

CNS MALIGNANCIES

Educational session

FPON

Muhammad Zulfiqar, MD

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Conflict of Interest

- Nothing to declare



Objectives

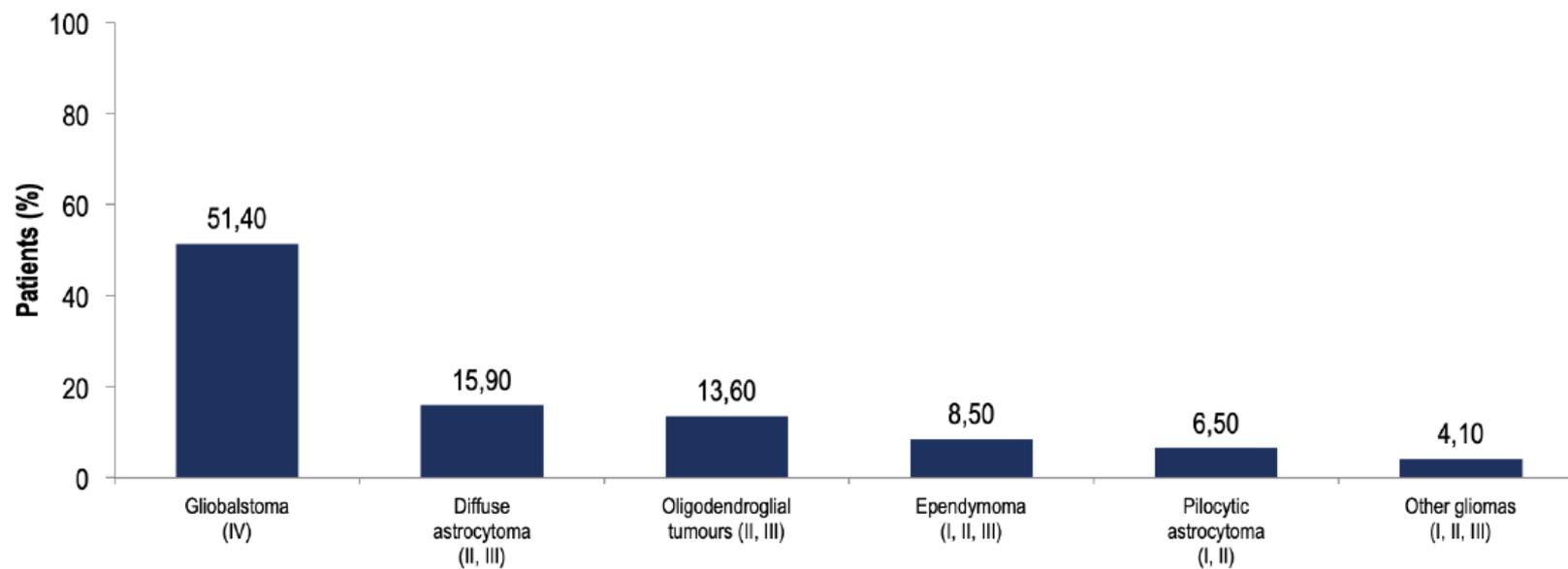
- **Recognize early signs and symptoms**
 - **Describe current management**
 - **Discuss supportive care and the role of the family physician.**
-
- Discussion of questions and comments

What is estimated in Canada

- In 2020, an estimated:
- 3,000 Canadians will be diagnosed with brain and spinal cord cancer.
- 2,500 Canadians will die from brain and spinal cord cancer.
- 1,700 men will be diagnosed with brain and spinal cord cancer and 1,400 will die from it.
- 1,350 women will be diagnosed with brain and spinal cord cancer and 1,050 will die from it.

Incidence

RELATIVE FREQUENCIES OF GLIOMAS



Roman numerals denote World Health Organisation (WHO) tumour grades.
Redrawn from: Preusser M, *et al.* *Ann Neurol* 2011;70(1):9–21.

Looks can be deceiving

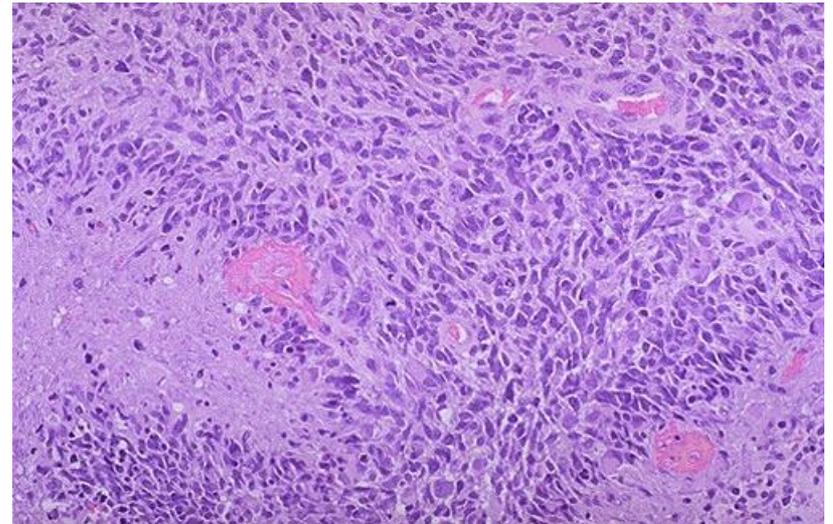
How does it look?

Vs

How it behaves?

How it looks?

- **Prominent anaplasia, vascular proliferation and palisading of tumor cells around necrosis**



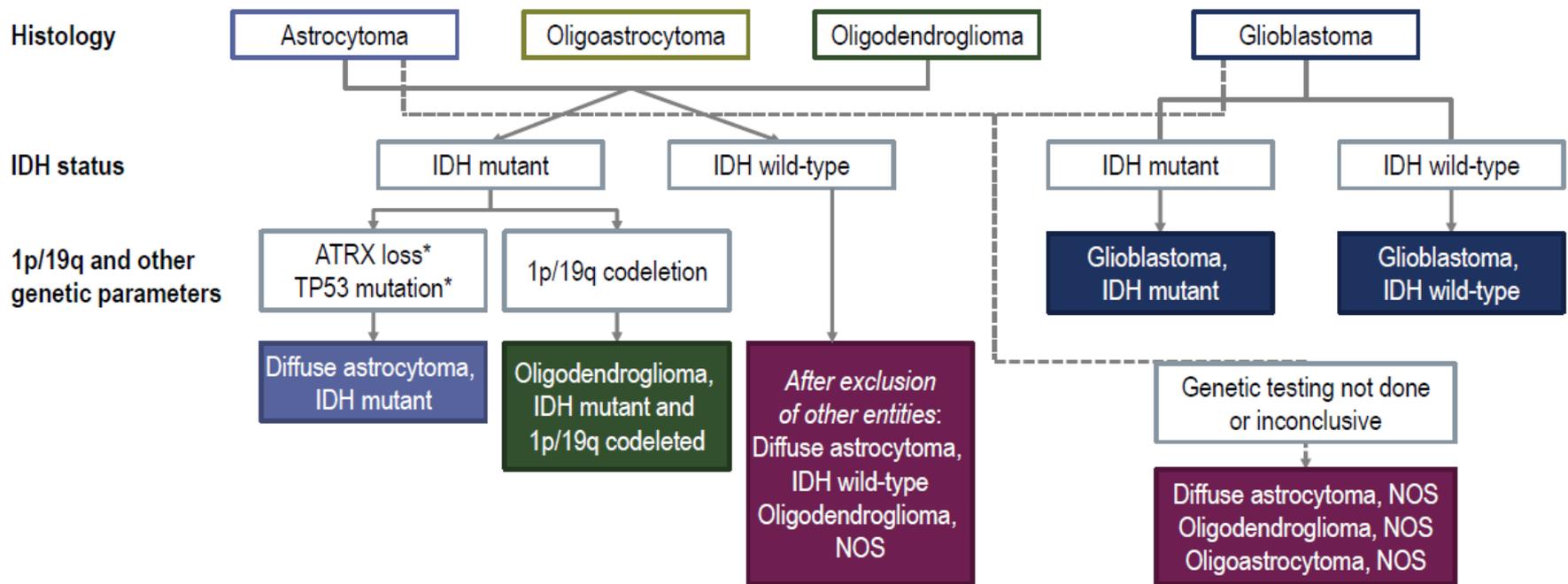
How it Behaves?

