# Rapid Early Stage Trials: Unique Clinical Trial Designs in Breast Cancer Brain Metastases (BCBM)

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# Moving Forward: The Challenge For Clinical Trials in BCBM

- Many new agents for treating cancer; many in development
- There is interest in testing the newer agents in the setting of BCBM
- Conventional phase I/II approaches time consuming and inefficient, especially for combination regimens
- New protocol designs and statistical strategies are needed to improve efficiency

# Progress to Date: Adapting the Glioma Paradigm

- In glioma, single agent ST modulators demonstrate only modest success
  - Imatinib
  - Gefitinib
  - Erlotinib
  - Tipifarnib
  - Enzastaurin
- Given the complex molecular pathways, combination strategies may be superior
- Treatments (single-agent and combinations) for BCBM have only recently begun to be biologically-driven

# Steps in Metastatic Process

- Metastatic process is highly complex
  - It's solution and effective interruption is the "holy grail" of oncology
- The multiple steps in metastasis formation are beginning to be understood
- To determine the benefit of a therapy in BCBM
  - Ultimately, the best approach may be to:
    - target a relevant component of metastatic process
    - at it's relevant and specific time point in the metastatic cascade
    - And measure outcomes relevant to the targeted component and the time point in the disease

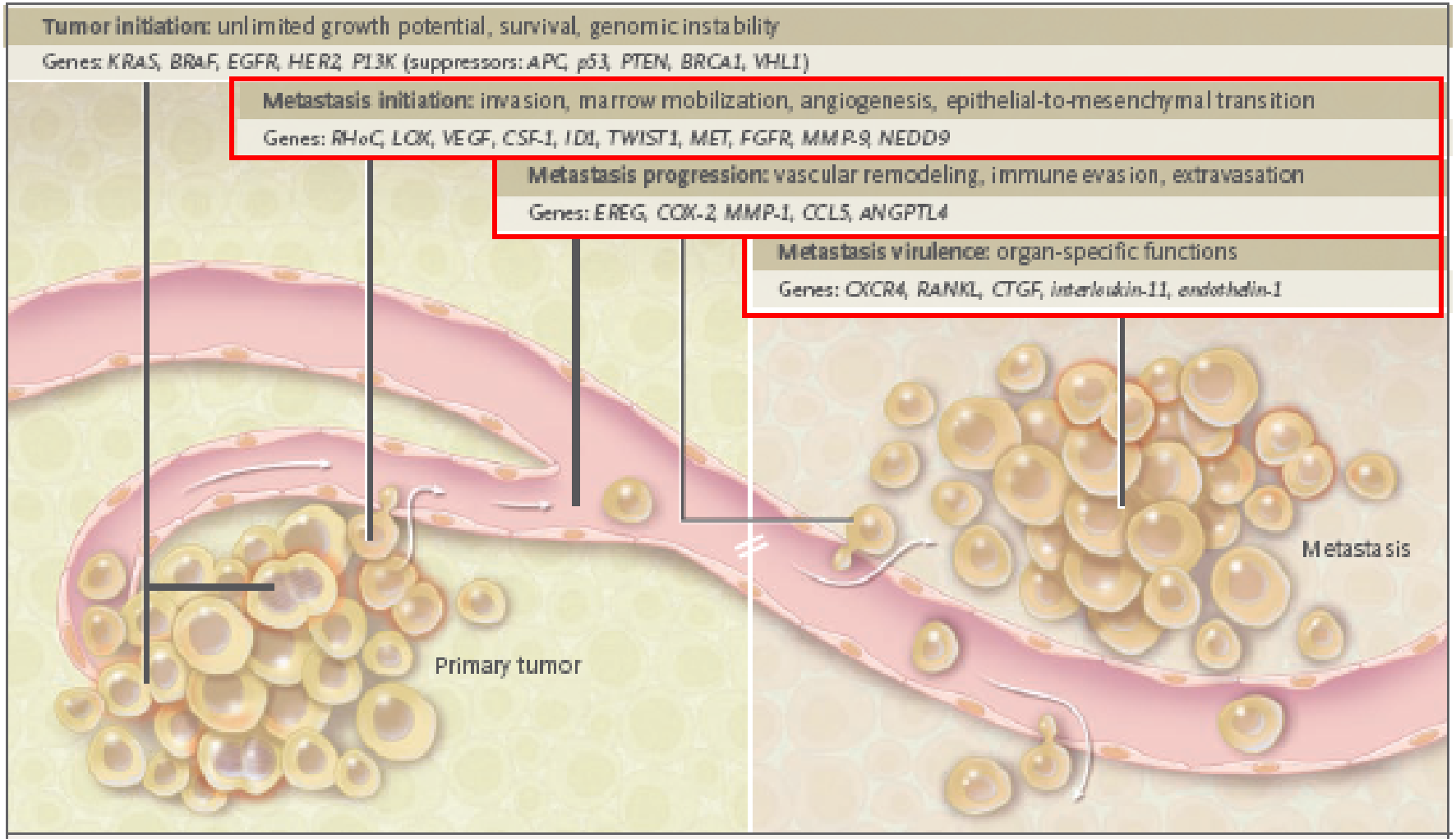



**Figure 1. Tumor Initiation and Metastasis.**

The initiation and progression of tumors depend on the acquisition of specific functions by cancer cells at both the primary and metastatic sites. Functions associated with tumor initiation are provided by oncogenic mutations and inactivation of tumor-suppressor genes. Functions associated with the initiation of metastasis include functions to which tumor cells resort for local invasion and for circumventing hypoxia and other limitations facing a growing tumor. Most functions for the initiation of both the tumor and metastasis remain essential for cancer cells to continue their metastatic development. Functions for metastasis progression provide a local advantage in a primary tumor and a distinct and sometimes organ-specific function during metastasis. Cancer cells that are endowed with these three sets of functions still depend on functions associated with metastasis virulence; these functions confer a selective advantage solely during the adaptation and takeover of a specific organ microenvironment. Genes associated with each of these functions have been identified in recent years.

