

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

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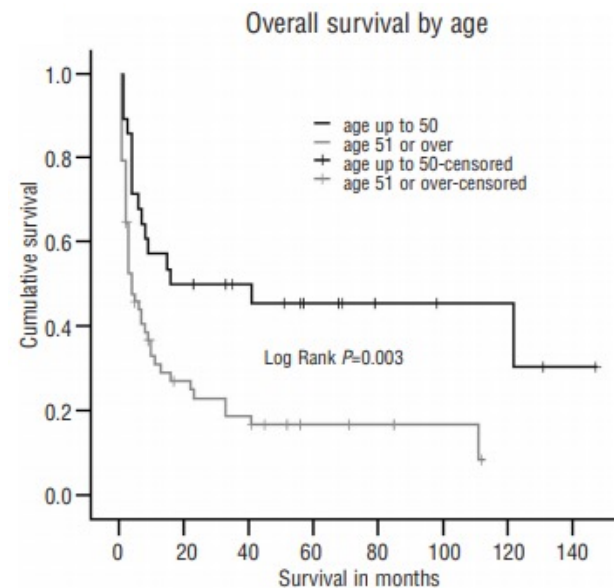
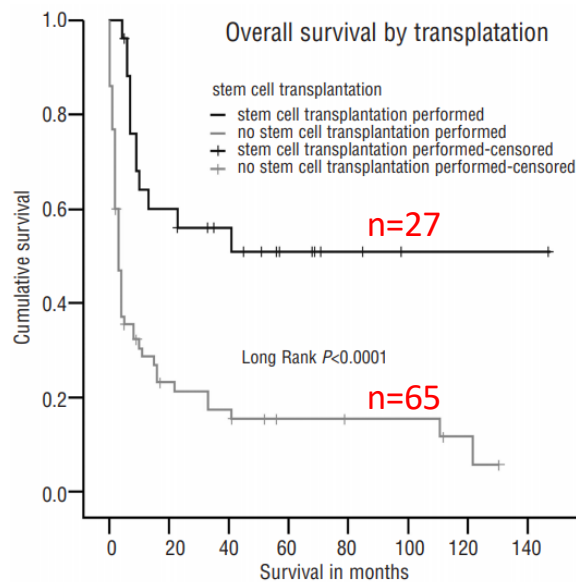
Disclosures for Jeremy Abramson

