Supplemental material

Contents

A description of cure models

The traditional survival models (such as Cox regression) assume that all patients will eventually experience the event of interest. That is, all the cases in the sample that have not experienced the event, are due to the short follow-up time. Hence, all those cases are considered censored. To this end, in order to model the survival probability at a given timepoint t, the mathematical formulation is $S(t) = 1 - P(t)$, where $S(t)$ is the probability that a subject does not experience the event until time t and $P(t)$ the probability that a subject experiences the event before time t.

Although the hypothesis that all subjects will eventually experience the event is reasonable when investigating risk factors associated with the time to death, it does not always hold. For example, not all patients will develop a second malignancy during their lifetime. In those cases, the total population comprises of two sub-populations: the susceptible/uncured (cases that will eventually experience the event) and the non-susceptible/cured (cases that will never experience the event). As a result, the mathematical formulation becomes $S(t) = (1 - p) + pS_s(t)$, where $S(t)$ is the probability that a subject does not experience the event until time t, p the probability that a subject is susceptible, and $S_s(t)$ the probability that a **susceptible** subject does not experience the event until time t. The above formulation actually means that the probability of a subject to not experience the event until time t is 1, if the subject is not susceptible, and $S_s(t)$, otherwise.

The main advantages of the cure rate models include:

1) When examining the risk factor, they tell whether the risk factor is associated with the probability of the event to occur and whether it is associated with the until this happens. For example, perhaps males would have a higher probability of experiencing an event but no difference in the time until this happens, and vice versa.
2) They give better estimates. The traditional Cox model may overestimate the actual times since it assumes that all subjects will experience the event, but at very long times.
3) The clinician obtains a better understanding of the impact of the risk factors on the outcome of a disease.
4) The Kaplan-Meier estimator is inconsistent in the right tail when there is a plateau.

In the literature, there are many statistical methods for estimating the risk factors associated with the risk of experiencing the event and the time until that happens. In our models, we used to logit link function for the former but no specific distribution for the latter. For a more comprehensive analysis of those models, the readers are referred to a review of the topic by Amico et al.

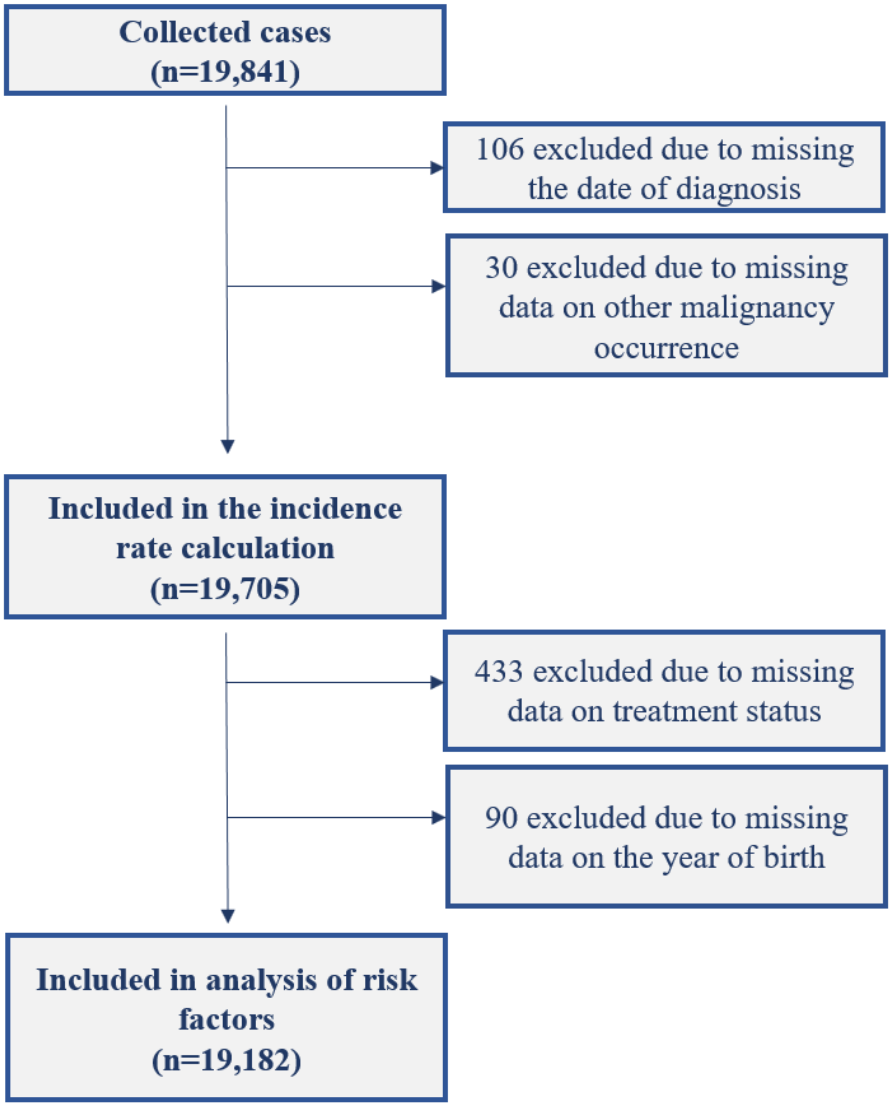
1. Amico M, Van Keilegom I. Cure models in survival analysis. *Annu Rev Stat Appl*. 2018;5:311-342

Data collection methods

We specifically designed a template for collecting all project-related information.

We sent the template to all investigators participated in the study and ask them to provide data on consecutive sets of patients diagnosed with CLL/small lymphocytic lymphoma (SLL) or high-count CLL-like monoclonal B-cell lymphocytosis (MBL) between 2000-2016. After the initial data collection, we run specifically designed validation tools to assess for inconsistencies, missing data and detect any potential bias in reporting. Only when all detected issues were resolved in collaboration with the respective investigators, we consider a dataset ready for analyses.

Figure 1. Flow diagram for study participants.



Similar to the overall population, the 433 patients that were excluded due to missing data on treatment status had a median age of 60 years and 258/433 (58·2%) were males. Most of these cases (422/433, 97·5%) were labeled as loss of contact, and thus they had a very short follow-up time.

Supplemental Table 1. Types of CLL-directed treatment at each line of treatment.

Type of treatment	1st line		2nd line		3rd line		4th line	
	N	%	N	%	N	%	N	%
FC +/- R	3,117	31·2	733	17·7	17·6	9·1	70	6
Chlorambucil +/- Anti- CD20 antibodies	2,646	26·5	407	9·9	9·8	6·7	56	4·8
Other Chemotherapy	1,181	11·8	216	5·1	5·2	4·7	54	4·6
Bendamustine +/- Anti- CD20 antibodies	1,172	11·7	774	18·5	18·6	14·7	139	11·9
Other Chemoimmunotherapy	798	8	483	11·6	11·6	12·2	166	14·2
BTKi +/- Anti- CD20 antibodies	507	5·1	726	17·6	17·5	22·5	272	23·3
Anti-CD20 antibodies monotherapy	235	2·4	271	6·5	6·5	8·4	113	9·7
Steroids only	115	1·2	82	2	2	2·2	32	2·7
BCL2i +/- Anti- CD20	75	0·8	175	4·3	4·2	6·8	104	8·9
Alemtuzumab	48	0·5	89	2·1	2·1	3·6	39	3·3
PI3K inhibitors + Anti- CD20 antibodies	45	0·5	105	2·5	2·5	5·8	67	5·8
BTKi+Venetoclax +/- Anti- CD20 antibodies	28	0·3	2	0	0	0·1	6	0·5
Other, unspecified	14	0·1	74	1·8	1·8	1·8	27	2·3
RT	3	0	5	0·1	0·1	0·3	1	0·1
Splenectomy	6	0·1	4	0·1	0·1	0·1	1	0·1
Allo-HCT	1	0	14	0·3	0·3	1	17	1·5
CAR-T therapy	0	0	0	0	0	0	1	0·1
Missing	155	1·5						

FC +/- R Fludarabine, cyclophosphamide with or without rituximab, *BTKi* Bruton's tyrosine kinase inhibitor, *BCL2i* B-cell lymphoma 2 inhibitor, *PI3K* Phosphatidylinositol-3 kinase, *RT* Radiation therapy, *Allo-HCT* Allogeneic hematopoietic cell transplantation, *CAR-T* Chimeric antigen receptor T-cell.

Supplemental table 2. Other hematological malignancies diagnosed after CLL diagnosis (excluding Richter transformation and B cell prolymphocytic leukemia).

