

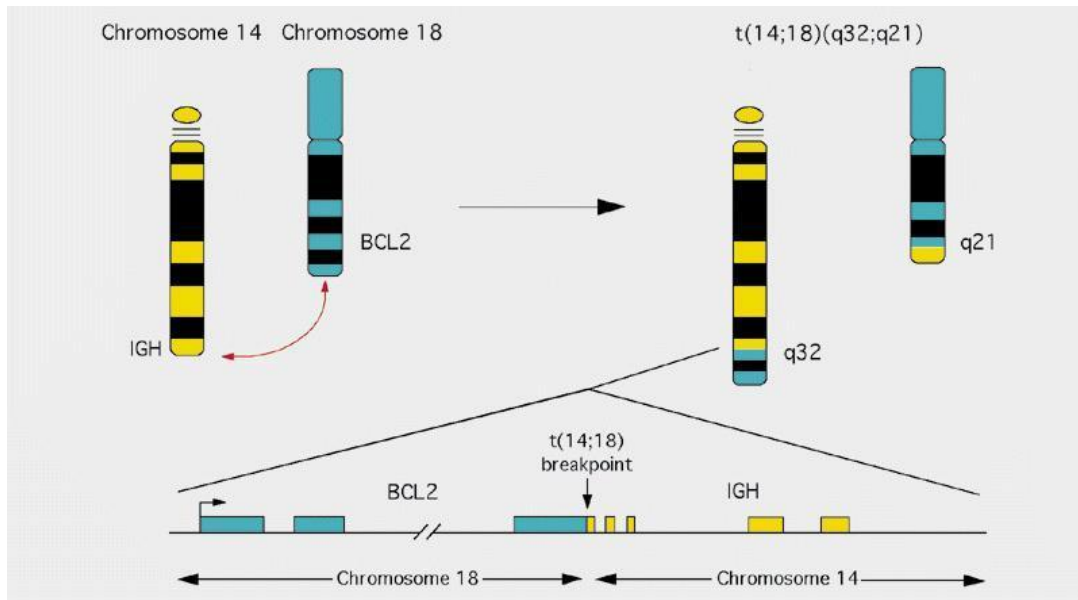
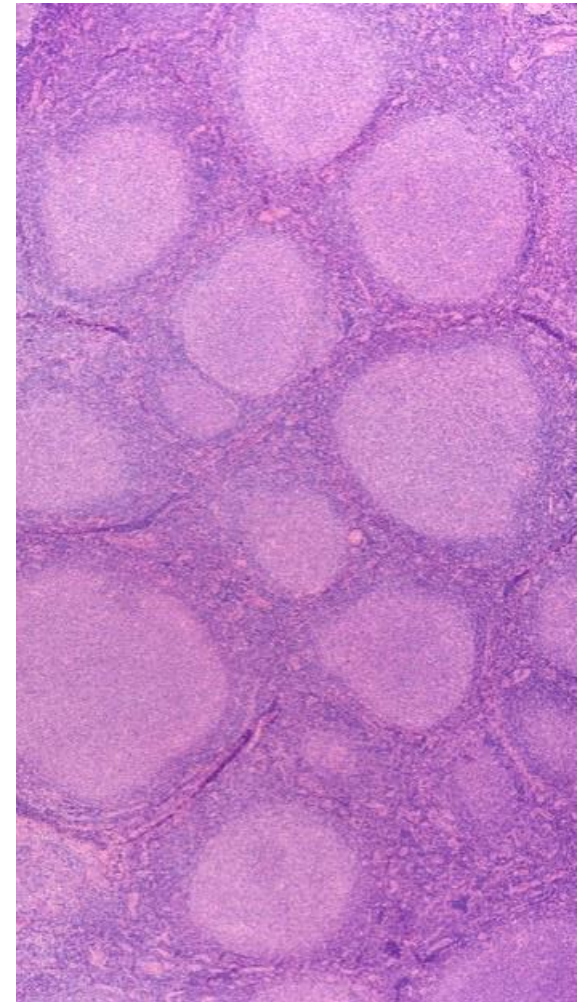
Enhancer Zeste Homolog 2 (EZH2) expression is associated with a shorter time to the first systemic therapy in follicular lymphoma