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



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

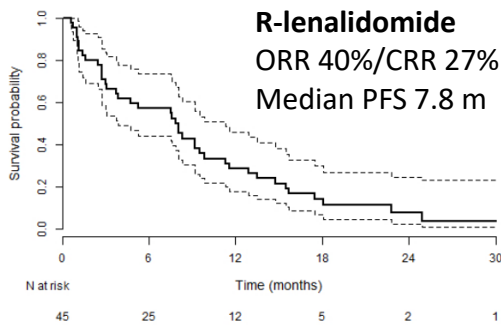
³Sierra del Rio, et al. J Neuroonc 2011

⁴Reni et al. BJC 2007

⁵Nayak, et al. Leuk Lymph 2013

⁶Raizer, et al. Cancer 2012

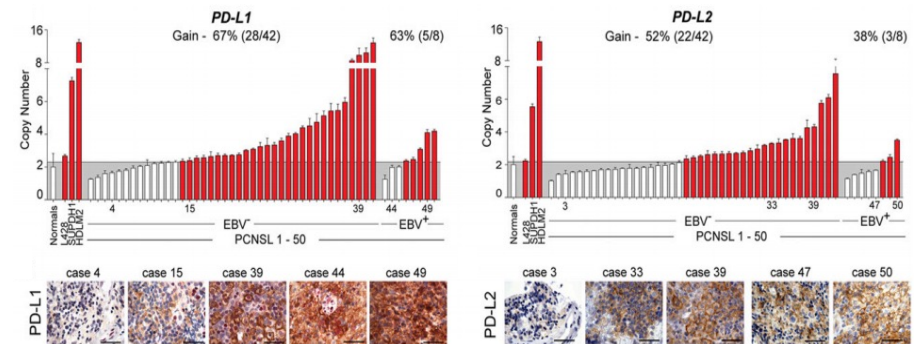
⁷Kasenda, et al. Proc ASH 2016



Ghesquieres, et al. Ann Oncol 2019

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

Grommes, et al. Proc ASH 2018



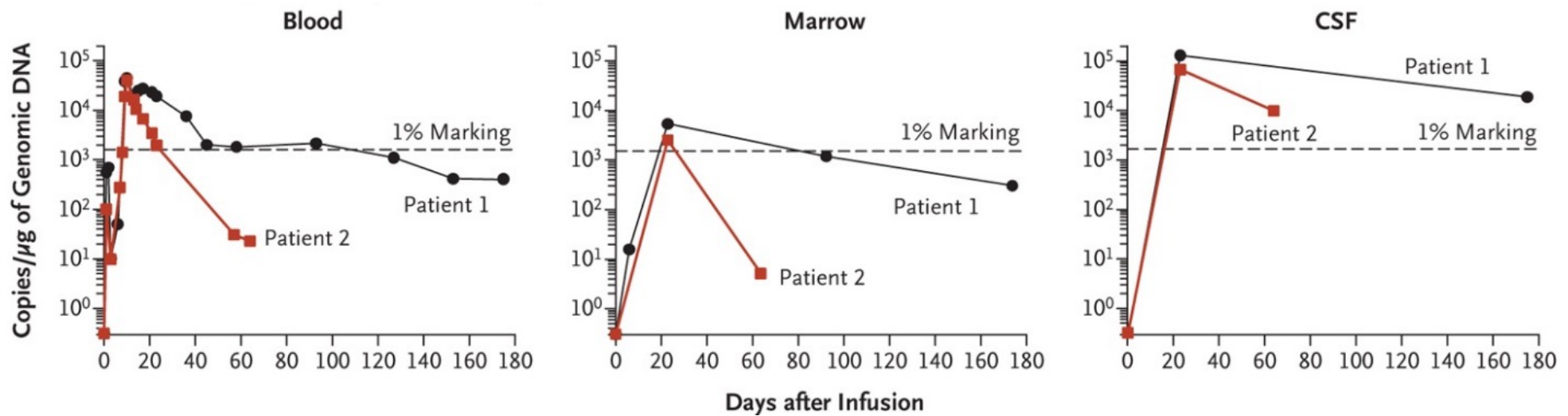
Chapuy, et al. Blood 2016

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?



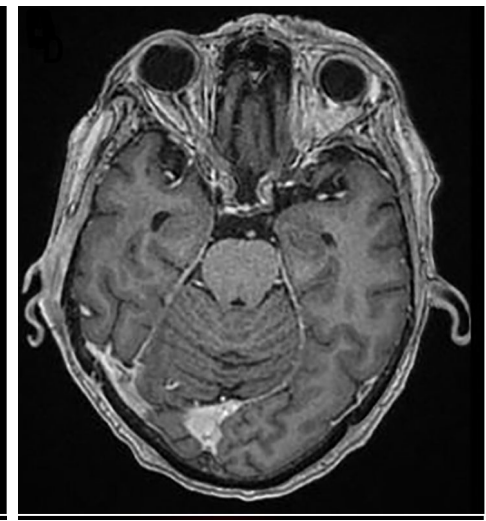
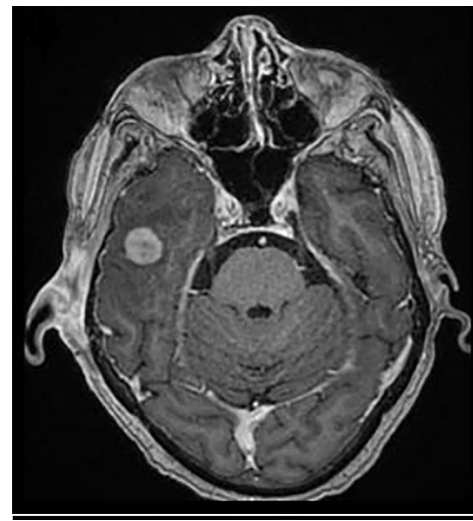
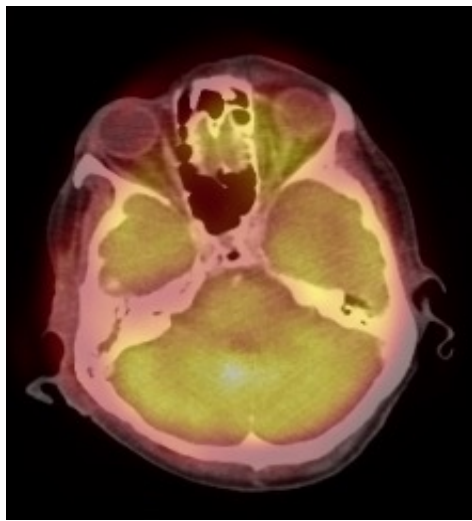
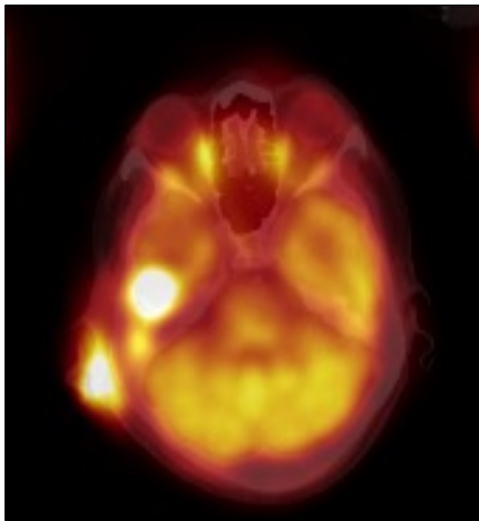
CAR T-cells traffic to CSF and persist in CSF



