

A Phase II Study of Lonafarnib (LF) in Patients with Locally Advanced and Metastatic Breast Cancer (MBC): Hoosier Oncology Group BRE07-126 (Abstract #598)



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I. INTRODUCTION

- LF is a potent, specific, reversible farnesyl transferase inhibitor (FTI). FT is an enzyme that catalyzes the covalent attachment of a 15-carbon farnesyl group to conserved amino acid residues at the carboxy terminus of certain proteins.
- FTIs were initially developed to target the ras family of oncoproteins (H-ras, K-ras, and N-ras), G-proteins that exist in a mutated (oncogenic) form in about 30% of human cancers.
- Oral administration of LF blocked tumor growth of a variety of human xenografts (glioblastoma, lung, pancreatic, prostate, colon, bladder, and CML) in nude mice.
- LF inhibits growth both ER+ and ER-, as well as HER2+ and HER2- breast cancer

II. METHODS

I. STUDY DESIGN

- Multi-institutional phase II
- Open label
- Non-Randomized

II. KEY ELIGIBILITY CRITERIA

- Locally advanced or metastatic adenocarcinoma of the breast
- Measurable disease per (RECIST)
- Unlimited Prior Therapy
- ECOG Performance Status (PS) 0-1
- Adequate hematological, hepatic, renal function

III. STUDY OBJECTIVES

Primary Objectives:

- Determine progression-free survival (PFS)

Secondary Objectives:

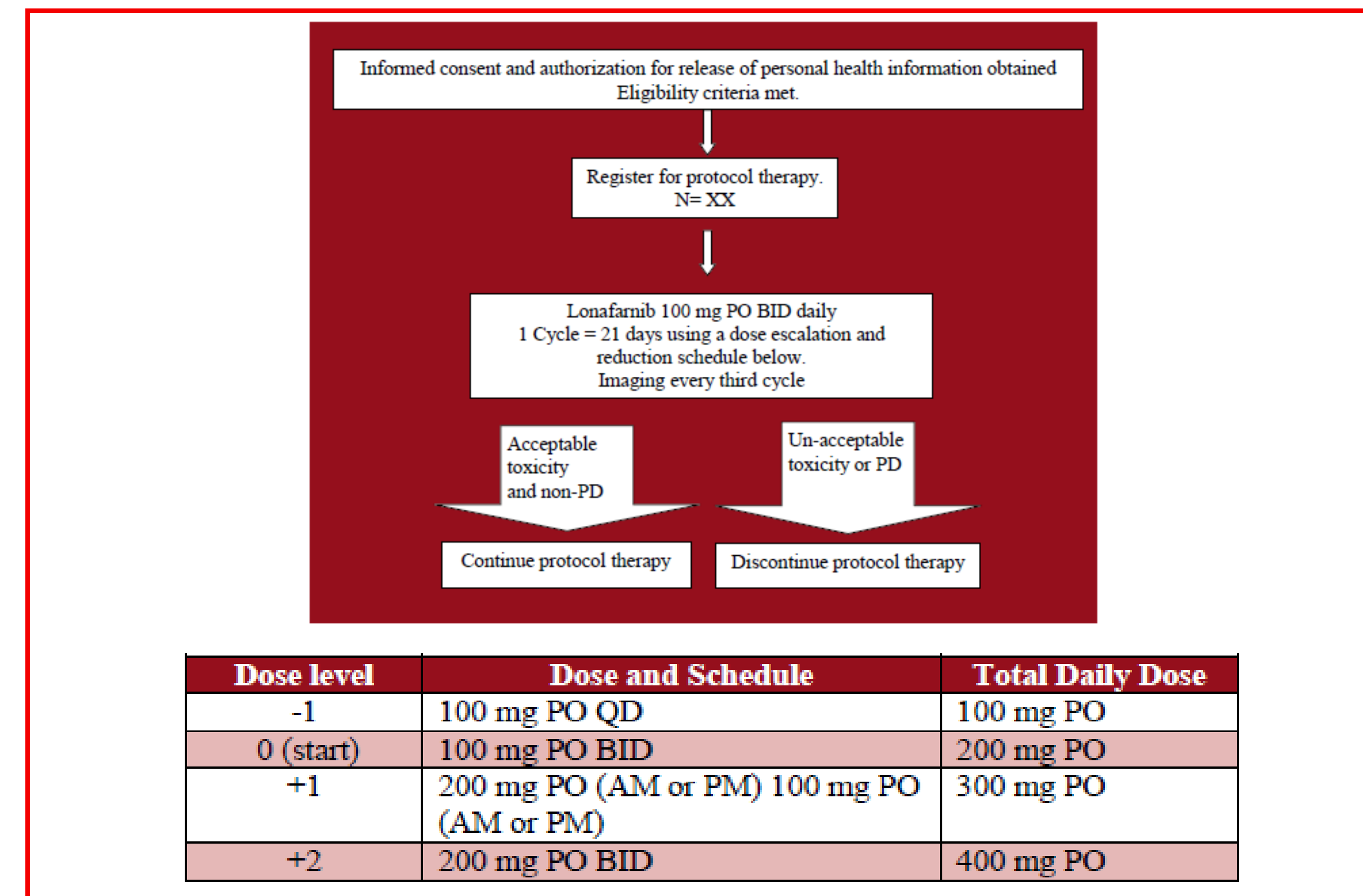
- Determine toxicity profile
- Determine overall response rate
- Determine the clinical benefit response rate (CR+PR+SD > 180 day duration).

