Treatment options for patients with relapsed/refractory follicular lymphoma

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DES, 2017

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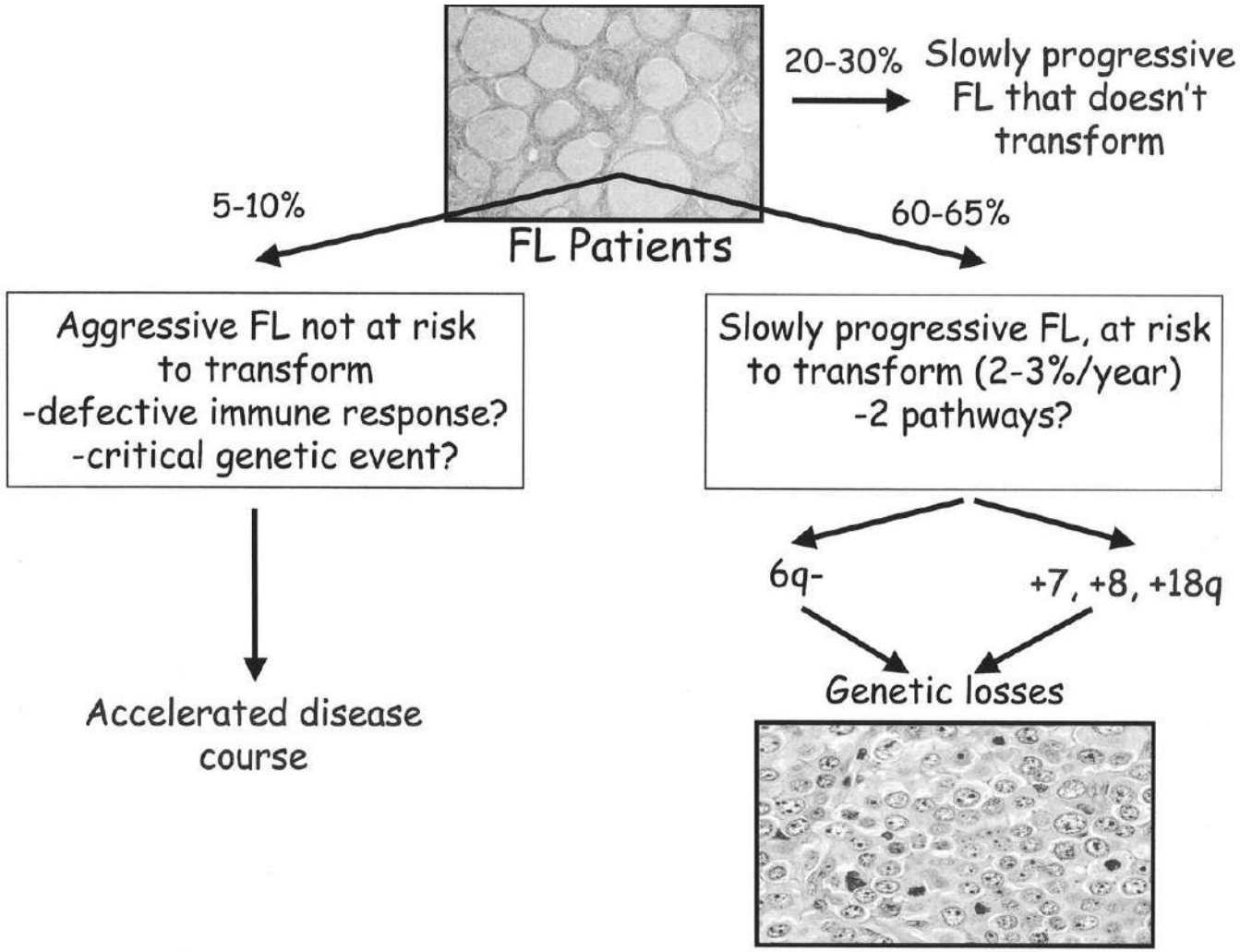
Lysa

Université de Lille 2 DROIT ET SANTÉ

Schematic of hypothetical disease progression in follicular lymphoma (FL).



Gascoyne R D Hematology 2005;2005:299-306

Many Treatment Options in R/R FL

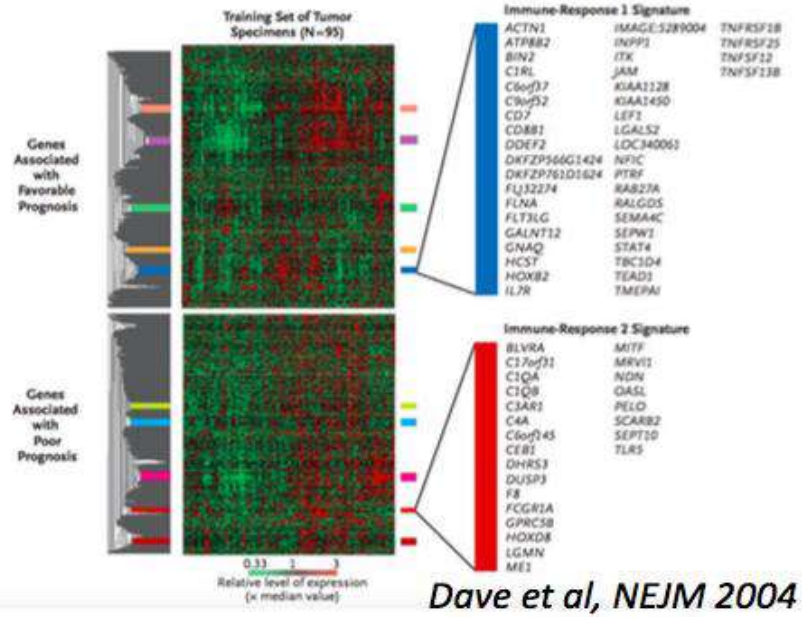
- W&W
- Palliative radiotherapy
- Radiolabelled antibody
- Conventional salvage +/-R (FCM, DHAP/Ox/C, Bendamustine,…)
- Autologous transplant if chemosensitivity to salvage and/or anti-CD20 maintenance
- Allogeneic transplant
- New agents …
  - New antibodies (afucosylated anti CD20, ADC, immune checkpoints inhibitors)
  - IMiDs-based combinations
  - BH3 mimetics, BCR pathway antagonists
  - Epigenetic modifiers (HDAC, EZH2 inhibitors)
  - CART cells?

Treatment of relapse/progression in FL
Guidance tools

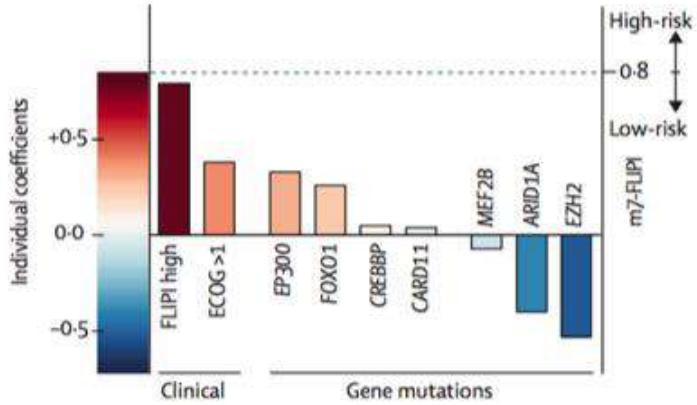
- Treatment choice depends on
  - Line of relapse: 1st, 2nd, >2nd
  - Refractory disease
  - Time to progression
    - Early PD :POD12? POD24?
    - Late PD > 24 Mo? > Presumed median PFS?
  - Previous treatment(s)
  - Histological transformation
  - Patient's age, comorbidities
  - Patient wishes
  - ….

CAN WE PREDICT OUTCOME OF FL PATIENTS ?

- Patients with follicular lymphoma (FL) have heterogeneous outcomes
- Gene-expression profiling studies highlighted the role of non-tumor subsets in FL outcome
- Clinicogenetic risk models recently described

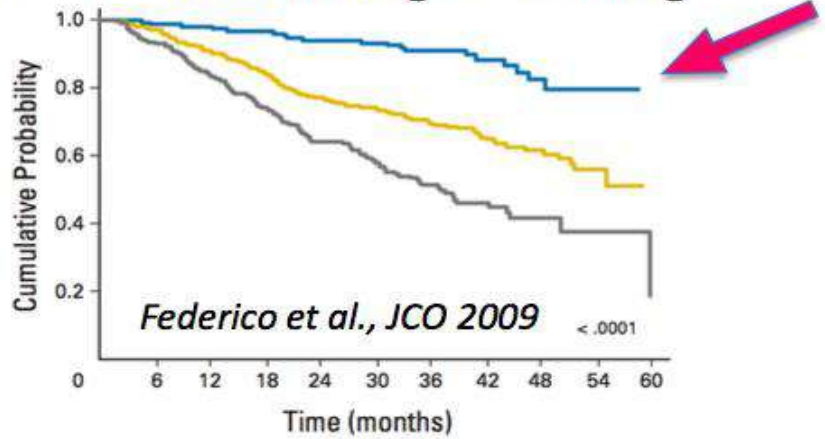


Dave et al, NEJM 2004



Pastore et al, Lancet Oncol 2015

… but we are still missing something



See abstract #086

Can we predict early POD or refractory FL?

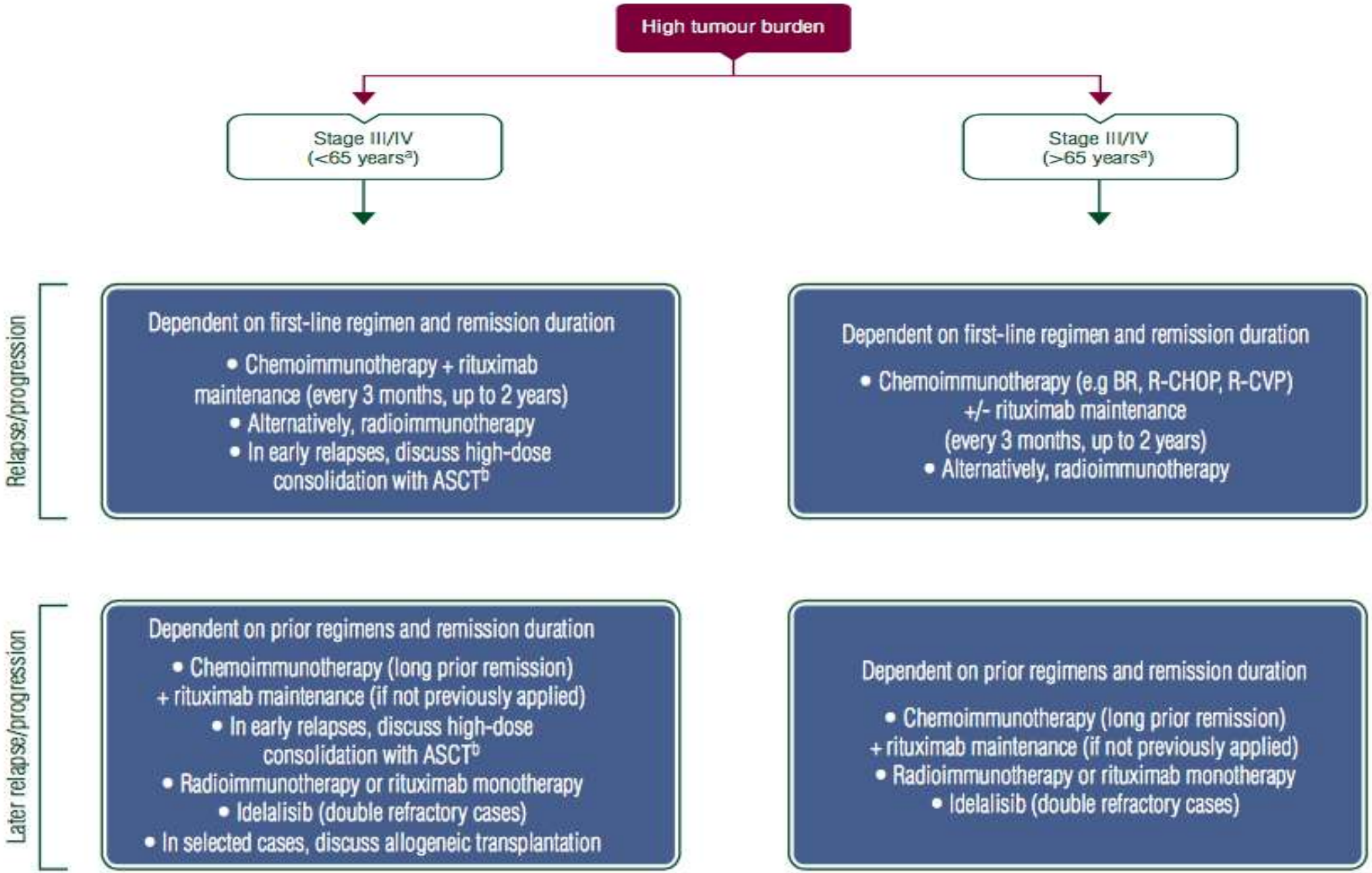
- FLIPI 1? FLIPI 2 (revised)
- Immunohistochemistry (IHC)?
- PET? SUV max? Tumor volume (TMTV)?
- Gene expression profiling (GEP)?
- Combined clinico-biologic models (m7-FLIPI, POD 24-PI;TMTV0+FLIPI2)?

Not yet but work in progress!

Treatment of first relapse

- Objectives
  - To achieve the longest survival
    - To reach the longest disease control (PFS)
    - Try to achieve a 2nd CR?
    - Preserve quality of life and use less toxic regimens even if less CRs?
    - Avoid long-term toxicity

ESMO Clinical Practice Guidelines FL 2016



Main questions in the treatment of R/R FL

- ASCT or not ASCT as part of second-line?
  - If yes, for whom?
- New anti-CD20 MoAbs?
  - Why can they overcome resistance to rituximab?
- New agents beyond anti-CD20?
  - Targeting both tumor and immune contexture
- Allo SCT or CART cells: who and when?

Autogreffe : des études pré-rituximab

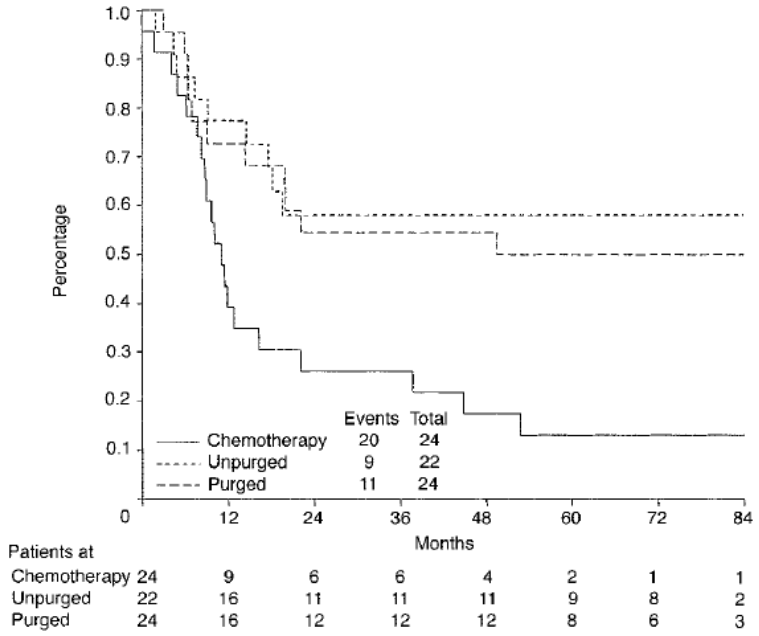
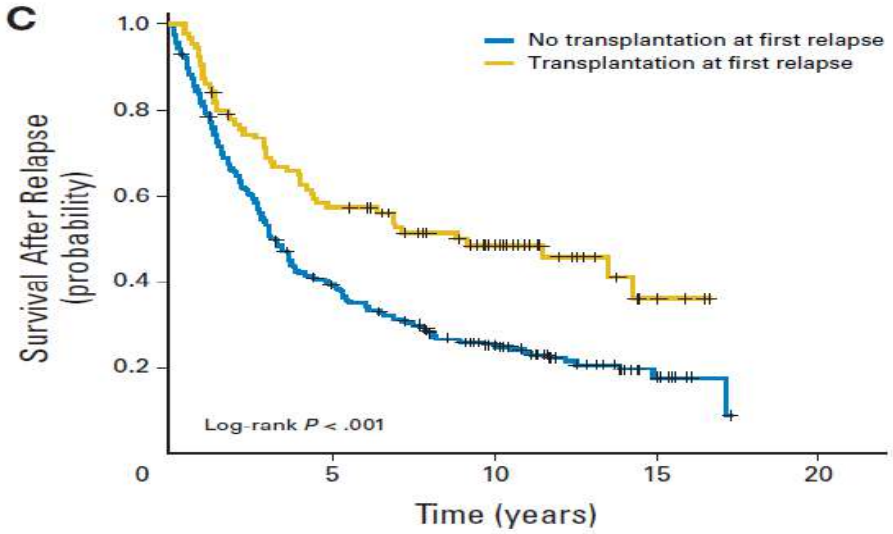
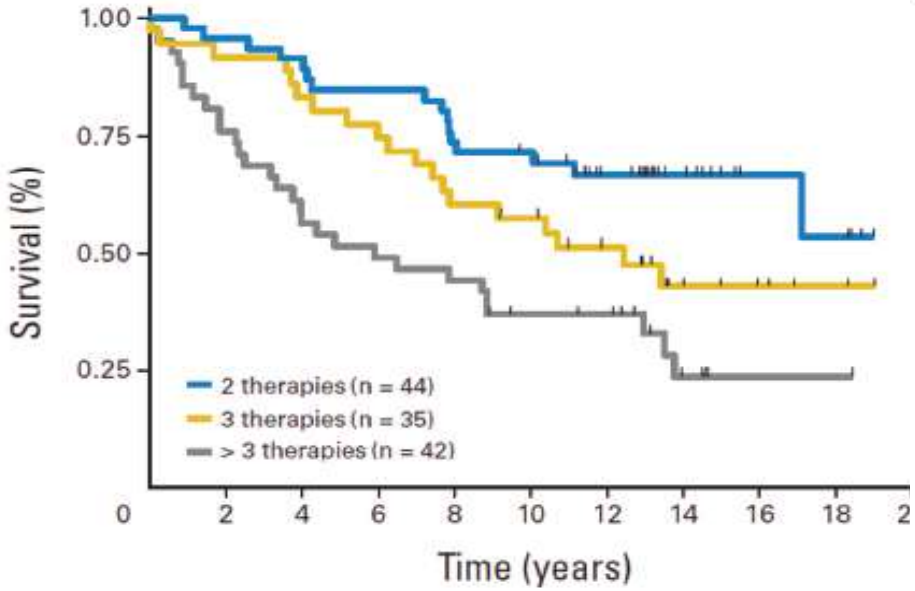


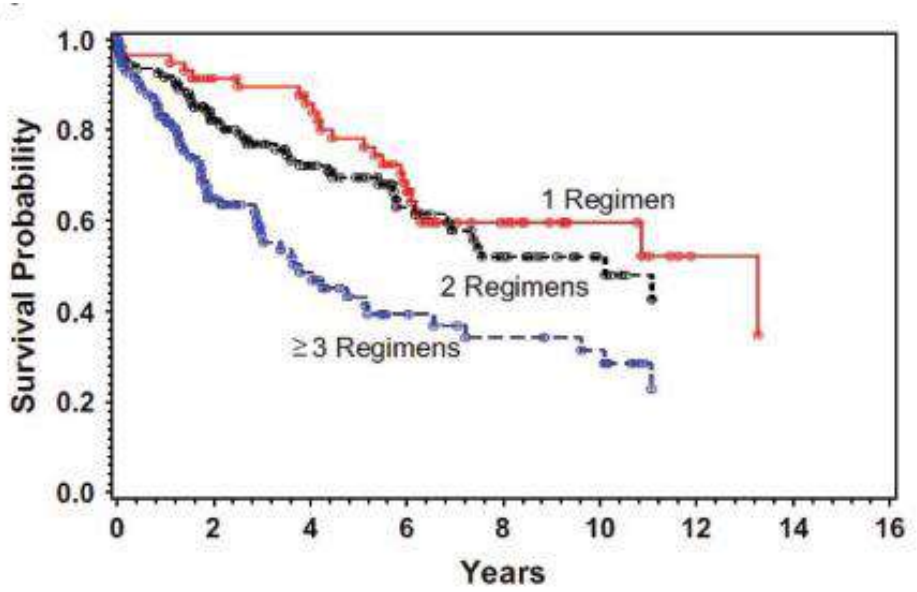
Fig 4. Progression-free survival for patients randomized to three arms.



Schouten et al, *J Clin Oncol* 2003 ; Bachy et al, *J Clin Oncol* 2010

Impact des traitements antérieurs





Rohatiner et al. *J Clin Oncol* 2007
Vose et al. *Biol Bone Marrow Transplant* 2008

FL2000 : impact de l'autoreffe à la rechute

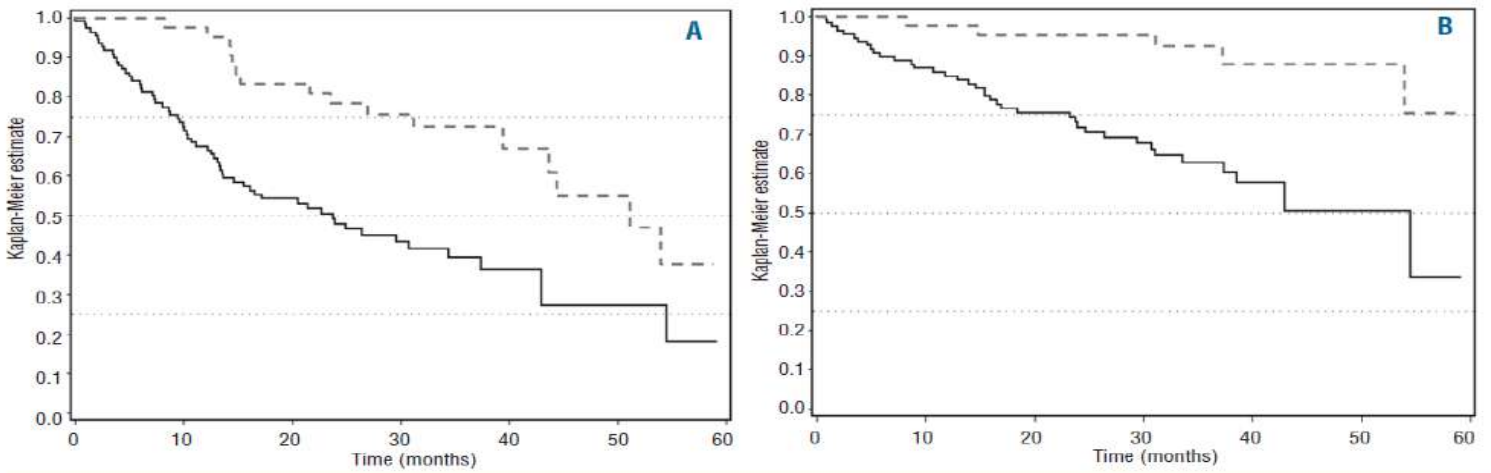


Figure 2. Outcome of patients (under the age of 70 years) according to transplantation at first progression: ----transplanted patients (n=42); —— non-transplanted patients (n=111). (A) Event-free survival (P=0.0005). (B) Overall survival (P=0.0003).