- *IDH* wild-type
- glioma with *TERT* mutations and polysomy of chromosome 7
- plus loss of heterozygosity of chromosome 10q have similar
- outcomes compared with those with GBM

1. Aibaidula A, Chan AK, Shi Z, et al. Adult IDH wild-type lower-grade gliomas should be further stratified. *Neuro Oncol.* 2017;19:1327-1337.
2. Wijnenga MMJ, Dubbink HJ, French PJ, et al. Molecular and clinical heterogeneity of adult diffuse low-grade IDH wild-type gliomas: assessment of *TERT* promoter mutation and chromosome 7 and 10 copy number status allows superior prognostic stratification. *Acta Neuropathol.* 2017;134:957-959.

Current WHO Classification

WHO CLASSIFICATION



*Characteristic but not required for diagnosis.

How do these malignancies present?

- Headache
- Seizure
- Focal neurological symptoms
- Cognitive issues

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Spectrum:

Target
Angiogenesis
Bevacizumab

Radiation Therapy and
Alkylating agents
STUPP

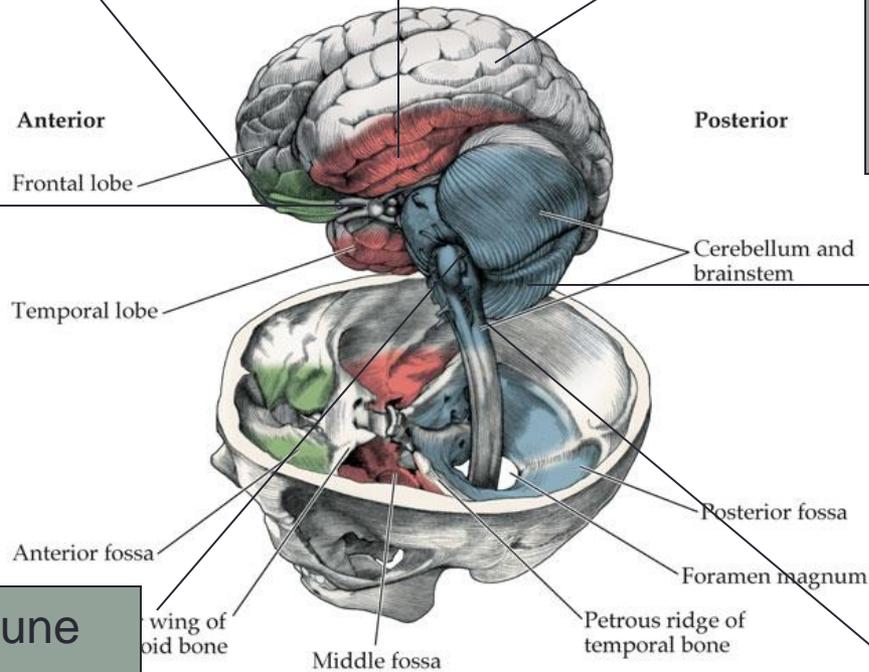
Check point Inhibitors
PD-1
PDL-1
CTLA-4

T-Cell Therapy
DC Therapy
Oncolytic Viral

Peptide Vaccines

Combination Immune
Strategies
Nivolumab and DC vaccine

Tumor Treating
Fields



PHASE III TRIAL OF CONCOMITANT AND ADJUVANT TEMOZOLOMIDE AND RADIOTHERAPY FOR NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME

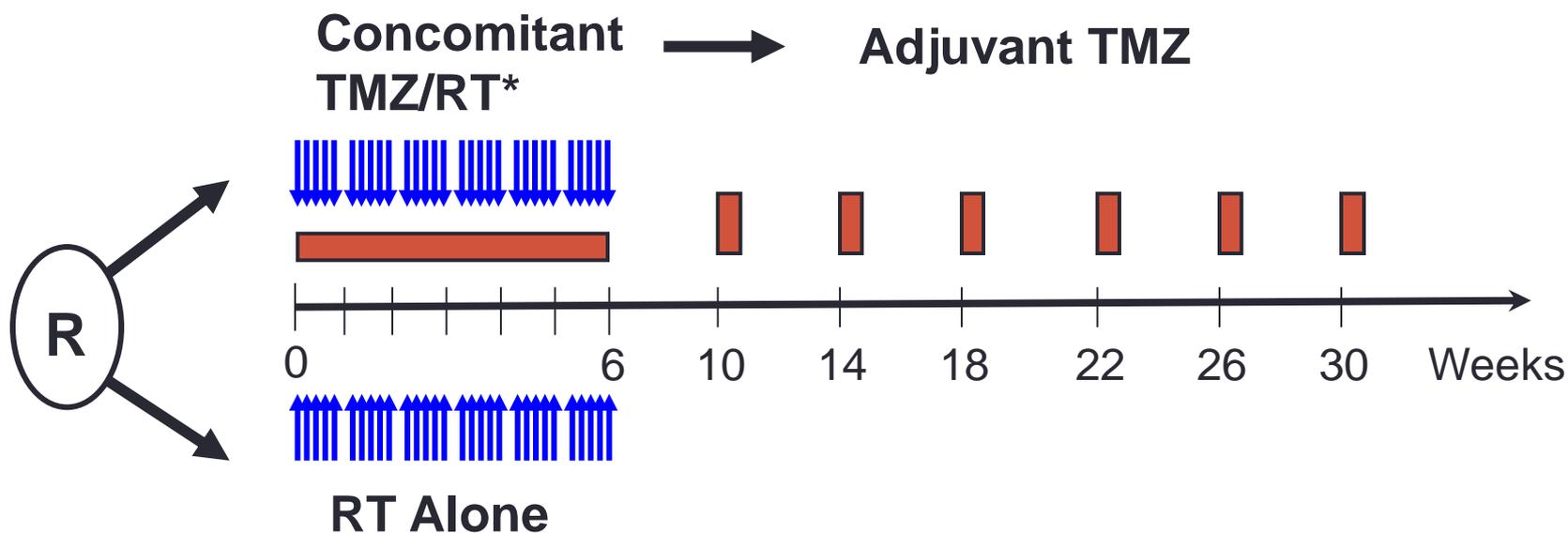
Roger Stupp, WP Mason, MJ Van Den Bent, M Weller,
B Fisher, M Taphoorn, AA Brandes, G Cairncross,
D Lacombe, RO Mirimanoff

On behalf of the European Organization for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and National Cancer Institute of Canada Clinical Trials Group

