

# Double Hit 淋巴瘤的诊断与治疗



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# 内 容

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- **什么是Double-Hit 淋巴瘤**
- **Double-Hit与Double-Expressor**
- **Double-Hit 对淋巴瘤预后的影响**
- **Double-Hit 淋巴瘤的治疗**



# Aggressive B cell lymphoma

## ■ Burkitt lymphoma

} Gray Zone

## ■ Diffuse large B cell lymphoma

### ❖ Prognostic factors

#### ➤ IPI (international Prognostic Index)

- Age >60
- ECOG PS  $\geq$  2
- Stage III or IV
- Extranodal site >1
- LDH > normal

#### ➤ Immunophenotype

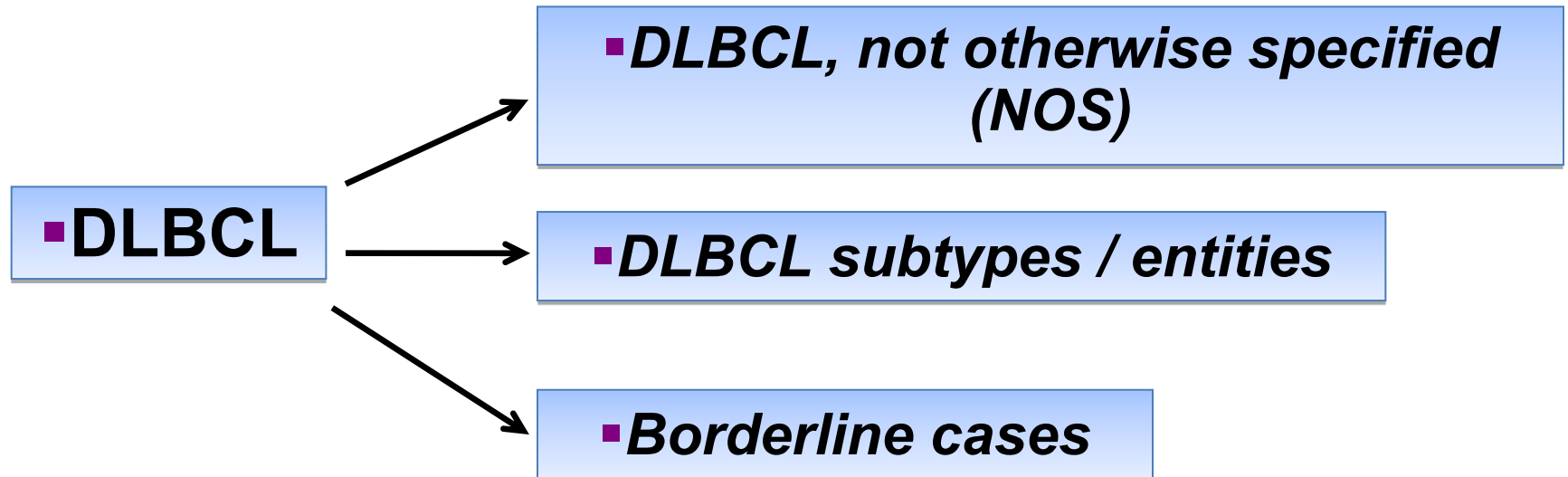
- Germinal-center B cells (GCB), activated B cells (ABC)

#### ➤ Gene rearrangement and protein expressions

- *BCL2*, *BCL6*, *c-MYC*



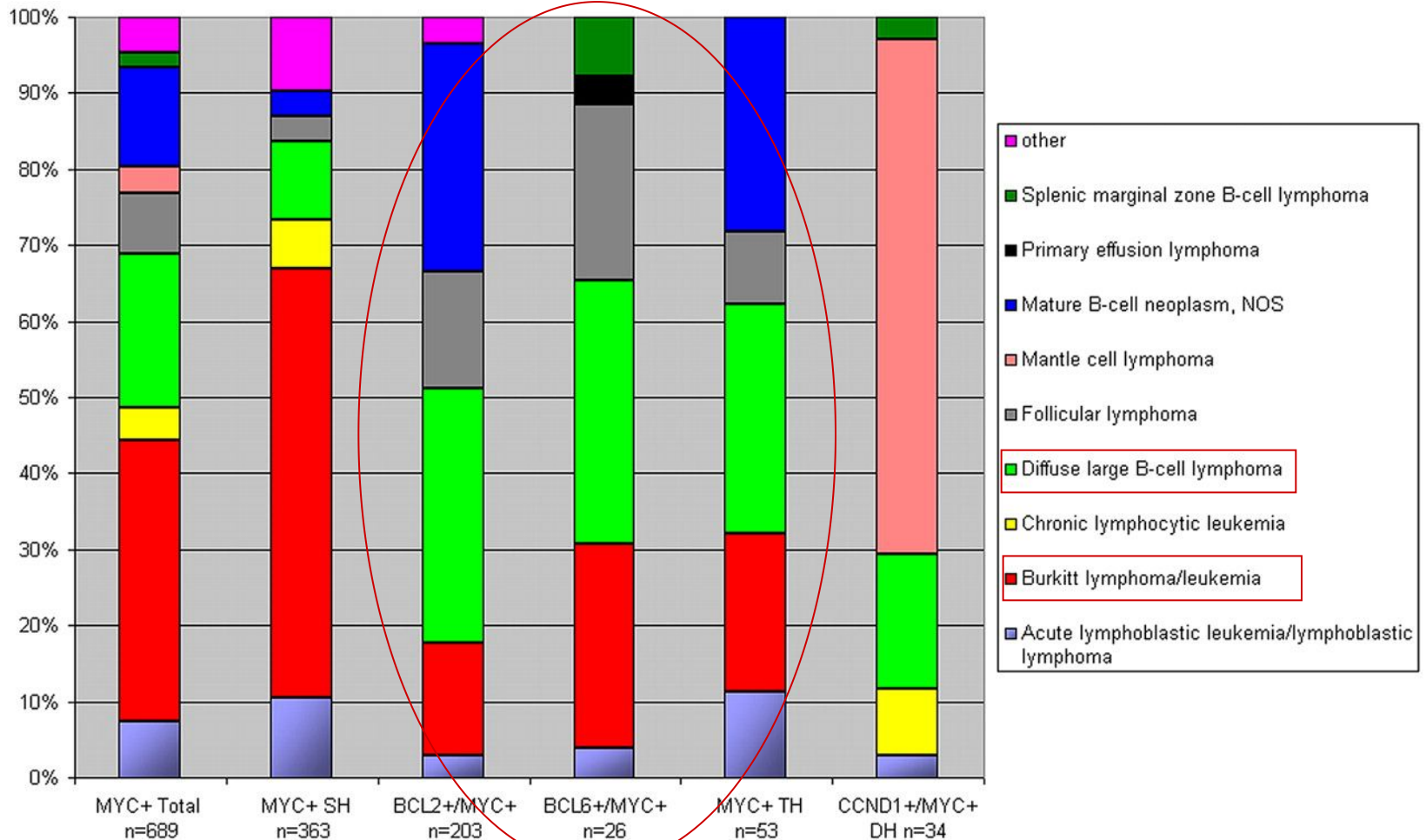
# 2008 WHO-Classification of the Diffuse large B-Cell-Lymphomas



**BCLU**, with features intermediate between DLBCL and Burkitt lymphoma (“gray zone” lymphoma)

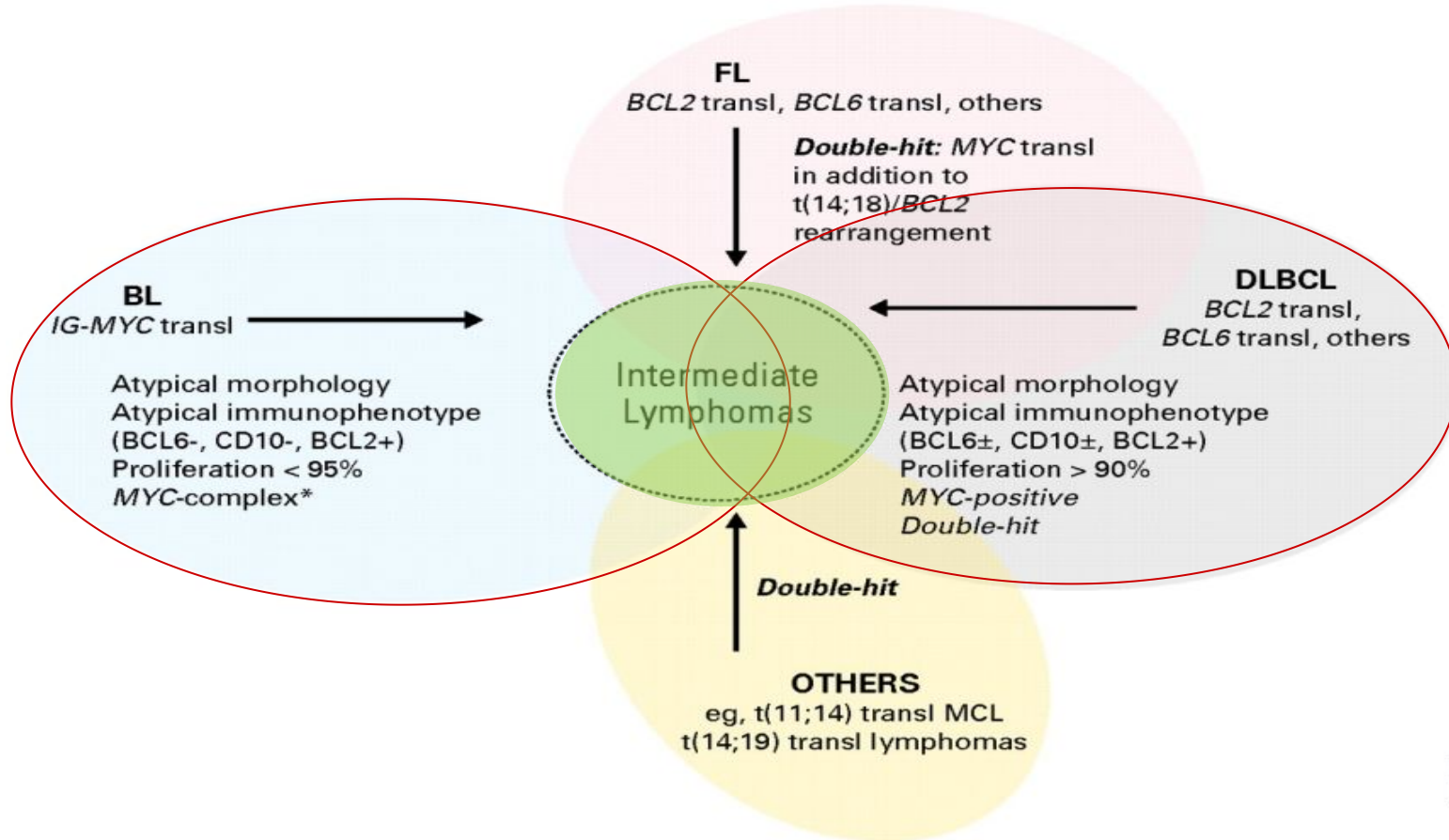


# Distribution of morphologies according to breakpoints





# Double-Hit 淋巴瘤 ( DHL )





# Double-Hit 淋巴瘤定义

- 目前主要指大B细胞淋巴瘤同时有Myc和BCL-2表达或者Bcl-6表达（或者三者同时并存的Triple-Hit）
  - 通常肿瘤细胞的属于中间大小的类型
- 不包括MYC合并其他基因易位的淋巴瘤
  - 如MCL，同时又CCND1/IGH和MYC易位，但仍只是定义为MCL
- 目前还不是一个独立的诊断，是对合并双打击的B细胞淋巴瘤一个新术语



