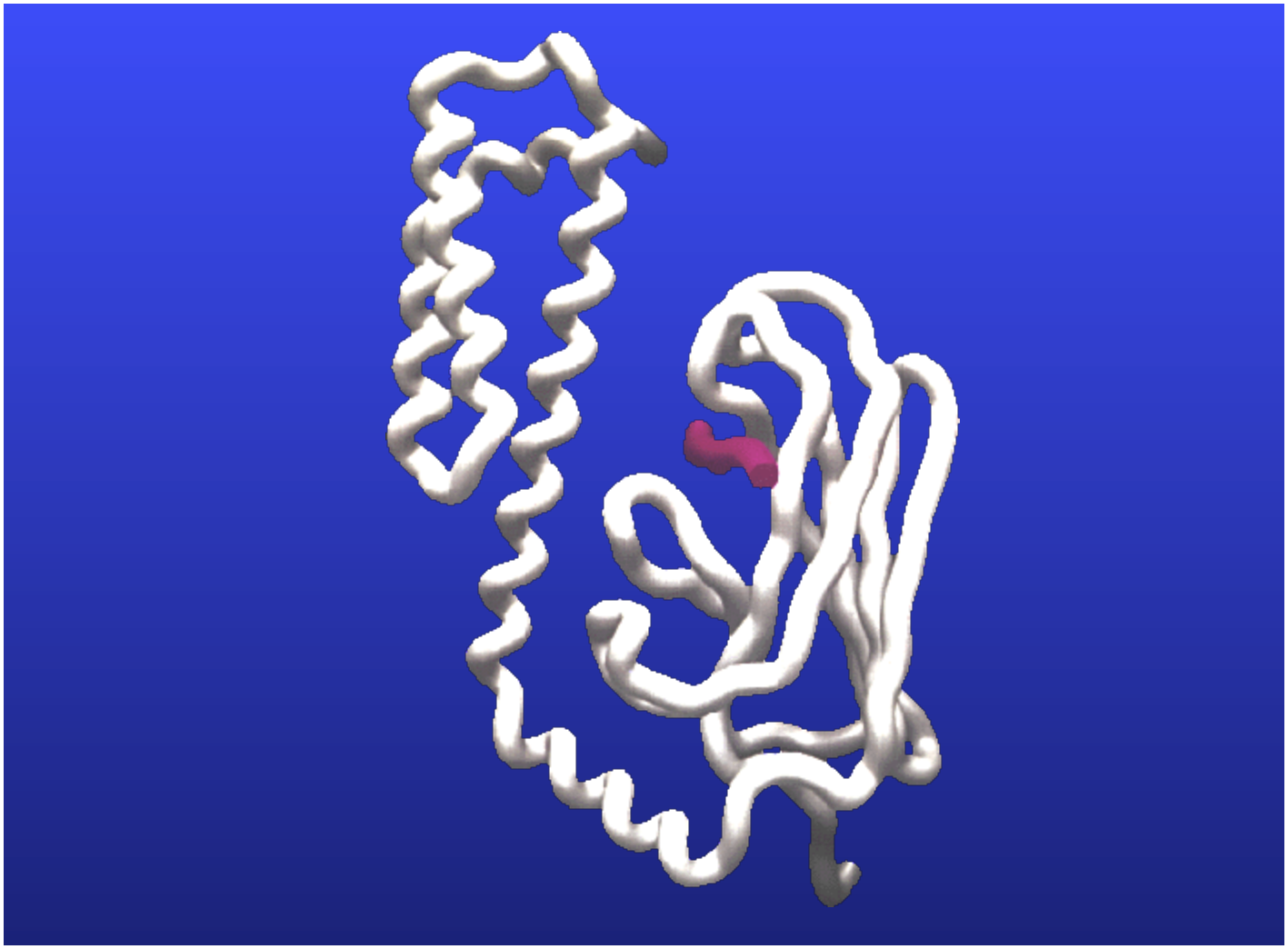
Substrate Binding by DnaK (HSP70 family)

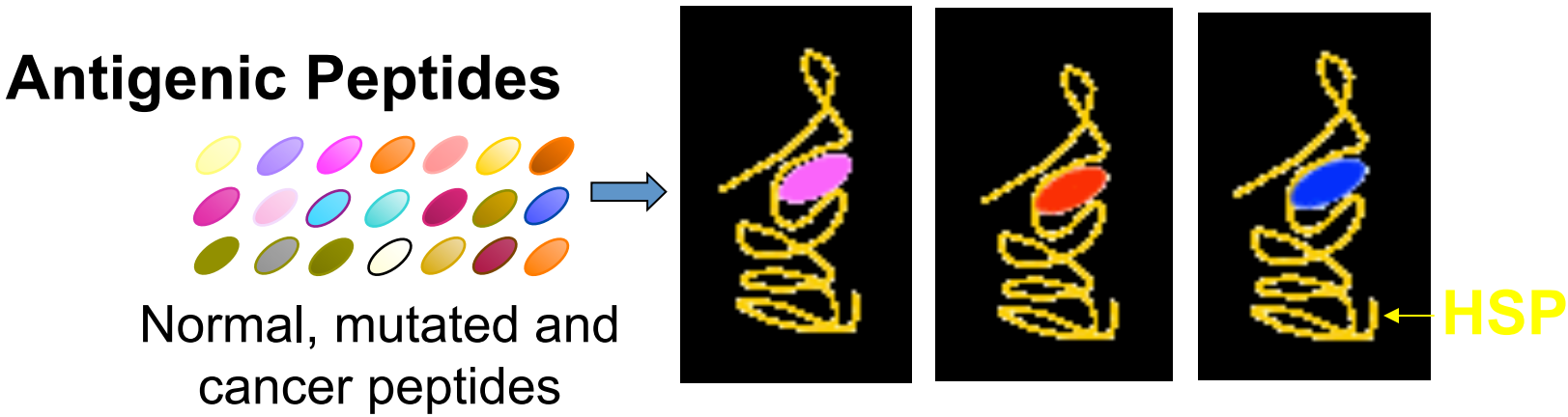


Zhu X *et al*. *Science* 1996;272:1606–1614.

