UW/SCCA Institutional Experience with Single Agent Ipilimumab in Advanced Unresectable/Metastatic Melanoma

Nichole Pelz

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Masters of Public Health

University of Washington

2015

Reading Committee:

Ian Painter, Chair

Shailender Bhatia, Committee

Program Authorized to Offer Degree:

Executive Masters of Public Health

University of Washington

Abstract

UW/SCCA Institutional Experience with Single Agent Ipilimumab in Advanced Unresectable/Metastatic Melanoma

Nichole Pelz

Chair of the Supervisory Committee:
Ian Painter, Clinical Assistant Professor,
Health Services

Background: Ipilimumab immunotherapy was the first treatment ever to be associated with improved survival in a phase III clinical trial of patients with metastatic melanoma and was approved by the US Food and Drug Administration (FDA) in 2011. However, the response rates with ipilimumab are low (~10%) and toxicities considerable. The optimal dose and schedule still remain unclear and there is an unmet need to identify predictors of clinical benefit. To gain further insight into some of these questions, we performed this retrospective study of metastatic melanoma patients treated at the Seattle Cancer Care Alliance (SCCA).

Methods: We performed a chart review on 126 patients with metastatic melanoma treated with single agent ipilmumab from 2006 to 2012 at the SCCA. These patients had received ipilimumab at either the investigational 10 mg/kg dose (with maintenance scheduling) or the 3 mg/kg dose (without maintenance, similar to the FDA approved dose). Efficacy and safety outcomes and baseline characteristics were subjected to univariate analysis. Efficacy endpoints included overall survival (OS), progression free survival (PFS), objective response rate (ORR) and Duration of Clinical Benefit (DCB) defined as the time from Ipilimumab initiation until documented progression or change in therapy (for non-trial patients). Immune-related adverse events (IRAEs), absolute

lymphocyte count (ALC), concordance of disease response by metastatic site, and use of radiation therapy (RT) were also analyzed.

Results: The median age was 57.7 yrs. The 3 mg/kg (N=83; 65.8%) and 10 mg/kg (N=42; 33%) cohorts matched well for standard prognostic criteria. The efficacy endpoints, including OS, PFS, DCB, and ORR (see **table 2**) were not significantly different for the 3 mg/kg and 10 mg/kg cohorts. However, grade III/IV IRAEs were more frequent in the 10 mg/kg group (33% vs 17%, p=0.04). There was a significant correlation between efficacy outcomes and development of IRAEs (see **figure 2**). Baseline ALC or changes in ALC at 7 weeks post-therapy and concurrent RT administration did not significantly correlate with improved outcomes.

Conclusions: Our data supports the currently FDA approved dose of 3mg/kg. The development of IRAEs was significantly associated with clinical benefit and further confirmation of this association is warranted.

TABLE OF CONTENTS

Background 6

Methods 11

Results 13

Discussion 15

Conclusion 16

References 18

List of Tables 19

List of Figures 22

BACKGROUND

Metastatic Melanoma: Prognosis and Treatment

The American Cancer Society estimates that 73,870 new melanomas will be diagnosed and about 9,940 deaths related to melanoma in the United States in 2015 [1]. Historically, the 10 year survival rate for patients with metastatic melanoma is 10-15% [2], with limited therapeutic options. In 2015, Many factors are associated with poor prognosis including sites of disease, presence of elevated serum lactate dehydrogenase (LDH), older age, poor performance status, male sex, and greater number of metastatic sites [3].

Systemic treatment for metastatic melanoma is necessary to address clinically detectable and subclinical sites of metastases [4]. Broadly speaking, there are three groups of therapies used to treat metastatic melanoma. These groups can be classified as cytotoxic chemotherapy, molecular targeted therapy, and immunotherapy. Chemotherapeutic agents have shown modest antitumor efficacy, and although combining cytotoxic agents show higher response rates, they are also associated with greater toxicity without extending survival significantly [5]. For more than three decades the cytotoxic chemotherapy, dacarbazine, which was FDA approved in 1975, has been the standard of care therapy. In 1998, the FDA approved high-dose interleukin-2 (HD IL-2 [Proleukin]), an immunotherapy, which can lead to durable complete responses but only in a small subset of patients [3]. An analysis of 270 patients treated with HD IL-2 showed an overall response rate (ORR) of 16% (CR 6%, PR 10%). Impressively, 60% of

the complete responders showed ongoing benefit at the time of the report (duration >42 months to >122 months) and 44% of responders were alive beyond 5 years [3].

Ipilimumab: Efficacy and Safety Data

The success of HD IL-2 inspired additional research into novel immunotherapies that are now recognized as a powerful treatment modality with the potential to induce long duration remissions. In March 2011, the FDA approved a new immunotherapy, ipilimumab. Two separate phase III trials with ipilimumab demonstrated significantly improved overall survival and were instrumental to its approval [4].

Roberts et al. conducted a study comparing ipilimumab plus dacarbazine (DTIC) for previously untreated metastatic melanoma patient randomizing 1:1 to ipilimumab at 10 mg/kg plus DTIC at 850 mg/m or DTIC (850 mg/m) plus placebo. Patients who were randomized to the combination arm received 4 cycles of ipilimumab plus DTIC then continued DTIC therapy alone until week 22. If stable disease was seen at 22 weeks patients were then eligible to receive maintenance dosing of ipilimumab until progression of disease. Enrollment consisted of 502 patients and they saw a 24% reduction in risk of progression in the ipilimumab plus DTIC arm (HR, 0.76; P=0.006). Overall survival was significantly longer with the combination of ipilimumab plus DTIC as compared to DTIC therapy alone (11.2 vs 9.1 mo). Roberts et al also saw that grade 3 or 4 adverse events occurred in 56.3% of ipilimumab plus DTIC patients vs 27.5% with DTIC plus placebo patients (P<0.001). This study shows impressive response results with the addition of the

10 mg/kg dose of ipilimumab to standard of care therapy (DTIC) supporting its effectiveness and ability to prolong survival utilizing maintenance scheduling [6].

Another group, Hodi et al., studied the combination of ipilimumab with the vaccine glycoprotein 100 (gp100). Their study enrolled 676 HLA-A*0201 positive patients with previously treated unresectable stage III/IV metastatic melanoma. Patients were randomized 3:1:1 to receive ipilimumab plus gp100 (403 patients), ipilimumab alone (137 patients), or gp100 alone (136 patients). The ipilimumab dose used was 3 mg/kg and was given with or without gp100 every 3 weeks for up to 4 treatments only (induction). Patients could be eligible to receive reinduction therapy of ipilimumab with or without gp100 if they had an initial response of complete response, partial response, or stable disease followed by progression of disease at a later date. Results of the Hodi et al study showed improved overall survival for both the ipilimuamb plus gp100 and ipilimumab alone arms (median survival 10 mo ipi+gp100, 10.1 mo ipi alone and 6.4 mo gp100 alone; HR 0.66, P=0.003, ipi+gp100 comparted to gp100 alone; HR 0.68, P<0.001, ipi alone compared to gp100 alone). Grade 3 or 4 immune-related adverse events (IRAEs) also occurred in 10 to 15% of patients treated with ipilimumab and only in 3% treated with gp100 alone. This study is evidence that the lower dose of 3 mg/kg and induction scheduling is also effective in prolonging overall survival but is also correlated with grade 3 or 4 IRAEs [7].

