

Multidisciplinary management of brain metastases arising from breast cancer

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Disclosures

- Dr. Zagar:
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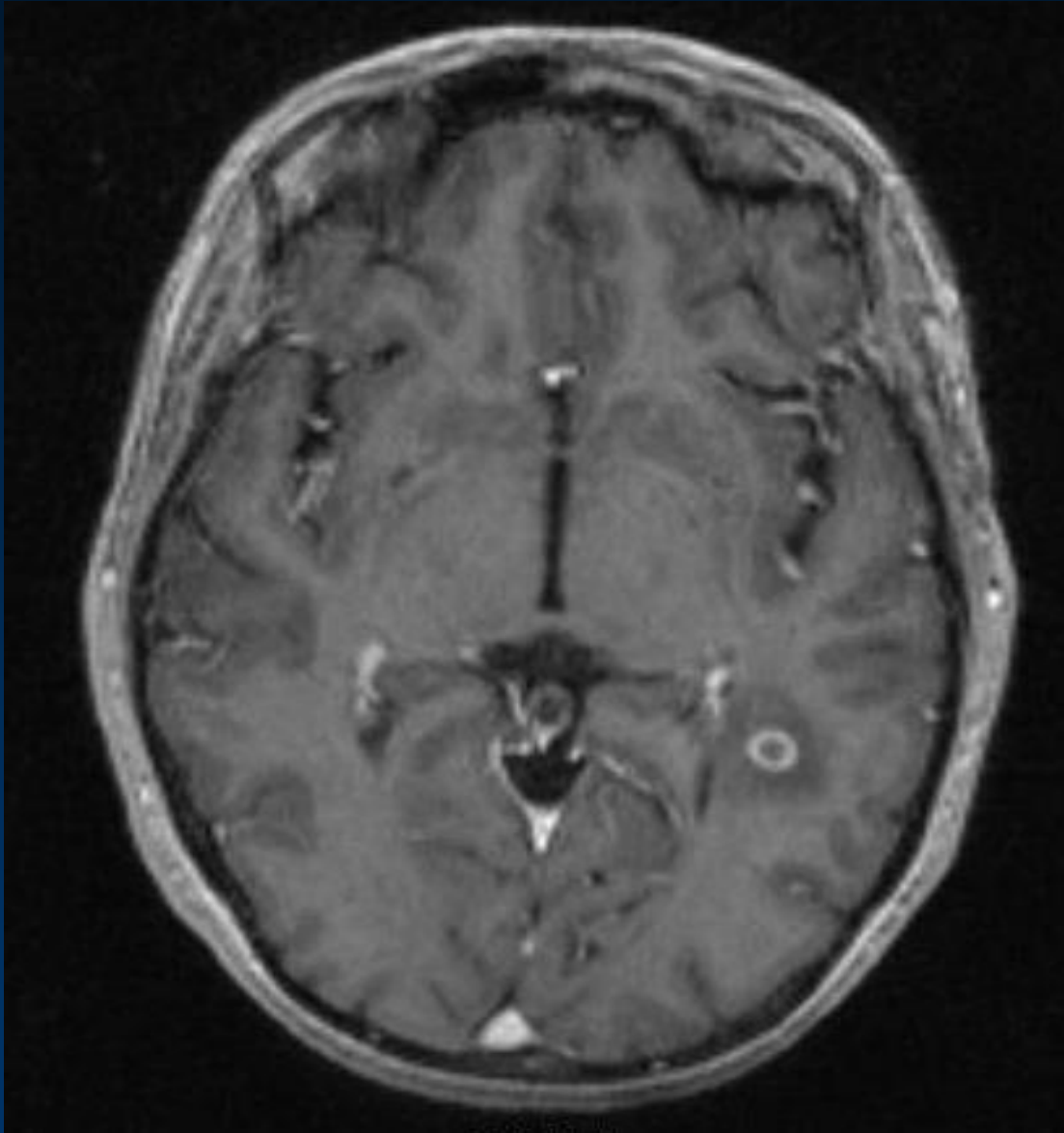
Overview

- Background
- What are brain metastases?
- What prognostic factors are important?
- What are the best treatment options?
 - Surgery, whole brain radiation, radiosurgery, chemotherapy
- Future directions

Breast cancer Brain Metastases: Challenges faced...

- Devastating, feared and increasingly common consequence of breast cancer
 - Incidence 30% Her2+¹, 50% triple negative² advanced BC
- Blood brain barrier limits exposure to chemotherapy
- Until recently, preclinical model systems were scarce
- Clinical trials frequently exclude patients with CNS disease
 - Trials specifically targeting patients with brain metastases few

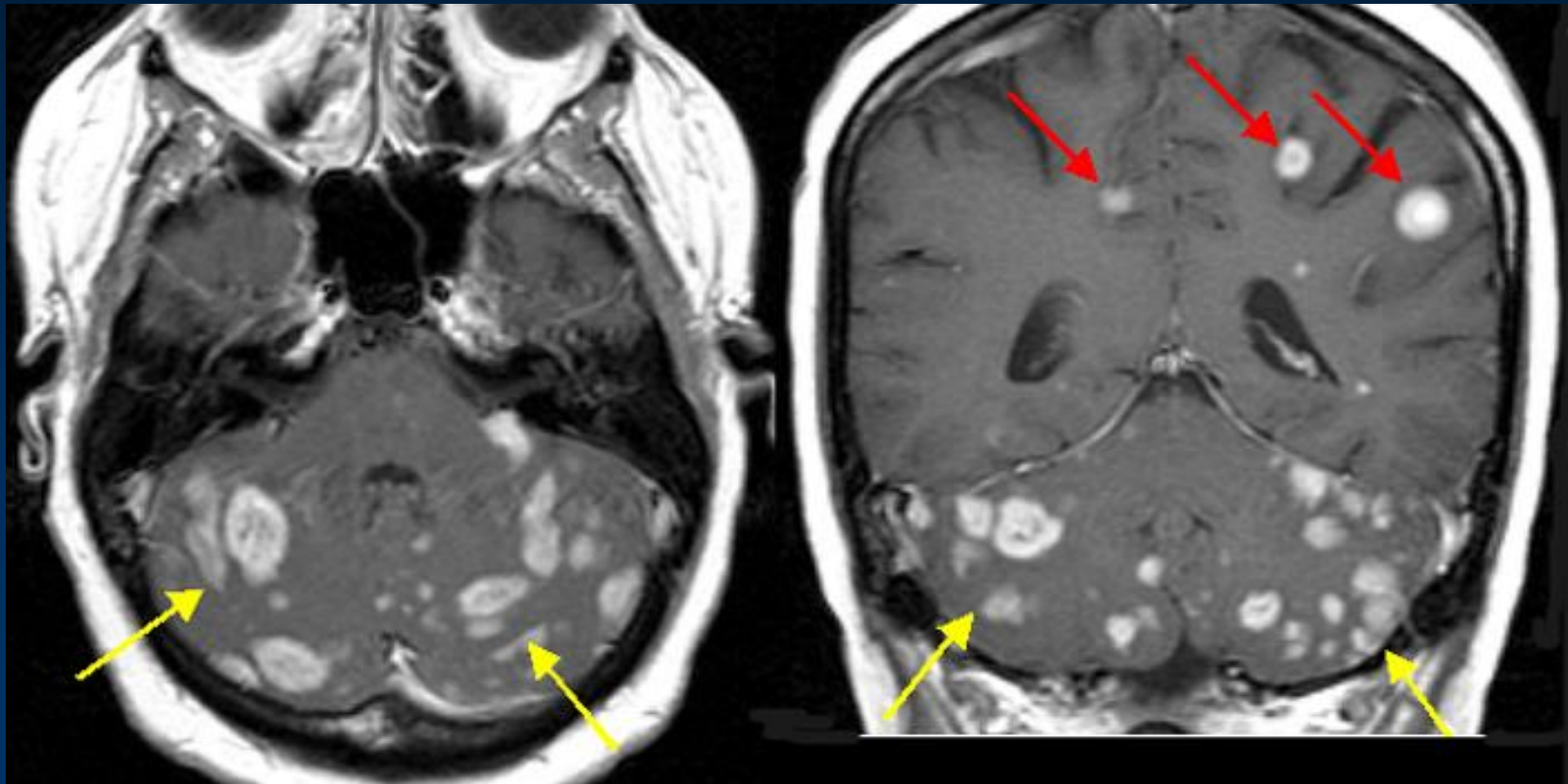




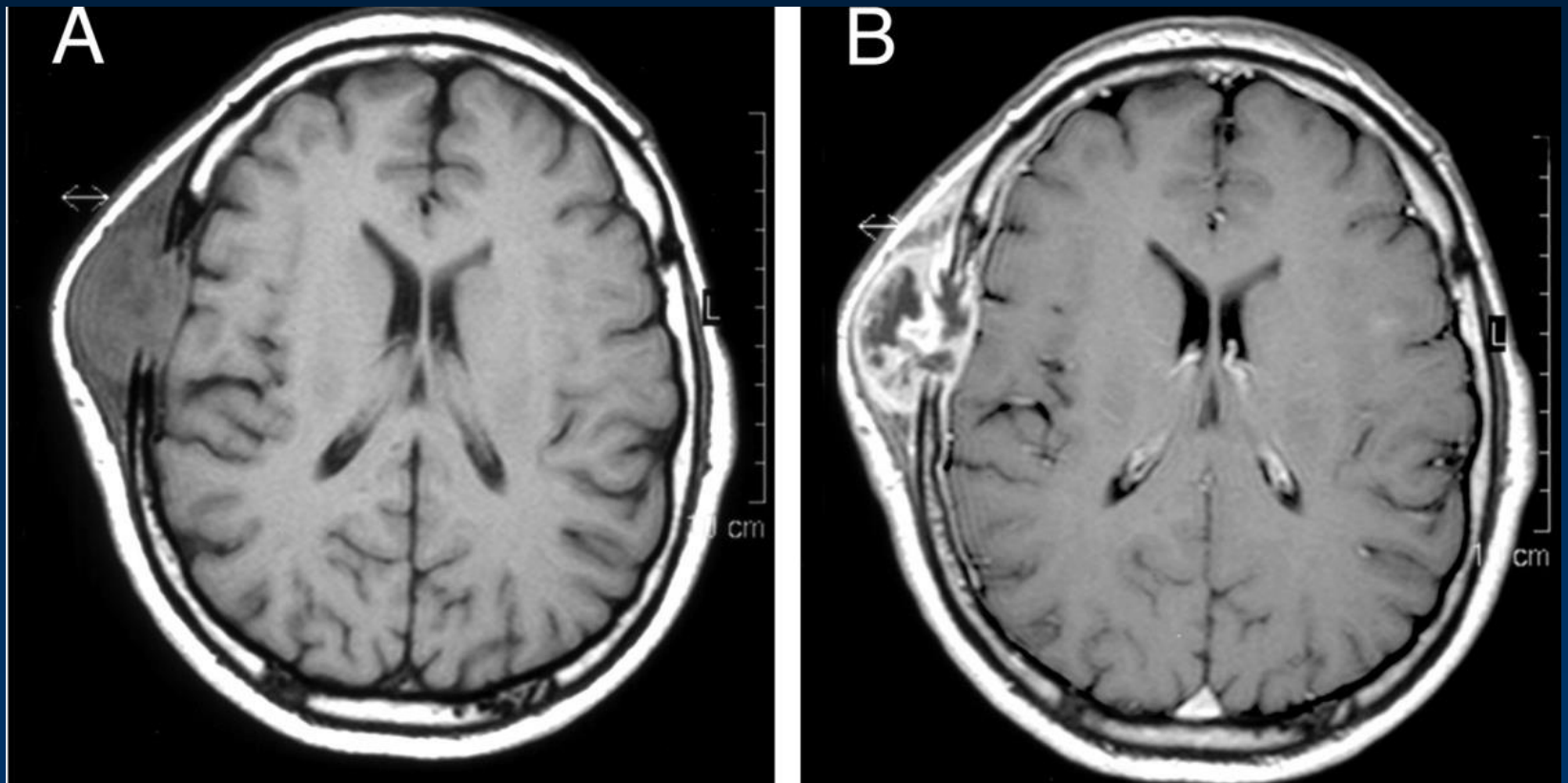
What is a brain metastasis?

