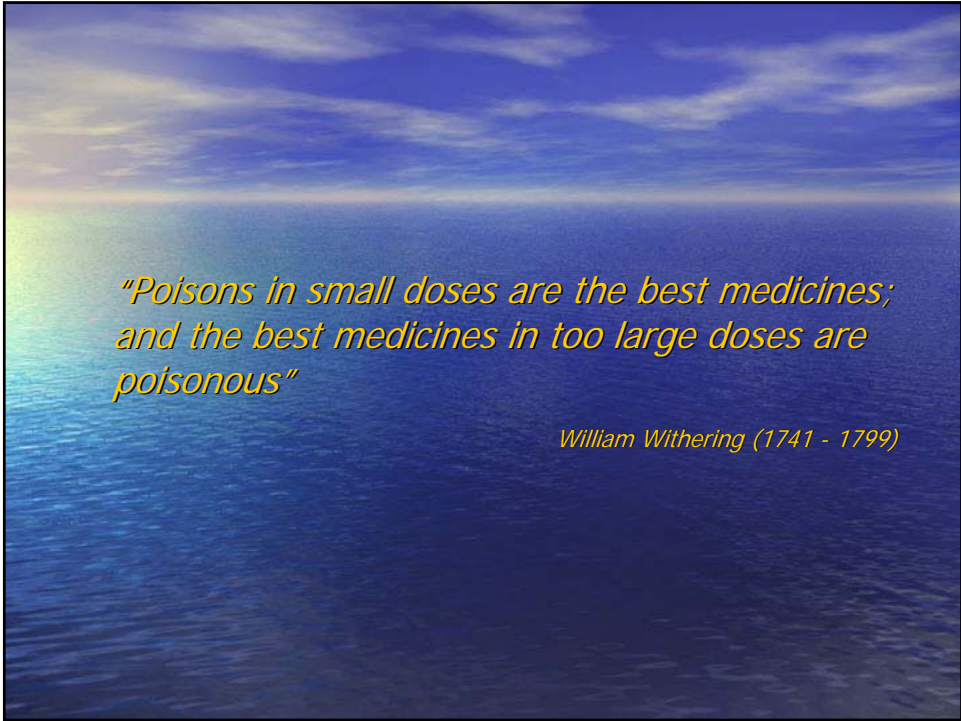




# CHEMOTHERAPY OVERVIEW

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*"Poisons in small doses are the best medicines;  
and the best medicines in too large doses are  
poisonous"*

*William Withering (1741 - 1799)*

## INTRODUCTION

A chemotherapeutic agent is a substance that can target and selectively kill transformed cells.

## Goals of Therapy

- Resectable Disease (image complete)
  - Prevent relapse
- Unresectable Disease (post biopsy)
  - Prevent Growth
  - Can lead to Surgery?

## Principles of Cancer Treatment

### Local Therapy

*Surgery*  
*Radiation therapy*

### Systemic Therapy

*Chemotherapy*  
*Hormonotherapy*  
*Immunotherapy*  
*Targeted therapy*

## What is Standard of Care?

- Standard of Care
  - Published/approved standard
    - Peer reviewed literature
    - National meetings, cooperative groups, research groups
  - Community standard of care
    - Rural vs. Urban community
    - Access to care
  - **NSI's standard of care**
    - Clinical trials
    - Research on the cusp...

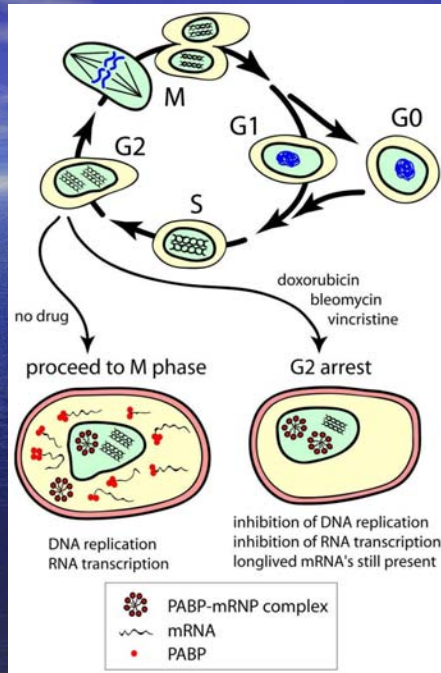
# Treatment

- Post surgery (resectable disease)
  - *Standard of care:* XRT/Temodar
  - Research Protocols: Vaccine Trials
  - **Novel Therapeutics**
- Unresectable disease
  - NO real standard of care
  - XRT/Chemo/Vaccine
  - **Novel Therapeutics**
- Relapsed Disease/Recurrence
  - More XRT/stereotactic
  - Chemo
  - **Novel Therapeutics**

