Follicular Lymphomas Workshop

Bologna
Royal Hotel Carlton
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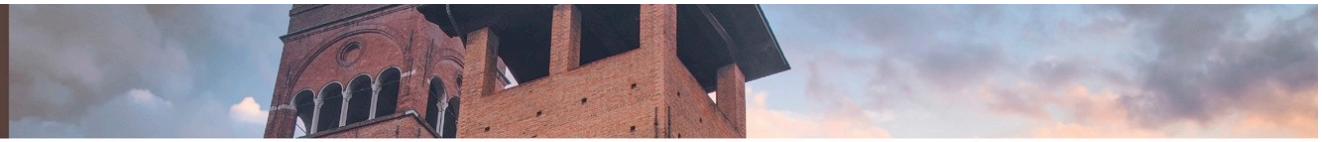
President: *Pier Luigi Zinzani*

Targeting EZH2 in Lymphoma: tazemetostat

Vincent Ribrag DITEP Gustave roussy

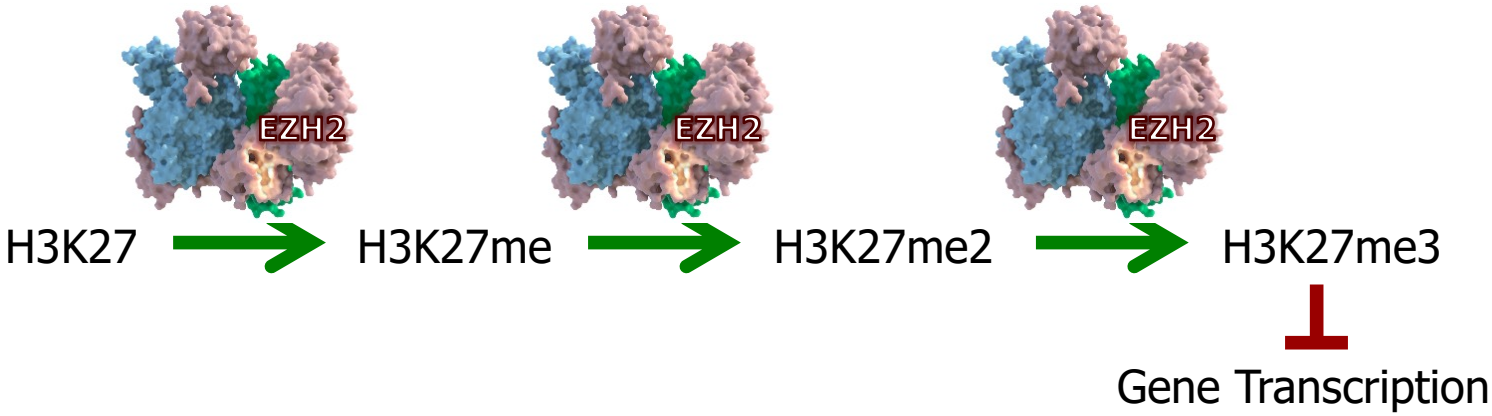


Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
ABBVIE					X		
Astex	X						
AZ			X				
BEIGENE					X		
GSK	X						
IPSEN					X		
Lilly						X	
Pegascy		X					