Aka brain met

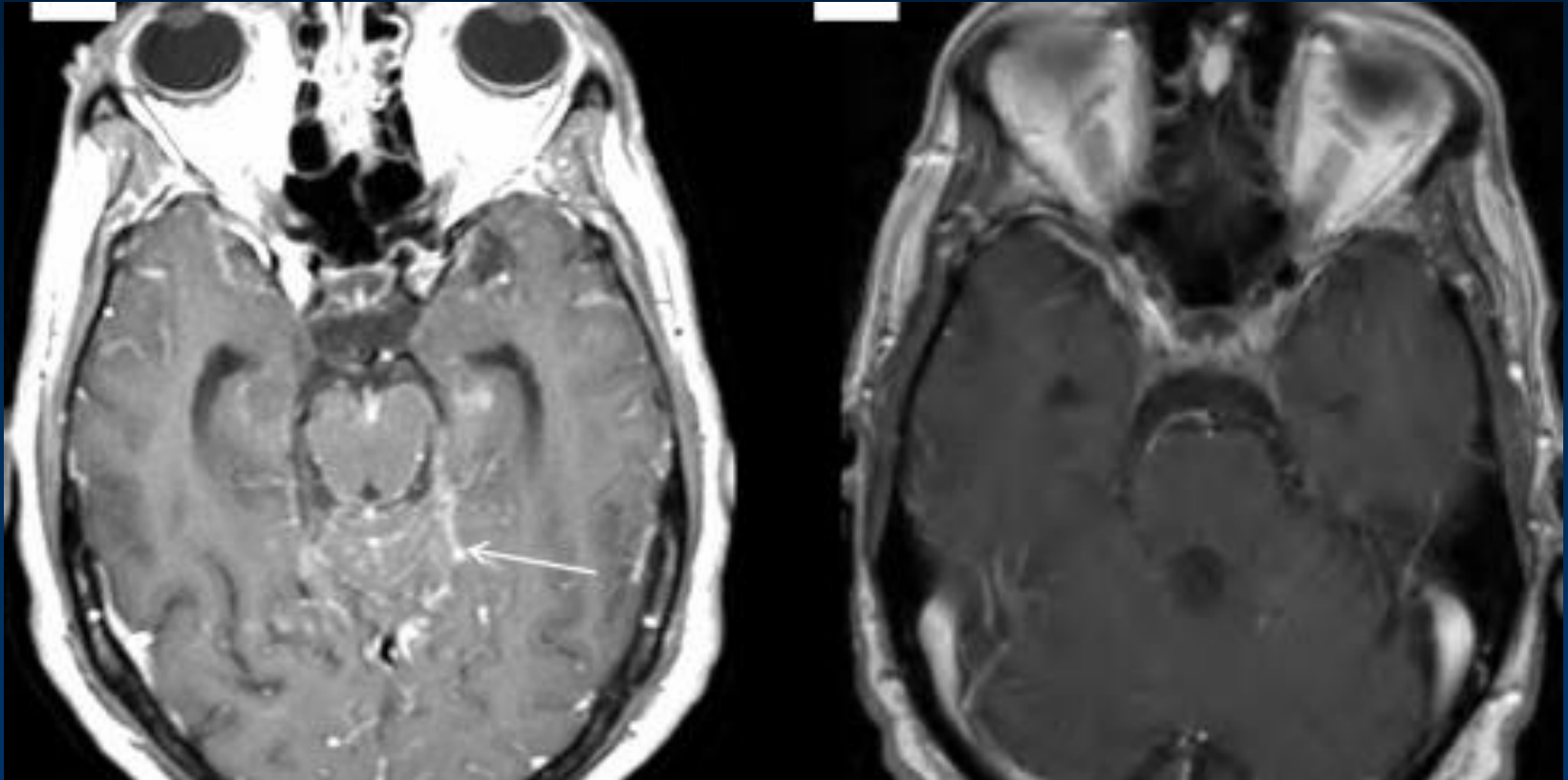
Not all brain mets are created equal



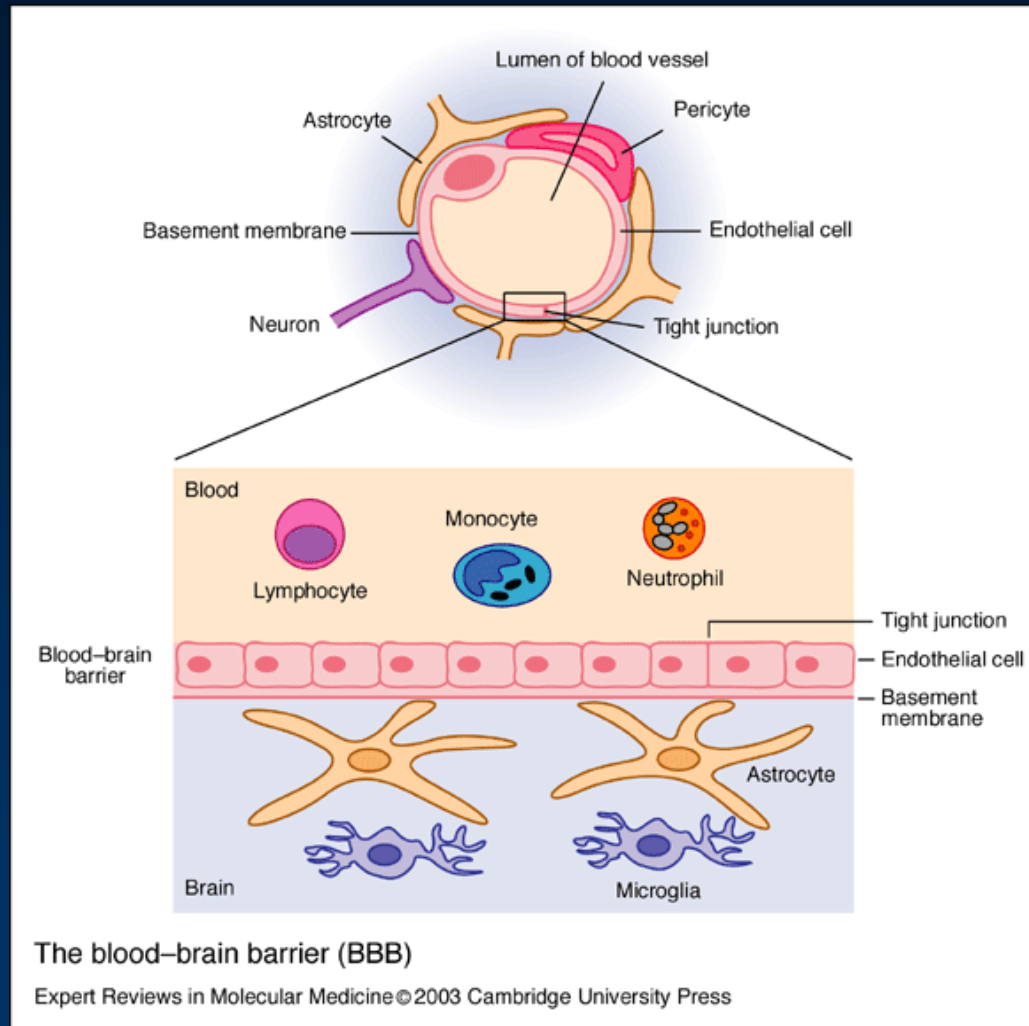
Bone metastasis, not brain



Leptomeningeal spread

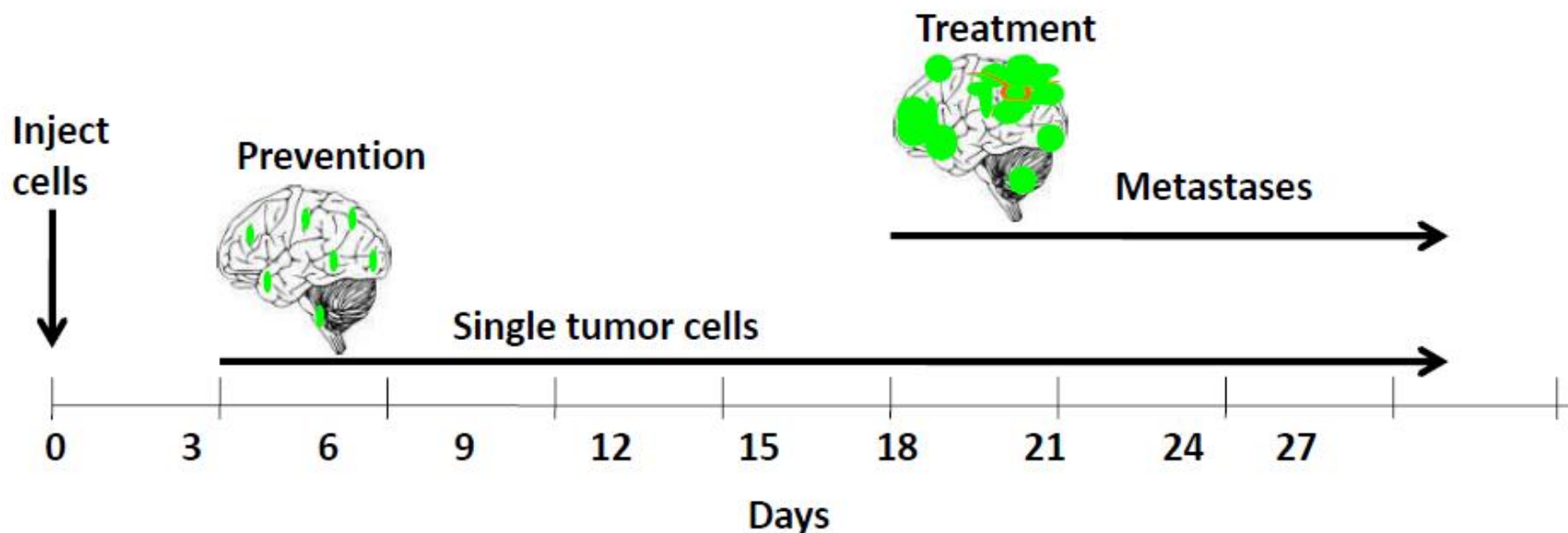


The Blood Brain *Barrier*



231-BR Brain Metastasis Models for Preclinical Drug Testing

- Intracardiac Injection
- 4 week assay
- Count micrometastases and large metastases



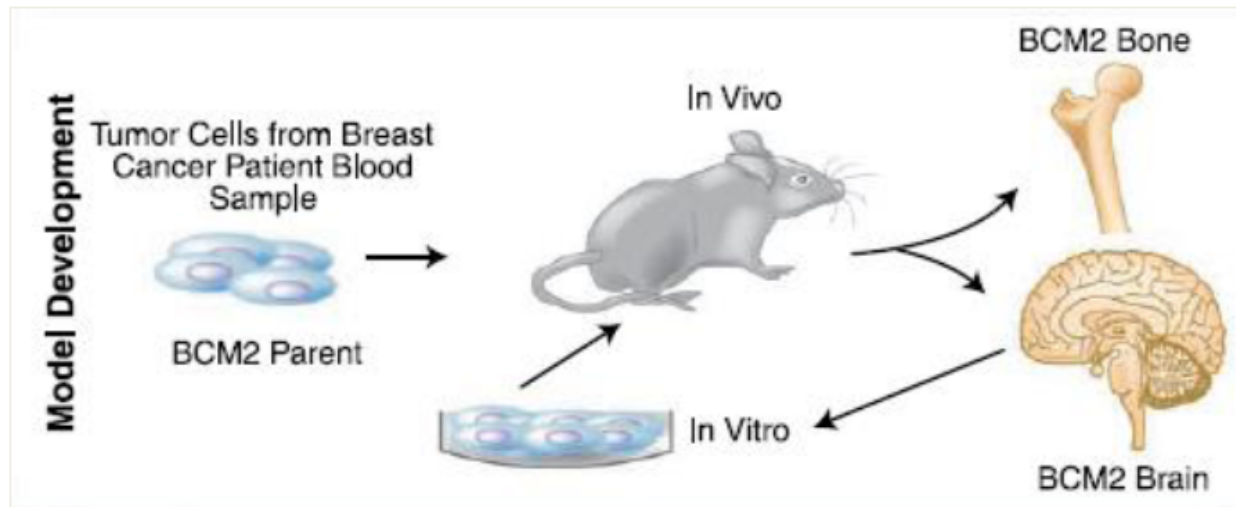
Endpoints:

Prevention - Prevent development of brain metastases

Treatment - Shrink or stabilize size of already developed metastases
- Similar to most clinical trials

