Title

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The Effect of Prior Androgen Synthesis Inhibition on Outcomes of Subsequent Therapy with Docetaxel in Patients with Metastatic Castrate Resistant Prostate Cancer: Results from a Retrospective Analysis of a Randomized Phase 3 Clinical Trial (CALGB 90401) (Alliance)

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Abstract

Background—Preliminary data suggests a potential decreased benefit of docetaxel in metastatic castration-resistant prostate cancer (mCRPC) patients previously treated with abiraterone acetate, a novel androgen synthesis inhibitor (ASI). CALGB 90401 (Alliance), a phase 3 trial of mCRPC patients treated with docetaxel-based chemotherapy, offered the opportunity to evaluate effect of prior ketoconazole, an earlier generation ASI, on clinical outcomes following docetaxel.

Methods—CALGB 90401 randomized 1050 men with chemotherapy-naïve, mCRPC to treatment with docetaxel and prednisone with either bevacizumab or placebo. 1005 men (96%) had data available regarding prior ketoconazole therapy. The effect of prior ketoconazole on overall survival (OS), progression-free survival (PFS), PSA decline, and objective response rate (ORR) observed was assessed using proportional hazards and Poisson regression method adjusted for validated prognostic factors and treatment arm.

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Results—Baseline characteristics between patients with (N=277) and without (N=728) prior ketoconazole therapy were similar. There were no statistically significant differences between patients with and without prior ketoconazole therapy with respect to OS (median OS 21.1 vs. 22.3 months, stratified log-rank p-value=0.635); PFS (median PFS 8.1 vs. 8.6 months, stratified log-rank p-value=0.342); ≥50% PSA decline (61% vs. 66%, relative risk=1.09, adjusted p-value=0.129); or ORR (39% vs. 43%, relative risk=1.11, adjusted p-value=0.366).

Conclusions—As measured by OS, PFS, PSA and ORR, there is no evidence that prior treatment with ketoconazole impacts clinical outcomes in mCRPC patients treated with subsequent docetaxel-based therapy. Prospective studies are needed to assess for potential cross-resistance with novel ASIs and to define the optimal sequence of therapy in mCRPC.

Introduction

Prostate cancer is the second-leading cause of cancer-related mortality among men in the United States [1]. Although a significant number of men with advanced disease eventually succumb to metastatic castrate resistant prostate cancer (mCRPC), the past decade has borne witness to multiple agents with varying mechanisms of action that have demonstrated an improvement in overall survival in randomized phase 3, placebo-controlled, clinical trials. Among these agents are taxane-based cytotoxic chemotherapy [2–4], androgen synthesis inhibitors (ASIs) such as abiraterone acetate [5, 6], and the novel androgen receptor (AR) antagonist enzalutamide (MDV3100) [7, 8]. Optimizing the sequence (or combinations) of therapy, assessing for evidence of acquired cross-resistance, and discovering mechanisms of treatment resistance have become of increasing clinical importance in the treatment of mCRPC patients.

A retrospective, single institution series suggested that patients with mCRPC who are treated with adrenal ASIs such as abiraterone acetate may acquire cross-resistance to subsequent taxane-based chemotherapy [9]. The putative biological mechanism explaining this cross-resistance stems from the observation that taxanes exert their anti-neoplastic effect in prostate cancer in part by down-regulating signaling via the AR pathway. Taxanes exert this effect by targeting AR association with tubulin, inhibiting AR nuclear translocation, and down-regulating AR-mediated gene expression [10]. Thus, it is hypothesized that prior exposure to agents targeting the androgen axis such as abiraterone acetate may shift the tumor phenotype towards a more “androgen insensitive” disease state that is partially resistant to further inhibition of androgen signaling with taxane-based chemotherapy.

