



# **MOLECULAR PROFILING IN NEURO ONCOLOGY AND THE FUTURE OF PERSONALIZED ONCOLOGY:**

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## DISCLOSURES:

- NO RELEVANT FINANCIAL DISCLOSURES AND CONFLICT OF INTERESTS
- 

**HARVEY CUSHING, MD (1869-1939): FATHER OF MODERN NEUROSURGERY 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* —

AZ QUOTES



*"The capacity of man himself is only revealed when, under stress and responsibility, he breaks through his educational shell, and he may then be a splendid surprise to himself no less than to his teachers."*

*Harvey Cushing*



# NEWLY DIAGNOSED GLIOBLASTOMA OR OTHER HIGH GRADE GLIOMAS:

- MAXIMAL SAFE SURGICAL RESECTION
- RADIATION (IMRT / EBRT)
- TEMOZOLOMIDE
- BEVACIZUMAB
- CARMUSTINE / BCNU WAFERS (GLIADEL WAFER)
- NOVO TTF 100 A SYSTEM (OPTUNE)
- **EXPERIMENTAL TRIALS RESEARCH**
- **MOLECULAR ONCOLOGY / PERSONALIZED ONCOLOGY**

## TREATMENT OPTIONS (FEW EXAMPLES):

- PCV (PROCARBAZINE, CCNU, VINCRISTINE) FOR OLIGODENDROGLIOMAS
- METHOTREXATE, RITUXIMAB, TEMOZOLOMIDE FOR CNS LYMPHOMA
- IBRUTINIB (IMBRUVICA) FOR CNS LYMPHOMA
- CARBOPLATIN, CCNU, IRINOTECAN FOR RECURRENT GLIOMAS
- PLATINUM AGENTS WITH ETOPOSIDE, CCNU, VINCRISTINE FOR MEDULLOBLASTOMAS AND GERM CELL TUMORS
- INTRA THECAL CHEMOTHERAPY AS METHOTREXATE, THIOTEPA, CYTARABINE, RITUXIMAB, TRASTUZUMAB, DEPOCYT (CURRENTLY UNAVAILABLE)

# PERSONALIZED / MOLECULAR ONCOLOGY:

- PD1 / PDL1 MUTATIONS (PEMBROLIZUMAB, NIVOLUMAB, ATEZOLIZUMAB, DURVALUMAB)
- BRAF MUTATIONS (VEMURAFENIB, DABRAFENIB)
- MEK INHIBITION (COBIMETINIB, TREMETINIB)
- MGMT METHYLATION AND TRIALS BASED ON MGMT + / -
- TOPO 1 MUTATION (IRINOTECAN)
- EGFR MUTATIONS / EGFRVIII VARIANT (ERLOTINIB, GEFITINIB)
- EGFR MUTATION (ABT 414, CLINICAL TRIALS BASED ON EGFR + / -)
- T790M MUTATION (OSIMERTINIB)



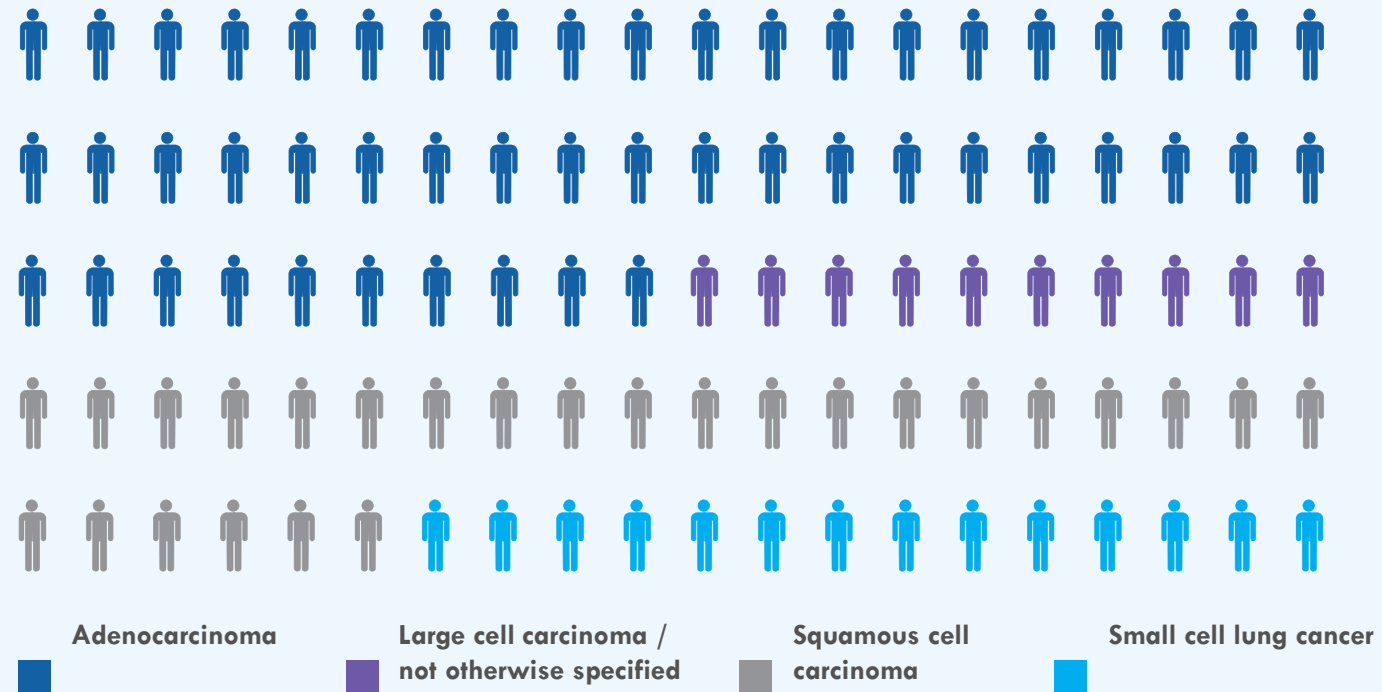
# PERSONALIZED ONCOLOGY:

- IDH 1,2 MUTATIONS (TRIAL ENROLLMENT)
- 1 P AND 19 Q CO – DELETIONS (PCV)
- P53 MUTATION (TARGETED AGENTS IN DEVELOPMENT)
- ATRX
- H3 K27M (TARGETED AGENTS IN TRIALS)
- ALK / EMLA4 MUTATION (CRIZOTINIB, ALECTINIB)