Slide courtesy of P. Steeg, PhD

Intracranial Triple Negative Breast Cancer Murine Model



Successive rounds of culture →
rejection of brain metastasis cells →
sublines of breast cancer cell lines that hone to CNS/bone

MDA-MB-231 (Br) and (Bo)

Subtype-Specific Patterns of Metastases

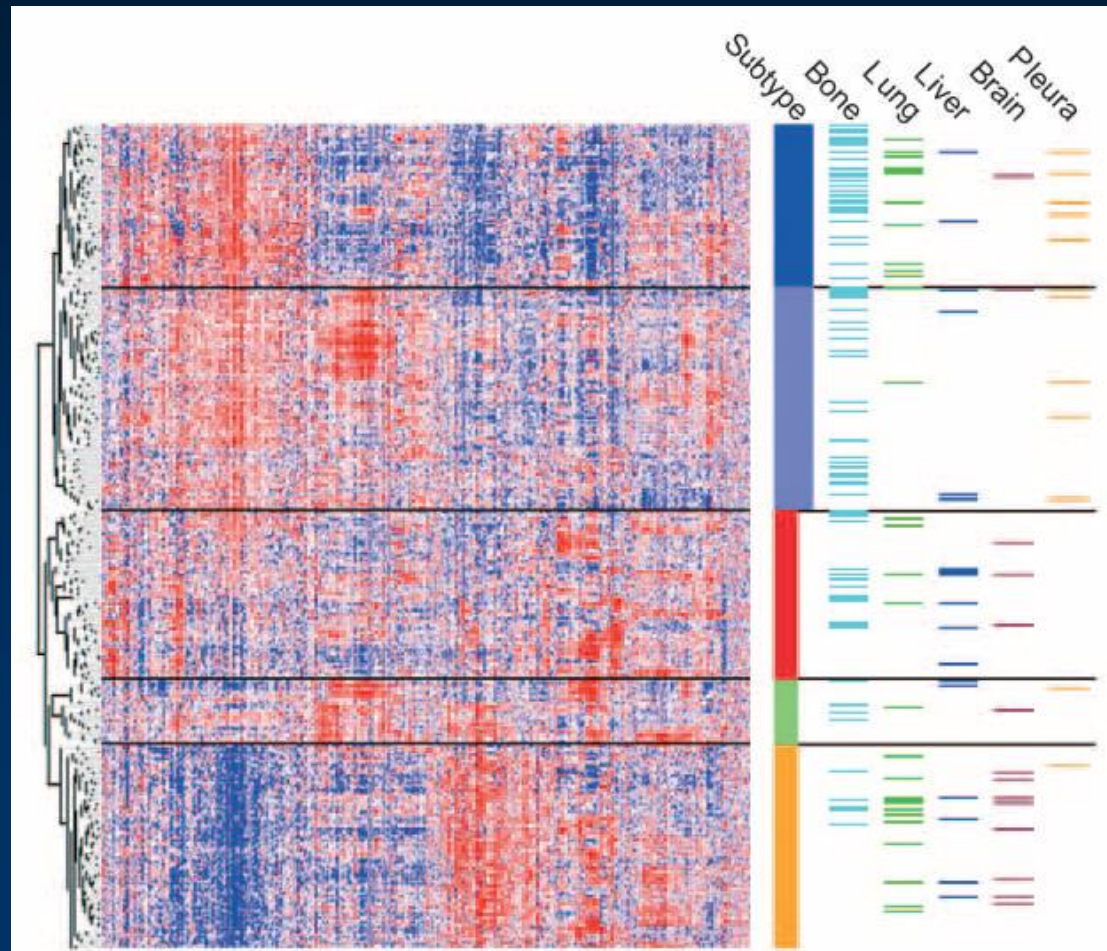
Luminal B

Luminal A

Her2

Normal

Basal-like



Breast cancer brain mets \neq other cancer brain mets

- Most of the data in brain metastases is from patients with ALL types of cancer \rightarrow breast patients are clearly different than lung cancer patients for example
- Extrapolating data from old trials is a problem

Other prognostic factors

- Age
- Performance status
- Status of other disease outside the brain
- Number of brain metastases

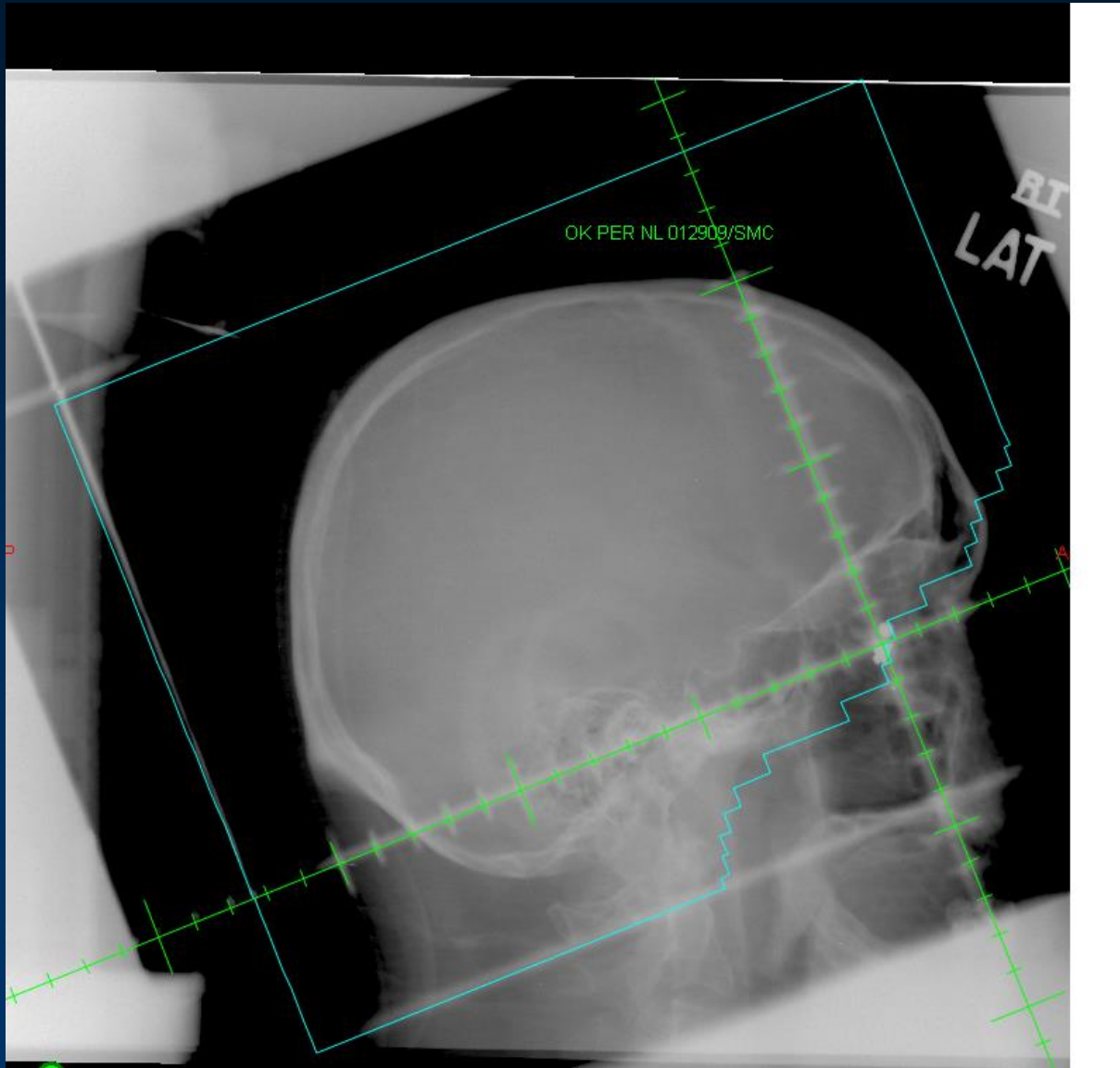
Symptoms

- Headache
- Focal neurologic dysfunction
 - E.g. Weakness on one side
- Cognitive dysfunction
 - “not myself,” problems concentrating
- Stroke
- Seizures

What are treatment options?

- Supportive care
 - Steroids
 - Antiepileptics
- Whole Brain Radiation Therapy (WBRT)
- Local Therapy
 - Surgical Resection
 - Stereotactic Radiosurgery (SRS)
- Combination of Local Therapy and WBRT
 - Surgery followed by WBRT or SRS
 - WBRT followed by Surgery or SRS
 - SRS followed by WBRT
- Systemic Therapy (Chemotherapy, Targeted Agents)

Whole brain radiation



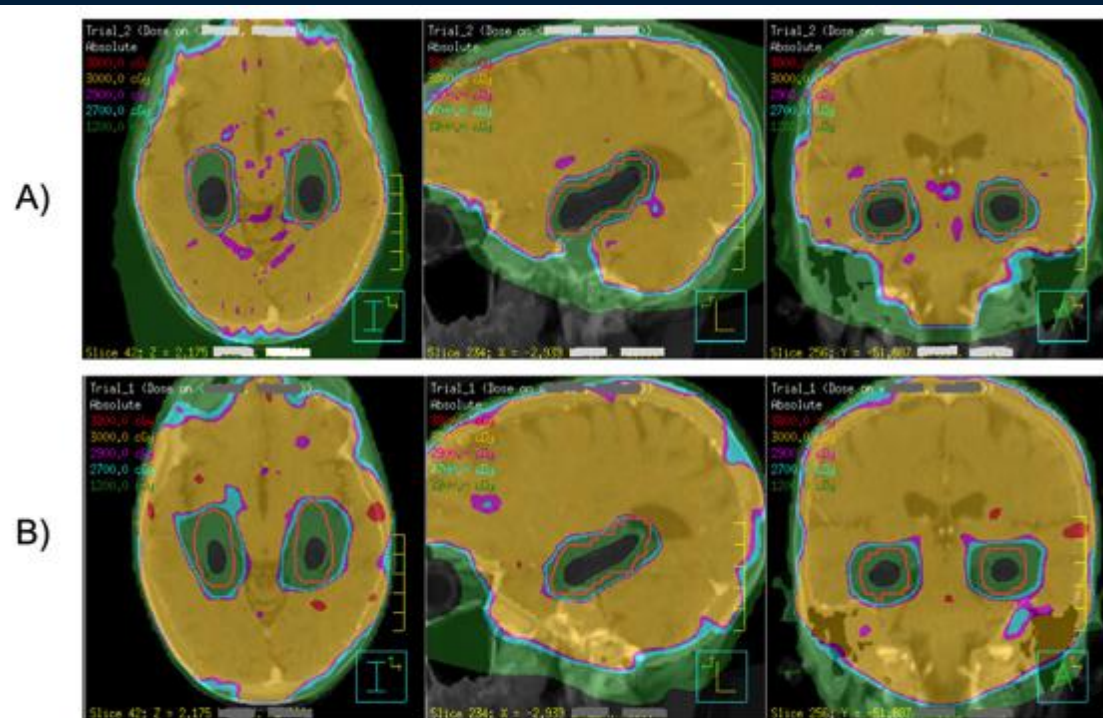
Whole brain radiation

- Treats the whole brain, not just the diseased areas
 - decreases chances of developing new areas
- Sounds good, right?

Whole brain radiation

- FATIGUE
- Hair loss
- Neurocognitive dysfunction
 - Trouble with short term memory
 - In old days → Alzheimer's like dementia
 - Namenda (memantine)?

Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial



Gray shade: Hippocampus

Orange contour: Hippocampal avoidance region

- N=113
- 3000 cGy
- 4 months Hopkins Verbal Learning Test-Revised Delayed recall
- 7% decline, better than historical data

Is there a radiation alternative to whole brain radiation?

