetwork which included only those studies in patients ineligible for full-dose fludarabine treatment (referred to below as the fludarabine-ineligible population). NMAs based on these two networks were considered the 'base-case' analyses. Additionally, to account for variability among trial populations in potentially important prognostic factors and considering that one of the RCTs (RESONATE-2) enrolled only patients aged ≥ 65 years who did not have a del17p mutation, the following populations were identified and explored as 'subgroup' analyses where data permitted: patients aged ≥ 65 years; those with unmutated IgVH; those with del11q mutation; and those without del17p mutation. Because information on these variables was not consistently reported across studies, the potential impact of these factors was investigated as sensitivity analyses within those studies that could be stratified or had outcomes reported by similar strata.

Analyses included

The outcomes assessed in the base-case NMA for each of the two networks (i.e., overall front-line CLL patients and fludarabine-ineligible patients) included overall survival (OS), independent review committee (IRC)-assessed progression-free survival (PFS), investigator (INV)-assessed PFS and safety outcomes, including overall proportion

of patients who discontinued treatment (total discontinuations [TD]) and the proportion with treatment discontinuations due to adverse events (DAE). For each outcome, a model was used to estimate the mean relative treatment effect along with a 95% credible interval, and the posterior distribution was used to determine the probability that a given regimen was the best among all treatments within the analyzed network. Specifically, the methodological approach in these analyses followed long-established techniques for integrating odds ratios (OR) and hazard ratios (HR) into NMAs, including those used and/or recommended by the NICE [10,11]. Accordingly, the analyses used both random-effect models and fixed-effect models. Random-effect analyses are widely accepted as the appropriate, more conservative approach when generalizations need to be made on a greater group of studies and populations and/or when there is heterogeneity across study methods. By contrast, fixed-effect models assume that effect size associated with a given intervention does not vary from study to study, and they may be particularly appropriate when only few studies are available for analysis. The best model fit for each network was selected on the basis of a review of the deviance information criterion and a clinical evaluation of the different model assumptions.

In the case of the overall front-line CLL patient NMA, random-effect analyses could be used, as there were sufficient studies for a between-effects variance to be estimated, with some uncertainty, from the data. These analyses used two different priors for the between-study variability (which was assumed to be identical across all comparisons) that were vaguely informative, $N(0, 1.0)$ and $N(0, 0.4)$, since the power to detect random variation among all studies was limited and the results were expected to be sensitive to the selection of the prior. Given the sparseness of the evidence networks for safety outcomes in the overall population and in the fludarabine-ineligible population, only fixed-effects Bayesian NMAs were conducted for these networks. Fixed-effects Bayesian NMAs were also conducted in the four subgroups of interest, to evaluate INV-assessed PFS, OS and DAEs in the fludarabine-ineligible population only (due to the limited data available).

Chlorambucil was chosen as the common comparator across both evidence networks given that it was used as a comparator in the majority of studies (10 of 15 studies in the overall front-line network and four of five studies in the fludarabine-ineligible network). As both evidence networks relied on chlorambucil as the key common comparator, this raised a potential issue given that there were known to be marked between-study differences in chlorambucil dosing (with regards to dose unit, number of cycles and cycle length), and this variation could have had an impact on the treatment effects observed from study to study and thus on the results of the NMAs. To explore this possibility, regression analyses of PFS and OS using cumulative chlorambucil dose as a covariate was carried out as a sensitivity analysis. Specifically, this analysis was used the estimated cumulative chlorambucil dose in milligram at 24 weeks, calculated using reported doses and scheduling in the study protocols and assuming a mean patient body surface area of 1.69 m^2 and weight of 63.5 kg.

The research presented in this article is based on previously conducted studies and did not involve any new studies of human or animal subjects performed by any of the authors.

Results

Systematic literature review

Of the 2367 abstracts screened for the SLR, 1911 references were excluded at the abstract level through application of screening criteria listed in the 'Materials & methods' section. Among the remaining 456 publications, 146 reported data on a total of 58 primary studies that investigated the front-line treatments of interest. The 58 RCTs were examined for comparability with the RESONATE-2 patient population. This process identified five RCTs [12,13,14] that had investigated front-line treatment in CLL patients ineligible for full-dose fludarabine and ten RCTs [15,16] that had investigated fludarabine or fludarabine-based regimens as front-line treatment in treatment-naïve patients with CLL, and which had reported outcomes of interest (see the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram in Figure 1). Collectively, the 15 RCTs included over 5300 patients and provided adequate evidence to support an NMA to estimate the comparative efficacy and safety of treatments of interest in the front-line setting. Of note, the updated search conducted in April 2017 identified that no additional relevant RCT data that could affect the NMA had been published since the original SLR in October 2015.

Patient characteristics at study baseline are shown in Table 1. Across the overall network, most studies that reported the number of evaluable patients at baseline included at least 100 participants in each treatment arm, with exceptions being the MaBLLe [14], Mulligan *et al.* [17] and CLL5 [18] studies, in which the number of evaluable patients per treatment arm ranged from 40 to 93. Of the 13 studies that reported follow-up duration, the median value ranged from 22 to 83 months in the fludarabine-based studies and from 18.4 to 54 months in the studies of fludarabine-ineligible patients. The mean patient age at baseline ranged from 58 to 71 years across the

Table 1. Study and patient characteristics for included randomized controlled trials.

Trial name, study [Ref.]	Related publications, study (year) [Ref.]	Group descriptor	Median follow-up (months)	N evaluated at baseline	Primary end point	Male (%)	Age (years), median (range)	ECOG (%) 0/>0/>1	17p/11q/unmutated IgVH (%)	Binet (%) A/B/C	Rai (%) 0-II/I-II/III-IV
Front-line treatments in fludarabine-ineligible population											
RESONATE-2, Burger et al. (2015) [13]	–	Ibrutinib	18.4	136	PFS	64.7	73 (65–89)	44.1/55.9/8.1	0/21.3/43	25.7/30.1/44.1 ¹	55.9/53.7/44.1
COMPLEMENT1, Hillmen et al. (2015) [19]	Online appendix to Hillmen et al. (2015) [19]	Chi	28.9	133	PFS	60.9	72 (65–90)	40.6/59.4/9	0/18.8/45	22.6/30.8/46.6 ¹	53.4/51.9/46.6
		Ofa-Chi		221		64.3	69 (35–92)	38.9/61.1/8	4.5/19/57	34.8/33.5/31.7	–/51.1/42.1
CLL11, Goede et al. (2014) [12]	Hallek et al. (2012) [20]	Chi	NR	226	PFS	61.9	70 (36–91)	37.2/62.8/8	7.5/11.1/56	31/38.5/30.5	–/50.9/38.9
		Obi-Chi		238		58.8	74 (39–88)	–/–/–	6.7/13.4/61	23.1/41.2/35.7	–/–/–
Knauf et al. (2012) [23]	Goede et al. (2013) [21]	R-Chi	54	233	OR	63.9	73 (40–90)	–/–/–	3.9/16.3/62	21/42.9/36.1	–/–/–
	Goede et al. (2013) [22]	Chi		118		63.6	72 (43–87)	–/–/–	8.5/11.9/59	20.3/42.4/37.3	–/–/–
	Knauf et al. (2007) [24]	Bendamustine		162		63	63 (45–77)	69.8/–/–	–/–/–	0/71.6/28.4	–/–/–
MaBLe, Michallet (2015) [14]	Knauf et al. (2009) [25]	Chi	NR	157	NR	60.5	66 (35–78)	65/–/–	–/–/–	0/70.7/29.3	–/–/–
	–	BR		40		–	–/–/–	–/–/–	–/–/–	–/–/–	–/–/–
		R-Chi		45		–	–	–/–/–	–/–/–	–/–/–	–/–/–
Front-line treatments with fludarabine or fludarabine-based regimens in CLL											
Mulligan et al. (2014) [17]	Karlsson et al. (2007) [26]	Fludarabine	83	74	OR	81.1	63.5	–/–/–	–/–/53.7	27/25.7/47.3	43.2/36.5/56.8
CLL4, Eichhorst et al. (2006) [28]	Karlsson et al. (2004) [27]	Chi	22	77	NR	74	63	–/–/–	–/–/65	23.4/35.1/41.6	54.5/49.4/45.5
	Eichhorst et al. (2005) [29]	Fludarabine		182		70.3	59 (43–65)	52.7/47.3/2.2	–/–/–	11/53.8/35.2	58.8/56.6/41.2
	Eichhorst et al. (2005) [30]										
	Eichhorst et al. (2003) [31]										
E2997, Flinn et al. (2007) [33]	Grever et al. (2007) [34]	Fludarabine	24	137	Response	70.1	61 (33–83)	48.9/–/–	6.6/11.7/47	–/–/–	61.1/58.3/38.9
		FC		141		70.2	61 (39–86)	45.4/–/–	7.1/17/47	–/–/–	53.9/51.1/44.7
The sources of data stated in the table may include the primary publication and related publications listed for each study. ¹ Calculated with the patient-level data from the RESONATE-2 trial (data on file), equating Rai stages 0–I with Binet stage A, Rai stage II with Binet stage B and Rai stage III–IV with Binet stage C. BR: Bendamustine + rituximab; CLL: Chronic lymphocytic leukemia; ECOG: Eastern Cooperative Oncology Group; FC: Fludarabine + cyclophosphamide; F-Chi: Fludarabine + chlorambucil; FCR: Fludarabine + cyclophosphamide + rituximab; where fludarabine was given at relatively low frequency (dose); NR/–: Not reported; Obi-Chi: Obinutuzumab + chlorambucil; Ofa-Chi: Ofatumumab + chlorambucil; OR: Overall response; OS: Overall survival; PFS: Progression-free survival; R-Chi: Rituximab + chlorambucil											

The sources of data stated in the table may include the primary publication and related publications listed for each study.

