ENGELBERG CENTER for Health Care Reform at BROOKINGS

FRIENDS of CANCER RESEARCH

Conference on Clinical Cancer Research

Panel Two:

Evidence for Use of Maintenance Therapy

November 10, 2011 • Washington, DC

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Evidence for Use of Maintenance Therapy

Richard L. Schilsky
University of Chicago Comprehensive Cancer Center

November 10, 2011 • Washington, DC

What is maintenance therapy?

- The continued use of chemotherapy or targeted therapy to lower the risk of tumor progression following first-line therapy
- Types of maintenance therapy*
  - **Switch maintenance**= treating a patient with a second-line drug immediately after that patient obtains maximal response to first-line induction therapy
  - **Continuation maintenance**= patient continues to receive a targeted drug after first-line therapy with that drug in combination with chemotherapy

* “Switch” and “Continuation” terms from NCCN Guidelines

Potential advantages of maintenance therapy

- May prevent or delay tumor progression and the development or worsening of tumor-related symptoms.
- May improve overall survival
- Increases the number of patients who have an opportunity to benefit from an active drug.
- Certain therapeutics can be administered infrequently in the maintenance setting.

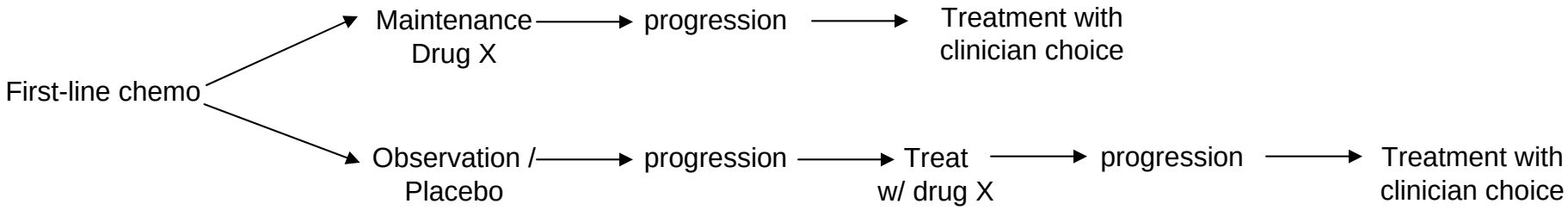
Potential disadvantages of maintenance therapy

- Not all patients need or benefit from maintenance therapy
- May not be superior to second line treatment with same agent
- Unclear benefit to patients of delaying progression if no survival benefit
- Risk of acute and cumulative toxicities may be increased
- Risk of developing drug resistance may be increased
- Significantly increases cost and inconvenience for the patient

Recent examples- Switch maintenance in NSCLC

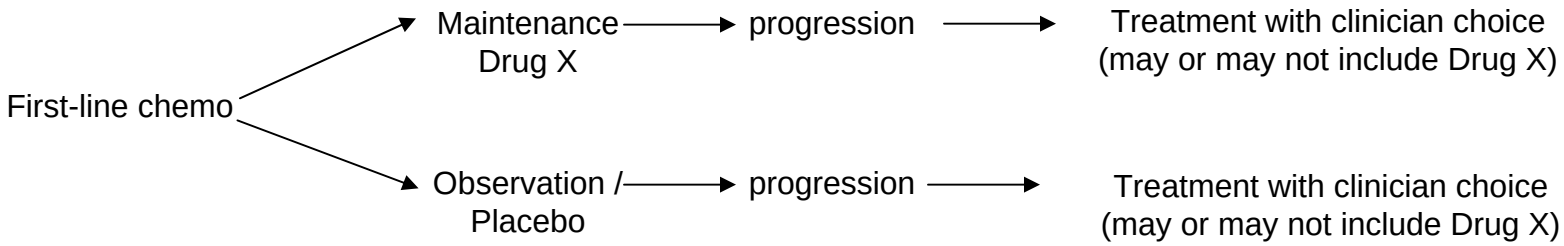
- Rationale: Patients typically respond well to first-line chemotherapy but relapse and progress quickly with a median survival less than 1 year.
- FDA-approved maintenance therapies in patients without progressive disease following 4 cycles platinum chemotherapy
  - Alimta (pemetrexed) – July, 2009
  - Tarceva (erlotinib) – April, 2010

ODAC Discussion: maintenance versus delayed treatment (ODAC 12.16.2009)



Measure: Overall survival and quality of life (symptoms)

Alimta and Tarceva trial designs for maintenance therapy of NSCLC



Results- significant PFS and OS increase in maintenance arm. Overall survival results confounded by lack of consistency in subsequent lines of therapy.

Recent Example- Continuation maintenance with Rituximab

- Approved by FDA (Jan, 2011) for continuation maintenance treatment of follicular lymphoma in patients who achieve a response to induction therapy with rituximab
- Rationale:
  - Minimal toxicity
  - Targets a stable epitope
  - Long half-life allows it to be administered infrequently

Charge to this Panel

Describe the optimal design of clinical trials to demonstrate the benefit of maintenance therapy

Speakers

- Richard L. Schilsky, M.D., University of Chicago
- Patty Spears, Komen Foundation
- Margaret Mooney, M.D., NCI
- Tal Zaks, M.D., Sanofi-Aventis
- Anthony Murgo, M.D., FDA

Maintenance Therapy

Patient Perspective

Patty Spears

Susan G. Komen for the Cure

Maintenance Therapy….

To reach remission or minimal disease (maximal response) after first line chemotherapy…

then to keep the cancer from returning or progressing, or even extending survival by…

receiving Maintenance Therapy with an agent that has low toxicity…

From the Patient Perspective

- It does sound good….
- But there are also some things to keep in mind.

This panel will discuss the clinical trials necessary to provide evidence of clinical benefit.

What else should patients be aware of?

Benefits and Risks

- What outcome is a clinically important outcome for maintenance therapy?
- Benefit –
  - Improving overall survival
  - Keeping the cancer from progressing
  - Delaying additional chemotherapy
  - Delaying onset/worsening of symptoms
- Risk -
  - Toxicity of therapy – cumulative if given a long time
  - Resistance to a certain type of therapy – may not be able to use a drug in that class in the future.

What else?

- Psychological concerns
  - Emotionally, maintenance therapy may be perceived differently in different patients.
    - A patient may feel optimistic that they are still actively fighting the cancer and keeping progression away
    - A patient may be distressed by continuing treatment even after remission
      - No break from treatment and constantly thinking about treatment.