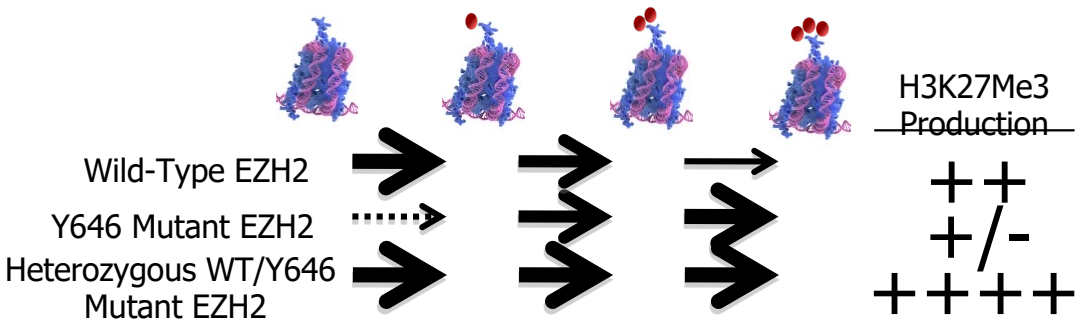
EZH2 Catalyzed Chromatin Remodeling

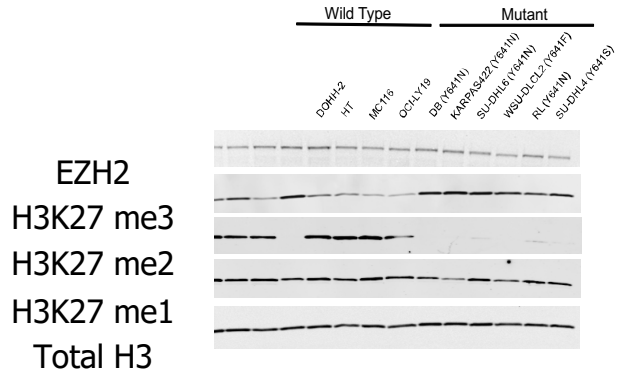
- EZH2 is the catalytic subunit of the multi-protein PRC2 (polycomb repressive complex 2)
- PRC2 is the only protein methyltransferase that can methylate H3K27
  - Catalyzes mono-, di- and tri-methylation of H3K27
  - H3K27me3 is a transcriptionally repressive histone mark
- Aberrant trimethylation of H3K27 is oncogenic in a broad spectrum of human cancers, such as B-cell NHL



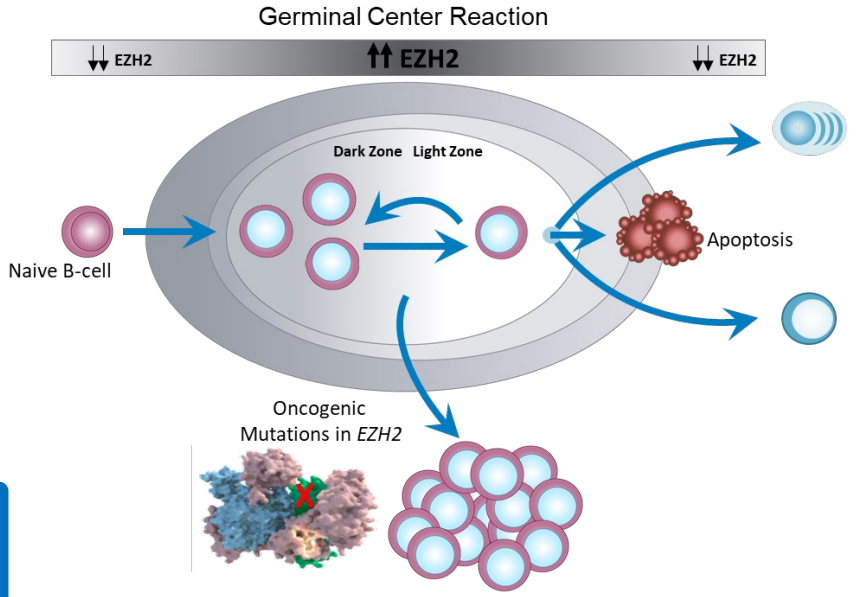
Chase & Cross, Clin. Cancer Res., 2011

EZH2 Gain of Function Mutations Result in Elevated H3K27me3 Levels





20% FL
10% DLBCL (GC)

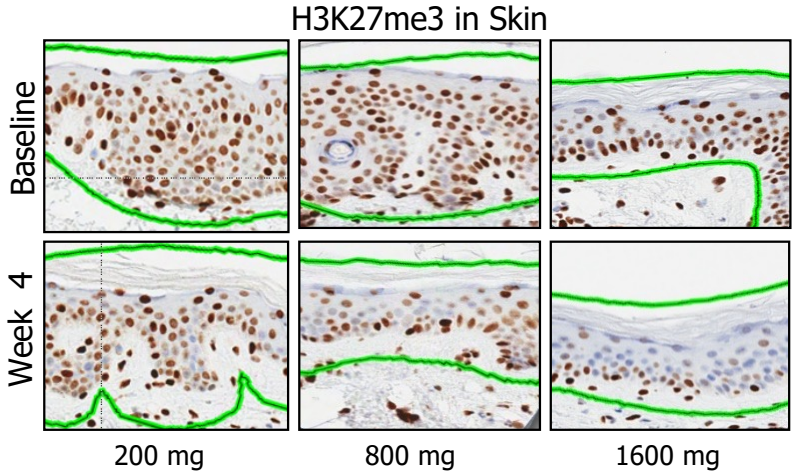


Sneeringer et al, PNAS, 2010

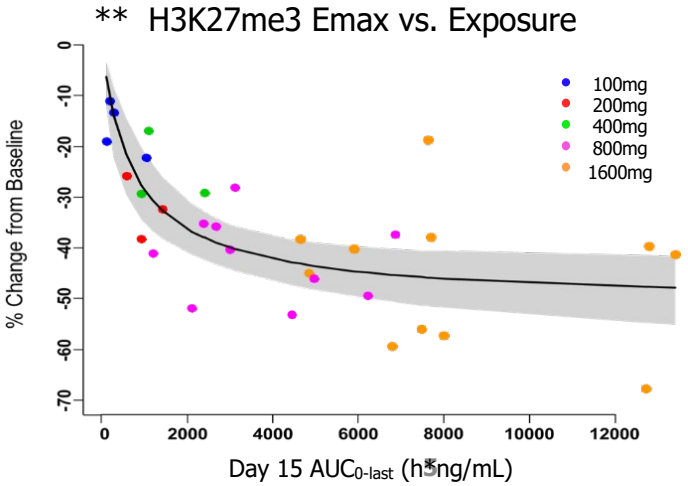
Tazemetostat Phase 2 Dose Selection

Dose BID	Efficacy	Safety	PK/PD
	Response in NHL (%)	Grade ≥3 TEAE *	H3K27me3 Inhibition Emax **
<800 mg	2/9 (22%)	7/24 (29%)	-
800 mg	5/8 (62%)	3/19 (16%)	81%
1600 mg	2/4 (50%)	4/12 (33%)	91%