¹Calculated with the patient-level data from the RESONATE-2 trial (data on file), equating Rai stages 0–I with Binet stage A, Rai stage II with Binet stage B and Rai stage III–IV with Binet stage C.

BR: Bendamustine + rituximab; CLL: Chronic lymphocytic leukemia; ECOG: Eastern Cooperative Oncology Group; FC: Fludarabine + cyclophosphamide; F-Chi: Fludarabine + chlorambucil; FCR: Fludarabine + cyclophosphamide + rituximab; FCR-Lite: Reduced-dose fludarabine + cyclophosphamide + rituximab, where fludarabine was given at relatively low frequency (dose); NR/–: Not reported; Obi-Chi: Obinutuzumab + chlorambucil; Ofa-Chi: Ofatumumab + chlorambucil; OR: Overall response; OS: Overall survival; PFS: Progression-free survival; R-Chi: Rituximab + chlorambucil.

Table 1. Study and patient characteristics for included randomized controlled trials (cont.).

Trial name, study [Ref.]	Related publications, study (year) [Ref.]	Group descriptor	Median follow-up (months)	N evaluated at baseline	Primary end point	Male (%)	Age (years), median (range)	ECOG (%) 0/>0/>1	17p/11q/ unmutated IgVH (%)	Binet (%) A/B/C	Rai (%) 0-II/I-II/III-IV
CALGB 9011, Rai <i>et al.</i> (2000) [16]	Morrison <i>et al.</i> (2001) [35]	Fludarabine	62	179	NR	70.9	64 (33–88)	63.1/–/–	–/–/–	–/–/–	–/60.9/39.1
		Chi		193		66.8	62 (36–89)	62.7/37.3/4.1	–/–/–	–/–/–	–/59.1/40.9
		F-Chi		137		65.7	63 (32–83)	51.8/46.7/5.8	–/–/–	–/–/–	–/61.3/38.7
LRF CLL4, Catovsky <i>et al.</i> (2007) [15]	Skowronska <i>et al.</i> (2012) [36] Dearden <i>et al.</i> (2011) [37]	Fludarabine	41	194	OS	73.2	64 (38–85)	–/–/–	5.2/–/–	23.7/46.9/29.4	–/–/–
		Chi		387		73.9	65 (35–85)	–/–/–	3.6/–/–	24.8/44.4/30.7	–/–/–
		FC		196		74	65 (40–86)	–/–/–	4.6/–/–	25/45.4/29.6	–/–/–
CLL8, Gramer <i>et al.</i> (2013) [38]	Adena <i>et al.</i> (2014) [39] Hallek <i>et al.</i> (2010) [40] Main <i>et al.</i> (2010) [41] Hallek <i>et al.</i> (2008) [42] Stilgenbauer <i>et al.</i> (2014) [43]	FC	47	409	PFS	74.3	61 (36–81)	55.3/–/–	7.1/16.9/63	5.4/63.3/30.8	–/–/–
CLL5, Eichhorst <i>et al.</i> (2009) [18]	Eichhorst <i>et al.</i> (2013) [44] Eichhorst <i>et al.</i> (2004) [45] Eichhorst <i>et al.</i> (2007) [46] Schmitt <i>et al.</i> (2002) [47] Eichhorst <i>et al.</i> (2003) [48]	FCR	42	93	PFS and OS	74.3	61 (30–80)	54.2/–/–	5.4/20.6/63	4.4/64.5/30.9	–/–/–
		Fludarabine				65.6	71 (65–78)	46.2/53.8/2.2	5.4/15.1/–	12.9/50.5/36.6	60.2/54.8/39.8
		Chi		100		63	70 (65–78)	42/58/9	5/8/–	16/44/40	57/52/43
CLL1 EORTC, Jaksic <i>et al.</i> (2000) [49]	Jaksic <i>et al.</i> (1996) [50] Jaksic <i>et al.</i> (1998) [51]	Chi	33	NR	Response	NR	NR	NR	NR	NR	NR
		Fludarabine		NR		NR	NR	NR	NR	NR	NR
CLL10, Eichhorst <i>et al.</i> (2013) [52]	Langerbeins <i>et al.</i> (2014) [53] Eichhorst <i>et al.</i> (2014) [54]	FCR	27.9	282	NR	–	NR	NR	–/–/55	NR	NR
		BR		279		–	NR	NR	–/–/68	NR	NR
Rai <i>et al.</i> (1996) [55]	Rai <i>et al.</i> (1995) [56]	Fludarabine	30	NR	NR	–	NR	NR	NR	NR	NR
		Chi		NR		–	NR	NR	NR	NR	NR

The sources of data stated in the table may include the primary publication and related publications listed for each study.

¹C: Calculated with the patient-level data from the RESONATE-2 trial (data on file), equating Rai stages 0–I with Binet stage A, Rai stage II with Binet stage B and Rai stage III–IV with Binet stage C.

BR: Bendamustine + rituximab; CLL: Chronic lymphocytic leukemia; ECOG: Eastern Cooperative Oncology Group; FC: Fludarabine + cyclophosphamide; F-Chi: Fludarabine + chlorambucil; FCR: Fludarabine + cyclophosphamide + rituximab; where fludarabine was given at relatively low frequency (dose); NR/–: Not reported; Obi-Chi: Obinutuzumab + chlorambucil; Ofa-Chi: Ofatumumab + chlorambucil; OR: Overall response; OS: Overall survival; PFS: Progression-free survival; R-Chi: Rituximab + chlorambucil.

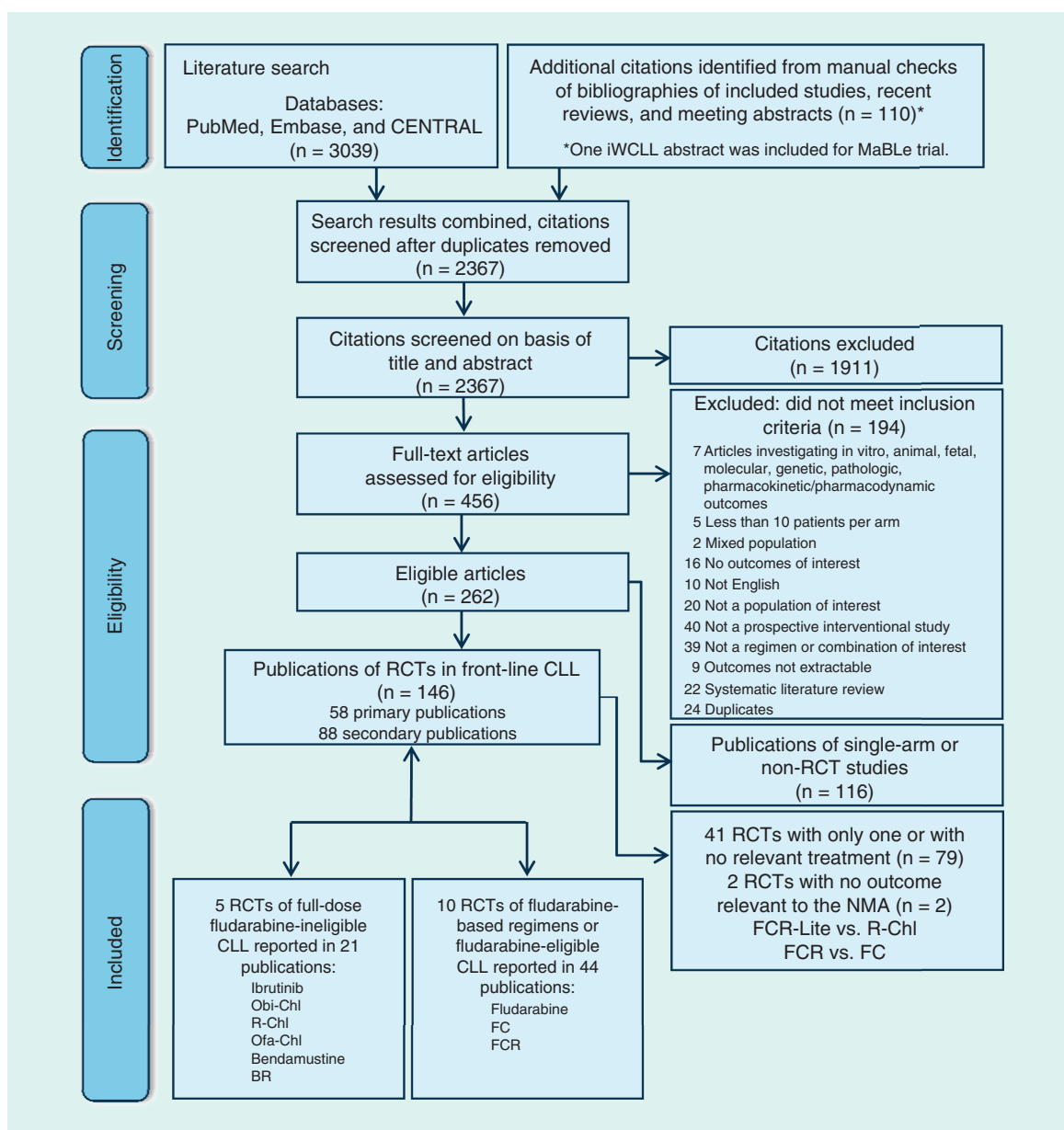


Figure 1. Preferred reporting items for systematic reviews and meta-analyses diagram.