N=153 rechutes de moins de 70 ans, 42 patients autogreffés (28%)
N=105 biopsies, N=14 transformations histologiques
Impact sur la survie globale en particulier dans les rechutes précoces

Le Gouill et al. *Haematologica*, 2011

Impact du Rituximab : rechute du FL2000

	EFS						OS					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age at progression	1.02	1-1.04	0.033	1.01	1-1.04	0.3	1.04	1.01-1.07	0.0036	1.03	1-1.06	0.075
Sex	1.4	0.92-2.14	0.11	1.5	0.95-2.4	0.08	1.44	0.83-2.5	0.2	–	–	–
First-line CHVP-I *vs.* R-CHVP-I	0.75	0.48-1.17	0.2	0.78	0.47-1.3	0.33	1.09	0.62-1.9	0.77	–	–	–
FLIPI score (reference=0-1)												
vs. 2	0.46	0.27-0.8	0.013	0.38	0.17-0.85	0.0517	0.49	0.24-1	0.0045	1.48	0.31-7.12	0.214
vs. 3-5	1.9	1.2-3		0.63	0.31-1.3		3.09	1.58-6.05		2.5	0.58-10.8	
Progression/relapse period												
Induction *vs.* follow up	1.64	1.03-2.63	0.001	2.5	1.4-4.38	0.004	1.98	1.1-3.56	0.0004	4.08	1.97-8.4	0.0001
Consolidation *vs.* follow up	1.9	1.14-3.13		2.76	1.55-4.9		2.25	1.22-4.14		3.83	1.83-8	
Chemotherapy type at first relapse												
Fludarabine-based *vs.* other	1.17	0.68-2	0.58	–	–	–	1.63	0.85-3.11	0.14	–	–	–
Anthracycline-based *vs.* other	1	0.6-1.63	0.95	–	–	–	1.54	0.84-2.82	0.16	–	–	–
Cytarabine-based *vs.* other	0.93	0.57-1.52	0.78	–	–	–	1.38	0.76-2.5	0.29	–	–	–
Cyclophosphamide-based *vs.* other	1	0.61-1.63	0.98	–	–	–	1.04	0.56-1.96	0.9	–	–	–
Rituximab at progression (Yes *vs.* No)	0.66	0.42-1.05	0.077	0.65	0.4-1.08	0.095	0.99	0.54-1.8	0.96	–	–	–
Transplantation at progression (Yes *vs.* No)	0.41	0.24-0.71	0.0015	0.38	0.2-0.72	0.003	0.22	0.09-0.56	0.0014	0.26	0.1-0.68	0.006

Rituximab la rechute : CHVP 73%, R-CHVP 50%
Bénéfice limité aux patients du bras CHVP-i

Le Gouill et al. *Haematologica*, 2011

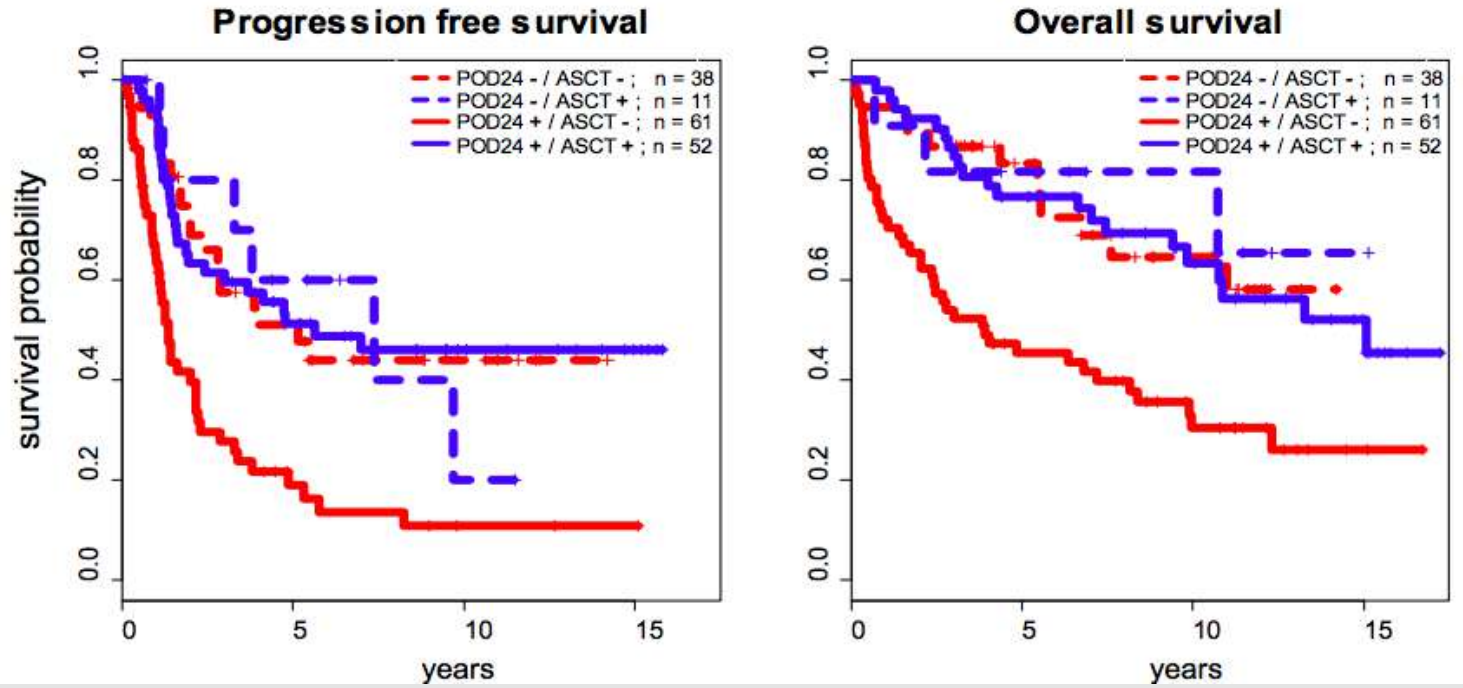
Autologous Stem Cell Transplantation for Patients with Early Progression of FL
Retrospective Analysis of 2 Randomized Trials of the GLSG

Applied treatment strategies for patients with or without POD24

	ASCT	no ASCT
POD24	52	61
no POD24	11	38

Patients with POD24 were significantly more likely to receive ASCT as 2nd-line treatment ($p = 0.0080$).

Treatment outcome for patients with or without POD24 by ASCT *vs* no ASCT



SdV Oct 2011

Jurinovic & Weigert, ASH 2016

Autologous Stem Cell Transplantation for Patients with Early Progression of FL
Retrospective Analysis of 2 Randomized Trials of the GLSG

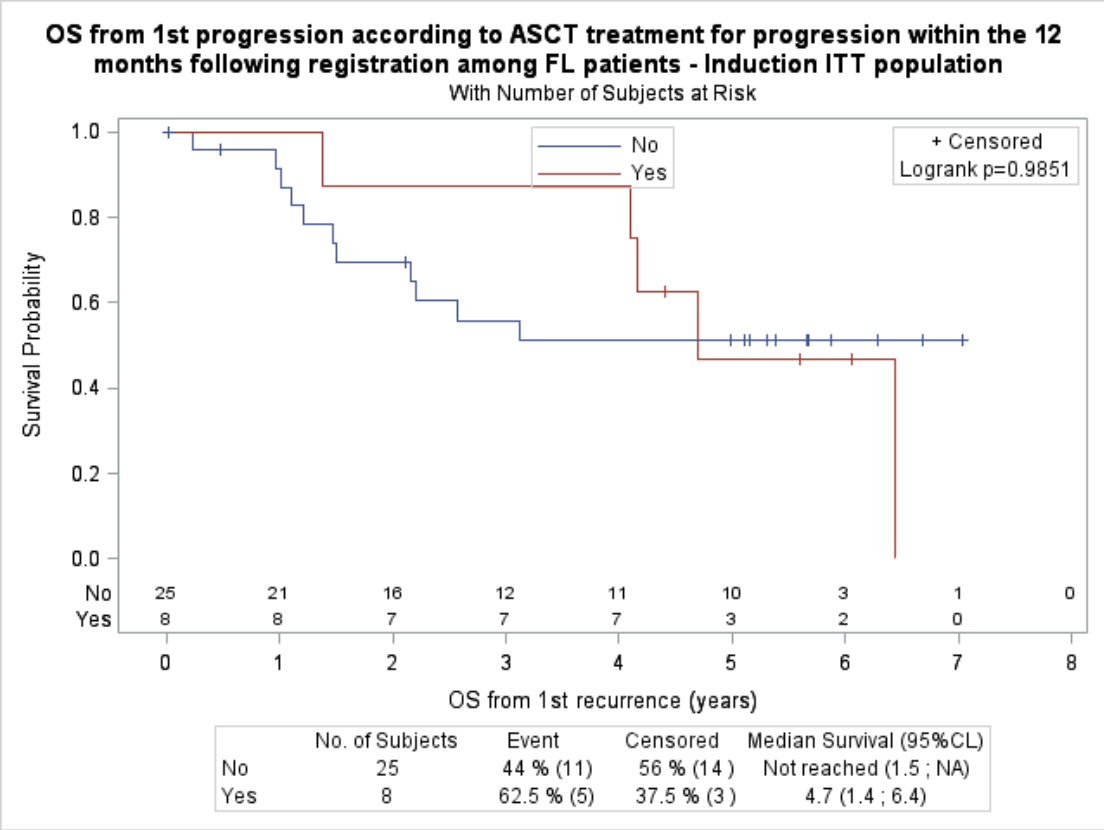
Patient characteristics for POD24 cohort

Patients with POD24 (n=113)		ASCT (n=52)	no ASCT (n=61)	*p*-value
male		73%	51%	0.026
1st-line treatment	*MCP*	10%	20%	0.11
	CHOP	71%	72%	
	R-CHOP	19%	8%	
age (yrs)		48	52	0.014
>4 LN areas (evaluable n=92)		37%	31%	0.65
elevated LDH (evaluable n=73)		14%	41%	0.022
low Hb (evaluable n=83)		18%	41%	0.042
ECOG > 1 (evaluable n=77)		7%	11%	0.91
FLIPI 1st-line (evaluable n=112)	*low*	10%	10%	0.76
	intermediate	51%	44%	
	high	39%	46%	
Rituximab 1st-line		19%	8%	0.15
Rituximab 2nd-line		48%	48%	>0.99

Jurinovic & Weigert, ASH 2016

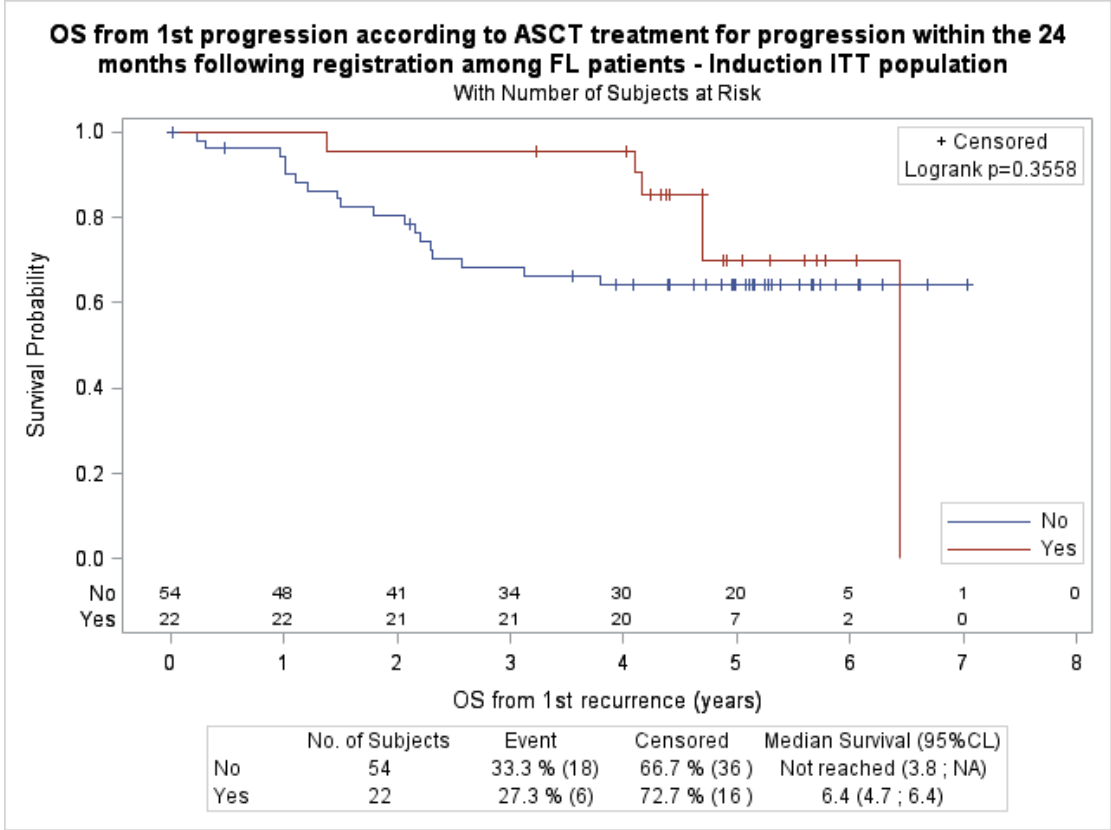
PRIMA
No OS benefit for ASCT in FL patients with early POD

ASCT or not for FL with POD12



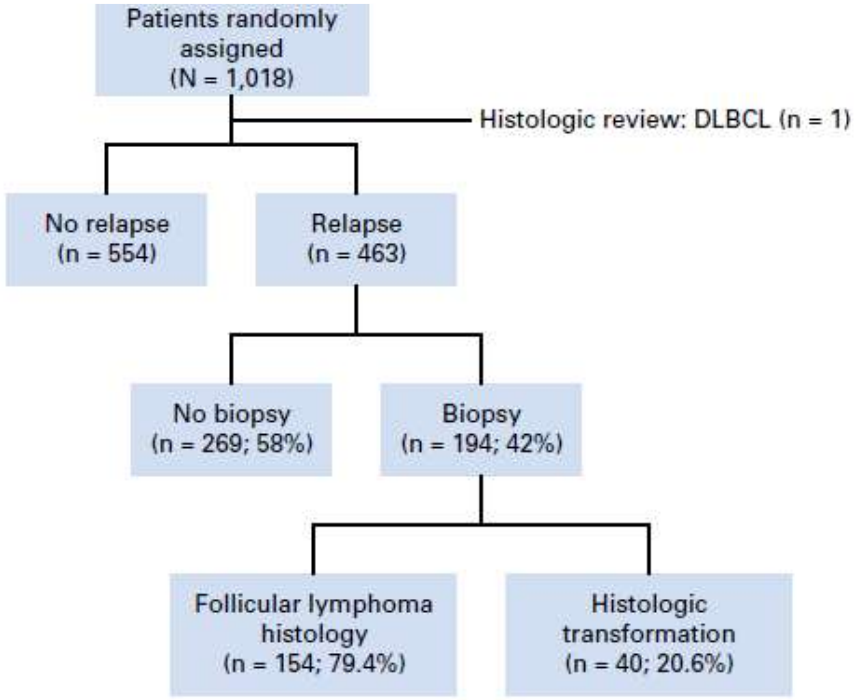
	No. of Subjects	Event	Censored	Median Survival (95%CL)
No	25	44 % (11)	56 % (14)	Not reached (1.5 ; NA)
Yes	8	62.5 % (5)	37.5 % (3)	4.7 (1.4 ; 6.4)

ASCT or not for FL with POD24



	No. of Subjects	Event	Censored	Median Survival (95%CL)
No	54	33.3 % (18)	66.7 % (36)	Not reached (3.8 ; NA)
Yes	22	27.3 % (6)	72.7 % (16)	6.4 (4.7 ; 6.4)

ASCT at relapse/progression in PRIMA
Histological transformation



- **Most of HT occured in the first year after randomization**
  - **with a median time from randomization of 9.6 months**
  - **compared to 22.8 months for progression with FL histology**
- **Cumulative incidence of HT:**
  - **2.4% at 1 year**
  - **3.8% at 5 years**
  - **Between 1-6 years: < 2%**
- **If extrapolating to all patients (those with and without biopsy all included): 9.4% at 6 years**

Sarkozy et al, JCO 2016

Facteurs de risque de transformation

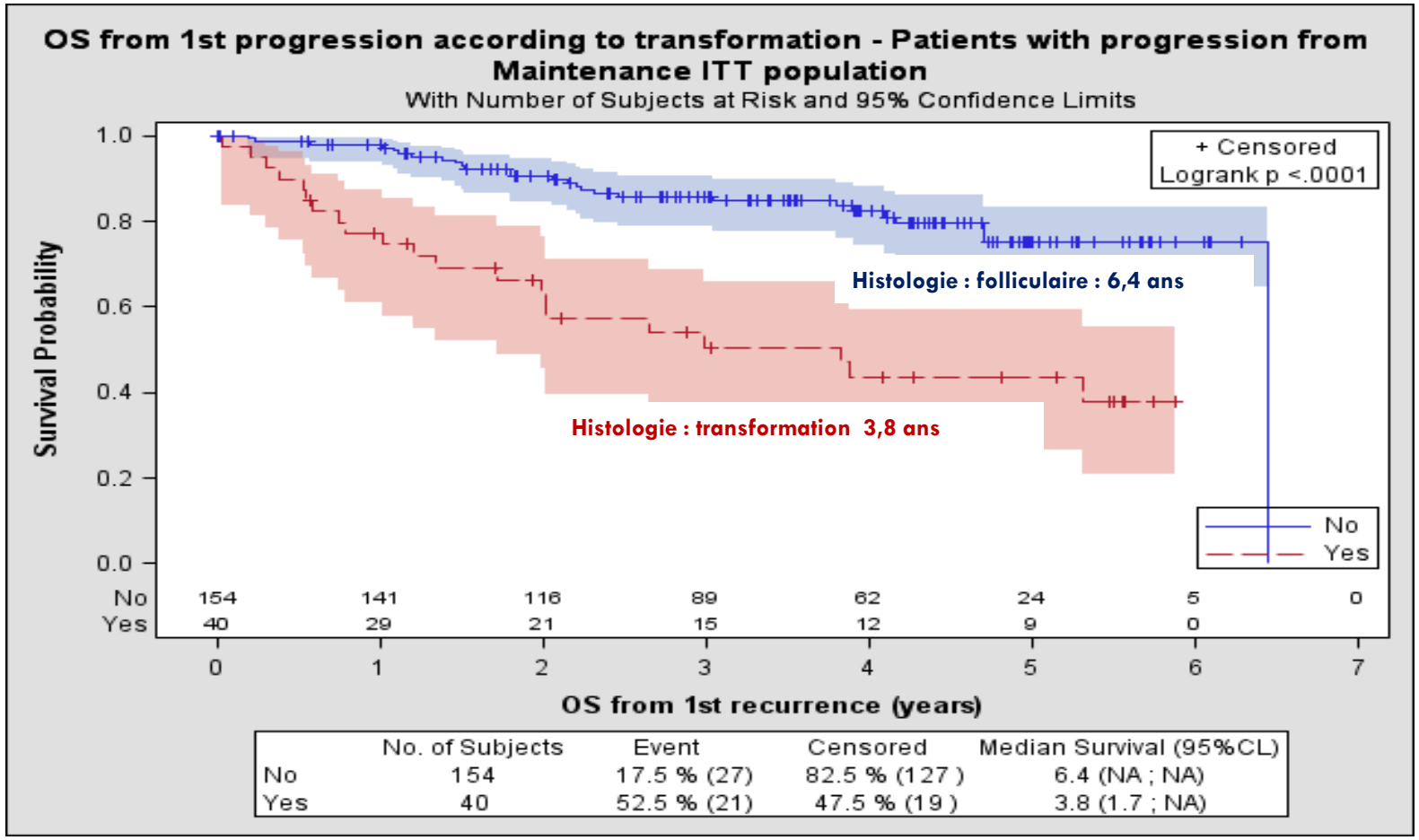
At diagnosis	No transformation, N=708	Histological transformation, N=40	Test
Age (median)	57	57	P=0.84
Gender (F)	50,6%	40%	P=0.19
FL grade (1/2/3)	43%/36%/21%	20%/47%/33%	**P=0.02**
Performance Status (2-4)	2,7%	15%	**P<0.001**
B symtoms (yes)	29,8%	45%	**P=0.042**
N extra-nodal sites	1,4 (mean)	1,6 (mean)	P=0.33
N nodal sites	5 (mean)	5,4 (mean)	P=0.29
Bulky disease (yes)	47,4%	56,4%	P=0.27
Ann Arbor stage (3-4)	88,6%	97,5	P=0.11
Anemia	17,9%	40%	**P<0.001**
LDH>N	31%	47%	**P=0.029**
FLIPI (0-1/2/3-5)	25%/35%/40%	7,5%30%/62,5%	**P=0.007**
Albumin < 35 g/L	8,4%	18,2%	P=0,105
B2microglobulin>3	27%	30,6%	P=0,605

Analyse multivariée : seuls PS≥2 et anémie <12g/dL étaient associés à une transformation à la rechute

Pas d'impact de : chimiothérapie initiale, qualité de la réponse, entretien

Sarkozy et al, *J Clin Oncol* 2016

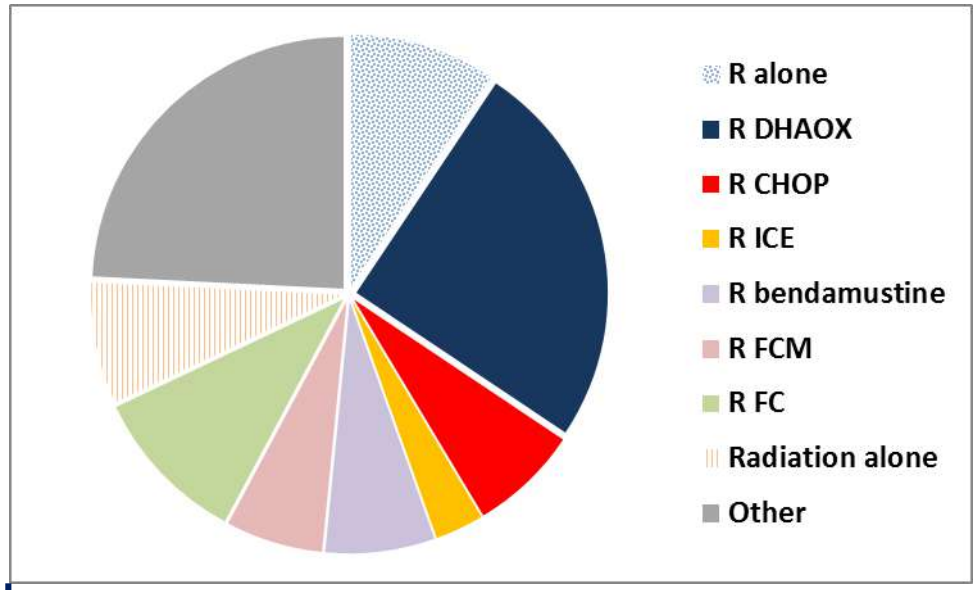
Pronostic de l'analyse histologique (1)



Sarkozy et al, *J Clin Oncol* 2016

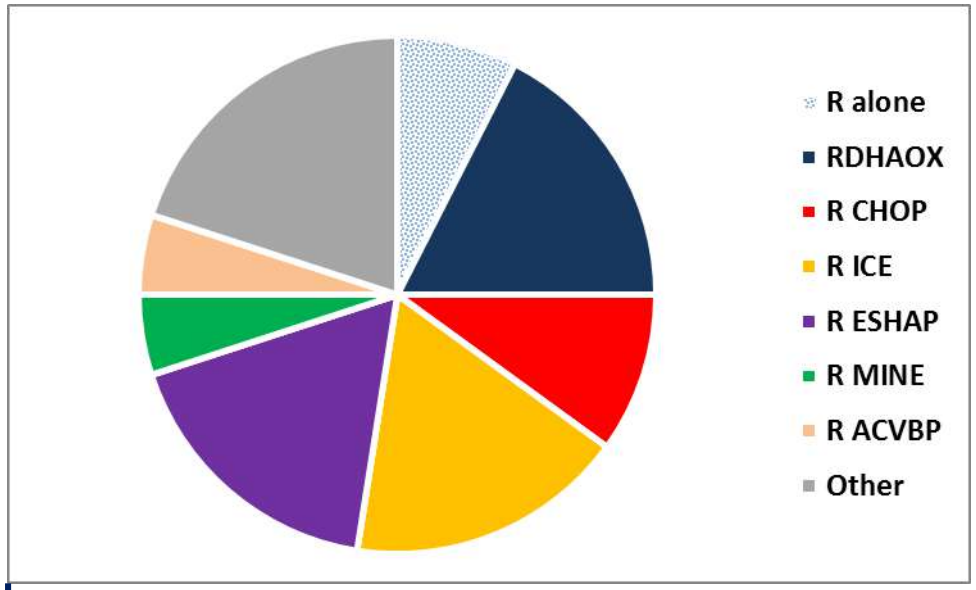
Results: salvage in PRIMA

Follicular lymphoma histology



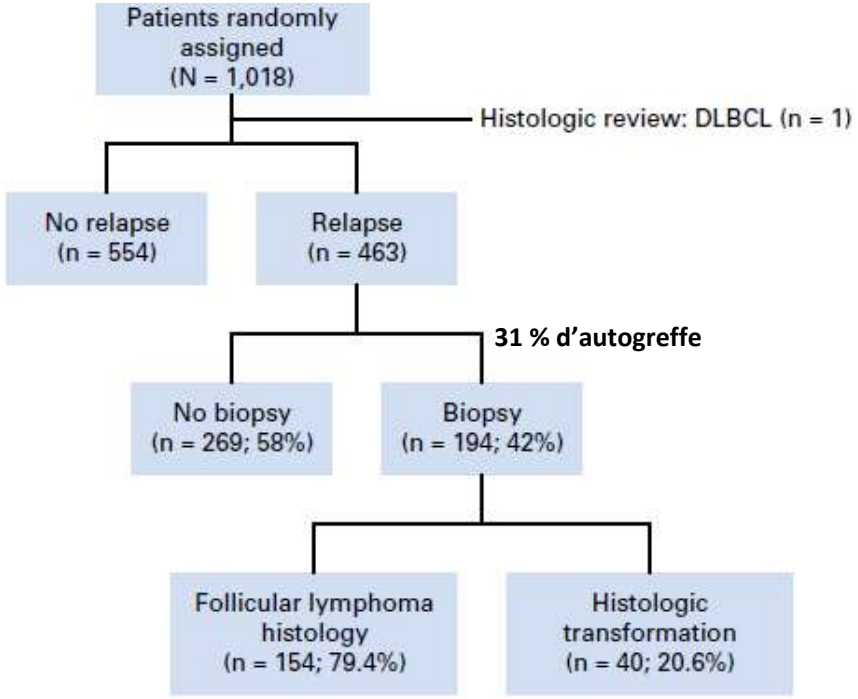
73% treated immediatly
Various regimen including R alone, radiation therapy or R-chemo
ASCT: 44 (28%)