# 内 容

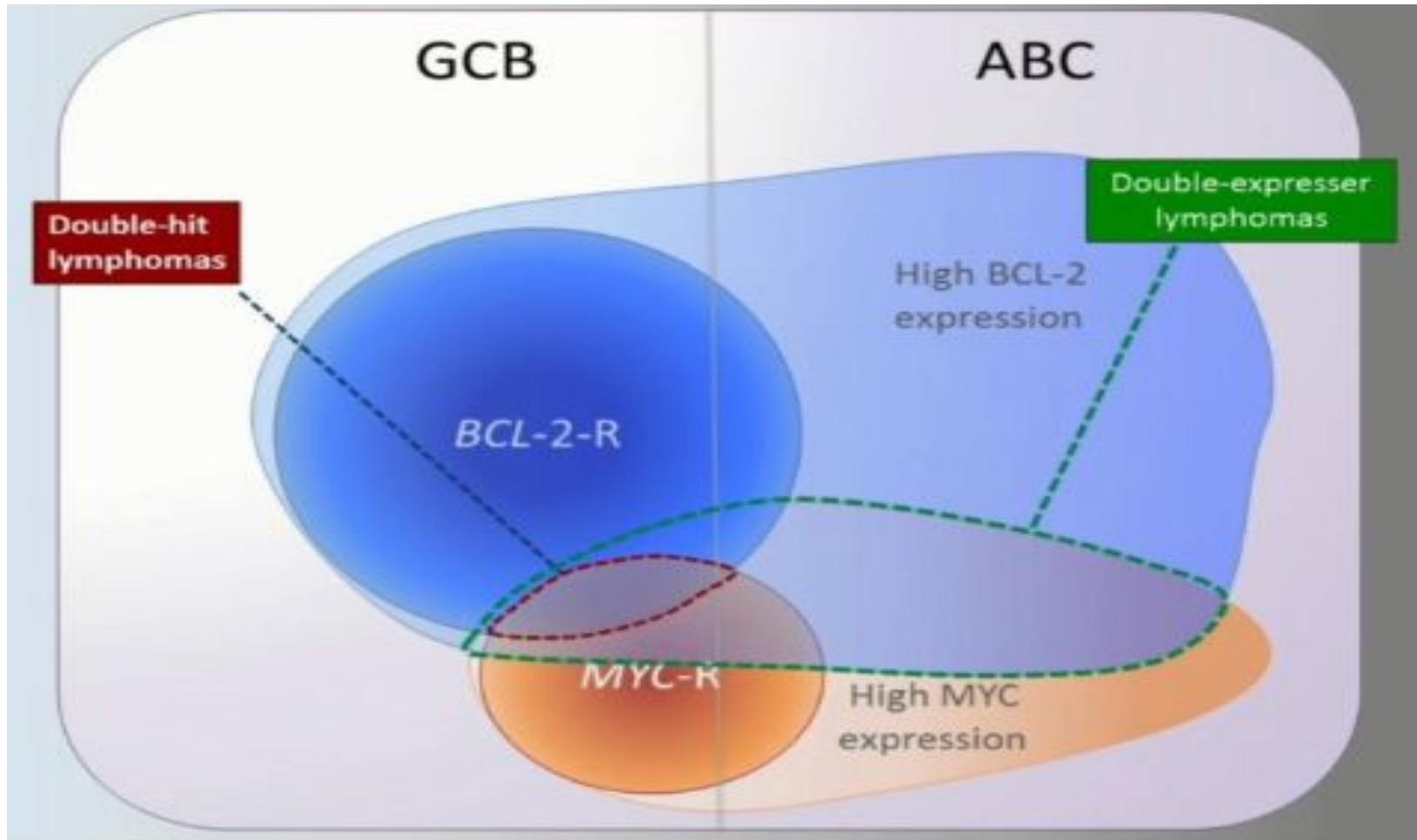
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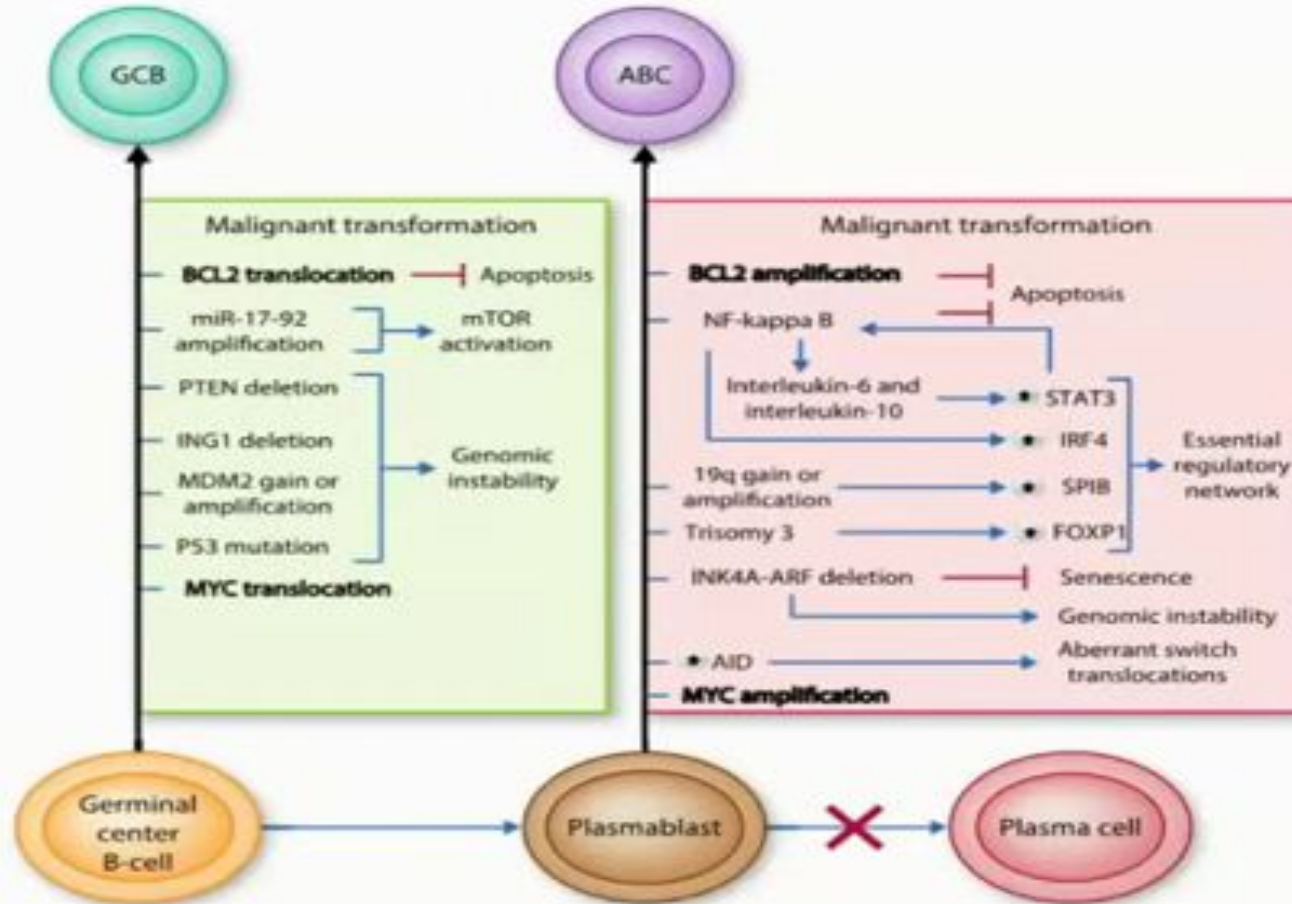


# Double-Hit 与 Double-expressor





# Double-Hit 与 Double-expressor

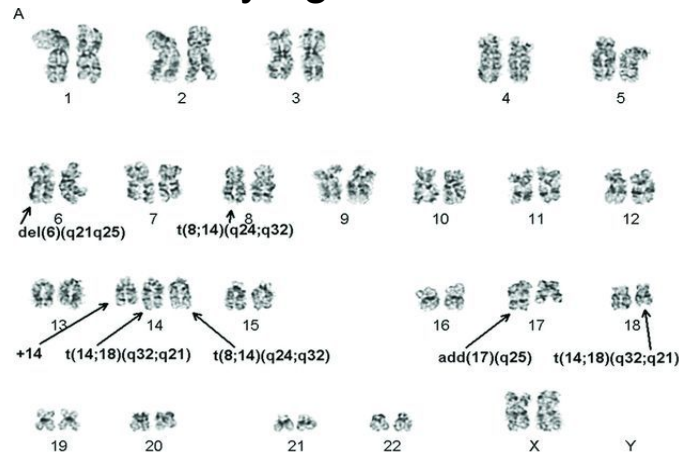


Adapted from Lenz and Staudt, NEJM, 2010

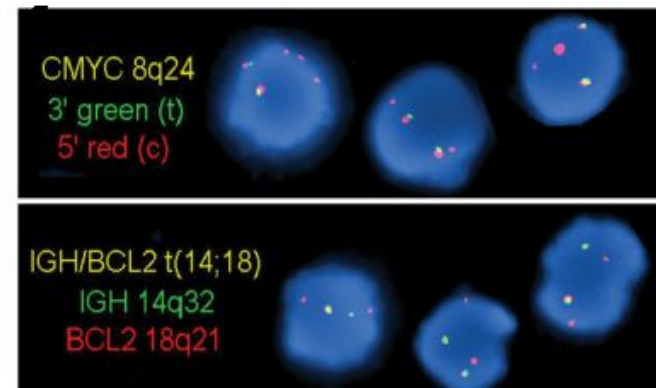
# Double-Hit and Double-expressor

- MYC-R combination with BCL2-R, BCL6-R (Double-Hit) or with BCL2-R + BCL6-R (Triple-Hit)
  - ❖ 2%–12% of DLBCL, 32%–78% of BCLU are DHL
  - ❖ The incidence of DH/THL increases with patient age
  - ❖ Poor prognosis with a median OS of <2 years
  - ❖ Detecting techniques

## cytogenetics



## FISH

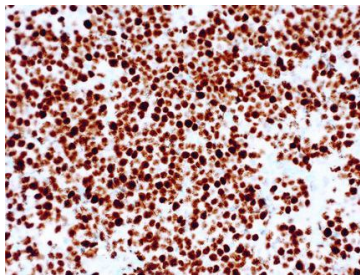




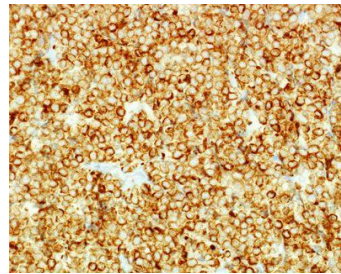
# Double-Hit and Double-expressor

- 40% MYC and 50%-70% BCL2 protein expression in cells, more common than DHL/THL
  - Not equivalent to DHL/THL, even if 80%-90% of the DHL/THL are DE. MYC and BCL2 can be activated through other mechanisms, leading to high expression of the protein products
  - More likely to have a non-GCB phenotype
  - Generally aggressive, 3-year OS 43%, 5-year OS only 30%–36%
  - Detecting techniques