ASCO Plenary Session / June 7, 2004

EORTC 26981-22981 and NCIC CE.3

Treatment Schema

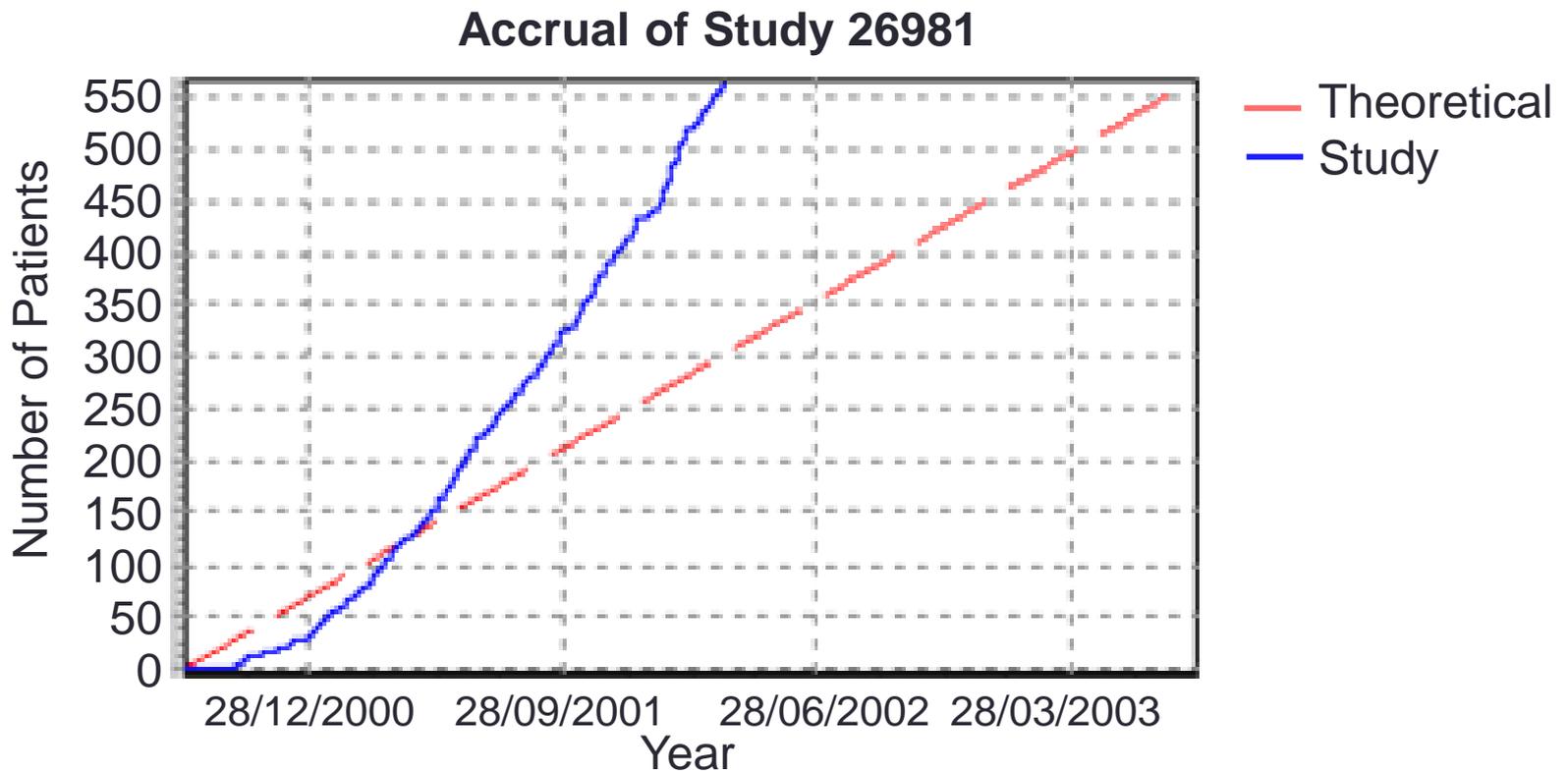


-
-  **Temozolomide** 75 mg/m² po qd for 6 weeks, then 150–200 mg/m² po qd d1–5 every 28 days for 6 cycles
 -  **Focal RT** daily — 30 x 200 cGy
Total dose 60 Gy

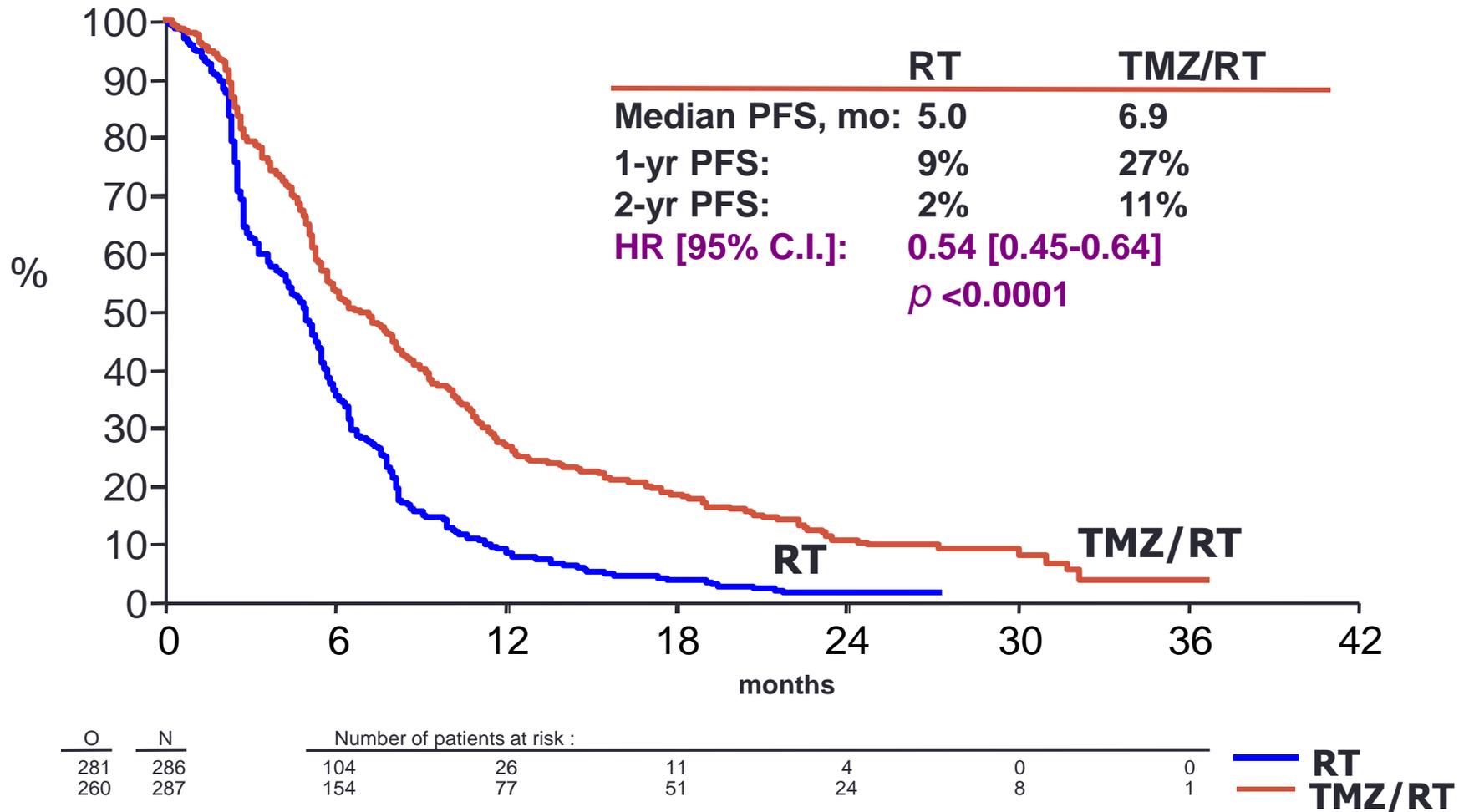
*PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.

