BRING NEW AND INNOVATIVE GLIOBLASTOMA TREATMENTS TO CLINICAL PRACTICE

SAJEEL CHOWDHARY, MD
PROGRAM DIRECTOR, NEURO – ONCOLOGY / NEUROLOGY

LYNN CANCER INSTITUTE (LCI)
MARCUS NEUROSCIENCE INSTITUTE (MNI)
BOCA RATON REGIONAL HOSPITAL (BRRH)
BAPTIST HOSPITAL SOUTH FLORIDA (BHSF)

MEDICAL STAFF, DELRAY MEDICAL CENTER

ASSOCIATE PROFESSOR OF NEURO – ONCOLOGY AND NEUROLOGY
CHARLES E SCHMIDT COLLEGE OF MEDICINE
FLORIDA ATLANTIC UNIVERSITY (FAU)

Disclosures:

- **NO RELEVANT FINANCIAL DICLOSURES OR CONFLICTS OF INTEREST IN REGARDS TO THIS PRESENTATION**

J K ROWLING:

- **“It is impossible to live without failing at something unless you live so cautiously that you might as well not have lived at all – in which case, you fail by default.”**

NEWLY DIAGNOSED GLIOBLASTOMA + OTHER HIGH GRADE GLIOMAS:

- **How do we currently treat Glioblastoma?**

NEWLY DIAGNOSED GLIOBLASTOMA + OTHER HIGH GRADE GLIOMAS:

- Maximal Safe Resections
- "Supra Maximal" Resections
- Intra – operative MRI capability
- MR Spectroscopy Guided Surgery
- MR Perfusion Guided Surgery
- Fluorescence Guided Surgery, 5 ALA (5 aminolevulinic acid)
  - Better delineation of tumor margins with 5 ALA versus conventional "white light microscopy"

NEWLY DIAGNOSED GLIOBLASTOMA + OTHER HIGH GRADE GLIOMAS:

- Radiation
- Photon based Intensity Modulated RT (IMRT)
- 60 GY in 30 Fractions, classic schema
- Hypofractionation, as in the elderly, 40 GY in 15 Fractions (James Perry data from Toronto)
- Stereotactic Radiosurgery (SRS), may have a role in select cases and in the recurrent setting

