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# Aggressive lymphomas ASH 2015

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# LNH-84 Regimen: A Multicenter Study of Intensive Chemotherapy in 737 Patients With Aggressive Malignant Lymphoma

By Bertrand Coiffier, Christian Gisselbrecht, Raoul Herbrecht, Hervé Tilly, André Bosly, and Nicole Brousse

**Table 1. Distribution of Patients According to Working Formulation Histologic Types of Phenotypes**

| Histologic Subtypes | N | (%) | Immunophenotype B | T | Nontyped |
|---|---|---|---|---|---|
| Intermediate-grade | | | | | |
| Follicular large-cell | 25 | (3) | 8 | — | 17 |
| Diffuse small–cleaved-cell | 17 | (2) | 7 | 4 | 6 |
| Diffuse mixed | 122 | (17) | 25 | 37 | 60 |
| Diffuse large-cell | 278 | (38) | 110 | 16 | 152 |
| High-grade | | | | | |
| Immunoblastic | 160 | (22) | 35 | 37 | 88 |
| Lymphoblastic | 25 | (3) | 2 | 12 | 11 |
| Small–noncleaved-cell | 36 | (5) | 19 | — | 17 |
| Others | | | | | |
| Ki-1+ | 16 | (2) | — | 8 | 8 |
| Unclassified | 41 | (6) | 6 | 4 | 31 |
| Unclassifiable | 17 | (2) | 5 | 5 | 7 |
| Total | 737 | | 217 | 123 | 397 |

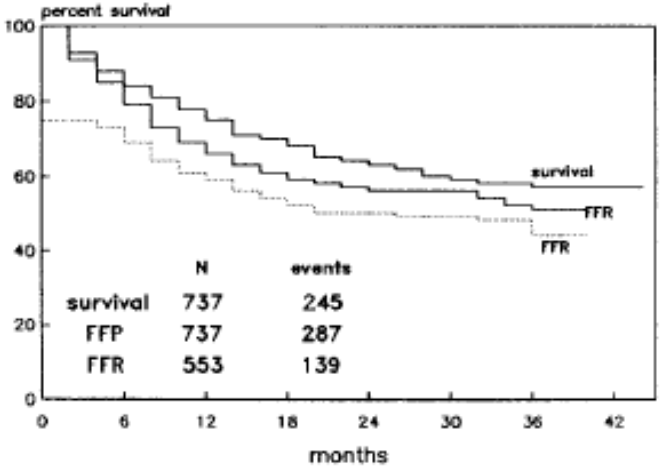
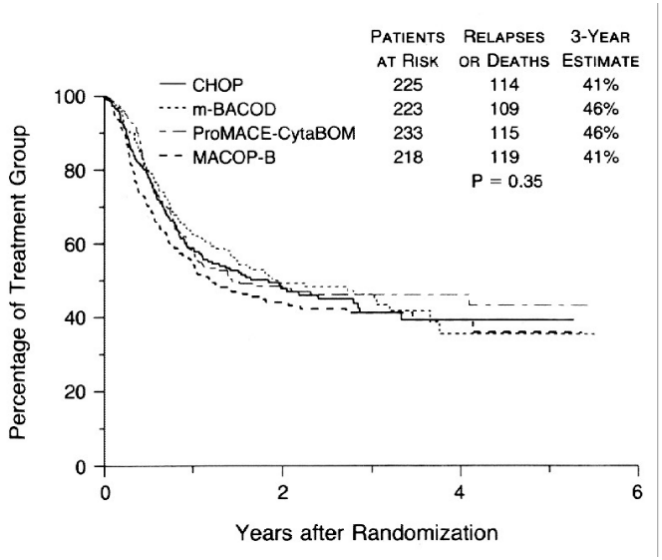
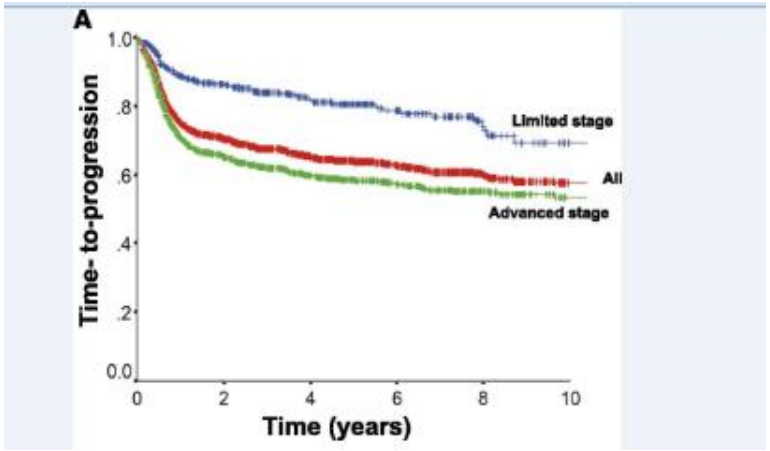



**Fig 2. Overall survival (S), time to failure (TTF) survival, and time to relapse (TTR) survival of the 737 patients with aggressive lymphoma included in the LNH-84 protocol.**



CHOP

1992

2002

R-CHOP

For DLBCL

~~High dose chemo With PBSCT~~

# Aggressive lymphomas

1. DLBCL
2. Primary Mediastinal Lymphoma
3. CNS lymphoma
4. Burkitt lymphoma
5. Mantle cell lymphoma
6. Take home message

# Not all lymphomas are equal

**Treating all DLBCL with RCHOP is no longer appropriate.**

We are moving quickly to "precision medicine" approach to treatment of DLBCL.