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	1
Leptomeningeal only	3
Both Parenchymal and Leptomeningeal	2

Efficacy:

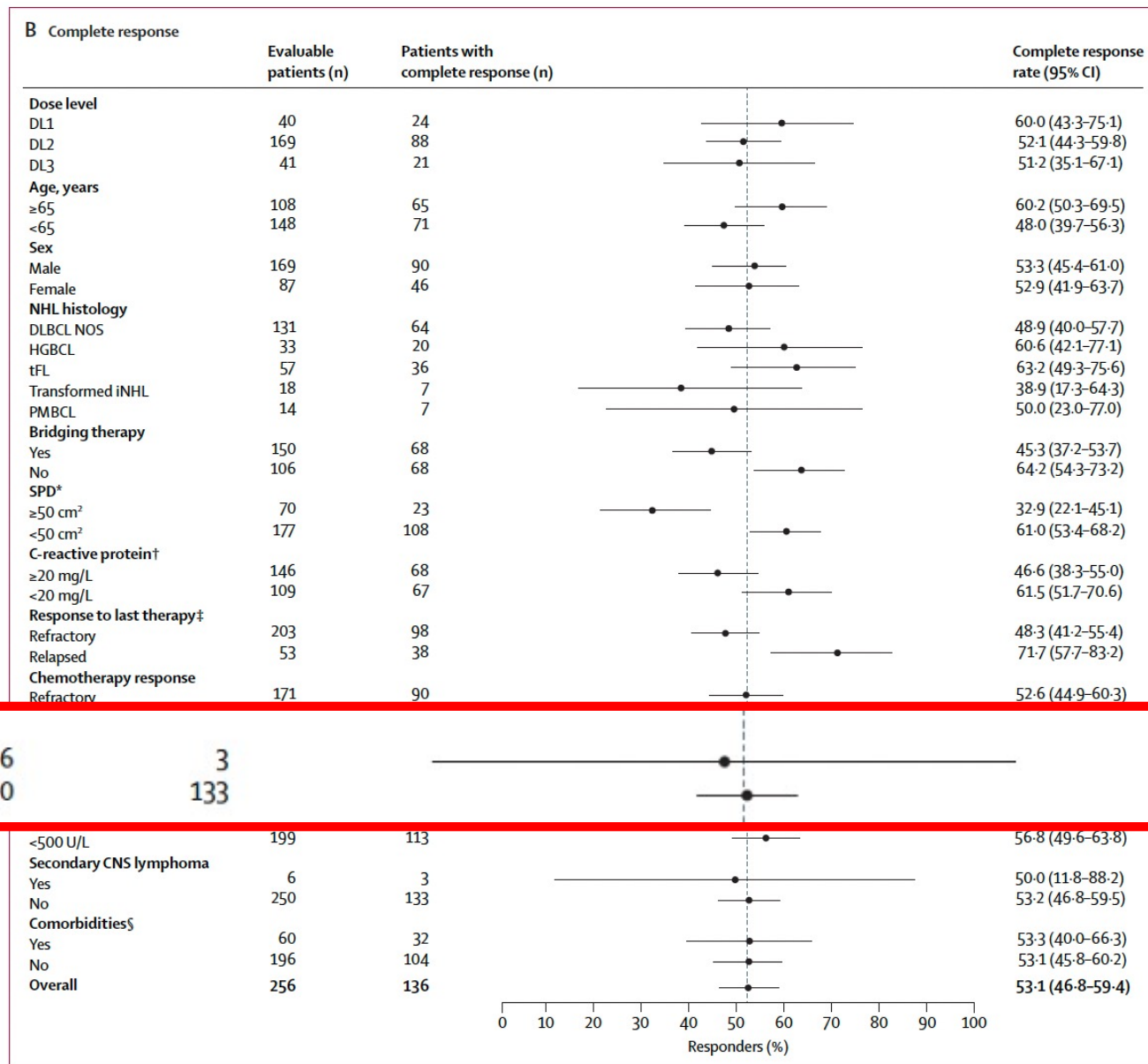
- 3/6 patients achieved CR
- 3 CNS CRs ongoing at last f/u (239, 365*, 533 days)
- Responses included both parenchymal and LM

* 1 patient died of systemic relapse with CD19- disease

Safety:

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





Tisagenlecleucel in secondary CNS DLBCL: *MGH experience*

Features	N=8
Age, median (range)	50 years (17-79)
Lymphoma subtype	
DLBCL	5
HGBCL	2
PMBCL	1
Isolated CNS involvement	6
Localization	
Parenchymal only	3
Leptomeningeal only	3
Both Parenchymal and Leptomeningeal	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