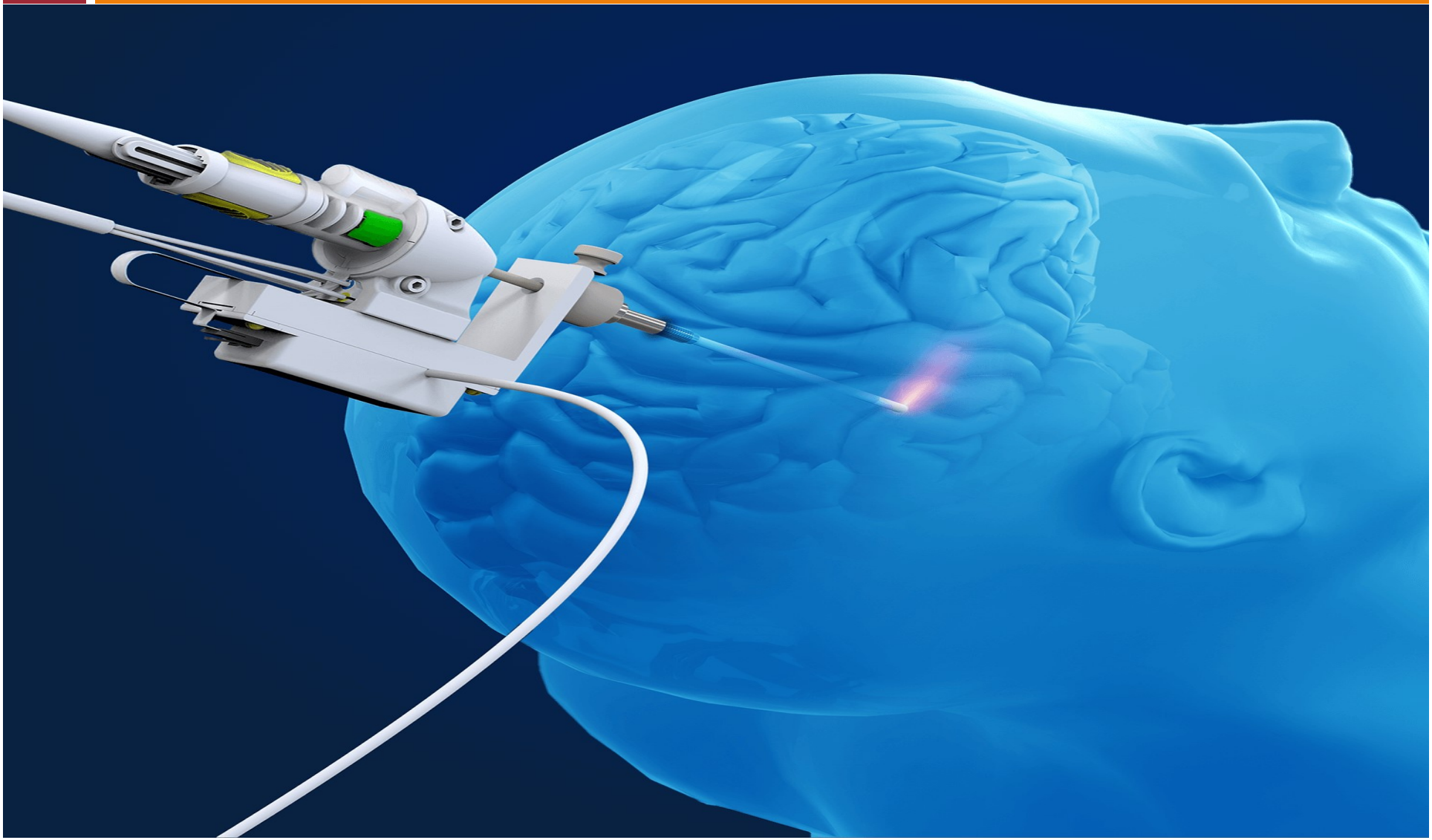
NEWLY DIAGNOSED GLIOBLASTOMA + OTHER HIGH GRADE GLIOMAS:

- **Does Proton Beam Radiation have superiority?**
- **Not clear at the moment?**
- **NRG and ALLIANCE conducting clinical trials**
  - **NRG BN 001: new GBM, Photon RT versus Proton RT and dose escalation to 60 GY – 75 GY**
  - **NRG BN 005: IDH mutated WHO Grade II / III Astrocytoma and Anaplastic Astrocytoma, Proton RT compared to Photon RT with**

NEWLY DIAGNOSED GLIOBLASTOMA + OTHER HIGH GRADE GLIOMAS:

- **Laser Interstitial Thermal Therapy (LITT)**
  - **Thermal ablation**
  - **Intra operative MRI guided (could be without too)**
  - **Multiple tumor types can be treated as Gliomas, Meningiomas and CNS metastasis**
  - **Necrosis (as post RT necrosis) can also be treated successfully**

NEWLY DIAGNOSED GLIOBLASTOMA + OTHER HIGH GRADE GLIOMAS:



NEWLY DIAGNOSED GLIOBLASTOMA + OTHER HIGH GRADE GLIOMAS:

- Gamma Tiles
  - Surgically Targeted Radio Therapy (STaRT)
  - Surgically implanted local RT delivery system

