高增殖活性DLBCL的治疗决策

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内容

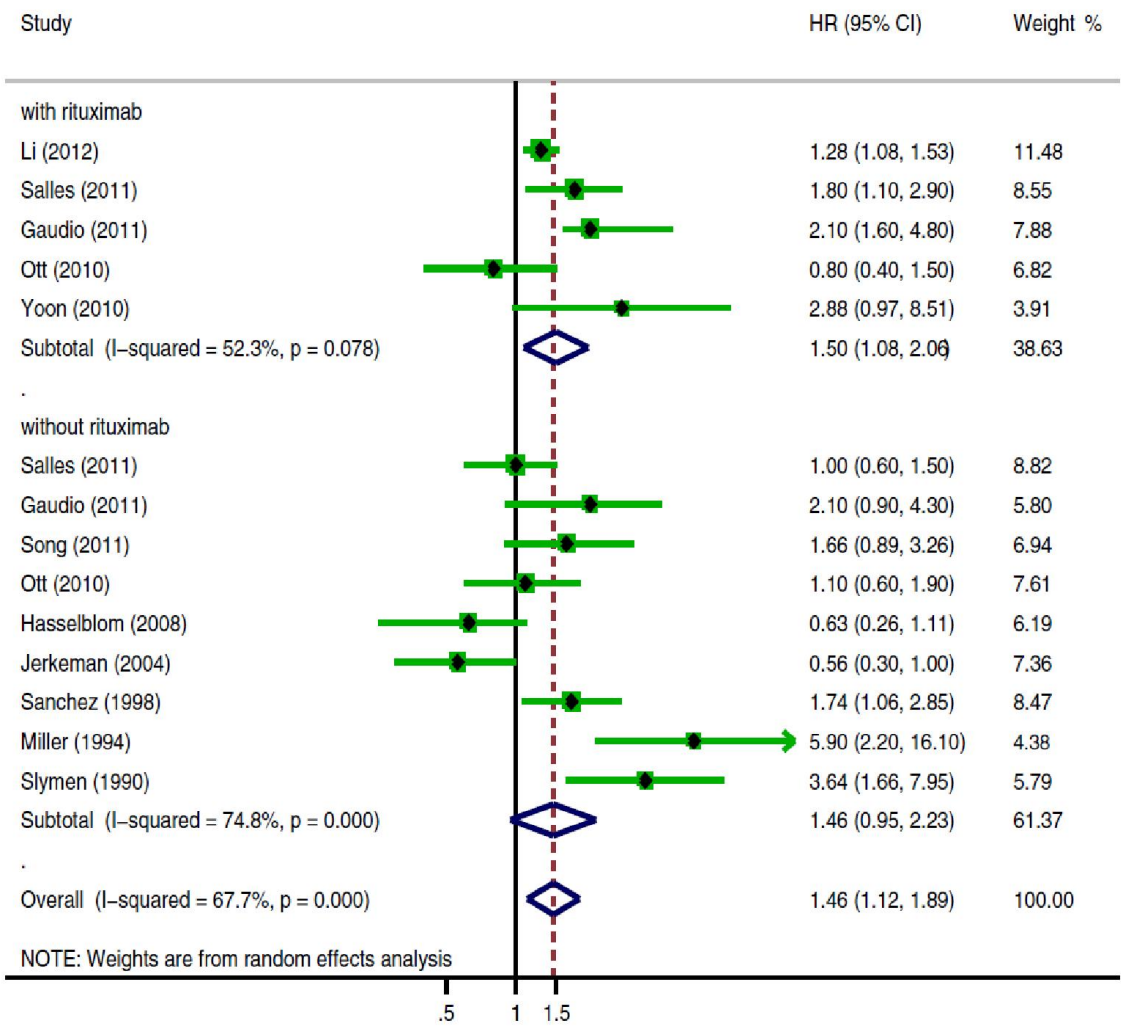
- Ki-67的概述
- Ki-67在DLBCL中的预后指导意义
- Ki-67结果判定存在的问题
- Ki-67对于DLBCL鉴别诊断的作用
- Ki-67与MYC+/DH淋巴瘤的相关性
- 针对高增殖活性DLBCL的治疗方案
- 小结

Ki-67的概述

- Ki-67是由*MKI67*基因编码的核蛋白
- Ki-67的功能与细胞增殖和核糖核酸转录有关
- 除了G0期细胞，Ki-67可以在处于增殖期的细胞核中表达
- Ki-67可以有效反映某个细胞群的生长分数
- Ki-67的分数与癌症的生物学行为具有相关性
- 在癌症的相关研究中，Ki-67具有诊断和预后价值