Prior studies have utilized varying doses and schedules of ipilimumab. Optimal dosing of ipilimumab remains undetermined and doses from 0.3 to 20 mg/kg have been

tested with the suggestion of a dose response, however, more severe IRAEs have been associated with higher doses. Common IRAEs associated with ipilimumab are rash, pruritis, hepatitis, hypophisitis, thyroiditis, and colitis. The severity of these immune events are assessed using the National Cancer Institute standardized "Common Terminology Criteria for Adverse Events (CTCAE) criteria [8].

Ipilimumab: Optimal dosing and the need for predictive biomarkers

After the FDA approval of ipilimumab there were many questions remaining:

1. What is the optimal dose of Ipilimumab? Is the 3 mg/kg dose as effective as the 10 mg/kg?
2. How does the toxicity profile of the 10 mg/kg dose as compared to that of the 3 mg/kg dose? Is there a clinical predictor that could help determine who will have serious toxicities?
3. Is there a low risk clinical marker that could predict response? Due to the potential for serious toxicity and only a minority of patients who respond to ipilimumab, there has been significant effort to identify clinical parameters or laboratory based biomarkers which could predict response. Identifying a laboratory based biomarker is particularly appealing as they could be performed with low risk and at low cost. Laboratory biomarkers would also be useful in monitoring and managing patients on therapy as responses can be delayed.

Many studies have reported that the presence of IRAE toxicity correlates with better response outcomes. Attia et al. completed a study specifically assessing this correlation and suggest that toxicity can be a predictor of beneficial response outcomes: Their study included 56 patients with progressive stage IV melanoma and no history of autoimmune comorbidities. The treatment regimens were 3 mg/kg ipilimumab given every 3 weeks, 3 mg/kg initial dose with subsequent doses reduced to 1 mg/kg every 3 weeks. Data from this study showed an overall objective response rate of 13%, and 36% of patients (5/14) who had grade 3 or 4 autoimmune toxicity also had a clinical response (PR or CR). Patients who had no autoimmune toxicity had a 5% response rate (2/42; P=0.008). This study, as well as others, gives strong evidence that the presence of IRAE toxicity is associated with better clinical outcomes [9].

Due to the likelihood of potential serious toxicities related to ipilimumab, finding an easily accessible clinical biomarker to predict response is increasingly important. Prior studies have investigated predictive biomarkers with some success. Ku et al. explored the absolute lymphocyte count as a potential laboratory based biomarker to predict response in “Singe-Institution Experience with Ipilimumab in Advanced Melanoma Patients in the Compassionate Use Setting” [10]. Ku et al. found that lymphocyte counts correlate with survival outcomes after two doses of ipilimumab. Absolute lymphocyte count (ALC) was captured at baseline and again after 2 doses of ipilimuamb. Patients with an ALC > 1000/uL after 2 ipilimumab treatments (week 7) had a significantly improved clinical benefit rate (51% vs 0%) compared to those with an ALC < 1000/uL. Like prior studies these results confirm that ipilimumab is clinically active in improving progression free

survival (PFS) and overall survival (OS) in patients with advanced refractory melanoma. The ALC after 2 treatments with ipilimumab appears to correlate with clinical benefit and OS and should be prospectively validated [10].

The goal of this retrospective study is to evaluate our institutional cohort of patients with metastatic melanoma who have been treated with single agent ipilimumab to gain insight into these questions. Because of our participation in several clinical trials since 2006, our institution had data available for both the investigational 10 mg/kg dose and maintenance schedule as well as the FDA approved 3 mg/kg dose and induction schedule.

METHODS

Study Cohort: We performed a retrospective chart review of 126 metastatic or unresectable melanoma patients treated with single agent ipilimumab at the SCCA/UW between 2006 and 2012. This included patients who had received ipilimumab in the context of a clinical trial prior to its FDA approval in March 2011 and those who had received ipilimumab as standard of care therapy following FDA approval. Only those patients who had received monotherapy were included.

Demographics: Demographic data was collected for all patients including: sex, age, and performance status (ECOG). Baseline disease characteristics and prognostic factors were captured for all patients and included: primary site of disease, metastasis stage (M stage) at start of ipilimumab treatment (TNM staging criteria), central nervous system (CNS) tumor involvement, and BRAF mutation status. Prior therapy status was collected,

including cytotoxic therapy, immune therapy, and radiotherapy. Dosage details were captured for each patient (3 mg/kg or 10 mg/kg), schedule of dosing (maintenance dosing status), and median number of doses (see **Table 2**).

Efficacy Endpoints: Data included 98 patients who participated in clinical trials at our site, who had standardized response measurements as required by the trial and 28 patients who received standard of care therapy and did not have standardized response measurements done. To compare patients from trials and those who received standard of care therapy we calculated the duration of clinical benefit (DCB), defined as the time from initiation of ipilimumab until death, documented progression or change in therapy. Formal response measurements were classified as complete response (CR) (a complete disappearance of all tumors being followed); partial response (PR) (at least a 30% decrease in the sum of diameters of tumors being followed); progressive disease (PD) (at least 20% increase in the sum of diameters of tumors being followed); and stable disease (SD) (neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD) [11]. Other outcome measurements were overall survival (OS) (length of time before death); progression free survival (PFS) (length of time before PD); disease control rate (DCR), defined as proportion of patients who achieved CR/PR/SD; and best objective response rate (ORR) defined as proportion of all patients with CR/PR at 12 weeks and at time of best response.

Safety Endpoints: For all patients, each dose coincided with routine laboratory tests. Laboratory data is instrumental in detecting some of the most common immune related

adverse events (IRAEs). All IRAEs were graded according to national Cancer Institute Common Terminology Criteria for Adverse Events.

Biomarkers: Laboratory data was used to explore any predictive biomarkers for response in our cohort of patients.

Statistics: Statistical analysis was done using R v2.0 or higher. Event rates were compared between groups using Fisher's exact test. Survival functions were estimated using the Kaplan–Meier estimator. ALC response was analyzed using Kaplan-Meier estimator.

RESULTS

Baseline Characteristics: Of the 126 patients evaluated 60% were male, 40% were female, and the median age was 57.7 years (range 19-86). The majority of patients had good to excellent ECOG performance status (75% ECOG 0 or 1) and 57% had received a prior cytotoxic therapy. More than half of our patients received the 3 mg/kg dose (65.8% versus 33.3%) and the median number of ipilimumab doses was 4 (range 1-17) (**table 1**).