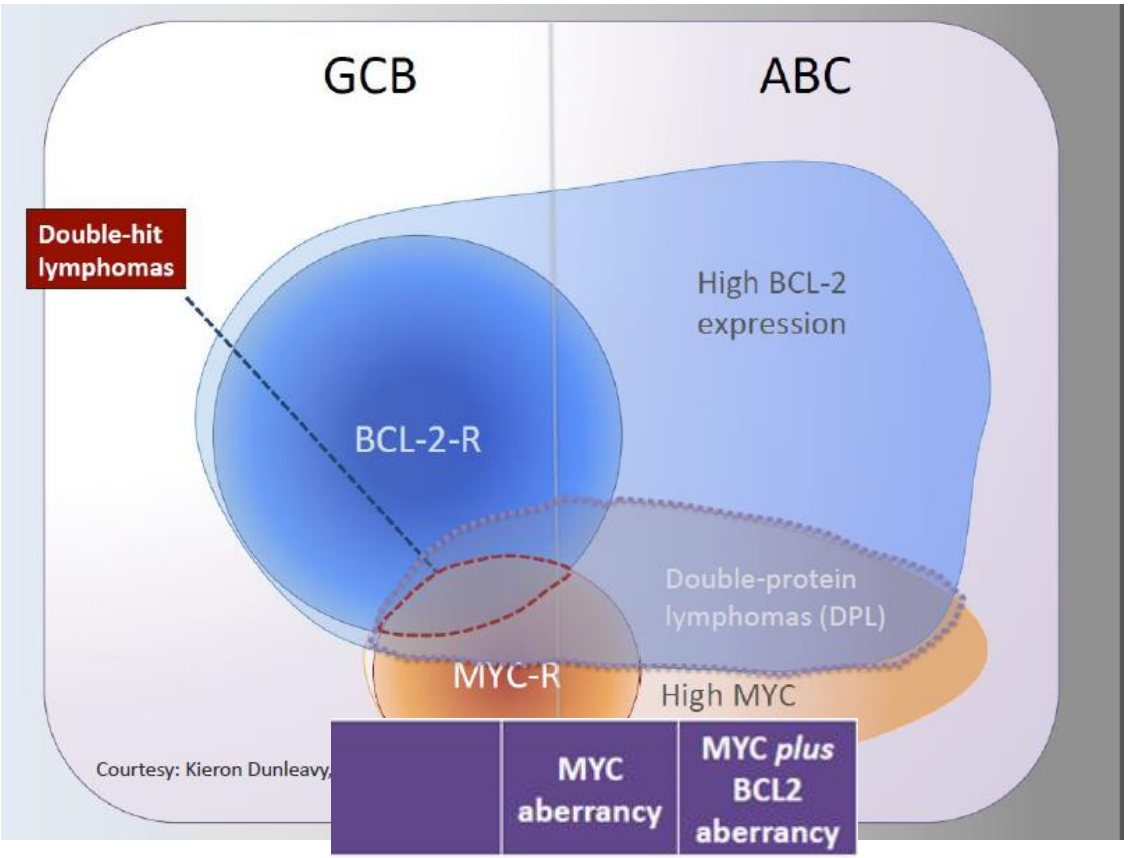
Jonathan Friedberg, ASH 2015

1. Diagnostic accuracy and prognosis
2. New treatments for subgroups ?

# Double Hit and Double Expression lymphomas (DHL/DEL)

- DHL: studies show these are very aggressive with median survivals of < 1 year
  - MYC-R in combination with either BCL2-R or BCL6-R
  - Immunophenotype is usually of GCB (80-90 %)
  - MYC/BCL6 DHL may differ from MYC/BCL2
- DEL : IHC positive for MYC and BCL-2
  more ABC than GCB

# DHL or DEL




| | MYC aberrancy | MYC *plus* BCL2 aberrancy |
|---|---|---|
| IHC | 37% | 26% |
| FISH | 12% | 8% |

% of DLBCL cases

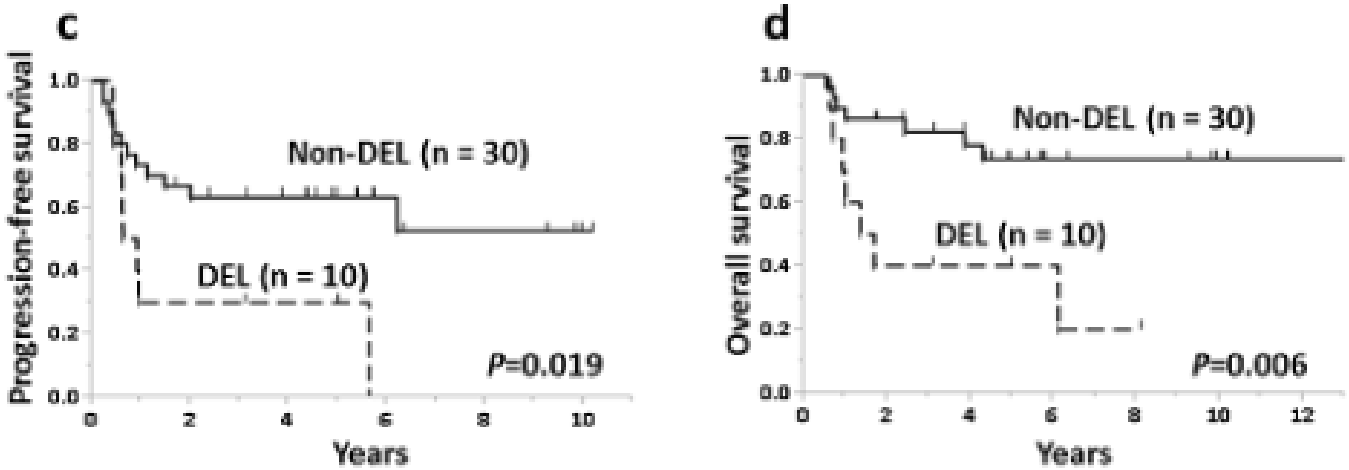
## DHL : FISH

| pathology | |
|---|---|
| DLBCL | 50 % |
| BCLu | 48 % |
| **Partner** | |
| BCL2 | 87 % |
| BCL6 | 8 % |
| **COO** | |
| GCB | 90 % |
| ABC | 9 % |