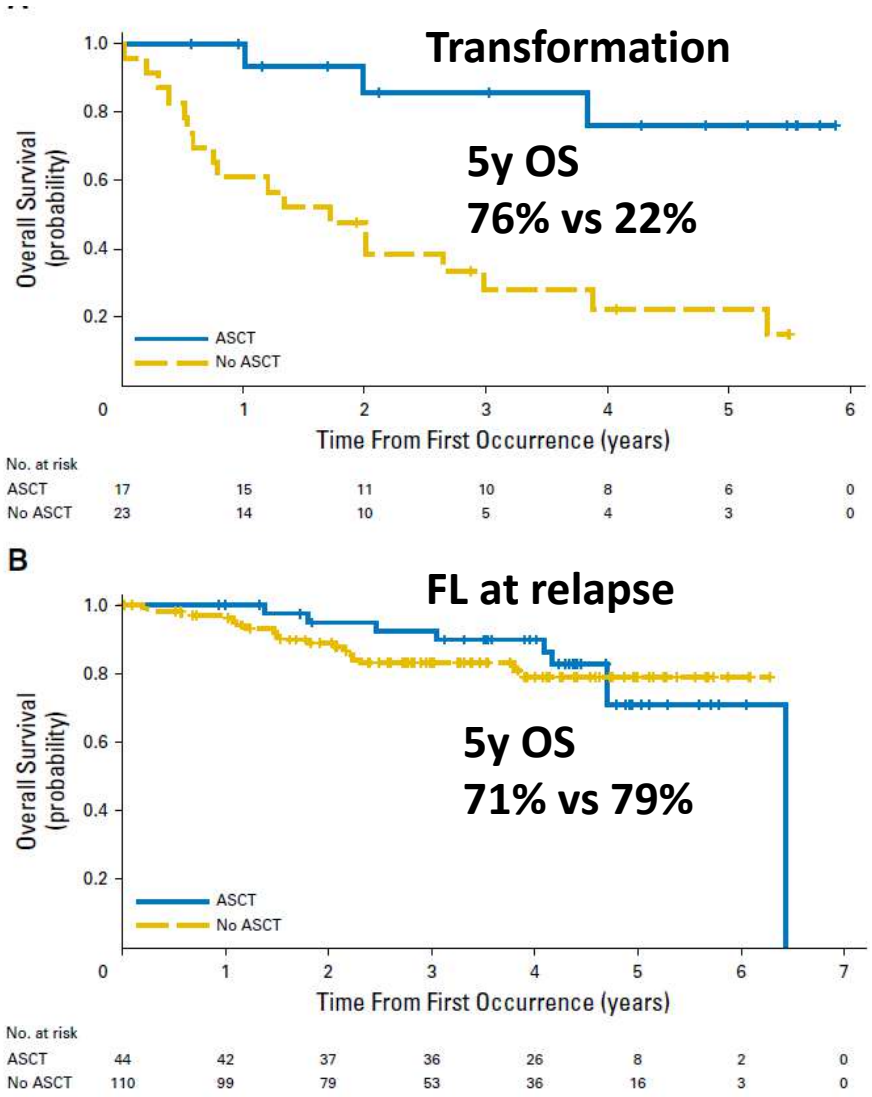
Histological transformation



86% treated immediatly
R alone, DLBCL-like treatment (R-chemo, intensive regimen)
ASCT: 17 (42%)

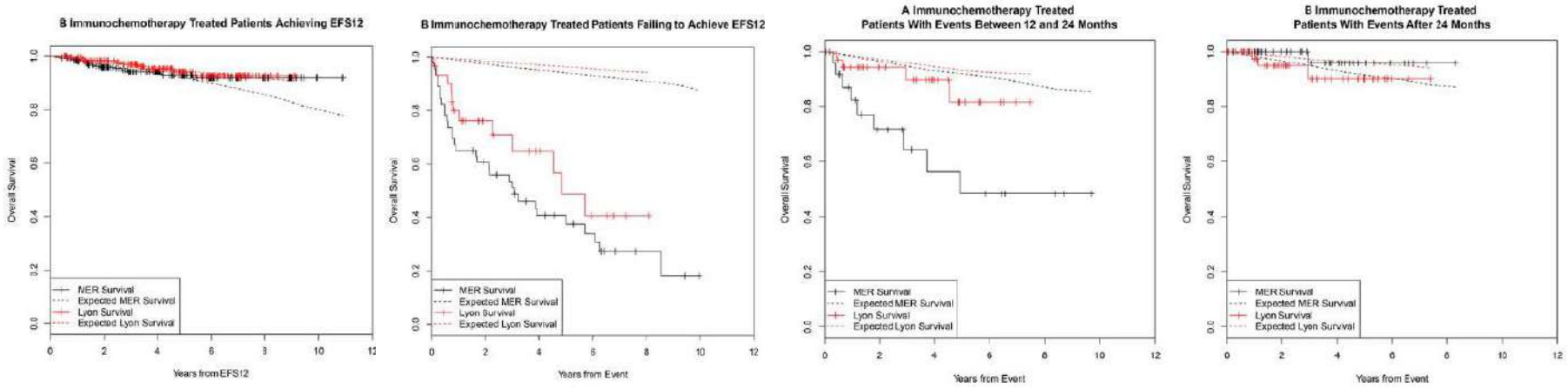
ASCT at relapse/progression in PRIMA
Patients with an HT derive benefit from ASCT





Sarkozy et al, JCO 2016

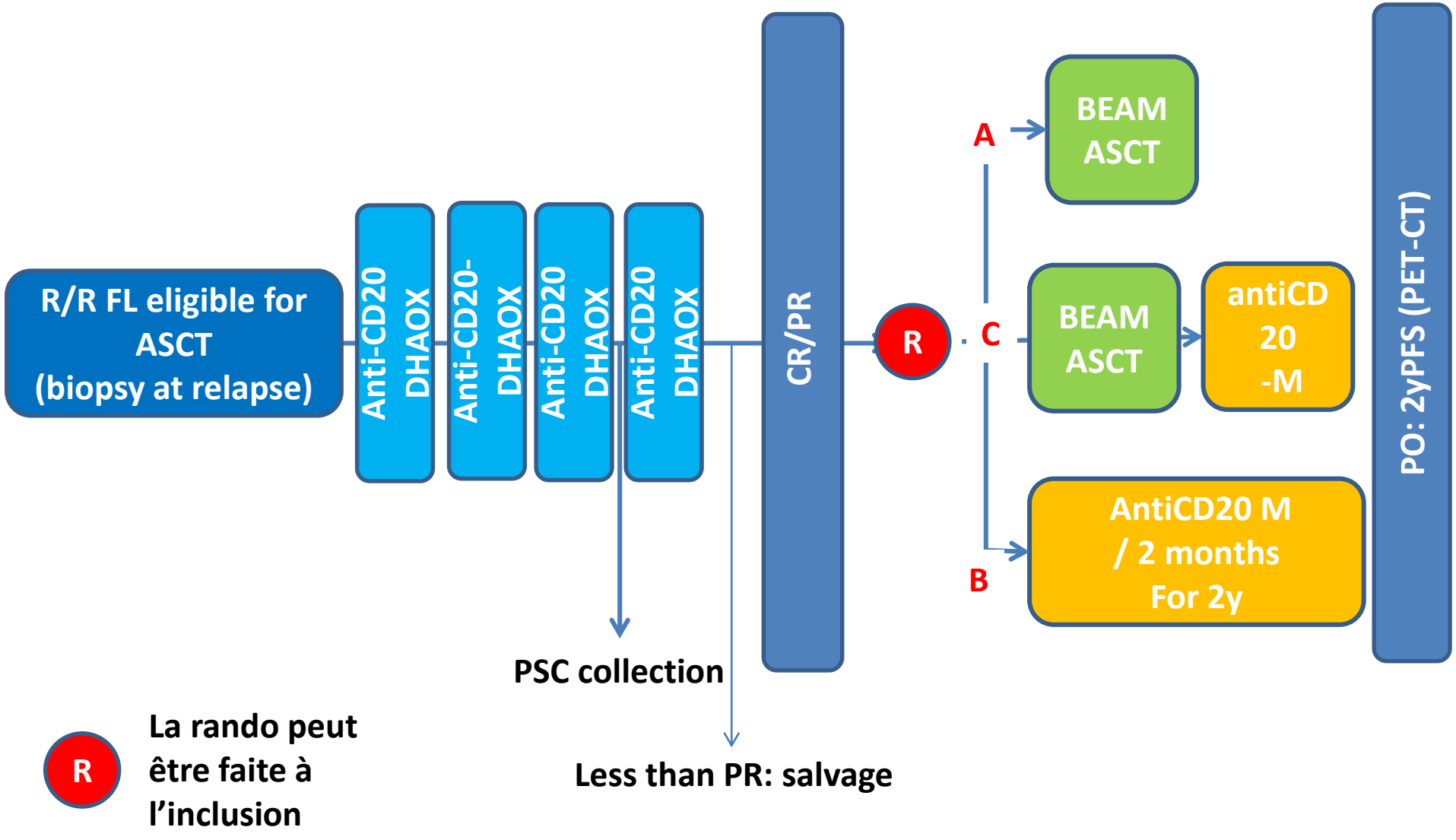
EFS12 ET EFS 24



	Cohorte MER	Cohorte Lyon
N	**920 patients** Traitements : w&w 33% ; R-mono 12% ; R-chimio 38%.	**412 patients** Traitements : w&w 20% ; R-mono 10% ; R-chimio 59%.
EFS 12	**83%,**	**82%**
EFS 24	**71%**	**67%**

Maurer et al, *Ann Hematol* 2016

Phase 3 to answer the question



Take home messages

- Biopsie à la rechute : éliminer transformation
  - D'autant que : hypermétabolisme important, rechute précoce
  - Car impact pronostic
  - Car impact thérapeutique : indication autogreffe plus formelle
- Autogreffe à la rechute
  - Incontournable si transformation, plus discutable sinon
- Rituximab à la rechute
  - Pas d'impact démontré si rituximab en première ligne

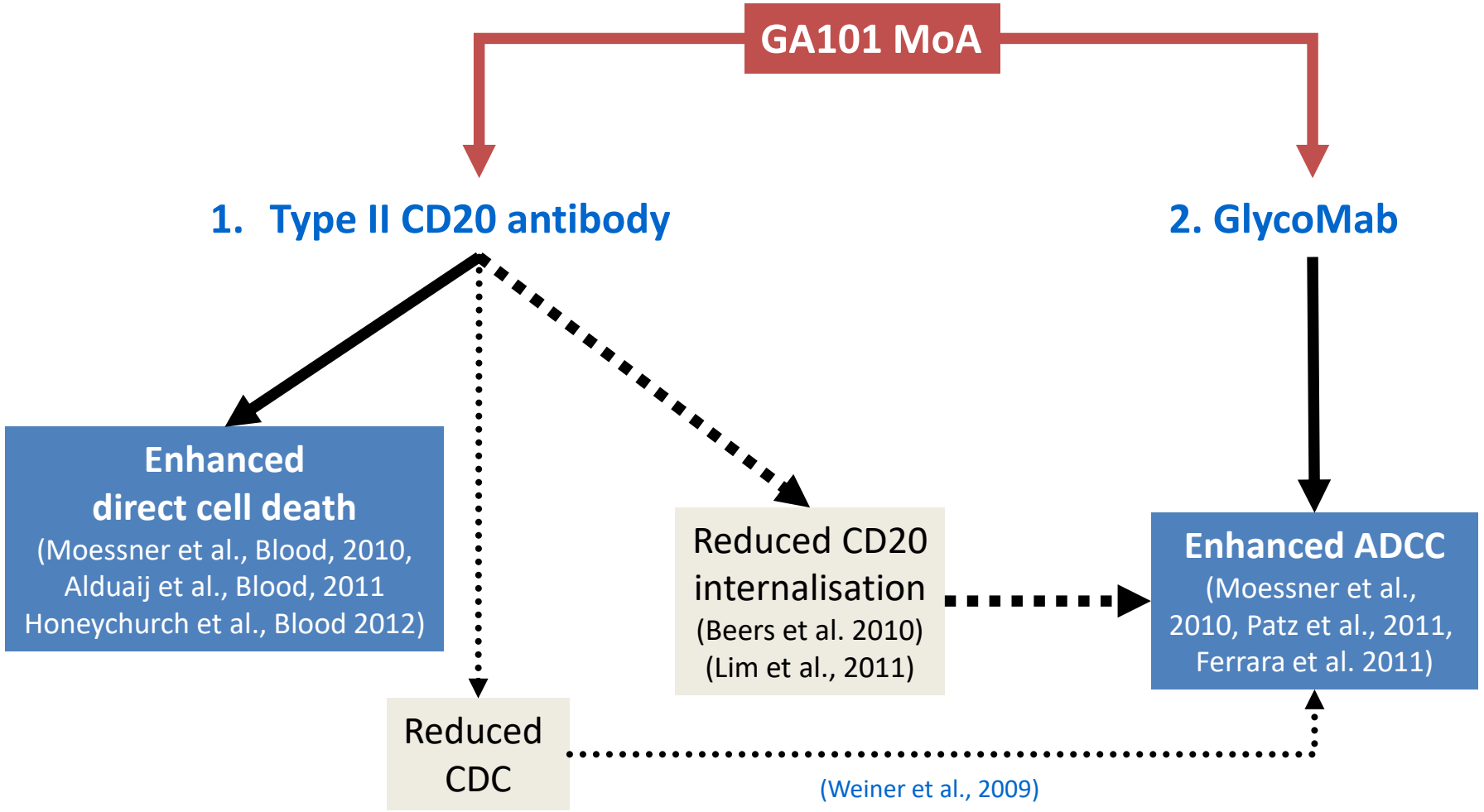
Main questions in the treatment of R/R FL

- ASCT or not ASCT as part of second-line?
  - If yes, for whom?
- New anti-CD20 MoAbs?
  - Why can they overcome resistance to rituximab?
- New agents beyond anti-CD20?
  - Targeting both tumor and immune contexture
- Allo SCT or CART cells: who and when?

Mecanisms of resistance to rituximab

- Loss of CD20
  - true mechanism of resistance but rare, mainly documented in DLBCL
- CD20 « Shaving »
  - has been proposed in CLL, but no clear data in FL
- Loss of direct effects “signaling” has been looked at in cell lines,
  - but not any convincing patient derived info.
- Combination of loss of « signaling » and loss of immune effector cells and resistance to immune mediated cell killing mostly with ADCC.
- Dose related issues
  - this has been very hard to show.
  - No one has done the experiment to see if patients not responding to a standard dose will respond to a much higher dose…

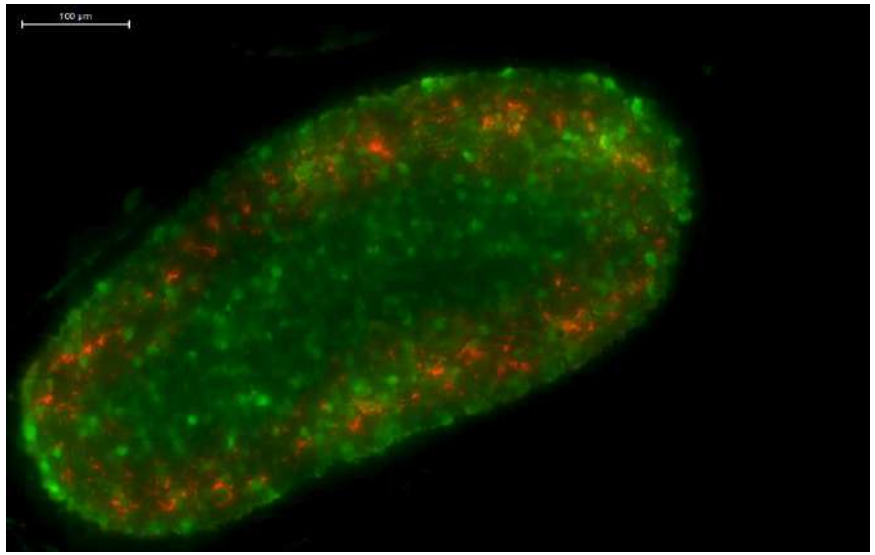
GA101 putative mechanisms of action



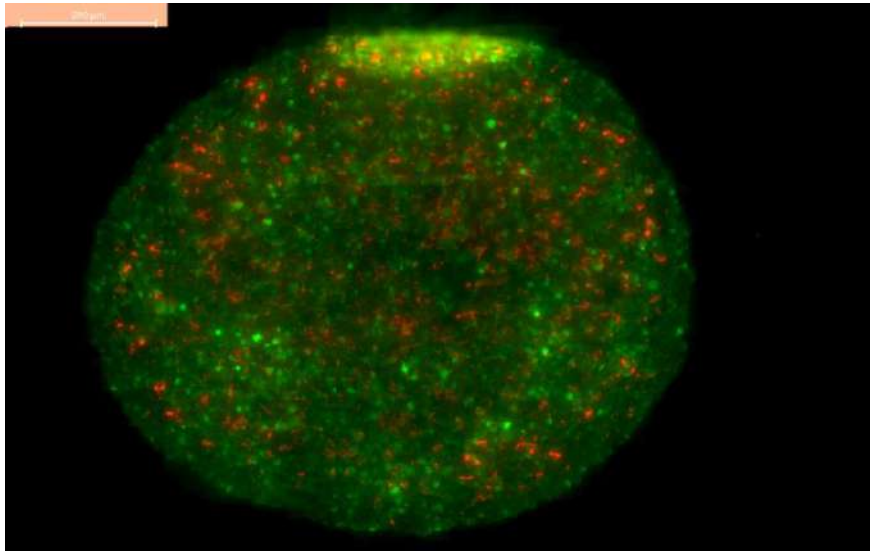
Moessner et al., Blood, 2010; Niederfellner et al., Blood, 2011; Dalle et al., Mol Cancer Ther, 2011; Jak et al., Blood, 2011; Alduaij et al., Blood, 2011; Lim et al., Blood, 2011; Honeychurch et al., Blood, 2012; Pievani et al., Blood, 2011; Bologna et al., J Immunol, 2011; Braza et al., Haematologica, 2011; Patz et al., B J Haematol, 2011; Paz-Ares et al., J Clin Oncol, 2011; Ferrara et al, PNAS, 2011; Weiner et al., 2009; Beers et al, 2010

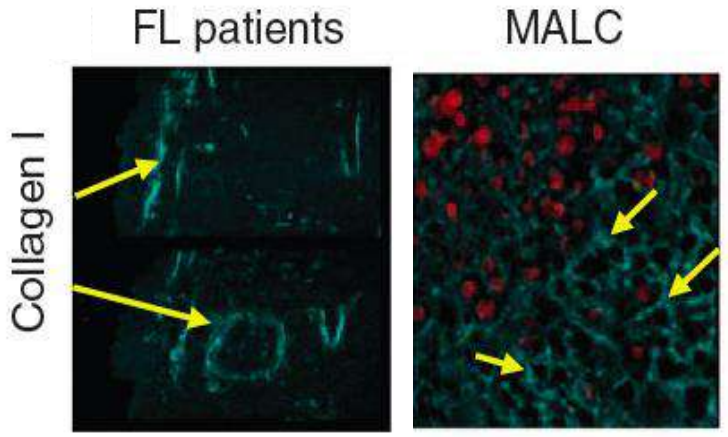
3D organisation is key for penetration of therapies

Rituximab 24h



Obinutuzumab 24h





Obinutuzumab vs rituximab with maintenance in relapsed iNHL: the GAUSS study

All patients relapsing after R-containing treatment

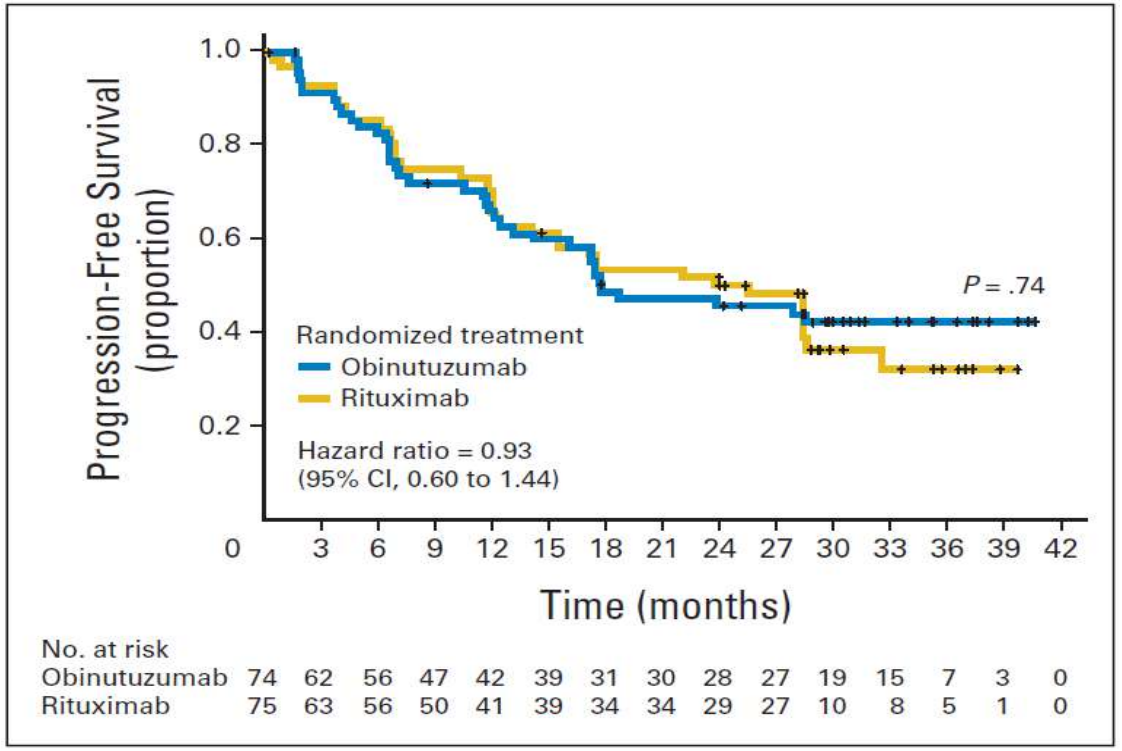


Fig 2. Progression-free survival of patients with follicular lymphoma treated with obinutuzumab versus rituximab monotherapy.

ORR

- **GA101: 44.6%**
- **RITUXIMAB: 26.7%**

***p* = 0.01**

Weekly x 4

O: 1000 mg
R: 375 mg/m2

Sehn L et al, JCO, 2015

GAUGUIN iNHL Phase II: EoTR

EoTR was 50% in patients with FL receiving GA101 1600/800 mg

Cohort	CR	PR	SD	PD	ORR*
All patients (n=40)					
1600/800 mg (n=22)	2	10	6	4	55%
400 mg (n=18)	0	3	6	9	17%
Rituximab-refractory patients (n=22)					
1600/800 mg (n=10)	1	4	3	2	50%
400 mg (n=12)	0	1	4	7	8%
FL patients (n=34)					
1600/800 mg (n=20)	2	8	6	4	50%
400 mg (n=14)	0	3	4	7	21%

* ORR based on evaluable patients

Salles G, *et al*. Oral presentation at ASH 2011 (Abstract 268);
Salles G, *et al*. Oral presentation at ICML 2011 (Abstract 066);
Salles G, *et al.* Oral presentation at EHA 2010 (Abstract 0558); Roche/Genentech. Data on file

GADOLIN
Outcome- ASH 2016

	ITT Population G-B vs B	LF G-B vs B
Median PFS	**25.8** mo vs, **14.1** mo HR **0.57** (95% CI 0.44, 0.73; p<0.0001)	**25.3** mo vs. **14.0** mo HR **0.52** (95% CI 0.39, 0.69; p<0.0001)
Median OS	**Non reached** HR **0.67** (95% CI 0.47, 0.96; p=0.0269)	**Non reached** vs. **53.9** mo HR **0.58** (95% CI 0.39, 0.86; p=0.0061)
TTNT *Time to new anti-lymphoma treatment*	**40.8** mo vs. **19.4** mo HR **0.59** (95% CI 0.45, 0.77)	**33.6** mo vs. **18.0** mo HR **0.57** (95% CI 0.43, 0.75]).

