SYSTEMIC THERAPIES FOR BRAIN TUMORS:

SAJEEL CHOWDHARY, MD
PROGRAM DIRECTOR, NEURO – ONCOLOGY / NEUROLOGY
LYNN CANCER INSTITUTE (LCI)
MARCUS NEUROSCIENCE INSTITUTE (MNI)
BOCA RATON REGIONAL HOSPITAL (BRRH)
MEDICAL STAFF, DELRAY MEDICAL CENTER

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

DISCLOSURES:

- I HAVE NO RELEVANT FINANCIAL DICLOSURES AND CONFLICT OF INTERESTS

HARVEY CUSHING, MD (1869-1939): **FATHER OF MODERN NEURO-SURGERY AND BRAIN TUMOR CLASSIFICATION.**

“A PHYSICIAN IS OBLIGATED TO CONSIDER MORE THAN A DISEASED ORGAN, MORE EVEN THAN THE WHOLE MAN - HE MUST VIEW THE MAN IN HIS WORLD.”

HARVEY CUSHING, MD

VENOUS THROMBOEMBOLISM (VTE):

- **ALLIANCE FOUNDATION TRIAL (AFT 28)**
  - ***CANVAS TRIAL***
  - DIRECT ORAL ANTICOAGULANTS VERSUS LOW MOLECULAR WEIGHT HEPARIN + / - WARFARIN
  - TRIAL OPEN

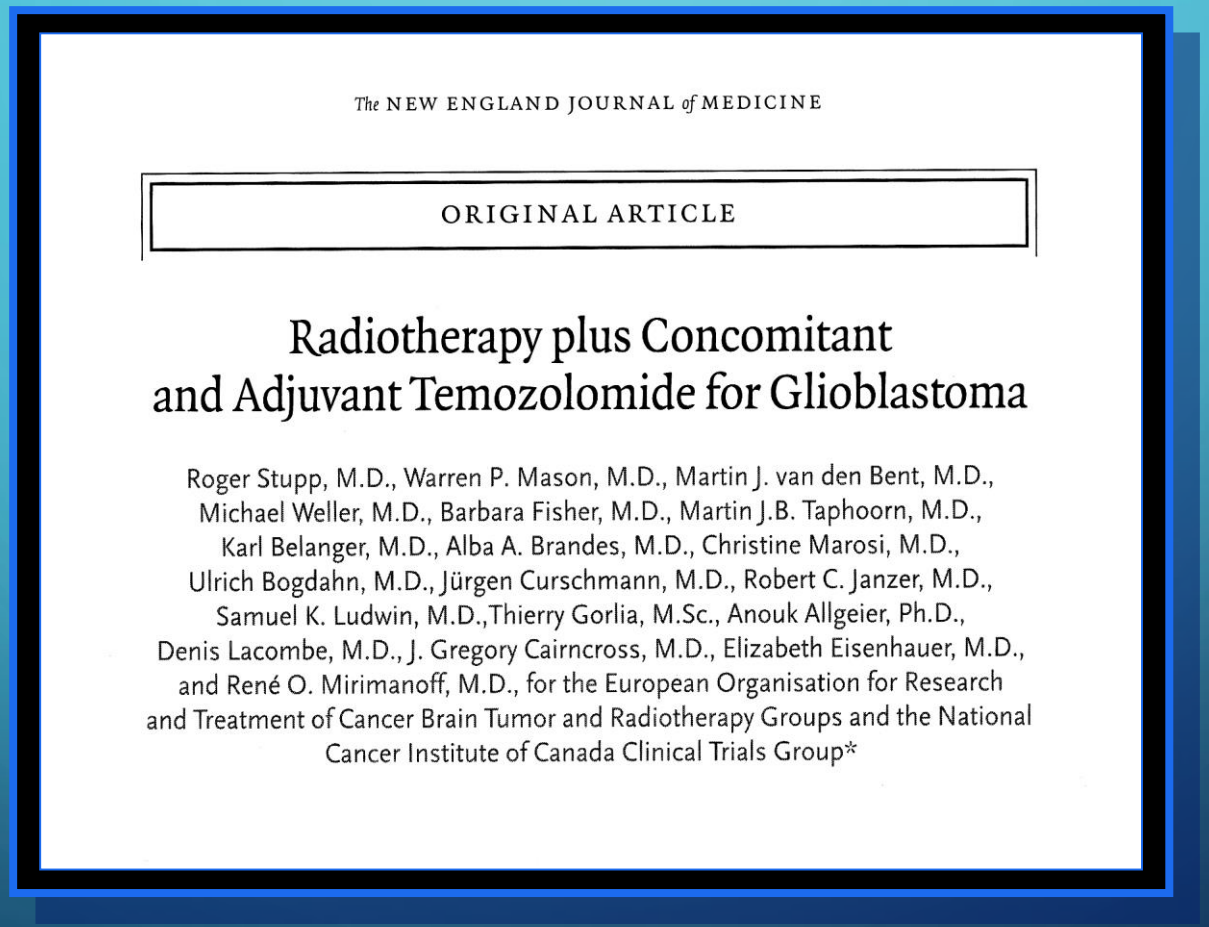
LEPTOMENINGEAL SPREAD:

- **NRG 1605: BRAIN METASTASIS REQUIRING SURGERY**
- PRE SURGICAL RADIOSURGERY FOLLOWED BY SURGICAL RESECTION
- PRIMARY END POINT: MINIMIZATION OF LEPTOMENINGEAL SPREAD
- TRIAL IN PIPELINE

OPTIONS (NEWLY DIAGNOSED GLIOBLASTOMA):

- Maximal Safe Surgical Resection
- Radiation (IMRT)
- Temozolomide
- Bevacizumab
- Carmustine / BCNU Wafers
- Novo TTF
- Experimental Trials

RADIOTHERAPY PLUS CONCOMITANT AND ADJUVANT TEMOZOLOMIDE FOR GLIOBLASTOMA



The NEW ENGLAND JOURNAL of MEDICINE

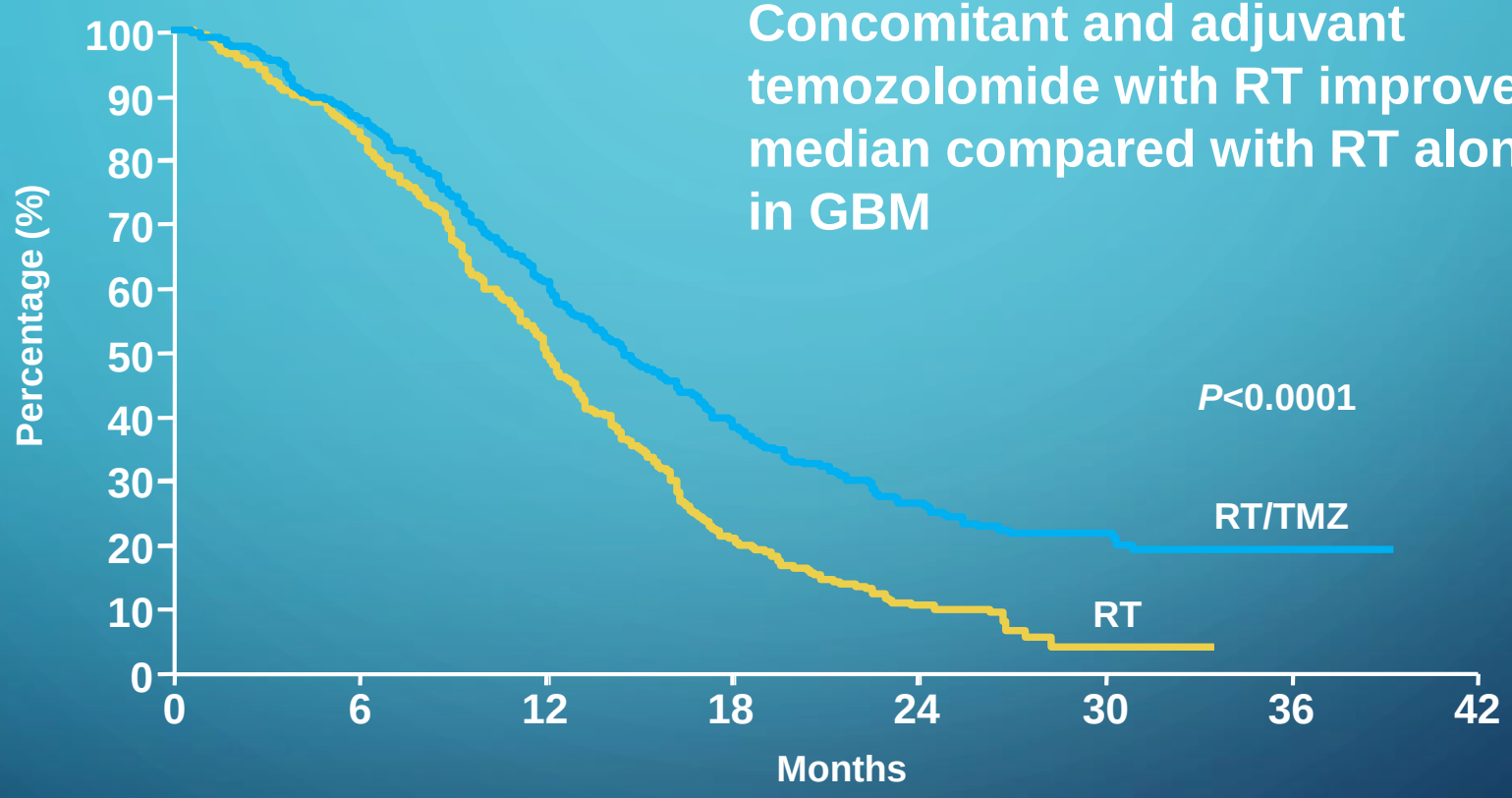
ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