## DEL : IHC

| COO | |
|---|---|
| GCB | 35 % |
| ABC | 65 % |

# DEL : inferior outcome

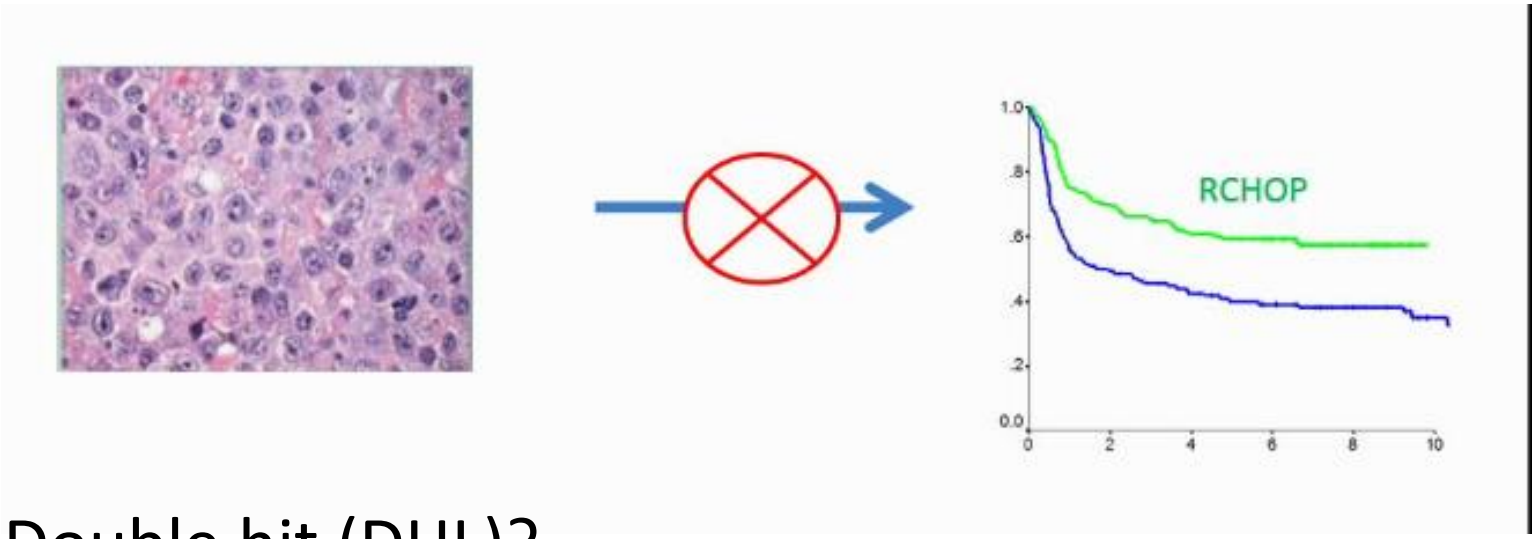



Figure

Takahashi, ASH 2015

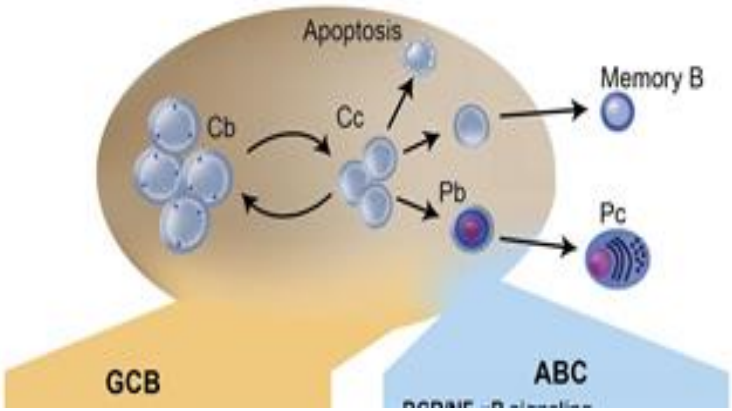
ALL patients were treated with intensive induction and autologous SCT

# Diagnostic accuracy: pathology




1. Double hit (DHL)?
   - Fish for MYC: all cases ? if GCB or if Myc+ on IHC ?
   - if positive: FISH for BCL-2 and BCL-6
2. IHC for MYC and BCL-2: Double expression (DEL) or Double Protein Lymphoma (DPL)
3. Cell of origin (COO): GCB or ABC: IHC or GEP ?

# COO: ABC or GCB: implications for treatment ?



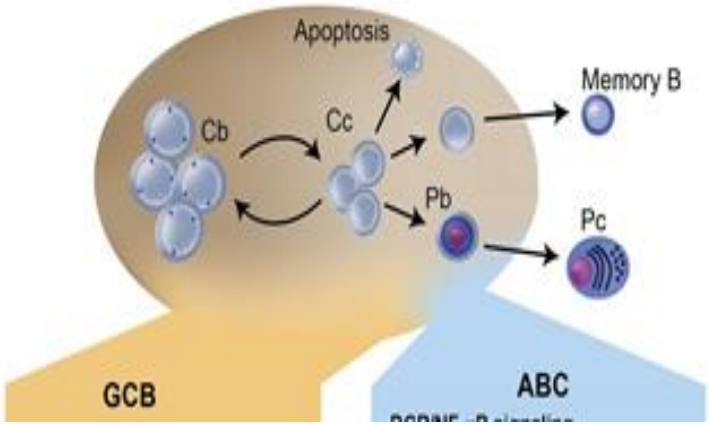

**NO**

Remodl-B-Trial : 1147 patients: classification by GEP
(Barrans, ASH 2015)

ABC 23 %
GCB 44 %
unclassified 19 %
unsuitable 14 %

Difference in prognosis ? Not always confirmed

# COO – directed treatment: ?
# ABC subtype




BCR/Nfkappa B signalling
CD79A/B, CARD11, MYD88 mutations

CREBBP mutations

MYC translocations, MYC and BCL2 protein overexpression

JAK/Stat activation

→ bortezomib

→ BCRi
Ibrutinib,…

→ lenalidomide

# ABC subtype: bortezomib ?

3 randomised trials : no effect if bortezomib added to R-CHOP

- LYM-2034 trial, ICH; Offner, Blood 2015
- Remodl-B trial: GEP; Davies, ASH
- Pyramid trial: IHC; Leonard, ASH

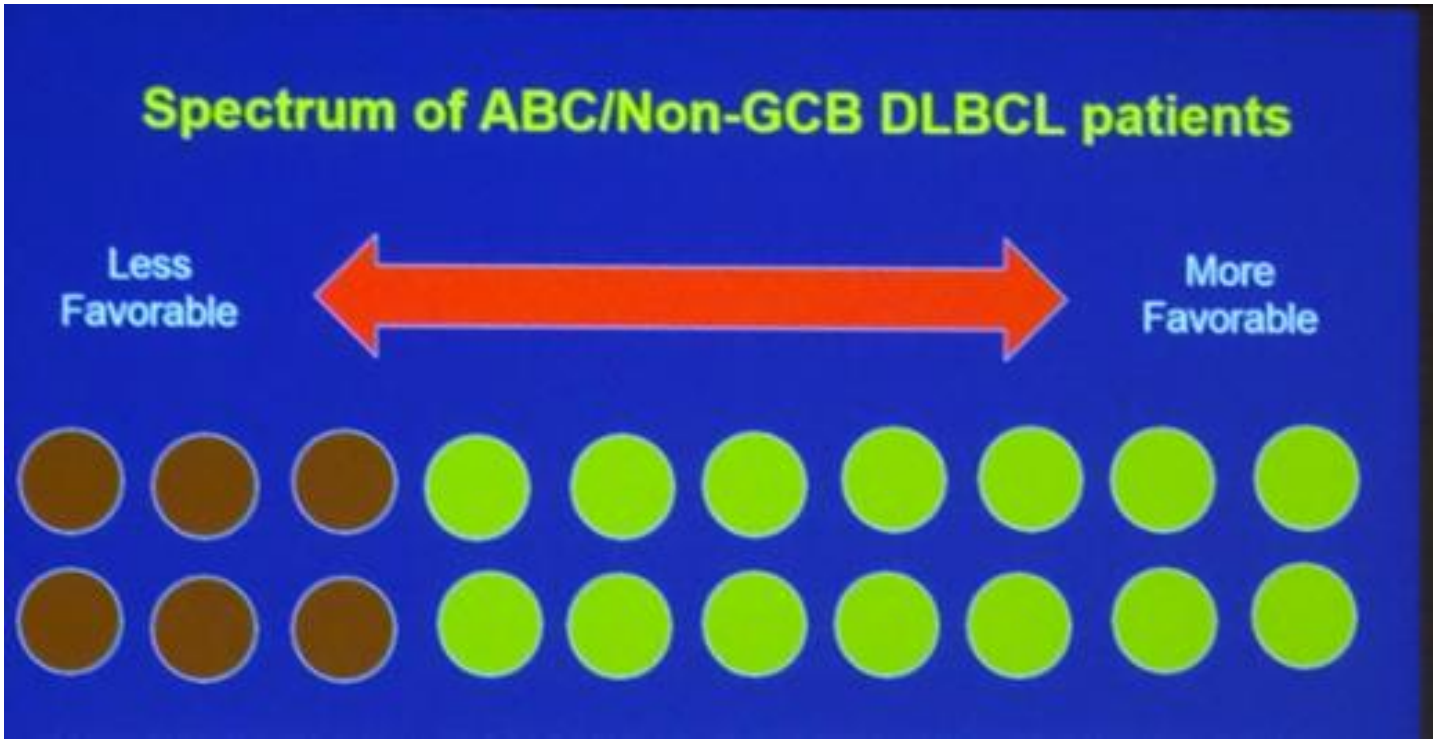
R-CHOP for ABC did better as expected

reason ?

IHC vs GEP ?

selection of good patients ?