Median FU : 31,8 months

Cheson et al, ASH 2016, Abstract 615

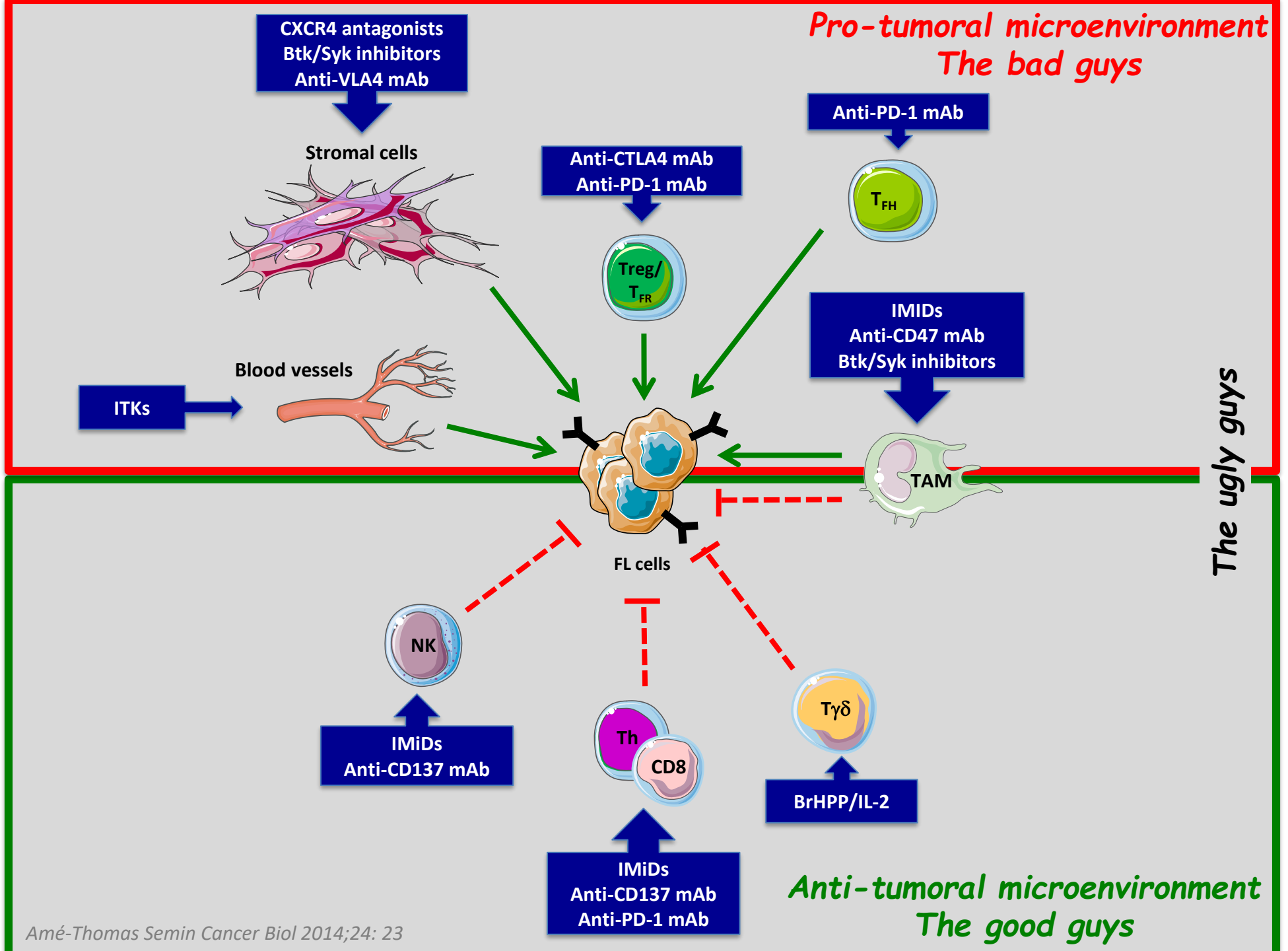
GADOLIN
Grade 3–5 adverse events in the iNHL population

Grade 3–5 AEs of interest by treatment arm and treatment phase

	Induction		Maintenance	Overall	
% (n)	G-B, n=204	B, n=205†	G-B, n=158*	G-B, n=204	B, n=203*
Neutropenia‡	27.5 (56)	26.8 (55)	10.8 (17)	34.8 (71)	27.1 (55)
Thrombocytopenia‡	10.3 (21)	15.6 (32)	1.3 (2)	10.8 (22)	15.8 (32)
Infections and infestations§	7.8 (16)	12.2 (25)	10.1 (16)	22.5 (46)	19.2 (39)
Infusion-related reactions‡	8.8 (18)	3.4 (7)	0.6 (1)	9.3 (19)	3.4 (7)
Neoplasms§¶	1.0 (2)	1.0 (2)	2.5 (4)	5.9 (12)	5.4 (11)
Cardiac disorders§**	2.5 (5)	1.0 (2)	1.9 (3)	4.4 (9)	1.5 (3)

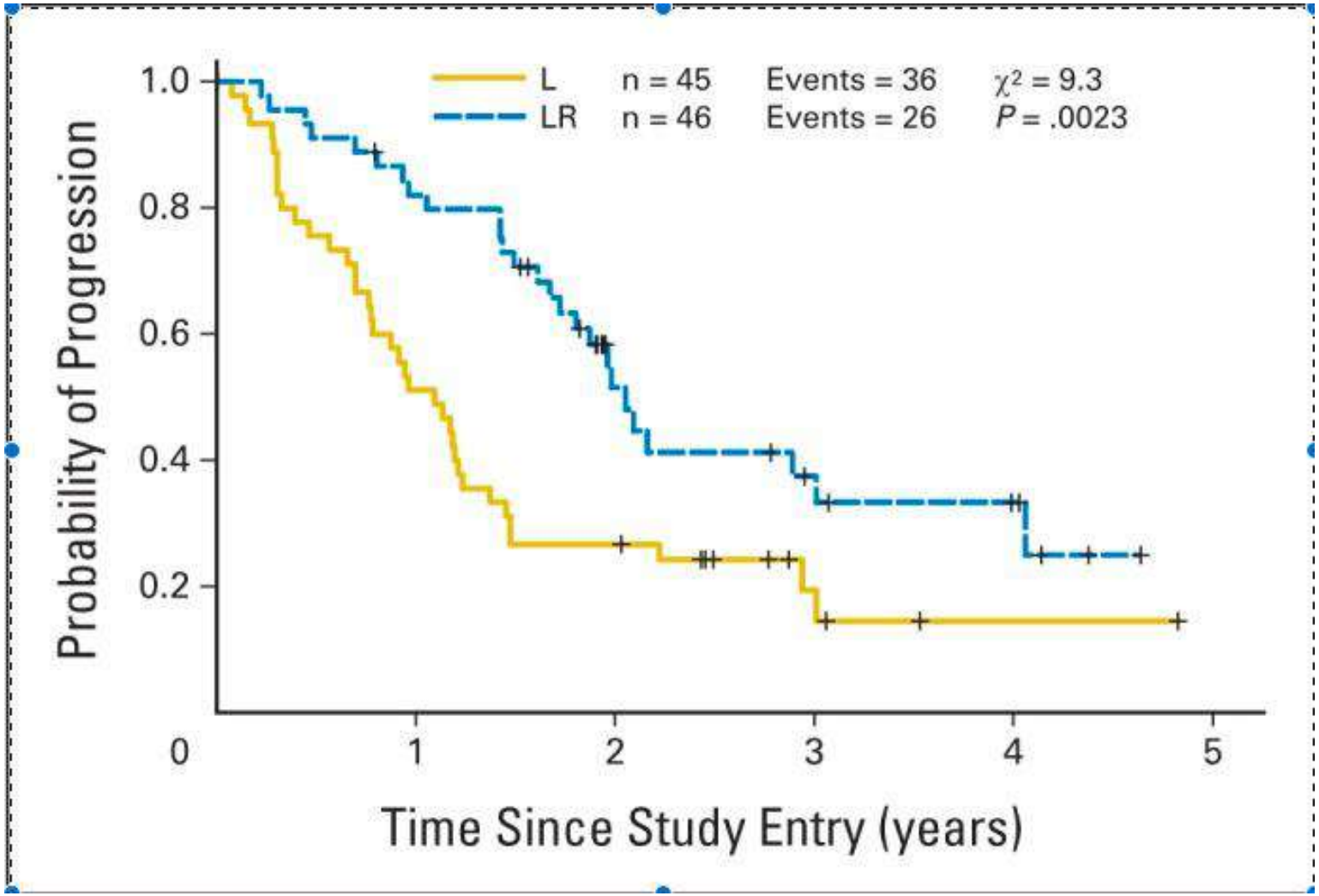
Main questions in the treatment of R/R FL

- ASCT or not ASCT as part of second-line?
  - If yes, for whom?
- New anti-CD20 MoAbs?
  - Why can they overcome resistance to rituximab?
- New agents beyond anti-CD20?
  - Targeting both tumor and immune contexture
- Allo SCT or CART cells: who and when?



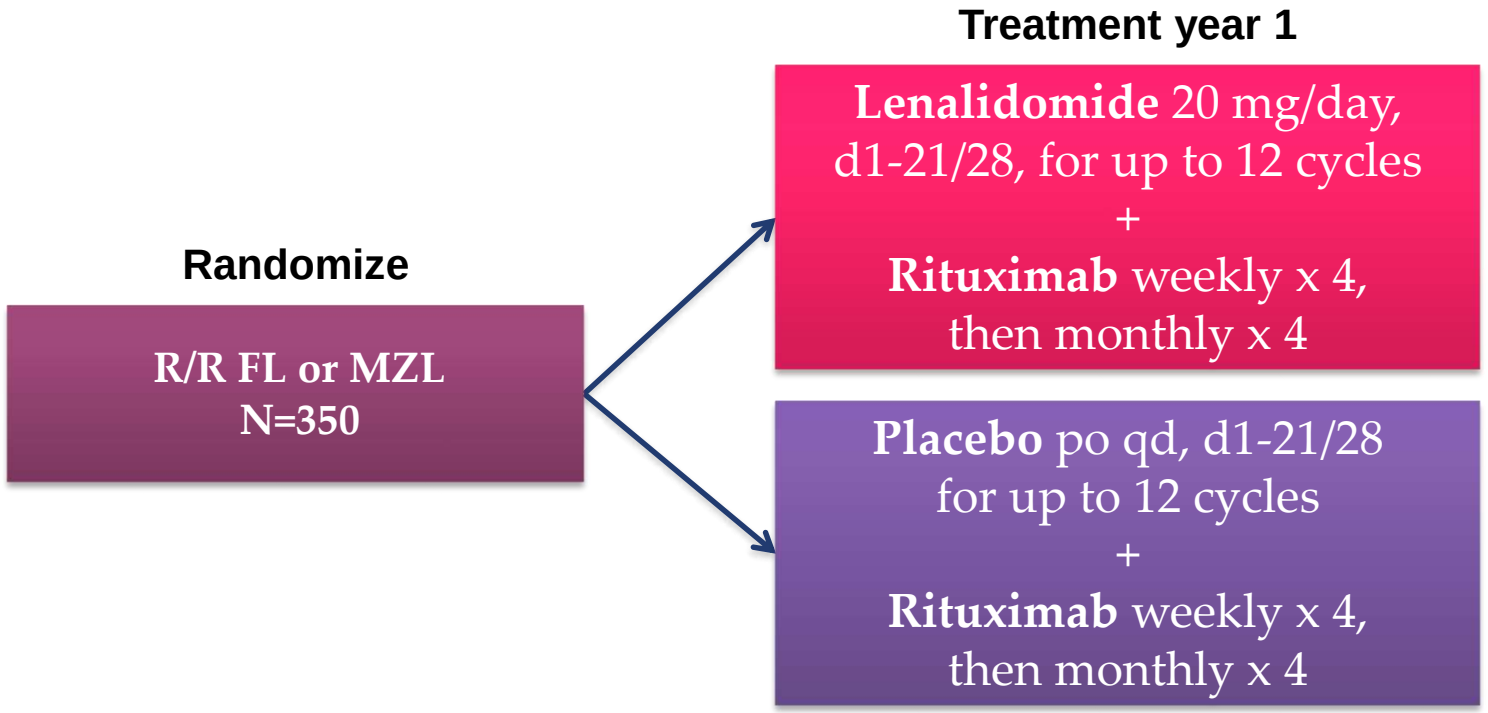
Amé-Thomas Semin Cancer Biol 2014;24: 23

Lenalidomide versus R2 in relapsed FL
Median TTP: 1 *v* 2 years



Leonard et al*J Clin Oncol 2015 33:3635-3640*

NHL-007 (AUGMENT): Phase 3 Registration Study of R vs. R² in R/R iNHL



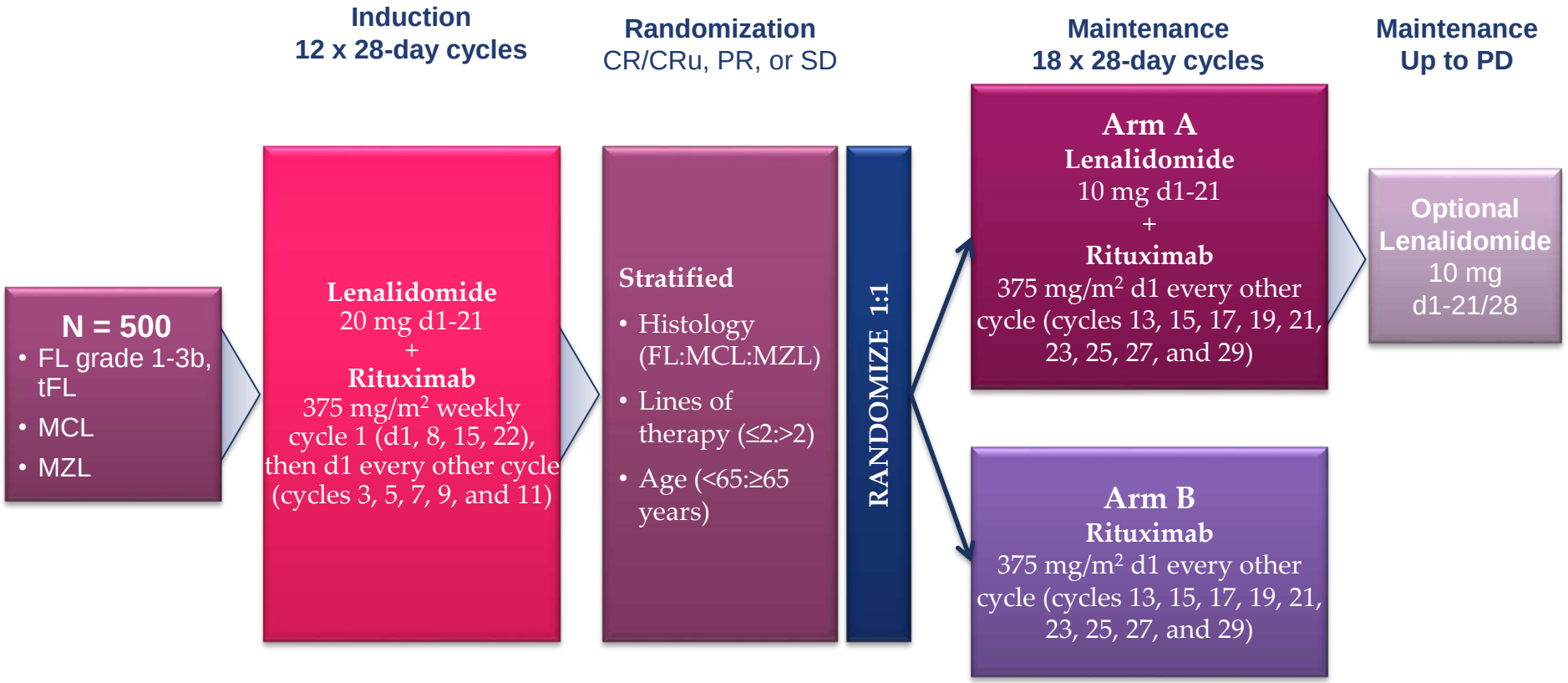
Primary endpoint: PFS

Secondary endpoints: ORR, CR, DOR, safety, SPM

NCT01938001.

NHL-008 (MAGNIFY): R2 in R/R FL, tFL, MCL, and MZL

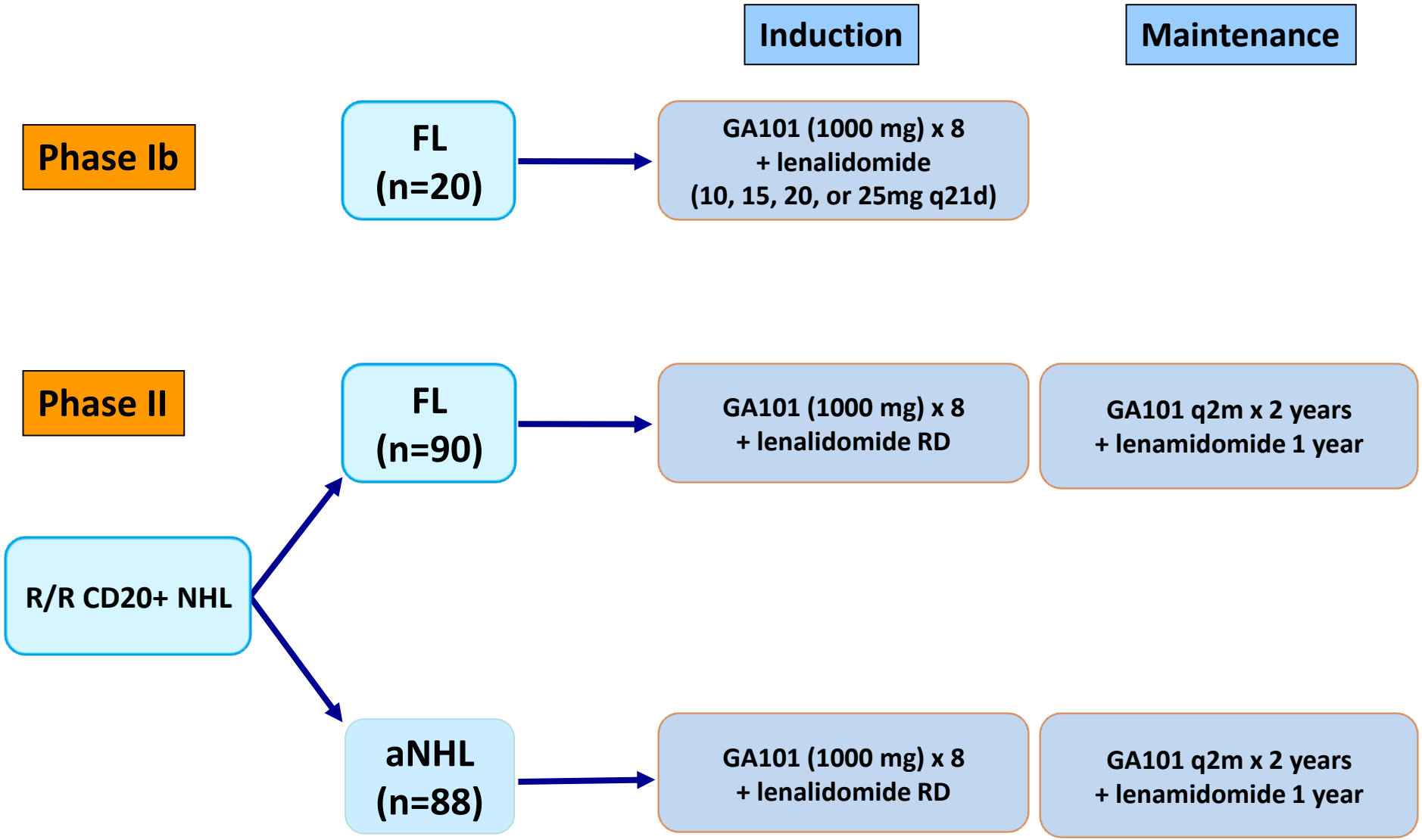
Phase 3 Study of R^2 Followed by R Maintenance vs. R^2 Followed by Lenalidomide Maintenance in R/R FL, MCL, MZL



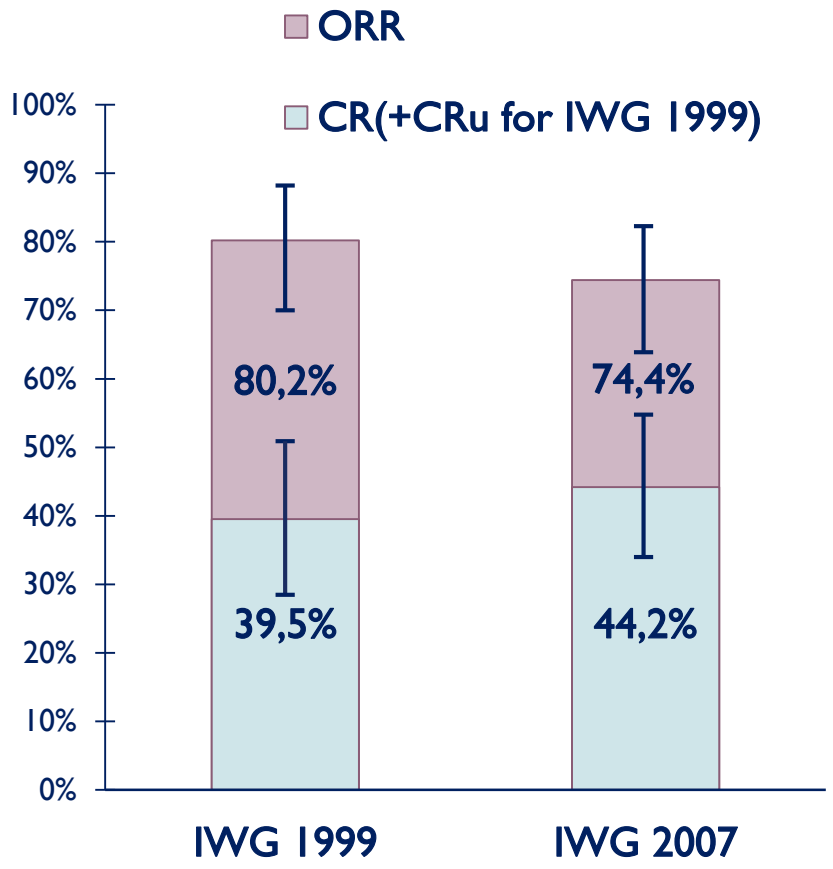
Primary endpoint: PFS (191 maintenance events needed)
Secondary endpoints: OS, IOR, ORR, CR, DOR, DOCR, TTNLT, TTHT, safety
Exploratory: subgroup analysis of efficacy and safety by histology and QOL

NCT01996865.