Chiang and Massague, NEJM, Dec 2008, 2814-23

# New Clinical Trial Designs

- Improve efficiency
  - Rapid elimination of ineffective regimens
  - Test multiple combinations simultaneously
  - Shorter path to definitive testing
- Designs
  - “Pick the Winner”
  - Seamless integration of phase II/III trials
  - Sequential Accrual Design for Phase I/II studies
  - Factorial Design
  - Adaptive Randomization
  - Randomized Discontinuation Design

# “Pick the Winner”

- Typically a series of phase II trials
- Similar eligibility criteria
- Same primary endpoint
- Does not prove best treatment, but
- Provides some assurance that chosen regimen is not inferior
- Example of NABTC/MDACC series of recurrent phase II studies in GBM

# Cytostatic + Alkylating Agents for Recurrent or Progressive GBM

| Combination | Patients, n | Objective Response (PR) (%) | Overall Response (PR+SD) (%) | PFS-6 |
|---|---|---|---|---|
| TMZ + IFNa2b | 33 | 9 | 67 | 22 |
| TMZ + Thal | 44 | 7 | 58 | 24 |
| TMZ + cRA | 40 | 8 | 58 | 32 |
| TMZ + Marimastat | 42 | 14 | 73 | 39 |
| TMZ alone | 112 | 5 | 46 | 21 |
| BCNU + Thal | 40 | - | - | 24 |

Yung WKA, et al. *Neuro-Oncology* 1999. Abstract 217. Jaeckle KH, et al. *Neuro-Oncology* 2003;21:23-5-2311. Groves MD, et al. *J Clin Oncol* 2002;20:1383-88. Yung WKA, et al. *J Clin Oncol.* 1999;17:2762-71. Fine HA, et al. *J Clin Oncol.* 2003;21:2299-2304. Groves MD et al. *J Neuro-Oncology* 2007; 81: 271-7.

# Integrative phase II/phase III studies with multiple arms

- Pick the best 2 arms from the phase II study to continue into phase III
- Relatively time efficient
  - Phase III design can already be approved
  - Accrual to the phase II component can count towards the phase III
- Phase II efficacy measure may differ from phase III (usually survival)

# Sequential Accrual Design for Phase I/II studies

- Multiple arm trial evaluating multiple combinations
- Functionally equivalent to multiple phase I/II trials but…
- Eliminates open/close issue with phase I studies
- Reduces wait time with 2-stage design in phase II component

# Sequential Accrual Design for Phase I/II studies

- Example of 3-arm signal transduction modulation combination regimen in glioma (NABTC 05-02) (a pattern to follow for BCBM studies)
  - Arm 1: Sorafenib + tipifarnib
  - Arm 2: Sorafenib + temsirolimus
  - Arm 3: Sorafenib + erlotinib

# Phase I Component

- Standard dose escalation
- Three patients per cohort
- Sequential enrollment to all three arms
  - 3 patients onto Arm 1, Level 1
  - 3 patients onto Arm 2, Level 1
  - 3 patients onto Arm 3, Level 1
  - Then, 3 patients onto Arm 1, Level 2
  - etc...