# Chemotherapy I

- Chemical Compounds designed to damage your DNA
  - Hope to damage cancer DNA more
- Stops cell growth and division
- Intravenous forms
- Oral agents (Temodar, CCNU, others)
- Side effects

- Generalized Schema of Chemotherapy

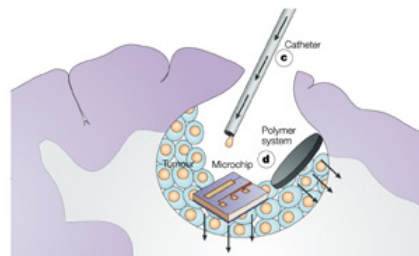
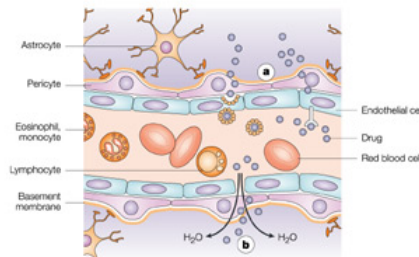


### Blood Brain Barrier

- Drugs which penetrate the BBB

- Carboplatin
- BCNU/CCNU
- Etoposide (VP16)
- Temozolomide**
- Cytarabine
- Tamoxifen
- Procarbazine
- Vincristine
- Methotrexate

- Small Molecules**
- Cediranib (Pan VEGF)
- Erlotinib



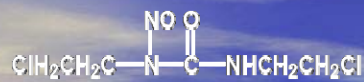
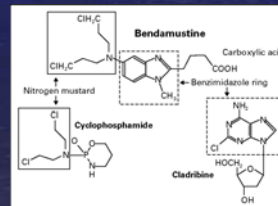
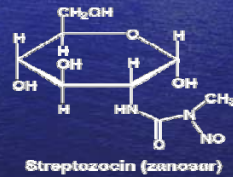
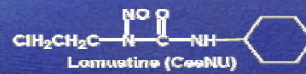
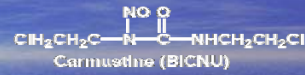
## Chemotherapy II

- Limited choices
  - Relapsed and unresectable settings
    - Temodar
    - CCNU/Lomustine
    - BCNU
    - CPT-11

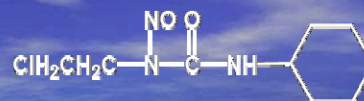
Glioblastoma  
Anaplastic Astrocytoma  
Anaplastic Oligodendrogliomas  
Mixed Astrocytomas  
some low grade gliomas

## Nitrosoureas

- Carmustine (BiCNU) Bifunctional alkylating agent, IV administration
- Lomustine (CeeNU) monofunctional alkylating agent, oral administration
- Streptozocin (zanosar)
- Fotemustine
- Bendamustine (CSMC Trial)



Carmustine (BiCNU)



Lomustine (CeeNU)

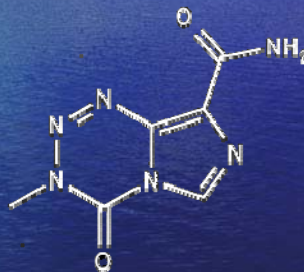
- Carmustine and lomustine are lipid soluble drugs; penetrate the nervous system ( treat central nervous system malignancies, *optic and neurological complications were reported*)
- Used also for treating malignant lymphomas, melanomas and some GIT tumors
- Myelosuppression is the dose-limiting toxicity
- Cause nausea and vomiting
- Long term use of carmustine may cause *pulmonary toxicity*

## Gliadel wafers?



- Phase 3 Trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma (Westphal- Neuro-Oncology, 2004)
- Biodegradable polyanhydride copolymer containing BCNU; implanted on the surface of surgical resection cavity (usually up to 8 wafers); release BCNU slowly over a 2-3 week period
- Median overall survival: 13.9 months (vs 11.6 months)  $p < 0.05$
- FDA approved

## Temozolomide (Temodar)



3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide

## Temozolomide (Temodar)

### Mechanism of Action:

- **Temozolomide is not directly active but undergoes conversion to MTIC when it passes through the blood brain barrier.**
- Active metabolite that methylates DNA at guanine's O<sup>6</sup> position

### Metabolism and Elimination:

Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC.