IHC

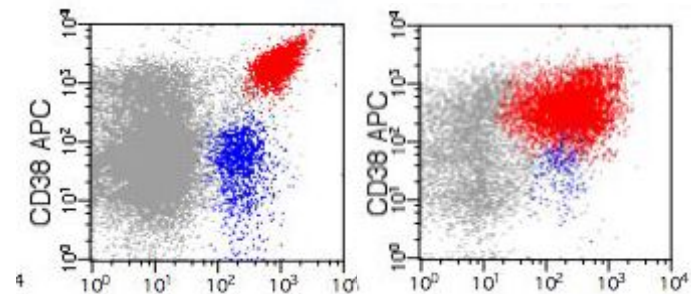


MYC



BCL2

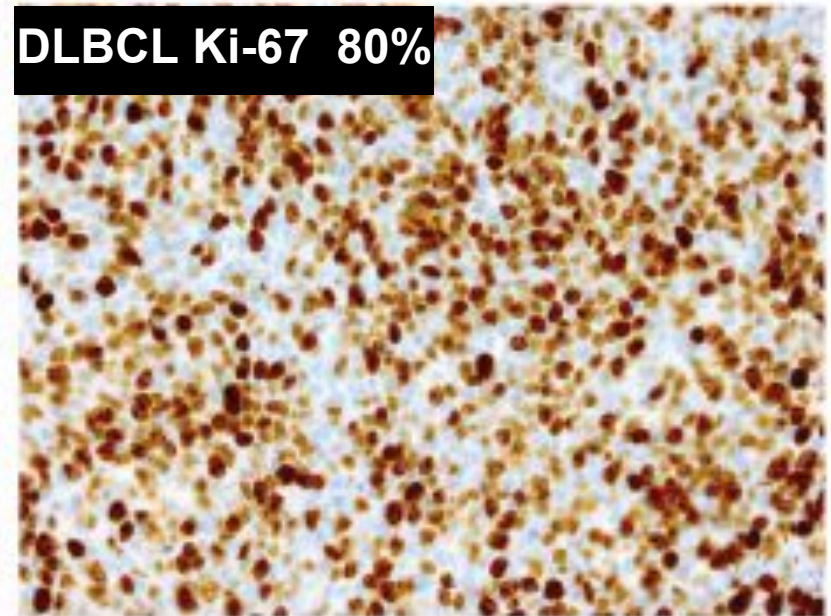
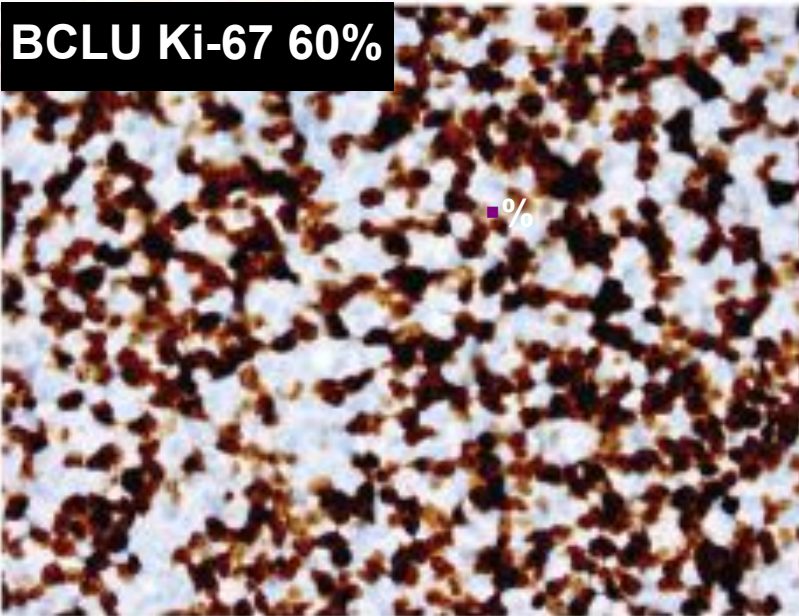
FCM



CD20 PerCP



# Double-Hit 淋巴瘤的 Ki-67



- 从侵袭性B细胞淋巴瘤中检出 DHL/THL的敏感性：
  - ❖ Ki-67 > 90%: 0.54; Ki-67 > 75%: 0.77
  - ❖ 57% : cutoff of 0.80 (凡Ki-67 > 60% , 应该排查DHL)



# DHL 的临床特征

- 中老年发病 (51-65 years)
- 高LDH, 疾病呈进展状态, 高IPI评分
- BM/CNS 受累 (9-50%)
- 细胞遗传学
  - ❖ 复杂核型 (MYC-complex)
  - ❖ IG-MYC (IG-MYC), 或 Non-IG-MYC
- 临床过程呈侵袭性, 对常规化疗耐药
- 预后很差, 中位 OS < 2 年



# 内 容

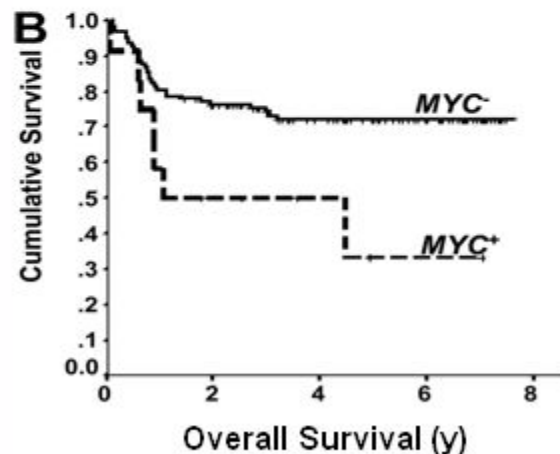
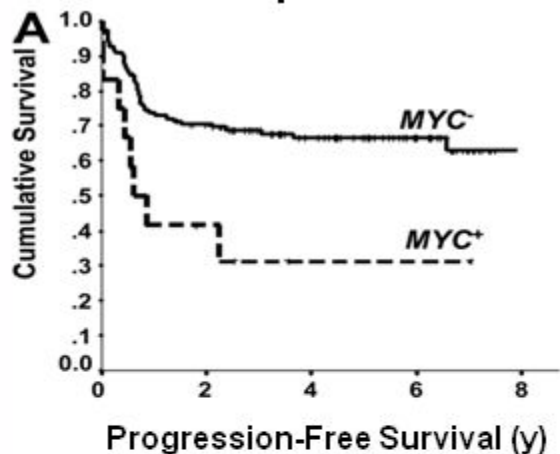
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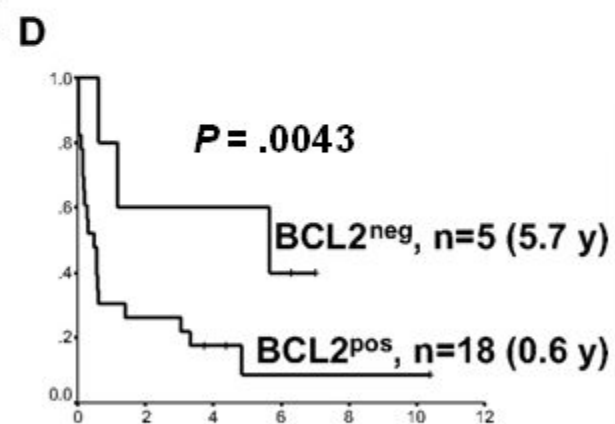
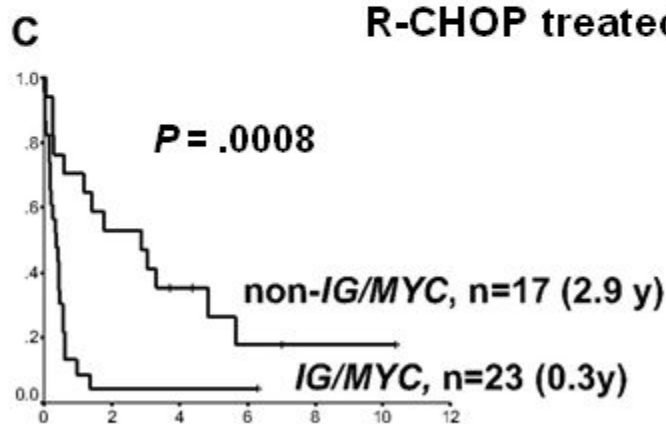
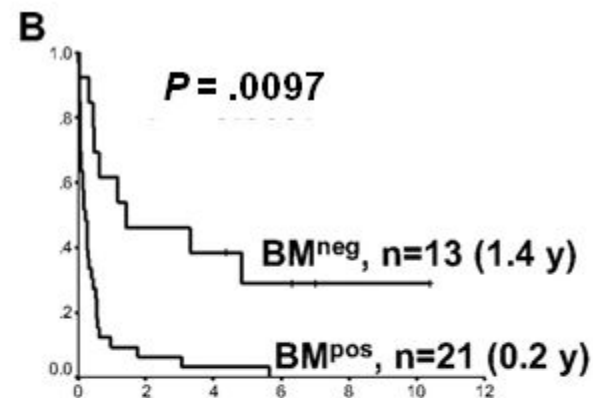
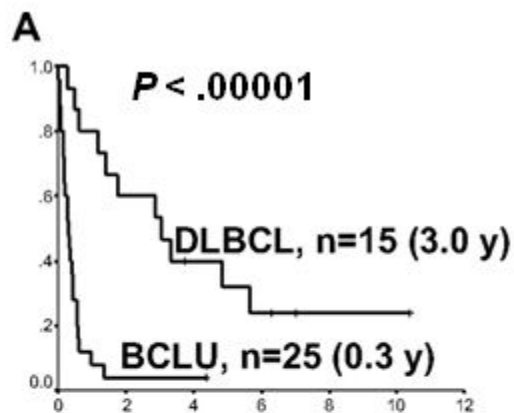


# DHL与预后

MYC-positive<sup>[a]</sup>



BCL2/MYC-translocated<sup>[b]</sup>



a. Savage KJ, et al. *Blood*. 2009;114:3533-3537.

