原发中枢淋巴瘤的治疗进展

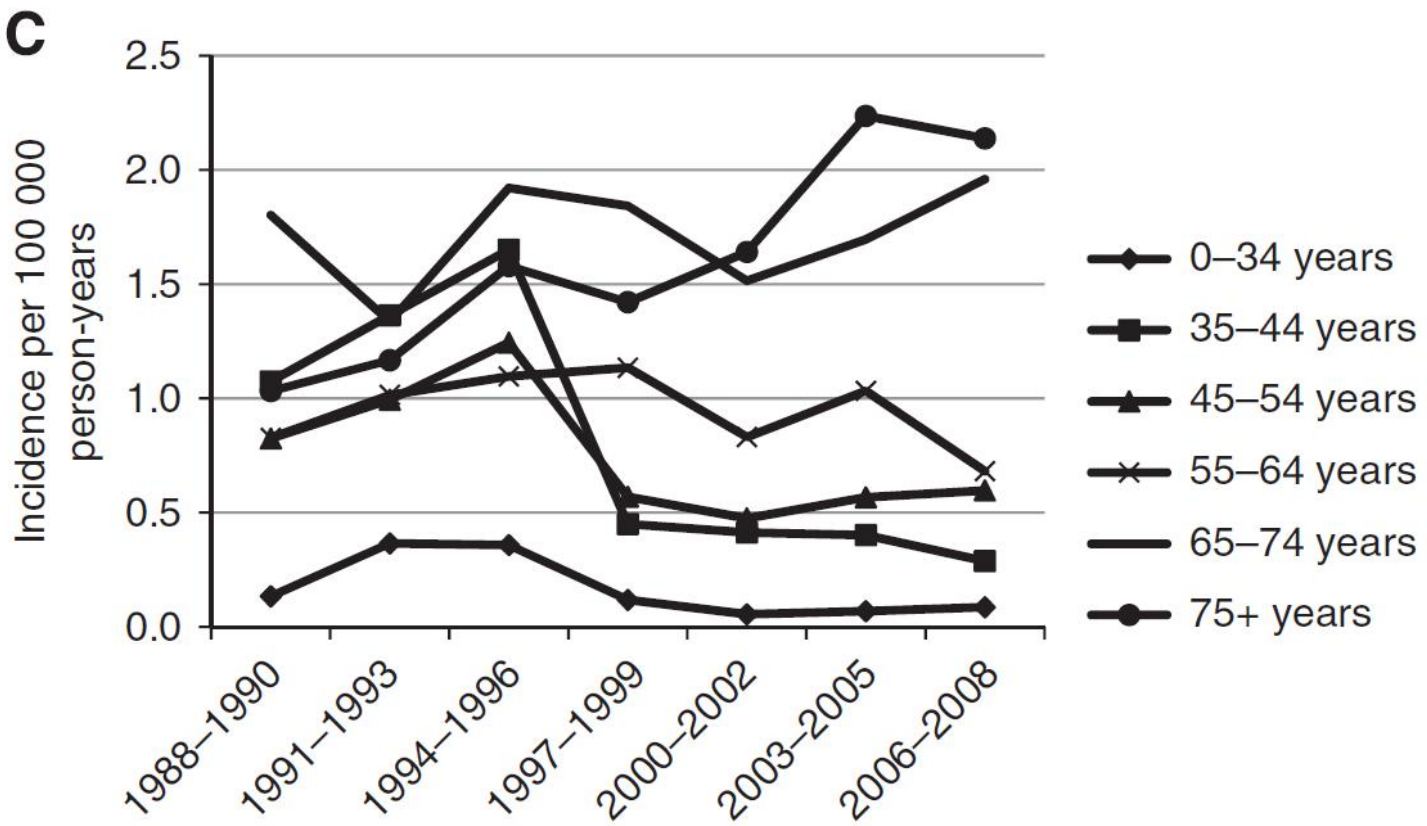
郭 晔

同济大学附属东方医院

2018-3-31 北京

流行病学

- 发病率：约占脑瘤的3%，NHL的2-3%

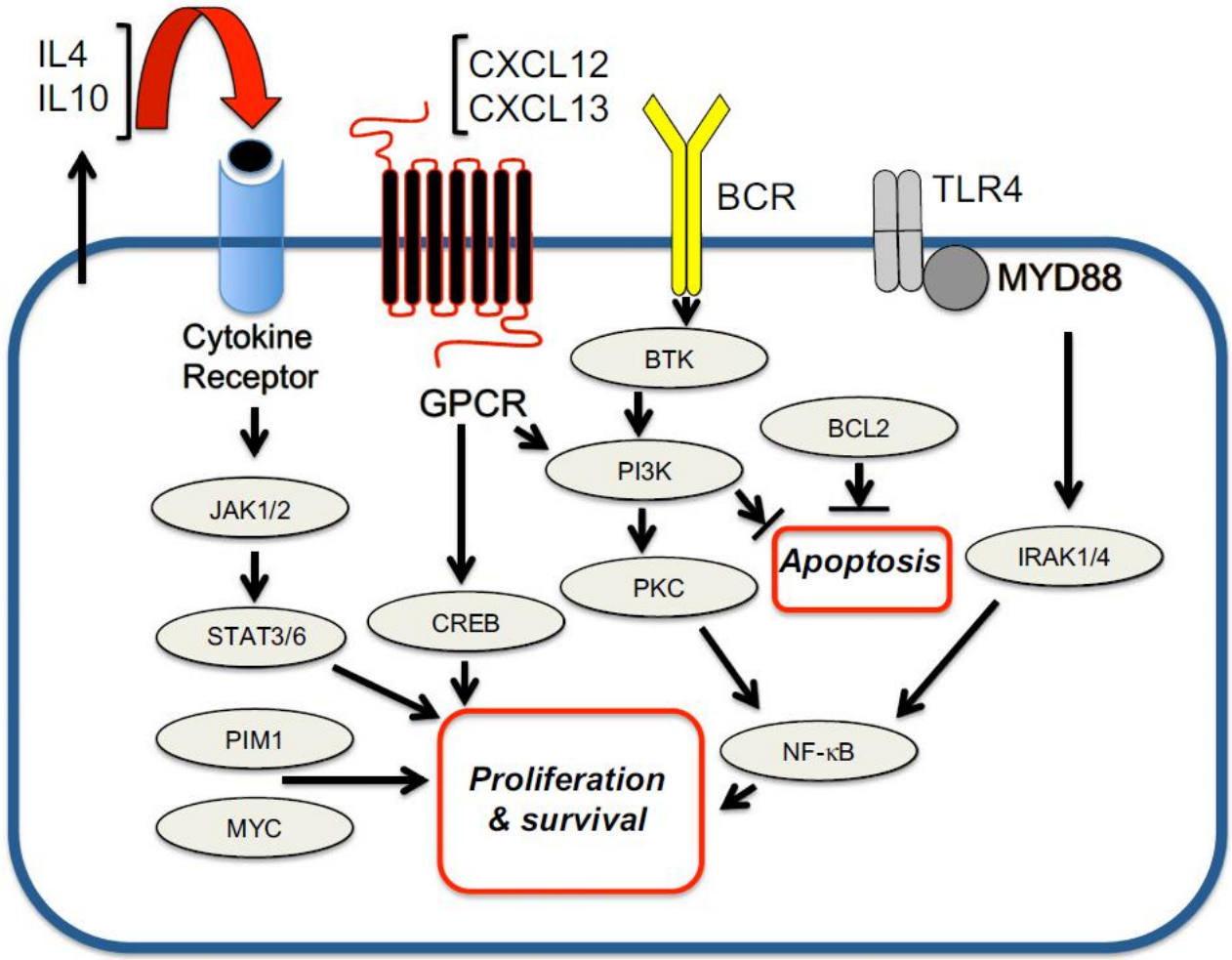


Villano JL, et al. Br J Cancer 2011;105:1414

病理

- 组织学类型
  - DLBCL：95% (WHO 2008 独立亚型)
  - 其他：Burkitt, MCL, 淋母, T细胞淋巴瘤
- 免疫表型
  - BCL-2：56-93%
  - CD10：< 10%
  - BCL-6：50-80%
  - MUM1：> 95%

信号传导通路


IL4
IL10
CXCL12
CXCL13
BCR
TLR4
MYD88
Cytokine Receptor
GPCR
BTK
PI3K
BCL2
JAK1/2
Apoptosis
IRAK1/4
PKC
STAT3/6
CREB
PIM1
MYC
Proliferation & survival
NF-κB

预后因素 (IELSG)

Table 3 International Extranodal Lymphoma Study Group Score

Parameters	Prognostic Groups	2-Year OS, %
Age > 60 years ECOG PS > 1 LDH > normal level High CSF protein Deep brain lesions	0-1	80
	2-3	48
	4-5	15

Abbreviations: CSF = cerebrospinal fluid; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; OS = overall survival; PS = performance status

Ferreri A, et al. J Clin Oncol 2003;21:266

预后因素 (MSKCC)

Table 4 Memorial Sloan-Kettering Cancer Center Prognostic Model

Parameters	Prognostic Groups	Median OS, Years
Age ≤ 50 years or > 50 years KPS < 70% or ≥ 70%	Age ≤ 50 years	8.5
	Age > 50 years and KPS ≥ 70%	3.2
	Age > 50 years and KPS < 70%	1.1

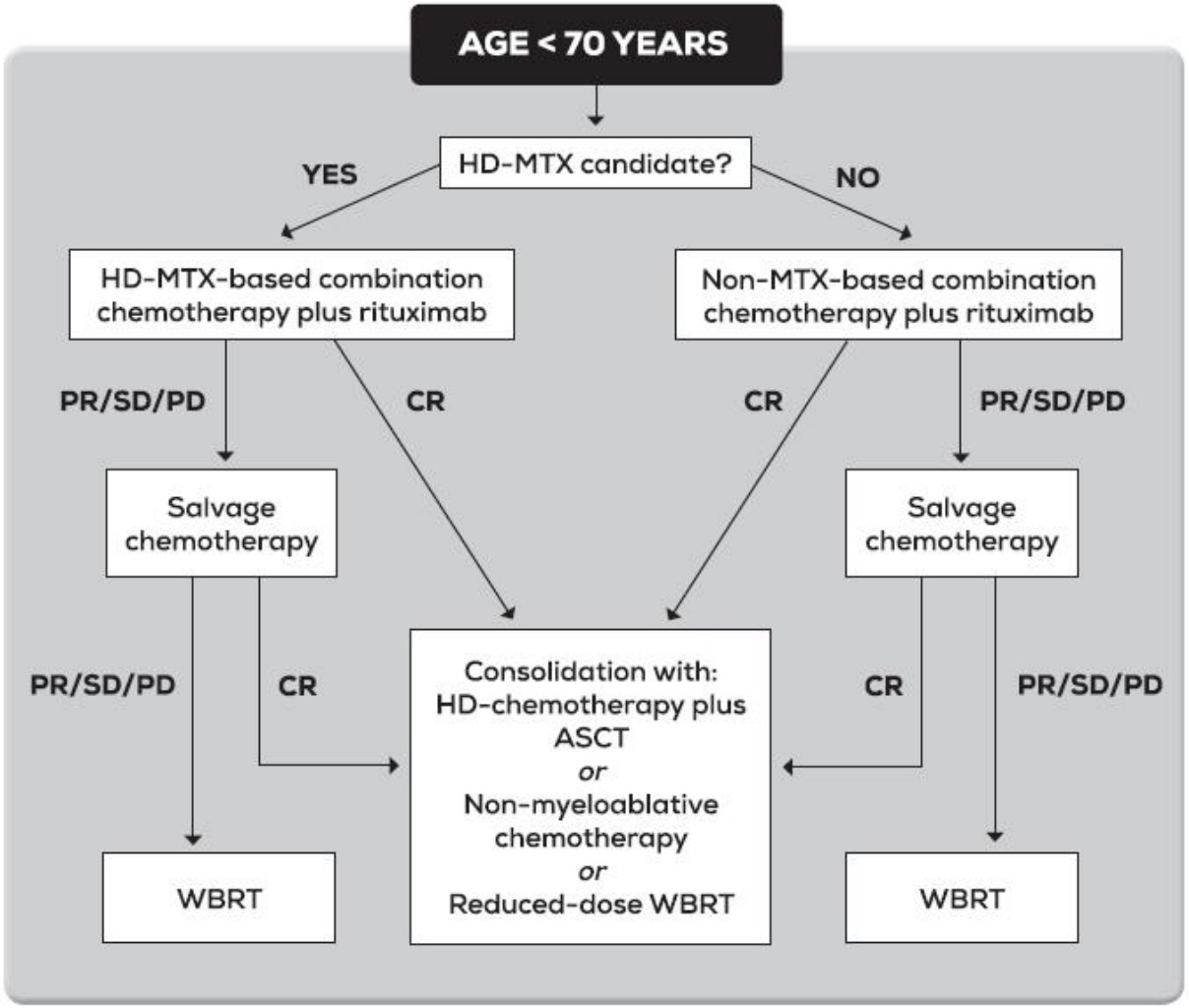
Abbreviations: KPS = Karnofsky performance status; OS = overall survival

Abrey LE, et al. J Clin Oncol 2006;24:5711

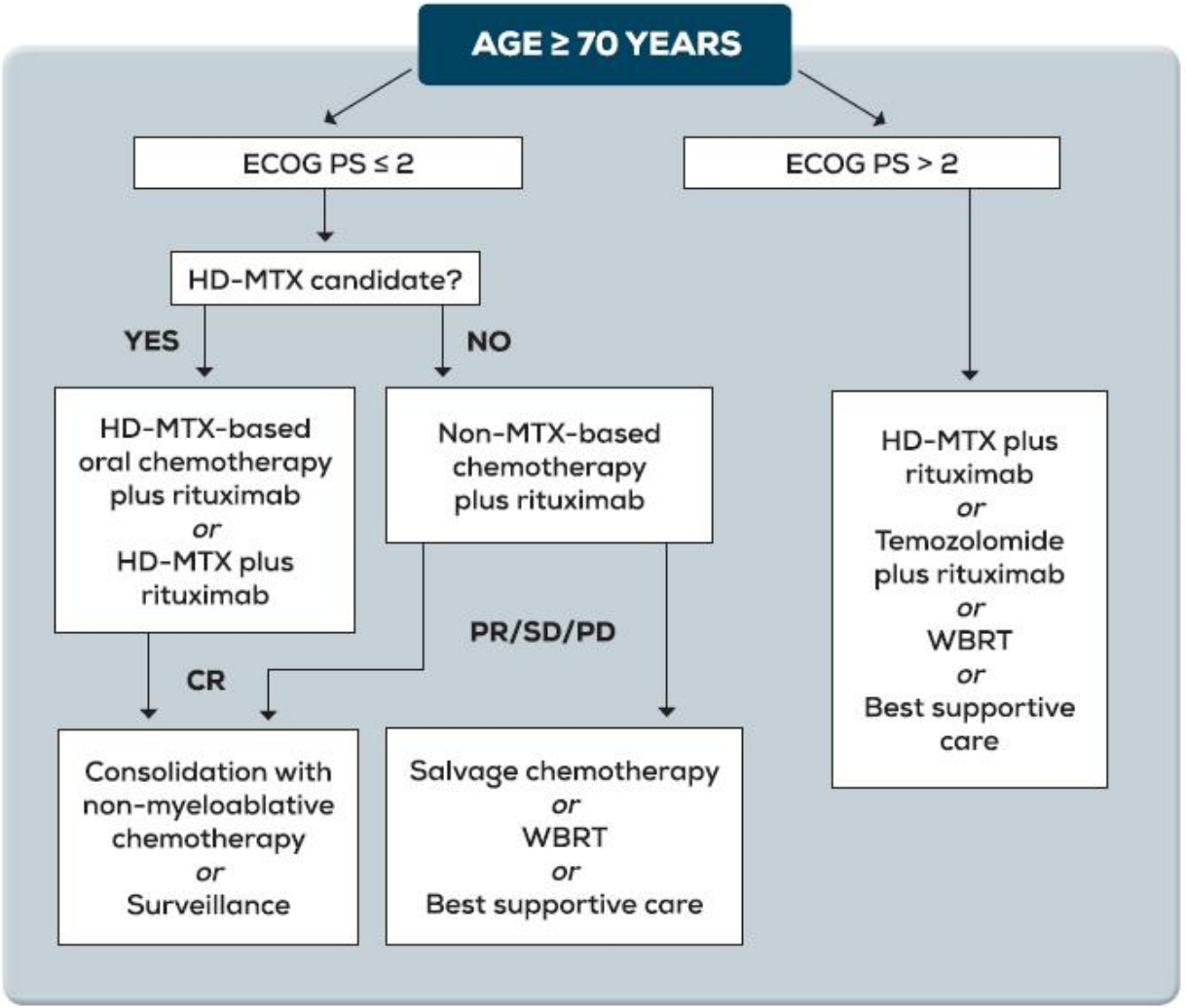
疗效评价标准

Response	Brain Imaging	Corticosteroid Dose	Eye Examination	CSF Cytology
Complete response	No contrast-enhancing lesion	None	Normal	Negative
Unconfirmed complete response	No contrast-enhancing lesion	Any	Normal	Negative
	Minimal abnormality	Any	Minor retinal pigment epithelium abnormality	Negative
Partial response	50% decrease in enhancing lesion	Irrelevant	Normal or minor retinal pigment epithelium abnormality	Negative
	No contrast-enhancing lesion	Irrelevant	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
Progressive disease	25% increase in enhancing lesion	Irrelevant	Recurrent or new ocular disease	Recurrent or positive
	Any new site of disease: central nervous system or systemic			
Stable disease	All cases not covered by responses above			