- The answer is “yes”...
- In select cases

Radiosurgery

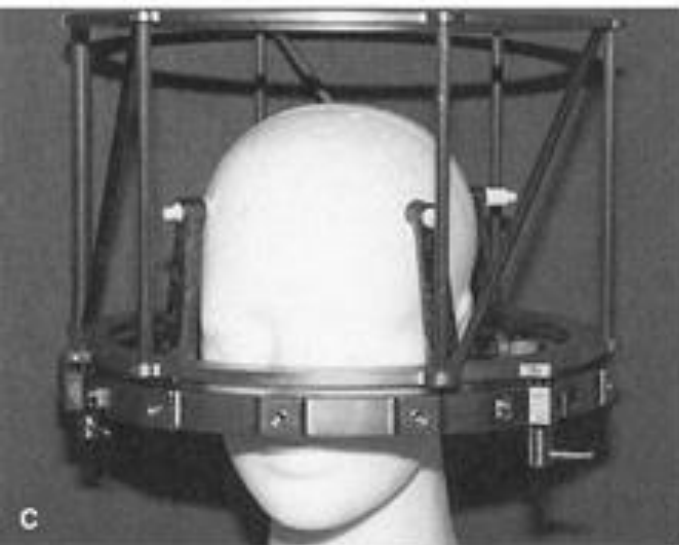
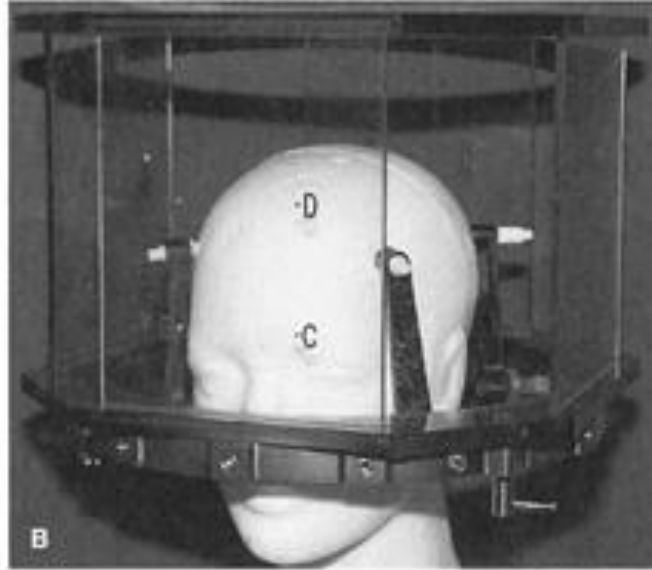
CyberKnife for brain metastases



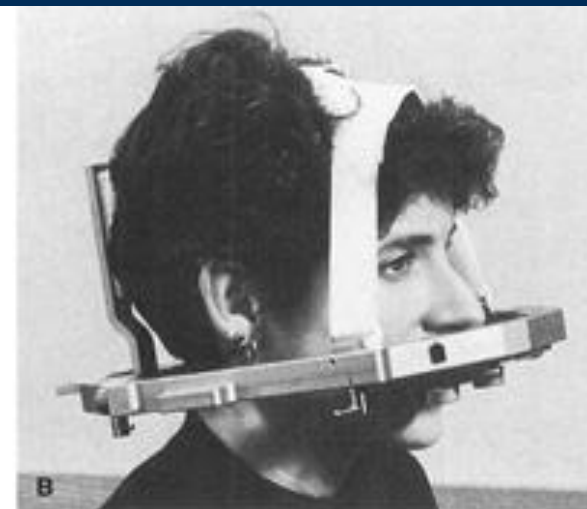
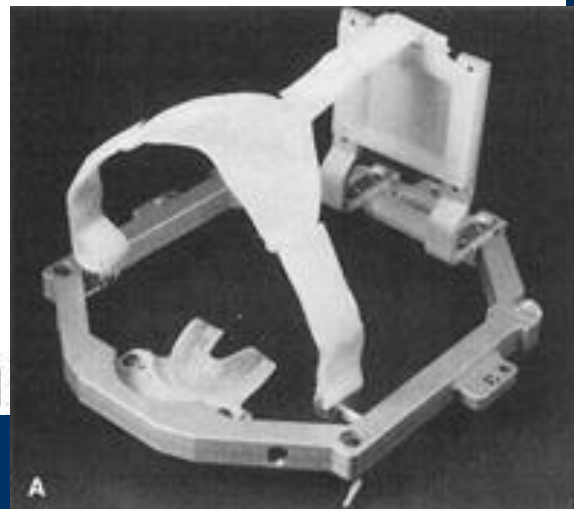
High dose: 1 to 5 fractions

- Radiosurgery delivers high radiation doses to precise locations
- Accomplished with advanced technology

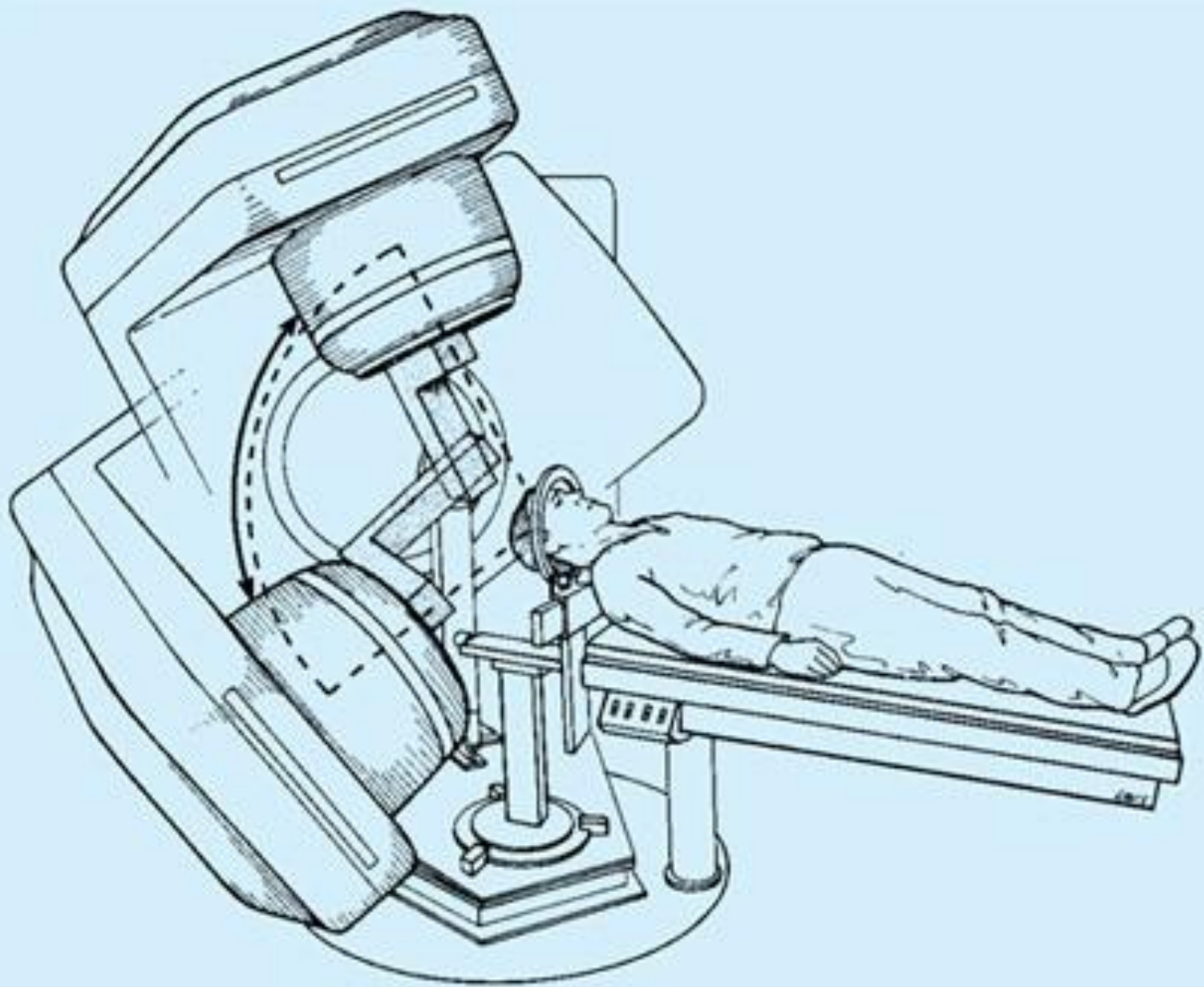




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CyberKnife

- Deliver radiosurgery accuracy without requiring the harsh restraints

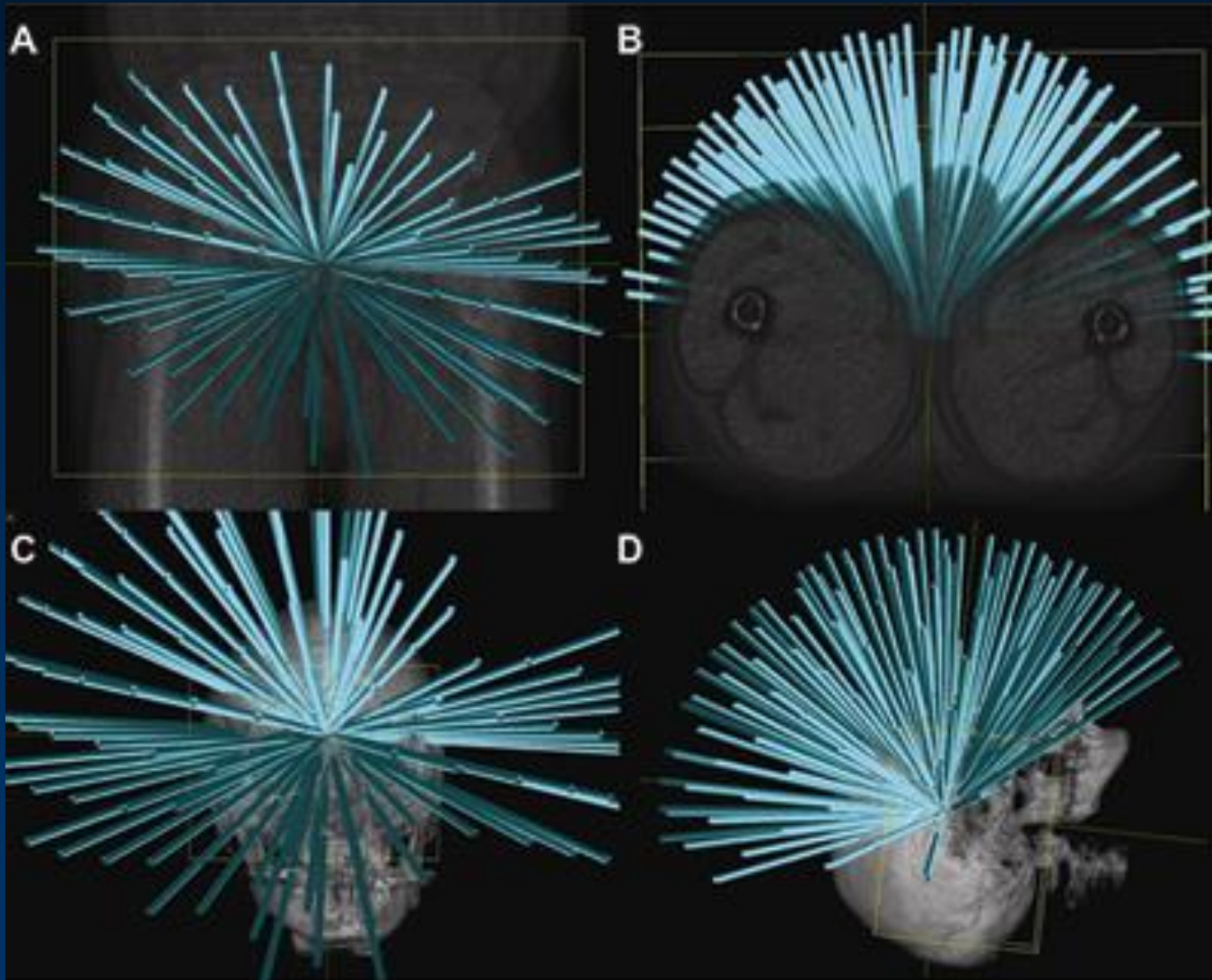


CyberKnife

- The CK is built on a KUKA robot
- This gives great flexibility in beam direction



