Hôpital Erasme

ULB

Post-ASH 2016 Lymphoma

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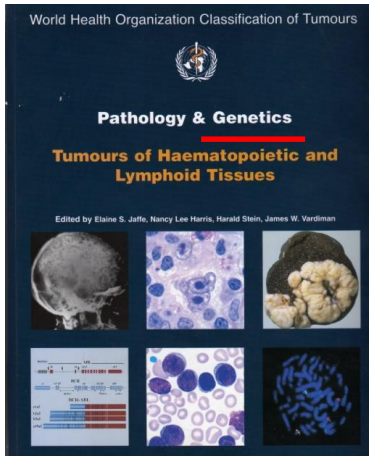
Hôpital Erasme, Brussels

13.01.2017

Introduction · FLymphoma · DLBCLymphoma · MCLymphoma · PTCLymphoma

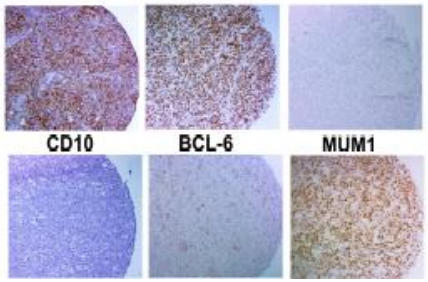
Pre-Genomic area

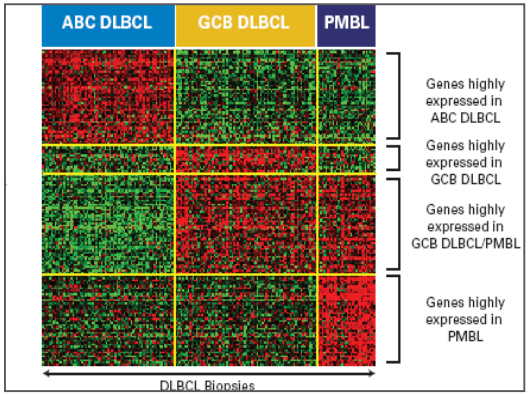


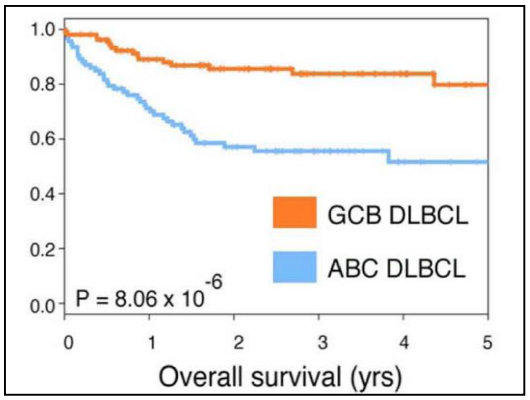
2016 WHO classification

Diffuse large B-cell lymphoma (DLBCL), NOS	DLBCL GC
Germinal center B-cell type*	DLBCL Non-GC
Activated B-cell type*	
T-cell/histiocyte-rich large B-cell lymphoma	
Primary DLBCL of the central nervous system (CNS)	
Primary cutaneous DLBCL, leg type	
EBV$^+$ DLBCL, NOS*	
*EBV$^+$ mucocutaneous ulcer**	
DLBCL associated with chronic inflammation	
Lymphomatoid granulomatosis	
Primary mediastinal (thymic) large B-cell lymphoma	
Intravascular large B-cell lymphoma	
ALK$^+$ large B-cell lymphoma	
Plasmablastic lymphoma	
Primary effusion lymphoma	
*HHV8$^+$ DLBCL, NOS**	
Burkitt lymphoma	
*Burkitt-like lymphoma with 11q aberration**	
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*	
High-grade B-cell lymphoma, NOS*	
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma	

Hans algorythm







Hans C et al. Blood 2004 , Alizadeh A et al. Nature 2000, Rosenwald A et al. N Engl J Med 2002

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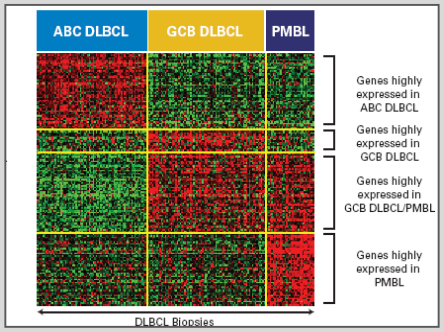
Genomic area: the DLBCL example

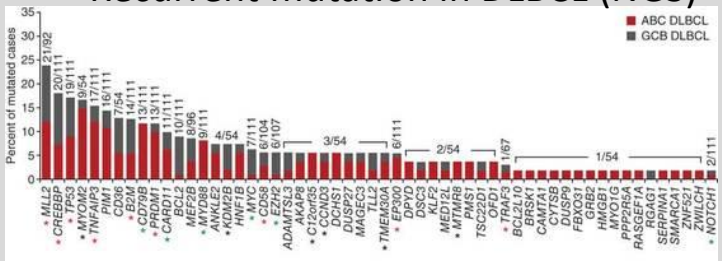
Selected gene analysis

Gene expression profile (GEP)[1]

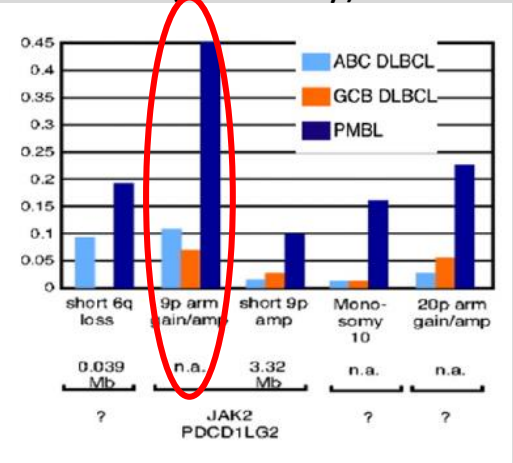


Whole exome/transcriptome/epigenetic analysis

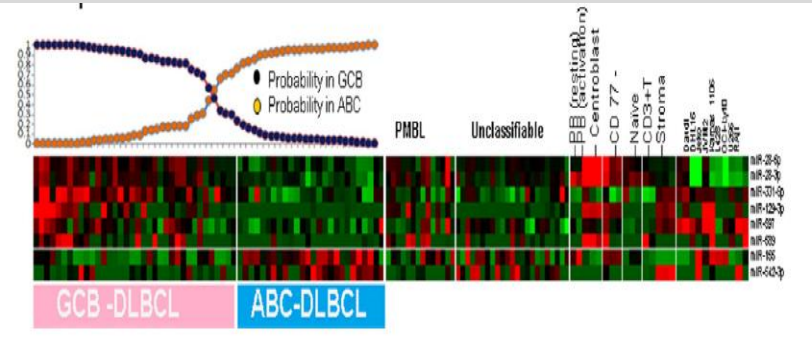
Recurrent mutation in DLBCL (NGS)[2]



Copy number alteration (CGHarray)[3]



MicroRNA profile [4]



Methylation profile [5]

Alizadeh A. Nat 2000[1] ,Pasqualucci Nat Gen 2011[2], Lenz G PNAS 2008[3], Iqbal J. Blood 2015[4], Chambwe N. Blood 2014[5]

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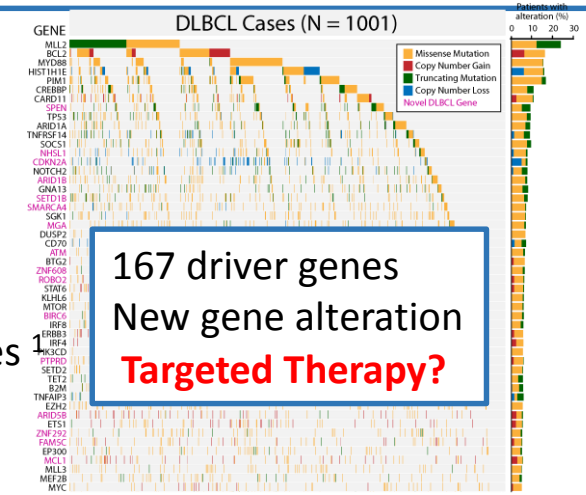
❖ Genomic area: The 1001 DLBCL Study[1]

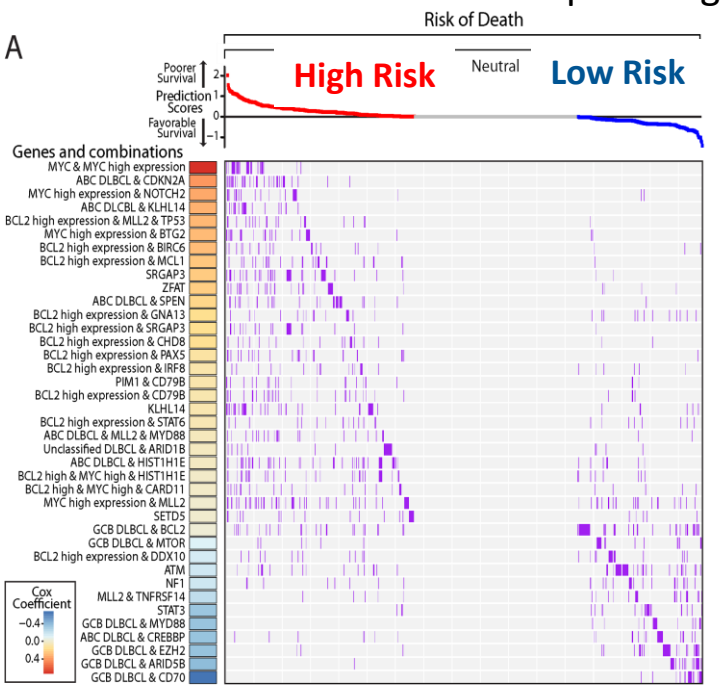
Objective : Connection of genomic landscape to clinical outcome

Technically:

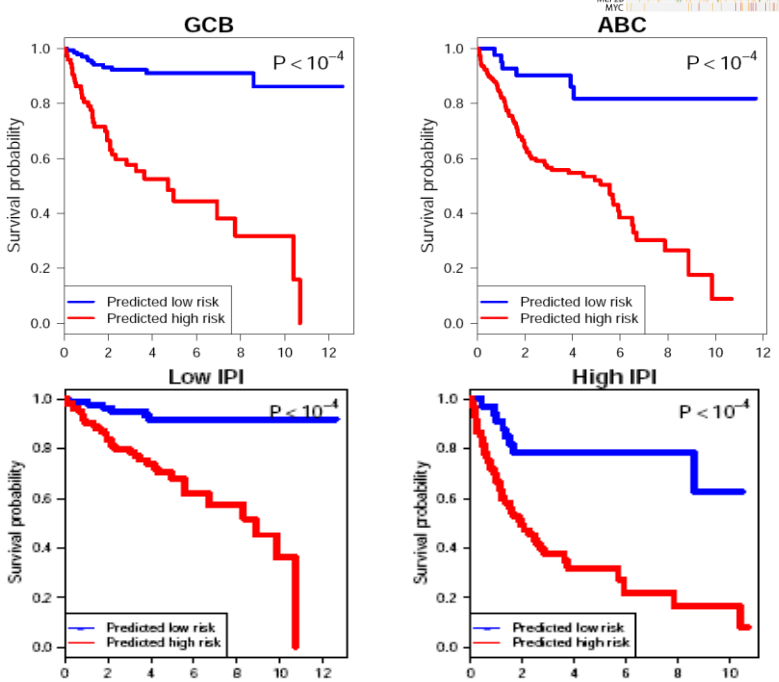
- Define gene expression, mutational AND copy number alteration
- Feasibility of NGS from FFPE (formalin fixed, paraffin-embedded) samples [1]
- Unable the use of multicenter pathology archives



167 driver genes
New gene alteration
Targeted Therapy?