GALEN – Phase Ib/II



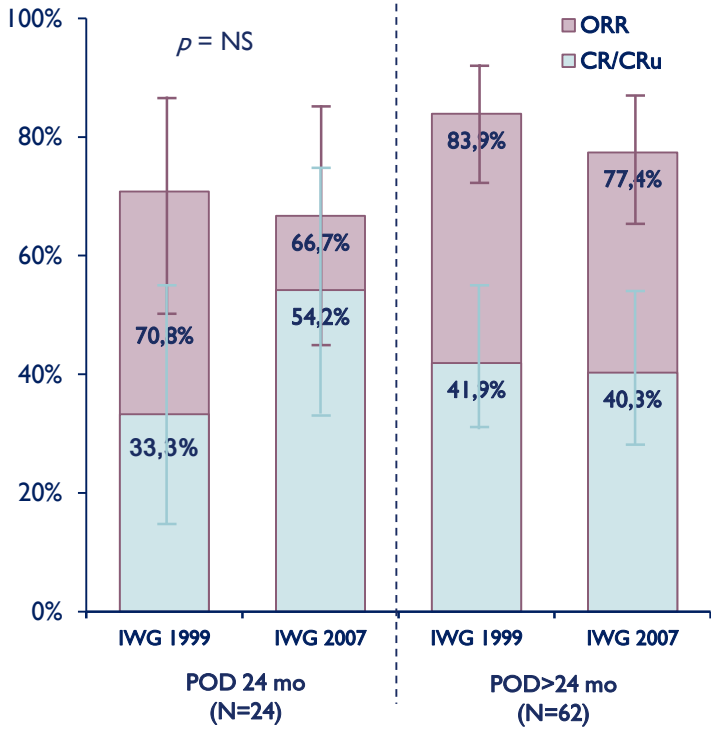
RESPONSE RATES: END OF INDUCTION



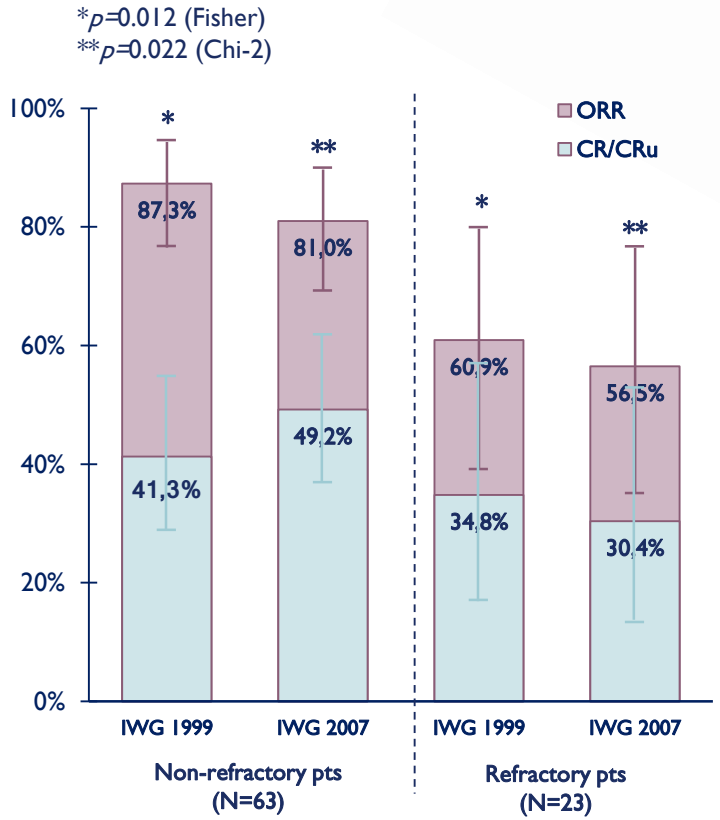
Morschhauser et al, ICML 2017

RESPONSE RATES: END OF INDUCTION

Time to First Relapse



Refractory Status



MAGNIFY

Best response for evaluable patients in induction and maintenance.

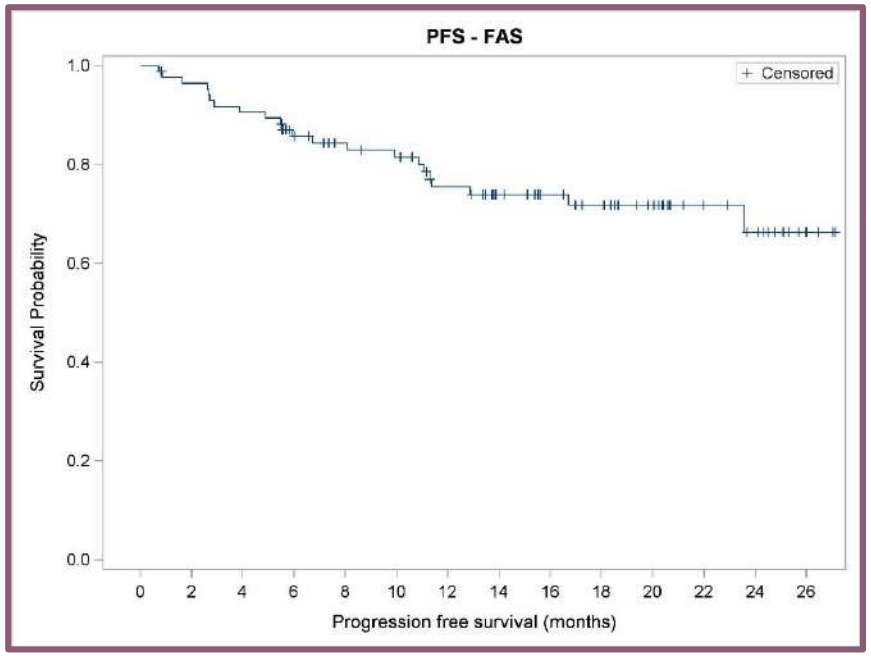
Response status, n (%)	DR (n = 28)	ER (n = 33)	All FL (N = 91)
ORR	13 (46)	16 (48)	61 (67)
95% CI	28%-61%	31%-67%	56%-77%
CR/CRu	6 (21)	4 (12)	33 (36)
PR	7 (25)	12 (36)	28 (31)
SD	10 (36)	13 (39)	21 (23)
PD*	5 (18)	4 (12)	9 (10)

*Includes PD and/or death prior to response evaluation completion.

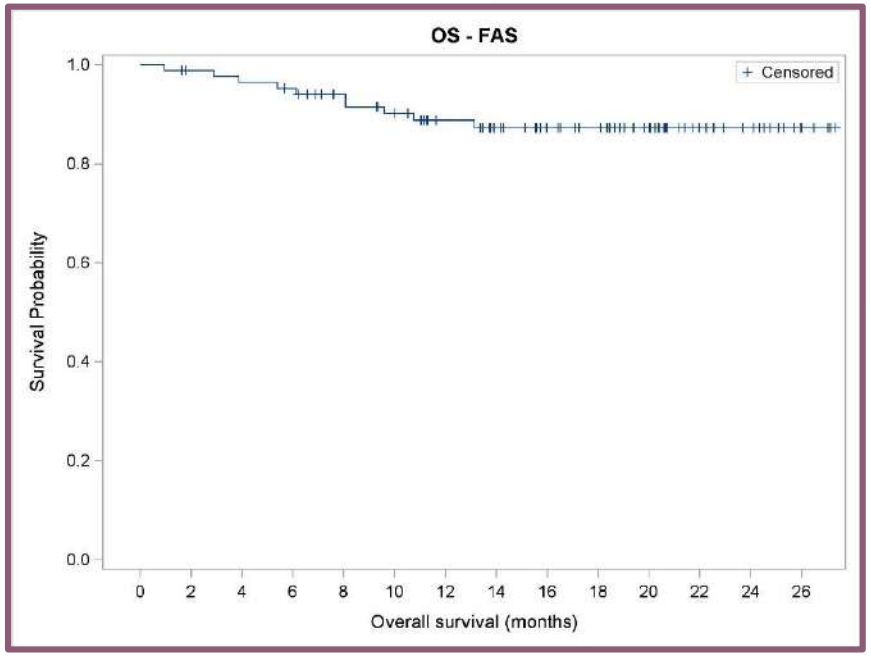
Andorsky et al, ASCO 2017

OUTCOME

PFS



OS

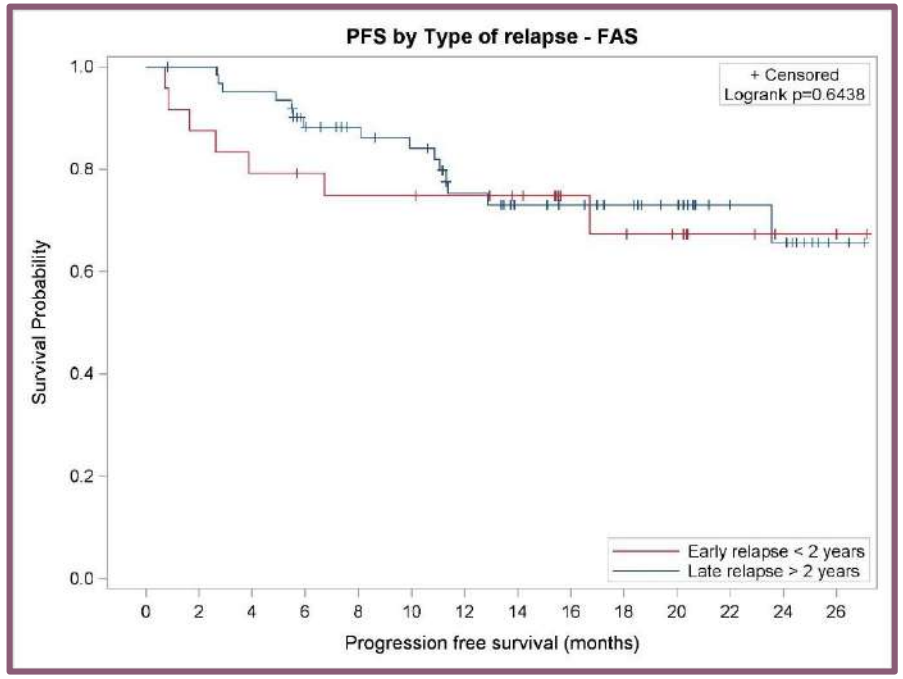


- Median FU = 18.1 months

OUTCOME	All pts (N=86)
1-y PFS % (95%CI)	75.5 (64.2-83.7)
1-y OS % (95%CI)	88.8 (79.5-94.0)

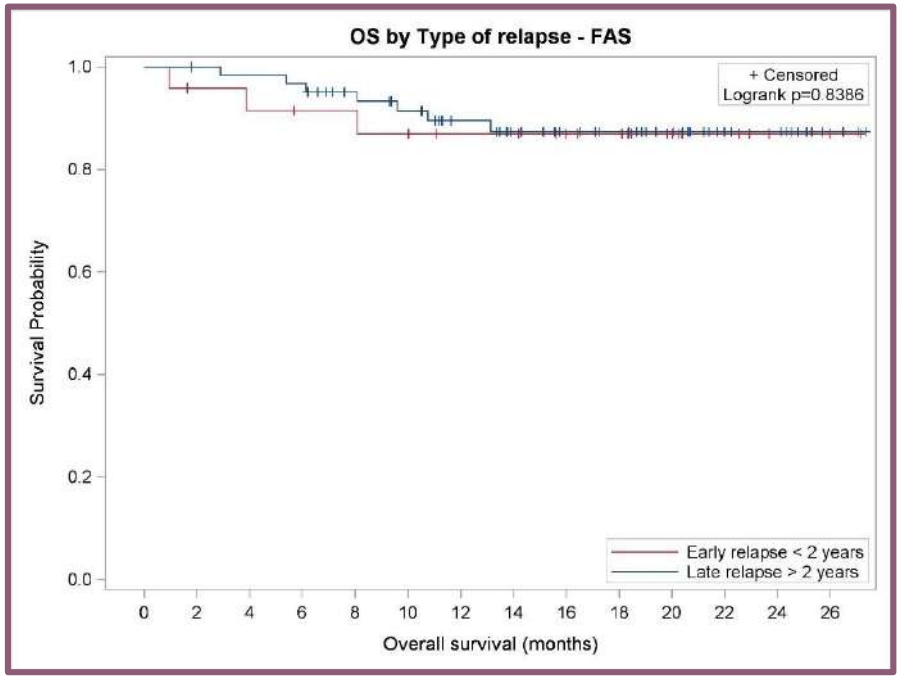
OUTCOME
BASED ON POD24 OR POD>24MO

PFS



	POD24 (N=24)	POD>24m (N=62)	All pts (N=86)
1-y PFS % (95%CI)	74.8 52.2-87.8	75.3 60.9-85.0	75.5 64.2-83.7

OS

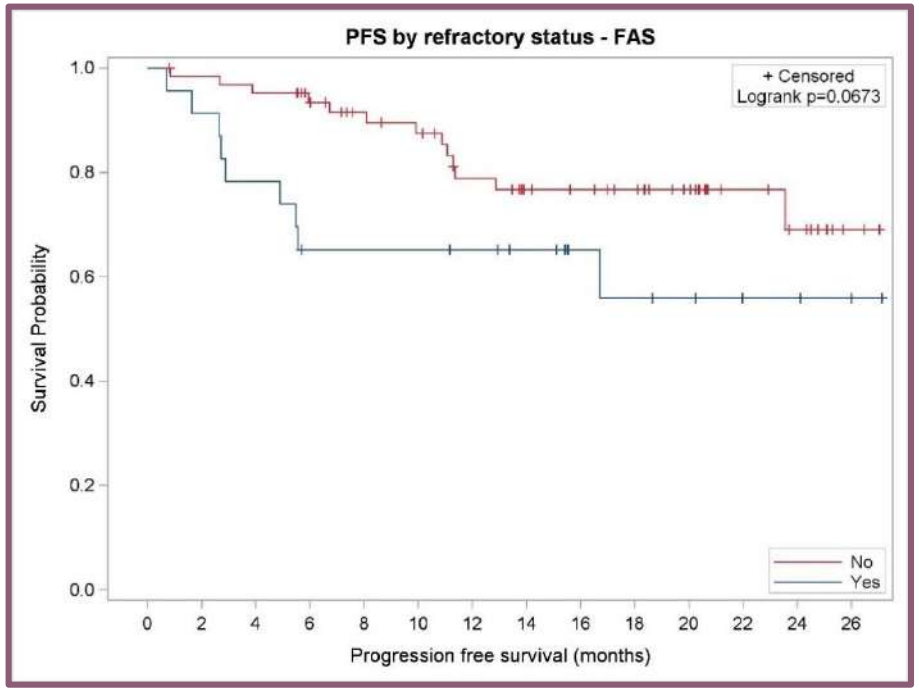


	POD24 (N=24)	POD>24 (N=62)	All pts (N=86)
1-y OS % (95%CI)	86.9 64.6-95.6	89.5 78.1-95.2	88.8 79.5-94.0

OUTCOME

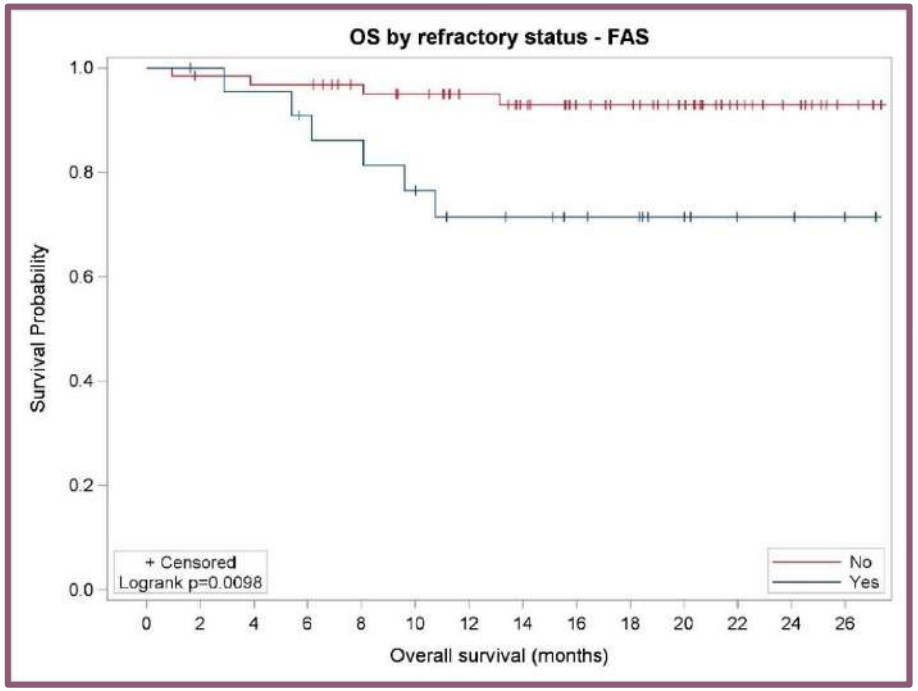
BASED ON REFRACTORY STATUS

PFS



	Ref (N=23)	Non-Ref (N=63)	All pts (N=86)
1-y PFS % (95%CI)	65.2 42.3-80.8	78.9 64.9-87.8	75.5 64.2-83.7

OS



	Ref (N=23)	Non-Ref (N=63)	All pts (N=86)
1-y OS % (95%CI)	71.5 47.1-86.1	95.0 85.4-98.4	88.8 79.5-94.0

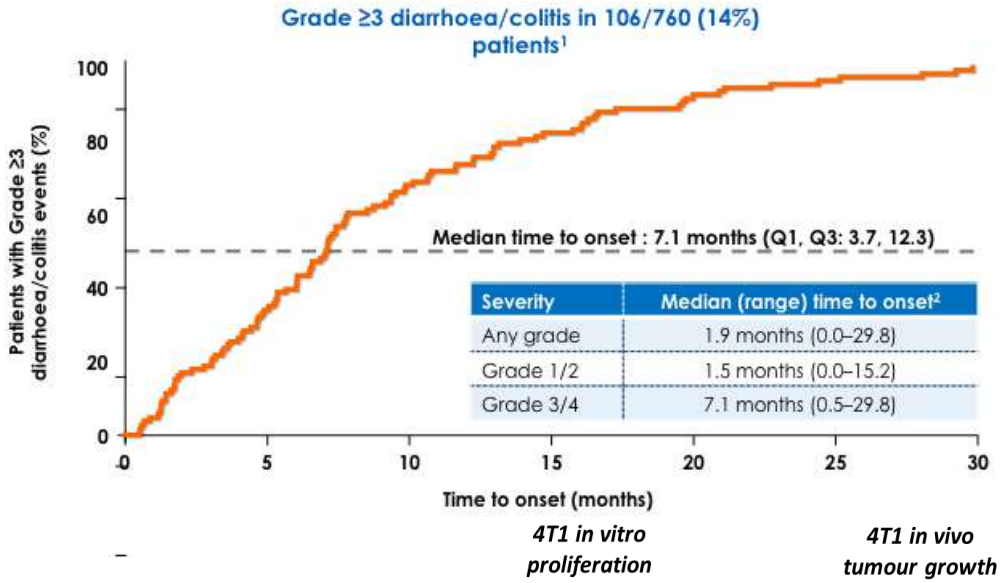
Treg inhibition with idelalisib ?

Impaired B and T Cell Antigen Receptor Signaling in p110δ PI 3-Kinase Mutant Mice

Klaus Okkenhaug,[1] Antonio Bilancio,[1]* Géraldine Farjot,[1]* Helen Priddle,[2]*† Sara Sancho,[3] Emma Peskett,[1] Wayne Pearce,[1] Stephen E. Meek,[2] Ashreena Salpekar,[1] Michael D. Waterfield,[1,4] Andrew J. H. Smith,[2] Bart Vanhaesebroeck[1,4]‡

Class IA phosphoinositide 3-kinases (PI3Ks) are a family of p85/p110 heterodimeric lipid kinases that generate second messenger signals downstream of tyrosine kinases, thereby controlling cell metabolism, growth, proliferation, differentiation, motility, and survival. Mammals express three class IA catalytic subunits: p110α, p110β, and p110δ. It is unclear to what extent these p110 isoforms have overlapping or distinct biological roles. Mice expressing a catalytically inactive form of p110δ (p110δ^{D910A}) were generated by gene targeting. Antigen receptor signaling in B and T cells was impaired and immune responses in vivo were attenuated in p110δ mutant mice. They also developed inflammatory bowel disease. These results reveal a selective role for p110δ in immunity.

- Coutre S, Leuk Lymphoma 2015

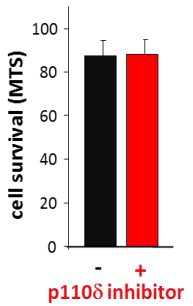


Inactivation of PI(3)K p110δ breaks regulatory T-cell-mediated immune tolerance to cancer

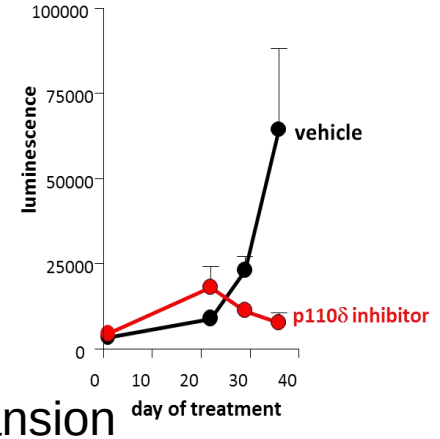
Khaled Ali[1]†, Dalya R. Soond[2]*†, Roberto Piñeiro[1]*, Thorsten Hagemann[3], Wayne Pearce[1], Ee Lyn Lim[2], Hicham Bouabe[2], Cheryl L. Scudamore[4], Timothy Hancox[5], Heather Maecker[6], Lori Friedman[6], Martin Turner[2], Klaus Okkenhaug[2]§ & Bart Vanhaesebroeck[1]§