- 85 institutions, 14 countries, 573 patients

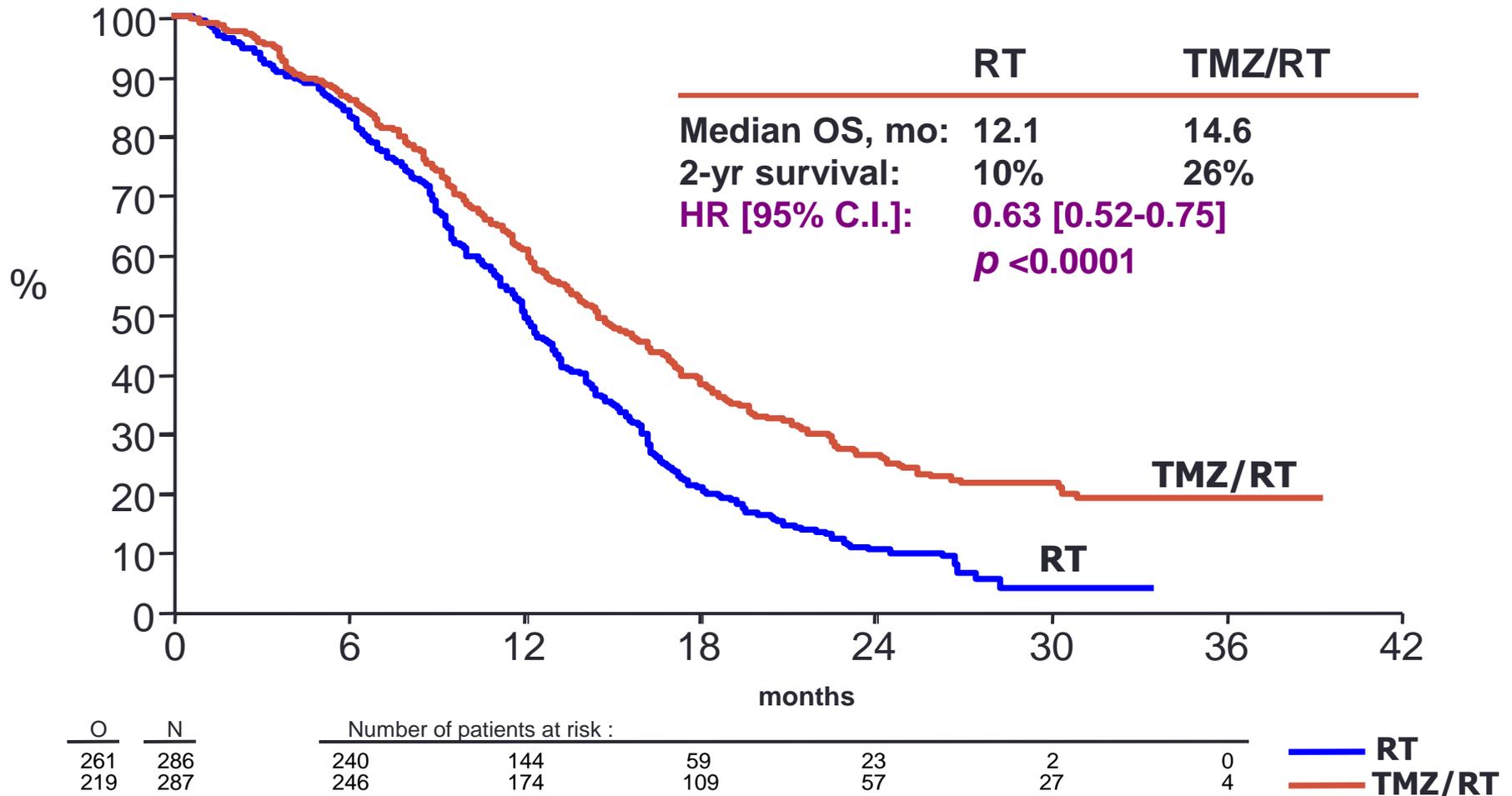
Patient Accrual



Progression Free Survival



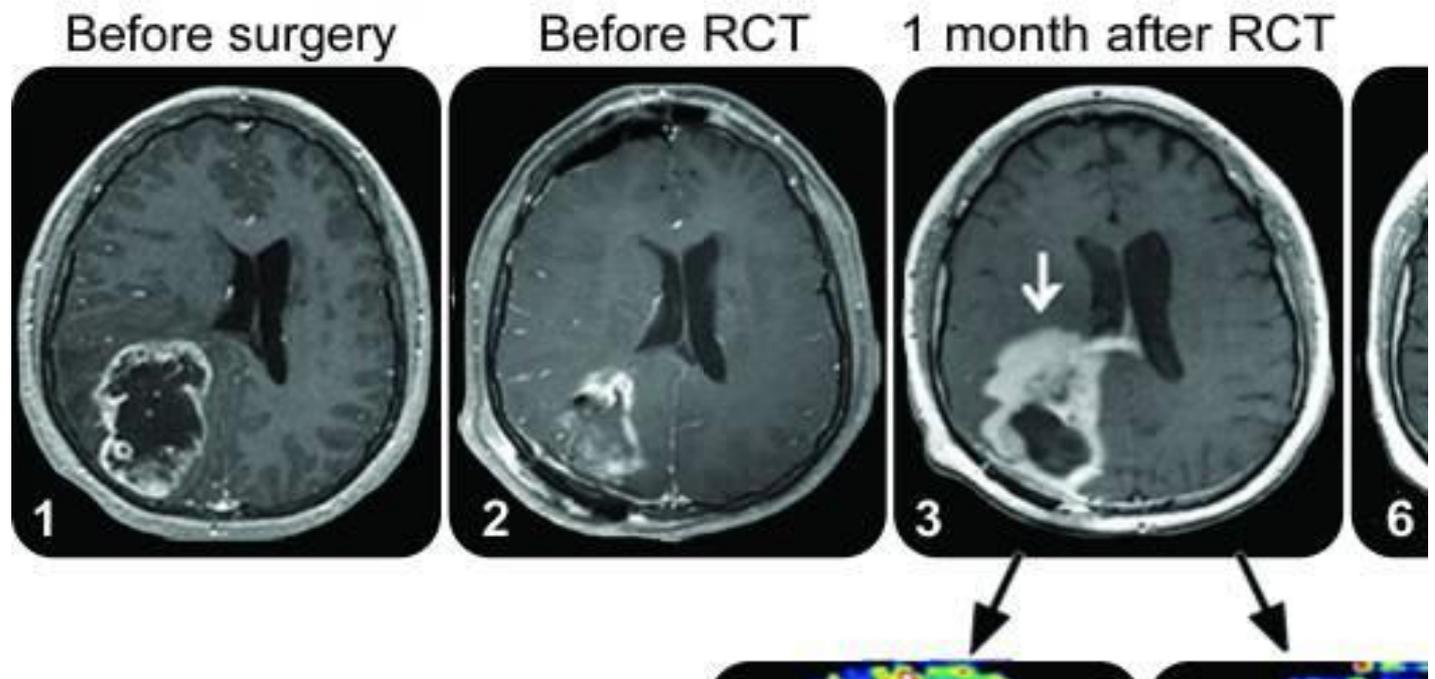
Overall Survival



45 years old gentleman

- Glioblastoma
- Treated with STUPP protocol.

Images



Appropriate next step:

1. Disease progression. Move to second line treatment
2. Options are limited. Continue same treatment.
3. Re-image in 8 weeks
4. Continue same treatment as it falls into the right timeframe of pseudo progression

Bavacizumab at Progression

- Phase 2
- 6 month PFS of 40% to 50%
- Median OS of 8 to 9 months.