Other Patient Concerns

- Time commitment (especially if it's an injectable therapy)
- More appointments
- Increase cost with increase in treatment
- Additional side effects (more than NO treatment)

Clinical Benefit

- What major clinical outcome should be measured?
- How will maintenance therapy affect the clinical outcome?
  - Overall Survival - *Definitely a clinical benefit.*
  - Progression free survival – *Maybe….*
    - Quality of Life must also be improved or at least not negatively affected
    - Meaningful time delayed before progression

Questions

- When and how should maintenance therapy be used?
  - Scenario 1 (switch) or Scenario 2 (continuous)?
- What agents should be used as maintenance therapy?
  - Does the agent have to have shown activity as a single agent?
  - Must be safe to be given over a long period of time
  - Toxicity must be known and tolerable.
    - Lower doses? Less often?

Final Thoughts

- Designing the right clinical trials to assess the value of maintenance therapy is critical.
  - Will placebo arm affect accrual, particularly if the test agent is available for a different indication?
- Challenges of assessing efficacy:
  - Tumor regression is not assessable
  - Side effects will be critical to obtain
    - QOL instruments
    - Patient reported outcomes
  - Is overall survival the only meaningful endpoint?
  - Is progression free survival a realistic surrogate?
    - Subsequent treatments and crossover confound the overall survival measurement.

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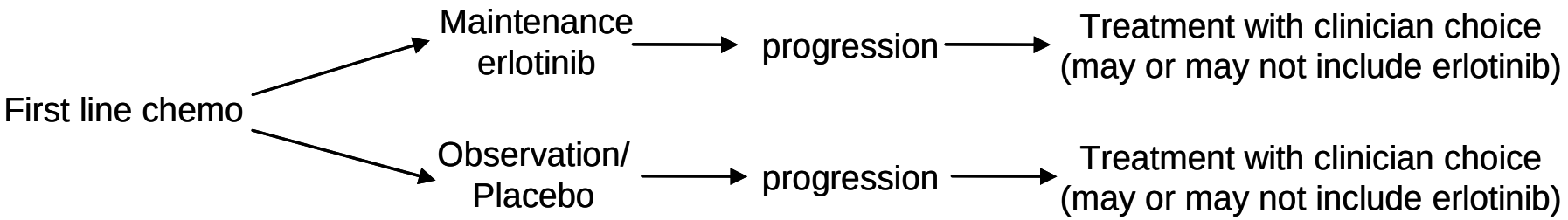
Scenario 1: SATURN



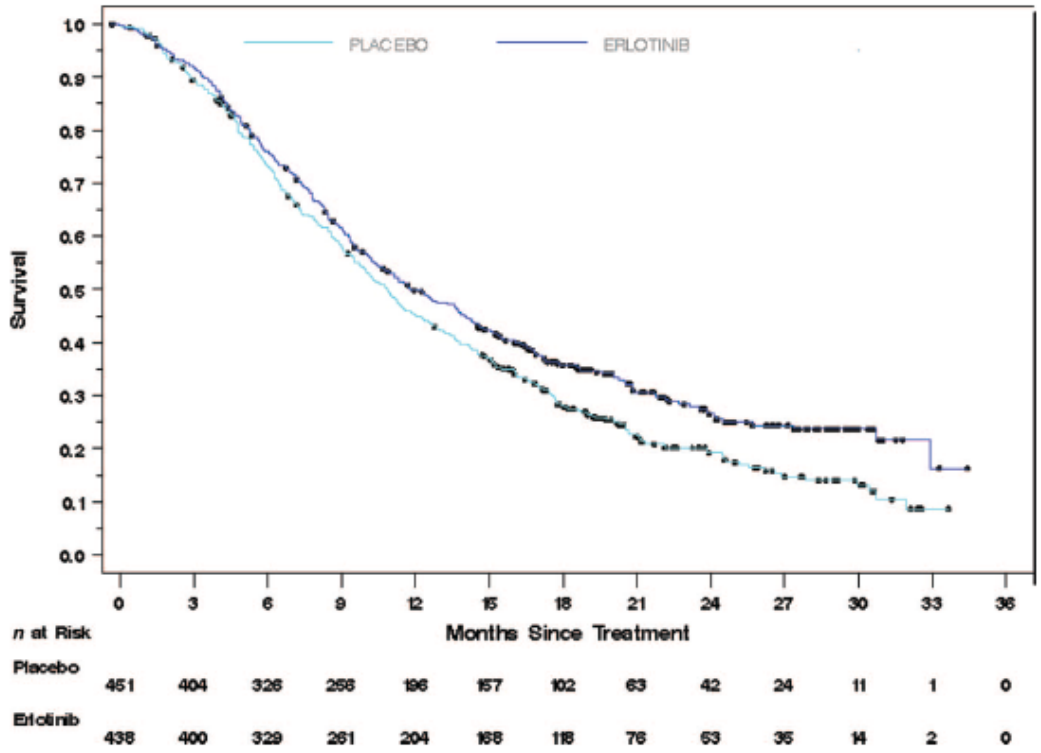
- Supported approval of erlotinib for NSCLC maintenance
- Median OS 12 months in maintenance arm; 11 months in placebo arm; HR=0.81 (for PFS 2.8 vs. 2.6 m, HR=0.71)
- 14% of placebo treated patients received erlotinib or gefitinib on progression