# Phase II Component

- Trial design
  - 3 arm, 2-stage design
  - each arm will use the doublet dose from the phase I study
  - sequential enrollment onto each arm
  - Arm 1: 20 patients→ if $\geq$ 4 responses (PFS at 6 months) then onto stage II
  - Arm 2: 20 patients→ if $\geq$ 4 responses (PFS at 6 months) then onto stage II
  - Arm 3: 20 patients→ if $\geq$ 4 responses (PFS at 6 months) then onto stage II

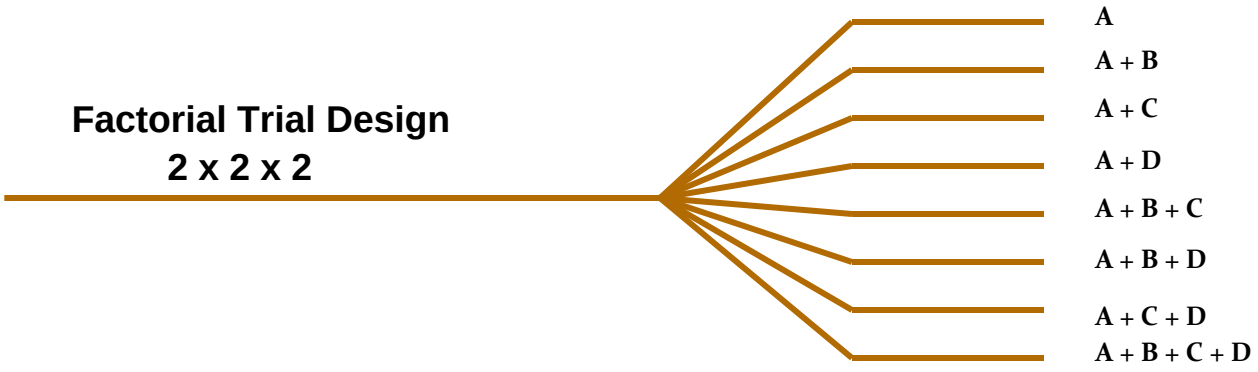
# Sequential Accrual Design for Phase I/II studies BCBM

- Arm 1: CDDP (or capecitabine) + bevacizumab
- Arm 2: CDDP + PARPi
- Arm 3: CDDP (or capecitabine) + SAHA

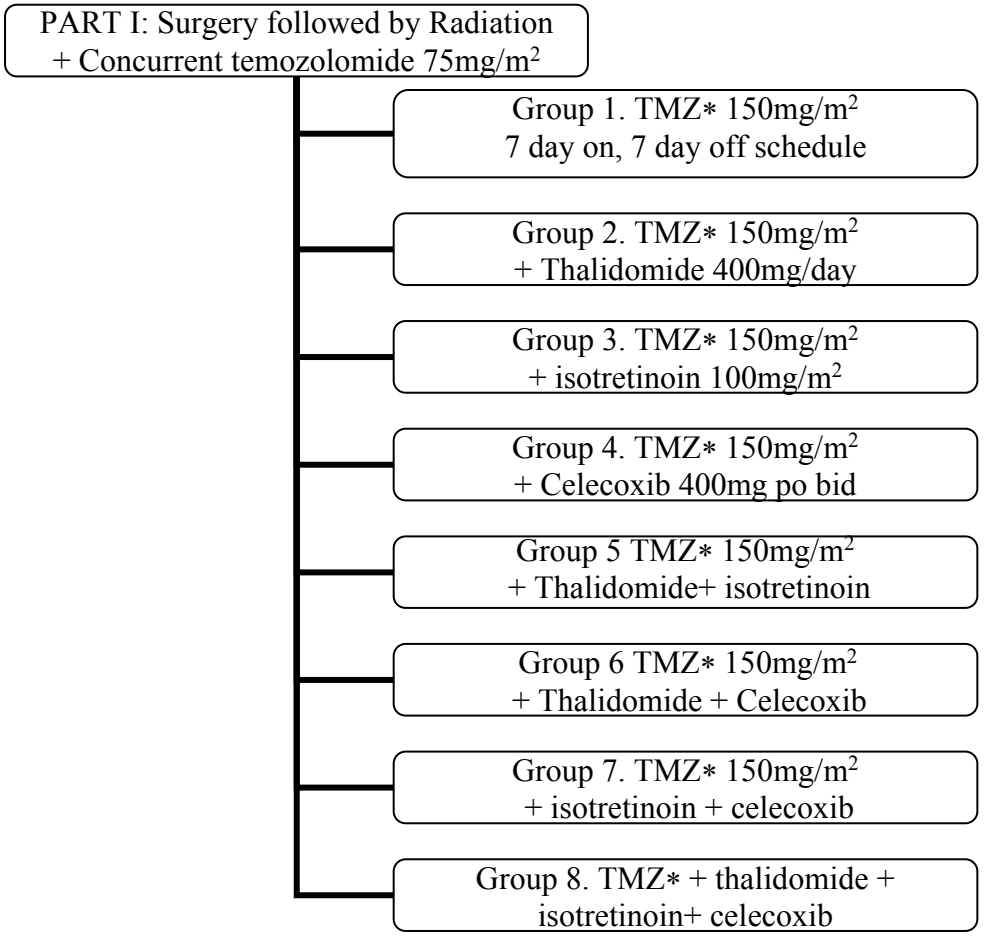
*These are examples of possible phase I & II trials. Endpoints and patient numbers would need re-design.
The best combinations from a biological, feasibility and funding standpoint are open to debate.