# PERSONALIZED ONCOLOGY:

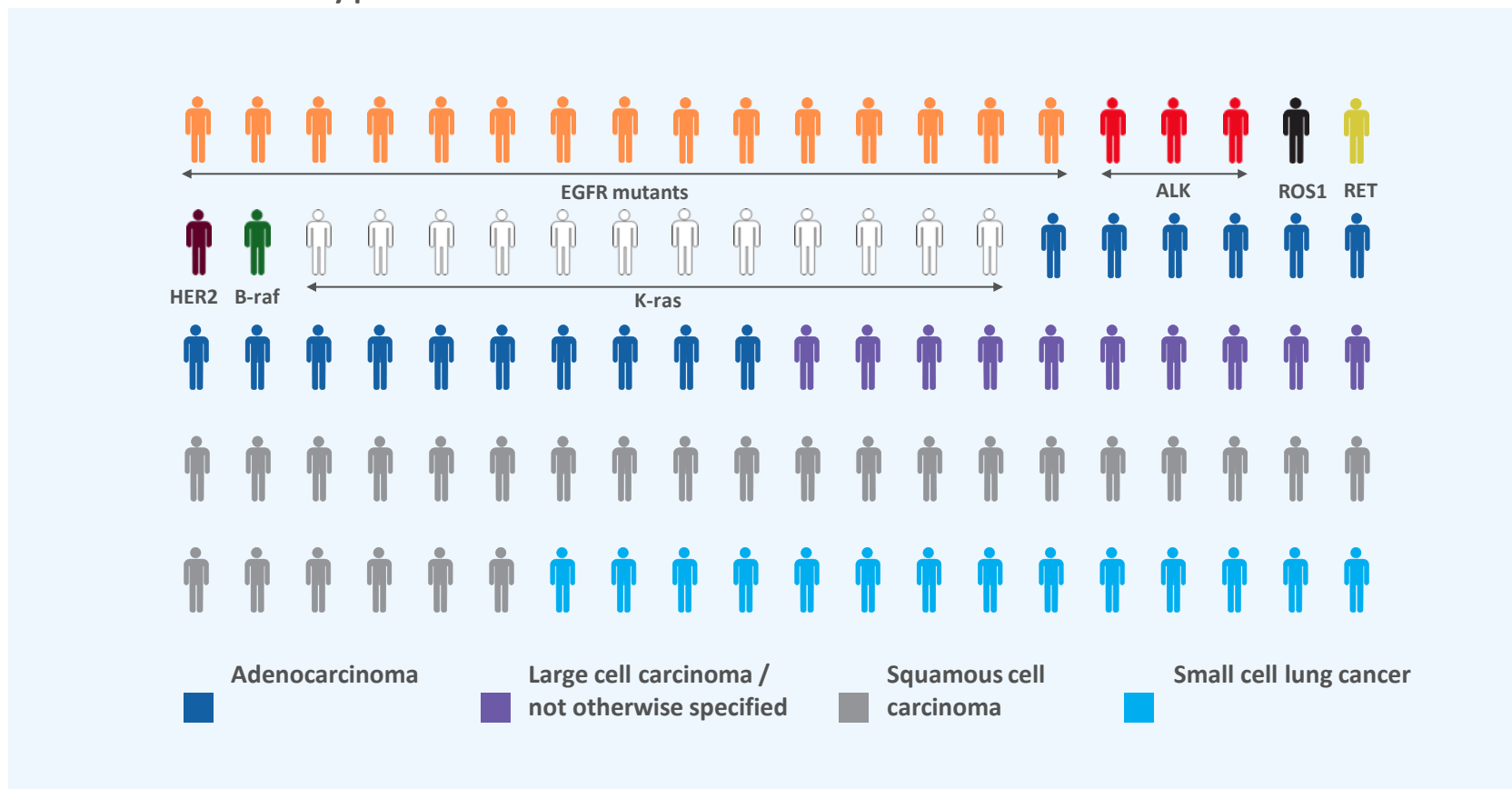
- ROS 1
- KRAS
- RET
- HER 2
- MET
- ERCC1 (PLATINUM AGENT SENSITIVITY)

# LUNG CARCINOMA SUB TYPES: THE BEGINNING



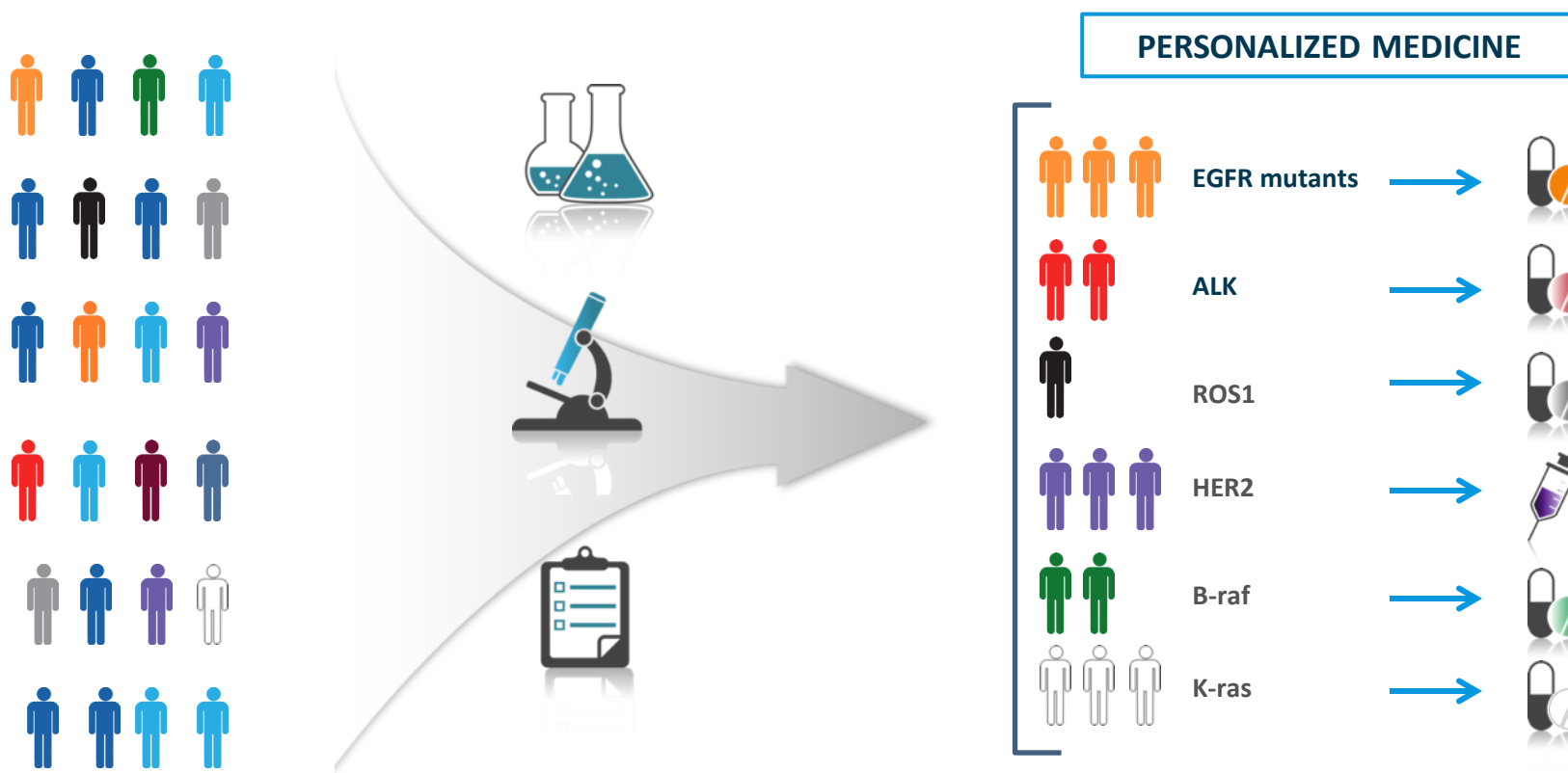
# Where We Have Evolved

## Molecular Subtypes



Adapted from Scagliotti, GV. Individualized therapy in lung cancer: where are we in 2012? 13th International Lung Cancer Congress; July 19-22, 2012; Huntington Beach, CA. - See more at: <http://www.onclive.com/publications/obtn/2012/september-2012/molecular-discoveries-pave-way-for-rapid-advances-in-lung-cancer/2#sthash.0tvpHdzu.dpuf>

# Genomic Profiling Enables Personalized Medicine





# CGP+ with Caris Molecular Intelligence®

Understanding the molecular phenotypes of cancer to personalize therapy requires more than DNA sequencing.



