SUPPLEMENTARY MATERIAL

A: Search Strategy

The search strategy employed for the clinical review in Embase® with the search hits as of February 27, 2013 is presented in Table S1. The combined search strings for the Cochrane database using the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects as product filter are presented in Table S2. The combined search strings for MEDLINE® In-Process are presented in Table S3.

Table S1 Search strategy for clinical review in Embase® and MEDLINE® (searched through Embase.com on February 27, 2013)

No.	Query	Results
1	'clinical trial'/exp	940 678
2	'randomization'/de	60 237
3	'controlled study'/de	3 972 102
4	'comparative study'/de	662 870
5	'single blind procedure'/de	16 468
6	'double blind procedure'/de	112 466
7	'crossover procedure'/de	35 411
8	'placebo'/de	227 169
9	'clinical trial'	1 082 859
10	'clinical trials'	191 470
11	'controlled clinical trial'	472 240
12	'controlled clinical trials'	11 789
13	'randomised controlled trial'	12 409
14	'randomized controlled trial'	368 714
15	'controlled trials'	59 891
16	'randomized controlled trials'	29 448
17	'randomisation'	5181
18	'randomization'	73 289
19	random*	909 291
20	rct	13 190
21	'random allocation'	1342
22	'randomly allocated'	18 522
23	'allocated randomly'	1864
24	allocated NEAR/2 random	797
25	assign* NEAR/2 random*	76 504
26	randomi*	617 058
27	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)	196 738
28	placebo*	305 678
29	'prospective study'/de	216 805
30	Nrct	46
31	'n rct'	1
32	n?rct	24
33	'controlled clinical trial'/exp	439 628
34	'prospective study'/exp	216 805

35	**'intervention study'/exp**	**15 627**
36	(clinical NEXT/1 trial*):ab,ti	250 077
37	'major clinical study'/exp	2 049 241
38	compar*:ab,ti	3 992 223
39	group*:ab,ti	2 909 497
40	OR/1-39	9 600 141
41	'case study'/de	20 489
42	'case report'	1 943 789
43	'abstract report'/de	89 565
44	'letter'/de	781 077
45	OR/41-44	2 669 114
46	#40 NOT #45	9 343 300
47	'chronic lymphatic leukemia'/de	21 060
48	'b cell leukemia'/exp	4973
49	lymphom* near/2 lymphocyt*	6862
50	(leuk?em* OR leu?em* OR lymph*) near/2 (lymphocyt* OR lymphoblast* OR linfoid* OR 'b cell')	417 736
51	(chronic OR cronic OR 'well differential')	964 357
52	#50 AND #51	50 117
53	OR/47-49, 52	64 003
54	'chlorambucil'/syn OR amboclorin OR 'cb 1348' OR cb1348 OR chlorambacil OR chloraminophene OR chlorbutin OR chloroambucil OR chorambucil OR ecloril OR leuceran OR leukeran OR linfolysin OR lympholysin OR nsc 3088 OR nsc3088	16 346
55	'fludarabine'/syn OR fludara	16 123
56	'cladribine'/syn OR biodribin OR ntocel OR leustat OR leustatin OR leustatine OR litak OR litax OR movectro OR mylinax OR 'rwj 26251' OR rwj26251	4787
57	'bendamustine'/syn OR 'cimet 3393' OR cytostasan OR cytostasan r OR cytostasane OR 'imet 3393' OR levact OR ribomustin OR treanda	1521
58	'alemtuzumab'/syn OR campath OR 'ldp 103' OR 'ldp103' OR lemtrada OR mabcampath	8902
59	'rituximab'/syn OR 'idec c2b8' OR mabthera OR reditux OR rituxan OR rituxin	32 061
60	'ofatumumab'/syn OR arzerra OR 'gsk 1841157' OR gsk1841157 OR 'humac CD20' OR HuMax-CD20 OR 'HuMax CD20' OR HuMaxCD20	876
61	'lenalidomide'/syn OR 'cc 5013' OR cc5013 OR 'cdc 501' OR cdc 5013 OR cdc501 OR cdc5013 OR 'enmd 0997' OR enmd0997 OR 'imid 3' OR imid3 OR revimid OR revlimid	6597
62	'gs 1101'/syn OR 'cal 101' OR cal101 OR 'gs 1101' OR gs1101 OR idelalisib	265
63	'obinutuzumab'/syn OR afutuzumab OR 'ga 101' OR ga101 OR r 7159 OR r7159 OR 'ro 5072759' OR ro5072759	270
64	'cyclophosphamide'/syn OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR 'cyclofos amide' OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR 'cyclophosphamide isopac' OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cyclostin n OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR 'cytoxan lyophilized' OR 'endocyclo phosphate' OR endoxan OR endoxan-asta OR 'endoxan asta' OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR 'lyophilized cytoxan' OR mitoxan OR neosan OR neosar OR noristan OR 'nsc 26271' OR 'nsc 2671' OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid	164 147
65	cop NEAR/2 regimen	70
66	chop NEAR/2 regimen	701
67	Or/54-66	204 213
68	#46 AND #53 AND #67 AND [1992-2013]/py AND AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [erratum]/lim OR [note]/lim OR [short survey]/lim)	4318

Table S2 Search strategy for clinical review in Cochrane (searched through Cochrane Library interface on February 27, 2013)

No.	Query	Results
1	MeSH descriptor: [Leukemia, Lymphocytic, Chronic, B-Cell] explode all trees	197
2	'b cell leukaemia' OR 'b cell leukemia'	1294
3	lymphom* near/2 lymphocyt*	81
4	(leuk?em* OR leu?em* OR lymph*) near/2 (lymphocyt* OR lymphoblast* OR linfoid* OR 'b cell')	11 116
5	(chronic OR cronic OR 'well differential')	58 350
6	#4 AND #5	1878
7	OR/1-3, 6	2857
8	MeSH descriptor: [Chlorambucil] explode all trees	214
9	(chlorambucil OR amboclorin OR 'cb 1348' OR cb1348 OR chlorambacil OR chloraminophene OR chlorbutin OR chloroambucil OR chorambucil OR ecloril OR leuceran OR leukeran OR linfolysin OR lympholysin OR nsc 3088 OR nsc3088):ab,ti,kw	402
10	(fludarabine OR fludara):ab,ti,kw	340
11	MeSH descriptor: [Cladribine] explode all trees	1
12	(cladribine OR biodribin OR ntocel OR leustat OR leustatin OR leustatine OR litak OR litax OR movectro OR mylinax OR 'rwj 26251' OR rwj26251): ab,ti,kw	125
13	(bendamustine OR 'cimet 3393' OR cytostasan OR cytostasan r OR cytostasane OR 'imet 3393' OR levact OR ribomustin OR treanda): ab,ti,kw	34
14	(alemtuzumab OR campath OR 'ldp 103' OR 'ldp103' OR lemtrada OR mabcampath): ab,ti,kw	157
15	(rituximab OR 'idec c2b8' OR mabthera OR reditux OR rituxan OR rituxin): ab,ti,kw	648
16	(ofatumumab OR arzerra OR 'gsk 1841157' OR gsk1841157 OR 'humac CD20' OR HuMax-CD20 OR 'HuMax CD20' OR HuMaxCD20): ab,ti,kw	16
17	(lenalidomide OR 'cc 5013' OR cc5013 OR 'cdc 501' OR cdc 5013 OR cdc501 OR cdc5013 OR 'enmd 0997' OR enmd0997 OR 'imid 3' OR imid3 OR revimid OR revlimid): ab,ti,kw	106
18	('gs 1101' OR 'cal 101' OR cal101 OR 'gs 1101' OR gs1101 OR idelalisib): ab,ti,kw	2
19	(obinutuzumab OR afutuzumab OR 'ga 101' OR ga101 OR r 7159 OR r7159 OR 'ro 5072759' OR ro5072759): ab,ti,kw	12
20	MeSH descriptor: [Cyclophosphamide] explode all trees	3719
21	(cyclophosphamide OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR 'cyclofos amide' OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR 'cyclophosphamide isopac' OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cyclostin n OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR 'cytoxan lyophilized' OR 'endocyclo phosphate' OR endoxan OR endoxan-asta OR 'endoxan asta' OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR 'lyophilized cytoxan' OR mitoxan OR neosan OR neosar OR noristan OR 'nsc 26271' OR 'nsc 2671' OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid): ab,ti,kw	6416
22	cop NEAR/2 regimen	21
23	chop NEAR/2 regimen	120
24	OR/8-23	8002
25	#7 and #24 from 1992 to 2013, in Cochrane Reviews (Reviews and Protocols), Other Reviews and Trials	403