* Treatment Emergent Adverse Events in all patients (n=55)

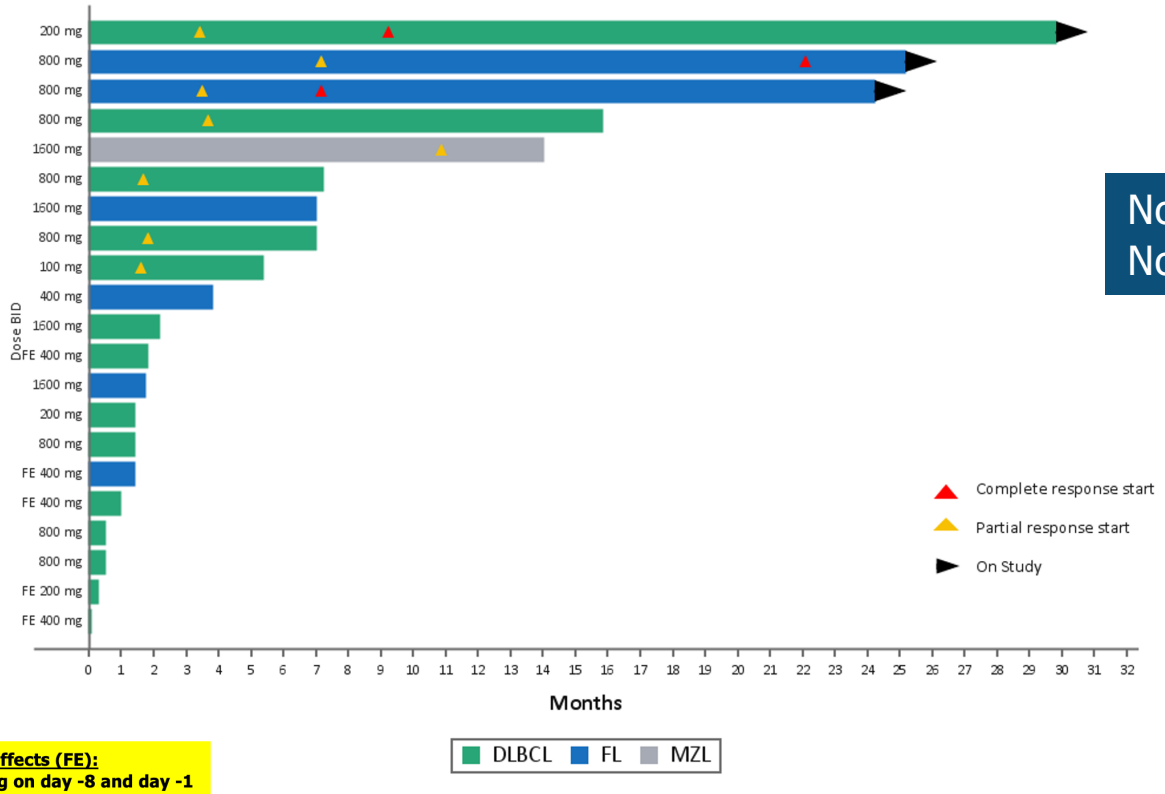


from Ribrag et al., ASH 2015



Objective Response in NHL
All Patients (n=21) and solid tumors (SWI-SNIF abnormalities)

Objective Response in NHL
All Patients (n=21)