治疗原则 (1)


AGE < 70 YEARS
HD-MTX candidate?
YES
NO
HD-MTX-based combination chemotherapy plus rituximab
Non-MTX-based combination chemotherapy plus rituximab
PR/SD/PD
CR
CR
PR/SD/PD
Salvage chemotherapy
Salvage chemotherapy
PR/SD/PD
CR
CR
PR/SD/PD
Consolidation with:
HD-chemotherapy plus ASCT
or
Non-myeloablative chemotherapy
or
Reduced-dose WBRT
WBRT
WBRT

治疗原则 (2)

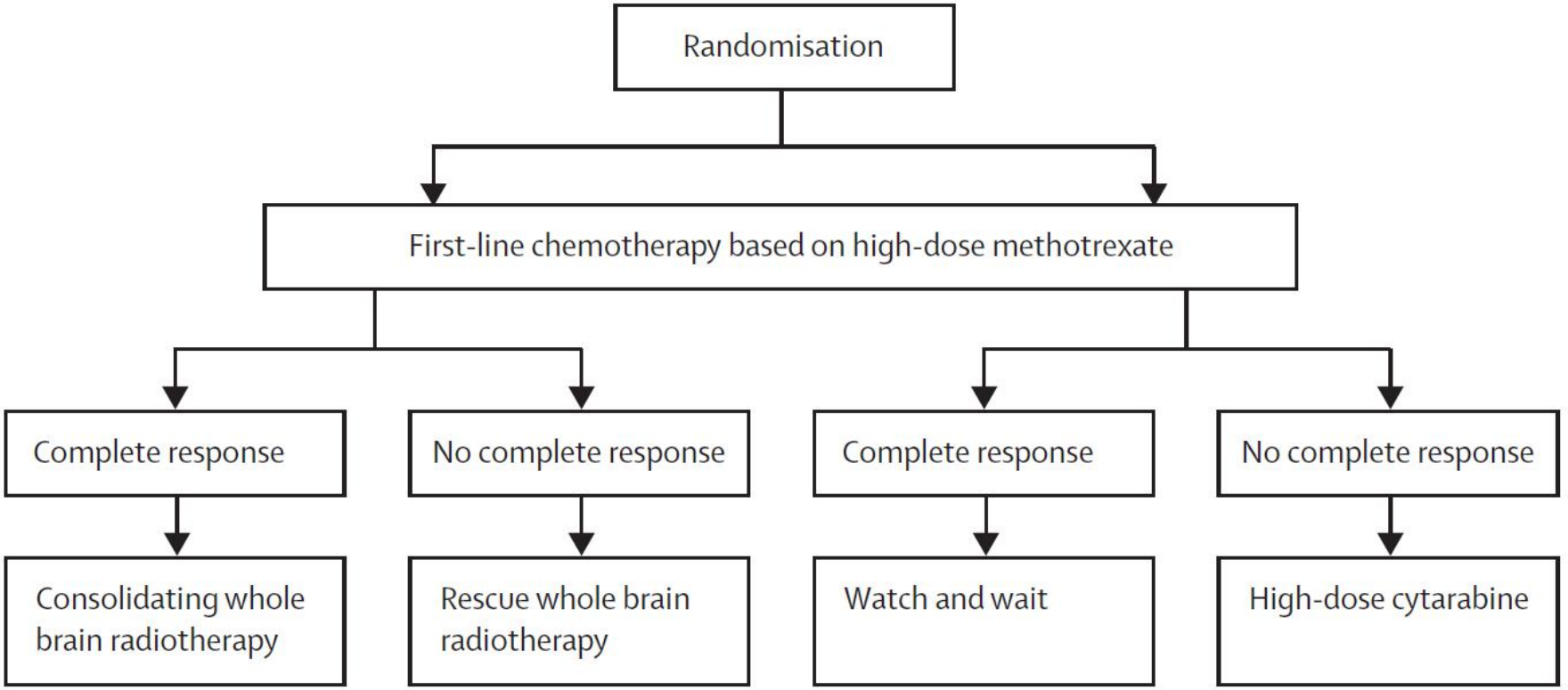

AGE ≥ 70 YEARS
ECOG PS ≤ 2
ECOG PS > 2
HD-MTX candidate?
YES
NO
HD-MTX-based oral chemotherapy plus rituximab or HD-MTX plus rituximab
Non-MTX-based chemotherapy plus rituximab
HD-MTX plus rituximab or Temozolomide plus rituximab or WBRT or Best supportive care
PR/SD/PD
CR
Consolidation with non-myeloablative chemotherapy or Surveillance
Salvage chemotherapy or WBRT or Best supportive care

单纯放疗

Study	N	WBRT Dose	ORR (CR/PR)	2-Year Survival	OS (Months)
RTOG 8315[a]	41	40 Gy (+ 20 Gy tumor boost)	90% (55%/35%)	28%	**11.6**
JASTRO[b]	132	40 Gy (Median tumor dose = 50 Gy)	NR	39%	**18**

Nelson DF, et al. Int J Radiat Oncol Biol Phys 1992;23:9
Shibamoto Y, et al. Int J Radiat Oncol Biol Phys 2005;62:809

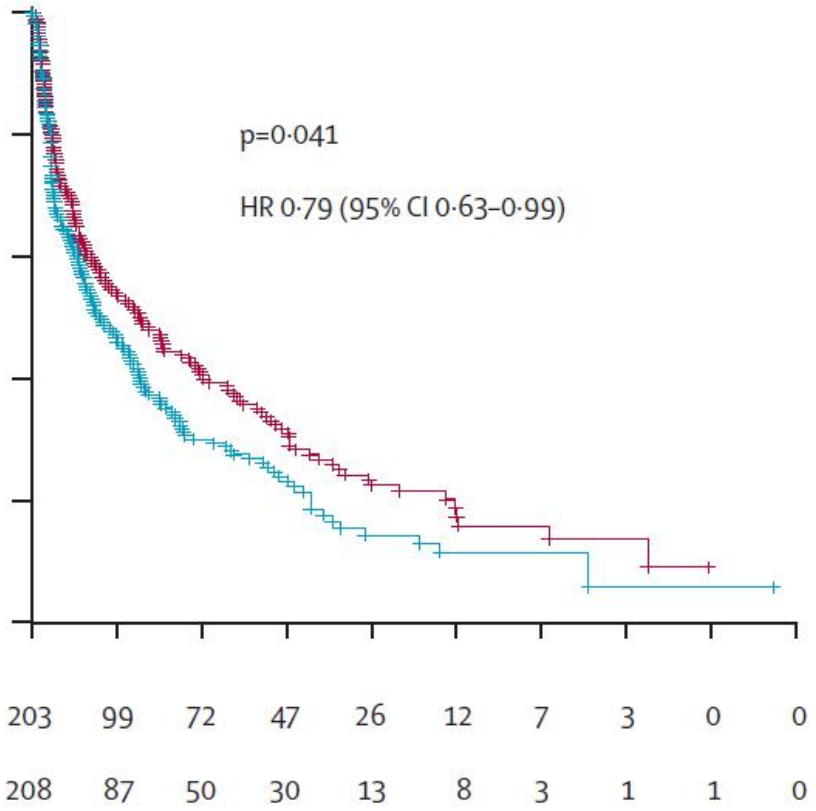
巩固放疗 (G-PCNSL-SG-1)



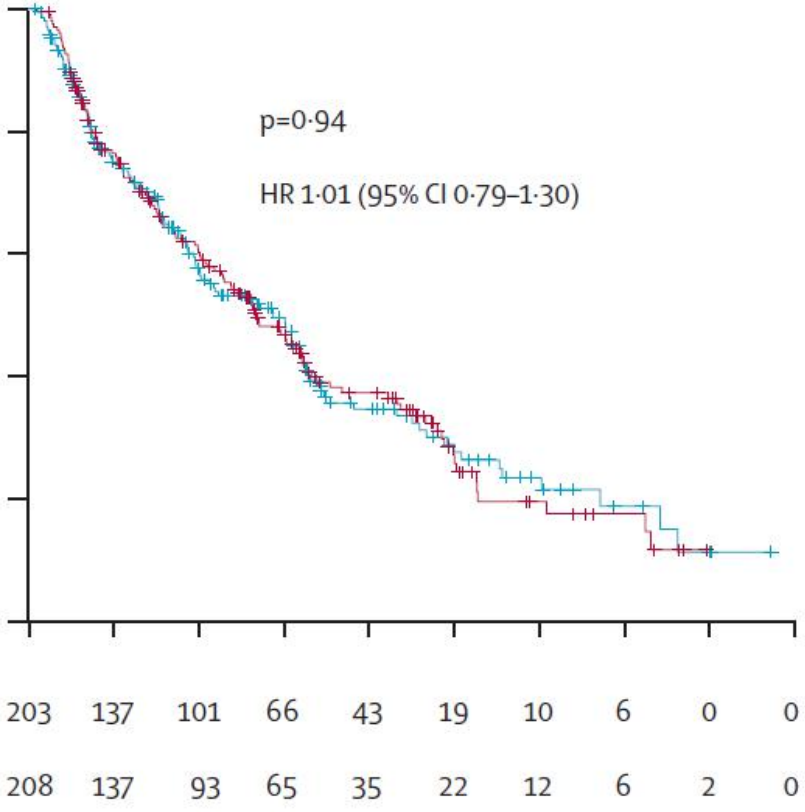
Thiel E, et al. Lancet Oncol 2010;11:1036

放疗的作用

PFS



OS



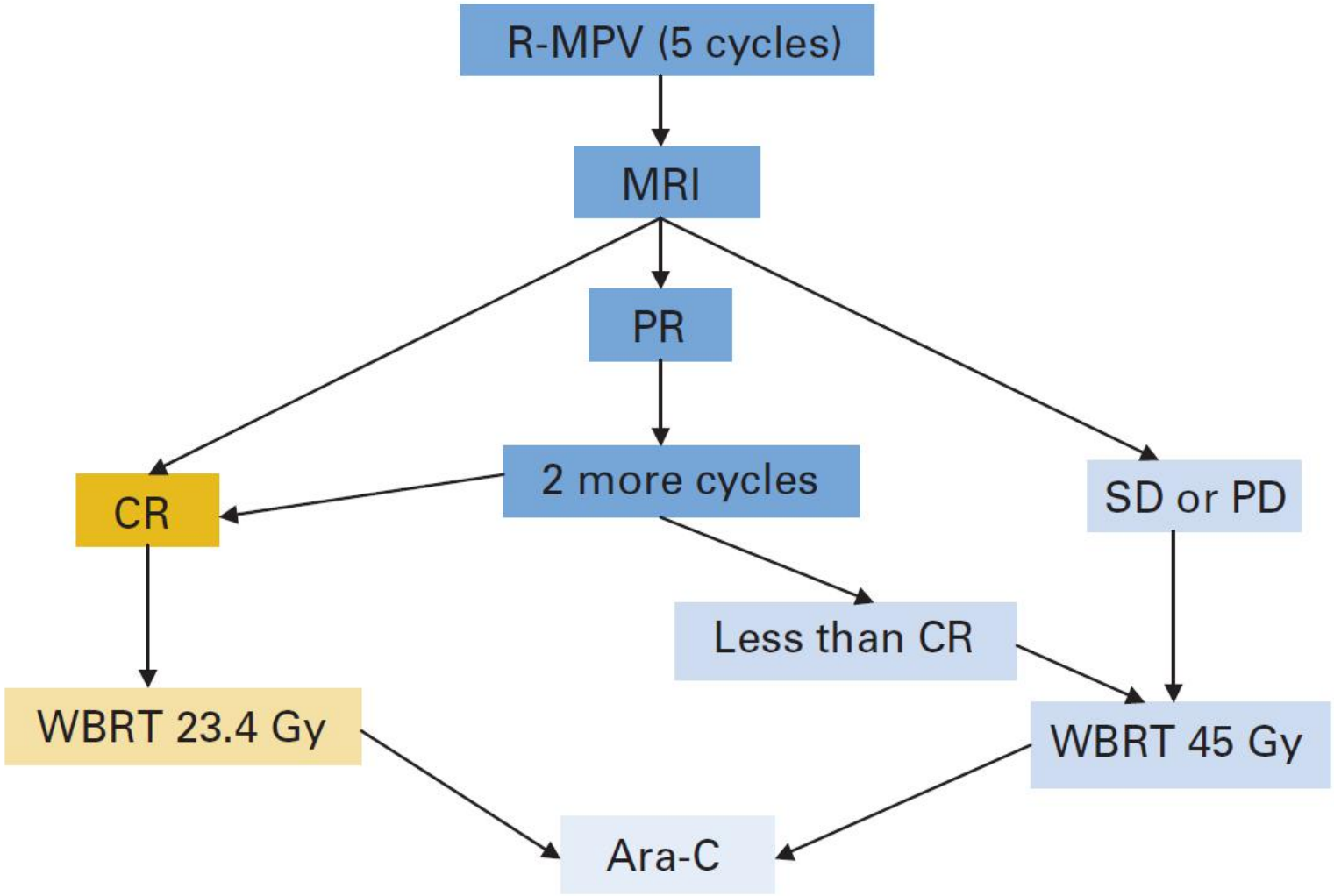
Thiel E, et al. Lancet Oncol 2010;11:1036