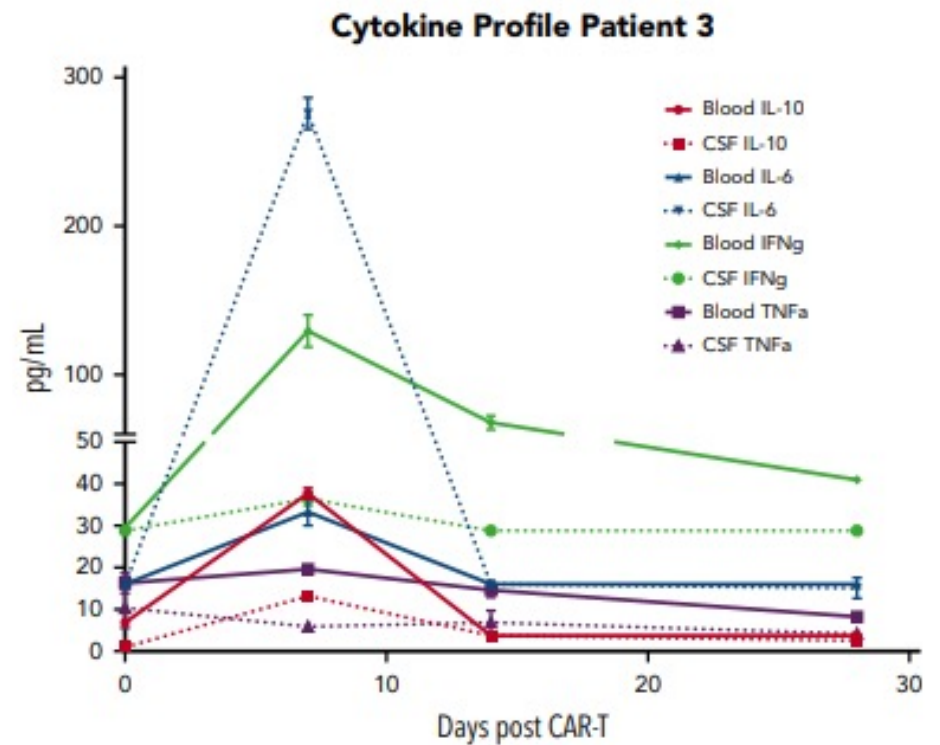
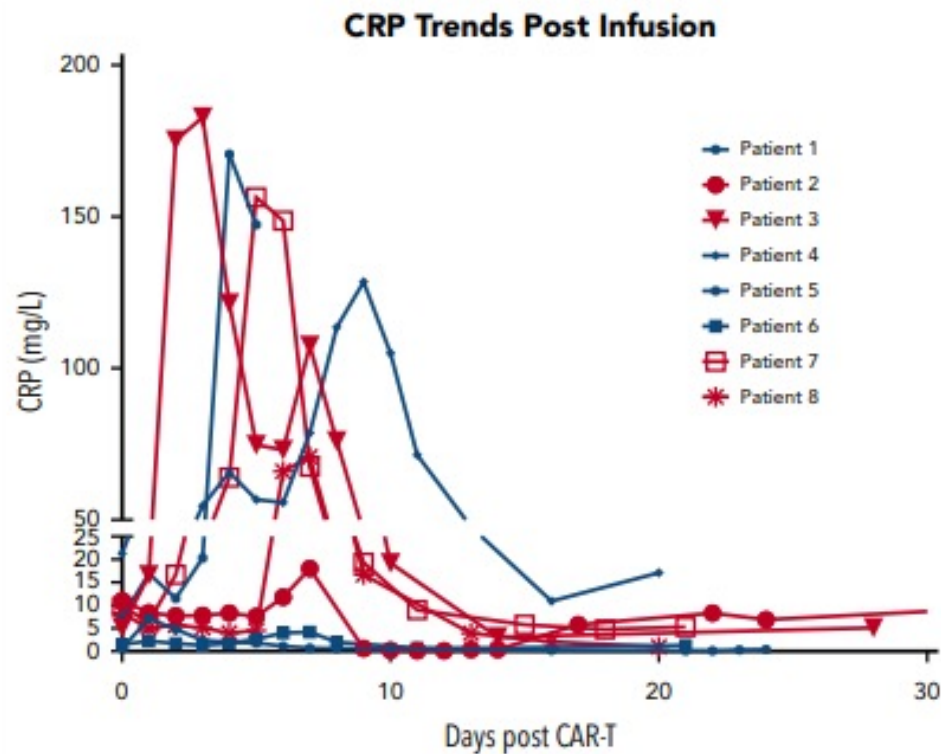
* 1 patient had localized systemic relapse, radiated with ongoing CR