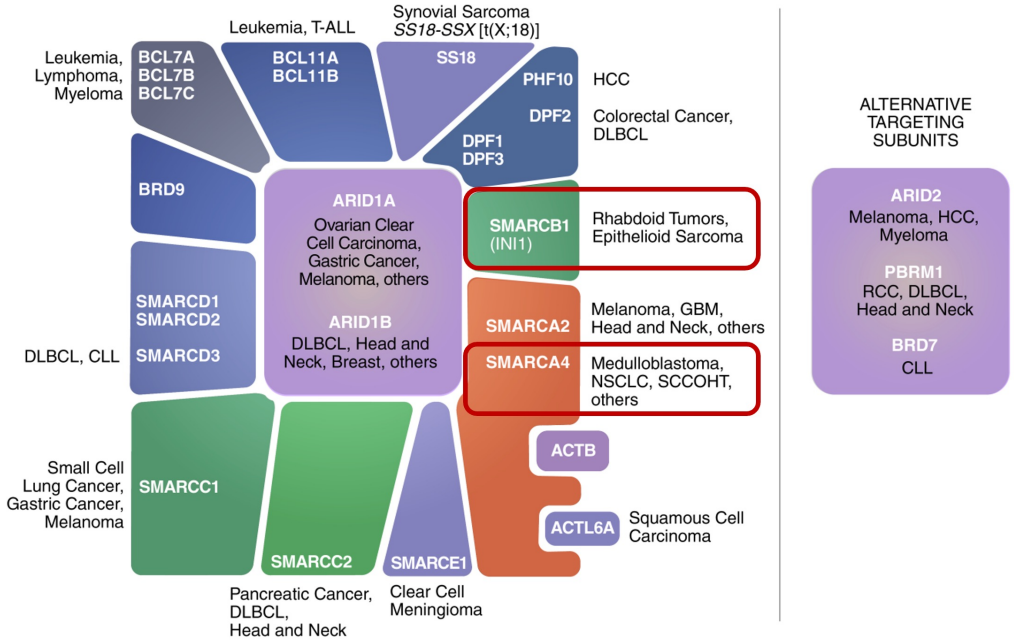
per Cheson/IWG Criteria, 2007

Food Effects (FE):
200 mg on day -8 and day -1
400 mg BID from day 1

No drug-drug interaction identified
No Food drug effect on PK

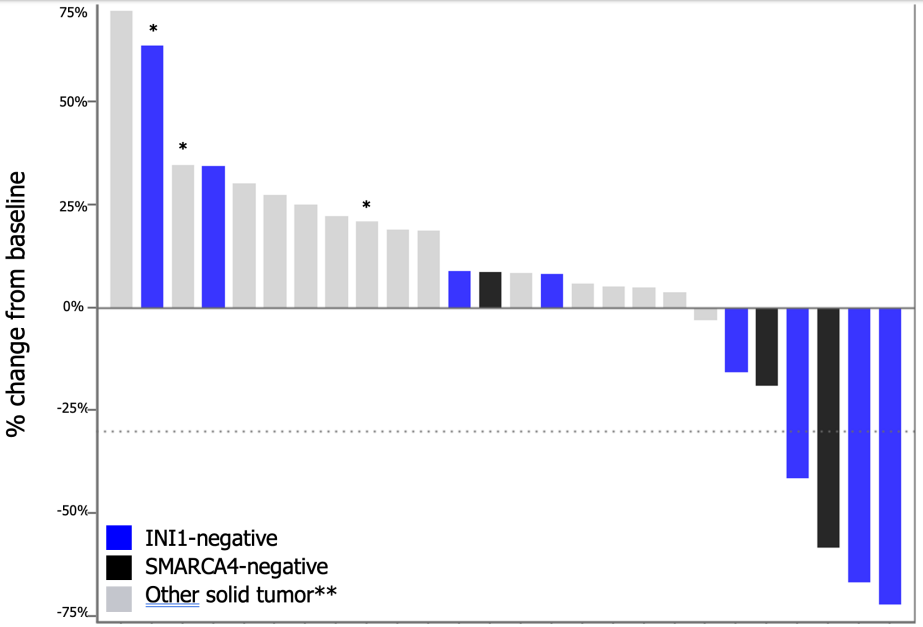
Inhibiting EZH2: a "specific" H3K27 epigenetic process

Subunits of SWI/SNF Complexes Are Mutated Across Many Indications



Adapted from Kadoch 2015

Best Response in Patients with Solid Tumors

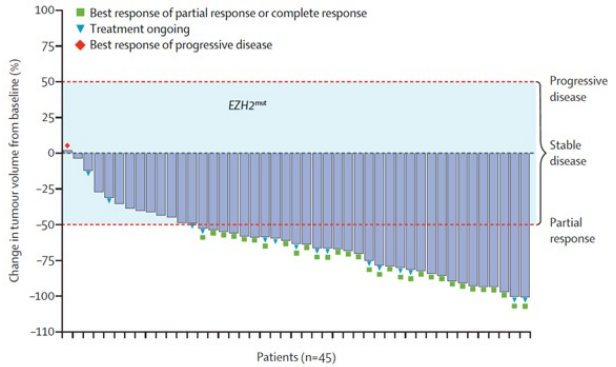


And open transcription (opposite effect to PRC2-EZH2)

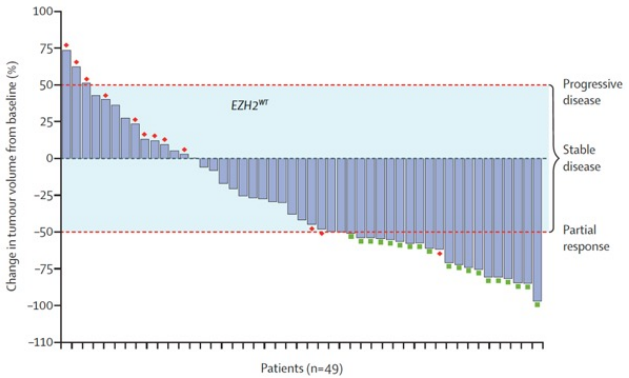
Loss of function of the SWI/SNF complex
EZH2 avid tumor : epigenetic lethality