Stupp R, et al. *N Engl J Med*. 2005;352:987-996.

OVERALL SURVIVAL – 2005 RESULTS



Concomitant and adjuvant temozolomide with RT improved median compared with RT alone in GBM

Stupp R, et al. *N Engl J Med.* 2005;352:987-996

RADIATION COMPICATIONS:

- VASOGENIC EDEMA (INFLAMMATORY SYMPTOMS)
- SEIZURES
- ACUTE RADIATION TOXICITY
- PSEUDO-PROGRESSION
- LATE DELAYED TOXICITY (COGNITIVE CHANGES)
- FATIGUE
- LACK OF APPETITE

RADIATION COMPICATIONS:

- HYDROCEPHALUS (COMMUNICATIVE OR OBSTRUCTIVE)
- DEPRESSION
- HEMATOLOGICAL ABNORMALITIES

PSEUDO-PROGRESSION:

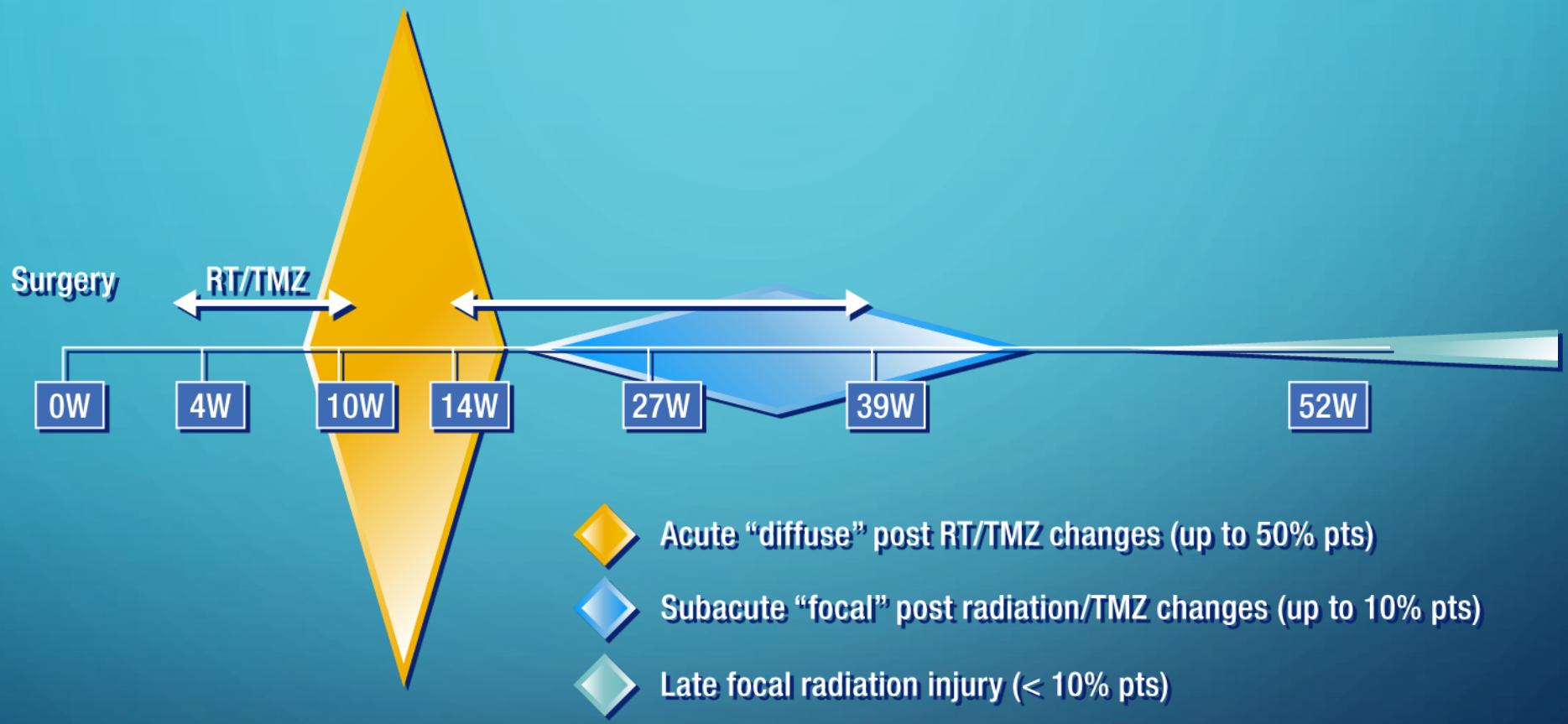
- DECEPTIVE, CRITICAL TO RECOGNIZE
- GENERALLY WITHIN 1-3 MONTHS OF XRT
- CAN OCCUR IN HIGH GRADE GLIOMA, LOW GRADE GLIOMA, BRAIN METASTASIS AND OTHER TUMOR TYPES
- MR PERFUSION / SPECTROSCOPY CAN ASSIST
- BRAIN PET SCAN CAN BE HELPFUL
- SURGICAL DIAGNOSIS

