

# What's new in the treatment of Follicular Lymphoma?

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# Topics

- **Follicular Lymphoma Background**
- **1<sup>st</sup> Line Treatment of Follicular lymphoma**
- **Maintenance**
- **Relapsed Follicular Lymphoma – Targeted therapies**

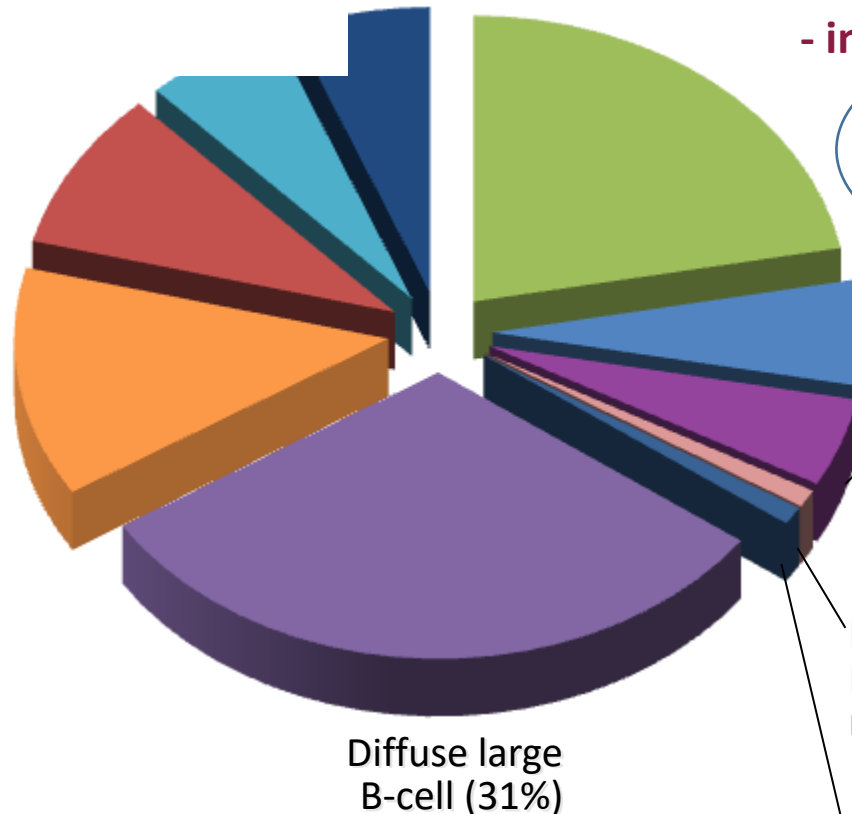
# NHL SUBTYPES IN ADULTS

## Mantle cell lymphoma

- more rapid growing lymphoma
- incurable

Other subtypes with a frequency  $\leq 2\%$  (9%)

Composite lymphomas (13%)



## Indolent NHL

- slow growing lymphomas
- incurable

Follicular lymphoma (FL) (22%)

Small lymphocytic lymphoma (SLL) (6%)

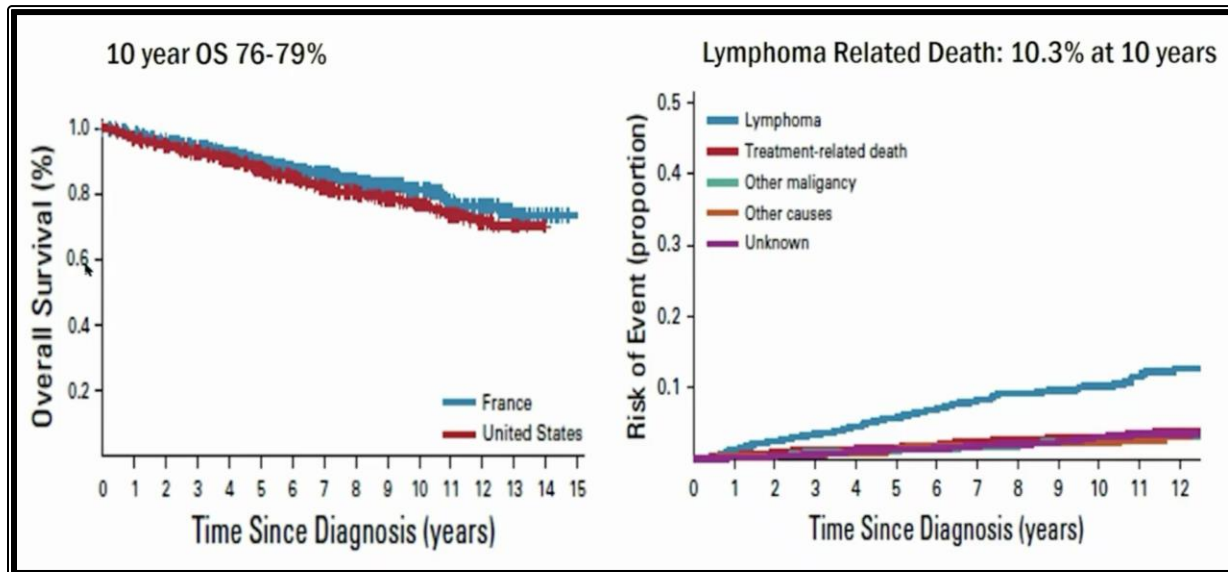
Marginal zone B-cell lymphoma (MALT type) (5-8%)

Marginal zone B-cell lymphoma nodal type (1%)

Lymphoplasmacytic lymphoma (LPL) (1%)

# FOLLICULAR LYMPHOMA

- Follicular lymphoma (FL) is the most common type of indolent NHL
- represents ~70% of indolent NHL and 20–25% of NHL overall<sup>1,2</sup>
- Median OS 12-15 years, med PFS 6-8y
- 10 year OS about 80%
- Cure unlikely



1. The Non-Hodgkin's Lymphoma Classification Project. *Blood* 1997; 89:3909–3918.

2. Cheson BD and Coiffier B. In *Atlas of Clinical Hematology 2<sup>nd</sup> edition*. Springer: Armitage JO ed

3. Sarkozy et al, *JCO* 2019

# Treatment of advanced Follicular NHL

# Lymphoma survival

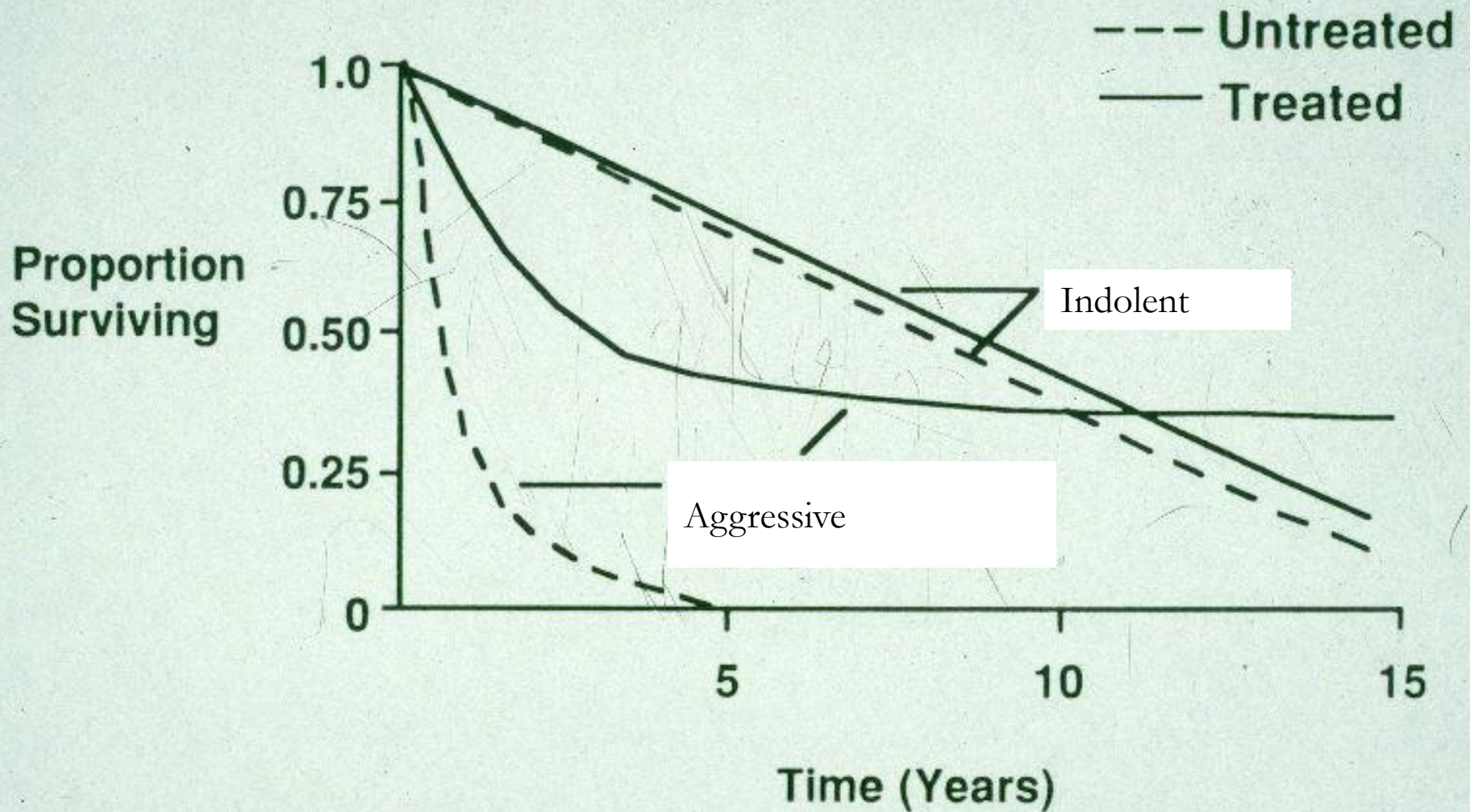
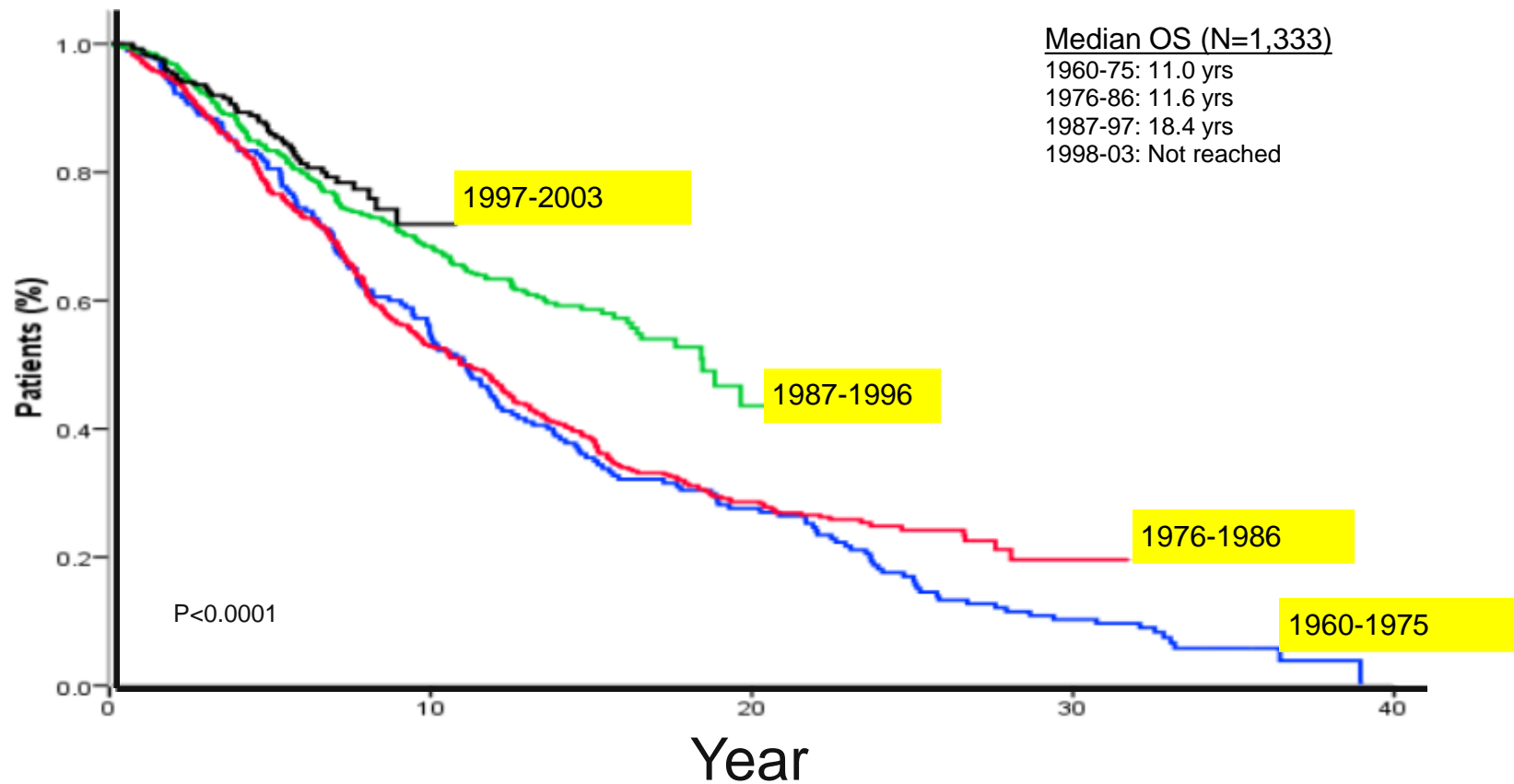
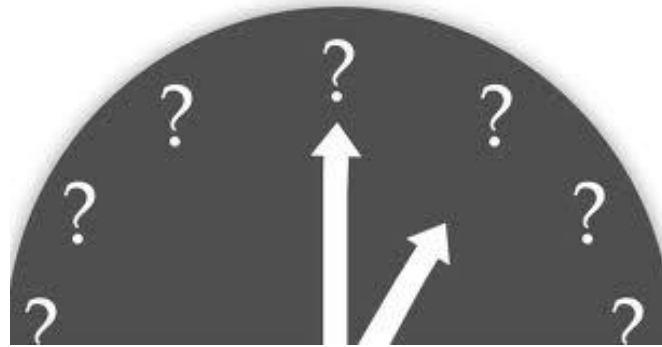


Figure 1. Lymphoma survival.

# Survival of patients with Follicular Lymphoma: the Stanford experience, 1960–2003



# When to initiate treatment?



GELF = Groupe d'Etude des Lymphomes Folliculaires

BNLI = British National Lymphoma Investigation Group

# TO TREAT OR NOT TO TREAT ????

## GELF criteria

Involvement of  $\geq 3$  nodal sites, each with a diameter of  $\geq 3$  cm

Any nodal or extranodal tumor mass with a diameter of  $\geq 7$  cm

B symptoms

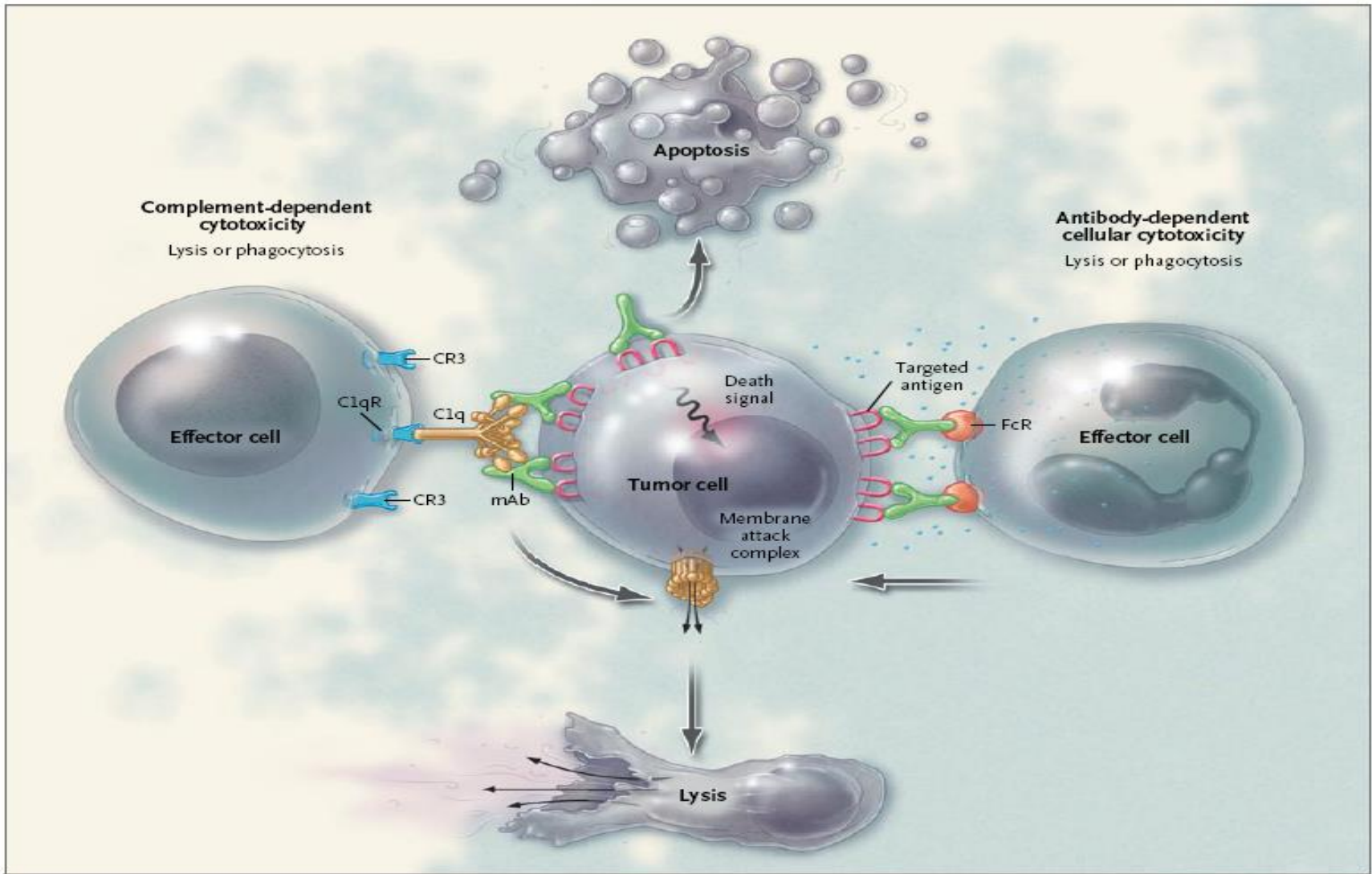
Splenomegaly

Pleural effusions or peritoneal ascites

Cytopenias (leukocytes  $< 1.0 \times 10^9/L$  and/or platelets  $< 100 \times 10^9/L$ )