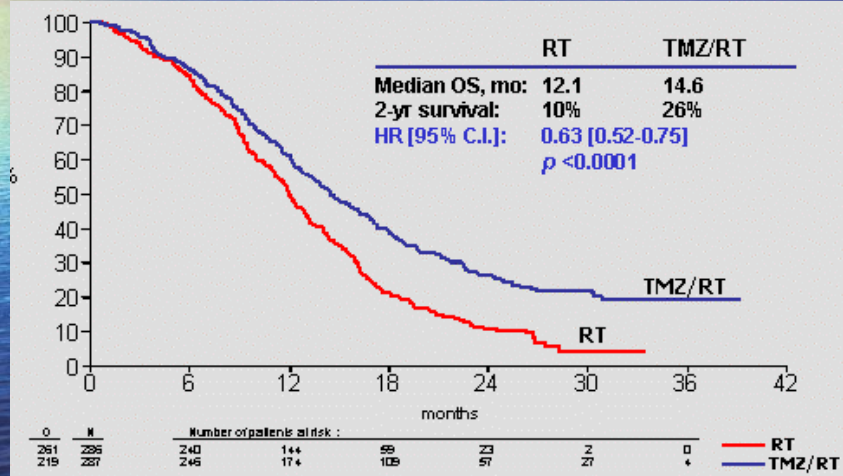
- \* **So there are few drug interactions !**

## What to expect from TMZ?

- **The most commonly used drug**
- Well tolerated
- Fatigue, N/V, myelosuppression, headaches
- Regimens:
  - 150-200 mg/m<sup>2</sup> for 5 days every 28 days
  - 75 mg/m<sup>2</sup> while on RT, wait 4 weeks then re-start with regimen above

# What to expect from TMZ?

- Phase III trial chemoradiation:



Median overall and 2-year survival according to *methylguanine methyltransferase* promoter status (MGMT) – indirect measure of DNA Repair

MGMT promoter status	Radiotherapy	Radiotherapy + temozolomide
Overall survival (mo)		
Hypomethylated	11.8	12.7
Hypermethylated (Less DNA Repair)	15.3	21.7
2-y survival (%)		
Hypomethylated	<2.0	13.8
Hypermethylated	22.7	46.0

Data from Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352(10):987–96.

## Temozolomide Rechallenge in Recurrent Malignant Glioma by Using a Continuous Temozolomide Schedule

The "Rescue" Approach

James R. Parry, <sup>1</sup>  
Philippe Rizak,<sup>1</sup>  
Rosemary Cashman, <sup>2</sup>  
Meredith Morrison, <sup>3</sup>  
Tim Morrison, <sup>1</sup>

<sup>1</sup> Cella Family Brain Tumour Research Unit, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada.

<sup>2</sup> BC Cancer Agency, Vancouver, British Columbia, Canada.

<sup>3</sup> Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania.

**BACKGROUND.** Despite advances in first-line therapy there are few data on treatment of glioblastoma multiforme (GBM) at recurrence. Temozolomide (TMZ) is well tolerated and may have activity despite prior TMZ exposure if novel dose schedules are used.

**METHODS.** The authors reviewed their experience with a continuous TMZ schedule (50 mg/m<sup>2</sup> daily), given at progression after conventional 5-day TMZ. Patients were reported in 3 groups: 1) GBM after progression on conventional TMZ; 2) GBM at first recurrence after completion of standard concomitant and adjuvant TMZ; and 3) patients with other anaplastic gliomas at second relapse on conventional TMZ.