Results of SATURN Trial

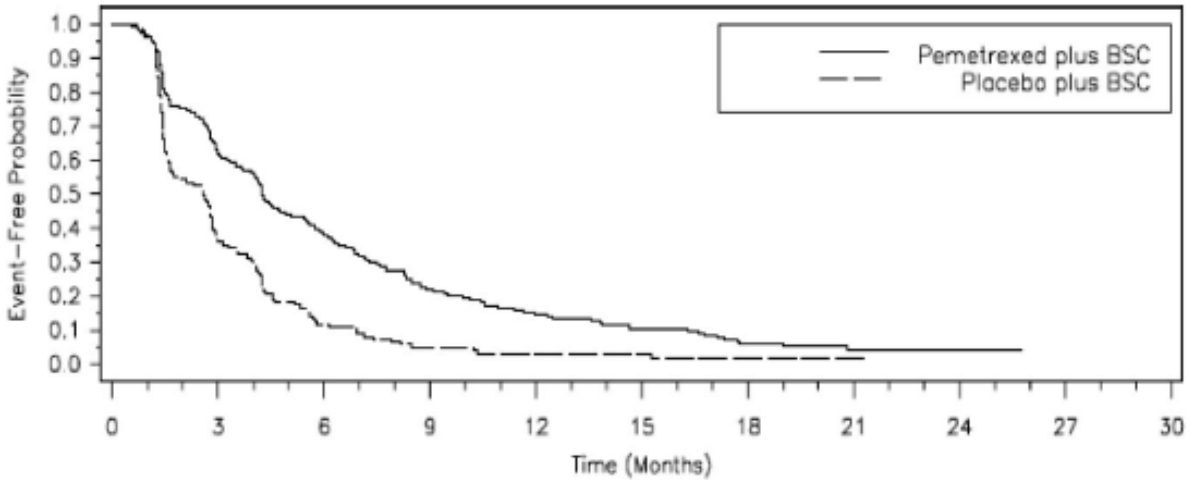
Table 4. Overall survival

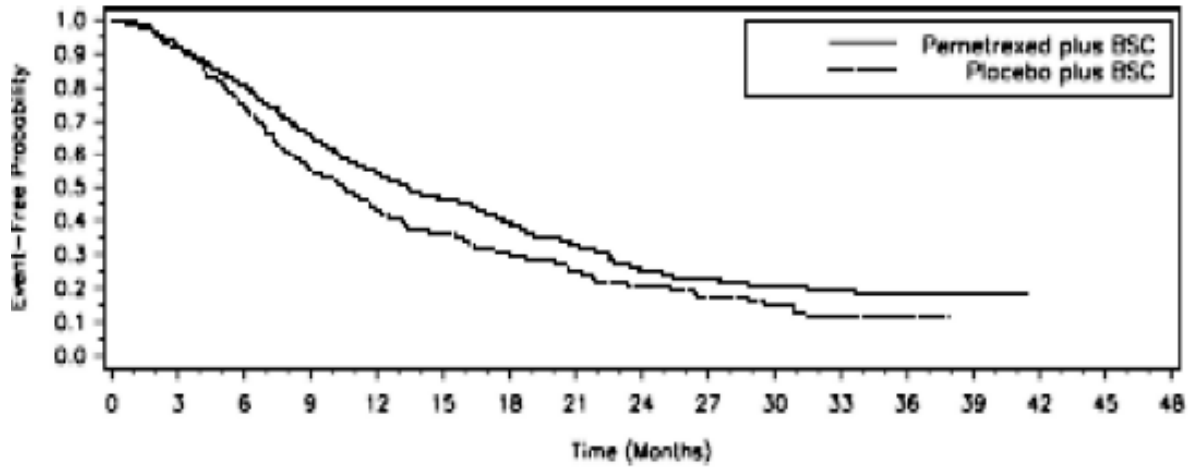
	Median, mos (95% CI)		Hazard ratio[a] (95% CI)	*p*-value[b]
	Erlotinib	Placebo		
All patients: erlotinib, n =438; placebo, n = 451	12.0 (10.6–13.9)	11.0 (9.9–12.1)	0.81 (0.70–0.95)	.009
EGFR$^+$ by IHC: erlotinib, n = 308; placebo, n = 313	12.8 (10.9–14.9)	11.0 (9.7–12.8)	0.77 (0.64–0.93)	.006

[a]Univariate Cox regression model.
[b]Unstratified log-rank test.
Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry.



Pemetrexed Switch Maintenance

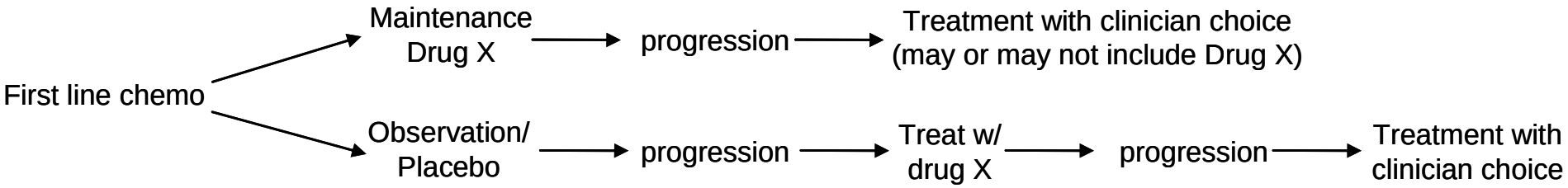




Problem with this approach

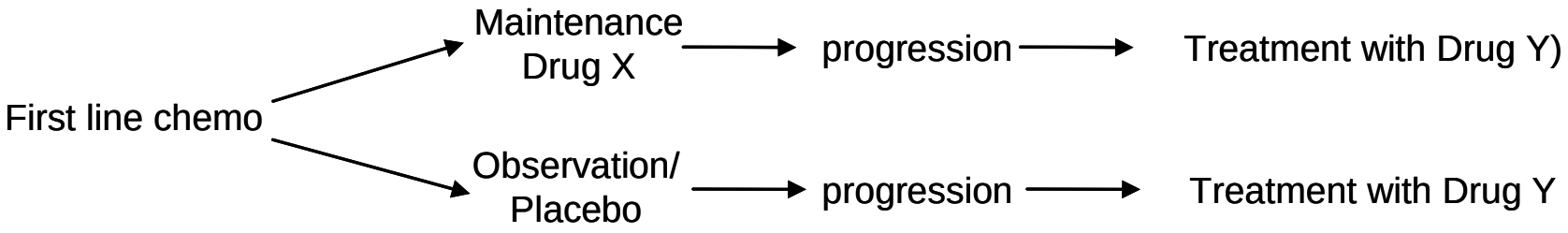
- Does not determine the relative benefit of maintenance vs. 2nd line use of “maintenance” drug at progression
- If maintenance is superior then all patients potentially benefit
- If no difference between these approaches then many patients will receive maintenance needlessly
- Slightly different patient populations as those who receive 2nd line treatment are a subset of those who could receive maintenance

Alternative Design: Maintenance vs. Delayed Therapy



- When Drug X has already demonstrated some activity against the cancer being studied
- For NSCLC example: 1170 patients would have to be randomized over 3.25 years to power a study for overall survival to detect a HR of 0.81; median OS 11 vs 13.6 m

Alternative Design: Maintenance vs. Delayed Therapy



- When Drug X has not yet been tested against the cancer being studied
- Compelling rationale that Drug X would be effective as a maintenance therapy
- Requires that all patients receive same post-progression drug (“Drug Y”)
- Primary endpoint: OS

Are there endpoints other than OS that can demonstrate clinical benefit?

- Time to worsening of tumor-related symptoms?
- Health related quality of life?

