IL13Ra2 CAR-T Immunotherapy for Recurrent Malignant Gliomas; Phase 1; Experience and Future perspective

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Uniqueness of Brain TME (I)

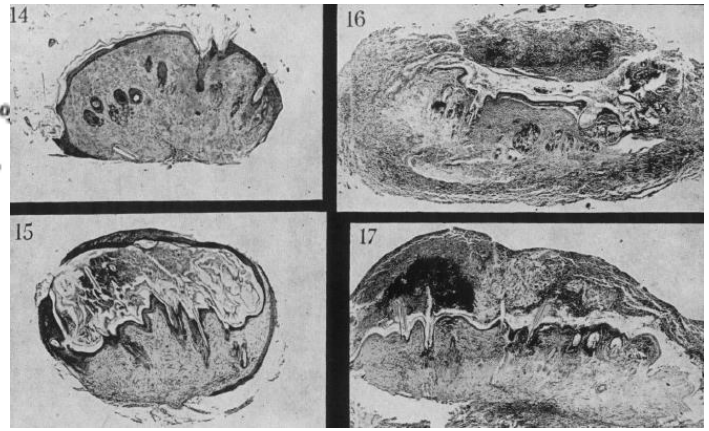
- **CNS lymphatics**
  - CNS is often described as an immune-privileged organ

IMMUNITY TO HOMOLOGOUS GRAFTED SKIN. III. THE FATE OF SKIN HOMOGRAFTS TRANSPLANTED TO THE BRAIN, TO SUBCUTANEOUS TISSUE, AND TO THE ANTERIOR CHAMBER OF THE EYE.

P. B. MEDAWAR.

From the Department of Zoology, University o

Received for publication December 8,

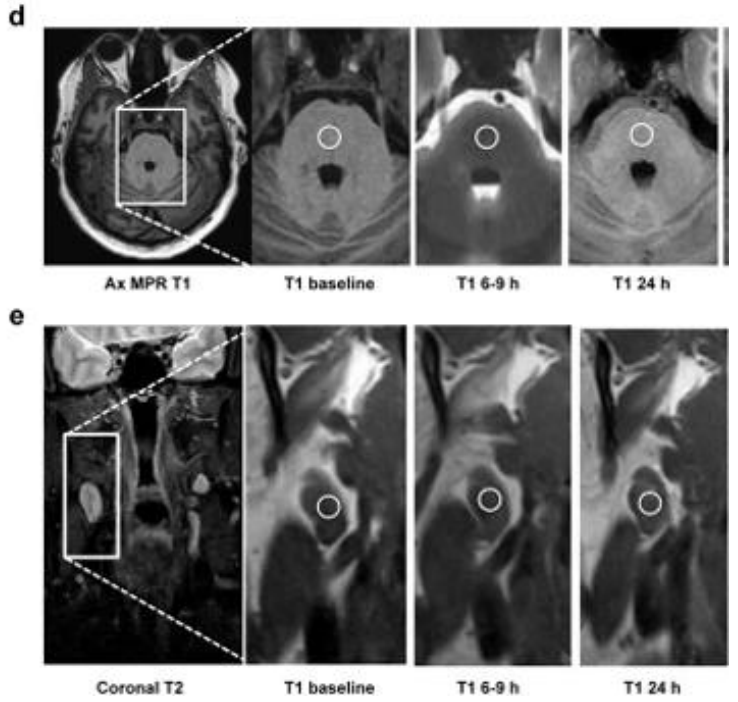


  - with the consensus that since the brain does not contain lymphatic vessels
  - a functional connection from the CNS to the cervical lymph nodes using tracers in animal studies and cadaver

SCIENTIFIC REPORTS

Magnetic resonance imaging provides evidence of glymphatic drainage from human brain to cervical lymph nodes

Per Kristian Eide[1,2], Svein Are Sirirud Vatnehol[2,3], Kyrre Eeg Emblem[3,4] & Geir Ringstad[2,5]

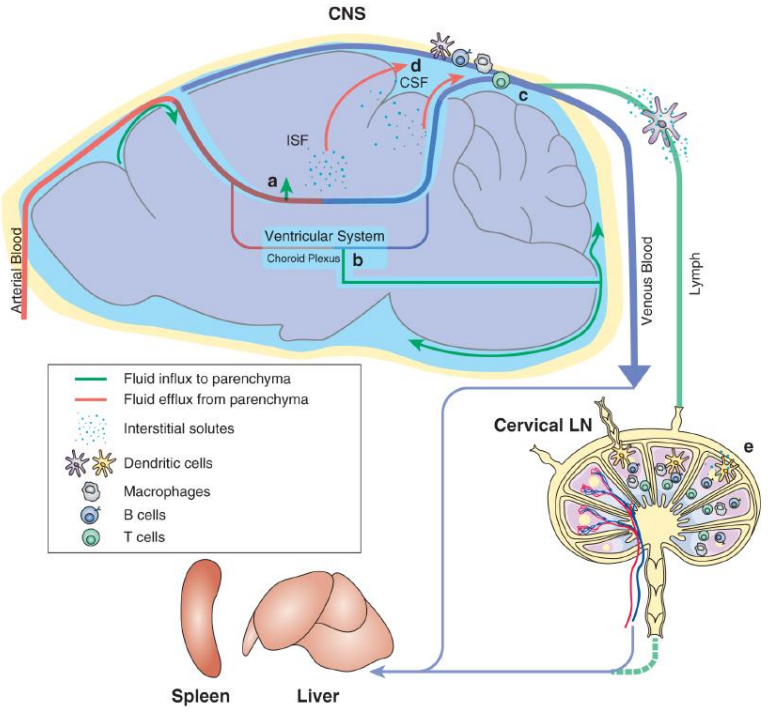


Uniqueness of Brain TME (II)

- Antigen Presenting Cells (APCs)
  - Brain parenchyma is continuously surveyed by its only resident leukocyte. 'microglia'
  - their capacity as APC remains in question, do not appear capable of migrating from the parenchyma to the vascular system for the induction of an adaptive immune response
  - but express MHCII in inflammatory conditions such as multiple sclerosis, viral infection and Alzheimer
  - dendritic cells (DCs) normally serve as phagocytes, but once activated, process the antigen and carry it to lymph nodes where they function as potent APCs

- Meningeal DCs are surveil material crossing the blood-CSF barrier or BBB
- Although migratory DCs, monocytes, and resident DCs rotate through most tissues, there is less evidence for the turnover of this population in the CNS; Ag reaches LN w/o inflammation may be utilized to maintain self-tolerance

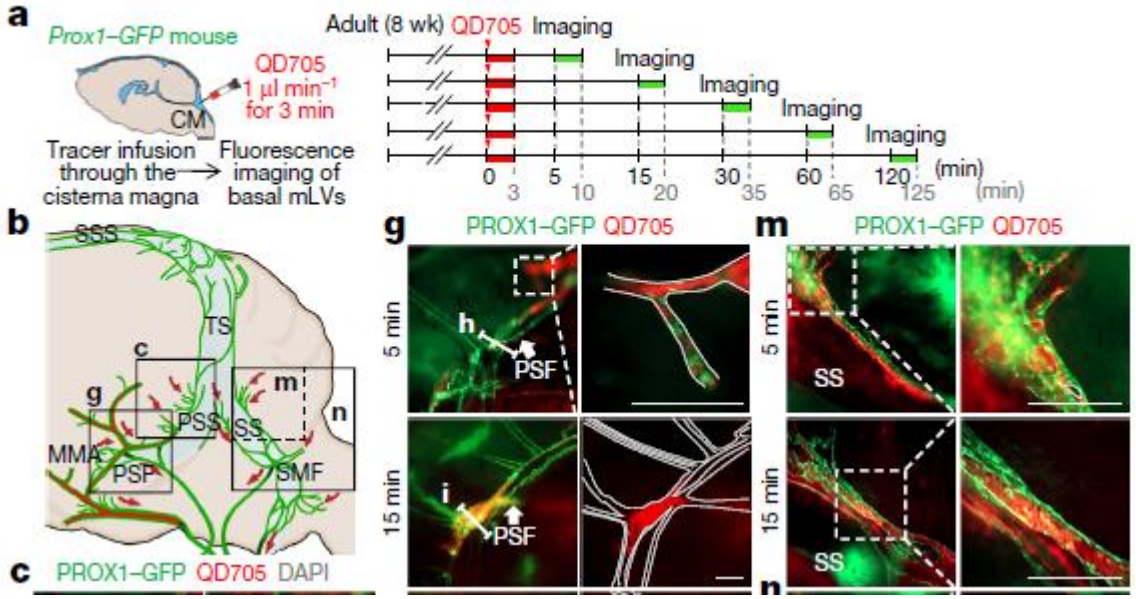
Anatomical (O)
Functional (?)



Meningeal lymphatic vessels at the skull base drain cerebrospinal fluid

Ji Hoon Ahn[1,6], Hyunsoo Cho[2,6], Jun-Hee Kim[3,6], Shin Heun Kim[4], Je-Seok Ham[3], Intae Park[2], Sang Heon Suh[1], Seon Pyo Hong[2], Joo-Hye Song[2], Young-Kwon Hong[5], Yong Jeong[1,3,4], Sung-Hong Park[3,4,7]* & Gou Young Koh[1,2,7]*

In this study, we successfully characterized the specialized morphologic features of basal mLVs in distinct locations by careful dissectionof the skull base in mice



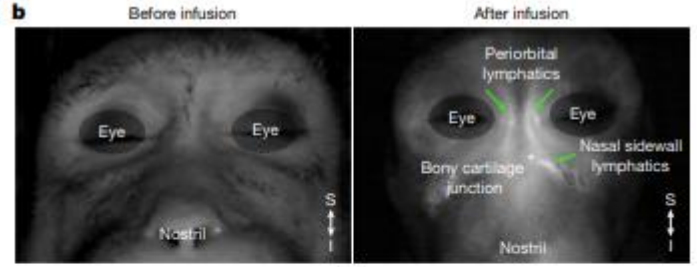
Article

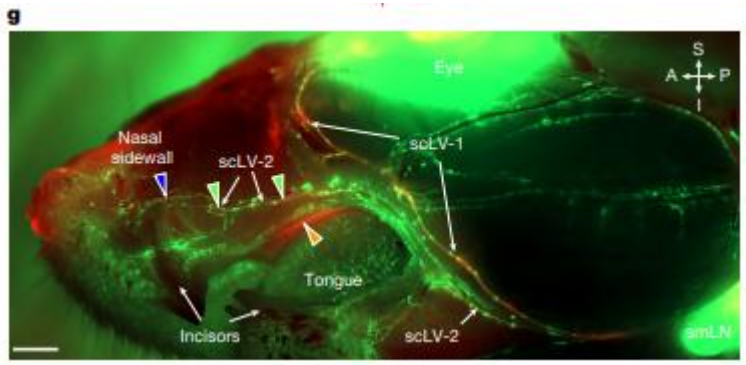
Increased CSF drainage by non-invasive manipulation of cervical lymphatics

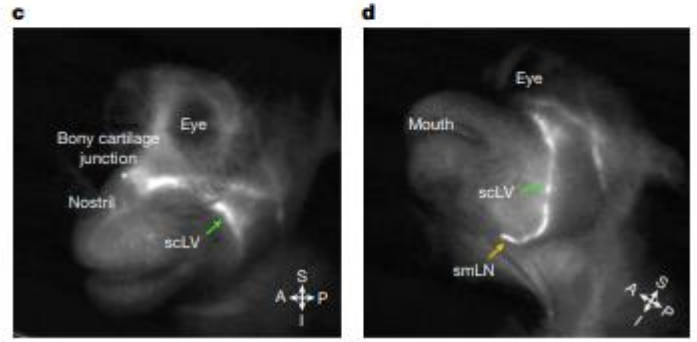
https://doi.org/10.1038/s41586-025-09052-5

Received: 24 September 2024

Hokyung Jin[1,2,9], Jin-Hui Yoon[1,9], Seon Pyo Hong[1,9], Yu Seok Hwang[3], Myung Jin Yang[1], Jieun Choi[2], Hae Jin Kang[1], Seung Eun Baek[1], Cheolhwa Jin[1,2], Junho Jung[1], Hae Jin Kim[4], Jinche







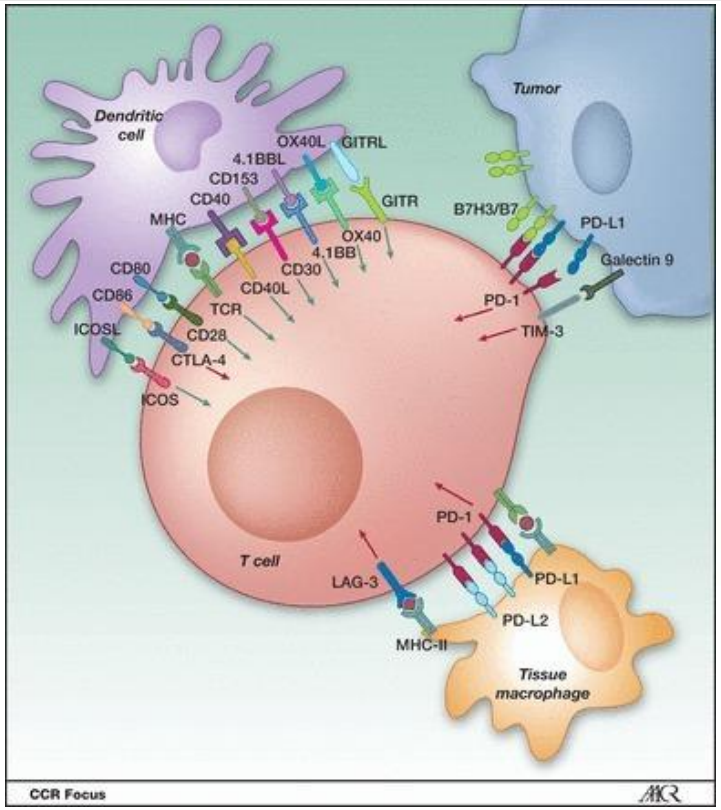
Immune-check point PD-1/PD-L1

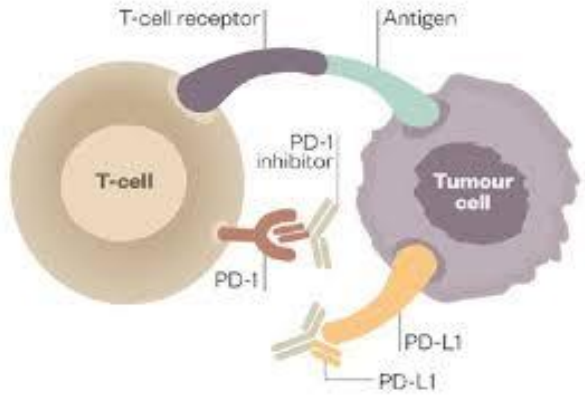
New immunotherapy drug behind Jimmy Carter's cancer cure

Former president given pembrolizumab, one of the most promising new drugs in the treatment of cancer

Histology	Number of patients	AJCC stage	Agent(s)	Grade 3 or higher toxicity (%)	Pathologic response
Melanoma[5]	23	IIIB-IV	Nivolumab +/- ipilimumab	73%	45% pCR
NSCLC[12]	21	I-IIIA	Nivolumab	23%	45% MPR
Breast[15]	784	II-III	Pembrolizumab + chemotherapy	76%	64.8% pCR
Head and neck squamous cell cancer[14]	36	III-IVB HPV unrelated	Pembrolizumab	8%	44% pTR > 10%
Undifferentiated pleomorphic sarcoma[13]	9	I-III	Nivolumab/XRT +/- ipilimumab	56%	89% < 15% viable tumor
Dedifferentiated liposarcoma[13]	14	II-III	Nivolumab +/- ipilimumab	29%	37% pTR > 20%

MPR: major pathologic response; pCR: pathologic complete response; pTR: pathologic tumor response





"CNS is no more an immune privilege site, but Gliomas actively escape from adaptive cytotoxic immunity"

Table 3

Clinical trials evaluating immune checkpoint blockade in malignant gliomas with available data.

Study Identifier	Study title	Study design	Target population (N)	Intervention	Primary endpoint	Results	Status
NCT02017717 [60-62]	A Randomized Phase 3 Open Label Study of Nivolumab Versus Bevacizumab and Multiple Phase 1 Safety Cohorts of Nivolumab or Nivolumab in Combination With Ipilimumab Across Different Lines of GBM (Checkmate 143)	Open label multicohort phase I/III	Recurrent GBM N = 40 (NIVO3=10; NIVO1+IPI3=10; NIVO3+IPI1=20)	*Cohort 1, 1b* Nivo +/- Ipi	Safety and tolerability	No new safety signals NIVO3 better tolerated than either combinations OS-12: NIVO3 40% NIVO1+IPI3 30%, NIVO3+IPI1 35%	Active, not recruiting
			Newly diagnosed GBM N = 113	*Cohort 1c, 1d* Nivo + RT +/- TMZ	Safety and tolerability	No new safety signals	
			Recurrent GBM N = 184 vs 185	*Cohort 2* Nivo vs BEV	OS	mPFS: 1.5 vs 3.5 mo mOS: 9.8 vs 10 mo ORR 8% vs 23% mDOR 11.1 mo vs 5.3 mo G3-4 TRAEs 18% vs 15%	

Check mate 143

Safety of Nivo add-on to GBM CCRT

PD-L1 expression from initial GBM

Newly diagnosed GBM

				MGMT	
Nivolumab	NCT02667587 (CheckMate-548)	Recruiting	II	unmet	TMZ CCRT vs. Nivo + RT
Nivolumab	NCT02617589 (CheckMate-498)	Recruiting	III	met	TMZ CCRT w/ or w/o Nivo

Phase I/II on-going

NCT02336165 [63-64]	Phase 2 Study to Evaluate the Clinical Efficacy and Safety of Durvalumab in Patients With GBM	Open label multicohort phase II	N = 68 Recurrent GBM, BEV-refractory N = 22	*Cohort C* DUR + BEV	OS-6	36% of pts OS ≥ 22 weeks 50% of pts PFS ≥ 8 weeks G3-4 TRAEs 4.5%	
NCT02054806 [65]	Phase IB Study of Pembrolizumab in Subjects With Select Advanced Solid Tumors	Phase Ib	Recurrent GBM PD-L1 expression ≥1% by IHC N = 26	Pembrolizumab	BOR	mPFS 2.8 mo mOS 14.4 mo G3-4 TRAEs 15.4%	Active, not recruiting
NCT02313272 [66]	A Phase I Trial of HFSRT With Pembrolizumab and Bevacizumab in Patients With Recurrent High Grade Gliomas	Open label phase I	Recurrent GBM or anaplastic astrocytomas N = 23	pembrolizumab BEV HFSRT	MTD	OS-6 94% OS-12 64% ORR 53%	Recruiting
NCT02337491	Phase II Study of Pembrolizumab With and Without Bevacizumab for Recurrent Glioblastoma	Randomized phase II	Recurrent GBM N = 6	*Safety lead-in* (pembro + BEV)	MTD/RP2D	mOS 6.8 mo No new safety signals	

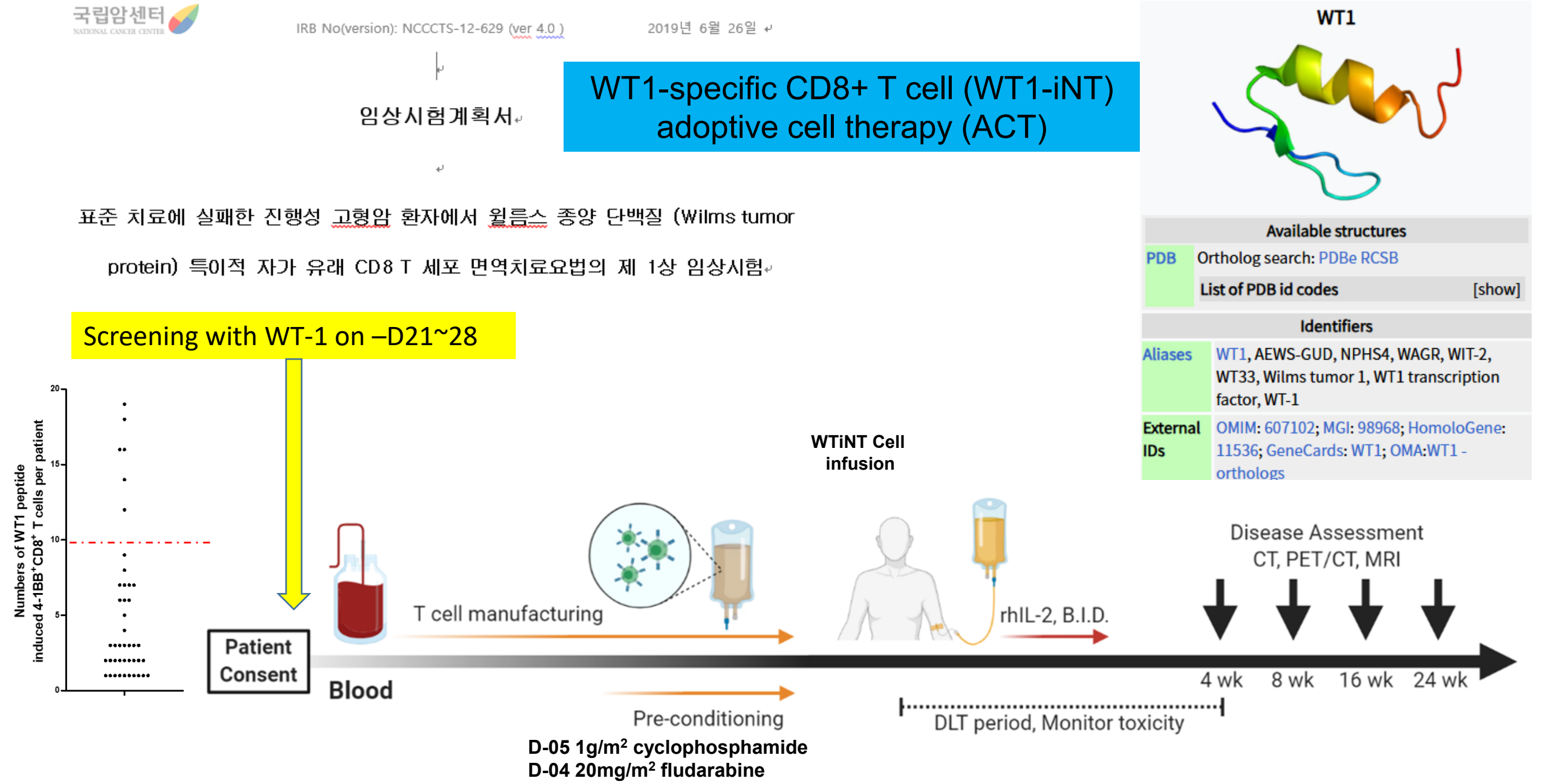
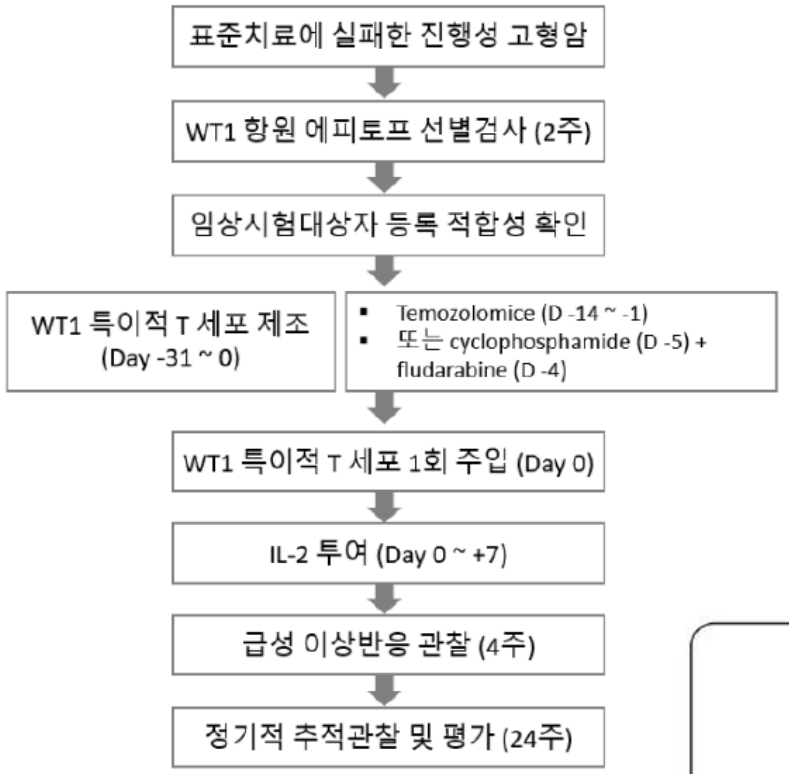


Figure 3. Schematic diagram depicting WT-1 adoptive immune cell therapy.

<study flow>



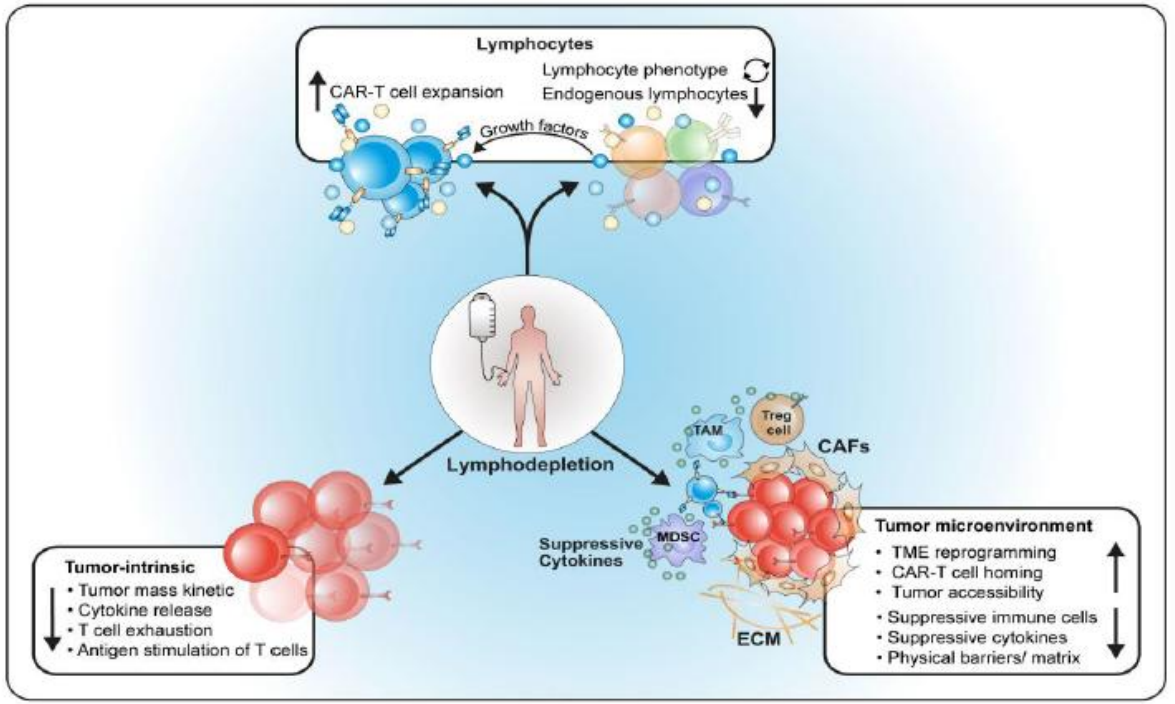
lymphodepletion

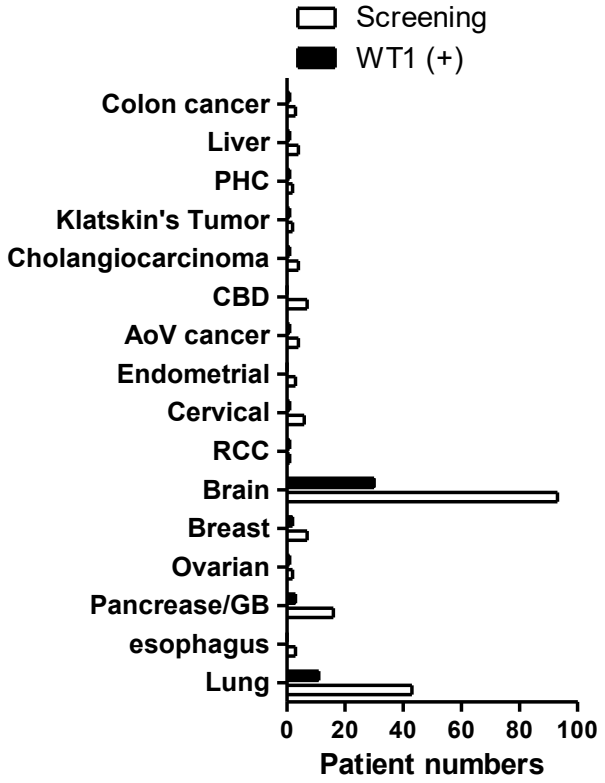
치료단계

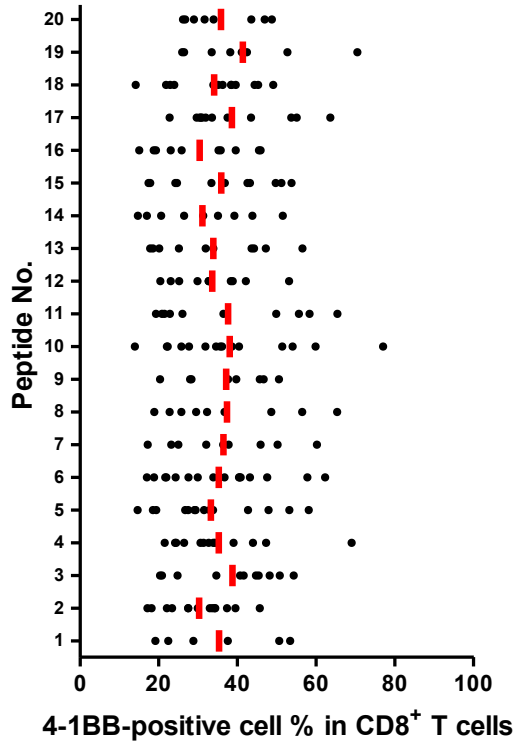
치료 단계	Temozolomide (Day -14~-1)	Cytoxan Day-5	Fludarabine Day-4	CD8 T 세포 수 (개/체표면적 m^2)	IL-2 (Day0~+7) (BID/day)
1	0			1.0×10^8	0
2	50 mg/m^2			1.0×10^8	0
3	50 mg/m^2			4.0×10^8	0
4		1 g/m^2	20 mg/m^2	4.0×10^8	250,000 IU/m^2
5		1 g/m^2	20 mg/m^2	8.0×10^8	250,000 IU/m^2
6		1 g/m^2	20 mg/m^2	1.6×10^9	250,000 IU/m^2
7		1 g/m^2	20 mg/m^2	3.2×10^9	250,000 IU/m^2

Cytoxan: Cyclophosphophamide, BID: Twice a day

- Decrease both ‘cytokine sinks’ and T_{reg}







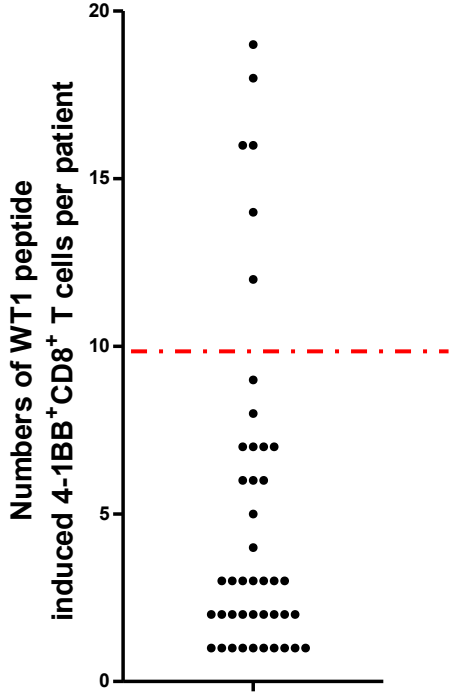


Table 10.1-1 Subject Disposition (All Screened Subjects)

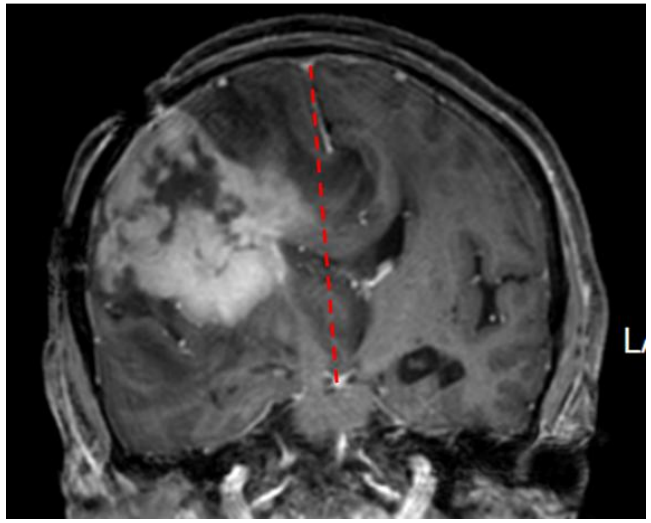
Subject Disposition	치료 단계 1	치료 단계 2	치료 단계 3	치료 단계 4	치료 단계 5	치료 단계 6	치료 단계 7	Total
Screened								221
Screening Failure								197
Enrolled	3	3	3	3	3	3	6	24
Completion	1	0	0	1	2	0	2	6
Discontinuation	2	3	3	2	1	3	4	18
Reason for discontinuation	2	3	3	2	1	3	4	18
Voluntarily consent withdrawal	0	0	0	0	0	0	0	0
Lost to follow-up	1	0	0	0	0	0	0	1
Death	0	0	0	0	0	0	0	0
Progressive Disease	1	3	3	2	1	3	4	17

89% failure rate

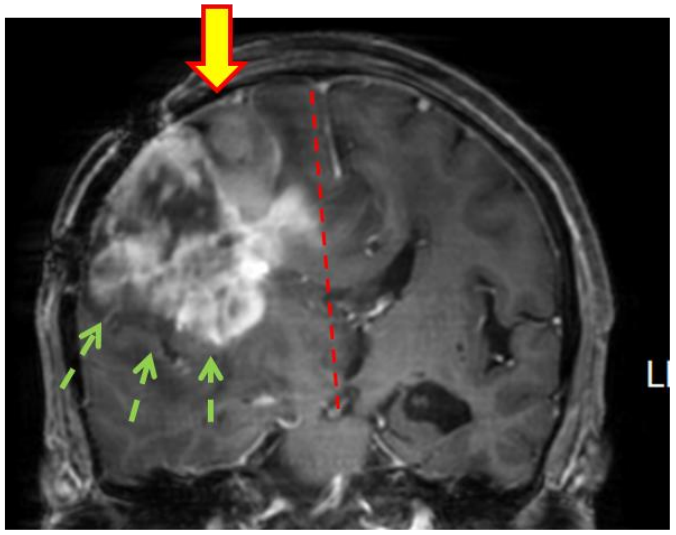
Neither DLT nor Objective response

WT1-052

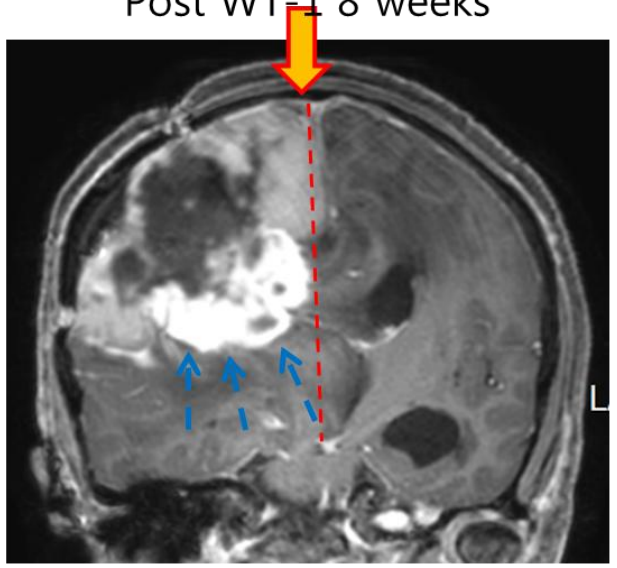
Pre WT-1



Post WT-1 4 weeks



Post WT-1 8 weeks



Decreased midline shift 11 -> 7 mm

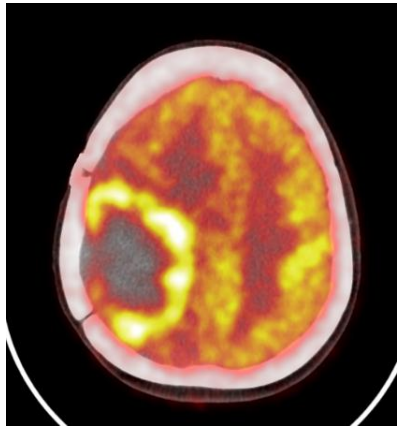
Increased midline shift 7-> 12 mm

Partial response of lower part

Outgrowing of lower medial part

Outgrowing of upper medial part

Midline involvement

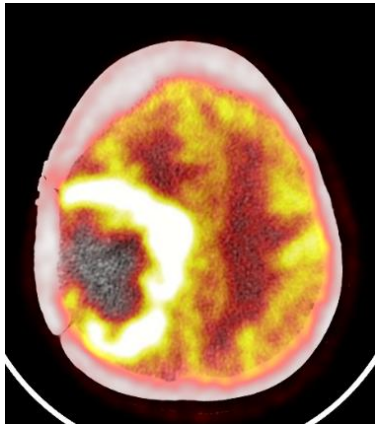


Clinical improvement: HA, alertness, obey command, etc.