# Factorial design

- Multiple arm study
- Requires fewer patients per arm than phase II
- Enrollment to each arm is random
- Optimal design involves combinations of the same group of agents
- Examples of ongoing M. D. Anderson/BTTC factorial design protocol for newly diagnosed glioblastoma



# Factorial Protocol



# Advantages and Analysis using the Factorial Design

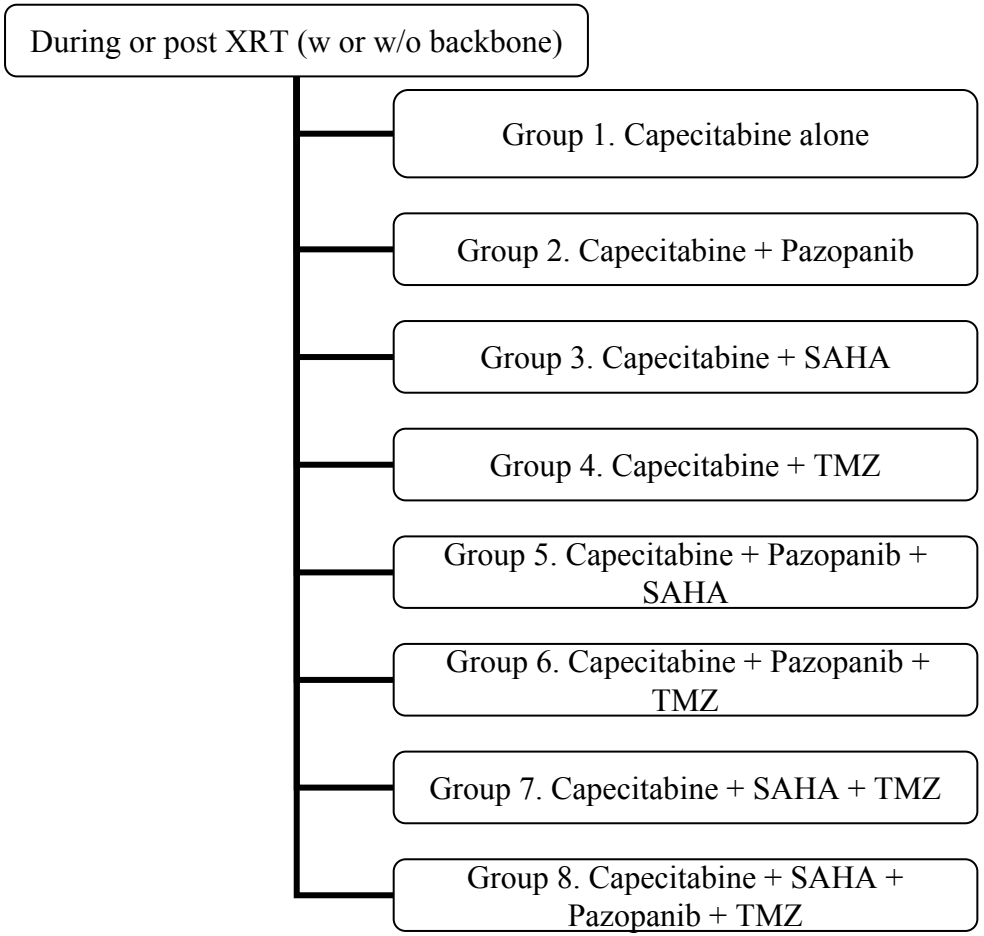
- Multiple combinations tested with fewer patients: 20 per arm in MDACC study
- Can compare effect of each agent
  - E.g.: 80 patients receive therapy with thalidomide (arms 2,5,6,8) vs. 80 patients without thalidomide (arms 1, 3,4,7)
    - Powered (95%) to determine a 50% reduction in hazard rate (HR)
- Compare impact of number of agents
  - Doublet treatment (arms 2,3,4 = 60 patients) vs triplet therapy (arms 5,6,7 = 60 patients) with 90% power to see a 50%↓ in HR
- Evaluate impact of cytostatic combinations
  - TMZ + Thal + cRA (arms 5 + 8; n = 40) compared with others not containing this combination (78% power to see a 50%↓ in HR)