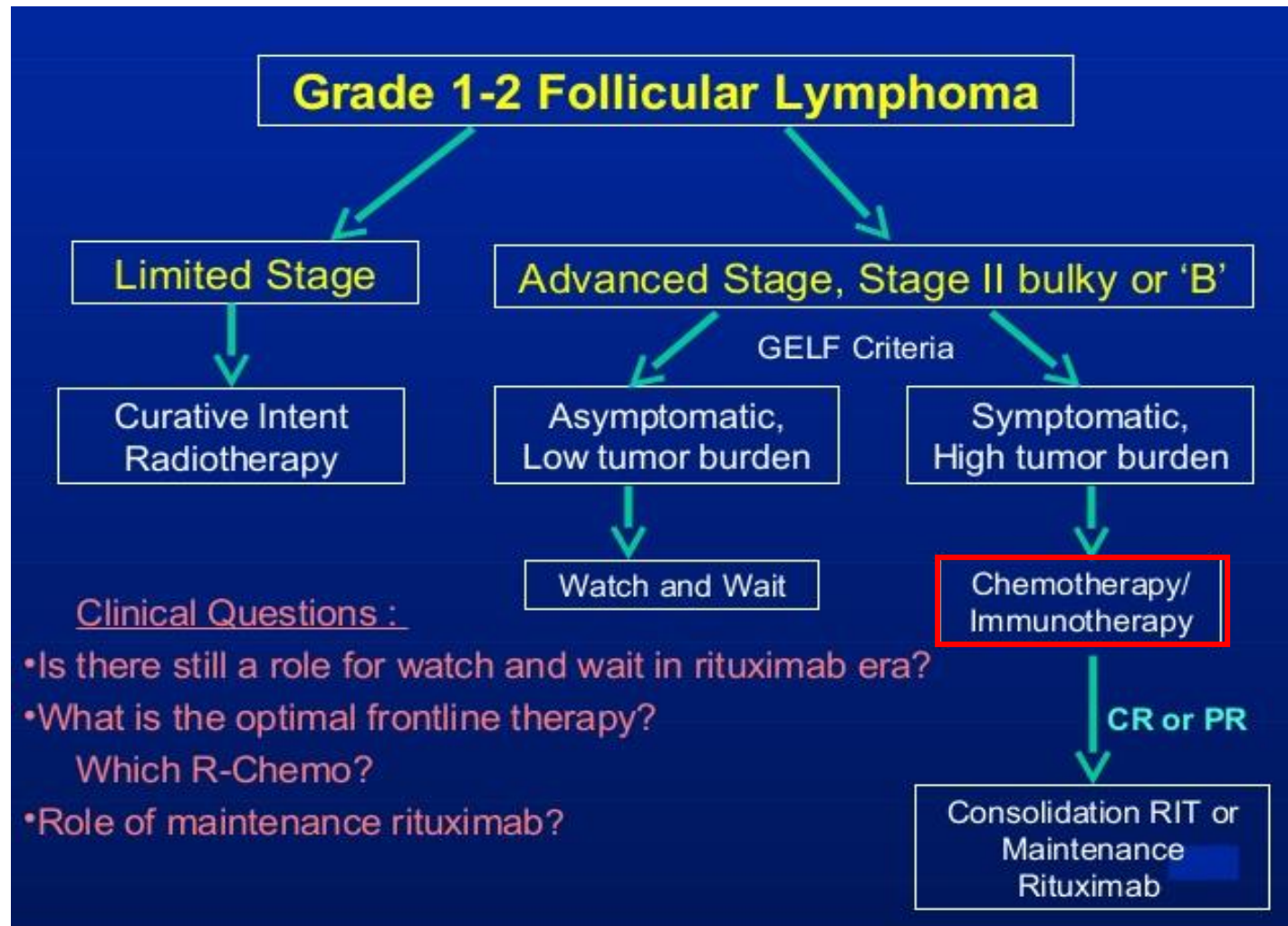
Leukemia ( $> 5.0 \times 10^9/L$  circulative malignant cells)

# Rituximab - Mechanism of action



# Rituximab plus chemotherapy for first line treatment of advanced Follicular NHL

# TREATMENT OF FOLLICULAR LYMPHOMA



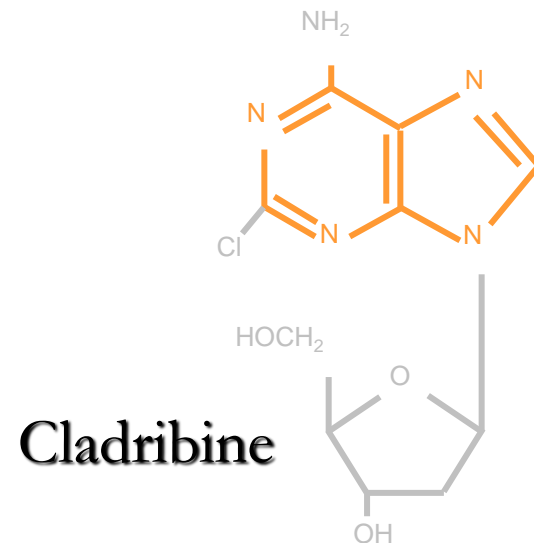
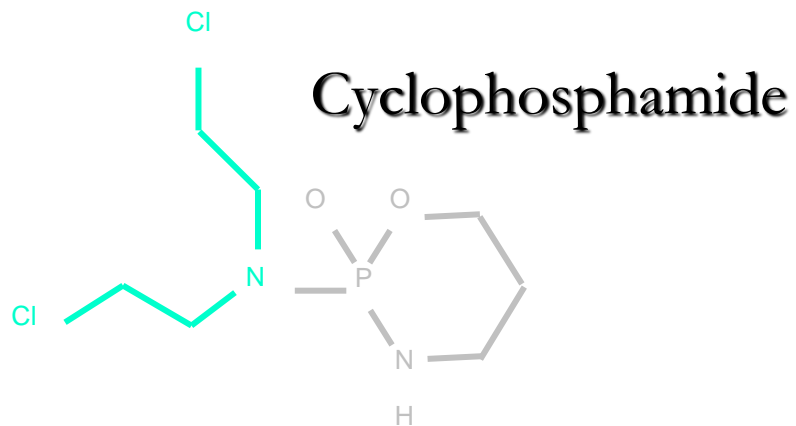
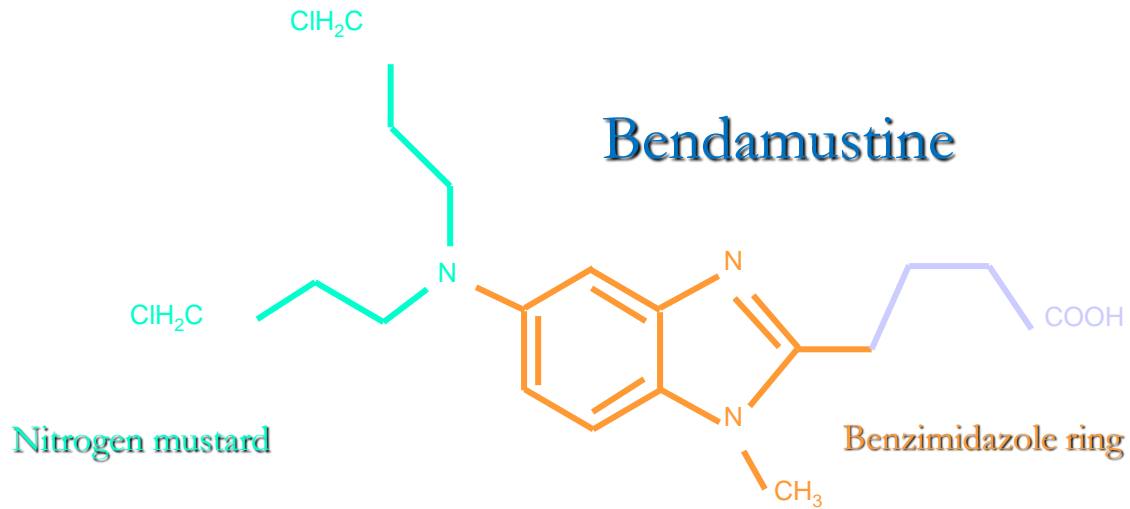
# INITIAL TREATMENT FOR ADVANCED DISEASE

CIT is generally recommended for active therapy			R <sup>2</sup> considered for certain patients (eg, those desiring chemo-free regimens)	R maintenance for patients who respond to induction therapy
StiL <sup>1</sup> Phase 3 BR vs R-CHOP	BRIGHT <sup>2</sup> Phase 3 BR vs R-CHOP/R-CVP	GALLIUM <sup>3</sup> Phase 3 G- vs R-chemo	RELEVANCE <sup>4</sup> Phase 3 R <sup>2</sup> (lenalidomide + R) vs R-chemo	PRIMA <sup>5,6</sup> Phase 3 Rituximab maintenance
<ul style="list-style-type: none"> <li>BR superior to R-CHOP</li> </ul>	<ul style="list-style-type: none"> <li>Trend towards PFS benefit with BR vs R-CHOP/R-CVP</li> </ul>	<ul style="list-style-type: none"> <li>Superior PFS with G- vs R-chemo, but no difference in OS</li> <li>More grade 3-5 AEs with G (75% vs 68%)</li> <li>Approval in 2017 for initial chemotherapy and maintenance G</li> </ul>	<ul style="list-style-type: none"> <li>Similar efficacy with R<sup>2</sup> compared with R-chemotherapy</li> <li>Less hematologic toxicity with R<sup>2</sup>, but more grade 3/4 cutaneous toxicity (7% vs 1%)</li> </ul>	<ul style="list-style-type: none"> <li>Superior PFS (and TTNT), but not OS, with R maintenance</li> <li>FDA approved in 2011 as maintenance therapy in patients with FL who respond to induction therapy</li> </ul>

1. Rummel MJ, et al. *Lancet*. 2013;381:1203. 2. Flinn IW, et al. *J Clin Oncol*. 2019;37:984.  
3. Marcus R, et al. *N Engl J Med*. 2017;377:1331. 4. Morschhauser F, et al. *N Engl J Med*. 2018;379:934.  
5. Salles G, et al. *Lancet*. 2011;377:42. 6. Bachy E, et al. *J Clin Oncol*. 2019;37:2815.

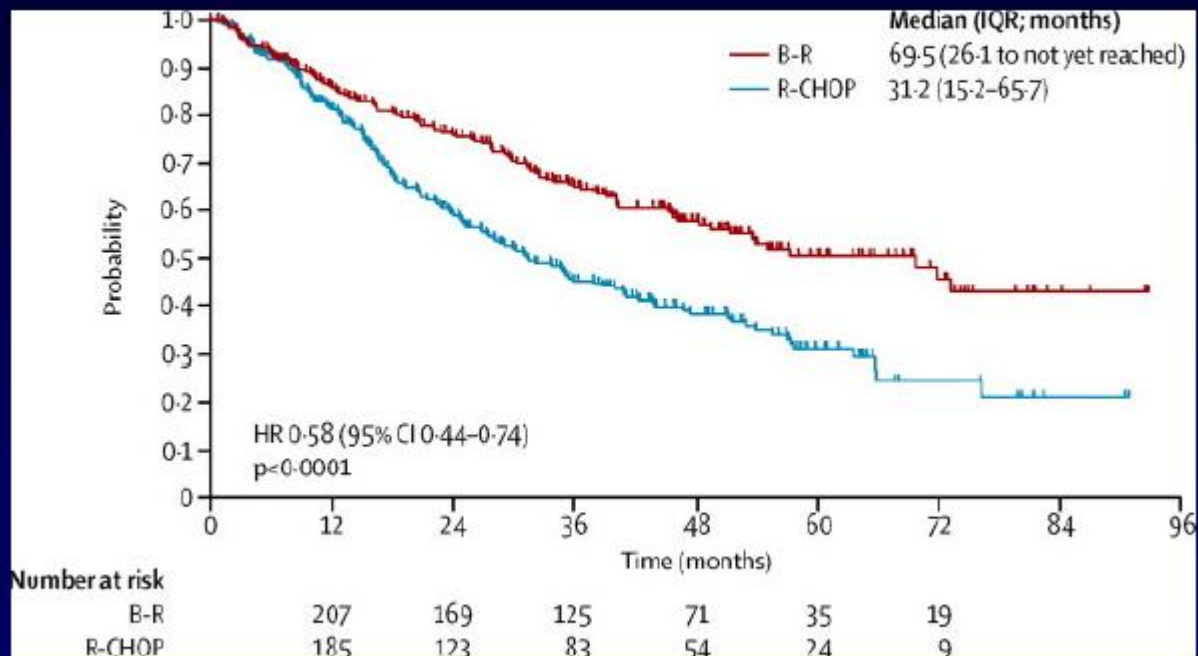
# Bendamustine

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# RCHOP or R-bendamustine?

## Advanced-Stage Indolent NHL Chemotherapy: R-CHOP vs R-Benda

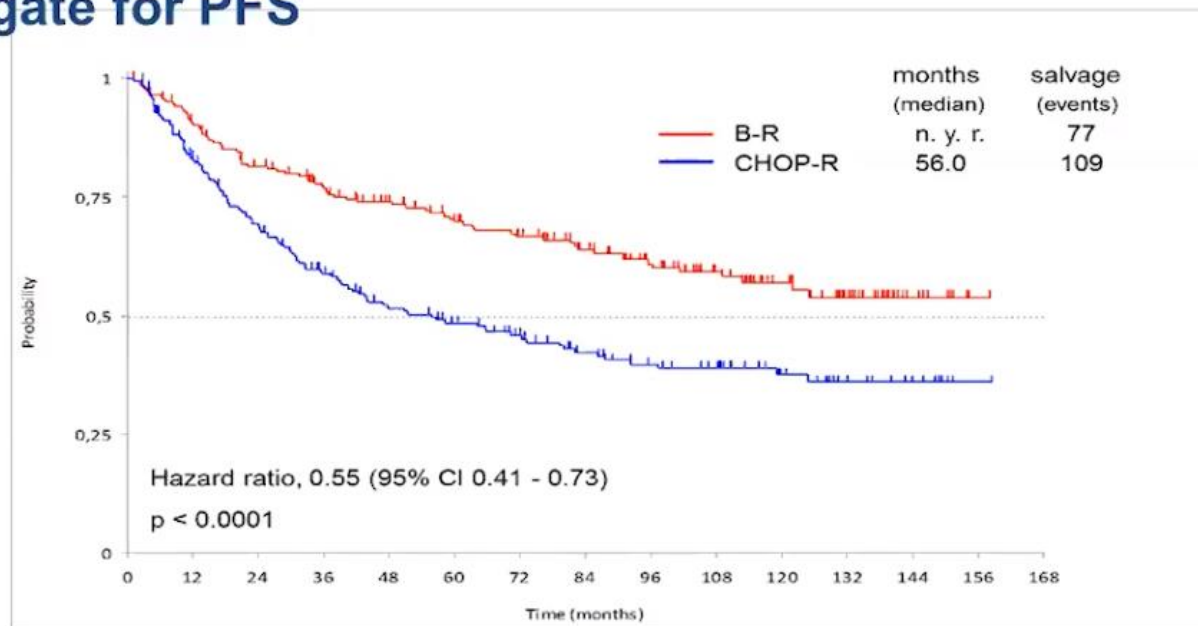


Rummel M, et al. *Lancet*. 2013;381(9873):1203-1210.