Adaptive immunity

⇕

Glioma heterogeneity



Long-Term Remission of Recurrent Anaplastic Oligodendroglioma With WT-1-Specific CD8+ T-Cell Therapy: A Case Report

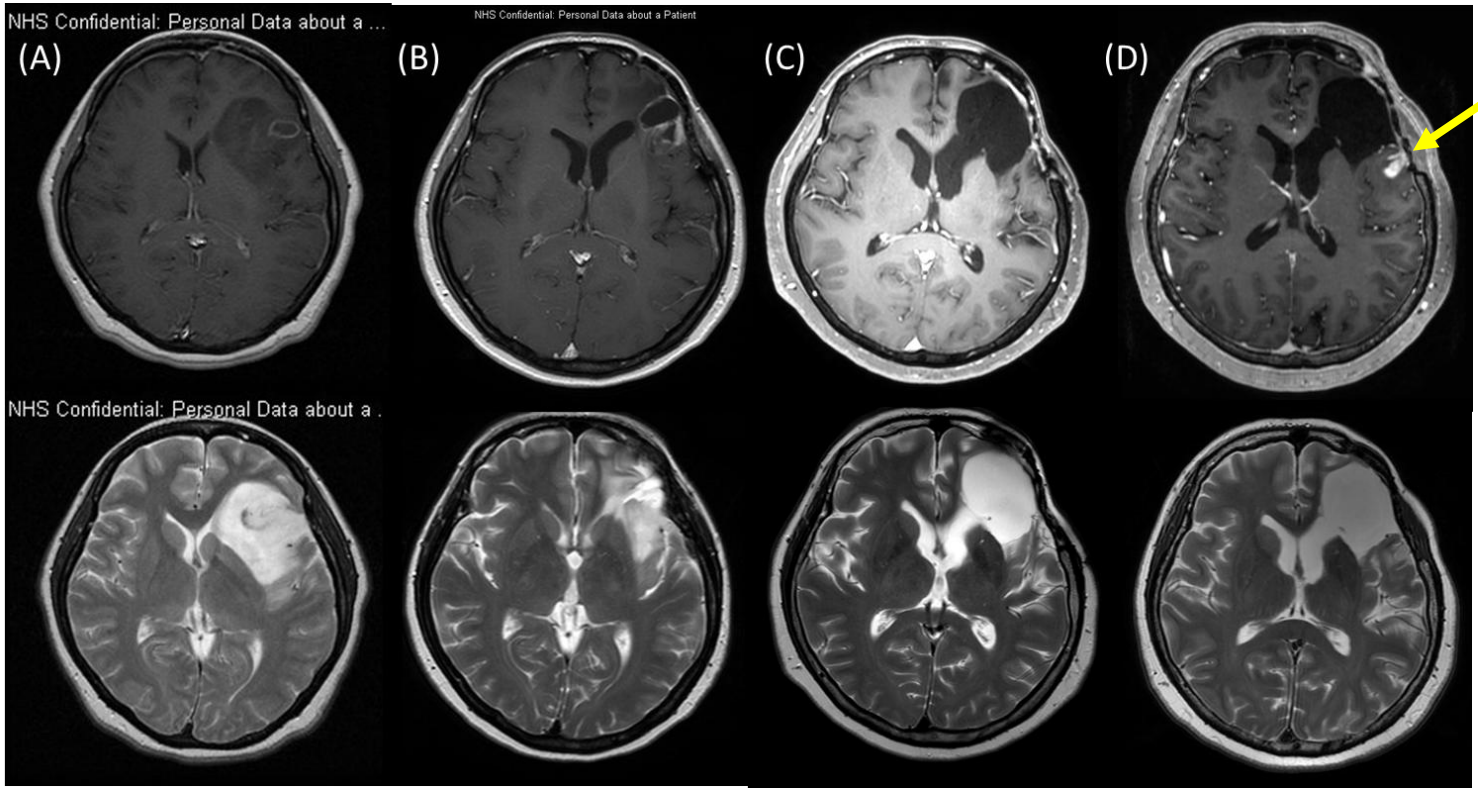
CASE REPORT
Brain Tumor Res Treat 2025;13(2):65-72
https://doi.org/10.14791/btrt.2025.0010

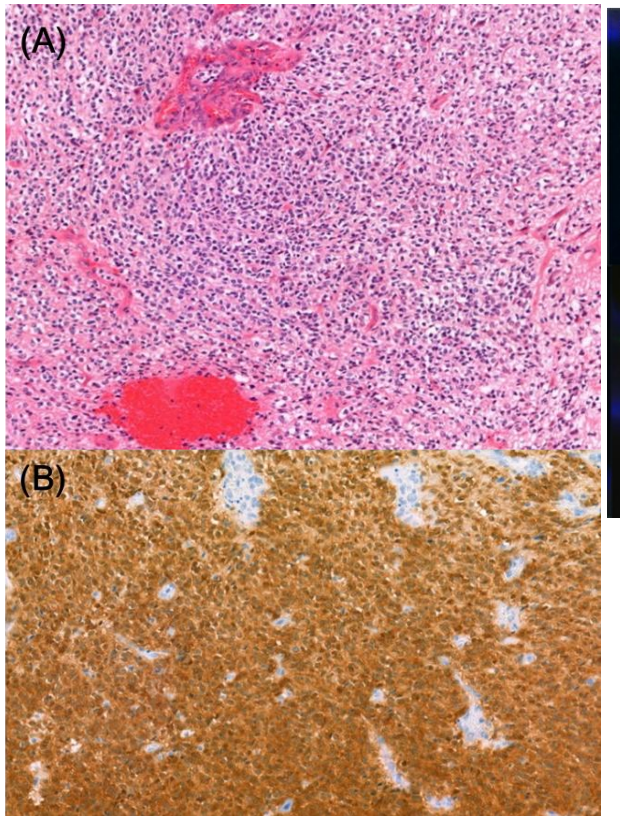
Ho-Shin Gwak[1], Beom Kyu Choi[2], Young Joo Lee[3], Na Young Han[4], Kook Hee Yang[5]

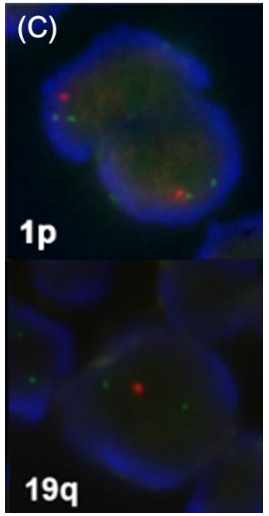
1st. Jun, 2009
Oilgodendroglioma
(WHO G2)

2nd. Dec, 2011
Anaplastic ODG
(WHO G3)

3rd. Sep, 2016
Anaplastic ODG
(WHO G3)

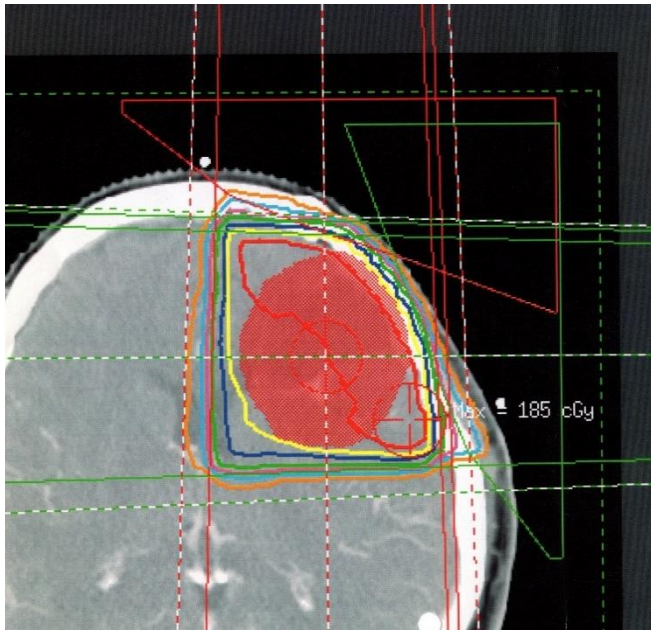




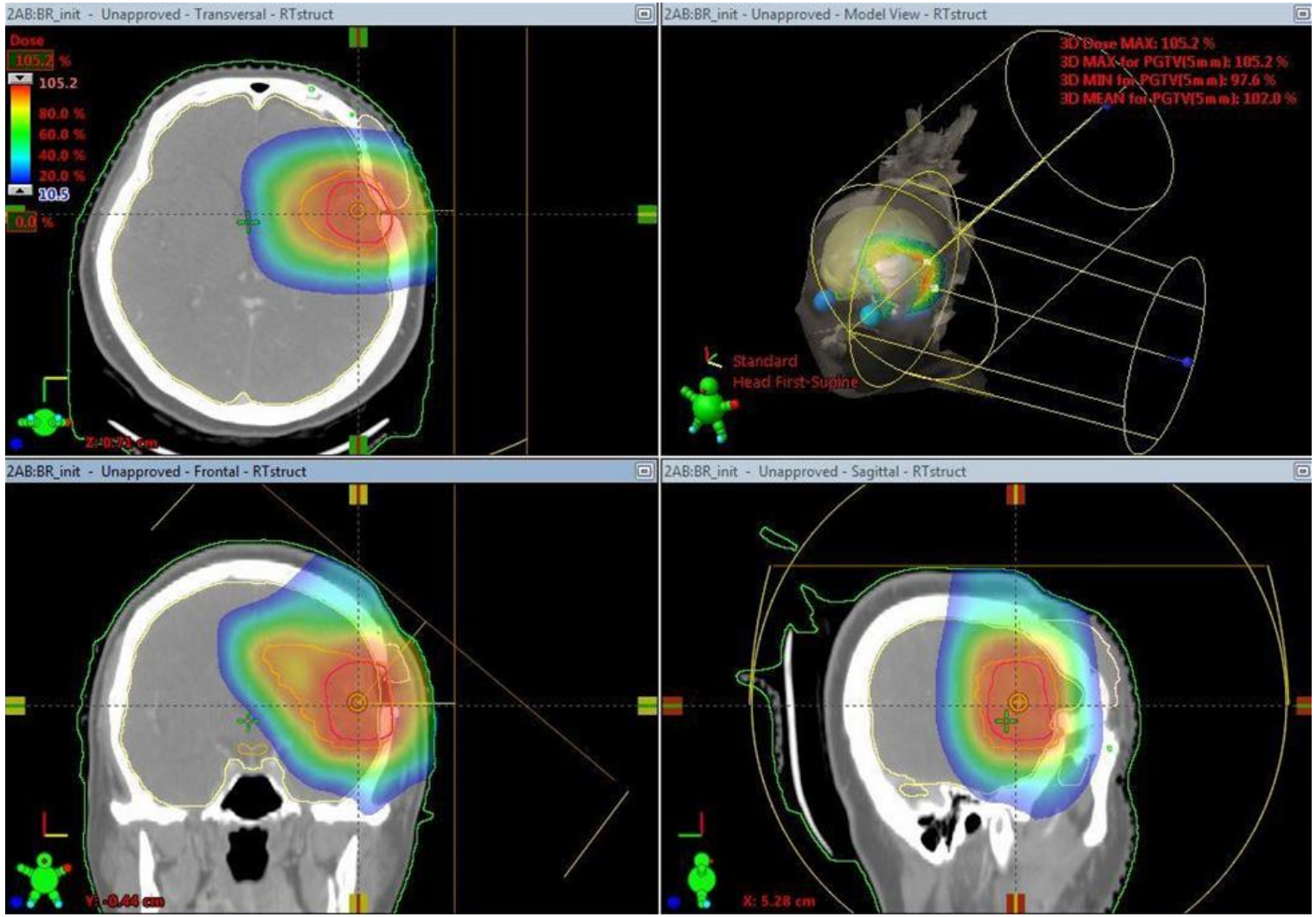


1p19p-codel
IDH1-mt

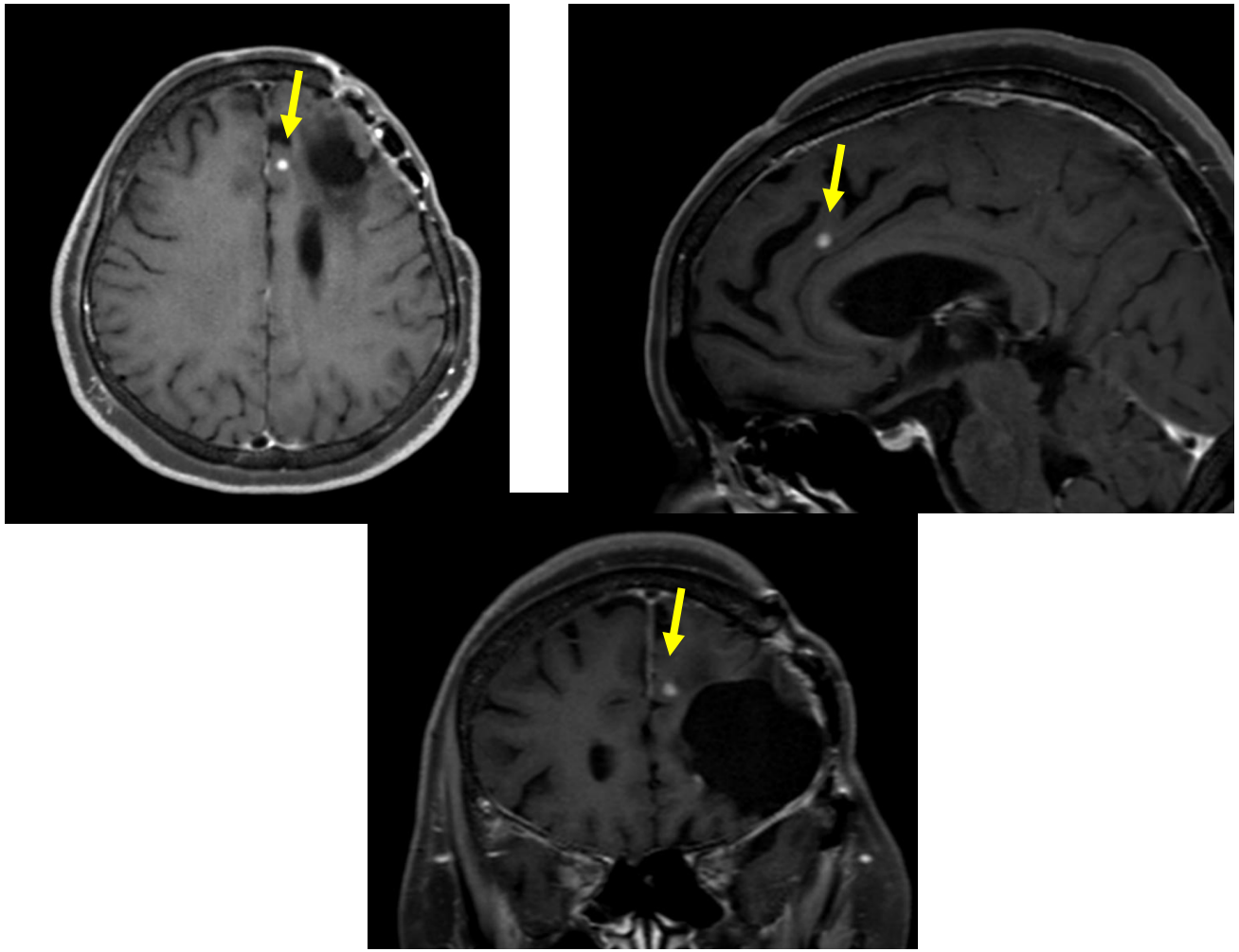
Radiation therapy 5,400 cGy after 1st craniotomy



Proton beam therapy 4,000 cGy after 3rd craniotomy



(2019-07-10) just finished 24th TMZ, 7.8 yrs after the 1st recurrence, 10 yrs after the 1st op



- Radiologist: R/O recur >> RT change, the lesion is too small for perfusion MRI
- Multi-disciplinary BT board recommend 1) excisional biopsy

  2) WT-1 ACT

- Patient's KPS = 90
- Her refused any further surgery but accept phase 1 WT-1 ACT

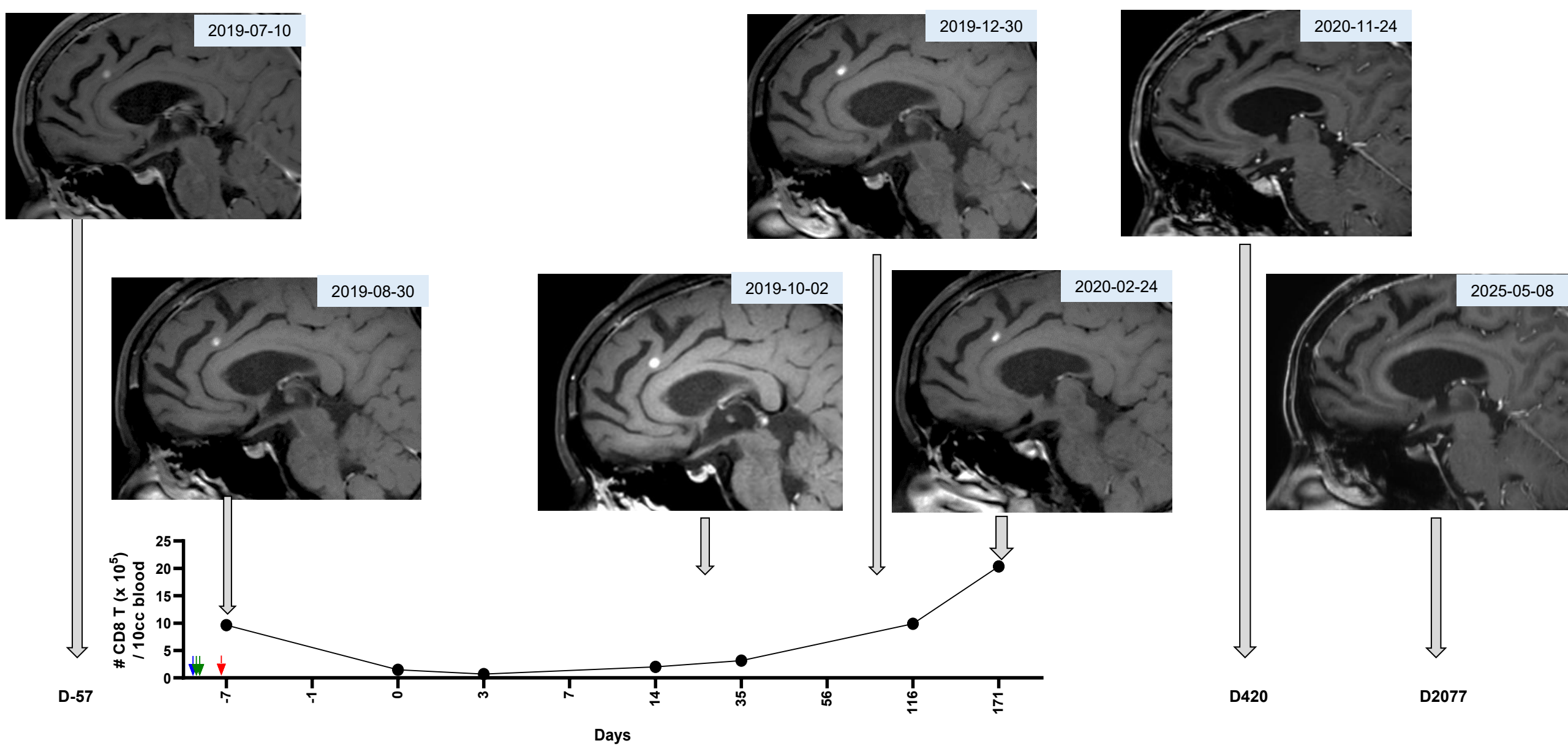


Figure 4. Tumor response and CD8+ T-cell kinetics following Wilms tumor 1 adoptive immune cell therapy. Chronological changes in the medial frontal tumor mass size and peripheral CD8+ T-cell concentration. The transient increase in tumor size at day 28, likely due to 'pseudo-progression,' eventually decreased, leading to complete remission at day 420. Complete remission was maintained for up to 5.7 years post-treatment.

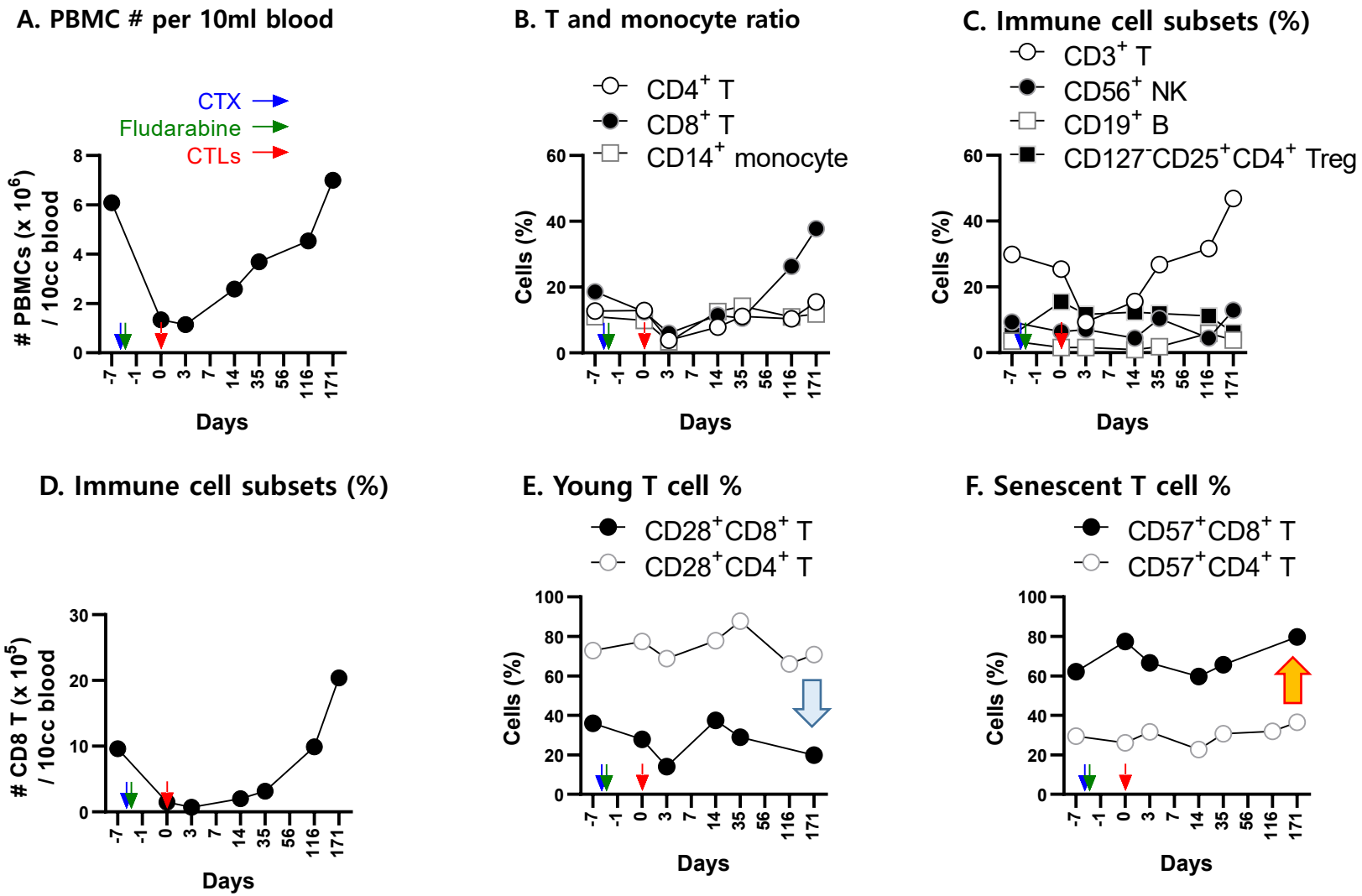


Figure 5. Kinetics of immune subsets in patient's blood. Heparinized bloods were collected at indicated days. Peripheral blood monocytes (PBMC) were isolated by Ficoll-gradient centrifugation, stained with specific mAbs and analyzed by FACSCalibur (BD Science). (A) Absolute numbers of PBMCs at the indicated days, (B) Percentages of $CD4^+$ T, $CD8^+$ T and $CD14^+$ monocytes in PBMCs, (C) Absolute numbers of $CD8^+$ T cells, (D) Percentages of $CD3^+$ T, $CD56^+$ NK, $CD19^+$ B and $CD127^+CD25^+CD4^+$ naïve regulatory T cells (Treg), (F) Percentages of $CD28^+$ cells in $CD4^+$ and $CD8^+$ T cells, and (G) Percentages of $CD57^+$ cells in $CD4^+$ and $CD8^+$ T cells.

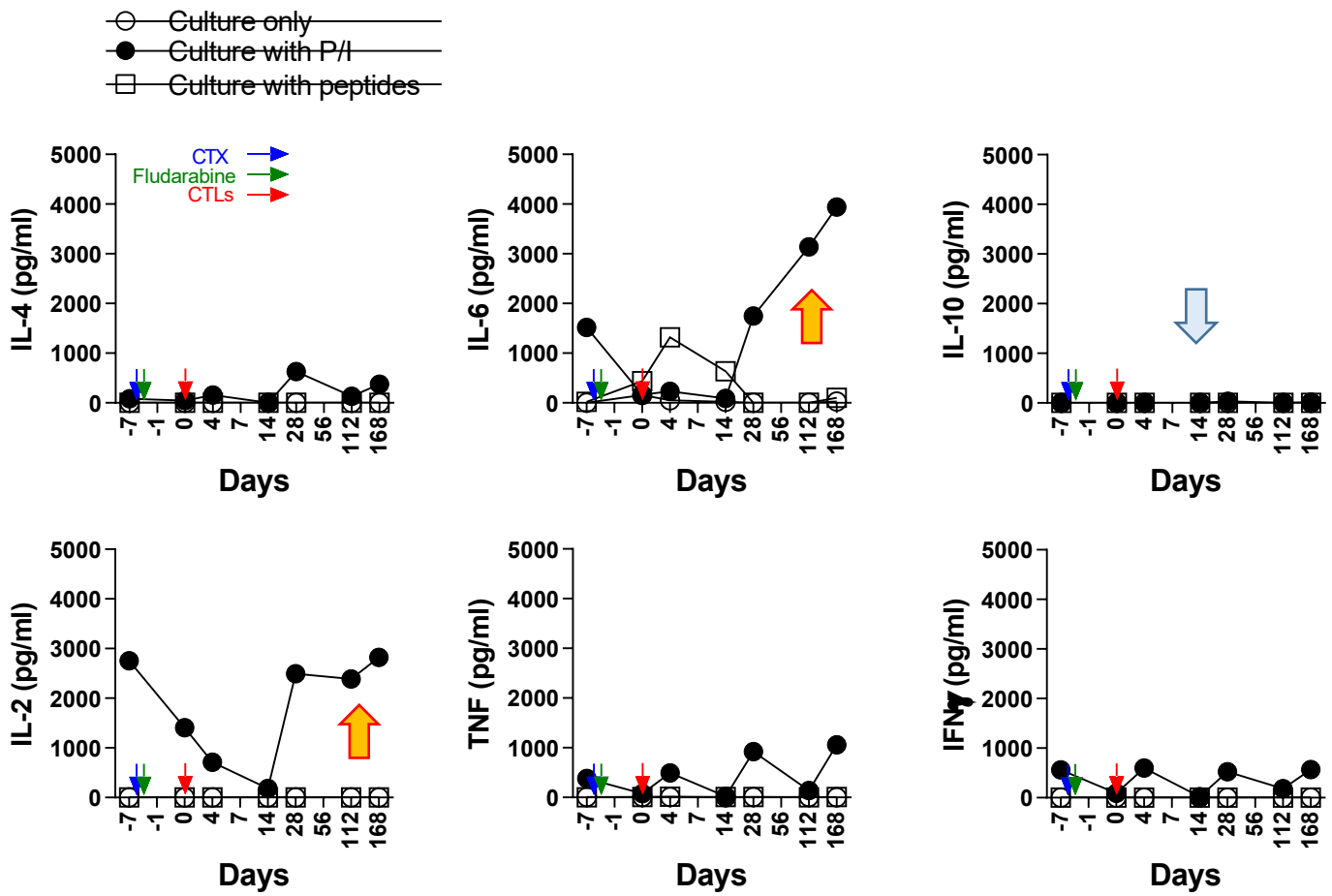


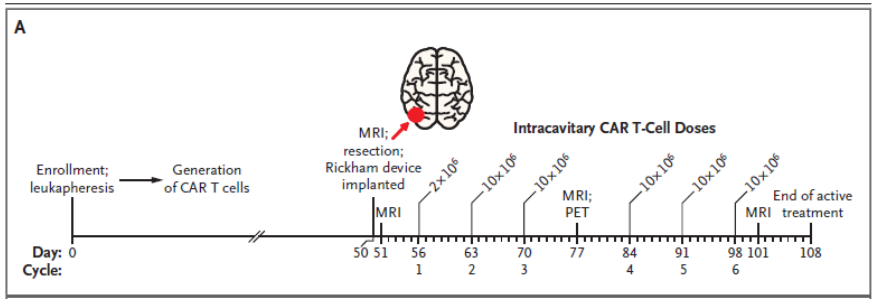
Figure 6. Cytokine profile of PBMCs. PBMCs were isolated by Ficoll-gradient centrifugation from heparinized bloods of patient at indicated days. PBMC were plated in 48 well culture plate (5×10^5 cells/1ml/well) and stimulated with PMA + ionomycin (P/I) or 4 different WT1 peptides that used to produce WT1-specific $CD8^+$ T cells for 48 hr. Cytokines in culture supernatant were measured with Th1/2/17 CBA kit (BD Bioscience).

