Comorbidities and Other Cancers in Chronic Lymphocytic Leukemia

Alessandra Ferrajoli, M.D.

Department of Leukemia

The University of Texas MD Anderson Cancer Center

aferrajo@mdanderson.org

Disclosures

- Research Support:

  Celgene, Genentech, Acerta, BeiGene

- Advisory Boards:

  Astra-Zeneca, Janssen

Chronic Lymphocytic Leukemia (CLL): SEER Data

US 2019(ext): 20,720 new cases of CLL

4.7/100,000 person per year

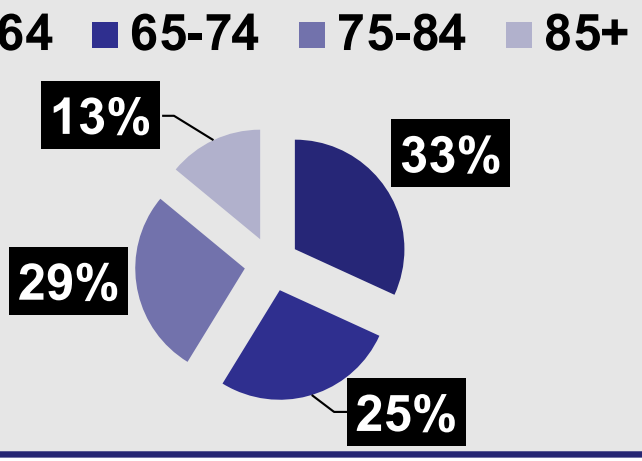
5 years survival 86%

68% in 1975

- Age distribution at diagnosis:
  - 65-74 y 28.8%
  - 75-84 y 25.3 %
  - 85 y + 13.0%

67%

- Median age at diagnosis: 72 y
- Median age at treatment: 70 y

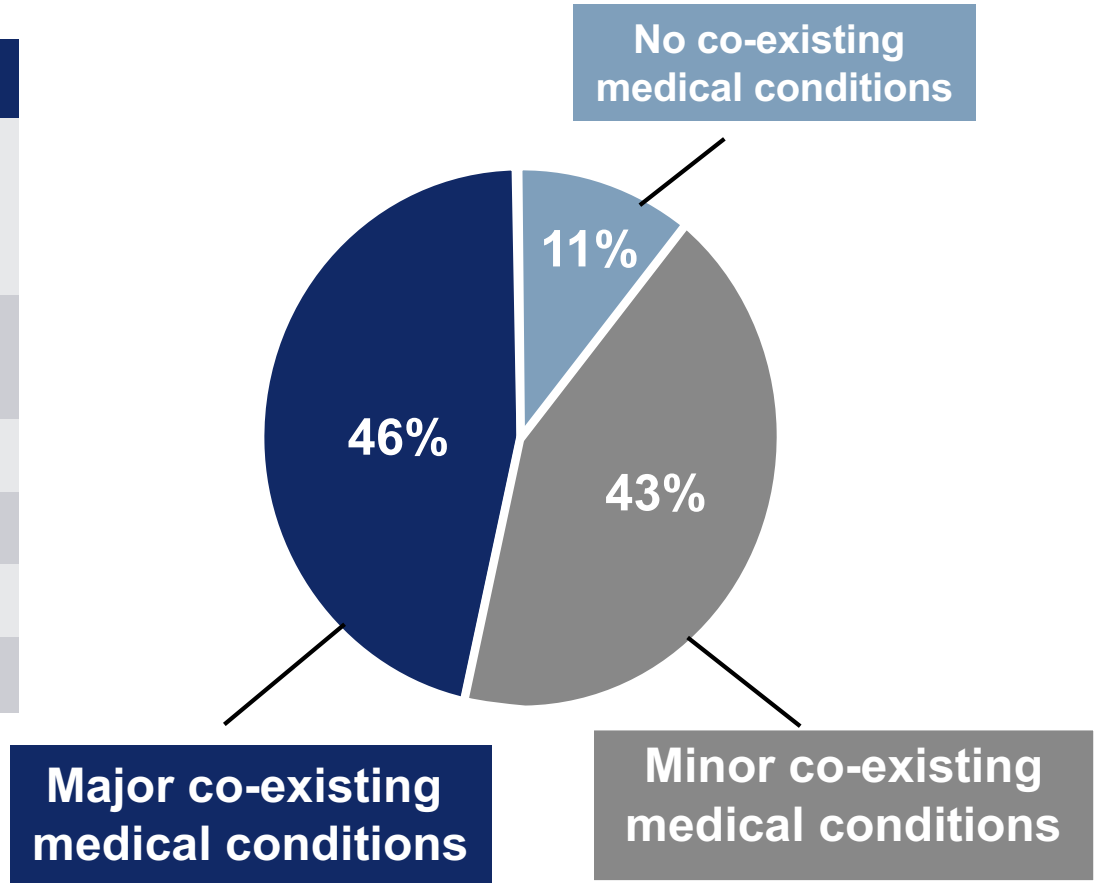


SEER . Available at: http://seer.cancer.gov/statfacts/html/clyl.html.
Siegel RL CA Cancer J Clin 2019;69:7-34

Patients with CLL and co-existing Medical Conditions

US patient population:

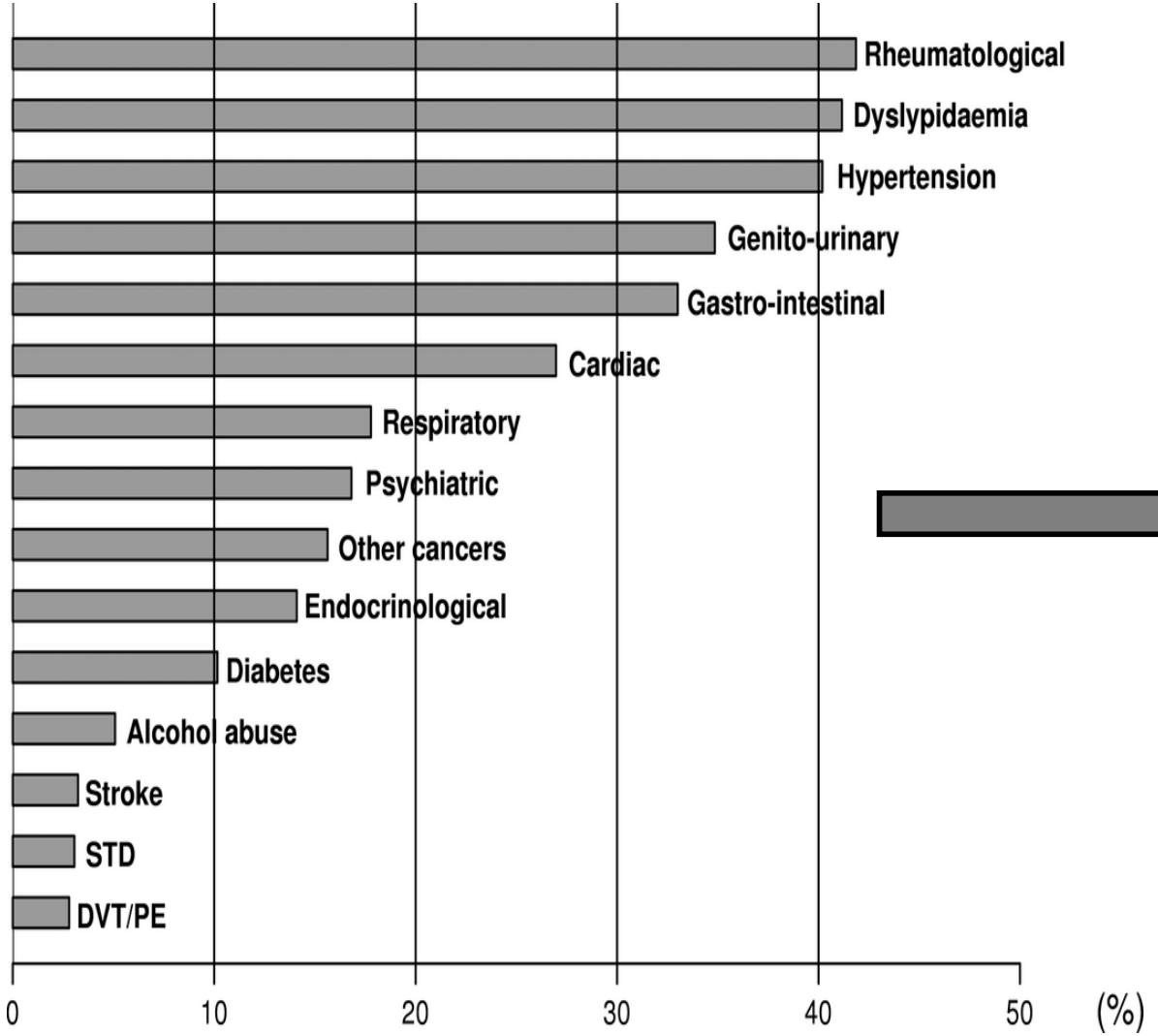
Major comorbidity	%
Coronary artery/ peripheral vascular disease	16
Cardiovascular disease/ transient ischemic attack	6
Other cardiac	13
Diabetes mellitus	11
COPD	7
Second cancer	14

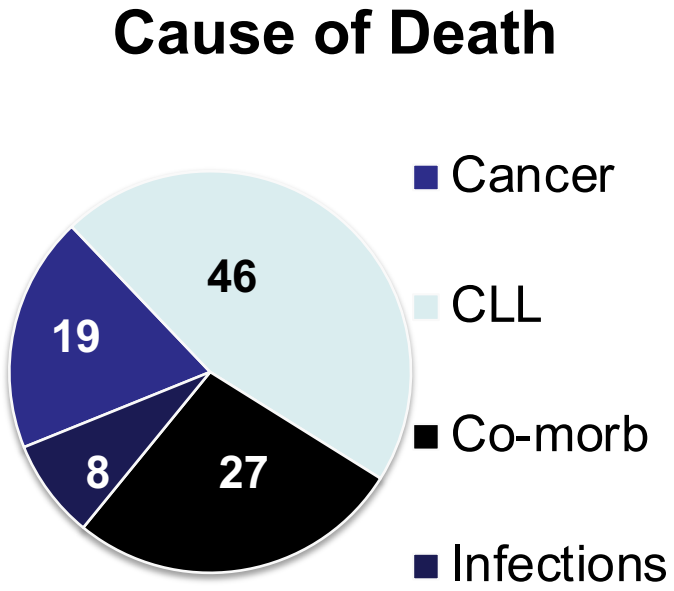


- COPD = chronic obstructive pulmonary disease.

Thurmes P, *et al*. *Leuk Lymphoma* 2008; 49:49–56.

Co-existing Medical Conditions at Time of CLL Diagnosis (1,143 Patients)





Strati P. et al. British Journal of Haematology: 178, 394-402, 2017

Atrial Fibrillation - Ibrutinib

- Cumulative incidence 5-7.7%.[1-4] Meta analysis of 4 RCTs → RR 3.5.[5]
- Up to 16% in single center long-term follow-up studies.[6]
- Mayo Clinic cohort study of >2,000 CLL patients followed for a median of 7y demonstrated[7]:

  2x prevalence compared to general population.

  Incidence of ~1% per year.

[1]Byrd NEJM 2013. [2]Burger NEJM 2015. [3]Chanan-Khan Lancet Oncology 2017, 200-11. [4]Dreyling, Lancet 2016. [5]Leong et al Blood 2016. [6]Thompson PA et al. Blood 2016. [7]Shanafelt et al Leuk and Lymph 2017.

Atrial Fibrillation – Risk Factors

- Risk factors in the Mayo cohort were:

1. Older age (HR 2.4 for age 65-74, 3.7 for ≥75).
2. Male gender.
3. Valvular heart disease (HR 2.4)
4. Hypertension (HR 1.5)

Shanafelt et al Leuk and Lymph 2017.