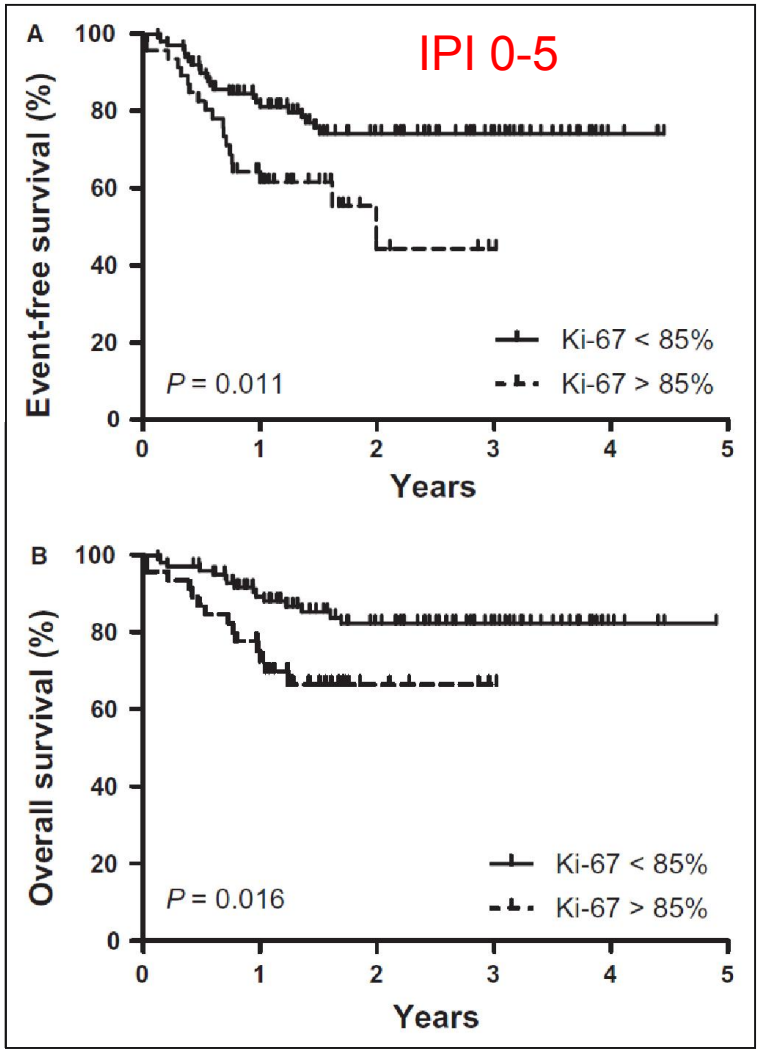
Ki-67在DLBCL中的预后指导意义

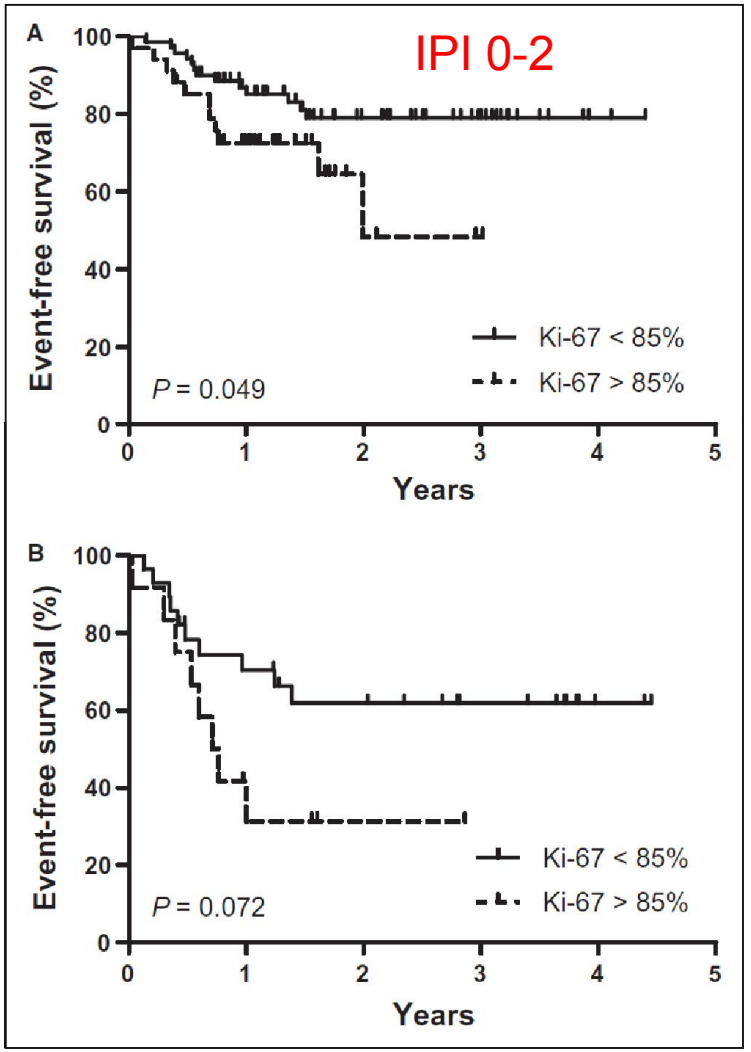
荟萃分析



He X, et al. BMC Cancer 2014;14:153

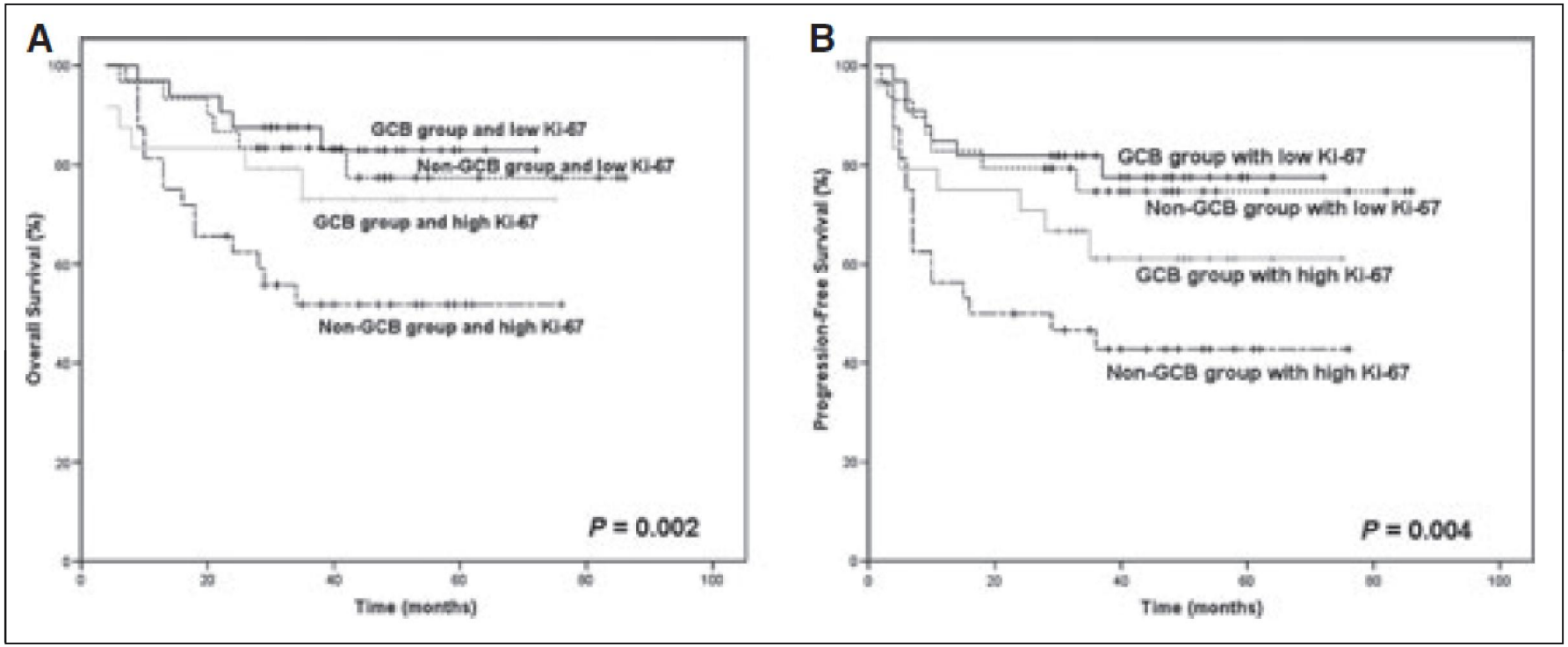
Ki-67与IPI





Yoon DH, et al. Eur J Haematol 2010;85:149

IPI与细胞起源



GCB/low Ki-67 > non-GCB/low Ki-67 > GCB/high Ki-67 > non-GCB/high Ki-67
* Ki-67 cutoff: 70%

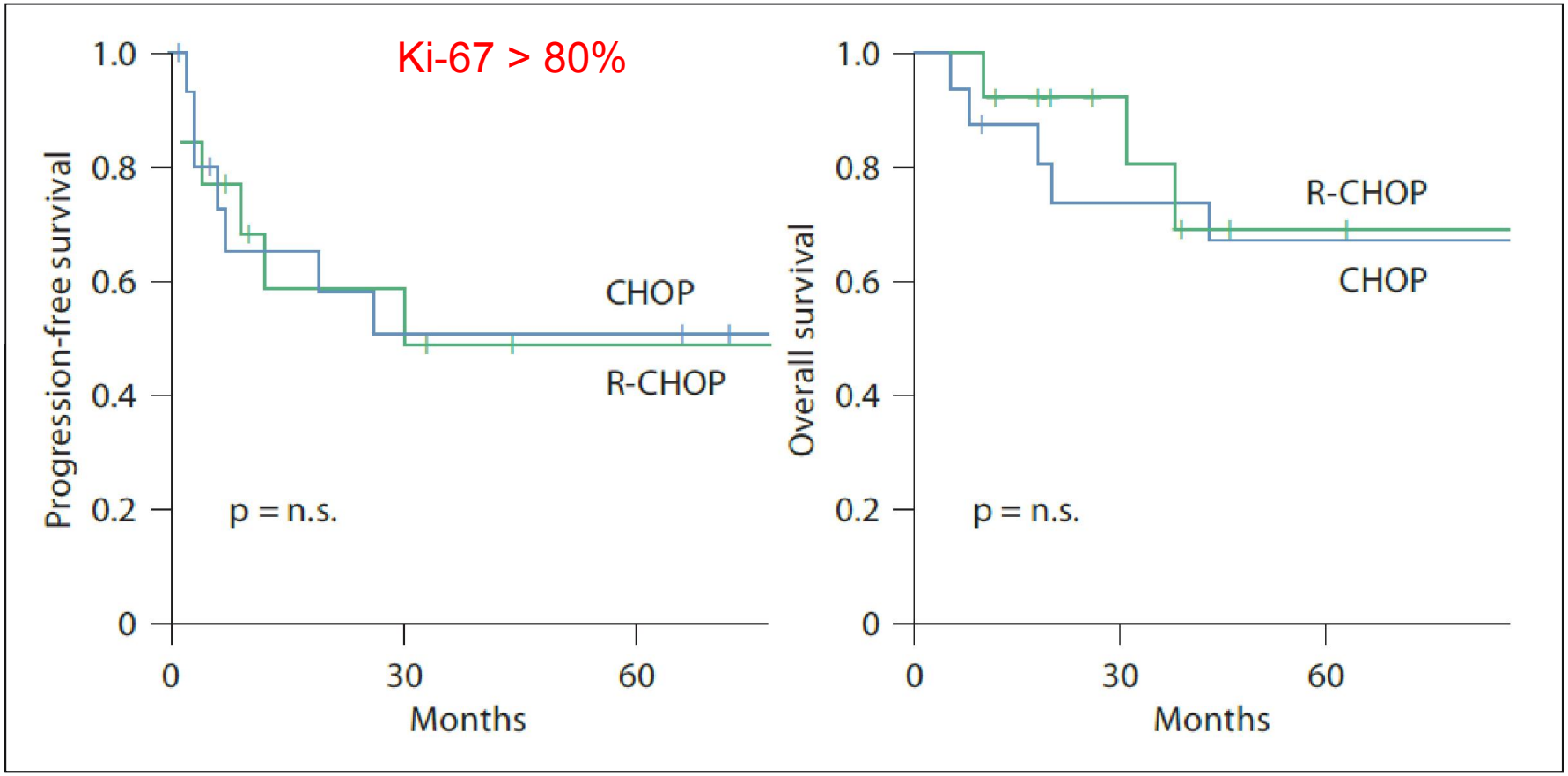
Li ZM, et al. Eur J Haematol 2012;88:510

Ki-67是R-CHOP治疗后独立的预后因素

Patients' characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	P
Progression-free survival						
Age >60 years	3.3	1.5–8.3	0.023	–	–	–
PS ≥2	1.6	0.9–3.3	0.047	–	–	–
Stage III–IV	2.7	1.5–6.8	0.012	–	–	–
Bulky disease	3.7	2.1–6.4	0.045	2.1	1.2–5.3	0.031
IPI 3–5	3.2	1.2–4.9	0.034	–	–	–
Ki67 >80%	2.7	1.2–4.2	0.034	2.6	1.2–3.8	0.033
Overall survival						
Bulky disease	2.2	1.8–4.4	0.044	–	–	–
IPI 3–5	3.2	1.2–5.6	0.025	–	–	–
Ki67 >80%	3.4	2.1–5.2	0.018	2.1	1.6–4.8	0.036