Abiraterone acetate has only recently been FDA approved in mCRPC in both the pre- and post-docetaxel setting. Ketoconazole is a generic, widely available androgen synthesis inhibitor that has been in clinical use for mCRPC since the 1990s. Ketoconazole blocks androgen synthesis via inhibition of several enzymes within the androgen synthetic pathway, including side chain cleavase (which converts cholesterol to pregnenolone) and CYP 17 (which converts pregnenolone to the androgen dehydroepiandrostenedione (DHEA) via two enzymatic steps, and is the same enzyme targeted by abiraterone) [11–14]. Ketoconazole has demonstrated significant clinical activity in mCRPC in several prior prospective clinical trials and is a standard treatment option in this disease setting [15, 16]. The Cancer and Leukemia Group B, now a part of the Alliance for Clinical Trials in Oncology, designed CALGB 90401, a randomized phase 3 trial in which 1050 mCRPC patients were treated with docetaxel-based chemotherapy. This trial offered the opportunity to evaluate the effect of prior treatment with ketoconazole, an earlier generation ASI, on clinical outcomes following docetaxel treatment.

Patients and Methods

Study Design and Hypothesis

A retrospective analysis of data collected from the intergroup study CALGB 90401, a randomized, placebo-controlled phase 3 trial of docetaxel and prednisone with or without bevacizumab in men with mCRPC [17] was undertaken. The objective was to assess whether prior androgen synthesis inhibition with ketoconazole impacted clinical outcomes with subsequent docetaxel-based chemotherapy, as a means to further investigate the potential for acquired cross-resistance between these therapeutic approaches for men with mCRPC.

Study Population

The eligibility requirements for CALGB 90401 have been previously described [17]. In brief, eligible patients had metastatic prostate cancer with disease progression in the setting of a castrate level of serum testosterone (≤ 50 ng/dL) and following anti-androgen withdrawal, as defined by the Prostate-Specific Antigen Working Group1 consensus criteria [18]. Patients were required to be ≥ 4 weeks from discontinuation of secondary hormonal therapies including ketoconazole or antiandrogens. 5-Alpha reductase inhibitors were required to be discontinued at any time prior to study entry. Prior bisphosphonate use was allowed provided that the dose was stable for > 4 weeks prior to protocol therapy (denosumab was not commercially available at the time). Key exclusion criteria included prior chemotherapy or anti-angiogenic therapy, ECOG performance status > 2, uncontrolled hypertension, congestive heart failure (New York Heart Association class II, III, or IV), arterial thromboembolic event within 12 months of study entry, or grade ≥ 2 peripheral neuropathy.

CALGB 90401 Study Design and Treatment

Patients enrolled onto CALGB 90401 were randomized with equal probability to receive docetaxel/prednisone plus placebo or docetaxel/prednisone plus bevacizumab [17]. Randomization was stratified by: age (< 65 years, ≥ 65 years), predicted 24-month survival probability using a validated CRPC nomogram [19] (< 10%, 10 to 29.9%, ≥ 30%), and prior history of arterial thromboembolic events (yes, no). Treatment was continued until disease progression or unacceptable toxicity for a maximum of 2 years. Patients were assessed by serum PSA with each cycle of therapy and by bone scan + CT abdomen/pelvis every 3 months. The primary endpoint was overall survival, and as has been previously reported, no difference between the arms was detected [17]. 1,050 patients were accrued between May 2005 and December 2007 across 310 investigational sites within the United States. CALGB 90401 was approved by the local ethics committees of all participating centers. Each participant signed an IRB-approved, protocol-specific informed consent in accordance with federal and institutional guidelines.

As part of the quality assurance program of the CALGB, members of the Audit Committee visit all participating institutions at least once every three years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was performed for a subgroup of 141 patients (13%) of the 1050 patients under this study.

Statistical Methods and Data Analysis

The primary endpoint was overall survival (OS), which was defined as the time interval from date of randomization to date of death from any cause. In addition, the effect of prior ketoconazole use on other endpoints such as progression-free survival (PFS), ≥ 50% decline

in PSA from baseline, and objective response proportion as defined by RECIST 1.0 criteria) was evaluated. PFS was defined from the date of randomization to date of progression or death due to any cause, whichever occurred first. Progression was defined by using PSA Working Group 1 criteria [18] with the exception that more than two new bone lesions were required for bone progression on a bone scan.