BR: Bendamustine + rituximab; CLL: Chronic lymphocytic leukemia; FC: Fludarabine + cyclophosphamide;

FCR: Fludarabine + cyclophosphamide + rituximab; FCR-Lite: Reduced-dose

fludarabine + cyclophosphamide + rituximab, where fludarabine was given at relatively low frequency (dose);

iWCLL: International Workshop on Chronic Lymphocytic Leukemia; NMA: Network meta-analysis;

Obi-Chl: Obinutuzumab + chlorambucil; Ofa-Chl: Ofatumumab + chlorambucil; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis; R-Chl: Rituximab + chlorambucil; RCT: Randomized controlled trial.

fludarabine-based studies and 63 to 74 years in the fludarabine-ineligible studies. Of the studies that reported Eastern Cooperative Oncology Group performance status, the majority were restricted to patients with Eastern Cooperative Oncology Group 0 to 1. Across the 15 RCTs, PFS and OS outcomes were available for all but three studies and the PFS outcomes were either INV- or IRC-assessed (Table 2). IRC results were used preferentially for the NMA wherever reported (in three of the eight studies in the overall front-line CLL network, and in four of the five studies in the fludarabine-ineligible network) as they are considered less prone to bias than INV assessments. Where the reporting methodology for PFS was not specified, it was included in the analyses as INV-assessed PFS.

Table 2. Reported outcomes of front-line treatments in chronic lymphocytic leukemia from studies included in network meta-analysis.

Trial Name, study (year) [Ref.]	Comparison	Median follow-up (months)	Cumulative dose (mg)	PFS HR (95% CrI)	OS HR (95% CrI)	Percentage of patients with TDs	Percentage of patients with DAEs
Front-line treatments in fludarabine-ineligible population							
RESONATE-2, Burger <i>et al.</i> (2015) [13]	Ibrutinib versus Chl	18.4	450	IRC 0.16 [0.09, 0.28] INV 0.09 [0.04, 0.17]	0.16 [0.05, 0.56]	Ibrutinib: 12.6% Chl: 59.4%	Ibrutinib: 8.8% Chl: 23.3%
CLL11, Goede <i>et al.</i> (2014) [12]	Obi-Chl versus Chl R-Chl versus Chl	NR	384	IRC 0.19 [0.14, 0.27] INV 0.18 [0.13, 0.24] IRC 0.46 [0.35, 0.61] INV 0.44 [0.34, 0.57]	0.41 [0.23, 0.74] 0.66 [0.39, 1.11]	Obi-Chl: 20% R-Chl: 12.8% Chl: 33.9%	Obi-Chl: 12.7% R-Chl: 7.1% Chl: 13.5%
COMPLEMENT1, Hillmen <i>et al.</i> (2015) [19]	Ofa-Chl versus Chl	28.9	772.8	IRC 0.58 [0.46, 0.73] INV 0.54 [0.41, 0.69]	0.91 [0.57, 1.43]	Ofa-Chl: 23.5% Chl: 32.5%	Ofa-Chl: 12.9% Chl: 12.7%
Knauf <i>et al.</i> (2012) [23]	Bendamustine versus Chl	35	720	IRC 0.23 [0.16, 0.33] INV 0.35 [0.27, 0.46]	0.77 [0.52, 1.12]	–	Bendamustine: 11.1% Chl: 3.3%
MaBLE trial, Michallet (2015) [14]	BR versus R-Chl	24	–	IRC or INV 0.52 [0.34, 0.81] ‡	0.98 [0.51, 1.9]	–	–
Front-line treatments with fludarabine or fludarabine-based regimens in CLL							
Mulligan <i>et al.</i> (2014) [17]	Fludarabine versus Chl	83	1104	IRC 1.14 [0.85, 1.51] †	1.08 [0.72, 1.63]	–	–
CLL4, Eichhorst <i>et al.</i> (2006) [28]	FC versus fludarabine	22	–	IRC or INV 0.56 [0.39, 0.81] ‡	1.15 [0.60, 2.19]	–	Fludarabine: 14% FC: 30%
E2997, Flinn <i>et al.</i> (2007) [33]	FC versus fludarabine	24	–	IRC or INV 0.51 [0.37, 0.71]	1.06 [0.62, 1.79]	–	–
CALGB 9011, Rai <i>et al.</i> (2000) [16]	Fludarabine versus Chl	62	441.6	IRC or INV 0.65 [0.51, 0.82] †	0.78 [0.59, 1.05]	–	–
LRF CLL4, Catovsky <i>et al.</i> (2007) [15]	Fludarabine versus Chl FC versus fludarabine FC versus Chl	41	772.8	IRC 0.86 [0.71, 1.04] IRC 0.46 [0.37, 0.58] IRC 0.41 [0.32, 0.52]	1.24 [0.90, 1.70] † 0.87 [0.64, 1.12] † 1.14 [0.82, 1.57] †	–	–
CLL8, Cramer <i>et al.</i> (2013) [38]	FCR versus FC	47	–	IRC 0.56 [0.46, 0.69]	0.67 [0.48, 0.92]	–	FCR: 18% FC: 18%
CLL5, Eichhorst <i>et al.</i> (2009) [18]	Fludarabine versus Chl	42	450	IRC or INV 0.98 [0.72, 1.31] †	1.39 [0.87, 2.23]	–	Fludarabine: 26% Chl: 19%
CLL10, Eichhorst <i>et al.</i> (2013) [52]	BR versus FCR	27.9	–	IRC or INV 1.42 [1.02, 1.98]	0.61 [0.31, 1.20]	–	–

The sources of data stated in the table may include the primary publication and related publications listed for each study.

Results in **bold font** represent statistically significant advantages for the tested treatment over the comparator (e.g., with an HR < 1, with the upper end of 95% CI < 1 indicating a survival benefit for treatment vs comparator).

†PFS/OS imputed from survival curves.

‡Study was presented in meeting abstract, which did not specify whether PFS was assessed by investigator or IRC.

–: Not reported; BR: Bendamustine + rituximab; Chl: Chlorambucil; CLL: Chronic lymphocytic leukemia; CrI: Credible interval; FC: Fludarabine + cyclophosphamide; FCR: Fludarabine + cyclophosphamide + rituximab; HR: Hazard ratio; INV: Investigator; IRC: Independent review committee; Obi-Chl: Obinutuzumab + chlorambucil; Ofa-Chl: Ofatumumab + chlorambucil; OS: Overall survival; PFS: Progression-free survival; R-Chl: Chlorambucil + rituximab; TD: Total treatment discontinuation.

Safety data were considerably scarcer across the 15 RCTs, with five studies reporting DAE outcomes and three studies TD outcomes.

Base-case NMA results

The results for the base-case analyses for both the overall front-line population and the fludarabine-ineligible population are described below.

Survival outcomes: overall front-line population

Thirteen studies contributed to the NMA of PFS and OS outcomes in the base-case analysis (Figure 2A). The base-case random-effects NMA for the overall front-line population suggested that ibrutinib was superior to the other treatments in improving IRC-assessed PFS, with HRs (and the associated probability of being more effective) ranging from 0.16 ($P[\text{HR} < 1] = 100.0\%$; vs chlorambucil) to 0.82 ($P[\text{HR} < 1] = 69.3\%$; vs Obi-Chl) (Figure 3A). Results based on INV-assessed PFS showed a similar trend, with HRs between 0.09 ($P[\text{HR} < 1] = 100.0\%$; vs chlorambucil) and 0.44 ($P[\text{HR} < 1] = 95.5\%$; vs bendamustine) (Figure 3B). Similarly, ibrutinib showed the greatest OS benefit, with HRs ranging from 0.14 ($P[\text{HR} < 1] = 99.8\%$; vs fludarabine + cyclophosphamide) to 0.41 ($P[\text{HR} < 1] = 89.2\%$; vs Obi-Chl) (Figure 3C). Overall, ibrutinib had the highest probability of being the best treatment in the network for improving both IRC-assessed PFS (59.9%) and OS (87.7%) (Figure 4A).

Survival outcomes: fludarabine-ineligible population

Five RCTs contributed to the NMA of survival outcomes in the base-case analysis for the population of fludarabine-ineligible patients. The network comprised seven treatment arms (pairs depicted in Figure 2B). The base-case fixed-effects NMA for the fludarabine-ineligible CLL population found that the IRC-assessed PFS HRs (and probabilities of being better) ranged from 0.16 ($P[\text{HR} < 1] = 100.0\%$; vs chlorambucil) to 0.85 ($P[\text{HR} < 1] = 69.2\%$; vs Obi-Chl) (Figure 3D); INV-assessed PFS HRs ranged from 0.09 ($P[\text{HR} < 1] = 100.0\%$; vs chlorambucil) to 0.48 ($P[\text{HR} < 1] = 97.0\%$; vs Obi-Chl) (Figure 3E); and OS HRs ranged from 0.16 ($P[\text{HR} < 1] = 99.9\%$; vs chlorambucil) to 0.40 ($P[\text{HR} < 1] = 91.1\%$; vs Obi-Chl) (Figure 3F). In the fludarabine-ineligible network, ibrutinib had the highest probability of being the best treatment in the network for improving both PFS (62.7%) and OS (89.9%) (Figure 4B).

