

CAR T-cells in Secondary CNS Diffuse Large B-cell Lymphoma

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Disclosures for Jeremy Abramson

Consulting for AbbVie, Astra-Zeneca, BeiGene, Bristol Myers Squibb, Caribou Biosciences, Cellectar, Genentech, Gilead, Incyte, Interius, Janssen, Lilly, Novartis, Roche, Takeda

Secondary CNS Lymphoma is an unmet medical need

- Occurs in 2-5% of DLBCL
- Risk increased in patients with high risk CNS-IPI scores, and in high grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6 (double hit lymphoma)
- Outcome appears improved with high dose chemotherapy and ASCT





Bromberg, et al. Haematologica 2013

Few effective salvage options for relapsed PCNSL

Treatment	n	ORR/CRR	PFS	OS
WBXRT ¹	27	74%/37%	10 m	11 m
MTX-based ²	39	85%/75%	16 m	41 m
HiDAC-based ³	22	59%/27%	9 m	2y 68%
Temozolamide ⁴	36	31%/25%	3 m	4 m
R-Temozolamide ⁵	16	36%/14%	2 m	1y 71%
Pemetrexed ⁶	11	55%/36%	6 m	10 m
Thiotepa-based ASCT ⁷	39	72%/56%	12 m	2y 56%

¹Nguyen, et al. JCO 2005 ²Pentsova, et al. J Neuroonc 2014 ³Sierra del Rio, et al. J Neuroonc 2011 ⁴ Reni et al. BJC 2007 ⁵Nayak, et al. Leuk Lymph 2013 ⁶Raizer, et al. Cancer 2012 ⁷ Kasenda, et al. Proc ASH 2016



Ibrutinib in PCNSL/SCNSL N=44 ORR 78%, CRR 39% Median PFS 4 m





Ghesquieres, et al. Ann Oncol 2019

Grommes, et al. Proc ASH 2018

Chapuy, et al. Blood 2016

Essential questions regarding CAR T-cell therapy in the CNS

- Is secondary CNS DLBCL a distinct disease?
- Will CAR T-cells traffic and persist in the CNS?
- Will CAR T-cells expand and persist in the absence of systemic disease?
- Will CAR T-cells induce remissions in CNS disease akin to systemic disease?
- Will CAR T-cells for CNS lymphoma augment neurologic toxicities?



CAR T-cells traffic to CSF and persist in CSF





CAR T-cells for parenchymal brain disease

67-year-old woman with refractory DLBCL

- 5 prior lines of therapy and an allo stem cell transplant
- Right sided mass by her ear, and a temporal lobe brain lesion
- Treated with lisocabtagene maraleucel (anti-CD19-41BB-CD3z)





Lisocabtagene maraleucel for concurrent CNS and systemic DLBCL at initial treatment on TRANSCEND NHL study

Features	N=6
Age, median (range)	62 years (47-73)
Number of prior tx, median (range)	3 (2-5)
Refractory to prior tx	6
Prior SCT	2
Localization Parenchymal only Leptomeningeal only Both Parenchymal and Leptomeningeal	1 3 2

Efficacy:

- 3/6 patients achieved CR
- 3 CNS CRs ongoing at last f/u (239, 365*, 533 days)
- Responses included both
 parenchymal and LM

* 1 patient died of systemic relapse with CD19- disease

Safety:

- No CRS
- NT (grade 3) in 2 patients, both resolved



	B Complete response	Evaluable	Patients with		Complete response	
		patients (n)	complete response (n)	rate (95% CI)	
	Dose level					
	DL1	40	24		60.0 (43.3-75.1)	
	DL2	169	88		52.1 (44.3-59.8)	
	DL3	41	21		51.2 (35.1-67.1)	
	Age, years					
	≥65	108	65	•	60.2 (50.3-69.5)	
	<65	148	71		48.0 (39.7-56.3)	
	Sex					
	Male	169	90	•	53.3 (45.4-61.0)	
	Female	87	46		52.9 (41.9-63.7)	
	NHL histology					
	DLBCL NOS	131	64		48.9 (40.0-57.7)	
	HGBCL	33	20	•	60.6 (42.1-77.1)	
	tFL	57	36		63·2 (49·3–75·6)	
	Transformed iNHL	18	7	• • •	38.9 (17.3-64.3)	
	PMBCL	14	7	•	50.0 (23.0-77.0)	
	Bridging therapy					
	Yes	150	68		45.3 (37.2-53.7)	
	No	106	68		64-2 (54-3-73-2)	
	SPD*					
	≥50 cm ²	70	23		32.9 (22.1-45.1)	
	<50 cm ²	177	108		61.0 (53.4-68.2)	
	C-reactive protein†				10000000000000000	
	≥20 mg/L	146	68		46.6 (38.3-55.0)	
	<20 mg/L	109	67	•	61.5 (51.7-70.6)	
	Response to last therapy‡		1.002			
	Refractory	203	98		48.3 (41.2-55.4)	
	Relapsed	53	38		71.7 (57.7-83.2)	
	Chemotherapy response					
	Refractory	171	90		52.6 (44.9-60.3)	
Coundary CNC humahama						
Secondary CNS lymphoma		-				
Yes	6	3		•		50.0 (11.8-88.2)
	250 13	33				53.2 (46.8-59.5)
No	230	00				55.2 (40.0-55.5)
	50011/1	199	113		56.8 (49.6–63.8)	
	<500 U/L		115		30.0 (43.0 03.0)	
	Secondary CNS lymphoma	6	3		50.0 (11.8-88.2)	
	Yes	250	133		53.2 (46.8–59.5)	
	No				552 (40 0 55 5)	
	Comorbidities§	60	32		53.3 (40.0-66.3)	
	Yes No	196	104		53.1 (45.8-60.2)	
	Overall			Former Former Former		
	Overall	256	136		53.1 (46.8-59.4)	
			0 10	0 20 30 40 50 60 70 80	90 100	
				Responders (%)	J. 100	
Abramson, et al. Lancet 2020.				responders (%)		
A STATISTIC CON LUNCEL 2020.						