Information about prior ketoconazole use was prospectively collected at the time of study entry, prior to randomization, but data on duration of prior ketoconazole use, whether ketoconazole was used in the hormone-sensitive or castration-resistant setting, or prior response to ketoconazole were not prospectively collected on this trial. The Kaplan-Meier product limit approach [20] was used to estimate the overall and progression-free survival distribution as a function of prior ketoconazole use. The proportional hazards model [21] was used to assess the prognostic significance of prior ketoconazole use in predicting OS and PFS adjusting for the prospectively defined stratification factors and for the PFS endpoint, the treatment arm (which has been previously reported to have an effect on PFS, but not OS). The Poisson regression method [22] was used to assess the prognostic significance of prior ketoconazole use in predicting the probability of at least 50% decline in serum PSA from baseline and the probability of experiencing an objective response as defined by RECIST 1.0 criteria adjusting for the stratification factors and treatment arm [23]. Tests of treatment arm by prior ketoconazole use interaction in predicting outcomes on docetaxel were performed and no significant interactions between were noted in predicting clinical outcomes. Data collection and analysis was undertaken by the Alliance (formerly CALGB) Statistical and Data Center. The date of data lock was January 13th, 2013.

S-plus statistical software (TIBCO Spotfire S^{+} version 8.1, TIBCO Spotfire Inc., Somerville, MA) was used for the data analyses and all statistical tests were two-sided. No adjustment was made for multiple comparisons for this retrospective analysis.

Results

Patient Disposition and Baseline Characteristics

1050 patients were randomized to receive docetaxel plus prednisone with or without bevacizumab. Of these 1050 patients, 1005 (96%) had data available regarding prior ketoconazole use (Figure 1). The baseline characteristics for these 1005 patients, including known prognostic factors in mCRPC, are summarized in Table 1. Not surprisingly, the 4% of patients for whom data was not available with regards to prior ketoconazole use had similar demographic and baseline patient characteristics to the 96% of patients with available data. Of the 1005 patients available for analysis, 28% had received prior treatment with ketoconazole for CRPC. The two groups (those with and without prior ketoconazole) had similar baseline characteristics including age, ECOG performance status, median alkaline phosphatase and hemoglobin, and presence of visceral metastases. There were numerical differences between groups in median baseline serum PSA and LDH, which were higher in the group of patients with prior ketoconazole therapy. However, the two groups had similar 24 month predicted survival probability using a validated prognostic model in CRPC which incorporates PSA and LDH levels amongst its seven factors [19]. The median baseline serum testosterone levels and study arm assignment between patients with and without prior ketoconazole therapy were similar.

Impact of Prior Ketoconazole Therapy on Clinical Outcomes

A total of 968 deaths were observed and the median follow-up time for the alive patients was 57 months (95% CI 52.3–59.7). The median overall survival times on CALGB 90401 was 21.1 months (95% CI 19.6–23.8) for patients with prior ketoconazole therapy and 22.3

months (95% CI 21.1–24.0) for patients without prior ketoconazole use (p = 0.315). The Kaplan-Meier overall survival curves are depicted in Figure 2A. Adjusting for the stratification factors, the hazard ratio for death for patients who had prior ketoconazole use was 1.04 compared with patients who did not use ketoconazole (95% CI 0.89–1.20, p = 0.635).

Similar results were obtained for progression-free survival; median PFS times for patients with prior ketoconazole was 8.1 months (95% CI 7.6–9.4) versus 8.6 months (95% CI 8.0–9.1) for patients without prior ketoconazole exposure (p = 0.177). Using a proportional hazards model adjusting for treatment arm and the stratification factors, the hazard ratio for PFS for patients who had prior ketoconazole use was 1.07 compared with patients without ketoconazole use (95% CI 0.92–1.23, p = 0.342). The Kaplan-Meier PFS curves are shown in Figure 2B.

Additional analyses were carried out examining the impact of prior ketoconazole therapy on objective response rate (among patients with measurable disease at baseline) according to RECIST 1.0 criteria as well as proportion of patients with ≥ 50% decline in PSA from baseline on protocol docetaxel-based chemotherapy. There was no significant effect of prior ketoconazole use on objective response rate or PSA declines ≥ 50% from baseline with docetaxel-based therapy (Table 2).