Dose Comparison: Our data showed no discernible difference in efficacy measures between the 3 mg/kg dose and 10 mg/kg dose cohorts (**Figure 1; A, B, and C**). Severe (grade 3 or 4) IRAEs, however, were more common in the high dose cohort (**Figure 2A**). This data supports the current FDA approved 3 mg/kg induction dose as the higher dose was associated with more severe adverse events without any evidence of increased benefit.

Within the 126 patients evaluated we saw the following responses at 12 weeks: complete response/partial response = 17/106 (16%) and a disease control rate of (CR/PR/SD) = 55/106 (52%). Complete response and partial responses at best response time was 24/124 (19%); complete response/partial response/and stable disease was 61/124 (49%) and the median time to complete response or partial response at best response time was 25 weeks (8-171 weeks) (**table 2**).

In agreement with previous studies, **Figure 2** shows that IRAEs of any grade were associated with better outcomes. Patients were first evaluated for clinical benefit, progression free survival, and overall survival. Of the proportion of patients who achieved a complete response, partial response, or stable disease as a best response the following IRAE grades were seen: grade 0=19%, grade I/II=55%, grade III/IV=79% ($p<0.0001$). Patients whose best objective response rate was complete response or partial response the following IRAE grades were seen: grade 0=11%, grade I/II=19%, grade III/IV=32% ($p=0.10$). Similar to previous studies, patients with any grade IRAE had significantly better outcomes (DCB, PFS, OS) compared to patients without any immune related toxicity. Common IRAEs included: rash, pruritis, hepatitis, hypophisitis, thyroiditis, and colitis.

Predictors: Our patients were evaluated for clinical benefit, progression free survival, and overall survival. In **figures 3A, B, C, and D**, we calculated percent change in absolute lymphocyte count from baseline to 7 weeks and analyzed according to response

(clinical benefit, progression free survival, and overall survival) from the clinical laboratory collected prior to each ipilimumab infusion. This was also done for the absolute change in ALC from baseline to 7 weeks (**Figures 3E, F, and G**). Both analyses trend towards better outcomes with increased change in ALC but were not statistically significant. In contrast to prior studies, baseline absolute lymphocyte levels did correlate with responses.

DISCUSSION

The SCCA experience with single agent ipilimumab in unresectable or metastatic melanoma patients is consistent with previous data showing correlation between better response outcomes and development of higher-grade toxicities. Our data validates the FDA approval of the induction schedule using 3 mg/kg dose over the 10 mg/kg dose with maintenance schedule.

This was designed as a retrospective study to address the remaining questions following ipilimumab's FDA approval. The vary nature of a retrospective study limited our ability to evenly compare our cohort of patients. Patients were treated by a variety of providers and clinical assessments were not defined at the outset of treatment. We were unable to control clinical management or efficacy assessments and therefore relied heavily on interpretation of past documentation. These factors make accurate comparisons difficult between trial patients and those who received standard of care therapy.

Grade 3 or 4 toxicities seen with ipilimumab treatment can be severe or even life threatening. Some can result in permanent damage to the body's normal functions and continued management of toxicities well past completion of ipilimumab therapy. Due to this potential of toxicity the search to identify clinical parameters or laboratory based biomarkers to help predict response outcomes continue. The use of a laboratory based biomarker would be useful in monitoring and managing patients on therapy as responses can be delayed. Many other questions remain concerning ipilimumab and best clinical practices. Future research into patterns of relapse and concordance in responses by disease site should be explored. Our data did not allow us to examine the differences in response based on prior therapies such as radiotherapy or differences in response based on BRAF mutation status. Future research into these areas may help define best clinical practices by providing guidelines for choosing appropriate patients for ipilimumab therapy.

A randomized phase III trial comparing 3 mg/kg and 10 mg/kg dose to obtain definitive data showing differences in efficacy and toxicity between the two doses is ongoing and results have not been published yet.

CONCLUSION

The results of our retrospective study support the currently FDA approved dose of 3 mg/kg. Efficacy outcomes seen within our data are similar for the 3 mg/kg and 10 mg/kg dose, while toxicity was significantly higher with the latter dose. The response outcomes correlated strongly with toxicities, which supports the mechanism of action for

anti-CTLA-4 therapy, like ipilimumab. Prospective confirmation of these findings is warranted.

REFERENCES

1. What are the key statistics about melanoma skin cancer? American Cancer Society. http://www.cancer.org/cancer/skincancer-melanoma/index Last revised March 20, 2015.

2. What are the survival rates for melanoma skin cancer, by stage? American Cancer Society. http://www.cancer.org/cancer/skincancer-melanoma/index Last revised March 20, 2015.

3. Bhatia MD, Tykodi MD PhD, Thompson MD. Treatment of Metastatic Melanoma: An Overview. ONCOLOGY. 2009; VOLUME 23, NUMBER 6; 488-515.

4. Bhatia MD, Tykodi MD PhD, Lee MD, Thompson MD. **Systemic Therapy of Metastatic Melanoma: On the Road to Cure. ONCOLOGY.** February 2015; 126-135.

5. Bhatia MD, Thompson MD. **Systemic Therapy for Metastatic Melanoma in 2012: Dawn of a New Era.** Journal of the National Comprehensive Cancer Network. March 2012; Volume 10, Number 3; 403-412.

6. Robert MD PhD, Bondarenko MD PhD, O'Day MD, et al. Ipilumumab plus dacarbazine for previously untreated metastatic melanoma. New England Journal of Medicine. 2011; vol. 364 no. 26; 2517-2526.

7. Hodi MD, O'Day MD, McDermott MD, et al. Improved survival with ipilimumab in patients with metastatic melanoma. New England Journal of Medicine. 2010; vol. 363 no. 8; 711-723.

8. National Cancer Institute. "Common Terminology Criteria for Adverse Events (CTCAE)". http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm Published May 28, 2009.

9. Attia, Phan, Maker, et al. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-CTLA-4. Journal of Clinical Oncology. September 2005; 23(25); 6043-6053.

10. Ku , Yuan, Page, et al. Single institution experience with ipilimumab in advanced melanoma patients in the compassionate use setting: lymphocyte count after 2 doses correlates with survival. Cancer. April 2010; 116(7); 1767-1775.

11. E.A. Eisenhauera et al. "New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)". EUROPEAN JOURNAL OF CANCER 45. 2009; 228–247. http://ctep.cancer.gov/protocolDevelopment/docs/Recist_Guideline.pdf

LIST OF TABLES

Table 1. Baseline characteristics of patient cohort**.**
*The Eastern Cooperative Oncology Group (ECOG) performance status ranges from 0 to 5, with higher scores indicating greater deficiency (5 indicates death).
^ The metastasis stage (M) was classified according to the tumor-node-metastasis (TNM) categorization for melanoma as defined by the American Joint Committee on Cancer.