**RESULTS.** In Group 1, 21 patients with a median age of 54 years (range, 33 years-86 years) received a median of 3 cycles (range, 2-12 cycles) of continuous TMZ at 50 mg/m<sup>2</sup>. Overall clinical benefit (complete response, partial response, and stable disease) was 47%, with 6-month progression-free survival (PFS) of 17%. In Group 2, 14 patients with GBM, median age 52 years (range, 39 years-62 years) received continuous TMZ at progression after initial TMZ radiotherapy (RT) and adjuvant TMZ. The median interval after adjuvant TMZ was 3 months (range, 2 months-16 months). A median of 5 cycles of TMZ was given, and 6-month PFS was 57%. In Group 3, 14 patients with a median age of 49 years (range, 34 years-86 years) received continuous TMZ; 2 partial responses and 6 with stable disease were seen, with a 6-month PFS of 42%. Toxicities were mild and well tolerated; lymphopenia was common but no serious opportunistic infections were identified.

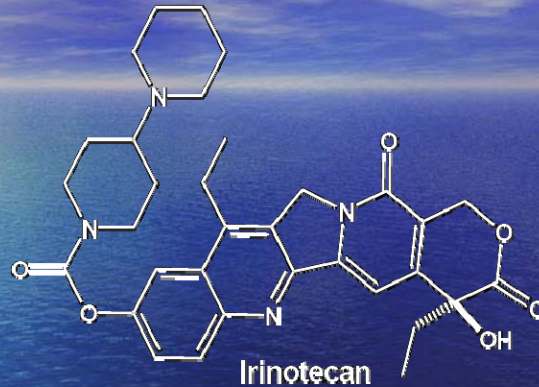
**CONCLUSIONS.** Although retrospective, our results demonstrate that continuous daily administration of TMZ is an active regimen despite prior TMZ therapy. The excellent tolerability of this regimen may allow future combination with other alkylating agents or with novel therapies. *Cancer* 2008;113:2152-7. © 2008 American

### Alternative Temozolomide Dosing

- 75 mg/M2 21days/7days off
  - 50 mg/M2 daily
  - 200 mg/M2 7 days on 7 days off (150 mg/M2 7 days on 7 days off)
- Twice daily dosing

Temozolomide Rechallenge Response Rates as High as 47%

## Irinotecan (CPT-11)



- Used to treat metastatic carcinoma of colon and rectum
- Severe diarrhea is the dose-limiting toxicity (dehydration + electrolyte imbalance)

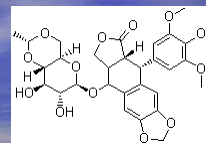
## Irinotecan

### Mechanism of Action

- Interfere with the activity of *Topoisomerase I* (*impairs binding of DNA*) Resulting in DNA damage
- ***Irinotecan***- a prodrug that is metabolized to an active Top I inhibitor, SN-38
- Big Side Effect - Diarrhea

## Etoposide phosphate (VP-16)

### Mechanism of Action



- An inhibitor of the enzyme Topoisomerase II
- Used to treat Ewing's Sarcoma, Lung Cancer, Testicular Cancer, Lymphoma, Leukemia
- Derived from a toxin found in the American Mayapple

