

Primary Central Nervous System Lymphoma : An Update on Diagnosis and Management

原发性中枢神经系统淋巴瘤：诊断与治疗的最新进展

Lakshmi Nayak, M.D.

Director, Center for CNS Lymphoma
Center for Neuro-Oncology, Dana-Farber Cancer Institute

Assistant Professor of Neurology
Harvard Medical School



Dana-Farber
Cancer Institute



泽诺 译

Dr Lakshmi Nayak

Assistant Professor of Neurology

Harvard Medical School

Director, Center for CNS Lymphoma

Dana-Farber Cancer Institute

Center for Neuro-Oncology

Boston, MA, USA



Primary CNS lymphoma - Advances in 2022



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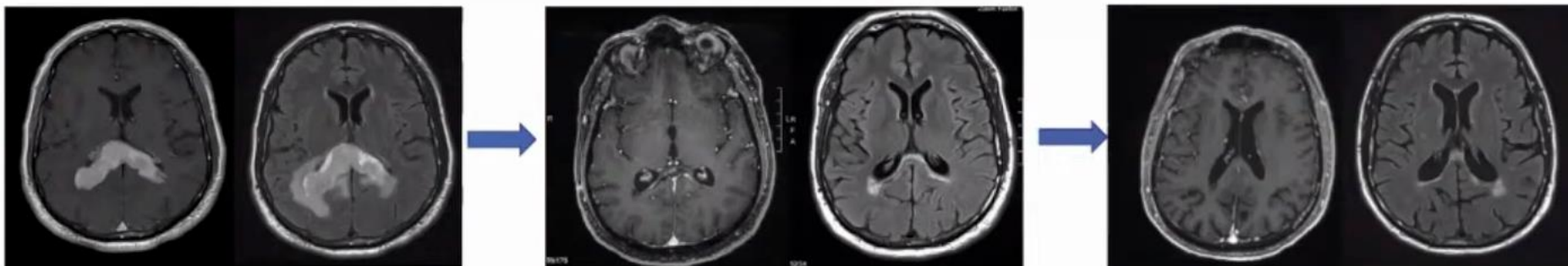


Event Partner



Case

A 62 y/o RHM presented with mental status changes. His family reported that he had been quite withdrawn and less talkative over the last few weeks. He was also noted to have a left visual field cut. MRI brain revealed contrast enhancing lesion in the corpus callosum. He underwent brain biopsy which confirmed DLBCL. CSF studies, ophthalmologic exam, bone marrow biopsy and body PET/CT were unremarkable. Diagnosis of PCNSL was made. He was treated with MTR followed by TBC autologous transplant. He remains in remission at 5 years.



案例

62岁右利手男性患者因精神状态改变而就诊。他的家人报告说，在过去的几周里，他一直很孤僻，不太爱说话。且有左眼视野缺损。头部MRI显示胼胝体有对比增强的病变。脑活检证实为DLBCL（弥漫大B细胞淋巴瘤）。脑脊液检查、眼科检查、骨髓活检和全身PET/CT均无异常。诊断为PCNSL。接受了MTR治疗，随后进行了TBC自体移植，5年来他一直处于缓解。

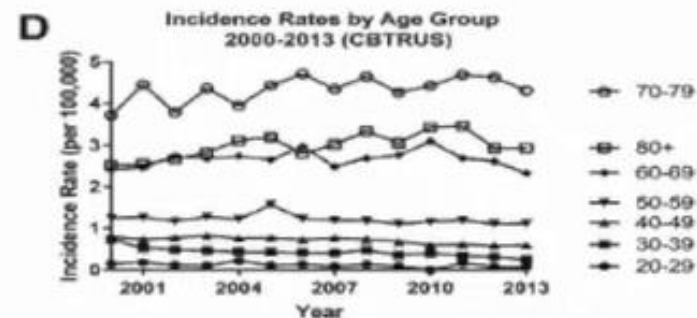
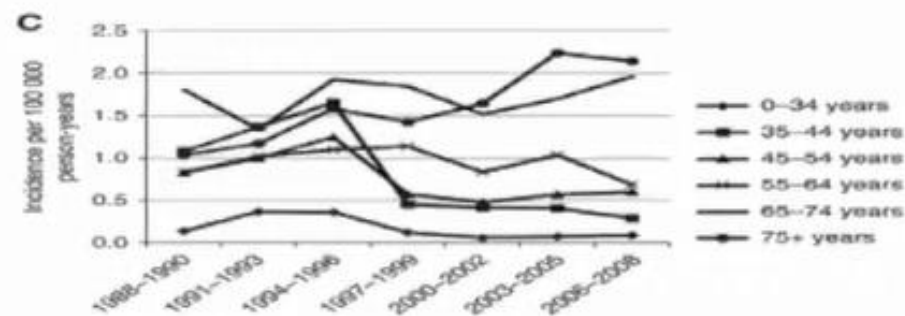
Introduction

- Primary Central Nervous System Lymphoma (PCNSL) :
 - Poor prognosis variant of extranodal non-Hodgkin's lymphoma
 - Arising from the brain, meninges, eyes or spinal cord
 - Absence of systemic disease

- 原发性中枢神经系统淋巴瘤
 - 预后不良的结外非霍奇金淋巴瘤分型
 - 起源于脑、脑膜、眼或脊髓
 - 不存在系统性的淋巴瘤

Epidemiology

- 6% of all malignant primary CNS tumors
占有所有恶性原发性中枢神经系统肿瘤的6%
- Incidence rate : 0.4 per 100,000 py
 - 4.3 per 100,000py in >70y发病率：0.4/100,000每年；大于70岁：4.3/100,000每年
- Median age : 65 y
 - Older pts account for approximately half the cases中位年龄：65岁
老年患者约占一半的病例。
- Incidence rates increasing in age group >65y since 2000s
自2000年以来，大于65岁的年龄组发病率在增加。



Shiels M et al. *Br J Haematol* 2016; 174: 417-24

Mendez J et al. *Neuro Oncol* 2017; Oct 3

Houillier et al. *Neurology* 2020

Diagnosis

诊断

- Brain biopsy or ?surgical resection 脑活检或？手术切除
 - Defer corticosteroids until histologic confirmation
推迟使用皮质类固醇直到组织学确认
 - **Early diagnosis → early institution of treatment → neurologic recovery**
早期诊断->早期治疗->神经系统恢复
- Other diagnostic procedures have low-yield & may delay diagnosis and treatment
 - CSF cytopathologic analysis
 - Vitreous aspirate analysis

其他诊断检查收益率低，且可能延误诊断和治疗

- 脑脊液（CSF）细胞病理学分析
- 玻璃体抽吸物分析

Baseline Evaluation : IPCG criteria

(IPCG: International Primary CNS lymphoma Collaborative Group)

基线评估: IPCG标准

(IPCG:国际原发性中枢神经系统淋巴瘤协作组)

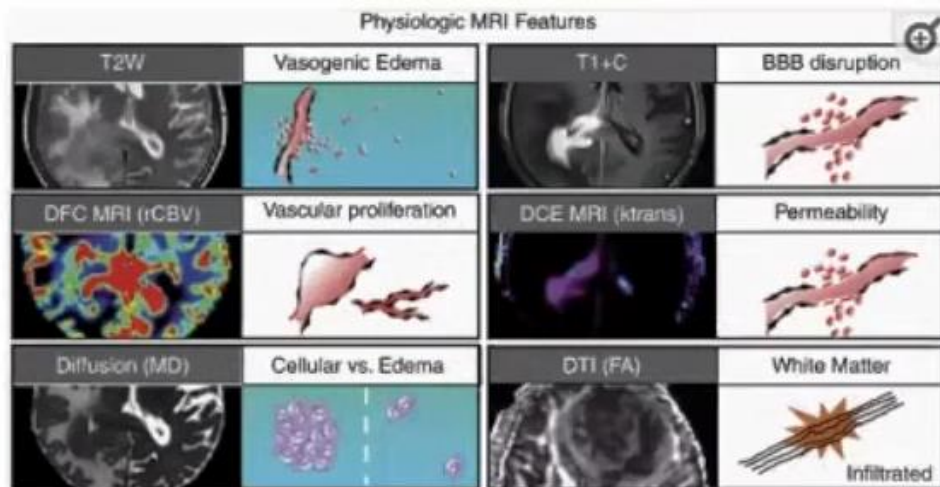
- Clinical Evaluation: 临床评估
 - Prognostic factors (Age, Performance status) 预后因素 (年龄, 表现状态)
 - Laboratory Evaluation 实验室评估
 - Extent of disease evaluation: 疾病的程度评估
 - Brain/Spine: MRI or CT
 - CSF studies
 - Eyes: Slit lamp examination
 - Body: PET/CT body, **testicular US in older men**
 - Bone marrow biopsy – ok to skip if not on trial
- 脑/脊柱: MRI或CT
 - CSF研究
 - 眼睛: 裂隙灯检查
 - 身体: PET/CT身体, 老年男性的睾丸检查
 - 骨髓活检-如果不参加试验可以不做

Abrey et al. J Clin Oncol 2005; 22: 5034-43

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Diagnosis

- IPCG guidelines
 - Assessment of non-enhancing tumor
 - Infiltrative disease (CE-T2W-FLAIR)
 - Tumor relapse vs Treatment effect
 - DCE MRI – (K^{trans}) vascular permeability
 - DSC MRI – rCBV
 - DWI
 - PET
- Circulating tumor DNA in CSF
 - Diagnosis
 - ? MRD



诊断

- IPCG指南
 - 非增强型肿瘤的评估
 - 渗透性疾病(CE-T2W-FLAIR)
 - 肿瘤复发与治疗效果的鉴别
 - DCE MRI-(K^{trans})血管通透性
 - DSC MRI-rCBV
 - DWI
 - PET
- CSF中的循环肿瘤DNA(ctDNA)
 - 诊断
 - ? MRD

Barajas et al. NeuroOncol 2021; 23 (7):1056

Mutter et al. Blood 2021 (ASH plenary) 泽诺 译

IPCG Response Criteria for PCNSL

IPCG PCNSL的缓解标准

Response	Imaging	Corticosteroid dose	Eye examination	CSF cytology
CR	No contrast enhancement	None	Normal	Negative
CRu	No contrast enhancement	Any	Normal	Negative
	Minimal abnormality	Any	Minor RPE abnormality	Negative
PR	50% decrease in enhancement	Irrelevant	Normal or Minor RPE abnormality	Negative
	No enhancement	Irrelevant	Decreased vitreous cells or retinal infiltrate	Persistent/ suspicious
PD	25% increase in lesion Any new site of disease	Irrelevant	Recurrent or new ocular disease	Recurrent or positive
SD	All other scenarios			

Abrey et al. J Clin Oncol 2005; 22: 5034-43

缓解	影像	皮质激素剂量	眼科检查	脑脊液细胞学检查
完全缓解	无对比增强	无	正常	阴性
不确定的完全缓解	无对比增强 极小的异常	任意剂量 任意剂量	正常 微小的视网膜色素 上皮异常	阴性 阴性
部分缓解	增强减少50% 无增强	无关 无关	正常或微小的视网 膜色素上皮异常 玻璃体细胞或者视 网膜浸润减少	阴性 持续/可疑
疾病进展	病损增加25% 任何新增的病灶	无关	复发或新的眼部疾 病	复发/阳性
疾病稳定	所有其他情况			

泽诺 译

Prognostic Factors

MSKCC prognostic model

- Age ≥ 50 y
- KPS < 70

IELSG prognostic score

- Age > 60 y
- ECOG PS > 1 , KPS < 70
- Elevated serum LDH
- High CSF protein
- Deep brain involvement