IV. TREATMENT PLAN

Lonafarnib (LF):

- 21 day cycle
- Pt. 1-4 treated with 200mg PO BID daily, however, due to early onset of intolerable diarrhea, study design modified to a dose escalation model.
- Dose escalation started at 200mg PO daily up to 400mg PO daily.
- If LF was tolerated for 7 days, patients were escalated to 300mg total daily dose (TDD) and then 400mg TDD.

II. METHODS



III. RESULTS

Patient Characteristics

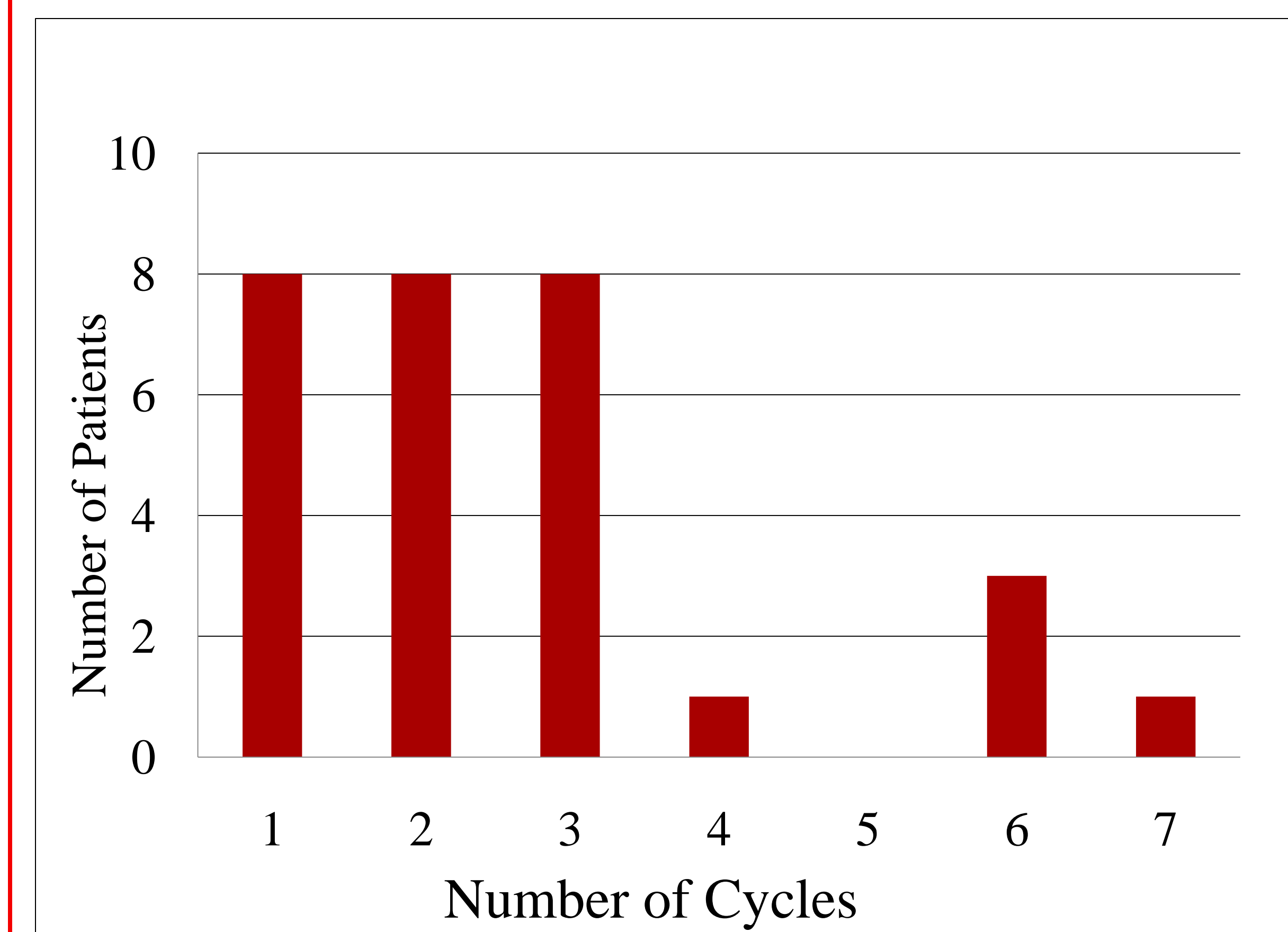
Patient Characteristics	Total
Patients Enrolled	29
Age (in years)	
Median (Range)	56 (41-76)
Sex	
Female/Male	29/0
Race	
White	26 (90%)
Black	3 (10%)
Ethnicity	
Hispanic/Latino	1 (3.5%)
Non-Hispanic	27 (93.1%)
Unknown	1(3.5%)
ECOG PS	
0	18 (62%)
1	11 (38%)
Primary Tumor Diagnosis (n=25)	
Breast Carcinoma	14 (12%)
Ductal Breast Carcinoma	20 (80%)
Lobular Breast Carcinoma	1 (4%)
Other	1 (4%)
ER/PR/HER2 Status	
ER (n=24)	
Negative	9 (37.5%)
Positive	15 (62.5%)
PR(n=24)	
Negative	13 (54%)
Positive	11 (46%)
HER2(n=24)	
Negative	17 (71%)
Positive	3 (12.5%)
Unknown	4 (16.5%)
Number of Prior Therapies (n=29)	
Median (Range)	8.4 (0-20)

III. RESULTS

Most Frequent Toxicity ≥ Grade 3

TOXICITY	Grade 3/4	Grade 5	Percentage
Diarrhea	6		23%
Dehydration	2		8%
Encephalopathy		1	4%
Disease Progression NOS		1	4%

Number of Cycles Administered (n=29)