Objective Response in phase II FLNHL

Mutated



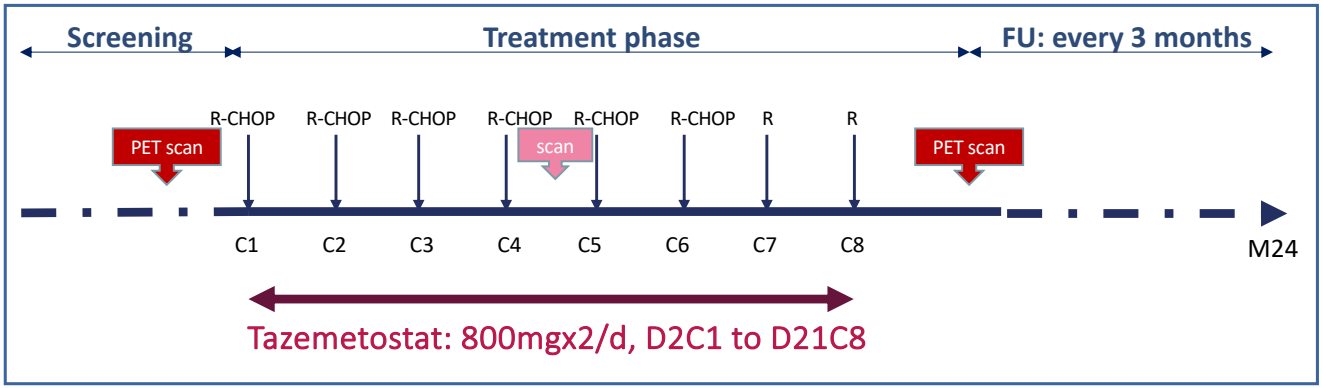
WT



- FDA approved in epithelioid sarcoma (Jan-2020)
- FDA approved for RR-FL (june-2020)

Epi-RCHOP: Phase Ib-II study of R-CHOP + Tazemetostat

- Elderly (60-80 y/o) newly diagnosed DLBCL



Prophylaxis with G-CSF, valaciclovir and trimethoprim sulfamethoxazole strongly recommended.

- Phase Ib: RP2D 800mgx2/D *(Sarkozy et al, CCR 2018)*
- **Phase II: Primary objective is Metabolic complete response rate (Lugano 2014)**
- Sample size:
  - H0 70% (*GOYA, REMARC*), H1 80%
  - Power 90%, alpha 0.05, drop out 5%
  - **122 included patients**

Vitolo et al, J Clinic Oncol , 2017
Thieblemont et al, J Clinic Oncol 2017

Primary endpoint: sensitivity analysis

- **Sensitivity set: CMR 82.1%**

N=10 pts with consent withdrawal removed

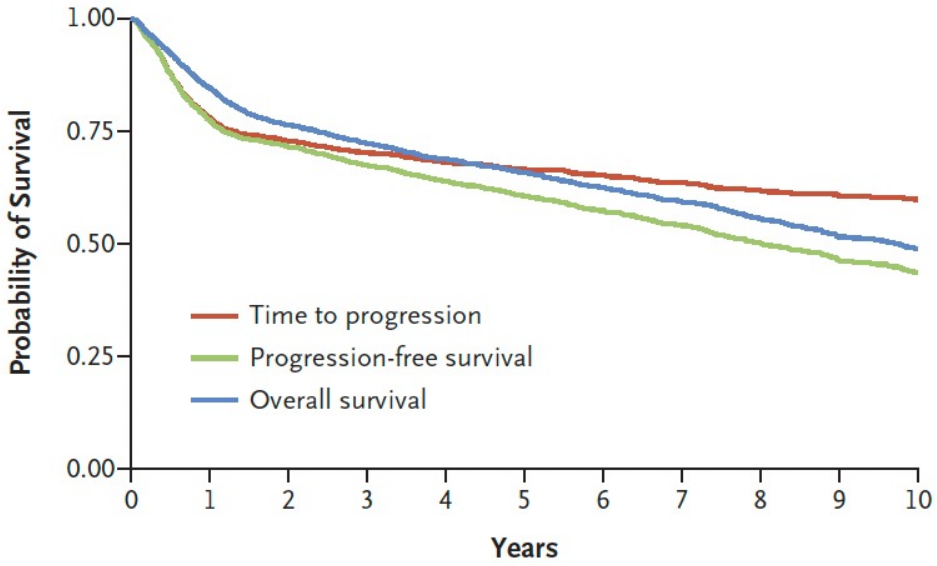
Analysis sets	Safety set, N=122	Sensitivity set, N=112
ORR	100 (82%)	100 (89.3%)
CMR	**92 (75.4%)**	**92 (82.1%)**
PMR	8 (6.6%)	8 (7.1%)
Progressive disease	5 (4.1%)	5 (4.5%)
Death	2 (1.6%)	2 (1.8%)
Not evaluated	**15 (12.3%)**	**5 (4.5%)**