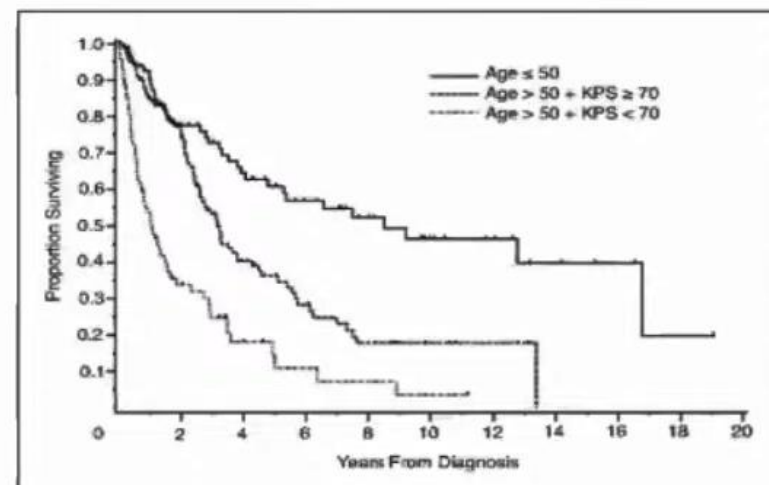
预后因素

MSKCC预后模型

- 50岁及以上
- KPS <70

IELSG预后评分

- 60岁以上
- ECOG PS >1 分, KPS <70
- 血清LDH升高
- 脑脊液高蛋白
- 脑深部受累



Abrey et al. *J Clin Oncol* 2006; 24: 5711-15
Ferreri et al. *J Clin Oncol* 2003; 21: 266-72

Prognosis

- Historically, the prognosis of PCNSL pts has been poor
 - 1yOS - 51%
- With recent advances in optimization of treatments, the mOS is increasing
 - mOS - 12 mo in 1970s → 26 mo in 2010s.
 - 5yOS - 31%
 - 5yOS - 13% in elderly
 - No change in survival in the elderly over time (since 1970s)

Ferreri A *et al.* *Critical Rev In Oncol Hematol* 2017; 113: 97-110
Mendez J *et al.* *Neuro Oncol* 2017; Oct 3
Houillier *et al.* *Neurology* 2020

预后

从历史上看，PCNSL患者的预后一直较差。

- 1yOS（1年总生存率）- 51%。

近年来随着治疗方法的进步，mOS（中位总生存期）在不断增加。

- mOS：70年代的12个月→2010年代的26个月
- 5yOS（5年总生存率）：31%
- 老年人5yOS：13%。
- 随着时间的推移，老年人的生存率没有变化（自1970年代以来）

Evolution of Treatment

治疗方法的进步

1980s

Whole Brain Radiation Therapy (WBRT) 全脑放疗

1990s

WBRT + Chemotherapy (HD-MTX)

全脑放疗+化疗（大剂量甲氨蝶呤）

2000s

high-dose Chemotherapy + Autologous stem cell rescue

大剂量化疗+自体干细胞移植

2020s

Targeted therapy, Immunotherapy

靶向治疗+免疫治疗

Upfront Therapy – Newly Diagnosed PCNSL

- Induction Therapy

- Goal – complete response

- **HD-MTX based chemotherapy**

- **MTR-A** (MTX, temozolomide, rituximab followed by AraC)
- **RMPV-A** (Rituximab, MTX, procarbazine, vincristine followed by AraC)
- **MATRix** (MTX, AraC, thiotepa, rituximab)
- **R-MBVP-A** (Rituximab, MTX, carmustine, teniposide, prednisone followed by AraC)

前期治疗-新诊断的PCNSL

- 诱导疗法

- 目标：完全缓解(CR)

- 基于HD-MTX的化疗

- MTR-A (MTX、替莫唑胺、利妥昔单抗、阿糖胞苷)
- RMPV-A (利妥昔单抗、MTX、丙卡巴肼（也叫甲基苄肼）、长春新碱、阿糖胞苷)
- MATRix (MTX、阿糖胞苷、塞替派、利妥昔单抗)
- R-MBVP-A (利妥昔单抗、MTX、卡莫司汀、替尼泊苷、泼尼松、阿糖胞苷)

中文名	英文名	缩写
甲氨蝶呤	methotrexate	MTX/M
替莫唑胺	temozolomide	T
利妥昔单抗	rituximab	R
阿糖胞苷	cytarabine/arabinosylcytosine	Ara-C/A
丙卡巴肼（也叫甲基苄肼）	procarbazine	P
长春新碱	vincristine	V
塞替派	thiotepa	T
卡莫司汀	carmustine	B
替尼泊苷	teniposide	V
泼尼松/强的松	prednisone	P

Upfront Regimens

Regimen	No. of pts	CR	ORR	2y PFS
MTX alone	25	52%	74%	mPFS 12.8 mo
RMPV-A + LD WBRT	52	60%	79%	57%
RMPV-A + ASCT	33	66%	94%	79%
MTR + EA	44	66%	77%	57%
MTR-A + EA/ASCT	113	50%	65.7%	51%/73%
MATRix + WBRT/ASCT	75	49%	87%	61%
RMBVP-A + WBRT	99	45%	82%	1y PFS: 65%
HD-MTX based*	1002	46%	59%	-

Bachelor et al., J Clin Oncol 2003; Morris et al. J Clin Oncol 2013; Omuro et al., Blood 2015; Rubenstein et al., J Clin Oncol 2013; Batchelor et al. J Clin Oncol (ASCO abs) 2021; Ferreri et al. Lancet Hemat 2016, 2017; Bromberg et al. Lancet Oncol 2019; *Houillier et al Neurology 2020

- MTR-A (MTX、替莫唑胺、利妥昔单抗、阿糖胞苷)
- RMPV-A (利妥昔单抗、MTX、丙卡巴肼（也叫甲基苄肼）、长春新碱、阿糖胞苷)
- MATRix (MTX、阿糖胞苷、塞替派、利妥昔单抗)
- R-MBVP-A (利妥昔单抗、MTX、卡莫司汀、替尼泊苷、泼尼松、阿糖胞苷)
- EA（依托泊苷、阿糖胞苷）
- WBRT（全脑放疗）、LD WBRT（低剂量全脑放疗）
- ASCT（自体干细胞移植）

IELSG 32 - 1st randomization

N=227 pts enrolled



	Methotrexate- cytarabine (group A; n=75)	Methotrexate- cytarabine plus rituximab (group B; n=69)	Methotrexate- cytarabine plus rituximab and thiotepa (group C; n=75)	HR (95% CI) for group A vs group B	p value	HR (95% CI) for group A vs group C	p value	HR (95% CI) for group B vs group C	p value
Complete remission	17 (23%; 95% CI 14–31)	21 (30%; 95% CI 21–42)	37 (49%; 95% CI 38–60)	0.74 (0.43–1.29)	0.29	0.46 (0.28–0.74)	0.0007	0.61 (0.40–0.94)	0.020
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)	0.69 (0.54–0.88)	0.010	0.61 (0.49–0.77)	0.00001	0.89 (0.76–1.03)	0.053
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%)

HR=hazard ratio. *Overall response=complete response and partial response.

Table 3: Response rates by group

Ferreri *et al.* Lancet Haematol. 2016

泽诺 译

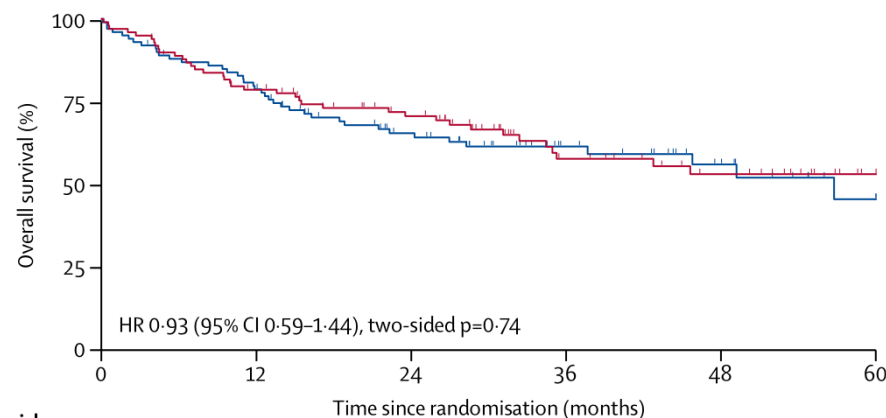
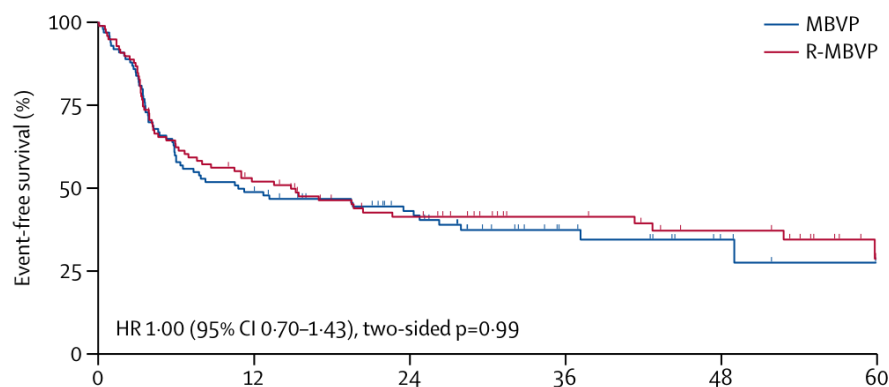
Role of Rituximab in PCNSL: HOVON105/ALLG NHL24

利妥昔单抗在PCNSL中的作用

Rituximab in patients with primary CNS lymphoma (HOVON 105/ALLG NHL 24): a randomised, open-label, phase 3 intergroup study

随机、开放标签、3期组内研究

Jacoline E C Bromberg, Samar Issa, Katerina Bakunina, Monique C Minnema, Tatjana Seute, Marc Durian, Gavin Cull, Harry C Schouten, Wendy B C Stevens, Josee M Zijlstra, Joke W Baars, Marcel Nijland, Kylie D Mason, Aart Beeker, Martin J van den Bent, Max Beijert, Michael Gonzales, Daphne de Jong, Jeanette K Doorduyn

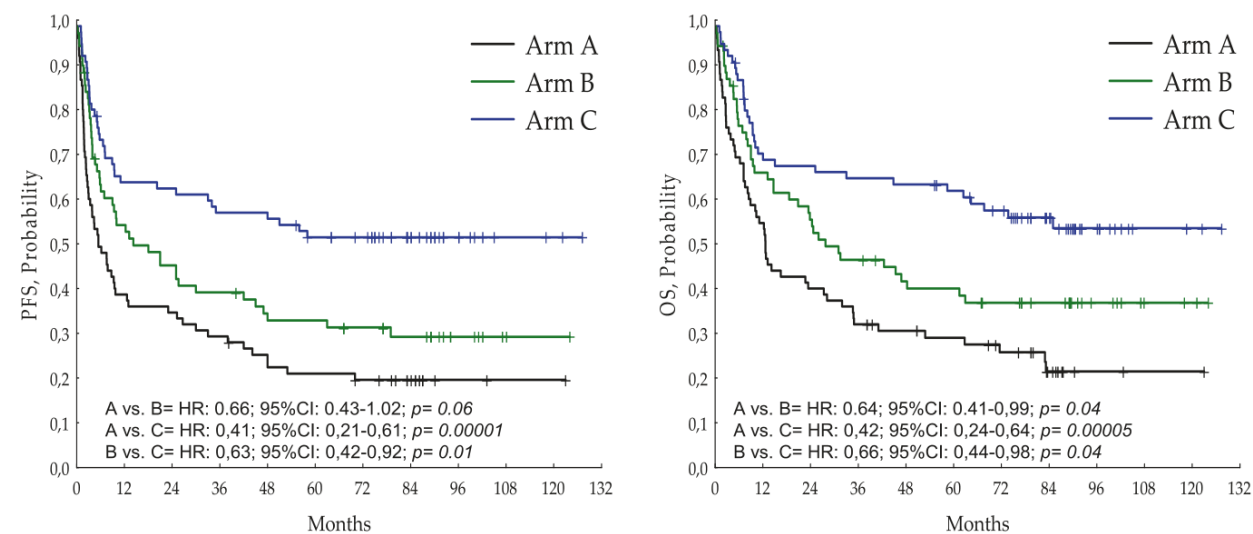


讲者：
无论EFS还是OS，两组生存并无统计学差异
但是否与特定的化疗方案（即MBVP）相关？
HOVON研究中，观察到年轻患者的利妥昔单抗组有优势趋势，但老年组无