Safety outcomes: overall front-line population

The network of evidence for analysis of TDs included three RCTs (RESONATE-2 [13], COMPLEMENT1 [19] and CLL11 [12]). The random-effects NMA showed that patients receiving ibrutinib experienced fewer TDs than those in other treatment groups, with ORs (and probabilities of being better [i.e., associated with fewer discontinuations]) ranging from 0.10 ($P[\text{OR} < 1] = 99.8\%$; vs chlorambucil) to 0.35 ($P[\text{OR} < 1] = 89.9\%$; vs R-Chl). Five studies reported DAEs and were therefore included in the network for this outcome. Compared with eight other treatments, ORs for ibrutinib (and this drug's probabilities of being the better treatment) ranged from 0.08 ($P[\text{OR} < 1] = 99.0\%$; vs bendamustine) to 0.66 ($P[\text{OR} < 1] = 70.4\%$; vs R-Chl) (Table 3). Ibrutinib was least likely to be associated with negative safety outcomes, having an 87.8% probability of having the lowest risk of TDs and 60.8% probability of having the lowest risk of DAEs (Figure 4C).

Safety outcomes: fludarabine-ineligible population

Of the five RCTs that investigated treatment in fludarabine-ineligible patients, three reported the proportions of patients with TDs, and four reported proportions of patients with DAEs. ORs and probabilities of ibrutinib being better in terms of TDs ranged from 0.10 ($P[\text{OR} < 1] = 100\%$; vs chlorambucil) to 0.34 ($P[\text{OR} < 1] = 99.4\%$; vs R-Chl) and in terms of DAEs from 0.08 ($P[\text{OR} < 1] = 100\%$; vs bendamustine) to 0.65 ($P[\text{OR} < 1] = 79.2\%$; vs R-Chl) (Table 3). Fixed-effect modeling results indicated that ibrutinib was most likely to be the best treatment, with the lowest relative chance of experiencing TDs (99.4% probability of being best) and DAEs (78.9% probability of being best) (Figure 4D).

Regression analyses for survival outcomes using chlorambucil dosing as covariate

There was significant variation in chlorambucil dosing across the RCTs that had investigated this treatment, and this was particularly marked in the fludarabine-ineligible network. For instance, in that network, the median cumulative chlorambucil dose in CLL11 was 384 mg, while in RESONATE-2, the mean dose ranged between 252 and 672 mg.

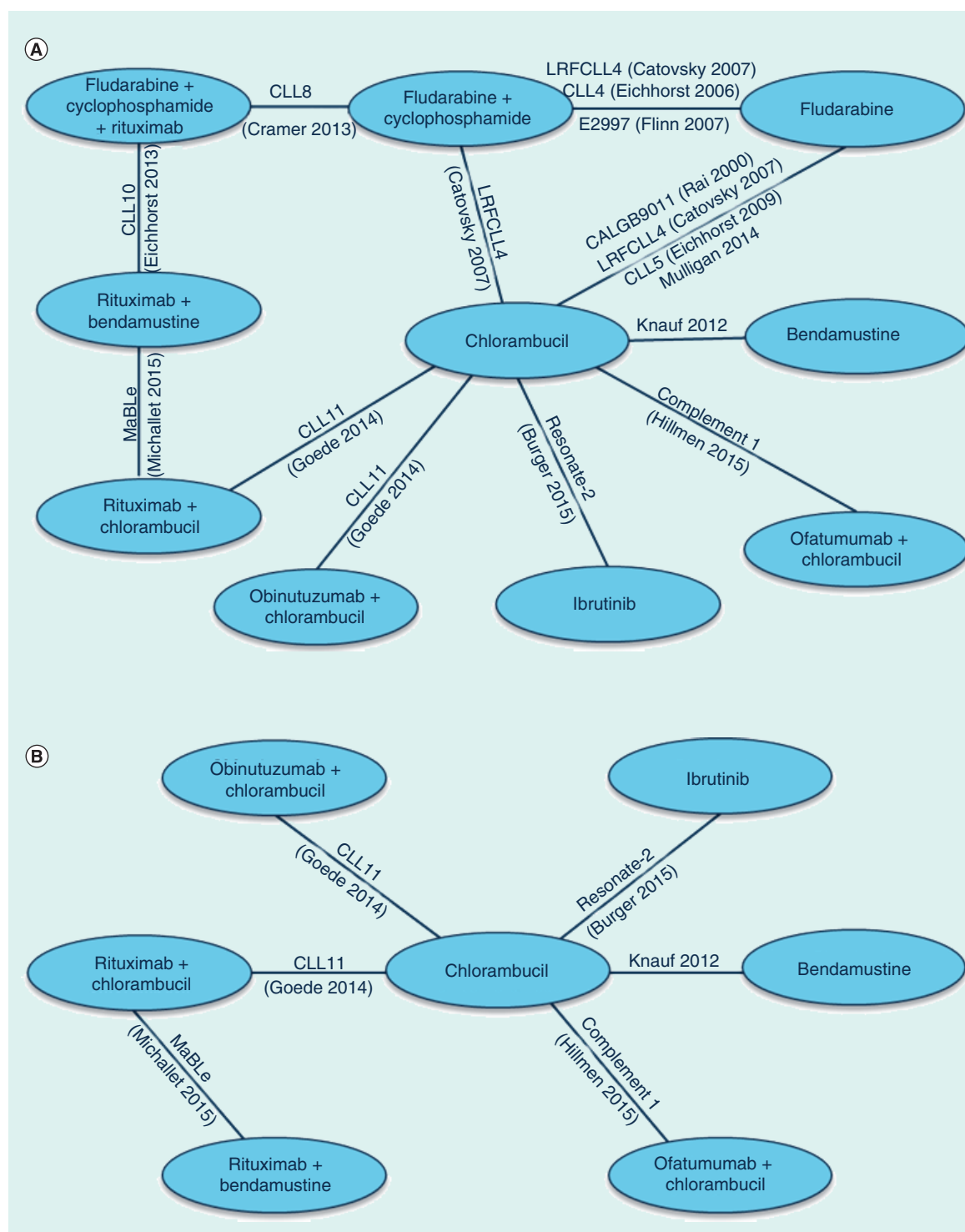


Figure 2. Network of randomized controlled trials in patients with chronic lymphocytic leukemia receiving front-line treatment. Network of studies and treatments included in the NMAs for the (A) overall front-line CLL population and (B) fludarabine-ineligible population (2-part figure, A & B). In CLL11, the results for the comparison between Obi-Chl and R-Chl included 190 additional patients who were randomized after termination of the chlorambucil arm (i.e., stage 2), and these data were not considered to be relevant evidence for the NMA. Therefore, no link between these two treatments is presented in the network.
 CLL: Chronic lymphocytic leukemia; NMA: Network meta-analysis; Obi-Chl: Obinutuzumab + chlorambucil; R-Chl: Chlorambucil + rituximab; RCT: Randomized controlled trial.