- No significant correlation between *EZH2* mutational status in ctDNA and CMR (N=119, p=0.37) or EZB subgroup (tumor biopsy, N=76, p=0.12)

Outcome

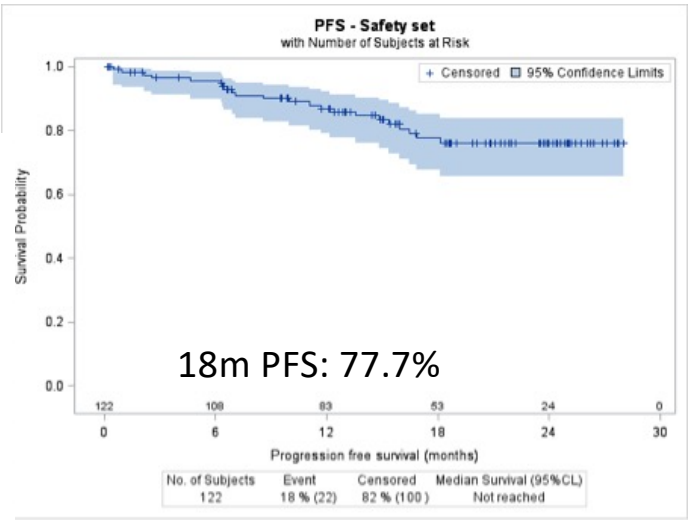
- Median Follow-up: 18.5m (15.4-21m)
- 17 patients had a progression (13.9%),
    - 5 deaths w/o progression
- 12 patients died while on study:
    - Lymphoma, N=4
    - Toxicity, N=4 (AML, heart failure, 2 sepsis)
    - COVID, N=2 and ARDS, N=1
    - Unknown, N=1, in CR
- No difference in PFS based on *EZH2* mutational status or EZB subtype