Diagnosis	**N=342**	**%**
MDS	84	24·6
Plasma cell disorders	42	12·3
MM	*26*	*7·6*
MGUS	*11*	3·2
Other plasma cell disorders	*5*	*1·5*
MPN	41	12
PV	*11*	*3·2*
ET	*9*	*2·6*
MF	*18*	*5·3*
Other MPN	*3*	*0·9*
AML	39	11·4
MZL	22	6·4
EMZL	*9*	*2·6*
SMZL	*8*	*2·3*
nodal MZL	*5*	*1·5*
T or NK NHL	25	7·3
Other, *unspecified*	21	6·1
Other B-NHL	16	4·7
FL	7	2
HCL	1	0·3
CML	18	5·3
ALL	8	2·3
B-ALL	*7*	*2*
T-ALL	*1*	*0·3*
MDS/MPN	4	1·2
CMML	4	1·2
WM	3	0·9
MCL	3	0·9
HDCN	3	0·9
Mastocytosis	1	0·3

MDS myelodysplastic syndrome, *MM* multiple myeloma, *MGUS* monoclonal gammopathy of undetermined significance, *MPN* myeloproliferative neoplasm, *PV* polycythemia vera, *ET* essential thrombocythaemia, *MF* myelofibrosis, *AML* acute myeloid leukemia, *MZL* marginal zone lymphoma, *EMZL* extranodal marginal zone lymphoma, *SMZL* splenic marginal zone lymphoma, *NHL* non-Hodgkin lymphoma, *FL* follicular lymphoma , *HCL* hairy cell leukemia, *CML* chronic myeloid leukemia, *ALL* acute lymphocytic leukemia , *MDS/MPN* myelodysplastic syndrome/myeloproliferative neoplasm, *CMML* chronic myelomonocytic leukemia, *WM* waldenstrom macroglobulinemia, *MCL* mantle cell lymphoma, *HDCN* histiocytic and dendritic cell neoplasm.

Supplemental table 3. Non-hematological second primary malignancies diagnosed before and after CLL diagnosis.

Site of non-hematological second primary malignancy	**N**	**%**
Non-melanoma skin	987	25·8
Prostate	530	13·9
Colon	382	10·1
Breast	343	9
Bronchus and lung	262	6·9
Melanoma of skin	190	5·3
Bladder	196	5·1
Kidney	150	3·9
Thyroid gland	90	2·4
Stomach	80	2·1
Pancreas	53	1·4
Malignant neoplasms of lip, oral cavity and pharynx	52	1·4
Liver	44	1·2
Malignant neoplasm - primary site unknown	39	1
Brain	38	1
Ovary	37	1
Corpus uteri	34	0·9
Other connective and soft tissue	31	0·8
Cervix uteri	30	0·8
Larynx	25	0·7
Meninges	22	0·6
Other endocrine glands and related structures	22	0·6
Oesophagus	16	0·4
Intrahepatic bile ducts	15	0·4
Kaposi sarcoma	14	0·4
Ureter	13	0·3
Renal pelvis	11	0·3
Small intestine	11	0·3
Peripheral nerves and autonomic nervous system	10	0·3
Eye and adnexa	8	0·2
Bone and articular cartilage	7	0·2
Gallbladder	7	0·2
Vulva	7	0·2
Mesothelioma	6	0·2
Retroperitoneum and peritoneum	6	0·2
Testis	6	0·2
Other and unspecified female genital organs	4	0·1
Penis	4	0·1
Thymus	4	0·1
Nasal cavity	3	0·1
Spinal cord - cranial nerves and other parts of central nervous system	3	0·1
Adrenal gland	2	0·1
Other and unspecified male genital organs	2	0·1
Accessory sinuses	1	0
Middle ear	1	0
Trachea	1	0
Vagina	1	0

Supplemental table 4. Univariate analyses of risk factors for AML and MDS after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	1·99	1·16-3·41	0·013	0·85	0·35-2·06	0·714
Binet stage at diagnosis	B	1·41	0·95-2·08	0·085	2·05	1·2-3·51	0·008
	C	1·58	0·53-4·73	0·41	1·94	1·04-3·62	0·036
IGHV gene status	Unmutated[a]	0·62	0·37-1·04	0·069	1·95	1·08-3·5	0·026
del(13q)	Positive	0·85	0·44-1·61	0·612	0·81	0·35-1·85	0·609
del(11q)	Positive	0·33	0·11-0·99	0·049	1·61	0·17-15·07	0·675
del(17p)	Positive	1·31	0·59-2·9	0·508	2·47	1·44-4·22	0·001
TP53 mutation status	Unmutated	1·19	0·53-2·65	0·672	0·49	0·26-0·92	0·026
trisomy 12	Positive	2·88	0·66-12·51	0·158	1·01	0·27-3·76	0·987
Treatment status (*before MDS/AML*)	Treated	1·01	0·49-2·08	0·985	2·95	1·88-4·63	<0·001
Age at diagnosis		1·03	1·02-1·05	<0·001	1	0·99-1·02	0·395
FC +/- R at any line *(before MDS/AML)*	Yes	0·89	0·63-1·26	0·513	3·7	2·79-4·91	<0·001
Bendamustine at any line *(before MDS/AML)*	Yes	0·45	0·13-1·55	0·21	3·06	1·22-7·69	0·017
Chlorambucil at any line *(before MDS/AML)*	Yes	0·66	0·3 - 1·43	0·28	1·61	0·62 - 4·17	0·32
Total lines *(before MDS/AML)*		0·7	0·56 – 0·88	0·002	1·65	1·35 – 2·03	<0·001
Age at the time of malignancy		1·04	1·02-1·06	<0·001	1·05	1·03-1·06	<0·001

AML acute myeloid leukemia, *MDS* myelodysplastic syndrome, *OR* odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 5. Univariate and multivariate analyses of risk factors for MDS after CLL diagnosis.

Univariate analyses							
Risk factor	**Category**	**HR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Sex assigned at birth	Male	1·98	1·02-3·85	0·043	0·75	0·27-2·07	0·574
Binet stage at diagnosis	B	1·42	0·91-2·23	0·126	1·74	0·86-3·55	0·127
	C	1·53	0·52-4·52	0·444	2·04	1·32-3·13	0·001
IGHV gene status	Unmutated[a]	0·62	0·3-1·26	0·182	2·16	1·09-4·26	0·027
del(13q)	Positive	0·7	0·37-1·32	0·273	0·87	0·34-2·25	0·781
del(11q)	Positive	0·52	0·14-1·94	0·33	1·48	0·24-9·18	0·672
del(17p)	Positive	1·63	0·58-4·55	0·35	2·17	1·07-4·41	0·032
TP53 mutation status	Unmutated	1·06	0·4-2·78	0·91	0·45	0·18-1·12	0·085
trisomy 12	Positive	1·85	0·73-4·7	0·196	1·79	0·46-7·03	0·402
Treatment status (*before MDS/AML*)	Treated	1·25	0·64-2·42	0·513	2·63	1·72-4·02	<0·001
Age at diagnosis		1·04	1·02-1·06	<0·001	1·01	1-1·02	0·049
FC +/- R at any line *(before MDS/AML)*	Yes	1·1	0·7-1·71	0·686	3·19	2·03-5·01	<0·001
Bendamustine at any line *(before MDS/AML)*	Yes	0·67	0·32-1·42	0·301	2·95	1·96-4·43	<0·001
Total lines *(before MDS/AML)*		0·76	0·58-0·98	0·036	1·6	1·31-1·96	<0·001
Age at the time of MDS		1	0·98-1·01	0·77	1·01	0·99-1·02	0·47
Multivariate analyses							
Risk factor	**Category**	**HR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Age at diagnosis		-	-	-	1·02	1·01-1·03	0·02
FC +/- R at any line *(before MDS/AML)*	Yes	1·82	1·05-3·13	0·032	3·09	1·44-6·6	0·004

MDS myelodysplastic syndrome, *OR* odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 6. Univariate* and multivariate analyses of risk factors for AML after CLL diagnosis.

Univariate analyses							
Risk factor	**Category**	**HR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Sex assigned at birth	Male	1·02	0·41-2·51	0·973	3·04	1·51-6·1	0·002
IGHV gene status	Unmutated[a]	0·55	0·16-1·96	0·361	2·66	0·23-30·12	0·43
TP53 aberrations	Present	0·86	0·15-4·75	0·859	11·46	1·46-89·91	0·02
Treatment status (*before MDS/AML*)	Treated	0·93	0·45-1·91	0·833	2·99	1·45-6·14	0·003
Age at diagnosis		1·01	0·97-1·05	0·794	1	1-1	0·759
FC +/- R at any line *(before MDS/AML)*	Yes	0·68	0·35-1·31	0·25	5·56	3·45-8·96	<0·001
Bendamustine at any line *(before MDS/AML)*	Yes	0·67	0·32-1·42	0·301	2·95	1·96-4·43	<0·001
Total lines *(before MDS/AML)*		0·63	0·41-0·97	0·035	1·36	1·06-1·76	0·016
Age at the time of AML		0·97	0·95-0·99	0·012	0·99	0·99-1	0·004
Multivariate analyses							
Risk factor	**Category**	**HR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Sex assigned at birth	Male	-	-	-	2·15	0·93-4·97	0·07
FC +/- R at any line *(before MDS/AML)*	Yes	-	-	-	4·55	2·55-8·14	<0·001
Age at the time of AML		0·97	0·94-1	0·08	-	-	-

AML acute myeloid leukemia, *OR* odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

*A restricted number of risk factors was assessed due to the small number of cases with AML.