Multivariate analysis (OS)

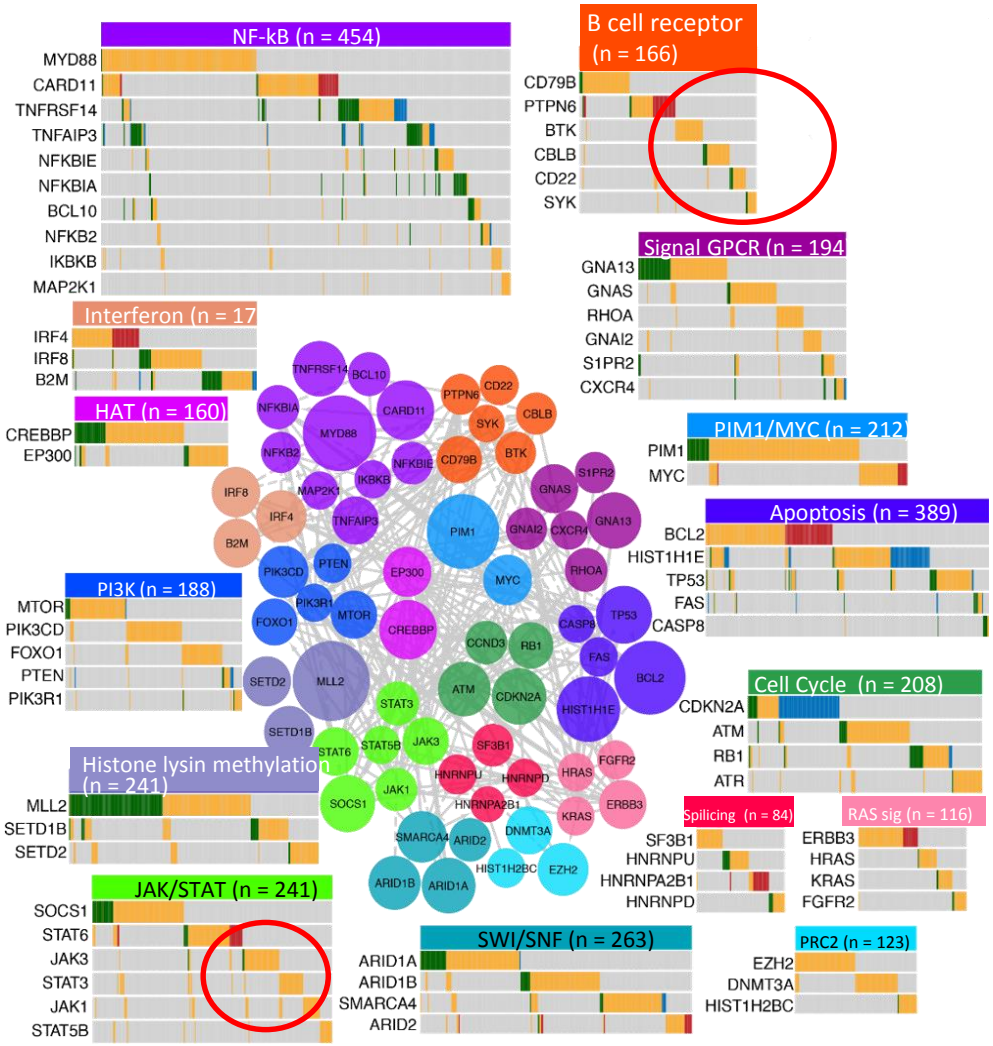


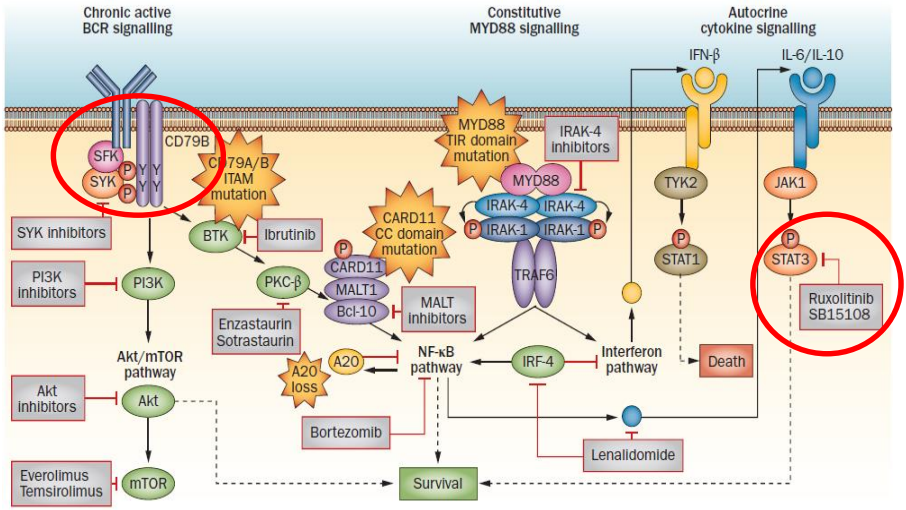
Better identification of bad prognostic at diagnosis

Overall survival (years)

Courtesy of Sandeep D # 4095, Van Allen EM, Garraway LA. Nat Med. 2014 [1]

Genomic area: Precision medecine - Individual therapy – targeted therapy ?



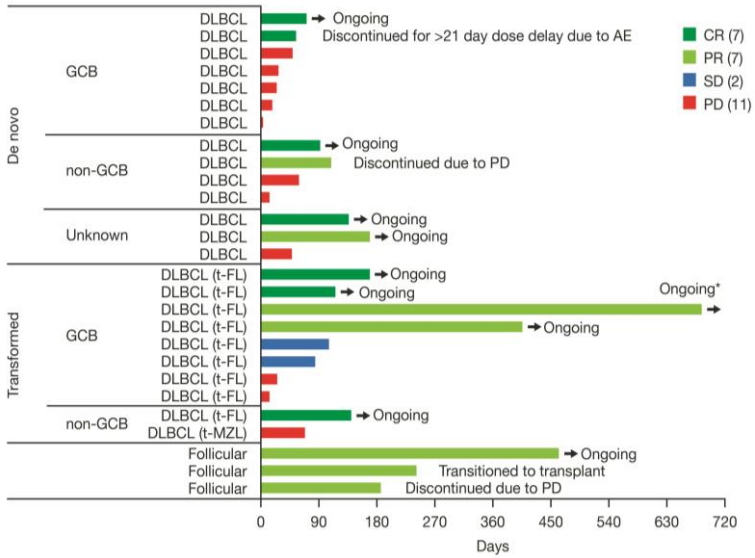


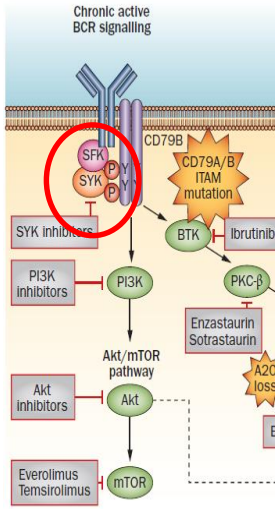
Courtesy of Sandeep D # 4095, Roschewski et al. Nat Rev Clin Oncol 2014

Targeted therapy : Syk inhibition

❖ **Phase I study: oral Syk inhibitor TAK659[1]**

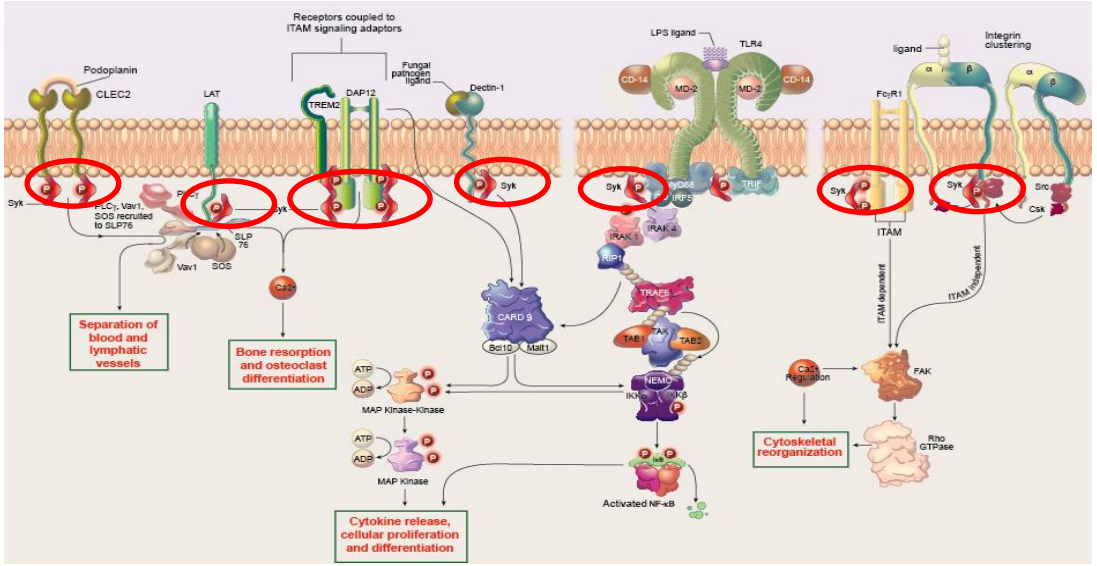
Relapsing/refractory lymphoma n=27
Acceptable toxicity profile (Pneumonia 9 %)
ORR 46% DLBCL, 100%FL
Mutational status of SYK/CD79 not evaluated





❖ **Phase 1b/2 Study of TAK-659 in R/R AML[2]**

Syk is also play a role in myeloid malignancies and is a key regulator of FLT3 (FLT3 Mutated in 30 % of AML) [3]



Kaplan JB. # 0624 [1] , Kaplan JB Abst 2834 ASH 2016 [2] ,Puissant A Cancer cell 2014[3]

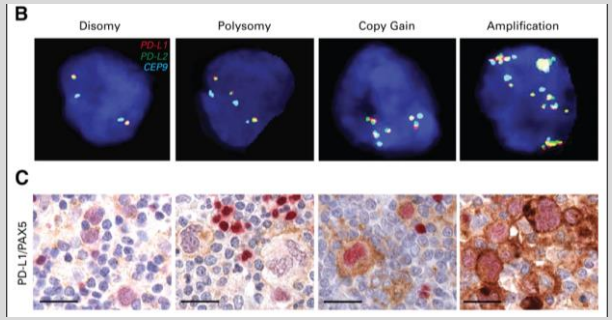
Targeted therapy: JAK1/2 inhibitor

❖ **Two Phase II study oral JAK1/2 Inhibitor Ruxolitinib in R/R Hodgkin lymphoma** [1,2]

Back ground :

Copy number alteration of 9p24 region[3]

Lead to JAK/STAT and PDL1 /PDL2 amplification

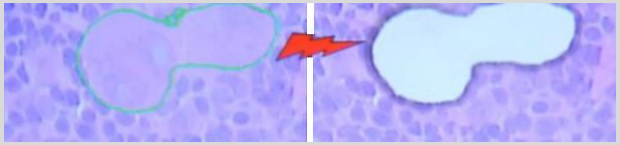


Mutated gene in HK[4]

Whole exome sequencing of Reed-Sternberg cells

Microdissection

Recurrent mutations in JAK/STAT pathway (STAT6/3, NFKB , SOC1, XPO1 mutations)



Relapsing/refractory Advanced Hodgkin lymphoma

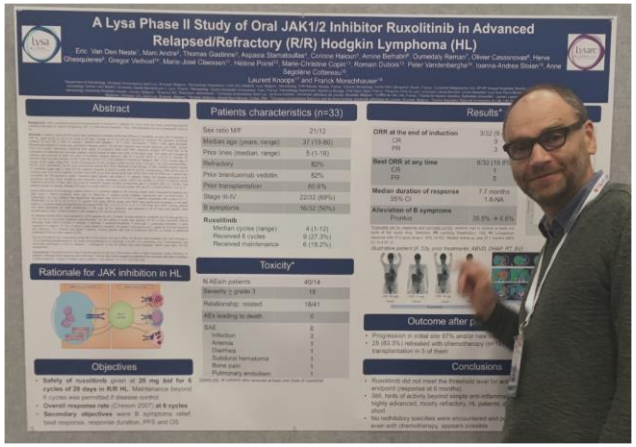
n=33, n= 14

OR : 19-40%

Median duration of response: 5-8- months

Toxicity was limited

Could be combined with other treatments



Van Den Neste # 4160 [1], Seok J Kim # 1820 [2], Roemer M JCO 2016 [3], Tiacci # 1088 [4]

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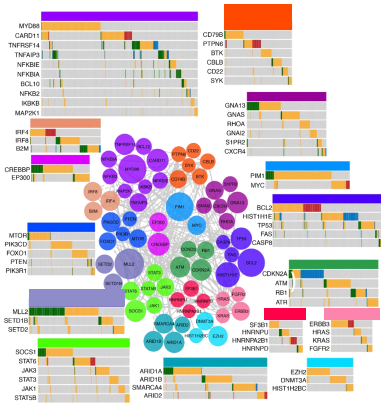
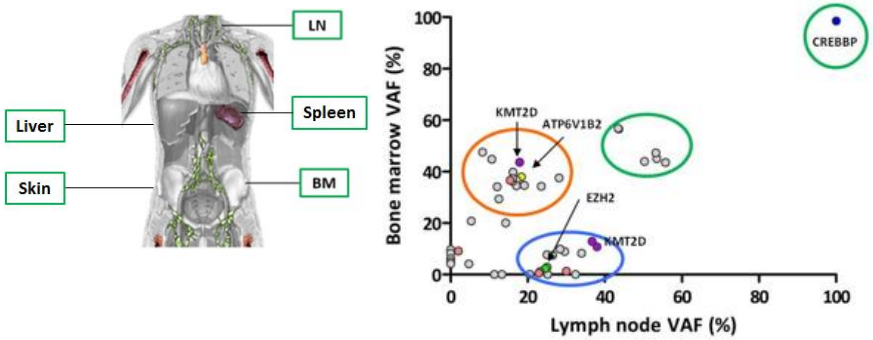
Genomic area: Are we ready for targeted therapy based on individual alteration profile ?