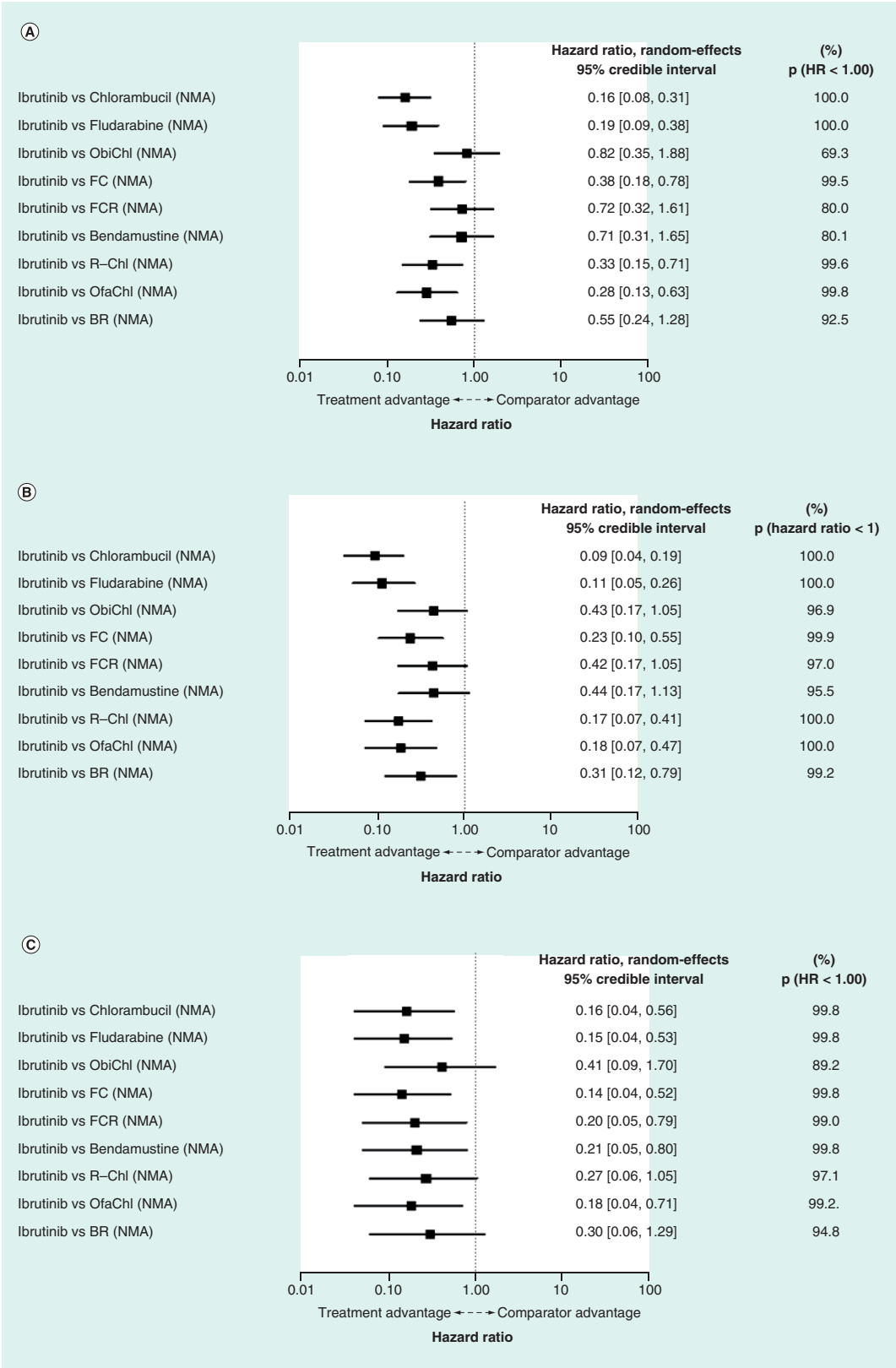


Figure 3. Progression-free survival and overall survival of front-line treatments in chronic lymphocytic leukemia. (A) IRC-assessed progression-free survival (PFS) network meta-analysis (NMA) outcomes: overall front-line population. (B) INV-assessed PFS NMA outcomes: overall front-line population. (C) OS NMA outcomes: overall front-line population. (D) IRC-assessed PFS NMA outcomes: fludarabine-ineligible population. (E) INV-assessed PFS NMA outcomes: fludarabine-ineligible population. (F) OS NMA outcomes: fludarabine-ineligible population (6-part figure, A–F). CLL: Chronic lymphocytic leukemia; INV: Investigator; IRC: Independent review committee; OS: Overall survival.

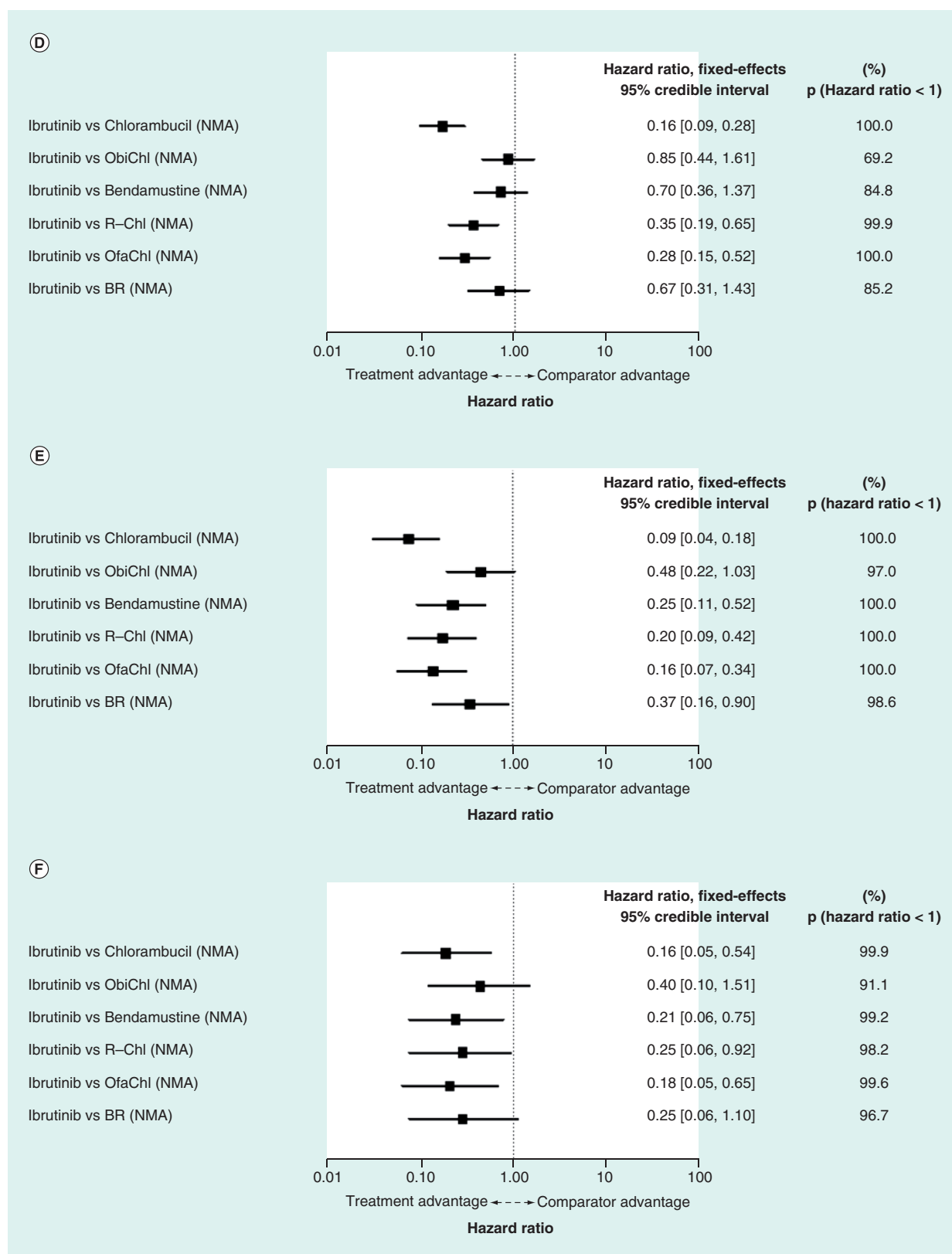


Figure 3. Progression-free survival and overall survival of front-line treatments in chronic lymphocytic leukemia (cont.).

(A) IRC-assessed progression-free survival (PFS) network meta-analysis (NMA) outcomes: overall front-line population. (B) INV-assessed PFS NMA outcomes: overall front-line population. (C) OS NMA outcomes: overall front-line population. (D) IRC-assessed PFS NMA outcomes: fludarabine-ineligible population. (E) INV-assessed PFS NMA outcomes: fludarabine-ineligible population. (F) OS NMA outcomes: fludarabine-ineligible population (6-part figure, A–F).

CLL: Chronic lymphocytic leukemia; INV: Investigator; IRC: Independent review committee; OS: Overall survival.