单因素和多因素分析

	Univariate analysis (simple Cox regression model)		Multivariate analysis (multiple Cox regression model without variable selection)	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Progression-free survival				
Age*	1·22 (0·95–1·59)	0·13	1·11 (0·84–1·49)	0·46
Karnofsky performance score†	1·09 (1·01–1·18)	0·02	1·11 (1·02–1·20)	0·012
Sex‡	0·84 (0·65–1·09)	0·19	0·73 (0·55–0·98)	0·037
Study group§	0·82 (0·64–1·07)	0·14	0·82 (0·62–1·09)	0·18
Drug treatment¶	0·94 (0·66–1·34)	0·74	0·82 (0·55–1·22)	0·33
Overall survival				
Age*	1·69 (1·26–2·26)	0·0004	1·54 (1·12–2·12)	0·008
Karnofsky performance score†	1·16 (1·07–1·26)	0·0005	1·16 (1·07–1·27)	0·001
Sex‡	0·82 (0·61–1·09)	0·17	0·70 (0·51–0·97)	0·031
Study group§	1·06 (0·80–1·40)	0·71	1·05 (0·77–1·44)	0·74
Drug treatment¶	1·05 (0·66–1·65)	0·84	1·11 (0·68–1·81)	0·69

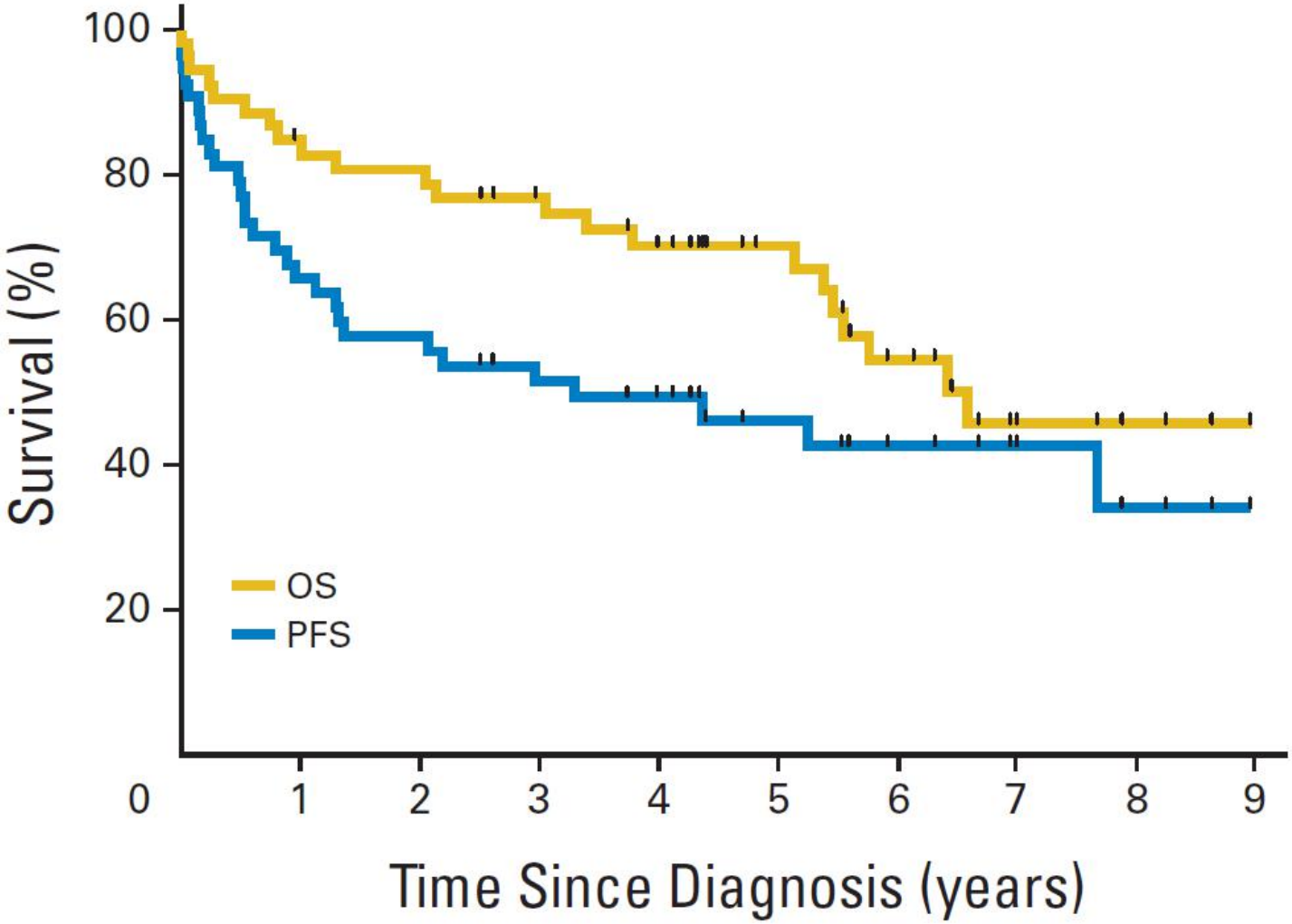
Thiel E, et al. Lancet Oncol 2010;11:1036

RTOG研究



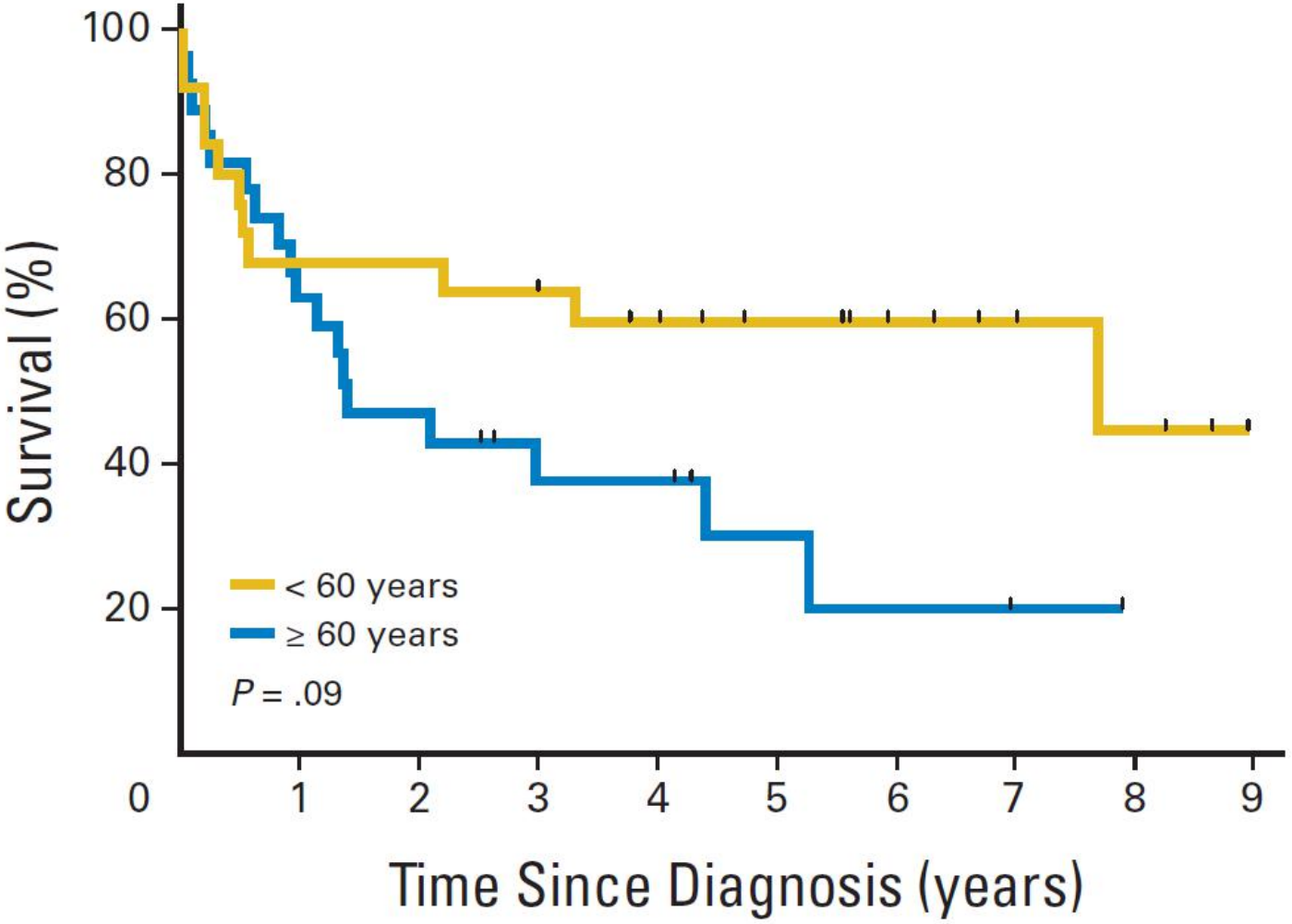
Shah GD, et al. J Clin Oncol 2007;25:4730

生存



Morris PG, et al. J Clin Oncol 2013;31:3971

无进展生存 (年龄分组)



Morris PG, et al. J Clin Oncol 2013;31:3971

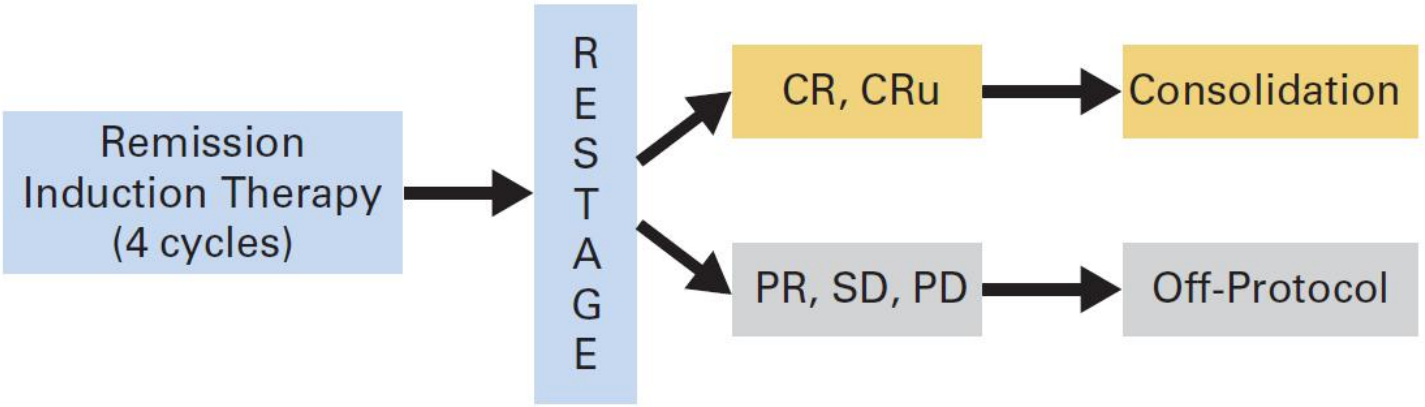
神经毒性 (脑白质改变)

Table 2. White Matter Changes in Patients Undergoing Neuropsychological Evaluation After Receiving Reduced-Dose Whole-Brain Radiotherapy (Fazekas Scale; n = 12)[20]

Grade	Baseline	Post R-MPV (prior to rdWBRT)	1 Year	2 Years	3 Years	4 Years
0	2	0	0	0	0	0
1	5	11	8	8	5	5
2	3	1	3	3	5	5
3	2	0	1	1	2	2
4	0	0	0	0	0	0
5	0	0	0	0	0	0

Morris PG, et al. J Clin Oncol 2013;31:3971

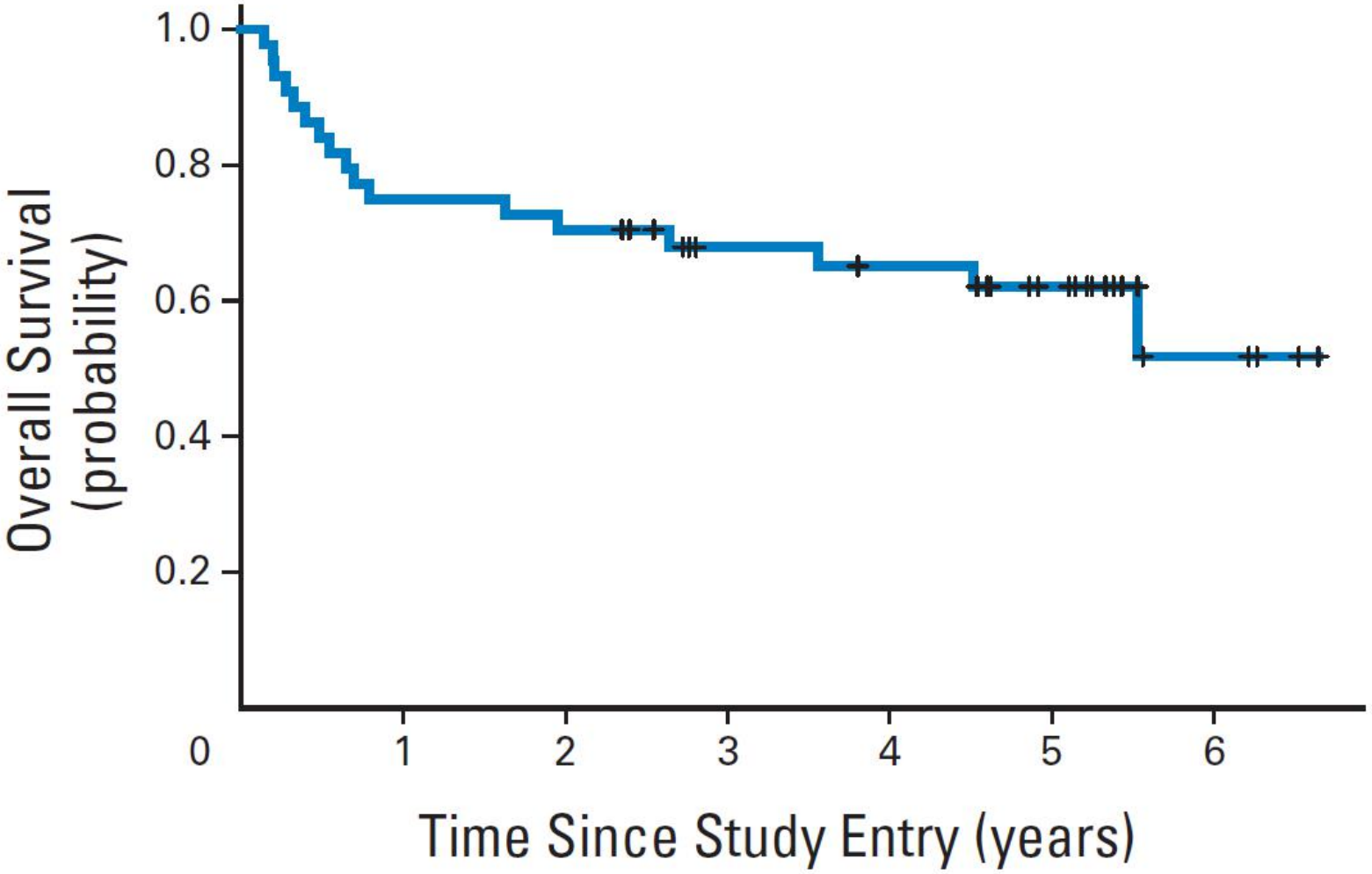
巩固化疗 (CALGB 50202)



Remission Induction Therapy: MT-R (14-day cycle)	
Day 1	Methotrexate 8 grams/m^2 IV over 4 hrs
Day 2	Leucovorin 100 mg/m^2 every 6 hrs, until methotrexate < 0.05 mM
Day 3	Rituximab 375 mg/m^2 IV cycles 1 through 6
Day 7-11	Temozolomide 150 mg/m^2 PO (odd cycles only)
Consolidation Therapy: EA	
Day 1-4	Etoposide 40 mg/kg continuous IV over 96 hrs
Day 1-4	Cytarabine 2 gm/m^2 IV over 2 hrs every 12 hrs × 8 doses