Gaudio F, et al. Acta Haematol 2011;126:44

IPI与治疗方案



Gaudio F, et al. Acta Haematol 2011;126:44

LLBC 研究

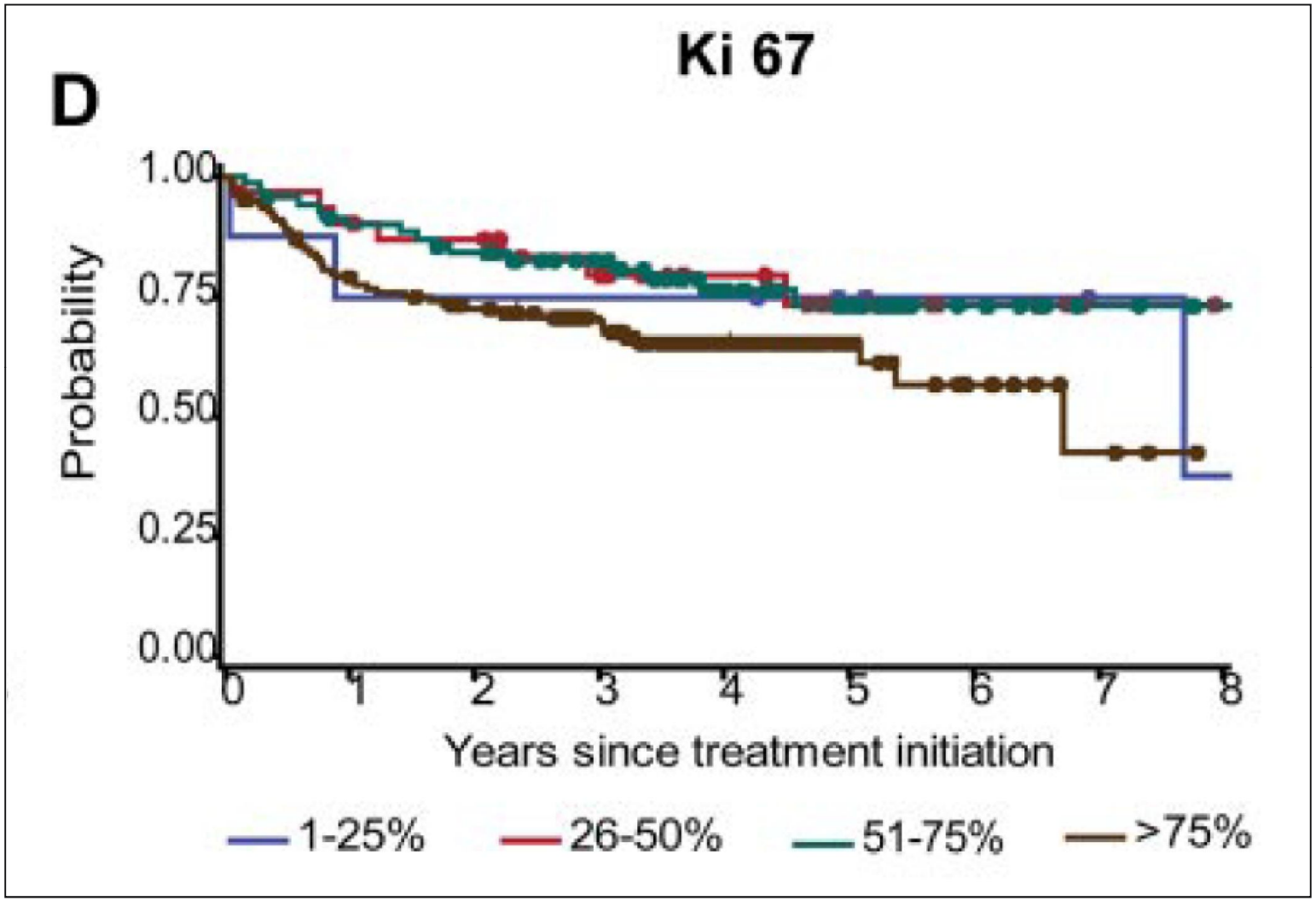
blood
2011 117: 7070-7078
doi:10.1182/blood-2011-04-345256 originally published online May 2, 2011

Prognostic significance of immunohistochemical biomarkers in diffuse large B-cell lymphoma: a study from the Lunenburg Lymphoma Biomarker Consortium

- LLBC：Lunenburg Lymphoma Biomarker Consortium
- 分析了来自欧洲和北美12个研究总共2451例DLBCL患者
- 临床因素：International Prognostic Index (IPI)
- IHC标记物：BCL2, BCL6, CD5, CD10, MUM1, Ki67, HLA-DR

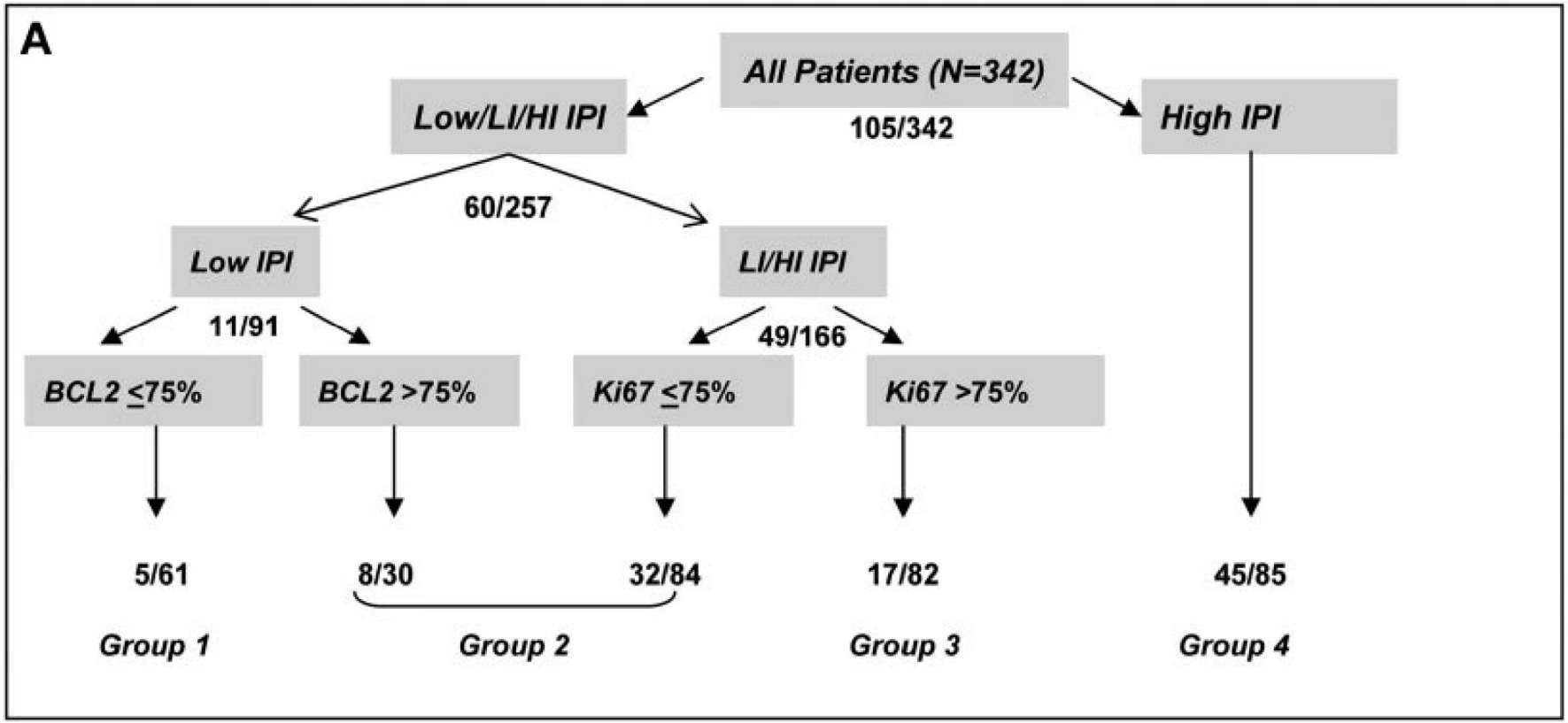
Salles G, et al. Blood 2011;117:7070

Ki-67的预后指导意义



Salles G, et al. Blood 2011;117:7070

IPI/Ki-67的预后评分体系



Salles G, et al. Blood 2011;117:7070

预后

B	Cox PH Regression Model Results			
	Group 1	Group 2	Group 3	Group 4
N. and % of patients	56 (20)	84 (30)	58 (20)	86 (30)
4-year OS (%)	94	81	62	45
HR without imputation (95% CI)	1	3.6 (1.1, 12)	8.4 (2.5, 28)	13 (3.9, 41)
HR with imputation (95% CI)	1	2.1 (0.8, 5.7)	4.5 (1.8, 12)	7.5 (3,19)

