Targeted Brain Tumor Therapy-Revisiting the Past

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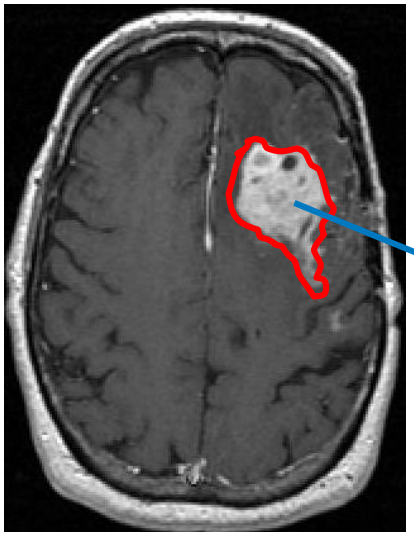
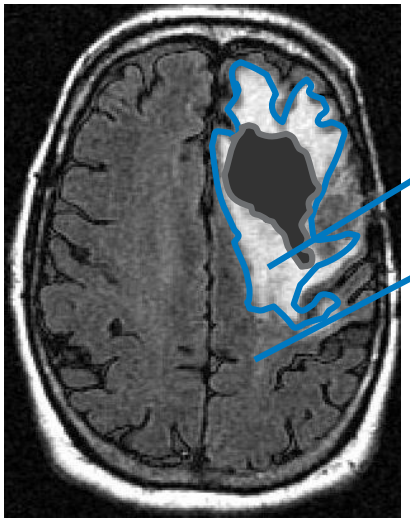
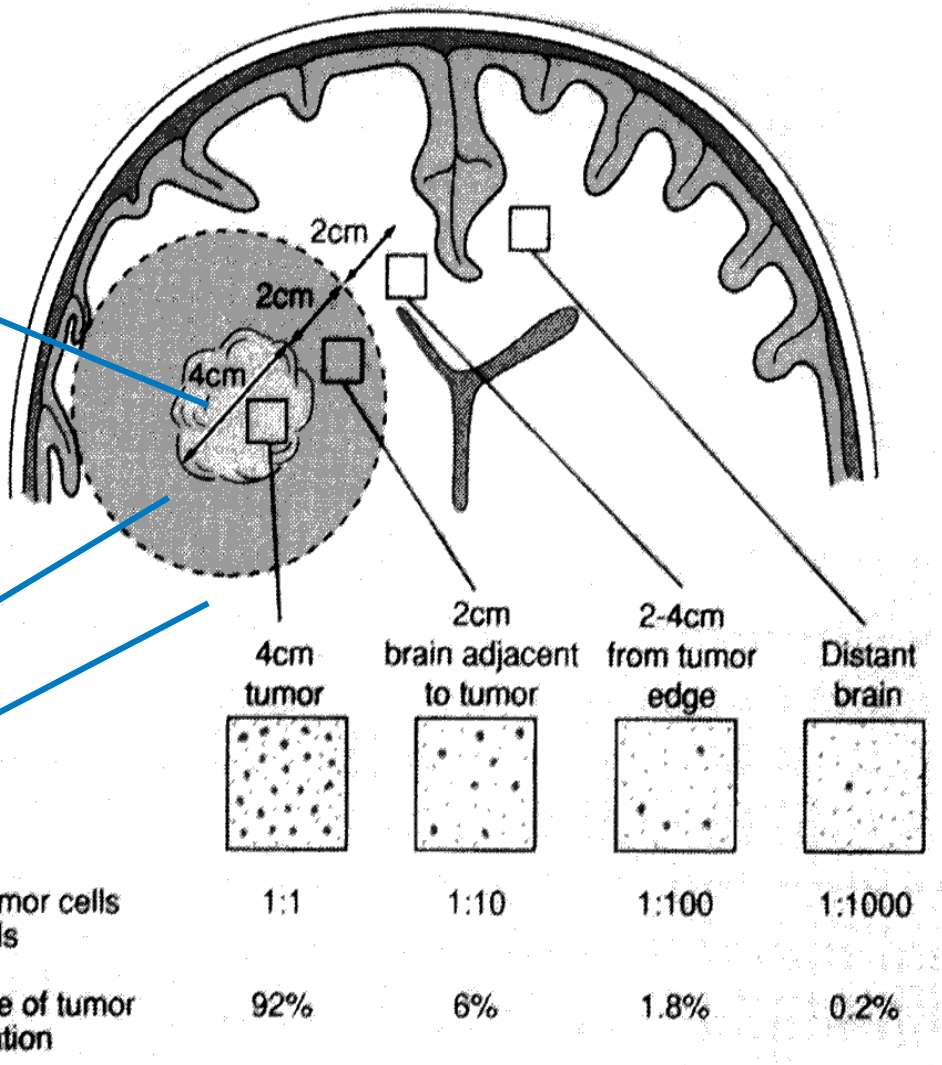
Glioblastoma Multiforme
Solid and Infiltrative Tumor







GBM – Limited Treatment Options

- Surgery
  - Survival benefit has been shown for a gross-total or near-total resection (typical 6 week improvement)
  - Not curative due to infiltrative nature of tumor
- Radiation Therapy
  - Survival benefit is clear
  - Not curative due to normal tissue tolerance
- Chemotherapy – limited impact due to delivery barrier
  - BCNU IV (FDA approved in 1973)
  - Gliadel® (BCNU) Wafers (FDA approved in 1996 [recurrent] and 2003 [newly diagnosed])
  - Temozolomide (FDA approved in 2005 [newly diagnosed])
- Combined Best Practices
  - Aggressive Surgery
  - Postoperative Chemoradiation (XBRT with Temozolomide)
  - Median survival 18 months

Anti-Tumor Therapy List

Radiation Therapy

- **Cranial RT NOS**
- **Gliasite RTS**
- **^{131}I-Chlorotoxin**
- **Radiosurgery**
- **Gamma Tile**

Biological/Cytostatic Agents

- **Bevacizumab**
- **Celecoxib**
- **Cis retinoic acid**
- **Erlotinib**
- **Gefitinib**
- **Imatinib**
- **Interferon alpha**
- **Rapamycin**
- **Sorafenib**
- **Tamoxifen**
- **Thalidomide**

Cytotoxic Agents

- **Carboplatin**
- **Carboplatin/etoposide**
- **Carmustine**
- **Cisplatin**
- **Cisplatin/etoposide**
- **Cyclophosphamide**
- **Cytotoxic agents NOS**
- **Etoposide**
- **Fotemustin**
- **Hydroxyurea**
- **Hydroxyurea/imatinib**
- **Irinotecan**
- **Liposomal doxorubicin**
- **Lomustine**
- **Procarbazine**
- **Temozolomide**
- **Vincristine**
- **Vinorelbine**

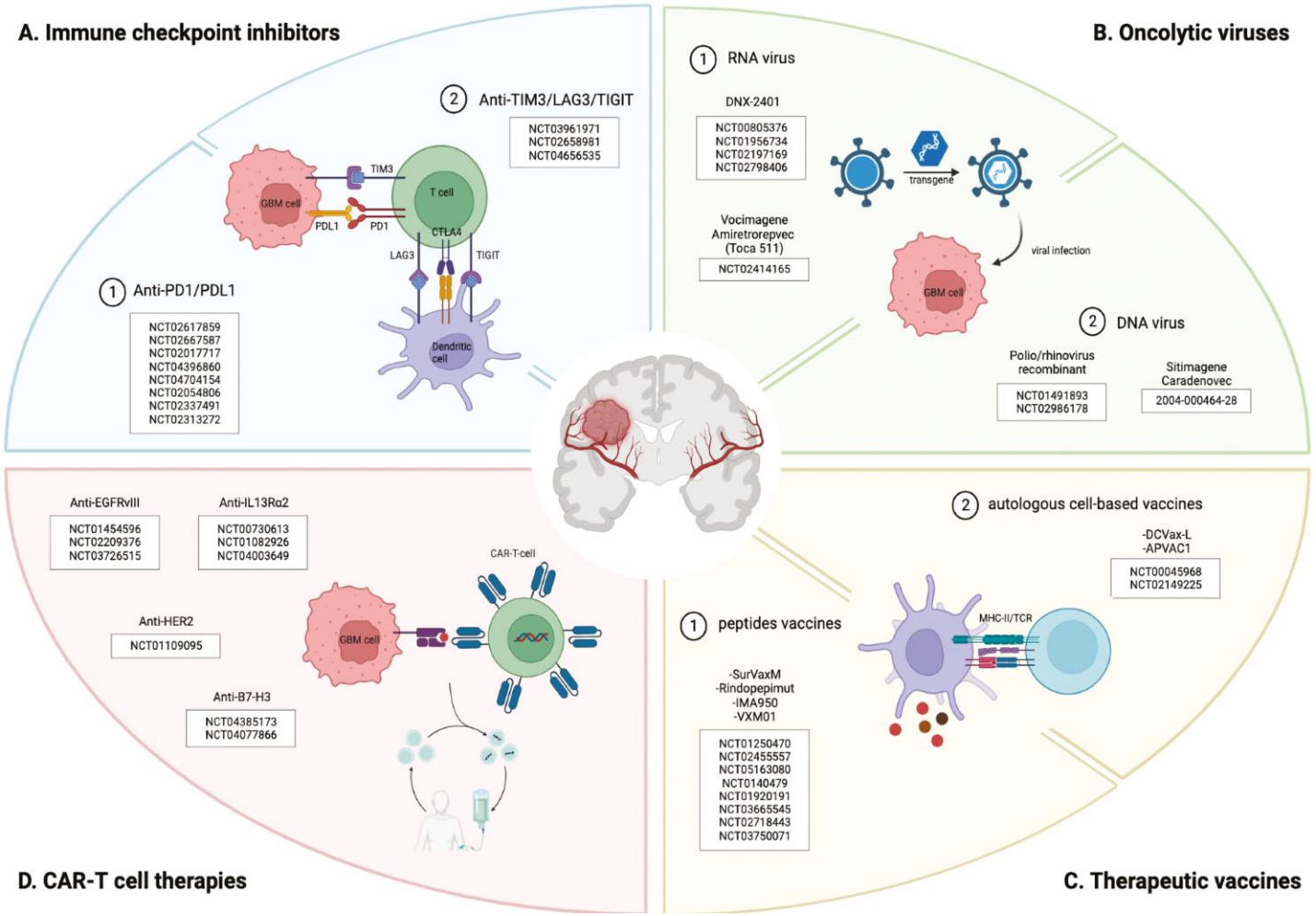
Investigational Agents

- **2-methoxyestradiol**
- **Artemisinin**
- **Cilengitide**
- **Depsipeptide**
- **Enzastaurin**
- **Everolimus**
- **Immunotherapy**
- **Investigational agent NOS**
- **Suberoylanilide Hydroxyamic acid**