# 10-year update of the StiL study

Median f-up 117 months – All histologic subtypes of iNHL

**Used TNTT as a surrogate for PFS**



Presented by Mathias Rummel, MD, ASCO 2018

# Follicular Lymphoma- Maintenance Therapy

# Rationale for maintenance therapy in first-line FL

- R-chemotherapy has improved survival in FL,<sup>1</sup> but most patients will eventually relapse
- Remissions become progressively shorter with multiple lines of therapy<sup>2</sup>
- Quality of response predicts for overall survival:<sup>3</sup> maintenance aims to convert PRs to CRs
- First-line treatment offers the best opportunity for prolonged remission and possible 'cure'

1. Schulz H, *et al. J Natl Cancer Inst* 2007; 99:706–714.

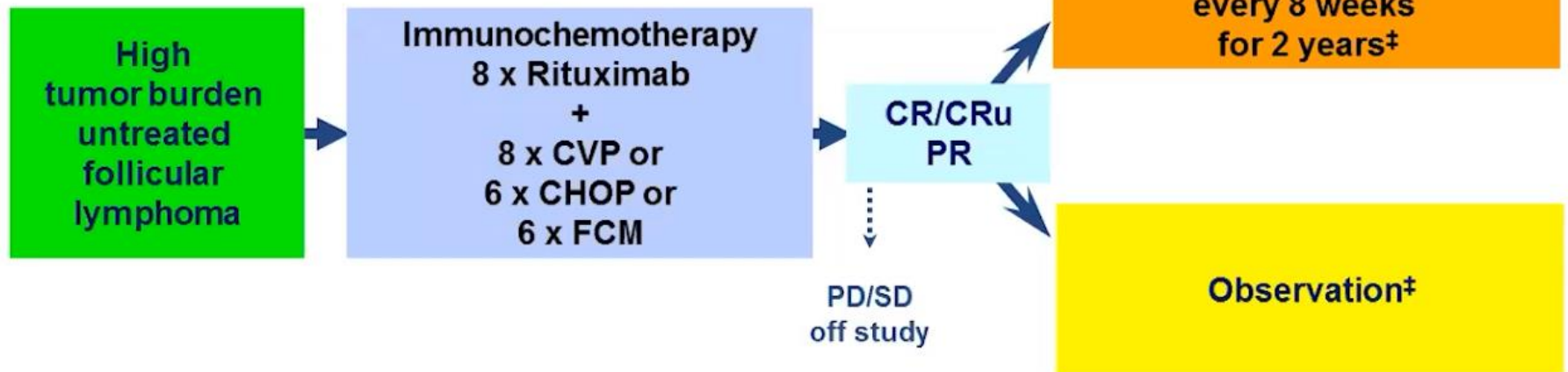
2. Johnson PWM, *et al. J Clin Oncol* 1995; 13:140–147.

3. Bachy E, *et al. J Clin Oncol* 2010; 28:822–829.

## INDUCTION

## MAINTENANCE

# PRIMA: study design

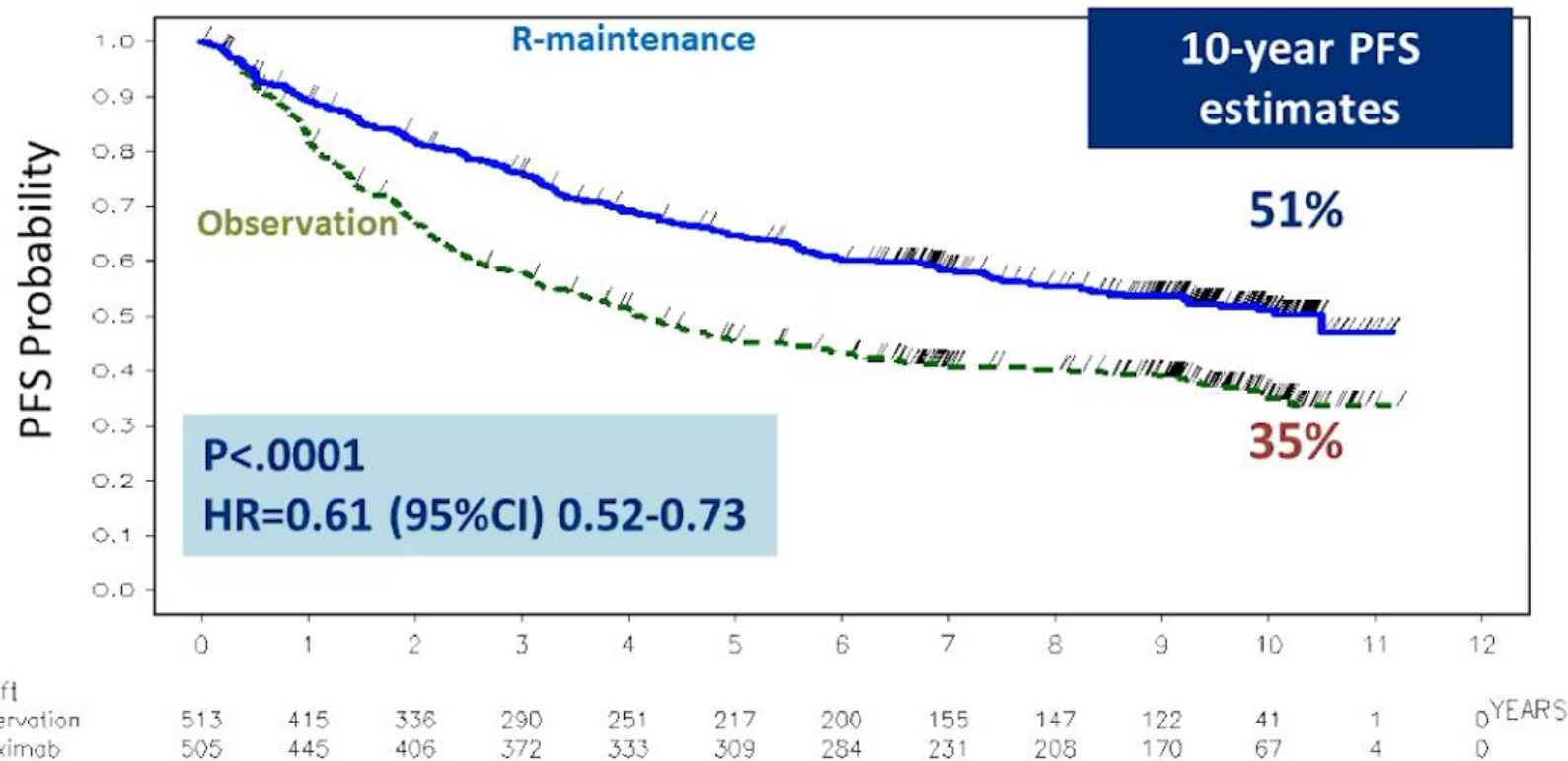


\* Stratified by response after induction, regimen of chemo, and geographic region

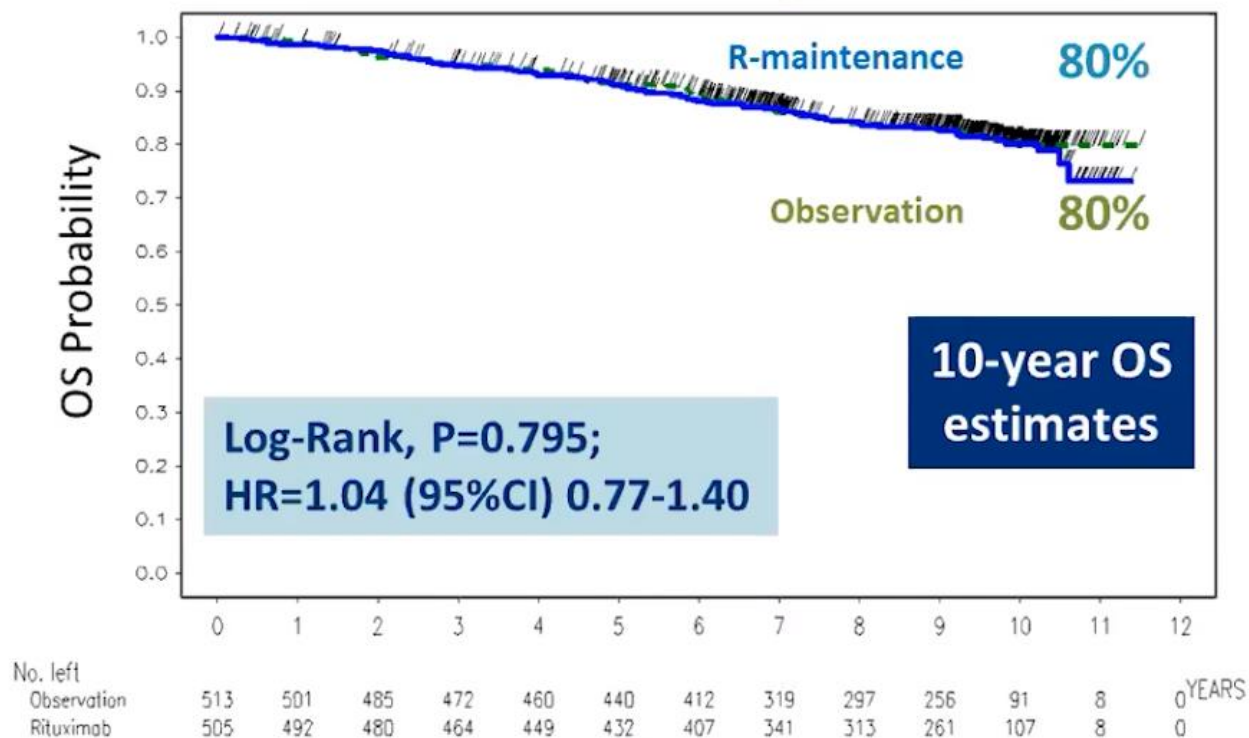
‡ Frequency of clinical, biological and CT-scan assessments identical in both arms

**Five additional years of follow-up**

## PRIMA : PFS at 10 years (from randomization)



## PRIMA : Overall Survival at 10 years(from randomization)



Bachy et al. JCO 2019



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

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## Original Research

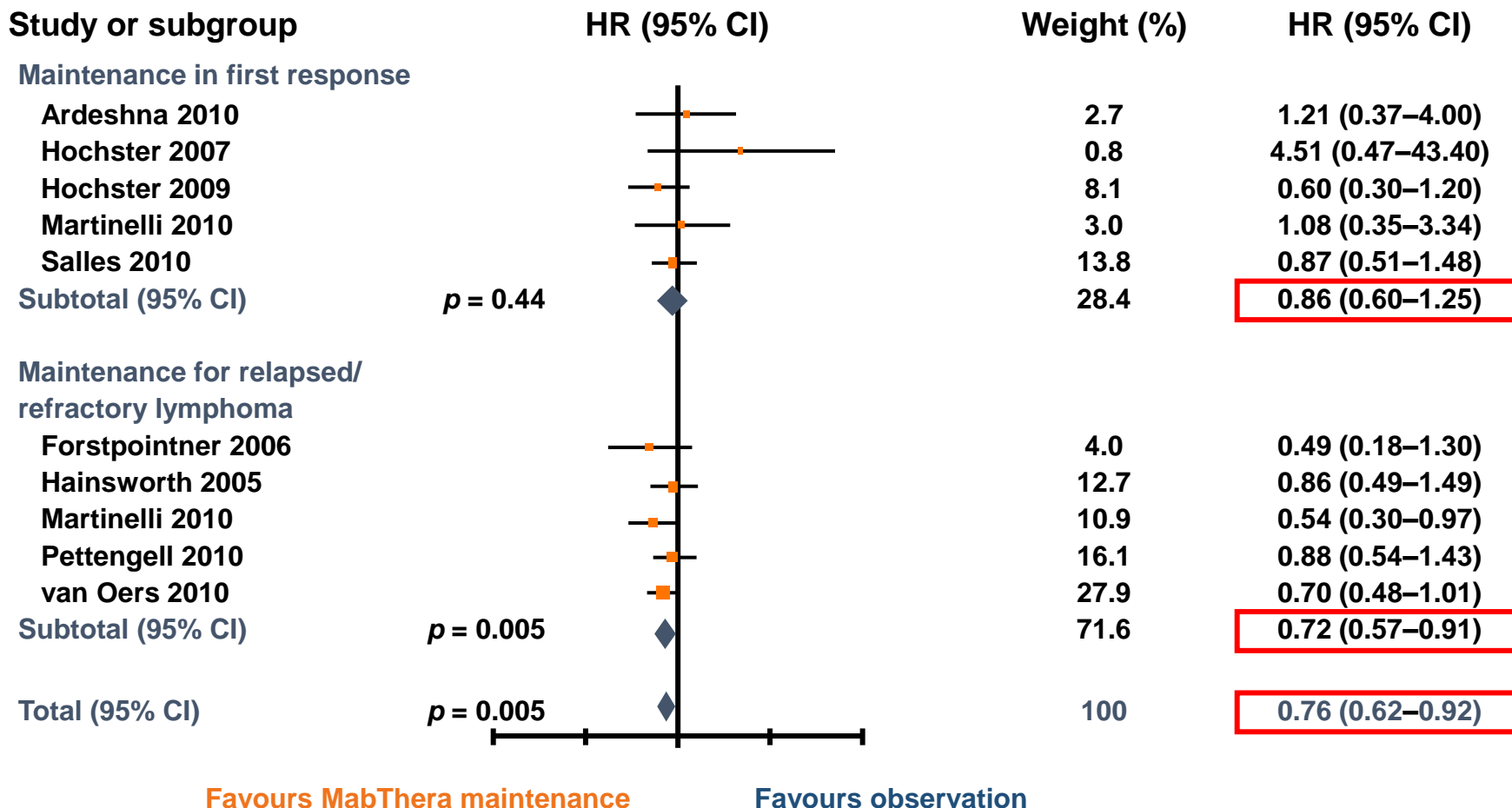
# Rituximab maintenance improves overall survival of patients with follicular lymphoma—Individual patient data meta-analysis



Liat Vidal <sup>a,b,\*</sup>, Anat Gafer-Gvili <sup>a,c</sup>, Gilles Salles <sup>d</sup>, Sami Bousseta <sup>e</sup>,  
Bernice Oberman <sup>f</sup>, Carmit Rubin <sup>f</sup>, Marinus H.J. van Oers <sup>g</sup>,  
Catherine Fortpied <sup>h</sup>, Michele Ghielmini <sup>i,j</sup>, Ruth Pettengell <sup>k</sup>,  
Mathias Witzens-Harig <sup>l</sup>, Peter Dreger <sup>m</sup>, Umberto Vitolo <sup>n</sup>,  
Maria Gomes da Silva <sup>o</sup>, Andrea Evangelista <sup>p</sup>, Hailun Li <sup>q</sup>,  
Laurence Freedman <sup>f</sup>, Thomas M. Habermann <sup>r</sup>, Ofer Shpilberg <sup>s</sup>

# Meta-analysis : Rituximab maintenance improves overall survival in relapsed FL

## 9 studies, 2,586 patients



# Meta-analysis : Rituximab maintenance Safety

Table 4  
Adverse events.