Safety:

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

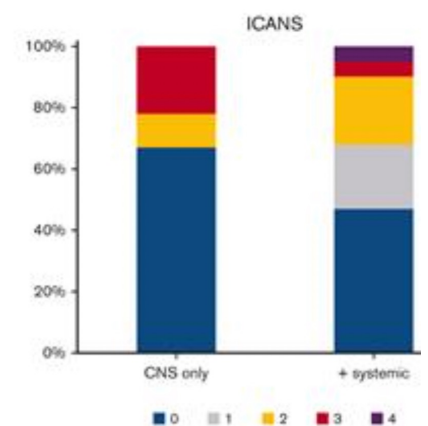
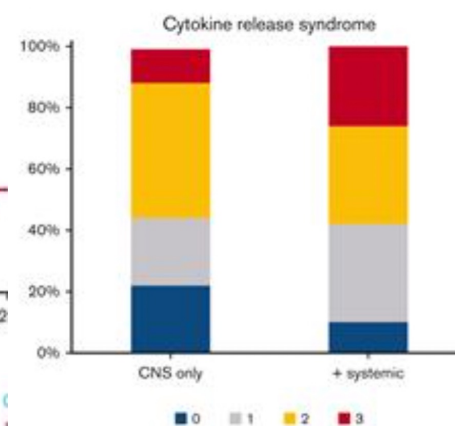
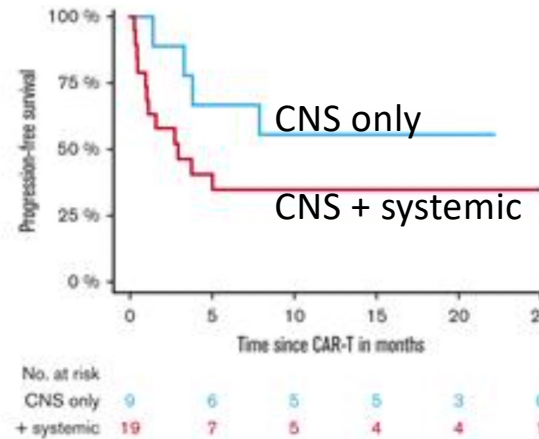
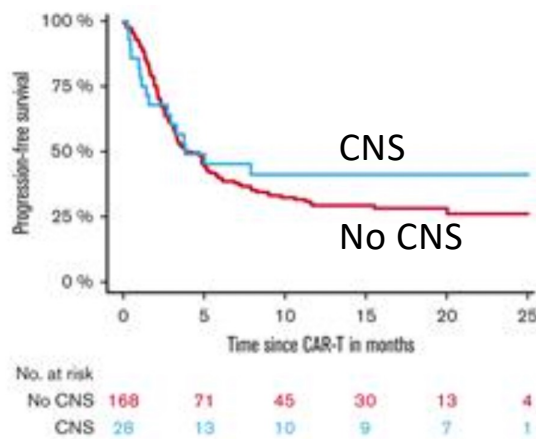