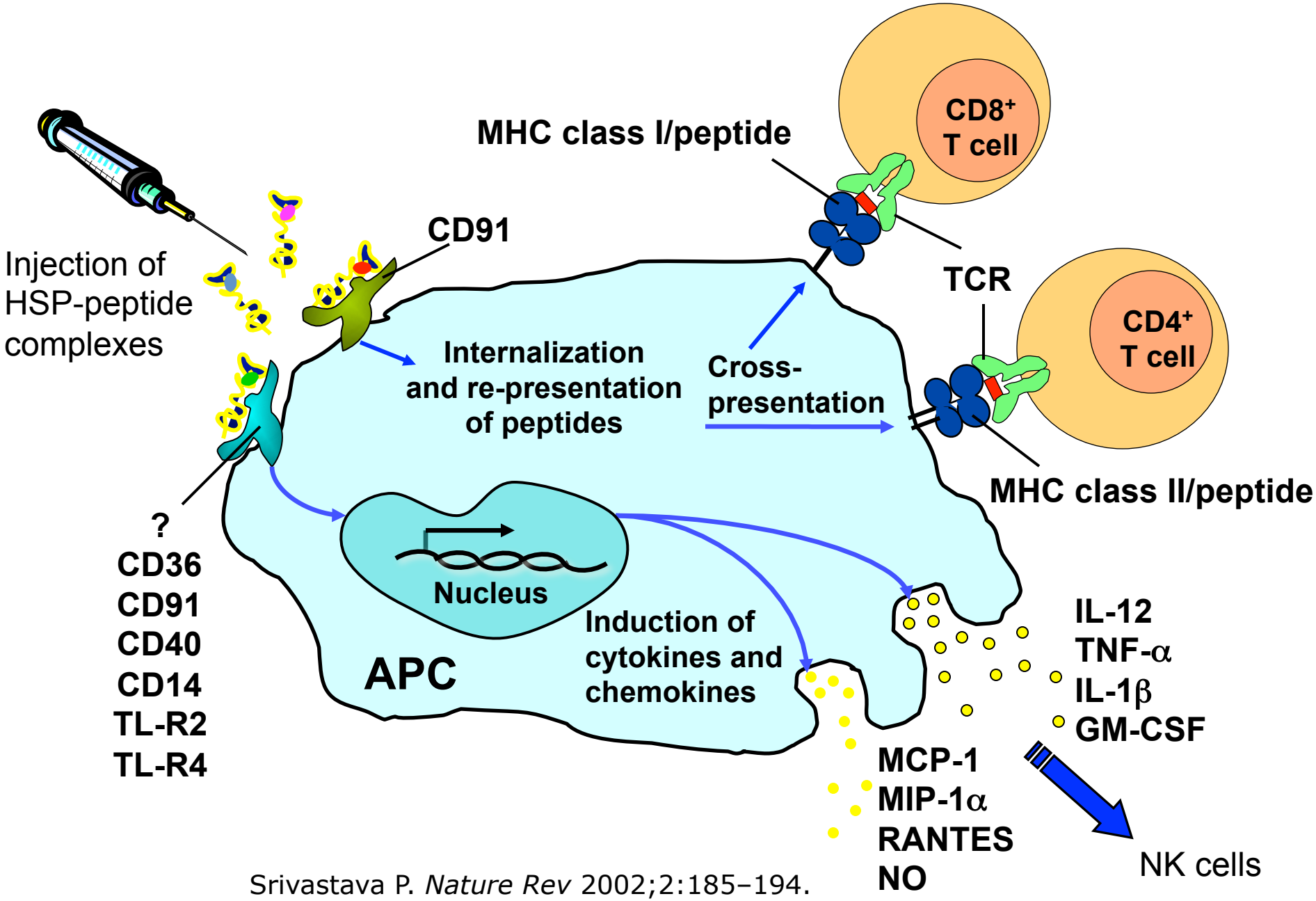
Antigenic Peptides Bind to HSPs

HSPs Bind Peptides: Normal, Mutated and Cancer Peptides

HSPs function as peptide chaperones in every nucleated cell



Mechanism of Action



Srivastava P. *Nature Rev* 2002;2:185–194.