## Carboplatin



Its effect is equal cisplatin in ovarian carcinoma

Used in treatment of lung, head and neck tumors

Carboplatin is cleared renally and lacks renal toxicity

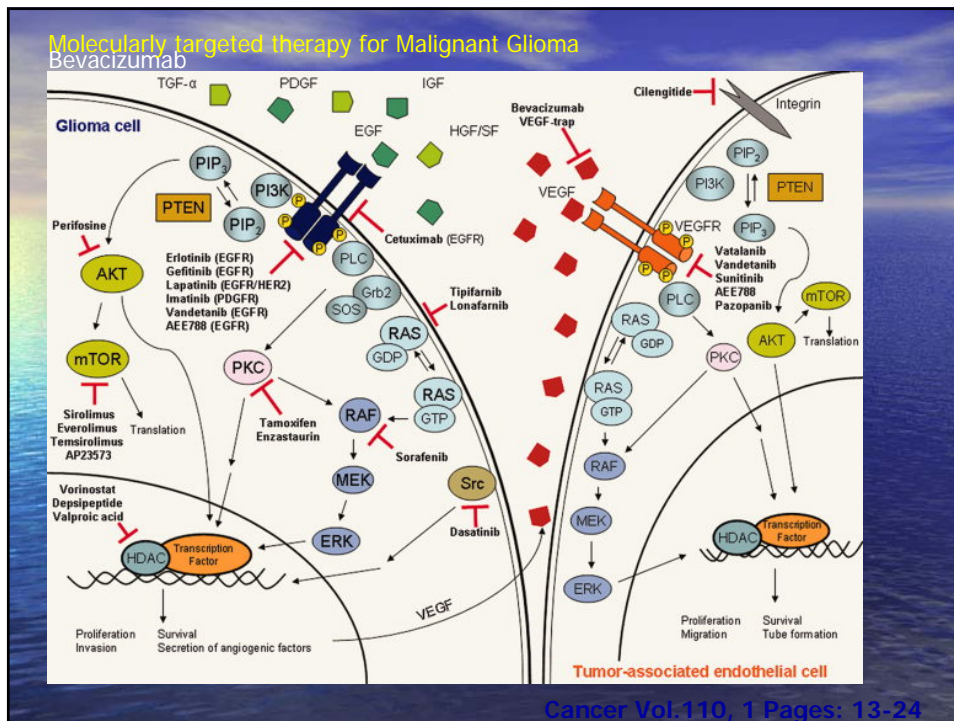
Causes more myelosuppression than cisplatin

## How do we target?

- Monoclonal Antibodies (IV)
  - Literally bind to the cell surface and block
  - I.e. Avastin
- Small Molecule (oral)
  - Bind to cell surface and block
  - I.e. Tarceva
- Tyrosine Kinase inhibitors (oral)
  - Block a pathway in the cell
  - I.e. Gleevec
- Multi-kinase inhibitors (oral)
  - Block multiple pathways in the cell
  - i.e. Nexavar/Sorafenib, Sutent/Sunitinib
- Immunomodulators (oral)
  - Unknown mechanism
  - I.e. Thalomid, revlimid

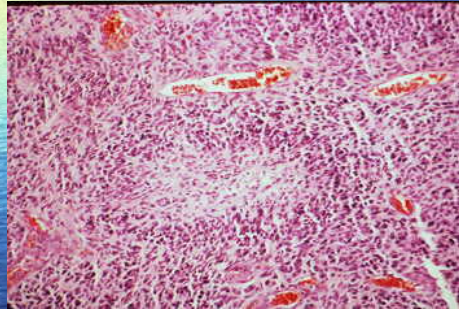
# Is there a target in Gliomas?

- Glioblastoma Multiforme (GBM)
  - Pathologically show increased blood vessel density
  - Laboratory models and animal models predict enhanced angiogenesis (increased blood vessels) as a mode of growth.
  - Theorized that increased T2 enhancement on MRI is due to neo-vascularization
  - Can we reduce enhancement?
    - Does it matter?

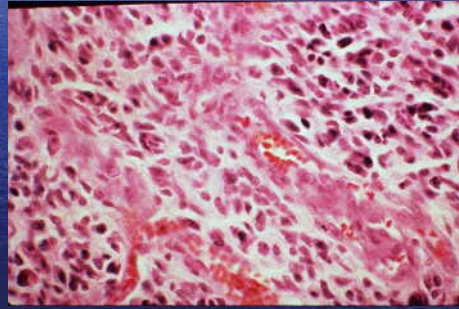


## Tissue slide

- Low mag



- High mag

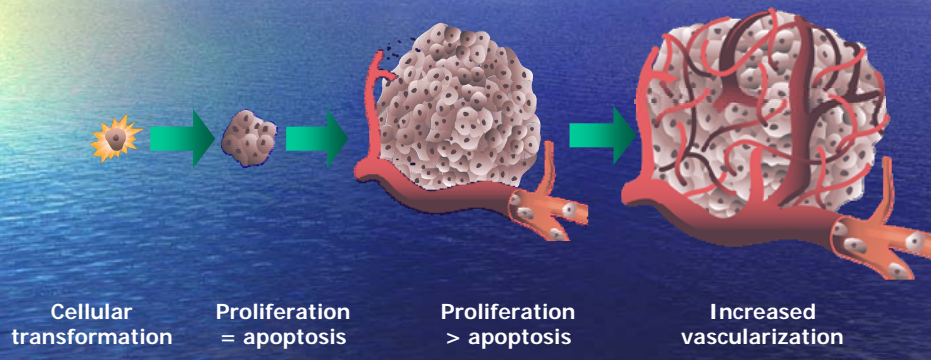


### The mantra...

- Solid tumors need blood vessels to grow.
- Angiogenesis is the process by which new vessels sprout from existing vessels.
- VEGF drives angiogenesis.