Correlative markers of CAR T-cell expansion



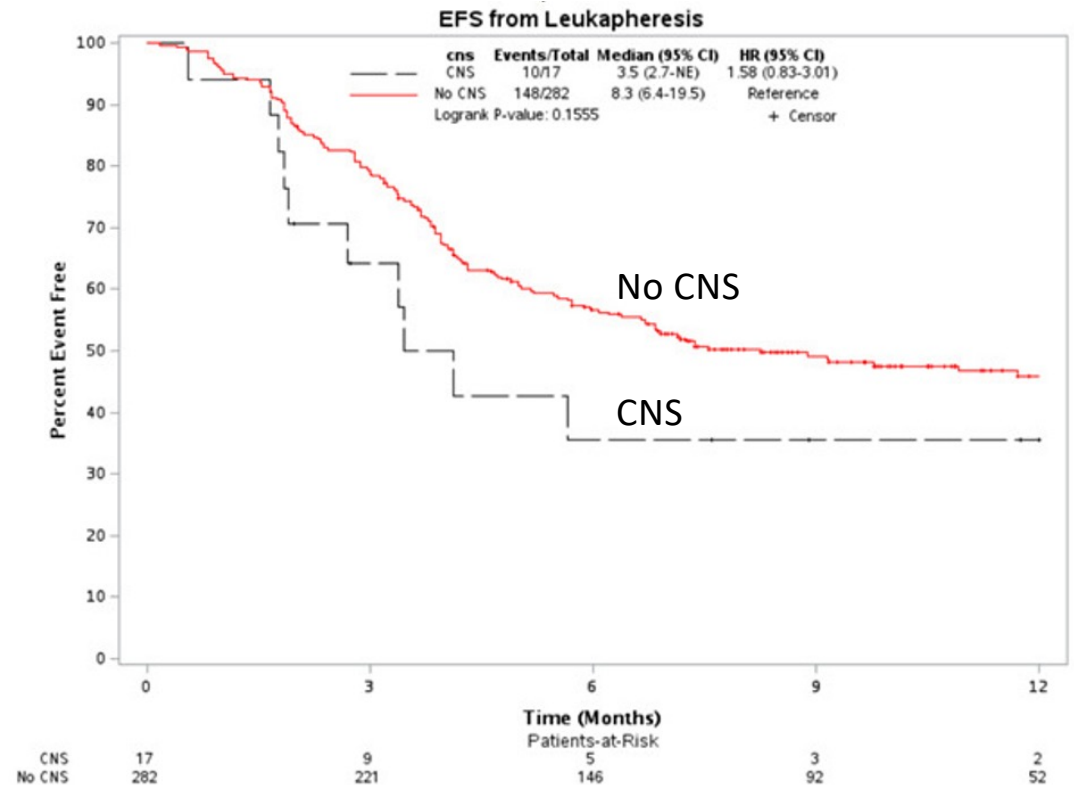
German experience: GLA/DRST registry

- 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

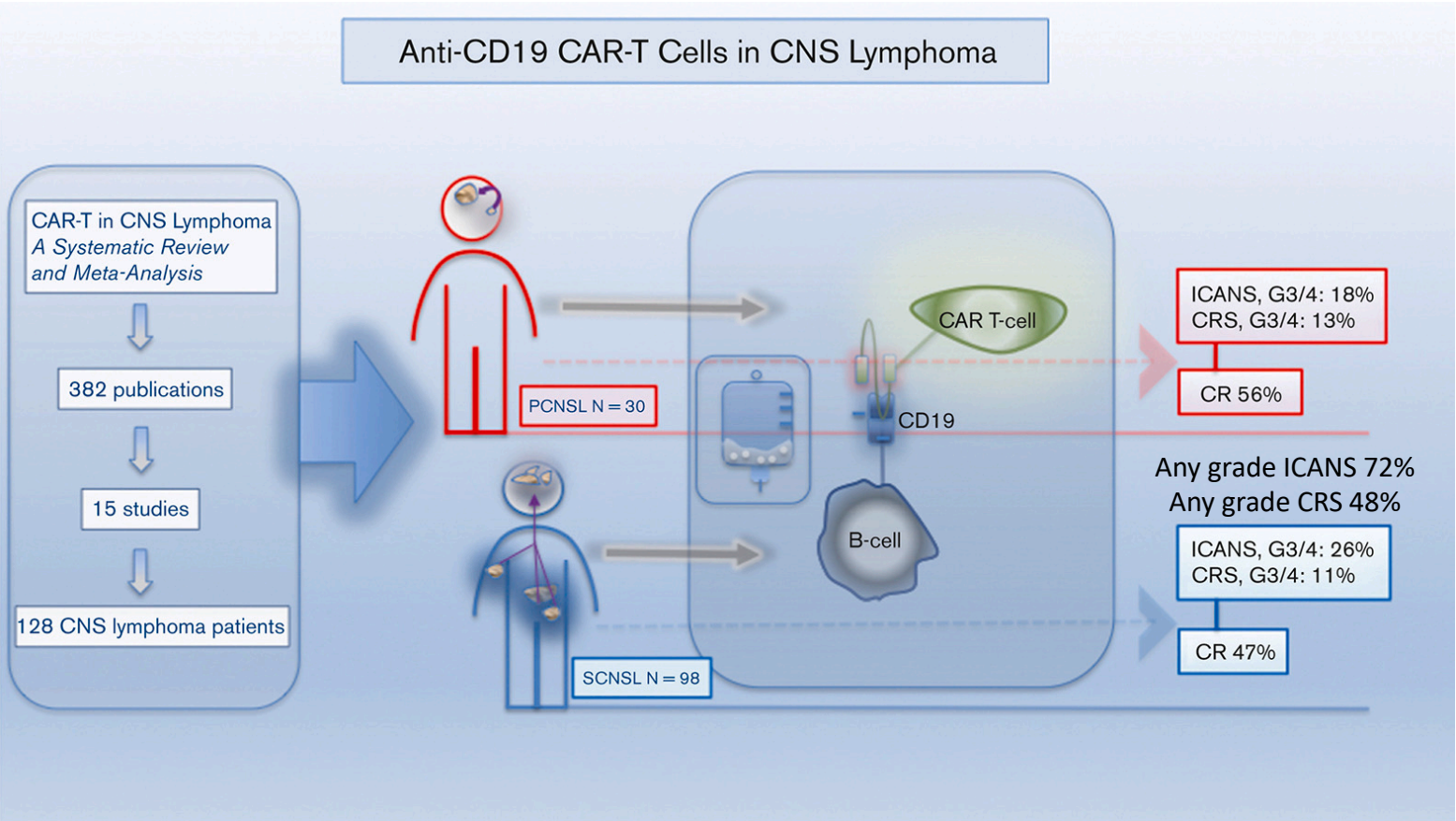
- Site of CNS involvement: 4 parenchymal disease, 10 leptomeningeal, 3 missing
- Median 4 prior lines of tx.
- HGBCL/DLBCL: 24%/76%
- ABC subtype 53%
- 5 patients had active CNS disease at time of infusion
- 82% bridged, 88% infused