Discussion

The current analysis suggests that prior exposure to the androgen synthesis inhibitor ketoconazole does not impact clinical outcomes following docetaxel-based therapy in a large cohort of patients with mCRPC, as measured by overall and progression-free survival, objective response rate, and PSA decline ≥ 50%. The study results provide no evidence of cross-resistance between androgen synthesis inhibition and taxane-based chemotherapy in mCRPC. Though the use of ketoconazole in current clinical practice has significantly declined with the introduction of agents like abiraterone and enzalutamide, the study results may have implications for the sequencing of contemporary androgen synthesis inhibitors prior to taxane-based chemotherapy in mCRPC, including abiraterone acetate and others in clinical development (i.e. orteronel, galeterone). These newer agents share a similar mechanism of action as ketoconazole with respect to inhibiting adrenal androgen production, a key source of ligand for the androgen receptor in the castrate-resistant state [24].

Two retrospective series of patients treated with abiraterone followed by docetaxel have been recently reported [9, 25]. In one series of 35 patients treated with docetaxel following disease progression on abiraterone, 25.7% (95% CI 12.5–43.3%) had a PSA decline ≥ 50%. The median time to PSA progression and OS were 4.6 months (95% CI 4.2 – 5.9) and 12.5 months (95% CI 10.6 – 19.4), respectively, outcomes that are seemingly inferior to those achieved in the registrational phase III trials of docetaxel in mCRPC [2, 3]. In contrast, in another small retrospective case series of 14 patients treated with docetaxel following disease progression on abiraterone, 43% of patients achieved ≥ 50% decline from baseline in serum PSA, and the median time to progression on docetaxel (4.3 months) was qualitatively similar to that achieved on prior abiraterone therapy (4.8 months) [25].

These retrospective analyses are intriguing. However, caution in their interpretation is warranted, given the small sample sizes, the lack of comparator arms, and the potential for selection bias as docetaxel therapy was chosen per individual treating physician discretion in both series. In the current analysis, the large numbers of patients (1005 of the 1050 patients enrolled onto CALGB 90401), the similar distribution in baseline prognostic factors among

men with and without prior ketoconazole exposure, and the prospectively assessed outcomes on docetaxel-based chemotherapy, provide support to the hypothesis that androgen synthesis inhibition does not have a detrimental impact on subsequent taxane-based chemotherapy.

There are, however, a number of limitations to the present results. First, it is not known if the potency of prior androgen synthesis inhibition may influence clinical outcomes with subsequent taxane-based chemotherapy. Pre-clinical studies have demonstrated that ketoconazole is a less potent androgen synthesis inhibitor compared to abiraterone acetate, which selectively targets the CYP 17 enzyme [24]. In contrast to abiraterone, ketoconazole has not demonstrated an overall survival benefit in the CRPC disease setting [16]. It is not known if more potent androgen synthesis inhibition will result in the emergence of cross-resistance to subsequent taxane-based chemotherapy.

Second, these results may have been confounded by a heterogeneous study population with respect to duration of prior ketoconazole therapy, whether ketoconazole was applied in the hormone-sensitive or castration-resistant setting, and reason for discontinuation of ketoconazole, none of which were prospectively captured on CALGB 90401 and may influence patterns of cross-resistance. It is possible that many patients received other secondary hormonal agents prior to study enrollment, which may have influenced subsequent clinical outcomes with ketoconazole and/or docetaxel-based chemotherapy. Duration of and response to secondary hormonal maneuvers such as ketoconazole therapy may provide a clinical measure of “androgen sensitivity” which could potentially influence treatment outcomes with subsequent docetaxel therapy.

While the results of the current analysis suggest a lack of deleterious effect of prior androgen synthesis inhibition on the efficacy of docetaxel-based chemotherapy, this does not rule out the possibility of cross-resistance and ultimately highlights the need for future studies addressing the sequencing of therapy in mCRPC. Prospective clinical trials designed with adequate statistical power will be needed to test for potential cross-resistance between various modalities of therapy and to define the optimal sequence of therapy in mCRPC.

Conclusions

As measured by OS, PFS, objective response rate, and decline in PSA ≥ 50%, there is no evidence that prior treatment with the androgen synthesis inhibitor ketoconazole has an impact on clinical outcomes in mCRPC patients with subsequent docetaxel therapy. Future prospectively designed studies are needed to further assess for potential cross-resistance between novel androgen synthesis inhibitors such as abiraterone acetate and taxane-based chemotherapy and to define the optimal sequence of therapy as additional agents become available for clinical use in mCRPC.