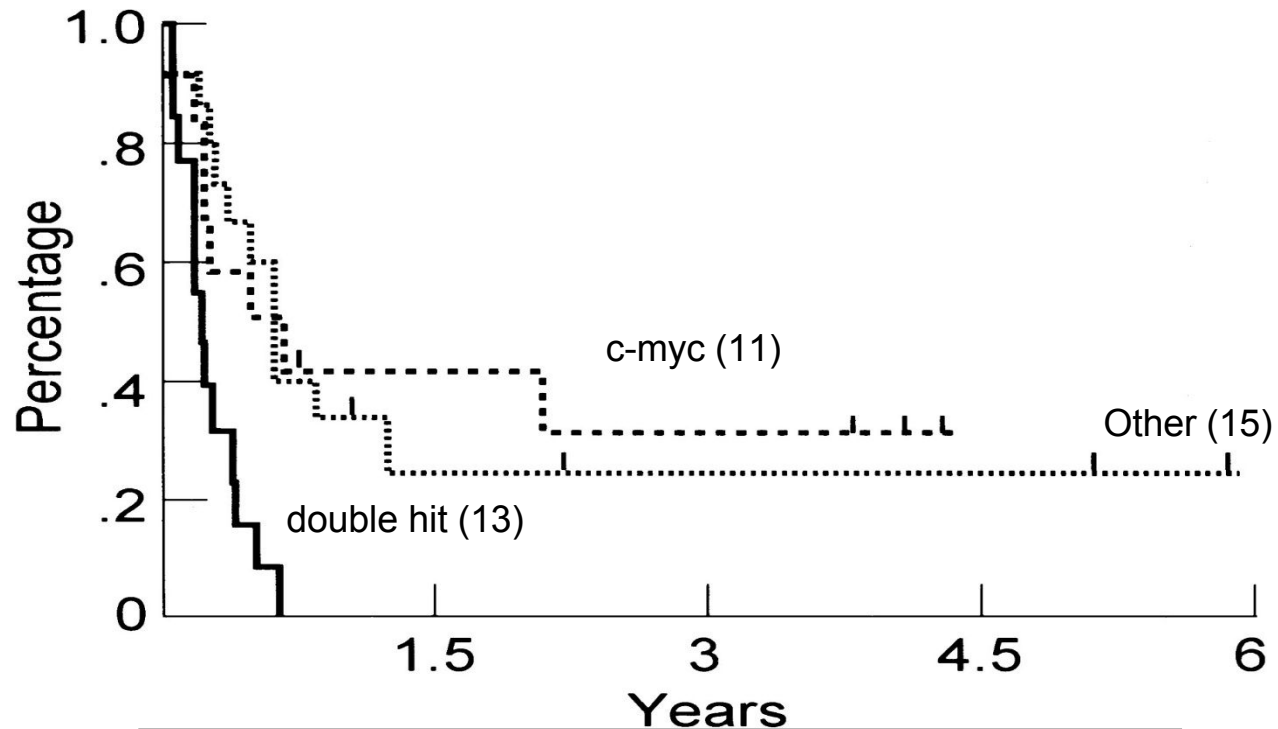
b. Johnson NA, et al. *Blood*. 2009;114:2273-2279.





# Overall Survival by Clonal Karyotype

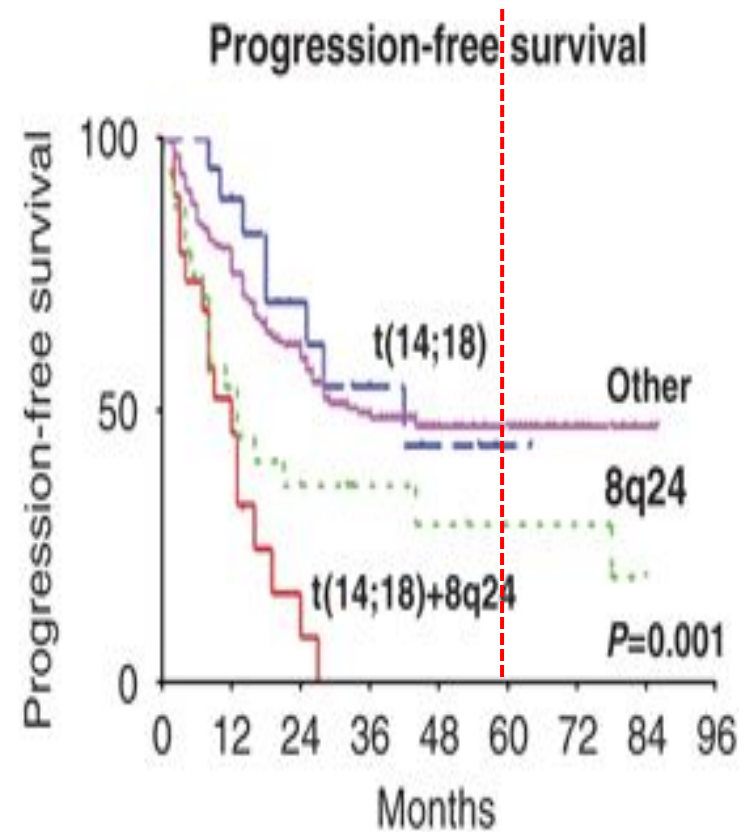
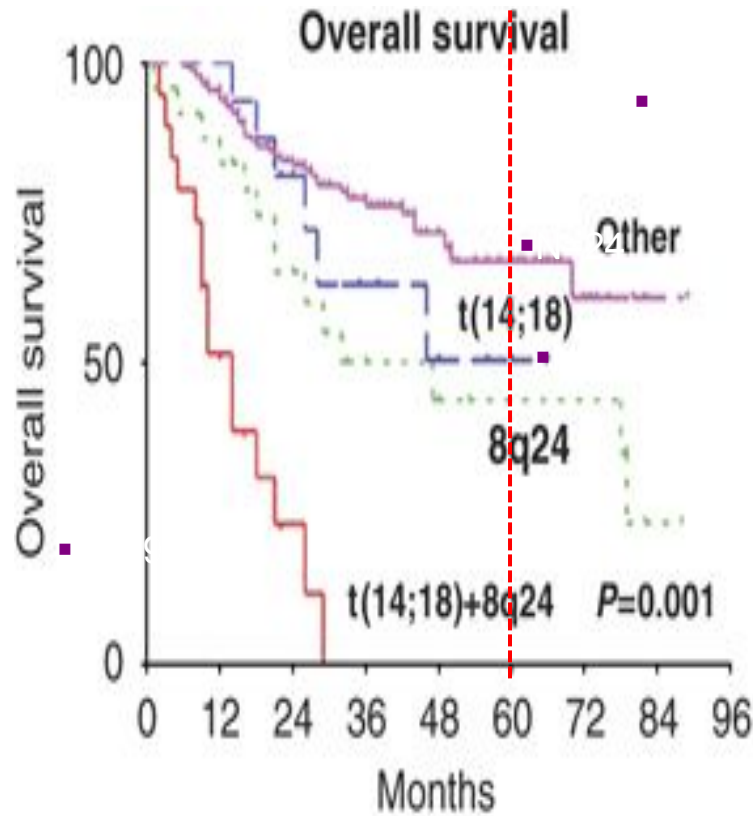
British Columbia Cancer Agency 1986-1996



	<i>c-myc</i>	Other	Double hit	<i>P</i>
Median survival, months	7	8	2.5	< .001
2-Year overall survival, %	32	25	0	< .001