Salles G, et al. Blood 2011;117:7070

Ki-67结果判定存在的问题

LLBC 研究

VOLUME 25 · NUMBER 7 · MARCH 1 2007

JOURNAL OF CLINICAL ONCOLOGY

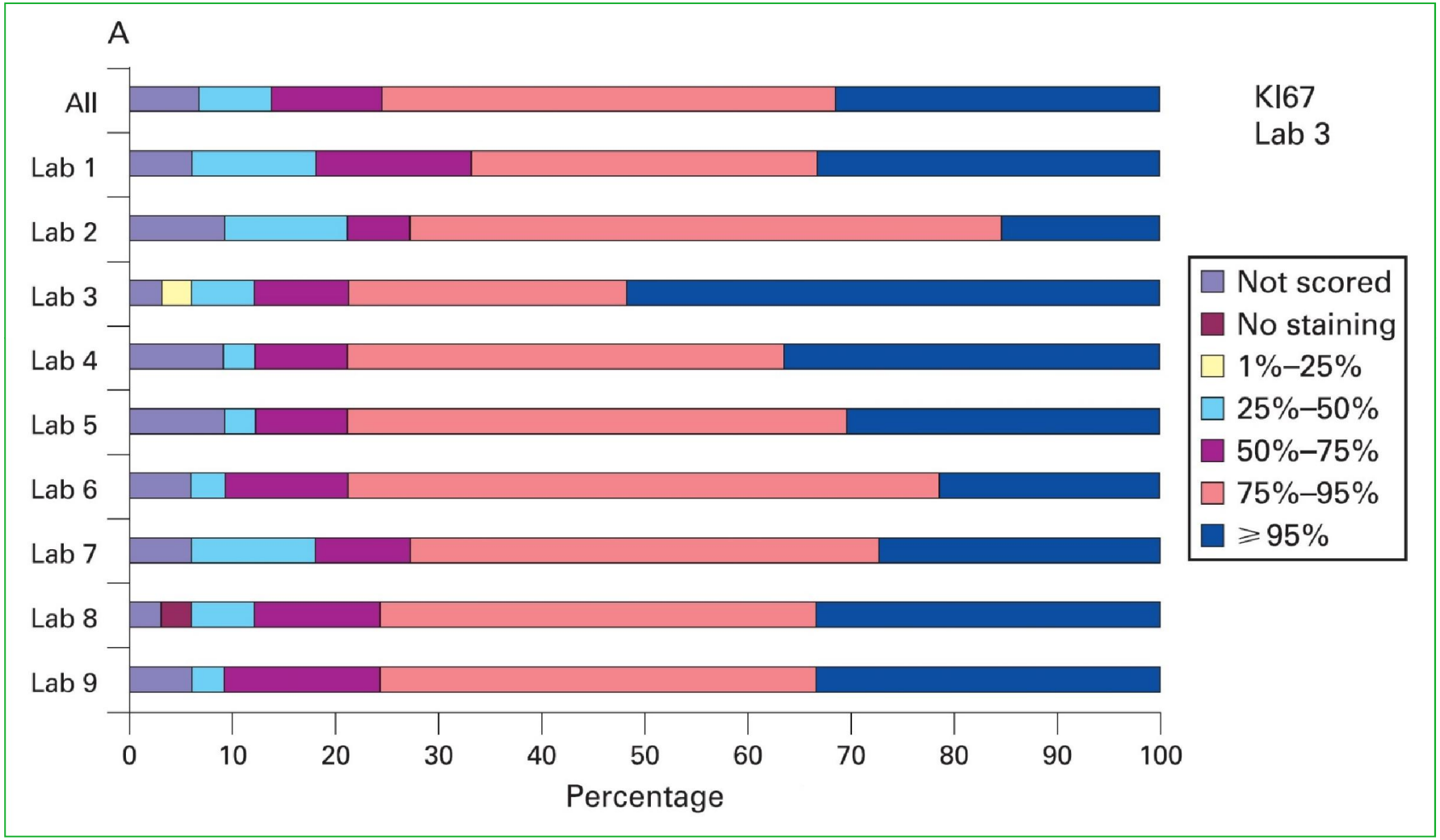
ORIGINAL REPORT

Immunohistochemical Prognostic Markers in Diffuse Large B-Cell Lymphoma: Validation of Tissue Microarray As a Prerequisite for Broad Clinical Applications—A Study From the Lunenburg Lymphoma Biomarker Consortium

- 分析了36例DLBCL的病理切片
- 9位病理学家同时阅片，分析评分差异
- IHC标记物：CD20, CD5, bcl-2, bcl-6, CD10, HLA-DR, MUM1, Ki-67

de Jong D, et al. J Clin Oncol 2007;25:805

Ki-67评分的差异



de Jong D, et al. J Clin Oncol 2007;25:805

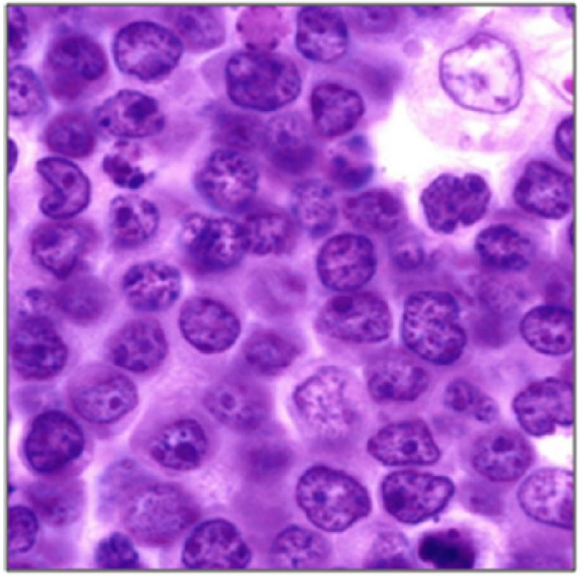
Take-home messages

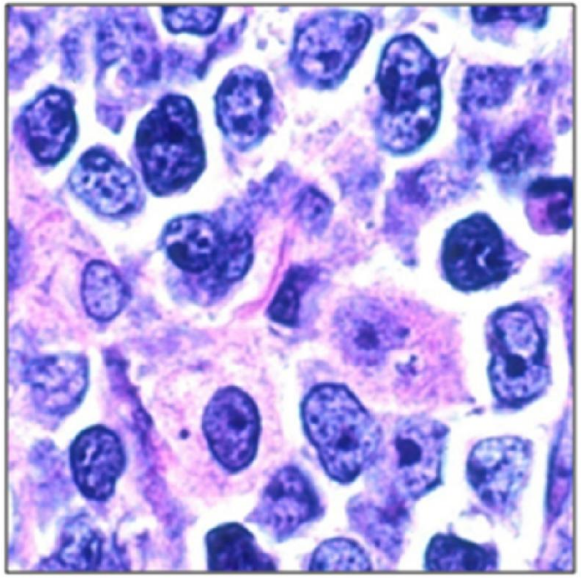
- Immunohistochemical markers in lymphoma should only be scored in the presence of adequate staining of cell populations as internal controls.
- Due to high levels of technical and scoring variations, comparison of published series of immunohistochemical markers in lymphoma should be done with caution.
- At this stage, clinical decisions based on immunohistochemical stratification should only be performed in the context of clinical trials with centralised consensus review and validated assessment of biomarkers, and not on results of individual local centres.

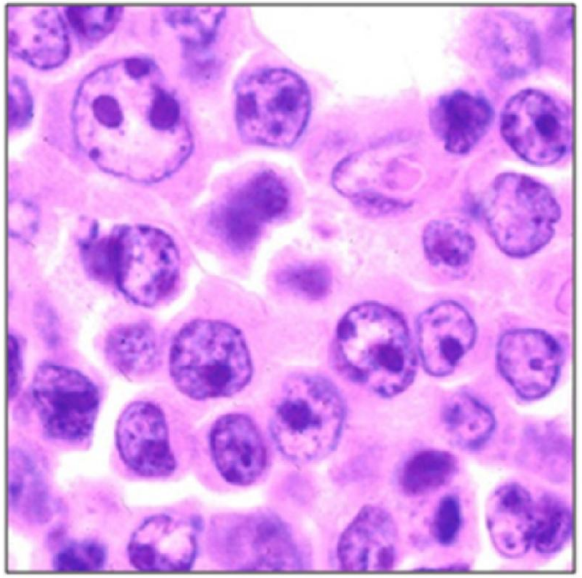
de Jong D, et al. J Clin Oncol 2007;25:805

Ki-67对于DLBCL鉴别诊断的作用

DLBCL的鉴别诊断







Burkitt	B-UNC/BL/DLBCL	DLBCL GCB
CD10 +	CD10 +	CD10 +
BCL6 +	BCL6 +/-	BCL6 +
BCL2 –	BCL2 +	BCL2 +/-
MIB-1 > 98%	MIB-1 < 90%	MIB-1 Variable
MYC simple	MYC complex	MYC rare +
EBV +/-	EBV -	EBV -