Adverse event	Hazard ratio MR versus observation	95% confidence interval	Rate with MR	Rate without MR
Any, grade 1–4	1.27	1.12, 1.45	52%	40%
Any, grade 3–4	1.31	1.08, 1.58	23%	17%
Infection, grade 1–4	1.41	1.2, 1.66	33.6%	23.6%
Infection, grade 3–4	1.48	1.04, 2.11	7.1%	4.9%
Neutropenic fever	0.78	0.43, 1.43	1.8%	2.1%

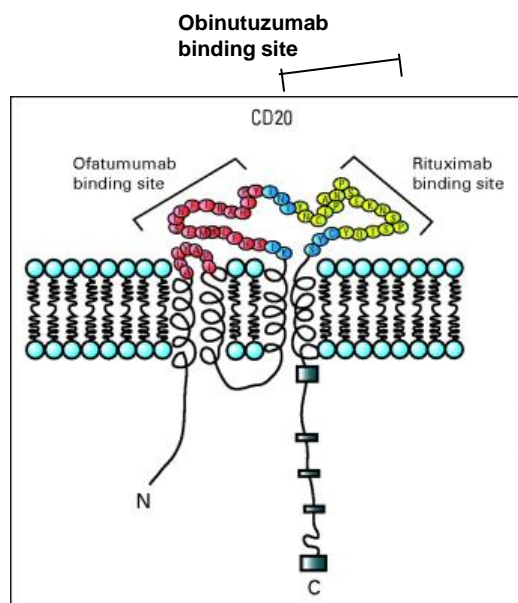
ORIGINAL ARTICLE

# Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

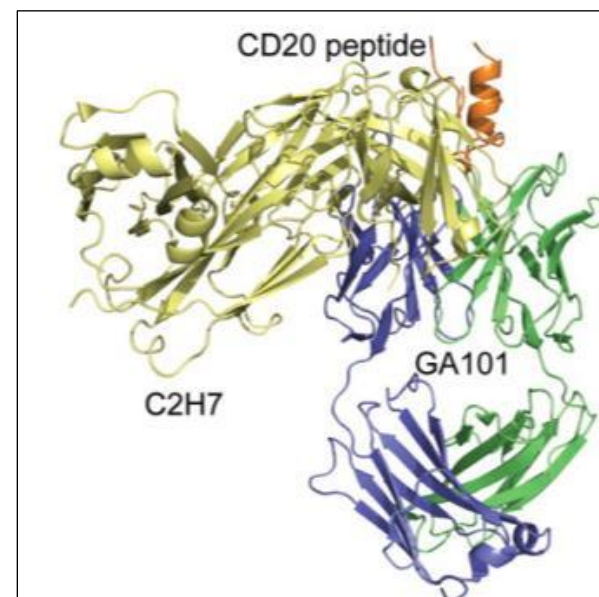
R. Marcus, A. Davies, K. Ando, W. Klapper, S. Opat, C. Owen, E. Phillips, R. Sangha, R. Schlag, J.F. Seymour, W. Townsend, M. Trněný, M. Wenger, G. Fingerle-Rowson, K. Ruibach, T. Moore, M. Herold, and W. Hiddemann

# Comparison of FDA-approved Anti-CD20 Antibodies

	Rituximab	Ofatumumab	Obinutuzumab
Type	I	I	II
Apoptosis	+	-/+	++
ADCC	++	+/-	+++
Complement fixation	++	+++	+/-

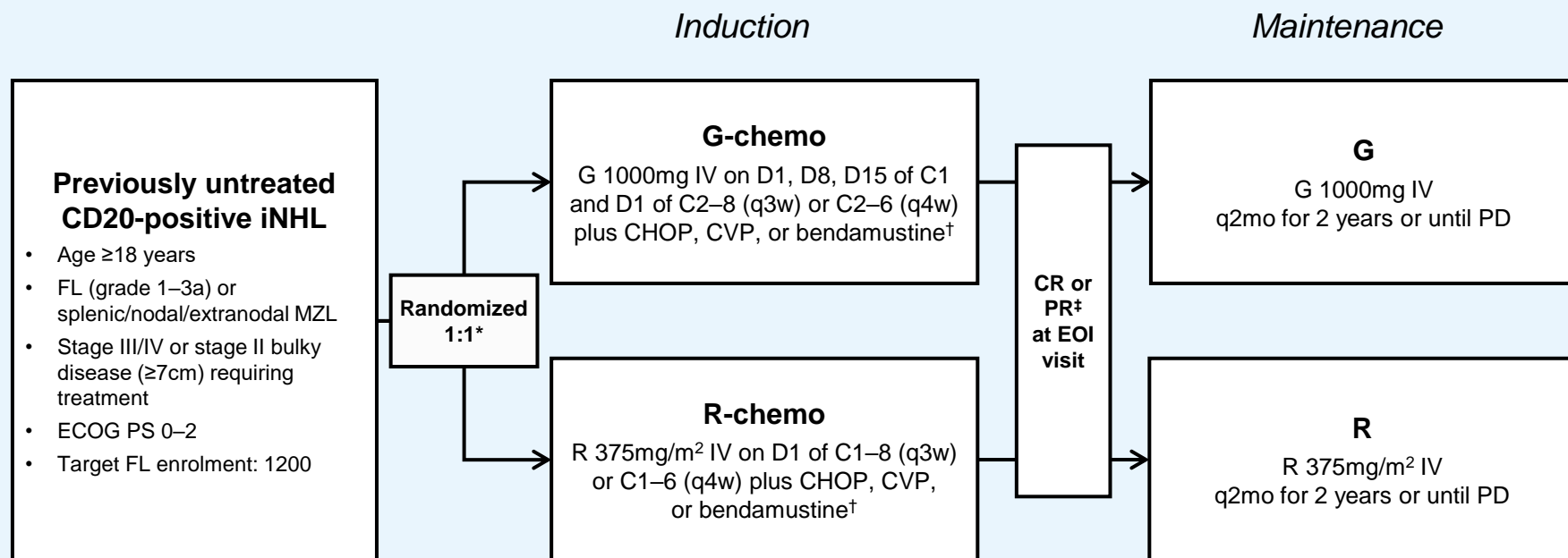


Rituximab



# GALLIUM STUDY

*International, open-label, randomized Phase III study*



## Primary endpoint

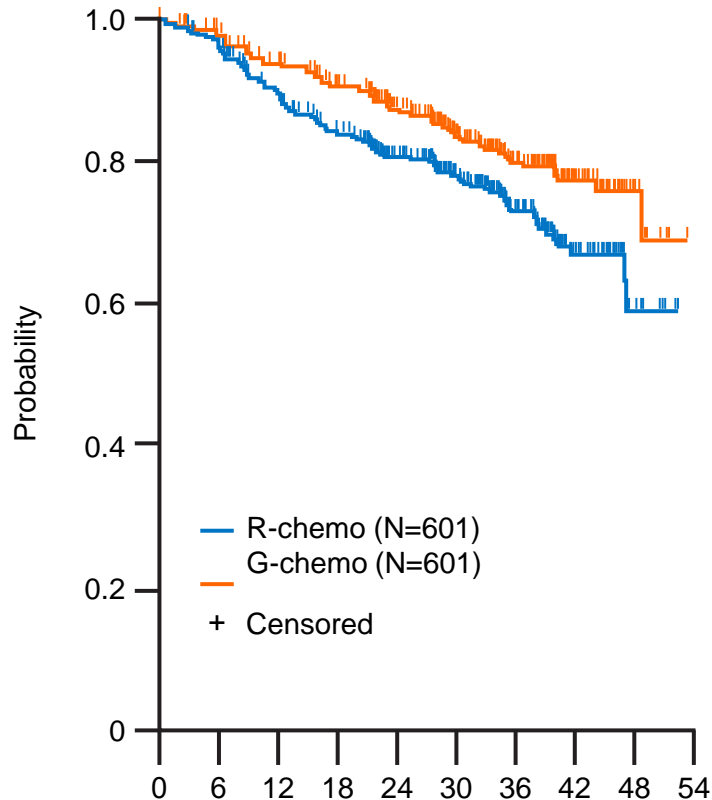
- PFS (INV-assessed in FL)

## Secondary and other endpoints

- PFS (IRC-assessed)<sup>§</sup>
- OS, EFS, DFS, DoR, TTNT
- CR/ORR at EOI (+/- FDG-PET)
- Safety

\*FL and MZL pts were randomized separately; stratification factors: chemotherapy, FLIPI (FL) or IPI (MZL) risk group, geographic region; †CHOP q3w × 6 cycles, CVP q3w × 8 cycles, bendamustine q4w × 6 cycles; choice by site (FL) or by pt (MZL); ‡Pts with SD at EOI were followed for PD for up to 2 years; §Confirmatory endpoint

# Progression Free survival



	<i>R-chemo, n=601</i>	<i>G-chemo, n=601</i>
Pts with event, n (%)	144 (24.0)	101 (16.8)
3-yr PFS, % (95% CI)	73.3 (68.8, 77.2)	80.0 (75.9, 83.6)
HR (95% CI), p-value*	0.66 (0.51, 0.85), p=0.0012	

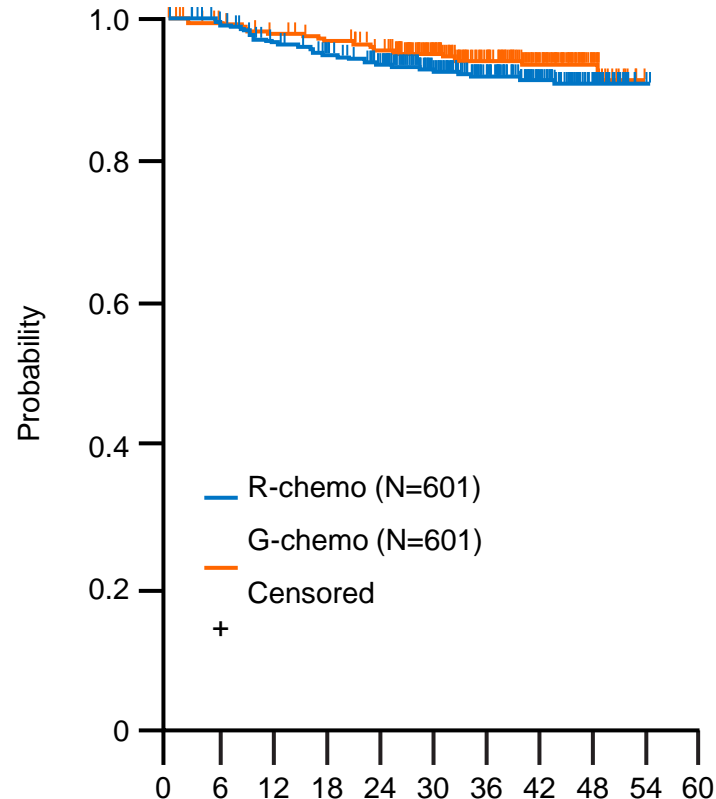
*Median follow-up: 34.5 months*

No. of patients at risk		Time (months)									
R-chemo	G-chemo	601	562	505	463	378	266	160	68	10	0
		601	570	536	502	405	278	168	75	13	0

\*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

Marcus R, Davies A, Ando K, et al. . Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med. 2017;377(14):1331-1344.

# Overall Survival



	<i>R-chemo,</i> <i>n=601</i>	<i>G-chemo,</i> <i>n=601</i>
Pts with event, n (%)	46 (7.7)	35 (5.8)
3-yr OS, % (95% CI)	92.1 (89.5, 94.1)	94.0 (91.6, 95.7)
HR (95% CI), p-value*	0.75 (0.49, 1.17), p=0.21	

*Median follow-up: 34.5 months*

		Time (months)									
Pts at risk, n		0	6	12	18	24	30	36	42	48	54
R-chemo	601	588	566	549	527	399	265	160	58	2	
G-chemo	601	584	573	563	549	416	271	161	55		

\*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

# GALLIUM - Safety

% (n)	<i>R-chemo</i> (n=597)	<i>G-chemo</i> (n=595)
Any AE	98.3% (587)	99.5% (592)
Grade ≥3 AEs (>5% in either arm)	67.8% (405)	74.6% (444)
Neutropenia	37.9% (226)	43.9% (261)
Leucopenia	8.4% (50)	8.6% (51)
Febrile neutropenia	4.9% (29)	6.9% (41)
IRRs*	3.7% (22)	6.7% (40)
Thrombocytopenia	2.7% (16)	6.1% (36)
Grade ≥3 AEs of special interest by category (selected)		
Infections†	15.6% (93)	20.0% (119)
IRRs‡	6.7% (40)	12.4% (74)
Second neoplasms§	2.7% (16)	4.7% (28)
SAEs	39.9% (238)	46.1% (274)
AEs causing treatment discontinuation	14.2% (85)	16.3% (97)
Grade 5 (fatal) AEs	3.4% (20)	4.0% (24)**
Median (range) change from baseline in IgG levels at end of induction, g/l¶	-1.46 (-16.4-9.1)††	-1.50 (-22.3-6.5)‡‡

GALLIUM: AEs by chemotherapy backbone differed although comparisons are confounded by non-random chemo allocation<sup>1</sup>

Patients reporting $\geq 1$ AE, n (%)	R-benda (n=338)	G-benda (n=338)	R-CHOP (n=203)	G-CHOP (n=193)	R-CVP (n=56)	G-CVP (n=61)
Any AE	331 (98)	338 (100)	201 (99)	191 (99)	56 (100)	61 (100)
Grade 3-5 AE	228 (67)	233 (69)	151 (74)	171 (89)	30 (54)	42 (69)
SAE	160 (47)	176 (52)	67 (33)	76 (39)	19 (34)	26 (43)
Grade 5 (fatal) AE*	16 (5)	20 (6)	4 (2)	3 (2)	1 (2)	1 (2)
AE leading to treatment discontinuation	48 (14)	52 (15)	31 (15)	32 (17)	9 (16)	11 (18)

- Grade 3–5 AEs most frequently occurred with CHOP (neutropenia, leukopenia, febrile neutropenia, infusion-related reactions); SAEs and fatal AEs most commonly occurred with bendamustine
- Frequency of grade 5 AEs was similar to those reported in the R-CHOP arms of SABRINA (5.7% IV, 3.6% SC)<sup>2</sup>

# GALLIUM - conclusions

**Obinutuzumab is more active in front line FL combined with chemotherapy (Benda, CHOP, CVP)**

- response rate, MRD, PET-CT, PFS, TNTT
- not OS, but usual in FL

**The pattern of toxicities raises some questions:**

**more infectious toxicities with G in R-CHOP/CVP**

**more toxicities in both Benda arms**

**→ only monitored randomized trials provide an accurate evaluation of new agents toxicities**

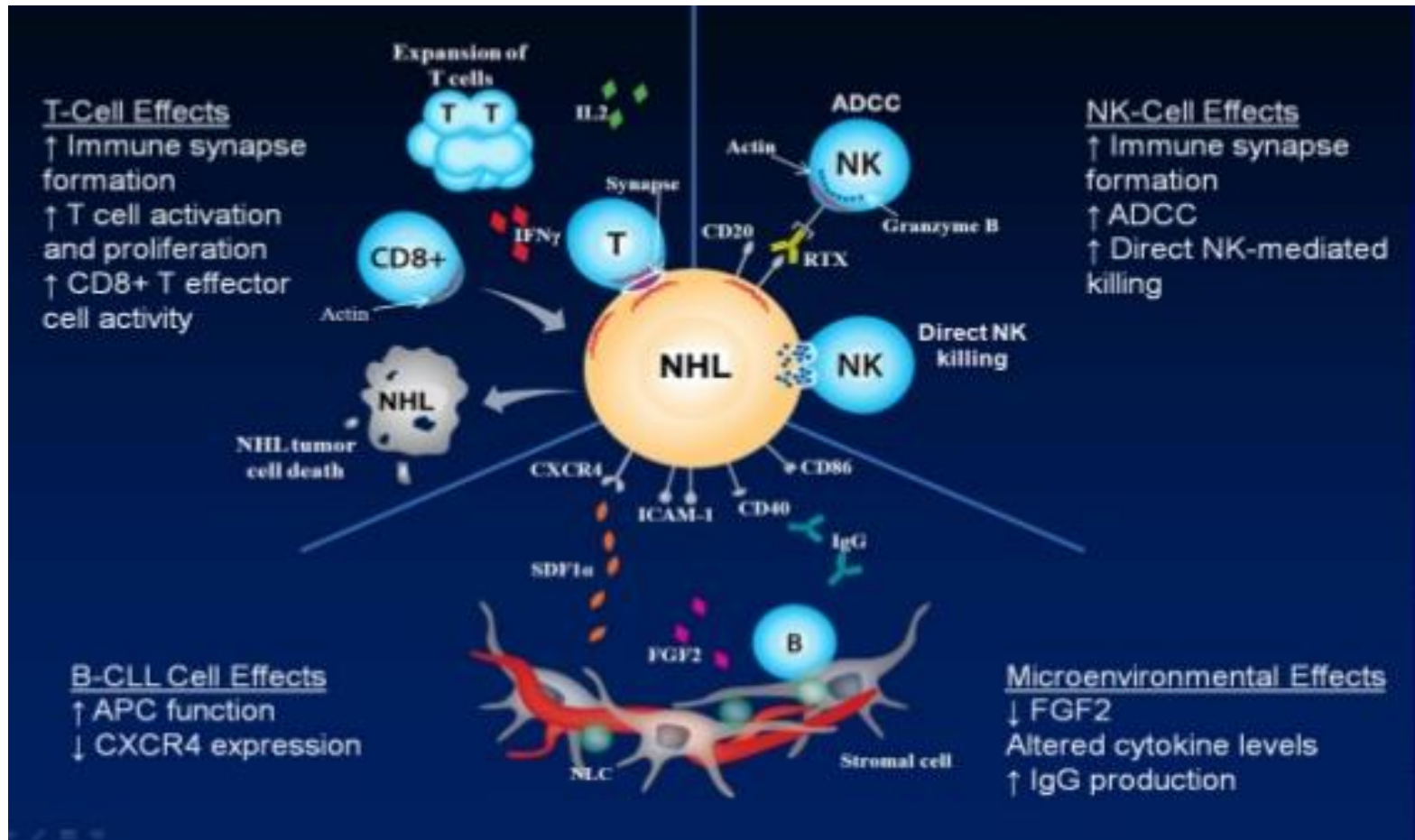
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<ul style="list-style-type: none"> <li>BR superior to R-CHOP</li> </ul>	<ul style="list-style-type: none"> <li>Trend towards PFS benefit with BR vs R-CHOP/R-CVP</li> </ul>	<ul style="list-style-type: none"> <li>Superior PFS with G- vs R-chemo, but no difference in OS</li> <li>More grade 3-5 AEs with G (75% vs 68%)</li> <li>Approval in 2017 for initial chemotherapy and maintenance G</li> </ul>	<ul style="list-style-type: none"> <li>Similar efficacy with R<sup>2</sup> compared with R-chemotherapy</li> <li>Less hematologic toxicity with R<sup>2</sup>, but more grade 3/4 cutaneous toxicity (7% vs 1%)</li> </ul>	<ul style="list-style-type: none"> <li>Superior PFS (and TTNT), but not OS, with R maintenance</li> <li>FDA approved in 2011 as maintenance therapy in patients with FL who respond to induction therapy</li> </ul>