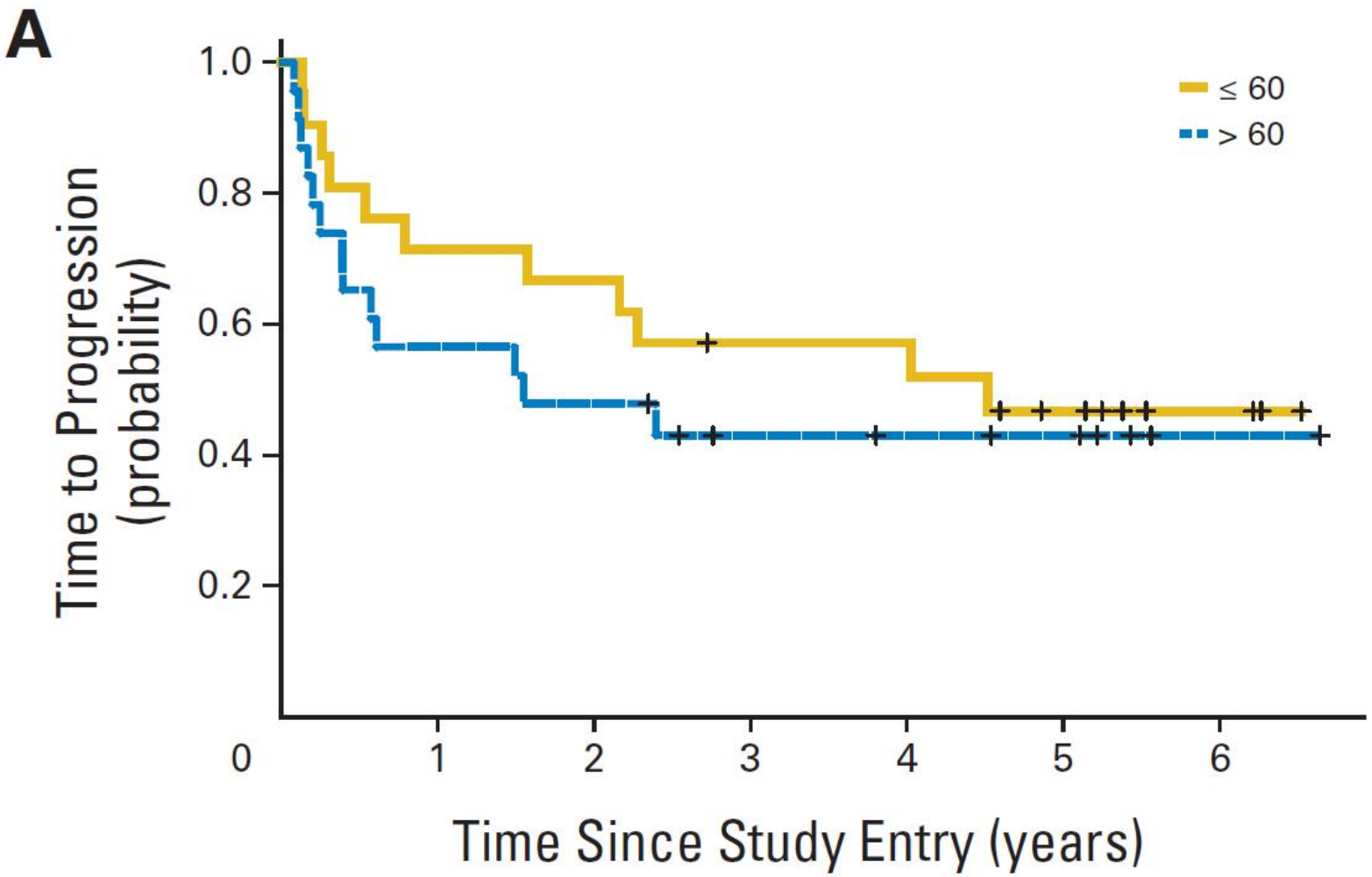
Rubenstein JL, et al. J Clin Oncol 2013;31:3061

总生存



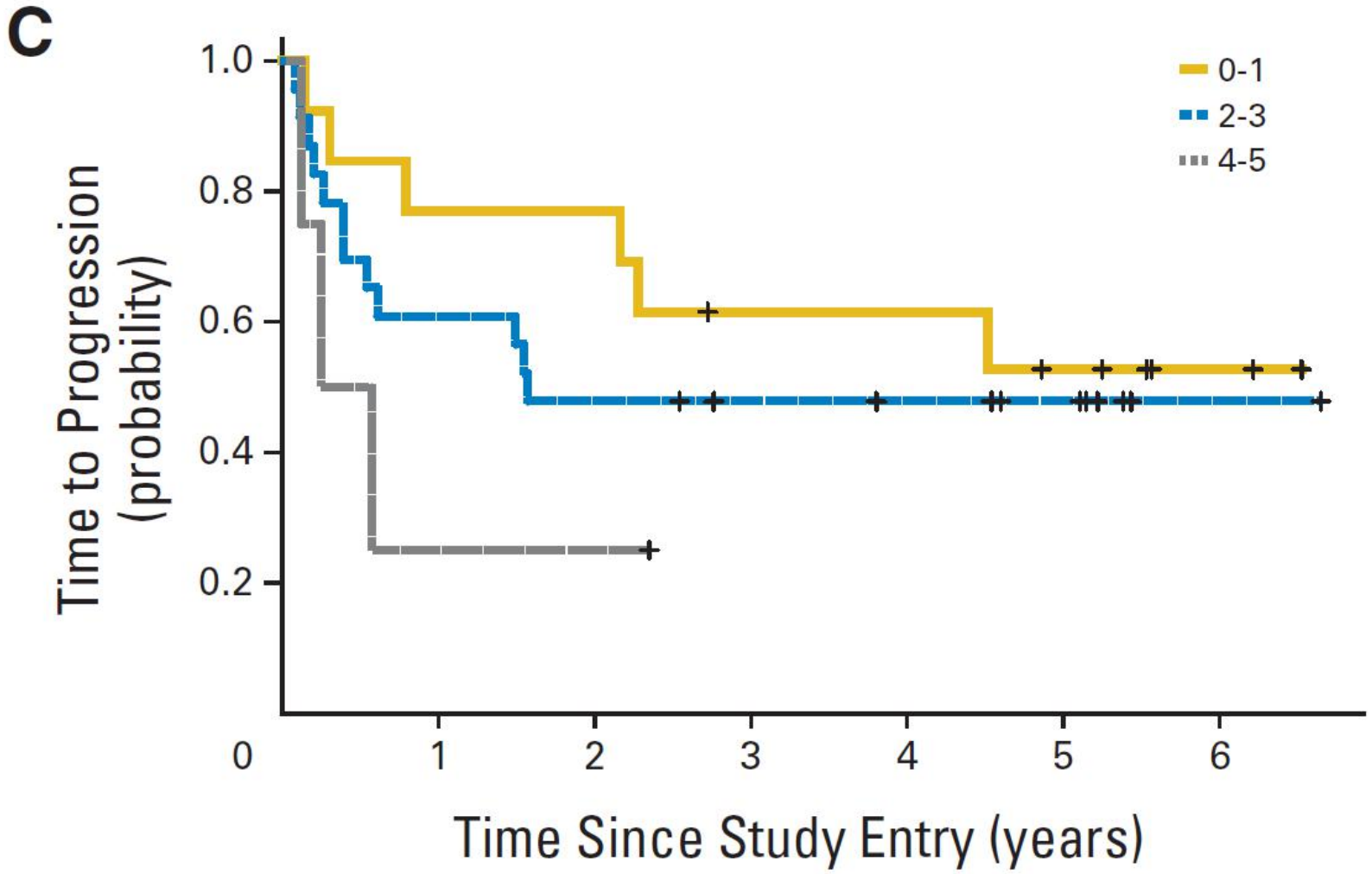
Rubenstein JL, et al. J Clin Oncol 2013;31:3061

疾病进展时间 (年龄分组)



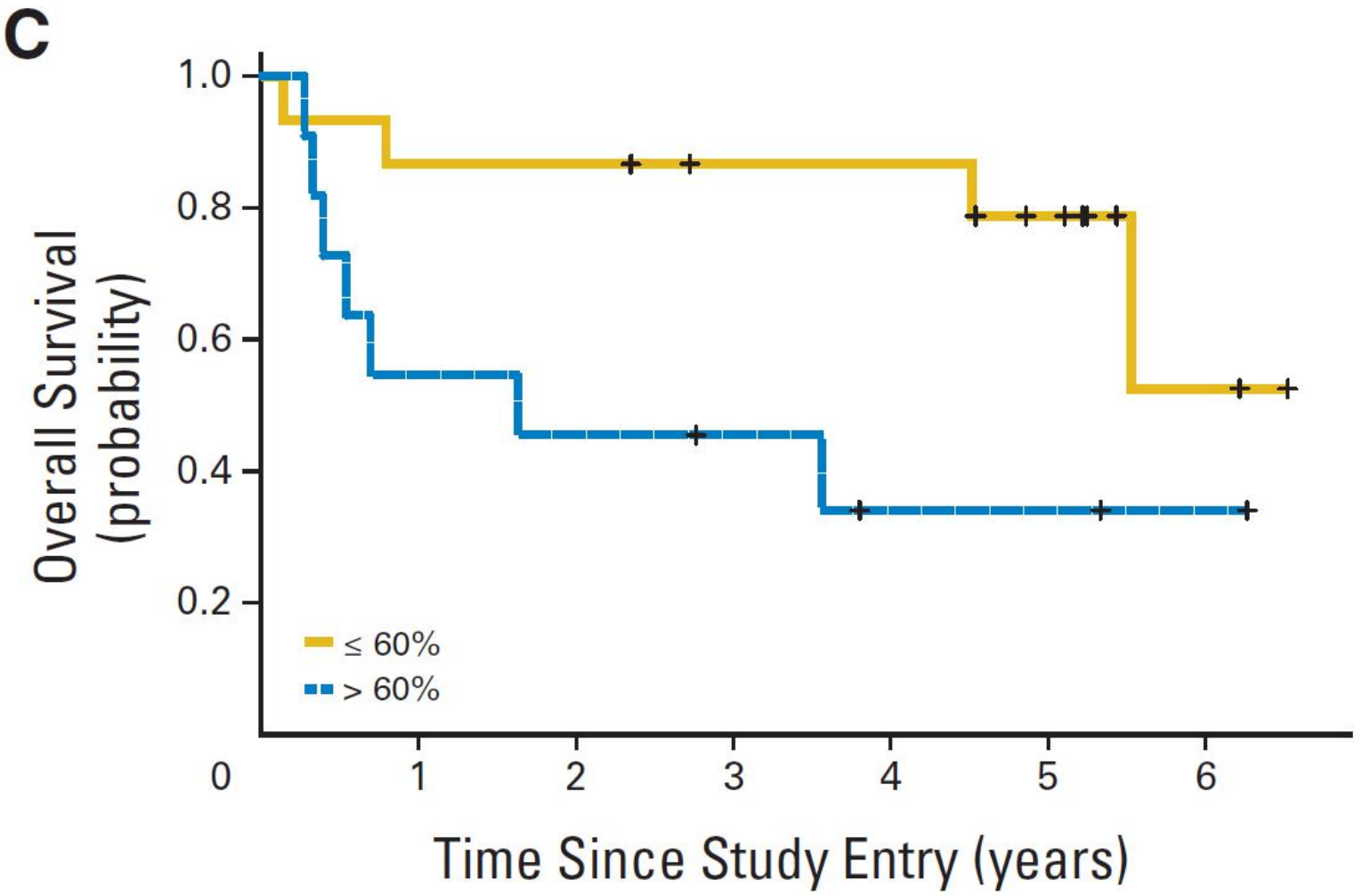
Rubenstein JL, et al. J Clin Oncol 2013;31:3061

疾病进展时间 (IESLG)



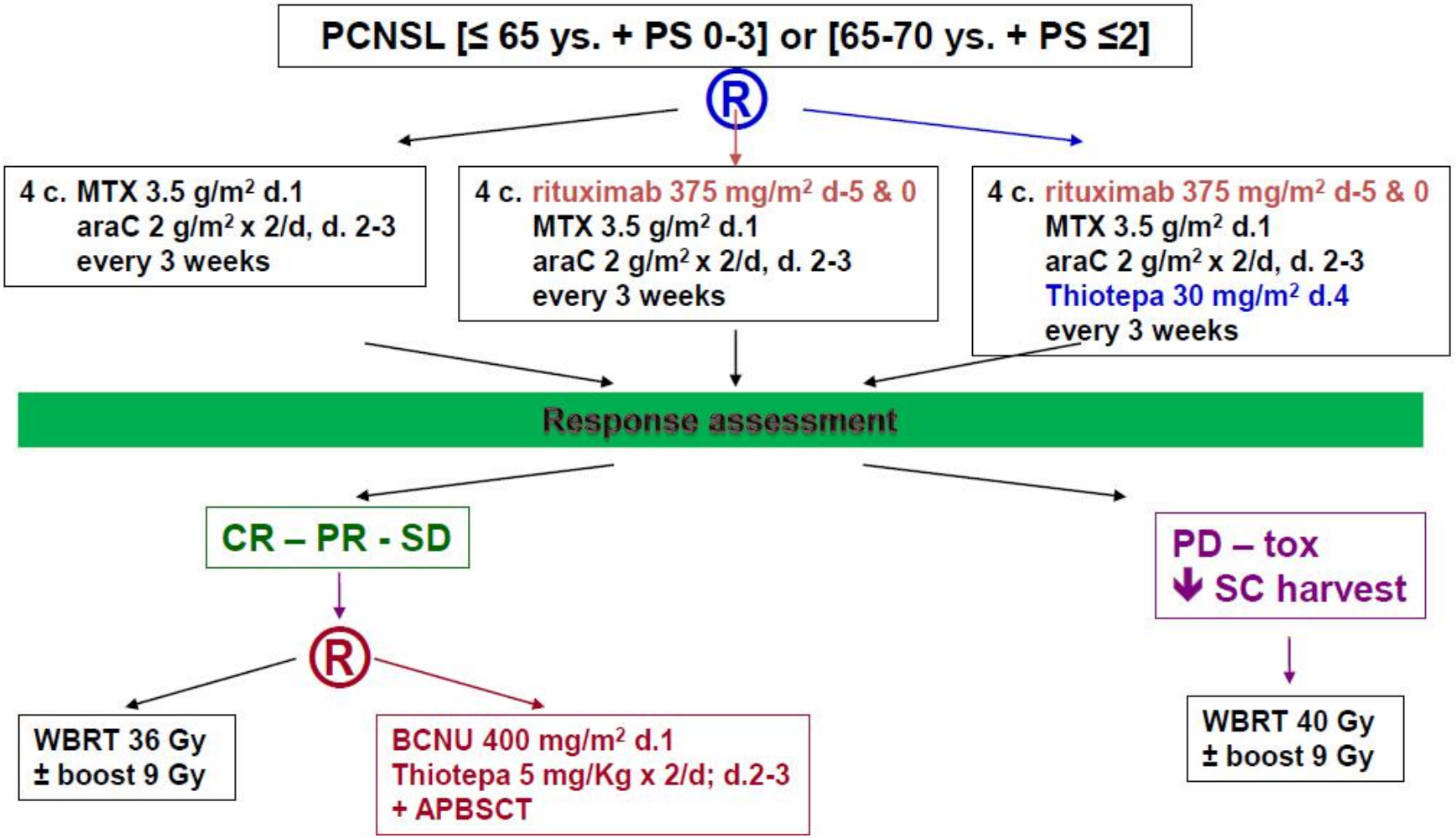
Rubenstein JL, et al. J Clin Oncol 2013;31:3061