# Possible Disadvantages of the Factorial Design

- Arm to arm comparison
  - less power for comparison (20 vs 20)
  - although preliminary response assessment possible (number of subjects similar to stage I component of a 2-stage design)
- Treatment interactions[1]
  - Reduces the power of interpretation of individual components if there are negative or positive interactions
    - Increases the complexity of the model
- Statistical interactions[2]
  - Interpretation may be difficult if model is incorrect
  - Example: If model is multiplicative but data is additive
    - T vs. T + A → HR ↓ to 0.5
    - T + A vs T + A + B → HR ↓ to 0.375 (additive) vs expected HR ↓ to 0.25 (multiplicative model)


1. McAlister F, et al. JAMA, 2003, 289:2545-2553
2. Green S, et al. JCO 2002, 20:3424-3430

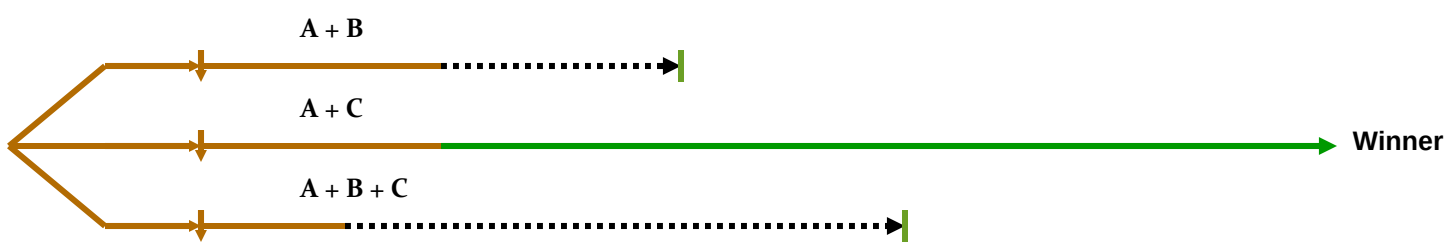
# Example Factorial Protocol for BCBM




* Insert “backbone” and “add-on” drugs of choice

# Adaptive Randomization Strategies

- Multiple arm study
- Allocation of patients based on Bayesian probability of treatment efficacy
- Treatment arms with success are more likely to accrue patients
- Treatment arms with poor results are dropped, alternative arms added and accrual continues until clear evidence of superior treatment(s) emerge




**Adaptive Randomized "Bayesian" Design**

# Application of Adaptive Randomization in Glioma

- Randomized study: SAHA + (Accutane or Carboplatin or Accutane+Carboplatin)
- 3-arm trial
  - SAHA + Accutane
  - SAHA + Carboplatin
  - SAHA + Accutane + Carboplatin

•Design can be modified to include marker driven accrual in each arm after a “learning” period