**DNA**

Mutations, Indels &  
Copy Number Variants



**RNA**

Fusions & Variant Transcripts



**Protein**

Immunohistochemistry

**Comprehensive Genomic Profiling *Plus* = Standard of Care + Clinical Trial Biomarkers**

Immunotherapy

Targeted Therapy

Chemotherapy



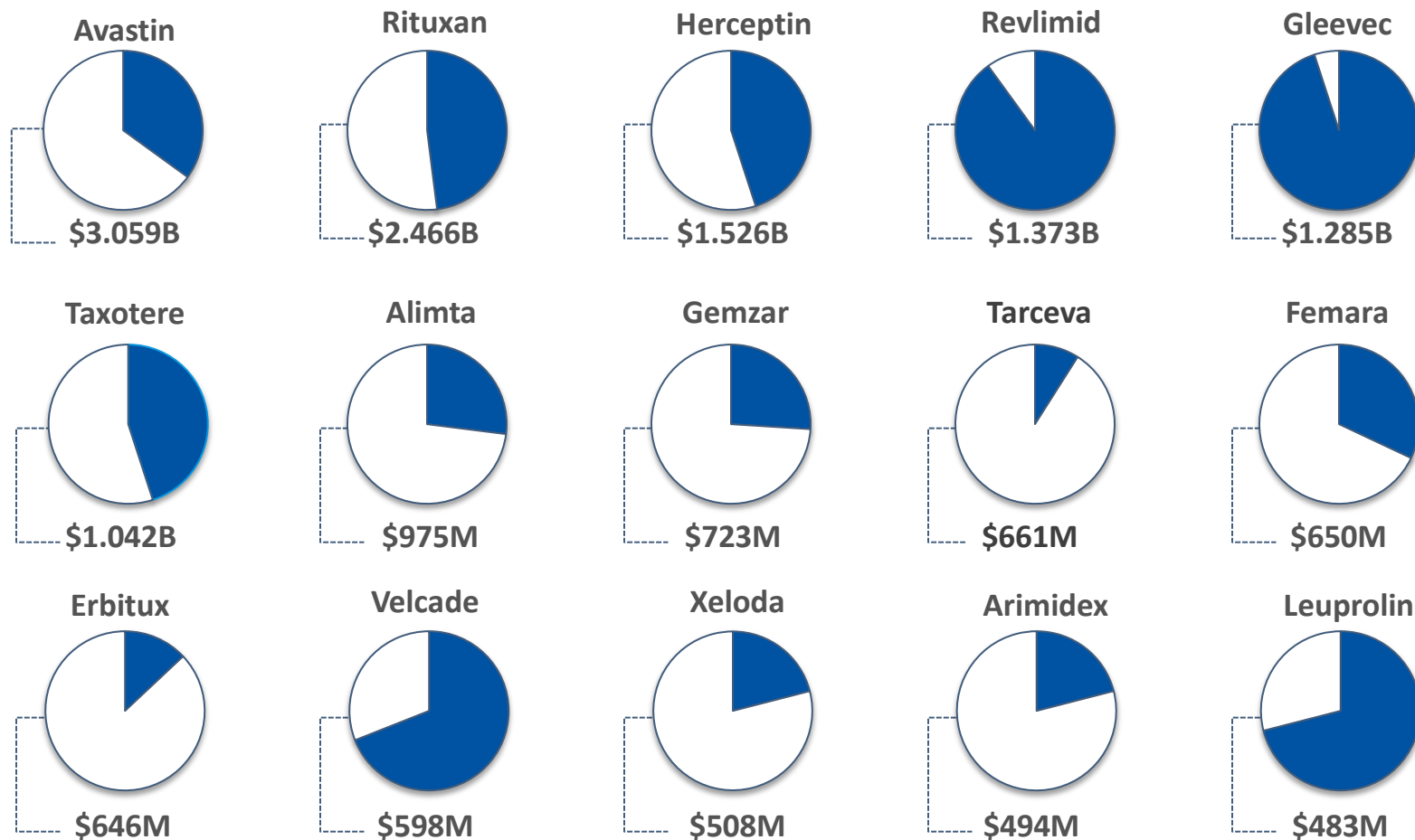
## Tumor Interrogation Technologies:

- IHC
- ISH
- Next-Generation Sequencing – DNA 592 genes
- Next-Generation Sequencing – RNA 53 genes
- Pyrosequencing

## Official Partner for:



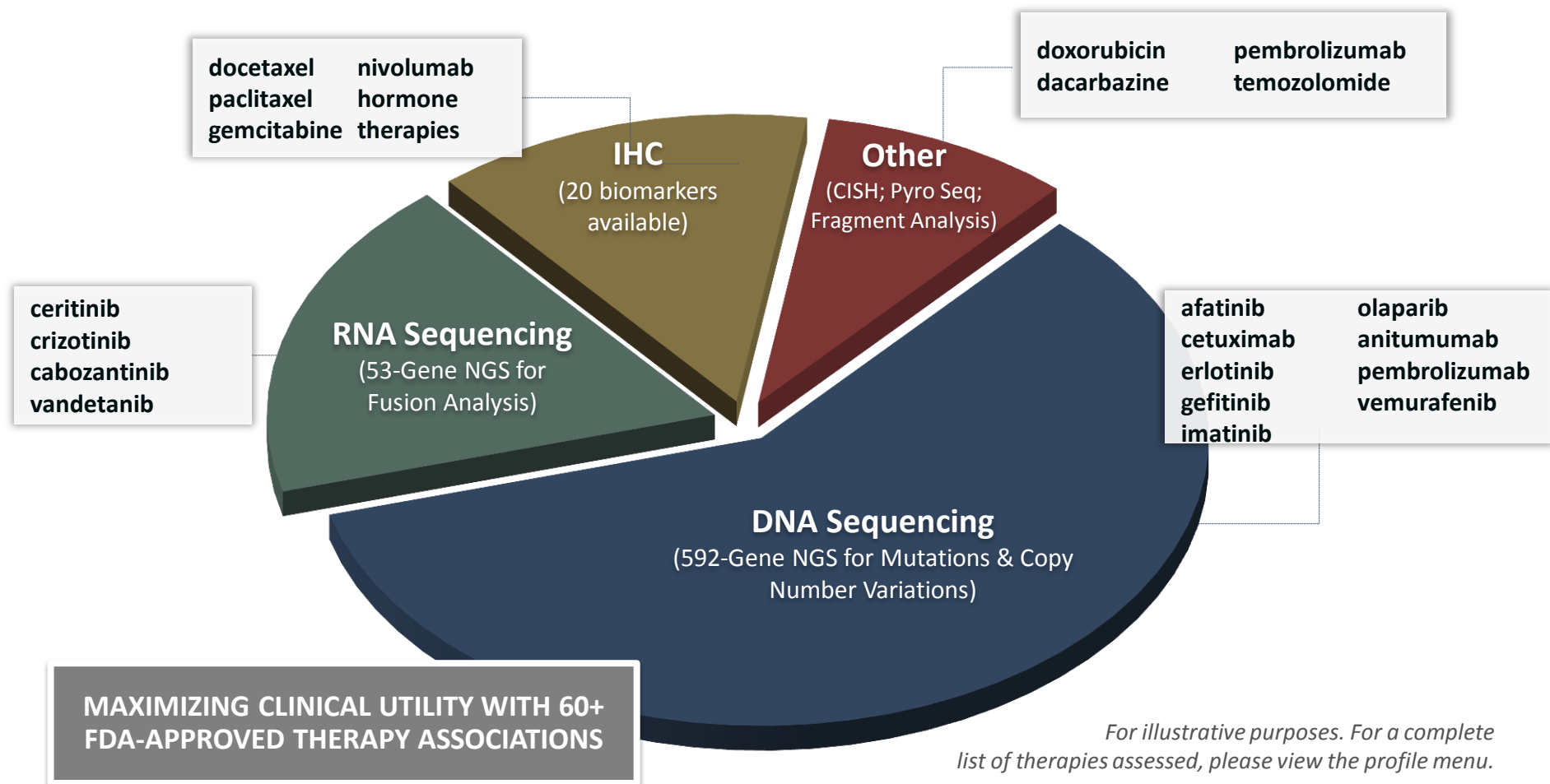
# The Financial Burden of Non-Responders