Intracerebral Agents

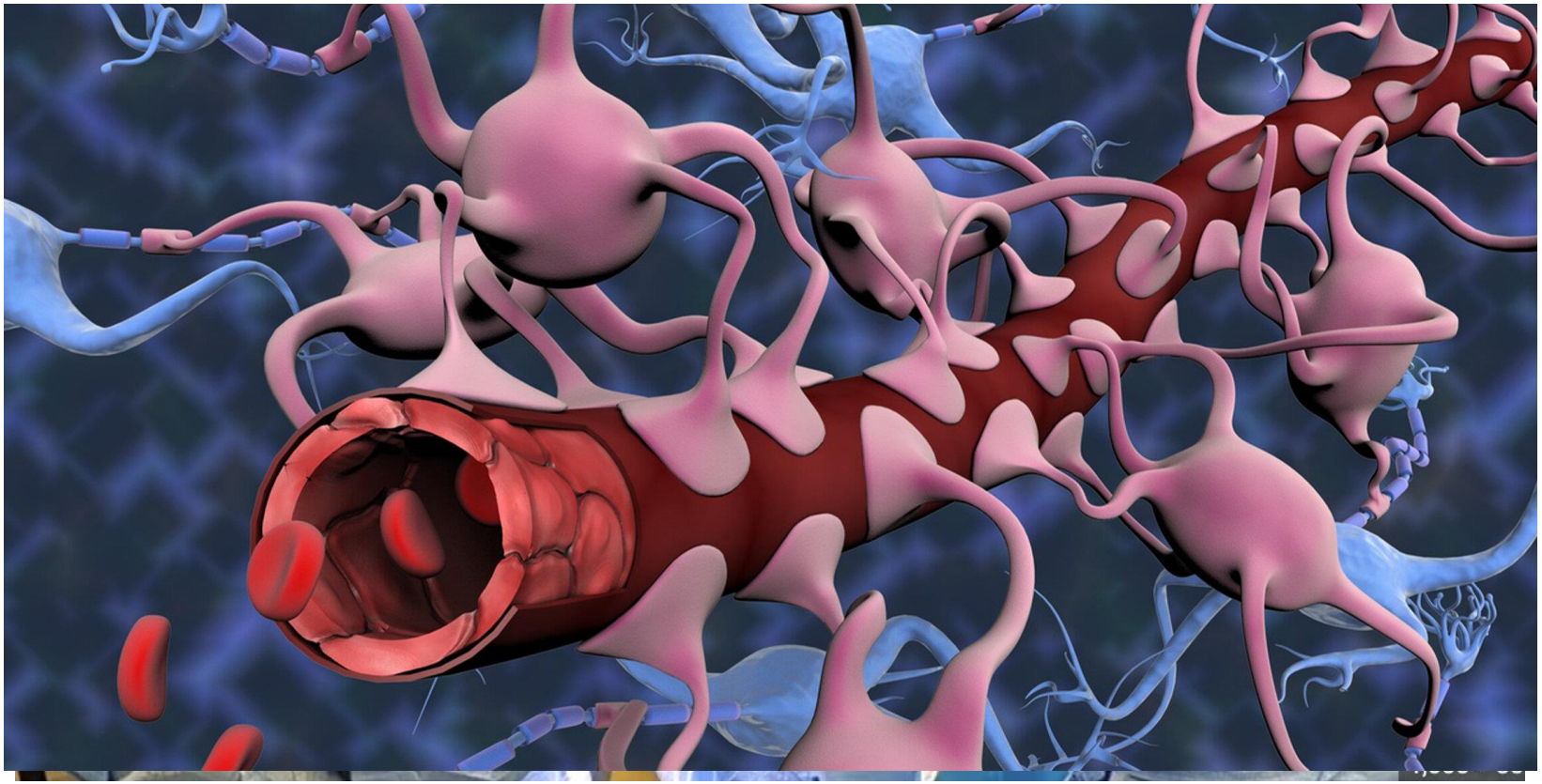
- **Carmustine wafer**
- **IL13-PE38**
- **Transferrin-CRM107**
- **Antisense oligo TGF-beta**
- **HSV (CAN-3110)**
- **Polio Virus**

Immunotherapy for Glioblastoma Multiforme…



Oncologist, oyad321, https://doi.org/10.1093/oncolo/oyad321

Drug Delivery –
The pitfall of most therapies



Blood Brain Barrier

Drug Delivery – The pitfall of most therapies

- Systemic therapy (blood-brain barrier)
  - ¬ Less than 0.1% of systemic chemotherapies enter the CNS tissue
  - ¬ Less than 0.006% of proteins delivered systemically enter the CNS tissue
- Direct therapy (diffusion based)
  - ¬ Intrathecal therapy
    - methotrexate penetration into tissue is less than 4 mm from surface
    - albumin less than 2mm from surface
  - ¬ Intracavitary (polymer based)/intracerebral injection
    - Small molecule penetration into tissue 3-6 mm from point source
    - Gene therapy transfection seen within 2 mm from point source

CONVECTION ENHANCED DELIVERY (CED) VS. STANDARD DELIVERY (DIFFUSION)

Systemic (oral or I.V.) delivery of drug (+/- BBB disruption)

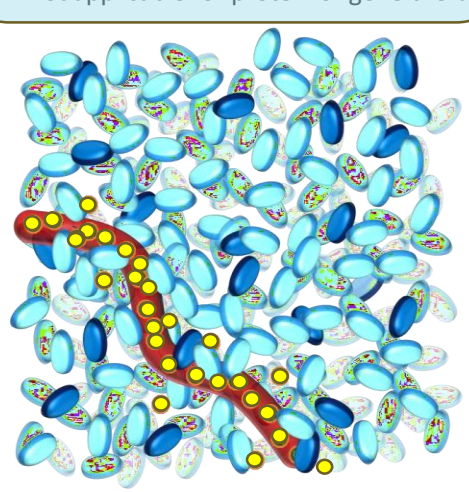
- Limited by capillary density and BBB
- <0.01% of drug enters the brain tissue
- High risk of systemic toxicity
- High risk of-off target effects
- Not applicable for protein or gene therapy

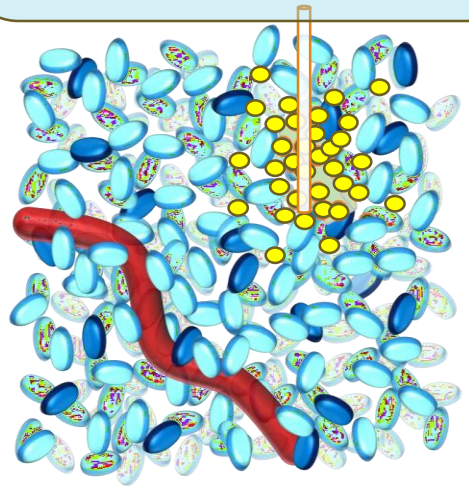
Injection (or local release) of drug (limited by diffusion)

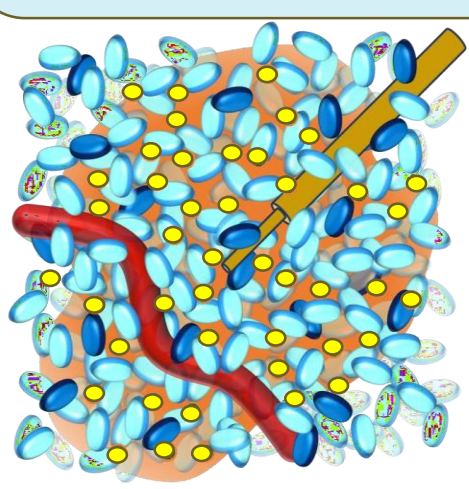
- Penetration into tissue 2-4 mm from source
- Limited systemic toxicity
- High risk of local toxicity
- Not applicable for protein or gene therapy

Convection enhanced Delivery (CED)

- homogeneous drug distribution in large volumes of brain tissue
- Drug concentration >1,000,000X achievable
- No systemic toxicity
- No local toxicity
- Can be used for protein and gene therapy

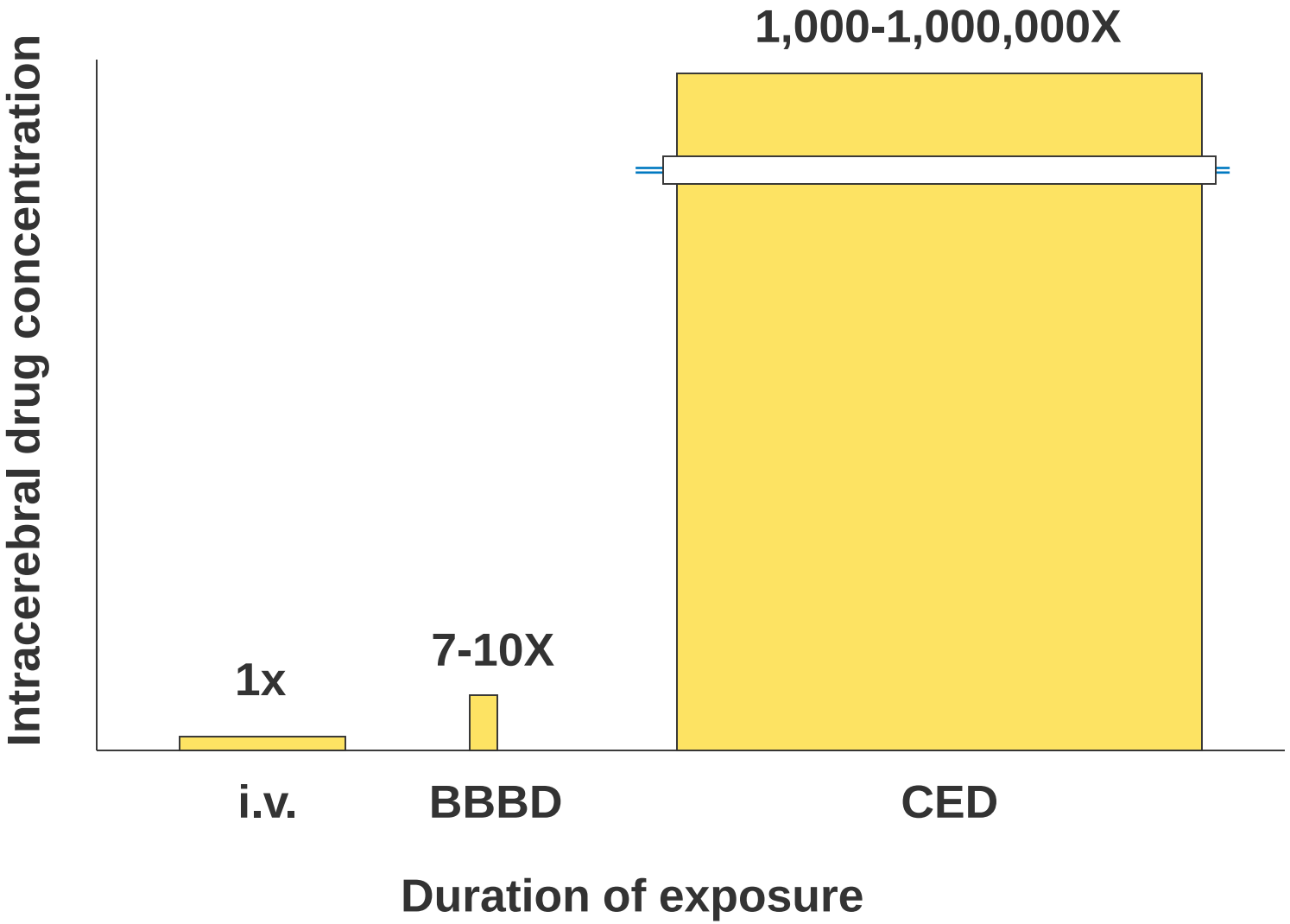






Brain tissue (blue) Blood vessel (red) Drug (yellow =)