Pseudo improvement

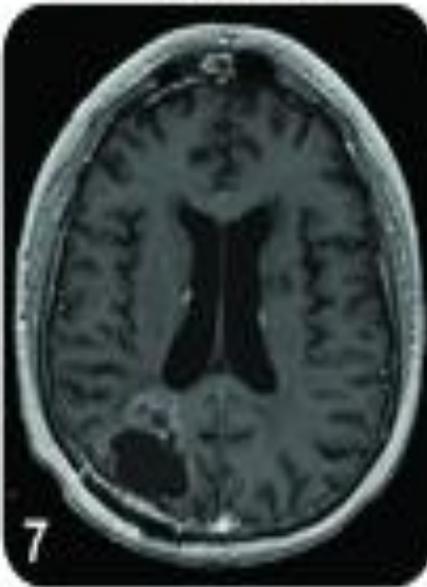
1 month after RCT



BEV 1x



BEV 2x

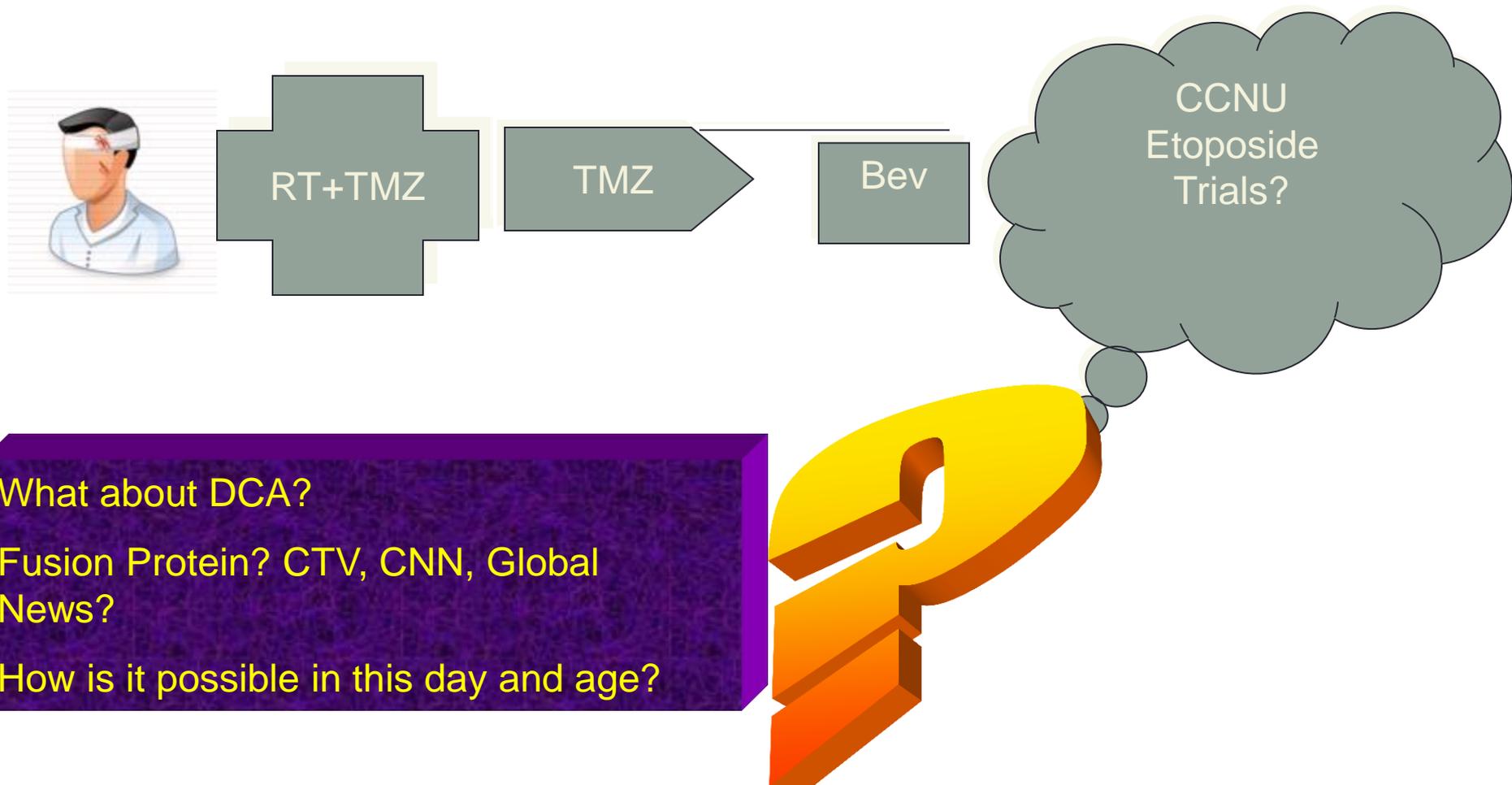


BEV 6X



T1+
Gd

Course of Events



Checkpoint Inhibitors

Checkpoint inhibitors gliomas

1. Have game changing effect
2. Are under investigation
3. Not as promising as they are in other solid tumors

FDA Approval of Checkpoint Agents

Drug Name	Company	Mode of Action	Cancers Treated	Year approved
Opdivo/Nivolumab	Bristol-Myers Squibb	Anti-PD-1	Bladder	2017
			Colorectal	
			Liver	
			Head and Neck	2016
			Hodgkin's Lymphoma	
Renal Cell CA				
			NSCLC	2015
			Melanoma	2015
				2014
Atezolizumab	Genentech	Anti-PD-L1	Lung Bladder	2016
Durvalumab	Medimmune/AstraZeneca	Anti-PD-L1	Bladder Lung	2017
Avelumab	Pfizer	Anti-PD-L1	Merkel Cell Bladder	2017

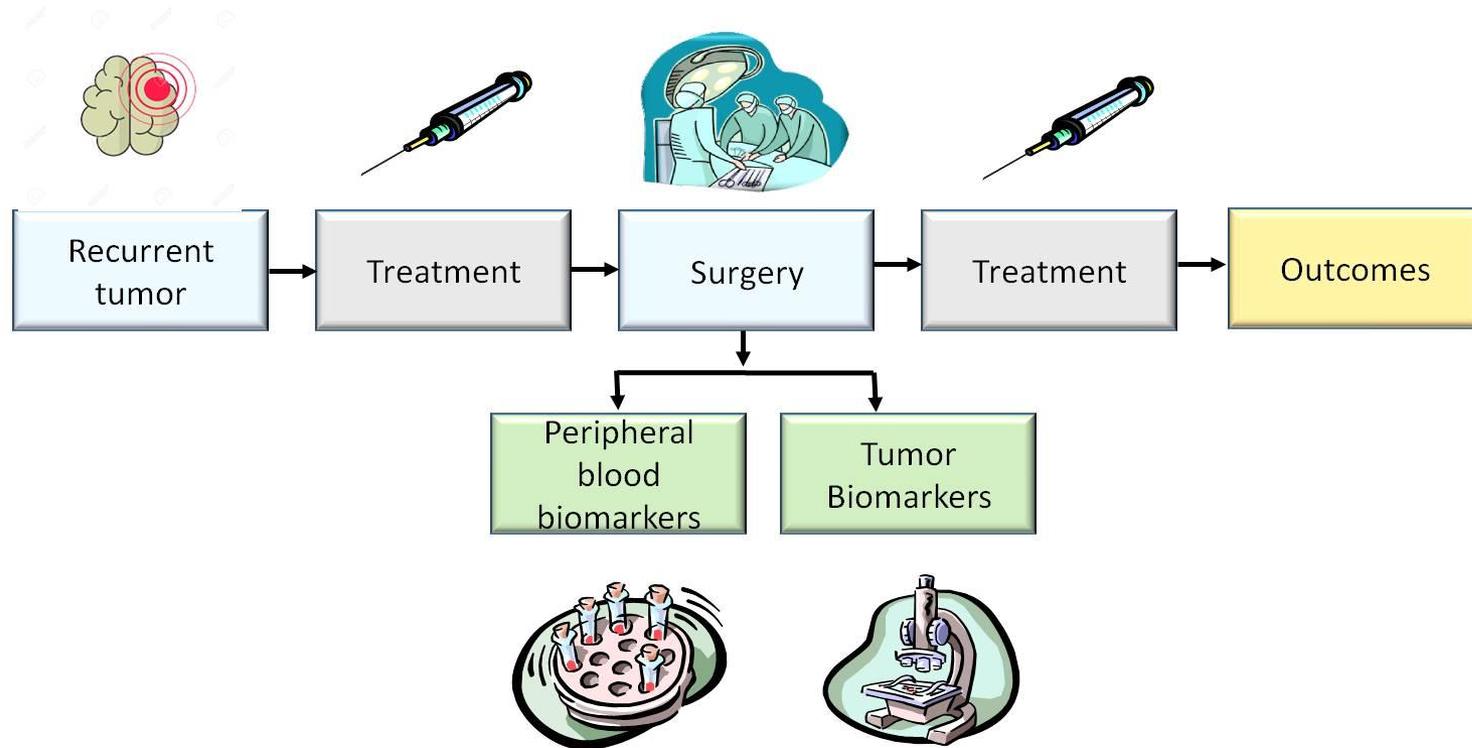
FDA Approval of Checkpoint Agents

Drug Name	Company	Mode of Action	Cancers Treated	Year approved
Keytruda/ Pembrolizumab	Merck	Anti-PD-1	MSI High	2017
			Bladder	
			Stomach/GE	
			Lung (first line)	
			Lymphoma	
			Lung	2016
			Head and Neck	
			NSCLC	2015
			Melanoma	2014
Nivolumab + Ipilimumab	Bristol-Myers Squibb	Anti-PD-1 + Anti-CTLA-4	Metastatic Melanoma	2015
Yervoy/Ipilimumab	Bristol-Myers Squibb	Anti-CTLA-4	Metastatic Melanoma	2011