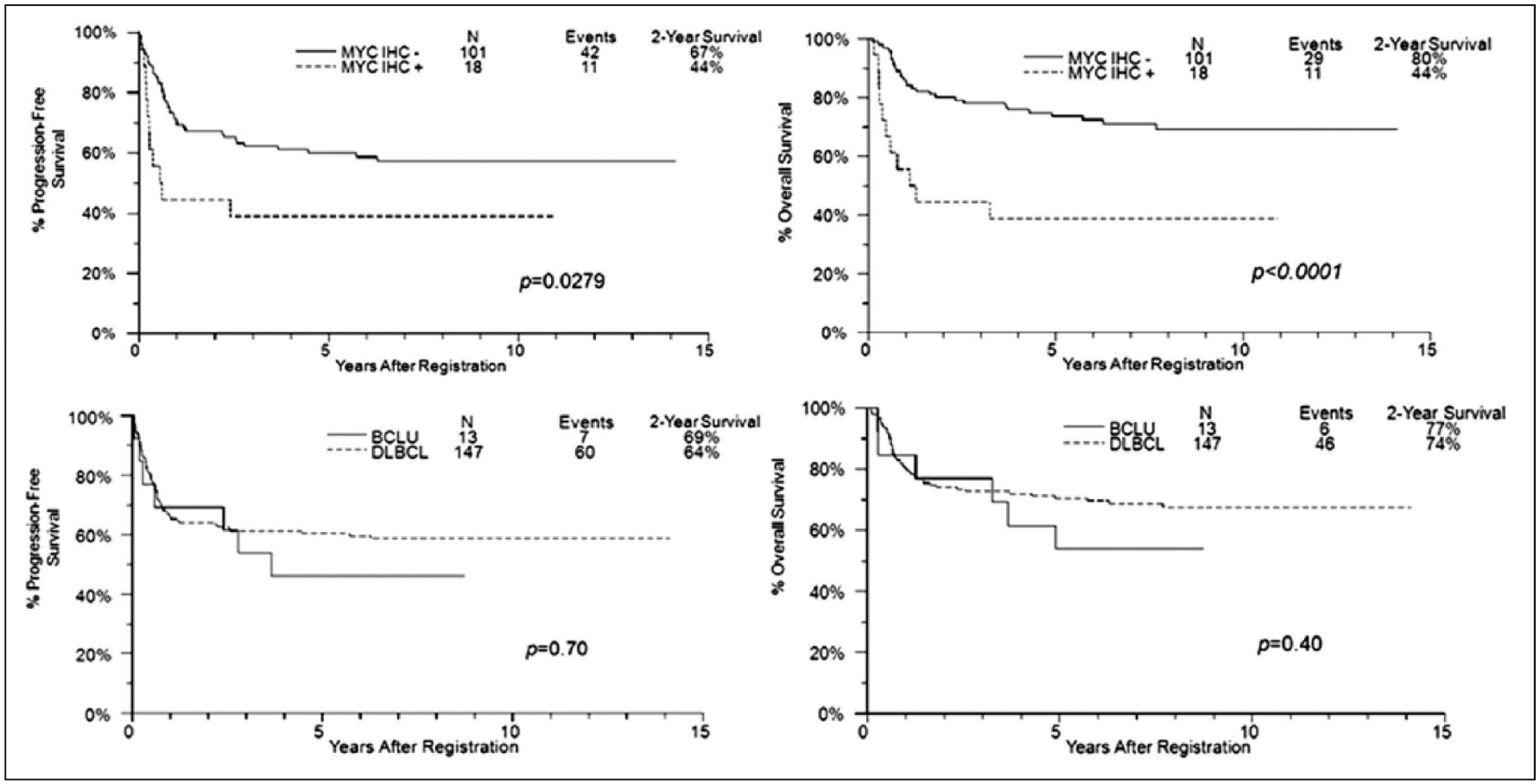
SWOG 9704

TABLE 3. Pathologic Features by Morphology

	BCLU Morphology N = 31	DLBCL Morphology N = 229	All Cases N = 260	*P**
Ki67 IHC				
Median (%)	80	50	60	< 0.001
Range (%)	30-100	10-90	10-100	
Not assessed	5	190	195	
MYC FISH (n [%])				
Positive	8 (33)	8 (15)	16 (21)	0.068
Negative	16 (67)	45 (85)	61 (79)	
Not assessed	7	176	183	

Cook JR, et al. Am J Surg Pathol 2014;38:494

预后

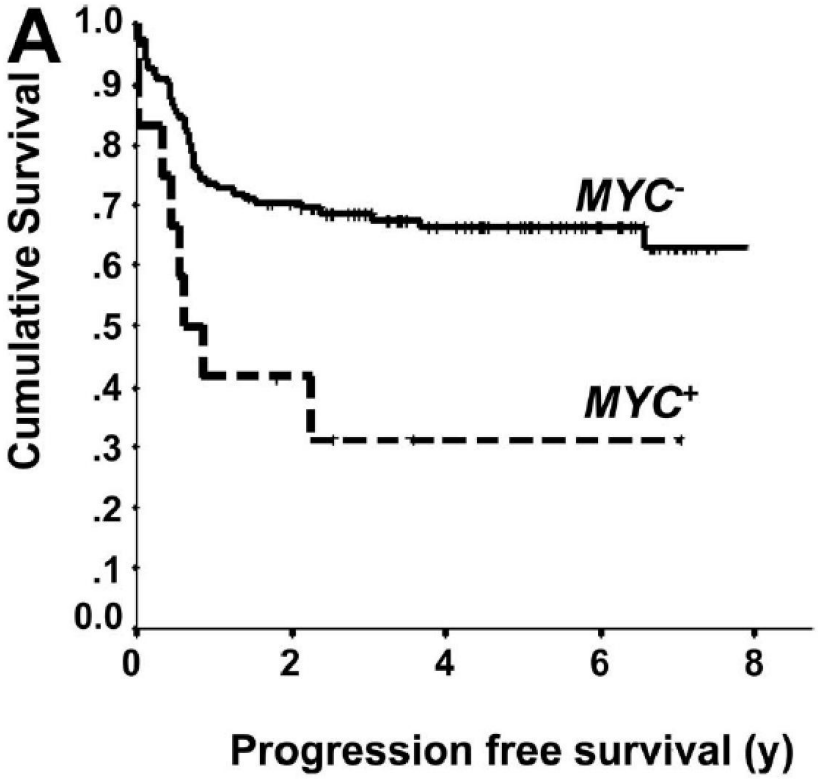


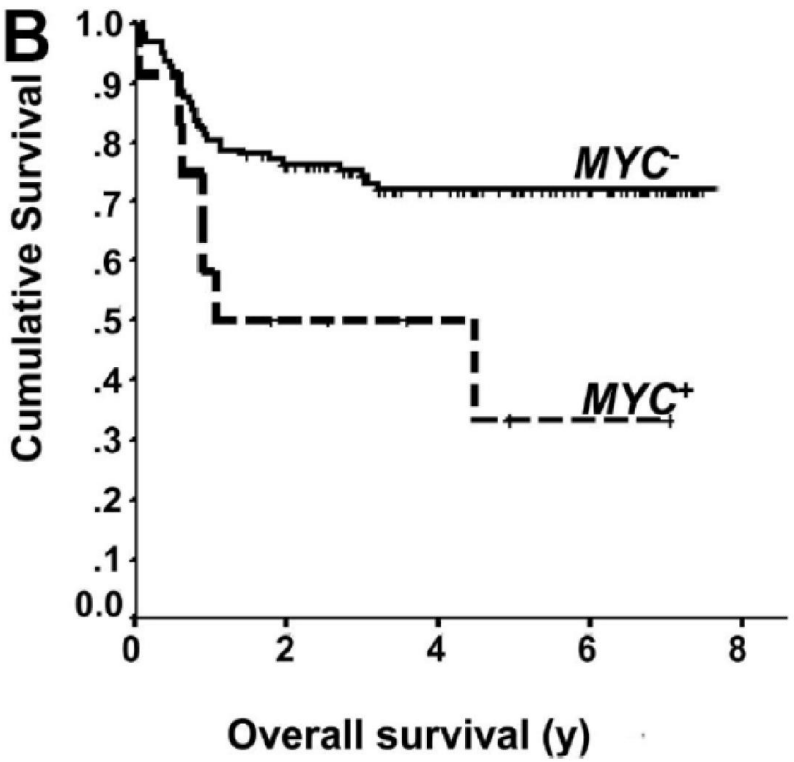
Cook JR, et al. Am J Surg Pathol 2014;38:494

Ki-67与MYC+/DH淋巴瘤的相关性

MYC+ DLBCL的一线治疗结果

- 135例DLBCL接受R-CHOP方案治疗，其中*MYC*基因易位为12例 (8.8%)

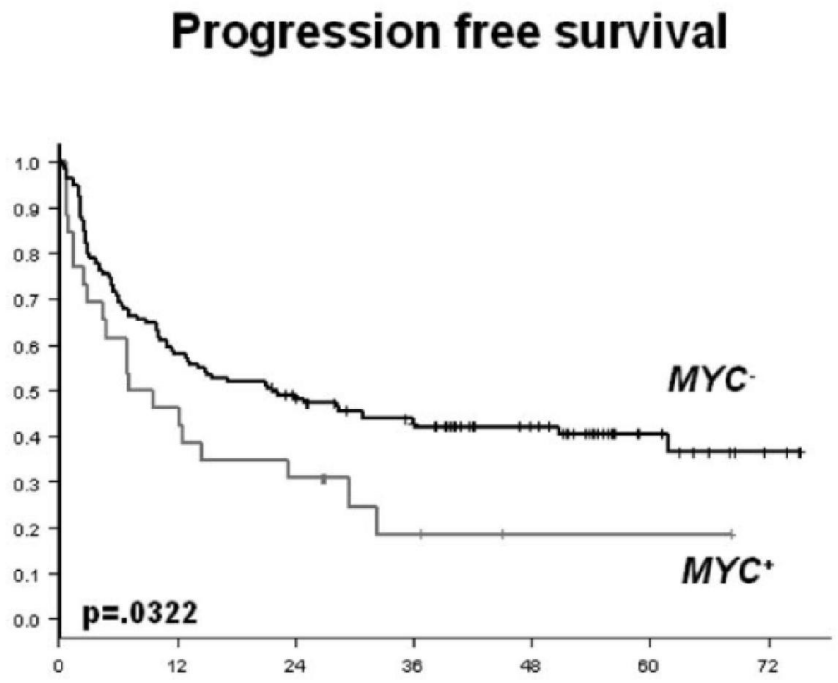


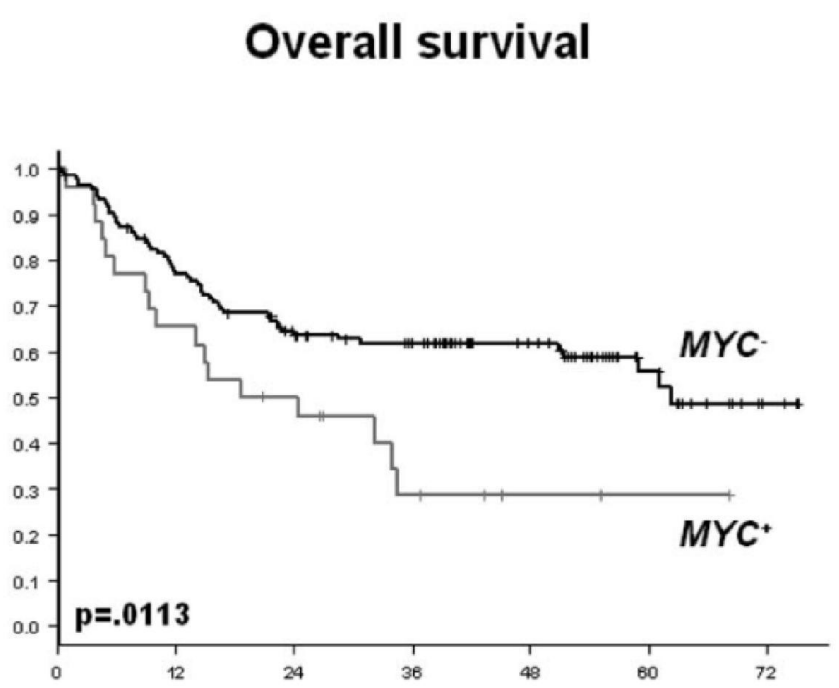


Savage KJ, et al. Blood 2009;114:3533

MYC+ DLBCL的解救治疗结果

- CORAL研究中，161例复发/难治性DLBCL接受R-ICE/R-DHAP方案解救治疗，其中*MYC*基因易位为28例 (17%)

