What Treatments Excite Your Doctors?
ABTA National Conference, Sept. 6, 2019

Glenn J. Lesser, MD FACP
Louise McMichael Miracle Professor and Associate Chief,
Section on Hematology and Oncology
Neuro-Oncology Co-Program Leader
Wake Forest Baptist Comprehensive Cancer Center
Disclosures

• Research Funding (Clinical Trials):
  ▪ Incyte, Novartis, Immunocellular Therapeutics, New Link Genetics, Pfizer, Vascular Biogenics, Orbus

• DSMB:
  ▪ Stemline Therapeutics

• Consulting:
  ▪ Monteris, BTG International, CEN
Overview* of Today’s Presentation

29,029 Feet
Topics To Touch On

- Where Are We Now
  - Brief overview of brain tumors and current standard treatment backbone
  - Why are brain tumors so hard to treat?
    - Unique challenges to therapy

- Where Are We Going
  - Targeted therapies
    - Precision/Personalized Medicine
  - Immunotherapy
  - Tumor Treating Fields

- Symptom Science Challenges and Opportunities
  - Neurocognitive protection from “Chemo-Brain” and “Beamo-Brain”
Distribution of All Primary Brain and CNS Tumors by Histology

- Glioblastoma: 20.3%
- Astrocytomas: 9.8%
- Ependymomas: 2.3%
- Oligodendrogliomas: 3.7%
- Embryonal, including medulloblastoma: 1.7%
- Meningioma: 30.1%
- Pituitary: 6.3%
- Lymphoma: 3.1%
- Nerve sheath: 8.0%
- Craniopharyngioma: 0.7%
- All others: 13.9%

Distribution of All Gliomas by Histology Subtypes

- Glioblastoma: 50.7%
- All other astrocytomas: 9.1%
- Anaplastic astrocytoma: 7.9%
- Diffuse astrocytoma: 1.7%
- Pilocytic astrocytoma: 5.7%
- Ependymomas: 5.6%
- Oligodendrogliomas: 9.2%
- All other gliomas: 10.1%

Glioblastoma = Grade IV Astrocytoma
Anaplasia(2), Vascular Proliferation(3), Pseudopalisading(4)

http://neuropathology-web.org/chapter7/chapter7bGliomas.html
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma


TMZ 200 mg/m²/d × 5 days repeat every 28 days

TMZ 75 mg/m²/d × 7 days for 6-7 weeks

Focal RT (30 x 2 Gy, 60 Gy) Tumor volume with 2-3 cm margin
Why Are Brain Tumors So Hard to Treat?
Unique Concerns/Features That Differentiate Brain Tumors and Impact Treatment

• The skull has a fixed volume
• Can be hard to measure success
  ▪ Brain imaging studies are “estimates”
  ▪ Steroid effects
  ▪ Clinical deficits may be permanent
• The tumors infiltrate into surrounding tissue
• The blood-brain barrier
  ▪ Keeps drugs out of the brain and the tumor
Brain Tumor Imaging
Glucocorticoid (Steroid) Effects
Profound Clinical and Imaging Effects of Glucocorticoids (Dex 4mg TID)
Anti-GFP Staining Shows Highly Invasive Tumor Cells

Slide Courtesy of Eric Holland
Figure 13.1. At the ultrastructural level, the mammalian blood-brain barrier from 1 day neonatal age to the adult exhibits circumferential belts of tight junctional complexes (arrow and inset) between contiguous, nonfenestrated endothelial cells. The tight junctions preclude the bidirectional passage of nonlipid-soluble macromolecules between the blood and brain interstitial fluid.
The Blood-Brain Barrier Limits the Entry of Many Chemotherapeutic Agents

Precision/Personalized Targeted Therapy
Major Signaling Pathways in Cancer
The London Underground
"Driver Mutations"

Figure 2. Frequency of molecular aberrations in various driver oncopgenes in lung adenocarcinomas and current available drugs against these oncopogenic proteins. These frequencies are a combination of data from the Lung Cancer Mutation Consortium and frequencies listed in Shea et al. Shown in the boxes are the available drugs in addition to their developmental phase. EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma receptor tyrosine kinase; MET, mesenchymal-epithelial transition factor; HER2, erb-b2 receptor tyrosine kinase 2; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; BRAF, B-Raf proto-oncogene, serine/threonine kinase; RET, ret proto-oncogene; NTRK1, neurotrophic tyrosine kinase receptor type 1; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; MEK1, mitogen-activate protein kinase kinase 1; KRAS, Kirsten rat sarcoma viral oncogene homolog.
FoundationOne CDs is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and that are actionable drivers of oncogenesis based on current knowledge. The current assay interrogates 25 genes as well as introns of 6 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