Nature 2014:509:407

4T1 in vitro proliferation



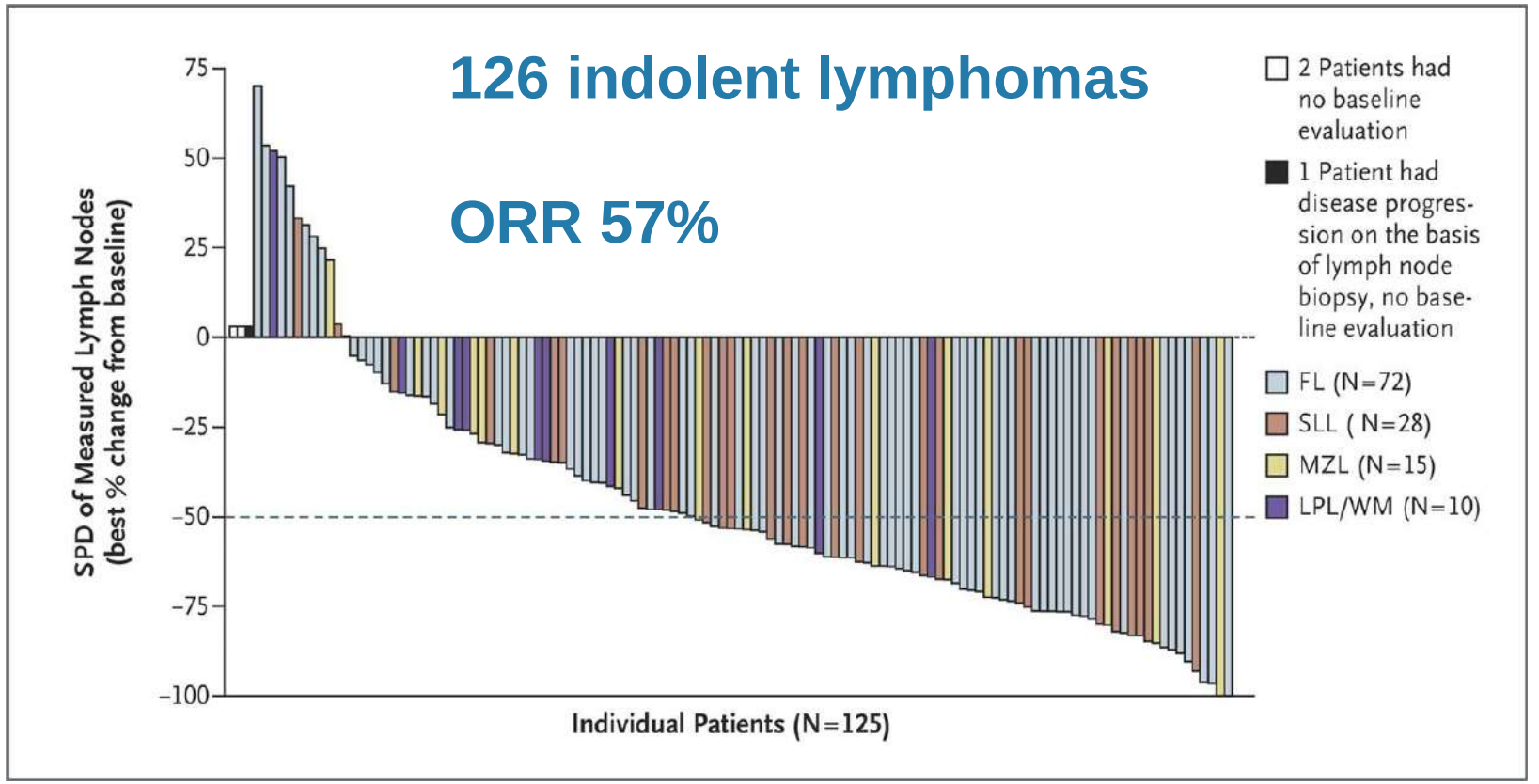
4T1 in vivo tumour growth



PI-3Kδ inhibition blocks Treg differentiation favoring CTL expansion

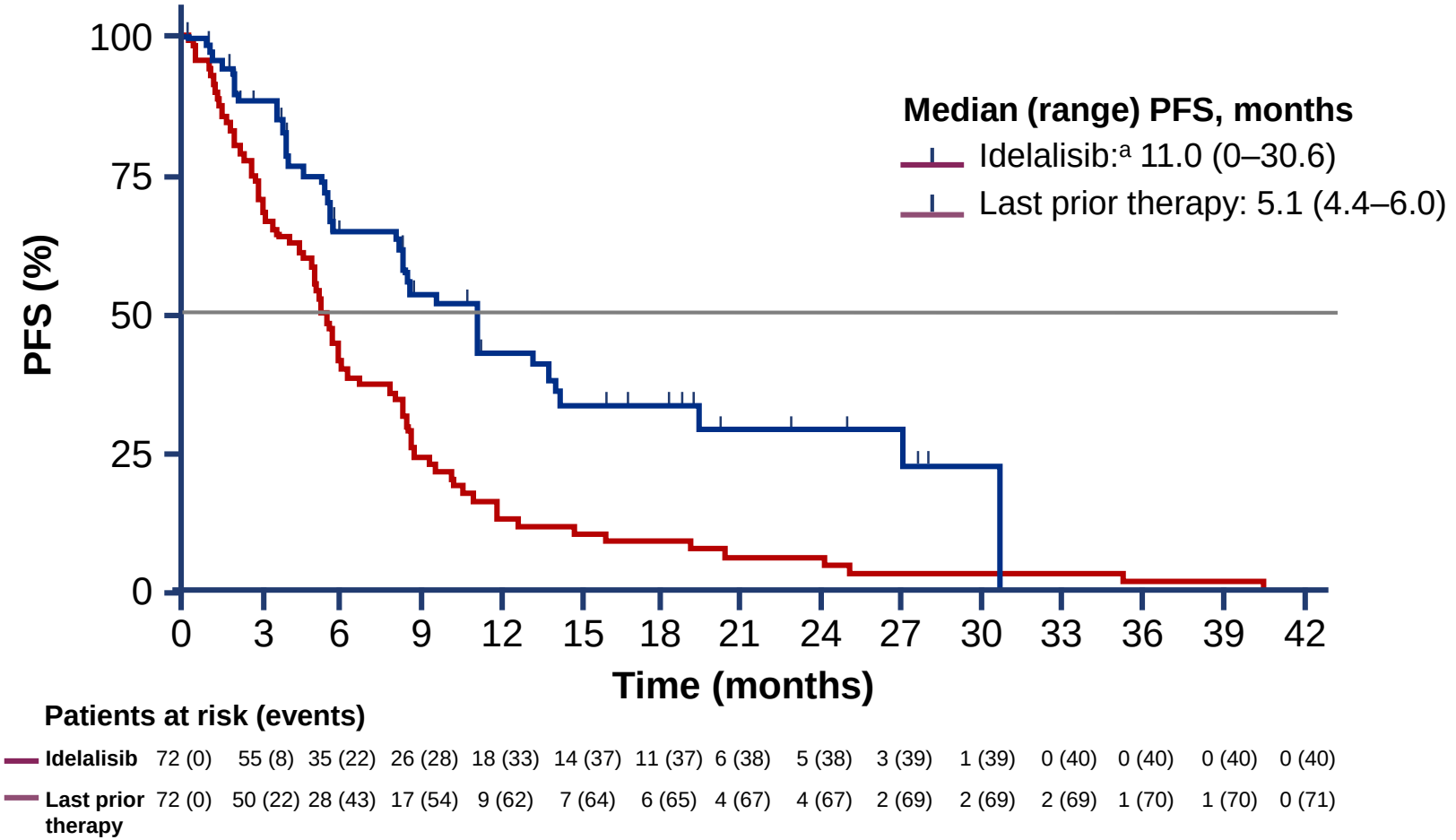
This immunomodulatory effect is INdependent from PI-3Kδ activity within tumor cells

Idelalisib approved for R/R iNHL



Gopal AK , NEJM, 2014

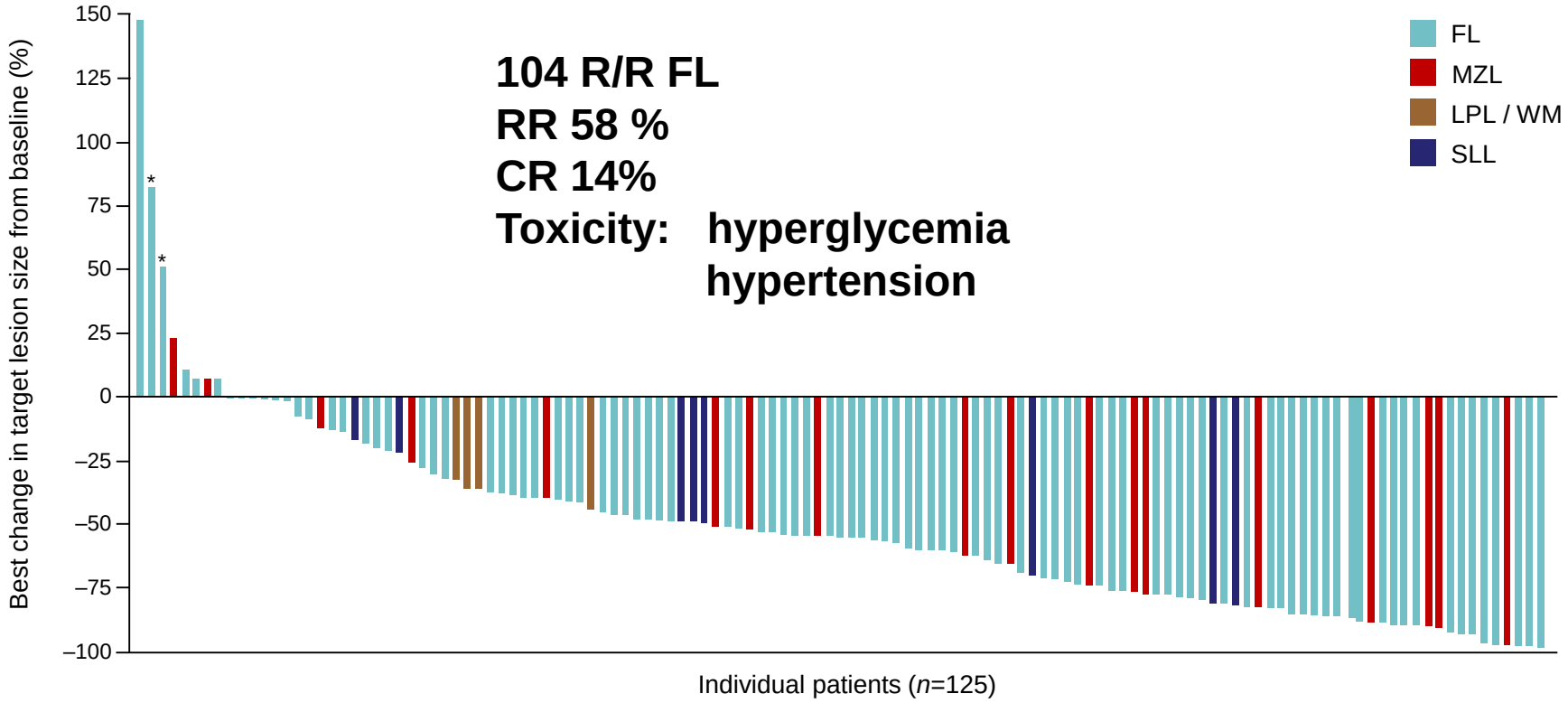
Study 101-09
Idelalisib : PFS vs. last prior therapy
FL subgroup



[a] Long-term follow-up (June 2014 cut-off)
PFS: progression-free survival

Salles GA, *et al.* ASCO 2015 (Abstract 8529; poster presentation).

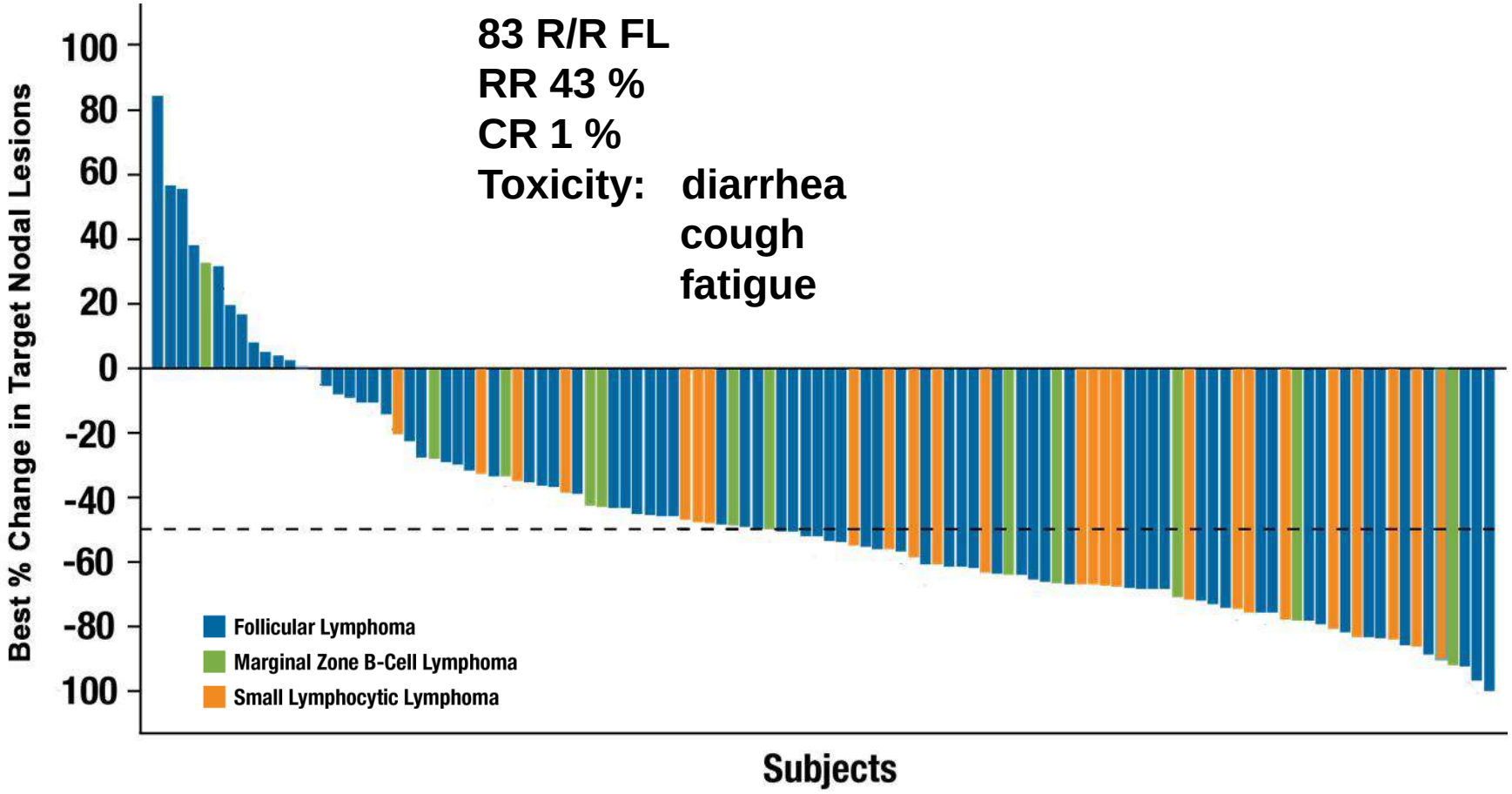
i.v. Copanlisib in R/R NHL



Dreyling et al, ICML 2017, abstract 108

Zinzani et al, ICML 2017, abstr 58

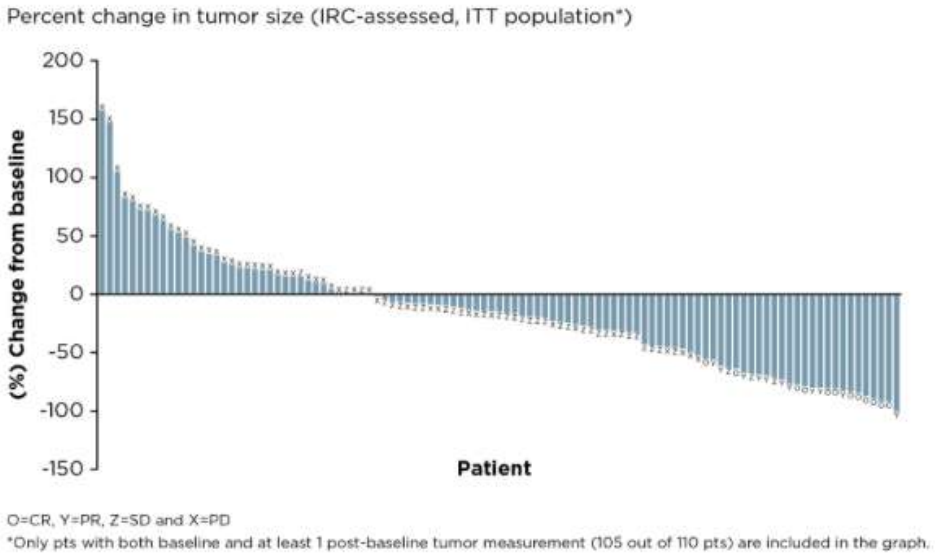
Duvelisib in double refractory indolent NHL



Zinzani et al, ICML 2017, abstr 58

Ibrutinib in R/R FL (DAWN trial)

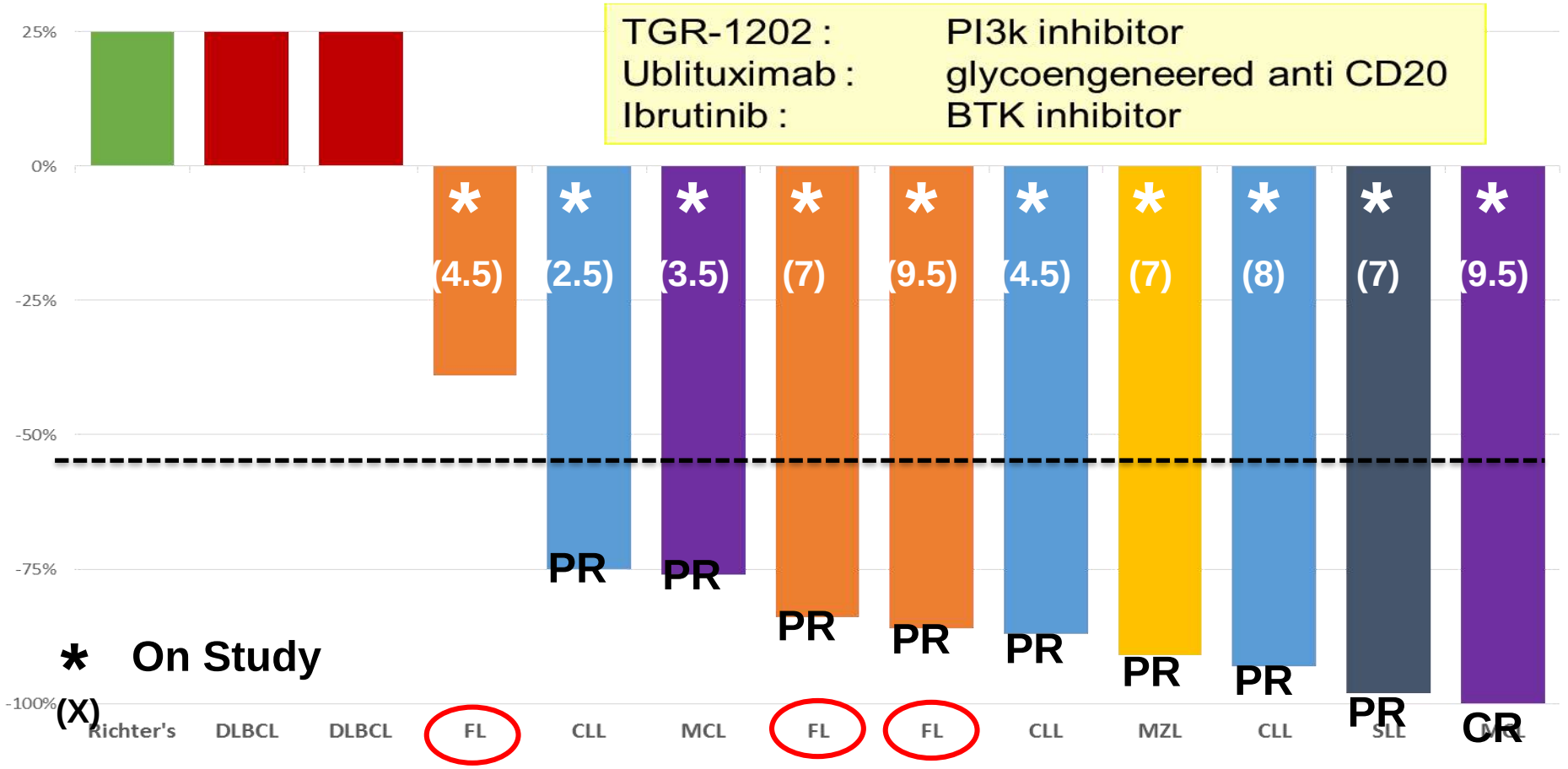
When it works…How does it work? Tumor inhibition or T-cell ITK inhibition?



- Single agent ibrutinib has modest antitumor activity in 110 relapsed or refractory (41%) FL with an **ORR of 21% (11%CR)**
  - Suggestion that ORR higher in rituximab sensitive disease median PFS of 4.6 months
  - Median duration of response:19.4 months
- safety profile in FL consistent with labeled indications

Gopal et al, ASH 2016, abstr 1217

“Triplet”:
TGR-1202 + Ublituximab + Ibrutinib



Nastoupil et al, ICML 2015, Lugano

Combinations of targeted drugs can be unexpectedly toxic!

Rituximab + Lenalidomide + Idelalisib (R^2-Idela)

Smith S. et al (Alliance)
ASH 2014

8 patients

4 DLT Hepatotoxicity
Septic syndrome

Cheah C. et al (MDACC)
Blood 2015

7 patients

6 DLT Hepatotoxicity

2 died of it

Explanation: probably excessive immune activation

PD-1/PD-L1 immunostat in FL

- Only few infiltrating Macrophages but no tumors cells express PD-L1
- Strong expression of PD1 on Tfh and Tfr, both functional, and also to a lesser extent on T-cell exhausted (mainly T CD8)
- Therefore, targeting PD1 or PDL1 may lead to:
  - Depletion of protumoral Tfh (using anti-PD1 IgG1)
  - Stimulation of protumoral Tfh as well as anti-tumor CD8 Teff (using anti-PDL1 or anti-PD1 IgG4 type).
  - Urgent need for better knowledge of intratumor T-cell mandatory

CA 209-039 trial: Nivolumab Best Response and Durability

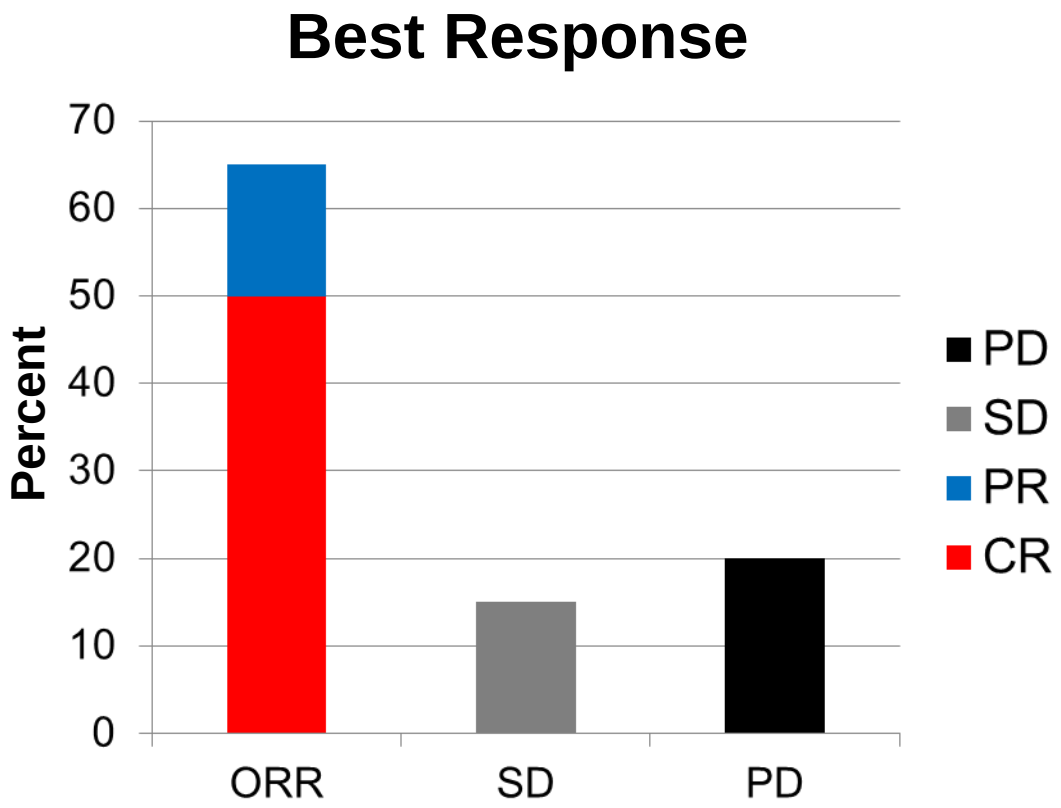
Tumor type	n	ORR	Median Follow-up in weeks	Median Response Duration in weeks	Ongoing Responses
Multiple Myeloma	27	1 (4%)	46	12+	1 (100%)
DLBCL	11	4 (36%)	23	22 (6 , 77+)	1 (25%)
Follicular NHL	10	4 (40%)	91	NR (27+ , 82+)	3 (75%)
CTCL/MF	13	2 (15%)	43	NR (24+ , 50+)	2 (100%)
PTCL	5	2 (40%)	31	NR (11 , 79+)	1 (50%)
Hodgkin Lymphoma	23	20 (87%)	86	NR (2 , 91+)	10 (50%)

Armand et al, EHA 2015

R-pembrolizumab
In relapsed R-sensitive FL

- 20 evaluable for response
- **ORR was 65%**

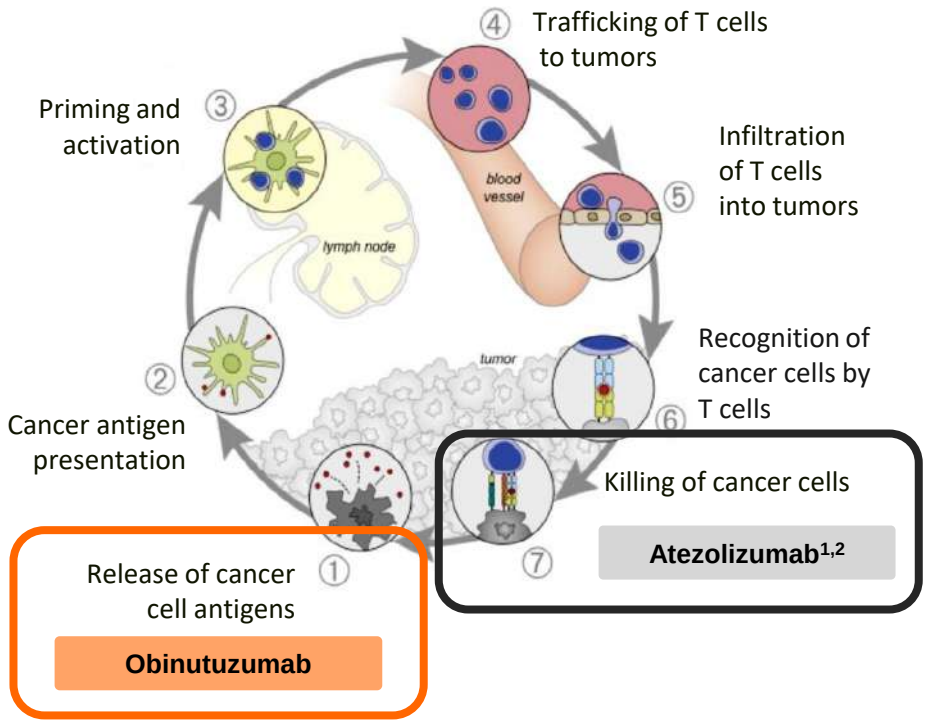
  (CR N=10/PR N=3)
- **CR rate was 50%**
- 3 patients with stable disease and 4 with progressive disease as best response