Table S3 Search strategy for clinical review in MEDLINE®-In Process (searched through PubMed.com interface on February 27, 2013)

No	Query	Results
1	"Leukemia, Lymphocytic, Chronic, B-Cell"[Mesh terms]	10 777
2	"chronic lymphocytic leukaemia"[All Fields] OR ("leukemia"[All Fields] AND "lymphocytic"[All Fields] AND "chronic"[All Fields] AND "b-cell"[All Fields]) OR "b-cell chronic lymphocytic leukemia"[All Fields] OR ("chronic"[All Fields] AND "lymphocytic"[All Fields] AND "leukemia"[All Fields]) OR "chronic lymphocytic leukemia"[All Fields]	17 425
3	Search (#1 or #2)	17 425
4	(chlorambucil OR amboclorin OR 'cb 1348' OR cb1348 OR chlorambacil OR chloraminophene OR chlorbutin OR chloroambucil OR chorambucil OR ecloril OR leuceran OR leukeran OR linfolysin OR lympholysin OR nsc 3088 OR nsc3088)	4570
5	(fludarabine OR fludara)	3988
6	(cladribine OR biodribin OR ntocel OR leustat OR leustatin OR leustatine OR litak OR litax OR movectro OR mylinax OR 'rwj 26251' OR rwj26251)	1886
7	(bendamustine OR 'cimet 3393' OR cytostasan OR cytostasan r OR cytostasane OR 'imet 3393' OR levact OR ribomustin OR treanda)	529
8	(alemtuzumab OR campath OR 'ldp 103' OR 'ldp103' OR lemtrada OR mabcampath)	2066
9	(rituximab OR 'idec c2b8' OR mabthera OR reditux OR rituxan OR rituxin)	10 846
10	(ofatumumab OR arzerra OR 'gsk 1841157' OR gsk1841157 OR 'humac CD20' OR HuMax-CD20 OR 'HuMax CD20' OR HuMaxCD20)	6980
11	(lenalidomide OR 'cc 5013' OR cc5013 OR 'cdc 501' OR cdc 5013 OR cdc501 OR cdc5013 OR 'enmd 0997' OR enmd0997 OR 'imid 3' OR imid3 OR revimid OR revlimid)	1729
12	('gs 1101' OR 'cal 101' OR cal101 OR 'gs 1101' OR gs1101 OR idelalisib)	35
13	(obinutuzumab OR afutuzumab OR 'ga 101' OR ga101 OR r 7159 OR r7159 OR 'ro 5072759' OR ro5072759)	49
14	(cyclophosphamide OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR 'cyclofos amide' OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR 'cyclophosphamide isopac' OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cyclostin n OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR 'cytoxan lyophilized' OR 'endocyclo phosphate' OR endoxan OR endoxan-asta OR 'endoxan asta' OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR 'lyophilized cytoxan' OR mitoxan OR neosan OR neosar OR noristan OR 'nsc 26271' OR 'nsc 2671' OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid)	496 503
15	"cop regimen"	43
16	"chop regimen"	340
17	OR/4-16	527 769
18	Search (#3 AND #17)	3955
19	Search (#18 AND (in process[sb] OR pubstatusaheadofprint))	98