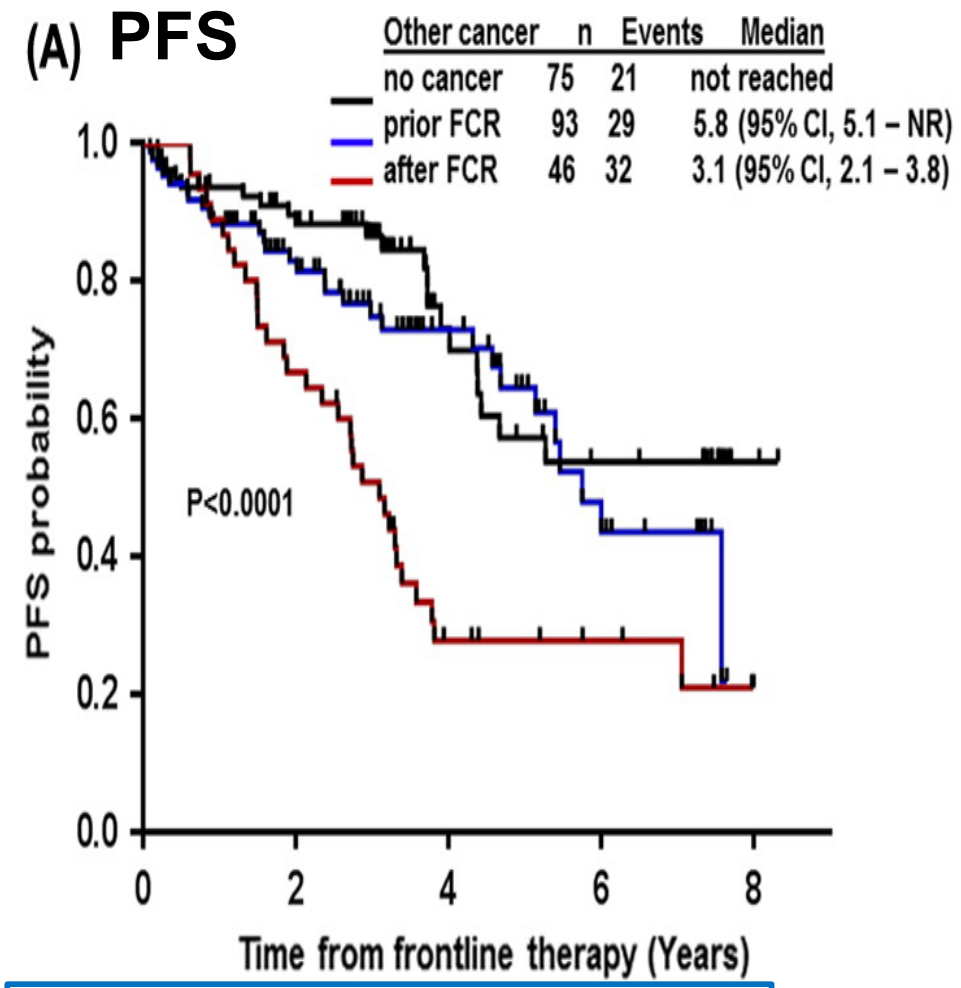
MDACC: OC in Patients Treated with FCR

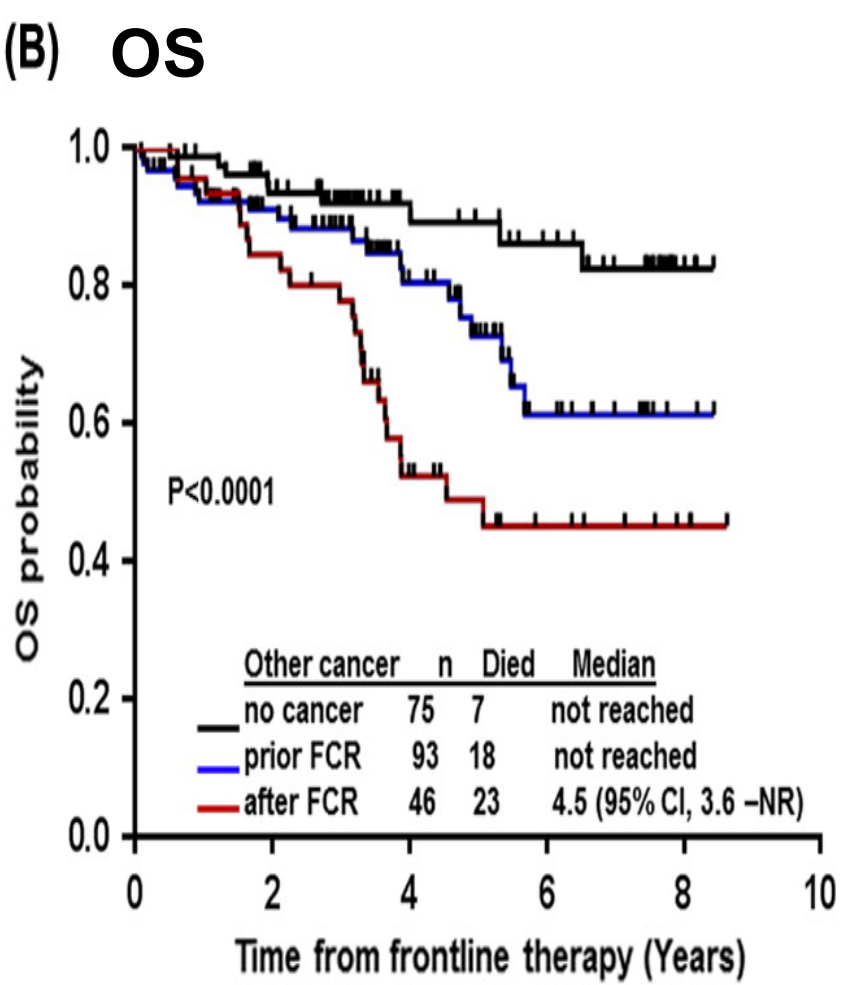
234 patients treated with FCR (FCR, FCR3 and CFAR) as frontline therapy

- ✓ 2.38 increased risk for OC
- ✓ 156 OC
  - 93 prior to FCR (NMSC, MM, prostate, breast)
  - 66 after FCR (MDS/AML, lung)

Benjamini O. et al.; *Leukemia & Lymphoma* 2015, 56, 1643-1650.

Second cancer after FCR are associated with shorter PFS and OS





Actuarial 5-years OS
No cancer 92%
Prior FCR 74%
After FCR 48%

Benjamini O. et al. ; *Leukemia & Lymphoma* 2015, 56, 1643-1650.