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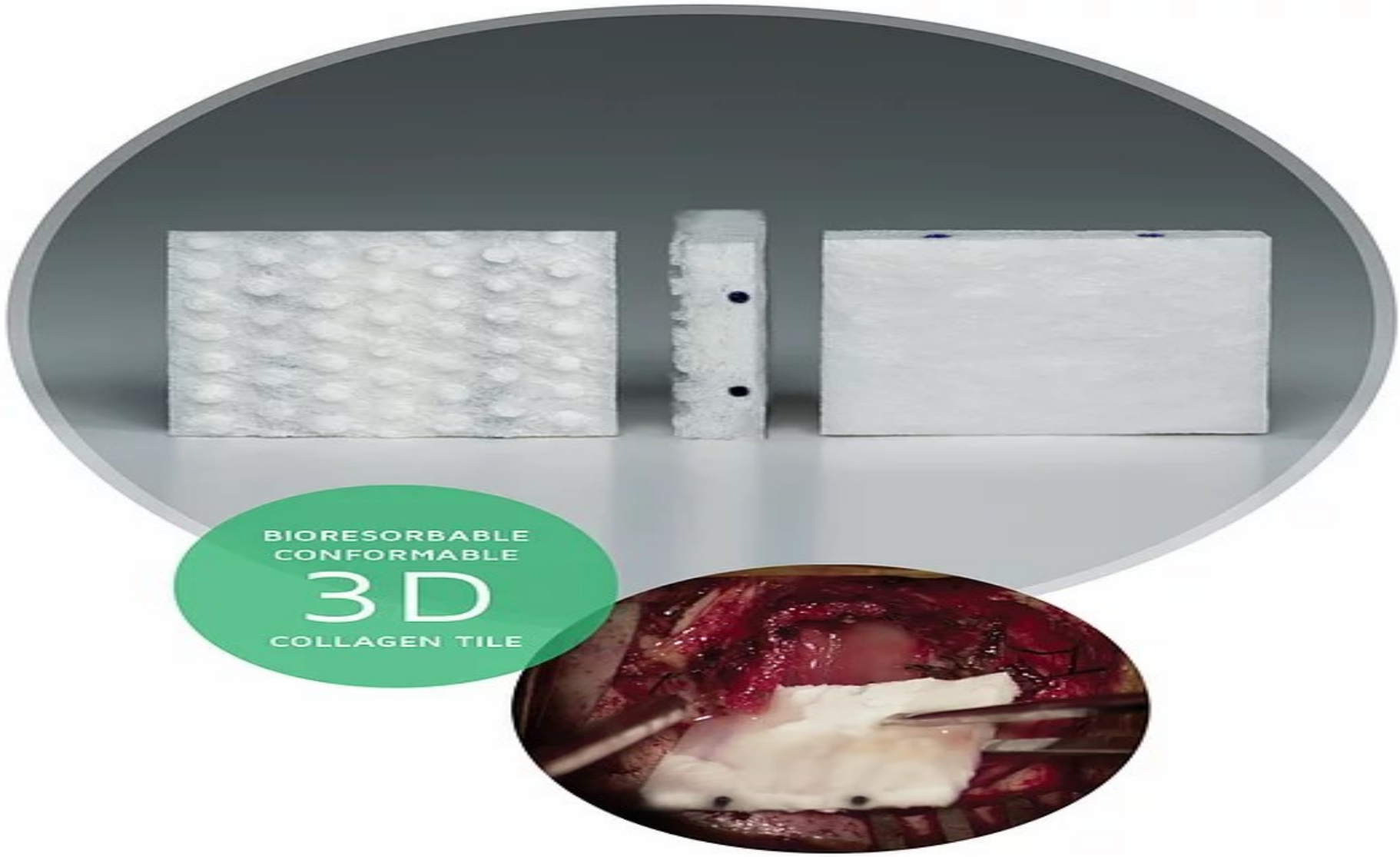

NEWLY DIAGNOSED GLIOBLASTOMA + OTHER HIGH GRADE GLIOMAS:

- Systemic Targeted Therapies
  - Temozolomide
  - Carmustine wafers
  - Bevacizumab
  - CCNU / BCNU
  - Carboplatin, Cytoxan
  - Irinotecan
  - BEV combinations (as BEV + CCNU)

NEWLY DIAGNOSED GLIOBLASTOMA + OTHER HIGH GRADE GLIOMAS:

- Tumor Treating Fields
  - Disrupts mitosis
  - Impairs microtubular assembly
  - Impedes midline localization of the cytokinetic band
  - Induction of intracellular dielectrophoresis
  - Mitotic failure
  - Apoptosis

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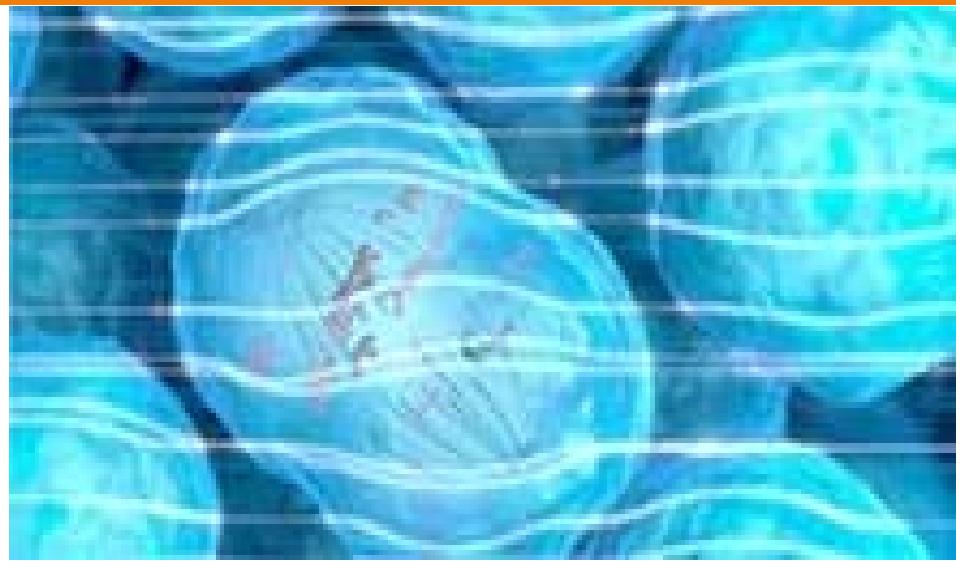