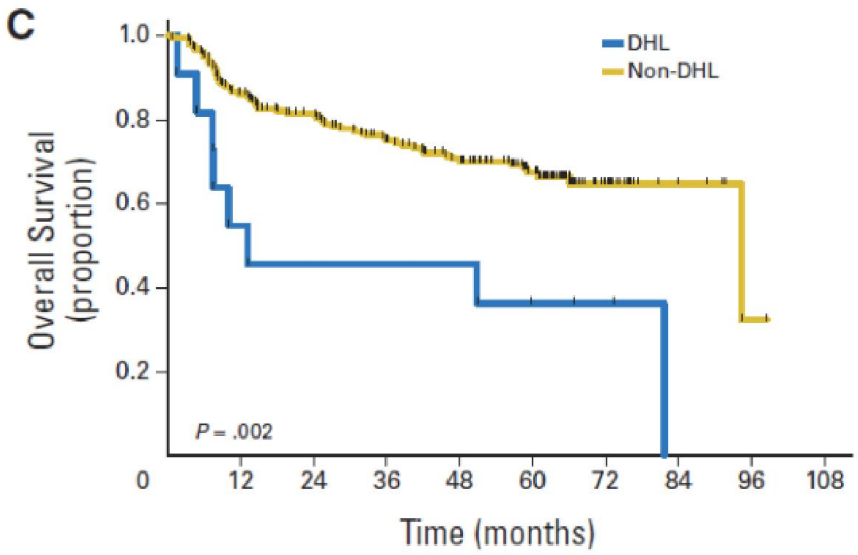


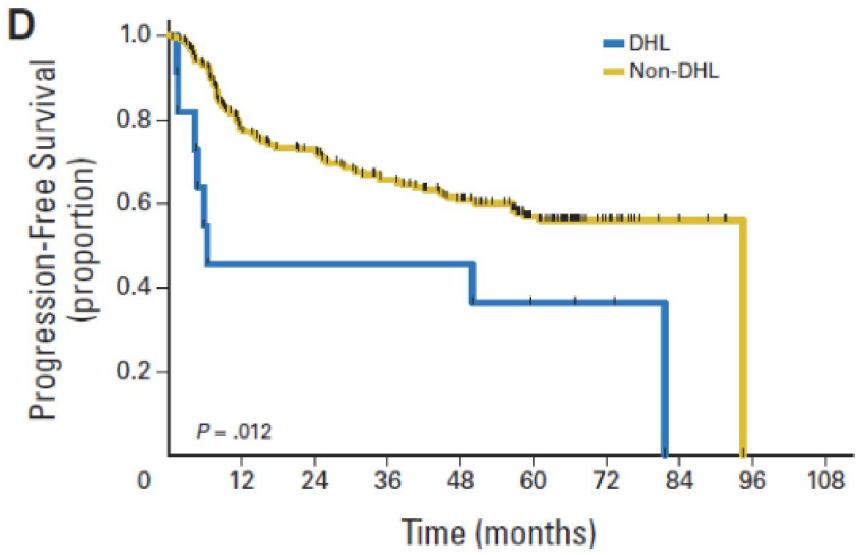


Cuccuini W, et al. Blood 2012;119:4619

DH DLBCL的治疗预后

- 193例DLBCL接受R-CHOP方案治疗，其中*MYC*基因易位为21(11%)，*BCL2*基因易位为47例 (25%)，Double-Hit为11例 (6%)





Green TM, et al. J Clin Oncol 2012;30:3460

问题：High Ki-67是否能预测MYC+ DLBCL?

Ki-67和MYC+具有相关性

Feature	*MYC*$^{+}$, n (%) (n = 12)	*MYC*$^{-}$, n (%) (n = 123)	*P*
Median age, y	68	61	—
Age > 60 y	8 (67)	68 (55)	.448
Male sex	9 (75)	73 (59)	.289
Stage 3 or 4	6 (50)	75 (61)	.459
B symptoms			
Extranodal any site	8 (67)	72 (58)	.584
Extranodal > 1	4 (33)	25 (20)	.295
Bulky disease*	4 (33)	31 (26)	.575
PS > 2*	5 (42)	42 (36)	.677
LDH abnormal*	9 (75)	54 (50)	.100
LDH > 2× ULN	3 (25)	28 (26)	.930
IPI 0-2 vs 3-5	6 (50)	48 (39)	.459
Ki-67†			
More than 80%	7 (58)	27 (22.5)	.007
More than 90%	6 (50)	9 (7.5)	< .001
More than 95%	4 (12)	8 (6.7)	.002
BCL2 protein^{+}‡	8 (67)	86 (70)	.782
GCB phenotype§	7 (58)	61 (51)	.640

Savage KJ, et al. Blood 2009;114:3533

Ki-67和MYC+不具有相关性

Characteristic	CHOP-R Treated		*MYC* Rearranged				
			Yes		No		
	No.	%	No.	%	No.	%	*P*
Total	303	100	35	100	210	100	
Sex							.20
Male	156	51.5	15	42.9	118	56.2	
Female	147	48.5	20	57.1	92	43.8	
Stage							**.01***
I	64	23.9	**6**	**19.4**	**45**	**24.5**	
II	62	23.1	**4**	**12.9**	**46**	**25.0**	
III	51	19.0	**3**	**9.7**	**40**	**21.7**	
IV	91	34.0	**18**	**58.6**	**53**	**28.8**	
Not known	36		**4**		**26**		
IPI							**.064 (.010†)**
Low (0,1)	74	26.8	**5**	**14.7**	**55**	**28.9**	
Intermediate (2,3)	155	56.2	**19**	**55.9**	**106**	**55.8**	
High (4,5)	47	17.0	**10**	**29.4**	**29**	**15.3**	
Not known	27		1		20		
Age-removed IPI							**< .001**
Low (0,1)	146	52.9	**8**	**23.5**	**112**	**58.9**	
Intermediate (2)	79	28.6	**15**	**44.1**	**47**	**24.7**	
High (3,4)	51	18.5	**11**	**32.4**	**31**	**16.3**	
Not known	27		1		20		
Ki67 fraction %							.93
Median	71		76		70		
Range	30-100		50-100		30-100		

Barrans S, et al. J Clin Oncol 2010;28:3360

问题：High Ki-67是否能预测DH/TH DLBCL?

来自新加坡的研究

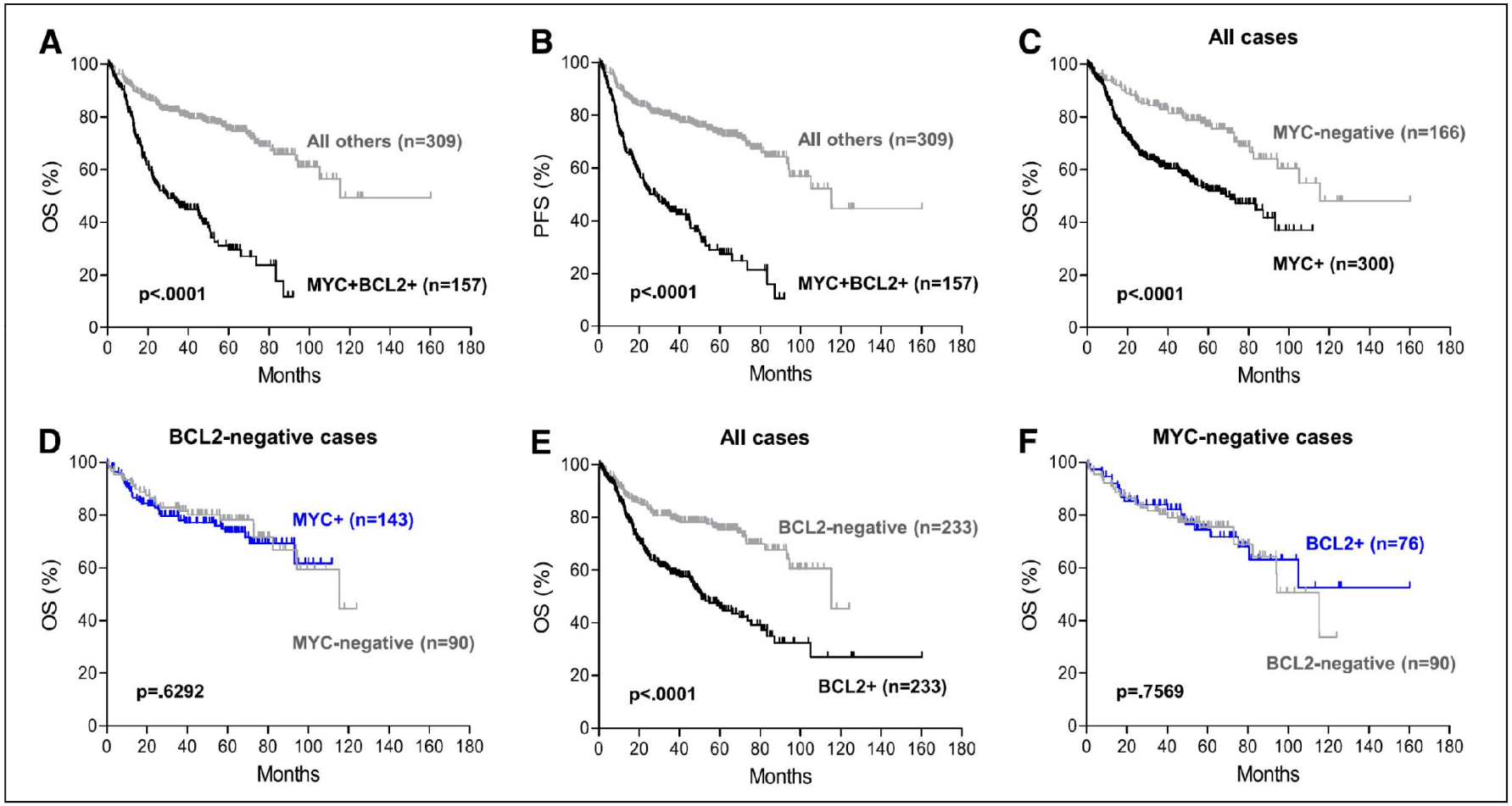
Proliferation fraction using Ki67 > 75% as cut-off			
Lymphoma	Ki67 < 75%	Ki67 > 75%	Total
DLBCL with *MYC*$^+$ double-/triple-hit translocations	6	20	26
DLBCL without *MYC*$^+$ double-/triple-hit translocations	148	258	406
Total	154	278	432
Proliferation fraction using Ki67 > 90% as cut-off			
Lymphoma	Ki67 < 90%	Ki67 > 90%	Total
DLBCL with *MYC*$^+$ double-/triple-hit translocations	12	14	26
DLBCL without *MYC*$^+$ double-/triple-hit translocations	251	155	406
Total	263	169	432