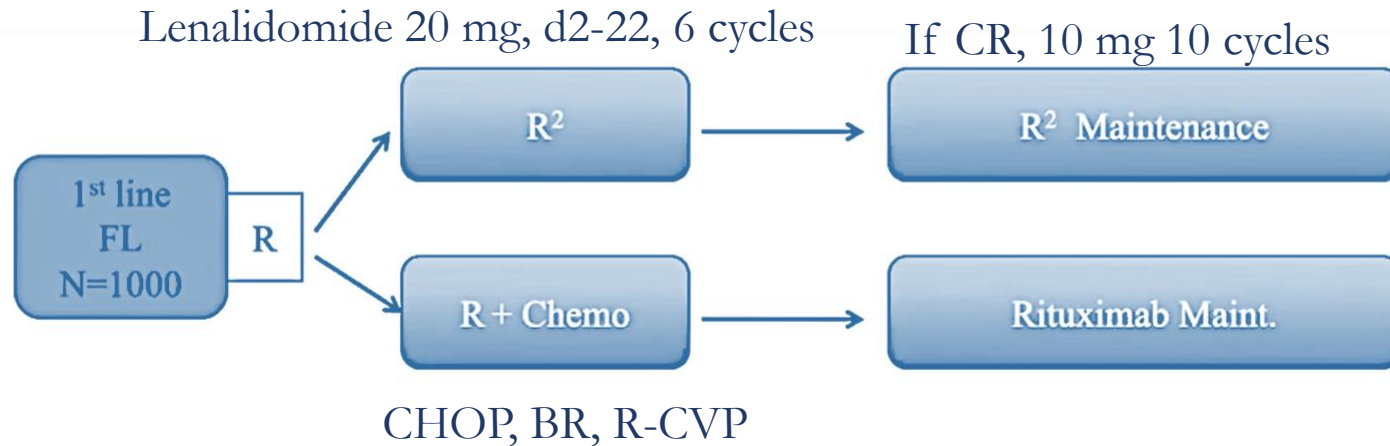
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5. Salles G, et al. *Lancet*. 2011;377:42. 6. Bachy E, et al. *J Clin Oncol*. 2019;37:2815.

# LENALIDOMIDE

## REVLIMID, LENALIDOMIDE-TEVA



## RELEVANCE TRIAL ( $R^2$ ) - NOVEL APPROACHES TO FRONTLINE



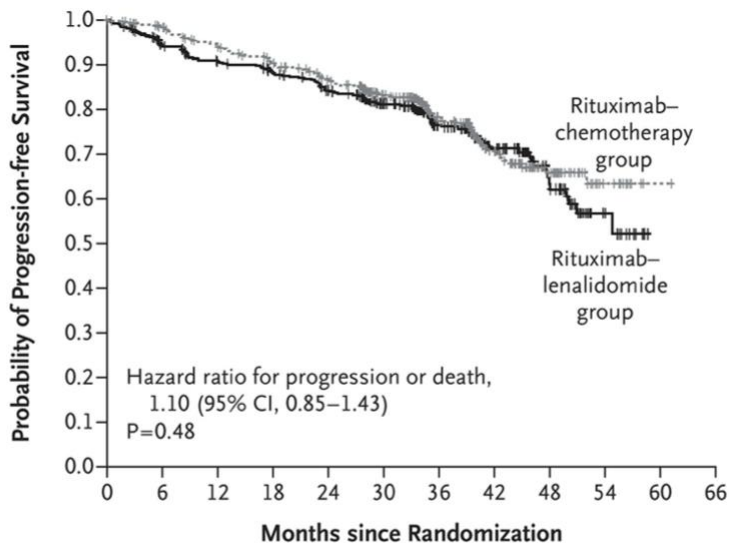
Primary End Point for efficacy:

CR rate final analysis at 120 weeks

PFS at interim analysis 120 weeks

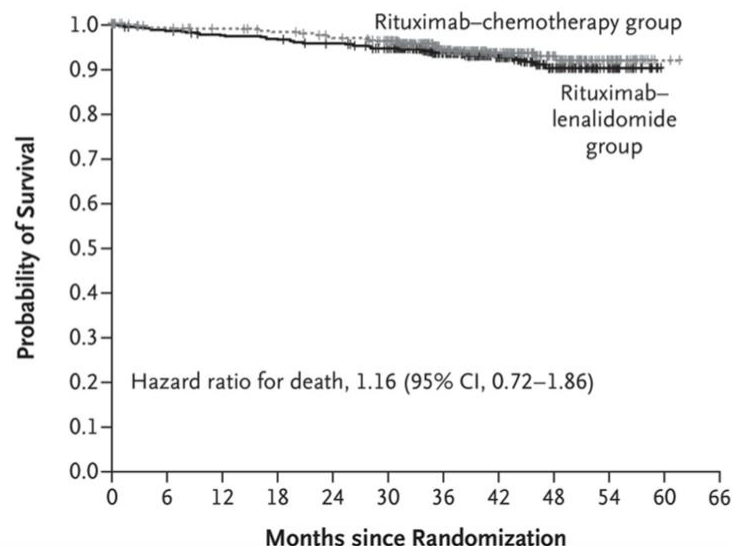
# RELEVANCE TRIAL -NOVEL APPROACHES TO FRONTLINE

Progression-free Survival



3- year PFS R2 77% vs R+CMT 78%

Overall Survival



3- year OS 94%

**Similar efficacy**

**Different safety profiles:**

- rituximab-chemotherapy group: A higher percentage of grade 3 or 4 neutropenia (32% vs. 50%) and febrile neutropenia (2% vs. 7%)
- rituximab-lenalidomide group: a higher percentage of grade 3 or 4 cutaneous reactions (7% vs. 1%)

# FOLLICULAR LYMPHOMA 1<sup>ST</sup> LINE TREATMENT

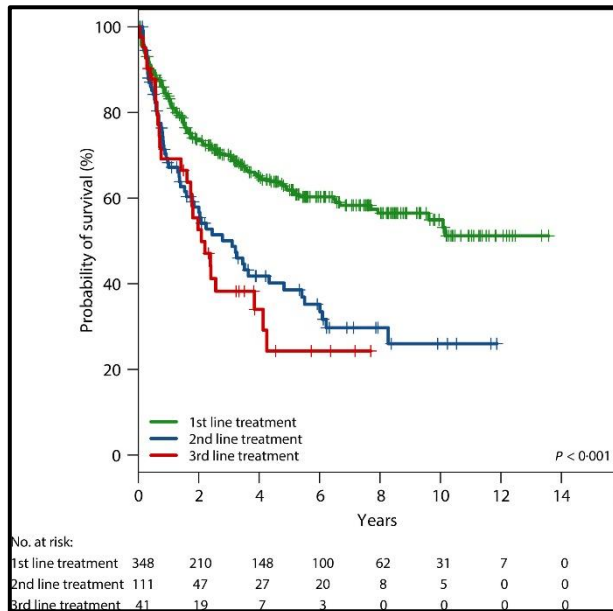
- Advanced with indication for treatment:
- 1<sup>st</sup> line – anti CD20 + chemo is the standard of care
- According to data from RCTs:
  - R-benda  $\geq$  R-CHOP >> R-COP for PFS, no difference in OS
  - Obinutuzumab improves PFS over R (not OS)
  - Rituximab maintenance improves PFS in first line (not OS)
  - No RCT for maintenance after R-benda
- Options:
  - R-CHOP/R-COP/R-bendamustine (BR)
  - G-CHOP/G-COP/G-bendamustine (BG)
- We can choose according to age, patient preference, comorbidity

# Relapsed/Refractory Follicular Lymphoma

# RELAPSED FOLLICULAR LYMPHOMA

Patients with FL will experience multiple relapses

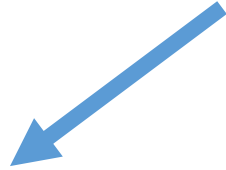
Response duration and survival shorten after each relapse



**Response duration  
after each line of  
treatment**

Treatment Line	Median PFS, Years (95% CI)
First	6.62 (6.10-7.20)
Second	1.50 (1.35-1.70)
Third	0.83 (0.68-1.09)
Fourth	0.69 (0.50-0.97)
Fifth	0.68 (0.43-0.88)

# TREATMENT STRATEGIES



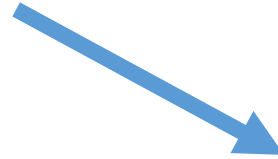
## CONVENTIONAL

Chemotherapy (Benda, CHOP, CVP) +  
mOAb

Rituximab single agent

Radiation therapy

HD CMT+HSCT



## TARGETED THERAPIES

Lenalidomide based therapy

PI3 Kinase inhibitors

Tazemetostat (EZH2 inhibitor)

Bi- specific T-cell engager (BiTE)

CAR T- cellular therapy

## Efficacy data

Regimen	MOA/Target	N	ORR	CR	mPFS
Lenalidomide-Rituximab	IMiD	147	78%	34%	25-39 months
Rituximab	antiCD20 MoAb	148	53%	18%	14 months
Idelalisib	PI3K inhibitor	72	60%	15%	11 months
Copanlisib	PI3K inhibitor	104	60%	14%	11 months
Duvelisib	PI3K inhibitor	83	48%	2%	10 months
Umbralisib	PI3K inhibitor	117	45%	5%	11 months
Tazemetostat (mutated)	EZH2 inhibitor	45	69%	13%	14 months
Tazemetostat (wild type)	EZH2 inhibitor	54	35%	4%	11 months
Axi-Cel	antiCD19 CAR-T	84	94%	80%	NR

# AUGMENT TRIAL PHASE 3 RCT OF R<sup>2</sup> VS R + PLACEBO IN R/R FL AND MZL

12 cycles or until PD, relapse, intolerability

Relapsed/refractory  
FL and MZL  
(N=358)

1:1

n=  
178

## R-lenalidomide (R<sup>2</sup>)

Rituximab: 375 mg/m<sup>2</sup> d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5  
Lenalidomide: 20 mg/d,\* d1-21/28 (12 cycles)

n=  
180

## R-placebo

Rituximab: 375 mg/m<sup>2</sup> d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5  
Placebo: matched capsules (12 cycles)

**Primary  
endpoint:**  
PFS by IRC

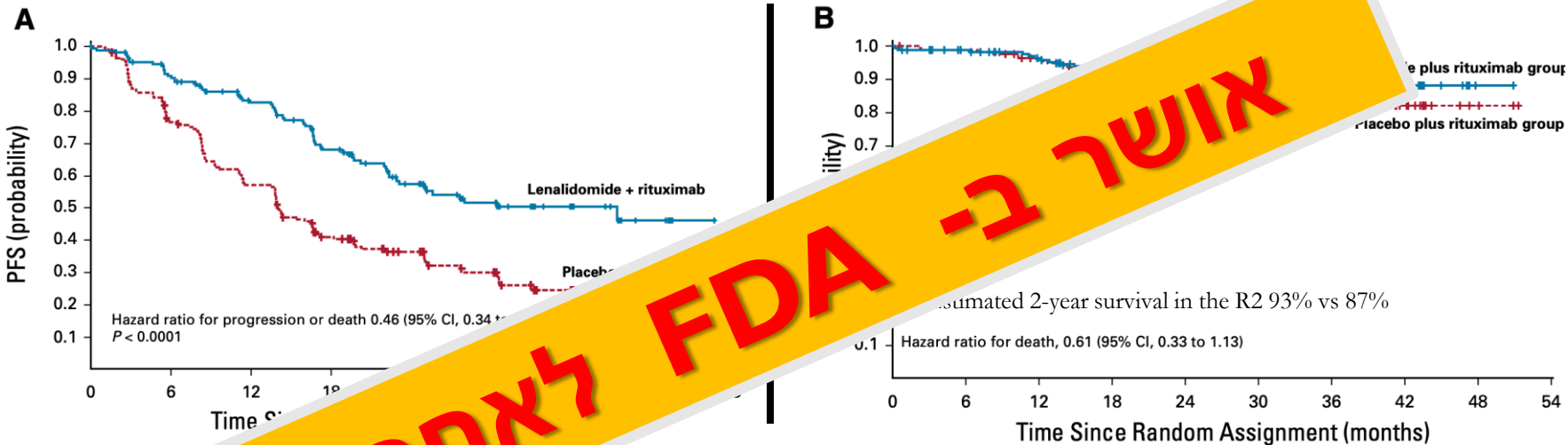
### Key eligibility criteria

MZL or FL (grades 1 to 3a)  
Treatment indication  
≥ prior line of CIT  
Not rituximab refractory

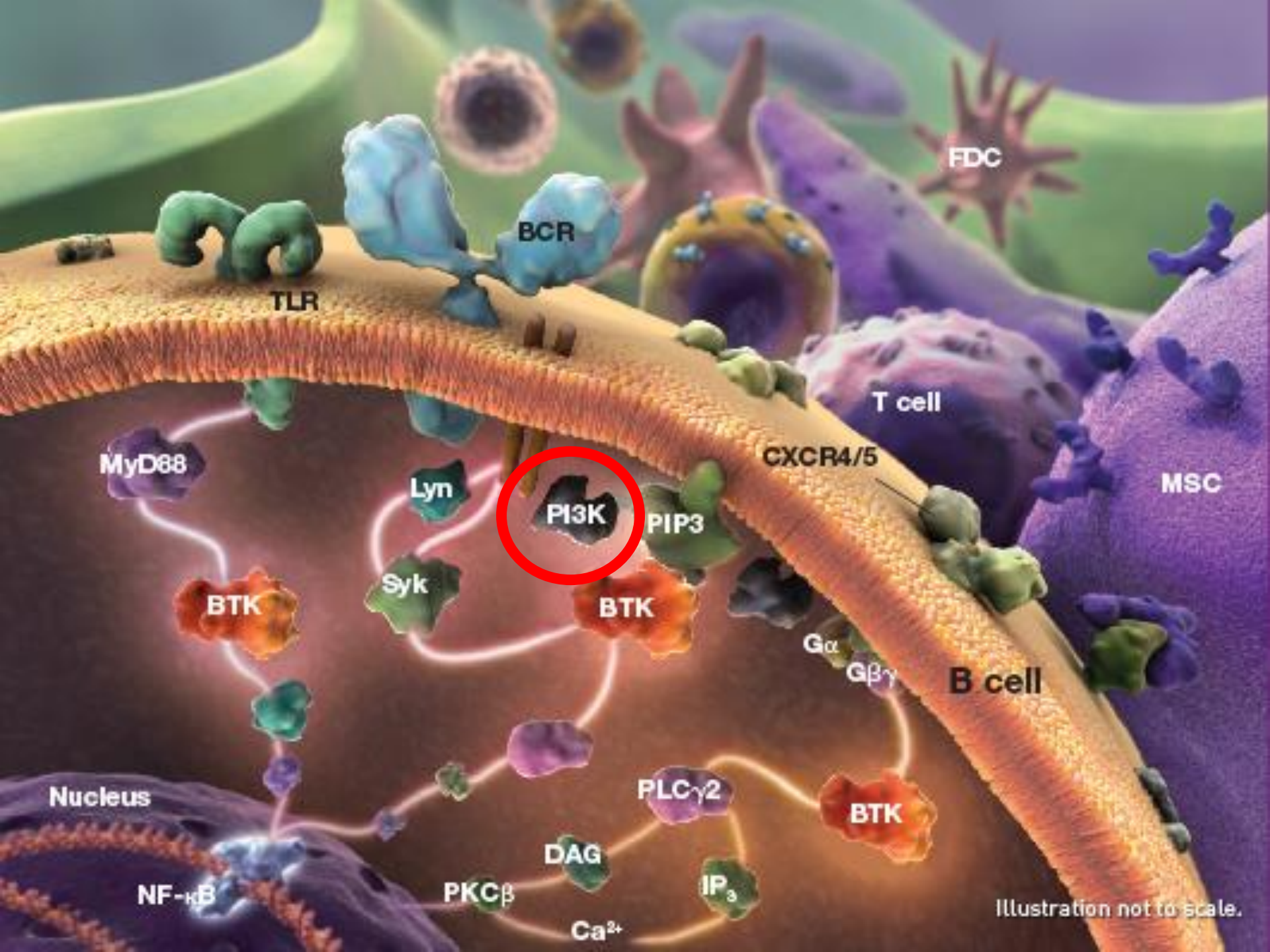
Characteristic	Lenalidomide + Rituximab (n = 178)	Placebo + Rituximab (n = 180)	Total (N = 358)
Median age, years (range)	64 (26-86)	62 (35-88)	63 (26-88)
Age ≥ 65 years	82 (46)	73 (41)	155 (43)
Male sex	75 (42)	97 (54)	172 (48)
ECOG performance status*			
0	116 (65)	128 (71)	244 (68)
1	60 (34)	50 (28)	110 (31)
2	2 (1)	2 (1)	4 (1)
Ann Arbor stage†			
I or II	41 (23)	56 (31)	97 (27)
III or IV	137 (77)	124 (69)	261 (73)
Bulky disease‡	45 (25)	49 (27)	94 (26)
High tumor burden per GELF criteria	97 (54)	86 (48)	183 (51)
No. of prior systemic antilymphoma regimens			
1	102 (57)	97 (54)	199 (56)
2	31 (17)	42 (23)	73 (20)