Supplemental table 7. Univariate analyses of risk factors for Hematological malignancies (excluding Richter transformation, AML and MDS) after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	0·73	0·44-1·2	0·21	1·44	0·86-2·41	0·171
Binet stage at diagnosis	B	0·97	0·52-1·83	0·93	1·75	0·9-3·4	0·1
	C	0·9	0·3-2·69	0·85	1·74	0·33-9·27	0·52
IGHV gene status	Unmutated[a]	1·29	0·62-2·68	0·498	1·37	0·5-3·73	0·543
del(13q)	Positive	0·3	0·14-0·67	0·003	1·67	0·98-2·85	0·06
del(11q)	Positive	1·54	0·79-3·02	0·204	1·23	0·63-2·42	0·546
del(17p)	Positive	1·27	0·42-3·84	0·672	1·07	0·3-3·83	0·917
TP53 mutation status	Unmutated	1	0·34-2·97	0·995	4·14	1·21-14·14	0·024
trisomy 12	Positive	0·59	0·22-1·53	0·277	1·76	0·65-4·76	0·264
Treatment status (before malignancy)	Treated	0·23	0·15-0·35	<0·001	1·64	1·11-2·44	0·013
Age at diagnosis		1·04	1·02-1·05	<0·001	1	0·98-1·02	0·904
FCR +/- R at any line (before malignancy)		0·35	0·23-0·53	<0·001	2·23	1·27-3·92	0·005
Total lines (before malignancy)		0·64	0·52-0·79	<0·001	1·29	1·04-1·6	0·019
Age at the time of malignancy		1·03	1·02-1·04	<0·001	1·06	1·04-1·07	<0·001

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 8. Univariate analyses of risk factors for all non-Hematological malignancies (excluding non-melanoma skin cancers) after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	0·88	0·62-1·26	0·489	1·91	1·42-2·58	<0·001
Binet stage at diagnosis	B	0·57	0·36-0·89	0·014	2·12	1·07-4·18	0·03
	C	0·69	0·41-1·17	0·169	2·59	1·39-4·84	0·003
IGHV gene status	Unmutated[a]	0·61	0·44-0·87	0·005	2·18	1·26-3·74	0·005
del(13q)	Positive	0·78	0·46-1·32	0·357	1·15	0·7-1·9	0·58
del(11q)	Positive	0·64	0·24-1·74	0·382	1·51	0·45-5·09	0·504
del(17p)	Positive	0·74	0·38-1·45	0·381	1·28	0·38-4·37	0·532
TP53 mutation status	Unmutated	1·32	0·44-3·92	0·618	1·1	0·34-3·61	0·872
trisomy 12	Positive	1·2	0·67-2·13	0·54	0·93	0·57-1·51	0·762
Treatment status (before malignancy)	Treated	0·31	0·23-0·41	<0·001	1·62	1·17-2·26	0·004
Age at diagnosis		1·03	1·01-1·04	<0·001	1·01	0·99-1·02	0·232
FC +/- R at any line (before malignancy)		0·35	0·26-0·46	<0·001	3·16	2·22-4·5	<0·001
Total lines (before malignancy)		0·79	0·71-0·78	<0·001	1·16	1·02-1·32	0·03
Age at the time of malignancy		0·98	0·97-0·98	<0·001	1·13	1·12-1·14	<0·001

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 9. Univariate analyses of risk factors for bladder cancer after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	2·72	1·86-3·96	<0·001	5·25	3·35-8·25	<0·001
Binet stage at diagnosis	B	0·76	0·49-1·17	0·21	0·54	0·23-1·24	0·15
	C	1·54	1·07-2·22	0·02	0·87	0·48-1·56	0·64
IGHV gene status	Unmutated[a]	0·97	0·18-5·2	0·976	0·53	0·15-1·83	0·314
del(13q)	Positive	0·72	0·43-1·2	0·21	1·62	0·99-2·65	0·054
del(11q)	Positive	1·04	0·57-1·92	0·893	1·41	0·41-4·82	0·586
del(17p)	Positive	0·88	0·49-1·58	0·666	1·38	0·46-4·14	0·567
TP53 mutation status	Unmutated	1·3	0·41-4·09	0·651	1·48	0·16-13·56	0·728
trisomy 12	Positive	2·16	0·53-8·89	0·284	0·35	0·17-0·7	0·003
Treatment status (before malignancy)	Treated	0·26	0·1-0·64	0·003	1·08	0·45-2·61	0·863
Age at diagnosis		1·03	1·02-1·04	<0·001	1·01	0·99-1·03	0·446
FC +/- R at any line (before malignancy)		0·45	0·27-0·74	0·002	1·42	0·48-4·24	0·529
Total lines (before malignancy)		0·79	0·67-0·94	0·008	1·07	0·83-1·38	0·603
Age at the time of malignancy		1·04	1·03-1·05	<0·001	1·03	1·03-1·04	<0·001

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 10. Univariate analyses of risk factors for breast cancer after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	0·12	0·06-0·25	<0·001	0·25	0·22-0·29	<0·001
Binet stage at diagnosis	B	0·96	0·59-1·58	0·88	0·7	0·36-1·34	0·28
	C	1·42	0·62-3·24	0·41	0·54	0·18-1·56	0·25
IGHV gene status	Unmutated[a]	0·43	0·24-0·76	0·004	1·89	1·25-2·86	0·002
del(13q)	Positive	0·84	0·36-1·94	0·683	1·18	0·45-3·07	0·739
del(11q)	Positive	0·65	0·26-1·66	0·368	0·42	0·17-1·09	0·074
del(17p)	Positive	0·67	0·1-4·33	0·677	0·21	0·02-1·97	0·172
TP53 mutation status	Unmutated	0·55	0·13-2·32	0·417	1·81	1-3·25	0·048
trisomy 12	Positive	0·86	0·56-1·31	0·477	0·57	0·21-1·5	0·254
Treatment status (before malignancy)	Treated	0·6	0·29-1·26	0·18	0·36	0·18-0·71	0·004
Type of treatment (before malignancy)	Chemotherapy or CIT				0·29	0·18 - 0·49	< 0·001
Age at diagnosis		1·01	1-1·03	0·097	1	0·99-1·01	0·665
Total lines (before malignancy)		0·82	0·64-1·03	0·093	0·79	0·67-0·93	0·004
Age at the time of malignancy		1·02	1·01-1·03	0·042	1·02	1·01-1·03	<0·001

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *CIT* chemoimmunotherapy.

[a]Unmutated: ≥98% germline identity.

Supplemental table 11. Univariate analyses and multivariate analyses of risk factors for female breast cancer after CLL diagnosis.

Univariate analyses							
Risk factor	**Category**	**HR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Binet stage at diagnosis	B	0·85	0·46-1·59	0·618	1·24	0·6-2·55	0·568
	C	1·34	0·64-2·78	0·441	0·91	0·16-5·25	0·916
IGHV gene status	Unmutated[a]	0·32	0·14-0·72	0·006	3·03	1·69-5·43	<0·001
del(13q)	Positive	0·71	0·31-1·66	0·434	1·21	0·49-2·96	0·678
del(11q)	Positive	0·46	0·16-1·31	0·144	1·16	0·17-8·08	0·881
del(17p)	Positive	0·92	0·37-2·3	0·864	0·16	0·04-0·62	0·008
TP53 mutation status	Unmutated	0·55	0·17-1·77	0·314	2·81	0·54-14·48	0·218
trisomy 12	Positive	0·73	0·37-1·45	0·368	0·79	0·14-4·4	0·789
Treatment status (before malignancy)	Treated	0·58	0·26-1·28	0·178	0·46	0·21-1·01	0·052
Type of treatment (before malignancy)	Chemotherapy or CIT	0·88	0·37-2·1	0·775	0·4	0·27-0·78	0·007
Age at diagnosis		1·02	0·99-1·04	0·251	0·99	0·97-1·01	0·350
Total lines (before malignancy)		0·85	0·6-1·21	0·37	0·8	0·62-1·02	0·076
Age at the time of malignancy		1	0·96-1·05	0·88	0·96	0·92-1	0·036
Multivariate analyses							
Risk factor	**Category**	**HR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Type of treatment (before malignancy)	Chemotherapy or CIT	-	-	-	0·4	0·19-0·85	0·016

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *CIT* chemoimmunotherapy.

[a]Unmutated: ≥98% germline identity.

Supplemental table 12. Univariate analyses of risk factors for colon cancer after CLL diagnosis.