Category	Subcategory	Number (%)
Sex	**Male**	**76 (60)**
	Female	**50 (40)**
Median Age		**57.7 (19-86)**
ECOG PS*	**0**	**79 (63)**
	1	**40 (32)**
	2	**6 (5)**
	3	**1 (1)**
Primary Site	**Cutaneous**	**93 (74)**
	Mucosal	**4 (3.1)**
	Ocular	**5 (3.9)**
	Unkown	**24 (19)**
M Stage at ipilumumab initiation^	**M0**	**8 (6.3)**
	M1a	**15(11.9)**
	M1b	**19 (15)**
	M1c	**84 (67)**
CNS Lesions at initiation	**Treated**	**25 (19.8)**
	Untreated	**11 (8.7)**

BRAF Mutation?	**Yes**	**15**
	No	**34**
	Unknown	**75**

Prior Cytotoxic Therapy?	**Yes**	**72 (57)**
	No	**57 (42)**
Prior Immune Therapy?	**Yes**	**68 (54)**
	No	**58 (46)**
Previous XRT?	**Yes**	**55 (24)**
	No	**70 (56)**
Ipilimumab Dosage	**3mg/kg**	**83 (65.8)**
	10mg/kg	**42 (33.3**
Maintenance Dosing	**No**	**114 (90.4)**
	Yes	**12 (9.5)**
Median # Doses	**4 (1-17)**	

Table 2. Ipilimumab dosage: outcomes summary**.**

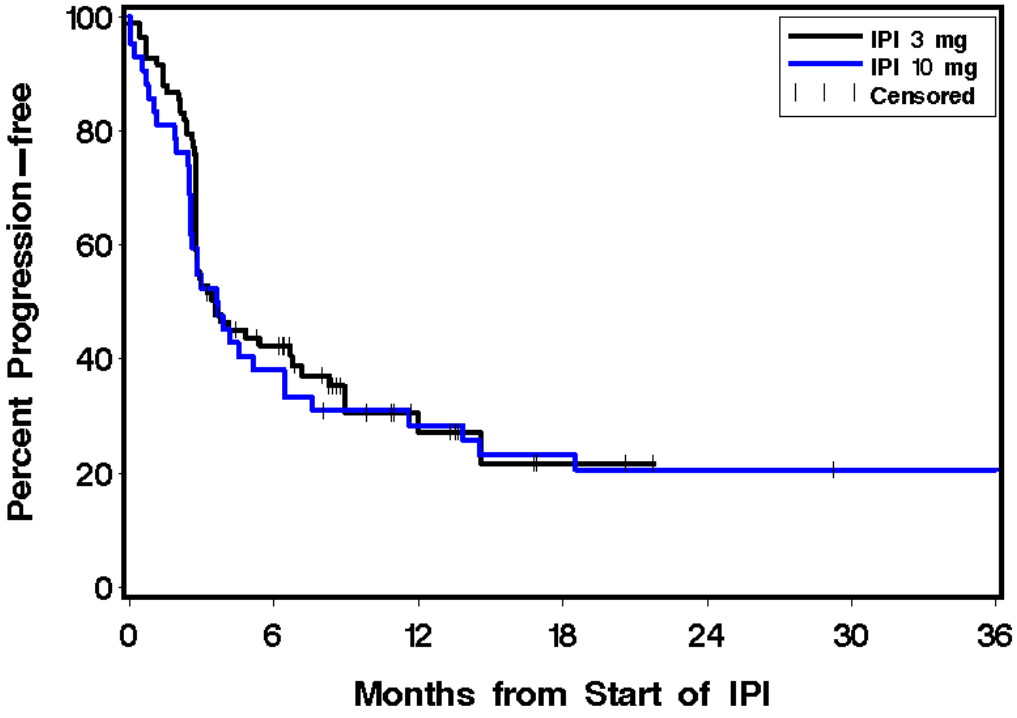
CR/PR at 12 weeks (BORR)	**All**	**17/106 (16%)**
	3mg/kg	**10/72 (14%)**

	10mg/kg	**7/34 (21%)**
		P=0.40
CR/PR/SD at 12 weeks	**All**	**55/106 (52%)**
	3mg/kg	**38/72 (53%)**
	10mg/kg	**17/ 34 (50%)**
		P=0.84

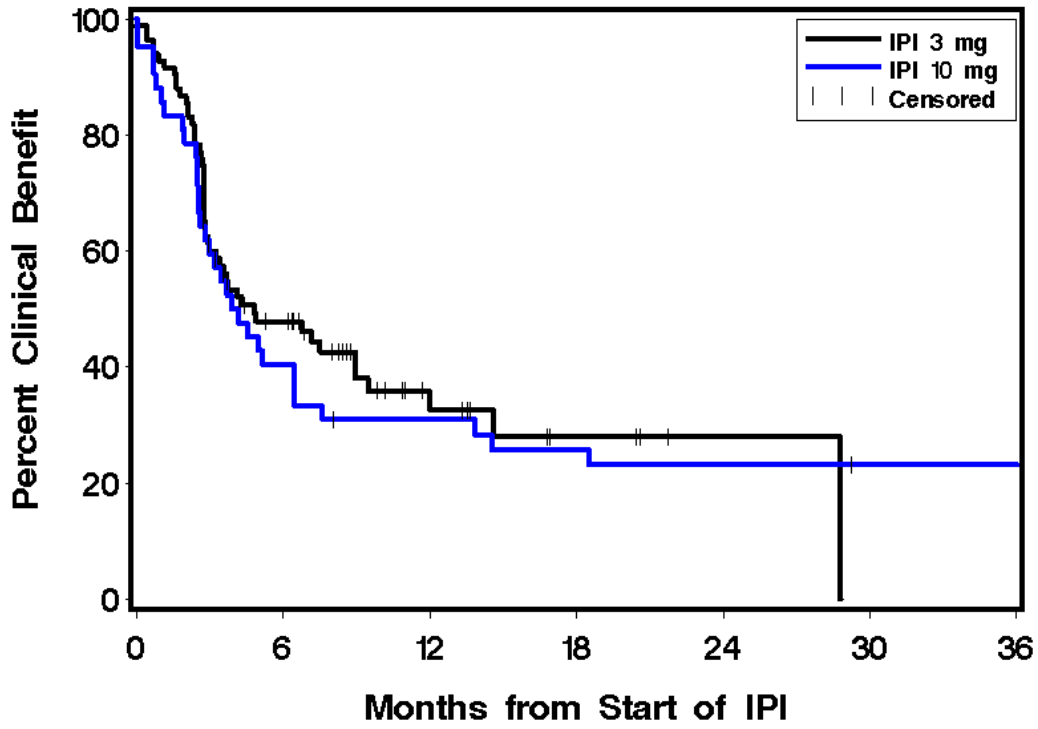
CR/PR/SD at best response (DCR)	**All**	**61/124 (49%)**
	3mg/kg	**39/82 (47%)**
	10mg/kg	**22/41 (54%)**
		P=0.57
Median time to CR/PR as best response (in weeks)	**All**	**25 (8-171)**
	3mg/kg	**25 (11-48)**
	10mg/kg	**36 (8-171)**
		P=0.45