泽诺 译
Bromberg *et al.* Lancet Oncol. 2019

Role of Rituximab in PCNSL: Long-term results IELSG32

利妥昔单抗在PCNSL中的作用：IELSG32的长期结果



	MA	MARix	MATRix
CR	23%	30%	49%
ORR	53%	74%	87%
7y OS	21%	37%	56%

Ferreri *et al.* Leukemia 2022

泽诺 译

Upfront Therapy – Newly Diagnosed PCNSL

前期治疗 – 新诊断的PCNSL

Consolidation Therapy

- Goal : prevent disease recurrence
- WBRT
- HDCT & ASCT
- Chemotherapy alone
- N=1002 pts
- 21% underwent consolidation
 - WBRT: 15%
 - ASCT: 6%
 - 77% <60 y
 - 11% >60 y

巩固疗法

- 目标：预防疾病复发
- 全脑放疗
- 大剂量化疗及自体干细胞移植
- 单独的化疗

Houillier et al. Neurology 2020

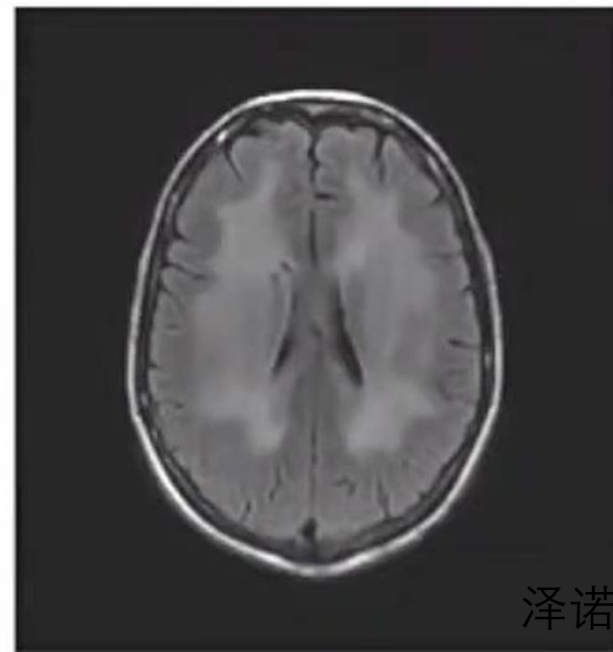
泽诺 译

Chemotherapy + Radiation induced Neurotoxicity

化疗+放疗 引发的神经毒性

- Treatment-related neurotoxicity 治疗相关的神经毒性
 - Impaired attention, executive function, verbal memory, psychomotor speed
受损：注意力、执行功能、语言记忆、精神运动速度
 - Worse with HD-MTX+WBRT (50% pts unemployed) vs HD-MTX alone
相比于单独使用HD-MTX，HD-MTX+WBRT神经毒性更严重（50%患者失业）
 - Worse in older pts (>60 y)
老年患者更严重（大于60岁）
 - Incidence increases with prolonged survival (25-30%)
生存时间延长后，概率增加（25-30%）
 - Progressive & fatal
复发和死亡

Abrey LE et al. J Clin Oncol 1998
Correa DD et al. Ann Oncol 2007
Correa DD et al. Neuro Oncol 2012



泽诺 译

Omit WBRT?

Results of a randomized phase III trial

排除全脑放疗？

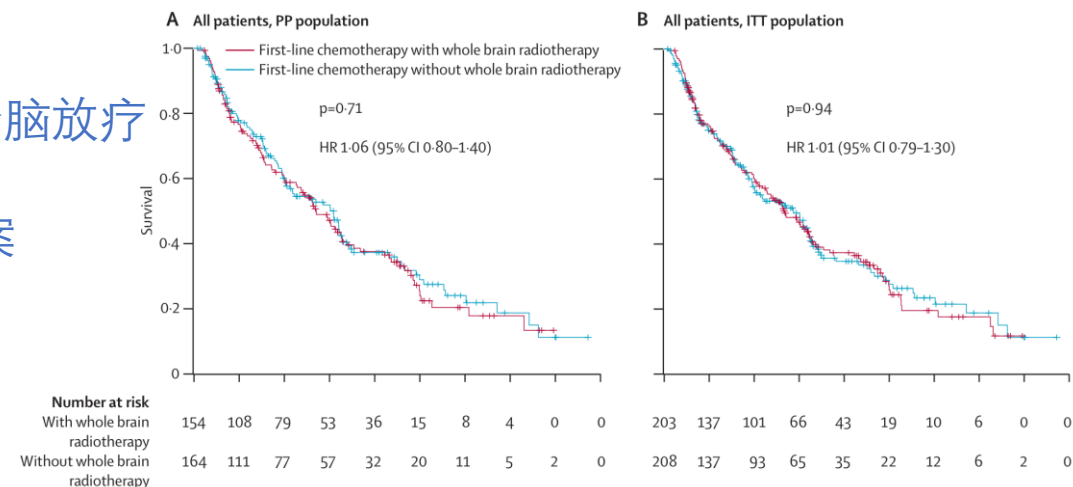
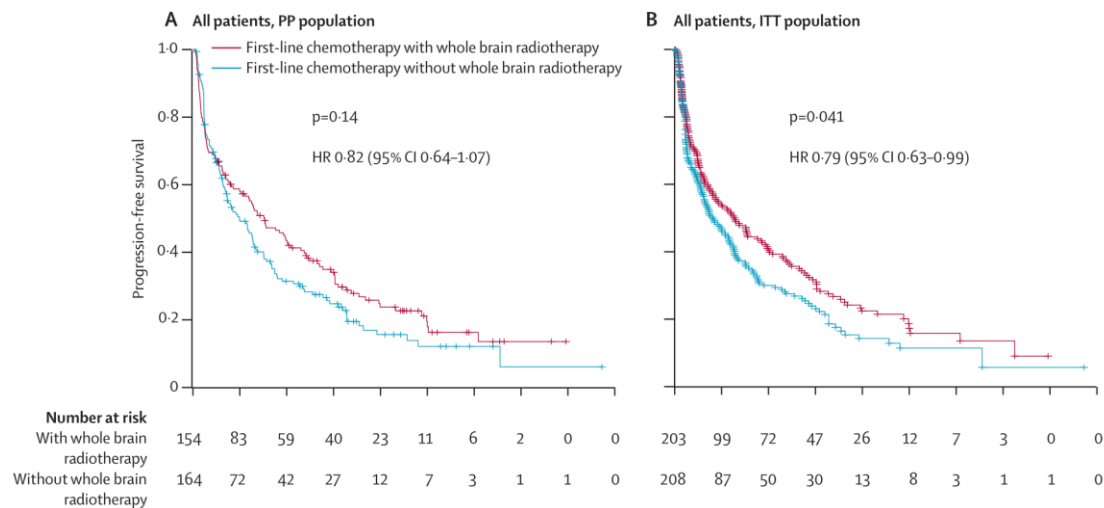
一项3期随机试验的结果

G-PCNSL-SG1:HD-MTX WBRT

N=551 pts

318 treated per protocol

大剂量甲氨喋呤 全脑放疗
共551位患者
318位符合研究方案



Median PFS: 18 mo vs 12 mo

中位PFS: 18个月 vs 12个月

Median OS: 32 mo vs 37 mo

中位OS: 32个月 vs 37个月

Thiel *et al.* G-PCNSL-SG1. Lancet Oncol. 2010

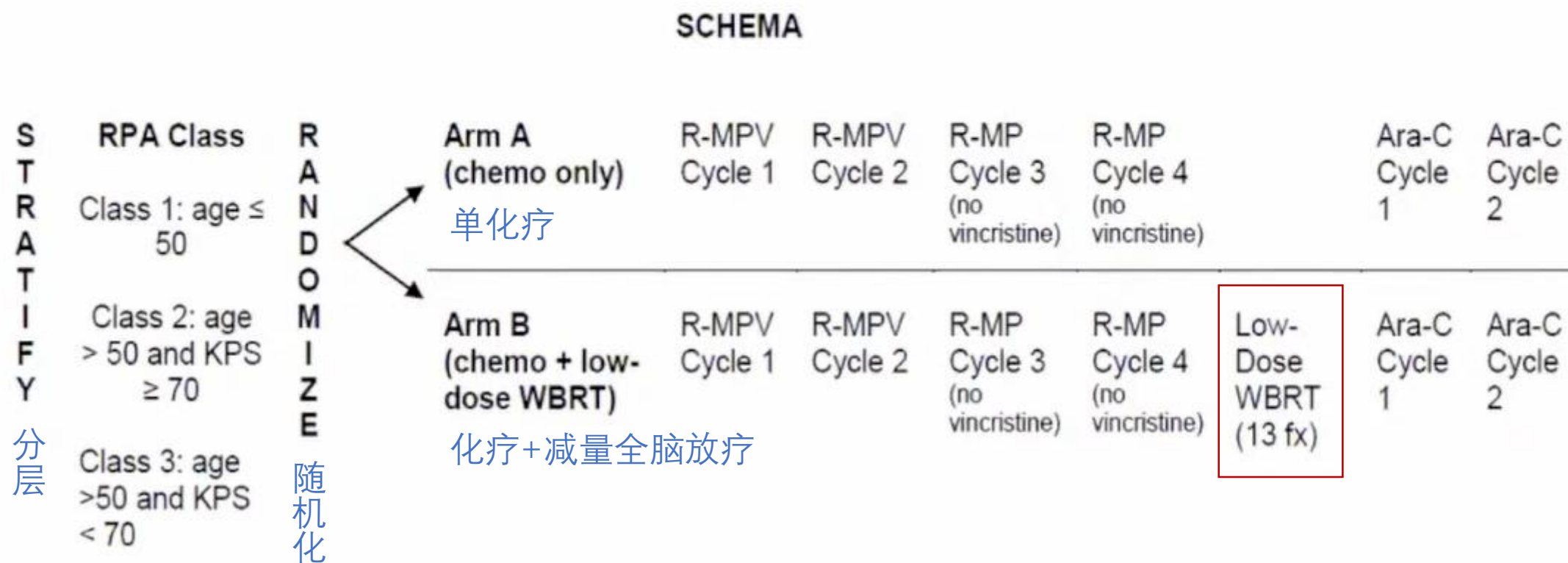
10 泽诺 译

Is reduced dose RT safer and as effective?