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Follicular lymphoma

- *Originates from germinal/follicular center B cells*
- *IHC:*
 - (+): *CD10, CD19, CD20, CD79a*
 - (-): *CD5, cyclin D1*
- *t(14;18)(q32;q21), which occurs in 90% of cases, causes overexpression of BCL2*

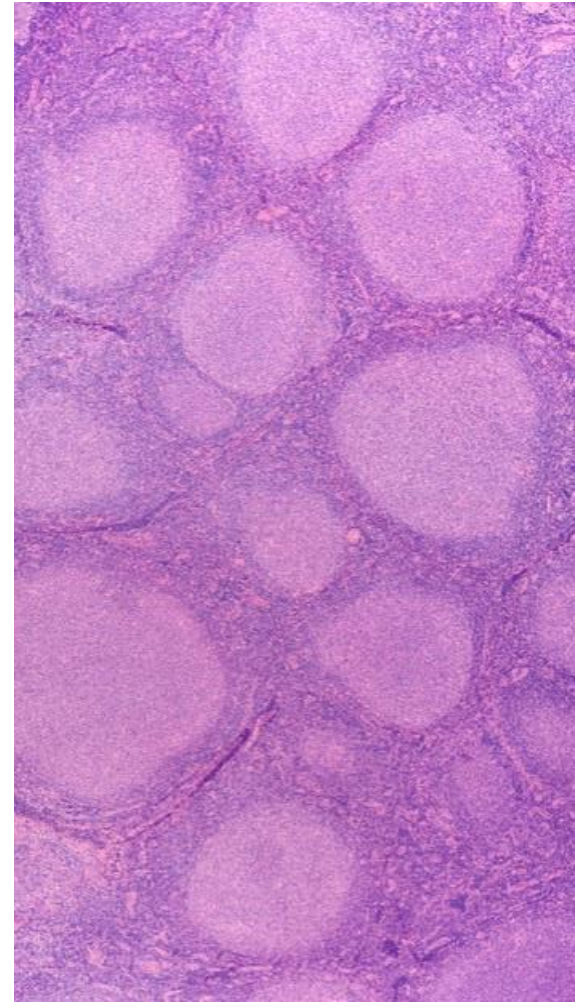


Follicular lymphoma

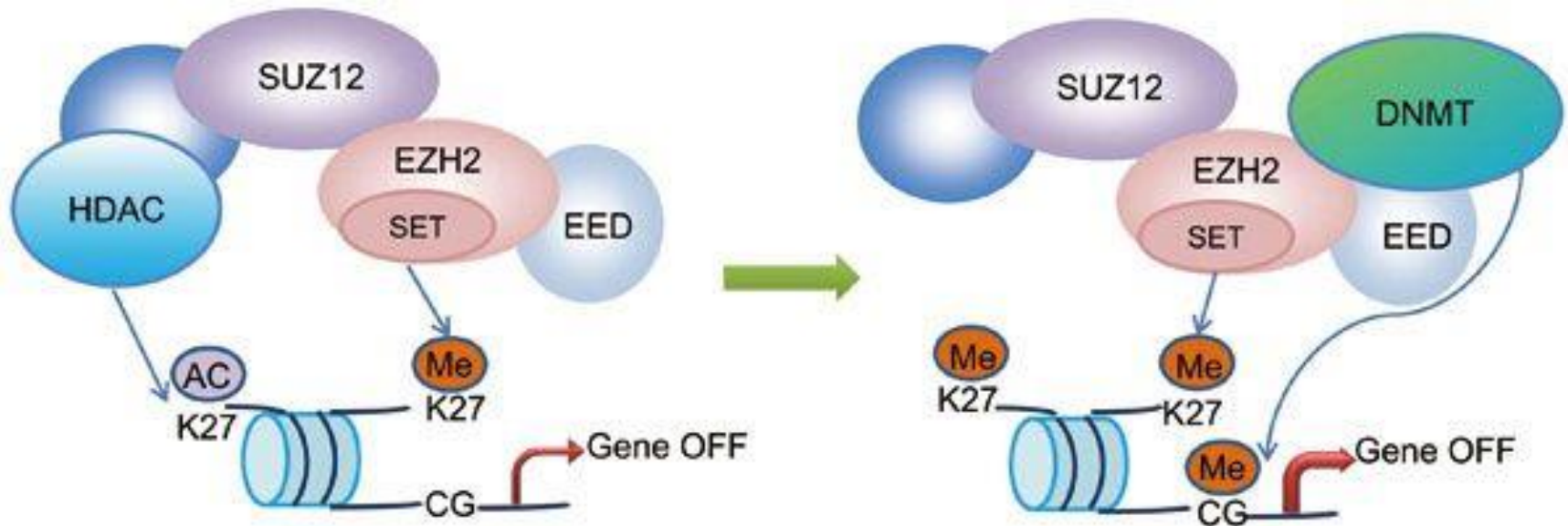
- *One of the most frequent non-Hodgkin lymphomas (20-40% of NHL)*
- *Adults with a median age in the sixth decade of life*
- *USUALLY indolent*
- *Transformation to diffuse large B cell lymphoma occurs in 20 - 30%*