Nastoupil et al, ICML2017, abstr 109

Scientific Rationale

Atezolizumab + Obinutuzumab in NHL



- Obinutuzumab, a glycoengineered type II anti-CD20 mAb, triggers enhanced ADCC and direct cell killing vs rituximab[3,4]
  - Encouraging single-agent activity has been observed in R/R NHL[5]
- Atezolizumab, an engineered IgG1 mAb with an Fc domain modification to eliminate ADCC, selectively targets PD-L1 to prevent its interaction with PD-1 and B7.1, leading to reinvigorated anti-cancer immune responses[1,2]
  - PD-L1 binding to PD-1 and B7.1 results in inhibition of anti-cancer T-cell activity[2,6]
  - TILs and neoplastic cells in many lymphoma subtypes express PD-L1[7,8]

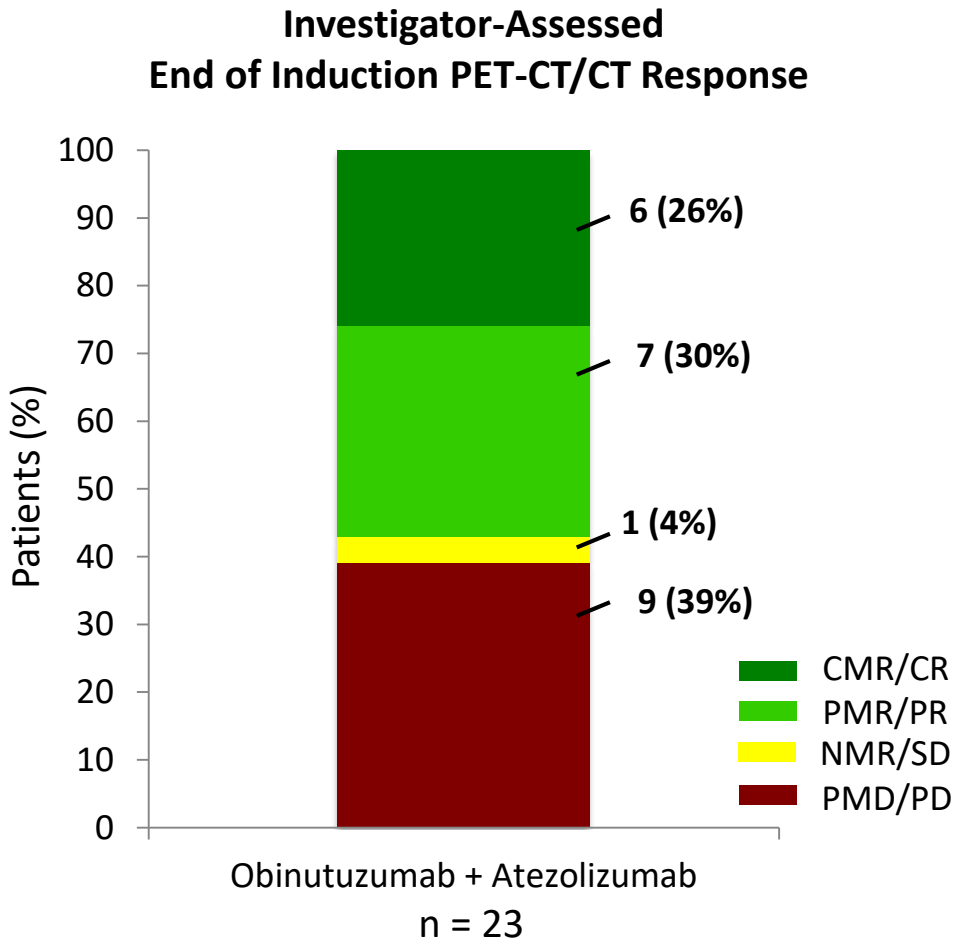
- Atezolizumab + obinutuzumab may be a promising treatment option for heavily pretreated patients with R/R NHL due to their complementary mechanisms of action (activation of innate and adaptive immunity) and distinct safety profiles

ADCC, antibody-dependent cell-mediated cytotoxicity; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; R/R, relapsed or refractory.

1. Herbst. *Nature.* 2014; 2. Chen. *Immunity.* 2013; 3. Tobinai. *Adv Ther.* 2017; 4. Ma. *Cancer Manag Res.* 2017; 5. Salles. *J Clin Oncol.* 2013; 6. Zou. *Nat Rev Immunol.* 2008; 7. Wilcox. *Leuk Lymphoma.* 2012; 8. Sznol. *Clin Cancer Res.* 2013.

Efficacy

Clinical Response in R/R FL



- 56% ORR (CMR + PMR) at the End of Induction response assessment
- 6 (26%) patients achieved CMR at End of Induction, with all patients achieving response (CMR/PMR) by the Mid Induction response assessment
- Median PFS was 311 days
  - 6-month PFS rate: 82%
  - 12-month PFS rate: 45%

CMR, complete metabolic response; CR, complete response; NMR, no metabolic response; ORR, overall response rate; PFS, progression-free survival, PMD, progressive metabolic disease; PMR, partial metabolic response; PR, partial response; SD, stable disease.

Palomba et al. Atezolizumab + Obinutuzumab in NHL, ICML 2017. http://tago.ca/1BGT

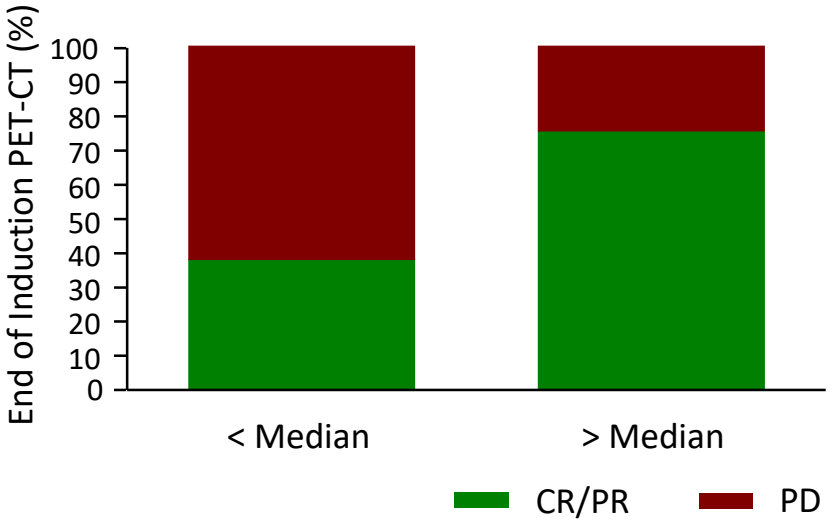
Biomarkers

Pre-Treatment CD8 Tumor Infiltrates and Clinical Response in R/R FL

Response by Pre-Treatment CD8 Tumor Infiltrates

PET-CT	CR/PR, n (%)	SD, n (%)	PD, n (%)
Evaluable patients, n	9	0	7
< Median	3 (33%)	0	5 (71%)
> Median	6 (67%)	0	2 (29%)

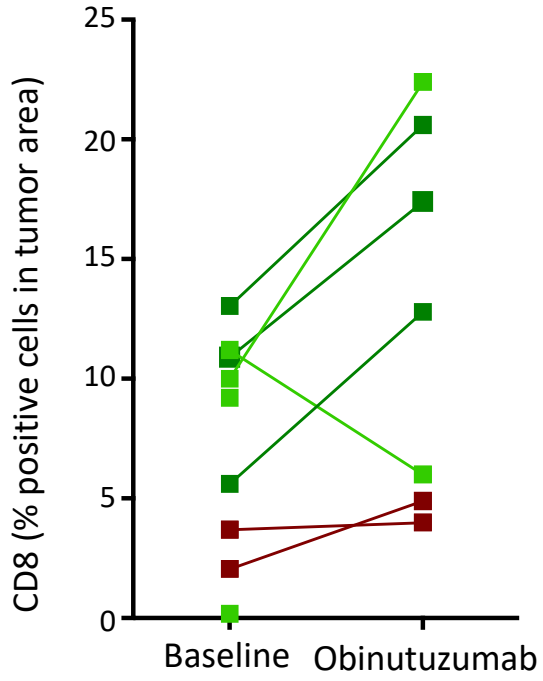
CD8 Expression Relative to Response



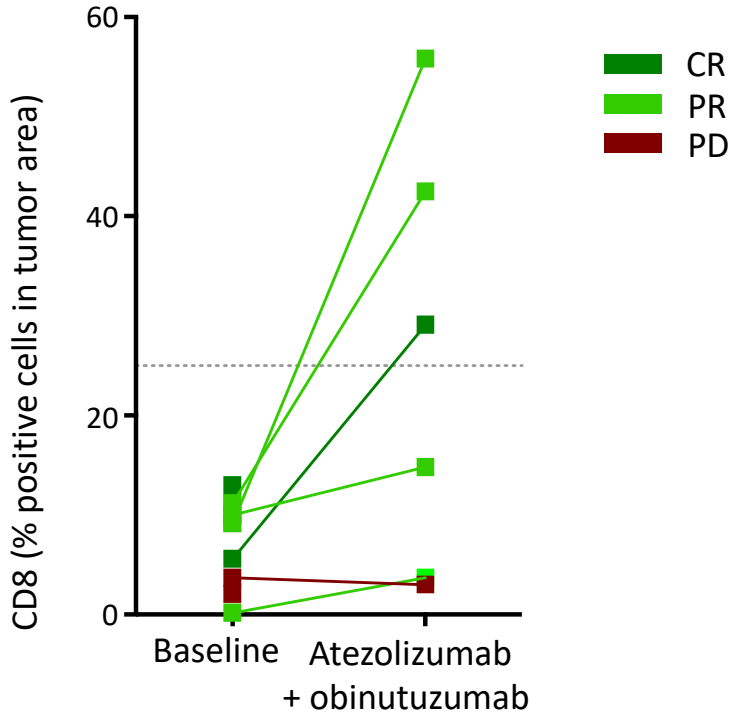
- Clinical response rate (PET-CT) was more than double among patients with FL with high pre-treatment CD8 tumor infiltrates
- 67% (6/9) of responding patients (PR/CR) had “high” CD8 staining vs 29% (2/7) of non-responding patients (PD)

Biomarkers

Changes in CD8 T-Cell Infiltrates in R/R FL



Obinutuzumab alone increased CD8 T-cell infiltration in 6 of 7 patients



Atezolizumab + obinutuzumab increased CD8 T-cell infiltration in 5 of 6 patients

- Paired biopsies were obtained to compare baseline CD8 T-cell infiltration to infiltration following treatment with obinutuzumab (n = 7) or atezolizumab + obinutuzumab (n = 6)
- Elevated baseline CD8 T cells or CD8 T cell increase on-treatment correlated with response
- CD8 T cell increase seen with obinutuzumab may prime for atezolizumab response

Palomba et al. Atezolizumab + Obinutuzumab in NHL, ICML 2017. http://tago.ca/1BGT

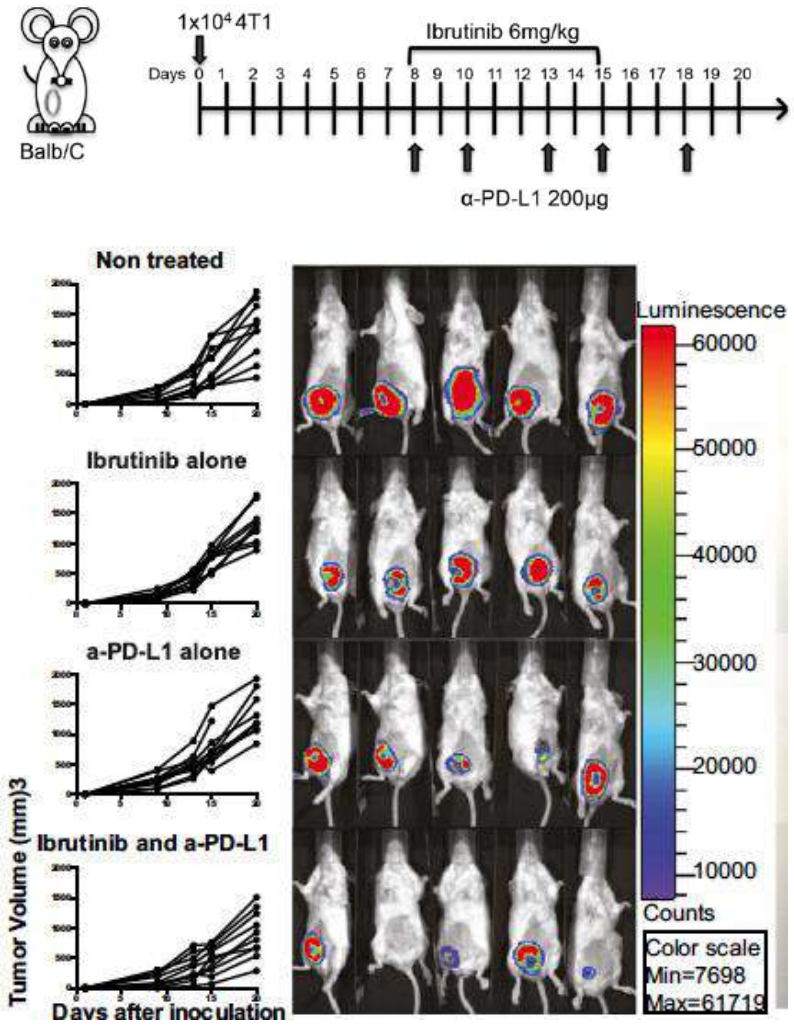
2 BO29562

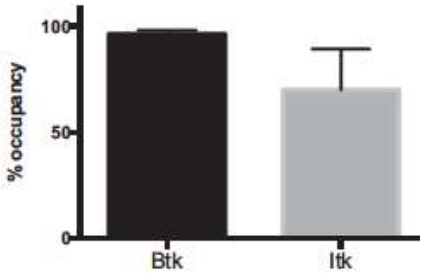
Obinutuzumab + Lenalidomide + aPDL1

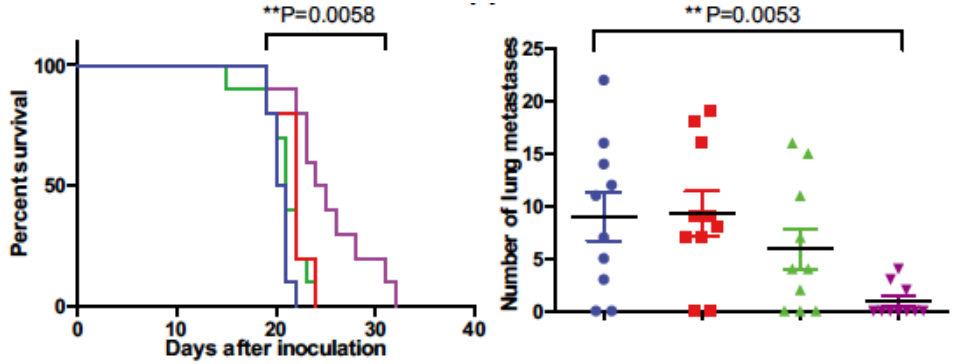
R/R FL

- Goal is to provide improved, chemo-free immunotherapy
- Increase clinical benefit by replacing systemic chemotherapy
- Potential to become best-in-class in R/R FL

Blocking PD-L1 and T-cell ITK rather than tumor kinase using ibrutinib







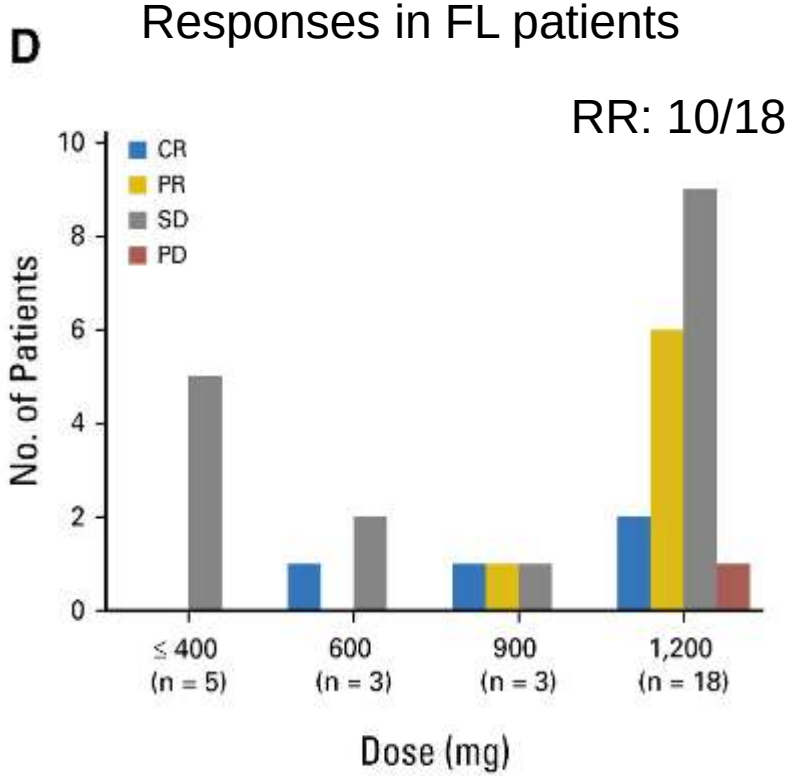
Of note:
Both αPD-L1 and ibrutinib have no efficacy
Ibrutinib doesn't modulate PD-L1
Combo is active on memory T_{eff},
Re-challenge J90: tumor eradication

Sagiv-Barfi I, PNAS 2015

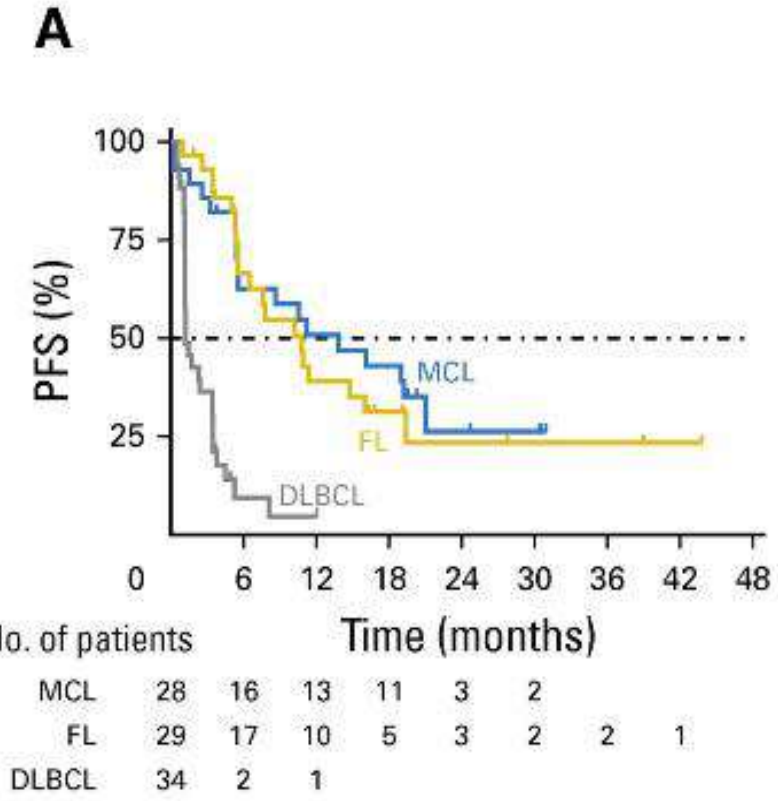
Ph I of venetoclax (oral anti-bcl2)

Responses in FL patients

RR: 10/18



PFS by histology



Davids M et al, JCO 2017

LYSA strategies in R/R CD20+ NHL: PD-L1 blockade + direct cell killing

Induction:
chemo-free based

Response assessment

Maintenance:
PD-L1 based

PFS
OS
bioancillary studies

CURE ?

GATA

VENETOCLAX
Anti CD20
Anti PDL1

6 mo

Anti-CD20
VENETOCLAX

12 mo

INVICTUS in GATA failures

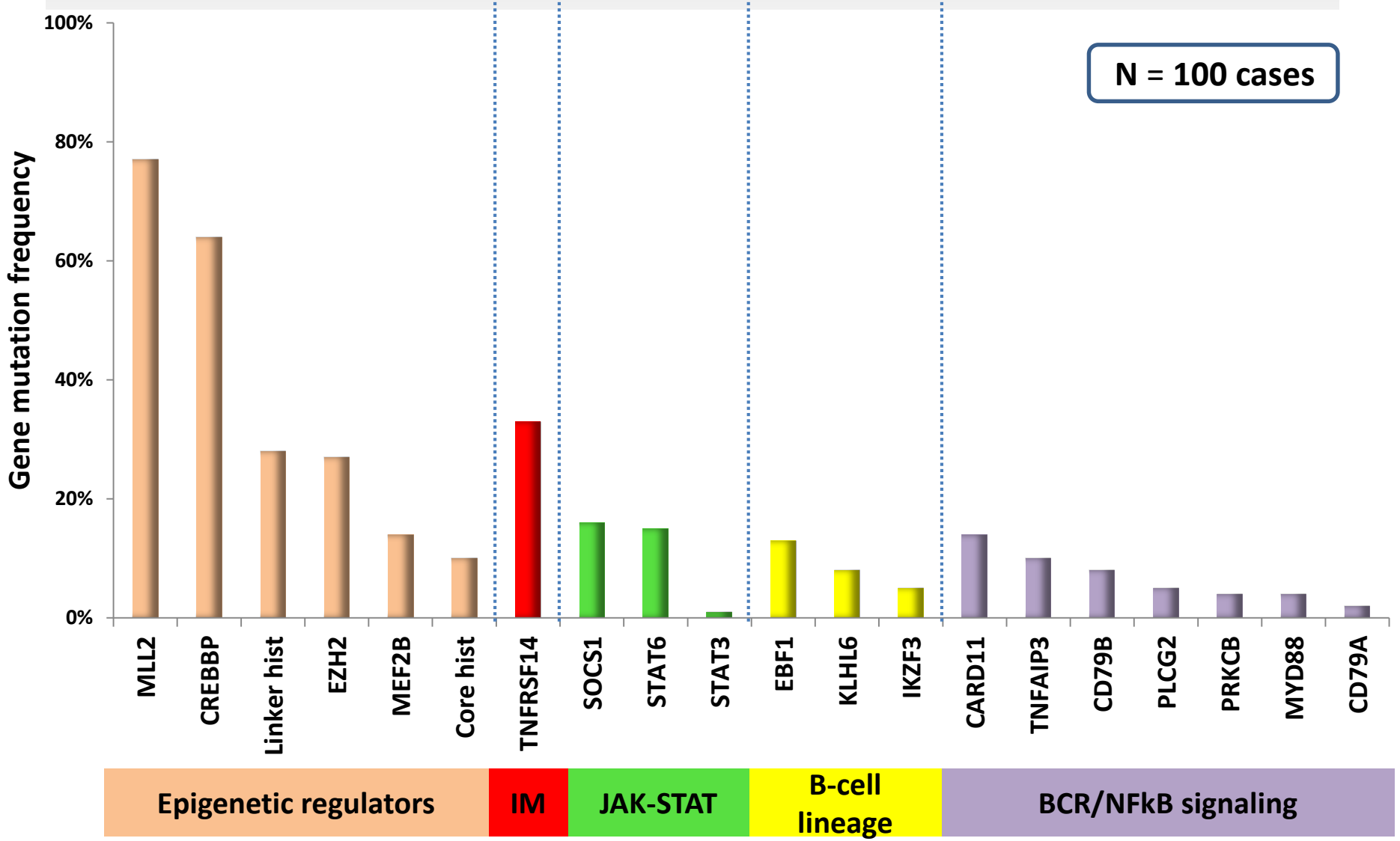
VENETOCLAX
IBRUTINIB
Then, at d15:
Anti-PDL1

