

# **Regulatory Background**

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# Outline

- Regular and accelerated drug approval requirements
- Brain cancer drug approvals
- January 1999 ODAC
- January 2006 Brain Tumor Endpoints Workshop

# Regular Approval

## Clinical benefit

- Life prolongation
- Favorable effect on valid measure of how patient feels or functions
- Favorable effect on an established surrogate

# Accelerated Approval

Serious or life-threatening disease

- Improvement over available therapy
- Surrogate endpoint reasonably likely to predict clinical benefit
- Requires confirmation of benefit

# Oncology Surrogates

- For regular approval
  - Durable CR in acute leukemias
  - PFS in CLL, renal cell cancer
  - DFS in adjuvant breast CA
- For accelerated approval
  - Response rate with duration in solid tumors

# Brain Cancer Drug Approvals

Drug	Year	Endpoint	Indication
Nitrosoureas	1970's	RR	Primary and metastatic brain tumors
Carmustine wafer	1996	OS	Recurrent GBM as adjunct to Sx
	2003	OS	1 <sup>st</sup> line high grade glioma as adjunct to Sx and RT
Temozolomide	1999	Durable RR	Refractory anaplastic astrocytoma
	2005	OS	1 <sup>st</sup> line GBM concomitantly with RT and then as maintenance therapy

# Carmustine Wafer: Indications

- Recurrent glioblastoma as an adjunct to surgery
  - median survival 6.4 months vs. 4.6 months (placebo)
- Newly diagnosed high-grade malignant glioma as an adjunct to surgery and radiotherapy
  - Randomized, placebo controlled trial in newly diagnosed high-grade glioma undergoing resection craniotomy
  - 240 pts, median survival 13.9 months vs 11.6 months (placebo)
  - HR 0.73 (95% CI 0.56-0.95), log-rank  $p < 0.05$

# Temozolomide & GBM

- Relapsed GBM: not approved (1999)
  - Single arm trial TMZ monotherapy
  - RCT TMZ vs TMZ/procarbazine
  - RR primary endpoint for both trials
- Newly diagnosed GBM: regular approval (2005)
  - EORTC randomized trial: 573 pts
  - Median survival 12.1 months (RT) vs 14.6 months (RT/TMZ)
  - HR 0.63 (95% CI 0.52-0.75), log-rank  $p < 0.0001$

# TMZ 1/1999 ODAC Meeting

Endpoints based on imaging for brain tumors

- Adequate surrogate?
- Accuracy
  - Delayed effects of RT, corticosteroid withdrawal
  - Discordance between MRI and clinical progression
- **Magnitude of effect**
- **Blinded review**

# Brain Tumor Endpoints Workshop

- PROs metrics: not yet sufficiently developed
- PFS-6m: needs further study
- Composite endpoints
  - New radiological tests: premature
  - Radiographic response + evidence of functional or symptomatic improvement

# Brain Tumor Endpoints Workshop (2)

- Response Rate
  - **Magnitude of effect**
  - Duration of response
  - Correlated with clinical status
  - **Effect of therapy on images**
  - Relationship between response rate – TTP
  - Time to exert effects

# Conclusions

- RR assessments may be complicated by a drug that has an effect on medical imaging.
- By modern standards, RR has not been accepted as surrogate endpoint for accelerated approval in GBM.

“... few effective treatments exist for primary brain tumors. No systemic therapy is approved for recurrent GBM.

The literature from which to derive historical control data is largely undependable. Evaluation of clinical trials is affected by patient and tumor heterogeneity, factors shown to have a greater impact than any given therapy on patients' outcome. Survival is the only clearly accepted trial endpoint.”



# FDA Guest Speaker

Dr. Victor A. Levin

Professor and Bernard W. Biedenharn

Chair for Cancer Research

Department of Neuro-Oncology

MD Anderson Cancer Center