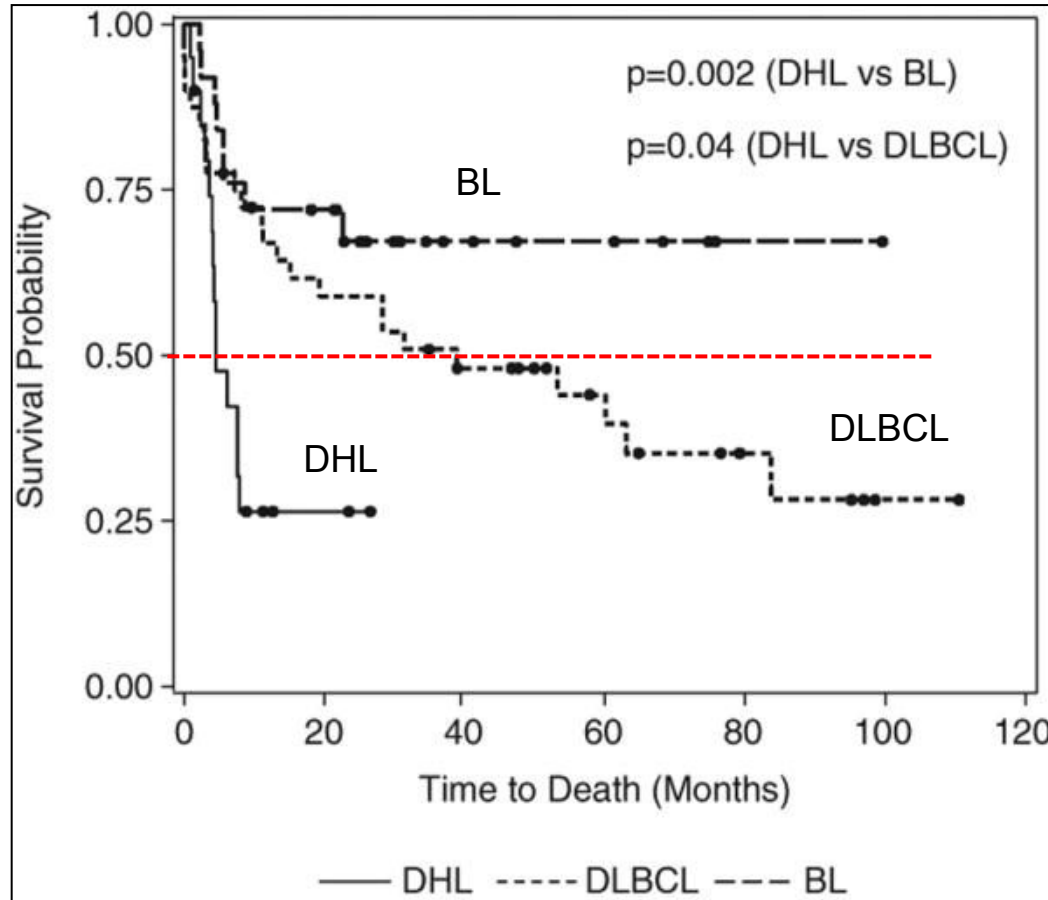


# Adult Lymphoma Treatment Study Group Japan, 1998-2007





# Massachusetts General Hospital 2004-2009



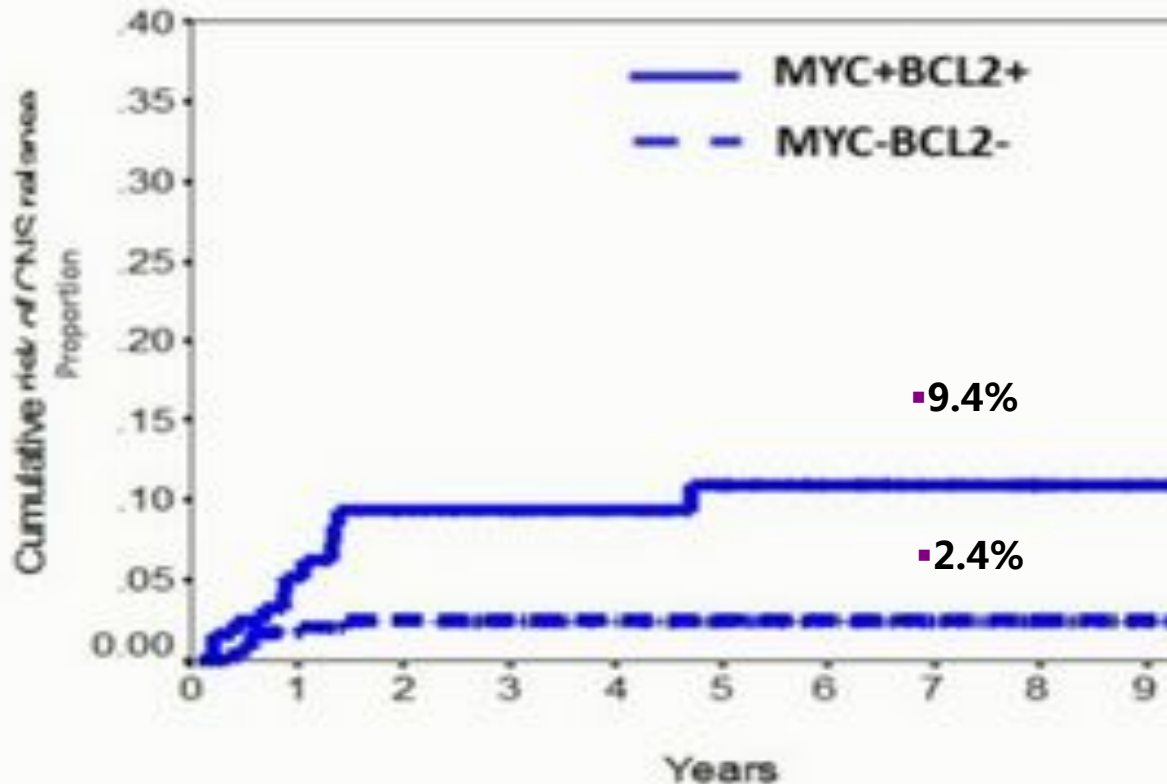
DHL N=20

BL N=25

DLBCL N=40



# MYC+BCL2+的DLBCL患者 CNS复发的风险更高



▪ Savage J et al. Blood. 2009 Oct 22;114(17):3533-7



# DHL与预后

- 研究发现DHL的形态学区别 ( GCB vs ABC ) 对预后影响都差 ( Mod Pathol 2012 ; 25 : 145 Cancer 2014 ; 120 : 1677 Bood 2014 ; 124 : 2354 )
- BCL-2蛋白的缺失或者低MYC蛋白表达 ( <40% ) 可能会有更好的预后 ( Blood 2009 ; 114 : 2273 & Blood 2013 ; 121 : 2253 & JCO 2012 ; 30 : 3452 )
  - ❖ 研究认为同时存在MYC和IG ( IGH , K or  $\lambda$  ) 重排的患者预后更差 ( Eur J Haem 2013 ; 92 : 42 )
- MYC+BCL2+的DLBCL患者CNS复发的风险更高



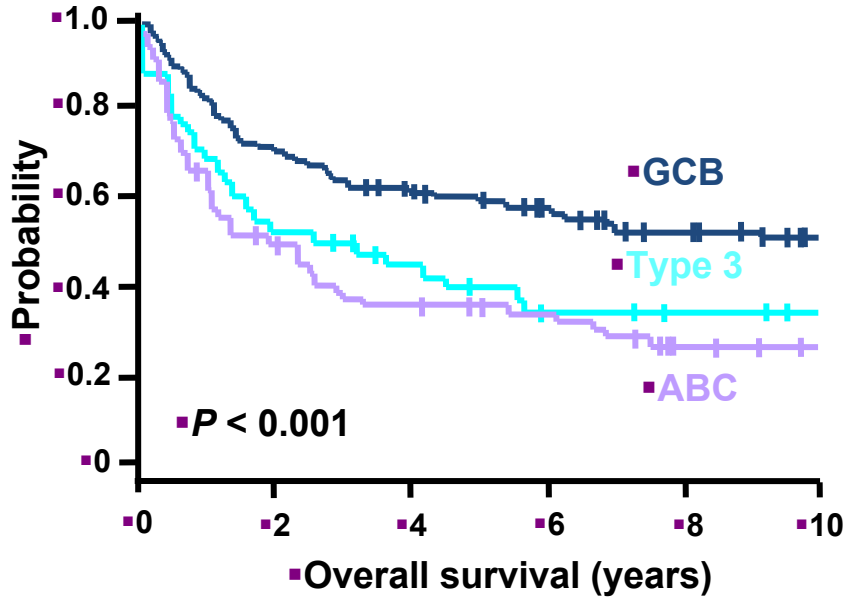
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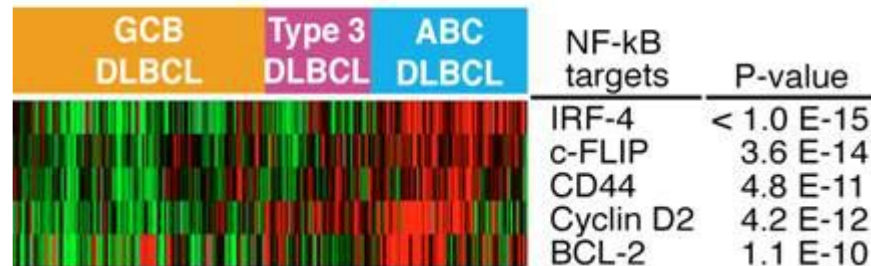


# DLBCL使用R-CHOP治疗后的结果



	GCB	Type 3	ABC
C-rel amplification	17	0	0
BCL-2 t(14;18) PCR +	26	0	0

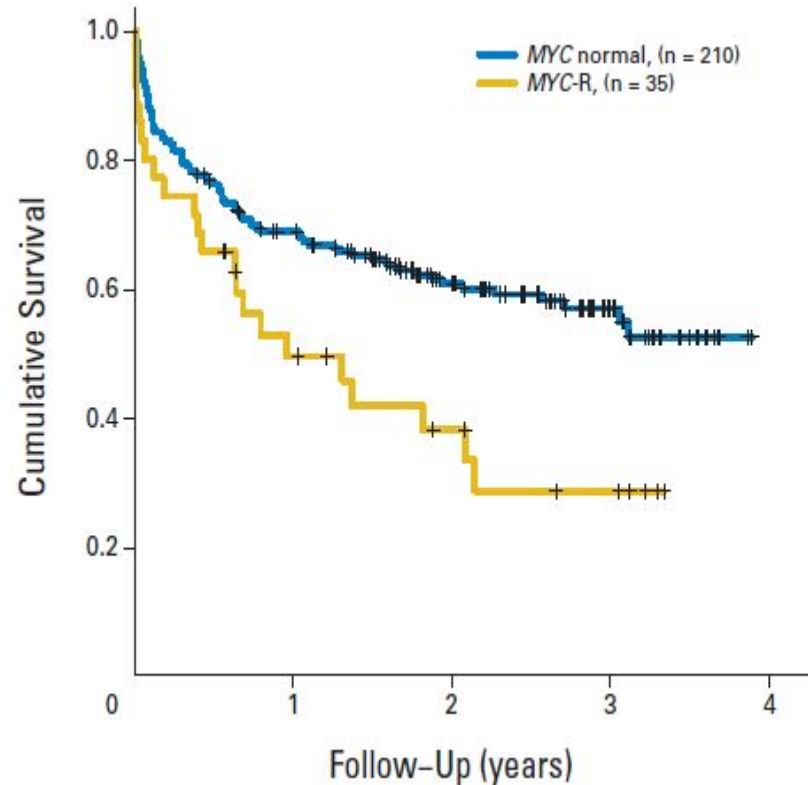
Preferential Expression of NF-kB Target Genes in Activated B Cell-like DLBCL





# MYC-R DLBCL 患者R-CHOP方案的疗效

- 303例DLBCL患者，
- 245例有FISH检测。
- **35例 ( 14% ) cMYC-R**
- 6例 ( 17% ) 仅有MYC异常
- 19例 ( 54% ) 合并BCL-2-R
- 3例 ( 8% ) 合并BCL-6-R
- 7例 ( 20% ) 同时有MYC/BCL-2/BCL-6
- MYC的患者通常来源于GCB且有高的IPI评分







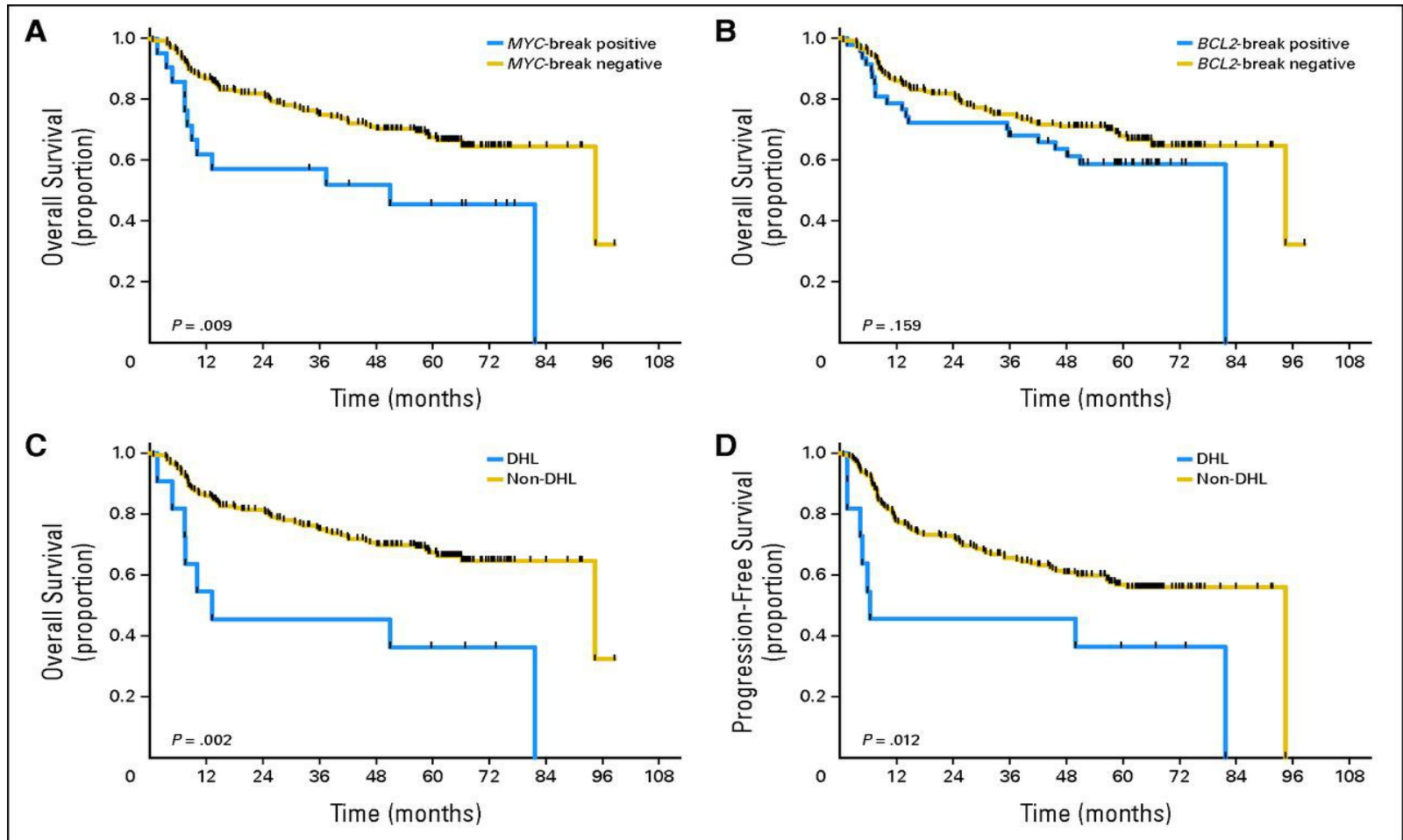
# MYC-R的DLBCL使用CHOP/R-CHOP的疗效

作者	例数	治疗方案	MYC-R%	DHL% ( BCL-2-R )	结果
Barrans et al.	303	R-CHOP	14%	11%	2Y OS: MYC-R 35% MYC-N 61%
Savage et al.	135	R-CHOP	9%	2%	5Y OS: MYC-R 33% MYC-N 72%
Cunningham et al.	1080	R-CHOP-14/R-CHOP-21	6%	3%	MYC-R 2Y OS not inferior