Randomized Phase II trial : NRG Oncology/ RTOG 1114

减量放疗同样有效且更安全吗？

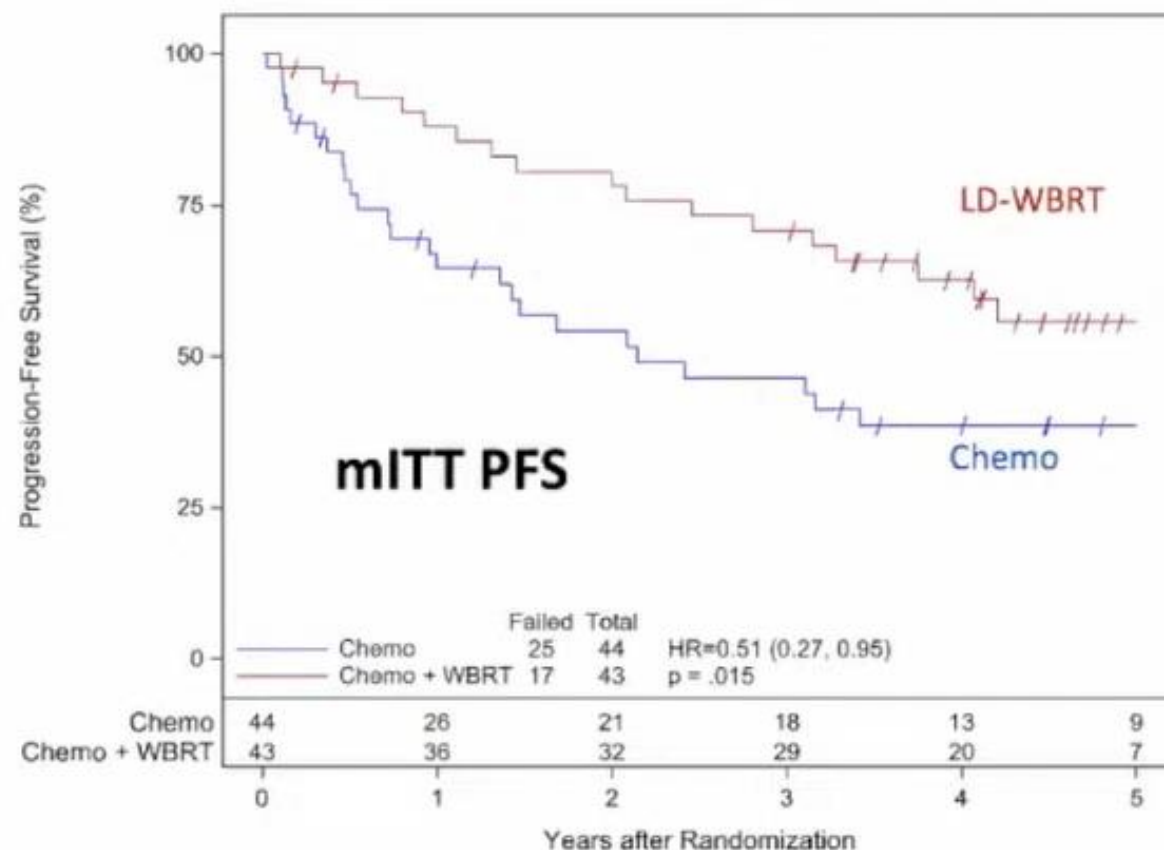
II期随机试验



Slide courtesy of Antonio Omuro

泽诺 译

NRG Oncology/ RTOG 1114



- N= 87 pts 共87位患者
- ORR following induction (IPCG): 83% (chemo) vs 81% (LD-WBRT) 诱导化疗后的ORR: 83% (单化疗) vs 81% (减量全脑放疗)
- LD-WBRT delivered to 86% of pts in the LD-WBRT arm (4 refused) 减量全脑放疗组86%的患者进行了减量全脑放疗 (4位拒绝)
- Primary endpoint mITT PFS: 主要终点 mITT PFS
 - HR= 0.51 (95%CI 0.27-0.95); p=0.015
 - mPFS= 2.1 y (chemo) vs not reached (LD-WBRT) 中位PFS=2.1年 (单化疗) vs 未到达 (减量全脑放疗)
- OS data maturing OS数据收集中
 - Median OS not reached in either arm
 - Med follow-up: 4.6y 医疗随访: 4.6年
- Neuropsych testing ongoing 神经心理测试进行中

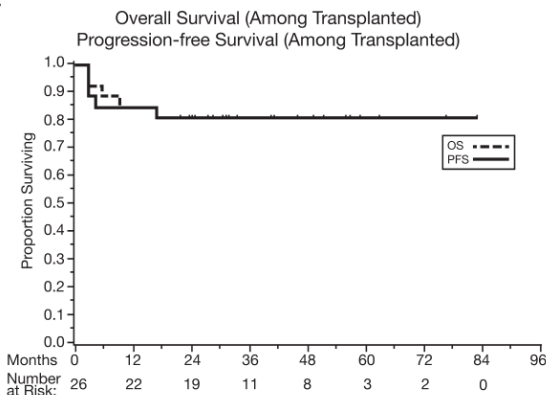
Slide courtesy of Antonio Omuro

泽诺 译

Encouraging results with ASCT

自体干细胞移植可喜的结果

C

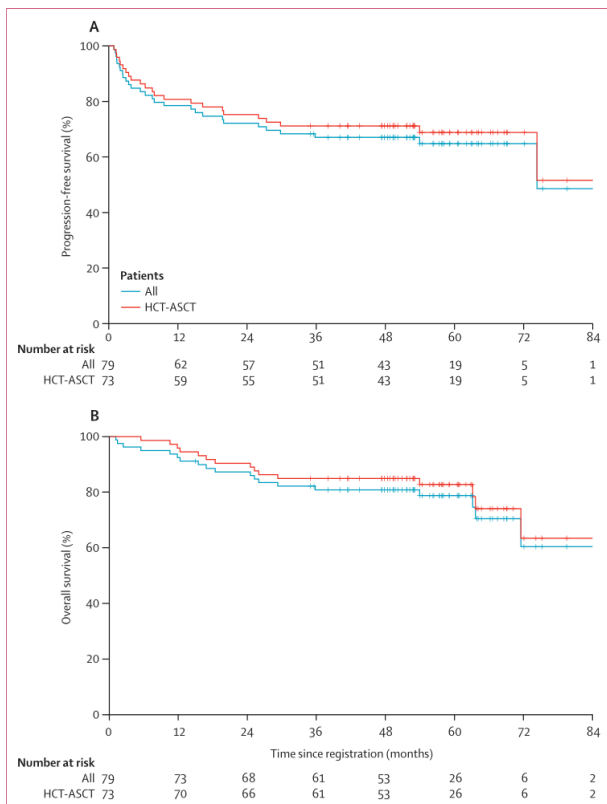


TBC regimen with autoSCT

- TBC=Thiotepa, Busulfan, Cyclophosphamide
- N=32, median age 57y
- 2-year PFS of 79% and 2y-OS of 81%
- 9% TR deaths

TBC方案伴自体干细胞移植

- TBC = 塞替派、白消安、环磷酰胺
- 32例，中位年龄57岁
- 2年 PFS: 79%; 2年OS: 81%
- 9%治疗相关死亡



BT regimen with autoSCT

- BT = BCNU, Thiotepa
- N= 81, median age 56y
- 5-year PFS of 65% and 5y-OS of
- 5% TR deaths

BT方案伴自体干细胞移植

- BT = 卡莫司汀、塞替派
- 81例，中位年龄56岁
- 5年 PFS: 65%; 5年OS
- 5%治疗相关死亡

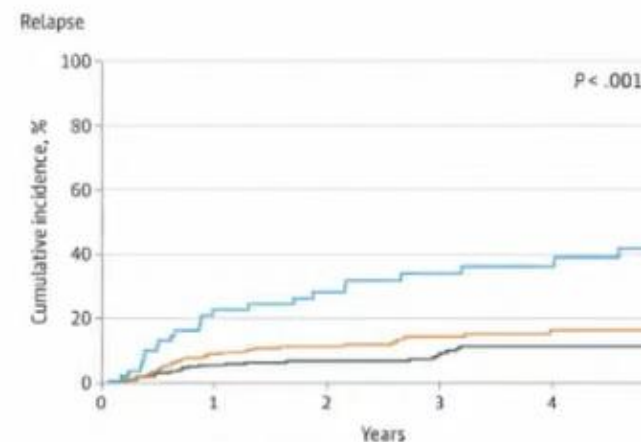
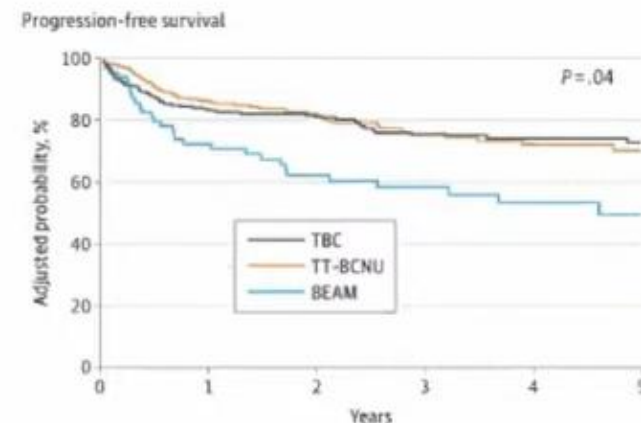
Omuro *et al.* Blood. 2015;
Illerhaus *et al.* Lancet Haematol. 2016;

泽诺 译

TBC vs TT-BCNU vs BEAM – Observational Study

TBC vs TT-BCNU vs BEAM –观察性研究

- TBC (n = 263), TT-BCNU (n = 275), BEAM (n = 65)
TBC (263例) , TT-BCNU (275例) , BEAM (65例)
- 3-year adjusted PFS rates: 3年调整PFS率:
 - TBC: 75%
 - TT-BCNU: 76%
 - BEAM: 58% ($P = 0.03$)
- TT-BCNU vs TBC:
 - Higher relapse risk (HR, 1.79; 95% CI, 1.07-2.98; $P = .03$),
 - Lower risk of non-relapse mortality (NRM) 4% vs 11% (HR, 0.50; 95% CI, 0.29-0.87; $P = .01$), and
 - Similar risk of all-cause mortality >6 mo post HCT (HR, 1.54; 95% CI, 0.93-2.55; $P = 0.10$)



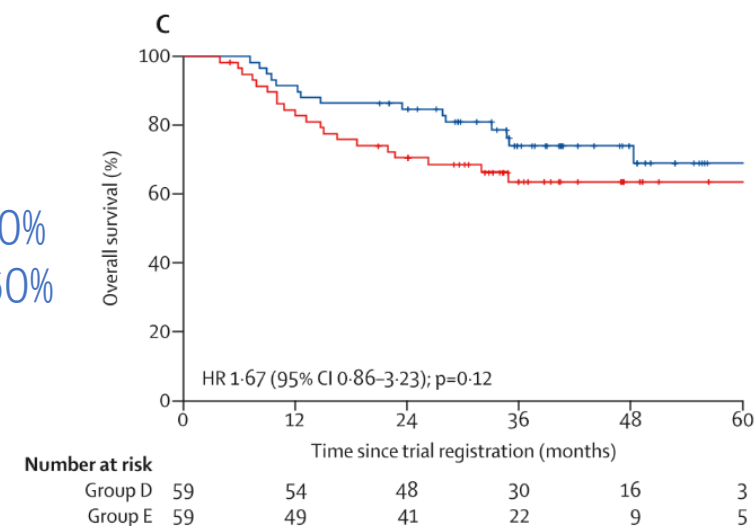
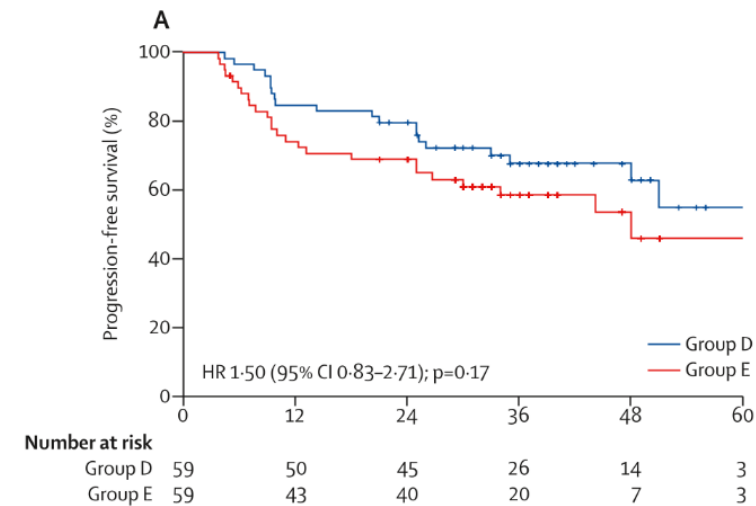
Scordo et al. JAMA Oncol 2021;7(7):993-1003

TT-BCNU对比TBC:

- 更高的复发率 (HR,1.79;95%CL,1.07-2.98; $P=.03$)
- 更低的非复发死亡率 (NRM) 4% vs 11% (HR, 0.50;95%CI,0.29-0.87; $P=.01$)
- 造血干细胞移植大于6个月后, 相近的全因死亡风险 (HR, 1.54;95%CI,0.93-2.55; $P=0.10$)