Drug delivery - AUC



Advantages of CED:

- Method of delivery is safe into functional brain tissue (evidence from animal and human studies).
- Small amounts of drug are necessary for therapy (no dilution into 5L of blood as in systemic therapies).
- Pharmokinetics simplified (no first pass effect, liver/renal metabolism).
- Significantly increased AUC (area under the curve).
- Systemic toxicities eliminated.*
- Opens up the therapeutic window

*dependent on physical parameters of drug

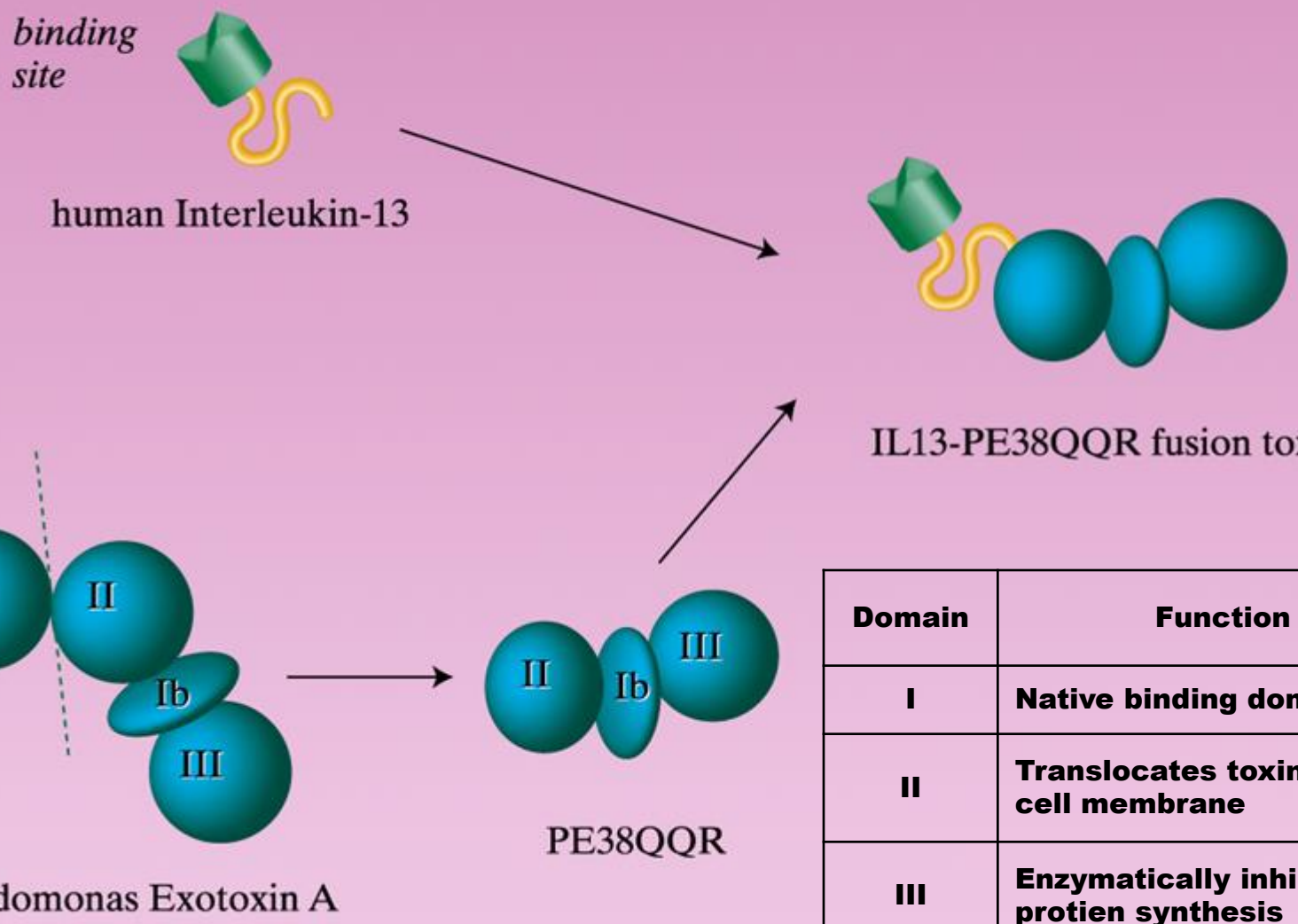
Disadvantages of CED:

- Invasive therapy (requires an operative procedure)
- Feasability of multiple treatments or prolonged (sustained) treatment unknown.
- Not applicable to all drugs
- Costs
- Distribution is affected by target site anatomy and technical parameters
  - Heterogeneity of tissue
  - Technical limitation of surgical delivery

Convection Enhanced Delivery Clinical Trials

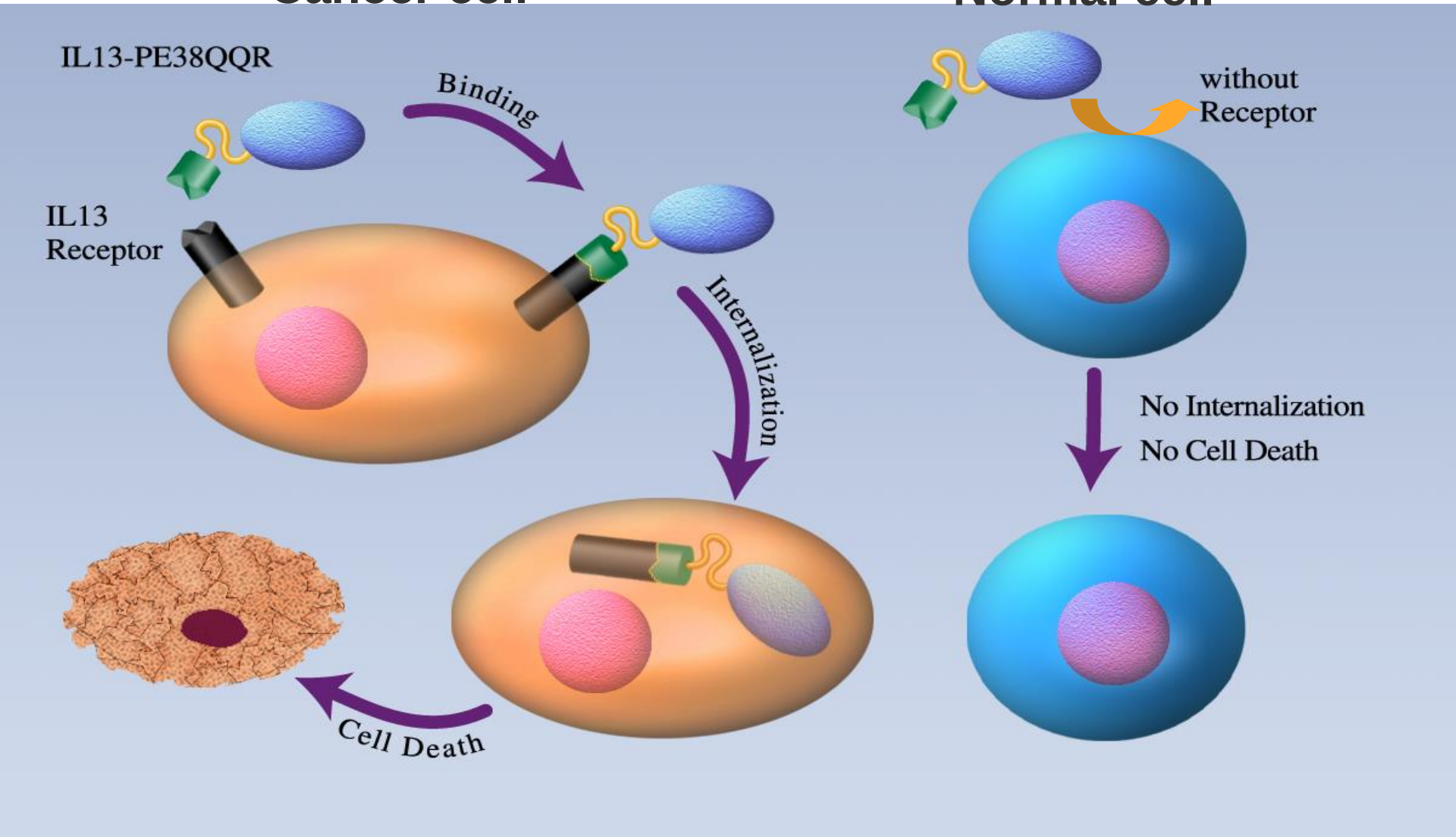
- **Recombinant Toxins (GBM)**
  - Transferrin-Diptheria Toxin (TransMID, Xenova)
  - IL4PE (Neurocrine/Protox), development stalled
  - TP38 (TGFa-PE38, IVAX/TEVA), development stalled
  - ***Cintredekin Besudotox (IL13PE38, Neopharm)***
  - IL4-PE38 (MDNA-55) - Medicinna
- **Immune modulation (GBM)**
  - Antisense TGF-beta
  - CpG oligo
- **Gene Therapy**
  - AAV-AADC (Parkinson's, AADC Gene def syndrome)
  - AAV-GDNF (Parkinson's)
  - AAV-GAD (Parkinsons's
  - AAV-BDNF (Alzheimer's)