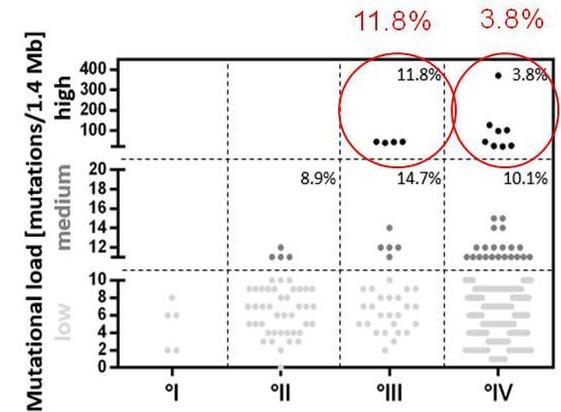
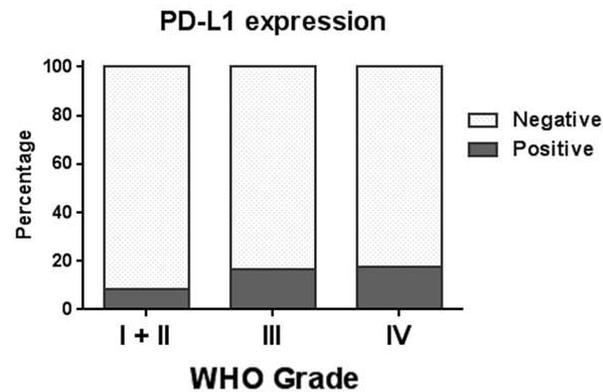
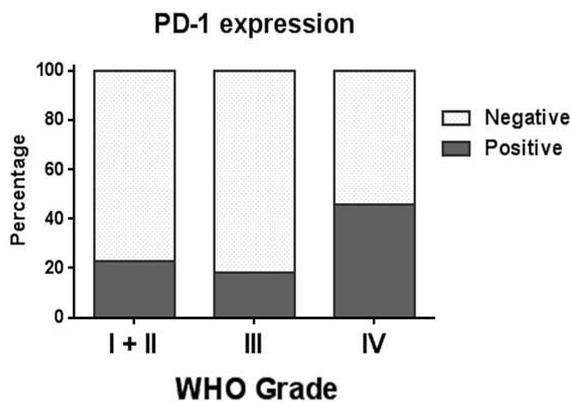
Ongoing Experience with Checkpoint Blockade in Glioblastoma

- **CheckMate-143:** randomized trial of Nivolumab (anti-PD-1) compared to Bevacizumab in recurrent GBM (N = 369 patients)
 - No difference in OS-12 (42%) or median OS (9.8 vs 10 months)
- **CheckMate-498 (Methylated):** An Investigational Immuno-therapy Study of Nivolumab Compared to Temozolomide, Each Given With Radiation Therapy, for Newly-diagnosed Patients With Glioblastoma
- **CheckMate-548 (Unmethylated):** An Investigational Immuno-therapy Study of Temozolomide Plus Radiation Therapy With Nivolumab or Placebo, for Newly Diagnosed Patients With Glioblastoma

Window of Opportunity Clinical Trials to Monitor Immune Responses in GBM patients



Data in Context of Biomarker Predictors for Response to Immune Checkpoint Inhibitors



Hodges, Neuro-Oncology, 2017; Garber, Neuro-Oncology, 2016; Nduom, Neuro-Oncology, 2015

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DR. EVANGELOS MICHELAKIS
University of Alberta

CURE FOR
CANCER

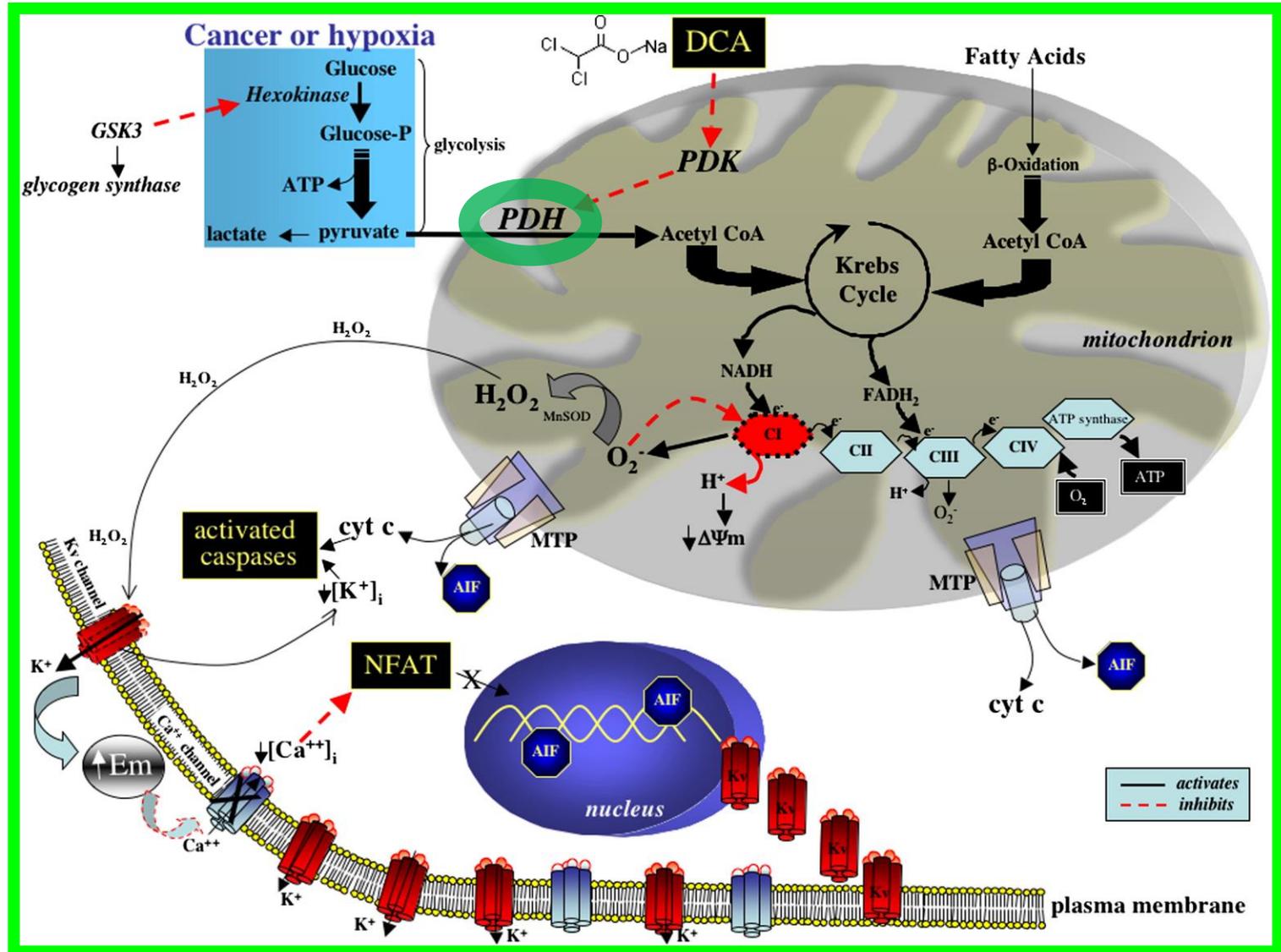


HEALTH PRIME
DAY 2016 CONVICTED SEX OFFENDER ALFONSO RODRIGUEZ WAS SE

DCA's Promise at two levels

- Electrical
 - High mitochondrial membrane potential
 - Low expression of K^+ channels
- Metabolic
 - Aerobic glycolysis