Ki-67 > 75%：敏感度 0.77 特异度 0.36
Ki-67 > 90%：敏感度 0.54 特异度 0.62

Mationg-Kalaw E, et al. Histopathology 2012;61:1214

MYC/BCL-2 IHC 双表达

MYC/BCL-2 各组预后



Hu S, et al. Blood 2013;121:4021

患者资料

	Overall			DP	Non-DP	
	N (%)	OS, *P*	PFS, *P*	N (%)	N (%)	*P* value
Patients	466 (100)			157 (100)	309 (100)	
Age						
≤60	194 (42)	.0004	.0016	49 (31)	145 (47)	.0011
>60	272 (58)			108 (69)	164 (53)	
B symptoms*						
Absence	276 (68)	.0015	.0014	88 (62)	188 (72)	.0541
Presence	127 (32)			53 (38)	74 (28)	
ECOG performance status*						
<2	350 (88)	<.0001	<.0001	111 (83)	239 (90)	.0453
≥2	50 (12)			23 (17)	27 (10)	
Stage*						
I-II	219 (49)	<.0001	<.000l	50 (33)	169 (57)	<.0001
III-IV	228 (51)			100 (67)	128 (43)	
Extranodal sites*						
<2	346 (78)	<.0001	<.000l	106 (72)	240 (82)	.0160
≥2	96 (22)			42 (28)	54 (18)	
IPI risk group*						
0-2	263 (64)	<.000l	<.0001	70 (51)	193 (70)	.0001
3-5	148 (36)			67 (49)	81 (30)	
Treatment response						
CR	354 (76)	<.000l	<.000l	103 (66)	251 (84)	<.0001
Others	112 (24)			54 (34)	48 (16)	
COO classification						
GCB	241 (52)	.0080	.0075	53 (34)	188 (61)	<.0001
ABC	225 (48)			104 (66)	121 (39)	
Ki-67*						
<7O	158 (34)	.2998	.3434	41 (26)	117 (38)	.0086
≥70	304 (66)			116 (74)	188 (62)	

MYC IHC vs. FISH

Percentage of MYC IHC+	Sensitivity	Specificity	PPV	NPV
40% or more	1	0.45	0.37	1
50% or more	1	0.61	0.45	1
60% or more	1	0.71	0.53	1
70% or more	1	0.84	0.67	1
80% or more	0.89	0.88	0.67	0.96

FISH, fluorescence *in situ* hybridisation; IHC, immunohistochemistry; NPV, negative predictive value; PPV, positive predictive value.