Effect of First-line Therapy on Second Primary Malignancies in CLL

1,498 patients (CLL 4-5-8-2M) start of Rx-2013

- Median age 61y, 72.5% male
- Median observation time 69/45 months

❖ **191 SPM**

- 112 solid tumor (lung, prostate) (7.7%)
- 38 basal/squamous cell (2.3%)
- 19 AML/MDS (1.2%)

⇑ SIR 1.23 (German 2012 Cancer Registry)

⇑ Risk factors: older age, male, 1+ comorbidities

Maurer C et al. *Leukemia*:30, 2019-15, 2016

Other Cancers in Patients with Chronic Lymphocytic Leukemia (10+ years)

797 patients (both treated and untreated)

- 286 patients had a OC (36%)
- 86 cases (30 % of OC) of non-melanoma skin cancers

Median time to OC is 9.8 years

Falchi L. et al, Ann Oncol 27:1100-6, 2016

Characteristics of 797 Survivors of CLL

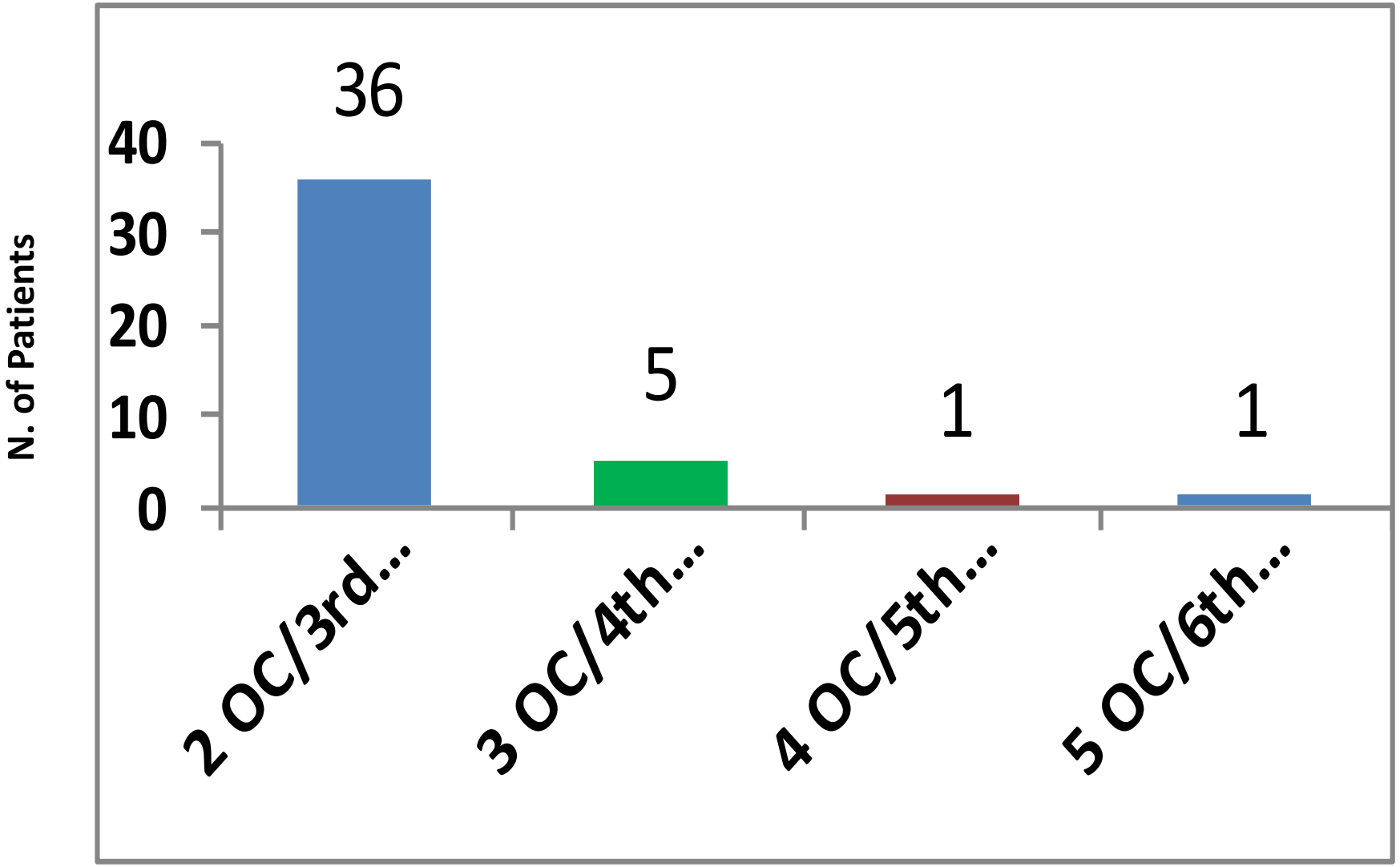
(median follow-up 154 months [120-485])

Characteristic	No. or Median	(%) or [range]
Age, years	56	[24-88]
Male gender	454	57
All pts with OC	286	36
OC diagnosed before CLL	*100/286*	*35*
OC diagnosed after CLL	*186/286*	*65*
Pts requiring therapy	570	71
OC in pts requiring therapy	*205/570*	*36*
OC in watch-and-wait pts	*81/227*	*36*

Falchi L. et al, Ann Oncol 27:1100-6, 2016

When Cancer Strikes Twice……Three Times and Four Times

CLL: Additional OC after First OC (Pts=286)



Falchi L. et al, Ann Oncol 27:1100-6, 2016

10+ years CLL Survivors: Standardized Incidence Ratio (SIR) for OC Entire Population (N=797)

Variable	O	E	Person-years	SIR (O/E)	95% CI for O/E	P-value
Overall	**148**	**123.34**	**10956**	**1.20**	**1.01 - 1.40**	**0.034**
Male	**96**	**73.4**	**5885**	**1.31**	**1.06 - 1.58**	**0.013**
Female	52	49.93	5071	1.04	0.78 - 1.36	0.67
Age ≥60	60	54.33	3416	1.10	0.84 - 1.42	0.44
Age <60	**88**	**69.02**	**7540**	**1.27**	**1.02 - 1.57**	**0.027**