……..



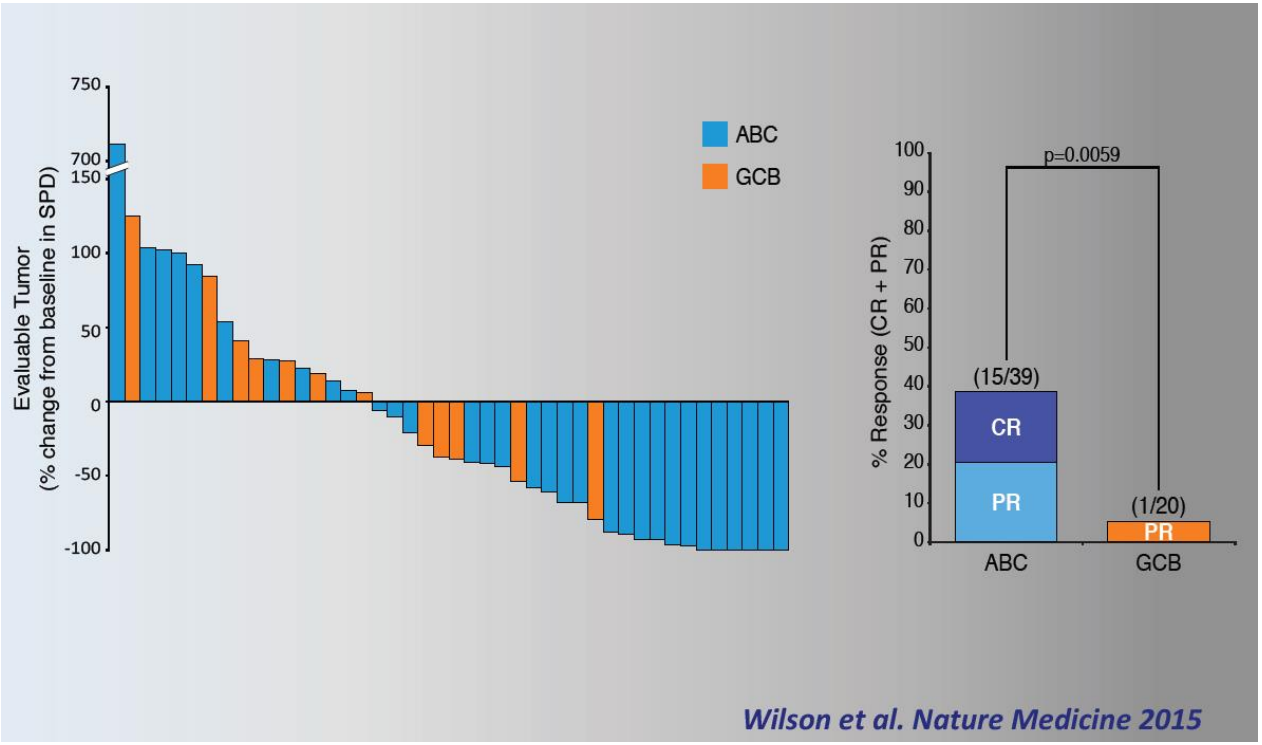

**Excluded due to concerns about delays/risk**

**Randomised in a selected patient Population (who could wait for evaluation/randomisation)**

# ABC subtype: BCRi ?

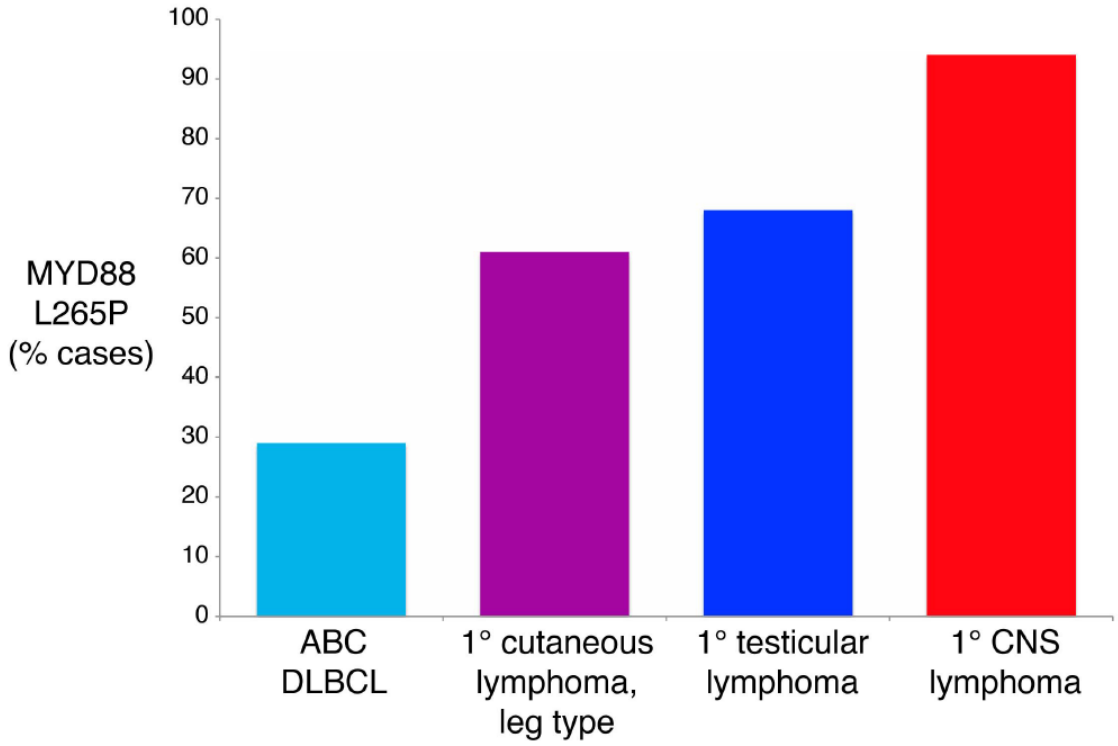
ABC subtype: trials running

BCRi: ibrutinib



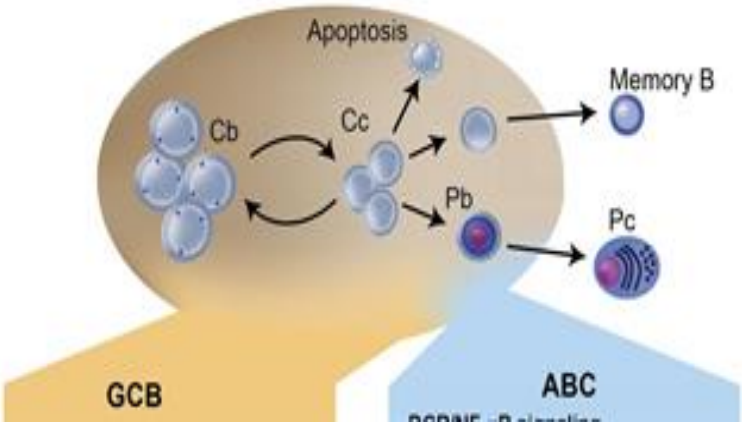
# BCR inhibitors in DLBCL ?