*Therefore, inhibiting VEGF  
stops tumor growth.*

# Characteristics of Cancer



Cellular transformation

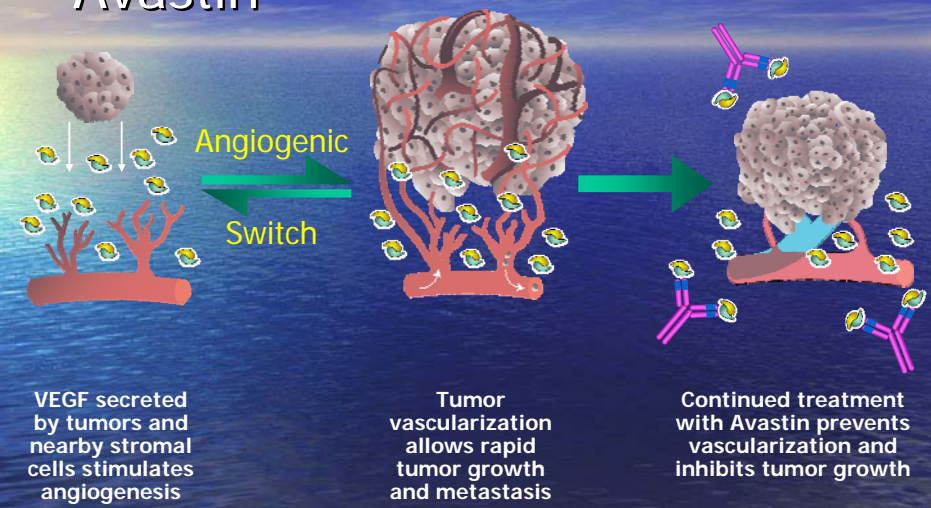
Proliferation = apoptosis

Proliferation > apoptosis

Increased vascularization

Hanahan and Weinberg. *Cell*. 2000;100:57.

# Antiangiogenic Therapy With Avastin



VEGF secreted by tumors and nearby stromal cells stimulates angiogenesis

Tumor vascularization allows rapid tumor growth and metastasis

Continued treatment with Avastin prevents vascularization and inhibits tumor growth

Bergers and Benjamin. *Nat Rev Cancer*. 2003;3:401.

## Angiogenesis inhibitors: Selected drugs...

### Anti-VEGF ligands

Bevacizumab (Avastin)  
Aflibercept (VEGF-Trap)

### Target

VEGF-A  
VEGF-A/B, PlGF

### Receptor Tyrosine Kinase Inhibitors

Cediranib, AZD2171  
Dasatinib (Sprycel)  
Pazopanib, GW786034  
Sorafenib (Nexavar)  
Sunitinib (Sutent)  
Vandetanib (Zactima)  
Vatalanib, PTK787/ZK222584  
Tandutinib, MLN 518

VEGFR, PDGFR, c-Kit  
PDGFR, Src, Bcr-Abl  
VEGFR, c-Kit  
VEGFR, PDGFR, c-Kit, Raf  
VEGFR, PDGFR, c-Kit, FLT-3  
VEGFR, EGFR, RET  
VEGFR, PDGFR, c-Kit  
VEGFR, c-Met

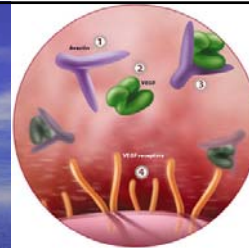
### Others

Cilengitide, EMD121974  
Enzastaurin  
Metronomic chemotherapy  
Thalidomide, lenalidomide

$\alpha\beta_3$  and  $\alpha\beta_5$  integrins  
PKC- $\beta$  and Akt  
Tumor endothelium  
Multiple including FGF