**DNA GENE LIST:** For the Detection of Base Substitutions, Insertion/Deletions, and Copy Number Alterations

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL1</td>
<td>ACF5B</td>
<td>AKT1</td>
<td>AKT2</td>
<td>AKT3</td>
<td>AKT4</td>
<td>ACTA2</td>
<td>ACTB</td>
</tr>
<tr>
<td>AR</td>
<td>ARRAF</td>
<td>ATM1</td>
<td>ATM2</td>
<td>ATM3</td>
<td>ATM4</td>
<td>ATP1</td>
<td>ATP5</td>
</tr>
<tr>
<td>AURKB</td>
<td>AXIN1</td>
<td>BCL2</td>
<td>BCL2L3</td>
<td>BCL2L6</td>
<td>BCL6</td>
<td>AURKA</td>
<td>AURKB</td>
</tr>
<tr>
<td>BCR</td>
<td>BCR-ABL</td>
<td>CALM2</td>
<td>CALR</td>
<td>CARD10</td>
<td>CASK</td>
<td>CFRA</td>
<td></td>
</tr>
<tr>
<td>BTK</td>
<td>CALY</td>
<td>CDH2</td>
<td>CDH8</td>
<td>CDH10</td>
<td>CDH13</td>
<td>CDH17</td>
<td></td>
</tr>
<tr>
<td>CCND2</td>
<td>CCNE1</td>
<td>CDK4</td>
<td>CDK6</td>
<td>CDK8</td>
<td>CDK11</td>
<td>CDK13</td>
<td></td>
</tr>
<tr>
<td>CDH1</td>
<td>CDH12</td>
<td>CDH4</td>
<td>CDH11</td>
<td>CDH12</td>
<td>CDH14</td>
<td>CDH15</td>
<td></td>
</tr>
<tr>
<td>CCL2C1</td>
<td>CHEK1</td>
<td>CHEK2</td>
<td>CHK1</td>
<td>CHK2</td>
<td>CHK3</td>
<td>CHK4</td>
<td></td>
</tr>
<tr>
<td>CTR</td>
<td>CTRAP1</td>
<td>CUL4A</td>
<td>CUL5A</td>
<td>CUL6A</td>
<td>CUL7A</td>
<td>CUL8A</td>
<td></td>
</tr>
<tr>
<td>DND1</td>
<td>DNA2</td>
<td>DMDM2</td>
<td>DMDM3</td>
<td>DMDM4</td>
<td>DMDM5</td>
<td>DMDM6</td>
<td></td>
</tr>
<tr>
<td>EPHB4</td>
<td>EPHB4</td>
<td>EPHB5</td>
<td>EPHB6</td>
<td>EPHB7</td>
<td>EPHB8</td>
<td>EPHB9</td>
<td></td>
</tr>
<tr>
<td>FANCC</td>
<td>FANCA</td>
<td>FANC1</td>
<td>FANC1A</td>
<td>FANC2</td>
<td>FANC3</td>
<td>FANC4</td>
<td></td>
</tr>
<tr>
<td>FGFR3</td>
<td>FGFR4</td>
<td>FGFR5</td>
<td>FGFR6</td>
<td>FGFR7</td>
<td>FGFR8</td>
<td>FGFR9</td>
<td></td>
</tr>
<tr>
<td>GATA4</td>
<td>GATA6</td>
<td>GATA7</td>
<td>GATA8</td>
<td>GATA9</td>
<td>GATA10</td>
<td>GATA11</td>
<td></td>
</tr>
<tr>
<td>HDMC1</td>
<td>HMG1A</td>
<td>HMG2A</td>
<td>HMG2B</td>
<td>HMG2C</td>
<td>HMG2D</td>
<td>HMG2E</td>
<td></td>
</tr>
<tr>
<td>JUN</td>
<td>JUN1</td>
<td>JUN2</td>
<td>JUN3</td>
<td>JUN4</td>
<td>JUN5</td>
<td>JUN6</td>
<td></td>
</tr>
<tr>
<td>KMT2C (MLL3)</td>
<td>KMT2D (MLL2)</td>
<td>KMT4A</td>
<td>KMT4B</td>
<td>KMT4C</td>
<td>KMT4D</td>
<td>KMT4E</td>
<td></td>
</tr>
<tr>
<td>MAP1K1</td>
<td>MAP2K1</td>
<td>MAP2K2</td>
<td>MAP2K3</td>
<td>MAP2K4</td>
<td>MAP2K5</td>
<td>MAP2K6</td>
<td></td>
</tr>
<tr>
<td>MAPK1K1</td>