OC after the diagnosis of CLL
O: observed, E: expected

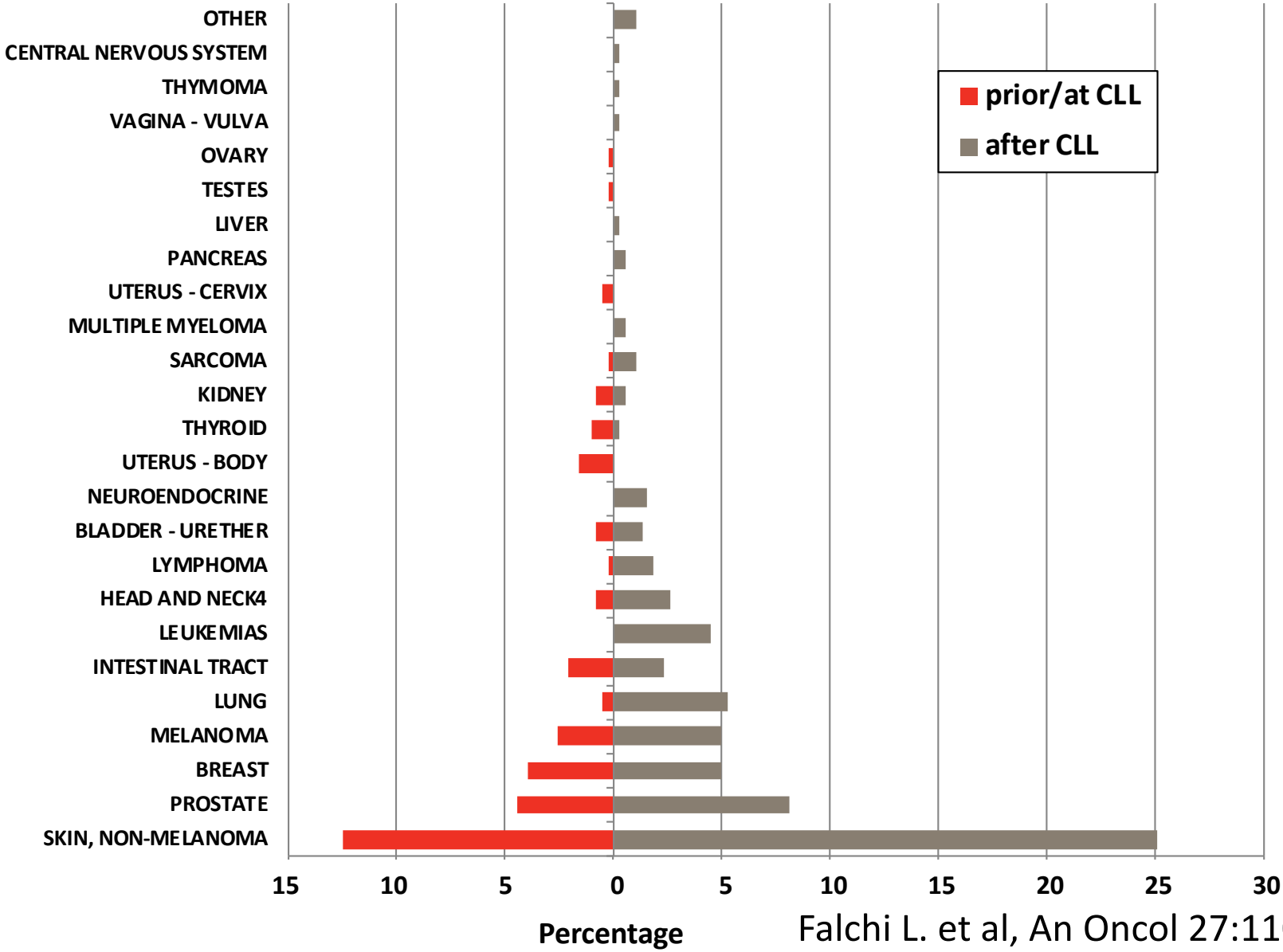
Falchi L. et al, An Oncol 27:1100-6, 2016

10+ years CLL Survivors SIR for OC by OC Type (Pts=797)

Variable	O	E	Person-years	O/E	95% CI	P
Prostate	27	25.88	11801	1.04	0.68 – 1.52	0.85
Lung	19	29.08	11942	0.65	0.39 – 1.02	0.06
Breast	18	18.67	11869	0.96	0.57 – 1.52	0.91
Melanoma	**16**	**4.23**	**11926**	**3.78**	**2.16 – 6.14**	**<0.0001**
Leukemia	**15**	**4.27**	**12009**	**3.51**	**1.96 – 5.797**	**<0.0001**
NHL	6	6.38	11996	0.94	0.34 – 2.05	1.00
Digestive*(e,l)	15	40.37	11933	0.37	0.20 – 0.61	<0.0001
Colon	8	19.42	11972	0.41	0.18 – 0.81	0.006
Pancreas	2	4.83	12024	0.41	0.05 – 1.49	0.18
Rectal	3	8.69	12011	0.34	0.07 – 1.00	0.05
Bladder	3	11.18	11993	0.27	0.05 – 0.78	0.009
Myeloma	2	1.98	12012	1.01	0.12 – 3.64	1.00
Lip	**3**	**0.02**	**12015**	**150**	**31.00 – 43.85**	**<0.0001**
Salivary gland	**2**	**0.03**	**12026**	**66.66**	**8.00 – 240.06**	**<0.0001**