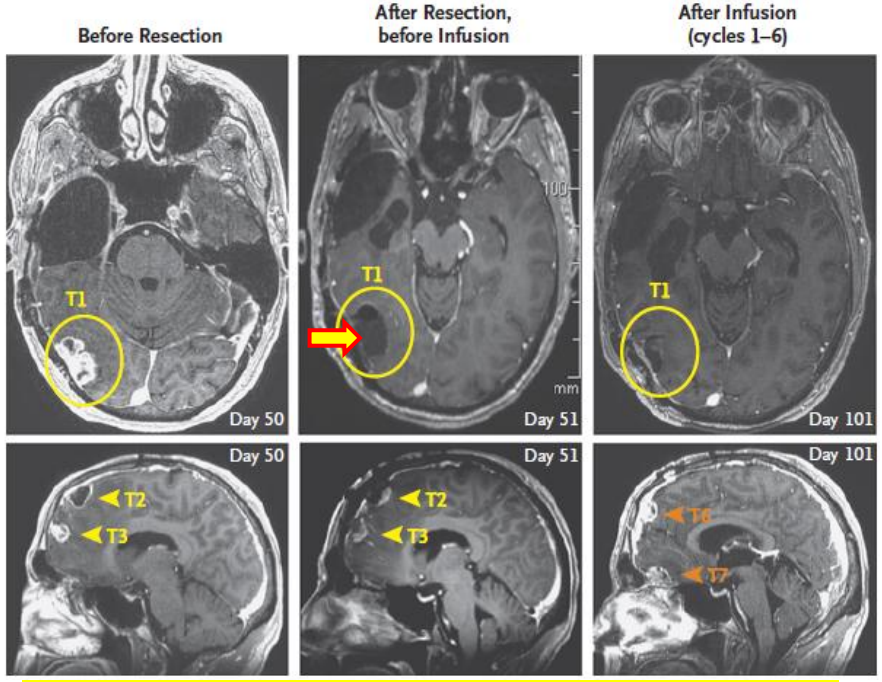
BRIEF REPORT

Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy

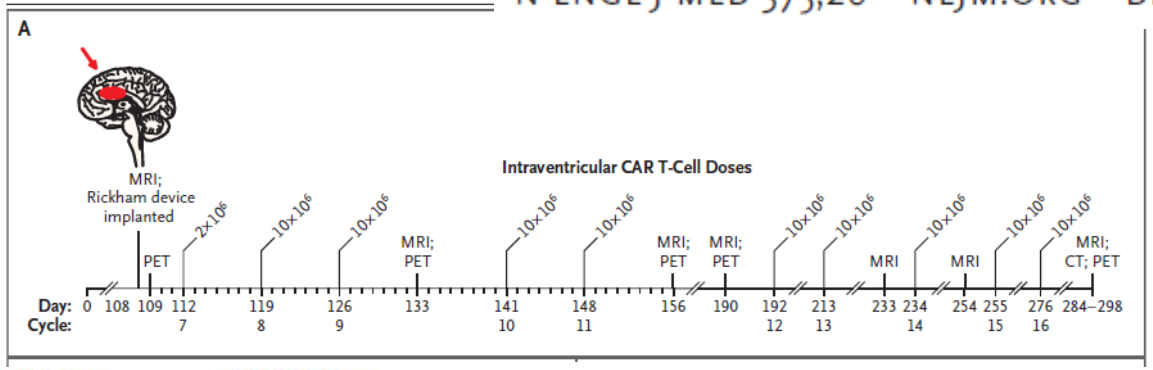
Christine E. Brown, Ph.D., Darya Alizadeh, Ph.D., Renate Starr, M.S.,

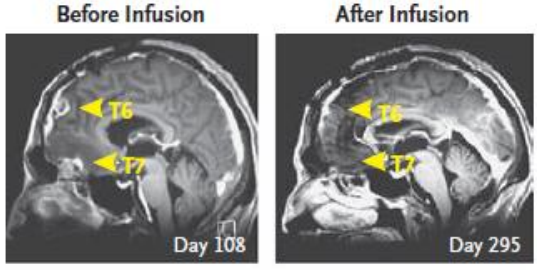
N ENGL J MED 375;26 NEJM.ORG DECEMBER 29, 2016

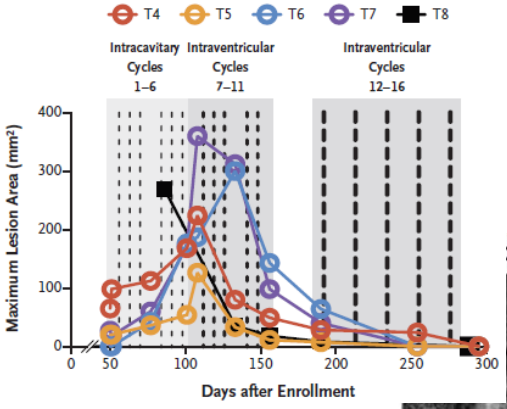


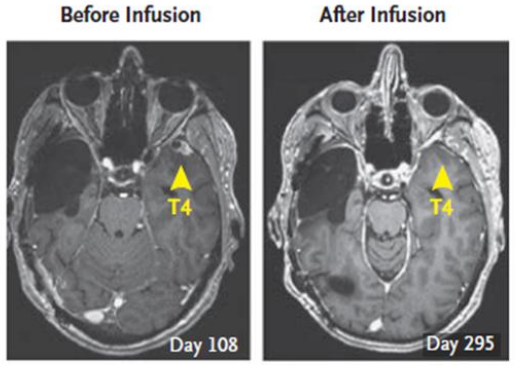


Intracavitary CAR-T infusion achieved local control but distant progression

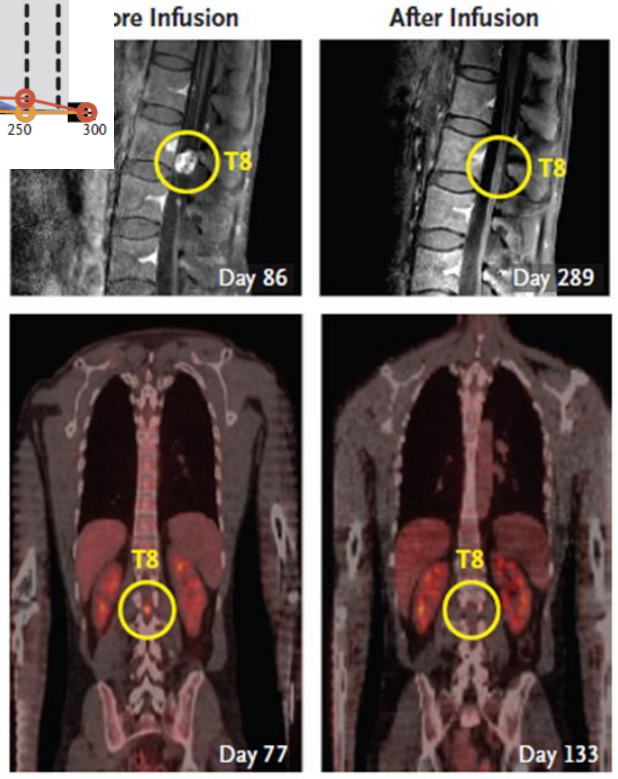








183 days after intraventricular CAR-T infusion (1x10⁶/cycle)



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CellabMED
(주)셀랩메드

회의명	YYB-103 임상논의 1차		
작성자	셀랩메드 김기완 차장		
일 시	2020년 03월 26일 PM 12:00~PM 01:00	장소	국립암센터
참 석 자	➢ 셀랩메드 – 송성원 대표(송), 이송재 부장(이), 조현태 차장(조), 김기완 차장(완) ➢ 국립암센터 – 곽호신 교수(곽), 엄현석 교수(엄), 윤탁 교수(탁), 최범규 박사(최), 윤지혜 임상간호사(윤), ➢ 클립스 – 이해림 부장(해), 박승희 대리(박)		

회의 내용

1. **대상환자군**

- Grade III는 standard therapy는 RT이고 TMZ는 보험이 되지 않음, 단, 재발 시 TMZ에 대한 보험적용이 가능. Grade IV는 CCRT를 standard로 진행

➔ Grade III, IV를 모두 포함하는 것이 유리할 것으로 보이며 **Grade III를 포함한 임상으로 진행**(곽)

2. **투여경로**

- IV투여를 통해서 brain에 약물전달 효율이 쉽지 않음. Brain에 직접 투여 고려필요.

➔ Brain에 직접 투여 시 safety우려에 의한 허가적인 issue있음. IV우선 진행 후 Brain투여 계획 중. (송, 최)

➔ IV로 투여하는 것이 systemic한 독성 우려가 더 많지 않은 지? (곽)

➔ IL13Rα2는 testis에만 발현하기에 systemic toxicity가 낮을 것으로 보임(최)

➔ brain에서 neurotoxicity에 의한 concern도 있음. (송)

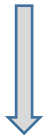
- nejm논문의 환자 케이스를 볼 때 전형적인 recur pattern 아니고 **CSF를 따라 전이가 발생하는 pattern. (Leptomeningeal metastases)**

Things to be discussed

- Biomarker of IL-13a
  - H-score; impact (1~3) * % (area)
  - Serum/ CSF marker (?)
  - CSF is in direct contact with tumor
  - LC-MS/ proteomics is possible
  - Simple flow cytometric analysis is hard to obtain
- Drug delivery route
  - Intracavitary delivery after resection or intraventricular delivery for distant lesion in a City of Hope case; leptomeningeal >> parenchymal
  - Intravenous: need a PET study to prove drug delivery

- Phase 1 of '3+3' design
  - Allow repeated injection (dose escalation)
  - SOP for SAE (i.e. cytokine storm)

- **Intravenous route는 회사가 선호**
- **Lymphodepletion은 PI가 기피**



- **근데 일단 전임상 data를 좀 봅시다. 가능하면 publication하여 공증(?)합시다**
- **Tumor archive에서 IHC로 expression을 확인해봅시다**

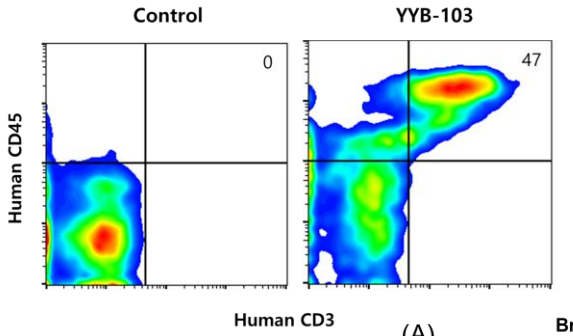
frontiers in Immunology

ORIGINAL RESEARCH
published: 08 November 2021
doi: 10.3389/fimmu.2021.715000

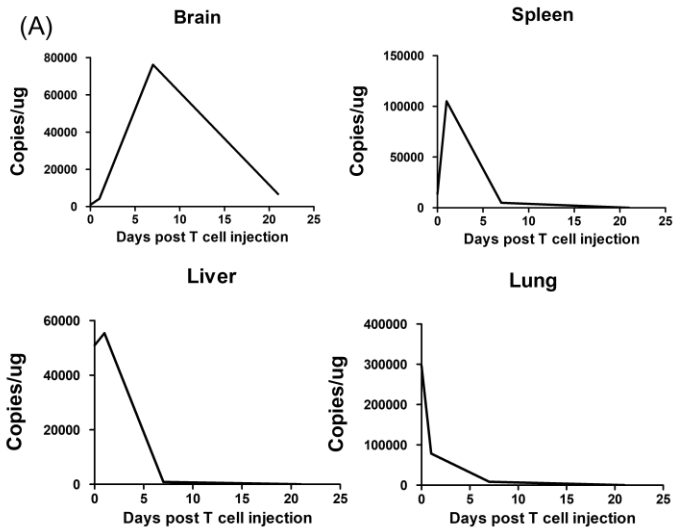
Chimeric Antigen Receptor T Cells With Modified Interleukin-13 Preferentially Recognize IL13Rα2 and Suppress Malignant Glioma: A Preclinical Study

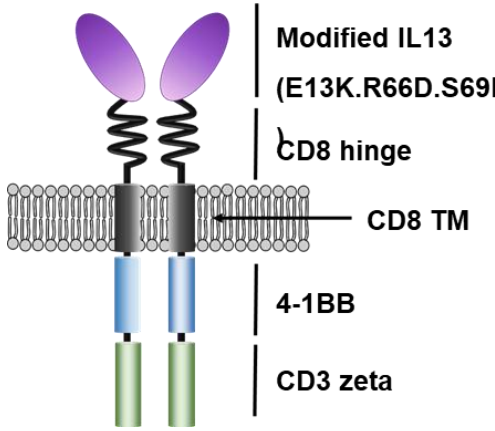
Kiwan Kim[1†], Ho-Shin Gwak[2†], Nayoung Han[3], Eun Kyung Hong[3], Beom K. Choi[4],

(B)

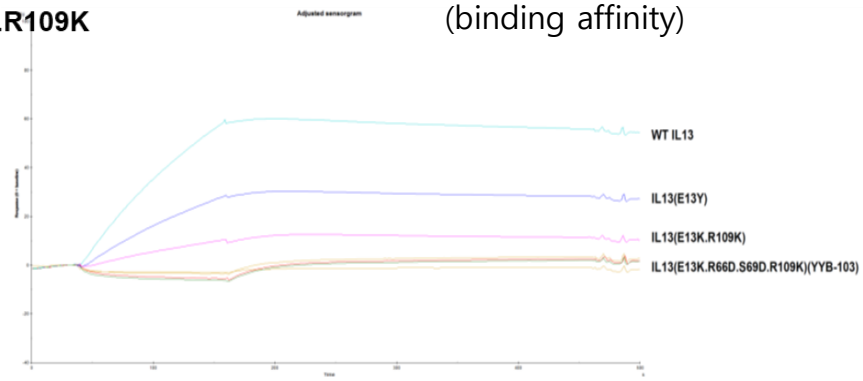


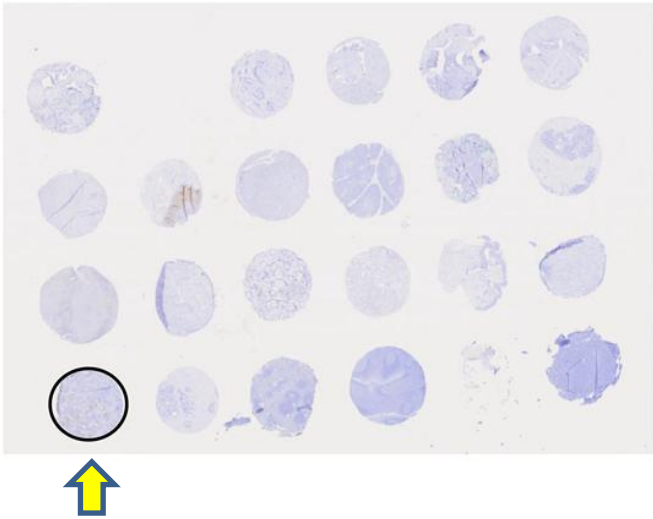
(A)



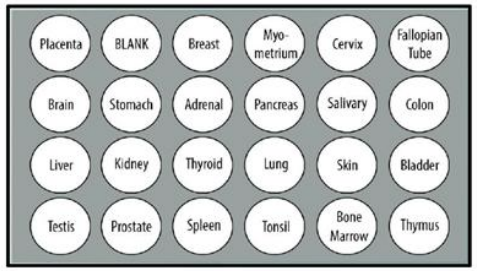


SRP assay
(binding affinity)



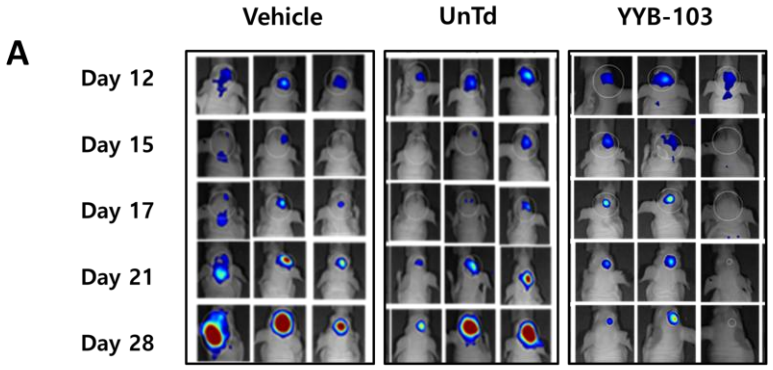


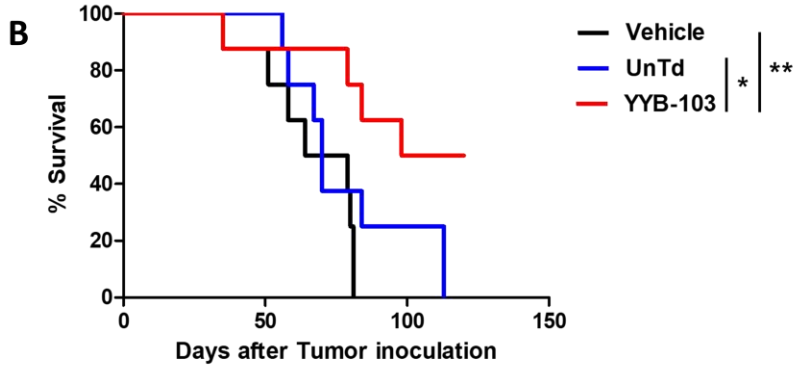
TMA
(commercially available human tissue)

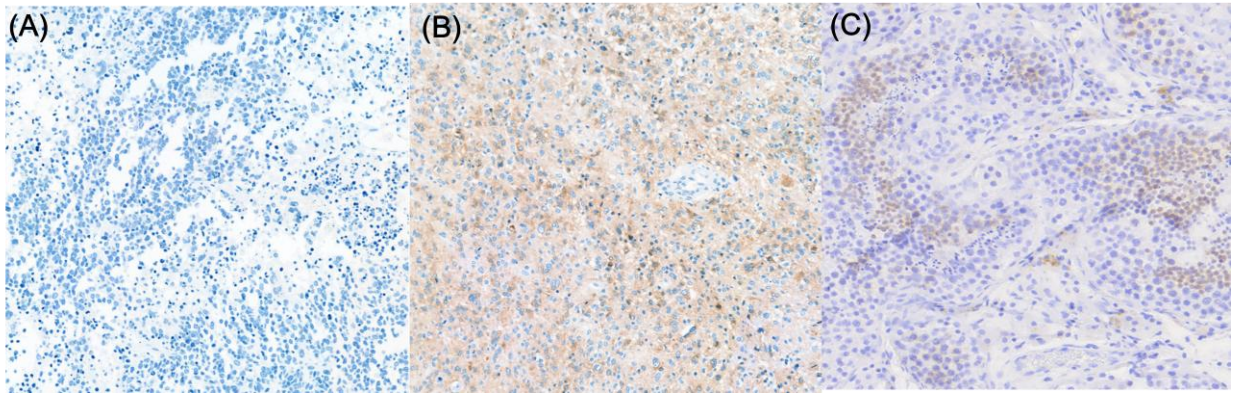


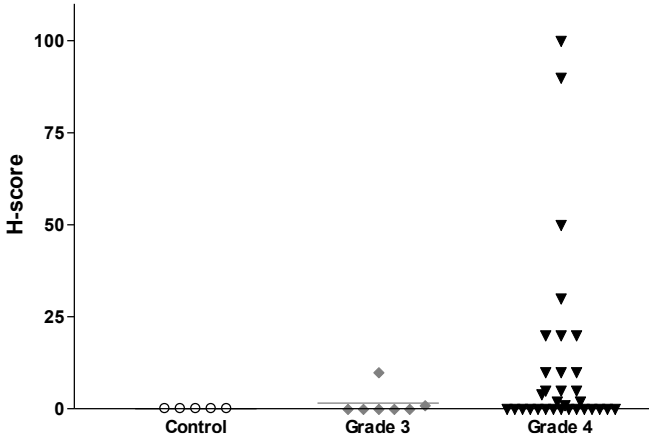
Interleukin-13 receptor a2 protein is not expressed after thymus modulated suppression except testis

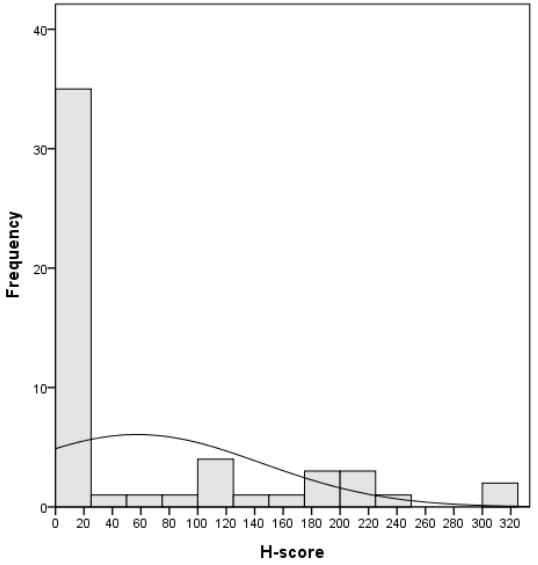
Cancer-germline antigens shared expression in both normal gametogenic cells and human cancer









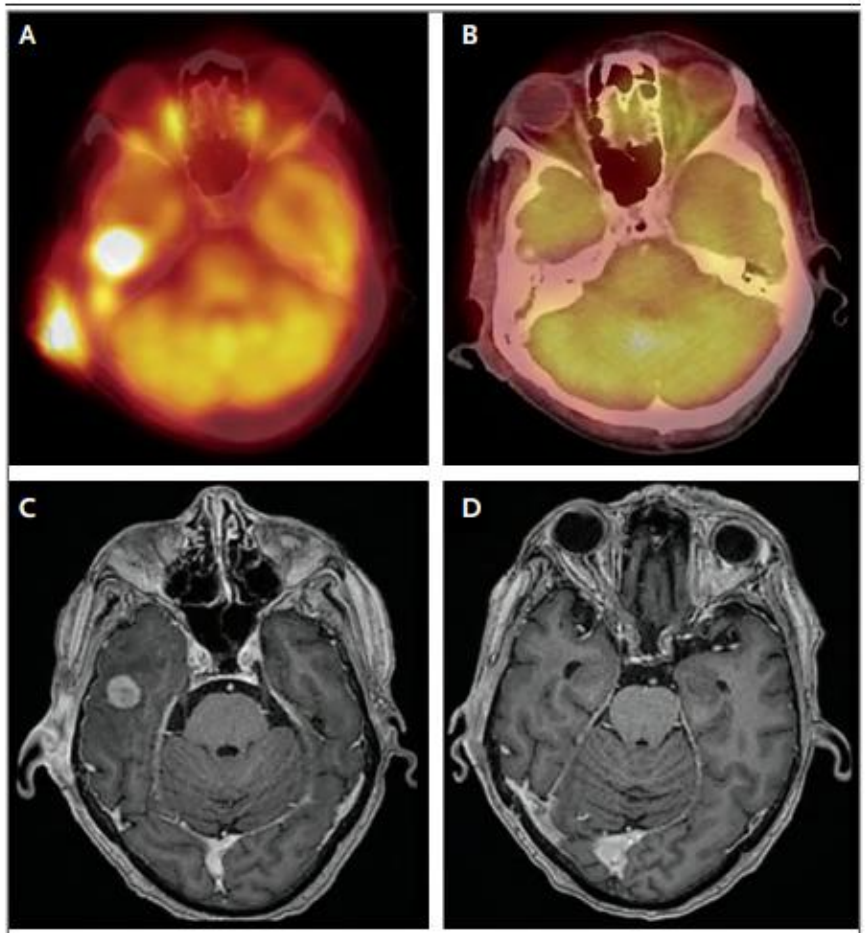


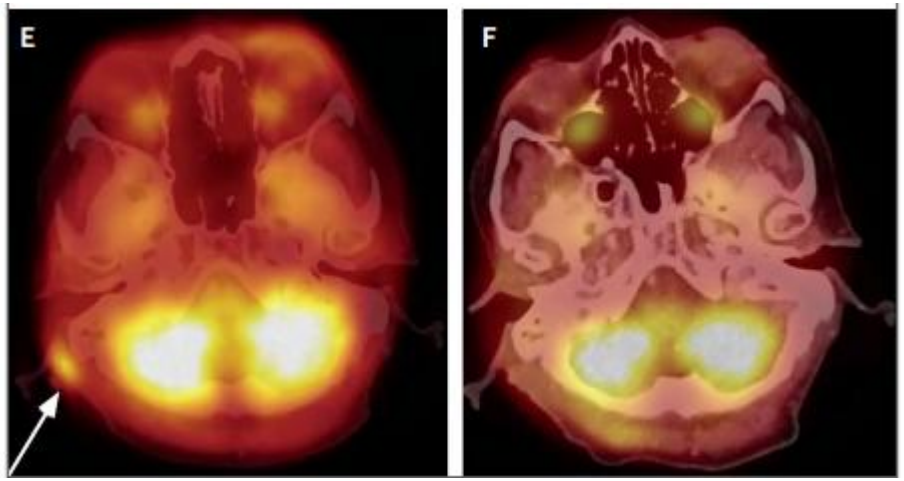
Molecular markers	Number of samples	H-score,mean (SD)	*p*-Value
P53			0.33
(+)	21	72.0 (104.9)	
(–)	11	38.6 (68.3)	
EGFR			0.57
(+)	19	24.0 (56.6)	
(–)	3	4.67 (5.03)	
IDH-1			0.003
Mutant	3	6.7 (11.5)	
Wild type	27	72.7 (99.1)	
Synaptophysin			0.45
(+)	4	48.8 (87.6)	
(–)	9	101.8 (122.1)	
MGMT			0.002
Methylated	3	5.0 (5.0)	
Unmethylated	23	78.0 (99.6)	

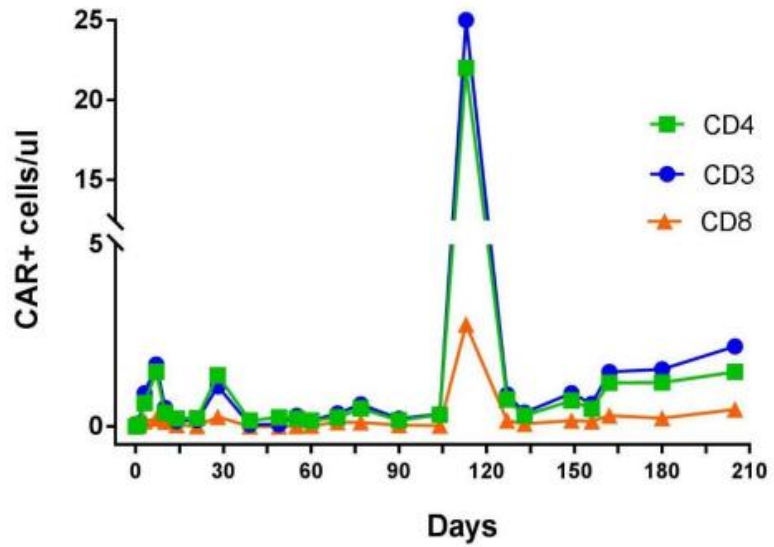
Recurrent MG
5/10 (+)

Anti-CD19 CAR T Cells in CNS Diffuse Large-B-Cell Lymphoma

The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 377;8 NEJM.ORG AUGUST 24, 2017





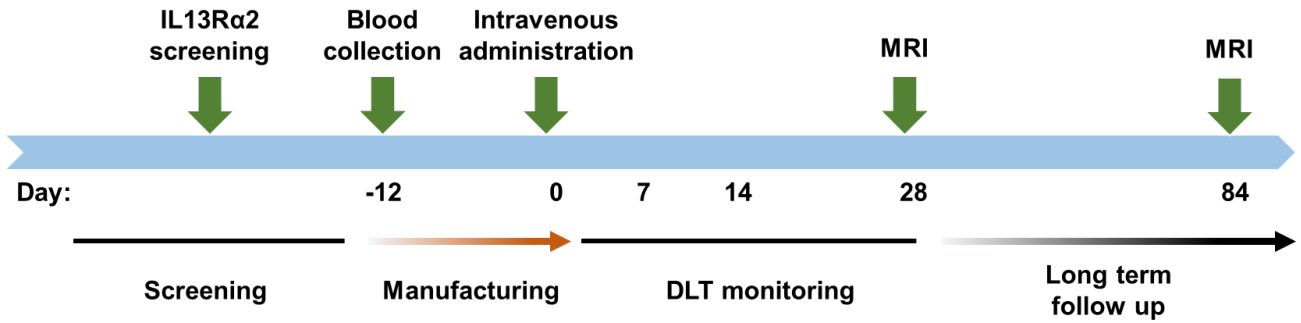


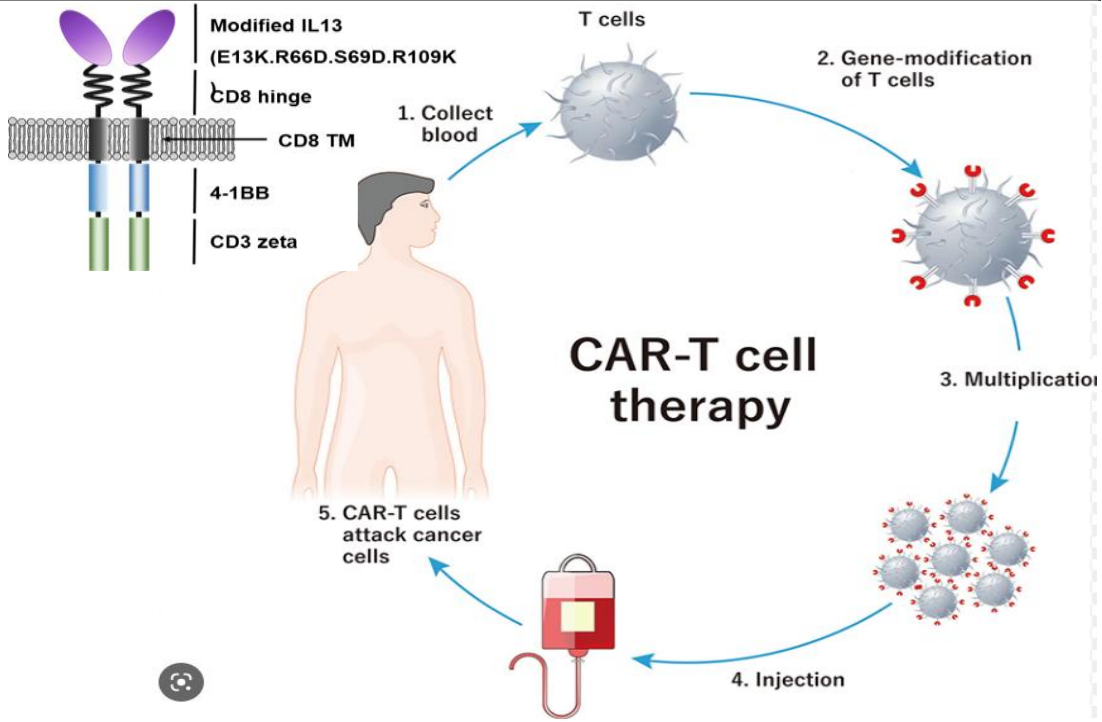
"We have identified anti-CD19 CAR T cells in the CSF, confirming the ability of these cells to cross the BBB…"

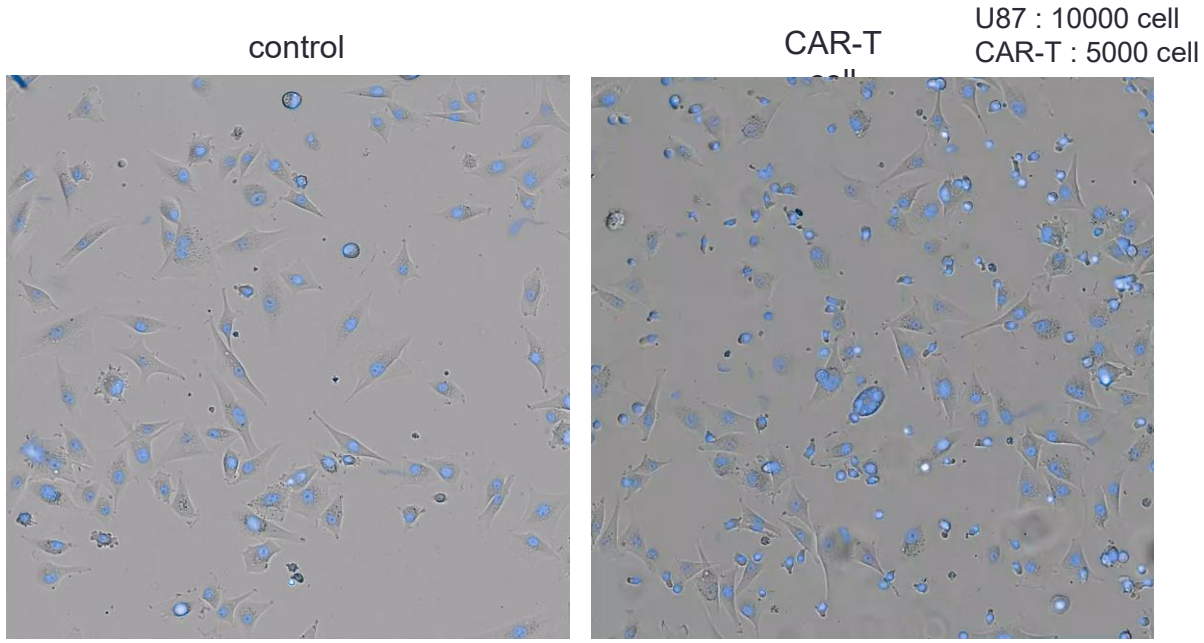
임상시험 제목	표준요법에 불응한 또는 재발성 악성 뇌교종 환자를 대상으로 **IL13Rα2** 특이적 Chimeric Antigen Receptor-T Cell **(CAR-T) YYB-103**의 안전성 및 내약성을 평가하기 위한 단일기관, 단일군, 공개, **제 1상** 임상시험 A Single-center, Single-arm, Open-Label Phase 1 Clinical Trial to Assess the Safety and Tolerability of YYB-103, IL13Rα2 Targeted Chimeric Antigen Receptor-T Cell (CAR-T) in Treating Patients with Refractory or Recurrent Malignant Glioma
임상시험 기간	Enroll기준 2022-11-02 ~ 2024-05-07 (1년 6개월)

3 + 3 design	시험대상자 수
1단계 ($1.0x10^7$ cells/kg)	3 + 1명
2단계 ($3.0x10^7$ cells/kg)	3명
3단계 ($1.0x10^8$ cells/kg)	3명

< Protocol schema>







- Fresh (not frozen) CAR-T
- IP intravenous injection (100 mL, over 1h at RT)

< Patients flow in trial>

Screened (signed consent) (*n*=39)

Excluded
- IHC (-) for IL13Ra2 (*n*=13)
- Exclusion criteria (*n*=11)
- Withdrawal of consent by the subject (*n*=5)

Enrolled / Treated (*n*=10)

Cohort 1 ($1.0x10^7$ cells/kg) (*n*=3+1)

Cohort 2 ($3.0x10^7$ cells/kg) (*n*=3)

Cohort 3 ($1.0x10^8$ cells/kg) (*n*=3)

Inclusion criteria

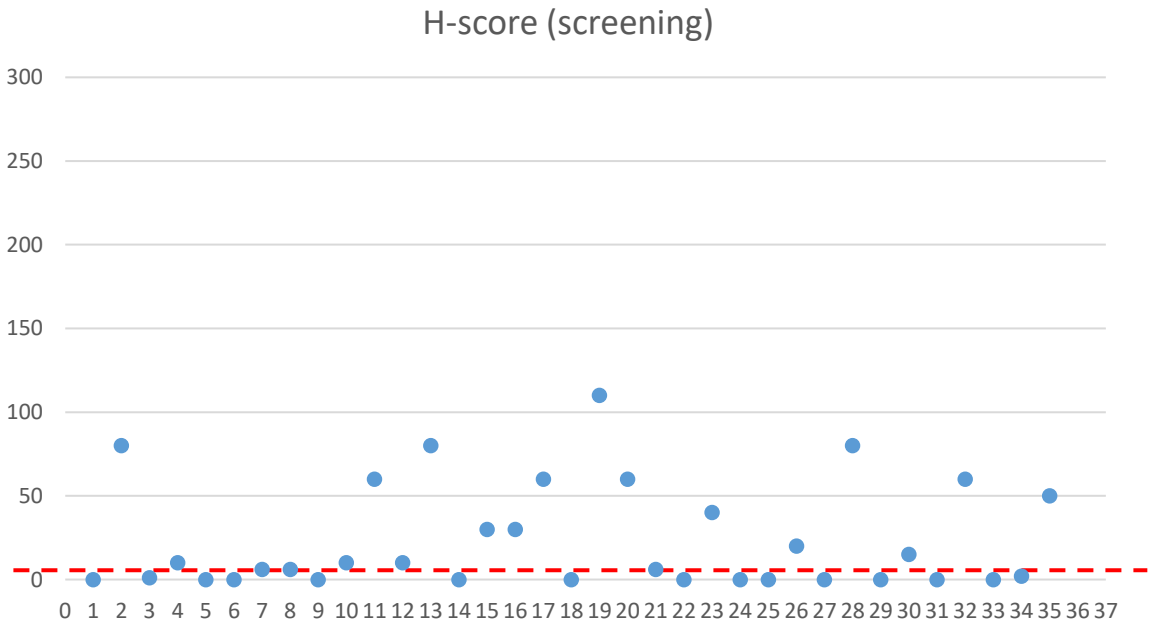
1차 선정기준 (Screening Criteria, 방문 1, D-19)
: 아래의 모든 조건에 부합되는 대상자에 한해 이 시점에서 IHC 및 PBMC를 포함한 검진 및 검사를 실시

1. 본 임상시험 참여에 **자발적으로 서면동의**한 자
2. **만 19세 이상 만 75세 미만**의 남·녀
3. 조직학적으로 혹은 세포학적으로 확인된 **진행성 악성 뇌교종 환자**(WHO 기준에 따라 Grade Ⅲ 또는 Ⅳ)로 각 단계별 표준치료에 해당하는 치료를 받았음에도 불구하고 불응 또는 재발(미국신경종양학회(Society for Neuro-Oncology)에서 정의한 Response Assessment for Neuro-Oncology(RANO) criteria for high grade gliomas를 기준으로 "Progression Disease(PD)'에 해당하는 경우) 을 확인할 수 있는 조직학적 및/또는 영상학적 자료가 있는 자
4. 일상수행능력 척도 **Kamofsky Performance Status (KPS) Scale이 60 이상**인 자
5. 시험자 판단에 따른 대상자의 남은 **기대 수명이 최소 12주 이상**으로 예상되는 자