B: Systematic Literature Search and Screening Process for Trials

Fig. S1 Original systematic review conducted in February, 2013

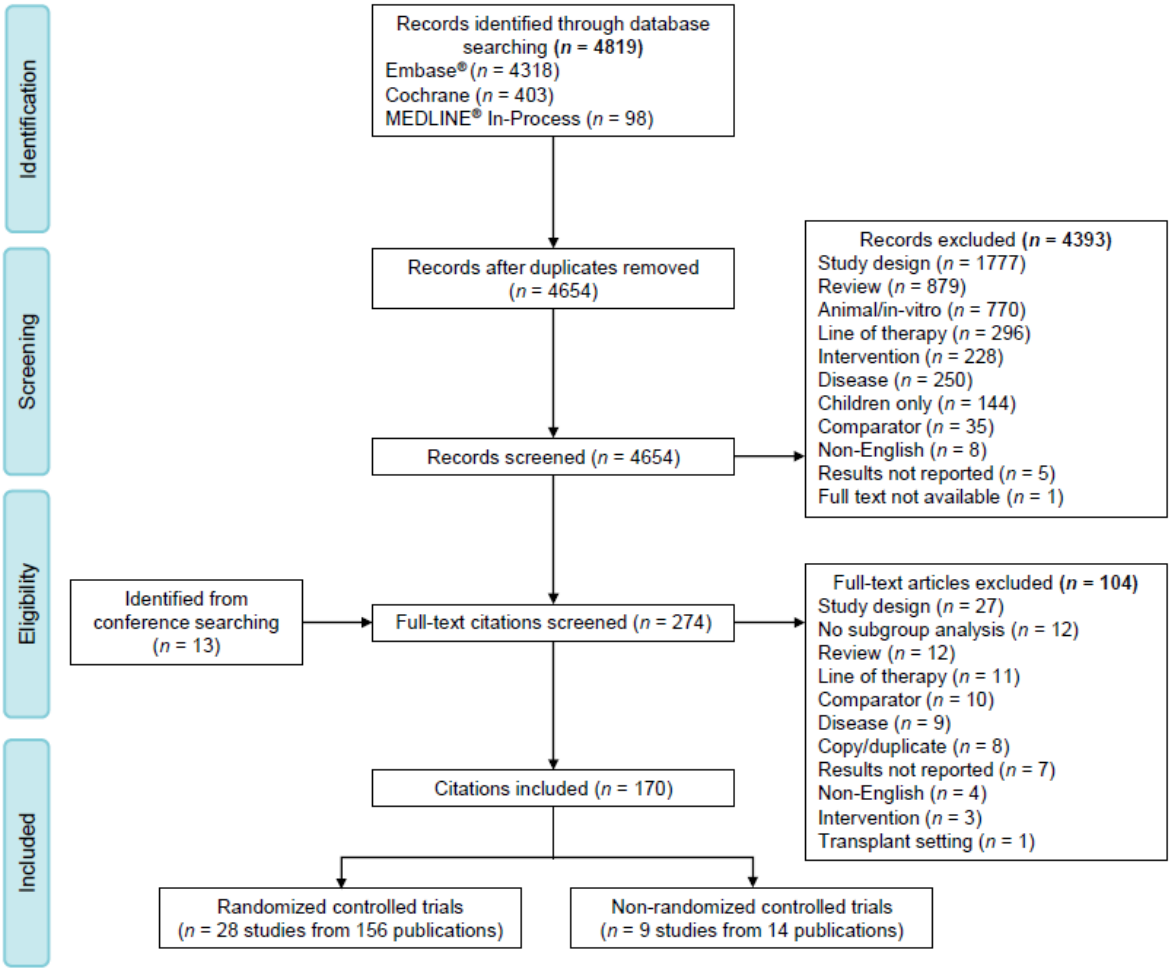


Fig. S2 First update of original systematic review conducted in April, 2014

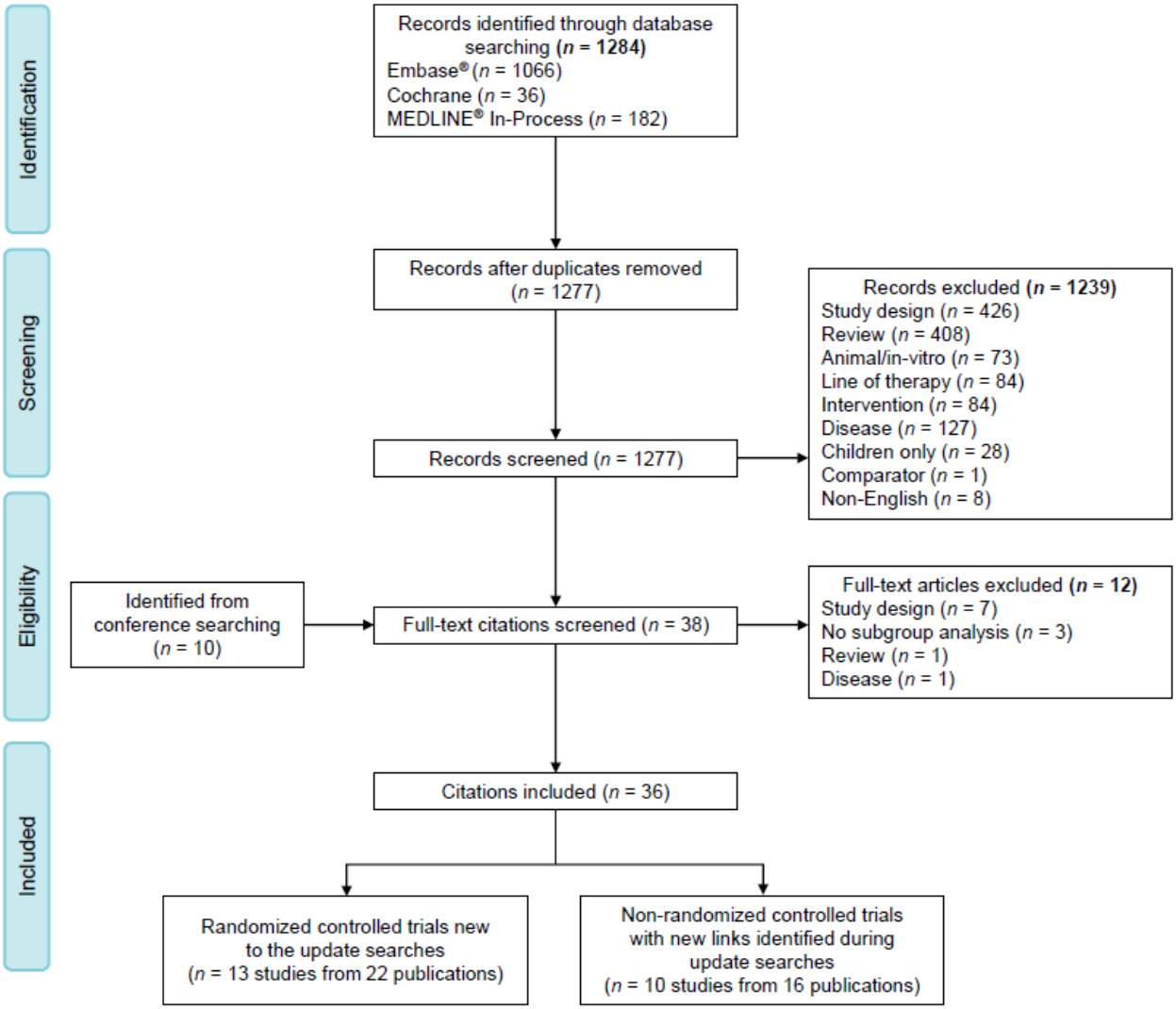
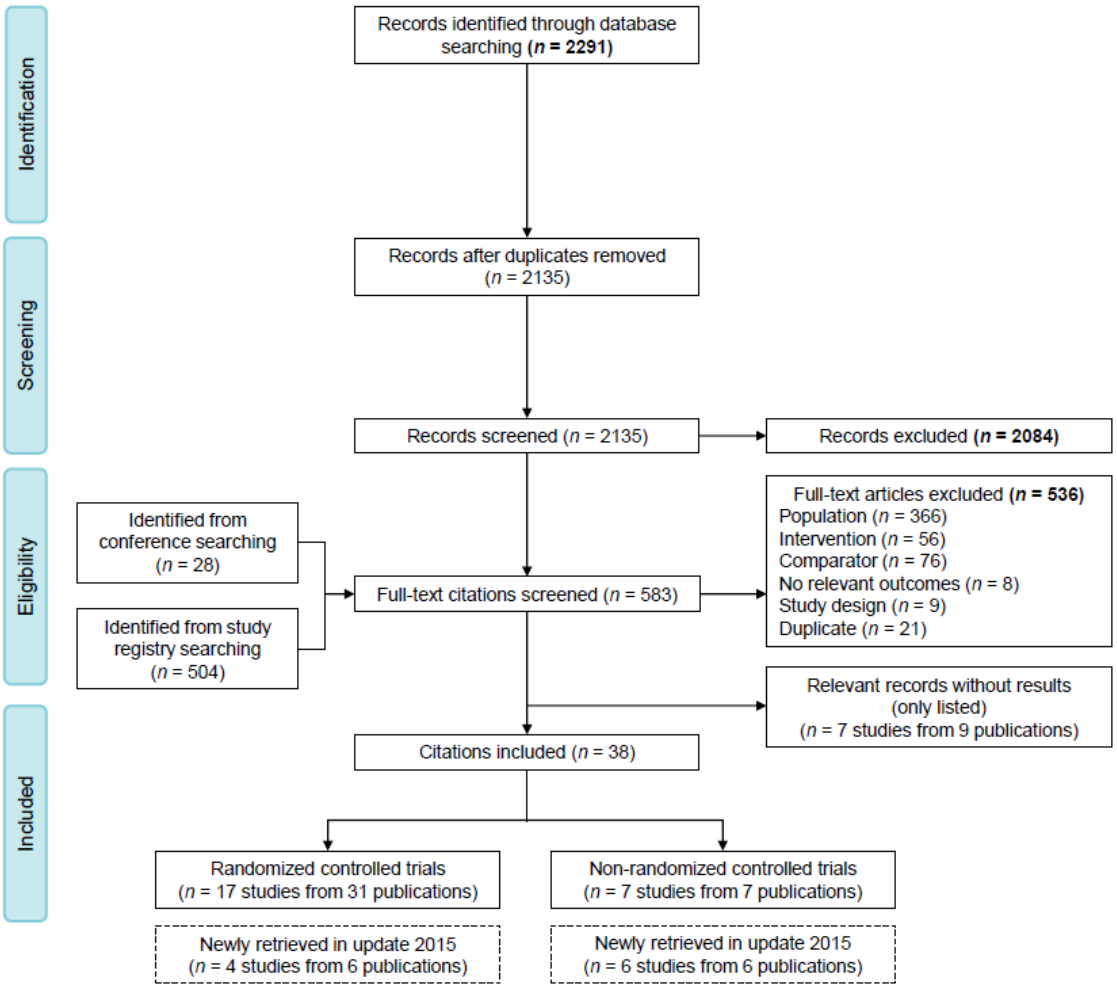