Oncophage Manufacturing: Purification

Primary recovery

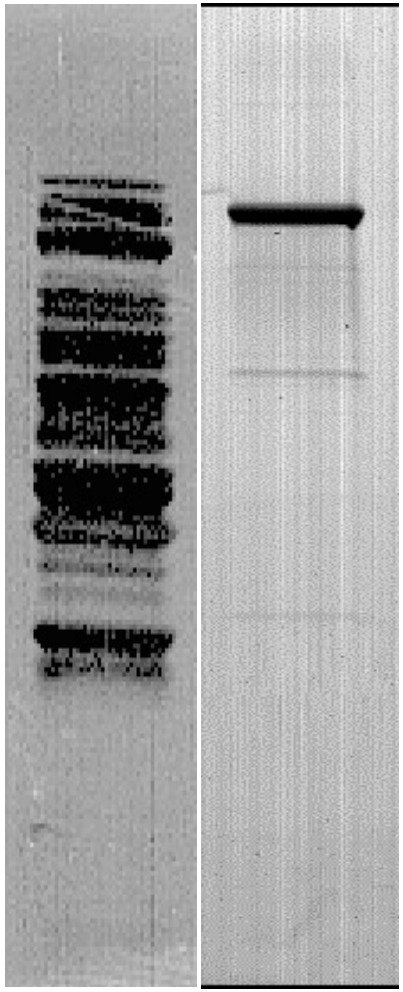
Tissue processing (break open cells) → Remove solids (clarification)

Purification

Affinity chromatography → Ion-exchange chromatography

Finishing

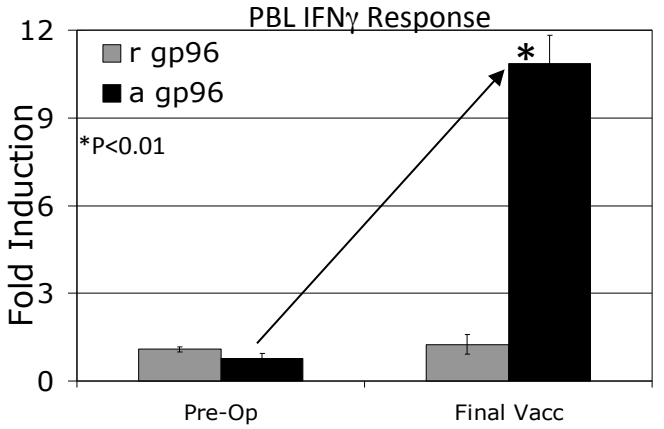
Buffer exchange → Sterile filtration → Vial fill

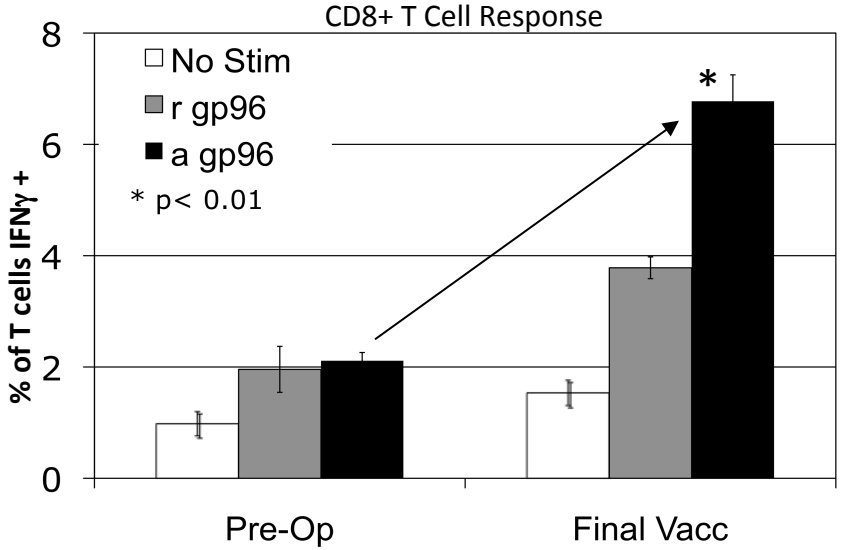


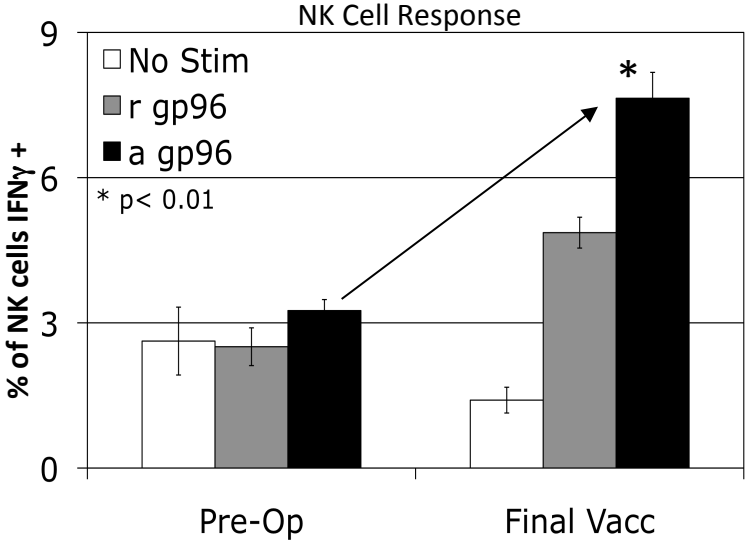
Adaptive and Innate Immune Responses

Phase 2 Multi-Center

Adaptive immune responses (CD8+) and innate immune responses (NK) are measured in an ex vivo antigen presentation assay controlled for non-specific effects of HSP with recombinant HSP (r gp96). For patients who undergo resection after vaccination at progression site, directed brain biopsies were performed to assess extent of gamma interferon positive CD 8 + T cells and NK cells. All patients tested to date have demonstrated a significant Adaptive and Innate Immune response peripherally, and at the site of tumor resection in situ when biopsies were performed. A typical patient's response profile is shown here; demonstrating significant peripheral and site specific anti-tumor immunity. This patient received a total of 8 injections of HSPPC-96 and underwent biopsy for suspicion of disease progression.