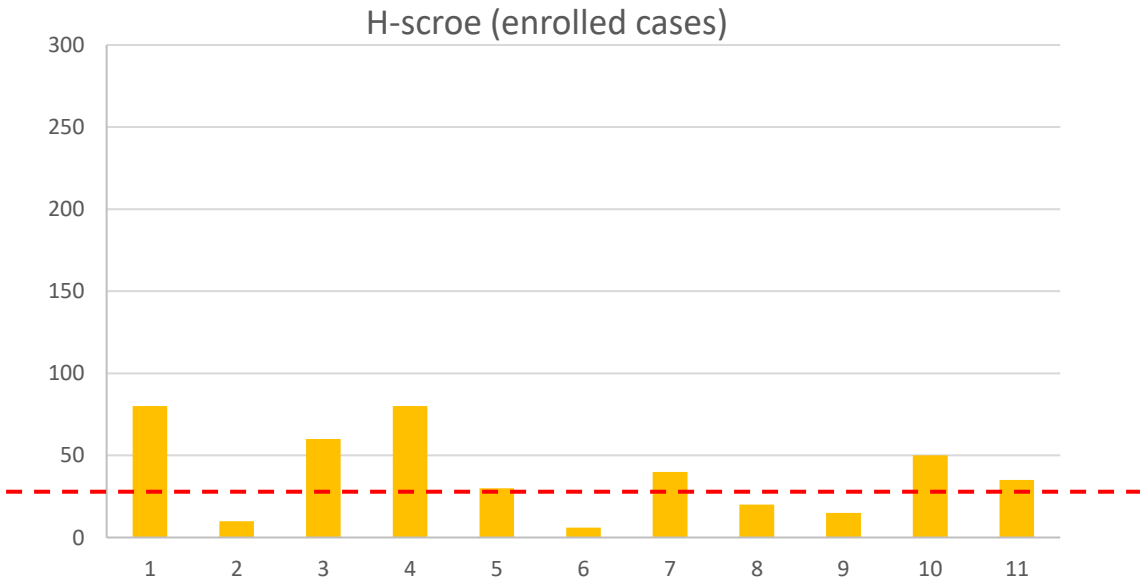
Immunohistochemistry of primary tumor > 1/ 300

IL13Ra2 screening

- Screening entry (*n*=39) => 3 failure (histology, PMHx and withdrawal)
- IHC (n=36) => IHC (-) exclusion (*n*=13) = 23
  => other exclusion criteria (+) (*n*=13)



- **IHC (-) = 13/36 (34%)**
- Median = 6/300 (range 0-80)



- Median = 35/300 (range 6-80)
- Mean = 39.1

Exclusion criteria

5. 이전의 치료이력의 차수와 상관 없이 다음의 치료 조건을 만족하는 자

- 최종 진행된 **방사선 치료 완료 후 최소 12주**가 지난 자
- 상기 언급되지 않은 **기타 세포 독성 요법** : **최소 3주**가 경과된 자
- **비세포독성제**(예, 인터페론, 타목시펜 등) : **최소 1주**가 경과된 자
- 이전 치료로 인해 발생하는 **독성 및 이상반응(탈모 및 백반증은 제외)이 모두 치료가 완료**된 자

1. 스크리닝 시점에 확보된 영상학적 검사에서 **뇌실의 파종성 전이(ventricular seeding), 척수 내 전이(spinal drop metastasis), 연수막 전이(leptomeningeal metastasis)가 진단**된 자
2. **면역 결핍, 자가 면역질환** 또는 **염증성 질환의 소견**이 있는 자
3. 다음을 포함한 **유의한 활성 심장 혈관 질환**을 가진 자

- 조절되지 않는 고혈압 (SBP > 180mmHg 또는 DBP > 110mmHg), 불안정형 협심증, 폐색전증, 뇌혈관 질환, 판막증, 심부전, 혹은 지난 6개월 이내에 발생한 심근 경색 또는 중대한 심장성 부정맥

4. 스크리닝 기준 **5년 이내 임상시험 대상질환 이외의 악성종양의 기왕력**이 있는 자 (적절히 치료된 자궁경부, 상피내암, 기저 또는 편평세포 피부암, 국소 전립선암, 유방관 상피내암 등)의 경우 스크리닝 기준 3년 이내)

High dose dexamethasone > 6 mg/ day

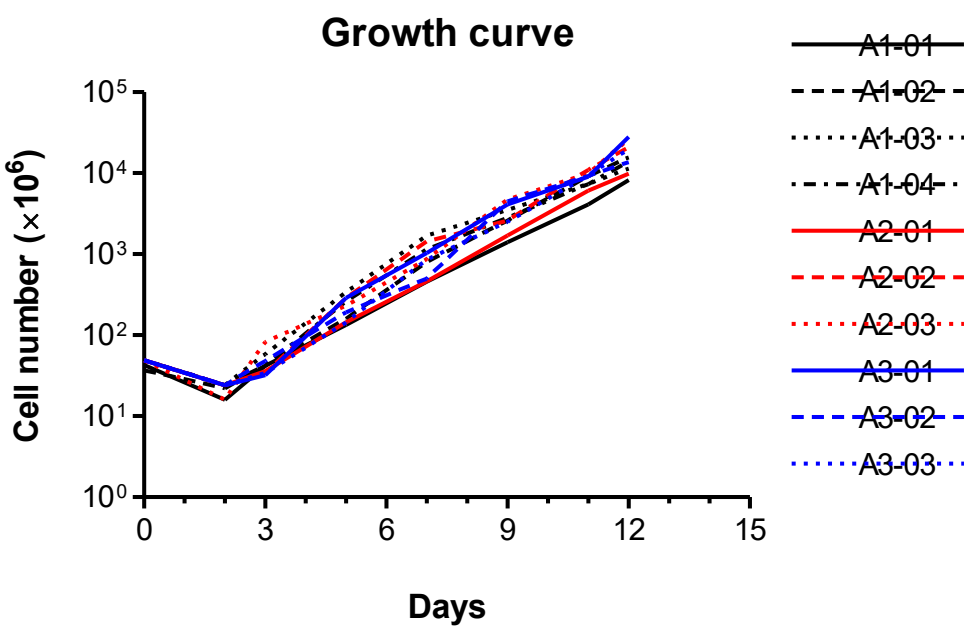
Baseline patients characteristics

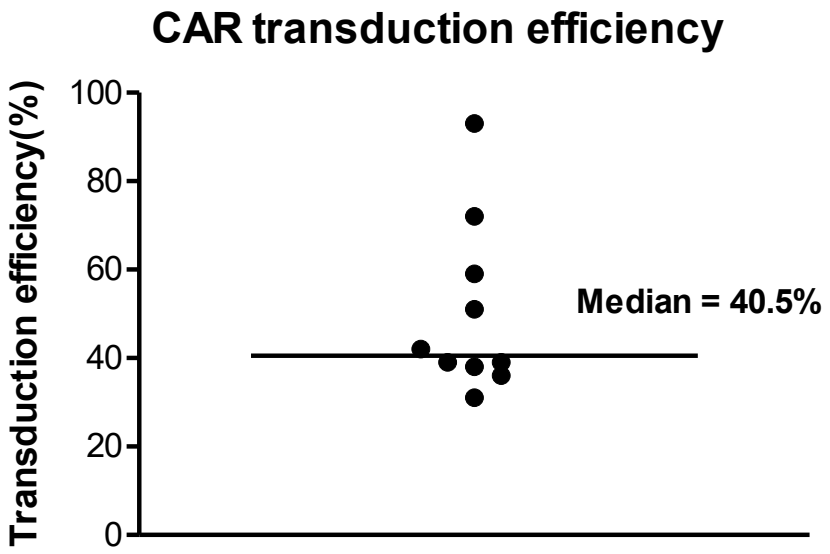
	Cohort 1 ($1.0x10^7$ cells/kg) (*n*=4)	Cohort 2 ($3.0x10^7$ cells/kg) (*n*=3)	Cohort 3 ($1.0x10^8$ cells/kg) (*n*=3)	Total (*n*=10)
Age (years old)				
Median	54.0 (49.0-60.0)	45.0 (39.0-55.0)	47.0 (42.0-48.0)	48.5 (39.0-60.0)
Sex, n(%)				
Male	3	2	2	7 (70)
Female	1	1	1	3 (30)
KPS at baseline,				
Median (range)	65 (50-70)	70 (60-80)	80 (60-90)	70 (50-90)
WHO grade				
3	1	0	0	1(10)
4	3	3	3	9(90)
IL13Rα2 H-score				
Median (range)	70 (10-80)	30 (6-40)	20 (15-50)	35 (6-80)
Multifocal	1	2	1	4 (40)
[a]Tumor size				
Median (range)	1353 (560-2925)	45 (40-682)	2556 (180-4284)	903 (40-4284)
Recurrence				
First	1	1	1	3 (30)
Second	1	1	-	2 (20)
Third or more	2	1	2	5 (50)
Steroid use as baseline	3	1	1	6 (50)
Prior Temozolomide	4	3	3	10 (100)
Prior Bevacizumab	2	3	1	6 (60)

*Sum of product of perpendicular diameter (refer to RANO 2.0)
*Max tumor d = mean 3.4 cm

Supplementary table 3. Release criteria and selected batch attributes of YYB-103 products administered to each patient

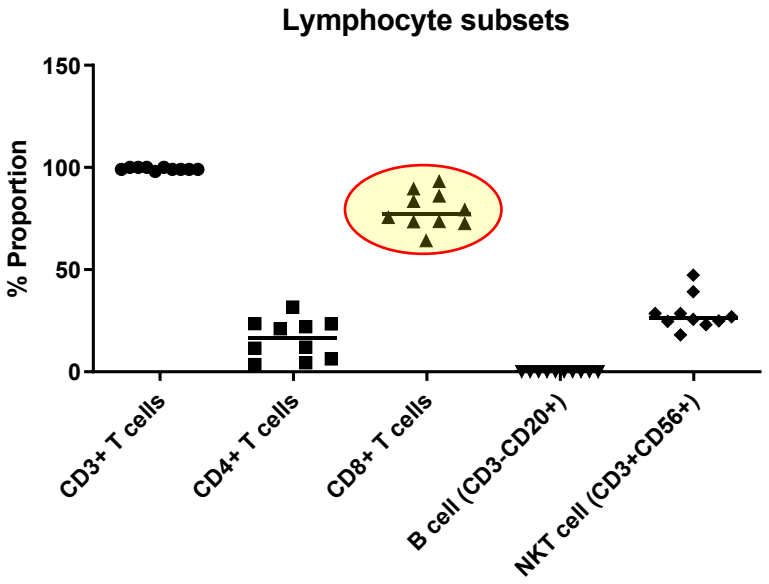
Test parameter	Release criteria	A1-01	A1-02	A1-03	A1-04	A2-01	A2-02	A2-03	A3-01	A3-02	A3-03
Dose level (cells/kg)		1 × 10^7 / Kg	1 × 10^7 / Kg	1 × 10^7 / Kg	1 × 10^7 / Kg	3 × 10^7 / Kg	3 × 10^7 / Kg	3 × 10^7 / Kg	1 × 10^8 / Kg	1 × 10^8 / Kg	1 × 10^8 / Kg
Infused cell number (Total viable cells)	N/A	6.7 × 10^8	5.4 × 10^8	5.6 × 10^8	7.8 × 10^8	1.6 × 10^9	2.6 × 10^9	2.9 × 10^9	7.3 × 10^9	5.2 × 10^9	7.8 × 10^9
Infused CAR⁺ cells		4.0 × 10^8	1.7 × 10^8	2.1 × 10^8	3.0 × 10^8	1.5 × 10^9	0.9 × 10^9	1.2 × 10^9	2.8 × 10^9	3.7 × 10^9	4.0 × 10^9
Cell viability (%)	> 75%	94	96	95	96	97	97	97	95	96	95
CD3+ (%)	> 95%	98	100	99	99	99	99	100	100	100	99
CAR⁺ cells (%)	> 10%	59	31	38	39	93	36	42	39	72	51
Relative cytotoxicity (%)	> 25%	42.7	30.0	42.6	25.9	30.3	58.7	63.4	56.7	36.4	30.8
Vector copy number (copies/cell)	< 4 copies/cell	1.9	1.2	1.3	1.0	3.0	1.1	1.2	3.0	3.8	3.2

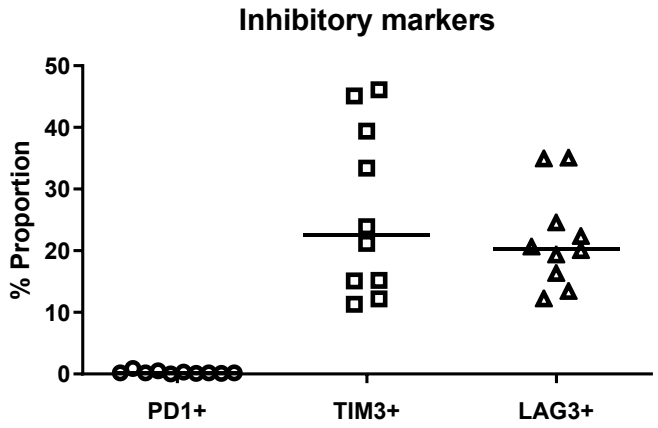


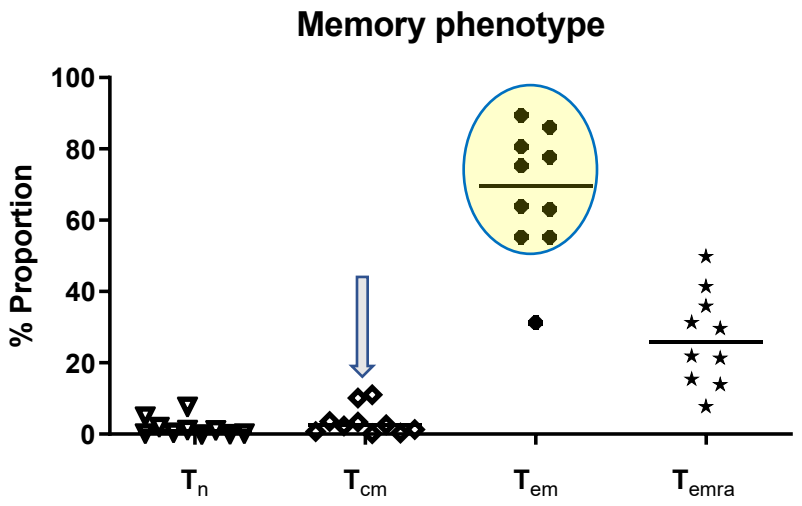


Supplementary table 4. Immunophenotypic composition of YYB-103 products administered to each patient

Patient	CD3+ (%)	CD4+ (%)	CD8+ (%)	B cell (%) (CD3-CD20+)	NKT cell (%) (CD3+CD56+)	PD1 (%) (CD3+PD1+)	TIM3 (%) (CD3+TIM3+)	LAG3 (%) (CD3+LAG3+)	Naïve T cells (%) (CD45RA+CCR7+)	Tcm (%) (CD45RA-CCR7+)	Tem (%) (CD45RA-CCR7-)	Temra (%) (CD45RA+CCR7-)
A1-01	98	6.3	86.0	0.0	28.5	0.3	15.2	20.0	5.0	10.1	55.3	29.6
A1-02	100	12.1	83.4	0.0	18.0	0.1	23.9	12.2	7.8	11.0	31.3	49.8
A1-03	99	21.1	75.5	0.0	28.6	0.9	45.1	20.6	2.1	1.3	55.2	41.4
A1-04	99	23.4	73.5	0.0	23.0	0.5	33.4	19.3	1.3	3.5	63.9	31.3
A2-01	99	3.6	93.2	0.0	47.3	0.2	46.1	16.3	1.2	2.3	75.2	21.3
A2-02	99	23.6	72.5	0.0	25.7	0.2	21.2	22.3	0.5	3.4	80.6	15.4
A2-03	100	11.5	79.3	0.0	24.9	0.1	11.3	35.0	0.0	0.1	86.0	13.9
A3-01	100	4.4	89.6	0.0	39.2	0.0	15.1	24.5	0.3	2.6	89.4	7.7
A3-02	100	31.7	64.2	0.0	26.9	0.2	39.4	34.9	0.1	0.3	77.7	21.9
A3-03	99	22	73.4	0.0	24.7	0.2	12.2	13.4	0.3	0.7	63.0	35.9
Median	99	16.6	77.4	0	26.3	0.2	22.55	20.3	0.85	2.45	69.55	25.75
Min	98	3.6	64.2	0	18	0	11.3	12.2	0	0.1	31.3	7.7
Max	100	31.7	93.2	0	47.3	0.9	46.1	35	7.8	11	89.4	49.8





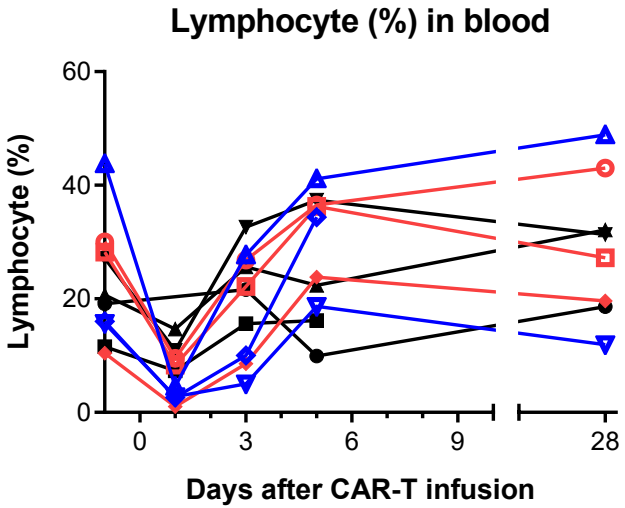


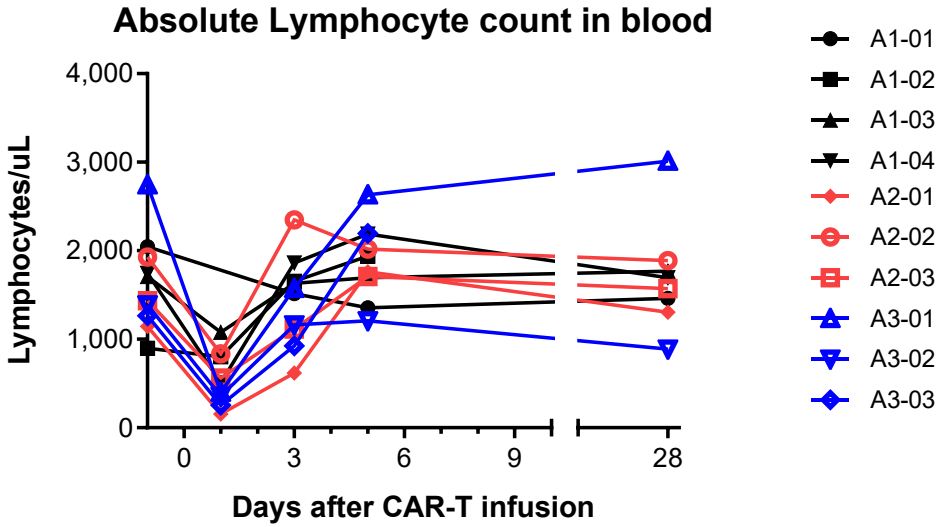
Treatment related Adverse events

	Cohort 1 (n = 4)	Cohort 2 (n = 3)	Cohort 3 (n = 3)	Total (n = 10)
Investigations (grade)				
AST/LT increased	2 (1, 3)	2 (1, 1)	3 (1, 1, 1)	7 (6 of 1, 3)
Thrombocytopenia	-	2 (1, 2)	2 (1, 1)	4 (3 of 1, 2)
Creatinine elevation			1 (1)	1 (1)
Fever	2 (1, [a]2)	3 (1, 1, 2)	3 (1, 2, 2)	8 (4 of 1, 4 of 2)
Nervous system disorders (grade)				
Headache		1(1)	2 (1, 1)	3 (3 of 1)
*Muscle weakness left-sided			1 (2)	1 (2)
*Seizure	1 (1)	1 (2)	1 (1)	3 (2 of 1, 3)
Gastrointestinal disorders (grade)				
Constipation			2 (1, 2)	2 (1, 2)
Diarrhea	1 (1)			1
Musculoskeletal and connective tissue disorders (grade)				
Joint range of motion decreased			1 (1)	1 (1)
Myalgia			1 (2)	1 (2)
Others (grade)				
*Hypertension		1 (3)		1 (3)
*Blurred vision			1 (2)	1
Hiccups	1 (2)			

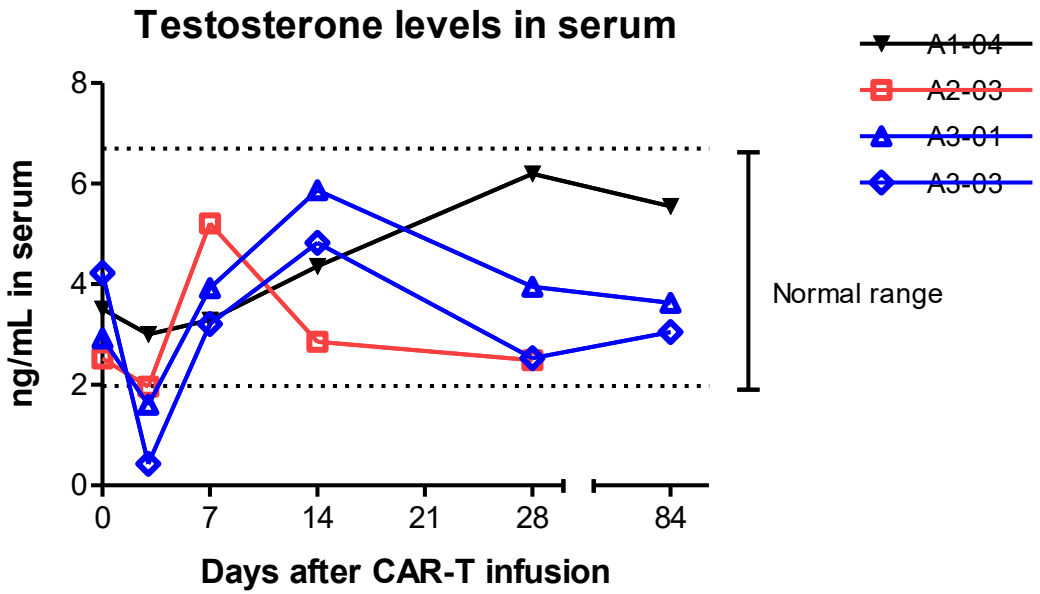
- No DLT (≤ G3, CTCAE v 4.0)
  - Pneumonia, unrelated
- No ICANS
- CRS
  - Pyrexia G3 (all cohort 3)
  - AST/LT elevation G3 (n=1)

Transient lymphopenia





On-target off-tumor



1st case Known Anaplastic ODG

=> RT w/o resection (2011년 2월~ 4월) 27회

=> 2011-06-29~10-12 TMZ

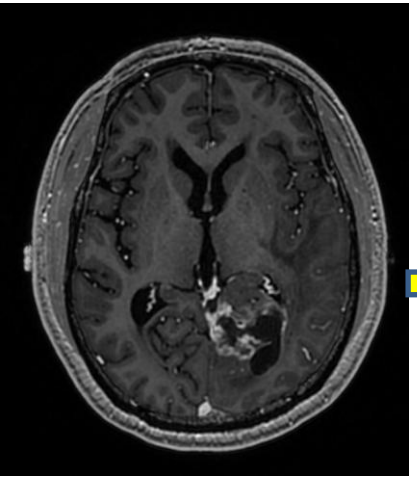
=> PD로 CK radiosurgery(2018-01-24)

=> s/p BEV # 10 cycles (2018-03-07~2020-02-03)

=> 2021-07-26 resection on progression: Bx Anaplastic ODG

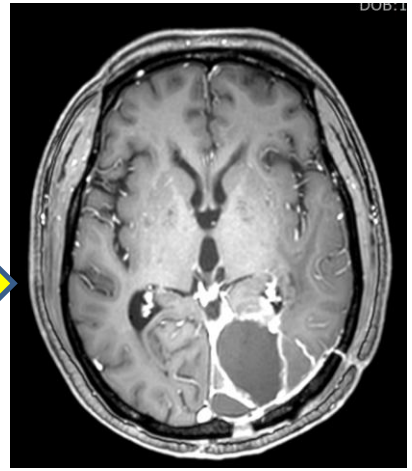
Screening & IP prep.

2021-07-25



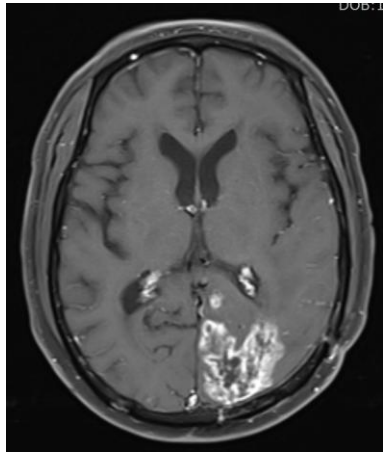
Craniotomy

Bx: AODG



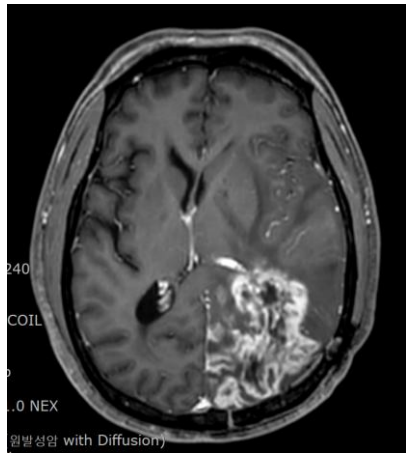
PCV#6

2022-08-29



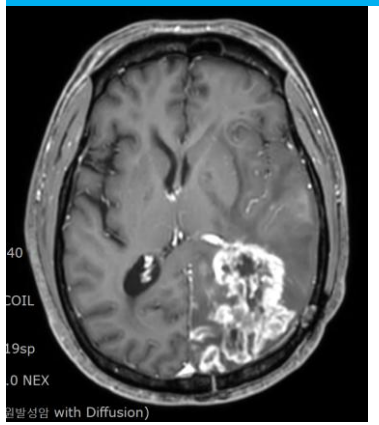
KPS 70 -> 60 (fall down, skull fracture)

2022-11-03 (D-1)



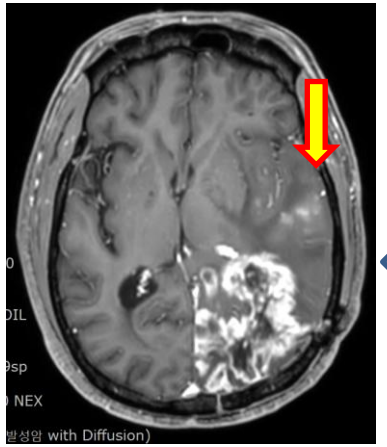
YYB-103 CAR-T (1.0x10^7 cells/kg)

2022-12-02 (D28)



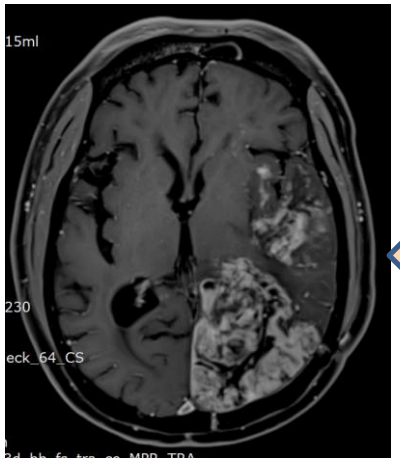
KPS 60 -> 70 (walk alone)

D84

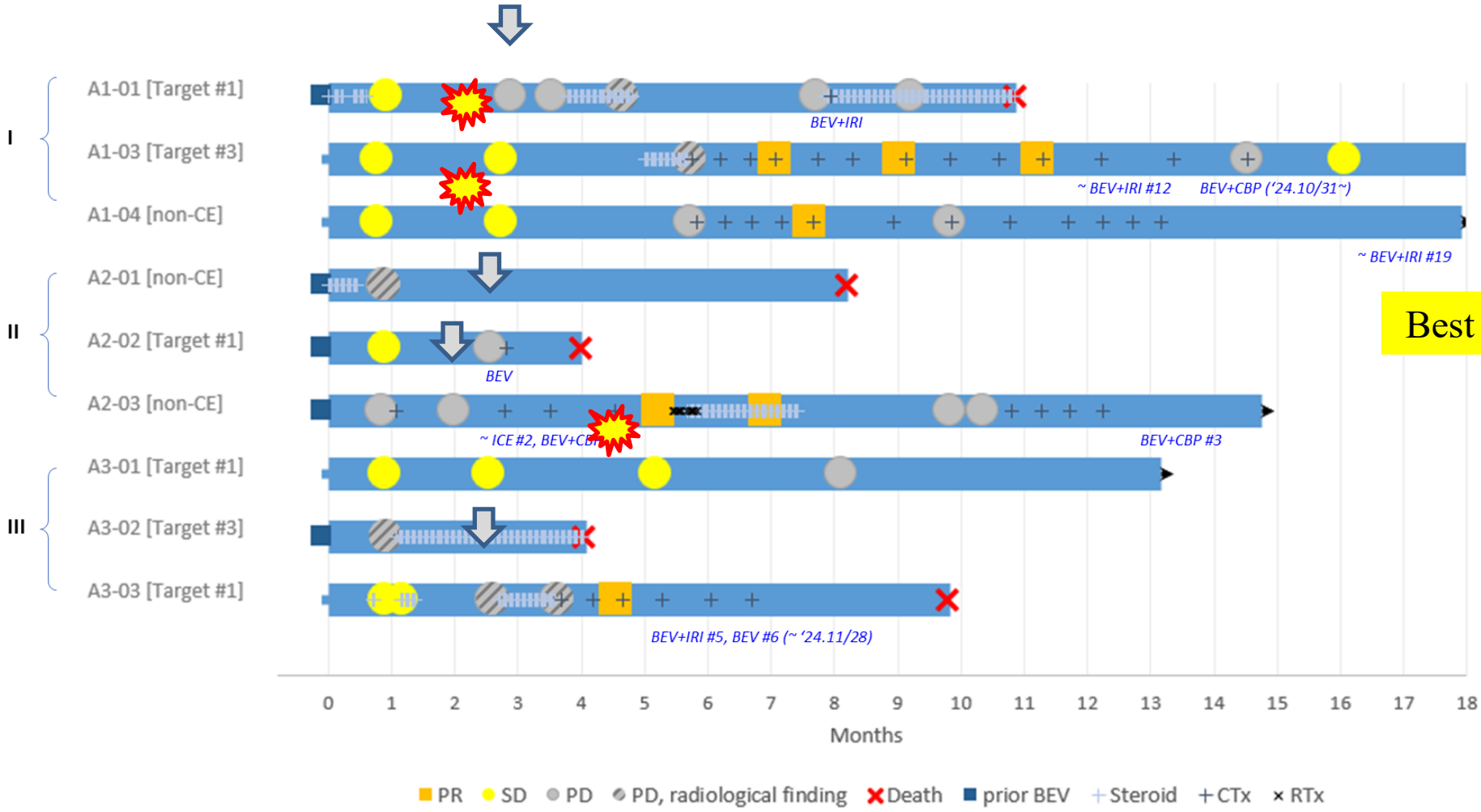


Patient still stable but new lesion

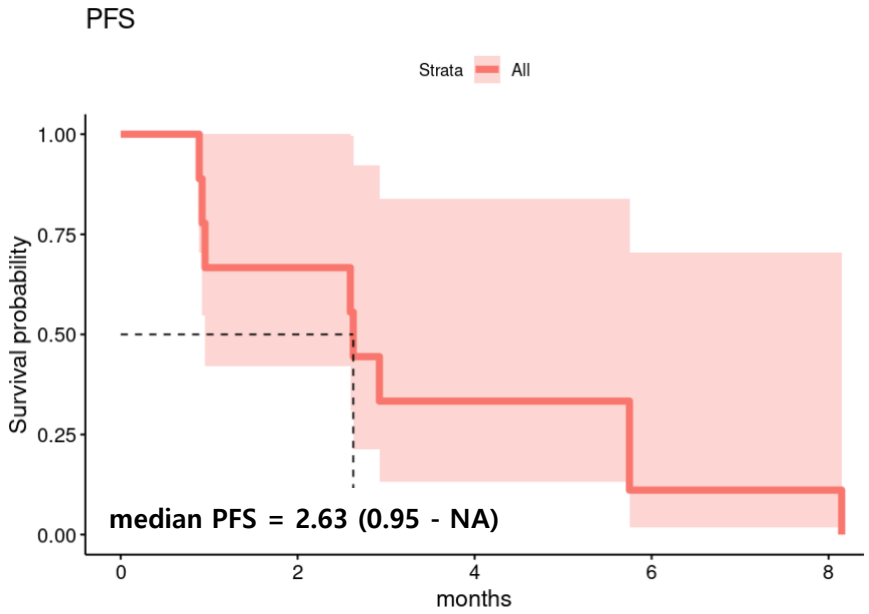
D238

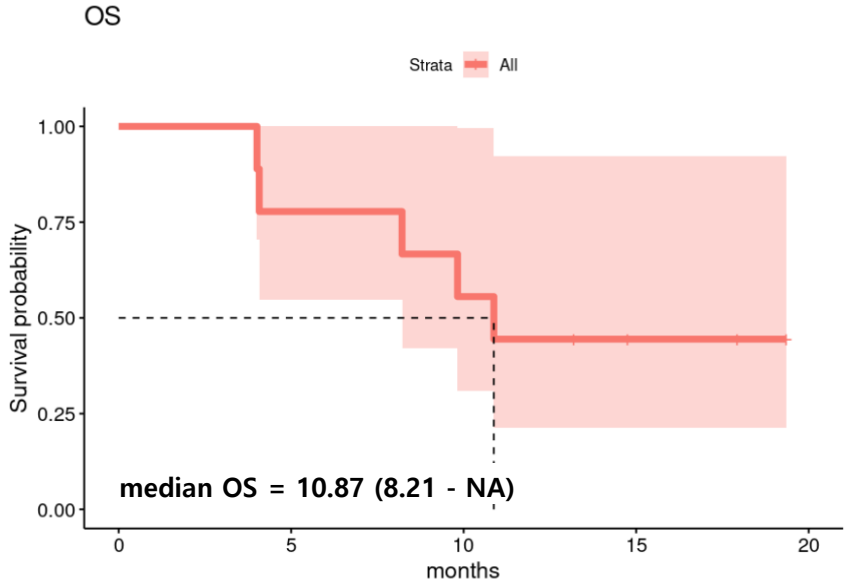


Tumor response (RANO 2.0)