<td>MAPK1K2</td>
<td>MAPK1K3</td>
<td>MAPK1K4</td>
<td>MAPK1K5</td>
<td>MAPK1K6</td>
<td>MAPK1K7</td>
<td></td>
</tr>
<tr>
<td>MDR1K</td>
<td>MERTK</td>
<td>MERTK2</td>
<td>METTL1</td>
<td>METTL3</td>
<td>METTL4</td>
<td>METTL5</td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td>MTH1</td>
<td>MTH2</td>
<td>MTH3</td>
<td>MTH4</td>
<td>MTH5</td>
<td>MTH6</td>
<td></td>
</tr>
<tr>
<td>MTH1F1</td>
<td>MTH1F2</td>
<td>MTH1F3</td>
<td>MTH1F4</td>
<td>MTH1F5</td>
<td>MTH1F6</td>
<td>MTH1F7</td>
<td></td>
</tr>
<tr>
<td>NBN</td>
<td>NBS1</td>
<td>NT5E1</td>
<td>NT5E2</td>
<td>NT5E3</td>
<td>NT5E4</td>
<td>NT5E5</td>
<td></td>
</tr>
<tr>
<td>NFI</td>
<td>NFI1</td>
<td>NFIC</td>
<td>NFIB</td>
<td>NFIA</td>
<td>NGFI-B</td>
<td>NGFI-C</td>
<td></td>
</tr>
<tr>
<td>PARK2</td>
<td>PARK2</td>
<td>PARK2A</td>
<td>PARK2B</td>
<td>PARK2C</td>
<td>PARK2D</td>
<td>PARK2E</td>
<td></td>
</tr>
<tr>
<td>PARK2X</td>
<td>PARK2Y</td>
<td>PARK2Z</td>
<td>PARK2A</td>
<td>PARK2B</td>
<td>PARK2C</td>
<td>PARK2D</td>
<td></td>
</tr>
<tr>
<td>PCF11</td>
<td>PCF11</td>
<td>PCF11A</td>
<td>PCF11B</td>
<td>PCF11C</td>
<td>PCF11D</td>
<td>PCF11E</td>
<td></td>
</tr>
<tr>
<td>POL1</td>
<td>POL2</td>
<td>POL3</td>
<td>POL4</td>
<td>POL5</td>
<td>POL6</td>
<td>POL7</td>
<td></td>
</tr>
<tr>
<td>POLH1</td>
<td>POLH1</td>
<td>POLH1A</td>
<td>POLH1B</td>
<td>POLH1C</td>
<td>POLH1D</td>
<td>POLH1E</td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>PTEN1</td>
<td>PTEN2</td>
<td>PTEN3</td>
<td>PTEN4</td>
<td>PTEN5</td>
<td>PTEN6</td>
<td></td>
</tr>
<tr>
<td>RHO1</td>
<td>RHO1G</td>
<td>RHO1G2</td>
<td>RHO1G3</td>
<td>RHO1G4</td>
<td>RHO1G5</td>
<td>RHO1G6</td>
<td></td>
</tr>
<tr>
<td>RICTOR</td>
<td>RICTOR</td>
<td>RICTOR2</td>
<td>RICTOR3</td>
<td>RICTOR4</td>
<td>RICTOR5</td>
<td>RICTOR6</td>
<td></td>
</tr>
<tr>
<td>STAB2</td>
<td>STAB2</td>
<td>STAB2A</td>
<td>STAB2B</td>
<td>STAB2C</td>
<td>STAB2D</td>
<td>STAB2E</td>
<td></td>
</tr>
<tr>
<td>SUI1</td>
<td>SUI1G</td>
<td>SUI1H</td>
<td>SUI1I</td>
<td>SUI1J</td>
<td>SUI1K</td>
<td>SUI1L</td>
<td></td>
</tr>
<tr>
<td>SYK</td>
<td>SYK1</td>
<td>SYK2</td>
<td>SYK3</td>
<td>SYK4</td>
<td>SYK5</td>
<td>SYK6</td>
<td></td>
</tr>
<tr>
<td>TEC1</td>
<td>TEC2</td>
<td>TEC3</td>
<td>TEC4</td>
<td>TEC5</td>
<td>TEC6</td>
<td>TEC7</td>
<td></td>
</tr>
<tr>
<td>XRC2</td>
<td>XRC2D</td>
<td>XRC2E</td>
<td>XRC2F</td>
<td>XRC2G</td>
<td>XRC2H</td>
<td>XRC2I</td>
<td></td>
</tr>
</tbody>
</table>