LIST OF FIGURES

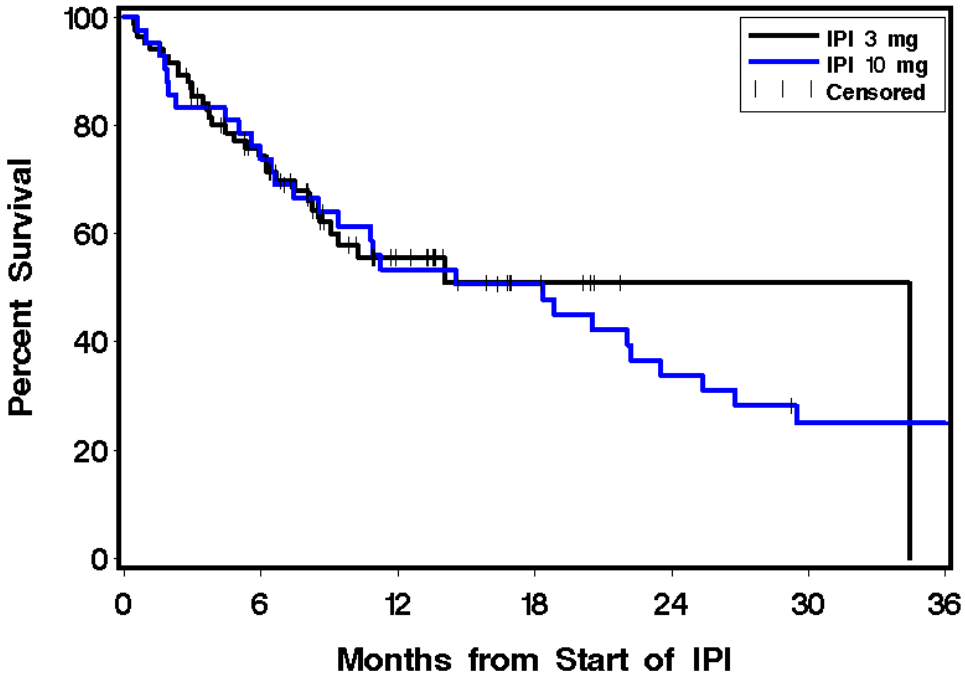
Figure 1. Efficacy Endpoint by Ipilimumab Dosage.