Fig. S3 Second update of original systematic review conducted in August, 2015



C: BUGS Code Used for the Network Meta-Analysis

This section presents BUGS code used for the network meta-analysis (NMA). It is based on the code published by Dias et al [1]. All analyses were performed using the computing environment R. The R package 'R2jags' was used for Markov Chain Monte Carlo simulations.

Fixed-Effects NMA Model

```
# Normal likelihood, identity link, trial-level data given as treatment differences
# Fixed effects model for multi-arm trials

model{              # *** PROGRAM STARTS
 for(i in 1:ns2) {                  # LOOP THROUGH 2-ARM STUDIES
  y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
  #Deviance contribution for trial i
  resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
 }
 for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM STUDIES
  for (k in 1:(na[i]-1)) {    # set variance-covariance matrix
   for (j in 1:(na[i]-1)) {
    Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + va[i,k+1]*equals(j,k)
   }
  }
  Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,])  #Precision matrix
  # multivariate normal likelihood for 3-arm trials
  y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
  #Deviance contribution for trial i
  for (k in 1:(na[i]-1)){  # multiply vector & matrix
```

```
      ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
      z[i,k]<- inprod(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
    }
    resdev[i]<- inprod(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
  }
  for(i in 1:(ns2+ns3)){                #   LOOP THROUGH ALL STUDIES
    for (k in 2:na[i]) {             #  LOOP THROUGH ARMS
      va[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/va[i,k]      # set precisions
      delta[i,k] <-  d[t[i,k]] - d[t[i,1]]
    }
  }
  totresdev <- sum(resdev[])           #Total Residual Deviance
  d[1]<-0       # treatment effect is zero for reference treatment
  # vague priors for treatment effects
  for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

  sd<-0 #between-trial variation is zero (fixed-effects model)
  B<-0 #no meta-regression

} # *** PROGRAM ENDS
```

Random-Effects NMA Model (with Half-Normal Prior for the Heterogeneity Parameter)

```
# Normal likelihood, identity link, trial-level data given as treatment differences
# Random effects model for multi-arm trials
# Half-normal prior on heterogeneity parameter

model{                              # *** PROGRAM STARTS
 for(i in 1:ns2) {                   #LOOP THROUGH 2-ARM STUDIES
   y[i,2] ~ dnorm(delta[i,2],prec[i,2])  # normal likelihood for 2-arm trials
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]  #Deviance contribution for trial i
 }
 for(i in (ns2+1):(ns2+ns3)) {          # LOOP THROUGH THREE-ARM STUDIES
  for (k in 1:(na[i]-1)) {             # set variance-covariance matrix
    for (j in 1:(na[i]-1)) {
      Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + va[i,k+1]*equals(j,k)
    }
  }
  Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,])  #Precision matrix
  # multivariate normal likelihood for 3-arm trials
  y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
  #Deviance contribution for trial i
  for (k in 1:(na[i]-1)){  # multiply vector & matrix
    ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
    z[i,k]<- inprod(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
  }
  resdev[i]<- inprod(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
 }

 for(i in 1:(ns2+ns3)){                  #   LOOP THROUGH ALL STUDIES
  w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
```

```
   delta[i,1] <- 0            # treatment effect is zero for control arm
   for (k in 2:na[i]) {           #  LOOP THROUGH ARMS
     va[i,k] <- pow(se[i,k],2)   # calculate variances
     prec[i,k] <- 1/va[i,k]      # set precisions
   }
   for (k in 2:na[i]) {           # LOOP THROUGH ARMS
     # trial-specific LOR distributions
     delta[i,k] ~ dnorm(md[i,k],taud[i,k])
     # mean of random effects distributions, with multi-arm trial correction
     md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
     # precision of random effects distributions (with multi-arm trial correction)
     taud[i,k] <- tau *2*(k-1)/k
     # adjustment, multi-arm RCTs
     w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
     # cumulative adjustment for multi-arm trials
     sw[i,k] <- sum(w[i,1:k-1])/(k-1)
   }
 }
 totresdev <- sum(resdev[])          #Total Residual Deviance
 d[1]<-0       # treatment effect is zero for reference treatment
 # vague priors for treatment effects
 for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
 sd~dnorm(0,prec2)I(0,1.0E8) # half-normal prior for heterogeneity parameter
prec2<-pow(sig,-2)
 tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)

 B<-0 #no meta-regression

}        # *** PROGRAM ENDS
```

D: Summary of Results for the Main Analysis and Additional Analysis Using the Random Effects, with Informative Prior, Model

Table S4 Main analysis: treatment ranking for PFS and OS. Analysis excludes studies Knauf, Cam307, and Calgb_9011 (expert recommendation)

	Random effects model, informative prior	
	Probability best	**Median rank (CrI)**
PFS		
G-Clb	0.53	1 (1, 3)
RFC-lite	0.3	2 (1, 3)
R-Benda	0.17	3 (1, 3)
R-Clb	0	4 (4, 5)
O-Clb	0	5 (4, 6)
F	0	6 (5,7)
Clb	0	7 (6, 7)
OS		
G-Clb	0.55	1 (1, 4)
R-Benda	0.25	3 (1, 6)
R-Clb	0.08	3 (1, 5)
O-Clb	0.02	4 (2, 6)
Clb	0	5 (3, 6)
F	0.09	6 (1, 6)

Clb chlorambucil, *CrI* credible interval, *F* fludarabine, *G-Clb* obinutuzumab + chlorambucil, *O-Clb* ofatumumab + chlorambucil, *OS* overall survival, *PFS* progression-free survival, *R-Benda* rituximab + bendamustine, *R-Clb* rituximab + chlorambucil, *RFC* rituximab + fludarabine + cyclophosphamide

Table S5 Additional analysis: treatment ranking for PFS and OS. Studies Knauf, Cam307, and Calgb_9011 included in analysis