According to the WHO criteria, the disease is morphologically graded into:

- grade 1 (<5 centroblasts /hpf)
- grade 2 (6–15 centroblasts/hpf)
- grade 3 (>15 centroblasts/hpf).
- grade 3 subdivided into:
 - grade 3A (centrocytes still present)
 - grade 3B (the follicles consist almost entirely of centroblasts)



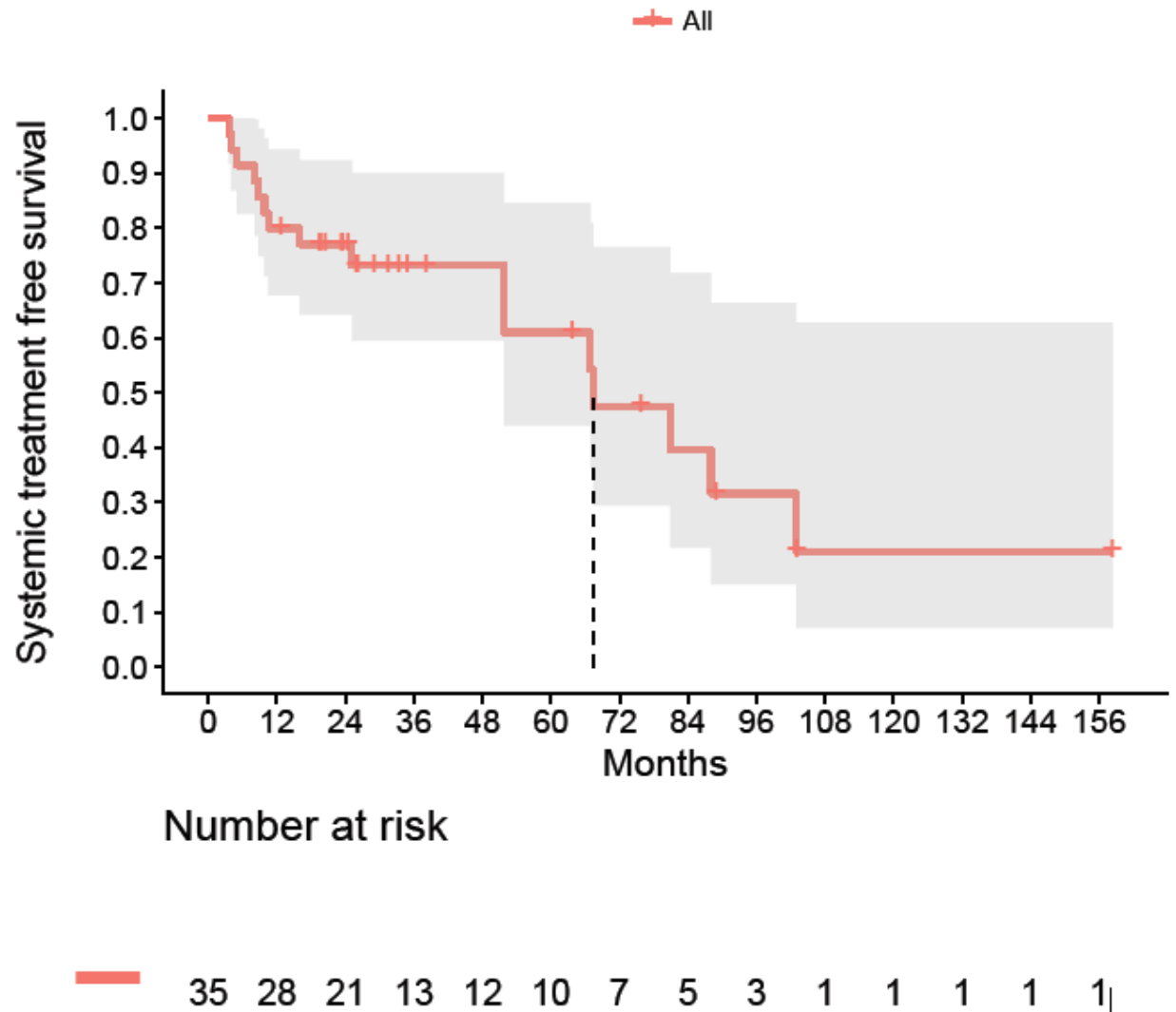
Enhancer of Zeste Homolog 2 (EZH2)