Lots o' beams

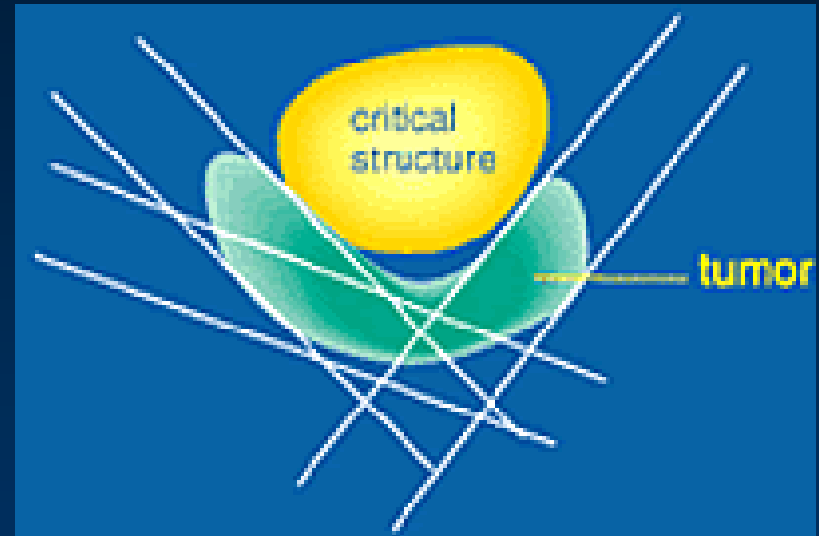


CyberKnife



Dose conformality

- This allows great flexibility in beam direction
- Improved conformality becomes possible
- Less “normal” brain treated → less neurocognitive decline (we think)



Radiosurgery

- Less fatigue
- Usually no hair loss
- Often can go on to receive chemotherapy faster than after whole brain radiation
- Risk of radiation necrosis requiring neurosurgery

B A=0 B=2

A

Ray High (C)

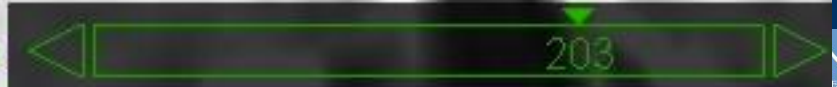


R

L



P



CyberKnife Treatment Planning

ACCURAY®
CyberKnife
MultiPlan

Fuse Contour Align Plan Visualize Utilities Settings Help

Setup Isocentric Conformal Sequential Evaluate Finetune

A A=0 B=2

B A=0 B=2

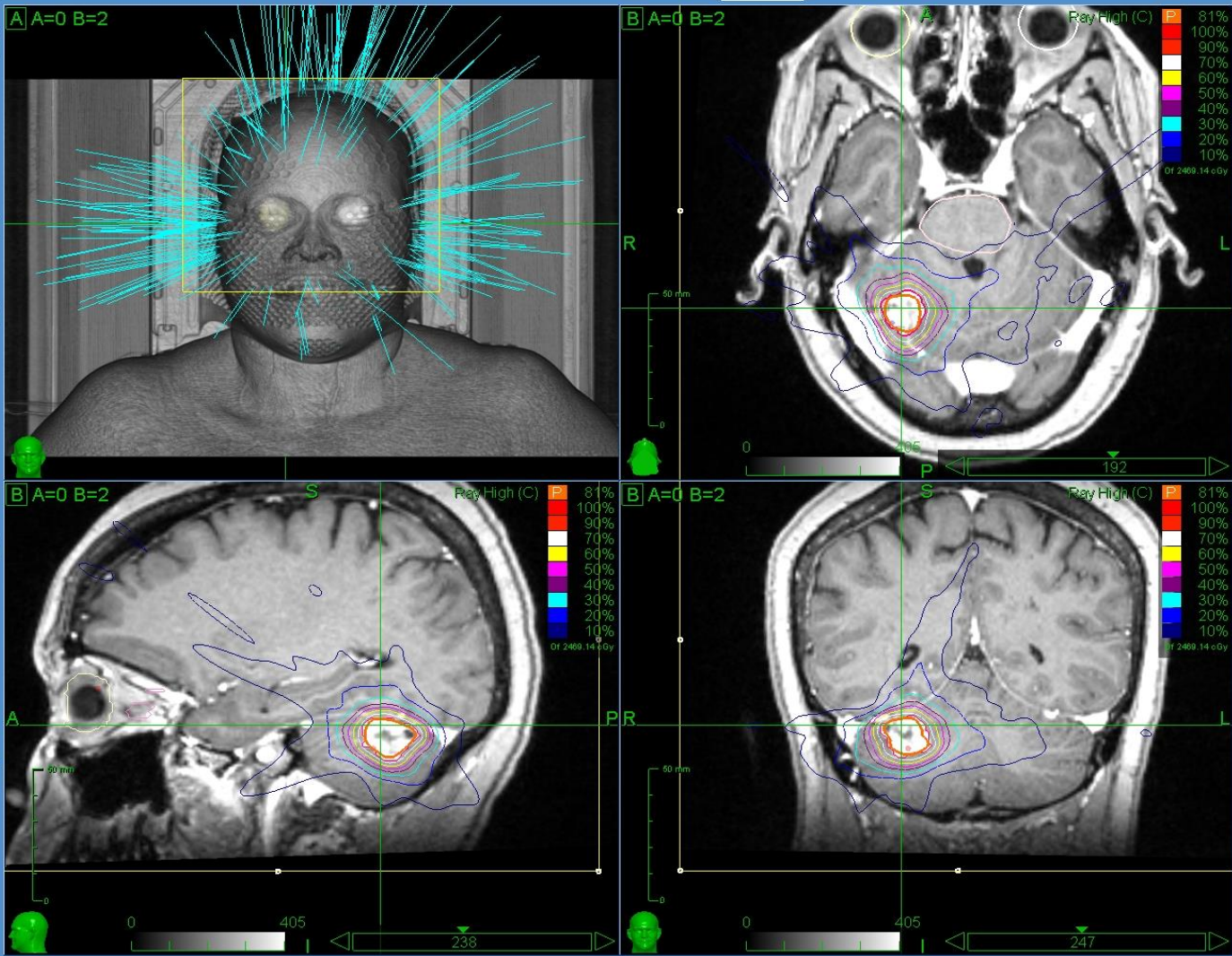
B A=0 B=2

B A=0 B=2

Dose Calculation
Algorithm: Ray-Tracing
Resolution: High
Uncertainty %: 0
Calculate
Prescription
Reference Point
 Use max dose point
Dose (cGy): 2469.14
Point: Go to >> 16.41, 108.64, -397.00
Set to Cross-hair Point
Save Plan
Standard Display

Ray High (C) P 81% 100% 90% 70% 60% 50% 40% 30% 20% 10% Of 2469.14 cGy

ACCURAY®



Conclusions

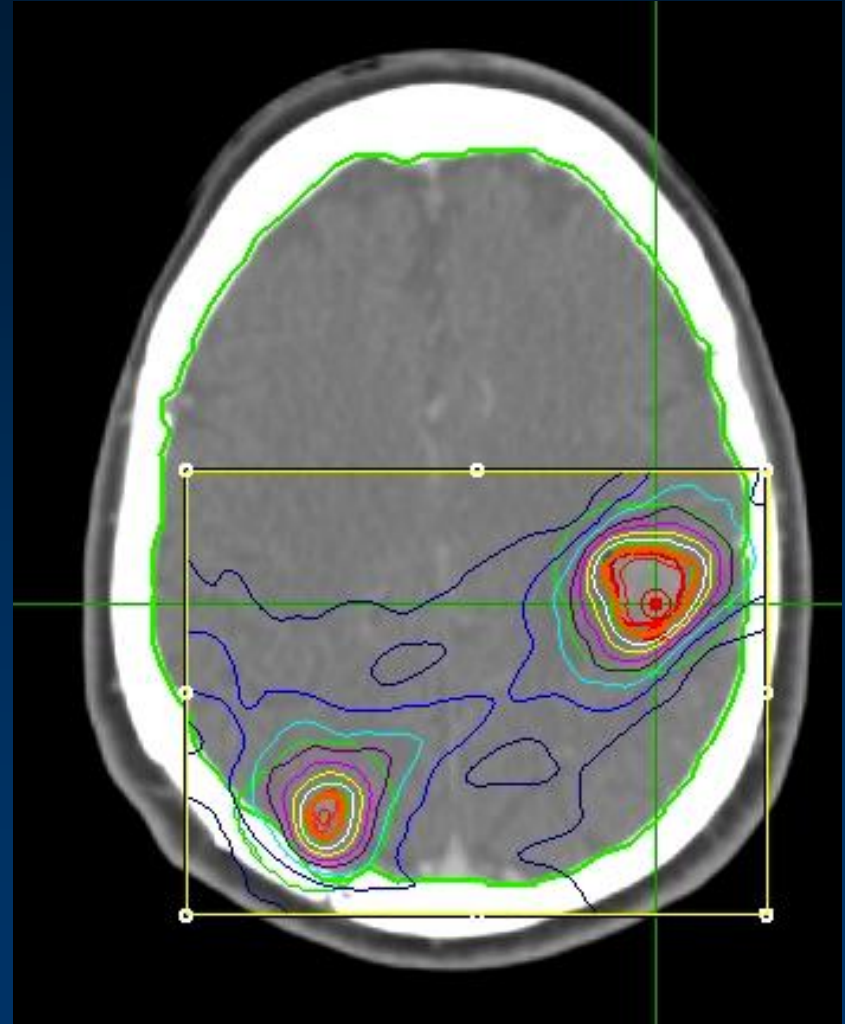
- CyberKnife delivers high doses with sub-millimeter accuracy to patients
- Only light patient immobilization
- Sounds great...so why doesn't everyone get it?

Radiosurgery drawbacks

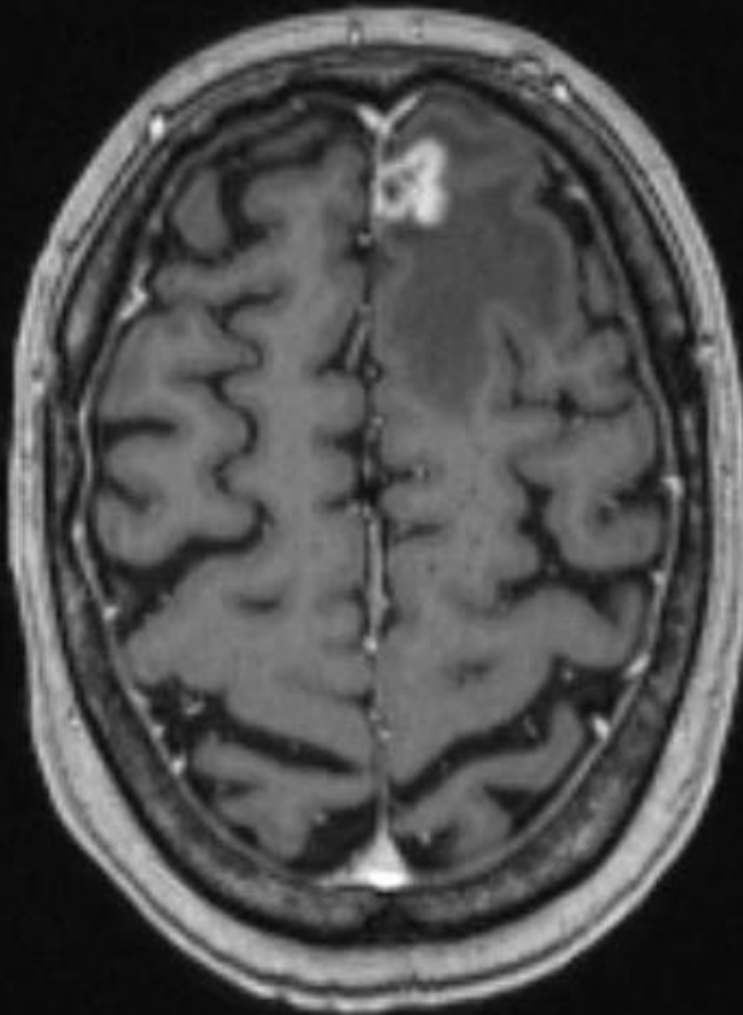
- Can only do for a “few” metastases
 - Risk of radiation necrosis increases the more you treat
- CyberKnife (or any other method of delivering radiosurgery) only works where we point it
 - Non-treated areas are still at risk for developing new metastases

More than 1

- “Low” dose radiation spill
- The more areas targeted, the more potential for dose overlap
 - Risk of radiation necrosis