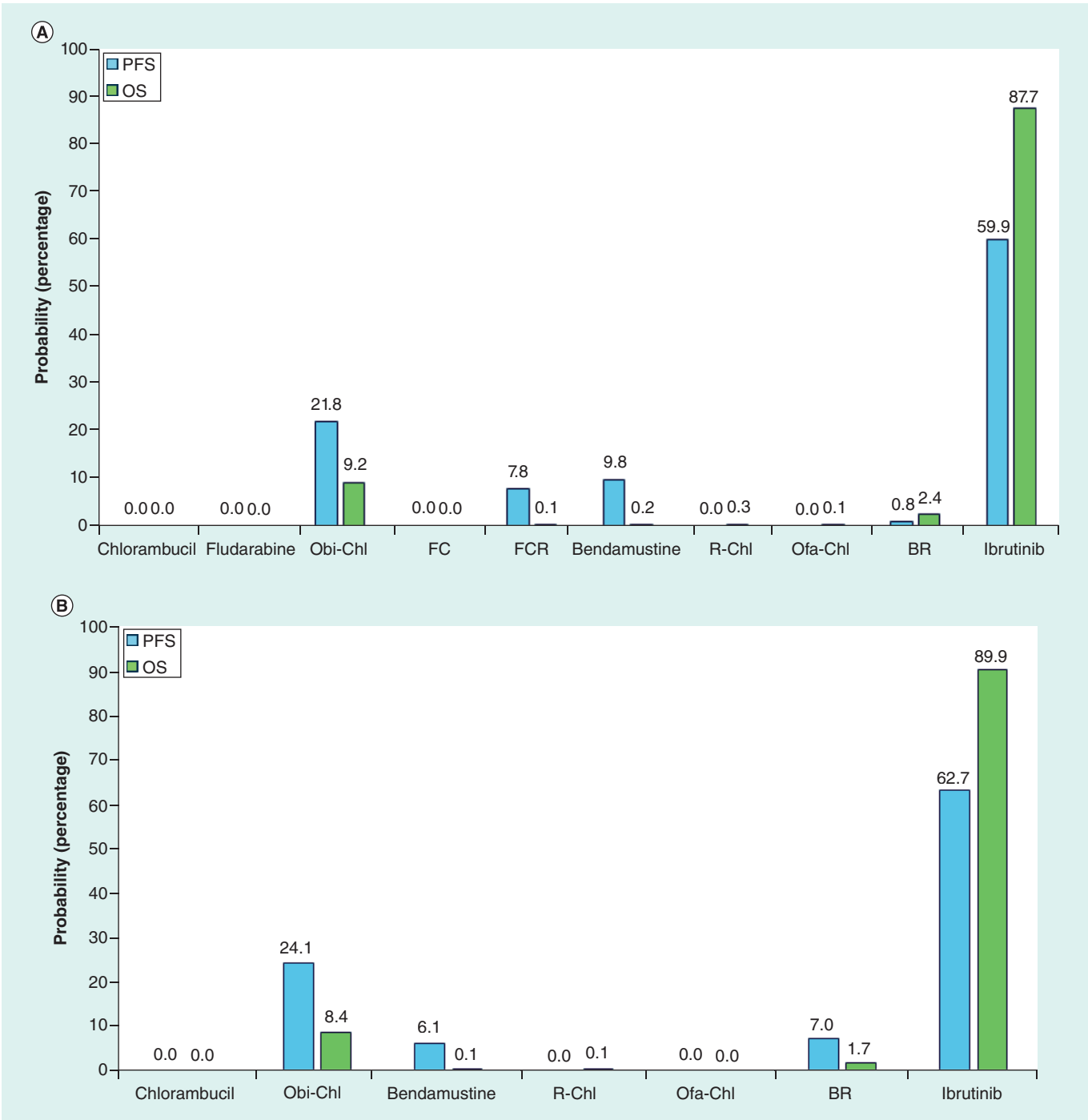


Figure 4. Probability of being best treatment in network.
(A) Probability of being best treatment in network in terms of IRC-assessed PFS and OS in the overall front-line population. (B) Probability of being best treatment in network in terms of IRC-assessed PFS and OS in the fludarabine-ineligible population. (C) Probability of being best treatment in network in terms of TDs and DAEs in the overall front-line population. (D) Probability of being best treatment in network in terms of TDs and DAEs in the fludarabine-ineligible population (4-part figure, A–D).
BR: Bendamustine + rituximab; DAE: Discontinuation due to adverse event; FC: Fludarabine + cyclophosphamide; FCR: Fludarabine + cyclophosphamide + rituximab; IRC: Independent review committee; Obi-Chl: Obinutuzumab + chlorambucil; Ofa-Chl: Ofatumumab + chlorambucil; OS: Overall survival; PFS: Progression-free survival; R-Chl: Rituximab + chlorambucil; TD: Total discontinuation.

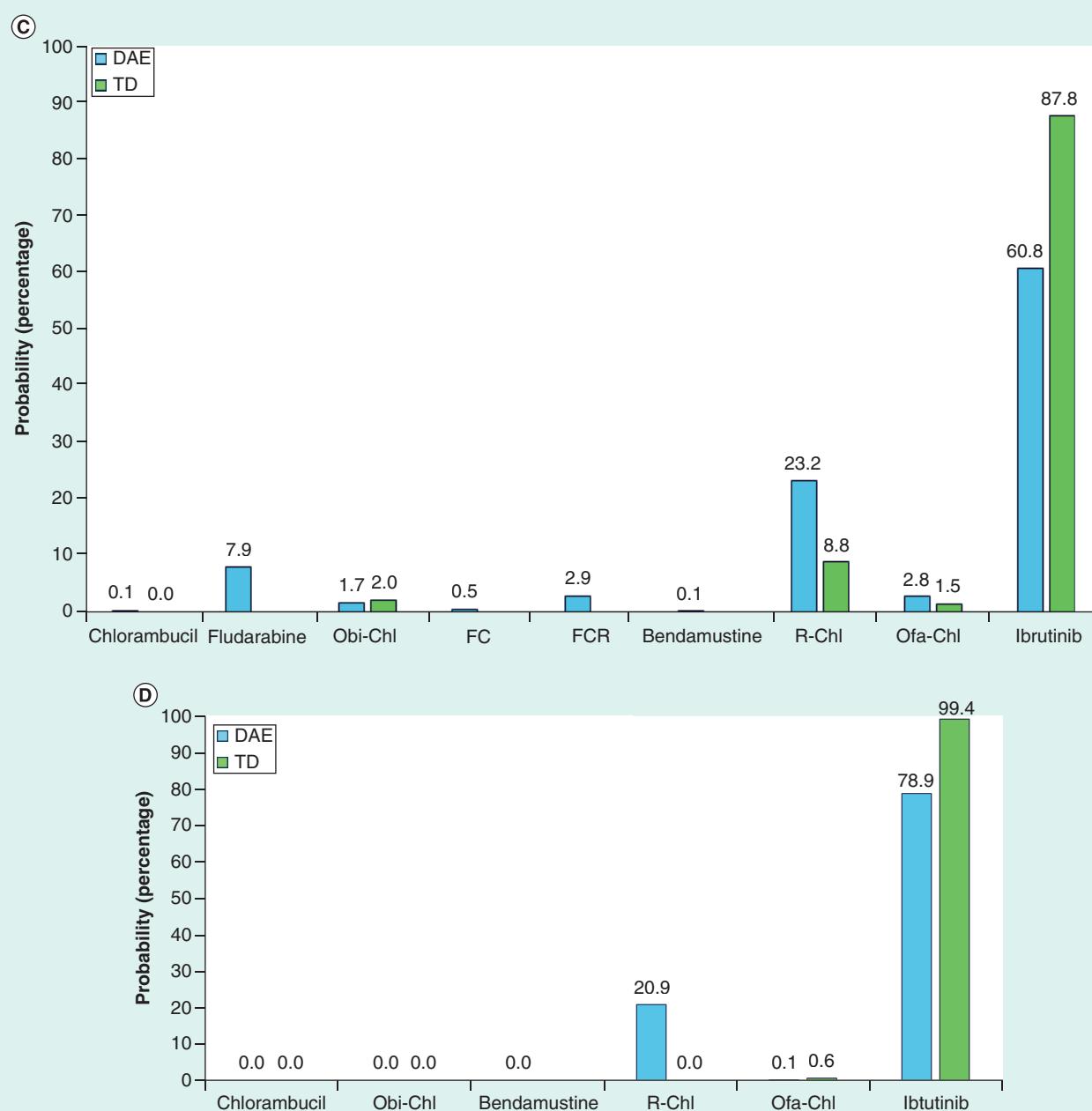


Figure 4. Probability of being best treatment in network (cont.).

(A) Probability of being best treatment in network in terms of IRC-assessed PFS and OS in the overall front-line population. (B) Probability of being best treatment in network in terms of IRC-assessed PFS and OS in the fludarabine-ineligible population. (C) Probability of being best treatment in network in terms of TDs and DAEs in the overall front-line population. (D) Probability of being best treatment in network in terms of TDs and DAEs in the fludarabine-ineligible population (4-part figure, A–D).

BR: Bendamustine + rituximab; DAE: Discontinuation due to adverse event; FC: Fludarabine + cyclophosphamide; FCR: Fludarabine + cyclophosphamide + rituximab; IRC: Independent review committee; Obi-Chl: Obinutuzumab + chlorambucil; Ofa-Chl: Ofatumumab + chlorambucil; OS: Overall survival; PFS: Progression-free survival; R-Chl: Rituximab + chlorambucil; TD: Total discontinuation.

Table 3. Network meta-analysis safety outcomes.

	Ibrutinib versus chlorambucil	Ibrutinib versus Obi-Chl	Ibrutinib versus R-Chl	Ibrutinib versus Ofa-Chl	Ibrutinib versus ben- damustine	Ibrutinib versus fludarabine	Ibrutinib versus FC	Ibrutinib versus FCR
Safety outcomes, overall front-line population								
TD, random-effects	0.1	0.21	0.35	0.15	NA	NA	NA	NA
OR [95% CrI]	[0.02, 0.37]	[0.03, 1.35]	[0.05, 2.28]	[0.02, 0.99]				
Probability ibrutinib is better	99.8%	95.8%	89.9%	79.5%				
DAE, random-effects	0.32	0.31	0.66	0.31	0.08	0.46	0.21	0.21
OR [95% CrI]	[0.08, 1.18]	[0.05, 2]	[0.1, 4.31]	[0.05, 1.9]	[0.01, 0.6]	[0.07, 2.99]	[0.03, 1.74]	[0.02, 2.35]
Probability ibrutinib is better	96.2%	91.5%	70.4%	92.2%	99%	83.5%	92.2%	92.2%
Safety outcomes, fludarabine-ineligible population								
TD, fixed-effects	0.1	0.2	0.34	0.15	NA	NA	NA	NA
OR [95% CrI]	[0.05, 0.17]	[0.09, 0.44]	[0.15, 0.78]	[0.07, 0.32]				
Probability ibrutinib is better	100%	100%	99.4%	100%				
DAE, fixed-effects	0.23	0.31	0.65	0.31	0.08	NA	NA	NA
OR [95% CrI]	[0.15, 0.63]	[0.11, 0.8]	[0.23, 1.81]	[0.12, 0.77]	[0.02, 0.27]			
Probability ibrutinib is better	100%	99.3%	79.2%	99.5%	100%			

Results in **bold font** represent statistically significant advantages for the tested treatment over the comparator (e.g., with an OR < 1 with upper end of 95% CI < 1 indicating a statistically significant safety benefit for the tested treatment or ibrutinib over comparator/s).
CrI: Credible interval; DAE: Discontinuation due to adverse event; FC: Fludarabine + cyclophosphamide; FCR: Fludarabine + cyclophosphamide + rituximab; NA: Not applicable; NMA: Network met-analysis; Obi-Chl: Obinutuzumab + chlorambucil; Ofa-Chl: Ofatumumab + chlorambucil; OR: Odds ratio; OS: Overall survival; R-Chl: Chlorambucil + rituximab; TD: Total treatment discontinuation.