■ Responder    □ Non-Responder    \$ Total Drug Sales

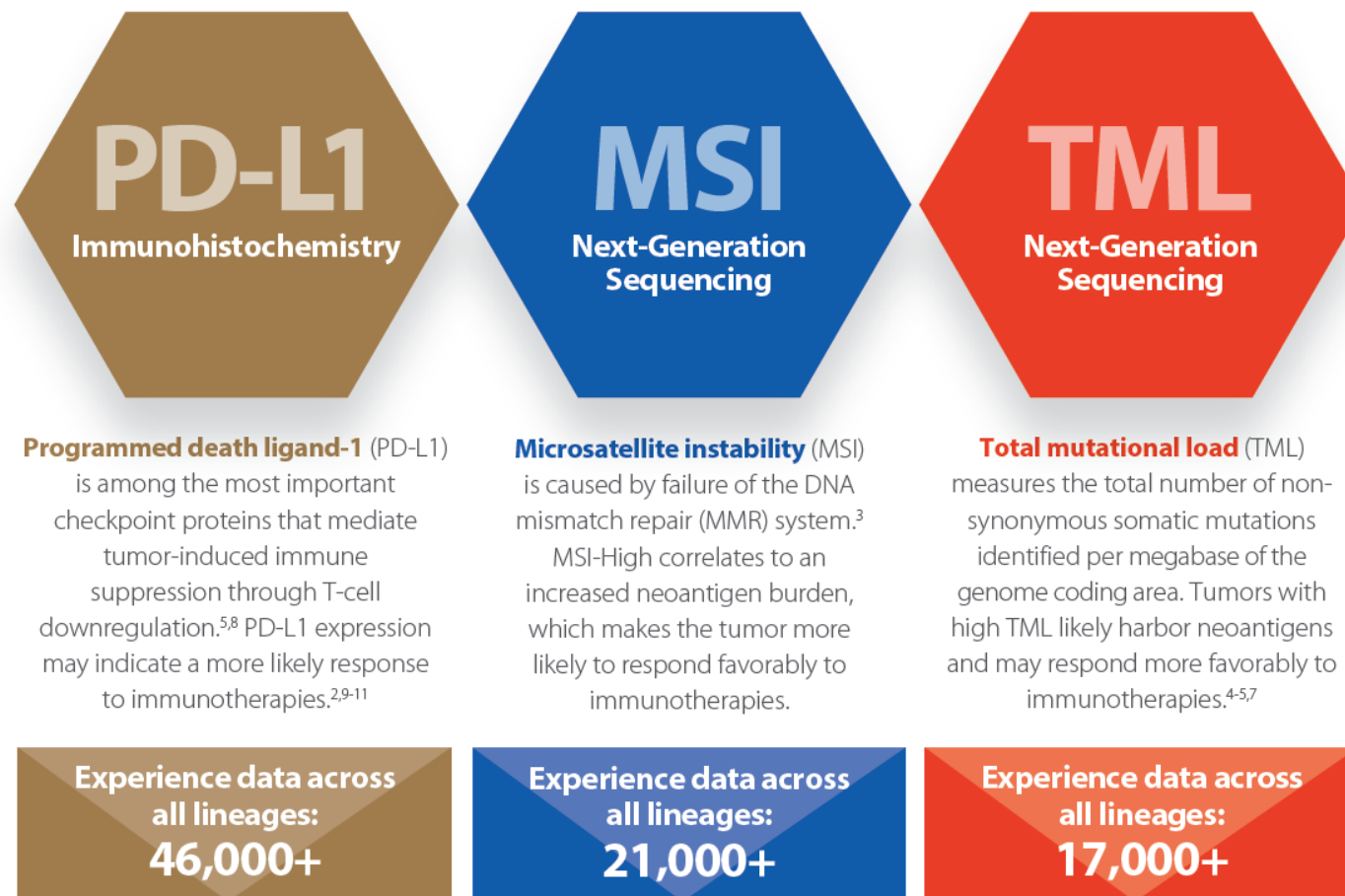
Sources: Individual Drug Labels. US Food and Drug Administration. [www.fda.gov](http://www.fda.gov)  
Market and Product Forecasts: Top 20 Oncology Therapy Brands. DataMonitor, 2011.

## Companion Dxs & NCCN-Guidelines Require a Multi-Technology Approach



# Unlock the Power of Immune Checkpoint Inhibitors

Comprehensive genomic and proteomic profiling can help you make more informed therapy decisions when considering immune checkpoint inhibitors.



3. Le DT. *N Engl J Med.* 2015;372:2509-2520.

4. Rizvi NA. *Science.* 2015;384(6230):124-128.

5. Rosenberg JE. *The Lancet.* 2016;387(10031):1909-1920.

6. Motzer RJ. *N Engl J Med.* 373:1803-1813.

7. Snyder A. *N Engl J Med.* 2014;371:2189-2199. doi:10.1056/NEJMoa1406498.

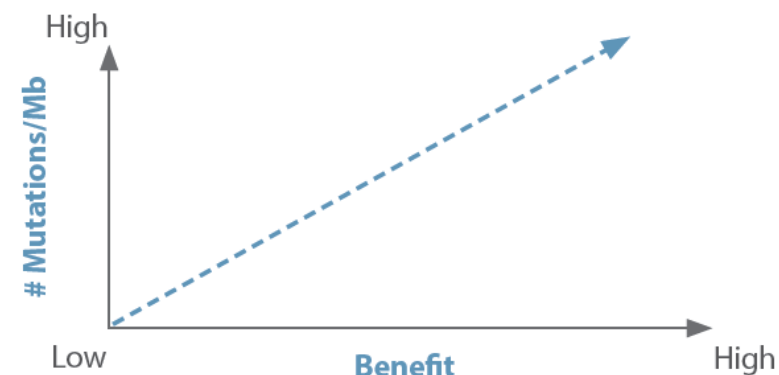
8. Mellman L. *Nature.* 2011;480:480-489. doi:10.1038/nature10673.

# Total Mutational Load (TML)

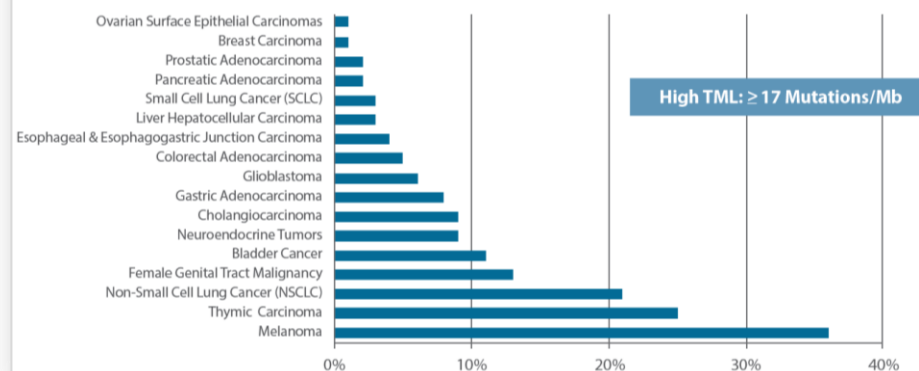
TML by NGS measures the total number of non-synonymous, somatic mutations identified per megabase (Mb) of the genome coding area (a megabase is 1,000,000 DNA basepairs).

- Non-synonymous mutations are changes in DNA that result in amino acid changes in the protein.
- The new protein changes result in new shapes (neo-antigens) that are considered to be foreign to the immune system.
- Immune checkpoint inhibitors are able to stimulate and allow the immune system to detect these neoantigens and destroy the tumor.
- Germline (inherited) mutations are not included in TML because the immune system has a higher likelihood of recognizing these alterations as normal.

## TML: Immune Checkpoint Indication for Response



## High TML Across Caris Molecular Intelligence Cases





# MOLECULAR PROFILING AND IMPACT IN NEURO ONCOLOGY

- NEXT GENERATION SEQUENCING
- GENOMICS (DNA – “OMICS”)
- RNA – “OMICS”
- PROTEOMICS

# MGMT GENE PROMOTER METHYLATION AND RISK FOR 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

# PSEUDO-PROGRESSION RISK:

- HIGHER IN **MGMT METHYLATED** HIGH GRADE GLIOMAS
- PREDICTIVE VALUE

# EXPERIMENTAL THERAPEUTICS AND MOLECULAR PROFILING:

- **NRG / RTOG TRIALS**
- **ALLIANCE TRIALS**
- **PHARMA TRIALS**
- **CONVECTION ENHANCED DELIVERY (CED) TRIALS (MEDICENNA MDNA 55 TRIAL, PVS RIPO POLIO VIRUS TRIAL)**