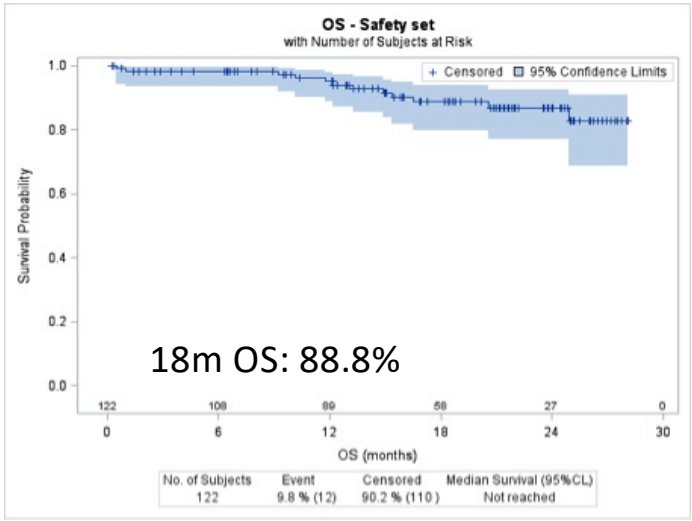
Outcome



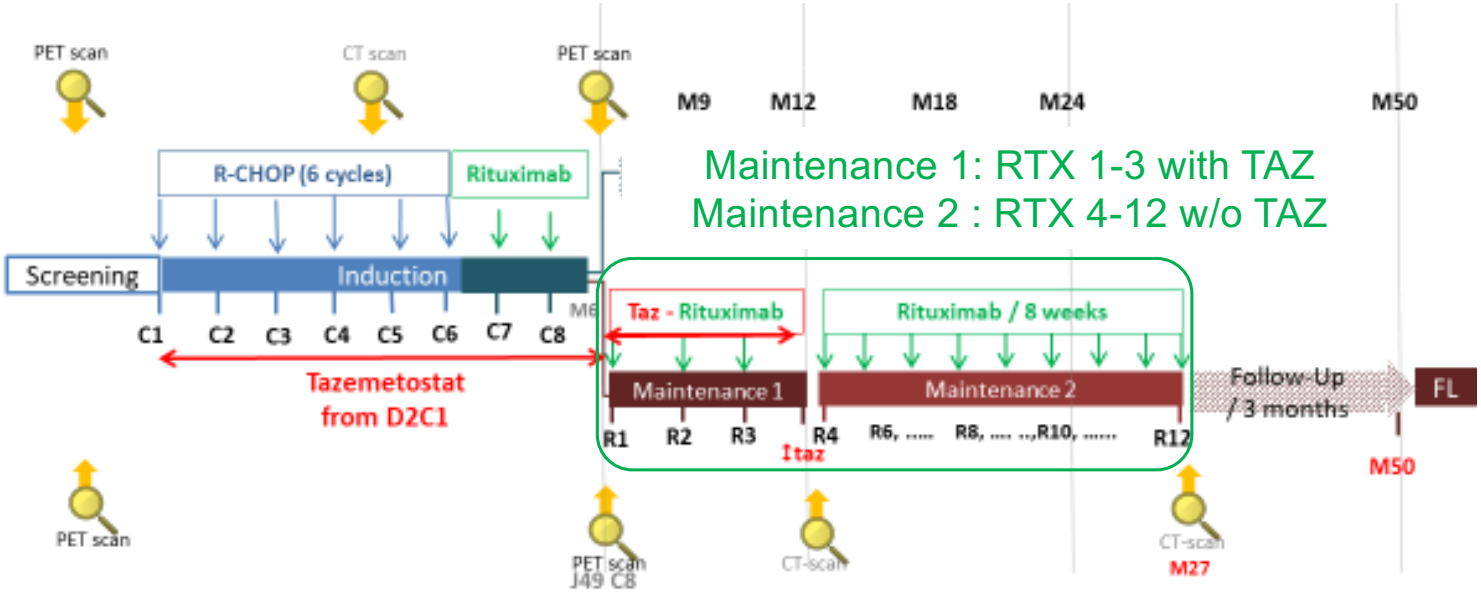
No. at Risk

Time to progression	3082	2133	1775	1446	1236	1048	830	700	585	468	391
Progression-free survival	3082	2132	1774	1445	1235	1047	829	699	584	467	390
Overall survival	3082	2336	1900	1558	1338	1140	911	767	647	519	437





Epi-RCHOP: two sub-studies in frontline FL & elderly DLBCL



Information about treatment

R-CHOP

Induction by 6 cycles + 2 cycles R, every 21 days

- Rituximab: D1 - 375mg/m² + C7 et C8
- Prednisolone: D1 to D5 - 40mg/m²
- Cyclophosphamide: D1 - 750mg/m²
- Doxorubicine: D1 - 50mg/m²
- Vincristine: D1 – **1 mg TOTAL DOSE**

TAZEMETOSTAT

800mg BID continuously

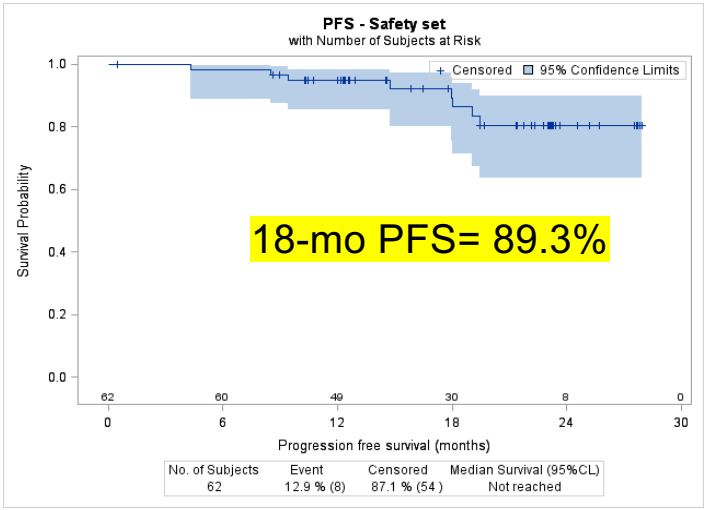
- DLBCL : 167 days
- FL : 167 days + 6 months

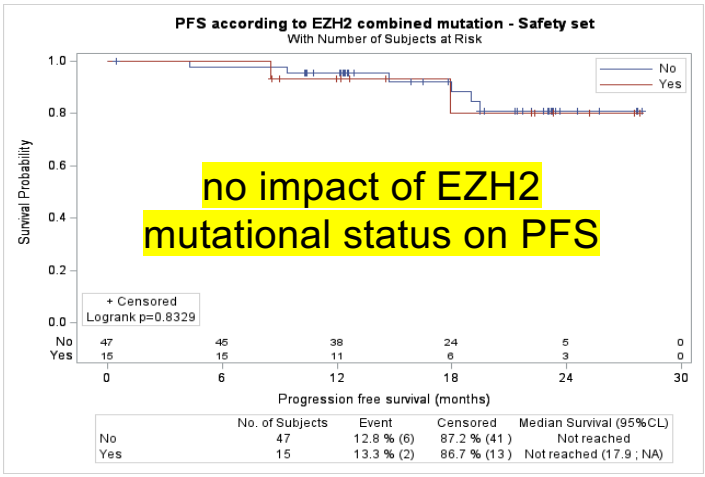
Phase Ib TAZ+R-CHOP: 800mg BiD was the RP2D (consistent with TAZ monotherapy)