# AUGMENT TRIAL PHASE 3 RCT OF R<sup>2</sup> VS R + PLACEBO IN R/R FL AND MZL

Median follow-up was 28.3 months



Variable	Lenalidomide + Rituximab (n = 178)	Placebo + Rituximab (n = 180)	Hazard Ratio (95% CI)	P
Median PFS, months (95% CI)				
As assessed by IRC	39.4 (22.9 to NR)	14.1 (11.4 to 16.7)	0.46 (0.34 to 0.62)	< .0001
Median TTNLT, months (95% CI)	NR (NR to NR)	32.2 (23.2 to NR)	0.54 (0.38 to 0.78)	.0007



## Approved PI3K Inhibitors for FL: Indication and Dosing

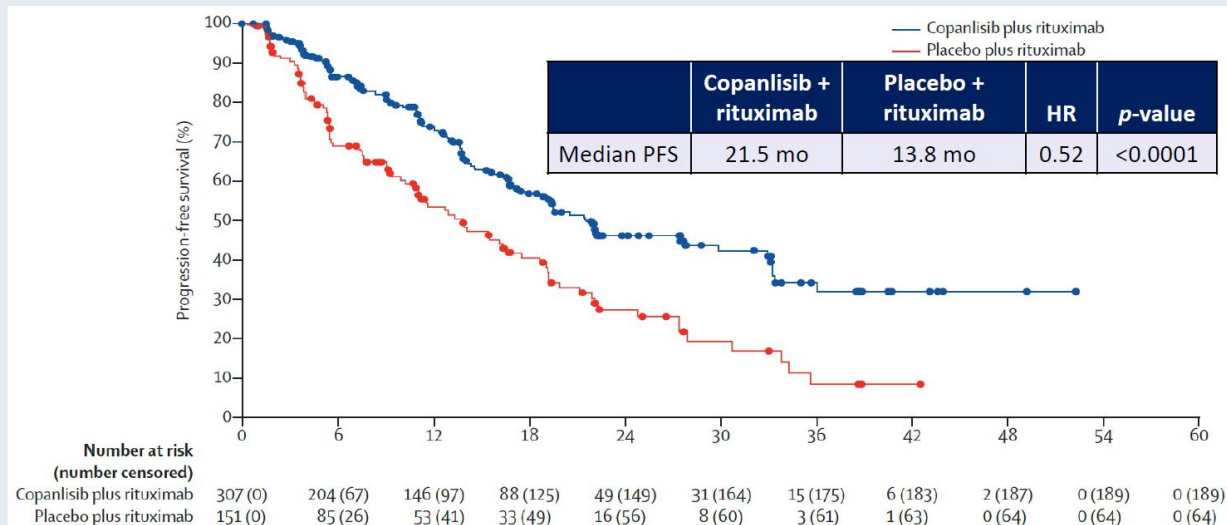
	<b>Idelalisib<sup>1</sup></b>	<b>Copanlisib<sup>2</sup></b>	<b>Duvelisib<sup>3</sup></b>	<b>Umbralisib<sup>4</sup></b>
<b>Mechanism of action</b>	Selective PI3K $\delta$ inhibitor	Dual inhibitor of PI3K $\delta$ , $\alpha$	Dual inhibitor of PI3K $\delta$ , $\gamma$	Dual inhibitor of PI3K $\delta$ and casein kinase CK1 $\epsilon$
<b>Indication</b>	Relapsed FL after at least 2 prior systemic therapies	Relapsed FL after at least 2 prior systemic therapies	R/R FL after at least 2 prior systemic therapies	R/R FL after at least 3 prior systemic therapies
<b>Dosing</b>	150 mg orally, twice daily	60 mg as a 1-hour IV infusion weekly (3 weeks on, 1 week off)	25 mg orally, twice daily	800 mg orally, once daily



# Copanlisib plus rituximab versus placebo plus rituximab in patients with relapsed indolent non-Hodgkin lymphoma (CHRONOS-3): a double-blind, randomised, placebo-controlled, phase 3 trial

Matthew J Matasar, Marcelo Capra, Muhit Özcan, Fangfang Lv, Wei Li, Eduardo Yañez, Katya Sapunarova, Tongyu Lin, Jie Jin, Wojciech Jurczak, Aryan Hamed, Ming-Chung Wang, Ross Baker, Igor Bondarenko, Qingyuan Zhang, Jifeng Feng, Klaus Geissler, Mihaela Lazaroiu, Guray Saydam, Árpád Szomor, Krimo Bouabdallah, Rinat Galiulin, Toshiki Uchida, Lidia Mongay Soler, Anjun Cao, Florian Hiemeyer, Aruna Mehra, Barrett H Childs, Yuankai Shi, Pier Luigi Zinzani

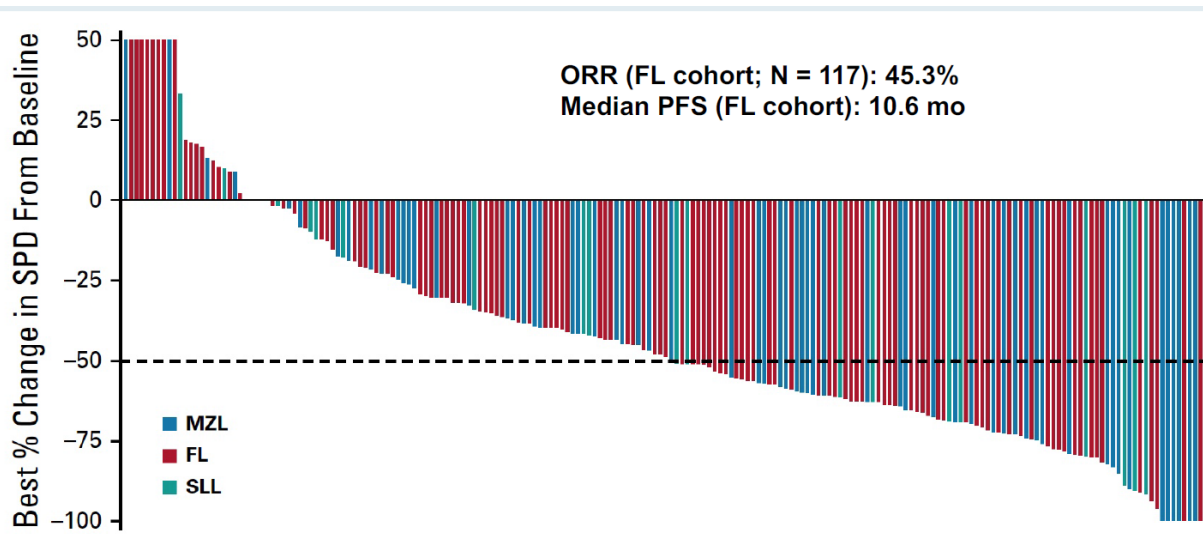
## CHRONOS-3: Progression-Free Survival in R/R Indolent NHL



# Umbralisib, a Dual PI3K $\delta$ /CK1 $\epsilon$ Inhibitor in Patients With Relapsed or Refractory Indolent Lymphoma

Nathan H. Fowler, MD<sup>1</sup>; Felipe Samaniego, MD<sup>1</sup>; Wojciech Jurczak, MD, PhD<sup>2</sup>; Nilanjan Ghosh, MD, PhD<sup>3</sup>; Enrico Derenzini, MD<sup>4,5</sup>; James A. Reeves, MD<sup>6</sup>; Wanda Knopińska-Postuszny, MD<sup>7</sup>; Chan Y. Cheah, DMSc<sup>8</sup>; Tycel Phillips, MD<sup>9</sup>; Ewa Lech-Maranda, MD, PhD<sup>10</sup>; Bruce D. Cheson, MD<sup>11</sup>; Paolo F. Caimi, MD<sup>12</sup>; Sebastian Grosicki, MD, PhD<sup>13</sup>; Lori A. Leslie, MD<sup>14</sup>; Julio C. Chavez, MD<sup>15</sup>; Gustavo Fonseca, MD<sup>16</sup>; Sunil Babu, MD<sup>17</sup>; Daniel J. Hodson, MD<sup>18</sup>; Spencer H. Shao, MD<sup>19</sup>; John M. Burke, MD<sup>20</sup>; Jeff P. Sharman, MD<sup>21</sup>; Jennie Y. Law, MD<sup>22</sup>; John M. Pagel, MD, PhD<sup>23</sup>; Hari P. Miskin, MSc<sup>24</sup>; Peter Sportelli, BS<sup>24</sup>; Owen A. O'Connor, MD, PhD<sup>24,25</sup>; Michael S. Weiss, JD<sup>24</sup>; and Pier Luigi Zinzani, MD, PhD<sup>26,27</sup>

*J Clin Oncol* 2021;39:1609-18



## PI3K Inhibitors: Safety

Agent	Idelalisib <sup>[1,2]</sup>	Copanlisib <sup>[3,4]</sup>	Duvelisib <sup>[5,6]</sup>
PI3K isoform target	delta	alpha, delta	delta, gamma
Dose/delivery	150 mg orally BID	60 mg IV weekly (3 wks on, 1 wk off)	25 mg orally BID
Grade ≥ 3 AE, %	(n = 125)	(n = 142)	(n = 129)
▪ ↓ ANC/PLT level	27/6	24/7	25/12
▪ ALT/AST elevations	13/8	2/2	5/3
▪ Diarrhea/colitis	13/4	5/1	15/5
▪ Pneumonia	7	15	5
▪ Hyperglycemia	–	41	–
▪ Hypertension	–	24	–
Serious AEs of special interest	Sepsis, opportunistic infections, diarrhea/colitis, cutaneous rxn, pneumonitis, hepatotoxicity, intestinal perforation, anaphylaxis	Opportunistic infections, pneumonitis, severe cutaneous rxn	Opportunistic infections, diarrhea/colitis, cutaneous rxn, pneumonitis
Monitoring	LFTs, blood counts, signs of serious AEs, PJP infection, CMV reactivation/infection	BP, blood sugar, blood counts, PJP infection, CMV reactivation/infection	LFTs, blood counts, signs of serious AEs, PJP infection, CMV reactivation/infection

1. Gopal. NEJM. 2014;370:1008. 2. Idelalisib PI. 3. Dreyling. Am J Hematol 2019;95:362. 4. Copanlisib PI. 5. Flinn. JCO. 2019;37:912. 6. Duvelisib PI.

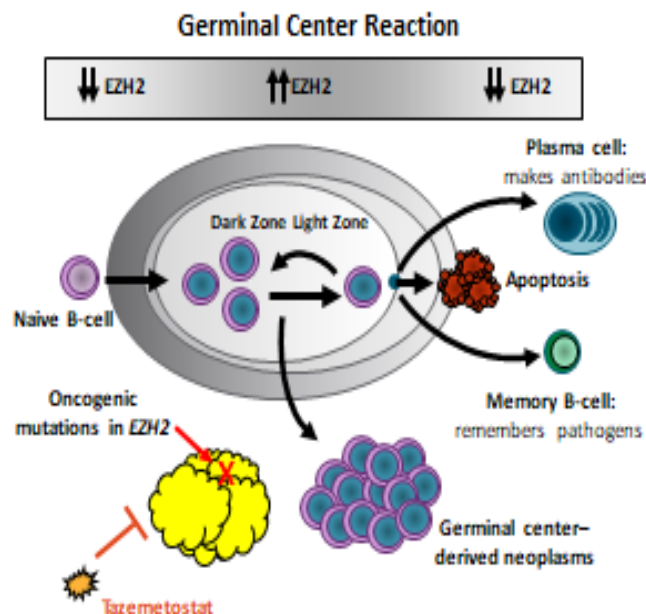


Slide credit: [clinicaloptions.com](http://clinicaloptions.com)

Hepatic toxicity and immune-related colitis are the most clinically concerning with idelalisib and duvelisib  
hyperglycemia and hypertension with copanlisib

## EZH2, a Histone Methyltransferase, in FL

- In normal B-cell biology, EZH2 regulates germinal center formation
- *EZH2* mutations can lead to oncogenic transformation by locking B-cells in germinal state and preventing terminal differentiation
- *EZH2*-activating mutations found in ~ 20% of patients with FL
- Whether WT or mutant, *EZH2* biology relevant to FL
- **Tazemetostat**: selective, oral, first-in-class EZH2 inhibitor



***Lancet Oncol 2020;21:1433-42***

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# **Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial**

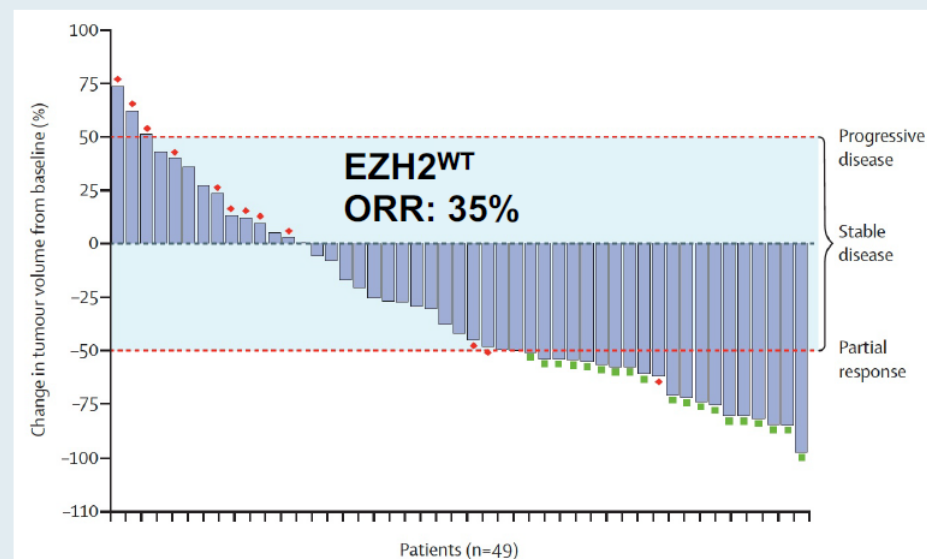
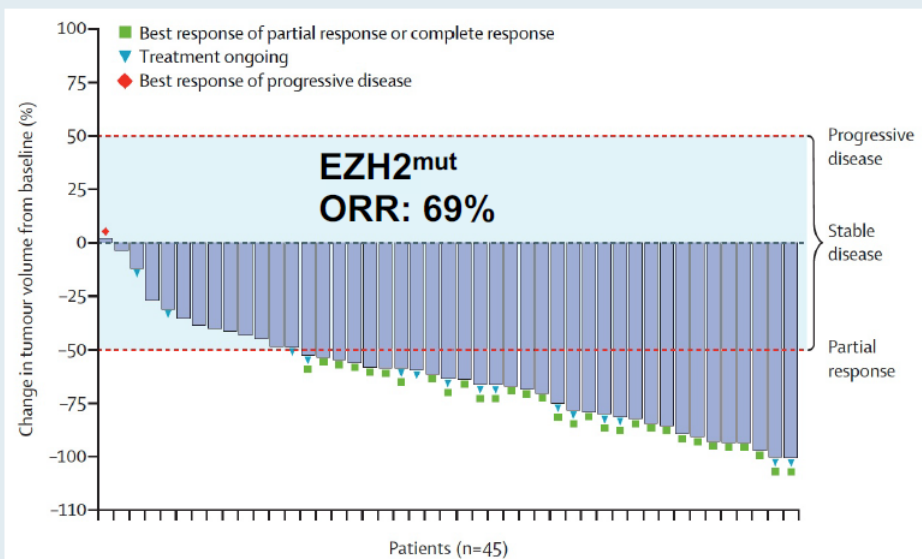


*Franck Morschhauser, Hervé Tilly, Aristeidis Chaidos, Pamela McKay, Tycel Phillips, Sarit Assouline, Connie Lee Batlevi, Phillip Campbell, Vincent Ribrag, Gandhi Laurent Damaj, Michael Dickinson, Wojciech Jurczak, Maciej Kazmierczak, Stephen Opat, John Radford, Anna Schmitt, Jay Yang, Jennifer Whalen, Shefali Agarwal, Deyaa Adib, Gilles Salles*

Open-label, multicenter study of tazemetostat 800 mg BID  
45 *EZH2* MUT, 54 *EZH2* WT patients