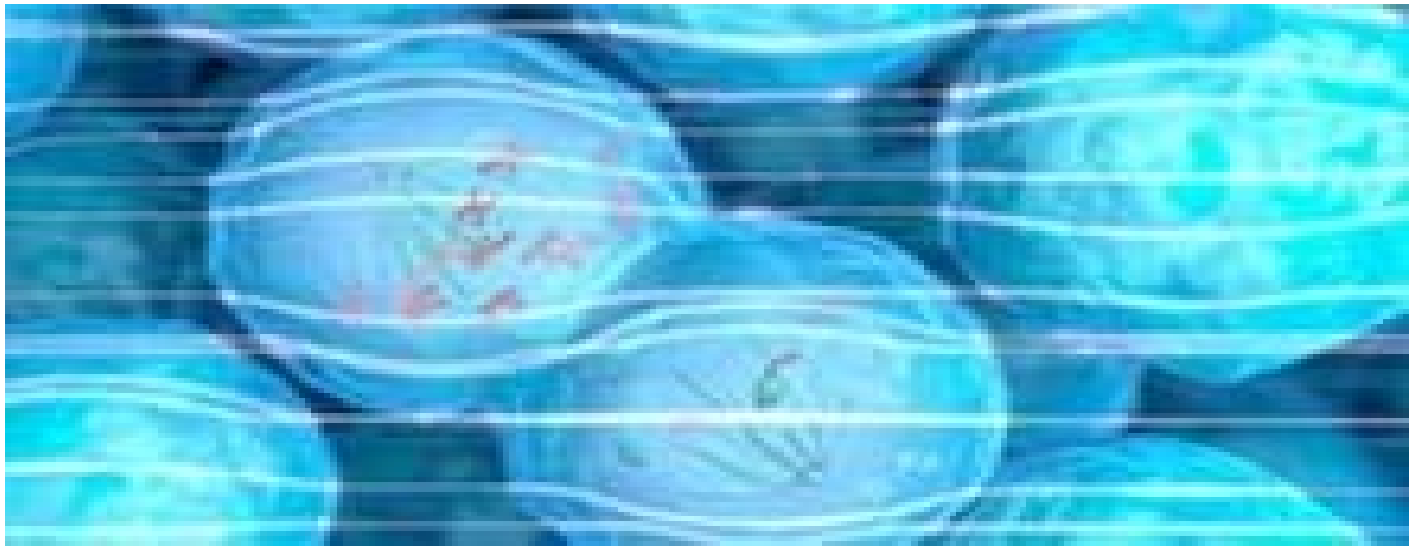

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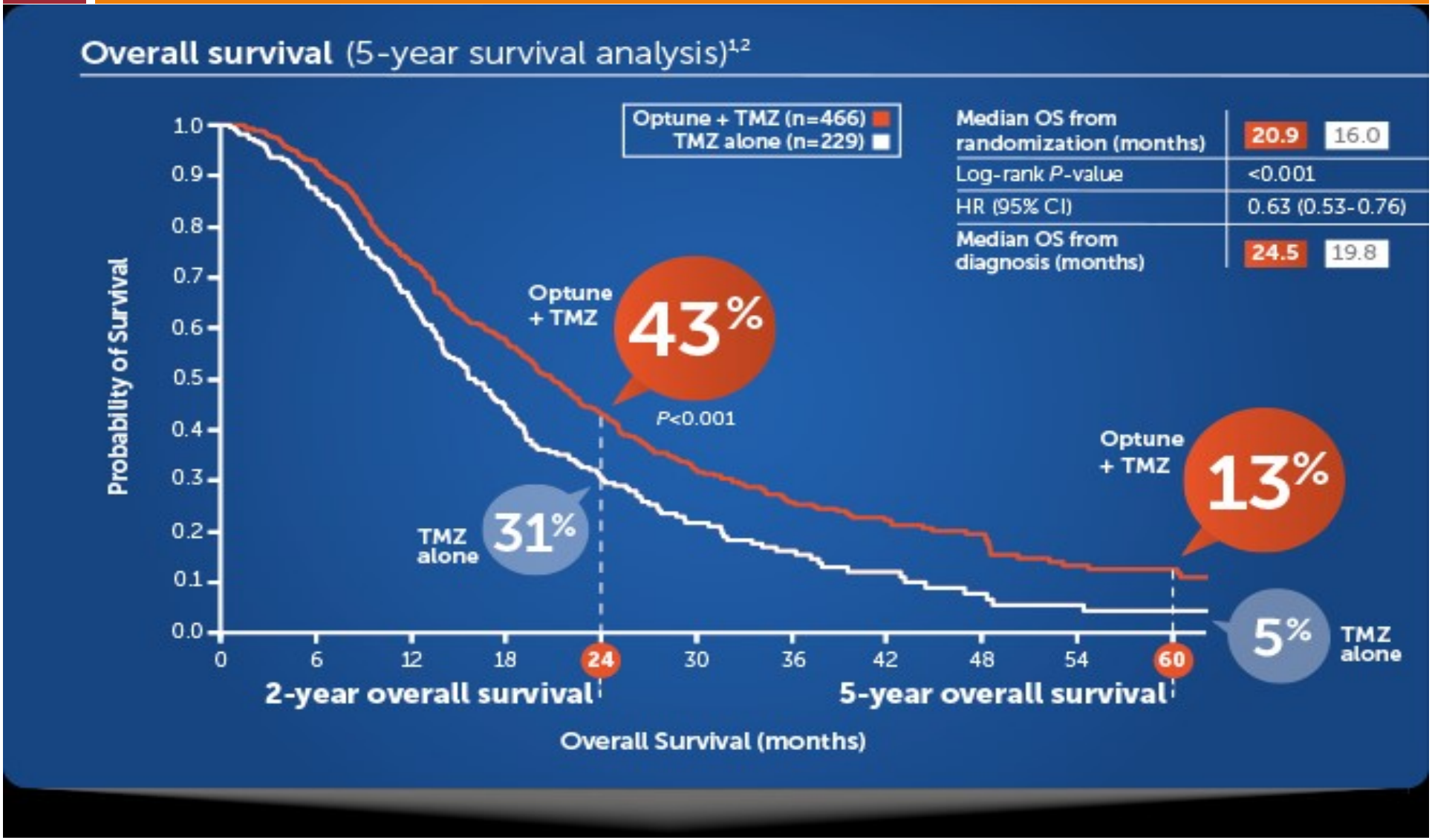