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



Meta-analysis including 128 patients with CNS lymphoma

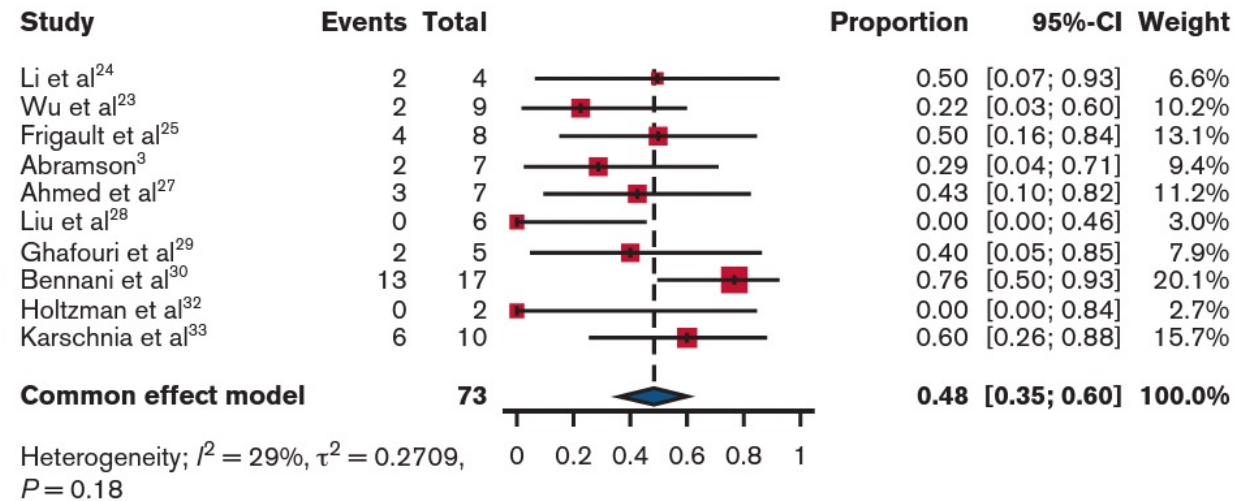


CAR product	N (%)
Axi-cel	50 (51)
Tisa-cel	12 (12)
Liso-cel	7 (7)