## High Prevalence of *Myd88* L265P Mutation in Extra-nodal DLBCL with an ABC Phenotype




K Dunleavy, ASH

# COO – directed treatment ?
# GCB subtype




EZH2 mutations
MLL2 mutations
CREBBP mutations

→ TAZEMETOSTAT (Ribrag)

MYC and BCL2
Translocations (DHL)
and DEL

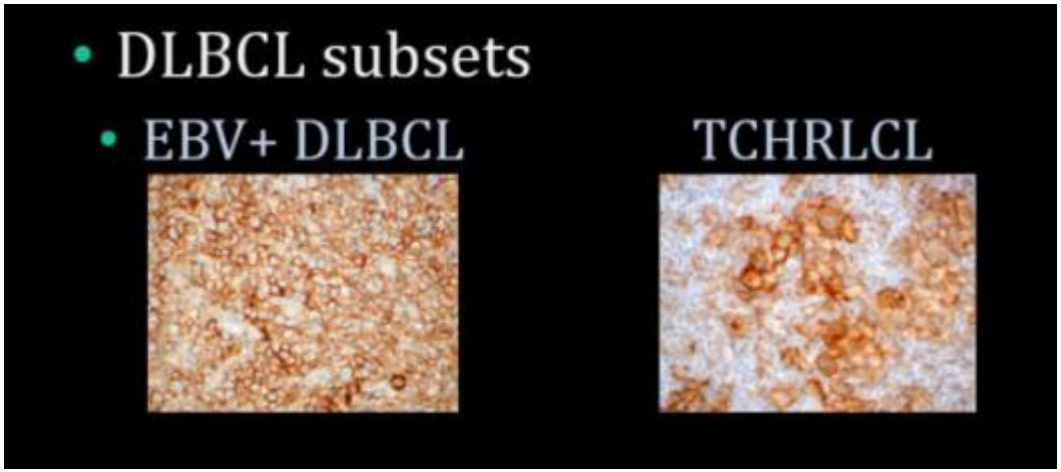
→ DEL/DHL: downregulation of expression of myc
CUDC-907 (Younes)
SEL24 (Jablonska)

PTEN deletion

# Checkpoint inhibitors in DLBCL ?

Generally not very effective: ORR 35 %, but response not durable

DLBCL subsets: EBV+ DLBCL, T-Cell Rich LCL: PD-L1 positive ?




But: assays differ, dynamic event, mutational load, microenvironment, no good correlation with response (myeloma,FL)…

# CAR-T cells in relapsed DLBCL

Modified T Cells against CD-19

overall response in R/R DLBCL 47 %

side effects:

- cytokine release syndrome: also dependend on lymphodepletion chemotherapy before infusion of CAR T cells
- Neurotoxicity

All pts in CR remain in CR

# Primary mediastinal lymphoma

- First line treatment: DA-EPOCH, no radiotherapy (?)
- Relapsed patients: checkpoint inhibitor ?

Genetically related to Hodgkin lymphoma: 9p24 copy gain/ amplification in 60 – 70 %
Frequent PDL-1L expression

Phase I pembrolizumab (Zinzani, ASH)

ORR 40 % , mostly partial
duration of remission > 1 y

phase 2 study launching

# CNS lymphoma: first treatment

**MSKCC: Transplant (n = 32)**

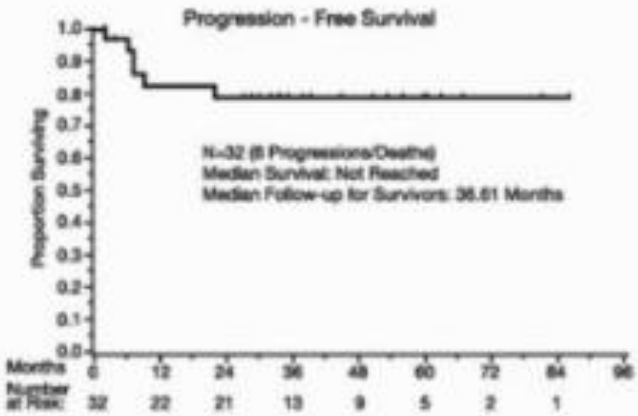
R-MPV x 5-7 cycles

PD → Off

PR/CR → TBC + ASCT

R-MPV: R (500/m2); Mtx(3.5 g/m2); Vcr (1.4 mg/m2); Procarb (100 mg/m2 D2-8)

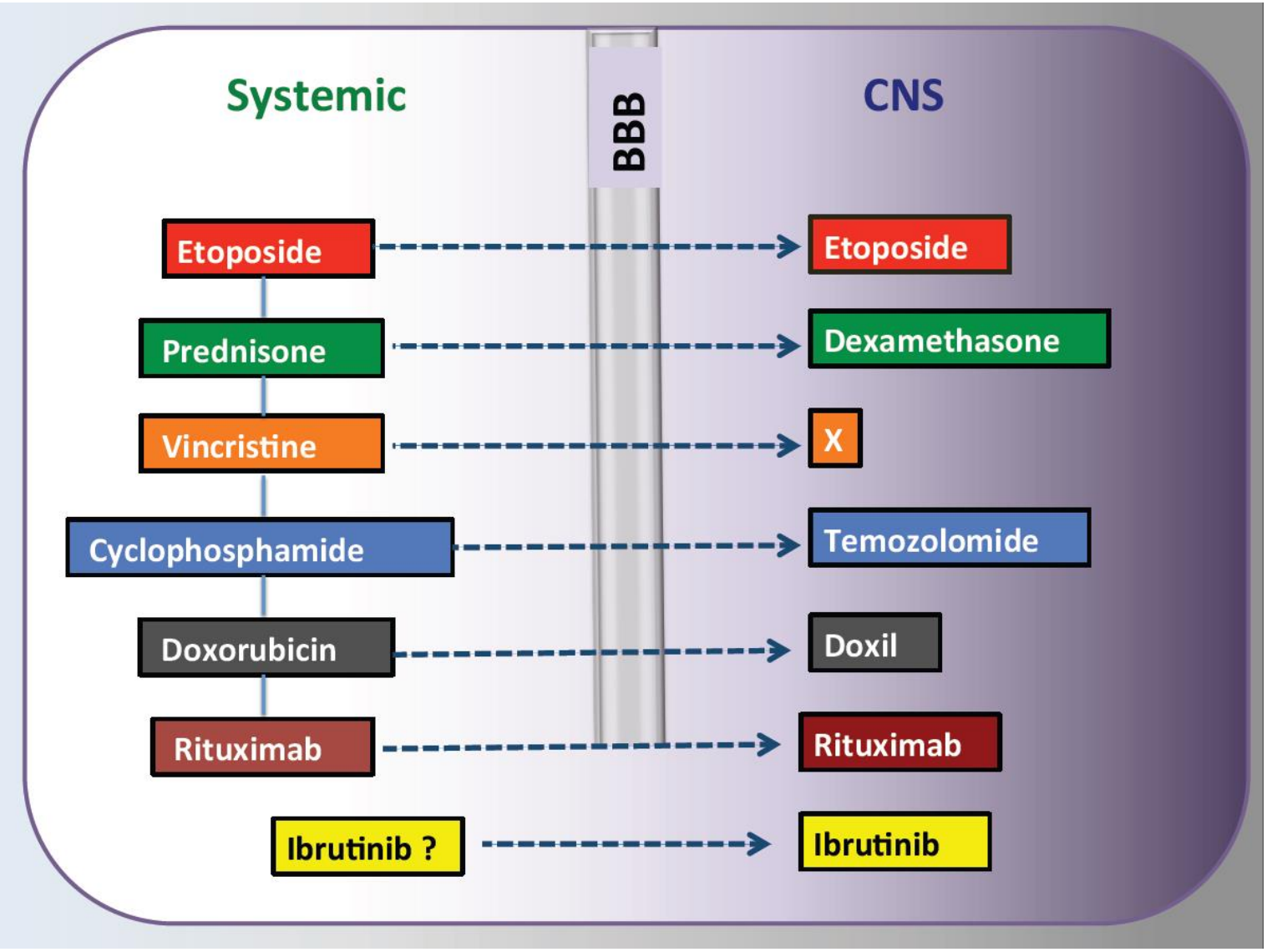
TBC: Thiotepa (250 mg/m2 x 3); Bu(3.2 mg/kg x 3) Cyclo (60 mg/kg x 2)