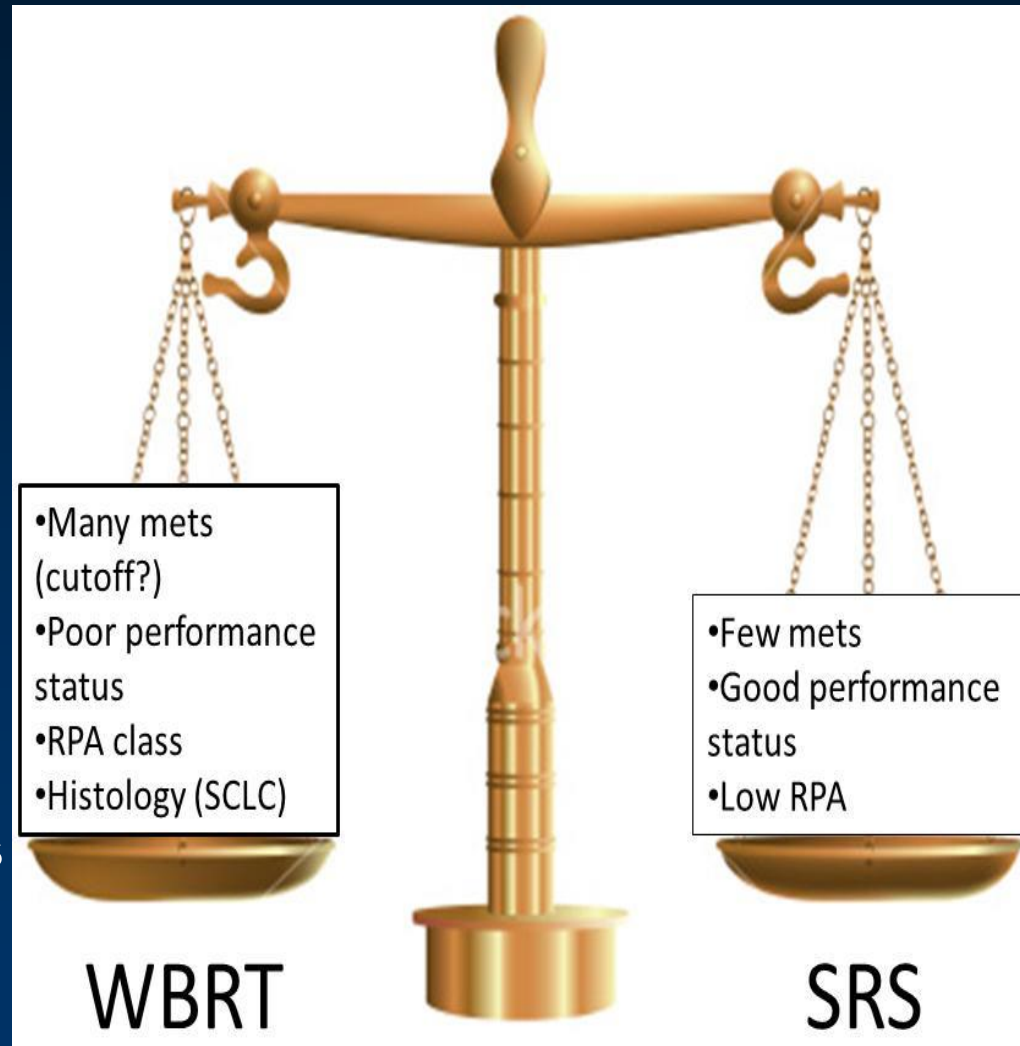
R
1
0
3



D119

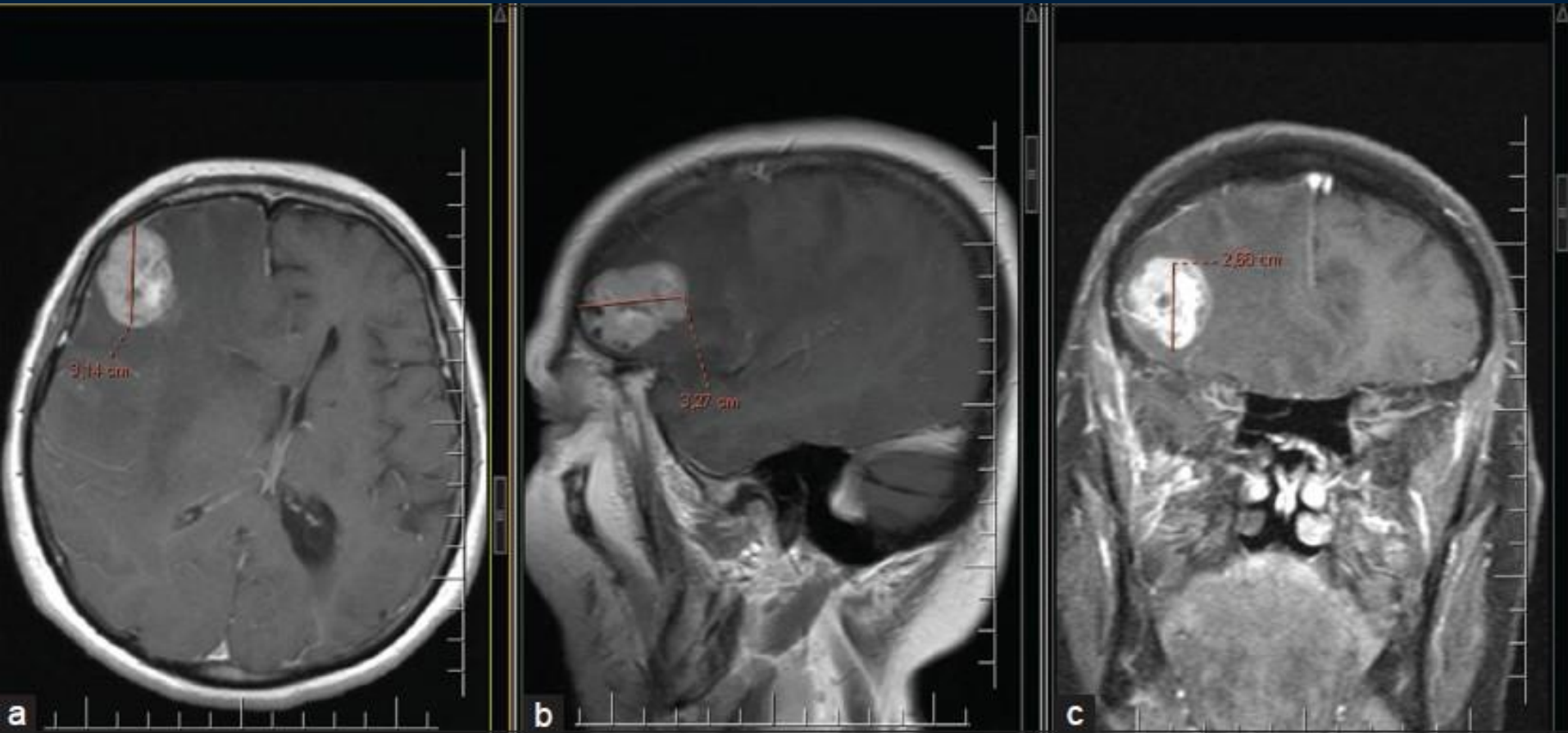
Radiotherapy Treatment Options

- Better “distant” whole brain microscopic disease control
- Risk of long-term neurotoxicity and side-effects



- Avoid side-effects of WBRT
- Availability of salvage treatments
- Negative impact of tumor progression

Neurosurgery



What about surgery?

- Often when there is 1 metastasis (rarely 2)
- When symptomatic
- When diagnosis is in question
- Not enough—need more treatment after resection

When do we consider systemic therapy to treat brain metastases?

Systemic Therapy for Breast Cancer Brain Metastases

- When to consider?
 - Recurrent or progressive CNS disease after surgery and/or radiation
 - In patients with minimal CNS disease in setting of significant systemic disease
 - ?? After SRS alone to delay/avoid need for WBRT
 - No prospective data from clinical trials
 - ?? In the highly motivated, informed patient with newly diagnosed brain metastases and limited CNS disease
 - *No drugs with FDA approval for systemic treatment of brain metastases*

Overview of Systemic Therapies for Breast Cancer Brain Metastases

Chemotherapy

- Etoposides, Irinotecan/TMZ, Carrier-mediated agents (2B3-101, ANG1005)

Targeted Agents

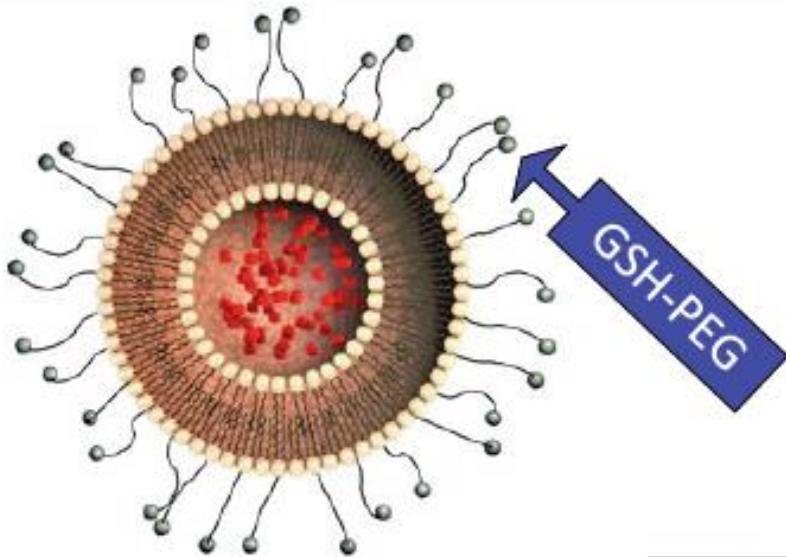
- HER2-targeted (namely Lapatinib), Parp Inhibitors (Veliparib), CDK4/6 inhibitors (abemaciclib)

Preclinical

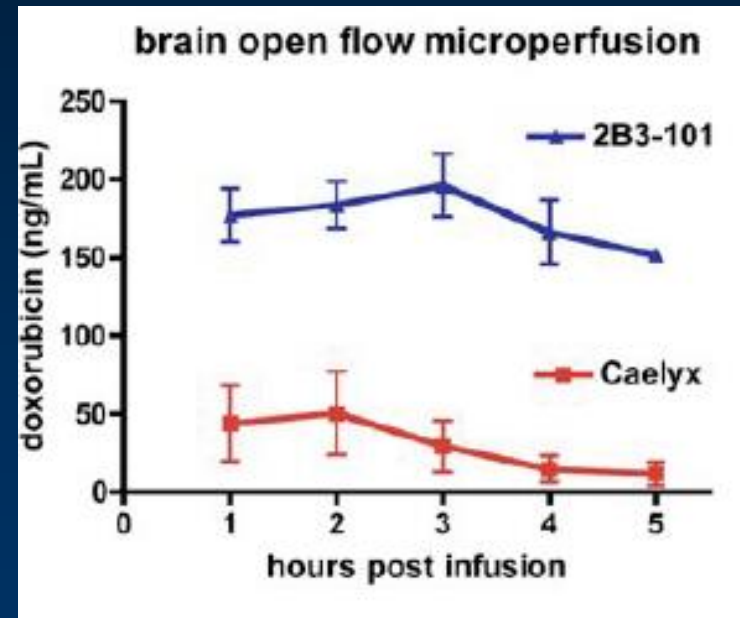
- mTOR, MEK and PI3K inhibitors and beyond!