Development of IL13-PE38QQR

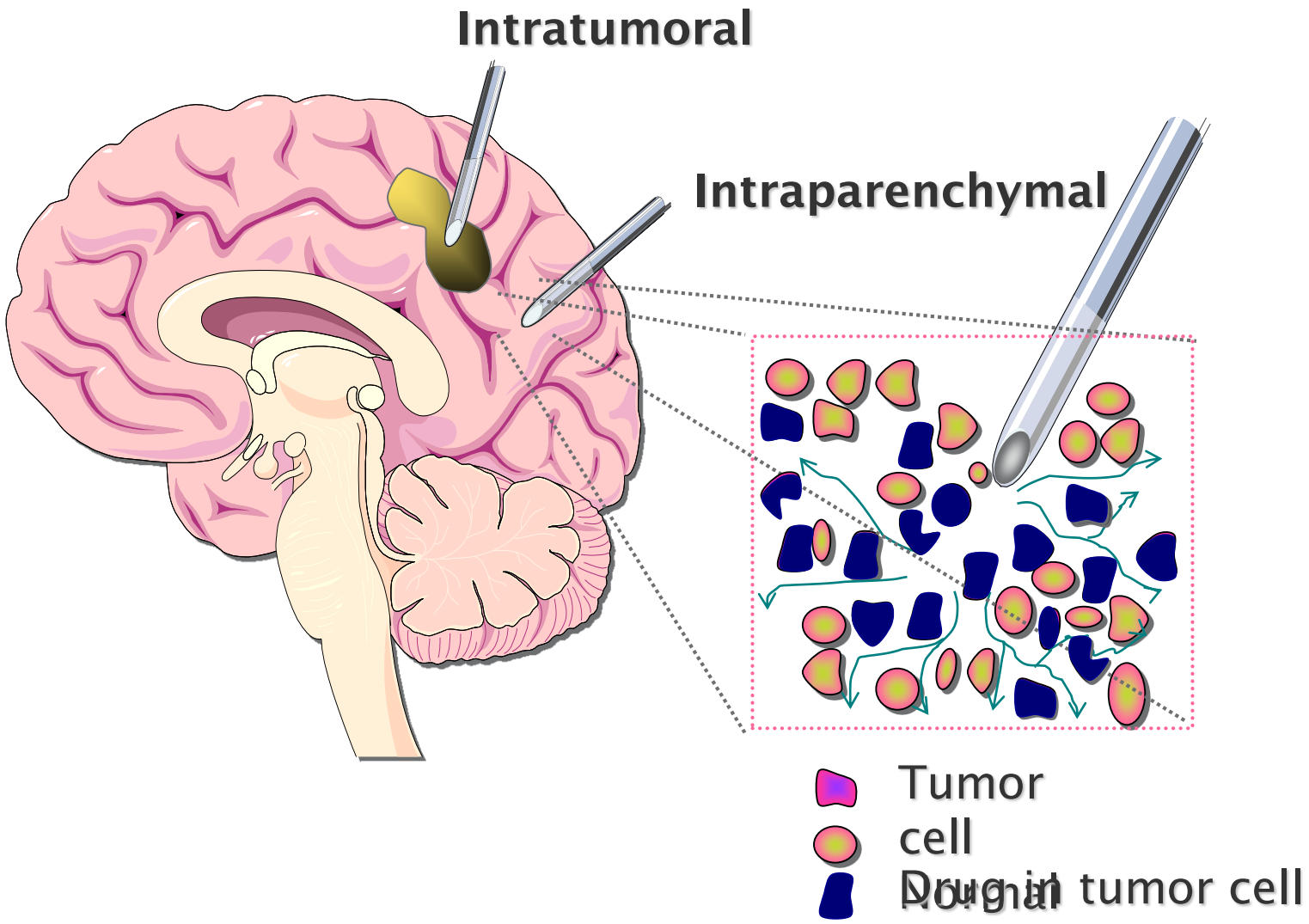


Domain	Function
I	Native binding domain
II	Translocates toxin across cell membrane
III	Enzymatically inhibits protien synthesis

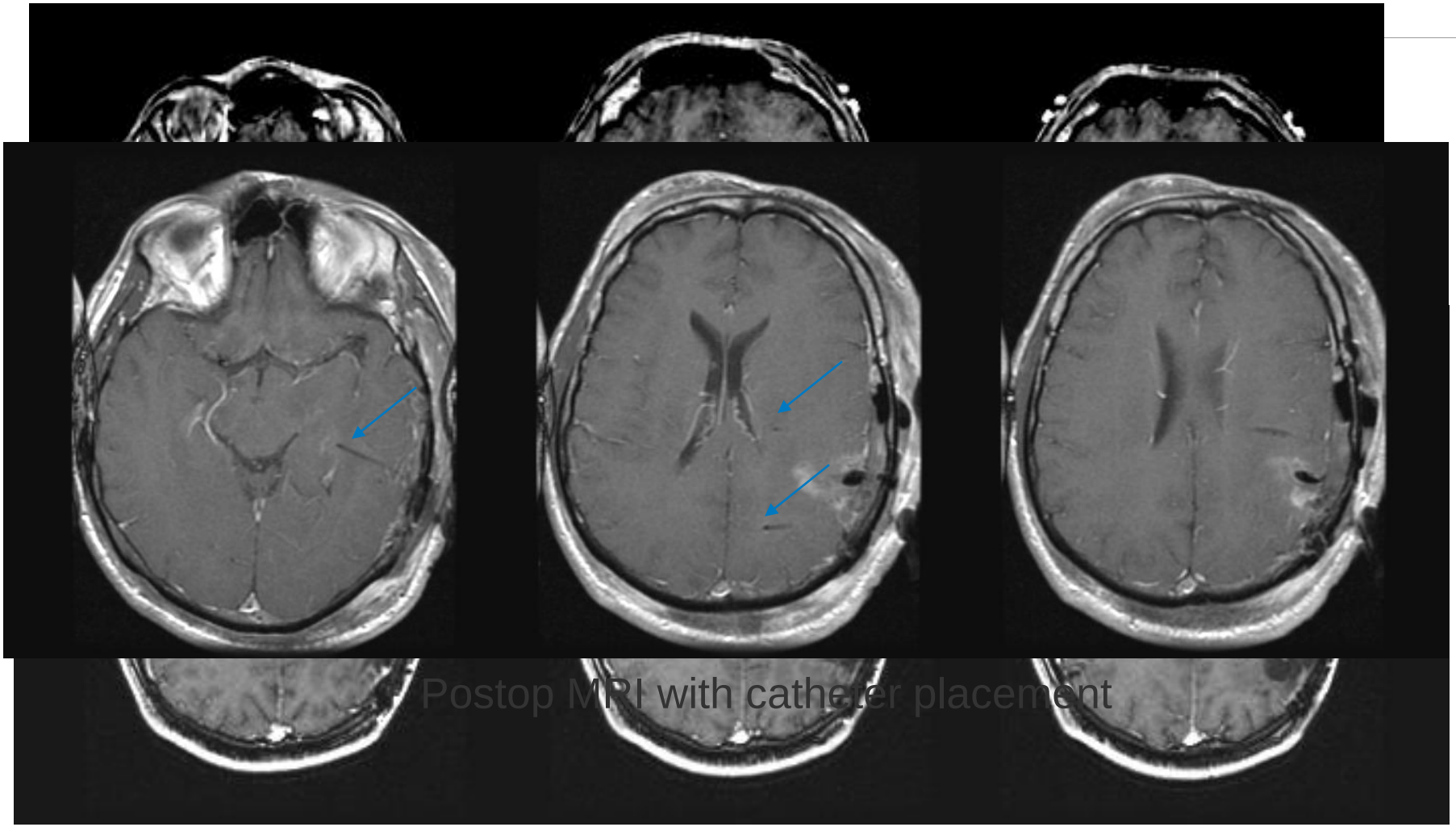
Cintredekin Besudotox
Specificity of Action: *Selective for Tumor Cells*



Convection-Enhanced Delivery (CED)

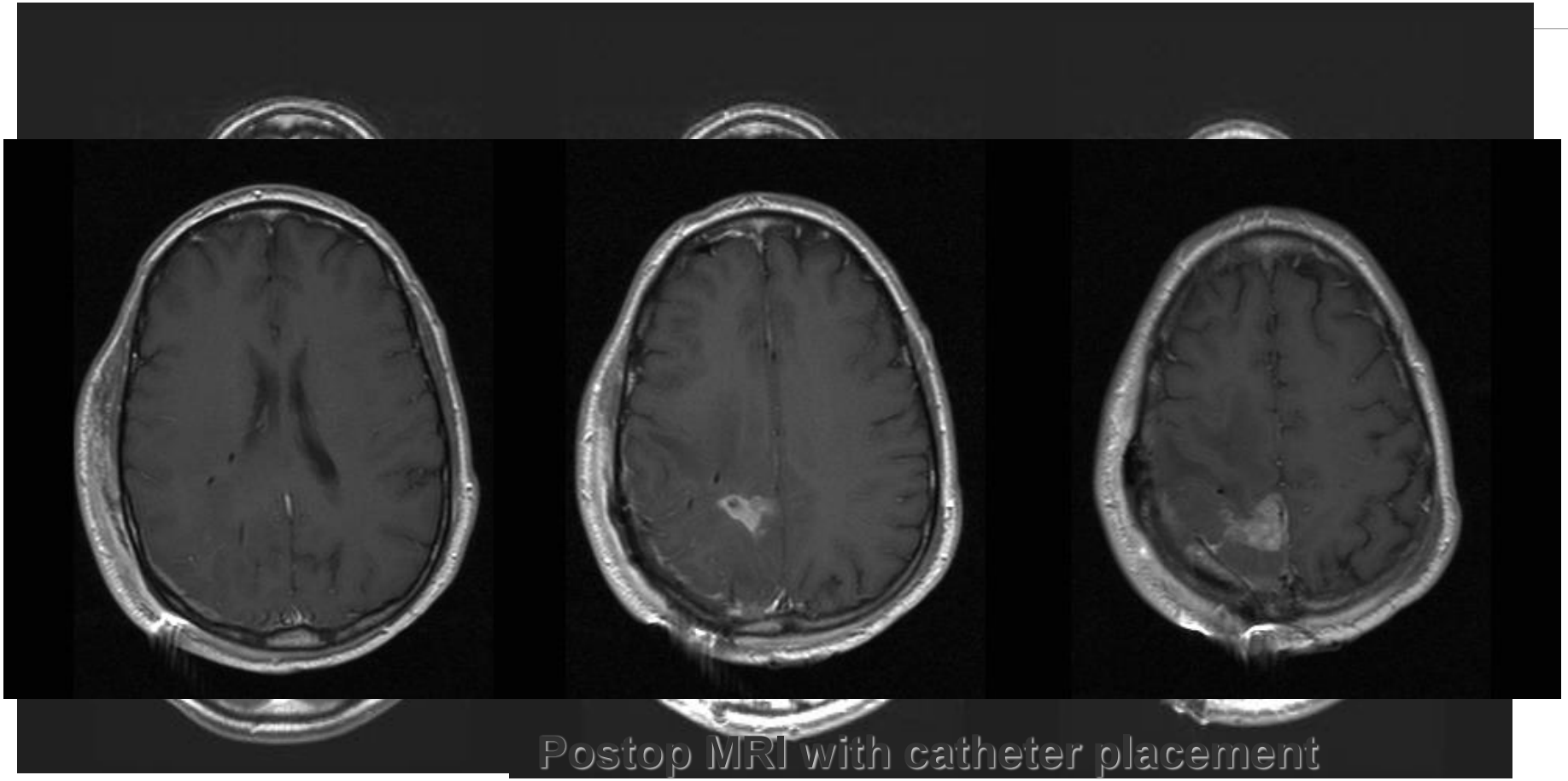


Delayed, focal recurrence (N=9)