COMPLEMENT1 had the highest cumulative chlorambucil dose among the five RCTs (reported to be median 728 mg and range 98–1848 mg). To explore the potential effect of such differences, regression analyses for PFS and OS, using cumulative chlorambucil dose at 24 weeks as a covariate, were conducted for both networks. This analysis showed a strong correlation between dose and PFS/OS outcomes in studies involving fludarabine-eligible patients, but no correlation in studies of fludarabine-ineligible patients.

Subgroup analyses in fludarabine-ineligible patients

RESONATE-2 enrolled only patients aged at least 65 years and who did not have del17p mutation. Across the other trials, there were between-study differences in patient age and the proportion of participants without del17p mutations, as well as in the proportion of patients with other mutations, including IgVH and del11q. As both age and mutation status are prognostic indicators and potential treatment-effect-modifiers in CLL [6], analyses were conducted, where data permitted, on the subgroups of patients aged ≥65 years, those with unmutated IgVH, those with del11q mutation and those without del17p mutation.

Some or all outcomes of interest for the four subgroups were available from four RCTs: RESONATE-2 [13], CLL11 [12], COMPLEMENT1 [19] and Knauf *et al.* [23]. Pairwise comparisons were conducted for ibrutinib versus Obi-Chl, R-Chl, Ofa-Chl and bendamustine, respectively, and effects were tested in the subgroups for which data were available. The data inputs used in the subgroup NMAs are presented in Table 4.

Overall, results of the Bayesian NMA in the subgroups showed comparable or even higher relative efficacy of ibrutinib versus the other treatments, compared with that shown in the base-case analyses (Table 5). Analysis of the age ≥65 years subgroup resulted in very similar INV-assessed PFS, OS and DAE HRs or ORs compared with the all-patient base-case analyses, as did analysis of the population without del17p in terms of INV-assessed PFS. Results from the analyses of the del11q and IgVH unmutated populations indicated that in these high-risk subgroups ibrutinib may confer a particularly large PFS advantage over Obi-Chl (del11q: HR = 0.06, P[HR<1] = 99.9%; IgVH unmutated: HR = 0.27, P[HR<1] = 91.8%) and R-Chl (del11q: HR = 0.02; P[HR<1] = 100.0% and IgVH unmutated: HR = 0.11; P[HR<1] = 100.0%), as suggested by the much lower HRs compared with the all-patient base-case analyses. These comparative estimates were associated with a very high (i.e., nearly 100%) probability that ibrutinib was the most effective treatment within the network.

Discussion

The NMA results for the overall front-line CLL population showed that ibrutinib treatment was associated with greater benefit than other treatments in improving IRC- and INV-assessed PFS and OS. Specifically, ibrutinib showed the highest probability of being the most effective treatment in the network in terms of improving both IRC-assessed PFS (59.9%) and OS (87.7%). Also, NMA results for all survival outcomes were very similar when

Table 4. Subgroup network meta-analysis inputs.

	Ibrutinib versus Chl	Obi-Chl versus Chl	R-Chl versus Chl	Ofa-Chl versus Chl	Bendamustine versus Chl
INV-assessed PFS (subgroup ≥ 65 years) HR [95% CI]	0.09 [0.04, 0.17]	0.21 [0.15, 0.3]		NA	NA
INV-assessed PFS (subgroup with 11q mutation) HR [95% CI]	0.024 † [0.003, 0.186]	0.37 [0.17, 0.81]	0.99 [0.49, 2.03]	NA	NA
INV-assessed PFS (IgVH unmutated subgroup) HR [95% CI]	0.06 ‡ [0.02, 0.18]	0.23 [0.16, 0.34]	0.54 [0.38, 0.76]	NA	NA
INV-assessed PFS (subgroup without 17p) HR [95% CI]	0.09 [0.04, 0.17]	0.25 [0.18, 0.33]	0.42 [0.33, 0.55]	NA	NA
OS (subgroup ≥ 65 years) HR [95% CI] [†]	0.16 [0.05, 0.56]	NA	NA	NA	0.92 [0.55, 1.55]
DAE (subgroup ≥ 65 years) OR [95% CI] [‡]	0.32 † [0.16, 0.66]	NA	NA	0.96[§] [0.51, 1.8]	NA

Results in **bold font** represent statistically significant advantages for the tested treatment over the comparator (e.g., with an HR/OR < 1 with upper end of 95% CI < 1 indicating a statistically significant safety benefit for the tested treatment or ibrutinib over comparator/s).

[†]Relative results were derived using the number or proportion of patients that achieved an overall response as reported in the study publications.

[‡]Relative results were derived using the patient-level data from RESONATE-2.

[§]Relative results were derived using the number or proportion of patients that experience event (discontinuation or adverse event) as reported in the study publications.

Chl: Chlorambucil; DAE: Discontinuation due to adverse event; HR: Hazard ratio; INV: Investigator; NA: Not available; NMA: Network meta-analysis; Obi-Chl: Obinutuzumab + chlorambucil; Ofa-Chl: Ofatumumab + chlorambucil; OR: Odds ratio; OS: Overall survival; PFS: Progression-free survival; R-Chl: Chlorambucil + rituximab.

Table 5. Subgroup network meta-analysis outcomes.

	Ibrutinib versus Obi-Chl	Ibrutinib versus R-Chl	Ibrutinib versus Ofa-Chl	Ibrutinib versus bendamustine
INV-assessed PFS (≥ 65 years subgroup) HR [95% CrI] Probability ibrutinib is better	0.41 [0.19, 0.89] 98.8%	0.19 [0.09, 0.41] 100.0%	NA	NA
INV-assessed PFS (subgroup with 11q mutation) HR [95% CrI] Probability ibrutinib is better	0.06 [0.01, 0.58] 99.9%	0.02 [0, 0.21] 100.0%	NA	NA
INV-assessed PFS (IgVH unmutated subgroup) HR [95% CrI] Probability ibrutinib is better	0.27 [0.04, 1.68] 91.8%	0.11 [0.04, 0.34] 100.0%	NA	NA
INV-assessed PFS (subgroup without 17p) HR [95% CrI] Probability ibrutinib is better	0.35 [0.16, 0.75] 99.7%	0.20 [0.1, 0.43] 100.0%	NA	NA
OS (≥ 65 years subgroup) OR [95% CrI] [†]	NA	NA	NA	0.18 [0.05, 0.67]
DAE (≥ 65 years subgroup) OR [95% CrI] [†]	NA	NA	0.37 [0.12, 0.84]	NA

[†]A total of 31% patients in the COMPLEMENT1 ITT population were younger than 65 years.

Chl: Chlorambucil; CrI: Credible interval; DAE: Discontinuation due to adverse event; HR: Hazard ratio; INV: Investigator; NA: Not available; NMA: Network meta-analysis; Obi-Chl: Obinutuzumab + chlorambucil; Ofa-Chl: Ofatumumab + chlorambucil; OR: Odds ratio; OS: Overall survival; PFS: Progression-free survival; R-Chl: Chlorambucil + rituximab.

the network was restricted to studies in fludarabine-ineligible patients only, with ibrutinib again having the highest probability of being the most effective treatment in the network in terms of IRC-assessed PFS (62.7%) and OS (89.9%). Ibrutinib showed the lowest risk in the network for negative safety outcomes, including likelihood of experiencing TDs and DAEs in both the overall front-line population and in the fludarabine-ineligible population. The safety outcomes indicate with high certainty that ibrutinib resulted in fewer patients with TDs and DAEs than each of the other treatments. In addition, subgroup analyses showed that ibrutinib had either comparable (age ≥ 65 years subgroup, subgroup without del17p) or superior (subgroup with del11q, IgVH unmutated subgroup) treatment effect estimates compared with those demonstrated in the general fludarabine-ineligible NMA. Overall, therefore, the NMA results provide strong evidence that ibrutinib offers better efficacy and safety outcomes than does a range of comparators, especially in high-risk, previously untreated patients with genetic mutations.

Of note, the data source for ibrutinib was the RESONATE-2 trial with a median follow-up of 18.4 months [13]. Survival data at a longer follow-up from this study were recently published [57]; however, these were not used because by this time 41% of the patients originally randomized to chlorambucil had crossed over to the ibrutinib arm;

an NMA based on this data cut would have produced a substantially increased survival estimate for chlorambucil and significantly underestimated the survival benefit from ibrutinib. Therefore, the NMA used the data cut per the final trial analyses reported in Burger *et al.* [13] at which point the much lower proportion of patients who had switched to ibrutinib upon progression would have had only a minor effect on the estimated relative efficacy of the two treatments.