■MYC-R: MYC rearrangement



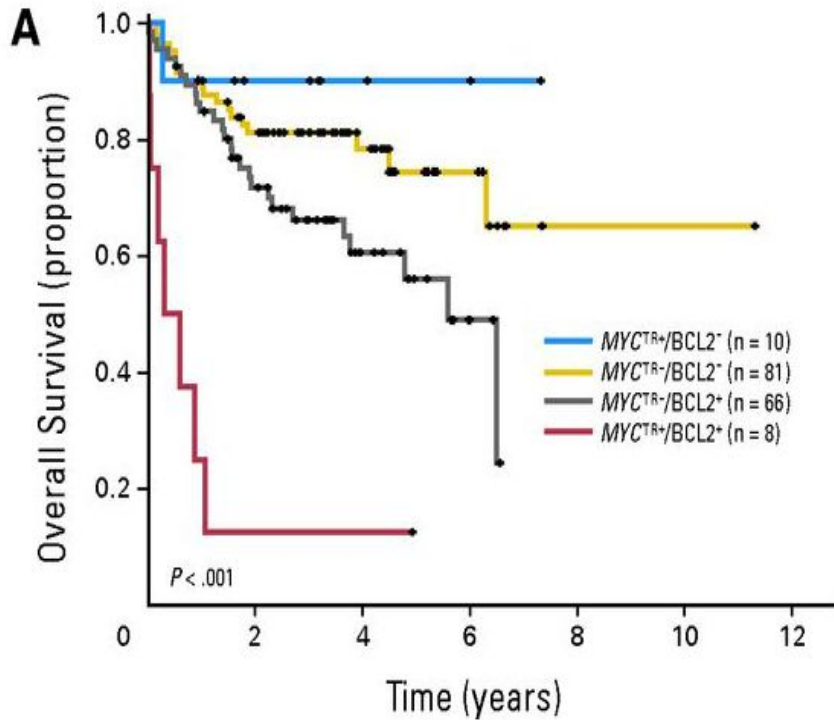
# MYC-R和BCL2-R的DLBCL R-CHOP治疗后的结果



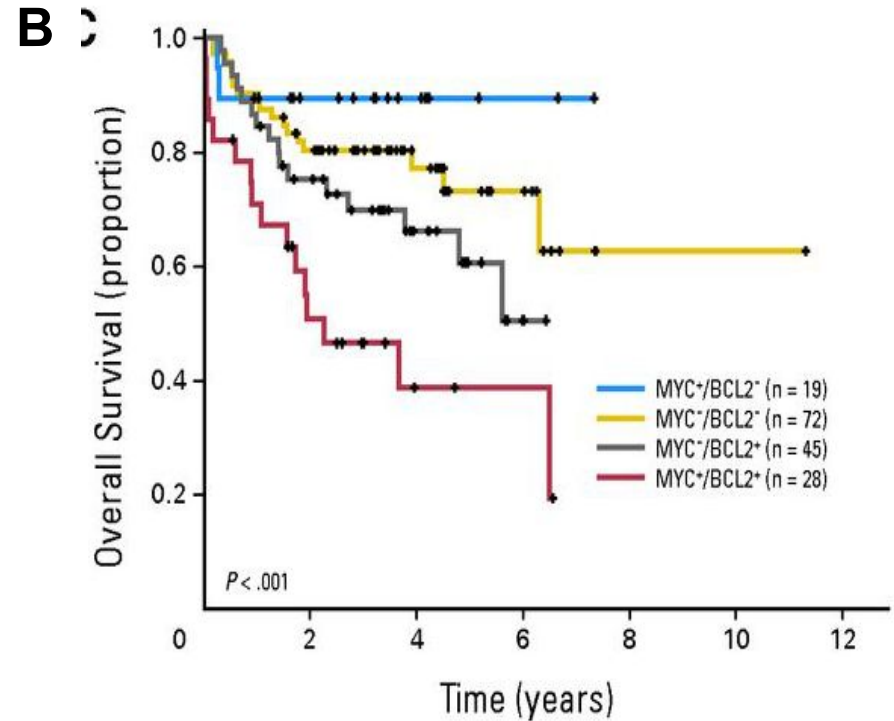


# OS: DLBCL treated with R-CHOP based on alterations in MYC and BCL2

MYC-R and BCL2 protein expression



MYC and BCL2 protein expression





# MDACC: Double-Hit 淋巴瘤的治疗结果

129例患者

● IPI评分

0-1分 : 13%

2-3分 : 61%

4-5分 : 26%

● DLBCL 或者 BCLU 92%

● 基因易位类型

MYC : 81%

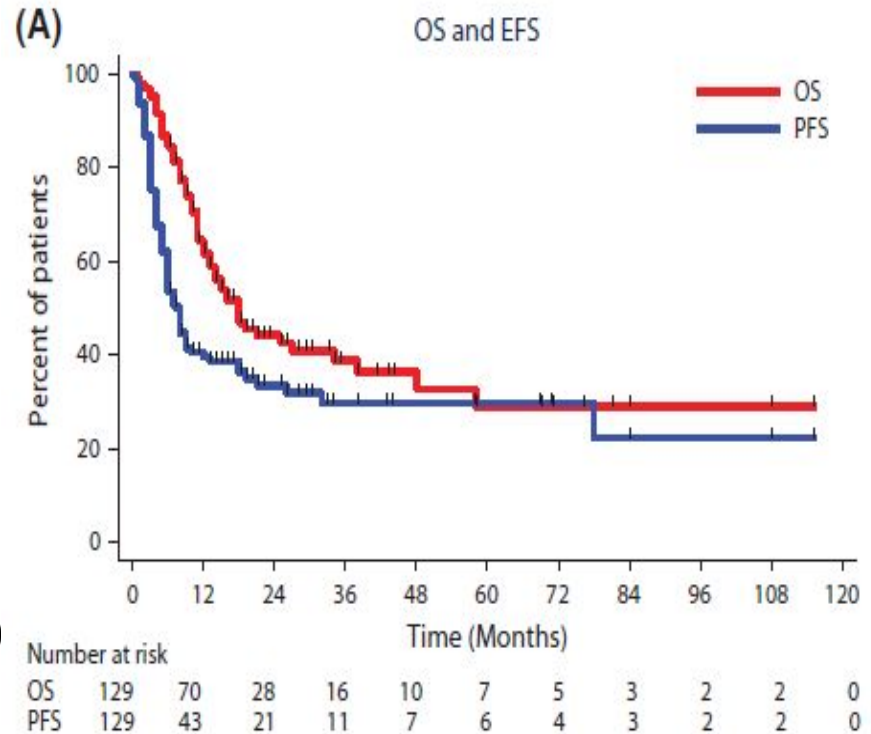
BCL2 : 84%

BCL6 : 12%

MYC&BCL2 : 72% ( 93例 )

Triple Hit :11% ( 14例 )