Response

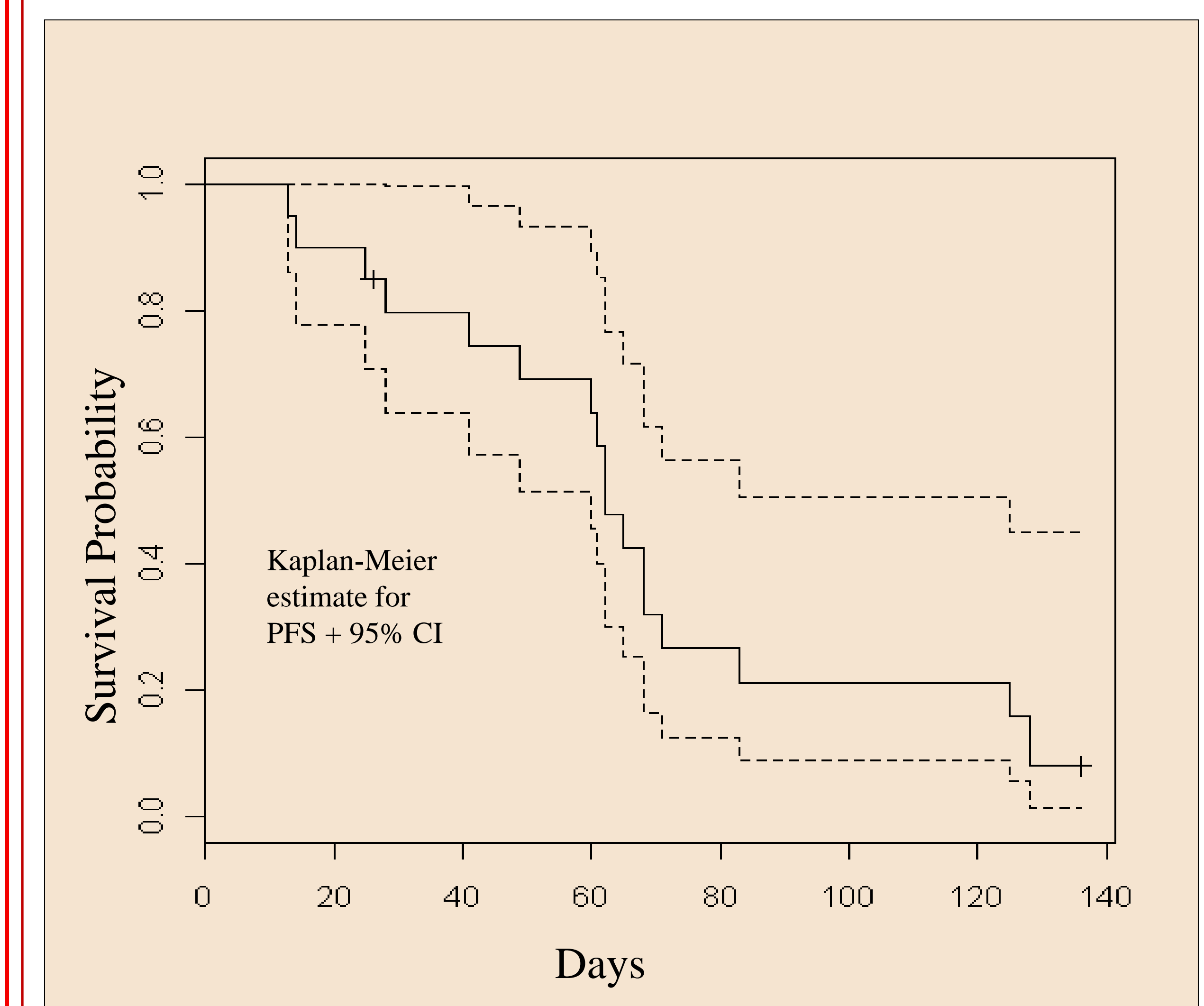
Best Response	Total Patients (n=17)	Percentage
CR	0	0
PR	0	0
SD	5	29%
PD	12	71%

Overall Response Rate n=17 (PR+CR): 0
Clinical Benefit Rate n=20 (CR+PR+SD>180days): 0

III. RESULTS (continued)

Progression Free Survival in Days (n=20)

Mean	Median (95% CI)	Range
65.5	62 (60,125)	13-136



IV. CONCLUSIONS

- Results based on 20 pts do not support improved PFS or ORR compared to historical controls
- Further follow up and biomarker correlations are ongoing

V. REFERENCES

- Greenberg PA, Hortobagyi GN, Smith TL, Ziegler LD, Frye DK, Buzdar AU. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. J Clin Oncol 1996;14(8):2197-205.
- Gasparini G. Angiogenesis in breast cancer. Role in biology, tumor progression, and prognosis. In: Bowcock A, ed. Breast Cancer: Molecular Genetics, Pathogenesis, and Therapeutics. Totowa, NJ: Humana Press Inc.; 1999:347-71.