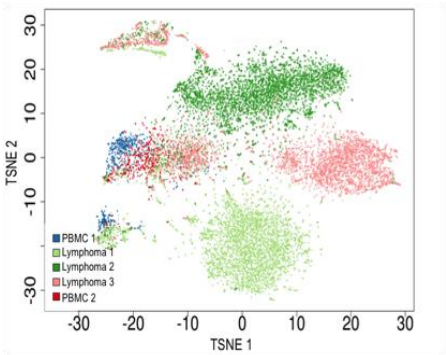
- Not a single gene alteration but a network of gene alterations



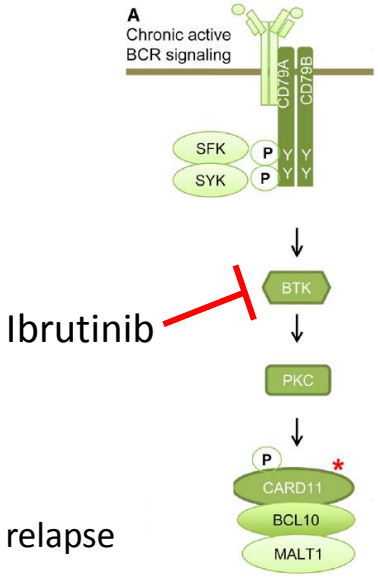
- Tumor heterogeneity (ex: follicular lymphoma)[1,2]

Massive single cell RNA-seq



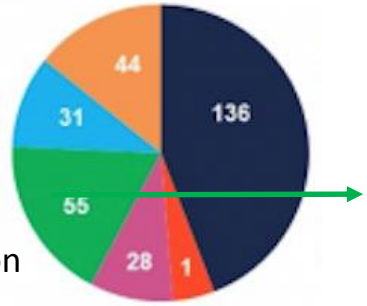


- Canonical pathways are involved: many diseases/normal cells
  > side effects/new mutations and alternative pathways upregulation



Retrospective analysis of CLL Patients from 4 clinical trials (n=308)
Median follow up of 40 months

- Still on treatment
- Stop > side effects
- Stop > Infections
- Stop > Progression
- Stop >Transformation



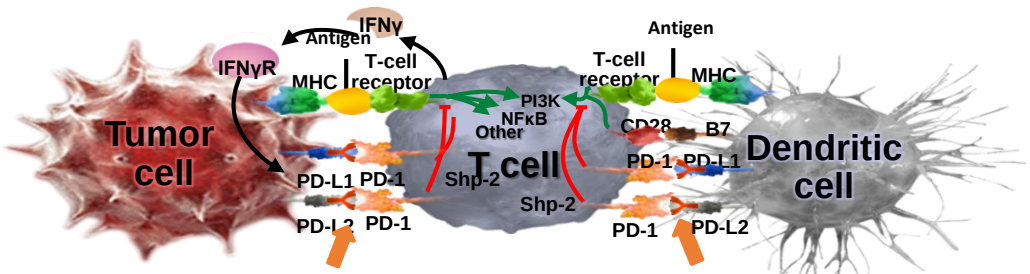
85 % aquired BTK or PLCG2 mutations
Enhance BCR signaling
Median of 9,3 months prior to clinical relapse

Araf, Fest et al, EHA 2016 [1], Andor N # 1090 [2], Woyach J # 055

Immune Check points inhibitors

❖ **Update CheckMate 205 Study (Cohort B)** [1]

R/R Hodgkin lymphoma
Phase II international multicohort study
Minimum follow-up 12 months
n=80



Nivolumab blocks the PD-1 receptor

R/R HK
Post-ASCT
AND
post-BV[1]

Belgium reimbursement 01/01/2017

→ **Nivolumab 3 mg/kg IV Q2W**
Treatment until
disease progression or toxicity

→ ?

Patients could discontinue nivolumab and proceed to allogeneic (allo)-HSCT

Younes A Lancet Oncol 2016[1], Up date: Timmerman J # 1110

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Immune Check points inhibitors

Update of CheckMate 205 Study (Cohort B) [1]

R/R Hodgkin lymphoma
Phase II international study
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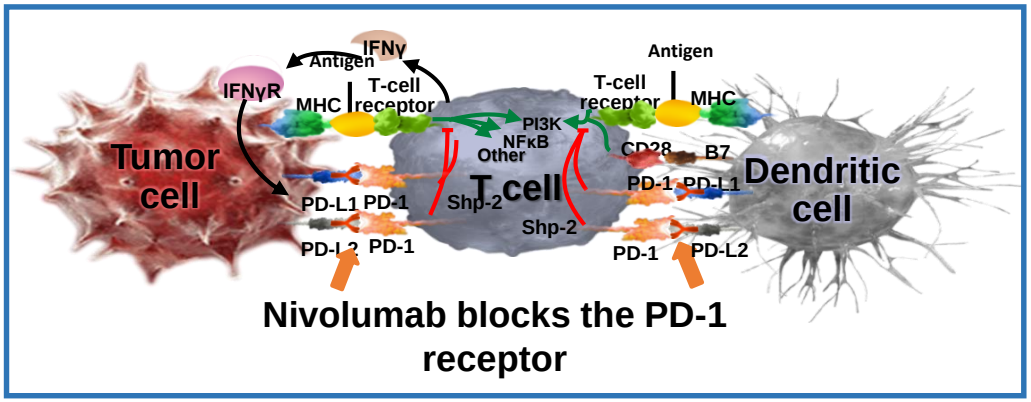
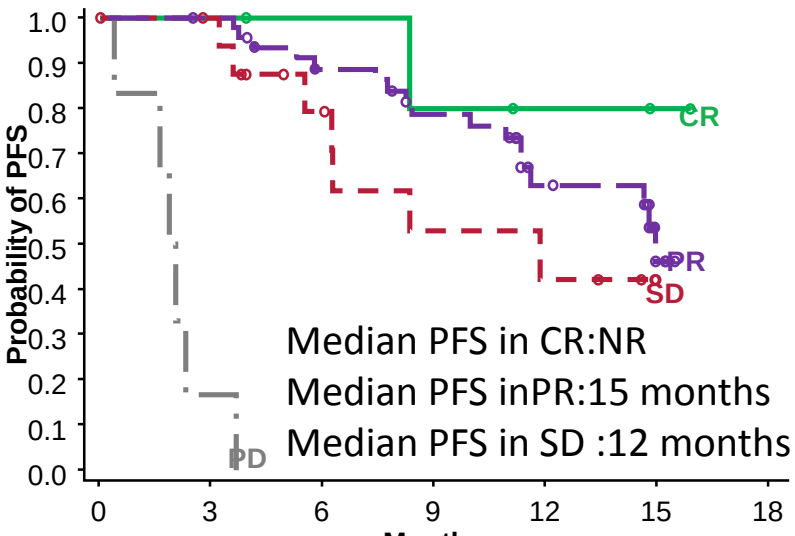


PFS (secondary endpoint)

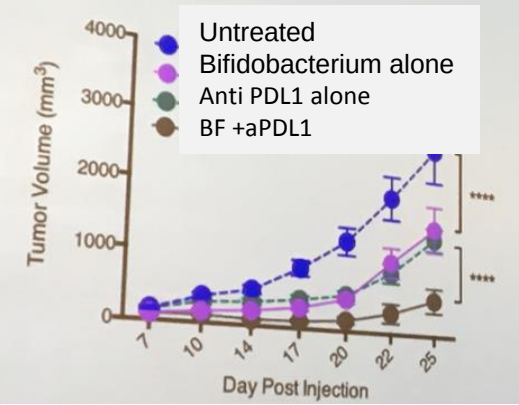


No. of patients at risk

CR	6	6	5	4	2	1	0
PR	48	47	37	30	16	3	0
SD	17	16	10	6	4		
PD	7	1	0	0	0		

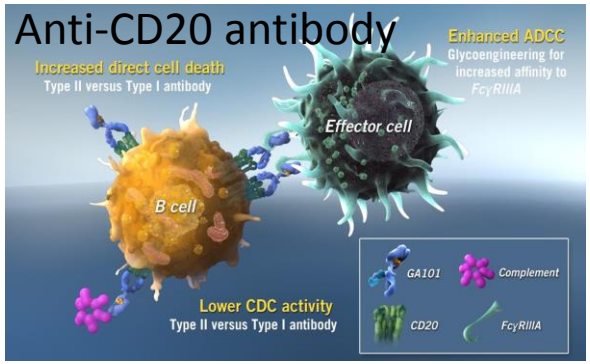
ORR: 54(68%), CR 8% , PR 60%
Median duration of response:13 months
Safety profile (Arthralgia, hepatitis,..)
43 patients still on treatment
11 patients proceed to allograft (4 grade 2-4 aGVHD)

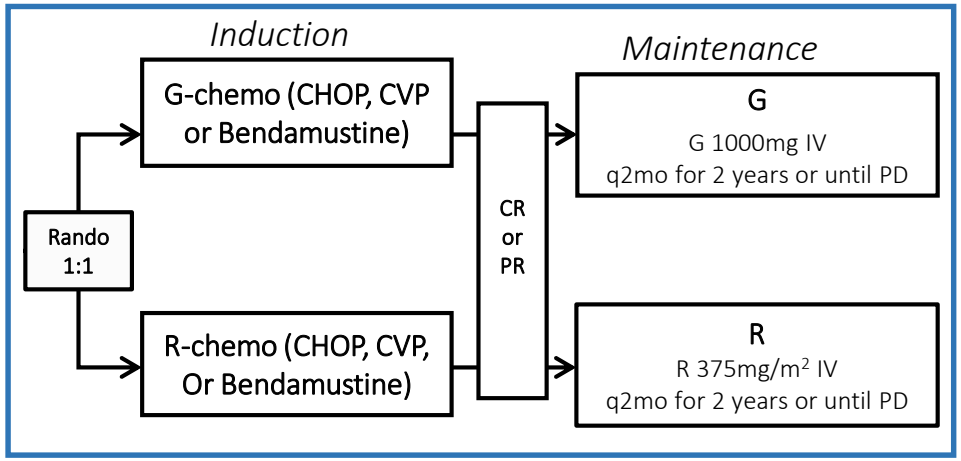
- **Pre-Clinical data on anti-PDL1 (melanoma)**



Younes A Lancet Oncol 2016[1], Up date: Timmerman J # 1110, Corrales S science 2015

Treatment of Follicular lymphomas :
GA101 (= Obinutuzumab =Gazyvaro ®) ?



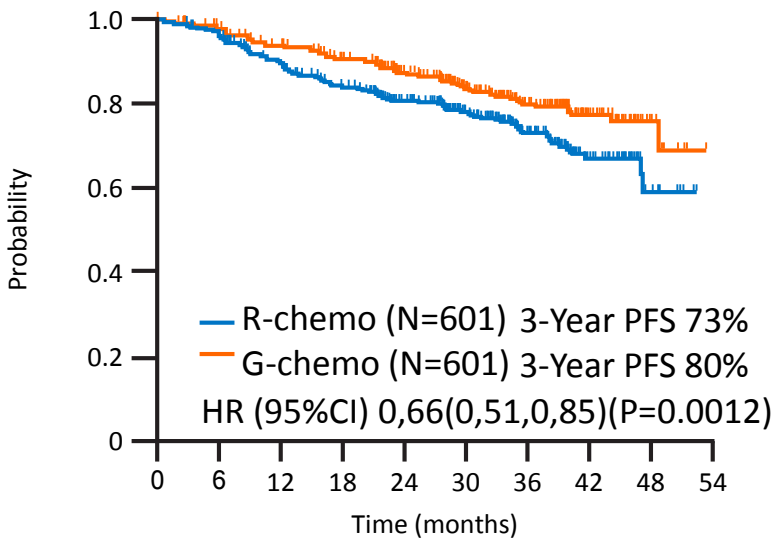


R/R follicular lymphoma: GADOLIN Study[1] :
Rituximab refractory indolent NH Lymphoma
Bendamustine alone vs G-Benda + G maintenance
Addition of GA101 improve PFS AND OS
Median OS NR vs 53,9 months (HR:0,58)

Frontline treatment : GALLIUM Study[2]:
International, open-label, randomized phase III
N=1202
Median follow-up: 34,5 months

Key inclusion criteria :
FL(grade 1-3a) or MZL
Stage III/IV or Stage II bulky

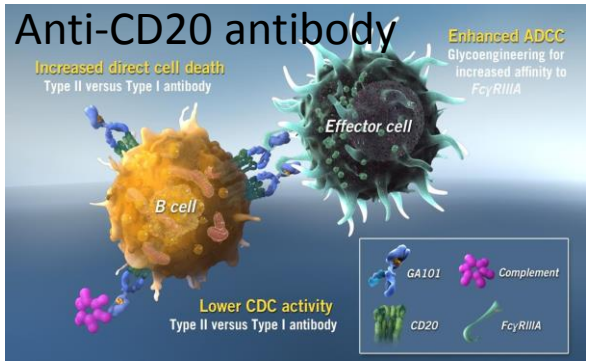
PFS (primary endpoint)