ARE WE REALLY WINNING?

J K ROWLING:

- “Failure is so important. We speak about success all the time. It is the ability to resist failure or use failure that often leads to greater success.”

HOW CAN WE DO BETTER IN GBM?

- What is new out there?
- What are the new promising therapies being explored?
- New clinical trials with “real” promise?
- Why is the GBM “space” so convoluted?
- How can we use genomic profiling and next generation sequencing (NGS) in our favor?

CURRENT CHALLENGES IN NEURO – ONCOLOGY:

- INTRA-TUMORAL HETEROGENEITY
- INTER-TUMORAL HETEROGENEITY
- “TEMPORAL” HETEROGENEITY
- DRIVER MUTATIONS

CURRENT CHALLENGES IN NEURO – ONCOLOGY:

- DRUG
- TARGET
- DRUG DELIVERY (?DOES IT CROSS THE BLOOD BRAIN BARRIER)
- BLOOD BRAIN BARRIER DISRUPTION (?Focused Ultrasound)
- BETTER DESIGNED CLINICAL TRIALS
- “FREE SPIRITED” THINKING

NEW "WHO" BRAIN TUMOR CLASSIFICATION:

- NEURO – PATHOLOGY HAS CHANGED
- "LAYERED DIAGNOSIS" (IDH STATUS, 1P/19Q STATUS, MGMT STATUS)
- PRONEURAL SUBTYPE GBM (PDGFR+, P53+)
- CLASSIC SUBTYPE GBM (PTEN MUTATION +, EGFR+)
- MESENCHYMAL SUBTYPE GBM (NF1+, P53+)

NEW "WHO" BRAIN TUMOR CLASSIFICATION:

- **Integrated diagnosis (histo-pathology + molecular alterations)**
- **GBM (IDH1 R132H mutational status?)**
- **GBM (MGMT Gene Protomotor methylation status)**
- **New "inclusion": Epithelioid GBM (IDH1 Wild type)**
- **New "exclusion": Gliomatosis Cerebri no longer in the current classification**

NEW “WHO” BRAIN TUMOR CLASSIFICATION:

- **New “inclusion”: Diffuse Midline Gliomas, H3 K27M positive**

Newly Diagnosed GBM:

- **TRIDENT TRIAL EF 32:**
  - **Tumor Treating Fields / TT Fields**
  - **Transducer Arrays to be worn during Radiation**
  - **TT Fields + IMRT + Temozolomide**
  - **Followed by TT Fields + Temozolomide**

Newly Diagnosed GBM:

- **DENOVO TRIAL:**
  - **Enzastaurin (DB102) versus Placebo**
  - **DGM1 Biomarker**
  - **Double blinded, Placebo controlled**
  - **IMRT + Temozolomide + Enzastaurin / Placebo**
  - **Work by Nicholas Butowski, MD and team at UCSF**

Newly Diagnosed GBM:

- **NRG BN 007 Trial:**
  - **MGMT Un Methylated:**
  - **Ipilimumab + Nivolumab + IMRT (experimental arm)**
  - **IMRT + Temozolomide (control arm)**

Recurrent GBM:

- **ALLIANCE A071702 Trial: Somatically Hypermutated Recurrent GBM**
  - **Immune check point blockade**
  - **Ipilimumab + Nivolumab**
  - **Tumor Mutational Burden (TMB) > / = 20**
  - **Newly activated trial at ALLIANCE**

CASE 1: PATIENT “DP”

- 27 YEAR OLD WITH A RECURRENT GLIOBLASTOMA (MGMT +)
- ALREADY RECEIVED AND FAILED: 2 OPERATIONS, 2 COURSES OF RADIATION, TEMOZOLOMIDE
- BRAF V600 E MUTATION POSITIVE: VEMURAFENIB + TEMOZOLOMIDE METRONOMIC (PROLONGED POSITIVE RESPONSE)
- FURTHER PROGRESSION
- PDL1 MUTATION: PEMBROLIZUMAB
- AT PROGRESSION WE PLAN TO ADD BEVACIZUMAB TO PEMBROLIZUMAB
- CLINICAL TRIAL OPTIONS

CASE 2: PATIENT “PV”

- YOUNG MAN IN HIS 40’S
- NEWLY DIAGNOSED WHO GRADE II OLIGODENDROGLIOMA
- 1P / 19Q CO – DELETED, MGMT PROMOTER HYPER METHYLATED, IDH1 MUTATED
- “TRIPLE POSITIVE”: POSITIVE PROGNOSTIC COMPREHENSIVE GENOMIC PROFILE
- ENROLLED UPON ALLIANCE N0577 TRIAL: IMRT + TEMOZOLOMIDE OR PCV
- RANDOMIZED TO THE TEMOZOLOMIDE (EXPERIMENTAL ARM)
- COMPLETED TREATMENT (IN FOLLOW UP)

CASE 3: PATIENT “BB”

- PATIENT IN HIS 50’S
- RECURRENT AND PROGRESSIVE WHO GRADE II ATYPICAL MENINGIOMA
- FAILED SURGERY AND IMRT
- REPEAT SURGERY WAS DEEMED HIGH RISK
- NF2 MUTATION POSITIVE
- ALLIANCE A071401 RECURRENT MENINGIOMA TRIAL FOR TUMORS WITH SMO / AKT / NF2 / CDK MUTATIONS
- NF2 MUTATION: GSK 2256098 C (FOCAL ADHESION KINASE / FAK INHIBITOR)
- ORAL AGENT
- STABLE DISEASE, IN REGULAR FOLLOW UP

CASE 4: PATIENT "CN"

- PATIENT IN HER 50'S
- NEWLY DIAGNOSED GLIOBLASTOMA
- MGMT GENE PROMOTER METHYLATED
- ALLIANCE A071102 ABT – 888 (VELIPARIB) TRIAL
- MGMT METHYLATED GBM MORE RESPONSIVE TO THIS PARP INHIBITOR
- XRT + TEMOZOLOMIDE + ABT – 888 / OR PLACEBO
- UPON PROGRESSION: MEDICENNA MDNA 55 CED TRIAL / ENROLLED
- NOW ON PEMBROLIZUMAB + BEVACIZUMAB (STABLE DISEASE, IN REGULAR FOLLOW UP)

CASE 5: PATIENT “ND”

- PATIENT IN HIS 60’S
- NEW GBM
- WAS ON NATIVIS NAT 109 TRIAL
- XRT + TMZ
- IDH 1 UN – MUTATED (IDH WILD TYPE)
- UPON PROGRESSION ON MEDICENNA MDNA 55 CED TRIAL
- NOW ON PEMBROLIZUMAB + BEVACIZUMAB (STABLE DISEASE, IN REGULAR FOLLOW UP)

Upcoming important meetings:

- **ALLIANCE MEETING: MAY, 2021 (CHICAGO)**
- **NRG MEETING: JANUARY 2021 (VIRTUAL MEETING)**
- **SOCIETY FOR NEURO-ONCOLOGY (SNO) MEETING: NOVEMBER 2020 (AUSTIN)**

Discussion