	Random effects model, informative prior	
	Probability best	**Median rank (CrI)**
PFS		
G-Clb	0.51	1 (1, 3)
RFC-Lite	0.31	2 (1, 4)
R-Benda	0.17	3 (1, 4)
Benda	0.01	4 (2, 6)
R-Clb	0	5 (4, 7)
O-Clb	0	6 (4, 8)
Alm	0	7 (4, 8)
F	0	8 (6, 9)
Clb	0	9 (8, 9)
OS		
G-Clb	0.57	1 (1, 4)
R-Benda	0.28	3 (1, 7)
R-Clb	0.08	3 (1, 6)
Benda	0.05	4 (1, 7)
O-Clb	0.02	5 (2, 7)
F	0.01	5 (2, 7)
Clb	0	6 (4, 7)

Alm alemtuzumab, *Benda* bendamustine, *Clb* chlorambucil, *CrI* credible interval, *F* fludarabine, *G-Clb* obinutuzumab + chlorambucil, *O-Clb* ofatumumab + chlorambucil, *OS* overall survival, *PFS* progression-free survival, *R-Benda* rituximab + bendamustine, *R-Clb* rituximab + chlorambucil, *RFC* rituximab + fludarabine + cyclophosphamide

Fig. S4 Main analysis (Knauf, Cam307, and Calgb_9011 excluded): effect of interventional treatments on PFS and OS using a random effects, with informative prior, model. Forest plots show relative effect of each treatment on PFS and OS as compared with the reference combination treatment G-Clb. Median HRs and CrIs are shown.

Clb chlorambucil, *CrI* credible interval, *F* fludarabine, *G-Clb* obinutuzumab + chlorambucil, *HR* hazard ratio, *O-Clb* ofatumumab + chlorambucil, *OS* overall survival, *PFS* progression-free survival, *R-Benda* rituximab + bendamustine, *R-Clb* rituximab + chlorambucil, *RE* random effects, *RFC* rituximab + fludarabine + cyclophosphamide

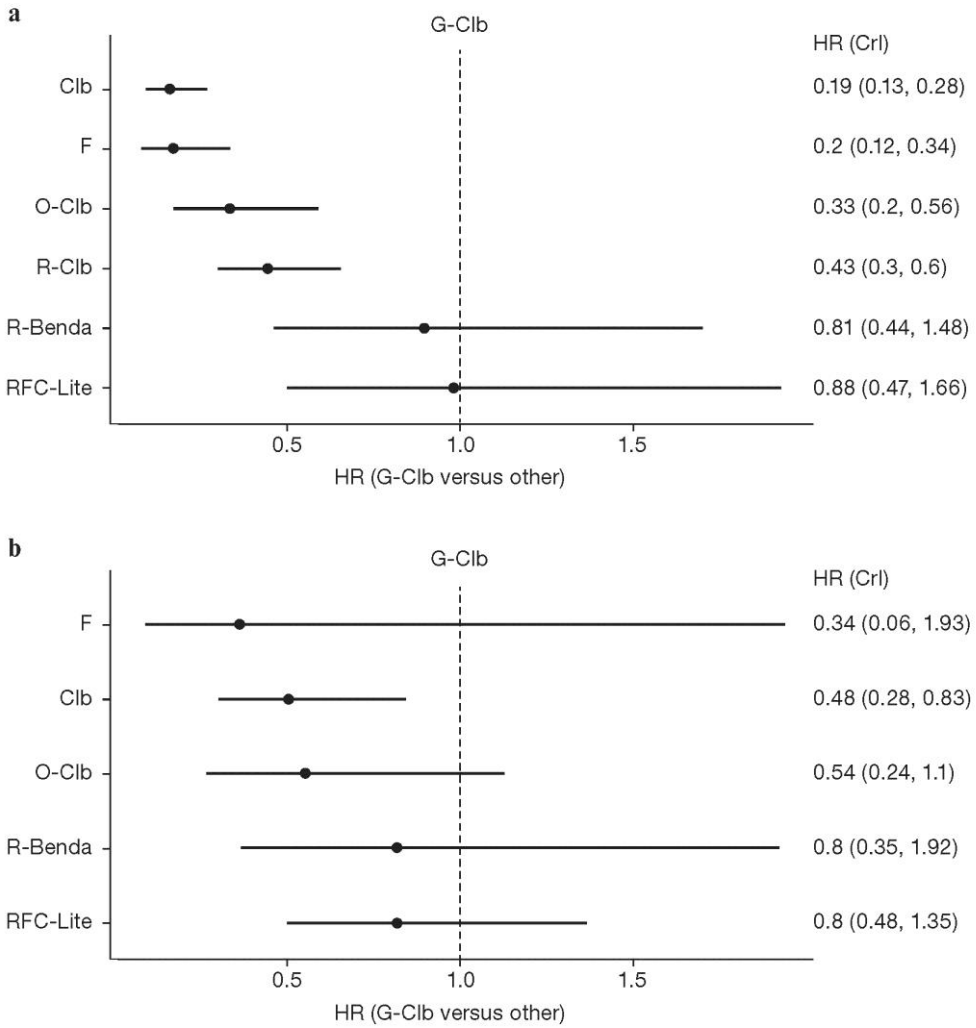
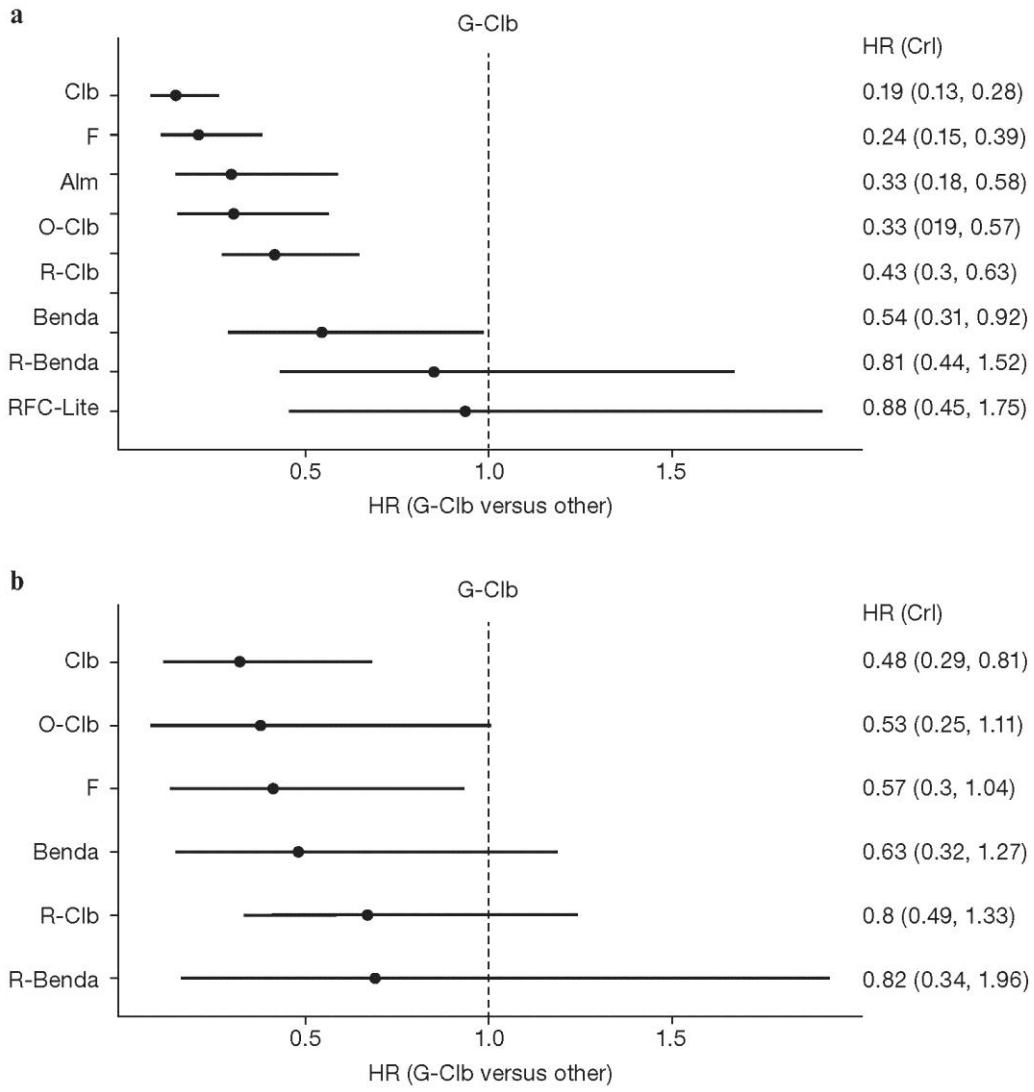