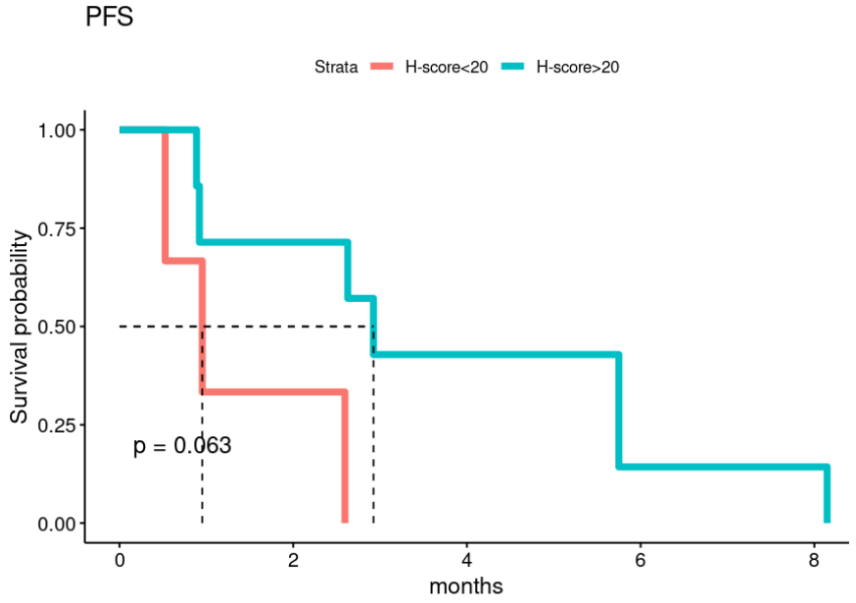


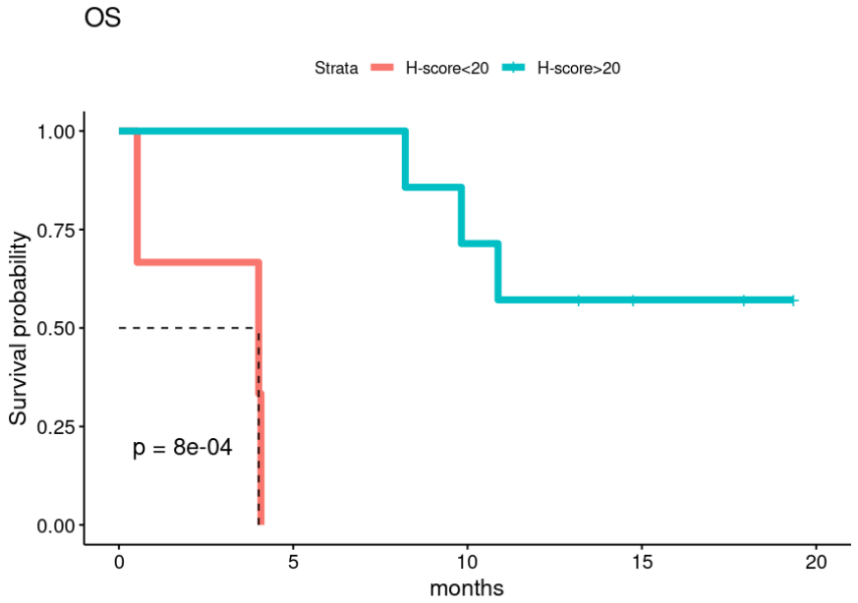
Best response; SD at 3 mos (3/6)





<Stratification according to H-score>





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https://doi.org/10.1007/s11060-018-2780-1

CLINICAL STUDY

Rechallenge with bevacizumab in patients with glioblastoma progressing off therapy

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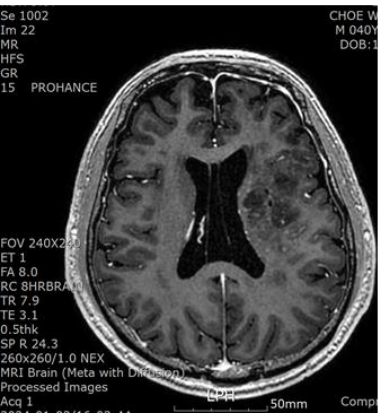
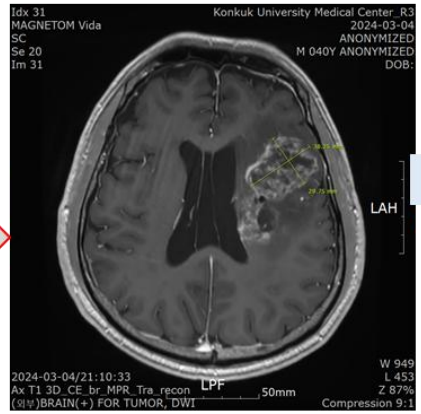
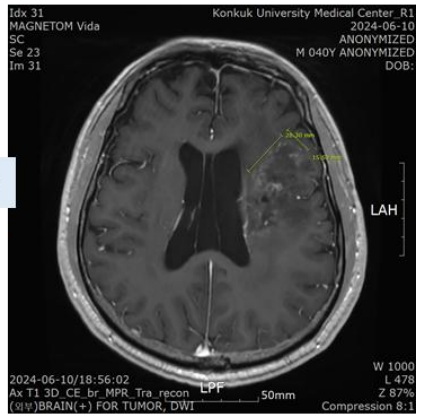
A2-03, Basal



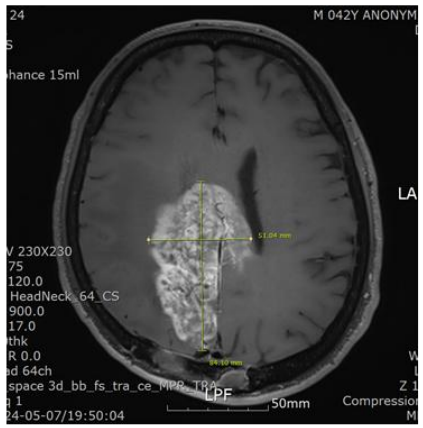
IP



BEV+CBP



A3-03, Basal



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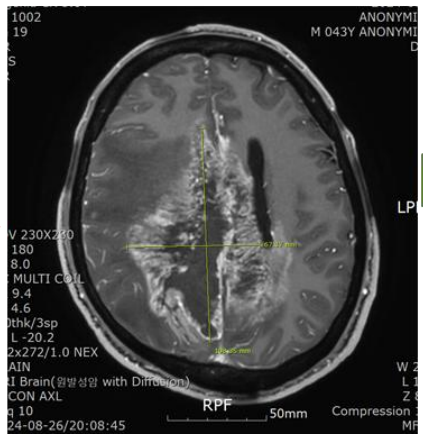
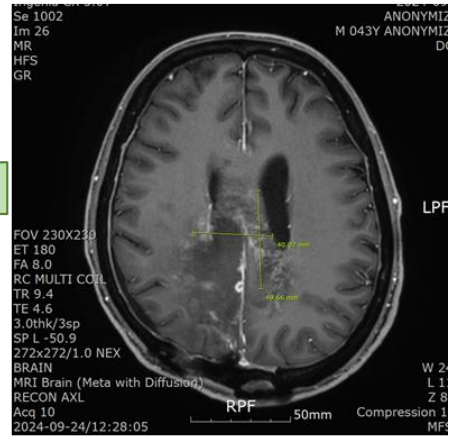
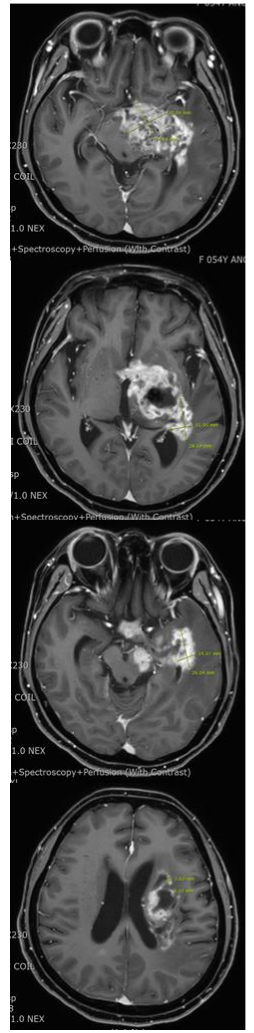


BEV+IRT



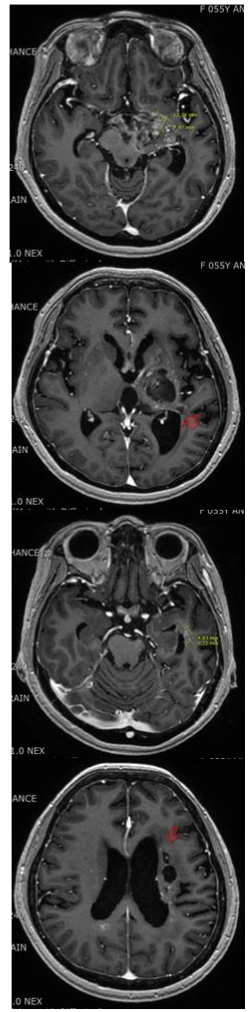
A2-01

D175



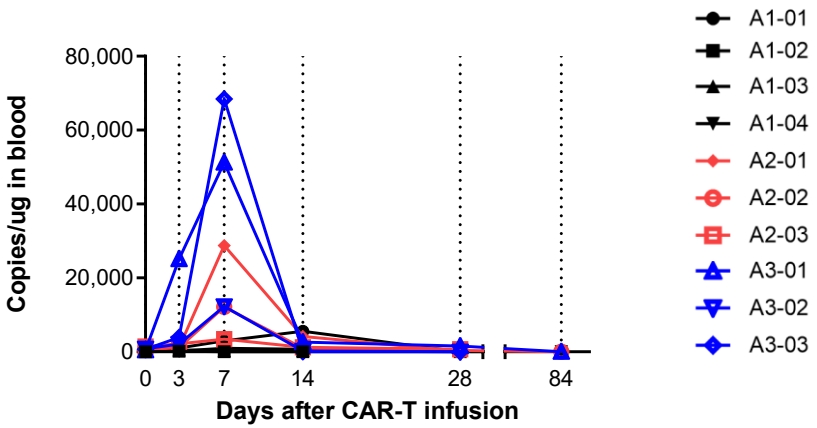
After 8 cycles of BEV + IRT

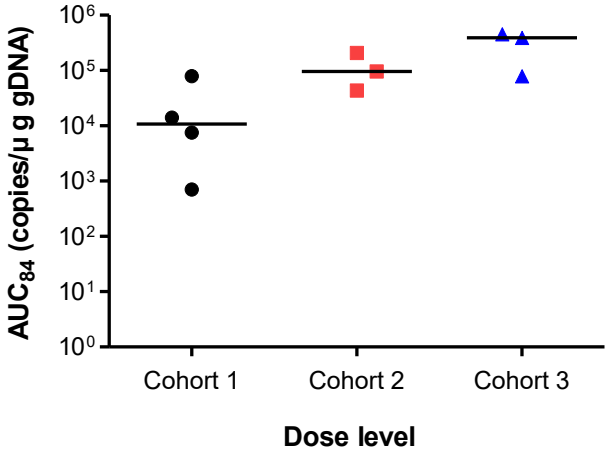
D343



YYB-103 CAR-T transgene

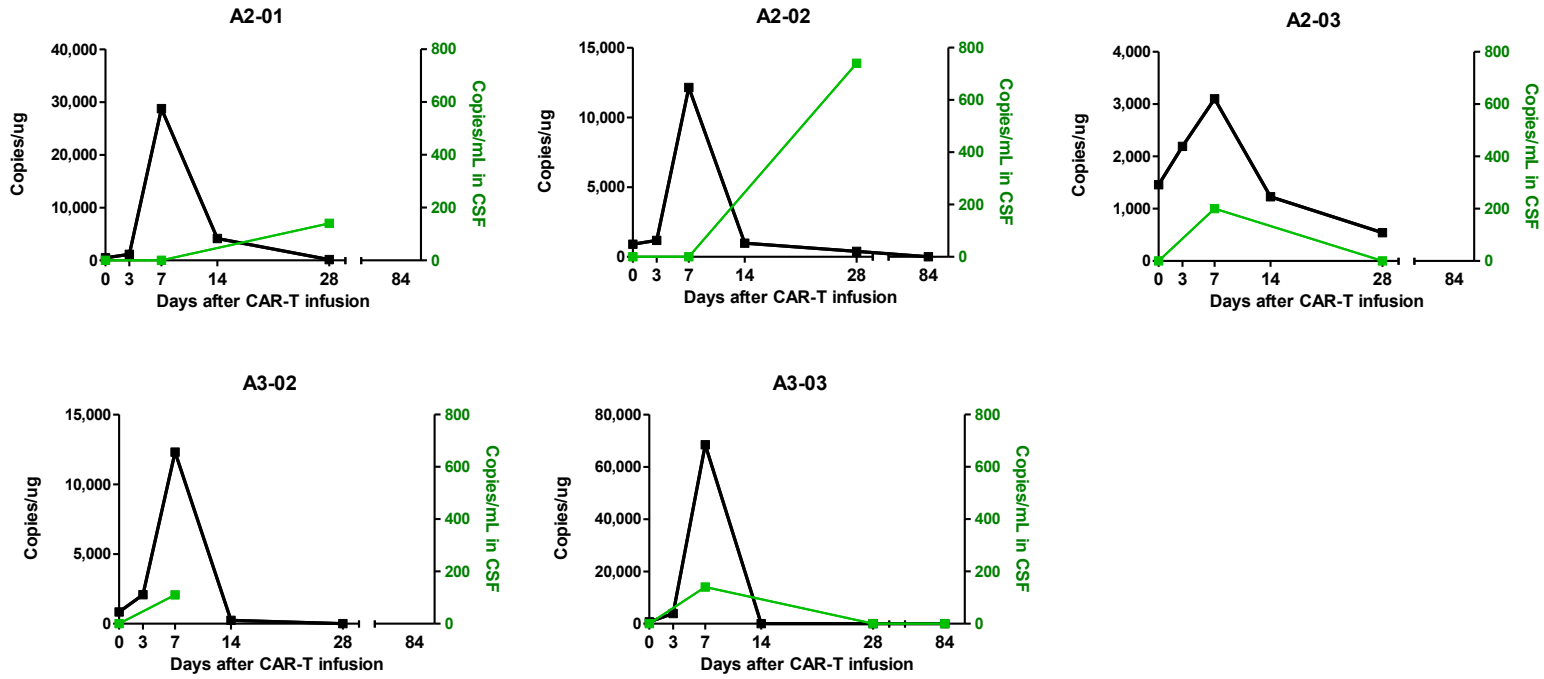
Serum

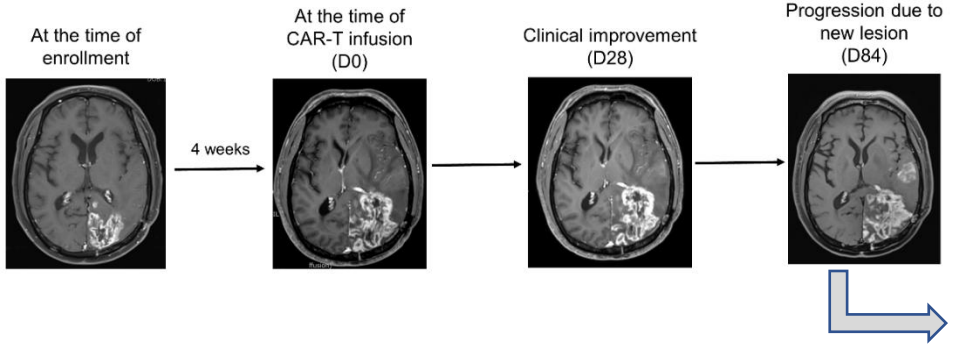




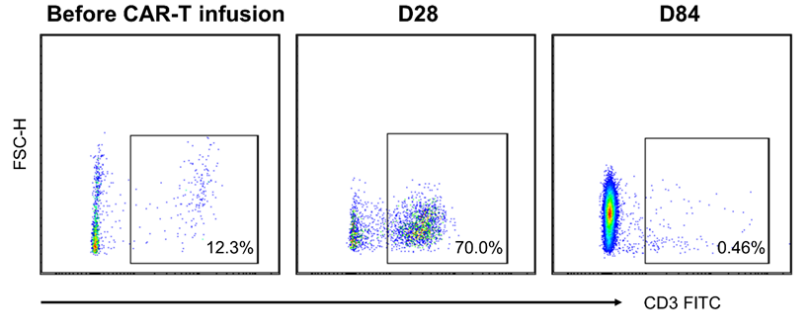
CSF

No CSF CAR-T at Cohort 1(1.0x10^7 cells/kg)

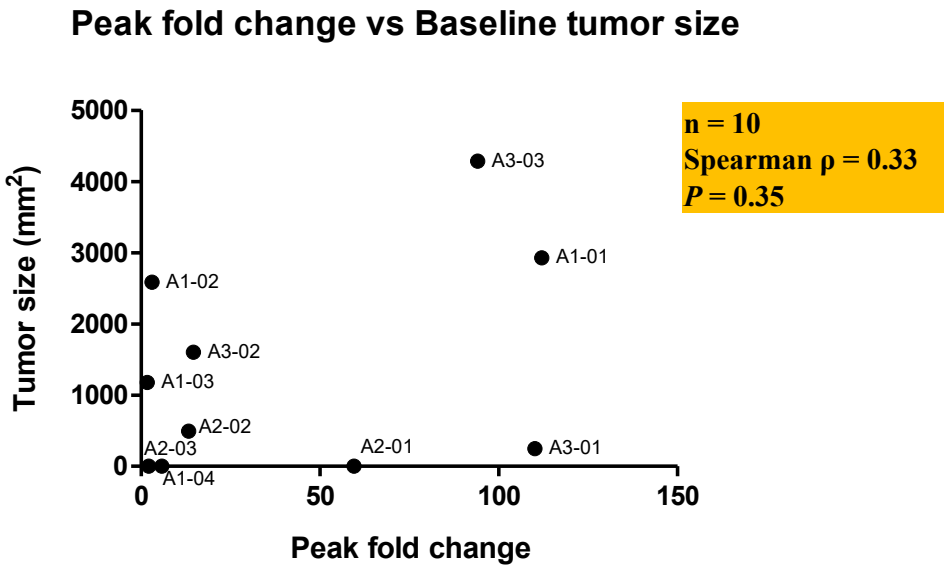




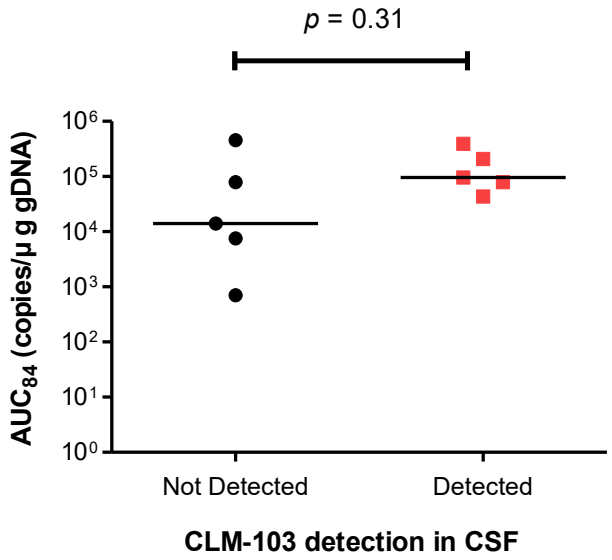
CSF *not* CAR-T *but* T cells



Exploratory correlation between peak fold change in peripheral blood and baseline tumor size

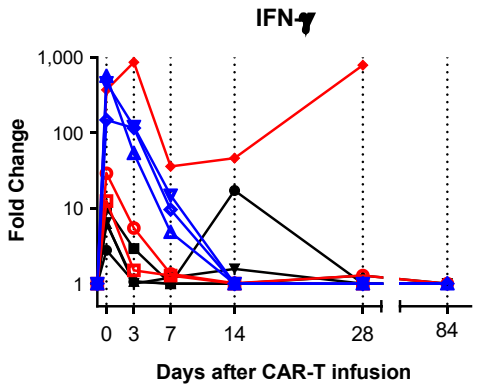


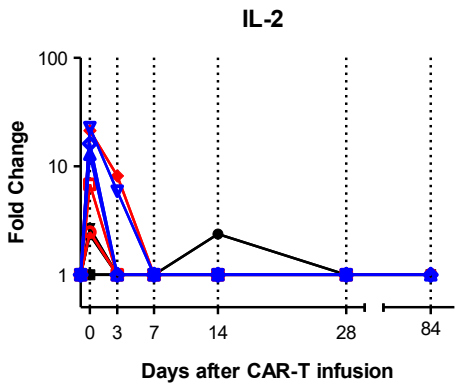
Peripheral blood AUC_{84} according to CSF detection status. Patients were stratified into CSF-detected and CSF-not-detected groups

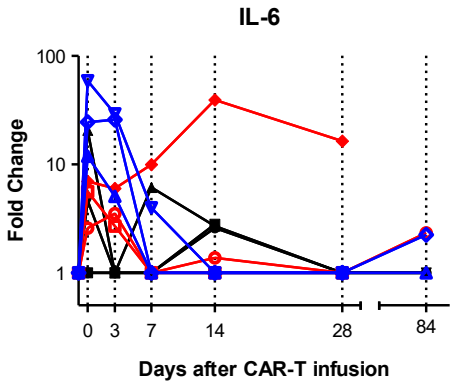


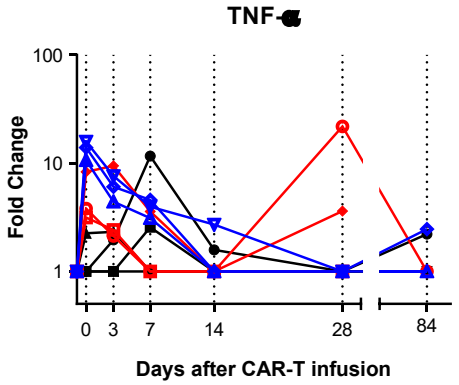
Cytokines

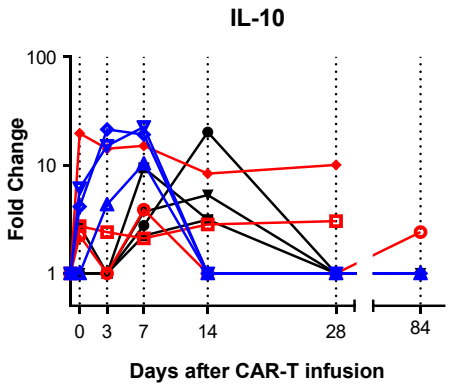
Serum



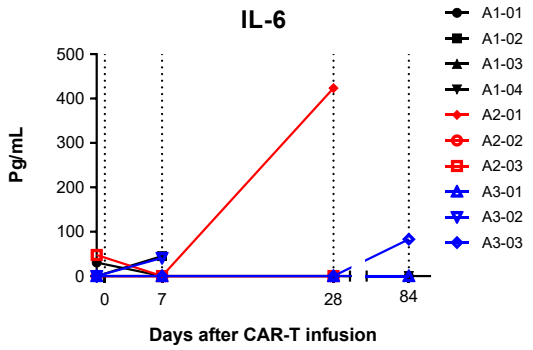


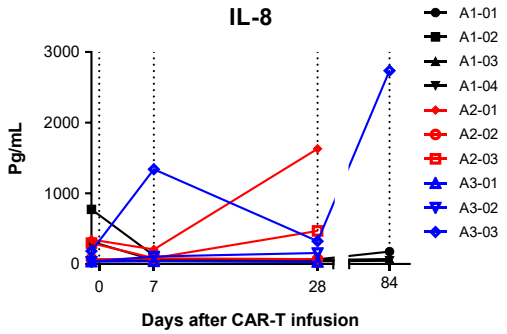






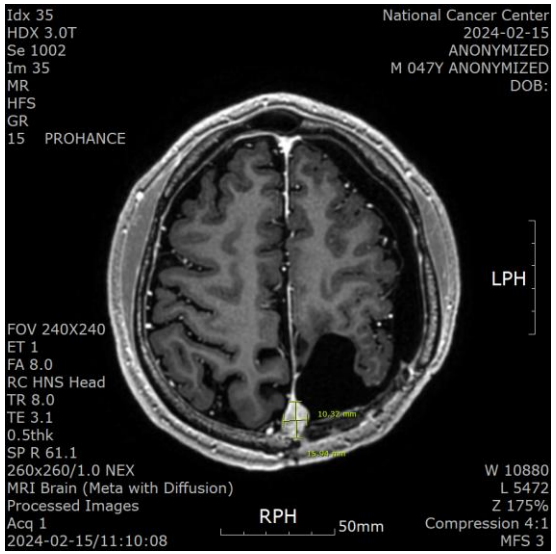
CSF



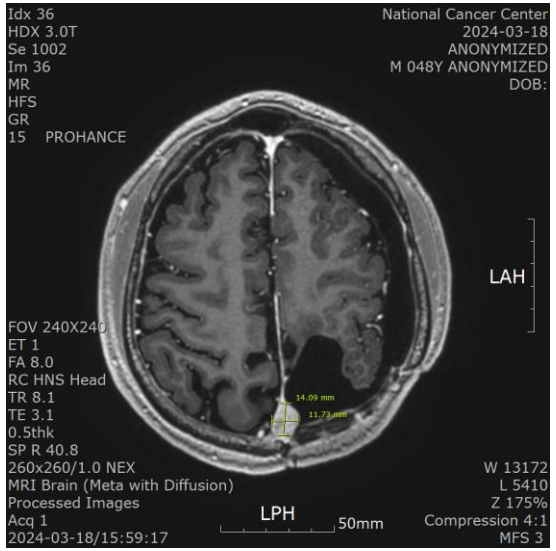


Ag depletion

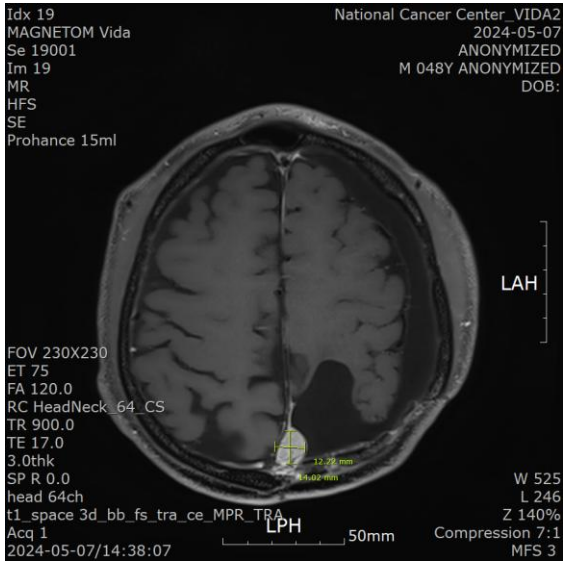
D-1



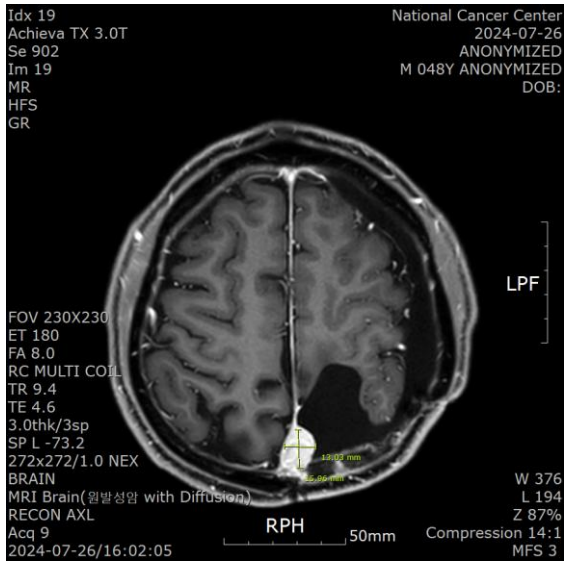
D28



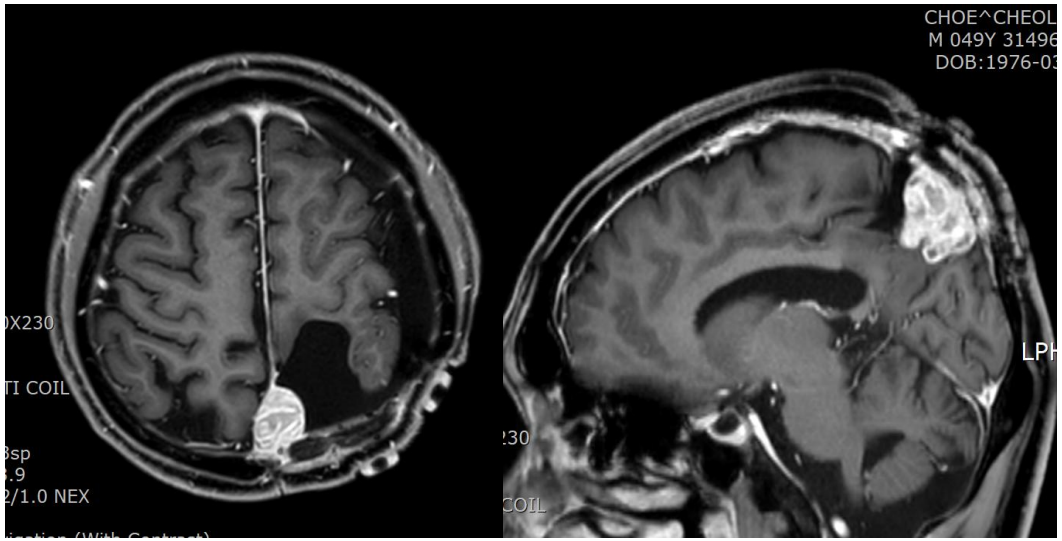
D84; SD

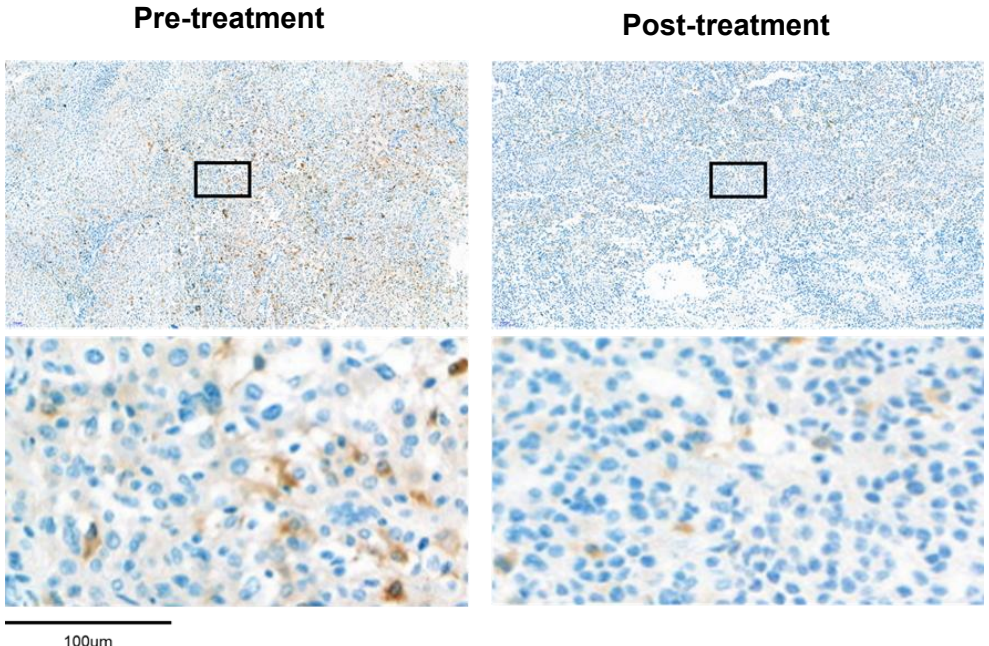


D158 => PD



D392 => craniotomy & removal





BERLIN 2025 ESMO congress

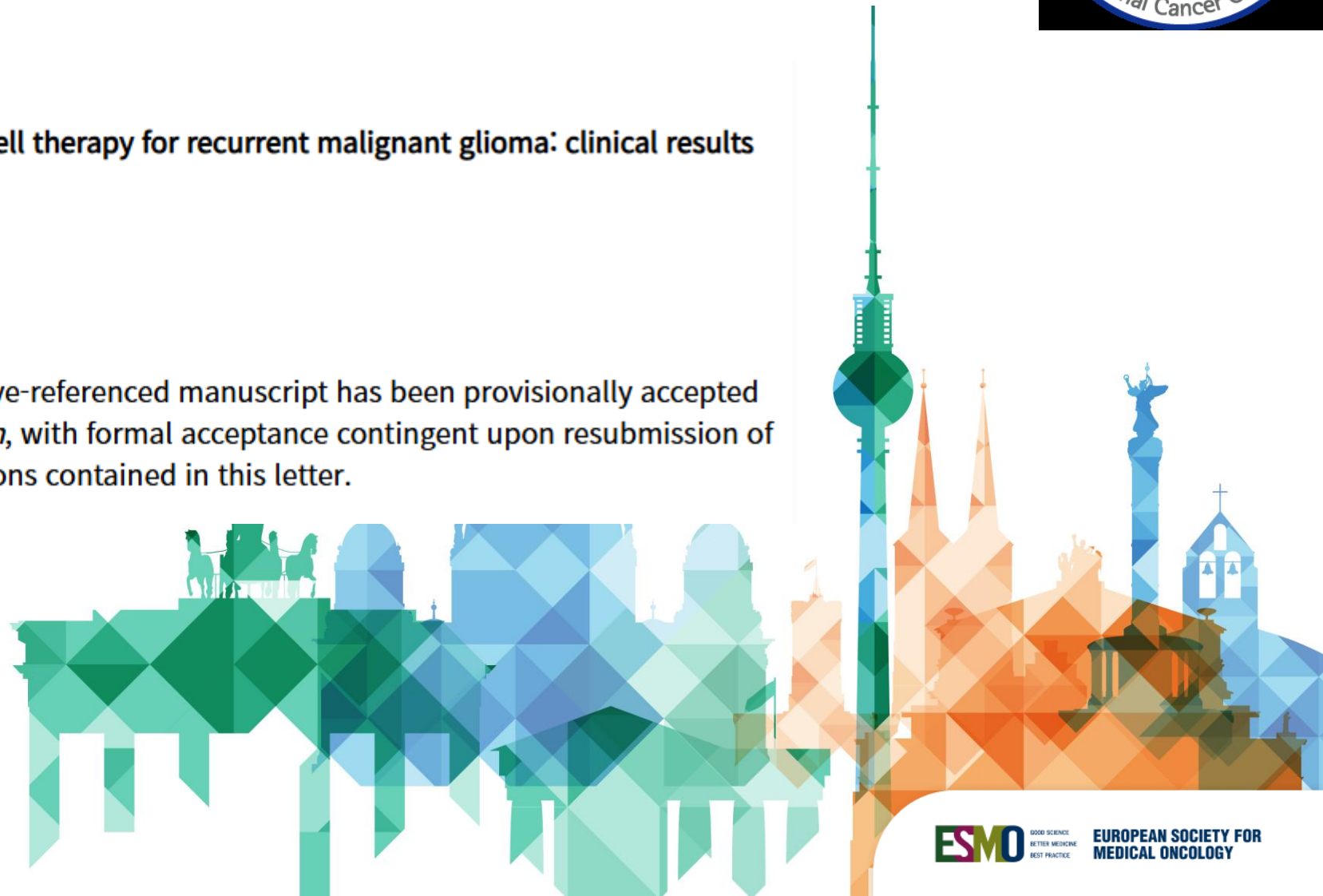
Graduate School of Cancer Science and Policy · National Cancer Center · GCSP NCC

Re: CCR-26-0645R

"Phase I trial of IL13Rα2-targeted CAR-T cell therapy for recurrent malignant glioma: clinical results and pharmacokinetics"

Dear Dr. Gwak:

I am pleased to inform you that your above-referenced manuscript has been provisionally accepted for publication in *Clinical Cancer Research*, with formal acceptance contingent upon resubmission of a final version that addresses all instructions contained in this letter.