# EXPERIMENTAL THERAPEUTICS AND MOLECULAR PROFILING:

- REGISTRY TRIALS (SE GLIOMA MOFFITT TRIAL, FLORIDA CENTER FOR BRAIN TUMOR RESEARCH TRIAL / FCBTR, NEOPLASTIC MENINGITIS REGISTRY TRIAL / “NE ME RE” TRIAL)
- COLLABORATIVE TRIALS (SCRIPPS / 3D CELL CULTURE GLIOMA AND DRUG SENSITIVITY TRIAL)
- U OF FLORIDA COLLABORATIVE WORK (FLORIDA NETWORK OF COLLABORATIVE TRIALS)



# EGFR MUTATION: NEW GLIOBLASTOMA

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

# MOLECULAR PROFILE DATA REQUIRED: NRG BN 001 NEW GLIOBLASTOMA

- NEWLY DIAGNOSED GBM
- 4 ARM TRIAL
- PHOTONS VERSUS PROTONS
- 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

# **PDL1 MUTATION: NRG BN 002 NEW GLIOBLASTOMA**

- NEWLY DIAGNOSED GLIOBLASTOMA
- IPILIMUMAB AND NIVOLUMAB
- WITH STANDARD THERAPIES
- PHASE I PORTION COMPLETED
- PHASE II ABOUT TO OPEN AT NRG

# IDH 1 MUTATION: NRG BN 005: LOW GRADE GLIOMA

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

# MOLECULAR PROFILE DATA REQUIRED: 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



# MGMT PROMOTER HYPER - METHYLATION: ALLIANCE A071102 NEW GLIOBLASTOMA

- MGMT METHYLATED (35%-40% OF PRIMARY GBM)
- ABT – 888 (VELIPARIB)
- PARP INHIBITOR (NEXT GENERATION)
- RANDOMIZED TRIAL
- 50 / 50 RANDOMIZATION
- PLACEBO CONTROLLED

# **SMO / AKT / NF2 / PTCH MUTATIONS: 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 2256098 C

# **BRAF / MEK MUTATIONS: ALLIANCE A071601**

## **PAPILLARY CRANIOPHARYNGIOMA**

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

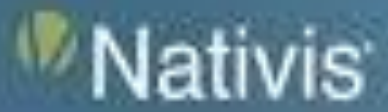
# MOLECULAR PROFILE DATA REQUIRED: NAT – 109

## NEW GLIOBLASTOMA

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

# **MOLECULAR PROFILE DATA REQUIRED: NATIVIS NAT – 101 RECURRENT GLIOBLASTOMA**

- RECURRENT GLIOBLASTOMA
- NATIVIS VOYAGER SYSTEM DEVICE + CCNU



## A Disruptive Approach to Cancer Treatment



Management Presentation

January 24, 2018 -





# 1P / 19Q CO – DELETED: ALLIANCE N0577 OLIGODENDROGLIOMA

- OLIGODENDROGLIOMA WHO GRADE II AND III
- 1P / 19Q CO – DELETED
- MGMT METHYLATION
- IDH1, 2 MUTATIONAL STATUS
- PROCARBAZINE, CCNU AND VINCRISTINE (PCV) VERSUS TEMOZOLOMIDE

# IDH 1 UN – MUTATED: MDNA 55 RECURRENT GLIOBLASTOMA

- INTRA-TUMORAL IMMUNOTOXIN
- SURGERY NEEDED
- CONVECTION ENHANCED DELIVERY (CED) TRIAL
- DIRECT INTRA – TUMORAL INFUSION OF IMMUNOTOXIN

# MOLECULAR PROFILE DATA REQUIRED: POLIO VIRUS TRIAL / PVS RIPO

- RECURRENT GLIOBLASTOMA
- INTRA-TUMORAL VIRUS INJECTION
- DUKE COLLABORATION
- CONVECTION ENHANCED DELIVERY (CED) TRIAL

# MOLECULAR PROFILE DATA REQUIRED: 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
- RELAPSED AND RECURRENT GERM CELL TUMORS
- COULD BE EXTRA CRANIAL / SYSTEMIC OR INTRA CRANIAL

# MOLECULAR PROFILE DATA REQUIRED: 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
- WHETHER CONTINUATION OF BEVACIZUMAB IS HELPFUL OR UN HELPFUL
- COST EFFECTIVITY
- TO DISCONTINUE BEVACIZUMAB WHEN INEFFECTIVE

# ALLIANCE A221101 FATIGUE TRIAL:

- GBM FATIGUE
- ARMODAFINIL TRIAL

# BRAIN METASTASIS:

- **NRG CC 001 TRIAL: WHOLE BRAIN XRT WITH OR WITHOUT HIPPOCAMPAL AVOIDANCE WITH MEMANTINE (MEMANTINE / NAMENDA)**
- **NRG CC 003 TRIAL: SCLC WHOLE BRAIN XRT WITH OR WITHOUT HIPPOCAMPAL AVOIDANCE (MEMANTINE / NAMENDA OPTIONAL)**



# **POST SRS RADIO-NECROSIS:**

- **ALLIANCE A221208 POST SRS NECROSIS**
- **BEST TRIAL**
- **BEVACIZUMAB + STEROIDS VERSUS PLACEBO + STEROIDS**

# CNS METASTASIS:

- COMPREHENSIVE GENOMIC PROFILE OF THE PRIMARY TUMOR MAY DIFFER FROM THE CNS METASTATIC DEPOSIT / DEPOSITS
- ALLIANCE TRIAL BEING DEVELOPED LOOKING AT MOLECULAR PROFILE OF THE CNS DEPOSIT AND TREATING THE CNS METASTASIS WITH STEREOTACTIC RADIOSURGERY (AS CYBER KNIFE OR GAMMA KNIFE) ALONG WITH THE APPROPRIATE AGENT (ACTIONABLE MUTATIONS)
- T790M MUTATION = OSIMERTINIB
- ALK EMLA4 MUTATION = CRIZOTINIB OR ALECTINIB

# CASE 1: PATIENT “DP”

- 27 YEAR OLD WITH A RECURRENT GLIOBLASTOMA
- 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

# 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 / PTCH MUTATIONS
- NF2 MUTATION: GSK 2256098 C (FOCAL ADHESION KINASE / FAK INHIBITOR)
- ORAL AGENT
- STABLE DISEASE THUS FAR