3 mo

Anti-PDL1
IBRUTINIB

24 mo

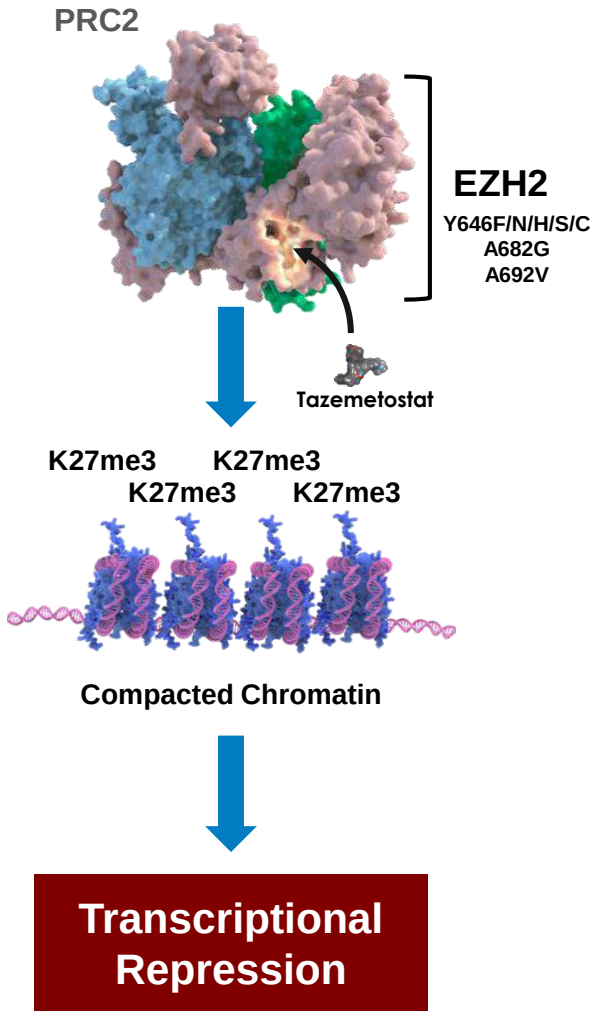
Recurrently mutated (epi)genetic genes in FL



Okosun et al, ICML 2013

TAZEMETOSTAT FOR THE TREATMENT OF B-CELL NHL

- EZH2 is an epigenetic regulator of gene expression and plays a critical role in multiple forms of cancer
  - Activating mutations of EZH2 can act as an oncogenic driver for cancers, especially in FL and GCB-DLBCL, present in ~20% of patients
- Tazemetostat
  - First-in-class, potent and selective oral inhibitor of mutated and wild-type EZH2
  - Preclinical activity in DLBCL cells lines, with greater activity in EZH2 mutant models
  - Monotherapy activity and favorable safety in phase 1 studies in patients with relapsed or refractory (R/R) NHL, as well as certain genetically defined solid tumors



Morschhauser et al, ICML 2017

PHASE 2 NHL DEMOGRAPHICS & DISEASE CHARACTERISTICS

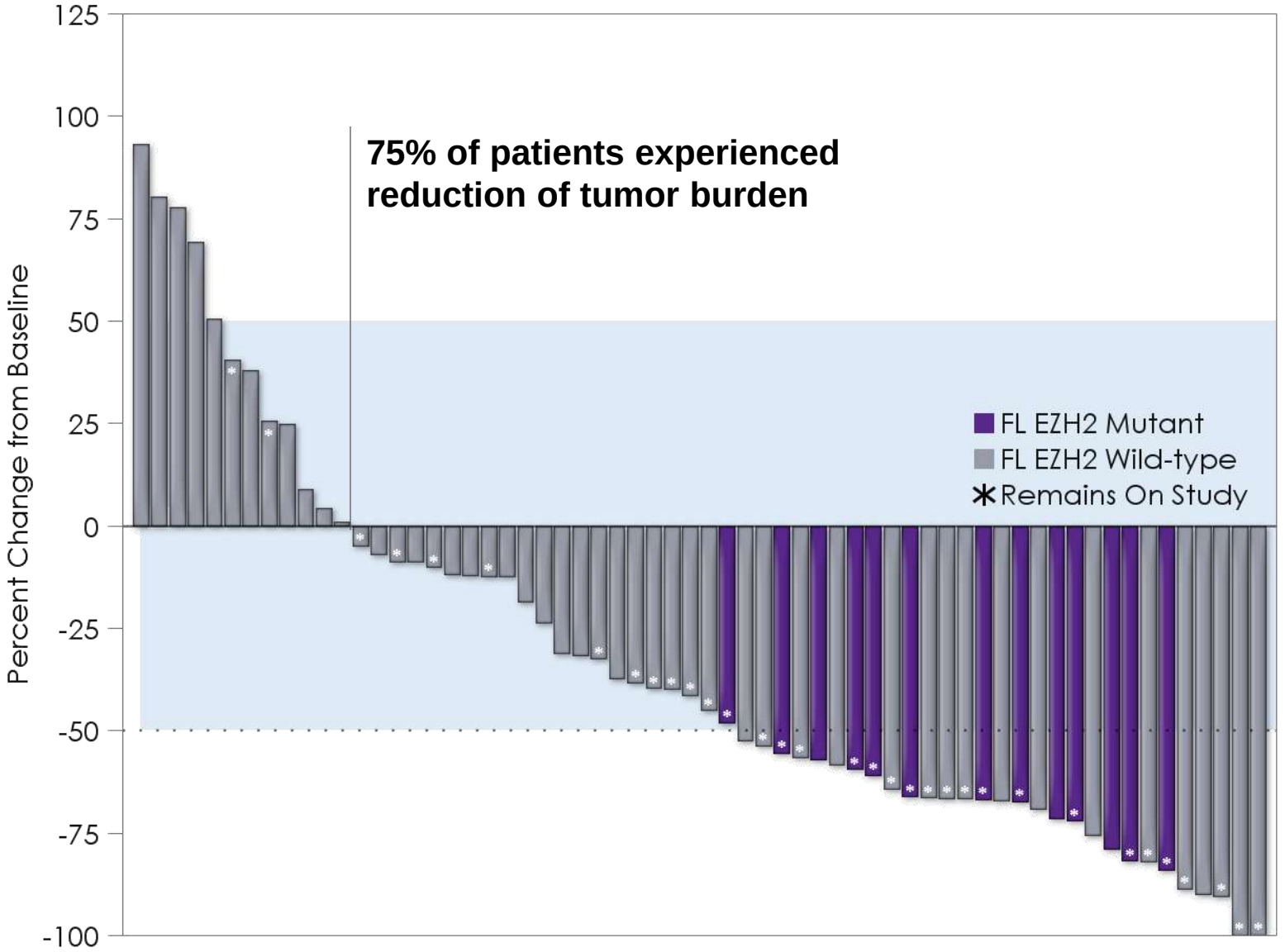
Characteristic		Follicular Lymphoma		DLBCL	
EZH2 Status		Mutant	Wild-type	Mutant	Wild-type
n		13	54	17	120
Age, median	years	62	61	61	69
Males		46%	63%	53%	58%
ECOG PS, median (range)		0 (0 - 2)	0 (0 - 2)	1 (0 - 2)	1 (0 - 2)
Prior lines of therapy, n (%)	1	1 (8%)	0	0	3 (3%)
	2	2 (15%)	11 (20%)	4 (24%)	40 (33%)
	3	3 (23%)	9 (17%)	7 (41%)	28 (23%)
	4	1 (8%)	14 (26%)	3 (18%)	18 (15%)
	≥ 5	6 (46%)	20 (37%)	3 (18%)	31 (26%)
	median	4	4	3	3
Refractory to last regimen, n (%)		7 (54%)	26 (48%)	14 (82%)	75 (63%)
Prior HSCT		23%	41%	41%	24%
Median time from initial diagnosis	years	7.4	4.9	1.0	2.0
Median time from last prior therapy	weeks	13.0	41.3	8.6	11.6

Morschhauser et al, ICML 2017

Data as of 6/1/2017

Refractory to last regimen defined as SD or PD as best response to most recent prior therapy

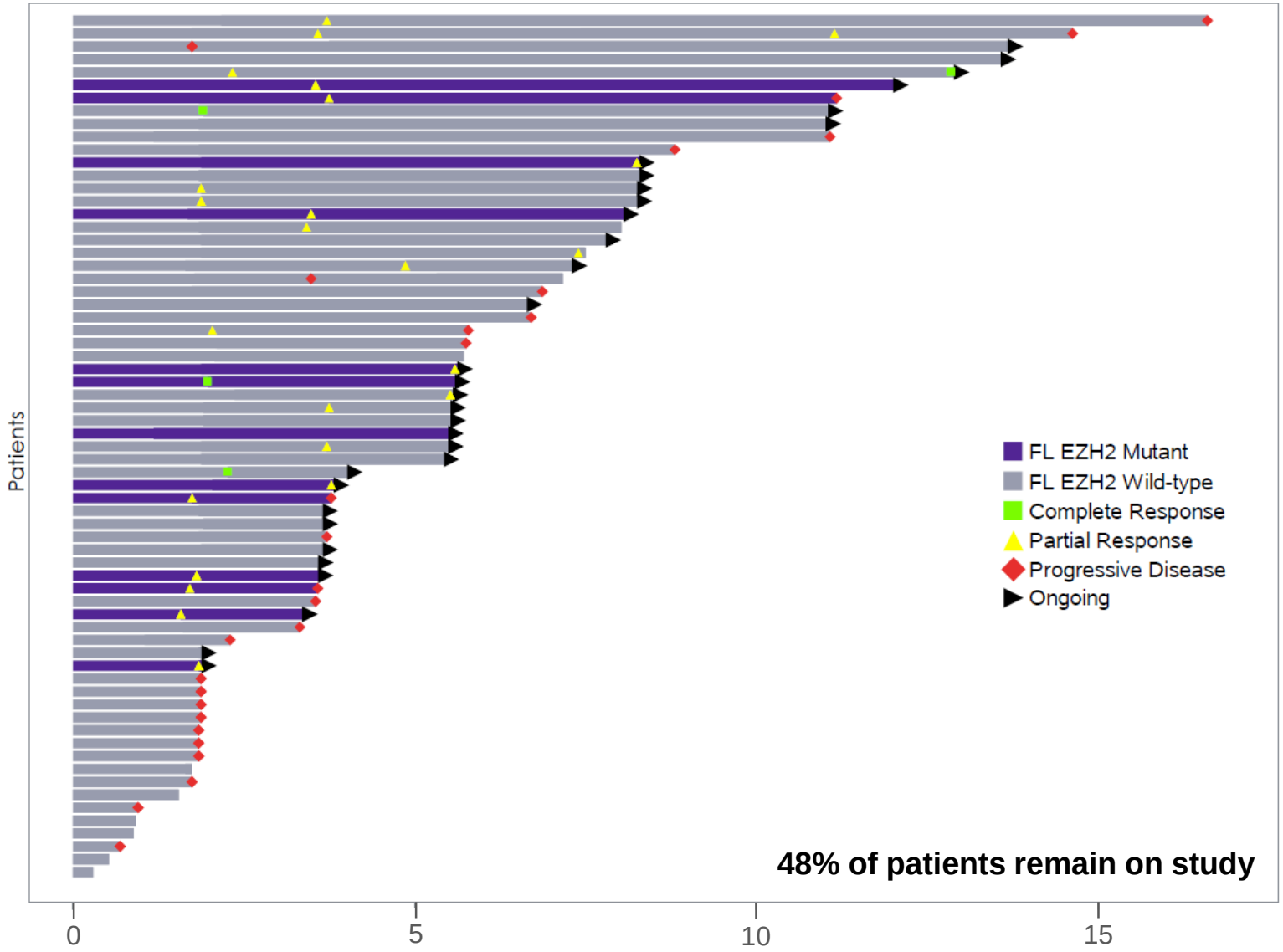
TUMOR REDUCTION IN FOLLICULAR LYMPHOMA



Data as of 6/1/2017

Morschhauser et al, ICML 2017

DURATION OF TUMOR RESPONSE IN FOLLICULAR LYMPHOMA



Data as of 6/1/2017

Morschhauser et al, ICML 2017

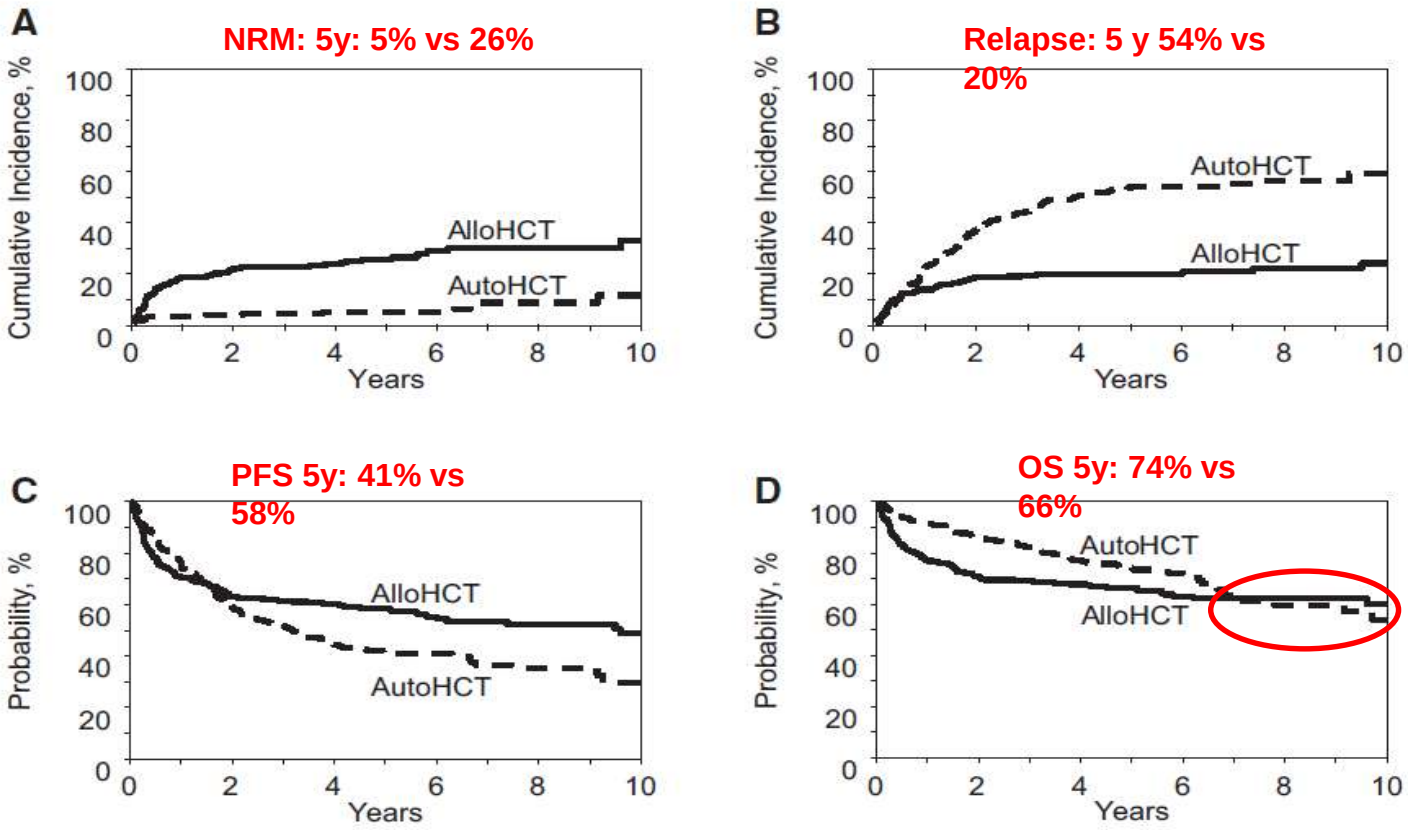
Synergy With BCL2 Inhibitors

Mechanism	Drug	Mutant EZH2 GCB		WT EZH2 GCB			WT EZH2 ABC
		WSU-DLCL2	SU-DHL-10	DOHH2	OCI-LY19	SUDHL5	Toledo
Glucocorticoid	Prednisolone	Synergy	Synergy	Synergy	Synergy	Synergy	No effect
	Dexamethasone	Synergy	Synergy	Synergy	Synergy	Synergy	No effect
BCL2	Navitoclax	Synergy	Synergy	No effect	Synergy	No effect	No effect
	Obatoclax	Additive	Additive	No effect	No effect	No effect	No effect
	ABT-199	Synergy	Additive	No effect	Synergy	No effect	No effect
B-cell Receptor Pathway	Everolimus	Synergy	Synergy	No effect	No effect	Synergy	No effect
	Trametinib	Synergy	Synergy	No effect	No effect	Synergy	No effect
	Bortezomib	Additive	Additive	No effect	No effect	No effect	No effect
	MK-2206	Synergy	Synergy	No effect	Synergy	Synergy	No effect
	Ibrutinib	Synergy	Synergy	No effect	No effect	Synergy	No effect
	Idelalisib	Synergy	Synergy	No effect	No effect	Synergy	No effect
	Tamatinib	Synergy	Synergy	No effect	No effect	Synergy	No effect

Main questions in the treatment of R/R FL

- ASCT or not ASCT as part of second-line?
  - If yes, for whom?
- New anti-CD20 MoAbs?
  - Why can they overcome resistance to rituximab?
- New agents beyond anti-CD20?
  - Targeting both tumor and immune contexture
- Allo SCT or CART cells: who and when?

L’allogreffe



LF en rechute, auto- ou allogreffe comme première transplantation

Klyuchnikov et al, *BBMT* 2015

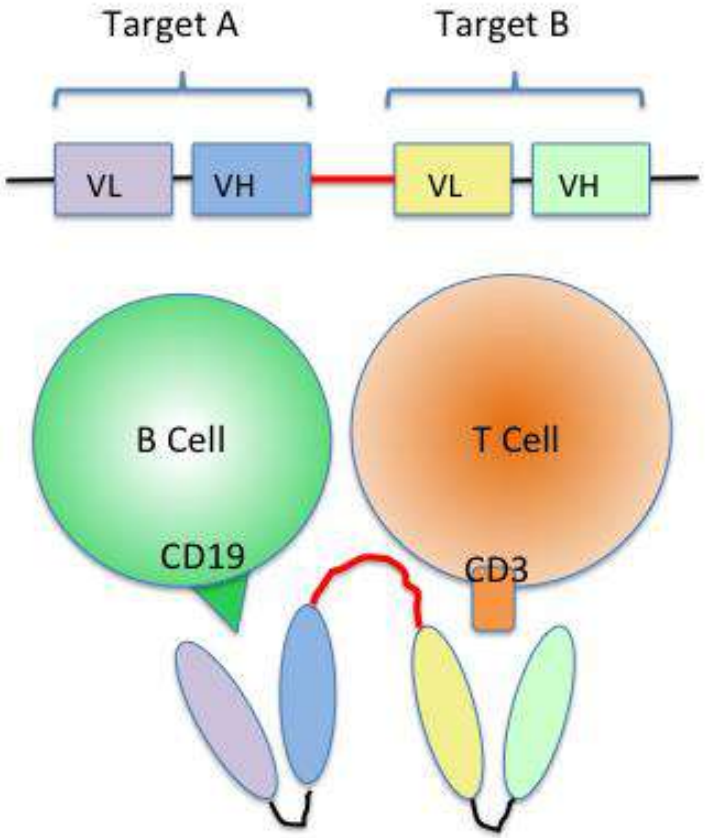
RIC-allogeneic transplant in FL

Study	3-yr TRM	3-yr RR	3-yr OS	3-yr EFS/PFS	cGVHD
Robinson, 2002	31%	20%	65%	54%	16% (ext: 9%)
Morris, 2004	11%	44%	73%	65/49%	7% (+ 20% post DLI)
Vigouroux, 2007	40%	10%	56%	51%	43% (ext: 20%)
Rezvani, 2007	40%	14%	52%	43%	Ext: 47%
Khouri, 2008	NR	NR	85%	83%	60% (ext: 36%)
Hari, 2008	28%	17%	62%	55%	62%
Ingram, 2008	20%	20%	69%	58%	20%
Thomson, 2010	15% /8%	26% /25%	76% /90	76% /87	Ext: 32% (incl post DLI) /11% (30% post DLI)
Piñana, 2010	37%	8%	57%	55%	Ext: 53%

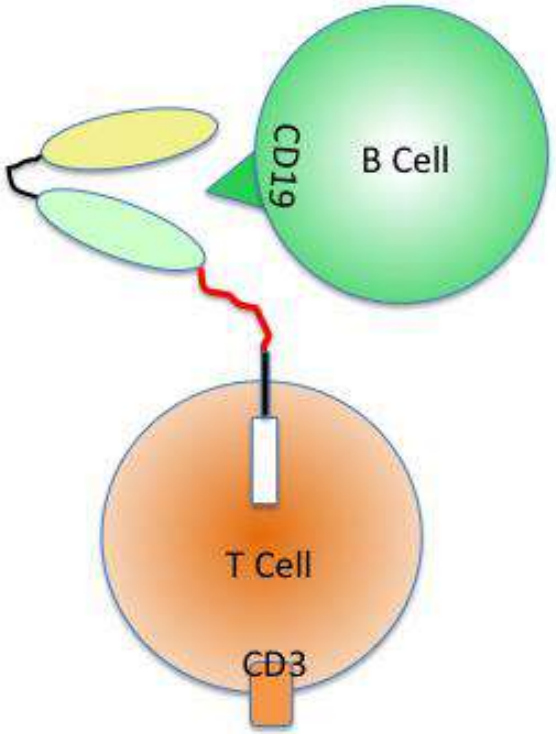
3-yr TRM: 20-30%, 3-yr RR: 15-20%, 3-yr OS: 50-65%, 3-yr PFS: 50-60%

Direct recruitment of T-cells against B-cell lymphoma

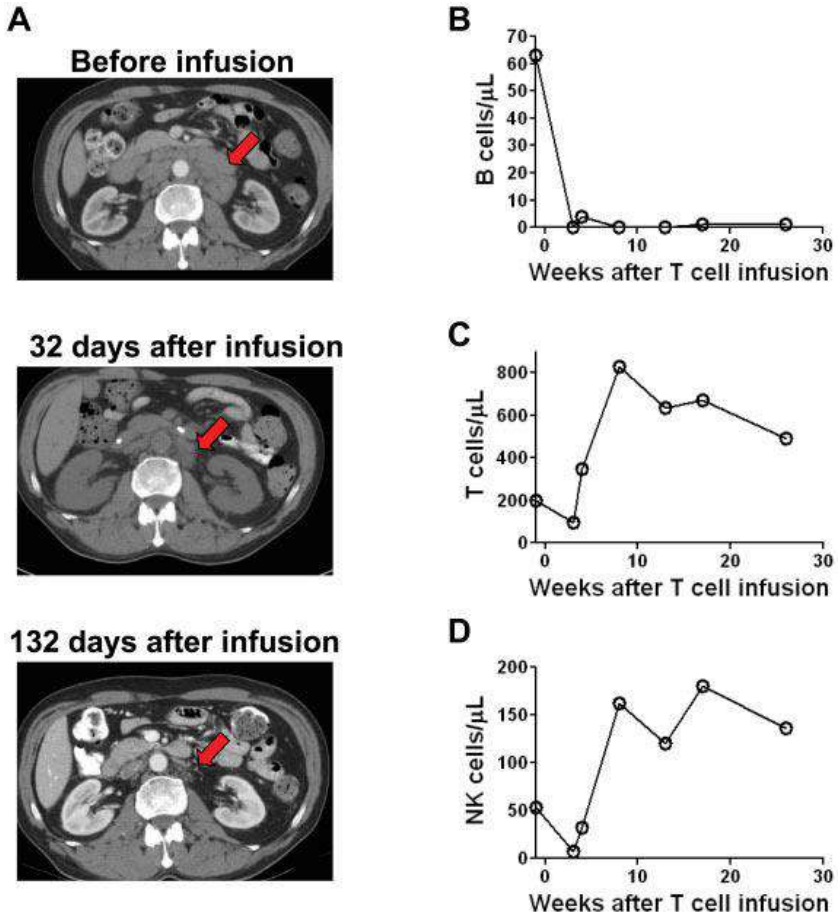
A. Bispecific T Cell Engager (BiTE)



B. Chimeric Antigen Receptor (CAR)



CAR-T cells clinical results



NCI, Bethesda
Responses in relapsed patients

4/5 FL
7/8 CLL
6/7 DLBCL (4 CR)

3/10 pat in relapse after allo-BMT
(donor-derived CAR-T)

Side effects:
- **Severe hypotensions**
- **Severe neurologic**

Kochenderfer et al,, Blood 2013 and JCO 2014.

BiTE for the treatment of R/R FL

- Phase I-II of BiTE (blinatumomab) in R/R NHL
- Dose escalation 0.5 to 90 ug/m2/day (MTD = 60 ug)
- Continuous infusion through portable mini-pump for 4-8 weeks

- Toxicity: 22% grade 3 neurologic events (reversible)

- In 15 R/R FL: RR 80% (6 CR + 6 PR)

Goebeler et al. JCO 2016

Conclusions

- ASCT better option in HT
- G-Benda and other G-based combinations challenge ASCT in Refractory FL
- Urgent need to better understand the biology to impact treatment choice
- New strategies should target both the microenvironement and the tumor
- The future of new agents is in combination.
- Allo-SCT or CART-cells after 3 lines including G and new agents