总生存 (BCL-6表达)



Rubenstein JL, et al. J Clin Oncol 2013;31:3061

IELSG-32



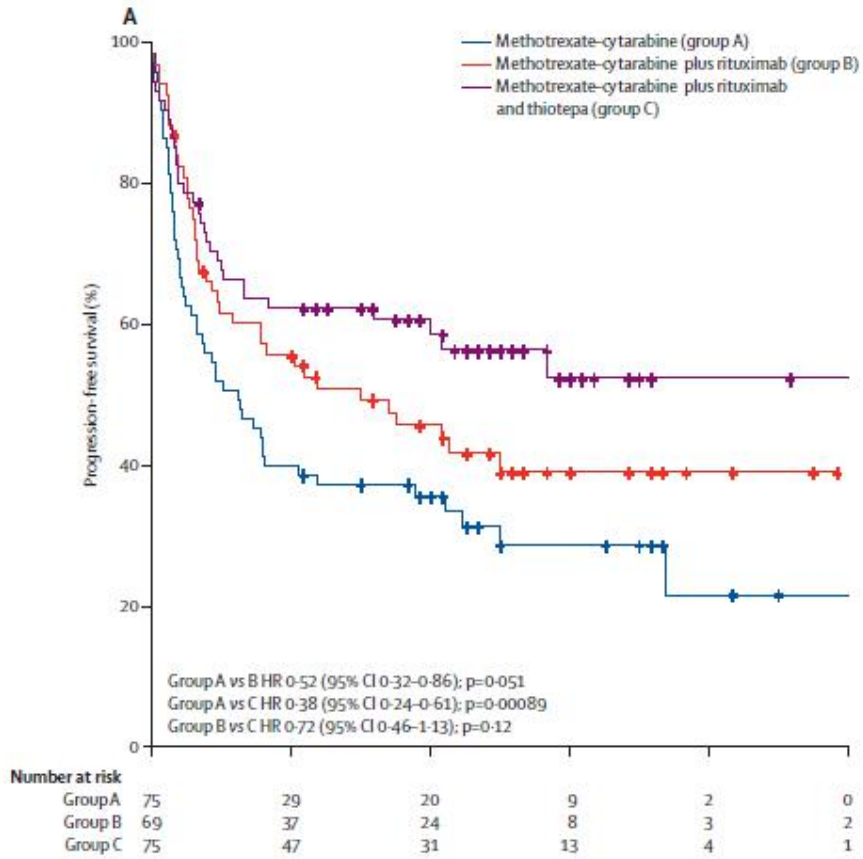
Ferreri AJM, et al. Lancet Haematol 2016;3:e217

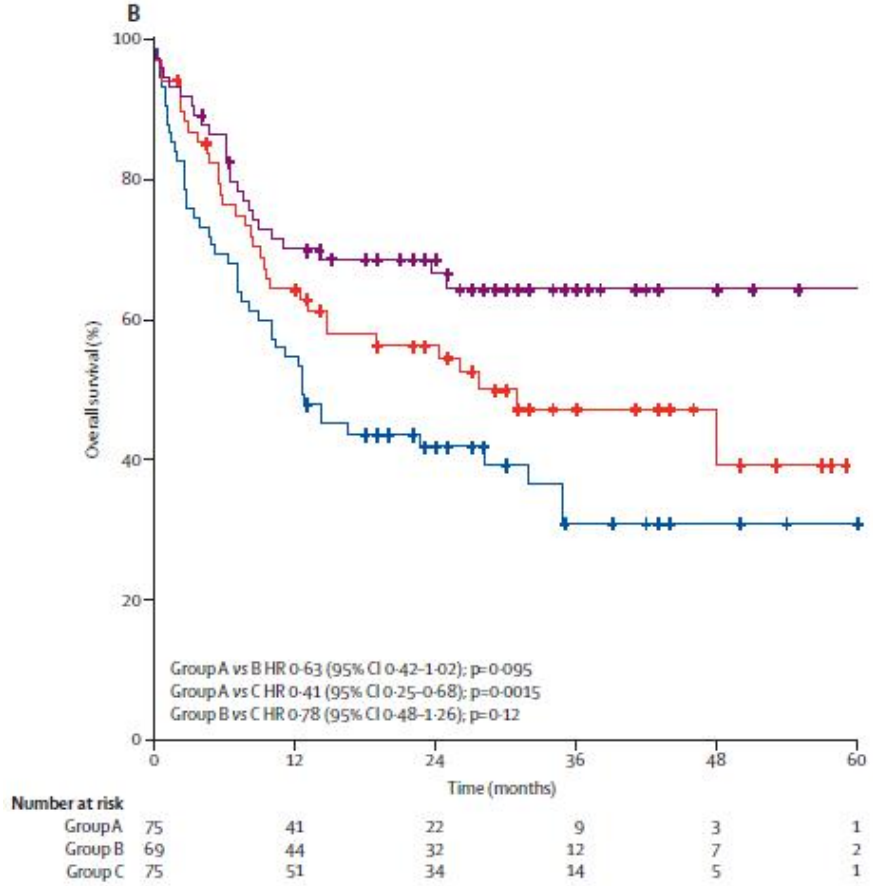
缓解率

	Methotrexate–cytarabine (group A; n=75)	Methotrexate–cytarabine plus rituximab (group B; n=69)	Methotrexate–cytarabine plus rituximab and thiotepa (group C; n=75)
Complete remission	17 (23%; 95% CI 14–31)	21 (30%; 95% CI 21–42)	37 (49%; 95% CI 38–60)
Partial response	23 (31%)	30 (43%)	28 (37%)
Overall response*	40 (53%; 95% CI 42–64)	51 (74%; 95% CI 64–84)	65 (87%; 95% CI 80–94)
Stable disease	6 (8%)	4 (6%)	1 (1%)
Progressive disease	22 (29%)	11 (16%)	6 (8%)
Deaths due to toxicity	7 (9%)	3 (4%)	3 (4%)

Ferreri AJM, et al. Lancet Haematol 2016;3:e217

生存





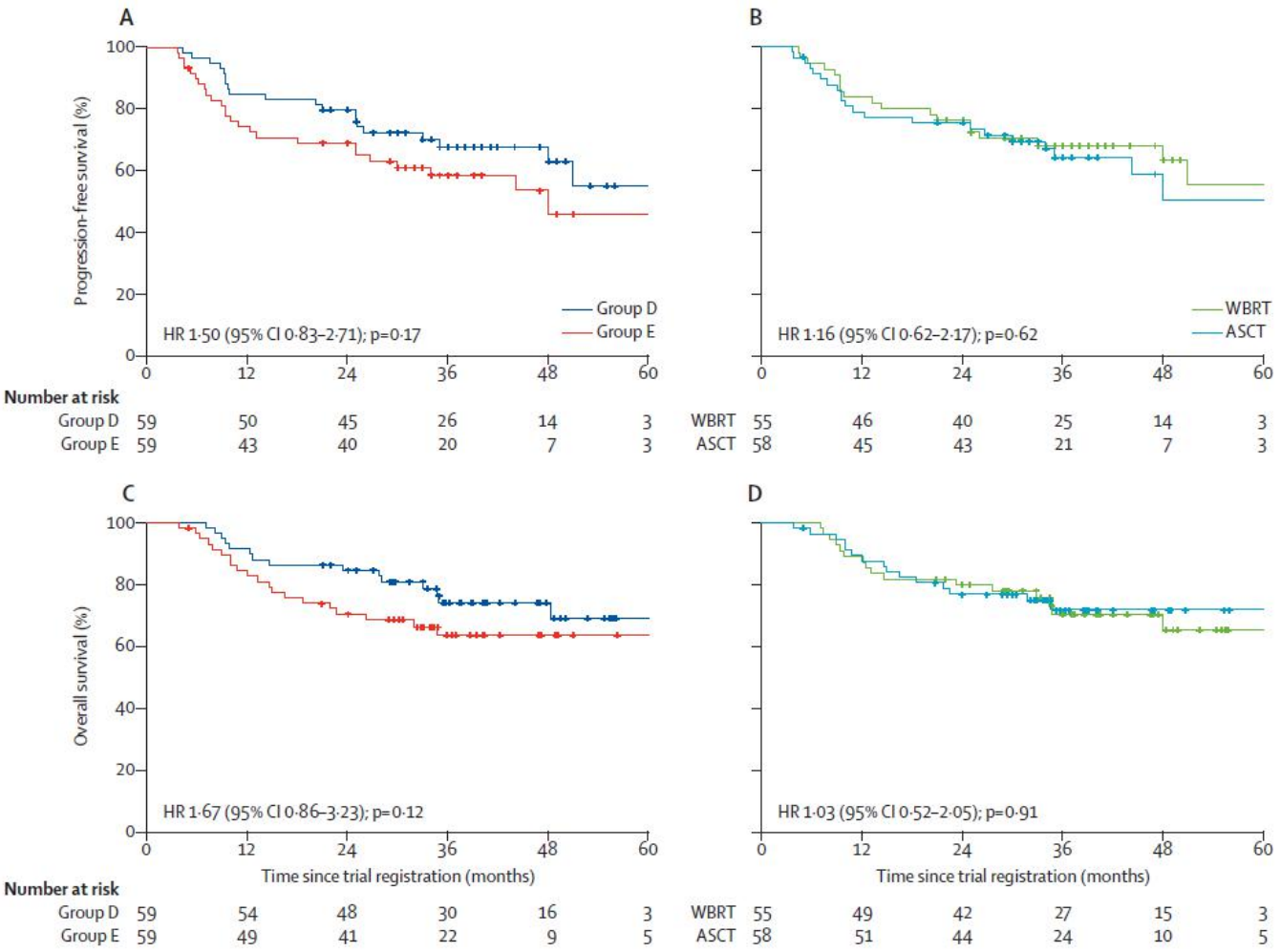
Ferreri AJM, et al. Lancet Haematol 2016;3:e217

毒性

	Methotrexate–cytarabine (group A; n=75); 223 (74%) courses delivered*				Methotrexate–cytarabine plus rituximab (group B; n=69); 236 (86%) courses delivered*				Methotrexate–cytarabine plus rituximab and thiotepa (group C; n=75); 274 (91%) courses delivered*			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Neutropenia	12 (5%)	18 (8%)	99 (44%)	0	24 (10%)	15 (6%)	119 (50%)	0	14 (5%)	31 (11%)	153 (56%)	0
Thrombocytopenia	18 (8%)	43 (19%)	116 (52%)	0	27 (11%)	36 (15%)	140 (59%)	0	21 (8%)	27 (10%)	200 (73%)	0
Anaemia	115 (52%)	63 (28%)	9 (4%)	0	124 (53%)	77 (33%)	6 (3%)	0	131 (48%)	116 (42%)	14 (5%)	0
Febrile neutropenia/ infections	11 (5%)	32 (14%)	10 (4%)	6 (3%)	21 (9%)	23 (10%)	7 (3%)	2 (<1%)	18 (7%)	42 (15%)	3 (1%)	0
Hepatotoxicity	71 (32%)	20 (9%)	6 (3%)	0	76 (32%)	25 (11%)	3 (1%)	0	77 (28%)	19 (7%)	1 (<1%)	0
Nephrotoxicity	28 (13%)	3 (1%)	0	0	31 (13%)	4 (2%)	0	0	17 (6%)	2 (<1%)	1 (<1%)	0
Cardiotoxicity	0	0	0	0	0	2 (<1%)	0	0	0	2 (<1%)	1 (<1%)	0
Coagulopathy/deep vein thrombosis (including pulmonary embolism)	2 (1%)	3 (1%)	0	0	3 (1%)	3 (1%)	1 (<1%)	1 (<1%)	0	2 (<1%)	2 (<1%)	2 (<1%)
Gastrointestinal	35 (16%)	1 (<1%)	0	0	106 (45%)	5 (2%)	1 (<1%)	0	81 (30%)	9 (3%)	1 (<1%)	0
Mucositis	20 (9%)	3 (1%)	0	0	37 (16%)	2 (<1%)	2 (<1%)	0	45 (16%)	1 (<1%)	0	0
Acute neurotoxicity	28 (13%)	3 (1%)	3 (1%)	0	34 (14%)	4 (2%)	0	0	19 (7%)	6 (2%)	2 (<1%)	0
Hyperglycaemia	0	4 (2%)	0	0	0	0	0	0	0	0	1 (<1%)	0
Sudden death†	..	..	..	1 (<1%)	..	..	..	0	..	..	..	1 (<1%)
Non-lethal interruptions	0	0	2 (<1%)	0	0	0	2 (<1%)	0	0	0	1 (<1%)	0

Ferreri AJM, et al. Lancet Haematol 2016;3:e217

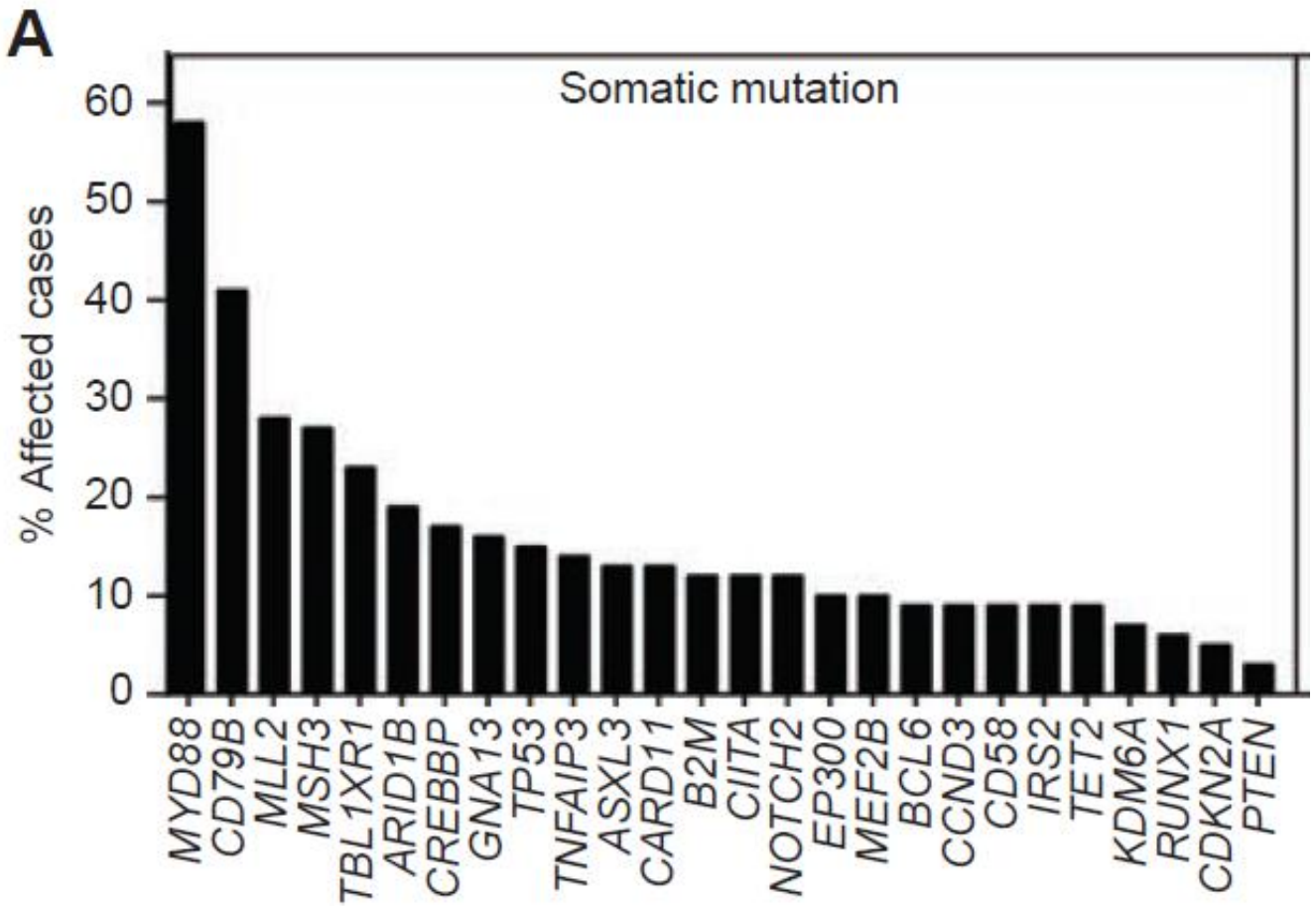
巩固治疗 (移植 vs. 放疗)