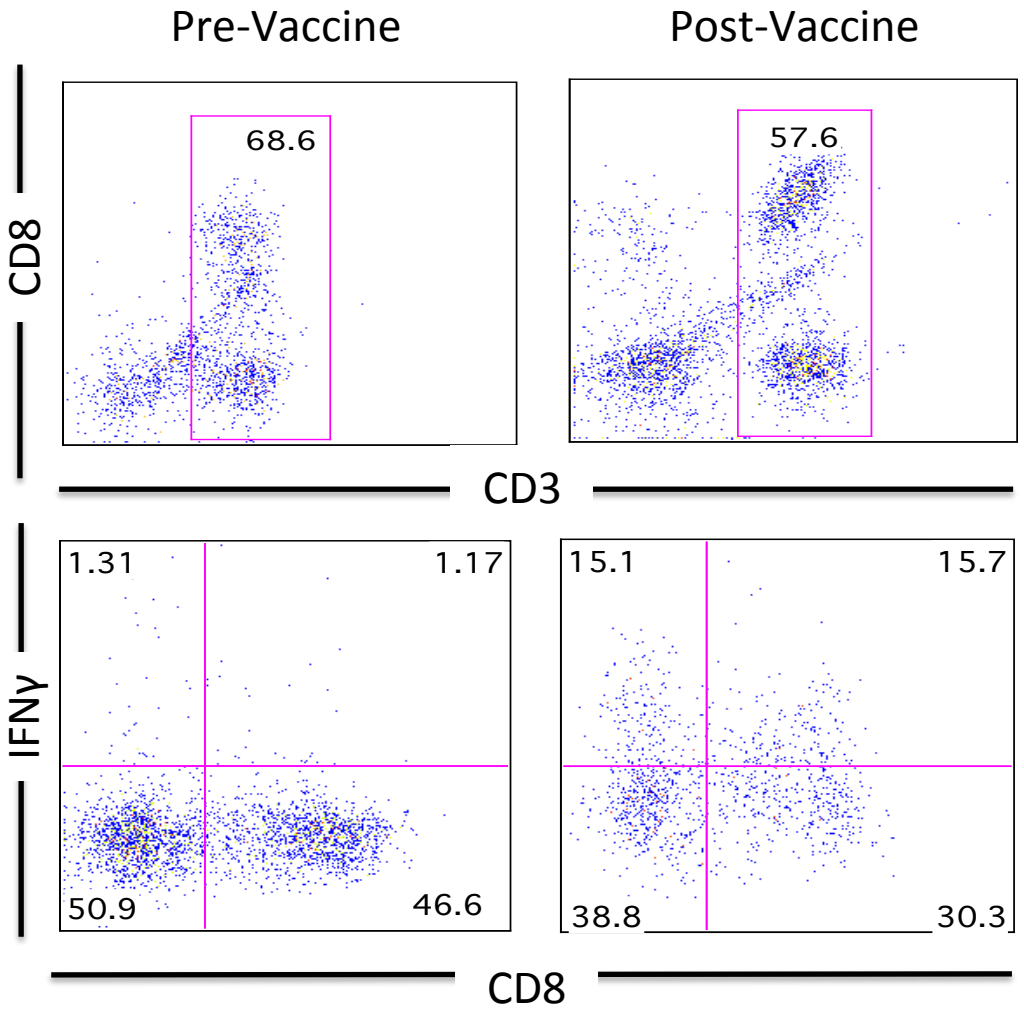




Parsa et al. *J Clin Oncol* 29: 2011 (suppl; abstr 2565)