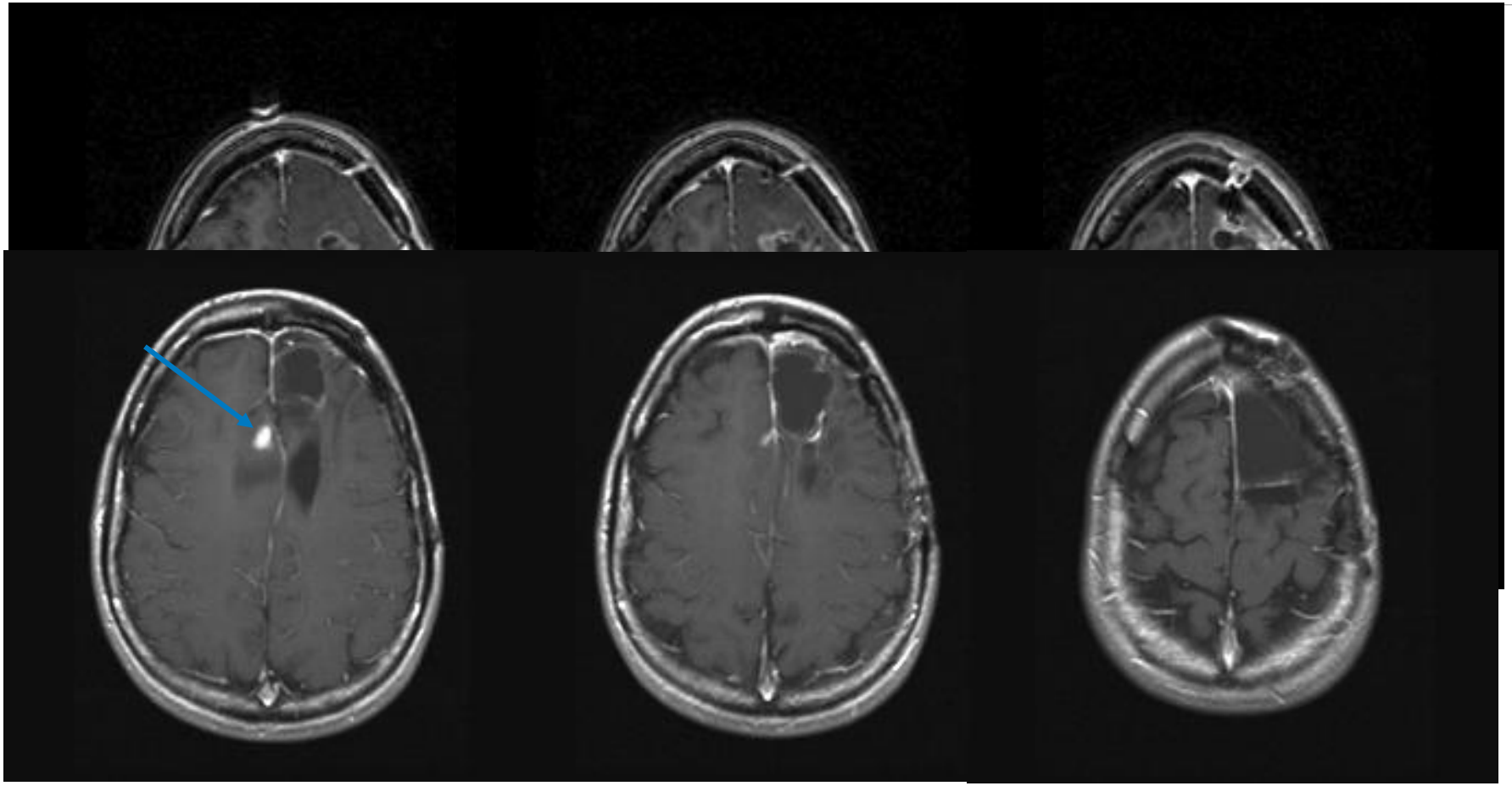
28 month post-IL13PE38 follow-up MRI scan following IL13PE38

Delayed, distant recurrence (N=4)



26 month follow-up MRI scan showing contralateral recurrence
Primary tumor site progression free

Delayed, distant recurrence (N=4)



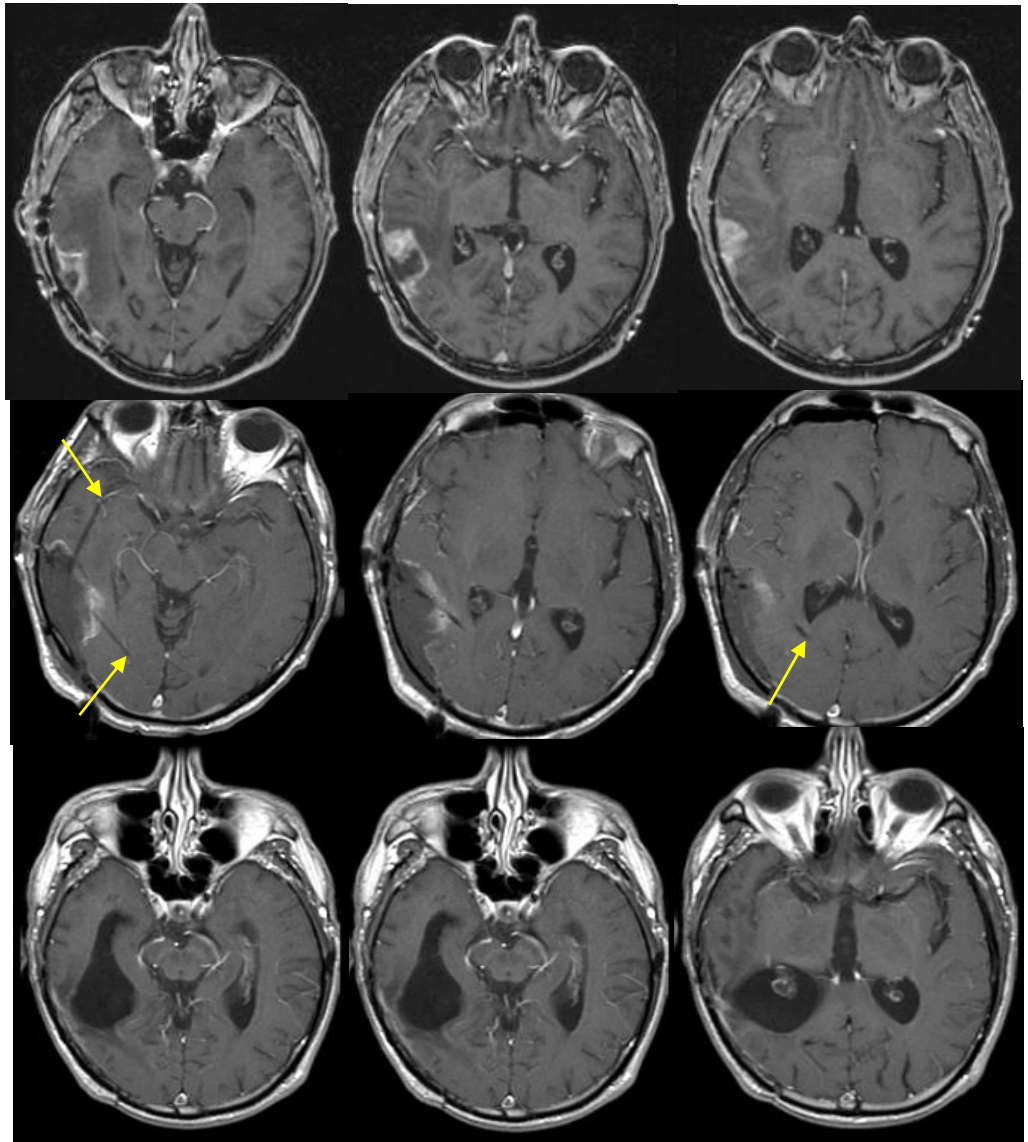
43 month post-IL13PE38 follow-up MRI showing contralateral recurrence
Primary site progression free

Prolonged Disease Free Survival (n=4)
58 year old Recurrent Right Temporal GBM

Pre-op

Post-op with catheters

Follow-up 62 months (Aug, 2006)