Risk factor	**Category**	**HR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Sex assigned at birth	Male	0·98	0·58-1·65	0·939	1·53	0·79-2·96	0·211
Binet stage at diagnosis	B	0·93	0·38-2·24	0·86	0·96	0·38-2·47	0·94
	C	0·91	0·41-2	0·81	1·33	0·28-6·24	0·72
IGHV gene status	Unmutated[a]	2·18	1-4·76	0·049	0·64	0·36-1·11	0·112
del(13q)	Positive	0·57	0·32-1	0·049	1·05	0·58-1·89	0·874
del(11q)	Positive	1·15	0·64-2·05	0·647	0·43	0·17-1·13	0·086
del(17p)	Positive	0·75	0·5-1·13	0·173	1·06	0·18-6·25	0·944
TP53 mutation status	Unmutated	1·03	0·49-2·15	0·932	1·24	0·17-8·95	0·834
trisomy 12	Positive	0·8	0·31-2·09	0·655	1·23	0·55-2·76	0·616
Treatment status (before malignancy)	Treated	0·48	0·26-0·86	0·014	0·64	0·48-0·86	0·003
Age at diagnosis		1·02	1·01-1·03	<0·001	1·03	1·01-1·05	0·001
FC +/- R at any line (before malignancy)		0·49	0·27-0·89	0·019	1·07	0·56-2·03	0·838
Total lines (before malignancy)		0·82	0·7-0·96	0·013	0·9	0·74-1·1	0·323
Age at the time of malignancy		1·02	1·02-1·03	<0·001	1·09	1·07-1·11	<0·001

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 13. Univariate analyses of risk factors for bronchus and lung cancer after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	1·02	0·69-1·5	0·921	2·65	1·89-3·72	<0·001
Binet stage at diagnosis	B	0·38	0·21-0·66	<0·001	3·21	2·14-4·82	<0·001
	C	0·74	0·43-1·27	0·27	2·89	1·45-4·6	0·001
IGHV gene status	Unmutated[a]	0·68	0·39-1·19	0·178	2·8	1·85-4·24	<0·001
del(13q)	Positive	0·65	0·33-1·26	0·198	1·28	0·59-2·78	0·532
del(11q)	Positive	0·72	0·4-1·3	0·276	2·28	1·04-4·97	0·039
del(17p)	Positive	0·37	0·09-1·54	0·173	2·08	0·16-26·42	0·572
TP53 mutation status	Unmutated	0·6	0·07-5·23	0·643	1·03	0·25-4·3	0·963
trisomy 12	Positive	2·62	1·39-4·92	0·003	0·49	0·28-0·85	0·011
Treatment status (before malignancy)	Treated	0·33	0·24-0·44	<0·001	1·63	1·16-2·28	0·005
Age at diagnosis		1·04	1·01-1·07	0·004	1	0·98-1·01	0·57
FC +/- R at any line (before malignancy)		0·34	0·2-0·59	<0·001	2·46	1·34-4·52	0·004
Total lines (before malignancy)		0·67	0·58-0·76	<0·001	1·36	1·17-1·6	<0·001
Age at the time of malignancy		1·02	1·02-1·03	<0·001	1·05	1·04-1·06	<0·001

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 14. Univariate analyses of risk factors for melanoma after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	1·11	0·77-1·61	0·566	1·9	1·4-2·57	<0·001
Binet stage at diagnosis	B	1·3	0·76-2·23	0·34	1·18	0·44-3·16	0·74
	C	1·71	0·98-2·99	0·06	1·75	1·15-2·64	0·008
IGHV gene status	Unmutated[a]	1·07	0·59-1·93	0·83	1·46	0·93-2·3	0·102
del(13q)	Positive	1·64	0·47-5·66	0·434	0·57	0·17-1·93	0·366
del(11q)	Positive	1·39	0·64-3·04	0·408	0·35	0·24-0·52	<0·001
del(17p)	Positive	0·48	0·03-6·68	0·583	2·59	0·54-12·44	0·235
TP53 mutation status	Unmutated	0·68	0·24-1·92	0·466	1·85	0·72-4·73	0·199
trisomy 12	Positive	1·15	0·29-4·58	0·838	1·32	0·34-5·09	0·69
Treatment status (before malignancy)	Treated	0·45	0·24-0·82	0·009	1·39	0·78-2·48	0·259
Age at diagnosis		1·03	1·01-1·05	0·001	1·01	0·99-1·02	0·256
FC +/- R at any line (before malignancy)		0·65	0·35-1·18	0·157	2·08	1·51-2·87	<0·001
Total lines (before malignancy)		0·75	0·64-0·88	<0·001	1·26	1-1·58	0·049
Age at the time of malignancy		1·03	1·02-1·04	<0·001	1·04	1·02-1·06	<0·001

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 15. Univariate analyses of risk factors for non-melanoma skin cancers after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	0·93	0·56-1·55	0·772	2·71	1·5-4·87	0·001
Binet stage at diagnosis	B	1·39	0·61-3·16	0·43	1·02	0·48-2·14	0·97
	C	2·25	0·78-6·53	0·14	0·96	0·39-2·36	0·93
IGHV gene status	Unmutated[a]	1·09	0·59-2·01	0·782	1·37	0·58-3·2	0·474
del(13q)	Positive	1·15	0·64-2·08	0·644	0·89	0·47-1·72	0·739
del(11q)	Positive	0·82	0·32-2·09	0·684	2·13	0·65-6·97	0·213
del(17p)	Positive	0·54	0·21-1·39	0·199	3·8	1·26-11·49	0·018
TP53 mutation status	Unmutated	1·15	0·49-2·72	0·75	1·27	0·39-4·13	0·686
trisomy 12	Positive	1·5	0·83-2·72	0·184	0·79	0·44-1·42	0·429
Treatment status (before malignancy)	Treated	0·51	0·33-0·8	0·004	2	1·17-3·43	0·012
Age at diagnosis		1·03	1·02-1·05	<0·001	1·03	1·01-1·05	<0·001
FC+/- R at any line (before malignancy)		0·33	0·2-0·55	<0·001	4·62	1·93-11·05	0·001
Total lines (before malignancy)		0·86	0·76-0·96	0·01	1·34	1·15-1·56	<0·001
Age at the time of malignancy		1·02	1·01-1·03	<0·001	1·12	1·1-1·14	<0·001

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 16. Univariate analyses of risk factors for prostate cancer after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Binet stage at diagnosis	B	0·71	0·22-2·31	0·56	1·57	0·52-4·72	0·42
	C	0·35	0·12-0·99	0·049	5·4	1·75-16·68	0·003
IGHV gene status	Unmutated[a]	0·34	0·15-0·77	0·01	3·42	1·69-6·94	0·001
del(13q)	Positive	0·75	0·4-1·42	0·377	1·1	0·59-2·05	0·765
del(11q)	Positive	1·28	0·73-2·26	0·391	0·86	0·43-1·74	0·681
del(17p)	Positive	0·89	0·63-1·25	0·5	1·96	1·14-3·38	0·015
TP53 mutation status	Unmutated	1·27	0·7-2·31	0·425	3·39	0·71-16·11	0·125
trisomy 12	Positive	1·19	0·46-3·08	0·722	0·81	0·46-1·45	0·479
Treatment status (before malignancy)	Treated	0·22	0·11-0·44	<0·001	2·11	1·12-3·97	0·021
Age at diagnosis		1·06	1·03-1·08	<0·001	0·98	0·96-1	0·078
FC +/- R at any line (before malignancy)		0·3	0·12-0·73	0·008	3·81	1·59-9·15	0·003
Total lines (before malignancy)		0·82	0·69-0·97	0·023	1·15	1·01-1·32	0·035
Age at the time of malignancy		1·02	1·02-1·03	<0·001	1·05	1·04-1·07	<0·001

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 17. Most common other malignancies diagnosed before and after CLL diagnosis.

Type of solid tumor	Diagnosed before CLL		Diagnosed after CLL		Total
	N	%	N	%	
Bladder	69	36·7	119	63·3	188
Breast	185	55·6	148	44·4	333
Bronchus and Lung	38	14·8	219	85·2	257
Colon	130	34·8	244	65·2	374
Kidney	49	33·8	96	66·2	145
Melanoma	55	29·7	130	70·3	185
Non-melanoma skin	32	14·9	754	85·1	886
Prostate	196	38·6	312	61·4	508
MDS/AML	10	7	131	93	141
Pancreas	7	13·2	46	86·8	53
Stomach	18	24	57	76	75
Thyroid gland	49	57·6	36	42·4	85
Lip, oral and pharynx	7	15·9	37	84·1	44
Lymphoma*#	28	3·9	691	96·1	719

AML acute myeloid leukemia, *MDS* myelodysplastic syndrome.

*Including Richter transformation.

#Not including hairy cell leukemia and B cell prolymphocytic leukemia

Supplemental table 18. Characteristics of all cases that developed AML or MDS.

Patient characteristics		AML (n=42)	MDS (n=90) or MDS/MPN (n=5) or CMML(n=4) (n=99)
Sex assigned at birth	Female	10 (23·8%)	34 (34·3%)
	Male	32 (76·2%)	65 (65·7%)
After CLL diagnosis	Yes	39 (93%)	92 (93%)
Median age (IQR)		66·5 (57-71·5)	70 (60-76)
Treatment status	Treated	28 (66·7%)	76 (76·8%)
	Untreated	14 (33·3%)	23 (23·2%)
Treatment before AML or MDS	Yes	26 (61·9%)	73 (73·7%)
	No	16 (38·1%)	26 (26·3%)
Lines of treatment before AML or MDS	1	18 (69·2%)	47 (64·4%)
	2	7 (26·9%)	22 (30·1%)
	≥3	1 (3·9%)	4 (5·5%)
Types of first-line treatment before AML or MDS	FC+/-R	11(42·3%)	31 (42·5%)
	Bendamustine +/- Anti- CD20 antibodies	1 (3·8%)	8 (11%)
	Chlorambucil +/- Anti- CD20 antibodies	4 (15·4%)	17 (23·3%)
	Other CIT or chemotherapy	7 (26·9%)	7 (9,6%)
	Anti- CD20 antibodies	2 (7·6%)	4 (5·5%)
	PI3K inhibitors + Anti- CD20 antibodies	0	2 (2·7%)
	Other	1 (3·8%)	4 (5·5%)
Types of second-line treatment before AML or MDS	FC+/-R	5 (71·4%)	6 (27·3%)
	BTKi +/- Anti- CD20 antibodies	1 (14·3%)	4 (18·2%)
	Other CIT or chemotherapy	1 (14·3%)	2 (9·1%)
	Bendamustine +/- Anti- CD20 antibodies	0	2 (9·1%)
	Chlorambucil +/- Anti- CD20 antibodies	0	1 (4·5%)
	Anti- CD20 antibodies	0	3 (13·2%)
	Other	0	4 (18·2%)
2 lines of FC +/-R before AML or MDS	Yes	2	3

IQR interquartile range, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndrome, *MDS/MPN* myelodysplastic syndrome/myeloproliferative neoplasm, *CMML* chronic myelomonocytic leukemia, FC *+/- R* fludarabine, cyclophosphamide with or without rituximab.