MECHANISMS OF PSEUDOPROGRESSION

- Gadolinium (Gd) enhancement represents areas of breakdown of the blood-brain barrier (BBB)
- RT causes changes in BBB
  - Loosening of endothelial tight junctions
  - Endothelial cell death
  - Results in vascular leakage

Temozolomide should be discontinued if determination of progression is made.
Brandsma D, et al. *Lancet Oncol*. 2008;9:452-461.

DIFFERENT TYPES OF PSEUDO-PROGRESSION



Temozolomide should be discontinued if determination of progression is made.

Brandsma D, et al. *Lancet Oncol*. 2008;9:452-461.
Chaskis C, et al. *Surg Neurol*. 2009;epub. DOI:10.1016/j.surneu.2008.09.023.

PSEUDO-PROGRESSION AND NECROSIS:

- **ALLIANCE A221208 (*BEST TRIAL*): BEVACIZUMAB + STEROIDS VERSUS PLACEBO + STEROIDS**
- BRAIN METASTASIS POST RADIOSURGERY
- DOUBLE BLINDED PLACEBO CONTROLLED
- TRIAL OPEN

LATE DELAYED TOXICITY (COGNITIVE CHANGES):

- RADIATION FOR PRIMARY BRAIN TUMORS AS GLIOMAS
- RADIATION FOR BRAIN METASTASIS (WHOLE BRAIN XRT OR SRS)

LATE DELAYED TOXICITY (COGNITIVE CHANGES):

- **NRG CC 001: WHOLE BRAIN XRT FOR BRAIN METASTASIS WITH MEMANTINE WITH OR WITHOUT HIPPOCAMPAL AVOIDANCE SPARING (HA/HS)**
- PHASE III
- TRIAL OPEN

LATE DELAYED TOXICITY (COGNITIVE CHANGES):

- **NRG CC 003: SMALL CELL LUNG CANCER (SCLC)**
- PROPHYLACTIC CRANIAL IRRADIATION (PCI) WITH OR WITHOUT HIPPOCAMPAL AVOIDANCE / SPARING (HA/HS)
- MEMANTINE ALLOWED AND OPTIONAL AS PER PHYSICIAN
- PHASE II / III
- TRIAL OPEN

CANCER RELATED FATIGUE:

- **ALLIANCE A221101: ARMODAFINIL TRIAL**
- GLIOBLASTOMA
- PLACEBO CONTROLLED DOUBLE BLINDED
- 2:1RANDOMIZATION
- 150MG AND 250MG DOSAGES
- PHASE III
- TRIAL OPEN

SYSTEMIC TARGETED THERAPIES AND CLINICAL TRIALS RELATED COMPLICATIONS:

- HEMATOLOGICAL TOXICITY
- LIVER, RENAL AND OTHER ORGAN RELATED TOXICITY
- FATIGUE
- IMMUNOTHERAPY TOXICITY (ENDOCRINE, PNEUMONITIS, PANCREATITIS, HEPATITIS)
- DERMATOLOGICAL EFFECTS
- COGNITIVE IMPACT