**Appendix**

**Genes Assayed in FoundationOneCDx**

**Additional Assays for the Detection of Select Cancer Biomarkers**

<table>
<thead>
<tr>
<th>Loss of Heterozygosity (LOH) Score</th>
<th>Microsatellite (MS) Status</th>
<th>Tumor Mutational Burden (TMB)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TERT</strong> (Promoter of TERT Is Interrogated)**</td>
<td><strong>Promoter region of TERT is Interrogated</strong></td>
<td><strong>Promoter region of TERT is Interrogated</strong></td>
</tr>
</tbody>
</table>
Biomarker Findings
Microsatellite status - M5-Stable
Tumor Mutational Burden - TMB-High (105 Muts/Mb)

Genomic Findings
For a complete list of the genes assayed, please refer to the Appendix.

PIK3CA D725N - subclonal†
TSC1 P1021S
CCND2 amplification - equivocal†
IDH1 R132H
ATRX R1138fs*8
CDKN2A/B loss
FGF23 amplification - equivocal†
FGF6 amplification - equivocal†
MSH6 loss
RAD54L P418S - subclonal†
SMAD4 W398* - subclonal†
TPS3 R273C

2 Disease relevant genes with no reportable alterations: EGFR, PDGFRA

† See About the Test in appendix for details.
## BIOMARKER FINDINGS

**Microsatellite status** - MS-Stable

**Tumor Mutational Burden** - TMB-High (105 Muts/Mb)

## GENOMIC FINDINGS

**PIK3CA** - D725N - subclonal

<table>
<thead>
<tr>
<th>Genes</th>
<th>Status</th>
<th>Trials</th>
<th>Details</th>
<th>See Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSC1</strong></td>
<td>P1021S</td>
<td>10</td>
<td></td>
<td>p. 18</td>
</tr>
<tr>
<td><strong>CCND2</strong></td>
<td>amplification - equivocal</td>
<td>10</td>
<td></td>
<td>p. 13</td>
</tr>
<tr>
<td><strong>IDH1</strong></td>
<td>R132H</td>
<td>1</td>
<td></td>
<td>p. 15</td>
</tr>
</tbody>
</table>

## ACTIONABILITY

**No therapies or clinical trials.** see Biomarker Findings section

### THERAPIES WITH CLINICAL BENEFIT (IN PATIENT’S TUMOR TYPE)

- None

### THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)

- Alpelisib
- Everolimus
- Temsirolimus

<table>
<thead>
<tr>
<th>Genes</th>
<th>Status</th>
<th>Trials</th>
<th>Details</th>
<th>See Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSC1</strong></td>
<td>P1021S</td>
<td>10</td>
<td></td>
<td>p. 18</td>
</tr>
<tr>
<td><strong>CCND2</strong></td>
<td>amplification - equivocal</td>
<td>10</td>
<td></td>
<td>p. 13</td>
</tr>
<tr>
<td><strong>IDH1</strong></td>
<td>R132H</td>
<td>1</td>
<td></td>
<td>p. 15</td>
</tr>
</tbody>
</table>

### THERAPIES WITH CLINICAL BENEFIT (IN PATIENT’S TUMOR TYPE)

- None

### THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)

- Everolimus
- Temsirolimus
- None

- None

- None

- None
Patient With a BRAF V600E Mutated Papillary Craniopharyngioma Treated With Vem/Cobi