# Possible Markers and Drugs for a Marker Driven Adaptive Randomization Trial in BCBM

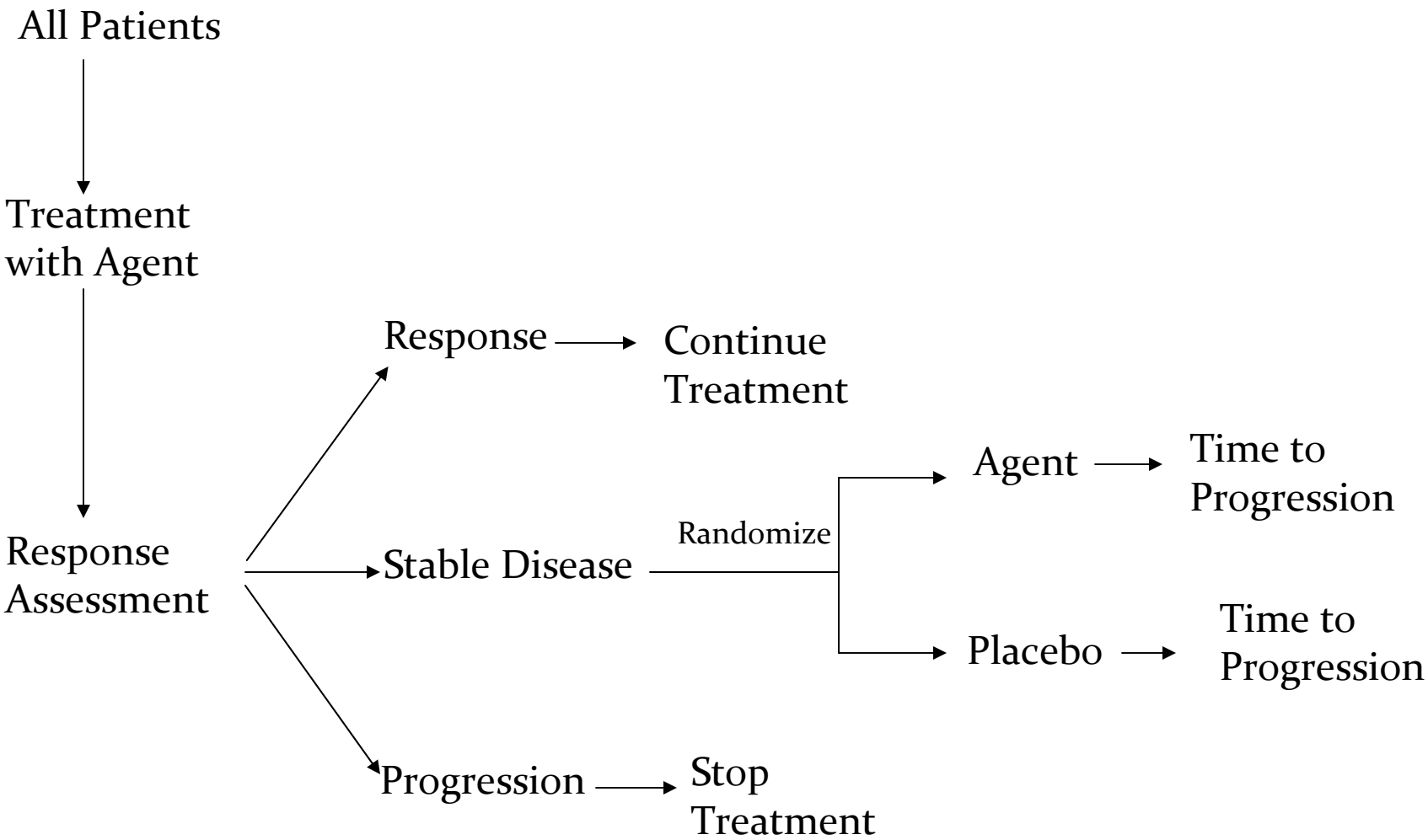
- HER2- tumors
  - Markers: VEGF, EGFR, CXCR4, others
  - Drugs: bevacizumab/pazopanib, erlotinib, plerixafor, others
- For HER2+ tumors
  - Markers: 13 gene array (per Dr. Badve)
  - Drugs: lapatinib, bevacizumab/pazopanib, thalidomide, imatinib, others

# Randomized Discontinuation Design

- First proposed in 1975[1]
- Designed to minimize use of placebo
- Enrichment design where all patients receive study drug at treatment initiation
- Logistics
  - Patients with response continue on treatment
  - Patients with progression stop treatment
  - Patients with stable disease are randomized (blinded) to placebo or continue treatment
- Design increases statistical power with a smaller number of patients