8 Omuro et al. Blood 2015; 125:1403-1410

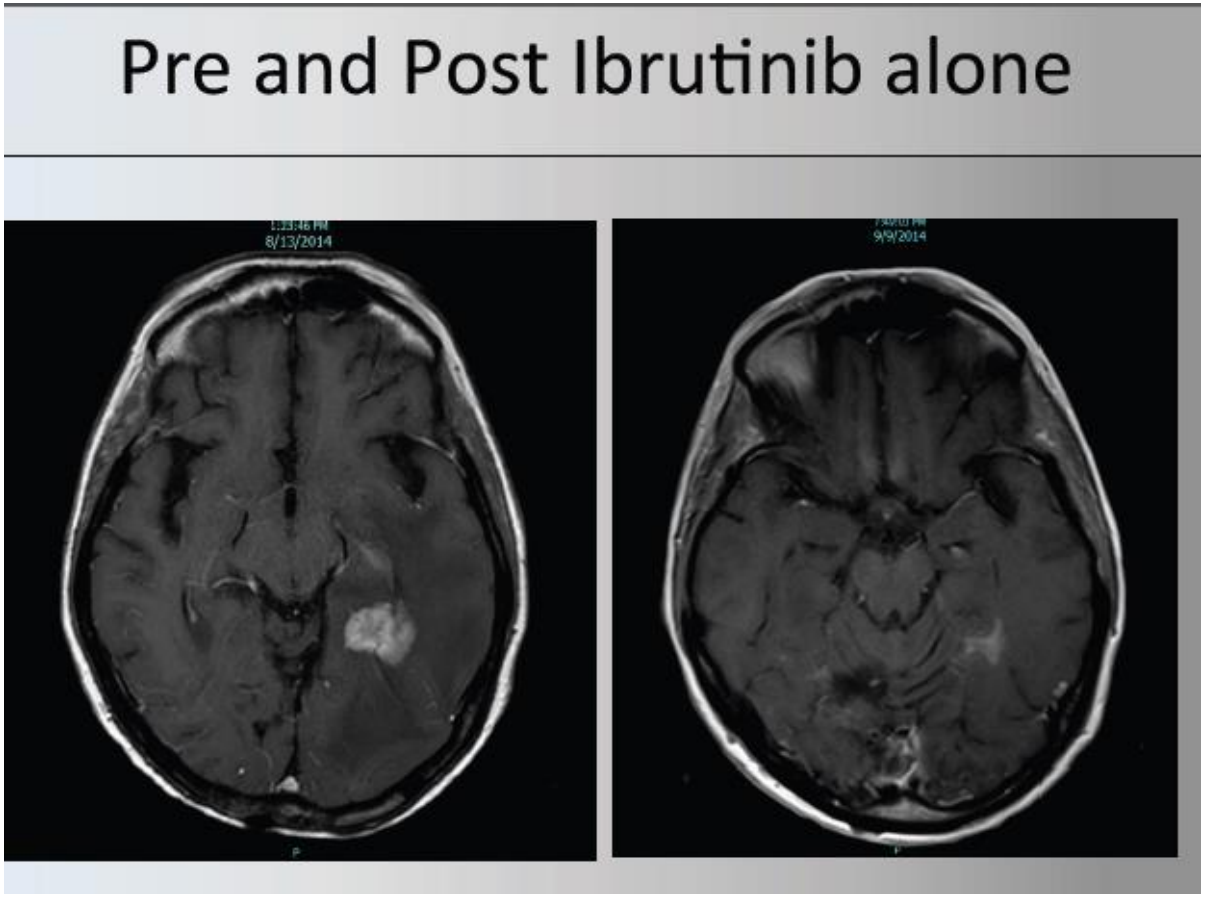
For fit patients: autologous transplantation standard of care ?

# CNS lymphoma: DA-TEDDI

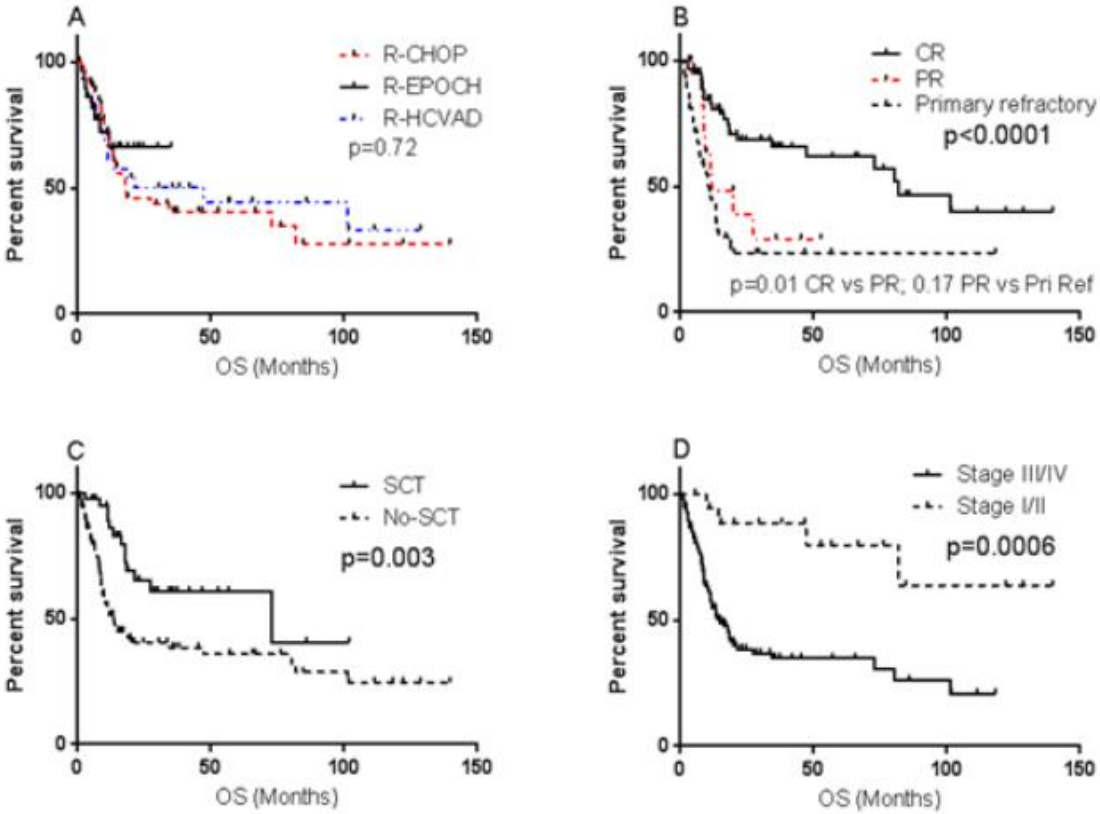


# CNS lymphoma: relapse

ibrutinib ?