Forbes 2004

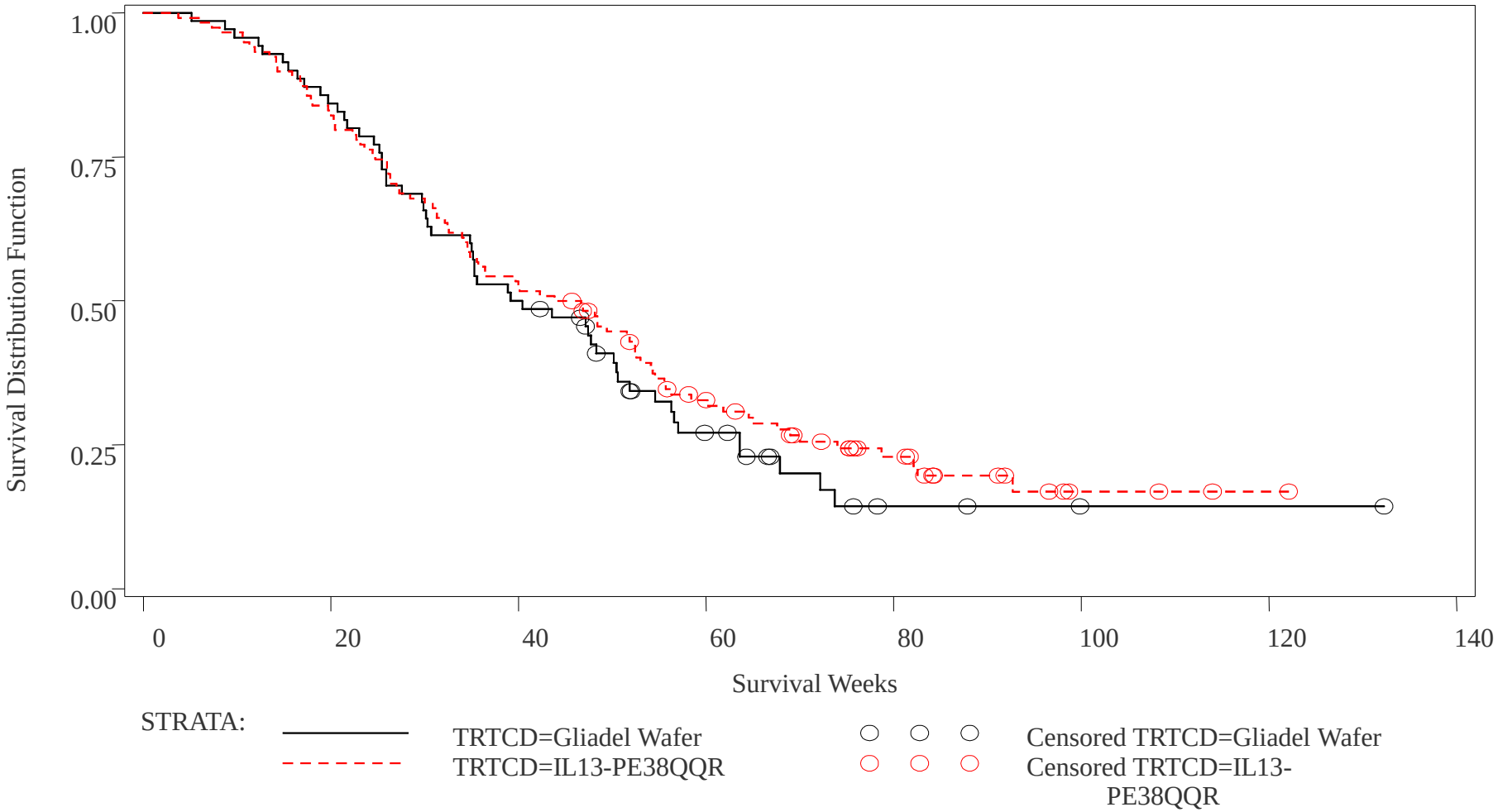
Lessons Learned

Drug infusion is well tolerated in the post-resection period

PRECISE Phase 3 Study

- Largest pivotal surgically-based randomized controlled study with an active comparator (Gliadel wafer) in recurrent GBM
- International multi-center study; 52 leading neurosurgery sites in the U.S., Canada, Europe and Israel
- 300 patients randomized in a 2:1 ratio (IL-13:Gliadel®) planned
- Study initiated March 4, 2004 and enrollment completed December 14, 2005
- Sponsor blinded to study results until protocol-defined (215 deaths) efficacy analysis trigger by Data Monitoring Committee (DMC)
- Independent oversight of the study by a DMC
- **Investigator Steering Committee (blinded to study results) to assess compliance with surgical procedures**

Overall Survival KM Estimate – Efficacy Evaluable Population



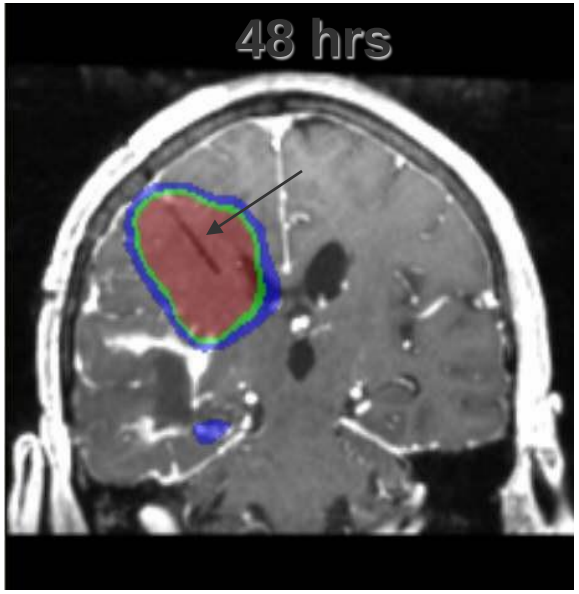
Treatment = IL13-PE38QQR: Total (Censored) = 118 (28) Median (95% CI) = 45.3 (34.71, 52.57)

Treatment = Gliadel wafer: Total (Censored) = 70 (16) Median (95% CI) = 39.8 (34.86, 50.43)

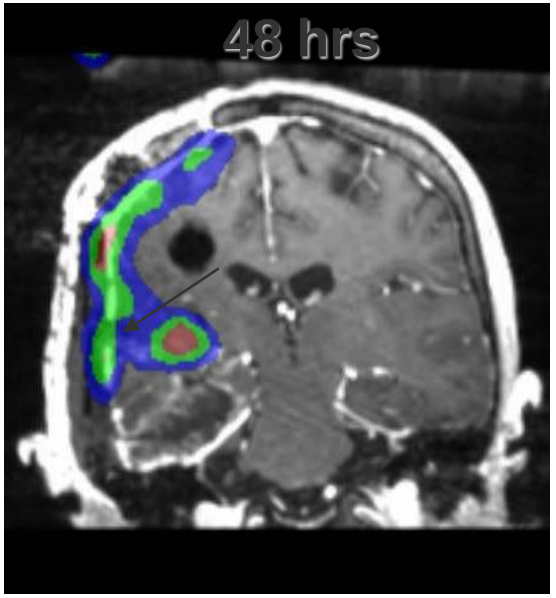
CB compared to Gliadel wafer hazard ratio: (2-sided 95% CI): 0.81 (0.58 to 1.14), p-value = 0.234

Poor drug distribution as a possible explanation for the results of the PRECISE trial.

Sampson JH, Archer G, Pedain C, Wembacher-Schröder E, Westphal M, Kunwar S, Vogelbaum MA, Coan A, Herndon JE, Raghavan R, Brady ML, Reardon DA, Friedman AH, Friedman HS, Rodríguez-Ponce MI, Chang SM, Mittermeyer S, Croteau D, Puri RK; PRECISE Trial Investigators. J Neurosurg. 2010 Aug;113(2):301-9. doi: 10.3171/2009.11.JNS091052. PMID: 20020841.

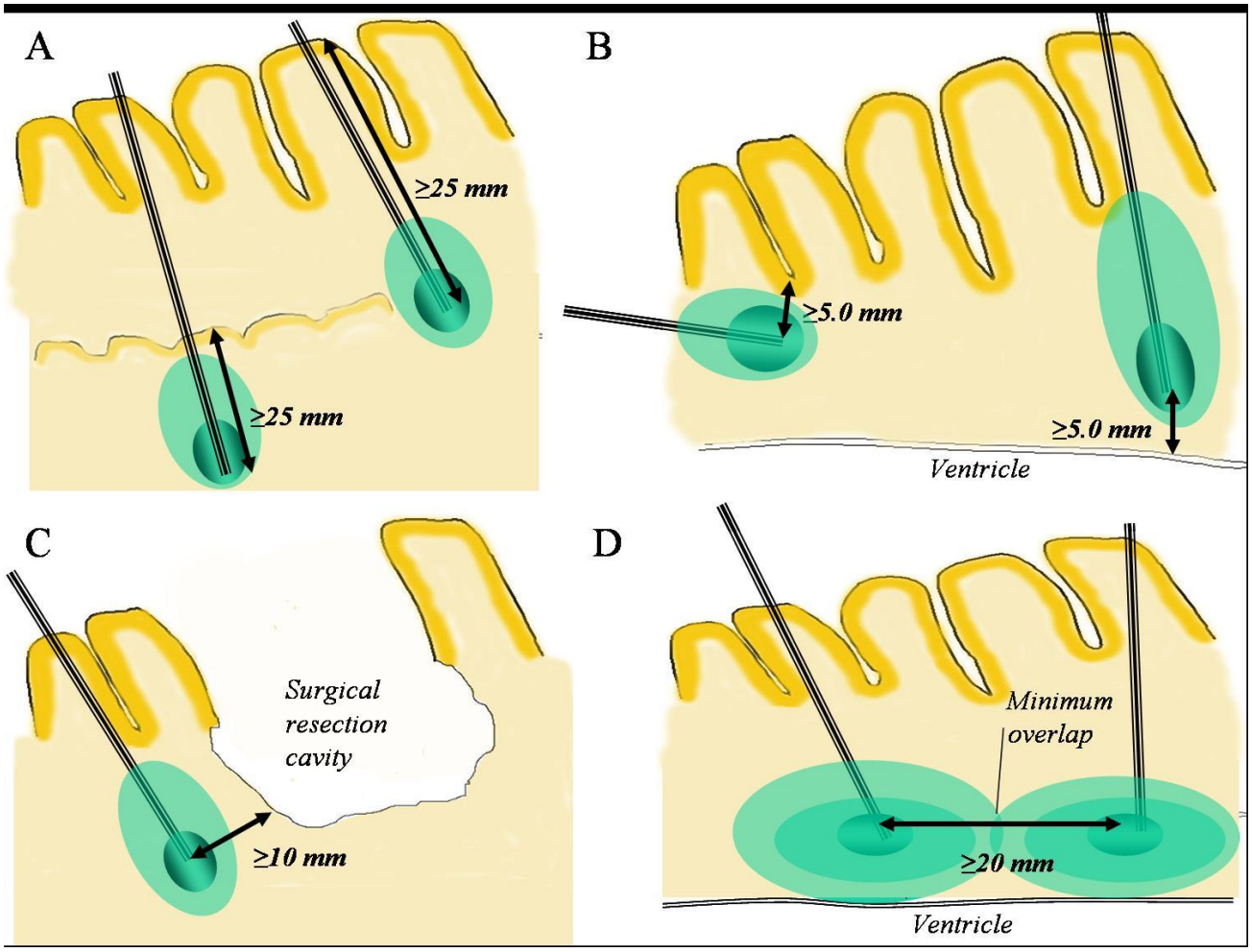


Good Distribution with Adequate Catheter Positioning

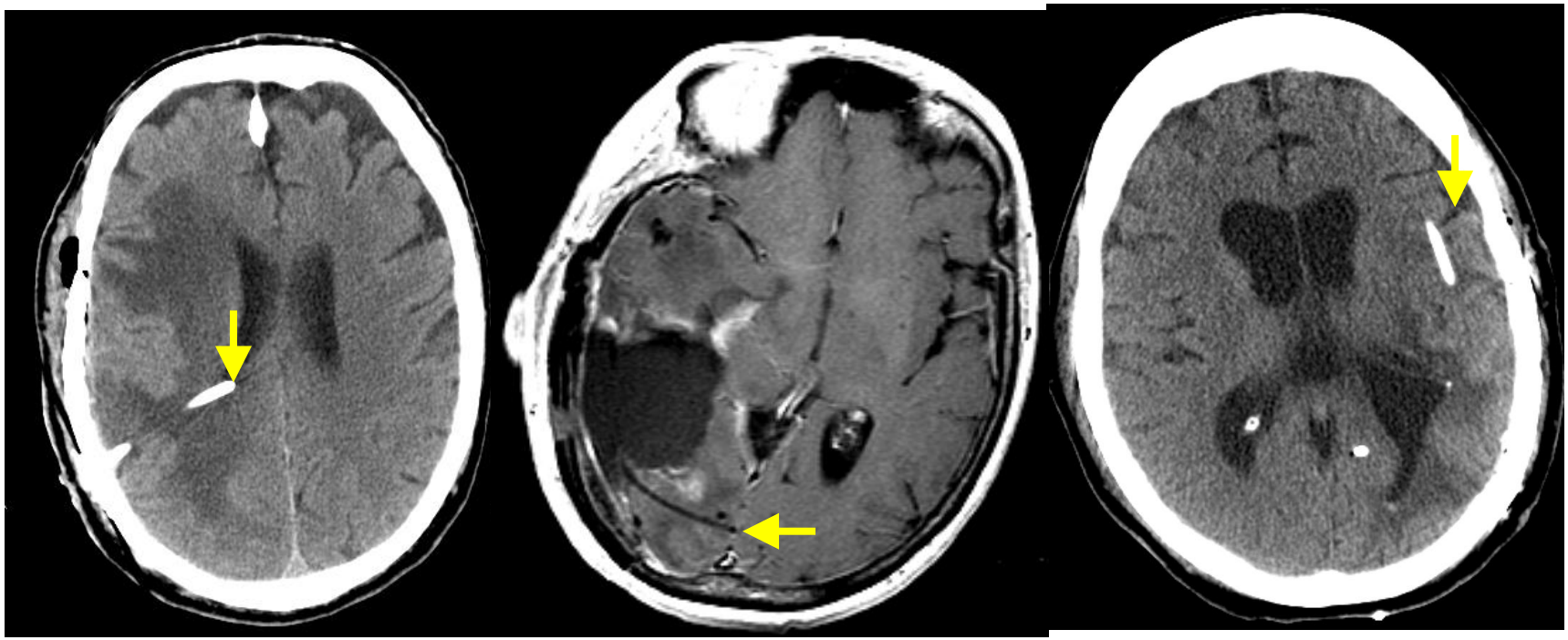


Poor Distribution due to Inadequate Catheter Positioning

SPECT superimposed on T1-weighted MRI with gadolinium;
SPECT signal range is shown as percentage of peak 6-hour signal:
25-50% (blue), 50-75% (green), and 75-100% (red).