A. Progression Free Survival assessment by ipilimumab dosage.

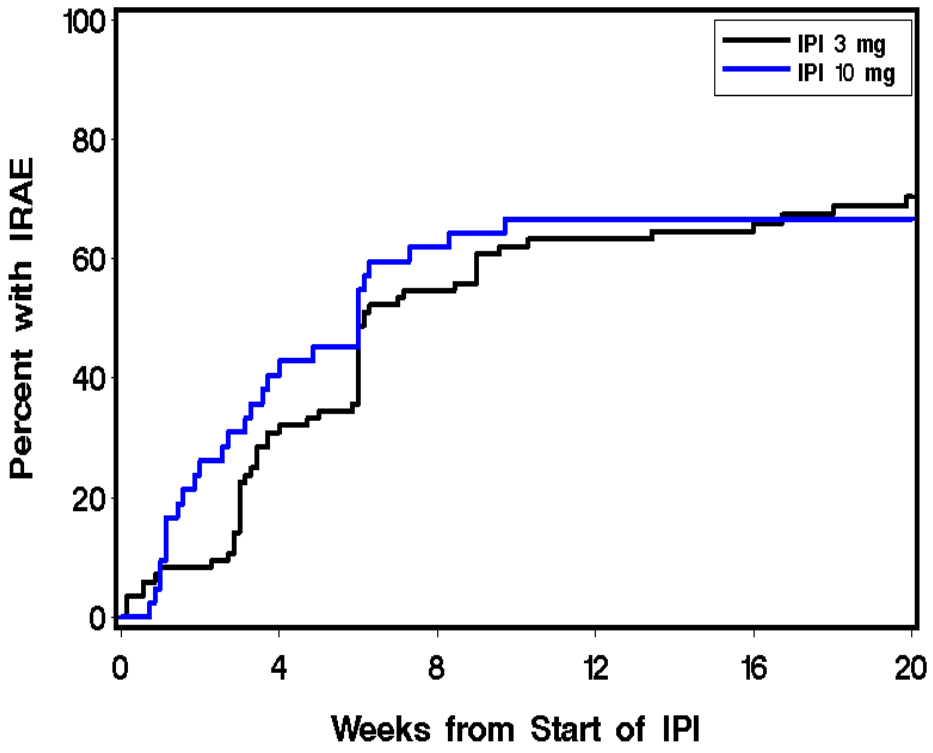


B. Duration of Clinical Benefit (DCB) assessment by ipilimumab dosage.

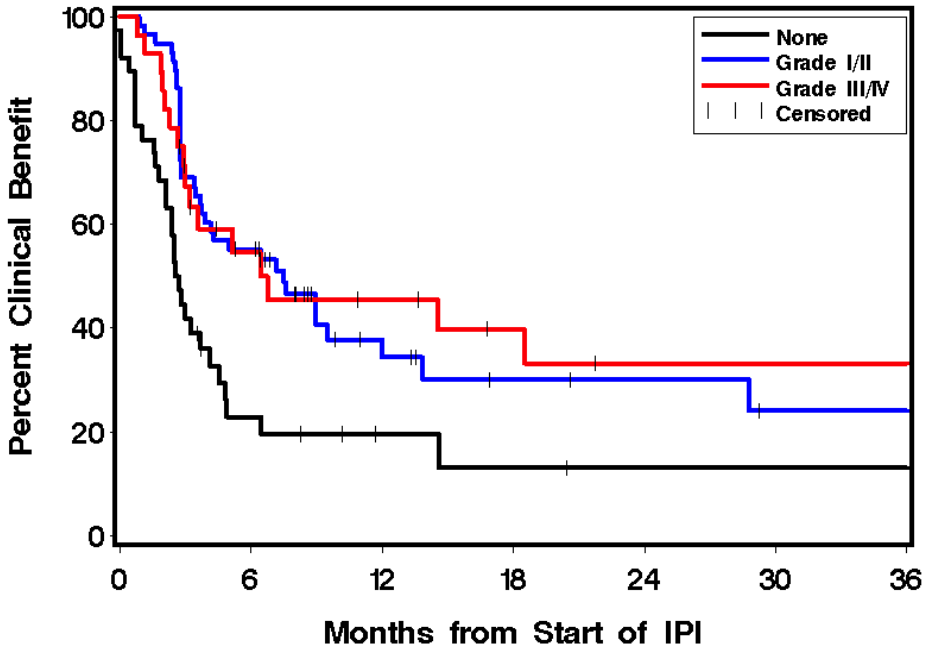


C. Overall Survival assessment by ipilimumab dosage.

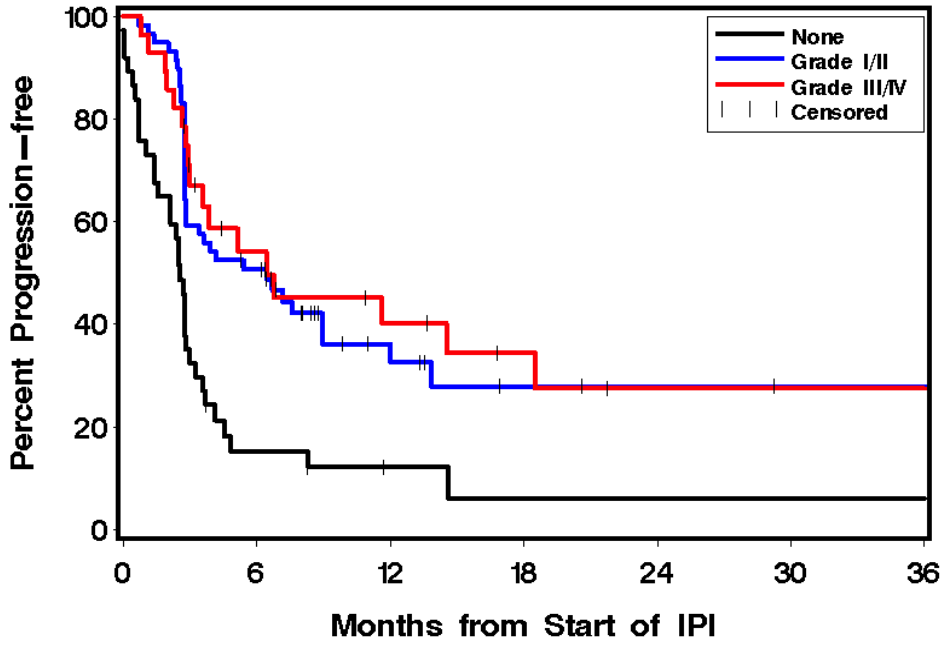
Figure 2. The presence of IRAEs and response**.**
The Kaplan-Meier curves for overall survival, progression free survival, and duration of clinical benefit all show that the presence of any grade IRAE correlate with clinical benefit.



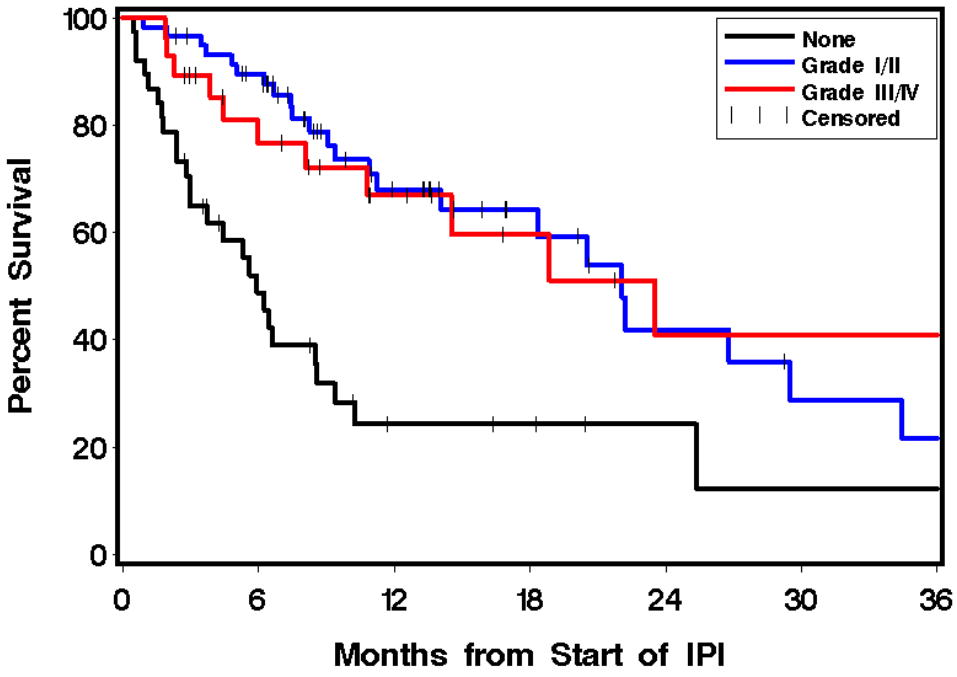
A. Toxicity assessed by ipilimumab dosage**.**
All Grade III and IV immune related adverse events were captured. Within the entire cohort grade III/IV IRAE's = 22%; 3 mg/kg dose = 17%; and 10 mg/kg = 33% (P=0.04). Grade III/IV IRAE's occurred at a higher frequency in the 10 mg/kg cohort.