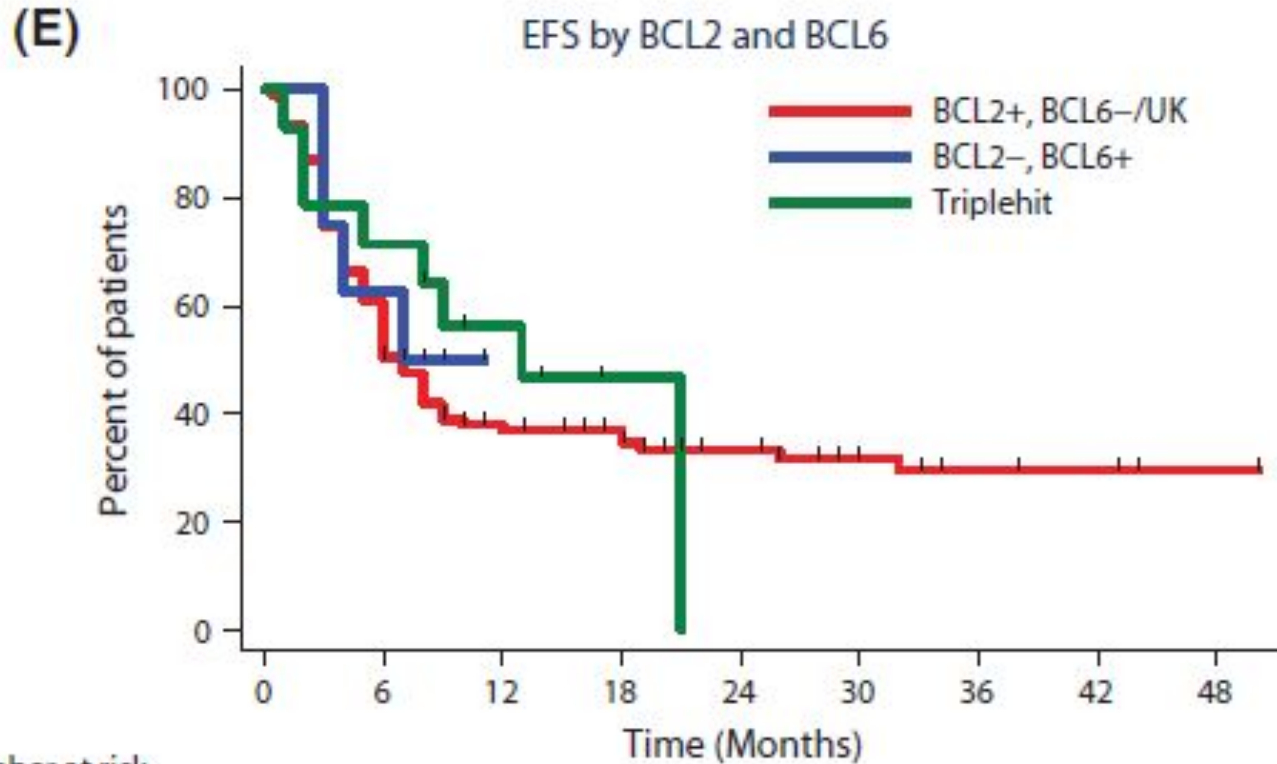
● GCB:>90%



CHOP+/-R; Hyper-CVAD; R-EPOCH; Other



# Translocation partner : 对EFS无影响

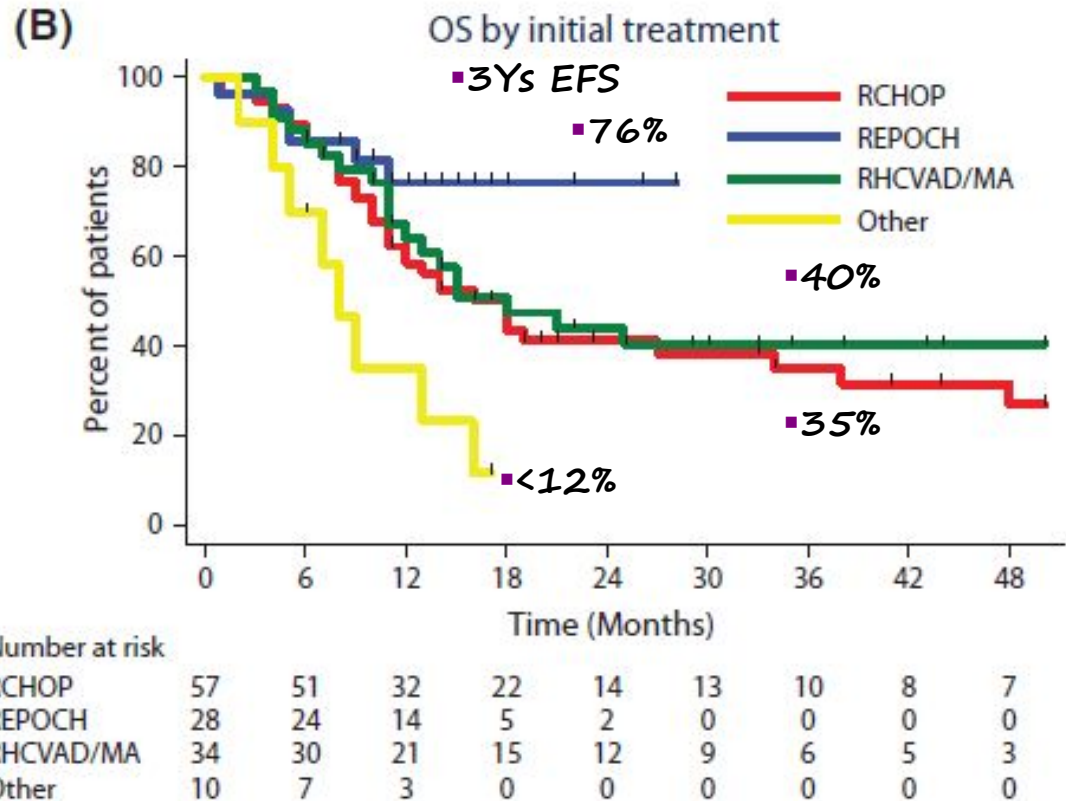


Number at risk	0	6	12	18	24	30	36	42	48
BCL2+, BCL6-/UK	107	65	37	31	21	16	11	10	7
BCL2-, BCL6+	8	5	0	0	0	0	0	0	0
Triplehit	14	10	6	1	0	0	0	0	0



# EPOCH-R方案有更好的EFS

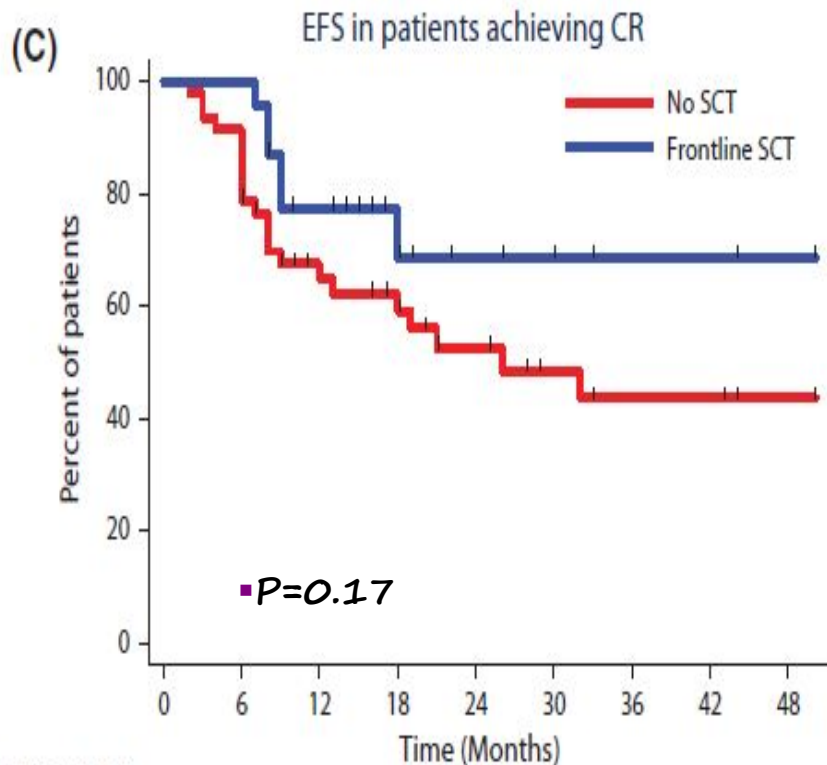
- R-CHOP:57(44%)
- R-EPOCH:28(23%)
- R-HCVAD/MA:34(26%)
- Other 10(7%)
  
- 中位年龄：
- R-CHOP：62岁
- R-EPOCH：65岁
- RHCVAD/MA：55岁



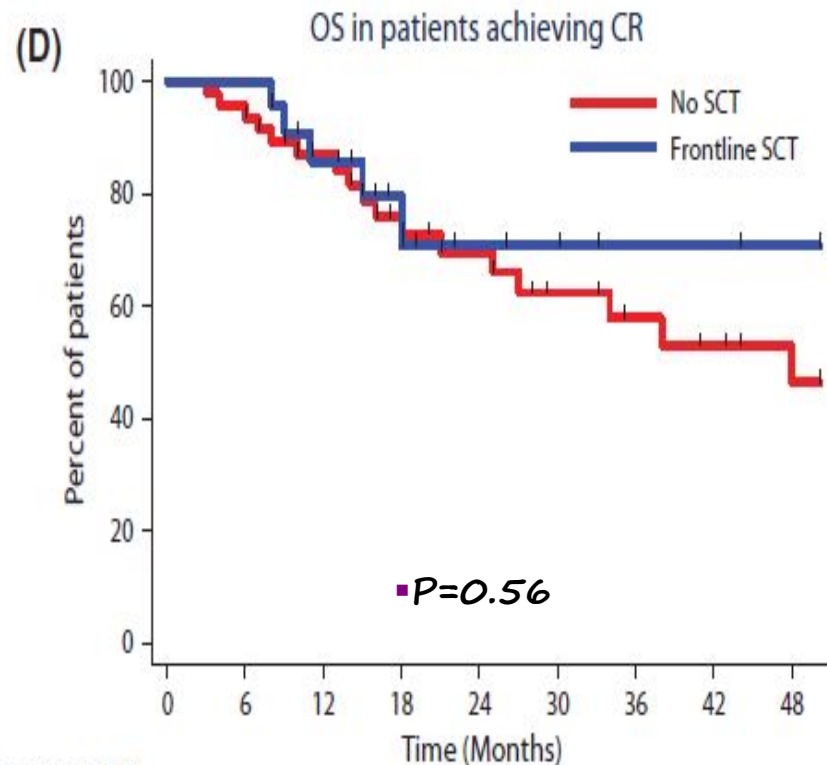
■ Oki et al. Br J Hematol,2014



# CR后给予SCT一线巩固治疗： 并没有提高EFS/OS



Number at risk	0	6	12	18	24	30	36	42	48
No SCT	47	43	25	21	14	10	8	8	6
Frontline SCT	23	23	15	9	5	4	2	2	1



Number at risk	0	6	12	18	24	30	36	42	48
No SCT	47	45	33	25	20	15	12	10	8
Frontline SCT	23	23	17	9	5	4	2	2	1

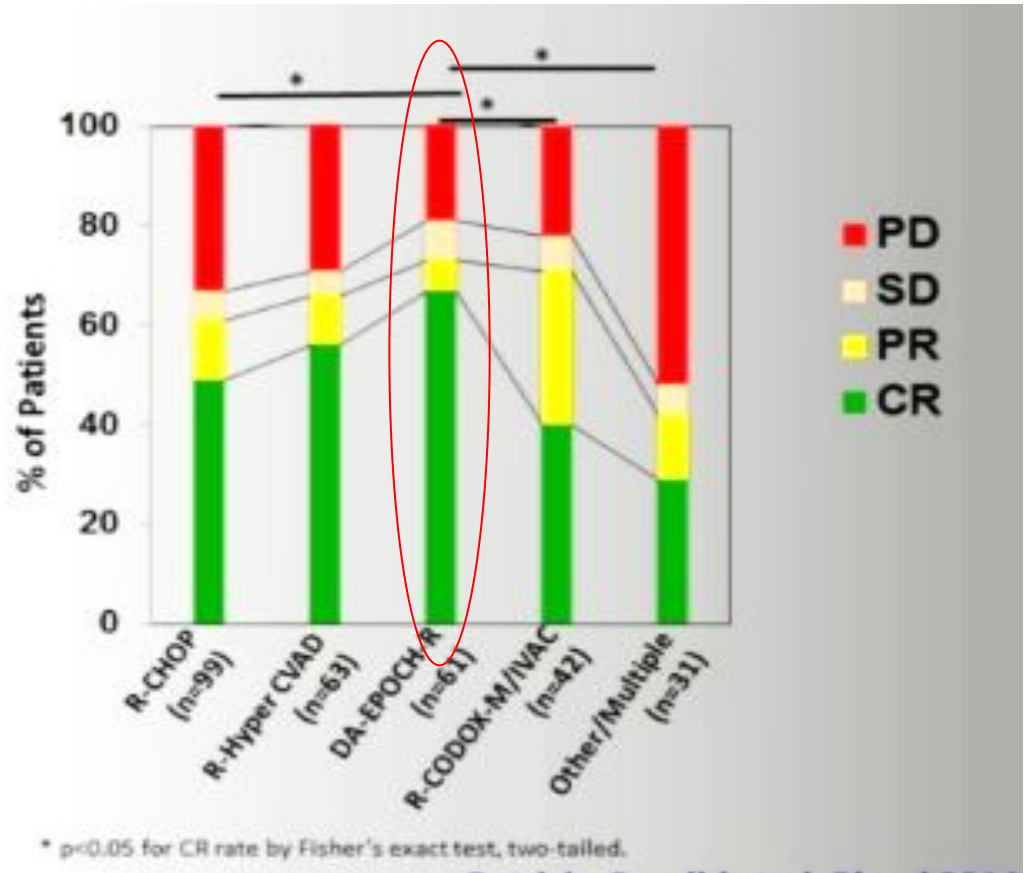
■ Oki et al. Br J Hematol, 2014



# DA-EPOCH-R方案可以获得更高的CR率

## 患者比例

- R-CHOP:33%
- R-Hyper CVAD :21%
- DA-EPOCH-R:21%
- R-CODOX-M/IVAC:15%
- Others:10%