Ferreri AJM, et al. Lancet Haematol 2017;4:510

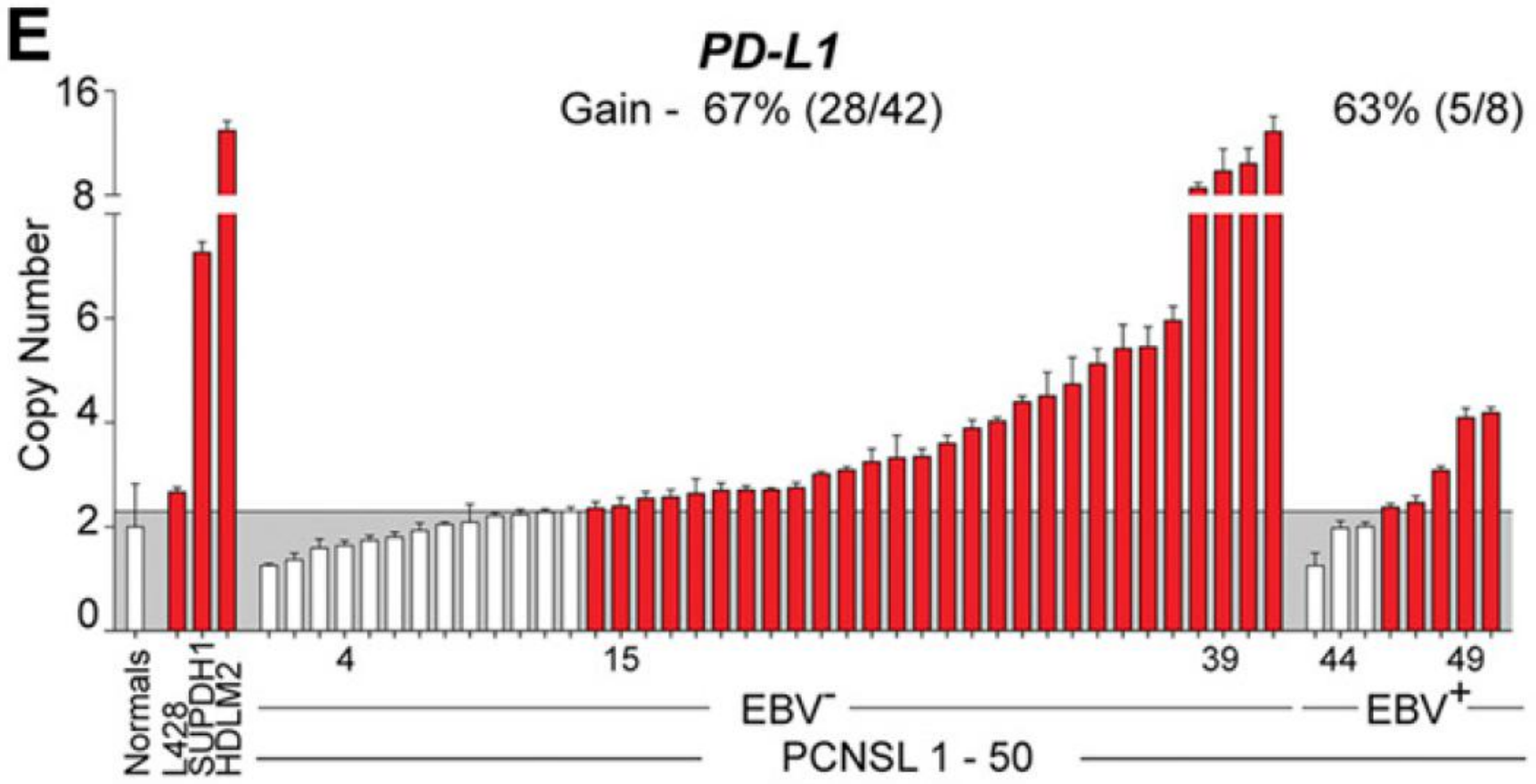
新药

MYD88突变



Chapuy B, et al. Blood. 2016;127:869

PD-L1高表达



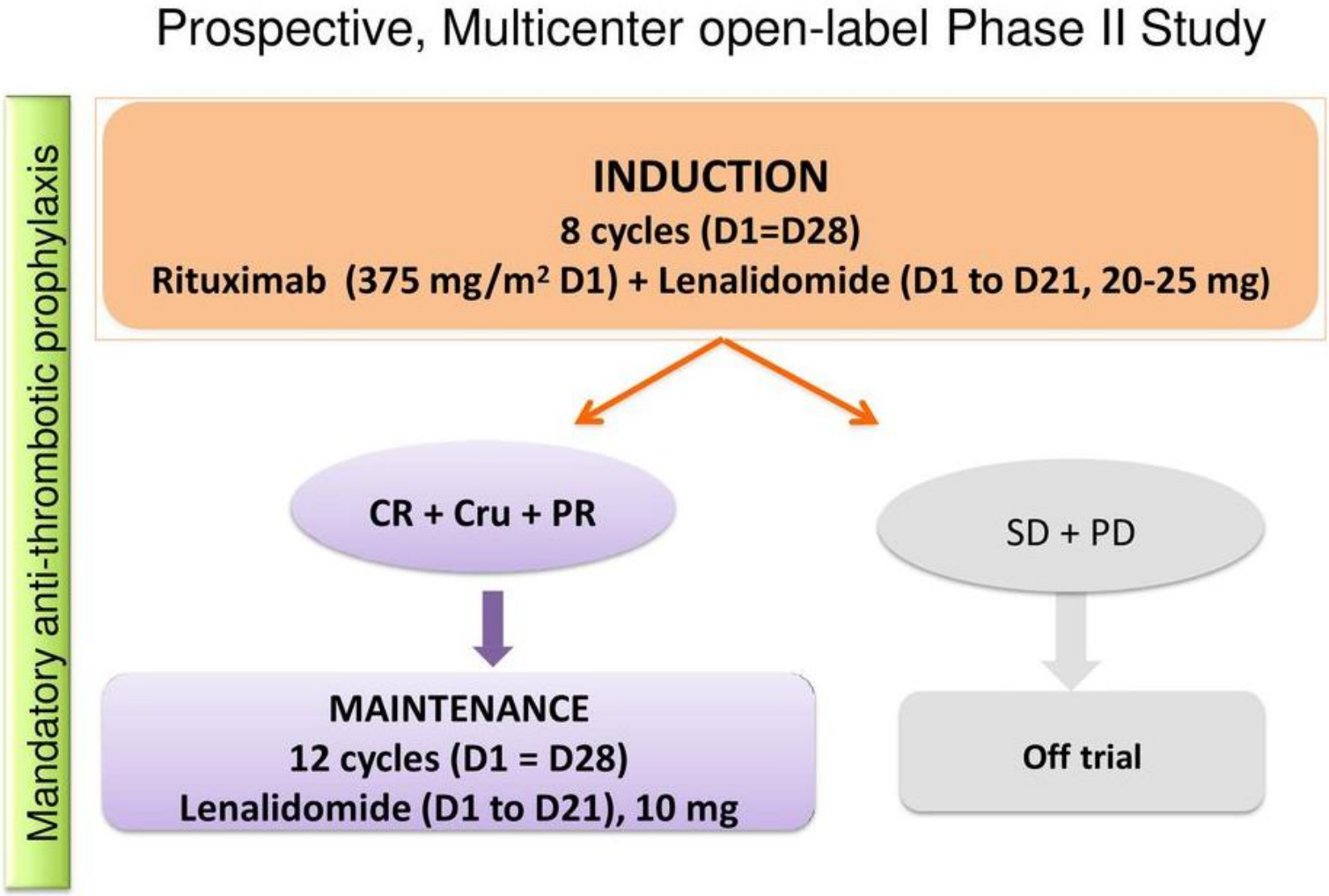
Chapuy B, et al. Blood. 2016;127:869

分子特征

	DLBCL		PTL	EBV⁻ PCNSL	PMBL
	All	ABC-type			
Genomic instability					
CDKN2A^{loss}	24% (43/180)[a]	35% (19/55)[a]	88% (44/50)[c]	71% (15/21)[k]	0% (0/11)
bi-alleic	19% (8/43)[a]	26% (5/19)[a]	77% (34/44)	73% (11/15)	0% (0/11)
CNAs of additional p53/cell cycle components	multiple[a,b]	multiple[a,b]	no	rare[d]	no
Total CNAs	high	high	high	high	low
Oncogenic TLR and BCR Signaling					
MYD88^{L265P}	12% (6/49)[e]	29% (45/155)[f]	78% (38/49)[g]	60% (33/55)[l]	NA
NFKBIZ^{gain}	9% (16/180)[a]	20% (11/55)[a]	42% (21/50)[h]	45% (28/62)[m]	0% (0/11)
NFKBIZ^{gain} and/or *MYD88*^{L265P}	NA	NA	92% (45/49)	83% (44/53)[n]	NA
CD79B^{Y196mut}					
Total	16% (8/49)[e]	23% (35/155)[f]	49% (22/45)[i]	38% (19/50)[o]	NA
Concurrent with *MYD88*^{L265P}	38% (3/8)[e]	43% (15/35)[f]	91% (20/22)	89% (17/19)	NA
PD-1 Ligand Deregulation					
9p24.1/*PD-L1*^{gain} and/or *PD-L2*^{gain}	6% (11/180)[a]	7% (4/55)[a]	54% (26/50)[h]	52% (33/63)[p]	55% (6/11)
PD-L1 or *PDL-2* translocation	NA	NA	4% (2/50)[j]	6% (4/66)[q]	20% (25/125)[r]

Chapuy B, et al. Blood. 2016;127:869

利妥昔单抗+来那度胺



Ghesquieres H, et al. ASH 2016;abstract 785

缓解率

	CR+ uCR	PR	SD	PD	NA
Best response	18 (40 %)	12 (27 %)	5 (11 %)	10 (22 %)	
	ORR = 67 % [51-80]				

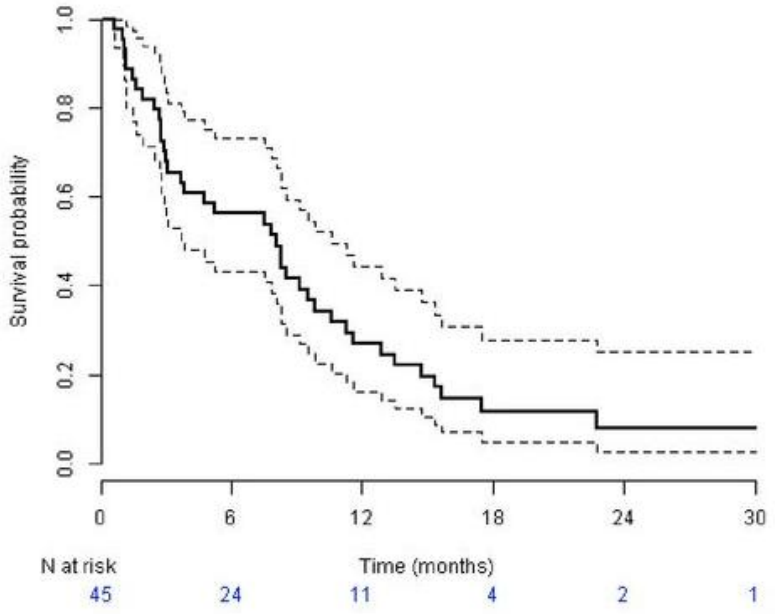
- Total of 50 patients

Ghesquieres H, et al. ASH 2016;abstract 785

PFS

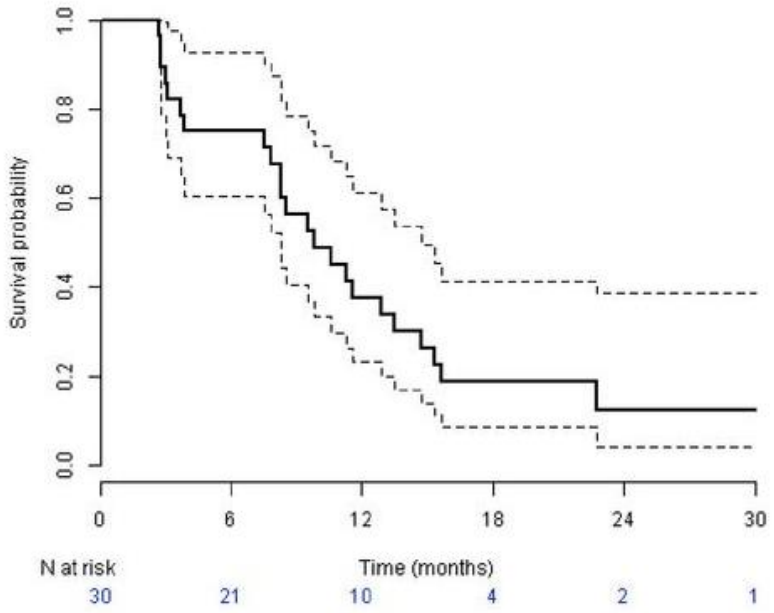
Whole population

Median PFS = 8.1 months, [3.7 ; 10.56]



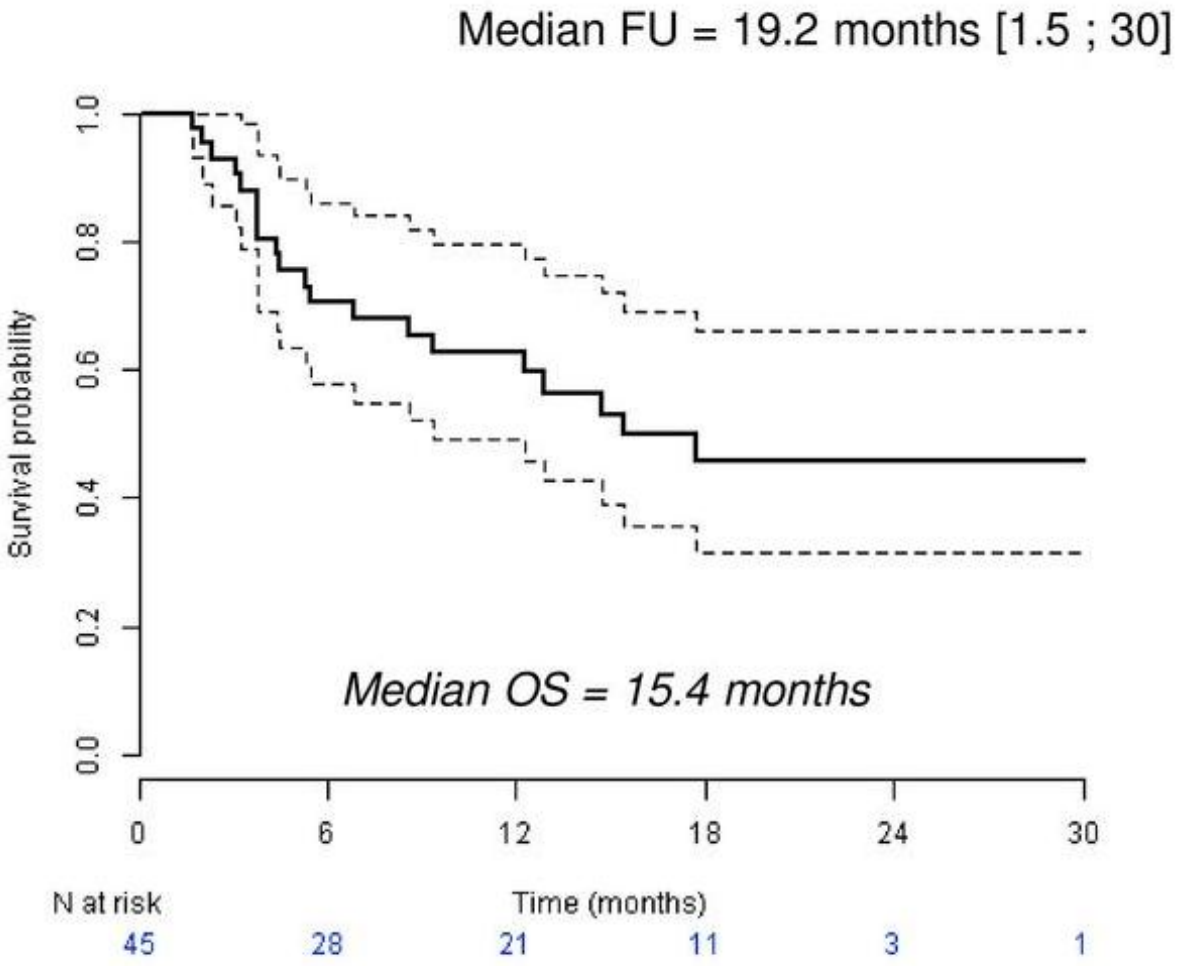
Responder patients (N= 30)