Are there endpoints other than OS that can demonstrate clinical benefit?

- Time to worsening of tumor-related symptoms?
- Health related quality of life?

Challenges:

Definition and description of tumor-related symptoms

What magnitude of difference constitutes clinical benefit?

Need for blinding

Multiple endpoints/hypotheses

Missing data

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Margaret Mooney
National Cancer Institute

November 10, 2011 • Washington, DC

Bevacizumab in Combination with Chemotherapy in Advanced Colorectal Cancer

- Bevacizumab in combination with chemotx was shown to improve overall survival (OS) in the 1st line & 2nd-line clinical setting for patients with metastatic colorectal cancer (mCRC) who had not previously received bevacizumab

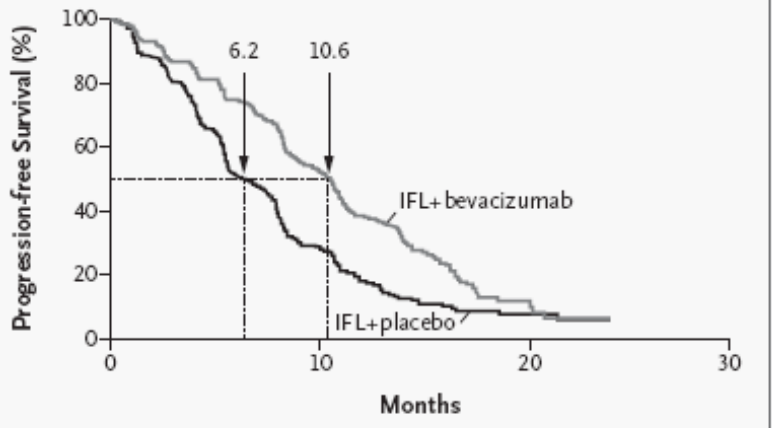
- An observational cohort study of bevacizumab combined with chemotx as used in clinical practice for 1st-line tx of mCRC suggested that continued vascular endothelial growth factor inhibition beyond initial progressive disease (PD) could improve OS for patients

- Randomized phase 3 studies were designed to evaluate if there was a survival advantage with continued use of bevacizumab in 2nd-line setting after initial tx with agent in combination with chemotx in 1st line setting

Phase III Trial of Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Previsouly Untreated Metastatic Colorectal Cancer

813 patients with previously untreated mCRC were randomized to:

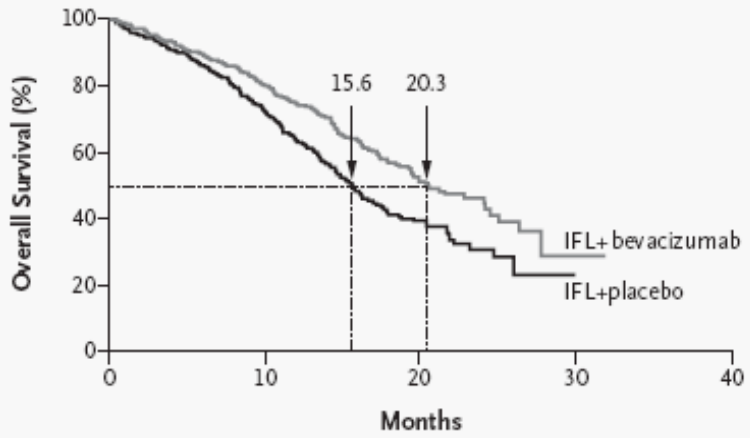
- **IFL plus bevacizumab**
- **IFL Alone**



No. at Risk						
IFL+bevacizumab	402	269	143	36	6	0
IFL+placebo	411	225	73	17	8	0

Figure 2. Kaplan–Meier Estimates of Progression-free Survival.

The median duration of progression-free survival (indicated by the dotted lines) was 10.6 months in the group given irinotecan, fluorouracil, and leucovorin (IFL) plus bevacizumab, as compared with 6.2 months in the group given IFL plus placebo, corresponding to a hazard ratio for progression of 0.54 (P<0.001).



No. at Risk								
IFL+bevacizumab	402	362	320	178	73	20	1	0
IFL+placebo	411	363	292	139	51	12	0	0

Figure 1. Kaplan–Meier Estimates of Survival.

The median duration of survival (indicated by the dotted lines) was 20.3 months in the group given irinotecan, fluorouracil, and leucovorin (IFL) plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo, corresponding to a hazard ratio for death of 0.66 (P<0.001).

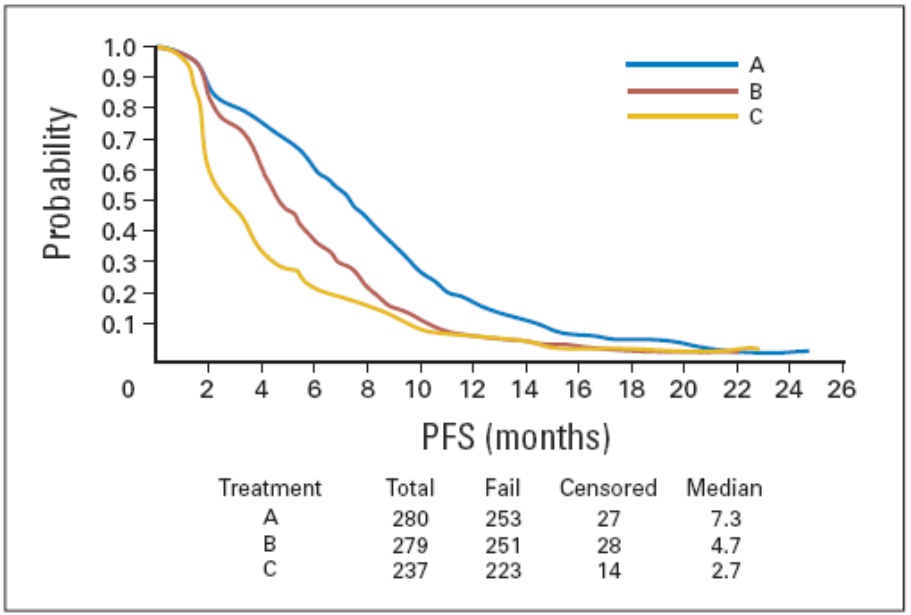
Hurwitz H, Fehrenbacker L, Novotny W, et al. N Engl J Med 2004;350:2335-42.