Sarkozy C et al, Clin Can Res 2018

Outcomes, PFS and OS

- Median Follow-up: 19 mo
- 18-mo PFS= 89.3%
- 7 patients (11.3%) had a progression (4-19 mo)
  - 5 received a new line of therapy
- 2 patients died while on study:
  - Lymphoma, N=1
  - Covid-19, N=1





Background and SYMPHONY-1 phase 1b trial design

Dose-escalating 3+3 design

Patients with R/R FL (N=44)

TAZ (12 cycles):
400/600/800 mg PO BID*
Rituximab (5 cycles):
375 mg/m^2 IV†
Lenalidomide (12 cycles):
20/10 mg PO QD‡

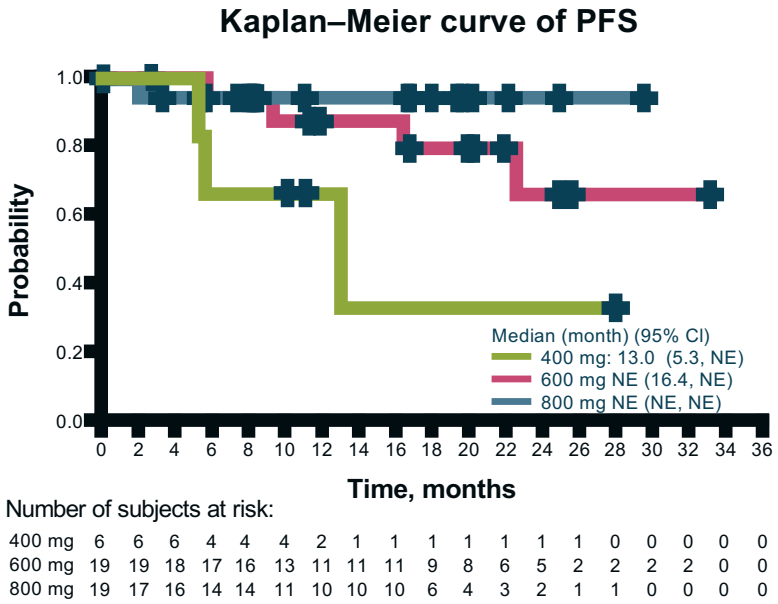
RP3D:
800 mg BID TAZ (24 cycles)§

- **Primary endpoints:** Safety and tolerability, RP3D of TAZ in combination with R[2]
- **Secondary endpoints:** PK parameters
- **Efficacy analysis (ITT):** Best overall response, PFS and DOR (investigator assessment, according to Lugano 2014 response criteria)[1]

- EZH2 is an important regulator of B cell development; gain of function mutations (MT EZH2) or uncontrolled upregulation of wild type (WT) EZH2 may lead to the development of FL, making EZH2 a therapeutic target in FL[2–4]
- TAZ is a small molecule inhibitor of the epigenetic enzyme EZH2[2–4]

- TAZ is FDA-approved[5] for treatment of adult patients with:
  - R/R FL with MT EZH2 and ≥2 prior therapies
  - R/R FL with no satisfactory alternative treatment options

Long-lasting PFS and durable response at TAZ RP3D (800 mg) + R^2



	TAZ dose + R^2			
DOR event rate, % (95% CI)	400 mg (n=6)	600 mg (n=19)	800 mg (n=19)	otal (N=44)
6 months	66.7 (19.5, 90.4)	94.4 (66.6, 99.2	100.0 (100.0, 100.0)	92.2 77.8, 97.4)
12	33.3 (1.4, 75.5)	87.7 (58.8, 96.8	100.0 (100.0, 100.0)	85.1 67.3, 93.6)
18	33.3 (1.4, 75.5)	79.7 (48.7, 93.1	100.0 (100.0, 100.0)	81.0 61.8, 91.2)
24	33.3 (1.4, 75.5)	66.4 (29.8, 87.1	100.0 (100.0, 100.0)	72.0 45.3, 87.3)

- **Median PFS and DOR were not reached at 22.5 months**
- **PFS appeared dose-dependent**
- **18-month PFS estimates:**
  - **79.5% (ITT; N=44)**
  - **94.4% (800 mg cohort; n=19)**

Kaplan-Meier estimate for DOR events at each timepoint by dose group (ITT). DOR defined for each subject with response as time from first date of response (complete or partial, whichever is first) to first objectively documented disease progression or death.
CI, confidence interval; DOR, duration of response; ITT, intent-to-treat; NE, not evaluable; PFS, progression-free survival; R^2, lenalidomide and rituximab; TAZ, tazemetostat.

conclusions

- Targeting EZH2 is a targeted therapy in hematology and oncology
- Symphony results are not still mature
- First trials combining Tazemetostat and R-CHOP in FL and DLBCL
- Safety profile acceptable: 84.4% of the pts received 6 cycles R-CHOP and 77% the planned do
    - Incidence of hematological toxicities comparable to R-CHOP-X studies.
    - Incidence of digestive toxicities decreased with caping of vincristine dosage
    - Infection: COVID era & an elderly population