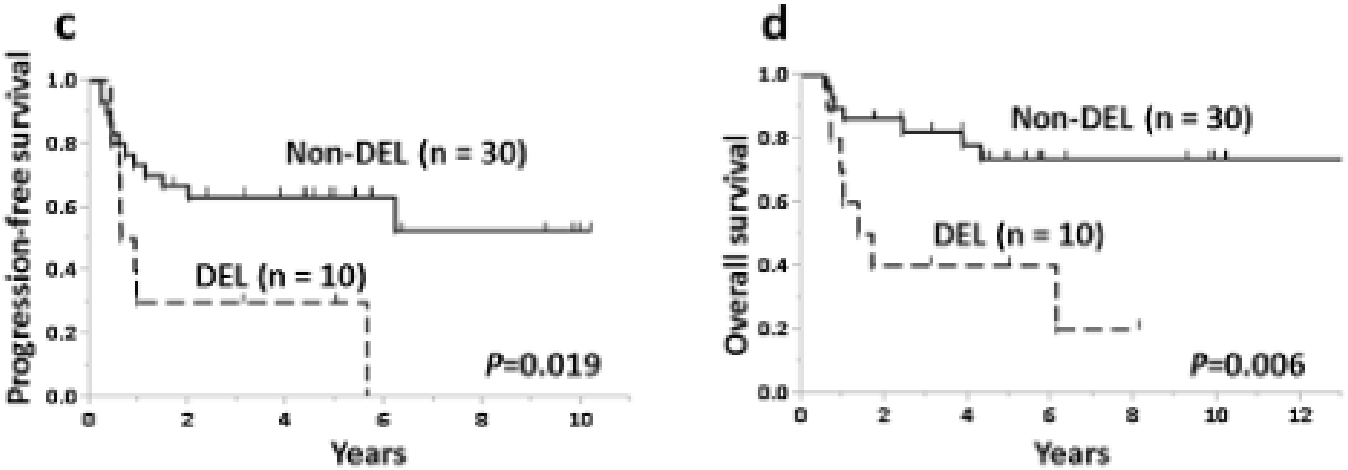
# DHL lymphoma




Saksena, ASH 2015
157 pts with DHL

- Intensive induction ?
  RCHOP not enough
- most important:
  - CR
  - Stage
  - auto SCT

# DEL lymphoma




Figure

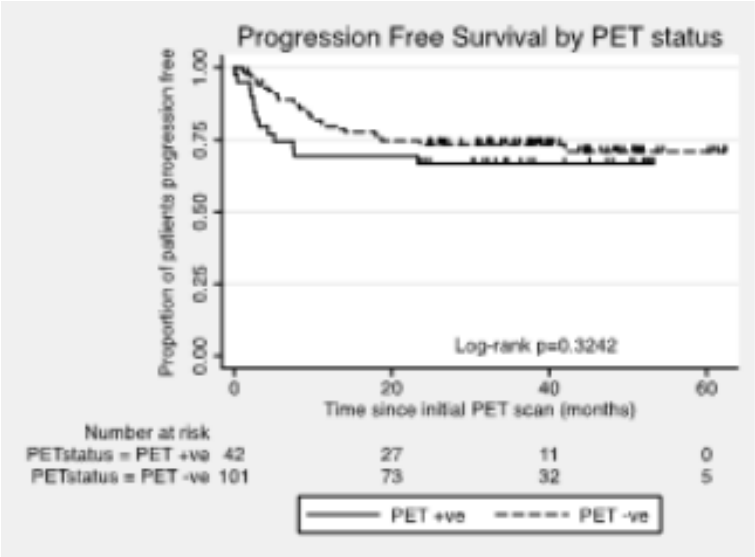
- No good data on best induction therapy; R-CHOP poor outcome
- Role of transplant is not well studied
- Urgent need for better induction treatment

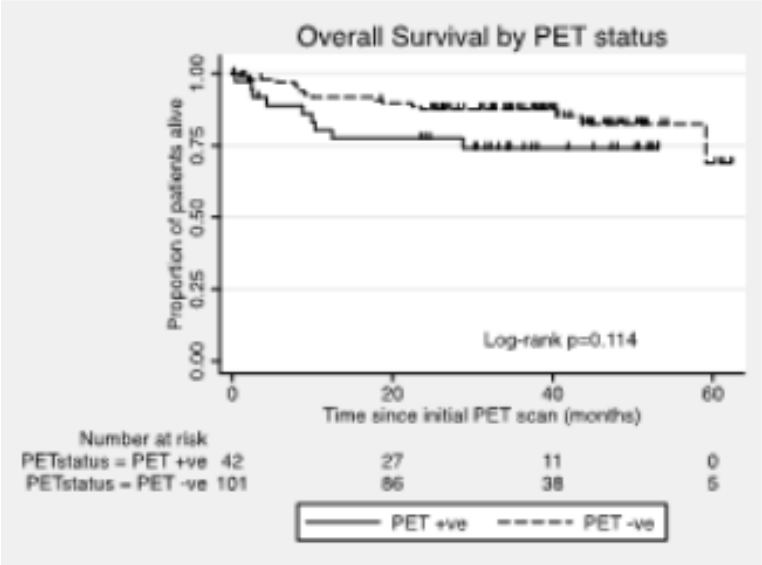
# First-line autotransplants in DLBCL ?

No benefit for consolidative autotransplants in low, intermediate or high-intermediate risk

Potential benefit for early autotransplant in PFS/OS for high risk/DHL/DEL

Pts with PET positive responsive disease after routine induction: biopsy and if not in CR : appropriate candidates for autologous transplant (after salvage chemotherapy ? )