- A model for the collaboration of epigenetic silencing enzymes, including core of the PRC2 complex, DNA methyltransferase (DNMT), and histone deacetylase (HDAC). In this model, if K27 is pre-acetylated, HDAC may first deacetylates it, and then the target genes are silenced through the methylation of K27 by PRC2. DNMTs may also be recruited by PRC2, and after methylating CpG DNA of target genes, making the chromatin state more deeply silenced. Ac, acetyla <https://www.nature.com/articles/aps2013161/figures/2tion>; and Me, methylation.

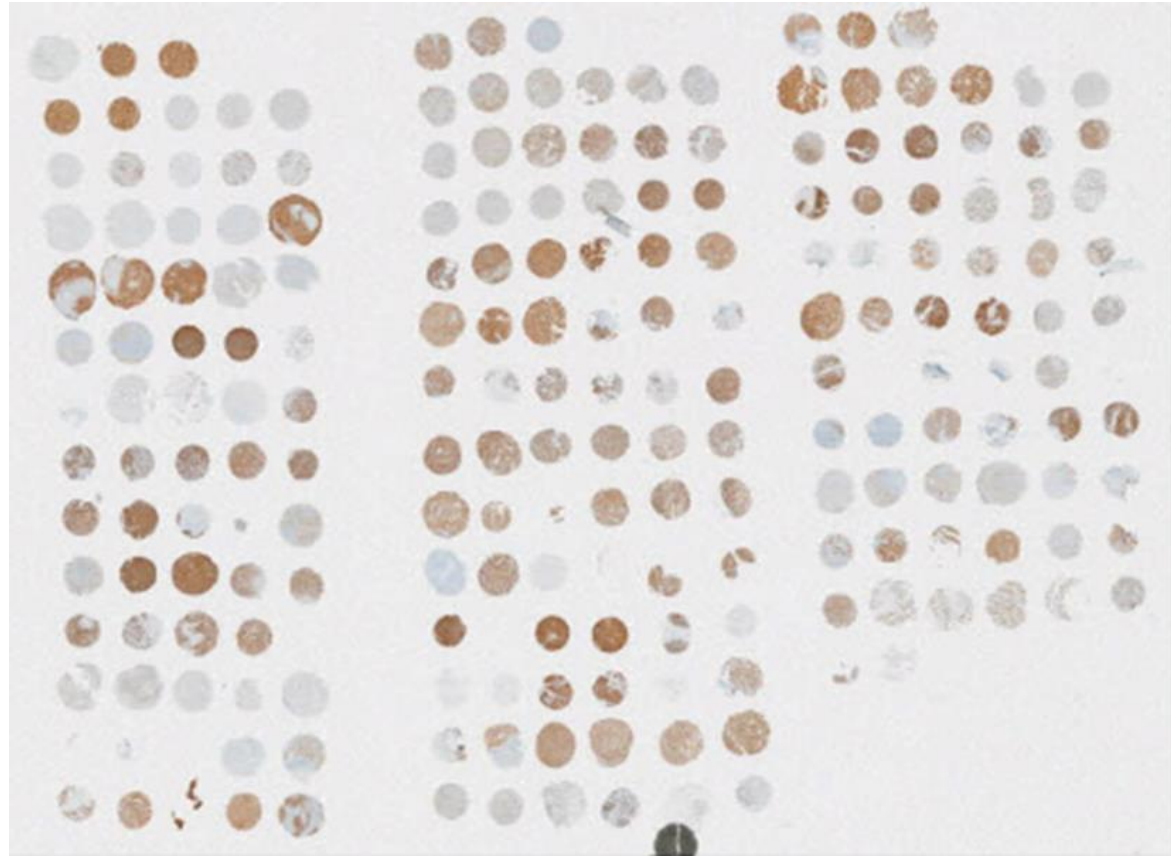
• Method

- 35 patients
- 2 sub-cohorts:
 - -before 24 months
 - -after 24 months



• Method

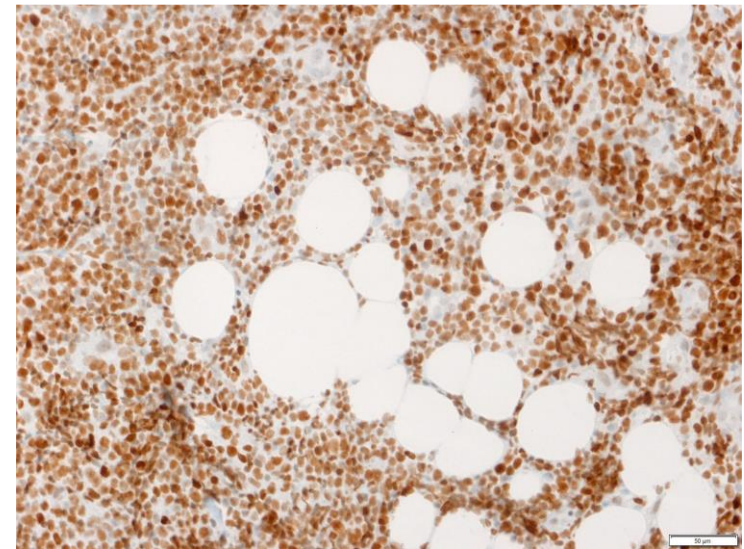
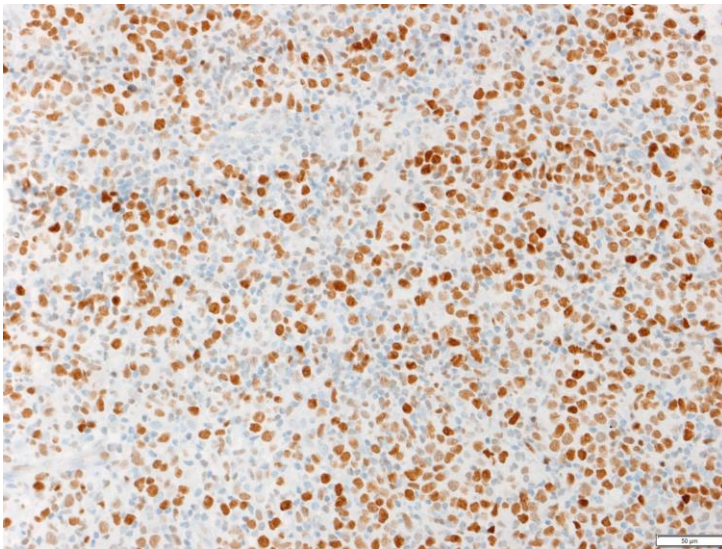
- FL cases 1999 – 2017
- Tissue microarrays were constructed
- Immunohistochemical assessment of EZH2 (Ventana, SP129, RTU)
- cut-off points: EZH2 $\geq 70\%$