Baseline

Following 2 months of Tx
Tumor Treating Fields
Tumor Treating Fields

- TTFields -- novel cancer therapy
- Device consists of:
  - Insulated transducer arrays
  - Electric field generator
  - Battery pack
- Generates alternating electric fields through tumor
- Set at frequency of 200 kHz
- Interferes with mitosis
- FDA approved April 2011

Figure 3.
Second-generation Optune device. The complete system consists of an electric field generator (A), rechargeable battery pack (B), carrying pouch (C), and two pairs of disposable ceramic transducer arrays (D). Figure copyright Novocure, 2018.
Dermatologic Adverse Event: Contact Dermatitis

TWO POTENTIAL FORMS OF CONTACT DERMATITIS

Allergic contact dermatitis*
Allergy to tape and/or hydrogel

Irritant contact dermatitis†
Chemical irritation from hydrogel, moisture, and/or alcohol

- Do not use Optune in patients that are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

* Photo used with permission from patient; † photo courtesy of Dr. M. Lacouture, May 25, 2014.
EF14: Treatment Scheme and Study Design

Tumor Treating Fields
(>18 h/day) until second progression (or max 24 months)

Concomitant TMZ/XRT

Stratification:
Resection: complete vs partial vs biopsy
MGMT methylation status

EF-14: Long-term Survival Rates (5-year survival analysis)\textsuperscript{1,2}

- Optune + TMZ provides unprecedented 5-year survival rates in newly diagnosed GBM

\[\begin{array}{c|cc|cc|cc|cc|}
\text{Years From Randomization} & \text{Optune + TMZ} & \text{TMZ Alone} \\
1 & 73\% & 65\% & P=0.0258 \\
2 & 43\% & 31\% & P=0.0008 \\
3 & 26\% & 16\% & P=0.0039 \\
4 & 20\% & 8\% & P=0.0002 \\
5 & 13\% & 5\% & P=0.0037 \\
\end{array}\]

TMZ, temozolomide.
“Dose Response” Effects of TTF

Fig. 3 The annual survival rate was highest for newly diagnosed GBM patients with compliance rates >90% with a 29.3% survival rate over 5 years from randomization.
# EF-14: Subgroup Analysis for Overall Survival (5-year survival analysis)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients (%)</th>
<th>Hazard Ratio</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>695 (100)</td>
<td></td>
<td>20.9</td>
</tr>
<tr>
<td>MGMT (central)</td>
<td></td>
<td></td>
<td>16.9</td>
</tr>
<tr>
<td>Unmethylated</td>
<td>304 (44)</td>
<td></td>
<td>14.7</td>
</tr>
<tr>
<td>Methylated</td>
<td>214 (31)</td>
<td></td>
<td>21.2</td>
</tr>
<tr>
<td>Resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>89 (13)</td>
<td></td>
<td>16.5</td>
</tr>
<tr>
<td>Partial</td>
<td>234 (34)</td>
<td></td>
<td>15.1</td>
</tr>
<tr>
<td>Gross total</td>
<td>372 (53)</td>
<td></td>
<td>18.5</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>583 (84)</td>
<td></td>
<td>21.6</td>
</tr>
<tr>
<td>65+ y</td>
<td>112 (16)</td>
<td></td>
<td>17.1</td>
</tr>
<tr>
<td>KPS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-100</td>
<td>457 (67)</td>
<td></td>
<td>23.3</td>
</tr>
<tr>
<td>≤80</td>
<td>228 (33)</td>
<td></td>
<td>17.8</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>222 (32)</td>
<td></td>
<td>24.6</td>
</tr>
<tr>
<td>Male</td>
<td>473 (68)</td>
<td></td>
<td>18.5</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- TMZ: temozolomide
- MGMT: O-6-methylguanine-DNA methyltransferase
- KPS: Karnofsky Performance Score

Laser Interstitial Thermal Therapy (LITT)
Monteris Neuroblate Laser Interstitial Thermal Therapy

- Stereotactically inserted
- Directional, cooled
- Nd:YAG (neodymium-doped yttrium aluminium garnet; Nd:Y\textsubscript{3}Al\textsubscript{5}O\textsubscript{12}) laser
Laser Interstitial Thermal Therapy (LITT)
Laser Interstitial Thermal Therapy (LITT)