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Appendix

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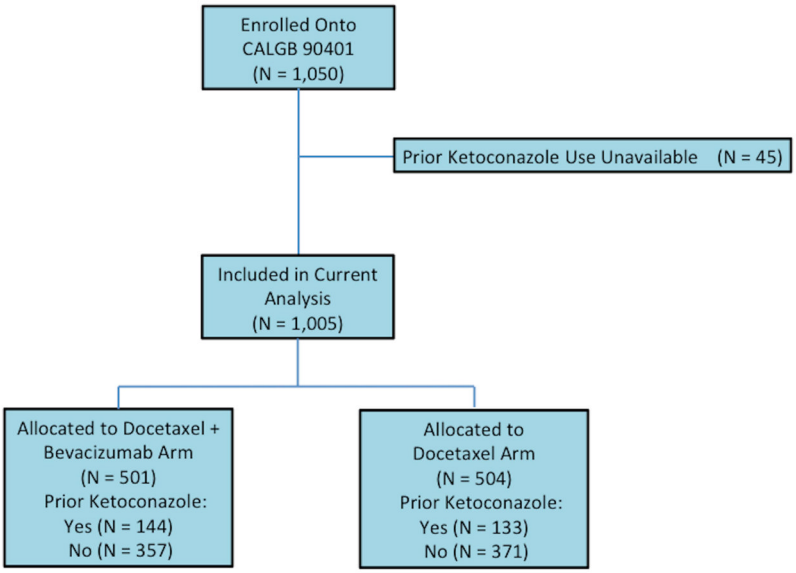

Figure 1.
Patient disposition. 1050 patients were enrolled onto CALGB 90401.