Fig. S5 Additional analysis (Knauf, Cam307, and Calgb_9011 included): effect of interventional treatments on PFS and OS using a random effects, with informative prior, model. Forest plots show relative effect of each treatment on PFS and OS as compared with the reference combination treatment G-Clb. Median HRs and CrIs are shown.

Alm alemtuzumab*, Benda* bendamustine*, Clb* chlorambucil, *CrI* credible interval, *F* fludarabine, *G-Clb* obinutuzumab + chlorambucil, *HR* hazard ratio, *O-Clb* ofatumumab + chlorambucil, *OS* overall survival, *PFS* progression-free survival, *R-Benda* rituximab + bendamustine, *R-Clb* rituximab + chlorambucil, *RE* random effects, *RFC* rituximab + fludarabine + cyclophosphamide


a
G-Clb
HR (Crl)
Clb
F
Alm
O-Clb
R-Clb
Benda
R-Benda
RFC-Lite
0.19 (0.13, 0.28)
0.24 (0.15, 0.39)
0.33 (0.18, 0.58)
0.33 (019, 0.57)
0.43 (0.3, 0.63)
0.54 (0.31, 0.92)
0.81 (0.44, 1.52)
0.88 (0.45, 1.75)
0.5
1.0
1.5
HR (G-Clb versus other)
b
G-Clb
HR (Crl)
Clb
O-Clb
F
Benda
R-Clb
R-Benda
0.48 (0.29, 0.81)
0.53 (0.25, 1.11)
0.57 (0.3, 1.04)
0.63 (0.32, 1.27)
0.8 (0.49, 1.33)
0.82 (0.34, 1.96)
0.5
1.0
1.5
HR (G-Clb versus other)

E: Summary of Hazard Ratios for all Pairwise Comparisons

Table S6 Main analysis: summary of HRs and CrIs for PFS for all pairwise comparisons using a fixed effects and random effects, with informative prior, model

	HR (CrIs)						
	Clb	**R-Clb**	**O-Clb**	**F**	**RFC-Lite**	**R-Benda**	**G-Clb**
Fixed effects model							
Clb	1 (1, 1)	2.25 (1.76, 2.91)	1.75 (1.38, 2.21)	1.05 (0.78, 1.43)	4.64 (2.69, 8.06)	4.26 (2.56, 7.11)	5.27 (3.94, 7.03)
R-Clb	0.44 (0.34, 0 57)	1 (1, 1)	0.78 (0.55, 1.09)	0.47 (0.32, 0.69)	2.07 (1.26, 3.35)	1.89 (1.21, 2.93)	2.33 (1.84, 2.95)
O-Clb	0.57 (0.45, 0.72)	1.29 (0.92, 1.83)	1 (1, 1)	0.6 (0.41, 0.89)	2.66 (1.44, 4.9)	2.42 (1.4, 4.29)	3.01 (2.06, 4.39)
F	0.95 (0.7, 1.28)	2.15 (1.44, 3.16)	1.67 (1.12, 2.43)	1 (1, 1)	4.41 (2.34, 8.23)	4.05 (2.23, 7.28)	5.01 (3.27, 7.55)
RFC-Lite	0.22 (0.12, 0.37)	0.48 (0.3, 0.79)	0.38 (0.2, 0.69)	0.23 (0.12, 0.43)	1 (1, 1)	0.92 (0.48, 1.77)	1.13 (0.66, 1.97)
R-Benda	0.23 (0.14, 0.39)	0.53 (0.34, 0.83)	0.41 (0.23, 0.71)	0.25 (0.14, 0.45)	1.09 (0.57, 2.09)	1 (1, 1)	1.24 (0.75, 2.03)
G-Clb	0.19 (0.14, 0.25)	0.43 (0.34, 0.54)	0.33 (0.23, 0.49)	0.2 (0.13, 0.31)	0.88 (0.51, 1.52)	0.81 (0.49, 1.33)	1 (1, 1)
Random effects, with informative prior, model							
Clb	1 (1, 1)	2.26 (1.56, 3.24)	1.76 (1.25, 2.49)	1.05 (0.71, 1.58)	4.62 (2.46, 9.12)	4.26 (2.27, 7.88)	5.28 (3.59, 7.74)
R-Clb	0.44 (0.31, 0.64)	1 (1, 1)	0.78 (0.48, 1.3)	0.46 (0.27, 0.79)	2.05 (1.2, 3.62)	1.89 (1.14, 3.1)	2.34 (1.66, 3.29)
O-Clb	0.57 (0.4, 0.8)	1.29 (0.77, 2.07)	1 (1, 1)	0.6 (0.35, 1.02)	2.63 (1.26, 5.55)	2.42 (1.17, 4.94)	2.99 (1.8, 5.04)
F	0.95 (0.63, 1.42)	2.15 (1.27, 3.64)	1.68 (0.98, 2.86)	1 (1, 1)	4.42 (2.08, 9.5)	4.05 (1.91, 8.39)	5.03 (2.92, 8.5)
RFC-Lite	0.22 (0.11, 0.41)	0.49 (0.28, 0.84)	0.38 (0.18, 0.79)	0.23 (0.11, 0.48)	1 (1, 1)	0.92 (0.44, 1.91)	1.14 (0.6, 2.11)

R-Benda	0.23 (0.13, 0.44)	0.53 (0.32, 0.88)	0.41 (0.2, 0.85)	0.25 (0.12, 0.52)	1.09 (0.52, 2.29)	1 (1, 1)	1.24 (0.68, 2.27)
G-Clb	0.19 (0.13, 0.28)	0.43 (0.3, 0.6)	0.33 (0.2, 0.56)	0.2 (0.12, 0.34)	0.88 (0.47, 1.66)	0.81 (0.44, 1.48)	1 (1, 1)