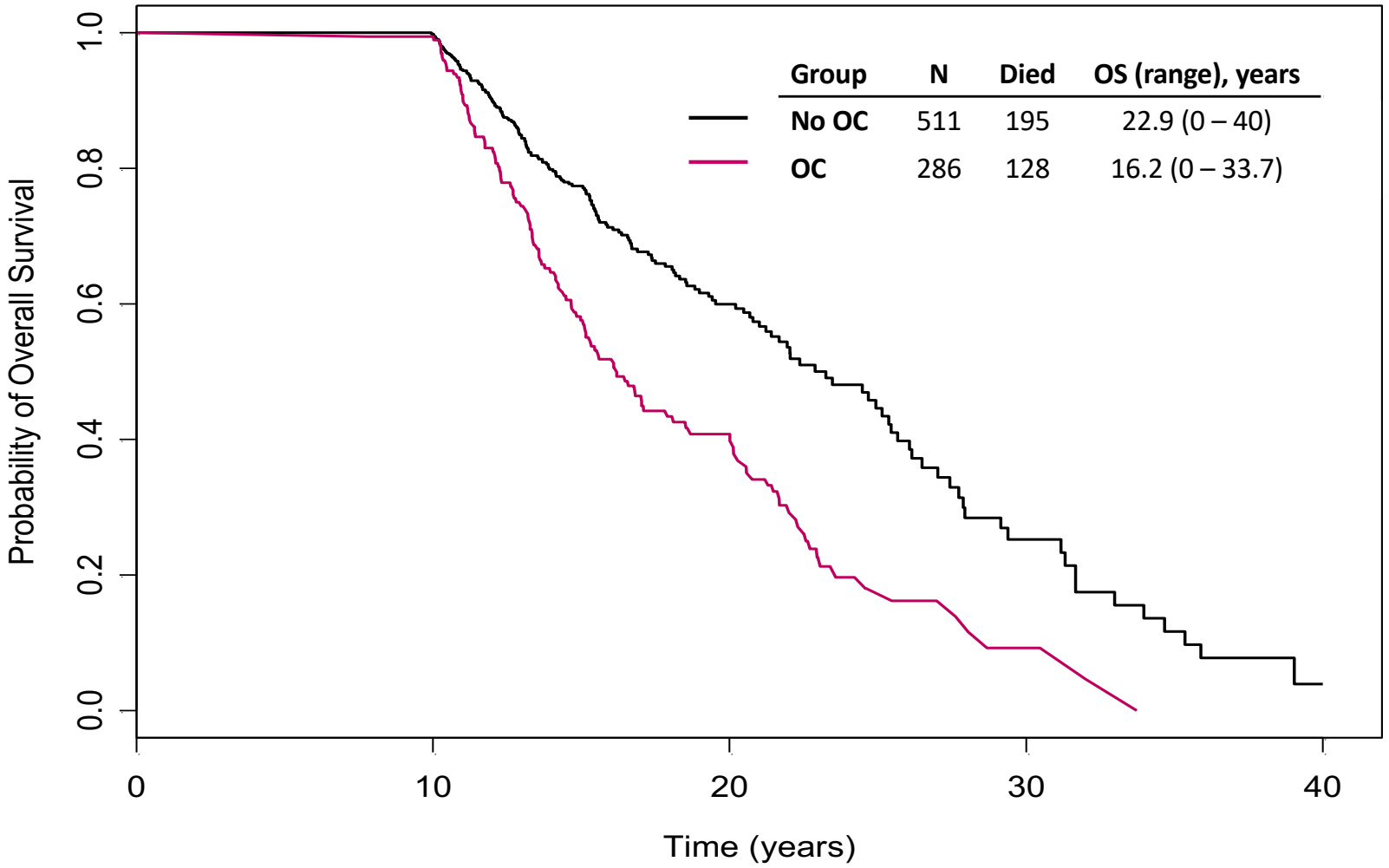
Falchi L. et al, Ann Oncol 27:1100-6, 2016

10+ years CLL Survivors: Distribution of OC Entire Population (N=797)



Falchi L. et al, An Oncol 27:1100-6, 2016

CLL Survivors: Overall Survival by Presence of OC



Note: presence of OC included as a time-dependent covariate

Falchi L. et al, An Oncol 27:1100-6, 2016

Malignant Melanoma in Survivors of NHL

Survivors	NHL 44,870	CLL/SLL 15,950
MM	202 (0.78%)	91 (1.37%)
Time to MM	3 y	3.5 y
Location/1-mm thick	Trunk 29%/28%	Face/Head/Neck 41%/43%

Table 1. Selected Characteristics of 44,870 1-Year Survivors of First Primary NHL, Overall and by NHL Subtype, Diagnosed at Age 66 to 83 Years, 16 SEER Registries, 1992 to 2009

			First Primary NHL Subtype*									
	Total NHL		CLL/SLL		DLBCL		FL		MZL		Other	
Variable	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of 1-year survivors	44,870		13,950		10,311		7,437		3,516		9,656	
Age at NHL diagnosis, years												
66-69	9,673	21.6	2,901	20.8	2,169	21.0	1,828	24.6	767	21.8	2,008	20.8
70-74	13,120	29.2	3,982	28.5	3,038	29.5	2,243	30.2	988	28.1	2,869	29.7
75-79	12,754	28.4	4,030	28.9	2,934	28.5	1,985	26.7	958	27.3	2,847	29.5
80-83	9,323	20.8	3,037	21.8	2,170	21.1	1,381	18.6	803	22.8	1,932	20.0
Sex												
Male	22,097	49.3	7,590	54.4	4,725	45.8	3,229	43.4	1,439	40.9	5,114	53.0
Female	22,773	50.8	6,360	45.6	5,586	54.2	4,208	56.6	2,077	59.1	4,542	47.0
Race												
White	40,752	90.8	12,841	92.1	9,222	89.4	6,888	92.6	3,090	87.9	8,711	90.2
Other/unknown	4,118	9.2	1,109	7.9	1,089	10.6	549	7.4	426	12.1	945	9.8
Year of NHL diagnosis												
1992-1997†	8,127	18.1	2,755	19.8	1,798	17.4	1,345	18.1	233	6.6	1,996	20.7
1998-2003	15,978	35.6	5,002	35.9	3,680	35.7	2,618	35.2	1,317	37.5	3,361	34.8
2004-2009	20,765	46.3	6,193	44.4	4,833	46.9	3,474	46.7	1,966	55.9	4,299	44.5
Residence at time of NHL diagnosis‡												
North	20,348	45.4	6,691	48.0	4,473	43.4	3,206	43.1	1,511	43.0	4,467	46.3
Central	12,778	28.5	3,727	26.7	3,107	30.1	2,260	30.4	1,041	29.6	2,643	27.4
South	11,744	26.2	3,532	25.3	2,731	26.5	1,971	26.5	964	27.4	2,546	26.4
Median age at NHL, years	74.0		75.0		74.0		74.0		75.0		74.0	
Mean person-years at risk	5.5		5.6		5.4		5.8		5.6		5.3	
No. of second melanomas	202		91		34		34		10		33	
Median interval from NHL to melanoma, years	3.0		3.3		2.9		2.8		3.0		2.6	
Site of melanoma§												
Face/head/neck	73	36.1	37	40.7	< 10	—	11	32.3	< 10	—	14	42.4
Trunk	56	27.7	23	25.3	13	38.2	< 10	—	< 10	—	< 10	—
Upper/lower extremities, other/unspecified	73	36.1	31	34.1	13	38.2	14	41.2	< 10	—	11	33.3
Thickness of melanoma, mm										—		
< 1.0	104	51.4	41	45.1	25	73.5	16	47.1	< 10	—	16	48.5
> 1.0	70	34.7	39	42.9	< 10	—	13	38.2	< 10	—	< 10	—
Unknown	28	13.9	11	12.1	< 10	—	< 10	—	< 10	—	< 10	—