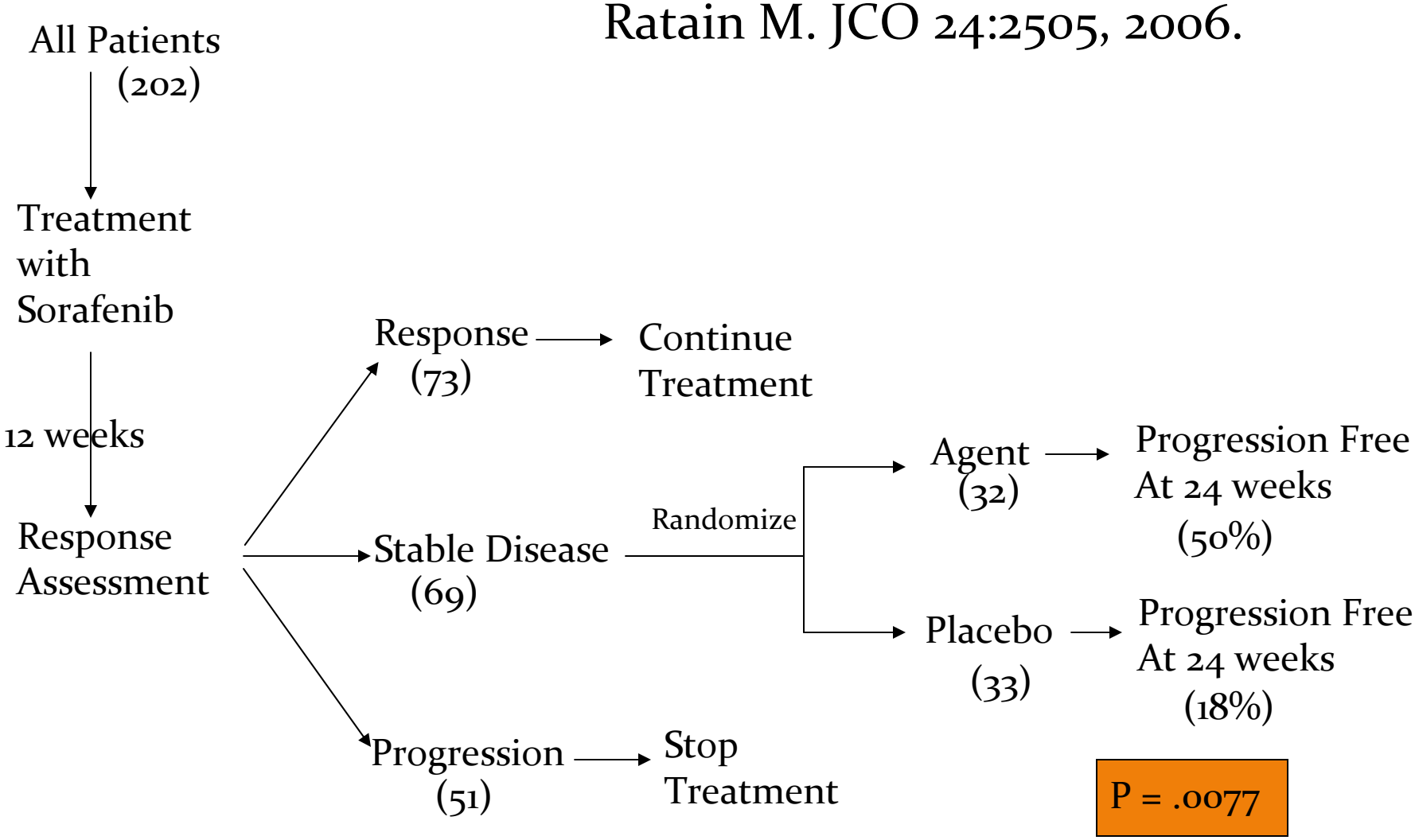
1 Amery, W. J Clin Pharmacol 15:674, 1975

# Design Schema



# Seminal Sorafenib in RCC Study

Ratain M. JCO 24:2505, 2006.



# Conclusions

- Novel clinical trial designs may facilitate and accelerate the evaluation of novel treatment regimens in BCBM.
- But, limitations of interpretation of results must be recognized prior to reporting of trial outcomes.
- Integration of novel designs with increasing knowledge of critical molecular pathways may be an important contribution to developing more effective treatment regimens.
- Interdigitating new molecular targets in brain metastasis trials will be challenging.