Median PFS = 9.8 months,[8.3 ; 14.8]



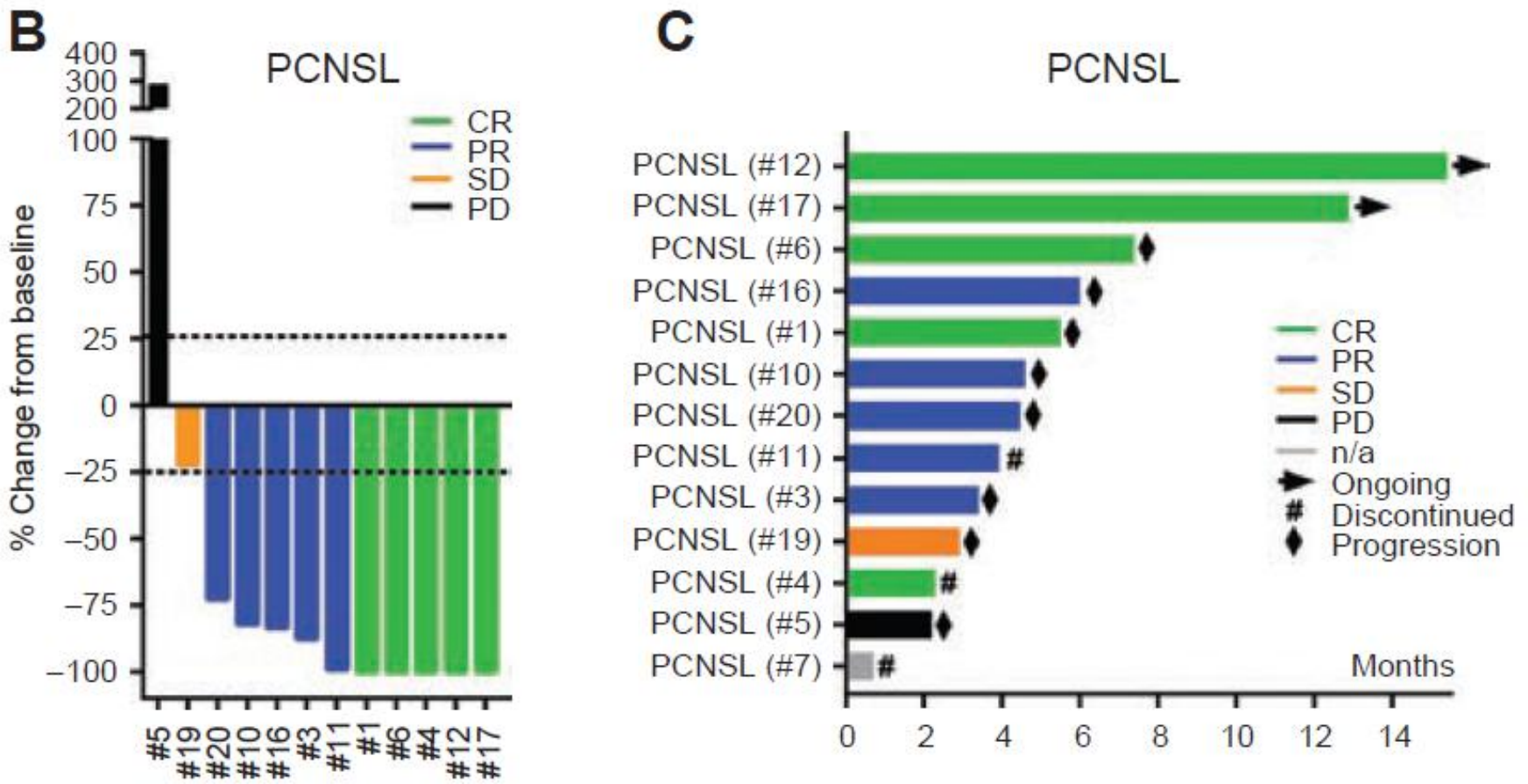
Ghesquieres H, et al. ASH 2016;abstract 785

OS



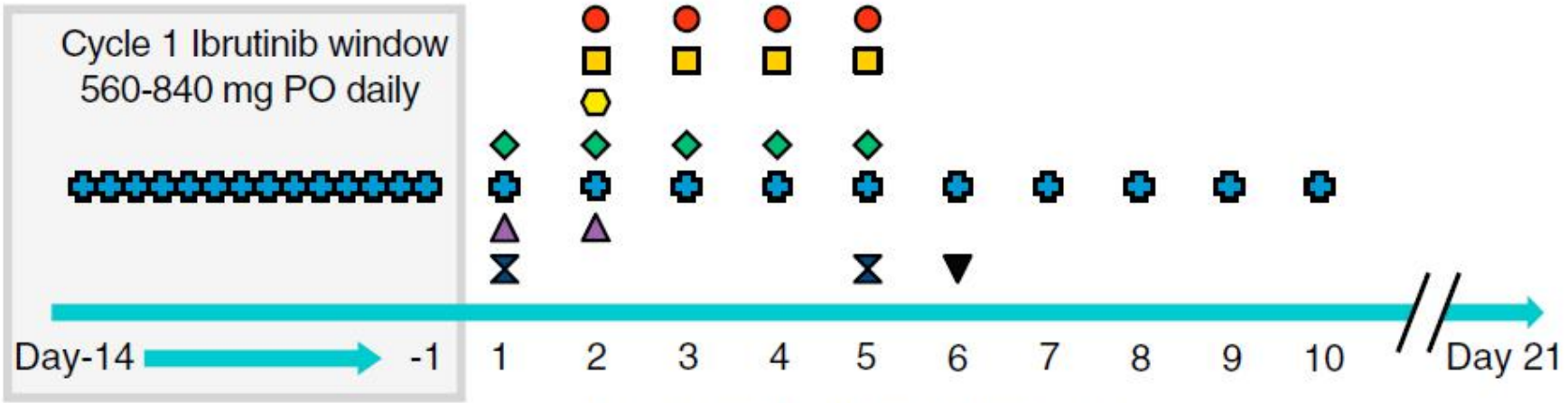
Ghesquieres H, et al. ASH 2016;abstract 785

依布替尼



Grommes C, et al. Cancer Discov 2017;7:1018

DA-TEDDi-R



- Temozolomide 100 mg/m^2/day IV
- Etoposide 50 mg/m^2/day IV
- Liposomal Doxorubicin 50 mg/m^{2}IV
- Dexamethasone 10 mg/m^2 PO
- Ibrutinib (560-840 mg) PO
- Rituximab 375 mg/m^2 IV
- Pegfilgrastim 6 mgs
- Cytarabine 70 mg IT or ICV cycles 2-6

Lionakis MS, et al. Cancer Cell 2017;31:833

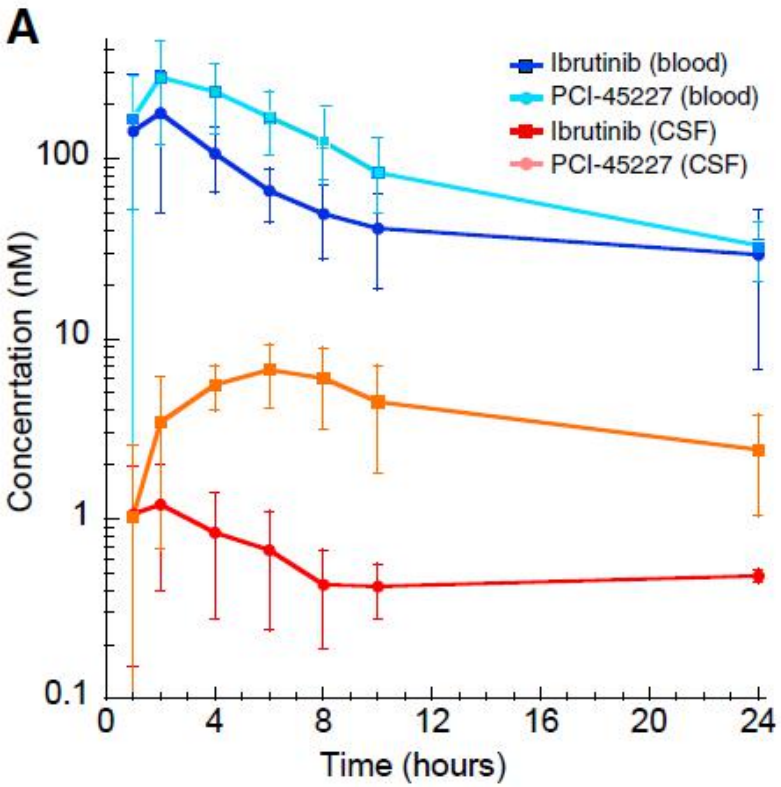
基线和毒性

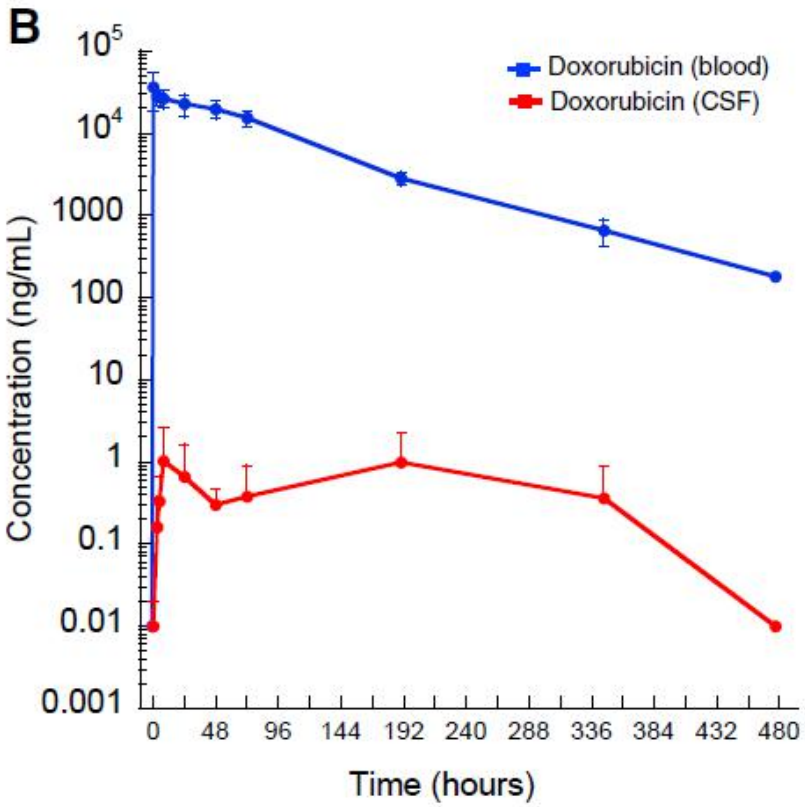
Characteristics	Number	Percent
Total enrolled	18	100
Age median (range)	66 (49–87) years	
Male sex	11	61
ECOG performance status		
1	13	72
2	3	17
3	2	11
Histology: large B cell lymphoma (PCNSL)	18	100
Untreated PCNSL	5	28
Previously treated PCNSL	13	72
Median (range) regimens	2 (1–6)	
Treatment refractory	11	85
Prior methotrexate	13	100
Prior rituximab	12	92
Prior cranial radiation	4	31
Autologous transplant	4	31
Disease sites		
CSF + flow cytometry	9	50
Intraocular	3	11
Deep brain lesions	13	72
Peripheral disease	3	11

Toxicity and Groups	Grade 3 No. (%)	Grade 4 No. (%)	Grade 5 No. (%)
Ibrutinib-Window Group Patients (n = 18)			
Non-hematological			
Pulmonary/CNS infection[a]			2 (11)
Hyponatremia	1 (6)		
DA-TEDDi-R Group Patients (n = 16)			
Hematological			
Neutropenia	10 (63)	15 (94)	
Thrombocytopenia	13 (81)	9 (56)	
Febrile neutropenia	10 (69)		1 (6)
Non-hematological			
Palmar-plantar erythrodysesthesia	2 (13)		
Mucositis	2 (13)	1 (6)	
Infection pulmonary[b]	8 (50)	1 (6)	
Infection other[c]	3 (19)		
Stroke			1 (6)
Ventricular arrhythmia			1 (6)
Intra-abdominal hemorrhage		1 (6)	
Nausea	1 (6)		
Diarrhea	2 (13)		