R-CHOP
PET/Ct after 4 cycles

Negative

Positive

R-ICE

Z-BEAM

Herzberg, ASH 2015

# Mantle cell lymphoma

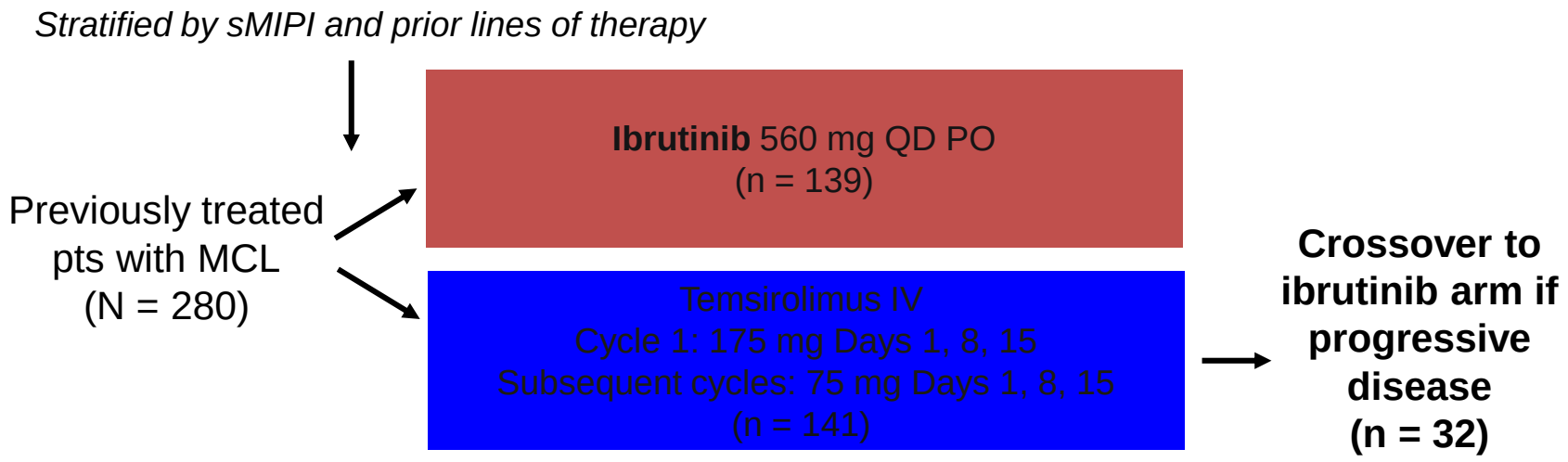
Rituximab maintenance after chemo/autoSCT: effective on PFS
(LYMA, ASH 2015; Toronto, ASH 2015)

Bortezomib maintenance after chemo/autoSCT : no effect
(HOVON,ASH 2015)

Ibrutinib maintenance after chemo/autoSCT: study starting
(TRIANGLE)

# Mantle cell lymphoma: MCL3001 (RAY):

- Randomized, open-label phase III trial



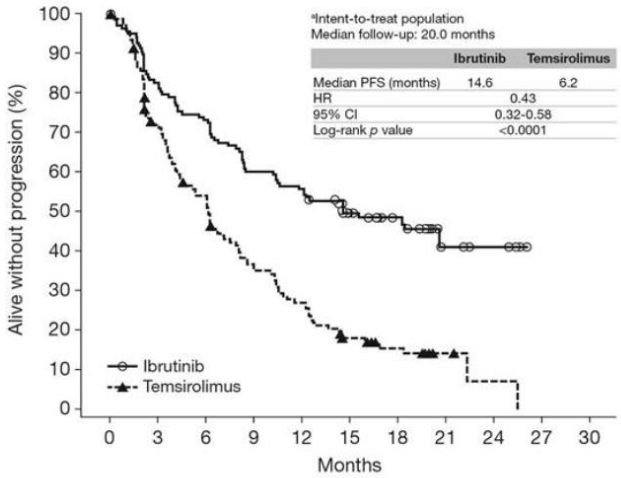

- Primary endpoint: PFS
- Secondary endpoints: ORR, OS, DoR, time to next treatment, and safety

# MCL3001 (RAY): Survival Outcomes

| Outcome | Ibrutinib (n = 139) | Temsirolimus (n =141) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| Median PFS, mos | 14.6 | 6.2 | 0.43 (0.32-0.58) | < .0001 |
| 2-year PFS rate, % | 41 | 7 | | |
| Median PFS2,* mos | 19.1 | 11.3 | 0.49 (0.36-0.69) | < .0001 |
| Median OS, mos | Not reached | 21.3 | 0.76 (0.53-1.09) | .1324 |

*After 1 subsequent line of therapy

Figure 1. IRC-Assessed PFS[a]

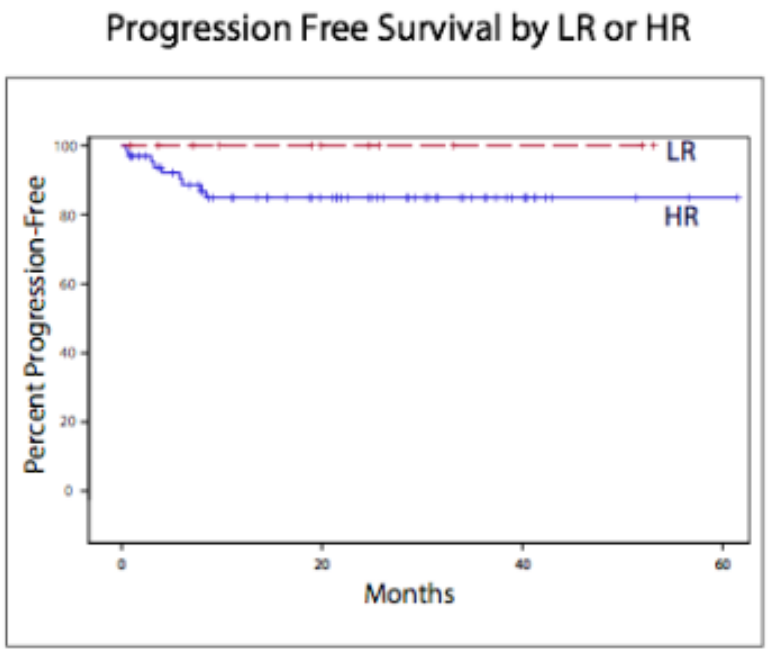



**Subjects at risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ibrutinib | 139 | 114 | 101 | 83 | 77 | 45 | 34 | 8 | 5 | 0 | 0 |
| Temsirolimus | 141 | 93 | 69 | 45 | 33 | 19 | 11 | 3 | 1 | 0 | 0 |

# Burkitt lymphoma: DA-R-EPOCH

| | | TTP | PFS | OS |
|---|---|---|---|---|
| Patients | N=77 | 92% | 87% | 88% |
| LR | 11 | 100% | 100% | 100% |
| HR | 66 | 91% | 85% | 86% |
| **p** | | **0.35** | **0.22** | **0.24** |
| HIV – | 57 | 96% | 88% | 90% |
| HIV + | 20 | 84% | 84% | 83% |
| **p** | | **0.1** | **0.66** | **0.53** |
| Age under 40 | 35 | 94% | 90% | 93% |
| Age over 40 | 42 | 91% | 84% | 83% |
| **p** | | **0.83** | **0.45** | **0.24** |




Low-risk (LR) patients (normal LDH, ECOG P.S. 0-1, stage I or II disease and a maximum tumor size < 7cm)

Dunleavy, ASH 2015

# Take home messages 1

1. Pathology report for DLBCL should include
   COO (IHC or GEP)
   DEL (IHC)
   DHL (FISH)
2. COO has yet no impact on choice of treatment:
   wait for trials
3. DHL: DA- R-EPOCH and autoSCT
4. DEL: R-CHOP, autoSCT but new ideas needed
   (high number of pts)

# Take home messages 2

5. Primary mediastinal lymphoma: DA-R-EPOCH (RT ?)
   relapse: checkpoint inhibitor
6. Primary CNS lymphoma:
   CNS directed chemo and autologous SCT
7. Mantle cell lymphoma:
   Rituximab maintenance after auto

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