## 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

## CASE 5: PATIENT “ND”

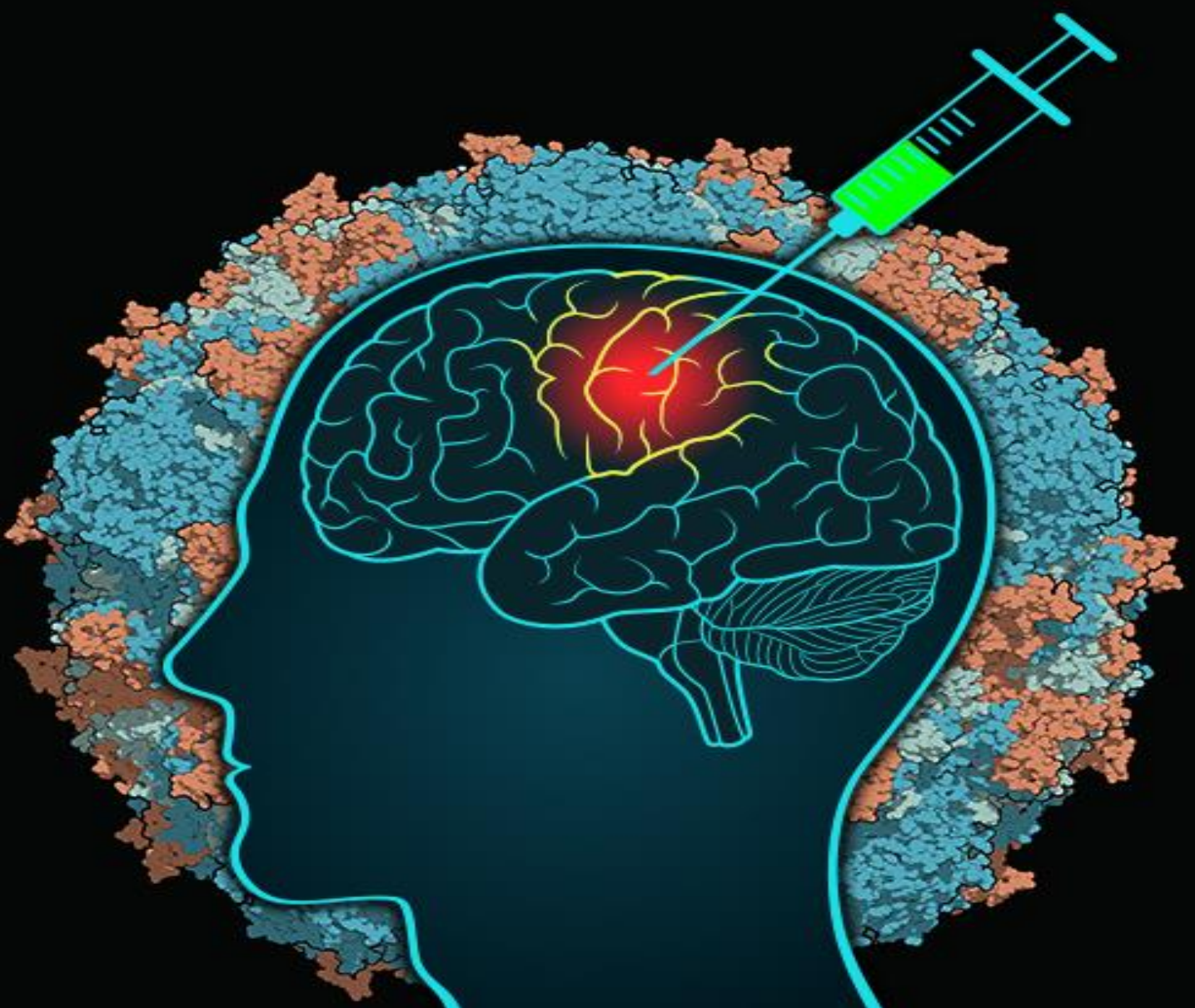
- PATIENT IN HIS 60'S
- NEW GBM
- WAS ON NATIVIS NAT 109 TRIAL
- XRT + TMZ
- IDH UN - MUTATED
- UPON PROGRESSION ON MEDICENNA MDNA 55 CED TRIAL
- ON TRIAL, IN FOLLOW UP