- Real time MR-thermometry
Metastatic Carcinoma Status Post Gamma Knife Laser Interstitial Thermal Thermal Therapy for Radiation Necrosis
Immunotherapeutic Approaches
Immunotherapy: PD-1 and PD-L1 Blockade

PD-L1 binds to PD-1 and inhibits T cell killing of tumor cell

Blocking PD-L1 or PD-1 allows T cell killing of tumor cell

Tumor cell

Antigen

T cell receptor

PD-L1

PD-1

T cell

T cell death

PD-L1

Anti-PD-L1

Anti-PD-1

PD-1

T cell
Immunotherapy And Brain Tumors

"Accelerators" and "Brakes" on T Cells Within the Tumor Environment

Immunotherapy: Dendritic Cell and Peptide Vaccine Trials in GBM

Immunotherapy: Oncolytic Viruses

FIGURE 7 | Prototypical mechanism of oncolytic viral therapy. The modified virus is infused into the tumor environment. (A) Normal cells exposed to viruses may have introduction of viral genetic information, but the viruses are modified to not replicate. (B) Viral particles then recognize enter cell based on specific surface proteins, such as CD155 in PVSRIPO and αvβ5 in Delta-24-RGD oncolytic adenovirus. (C) Oncolytic viral particles in tumors are replication-competent and recruit tumor cell replication machinery. (D) Viral replication results in cell lysis and release of viral particles to continue targeting tumor cells. (E) Macrophages detect and target virally infected cells, recruiting other APCs and effector T cells for secondary immune response against released tumor antigens.
Immunotherapy: CAR-T Cells

**Figure 6** Chimeric Antigen Receptor (CAR) T-cells each directed at a specific GBM-specific tumor antigen. Each CAR T-cell therapy developed for the treatment of glioblastoma utilizes a CAR directed toward one antigen such as HER2, EGFRvIII, or IL-13Ra2. (A) Engagement of tumor-specific CAR T-cells with target cell surface antigen present on tumor cells causes CAR T-cell activation. (B) Second and third generation CAR T-cells are synthesized with co-stimulatory molecules such as 41BB, CD28, and CD3 which lower the CAR T-cell barrier to activation. (C) Fully activated CARs attack target cells causing tumor cell lysis. (D) Cells negative for the CAR T-cell target demonstrate the heterogeneity of the tumor and represent a barrier to treat as these cells not targeted continue to proliferate.
Local Tumor Control after Intracavitary Delivery of IL13BBζ–Chimeric Antigen Receptor (CAR) T Cells

A

Enrollment: leukapheresis  Generation of CAR T cells

Day: 0  Cycle:

B

Before Resection  After Resection, before Infusion  After Infusion (cycles 1–6)
Neurocognitive Toxicity:
“Chemo Brain” & “Beamo-Brain”
I have CHEMO BRAIN!
What’s your excuse?
<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of action</th>
<th>Evidence of impact on cognition in cancer patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODAFINIL</td>
<td>Thought to inhibit GABA outflow tracts within the ventro-lateral preoptic area of the hypothalamus.</td>
<td>Clinical trials have looked at fatigue as a primary outcome and cognition as a secondary one, although most have demonstrated efficacy in improving cognition.</td>
</tr>
<tr>
<td>METHYLPHENIDATE</td>
<td>Dopaminergic and noradrenergic agonist which acts to increase levels of these neurotransmitters within the frontal striatal network.</td>
<td>Randomised, double-blind trials in childhood cancer patients suggest efficacy, but no evidence of superiority over placebo in adult trials.</td>
</tr>
<tr>
<td>DONEPEZIL</td>
<td>Centrally acting anticholinergic used in the management of Alzheimer’s Disease.</td>
<td>Open-label Phase II studies in glioma patients suggested statistically significant improvement in cognitive functioning.</td>
</tr>
<tr>
<td>LITHIUM</td>
<td>Cation with an unknown mechanism of action used in the management of bipolar mood disorder.</td>
<td>Murine models and efficacy data from bipolar patients suggest anti-apoptotic and neuroprotective potential.</td>
</tr>
<tr>
<td>PPARs</td>
<td>Nuclear hormone receptor functioning as a transcription factor, targeted in the control of type II diabetes mellitus.</td>
<td>Murine models have demonstrated protection against radiation induced cognitive dysfunction.</td>
</tr>
<tr>
<td>ARBs</td>
<td>Antagonism of the angiotensin II receptor used in the management of hypertension.</td>
<td>Murine models have demonstrated protection against radiation induced cognitive dysfunction.</td>
</tr>
<tr>
<td>NOS</td>
<td>Produces NO which functions as a neurotransmitter.</td>
<td>None, theoretical benefit through induction of NOS and subsequent antioxidant activities.</td>
</tr>
<tr>
<td>MEMANTINE</td>
<td>NMDA antagonist used in the management of Alzheimer’s Disease.</td>
<td>Recent randomised placebo-controlled double-blind trial in patients receiving whole brain radiation showed longer time to cognitive decline over placebo.</td>
</tr>
<tr>
<td>N-ACETYL CYSTEINE</td>
<td>Provides cysteine, the rate limiting step in the synthesis of the anti-oxidant glutathione.</td>
<td>Limited evidence of efficacy in Phase II trials in Alzheimer’s patients.</td>
</tr>
<tr>
<td>RESVERATROL</td>
<td>Unknown, demonstrates anti-apoptotic and anti-oxidant properties within cell cultures.</td>
<td>Phase II studies in Alzheimer’s patients suggest little to no cognitive benefit.</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>Inhibition of COX isoforms.</td>
<td>Recent Cochrane review indicates no significant impact in slowing cognitive decline in Alzheimer’s patients, Women’s Health study subanalysis echoes this finding.</td>
</tr>
</tbody>
</table>
Donepezil for Irradiated Brain Tumor Survivors: A Phase III Randomized Placebo-Controlled Clinical Trial

Stephen R. Rapp, D. Doug Case, Ann Peiffer, Michelle M. Naughton, Michael D. Chan, Volker W. Stieber, Dennis F. Moore Jr. Steven C. Falchuk, James V. Piephoff, William J. Edensfield, Jeffrey K. Giguerre, Monica E. Loghin, and Edward G. Shaw

See accompanying editorial doi: 10.1200/JCO.2014.60.2805

Phase II double-blind placebo-controlled of armodafinil for brain radiation-injury

Brandi R. Page, Edward G. Shaw, Lingyi Lu, David Bryant, Michelle J. Naughton, Stephen R. Rapp, Steven R. Sovon

Department of Radiation Oncology, Medical Center Blvd, Wake Forest University Baptist Medical Center, Wake Forest School of Medicine, Winston-Salem, North Carolina (S.R.S.); Department of Medical Oncology, Wake Forest School of Medicine, Winston-Salem, North Carolina (D.B.); Department of Neurosurgery, Greenville Health System Cancer Institute, Greenville, South Carolina (D.B.); Department of Radiation Oncology, Hefetra Northshore-Lakefront Health Care Center, New Orleans, Louisiana (L.S.); Department of Radiation Oncology, Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina (S.R.S.); Department of Pathology, Wake Forest School of Medicine, Winston-Salem, North Carolina (S.R.S.)

Corresponding Author: Brandi R. Page, MD, Department of Radiation Oncology, Wake Forest School of Medicine, Medical Center Blvd, Cancer Center 1st Floor, Winston-Salem, NC 27157; brandipage@gmail.com.

J Neurooncol

Clinical Study

Phase II study of Ginkgo biloba and cognitive function

Albert Attia · Stephen R. Rapp · L. Ralph D'Agostino · Glenn Lesser · Kevin McMullen · Robin Rosenthal

A study of donepezil in female breast cancer survivors with self-reported cognitive dysfunction 1 to 5 years following adjuvant chemotherapy

J. A. Lawrence · L. Griffin · E. P. Balcueva · D. L. Grotenhuis · T. A. Samuel · G. J. Lesser · M. J. Naughton · L. D. Case · E. G. Shaw · S. R. Rapp

DOI 10.1007/s11766-015-0463-x
### TABLE 3  Ongoing Late-Phase Clinical Trials for Newly Diagnosed Glioblastoma