DCA

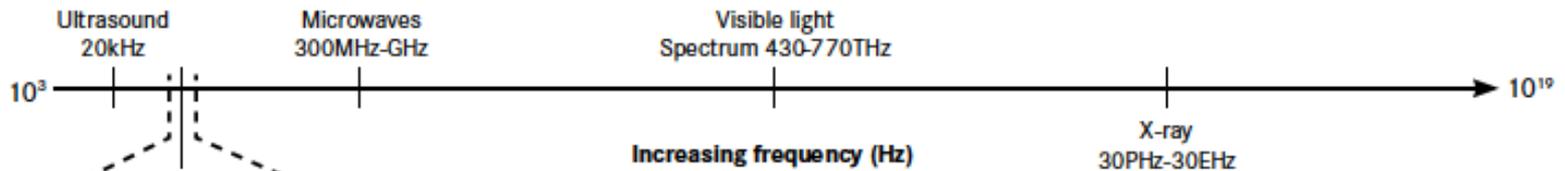
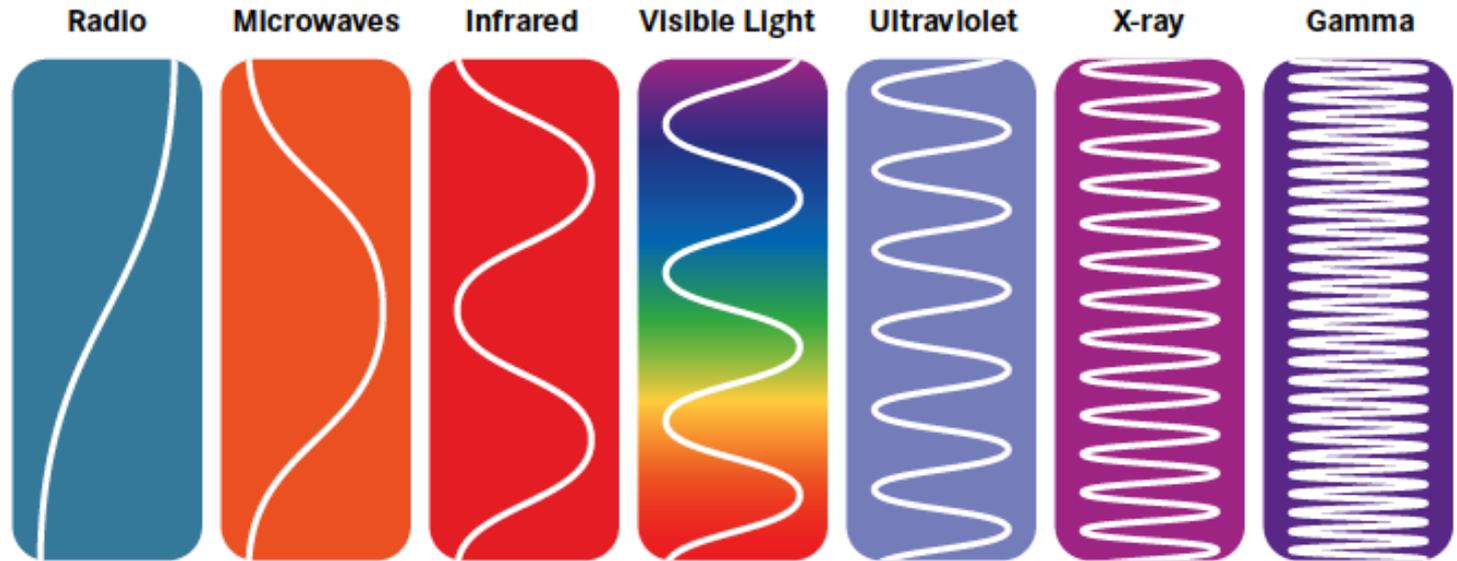


DCA

LACK OF CLINICAL
STUDIES

Tumor Treating Fields

- Mitotic arrest and apoptosis
- Increased sensitivity to chemotherapy in the presence of TTF



Tumor-treating fields 100 to 300kHz

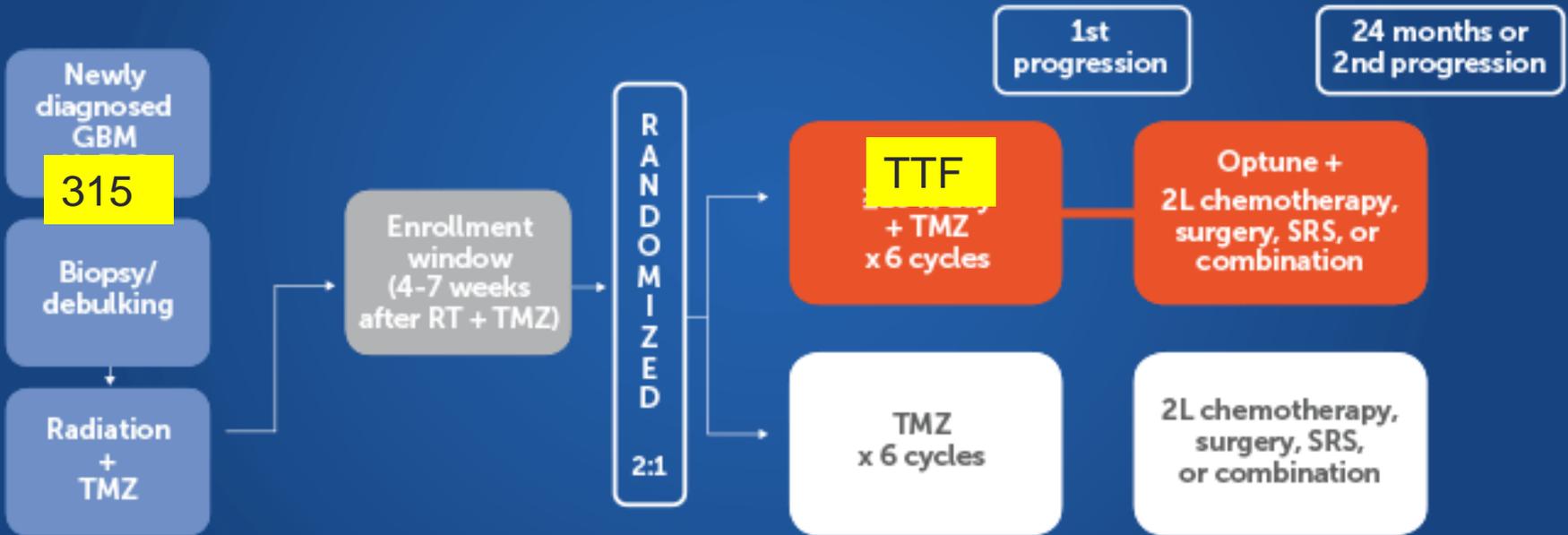
- 150kHz: Pancreatic, non-small cell lung cancers
- 200 kHz: Glioblastoma, ovarian cancer

Optune uses low-level electrical fields that alternate 100,000 to 300,000 times per second. Electromagnetic frequencies are on the lower end of the spectrum and range from 100 to 300 kHz, depending on the tumor type.

Tumor Treating Fields

EF-14 phase 3 pivotal trial—

TTF + TMZ vs TMZ alone in newly diagnosed GBM¹⁻³



Findings

- 210 patients randomized to TTFields plus temozolomide
- 105 randomized to temozolomide alone
- Stopped early due to ongoing benefit.
- median follow-up of 38 months (range, 18-60 months)
- PFS 7.1 months vs 4.0 months.
- OS 20.5 months vs 15.6 months.
- No increase in toxicity
- Main side effects from TTF was skin irritation, rash, ulceration and infection.

Sham Device?