IELSG 32- 2nd randomization

- 第一次随机化分配: AM vs AMR vs AMRTt
- 第二次随机化分配: WBRT vs BTt – ASCT
 - 主要终点指标: 2年 PFS (P_0 65% \rightarrow P_1 85%)
- AM vs AMR vs AMRTt \rightarrow **WBRT vs BTt-ASCT**
 - Primary endpoint: 2y PFS (P_0 65% \rightarrow P_1 85%)
- 118 pts (59 on each arm) • 118名患者 (每组59名)
- Median f/u: 40 mo • 中位随访时间: 40个月
 - Events (PD/deaths) in 34% and 42% on each arm
 - 事件 (疾病进展/死亡): 两组分别为34%和42%
- ITT 2y PFS :80% WBRT, 69% ASCT • ITT 2年 PFS: 全脑放疗组80%
自体移植组 60%
- 2y OS :85% WBRT, 71% ASCT
- 2年 OS: 全脑放疗组85%
自体移植组 71%



Ferri et al. *Lancet Hematol* 2017;4:510-14

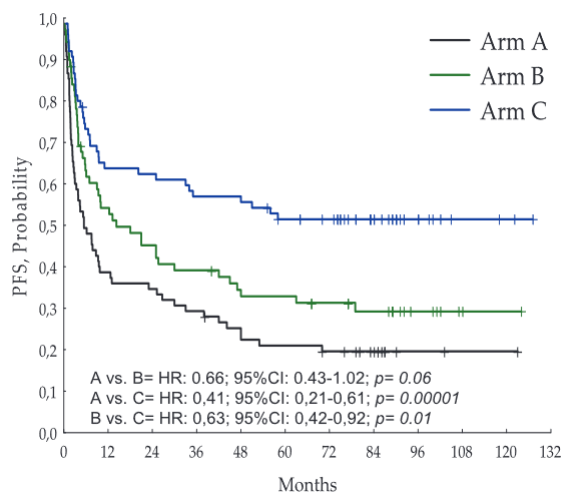
- AM: 阿糖胞苷、甲氨蝶呤
- AMR: 阿糖胞苷、甲氨蝶呤、利妥昔单抗
- AMRTt: 阿糖胞苷、甲氨蝶呤、利妥昔单抗、塞替派
- WBRT: 全脑放疗
- BTt – ASCT: 基于塞替派的自体干细胞移植

泽诺 译

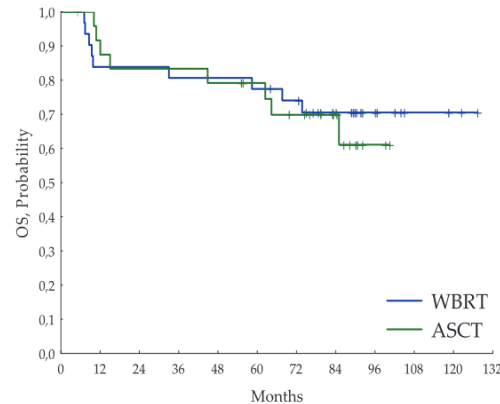
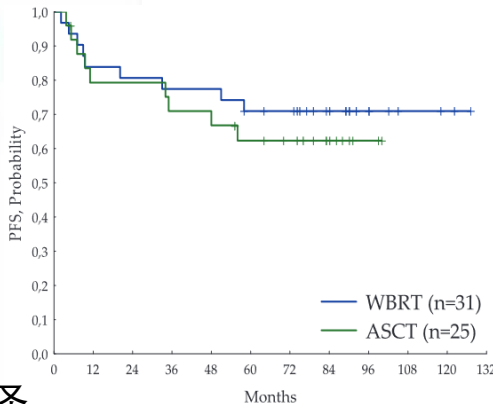
Long-term (7y) results of IELSG 32

IELSG 32的长期（7年）结果

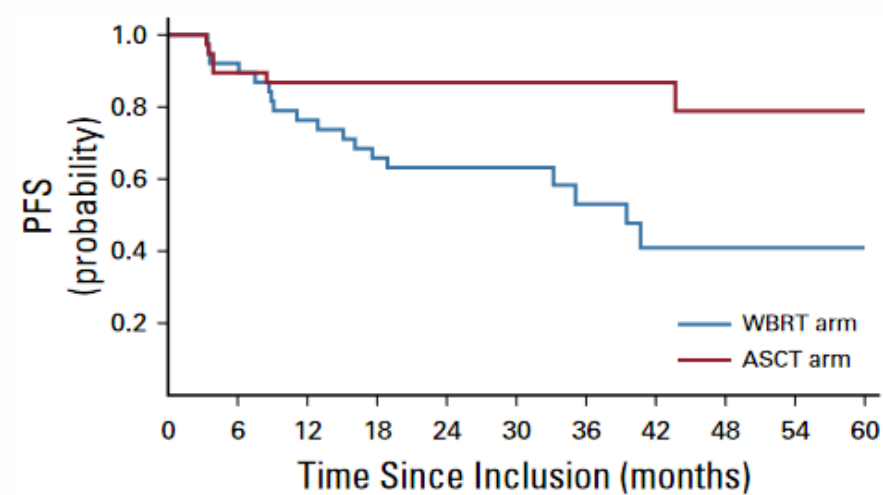
- Median f/u 88 mo
 - 40% alive
 - Majority deaths due to PD
 - 72% PD within the 1st year
 - 7y PFS & OS w MATRix: 52% & 56%
 - 7y OS w MATRix + consolidation: 70%
 - No difference in PFS & OS:
 - Based on consolidative regimen (WBRT vs ASCT)
 - Based on CR (65pts) vs PR (59pts) in pts w consolidation
- 中位随访时间：80个月
 - 40%存活
 - 主要死亡原因为疾病进展
 - 72%的疾病进展处于1年内
 - MATRix方案的7年 PFS与OS：52%与56%
 - MATRix方案并巩固治疗的7年 OS：70%
 - 在PFS和OS上并无差异
 - 两种巩固方案（全脑放疗 vs 自体干细胞移植）
 - 巩固治疗患者为CR（65名患者）或PR（59名患者）



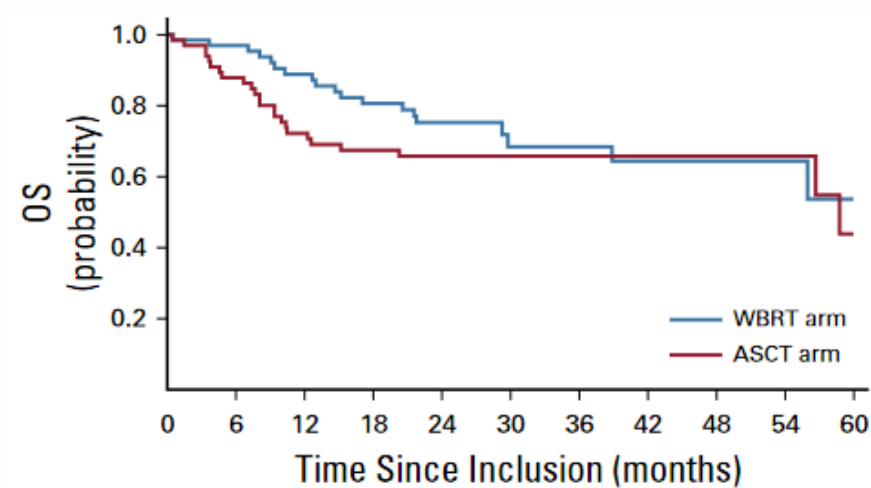
	MA	MARix	MATRix	WBRT	ASCT
7y OS (n=219)	21%	37%	56%		
7y OS (n=113)				71%	70%



ANOCEF-GOELAMS Randomized Phase II PRECIS study



No. at risk											
WBRT arm	38	35	29	25	24	13	10	6	4	4	3
ASCT arm	38	34	31	31	30	20	14	11	8	5	3



No. at risk											
WBRT arm	66	62	54	49	42	19	17	10	6	6	4
ASCT arm	66	57	46	41	38	24	17	14	9	6	4

	2 year PFS	2 year OS
WBRT	63% (49% - 81%)	75% (65% - 87%)
ASCT	87% (77 - 98%)	66% (55% - 79%)

- 神经认知:
- Neurocognition:
 - Worse after WBRT
 - Preserved or improved after ASCT
- Toxicity related deaths after ASCT : 11%
- 自体干细胞移植后毒性相关死亡: 11%

Upfront Therapy – Newly Diagnosed PCNSL

前期治疗 – 新诊断的PCNSL

Consolidation Therapy

- Goal : prevent disease recurrence
- WBRT
- HDCT & ASCT
- Chemotherapy alone
- N=1002 pts
- 21% underwent consolidation
 - WBRT: 15%
 - ASCT: 6%
 - 77% <60 y
 - 11% >60 y

巩固疗法

- 目标：预防疾病复发
- 全脑放疗
- 大剂量化疗及自体干细胞移植
- 单独的化疗
- N=1002名患者
- 21%进行了巩固治疗
 - 全脑放疗： 15%
 - 自体干细胞移植： 6%
 - 77%小于60岁
 - 11%大于60岁

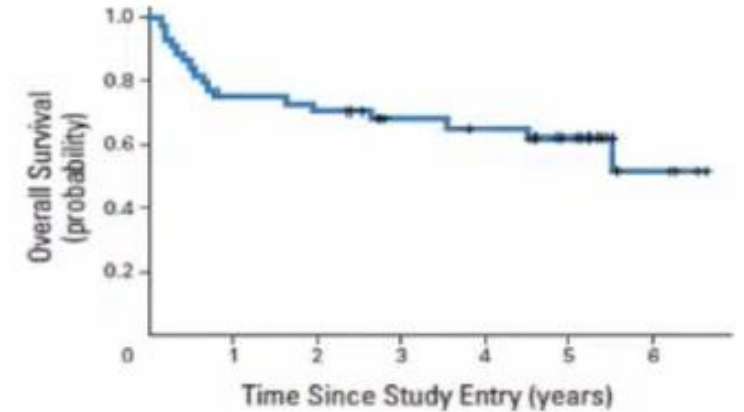
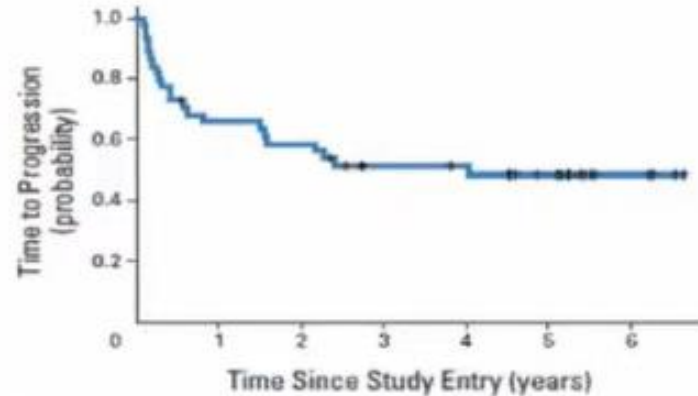
泽诺 译

Houillier et al. Neurology 2020

Non-myeloablative Chemotherapy Alone : CALGB 50202

单独的非清髓化疗：CALGB 50202

- Single arm, Phase II, multicenter trial
- N = 44 pts
- Induction: HD-MTX, TMZ, Rituximab (MTR) - CR 66%
- Consolidation: Etoposide + AraC (EA)
- 2y PFS 57%
- mPFS 2.4y, mOS NR
- 单臂、2期、多中心试验
- N = 44名患者
- 诱导化疗: HD-MTX, TMZ, Rituximab (MTR) – CR(66%)
- 巩固治疗: 依托泊苷 + 阿糖胞苷
- 2年 PFS 57%
- 中位PFS 2.4年, 中位OS 无数据