# POLIO VIRUS TRIAL: PVSRIPO

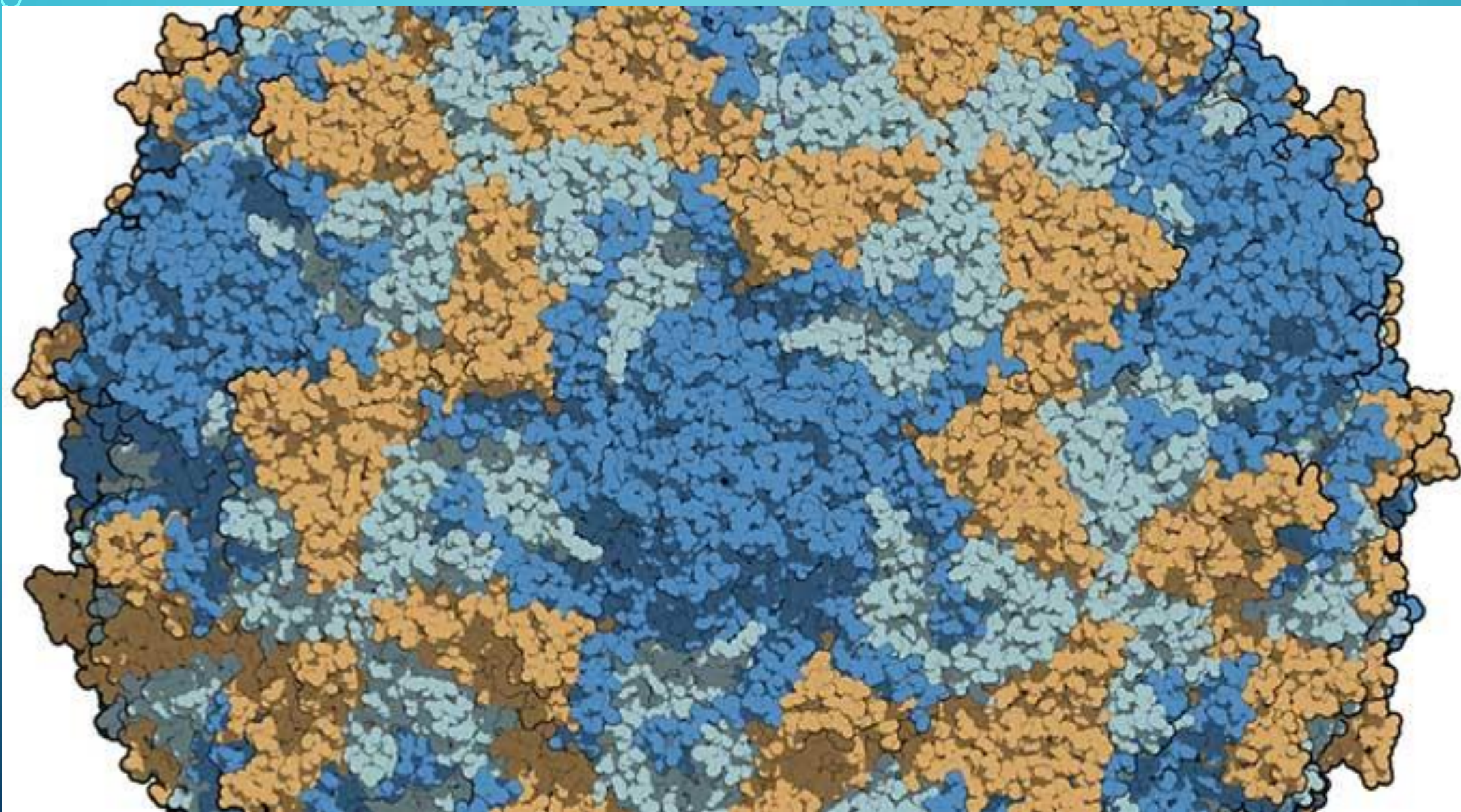
- RECURRENT GBM
- STRINGENT ENROLLMENT CRITERIA
- DUKE COLLABORATIVE WORK

MANUEL ALMAGRO RIVAS CC BY-SA 4.0





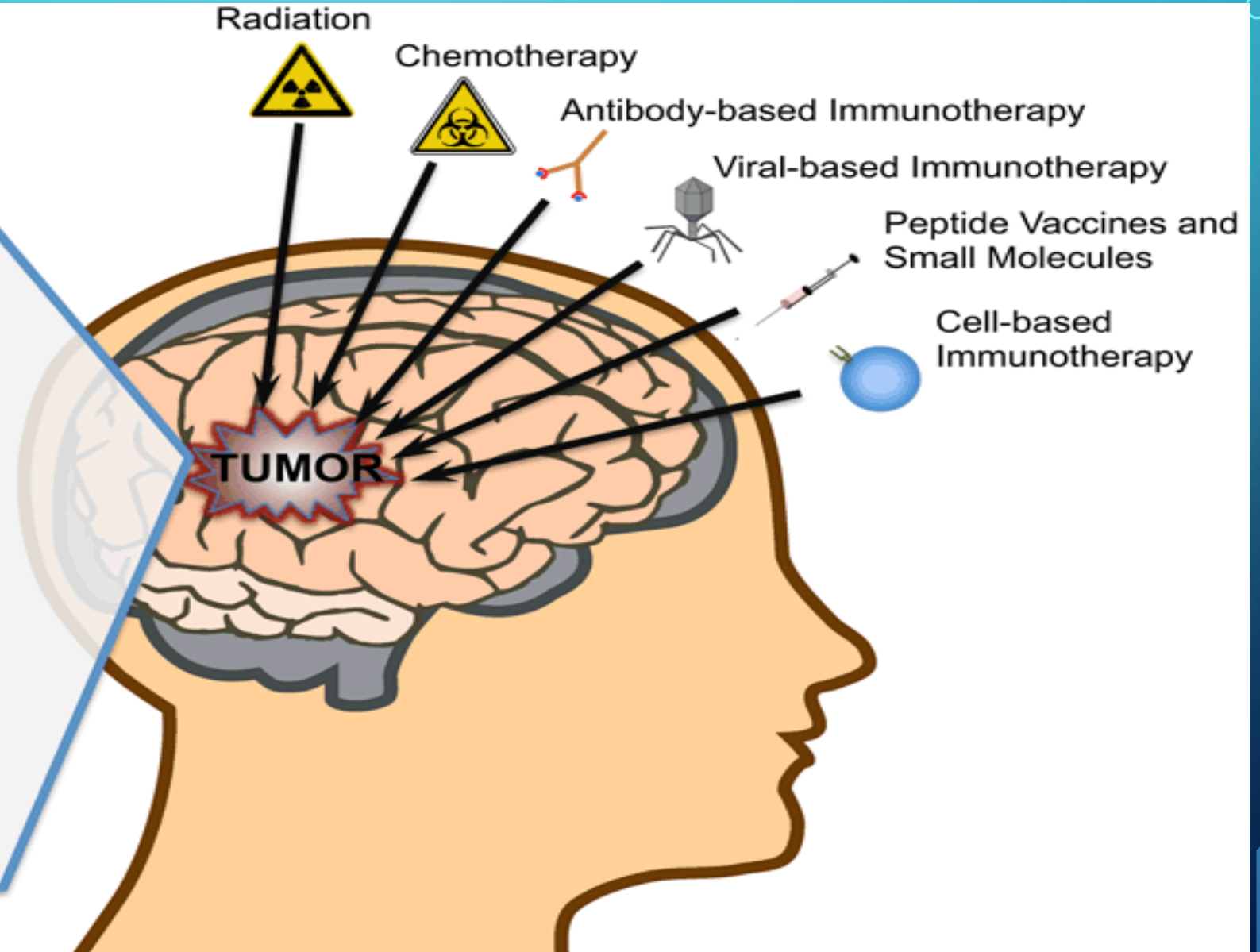






### Combinatorial Mechanisms of Action:

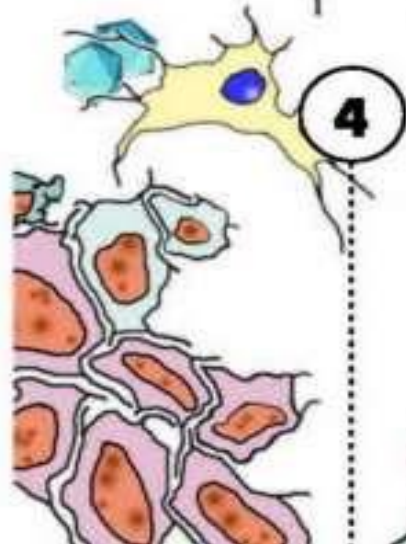
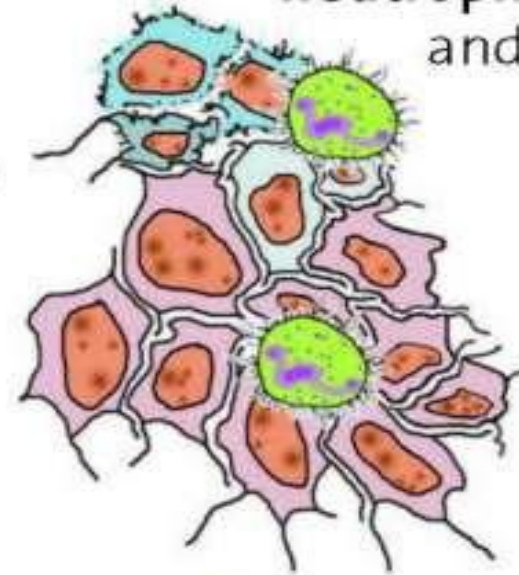
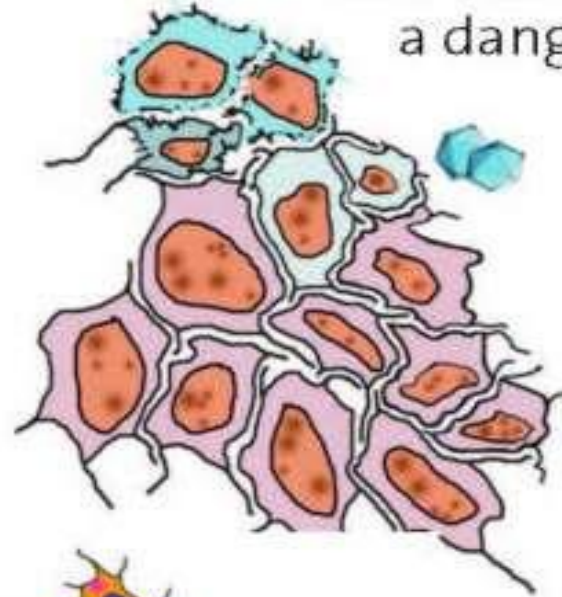
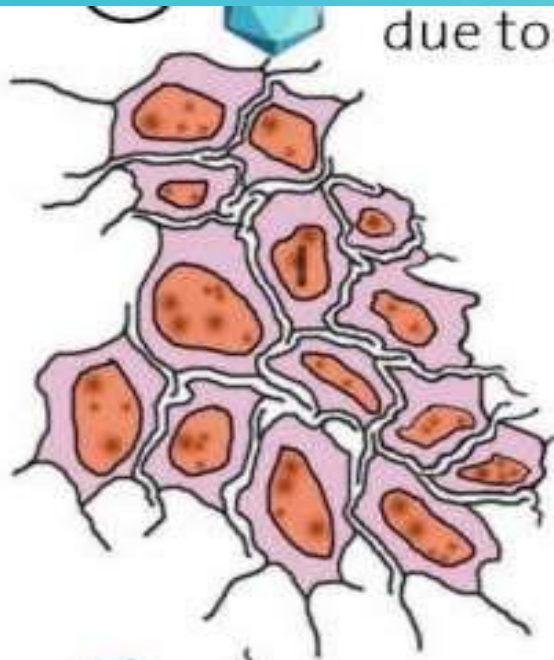
- Direct Cytotoxicity
  - Immunogenic cell death
  - Viral Oncolytic activity
- Enhanced Antigen Presentation
  - Induction of adaptive immune responses
  - Epitope Spreading
- Immune cell activation
  - Increased Lymphocyte Infiltration
  - Reversal of T-cell exhaustion
  - Attenuation of Immunosuppression
  - Cell mediated cytotoxicity
  - Memory T-cell formation



due to their abundance of a certain protein.