국립암센터 NATIONAL CANCER CENTER

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

IL13Ra2 CAR-T Biomarker- IHC

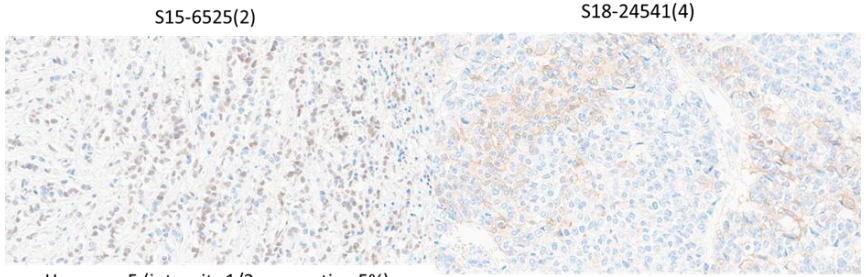
Problem

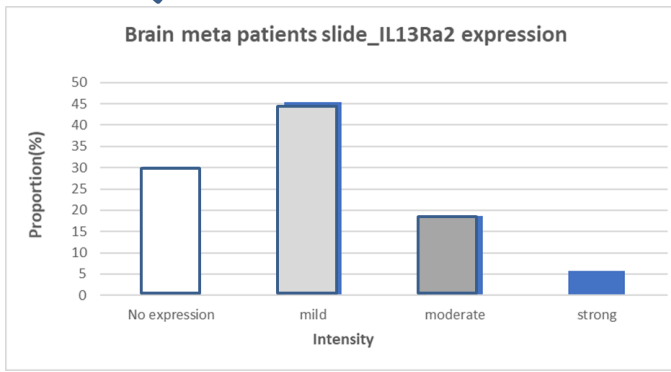
Trial include recurrent/ metastatic tumor
vs.
IHC from primary tissue

- IL13Ra2 (+) in BM RNA seq
  - Read 값이 0 이상인 sample 138/ 164 (84%)
  - Range; 10^6~$1.9x10^3$*

Need a biopsy of recurrent tumor?

- IL13Ra2 (+) is very low in NSCLC, breast ca.
  - Primary ca. IHC result (H-score)
  - NSLCL = 0/64, Breast ca. = 2/184





IL-13Rα2 expression	Number of samples (+)	Number of samples (-)	p-value
Gender			0.807
Female	68	14	
Male	70	13	
Age			0.816
< 60	80	15	
≥ 60	58	12	
KPS			0.250
≤ 60	15	1	
≥ 70	123	26	
RPA class			0.249
I	21	4	
II	102	22	
III	15	1	
Primary cancer			0.504
Breast	20	5	
Lung	80	11	
Others	38	11	
Primary cancer stage			0.191
Early (I)	10	2	
Advanced (II/III/IV)	107	17	
Time to brain metastasis			0.229
≤ 12	58	8	
> 12	80	19	
Chronology of BM			0.45
Metachronous	104	21	
Synchronous	34	6	
Primary ca. treatment			0.461
Surgery only	29	4	
Adjuvant treatment	109	23	
Systemic disease			0.602
controlled	64	14	
uncontrolled	74	13	
Multiplicity of BM			0.318
Single	94	21	
Multiple	44	6	
Tumor nature of BM			0.038
Cystic	28	1	
Solid	110	26	
Recur with LM			0.182
(+)	15	1	
(-)	67	17	

등록번호	성별	나이	조직-바이오뱅크 번호	원발장기	IL13RA2	Data ID	CSF 샘플 확보	원발암	병리번호	블럭번호	intensity	proportion
33177455	M	74	201201201110	skin	0.001859	Brain_M_137.gene		melanoma	S 04-0000753	2	2	5%
33184723	F	59	201801200763	Lung	0.001003	Brain_M_168.gene		NSCLC, ADC	S 04-0006503	단	2	<1%
33138366	F	46	201101200608	Lung	0.000626	Brain_M_105.gene		NSCLC, NEC	S 04-0014476	1	0	0
33145040	M	73	201201200299	Lung	0.000503	Brain_M_126.gene		NSCLC, ADC	S 10-0015268	4	1	10%
33274549	M	56	201801200795	Lung	0.000369	Brain_M_169.gene		NSCLC, ADC	S 11-0012328	1	2	20%
30469871	M	55	200401200078	Lung	0.000289	Brain_M_034.gene		NSCLC, SCC	S 11-0014115	1	2	100%
31588559	M	44	201001200180	Kidney	0.000143	Brain_M_083.gene		Renal cell ca.	S 12-0005315	1	0	0
33376011	M	62	201901201294	Lung	0.000106	Brain_M_194.gene		LCNE	S 12-0026813	4	1	20%
30548471	M	60	200401200679	Lung	0.000104	Brain_M_049.gene		NSCLC, ADC	S 14-0004420		0	0
33339378	F	84	201801201038	Lung	8.50E-05	Brain_M_171.gene		NSCLC, ADC	S 18-0014905	2	1	5%
33382623	F	60	202001200238	Ovary	7.20E-05	Brain_M_201.gene		Ovarian ca.	S 18-0015515	1	1	3%
33213923	F	60	201401200189	Kidney	7.10E-05	Brain_M_144.gene		Renal cell ca.	S 18-0020211	1	0	0
33114808	F	52	201001200987	Lung	6.70E-05	Brain_M_092.gene		NSCLC, SCC	S 19-0027679	3	1	5%
30171833	M	63	200401201452	Lung	5.00E-05	Brain_M_066.gene		NSCLC, ADC	S 20-0003008	1	1	<1%
33271254	F	49	201901200265	Ovary	2.30E-05	Brain_M_177.gene	(+)	Ovarian ca.	S 14-0019767	2	0	0
33149915	F	49	201401200778	Breast	1.60E-05	Brain_M_151.gene	(+)	Breast ca.	S 17-0009458	1	0	0
33182395	F	44	202001201023	Breast	1.50E-05	Brain_M_220.gene	(+)	Breast ca.	S 19-0012136	단	0	0
33356439	F	39	201901200253	Breast	9.00E-06	Brain_M_176.gene	(+)	Breast ca.	S 19-0020892	1	0	0
33278010	F	50	201701200307	Breast	9.00E-06	Brain_M_160.gene	(+)	Breast ca.	S 19-0029677	4	0	0
33151878	F	45	201901200445	Breast	8.00E-06	Brain_M_182.gene	(+)	Breast ca.	S 20-0008508	3	0	0
33323556	F	64	201901201387	Breast	5.00E-06	Brain_M_196.gene	(+)	Breast ca.	S 20-0015458	1	0	0
33411205	M	58	202101200004	Lung	5.00E-06	Brain_M_232.gene	(+)	NSCLC, ADC	S 21-0000011	단	0	0
33331407	F	47	201901201258	Breast	3.00E-06	Brain_M_193.gene	(+)	Breast ca.	S 21-0003610	1	0	0
33332215	M	75	201901200466	Rectum	3.00E-06	Brain_M_181.gene	(+)	Rectal ca.	S 21-0015387	1	0	0

paraffin embedded formalin fixed조직에서

노란색:BM RNA seq에서 read값 높았던 순위 14명 중 10명 IHC (+) 이고 잠정 threshold level 5.00E-05

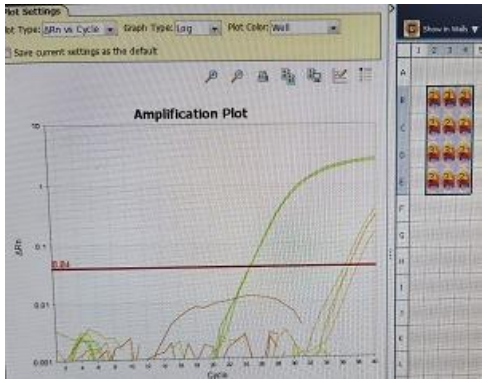
흰색: BM RNA seq에서 read값 평균이상, 이후 LM 발생, CSF(+) 10명은 모두 negative

CSF available sample < IL13Ra2 expression level 10^5

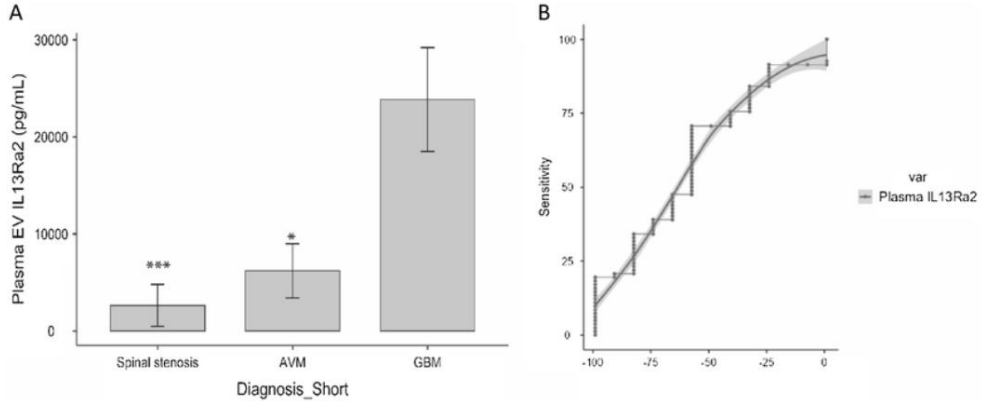
IL13Ra2 expression from CSF

장애 요소

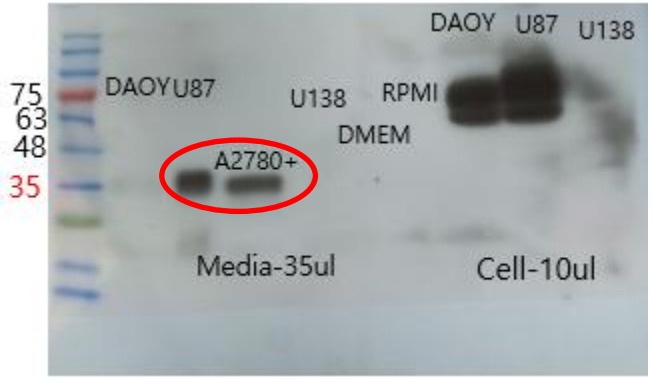
- CSF & CM RT-PCR has failed



- CSF & CM ELISA has failed



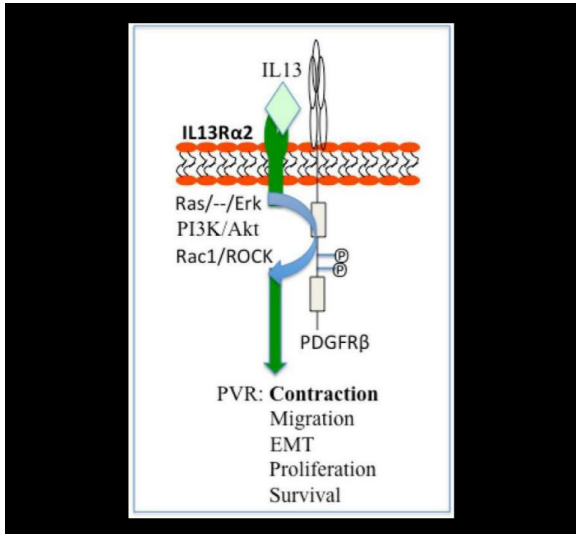
- CSF & CM WB has failed but



촉진 요소

- LC-MS/MS detect cleaved extracellular portion

	Checked	Protein FDR Confidence: Combined	Master	Accession	Description	Exp. q-value: Combined	Sum PEP Score	Coverage [%]	# Peptides	# PSMs	# Unique Peptides	# AAs	MW [kDa]	calc. pI	Score CHIMERY: CHIMERYS	# Peptides (by Search Engine): CHIMERYS
Gel#1	TRUE	High	Master Pr	Q14627	Interleukin-13 receptor subunit alpha-2	0	4.87	5	2	2	2	380	44.1	4.97	0.71	2
	TRUE	High	Master Pr	P02545	Prelamin-A/C [OS=Homo sapiens]	0	141.556	59	47	162	47	664	74.1	7.02	57.16	47
	TRUE	High	Master Pr	P11021	Endoplasmic reticulum chaperone BiP [(	0	113.698	49	34	166	32	654	72.3	5.16	55.9	34
	TRUE	High	Master Pr	P15924	Desmoplakin [OS=Homo sapiens]	0	71.667	9	31	49	31	2871	331.6	6.81	16.76	31
Gel#2	TRUE	High	Master Pr	P0DMV9	Heat shock 70 kDa protein 1B [OS=Homo	0	26.935	16	9	10	7	641	70	5.66	3.18	9
	TRUE	High	Master Pr	Q14627	Interleukin-13 receptor subunit alpha-2	0	26.89	14	6	12	6	380	44.1	4.97	5.43	6
	TRUE	High	Master Pr	Q08554	Desmocollin-1 [OS=Homo sapiens]	0	24.263	7	5	10	5	894	99.9	5.43	2.98	5
Gel#5	TRUE	High	Master Pr	P04083	Annexin A1 [OS=Homo sapiens]	0	14.534	16	5	7	5	346	38.7	7.02	2.81	5
	TRUE	High	Master Pr	Q5D862	Filaggrin-2 [OS=Homo sapiens]	0	12.092	3	5	7	5	2391	247.9	8.31	1.38	5
	TRUE	High	Master Pr	Q14627	Interleukin-13 receptor subunit alpha-2	0	11.498	9	4	7	4	380	44.1	4.97	2.98	4
	TRUE	High	Master Pr	P68104	Elongation factor 1-alpha 1 [OS=Homo sa	0	11.193	8	4	5	4	462	50.1	9.01	2.04	4



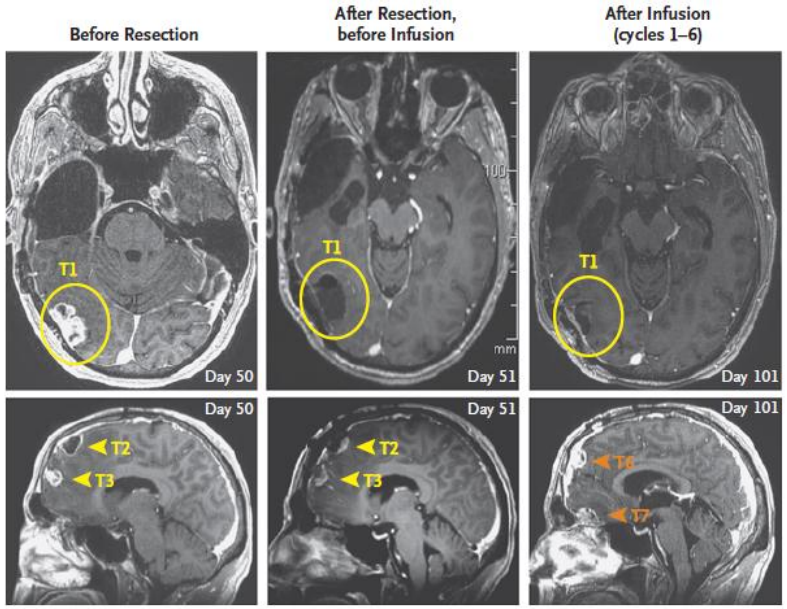
Intra-CSF delivery of CAR-T

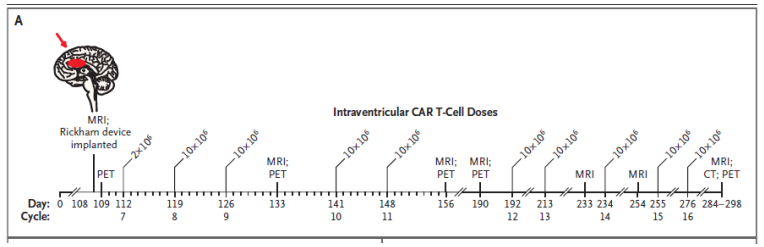
BRIEF REPORT

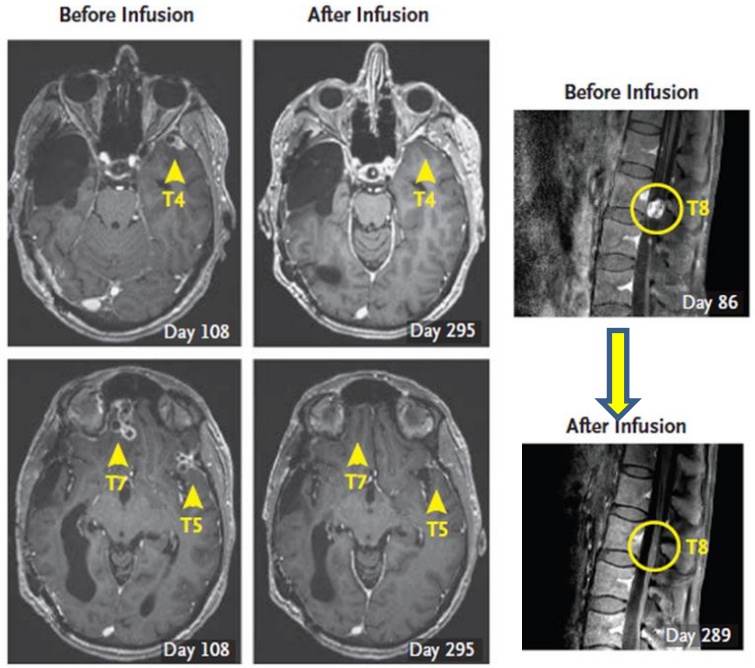
N ENGL J MED 375;26 NEJM.ORG DECEMBER 29, 2016

Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy

Christine E. Brown, Ph.D., Darya Alizadeh, Ph.D., Renate Starr, M.S.,







Intracavitary CAR-T infusion achieved local control but distant progression

nature medicine

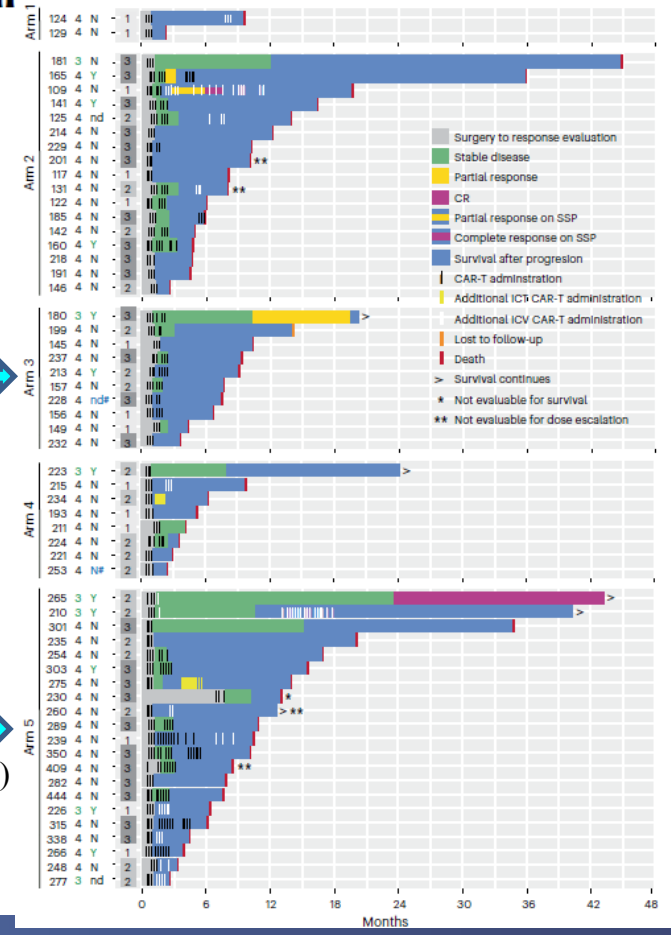
Article

https://doi.org/10.1038/s41591-024-02875-1

Locoregional delivery of IL-13Rα2-targeting CAR-T cells in recurrent high-grade glioma: a phase 1 trial

Intraventricular (ICV)

ICV + intratumoral (ICT)



Article https://doi.org/10.1038/s41591-025-03745-0

Intracerebroventricular bivalent CAR T cells targeting EGFR and IL-13Rα2 in recurrent glioblastoma: a phase 1 trial

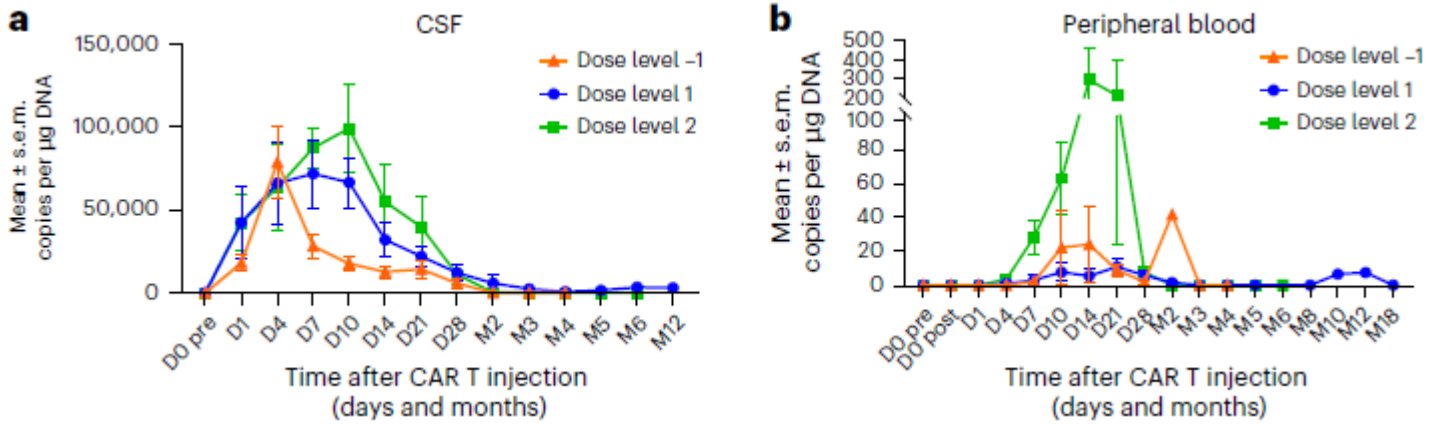
e-mail: sbagley@pennmedicine.upenn.edu; Donald.O'Rourke@pennmedicine.upenn.edu

nature medicine

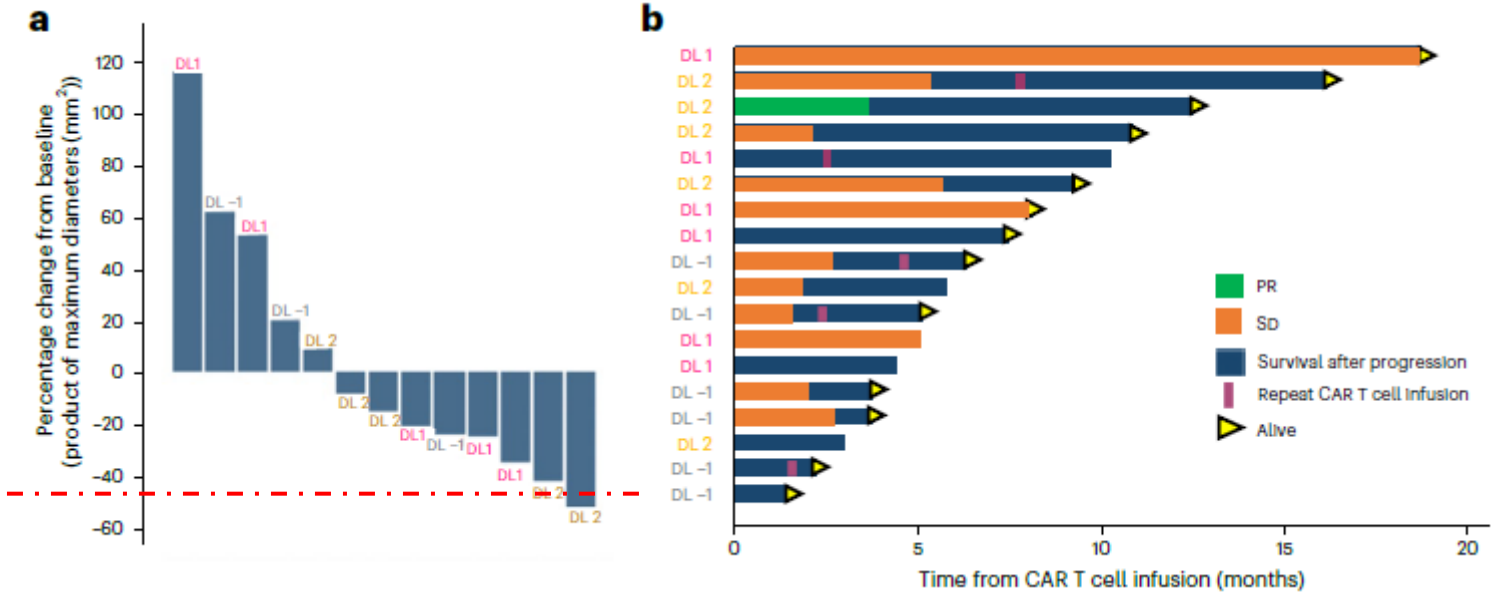
Received: 2 April 2025

Accepted: 29 April 2025

Published online: 01 June 2025



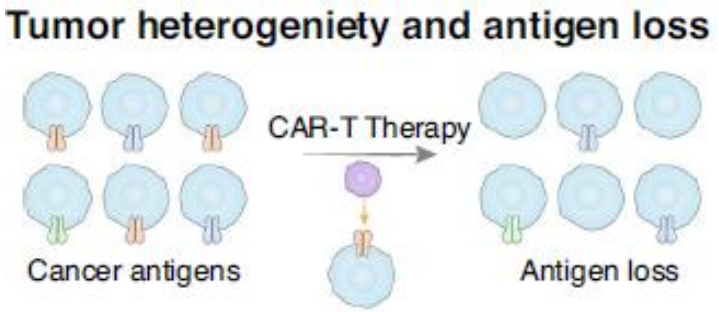
No evidence of CAR-T persistence despite remained tumor

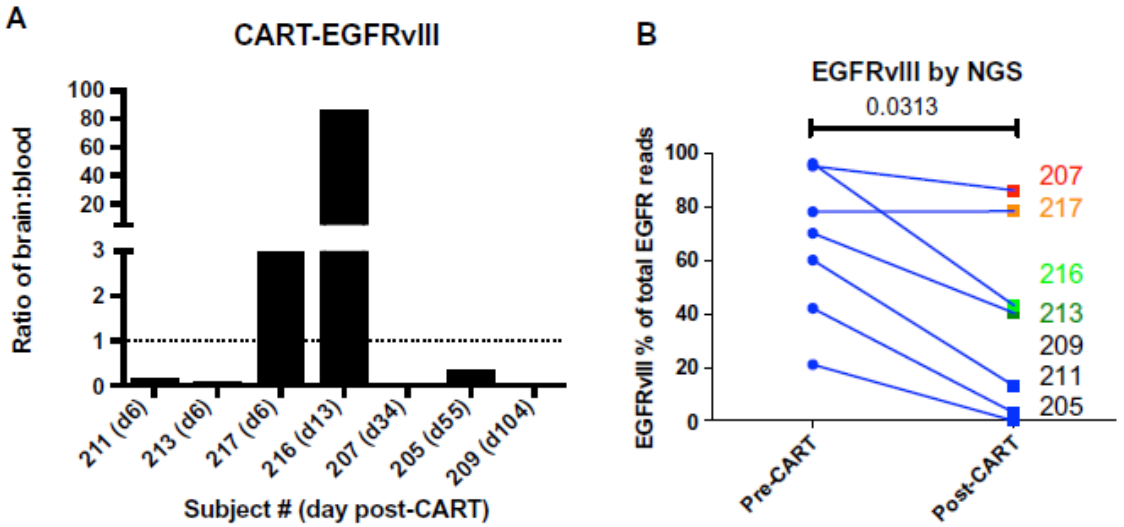


Discussion

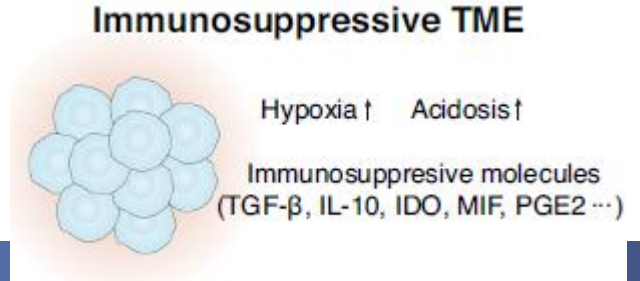
Ag depletion

- Continuous cancer-immune cycle
  - Tumor infiltration of CAR-T cells were proved with post-treatment Ag clearance (+) => ***immune escape*** *(?) reports of CD19-negative escape variants in the setting of ALL CAR-T*



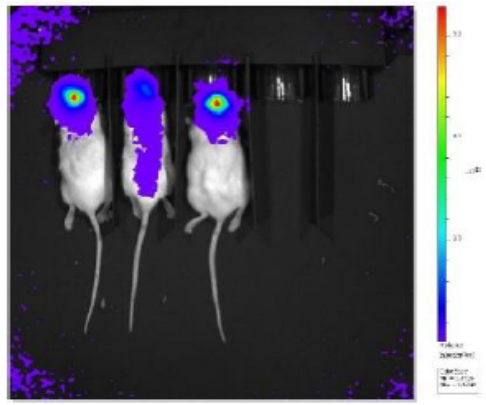


- Immunosuppressive TME
  - T-cell infiltration but T_{regs} with enhancement of several immune suppressive pathways, including PD-L1, IDO1, and IL10
  - Hypoxia & acidosis

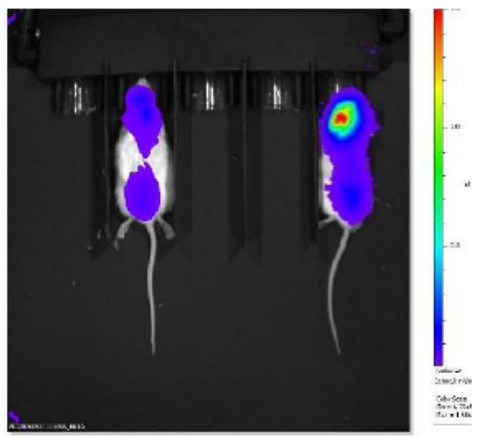


BM MDA-MB-231 유방암유래 연수막전이암 마우스에서 재발한 암의 IL13Ra2 확인

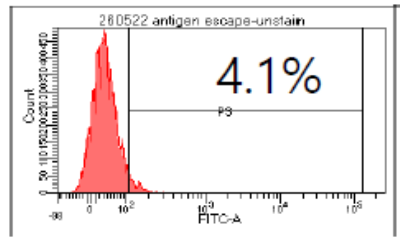
비투여



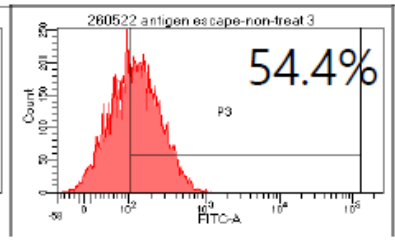
투여 후 재발



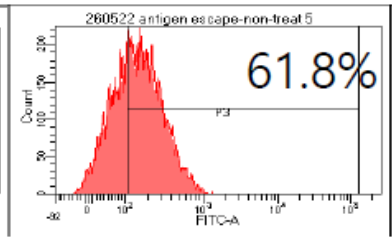
Unstain



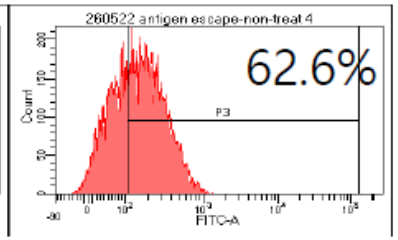
비투여 1



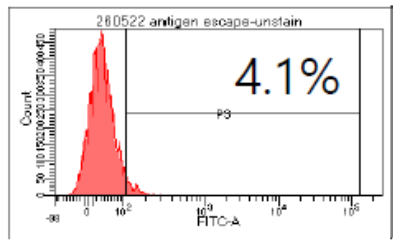
비투여 2



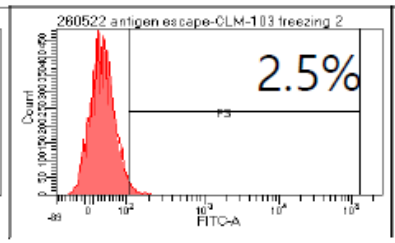
비투여 3



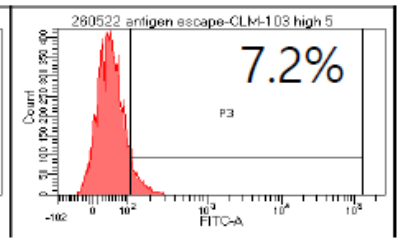
Unstain



투여 후 재발 1



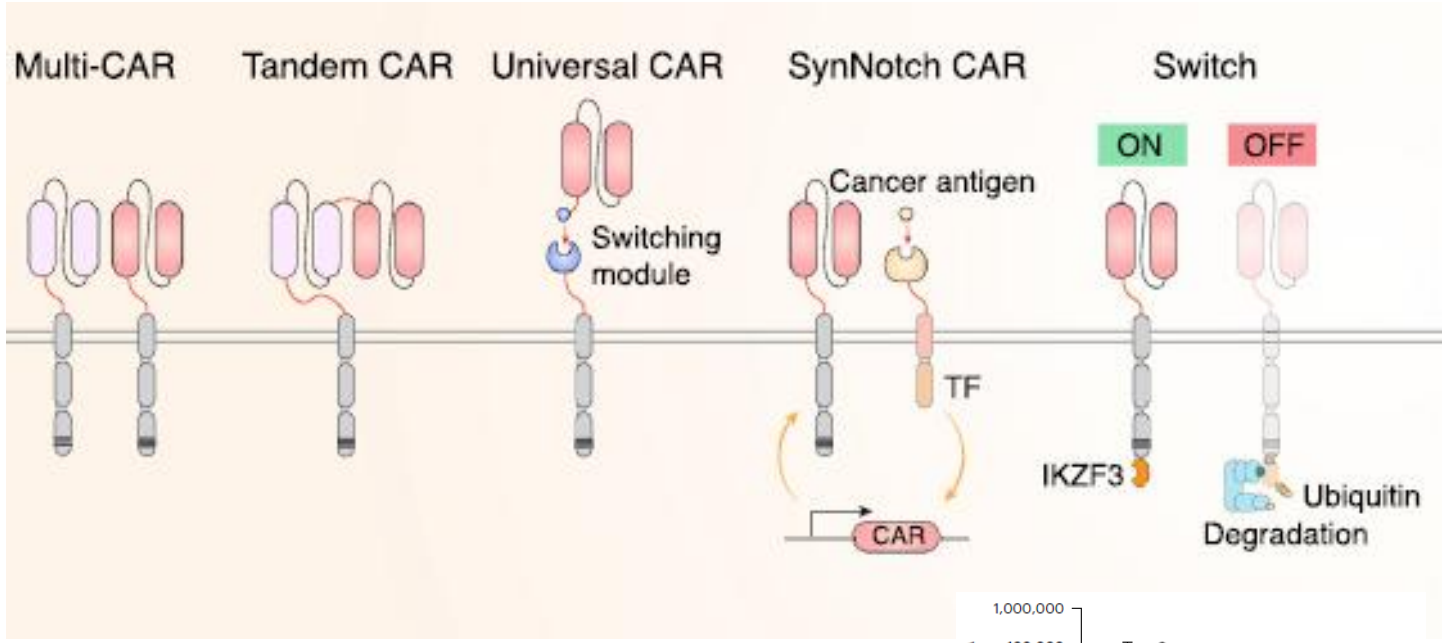
투여 후 재발 2



- 종양 세포 분리 후 배양(1day)하여 IL13Ra2 FACs 분석 결과 CLM-103 비투여한 mouse에서는 IL13Ra2가 54.4~62.6%발현
- CLM-103투여 후 재발한 mouse에서는 IL13Ra2가 거의 발현하지 않음(Unstain과 비슷) → IL13Ra2 (-)가 재발한 것으로 사료됨.