UNIQUE CLINICAL TRIAL RELATED TOXICITY:

- **RTOG FOUNDATION TRIAL (RTOG 3503, ABBVIE)**
- ABT 414 (EGFR TARGETED, MONOCLONAL ANTIBODY / DRUG CONJUGATE)
- NEW GLIOBLASTOMA
- DEPATUXIZUMAB / MAFODOTIN
- MICROCYSTIC KERATOPATHY
- REVERSIBLE

PROTON THERAPY VERSUS PHOTON / IMRT

- PROTONS HEAVIER PARTICULATE SIZE MAY IMPART IMPROVED PRECISION
- LESS COGNITIVE IMPAIRMENT AND OTHER TOXICITY
- INCREASED INTEREST IN PROSPECTIVE CLINICAL TRIALS TO DEFINE TRUE EFFICACY
- ALLIANCE AND NRG

NRG BN 001: NEW GLIOBLASTOMA

- NEWLY DIAGNOSED GBM
- 4 ARM TRIAL
- COMPARING 2 VARIABLES
- HYPOFRACTIONATED DOSE ESCALATED PHOTON IMRT OR PROTON BEAM THERAPY VERSUS CONVENTIONAL IMRT OR PROTON BEAM THERAPY
- MAIN END POINTS: TUMOR CONTROL / COGNITIVE IMPACT

NRG BN 002: NEW GLIOBLASTOMA

- NEWLY DIAGNOSED GLIOBLASTOMA
- IPILIMUMAB AND NIVOLUMAB
- WITH STANDARD THERAPIES

NRG BN 005: LOW GRADE GLIOMA

- HIGH RISK LOW GRADE GLIOMA
- IDH MUTATED TUMORS
- IMRT VERSUS PROTON BEAM THERAPY (PBT)
- TEMOZOLOMIDE
- TRIAL OPENED 07-17-2017
- MAIN END POINTS: TUMOR CONTROL / COGNITIVE IMPACT

NRG BN 003: ATYPICAL MENINGIOMA

- NEW WHO GRADE II MENINGIOMA (ATYPICAL)
- SIMPSON GRADE I, II OR III RESECTION
- UPFRONT IMRT VERSUS OBSERVATION
- MAIN END POINTS: TUMOR CONTROL / COGNITIVE EFFECTS
- TRIAL OPEN

ALLIANCE A071102: NEW GLIOBLASTOMA

- MGMT METHYLATED
- ABT - 888
- RANDOMIZED TRIAL

ALLIANCE A071101: RECURRENT GLIOBLASTOMA

- VACCINE TRIAL
- SURGICALLY RESECTABLE RECURRENT GLIOBLASTOMA
- HEAT SHOCK PROTEIN PEPTIDE COMPLEX 96 (HSPPC 96)
- WITH BEVACIZUMAB OR BEVACIZUMAB ALONE

ALLIANCE A071401: RECURRENT MENINGIOMA

- RECURRENT MENINGIOMA (WHO GRADE I, II OR III)
- FAILED STANDARD THERAPIES (SURGERY, IMRT, SRS, PROTON BEAM)
- SMO / AKT / NF2 / PTCH MUTATIONS POSITIVE MENINGIOMA
- VISMODEGIB
- GSK 2256098C

ALLIANCE A071601: PAPILLARY CRANIOPHARYNGIOMA

- RECURRENT PAPILLARY CRANIOPHARYNGIOMA
- BRAF / MEK INHIBITORS
- VEMURAFENIB
- COBIMETINIB

NAT – 109: NEW GLIOBLASTOMA

- NEWLY DIAGNOSED GBM
- NATIVIS VOYAGER SYSTEM DEVICE
- XRT + TEMOZOLOMIDE

NATIVIS NAT – 101: RECURRENT GLIOBLASTOMA

- RECURRENT GLIOBLASTOMA
- NATIVIS VOYAGER SYSTEM DEVICE + CCNU

ALLIANCE N0577: OLIGODENDROGLIOMA

- OLIGODENDROGLIOMA WHO GRADE II AND III
- 1P / 19Q CO – DELETED
- PROCARBAZINE, CCNU AND VINCRISTINE (PCV) VERSUS TEMOZOLOMIDE