B. Presence of IRAE's as compared to percent of patients who experienced clinical benefit (DCB).

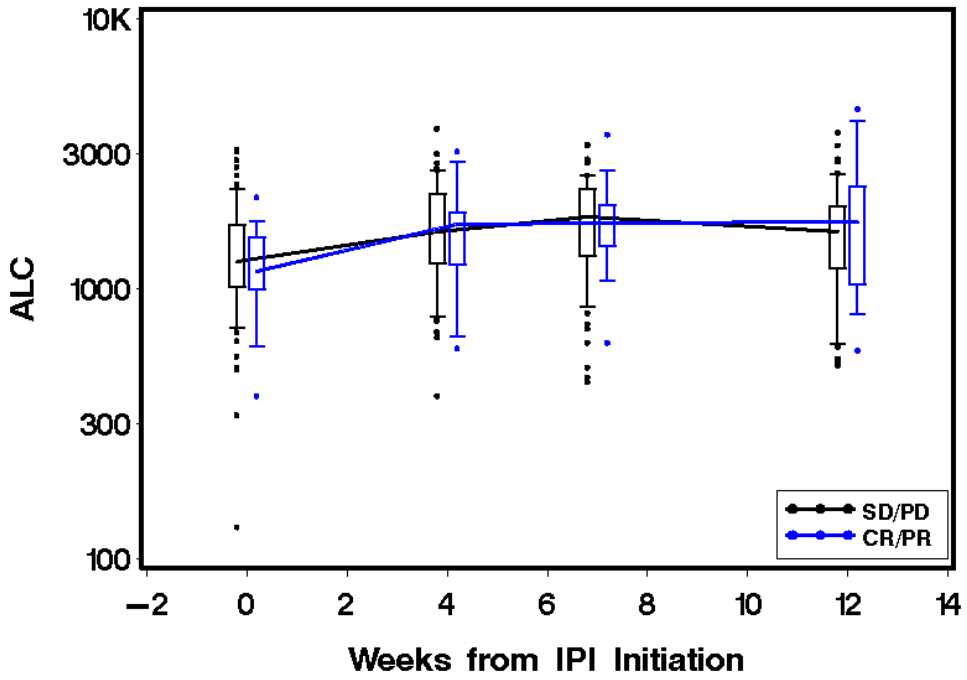


C. Presence of IRAE's compared to percent of patients who experienced progression free survival (PFS).

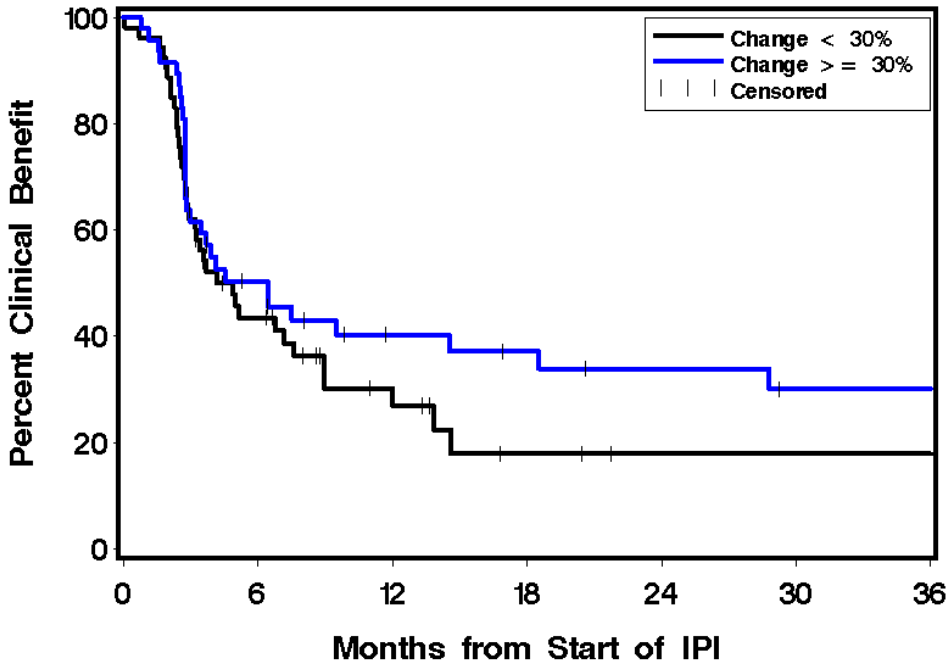


D. Presence of IRAE's compared to percent of patients who experienced overall survival (OS).

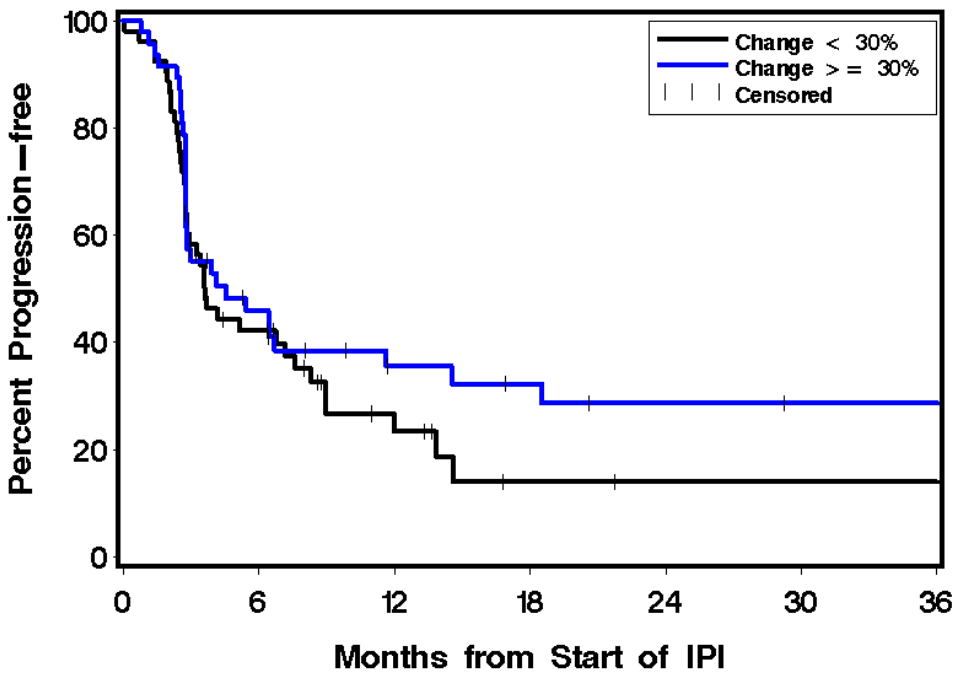
Figure 3. Candidate Predictive Biomarkers**:** Kaplan-Meier curves showing Absolute Lymphocyte Count (ALC)



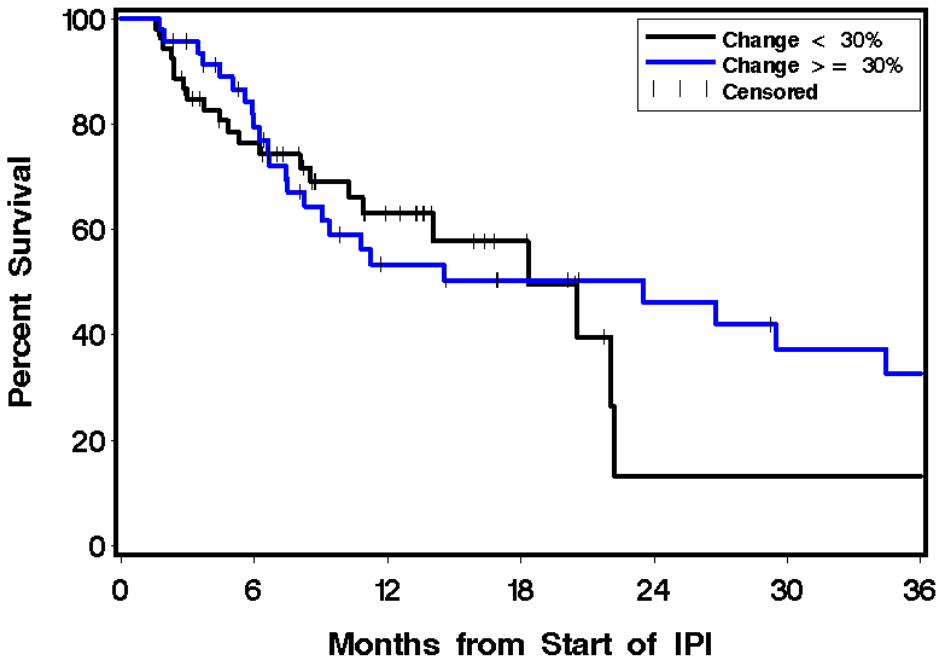
A. Absolute change in ALC by response (SD/PD vs CR/PR).