CAR-T modification Ag engineering

- Engineering CAR constructs that target multiple antigens simultaneously to mitigate tumor heterogeneity
- OR gate & AND-like effect

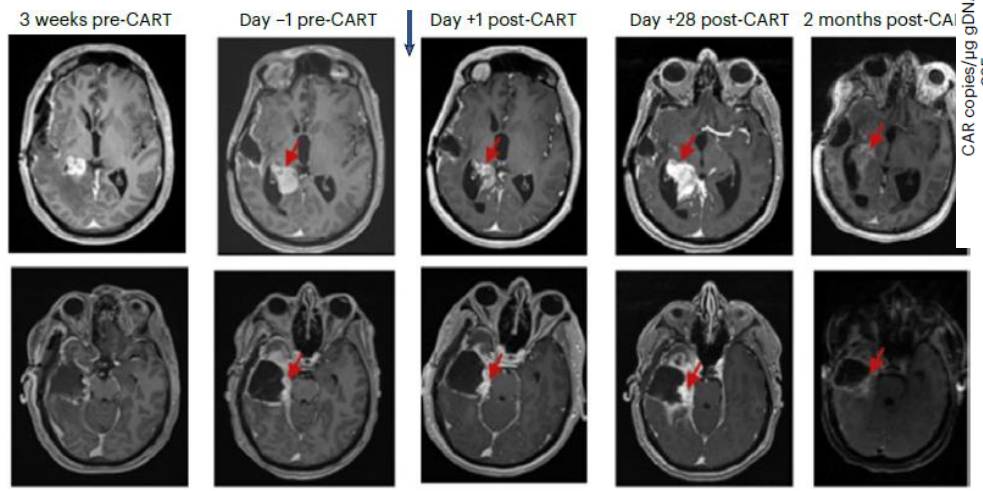


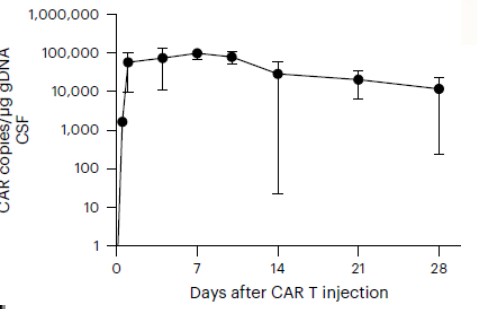
nature medicine

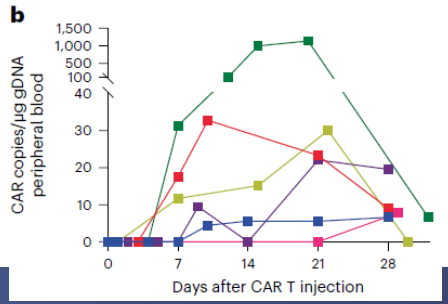
Article https://doi.org/10.1038/s41591-024-02893-z

Intrathecal bivalent CAR T cells targeting EGFR and IL13Rα2 in recurrent glioblastoma: phase 1 trial interim results

….Reductions in both tumor magnetic resonance imaging contrast enhancement and size were observed within 48 hours in all patients……







also linked to both tumor inflammation–associated neurotoxicity and immune effector cell–associated neurotoxicity syndrome (ICANS) across all evaluate

CAR–T modification

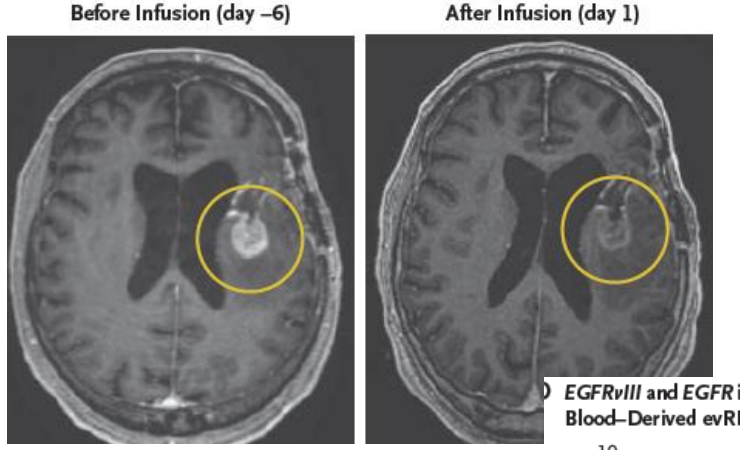
CARv3–TEAM–E

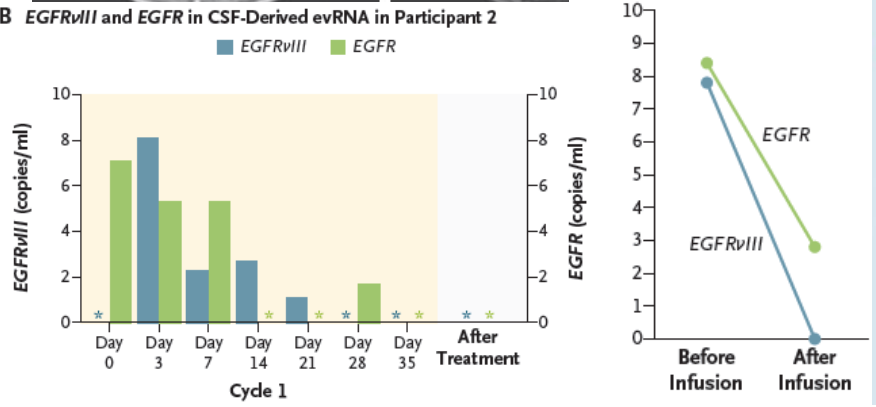
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

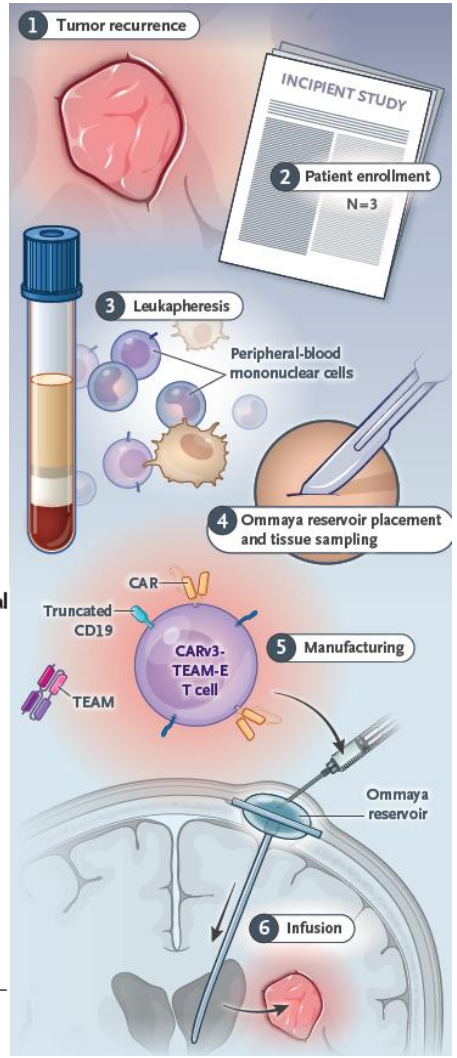
Intraventricular CARv3-TEAM-E T Cells in Recurrent Glioblastoma

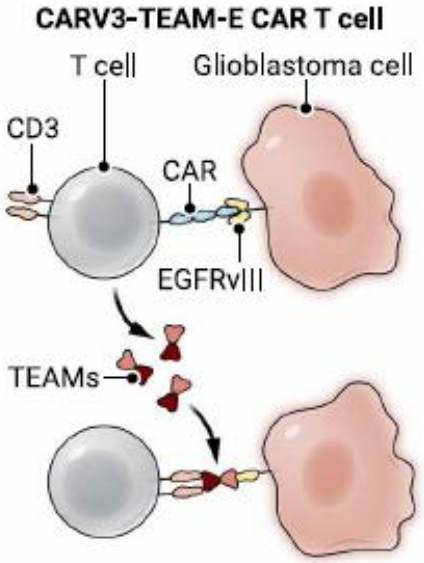
Bryan D. Choi, M.D., Ph.D., Elizabeth R. Gerstner, M.D.,

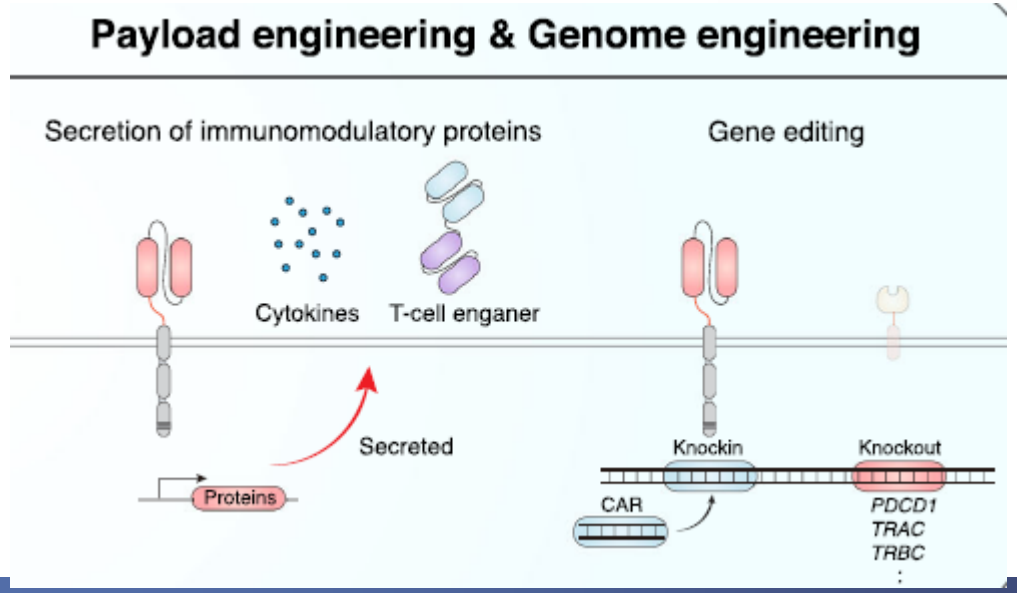




"T-cell–engaging antibody molecule" (TEAM)





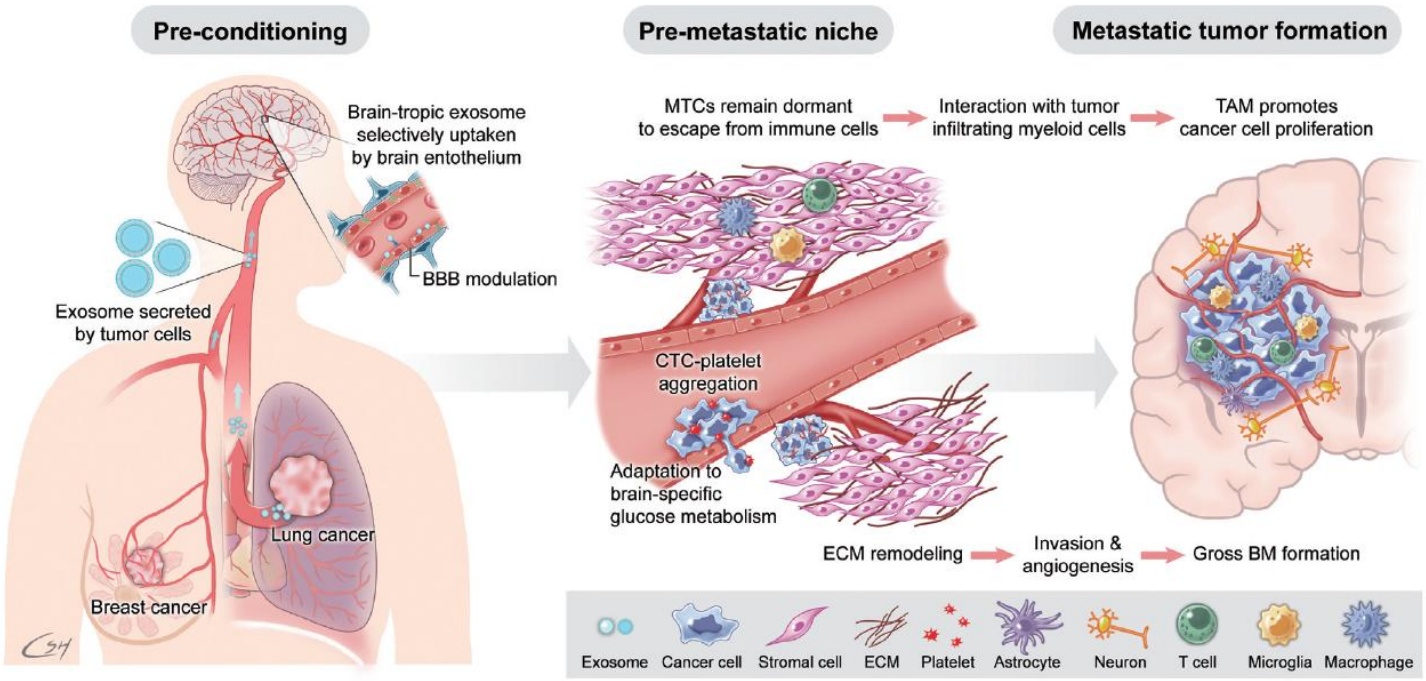


TME of Brain

Molecular Biology of Brain Metastases

REVIEW ARTICLE
Brain Tumor Res Treat 2023;11(1):8-15 / pISSN 2288-2405 / eISSN 2288-2413
https://doi.org/10.14791/btrt.2022.0045

Ho-Shin Gwak
Department of Cancer Control, National Cancer Center, Graduate School of Cancer Science and Policy. National Cancer Center, Goyang, Korea

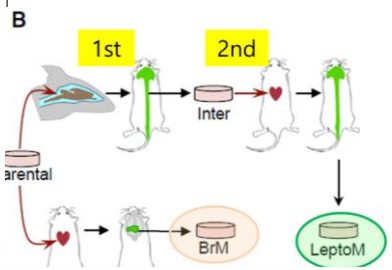


Suppressive TME

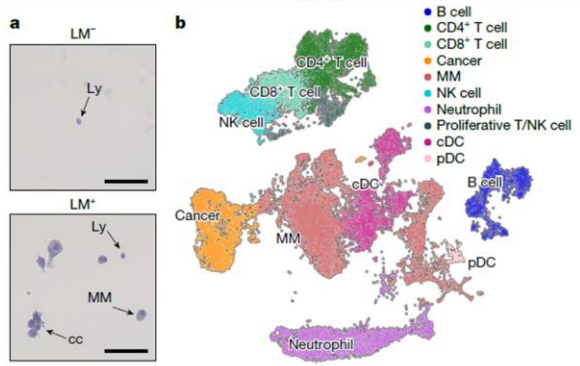
Article

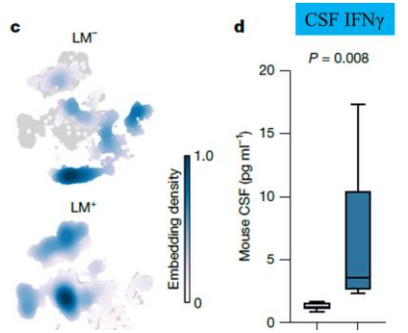
Interferon-γ orchestrates leptomeningeal anti-tumour response

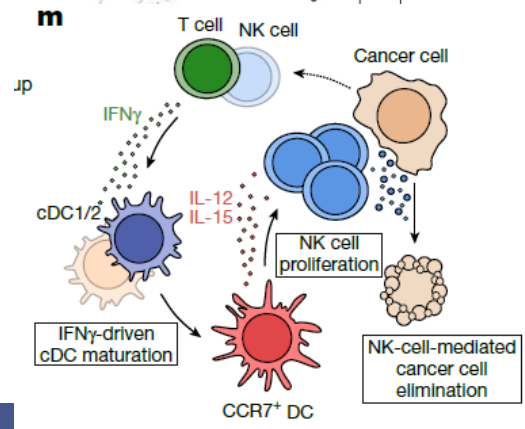
Nature | www.nature.com
Received: 14 March 2023
Accepted: 11 April 2025



LM drives the CSF cellular composition to myeloid-rich pleocytosis







Non-canonical Ag-independent

Summary

1. **Safety of intravenously injected YYB-103 CAR-T for IL13Rα2**
   - No ICANS, no severe CRS except fever & AST/LT elevation
   - No *"on-target off-tumor effect"* (transient Testosterone decrease)

2. **Efficacy of intravenously injected YYB-103 CAR-T for IL13Rα2**
   - CAR-T proliferation & activation in peripheral blood (peak at 7 days)
   - No evidence of long-term (> 3 months) persistence
   - Radiologically stable ds. In 3/9

3. **Future directions**
   - Real-time biomarker; detect Ag expression/ monitor Ag depletion possibly from CSF
   - Route and round of administration; intravenous << intra-CSF/ intra-cavitary
   - TME modulation; lymphodepletion, IDO-1 inhibitor etc.
   - Ag depletion; Bi-specific, Engager, etc

How could we induce 'cancer-immune' cycle in adoptive cell therapy?

세포 면역치료 사업단 (보건복지부)

고형암의 연수막 전이 치료를 위한 CAR-T 세포치료제 개발 연구

곽호신

국제암전문대학원대학교 암의생명과학과

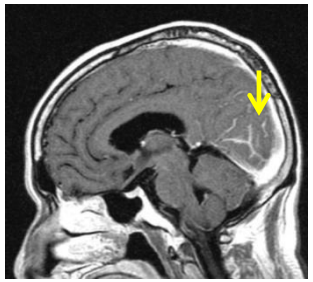
뇌척수종양 클리닉, 국립암센터

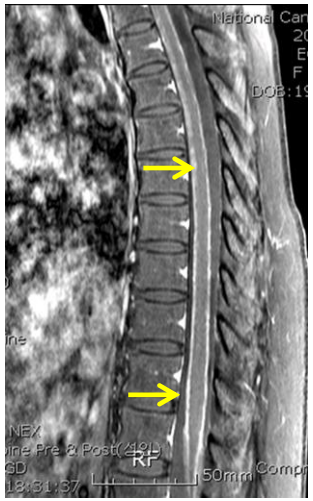
국립암센터
NATIONAL CANCER CENTER

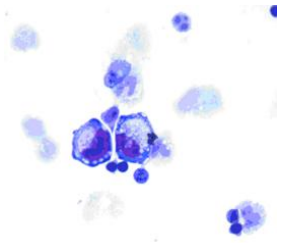
연구의 필요성 연수막 암전이

Leptomeningeal metastasis (LM) is rare but increasing

- Clinically
  - 2% to 8% of all patients with cancer; Melanoma, SCLC, Brest cancer, NSCLC
  - Difficult to diagnose early: false (-) of CSF cytology & non-specific MRI



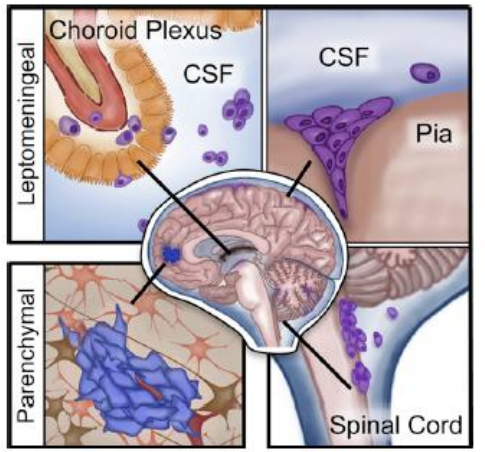




  - Rapidly devastating patients with increased ICP from CSF flow disturb., CN neuropathy, C. equine involve.

=> natural median OS = 2 months

- Biologically
  - Dx by floating cancer cells in the CSF, but disease from subarachnoid/subpial deposit
  - Sheet-like spread w/o mass formation



  - CSF; lack of nutrients & growth factors

No known pathogenesis

Treatment Modalities for LM

Leptomeningeal metastasis (LM) is formidable disease without a standard Tx

방사선 치료

WBRT and/or IF RT

뇌척수액 항암치료

- Intrathecal CTx
- Intraventricular CTx

전신 (일반) 항암치료

- Cytotoxic chemoTx.
- RTK inhibitor

J Korean Neurosurg Soc 58 (1) : 1-8, 2015

Review Article

Recent Advancements of Treatment for Leptomeningeal Carcinomatosis

Ho-Shin Gwak, M.D., Ph.D.,[1] Sang Hyun Lee, M.D., Ph.D.,[2] Weon Seo Park, M.D., Ph.D.,[3] Sang Hoon Shin, M.D., Ph.D.,[4] Heon Yoo, M.D., Ph.D.,[4] Seung Hoon Lee, M.D., Ph.D.[4]

Department of System Cancer Science,[1] Graduate School of Cancer Science and Policy, Departments of Diagnostic Radiology,[2] Pathology,[3]

Table 2. List of drugs introduced to intra-CSF chemotherapy in clinic

Author (year)	Drugs	Primary cancer	Treatment route (dose)	Features
Levin et al.[40] (1989)	ACNU	Various including leukemia	Intraventricular/intrathecal (4–16 mg/week)	Phase I trial 38% of cytology negative conversion
Laufman and Forsthoefel[42] (2001)	Herceptin	Breast (HER-2 positive)	Intraventricular (5–20 mg)	Concurrent intravenous and intrathecal chemotherapy
Blaney et al.[7] (2003)	Topotecan	Various including leukemia	Intraventricular/intrathecal MTX (0.025–0.7 mg)	Phase I trial
Blaney et al.[5] (2005)	Mafosfamide	CNS embryonal tumors	Alternately intraventricular and intrathecal (twice a week up to 14 mg)	Phase I trial
Gururangan et al.[33] (2006)	Buslfan	Primary brain tumor	Intraventricular/intrathecal (5–17 mg twice week for 2 weeks)	Phase I trial and MTD at 13 mg (microcrystalline formulation)
Bernardi et al.[3] (2008)	Gemcitabine	Various including leukemia	Intraventricular/intrathecal (5 mg/week–10 mg twice/week)	Phase I trial was terminated due to severe neurotoxicities

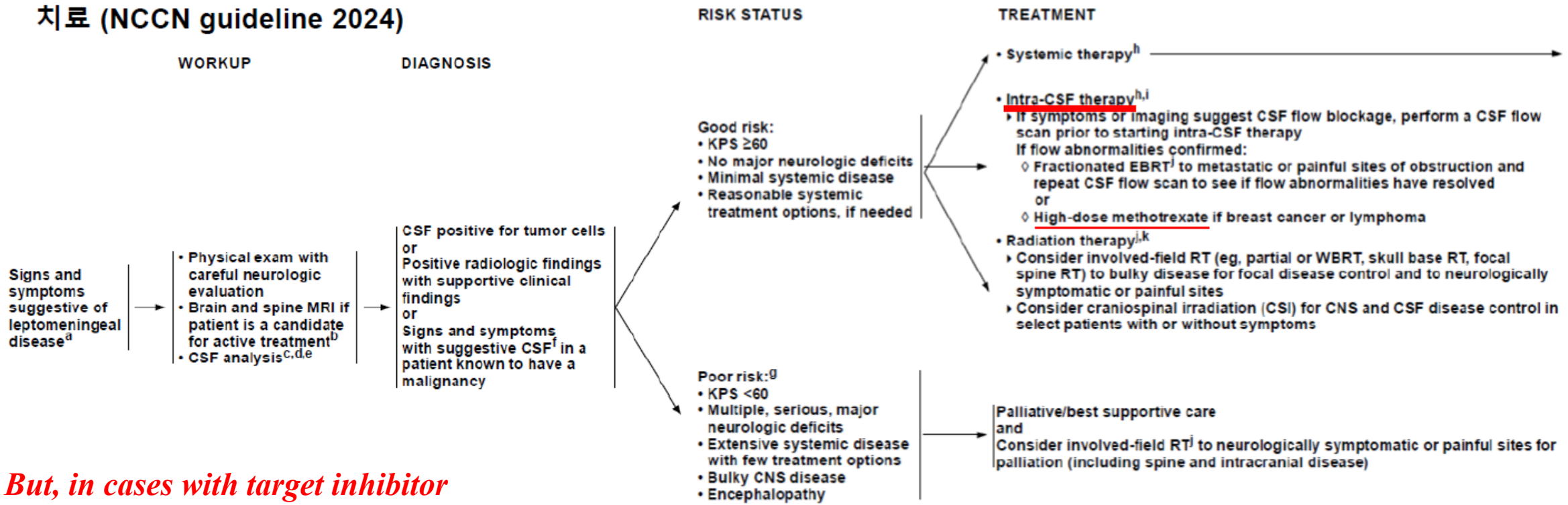
CSF : cerebrospinal fluid, ACNU : 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride, MTX : methotrexate, CNS : central nervous system, MTD : maximal tolerable dose

Radiation therapy fail to cover whole neuraxis

Intra-CSF CTx debate on neurotoxicity & low efficacy

Doubtful benefit of both RT and intra-CSF chemotherapy

Current Tx. status for LM



But, in cases with target inhibitor

	NSCLC	Breast Cancer	Melanoma
Preferred Regimens	Osimertinib EGFR mutation positive		
Other Recommended Regimens	– Weekly pulse erlotinib EGFR exon 19 deletion or exon 21 L858R Mutation – Intrathecal pemetrexed EGFR mutation positive	– Intra-CSF therapy: Methotrexate, Trastuzumab (HER2 positive)	
Useful in Certain Circumstances	Tepotinib (MET exon 14 mutated)	– High-dose methotrexate	– IT and IV nivolumab

Breast Cancer Res Treat (2013) 139:13–22
DOI 10.1007/s10549-013-2525-y

REVIEW

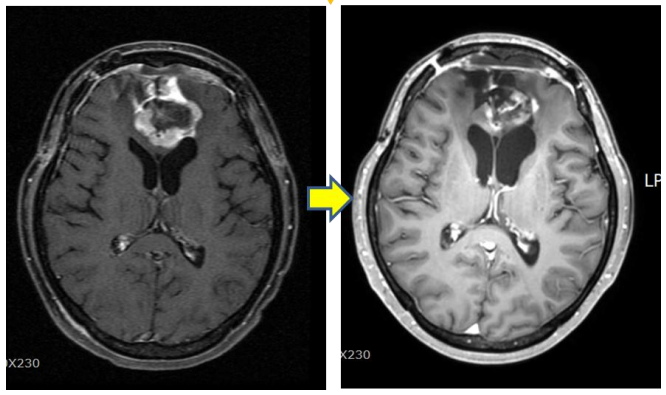
HER2 (+) Breast ca. *Herceptin*

Intrathecal administration of trastuzumab for the treatment of meningeal carcinomatosis in HER2-positive metastatic breast cancer: a systematic review and pooled analysis

Flora Zagouri · Theodoros N. Sergentanis · Rupert Bartsch · Anna S. Berghoff · Dimosthenis Chrysikos · Evandro de Azambuja · Meletios-Athanassios Dimopoulos · Matthias Preusser

17 pts from 13 articles

IT-herceptin x2



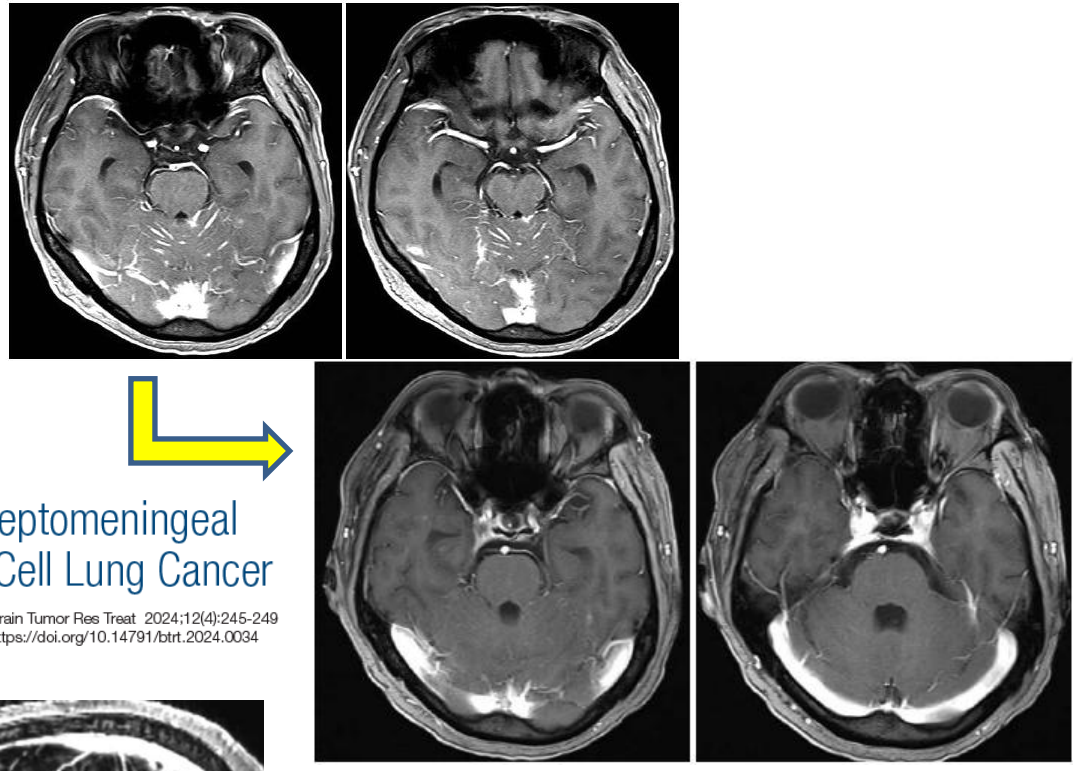
NSCLC with LM *RTKi*

Lorlatinib Therapy for Rapid and Dramatic Control of Brain and Spinal Leptomeningeal Metastases From ALK-Positive Lung Adenocarcinoma

CASE REPORT

Brain Tumor Res Treat 2021;9(2):99-104 / pISSN 2288-2405 / eISSN 2288-2413
https://doi.org/10.14791/btrt.2021.9.e19

Min-Gwan Sun[1], In-Young Kim[1], Young-Jin Kim[1], Tae-Young Jung[1], Kyung-Sub Moon[1], Shin Jung[1], In-Je Oh[2], Young-Cheol Kim[2], Yoo-Duk Choi[3]
Departments of [1]Neurosurgery, [2]Pulmonology, and [3]Pathology, Chonnam National University Hwasun Hospital,

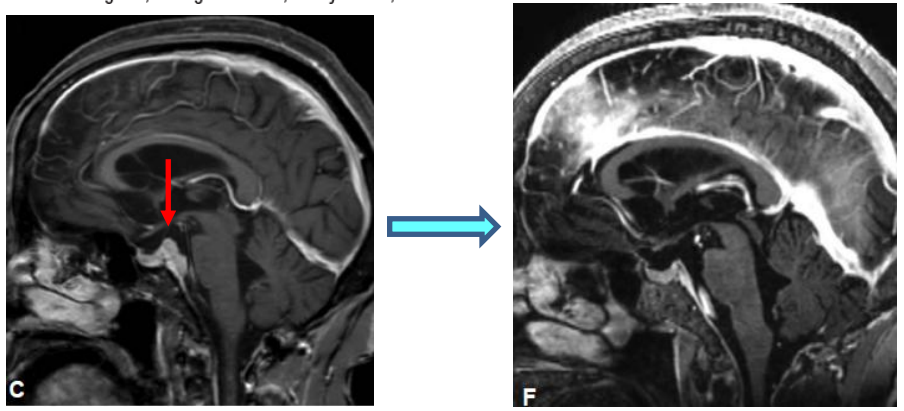


Complete Remission of Dural-Based Leptomeningeal Metastasis in Patient With Non-Small Cell Lung Cancer by Osimertinib

CASE REPORT

Brain Tumor Res Treat 2024;12(4):245-249
https://doi.org/10.14791/btrt.2024.0034

Jemin Hwang[1], Beung Chul Ahn[2], So Hyeon Ji[3], Ho-Shin Gwak[4]



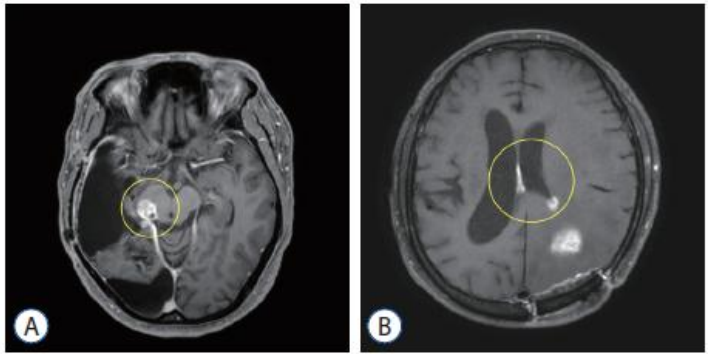
Brain metastasis in CSF pathway

- **Adult**

Leptomeningeal Metastasis in Gliomas : Clinical Characteristics and Risk Factors

J Korean Neurosurg Soc 2022 Dec 12. [
https://doi.org/10.3340/jkns.2022.0166

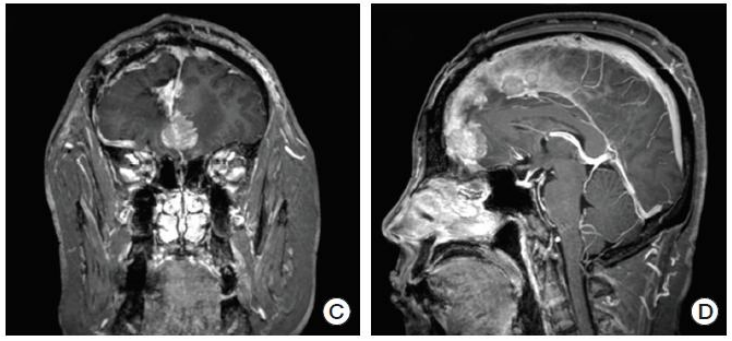
Jeyul Yang,[1] Ji-Woong Kwon,[2] Sang Hoon Shin,[2] Heon Yoo,[2] Kyu-Chang Wang,[2] Sang Heyon Lee,[3] Ho-Shin Gwak[2,4]



Effects of Postoperative Radiotherapy on Leptomeningeal Carcinomatosis or Dural Metastasis after Resection of Brain Metastases in Breast Cancer Patients

Cancer Res Treat. 2017;49(3):748-758

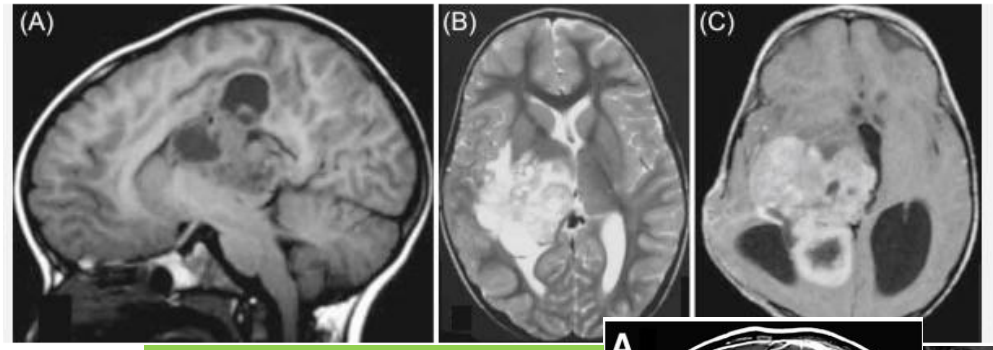
Boram Ha, MD[1]
Seung Yeun Chung, MD[2]
Yeon-Joo Kim, MD[1]
Ho-Shin Gwak, MD[3]