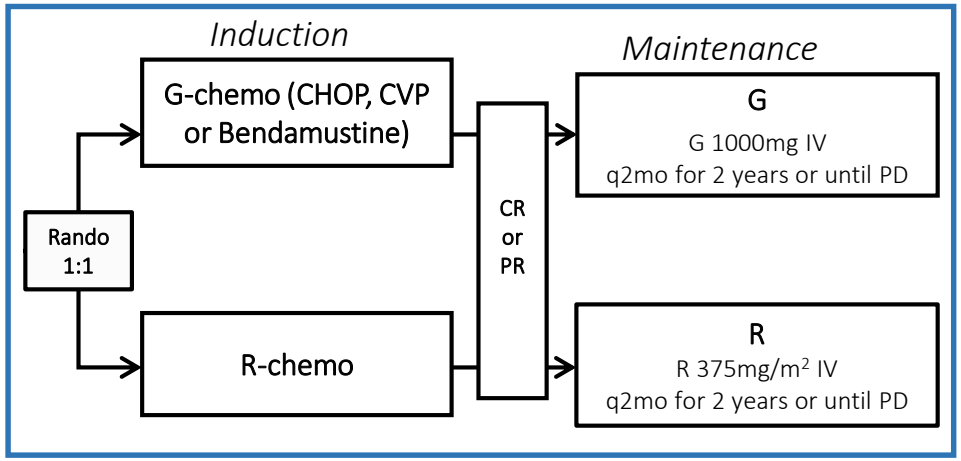


Up date Cheson B # 0615, Marcus R # 06

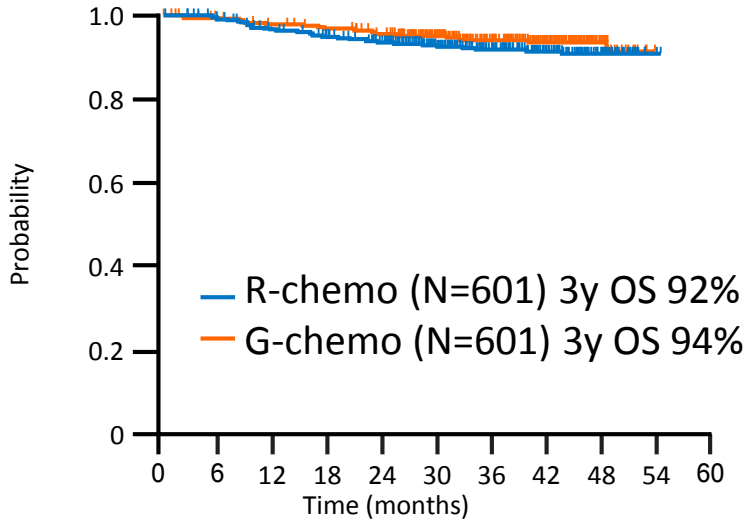
Frontline treatment of Follicular lymphomas :

GALLIUM Study

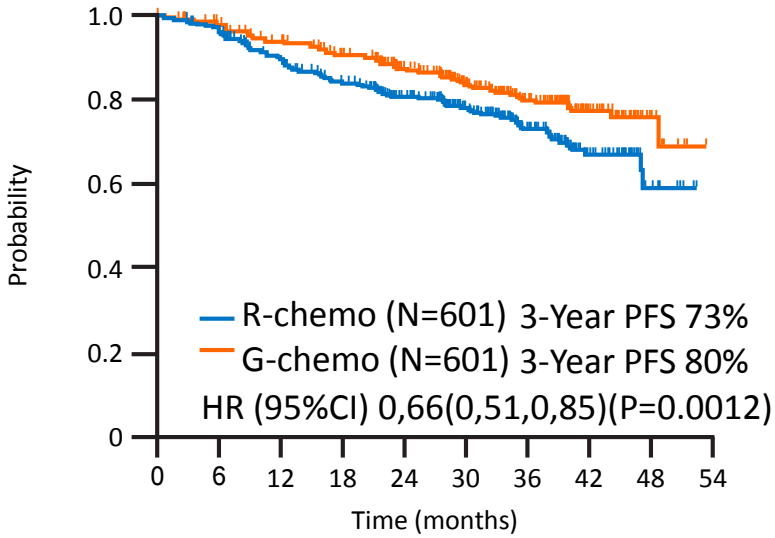




OS (secondary endpoint)



PFS (primary endpoint)

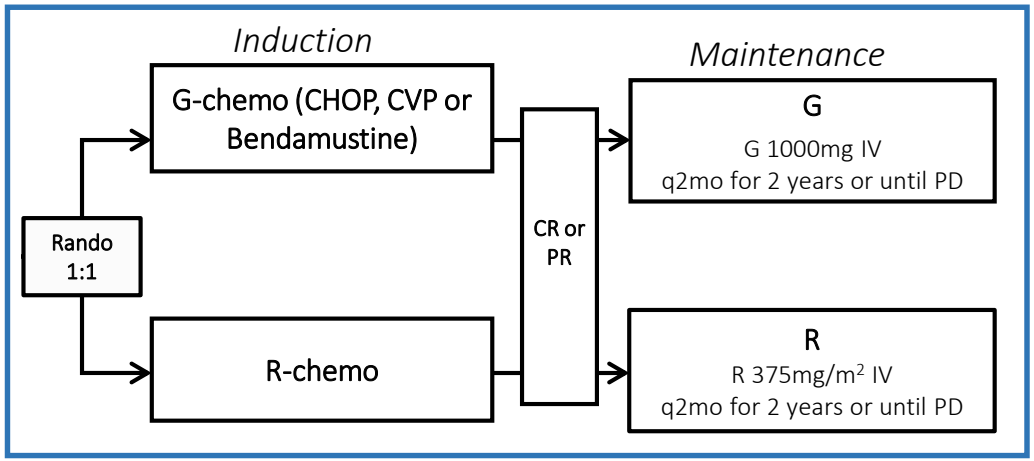


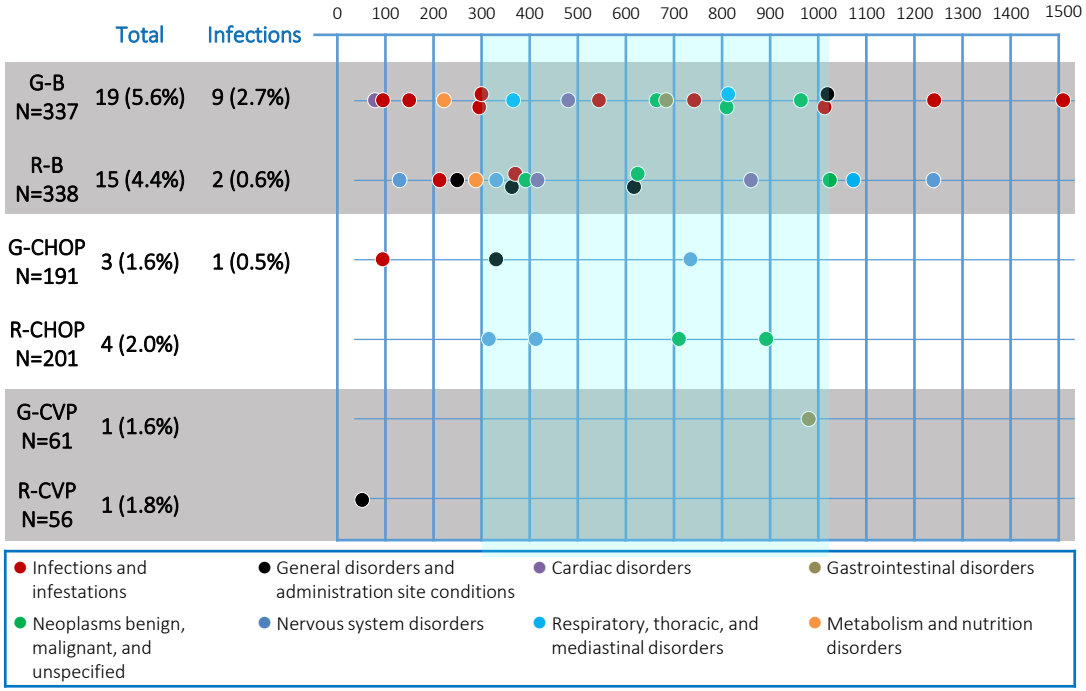
Cheson B # 0615, Marcus R # 06

Frontline treatment of Follicular lymphomas : GALLIUM Study

Toxcicity profile

% (n)	R-chemo (n=597)	G-chemo (n=595)
Any AE	98.3% (587)	99.5% (592)
Grade ≥3 AEs of special interest by category (selected)		
Infections†	15.6% (93)	20.0% (119)
Infusion reaction	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)





Conclusions:

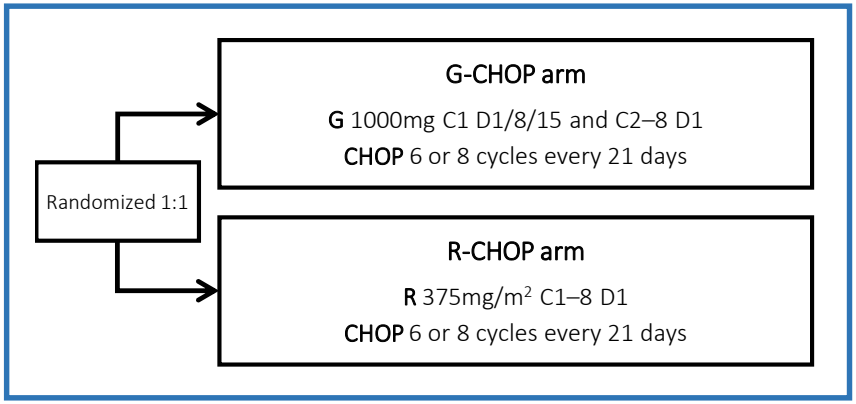
- G-chemo+maintenance improve PFS (HR=0,66) 34% reduction of risk
- Non-Fatal AEs were Higher in the G arm IRR, cytopenias, infections
- Fatal AEs more common in patients on bendamusine in BOTH arms

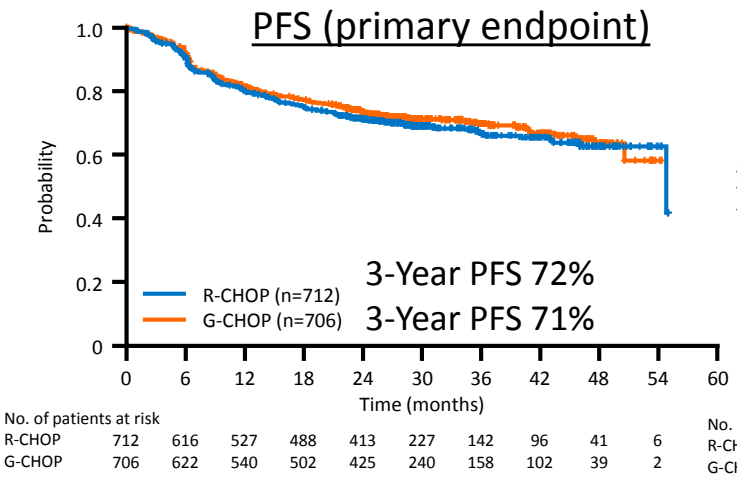
Marcus R # 06

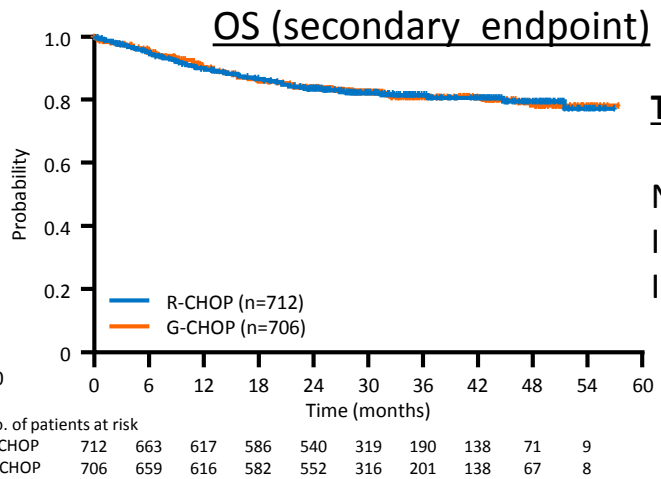
Front line treatment of Diffuse Large B Cell Lymphoma: Can we improve RCHOP with GA101 ?

Goya Study : Italian multicenter, randomized phase III trial
N=1418

Key inclusion criteria:
Age >18 y
De novo DLBCL







Toxicity profile : (RCHOP vs GCHOP)

Neutropenia :38 vs 46 %
Infection :15% vs 19%
Infusion reaction: 0,6% vs 3%

Subgroup analysis
COO assessed by GEP (Nanostring)
GCB DLBCL: 3-year PFS: 79% vs 70 % in favor of G-CHOP over RCHOP HR95%CI : 0,72 (0.05,1.01)

Front line treatment of Diffuse Large B Cell Lymphoma: Can we improve RCHOP with maintenance?