Supplemental table 19. Number of patients developing MDS or AML per type of first line treatment.

Type of treatment of 1L	Median follow-up time (IQR)*	MDS/AML cases within 5 years of follow-up	Total MDS/AML cases	Cases with at least 5 years of follow-up	Total number of cases
Bendamustine +/- Anti- CD20 antibodies	3·67 (2·12-5·27)	7 (2·1%)	9 (0·8%)	332	1,172
Chlorambucil +/- Anti- CD20 antibodies	3·61 (1·68-6·62)	18 (2%)	22 (0·8%)	880	2,646
BTKi +/- Anti- CD20 antibodies	2·25 (0·97-3·79)	0	0	44	507
FC +/- R	5·18 (2·79-7·9)	32 (2·3)	42 (1·4%)	1,408	3,117

1L first line treatment, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndrome, *IQR* interquartile range, *FC +/- R* Fludarabine, cyclophosphamide with or without rituximab, *BTKi* Bruton's tyrosine kinase inhibitor.

**Beginning from the treatment initiation.*

Supplemental table 20. Baseline characteristics for treated and untreated patients.

Patient characteristics	Results	Treated		Untreated	
		N	% *or otherwise specified*	N	% *or otherwise specified*
Sex assigned at birth	Female	3,549	35	3,889	42·6
	Male	6,597	65	5,237	57·4
Age at diagnosis	Median (IQR)	64	56-71	68	60-76
Survival status	Alive	6,352	63·4	6,744	74·5
	Dead	3,672	36·6	2,307	25·5
Follow-up time (years)	Median (IQR)	6·86	4·49-10·2	5·7	3·16-9
Comorbidities at diagnosis	No	2,384	30·1	1,880	29·9
	Yes	5,527	69·9	4,400	70·1
IGHV gene status	Mutated[a]	1,835	34·3	2,400	78·6
	Unmutated[b]	3,519	65·7	655	21·4
del(13q)	Negative	3,250	54·7	1,601	49·2
	Positive	2,696	45·3	1650	50·8
del(11q)	Negative	5,096	81·4	3,237	96
	Positive	1,168	18·6	135	4
trisomy 12	Negative	4,757	80·2	2,773	86·8
	Positive	1,173	19·8	423	13·2
del(17p)	Negative	5,692	87·8	3,298	95·2
	Positive	792	12·2	166	4·8
TP53 mutation status	Mutated	504	15·3	100	8·5
	Unmutated	2,787	84·7	1,070	91·5
Other malignant neoplasms	No	7,762	76·5	7,376	80·8
	Yes	2,384	23·5	1,750	19·2
Transformation	No	8,468	93·8	7,529	99·1
	Yes	563	6·2	70	0·9

IQR interquartile range, *IGHV* immunoglobulin heavy variable.

[a]Mutated: < 98% germline identity· [b]Unmutated: ≥98% germline identity.

Supplemental table 21. Characteristics of patients with at least one other malignancy after CLL diagnosis.

Patient characteristics	Results	N	%	Missing	%
Sex assigned at birth	Female	921	31·3	0	0
	Male	2,019	68·7		
Diagnosis	CLL	2,717	92·4	0	0
	MBL	124	4·2		
	SLL	99	3·4		
Survival status	Alive	1,575	53·6	0	0
	Dead	1,365	46·4		
Comorbidities at diagnosis	No	604	26·3		
	Yes	1,690	73·7	646	22
Treatment status	Treated	1,854	63·1	0	0
	Untreated	1,086	36·9		
Type of treatment	CIT or/and chemotherapy	1,203	67·3		
	CIT or/and chemotherapy and novel agents	489	27·4		
	Only Novel agents	95	5·3	67	3·6
IGHV gene status	Mutated[a]	605	45·2		
	Unmutated[b]	734	54·8	1,522	51·8
del(13q)	Negative	888	54·7		
	Positive	735	45·3	1,317	44·8
del(11q)	Negative	1,464	85·6		
	Positive	247	14·4	1,088	44·9
trisomy 12	Negative	1,332	82·6		
	Positive	281	17·4	1,229	41·8
del(17p)	Negative	1,537	88·8		
	Positive	193	11·2	1,327	45·1
TP53 mutation status	Mutated	105	13·1		
	Unmutated	695	86·9	1,210	41·2

CIT chemoimmunotherapy, *CLL* chronic lymphocytic leukemia, *SLL* small lymphocytic lymphoma, *MBL* monoclonal B lymphocytosis, *IGHV* immunoglobulin heavy variable.

[a]Mutated: < 98% germline identity· [b]Unmutated: ≥98% germline identity.

Supplemental table 22. Other malignancies in patients treated only with novel agents.

Patient characteristics	**Results**	**N=600**	**%** **or otherwise specified**
Sex assigned at birth	Female	225	37·5%
	Male	375	62·5%
Age at diagnosis	Median (IQR)	64	57 - 71
Follow-up time from diagnosis	Median (IQR)	6·67	5·09 - 9·26
Follow-up time from novel agent initiation	Median (IQR)	2·34	1·02 - 4·09
Type of first-line novel agent	BTKi-based	477	79·5
	Venetoclax-based	75	12·5
	BTKi+Venetoclax-based	28	4·6
	PI3Ki-based	20	3·3
Other malignancies after novel agent initiation			
Non-melanoma skin cancers		30	5
Transformation	DLBCL	17	2·9
	Hodgkin's lymphoma	2	0·3
Prostate cancer		10	1·7
Bronchus and lung cancer		8	1·3
Melanoma		8	1·3
Breast cancer		4	0·7
Colon cancer		4	0·7
Kidney cancer		4	0·7
Pancreatic cancer		4	0·7
Bladder cancer		2	0·3
Brain cancer		2	0·3
Malignant neoplasm of unknown primary site		2	0·3
Cancer of other endocrine glands and related structures		2	0·3
Nodal MZL		2	0·3
Other B-NHL		1	0·2

BTKi Bruton's tyrosine kinase inhibitor, *PI3Ki* Phosphatidylinositol-3 kinase inhibitor, *DLBCL* Diffuse large B-cell lymphoma, *MZL* marginal zone lymphoma, *NHL* non-Hodgkin lymphoma.

Supplemental table 23. Characteristics of patients with RT.

Patient characteristics	Results	DLBCL or other aggressive B-NHL		HL	
		N=580	% *or otherwise specified*	N=35	% *or otherwise specified*
Sex assigned at birth	Female	207	35·7	13	37·1
	Male	373	64·3	22	62·9
Age at diagnosis (years)	Median (IQR)	63	56-70	61	51-65·5
Survival status	Alive	198	34·1	21	60
	Dead	382	65·9	14	40
Follow-up time until RT (years)	Median (IQR)	4·8	2-8·7	6·5	3·6-9·6
Comorbidities at diagnosis	No	179	38·8	10	33·3
	Yes	282	61·2	20	66·7
IGHV gene status	Mutated[a]	65	26·2	3	21·4
	Unmutated[b]	183	73·8	11	78·6
del(13q)	Negative	198	60·7	10	62·5
	Positive	128	39·3	6	37·5
del(11q)	Negative	285	81·9	15	83·3
	Positive	63	18·1	3	16·7
trisomy 12	Negative	268	83	9	56·2
	Positive	55	17	7	43·8
del(17p)	Negative	276	79·1	17	94·4
	Positive	73	20·9	1	5·6
TP53 mutation status	Mutated	40	24·2	3	27·3
	Unmutated	125	75·8	8	72·7
Treatment status	Treated	510	87·9	32	91·4
	Untreated	70	12·1	3	8·6
Treatment status before RT	Treated	397	70·3	27	79·4
	Untreated	168	29·7	7	20·6
Type of treatment before RT	CIT or/and chemotherapy	225	58·1	12	46·2
	CIT or/and chemotherapy and novel agents	152	39·2	12	46·2
	Only novel agents	10	2·6	2	7·7

RT Richter transformation, *DLBCL* Diffuse large B-cell lymphoma, *NHL* non-Hodgkin lymphoma, *HL Hodgkin's* lymphoma, *CIT* chemoimmunotherapy, *CLL* chronic lymphocytic leukemia, *IGHV* immunoglobulin heavy variable.

[a]Mutated: < 98% germline identity· [b]Unmutated: ≥98% germline identity.

Supplemental table 24. Patient characteristics according to sex assigned at birth.