2B3-101: PEGylated liposomal anthracycline

2B3-101
GSH-PEG liposomal doxorubicin



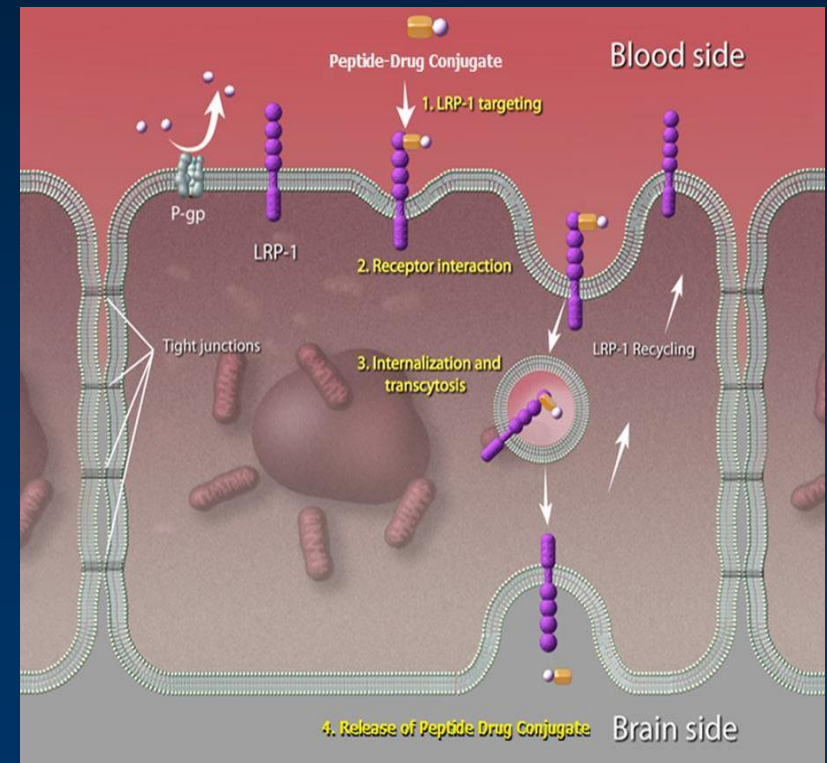
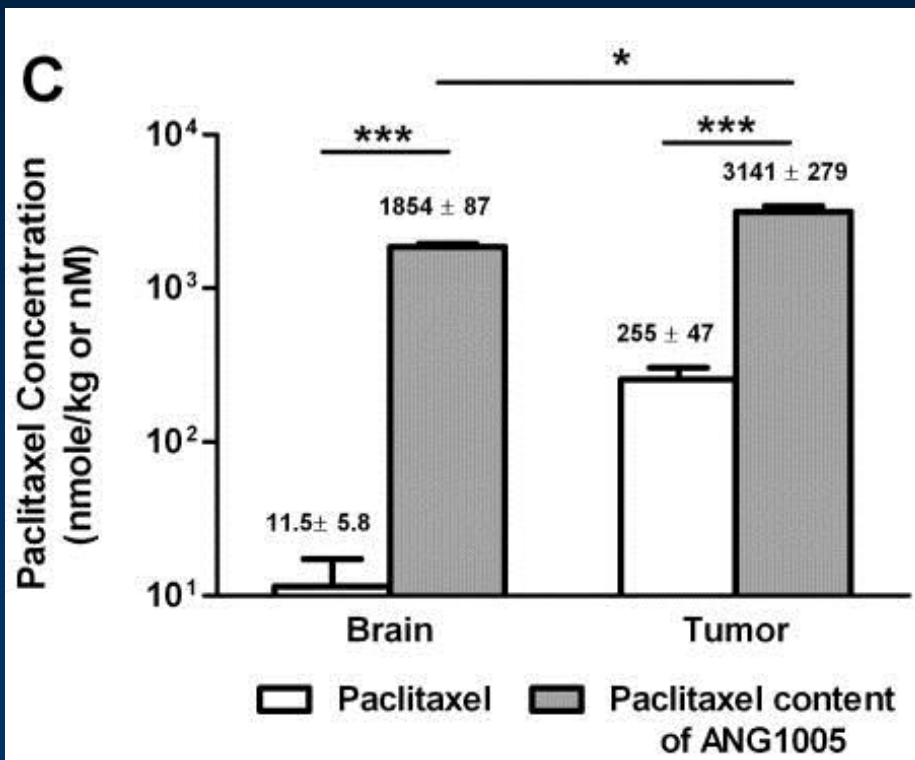
5X's greater brain exposure vs. Doxil®



Phase I study completed in Europe
Phase II study near completion in the US and Europe

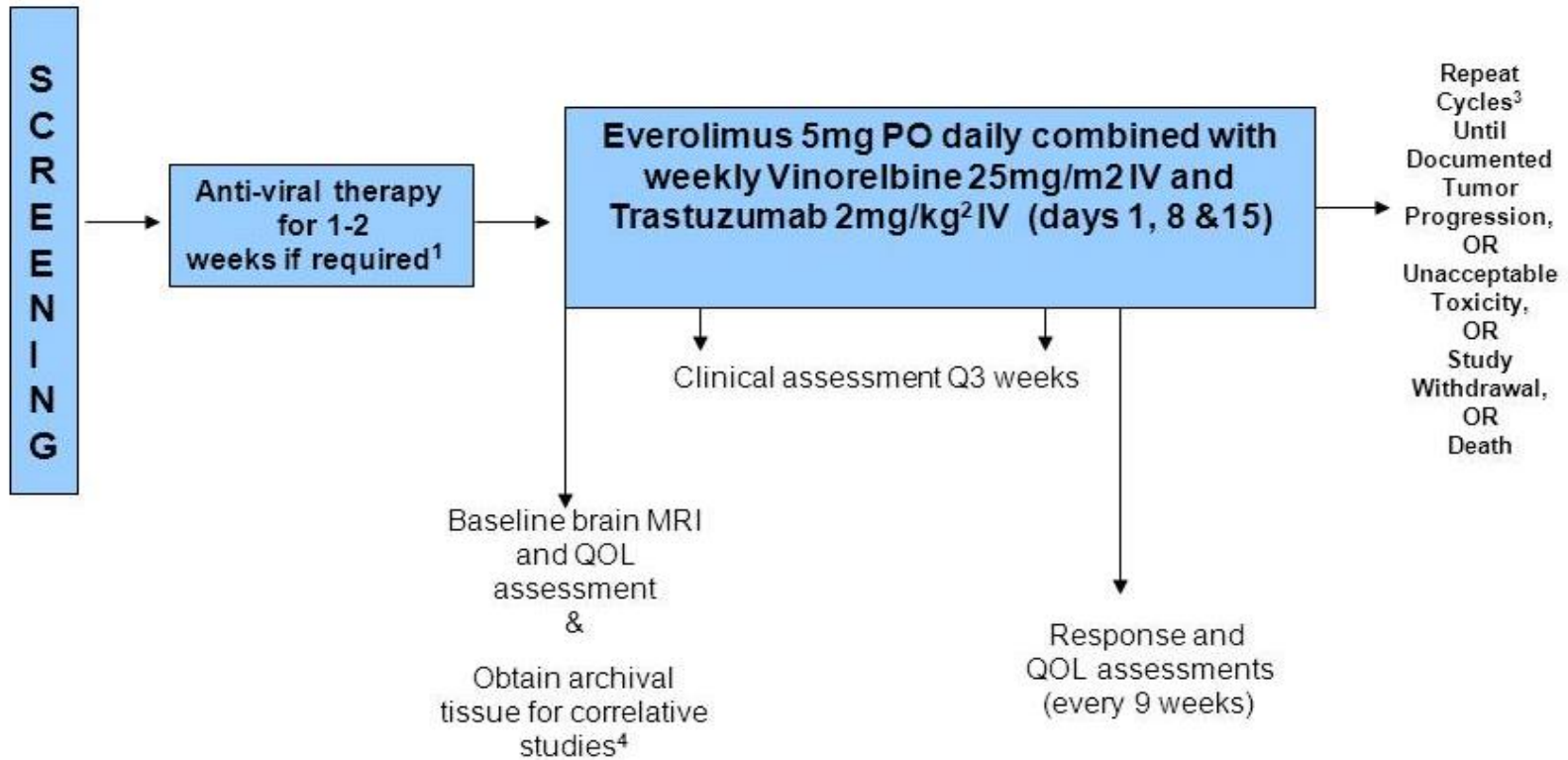
ANG-1005 (GRN-1005)

- Paclitaxel conjugated to Angiopep-2
- Targets the LRP-1 receptor, located at the BBB and up-regulated in brain tumors
- Facilitates receptor-mediated transcytosis across BBB



Phase II study of everolimus, navelbine and trastuzumab in HER2+ breast cancer brain metastases

N=10-36



¹ Required pending results of HBV screening

² Patients **NOT** receiving trastuzumab prior to enrollment in the study will receive 4mg/kg as a loading dose on Day 1 of cycle 1 followed by 2 mg/kg weekly for subsequent doses

³ One cycle = 21 days

⁴ See Section 7.0 and laboratory manual

Neratinib in Progressive HER2+ CNS Disease

Consent and Screening (n = 60)

No prior lapatinib (cohort 3a)
n=35

Prior lapatinib (cohort 3b)
n=25

Baseline brain MRI (≥ 1 measurable lesion)
CT Chest/Abdomen/Pelvis, CTCs

Neratinib (240 mg orally once daily) and
capecitabine 750 mg/m² BID for
14 days followed by 7 days rest

Diarrhea ppx,
RN phone call 24,
48, 72 hours

Follow-up every 3 weeks

Brain MRI & body CT
re-staging at week 6

Courtesy of PI:
Rachel Freedman, MD

CR, PR, SD – Continue therapy

Re-stage every 2 cycles while on study
until 18 weeks, then re-stage every 3 cycles

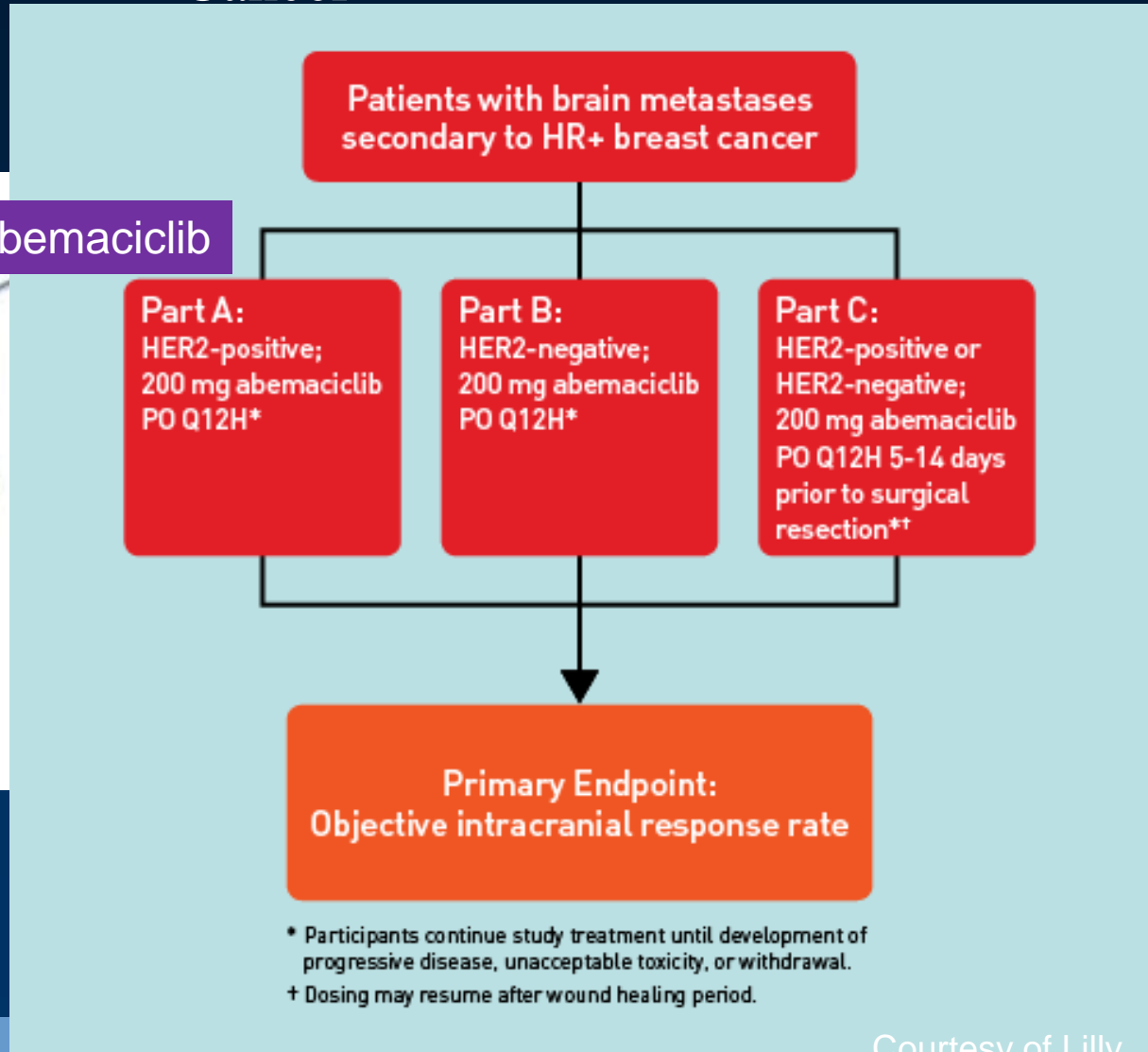
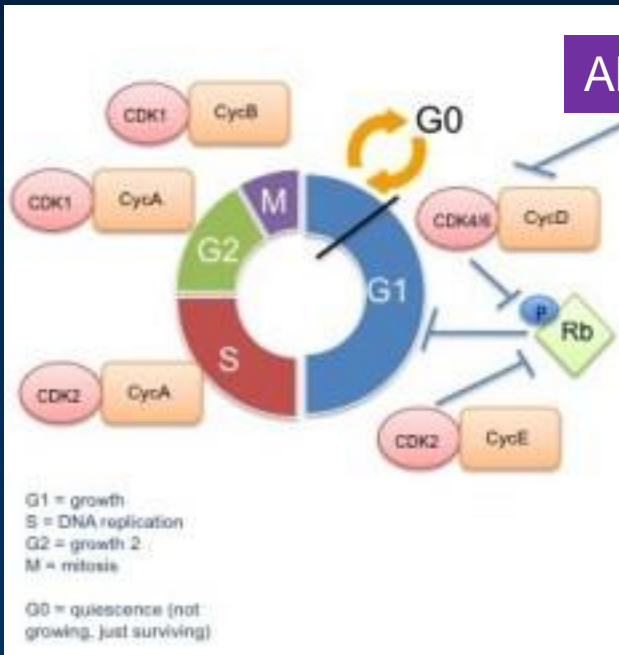
PD (CTCs)

- If CNS PD – Off study
- If non CNS PD – extension with trastuzumab offered

Other Brain Permeable Her2-targeted agents to keep your eye on....