REMARC Study :

International, phase III, placebo controlled

n=784

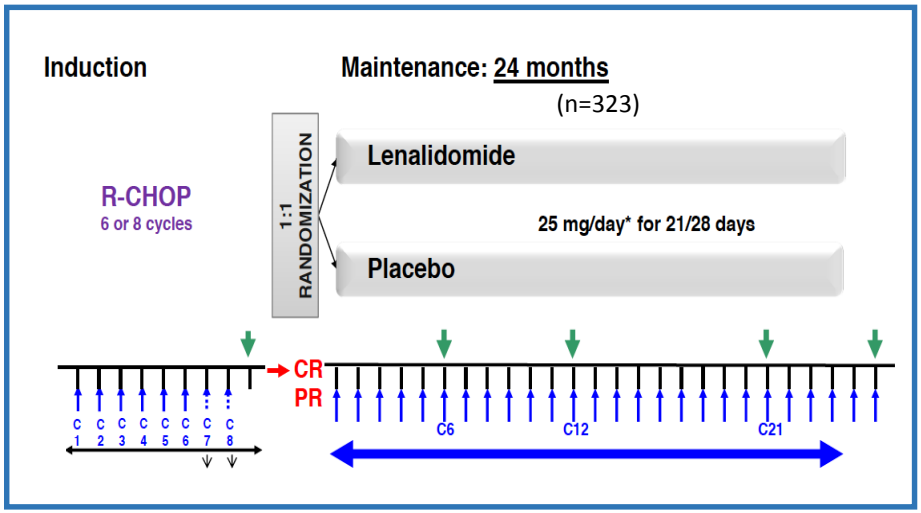
Median follow up 40 months

Key inclusion criteria:

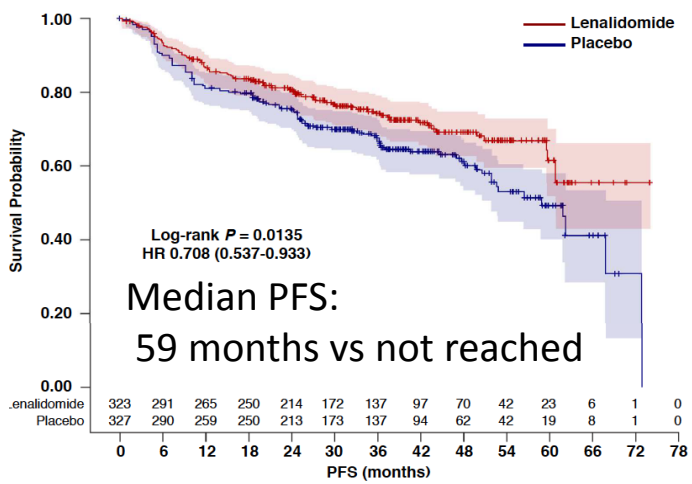
Age 60-80 y

De novo DLBCL CD20+

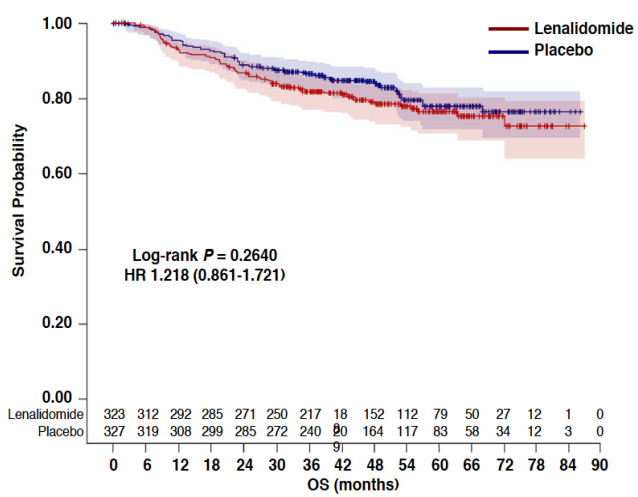
FL 3B and de novo transformed indolent lymphoma



PFS (primary endpoint)



OS (secondary endpoint)



Toxicity profile

	Lenalidomide (n = 322*)	Placebo (n = 323*)
Neutropenia	56%	22%
Infection	8%	6%
Thrombocytopenia	3%	1%
VTE	1%	0.3%
Cutaneous reaction	8%	1%
Diarrhea and constipation	2%	1%
Hepatic disorder	1%	0.3%
Peripheral neuropathy	1%	2%
Cardiac disorders	5%	3%
Number of deaths due to toxicity	0	2

Thieblemont C # 0471

Front line treatment of Diffuse Large B Cell Lymphoma : Can we improve RCHOP with maintenance?

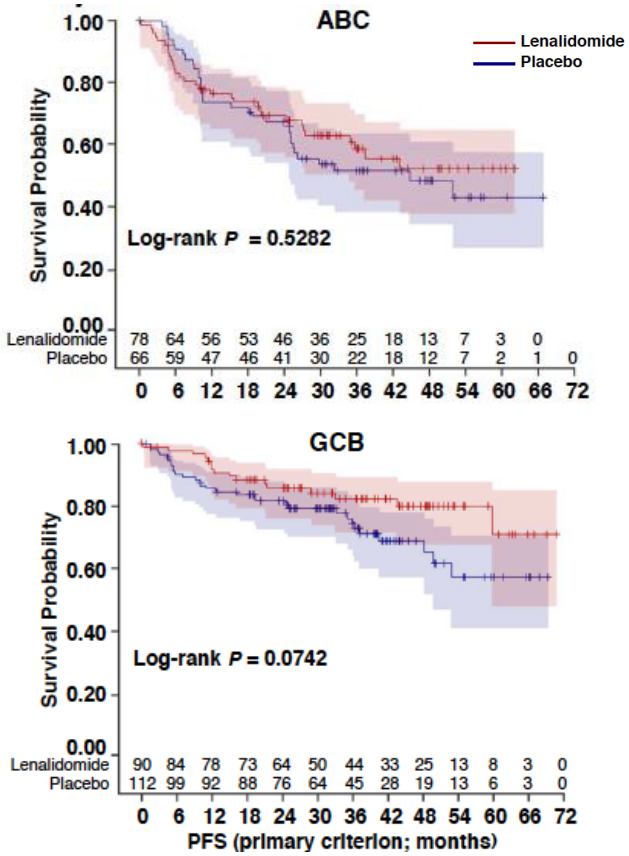
REMARC Study :

Subgroup analysis:

No difference regarding:

- Conversion of PR to CR
- COO (Hans algorythm and GEP)

	Treatment Arm		
	Lenalidomide (n = 69; 21%)	Placebo (n = 83; 25%)	*P* value
Conversion from PR to CR With Maintenance			
PR to CR, n (%)	23 (33)	24 (29)	0.557
Median time to conversion, months (range)	5.9 (3.9-26.5)	5.6 (3.2-24.8)	–



Conclusions:

- Lenalidomide maintenance after RCHOP improves PFS (but not OS) in elderly patients with DLBCL
- Identified subgroup with more benefit ?

Courtesy of Thieblemont C # 0471

Relapse/refractory DLBCL : The T CAR Solution ?

NCT 02030834 study: CTL019 cells[1]

Monocentric Phase IIa trial

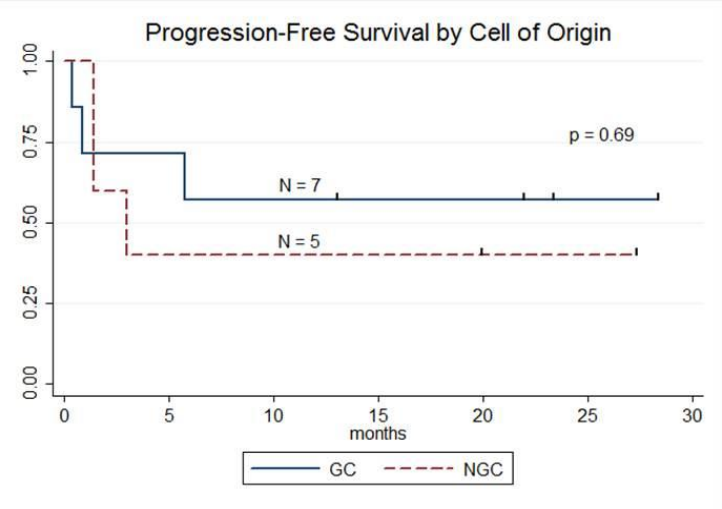
n=13

Median follow-up 23 months

Key inclusion criteria

R/R DLBCL, tFL not eligible for ASCT

or R/R disease after ASCT



Complete response at 6 months: 46%

86 % of responding patients maintain response

Longterm response

ZUMA -1 trial : Kte-CD19 cells[2]

First multicenter phase II trial

Central manufacturing of anti-CD19 CAR T cells

n=111 (from 22 institutions)

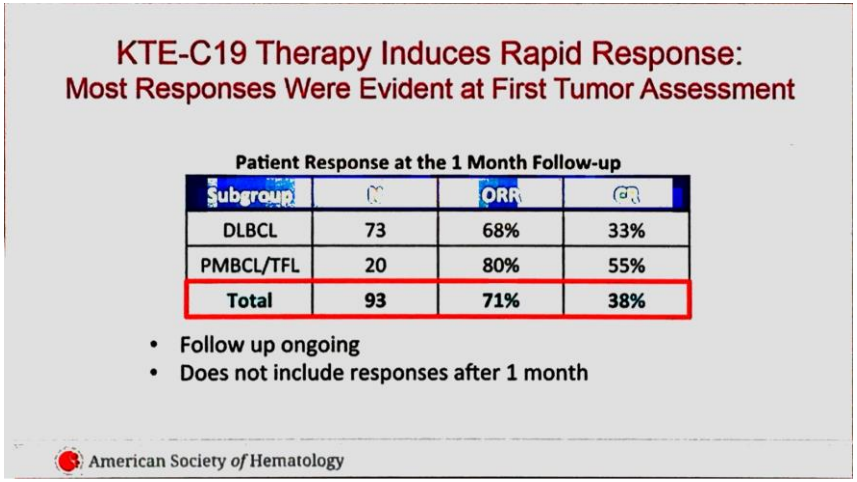
Key inclusion criteria

Cohort 1: R/R after ASCT DLBCL

Cohort 2: R/R PMBCL/tFL

KTE-C19 successfully manufactured in 99% of patients

Average time from apheresis to receipt of cells : 17 days



KTE-C19 Therapy Induces Rapid Response:
Most Responses Were Evident at First Tumor Assessment

Patient Response at the 1 Month Follow-up

Subgroup	N	ORR	CR
DLBCL	73	68%	33%
PMBCL/TFL	20	80%	55%
Total	93	71%	38%

- Follow up ongoing
- Does not include responses after 1 month

American Society of Hematology

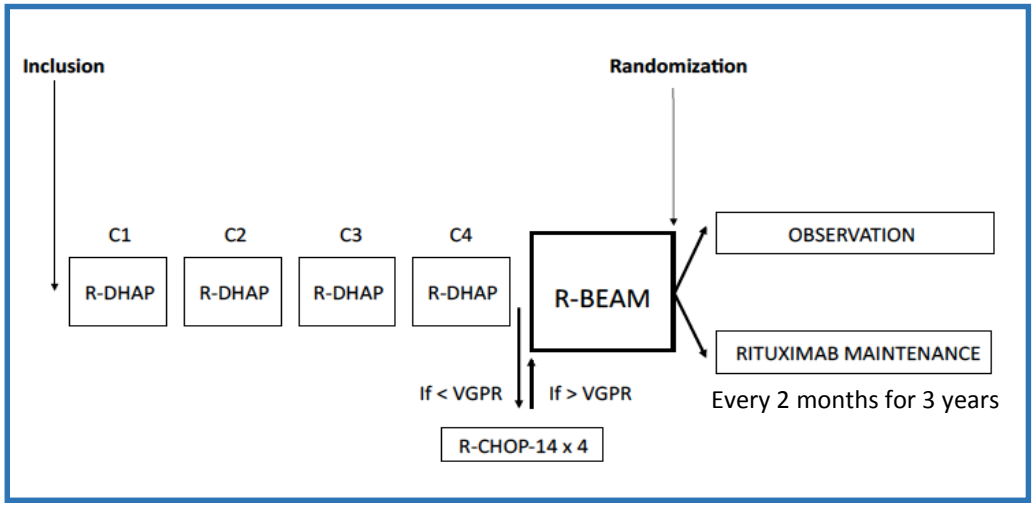
Multicenter feasibility/Safety

Schuster S # 3026[1]*, Neelapu Late breaking abstract 06*[2]

Front line treatment of MCL :
HDAraC + TX+maintenance strategy ?

Lyma study :
International, phase III, randomized trial
N=299 (n=240 at randomization 80%)
Median Follow up 50 months

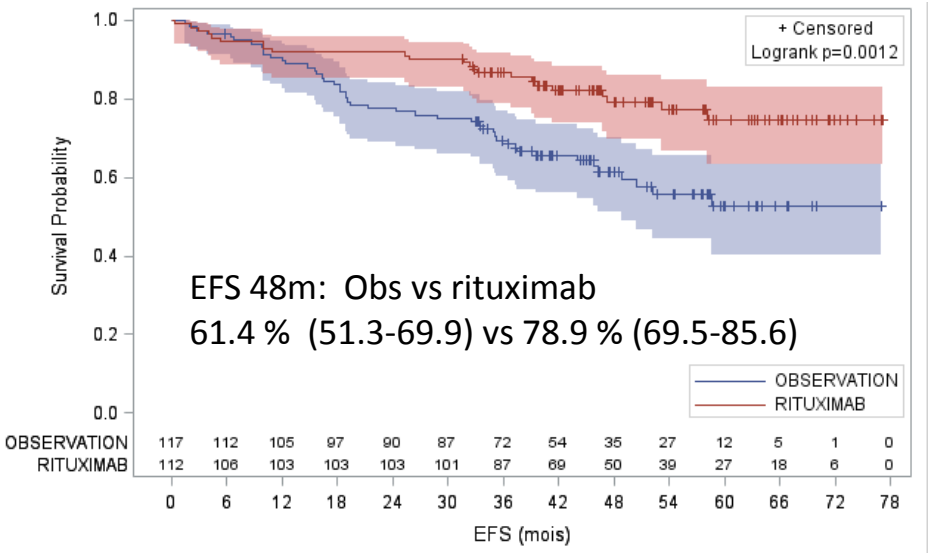
Key inclusion criteria:
Age 18-65 y
De novo MCL (presence of the t(11;14))



Response rate

Disease status-no.(%)	Observation n=120	Rituximab maintenance n=120
AFTER R-DHAP		
ORR	117 (97.5)	119 (99.2)
CR/CRu	104 (86.7)	102 (85)
AFTER ASCT		
ORR	120 (100)	119 (99.2)
CR/CRu	110 (91.7)	113 (94.2)