Clinician training and certification

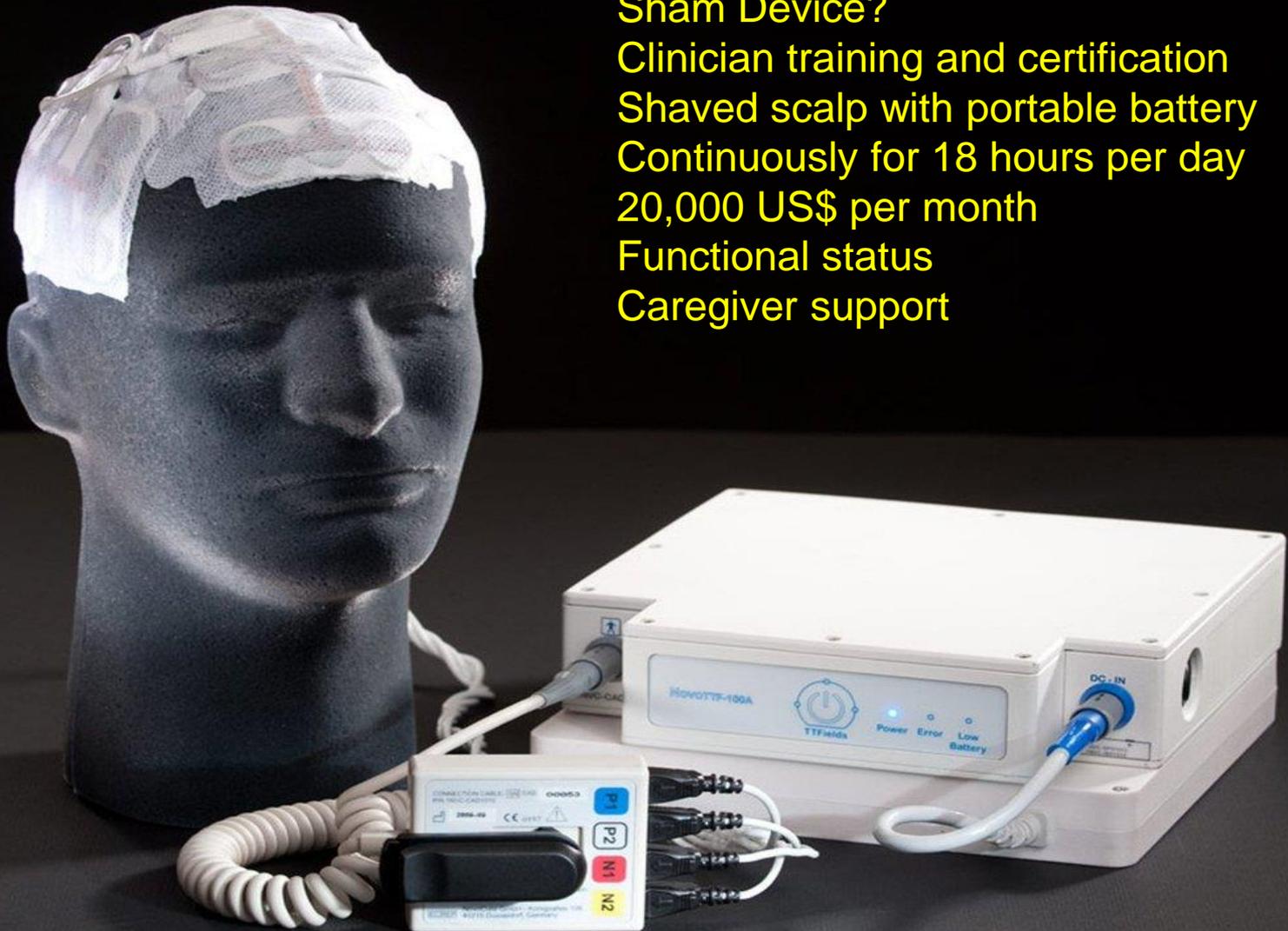
Shaved scalp with portable battery

Continuously for 18 hours per day

20,000 US\$ per month

Functional status

Caregiver support



Mind body medicine

1. Is a new age popular term with no scientific merits
2. Field of neuro-immunology supports evidence that mind plays pivotal role in healing
3. If there is any role, it is very limited at its best.

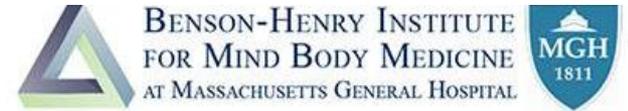


Mind Body Medicine:

Guiding Patients to Health & Happiness

Oct 19-21, 2017
Boston, MA

Featuring Mind Body Medicine Pioneers
Herbert Benson, MD
and Jon Kabat-Zinn, PhD



MBSR (Mindfulness based stress reduction)

Does increased stress promote cancer growth?

- Thaker et al (MD Anderson)
- Nude mice model (inoculation with ovarian cancer cells)
- Stressed out mice (growth rate 275% more than non stressed)
- Beta adrenergic receptor expression on tumor cells.
- Transcriptional upregulation of VEGF

Can decreasing stress have improvement in cancer outcome?

- Cancer. 2008;113:3450–3458. OSU and Walther Cancer Institute and NCI.
- Adjuvant Breast cancer (N=212)
 - Randomization between intervention (26 sessions teaching strategies to reduce stress, improve mood and alter health behaviors vs assessment only)
- 11 yrs of follow up
- Median survival 6.1 vs 4.8 yrs.
- Multivariate analysis HR 0.44; p=0.016)

Exercise

Melanoma B16F10



In 4 weeks

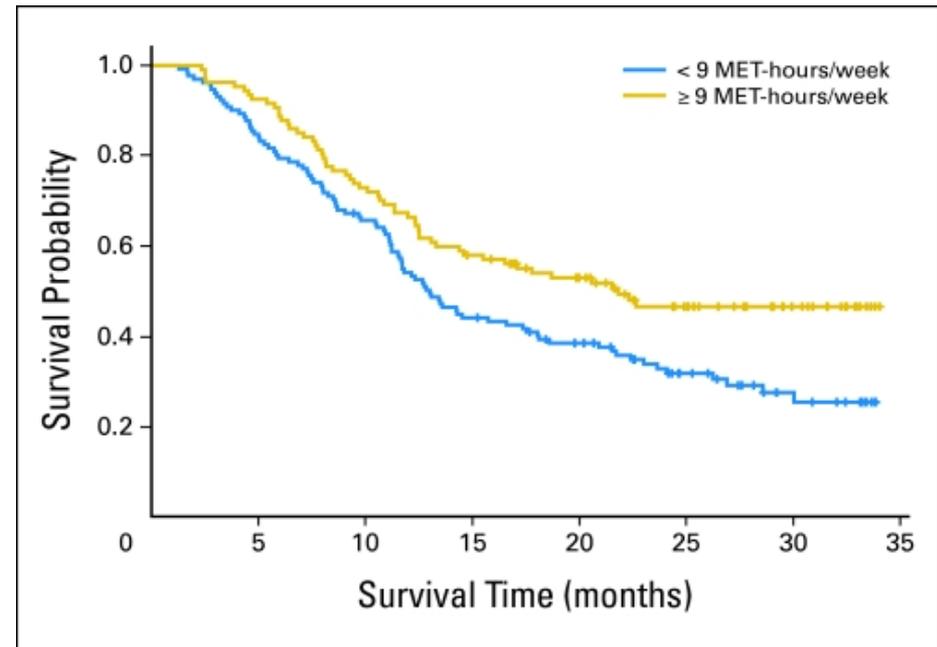
Increase NK cells

61% ; $p < 0.01$ reduction of cancer cells in exercising mice

Pedersen L, Idorn M, Olofsson GH, et al. Voluntary running suppresses tumor growth through epinephrine- and IL-6-dependent NK cell mobilization and redistribution. *Cell Metab.* 2016;23:554–562.

Exercise in high grade Glioma

- 243 patients with high grade glioma
- KPS 70 or higher
- Self administered questionnaire on exercise behavior
- 6 minute walk to assess functional capacity.
- Exercise was better predictor of survival than KPS, age, sex, grade and number of prior progression
- Adjusted HR 0.64 (95% CI 0.46-0.91)
- Strenuous exercise was independent predictor of survival.



Ruden E, Reardon DA, Coan AD, et al. Exercise behavior, functional capacity, and survival in adults with malignant recurrent glioma. *J Clin Oncol.* 2011;29:2918–2923

Nutrition

- Joint Study at PMH and Harvard Medical School.
- Thompson LU, Chen JM, Li T, et al. Dietary flaxseed alters tumor biological markers in postmenopausal breast cancer. Clin Cancer Res. 2005;11:3828–3835.
- Breast cancer patients
 - randomized to daily intake of either a 25 g flaxseed containing muffin (n = 19) or a control (placebo, n=13) muffin
- Reductions in Ki-67 labeling index (34.2%; P = 0.001) and in c-erbB2 expression (71.0%; P = 0.003) and an increase in apoptosis (30.7%; P = 0.007) were observed in the flaxseed, but not in the placebo group.
- Potential to reduce tumor growth.

Summary

- STUPP protocol remains standard of care
- Unique microenvironment of GBM does not allow immune check point inhibitors to work most effectively.
- There are no available clinical trial evidence for DCA
- In right situation, TTF is reasonable option to try as first line treatment.
- Several innovative combination immunomodulatory treatments are under active investigation
- Think about open clinical trial.
- Mind body medicine needs more attention going forward in an ever increasing field of expensive targeted interventions.

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Questions and Comments