Alliance 51101 - NCT01511562 : MTRA → EA vs ASCT

MTRA化疗后EA vs ASCT

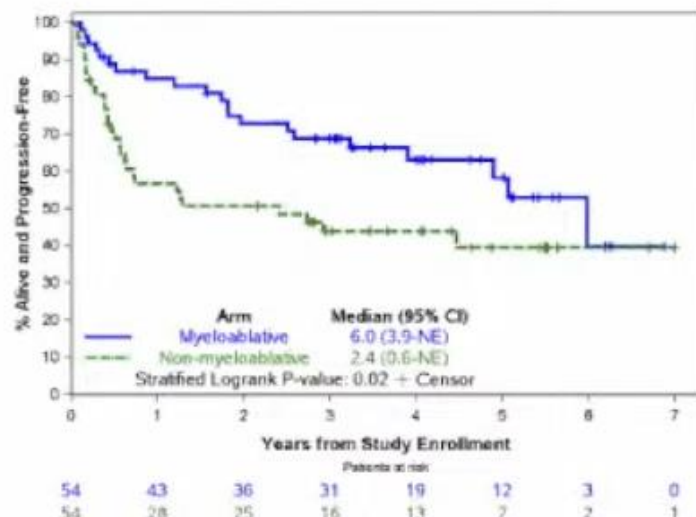
Response to Induction Therapy with MTR-A

Group	N	CR/CRu, %	95% CI	PD, %
All Subjects	108	50	40 - 60	
Myeloablative (ASCT)	54	56	41 - 69	11%
Non-Myeloablative (EA)	54	44	31 - 59	28% (p=0.05)

所有被试
清髓（自体干细胞移植）
非清髓（EA）

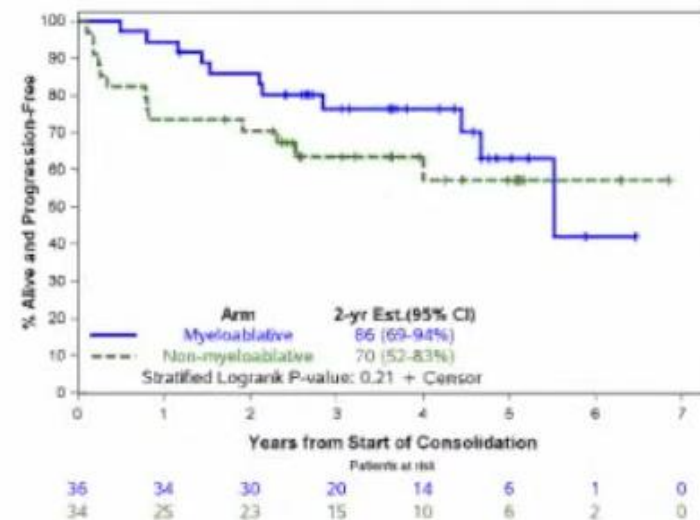
从诱导治疗开始的PFS

PFS from start of induction



从巩固治疗开始的PFS

PFS from start of consolidation



Slide courtesy of Tracy Batchelor, presented at ASCO 2021

泽诺 译

Challenges with Upfront Treatments

前期治疗的挑战

- ASCT & WBRT consolidation only for a very selected population
 - 77% vs 11% (<60y vs >60y)
 - Young patients without relevant comorbidity
 - Preserved neurocognitive function
 - Treatment related mortality neurotoxicity
- Approximately 1/2 of the patients do not qualify for consolidation
 - Will not contribute to improved outcome in elderly, which represent the majority of patients
 - 15-33% patients have refractory disease
- ASCT和WBRT巩固只适合一部分特定患者
 - 77% vs 11% (<60岁 vs >60岁)
 - 患者年轻且无相关共病
 - 保留的神经认知功能
 - 治疗相关的致死毒性
- 接近1/2的患者不符合巩固标准
 - 无助于提升老年患者的疗效，亦即大部分患者
 - 15-33%的患者的为难治疾病

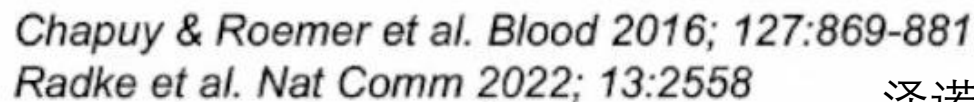
Salvage Treatment (Chemotherapy) 挽救治疗（化疗）

Reference	Treatment	N	ORR	mPFS (mo)	1yOS	mOS (mo)
Fischer L. Ann Oncol 2006	Topotecan	27	33%	2	39%	8.4
Voloschin AD. J Neurooncol 2008		15	40%	2	-	32.7
Reni, 2007	TMZ	23	31%	2.8	31%	3.9
Soussain, J Clin Oncol 2008	Ara-C+VP16→ HDCT +ASCT	43	47%	11.6	*	18.3
Batchelor, Neurology 2011	Rituximab	12	36%	1.9	-	20.9
Raizer JJ. Cancer 2012	Pemetrexed	11	55%	5.7	45%	10.1
Dietrich J. Oncologist 2020		17	57%	4.2		44.5
Nayak L. Leuk Lymph 2013	R-TMZ	16	14%	1.7	71%	NR
Ferreri et al. Blood Adv 2020	NGR-hTNF/RCHOP	28	75%	6**	-	-
Fox et al. Blood Adv 2021	TIER	27	52%	3	-	5

*2yOS 45%, **consolidation for some pts

泽诺 译

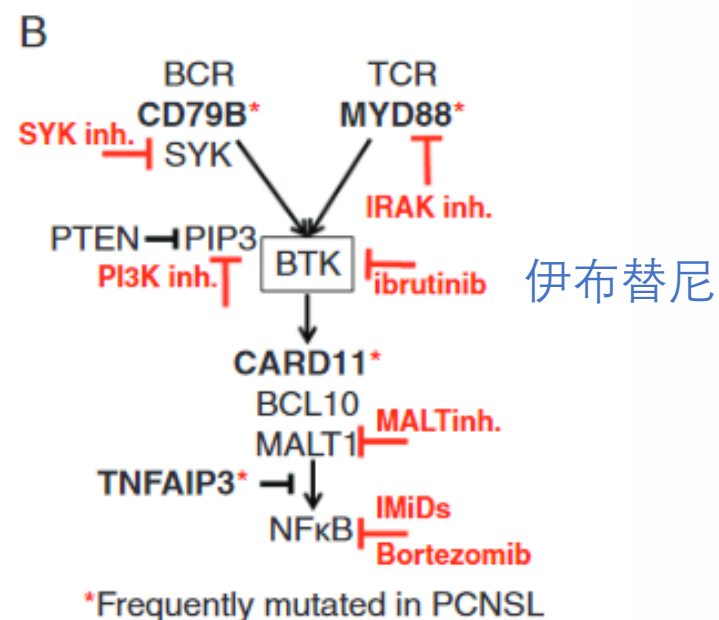
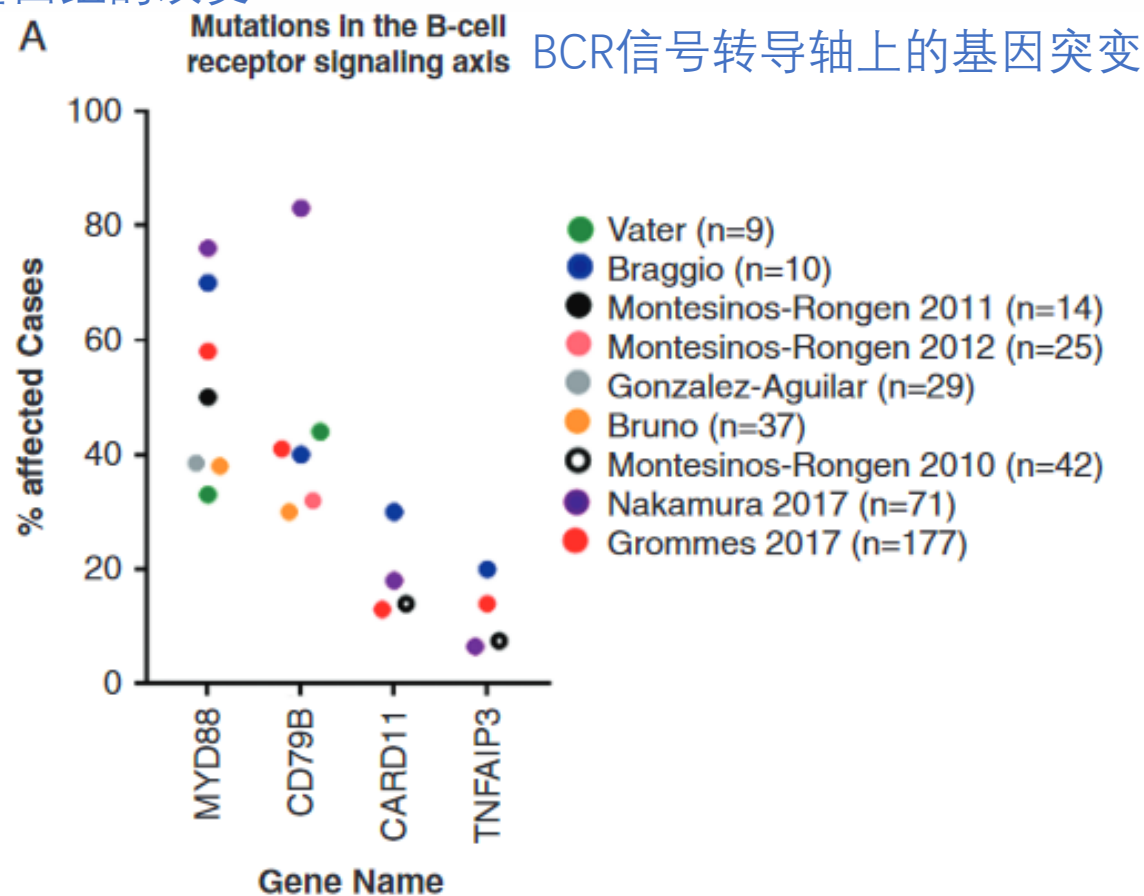
弥漫大B细胞淋巴瘤 与 原发性中枢系统淋巴瘤 基因组对比



泽诺 译

Genomic Alterations in PCNSL

PCNSL中基因组的改变

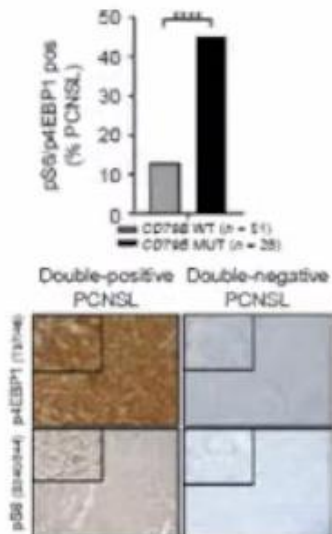
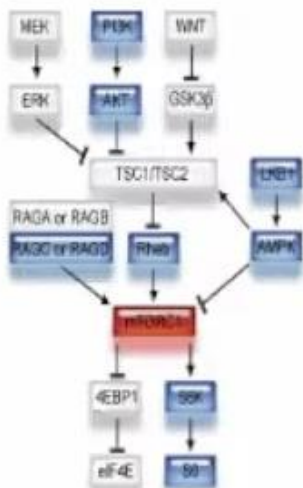


Grommes & Nayak et al. NeuroOncol 2019; 21:306-313

泽诺 译

PI3K/AKT/mTOR Pathway Inhibition

抑制PI3K/AKT/mTOR通路



VOLUME 34 · NUMBER 15 · MAY 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

坦西莫司治疗复发/难治PCNSL的2期临床试验

Phase II Trial of Temsirolimus for Relapsed/Refractory Primary CNS Lymphoma

Agnieszka Korfel, Uwe Schlegel, Ulrich Herrlinger, Martin Dreyling, Christian Schmidt, Luisa von Baumgarten, Antonio Pezzutto, Thomas Grobosh, Sied Kebir, Eckhard Thiel, Peter Martus, and Philipp Kiewe