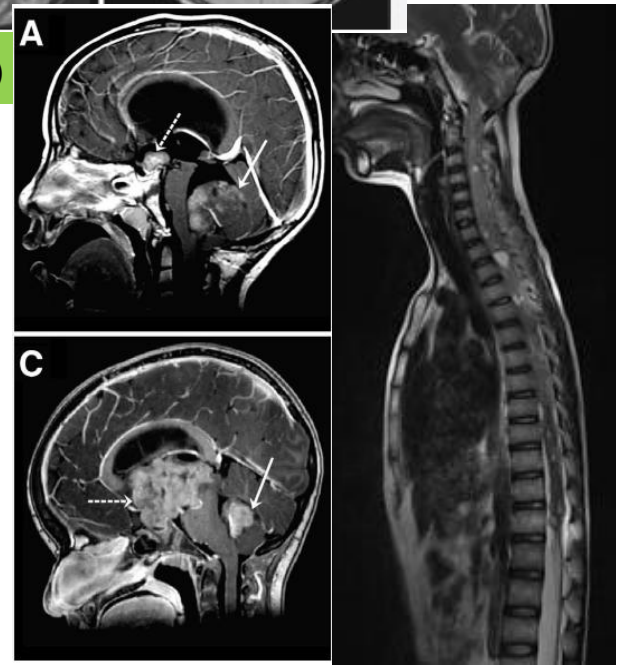
- **Pediatric BT**

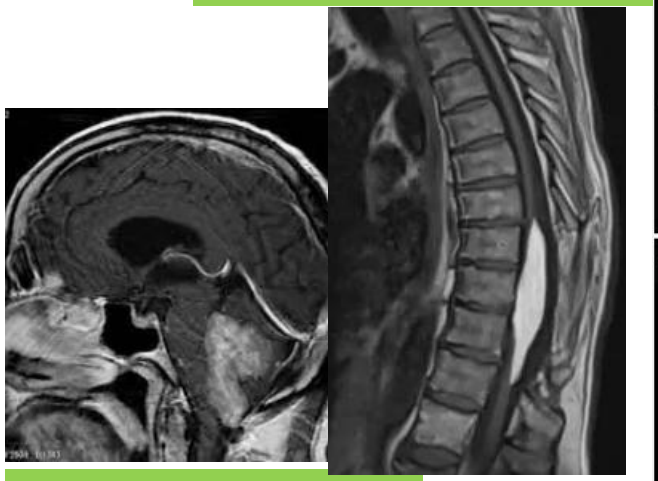
; grow and metastasis along CSF pathway

Atypical Teratoid Rhbdoid Tumor (ATRT)



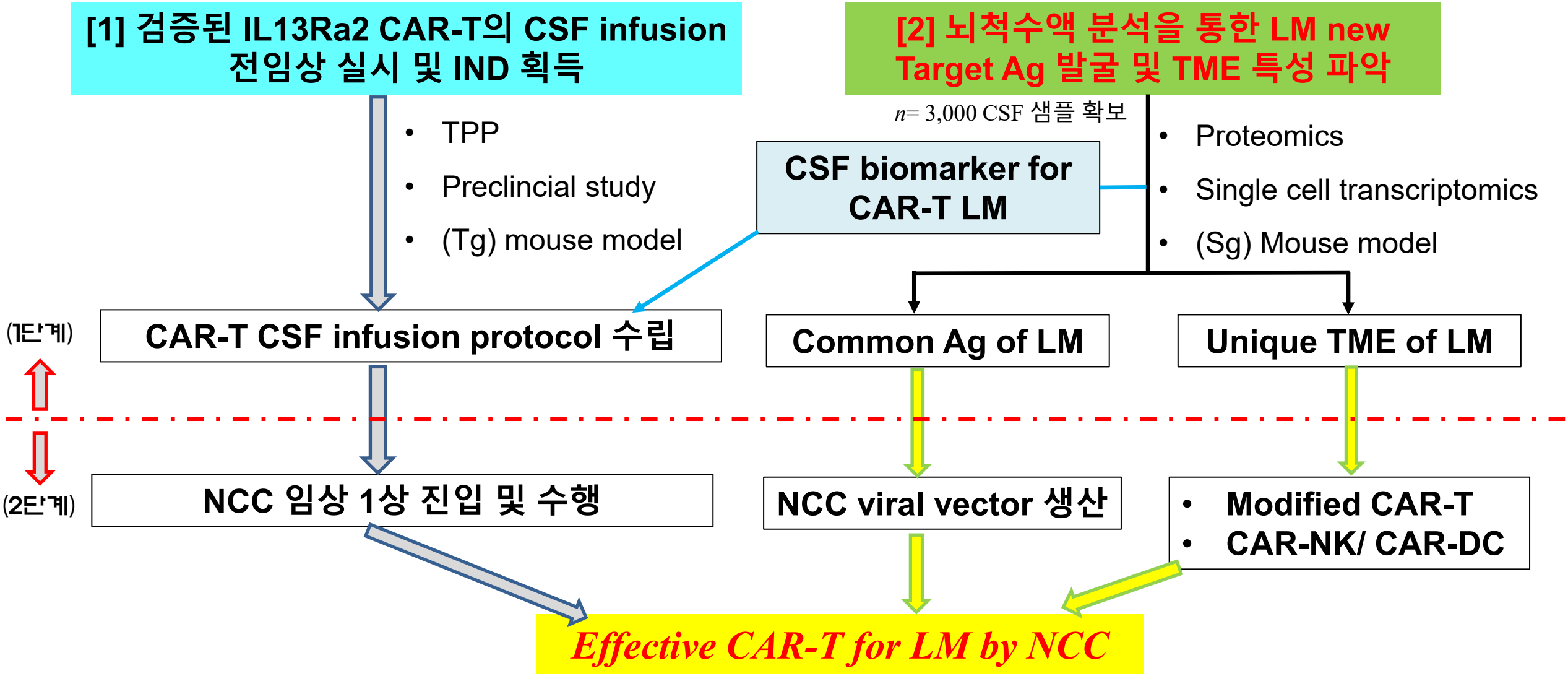
Medulloblastoma (MBL)





Ependymoma (EPN)

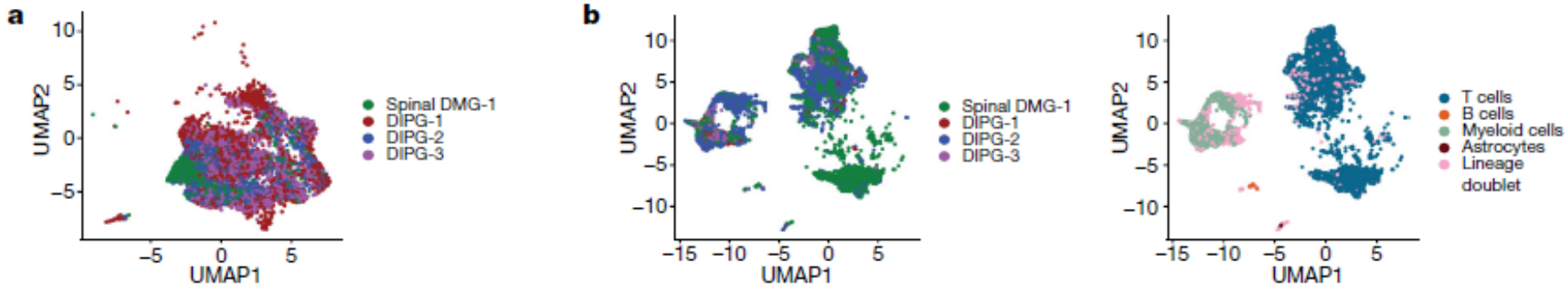
연구개발의 최종 목표

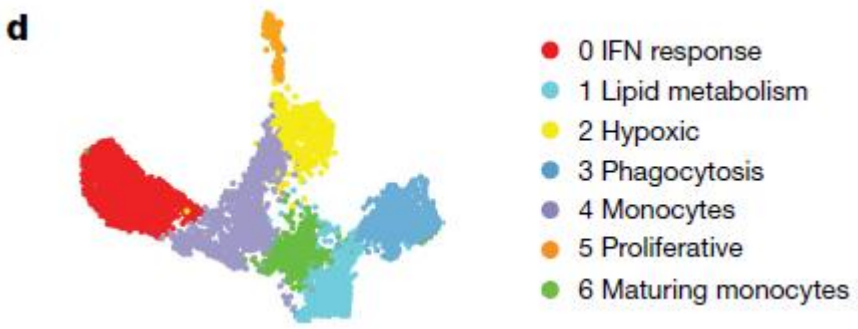

[1] 검증된 IL13Ra2 CAR-T의 CSF infusion 전임상 실시 및 IND 획득
[2] 뇌척수액 분석을 통한 LM new Target Ag 발굴 및 TME 특성 파악
n= 3,000 CSF 샘플 확보
TPP
Preclincial study
(Tg) mouse model
CSF biomarker for CAR-T LM
Proteomics
Single cell transcriptomics
(Sg) Mouse model
(1단계)
CAR-T CSF infusion protocol 수립
Common Ag of LM
Unique TME of LM
(2단계)
NCC 임상 1상 진입 및 수행
NCC viral vector 생산
Modified CAR-T
CAR-NK/ CAR-DC
Effective CAR-T for LM by NCC

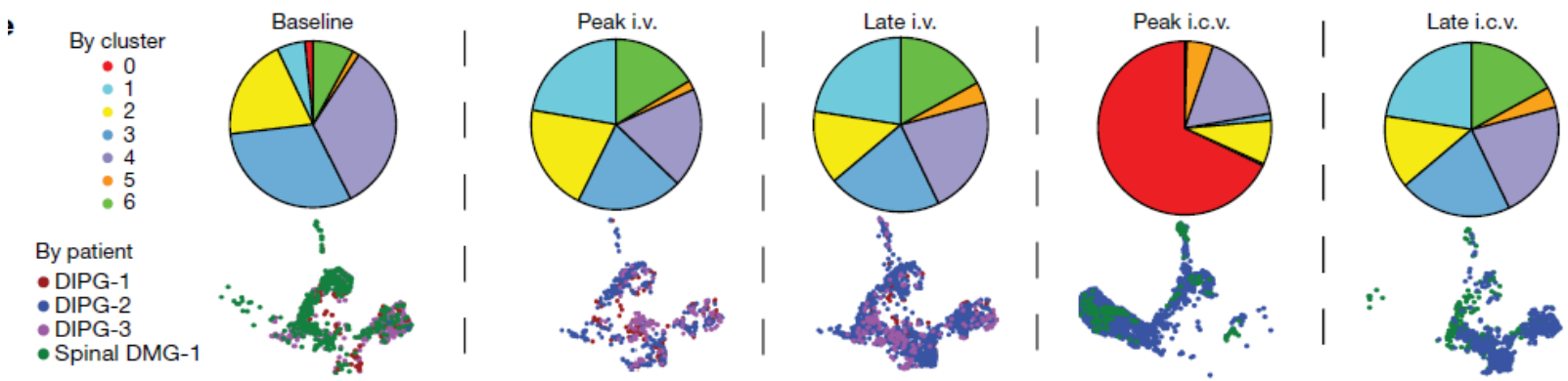
Nature | Vol 603 | 31 March 2022

GD2-CAR T cell therapy for H3K27M-mutated diffuse midline gliomas

[1]Stanford Center for Cancer Cell Therapy, Stanford Cancer Institute, Stanford University, Stanford, CA, USA







Article https://doi.org/10.1038/s41556-025-01660-7

nature cell biology

Metastatic medulloblastoma remodels the local leptomeningeal microenvironment to promote further metastatic colonization and growth

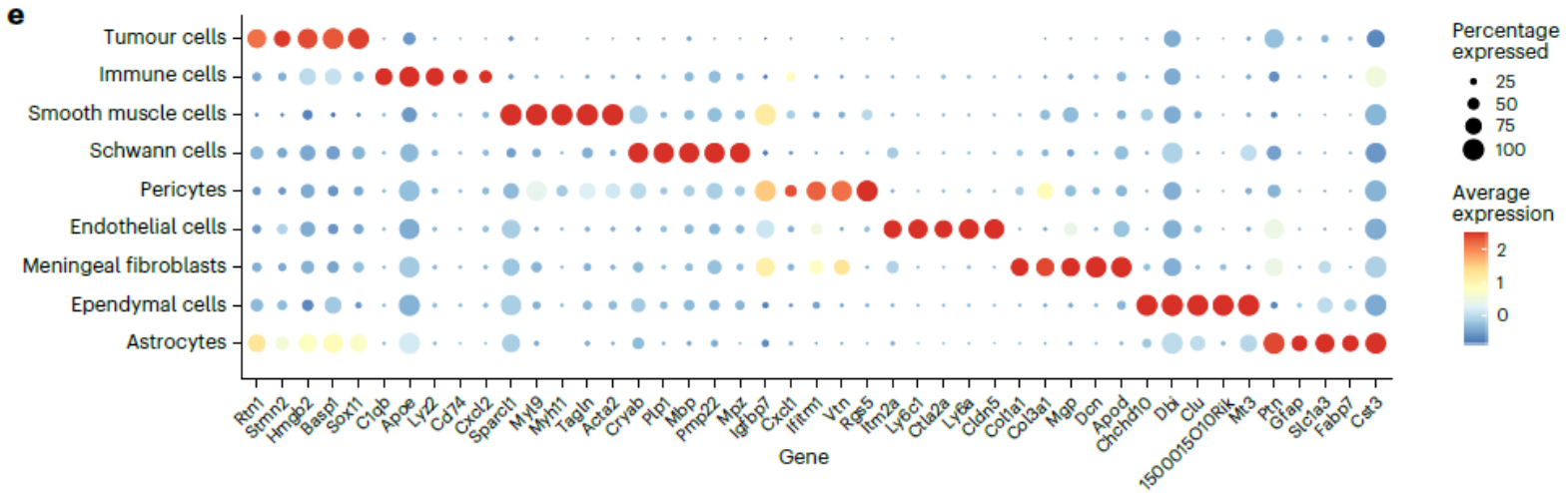
Marco Gallo[7,8], Jeremy N. Rich[13,14], Xiaochong Wu[1,2,7,8], Xi Huang[1,2,6] & Michael D. Taylor[1]

[1]Developmental and Stem Cell Biology Program, The Hospital for Sick Children, Toronto, Ontario, Canada. [2]The Arthur a

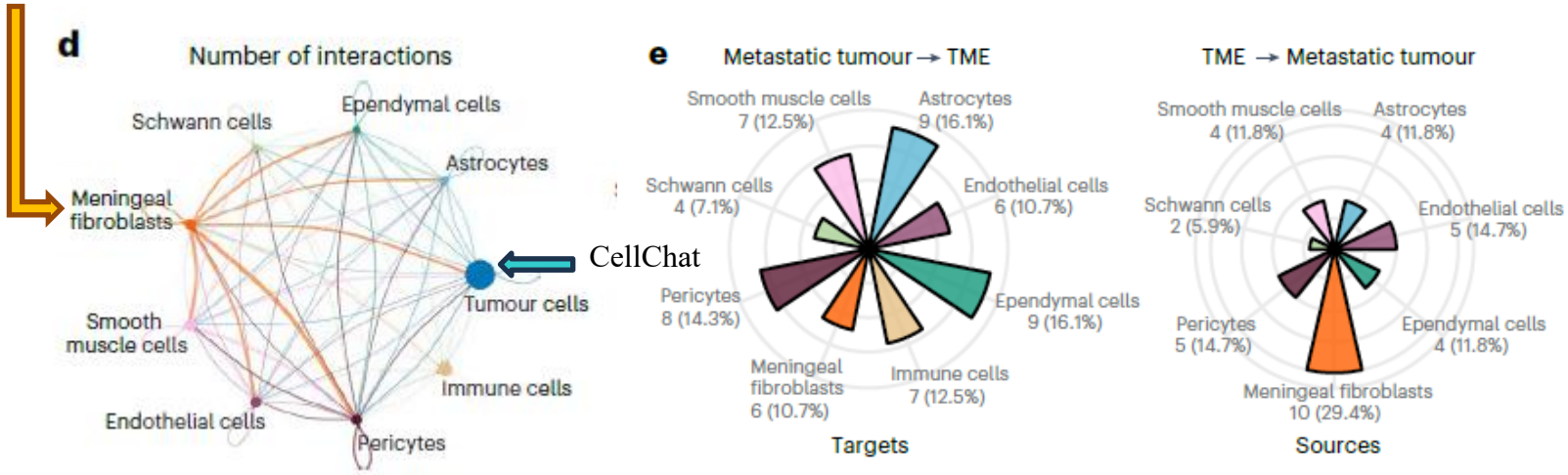
Received: 4 June 2024

Accepted: 25 March 2025

Published online: 22 April 2025



strongest intercellular communication



CSF s.c. seq

TME of LM

SC_일련번호	Sample date	Biomarker No	환자번호	환자명	CSF sample site	Sample amount (갯수, ml)	Patient group	Sample 구분	SC handling date	Sample status	CSF handling by	세포수	세포 viability (%)	SC 실험 진행 여부
I	2025-08-07	**1844**	33296517	박순희	Lumbar	50	4군-BT		2025-08-07	Fresh CSF	Decode cell	100,000	44.6	O
J	2025-08-14	**1845**	33155608	김수경	Lumbar	8	1군 (HC)		2025-08-14	Fresh CSF	Decode cell	10,000	90	O
K	2025-08-19	**4403**	33579716	최원구	Lumbar	6	3군-BM		2025-08-19	Fresh CSF	Decode cell	16,000	91	O
L	2025-08-27	**20623**	33528860	조태원	Lumbar	10	2군-LMC		2025-08-27	Fresh CSF	Decode cell	10,000	82.4	O
Q	2025-09-18	**1849**	33616697	남윤희	Lumbar	167	1군 (CC)		2025-09-18	Fresh CSF	Decode cell	15,500	86	O
R	2025-09-18	**20625**	33613770	전지현	Lumbar	10	2군-LMC		2025-09-18	Fresh CSF	Decode cell	5,000,000	96	O
S	2025-09-22	**3236**	33151913	박영규	Cisternal	6	3군-BM		2025-09-22	Fresh CSF	Decode cell	70,000	93	O
T	2025-10-02	**3238**	33581410	김종배	Cisternal	5	3군-BM		2025-10-02	Fresh CSF	Decode cell	200,000	98	O
U	2025-10-15	**1851**	30042005	박병곤	Lumbar	200	1군 (HC)		2025-10-15	Fresh CSF	Decode cell	600,000	82	O
W	2025-10-30	**20629**	33545817	최승진	Ventricle	9	2군-LMC		2025-10-30	Fresh CSF	Decode cell	7,000	80	O
Z	2025-11-03	**3240**	33195494	유형선	Lumbar	155	3군-BM		2025-11-03	Fresh CSF	Decode cell	23,000	92	O
AA	2025-12-10	**4409**	33345760	조순석	Lumbar	96	4군-BT		2025-12-10	Frozen cell stock (Cell Banker2)**	NCC	600,000	90	O
AB	2025-12-11	**1857**	33548851	이옥화	Lumbar	169	2군-LMC		2025-12-11	Fresh CSF	Decode cell	100,000	89	O
AC	2026-01-05	**1858**	20255828	강성숙	Ventricle	8	1군 (CC)		2026-01-05	Fresh CSF	Decode cell	32,000	100	O
AE	2026-01-20	**20632**	30941164	박국화	Lumbar	160	2군-LMC		2026-01-20	Fresh CSF	Decode cell	20,000	86	O
AG	2026-01-29	**1854**	33627530	최광태	Ventricle	10	1군 (CC)		2026-01-29	Fresh CSF	Decode cell	28,000	97	O
AH	2026-02-05	**20635**	33540683	김진설	Ventricle	12	2군-LMC		2026-02-05	Frozen cell stock (Cell Banker2)**	NCC	80,000	79	O
AK	2026-03-13	**20638**	33305490	유순심	Ventricle	10	2군-LMC		2026-03-13	Fresh CSF	Decode cell	17,000	83	O
AL	2026-04-03	**20651**	33630957	이준희	Lumbar	8.5	2군-LMC		2026-04-03	Fresh CSF	Decode cell	64,000	86	O
AM	2026-04-03	**20642**	33633114	김진모	Ventricle	9.5	2군-LMC		2026-04-03	Fresh CSF	Decode cell	45,000	100	O
AN	2026-04-10	**1873**	33591349	변기춘	Lumbar	58	1군 (CC)		2026-04-10	Fresh CSF 20ml / Freezing 38ml	Decode cell	53,000	96	O
AQ	2026-05-13	**20645**	33525576	최경숙	Lumbar	9	2군-LMC		2026-05-13	Fresh CSF	Decode cell	7,700	91	O
AR	2026-05-13	**20647**	33625420	박선옥	Lumbar	6	2군-LMC		2026-05-13	Frozen cell stock (Cell Banker2)**	NCC	5,425	78	O
AS	2026-05-13	**20649**	33625420	박선옥	Ventricle	11	2군-LMC		2026-05-13	Frozen cell stock (Cell Banker2)**	NCC	12,425	94	O
AT	2026-06-02	**20651**	33630062	윤수정	Ventricle	9.5	2군-LMC		2026-06-02	Fresh CSF	Decode			

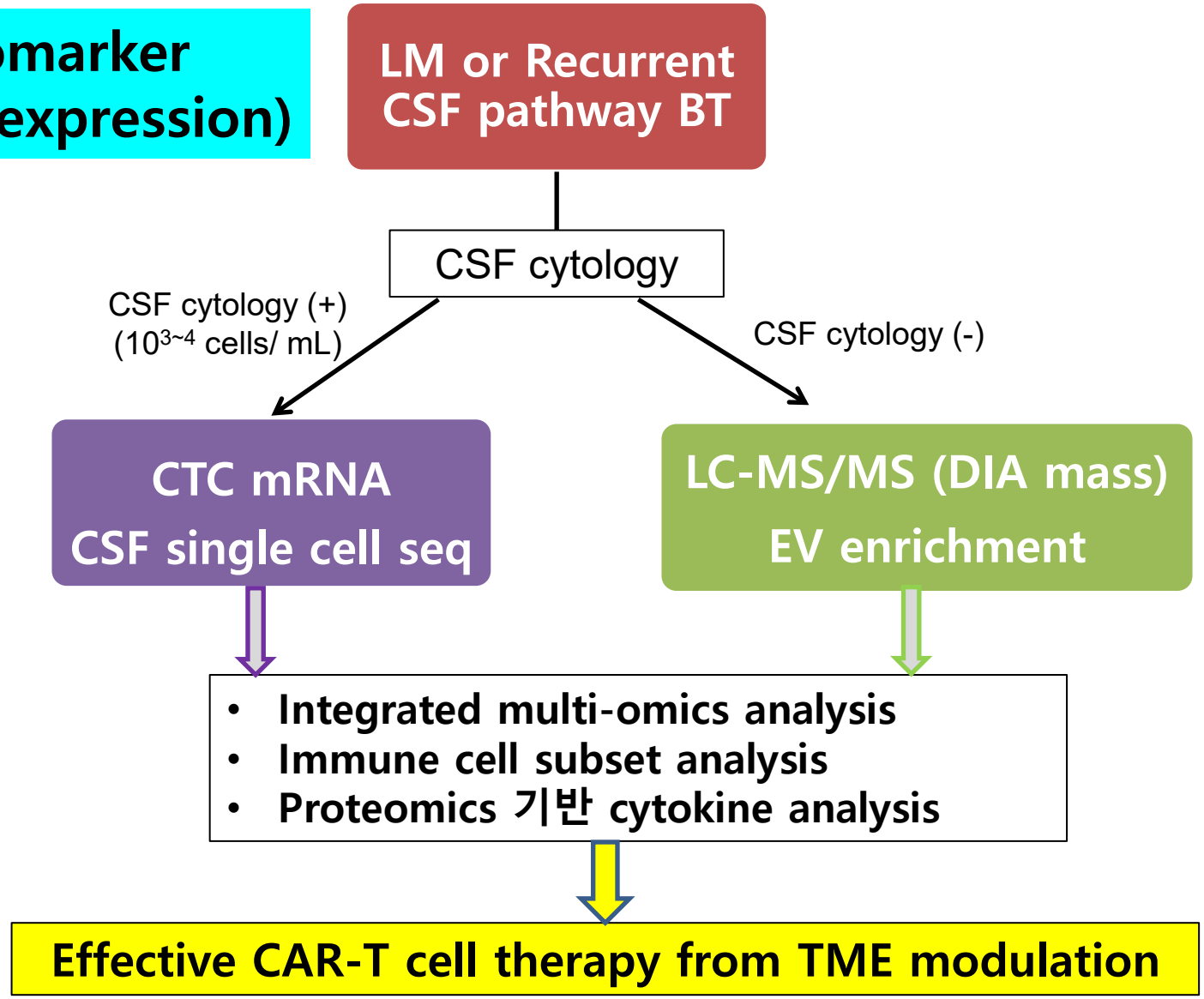
- 분석가능 세포수를 최소 환자군 1.0x10^4, 대조군 1.0x10^{3}으로 정하여 25/46 샘플 raw data확보
- LM 군 20개 이상, 대조군 각 10개 이상이 목표
- 단가는 500-700만원

scRNA SEQ 분석가능 샘플수	
N	**25**
1군 (HC, CC)	6
2군 (LMC)	13
3군 (BM)	4
4군 (BT)	2

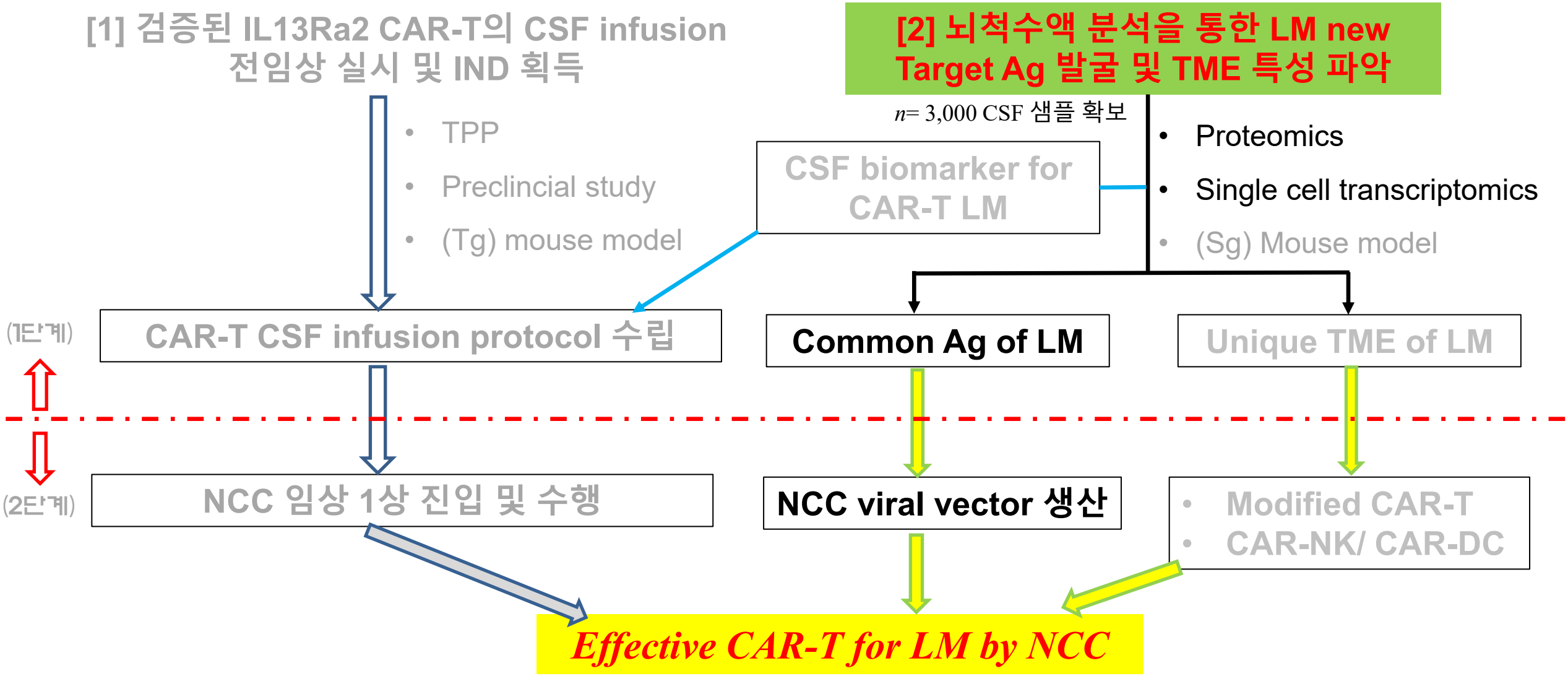
Raw data

File name	File size	md5sum
JTW_CSF_250827_WTA_1.fq.gz	11.17GB	50835a55c0867c3e0b17ef1028ad515f
JTW_CSF_250827_WTA_2.fq.gz	10.11GB	6903c9aa592d915d4b571131578d97e3
JTW_CSF_0910_WTA_1.fq.gz	6.42GB	3a1eb727f8b431dd0d96e0c8cf108150
JTW_CSF_0910_WTA_2.fq.gz	5.37GB	706c57aec1b98f02957edcb47dd3904e

CSF biomarker (target Ag expression)



연구개발의 최종 목표


[1] 검증된 IL13Ra2 CAR-T의 CSF infusion 전임상 실시 및 IND 획득
• TPP
• Preclincial study
• (Tg) mouse model
[2] 뇌척수액 분석을 통한 LM new Target Ag 발굴 및 TME 특성 파악
n= 3,000 CSF 샘플 확보
CSF biomarker for CAR-T LM
• Proteomics
• Single cell transcriptomics
• (Sg) Mouse model
(1단계)
CAR-T CSF infusion protocol 수립
Common Ag of LM
Unique TME of LM
(2단계)
NCC 임상 1상 진입 및 수행
NCC viral vector 생산
• Modified CAR-T
• CAR-NK/ CAR-DC
Effective CAR-T for LM by NCC

연구 추진 체계

연구총괄 책임자

곽호신

뇌척수 CRC

PI lab

윤지혜, 오승언

IL13Ra2 CSF admin 임상 진입 및 1상

셀렙메드, 박현진/박미림

- 전임상 평가
- LM transgenic mouse model
- 임상 IND 획득
- LM & CSF BM meta. 1상 수행

LM TME 분석 및 modulation

한충용, 박은정

- CSF s.c. transcriptomics
- LM immune subset analysis
- LM TME modulation strategy
- CAR-NK/CAR-DC in LM

LM New Ag 발굴 및 LM mouse model

곽호신. NCC Core

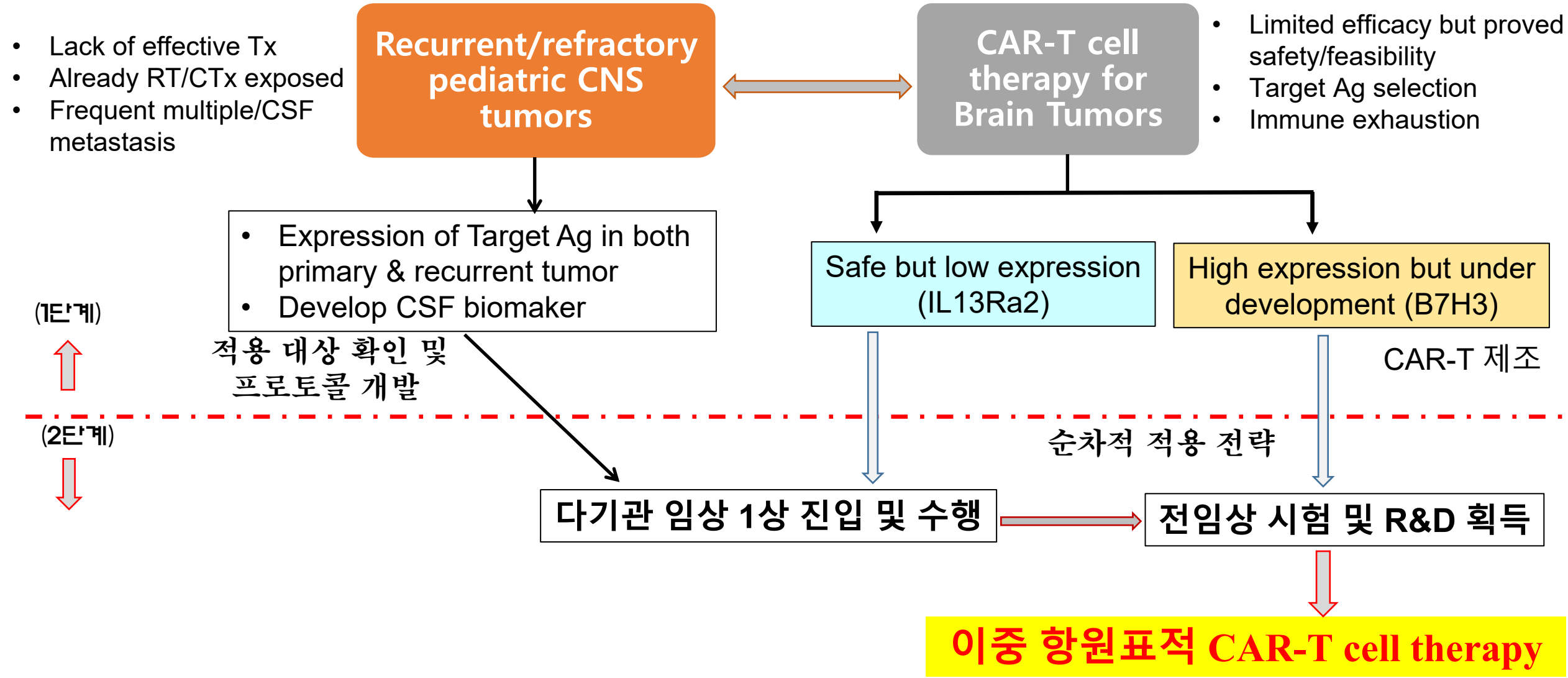
- CSF biomarker by LC-MS/MS
- CSF proteomics
- LM new target Ag validation
- LM syngenic mouse model
- LM TME modulation 실험

연구개발 성과의 활용방안 및 기대효과

지적재산권

- **CAR-T 뇌척수액 주입 protocol**
  - 뇌척수액 주입의 SAE 대처법 개발
  - 타기관의 소량 반복 주입에 비해 적정량 적정시기 반복 주입
  - LM 환자에 흔히 발생하는 CSF flow disturbance에 대응할 수 있는 protocol
  - CSF pathway metastasis의 tumor burden & growth pattern에 따른 최적의 protocol 개발
  - CSF 분석을 통한 CAR-T TME 연구의 귀중한 자료로 활용
- **기존에 치료법이 없는 LM 및 CSF pathway metastasis**
  - 독성 없는 효과적 치료 내지 완치를 기대
- **LM new target Ag 발굴**
  - 암종별 new target Ag의 가능성도 있음
  - 셀렙메드의 CMC 노하우와 국립암센터 면역세포 치료 사업단의 시너지로 해당 Ag의 viral vector 및 CAR-T 생산
  - LM 특유의 TME에 따른 target 발견 가능성; floating cancer cells vs. pial spread
- **LM CAR-T TME 연구**
  - 뇌척수액 특유 면역환경의 귀중한 자료
  - Modified CAR-T 또는 CAR-NK/ CAR-DC개발

<연구과제 수행 흐름도>


Lack of effective Tx
Already RT/CTx exposed
Frequent multiple/CSF metastasis
Recurrent/refractory pediatric CNS tumors
CAR-T cell therapy for Brain Tumors
Limited efficacy but proved safety/feasibility
Target Ag selection
Immune exhaustion
Expression of Target Ag in both primary & recurrent tumor
Develop CSF biomaker
Safe but low expression (IL13Ra2)
High expression but under development (B7H3)
(1단계)
적용 대상 확인 및 프로토콜 개발
CAR-T 제조
(2단계)
순차적 적용 전략
다기관 임상 1상 진입 및 수행
전임상 시험 및 R&D 획득
이중 항원표적 CAR-T cell therapy