Lynnhtun K, et al. Pathology 2014;46:211

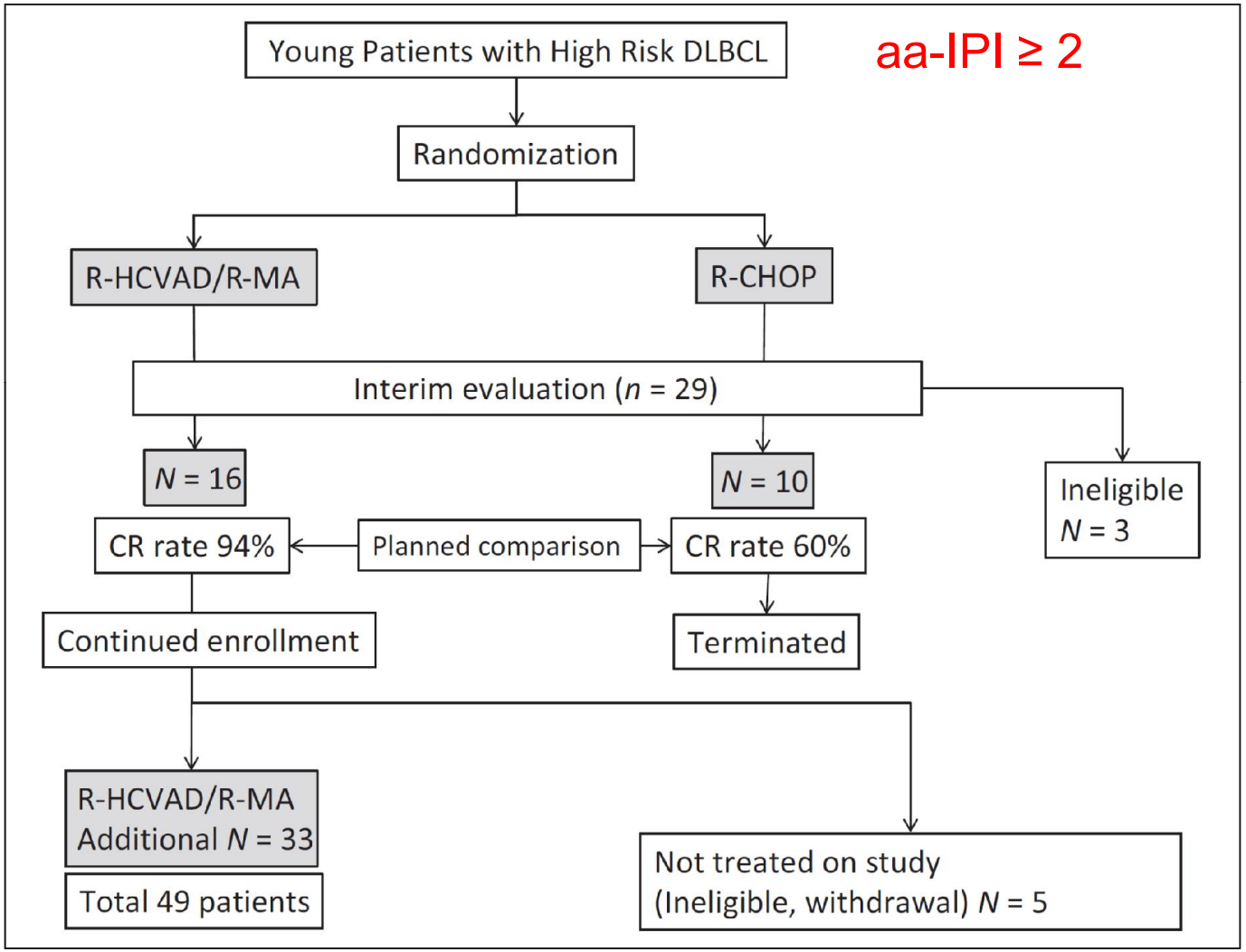
针对高增殖活性DLBCL的治疗方案

问题：针对高度侵袭性B细胞淋巴瘤的方案可否逆转高增殖活性DLBCL的不良预后

Hyper-CVAD/MA

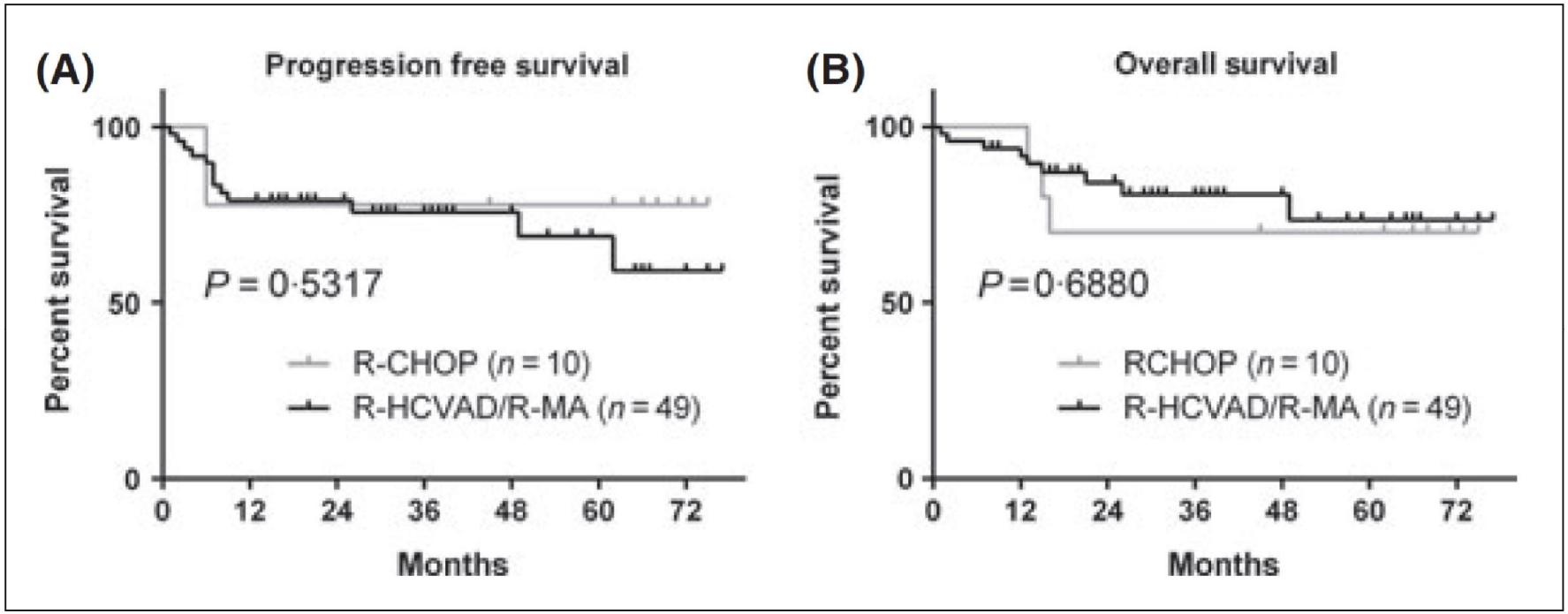
CODOX-M/IVAC

MDACC的前瞻性II期随机试验



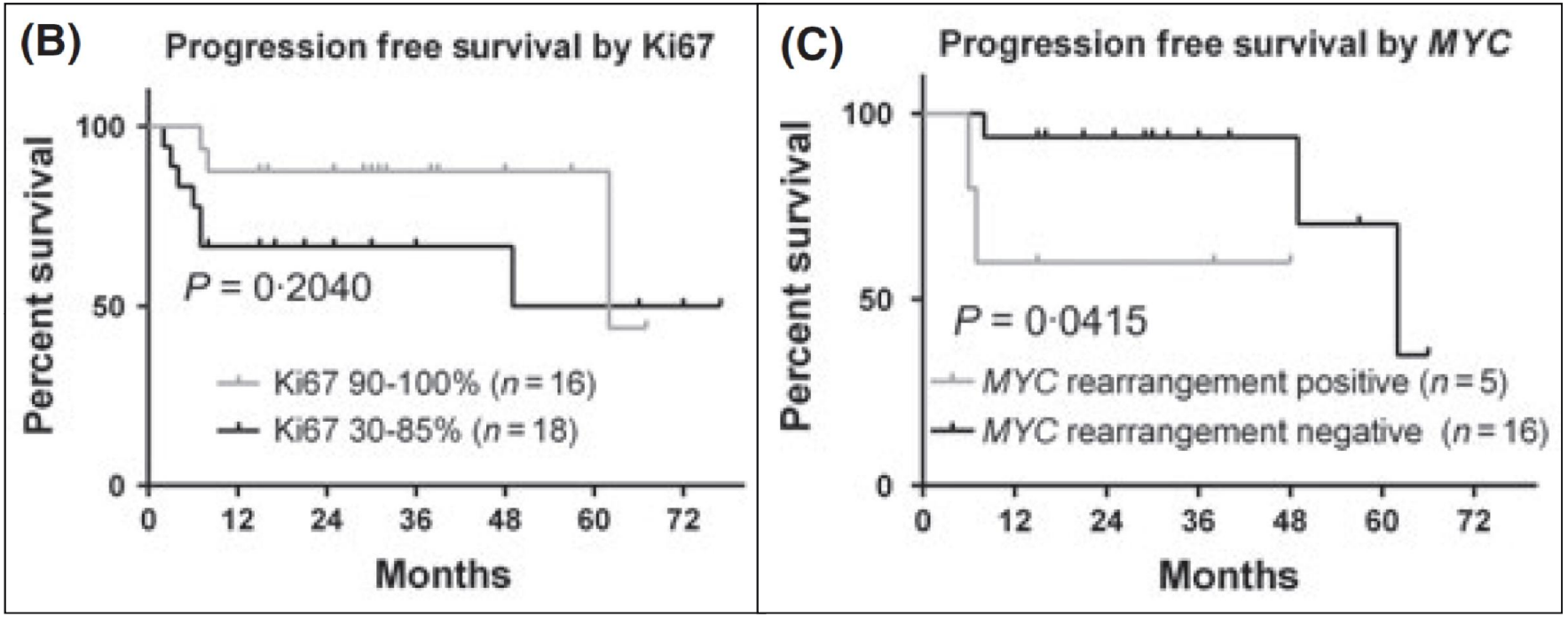
Oki Y, et al. Bri J Haematol 2013;163:611

生存



Oki Y, et al. Bri J Haematol 2013;163:611

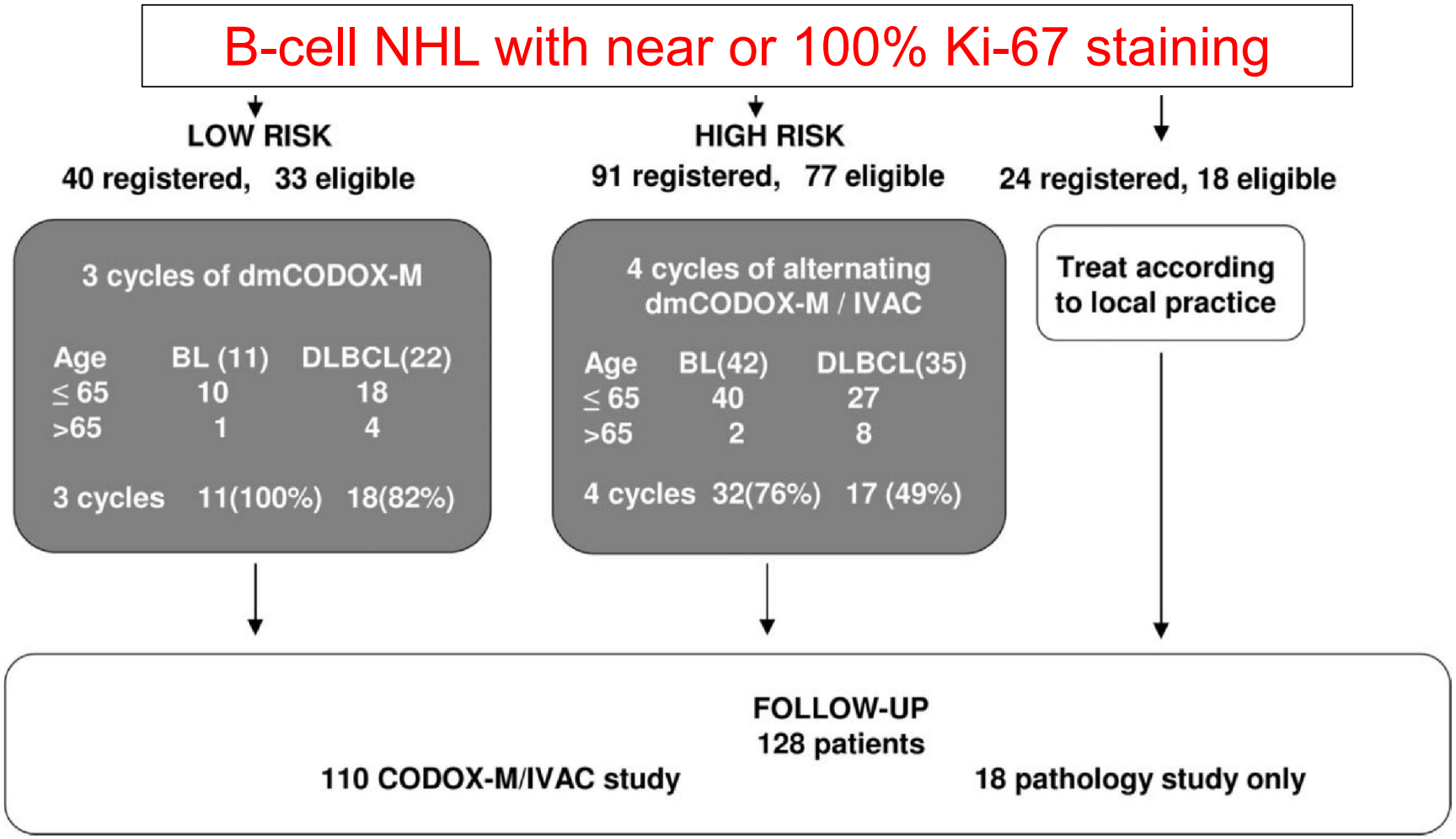
High Ki-67和MYC+仍然是不良预后因素



* 针对接受Hyper-CVAD/MA的患者

Oki Y, et al. Bri J Haematol 2013;163:611

MRC/NCRI LY10



Mead GM, et al. Blood 2008;112:2248

预后比较 (BL vs. DLBCL)

	BL	DLBCL	P 值	BL	DLBCL*	P 值
2年PFS (%)	65	55	0.38	64	27	0.017
2年OS (%)	67	59	0.38	67	40	0.052

DLBCL*：伴有MYC，BCL-2或BCL-6基因易位的DLBCL

小结

- Ki-67是一个判断DLBCL增殖活性的有效指标，部分有助于与Burkitt和BCLU的鉴别
- 在目前的免疫化疗时代，高增殖活性DLBCL的不良预后显得尤为明显
- 高Ki-67水平与MYC+/DH DLBCL无明显相关性，而预测MYC/BCL-2 IHC双表达还需要大样本前瞻性研究的证实
- 针对Burkitt淋巴瘤的治疗方案无法逆转高增殖活性DLBCL的不良预后，特别是对于具有MYC基因易位的病例
- 在目前的证据背景下，DLBCL应根据IPI/细胞起源/MYC基因状态等进行个体化治疗或研究，而并非高增殖活性

谢谢！