Localization of CD8+ IFNγ T cells to Tumor Site

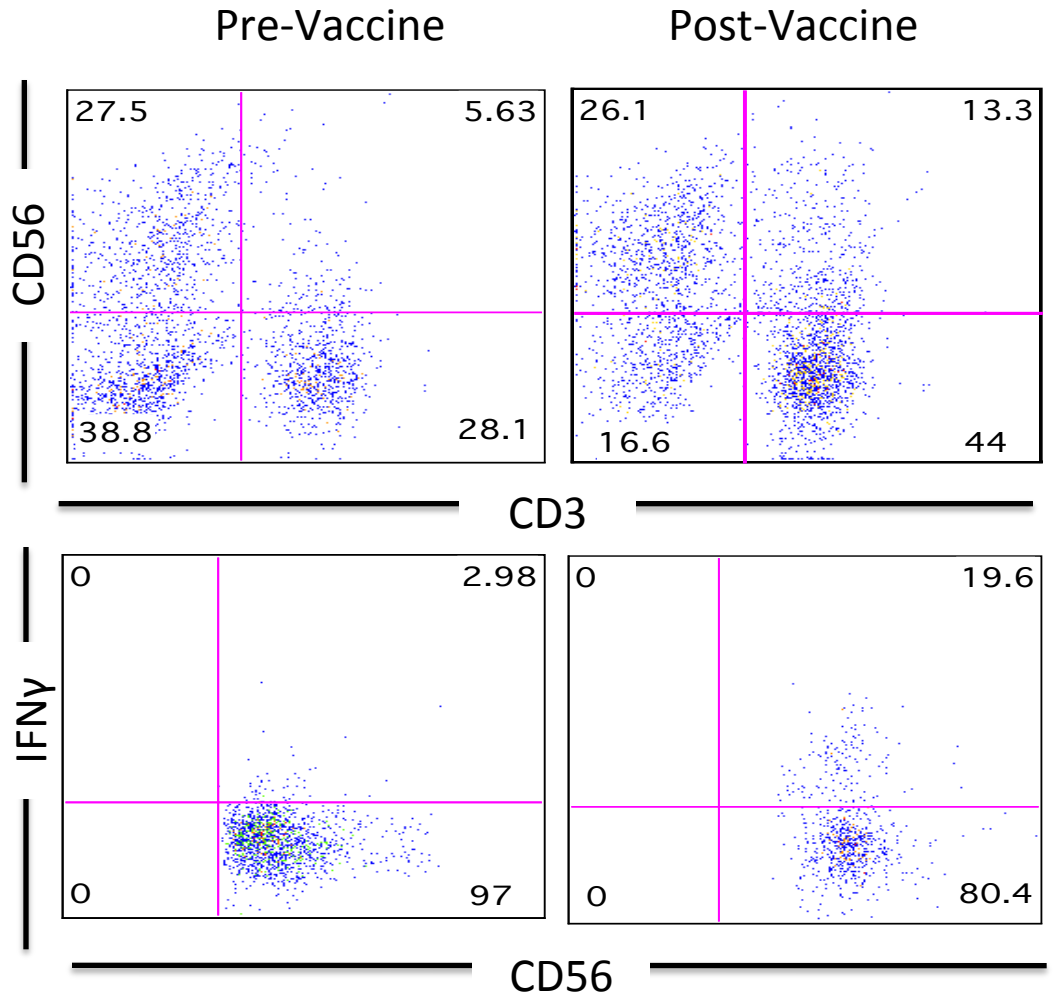
Phase 2 Multi-Center



Parsa et al. *J Clin Oncol* 29: 2011 (suppl; abstr 2565)

Localization of IFNγ+ Natural Killer cells to Tumor Site

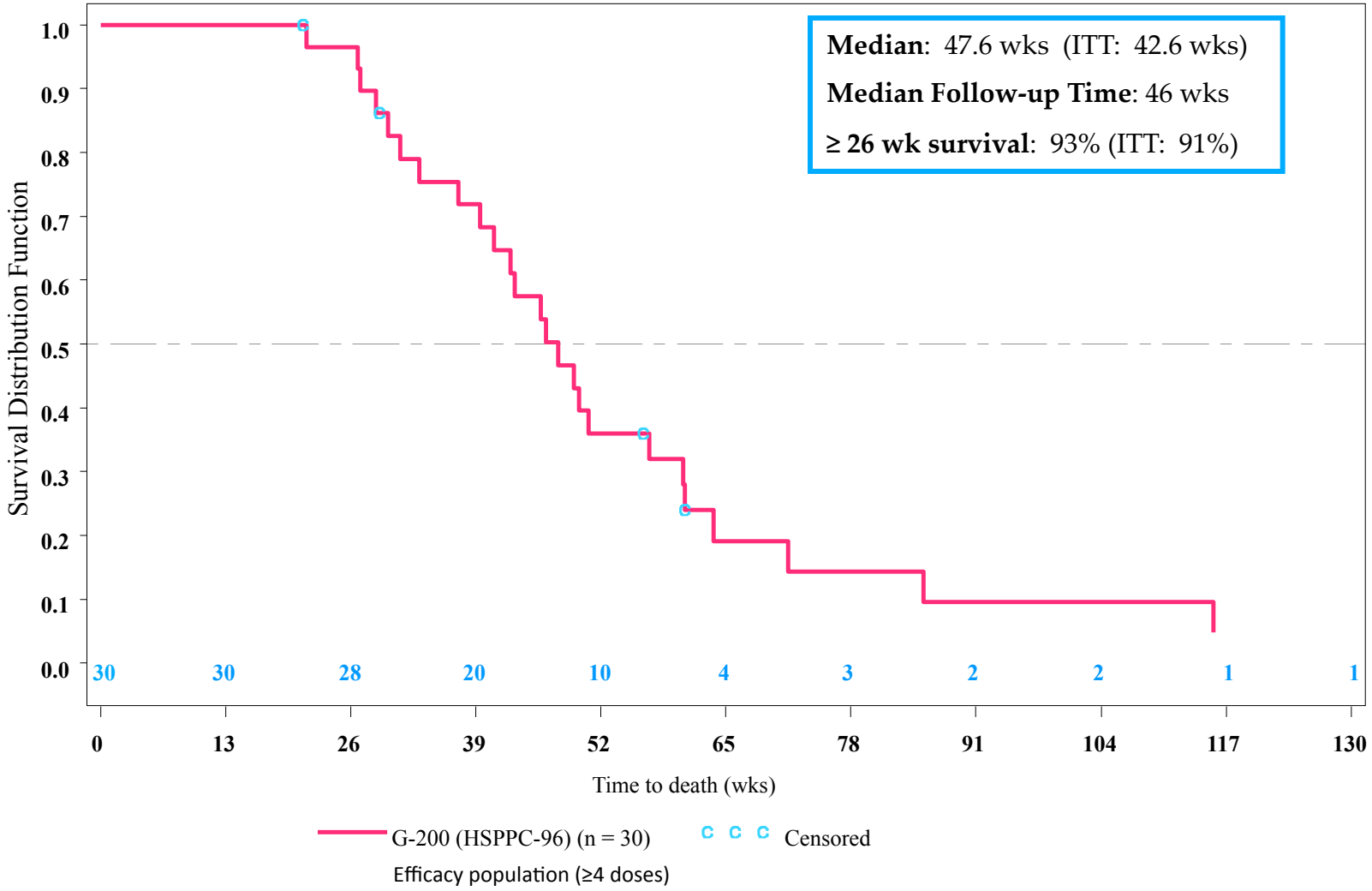
Phase 2 Multi-Center



Parsa et al. *J Clin Oncol* 29: 2011 (suppl; abstr 2565)