Bevacizumab in Combination With Oxaliplatin, Fluorouracil, and Leucovorin (FOLFOX4) for Previously Treated Metastatic Colorectal Cancer: Phase III Study E3200

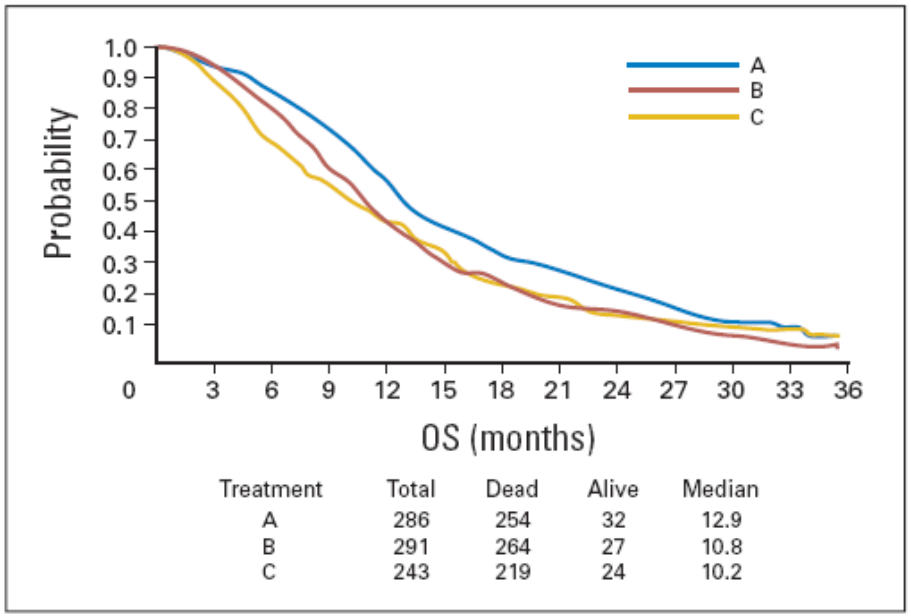
829 patients previously treated with a fluropyrimidine and irinotecan were randomized between Nov. 2001 and April 2003 to:

- **FOLFOX4 + Bevacizumab (Arm A)**
- **FOLFOX4 Alone (Arm B)**
- **Bevacizumab (Arm C)**

Bevacizumab alone arm was stopped early at an Interim Analysis on DSMB recommendation



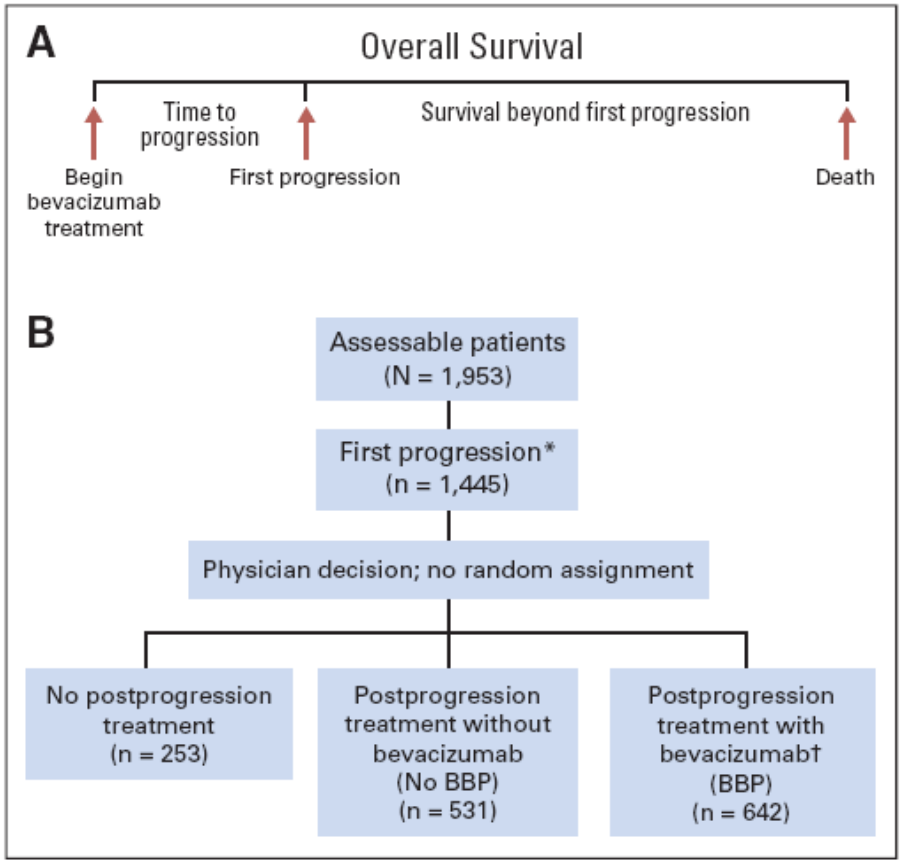
Treatment	Total	Fail	Censored	Median
A	280	253	27	7.3
B	279	251	28	4.7
C	237	223	14	2.7

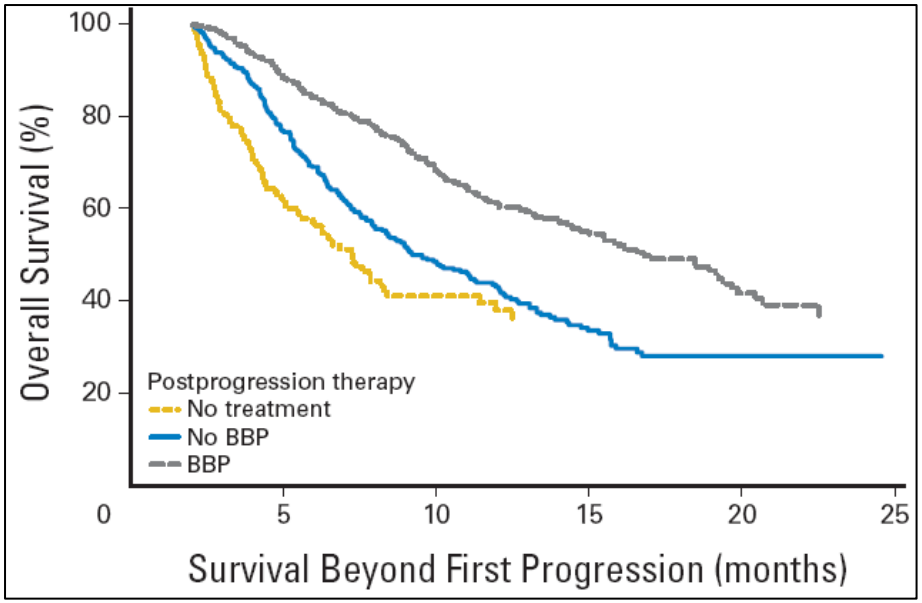


Treatment	Total	Dead	Alive	Median
A	286	254	32	12.9
B	291	264	27	10.8
C	243	219	24	10.2

Giantonio BJ, Catalano PJ, Meropol NJ, et al. J Clin Oncol 2007;25:1539-1544.