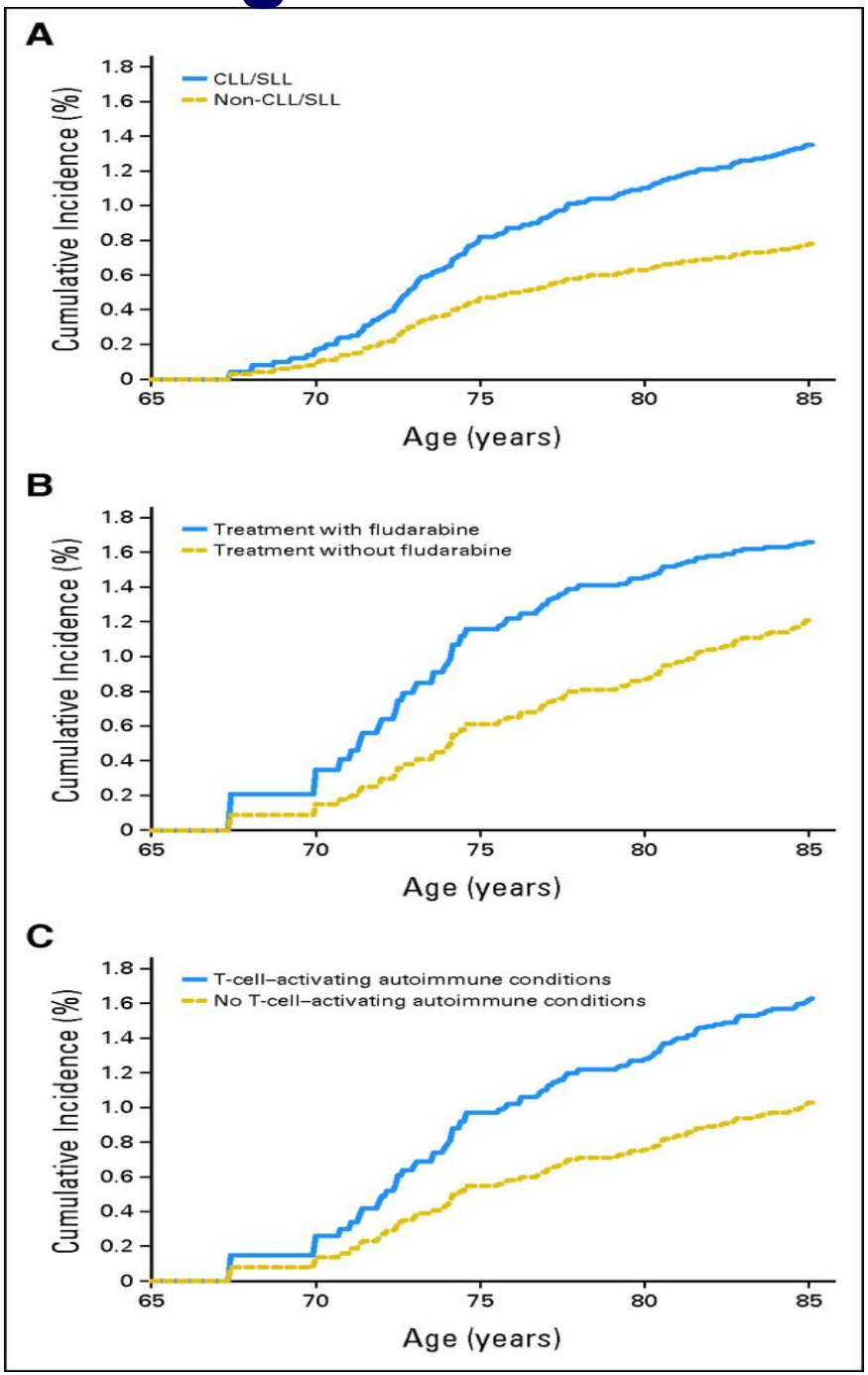
NOTE. Counts and percentages are not reported for fewer than 10 melanoma cases to protect patient confidentiality.
Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; ICD-O-3 International Classification of Diseases for Oncology, 3rd Edition; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma.
*First primary NHL subtype defined by ICD-O-3 as DLBCL (9678-9680, 9684 [B cell]), FL (9690-9691, 9695, 9698), CLL/SLL (9670, 9823), MZL (9689, 9699) and other NHL (9590-9596, 9671, 9673, 9675, 9684 [non B cell], 9687, 9700-9702, 9705, 9708-9709, 9714-9719, 9727-9729, 9827 [primary site, C42.0-42.1, C42.4]).
†1992-1997 includes 13 SEER registries, whereas 1998-2003 and 2004-2009 include 16 SEER registries.
‡Residence defined by SEER registry areas, including north (Connecticut, Detroit, Iowa, Seattle, and New Jersey), central (San Francisco, Utah, San Jose, Greater California, and Kentucky), and south (Hawaii, New Mexico, Atlanta, Los Angeles, Rural Georgia, Greater Georgia, and Louisiana).
§Melanoma site defined by ICD-O-3 as face/head/neck (C44.0-C44.4), trunk (C44.5), upper extremities (C44.6), lower extremities (C44.7), and other/unspecified (C44.8-C44.9).