Overall Survival

Phase 2 Multi-Center



Parsa et al. *J Clin Oncol* 29: 2011 (suppl; abstr 2565)

Survival Outcomes Compared with Similar Surgical Populations

Data Set	Median Survival	6-Month Survival Rate
G-200	47.6 weeks	93%
Gliadel (Kumar et al., 2010)	39.8 weeks	62%
NABTC Phase 2 trials from Feb. 1998 – Nov. 2008 (Clarke et al., 2011)	31.4 weeks*	56%*
UCSF Contemporary Control Database**	32.8 weeks	68%

*From Table 4, combined data with surgery

**N=86, Jan. 2005 – Aug. 2009, recurrent GBM with surgery, median age = 53 years, all pts with primary GBM, all previously received Stupp protocol, none received G-200, median KPS = 90

Adverse Events Related to G-200

Phase 2 Multi-Center

Event	G-200 (N=33)
Number of Patients with as Least One Related Adverse Event	17 (51.5%)
Fatigue	4 (12.1%)
Injection Site Stinging	1 (3.0%)
Injection Site Reaction	14 (42.4.%)
Skin Desquamation	1 (3%)

No Related Grade 3 or 4 Adverse Events

Parsa et al. *J Clin Oncol* 29: 2011 (suppl; abstr 2565)

Specific Concerns That We Addressed

1) Proposed eligible patient population, single agent activity of the HSPPC-96 vaccine in GBM, and uncertain clinical benefit of bevacizumab in the study patients (post-complete surgical resection of the GBM recurrence)—implications for the control and experimental arms.

2) Broadening the eligibility to include patients with residual disease after resection of the GBM recurrence.

3) The study is designed with a very optimistic view of the effect size which is not sufficiently supported bythe available data. At the same time, type I error rate is relaxed to control the sample size. A more conservative estimate of the effect size and tighter error rates should be considered.

4) Study should be monitored for futility and be closed for if the desirable effect is found to be an unlikely outcome.

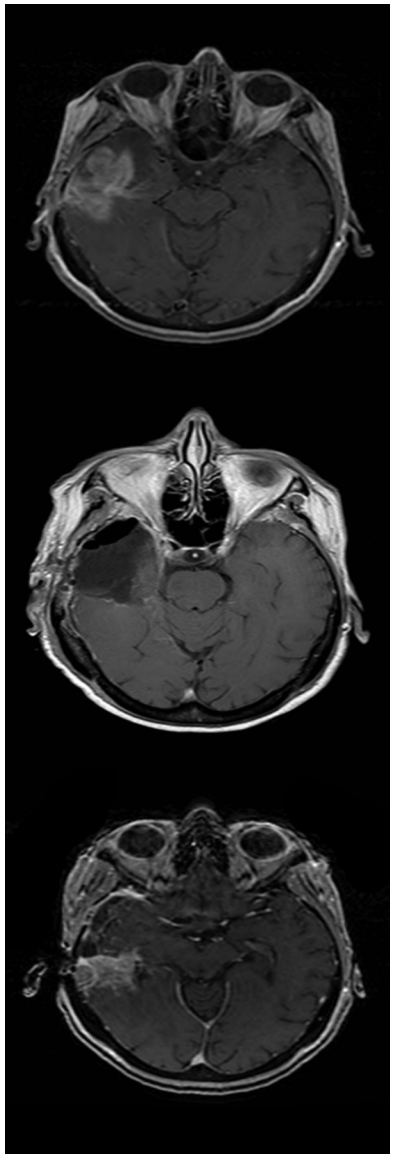
5) QOL and PRO outcomes should be evaluated.

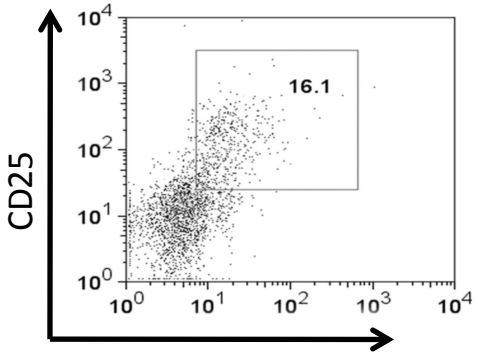
6) Previous failure of HSPPC-96 in renal cell carcinoma and melanoma