Results From a Large Observational Cohort Study (BRiTE): Bevacizumab Beyond First Progression Is Associated With Prolonged Overall Survival in Metastatic Colorectal Cancer

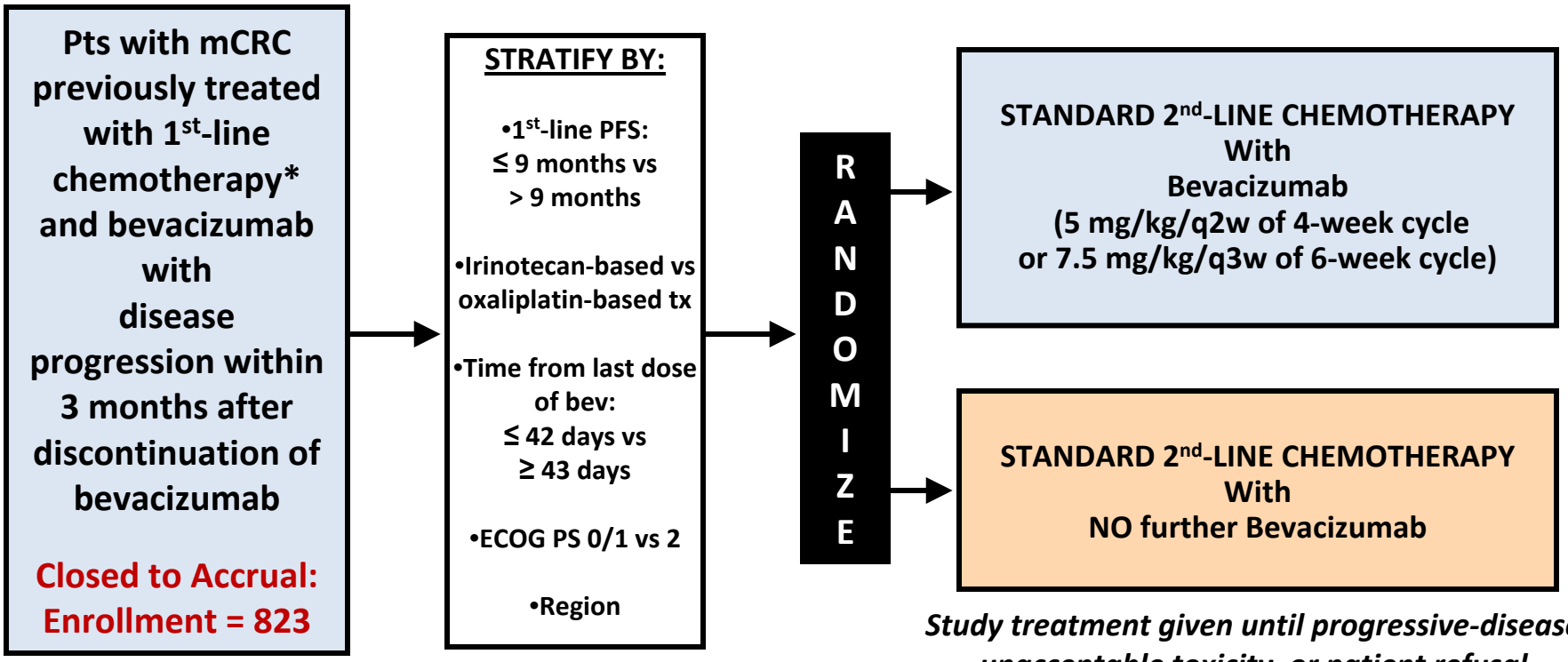




Survival starting from 2 months after 1st PD for patients who initiated post-PD therapy ± bevacziumab within 2 months from 1st PD

Grothey A, Sugrue MM, Purdie DM et al. J Clin Oncol. 2008 Nov 20;26(33):5326-5334

A Randomized Phase III Study: Effect of Adding Bevacizumab to Crossover Fluoropyrimidine-Based Chemotherapy (CTx) in Patients with mCRC and Disease Progression under 1st-line Standard CTx/Bevacizumab Combination *ML 18147 (formerly AIO_0504)*



Study treatment given until progressive-disease, unacceptable toxicity, or patient refusal.

In case of oxaliplatin- or irinotecan-related discontinuation, the flurorpyrimidine & bevacizumab should be continued.