Patient characteristics	Results	Female	Male
Diagnosis	CLL	7094 (38·6%)	11292 (61·4%)
	MBL	368 (46·5%)	423 (53·5%)
	SLL	218 (41·3%)	310 (58·7%)
Survival status	Alive	5506 (40·7%)	8018 (59·3%)
	Dead	2054 (34·3%)	3930 (65·7%)
Comorbidities at diagnosis	No	1572 (36·8%)	2699 (63·2%)
	Yes	3816 (38·4%)	6129 (61·6%)
Treatment status	Treated	3549 (35%)	6597 (65%)
	Untreated	3889 (42·6%)	5237 (57·4%)
Type of treatment	CIT or/and chemotherapy	2543 (35·7%)	4585 (64·3%)
	CIT or/and chemotherapy and novel agents	617 (31·8%)	1323 (68·2%)
	Only Novel agents	225 (37·5%)	375 (62·5%)
	Other	116 (35%)	215 (65%)
IGHV gene status	Mutated[a]	1676 (39·4%)	2580 (60·6%)
	Unmutated[b]	1417 (33·9%)	2763 (66·1%)
del(13q)	Negative	1716 (35·4%)	3135 (64·6%)
	Positive	1652 (38%)	2695 (62%)
del(11q)	Negative	3173 (38·1%)	5161 (61·9%)
	Positive	363 (27·9%)	940 (72·1%)
trisomy 12	Negative	2758 (36·6%)	4773 (63·4%)
	Positive	595 (37·3%)	1001 (62·7%)
del(17p)	Negative	3281 (36·5%)	5711 (63·5%)
	Positive	360 (37·6%)	598 (62·4%)
TP53 mutation status	Mutated	231 (38·2%)	373 (61·8%)
	Unmutated	1364 (35·4%)	2493 (64·6%)
Karyotype*	Normal	803 (38·1%)	1304 (61·9%)
	Abnormal	679 (35·2%)	1251 (64·8%)
Other malignant neoplasms	No	6242 (40·1%)	9329 (59·9%)
	Yes	1384 (33·5%)	2750 (66·5%)
Time of other malignant neoplasms	Before CLL diagnosis	343 (39·3%)	529 (60·7%)
	After CLL diagnosis	903 (30·7%)	2037 (69·3%)
	Before and after CLL	98 (30·4%)	224 (69·6%)
Multiple other malignant neoplasms	Two or more non-hematological	121 (26·1%)	343 (73·9%)
	Both non-hematological and hematological	62 (30·3%)	150 (70·7%)
	Two hematological	6 (37·5%)	10 (62·5%)
Transformation	No	7421 (38·9%)	11651 (61·1%)
	Yes	222 (35·1%)	411 (64·9%)
Type of transformation	DLBCL	194 (34·7%)	365 (65·3%)
	HL	13 (37·1%)	22 (62·9%)
	PLL	8 (44·4%)	10 (55·6%)
	Burkitt lymphoma	3 (100%)	0 (0%)
	Other	7 (38·9%)	11 (61·1%)

Supplemental table 25. Number of sites and patients per country.

Country	Number of centers	Number of patients
Italy	12	3,812
Czech Republic	5	2,475
Spain	13	1,986
Greece	7	1,797
Russia	3	1,654
Serbia	2	1,463
United Kingdom	3	1,037
France	6	1,026
Australia	2	661
Turkey	2	598
Israel	4	544
Germany	2	515
India	3	396
Croatia	2	267
Romania	1	267
The Netherlands	3	184
Kuwait	1	153
North Macedonia	1	153
Poland	2	150
Egypt	1	136
Hong Kong	2	91
Argentina	1	87
Pakistan	1	64
China	1	50
Qatar	2	41
Uruguay	1	40
Brazil	1	32
United States of America	1	26
Total: 28	**85**	**19,705**

Investigators in each center provided data on consecutively diagnosed patients between 2000-2016· Data restricted to shorter periods (between 2000-2016) were accepted as long as they included consecutively diagnosed patients for the respective period.

Supplemental table 26. Age-adjusted univariate analyses of risk factors for AML and MDS after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	1·34	(0·96-1·87)	0·081	1·33	(0·87-2·05)	0·188
Binet stage at diagnosis	B	1·64	(1·29-2·09)	<0·001	2·1	(1·34-3·29)	0·001
	C	1·88	(0·74-4·78)	0·184	1·85	(0·92-3·72)	0·085
IGHV gene status	Unmutated[a]	0·88	(0·55-1·44)	0·62	1·51	(0·97-2·34)	0·069
del(13q)	Positive	0·83	(0·5-1·36)	0·458	0·78	(0·43-1·4)	0·405
del(11q)	Positive	0·63	(0·35-1·14)	0·128	0·49	(0·19-1·23)	0·129
del(17p)	Positive	1·41	(0·82-2·45)	0·218	2·72	(1·4-5·3)	0·003
TP53 aberration status	Unmutated	1·89	(0·66-5·47)	0·238	0·29	(0·08-1·13)	0·074
trisomy 12	Positive	1·63	(1·12-2·38)	0·011	1·69	(1·14-2·5)	0·008
Treatment status (*before MDS/AML*)	Treated	1·41	(0·95-2·1)	0·09	2·51	(1·65-3·82)	<0·001
FC +/- R at any line *(before MDS/AML)*	Yes	1·75	(1·4-2·18)	<0·001	4·16	(2·55-6·81)	<0·001
Bendamustine at any line *(before MDS/AML)*	Yes	0·56	(0·14-2·34)	0·43	1·63	(0·5-5·32)	0·42
Chlorambucil at any line *(before MDS/AML)*	Yes	0·60	(0·36-1·02)	0·057	1·52	(0·9-2·55)	0·116
Total lines *(before MDS/AML)*		0·92	(0·71-1·2)	0·55	1·44	(1·25-1·66)	<0·001

AML acute myeloid leukemia, *MDS* myelodysplastic syndrome, *OR* odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 27. Age-adjusted univariate and multivariate analyses of risk factors for MDS after CLL diagnosis.

Univariate analyses							
Risk factor	**Category**	**HR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Sex assigned at birth	Male	1·31	(0·92-1·85)	0·131	1·18	(0·71-1·97)	0·527
Binet stage at diagnosis	B	1·74	(1·08-2·81)	0·023	1·74	(1-3·03)	0·049
	C	1·92	(0·81-4·55)	0·14	1·91	(1·15-3·18)	0·013
IGHV gene status	Unmutated[a]	0·91	(0·53-1·57)	0·736	1·49	(0·82-2·72)	0·192
del(13q)	Positive	0·75	(0·44-1·27)	0·276	0·79	(0·48-1·28)	0·334
del(17p)	Positive	1·73	(1·12-2·67)	0·013	2·02	(1·1-3·71)	0·023
TP53 mutation status	Unmutated	1·73	(0·26-11·6)	0·573	0·25	(0·05-1·33)	0·104
trisomy 12	Positive	1·7	(1·17-2·46)	0·005	1·64	(0·96-2·81)	0·069
Treatment status (*before MDS*)	Treated	1·74	(1·3-2·33)	<0·001	2·31	(1·89-2·81)	<0·001
FC +/- R at any line *(before MDS)*	Yes	2·35	(1·83-3·03)	<0·001	3·73	(2·5-5·55)	<0·001
Bendamustine at any line *(before MDS)*	Yes	0·91	(0·33-2·49)	0·851	1·82	(0·97-3·39)	0·061
Total lines *(before MDS)*		1·06	(0·91-1·23)	0·444	1·36	(1·2-1·54)	<0·001
Multivariate analyses							
Risk factor	**Category**	**HR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Age at diagnosis		-	-	-	1·02	1·01-1·03	0·02
FC +/- R at any line *(before MDS/AML)*	Yes	1·82	1·05-3·13	0·032	3·09	1·44-6·6	0·004

MDS myelodysplastic syndrome, *OR* odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 28. Age-adjusted univariate* and multivariate analyses of risk factors for AML after CLL diagnosis.

Univariate analyses							
Risk factor	**Category**	**HR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Sex assigned at birth	Male	1·27	(0·66-2·44)	0·424	2	(1·15-3·48)	0·02
IGHV gene status	Unmutated[a]	0·64	(0·19-2·14)	0·583	1·72	(0·58-5·06)	0·369
Treatment status (*before AML*)	Treated	1·15	(0·57-2·29)	0·699	2·24	(1·26-3·99)	0·006
FC +/- R at any line *(before AML)*	Yes	1·16	(0·5-2·69)	0·729	4·07	(1·92-8·63)	0·000
Total lines *(before AML)*		0·59	(0·4-0·86)	0·006	1·4	(1·02-1·92)	0·038
Multivariate analyses							
Risk factor	**Category**	**HR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Sex assigned at birth	Male	-	-	-	2·15	0·93-4·97	0·07
FC +/- R at any line *(before AML)*	Yes	-	-	-	4·55	2·55-8·14	<0·001
Age at the time of AML		0·97	0·94-1	0·08	-	-	-

AML acute myeloid leukemia, *OR* odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

*A restricted number of risk factors was assessed due to the small number of cases with AML.