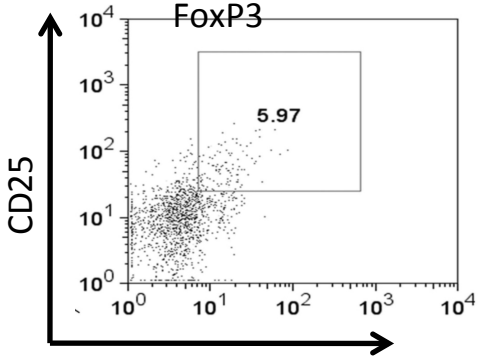
Pre-surgery

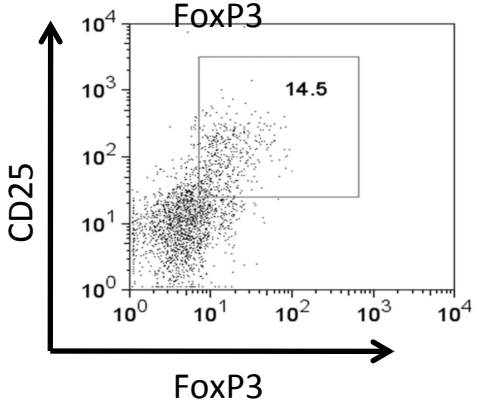
Post-surgery

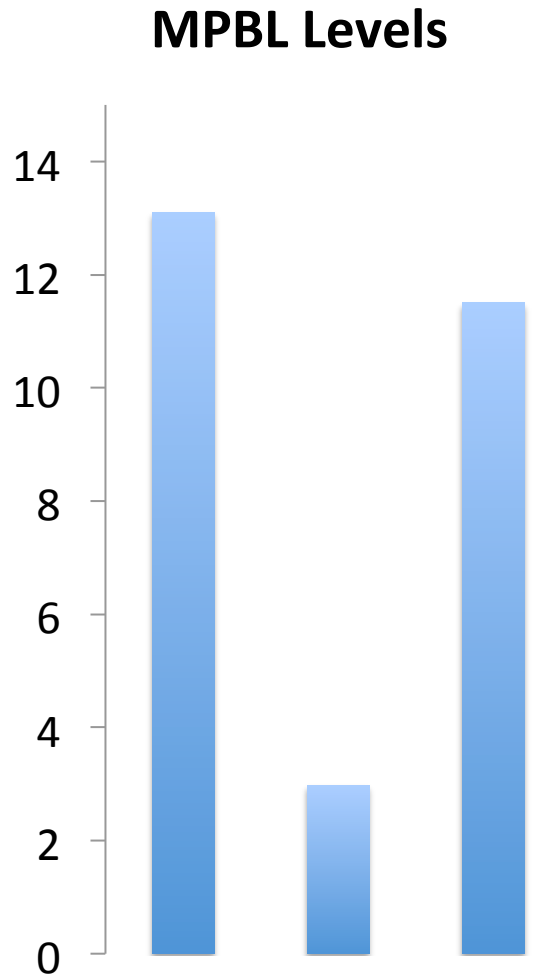
Recurrence





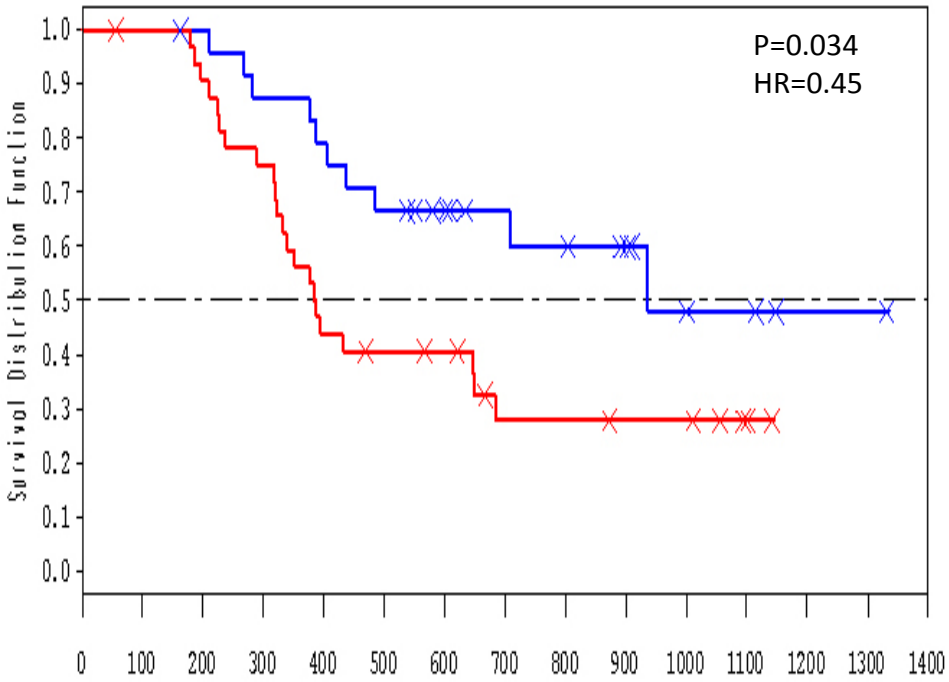






HSPPC in Patients With Less Tumor Burden

Melanoma M1a+M1b

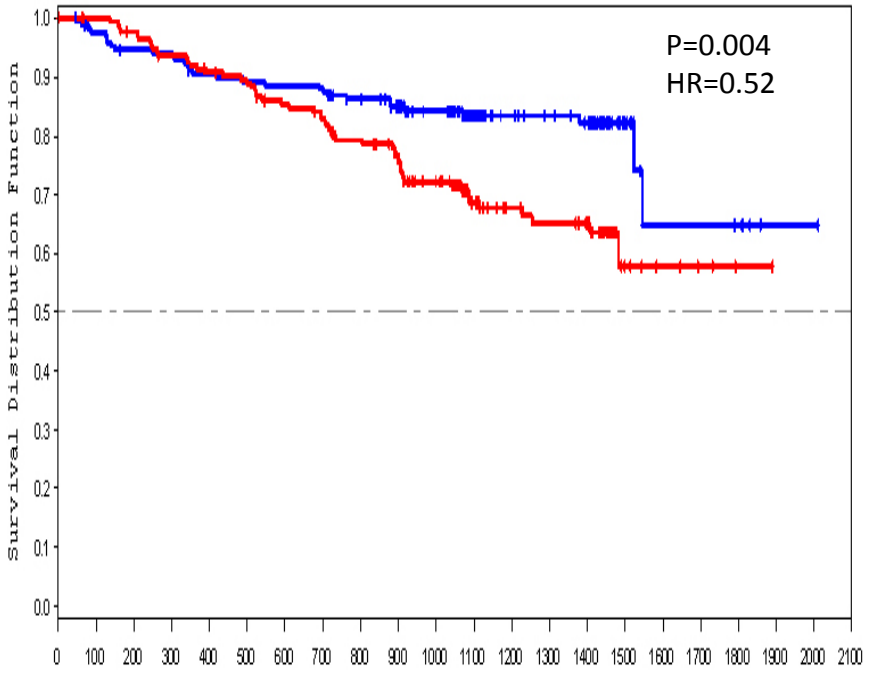


HSPPC-96 (N=25)
XXX Censored

PC (N=33)
XXX Censored

Testori et al. *J Clin Oncol*. 2008;26(6):955-962.