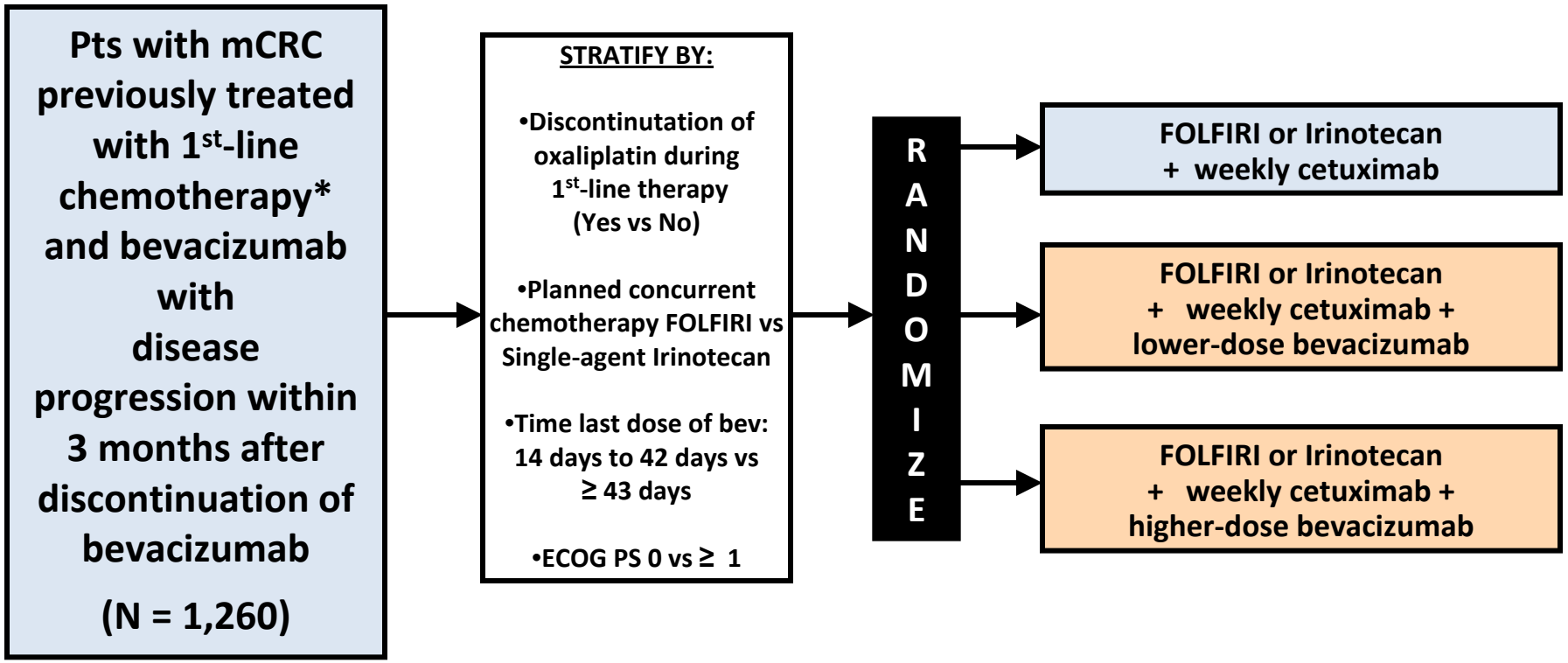
Endpoints: OS, PFS

*** 1st-line therapy: Bev + fluoropyrimidine/Oxaliplatin-based or Bev + fluoropyrimidine/Irinotecan based CTx**

Study Start Date Nov. 2005; Closed to Accrual; Estimated Study Completion Date: March 2012
ClinicalTrials.gov Identifier: NCT00700102 - accessed 11-1-2011

Phase III Trial of Irinotecan-Based Chemotherapy (CTx) Plus Cetuximab ± Bevacizumab as 2nd-Line Therapy for mCRC after Progression on Oxaliplatin-Based CTx with Bevaciuzmab

S0600/iBET - Initial Design of Trial When Activated in 2007



Primary endpoint: OS (90% power for HR 1.3 for improvement of 12 to 15.6 months for pairwise comparison for each BV arm to the CTx + Cetuximab arm with one-sided 0.0125 test for each of the 2 main comparisons)

* 1st-line therapy: Bev + FOLFOX, OPTIMOX, or XELOX

Activated 6/15/2007 and Closed 11/10/2010 due to poor accrual (iBET = Intergroup Bevacizumab Continuation Trial

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Sanofi-Aventis

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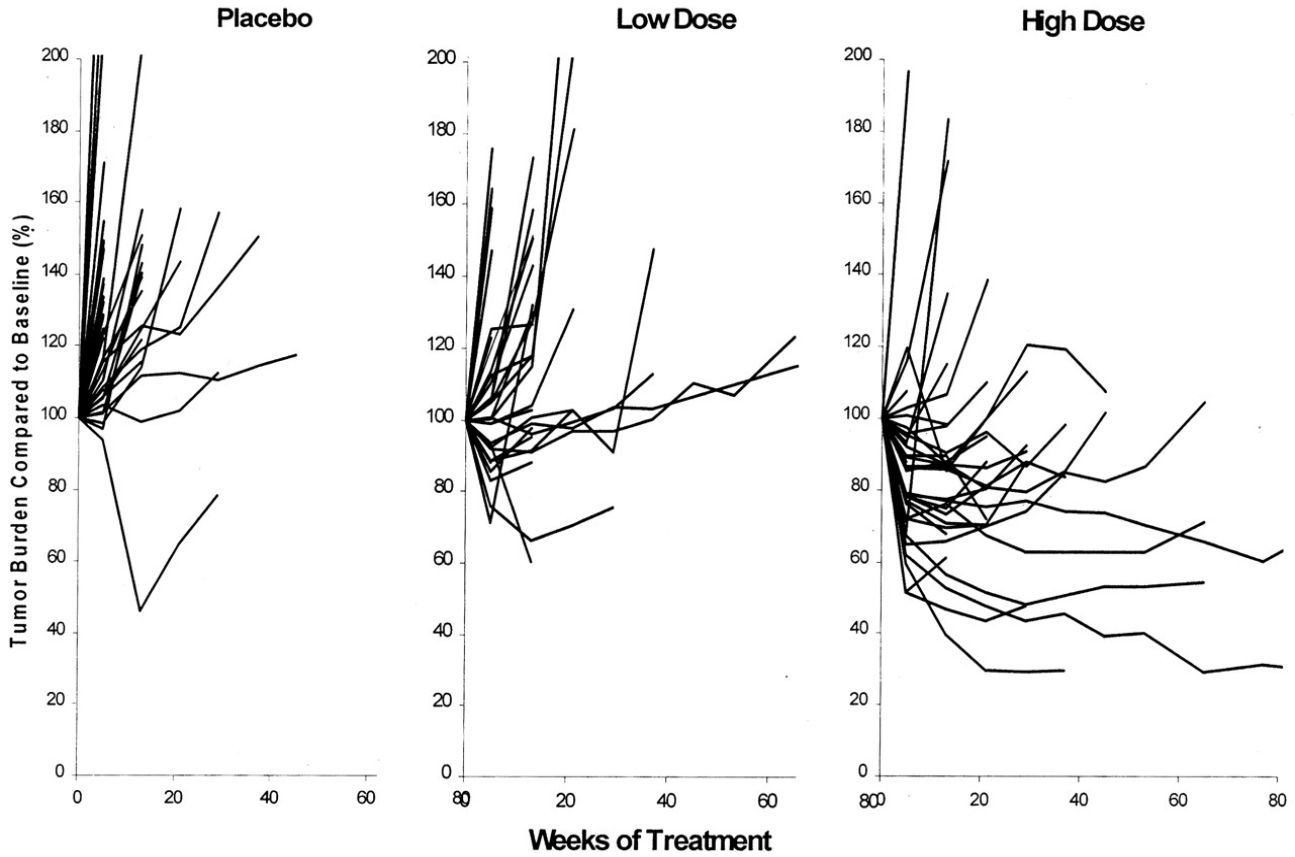
Bevacizumab as a single agent in RCC clearly delays the growth of tumors

Total measured tumor burdens (sum of products of perpendicular diameters) depicted as percentage of baseline burden for each patient with metastatic renal cancer during treatment with either placebo, 3 mg/kg of bevacizumab, or 10 mg/kg of bevacizumab



Yang J C Clin Cancer Res 2004;10:6367S-6370S

AACR Clinical Cancer Research

But does not improve OS—accelerated progression after discontinuation?