## Avastin(Bevacizumab)

FDA Approved – May 5<sup>th</sup> 2009



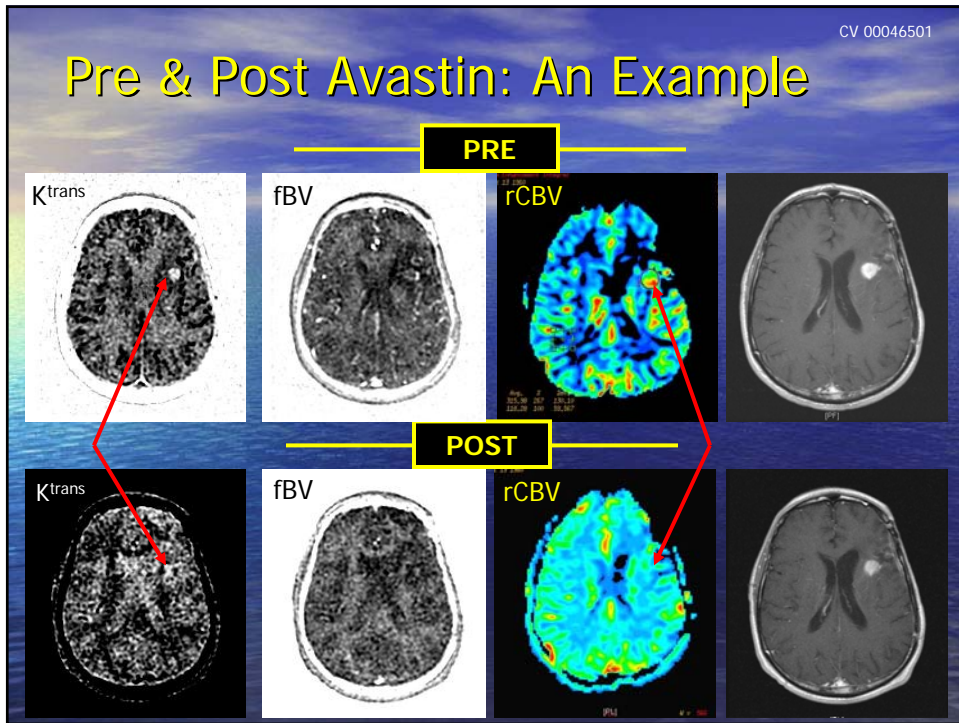
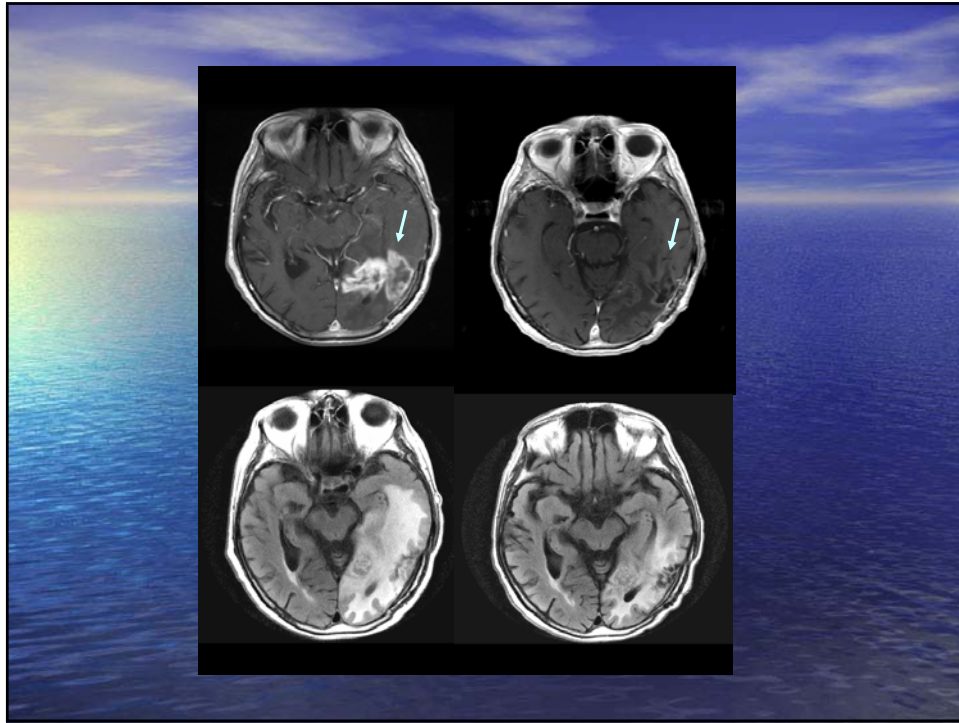
- Humanized monoclonal antibody that binds to and inhibits VEGF-A.
- VEGF secreted by glioma cells acts by paracrine mechanisms upon endothelial cells in the vicinity of the tumor, resulting in endothelial cell proliferation, survival, and migration
- The level of VEGF expression in gliomas correlates with blood vessel density, degree of malignancy, and prognosis
- Approved for Single Agent Usage