- *EZH2* MUT: median 2 (range: 1-11) prior lines tx, 49% refractory to rituximab, 49% refractory to last regimen
- *EZH2* WT: median 3 (range: 1-8) prior lines tx, 59% refractory to rituximab, 41% refractory to last regimen

# Response to Tazemetostat in Patients with R/R FL and EZH2-Mutated or EZH2 Wild-Type Tumors



Outcome	EZH2 MUT (n = 42)	EZH2 WT (n = 53)
ORR, %	69	34
■ CR	12	4
■ PR	57	30
Median DoR, mos (range)	10.9 (0+ to 22.1+)	13.0 (1.0 to 22.5+)
Median TTR, mos (range)	3.7 (1.6 to 10.9)	3.9 (1.6 to 16.3)
Median PFS (IRC), mos	13.8*	11.1*


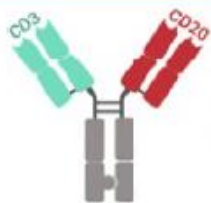
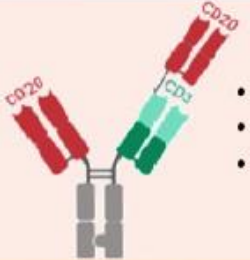
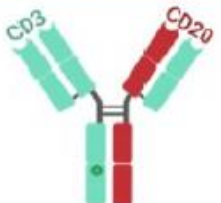

## Phase II Study: Tazemetostat Safety

Treatment-Emergent AE, %	N = 99	
	All	Grade $\geq 3$
Nausea	23	0
Asthenia	19	3
Diarrhea	18	0
Fatigue	17	2
Alopecia	17	0
Cough	16	0
Upper respiratory tract infection	15	0
Bronchitis	15	0
Anemia	14	5
Abdominal pain	13	1
Headache	12	0
Vomiting	12	1
Back pain	11	0
Pyrexia	10	0
Thrombocytopenia	10	5

- Tazemetostat generally well tolerated, with low rate of grade  $\geq 3$  treatment-related TEAEs
  - 8% discontinued tx due to TEAEs
  - 9% had dose reduction due to TEAEs
  - 27% had dose interruption due to TEAEs
- No treatment-related deaths

FDA approved for adults with *EZH2*mut<sup>+</sup> R/R FL after  $\geq 2$  prior systemic therapies or any adult with R/R FL without alternative treatment options

# Structure of Selected Bispecific Antibodies

Bi-Specific Antibody	Targets	Design	Ig Fragment Formats
<b>blinatumomab</b>	CD19 x CD3		<ul style="list-style-type: none"> <li>two murine scFv joined by a glycine-serine linker</li> <li>monovalent CD19 and monovalent CD3 binding</li> <li>cloned from anti-CD19 (clone HD37) and anti-CD3 (clone L2K-07) murine mAbs</li> </ul>
<b>mosunetuzumab</b>	CD20 x CD3		<ul style="list-style-type: none"> <li>humanized mouse heterodimeric IgG1-based antibody</li> <li>monovalent CD20 and monovalent CD3ε binding</li> <li>modified Fc devoid of FcγR and complement binding</li> </ul>
<b>glofitamab</b>	(CD20) <sub>2</sub> x CD3		<ul style="list-style-type: none"> <li>humanized mouse IgG1-based antibody</li> <li>bivalent CD20 and monovalent CD3ε binding</li> <li>modified Fc devoid of FcγR and complement binding</li> </ul>
<b>odronextamab</b>	CD20 x CD3		<ul style="list-style-type: none"> <li>fully human IgG4-based heterodimeric antibody</li> <li>monovalent CD20 and monovalent CD3ε binding</li> <li>Fc-dependent effector function-minimized antibody with Fc of the anti-CD3ε heavy chain modified to reduce Protein A binding</li> <li>common κ light chain from anti-CD3ε mAb</li> </ul>
<b>epcoritamab</b>	CD20 x CD3		<ul style="list-style-type: none"> <li>humanized mouse IgG1-based heterodimeric antibody</li> <li>monovalent CD20 and monovalent CD3 binding</li> <li>IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield</li> </ul>

## **FDA Grants Breakthrough Therapy Designation for the CD20 x CD3 Bispecific Cancer Immunotherapy Mosunetuzumab for Follicular Lymphoma**

**Press Release — July 14, 2020**

“The investigational CD20xCD3 T-cell engaging bispecific mosunetuzumab has been granted Breakthrough Therapy Designation (BTD) by the US Food and Drug Administration (FDA) for the treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma who have received at least two prior systemic therapies.

This designation was granted based on encouraging efficacy results observed in the phase I/Ib GO29781 study [NCT02500407] investigating mosunetuzumab in R/R non-Hodgkin lymphoma (NHL).

The safety profile of this T-cell engaging bispecific was consistent with its mechanism of action.”

# Mosunetuzumab Monotherapy is an Effective and Well-Tolerated Treatment Option for Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) who have Received $\geq 2$ Prior Lines of Therapy: Pivotal Results from a Phase I/II Study

**L Elizabeth Budde,<sup>1</sup> Laurie H Sehn,<sup>2</sup> Matthew Matasar,<sup>3</sup> Stephen J Schuster,<sup>4</sup> Sarit Assouline,<sup>5</sup> Pratyush Giri,<sup>6</sup> John Kuruvilla,<sup>7</sup> Miguel Canales,<sup>8</sup> Sascha Dietrich,<sup>9</sup> Keith Fay,<sup>10</sup> Matthew Ku,<sup>11</sup> Loretta Nastoupil,<sup>12</sup> Michael C Wei,<sup>13</sup> Shen Yin,<sup>13</sup> Michelle Y Doral,<sup>13</sup> Chi-Chung Li,<sup>13</sup> Huang Huang,<sup>14</sup> Raluca Negricea,<sup>15</sup> Elicia Penuel,<sup>13</sup> Carol O'Hear,<sup>13</sup> Nancy L Bartlett<sup>16</sup>**

<sup>1</sup>City of Hope, Duarte, CA, USA; <sup>2</sup>BC Cancer Centre for Lymphoid Cancer and University of British Columbia, Vancouver, BC, Canada; <sup>3</sup>Memorial Sloan Kettering Cancer Center, New York, NY, USA; <sup>4</sup>Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; <sup>5</sup>Jewish General Hospital, Montreal, QC, Canada; <sup>6</sup>Royal Adelaide Hospital, Adelaide, Australia; <sup>7</sup>Princess Margaret Cancer Centre, Toronto, ON, Canada; <sup>8</sup>Hospital Universitario La Paz, Madrid, Spain; <sup>9</sup>Universitätsklinikum Heidelberg, Heidelberg, Germany; <sup>10</sup>St Vincent's Hospital and Royal North Shore Hospital, Sydney, Australia; <sup>11</sup>St Vincent's Hospital, University of Melbourne, Melbourne, Australia; <sup>12</sup>MD Anderson Cancer Center, Houston, TX, USA; <sup>13</sup>Genentech, Inc., South San Francisco, CA, USA; <sup>14</sup>Hoffmann-La Roche Ltd, Mississauga, ON, Canada; <sup>15</sup>Roche Products Ltd, Welwyn Garden City, United Kingdom; <sup>16</sup>Steman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA

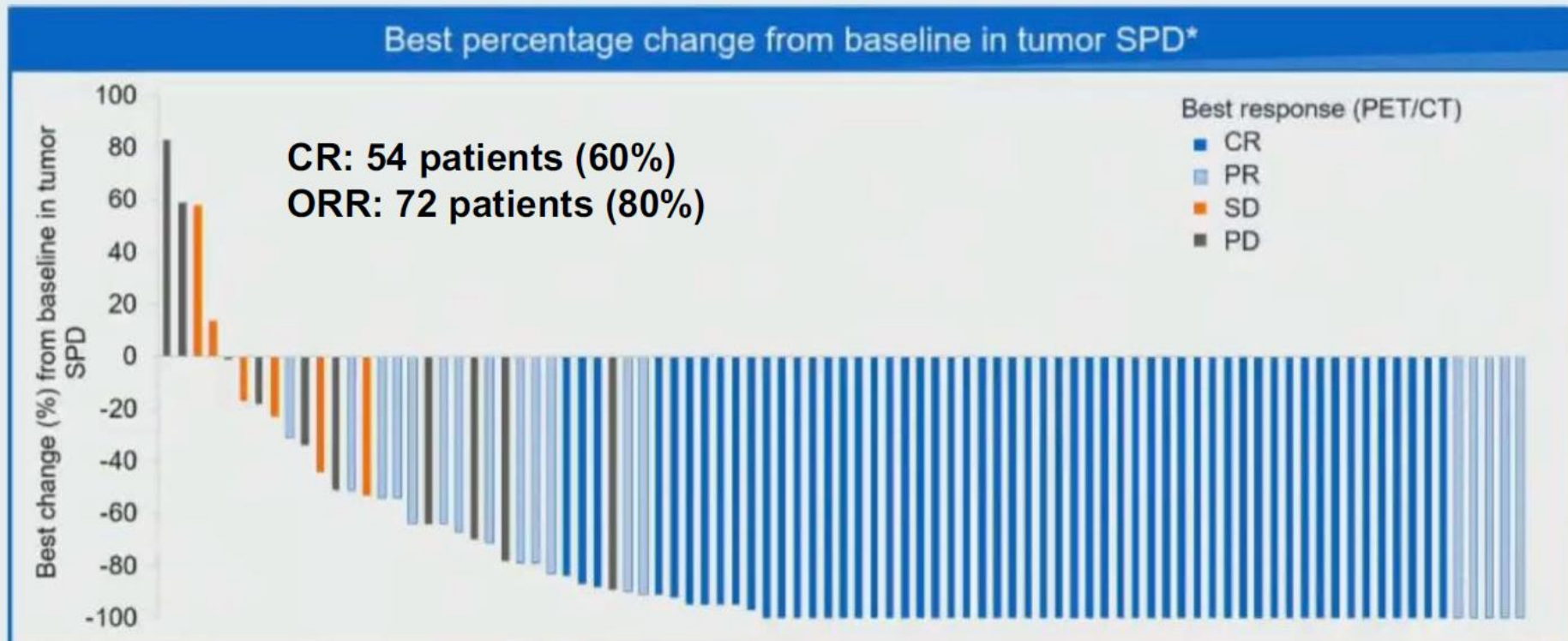
*Accepted as an Oral Presentation at the 63rd ASH Annual Meeting and Exposition*



## 63rd ASH<sup>®</sup> Annual Meeting and Exposition

**ASH 2021;Abstract 127.**

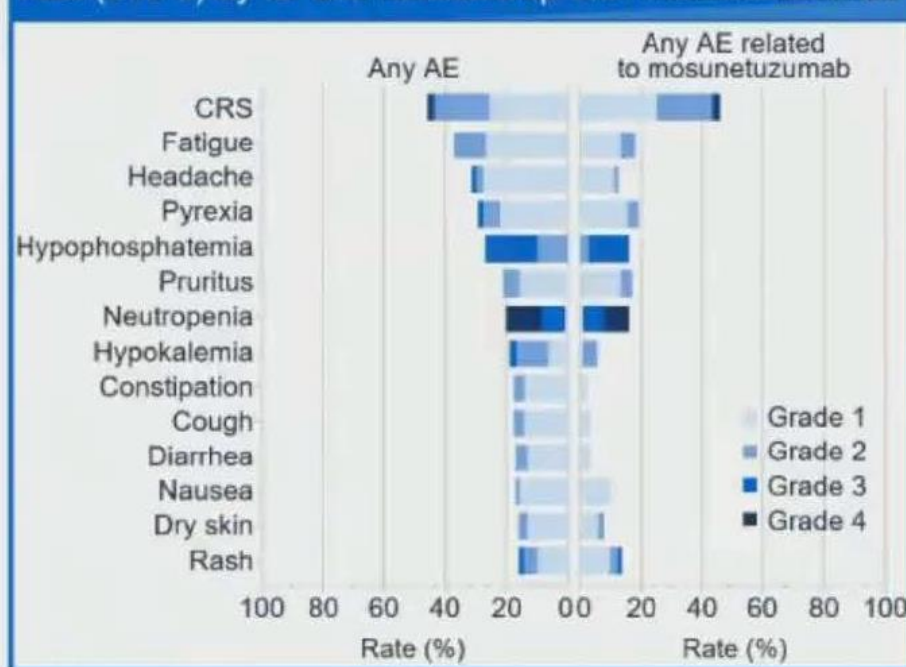
## Response to Mosunetuzumab Monotherapy in Patients with R/R FL Who Have Received $\geq 2$ Lines of Therapy



## Safety Profile of Mosunetuzumab Monotherapy for Patients with R/R FL Who Have Received $\geq 2$ Lines of Therapy

N (%)	N=90
AE	90 (100%)
Mosunetuzumab related*	83 (92.2%)
Grade 3–4 AE	63 (70.0%)
Mosunetuzumab related*	46 (51.1%)
Serious AE	42 (46.7%)
Mosunetuzumab related*	30 (33.3%)
Grade 5 (fatal) AE	2 (2.2%)†
Mosunetuzumab related*	0
AE leading to discontinuation of treatment	4 (4.4%)‡
Mosunetuzumab related*	2 (2.2%)‡

AEs ( $\geq 15\%$ ) by Gr and relationship with mosunetuzumab

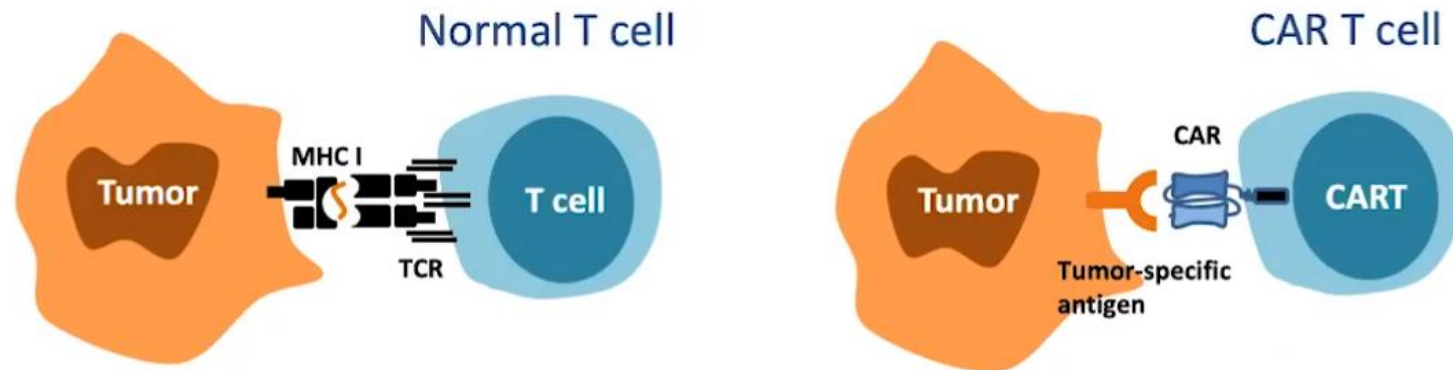


CAR-T cells

## What is a CAR T Cell?

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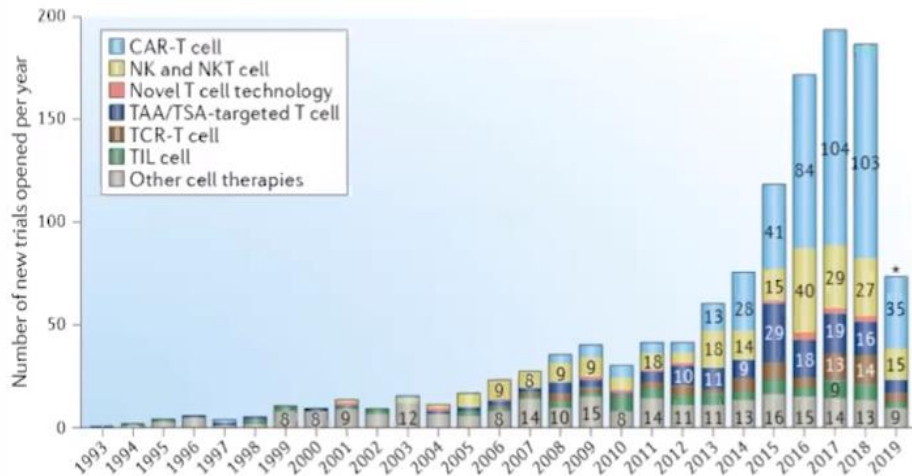
- A CAR T cell is a T cell that is genetically engineered to express a chimeric antigen receptor (CAR) that binds to a tumor antigen presented on the tumor cell surface.
- CAR receptors circumvents the need of MHC class I on the tumor.