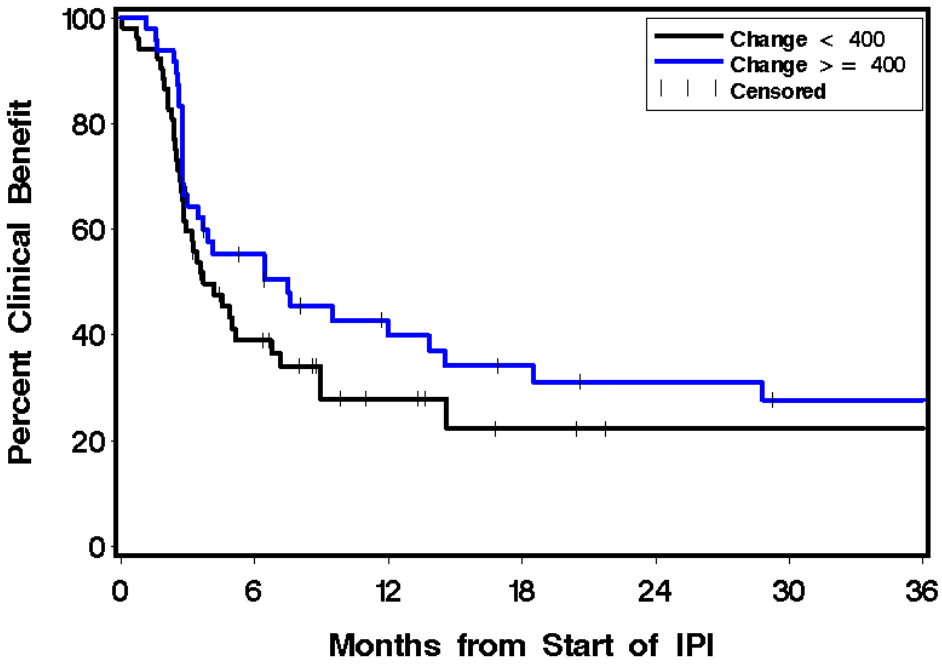
B. Percent ALC Change from Baseline to 7 weeks for patients who achieved clinical benefit.



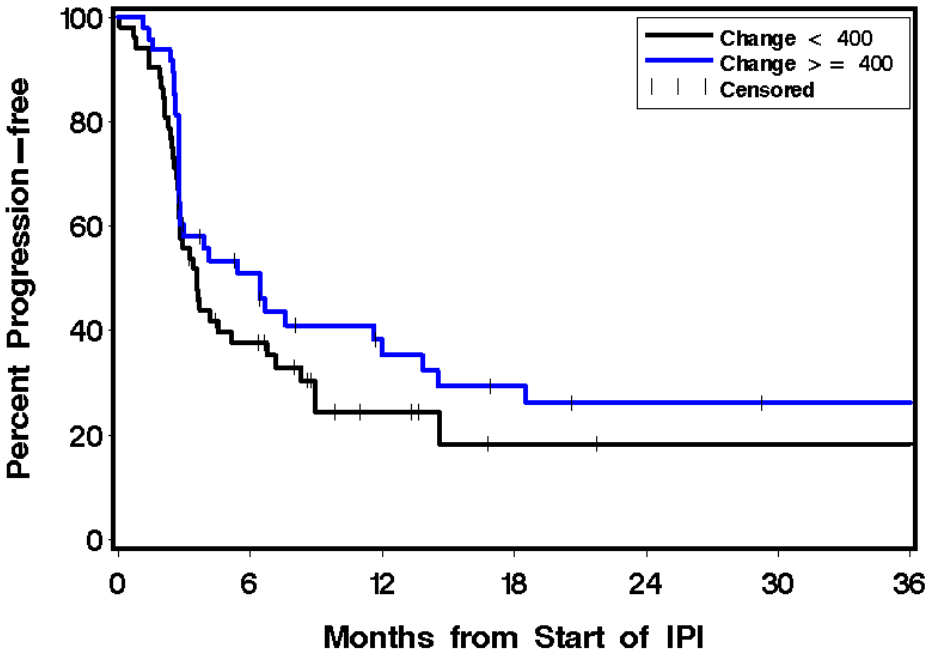
C. Percent ALC Change from Baseline to 7 weeks for patients with progression free



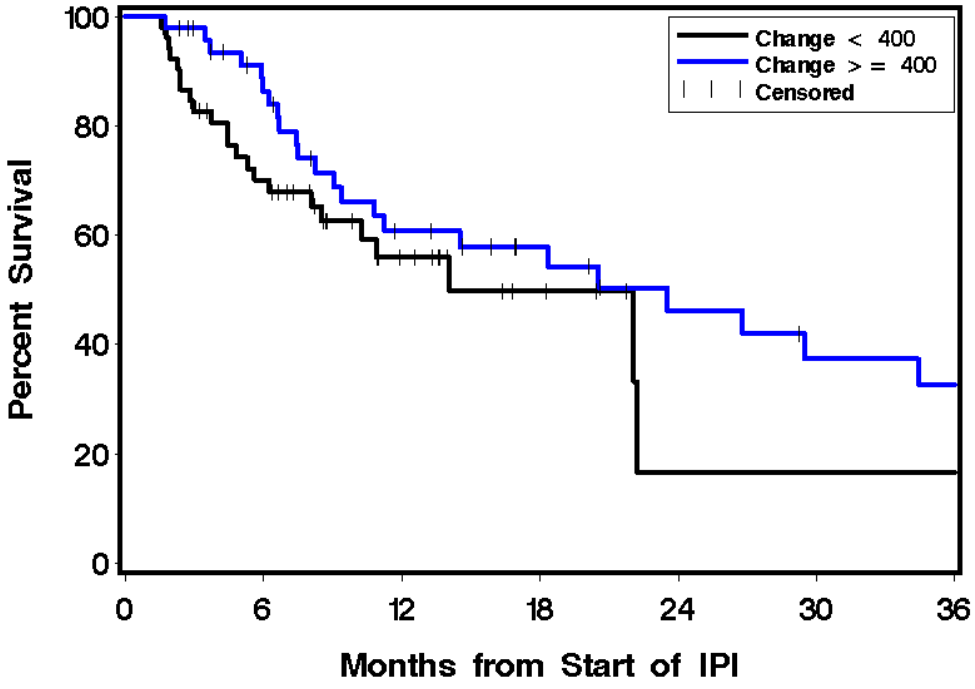
D. Percent ALC Change from Baseline to 7 weeks by overall survival



E. Absolute change in ALC from baseline to 7 weeks for patients who achieved clinical benefit.



F. Absolute change in ALC from baseline to 7 weeks by progression free survival



G. Absolute change in ALC from baseline to 7 weeks by overall survival