## Bevacizumab vs. Bevacizumab/CPT11

Phase II, open-label, multicenter, randomized

- 167 pt's randomized to either arm at recurrence (all upfront Temodar)
- every other week for up to two years (104 weeks)
- Hemorrhage occurred in 3 participants
- Better than expected results – Will present data to FDA for approval

Total = 167	Avastin	Avastin/ CPT11
6 Month PFS	36 %	51 %
Tumor Response Rate	21 % (18/85)	34% (28/82)
MST	8.2 Month	8.7 Months



## The Older Paradigm

### Bevacizumab vs. Bevacizumab/CPT11

Now.....

Bevacizumab/Carboplatin

Bevacizumab/Etoposide (VP16)

Bevacizumab/CCNU

Bevacizumab/Daily Temozolomide

Bevacizumab/(5/28 Temozolomide)

So how do we choose which drug ? Which drug is the best ?

Usually we base it on side effects and on additional factors such as MGMT Status and Blood counts etc....

### Cautious optimism...

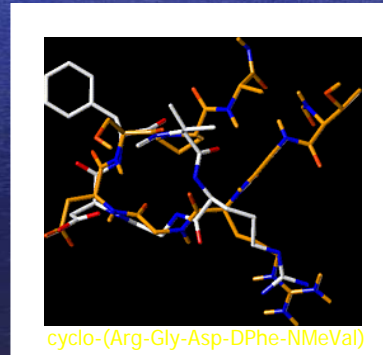
- Responses may be transient.
- Radiographic response doesn't necessarily translate into survival benefit.
- A significant proportion of patients don't respond at all.
- Alternative means of angiogenesis: (AKA Resistance )
  - May develop different forms of VEGF
  - upregulation of parallel pro-angiogenic pathways involving FGF, PDGF, angiopoietin
  - increased invasiveness with co-option of native vasculature

## Cilengitide – Angiogenesis-Inhibitor

Cilengitide (EMD 121974)

Inhibitor of Integrins  $\alpha v \beta 3$   
 $\alpha v \beta 5$

- Angiogenesis inhibition
  - Direct Anti-tumor activity [?]
- CSMC EMD Newly Diagnosed Glioblastoma with Radiation and Temozolomide



## Cediranib (Recentin AZD2171)

- A Phase III, Randomised, Parallel Group, Multi-Centre Study in Recurrent Glioblastoma Patients to Compare the Efficacy of Cediranib [RECENTIN™, AZD2171] Monotherapy and the Combination of Cediranib with Lomustine(CCNU)
- Tyrosine Kinase Inhibitor
- Targets all 3 VEGF Receptors

## Success in molecular medicine Oligodendrogliomas/Oligoastrocytomas

- 1p 19q deletion
  - Present in 60 to 90% of oligodendrogliomas
  - Prolonged survival in all grades with treatment with chemotherapy or radiation
  - Highly associated with morphology
    - 84% oligodendroglioma, 15% mixed oligoastrocytoma
- Caveat:
  - Reports of patients without the deletion but with prolonged survival are noted
    - Are usually young patients with low-grade tumors

## Summary

1. We are using molecular medicine to predict who will benefit from chemotherapy and personalized medicine is a reality
2. New Chemotherapies are emerging for the treatment of cancer and older drugs are finding new uses
3. New methods are being used to bypass the blood brain barrier
4. A combined approach using multiple modalities is necessary to defeat brain tumors