MDNA 55: RECURRENT GLIOBLASTOMA

- INTRA-TUMORAL IMMUNOTOXIN
- SURGERY NEEDED

POLIO VIRUS TRIAL / PVS RIPO

- RECURRENT GLIOBLASTOMA
- INTRA-TUMORAL VIRUS INJECTION
- DUKE COLLABORATION

TOCA 5FC / TOCA 511: RECURRENT GLIOBLASTOMA

- TOCA 511 VIRUS
- INTRA-TUMORAL INJECTION

RTOG 1114: PRIMARY CNS LYMPHOMA

METHOTREXATE, RITUXIMAB, PROCARBAZINE, CYTARABINE, VINCRISTINE

WITH OR WITHOUT LOW DOSE (12.5 GY) WHOLE BRAIN XRT

STUDY CLOSED TO ACCRUAL

?MORE SLOTS TO OPEN SOON

ALLIANCE A031102: RECURRENT AND REFRACTORY GERM CELL TUMORS

- PACLITAXEL + IFOSFAMIDE + CISPLATINUM (TIP) COMPARED WITH PACLITAXEL + IFOSFAMIDE FOLLOWED BY HIGH DOSE CARBOPLATIN + ETOPOSIDE (TI - CE)
- PHASE III TRIAL

ALLIANCE EAF 151: RELATIVE CEREBRAL BLOOD VOLUME AFTER BEVACIZUMAB

- RELATIVE CEREBRAL BLOOD VOLUME (R - CBV) MEASUREMENT FOLLOWING BEVACIZUMAB FOR RECURRENT GBM
- ?AS A BIOMARKER OF EARLY RESPONSE

PARANEOPLASTIC SYNDROMES:

- NOT CAUSED BY TUMOR ITSELF
- FROM THE IMMUNOLOGICAL RESPONSES THAT IT INVOKES

PARANEOPLASTIC SYNDROMES:,

- MYRIAD OF PRESENTATIONS:
- ENDOCRINE
- DERMATOLOGICAL
- RHEUMATOLOGICAL
- HEMATOLOGICAL
- NEUROLOGICAL

PRESENTATIONS:

- **PARANEOPLASTIC LIMBIC ENCEPHALITIS:**
- AMYGDALA, HIPPOCAMPUS, HYPOTHALAMUS
- SHORT TERM MEMORY LOSS, ENCEPHALOPATHY, SEIZURES
- MRI FINDINGS: T2 / FLAIR SIGNAL
- BLOOD AND CSF
- Lung and Testis and tumors of the Thymus (Thymoma) although other cancers can also be involved.
- ANTIBODIES: HU, Ma2, and CRMP5, NMDA receptor, GABA(B) receptor, AMPA receptor, Caspr2, mGluR5 antibodies
- NON ONCOLOGY RELATED: LGI1 (previously known as voltage-gated potassium channel antibodies or VGKC).

PRESENTATIONS:

- **PARANEOPLASTIC CEREBELLAR DEGENERATION:**
- COORDINATION ABNORMALITIES, SPEECH DIFFICULTIES, OSCILLOPSIA
- YO, TR, OR mGLUR1 ANTIBODIES.
- THE ASSOCIATED TUMORS INCLUDE, BUT ARE NOT LIMITED TO, GYNECOLOGICAL CANCERS (MAINLY OVARIAN CANCER), BREAST, LUNG, AND HODGKIN'S LYMPHOMA.

PRESENTATIONS:

- **PARANEOPLASTIC ENCEPHALOMYELITIS:**
- VARIOUS PARANEOPLASTIC ANTIBODIES ARE ASSOCIATED WITH PARANEOPLASTIC ENCEPHALOMYELITIS, INCLUDING HU, CRMP5, MA2, AND AMPHIPHYSIN.

OTHER PARANEOPLASTIC SYNDROMES:

- Paraneoplastic Encephalitis associated with anti-NMDAR Antibodies
- Paraneoplastic Stiff-Person Syndrome (anti-amphiphysin)
- Paraneoplastic Opsoclonus-Myoclonus or Opsoclonus-Ataxia
- Sensory Neuronopathy
- Paraneoplastic Neuropathies
- Vasculitis of the Nerve and Muscle

OTHER PARANEOPLASTIC SYNDROMES:

- Lambert Eaton Myasthenic Syndrome (LEMS)
- Myasthenia Gravis (MG)
- Polymyositis/Dermatomyositis
- Necrotizing Autoimmune Myopathy

TREATMENT:

- TUMOR TREATMENT
- ANTI CHOLINESTERASE INHIBITORS FOR MYASTHENIA OR LEMS
- IVIG
- PLASMAPHARESIS
- IMMUNOSUPRESSANTS