## Building on the success of CD19 CAR therapy

- 500 trials worldwide (clinicaltrials.gov)
- >20,000 infused patients
- 145 biotech/pharma CAR programs

The evolution of cell therapy trials for cancer since 1993



## The global pipeline of cell therapies for cancer

Jia Xin Yu, Vanessa M. Hubbard-Lucey and Jun Tang

Jia Xin Yu et al. *Nat Rev Drug Discov.* 2019

Interventional CAR clinical trials by country (< 2019)



## The therapeutic landscape for cells engineered with chimeric antigen receptors

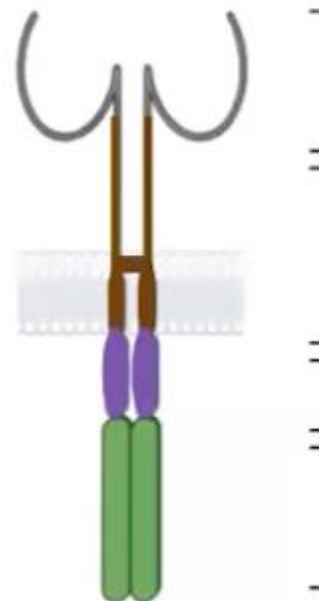
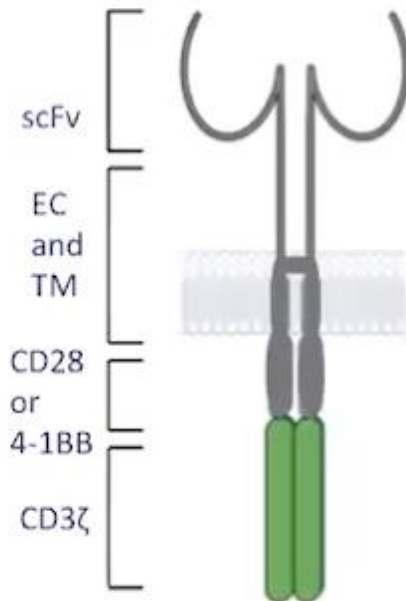
Matthew MacKay<sup>1,2,3,4</sup>, Ebrahim Afshinnekoo<sup>1,2,3</sup>, Jonathan Rub<sup>1,3</sup>, Ciaran Hassan<sup>5</sup>, Mihir Khunte<sup>5</sup>, Nithyashri Baskaran<sup>5</sup>, Bryan Owens<sup>5</sup>, Lauren Liu<sup>5</sup>, Gail J. Roboz<sup>6</sup>, Monica L. Guzman<sup>6</sup>, Ari M. Melnick<sup>6</sup>, Shixiu Wu<sup>7,8</sup> and Christopher E. Mason<sup>1,2,3,9</sup>

Matthew MacKay et al. *Nat Biotechnol.* 2020

Structure

CD28 CAR

4-1BB CAR



Antigen binding

- Epitope
- Affinity

Structure

- Affects binding
- Affects function

Costimulation

- Function
- Metabolism
- Persistence

Activation

- Function trigger
- Proliferation

Function

2<sup>nd</sup> Generation CAR



Antibody domain

Co-stimulatory domains (CD28 or 4-1BB)

T cell signaling domain

FDA approved in 2017  
 Axicabtagene Ciloleucel (Yescarta)    Tisagenlecleucel (Kymriah)

Prototypic CD19 CARs

# Treatment Protocol

## Preconditioning

- to reduce immunosuppressive cells
- immune cell depletion may induce bone marrow cytokine production that benefit initial CAR proliferation (homeostatic replication)

### **Axicabtagene ciloleucel**

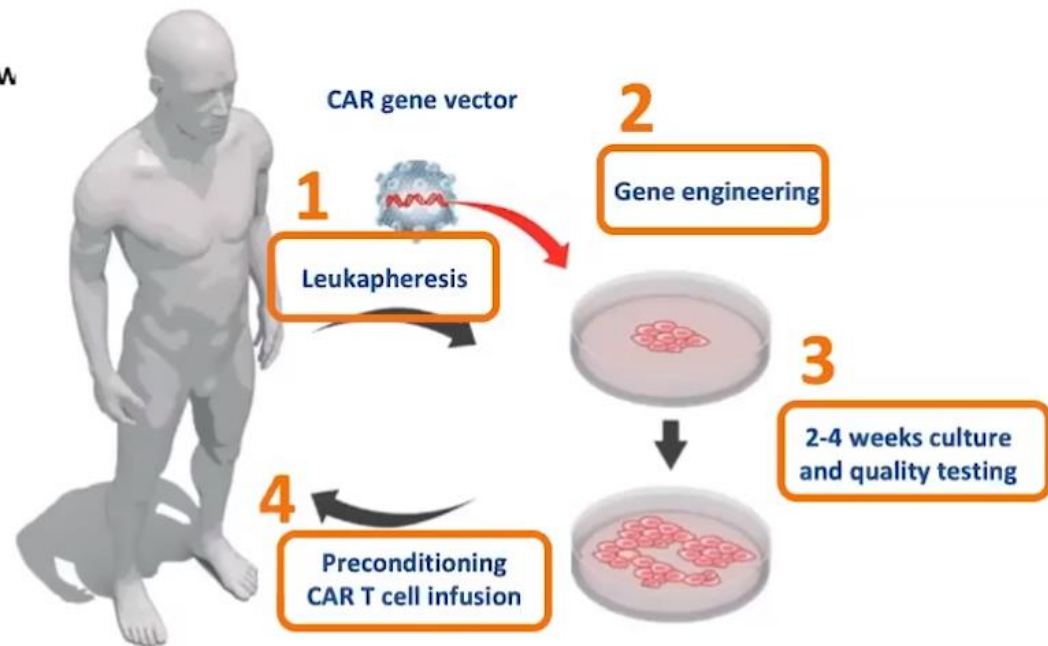
Flu 500mg/m<sup>2</sup> and Cy 30mg/m<sup>2</sup>x3 days  
2x10<sup>6</sup> cells/kg

### **Tisagenlecleucel**

Flu 250 mg/m<sup>2</sup> and Cy 25 mg/m<sup>2</sup>x3 days or  
Benda 90mg/m<sup>2</sup> c 2d  
Median 3x10<sup>8</sup> cells

### **Lisocabtagene maraleucel**

Flu 300 mg/m<sup>2</sup> and Cy 30mg/m<sup>2</sup> x3d  
1x10<sup>8</sup> cells



## Yescarta

## Kymriah

R/R DLBCL	Axi-Cel <sup>[a]</sup>	Tisa-Cel <sup>[b]</sup>	Liso-Cel <sup>[c]</sup>
Construct	antiCD19- <b>CD28</b> -CD3z	antiCD19- <b>4-1BB</b> -CD3z	antiCD19- <b>4-1BB</b> -CD3z
T-cell manufacturing	PBMCs, T cell, bulk	CD3+ T cells, bulk	1:1 ratio CD4:CD8
Dose	$2 \times 10^6/\text{kg}$ (max $2 \times 10^8$ )	0.1 to $6.0 \times 10^8$	DL1: $0.5 \times 10^7$ DL2: $1.0 \times 10^8$
Approval status After 2 lines or more	FDA/EMA-approved for DLBCL, HGBCL, transformed FL, PMBCL	FDA/EMA-approved for DLBCL, HGBCL, transformed FL	Not yet FDA/EMA-approved
	<b>ZUMA1<sup>1</sup></b> Kite/Gilead	<b>JULIET<sup>2-4</sup></b> Novartis	TRANSCEND <sup>5</sup> Juno/Celgene
Best ORR	83%	54%	75%
Durable ORR	36%	35%	57%
Durable CR	37%	30%	52%
PFS, median	5.9 mo	2.9 mo	NR

1. Locke FL, et al. *Lancet Oncol.* 2019; 2. Schuster S, et al. *N Engl J Med.* 2019; 3. Borchmann P, et al. EHA 2018 Abstract S799; 4. Schuster S. *Lancet Oncol.* 2019; 5. Abramson et al. *Blood.* 2017;130:581.

## CAR-T Therapy for R/R Indolent Lymphoma; ZUMA 5

### **Phase 2 (N = 151 enrolled)**

**R/R  
iNHL      N = 146 Treated  
(124 FL, 22 MZL)**

#### Key Eligibility Criteria

- R/R FL (Grades 1 – 3a) or MZL (nodal or extranodal)<sup>a</sup>
- ≥ 2 Prior lines of therapy—must have included an anti-CD20 mAb combined with an alkylating agent<sup>b</sup>

#### Conditioning Regimen

- Fludarabine 30 mg/m<sup>2</sup> IV and cyclophosphamide 500 mg/m<sup>2</sup> IV on Days –5, –4, –3

Axi-Cel: 2 × 10<sup>6</sup> CAR+ cells/kg

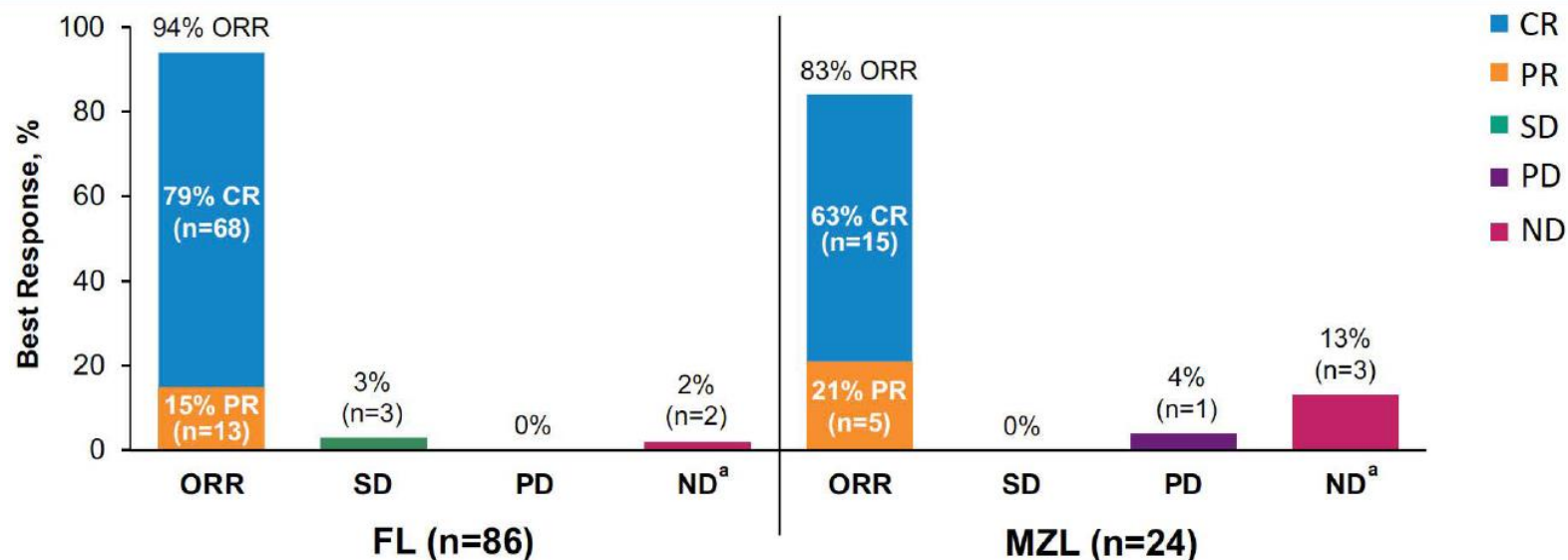
#### Primary Endpoint

- ORR (IRRC-assessed per the Lugano classification<sup>1</sup>)

#### Key Secondary Endpoints

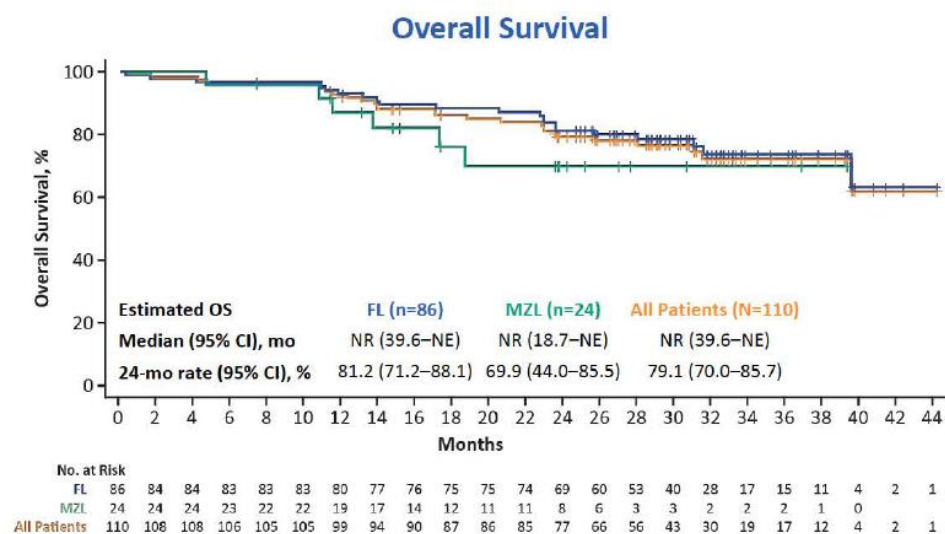
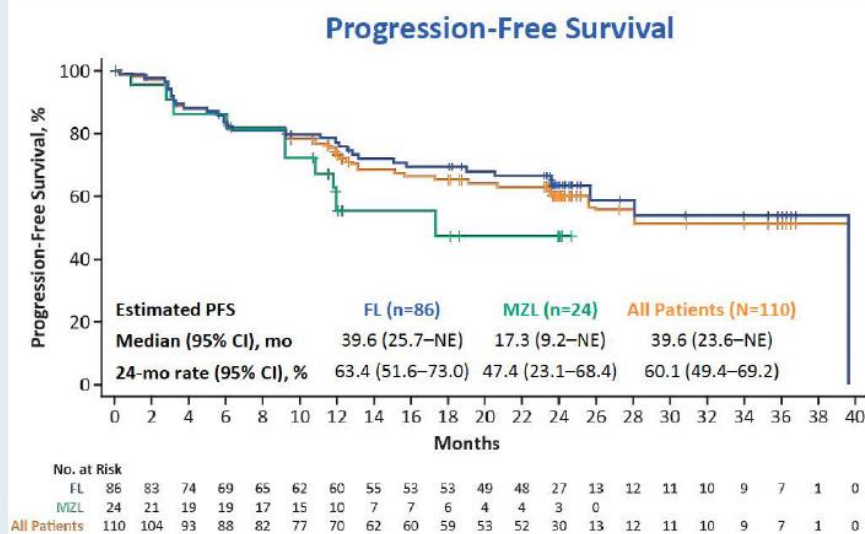
- CR rate (IRRC-assessed)
- Investigator-assessed ORR<sup>1</sup>
- DOR, PFS, OS
- AEs
- CAR T cell and cytokine levels

## ZUMA-5: ORR by Central Review



- Among efficacy-eligible patients with iNHL (n=110), the ORR was 92% (95% CI, 85–96), with a 75% CR rate
- Among all treated patients with iNHL (n=149), the ORR was 92% (95% CI, 86–96), with a 77% CR rate

# ZUMA-5: Progression-Free and Overall Survival



- Median OS was not yet reached in efficacy-eligible patients with FL or MZL
- Among patients with FL, 3 deaths occurred after Month 24<sup>a</sup>; no disease progression events occurred after Month 24

## ZUMA-5: AEs with First Occurrence After Primary Analysis Data Cutoff

AE, n (%)	Follicular Lymphoma (N=124)		Marginal Zone Lymphoma (N=25)		All Patients (N=149)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	27 (22)	14 (11)	11 (44)	6 (24)	38 (26)	20 (13)
Serious AE	11 (9)	11 (9)	4 (16)	4 (16)	15 (10)	15 (10)
Cytopenia	8 (6)	4 (3)	3 (12)	3 (12)	11 (7)	7 (5)
Infection	18 (15)	7 (6)	7 (28)	4 (16)	25 (17)	11 (7)
CRS	0 (0)	0 (0)	2 (8)	0 (0)	2 (1)	0 (0)
Neurologic event	0 (0)	0 (0)	2 (8)	0 (0)	2 (1)	0 (0)
Hypogammaglobulinemia	2 (2)	0 (0)	2 (8)	0 (0)	4 (3)	0 (0)
Tumor lysis syndrome	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

- Grade 5 AEs occurred in 6 patients after the data cutoff of the primary analysis<sup>b</sup>
  - Grade 5 infectious AEs occurred in 5 patients: 1 COVID-19 (FL, Day 717, unrelated), 1 COVID-19 pneumonia (FL, Day 780, related to axi-cel), 1 PML<sup>c</sup> (FL, Day 697, related to axi-cel and CC) and 2 sepsis (FL, Day 1204; MZL, Day 139; both unrelated)
  - Acute bilineal leukemia occurred in 1 patient (FL, Day 623, CC related)

<sup>a</sup> Includes all AEs that occurred after the primary analysis data cutoff date (March 12, 2020) and by the data cutoff date of the current analysis (March 31, 2021). <sup>b</sup> No Grade 5 AEs were due to progressive disease.

<sup>c</sup> The Grade 5 PML event occurred after axi-cel retreatment.

Thank You!