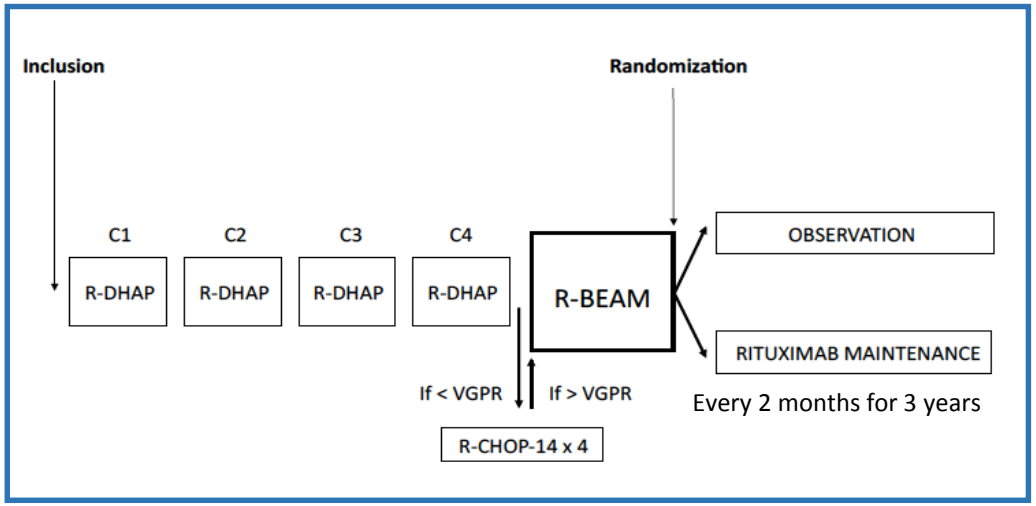
EFS (primary endpoint)



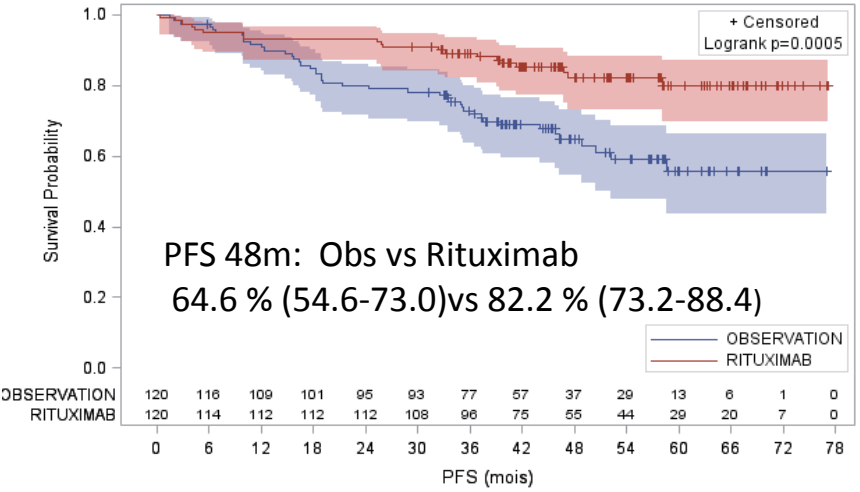
Courtesy of Le Gouill ASH 2013, Le Gouill S # 145

Front line treatment of MCL :
HDAraC +TX + maintenance strategy ?

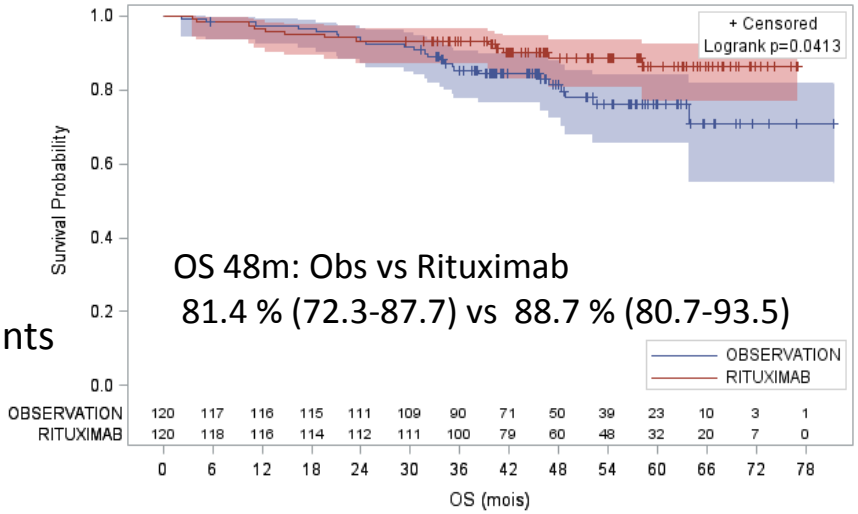
Lyma study :



PFS (secondary end point)



OS (secondary endpoint)



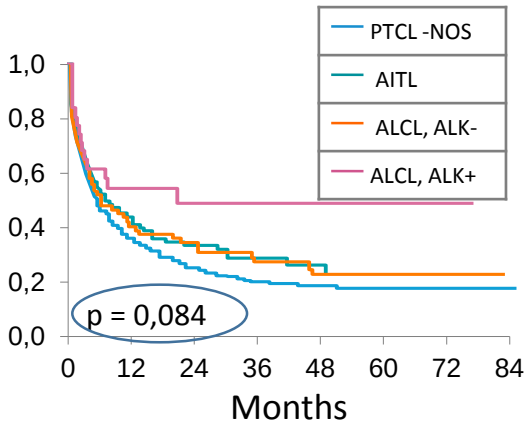
Conclusions:

- Rituximab maintenance 375mg/m2 should be recommanded to transplanted MCL patients
- Longterm disease control (PFS and EFS)
- Prolonged OS

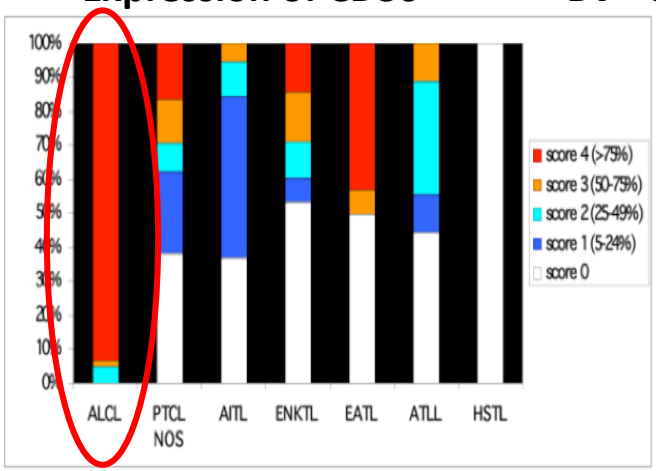
Courtesy of Le Gouill S # 145

Background

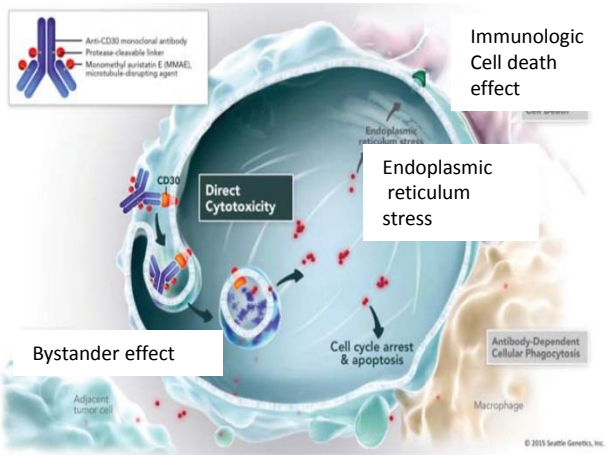
R/R T cell lymphomas (OS)[1]



Expression of CD30[2]

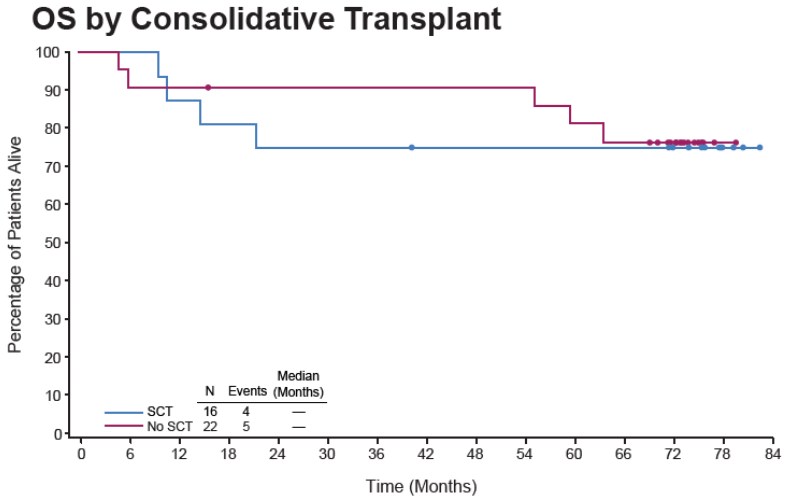


BV =CD30 directed antibody drug conjugate



R/R Anaplastic large T cell lymphoma

BV monotherapy in a phase II, open label study[3]
n=58 (42 =72 % ALK-)
38 patients achieved CR with BV monotherapy
16 underwent Transplant (8 allo, 8 auto)



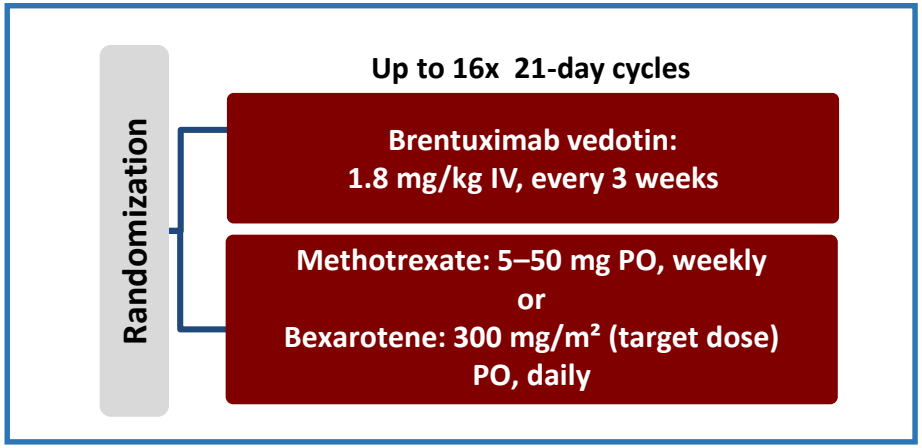
Frederico M # 0921[1] ,Bossard C Blood 2014[2] ,Pro B JCO 2012, Update Pro B # 4144[3]

Relapse/ refractory cutaneous T cell lymphoma

ALCANZA Study:
randomized, open-label, Phase III
n =128

Key inculions criteria

- Diagnosis of CD30+ MF or pcALCL
- ≥1 prior therapy
- ≥10% CD30+ on **either** neoplastic cells **or** lymphoid infiltrate



Patient characteristics:

	BV	MTX or Bexa
MF*, n (%)	48 (75)	49 (77)
Early (IA-IIA)	15 (31)	18 (37)
Advanced (IIB-IVB**)	32 (67)	30 (61)
pcALCL, n (%)	16 (25)	15 (23)
Skin only	9 (56)	11 (73)
Extracutaneous disease	7 (44)	4 (27)
Total number of prior therapies, median (range)	4.0 (0–13)	3.5 (1–15)

Endpoint	BV (n=64)	MTX or Bexa (n=64)	Statistical Significance
Primary endpoint			
ORR4, n (%)	36 (56.3%)	8 (12.5%)	p<0.0001
Key secondary endpoints			
CR, n (%)	10 (15.6%)	1 (1.6%)	p=0.0046
Median PFS, (months)	16.7	3.5	p<0.0001 HR=0.270 (95% CI: 0.169, 0.430)

reduction in patient-reported life quality symptom burden, measured by Skindex-29 (-27.96 vs -8.62)

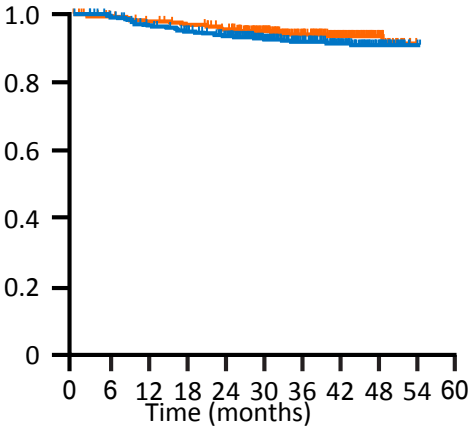
Conclusions:

- Improved efficacy of a BV over standard-of-care options
- Safety data consistent with established tolerability profile

Kim Y # 0182

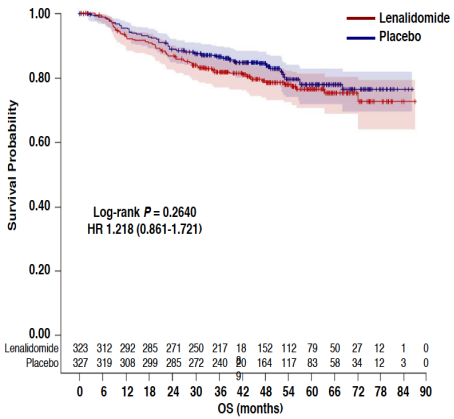
Conclusions

FL (Gallium Study)