Clb chlorambucil, *CrI* credible interval, *F* fludarabine, *G-Clb* obinutuzumab + chlorambucil, *HR* hazard ratio, *O-Clb* ofatumumab + chlorambucil, *PFS* progression-free survival, *R-Benda* rituximab + bendamustine, *R-Clb* rituximab + chlorambucil, *RFC* rituximab + fludarabine + cyclophosphamide

Table S7 Main analysis: summary of HRs and CrIs for overall survival for all pairwise comparisons using a fixed effects and random effects, with informative prior, model

	HR (CrI)					
	Clb	**R-Clb**	**O-Clb**	**F**	**R-Benda**	**G-Clb**
Fixed effects model						
Clb	1 (1, 1)	1.67 (1.07, 2.64)	1.1 (0.7, 1.72)	0.73 (0.16, 3.58)	1.67 (0.75, 3.73)	2.07 (1.29, 3.3)
R-Clb	0.6 (0.38, 0.94)	1 (1, 1)	0.66 (0.34, 1.25)	0.44 (0.09, 2.32)	1 (0.52, 1.93)	1.23 (0.8, 1.92)
O-Clb	0.91 (0.58, 1.44)	1.52 (0.8, 2.9)	1 (1, 1)	0.66 (0.13, 3.54)	1.53 (0.61, 3.8)	1.88 (0.96, 3.56)
F	1.37 (0.28, 6.45)	2.29 (0.43, 11.33)	1.51 (0.28, 7.57)	1 (1, 1)	2.31 (0.39, 12.85)	2.85 (0.54, 14.24)
R-Benda	0.6 (0.27, 1.32)	1 (0.52, 1.91)	0.65 (0.26, 1.65)	0.43 (0.08, 2.57)	1 (1, 1)	1.23 (0.56, 2.71)
G-Clb	0.48 (0.3, 0.78)	0.81 (0.52, 1.26)	0.53 (0.28, 1.04)	0.35 (0.07, 1.86)	0.81 (0.37, 1.78)	1 (1, 1)
Random effects, with informative prior, model						
Clb	1 (1, 1)	1.67 (2.74)	1.1 (0.64, 1.86)	0.72 (0.14, 3.6)	1.67 (0.69, 3.87)	2.07 (1.21, 3.52)
R-Clb	0.6 (0.36, 1)	1 (1, 1)	0.66 (0.31, 1.4)	0.43 (0.08, 2.34)	1 (0.5, 2.01)	1.24 (0.74, 2.06)
O-Clb	0.91 (0.54, 1.56)	1.52 (0.72, 3.24)	1 (1, 1)	0.66 (0.12, 3.46)	1.51 (0.55, 4.19)	1.87 (0.9, 4.11)
F	1.39 (0.28, 7.07)	2.33 (0.43, 12.03)	1.51 (0.29, 8.57)	1 (1, 1)	2.32 (0.37, 14.23)	2.9 (0.52, 15.4)
R-Benda	0.6 (0.26, 1.45)	1 (0.5, 1.99)	0.66 (0.24, 1.81)	0.43 (0.07, 2.69)	1 (1, 1)	1.25 (0.52, 2.89)
G-Clb	0.48 (0.28, 0.83)	0.8 (0.48, 1.35)	0.54 (0.24, 1.11)	0.34 (0.06, 1.93)	0.8 (0.35, 1.92)	1 (1, 1)

Clb chlorambucil, *CrI* credible interval, *F* fludarabine, *G-Clb* obinutuzumab + chlorambucil, *HR* hazard ratio, *O-Clb* ofatumumab + chlorambucil, *R-Benda* rituximab + bendamustine, *R-Clb* rituximab + chlorambucil

Table S8 Additional analysis: summary of HRs and CrIs for progression-free survival for all pairwise comparisons using a fixed effects and random effects, with informative prior, model

	HR (CrIs)								
	Clb	**R-Clb**	**Benda**	**O-Clb**	**F**	**Alm**	**RFC-Lite**	**R-Benda**	**G-Clb**
Fixed effects model									
Clb	1	2.26	2.82	1.76	1.31	1.73	4.64	4.27	5.27
	(1,1)	(1.76,2.9)	(2.14,3.71)	(1.37,2.23)	(1.1,1.57)	(1.28,2.31)	(2.67,8.26)	(2.58,7.21)	(3.97,6.99)
R-Clb	0.44	1	1.25	0.78	0.58	0.76	2.06	1.89	2.33
	(0.34,0.57)	(1,1)	(0.87,1.8)	(0.55,1.1)	(0.43,0.79)	(0.52,1.11)	(1.26,3.4)	(1.23,2.91)	(1.84,2.97)
Benda	0.35	0.8	1	0.62	0.46	0.61	1.65	1.51	1.87
	(0.27,0.47)	(0.55,1.16)	(1,1)	(0.43,0.9)	(0.34,0.64)	(0.41,0.91)	(0.9,3.08)	(0.85,2.69)	(1.26,2.78)
O-Clb	0.57	1.29	1.6	1	0.74	0.98	2.64	2.43	3.01
	(0.45,0.73)	(0.91,1.81)	(1.11,2.31)	(1,1)	(0.55,1.01)	(0.66,1.43)	(1.45,4.9)	(1.41,4.26)	(2.05,4.35)
F	0.76	1.73	2.15	1.34	1	1.32	3.55	3.27	4.03
	(0.64,0.91)	(1.27,2.34)	(1.55,2.97)	(0.99,1.82)	(1,1)	(0.94,1.84)	(1.99,6.42)	(1.91,5.7)	(2.9,5.65)
Alm	0.58	1.31	1.64	1.02	0.76	1	2.71	2.48	3.05
	(0.43,0.78)	(0.9,1.93)	(1.1,2.45)	(0.7,1.51)	(0.54,1.07)	(1,1)	(1.45,5.08)	(1.37,4.55)	(2.05,4.62)
RFC-Lite	0.22	0.49	0.6	0.38	0.28	0.37	1	0.91	1.14
	(0.12,0.37)	(0.29,0.8)	(0.33,1.12)	(0.2,0.69)	(0.16,0.5)	(0.2,0.69)	(1,1)	(0.48,1.77)	(0.65,1.97)
R-Benda	0.23	0.53	0.66	0.41	0.31	0.4	1.09	1	1.23
	(0.14,0.39)	(0.34,0.81)	(0.37,1.18)	(0.23,0.71)	(0.18,0.52)	(0.22,0.73)	(0.56,2.08)	(1,1)	(0.75,2.02)