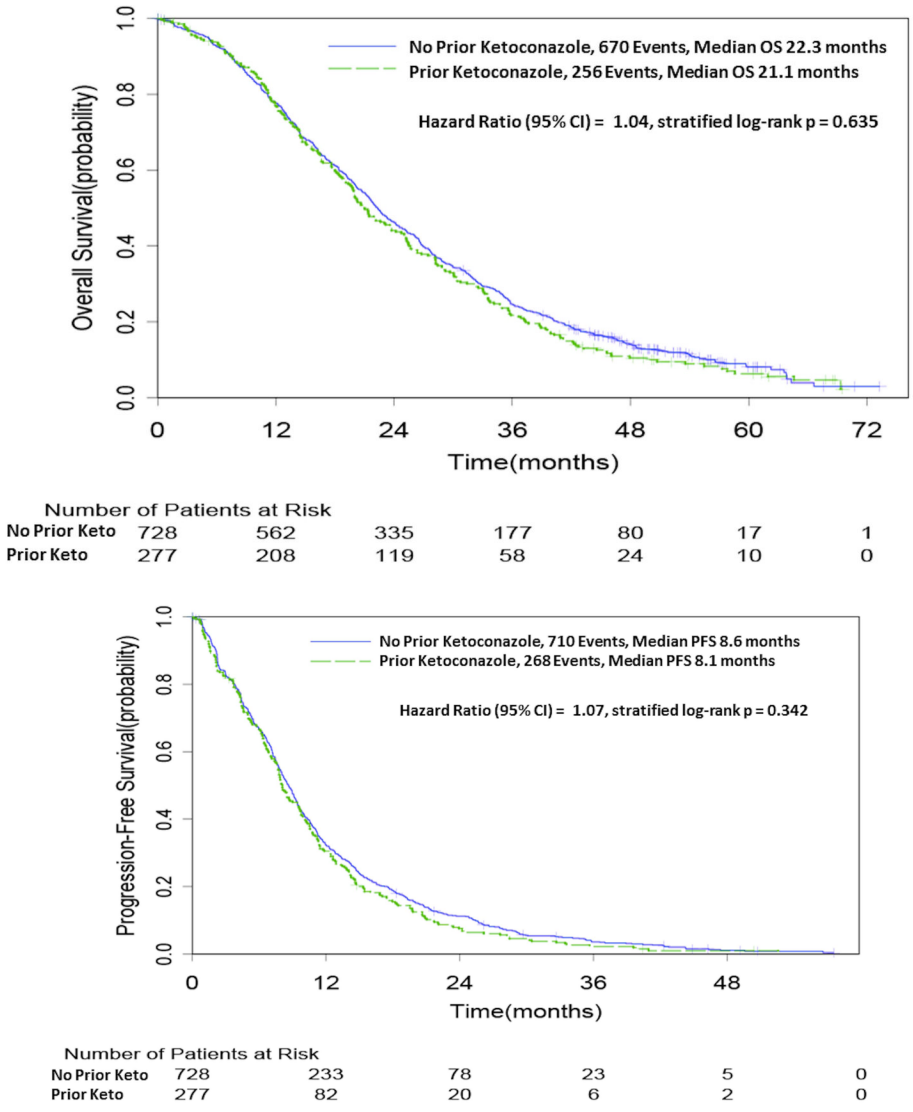

Figure 2.

(A) Kaplan-Meier curves for overall survival by prior ketoconazole exposure on CALGB 90401. OS = overall survival; keto = ketoconazole

(B) Kaplan-Meier curves for progression-free survival by prior ketoconazole exposure. PFS = progression-free survival

Table 1

Baseline Characteristics Among Men With and Without Prior Ketoconazole Use Enrolled Onto CALGB 90401

Variable	Prior Ketoconazole N=277	No Prior Ketoconazole N=728	Total N=1005
Race			
White	88%	88%	88%
Age			
<65	34%	33%	33%
65+ years	66%	67%	67%
Median, years (inter-quartile range)	69.0 (62.0–75.0)	68.0 (62.0–74.0)	69.0 (62.0–75.0)
Prior history of arterial events			
Yes	8%	8%	8%
No	92%	92%	92%
Predicted Survival Probability At 24-months *			
<10%	20%	17%	18%
10%–29.9%	34%	34%	34%
30%+	45%	48%	47%
ECOG Performance Status			
0	55%	55%	55%
1	42%	40%	41%
2	4%	5%	4%
Measurable Disease	52%	49%	50%
Sites of metastases			
Bone	88%	85%	86%
Liver	4%	6%	6%
Lung	10%	10%	10%
Lymph node	45%	42%	43%
Other	14%	14%	14%
Median (inter-quartile range)			
Alkaline Phosphatase U/L	122.0 (86.0–227.0)	117.0 (82.5–225.5)	119.0 (83.0–226.0)
Hemoglobin g/dL	12.7 (11.5–13.8)	12.7 (11.7–13.8)	12.7 (11.7–13.8)
LDH U/L	211.0 (170.0–332.0)	201.5 (164.0–282.5)	205.0 (166.0–298.0)
PSA ng/mL	121.9 (47.2–316.6)	73.3 (25.6–228.7)	85.3 (31.0–241.6)
Testosterone ng/dL	20.0 (10.0–26.0)	20.0 (11.0–27.0)	20.0 (11.0–27.0)
Treatment Arm			
Docetaxel & Bevacizumab	52%	49%	50%
Docetaxel Only	48%	51%	50%

*As assessed by a validated prognostic nomogram in CRPC [19].

Table 2

Multivariable Analyses: Impact of Prior Ketoconazole Use on Clinical Endpoints in CALGB 90401.

	Prior Ketoconazole Use			
Clinical Endpoint	**Yes (n=277)**	**No (n=728)**	**HR (95% CI)**	**p-value**
Median OS (months) (95% CI)	21.1 (19.7–24.2)	22.3 (21.2–24.0)	1.04 (0.90–1.20)	0.635 *
Median PFS (months) (95% CI)	8.1 (7.6–9.4)	8.6 (8.0–9.1)	1.07 (0.93–1.24)	0.342 **
≥50% decline in PSA (95% CI)	61% (54–67)	66% (63–70)	1.09 (0.98–1.21) ***	0.129 **
Objective Response (95% CI) (Patients with measurable disease)	39% (31–47) (156)	43% (38–49) (356)	1.11 (0.88–1.41) ***	0.366 **

* Adjusted for the stratification factors (age, prior history of AE and predicted overall survival probability at 24-months).

** Adjusted for the stratification factors (age, prior history of AE and predicted overall survival probability at 24-months) and treatment arm.

*** Relative risk estimate using a modified Poisson regression approach [22].