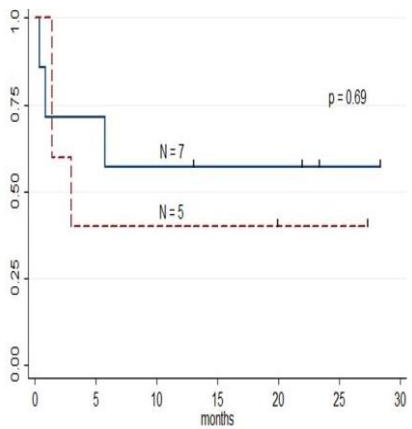
OS

DLBCL (REMARC study)



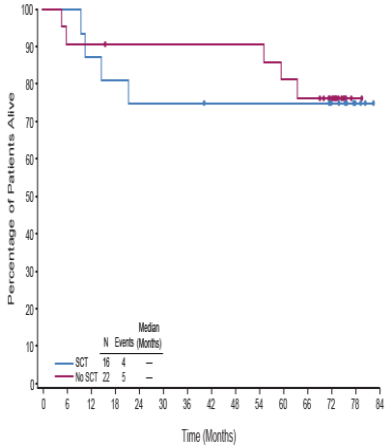
OS

R/R DLBCL (CAR)



PFS

R/R ALTCL (BV)



OS

- Is it the time to start tailoring therapy according to genomic profiling ?
- Personalized therapy starts with obtaining access to new drugs for individuals
- Individual therapy starts with making time to discuss with each patient

Thank you for your attention

Backup slides

Introduction · FLymphoma · DLBCLymphoma · MCLymphoma · PTCLymphoma

First line treatement of T cell lymphoma

BV CHP :
Front line PTCL , phase II (n=26)
Median follow up 52 months

Key inclusion criteria:
Adult PTCL (including 3 patients ALK+ IPI > ou = 2)
CD30 + if > ou= 1% maligan cells
Treatement :
Ajouter CVP++++
BV 1,8 mg /kg up to 16 cycles every 3 weeks
(No consolidative ASCT up front)
Tolerable safety profile
73% PNP (partially reversible)

Phase III randomized trial ongoing (NCT01777152 ECHELO

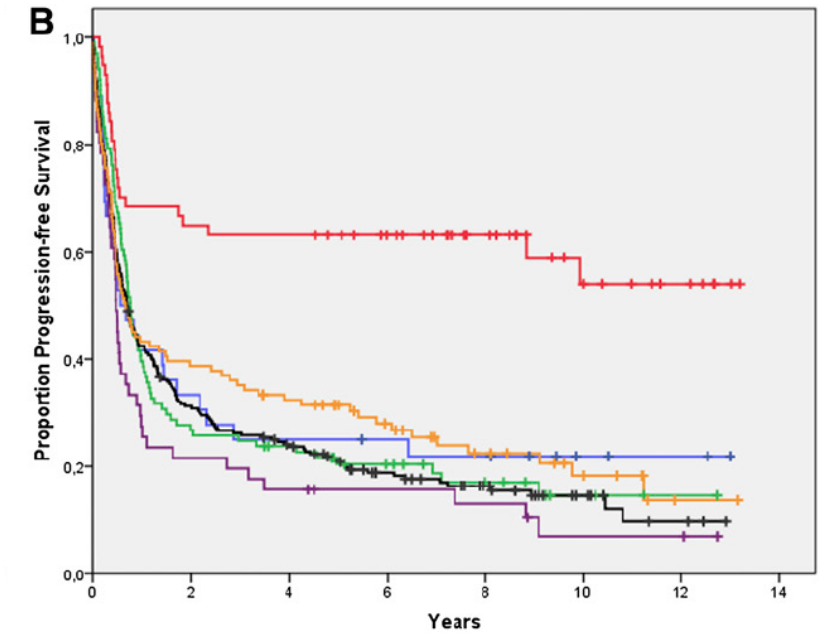
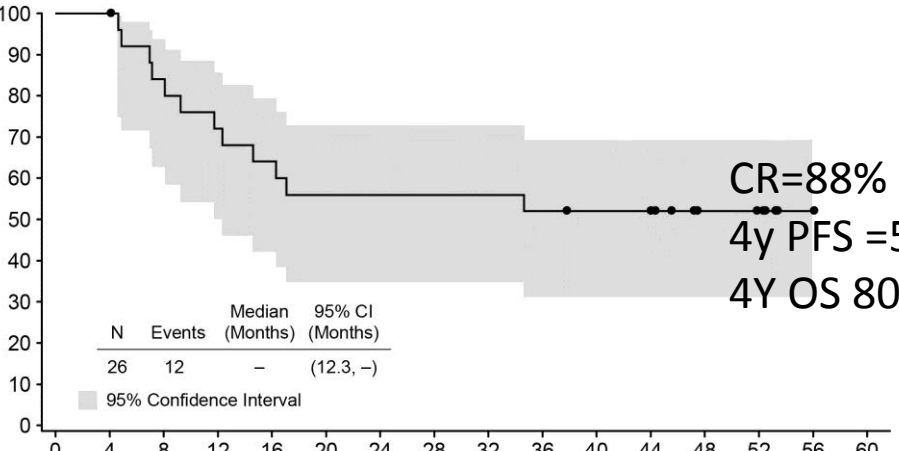


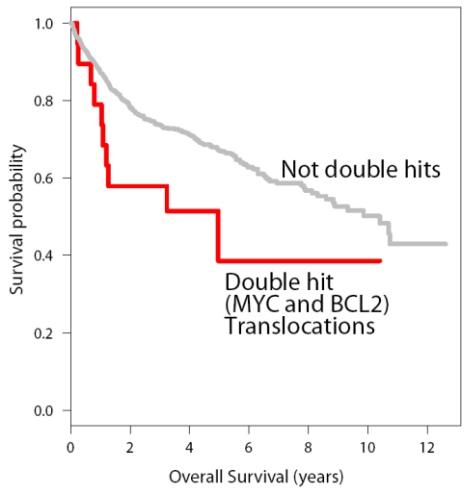
Figure 1. OS and PFS in 755 patients with PTCL. (A) OS among nodal subtypes: ALKpo (black line), AITL (green line), and TCL U (purple line). (B) PFS among nodal subtypes. ((green line), and EATL (black line). (D) PFS among extranodal subtypes.



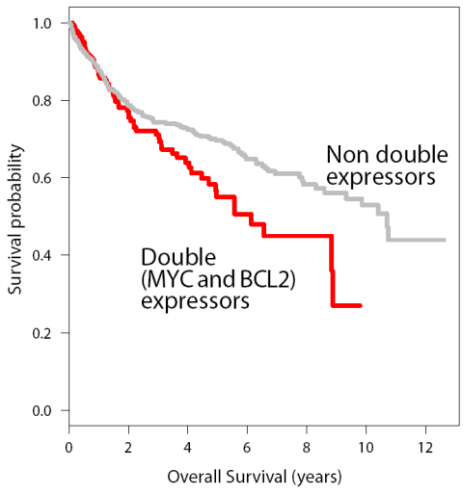
CR=88%
4y PFS =52%
4Y OS 80%

Fanale M #2993, Ellin F Blood 2014

MYC and BCL2 translocation and overexpression are associated with survival in DLBCL



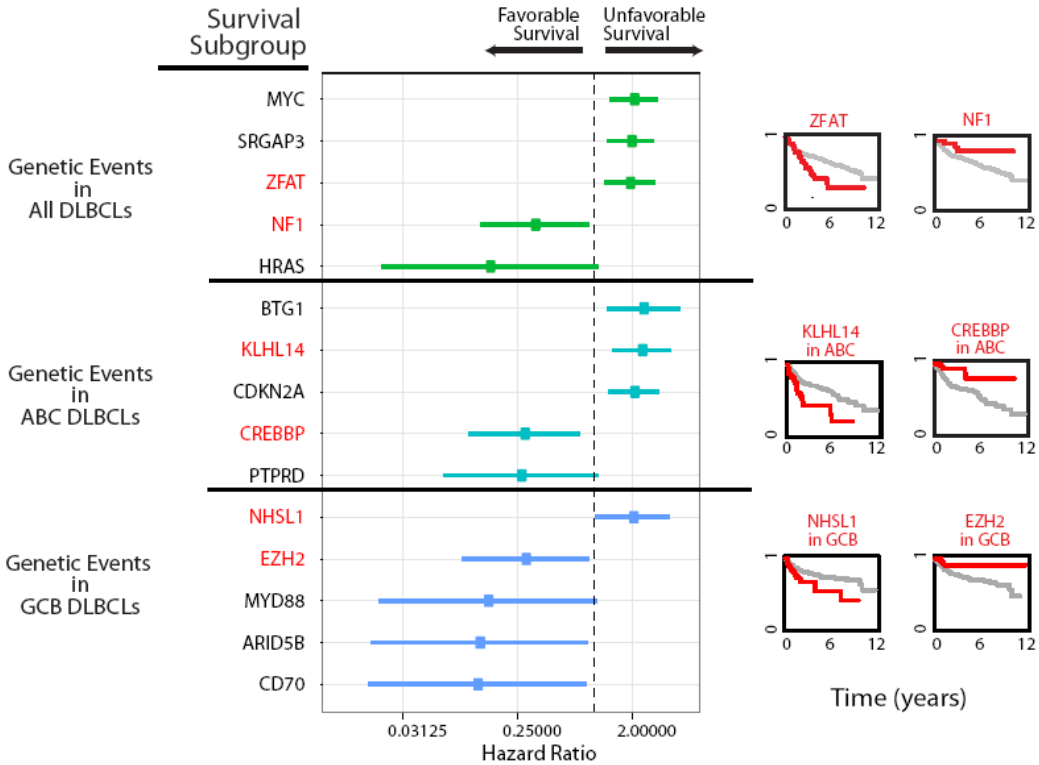
Translocation calls validated by FISH in over 500 cases



Expression values validated by IHC in over 500 cases

1001 DLBCL study

Univariate Analysis: Genetic Events Associated with DLBCL Survival



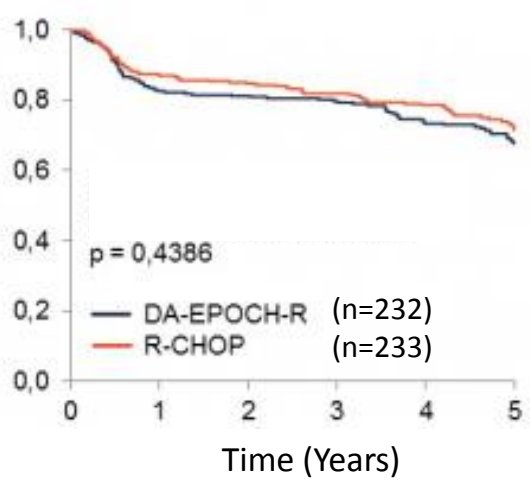
1001 DLBCL study

DLBCL

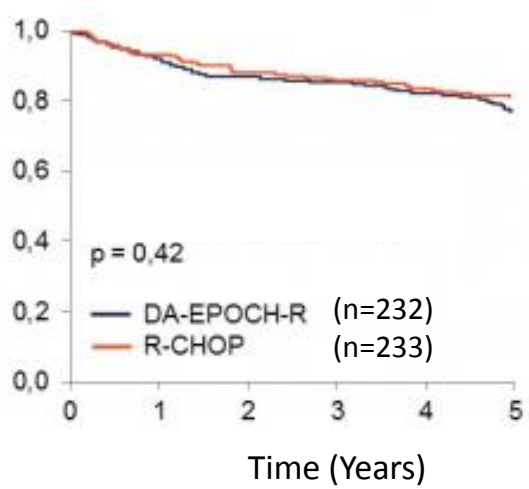
First line : improve RCHOP with R-DA-EPOCH?