- N= 37 pts
- ORR 54%
- mPFS 2.1 mo (95% CI, 1.1 to 3.0 mo)
- mOS 3.7 mo (95% CI, 1.5 to 5.8 mo)
- Toxicity – 13.5% mortality (pneumonia)

毒性 – 13.5% 死亡率 (肺炎)

Korfel et al. *J Clin Oncol* 2016;34:1757

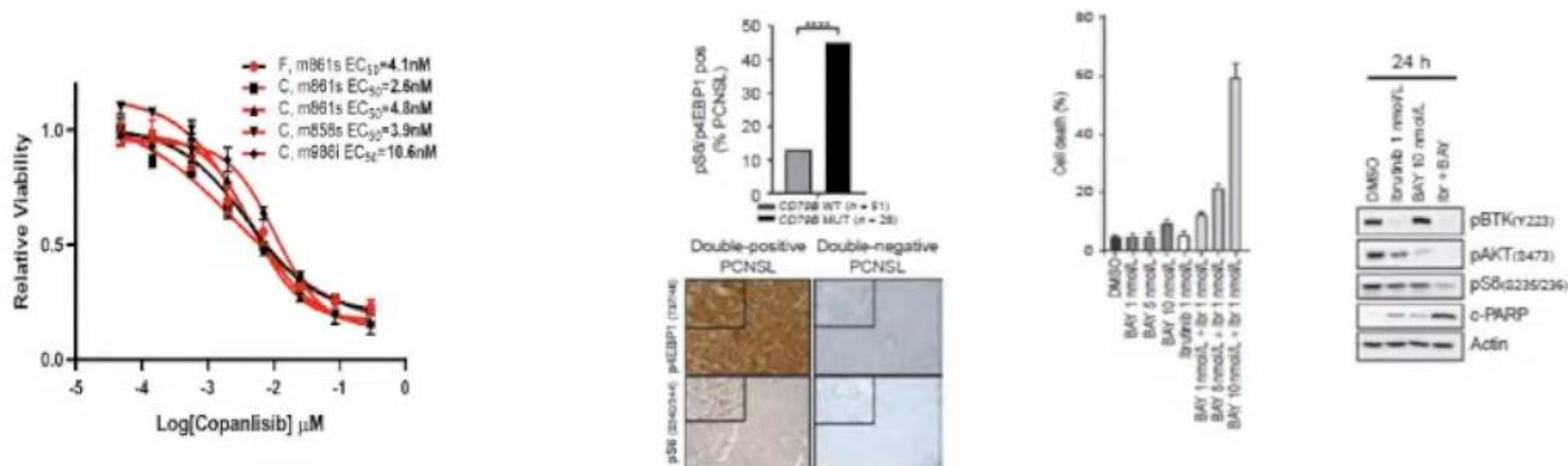
Nitta et al. *Sur Neurol Int* 2016;7:S474

Grommes et al. *Cancer Discov* 2017;7:1018

泽诺 译

PI3K/AKT/mTOR Pathway Inhibition

抑制PI3K/AKT/mTOR通路



- **NCT03581942** : Phase 1b study of **Copanlisib** with Ibrutinib in R/R PCNSL

可泮利塞联合伊布替尼治疗复发/难治PCNSL的1b期研究

- **NCT04906096** : Phase 2 study of **Paxalisib** in R/R PCNSL

Paxalisib 治疗复发/难治PCNSL的2期研究

Grommes et al. Cancer Discov 2017;7:1018

Meredith et al. NeuroOncol 2020 (SNO abs)

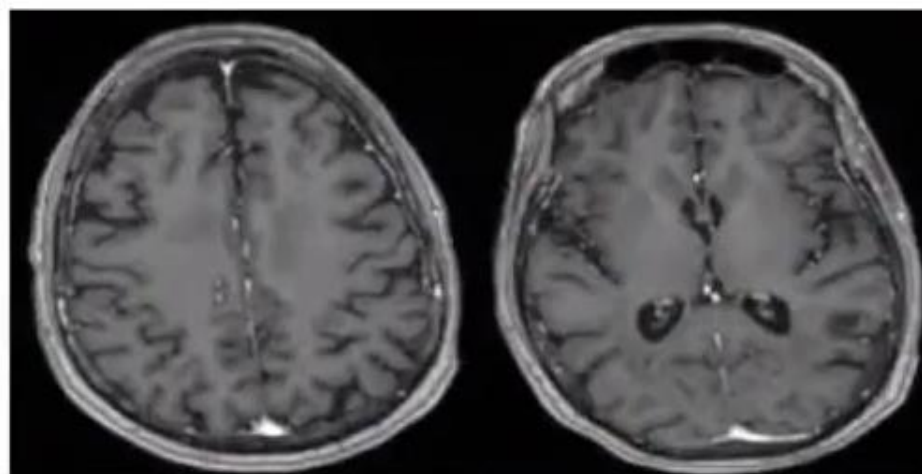
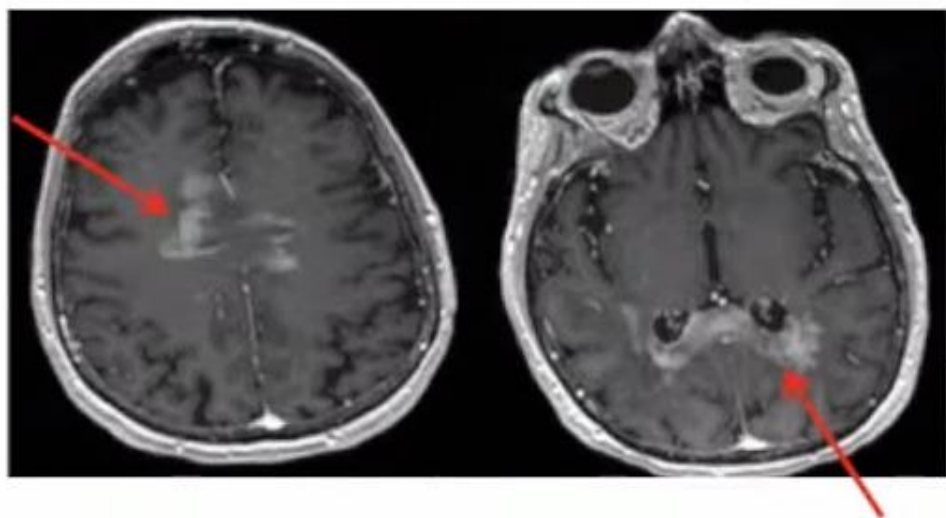
泽诺 译

BTK inhibition

抑制BTK

55 y/o woman with recurrent PCNSL (MTR→ASCT) treated with ibrutinib (840mg)

55岁女性，PCNSL复发（MTR→ASCT），伊布替尼以840mg的剂量治疗



泽诺 译

BTK inhibition with Ibrutinib

伊布替尼抑制BTK

- Ibrutinib – 1st in class oral BTK inhibitor 伊布替尼：第一代口服BTK抑制剂
- Genes encoding BCR/TLR pathways harbor high proportion of mutations including CD79B and MYD88 in PCNSL PCNSL中编码BCR/TLR通路的基因突变比例高，其中包括CD79B和MYD88
- Systemic DLBCL, CLL and Waldenström's macroglobulinemia with *MYD88*^{L265P} respond to ibrutinib 具有MYD88^{L265P}的系统性弥漫大B细胞淋巴瘤、慢性淋巴细胞白血病和华氏巨球蛋白血症，伊布替尼治疗有效

	DLBCL		PTL	EBV ⁺ PCNSL
	All	ABC-type		
Genomic instability				
CDKN2A ^{loss}	24% (43/180) ^a	35% (19/55) ^a	88% (44/50) ^d	71% (15/21) ^k
bi-allelic	19% (8/43) ^a	26% (5/19) ^a	77% (34/44)	73% (11/15)
CNAs of additional p53/cell cycle components	multiple ^{a,b}	multiple ^{a,b}	no	rare ^d
Total CNAs	high	high	high	high
Oncogenic TLR and BCR Signaling				
MYD88 ^{L265P}	12% (6/49) ^a	29% (45/155) ^f	78% (38/49) ^g	60% (33/55) ^j
NFKB1Z ^{gain}	9% (16/180) ^a	20% (11/55) ^a	42% (21/50) ^h	45% (28/62) ^m
NFKB1Z ^{gain} and/or MYD88 ^{L265P}	NA	NA	92% (45/49)	83% (44/53) ⁿ
CD79B ^{Y196mut}				
Total	18% (8/49) ^a	23% (35/155) ^f	49% (22/45) ^j	38% (19/50) ^o
Concurrent with MYD88 ^{L265P}	38% (3/8) ^e	43% (15/35) ^f	91% (20/22)	89% (17/19)

Bonzheim et al. Blood 2015; 126:76-79
Bernard S et al. Blood 2015, 126:1695
Tam et al. Br J Hematol 2017;176:829

泽诺 译

Therapeutic Targeting of BTK with Ibrutinib in PCNSL/SCNSL

伊布替尼靶向BTK治疗PCNSL/SCNSL

	Grommes et al	Soussain et al	Lionakis et al	Grommes et al
Phase	I (R/R P/S-CNSL) 1期 (难治/复发 原发/继发中枢)	II (R/R PCNSL/PVRL) 2期 (难治/复发 原发中枢/眼内)	I (unselected & R/R PCNSL)	I (R/R P/S-CNSL)
No. of patients	13 / 7 13名原发/7名继发	52 52名	18	9 / 6
Dose	560mg 840mg	560mg	560mg 720mg 840mg	560mg 840mg
Ibrutinib schedule	Single agent 单药	Single agent 单药	Combination DA-TEDDI-R	Combination Ibrutinib-R-MTX
ORR	77% / 71%	52%	72% (13/18 evaluable)	89% / 67%
mPFS	4.6 mo / 7.3mo	4.8 mo*	15.3mo	NR / 9.2 mo

- Ibrutinib conc adequate in CSF (higher dose tolerated well)
伊布替尼在脑脊液中的浓度适量 (更高剂量时耐受良好)
- ORR higher than reported in ABC DLBCL
相比于已报道的ABC型弥漫大B细胞, ORR更高

Grommes et al. Cancer Discov 2017;7:1018
Soussain et al. E J Cancer 2019; 117:121
Lionakis et al. Cancer Cell 2017; 31:833
Grommes et al. Blood 2019; 133:415

泽诺 译

Therapeutic Targeting of BTK with Ibrutinib in PCNSL/SCNSL

	Grommes et al	Choquet et al	Lionakis et al	Grommes et al
Phase	I (RR P/S-CNSL)	I (RR P/S-CNSL)	I (untreated & R/R PCNSL) 1期 (初治及复发/难治 原发)	I (RR P/S-CNSL) 1期 (复发/难治 原发/继发)
No. of patients	13 / 7	52	18	9 / 6
Dose	560mg 840mg	560mg 840mg	560mg 700mg 840mg	560mg 840mg
Ibrutinib schedule	Single agent	Single agent	Combination 联合 DA-TEDDI-R	Combination Ibrutinib-R-MTX
ORR	100%	100%	72% (13/14 evaluable)	89% / 67%
mPFS	4.6 mo / 7.3mo	4.8 mo	15.3mo	NR / 9.2 mo

Grommes et al. Cancer Discov 2017;7:1018
Soussain et al. E J Cancer 2019 117:121
Lionakis et al. Cancer Cell 2017; 31:833
Grommes et al. Blood 2019; 133:436

Unique Toxicities

独特的毒性

- Toxicity associated with DA-TEDDI-R:
 - 39% invasive aspergillosis (brain and lung)
 - 94% G4 febrile neutropenia
 - 28% deaths (2 with newly diagnosed PCNSL)
- 与DA-TEDDI-R相关的毒性
 - 39%侵袭性曲霉菌病（脑及肺）
 - 94% G4发热性中性粒细胞减少症
 - 28% 死亡（2例为新诊断的PCNSL）
- High rate of aspergillosis -
 - antagonism by ibrutinib of wild-type BTK in myeloid cells that mediate the innate immune control of aspergillus infection.
- 曲霉菌病发病率高
 - 伊布替尼拮抗野生型BTK骨髓细胞，这些细胞原本会介导对曲霉菌病感染的固有免疫控制
- Invasive aspergillosis in other studies <5%
- 其它研究中侵袭性曲霉菌病<5%