A
≥25 mm
≥25 mm
B
≥5.0 mm
≥5.0 mm
Ventricle
C
Surgical
resection
cavity
≥10 mm
D
Minimum
overlap
≥20 mm
Ventricle

Examples of Suboptimal Catheter Positioning

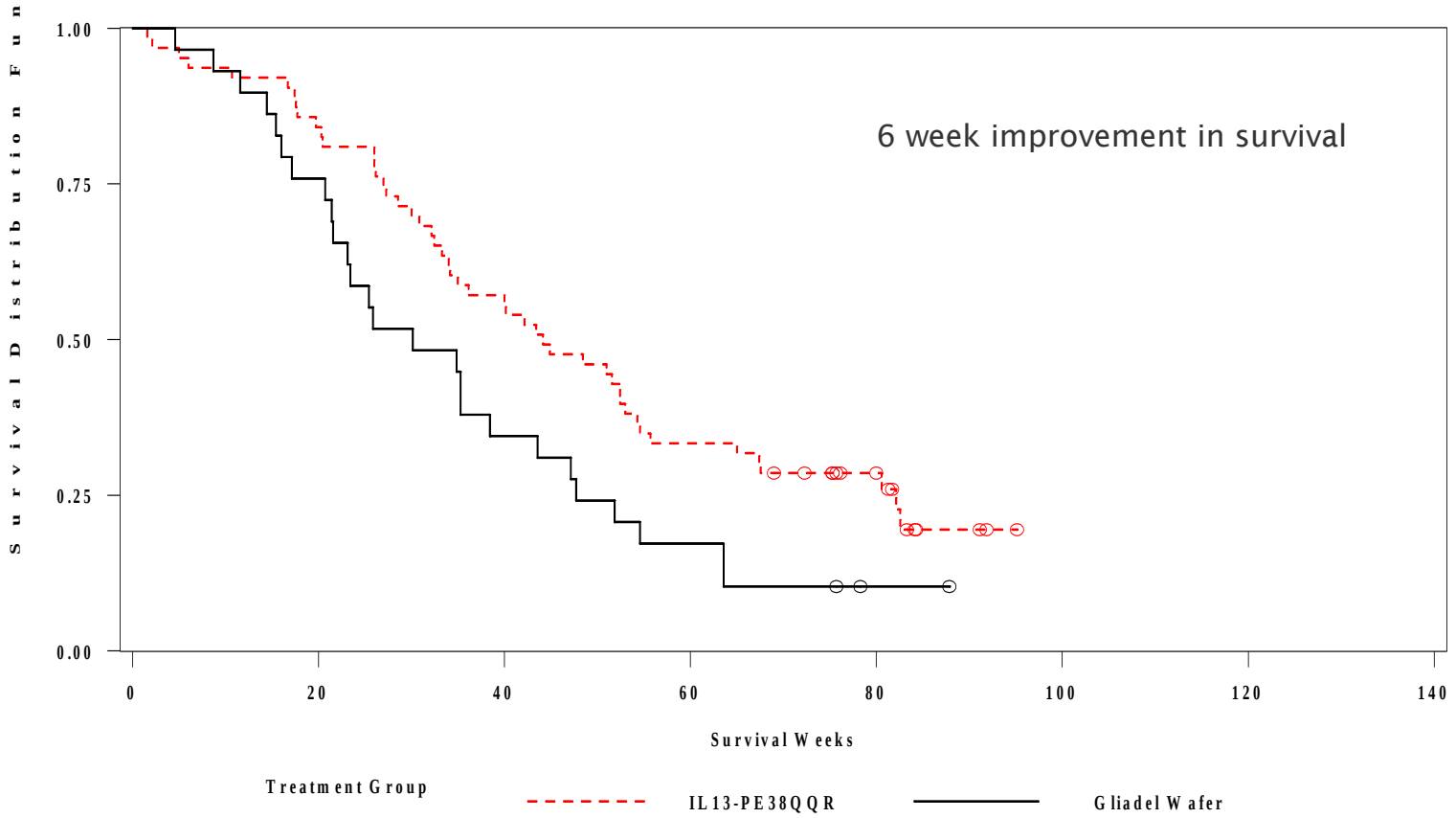


Catheter tip violating ependymal boundary and positioned in right lateral ventricle

Catheter tip violating pial boundary and positioned in interhemispheric fissure

Deep sulcus along catheter trajectory creating a path of outflow for infusate

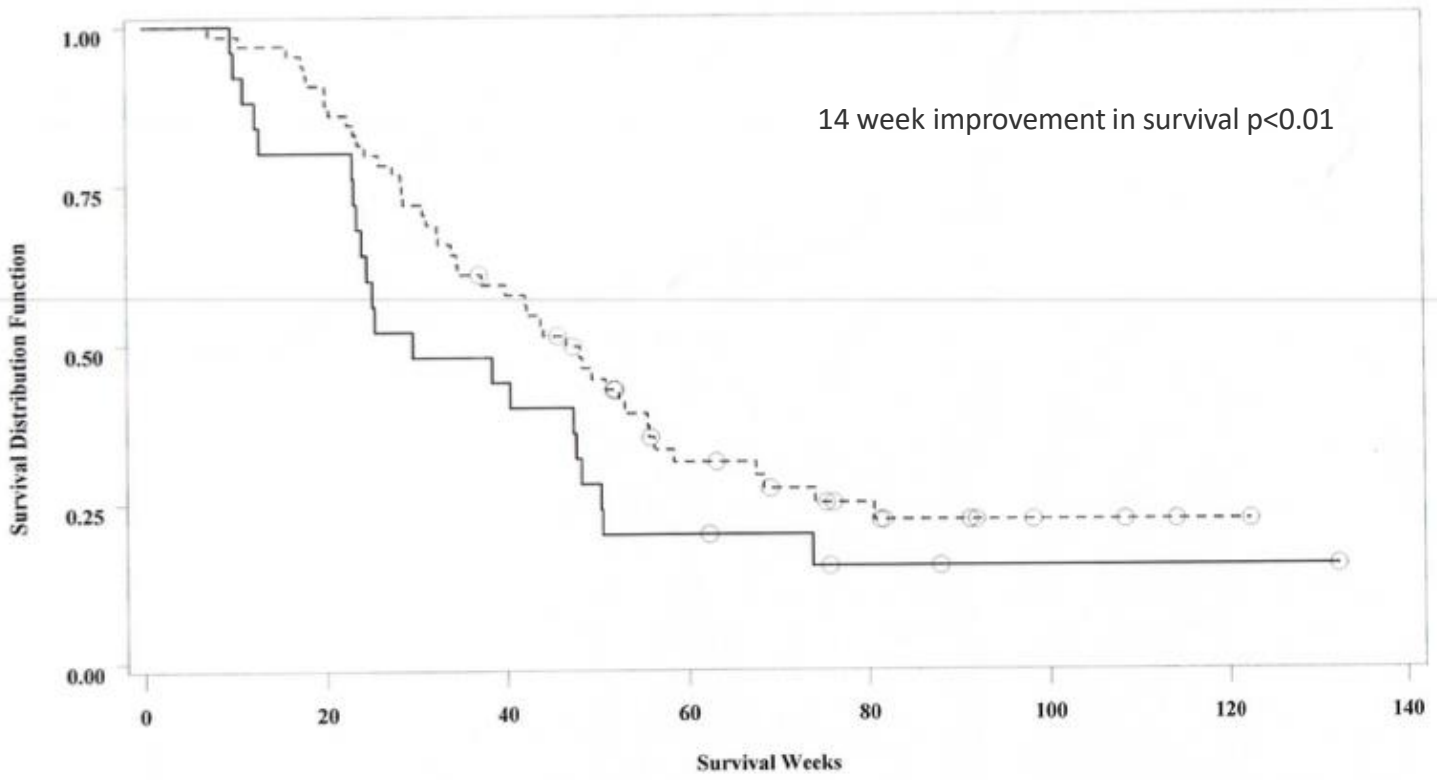
Overall Survival KM Estimate by Temporal Breakdown –Early Third



CB compared to Gliadel wafer hazard ratio: (2-sided 95% CI): 0.47 (0.28 to 0.80), p-value = 0.005

Treatment= IL13-PE38QQR : Total(Censored)= 63 (15), Median(95% CI)= 44.1 (34, 54.29)
Treatment= Gliadel Wafer: Total(Censored)= 29 (3), Median(95% CI)= 30.1 (21.57, 43.57)

Figure 14.2.x
Overall Survival (Weeks) / sites w/ 10+ patients excluding Israel



14 week improvement in survival p<0.01

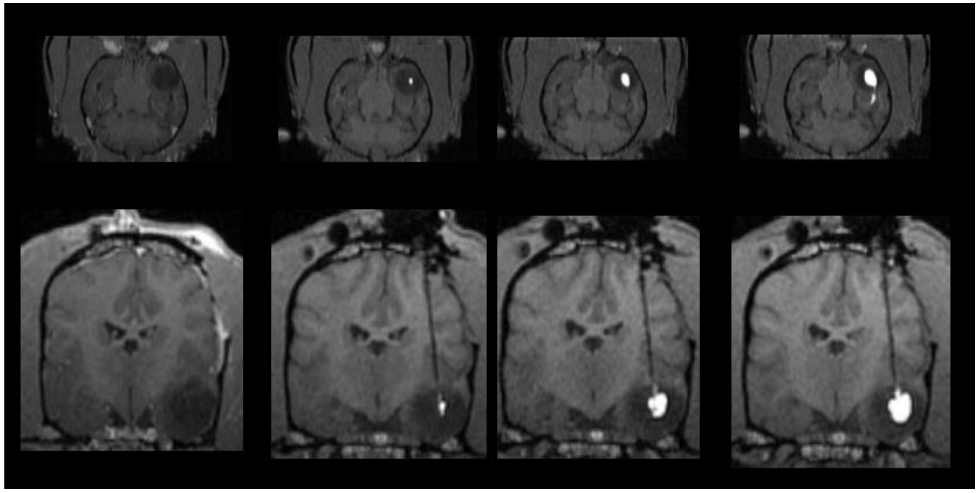
Treatment= IL13-PE38QQR : Total(Censored)= 64 (18) , Median(95% CI)= 46.7 (34.71, 55.57)
Treatment= Gliadel Wafer : Total(Censored)= 25 (4) , Median(95% CI)= 29.7 (23.43, 48.29)