Median age 74
Median FU 5.5 years

Higher risk: *Male*
White
Southern Regions

Clara J.K. Lam et al. JCO doi:10.1200/JCO.2014.60.2094

Malignant Melanoma in Survivors of NHL



NHL
Cumulative Incidence

CLL/SLL
Cumulative Incidence according to fludarabine treatment

CLL/SLL
Cumulative Incidence according to T-activating/autoimmune

Lam C.J. et al. J Clin Oncol 33:3096-104, 2015

Rochester Experience: Pts with CLL and Melanoma

- 407 pts with CLL followed for 2849 person-years

18 pts developed melanoma (**3.8%**), 22 cases
33.3% in situ
38.1% stage I
9.5% stage II
14.3% stage III
4.8% stage IV
Invasive melanoma:14 pts [**SIR 6.32** (3.45-10.6)]

Archibald WJ et al. Leuk. Res 71: 43-46, 2018

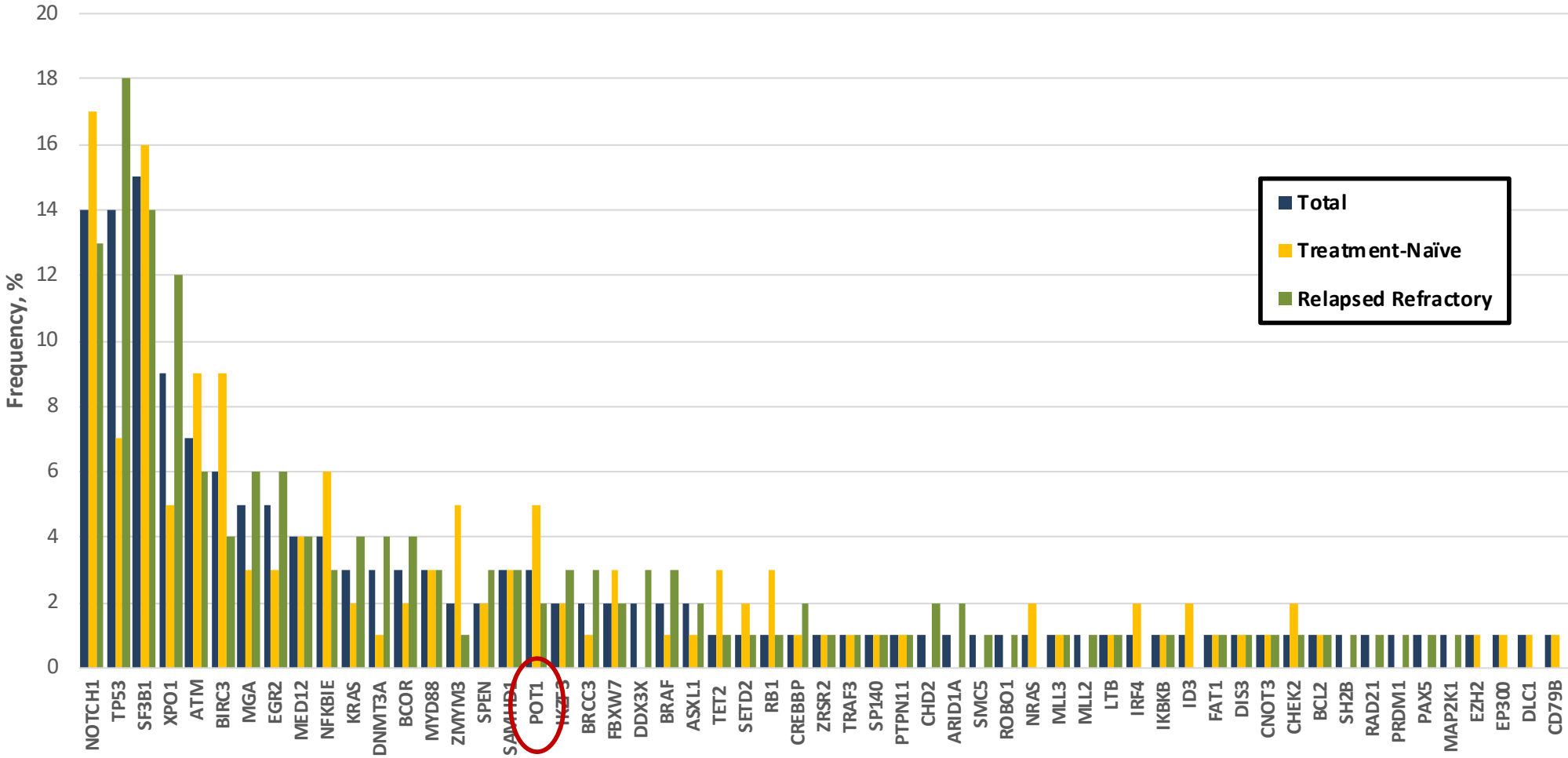
POT-1 Gene Mutations in CLL

- Mutations in protection of telomeres 1 gene (*POT1*) lead to uncapping of the telomeric ends, thereby enabling telomerase to aberrantly elongate the telomeres, causing fusion events and chromosomal aberrations.

- *POT1* is found to be mutated in approximately 4% of patients with CLL. Recent studies reported germline variants in *POT1* in patients with familial CLL and in familial melanoma, cardiac angiosarcoma, glioma and colorectal cancer.

Speedy HE et al. Blood 19:2319-2326, 2016

CLL patients on lenalidomide at MDACC. Frequency of mutations detected by targeted gene sequencing separated into treatment-naïve, relapsed/refractory and total patient cohorts.



B. Hu & K. Takahashi, Blood 2018 in press

Other Cancers and CLL: Bi-directional

Swedish Family Cancer Database: 18,407 patients with CLL, 2,773 OC (15.1%) median age 72 year, median time to OC 4 years

Risk of OC after CLL				Risk of CLL after OC		
Cancer	N	RR			N	RR
Skin SCC	235	24.58		CLL	231	2.6
Merkel Ca	11	14.36		CLL	3	7.39
SCC inv	396	7.63		CLL	183	3.02
Hodgkin	26	7.16		CLL	11	1.99
Kaposi	5	6.76		CLL	4	5.26
Melanoma	127	3.22		CLL	97	1.47
NHL	130	3.11		CLL	108	2.96

Zheng G. Br. J. Haematol, 185:232-9, 2019

Patients with CLL: Prevention

Health maintenance:

- ✓ Annual skin examination
- ✓ Use of sunscreen and USPTF recommendations to prevent skin cancer
- ✓ Colon, breast, cervical cancer screening
- ✓ Smoking cessation and lung cancer screening
- ✓ Exercise and nutritional programs
- ✓ Vaccination (Influenza, Pneumococcal Pneumonia, Tetanus, Zoster)