Tisagenlecleucel in secondary CNS DLBCL: *MGH experience*

Features	N=8
Age, median (range)	50 years (17-79)
Lymphoma subtype DLBCL HGBCL PMBCL	5 2 1
Isolated CNS involvement	6
Localization Parenchymal only Leptomeningeal only Both Parenchymal and Leptomeningeal	3 3 2
Number of prior tx, median (range)	5 (3-6)
Refractory to standard CNS tx	6
Refractory to novel agents (ibr, len, pembro)	5

Efficacy:

- 4/8 responded (3 CR, 1 PR)
- All CNS responses ongoing at last f/u (2 at 3 m, 2 at 6 m)*
- Responses included both parenchymal and LM

 * 1 patient had localized systemic relapse, radiated with ongoing CR

Safety:

- CRS in 5, all grade 1
- NT in 2, grade 1 tremor, neuropathy

Frigault, et al. Blood 2019.

Correlative markers of CAR T-cell expansion



German experience: GLA/DRST registry

- N=28 (1/2 axi-cel, 1/2 tisa-cel)
- 24 bridged, including XRT, IT chemo, ibrutinib, Pola, others. 10/24 responded. No CRs.
- ORR 64%, CR 32%
- 12 mo PFS 41% (axi-cel 62%, tisa-cel 19%)
- ICANS any/severe: 46%/15%





US consortium n=17 treated with axi-cel

- Site of CNS involvement: 4 parenchymal disease, 10 leptomeningeal, 3 missing
- Median 4 prior lines of tx.
- HGBCL/DLBCL: 24%/76%
- ABC subtype 53%
- 5 patients had active CNS disease at time of infusion
- 82% bridged, 88% infused





ORR 75%, DOR at 67 mo 41%. 6mo EFS 36%

Meta-analysis including 128 patients with CNS lymphoma



Cook. et al. Blood Adv 2023.



ICANS

CR at 6 mo

Study

Li et al²⁴

Wu et al²³

Frigault et al²⁵

Abbasi et al²⁶

Ahmed et al²⁷

Ghafouri et al²⁹

Nastoupil et al³¹

Karschnia et al³³

Abramson³

Liu et al²⁸

P = 0.53



Proportion	95%-Cl	Weight
0.56 0.38 1.00 0.43 0.86 0.50 0.60	[0.10; 0.82] [0.42; 1.00] [0.12; 0.88] [0.15; 0.95] [0.22; 0.66]	5.7% 12.7% 10.7% 2.4% 9.8% 4.9% 8.6% 6.8% 29.3%
0.20	[0.03; 0.56]	9.1%
0.47	[0.36; 0.59]	100.0%



CAR T- cells for Secondary CNS Lymphoma Multicenter retrospective analysis

Characteristic	n = 61
Median age (range), years	56 (18–82)
CNS only relapse, n(%)	20 (33)
CNS/systemic relapse, n(%)	41 (67)
CNS localization, n(%) Parenchymal Leptomeningeal Both	25 (42) 29 (48) 6 (10)
Lymphoma subtype, n(%) DLBCL, de novo Transformed FL Transformed MZL Other	50 (82) 5 (8) 2 (3) 4 (7)
Double hit, n(%)	16 (30)
Pre-CAR therapies	3 (1-5)
Prior ASCT, n(%)	14 (23)

CAR product	%
Axi-cel	49
Tisa-cel	31
Liso-cel	18
Brexu-cel	2

Best Response (n=56)			
ORR, n(%)	38 (68)		
CR	32 (57)		
PR	6 (11)		
SD	4 (7)		
PD	14 (25)		



Toxicity	Grade	%
CRS	Any grade Grade 3	70 16
ICANS	Any grade Grade 3	57 44

Epperla, et al. J Heme Onc. 2023

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Bridging Strategies for secondary CNS lymphoma

- Guided by prior therapies, organ function, molecular phenotyping
- Corticosteroids alone
- Chemotherapy including MTX and/or cytarabine based therapy
- BTK inhibition, especially non-GCB or NGS defined MYD88/CD79B
- Lenalidomide +/- rituximab <u>Acalabrutinib on clinical trial</u>: 7 days
- Stereotactic radiosurgery









Concluding thoughts

- CAR T-cells traffic and persist to the CNS, expand in the absence of systemic lymphoma, and induce CRs in all CNS compartments without excess toxicity
- Patients with secondary CNS DLBCL should be considered for anti-CD19 CAR T-cell therapy, just as would patients with any other extranodal site of DLBCL
- Unique approaches to bridging are warranted
- Careful attention to neurotoxicity risk including product selection and use of prophylactic antiepileptic



Thank you for your attention!