Characteristics of the stratified cohorts		
	<u>Systemic treatment after 24 months</u>	<u>Systemic treatment within 24 months</u>
Sex n (%)		
Female	17 (81.0)	7 (87.5)
Male	4 (19.0)	1 (12.5)
Age median (IQR)	52.00 (44.00, 60.00)	51.00 (47.75, 55.75)
FLIPI 1 <u>score</u> n(%)		
0	5 (23.8)	0 (0.0)
1	7 (33.3)	2 (25.0)
2	4 (19.0)	4 (50.0)
4	2 (9.5)	1 (12.5)
NA	3 (14.3)	1 (12.5)
FLIPI 2 <u>score</u> n (%)		
0	5 (23.8)	2 (25.0)
1	6 (28.6)	0 (0.0)
2	3 (14.3)	2 (25.0)
NA	7 (33.3)	4 (50.0)
Histological grade n (%)		
Low		
High	2 (9.5)	3 (37.5)
G 1	19 (90.5)	5 (62.5)
G 2	7 (33.3)	4 (50.0)
G 3a	12 (57.1)	1 (12.5)
	2 (9.5)	3 (37.5)
EZH (%)>=70%	3 (14.3)	5 (62.5)

Results

	<u>Systemic</u> <u>treatment after</u> <u>24 months</u>	<u>Systemic</u> <u>treatment within</u> <u>24 months</u>	<u>p-value</u>
EZH (%)>=70%	3 (14.3)	5 (62.5)	0.033



- ***EZH2 alterations in follicular lymphoma: biological and clinical correlations***

- *S Huet, L Xerri, B Tesson, S Mareschal, S Taix, L Mescam-Mancini, E Sohier, M Carrère, J Lazarovici, O Casasnovas, L Tonon, S Boyault, S Hayette, C Haioun, B Fabiani, A Viari, F Jardin, and G Salles, Blood Cancer J. 2017 Apr; 7(4)*

- **The protein level of EZH2 assessed by IHC showed a significant increased expression only for patients with a genomic gain ($P < 0.001$).**
- The presence of an *EZH2* genetic alteration was an independent factor associated with a **longer progression-free survival** (hazard ratio 0.58, 95% confidence interval 0.36–0.93, $P = 0.025$). We propose that the copy-number status of *EZH2* should also be considered when evaluating patient stratification and selecting patients for *EZH2* inhibitor-targeted therapies.
- **The presence of an alteration (gain and/or mutation) in *EZH2* had a favorable impact on PFS ($P = 0.026$).** Non-altered patients had a median PFS of 58 months, whereas it was not reached for patients carrying an *EZH2* alteration. !!!

- *Six Years (2012–2018) of Researches on Catalytic EZH2 Inhibitors: The Boom of the 2-Pyridone Compounds*

- *Rossella Fioravanti, Giulia Stazi, Clemens Zwergel, Sergio Valente, and Antonello Mai*

Chem Rec. 2018 Dec;18(12)

- EZH2 is expressed in a wide range of B-cell lymphomas including Burkitt's lymphoma, mantle cell lymphomas (MCLs), **follicular lymphoma (FL)**, and diffuse large B-cell lymphomas (DLBCLs), [15] and its **overexpression and high levels positively correlated with aggressiveness and unfavorable prognosis.**

- <https://onlinelibrary.wiley.com/doi/abs/10.1002/tcr.201800091>

• *Conclusons*

- EZH2 protein expression was more frequently observed in the group that required the introduction of systemic therapy within the first 24 months.
- EZH2 protein can be biomarker for a first line selection of patients for targeted EZH2 inhibitor therapies.

- *Last word – Future plans*

- EZH2 gen alteration
- EZH2 metylation products

THANK YOU!