Lionakis MS, et al. Cancer Cell 2017;31:833

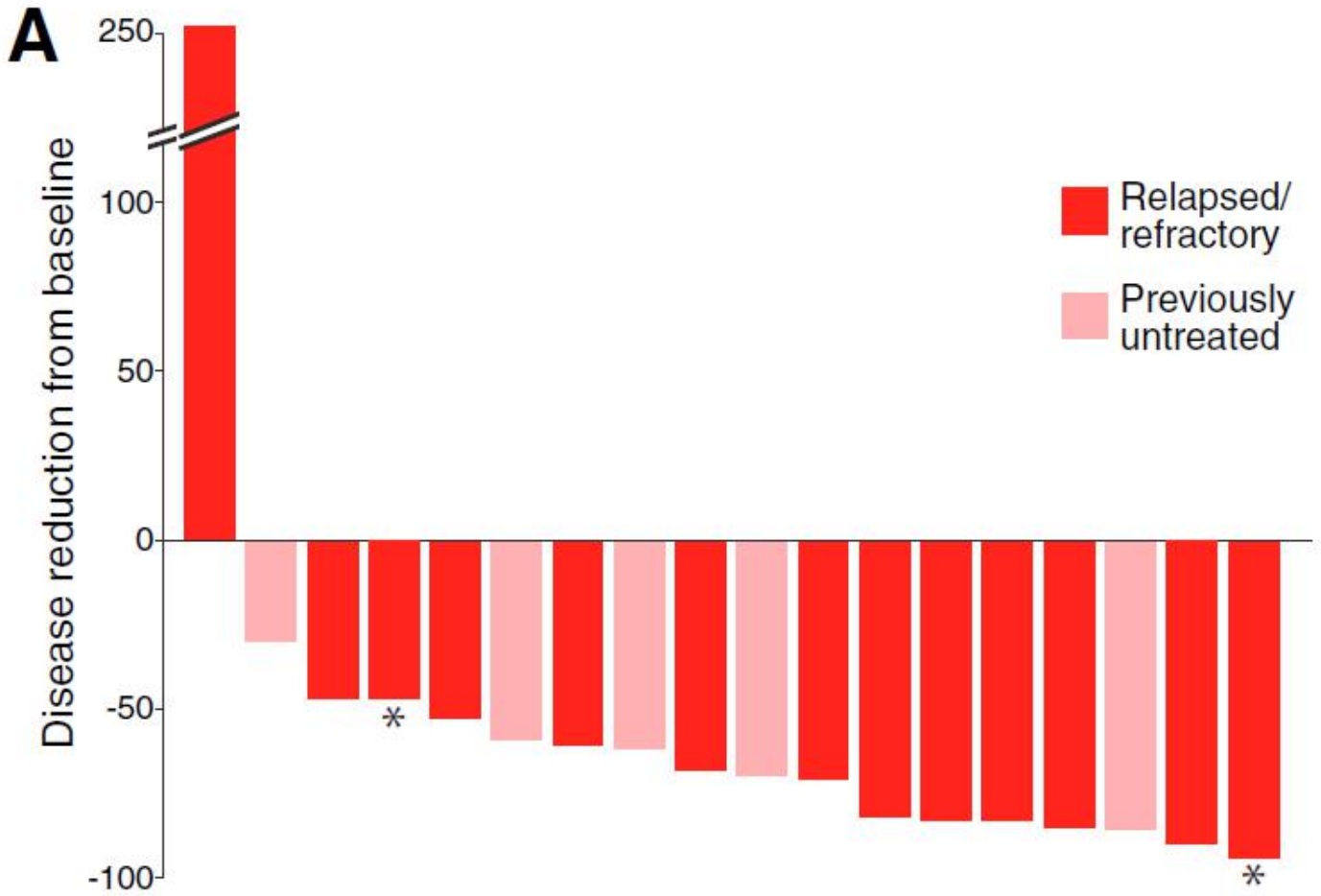
药物浓度





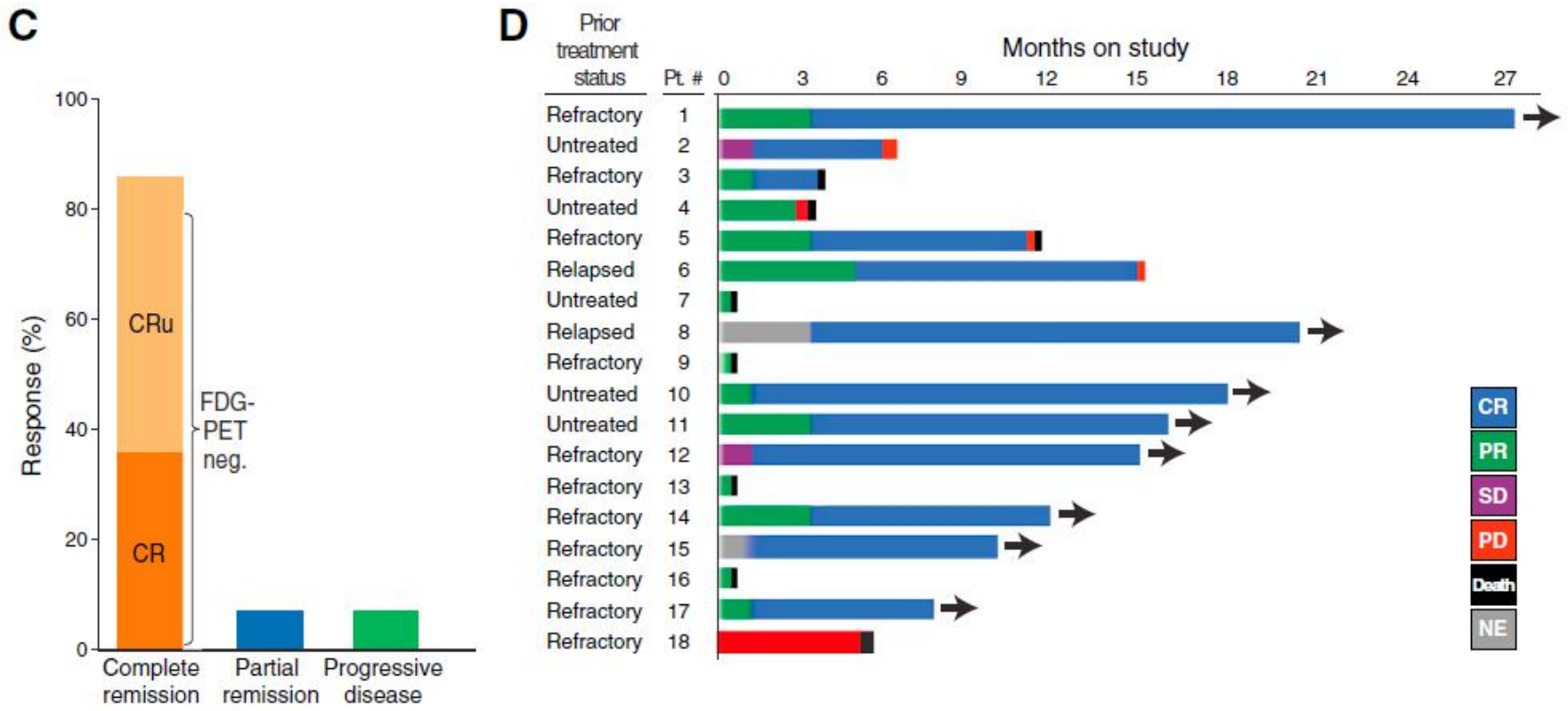
Lionakis MS, et al. Cancer Cell 2017;31:833

缓解瀑布图



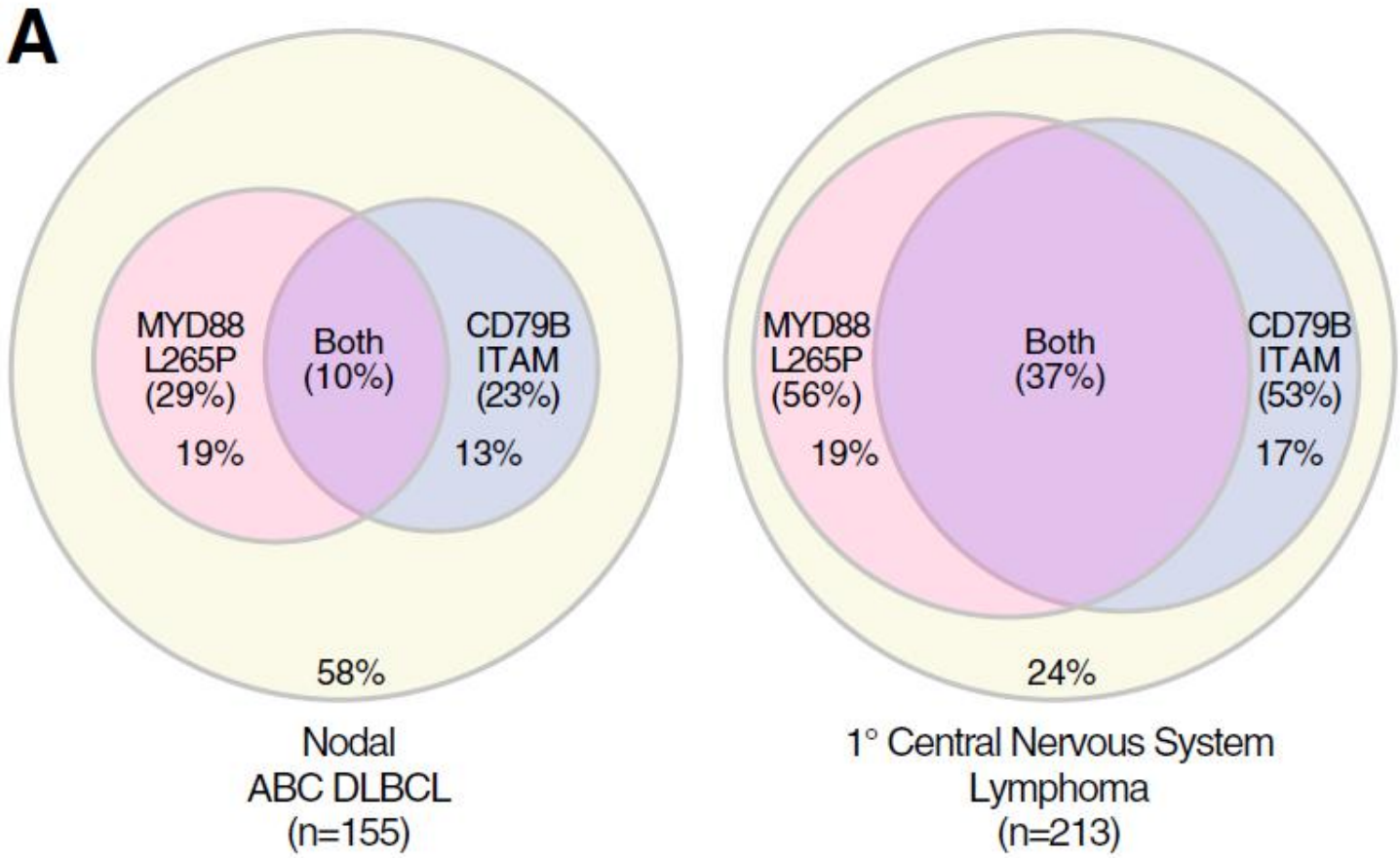
Lionakis MS, et al. Cancer Cell 2017;31:833

缓解率和缓解期



Lionakis MS, et al. Cancer Cell 2017;31:833

基因突变比较



Lionakis MS, et al. Cancer Cell 2017;31:833

举例

Pt. #	CD79B AA change	MYD88 AA change	Ibrutinib response	DA-TEDDi-R response
1	Y196C	WT	PR	CR
5	splice acceptor (Y196 deletion)	WT	PR	CR
6	WT	L265P	PR	CR
11	Y196C	L265P	PR	CR

Lionakis MS, et al. Cancer Cell 2017;31:833

Nivolumab

Brief Report

blood

CLINICAL TRIALS AND OBSERVATIONS

PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma

Lakshmi Nayak,[1,2] Fabio M. Iwamoto,[3] Ann LaCasce,[1,2] Srinivasan Mukundan,[1,2] Margaretha G. M. Roemer,[1] Bjoern Chapuy,[1] Philippe Armand,[1,2] Scott J. Rodig,[1,2] and Margaret A. Shipp[1,2]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; and [3]New York Presbyterian Hospital, New York, NY

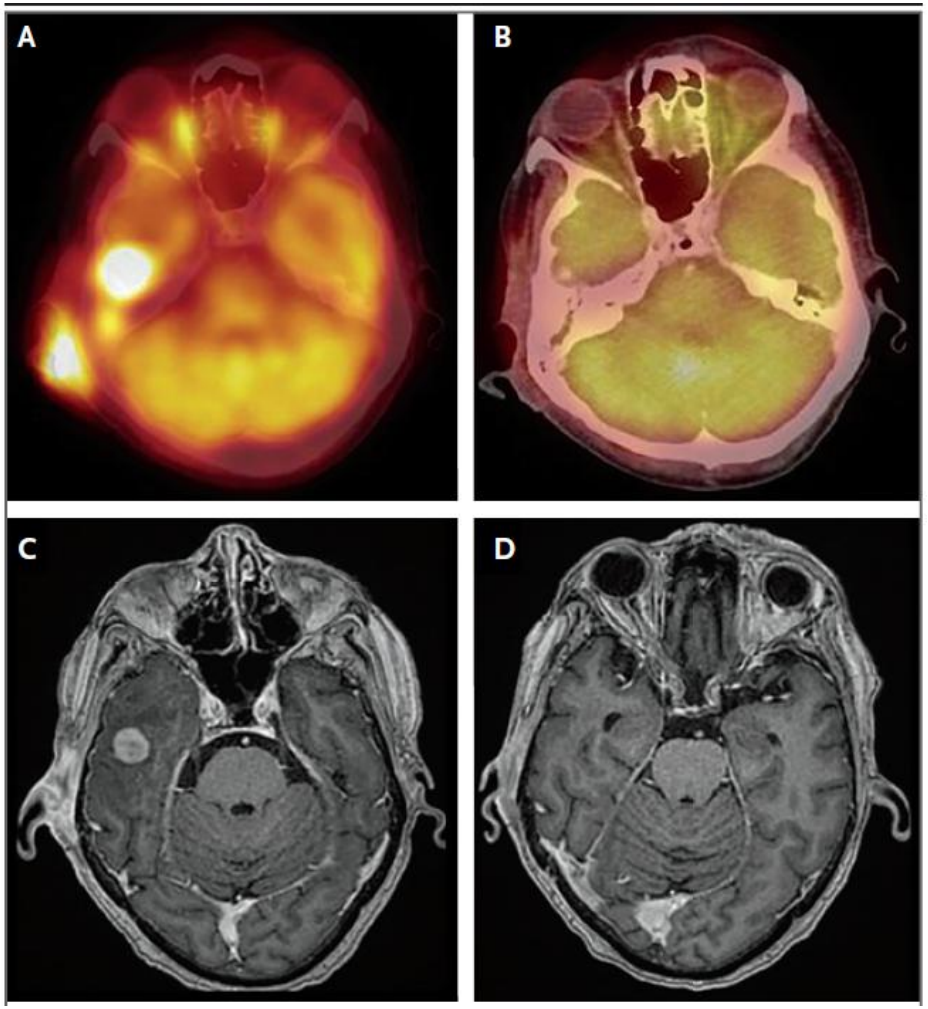
	Patient				
	1	2	3	4	5
Disease	Primary refractory PCNSL	Recurrent PCNSL	Recurrent PCNSL	Recurrent PCNSL	CNS recurrence of PTL
Symptoms at current presentation, KPS (%)	Subtle visual field deficit and cognitive changes; 70	Cognitive changes; 80	Nausea, vomiting, ataxia; 50	Asymptomatic; 80	Aphasia, impaired level of consciousness (LOC); 40
Radiographic response	Complete response	Complete response*	Partial response	Complete response	Complete response†
Neurologic/clinical response, KPS (%)	Resolution of visual field deficit and cognitive changes; 90	Resolution of cognitive changes; 80	Resolution of nausea, vomiting and ataxia; 70	Stable (asymptomatic); 80	Resolution of aphasia and impaired LOC; 80
Progression-free survival (mo)	13+	17	17+	14	14+

*The patient was subsequently unable to get gadolinium contrast due to renal insufficiency. The radiographic complete response reflects complete resolution of the nonenhancing T2 signal change in the area of prior involvement.

†The patient's parenchymal and leptomeningeal disease completely responded to nivolumab therapy; persistent intraocular disease was treated with ocular radiation.

Nayak L, et al. Blood 2017;129:3071

CAR-T



Jeremy S, et al. N Engl J Med 2017;377:783

小结

- 大剂量MTX仍然是治疗PCNSL的基石
- 一线方案需要根据患者的年龄等因素综合判断
- 一线治疗缓解后的放疗和移植巩固疗效相当，移植的短期毒性明显，而放疗的远期毒性值得关注
- 大部分PCNSL为ABC型，来那度胺有可能通过抑制NF-kappaB通路发挥作用
- PCNSL具有特征性的基因异常，抑制BCR通路和PD/PD-L1的药物显示出很高的疗效
- CAR-T治疗的效果和安全性有待进一步研究

谢谢！