Lionakis et al. Cancer Cell 2017; 31:833

泽诺 译

2nd generation BTK inhibitor : Tirabrutinib

二代BTK抑制剂: Tirabrutinib
(商品名: Velembu)

	Narita <i>et al.</i>
Phase	I/II (R/R PCNSL)
No. of patients	44
Dose	320mg, 480mg
MTD/ R2PD	480mg (fasting)
ORR	63.6%
mPFS	2.9 months

在日本已被批准治疗复发/难治 PCNSL

Approved for treatment of R/R PCNSL in Japan

MTD/ R2PD	480mg (fasting)
ORR	63.6%
mPFS	2.9 months

NCT04947319 : Study of **Tirabrutinib** (ONO-4059) in patients with PCNSL (**PROSPECT** study)

泽诺 译

IMiDs : Lenalidomide

免疫调节剂：来那度胺

- Lenalidomide is a small molecule immunomodulatory agent
 - anti-tumor effects including stimulation of T cell & NK expansion.
- 来那度胺是小分子免疫调节剂
 - 抗肿瘤效果包括刺激T细胞及NK细胞的扩增
- Cell-autonomous cytotoxic effects relevant to PCNSL
 - antagonism of IRF4 and MYC pro-survival signals.
 - >90% of PCNSL – IRF4/MUM1 positive
- 与PCNSL相关的细胞自主性细胞毒性
 - 拮抗IRF4和MYC的促生存信号
 - >90%的PCNSL – IRF4/MUM1 阳性
- Enhances antibody-dependent cell-mediated cytotoxicity & may overcome rituximab resistance.
- 加强抗体依赖的细胞介导细胞毒性，且有可能克服利妥昔单抗的耐药

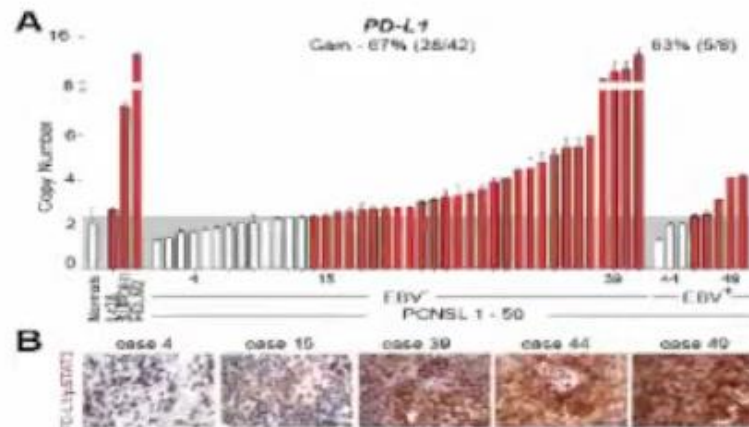
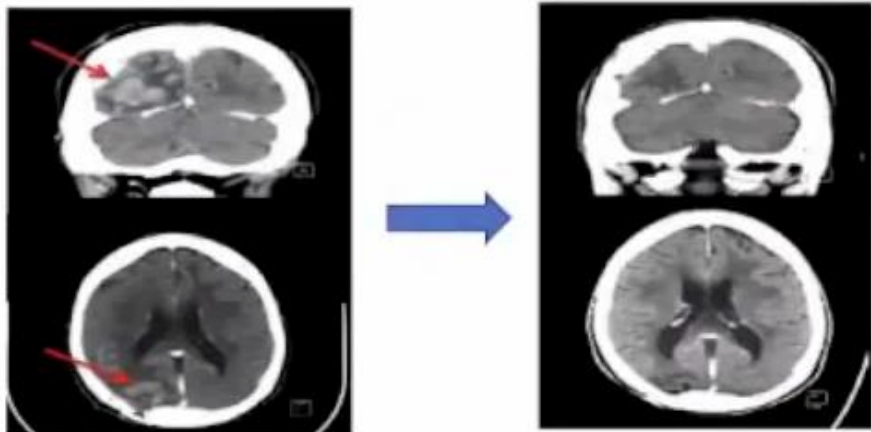
IMiDs (Immunomodulatory drugs)

	Rubenstein <i>et al</i>	Ghesquieres <i>et al</i> (REVRI)	Tun <i>et al</i>
Phase	I (P/S-CNSL)	II (PCNSL / PVRL)	I (PCNSL / PVRL)
No. of patients	14 (6/8)	50 (45: 34/11)	29
Treatment	Lenalidomide +/- IV/IO Rituximab	Rituximab + Lenalidomide	Pomalidomide + Dexamethasone
Dose of Lenalidomide	D1-21: 10, 15, 20 mg* DLTs at 20 mg/d	Induction: D1-21, 20- 25 mg/d x8 Maintenance: D1-21, 10mg/d x12	POM D1-21: 3, 5 mg Dex 40mg/week x 2 cycles
ORR	64%	67%	48%
mPFS	6 mo	7.8 mo	5.3 mo

Rubenstein et al. Blood Adv 2018;2:1595
Ghesquieres et al. Ann Oncol 2019;30:621
Tun et al. Blood 2018;132:2240

Checkpoint Inhibition

抑制免疫检查点



- **NCT02857426** : An international phase 2, open-label study of **nivolumab** in R/R PCNSL or R/R PTL (completed) nivolumab治疗复发/难治 PCNSL或复发难治 PTL的国际化、2期、开放标签研究
- **First Results of the Acsé Pembrolizumab Phase II in the PCNSL Cohort (NCT03012620)**
 - N: 50
 - ORR: 26%
 - mPFS: 2.6 mo
 - 6mo PFS 30%
 - Acse Pembrolizumab在PCNSL队列的2期最初结果
 - 50名患者
 - ORR: 60%
 - 中位PFS: 2.6个月
 - 6个月 PFS: 30%

Nayak L, et al. *Blood* 2017; 129(23):3071–3073

Chapuy & Roemer et al., *Blood* 2016; 127:869-881

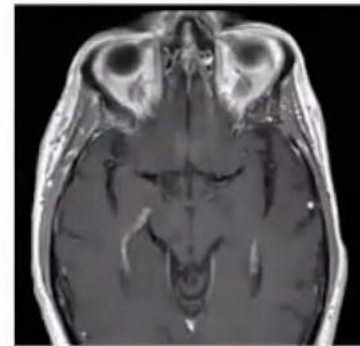
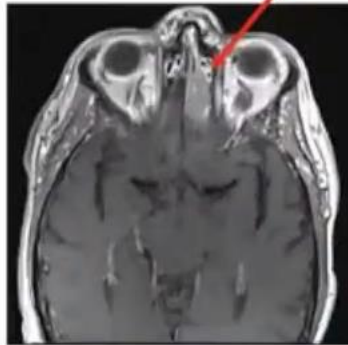
Hoang-Xuan et al. *Blood* 2020 (ASH abs)

泽诺 译

CD19 CAR T cells in secondary CNS DLBCL

CD19 CAR T细胞在继发CNS DLBCL中

- 66 y/o M with multiply recurrent DLBCL (RCHOP, RGDP, RICE) & CNSL (HD-MTX, CYVE → thiotepa ASCT) with systemic recurrence treated with Axicabtagene ciloleucel.
- 2 days after infusion of CAR T cells, he developed CRS and grade 1 neurotoxicity
- 66岁男性，多次复发弥漫大B细胞淋巴瘤（RCHOP, RGDP, RICE）& 中枢系统淋巴瘤（HD-MTX, CYVE→塞替派 自体干细胞移植），系统性复发淋巴瘤以Axicabtagene ciloleucel（阿基伦塞）治疗
- 回输CAR T细胞2天后，发生了CRS和1级神经毒性



Phase 1/2 trial of Tisagenlecleucel in PCNSL

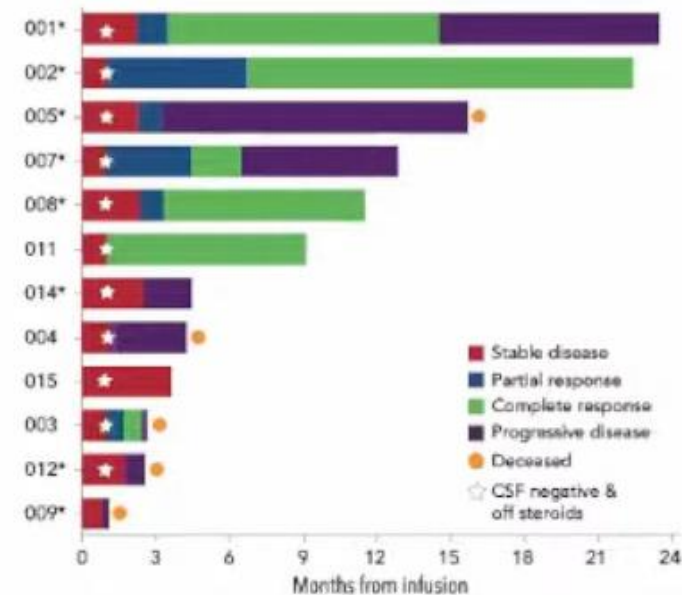
Tisagenlecleucel (诺华, Kymriah) 在PCNSL中的1/2期临床试验

Pt Characteristics

- N=12 pts (relapsed)
- Prior therapies:
 - HD-MTX: 12
 - ASCT: 3
 - BTKi: 12
- Bridging therapy: 12
- Median time from leukapheresis to infusion: 33 days

Results

- Toxicities:
 - Grade 1 CRS: 7
 - Any grade ICANS: 6
 - Grade 3: 1
- ORR: 7/12 (6 CR, 1 PR)
 - ongoing responses in 3 at median f/u of 12.2 mo
- CAR expansion in PB & CSF in 11 pts



- Ongoing trial of **Axicabtagene ciloleucel** in PCNSL & SCNSL (NCT04608487)

Frigault *et al.* Blood 2022;139:2306-2315

Challenges with Targeted Agents & Immunotherapies

靶向药和免疫疗法的挑战

- Responses not durable
 - Short PFS
 - Delayed Responses
 - Neurologic deterioration
 - Corticosteroids
 - Increase risk of life-threatening infections
 - Interfere with efficacy of checkpoint inhibitors
 - Concern for neurotoxicity
 - Blood Brain Barrier
 - **Combinations necessary**
- 缓解不持久
 - PFS短
 - 迟发反应
 - 神经功能恶化
 - 皮质激素
 - 增加危及生命的感染风险
 - 干扰免疫检查点抑制剂的疗效
 - 对神经毒性的担忧
 - 血脑屏障
 - 联合方案的重要性

Conclusion

总结

- PCNSL is a distinct disease with unique targets – TISSUE is necessary!
- PCNSL是一种具有独特靶点的独立疾病 – 组织学（译者注：病理）很必要
- Prognostic factors – age, performance status, ?molecular features
- 预后因素：年龄、活动状态、？分子特征
- Early diagnosis & institution of therapy is important
- 尽早诊断、专业诊疗机构治疗很重要
- HD-MTX based chemotherapy is the standard of care treatment for newly diagnosed PCNSL
- 大剂量甲氨蝶呤为基础的化疗是新诊断PCNSL的标准疗法
- Ibrutinib & lenalidomide : early data for response in pts
 - NCCN guidelines for R/R PCNSL
 - Higher doses for improved brain/CSF drug concentrations
- 伊布替尼和来那度胺：少量数据表明有效
 - NCCN指南建议复发/难治PCNSL
 - 更大剂量可以提高脑内/脑脊液的药物浓度
- Mechanisms of resistance
 - Tissue sampling
 - CSF ctDNA
 - 耐药机制
 - 组织活检
 - 脑脊液 ctDNA