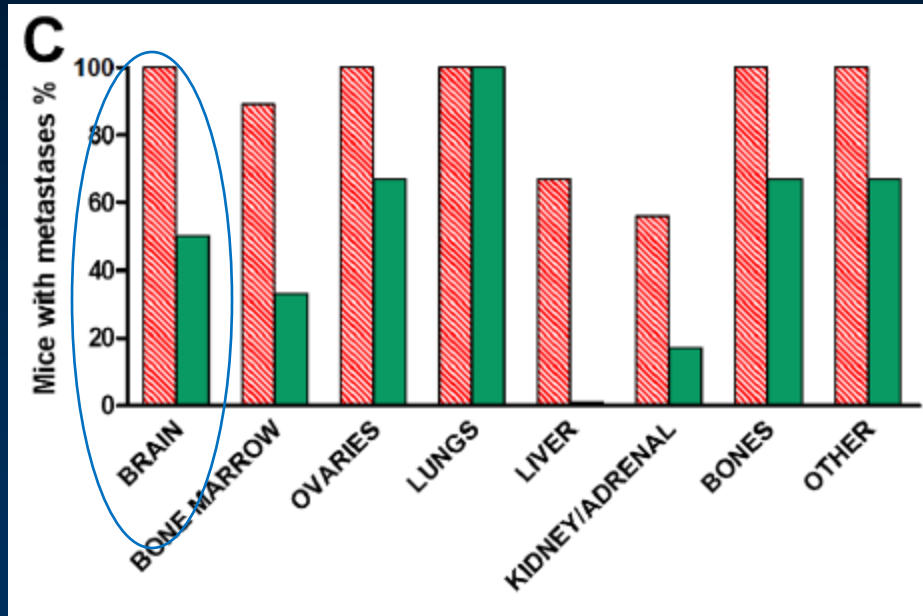
Drug Name	Company	MOA	Study Status
ARRY-380 (ONT-380)	Array-Biopharma	Selective HER2 inhibitor	Phase Ib (+trastuzumab; + TDM1)
KD019 (XL-647)	Kadmon Corp.	Multi-targeted TKI; Her2 and Src	Phase I w/ trastuzumab
TDM1 (??)	Genentech	Trastuzumab conjugated to Emtansine	Phase II in development

A Phase 2 Study of Abemaciclib in Patients With Brain Metastases Secondary to Hormone-Receptor-Positive Breast Cancer



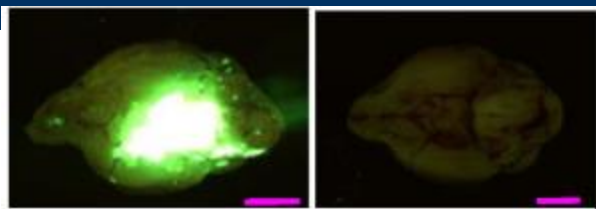
Preclinical Summary Slide: PI3K, MEK and mTOR inhibition

BKM120 (PI3K inhibition)



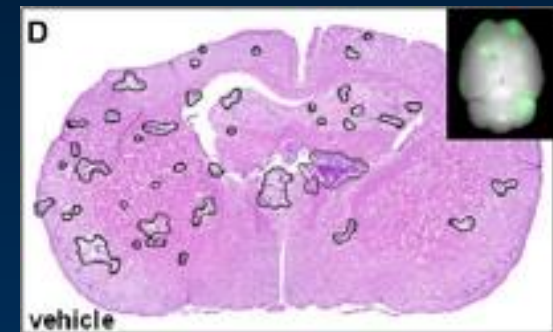
Vehicle

BKM120

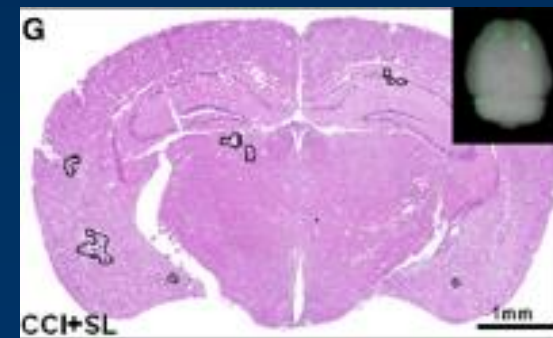


BRAIN

Vehicle



MEKi + mTORi

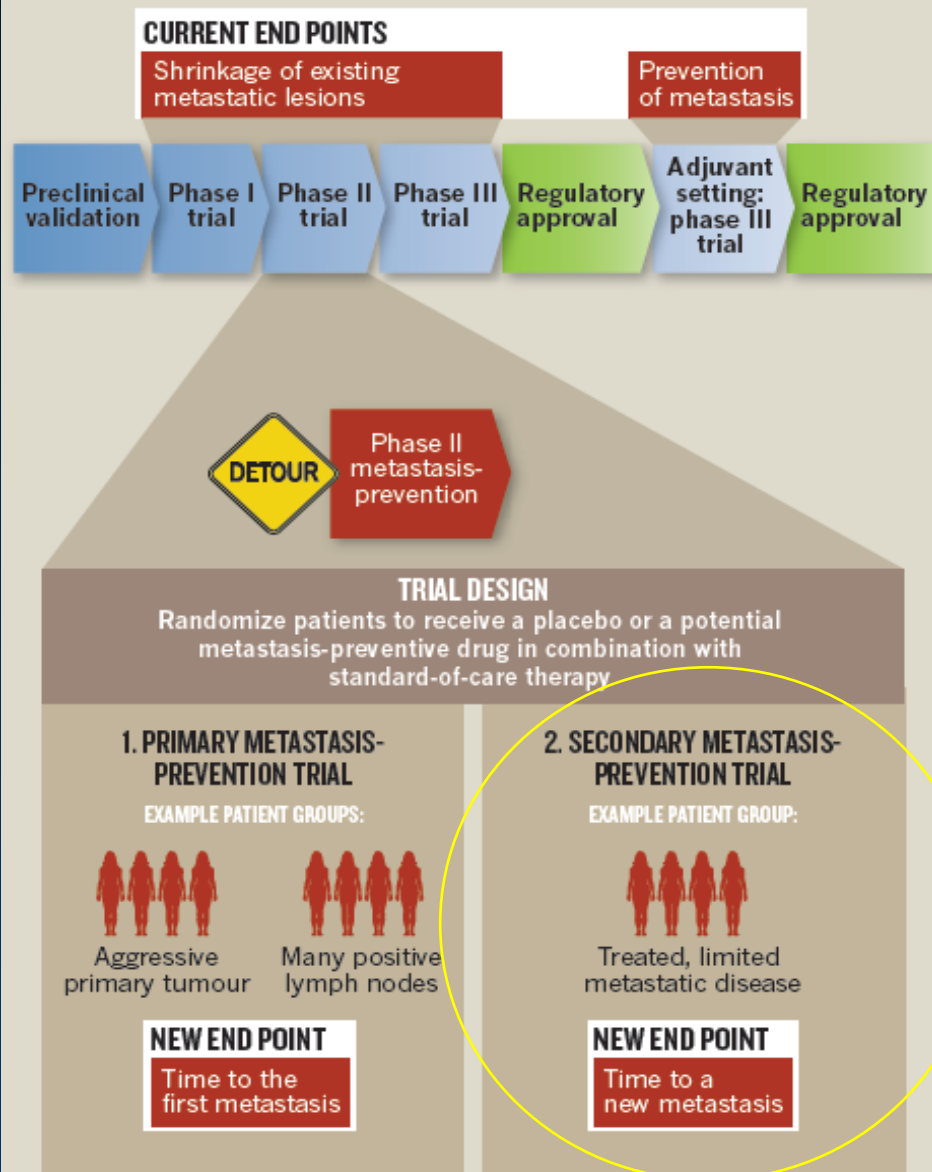


QUESTION:

Can we use systemic therapies to protect un-irradiated brain from metastases following radiation therapy?

THE ROAD TO APPROVAL

To clinically validate drugs for preventing metastases, new trial designs are needed to expand on the current phase II trials.



UNC/LCCC Multi-disciplinary Brain Metastases Specialty Clinic

Co-Directors



Carey K. Anders, MD
Medical Oncology



Matt Ewend, MD
NSU



Timothy Zagar, MD
Radiation Oncology

Early Phase Clinical Trials
Local Therapies
Radiosensitizers
Systemic Therapy



CNS Metastases Registry
-North Carolina and Surrounding States

<http://unclineberger.org/brain-metastases/>

Neurocognitive Outcomes
Onco-psychiatry
Don Rosenstein

University of North Carolina/LCCC
Multi-Disciplinary Brain Metastases Clinic

Novel Neuroimaging BRIC (Yueh Lee)
Keith Smith, MD

Prospective Tissue Collection
Archival FFPE
Fresh tumor biopsies
Whole Blood

Faculty Leaders:
Neurosurgery: Matt Ewend, MD
Radiation Oncology: Timothy Zagar, MD, Larry Marks, MD
Medical Oncology: C. Anders, MD, Stergios Moschos MD, Carrie Lee MD

Pre-clinical Collaborations
-CCNE collaborators (Zamboni and DeSimone)
-Radiosensitizers (Sambade, Miller)

Dedicated Research Coordinators and NP support

BCBM Specialty Clinic at UNC

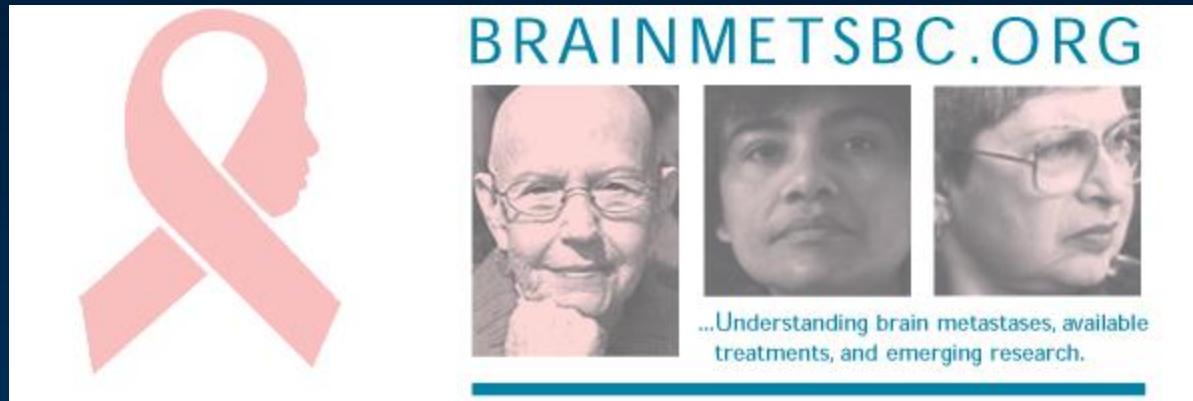
- Clinic is held every Wednesday morning
 - Radiation Oncology Department in the NCCH
 - Contact: 1-919-445-5295

<http://unclineberger.org/brain-metastases>



Resources for patients

www.brainmetsbc.org



Invaluable resource which includes information about Brain/CNS metastases, clinical trials, support and stories, ongoing research, scientists and clinicians all determined to make a difference in the treatment of patients with breast cancer and brain metastases.

- Thank you!
- Questions?