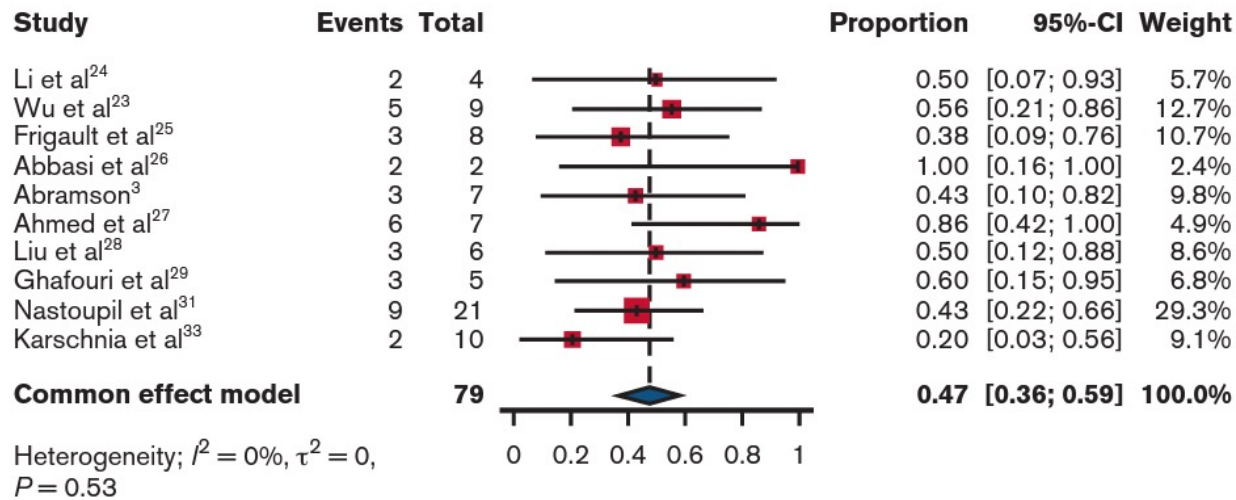
Response	
ORR	57%
CR	47%
Ongoing	46%



ICANS



CR at 6 mo



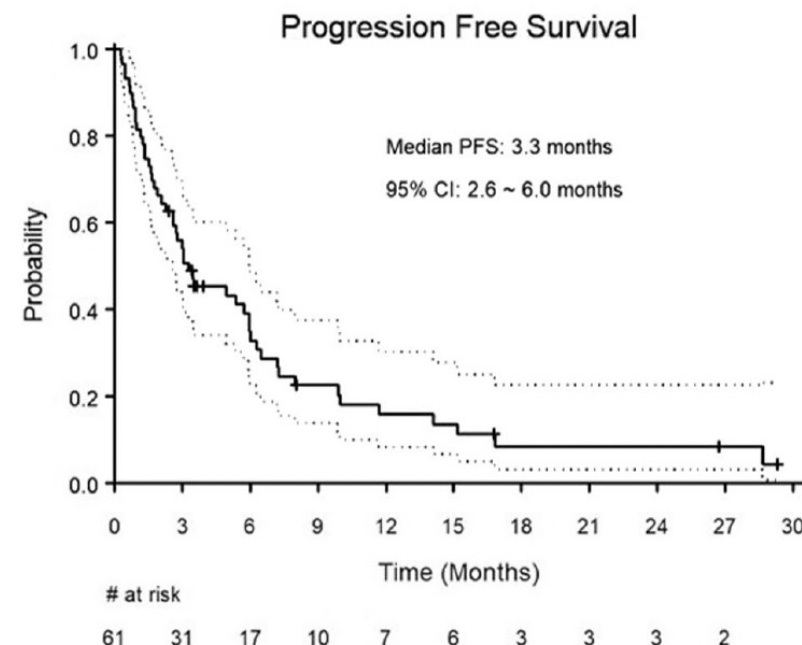
CAR T- cells for Secondary CNS Lymphoma

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	25 (42)
Leptomeningeal	29 (48)
Both	6 (10)
Lymphoma subtype, n(%)	
DLBCL, de novo	50 (82)
Transformed FL	5 (8)
Transformed MZL	2 (3)
Other	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	70
	Grade 3	16
ICANS	Any grade	57
	Grade 3	44

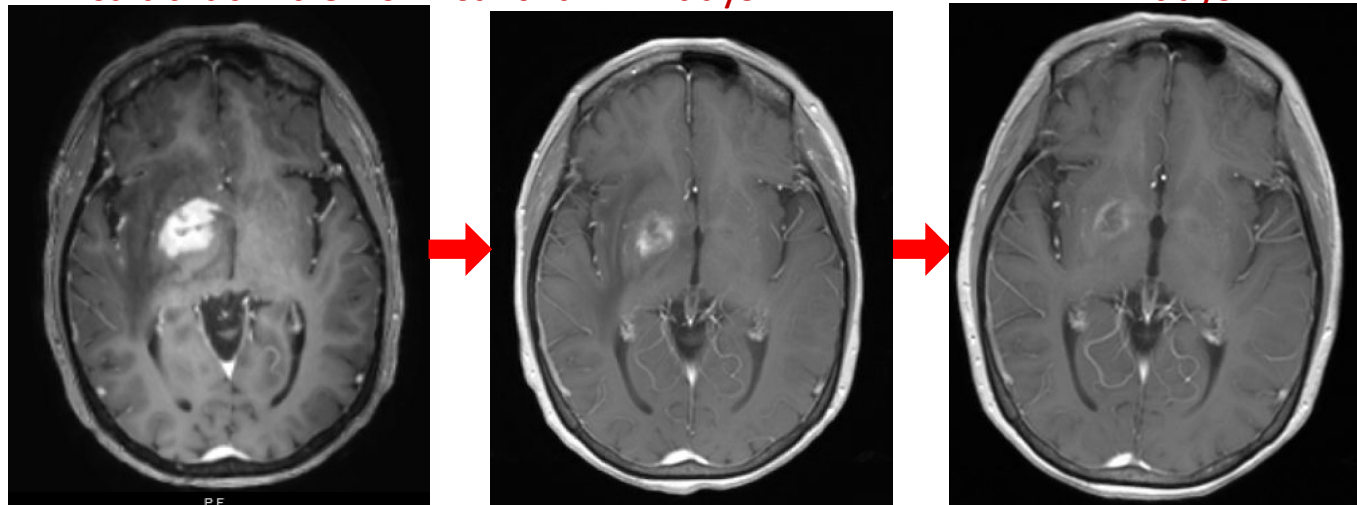


Bridging Strategies for secondary CNS lymphoma

- 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
- Stereotactic radiosurgery

Acalabrutinib on clinical trial: 7 days

21 days



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!



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