■ Petrich, Gandhi et al. Blood 2014

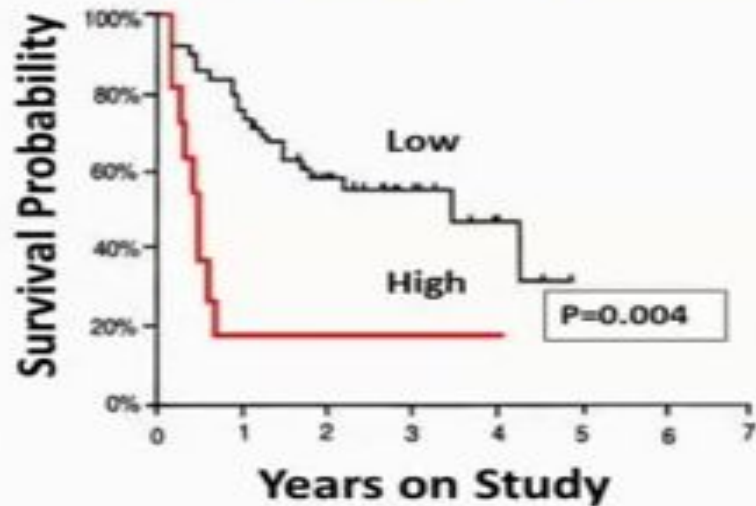




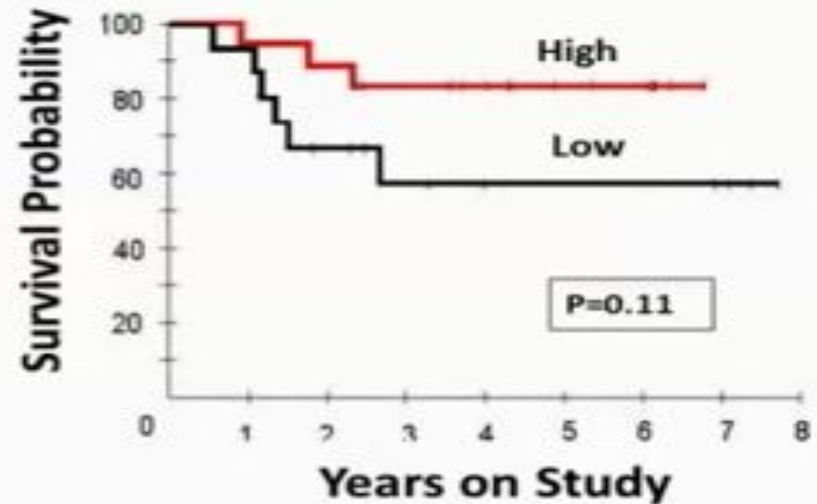
# DA-EPOCH提高疗效可能的机制

## Overcoming High Proliferation

CHOP (bolus)



DA-EPOCH (infusional)



■ High Proliferation (Ki67 > 80%)  
■ Low Proliferation (Ki67 < 80%)



# Double-Hit 淋巴瘤的治疗结果

作者	病例数	治疗方案	结果
Johnson , et al.	54	CHOP +/-R(63%);HD-Chemo;Other	中位OS : R-CHOP 组1.4年 CHOP组 1年
Li , et al.	52	R-CHOP ; R-Hyper-CVAD	中位OS18.6月 , <b>强化治疗或者SCT并没有提高OS</b>
Oki , et al.	129	CHOP+/-R ; Hyper-CVAD ; DA-EPOCH-R ; Other	2年EFS33% ; R-EPOCH方案结果更好 ; <b>SCT并没有带来获益</b>
Petrich , et al.	311	R-CHOP ; DA-EPOCH-R ; R-Hyper-CVAD ; CODOX-M/IVAC	2年DFS 40% ; DA-EPOCH-R的CR率最好 ; <b>SCT并没有带来获益。</b>



# DA-EPOCH-R方案可能提高PFS&OS

## Phase 2 Trial in Patients With *MYC*-Positive DLBCL or BCL-U

Outcomes After 6 Cycles (median follow-up, 14 mo)	DA-EPOCH-R, % (N = 52)
Overall PFS	79
PFS in double-hit patients	
FISH-positive for <i>BCL2</i> (n = 14)	87
IHC-positive for <i>BCL2</i> (n = 24)	64
OS	86
TTP	77

Dunleavy A, et al. ASH® 2014. Abstract 395.[1]



# 研发中的新药和新方法

## 分类

**BTK 抑制剂**      **Ibrutinib**

**PI3K 抑制剂**      **Idelalisib**

**BCL-2 抑制剂**      **ABT-199**

MYC 抑制剂

BET 结构域蛋白

BCL-6 抑制剂

Aurora酶 抑制剂

**CART细胞免疫治疗**

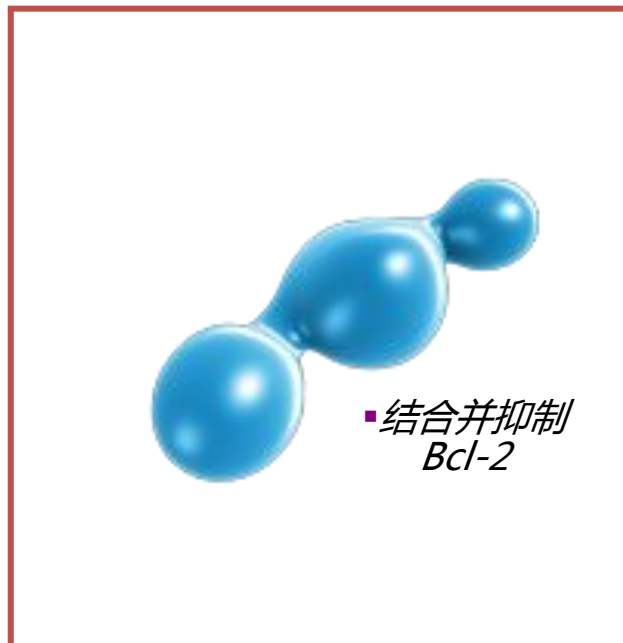


# GDC-0199 (RG7601, ABT-199): 分子概览

## 药物概述

化合物	RG7601
化合物类型	新分子实体
分子类型	小分子
作用机制	特异性的结合和抑制 Bcl-2导致细胞凋亡
目标适应症	复发或难治CLL, 复发或难治 NHL
研发阶段	I~II期

## 分子结构



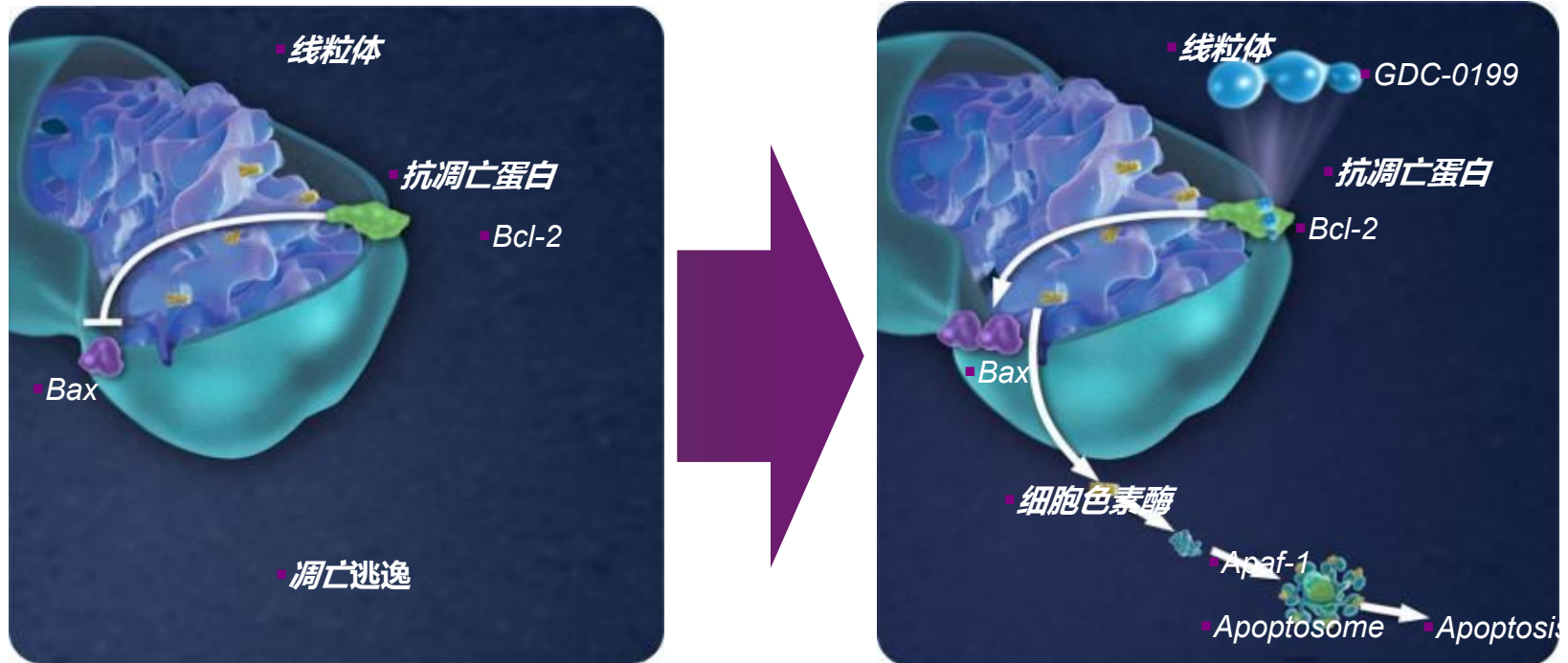
Bcl-2 过表达是血液肿瘤病理生理机制的基本特性。

- GDC-0199 是一类可口服的选择性小分子Bcl-2抑制剂
- GDC-0199 与 Bcl-2的结合亲和力高，而与Bcl-2家族其它蛋白(Bcl-X<sub>L</sub>, Bcl-w, and MCL-1)的亲和力却显著降低



# GDC-0199 (RG7601) 作用机制

抗凋亡蛋白Bcl-2的过表达和促凋亡蛋白的失调导致血液肿瘤细胞的凋亡逃逸  
GDC-0199特异性抑制Bcl-2功能，解除凋亡抑制



- Apaf-1, apoptotic protease activating factor 1; 凋亡蛋白酶激活因子 1
- Bax, Bcl-2-associated X protein. Bcl-2 相关X蛋白
- Jin Z, El-Deiry WS. Cancer Biol Ther. 2005;4(2):139-163; Lessene G, Czabotar PE, Colman PM. Nat Rev Drug Discov. 2008;7(12):989-1000.



# GDC-0199 (RG7601): 正在进行的临床试验概览\*

<b>患者人群</b>	R/R或初治 CLL	R/R或初治 CLL	R/R NHL	R/R CLL/NHL
<b>阶段/研究</b>	I期 GO28440	I期 GP28331	I期 M12-630	I期 M12-175
<b>患者例数</b>	N = 70	N = 64	N = 40	N = 118
<b>试验组</b>	GDC-0199 + 苯达莫司汀 + 利妥昔单抗	GDC-0199 + obinutuzuma b	GDC-0199 + 利妥昔单抗 + 苯达莫司汀	GDC-0199 (剂 量爬坡)
<b>主要研究 终点</b>	•安全性	•安全性	•安全性 •PK	•安全性 •PK
<b>研究状态</b>	入组中	入组中	入组中	入组中

■ ABT-199 trials. ClinicalTrials.gov website.  
<http://www.clinicaltrials.gov/ct2/results?term=ABT-199> as of June 2013.



# 总 结

- Double hit 淋巴瘤是一类侵袭性的B细胞淋巴瘤
- 细胞遗传学异常是MYC-R和BCL2-R/BCL6-R，其他机制也可影响表达异常，应当将MYC和BCL2/BCL6遗传学和免疫组化检查整合到诊断程序之中
- 以R-CHOP为基础的化疗方案并不适用，DA-EPOCH-R方案已展现出希望，SCT的疗效和价值尚未确定
- DHL患者有更多几率发生CNS进展，诊断时需要检查脑脊液且建议进行鞘注预防
- 需要更深入研究这类疾病，探索新的治疗方法：如小分子靶向治疗药物、细胞免疫治疗（CART）





# Thank You for your Attention



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