RCC Intermediate Risk



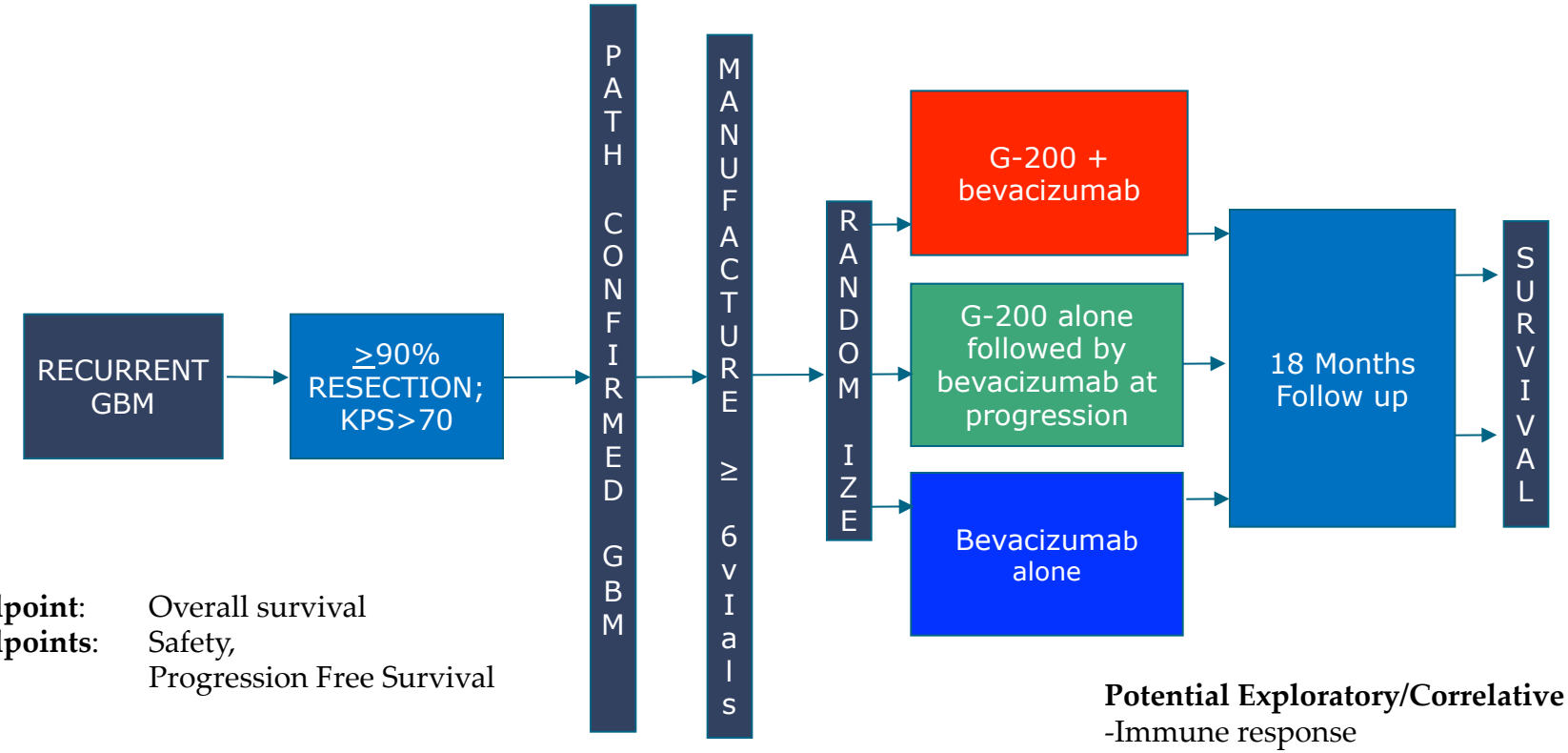
HSPPC-96 (N=184)
| | | Censored

Observation (N=178)
| | | Censored

Wood C et al. *Lancet*. 2008;372(9633):145-154.

“Alliance Trial” G-200+Bevacizumab

Multi-center, three arm, randomized trial



1º Endpoint: Overall survival
2º Endpoints: Safety,
Progression Free Survival

Sample Size: HR: 1.5 (estimates 13.5 months median survival in combination arms vs. 9 months in bevacizumab
α (1-sided) = 0.05; Power = 80%
Randomized 1:1:1; N = 255 (85 per arm)

Potential Exploratory/Correlative Studies:
-Immune response
-B7H1 expression
-PI3 Kinase activation
-Molecular profiling
(initial tumor tissue and on biopsy at presumed progression)

Dosing: G-200 given id 1x per wk for 4 wks; every other wk thereafter up to 12 total injections (up to 5 months of treatment). Bevacizumab given as standard dose (10 mg/kg) every 2 wks