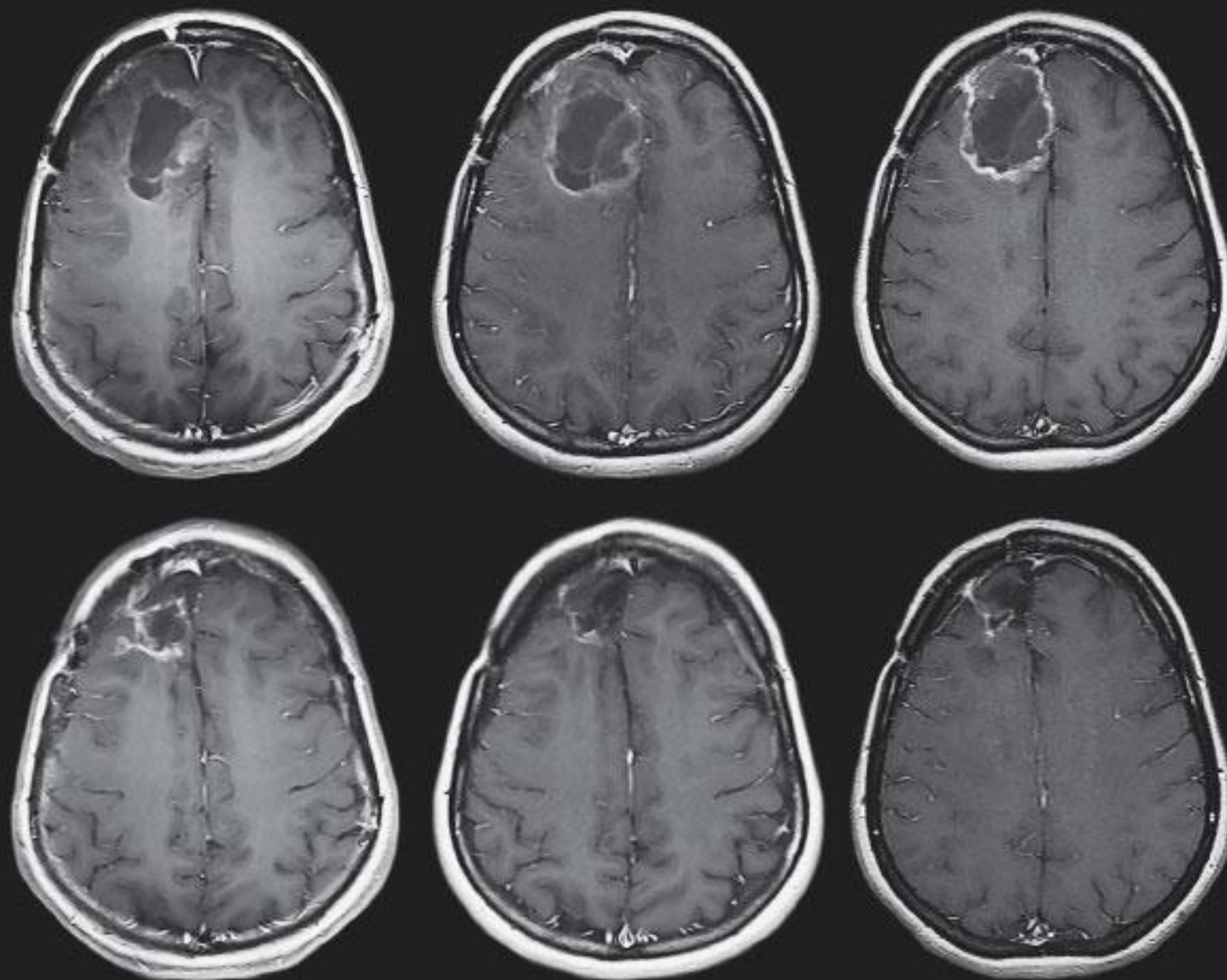
**2** **Virus** infects and damages tumor, releasing tumor antigen and broadcasting a danger signal...

**3** ...which causes **neutrophils** to invade and attack.

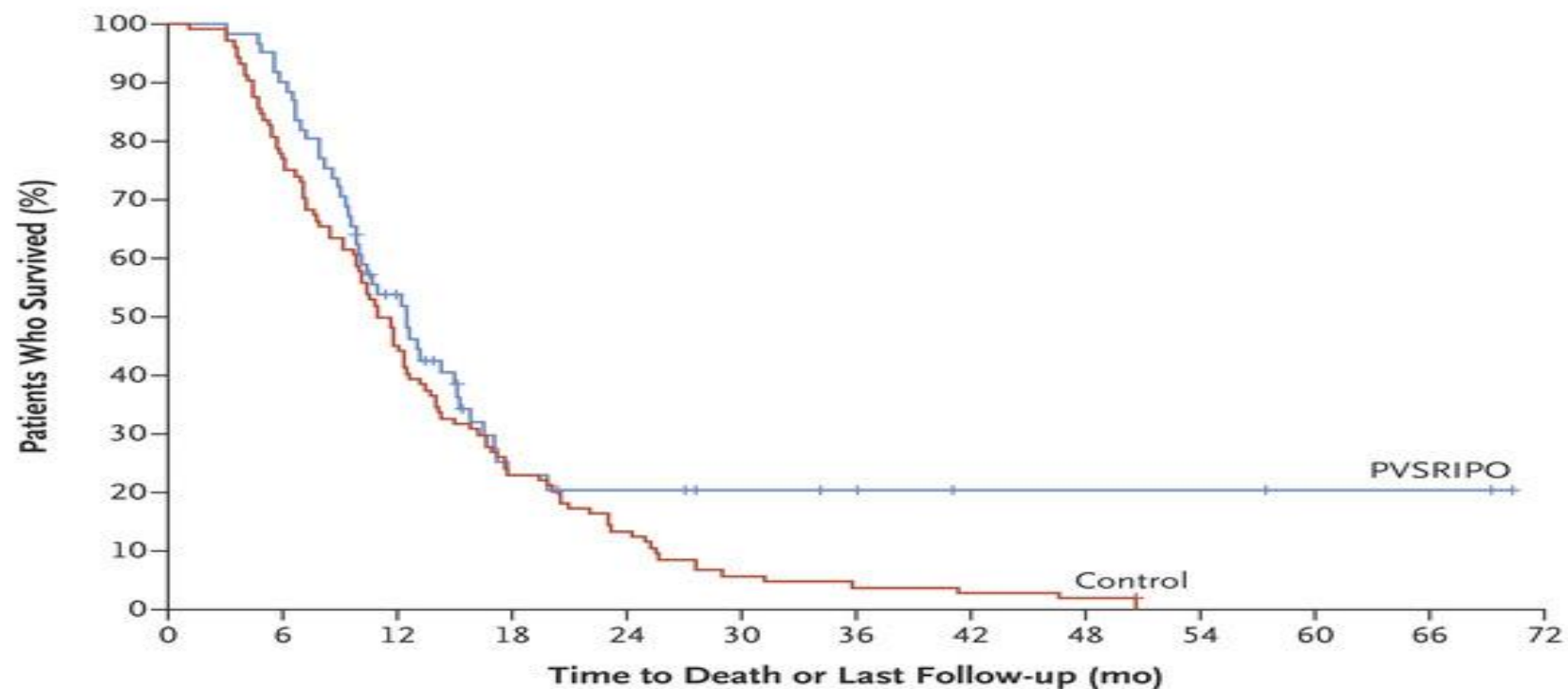


**6** T cells destroy









**No. at Risk**  
PVSRIPO  
Control

61	55	29	10	8	6	5	3	3	3	2	2	—
104	80	47	24	14	6	4	3	2	—	—	—	—

Group	Total No. of Patients	No. of Deaths	Median Survival (95% CI)	Survival Rate (95% CI)						
				6 Mo	12 Mo	18 Mo	24 Mo	36 Mo	48 Mo	60 Mo
PVSRIPO	61	44	12.5 (9.9–15.2)	90 (79–96)	54 (40–65)	23 (12–35)	21 (11–33)	21 (11–33)	21 (11–33)	21 (11–33)
Control	104	103	11.3 (9.8–12.5)	77 (68–84)	45 (36–54)	23 (16–32)	14 (8–21)	4 (1–9)	2 (<1–6)	—

ORIGINAL ARTICLE

# Recurrent Glioblastoma Treated with Recombinant Poliovirus

Annick Desjardins, M.D., Matthias Gromeier, M.D., James E. Herndon II, Ph.D.,  
Nike Beaubier, M.D., Dani P. Bolognesi, Ph.D., Allan H. Friedman, M.D.,  
Henry S. Friedman, M.D., Frances McSherry, M.A., Andrea M. Muscat, B.Sc.,  
Smita Nair, Ph.D., Katherine B. Peters, M.D., Ph.D., Dina Randazzo, D.O.,  
John H. Sampson, M.D., Ph.D., Gordana Vlahovic, M.D., William T. Harrison, M.D.,  
Roger E. McLendon, M.D., David Ashley, M.B., B.S., Ph.D.,  
and Darell D. Bigner, M.D., Ph.D.

## UPCOMING IMPORTANT MEETINGS:

- **NRG MEETING: FEBRUARY 7<sup>TH</sup> – 9<sup>TH</sup>, 2019 (PHOENIX)**
- **ALLIANCE MEETING: MAY 9<sup>TH</sup> – 11<sup>TH</sup>, 2019 (CHICAGO)**
- **SOCIETY FOR NEURO-ONCOLOGY (SNO) MEETING: NOVEMBER 20<sup>TH</sup> – 24<sup>TH</sup>, 2019 (PHOENIX)**