It is worth highlighting that there were between-study variations in age, patient fitness, presence of cytogenetic mutations and disease severity, and the cumulative dosage of the common comparator, chlorambucil. However, only characteristics known to be potential treatment-effect-modifiers are of relevance for the interpretation of the NMA results. Across the 13 RCTs, two studies excluded patients with del17p mutation, whereas IgVH mutation status or presence of del11q mutation was inconsistently reported across the studies. All of these characteristics are known to be adverse prognostic factors and potential treatment-effect-modifiers [6,7]. The impact of these differences on relative treatment effects was studied by performing subgroup analyses. These showed comparable or even larger benefit estimates for ibrutinib relative to comparators in the subgroups of patients with del11q and unmutated IgVH. The issue of whether differences in reported dosing of chlorambucil-impacted outcomes were explored by regression analyses for PFS and OS using 24-week cumulative chlorambucil dose as covariate. Regression analysis was performed for all studies identified in the SLR that had a chlorambucil treatment arm. The regression analysis (results not shown) indicated a very weak correlation between chlorambucil dose and PFS across fludarabine-ineligible studies, and a strong correlation between chlorambucil dose and PFS outcomes in the overall front-line population. This strong correlation was driven by a small number of studies conducted in young/fit patients, with relatively high chlorambucil dose. These results suggested that in the overall front-line population, the survival advantages of ibrutinib observed in the NMAs were conservative, given that they were demonstrable despite the bias toward better treatment outcomes from regimens that involved a high cumulative dose of chlorambucil. Also, the lack of correlation in the regression analysis of fludarabine-ineligible population, offers reassurance that any differences in cumulative chlorambucil dose did not introduce significant bias with regards to relative treatment effects in the survival NMAs conducted for that group.

Differences in the treatment schedules of the compared regimens complicate the interpretation of the analyzed safety outcomes, which comprised the proportion of patients with TDs and with DAEs. Importantly, ibrutinib was the only treat-to-progression treatment in contrast to all other interventions, which had fixed treatment durations. Once administration of a fixed-duration regimen is complete, the ratio of discontinuations between treatment arms does not change. However, with the ibrutinib treat-to-progression approach, patients were continually exposed to treatment and therefore continued to be at risk for TDs and DAEs. Outcomes for TD and DAE in this analysis were not adjusted for exposure time as no such data are available in any of the included studies publications, meaning that the reported safety outcomes are conservative for ibrutinib. This difference in the treatment schedule of ibrutinib compared with the other treatments is expected to have a substantial impact on the relative safety outcomes, with likely underestimation of the safety benefits of ibrutinib treatment.

Our analysis follows several previous NMAs conducted to compare PFS and OS outcomes of treatment regimens for the front-line treatment of CLL. However, we are not aware of any other that has been conducted since the publication of the pivotal front-line study of ibrutinib, RESONATE-2 and none of the previously published NMAs include ibrutinib in the studied networks. It is notable, though, that results for treatment regimens that were common across all these NMAs are consistent with the current analysis.

This broad agreement in findings is exemplified by the results of an NMA by Rancea *et al.* that included 33 RCTs of front-line treatment for patients with untreated CLL, evidence that was presented at the 19th Congress of the European Hematology Association (2014) [58]. The network in this study included 21 regimens for front-line CLL that were compared with chlorambucil in terms of their effect on PFS and OS [58]. Obi-Chl and FCR showed 99 and 95% probabilities of providing greater PFS benefit than chlorambucil, respectively (probability of each being the most effective treatment for PFS in the network not presented); whereas results for OS ranked Obi-Chl first (72%), followed by BR (16%), with FCR ranked fifth (1%) [58]. In the current analyses, ibrutinib had the highest probability of being the most effective of all front-line treatments in the network in terms of improving both PFS and OS (59.9 and 87.7%), followed by Obi-Chl (21.8 and 9.2%), bendamustine (9.8 and 0.2%), BR (0.8 and 2.4%) and FCR (7.8 and 0.1%). In summary, the Rancea NMA found that Obi-Chl had the highest probability of being the best treatment in improving OS [58], a result in line with findings of the present analysis, which ranked Obi-Chl second, after ibrutinib.

A more recent NMA by Stadler *et al.* compared the relative efficacy of front-line treatments (excluding ibrutinib) in patients with CLL who were unfit (because of comorbidities and/or ineligibility for full-dose fludarabine), in terms of PFS and OS, across eight RCTs [59]. The NMA (fixed-effects) results for PFS indicated Obi-Chl was ranked first (with a 56% probability of being the most effective), followed by reduced-dose FCR, BR, R-Chl, Ofa-Chl, fludarabine monotherapy and chlorambucil monotherapy [59]. The OS results were generally consistent with the PFS results, indicating an OS advantage with Obi-Chl over the other treatments [59]. The NMA presented in this paper shows that when included in the network of evidence, ibrutinib is the most effective treatment (i.e., ranked first, with the highest probability for OS and PFS). Obi-Chl was ranked the second most effective treatment, which is in line with previously published NMAs (that did not include ibrutinib) that ranked Obi-Chl first.

The presented analyses have various strengths. They were performed using a Bayesian analytic framework, which allowed the ranking of treatments in terms of various efficacy and safety end points. This approach provided a systematic and structured means of establishing relative outcomes for treatment arms that had not been directly compared in a head-to-head trial. Also, a wide range of front-line treatment regimens were included in the network, specifically reflecting recommendations in current treatment guidelines, and this is the first published indirect treatment comparison for front-line CLL treatment that includes ibrutinib.

There are also some limitations to our analyses, arising mainly from lack of data availability for some of the end points of interest, and inconsistency of data reporting across the included RCTs. An example is PFS, the most commonly reported outcome across the overall network. The definitions of this outcome were largely consistent across studies, with reporting of both INV- and IRC-assessed PFS. However, this approach was not used in one of the fludarabine-ineligible studies (MaBLE), and five of the fludarabine-eligible studies did not specify whether PFS was assessed by INV or IRC. In reality, these limitations would appear to have little or no bearing on the key findings of the NMA, given the broad consistency between the INV-assessed and IRC-assessed PFS results. Another limitation was that the reporting of safety outcomes was relatively sparse across the fludarabine-eligible RCTs. However, safety outcomes were more consistently reported across the fludarabine-ineligible RCTs, such that only one study (MaBLE) did not report the proportion of patients with either TDs or DAEs. Therefore, confident conclusions can be drawn about comparative treatment effects in a subgroup for whom therapeutic options are already more limited than for patients with CLL in general. The studies also varied in the range of follow-up periods (between 18 and 83 months). However, this is to be expected when the network includes both older studies, for which multiple time points may be reported, and more recent studies, for which follow-up to data might be more limited. This limitation can be overcome by updating the NMA results once data from the newer studies with longer follow-up periods become available. Finally, while the cut-off date for the SLR in our study (October 2015) could be seen as a limitation, in reality, an updated search conducted in April 2017 found no additional RCTs that would change the network for either the overall or the fludarabine-ineligible CLL population.

Conclusion

Overall, the results of the NMA demonstrate a clear therapeutic advantage for ibrutinib in the front-line treatment of CLL over other currently available treatment regimens in PFS, OS and safety outcomes. The observed treatment benefit was consistent in key high-risk subgroups and across both the overall network (patients considered eligible for full-dose fludarabine treatment) and the fludarabine-ineligible network (those considered ineligible due to patient age and fitness).

Financial & competing interests disclosure

Janssen-Cilag Ltd funded the study reported in this manuscript, development of the manuscript and the article processing charges. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis. S Baculea, S Côté, S van Sanden and J Diels are employees of Janssen-Cilag Ltd. Y Xu, E Dorman and K Fahrbach are employees of Evidera, a research and consulting firm for the biopharma industry. As a condition of their salaried employment, they are precluded from accepting any payment or honoraria directly from Evidera clients. Evidera received funding from Janssen-Cilag Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing assistance was utilized in the production of this manuscript. R Sallum (a former employee of Evidera) contributed substantially to the design and implementation of the SLR and NMA reported in this manuscript. Editorial assistance for the

Summary points

- There are numerous front-line treatment options for chronic lymphocytic leukemia (CLL), but the limited number of head-to-head clinical trials results in uncertainty regarding optimal treatment regimens for patient groups with differing levels of fitness.
- A systematic literature review without temporal limits was performed using MEDLINE, Medline In-Process, Embase, Embase In-Process, Cochrane Collection Central Register of Clinical Trials (CENTRAL) and Database of Abstracts of Reviews of Effects.
- Relative treatment effects of progression-free survival, overall survival and safety outcomes were estimated via network meta-analysis (NMA).
- Two networks, one based on an 'overall' patient population, leveraging data from 15 studies, and one based on a 'fludarabine-ineligible' patient population, leveraging data from five studies, were established and analyzed. Subgroup analyses explored relative treatment effects in patients with known treatment-effect-modifying characteristics.
- The 'overall' NMA network (overall front-line CLL population) included >5300 patients from 15 studies; of these, five were conducted in 'fludarabine-ineligible' patients, making up the 'fludarabine-ineligible' network. The base-case NMA for each network indicated that ibrutinib was superior to the other treatments in terms of progression-free survival and overall survival, and had the highest probability of having the lowest risk of discontinuations overall.
- Ibrutinib provides a clear benefit in survival and safety outcomes for front-line treatment of patients with CLL, including high-risk subgroups and patients considered ineligible for full-dose fludarabine treatment.

preparation of this manuscript was provided by L Rutherford of Evidera. C Gulea supported the execution of the SLR and write up of technical reports for both SLR and NMAs. Support for these contributions was funded by Janssen-Cilag Ltd.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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