G-Clb	0.19 (0.14,0.25)	0.43 (0.34,0.54)	0.54 (0.36,0.8)	0.33 (0.23,0.49)	0.25 (0.18,0.35)	0.33 (0.22,0.49)	0.88 (0.51,1.55)	0.81 (0.49,1.33)	1 (1,1)
Random effects, with informative prior, model									
Clb	1 (1,1)	2.26 (1.56,3.29)	2.84 (1.94,4.17)	1.75 (1.2,2.5)	1.29 (0.97,1.65)	1.72 (1.13,2.57)	4.68 (2.35,9.32)	4.26 (2.25,8.03)	5.27 (3.51,7.78)
R-Clb	0.44 (0.3,0.64)	1 (1,1)	1.25 (0.74,2.17)	0.77 (0.45,1.3)	0.57 (0.35,0.89)	0.76 (0.44,1.29)	2.05 (1.17,3.63)	1.87 (1.15,3.12)	2.32 (1.6,3.35)
Benda	0.35 (0.24,0.52)	0.8 (0.46,1.36)	1 (1,1)	0.62 (0.36,1.03)	0.45 (0.28,0.71)	0.61 (0.34,1.06)	1.65 (0.75,3.6)	1.5 (0.72,3.12)	1.86 (1.08,3.2)
O-Clb	0.57 (0.4,0.83)	1.3 (0.77,2.21)	1.62 (0.97,2.79)	1 (1,1)	0.74 (0.46,1.15)	0.98 (0.57,1.71)	2.68 (1.23,5.92)	2.45 (1.16,5.15)	3.01 (1.76,5.24)
F	0.78 (0.61,1.03)	1.76 (1.13,2.86)	2.2 (1.41,3.58)	1.36 (0.87,2.15)	1 (1,1)	1.35 (0.83,2.18)	3.64 (1.76,7.7)	3.33 (1.69,6.59)	4.1 (2.56,6.75)
Alm	0.58 (0.39,0.89)	1.32 (0.77,2.3)	1.65 (0.94,2.93)	1.02 (0.58,1.77)	0.74 (0.46,1.21)	1 (1,1)	2.72 (1.22,6.2)	2.48 (1.19,5.36)	3.07 (1.73,5.43)
RFC-Lite	0.21 (0.11,0.43)	0.49 (0.28,0.86)	0.61 (0.28,1.33)	0.37 (0.17,0.81)	0.27 (0.13,0.57)	0.37 (0.16,0.82)	1 (1,1)	0.91 (0.42,1.94)	1.13 (0.57,2.21)
R-Benda	0.23 (0.12,0.44)	0.53 (0.32,0.87)	0.67 (0.32,1.4)	0.41 (0.19,0.86)	0.3 (0.15,0.59)	0.4 (0.19,0.84)	1.1 (0.52,2.36)	1 (1,1)	1.23 (0.66,2.28)
G-Clb	0.19 (0.13,0.28)	0.43 (0.3,0.63)	0.54 (0.31,0.92)	0.33 (0.19,0.57)	0.24 (0.15,0.39)	0.33 (0.18,0.58)	0.88 (0.45,1.75)	0.81 (0.44,1.52)	1 (1,1)

Alm alemtuzumab, *Benda* bendamustine, *Clb* chlorambucil, *CrI* credible interval, *F* fludarabine, *G-Clb* obinutuzumab + chlorambucil, *HR* hazard ratio, *O-Clb* ofatumumab + chlorambucil, *OS* overall survival, *R-Benda* rituximab + bendamustine, *R-Clb* rituximab + chlorambucil, *RFC* rituximab + fludarabine + cyclophosphamide

Table S9 Additional analysis: summary of HRs and CrIs for overall survival for all pairwise comparisons using a fixed effects and random effects, with informative prior, model

	HR (CrIs)						
	Clb	**R-Clb**	**Benda**	**O-Clb**	**F**	**R-Benda**	**G-Clb**
Fixed effects model							
Clb	1 (1, 1)	1.66 (1.06, 2.6)	1.31 (0.89, 1.92)	1.11 (0.7, 1.76)	1.18 (0.95, 1.47)	1.66 (0.76, 3.67)	2.07 (1.3, 3.3)
R-Clb	0.6 (0.38, 0.95)	1 (1, 1)	0.79 (0.44, 1.42)	0.67 (0.36, 1.25)	0.71 (0.43, 1.17)	1 (0.52, 1.97)	1.25 (0.81, 1.91)
Benda	0.76 (0.52, 1.12)	1.27 (0.71, 2.3)	1 (1, 1)	0.85 (0.47, 1.51)	0.9 (0.59, 1.4)	1.27 (0.54, 3.05)	1.58 (0.88, 2.84)
O-Clb	0.9 (0.57, 1.43)	1.5 (0.8, 2.81)	1.18 (0.66, 2.14)	1 (1, 1)	1.06 (0.64, 1.77)	1.51 (0.61, 3.8)	1.87 (0.99, 3.57)
F	0.85 (0.68, 1.06)	1.41 (0.85, 2.34)	1.11 (0.71, 1.7)	0.94 (0.57, 1.56)	1 (1, 1)	1.41 (0.62, 3.2)	1.76 (1.05, 2.91)
R-Benda	0.6 (0.27, 1.32)	1 (0.51, 1.91)	0.79 (0.33, 1.87)	0.66 (0.26, 1.64)	0.71 (0.31, 1.62)	1 (1, 1)	1.25 (0.56, 2.73)
G-Clb	0.48 (0.3, 0.77)	0.8 (0.52, 1.24)	0.63 (0.35, 1.13)	0.54 (0.28, 1.01)	0.57 (0.34, 0.95)	0.8 (0.37, 1.78)	1 (1, 1)
Random effects, with informative prior, model							
Clb	1 (1, 1)	1.66 (1, 2.79)	1.3 (0.82, 2.09)	1.1 (0.65, 1.82)	1.17 (0.82, 1.61)	1.7 (0.69, 4.01)	2.07 (1.24, 3.47)
R-Clb	0.6 (0.36, 1)	1 (1, 1)	0.78 (0.39, 1.59)	0.66 (0.32, 1.37)	0.7 (0.37, 1.26)	1.01 (0.49, 2.07)	1.25 (0.75, 2.05)
Benda	0.77 (0.48, 1.22)	1.28 (0.63, 2.59)	1 (1, 1)	0.84 (0.42, 1.69)	0.9 (0.5, 1.58)	1.31 (0.48, 3.5)	1.59 (0.78, 3.16)
O-Clb	0.91 (0.55, 1.53)	1.51 (0.73, 3.15)	1.18 (0.59, 2.39)	1 (1, 1)	1.06 (0.57, 1.93)	1.54 (0.55, 4.26)	1.89 (0.9, 3.94)
F	0.86 (0.62, 1.21)	1.43 (0.79, 2.68)	1.11 (0.63, 2.02)	0.94 (0.52, 1.76)	1 (1, 1)	1.44 (0.56, 3.67)	1.77 (0.96, 3.28)

R-Benda	0.59 (0.25, 1.45)	0.99 (0.48, 2.03)	0.77 (0.29, 2.1)	0.65 (0.23, 1.82)	0.69 (0.27, 1.79)	1 (1, 1)	1.23 (0.51, 2.98)
G-Clb	0.48 (0.29, 0.81)	0.8 (0.49, 1.33)	0.63 (0.32, 1.27)	0.53 (0.25, 1.11)	0.57 (0.3, 1.04)	0.82 (0.34, 1.96)	1 (1, 1)

Benda bendamustine, *Clb* chlorambucil, *CrI* credible interval, *F* fludarabine, *G-Clb* obinutuzumab + chlorambucil, *HR* hazard ratio, *O-Clb* ofatumumab + chlorambucil, *R-Benda* rituximab + bendamustine, *R-Clb* rituximab + chlorambucil

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