Supplemental table 29. Age-adjusted univariate analyses of risk factors for Hematological malignancies (excluding Richter transformation, AML and MDS) after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	1·22	(0·54-2·75)	0·635	1·12	(0·55-2·3)	0·752
Binet stage at diagnosis	B	0·66	(0·34-1·31)	0·239	2·94	(1·66-5·19)	<0·001
	C	0·2	(0·02-2·09)	0·178	7·75	(1·93-31·08)	0·004
IGHV gene status	Unmutated[a]	0·96	(0·43-2·14)	0·919	1·64	(0·91-2·95)	0·097
del(13q)	Positive	0·45	(0·19-1·07)	0·072	1·26	(0·55-2·92)	0·584
del(11q)	Positive	1·19	(0·44-3·23)	0·732	1·17	(0·48-2·81)	0·731
del(17p)	Positive	1·05	(0·46-2·36)	0·913	1·79	(0·9-3·56)	0·095
TP53 aberration status	Unmutated	1·81	(0·49-6·64)	0·374	0·64	(0·1-4·24)	0·641
trisomy 12	Positive	1·08	(0·44-2·65)	0·871	1·24	(0·48-3·21)	0·658
Treatment status (before malignancy)	Treated	0·35	(0·23-0·52)	<0·001	2·3	(1·82-2·89)	<0·001
FCR +/- R at any line (before malignancy)		0·8	(0·61-1·05)	0·114	3·13	(2·3-4·26)	<0·001
Total lines (before malignancy)		0·68	(0·54-0·86)	0·001	1·46	(1·19-1·8)	<0·001

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 30. Age-adjusted univariate analyses of risk factors for all non-Hematological malignancies (excluding non-melanoma skin cancers) after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	0·97	(0·58-1·64)	0·913	1·82	(1·12-2·97)	0·017
Binet stage at diagnosis	B	0·4	(0·24-0·66)	<0·001	3·85	(2·01-7·35)	<0·001
	C	0·67	(0·35-1·28)	0·228	2·66	(1·1-6·45)	0·03
IGHV gene status	Unmutated[a]	0·6	(0·38-0·94)	0·026	2·19	(1·21-3·97)	0·009
del(13q)	Positive	0·73	(0·5-1·07)	0·104	1·22	(0·73-2·03)	0·443
del(11q)	Positive	0·49	(0·12-1·98)	0·314	2·11	(0·41-10·76)	0·369
del(17p)	Positive	0·47	(0·18-1·2)	0·115	1·95	(0·81-4·65)	0·134
TP53 aberration status	Unmutated	1·81	(0·43-7·56)	0·417	0·83	(0·16-4·2)	0·824
trisomy 12	Positive	0·97	(0·2-4·79)	0·974	1	(0·24-4·18)	0·995
Treatment status (before malignancy)	Treated	0·32	(0·26-0·39)	<0·001	1·73	(1·25-2·39)	0·001
FC +/- R at any line (before malignancy)		0·32	(0·24-0·41)	<0·001	6·5	(3·3-12·82)	<0·001
Total lines (before malignancy)		0·78	(0·73-0·84)	<0·001	1·19	(1·1-1·28)	<0·001

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 31. Age-adjusted univariate analyses of risk factors for bladder cancer after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	3·26	(2·03-5·22)	<0·001	3·06	(2·23-4·21)	<0·001
Binet stage at diagnosis	B	0·9	(0·48-1·69)	0·741	0·47	(0·21-1·06)	0·07
	C	1·5	(0·99-2·26)	0·054	0·84	(0·33-2·13)	0·715
IGHV gene status	Unmutated[a]	1·29	(0·4-4·11)	0·671	0·42	(0·24-0·72)	0·002
del(13q)	Positive	1·04	(0·7-1·53)	0·862	1·31	(0·79-2·16)	0·293
del(11q)	Positive	1·24	(0·88-1·74)	0·215	1·54	(0·63-3·77)	0·349
TP53 aberration status	Present	1·19	(0·58-2·44)	0·643	1·52	(0·53-4·35)	0·433
trisomy 12	Positive	0·91	(0·44-1·88)	0·8	0·55	(0·26-1·15)	0·112
Treatment status (before malignancy)	Treated	0·25	(0·08-0·76)	0·015	1·16	(0·45-2·99)	0·755
FC +/- R at any line (before malignancy)		0·84	(0·45-1·56)	0·583	1·16	(0·42-3·15)	0·776
Total lines (before malignancy)		0·78	(0·68-0·9)	0·001	1·11	(0·9-1·38)	0·324

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 32. Age-adjusted univariate analyses of risk factors for breast cancer after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	0·12	(0·03-0·47)	0·002	0·27	(0·22-0·33)	<0·001
Binet stage at diagnosis	B	0·95	(0·57-1·59)	0·837	0·75	(0·43-1·31)	0·312
	C	1·81	(0·89-3·7)	0·104	0·51	(0·25-1·04)	0·065
IGHV gene status	Unmutated[a]	0·25	(0·07-0·86)	0·027	2·84	(1·13-7·11)	0·026
del(13q)	Positive	0·95	(0·49-1·81)	0·868	1·06	(0·47-2·4)	0·89
del(11q)	Positive	0·57	(0·2-1·64)	0·299	0·51	(0·13-1·98)	0·332
TP53 aberration status	Present						
trisomy 12	Positive	0·59	(0·22-1·56)	0·288	0·75	(0·16-3·57)	0·718
Treatment status (before malignancy)	Treated	0·46	(0·28-0·76)	0·002	0·49	(0·33-0·74)	0·001
Type of treatment (before malignancy)	Chemotherapy or CIT	1·55	(0·58-4·11)	0·383	0·4	(0·18-0·89)	0·025
Total lines (before malignancy)		0·79	(0·68-0·92)	0·003	0·83	(0·71-0·98)	0·025

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *CIT* chemoimmunotherapy.

[a]Unmutated: ≥98% germline identity.

Supplemental table 33. Age-adjusted univariate analyses of risk factors for female breast cancer after CLL diagnosis.

Univariate analyses							
Risk factor	**Category**	**HR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Binet stage at diagnosis	B	0·89	(0·34-2·35)	0·809	1·17	(0·34-3·98)	0·804
	C	1·72	(0·61-4·89)	0·308	0·8	(0·17-3·79)	0·778
del(13q)	Positive	0·81	(0·24-2·73)	0·731	1·09	(0·44-2·67)	0·854
del(11q)	Positive	0·28	(0·1-0·79)	0·016	1·39	(0·22-8·87)	0·731
trisomy 12	Positive	0·27	(0·1-0·77)	0·014	1·43	(0·54-3·75)	0·471
Treatment status (before malignancy)	Treated	0·56	(0·29-1·09)	0·087	0·47	(0·31-0·71)	<0·001
Total lines (before malignancy)		0·87	(0·65-1·16)	0·348	0·79	(0·66-0·94)	0·007

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *CIT* chemoimmunotherapy.

[a]Unmutated: ≥98% germline identity.

Supplemental table 34. Age-adjusted univariate analyses of risk factors for colon cancer after CLL diagnosis.

Risk factor	**Category**	**HR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Sex assigned at birth	Male	1·17	(1·01-1·35)	0·041	1·75	(1·23-2·5)	0·002
Binet stage at diagnosis	B	1·26	(0·88-1·8)	0·204	0·77	(0·38-1·56)	0·473
	C	1·44	(0·84-2·5)	0·188	0·64	(0·13-3·17)	0·58
IGHV gene status	Unmutated[a]	1·61	(1·14-2·29)	0·007	0·74	(0·32-1·73)	0·487
del(13q)	Positive	0·77	(0·58-1·04)	0·088	0·74	(0·45-1·2)	0·223
del(17p)	Positive	1·03	(0·72-1·48)	0·868	0·41	(0·11-1·52)	0·184
trisomy 12	Positive	0·85	(0·57-1·27)	0·436	0·96	(0·4-2·3)	0·929
Treatment status (before malignancy)	Treated	0·61	(0·49-0·77)	<0·001	0·48	(0·36-0·63)	<0·001
FC +/- R at any line (before malignancy)		0·78	(0·55-1·09)	0·144	1·09	(0·57-2·12)	0·788
Total lines (before malignancy)		0·82	(0·74-0·91)	<0·001	0·92	(0·7-1·2)	0·535

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 35. Age-adjusted univariate analyses of risk factors for bronchus and lung cancer after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	1·24	(0·95-1·63)	0·115	2·71	(1·86-3·95)	<0·001
Binet stage at diagnosis	B	0·4	(0·13-1·22)	0·109	3·22	(1·68-6·14)	<0·001
	C	0·73	(0·31-1·7)	0·466	2·61	(1·33-5·11)	0·005
IGHV gene status	Unmutated[a]	0·88	(0·3-2·58)	0·818	2·5	(1·49-4·2)	0·001
del(13q)	Positive	0·54	(0·18-1·61)	0·27	1·36	(0·63-2·92)	0·431
del(11q)	Positive	0·86	(0·39-1·87)	0·699	1·82	(0·79-4·2)	0·163
del(17p)	Positive	0·34	(0·07-1·67)	0·183	1·71	(0·27-10·81)	0·566
TP53 aberration status	Unmutated	0·25	(0·04-1·64)	0·148	1·39	(0·45-4·34)	0·566
trisomy 12	Positive	1·84	(0·79-4·29)	0·155	0·62	(0·32-1·18)	0·145
Treatment status (before malignancy)	Treated	0·39	(0·2-0·79)	0·008	1·5	(0·97-2·32)	0·069
FC +/- R at any line (before malignancy)		0·34	(0·12-0·97)	0·043	3	(1·45-6·23)	0·003
Total lines (before malignancy)		0·71	(0·6-0·82)	<0·001	1·34	(1·19-1·49)	<0·001