Stein, Yang, Bates et al. ***The Oncologist*** 2008;13:1055–1062

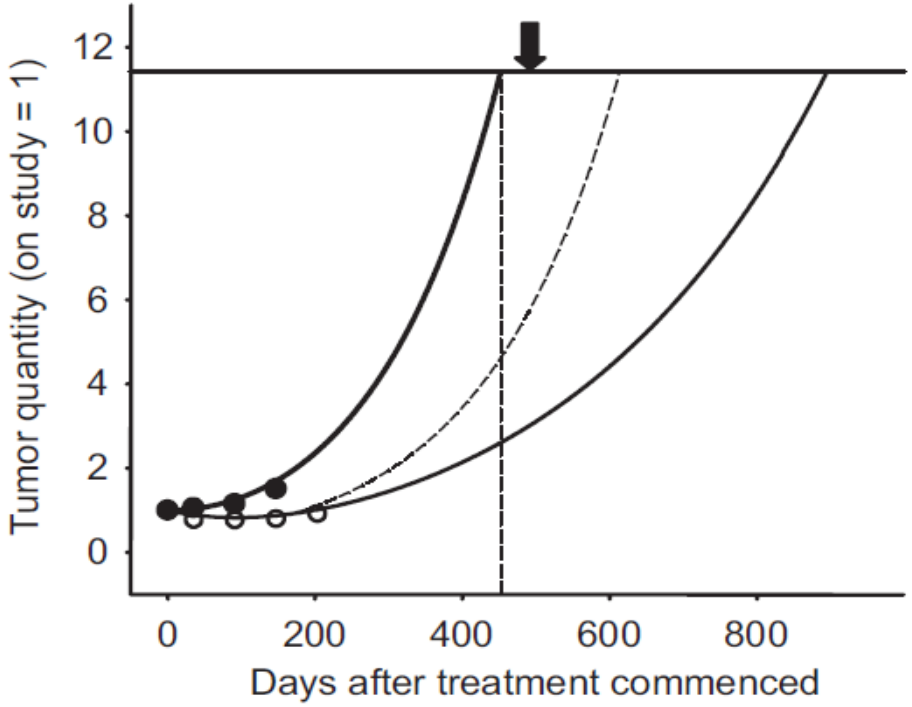


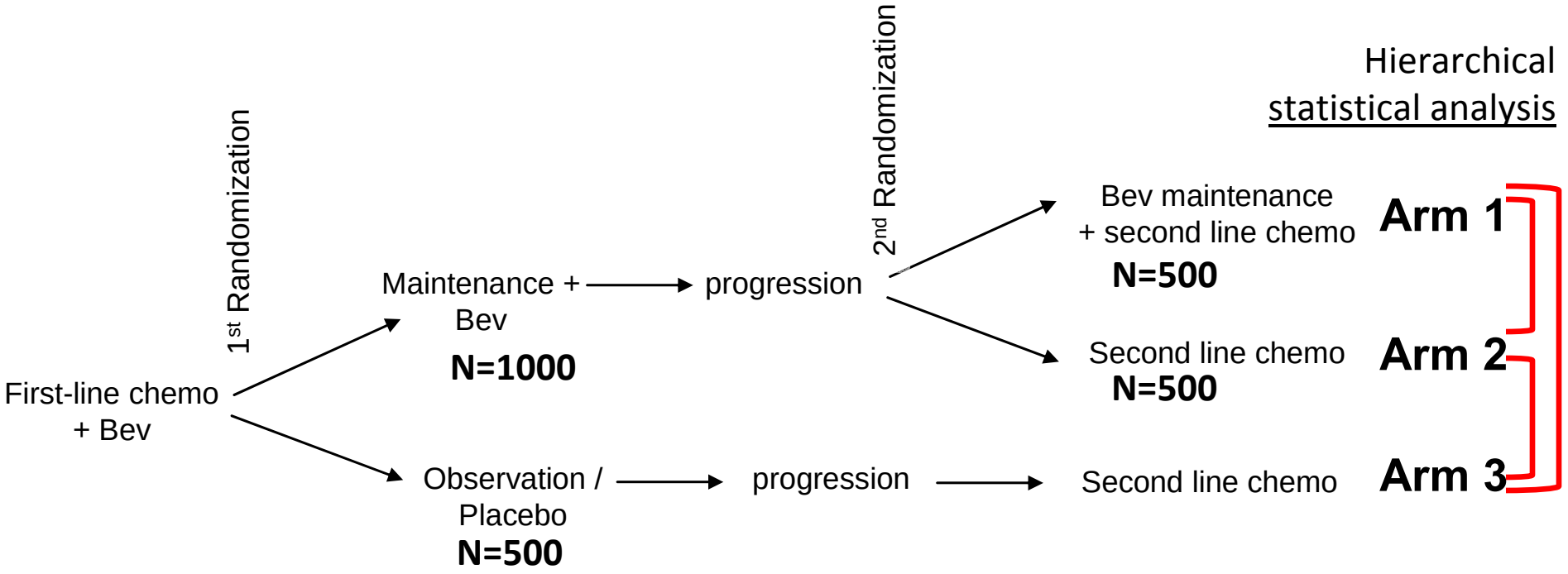
Figure 5. Theoretical predictions based on the *median* data for patients in the placebo and high-dose bevacizumab arms of the study.

Continuing anti-cancer treatment for maintenance of clinical benefit:

How to discern whether anti-VEGF therapy should be given beyond combination with chemo?

- Treat continuously *vs.* placebo until progression but power for OS?
- Treat continuously *vs.* placebo through progression, including second line of chemo? (long and complicated, many will drop out)
- Define accepted new paradigms of what constitutes clinical benefit?

Scenario 2: Continuation Maintenance



*** Assuming we're looking for a HR of 0.8 with a power of 80%, such a study in ovarian cancer would require ~1500 patients with an accrual rate of 300/year.**
*** The statistical analysis plan allows for greater efficiency by hierarchical determination first of whether anti-VEGF should be given continuously (comparing arm 1 to 3), then by evaluating what happens when it is stopped at progression (by comparison first to arm 1 then to arm 3)**

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