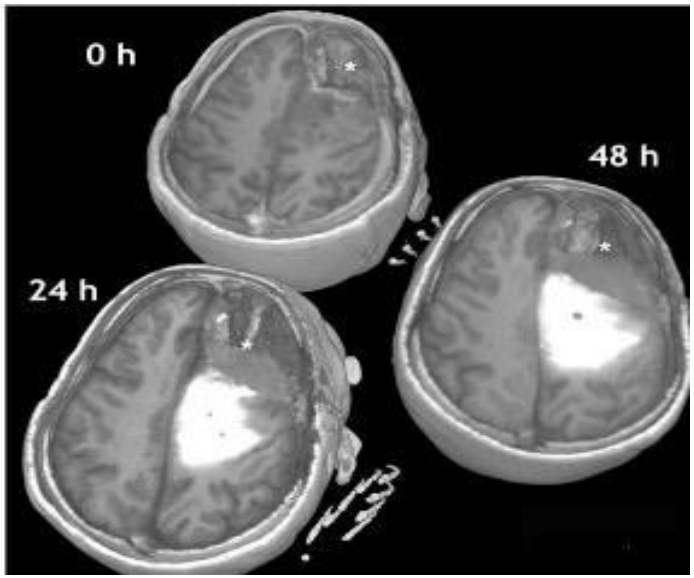
Advances in CED

- Improved catheter design
- Predictive software
- Real time imaging of drug distribution
- Rational cylical therapy

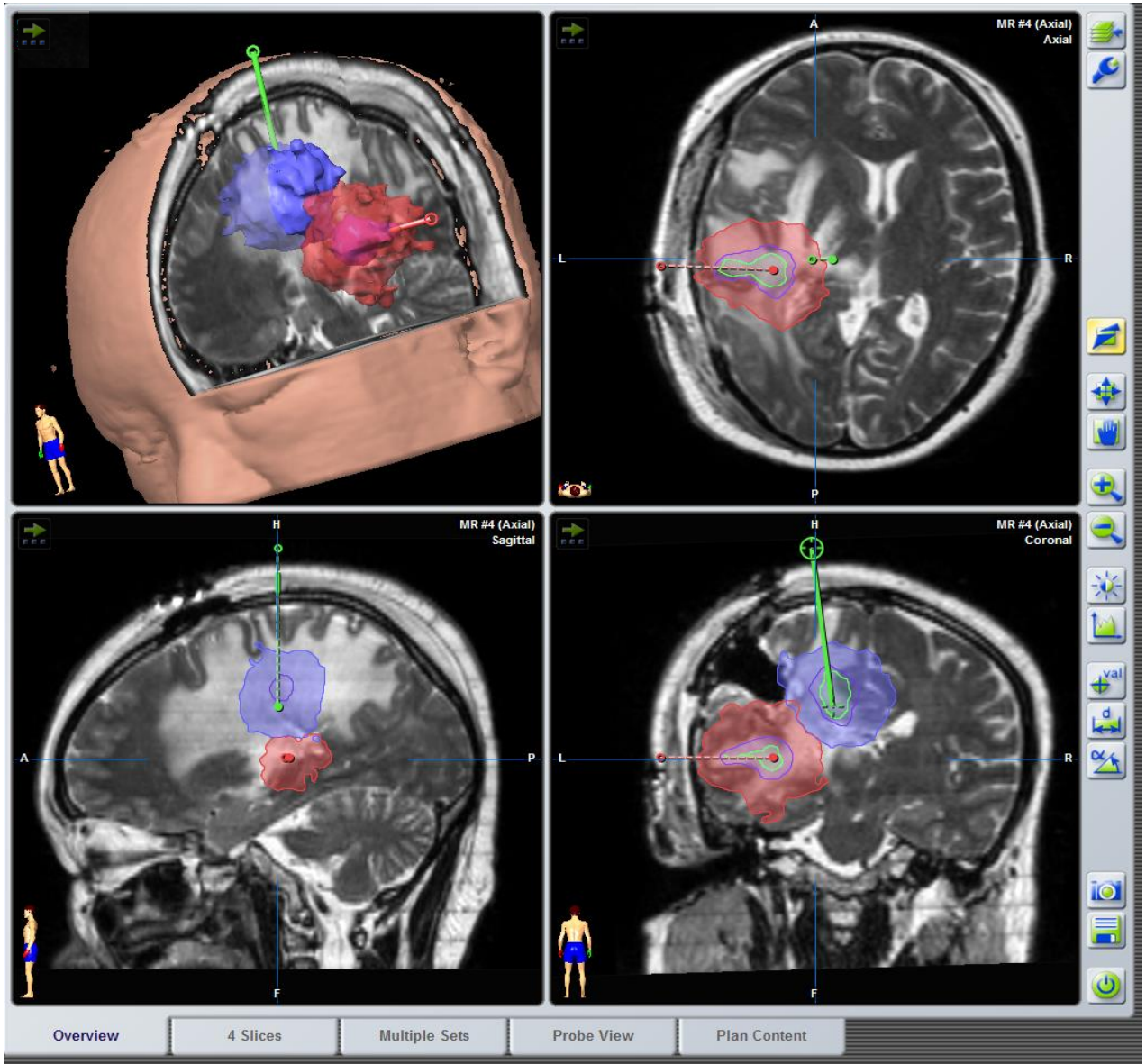
Advances in CED

- Real time imaging – Where is the drug going?





Prediction/Planning of Drug Delivery



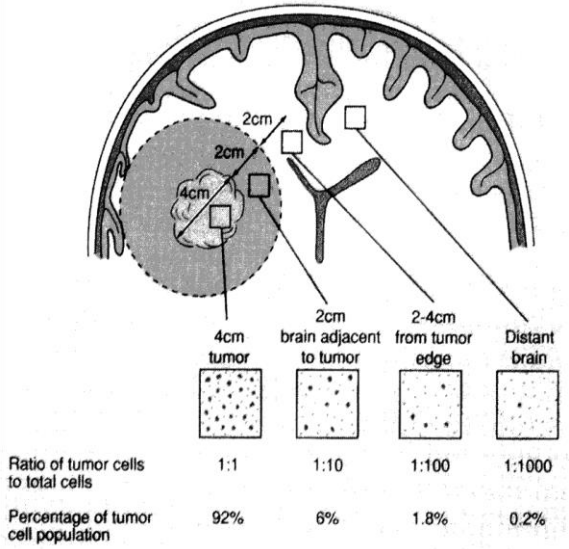
Advances in Understanding IL13Ra Receptor expression

ARTICLE

DOI: 10.1038/s41467-017-01392-9 OPEN

Interleukin-13 receptor alpha 2 cooperates with EGFRvIII signaling to promote glioblastoma multiforme

Jennifer P. Newman[1], Grace Y. Wang[1,15], Kazuhiko Arima[2], Shou P. Guan[1], Michael R. Waters[3], Webster K. Cavenee[4], Edward Pan[5], Edita Aliwarga[1], Siao T. Chong[1], Catherine Y.L. Kok[1], Berwini B. Endaya[6], Amyn A. Habib[7], Tomohisa Horibe[8], Wai H. Ng[9], Ivy A.W. Ho[1,16], Kam M. Hui[10,11,12,13], Tomasz Kordula[3] & Paula Y.P. Lam[1,11,14]



- IL13Rα present on GBM infiltrating stem cells
- Works with EGFRvIII signalling to promote proliferation
- “To go or to grow”

Am J Transl Res 2020;12(8):4702-4714
www.ajtr.org /ISSN:1943-8141/AJTR0109390

Original Article

IL13RA2 is overexpressed in malignant gliomas and related to clinical outcome of patients

Jing Zeng[1*], Ji Zhang[2*], Yuan-Zhong Yang[1*], Fang Wang[3], Hong Jiang[4], Hua-Dong Chen[4], Hui-Yu Wu[5], Ke Sai[2], Wan-Ming Hu[1]

Table 3. Univariate and Multivariate analysis for overall survivals

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Sex: (Male)	1.144 (0.821~1.595)	0.425		
Age: (years >45)	1.579 (1.145~2.178)	0.005*	1.010 (0.687-1.485)	0.959
Location: (Supratentorial)	1.218 (0.597~2.486)	0.587		
WHO Grade: (High)	2.617 (1.733~3.953)	<0.001*	1.472 (0.754-2.874)	0.258
IDH1/2: (Mutated)	0.362 (0.247~0.529)	<0.001*	0.609 (0.385-0.961)	0.033*
1p/19q: (Co-deleted)	0.319 (0.156~0.653)	0.002*	0.427 (0.200-0.915)	0.029*
ATRX: (Mutated)	0.736 (0.531~1.020)	0.065		
TERTp: (Mutated)	0.965 (0.688~1.355)	0.839		
MGMTp: (Methylated)	1.010 (0.616~1.657)	0.967		
P53: (>10%)	1.249 (0.884~1.764)	0.208		
Ki67: (>10%)	2.292 (1.444~3.638)	<0.001*	1.470 (0.700-3.089)	0.309
IL13RA2: (High)	2.036 (1.464~2.832)	<0.001*	1.528 (1.054-2.216)	0.025*

*P<0.05.

- IL13Ra correlated with poor prognosis p<0.025

CED: Lessons Learned to Date

- Safe and promising new drug delivery method
- Catheter placement is crucial and impacts outcome
  - Placement can be improved with individualized planning software
- Understanding drug distribution is essential
  - Real time imaging
- No limit to class of reagents that can be delivered
- No limit to class of disease
  - Ideally regional pathology
    - Glioblastoma Multiforme
    - Parkinsons
    - Epilepsy
    - Huntington's disease
- Improved catheter design (reflux resistant)
- CED drug simulation/planning

Next Step

- Perform pivotal study for CED of IL13-PE38 for glioblastoma multiforme
  - Using improved step microcatheter design to minimize reflux
  - Using planning/distribution software
- Improved drug delivery will correlate with improved treatment outcome
- IL13-PE38 targets the GBM stem cells which may explain the long term survival seen