<table>
<thead>
<tr>
<th>Trial Designation</th>
<th>NCT Number</th>
<th>Phase</th>
<th>Planned N</th>
<th>Novel Treatment</th>
<th>Treatment Regimen</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTG 3596A (Intelliance)</td>
<td>NCT02353234</td>
<td>III/IV</td>
<td>940</td>
<td>ABT-414, an EGFR-targeting antibody-drug conjugate</td>
<td>EGFR-amplified or EGFRvIII-mutated RT/ TMZ + TMZ vs RT/TMZ/ABT-414 + TMZ/ABT-414</td>
<td>Completed accrual</td>
</tr>
<tr>
<td>A071102</td>
<td>NCT02152692</td>
<td>III/IV</td>
<td>440</td>
<td>Veliparib, a PARP inhibitor</td>
<td>MGMT promoter methylated Post-RT/TMZ enrollment TMZ +/- TTP vs TMZ/veliparib +/- TTP</td>
<td>Completed accrual</td>
</tr>
<tr>
<td>N/A</td>
<td>NCT00049568</td>
<td>III</td>
<td>348</td>
<td>DCVax-L, an autologous dendritic cell vaccine</td>
<td>Post-RT/TMZ enrollment TMZ/placebo vs TMZ/DCVax-L</td>
<td>Completed accrual*</td>
</tr>
<tr>
<td>CheckMate-546</td>
<td>NCT02607587</td>
<td>III</td>
<td>693</td>
<td>Nivolumab, a PD-1 antibody</td>
<td>MGMT promoter methylated RT/TMZ + TMZ vs RT/TMZ/nivolumab + TMZ/nivolumab</td>
<td>Completed accrual</td>
</tr>
<tr>
<td>CheckMate-458</td>
<td>NCT02617889</td>
<td>III</td>
<td>550</td>
<td>Nivolumab, a PD-1 antibody</td>
<td>MGMT promoter unmethylated RT/TMZ + TMZ vs RT/nivolumab + nivolumab</td>
<td>Completed accrual</td>
</tr>
<tr>
<td>N/A</td>
<td>NCT03645095</td>
<td>III</td>
<td>750</td>
<td>Marizomib, a proteasome inhibitor</td>
<td>RT/TMZ + TMZ vs RT/TMZ/marizomib + TMZ/marizomib</td>
<td>Open to accrual</td>
</tr>
</tbody>
</table>

* Decision to use TTP fields is made prior to enrollment but is then continued throughout study treatment.

** Preliminary results.

DCVax-L = lysate-pulsed dendritic cell vaccine; EGFR = epidermal growth factor receptor; MGMT = O-6-methylguanine-DNA methyltransferase; NCT = National Clinical Trials; PARP = poly (ADP-ribose) polymerase; PD-1 = programmed death 1; RT = radiotherapy; RTDG = Radiation Therapy Oncology Group; TMZ = temozolomide; TTP = tumor-treating fields.
Thank you for joining us for our presentation on “Treatments That Excite Your Doctor”. We hope the information that you received was beneficial. This Presentation was offered by the American Brain Tumor Association, an Illinois not for profit corporation (the “Company”), at no charge to users of the World Wide Web, with the express condition that the Presentation’s attendees agree to be bound by the terms and conditions set forth herein.

The information provided from this Presentation was for informational purposes only. This Presentation: (i) was not intended as medical advice, diagnosis or treatment; (ii) was not a substitute for medical advice, diagnosis or treatment; and (iii) does not provide advice on diagnoses, treatments or conditions for individual patients. All health and treatment decisions must be made with your physician(s), utilizing your specific, confidential and individual medical information.

This Presentation may have contained sponsorships. Sponsors are solely responsible for ensuring that material submitted for inclusion in this Presentation on the Company’s website is accurate and complies with applicable laws.

A sponsor’s inclusion in this Presentation is not an endorsement or recommendation of any product, treatment, physician, hospital, test, procedure, opinion or other information that may be mentioned during this Presentation. Reliance on any information in this Presentation is solely at your own risk.

The Company, its affiliates, assigns and agents are not responsible, and expressly disclaim any liability, for errors or omissions in information provided in this Presentation or any actions resulting from the use of such information.

In addition, the references set out in this Presentation are provided for your convenience only. The Company does not endorse the information contained on linked websites or individual(s), companies or institutions operating such websites.

Please do not hesitate to contact us if you have any further questions. Thank you for being an exceptional audience.
Thank You! Questions?