CALGB/Alliance 50303 Study : Randomized phase III trial
N=524
Median follow up 5 years
Key inclusion criteria:
Age >18 y
De novo DLBCL, stade > or = 2
PMBCL (6,9% and 5,2%)

EFS (primary end point)



OS (secondary end point)



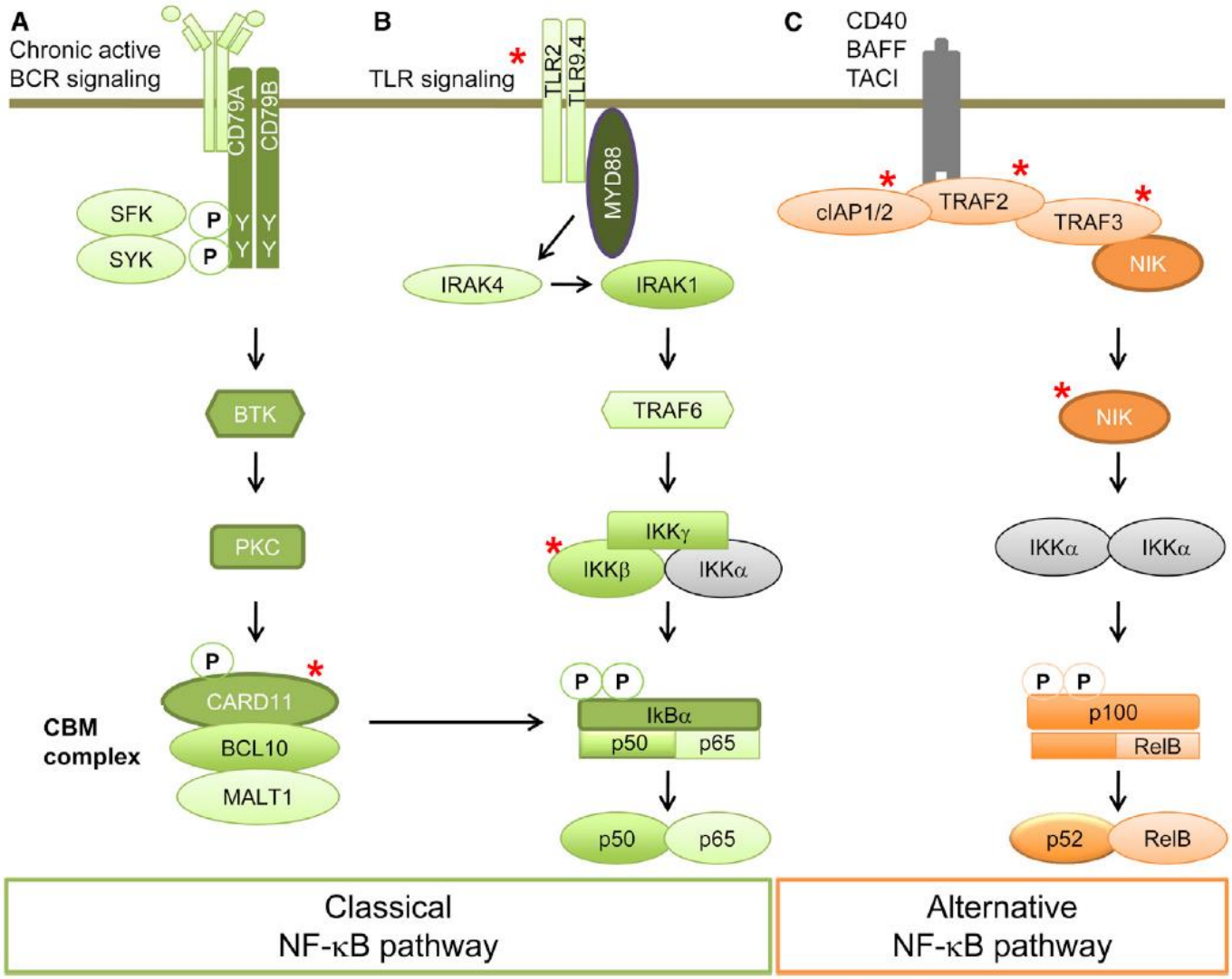
Toxicity profile : (RCHOP vs RDAEPOCH)

Neurtopenia :56% vs 90 %
Febrile neurtopenia :19% vs 37%
Treatement discontinuation: 1,7% vs 5,6%

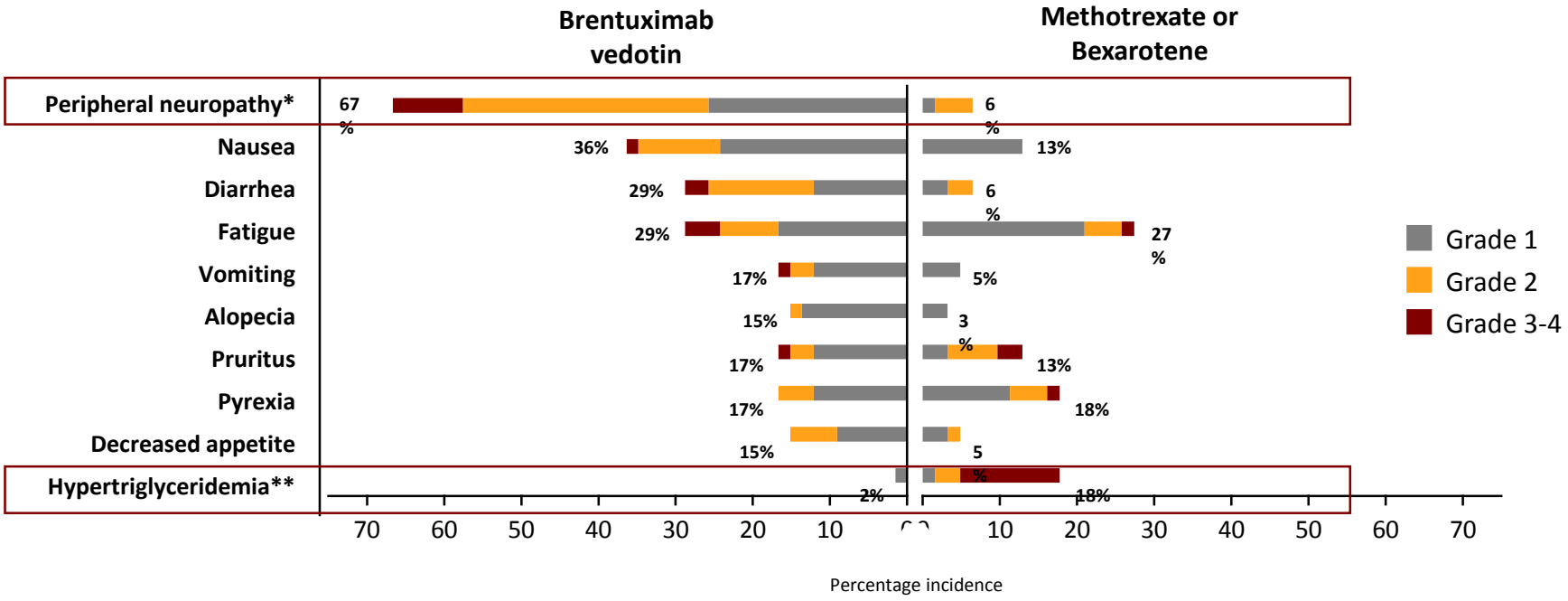
No Subgroup analysis
for PMBCL or Double HIT lymphoma

Bartlett N, # 469

NFκB & Ibrutinib



Commonly reported (≥15% of patients) treatment-emergent AEs



*No Gr 4 peripheral neuropathy was reported in the brentuximab vedotin (26% Gr 1, 32% Gr 2, 9% Gr 3) or physician's choice arms (2% Gr 1, 5% Gr 2). At last follow-up (median 22.9 months), 36/44 (82%) patients in the brentuximab vedotin arm had improvement or resolution of peripheral neuropathy.

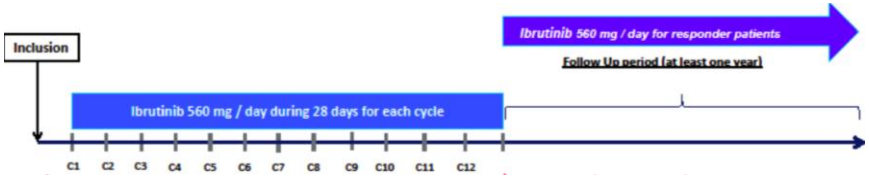
**Elevated triglycerides, were reported in 2% of patients receiving brentuximab vedotin versus 30% of patients receiving bexarotene (14% Gr 3, 8% Gr 4)

Length of drug exposure: median 12 cycles (36 weeks) of BV vs. 17 weeks of bexarotene or 9 weeks of methotrexate

Relapse/refractory Primary CNS lymphoma
« 2 Proof of concept phase II study »

iLOC Study : Ibrutinib [1]

Rational:
Single agent activity R/R DLBCL[2]
High rate of Myd88 and CD79b mutations
Preclinical data in PCNSL[3]
n=18

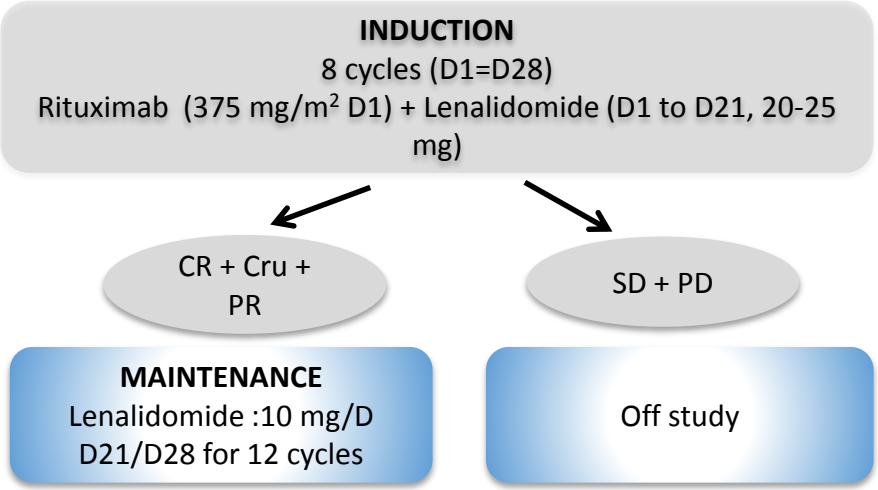


Disease control rate (CR+PR+SD)@2 months (primary objective):

- High DC rate (83%) @ 2 months
- ORR (55%) @ 2 months in R/R PCNS
- Responses in the 3 compartments: Brain, Isolated ocular disease, CSF

REVRI Study : Rituximab-Lenalidomide [4]

Rational: association active in R/R DLBCL[5]
n=45 (a majority with > 2 line of therapy))



	CR+ uCR	PR	SD/PD
After Cycle 1	9 (20 %)	19 (42 %)	9 (20%)
After Cycle 4	16 (36%)	5 (11 %)	6 (14%)
After Cycle 8	13 (29 %)	3 (7 %)	26 (57%)
	ORR (primary objective) = 35.6 % [21.9-51.2]		

Soussain C # 0784,Wilson Nat med 2015[2], Soussain C # 4170, Soussain C # , Wang Leukemia 2016[5]

Relapse/refractory Primary CNS lymphoma
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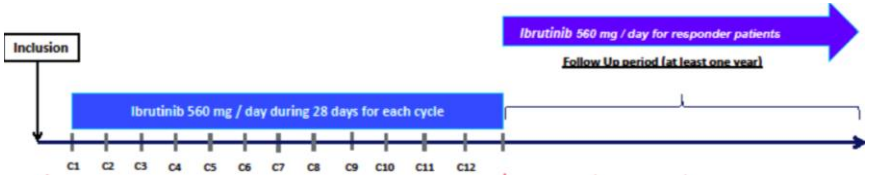

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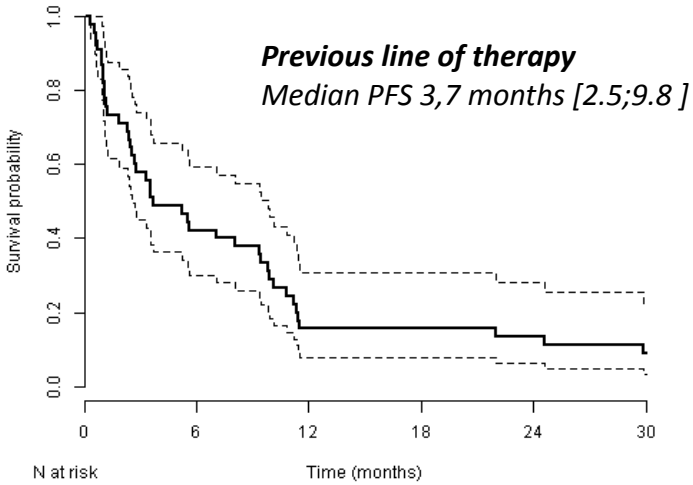

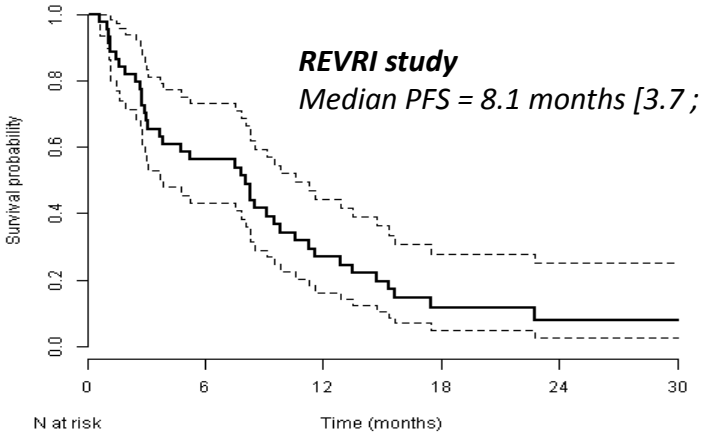

Soussain C # 0784,Wilson Nat med 2015[2], Soussain C # 4170, Soussain C # , Wang Leukemia 2016[5]

Safety Outcomes of Allo-HSCT After Nivolumab

	BV naïve post-ASCT Cohort A (n = 63)	BV post-ASCT Cohort B (n = 80)
Proceeded to allo-HSCT, n	**6**	**11**
Median time from last nivolumab dose to allo-HSCT, days (range)	**158 (27–411)**	**38 (23–271)**
Received additional therapy between nivolumab and allo-HSCT, n	**4**	**3**
Safety outcomes		
Grade 2–4 acute GVHD	**0**	**4**
Grade 3–4 acute GVHD	**0**	**1**
Transplant-related mortality	**0**	**0**

- No death due to disease progression was reported among patients who proceeded to allo-HSCT