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 36. Age-adjusted univariate analyses of risk factors for melanoma after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	1·3	(0·91-1·87)	0·151	1·87	(1·26-2·77)	0·002
Binet stage at diagnosis	B	1·46	(1-2·15)	0·05	1·3	(0·44-3·81)	0·63
	C	2·03	(1·37-3)	<0·001	1·83	(0·95-3·5)	0·07
IGHV gene status	Unmutated[a]	1·13	(0·71-1·79)	0·6	1·56	(0·99-2·46)	0·057
del(13q)	Positive	1·21	(0·79-1·86)	0·375	0·73	(0·33-1·58)	0·419
del(11q)	Positive	1·2	(0·6-2·41)	0·604	0·32	(0·11-0·91)	0·034
del(17p)	Positive	0·87	(0·21-3·66)	0·854	1·27	(0·31-5·23)	0·739
trisomy 12	Positive	1·02	(0·62-1·68)	0·922	1·38	(0·67-2·87)	0·385
Treatment status (before malignancy)	Treated	0·63	(0·36-1·11)	0·11	1·13	(0·69-1·84)	0·63
FC +/- R at any line (before malignancy)		1·11	(0·63-1·94)	0·717	2·76	(1·98-3·84)	<0·001
Total lines (before malignancy)		0·8	(0·64-1·01)	0·057	1·24	(1·08-1·43)	0·002

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 37. Age-adjusted univariate analyses of risk factors for non-melanoma skin cancers after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Sex assigned at birth	Male	0·97	(0·58-1·64)	0·913	1·82	(1·12-2·97)	0·017
Binet stage at diagnosis	B	0·4	(0·24-0·66)	<0·001	3·85	(2·01-7·35)	<0·001
	C	0·67	(0·35-1·28)	0·228	2·66	(1·1-6·45)	0·03
IGHV gene status	Unmutated[a]	0·6	(0·38-0·94)	0·026	2·19	(1·21-3·97)	0·009
del(13q)	Positive	0·73	(0·5-1·07)	0·104	1·22	(0·73-2·03)	0·443
del(11q)	Positive	0·49	(0·12-1·98)	0·314	2·11	(0·41-10·76)	0·369
del(17p)	Positive	0·47	(0·18-1·2)	0·115	1·95	(0·81-4·65)	0·134
TP53 aberration status	Unmutated	1·81	(0·43-7·56)	0·417	0·83	(0·16-4·2)	0·824
trisomy 12	Positive	0·97	(0·2-4·79)	0·974	1	(0·24-4·18)	0·995
Treatment status (before malignancy)	Treated	0·32	(0·26-0·39)	<0·001	1·73	(1·25-2·39)	0·001
FC+/- R at any line (before malignancy)		0·32	(0·24-0·41)	<0·001	6·5	(3·3-12·82)	<0·001
Total lines (before malignancy)		0·78	(0·73-0·84)	<0·001	1·19	(1·1-1·28)	<0·001

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Supplemental table 38. Age-adjusted univariate analyses of risk factors for prostate cancer after CLL diagnosis.

Risk factor	Category	HR	95% CI	p value	OR	95% CI	p value
Binet stage at diagnosis	B	1·11	(0·47-2·63)	0·818	0·95	(0·41-2·17)	0·897
	C	0·73	(0·05-10·32)	0·817	1·81	(0·3-10·81)	0·514
IGHV gene status	Unmutated[a]	0·79	(0·33-1·86)	0·583	1·48	(0·91-2·39)	0·111
del(13q)	Positive	1·12	(0·45-2·81)	0·808	0·81	(0·38-1·76)	0·597
del(11q)	Positive	1·43	(0·7-2·93)	0·328	0·71	(0·42-1·23)	0·222
del(17p)	Positive	0·91	(0·57-1·44)	0·689	2·18	(1·32-3·6)	0·002
TP53 aberration status	Present	0·71	(0·37-1·35)	0·295	1·82	(1·12-2·95)	0·016
trisomy 12	Positive	1·17	(0·51-2·71)	0·713	0·76	(0·38-1·53)	0·44
Treatment status (before malignancy)	Treated	0·28	(0·17-0·45)	<0·001	1·69	(0·97-2·94)	0·066
FC +/- R at any line (before malignancy)		0·22	(0·08-0·63)	0·004	6·77	(2·94-15·59)	<0·001
Total lines (before malignancy)		0·88	(0·74-1·04)	0·141	1·09	(0·94-1·25)	0·251

OR odds ratio, *CI* confidence interval, *HR* hazard ratio, *IGHV* immunoglobulin heavy variable, *FC +/- R* fludarabine, cyclophosphamide with or without rituximab.

[a]Unmutated: ≥98% germline identity.

Figure 2. Kaplan-Meier curves for hematological malignancies (excluding Richter Transformation) occurrence after CLL.

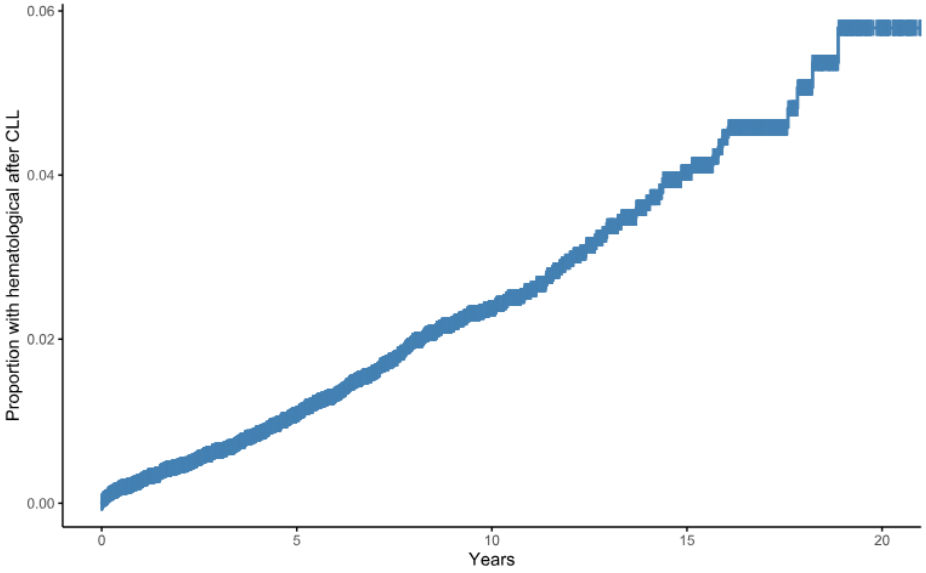


Figure 3. Kaplan-Meier curves for non-hematological malignancies occurrence after CLL.

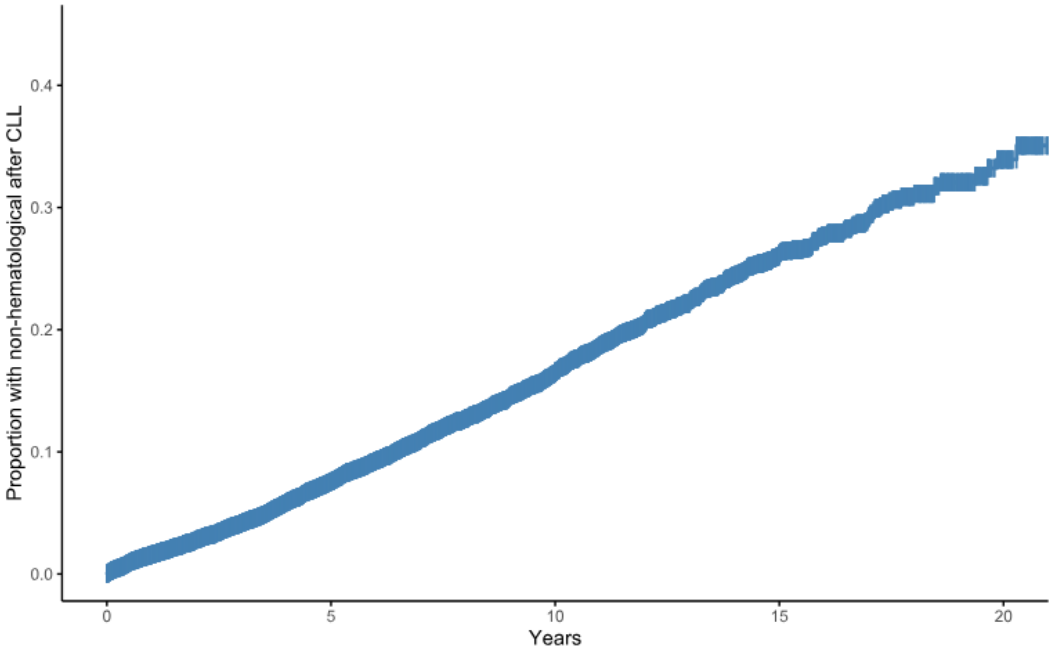


Figure 4. Kaplan-Meier curves for myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML) occurrence after CLL